Student Study Guide and Solutions Manual

ORGANIC CHEMISTRY

THIRD EDITION



DAVID KLEIN

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Student Study Guide and Solutions Manual, 3e

for

Organic Chemistry, 3e

David Klein

Johns Hopkins University

WILEY

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HOW TO USE THIS BOOK

Organic chemistry is much like bicycle riding. You cannot learn how to ride a bike by watching other people ride bikes. Some people might fool themselves into believing that it's possible to become an expert bike rider without ever getting on a bike. But you know that to be incorrect (and very naïve). In order to learn how to ride a bike, you must be willing to get on the bike, and you must be willing to fall. With time (and dedication), you can quickly train yourself to avoid falling, and to ride the bike with ease and confidence. The same is true of organic chemistry. In order to become proficient at solving problems, you must "ride the bike". You must try to solve the problems yourself (*without* the solutions manual open in front of you). Once you have solved the problems, this book will allow you to check your solutions. If, however, you don't attempt to solve each problem on your own, and instead, you read the problem statement and then immediately read the solution, you are only hurting yourself. You are not learning how to avoid falling. Many students make this mistake every year. They use the solutions manual as a crutch, and then they never really attempt to solve the problems on their own. It really is like believing that you can become an expert bike rider by watching hundreds of people riding bikes. The world doesn't work that way!

The textbook has thousands of problems to solve. Each of these problems should be viewed as an opportunity to develop your problem-solving skills. By reading a problem statement and then reading the solution immediately (without trying to solve the problem yourself), you are robbing yourself of the opportunity provided by the problem. If you repeat that poor study habit too many times, you will not learn how to solve problems on your own, and you will not get the grade that you want.

Why do so many students adopt this bad habit (of using the solutions manual too liberally)? The answer is simple. Students often wait until a day or two before the exam, and then they spend all night cramming. Sound familiar? Unfortunately, organic chemistry is the type of course where cramming is insufficient, because you need time in order to ride the bike yourself. You need time to think about each problem until you have developed a solution *on your own*. For some problems, it might take days before you think of a solution. This process is critical for learning this subject. Make sure to allot time every day for studying organic chemistry, and use this book to check your solutions. This book has also been designed to serve as a study guide, as described below.

WHAT'S IN THIS BOOK

This book contains more than just solutions to all of the problems in the textbook. Each chapter of this book also contains a series of exercises that will help you review the concepts, skills and reactions presented in the corresponding chapter of the textbook. These exercises

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are designed to serve as study tools that can help you identify your weak areas. Each chapter of this solutions manual/study guide has the following parts:

- ***Review of Concepts***. These exercises are designed to help you identify which concepts are the least familiar to you. Each section contains sentences with missing words (blanks). Your job is to fill in the blanks, demonstrating mastery of the concepts. To verify that your answers are correct, you can open your textbook to the end of the corresponding chapter, where you will find a section entitled *Review of Concepts and Vocabulary*. In that section, you will find each of the sentences, verbatim.
- ***Review of Skills***. These exercises are designed to help you identify which skills are the least familiar to you. Each section contains exercises in which you must demonstrate mastery of the skills developed in the *SkillBuilders* of the corresponding textbook chapter. To verify that your answers are correct, you can open your textbook to the end of the corresponding chapter, where you will find a section entitled *SkillBuilder Review*. In that section, you will find the answers to each of these exercises.
- ***Review of Reactions***. These exercises are designed to help you identify which reagents are not at your fingertips. Each section contains exercises in which you must demonstrate familiarity with the reactions covered in the textbook. Your job is to fill in the reagents necessary to achieve each reaction. To verify that your answers are correct, you can open your textbook to the end of the corresponding chapter, where you will find a section entitled *Review of Reactions*. In that section, you will find the answers to each of these exercises.
- ***Common Mistakes to Avoid***. This is a new feature to this edition. The most common student mistakes are described, so that you can avoid them when solving problems.
- ***A List of Useful Reagents***. This is a new feature to this edition. This list provides a review of the reagents that appear in each chapter, as well as a description of how each reagent is used.
- ***Solutions***. At the end of each chapter, you'll find detailed solutions to all problems in the textbook, including all SkillBuilders, conceptual checkpoints, additional problems, integrated problems, and challenge problems.

The sections described above have been designed to serve as useful tools as you study and learn organic chemistry. Good luck!

David Klein
Senior Lecturer, Department of Chemistry
Johns Hopkins University

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Chapter 1
A Review of General Chemistry: Electrons, Bonds and Molecular Properties

Review of Concepts

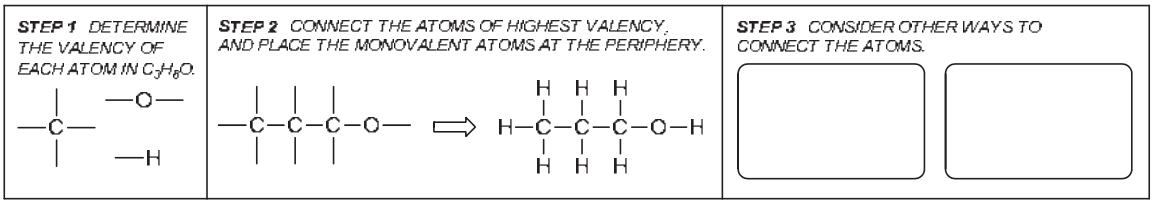
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 1. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- _____ **isomers** share the same molecular formula but have different connectivity of atoms and different physical properties.
- Second-row elements generally obey the _____ **rule**, bonding to achieve noble gas electron configuration.
- A pair of unshared electrons is called a _____.
- A **formal charge** occurs when an atom does not exhibit the appropriate number of _____.
- An **atomic orbital** is a region of space associated with _____, while a **molecular orbital** is a region of space associated with _____.
- Methane's tetrahedral geometry can be explained using four degenerate _____-**hybridized orbitals** to achieve its four single bonds.
- Ethylene's planar geometry can be explained using three degenerate _____-**hybridized orbitals**.
- Acetylene's linear geometry is achieved via _____-**hybridized** carbon atoms.
- The geometry of small compounds can be predicted using valence shell electron pair repulsion (**VSEPR**) theory, which focuses on the number of _____ bonds and _____ exhibited by each atom.
- The physical properties of compounds are determined by _____ forces, the attractive forces between molecules.
- **London dispersion forces** result from the interaction between transient _____ and are stronger for larger alkanes due to their larger surface area and ability to accommodate more interactions.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 1. The answers appear in the section entitled *SkillBuilder Review*.

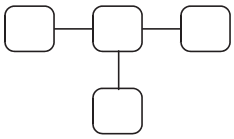
SkillBuilder 1.1 Drawing Constitutional Isomers of Small Molecules



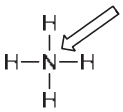
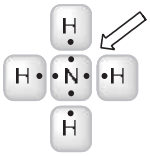
SkillBuilder 1.2 Drawing the Lewis Dot Structure of an Atom

STEP 1 - *DETERMINE THE NUMBER OF VALENCE ELECTRONS*	***STEP 2*** - *PLACE ONE ELECTRON BY ITSELF ON EACH SIDE OF THE ATOM*	***STEP 3*** - *IF THE ATOM HAS MORE THAN FOUR VALENCE ELECTRONS, PAIR THE REMAINING ELECTRONS WITH THE ELECTRONS ALREADY DRAWN*
Nitrogen is in Group ___ of the periodic table, and is expected to have ___ valence electrons.		

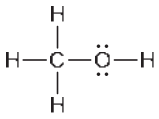
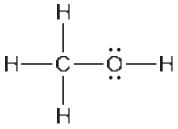
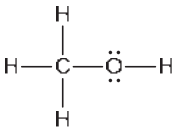
SkillBuilder 1.3 Drawing the Lewis Structure of a Small Molecule

STEP 1 - *DRAW THE LEWIS DOT STRUCTURE OF EACH ATOM IN CH_2O*	***STEP 2*** - *FIRST CONNECT ATOMS THAT FORM MORE THAN ONE BOND*	***STEP 3*** - *CONNECT THE HYDROGEN ATOMS*	***STEP 4*** - *PAIR ANY UNPAIRED ELECTRONS, SO THAT EACH ATOM ACHIEVES AN OCTET*
			

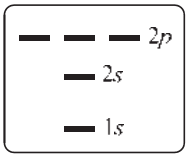
SkillBuilder 1.4 Calculating Formal Charge

STEP 1 - *DETERMINE THE APPROPRIATE NUMBER OF VALENCE ELECTRONS*	***STEP 2*** - *DETERMINE THE NUMBER OF VALENCE ELECTRONS IN THIS CASE*	***STEP 3*** - *ASSIGN A FORMAL CHARGE TO THE NITROGEN ATOM IN THIS CASE*
 Nitrogen is in Group ___ of the periodic table, and is expected to have ___ valence electrons.	 In this case, the nitrogen atom is using only ___ valence electrons.	

SkillBuilder 1.5 Locating Partial Charges Resulting from Induction

STEP 1 - *CIRCLE THE BONDS BELOW THAT ARE POLAR COVALENT*	***STEP 2*** - *FOR EACH POLAR COVALENT BOND, DRAW AN ARROW THAT SHOWS THE DIRECTION OF THE DIPOLE MOMENT*	***STEP 3*** - *INDICATE THE LOCATION OF ALL PARTIAL CHARGES ($\delta+$ and $\delta-$)*
		

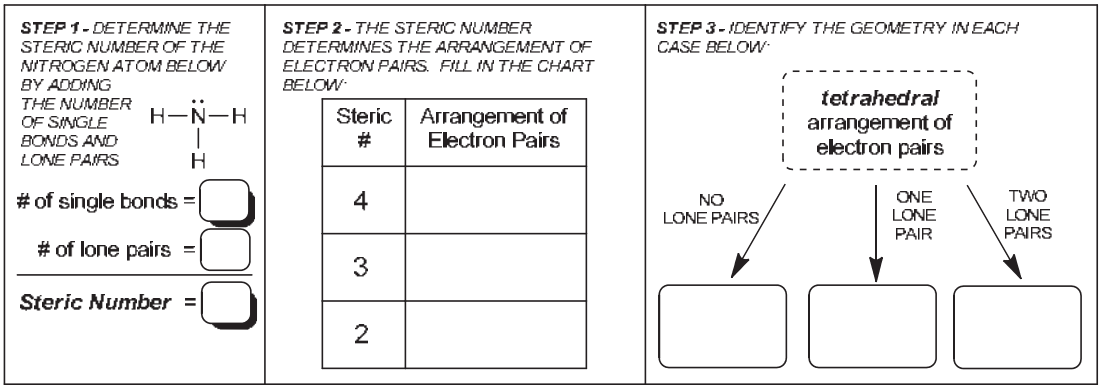
SkillBuilder 1.6 Identifying Electron Configurations

STEP 1 - *IN THE ENERGY DIAGRAM SHOWN HERE, DRAW THE ELECTRON CONFIGURATION OF NITROGEN (USING ARROWS TO REPRESENT ELECTRONS).*	***STEP 2*** - *FILL IN THE BOXES BELOW WITH THE NUMBERS THAT CORRECTLY DESCRIBE THE ELECTRON CONFIGURATION OF NITROGEN*
 Nitrogen	

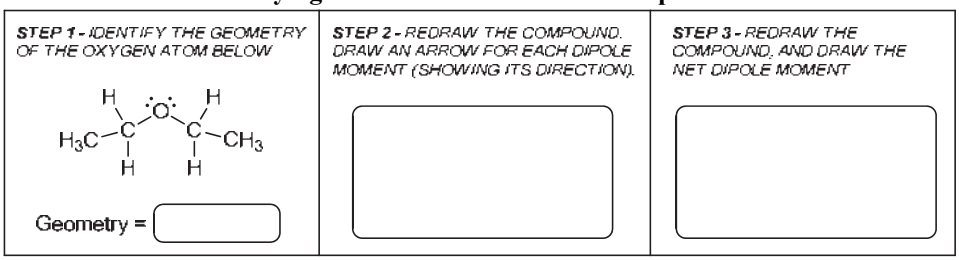
SkillBuilder 1.7 Identifying Hybridization States

A CARBON ATOM WITH FOUR SINGLE BONDS WILL BE _____ HYBRIDIZED	*A CARBON ATOM WITH ONE DOUBLE BOND WILL BE _____ HYBRIDIZED*	*A CARBON ATOM WITH A TRIPLE BOND WILL BE _____ HYBRIDIZED*
		

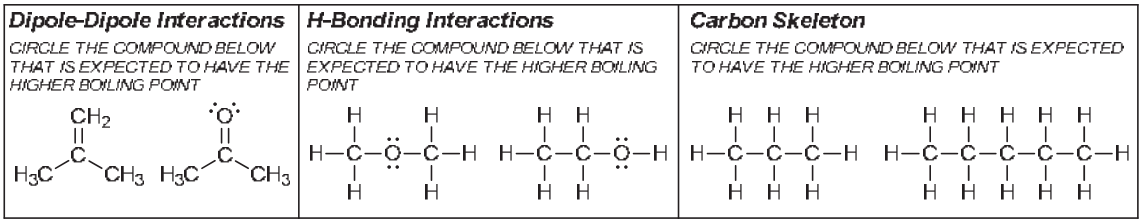
SkillBuilder 1.8 Predicting Geometry



SkillBuilder 1.9 Identifying the Presence of Molecular Dipole Moments

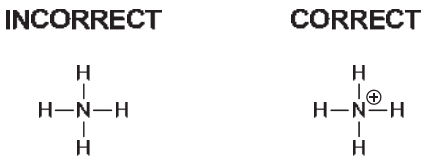


SkillBuilder 1.10 Predicting Physical Properties



A Common Mistake to Avoid

When drawing a structure, don't forget to draw formal charges, as forgetting to do so is a common error. If a formal charge is present, it MUST be drawn. For example, in the following case, the nitrogen atom bears a positive charge, so the charge must be drawn:



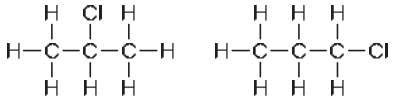
As we progress though the course, we will see structures of increasing complexity. If formal charges are present, failure to draw them constitutes an error, and must be scrupulously avoided. If you have trouble drawing formal charges, go back and master that skill. You can't go on without it. Don't make the mistake of underestimating the importance of being able to draw formal charges with confidence.

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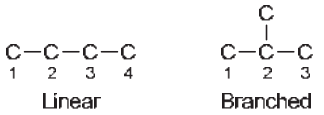
Solutions

1.1.

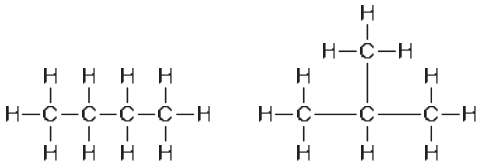
(a) Begin by determining the valency of each atom that appears in the molecular formula. The carbon atoms are tetravalent, while the chlorine atom and hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the three carbon atoms) should be drawn in the center of the compound. Then, the chlorine atom can be placed in either of two locations: i) connected to the central carbon atom, or ii) connected to one of the other two (equivalent) carbon atoms. The hydrogen atoms are then placed at the periphery.



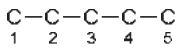
(b) Begin by determining the valency of each atom that appears in the molecular formula. The carbon atoms are tetravalent, while the hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the four carbon atoms) should be drawn in the center of the compound. There are two different ways to connect four carbon atoms. They can either be arranged in a linear fashion or in a branched fashion:



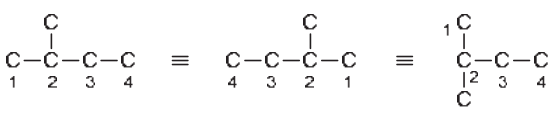
We then place the hydrogen atoms at the periphery, giving the following two constitutional isomers:



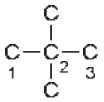
(c) Begin by determining the valency of each atom that appears in the molecular formula. The carbon atoms are tetravalent, while the hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the five carbon atoms) should be drawn in the center of the compound. So we must explore all of the different ways to connect five carbon atoms. First, we can connect all five carbon atoms in a linear fashion:



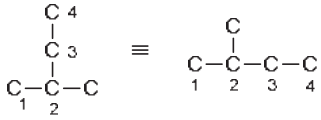
Alternatively, we can draw four carbon atoms in a linear fashion, and then draw the fifth carbon atom on a branch. There are many ways to draw this possibility:



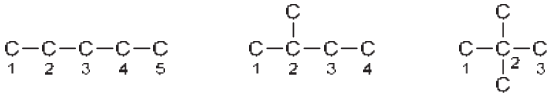
Finally, we can draw three carbon atoms in a linear fashion, and then draw the remaining two carbon atoms on separate branches.



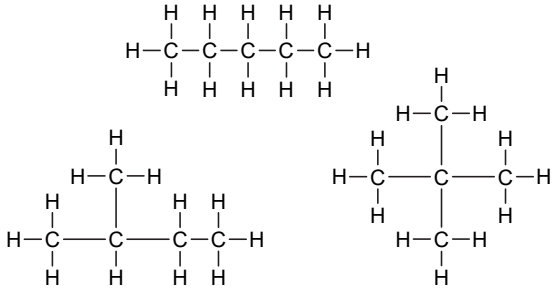
Note that we cannot place the last two carbon atoms together as one branch, because that possibility has already been drawn earlier (a linear chain of four carbon atoms with a single branch):



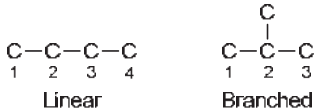
In summary, there are three different ways to connect five carbon atoms:



We then place the hydrogen atoms at the periphery, giving the following three constitutional isomers:

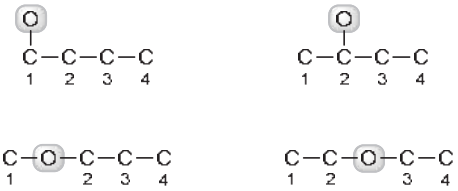


(d) Begin by determining the valency of each atom that appears in the molecular formula. The carbon atoms are tetravalent, the oxygen atom is divalent, and the hydrogen atoms are all monovalent. Any atoms with more than one bond (in this case, the four carbon atoms and the one oxygen atom) should be drawn in the center of the compound, with the hydrogen atoms at the periphery. There are several different ways to connect four carbon atoms and one oxygen atom. Let's begin with the four carbon atoms. There are two different ways to connect four carbon atoms. They can either be arranged in a linear fashion or in a branched fashion.

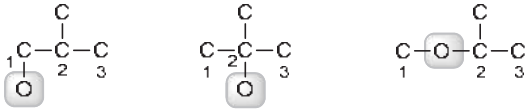


Next, the oxygen atom must be inserted. For each of the two skeletons above (linear or branched), there are

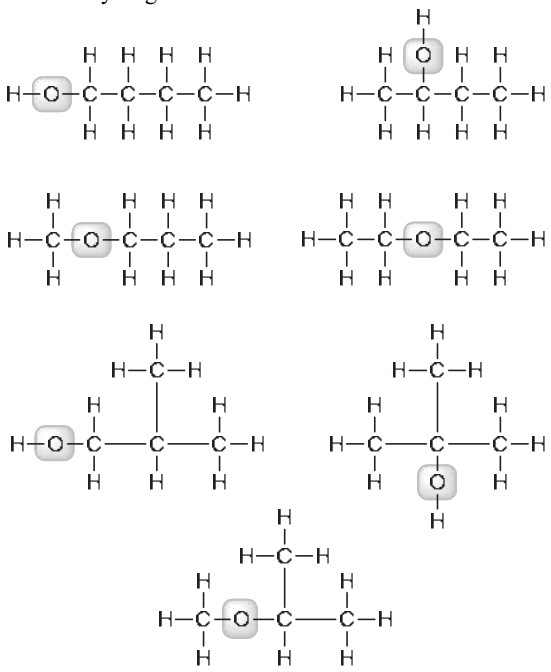
several different locations to insert the oxygen atom. The linear skeleton has four possibilities, shown here:



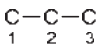
and the branched skeleton has three possibilities shown here:



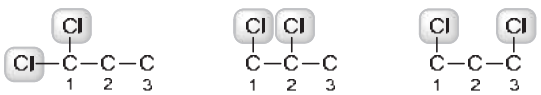
Finally, we complete all of the structures by drawing the bonds to hydrogen atoms.



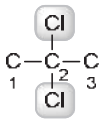
(e) Begin by determining the valency of each atom that appears in the molecular formula. The carbon atoms are tetravalent, while the chlorine atom and hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the three carbon atoms) should be drawn in the center of the compound. There is only way to connect three carbon atoms:



Next, we must determine all of the different possible ways of connecting two chlorine atoms to the chain of three carbon atoms. If we place one chlorine atom at C1, then the second chlorine atom can be placed at C1, at C2 or at C3:



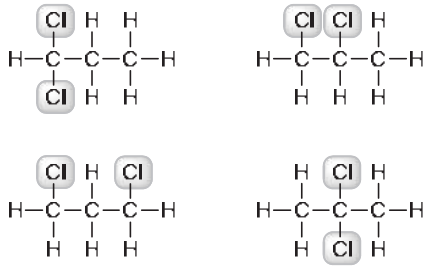
Furthermore, we can place both chlorine atoms at C2, giving a new possibility not shown above:



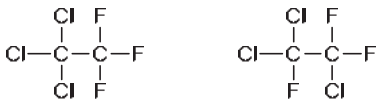
There are no other possibilities. For example, placing the two chlorine atoms at C2 and C3 is equivalent to placing them at C1 and C2:



Finally, the hydrogen atoms are placed at the periphery, giving the following four constitutional isomers:



1.2. The carbon atoms are tetravalent, while the chlorine atoms and fluorine atoms are all monovalent. The atoms with more than one bond (in this case, the two carbon atoms) should be drawn in the center of the compound. The chlorine atoms and fluorine atoms are then placed at the periphery, as shown. There are only two possible constitutional isomers: one with the three chlorine atoms all connected to the same carbon, and one in which they are distributed over both carbon atoms. Any other representations that one may draw must be one of these structures drawn in a different orientation.



1.3.

(a) Carbon belongs to group 4A of the periodic table, and it therefore has four valence electrons. The periodic symbol for carbon (C) is drawn, and each valence electron is placed by itself (unpaired), around the C, like this:



(b) Oxygen belongs to group 6A of the periodic table, and it therefore has six valence electrons. The periodic symbol for oxygen (O) is drawn, and each valence electron is placed by itself (unpaired) on a side of the O, until all four sides are occupied. That takes care of four of the six electrons, leaving just two more electrons to

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draw. Each of the two remaining electrons is then paired up with an electron already drawn, like this:



(c) Fluorine belongs to group 7A of the periodic table, and it therefore has seven valence electrons. The periodic symbol for fluorine (F) is drawn, and each valence electron is placed by itself (unpaired) on a side of the F, until all four sides are occupied. That takes care of four of the seven electrons, leaving three more electrons to draw. Each of the three remaining electrons is then paired up with an electron already drawn, like this:



(d) Hydrogen belongs to group 1A of the periodic table, and it therefore has one valence electron. The periodic symbol for hydrogen (H) is drawn, and the one and only valence electron is placed on a side of the H, like this:



(e) Bromine belongs to group 7A of the periodic table, and it therefore has seven valence electrons. The periodic symbol for bromine (Br) is drawn, and each valence electron is placed by itself (unpaired) on a side of the Br, until all four sides are occupied. That takes care of four of the seven electrons, leaving three more electrons to draw. Each of the three remaining electrons is then paired up with an electron already drawn, like this:



(f) Sulfur belongs to group 6A of the periodic table, and it therefore has six valence electrons. The periodic symbol for sulfur (S) is drawn, and each valence electron is placed by itself (unpaired) on a side of the S, until all four sides are occupied. That takes care of four of the six electrons, leaving just two more electrons to draw. Each of the two remaining electrons is then paired up with an electron already drawn, like this:



(g) Chlorine belongs to group 7A of the periodic table, and it therefore has seven valence electrons. The periodic symbol for chlorine (Cl) is drawn, and each valence electron is placed by itself (unpaired) on a side of the Cl, until all four sides are occupied. That takes care of four of the seven electrons, leaving three more electrons to draw. Each of the three remaining electrons is then paired up with an electron already drawn, like this:



(h) Iodine belongs to group 7A of the periodic table, and it therefore has seven valence electrons. The periodic symbol for iodine (I) is drawn, and each valence electron is placed by itself (unpaired) on a side of the I, until all four sides are occupied. That takes care of four of the seven electrons, leaving three more electrons to draw. Each of the three remaining electrons is then paired up with an electron already drawn, like this:



1.4. Both nitrogen and phosphorus belong to group **5A** of the periodic table, and therefore, each of these atoms has five valence electrons. In order to achieve an octet, we expect each of these elements to form three bonds.

1.5. Aluminum is directly beneath boron on the periodic table (group **3A**), and each of these elements has three valence electrons. Therefore, we expect the bonding properties to be similar.

1.6. The Lewis dot structure for a carbon atom is shown in the solution to Problem **1.3a**. That drawing must be modified by removing one electron, resulting in a formal positive charge, as shown below. This resembles boron because it exhibits three valence electrons.



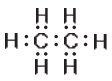
1.7.
(a) Lithium is in Group 1A of the periodic table, and therefore, it has just one valence electron.



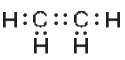
(b) If an electron is removed from a lithium atom, the resulting cation has zero valence electrons.



1.8.
(a) Each carbon atom has four valence electrons, and each hydrogen atom has one valence electron. Only the carbon atoms can form more than one bond, so we begin by connecting the carbon atoms to each other. Then, we connect all of the hydrogen atoms, as shown.



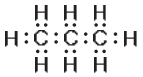
(b) Each carbon atom has four valence electrons, and each hydrogen atom has one valence electron. Only the carbon atoms can form more than one bond, so we begin by connecting the carbon atoms to each other. Then, we connect all of the hydrogen atoms, and the unpaired electrons are shared to give a double bond. In this way, each of the carbon atoms achieves an octet.



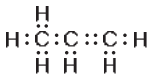
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(c) Each carbon atom has four valence electrons, and each hydrogen atom has one valence electron. Only the carbon atoms can form more than one bond, so we begin by connecting the carbon atoms to each other. Then, we connect all of the hydrogen atoms, and the unpaired electrons are shared to give a triple bond. In this way, each of the carbon atoms achieves an octet.

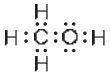
(d) Each carbon atom has four valence electrons, and each hydrogen atom has one valence electron. Only the carbon atoms can form more than one bond, so we begin by connecting the carbon atoms to each other. Then, we connect all of the hydrogen atoms, as shown.



(e) Each carbon atom has four valence electrons, and each hydrogen atom has one valence electron. Only the carbon atoms can form more than one bond, so we begin by connecting the carbon atoms to each other. Then, we connect all of the hydrogen atoms, and the unpaired electrons are shared to give a double bond. In this way, each of the carbon atoms achieves an octet.



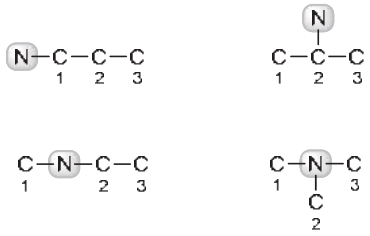
(f) The carbon atom has four valence electrons, the oxygen atom has six valence electrons, and each hydrogen atom has one valence electron. Only the carbon atom and the oxygen atom can form more than one bond, so we begin by connecting them to each other. Then, we connect all of the hydrogen atoms, as shown.



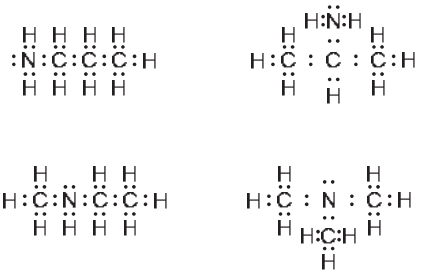
1.9. Boron has three valence electrons, each of which is shared with a hydrogen atom, shown below. The central boron atom lacks an octet of electrons, and it is therefore very unstable and reactive.



1.10. Each of the carbon atoms has four valence electrons; the nitrogen atom has five valence electrons; and each of the hydrogen atoms has one valence electron. We begin by connecting the atoms that have more than one bond (in this case, the three carbon atoms and the nitrogen atom). There are four different ways that these four atoms can be connected to each other, shown here.



For each of these possible arrangements, we connect the hydrogen atoms, giving the following four constitutional isomers.



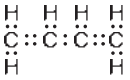
In each of these four structures, the nitrogen atom has one lone pair.

1.11.

(a) The carbon atom has four valence electrons, the nitrogen atom has five valence electrons and the hydrogen atom has one valence electron. Only the carbon atom and the nitrogen atom can form more than one bond, so we begin by connecting them to each other. Then, we connect the hydrogen atom to the carbon, as shown. The unpaired electrons are shared to give a triple bond. In this way, both the carbon atom and the nitrogen atom achieve an octet.

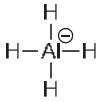


(b) Each carbon atom has four valence electrons, and each hydrogen atom has one valence electron. Only the carbon atoms can form more than one bond, so we begin by connecting the carbon atoms to each other. Then, we connect all of the hydrogen atoms as indicated in the given condensed formula ($CH_2CHCHCH_2$), and the unpaired electrons are shared to give two double bonds on the outermost carbons. In this way, each of the carbon atoms achieves an octet.



1.12.

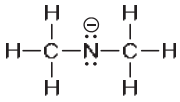
(a) Aluminum is in group 3A of the periodic table, and it should therefore have three valence electrons. In this case, the aluminum atom exhibits four valence electrons (one for each bond). With one extra electron, this aluminum atom will bear a negative charge.



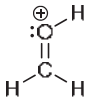
(b) Oxygen is in group 6A of the periodic table, and it should therefore have six valence electrons. In this case, the oxygen atom exhibits only five valence electrons (one for each bond, and two for the lone pair). This oxygen atom is missing an electron, and it therefore bears a positive charge.



(c) Nitrogen is in group 5A of the periodic table, and it should therefore have five valence electrons. In this case, the nitrogen atom exhibits six valence electrons (one for each bond and two for each lone pair). With one extra electron, this nitrogen atom will bear a negative charge.



(d) Oxygen is in group 6A of the periodic table, and it should therefore have six valence electrons. In this case, the oxygen atom exhibits only five valence electrons (one for each bond, and two for the lone pair). This oxygen atom is missing an electron, and it therefore bears a positive charge.



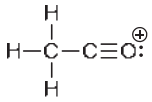
(e) Carbon is in group 4A of the periodic table, and it should therefore have four valence electrons. In this case, the carbon atom exhibits five valence electrons (one for each bond and two for the lone pair). With one extra electron, this carbon atom will bear a negative charge.



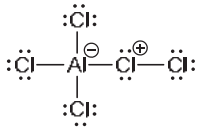
(f) Carbon is in group 4A of the periodic table, and it should therefore have four valence electrons. In this case, the carbon atom exhibits only three valence electrons (one for each bond). This carbon atom is missing an electron, and it therefore bears a positive charge.



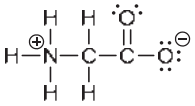
(g) Oxygen is in group 6A of the periodic table, and it should therefore have six valence electrons. In this case, the oxygen atom exhibits only five valence electrons (one for each bond, and two for the lone pair). This oxygen atom is missing an electron, and it therefore bears a positive charge.



(h) Two of the atoms in this structure exhibit a formal charge because each of these atoms does not exhibit the appropriate number of valence electrons. The aluminum atom (group 3A) should have three valence electrons, but it exhibits four (one for each bond). With one extra electron, this aluminum atom will bear a negative charge. The neighboring chlorine atom (to the right) should have seven valence electrons, but it exhibits only six (one for each bond and two for each lone pair). It is missing one electron, so this chlorine atom will bear a positive charge.

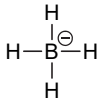


(i) Two of the atoms in this structure exhibit a formal charge because each of these atoms does not exhibit the appropriate number of valence electrons. The nitrogen atom (group 5A) should have five valence electrons, but it exhibits four (one for each bond). It is missing one electron, so this nitrogen atom will bear a positive charge. One of the two oxygen atoms (the one on the right) exhibits seven valence electrons (one for the bond, and two for each lone pair), although it should have only six. With one extra electron, this oxygen atom will bear a negative charge.



1.13.

(a) The boron atom in this case exhibits four valence electrons (one for each bond), although boron (group 3A) should only have three valence electrons. With one extra electron, this boron atom bears a negative charge.

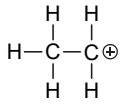


(b) Nitrogen is in group 5A of the periodic table, so a nitrogen atom should have five valence electrons. A negative charge indicates one extra electron, so this nitrogen atom must exhibit six valence electrons (one for each bond and two for each lone pair).

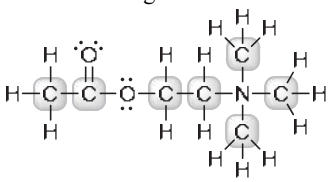


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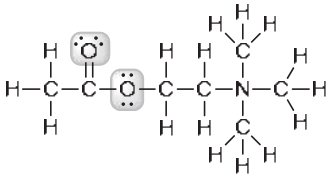
(c) One of the carbon atoms (below right) exhibits three valence electrons (one for each bond), but carbon (group 4A) is supposed to have four valence electrons. It is missing one electron, so this carbon atom therefore bears a positive charge.



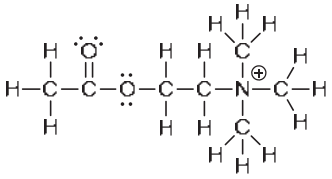
1.14. Carbon is in group 4A of the periodic table, and it should therefore have four valence electrons. Every carbon atom in acetylcholine has four bonds, thus exhibiting the correct number of valence electrons (four) and having no formal charge.



Oxygen is in group 6A of the periodic table, and it should therefore have six valence electrons. Each oxygen atom in acetylcholine has two bonds and two lone pairs of electrons, so each oxygen atom exhibits six valence electrons (one for each bond, and two for each lone pair). With the correct number of valence electrons, each oxygen atom will lack a formal charge.

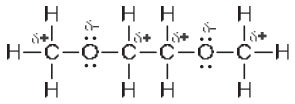


The nitrogen atom (group 5A) should have five valence electrons, but it exhibits four (one for each bond). It is missing one electron, so this nitrogen atom will bear a positive charge.

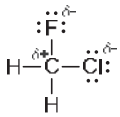


1.15.

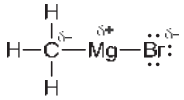
(a) Oxygen is more electronegative than carbon, and a C–O bond is polar covalent. For each C–O bond, the O will be electron rich (δ–), and the C will be electron-poor (δ+), as shown below.



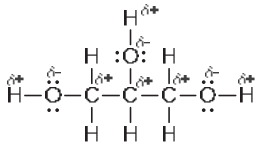
(b) Fluorine is more electronegative than carbon, and a C–F bond is polar covalent. For a C–F bond, the F will be electron-rich (δ–), and the C will be electron-poor (δ+). Chlorine is also more electronegative than carbon, so a C–Cl bond is also polar covalent. For a C–Cl bond, the Cl will be electron-rich (δ–), and the C will be electron-poor (δ+), as shown below.



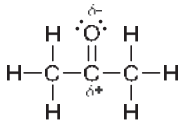
(c) Carbon is more electronegative than magnesium, so the C will be electron-rich (δ–) in a C–Mg bond, and the Mg will be electron-poor (δ+). Also, bromine is more electronegative than magnesium. So in a Mg–Br bond, the Br will be electron-rich (δ–), and the Mg will be electron-poor (δ+), as shown below.



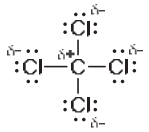
(d) Oxygen is more electronegative than carbon or hydrogen, so all C–O bonds and all O–H bond are polar covalent. For each C–O bond and each O–H bond, the O will be electron-rich (δ–), and the C or H will be electron-poor (δ+), as shown below.



(e) Oxygen is more electronegative than carbon. As such, the O will be electron-rich (δ–) and the C will be electron-poor (δ+) in a C=O bond, as shown below.



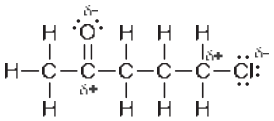
(f) Chlorine is more electronegative than carbon. As such, for each C–Cl bond, the Cl will be electron-rich (δ–) and the C will be electron-poor (δ+), as shown below.



1.16. Oxygen is more electronegative than carbon. As such, the O will be electron-rich (δ–) and the C will be electron-poor (δ+) in a C=O bond. In addition, chlorine is more electronegative than carbon. So for a C–Cl

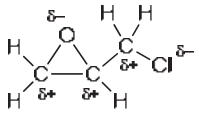
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bond, the Cl will be electron-rich (δ–) and the C will be electron-poor (δ+), as shown below.



Notice that two carbon atoms are electron-poor (δ+). These are the positions that are most likely to be attacked by an anion, such as hydroxide.

1.17. Oxygen is more electronegative than carbon. As such, the O will be electron-rich (δ−) and the C will be electron-poor (δ+) in a C─O bond. In addition, chlorine is more electronegative than carbon. So for a C─Cl bond, the Cl will be electron-rich (δ−) and the C will be electron-poor (δ+), as shown below. As you might imagine, epichlorohydrin is a very reactive molecule!



1.18.
(a) As indicated in Figure 1.10, carbon has two *1s* electrons, two *2s* electrons, and two *2p* electrons. This information is represented by the following electron configuration: $1s^2 2s^2 2p^2$
(b) As indicated in Figure 1.10, oxygen has two *1s* electrons, two *2s* electrons, and four *2p* electrons. This information is represented by the following electron configuration: $1s^2 2s^2 2p^4$
(c) As indicated in Figure 1.10, boron has two *1s* electrons, two *2s* electrons, and one *2p* electron. This information is represented by the following electron configuration: $1s^2 2s^2 2p^1$
(d) As indicated in Figure 1.10, fluorine has two *1s* electrons, two *2s* electrons, and five *2p* electrons. This information is represented by the following electron configuration: $1s^2 2s^2 2p^5$
(e) Sodium has two *1s* electrons, two *2s* electrons, six *2p* electrons, and one *3s* electron. This information is represented by the following electron configuration: $1s^2 2s^2 2p^6 3s^1$
(f) Aluminum has two *1s* electrons, two *2s* electrons, six *2p* electrons, two *3s* electrons, and one *3p* electron. This information is represented by the following electron configuration: $1s^2 2s^2 2p^6 3s^2 3p^1$

1.19.
(a) The electron configuration of a carbon atom is $1s^2 2s^2 2p^2$ (see the solution to Problem 1.18a). However, if a carbon atom bears a negative charge, then it must have one extra electron, so the electron configuration should be as follows: $1s^2 2s^2 2p^3$
(b) The electron configuration of a carbon atom is $1s^2 2s^2 2p^2$ (see the solution to Problem 1.18a). However, if a carbon atom bears a positive charge, then it must be missing an electron, so the electron configuration should be as follows: $1s^2 2s^2 2p^1$
(c) As seen in Skillbuilder 1.6, the electron configuration of a nitrogen atom is $1s^2 2s^2 2p^3$**.** However, if a nitrogen atom bears a positive charge, then it must be missing an electron, so the electron configuration should be as follows: $1s^2 2s^2 2p^2$
(d) The electron configuration of an oxygen atom is $1s^2 2s^2 2p^4$ (see the solution to Problem 1.18b). However, if an oxygen atom bears a negative charge, then it must have one extra electron, so the electron configuration should be as follows: $1s^2 2s^2 2p^5$

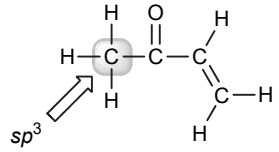
1.20. Silicon is in the third row, or period, of the periodic table. Therefore, it has a filled second shell, like neon, and then the additional electrons are added to the third shell. As indicated in Figure 1.10, neon has two 1*s* electrons, two 2*s* electrons, and six 2*p* electrons. Silicon has an additional two 3*s* electrons and two 3*p* electrons to give a total of 14 electrons and an electron configuration of $1s^2 2s^2 2p^6 3s^2 3p^2$.

1.21. The bond angles of an equilateral triangle are 60º, but each bond angle of cyclopropane is supposed to be 109.5º. Therefore, each bond angle is severely strained, causing an increase in energy. This form of strain, called ring strain, will be discussed in Chapter 4. The ring strain associated with a three-membered ring is greater than the ring strain of larger rings, because larger rings do not require bond angles of 60º.

1.22.
(a) The C=O bond of formaldehyde is comprised of one σ bond and one π bond.
(b) Each C–H bond is formed from the interaction between an sp^2 hybridized orbital from carbon and an *s* orbital from hydrogen.
(c) The oxygen atom is sp^2 hybridized, so the lone pairs occupy sp^2 hybridized orbitals.

1.23. Rotation of a single bond does not cause a reduction in the extent of orbital overlap, because the orbital overlap occurs on the bond axis. In contrast, rotation of a π bond results in a reduction in the extent of orbital overlap, because the orbital overlap is NOT on the bond axis.

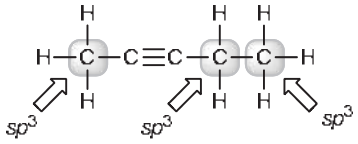
1.24.
(a) The highlighted carbon atom (below) has four σ bonds, and is therefore sp^3 hybridized. The other carbon atoms in this structure are all sp^2 hybridized, because each of them has three σ bonds and one π bond.



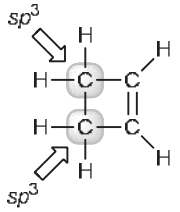
(b) Each of the highlighted carbon atoms has four σ bonds, and is therefore sp^3 hybridized. Each of the

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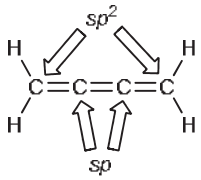
other two carbon atoms in this structure is *sp* hybridized, because each has two σ bonds and two π bonds.



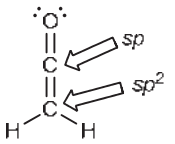
(b) Each of the highlighted carbon atoms (below) has four σ bonds, and is therefore sp^3 hybridized. Each of the other two carbon atoms in this structure is sp^2 hybridized, because each has three σ bonds and one π bond.



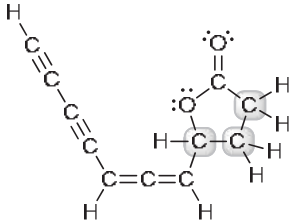
(d) Each of the two central carbon atoms has two σ bonds and two π bonds, and as such, each of these carbon atoms is *sp* hybridized. The other two carbon atoms (the outer ones) are sp^2 hybridized because each has three σ bonds and one π bond.



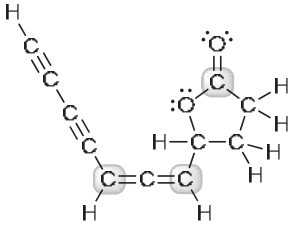
(e) One of the carbon atoms (the one connected to oxygen) has two σ bonds and two π bonds, and as such, it is *sp* hybridized. The other carbon atom is sp^2 hybridized because it has three σ bonds and one π bond.



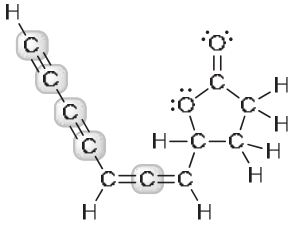
1.25. Each of the following three highlighted three carbon atoms has four σ bonds, and is therefore sp^3 hybridized:



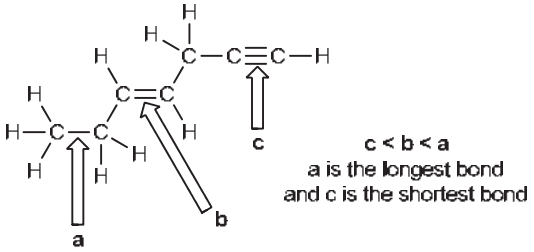
And each of the following three highlighted carbon atoms has three σ bonds and one π bond, and is therefore sp^2 hybridized:



Finally, each of the following five highlighted carbon atoms has two σ bonds and two π bonds, and is therefore *sp* hybridized.



1.26. Carbon-carbon triple bonds generally have a shorter bond length than carbon-carbon double bonds, which are generally shorter than carbon-carbon single bonds (see Table 1.2).



1.27

(a) In this structure, the boron atom has four σ bonds and no lone pairs, giving a total of four electron pairs (steric number = 4). VSEPR theory therefore predicts a tetrahedral arrangement of electron pairs. Since all of the electron pairs are bonds, the structure is expected to have tetrahedral geometry.

(b) In this structure, the boron atom has three σ bonds and no lone pairs, giving a total of three electron pairs (steric number = 3). VSEPR theory therefore predicts a trigonal planar geometry.

(c) In this structure, the nitrogen atom has four σ sigma bonds and no lone pairs, giving a total of four electron pairs (steric number = 4). VSEPR theory therefore predicts a tetrahedral arrangement of electron pairs. Since all of the electron pairs are bonds, the structure is expected to have tetrahedral geometry.

(d) The carbon atom has four σ bonds and no lone pairs, giving a total of four electron pairs (steric number = 4). VSEPR theory therefore predicts a tetrahedral

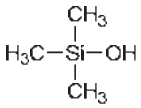
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arrangement of electron pairs. Since all of the electron pairs are bonds, the structure is expected to have tetrahedral geometry.

1.28. In the carbocation, the carbon atom has three bonds and no lone pairs. Since there are a total of three electron pairs (steric number = 3), VSEPR theory predicts trigonal planar geometry, with bond angles of 120^0. In contrast, the carbon atom of the carbanion has three bonds and one lone pair, giving a total of four electron pairs (steric number = 4). For this ion, VSEPR theory predicts a tetrahedral arrangement of electron pairs, with a lone pair positioned at one corner of the tetrahedron, giving rise to trigonal pyramidal geometry.

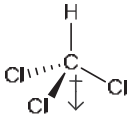
1.29. In ammonia, the nitrogen atom has three bonds and one lone pair. Therefore, VSEPR theory predicts trigonal pyramidal geometry, with bond angles of approximately 107^0. In the ammonium ion, the nitrogen atom has four bonds and no lone pairs, so VSEPR theory predicts tetrahedral geometry, with bond angles of 109.5^0. Therefore, we predict that the bond angles will increase (by approximately 2.5^0) as a result of the reaction.

1.30. The silicon atom has four σ bonds and no lone pairs, so the steric number is 4 (sp^3 hybridization), which means that the arrangement of electron pairs will be tetrahedral. With no lone pairs, the arrangement of the atoms (geometry) is the same as the electronic arrangement. It is tetrahedral.

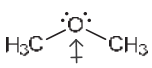


1.31.

(a) This compound has three C–Cl bonds, each of which exhibits a dipole moment. To determine if these dipole moments cancel each other, we must identify the molecular geometry. The central carbon atom has four σ bonds so we expect tetrahedral geometry. As such, the three C–Cl bonds do not lie in the same plane, and they do not completely cancel each other out. There is a net molecular dipole moment, as shown:



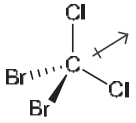
(b) The oxygen atom has two σ bonds and two lone pairs (steric number = 4), and VSEPR theory predicts bent geometry. As such, the dipole moments associated with the C–O bonds do not fully cancel each other. There is a net molecular dipole moment, as shown:



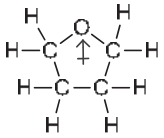
(c) The nitrogen atom has three σ bonds and one lone pair (steric number = 4), and VSEPR theory predicts trigonal pyramidal geometry (because one corner of the tetrahedron is occupied by a lone pair). As such, the dipole moments associated with the N–H bonds do not fully cancel each other. There is a net molecular dipole moment, as shown:



(d) The central carbon atom has four σ bonds (steric number = 4), and VSEPR theory predicts tetrahedral geometry. There are individual dipole moments associated with each of the C–Cl bonds and each of the C–Br bonds. If all four dipole moments had the same magnitude, then we would expect them to completely cancel each other to give no molecular dipole moment (as in the case of CCl_4). However, the dipole moments for the C–Cl bonds are larger than the dipole moments of the C–Br bonds, and as such, there is a net molecular dipole moment, shown here:

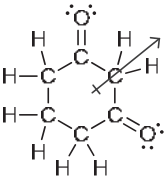


(e) The oxygen atom has two σ bonds and two lone pairs (steric number = 4), and VSEPR theory predicts bent geometry. As such, the dipole moments associated with the C–O bonds do not fully cancel each other. There is a net molecular dipole moment, as shown:



(f) There are individual dipole moments associated with each C–O bond (just as we saw in the solution to **1.31e**), but in this case, they fully cancel each other to give no net molecular dipole moment.

(g) Each C=O bond has a strong dipole moment, and they do not fully cancel each other because they are not pointing in opposite directions. As such, there will be a net molecular dipole moment, as shown here:

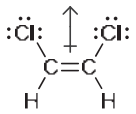


(h) Each C=O bond has a strong dipole moment, and in this case, they are pointing in opposite directions. As

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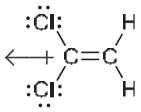
such, they fully cancel each other, giving no net molecular dipole moment.

(i) Each C–Cl bond has a dipole moment, and they do not fully cancel each other because they are not pointing in opposite directions. As such, there will be a net molecular dipole moment, as shown here:



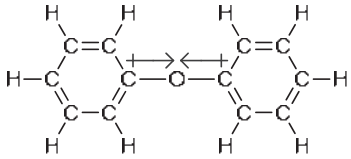
(j) Each C–Cl bond has a dipole moment, and in this case, they are pointing in opposite directions. As such, they fully cancel each other, giving no net molecular dipole moment.

(k) Each C–Cl bond has a dipole moment, and they do not fully cancel each other because they are not pointing in opposite directions. As such, there will be a net molecular dipole moment, as shown here:

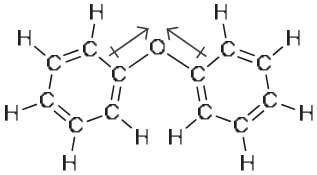


(l) Each C–Cl bond has a dipole moment, but in this case, they fully cancel each other to give no net molecular dipole moment.

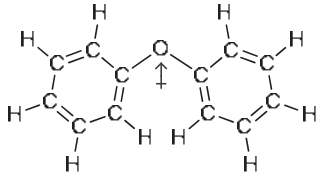
1.32. Each of the C–O bonds has an individual dipole moment, shown here.



To determine if these individual dipole moments fully cancel each other, we must determine the geometry around the oxygen atom. The oxygen atom has two σ bonds and two lone pairs, giving rise to a bent geometry. As such, the dipole moments associated with the C–O bonds do NOT fully cancel each other.

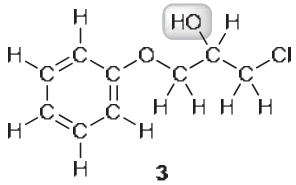


Therefore, there is a net molecular dipole moment, as shown:



1.33.
(a) The latter compound is expected to have a higher boiling point, because it is less branched.
(b) The latter compound is expected to have a higher boiling point, because it has more carbon atoms.
(c) The latter compound is expected to have a higher boiling point, because it has an OH bond, which will lead to hydrogen bonding interactions.
(d) The first compound is expected to have a higher boiling point, because it is less branched.

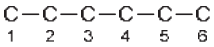
1.34. Compound **3** is expected to have a higher boiling point than compound **4**, because the former has an O-H group and the latter does not. Compound **4** does not have the ability to form hydrogen-bonding interactions with itself, so it will have a lower boiling point. When this mixture is heated, the compound that boils first (**4**) can be collected, leaving behind compound **3**.



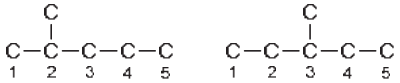
3

1.35.
(a) The carbon atoms are tetravalent, and the hydrogen atoms are all monovalent. Any atoms with more than one bond (in this case, the six carbon atoms) should be drawn in the center of the compound, with the hydrogen atoms at the periphery. There are five different ways to connect six carbon atoms, which we will organize based on the length of the longest chain.

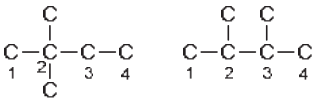
In a 6-carbon chain:



In a 5-carbon chain:

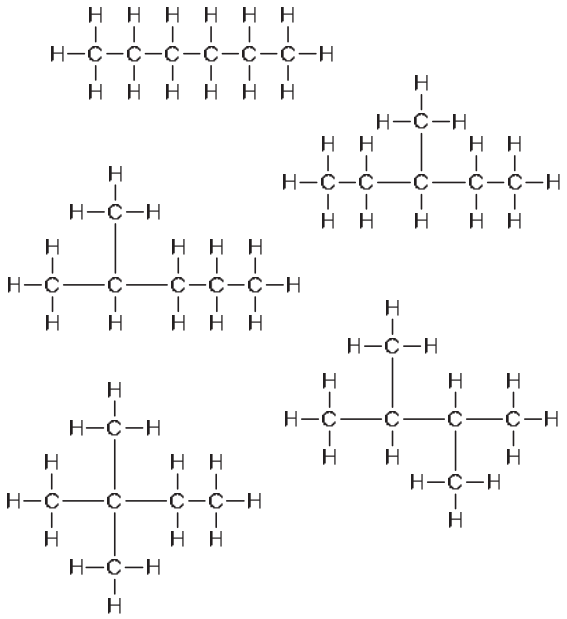


In a 4-carbon chain:

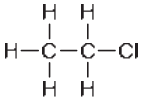


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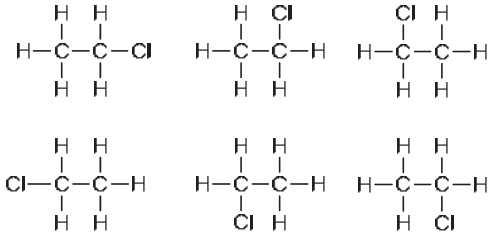
Finally, we complete all of the structures by drawing the bonds to hydrogen atoms.



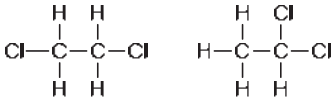
(b) The carbon atoms are tetravalent, while the chlorine atom and hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the two carbon atoms) should be drawn in the center of the compound. The chlorine atom and hydrogen atoms are then placed at the periphery, as shown.



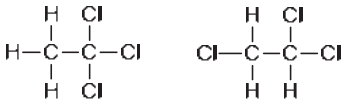
The chlorine atom can be placed in any one of the six available positions. The following six drawings all represent the same compound, in which the two carbon atoms are connected to each other, and the chlorine atom is connected to one of the carbon atoms.



(c) The carbon atoms are tetravalent, while the chlorine atoms and hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the two carbon atoms) should be drawn in the center of the compound. The chlorine atoms and hydrogen atoms are then placed at the periphery, and there are two different ways to do this. The two chlorine atoms can either be connected to the same carbon atom or to different carbon atoms, as shown.

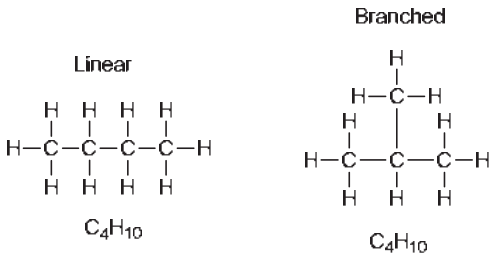


(d) The carbon atoms are tetravalent, while the chlorine atoms and hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the two carbon atoms) should be drawn in the center of the compound. The chlorine atoms and hydrogen atoms are then placed at the periphery, and there are two different ways to do this. One way is to connect all three chlorine atoms to the same carbon atom. Alternatively, we can connect two chlorine atoms to one carbon atom, and then connect the third chlorine atom to the other carbon atom, as shown here:

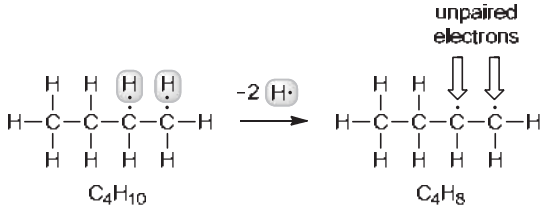


1.36.

(a) The molecular formula (C_4H_8) indicates that we must draw structures with four carbon atoms and eight hydrogen atoms. The carbon atoms are tetravalent, while the hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the four carbon atoms) should be drawn in the center of the compound, with the hydrogen atoms at the periphery. When we connect four carbon atoms, either in a linear fashion or in a branched fashion (see solution to 1.1b), we find that ten hydrogen atoms are required in order for all four carbons atom to achieve an octet (to have four bonds).

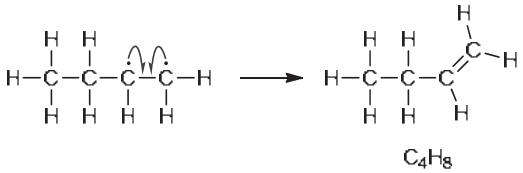


But the molecular formula (C_4H_8) indicates only eight hydrogen atoms, so we must remove two hydrogen atoms. This gives two carbon atoms that lack an octet, because each of them has an unpaired electron.

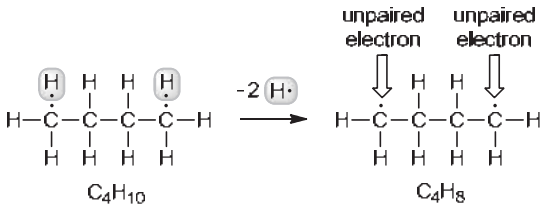


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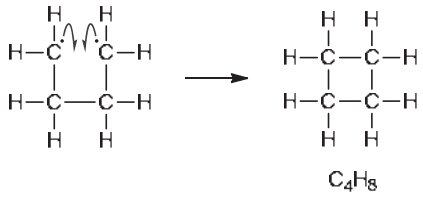
These electrons can be paired as a double bond:



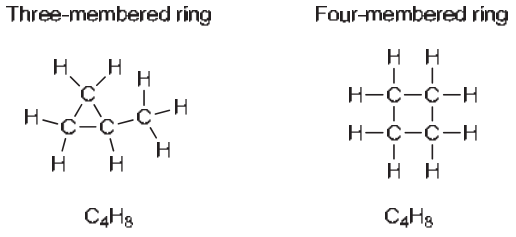
but the problem statement directs us to draw only those constitutional isomers in which all of the bonds are single bonds. So we must think of another way to pair up the unpaired electrons. It is difficult to see how this can be accomplished if the unpaired electrons are on adjacent carbon atoms. But suppose the unpaired electrons are on distant carbon atoms:



When drawn like this, it becomes apparent that we can pair the unpaired electrons by forming a C–C bond, giving a ring:

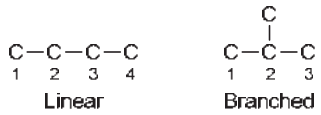


When the structure contains a ring, then eight hydrogen atoms are sufficient to provide all four carbon atoms with an octet of electrons. The ring can either be a 3-membered ring or a 4-membered ring, giving the following two constitutional isomers:

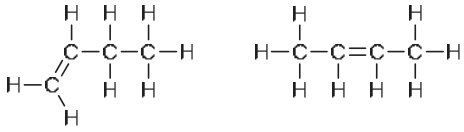


(b) See the solution to part (a) as an introduction to the following solution.

Since the unpaired electrons were paired as a double bond (rather than as a ring), we are looking for compounds that contain one double bond and do NOT have a ring. Since the structure does not contain a ring, we can imagine arranging the carbon atoms either in a linear fashion or in a branched fashion:

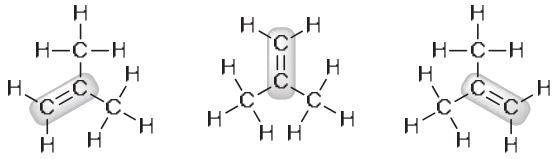


In the linear skeleton, there are two locations where we can place the double bond:

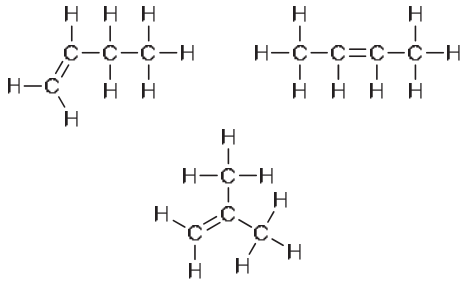


Notice that the double bond can be placed at C1-C2 or at C2-C3 (placing the double bond at C3-C4 is the same as placing it at C1-C2, because we can just assign numbers in the opposite direction).

Now let's explore the branched skeleton. There is only one location to place the double bond in a branched skeleton, because the following three drawings represent the same compound:



In summary, there are three constitutional isomers of C_4H_8 that contain a double bond:



1.37.

(a) According to Table 1.1, the difference in electronegativity between Br and H is 2.8 – 2.1 = 0.7, so an H–Br bond is expected to be polar covalent. Since bromine is more electronegative than hydrogen, the Br will be electron rich (δ–), and the H will be electron-poor (δ+), as shown below:



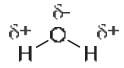
(b) According to Table 1.1, the difference in electronegativity between Cl and H is 3.0 – 2.1 = 0.9, so an H–Cl bond is expected to be polar covalent. Since chlorine is more electronegative than hydrogen, the Cl

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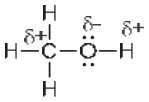
will be electron rich (δ–), and the H will be electron-poor (δ+), as shown below:



(c) According to Table 1.1, the difference in electronegativity between O and H is 3.5 – 2.1 = 1.4, so an O–H bond is expected to be polar covalent. Oxygen is more electronegative than hydrogen, so for each O–H bond, the O will be electron rich (δ–) and the H will be electron-poor (δ+), as shown below:



(d) Oxygen (3.5) is more electronegative than carbon (2.5) or hydrogen (2.1), and a C–O or H–O bond is polar covalent. For each C–O or H–O bond, the O will be electron rich (δ–), and the C or H will be electron-poor (δ+), as shown below:



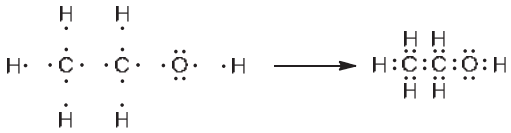
1.38.

(a) The difference in electronegativity between Na (0.9) and Br (2.8) is greater than the difference in electronegativity between H (2.1) and Br (2.8). Therefore, NaBr is expected to have more ionic character than HBr.

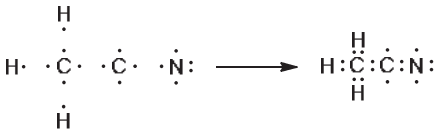
(b) The difference in electronegativity between F (4.0) and Cl (3.0) is greater than the difference in electronegativity between Br (2.8) and Cl (3.0). Therefore, FCl is expected to have more ionic character than BrCl.

1.39.

(a) Each carbon atom has four valence electrons, the oxygen atom has six valence electrons, and each hydrogen atom has one valence electron. In this case, the information provided in the problem statement (CH_3CH_2OH) indicates how the atoms are connected to each other:



(b) Each carbon atom has four valence electrons, the nitrogen atom has five valence electrons, and each hydrogen atom has one valence electron. In this case, the information provided in the problem statement (CH_3CN) indicates how the atoms are connected to each other:



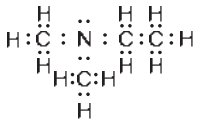
The unpaired electrons are then paired up to give a triple bond. In this way, each of the atoms achieves an octet.



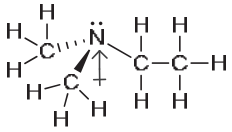
1.40. Each of the carbon atoms has four valence electrons; the nitrogen atom has five valence electrons; and each of the hydrogen atoms has one valence electron. We begin by connecting the atoms that have more than one bond (in this case, the four carbon atoms and the nitrogen atom). The problem statement indicates how we should connect them:



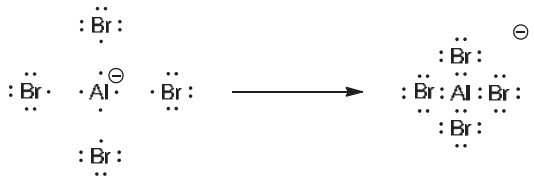
Then, we connect all of the hydrogen atoms, as shown.



The nitrogen atom has three σ bonds and one lone pair, so the steric number is 4, which means that the arrangement of electron pairs is expected to be tetrahedral. One corner of the tetrahedron is occupied by a lone pair, so the geometry of the nitrogen atom (the arrangement of atoms around that nitrogen atom) is trigonal pyramidal. As such, the individual dipole moments associated with the C–N bonds do not fully cancel each other. There is a net molecular dipole moment, as shown:

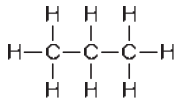


1.41. Bromine is in group 7A of the periodic table, so each bromine atom has seven valence electrons. Aluminum is in group 3A of the periodic table, so aluminum is supposed to have three valence electrons, but the structure bears a negative charge, which means that there is one extra electron. That is, the aluminum atom has four valence electrons, rather than three, which is why it has a formal negative charge. This gives the following Lewis structure:



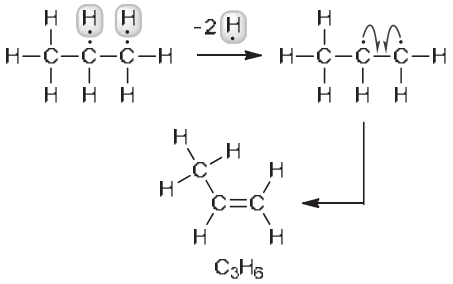
The aluminum atom has four bonds and no lone pairs, so the steric number is 4, which means that this aluminum atom will have tetrahedral geometry.

1.42. The molecular formula of cyclopropane is C_3H_6, so we are looking for a different compound that has the same molecular formula, C_3H_6. That is, we need to find another way to connect the carbon atoms, other than in a ring (there is only one way to connect three carbon atoms in a ring, so we must be looking for something other than a ring). If we connect the three carbon atoms in a linear fashion and then complete the drawing by placing hydrogen atoms at the periphery, we notice that the molecular formula (C_3H_8) is not correct:



C_3H_8

We are looking for a structure with the molecular formula C_3H_6. If we remove two hydrogen atoms from our drawing, we are left with two unpaired electrons, indicating that we should consider drawing a double bond:

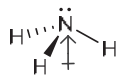


C_3H_6

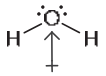
The structure of this compound (called propylene) is different from the structure of cyclopropane, but both compounds share the same molecular formula, so they are constitutional isomers.

1.43.
(a) C–H bonds are considered to be covalent, although they do have a very small dipole moment, because there is a small difference in electronegativity between carbon (2.5) and hydrogen (2.1). Despite the very small dipole moments associated with the C–H bonds, the compound has no net dipole moment. The carbon atom has tetrahedral geometry (because it has four σ bonds), so the small effects from each C-H bond completely cancel each other.

(b) The nitrogen atom has trigonal pyramidal geometry. As such, the dipole moments associated with the N–H bonds do not fully cancel each other. There is a net molecular dipole moment, as shown:



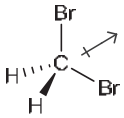
(c) The oxygen atom has two σ bonds and two lone pairs (steric number = 4), and VSEPR predicts bent geometry. As such, the dipole moments associated with the O–H bonds do not cancel each other. There is a net molecular dipole moment, as shown:



(d) The central carbon atom of carbon dioxide (CO_2) has two σ bonds and no lone pairs, so it is *sp* hybridized and is expected to have linear geometry. Each C=O bond has a strong dipole moment, but in this case, they are pointing in opposite directions. As such, they fully cancel each other, giving no net molecular dipole moment.

(e) Carbon tetrachloride (CCl_4) has four C–Cl bonds, each of which exhibits a dipole moment. However, the central carbon atom has four σ bonds so it is expected to have tetrahedral geometry. As such, the four dipole moments completely cancel each other out, and there is no net molecular dipole moment.

(f) This compound has two C–Br bonds, each of which exhibits a dipole moment. To determine if these dipole moments cancel each other, we must identify the molecular geometry. The central carbon atom has four σ bonds so it is expected to have tetrahedral geometry. As such, the C–Br bonds do not completely cancel each other out. There is a net molecular dipole moment, as shown:



1.44.
(a) As indicated in Figure 1.10, oxygen has two *1s* electrons, two *2s* electrons, and four *2p* electrons.
(b) As indicated in Figure 1.10, fluorine has two *1s* electrons, two *2s* electrons, and five *2p* electrons.
(c) As indicated in Figure 1.10, carbon has two *1s* electrons, two *2s* electrons, and two *2p* electrons.
(d) As seen in SkillBuilder 1.6, the electron configuration of a nitrogen atom is $1s^2 2s^2 2p^3$
(e) This is the electron configuration of chlorine.

1.45.
(a) The difference in electronegativity between sodium (0.9) and bromine (2.8) is 2.8 – 0.9 = 1.9. Since this difference is greater than 1.7, the bond is classified as ionic.

(b) The difference in electronegativity between sodium (0.9) and oxygen (3.5) is 3.5 – 0.9 = 2.6. Since this difference is greater than 1.7, the Na–O bond is classified as ionic. In contrast, the O–H bond is polar covalent, because the difference in electronegativity

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between oxygen (3.5) and hydrogen (2.1) is less than 1.7 but more than 0.5.

(c) Each C–H bond is considered to be covalent, because the difference in electronegativity between carbon (2.5) and hydrogen (2.1) is less than 0.5.
The C–O bond is polar covalent, because the difference in electronegativity between oxygen (3.5) and carbon (2.5) is less than 1.7 but more than 0.5. The Na–O bond is classified as ionic, because the difference in electronegativity between oxygen (3.5) and sodium (0.9) is greater than 1.7.

(d) Each C–H bond is considered to be covalent, because the difference in electronegativity between carbon (2.5) and hydrogen (2.1) is less than 0.5.
The C–O bond is polar covalent, because the difference in electronegativity between oxygen (3.5) and carbon (2.5) is less than 1.7 but more than 0.5. The O–H bond is polar covalent, because the difference in electronegativity between oxygen (3.5) and hydrogen (2.1) is less than 1.7 but more than 0.5.

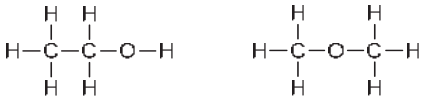
(e) Each C–H bond is considered to be covalent, because the difference in electronegativity between carbon (2.5) and hydrogen (2.1) is less than 0.5.
The C=O bond is polar covalent, because the difference in electronegativity between oxygen (3.5) and carbon (2.5) is less than 1.7 but more than 0.5.



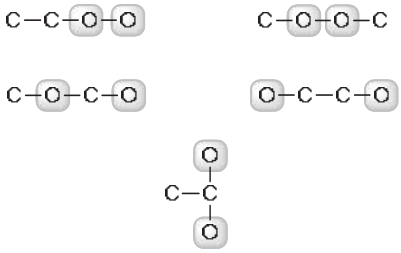
1.46.
(a) Begin by determining the valency of each atom in the compound. The carbon atoms are tetravalent, the oxygen atom is divalent, and the hydrogen atoms are all monovalent. Any atoms with more than one bond (in this case, the two carbon atoms and the oxygen atom) should be drawn in the center of the compound, with the hydrogen atoms at the periphery. There are two different ways to connect two carbon atoms and an oxygen atom, shown here:



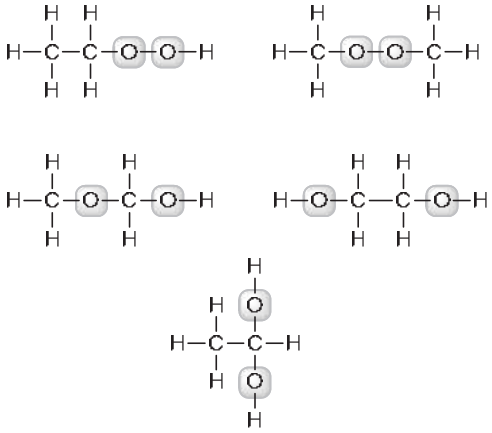
We then complete both structures by drawing the remaining bonds to hydrogen atoms:



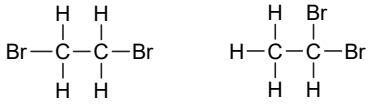
(b) Begin by determining the valency of each atom in the compound. The carbon atoms are tetravalent, the oxygen atoms are divalent, and the hydrogen atoms are all monovalent. Any atoms with more than one bond (in this case, the two carbon atoms and the two oxygen atoms) should be drawn in the center of the compound, with the hydrogen atoms at the periphery. There are several different ways to connect two carbon atoms and two oxygen atoms (highlighted, for clarity of comparison), shown here:



We then complete all of these structures by drawing the remaining bonds to hydrogen atoms:

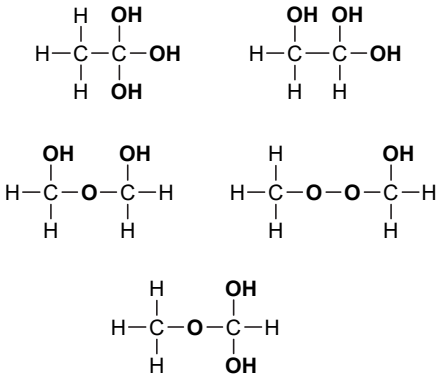


(c) The carbon atoms are tetravalent, while the bromine atoms and hydrogen atoms are all monovalent. The atoms with more than one bond (in this case, the two carbon atoms) should be drawn in the center of the compound. The bromine atoms and hydrogen atoms are then placed at the periphery, and there are two different ways to do this. The two bromine atoms can either be connected to the same carbon atom or to different carbon atoms, as shown.



1.47. Begin by determining the valency of each atom in the compound. The carbon atoms are tetravalent, the oxygen atoms are divalent, and the hydrogen atoms are all monovalent. Any atoms with more than one bond (in this case, the two carbon atoms and the three oxygen atoms) should be drawn in the center of the compound, with the hydrogen atoms at the periphery. There are many different ways to connect two carbon atoms and three oxygen atoms (see the solution to Problem 1.46b for comparison). Five such ways are shown, although there are certainly others:

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1.48.

(a) Oxygen is more electronegative than carbon, and the withdrawal of electron density toward oxygen can be indicated with the following arrow:



(b) Carbon is more electronegative than magnesium, and the withdrawal of electron density toward carbon can be indicated with the following arrow:



(c) Nitrogen is more electronegative than carbon, and the withdrawal of electron density toward nitrogen can be indicated with the following arrow:



(d) Carbon is more electronegative than lithium, and the withdrawal of electron density toward carbon can be indicated with the following arrow:



(e) Chlorine is more electronegative than carbon, and the withdrawal of electron density toward chlorine can be indicated with the following arrow:



(f) Carbon is more electronegative than hydrogen, and the withdrawal of electron density toward carbon can be indicated with the following arrow:



(g) Oxygen is more electronegative than hydrogen, and the withdrawal of electron density toward oxygen can be indicated with the following arrow:



(h) Nitrogen is more electronegative than hydrogen, and the withdrawal of electron density toward nitrogen can be indicated with the following arrow:



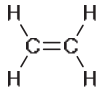
1.49.

(a) The oxygen atom has two σ bonds and two lone pairs (steric number = 4), and VSEPR theory predicts bent geometry. The C-O-H bond angle is expected to be approximately 105º, and all other bonds angles are expected to be 109.5º (because each carbon atom has four σ bonds and tetrahedral geometry).

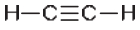
(b) The central carbon atom has three σ bonds and no lone pairs (steric number = 3), and VSEPR theory predicts trigonal planar geometry. As such, all bond angles are approximately 120º.



(c) Each of the carbon atoms has three σ bonds and no lone pairs (steric number = 3), and VSEPR theory predicts trigonal planar geometry. As such, all bond angles are approximately 120º.



(d) Each of the carbon atoms has two σ bonds and no lone pairs (steric number = 2), and VSEPR theory predicts linear geometry. As such, all bond angles are approximately 180º.

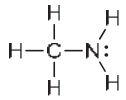


(e) The oxygen atom has two σ bonds and two lone pairs (steric number = 4), and VSEPR theory predicts bent geometry. Therefore, the C-O-C bond angle is expected to be around 105º. The remaining bond angles are all expected to be approximately 109.5º (because each carbon atom has four σ bonds and tetrahedral geometry).

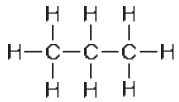
(f) The nitrogen atom has three σ bonds and one lone pair (steric number = 4), and VSEPR theory predicts trigonal pyramidal geometry, with bond angles of 107º. The carbon atom is also tetrahedral (because it has four

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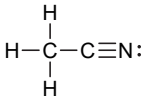
σ bonds), although the bond angles around the carbon atom are expected to be approximately 109.5º.



(g) Each of the carbon atoms has four σ bonds (steric number = 4), so each of these carbon atoms has tetrahedral geometry. Therefore, all bond angles are expected to be approximately 109.5º.



(h) The structure of acetonitrile (CH_3CN) is shown below (see the solution to Problem **1.39b**).



One of the carbon atoms has four σ bonds (steric number = 4), and is expected to have tetrahedral geometry. The other carbon atom (connected to nitrogen) has two σ bonds and no lone pairs (steric number = 2), so we expect linear geometry.
As such, the C–C≡N bond angle is 180º, and all other bond angles are approximately 109.5º.

1.50.
(a) The nitrogen atom has three σ bonds and one lone pair (steric number = 4). It is sp^3 hybridized (electronically tetrahedral), with trigonal pyramidal geometry (because one corner of the tetrahedron is occupied by a lone pair).

(b) The boron atom has three σ bonds and no lone pairs (steric number = 3). It is sp^2 hybridized, with trigonal planar geometry.

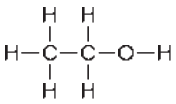
(c) This carbon atom has three σ bonds and no lone pairs (steric number = 3). It is sp^2 hybridized, with trigonal planar geometry.

(d) This carbon atom has three σ bonds and one lone pair (steric number = 4). It is sp^3 hybridized (electronically tetrahedral), with trigonal pyramidal geometry (because one corner of the tetrahedron is occupied by a lone pair).

1.51. The double bond represents one σ bond and one π bond, while the triple bond represents one σ bond and two π bonds. All single bonds are σ bonds. Therefore, this compound has sixteen σ bonds and three π bonds.

1.52.
(a) The latter compound is expected to have a higher boiling point, because it has an O–H bond, which will lead to hydrogen bonding interactions.
(b) The latter compound is expected to have a higher boiling point, because it has more carbon atoms, and thus more opportunity for London interactions.
(c) Both compounds have the same number of carbon atoms, but the first compound has a C=O bond, which has a strong dipole moment. The first compound is therefore expected to exhibit strong dipole-dipole interactions and to have a higher boiling point than the second compound.

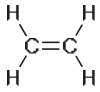
1.53.
(a) This compound possesses an O–H bond, so it is expected to exhibit hydrogen bonding interactions.



(b) This compound lacks a hydrogen atom that is connected to an electronegative element. Therefore, this compound cannot serve as a hydrogen bond donor (although the lone pairs can serve as hydrogen bond acceptors). In the absence of another hydrogen bond donor, we do not expect there to be any hydrogen bonding interactions.

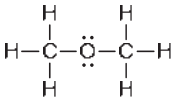


(c) This compound lacks a hydrogen atom that is connected to an electronegative element. Therefore, this compound will not exhibit hydrogen bonding interactions.



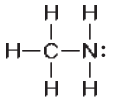
(d) This compound lacks a hydrogen atom that is connected to an electronegative element. Therefore, this compound will not exhibit hydrogen bonding interactions.

(e) This compound lacks a hydrogen atom that is connected to an electronegative element. Therefore, this compound cannot serve as a hydrogen bond donor (although lone pairs can serve as hydrogen bond acceptors). In the absence of another hydrogen bond donor, we do not expect there to be any hydrogen bonding interactions.

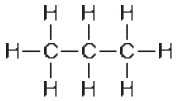


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(f) This compound possesses an N–H bond, so it is expected to exhibit hydrogen bonding interactions.



(g) This compound lacks a hydrogen atom that is connected to an electronegative element. Therefore, this compound will not exhibit hydrogen bonding interactions.



(h) This compound possesses N–H bonds, so it is expected to exhibit hydrogen bonding interactions.



1.54.

(a) Boron is in group 3A of the periodic table, and therefore has three valence electrons. It can use each of its valence electrons to form a bond, so we expect the molecular formula to be BH_3.

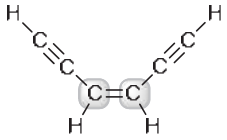
(b) Carbon is in group 4A of the periodic table, and therefore has four valence electrons. It can use each of its valence electrons to form a bond, so we expect the molecular formula to be CH_4.

(c) Nitrogen is in group 5A of the periodic table, and therefore has five valence electrons. But it cannot form five bonds, because it only has four orbitals with which to form bonds. One of those orbitals must be occupied by a lone pair (two electrons), and each of the remaining three electrons is available to form a bond. Nitrogen is therefore trivalent, and we expect the molecular formula to be NH_3.

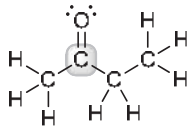
(d) Carbon is in group 4A of the periodic table, and therefore has four valence electrons. It can use each of its valence electrons to form a bond, and indeed, we expect the carbon atom to have four bonds. Two of the bonds are with hydrogen atoms, so the other two bonds must be with chlorine atoms. The molecular formula is CH_2Cl_2.

1.55.

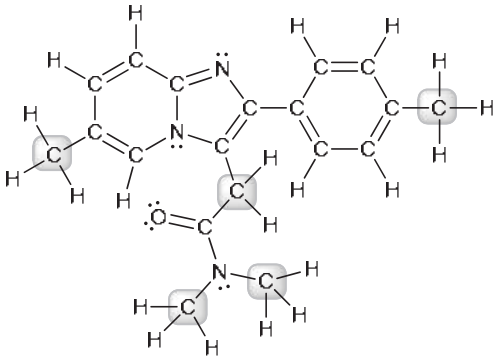
(a) Each of the highlighted carbon atoms has three σ bonds and no lone pairs (steric number = 3). Each of these carbon atoms is sp^2 hybridized, with trigonal planar geometry. Each of the other four carbon atoms has two σ bonds and no lone pairs (steric number = 2). Those four carbon atoms are all *sp* hybridized, with linear geometry.



(b) The highlighted carbon atom has three σ bonds and no lone pairs (steric number = 3). This carbon atom is sp^2 hybridized, with trigonal planar geometry. Each of the other three carbon atoms has four σ bonds (steric number = 4). Those three carbon atoms are all sp^3 hybridized, with tetrahedral geometry.



1.56. Each of the highlighted carbon atoms has four σ bonds (steric number = 4), and is sp^3 hybridized, with tetrahedral geometry. Each of the other fourteen carbon atoms in this structure has three σ bonds and no lone pairs (steric number = 3). Each of these fourteen carbon atoms is sp^2 hybridized, with trigonal planar geometry.



1.57.

(a) Oxygen is the most electronegative atom in this compound. See Table 1.1 for electronegativity values.

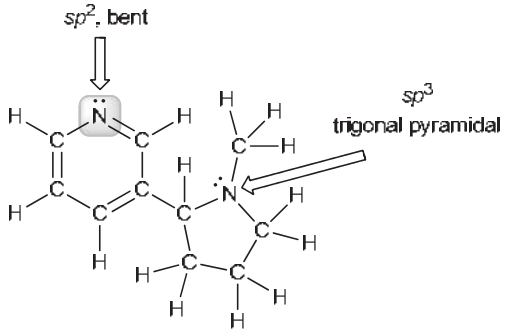
(b) Fluorine is the most electronegative atom. See Table 1.1 for electronegativity values.

(c) Carbon is the most electronegative atom in this compound. See Table 1.1 for electronegativity values.

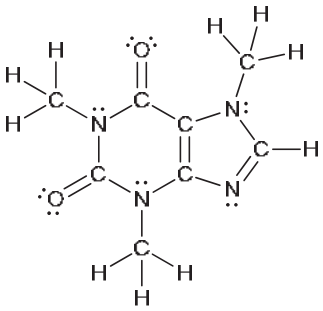
1.58. The highlighted nitrogen atom has two σ bonds and one lone pair (steric number = 3). This nitrogen atom is sp^2 hybridized. It is electronically trigonal planar, but one of the sp^2 hybridized orbitals is occupied by a lone pair, so the geometry (arrangement of atoms) is bent. The other nitrogen atom (not highlighted) has three σ bonds and a lone pair (steric number = 4). That nitrogen atom is sp^3 hybridized and electronically

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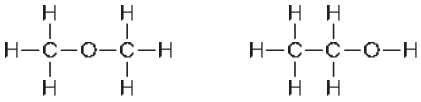
tetrahedral. One corner of the tetrahedron is occupied by a lone pair, so the geometry (arrangement of atoms) is trigonal pyramidal.



1.59. Each of the nitrogen atoms in this structure achieves an octet with three bonds and one lone pair, while each oxygen atom in this structure achieves an octet with two bonds and two lone pairs, as shown:



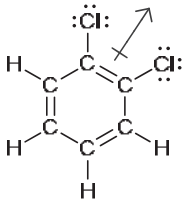
1.60. In the solution to Problem 1.46a, we saw that the following two compounds have the molecular formula C_2H_6O.



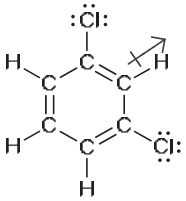
The second compound will have a higher boiling point because it possesses an OH group which can form hydrogen bonding interactions.

1.61.

(a) Each C–Cl bond has a dipole moment, and the two dipole moments do not fully cancel each other because they are not pointing in opposite directions. As such, there will be a net molecular dipole moment, as shown here:

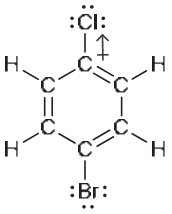


(b) Each C–Cl bond has a dipole moment, and the two dipole moments do not fully cancel each other because they are not pointing in opposite directions. As such, there will be a net molecular dipole moment, as shown here:



(c) Each C–Cl bond has a dipole moment, and in this case, the two dipole moments are pointing in opposite directions. As such, they fully cancel each other, giving no net molecular dipole moment.

(d) The C–Cl bond has a dipole moment, and the C–Br bond also has a dipole moment. These two dipole moments are in opposite directions, but they do not have the same magnitude. The C–Cl bond has a larger dipole moment than the C–Br bond, because chlorine is more electronegative than bromine. Therefore, there will be a net molecular dipole moment, as shown here:



1.62. The third chlorine atom in chloroform partially cancels the effects of the other two chlorine atoms, thereby reducing the molecular dipole moment relative to methylene chloride.

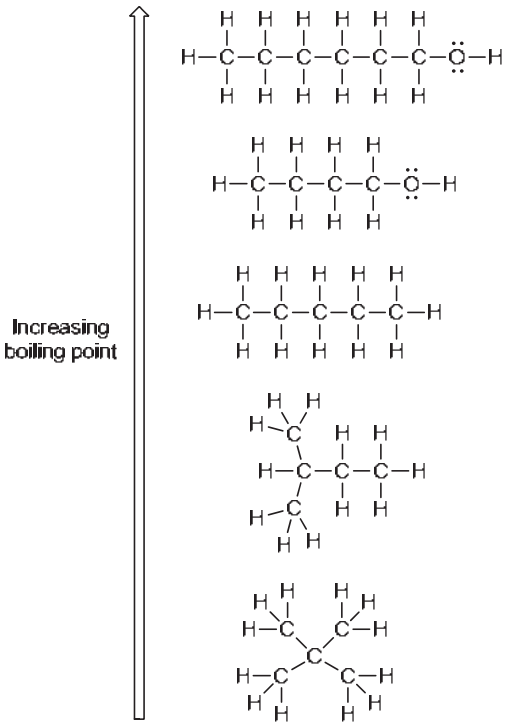
1.63. $CHCl_3$ is expected to have a larger molecular dipole moment than $CBrCl_3$, because the bromine atom in the latter compound serves to nearly cancel out the effects of the other three chlorine atoms (as is the case for CCl_4).

1.64. The carbon atom of O=C=O has two σ bonds and no lone pairs (steric number = 2) and VSEPR theory predicts linear geometry. As a result, the individual dipole moments of each C=O bond cancel each other completely to give no overall molecular dipole moment. In contrast, the sulfur atom in SO_2 has a steric number of three (because it also has a lone pair, in addition to the two S=O bonds), which means that it has bent geometry. As a result, the individual dipole moments of each S=O bond do NOT cancel each other completely, and the molecule does have a molecular dipole moment.

1.65. Two compounds possess OH groups, and these compounds will have the highest boiling points. Among these two compounds, the one with more carbon atoms (six) will be higher boiling than the one with fewer

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carbon atoms (four). The remaining three compounds all have five carbon atoms and lack an OH group. The difference between these three compounds is the extent of branching. Among these three compounds, the compound with the greatest extent of branching has the lowest boiling point, and the one with the least branching has the highest boiling point.



1.66.

(a) Compounds A and B share the same molecular formula (C_4H_9N) but differ in their constitution (connectivity of atoms), and they are therefore constitutional isomers.

(b) The nitrogen atom in compound B has three σ bonds and one lone pair (steric number = 4). It is sp^3 hybridized (electronically tetrahedral), with trigonal pyramidal geometry (because one corner of the tetrahedron is occupied by a lone pair).

(c) A double bond represents one σ bond and one π bond, while a triple bond represents one σ bond and two π bonds. A single bond represents a σ bond. With this in mind, compound B has 14 σ bonds, as compared with compounds A and C, which have 13 and 11 σ bonds, respectively.

(d) As explained in the solution to part (c), compound C has the fewest σ bonds.

(e) A double bond represents one σ bond and one π bond, while a triple bond represents one σ bond and two π bonds. As such, compound C exhibits two π bonds.

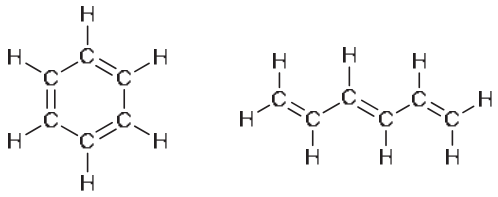
(f) Compound A has a C=N bond, in which the carbon atom has three σ bonds and no lone pairs (steric number = 3). It is sp^2 hybridized.

(g) Each of the carbon atoms in compound B is sp^3 hybridized with four σ bonds (steric number = 4). Similarly, the nitrogen atom in compound B has three σ bonds and one lone pair (steric number = 4). This nitrogen atom is also sp^3 hybridized.

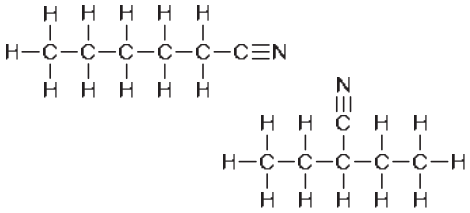
(h) Compound A has an N–H bond, and is therefore expected to form hydrogen bonding interactions. Compounds B and C do not contain an N–H bond, so compound A is expected to have the highest boiling point.

1.67.

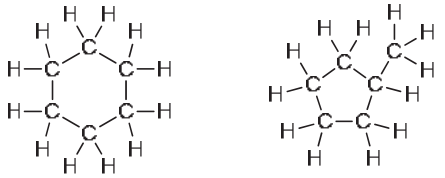
(a) In each of the following two compounds, all of the carbon atoms are sp^2 hybridized (each carbon atom has three σ bonds and one π bond). There are certainly many other possible compounds for which all of the carbon atoms are sp^2 hybridized.



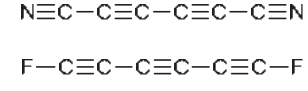
(b) In each of the following two compounds, all of the carbon atoms are sp^3 hybridized (because each carbon atom has four σ bonds) with the exception of the carbon atom connected to the nitrogen atom. That carbon atom has two σ bonds and is therefore *sp* hybridized. There are certainly many other acceptable answers.



(c) In each of the following two compounds, there is a ring, and all of the carbon atoms are sp^3 hybridized (because each carbon atom has four σ bonds). There are certainly many other acceptable answers.

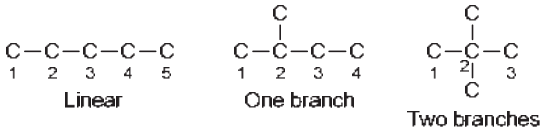


(d) In each of the following two compounds, all of the carbon atoms are *sp* hybridized (because each carbon atom has two σ bonds). There are certainly many other acceptable answers.



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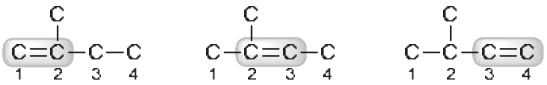
1.68. In the solution to Problem **1.1c**, we saw that there are three ways to arrange five carbon atoms:



For each of these three skeletons, we must consider each possible location where a double bond can be placed. The skeleton with two branches cannot support a double bond, because the central carbon atom already has four bonds to carbon atoms, and it cannot accommodate a fifth bond (it cannot form another bond with any one of the four carbon atoms to which it is already connected).
So we only have to consider the other two skeletons above (the linear skeleton and the skeleton with one branch). In the linear skeleton, the double bond can be placed at C1-C2 or at C2-C3.



Placing the double bond at C3-C4 is the same as placing the double bond at C2-C3. Similarly, placing the double bond at C4-C5 is the same as placing the double bond at C1-C2.
For the skeleton with one branch, there are three different locations where the double bond can be placed, shown here:

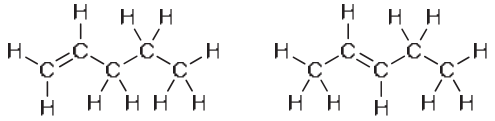


Be careful, the following two locations are the same:

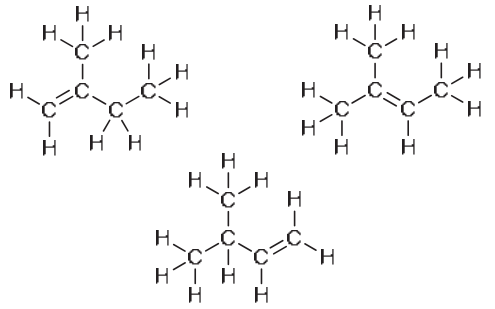


Finally, we complete all five possible structures by drawing the remaining bonds to the hydrogen atoms (see next page):

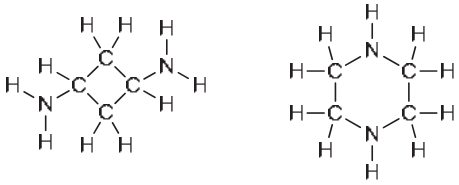
Linear skeleton



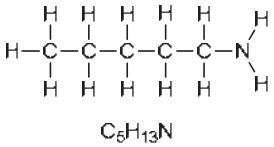
Branched skeleton



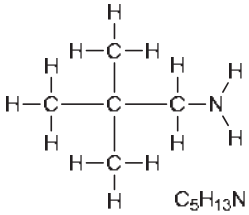
1.69. In each of the following two compounds, the molecular formula is $C_4H_{10}N_2$, there is a ring (as suggested in the hint given in the problem statement), there are no π bonds, there is no net dipole moment, and there is an N-H bond, which enables hydrogen bonding interactions.



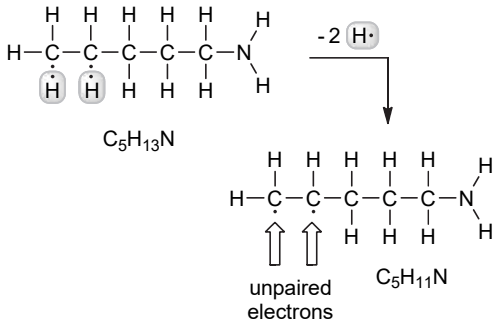
1.70. If we try to draw a linear skeleton with five carbon atoms and one nitrogen atom, we find that the number of hydrogen atoms is not correct (there are thirteen, rather than eleven):



This will be the case even if try to draw a branched skeleton:



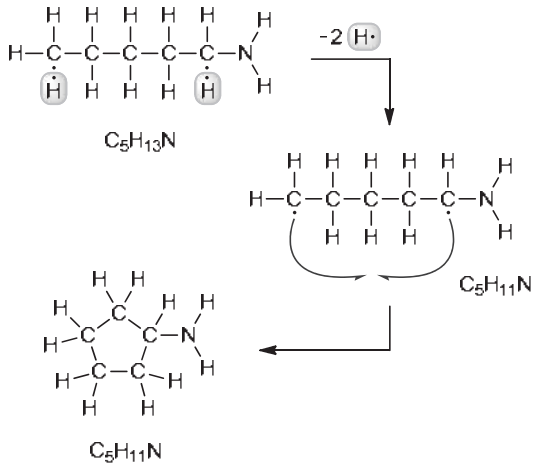
In fact, regardless of how the skeleton is branched, it will still have 13 hydrogen atoms. But we need to draw a structure with only 11 hydrogen atoms ($C_5H_{11}N$). So we must remove two hydrogen atoms, which gives two unpaired electrons:



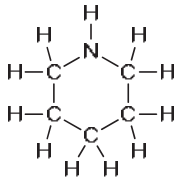
This indicates that we should consider pairing these electrons as a double bond. However, the problem statement specifically indicates that the structure cannot contain a double bond. So, we must find another way to pair the unpaired electrons. We encountered a similar issue in the solution to problem **1.36a**, in which we

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paired the electrons by forming a ring. We can do something similar here:



Now we have the correct number of hydrogen atoms (eleven), which means that our structure must indeed contain a ring. But this particular cyclic structure (cyclic = containing a ring) does not meet all of the criteria described in the problem statement. Specifically, each carbon atom must be connected to exactly two hydrogen atoms. This is not the case in the structure above. This issue can be remedied in the following structure, which has a ring, and each of the carbon atoms is connected to exactly two hydrogen atoms, as required by the problem statement.



1.71.

(a) In compound **A**, the nitrogen atom has two σ bonds and no lone pairs (steric number = 2). It is *sp* hybridized. The highlighted carbon atom has one σ bond and one lone pair (steric number = 2), so that carbon atom is *sp* hybridized.

(b) The highlighted carbon atom is *sp* hybridized, so the lone pair occupies an *sp* hybridized orbital.

(c) The nitrogen atom is *sp* hybridized and therefore has linear geometry. As such, the C-N-C bond angle in **A** is expected to be 180°.

(d) The nitrogen atom in **B** has two σ bonds and one lone pair (steric number = 3). It is sp^2 hybridized. The highlighted carbon atom has three σ bonds and no lone pairs (steric number = 3), and that carbon atom is sp^2 hybridized. Each of the chlorine atoms has three lone pairs and one bond (steric number = 4), and the chlorine atoms are sp^3 hybridized.

(e) The nitrogen atom is sp^2 hybridized, so the lone pair occupies an sp^2 hybridized orbital.

(f) The nitrogen atom is sp^2 hybridized so the C-N-C bond angle in **B** is expected to be approximately 120°.

1.72. By analyzing the data, we can see that C(sp^2)–Cl must be shorter than 1.79Å [compare with C(sp^3)–Cl], while C(*sp*)–I must be longer than 1.79Å [compare with C(*sp*)–Br]. Therefore, C(*sp*)–I must be longer than C(sp^2)–Cl.

1.73.

(a) In the first compound, the fluorine isotope (^{18}F) has no formal charge. Therefore, it must have three lone pairs (see Section 1.4 for a review of how formal charges are calculated). Since it has one σ bond and three lone pairs, it must have a steric number of 4, and is sp^3 hybridized. The bromine atom also has no formal charge. So, it too, like the fluorine isotope, must have three lone pairs. Once again, one σ bond and three lone pairs give a steric number of 4, so the bromine atom is sp^3 hybridized.

In the second compound, the nitrogen atom has no formal charge. Therefore, it must have one lone pair. Since the nitrogen atom has three σ bonds and one lone pair, it must have a steric number of 4, and is sp^3 hybridized.

In the product, the fluorine isotope (^{18}F) has no formal charge. Therefore, it must have three lone pairs. Since it has one σ bond and three lone pairs, it must have a steric number of 4, and is sp^3 hybridized. The nitrogen atom does have a positive formal charge. Therefore, it must have no lone pairs. Since it has four σ bonds and no lone pairs, it must have a steric number of 4, and is sp^3 hybridized. Finally, the bromine atom has a negative charge and no bonds. So it must have four lone pairs. With four lone pairs and no bonds, it will have a steric number of 4, and is expected to be sp^3 hybridized.

In summary, all of the atoms that we analyzed are sp^3 hybridized.

(b) The nitrogen atom is sp^3 hybridized. With four bonds, we expect the geometry around the nitrogen atom to be tetrahedral. So, the bond angle for each C-N-C bond is expected to be approximately 109.5°.

1.74. We must first draw the structure of HCN. To draw a Lewis structure, we begin by counting the valence electrons (H has 1, C has 4, and N has 5, for a total of 10). The structure must have 10 valence electrons (no more and no less). Carbon should have four bonds, and it can only form a single bond with the hydrogen atom, so there must be a triple bond between carbon and nitrogen:

H—C≡N:

The single bond accounts for two electrons, and the triple bonds accounts for another six electrons. The remaining two electrons must be a lone pair on nitrogen. This accounts for all 10 valence electrons, and it gives all atoms an octet.

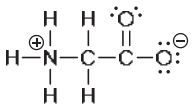
Since the carbon atom has a triple bond, it must be *sp* hybridized, with linear geometry.

1.75. The molecular formula of cyclobutane is C_4H_8. Of the four structures shown, only structure c has the same molecular formula (C_4H_8).

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1.76. Each of the structures has two carbon atoms and one oxygen atom. However, only the second structure has an OH group. This compound will have an elevated boiling point, relative to the other three structures, because of hydrogen bonding.

1.77. The first statement (a) is the correct answer, because an oxygen atom has a negative charge, and the nitrogen atom has a positive charge, as shown here:

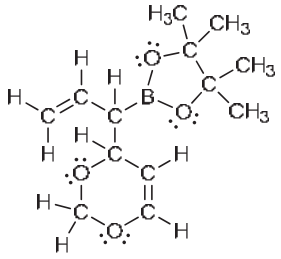


1.78.

(a) Boron is in group 3A of the periodic table and is therefore expected to be trivalent. That is, it has three valence electrons, and it uses each one of those valence electrons to form a bond, giving rise to three bonds. It does not have any electrons left over for a lone pair (as in the case of nitrogen). With three σ bonds and no lone pairs, the boron atom has a steric number of three, and is sp^2 hybridized.

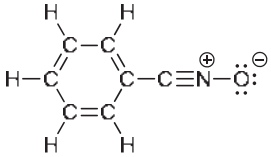
(b) Since the boron atom is sp^2 hybridized, we expect the bond angle to be approximately 120°. However, in this case, the O-B-O system is part of a five-membered ring. That is, there are five different bond angles (of which the O-B-O angle is one of them) that together must form a closed loop. That requirement could conceivably force some of the bond angles (including the O-B-O bond angle) to deviate from the predicted value. In fact, we will explore this very phenomenon, called ring strain, in Chapter 4, and we will see that five-membered rings actually possess very little ring strain compared with smaller rings.

(c) Each of the oxygen atoms has no formal charge, and must therefore have two bonds and two lone pairs. The boron atom has no lone pairs, as explained in the solution to part (a) of this problem.



1.79.

(a) If we analyze each atom (in both **1** and **2**) using the procedure outlined in Section 1.4, we find that none of the atoms in compound **1** have a formal charge, while compound **2** possesses two formal charges:



The nitrogen atom has a positive charge (it is supposed to be using five valence electrons, but it is actually using four), and the oxygen atom has a negative charge (it is supposed to be using six valence electrons, but it is actually using seven).

(b) Compound **1** possesses polar bonds, as a result of the presence of partial charges (δ+ and δ-). The associated dipole moments can form favorable interactions with the dipole moments present in the polar solvent molecules (dipole-dipole interactions). However, compound **2** has formal charges (negative on O and positive on N), so the dipole moment of the N-O bond is expected to be much more significant than the dipole moments in compound **1**. The dipole moment of the N-O bond in compound **2** is the result of full charges, rather than partial charges. As such, compound **2** is expected to experience much stronger interactions with the solvent molecules, and therefore, **2** should be more soluble than **1** in a polar solvent.

(c) In compound **1**, the carbon atom (attached to nitrogen) has three σ bonds and no lone pairs (steric number = 3). That carbon atom is sp^2 hybridized, with trigonal planar geometry. As such, the C-C-N bond angle in compound **1** is expected to be approximately 120°. However, in compound **2**, the same carbon atom has two σ bonds and no lone pairs (steric number = 2). This carbon atom is *sp* hybridized, with linear geometry. As such, the C-C-N bond angle in **2** is expected to be 180°. The conversion of **1** to **2** therefore involves an increase in the C-C-N bond angle of approximately 60°.

1.80.

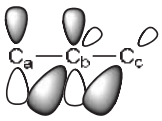
(a) C_a has three σ bonds and no lone pairs, so it has a steric number of 3, and is sp^2 hybridized. The same is true for C_c. In contrast, C_b has two σ bonds and no lone pairs, so it has a steric number of 2, and is therefore *sp* hybridized.

(b) Since C_a is sp^2 hybridized, we expect its geometry to be trigonal planar, so the bond angle should be approximately 120°.

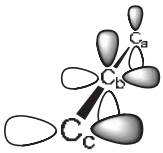
(c) Since C_b is *sp* hybridized, we expect its geometry to be linear, so the bond angle should be approximately 180°.

(d) The central carbon atom (C_b) is *sp* hybridized, so it is using two *sp* hybridized orbitals to form its two σ bonds, which will be arranged in a linear fashion. The remaining two *p* orbitals of C_b used for π bonding will be 90° apart from one another (just as we saw for the carbon atoms of a triple bond; see Figure 1.33).

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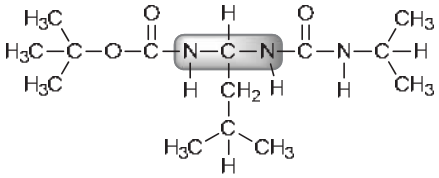


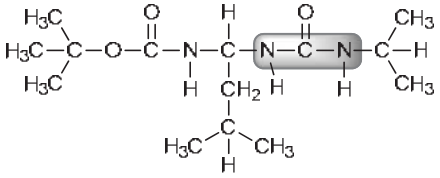
As a result, the two π systems are orthogonal (or 90°) to each other. Therefore, the *p* orbitals on C_a and C_c are orthogonal. The following is another drawing from a different perspective (looking down the axis of the linear C_a-C_b-C_c system.



1.81.

(a) The following highlighted regions represent the two different N-C-N units in the structure:

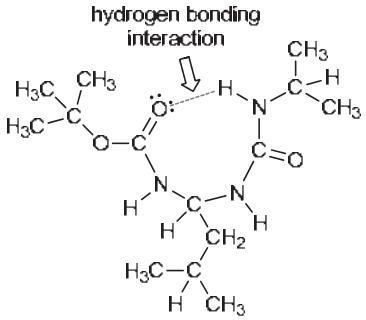




The first N-C-N unit (shown above) exhibits a central carbon atom that is sp^3 hybridized and is therefore expected to have tetrahedral geometry. Accordingly, the bond angles about that carbon atom are expected to be approximately 109.5°.

The other N-C-N unit exhibits a central carbon atom that is sp^2 hybridized and is therefore expected to have trigonal planar geometry. Accordingly, the bond angles about that carbon atom are expected to be approximately 120°.

(b) The non-covalent interaction is an intramolecular, hydrogen bonding interaction between the H (connected to the highlighted nitrogen atom) and the lone pair of the oxygen atom:



Chapter 2
Molecular Representations

Review of Concepts

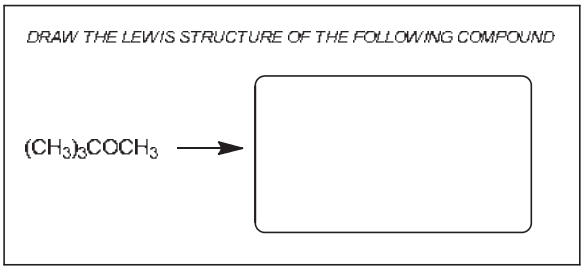
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 2. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- In **bond-line structures**, _____atoms and most _____ atoms are not drawn.
- A _____ is a characteristic group of atoms/bonds that show a predictable behavior.
- When a carbon atom bears either a positive charge or a negative charge, it will have _____, rather than four, bonds.
- In bond-line structures, a **wedge** represents a group coming _____ the page, while a **dash** represents a group _____ the page.
- _____ **arrows** are tools for drawing resonance structures.
- When drawing curved arrows for resonance structures, avoid breaking a _____ bond and never exceed _____ for second-row elements.
- The following rules can be used to identify the significance of resonance structures:
    1. The most significant resonance forms have the greatest number of filled _____.
    2. The structure with fewer _____ is more significant.
    3. Other things being equal, a structure with a negative charge on the more _____ element will be more significant. Similarly, a positive charge will be more stable on the less _____ element.
    4. Resonance forms that have equally good Lewis structures are described as _____ and contribute equally to the resonance hybrid.
- A _____ lone pair participates in resonance and is said to occupy a ____ orbital.
- A _____ lone pair does not participate in resonance.

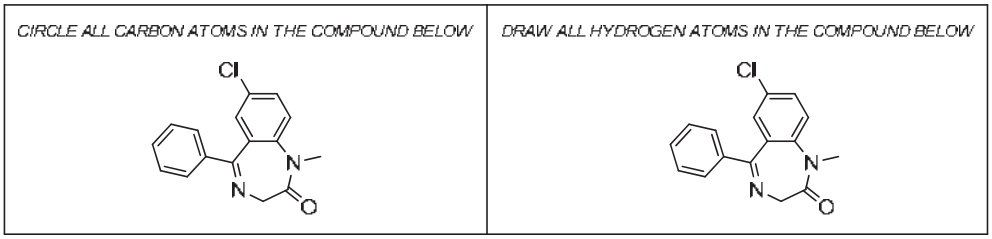
Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 2. The answers appear in the section entitled *SkillBuilder Review*.

SkillBuilder 2.1 Converting Between Different Drawing Styles

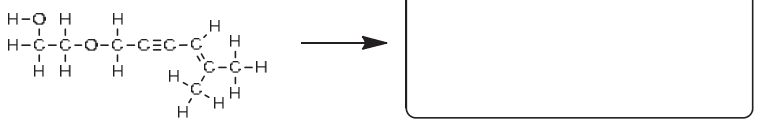


SkillBuilder 2.2 Reading Bond-Line Structures



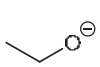
SkillBuilder 2.3 Drawing Bond-Line Structures

DRAW A BOND-LINE DRAWING OF THE FOLLOWING COMPOUND:

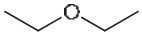


SkillBuilder 2.4 Identifying Lone Pairs on Oxygen Atoms

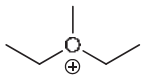
AN OXYGEN ATOM WITH A NEGATIVE CHARGE WILL HAVE ____ LONE PAIR(S)



AN OXYGEN ATOM WITH NO FORMAL CHARGE WILL HAVE ____ LONE PAIR(S)

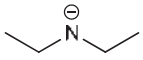


AN OXYGEN ATOM WITH A POSITIVE CHARGE WILL HAVE ____ LONE PAIR(S)

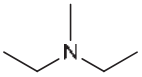


SkillBuilder 2.5 Identifying Lone Pairs on Nitrogen Atoms

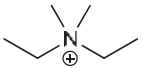
A NITROGEN ATOM WITH A NEGATIVE CHARGE WILL HAVE ____ LONE PAIR(S)



A NITROGEN ATOM WITH NO FORMAL CHARGE WILL HAVE ____ LONE PAIR(S)



A NITROGEN ATOM WITH A POSITIVE CHARGE WILL HAVE ____ LONE PAIR(S)



SkillBuilder 2.6 Identifying Valid Resonance Arrows

RULE 1: THE TAIL OF A CURVED ARROW CANNOT BE PLACED ON A _____

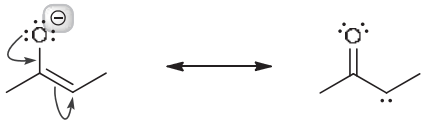


RULE 2: THE HEAD OF A CURVED ARROW CANNOT RESULT IN _____



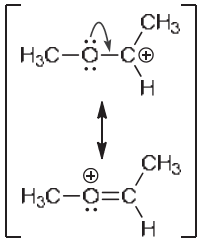
SkillBuilder 2.7 Assigning Formal Charges in Resonance Structures

INDICATE THE LOCATION OF THE NEGATIVE CHARGE IN THE SECOND RESONANCE STRUCTURE BELOW

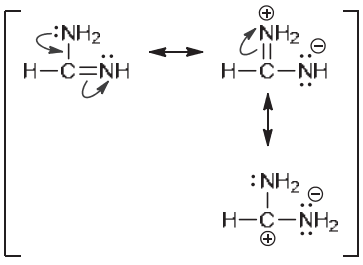


SkillBuilder 2.8 Ranking the Significance of Resonance Structures

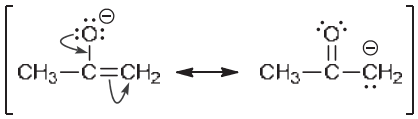
STEP 1 THE MOST SIGNIFICANT RESONANCE FORMS HAVE THE GREATEST NUMBER OF FILLED OCTETS. IDENTIFY WHICH FORM BELOW IS THE MAJOR CONTRIBUTOR.



STEP 2 THE STRUCTURE WITH FEWER FORMAL CHARGES IS MORE SIGNIFICANT. BASED ON STEPS ONE AND TWO, IDENTIFY WHICH FORM BELOW IS THE LARGEST CONTRIBUTOR, WHICH IS A MAJOR CONTRIBUTOR, AND WHICH IS A MINOR CONTRIBUTOR.



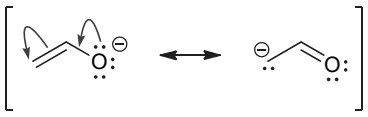
STEP 3 CONSIDER THE LOCATION OF THE FORMAL CHARGE(S), AND IDENTIFY THE MAJOR CONTRIBUTOR BELOW.



STEP 4 DETERMINE MAJOR AND MINOR CONTRIBUTORS, AND RANK RESONANCE FORMS. AS A GENERAL RULE, IF ONE OR MORE OF THE RESONANCE FORMS HAS ALL FILLED OCTETS, THEN ANY RESONANCE FORM MISSING AN OCTET WILL BE A MINOR CONTRIBUTOR.

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SkillBuilder 2.9 Drawing a Resonance Hybrid

STEPS 1 and 2 *AFTER DRAWING ALL RESONANCE STRUCTURES, IDENTIFY WHICH ONE IS MORE SIGNIFICANT.*	***STEP 3*** *REDRAW THE STRUCTURE, SHOWING PARTIAL BONDS AND PARTIAL CHARGES.*	***STEP 4*** *REVISE THE SIZE OF THE PARTIAL CHARGES TO INDICATE DISTRIBUTION OF ELECTRON DENSITY.*
		

SkillBuilder 2.10 Identifying Localized and Delocalized Lone Pairs

IDENTIFY WHETHER THE LONE PAIR ON THE NITROGEN ATOM BELOW IS DELOCALIZED	*IDENTIFY THE HYBRIDIZATION STATE OF THE NITROGEN ATOM*
	

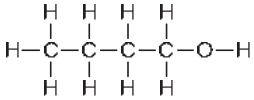
Common Mistakes to Avoid

When drawing a structure, make sure to avoid drawing a pentavalent carbon atom, or even a hexavalent or heptavalent carbon atom:

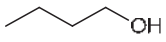


Carbon cannot have more than four bonds. Avoid drawing a carbon atom with more than four bonds, as that is one of the worst mistakes you can make as a student of organic chemistry.

Also, when drawing a structure, either draw all carbon atom labels (C) and all hydrogen atom labels (H), like this:



or don't draw any labels (except H attached to a heteroatom), like this:



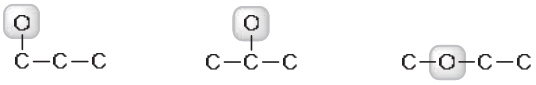
That is, if you draw all C labels, then you should really draw all H labels also. Avoid drawings in which the C labels are drawn and the H labels are not, as shown here:



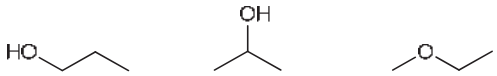
These types of drawings (where C labels are shown and H labels are not shown) should only be used when you are working on a scratch piece of paper and trying to draw constitutional isomers. For example, if you are considering all constitutional isomers with the molecular formula C_3H_8O, you might find it helpful to

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use drawings like these as a form of "short-hand" so that you can identify all of the different ways of connecting three carbon atoms and one oxygen atom:



But your final structures should either show all C and H labels, or no labels at all. The latter is the more commonly used method:



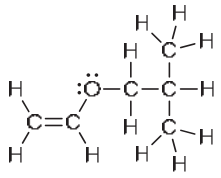
Solutions

2.1.

(a) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$CH_2{=}CHOCH_2CH(CH_3)_2$

Condensed structure

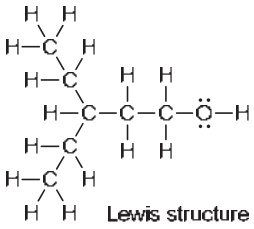


Lewis structure

(b) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$(CH_3CH_2)_2CHCH_2CH_2OH$

Condensed structure

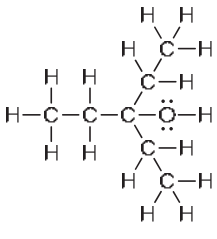


Lewis structure

(c) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$(CH_3CH_2)_3COH$

Condensed structure

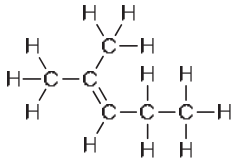


Lewis structure

(d) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$(CH_3)_2C{=}CHCH_2CH_3$

Condensed structure

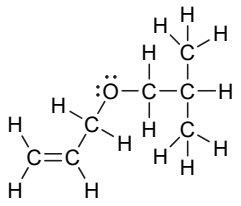


Lewis structure

(e) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$CH_2{=}CHCH_2OCH_2CH(CH_3)_2$

Condensed structure

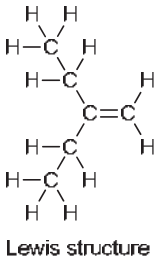


Lewis structure

(f) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$(CH_3CH_2)_2C{=}CH_2$

Condensed structure

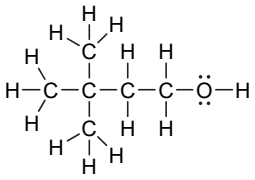


Lewis structure

(g) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis

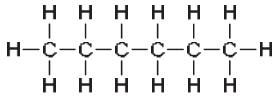
structure shows these connections more clearly, because every bond is drawn:

$(CH_3)_3CCH_2CH_2OH$
Condensed structure


Lewis structure

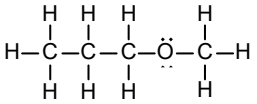
(h) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$CH_3CH_2CH_2CH_2CH_2CH_3$
Condensed structure


Lewis structure

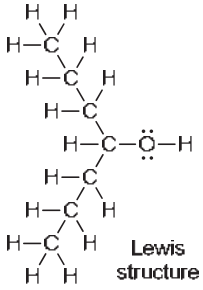
(i) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$CH_3CH_2CH_2OCH_3$
Condensed structure


Lewis structure

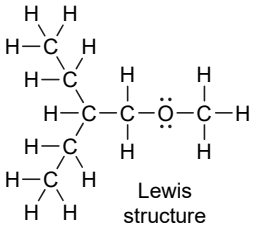
(j) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$(CH_3CH_2CH_2)_2CHOH$
Condensed structure


Lewis structure

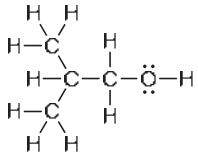
(k) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$(CH_3CH_2)_2CHCH_2OCH_3$
Condensed structure

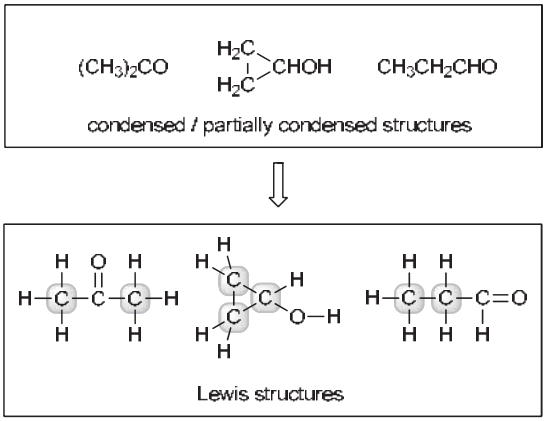

Lewis structure

(l) The condensed structure indicates the constitution (how the atoms are connected to each other). The Lewis structure shows these connections more clearly, because every bond is drawn:

$(CH_3)_2CHCH_2OH$
Condensed structure

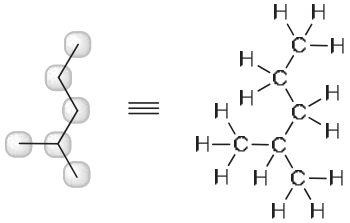

Lewis structure

2.2. Begin by drawing a Lewis structure for each isomer, so that the bonding of the carbon atoms is shown more clearly. Notice that in two of the isomers, a carbon atom is sharing a double bond with oxygen. Each of these carbon atoms is sp^2 hybridized. All of the other carbon atoms exhibit four single bonds and are sp^3 hybridized. These seven carbon atoms are highlighted, and thus the number of sp^3-hybridized carbons in the structures are two, three, and two, respectively:

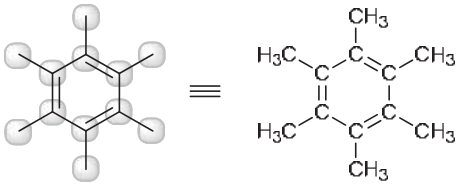


2.3.

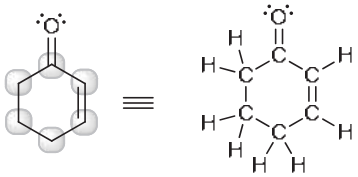
(a) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has six carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown:



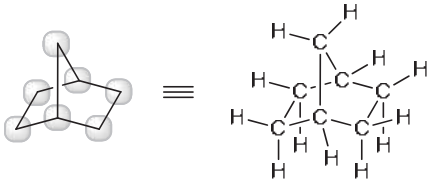
(b) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has twelve carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown:



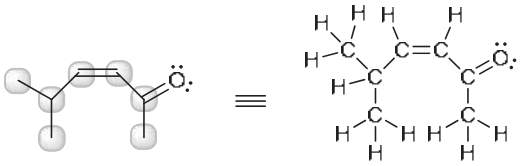
(c) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has six carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown:



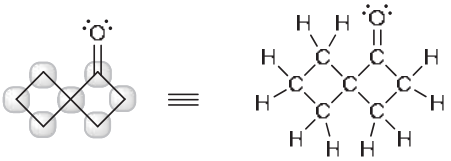
(d) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has seven carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown:



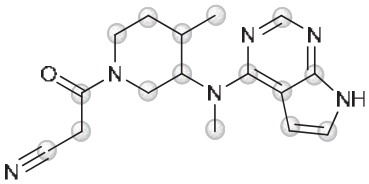
(e) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has seven carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown:



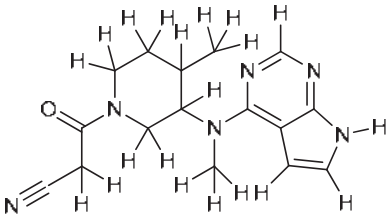
(f) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has seven carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown:



2.4. Remember that each corner and each endpoint represents a carbon atom. This compound therefore has 16 carbon atoms, highlighted below:

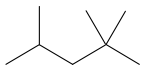


Each carbon atom should have four bonds. We therefore draw enough hydrogen atoms in order to give each carbon atom a total of four bonds. Any carbon atoms that already have four bonds will not have any hydrogen atoms:

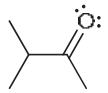


2.5. In each of the following structures, the carbon skeleton is drawn in a zig-zag format, in which carbon atoms represent each corner and endpoint. Hydrogen atoms are only drawn if they are connected to heteroatoms:

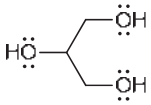
(a)



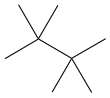
(b)



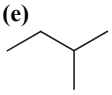
(c)



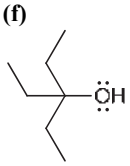
(d)



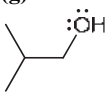
(e)



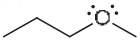
(f)



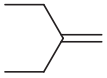
(g)



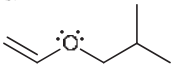
(h)



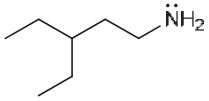
(i)



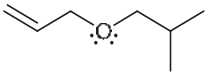
(j)



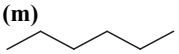
(k)



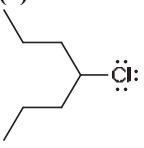
(l)



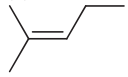
(m)



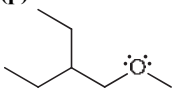
(n)



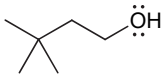
(o)



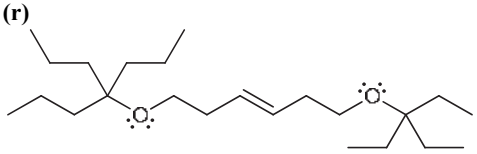
(p)



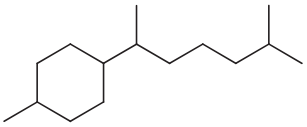
(q)



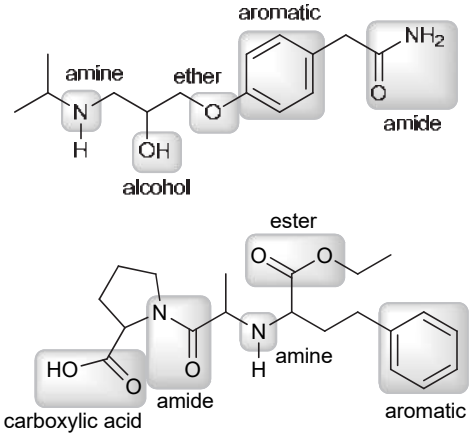
(r)



2.6. The carbon skeleton is drawn in a zig-zag format, in which carbon atoms represent each corner and endpoint.



2.7. The functional groups in the following compounds are highlighted and identified, using the terminology found in Table 2.1.

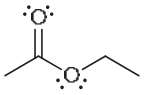


2.8.

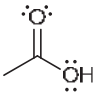
(a) In this case, the oxygen atom has two bonds and no formal charge, so it must have two lone pairs (see Table 2.2).



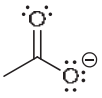
(b) In this case, each of the oxygen atoms has two bonds and no formal charge, so each oxygen atom must have two lone pairs (see Table 2.2).



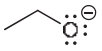
(c) In this case, each of the oxygen atoms has two bonds and no formal charge, so each oxygen atom must have two lone pairs (see Table 2.2).



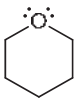
(d) One of the oxygen atoms has two bonds and no formal charge, so that oxygen atom must have two lone pairs (see Table 2.2). The other oxygen atom has one bond and a negative charge, so that oxygen atom must have three lone pairs.



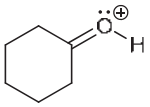
(e) In this case, the oxygen atom has one bond and a negative charge, so it must have three lone pairs (see Table 2.2).



(f) In this case, the oxygen atom has two bonds and no formal charge, so it must have two lone pairs (see Table 2.2).



(g) In this case, the oxygen atom has three bonds and a positive charge, so it must have one lone pair (see Table 2.2).



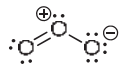
(h) In this case, the oxygen atom has three bonds and a positive charge, so it must have one lone pair (see Table 2.2).



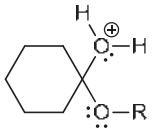
(i) From left to right, the first oxygen atom has two bonds and no formal charge, so it must have two lone

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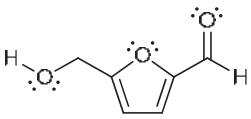
pairs (see Table 2.2). The second oxygen atom has three bonds and a positive charge, so it must have one lone pair. Finally, the third oxygen atom has one bond and a negative charge, so it has three lone pairs.



(j) One of the oxygen atoms has two bonds and no formal charge, so that oxygen atom must have two lone pairs (see Table 2.2). The other oxygen atom has three bonds and a positive charge, so that oxygen atom must have one lone pair.



2.9. Each oxygen atom in hydroxymethylfurfural lacks a charge and has two bonds, so each oxygen atom must have two lone pairs.

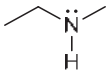


2.10.

(a) In this case, the nitrogen atom has three bonds and no formal charge, so it must have one lone pair (see Table 2.3).



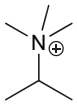
(b) In this case, the nitrogen atom has three bonds and no formal charge, so it must have one lone pair (see Table 2.3).



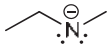
(c) In this case, the nitrogen atom has three bonds and no formal charge, so it must have one lone pair (see Table 2.3).



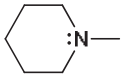
(d) In this case, the nitrogen atom has four bonds and a positive charge, so it must have no lone pairs (see Table 2.3).



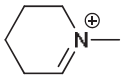
(e) In this case, the nitrogen atom has two bonds and a negative charge, so it must have two lone pairs (see Table 2.3).



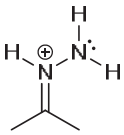
(f) In this case, the nitrogen atom has three bonds and no formal charge, so it must have one lone pair (see Table 2.3).



(g) In this case, the nitrogen atom has four bonds and a positive charge, so it must have no lone pairs (see Table 2.3).

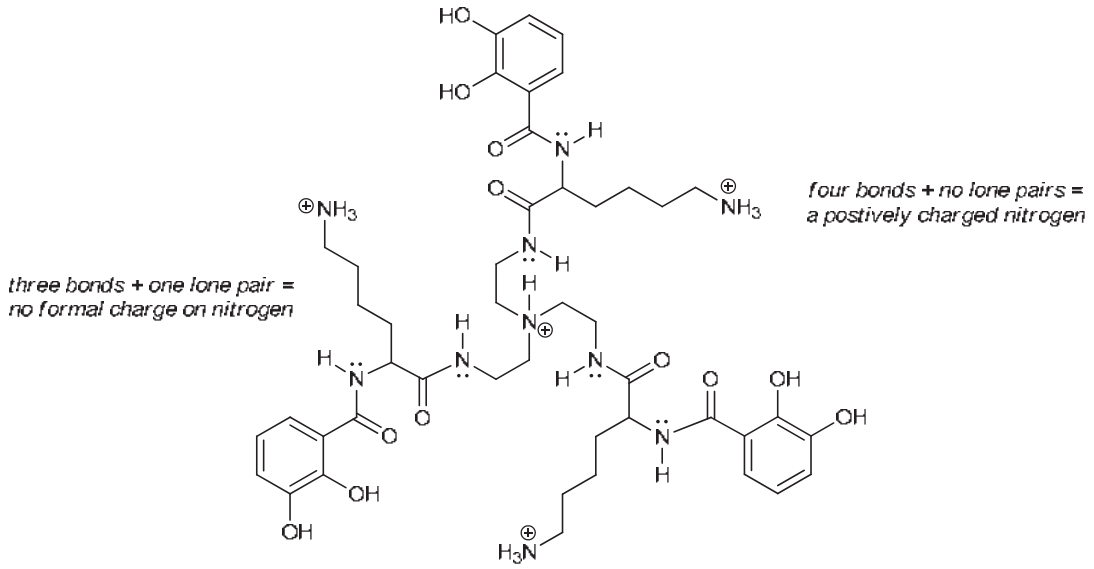


(h) One of the nitrogen atoms has four bonds and a positive charge, so it must have no lone pairs (see Table 2.3). The other nitrogen atom has three bonds and no formal charge, so it must have one lone pair.



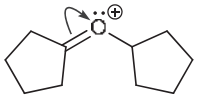
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2.11. Every uncharged nitrogen atom in this compound has three bonds and needs one lone pair of electrons to fill its octet. Every positively charged nitrogen atom has four bonds and no lone pairs.



2.12.
(a) This curved arrow violates the second rule by giving a fifth bond to a nitrogen atom.
(b) This curved arrow does not violate either rule.
(c) This curved arrow violates the second rule by giving five bonds to a carbon atom.
(d) This curved arrow violates the second rule by giving three bonds and two lone pairs to an oxygen atom.
(e) This curved arrow violates the second rule by giving five bonds to a carbon atom.
(f) This curved arrow violates the second rule by giving five bonds to a carbon atom.
(g) This curved arrow violates the first rule by breaking a single bond, and violates the second rule by giving five bonds to a carbon atom.
(h) This curved arrow violates the first rule by breaking a single bond, and violates the second rule by giving five bonds to a carbon atom.
(i) This curved arrow does not violate either rule.
(j) This curved arrow does not violate either rule.
(k) This curved arrow violates the second rule by giving five bonds to a carbon atom.
(l) This curved arrow violates the second rule by giving five bonds to a carbon atom.

2.13. The tail of the curved arrow must be placed on the double bond in order to avoid violating the first rule (avoid breaking a single bond).



2.14.
(a) This curved arrow violates the first rule (avoid breaking a single bond).
(b) This curved arrow does not violate either rule.
(c) This curved arrow violates the second rule (never exceed an octet for second-row elements) by giving five bonds to a carbon atom.
(d) This curved arrow violates the second rule by giving five bonds to a carbon atom.

2.15.
(a) The curved arrow indicates that we should draw a resonance structure in which the π bond has been pushed over. We then complete the resonance structure by assigning any formal charges. Notice that both resonance structures show a positive charge, but in different locations:



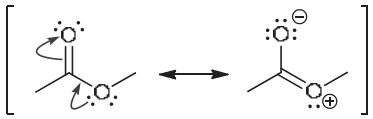
(b) The curved arrows indicate that we should draw a resonance structure in which the lone pair has been pushed to become a π bond, and the π bond has been pushed to become a lone pair. We then complete the resonance structure by assigning any formal charges. Notice that both resonance structures show a negative charge, but in different locations:



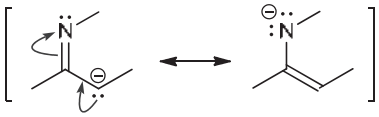
(c) The curved arrows indicate that we should draw a resonance structure in which a lone pair has been pushed

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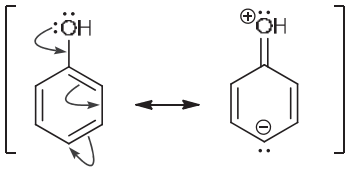
to become a π bond, and the π bond has been pushed to become a lone pair. We then complete the resonance structure by assigning any formal charges. Notice that both resonance structures have zero net charge:



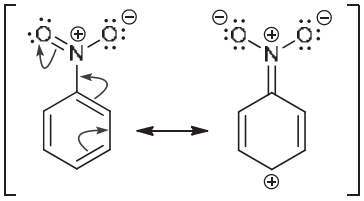
(d) The curved arrows indicate that we should draw a resonance structure in which a lone pair has been pushed to become a π bond, and the π bond has been pushed to become a lone pair. We then complete the resonance structure by assigning any formal charges. Notice that both resonance structures show a negative charge, but in different locations:



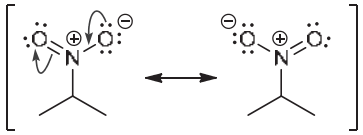
(e) The curved arrows indicate that we should draw the following resonance structure. Notice that both resonance structures have zero net charge:



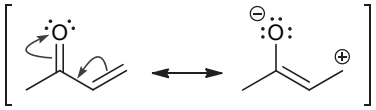
(f) The curved arrows indicate that we should draw the following resonance structure. Notice that both resonance structures have zero net charge:



(g) The curved arrows indicate that we should draw a resonance structure in which a lone pair has been pushed to become a π bond, and a π bond has been pushed to become a lone pair. We then complete the resonance structure by assigning any formal charges. Notice that both resonance structures have zero net charge, but they differ in the location of the negative charge:

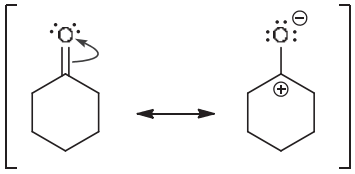


(h) The curved arrows indicate that we should draw the following resonance structure. Notice that both resonance structures have zero net charge:

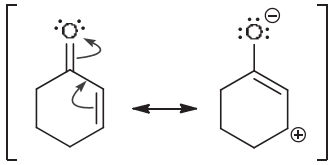


2.16.

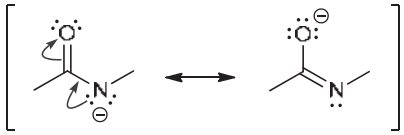
(a) One curved arrow is required, showing the π bond being pushed to become a lone pair:



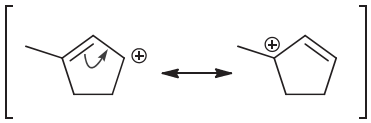
(b) Two curved arrows are required. One curved arrow shows the carbon-carbon π bond being pushed up, and the other curved arrow shows the carbon-oxygen π bond becoming a lone pair:



(c) Two curved arrows are required. One curved arrow shows a lone pair from the nitrogen atom becoming a π bond, and the other curved arrow shows the carbon-oxygen π bond becoming a lone pair:



(d) One curved arrow is required, showing the π bond being pushed over:

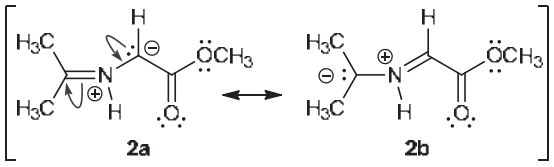


2.17.

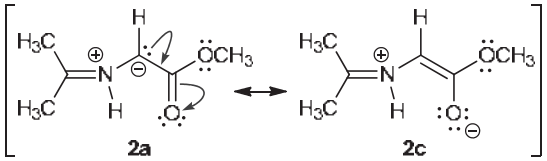
(a) Notice that there are two formal charges (positive and negative), but the positive charge is in the same locationi n all three resonance structures. Only the negative charge is spread out (over three locations). Two curved arrows are required to convert from resonance structure **2a** to resonance structure **2b**. One arrow shows that the lone pair on carbon can become a new carbon-nitrogen π bond while the other arrow shows that the electrons in

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the original carbon-nitrogen π bond can become a lone pair on a different carbon atom.

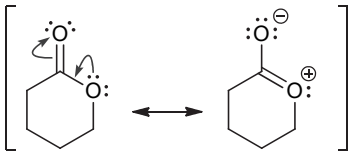


(b) Two curved arrows are required to convert resonance structure **2a** to resonance structure **2c**. One arrow shows that the lone pair on carbon can become a carbon-carbon π bond while the other arrow shows that the electrons in the carbon-oxygen π bond can become a third lone pair on oxygen.

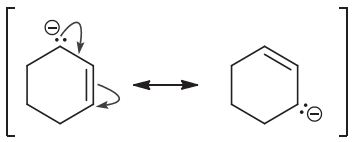


2.18.

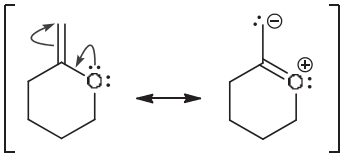
(a) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



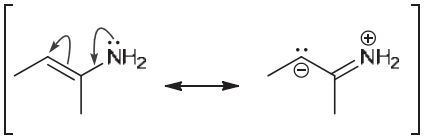
(b) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



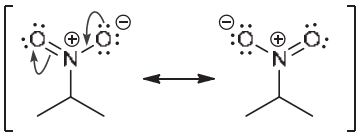
(c) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



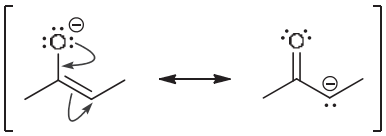
(d) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



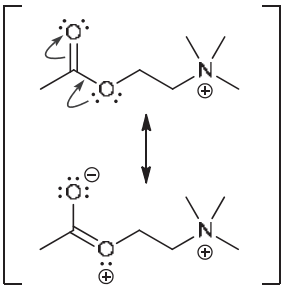
(e) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



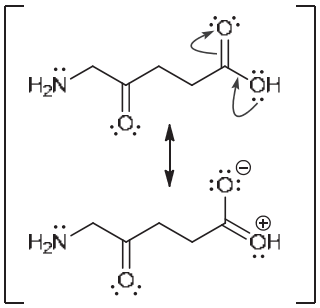
(f) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



(g) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



(h) This pattern (lone pair next to a π bond) has two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



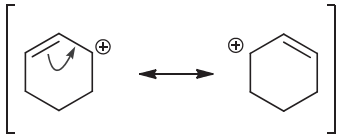
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2.19.

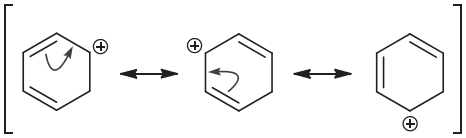
(a) This pattern has just one curved arrow, showing the π bond being pushed over:



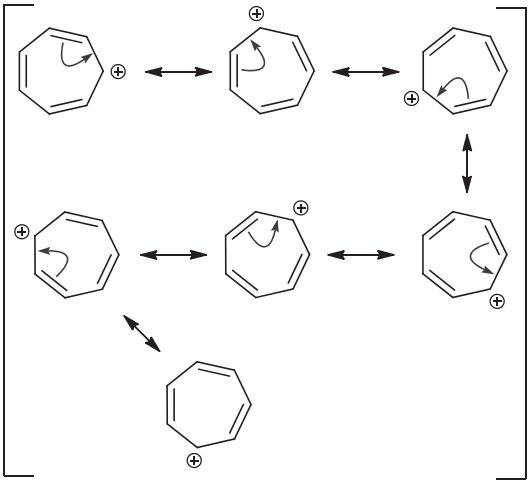
(b) This pattern has just one curved arrow, showing the π bond being pushed over:



(c) This pattern has just one curved arrow, showing the π bond being pushed over. But when we draw the resulting resonance structure, we find that the same pattern can be applied again, giving another resonance structure, as shown:

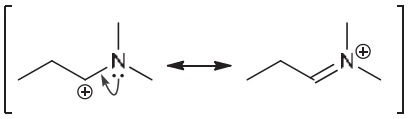


(d) This pattern has just one curved arrow, showing the π bond being pushed over. But when we draw the resulting resonance structure, we find that the same pattern can be applied again, giving another resonance structure. This process continues several more times, and we can see that the positive charge is spread (via resonance) over all seven carbon atoms of the ring:

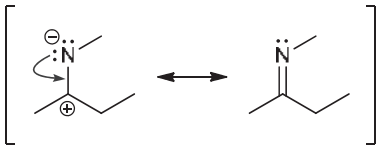


2.20.

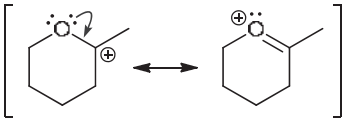
(a) This pattern has just one curved arrow, showing the lone pair becoming a π bond:



(b) This pattern has just one curved arrow, showing the lone pair becoming a π bond:

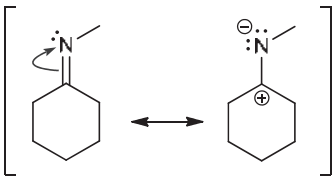


(c) This pattern has just one curved arrow, showing the lone pair becoming a π bond:

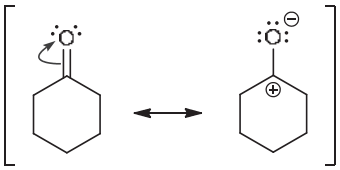


2.21.

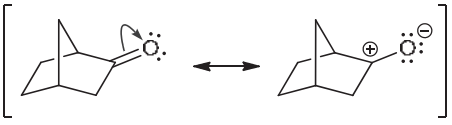
(a) This pattern has just one curved arrow, showing the π bond becoming a lone pair:



(b) This pattern has just one curved arrow, showing the π bond becoming a lone pair:

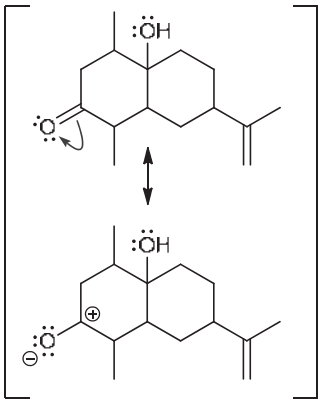


(c) This pattern has just one curved arrow, showing the π bond becoming a lone pair:

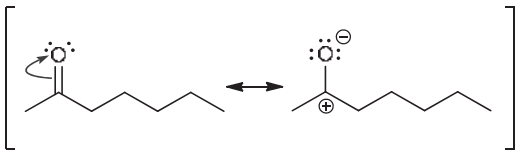


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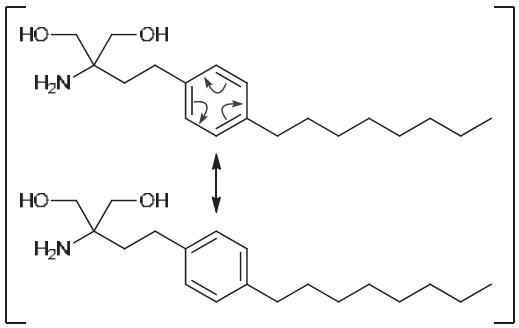
2.22. This pattern has just one curved arrow, showing the π bond becoming a lone pair:



2.23. This pattern has just one curved arrow, showing the π bond becoming a lone pair:

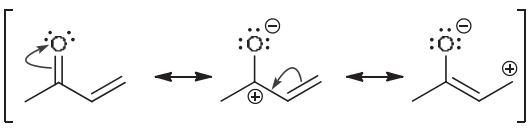


2.24. This pattern has three curved arrows, showing the π bonds moving in a circle.

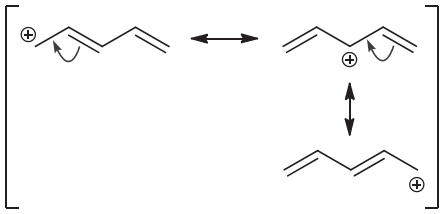


2.25.

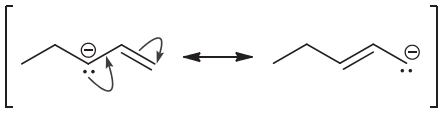
(a) We begin by looking for the five patterns. In this case, there is a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is an allylic positive charge, so we draw the curved arrow associated with that pattern (pushing over the π bond), shown here:



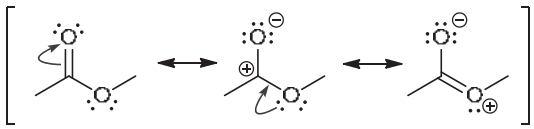
(b) The positive charge occupies an allylic position, so we draw the one curved arrow associated with that pattern (pushing over the π bond). The positive charge in the resulting resonance structure is again next to another π bond, so we draw one curved arrow and another resonance structure, as shown here:



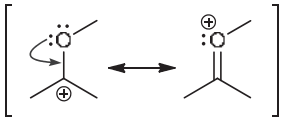
(c) The lone pair (associated with the negative charge) occupies an allylic position, so we draw the two curved arrows associated with that pattern. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



(d) We begin by looking for one of the five patterns that employs just one curved arrow (in this case, there is another pattern that requires two curved arrows, but we will start with the pattern using just one curved arrow). There is a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is a lone pair adjacent to a positive charge, so we draw the curved arrow associated with that pattern (showing the lone pair becoming a π bond), shown here:



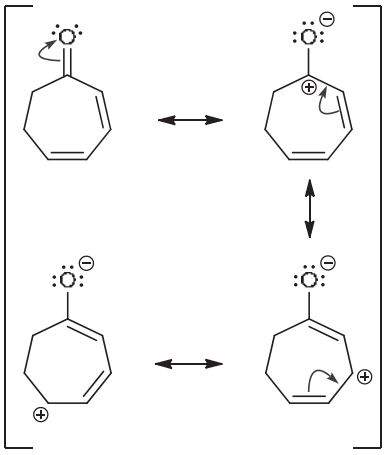
(e) This structure exhibits a lone pair that is adjacent to a positive charge, so we draw one curved arrow, showing a lone pair becoming a π bond:



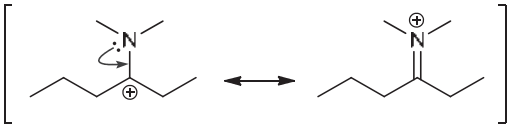
(f) This compound exhibits a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is an allylic positive charge,

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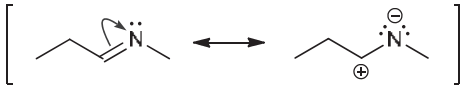
so we draw the curved arrow associated with that pattern (pushing over the π bond). The positive charge in the resulting resonance structure is next to another π bond, so we draw one more resonance structure, as shown here:



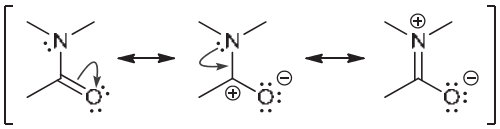
(g) This structure exhibits a lone pair that is adjacent to a positive charge, so we draw one curved arrow, showing a lone pair becoming a π bond:



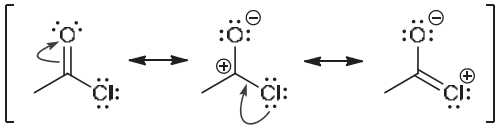
(h) This compound exhibits a C=N bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair:



(i) We begin by looking for one of the five patterns that employs just one curved arrow (in this case, there is another pattern that requires two curved arrows, but we will start with the pattern using just one curved arrow). There is a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is a lone pair adjacent to a positive charge, so we draw the curved arrow associated with that pattern (showing the lone pair becoming a π bond), shown here:

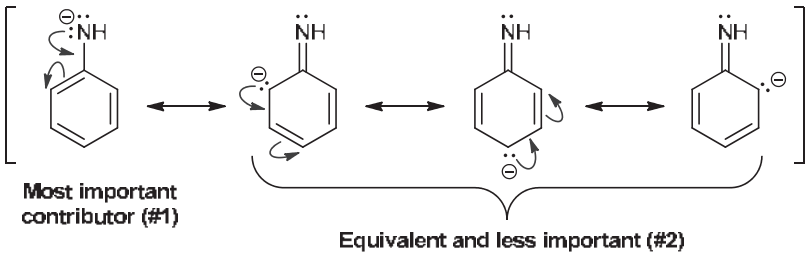


(j) We begin by looking for one of the five patterns that employs just one curved arrow (in this case, there is another pattern that requires two curved arrows, but we will start with the pattern using just one curved arrow). There is a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is a lone pair adjacent to a positive charge, so we draw the curved arrow associated with that pattern (showing the lone pair becoming a π bond), shown here:



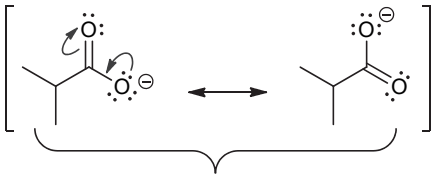
2.26.

(a) Using the skills developed in the previous SkillBuilders, we begin by drawing all significant resonance structures, shown below. None of the four structures have an atom with an incomplete octet, so they are all expected to be major contributors to the hybrid. The first resonance structure is the largest contributor because it has filled octets and the negative charge is on the more electronegative nitrogen atom. The other three resonance structures are approximately equivalent and they are less significant than the first structure because the negative charge is on the less electronegative carbon atom.

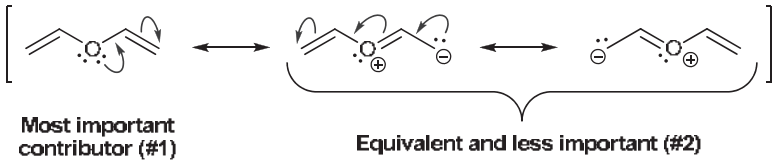


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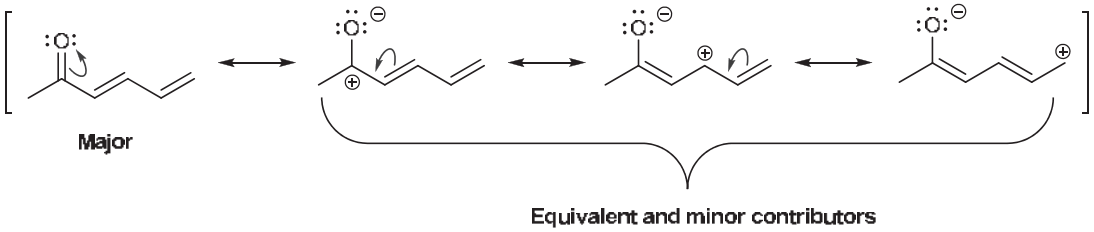
(b) Using the skills developed in the previous SkillBuilders, we begin by drawing all significant resonance structures, shown below. Both resonance structures have filled octets and a negative charge on an oxygen atom. Both resonance structures are equivalent and equally significant.



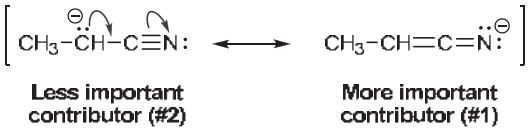
(c) Using the skills developed in the previous SkillBuilders, we begin by drawing all significant resonance structures, shown below. None of the three structures has an atom with an incomplete octet. The first resonance structure is the largest contributor because it has filled octets and no formal charges. The other two resonance structures are equivalent and less significant contributors because they contain formal charges.



(d) Using the skills developed in the previous SkillBuilders, we begin by drawing all significant resonance structures, shown below. The first resonance structure is the only major contributor because it is the only one with filled octets. Recall that a structure with filled octets and no formal charges is an ideal Lewis structure. The other three resonance structures are approximately equivalent and minor contributors because each one is missing an octet (they also have formal charges, but that is a less significant feature to consider when ranking resonance forms).



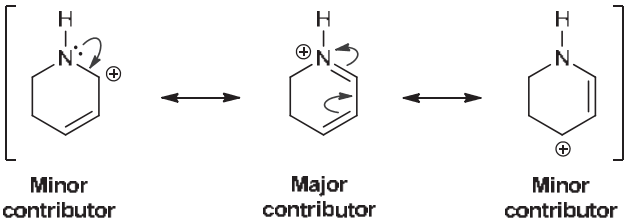
(e) Using the skills developed in the previous SkillBuilders, we begin by drawing all significant resonance structures, shown below. Neither resonance structure has an incomplete octet so they are both expected to be major contributors to the hybrid. The second resonance structure is the more significant contributor because it has the negative charge on the more electronegative nitrogen atom. The first resonance structure is less significant because the negative charge is on the less electronegative carbon atom.



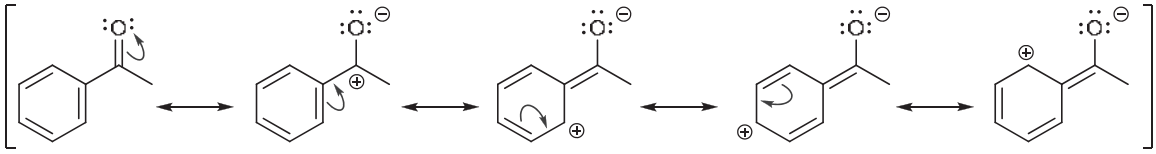
(f) This cation has two different resonance patterns that can be employed, using the lone pair or the π bond to fill the vacancy on carbon, giving a total of three resonance structures. The middle resonance structure is the only major contributor because it is the only one with filled octets. The other two structures are equivalent (missing one octet and

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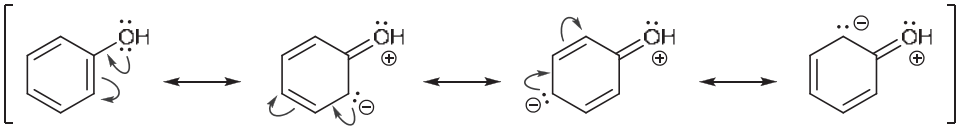
positive charge on carbon atom). They are minor and contribute equally to the hybrid. Note that the location of the charge (C^+ vs. N^+) is not as important in this problem, because filled octets are more important.



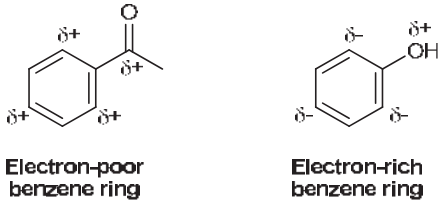
2.27. When looking for resonance in the first structure, we can begin with the carbonyl (C=O) group by relocating the π bond electrons to the more electronegative oxygen atom. This provides a resonance structure with an allylic C+ that can undergo allylic resonance throughout the ring, resulting in three more resonance structures. Be careful to use just one π bond at a time so you don't accidentally "jump" over a possible resonance structure.



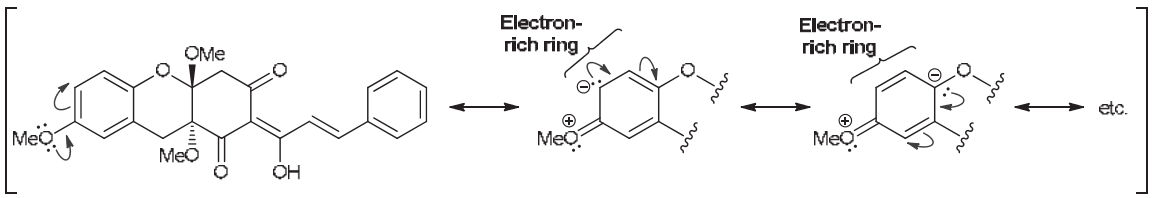
For the second compound, the allylic lone pair can be delocalized using one of the π bonds in the benzene ring, and this pattern can continue to use the remaining π bonds in the ring (again, one at a time!).



Overall, when we consider the contributions made by all resonance structures, we find that the ring in the first compound is electron-poor, with several electron-deficient sites on the ring, and the ring in the second compound is electron-rich, with several δ– sites on the ring.

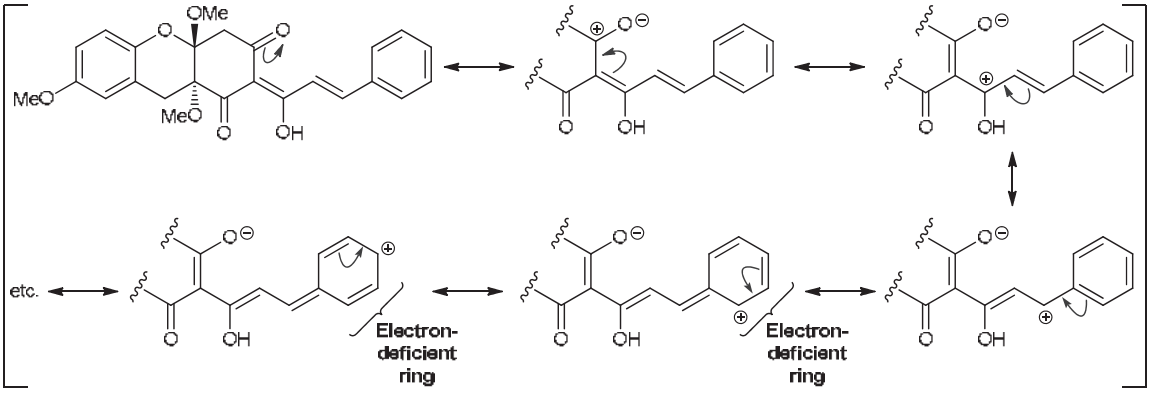


2.28. The benzene ring on the left has two oxygen atoms attached. Both oxygen atoms can *donate* electron density via allylic lone pair resonance, making this benzene ring electron-rich.

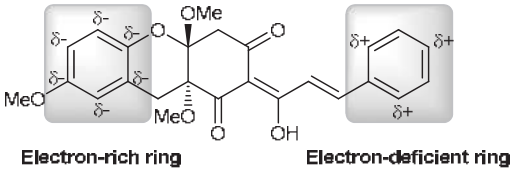


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The benzene ring on the right is "connected" to the carbonyl (C=O) groups by a series of alternating π bonds, so the resonance of each carbonyl group extends into the benzene ring. The carbonyl groups *withdraw* electron density via allylic carbocation resonance, making this ring electron-deficient.

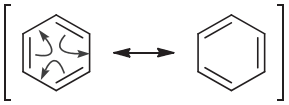


In summary, the benzene ring on the left is electron-rich due to resonance with the lone pairs of electrons on both attached oxygen atoms. The benzene ring on the left is electron-poor due to resonance with the carbonyl groups.



2.29.

(a) Begin by drawing all significant resonance structures. In this case, there are two:

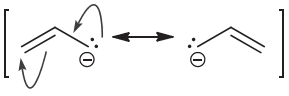


Both resonance structures are equally significant, so the resonance hybrid is the simple average of these two resonance structures. There are no formal charges, so only partial bonds need to be drawn.

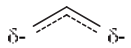


Resonance hybrid

(b) Begin by drawing all significant resonance structures. In this case, there are two:

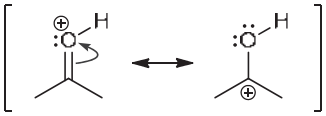


Both are equally significant, so the resonance hybrid is the simple average of these two resonance structures. Both partial bonds and partial charges are required, as shown:



Resonance hybrid

(c) Begin by drawing all significant resonance structures. In this case, there are two:

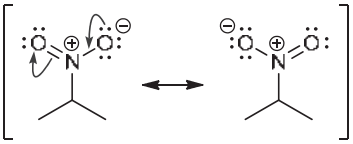


The left-hand structure is more significant because every atom has an octet. The resonance hybrid is a weighted average of these two resonance structures in which the oxygen atom has more of the charge than the carbon atom.

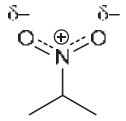


Resonance hybrid

(d) Begin by drawing all significant resonance structures. In this case, there are two:

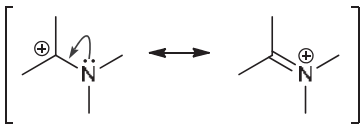


Both are equally significant, so the resonance hybrid is the simple average of these two resonance structures. Only the negative charge is delocalized, so partial charges are used for the negative charge but not for the positive charge.

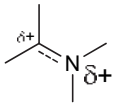


Resonance hybrid

(e) Begin by drawing all significant resonance structures. In this case, there are two:

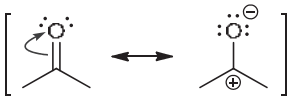


The structure on the right is more significant because every atom has an octet. The resonance hybrid is a weighted average of these two resonance structures in which the nitrogen atom has more of the charge than the carbon atom.



Resonance hybrid

(f) Begin by drawing all significant resonance structures. In this case, there are two:

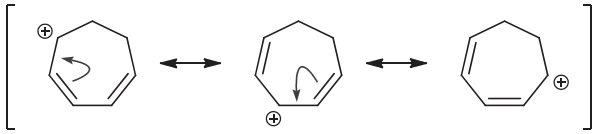


The structure on the left is more significant because every atom has an octet and it has no formal charges. The resonance hybrid is a weighted average of these two resonance structures, although we do not denote that by making the partial charges different sizes. In this example, the charges are opposite in sign, but they must be equal in magnitude so that the overall charge will be zero.

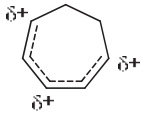


Resonance hybrid

(g) Begin by drawing all significant resonance structures. In this case, there are three:

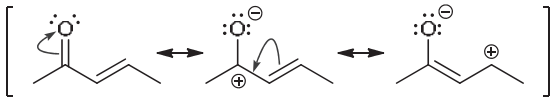


All three resonance structures are equally significant, so the resonance hybrid is the simple average of these three resonance structures, illustrating that the positive charge is delocalized over three carbon atoms.

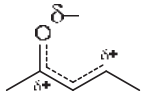


Resonance hybrid

(h) Begin by drawing all significant resonance structures. In this case, there are three:

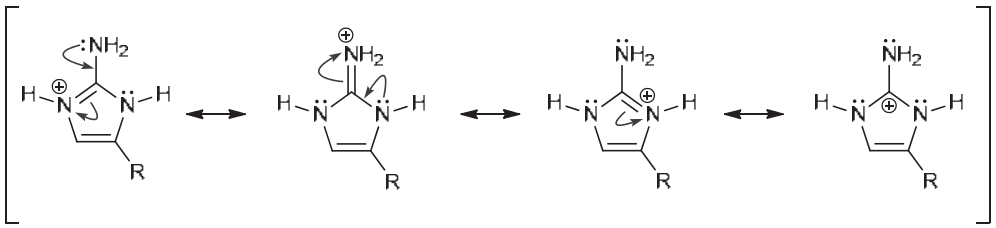


The structure on the left is most significant because every atom has an octet and it has no formal charge. The resonance hybrid is a weighted average of these three resonance structures. Since the partial positive charge is delocalized over two carbon atoms and the partial negative charge is localized on only one oxygen atom, the partial negative charge is drawn larger than each of the individual partial positive charges.



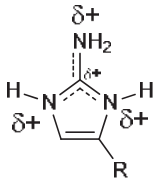
Resonance hybrid

2.30. Begin by drawing all significant resonance structures. In this case, there are four:



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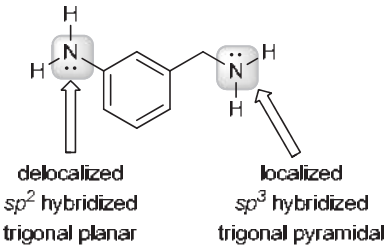
The first three resonance structures are the most significant, because all atoms have an octet in each of these three resonance structures. The fourth resonance structure (in which the carbon atom bears the positive charge) is the least significant because a carbon atom lacks an octet. If we compare the three most significant resonance structures, each has a positive charge on a nitrogen atom, so we expect these three resonance structures to contribute roughly equally to the resonance hybrid. To show this, we indicate δ+ at all three positions, with a smaller δ+ symbol at the central carbon atom (indicating the lower contribution of the fourth resonance structure). Also, if we compare the first three resonance structures, we find that the π bond is spread over three locations, and these locations are indicated with dashed lines in the resonance hybrid:



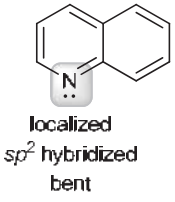
2.31.

(a) Let's begin with the nitrogen atom on the left side of the structure. The lone pair on this nitrogen atom is delocalized by resonance (because it is next to a π bond). Therefore, this lone pair occupies a *p* orbital, which means that the nitrogen atom is sp^2 hybridized. As a result, the geometry is trigonal planar.

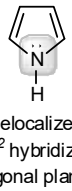
On the right side of the structure, there is a nitrogen atom with a localized lone pair (it does not participate in resonance). This nitrogen atom is therefore sp^3 hybridized, with trigonal pyramidal geometry, just as expected for a nitrogen atom with σ sigma bonds and a localized lone pair.



(b) As we saw with pyridine, the lone pair on this nitrogen atom is not participating in resonance, because the nitrogen atom is already using a *p* orbital for the π bond. As a result, the lone pair cannot join in the conduit of overlapping *p* orbitals, and therefore, it cannot participate in resonance. In this case, the lone pair occupies an sp^2 hybridized orbital, which is in the plane of the ring. Since this lone pair is not participating in resonance, it is localized. The nitrogen atom is sp^2 hybridized, and the geometry is bent.

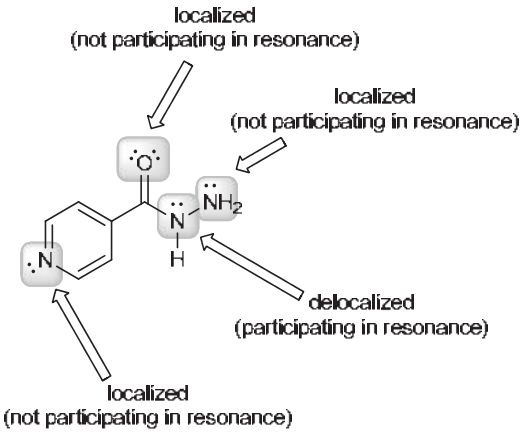


(c) The lone pair on this nitrogen atom is participating in resonance (it is next to a π bond), so it is delocalized via resonance. As such, the nitrogen atom is sp^2 hybridized, with trigonal planar geometry.



2.32. Each of these lone pairs is not participating in resonance. So each of these lone pairs is localized. Therefore, both lone pairs are expected to be reactive.

2.33. Lone pairs that participate in resonance are delocalized, while those that do not participate in resonance are localized:

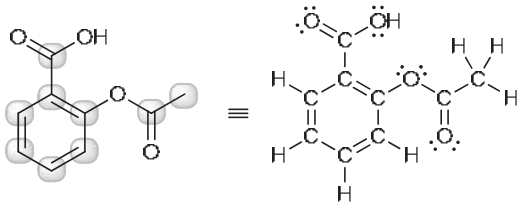


2.34.

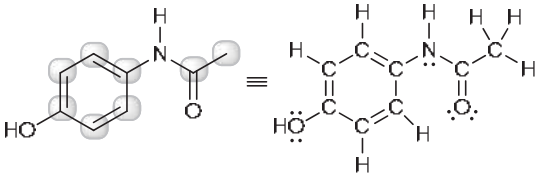
(a) Each corner and each endpoint represents a carbon atom (highlighted), so this compound has nine carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown. Each of the

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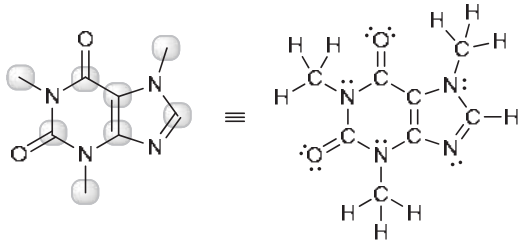
oxygen atoms has two bonds and no formal charge, so each oxygen atom will have two lone pairs.



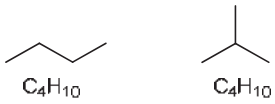
(b) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has eight carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown. Each of the oxygen atoms has two bonds and no formal charge, so each oxygen atom will have two lone pairs. The nitrogen atom has three bonds and no formal charge, so it must have one lone pair of electrons.



(c) Each corner and each endpoint represents a carbon atom (highlighted below), so this compound has eight carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, as shown. Each of the oxygen atoms has two bonds and no formal charge, so each oxygen atom will have two lone pairs. Each nitrogen atom has three bonds and no formal charge, so each nitrogen atom must have one lone pair of electrons.



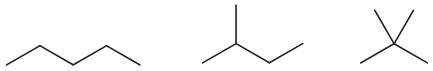
2.35. The molecular formula indicates that there are four carbon atoms. Recall that constitutional isomers are compounds that share the same molecular formula, but differ in constitution (the connectivity of atoms). So we are looking for different ways that four carbon atoms can be connected together. As described in the solution to Problem **1.1b**, the carbon atoms can be connected in a linear fashion (below left), or they can be connected with a branch (below right).



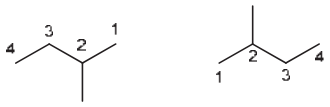
These two compounds are the only constitutional isomers that have the molecular formula C_4H_{10}, because there are no other ways to connect four carbon atoms without changing the number of hydrogen atoms. For example, if we try to connect the carbon atoms into a ring, we find that the number of hydrogen atoms is reduced:



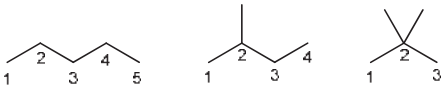
2.36. As described in the solution to Problem **1.1c**, there are only three constitutional isomers with the molecular formula C_5H_{12}, shown here again.



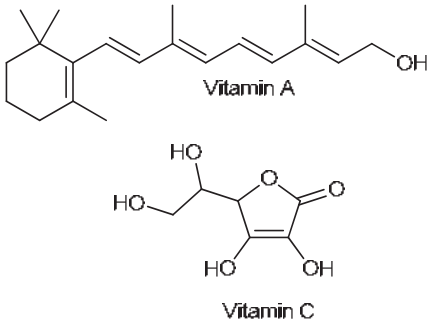
There are no other constitutional isomers with the molecular formula C_5H_{12}. The following two structures do NOT represent constitutional isomers, but are in fact two drawings of the same compound, as can be seen when the carbon skeletons are numbered, as shown:



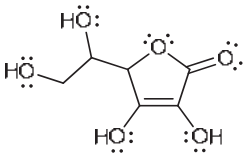
Notice that in both drawings, the longest linear chain is four carbon atoms, and there is a CH_3 group attached to the second carbon atom of the chain. As such, these two drawings represent the same compound. In contrast, we can see that all three constitutional isomers with the molecular formula C_5H_{12} exhibit different connectivity of the carbon atoms:



2.37. In each of the following structures, each corner and endpoint represents a carbon atom. Hydrogen atoms are only drawn if they are connected to heteroatoms (such as oxygen).



2.38. Each oxygen atom has two bonds and no formal charge. Therefore, each oxygen atom has two lone pairs, for a total of twelve lone pairs.



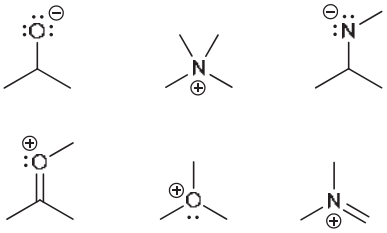
2.39. Carbon is in group **4A** of the periodic table, and it should therefore have four valence electrons. We are told that, in this case, the central carbon atom does not bear a formal charge.



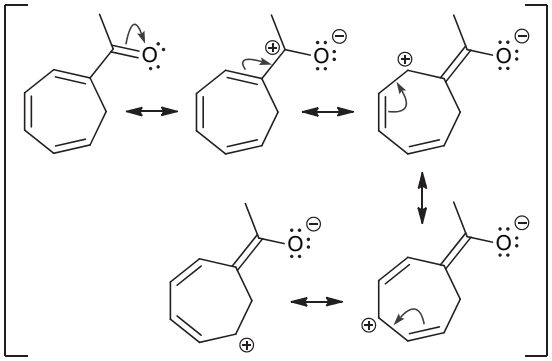
Therefore, it must exhibit the appropriate number of valence electrons (four). This carbon atom already has two bonds (each of which requires one valence electron) and a lone pair (which represents two electrons), for a total of 1+1+2=4 valence electrons. This is the appropriate number of valence electrons, which means that this carbon atom does not have any bonds to hydrogen.

Notice that the carbon atom lacks an octet, so it should not be surprising that this structure is highly reactive and very short-lived.

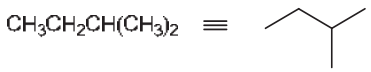
2.40. An oxygen atom will bear a negative charge if it has one bond and three lone pairs, and it will bear a positive charge if it has three bonds and one lone pair (see Table 2.2). A nitrogen atom will bear a negative charge if it has two bonds and two lone pairs, and it will bear a positive charge if it has four bonds and no lone pairs (see Table 2.3).



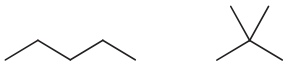
2.41. This compound exhibits a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is an allylic positive charge, so we draw the curved arrow associated with that pattern (pushing over the π bond). This pattern continues, many more times, spreading the positive charge over many locations, as shown here:



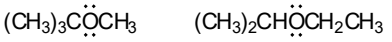
2.42. Recall that constitutional isomers are compounds that share the same molecular formula, but differ in constitution (the connectivity of atoms). The problem statement shows a compound with the molecular formula C_5H_{12} and the following structure:



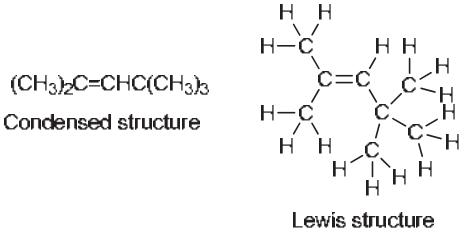
So we are looking for other compounds that also have the molecular formula C_5H_{12} but show a different connectivity of atoms. As seen in the solution to Problem **2.36**, there are only two such compounds:



2.43. The following two compounds are constitutional isomers because they share the same molecular formula ($C_5H_{12}O$). The third compound (not shown here) has a different molecular formula ($C_4H_{10}O$).



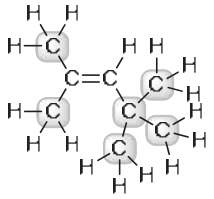
2.44. Begin by drawing a Lewis structure, so that the bonding of each carbon atom is shown more clearly:



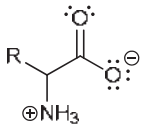
Notice that two of the carbon atoms are sharing a double bond. These two atoms are *sp*^{2} hybridized. Each of the other six carbon atoms exhibits four single bonds, and as

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such, each of these six carbon atoms (highlighted) is sp^3 hybridized.

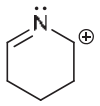


2.45. One of the oxygen atoms has two bonds and no formal charge, so that oxygen atom must have two lone pairs (see Table 2.2). The other oxygen atom has one bond and a negative charge, so that oxygen atom must have three lone pairs. The nitrogen atom has four bonds and a positive charge, so it does not have any lone pairs (see Table 2.3). Therefore, there are a total of five lone pairs in this structure.

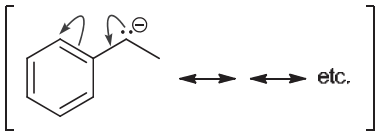


2.46.

(a) In order for the lone pair to participate in resonance, it must occupy a *p* orbital, which would render the nitrogen atom *sp* hybridizxed. With *sp* hybridization, the geometry of the nitrogen atom should be linear, which cannot be accommodated in a six-membered ring.

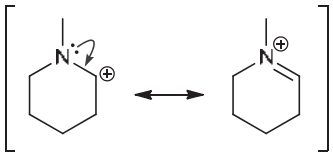


(b) There is a lone pair associated with the negative charge, and this lone pair is delocalized via resonance (the lone pair is allylic):



As such, the lone pair must occupy a *p* orbital.

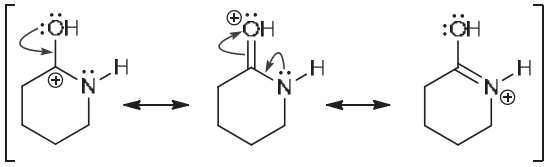
(c) The nitrogen atom has a lone pair, which is delocalized via resonance (there is an adjacent positive charge):



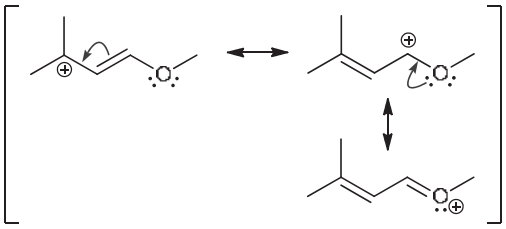
As such, the lone pair must occupy a *p* orbital.

2.47.

(a) This structure exhibits a lone pair that is adjacent to a positive charge. In fact, there are two such lone pairs (on the nitrogen and oxygen atoms). We will begin with a lone pair on the oxygen atom, although we would have arrived at the same solution either way (we will draw a total of three resonance structures, below, and it is just a matter of the order in which we draw them). We draw one curved arrow, showing a lone pair on the oxygen atom becoming a π bond. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is a lone pair next to a π bond, so we draw the two curved arrows associated with that pattern. The first curved arrow is drawn showing a lone pair on the nitrogen atom becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair on the oxygen atom:

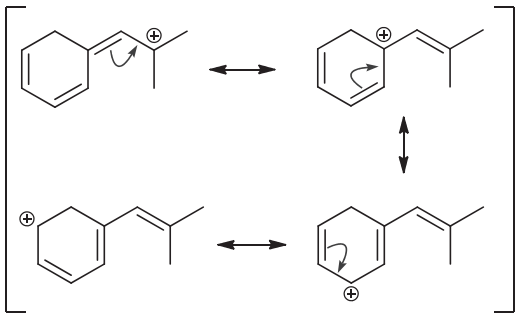


(b) This structure exhibits an allylic positive charge, so we draw one curved arrow showing the π bond being pushed over. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, the positive charge is adjacent to a lone pair, so we draw the curved arrow associated with that pattern (the lone pair is shown becoming a π bond):



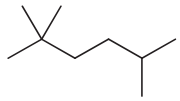
(c) This structure exhibits an allylic positive charge, so we draw one curved arrow showing the π bond being pushed over. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, the positive charge is again next to a π bond, so again, we draw the curved arrow associated with that pattern (pushing over the π bond again). The resulting resonance structure has the positive charge next to yet another π bond, so we draw a curved arrow showing the π bond being pushed over one more time to give our final resonance structure:

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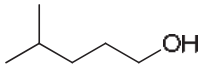
2.48.

(a) In a condensed structure, single bonds are not drawn. Instead, groups of atoms are clustered together, as shown here:



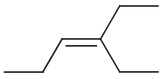
$(CH_3)_3CCH_2CH_2CH(CH_3)_2$

(b) In a condensed structure, single bonds are not drawn. Instead, groups of atoms are clustered together, as shown here:



$(CH_3)_2CHCH_2CH_2CH_2OH$

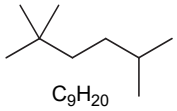
(c) In a condensed structure, single bonds are not drawn. Instead, groups of atoms are clustered together, as shown here:



$CH_3CH_2CH{=}C(CH_2CH_3)_2$

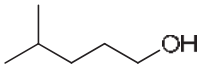
2.49.

(a) Each corner and each endpoint represents a carbon atom, so this compound has nine carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, giving a total of twenty hydrogen atoms. So the molecular formula is C_9H_{20}.



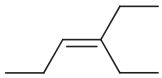
C_9H_{20}

(b) Each corner and each endpoint represents a carbon atom, so this compound has six carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, giving a total of fourteen hydrogen atoms. So the molecular formula is $C_6H_{14}O$.



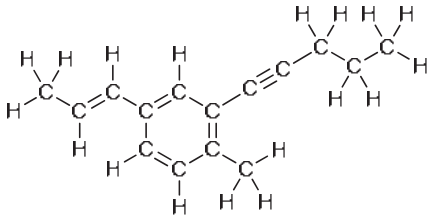
$C_6H_{14}O$

(c) Each corner and each endpoint represents a carbon atom, so this compound has eight carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, giving a total of sixteen hydrogen atoms. So the molecular formula is C_8H_{16}.



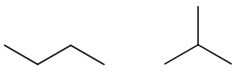
C_8H_{16}

2.50. Each corner and each endpoint represents a carbon atom, so this compound has fifteen carbon atoms. Each carbon atom will have enough hydrogen atoms to have exactly four bonds, giving a total of eighteen hydrogen atoms, as shown here:



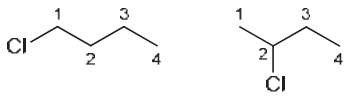
$C_{15}H_{18}$

2.51. As seen in the solution to Problem 2.35, there are only two ways to connect four carbon atoms in a compound with the molecular formula C_4H_{10}:



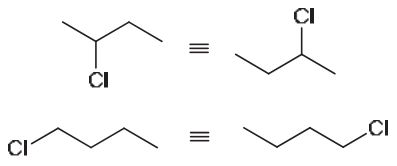
In our case, the molecular formula is C_4H_9Cl, which is similar to C_4H_{10}, but one H has been replaced with a chlorine atom. So, we must explore all of the different locations where a chlorine atom can be placed on each of the carbon skeletons above (the linear skeleton and the branched skeleton).

Let's begin with the linear skeleton. There are two distinctly different locations where a chlorine atom can be placed on this skeleton: either at position 1 or position 2, shown here.

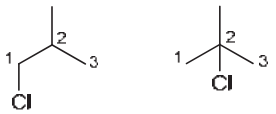


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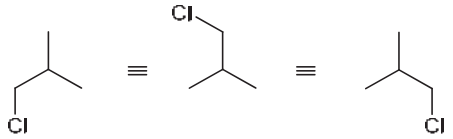
Placing the chlorine atom at position 3 would be the same as placing it at position 2; and placing the chlorine atom at position 4 would be the same as it as position 1:



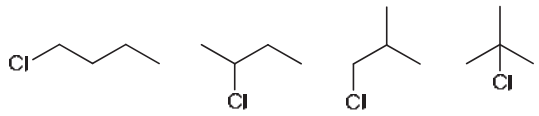
Next, we move on to the other carbon skeleton, containing a branch. Once again, there are two distinctly different locations where a chlorine atom can be placed: either at position 1 or position 2, shown here.



Placing the chlorine atom on any of the peripheral carbon atoms will lead to the same compound:

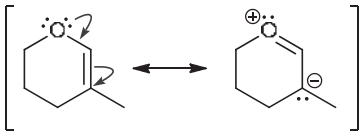


In summary, there are a total of four constitutional isomers with the molecular formula C_4H_9Cl:

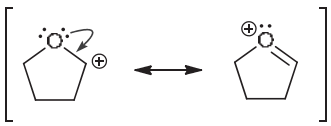


2.52.

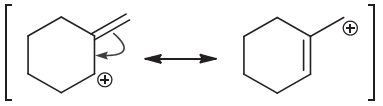
(a) This compound exhibits a lone pair next to a π bond, so we draw the two curved arrows associated with that pattern. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:



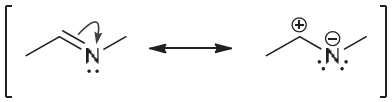
(b) This structure exhibits a lone pair that is adjacent to a positive charge, so we draw one curved arrow, showing a lone pair becoming a π bond:



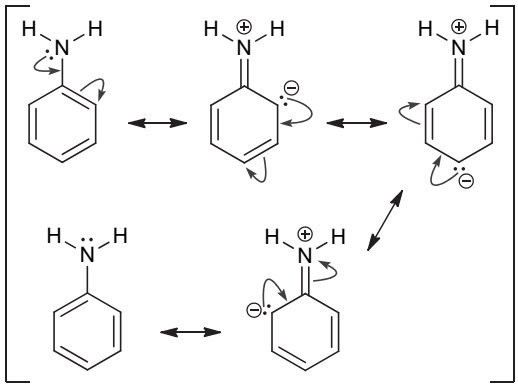
(c) This structure exhibits an allylic positive charge, so we draw one curved arrow showing the π bond being pushed over.



(d) This compound exhibits a C=N bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair.

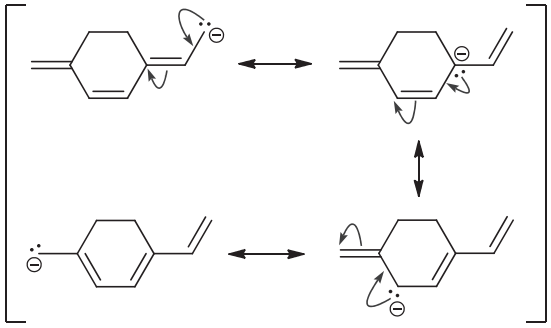


(e) This compound exhibits a lone pair next to a π bond, so we draw two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, the lone pair is now next to another π bond, so once again, we draw the two curved arrows associated with that pattern. The resulting resonance structure again exhibits a lone pair next to a π bond. This pattern continues again, thereby spreading a negative charge over many locations, as shown here:

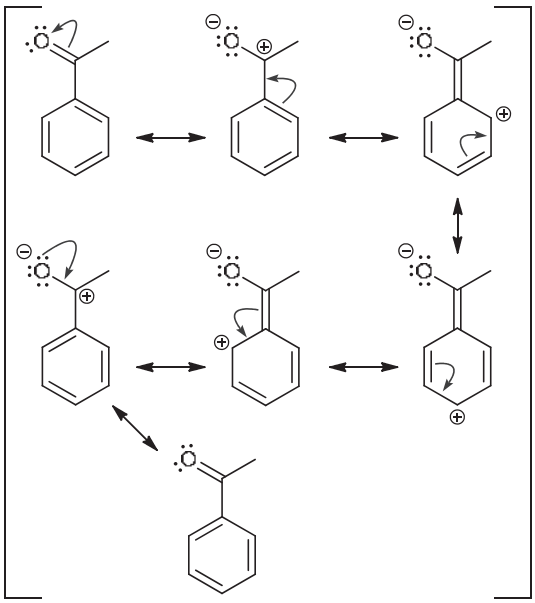


(f) This structure exhibits a lone pair next to a π bond, so we draw two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, the lone pair is now next to another π bond, so once again, we draw the two curved arrows associated with that pattern. The resulting resonance structure again exhibits a lone pair next to a π bond, so we draw one more resonance structure, as shown here:

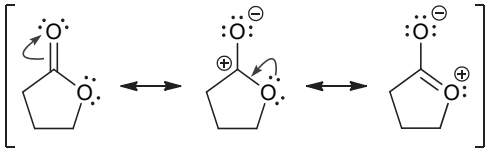
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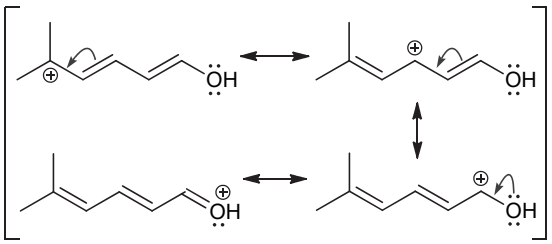
(g) This compound exhibits a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is an allylic positive charge, so we draw the curved arrow associated with that pattern (pushing over the π bond). This pattern continues, many more times, spreading the positive charge over many locations, as shown here:



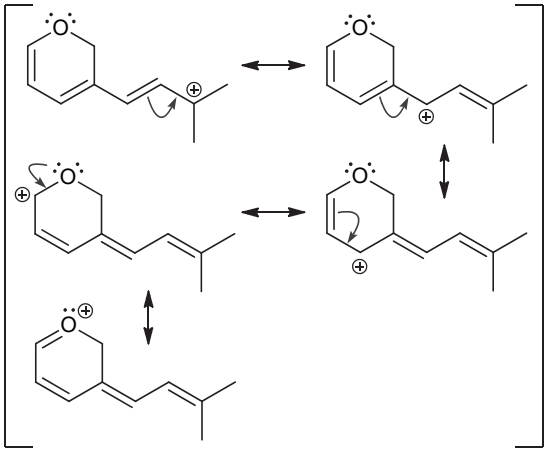
(h) We begin by looking for one of the five patterns that employs just one curved arrow (in this case, there is another pattern that requires two curved arrows, but we will start with the pattern using just one curved arrow). There is a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is a lone pair adjacent to a positive charge, so we draw the curved arrow associated with that pattern (showing the lone pair becoming a π bond), shown here:



(i) This structure exhibits an allylic positive charge, so we draw one curved arrow showing the π bond being pushed over. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, the positive charge is again next to a π bond, so again, we draw the curved arrow associated with that pattern (pushing over the π bond). The resulting resonance structure has a positive charge adjacent to a lone pair, so we draw the one curved arrow associated with that pattern (showing the lone pair becoming a π bond), shown here:



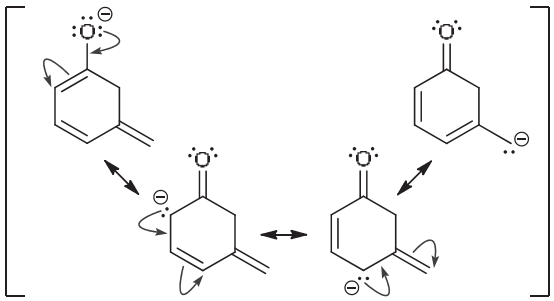
(j) This structure exhibits an allylic positive charge, so we draw one curved arrow showing the π bond being pushed over. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, the positive charge is again next to a π bond, so again, we draw the curved arrow associated with that pattern (pushing over the π bond). The resulting resonance structure again has a positive charge next to a π bond, so again, we draw the curved arrow associated with that pattern (pushing over the π bond). The resulting resonance structure has a positive charge adjacent to a lone pair, so we draw the one curved arrow associated with that pattern (showing the lone pair becoming a π bond), shown here.



2.53. These structures do not differ in their connectivity of atoms. They differ only in the placement of electrons.

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Therefore, these structures are resonance structures, as shown here:



2.54.

(a) These compounds both have the same molecular formula (C_7H_{12}), but they differ in their connectivity of atoms, or constitution. Therefore, they are constitutional isomers.

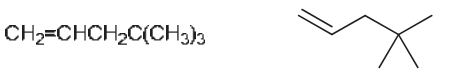
(b) These structures have the same molecular formula (C_7H_{16}), AND they have the same constitution (connectivity of atoms), so they represent the same compound.

(c) The first compound has the molecular formula C_5H_{10}, while the second compound has the molecular formula C_5H_8. As such, they are different compounds that are not isomeric.

(d) These compounds both have the same molecular formula (C_5H_8), but they differ in their connectivity of atoms, or constitution. Therefore, they are constitutional isomers.

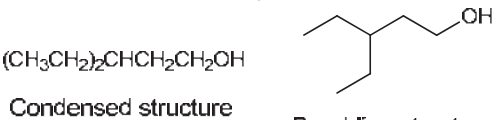
2.55.

(a) The condensed structure (shown in the problem statement) indicates the constitution (how the atoms are connected to each other). In the bond-line structure, hydrogen atoms are not drawn (they are implied). Each corner and each endpoint represents a carbon atom, so the carbon skeleton is shown more clearly.



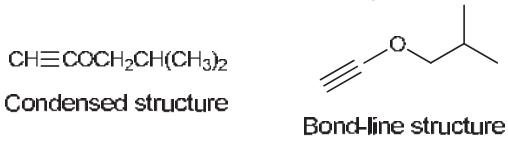
Condensed structure Bond-line structure

(b) The condensed structure indicates how the atoms are connected to each other. In the bond-line structure, hydrogen atoms are not drawn (they are implied), except for the hydrogen atom attached to the oxygen atom (hydrogen atoms must be drawn if they are connected to a heteroatom, such as oxygen). Each corner and each endpoint represents a carbon atom, so the carbon skeleton is shown more clearly.



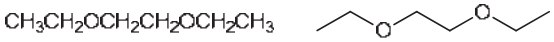
Condensed structure Bond-line structure

(c) The condensed structure indicates how the atoms are connected to each other. In the bond-line structure, hydrogen atoms are not drawn (they are implied). Each corner and each endpoint represents a carbon atom, so the carbon skeleton is shown more clearly.



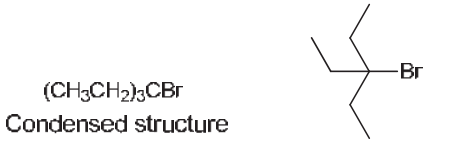
Condensed structure Bond-line structure

(d) The condensed structure indicates how the atoms are connected to each other. In the bond-line structure, hydrogen atoms are not drawn (they are implied). Each corner and each endpoint represents a carbon atom, so the carbon skeleton is shown more clearly.



Condensed structure Bond-line structure

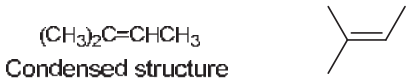
(e) The condensed structure indicates how the atoms are connected to each other. In the bond-line structure, hydrogen atoms are not drawn (they are implied). Each corner and each endpoint represents a carbon atom, so the carbon skeleton is shown more clearly.



Condensed structure

Bond-line structure

(f) The condensed structure indicates how the atoms are connected to each other. In the bond-line structure, hydrogen atoms are not drawn (they are implied). Each corner and each endpoint represents a carbon atom, so the carbon skeleton is shown more clearly.



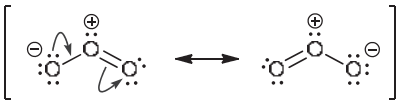
Condensed structure

Bond-line structure

2.56. The nitronium ion does *not* have any significant resonance structures because any attempts to draw a resonance structure will either 1) exceed an octet for the nitrogen atom or 2) generate a nitrogen atom with less than an octet of electrons, or 3) generate a structure with three charges. The first of these would not be a valid resonance structure, and the latter two would not be significant resonance structures.

2.57. The negatively charged oxygen atom has three lone pairs, while the positively charged oxygen atom has one lone pair (see Table 2.2). Notice that this compound exhibits a lone pair that is next to a π bond, so we must draw two curved arrows associated with that pattern. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair:

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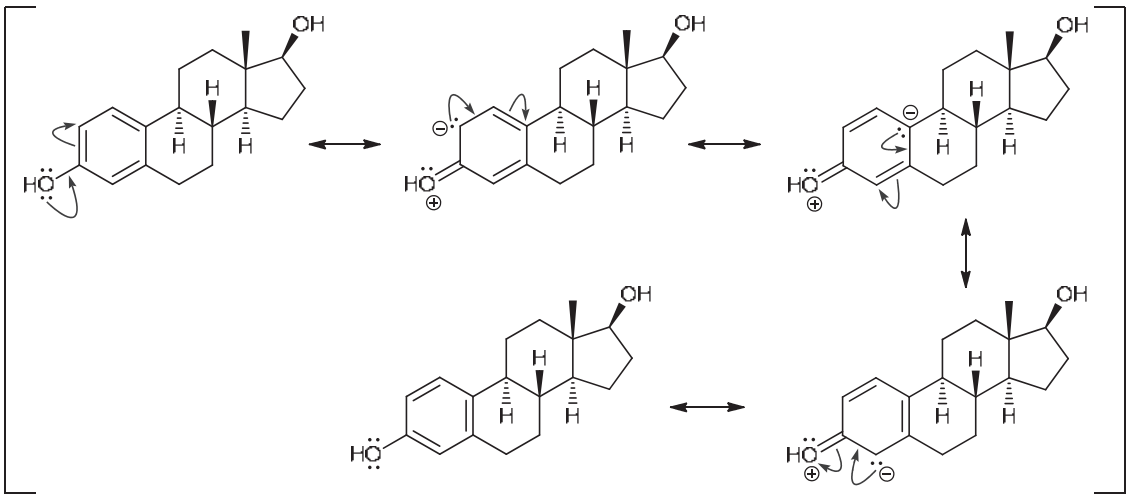


There are no other valid resonance structures that are significant.

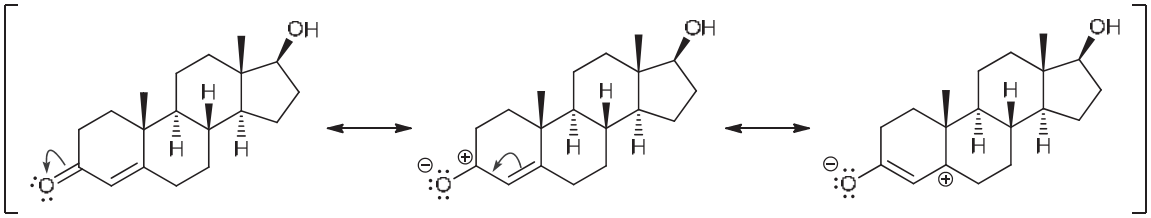
2.58. Each nitrogen atom has a lone pair that is delocalized via resonance. In order to be delocalized via resonance, the lone pair must occupy a *p* orbital, and therefore, each nitrogen atom must be sp^2 hybridized. As such, each nitrogen atom is trigonal planar.

2.59.

(a) This compound exhibits a lone pair next to a π bond, so we draw two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, the lone pair is next to another π bond, so once again, we draw the two curved arrows associated with that pattern. The resulting resonance structure again exhibits a lone pair next to a π bond, so again we draw two curved arrows and the resulting resonance structure. Once again, there is a lone pair next to a π bond, which requires that we draw one final resonance structure, shown below. This last resonance structure is not the same as the original resonance structure, because of the locations in which the π bonds are drawn.

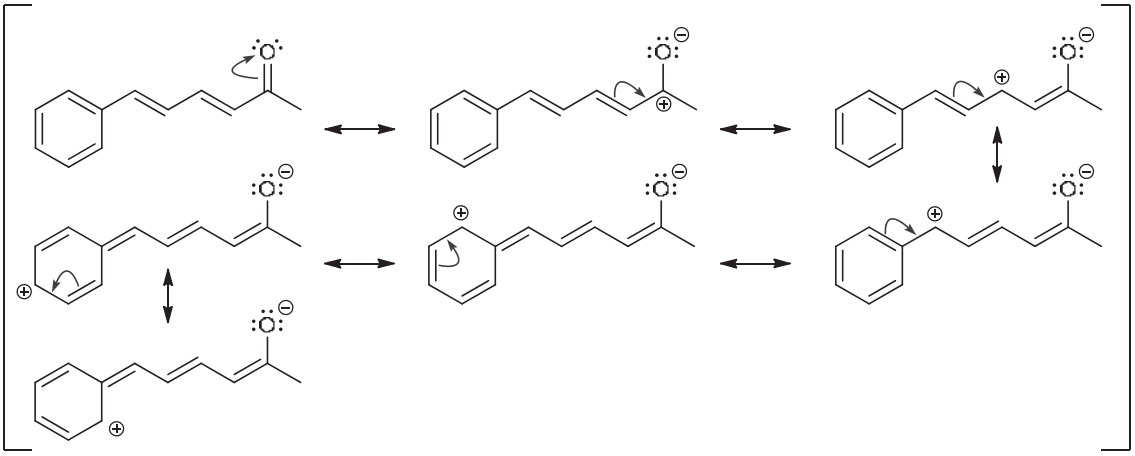


(b) The following compound exhibits a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is an allylic positive charge, so we draw the curved arrow associated with that pattern (pushing over the π bond), shown here:

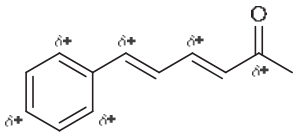


2.60. This compound exhibits a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is an allylic positive charge, so we draw the curved arrow associated with that pattern (pushing over the π bond), shown here. This pattern continues, many more times, spreading the positive charge over many locations:

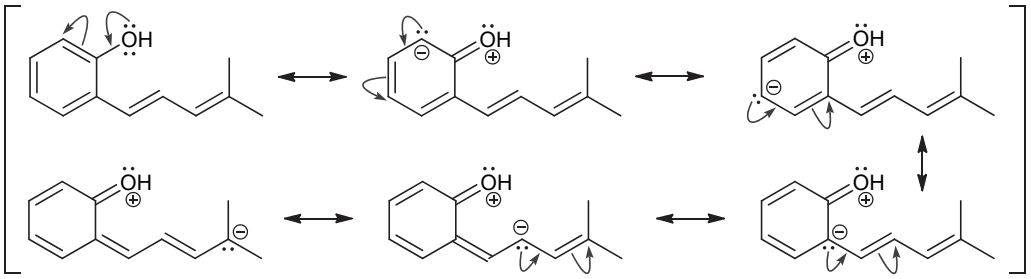
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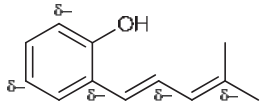
By considering the significant resonance structures (drawn above), we can determine the positions that are electron deficient (δ+). This information is summarized here.



2.61. This compound exhibits a lone pair next to a π bond, so we draw two curved arrows. The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is a lone pair next to a π bond, so once again, we draw the two curved arrows associated with that pattern. The resulting resonance structure again exhibits a lone pair next to a π bond. This pattern continues, many more times, spreading a negative charge over many locations:



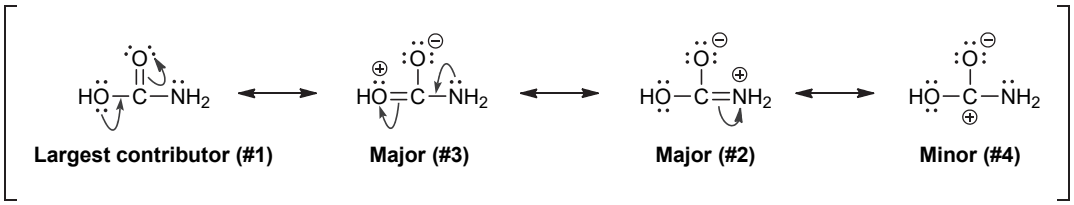
By considering the significant resonance structures (drawn above), we can determine the positions that are electron rich (δ–). This information is summarized here.



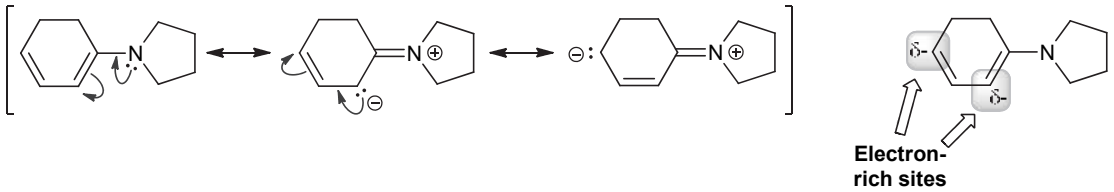
2.62. Two patterns of resonance can be identified on the given structure: carbonyl resonance and allylic lone pair resonance (involving either the oxygen or nitrogen lone pairs). All three of these options will be used. Since it is possible to start with any one of the three, you may have developed the resonance forms in a different order than presented here, but you still should have found four reasonable resonance forms. Only one of the four structures has an atom with an incomplete octet (the last resonance structure shown), so that is identified as the only minor contributor to the hybrid. The first resonance form is the largest contributor because it has filled octets and no formal charges. The middle two resonance structures both have filled octets and a negative charge on an oxygen atom, so they are ranked according to their only difference: the location of the positive charge. The third structure is the 2nd most significant resonance form because it has the positive charge on the less electronegative nitrogen atom. Note it is better to place a

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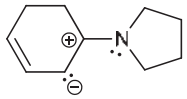
negative charge on a more electronegative atom, and it is better to place a *positive charge* on a less electronegative atom.



2.63. The only resonance pattern evident in the enamine is an allylic lone pair. After that pattern is applied, however, another allylic lone pair results so the resonance can ultimately involve both π bonds. There are a total of three major resonance forms that all have filled octets. Consideration of the hybrid of these resonance forms predicts two electron-rich sites.

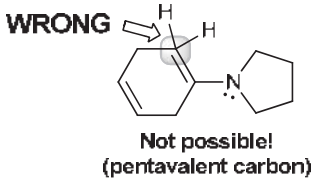


Did you draw the following additional structure (or something similar, with C+ and C-) and wonder why it was not shown in this solution?



This resonance form suffers from two major deficiencies: 1) it does not have filled octets, while the other resonance forms shown above all have filled octets, and 2) it has a negative charge on a carbon atom (which is not an electronegative atom). Either of these deficiencies alone would render the resonance form a minor contributor. But with both deficiencies together (C+ and C-), this resonance form is insignificant. The same is true for any resonance form that has both C+ and C-. Such a resonance form will generally be insignificant (there are very few exceptions, one of which will be seen in Chapter 17).

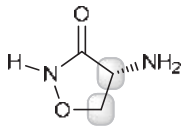
Also, note that the π bonds cannot be moved to other parts of the six-membered ring since the CH_2 groups are sp^3 hybridized. These carbon atoms cannot accommodate an additional bond without violating the octet rule.



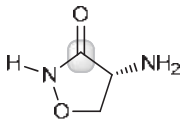
2.64.

(a) The molecular formula is $C_3H_6N_2O_2$.

(b) Each of the highlighted carbon atoms (below) has four sigma bonds (the bonds to hydrogen are not shown). As such, these two carbon atoms are sp^3 hybridized.

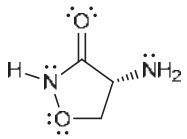


(c) There is one carbon atom that is using a *p* orbital to form a π bond. As such, this carbon atom (highlighted) is sp^2 hybridized.

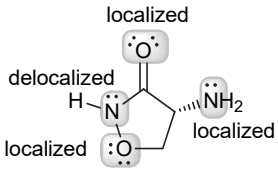


(d) There are no *sp* hybridized carbon atoms in this structure.

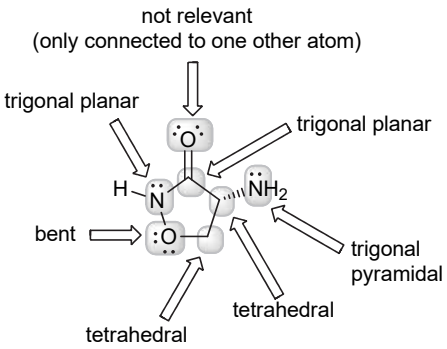
(e) There are six lone pairs (each nitrogen atom has one lone pair and each oxygen atom has two lone pairs):



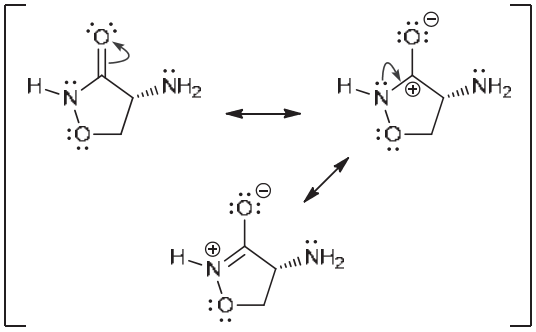
(f) Only the lone pair on one of the nitrogen atoms is delocalized via resonance (to see why it is delocalized, see the solution to 2.64h). The other lone pairs are all localized.



(g) The geometry of each atom is shown below (see SkillBuilder 1.8):



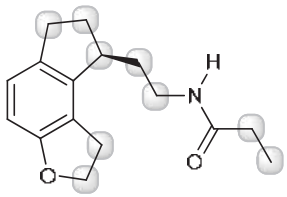
(h) We begin by looking for one of the five patterns that employs just one curved arrow (in this case, there is another pattern that requires two curved arrows, but we will start with the pattern using just one curved arrow). There is a C=O bond (a π bond between two atoms of differing electronegativity), so we draw one curved arrow showing the π bond becoming a lone pair. We then draw the resulting resonance structure and assess whether it exhibits one of the five patterns. In this case, there is a lone pair adjacent to a positive charge, so we draw the curved arrow associated with that pattern (showing the lone pair becoming a π bond), shown here:



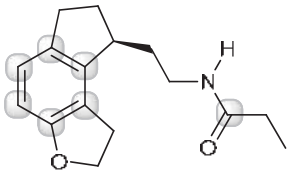
2.65.

(a) The molecular formula is $C_{16}H_{21}NO_2$.

(b) Each of the highlighted carbon atoms (below) has four sigma bonds (the bonds to hydrogen are not shown). As such, these nine carbon atoms are sp^3 hybridized.

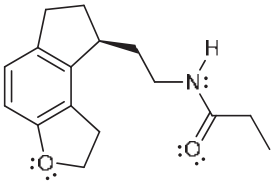


(c) There are seven carbon atoms that are each using a *p* orbital to form a π bond. As such, these seven carbon atoms (highlighted) are sp^2 hybridized.



(d) There are no *sp* hybridized carbon atoms in this structure.

(e) There are five lone pairs (the nitrogen atom has one lone pair and each oxygen atom has two lone pairs):



(f) The lone pairs on the oxygen of the C=O bond are localized. One of the lone pairs on the other oxygen atom is delocalized via resonance. The lone pair on the nitrogen atom is delocalized via resonance.

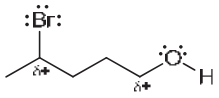
(g) All sp^2 hybridized carbon atoms are trigonal planar. All sp^3 hybridized carbon atoms are tetrahedral. The nitrogen atom is trigonal planar. The oxygen atom of the C=O bond does not have a geometry because it is

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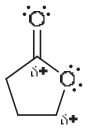
connected to only one other atom, and the other oxygen atom has bent geometry (see SkillBuilder 1.8).

2.66.

(a) In Section 1.5, we discussed inductive effects and we learned how to identify polar covalent bonds. In this case, there are two carbon atoms that participate in polar covalent bonds (the C–Br bond and the C–O bond). Each of these carbon atoms will be poor in electron density (δ+) because oxygen and bromine are each more electronegative than carbon:

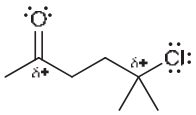


(b) There are two carbon atoms that are adjacent to oxygen atoms. These carbon atoms will be poor in electron density (δ+), because oxygen is more electronegative than carbon:



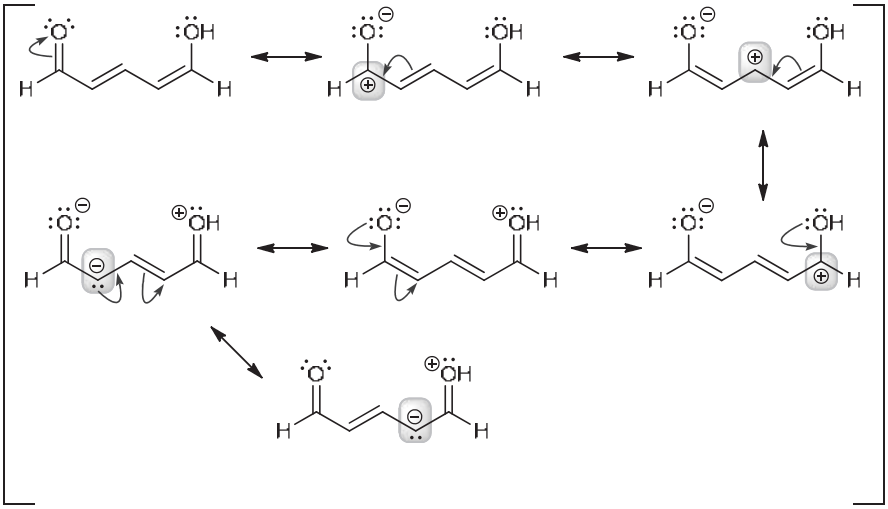
The carbon atom of the carbonyl (C=O) group is especially electron deficient, as a result of resonance.

(c) There are two carbon atoms that are adjacent to electronegative atoms. These carbon atoms will be poor in electron density (δ+), because oxygen and chlorine are each more electronegative than carbon:

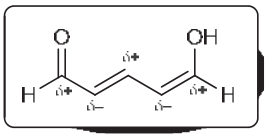


The carbon atom of the carbonyl (C=O) group is especially electron deficient, as a result of resonance.

2.67. We begin by drawing all significant resonance structures, and then considering the placement of the formal charges in each of those resonance structures (highlighted below)



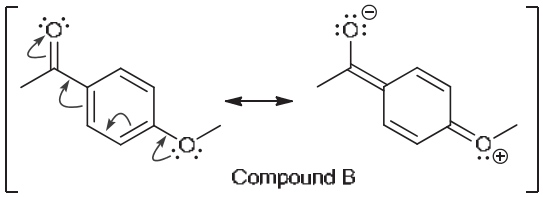
A position that bears a positive charge is expected to be electron deficient (δ+), while a position that bears a negative charge is expected to be electron rich (δ–). The following is a summary of the electron-deficient positions and the electron-poor positions, as indicated by the resonance structures above.



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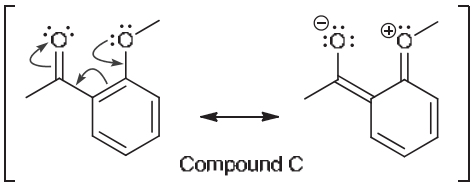
2.68.

(a) Compound **B** has one additional resonance structure that compound **A** lacks, because of the relative positions of the two groups on the aromatic ring. Specifically, compound **B** has a resonance structure in which one oxygen atom has a negative charge and the other oxygen atom has a positive charge:



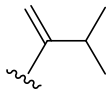
Compound **A** does *not* have a significant resonance structure in which one oxygen atom has a negative charge and the other oxygen atom has a positive charge. That is, compound **A** has fewer resonance structures than compound **B**. Accordingly, compound **B** has greater resonance stabilization.

(b) Compound **C** is expected to have resonance stabilization similar to that of compound **B**, because compound **C** also has a resonance structure in which one oxygen atom has a negative charge and the other oxygen atom has a positive charge:

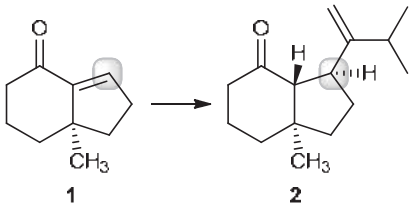


2.69.

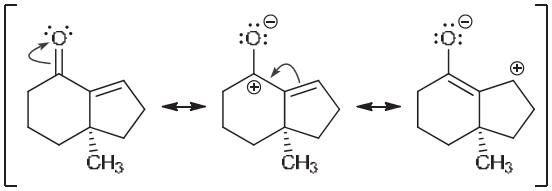
(a) The following group is introduced, and it contains five carbon atoms:



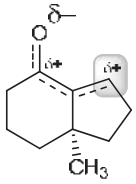
(b) The following highlighted carbon atom is involved in the reaction:



(c) Compound **1** has three significant resonance structures, shown here:

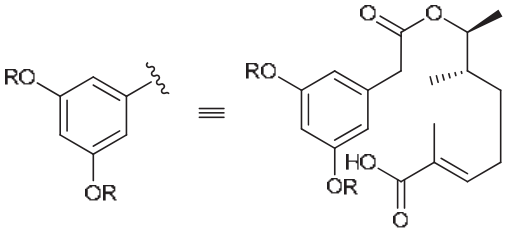


The structure on the left is the most significant, because every atom has an octet and it has no formal charges. The resonance hybrid is a weighted average of these three resonance structures. Since the partial positive charge is delocalized onto two carbon atoms and the partial negative charge is localized on only one oxygen atom, the partial negative charge is drawn larger than each of the individual partial positive charges.

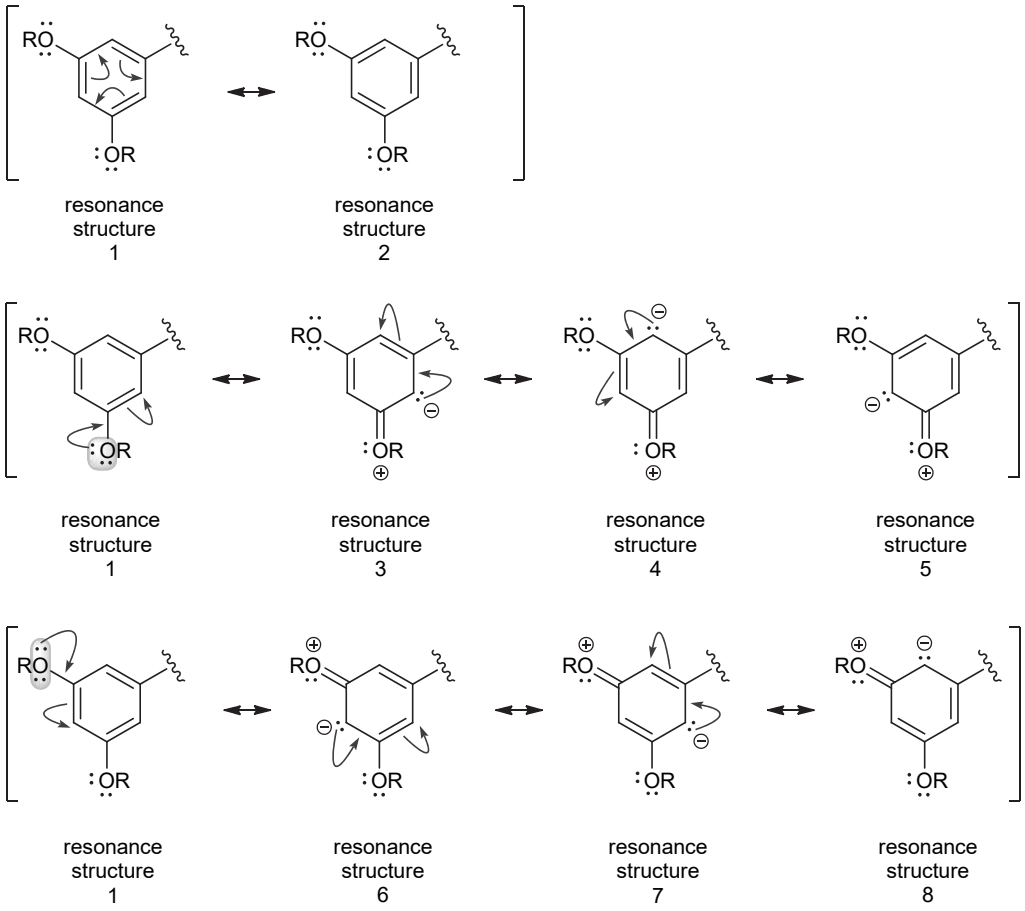


(d) The reactive site has partial positive character, which means that it is electron deficient. This is what makes it reactive. In the actual synthesis, this compound is treated with a carbanion (a structure containing a carbon atom with a negative charge). The reaction causes formation of a bond between the electron-deficient carbon atom and the electron-rich carbon atom. We will learn that reaction in Chapter 21.

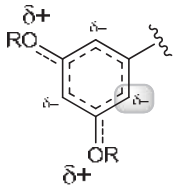
2.70. We will need to draw two resonance hybrids, one for each of the highlighted carbon atoms. One highlighted position is part of an aromatic ring, and we will begin by focusing on that position. In doing so, we can save time by redrawing only the relevant portion of the molecule, like this:



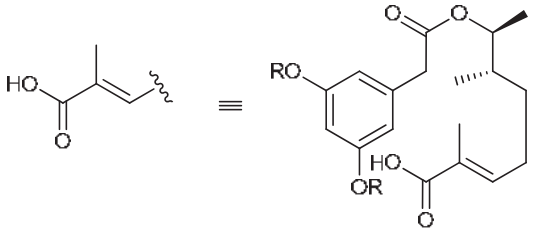
This aromatic ring has eight significant resonance structures, shown below:



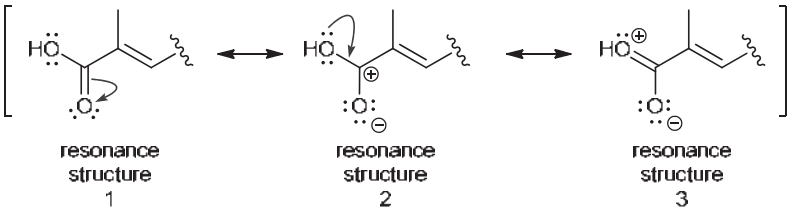
The resonance hybrid is a weighted average of these eight resonance structures. Resonance structures **1** and **2** are equally most significant because all atoms have an octet AND there are no formal charges. Resonance structures **3-8** are less significant than **1** and **2** but equally significant to each other because every atom has a full octet with a positive charge on an oxygen atom and a negative charge on a carbon atom. Since the partial negative charge is delocalized onto three carbon atoms and the partial positive charge is delocalized onto only two oxygen atoms, the partial positive charges are drawn slightly larger than the partial negative charges. The analysis allows us to draw the resonance hybrid for this portion of the molecule, and it demonstrates that the highlighted carbon atom is δ-.

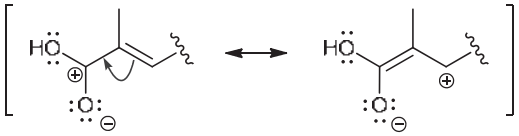


Now let's focus on our attention on the other highlighted carbon atom (the one that is part of a carboxylic acid group). Just as we did before, we will draw only the portion of the molecule that is of interest:

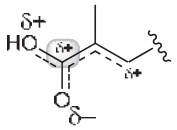


This portion of the molecule has four significant resonance structures, shown below:

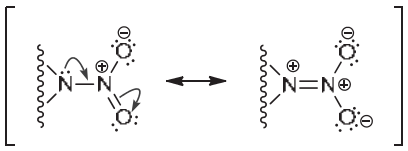




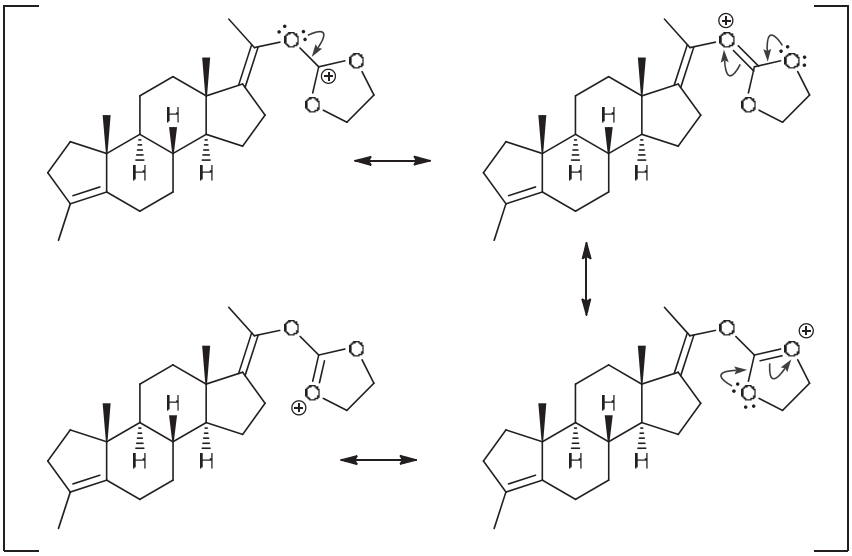
The resonance hybrid is a weighted average of these four resonance structures. Resonance structure **1** is most significant because all atoms have an octet AND there are no formal charges. Resonance structure **3** is the next most significant because there are formal charges, yet every atom has a full octet. Since the partial negative charge is localized on one oxygen atom, this partial charge is the largest. The partial positive charge is delocalized over three atoms, but it is larger on the oxygen (relative to either of the carbon atoms). The resonance hybrid demonstrates that this carbon atom is δ+.



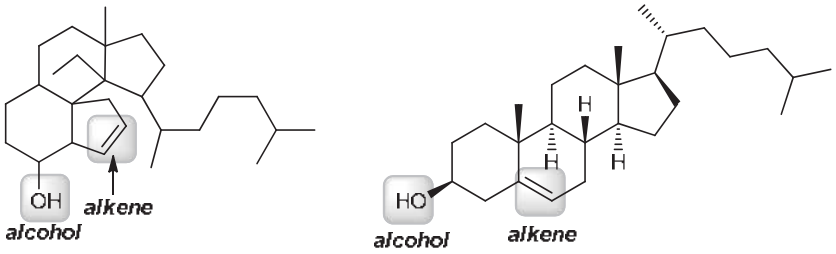
2.71.
(a) The molecular formula for CL-20 is $C_6H_6N_{12}O_{12}$. The molecular formula for HMX is $C_4H_8N_8O_8$.
(b) The lone pair is delocalized (see resonance structures below).



2.72.
This intermediate is highly stabilized by resonance. The positive charge is spread over one carbon atom and three oxygen atoms.

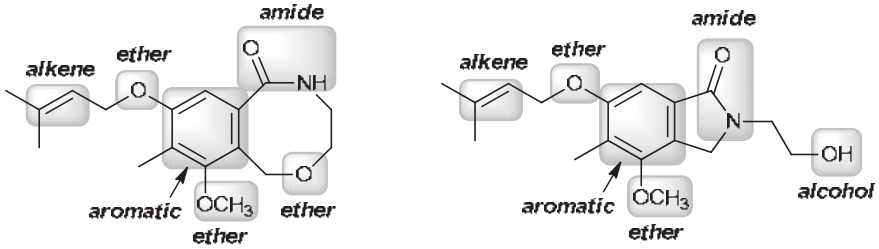


2.73.
(a) Both molecules have identical functional groups (alcohol + alkene).



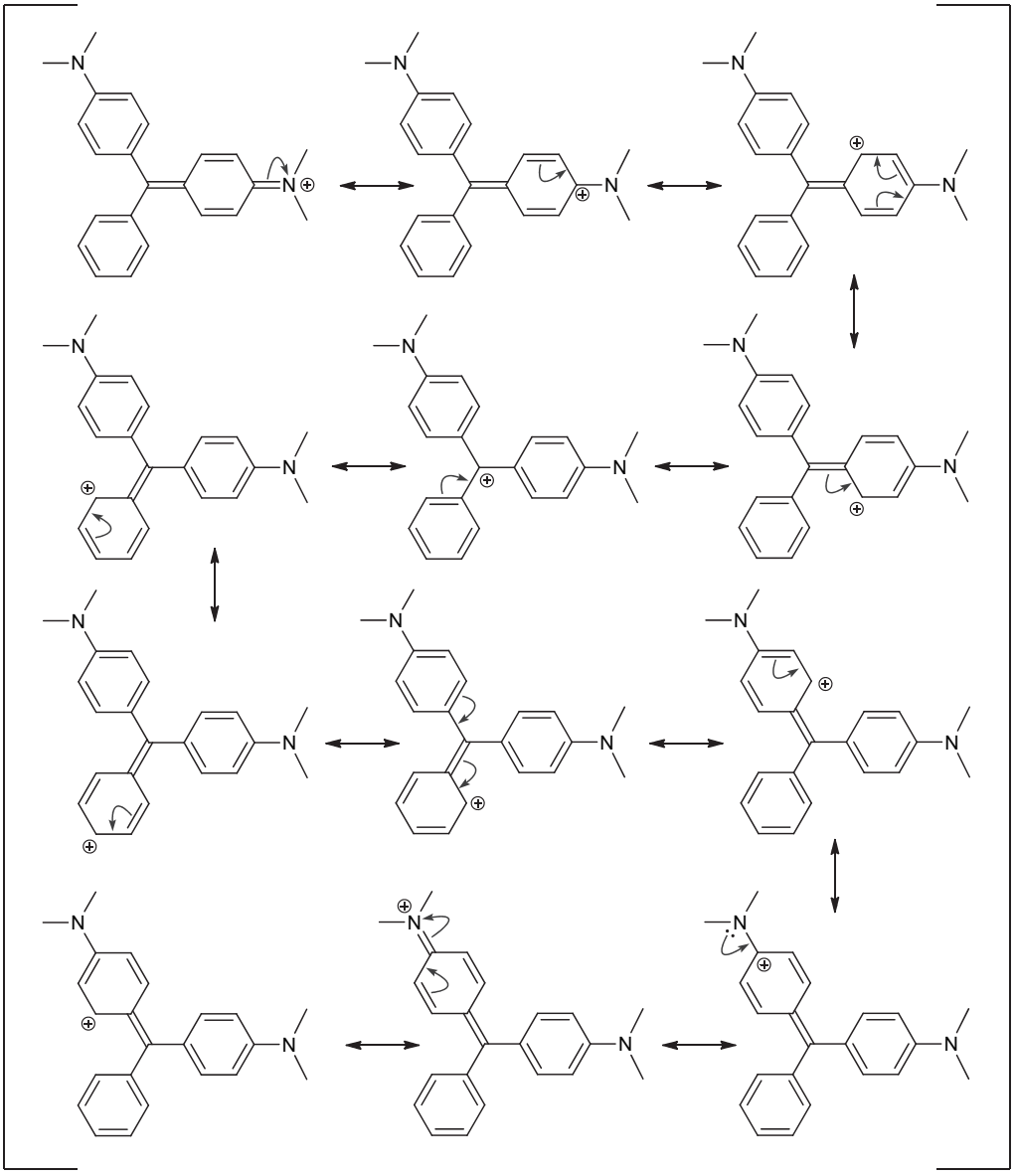
The structure on the left exhibits two six-membered rings and two five-membered rings, while the structure on the right has three six-membered rings and only one five-membered ring.
The long alkane group is apparently located in the wrong position on the five-membered ring of the incorrect structure.

(b) Both structures contain an alkene group, an aromatic ring, an amide group, and two ether functional groups. But the incorrect structure has a third ether functional group (in the eight-membered ring), while the correct structure has an alcohol functional group. The incorrect structure has an eight-membered ring, while the correct structure has a five-membered ring. The two carbon atoms and oxygen atom in the ring of the incorrect structure are not part of the ring for the correct structure.



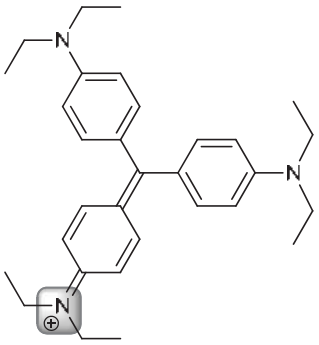
2.74.

(a) The positive charge in basic green 4 is resonance-stabilized (delocalized) over twelve positions (two nitrogen atoms and ten carbon atoms), as seen in the following resonance structures.



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(b) The positive charge in basic violet 4 is expected to be more stabilized than the positive charge in basic green 4, because the former is delocalized over thirteen positions, rather than twelve. Specifically, basic violet 4 has an additional resonance structure that basic green 4 lacks, shown below:



In basic violet 4, the positive charge is spread over ***three*** nitrogen atoms and ten carbon atoms.

2.75. Polymer 2 contains only ester groups, so the IR spectrum of polymer **2** is expected to exhibit a signal near 1740 cm^{-1} (typical for esters), associated with vibrational excitation (stretching) of the C=O bond. Polymer **4** lacks any ester groups, so the signal near 1740 cm^{-1} is expected to be absent in the IR spectrum of polymer **4**. Instead, polymer **4** has OH groups, which are expected to produce a broad signal in the range 3200-3600 cm^{-1}. Polymer **3** has both functional groups (alcohol group and ester group), so an IR spectrum of polymer **3** is expected to exhibit both characteristic signals. When polymer **3** is converted to polymer **4**, the signal near 1740 cm^{-1} is expected to vanish, which would indicate complete hydrolysis of polymer **3**.

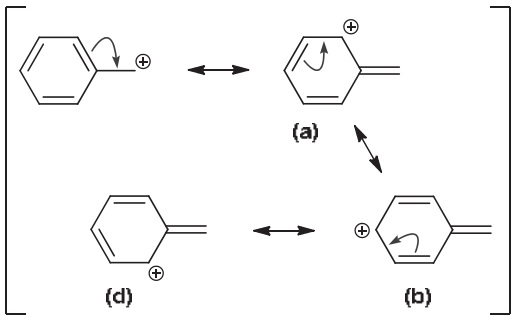
In practice, the signal for the C=O stretch in polymer 2 appears at 1733 cm^{-1}, which is very close to our estimated value of 1740 cm^{-1}.

2.76. Compound **1** has an OH group, which is absent in compound **2**. Therefore, the IR spectrum of **1** should exhibit a broad signal in the range 3200-3600 cm^{-1} (associated with O-H stretching), while the IR spectrum of **2** would be expected to lack such a signal. The conversion of **1** to **2** could therefore be confirmed with the disappearance of the signal corresponding with excitation of the O-H bond.

Another way to monitor the conversion of **1** to **2** is to focus on the C-H bond of the aldehyde group in compound **1**, which is expected to produce a signal in the range 2750-2850 cm^{-1}. Since the aldehyde group is not present in compound **2**, we expect this signal to vanish when **1** is converted to **2**.

There is yet another way to monitor this reaction with IR spectroscopy. Compound **1** possesses only one C=O bond, while compound **2** has two C=O bonds. As such, the latter should exhibit two C=O signals. One signal is expected to be near 1680 cm^{-1} (for the conjugated ketone), and the other signal should be near 1700 cm^{-1} (corresponding to the conjugated ester). In contrast compound **1** has only one C=O bond, which is expected to produce a signal near 1680 cm^{-1} (for the conjugated aldehyde). Therefore, the conversion of **1** to **2** can be monitored by the appearance of a signal near 1700 cm^{-1}.

2.77. Structures (a), (b) and (d) are all significant resonance structures, as shown:

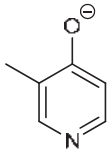


Structure (c) is not a resonance form at all. To see this more clearly, notice that the benzyl carbocation does not have any CH_2 groups in the ring, but structure (c) does have a CH_2 group in the ring:

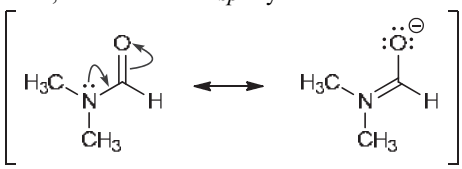


Resonance structures differ only in the placement of electrons. Since structure (c) differs in the connectivity of atoms, it cannot be considered a resonance structure of the benzyl carbocation. Therefore, the answer is (c).

2.78. The atoms in all four structures have complete octets. So we must consider the location of the negative charge. Structure (a) has a negative charge on an electronegative atom (oxygen). A negative charge is more stable on the more electronegative atom (oxygen) than it is on a nitrogen atom or a carbon atom. Therefore, structure (a) will contribute the most character to the resonance hybrid:

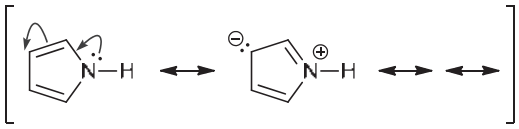


2.79. The nitrogen atom in structure (a) is delocalized by resonance, and is therefore sp^2 hybridized:

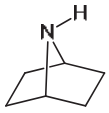


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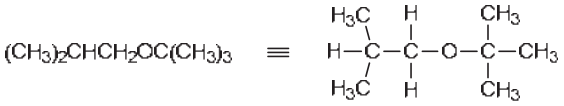
The nitrogen atom in structure (b) is also delocalized, so it is sp^2 hybridized as well:



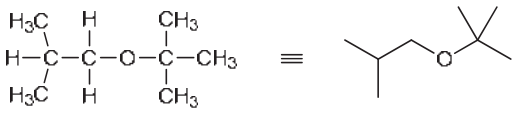
The nitrogen atom in structure (c) is also sp^2 hybridized, because this nitrogen atom must be using a *p* orbital to participate in π bonding (C=N). The nitrogen atom in structure (d) has three σ bonds, and its lone pair is localized. Therefore, this nitrogen atom is sp^3 hybridized:



2.80. We begin by considering all bonds in the compound, which is easier to do if we redraw the compound as shown:

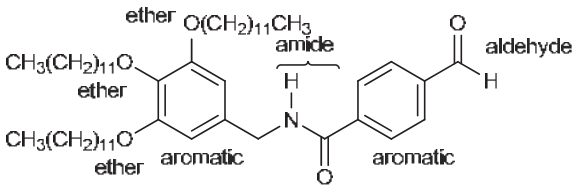


This compound corresponds to structure (c):

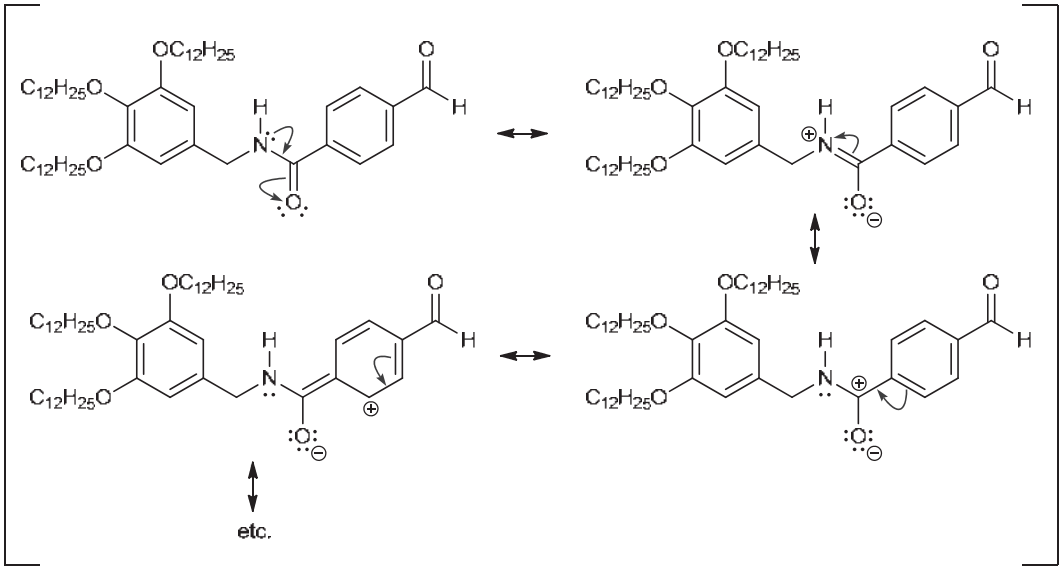


2.81.

(a) This compound contains the following functional groups:



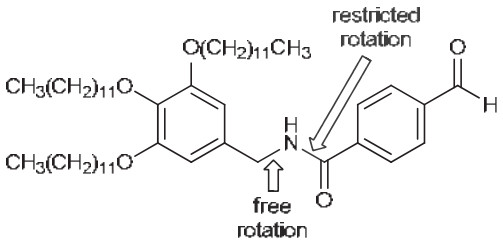
(b) The nitrogen atom has a lone pair that is delocalized via resonance:



In the second resonance structure shown, the C-N bond is drawn as a double bond, indicating partial double-bond character. This bond is thus a hybrid between a single and double bond; the partial double bond character results in

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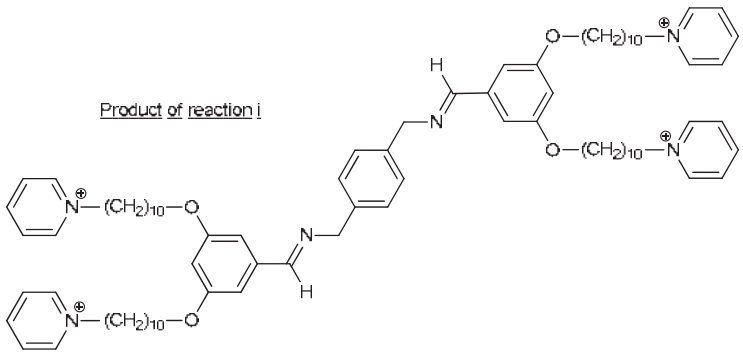
partially restricted rotation around this bond. In contrast, the C-N bond on the left experiences free rotation because that bond has only single-bond character.



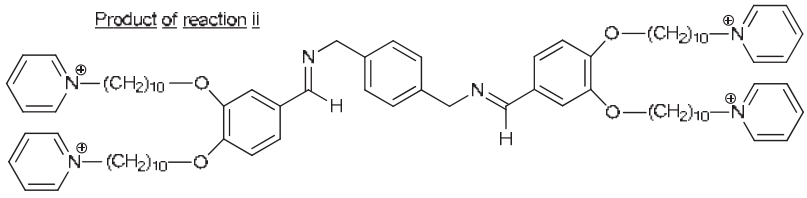
2.82.

(a) For each of the four reactions (i–iv), the product should have two imine groups, resulting from the reaction between a compound with two amino groups (**B** or **C**) with two equivalents of an aldehyde (**A** or **D**).

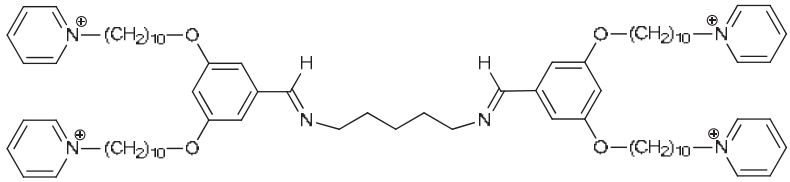
Product of reaction i



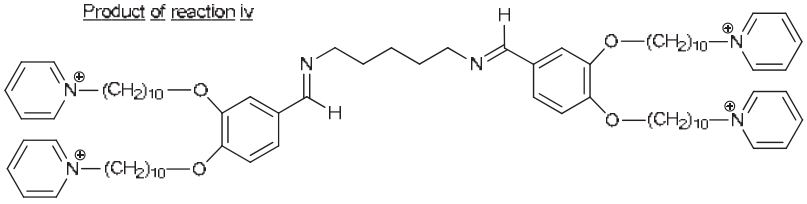
Product of reaction ii



Product of reaction iii



Product of reaction iv

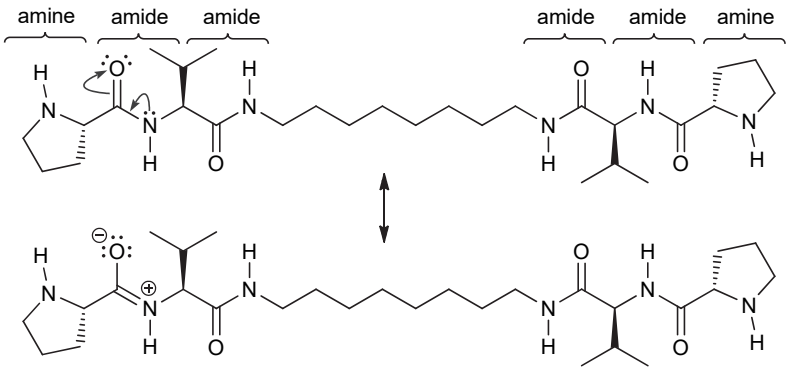


(b) The products of reactions iii and iv are constitutional isomers of each other. These products have the same molecular formula, but differ in their relative connectivity on the two central aromatic rings.

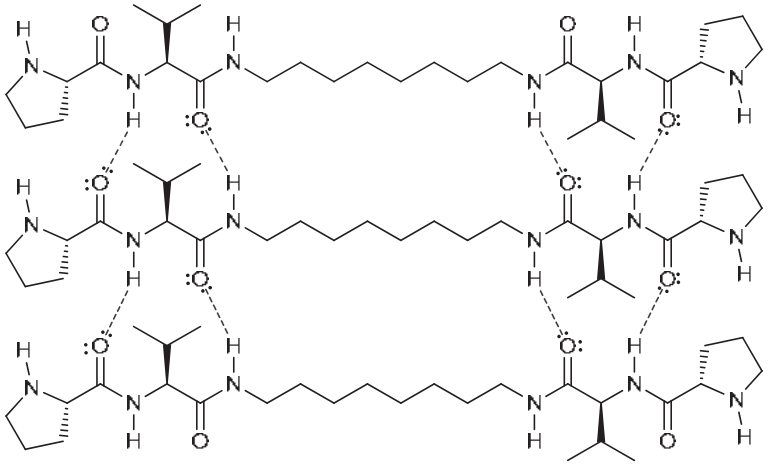
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2.83.

(a) Each of the four amides can be represented as a resonance hybrid (one example shown below). The charge-separated resonance structure indicates that there is a δ+ on the amide nitrogen, which thus pulls the electrons in the N-H bond closer to the nitrogen atom, leaving the hydrogen atom with a greater δ+. This resonance effect is not present in the N-H bond of the amines. Thus, the δ+ on an amide H is greater than that on an amine H, leading to a stronger hydrogen bond.

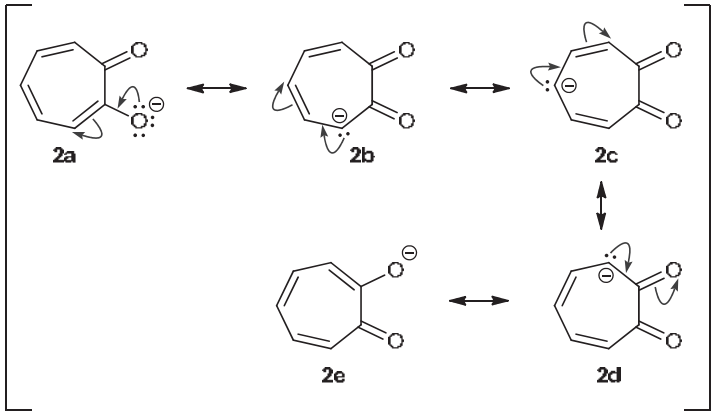


(b) The following intermolecular hydrogen bonds are formed during self-assembly:



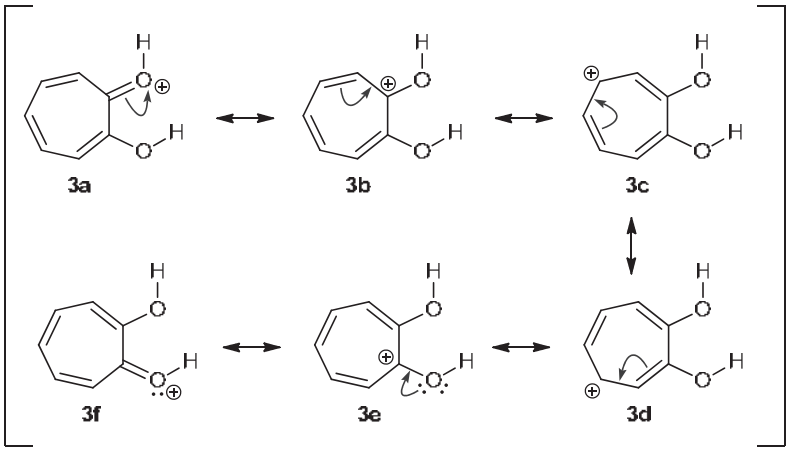
2.84.

(a) Anion **2** is highly stabilized by resonance (the negative charge is delocalized over two oxygen atoms and three carbon atoms). The resonance structures for **2** are as follows:

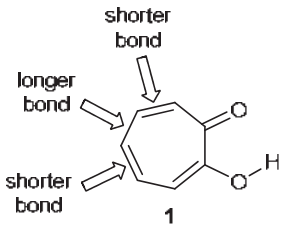


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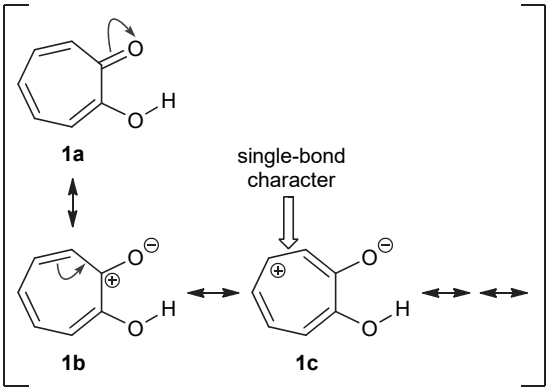
Cation **3** is highly stabilized by resonance (the positive charge is delocalized over two oxygen atoms and four carbon atoms). The resonance structures of **3** are as follows:



(b) Double bonds are shorter in length than single bonds (see Table 1.2). As such, the C-C bonds in compound **1** will alternate in length (double, single, double, etc.):

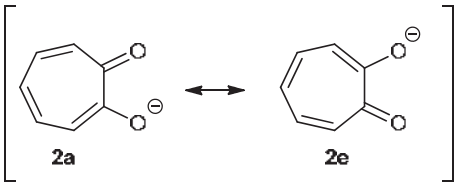


The double bonds do have some single-bond character as a result of resonance, as can be seen in resonance structure **1c**:



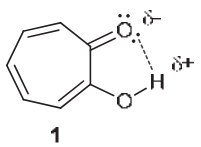
Similarly, the single bonds have some double-bond character, also because of resonance. However, this effect is relatively small, because there is only one resonance structure (**1a** above) in which all atoms have an octet AND there are no formal charges. Therefore, it is the greatest contributor to the overall resonance hybrid. As such, the double bonds have only a small amount of single-bond character, and the single bonds have only a small amount of double-bond character.

In contrast, anion **2** does not have a resonance structure that lacks charges. All resonance structures of **2** bear a negative charge. Among the resonance structures, two of them (**2a** and **2e**) contribute the most character to the overall resonance hybrid, because the negative charge is on an electronegative oxygen atom (rather than carbon).



In fact, these two resonance contributors will contribute equally to the overall resonance hybrid. As such, the bonds of the ring will be very similar in length, because they have both single-bond character and double-bond character in equal amounts. A similar argument can be made for compound **3**.

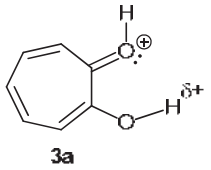
(c) In compound **1**, a hydrogen bonding interaction occurs between the proton of the OH group and the oxygen atom of the C=O bond:



This interaction is the result of the attraction between partial charges (δ+ and δ-). However, in cation **3**, a similar type of interaction is less effective because the O of the C=O bond is now poor in electron density, and

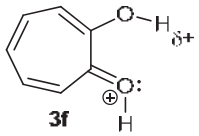
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therefore less capable of forming a hydrogen bonding interaction, as can be seen in resonance structure **3a**.



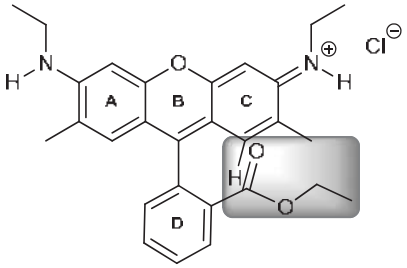
3a

The other oxygen atom is also ineffective at forming an intramolecular hydrogen bond because it too is poor in electron density, as can be seen in resonance structure **3f**:

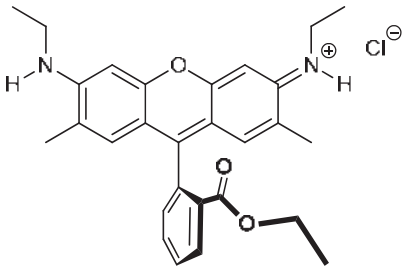


3f

2.85. In order for all four rings to participate in resonance stabilization of the positive charge, the *p* orbitals in the four rings must all lie in the same plane (to achieve effective overlap). In the following drawing, the four rings are labeled A-D. Notice that the D ring bears a large substituent (highlighted) which is trying to occupy the same space as a portion of the C ring:



This type of interaction, called a steric interaction, forces the D ring to twist out of plane with respect to the other three rings, like this:



In this way, the overlap between the *p* orbitals of the D ring and the *p* orbitals of the other three rings is expected to be less effective. As such, participation of the D ring in resonance stabilization is expected to be diminished with respect to the participation of the other three rings.

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Chapter 3
Acids and Bases

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 3. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- A **Brønsted-Lowry acid** is a proton _____, while a **Brønsted-Lowry base** is a proton _____.
- A **reaction mechanism** utilizes curved arrows to show the flow of _____ that account for a chemical reaction.
- The mechanism of **proton transfer** always involves at least _____ curved arrows.
- A strong acid has a _____ pK_a, while a weak acid has a _____ pK_a.
- There are four factors to consider when comparing the _____ of conjugate bases.
- The equilibrium of an acid-base reaction always favors the more _____ negative charge.
- A **Lewis acid** is an electron-pair _____, while a **Lewis base** is an electron-pair _____.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 3. The answers appear in the section entitled *SkillBuilder Review*.

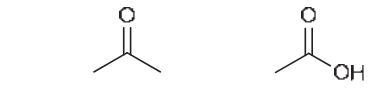
SkillBuilder 3.1 Drawing the Mechanism of a Proton Transfer

DRAW THE CURVED ARROWS FOR THE FOLLOWING ACID-BASE REACTION



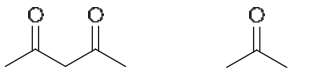
SkillBuilder 3.2 Using pK_a Values to Compare Acids

CIRCLE THE COMPOUND BELOW THAT IS MORE ACIDIC



SkillBuilder 3.3 Using pK_a Values to Compare Basicity

COMPARE THE FOLLOWING pK_a VALUES:

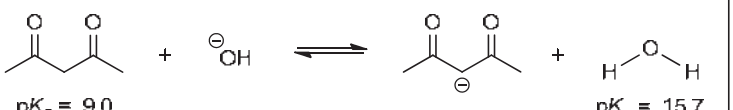


AND CIRCLE THE STRONGER BASE BELOW



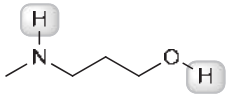
SkillBuilder 3.4 Using pK_a Values to Predict the Position of Equilibrium

CIRCLE THE SIDE OF THE EQUILIBRIUM THAT IS FAVORED:



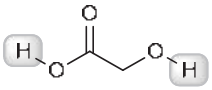
SkillBuilder 3.5 Assessing Relative Stability. Factor #1: Atom

COMPARE THE TWO HIGHLIGHTED PROTONS, AND CIRCLE THE ONE THAT IS MORE ACIDIC. USE THE EXTRA SPACE TO DRAW THE TWO POSSIBLE CONJUGATE BASES.



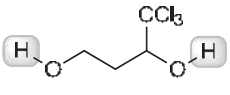
SkillBuilder 3.6 Assessing Relative Stability. Factor #2: Resonance

COMPARE THE TWO HIGHLIGHTED PROTONS. AND CIRCLE THE ONE THAT IS MORE ACIDIC. USE THE EXTRA SPACE TO DRAW THE TWO POSSIBLE CONJUGATE BASES.



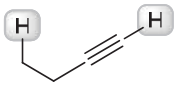
SkillBuilder 3.7 Assessing Relative Stability. Factor #3: Induction

COMPARE THE TWO HIGHLIGHTED PROTONS, AND CIRCLE THE ONE THAT IS MORE ACIDIC. USE THE EXTRA SPACE TO DRAW THE TWO POSSIBLE CONJUGATE BASES.



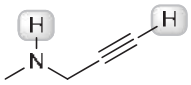
SkillBuilder 3.8 Assessing Relative Stability. Factor #4: Orbital

COMPARE THE TWO HIGHLIGHTED PROTONS, AND CIRCLE THE ONE THAT IS MORE ACIDIC. USE THE EXTRA SPACE TO DRAW THE TWO POSSIBLE CONJUGATE BASES.



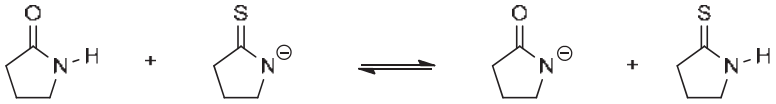
SkillBuilder 3.9 Assessing Relative Stability. Using All Four Factors

COMPARE THE TWO HIGHLIGHTED PROTONS, AND CIRCLE THE ONE THAT IS MORE ACIDIC. USE THE EXTRA SPACE TO DRAW THE TWO POSSIBLE CONJUGATE BASES.



SkillBuilder 3.10 Predicting the Position of Equilibrium Without the Use of pK_a Values

CIRCLE THE SIDE OF THE EQUILIBRIUM THAT IS FAVORED:



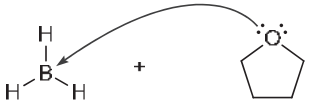
SkillBuilder 3.11 Choosing the Appropriate Reagent for a Proton Transfer Reaction

DETERMINE WHETHER WATER IS A SUITABLE PROTON SOURCE TO PROTONATE THE ACETATE ION, AS SHOWN BELOW:



SkillBuilder 3.12 Identifying Lewis Acids and Lewis Bases

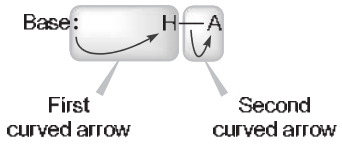
IDENTIFY THE LEWIS ACID AND THE LEWIS BASE IN THE FOLLOWING REACTION:



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Common Mistakes to Avoid

When drawing the mechanism of a proton transfer, two curved arrows are required. The first curved arrow shows the base attacking the proton, and the second curved arrow shows the bond to H being broken.



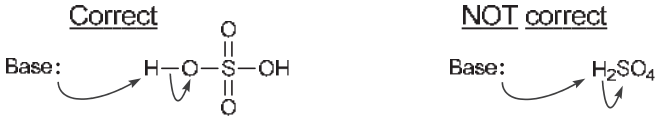
It is a common mistake to draw only the first curved arrow and not the second, so make sure to draw both curved arrows. When drawing the second curved arrow, make sure that the tail is placed on the middle of the bond to the H, as shown:



When the acid is H_3O^+, you must draw at least one of the O–H bonds in order to draw the second curved arrow properly.



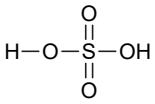
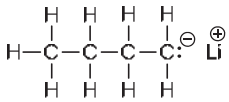
This is also the case for other acids:



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Useful reagents

In Chapter 3, we explored the behavior of acids and bases. Throughout the remainder of the textbook, many acids and bases will be frequently encountered. It would be wise to become familiar with the following reagents (and their uses), as they will appear many times in the upcoming chapters:

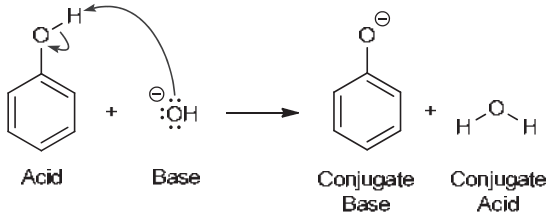
Structure	Name	Use
	Sulfuric acid	A very strong acid. Commonly used as a source of protons. Concentrated sulfuric acid is an aqueous mixture of H_2SO_4 and H_2O, and the acid present in solution is actually H_3O^+, because of the leveling effect. That is, H_3O^+ is a weaker acid than H_2SO_4, so the protons are transferred from H_2SO_4 to water, giving a high concentration of H_3O^+.
	Hydrochloric acid	A very strong acid. Similar in function to H_2SO_4. In an aqueous solution of HCl, the acid that is present is H_3O^+, because of the leveling effect, as described above for H_2SO_4.
	Acetic acid	A weak acid. Mild source of protons.
	Water	A weak acid and a weak base. It can function as either, depending on the conditions. When treated with a strong base, water will function as an acid (a source of protons). When treated with a strong acid, water will function as a base and remove a proton from the strong acid.
	An alcohol	R represents the rest of the compound. Alcohols are compounds that possess an O-H group, and will be the subject of Chapter 12. Alcohols can function very much like water (either as weak acids or as weak bases).
	Ammonia	A fairly strong base, despite the absence of a negative charge. It is a strong base, because its conjugate acid (NH_4^+), called an ammonium ion, is a weak acid ($pK_a = 9.2$).
CH_3CH_2ONa	Sodium ethoxide	The ethoxide ion ($CH_3CH_2O^-$) is a strong base, and Na^+ is the counterion. Other alkoxide ions (RO^-), such as methoxide (CH_3O^-), are also strong bases.
$NaNH_2$	Sodium amide	H_2N^- is a very strong base, and Na^+ is the counterion.
	Butyllithium	An extremely strong base. This is one of the strongest bases that you will encounter.

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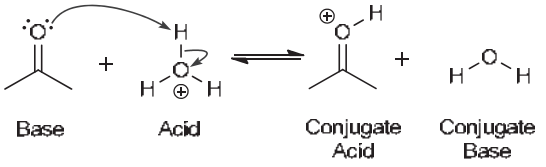
Solutions

3.1.

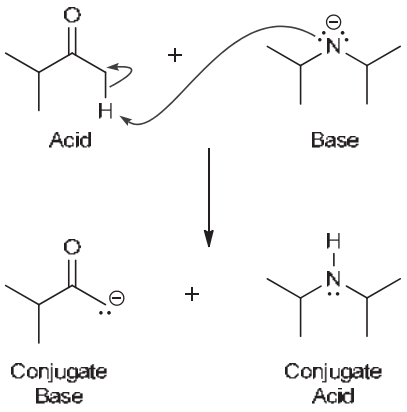
(a) Phenol (C_6H_5OH) loses a proton and is therefore functioning as an acid. Hydroxide (HO^-) functions as the base that removes the proton. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



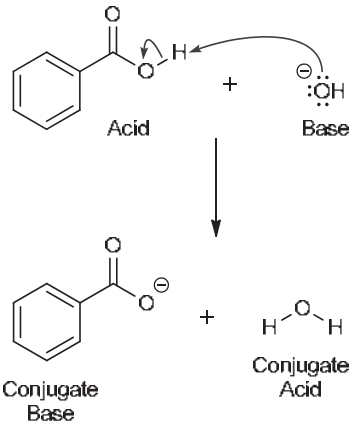
(b) H_3O^+ loses a proton and is therefore functioning as an acid. The ketone functions as the base that removes the proton. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton; the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



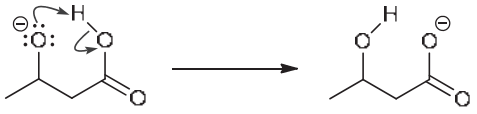
(c) The ketone loses a proton and is therefore functioning as an acid. The other reagent functions as the base that removes the proton. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the C–H bond (being broken) and goes to the carbon atom, as shown:



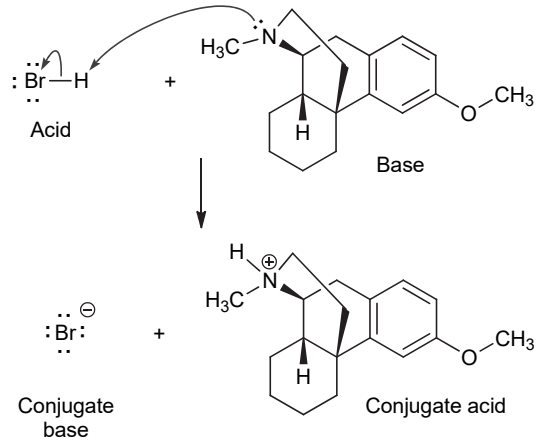
(d) Benzoic acid ($C_6H_5CO_2H$) loses a proton and is therefore functioning as an acid. Hydroxide (HO^-) functions as the base that removes the proton. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



3.2. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



3.3. The nitrogen atom is accepting a proton, so dextromethorphan is the base in this proton-transfer reaction, and HBr is the acid (proton donor). As usual, the mechanism involves two curved arrows. The salt product contains both the conjugate acid (protonated dextromethorphan) and the conjugate base (Br^-).



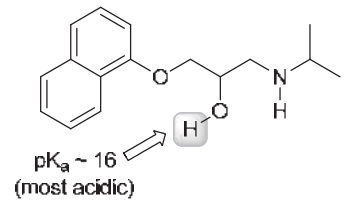
3.4.

(a) According to Table 3.1, phenol (C_6H_5OH) has a pK_a of 9.9, while water has a pK_a of 15.7. The former is more acidic because it has a lower pK_a value.

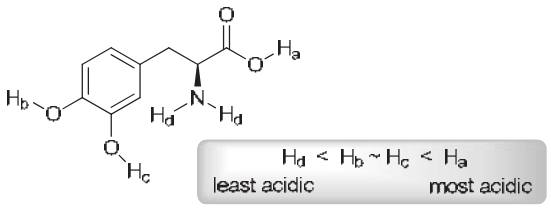
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(b) According to Table 3.1, $(CH_3)_3COH$ has a pK_a of 18, while water has a pK_a of 15.7. Water is more acidic because it has a lower pK_a value.
(c) According to Table 3.1, ammonia (NH_3) has a pK_a of 38, while acetylene (H–C≡C–H) has a pK_a of 25. As such, the latter is more acidic because it has a lower pK_a value.
(d) According to Table 3.1, H_3O^+ has a pK_a of -1.7, while HCl has a pK_a of -7. As such, the latter is more acidic because it has a lower pK_a value.
(e) According to Table 3.1, ethane (C_2H_6) has a pK_a of 50, while acetylene (H–C≡C–H) has a pK_a of 25. As such, the latter is more acidic because it has a lower pK_a value.
(f) According to Table 3.1, a protonated ketone (the first structure shown) has a pK_a of -7.3, while sulfuric acid (H_2SO_4) has a pK_a of -9. As such, the latter is more acidic because it has a lower pK_a value.

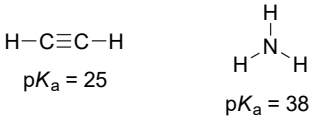
3.5. According to Table 3.1, the proton connected to the oxygen atom is expected to be the most acidic proton in the compound. That proton is expected to have a pK_a value near 16 (similar to CH_3CH_2OH). The proton connected to the nitrogen atom is expected to have a pK_a value near 38 (similar to NH_3).



3.6. According to Table 3.1, the proton of the carboxylic acid group (H_a below) is expected to be the most acidic (pK_a ~ 5). The two protons labeled H_b and H_c are expected to have a pK_a near 10 (like C_6H_5OH), and the protons labeled H_d are expected to have a pK_a near 38 (like NH_3). The order of acidity is shown below:



3.7.
(a) We first imagine protonating each base, and then we compare the pK_a values of the resulting compounds (using Table 3.1):



The first compound is more acidic because it has a lower pK_a value. As a result, the conjugate base of the first compound will be a weaker base than the conjugate base of the second compound:



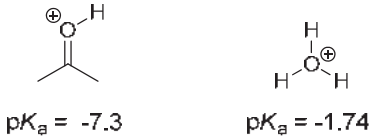
(b) We first imagine protonating each base, and then we compare the pK_a values of the resulting compounds (using Table 3.1):



The latter compound is more acidic because it has a lower pK_a value. As a result, the conjugate base of the latter compound will be a weaker base than the conjugate base of the former compound:



(c) We first imagine protonating each base, and then we compare the pK_a values of the resulting ions (using Table 3.1):



The former is more acidic because it has a lower pK_a value. As a result, the conjugate base of the former will be a weaker base than the conjugate base of the latter:



(d) We first imagine protonating each base, and then we compare the pK_a values of the resulting compounds (using Table 3.1):

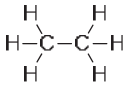


The former compound (water) is more acidic because it has a lower pK_a value. As a result, the conjugate base of the latter compound will be a stronger base than the conjugate base of water:

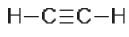


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(e) We first imagine protonating each base, and then we compare the pK_a values of the resulting compounds (using Table 3.1):

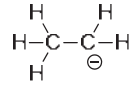


pK_a = 50

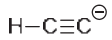


pK_a = 25

The latter compound is more acidic because it has a lower pK_a value. As a result, the conjugate base of the latter compound will be a weaker base than the conjugate base of the former compound:

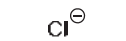


stronger base



weaker base

(f) We first imagine protonating each base, and then we compare the pK_a values of the resulting compounds (using Table 3.1). HCl has a pK_a of -7, while H_2O has a pK_a of 15.7. Since HCl has a lower pK_a value, it is more acidic than water (significantly). As a result, the conjugate base of HCl will be a much weaker base than the conjugate base of H_2O.

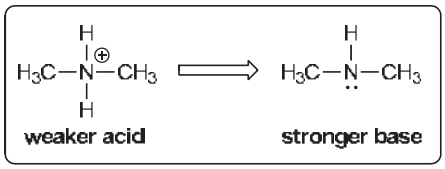


weaker base

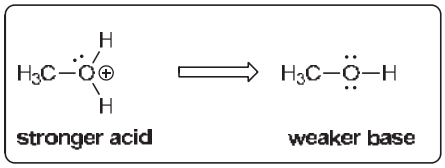


stronger base

3.8. The pK_a values indicate that a proton is more acidic when it is connected to a positively charged oxygen atom (pK_a ~ -2.2) than when it is connected to a positively charged nitrogen atom (pK_a ~ 10.6). The weaker acid ($R_2NH_2^+$) gives the stronger base upon deprotonation:

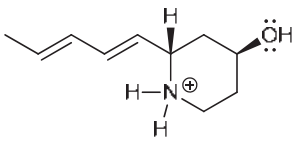


weaker acid stronger base



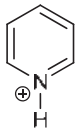
stronger acid weaker base

Therefore, in the structure of compound **1**, we expect that the lone pair on the nitrogen atom will be more basic than the lone pairs on the oxygen atom. When compound **1** is protonated, we expect the nitrogen atom to be protonated (rather than the oxygen atom) to give the following conjugate acid:

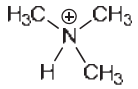


conjugate acid of 1

3.9. Inspection of structures **1** and **3** shows that the nitrogen atoms, and more specifically their lone pairs, serve as bases in the protonation of nicotine. In order to determine which nitrogen atom in structure **1** is more basic, we can compare the pK_a values for each of the acidic protons in structure **3**, using the pK_a table on the inside cover of the textbook:

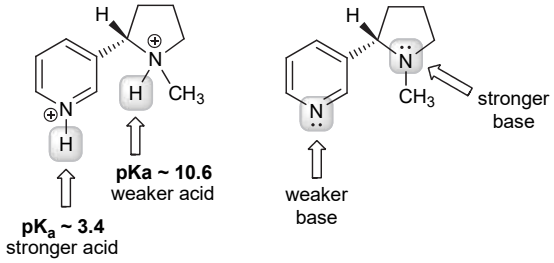


pK_a = 3.4

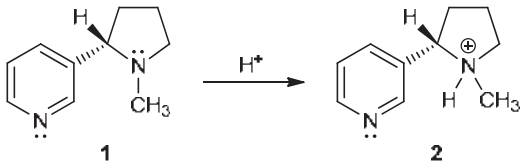


pK_a = 10.6

The second has a higher pK_a value, and is therefore a weaker acid. The weaker acid gives the stronger base upon deprotonation, so we expect the lone pair on the rightmost nitrogen atom (in structure **1**) to be more basic:



Therefore, when **1** is mono-protonated, the sp^3 hybridized nitrogen atom is protonated, as shown:



1 2

3.10.

(a) We begin by identifying the acid on each side of the equilibrium. In this case, the acid on the left side is ethanol (CH_3CH_2OH) and the acid on the right side is water (H_2O). We compare their pK_a values (Table 3.1), and we find that ethanol (pK_a = 16) is less acidic than water (pK_a = 15.7). The equilibrium will favor the weaker acid (ethanol).

(b) Identify the acid on each side of the equilibrium. In this case, the acid on the left side is phenol (C_6H_5OH) and the acid on the right side is water (H_2O). We compare their pK_a values (Table 3.1), and we find that water (pK_a = 15.7) is less acidic than phenol (pK_a = 9.9). The equilibrium will favor the weaker acid (water).

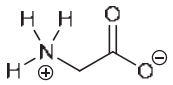
(c) Identify the acid on each side of the equilibrium. In this case, the acid on the left side is HCl and the acid on the right side is H_3O^+. We compare their pK_a values (Table 3.1), and we find that H_3O^+ (pK_a = -1.74) is less acidic than HCl (pK_a = -7). The equilibrium will favor the weaker acid (H_3O^+).

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(d) Identify the acid on each side of the equilibrium. In this case, the acid on the left side of the equilibrium is acetylene (H–C≡C–H), and the acid on the right side is ammonia (NH_3). We compare their pK_a values (Table 3.1), and we find that ammonia (pK_a = 38) is less acidic than acetylene (pK_a = 25). The equilibrium will favor the weaker acid (ammonia).

3.11. One way to answer this question is to look up (or at least estimate) the pK_a of the acid on each side of the equilibrium. Because phenolic protons (pK_a ~ 10) are more acidic than water (pK_a ~ 15.7), we can determine that the equilibrium should favor deprotonation of hydroquinone by hydroxide. The equilibrium will favor the weaker acid (water).

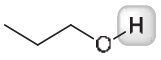
3.12. At a pH of 7.4, the carboxylic acid group (RCO_2H) will exist primarily as its conjugate base (RCO_2^-), called a carboxylate ion. At the same pH, the ammonium group (RNH_3^+) will retain its proton, and will primarily exist in the charged form, as shown here:



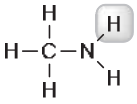
glycine

3.13.

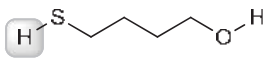
(a) Carbon and oxygen are in the same row of the periodic table, so we must compare their electronegativity values. Oxygen is more electronegative than carbon and can better stabilize the negative charge that will be generated upon deprotonation. Therefore, a proton connected to an oxygen atom is expected to be more acidic than a proton connected to a carbon atom:



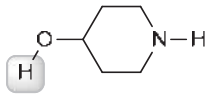
(b) Carbon and nitrogen are in the same row of the periodic table, so we must compare their electronegativity values. Nitrogen is more electronegative than carbon and can better stabilize the negative charge that will be generated upon deprotonation. Therefore, a proton connected to a nitrogen atom is expected to be more acidic than a proton connected to a carbon atom:



(c) Sulfur and oxygen are in the same column of the periodic table, so we must compare their size. Sulfur is larger than oxygen and can better stabilize the negative charge that will be generated upon deprotonation. Therefore, a proton connected to a sulfur atom is expected to be more acidic than a proton connected to an oxygen atom:



(d) Nitrogen and oxygen are in the same row of the periodic table, so we must compare their electronegativity values. Oxygen is more electronegative than nitrogen and can better stabilize the negative charge that will be generated upon deprotonation. Therefore, a proton connected to an oxygen atom is expected to be more acidic than a proton connected to a nitrogen atom:



3.14. We start by drawing the two possible conjugate bases:

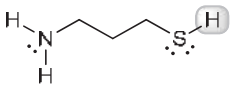


The first conjugate base has the negative charge on a nitrogen atom, while the second conjugate base has the negative charge on a sulfur atom. Nitrogen and sulfur are neither in the same row nor in the same column of the periodic table. However, nitrogen and oxygen are in the same row of the periodic table and sulfur and oxygen are in the same column of the periodic table, so it makes sense to use oxygen as a means of comparing nitrogen and sulfur. Oxygen is better able to stabilize a negative charge than nitrogen due to its greater electronegativity (the dominant factor when making comparisons in a row). Sulfur is better able to stabilize a negative charge than oxygen due to its larger size (the dominant factor when making comparisons in a column). So, we can deduce that sulfur must be more capable of stabilizing the negative charge than nitrogen:



less stable more stable

Therefore, the following highlighted proton is more acidic.



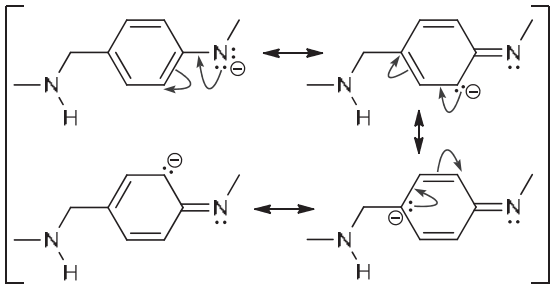
3.15.

(a) The proton marked in blue is expected to be more acidic than the proton marked in red, because deprotonation of the former leads to a resonance-stabilized anion, shown here:

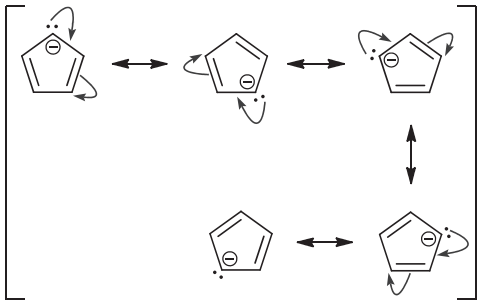


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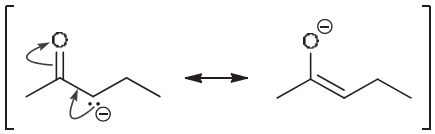
(b) The proton marked in blue is expected to be more acidic than the proton marked in red, because deprotonation of the former leads to a resonance-stabilized anion, shown here:



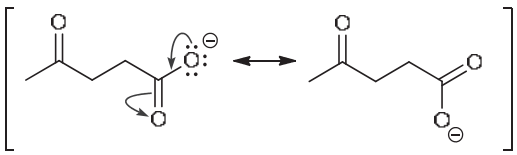
(c) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a resonance-stabilized anion, shown here:



(d) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a resonance-stabilized anion, shown here:

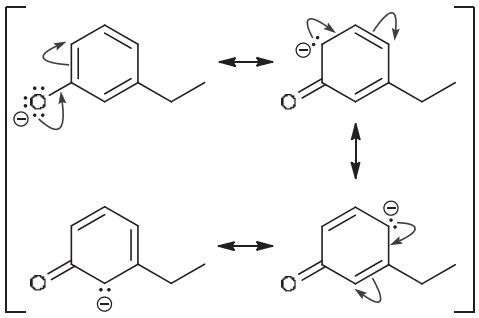


(e) The proton marked in blue is expected to be more acidic than the proton marked in red, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over two oxygen atoms.



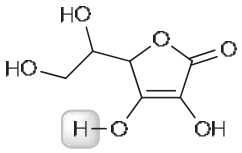
Deprotonation at the location of the red proton also leads to a resonance-stabilized anion, but the negative charge is spread over an oxygen atom and a carbon atom, which is less stable than spreading the charge over two oxygen atoms.

(f) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over one oxygen atom and three carbon atoms.

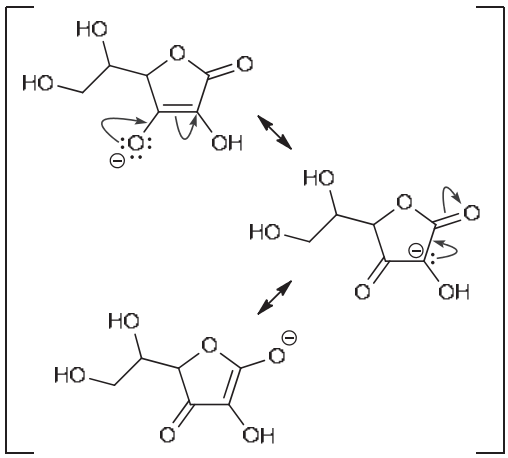


Deprotonation at the location of the blue proton also leads to a resonance-stabilized anion, but the negative charge is spread over four carbon atoms, which is less stable than spreading the charge over one oxygen atom and three carbon atoms.

3.16. The proton highlighted is the most acidic proton in the structure:



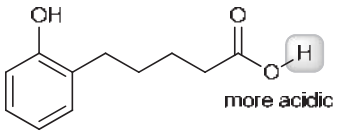
This proton is the most acidic, because deprotonation at that location generates a resonance-stabilized anion, in which the negative charge is spread over two oxygen atoms and one carbon atom:



3.17. Deprotonation at the location marked by the red proton leads to a resonance-stabilized anion in which the negative charge is spread over one oxygen atom and three carbon atoms, just as we saw in Problem **3.15f**. Deprotonation at the location marked by the blue proton leads to a resonance-stabilized anion in which the negative charge is spread over two oxygen atoms, just as

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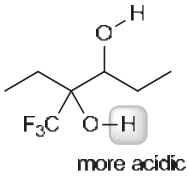
we saw in Problem **3.15e.** By comparing pK_a values from Table 3.1, we conclude that the following proton is more acidic (lower pK_a value).



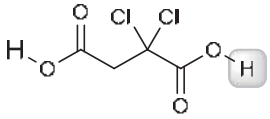
This suggests that a negative charge will be more stabilized when spread over two oxygen atoms, rather than being spread over one oxygen atom and three carbon atoms (oxygen is more electronegative than carbon).

3.18.

(a) The highlighted proton is the most acidic. When this location is deprotonated, the resulting conjugate base is stabilized by the electron-withdrawing effects of the electronegative fluorine atoms:

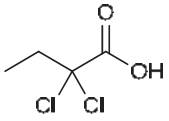


(b) The highlighted proton is more acidic. When this location is deprotonated, the resulting conjugate base is stabilized by the electron-withdrawing effects of the electronegative chlorine atoms, which are closer to this proton than the other acidic proton (left):

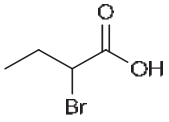


3.19.

(a) The compound with two chlorine atoms is more acidic, because of the electron-withdrawing effects of the additional chlorine atom, which helps stabilize the conjugate base that is formed when the proton is removed.

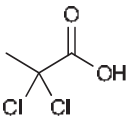


(b) The more acidic compound is the one in which the bromine atom is closer to the acidic proton. The electron-withdrawing effects of the bromine atom stabilize the conjugate base that is formed when the proton is removed.

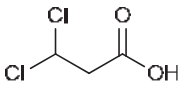


3.20.

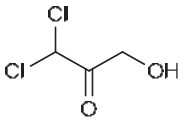
(a) In the following compound, one of the chlorine atoms has been moved closer to the acidic proton of the carboxylic acid group, which further stabilizes the conjugate base that is formed when the proton is removed.



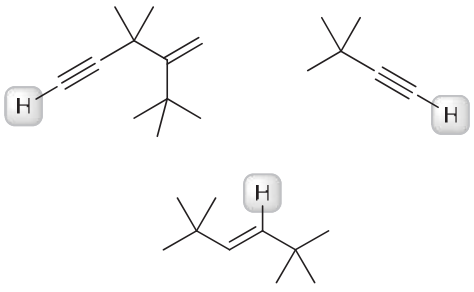
(b) In the following compound, one of the chlorine atoms has been moved farther away from the acidic proton of the carboxylic acid group, and the distant chlorine atom is less capable of stabilizing the conjugate base that is formed when the proton is removed.



(c) There are many acceptable answers to this question, since there are many constitutional isomers that lack the carboxylic acid functional group. One example is shown below. This compound is not a carboxylic acid, so its conjugate base is not resonance-stabilized:

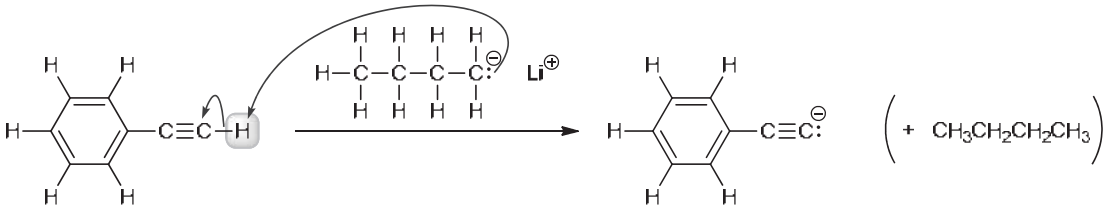


3.21. The most acidic proton is highlighted in each of the following compounds. For each of the first two compounds, deprotonation leads to a conjugate base in which the negative charge is associated with an *sp* hybridized orbital (which is more stable than being associated with an sp^2 or sp^3 hybridized orbital). In the final compound, deprotonation leads to a conjugate base in which the negative charge is associated with an sp^2 hybridized orbital (which is more stable than being associated with an sp^3 hybridized orbital).



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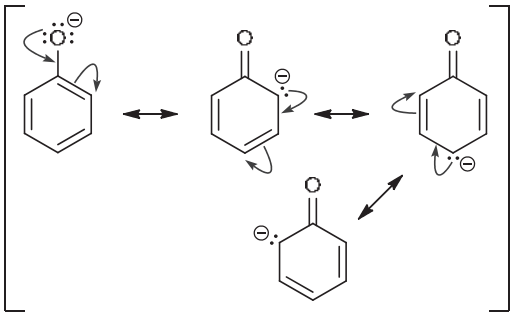
3.22. *n*-Butyllithium (*n*-BuLi) has a negative charge on an sp^3 hybridized carbon atom, so it is a very strong base and will remove the most acidic proton in the compound. All protons have been drawn below, and the most acidic one is highlighted. Deprotonation gives a conjugate base (shown below) in which the negative charge is associated with an *sp* hybridized orbital.



This negative charge is more stable than the negative charge in *n*-BuLi. All of the other protons are connected to sp^2 hybridized carbon atoms. So if any of those protons had been removed instead, the resulting conjugate base would have been less stable because the negative charge would have been associated with an sp^2 hybridized orbital (rather than an *sp* hybridized orbital).

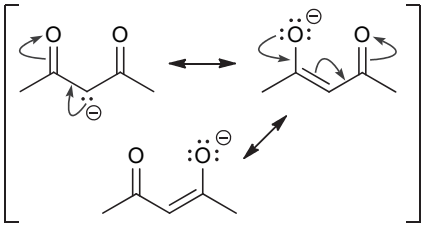
3.23.

(a) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over one oxygen atom and three carbon atoms:

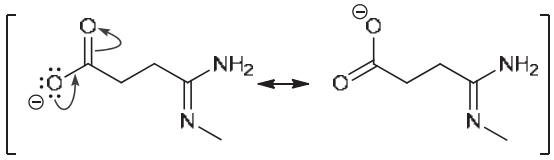


Removal of the proton marked in blue results in an anion that is not resonance stabilized.

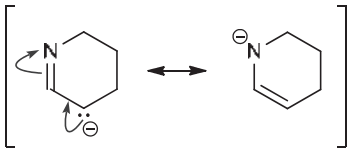
(b) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over two oxygen atoms, rather than just being spread onto one oxygen atom.



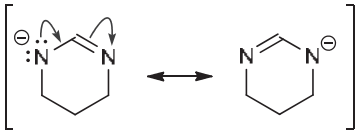
(c) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over two oxygen atoms, rather than being spread over two nitrogen atoms:



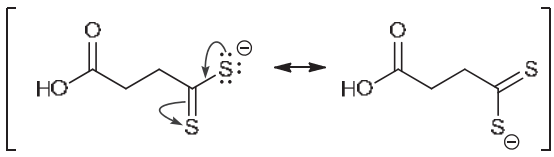
(d) The proton marked in blue is expected to be more acidic than the proton marked in red, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over a nitrogen atom and a carbon atom.



(e) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over two nitrogen atoms, rather than being spread over two carbon atoms.

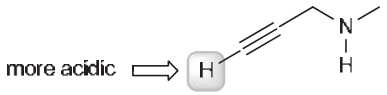


(f) The proton marked in blue is expected to be more acidic than the proton marked in red, because deprotonation of the former leads to a resonance-stabilized anion in which the negative charge is spread over two sulfur atoms, rather than two oxygen atoms.

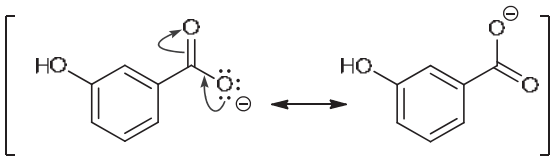


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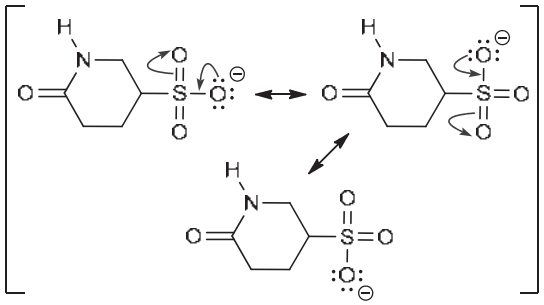
(g) The proton marked in red is expected to be more acidic than the proton marked in blue, because deprotonation of the former leads to a conjugate base in which the negative charge is associated with an *sp* hybridized orbital. This case represents an exception to the ARIO priority scheme: factor 4 (orbital) trumps factor 1 (atom).



(h) The proton marked in blue is expected to be more acidic than the proton marked in red, because deprotonation of the former leads to a conjugate base in which the negative charge is spread over two oxygen atoms, rather than being spread over one oxygen atom and three carbon atoms.



(i) The proton marked in blue is expected to be more acidic than the proton marked in red, because deprotonation of the former leads to a conjugate base in which the negative charge is spread over three oxygen atoms, rather than being spread over one nitrogen atom and one oxygen atom.



3.24.

(a) Bromine and chlorine are in the same column of the periodic table (group 7A), so we must compare their size. Bromine is larger than chlorine and can better stabilize the negative charge that will be generated upon deprotonation. HBr is expected to be more acidic than HCl.

(b) Sulfur and oxygen are in the same column of the periodic table (group 6A), so we must compare their size. Sulfur is larger than oxygen and can better stabilize the negative charge that will be generated upon deprotonation. Therefore, H_2S is expected to be more acidic than H_2O.

(c) Carbon and nitrogen are in the same row of the periodic table, so we must compare their electronegativity values. Nitrogen is more electronegative than carbon and can better stabilize the negative charge that will be generated upon deprotonation. Therefore, NH_3 is expected to be more acidic than CH_4.

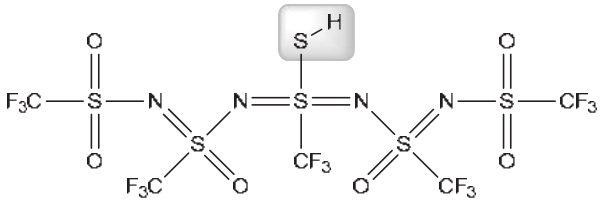
(d) Acetylene (H–C≡C–H) is more acidic. The conjugate base of acetylene has a negative charge associated with a lone pair in an *sp* hybridized orbital, which is more stable than a negative charge associated with a lone pair in an sp^2 hybridized orbital.

3.25.

(a) When the proton is removed, the resulting conjugate base is highly resonance-stabilized because the negative charge is spread over four nitrogen atoms and seven oxygen atoms. In addition, the inductive effects of the trifluoromethyl groups ($-CF_3$) further stabilize the negative charge.

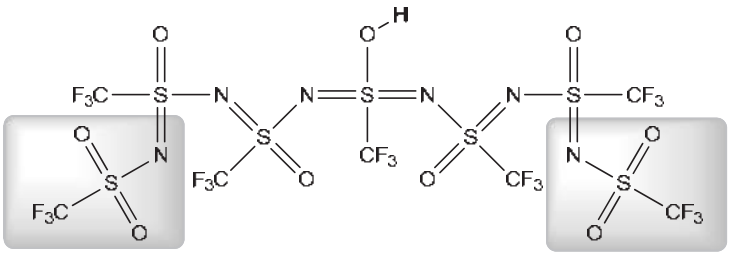
(b) There are certainly many, many acceptable answers to this problem. Below are two separate modifications that would render the compound even more acidic:

The OH group can be replaced with an SH group. Sulfur is larger than oxygen and more capable of stabilizing a negative charge:



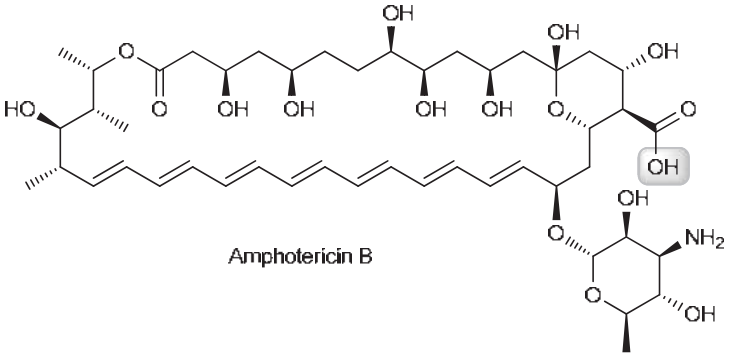
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Alternatively, the conjugate base could be further stabilized by spreading the charge over an even larger number of nitrogen and oxygen atoms. For example, consider the structural changes, highlighted here:



These additional structural units would enable the conjugate base to spread its negative charge over six nitrogen atoms and nine oxygen atoms, which should be even more stable than being spread over four nitrogen atoms and seven oxygen atoms.

3.26. The most acidic proton belongs to the carboxylic acid group (COOH). Deprotonation of this functional group gives a resonance-stabilized anion in which the negative charge is spread over two oxygen atoms.



3.27.

(a) We compare the bases on either side of the equilibrium. The first (left side) has a negative charge on a carbon atom, while the second (right side) has a negative charge on a nitrogen atom, so we turn to factor #1 (atom). Carbon and nitrogen are in the same row of the periodic table, so we compare their electronegativity values. Nitrogen is more electronegative than carbon, so a negative charge will be more stable on a nitrogen atom. As such, the reaction favors the products.

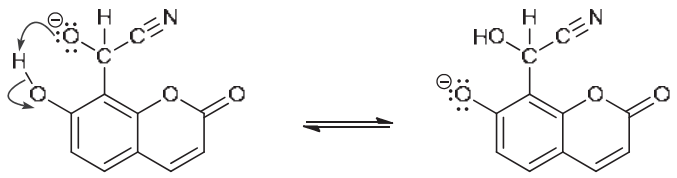
(b) We compare the bases on either side of the equilibrium. The base on the left side is a hydroxide ion, while the base on the right side is a resonance-stabilized anion, in which the negative charge is spread over one oxygen atom and three carbon atoms. The latter is more stable because of factor 2 (resonance). Therefore, the reaction favors the products.

3.28.

(a) First identify the acid and the base in the conversion of **2** into **3**. Anion **2** has its negative charge on an oxygen atom, and this oxygen atom functions as a base and accepts a proton during the conversion of **2** to **3**. The nearby hydroxyl group loses its proton during the reaction, thus it is functioning as the acid.

To draw a mechanism, remember to use two curved arrows. The tail of the first curved arrow is placed on a lone pair from the base. The head of the arrow is placed on the proton of the acid. The tail of the second curved arrow is placed on the bond between the acidic proton and the attached oxygen atom. The head of that arrow is placed on the oxygen atom that receives the negative charge as a result of the process.

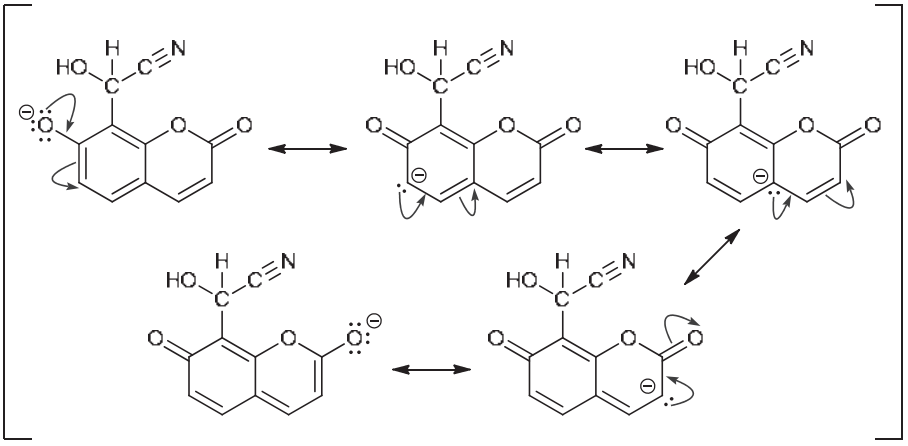
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(b) Compare the stability of the negative charge in **2** with the negative charge in **3** using the four factors (ARIO).

1. *Atom.* In each case, the negative charge is on an oxygen atom. Thus, the atom effect is not relevant.

2. *Resonance*. The anionic oxygen in **2** has no resonance stabilization, because it is attached to an sp^3 hybridized carbon atom. In contrast, anion **3** is highly stabilized by resonance, as shown here. Notice that the negative is spread over many locations, including two oxygen atoms.



3. *Induction.* The anionic oxygen in **2** is stabilized by the inductive effect of the nitrile nitrogen, the hydroxyl oxygen, and the ester oxygen atoms. However, each of these electronegative atoms are fairly far removed from the negative charge and thus probably play a minimal role in stabilizing **2**.
Anion **3** is also stabilized by the nitrile nitrogen and the other oxygen atoms in the molecule, but here the electronegative atoms are even more distant, thus the effects are even less than in **2**.

4. *Orbitals.* Orbitals are not a relevant factor in this case.

Recall that factors 1-4 are listed in order of priority. Thus, based on factor 2 (resonance), we would expect that anion **3** should be significantly more stable than anion **2**. The inductive effects that stabilize **2** are significantly less important than the resonance effects that stabilize **3**. Therefore, the equilibrium should favor **3** over **2**.

3.29.
(a) Yes, because a negative charge on an oxygen atom will be more stable than a negative charge on a nitrogen atom.
(b) Yes, because a negative charge on a nitrogen atom will be more stable than a negative charge on an sp^3 hybridized carbon atom.
(c) No, because a negative charge on an sp^2 hybridized carbon atom will be less stable than a negative charge on a nitrogen atom.
(d) No, because this base is resonance-stabilized, with the negative charge spread over two oxygen atoms and one carbon atom. Protonating this base with water would result in the formation of a hydroxide ion, which is less stable because the negative charge is localized on one oxygen atom.
(e) Yes, because a negative charge on an oxygen atom will be more stable than a negative charge on a carbon atom.
(f) Yes, because a negative charge on an *sp* hybridized carbon atom will be more stable than a negative charge on a nitrogen atom.

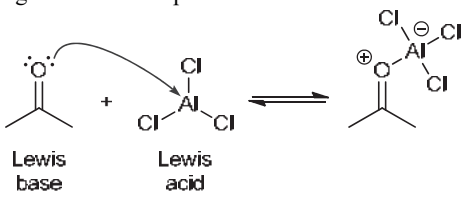
3.30.
(a) No, water will not be a suitable proton source to protonate this anion, because the anion is resonance-stabilized and is more stable than hydroxide.
(b) No, water will not be a suitable proton source to protonate this anion, because the anion is resonance-stabilized and is more stable than hydroxide.

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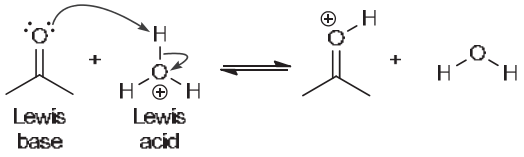
3.31. The CH_3CH_2 group in ethanol provides a small amount of steric bulk that is absent in water. As such, water is more acidic than ethanol (for the same reason that ethanol is more acidic than *tert*-butanol). Indeed, the pK_a of water (15.7) is slightly lower than the pK_a of ethanol (16).

3.32.

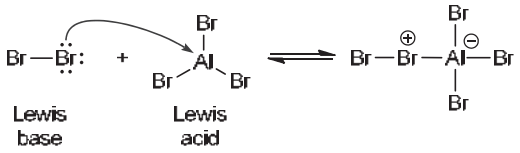
(a) A lone pair of the oxygen atom attacks the aluminum atom. $AlCl_3$ functions as the Lewis acid by accepting the electrons, and the ketone functions as the Lewis base by serving as an electron-pair donor.



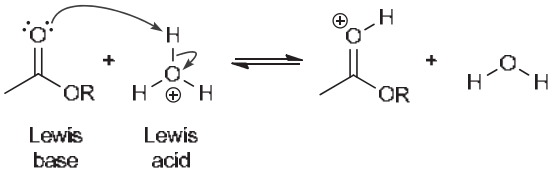
(b) A lone pair of the oxygen atom attacks a proton, as shown below. H_3O^+ functions as the Lewis acid by accepting the electrons, and the ketone functions as the Lewis base by serving as an electron-pair donor.



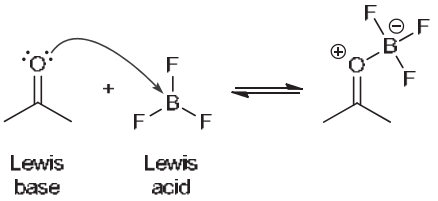
(c) A lone pair of a bromine atom attacks the aluminum atom. $AlBr_3$ functions as the Lewis acid by accepting the electrons, and molecular bromine (Br_2) functions as the Lewis base by serving as an electron-pair donor.



(d) A lone pair of the oxygen atom attacks a proton, as shown below. H_3O^+ functions as the Lewis acid by accepting the electrons, and the ester functions as the Lewis base by serving as an electron-pair donor.

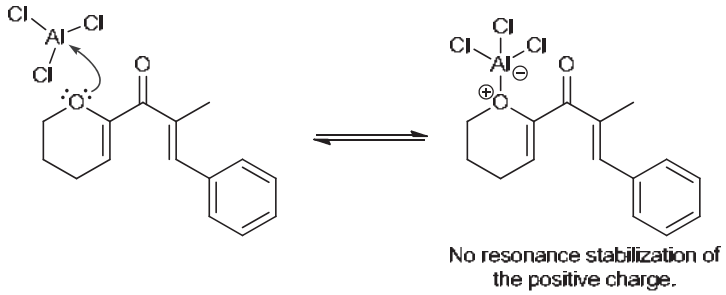


(e) A lone pair of the oxygen atom attacks the boron atom. BF_3 functions as the Lewis acid by accepting the electrons, and the ketone functions as the Lewis base by serving as an electron-pair donor.



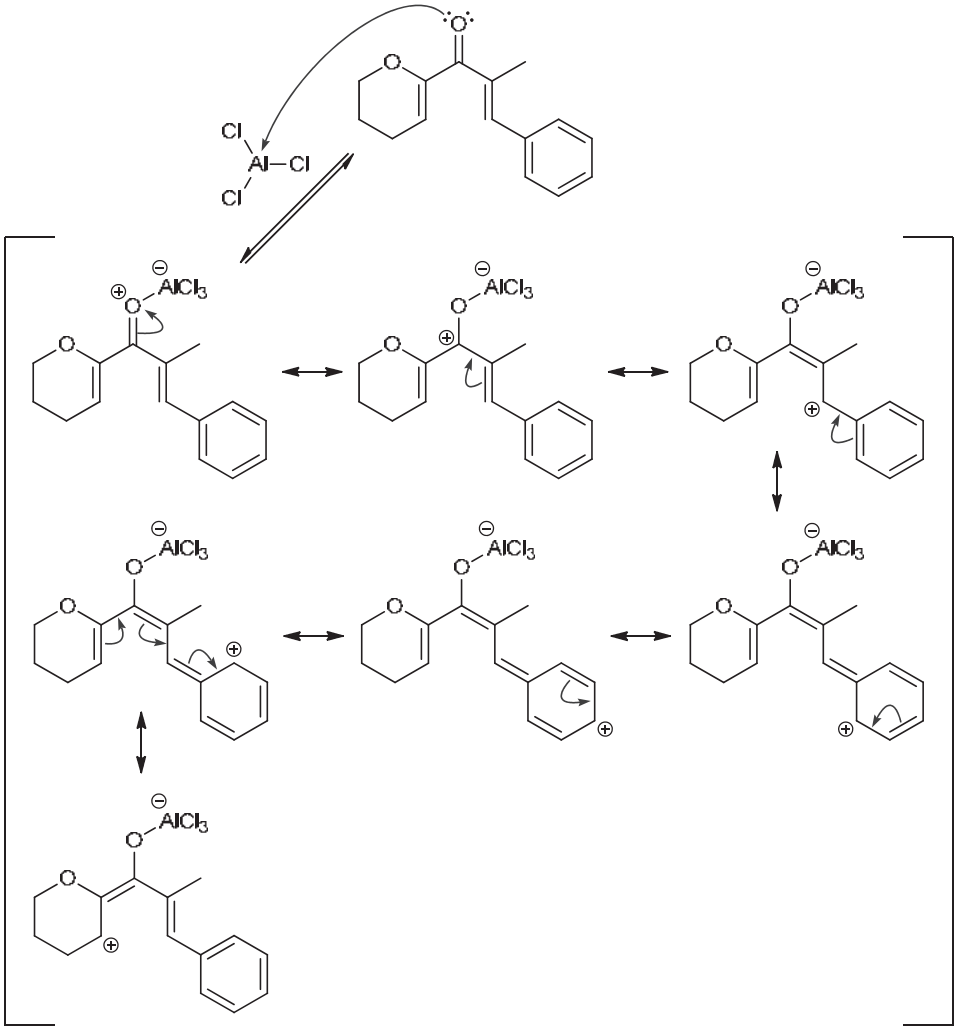
3.33. $AlCl_3$ is a Lewis acid. That is, it is capable of accepting electron density. So we must inspect compound **1** and determine the locations of high electron density. There are two oxygen atoms that bear lone pairs, and either location could certainly function as a Lewis base to donate an electron pair. But let's compare the structure of the complex that is obtained in each scenario.

If the oxygen atom of the ether group (left) interacts with $AlCl_3$, the following complex is obtained:

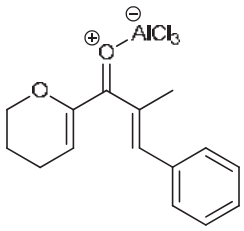


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Notice that the positive charge in this complex is not resonance stabilized. In contrast, if the oxygen atom of the C=O bond interacts with $AlCl_3$, then the following resonance-stabilized complex is obtained:



As such, we expect the oxygen atom of the C=O group to interact with the $AlCl_3$ to form the lower-energy, resonance-stabilized complex, show above.
The major contributor is the one that exhibits filled octets:

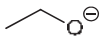


All other resonance structures exhibit a C+, which lacks an octet of electrons. Those resonance structures are minor contributors to the resonance hybrid.

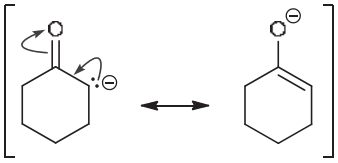
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3.34.

(a) The most acidic proton in the compound is the proton of the O-H group, because deprotonation at that location gives a conjugate base with a negative charge on an oxygen atom, shown below. Deprotonation at any other location would lead to a conjugate base with a negative charge on carbon (which is MUCH less stable).



(b) The most acidic proton in the compound is attached to a carbon atom adjacent to the C=O group. Deprotonation at that location gives a resonance-stabilized conjugate base, shown below. Deprotonation at any other location would lead to a conjugate base that is not resonance-stabilized, and therefore much less stable.



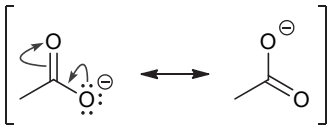
(c) Deprotonation of NH_3 gives the following conjugate base.



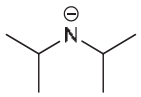
(d) Deprotonation of H_3O^+ gives the following conjugate base.



(e) The most acidic proton in the compound is the one attached to oxygen. Deprotonation at that location gives a resonance-stabilized conjugate base, in which the charge is spread over two oxygen atoms.



(f) The most acidic proton in the compound is the proton connected to nitrogen, because deprotonation at that location gives a conjugate base with a negative charge on a nitrogen atom, shown below. Deprotonation at any other location would lead to a conjugate base with a negative charge on carbon (which is less stable).



(g) Deprotonation of NH_4^+ gives the following conjugate base.



3.35.

(a) Protonation occurs at the site bearing the negative charge, giving the following compound:



(b) Protonation gives the following ketone:



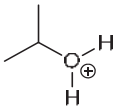
(c) Protonation of H_2N^- gives NH_3:



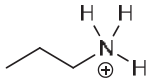
(d) Protonation of H_2O gives H_3O^+:



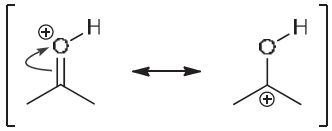
(e) One of the lone pairs of the oxygen atom can serve as a base. Protonation gives the following oxonium ion (a cation in which the positive charge is located on an oxygen atom).



(f) The lone pair of the nitrogen atom can serve as a base. Protonation gives the following ammonium ion (a cation in which the positive charge is located on a nitrogen atom).



(g) One of the lone pairs of the oxygen atom can serve as a base. Protonation gives the following resonance-stabilized cation.



(h) Protonation of HO^- gives H_2O:

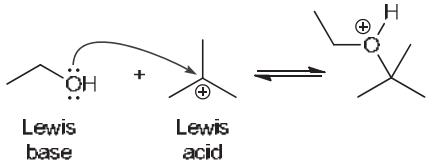


3.36. The difference in acidity between compounds A and B is 10 – 7 = 3 pK_a units. Each pK_a unit represents an order of magnitude, so compound A is 1000 times more acidic than compound B.

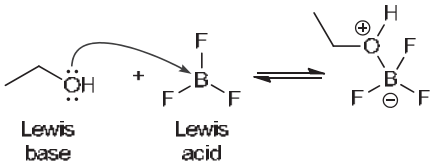
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3.37.

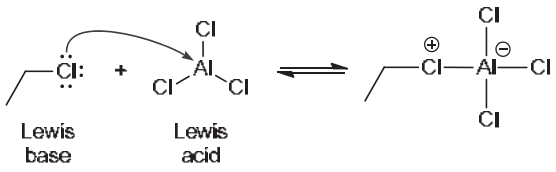
(a) A lone pair of the oxygen atom attacks the carbocation (C+), as shown below. The carbocation functions as the Lewis acid by accepting the electrons, and ethanol (CH_3CH_2OH) functions as the Lewis base by serving as an electron-pair donor.



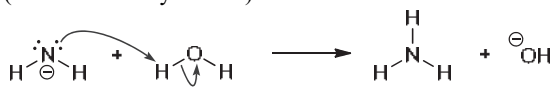
(b) A lone pair of the oxygen atom attacks the boron atom. BF_3 functions as the Lewis acid by accepting the electrons, and ethanol (CH_3CH_2OH) functions as the Lewis base by serving as an electron-pair donor.



(c) A lone pair of a chlorine atom attacks the aluminum atom. $AlCl_3$ functions as the Lewis acid by accepting the electrons, and ethyl chloride (CH_3CH_2Cl) functions as the Lewis base by serving as an electron-pair donor.



3.38. The amide ion (H_2N^-) is a strong base, and in the presence of H_2O, a proton transfer reaction will occur, generating hydroxide, which is a more stable base than the amide ion (Factor #1: oxygen is more electronegative than nitrogen). The reaction will greatly favor products (ammonia and hydroxide).



3.39. No, the reaction cannot be performed in the presence of ethanol, because the leveling effect would cause deprotonation of ethanol to form ethoxide ions, and the desired anion would not be formed under these conditions.

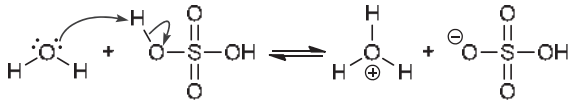
3.40. No, water would not be a suitable proton source in this case. This anion is the conjugate base of a carboxylic acid. The negative charge is resonance stabilized and is more stable than hydroxide.

3.41.

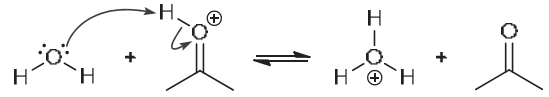
(a) Water functions as a base and deprotonates HBr. Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the H–Br bond (being broken) and goes to the bromine atom, as shown:



(b) Water functions as a base and deprotonates sulfuric acid (H_2SO_4). Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton. The second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:

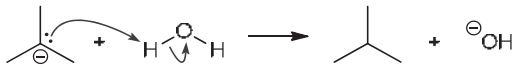


(c) Water functions as a base and deprotonates this strong acid (See Table 3.1). Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:

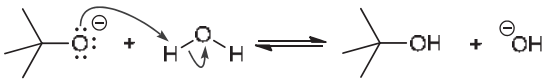


3.42.

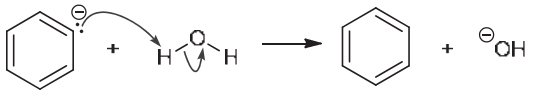
(a) Water functions as an acid in this case, by giving a proton to the strong base, as shown below. Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



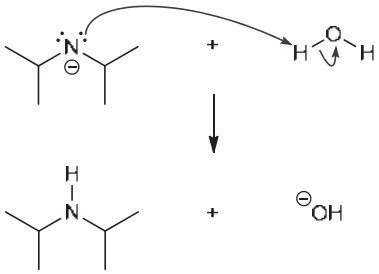
(b) Water functions as an acid in this case, by giving a proton to the base, as shown below. Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



(c) Water functions as an acid in this case, by giving a proton to the strong base, as shown below. Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



(d) Water functions as an acid in this case, by giving a proton to the strong base, as shown below. Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:



3.43.

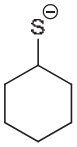
(a) The second anion is more stable because it is resonance stabilized.

(b) The second anion is more stable because the negative charge is on a nitrogen atom (factor #1 of ARIO), rather than an sp^3 hybridized carbon atom.

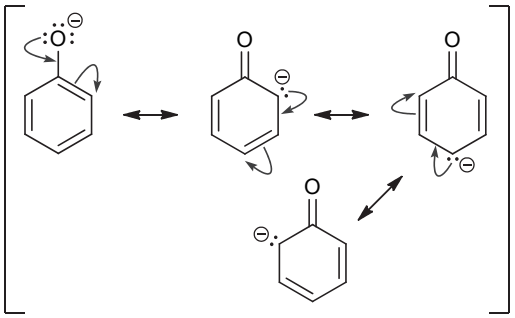
(c) The second anion is more stable because the negative charge is on an *sp* hybridized carbon atom, rather than an sp^3 hybridized carbon atom.

3.44.

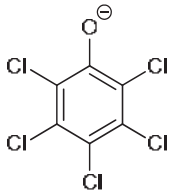
(a) The second compound is more acidic, because its conjugate base (shown below) has a negative charge on a sulfur atom, which is more stable than a negative charge on an oxygen atom (factor #1 of ARIO):



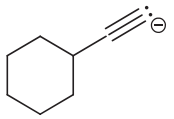
(b) The first compound (called phenol) is more acidic, because its conjugate base (shown below) is resonance stabilized (factor #2 of ARIO):



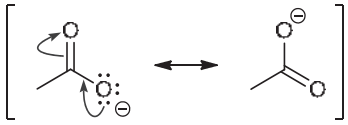
(c) The conjugate base for each of these compounds is resonance-stabilized (as in part b of this problem). The difference between these compounds is the presence of electron-withdrawing chlorine atoms. The first compound is more acidic as a result of the combined inductive effects of the five chlorine atoms which stabilize the conjugate base shown below (factor #3 of ARIO).



(d) The second compound is more acidic, because its conjugate base (shown below) has a negative charge associated with an *sp* hybridized orbital, while the first compound is less acidic because its conjugate base has a negative charge on a nitrogen atom. We learned that this example constitutes an exception to the order of priorities, ARIO. In this case, factor #4 (orbital) trumps factor #1 (atom). This exception applies whenever we compare a negative charge on an *sp* hybridized carbon atom and a negative charge on an sp^3 hybridized nitrogen atom.

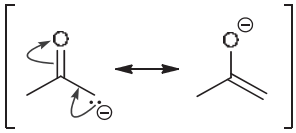


(e) The first compound is more acidic because its conjugate base (shown below) is resonance stabilized.

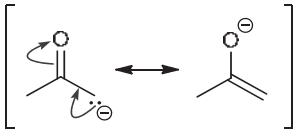


The conjugate base of the second compound is not resonance stabilized.

(f) The first compound is more acidic because its conjugate base (shown below) is resonance stabilized, and one of the resonance structures has the negative charge on an oxygen atom. The conjugate base of the second compound is not resonance stabilized (the negative charge would be localized on a carbon atom).



(g) The first compound is more acidic because its conjugate base (shown below) is resonance stabilized, and one of the resonance structures has the negative charge on an oxygen atom.



The conjugate base of the second compound is not resonance stabilized (the negative charge would be localized on a carbon atom).

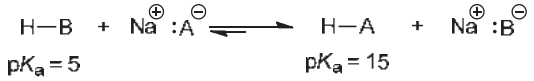
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(h) The second compound is more acidic because its conjugate base is resonance-stabilized, with the negative charge being spread over two oxygen atoms (shown below).



The conjugate base of the first compound is also resonance stabilized, but the negative charge would be spread over an oxygen atom and a nitrogen atom, which is less stable than being spread over two oxygen atoms (because oxygen is more electronegative than nitrogen, as described in factor #1 of ARIO):

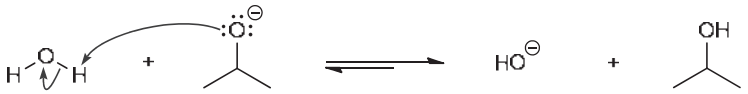
3.45. NaA represents an ionic compound, comprised of cations (Na^+) and anions (A^-). When H–B is treated with A^-, a proton can be transferred from H–B to A^-, as shown in the following equilibrium:



The equilibrium will favor the weaker acid (the acid with the higher pK_a value). In this case, the equilibrium favors formation of HA.

3.46.

(a) Water (H_2O) loses a proton and is therefore functioning as an acid. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton of water, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown. The equilibrium favors the products, which can be determined by comparing the bases on either side of the equilibrium. Hydroxide is more stable, and the equilibrium favors the more stable base. Alternatively, we could compare the pK_a values of the acids on either side of the equilibrium [H_2O and $(CH_3)_2CHOH$] and we would arrive at the same conclusion (the equilibrium will favor the products in this case because the equilibrium favors the weaker acid).



(b) Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the S–H bond (being broken) and goes to the sulfur atom, as shown. The equilibrium favors the products, which can be determined by comparing the bases on either side of the equilibrium. A negative charge on a sulfur atom is expected to be more stable than the negative charge on an oxygen atom (factor #1 of ARIO), and the equilibrium favors the more stable base. Alternatively, we could compare the pK_a values of the acids on either side of the equilibrium and we would arrive at the same conclusion (the equilibrium will favor the products in this case because the equilibrium favors the weaker acid).



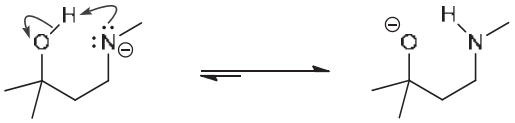
(c) Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base (HS^- in this case) attacking the proton, and the second curved arrow comes from the S–H bond (being broken) and goes to the sulfur atom, as shown. The equilibrium favors the products, which can be determined by comparing the bases on either side of the equilibrium. The base on the right side of the equilibrium is resonance stabilized, with the negative charge being spread over two sulfur atoms. The base on the left side of the equilibrium is not resonance stabilized, and the negative charge is localized on one sulfur atom. The equilibrium favors the more stable, resonance-stabilized base.



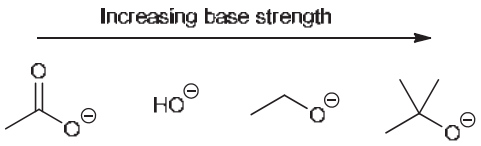
(d) Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base (the nitrogen atom) attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown. The equilibrium favors the products, which can be determined by comparing the bases on either side

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of the equilibrium. Factor #1 of ARIO indicates that the product is favored in this case, because a negative charge is more stable on an oxygen atom than a nitrogen atom.

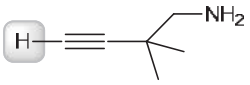


3.47. One of the anions is resonance stabilized, with the negative charge spread over two oxygen atoms. That anion is the weakest (most stable) base. Among the remaining three anions, they do not differ from each other in any of the four factors (ARIO), but they are expected to differ from each other in terms of solvent effects. That is, an anion will be less stable (stronger base) if it has steric bulk in close proximity with the negative charge. The steric bulk reduces the stability of the anion by limiting its ability to interact with solvent molecules, as described in Section 3.7.

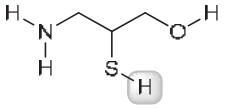


3.48.

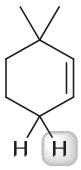
(a) The proton highlighted below is expected to be the most acidic, because deprotonation leads to a conjugate base in which the negative charge is associated with an *sp* hybridized orbital. This case represents an exception to the ARIO priority scheme, because factor #4 (orbital) trumps factor #1 (atom). This exception applies whenever we compare a negative charge on an *sp* hybridized carbon atom and a negative charge on an sp^3 hybridized nitrogen atom.



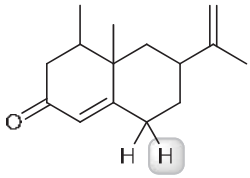
(b) The proton highlighted below is expected to be the most acidic, because deprotonation leads to a conjugate base in which the negative charge is on a sulfur atom (more stable than being on an oxygen atom or a nitrogen atom, according to factor #1 of ARIO).



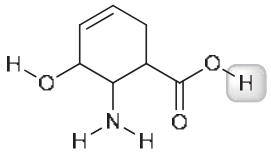
(c) The proton highlighted below is expected to be the most acidic, because deprotonation leads to a resonance-stabilized conjugate base.



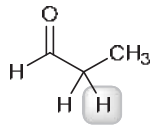
(d) The proton highlighted below is expected to be the most acidic, because deprotonation leads to a resonance-stabilized conjugate base in which the negative charge is spread over two carbon atoms and one oxygen atom.



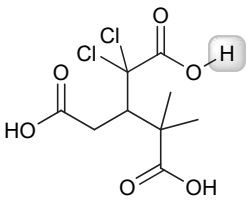
(e) The proton highlighted below is expected to be the most acidic, because deprotonation leads to a resonance-stabilized conjugate base in which the negative charge is spread over two oxygen atoms (factor #2 of ARIO).



(f) The proton highlighted below is expected to be the most acidic, because deprotonation leads to a resonance-stabilized conjugate base in which the negative charge is spread over one carbon atom and one oxygen atom (factor #2 of ARIO).



(g) There are three COOH groups, each of which bears an acidic proton. Removing any one of these protons will result in a resonance-stabilized conjugate base. Among these three protons, the highlighted proton is the most acidic because of the electron-withdrawing effects of the nearby chlorine atoms. When this proton is removed, the conjugate base is stabilized not only by resonance, but also by induction (factor #3 of ARIO).



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(h) The highlighted proton is expected to be the most acidic, because deprotonation leads to a conjugate base in which the negative charge is on a sulfur atom, which is more stable than being on an oxygen atom (factor #1 of ARIO).



3.49.

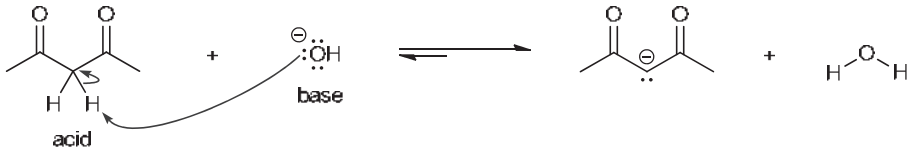
(a) Acetic acid (CH_3CO_2H) loses a proton and is therefore functioning as an acid. Hydroxide (HO^-) functions as the base that removes the proton. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown. The equilibrium favors the products, because the base on the right side of the equilibrium is resonance stabilized and therefore more stable than a hydroxide ion. The equilibrium favors the more stable base. Alternatively, we could compare the pK_a values of the acids on either side of the equilibrium and we would arrive at the same conclusion (the equilibrium will favor the products in this case because the equilibrium favors the weaker acid).



(b) Water (H_2O) loses a proton and is therefore functioning as an acid. The carbanion (an anion in which the negative charge is on a carbon atom) functions as the base that removes the proton. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown. The reaction favors the products, because hydroxide is more stable than a carbanion (factor #1 of ARIO). Alternatively, we could compare the pK_a values of the acids on either side of the equilibrium and we would arrive at the same conclusion (the reaction favors the products). In fact, the pK_a values of H_2O (15.7) and C_4H_{10} (~50) are so vastly different that the reaction is essentially irreversible.



(c) Hydroxide (HO^-) functions as a base and removes a proton from the acid. Two curved arrows must be drawn. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the C–H bond (being broken) and goes to the carbon atom, as shown.



Notice that the conjugate base is resonance stabilized, so its formation can alternatively be shown with more than two curved arrows (leading directly to the resonance structure that contributes the most character to the overall resonance hybrid).



The equilibrium favors the products, because the base on the right side of the equilibrium is resonance stabilized, with the negative charge spread over two oxygen atoms. This is more stable than the negative charge being localized on one oxygen atom, as in hydroxide. The equilibrium favors the more stable base. Alternatively, we could compare the pK_a

values of the acids on either side of the equilibrium and we would arrive at the same conclusion. That is, the equilibrium will favor the products in this case because the equilibrium favors formation of the weaker acid (H_2O).

3.50. Each of the carbon atoms is tetravalent; the sulfur atom is divalent; and each of the hydrogen atoms is monovalent. We begin by connecting the atoms that have more than one bond (in this case, the two carbon atoms and the sulfur atom). There are only two different ways that these three atoms can be connected to each other, shown below:

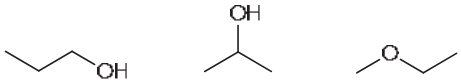
C—S—C C—C—S

For each of these arrangements, we connect the hydrogen atoms, giving the following two constitutional isomers:

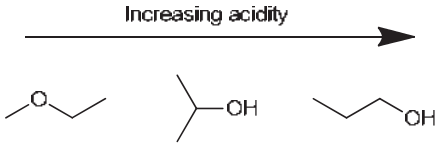


The second isomer is more acidic because deprotonation of that isomer gives a conjugate base with a negative charge on a sulfur atom. The first compound above is less acidic, because its conjugate base would have a negative charge on a carbon atom, which is much less stable (factor #1 of ARIO).

3.51. There are three constitutional isomers with the molecular formula C_3H_8O, shown here:



One of these compounds lacks an O-H group, so that compound will be the least acidic (its conjugate base will have a negative charge on a carbon atom). Of the two remaining compounds, the compound with the least branching will be the most acidic, because its conjugate base is the most stable (due to steric effects, discussed in Section 3.7).



3.52.

(a) A carbon atom must have four sigma bonds in order to be sp^3 hybridized. There is only one such carbon atom in cyclopentadiene, highlighted below.

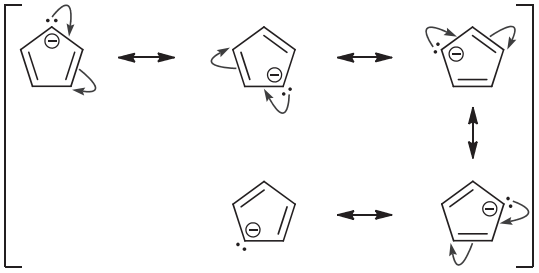


(b) The most acidic proton in cyclopentadiene is highlighted below:



The corresponding conjugate base is highly resonance stabilized (see the solution to Problem **3.15c**). In addition, the conjugate base is further stabilized by yet another factor that we will discuss in Chapter 18.

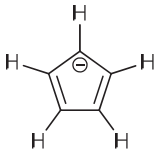
(c) Deprotonation of cyclopentadiene gives a conjugate base that is highly stabilized by resonance, as shown here:



(d) There are no sp^3 hybridized carbon atoms in the conjugate base. All five carbon atoms are sp^2 hybridized.

(e) All carbon atoms are sp^2 hybridized and trigonal planar. Therefore, the entire compound has planar geometry.

(f) There are five hydrogen atoms in the conjugate base.



(g) As seen in the resonance structures (see the solution to part c of this problem), there is one lone pair in the conjugate base, and it is highly delocalized.

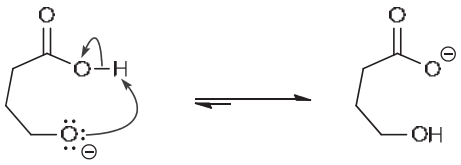
3.53. We begin by drawing the conjugate base of each compound and comparing them:



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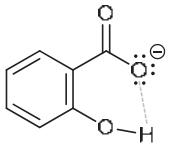
The first conjugate base is stabilized by resonance, while the second conjugate base is not. However, the second conjugate base exhibits a negative charge on a sulfur atom, which is larger than an oxygen atom. Therefore, there is a competition between two factors. Using the ARIO order of priority that is generally applied ("atom" is more important than "resonance"), we would expect that the second conjugate base should be more stable than the first. Yet, when we compare the pK_a values, we find that our prediction is not correct. Therefore, this is an exception, in which "resonance" is more important than "atom."

3.54. In an intramolecular acid-base reaction, a proton is transferred from one region of the molecule to another region within the same molecule, because the acid and base are tethered together, as in this case.

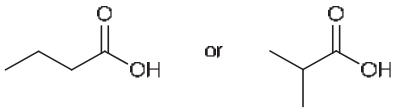


The equilibrium favors the product shown because the negative charge in the product is resonance-stabilized (factor 2), and the reaction will favor the formation of a weak base from a stronger one.

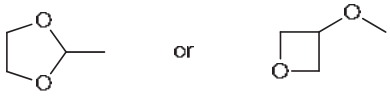
3.55. Two possible explanations can be given:
1) In salicylic acid, the inductive effect (electron-withdrawal) of the OH group is expected to be more pronounced because of its proximity to the site where deprotonation will occur.
2) When salicylic acid is deprotonated, the resulting conjugate base can be significantly stabilized by intramolecular hydrogen bonding (this explanation is likely more significant than the first explanation):



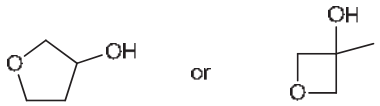
3.56.
(a) We are looking for a constitutional isomer with an acidic proton. The following two compounds are both carboxylic acids, because in each case, the conjugate base is resonance stabilized, with the negative charge being spread over two oxygen atoms. Carboxylic acids typically have a pK_a in the range of 4-5, while the structure shown in the problem statement is expected to have a pK_a in the range of 16-18. Therefore, the structures shown here satisfy the criteria described in the problem statement (they are both expected to be approximately one trillion times more acidic that the structure shown in the problem statement).



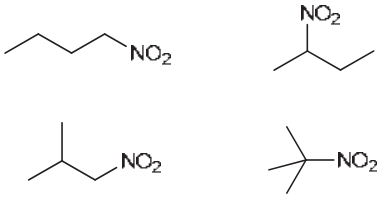
(b) The structure shown in the problem statement has an O-H group, and that proton is the most acidic proton in the compound. If we draw a constitutional isomer that lacks an O-H group, we would expect the resulting isomer to be significantly less acidic. The following two compounds fit this criterion. There are certainly many other constitutional isomers that also lack an O-H group, so there are many correct answers to this problem.



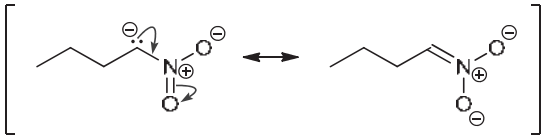
(c) Each of the following two isomers are expected to have a pK_a value that is similar to the pK_a of the structure shown in the problem statement, because each of these compounds possesses an O-H group. There are certainly many other constitutional isomers that also contain an O-H group, so there are many correct answers to this problem.



3.57. The four constitutional isomers are shown below.



The last compound is expected to have the highest pK_a because its conjugate base is not resonance stabilized. The other three compounds have resonance-stabilized conjugate bases, for example:

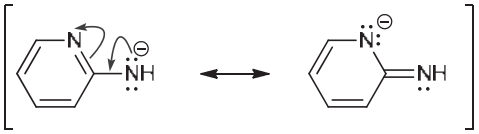


3.58. Compare the conjugate bases:

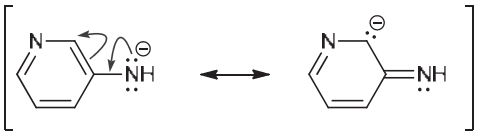


Both are resonance stabilized. But the conjugate base of the first compound has a negative charge spread over two nitrogen atoms and two carbon atoms:

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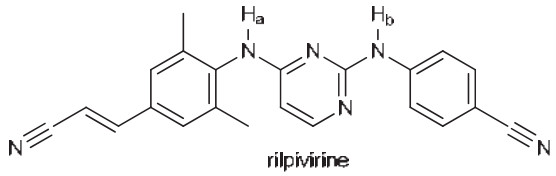
while the conjugate base of the second compound has a negative charge spread over one nitrogen atom and three carbon atoms:



Since nitrogen is more electronegative than carbon, nitrogen is more capable of stabilizing a negative charge. Therefore, the conjugate base of the first compound is more stable than the conjugate base of the second compound. As a result, the first compound will be more acidic.

3.59.

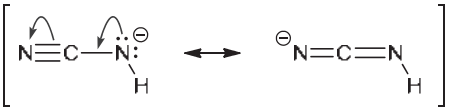
(a) The two most acidic protons are labeled H_a and H_b. Deprotonation at either site will lead to a resonance-stabilized anion in which the negative charge is highly delocalized (spread over many nitrogen atoms).



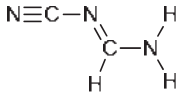
(b) H_a is expected to be slightly more acidic than H_b, because removal of H_a produces a conjugate base that has one more resonance structure than the conjugate base formed from removal of H_b. The former has the negative charge spread over four nitrogen atoms and *five* carbon atoms, while the latter has the negative charge spread over four nitrogen atoms and *four* carbon atoms.

3.60.

(a) When R is a cyano group, the conjugate base is resonance stabilized:

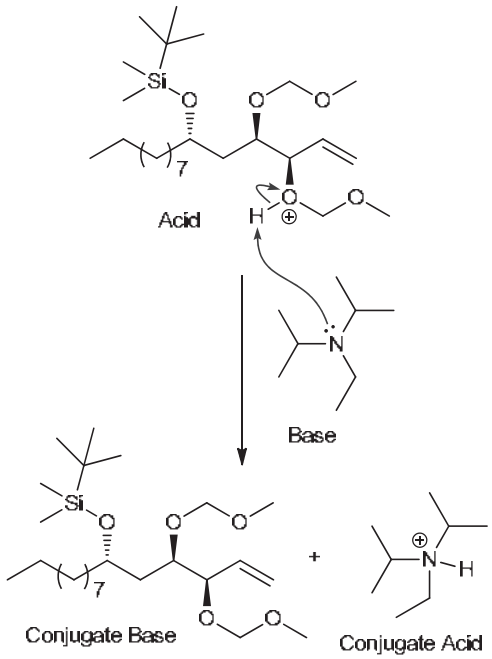


(b) There are many possible answers. Here is one example, for which the conjugate base has the negative charge spread over three nitrogen atoms, rather than just two nitrogen atoms:



3.61.

(a) The positively charged structure serves as the acid, while the lone pair on the nitrogen atom serves as the base. Two curved arrows are required. The first curved arrow shows a lone pair of the base attacking the proton, and the second curved arrow comes from the O–H bond (being broken) and goes to the oxygen atom, as shown:

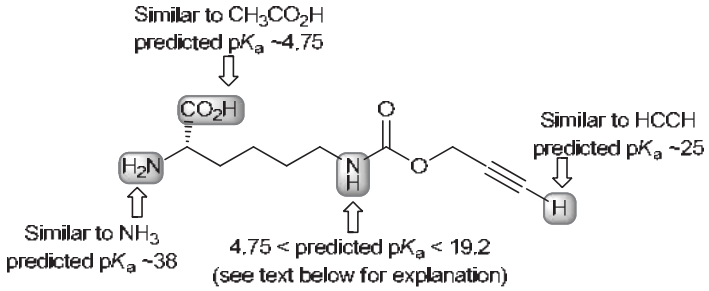


(b) Using the pK_a table on the inside cover of the textbook, we see that oxonium ions have a pK_a of approximately -2, while ammonium ions have a pK_a of approximately 11. Therefore, we expect the former to be 13 orders of magnitude more acidic than the latter, and as such, the acid-base reaction above will significantly favor the products.

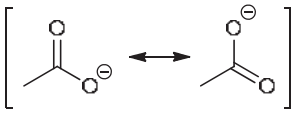
3.62. Let's estimate the relative acidity of the protons in the compound by comparing them to similar acids in Table 3.1. We focus on the protons directly bound to electronegative heteroatoms (O, N, etc) and protons bound to non-sp^3 carbons. Three of the four most acidic protons are directly comparable to acids in Table 3.1. Note that the pK_a values

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shown are not meant to be precise (due to other structural factors that can affect these values), but rather, they should be considered as rough approximations.

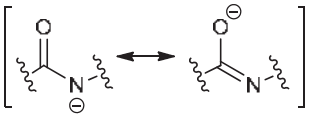


The proton on the nitrogen atom adjacent to the C=O group is also a good candidate for one of our four most acidic protons, because it is bound to an electronegative atom (nitrogen). In this case there is no obvious molecule of comparison in Table 3.1. However, we can still make a reasonable prediction of pK_a range by using our knowledge of the relationship between structure and acidity. First of all, we can predict that the pK_a of the indicated proton is **greater than 4.75** by making the following comparison:



This anion has two resonance structures, each with a negative charge on oxygen.

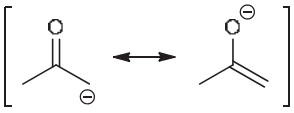
[The pK_a of the conjugate acid of this anion is 4.75]



In this case, the negative charge is shared between nitrogen and oxygen. Therefore, this anion is predicted to be *less stable* than the anion to the left. (Nitrogen is less electronegative than oxygen, so it is not as stable with a negative charge.)

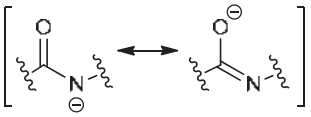
[The pK_a of the conjugate acid of this anion is predicted to be >4.75]

A second comparison with another molecule in Table 3.1 allows us to predict that the pK_a of the proton of interest is **lower than 19.2.**



This anion has two resonance structures, with the negative charge spread over carbon and oxygen.

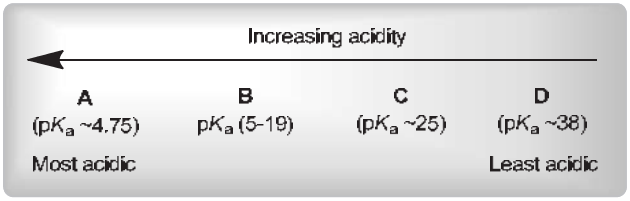
[The pK_a of the conjugate acid of this anion is 19.2]

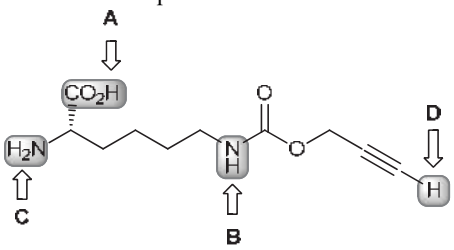


In this case, the negative charge is shared between nitrogen and oxygen. This anion is predicted to be *more stable* than the anion to the left. (Nitrogen is more electronegative than carbon and therefore more stable with a negative charge.)

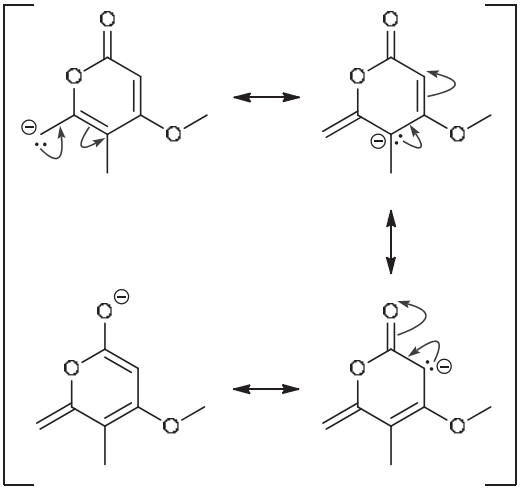
[The pK_a of the conjugate acid of this anion is predicted to be <19.2]

After determining the approximate pK_a values for each of the four most acidic protons, we can now rank them in order of increasing acidity. Recall that the lowest pK_a value is associated with the most acidic proton:

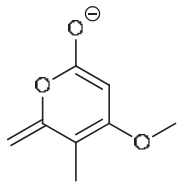




3.63. All significant resonance structures for anion **1** are shown here:



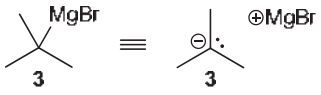
Only one of these structures has the negative charge on an oxygen atom. The other resonance structures have a negative charge on a carbon atom. Since oxygen is more electronegative than carbon, oxygen is more capable of stabilizing the charge. Therefore, the following resonance structure will contribute the most character to the resonance hybrid. The other resonance structures are all minor contributors.



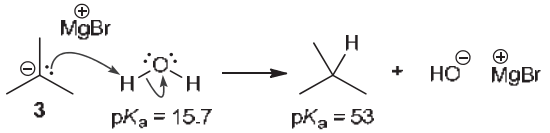
major contributor

3.64.

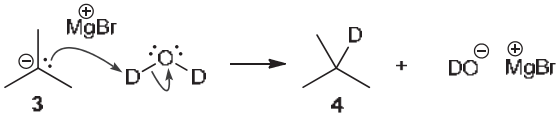
(a) As seen in Table 1.1, the electronegativity value for carbon is 2.5, while the electronegativity value for magnesium is only 1.2. The difference (1.3) is significant, and as explained in Section 1.5, this bond can be drawn as either covalent or ionic:



When drawn in this way, the anion exhibits a negative charge on a carbon atom (called a carbanion), which is a very strong base (because it is the conjugate base of a very, very weak acid). If compound **3** were treated with H_2O, we would expect the following proton-transfer reaction:



This reaction would be irreversible as a result of the enormous difference in pK_a values (see inside cover of the textbook for a table of pK_a values). In a similar way, if compound **3** is treated with D_2O, rather than H_2O, the following irreversible reaction occurs, in which a deuteron (rather than a proton) is transferred:



(b) As explained in Section 14.3, signals associated with the stretching of single bonds generally appear in the fingerprint region of an IR spectrum (400 – 1500 cm^{-1}), while signals associated with the stretching of double bonds and triple bonds appear in the diagnostic region (1500 – 4000 cm^{-1}). Notable exceptions are C-H bonds, which produce high-energy signals in the diagnostic region (2800 – 3000 cm^{-1}). This is explained in Section 14.3, by exploring the following equation, derived from Hooke's law:

$$\tilde{\nu} = \left(\frac{1}{2\pi c}\right)\left(\frac{f}{m_{red}}\right)^{\frac{1}{2}}$$

$$\text{reduced mass} = \left(\frac{m_1 m_2}{m_1 + m_2}\right)$$

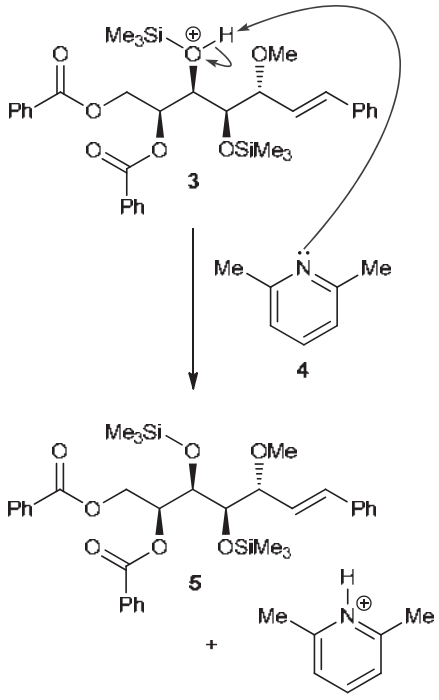
Specifically, mass is found in the denominator, rather than the numerator, and as such, atoms with lower mass produce higher energy signals. Hydrogen has the smallest mass of all atoms, which explains why C-H bonds appear in the range 2800 – 3000 cm^{-1}. Extending this logic, a C-D bond is also expected to produce a higher energy signal, although not quite as high as C-H, because D has greater mass than H. So, we expect the C-D signal to appear somewhere below 2800 cm^{-1}, but still within the diagnostic region (greater than 1500 cm^{-1}). There is only one signal in the IR spectrum of compound **4** that fits this description, and that is the signal at 2180 cm^{-1}.

Also, 2180 cm^{-1} is in the region of the IR spectrum where signals for triple bonds are expected to appear (2100 – 2300 cm^{-1}). But we know that compound **4** lacks a triple bond. So this signal must be attributed to something else, and the C-D bond is the only candidate, because the C-H bonds appear in the range 2800 – 3000 cm^{-1} and the C-C bonds appear in the range between 1250 and 1500 cm^{-1}.

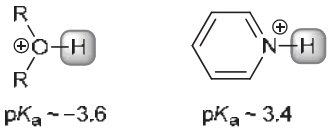
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3.65.

(a) The lone pair in compound **4** functions as a base and deprotonates intermediate **3**. This requires two curved arrows, as shown:



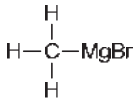
(b) If we consult the pK_a table found in the inside cover of the textbook, we find the following entries:



Notice that the first cation (an oxonium ion) has a pK_a value of approximately -3.6, while the second cation (a pyridinium ion) has a pK_a value of 3.4. The difference between them is seven pK_a units. In other words, an oxonium ion is approximately 10^7 (or 10,000,000) times more acidic than a pyridinium ion. Since a proton transfer step will proceed in the direction that favors the weaker acid, we expect compound **4** to be successful in deprotonating intermediate **3** to give compound **5**.

(c) The conversion of **1** to **5** involves the loss of an O-H bond. That is, the IR spectrum of compound **1** should exhibit a broad signal between 3200 and 3600 cm^{-1}, due to the O-H stretching vibration. This signal is expected to be absent in the IR spectrum of compound **5**, which lacks an O-H bond. This can be used to verify that the desired reaction has occurred. Specifically, the disappearance of the O-H signal indicates the conversion of **1** to **5**.

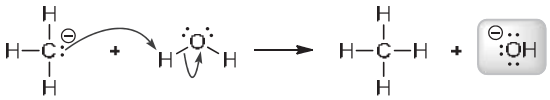
3.66. We begin by drawing methyl magnesium bromide (CH_3MgBr):



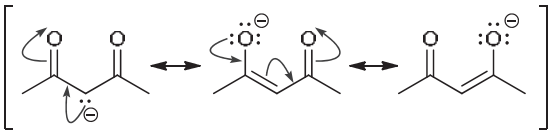
The difference in electronegativity between C and Mg is so great, that the C-Mg bond is sometimes drawn as ionic:



A carbanion (negative charge on C) is highly unstable. That is, the carbanion is a very strong base. However, as a result of the levelling effect, a base stronger than hydroxide is not possible in the presence of water. When treated with water, the carbanion above will be irreversibly protonated, giving hydroxide (highlighted below). The correct answer is (c).



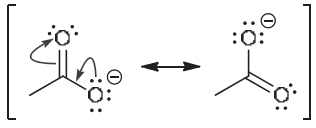
3.67. We compare the bases on either side of the equilibrium. On the left side, the base is hydroxide (HO^-). On the right side, the base is a resonance-stabilized anion, with the negative charge delocalized over two oxygen atoms and one carbon atom:



A negative charge will be more stable when it is delocalized over two oxygen atoms, rather than being localized on one oxygen atom (HO^-). The resonance-stabilized anion (above) will be more stable than hydroxide, and the equilibrium will favor the more stable base. Therefore, the correct answer is (a).

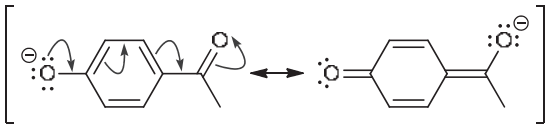
3.68. The conjugate base of (a) is HS^-, which is more stable than HO^-, because of factor #1 (the atom bearing the charge). Therefore, H_2S is expected to be more acidic than H_2O.

The conjugate base of (b) is resonance stabilized, with the negative charge being spread over two oxygen atoms:



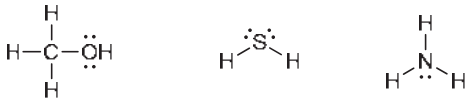
This resonance-stabilized anion will be more stable than hydroxide. Therefore, (b) is more acidic than water. Answer (d) is also more acidic than water, because its

conjugate base is resonance-stabilized, with the negative charge delocalized over two oxygen atoms:



The correct answer is (c). As a result of solvent effects, *tert*-butanol is less acidic than water.

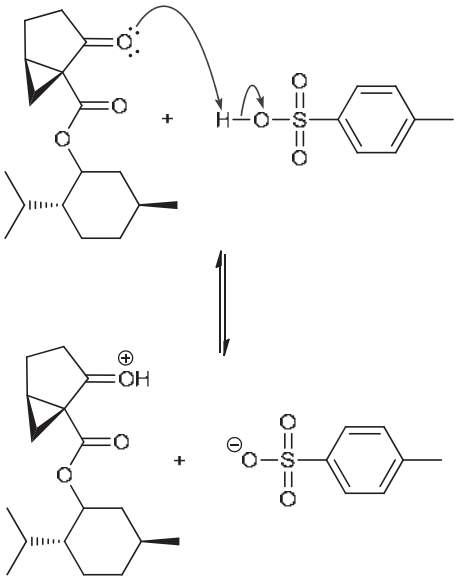
3.69. Each of the first three structures has a localized lone pair and can therefore function as a Lewis base:



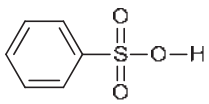
The final structure (CH_4) does not possess a lone pair, and therefore cannot function as a Lewis base.

3.70.

(a) One of the lone pairs on the ketone group functions as a base and abstracts a proton from *p*-TsOH. Two curved arrows are required, as shown:



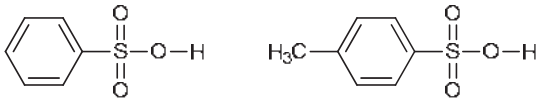
(b) Consult the pK_a table in the front cover of the textbook. Benzenesulfonic acid has a pK_a of –0.6:



benzenesulfonic acid

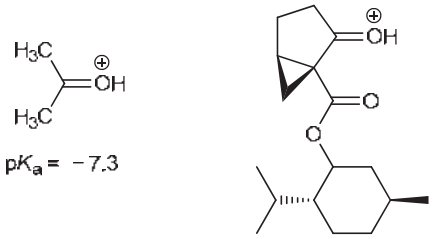
pK_a = – 0.6

p-TsOH is structurally similar to benzenesulfonic acid (the only difference is the presence of a methyl group),



benzenesulfonic acid *para*-toluenesulfonic acid

so we expect the pK_a of *p*-TsOH to be somewhere near –0.6. In contrast, the protonated ketone will have a pK_a that is approximately –7.3 (as seen in the pK_a table in the front cover of the textbook).

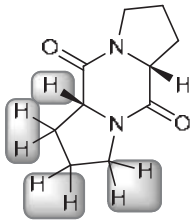


pK_a = – 7.3

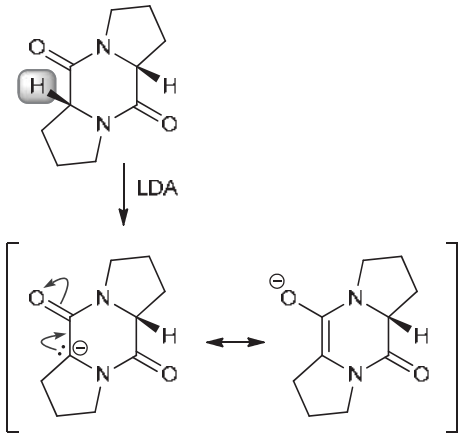
As such, the protonated ketone is more acidic, which means that the equilibrium will not favor the protonated ketone. That is, there will be very little protonated ketone present at any moment in time. In Chapter 19, we will see that the presence of even a catalytic amount of protonated ketone is sufficient to achieve the transformation shown in the problem statement.

3.71.

(a) If we take the structure of **1**, as drawn, and rotate it 180 degrees, the same image is obtained. As such, there are only four different locations (rather than eight) where deprotonation can occur.

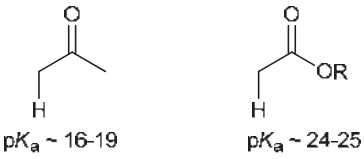


The most acidic proton is the one whose removal generates a resonance-stabilized conjugate base.

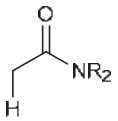


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(b) Quantitative argument: Comparing the pK_a values on the inside cover of the textbook, we see that amines (pK_a ~ 38–40) are *significantly* less acidic than ketones (16–19), or esters (24–25), both of which bear an acidic proton on the carbon atom connected to the C=O group, allowing for a resonance stabilized conjugate base.



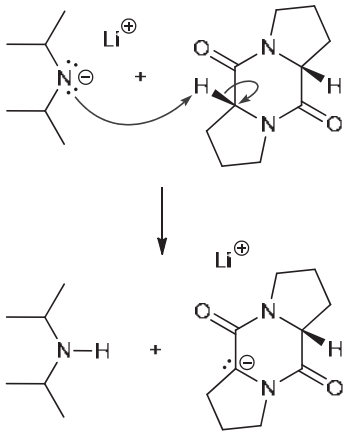
With this in mind, it is reasonable to expect the following proton of an amide to exhibit a lower pK_a than an amine:



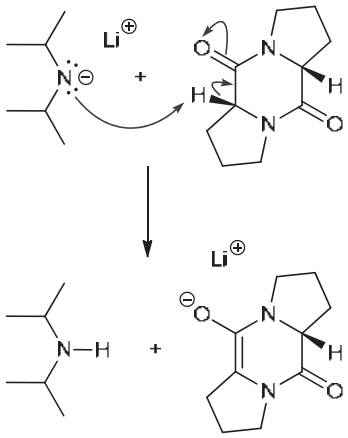
As such, the conjugate base of this compound should be more stable than the conjugate base of an amine. Therefore, LDA should be strong enough to remove a proton from compound **1**.

Qualitative argument: Compare the structures of the anions. LDA exhibits a negative charge that is localized on a nitrogen atom. In contrast, the conjugate base of **1** is resonance-stabilized, with a major resonance contributor that places the negative charge on the more electronegative oxygen atom. As such, the conjugate base of **1** is more stable than LDA, so LDA should be a suitable base.

(c) LDA functions as a base and deprotonates compound **1**. This proton transfer step can either be drawn with two curved arrows, like this,

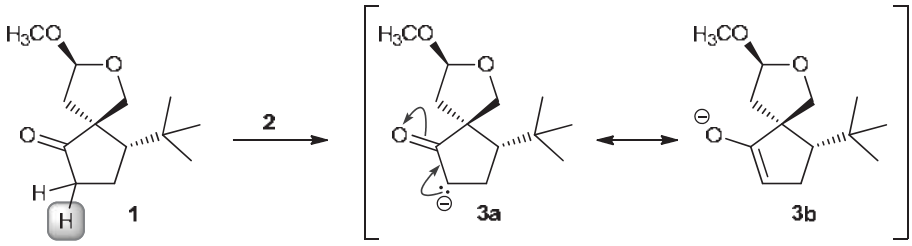


or with three curved arrows, like this:



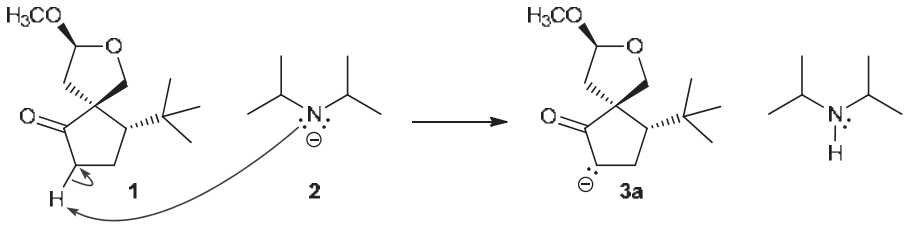
3.72.

(a) As seen in the previous problem, LDA (compound **2**) is a very strong base because it has a negative charge on a nitrogen atom (much like $NaNH_2$). So it will deprotonate compound **1** to give an anion. The most acidic proton in compound **1** is connected to the carbon atom adjacent to the C=O bond, since deprotonation at that location generates a resonance-stabilized conjugate base:

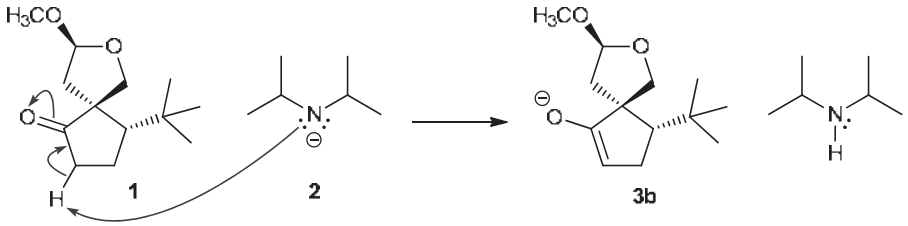


(b) Anion **3** is produced via a proton transfer step, in which the base removes a proton from compound **1**. The mechanism for this step requires at least two curved arrows:

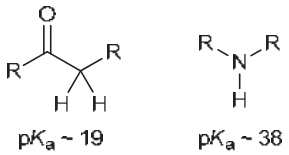
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Notice that these two curved arrows lead to resonance structure **3a**. Alternatively, the mechanism can be drawn with three curved arrows, which leads to resonance structure **3b**:

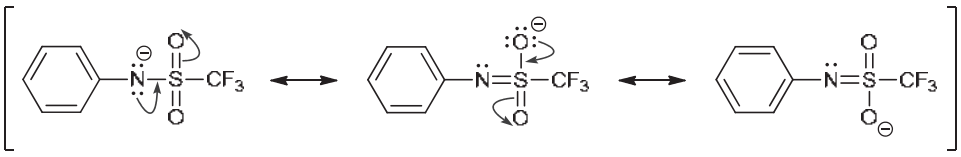


To evaluate the position of equilibrium for this process, we compare the pK_a values for the acid on either side of the equilibrium (compound **1** on the left, and R_2NH on the right). Clearly, we are not going to find the structure of compound **1** in Table 3.1. However, we can see from Table 3.1 that a proton connected to a carbon atom adjacent to the C=O bond of a ketone typically has a pK_a of approximately 19. In contrast, an amine is expected to have a pK_a near 38:

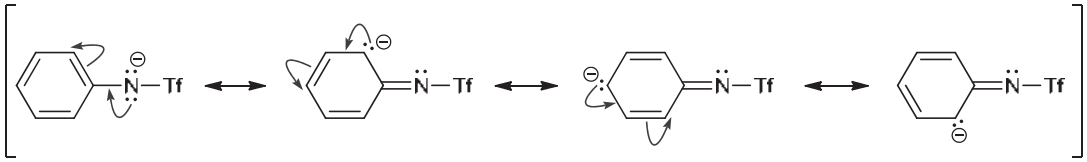


Notice that a ketone is significantly more acidic than an amine. The difference in acidity is approximately 21 pK_a units. In other words, a ketone is expected to be approximately 10^{21} times (1,000,000,000,000,000,000,000 times) more acidic than an amine. Since the difference is so large, we can treat this proton transfer step as irreversible.

(c) Compound **6** bears a negative charge on a nitrogen atom, which is generally fairly unstable. However, this anion is stabilized by several factors. The charge is delocalized into the neighboring triflate (Tf) group via resonance:



And the charge is further delocalized into the ring via resonance:

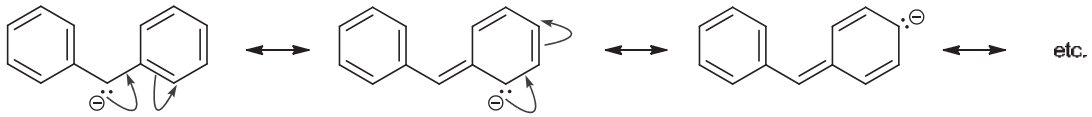


In total, the negative charge is spread over three carbon atoms, one nitrogen atom, and two oxygen atoms. The charge is therefore highly delocalized.

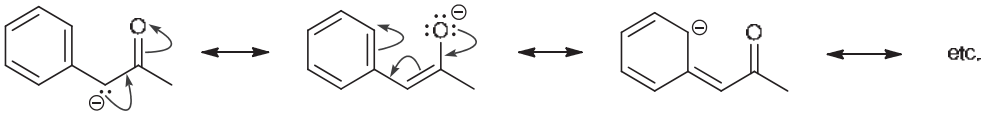
In addition, the electronegative fluorine atoms in the triflate group withdraw electron density via induction, thereby stabilizing the negative charge even further. As such the negative charge in this case is stabilized by resonance as well as induction, and is therefore highly stabilized.

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3.73. The conjugate base of compound **5** possesses many resonance contributors. The negative charge can be delocalized into both aromatic rings and so the conjugate base is highly stabilized. Notice, however, that the placement of the negative charge is exclusively on carbon atoms in the ring and never on an electronegative atom such as an oxygen atom that can better stabilize the charge.



In contrast, in the conjugate base of **6**, the negative charge is delocalized onto the carbonyl oxygen atom:



We now have to contend with two competing arguments: on the one hand, the conjugate base of **6** should be more stable than the conjugate base of **5** because the former has a resonance structure in which the negative charge is on an oxygen atom, while the latter lacks such a resonance structure. On the other hand, the conjugate base of **5** has more resonance structures (seven) than the conjugate base of **6** (which has only five resonance structures). In other words, is it more stable to spread a negative charge over seven carbon atoms or to spread the negative charge over four carbon atoms and an oxygen atom? The table of pK_a values will give us guidance on this question. It is apparent that compounds **1** and **3** represent the comparison we are asked to make in this problem. The conjugate base of compound **1** involves delocalization of the negative charge into the keto group while that of compound **3** will involve the aromatic ring. From the given pK_a values, it is clear that the keto group is more acidifying than the phenyl group. So, it is reasonable to conclude that the same trend must hold when comparing the acidities of **5** and **6**. Therefore, the keto group of the conjugate base of **6** is better able to stabilize the negative charge than the phenyl group of the conjugate base of **5**, despite the fact that there are overall more resonance contributors in the latter than the former.

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Chapter 4
Alkanes and Cycloalkanes

Review of Concepts

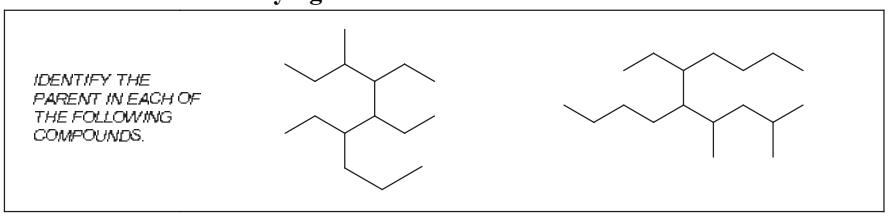
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 4. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Hydrocarbons that lack _____ are called **saturated hydrocarbons**, or _____.
- _____ provide a systematic way for naming compounds.
- Rotation about C-C single bonds allows a compound to adopt a variety of _____.
- _____ **projections** are often used to draw the various conformations of a compound.
- _____ **conformations** are lower in energy, while _____ **conformations** are higher in energy.
- The difference in energy between staggered and eclipsed conformations of ethane is referred to as _____ **strain**.
- _____ **strain** occurs in cycloalkanes when bond angles deviate from the preferred _____°.
- The _____ conformation of cyclohexane has no torsional strain and very little angle strain.
- The term **ring flip** is used to describe the conversion of one _____ conformation into the other. When a ring has one substituent…the equilibrium will favor the chair conformation with the substituent in the _____ position.

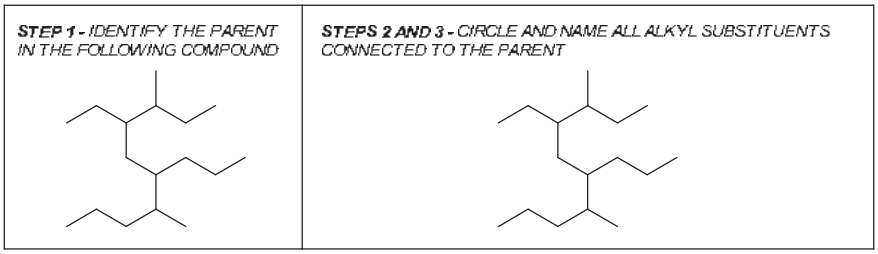
Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 4. The answers appear in the section entitled *SkillBuilder Review*.

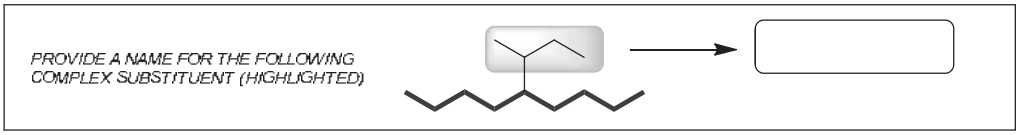
SkillBuilder 4.1 Identifying the Parent



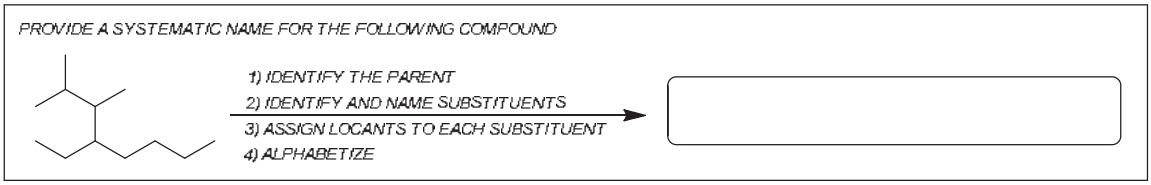
SkillBuilder 4.2 Identifying and Naming Substituents



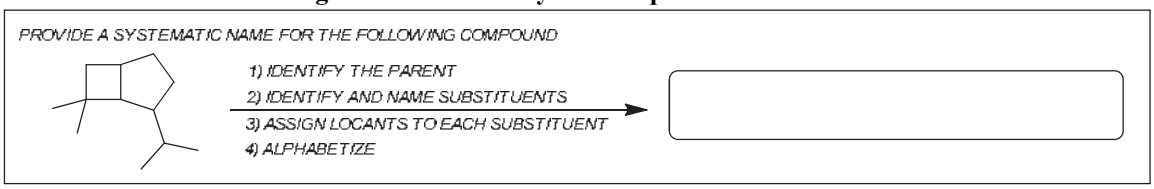
SkillBuilder 4.3 Identifying and Naming Complex Substituents



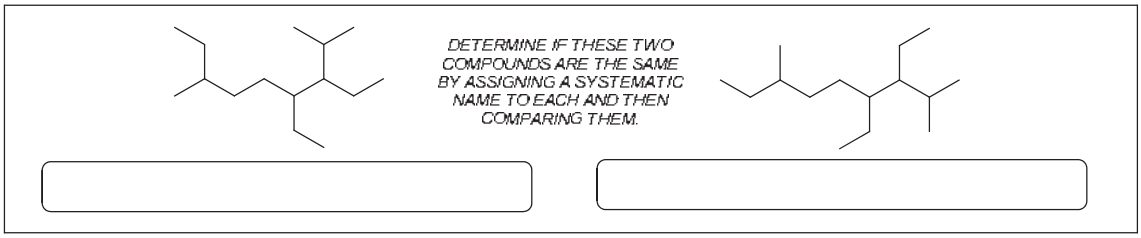
SkillBuilder 4.4 Assembling the Systematic Name of an Alkane



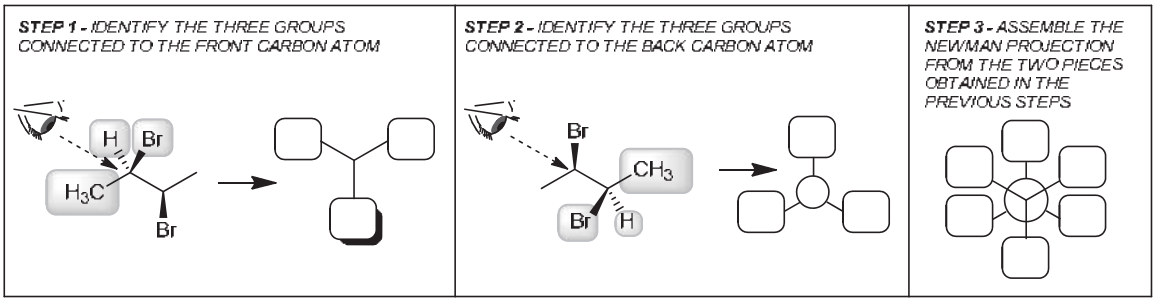
SkillBuilder 4.5 Assembling the Name of a Bicyclic Compound



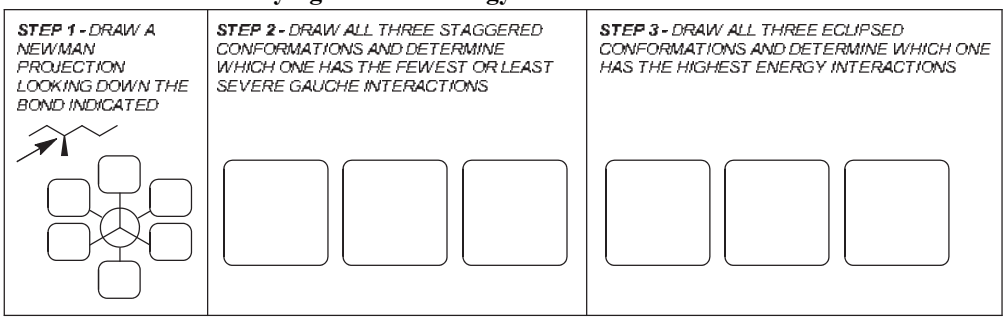
SkillBuilder 4.6 Identifying Constitutional Isomers



SkillBuilder 4.7 Drawing Newman Projections



SkillBuilder 4.8 Identifying Relative Energy of Conformations



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SkillBuilder 4.9
Drawing a Chair Conformation

DRAW A CHAIR CONFORMATION

SkillBuilder 4.10
Drawing Axial and Equatorial Positions

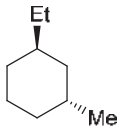
DRAW A CHAIR CONFORMATION SHOWING ALL SIX AXIAL POSITIONS AND ALL SIX EQUATORIAL POSITIONS

SkillBuilder 4.11 Drawing Both Chair Conformations of a Monosubstituted Cyclohexane

DRAW BOTH CHAIR CONFORMATIONS OF BROMOCYCLOHEXANE

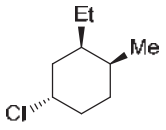
SkillBuilder 4.12 Drawing Both Chair Conformations of Disubstituted Cyclohexanes

DRAW BOTH CHAIR CONFORMATIONS OF THE FOLLOWING COMPOUND



SkillBuilder 4.13 Drawing the More Stable Chair Conformation of Polysubstituted Cyclohexanes

DRAW BOTH CHAIR CONFORMATIONS OF THE FOLLOWING COMPOUND AND DETERMINE WHICH ONE IS MORE STABLE



Common Mistakes to Avoid

You might find that you struggle with problems that ask you to draw constitutional isomers. Don't be discouraged. Many students struggle with drawing constitutional isomers. In particular, it is sometimes difficult to find ALL of the constitutional isomers with a particular molecular formula, and it is also difficult to avoid drawing the same compound more than once. However, these skills will be critical as we progress through the upcoming chapters. So, in order to get more proficient with constitutional isomers, do the following:

1) Skip to Section 14.16 of your textbook, and read that entire section (it is only a few pages, and you do not need any background to understand that section in its entirety). Then, do SkillBuilder 14.4, including all of the problems in that SkillBuilder.

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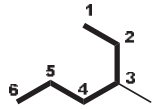
2) Review the methodical approach for drawing constitutional isomers that is presented in the solution to problem 4.3.
3) Try to do problem 4.15, using the approach outlined in the solution to problem 4.3, and then check the solution to problem 4.15 to make sure that you applied the approach correctly.

If you complete the three tasks above, you should gain confidence in your ability to draw constitutional isomers and to avoid drawing the same isomer twice.

Solutions

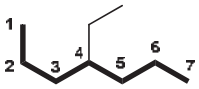
4.1.

(a) The longest chain is six carbon atoms (shown below), so the parent is hexane:



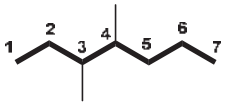
Parent = hexane

(b) The longest chain is seven carbon atoms (shown below), so the parent is heptane:



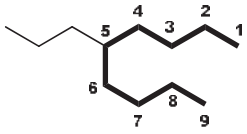
Parent = heptane

(c) The longest chain is seven carbon atoms (shown below), so the parent is heptane:



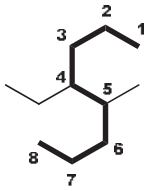
Parent = heptane

(d) The longest chain is nine carbon atoms (shown below), so the parent is nonane:



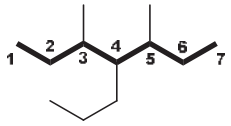
Parent = nonane

(e) The longest chain is eight carbon atoms (shown below), so the parent is octane:



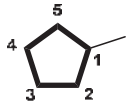
Parent = octane

(f) The longest chain is seven carbon atoms, so the parent is heptane. In this case, there is more than one seven-carbon chain. While the parent will be heptane regardless of which chain we choose, the correct parent chain is the one with the most substituents, shown below (this will be important later when we must use the numbering scheme to identify the locations of the substituents connected to the chain):



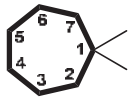
Parent = heptane

(g) This compound has a five-membered ring (shown below), so the parent is cyclopentane:



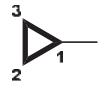
Parent = cyclopentane

(h) This compound has a seven-membered ring (shown below), so the parent is cycloheptane:



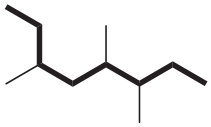
Parent = cycloheptane

(i) This compound has a three-membered ring (shown below), so the parent is cyclopropane:

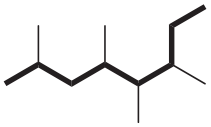


Parent = cyclopropane

4.2. Each of the following two compounds has a parent chain of eight carbon atoms (octane). The other two compounds that appear in the problem statement (not shown here) have parent chains of seven and nine carbon atoms, respectively.



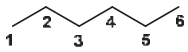
Parent = octane



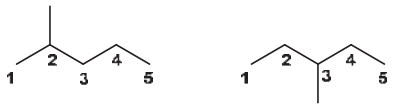
Parent = octane

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4.3. Recall that constitutional isomers are compounds that have the same molecular formula but differ in their constitution (connectivity of atoms). We must draw all constitutional isomers of hexane. Hexane is a linear chain of six carbon atoms:



The first step is to look for any constitutional isomers where the parent is pentane (five carbon atoms). There are only two such isomers. Specifically, we can either connect the extra CH_3 group to positions C2 or C3 of the pentane chain:



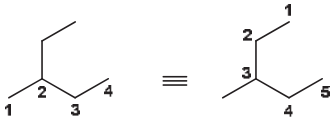
We cannot connect the CH_3 group to positions C1 or C5, as that would simply give us the linear chain (hexane), which we already drew (above). We also cannot connect the CH_3 group to position C4 as that would generate the same structure as placing the CH_3 group at the C2 position:



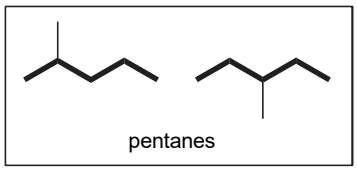
Next, we look for any constitutional isomers where the parent is butane (four carbon atoms). There are only two such isomers. Specifically, we can either connect two CH_3 groups to adjacent positions (C2 and C3) or the same position:

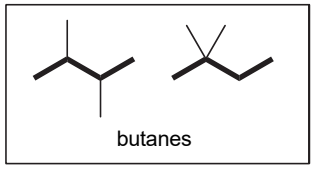


If we try to connect a CH_3CH_2 group to a butane chain, we end up with a pentane chain (an isomer already drawn above):



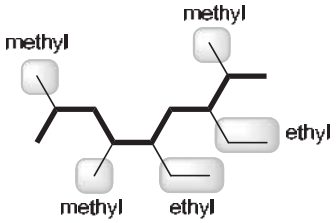
In summary, we have found the four isomers of hexane (two pentanes and two butanes):



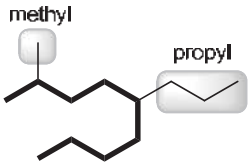


4.4.

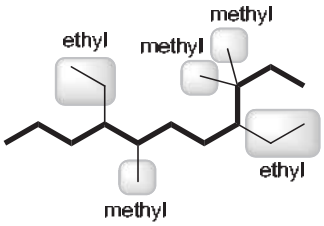
(a) First, we identify the parent (nonane), and then we identify any alkyl substituents (highlighted) that are connected to the parent.



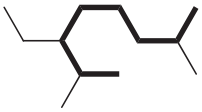
(b) First, we identify the parent (nonane), and then we identify any alkyl substituents (highlighted) that are connected to the parent.



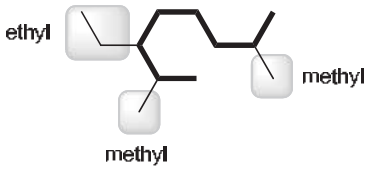
(c) First, we identify the parent (undecane), and then we identify any alkyl substituents (highlighted) that are connected to the parent.



4.5. First identify the parent by looking for the longest chain. In this case, there are two paths of equal length, so we choose the path with the greatest number of branches, as indicated below in bold.



The parent has eight carbon atoms (octane). Everything connected to the chain is a substituent, and we use Table 4.2 to name each substituent:

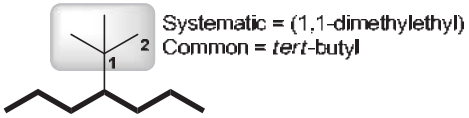


4.6.

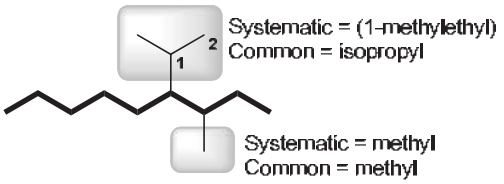
(a) First we identify the parent chain (heptane), and then we identify any alkyl substituents connected to the parent. In this case, the substituent (highlighted) is complex, so we treat it as a "substituent on a

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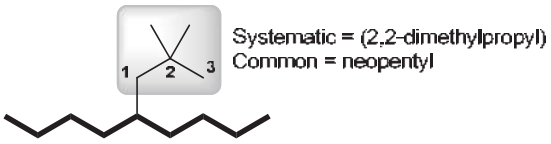
substituent," and we assign a name based on numbers going away from the parent:



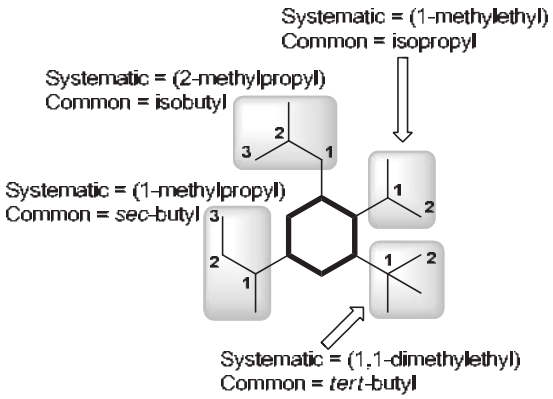
(b) First we identify the parent chain (nonane), and then we identify any alkyl substituents connected to the parent. In this case, one of the highlighted substituents is complex, so we treat it as a "substituent on a substituent," and we assign a name based on numbers going away from the parent:



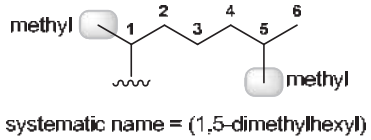
(c) First we identify the parent chain (nonane), and then we identify any alkyl substituents connected to the parent. In this case, the substituent (highlighted) is complex, so we treat it as a "substituent on a substituent," and we assign a name based on numbers going away from the parent:



(d) First we identify the parent chain (cyclohexane), and then we identify any alkyl substituents connected to the parent. In this case, all four substituents (highlighted) are complex, so we treat each of them as a "substituent on a substituent," and we assign a name based on numbers going away from the parent:



4.7. We treat this complex substituent as a "substituent on a substituent." The longest chain that starts at the attachment point has six carbon atoms, so this is a hexyl group. Then we assign numbers such that the attachment point is carbon 1. With this numbering scheme, shown below, there are two methyl substituents at positions 1 and 5, so the name of the side chain is (1,5-dimethylhexyl).



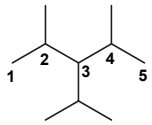
systematic name = (1,5-dimethylhexyl)

4.8. For each of the following compounds, we assign its name via a four-step process: First identify the parent, then the substituents, then assign locants, and finally, arrange the substituents alphabetically. In each case, use commas to separate numbers from each other, and use hyphens to separate letters from numbers.

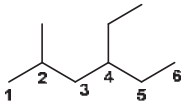
(a) 3,4,6-trimethyloctane
(b) *sec*-butylcyclohexane
(c) 3-ethyl-2-methylheptane
(d) 3-isopropyl-2,4-dimethylpentane
(e) 3-ethyl-2,2-dimethylhexane
(f) 2-cyclohexyl-4-ethyl-5,6-dimethyloctane
(g) 3-ethyl-2,5-dimethyl-4-propylheptane
(h) 2,2,6,6,7,7-hexamethylnonane
(i) 4-*tert*-butylheptane
(j) 1,3-diisopropylcyclopentane
(k) 3-ethyl-2,5-dimethylheptane

4.9.

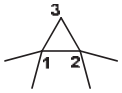
(a) The name indicates that the parent is a five-carbon chain and there are three substituents (a methyl group at C2, an isopropyl group at C3 and another methyl group at C4):



(b) The name indicates that the parent is a six-carbon chain and there are two substituents (a methyl group at C2 and an ethyl group at C4):



(c) The name indicates that the parent is a three-membered ring and there are four substituents (all methyl groups), as shown:



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4.10. For each compound, we assign its name in the following way: First identify the parent, then the substituents, and then assign locants (the final step, arranging the substituents alphabetically, is not needed for any of these examples). In each case, use commas to separate numbers from each other, and use hyphens to separate letters from numbers.

(a) 2,2-dimethylundecane

(b) 2-methyldodecane

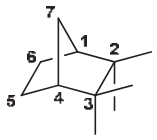
(c) 2,2-dimethyloctane

(d) butylcyclohexane

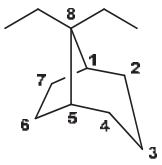
4.11. For each of the following compounds, we assign its name via a four-step process: First identify the parent, then the substituents, then assign locants, and finally, arrange the substituents alphabetically. When assigning locants, make sure to start at a bridgehead and continue numbering along the longest path to the second bridgehead. Then continue assigning locants along the second longest path, and then finally, along the shortest path that connects the two bridgehead positions.

(a) 4-ethyl-1-methylbicyclo[3.2.1]octane
(b) 2,2,5,7-tetramethylbicyclo[4.2.0]octane
(c) 2,7,7-trimethylbicyclo[4.2.2]decane
(d) 3-*sec*-butyl-2-methylbicyclo[3.1.0]hexane
(e) 2,2-dimethylbicyclo[2.2.2]octane

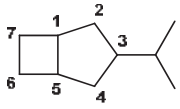
4.12.
(a) The name indicates a bicyclic parent with two methyl groups at C2 and two methyl groups at C3, as shown:



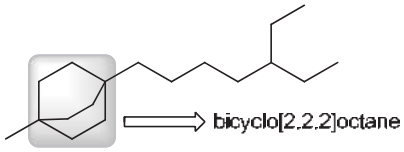
(b) The name indicates a bicyclic parent with two ethyl groups at C8, as shown:



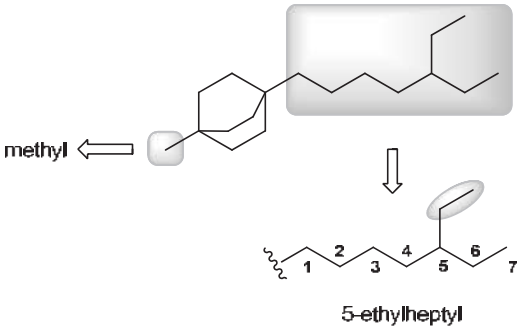
(c) The name indicates a bicyclic parent with an isopropyl group at C3, as shown:



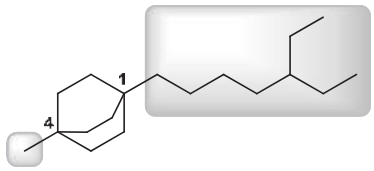
4.13. The bicyclic parent contains eight carbon atoms (highlighted below). There are two carbon atoms in each of the three possible paths that connect the bridgehead carbons, so this bicyclic parent is bicyclo[2.2.2.]octane.



There are two substituents on this bicyclic system. One is a methyl substituent and the other one is a complex substituent that is called 5-ethylheptyl, as shown below:



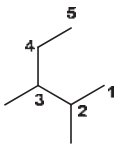
The locants for the two substituents are positions 1 and 4 on the bicyclic parent, and the lower number should be assigned according to which substituent comes first alphabetically.



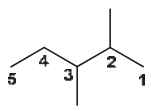
Finally, we arrange the substituents alphabetically and place them before the parent, giving the following complete IUPAC name:

1-(5-ethylheptyl)-4-methylbicyclo[2.2.2]octane

4.14.
(a) If we assign a systematic name for each of these structures, we find that they share the same name (2,3-dimethylpentane). Therefore, these drawings are simply different representations of the same compound.



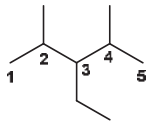
2,3-dimethylpentane



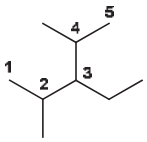
2,3-dimethylpentane

(b) If we assign a systematic name for each of these structures, we find that they share the same name (3-ethyl-2,4-dimethylpentane). Therefore, these drawings are simply different representations of the same compound.

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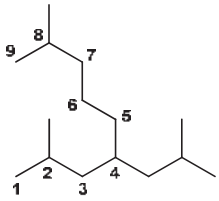


3-ethyl-2,4-dimethyl pentane

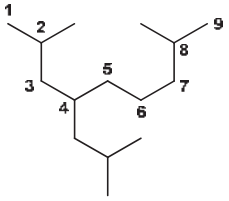


3-ethyl-2,4-dimethyl pentane

(c) If we assign a systematic name for each of these structures, we find that they share the same name (4-isobutyl-2,8-dimethylnonane). Therefore, these drawings are simply different representations of the same compound.

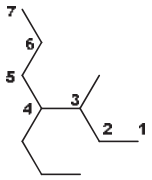


4-isobutyl-2,8-dimethyl nonane

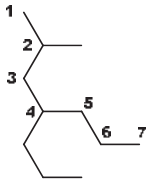


4-isobutyl-2,8-dimethyl nonane

(d) We assign a systematic name to each structure, and find that they have different names (shown below). Therefore, they must differ in their constitution (connectivity of atoms). These compounds are therefore different from each other, but they share the same molecular formula ($C_{11}H_{24}$), so they are constitutional isomers.

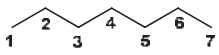


3-methyl-4-propyl heptane



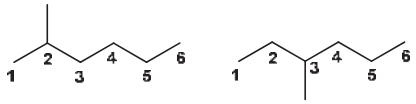
2-methyl-4-propyl heptane

4.15. We must draw all of the constitutional isomers of heptane:

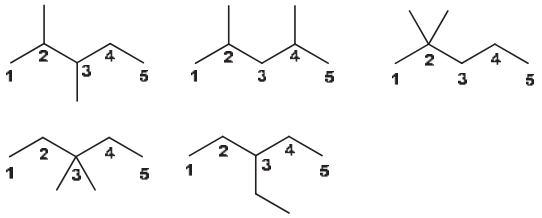


To accomplish the goal, we will follow the same methodical approach that we used in Problem **4.3**. We begin by drawing all possible substituted hexanes with the molecular formula C_7H_{16}. There are only two possibilities - the methyl group can be placed at either C2 or C3. Then, we move on to the pentanes, and finally any possible butanes. This methodical analysis gives the following constitutional isomers:

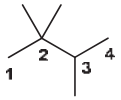
Parent = hexane



Parent = pentane

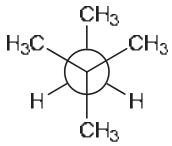


Parent = butane

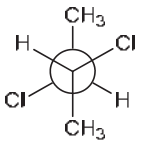


4.16.

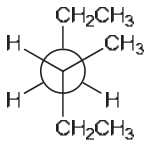
(a) When looking from the perspective of the observer (as shown in the problem statement), the front carbon is connected to three methyl groups and the back carbon is connected to one methyl group pointing up.



(b) When looking from the perspective of the observer (as shown in the problem statement), the front carbon is connected to a chlorine atom pointing up and to the right, as well as a methyl group pointing down. The back carbon atom is connected to a chlorine atom pointing down and to the left, as well as a methyl group pointing up.



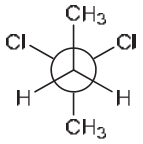
(c) When looking from the perspective of the observer (as shown in the problem statement), the front carbon is connected to a methyl group pointing up and to the right, as well as an ethyl group pointing down. The back carbon atom is connected to an ethyl group pointing up.



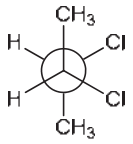
(d) When looking from the perspective of the observer (as shown in the problem statement), the front carbon is connected to a methyl group pointing up. The back

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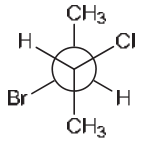
carbon atom is connected to a methyl group pointing down and two chlorine atoms, as shown.



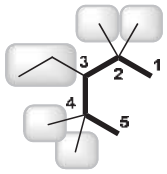
(e) When looking from the perspective of the observer (as shown in the problem statement), the front carbon is connected to a methyl group pointing up and a chlorine atom pointing down and to the right. The back carbon atom is connected to a methyl group pointing down and a chlorine atom pointing up and to the right, as shown.



(f) When looking from the perspective of the observer (as shown in the problem statement), the front carbon is connected to a chlorine atom pointing up and to the right, as well as a methyl group pointing down. The back carbon atom is connected to a methyl group pointing up and a bromine atom pointing down and to the left.

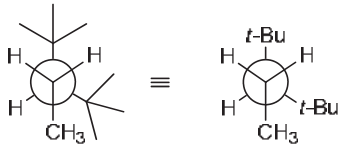


4.17. First we identify the parent chain (pentane). In this case, there are several choices for the parent (all of which are five carbon atoms), so we choose the one with the greatest number of substituents. This parent has five substituents: four methyl groups and one ethyl group, which are arranged alphabetically, together with their appropriate locants, to give the following IUPAC name:

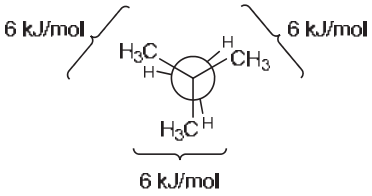


3-ethyl-2,2,4,4-tetramethylpentane

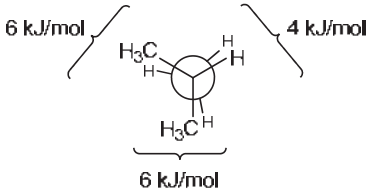
For the Newman projection, when looking from the perspective of the observer (as shown in the problem statement), the front carbon is connected to one methyl group pointing down, and the back carbon is connected to two *tert*-butyl groups: one pointing up and the other pointing down and to the right:



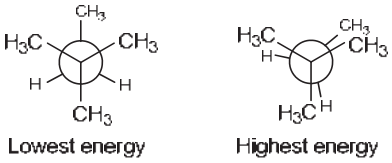
4.18.
(a) The energy barrier is expected to be approximately 18 kJ/mol (calculation below):



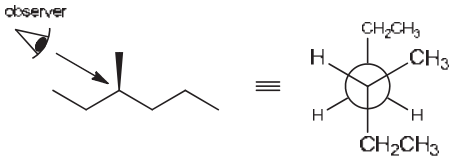
(b) The energy barrier is expected to be approximately 16 kJ/mol (calculation below):



4.19.
(a) In the Newman projection, the front carbon atom has three methyl groups, and the back carbon has one methyl group. Since the front carbon atom has three identical groups, we expect all staggered conformations to be degenerate. Similarly, we expect all eclipsed conformations to be degenerate as well. The lowest energy conformation is the staggered conformation, and the highest energy conformation is the eclipsed conformation.



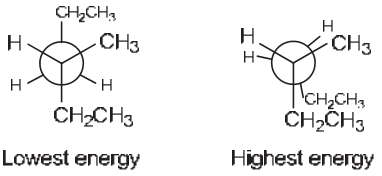
(b) We begin by converting the bond-line drawing into a Newman projection.



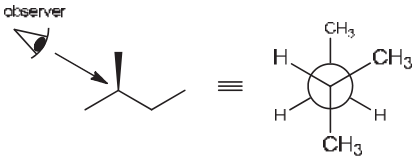
We expect the lowest energy conformation to be staggered and the highest energy conformation to be eclipsed. The lowest energy staggered conformation is the conformation in which the two ethyl groups are *anti* to each other, while the highest energy conformation is

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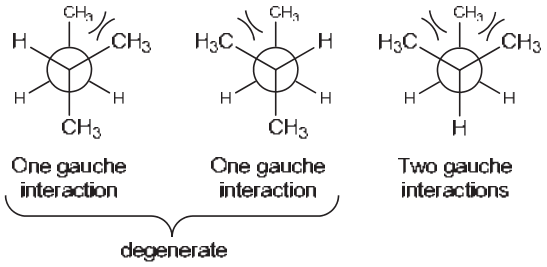
the eclipsed conformation in which the two ethyl groups are eclipsing each other:



(c) We begin by converting the bond-line drawing into a Newman projection.

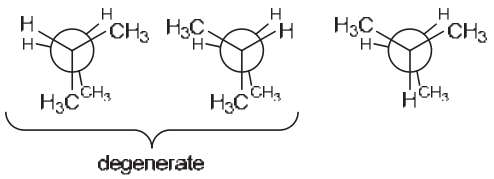


We expect the lowest energy conformation to be staggered and the highest energy conformation to be eclipsed. Let's first explore the three staggered conformations, shown below. One of these conformations exhibits two gauche interactions, while the other two staggered conformations are degenerate, with each having only one gauche interaction:



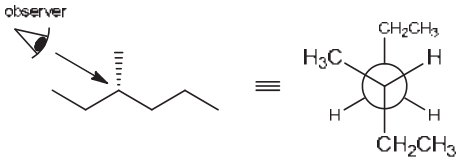
The two degenerate conformations are lowest in energy among all available conformations.

In order to determine which conformation is highest in energy, we must examine the eclipsed conformations. There are three eclipsed conformations, shown below. Two of these conformations are degenerate because they exhibit a methyl-methyl eclipsing interaction:

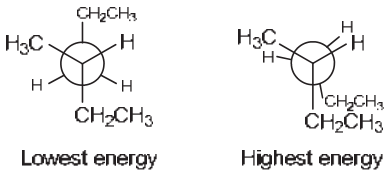


These two degenerate conformations are highest in energy among all available conformations.

(d) We begin by converting the bond-line drawing into a Newman projection.

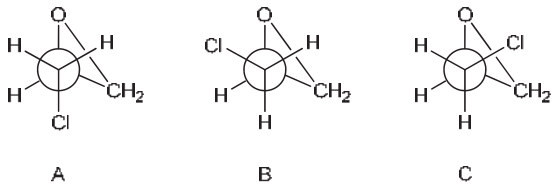


We expect the lowest energy conformation to be staggered and the highest energy conformation to be eclipsed. The lowest energy conformation is the staggered conformation in which the two ethyl groups are *anti* to each other, while the highest energy conformation is the eclipsed conformation in which the two ethyl groups are eclipsing each other:



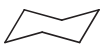
4.20.

(a) The three possible staggered conformations of **1**, viewed along the C_a-C_b bond, are as follows:

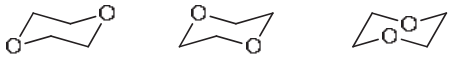


(b) In conformation **C**, there are two gauche interactions: one between the chlorine atom and the CH_2 group, and another between the chlorine atom and the oxygen atom. This conformation is the highest in energy (least stable) due to these two interactions. Conformations **A** and **B** each exhibit only one of these two gauche interactions.

4.21. The step-by-step procedure in the SkillBuilder should provide the following drawing:



4.22. The chair conformation for this compound is similar to the chair conformation of cyclohexane, but two of the carbon atoms have been replaced with oxygen atoms. Each of the following drawings represents dioxane, with oxygen atoms in the 1 and 4 positions:



All three drawings represent the same compound (viewed from different angles). This can be seen clearly if you build a molecular model of dioxane (in a chair conformation) and view it from different angles. Indeed, there are still more representations that could be drawn

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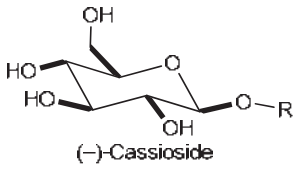
for dioxane in its chair conformation, looking from other perspectives.

4.23. The step-by-step procedure in the SkillBuilder should provide the following drawing:



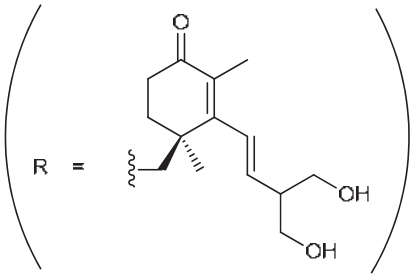
4.24.

(a) Note that the bonds to the attached groups are all parallel to a bond in the ring, and none are in a vertical position. All five groups attached to the six-membered ring occupy equatorial positions (indicated with bold bonds).

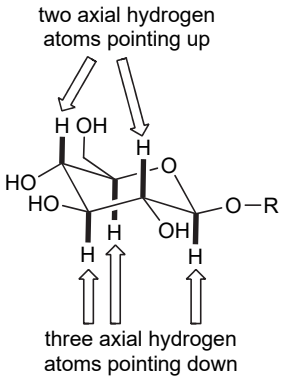


(–)-Cassioside

all five groups are in equatorial positions

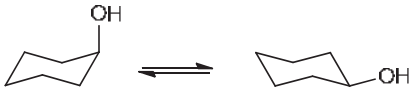


(b) Each carbon atom in the six-membered ring has a hydrogen atom in the axial position:

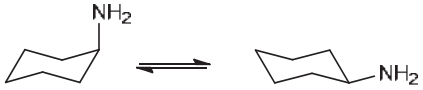


4.25.

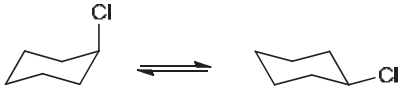
(a) In one chair conformation, the substituent (OH) occupies an axial position. In the other chair conformation, the substituent occupies an equatorial position:



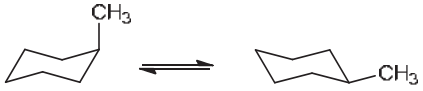
(b) In one chair conformation, the substituent (NH_2) occupies an axial position. In the other chair conformation, the substituent occupies an equatorial position:



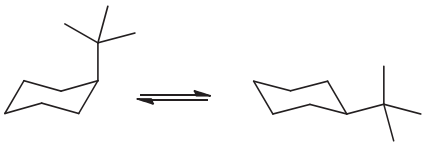
(c) In one chair conformation, the substituent (Cl) occupies an axial position. In the other chair conformation, the substituent occupies an equatorial position:



(d) In one chair conformation, the methyl group occupies an axial position. In the other chair conformation, the methyl group occupies an equatorial position:

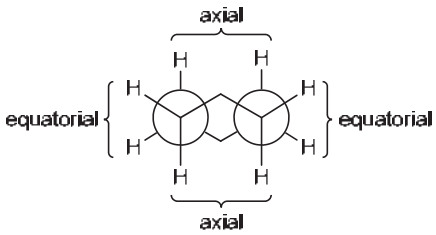


(e) In one chair conformation, the *tert*-butyl group occupies an axial position. In the other chair conformation, the *tert*-butyl group occupies an equatorial position:



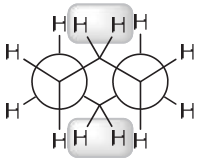
4.26.

(a) In a Newman projection of cyclohexane, the four hydrogen atoms that point straight up or straight down occupy axial positions, while the four hydrogen atoms that point out to either side are equatorial:

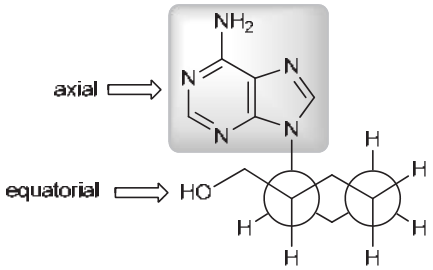


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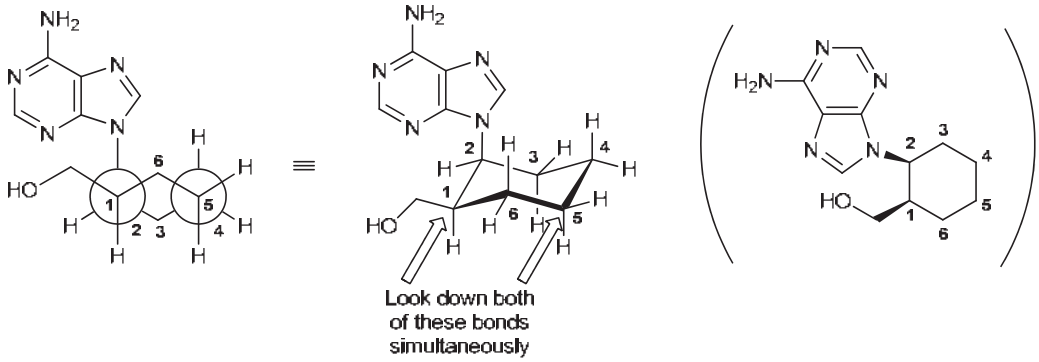
Notice that four of the twelve hydrogens are not drawn explicitly; rather they are implied by the bond line intersections (highlighted):



In the structure shown in the problem statement, the adenine group occupies an axial position and the CH_2OH group occupies an equatorial position.

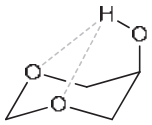


(b) The carbon atoms of the cyclohexane ring are numbered in the Newman projection and in the chair conformation (the bond-line structure is also included for reference). Note that these numbers do not necessarily have to be in accordance with IUPAC rules, but that is OK, because we are not assigning a name. Rather, we are using the numbers just to redraw the compound. In all depictions, the CH_2OH group is attached to carbon atom **1** and the adenine group is attached to carbon atom **2** (a clockwise relationship going from **1** to **2**).



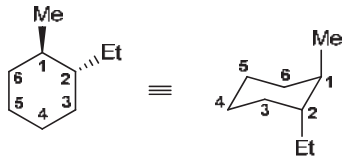
Carbon atoms **1** & **5** are the front carbon atoms in both forms; likewise, carbon atoms **2** & **4** are the back carbon atoms. The bond between carbon atoms **1** and **2** (and between carbon atoms **5** and **4**) are implied by the Newman projections. The CH_2OH group is up and equatorial in both forms, while the adenine is up and axial in both forms. The clockwise location of the adenine group compared to the CH_2OH is an important feature which must be maintained in all depictions of the structure; this will be explored in more detail in Chapter 5.

4.27. Although the OH group is in an axial position, this conformation is capable of intramolecular hydrogen bonding, which is a stabilizing effect:

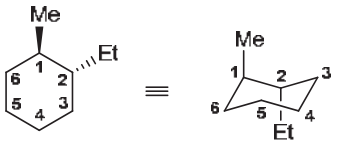


4.28.

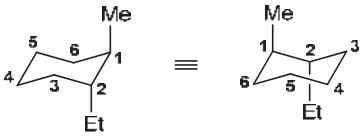
(a) Begin by assigning a numbering system (which does not need to adhere to IUPAC rules), and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and there is an ethyl group at C-2, which is down:



When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring. For example, it would be perfectly acceptable to draw the chair like this:

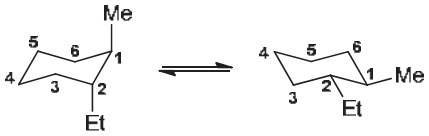


At first it might look like this is a different chair than the one previously drawn. But let's compare them:

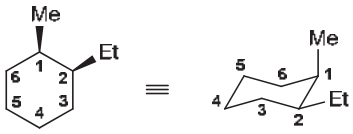


In both drawings, if we travel clockwise around the ring, we will encounter the methyl group first and the ethyl group second. Also, in both chair drawings, the methyl group is up and the ethyl group is down. Therefore, either of these drawings is an acceptable chair representation. Neither one is "more correct" than the other (to see this more clearly, you may find it helpful to build a molecular model and view it from different angles).

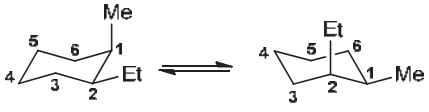
Once we have drawn the first chair conformation, we then draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



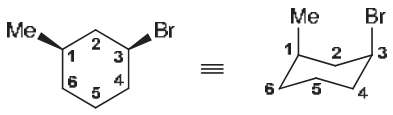
(b) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and there is an ethyl group at C-2, which is also up:



Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.

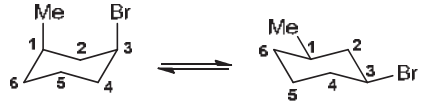


(c) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and there is a bromo group at C-3, which is also up:

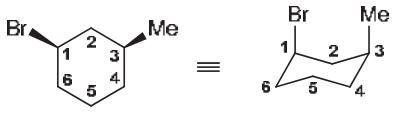


When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise).

Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.

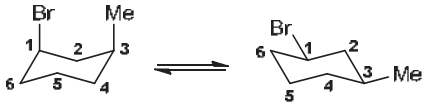


(d) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a bromo group at C-1, which is up, and there is a methyl group at C-3, which is also up:

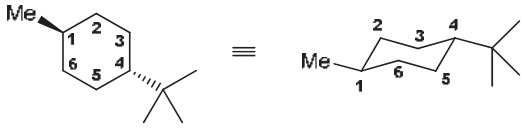


When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to part (a) of this problem.

Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



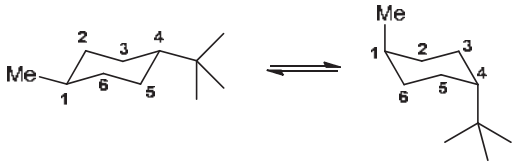
(e) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and a *tert*-butyl group at C-4, which is down:



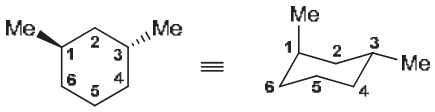
Notice that the numbering system need not adhere to IUPAC rules – the numbering system is simply a tool that we are using to guide us. When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as seen in the solution to part (a) of this problem.

Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.

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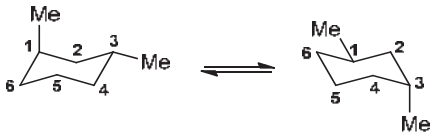


(f) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and another methyl group at C-3, which is down:

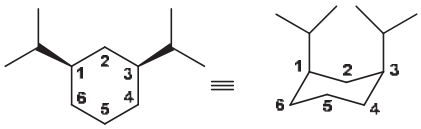


When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to part (a) of this problem.

Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.

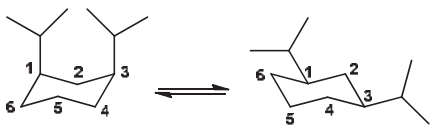


(g) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is an isopropyl group at C-1, which is up, and another isopropyl group at C-3, which is also up:



When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to part (a) of this problem.

Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



(h) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and another methyl group at C-4, which is also up:

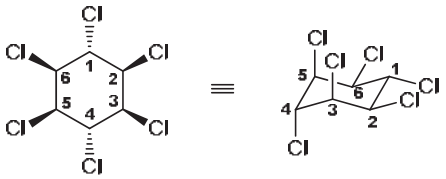


When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to part (a) of this problem.

Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.

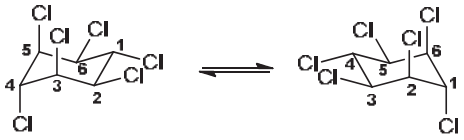


4.29. Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent:



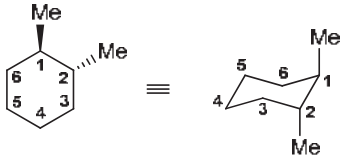
When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to part (a) of the previous problem.

Finally, we draw the second chair conformation, once again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



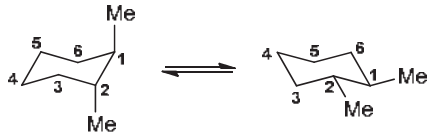
4.30.

(a) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and a methyl group at C-2, which is down:



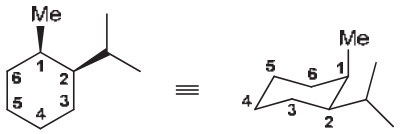
When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to Problem **4.28a**.

Once we have drawn the first chair conformation, we then draw the second chair conformation, again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



Finally, we compare both chair drawings and determine which one has fewer or less severe 1,3-diaxial interactions. In the first drawing, both substituents occupy axial positions, but in the second drawing, both substituents occupy equatorial positions. As such, the latter is more stable, since it lacks 1,3-diaxial interactions.

(b) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent. In this case, there is a methyl group at C-1, which is up, and an isopropyl group at C-2, which is also up:



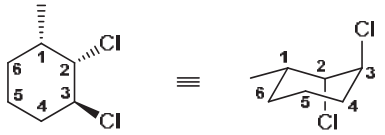
When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to Problem **4.28a**.

Once we have drawn the first chair conformation, we then draw the second chair conformation, again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



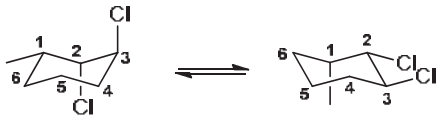
Finally, we compare both chair drawings and determine which one has fewer or less severe 1,3-diaxial interactions. In the first drawing, the methyl group occupies an axial position, but in the second drawing, the isopropyl group occupies an axial position. As such, the former is more stable, since it is expected to have less severe 1,3-diaxial interactions.

(c) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent:



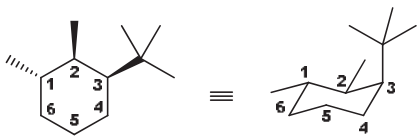
When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to Problem **4.28a**.

Once we have drawn the first chair conformation, we then draw the second chair conformation, again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



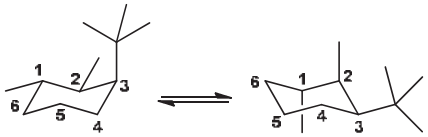
Finally, we compare both chair drawings and determine which one has fewer or less severe 1,3-diaxial interactions. In the first drawing, the methyl group occupies an equatorial position, while both chloro groups occupy axial positions. In the second drawing, the methyl group occupies an axial position, while both chloro groups occupy equatorial positions. According to the data presented in Table 4.8, each methyl group experiences 1,3-diaxial interactions of 7.6 kJ/mol, while each chloro group experiences 1,3-diaxial interactions of 2.0 kJ/mol. As such, the 1,3-diaxial interactions from the methyl group are more severe than the combined 1,3-diaxial interactions of the two chloro groups (4.0 kJ/mol). As such, the more stable conformation is the one in which the methyl group occupies an equatorial position.

(d) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent:



When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to Problem **4.28a**.

Once we have drawn the first chair conformation, we then draw the second chair conformation, again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



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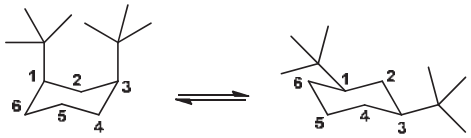
Finally, we compare both chair drawings and determine which one has fewer or less severe 1,3-diaxial interactions. In the first drawing, the *tert*-butyl group occupies an axial position, while both methyl groups occupy equatorial positions. In the second drawing, the *tert*-butyl group occupies an equatorial position, while both methyl groups occupy equatorial positions. According to the data presented in Table 4.8, each methyl group experiences 1,3-diaxial interactions of 7.6 kJ/mol, while a *tert*-butyl group experiences 1,3-diaxial interactions of 22.8 kJ/mol. As such, the 1,3-diaxial interactions from the one *tert*-butyl group are more severe than the combined 1,3-diaxial interactions of the methyl groups (15.2 kJ/mol). As such, the more stable conformation is the one in which the *tert*-butyl group occupies an equatorial position.

(e) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent:



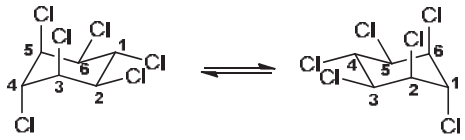
When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to Problem **4.28a**.

Once we have drawn the first chair conformation, we then draw the second chair conformation, again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



Finally, we compare both chair drawings and determine which one has fewer or less severe 1,3-diaxial interactions. In the first drawing, both *tert*-butyl groups occupy axial positions, but in the second drawing, both occupy equatorial positions. As such, the latter is more stable, since it lacks 1,3-diaxial interactions.

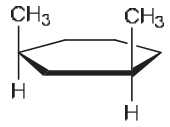
4.31. Each chair conformation has three substituents occupying equatorial positions and three substituents occupying axial positions:



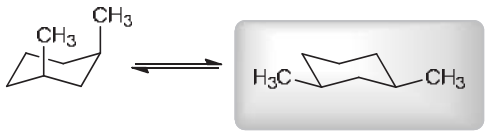
As such, the two chair conformations of lindane are degenerate. There is no difference in energy between them.

4.32. *trans*-1,4-di-*tert*-butylcyclohexane exists predominantly in a chair conformation, because both substituents can occupy equatorial positions. In contrast, *cis*-1,4-di-*tert*-butylcyclohexane cannot have both of its substituents in equatorial positions. Each chair conformation has one of the substituents in an axial position, which is high in energy. The compound can achieve a lower energy state by adopting a twist boat conformation.

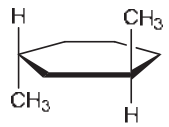
4.33. *cis*-1,3-dimethylcyclohexane is expected to be more stable than *trans*-1,3-dimethylcyclohexane because the former can adopt a chair conformation in which both substituents are in equatorial positions (highlighted below):



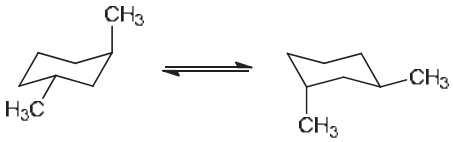
cis-1,3-dimethylcyclohexane



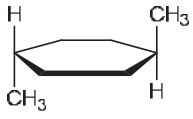
In contrast, *trans*-1,3-dimethylcyclohexane cannot adopt a chair conformation in which both substituents are in equatorial positions. Each chair conformation has one methyl group in an axial position:



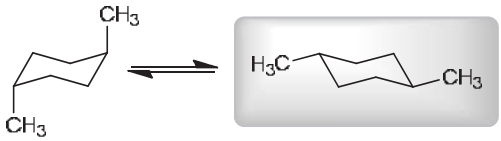
trans-1,3-dimethylcyclohexane



4.34. *trans*-1,4-dimethylcyclohexane is expected to be more stable than *cis*-1,4-dimethylcyclohexane because the former can adopt a chair conformation in which both substituents are in equatorial positions (highlighted below):

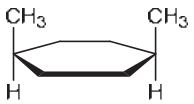


trans-1,4-dimethylcyclohexane

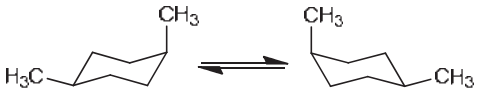


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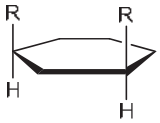
In contrast, *cis*-1,4-dimethylcyclohexane cannot adopt a chair conformation in which both substituents are in equatorial positions. Each chair conformation has one methyl group in an axial position:



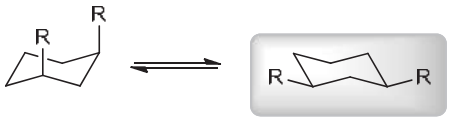
cis-1,4-dimethylcyclohexane



4.35. *cis*-1,3-di-*tert*-butylcyclohexane can adopt a chair conformation in which both *tert*-butyl groups occupy equatorial positions (highlighted below), and as a result, it is expected to exist primarily in that conformation.

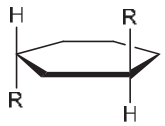


cis-1,3-di-*tert*-butylcyclohexane

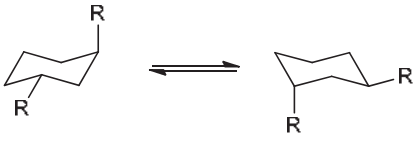


(R = *tert*-butyl group)

In contrast, *trans*-1,3-di-*tert*-butylcyclohexane cannot adopt a chair conformation in which both *tert*-butyl groups occupy equatorial positions. In either chair conformation, one of the *tert*-butyl groups occupies an axial position.



trans-1,3-di-*tert*-butylcyclohexane



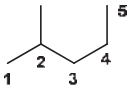
(R = *tert*-butyl group)

This compound can achieve a lower energy state by adopting a twist-boat conformation.

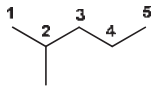
4.36. For each of the following compounds, we assign its name via a four-step process: First identify the parent, then the substituents, then assign locants, and finally, arrange the substituents alphabetically. In each case, use commas to separate numbers from each other, and use hyphens to separate letters from numbers.

(a) 4-ethyl-3-methyloctane
(b) 5-isopropylnonane
(c) 4-propyl-2-methyloctane:
(d) 4-*tert*-butylheptane
(e) 5-*sec*-butyl-4-ethyl-2-methyldecane
(f) 3-ethyl-6-isopropyl-2,4-dimethyldecane
(g) 3,5-diethyl-2-methyloctane
(h) 2,3,5-trimethyl-4-propylheptane
(i) 1,2,4,5-tetramethyl-3-propylcyclohexane
(j) 2,3,5,9-tetramethylbicyclo[4.4.0]decane
(k) 1,4-dimethylbicyclo[2.2.2]octane

4.37.
(a) If we assign a systematic name for each of these structures, we find that they share the same name (2-methylpentane). Therefore, these drawings are simply different representations of the same compound.

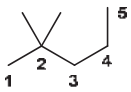


2-methylpentane

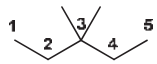


2-methylpentane

(b) We assign a systematic name to each structure, and find that they have different names (shown below). Therefore, they must differ in their constitution (connectivity of atoms). These compounds are therefore different from each other, but they share the same molecular formula (C_7H_{16}), so they are constitutional isomers.

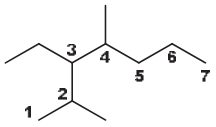


2,2-dimethylpentane

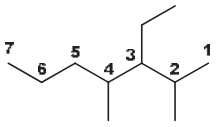


3,3-dimethylpentane

(c) If we assign a systematic name for each of these structures, we find that they share the same name (3-ethyl-2,4-dimethylheptane). Therefore, these drawings are simply different representations of the same compound.



3-ethyl-2,4-dimethyl heptane

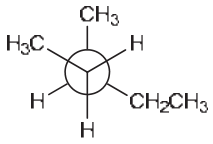


3-ethyl-2,4-dimethyl heptane

4.38. When looking down the C2-C3 bond, the front carbon atom has one methyl group and two H's, while the back carbon atom has an ethyl group, a methyl group, and a hydrogen atom. The lowest energy conformation is the staggered conformation with the fewest and least severe gauche interactions, shown here. In this

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conformation, there is only one Me-Me gauche interaction.

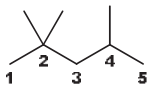


4.39. Both compounds share the same molecular formula (C_6H_{14}). That is, they are constitutional isomers, and the unbranched isomer is expected to have the larger heat of combustion:

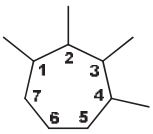


4.40.

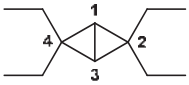
(a) The name indicates that the parent is a five-carbon chain and there are three substituents (two methyl groups at C2, and one methyl group at C4):



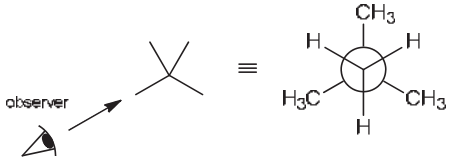
(b) The name indicates that the parent is a seven-membered ring and there are four substituents (all methyl groups), as shown:



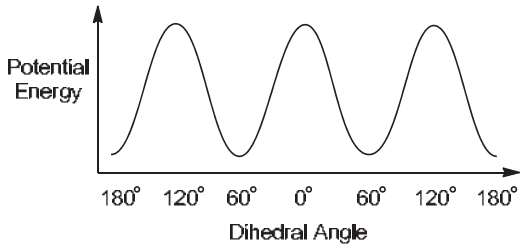
(c) The name indicates a bicyclic parent with two ethyl groups at C2 and two ethyl groups at C4, as shown:



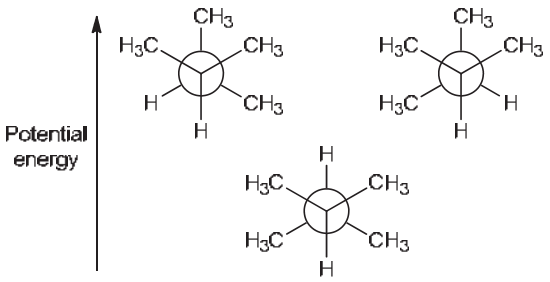
4.41. We begin by drawing a Newman projection of 2,2-dimethylpropane:



Notice that the front carbon has three identical groups (all H's), and the back carbon atom also has three identical groups (all methyl groups). As such, we expect all staggered conformations to be degenerate, and we expect all eclipsed conformations to be degenerate as well. Therefore, the energy diagram will more closely resemble the shape of the energy diagram for the conformational analysis of ethane.

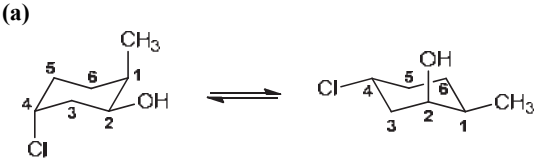


4.42. Two of the staggered conformations are degenerate. The remaining staggered conformation is lower in energy than the other two, as shown:

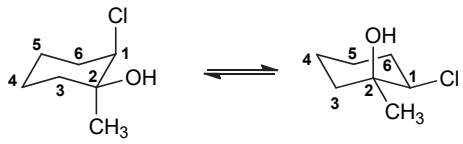


4.43. For each of the following cases, we draw the second chair conformation using a numbering system to ensure the substituents are placed correctly. The numbering system does NOT need to adhere to IUPAC rules, as it is just a tool that we are using to draw both chair conformations correctly. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.

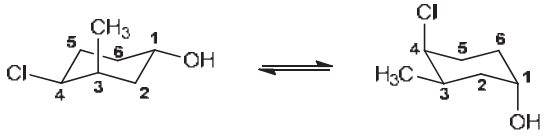
(a)



(b)



(c)



4.44.

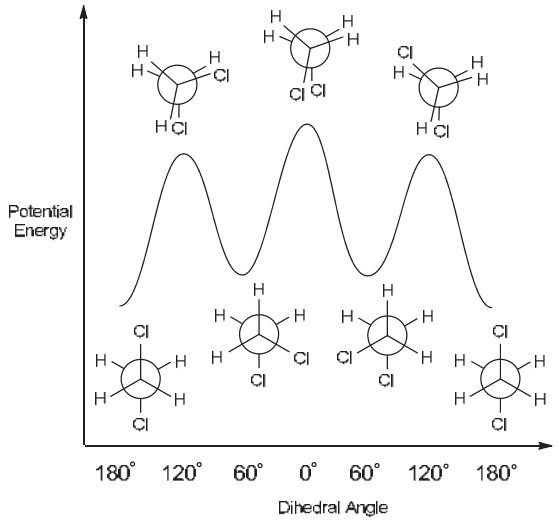
(a) The second compound is expected to have a higher heat of combustion because it has more carbon atoms.

(b) The first compound is expected to have a higher heat of combustion because it cannot adopt a chair conformation in which both methyl groups occupy equatorial positions.

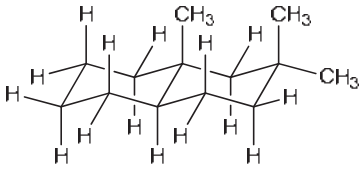
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(c) The second compound is expected to have a higher heat of combustion because it cannot adopt a chair conformation in which both methyl groups occupy equatorial positions.
(d) The first compound is expected to have a higher heat of combustion because it cannot adopt a chair conformation in which both methyl groups occupy equatorial positions.

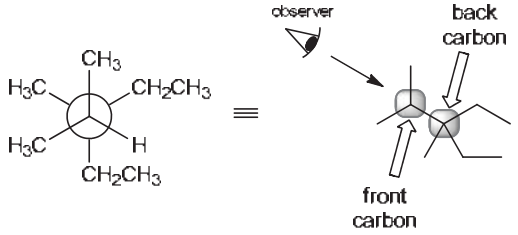
4.45. The energy diagram of 1,2-dichloroethane is similar to the energy diagram of butane (see Figure 4.11). The CH_3 groups have simply been replaced with chloro groups.



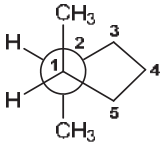
4.46. There are eight hydrogen atoms in axial positions and seven hydrogen atoms in equatorial positions.



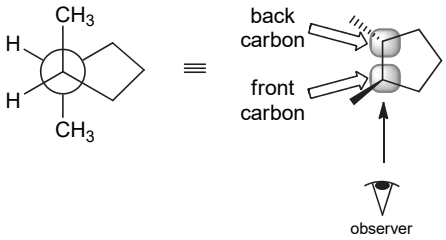
4.47.
(a) The Newman projection indicates that the front carbon atom is connected to two methyl groups, while the back carbon atom is connected to two ethyl groups and a methyl group. This corresponds with the following bond-line drawing:



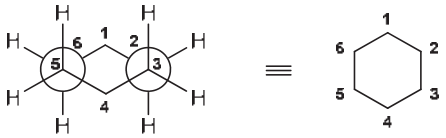
(b) The Newman projection indicates that the front carbon atom and the back carbon atom are part of a five-membered ring:



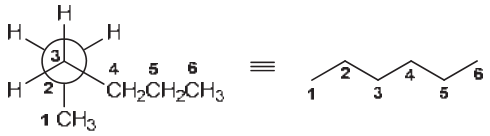
The front carbon atom is connected to a methyl group pointing above the ring, while the back carbon atom is connected to a methyl group pointing below the ring. This corresponds with the following bond-line drawing:



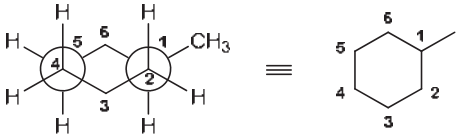
(c) In this case, there are two Newman projections connected to each other, indicating a ring. If we count the carbon atoms, we can see that it is a six-membered ring (cyclohexane):



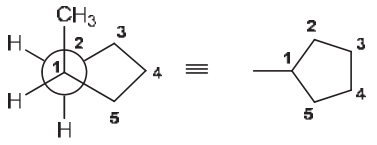
4.48.
(a) We first convert the Newman projection into a bond-line drawing, because it is easier to assign a systematic name to a bond-line drawing. In this case, the compound is hexane:



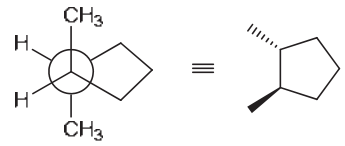
(b) We first convert the Newman projection into a bond-line drawing, because it is easier to assign a systematic name to a bond-line drawing. In this case, the compound is methylcyclohexane:



(c) We first convert the Newman projection into a bond-line drawing, because it is easier to assign a systematic name to a bond-line drawing. In this case, the compound is methylcyclopentane:

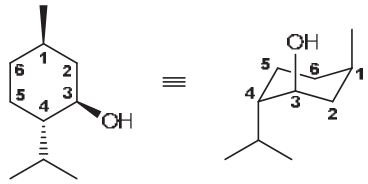


(d) As seen in the solution to Problem **4.47b**, this compound is *trans*-1,2-dimethylcyclopentane:



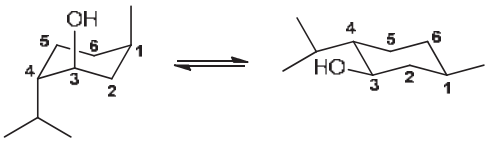
4.49. Each H-H eclipsing interaction is 4 kJ/mol, and there are two of them (for a total of 8 kJ/mol). The remaining energy cost is associated with the Br-H eclipsing interaction: 15 – 8 = 7 kJ/mol.

4.50. In order to draw the first chair conformation, begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent:



When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to Problem **4.28a**.

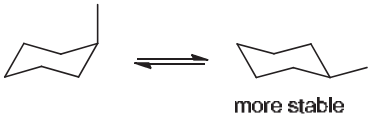
Once we have drawn the first chair conformation, we then draw the second chair conformation, again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



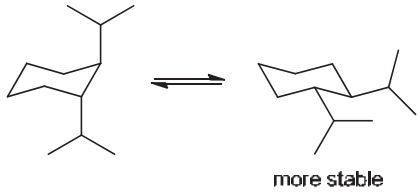
Finally, we compare both chair drawings and determine which one has fewer or less severe 1,3-diaxial interactions. In the first drawing, all three substituents occupy axial positions, but in the second drawing, they all occupy equatorial positions. As such, the latter is more stable.

4.51.

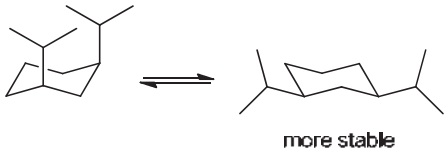
(a) The methyl group occupies an axial position in one chair conformation, and occupies an equatorial position in the other chair conformation. The latter is more stable because it lacks 1,3-diaxial interactions.



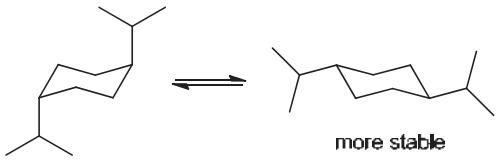
(b) Both isopropyl groups occupy axial positions in one chair conformation, and both occupy equatorial positions in the other chair conformation. The latter is more stable because it lacks 1,3-diaxial interactions.



(c) Both isopropyl groups occupy axial positions in one chair conformation, and both occupy equatorial positions in the other chair conformation. The latter is more stable because it lacks 1,3-diaxial interactions.



(d) Both isopropyl groups occupy axial positions in one chair conformation, and both occupy equatorial positions in the other chair conformation. The latter is more stable because it lacks 1,3-diaxial interactions.



4.52.

(a) The second compound can adopt a chair conformation in which all three substituents occupy equatorial positions. Therefore, the second compound is expected to be more stable.

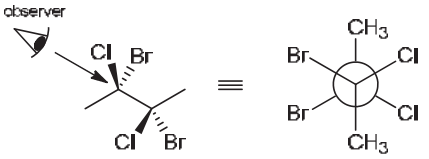
(b) The first compound can adopt a chair conformation in which all three substituents occupy equatorial positions. Therefore, the first compound is expected to be more stable.

(c) The first compound can adopt a chair conformation in which both substituents occupy equatorial positions. Therefore, the first compound is expected to be more stable.

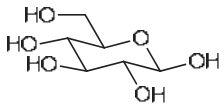
(d) The first compound can adopt a chair conformation in which all four substituents occupy equatorial positions. Therefore, the first compound is expected to be more stable.

4.53. When looking from the perspective of the observer (as shown in the problem statement), the front carbon has a chlorine atom pointing up and to the right, a bromine atom pointing up and the left, and a methyl group pointing down. The back carbon atom has a chlorine atom pointing down and to the right, a bromine atom pointing down and to the left, as well as a methyl group pointing up.

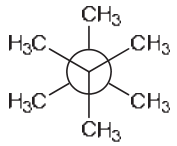
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4.54. Two chair conformations can be drawn. In one of these conformations, all substituents occupy equatorial positions. In the other conformation, all substituents occupy axial positions. The former (shown below) lacks 1,3-diaxial interactions, and is therefore the most stable conformation of glucose:

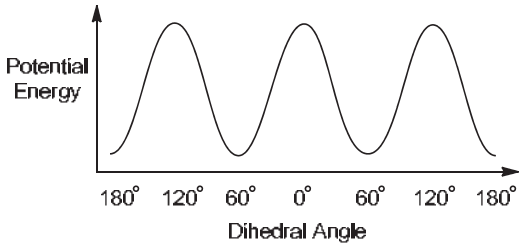


4.55. Begin by drawing a Newman projection:



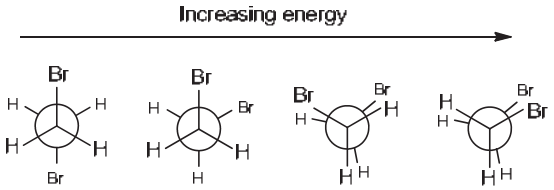
2,2,4,4-tetramethylbutane

All staggered conformations are degenerate, and the same is true for all eclipsed conformations. As such, the energy diagram has a shape that is similar to the energy diagram for the conformational analysis of ethane:



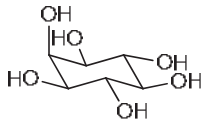
The staggered conformations have six gauche interactions, each of which has an energy cost of 3.8 kJ/mol. Therefore, each staggered conformation has an energy cost of 22.8 kJ/mol. The eclipsed conformations have three methyl-methyl eclipsing interactions, each of which has an energy cost of 11 kJ/mol. Therefore, each eclipsed conformation has an energy cost of 33 kJ/mol. The difference in energy between staggered and eclipsed conformations is therefore expected to be approximately 10.2 kJ/mol.

4.56. The two staggered conformations are lower in energy than the two eclipsed conformations. Among the staggered conformations, the *anti* conformation is the lowest in energy. Among the eclipsed conformations, the highest energy conformation is the one in which the bromine atoms are eclipsing each other. This information is summarized here:

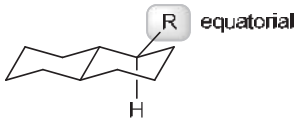


4.57.
(a) This conformation has three gauche interactions, each of which has an energy cost of 3.8 kJ/mol. Therefore, this conformation has a total energy cost of 11.4 kJ/mol associated with steric strain.
(b) This conformation has two methyl-H eclipsing interactions, each of which has an energy cost of 6 kJ/mol. In addition, it also has one methyl-methyl eclipsing interaction, which has an energy cost of 11 kJ/mol. Therefore, this conformation has a total energy cost of 23 kJ/mol associated with torsional strain and steric strain.

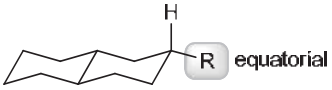
4.58. There are two chair conformations that can be drawn. In one chair conformation, all groups are equatorial except for one. In the other chair conformation, all groups are axial except for one. The former conformation is more stable because it has fewer 1,3-diaxial interactions.



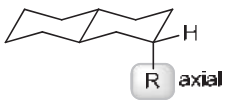
4.59.
(a) A group at C-2, pointing up, will occupy an equatorial position, as seen here:



(b) A group at C-3, pointing down, will occupy an equatorial position, as seen here:

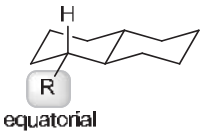


(c) A group at C-4, pointing down, will occupy an axial position, as seen here:

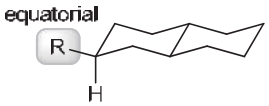


(d) A group at C-7, pointing down, will occupy an equatorial position, as seen here:

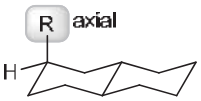
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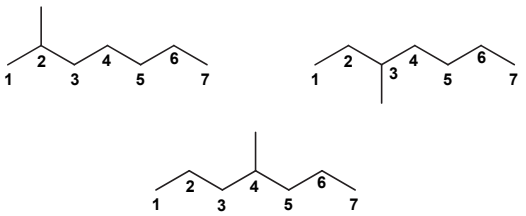
(e) A group at C-8, pointing up, will occupy an equatorial position, as seen here:



(f) A group at C-9, pointing up, will occupy an axial position, as seen here:



4.60. We are looking for constitutional isomers of C_8H_{18} that have a parent chain of seven carbon atoms (heptane). The extra CH_3 group can be placed in any of three positions (C2, C3, or C4) giving the following three constitutional isomers:

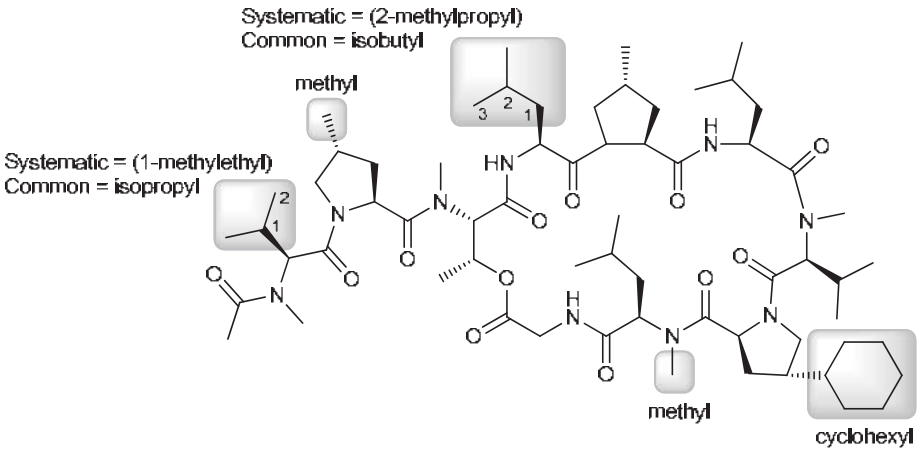


We cannot connect the CH_3 group to positions C1 or C7, as that would give a parent chain of eight carbon atoms (octane). We also cannot connect the CH_3 group to position C5 as that would generate the same structure as placing the CH_3 group at the C3 position:

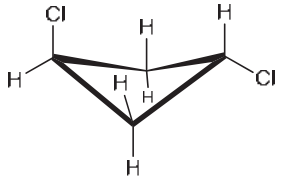


Similarly, we cannot connect the CH_3 group to position C6 as that would generate the same structure as placing the CH_3 group at the C2 position. In summary, there are only three constitutional isomers of C_8H_{18} that have a parent name of heptane (shown above).

4.61. There are five highlighted groups: two methyl groups, one cyclohexyl group and two complex substituents. For each of the complex substituents, we treat it as a "substituent on a substituent," and we assign a name based on numbers going away from the parent, as shown:



4.62. As mentioned in Section 4.9, cyclobutane adopts a slightly puckered conformation in order to alleviate some of the torsional strain associated with the eclipsing hydrogen atoms:



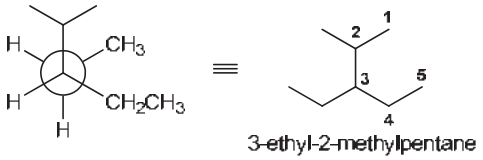
In this non-planar conformation, the individual dipole moments of the C-Cl bonds in *trans*-1,3-dichlorocyclobutane do not fully cancel each other, giving rise to a small molecular dipole moment.

4.63.

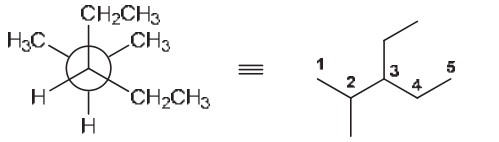
(a) If we convert each Newman projection into a bond-line structure, we will be able to compare the two structures more easily. Then, if we assign a systematic name to each bond-line structure, we find that they have

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the same name. Therefore, these two structures represent the same compound.



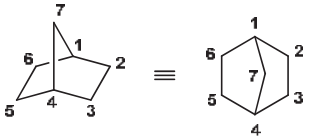
3-ethyl-2-methylpentane



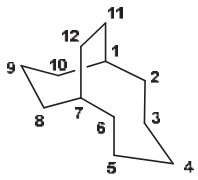
3-ethyl-2-methylpentane

(b) In the first compound, the two methyl groups are attached to C-1 and C-2, but in the second compound, the two methyl groups are attached to C-1 and C-3. These compounds share the same molecular formula (C_8H_{16}), but they have different constitution (connectivity of atoms). Therefore, these two compounds are constitutional isomers.

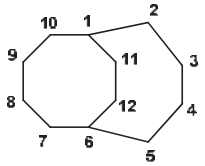
(c) These two structures are both representations of bicyclo[2.2.1]heptane, as can be seen when we apply the numbering system below. These two compounds are the same.



(d) We assign a systematic name to each structure, and find that they have different names (because they have different ring fusions, shown below). Therefore, they differ in their constitution (connectivity of atoms). These compounds are different from each other, but they share the same molecular formula ($C_{12}H_{22}$), so they are constitutional isomers.



Bicyclo[5.3.2]dodecane



Bicyclo[4.4.2]dodecane

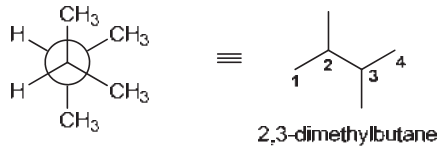
(e) Both of these structures are *cis*-1,4-dimethylcyclohexane. They are representations of the same compound.

(f) The first compound is *cis*-1,4-dimethylcyclohexane, and the second compound is *trans*-1,4-dimethylcyclohexane. These compounds are different, but they do not differ in their constitution. They differ in the 3D arrangement of atoms, so they are stereoisomers.

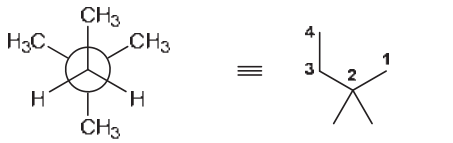
(g) The first compound is *cis*-1,2-dimethylcyclohexane (both methyl groups are in UP positions), and the second compound is *trans*-1,2-dimethylcyclohexane (one methyl group is UP and the other is DOWN). These compounds are different, but they do not differ in their constitution. They differ in the 3D arrangement of atoms, so they are stereoisomers.

(h) The first compound is *cis*-1,2-dimethylcyclohexane (both methyl groups are in UP positions), and the second compound is *trans*-1,2-dimethylcyclohexane (one methyl group is UP and the other is DOWN). These compounds are different, but they do not differ in their constitution. They differ in the 3D arrangement of atoms, so they are stereoisomers.

(i) If we convert each Newman projection into a bond-line structure, we will be able to compare the two structures more easily. Then, if we assign a systematic name to each bond-line structure, we find that they have different names. Since they share the same molecular formula, they are constitutional isomers.



2,3-dimethylbutane



2,2-dimethylbutane

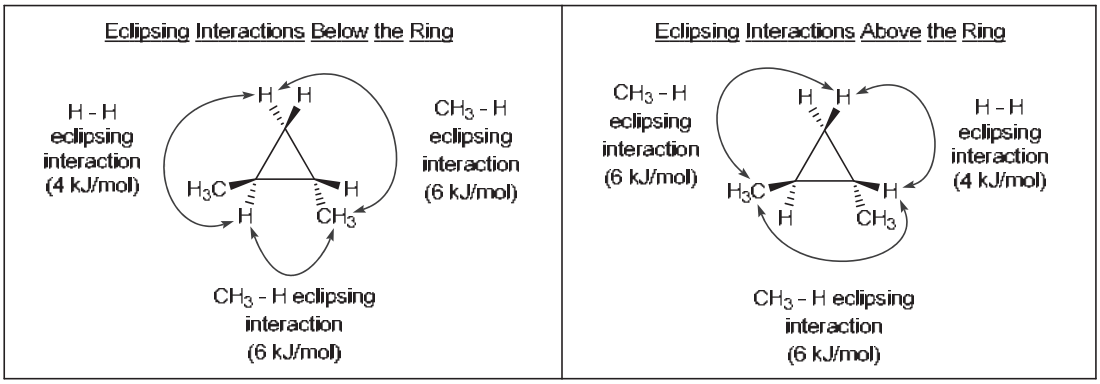
(j) The first compound is *cis*-1,3-dimethylcyclohexane, and the second compound is *trans*-1,3-dimethylcyclohexane. These compounds are different, but they do not differ in their constitution. They differ in the 3D arrangement of atoms, so they are stereoisomers.

(k) In the first compound, the two methyl groups are attached to C-1 and C-3, but in the second compound, the two methyl groups are attached to C-1 and C-2. These compounds share the same molecular formula (C_8H_{16}), but they have different constitution (connectivity of atoms). Therefore, these two compounds are constitutional isomers.

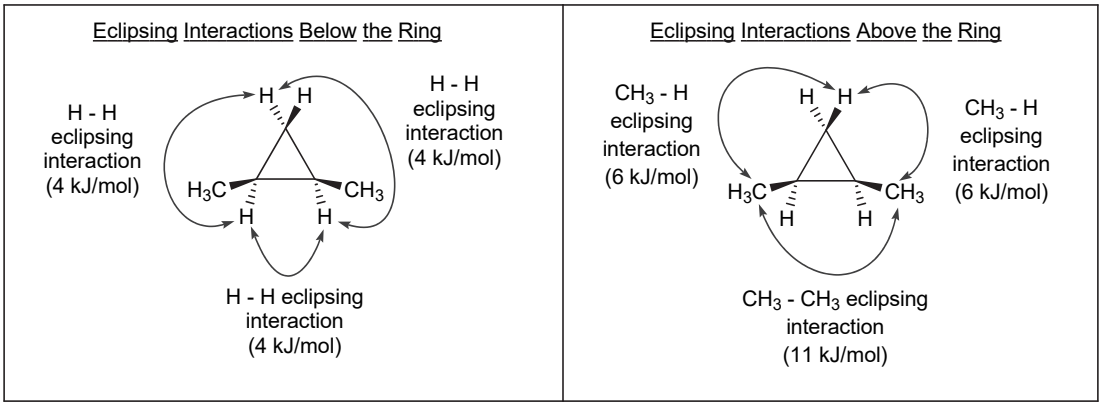
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4.64.
(a) The *trans* isomer is expected to be more stable, because the *cis* isomer has a very high-energy methyl-methyl eclipsing interaction (11 kJ/mol). See calculation below.

(b) We calculate the energy cost associated with all eclipsing interactions in both compounds. Let's begin with the *trans* isomer. It has the following eclipsing interactions, below the ring and above the ring, giving a total of 32 kJ/mol:

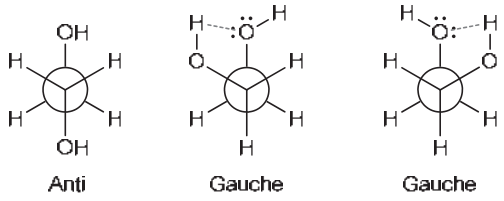


Now let's focus on the *cis* isomer. It has the following eclipsing interactions, below the ring and above the ring, giving a total of 35 kJ/mol:

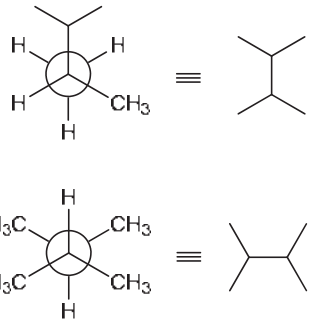


The difference between these two isomers is therefore predicted to be (35 kJ/mol) – (32 kJ/mol) = 3 kJ/mol.

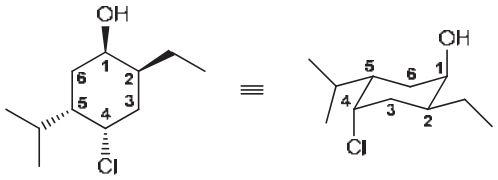
4.65. The gauche conformations are capable of intramolecular hydrogen bonding, as shown below. The *anti* conformation lacks this stabilizing effect.



4.66. If we convert each Newman projection into a bond-line structure, we see that these structures are representations of the same compound (2,3-dimethylbutane). They are not constitutional isomers.

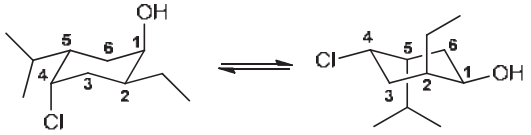


4.67.
(a) Begin by assigning a numbering system, and then determine the location and three-dimensional orientation of each substituent:



When assigning the numbers to the chair drawing, the first number can be placed anywhere on the ring (as long as the numbers go clockwise), as explained in the solution to Problem **4.28a**.

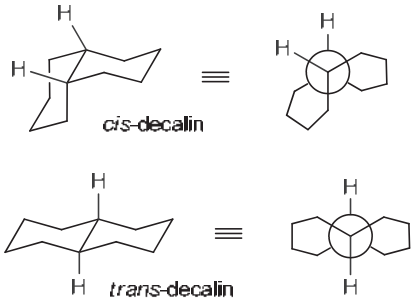
Once we have drawn the first chair conformation, we then draw the second chair conformation, again using a numbering system. Notice that a ring flip causes all equatorial groups to become axial groups, and vice versa.



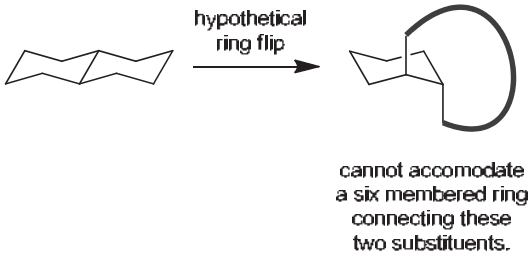
(b) Comparison of these chair conformations requires a comparison of the energy costs associated with all axial substituents (see Table 4.8). The first chair conformation has two axial substituents: an OH group (energy cost = 4.2 kJ/mol) and a Cl group (energy cost = 2.0 kJ/mol), giving a total of 6.2 kJ/mol. The second chair conformation has two axial substituents: an isopropyl group (energy cost = 9.2 kJ/mol) and an ethyl group (energy cost = 8.0 kJ/mol), giving a total of 17.2 kJ/mol. The first chair conformation has a lower energy cost, and is therefore more stable.

(c) Using the numbers calculated in part (b), the difference in energy between these two chair conformations is expected to be (17.2 kJ/mol) – (6.2 kJ/mol) = 11 kJ/mol. Using the numbers in Table 4.8, we see that a difference of 9.2 kJ/mol corresponds with a ratio of 97:3 for the two conformations. In this case, the difference in energy is more than 9.2 kJ/mol, so the ratio should be even higher (more than 97%). Therefore, we do expect the compound to spend more than 95% of its time in the more stable chair conformation.

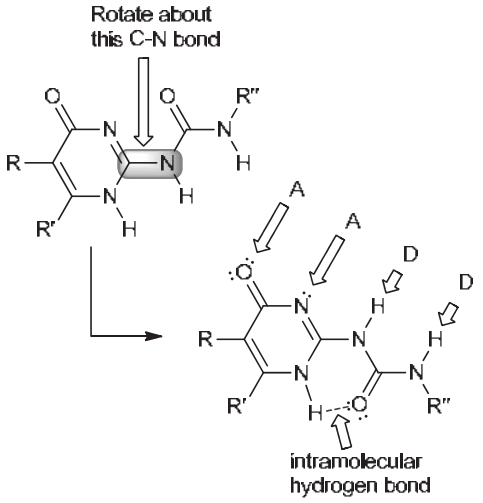
4.68.
(a) *cis*-Decalin has three gauche interactions, while *trans*-decalin has only two gauche interactions. Therefore, the latter is expected to be more stable.



(b) *trans*-Decalin is incapable of ring flipping, because a ring flip of one ring would cause its two alkyl substituents (which comprise the second ring) to be too far apart to accommodate the second ring.

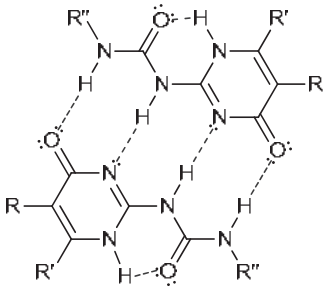


4.69. First, to get the molecule in the right conformation, rotate by 180° around the C-N bond indicated. The resulting conformation allows for an intramolecular hydrogen bond as indicated below by a dotted line. In this conformation, there are two hydrogen-bond acceptors ("A") and two hydrogen bond donors ("D") along the top edge of the molecule as drawn.



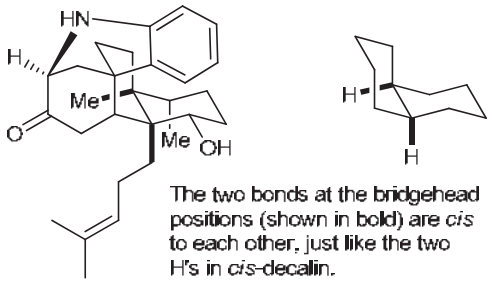
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Next, to show the four intermolecular hydrogen bonds, we draw a second molecule rotated by 180° relative to the first. In this orientation the donor/donor/acceptor/acceptor pattern of the bottom molecule is complementary to the acceptor/acceptor/donor/donor motif on the top molecule resulting in a bimolecular complex with the four intermolecular hydrogen bonds shown below.

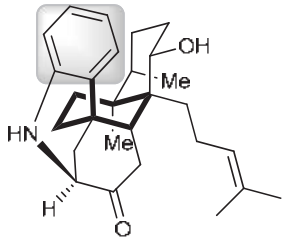


4.70.

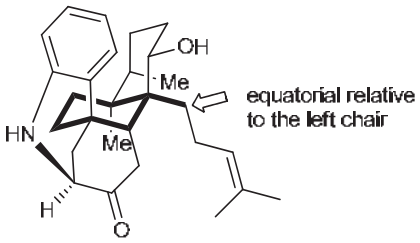
(a) The two substituents at the bridgehead carbons are *cis* to each other, analogous to the two bridgehead hydrogen atoms on *cis*-decalin.



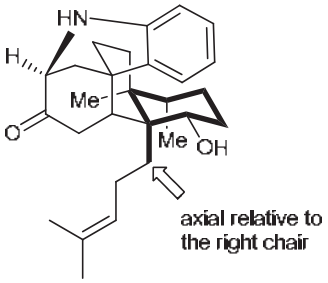
(b) The aromatic ring is in an axial position:



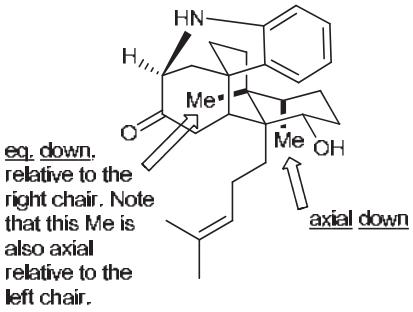
(c) The branch is *equatorial* to the left chair,



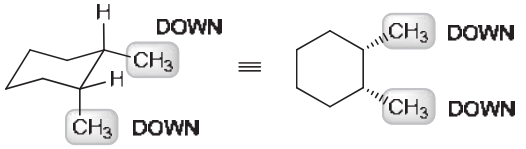
but *axial* to the right chair (note, this structure has been rotated to see the other chair more clearly):



(d) The dihedral angle between the two methyl groups should be approximately 60° (From the perspective of the chair on the right, one is equatorial down, and the other is axial down. They are gauche to each other.)

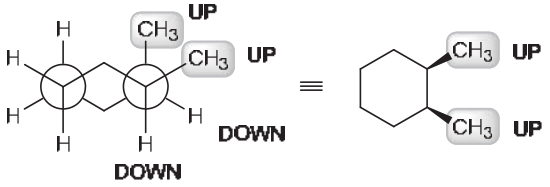


4.71. Compound (a) is *cis*-1,2-dimethylcyclohexane, which can be seen more clearly when the hydrogen atoms are drawn, and it is clear that both methyl groups are DOWN:

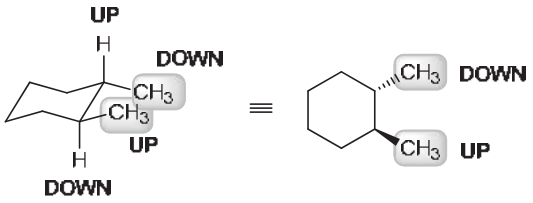


Compound (b) is a Haworth projection of *cis*-1,2-dimethylcyclohexane.

Compound (c) is also *cis*-1,2-dimethylcyclohexane:

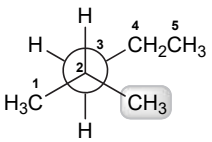


Compound (d) is the correct answer, because this compound is NOT *cis*-1,2-dimethylcyclohexane. Rather, it is *trans*-1,2-dimethylcyclohexane, which can be seen more clearly when the hydrogen atoms are drawn:



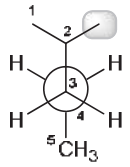
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4.72. As shown below, compound (a) has a five-carbon parent chain, with a methyl group (highlighted) connected to C2. Therefore, this compound is 2-methylpentane:



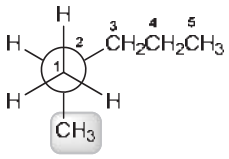
2-methylpentane

Compound (c) also has a five-carbon parent chain, with a methyl group connected to C2, so this compound is also 2-methylpentane:



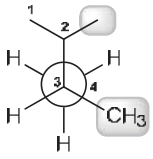
2-methylpentane

Similarly, compound (d) also has a five-carbon parent chain, with a methyl group connected to C2. Therefore, this compound is also 2-methylpentane:



2-methylpentane

The correct answer is compound (b). If we assign numbers to the carbon atoms in compound (b), we find that compound (b) is not 2-methylpetane. Indeed, it is 2,3-dimethylbutane:

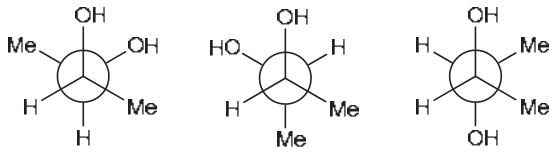


2,3-dimethylbutane

4.73. The compound with the largest heat of combustion will be the compound that is highest in energy. All of the compounds are cycloalkanes with the molecular formula C_5H_{10}, but they differ in the size of the rings. Smaller rings have more ring strain (higher energy), so compounds (a) and (b) are not the correct answers. The answer must be compound (c) or (d), both of which have a highly strained, 3-membered ring. The difference between them is the relative orientation of the methyl groups. The *cis* isomer is expected to have more torsional strain than the *trans* isomer, because the methyl groups are necessarily eclipsed (or close to being so), so compound (c) is the highest energy isomer. Compound (c) is therefore the correct answer.

4.74. Heptane has the molecular formula C_7H_{16}, so we are looking for another compound with the same molecular formula. Compound (a) does not have the correct molecular formula (it is C_7H_{14}, rather than C_7H_{16}) so it is not a constitutional isomer of heptane. Similarly, compound (b) also has the molecular formula C_7H_{14}, so it is also not a constitutional isomer of heptane. Compound (c) has eight carbon atoms, so it is definitely not a constitutional isomer of heptane. Compound (d) is the correct answer, since it has the molecular formula C_7H_{16}.

4.75. The three staggered conformations are as follows:



A **B** **C**

Several types of gauche interactions are present in these conformers (Me-Me, Me-OH, and/or OH-OH). The strain of a methyl-methyl gauche interaction is 3.8 kJ/mol (see Table 4.6). The destabilization due to a Me-OH gauche interaction can be estimated as being roughly half of the value for the 1,3-diaxial interaction associated with an OH group (an OH group in an axial position experiences two gauche interactions, each of which might be expected to be somewhat similar to a Me-OH gauche interaction). Therefore, a Me-OH gauche interaction is expected to be approximately 4.2 / 2 = 2.1 kJ/mol (see Table 4.8).

Before exploring the OH-OH gauche interaction, our analysis thus far gives the following calculations for each conformer

Conformer **A**: 2 x 2.1 kJ/mol = 4.2 kJ/mol
Conformer **B**: 3.8 kJ/mol
Conformer **C**: 2 x 2.1 kJ/mol + 3.8 kJ/mol = 8.0 kJ/mol

This calculation must be modified when we take into account the effect of two OH groups that are gauche to each other, as seen in conformers **A** and **B**. We should expect an OH-OH gauche interaction to be less than a Me-Me gauche interaction (less than 3.8 kJ/mol), because an OH group appears to be less sterically encumbering than a methyl group (compare CH_3 and OH in Table 4.8). Therefore, the destabilizing effect associated with an OH-OH gauche interaction (less than 3.8kJ/mol) should be overshadowed by the *stabilizing* effect that results from the hydrogen bonding interactions between the two OH groups, which is expected to be approximately 20 kJ/mol (see section 1.12). As a result, we expect extra stabilization to be associated with any conformer in which two OH groups are gauche to each other. This occurs in conformers **A** and **B**, but the hydroxyl groups in **C** are too far to form this type of interaction. If we assume that the stabilization achieved through hydrogen bonding is the

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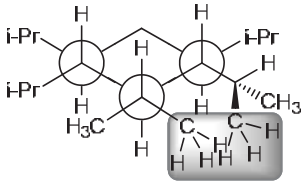
same for conformers **A** and **B**, then conformer **B** should be the lowest-energy staggered conformation for this isomer of 2,3-butanediol.

4.76.

(a) The all-equatorial chair conformation of compound **2** experiences severe steric repulsion due to the nearby isopropyl groups as evident in the following drawing, in which we focus on the interactions between a pair of neighboring isopropyl groups. These interactions, highlighted below, occur for each pair of neighboring isopropyl groups.



A Newman projection of **2**, viewed down one of the C-C bonds connecting an equatorial isopropyl group to the cyclohexane ring, shows how crowded the equatorial groups are as the methyl groups are in constant contact with each other. These interactions, highlighted below, occur for each pair of neighboring isopropyl groups.


i-Pr
i-Pr
i-Pr
i-Pr
H
H
H

Chapter 5
Stereoisomerism

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 5. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

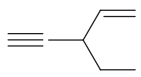
- _____**isomers** have the same connectivity of atoms but differ in their spatial arrangement.
- **Chiral** objects are not **superimposable** on their _____. The most common source of molecular chirality is the presence of a _____, a carbon atom bearing _____ different groups.
- A compound with one chiral center will have one non-superimposable mirror image, called its _____.
- The Cahn-Ingold-Prelog system is used to assign the _____ of a chiral center.
- A **polarimeter** is a device used to measure the ability of chiral organic compounds to rotate the plane of _____ light. Such compounds are said to be _____ **active**.
- A solution containing equal amounts of both enantiomers is called a _____ **mixture**. A solution containing a pair of enantiomers in unequal amounts is described in terms of **enantiomeric** _____ (*ee*).
- For a compound with multiple chiral centers, a family of stereoisomers exists. Each stereoisomer will have at most one enantiomer, with the remaining members of the family being _____.
- A _____ **compound** contains multiple chiral centers but is nevertheless achiral because it possesses reflectional symmetry.
- _____ **projections** are drawings that convey the configuration of chiral centers, without the use of wedges and dashes.
- Compounds that contain two adjacent C=C bonds are called _____, and they are another common class of compounds that can be chiral despite the absence of a chiral center.
- The stereodescriptors *cis* and *trans* are generally reserved for alkenes that are disubstituted. For trisubstituted and tetrasubstituted alkenes, the stereodescriptors ____ and ____ must be used. ____ indicates priority groups on the same side, while ____ indicates priority groups on opposite sides.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 5. The answers appear in the section entitled *SkillBuilder Review*.

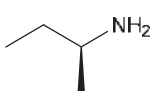
SkillBuilder 5.1 Locating Chiral centers

CIRCLE THE CHIRAL CENTER IN THE FOLLOWING COMPOUND



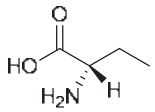
SkillBuilder 5.2 Drawing an Enantiomer

SHOW THREE WAYS TO DRAW THE ENANTIOMER OF THE FOLLOWING COMPOUND. PLACE YOUR ANSWERS IN THE BOXES SHOWN.



SkillBuilder 5.3 Assigning Configuration

ASSIGN THE CONFIGURATION OF THE CHIRAL CENTER IN THE FOLLOWING COMPOUND



SkillBuilder 5.4 Calculating specific rotation

CALCULATE THE SPECIFIC ROTATION GIVEN THE FOLLOWING INFORMATION:

0.300 grams sucrose dissolved in 10.0 mL of water
sample cell = 10.0 cm
observed rotation = +1.99°

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{c \times l} = \frac{\square}{\square \times \square} = \square$$

SkillBuilder 5.5 Calculating % *ee*

CALCULATE THE ENANTIOMERIC EXCESS GIVEN THE FOLLOWING INFORMATION:

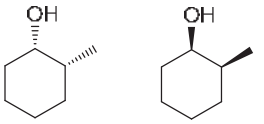
The specific rotation of optically pure adrenaline is –53 .
A mixture of (*R*)- and (*S*)-adrenaline was found to have a specific rotation of –45.
Calculate the % *ee* of the mixture

$$\%\,ee = \frac{\text{observed } [\alpha]}{[\alpha] \text{ of pure enantiomer}} \times 100\,\%$$

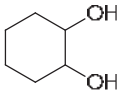
$$= \frac{\square}{\square} \times 100\,\% = \square$$

SkillBuilder 5.6 Determining Stereoisomeric Relationship

IDENTIFY THE STEREOISOMERIC RELATIONSHIP BETWEEN THE FOLLOWING TWO COMPOUNDS



SkillBuilder 5.7 Identifying *Meso* Compounds



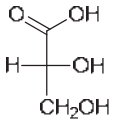
DRAW ALL POSSIBLE STEREOISOMERS OF 1,2-CYCLOHEXANEDIOL (SHOWN LEFT). AND THEN LOOK FOR A PLANE OF SYMMETRY IN ANY OF THE DRAWINGS. THE PRESENCE OF A PLANE OF SYMMETRY INDICATES A MESO COMPOUND

☐ + ☐ = ☐ ☐

ENANTIOMERS ***MESO***

SkillBuilder 5.8 Assigning configuration from a Fischer projection

ASSIGN THE CONFIGURATION OF THE CHIRAL CENTER IN THE FOLLOWING COMPOUND



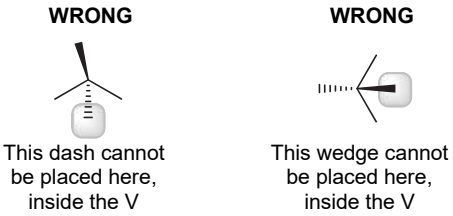
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Common Mistakes to Avoid

When drawing a chiral center, the four groups connected to the chiral center must be drawn so that one group is on a wedge (which indicates that it is coming out of the page), and one group is on a dash (which indicates that it is going behind the page), and two groups are on straight lines (which indicate that these two groups are in the plane of the page), as seen in each of the following drawings:



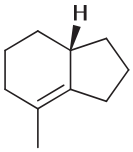
Notice that in all of these cases, the two straight lines form a V, and neither the dash nor the wedge is placed inside that V. This is very important. If either the dash or the wedge is placed inside the V, the drawing becomes ambiguous and inaccurate. Don't make this mistake, as it is a common mistake:



The drawings above do not make any sense, and if a chiral center is drawn like either of the drawings above, it would be impossible to assign a configuration to the chiral center. Never draw a chiral center that way. For the same reason, never draw a chiral center like this:



These two drawings imply square planar geometry, which is not the case for an sp^3 hybridized carbon atom (the geometry is tetrahedral). In some rare cases, you might find a chiral center for which three of the lines are drawn as straight lines, as in the following example:



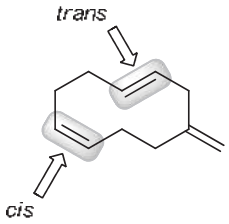
This compound has one chiral center, and its configuration is unambiguous (and therefore acceptable), although you will not encounter this convention often. In most cases that you will encounter in this course, a chiral center will be drawn as two lines (making a V), and one wedge and one dash that are both *outside* of the V:



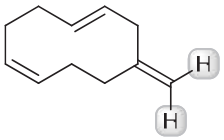
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Solutions

5.1.
There are two C=C units in the ring (highlighted), and their configurations are shown below.



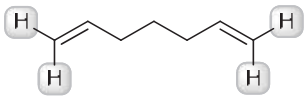
The remaining C=C unit is not stereoisomeric, because it has two identical groups (hydrogen atoms) connected to the same position.



5.2. We first draw a bond-line structure, which makes it easier to see the groups that are connected to each of the double bonds.

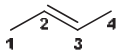


Each of the double bonds has two identical groups (hydrogen atoms) connected to the same position.

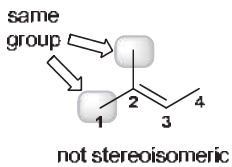


As such, neither double bond exhibits stereoisomerism, so this compound does not have any stereoisomers.

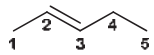
5.3.
(a) Compound X must contain a carbon-carbon double bond in the *trans* configuration, which accounts for four of the five carbon atoms:



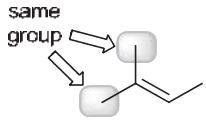
Now we must decide where to place the fifth carbon atom. We cannot attach this carbon atom to a vinylic position (C2 or C3), as that would give a double bond that is not stereoisomeric, and compound X is supposed to have the *trans* configuration.



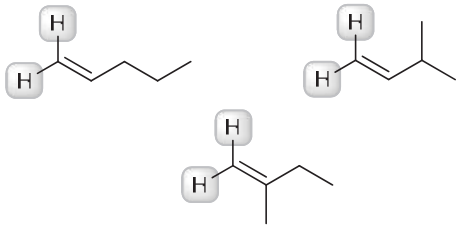
Therefore, we must attach the fifth carbon atom to an allylic position, giving the following compound:



(b) Compound Y possesses a carbon-carbon double bond that is not stereoisomeric, which means that it must contain two identical groups connected to the same vinylic position. Those identical groups can be methyl groups, as in the following compound,

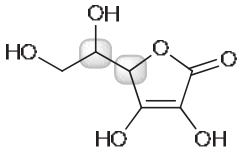


or the identical groups can be hydrogen atoms, as in the following three compounds:

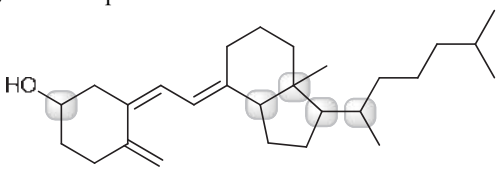


5.4. In each of the following cases, we ignore all sp^2 hybridized carbon atoms, all *sp* hybridized carbon atoms, and all CH_2 and CH_3 groups. We identify those carbon atoms (highlighted below) bearing four different groups:

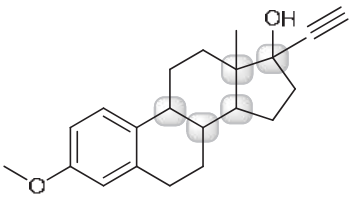
(a) This compound has two chiral centers:



(b) This compound has five chiral centers:

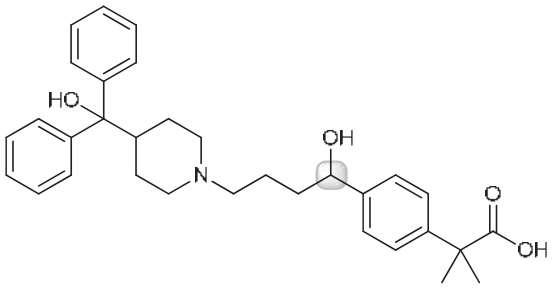


(c) This compound has five chiral centers:



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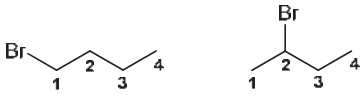
(d) This compound has only one chiral center:



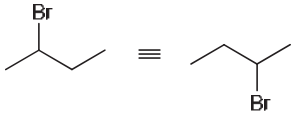
5.5. Recall that constitutional isomers are compounds that share the same molecular formula, but differ in constitution (the connectivity of atoms). There are two different ways that four carbon atoms can be connected together. They can be connected in a linear fashion (below left), or they can be connected with a branch (below right).



For each of these skeletons, we must consider the different locations where a bromine atom can be placed. In the linear skeleton, the bromine atom can either be placed at C1 or at C2.



Placing the bromine atom at C3 is the same as placing it at C2:

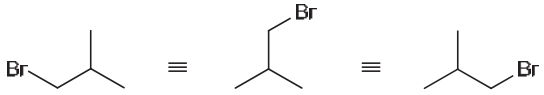


Similarly, placing the bromine atom at C4 is the same as placing it at C1.

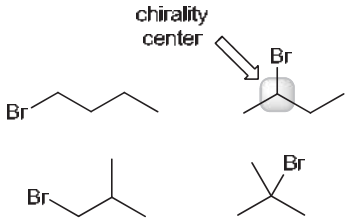
Now let's consider the branched skeleton. There are two unique locations where the bromine atom can be placed (either at C1 or at C2).



Placing the bromine atom at C3 or C4 is the same as placing it at C1:



In summary, we have found four constitutional isomers with the molecular formula C_4H_9Br, shown again here:

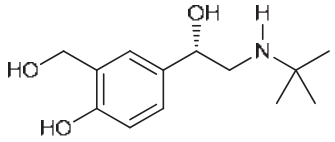


Note that only one of these isomers exhibits a carbon atom that is connected to four different groups, which makes it a chiral center.

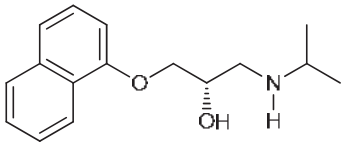
5.6. The phosphorus atom has four different groups attached to it (a methyl group, an ethyl group, a phenyl group, and a lone pair). This phosphorous atom therefore represents a chiral center. This compound is not superimposable on its mirror image (this can be seen more clearly by building and comparing molecular models).

5.7.

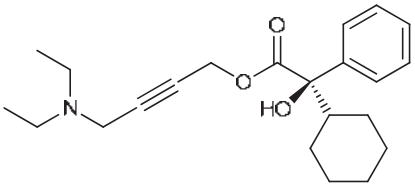
(a) To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace the wedge with a dash, as shown:



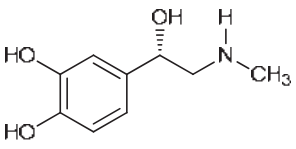
(b) To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace the wedge with a dash, as shown:



(c) To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace the wedge with a dash, and we replace the dash with a wedge, as shown:

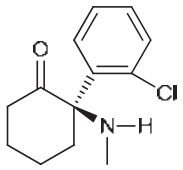


(d) To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace the wedge with a dash, as shown:

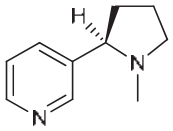


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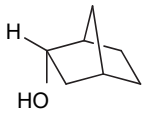
(e) To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace the wedge with a dash, and we replace the dash with a wedge, as shown:



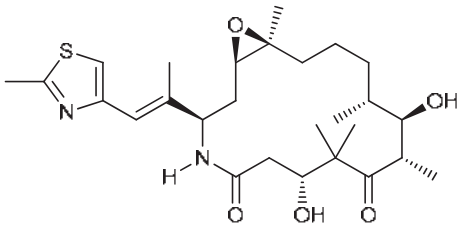
(f) To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace the wedge with a dash, and we replace the dash with a wedge, as shown:



(g) Wedges and dashes are not drawn in the structure in the problem statement, because the three-dimensional geometry is implied by the drawing. In this case, it will be easier to place the mirror on the side of the molecule, giving the following structure for its enantiomer:

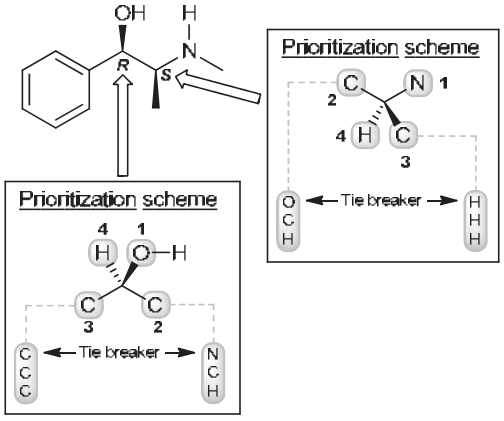


5.8. To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace all of the wedges with dashes, and we replace all of the dashes with wedges, as shown:

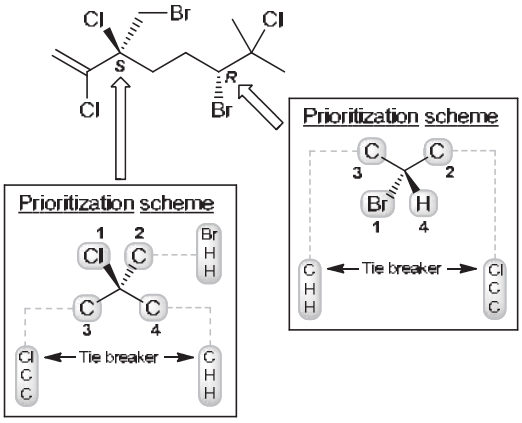


5.9.

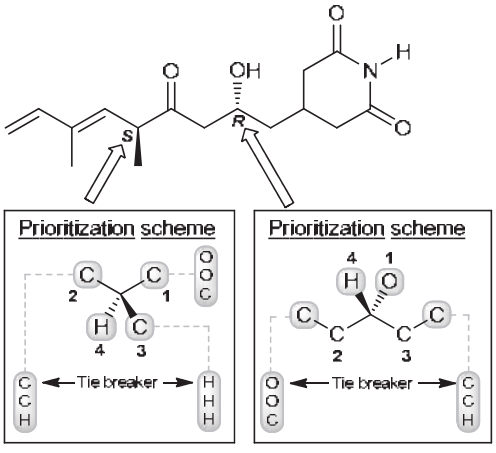
(a) This compound has two chiral centers, shown here. The following prioritization schemes led to the assignment of configuration for each chiral center.



(b) This compound has two chiral centers, shown below. The following prioritization schemes led to the assignment of configuration for each chiral center.

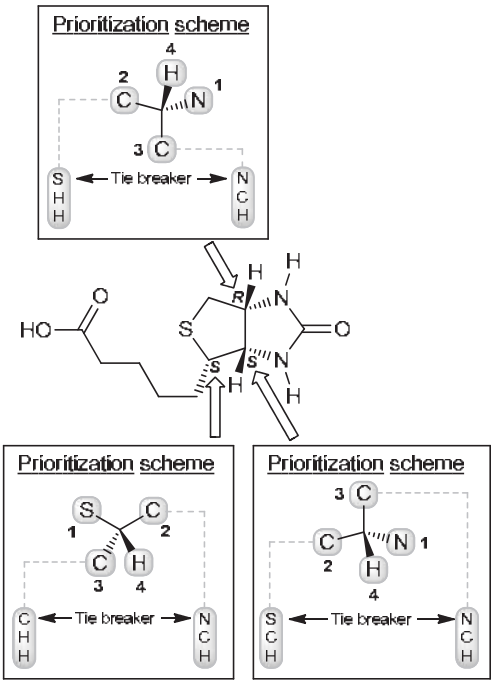


(c) This compound has two chiral centers, shown below. The following prioritization schemes led to the assignment of configuration for each chiral center.

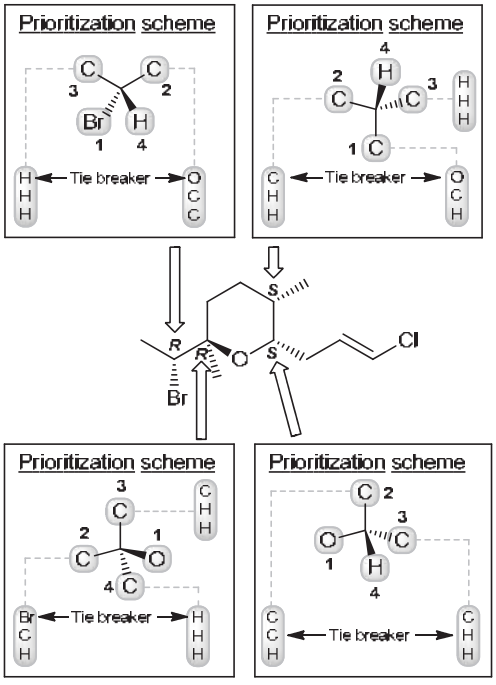


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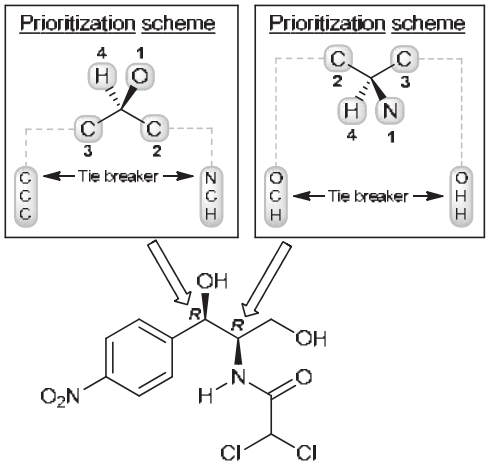
(d) This compound has three chiral centers. The following prioritization schemes led to the assignment of configuration for each chiral center.



(e) This compound has four chiral centers, shown below. The following prioritization schemes led to the assignment of configuration for each chiral center.

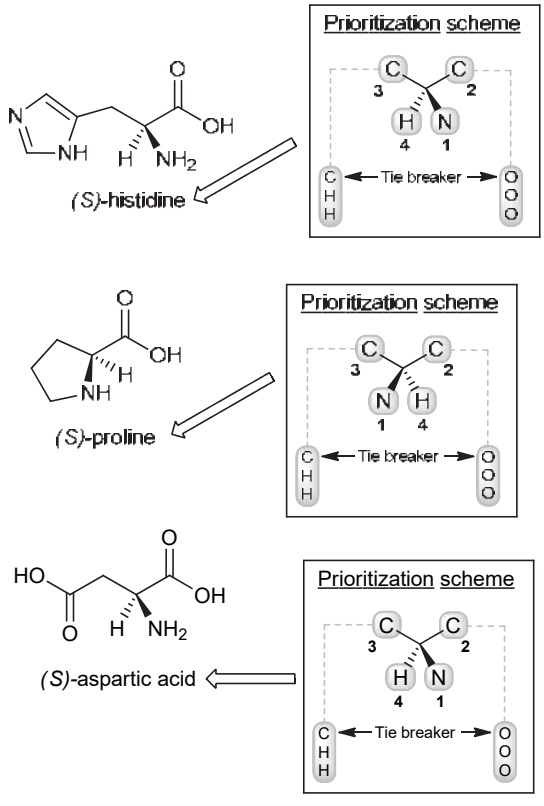


(f) This compound has two chiral centers, shown here. The following prioritization schemes led to the assignment of configuration for each chiral center.



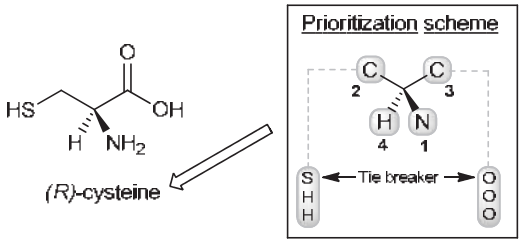
5.10.

(a) At the alpha carbon of every naturally occurring chiral amino acid, hydrogen is the lowest priority (#4) and nitrogen is the highest priority (#1). The other two atoms at the chiral center are both carbon (the carboxylic acid group and the so-called "side chain," R, of the amino acid). In almost every amino acid, including histidine, proline and aspartic acid, the oxygen atoms of the carboxylic acid functional group give that carbon a higher priority (#2), resulting in an *S* configuration.



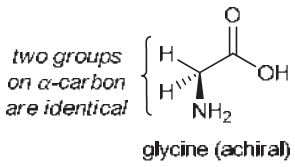
The only exception is cysteine; because the attached sulfur atom has a higher atomic number than oxygen, it has the *R* configuration.

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Note that the (S, H, H) on the side chain carbon is a higher priority than the (O, O, O) on the other because the one S has a higher atomic number than each of the three O's.

(b) Glycine is achiral because the side chain is a hydrogen atom, so there are two hydrogen atoms connected to the alpha carbon. As a result, it cannot be a chiral center, because it doesn't have four unique groups.



5.11. The problem statement indicates that 0.575 grams are dissolved in 10.0 mL, so the concentration is 0.575g/10.0 mL = 0.0575g/mL. The path length is 10.0 cm, which is equivalent to 1.00 dm, and the observed rotation is +1.47°. Plugging these values into the equation, we get the following:

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{c \times l}$$

$$= \frac{(+1.47^{\circ})}{(0.0575\ \text{g/mL}) \times (1.00\ \text{dm})} = +\mathbf{25.6}$$

5.12. The problem statement indicates that 0.095 grams are dissolved in 1.00 mL, so the concentration is 0.095g/1.00 mL = 0.095g/mL. The path length is 10.0 cm, which is equivalent to 1.00 dm, and the observed rotation is -2.99°. Plugging these values into the equation, we get the following:

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{c \times l}$$

$$= \frac{(-2.99^{\circ})}{(0.095\ \text{g/mL}) \times (1.00\ \text{dm})} = -\mathbf{31.5}$$

5.13. The problem statement indicates that 1.30 grams are dissolved in 5.00 mL, so the concentration is 1.30g/5.0 mL = 0.260g/mL. The path length is 10.0 cm, which is equivalent to 1.00 dm, and the observed rotation is +0.57°. We then plug this value into the equation, as shown:

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{c \times l}$$

$$= \frac{(+0.57^{\circ})}{(0.260\ \text{g/mL}) \times (1.00\ \text{dm})} = +\mathbf{2.2}$$

5.14.

(a) In this problem we are solving for the observed rotation, α, with a known specific rotation, [α]. The concentration (*c*) must be calculated to obtain the proper units of grams per milliliter. A 500 mg tablet is equivalent to 0.500 grams, and with 10.0 mL of solvent, the concentration (*c*) is calculated to be 0.0500 g/mL. The pathlength (*l*) is given as 10.0 cm, which is equivalent to 1.00 dm.

$[\alpha] = -93.4$

$\alpha = ?$

$c = (0.500\ \text{g}) / (10.0\ \text{mL}) = 0.0500\ \text{g/mL}$

$l = 10.0\ \text{cm} = 1.00\ \text{dm}$

Plugging these values into the equation and solving for α gives an expected observed rotation of –4.67°.

$$[\alpha] = \frac{\alpha}{c \times l}$$

$$-93.4 = \frac{\alpha}{0.0500\ \text{g/mL} \times 1.00\ \text{dm}}$$

$$\alpha = (-93.4)(0.0500)(1.00) = -4.67^{\circ}$$

(b) Because this enantiomer has a negative $[\alpha]^{20}$ value, it is described as levorotatory. A clever combination of levorotatory and etiracetam leads to the drug's name, levetiracetam. It is good to point out the sometimes confused, but completely separate, properties of having an *S* configuration (a result of applying IUPAC rules) and being levorotatory (as measured by a polarimeter). You will recall that a compound with an *S* configuration might be either dextrorotatory (optical rotation $\alpha > 0$) or levorotatory (optical rotation $\alpha < 0$), which can only be determined experimentally.

5.15. The % ee is calculated in the following way:

$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\ \%$$

$$= \frac{37}{39.5} \times 100\ \%$$

$$= 94\ \%$$

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5.16. The % ee is calculated in the following way:

$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\,\%$$

$$= \frac{6.0}{6.3} \times 100\,\%$$

$$= 95\,\%$$

5.17. The % ee is calculated in the following way:

$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\,\%$$

$$= \frac{85}{92} \times 100\,\%$$

$$= 92\,\%$$

5.18. The magnitude of the specific rotation for **1** is calculated using the reported *ee*; the calculation below indicates a value of 74.4.

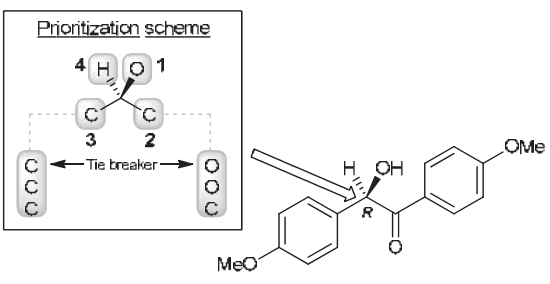
$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\%$$

$$[\alpha]_{observed} = \frac{\%\ ee \times [\alpha]_{pure}}{100\%}$$

$$= \frac{84\% \times 88.6}{100\%}$$

$$= 74.4$$

Next, we must determine the sign (+ or –) of the specific rotation. The problem statement indicates that the pure (*S*) enantiomer is dextrorotatory. Since **1** has the (*R*) configuration (see below), we conclude that it must be levorotatory. Therefore, the specific rotation [α] should be –74.4.



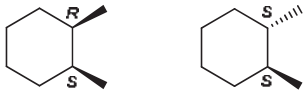
5.19.

(a) We assign a configuration to each chiral center in each compound, and we compare:



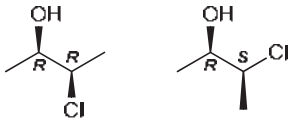
In the first compound, both chiral centers have the *R* configuration, while in the second compound, both chiral centers have the *S* configuration. These compounds are mirror images of each other, but they are nonsuperimposable. That is, if you try to rotate the first compound 180 degrees about a horizontal axis, you will not generate the second compound (if you have trouble seeing this, you may find it helpful to build a molecular model). These compounds are therefore enantiomers.

(b) We assign a configuration to each chiral center in each compound, and we compare:



In the first compound, the configurations of the chiral centers are *R* and *S*, while in the second compound, they are *S* and *S*. These compounds are stereoisomers, but they are not mirror images of each other. Therefore, they are diastereomers.

(c) We assign a configuration to each chiral center in each compound, and we compare:



In the first compound, the configurations of the chiral centers are *R* and *R*, while in the second compound, they are *R* and *S*. These compounds are stereoisomers, but they are not mirror images of each other. Therefore, they are diastereomers.

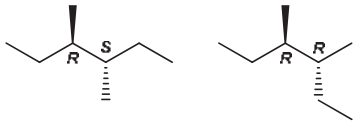
(d) We assign a configuration to each chiral center in each compound, and we compare:



In the first compound, the configurations of the chiral centers are *R*, *S*, and *R*, respectively. In the second compound, they are *S*, *S*, and *R*. These compounds are stereoisomers, but they are not mirror images of each other. Therefore, they are diastereomers.

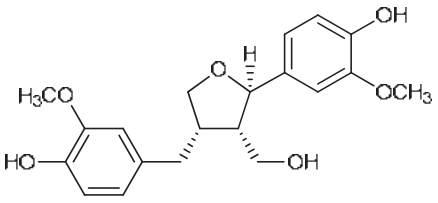
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(e) We assign a configuration to each chiral center in each compound, and we compare:

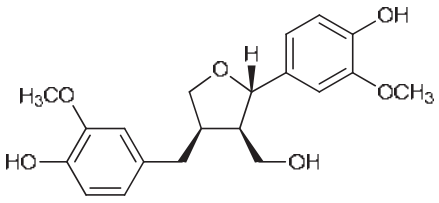


In the first compound, the configurations of the chiral centers are *R* and *S*, while in the second compound, they are *R* and *R*. These compounds are stereoisomers, but they are not mirror images of each other. Therefore, they are diastereomers.

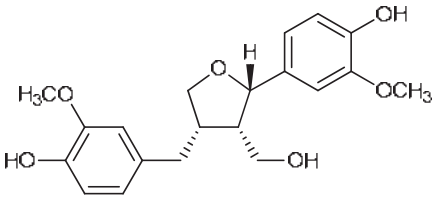
5.20. (–)-Lariciresinol has 3 chiral centers, so the maximum number of stereoisomers = $2^3 = 8$. The original compound is included in the total, so there are 7 additional stereoisomers. A molecule can only have one enantiomer, so the remaining 6 stereoisomers are all diastereomers of (–)-lariciresinol.



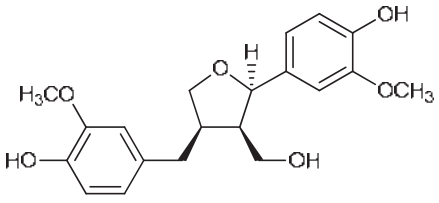
(–)-lariciresinol



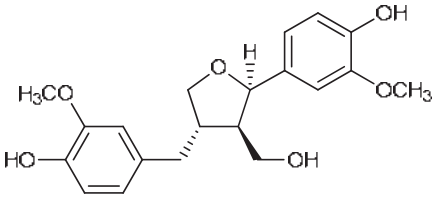
enantiomer = (+)-lariciresinol



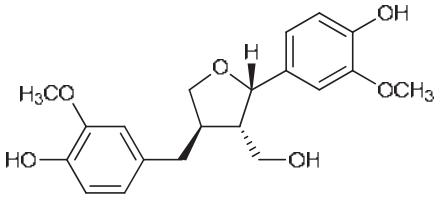
diastereomer



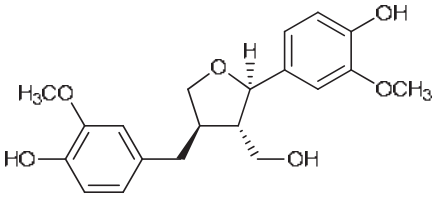
diastereomer



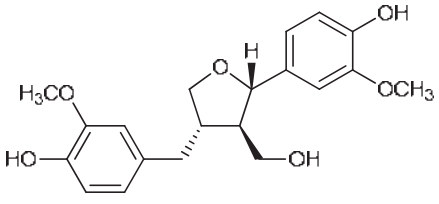
diastereomer



diastereomer



diastereomer



diastereomer

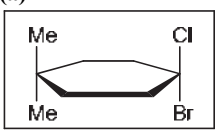
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5.21.
(a) Yes, there is a plane of symmetry that chops the goggles in half, with the right side reflecting the left side.
(b) Yes, there is a plane of symmetry that goes through the handle of the cup.
(c) No, there is no plane of symmetry.
(d) Yes, there is a plane of symmetry that chops the whistle in half.
(e) Yes, there are three planes of symmetry in this cinder block.
(f) No, there are no planes of symmetry in a hand.

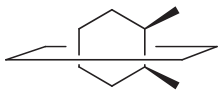
5.22. The cinder block (5.21e) has three planes of symmetry, each of which chops the block in half.

5.23. Each of the following compounds has a plane of symmetry, as shown:

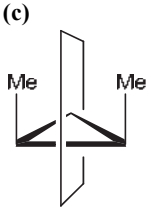
(a)



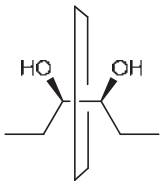
(b)



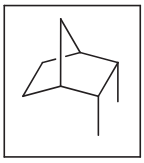
(c)



(d)



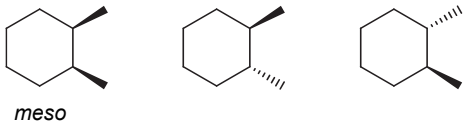
(e)



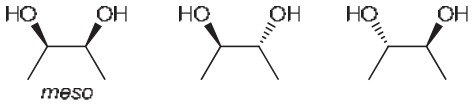
(f)



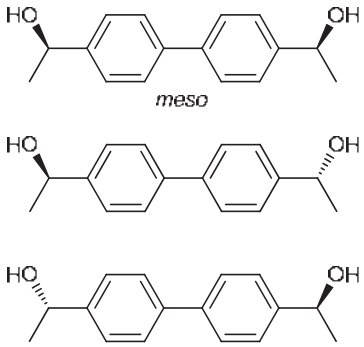
5.24.
(a) With two chiral centers, we would expect four stereoisomers. However, there are only three stereoisomers in this case, because the first one shown below is a *meso* compound.



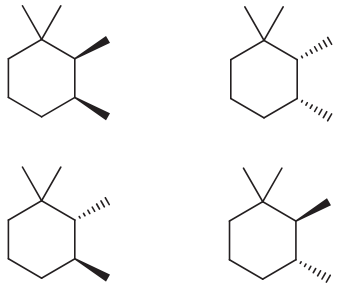
(b) With two chiral centers, we would expect four stereoisomers. However, there are only three stereoisomers in this case, because the first one shown below is a *meso* compound.



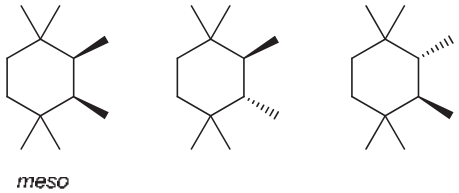
(c) With two chiral centers, we would expect four stereoisomers. However, there are only three stereoisomers in this case, because the first one shown below is a *meso* compound.



(d) With two chiral centers, there are four stereoisomers (no *meso* compounds).

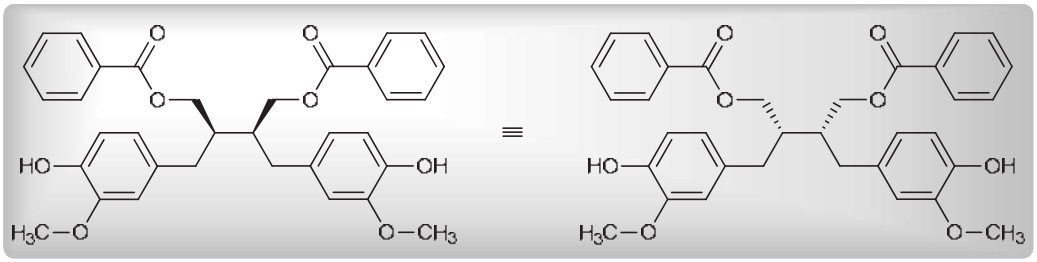


(e) With two chiral centers, we would expect four stereoisomers. However, there are only three stereoisomers in this case, because the first one shown below is a *meso* compound.

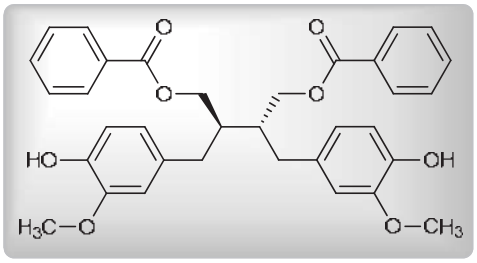


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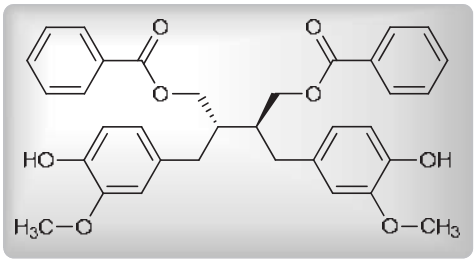
5.25. For a molecule with two chiral centers, we would expect up to four stereoisomers. However, there are only three stereoisomers in this case, because one is a *meso* compound, shown first below.



meso
(achiral)



chiral

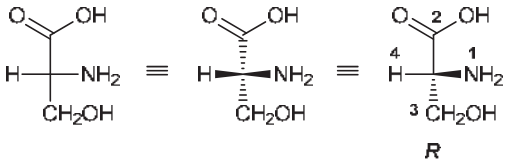


chiral

The *meso* compound is achiral. The other two stereoisomers are chiral, and they are enantiomers of each other. The problem statement indicates that a racemic mixture (a pair of enantiomers) was isolated from the plant. Therefore, the two chiral stereoisomers must have been isolated from the plant.

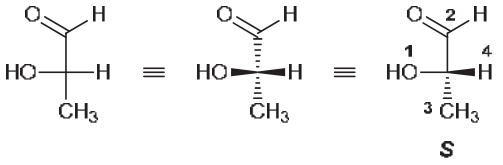
5.26.

(a) This chiral center has the *R* configuration, as shown below:



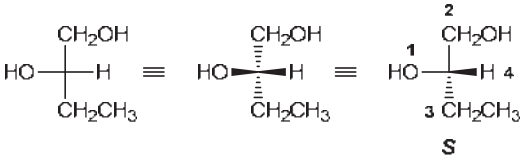
R

(b) This chiral center has the *S* configuration, as shown below:



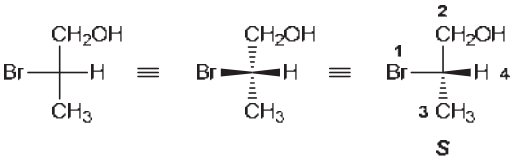
S

(c) This chiral center has the *S* configuration, as shown below:



S

(d) This chiral center has the *S* configuration, as shown below:



S

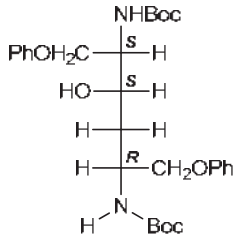
5.27.

(a) For each chiral center, we follow the same procedure that we used in the previous problem. We first redraw the chiral center so that there are two lines, one wedge, and one dash:

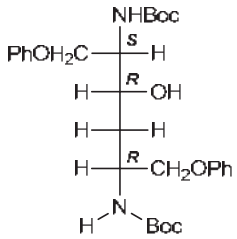


Then, we assign priorities, and determine the configuration. If we repeat this process for each chiral center, we find the following configurations:

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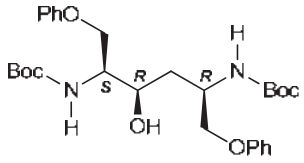


1



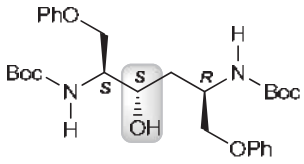
2

(b) These compounds differ in the configuration of only one chiral center, so they are diastereomers. That is, they are stereoisomers that are not mirror images.
(c) Fischer projections show the eclipsed conformations of neighboring bonds, whereas bond-line structures show the staggered conformations of neighboring bonds. Visualizing the conversion between Fischer projections and bond-line structures therefore involves bond rotations. Instead, let's use R/S assignments to compare bond-line structures and Fischer projections, without the need to rotate bonds. For convenience, we start by drawing the bond-line structure using wedges for all of the chiral centers so that the low-priority hydrogen atoms will all be in the back (on dashes). Then, we can assign each configuration and determine which chiral centers were drawn correctly (and which need to be changed). In this case, if we use this method and assign configurations, we find that the R/S assignments all match that of compound **2**. So this is compound **2**.



Compound 2

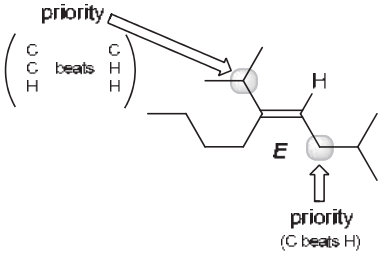
We can easily draw compound **1** from compound **2**, because these two compounds differ in the configuration of only one chiral center. Changing the wedge (on the OH group) to a dash will necessarily change the configuration from *R* to *S*.



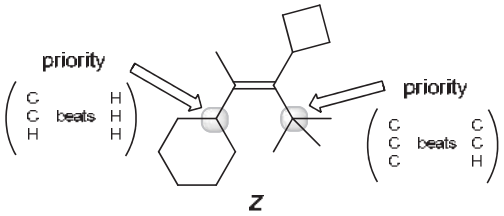
Compound 1

5.28.
(a) On the left side of the structure, the two groups are different (methyl and H), but the two groups on the right side are the same (both are methyl groups). In order to be chiral, the two groups on the right would have to be different also. This compound is not chiral.
(b) The two groups on the left are different (methyl and H), and the two groups on the right are also different (ethyl and H), so this allene is chiral.
(c) The two groups on the left are the same (going either way around the cyclopentane ring). In order to be chiral, the two groups would have to be different. This compound is not chiral.
(d) The two groups on the left are different, and the two groups on the right are also different, so this allene is chiral.

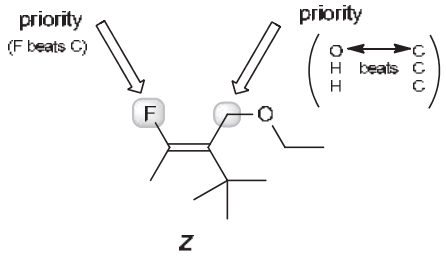
5.29.
(a) The priorities (as shown below) are on opposite sides of the double bond, so this alkene has the *E* configuration.



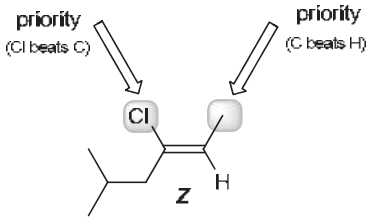
(b) The priorities (as shown below) are on the same sides of the double bond, so this alkene has the *Z* configuration.



(c) The priorities (as shown below) are on the same sides of the double bond, so this alkene has the *Z* configuration.

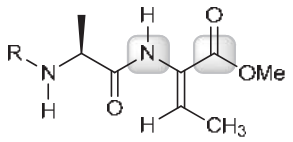


(d) The priorities (as shown below) are on the same sides of the double bond, so this alkene has the *Z* configuration.

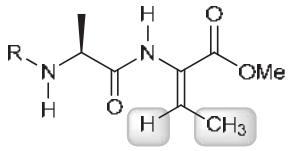


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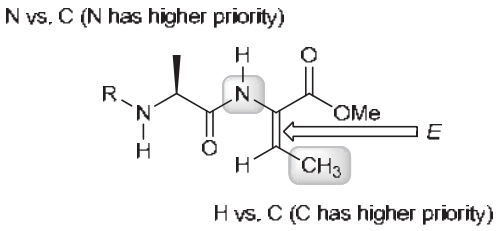
5.30. Attached to the top vinylic position, we see nitrogen and carbon (highlighted):



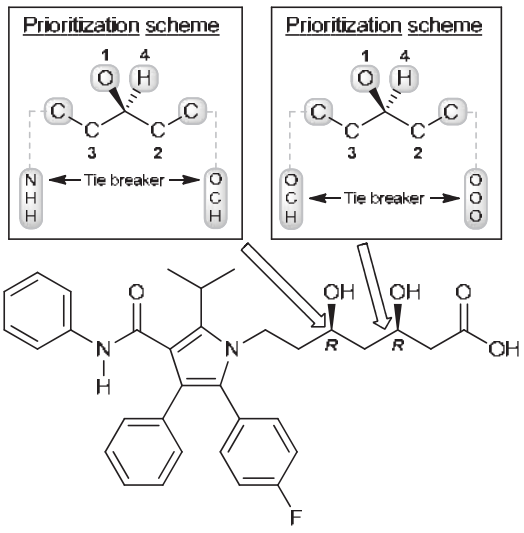
N has a higher atomic number than C, so the nitrogen group has the higher priority. Attached to the bottom vinylic position, we see hydrogen and carbon (highlighted):



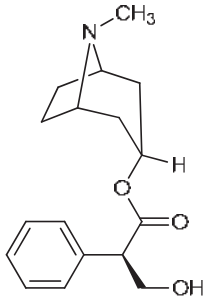
C has a higher atomic number than H so the methyl group has the higher priority.
Since the higher priority groups are on opposite sides of the double bond, the configuration is *E*:



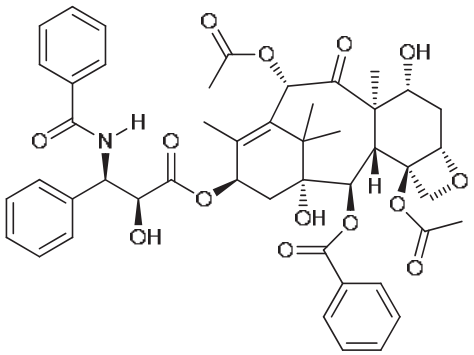
5.31. This compound has two chiral centers, shown below. The following prioritization schemes led to the assignment of configuration for each chiral center.



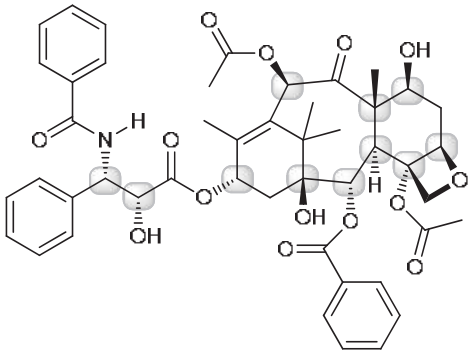
5.32. In this case, it will be easiest to place the mirror behind the molecule, giving the following structure for its enantiomer:



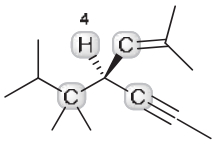
5.33.
(a) In order to draw the enantiomer of paclitaxel, we convert every wedge into a dash, and we convert every dash into a wedge, as shown:



(b) Paclitaxel has eleven chiral centers (highlighted below).



5.34. To assign the configuration, we must first assign a prioritization scheme to the four atoms connected to the chiral center:



One of these atoms is H, so that atom is immediately assigned the fourth priority. The remaining three atoms are all carbon atoms, so for each of them, we prepare a

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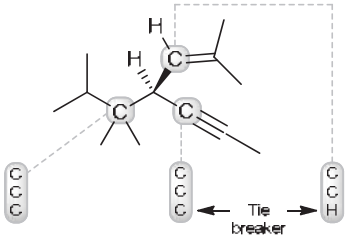
list of the atoms attached to them. Let's begin with the double bond. Recall that a double bond is comprised of one σ bond and one π bond. For purposes of assigning configurations, we treat the π bond as if it were a σ bond to another carbon atom, like this:



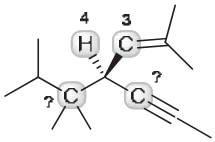
We treat a triple bond similarly. Recall that triple bonds are comprised of one σ bond and two π bonds. As such, each of the two π bonds is treated as if it were a σ bond to another carbon atom:



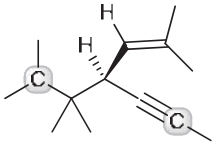
This gives the following competition:



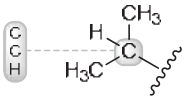
Among these groups, the double bond is assigned the third priority in our prioritization scheme, and we must continue to assign the first and second priorities.



We move one carbon atom away from the chiral center, and we compare the following two positions:



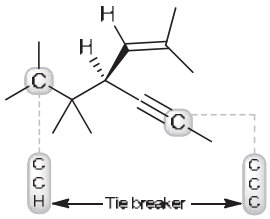
In each case, we must construct a list of the three atoms that are connected to each position. This is easy to do for the left side, which is connected to two carbon atoms and one hydrogen atom:



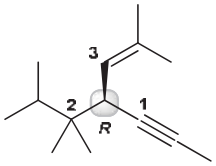
For the right side, the highlighted carbon atom is part of a triple bond, so we treat each π bond as if it were a sigma bond to another carbon atom:



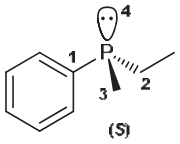
As such, the right side wins the tie-breaker:



Our prioritization scheme indicates that the chiral center has the *R* configuration:



5.35. The chiral center has the *S* configuration, determined by the prioritization scheme shown here.



5.36.

(a) If we rotate the first structure 180 degrees about a horizontal axis, the second structure is generated. As such, these two structures represent the same compound.

(b) These compounds have the same molecular formula, but they differ in their constitution. The bromine atom is connected to C3 in the first compound, and to C2 in the second compound. Therefore, these compounds are constitutional isomers.

(c) These compounds are stereoisomers, but they are not mirror images of each other. Therefore, they are diastereomers.

(d) If we assign a name to each structure, we find that both have the same name:

(*S*)-3-methylhexane

Therefore, these structures represent the same compound.

(e) These compounds are nonsuperimposable mirror images of each other. Therefore, they are enantiomers.

(f) These structures represent the same compound (rotating the first compound 180 degrees about a vertical axis generates the second compound).

(g) These structures represent the same compound, which does not contain a chiral center, because there are two ethyl groups connected to the central carbon atom.

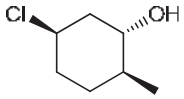
(h) These structures represent the same compound (rotating the first compound 180 degrees about a vertical axis generates the second compound).

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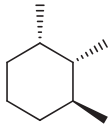
5.37.
(a) There are three chiral centers (n=3), so we expect $2^n = 2^3 = 8$ stereoisomers.
(b) There are two chiral centers (n=2), so we initially expect $2^n = 2^2 = 4$ stereoisomers. However, one of the stereoisomers is a *meso* compound, so there will only be 3 stereoisomers.
(c) There are four chiral centers (n=4), so we expect $2^n = 2^4 = 16$ stereoisomers.
(d) There are two chiral centers (n=2), so we initially expect $2^n = 2^2 = 4$ stereoisomers. However, one of the stereoisomers is a *meso* compound, so there will only be 3 stereoisomers.
(e) There are two chiral centers (n=2), so we initially expect $2^n = 2^2 = 4$ stereoisomers. However, one of the stereoisomers is a *meso* compound, so there will only be 3 stereoisomers.
(f) There are five chiral centers (n=5), so we expect $2^n = 2^5 = 32$ stereoisomers.

5.38. In each case, we draw the enantiomer by replacing all wedges with dashes, and all dashes with wedges. For Fischer projections, we simply change the configuration at every chiral center by switching the groups on the left with the groups on the right:

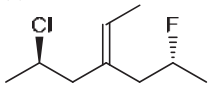
(a)



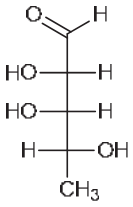
(b)



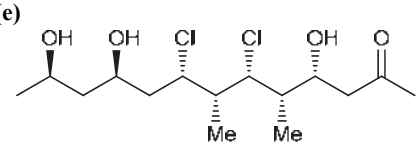
(c)



(d)

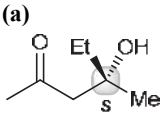


(e)

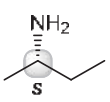


5.39. The configuration of each chiral center is shown below:

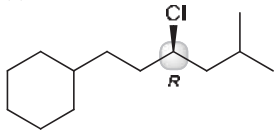
(a)



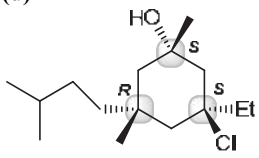
(b)



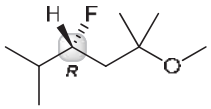
(c)



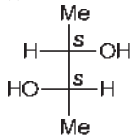
(d)



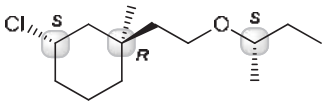
(e)



(f)

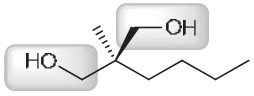


(g)



5.40. In this case, there is a 96% excess of A (98 – 2 = 96). The remainder of the solution is a racemic mixture of both enantiomers (2% A and 2% B). Therefore, the enantiomeric excess (*ee*) is 96%.

5.41. This compound does not have a chiral center, because two of the groups are identical:



Accordingly, the compound is achiral and is not optically active. We thus predict a specific rotation of zero.

5.42.

$$[\alpha] = \frac{\alpha}{c \times l}$$

$$\alpha = [\alpha] \times c \times l$$

$$= (-13.5)(0.100 \text{ g/mL})(1.00 \text{ dm}) = -1.35°$$

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5.43. Observed $[\alpha] = \dfrac{\alpha}{c \times l}$

$$= \frac{(+0.78^{\circ})}{(0.350\ \text{g/mL}) \times (1.00\ \text{dm})} = +\mathbf{2.2}$$

$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\ \%$$

$$= \frac{2.2}{2.8} \times 100\ \%$$

$$= 79\ \%$$

5.44.
(a) One of the chiral centers has a different configuration in each compound, while the other chiral center has the same configuration in each compound. As such, these compounds are stereoisomers, but they are not mirror images of each other. They are diastereomers.
(b) Each of the chiral centers has a different configuration when comparing these compounds. As such, these compounds are nonsuperimposable mirror images. They are enantiomers.
(c) These structures represent the same compound (rotating the first compound 180 degrees about a horizontal axis generates the second compound).
(d) These compounds are nonsuperimposable mirror images. Therefore, they are enantiomers.

5.45.
(a) One of the chiral centers has a different configuration in each compound, while the other chiral center has the same configuration in each compound. As such, these compounds are stereoisomers, but they are not mirror images of each other. They are diastereomers.
(b) Each of the chiral centers has a different configuration when comparing these compounds. As such, these compounds are nonsuperimposable mirror images. They are enantiomers.
(c) Each of the chiral centers has a different configuration when comparing these compounds. As such, these compounds are nonsuperimposable mirror images. They are enantiomers.
(d) One of the chiral centers has a different configuration in each compound, while the other chiral center has the same configuration in each compound. As such, these compounds are stereoisomers, but they are not mirror images of each other. They are diastereomers.

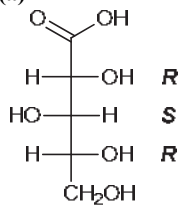
5.46.
(a) True.
(b) False. A *meso* compound cannot have an enantiomer. Its mirror image IS superimposable.
(c) True. In a Fischer projection, all horizontal lines represent wedges, and all vertical lines represent dashes. If we rotate the structure by 90 degrees, we are changing all wedges into dashes and all dashes into wedges. Therefore, the new structure will be an enantiomer of the original structure. Be careful though – you can only rotate a Fischer projection by 90 degrees (to draw the enantiomer) if there is one chiral center. If there is more than one chiral center, then you cannot rotate the Fischer projection by 90 degrees in order to draw its enantiomer. Instead, you must change the configuration at every chiral center by switching the groups on the left with the groups on the right.

5.47. For each chiral center, we first redraw the chiral center so that there are two lines, one wedge and one dash:

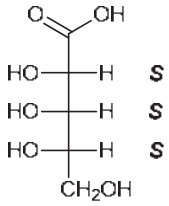


Then, we assign priorities, and determine the configuration. This process gives the following configurations:

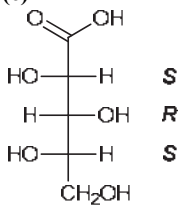
(a)



(b)

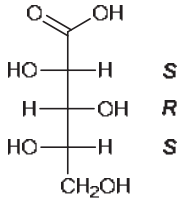


(c)

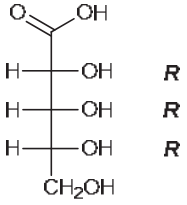


5.48. In order to draw the enantiomer for each compound, we simply change the configuration at every chiral center by switching the groups on the left with the groups on the right.

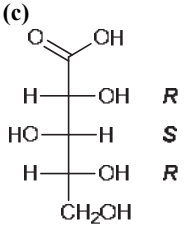
(a)



(b)



(c)



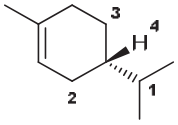
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5.49. specific rotation = $[\alpha] = \dfrac{\alpha}{c \times l}$

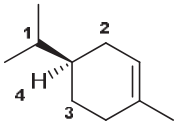
$$= \frac{(-0.47^{\circ})}{(0.0075\ \text{g/mL}) \times (1.00\ \text{dm})} = \mathbf{-63}$$

5.50.

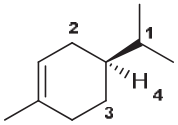
(a) This compound is (*S*)-limonene, as determined by the following prioritization scheme:



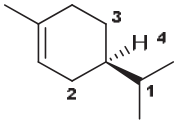
(b) This compound is (*R*)-limonene, as determined by the following prioritization scheme:



(c) This compound is (*S*)-limonene, as determined by the following prioritization scheme:

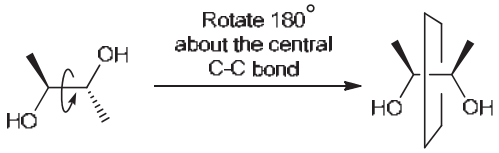


(d) This compound is (*R*)-limonene, as determined by the following prioritization scheme:

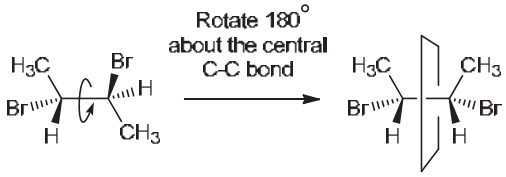


5.51.

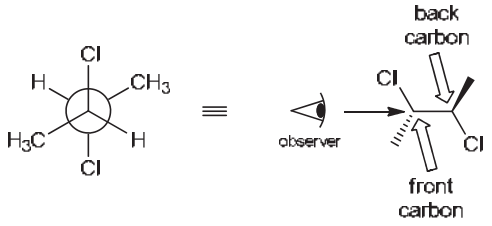
(a) We must first rotate 180 degrees about the central carbon-carbon bond, in order to see more clearly that the compound possesses a plane of symmetry, shown below:



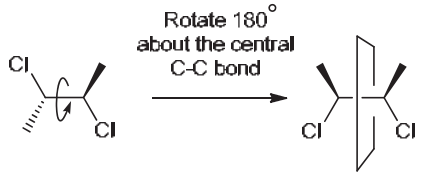
(b) We must first rotate 180 degrees about the central carbon-carbon bond, in order to see more clearly that the compound possesses a plane of symmetry, shown below:



(c) We first convert the Newman projection into a bond-line drawing:



Then, we rotate 180 degrees about the central carbon-carbon bond, in order to see more clearly that the compound possesses a plane of symmetry, shown below:



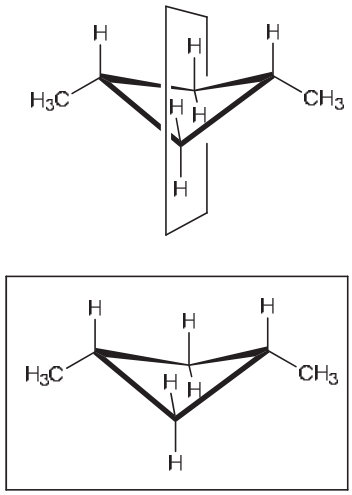
Alternatively, we can identify the plane of symmetry without converting the Newman projection into a bond-line drawing. Instead, we rotate the central carbon-carbon bond of the Newman projection 180°, and we see that the two chlorine atoms are eclipsing each other, the two methyl groups are eclipsing each other, and the two H's are eclipsing each other.



In this eclipsed conformation, we can clearly see that the molecule has an internal plane of symmetry (it is a *meso* compound). Therefore, the compound is optically inactive.

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5.52. As seen in Section 4.9, cyclobutane adopts a slightly puckered conformation. It has two planes of symmetry, shown here:

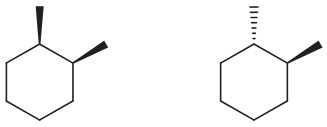


5.53.

(a) One of the chiral centers has a different configuration in each compound, while the other chiral center has the same configuration in each compound. As such, these compounds are stereoisomers, but they are not mirror images of each other. They are diastereomers.

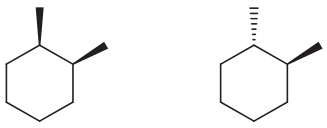
(b) These compounds have the same molecular formula (C_8H_{16}), but they differ in their constitution. The first compound is 1,2-disubstituted, while the second compound is 1,3-disubstituted. Therefore, they are constitutional isomers.

(c) Let's redraw the compounds in a way that shows the configuration of each chiral center without showing the conformation (chair). This will make it easier for us to determine the stereoisomeric relationship between the two compounds:



When drawn in this way, we can see clearly that one of the chiral centers has a different configuration in each compound, while the other chiral center has the same configuration in each compound. As such, these compounds are stereoisomers, but they are not mirror images of each other. They are diastereomers.

(d) Let's redraw the compounds in a way that shows the configuration of each chiral center without showing the conformation (chair). This will make it easier for us to determine the stereoisomeric relationship between the two compounds:



When drawn in this way, we can see clearly that one of the chiral centers has a different configuration in each compound, while the other chiral center has the same configuration in each compound. As such, these compounds are stereoisomers, but they are not mirror images of each other. They are diastereomers.

(e) It might appear as if each of the chiral centers has a different configuration when comparing these compounds. However, each of these compounds has an internal plane of symmetry (horizontal plane). As such, both structures represent the same *meso* compound. These two structures are the same.

(f) Each of the chiral centers has a different configuration when comparing these compounds. As such, these compounds are nonsuperimposable mirror images. They are enantiomers.

5.54.

(a) The specific rotation of (*R*)-carvone should be the same magnitude but opposite sign as the specific rotation of (*S*)-carvone (assuming both are measured at the same temperature). Therefore, we expect the specific rotation of (*R*)-carvone at 20°C to be –61.

(b)

$$\%\ ee = \frac{|\text{observed } \alpha|}{|\alpha \text{ of pure enantiomer}|} \times 100\,\%$$

$$= \frac{55}{61} \times 100\,\%$$

$$= 90\,\%$$

(c) Since the *ee* is 90%, the mixture must be comprised of 95% (*R*)-carvone and 5% (*S*)-carvone (95 – 5 = 90).

5.55.

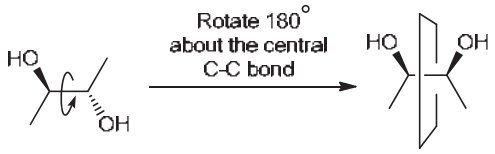
(a) This compound has a non-superimposable mirror image, and therefore it is chiral.

(b) This compound has a non-superimposable mirror image, and therefore it is chiral.

(c) This compound lacks a chiral center and is therefore achiral.

(d) This compound has a non-superimposable mirror image, and therefore it is chiral.

(e) This compound is a *meso* compound, which we can see more clearly if we rotate the central carbon-carbon bond by 180 degrees, shown below. Since the compound is *meso*, it must be achiral.



(f) This compound has an internal plane of symmetry and is therefore a *meso* compound. As such, it must be achiral.

(g) This compound has an internal plane of symmetry (chopping the OH group in half and chopping the methyl

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group in half) and is therefore a *meso* compound. As such, it must be achiral.

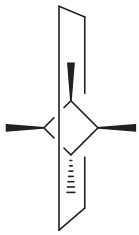
(h) This compound has a non-superimposable mirror image, and therefore it is chiral.

(i) This compound has a non-superimposable mirror image, and therefore it is chiral.

(j) This compound lacks a chiral center and is therefore achiral.

(k) This compound has an internal plane of symmetry and is therefore a *meso* compound. As such, it must be achiral.

(l) This compound has an internal plane of symmetry (shown below), and is therefore a *meso* compound. As such, it must be achiral.



5.56.

$$[\alpha] = \frac{\alpha}{c \times l}$$

$$\alpha = [\alpha] \times c \times l$$

$$= (+24)(0.0100 \text{ g / mL})(1.00 \text{ dm}) = +0.24^{\circ}$$

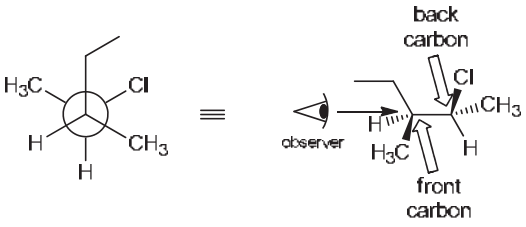
5.57.

(a) If we rotate the central carbon-carbon bond of the Newman projection 180°, we arrive at a conformation in which the two OH groups are eclipsing each other, the two methyl groups are eclipsing each other, and the two H's are eclipsing each other.



In this eclipsed conformation, we can clearly see that the molecule has an internal plane of symmetry (it is a *meso* compound). Therefore, the compound is optically inactive.

(b) We first convert the Newman projection into a bond-line drawing:



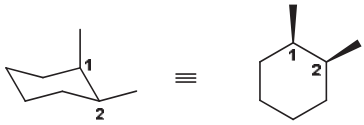
When drawn in bond-line format, we can see that the compound has two chiral centers (highlighted):



This compound is chiral and therefore optically active.

(c) This compound has a non-superimposable mirror image, so it is chiral. Therefore, it is optically active.

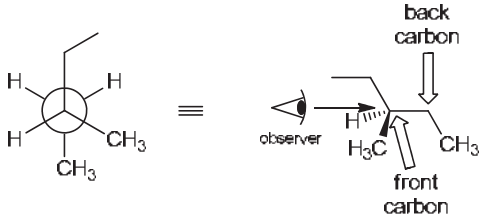
(d) Let's redraw the compound in a way that shows the configuration of each chiral center without showing the conformation (chair). This will make it easier for us to evaluate:



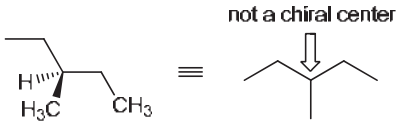
This compound has an internal plane of symmetry, so it is a *meso* compound. As such, it is achiral and optically inactive.

(e) This compound has a non-superimposable mirror image, so it is chiral. Therefore, it is optically active.

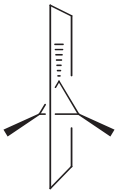
(f) We first convert the Newman projection into a bond-line drawing:



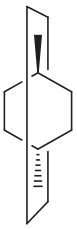
This compound is 3-methylpentane, which does not have a chiral center. Therefore, it is optically inactive.



(g) This compound has an internal plane of symmetry (a vertical plane that chops one of the methyl groups in half), so it is a *meso* compound. As such, it is achiral and optically inactive.

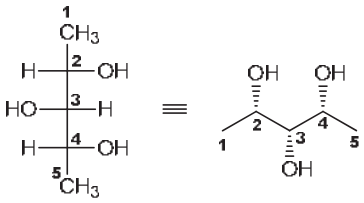


(h) This compound has an internal plane of symmetry, so it is a *meso* compound. As such, it is achiral and optically inactive.

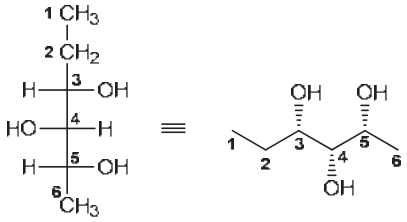


5.58. In each case, begin by numbering the carbon atoms in the Fischer projection (from top to bottom) and then draw the skeleton of a bond-line drawing with the same number of carbon atoms. Then, place the substituents in their correct locations (by comparing the numbering system in the Fischer projection with the numbering system in the bond-line drawing). When drawing each substituent in the bond-line drawing, you must decide whether it is on a dash or a wedge. For each chiral center, make sure that the configuration is the same as the configuration in the Fischer projection. If necessary, assign the configuration of each chiral center in both the Fischer projection and the bond-line drawing to ensure that you drew the configuration correctly. With enough practice, you may begin to notice some trends (rules of thumb) that will allow you to draw the configurations more quickly.

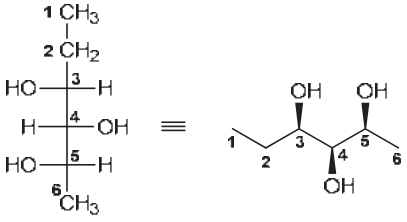
(a)



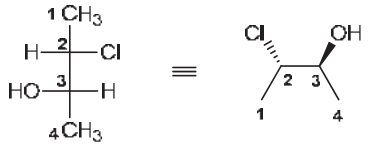
(b)



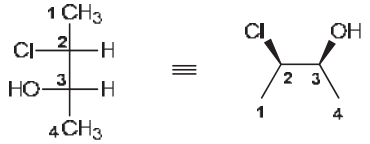
(c)



(d)

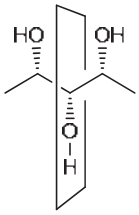


(e)



5.59.

(a) The compound in part (a) of the previous problem has an internal plane of symmetry, and is therefore a *meso* compound:

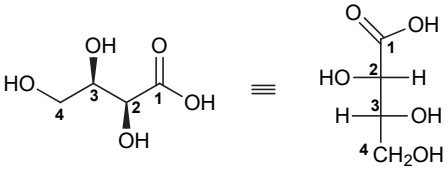


(b) The structures shown in parts (b) and (c) of the previous problem are enantiomers. An equal mixture of these two compounds is a racemic mixture, which will be optically inactive.

(c) Yes, this mixture is expected to be optically active, because the structures shown in parts (d) and (e) of the previous problem are not enantiomers. They are diastereomers, which are not expected to exhibit equal and opposite rotations.

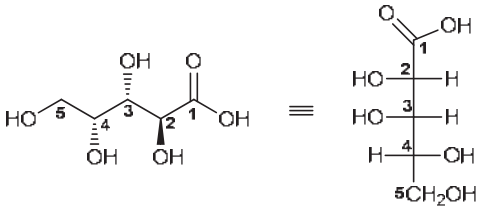
5.60. As we saw in problem **5.58**, it is helpful to use a numbering system when converting one type of drawing into another. When drawing each substituent in the Fischer projection, you must decide whether it is on the right or left side of the Fischer projection. For each chiral center, make sure that the configuration is the same as the configuration in the bond-line drawing. If necessary, assign the configuration of each chiral center in both the Fischer projection and the bond-line drawing to ensure that you drew the configuration correctly. With enough practice, you may begin to notice some trends (rules of thumb) that will allow you to draw the configurations more quickly.

(a)

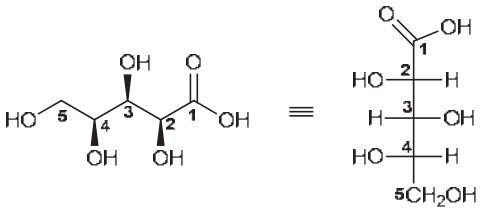


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(b)



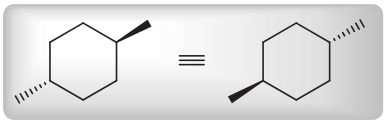
(c)



5.61. As shown below, there are only two stereoisomers (the *cis* isomer and the *trans* isomer).



cis

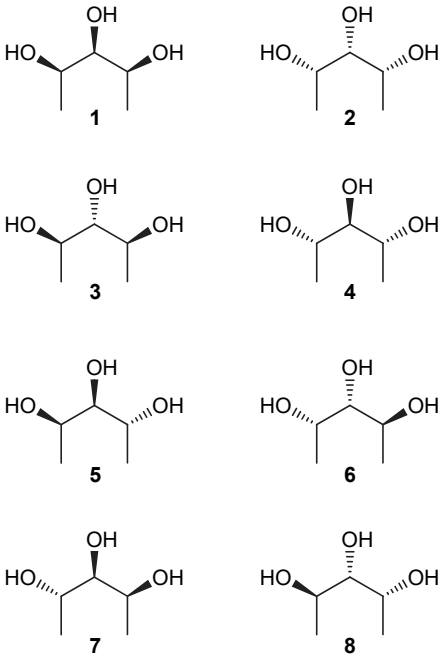


trans

With two chiral centers, we might expect four possible stereoisomers, but two stereoisomers are *meso* compounds, as shown above, so these are the only two isomers.

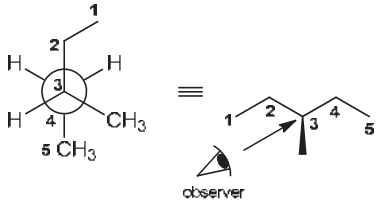
5.62. With three chiral centers, we would expect eight stereoisomers ($2^3 = 8$), labeled **1–8**. However, structures **1** and **2** represent one compound (a *meso* compound), while structures **3** and **4** also represent one compound (a *meso* compound). In addition, structure **5** is the same as structure **8**, while structure **6** is the same as structure **7** (you might find it helpful to build molecular models to see this). Structures **5-8** are not *meso* structures. The reason for the equivalence of structures **5** and **8** (and also for the equivalence of **6** and **7**) is that the central carbon atom in each of these four structures is actually not a chiral center. For structures **5-8**, changing the "configuration" at the central carbon atom does not produce a stereoisomer, which proves that the central carbon atom is not a chiral center in these cases.

In summary, there are only four stereoisomers (structures **1**, **3**, **5**, and **6**).



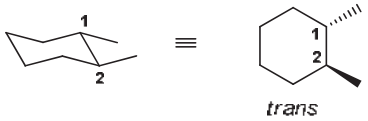
5.63.

(a) The second compound is 2-methylpentane. If we redraw the first compound as a bond-line drawing, rather than a Newman projection, we see that the first compound is 3-methylpentane.



These two compounds, 2-methylpentane and 3-methylpentane, have the same molecular formula (C_6H_{14}) but different constitution, so they are constitutional isomers.

(b) The first compound is *trans*-1,2-dimethylcyclohexane:

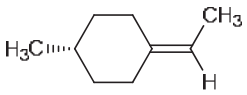


trans

In contrast, the second compound is *cis*-1,2-dimethylcyclohexane. These compounds are stereoisomers, but they are not mirror images of each other. Therefore, they are diastereomers.

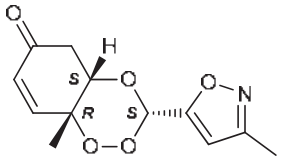
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5.64. The compound is chiral because it is not superimposable on its mirror image, shown below.

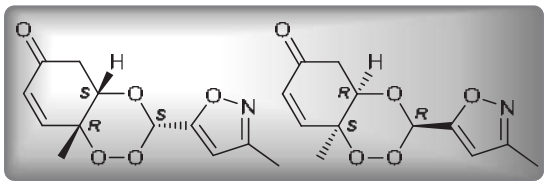


5.65. This compound has a center of inversion, which is a form of reflection symmetry. As a result, this compound is superimposable on its mirror image and is therefore optically inactive.

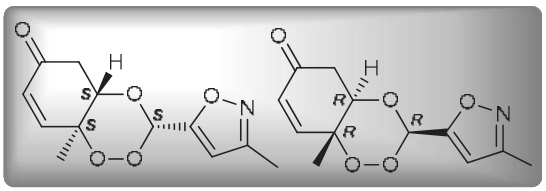
5.66. The compound contains three chiral centers, with the following assignments:



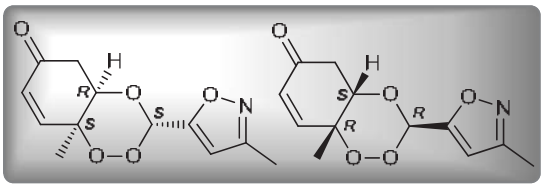
With three chiral centers, there should be a total of $2^3 = 8$ stereoisomers, shown below. Pairs of enantiomers are highlighted together. All other relationships are diastereomeric.



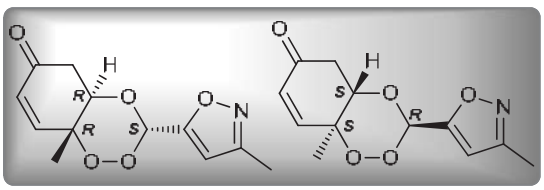
enantiomers



enantiomers



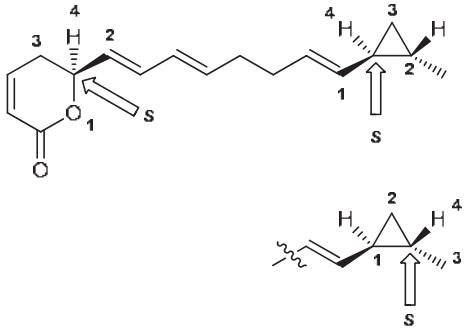
enantiomers



enantiomers

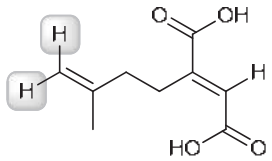
5.67.

(a) The following are the prioritization schemes that give rise to the correct assignment of configuration for each chiral center.

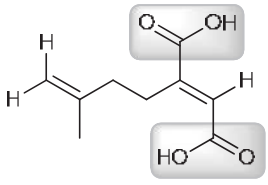


(b) The total number of possible stereoisomers is 2^n (where n = the number of chiral centers). With three chiral centers, we expect $2^3 = 8$ possible stereoisomers, one of which is the natural product coibacin B.

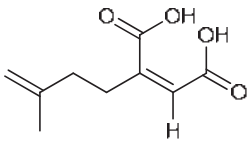
5.68. There are two different C=C π bonds in this compound. For clarity, some of the hydrogen atoms have been drawn explicitly in the drawing below. The C=C π bond on the left is not stereoisomeric, because there are two hydrogen atoms (highlighted) attached to the same position.



The C=C π bond on the right is stereoisomeric. The two high-priority carboxylic acid groups on opposite sides of the π bond, giving the *E* configuration.

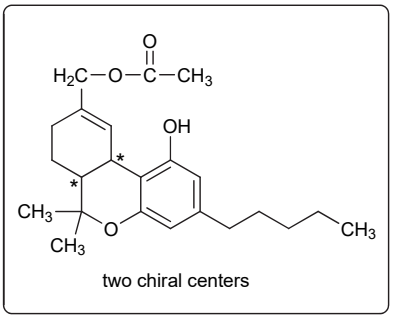


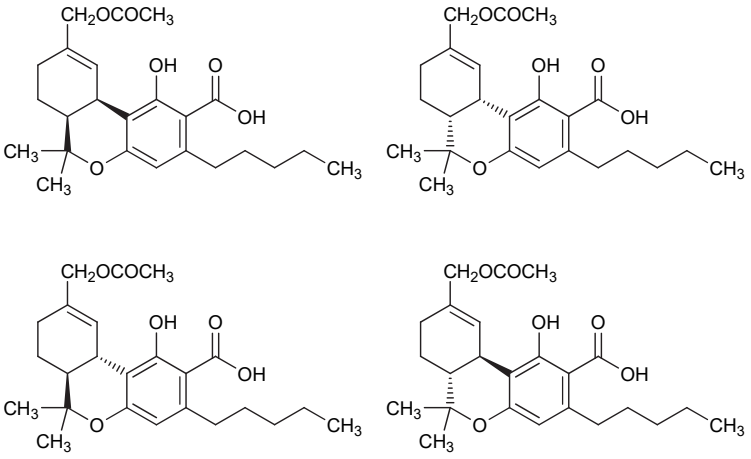
This compound has one stereoisomer, in which the carboxylic acid groups are on the same side of the π bond (the *Z* configuration), shown below:



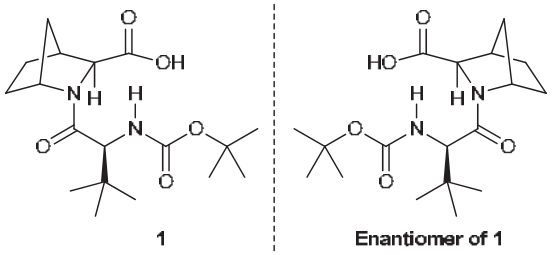
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5.69. When you draw out the condensed group at the top, you will find that, as an ester, it contains no chiral center. There are only two carbon atoms, marked with asterisks below, that bear four different groups. To draw the four possible stereoisomers, draw the various combinations of dashed and wedged bonds at these two chiral centers (the hydrogens at the chiral centers have been omitted for clarity). Since there are two chiral centers, there will be 2^2, or 4, stereoisomers.



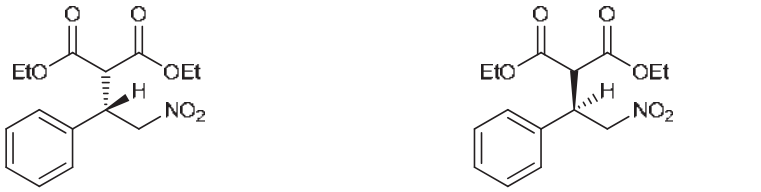


5.70. The enantiomer of a chiral molecule is its mirror image. The mirror can be placed anywhere, so there are multiple ways of correctly representing the enantiomer depending on where you place the mirror. In this case, the stereochemistry of the bicyclic part of the compound is implied by the drawing, so the mirror is most easily placed on the side of the molecule. Notice that the wedge remains a wedge because a mirror placed on the side reverses left and right sides only; it does not exchange front and back.



5.71.

(a) The product has one chiral center, which can either have the *S* configuration or the *R* configuration, as shown here.

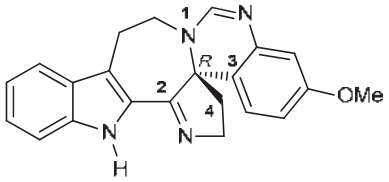


(b) Acetonitrile (CH_3CN) is the best choice of solvent because it results in the highest combination of enantioselectivity (72% *ee)* and percent yield (55%). While toluene gives the same % yield, enantioselectivity in this solvent is significantly lower.

Solvent	%*ee*	%*S*	%*R*
toluene	24	62	38
tetrahydrofuran	48	74	26
CH_3CN	72	86	14
$CHCl_3$	30	65	35
CH_2Cl_2	46	73	27
hexane	51	75.5	24.5

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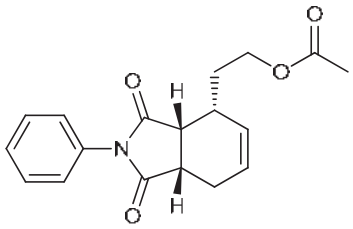
5.72. There is one chiral center, which was incorrectly assigned. So, it must have the *R* configuration, as shown below, rather than the *S* configuration (as originally thought).



Correct structure of (+)-trigonoliimine A
(enantiomer of the structure reported in 2010).

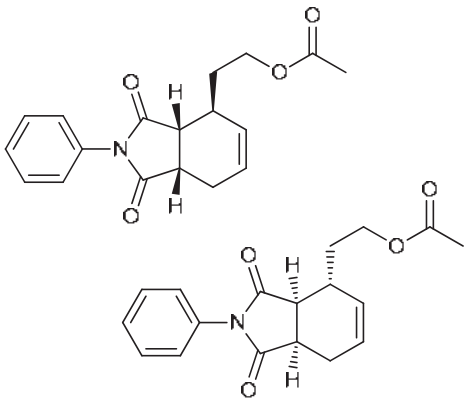
5.73.

(a) To draw the enantiomer, we simply redraw the structure in the problem statement, except that we replace all dashes with wedges, and all wedges with dashes, as shown:



(2nd major product)

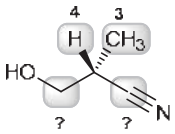
(b) The following compounds are the minor products, as described in the problem statement.



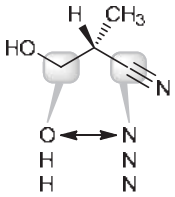
(c) The minor products are nonsuperimposable mirror images of each other. Therefore, they are enantiomers.

(d) They are stereoisomers, but they are not mirror images of each other. Therefore, they are diastereomers.

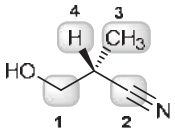
5.74. The configuration of a chiral center (called a "stereocenter" in the problem statement) does not depend on temperature, so (d) is not the correct answer. The answer also cannot be (c), because the term *Z* is used to designate the configuration of an alkene (this term is not used for chiral centers). In order to determine whether the configuration is *R* or *S*, we must assign priorities to each of the four groups connected to the chiral center. The hydrogen atom certainly receives the fourth priority, and the methyl group receives the third priority:



In order to determine which of the two highlighted carbon atoms receives the highest priority, we must construct a list of the three atoms connected to each of those positions, and we look for the first point of difference:



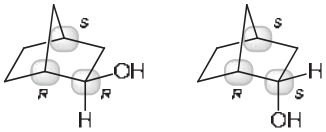
Since O has a higher atomic number than N, the priorities are as follows:



Since the fourth priority (H) is on a wedge (rather than a dash), these priorities correspond with an *R* configuration, so the correct answer is (a).

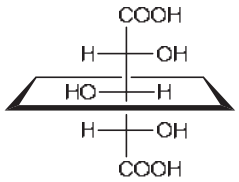
5.75. These compounds have the same connectivity – they differ only in the spatial arrangement of atoms. Therefore, they must be stereoisomers, so the answer is not (c) or (d). To determine whether these compounds are enantiomers or diastereomers, we must decide whether the compounds are mirror images or not. These compounds are NOT mirror images of each other, so they cannot be enantiomers. Since they are stereoisomers but not enantiomers, they must be diastereomers.

Note that there are three chiral centers (highlighted below) in each of these compounds. These compounds differ from each other only in the configuration of one of these chiral centers, thereby justifying their designation as diastereomers:

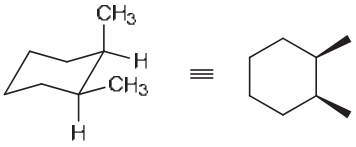


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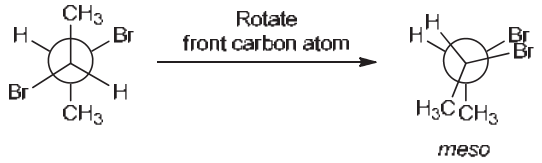
5.76. Compound (a) has a plane of symmetry and is therefore a *meso* compound. This compound will be optically inactive:



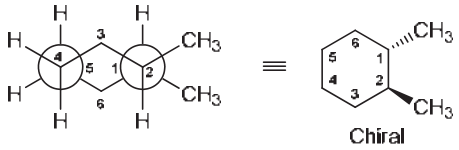
Compound (b) is shown in a chiral conformation, but this conformation equilibrates with its enantiomer via conformational changes that occur readily at room temperature. Therefore, this compound will be optically inactive.



Compound (c) is also a *meso* compound, as shown below, so it is also optically inactive:

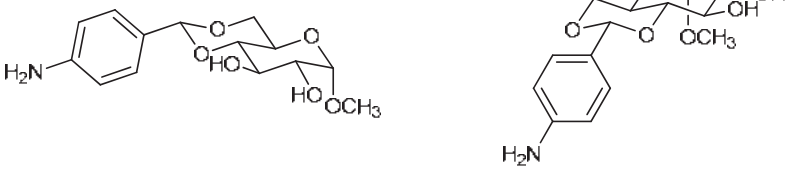


By process of elimination, the correct answer must be (d). Indeed, this compound is chiral and therefore optically active:

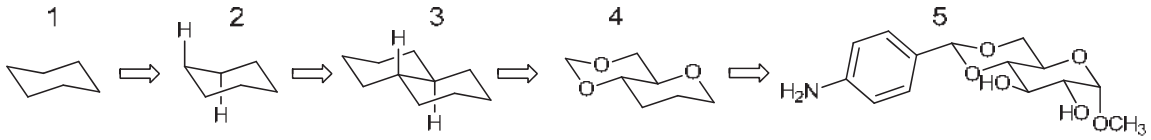


5.77.

The following are two examples of correct answers, where the molecule is viewed from different perspectives.



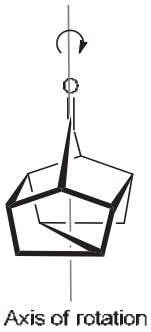
A suggested approach to this problem:



1) Draw a chair structure of the ring on the right side of the compound.
2) Now, to find an appropriate place to connect the second ring, find two axial positions on adjacent carbon atoms so that they are down and up when going counterclockwise around the ring, as they are in the wedge and dash drawing. These are the two bridgehead positions.
3) Draw the second ring (with connecting bonds equatorial to the first ring).
4) Replace appropriate methylene groups in the rings with oxygen atoms.
5) Draw all substituents.

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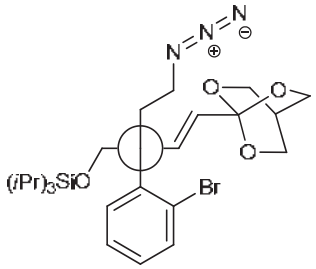
5.78.
(a) The compound exhibits rotational symmetry, because it possesses an axis of symmetry (consider rotating the molecule 180º about this vertical axis). You might find it helpful to construct a molecular model of this compound.



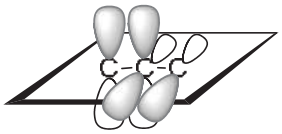
(b) The compound lacks reflectional symmetry; it does not have a plane of symmetry.
(c) Chirality is not dependent on the presence or absence of rotational symmetry. It is only dependent on the presence or absence of reflectional symmetry. This compound lacks reflectional symmetry and is therefore chiral. That is, it has a non-superimposable mirror image, drawn here:



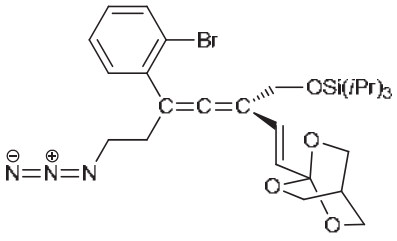
5.79.
(a) In the following Newman projection, the front carbon atom is connected to only two groups, and the back carbon atom is also connected to only two groups:

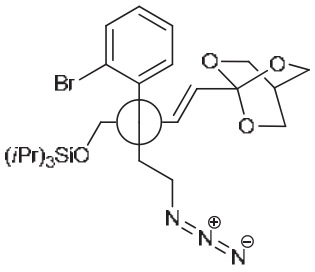


Notice that the two groups connected to the front carbon atom are twisted 90º with respect to the two groups connected to the back carbon atom. This is because the central carbon atom (in between the front carbon atom and the back carbon atom) is *sp* hybridized – it has two *p* orbitals, which are 90º apart from each other. One *p* orbital is being used to form one π bond, while the other *p* orbital is being used to form the other π bond.



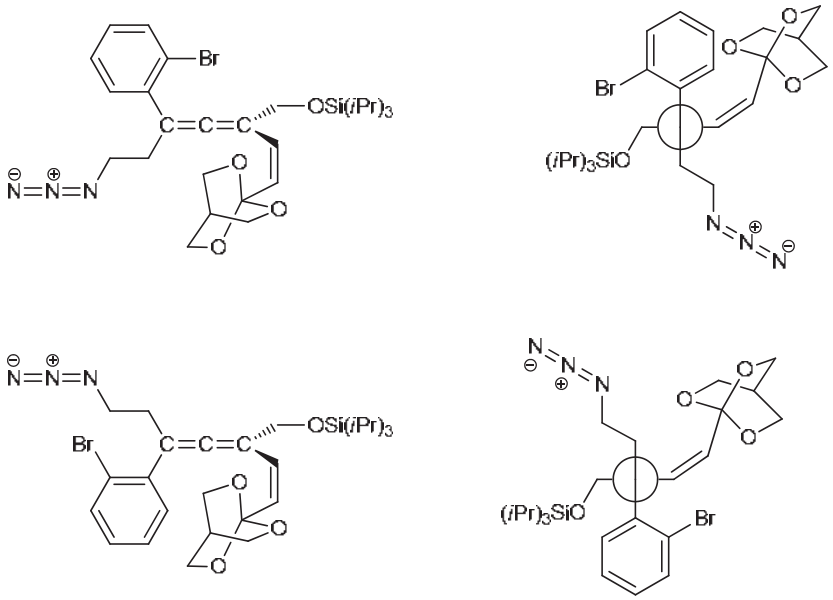
(b) To draw the enantiomer, we could either switch the two groups connected to the front carbon atom, or we could switch the two groups connected to the back carbon atom. The former is shown here, in both bond-line format and in a Newman projection.





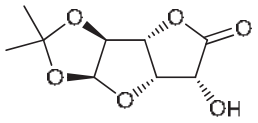
(c) To draw a diastereomer of the original compound, simply convert the *trans* configuration of the alkene to a *cis* configuration. The two diastereomers (both *cis* alkenes) are enantiomers of each other.

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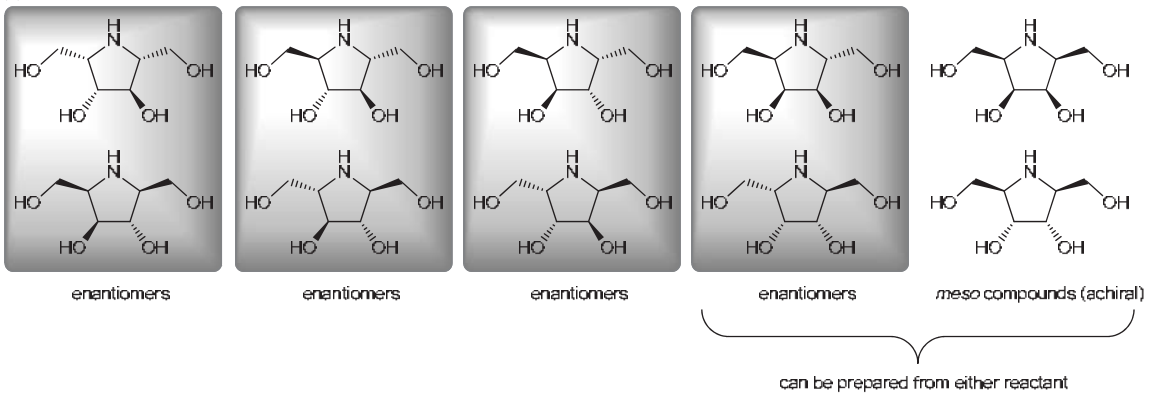
5.80.

(a) Glucuronolactone 1L is the enantiomer of 1D, which is shown in the problem statement. To draw the enantiomer of 1D, we simply redraw it, except that we replace all dashes with wedges, and all wedges with dashes, as shown:



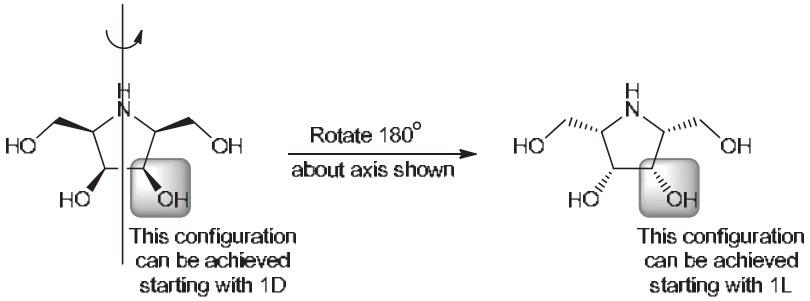
(b) There are 5 chiral centers, so there are 32 (or 2^5) possible stereoisomers.

(c)

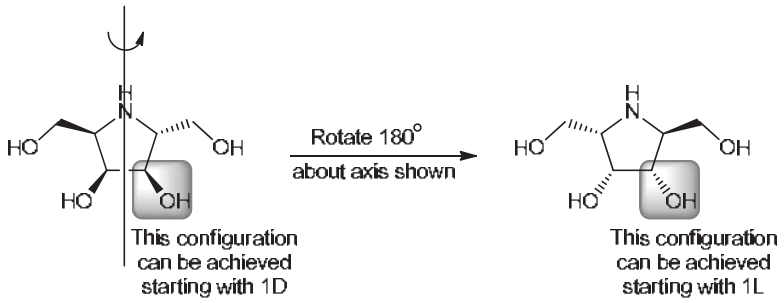


(d) The four products that are accessible from either of the reactants are the four products shown on the right in the solution to part c, as indicated above. Recall that the synthetic protocol allows for control of configurations at C2, C3 and C5, but not at C4. Therefore, in order for a specific stereoisomer to be accessible from either 1D or from 1L, that stereoisomer must display a specific feature. To understand this feature, we must draw one of the ten stereoisomers and then redraw it again after rotating it 180 degrees about a vertical axis. For example, let's do this for one of the *meso* compounds:

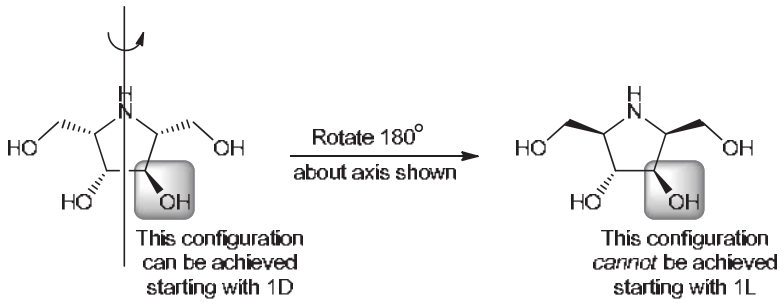
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Now we look at the configuration of the chiral center in the bottom right corner of each drawing above (highlighted in gray). Notice that they have opposite configuration. This is the necessary feature that enables this compound to be accessible from either 1D or from 1L. Here is another example:



Once again, this stereoisomer will be accessible from either 1D or from 1L. In contrast, the first six structures (in the answer to part c) do not have this feature. For example, consider the first structure: let's draw it, rotate it 180 degrees, and then inspect the configuration in the bottom right corner of each drawing:



Note that in this case, the configuration in the bottom right corner of each drawing of this structure is the same. Therefore, this stereoisomer can ONLY be made from 1D. It cannot be made from 1L. A similar analysis for the first six stereoisomers (in the answer to part c) shows that all six of these stereoisomers require a specific enantiomer for the starting material. Only the last four stereoisomers can be made from either 1D or from 1L.

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Chapter 6
Chemical Reactivity and Mechanisms

Review of Concepts

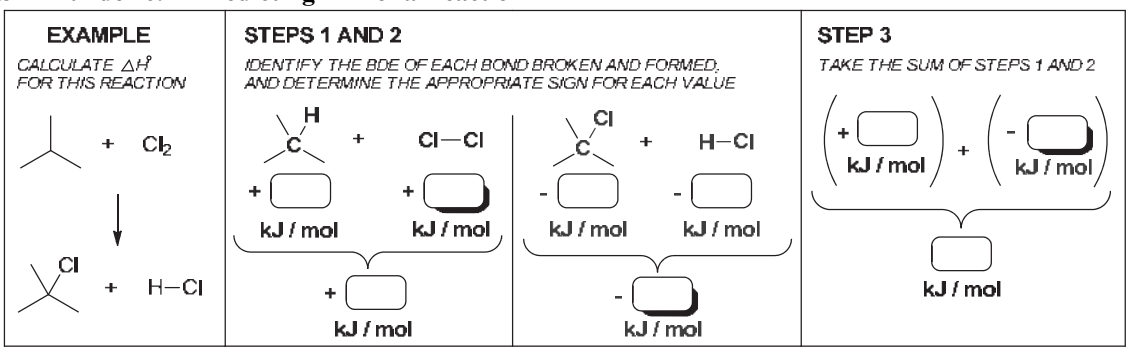
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 6. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- _____ reactions involve a transfer of energy from the system to the surroundings, while _____ reactions involve a transfer of energy from the surroundings to the system.
- Each type of bond has a unique _____ **energy**, which is the amount of energy necessary to accomplish **homolytic bond cleavage**.
- **Entropy** is loosely defined as the _____ of a system.
- In order for a process to be spontaneous, the change in _____ must be negative.
- The study of relative energy levels and equilibrium concentrations is called _____.
- The study of reaction rates is called _____.
- _____ speed up the rate of a reaction by providing an alternate pathway with a lower **energy of activation**.
- On an energy diagram, each peak represents a _____, while each valley represents _____.
- A _____ has an electron-rich atom that is capable of donating a pair of electrons.
- An _____ has an electron-deficient atom that is capable of accepting a pair of electrons.
- For **ionic reactions**, there are four characteristic arrow-pushing patterns: 1) _____, 2) _____, 3) _____, and 4) _____.
- As a result of **hyperconjugation**, _____ carbocations are more stable than secondary carbocations, which are more stable than _____ carbocations.

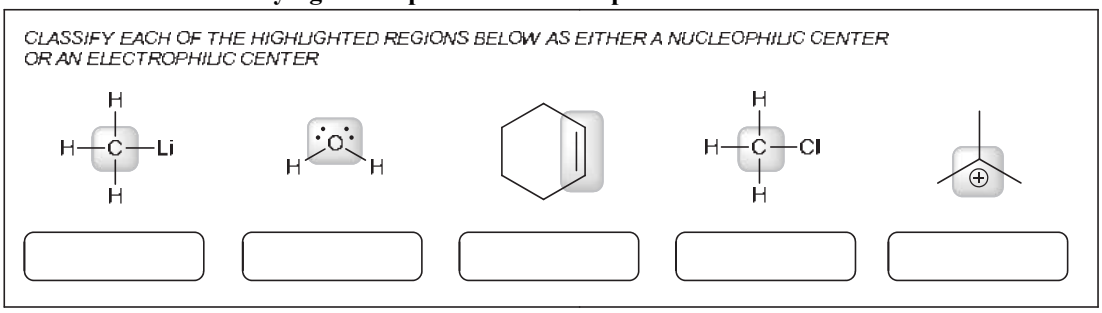
Review of Skills

Fill in the empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 6. The answers appear in the section entitled *SkillBuilder Review*.

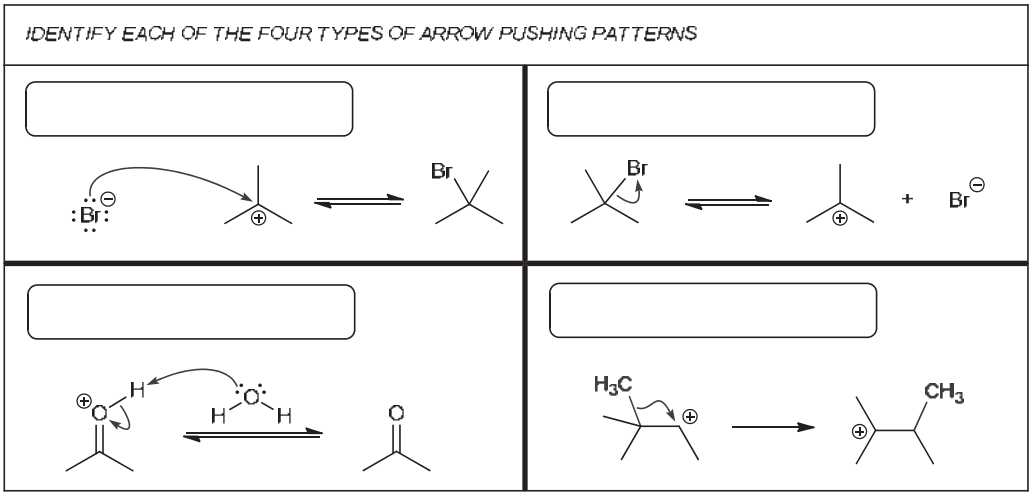
SkillBuilder 6.1 Predicting ΔH^o of a Reaction



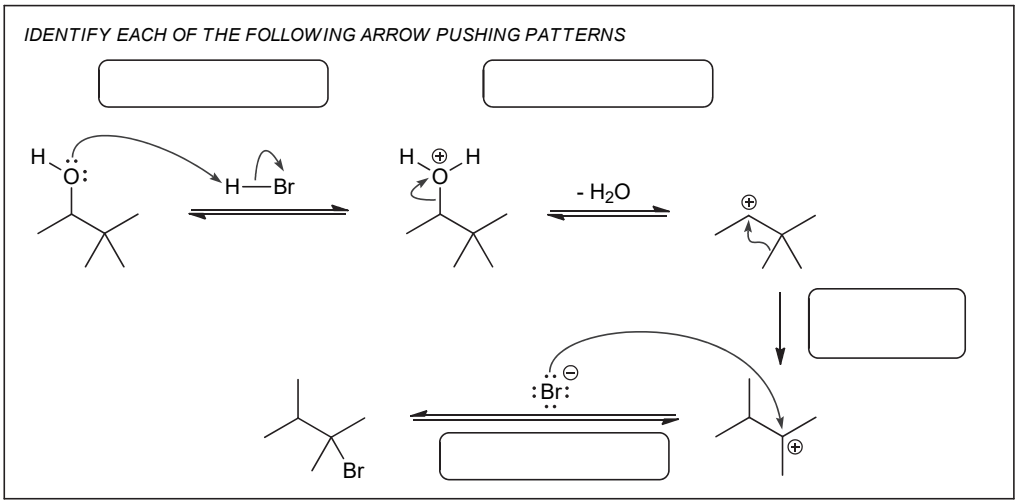
SkillBuilder 6.2 Identifying Nucleophilic and Electrophilic Centers



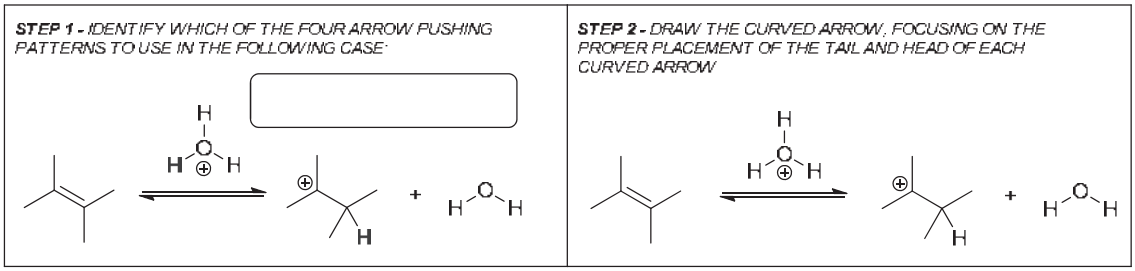
SkillBuilder 6.3 Identifying an Arrow Pushing Pattern



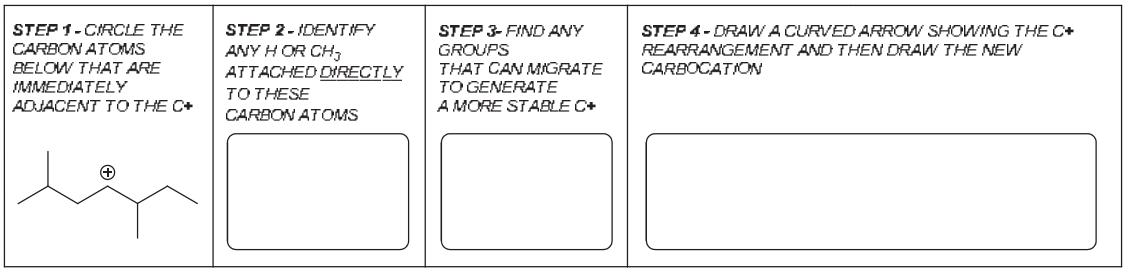
SkillBuilder 6.4 Identifying a Sequence of Arrow Pushing Patterns



SkillBuilder 6.5 Drawing Curved Arrows

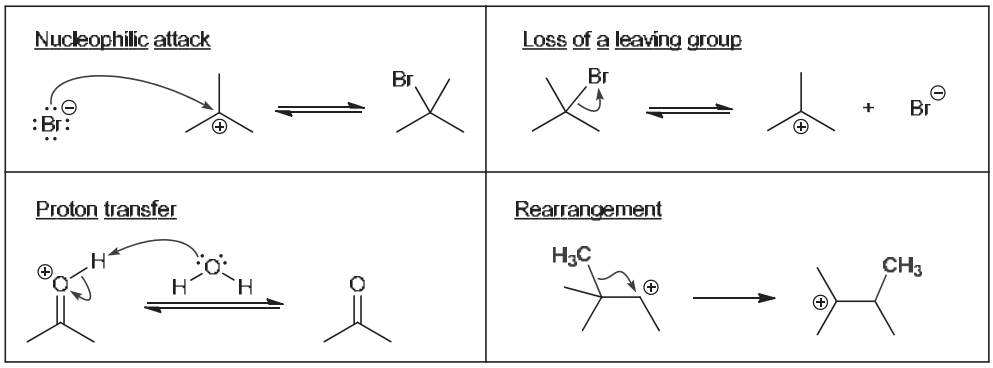


SkillBuilder 6.6 Predicting Carbocation Rearrangements



Common Mistakes to Avoid

In this chapter, we learned many skills that are necessary for drawing reaction mechanisms (identifying nucleophilic and electrophilic centers, drawing curved arrows, identifying arrow-pushing patterns, etc.). We will use these skills frequently in the upcoming chapters. In particular, it is important to become proficient with curved arrows, as they represent the language of reaction mechanisms, and you will have to become fluent in that language as we progress through the chapters. There are many common mistakes that students make when drawing curved arrows, and most of those mistakes can be avoided if you always remember that curved arrows represent the motion of electrons. That is, the tail of every curved arrow must identify which electrons are moving, and the head of every curved arrow must show where those electrons are going. Let's first focus on the tail. The tail must always be placed on electrons, which means that it must be placed either on a lone pair or on a bond. If we examine each of the four characteristic arrow-pushing patterns below, we see this clearly:



Notice that the tail of each curved arrow is placed on a lone pair or on a bond. Similarly, the head of every curved arrow must either show the formation of a lone pair or the formation of a bond. Look at all of the curved arrows above and convince yourself that this is correct. If you keep this in mind when drawing curved arrows, you can avoid many silly errors.

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Solutions

6.1.
(a) Using Table 6.1, we identify the bond dissociation energy (BDE) of each bond that is either broken or formed. For bonds broken, BDE values will be positive. For bonds formed, BDE values will be negative.

Bonds Broken	**kJ/mol**
H—$CH(CH_3)_2$	**+ 397**
Br—Br	**+ 193**

Bonds Formed	**kJ/mol**
$(CH_3)_2CH$—Br	**– 285**
H—Br	**– 368**

The net sum is **– 63 kJ/mol**. ΔH^o for this reaction is negative, which means that the system is losing energy. It is giving off energy to the environment, so the reaction is exothermic.

(b) Using Table 6.1, we identify the bond dissociation energy (BDE) of each bond that is either broken or formed. For bonds broken, BDE values will be positive. For bonds formed, BDE values will be negative.

Bonds Broken	**kJ/mol**
$(CH_3)_3C$—Cl	**+ 331**
H—OH	**+ 498**

Bonds Formed	**kJ/mol**
$(CH_3)_3C$—OH	**– 381**
H—Cl	**– 431**

The net sum is **+ 17 kJ/mol**. ΔH^o for this reaction is positive, which means that the system is gaining energy. It is receiving energy from the environment, so the reaction is endothermic.

(c) Using Table 6.1, we identify the bond dissociation energy (BDE) of each bond that is either broken or formed. For bonds broken, BDE values will be positive. For bonds formed, BDE values will be negative.

Bonds Broken	**kJ/mol**
$(CH_3)_3C$—Br	**+ 272**
H—OH	**+ 498**

Bonds Formed	**kJ/mol**
$(CH_3)_3C$—OH	**– 381**
H—Br	**– 368**

The net sum is **+ 21 kJ/mol**. ΔH^o for this reaction is positive, which means that the system is gaining energy. It is receiving energy from the environment, so the reaction is endothermic.

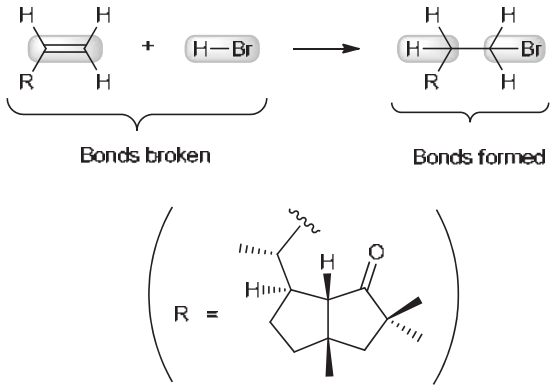
(d) Using Table 6.1, we identify the bond dissociation energy (BDE) of each bond that is either broken or formed. For bonds broken, BDE values will be positive. For bonds formed, BDE values will be negative.

Bonds Broken	**kJ/mol**
$(CH_3)_3C$—I	**+ 209**
H—OH	**+ 498**

Bonds Formed	**kJ/mol**
$(CH_3)_3C$—OH	**– 381**
H—I	**– 297**

The net sum is **+ 29 kJ/mol**. ΔH^o for this reaction is positive, which means that the system is gaining energy. It is receiving energy from the environment, so the reaction is endothermic.

6.2. Begin by identifying all of the bonds that are being made or broken in the reaction. For simplicity, we will focus on the region of the molecule where the change is taking place, and we redraw the reaction as follows:



The highlighted bonds represent the bonds that are broken or formed. Notice that the C=C bond is not completely broken, but it is converted to a single bond. That is, only the π bond is broken, not the σ bond. Table 6.1 lists only σ bonds (it does not list the π component of a C=C bond), but we can determine the value of the π component, given the value of the entire double bond:

$$BDE(\sigma) + BDE(\pi) = BDE \text{ (double)}$$
$$356 \text{ kJ/mol} + BDE(\pi) = 607 \text{ kJ/mol}$$
$$BDE(\pi) = 251 \text{ kJ/mol}$$

We are using the BDE of CH_3CH_2-CH_3 as the best estimate for the σ bond of our double bond because the substitution pattern is the same. Notice that the π component is not as strong as the σ component of the C=C bond. Indeed, this is why the π component of the C=C bond is broken while the σ component remains intact.
The calculation for ΔH is as follows:

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Bonds Broken	**kJ/mol**
C=C (just the π component)	+251
H-Br	+368

Bonds Formed	**kJ/mol**
primary C-Br (approximated by CH_3CH_2-Br)	−285
secondary C-H (approximated by H-$CH(CH_3)_2$)	−397

The net sum is −63 kJ/mol. Since ΔH□ is predicted to be negative, we can also predict that this reaction will be exothermic.

6.3.
(a) ΔS_{sys} is expected to be negative (a decrease in entropy) because two molecules are converted into one molecule.
(b) ΔS_{sys} is expected to be negative (a decrease in entropy) because an acylic compound is converted into a cyclic compound.
(c) ΔS_{sys} is expected to be positive (an increase in entropy) because one molecule is converted into two molecules.
(d) ΔS_{sys} is expected to be positive (an increase in entropy) because one molecule is converted into two ions.
(e) ΔS_{sys} is expected to be negative (a decrease in entropy) because two chemical entities are converted into one.
(f) ΔS_{sys} is expected to be positive (an increase in entropy) because a cyclic compound is converted into an acyclic compound.

6.4.
(a) There is a competition between the two terms contributing to ΔG. In this case, the reaction is endothermic, which contributes to a positive value for ΔG, but the second term contributes to a negative value for ΔG:

$$\Delta G = \underset{\oplus}{\Delta H} + \underset{\ominus}{(-T\Delta S)}$$

The sign of ΔG will therefore depend on the competition between these two terms, which is affected by temperature. A high temperature will cause the second term to dominate, giving rise to a negative value of ΔG. A low temperature will render the second term insignificant, and the first term will dominate, giving rise to a positive value of ΔG.

(b) In this case, both terms contribute to a negative value for ΔG, so ΔG will definitely be negative (the process will be spontaneous).

(c) In this case, both terms contribute to a positive value for ΔG, so ΔG will definitely be positive (the process will not be spontaneous).

(d) There is a competition between the two terms contributing to ΔG. In this case, the reaction is exothermic, which contributes to a negative value for ΔG, but the second term contributes to a positive value for ΔG:

$$\Delta G = \underset{\ominus}{\Delta H} + \underset{\oplus}{(-T\Delta S)}$$

The sign of ΔG will therefore depend on the competition between these two terms, which is affected by temperature. A high temperature will cause the second term to dominate, giving rise to a positive value of ΔG. A low temperature will render the second term insignificant, and the first term will dominate, giving rise to a negative value of ΔG.

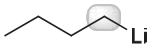
6.5. A system can only achieve a lower energy state by transferring energy to its surroundings (conservation of energy). This increases the entropy of the surroundings, which more than offsets the decrease in entropy of the system. As a result, ΔS_{tot} increases.

6.6.
(a) A positive value of ΔG favors reactants.
(b) A reaction for which $K_{eq} < 1$ will favor reactants.
(c) $\Delta G = \Delta H - T\Delta S$ = (33 kJ/mol) – (298 K)(0.150 kJ/mol • K) = -11.7 kJ/mol
A negative value of ΔG favors products.
(d) Both terms contribute to a negative value of ΔG, which favors products.
(e) Both terms contribute to a positive value of ΔG, which favors reactants.

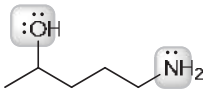
6.7.
(a) Process D will occur more rapidly because it has a lower energy of activation than process A.
(b) Process A will more greatly favor products than process B, because the former is exergonic (the products are lower in energy than the reactants) while the latter is not exergonic.
(c) None of these processes exhibits an intermediate, because none of the energy diagrams has a local minimum (a valley). But all of the processes proceed via a transition state, because all of the energy diagrams have a local maximum (a peak).
(d) In process A, the transition state resembles the reactants more than products because the transition state is closer in energy to the reactant than the products (the Hammond postulate).
(e) Process A will occur more rapidly because it has a lower energy of activation than process B.
(f) Process D will more greatly favor products at equilibrium than process B, because the former is exergonic (the products are lower in energy than the reactants) while the latter is not exergonic.
(g) In process C, the transition state resembles the products more than reactants because the transition state is closer in energy to the products than the reactants (the Hammond postulate).

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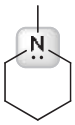
6.8.
(a) Carbon is significantly more electronegative than lithium. As such, the carbon atom of the C-Li bond withdraws electron density (via induction) from the lithium atom, rendering that carbon atom highly nucleophilic.



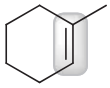
(b) Lone pairs are regions of high electron density. As such, this compound has nucleophilic centers, highlighted below:



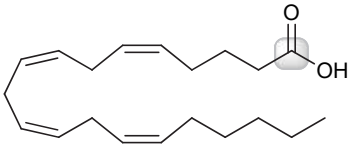
(c) The lone pair on the nitrogen atom constitutes a nucleophilic center:



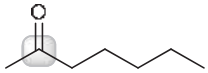
(d) The π bond (highlighted) is a nucleophilic center:



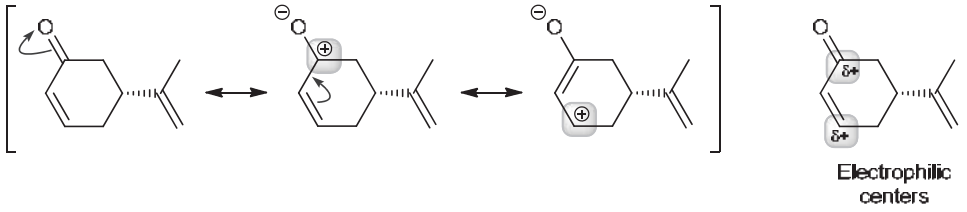
6.9.
(a) The carbon atom of the carboxylic acid group (COOH) is electrophilic. This is the only electrophilic center in the compound.



(b) The carbon atom of the carbonyl group (C=O) is electrophilic. This is the only electrophilic center in the compound.



6.10. When we draw all significant resonance structures, we find that there are two positions (highlighted) that are deficient in electron density and, therefore, are electrophilic. Of the two carbon-carbon π bonds, the one that is conjugated with the carbon-oxygen π bond is the one that is electrophilic:



6.11.
(a) The curved arrow indicates a hydride shift, which is a type of carbocation rearrangement.
(b) The curved arrow indicates a nucleophilic attack. In this case, water functions as a nucleophile and attacks the carbocation.
(c) The curved arrows indicate a proton transfer. In this case, water functions as the base that removes the proton.
(d) The curved arrows indicate a nucleophilic attack. In this case, one of the lone pairs on the oxygen atom functions as the nucleophilic center that attacks the electrophilic center.
(e) The curved arrow indicates loss of a leaving group (Cl^-).

6.12. The curved arrow indicates a proton transfer. In this case, the nitrogen atom functions as the base that removes the proton from the oxygen atom.

6.13.
(a) The sequence of arrow-pushing patterns is as follows:
(i) nucleophilic attack
(ii) proton transfer
(iii) proton transfer

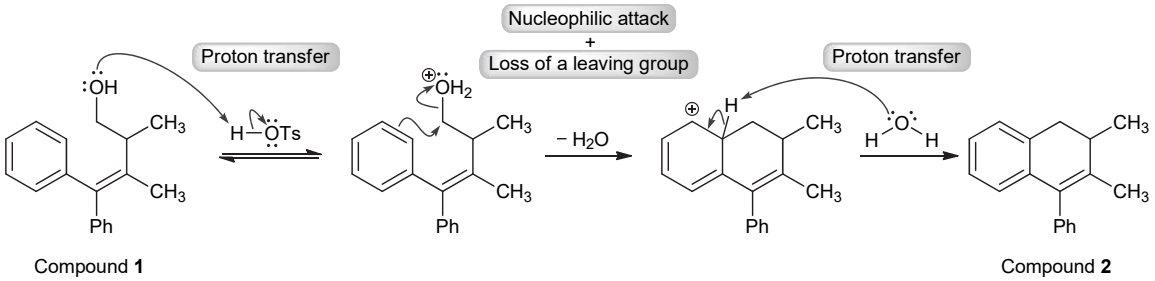
(b) The sequence of arrow-pushing patterns is as follows:
(i) proton transfer
(ii) nucleophilic attack
(iii) loss of a leaving group

(c) The sequence of arrow-pushing patterns is as follows:
(i) proton transfer
(ii) loss of a leaving group
(iii) nucleophilic attack
(iv) proton transfer

(d) The sequence of arrow-pushing patterns is as follows:
(i) proton transfer
(ii) nucleophilic attack
(iii) proton transfer

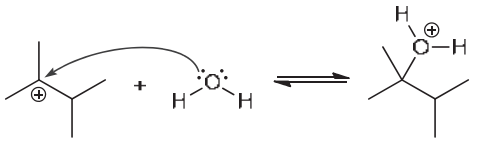
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6.14. The first step is a typical proton transfer, requiring two curved arrows. The second step is a nucleophilic attack (recall that a π bond can function as a nucleophile) combined with the loss of a leaving group, each of which requires one arrow, for a total of two curved arrows. The third step is another proton transfer, which requires two curved arrows. In this last step, the electrons from the breaking C-H bond are used to make a new π bond.

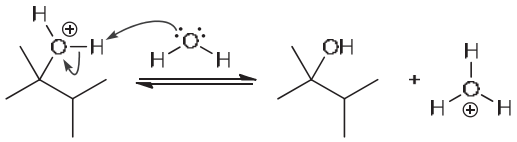


6.15.

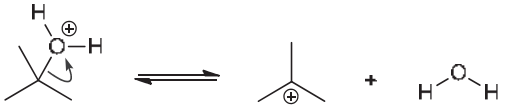
(a) In this case, a C–O bond is formed, indicating a nucleophilic attack. Water (H_2O) functions as a nucleophile and attacks the carbocation. This is shown with one curved arrow. The tail of this curved arrow is placed on the lone pair of the oxygen atom, and the head is placed on the electrophilic center (the empty *p* orbital of the carbocation), as shown here:



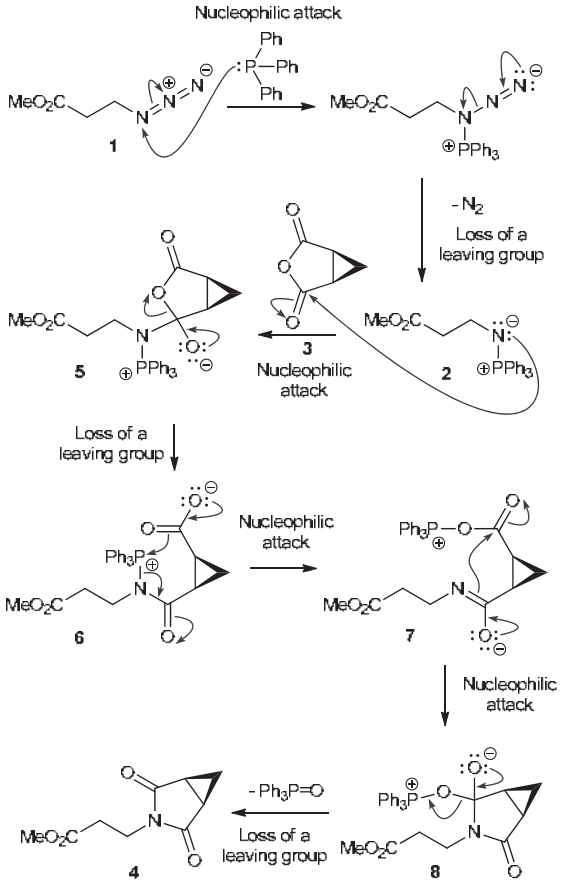
(b) This is a proton transfer step, in which water functions as a base and removes a proton, thereby generating H_3O^+. A proton transfer step requires two curved arrows. The tail of the first curved arrow is placed on a lone pair of H_2O, and the head is placed on the proton that is being transferred. Don't forget the second curved arrow. The tail is placed on the O–H bond (that is being broken) and the head is placed on the oxygen atom, as shown:



(c) This step represents the loss of a leaving group (where the leaving group is H_2O). One curved arrow is required. The tail is placed on the C–O bond that is broken, and the head is placed on the oxygen atom.



6.16. The conversion of **1** to **2** involves two steps: First the lone pair on the phosphorus atom functions as a nucleophile and attacks the azide (RN_3), followed by loss of a leaving group to give compound **2**. Note that nitrogen gas (N_2) is liberated, which renders the conversion from **1** to **2** irreversible. When **2** is treated with **3**, the nitrogen atom of **2** functions as a nucleophile and attacks one of the C=O bonds in **3** to give **5**. Loss of a leaving group gives **6**, which undergoes an intramolecular nucleophilic attack to give **7**. Another intramolecular nucleophilic attack gives **8**, which then undergoes loss of a leaving group to give the product (**4**). The curved arrows are drawn here:

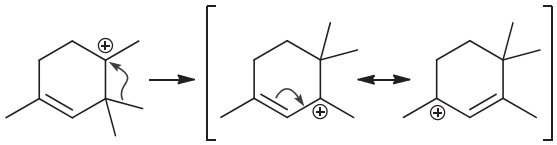


6.17.
(a) This carbocation is secondary, and it can rearrange via a hydride shift (shown below) to give a more stable, tertiary carbocation:



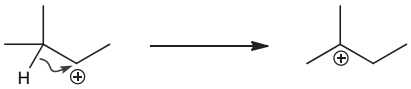
(b) This carbocation is tertiary, and it cannot become more stable via a rearrangement.

(c) This carbocation is tertiary. Yet, in this case, rearrangement via a methyl shift will generate a more stable, tertiary allylic carbocation, which is resonance stabilized, as shown:



(d) This carbocation is secondary, but there is no way for it to rearrange to form a tertiary carbocation.

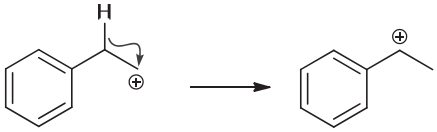
(e) This carbocation is secondary, and it can rearrange via a hydride shift (shown below) to give a more stable, tertiary carbocation:



(f) This carbocation is secondary, and it can rearrange via a methyl shift (shown below) to give a more stable, tertiary carbocation:

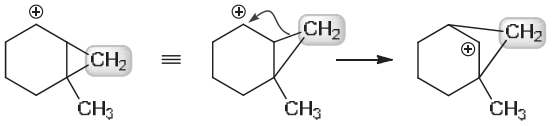


(g) This carbocation is primary, and it can rearrange via a hydride shift (shown below) to give a resonance stabilized carbocation (we will see in Chapter 7 that this carbocation is called a benzylic carbocation):

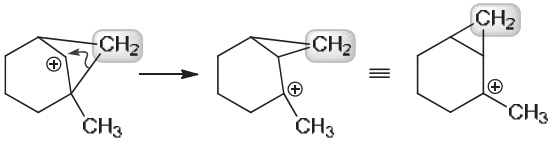


(h) This carbocation is tertiary and it is resonance-stabilized (we will see in Chapter 7 that this carbocation is called a benzylic carbocation). It will not rearrange.

6.18. In the first rearrangement, a three-membered ring is being converted into a four-membered ring (a process called ring expansion). In order for this to occur, the migrating methylene group (highlighted) must be part of the three-membered ring. The migrating carbon atom is highlighted below:



In the second rearrangement, a four-membered ring is being converted into a three-membered ring (a process called ring contraction). In order for this to occur, the migrating carbon atom must be part of the four-membered ring. Once again, the same methylene group migrates (highlighted):



6.19.
(a) A carbon-carbon triple bond is comprised of one σ bond and two π bonds, and is therefore stronger than a carbon-carbon double bond (one σ and one π bond) or a carbon-carbon single bond (only one σ bond). Therefore, the carbon-carbon triple bond is expected to have the largest bond dissociation energy.
(b) The data in Table 6.1 indicate that the C-F bond will have the largest bond dissociation energy.

6.20.
(a) Using Table 6.1, we identify the bond dissociation energy (BDE) of each bond that is either broken or formed. For bonds broken, BDE values will be positive. For bonds formed, BDE values will be negative.

Bonds Broken	**kJ/mol**
RCH_2—Br	**+ 285**
RCH_2O—H	**+ 435**

Bonds Formed	**kJ/mol**
RCH_2—OR	**– 381**
H—Br	**– 368**

The net sum is **– 29 kJ/mol**. ΔH^o for this reaction is negative, which means that the system is losing energy. It is giving off energy to the environment, so the reaction is exothermic.
(b) ΔS of this reaction is positive because one mole of reactant is converted into two moles of product.
(c) Both terms (ΔH) and ($-T\Delta S$) contribute to a negative value of ΔG.
(d) Since both terms (ΔH and $-T\Delta S$) have negative values, the value of ΔG will be negative at all temperatures.
(e) Yes. At high temperatures, the value of $-T\Delta S$ is large and negative (while at low temperatures, the value of $-T\Delta S$ is small and negative).
Since $\Delta G = \Delta H + (-T\Delta S)$, the magnitude of ΔG will be dependent on temperature.

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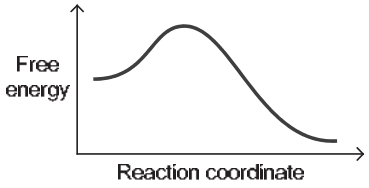
6.21.
(a) A reaction for which $K_{eq} > 1$ will favor products.
(b) A reaction for which $K_{eq} < 1$ will favor reactants.
(c) A positive value of ΔG favors reactants.
(d) Both terms contribute to a negative value of ΔG, which favors products.
(e) Both terms contribute to a positive value of ΔG, which favors reactants.

6.22. $K_{eq} = 1$ when $\Delta G = 0$ kJ/mol (See Table 6.2).

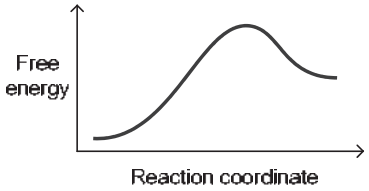
6.23. $K_{eq} < 1$ when ΔG has a positive value. The answer is therefore "a" (+1 kJ/mol)

6.24.
(a) ΔS_{sys} is expected to be negative (a decrease in entropy) because two moles of reactant are converted into one mole of product.
(b) ΔS_{sys} is expected to be positive (an increase in entropy) because one mole of reactant is converted into two moles of product.
(c) ΔS_{sys} is expected to be approximately zero, because two moles of reactant are converted into two moles of product.
(d) ΔS_{sys} is expected to be negative (a decrease in entropy) because an acylic compound is converted into a cyclic compound.
(e) ΔS_{sys} is expected to be approximately zero, because one mole of reactant is converted into one mole of product, and both the reactant and the product are acyclic.

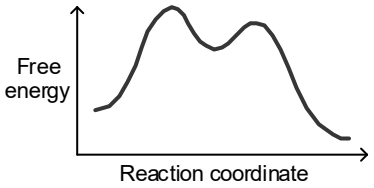
6.25.
(a) If the reaction has only one step, then the energy diagram will have only one peak. Since ΔG for this reaction is negative, the product will be lower in free energy than the reactant, as shown here.



(b) If the reaction has only one step, then the energy diagram will have only one peak. Since ΔG for this reaction is positive, the product will be higher in free energy than the reactant, as shown here.



(c) If the reaction has two steps, then the energy diagram will have two peaks. Since ΔG for this reaction is negative, the product will be lower in free energy than the reactant. And the problem statement indicates that the transition state for the first step is higher in energy than the transition state for the second step, as shown here.



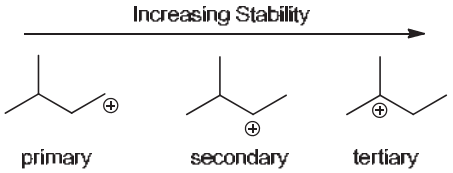
6.26.
(a) Energy diagrams B and D each exhibit two peaks, characteristic of a two-step process.
(b) Energy diagrams A and C each exhibit only one peak, characteristic of a one-step process.
(c) The energy of activation (E_a) is determined by the difference in energy between the reactants and the transition state (the top of the peak in the energy diagram). This energy difference is greater in C than it is in A.
(d) Energy diagram A has a negative ΔG, because the products are lower in free energy than the reactants. This is not the case in energy diagram C.
(e) Energy diagram D has a positive ΔG, because the products are higher in free energy than the reactants. This is not the case in energy diagram A.
(f) The energy of activation (E_a) is determined by the difference in energy between the reactants and the transition state (the top of the peak in the energy diagram). This energy difference is greatest in D.
(g) $K_{eq} > 1$ when ΔG has a negative value. This is the case in energy diagrams A and B, because in each of these energy diagrams, the products are lower in free energy than the reactants.
(h) $K_{eq} = 1$ when $\Delta G = 0$ kJ/mol. This is the case in energy diagram C, in which the reactants and products have approximately the same free energy.

6.27.
(a) The curved arrow indicates loss of a leaving group (Cl^-).
(b) The curved arrow indicates a methyl shift, which is a type of carbocation rearrangement.
(c) The curved arrows indicate a nucleophilic attack.
(d) The curved arrows indicate a proton transfer. In this case, the proton transfer step occurs in an intramolecular fashion (because the acidic proton and the base are tethered together in one structure).

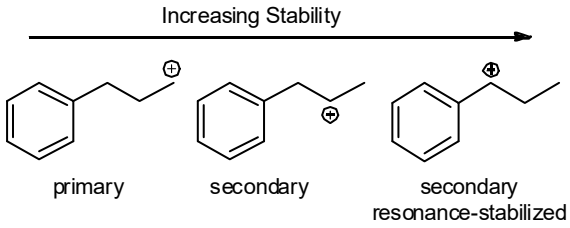
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6.28.

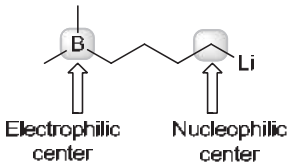
(a) A tertiary carbocation is more stable than a secondary carbocation, which is more stable than a primary carbocation.



(b) The most stable carbocation is the one that is resonance-stabilized. Among the other two carbocations, the secondary carbocation is more stable than the primary carbocation, as shown here.

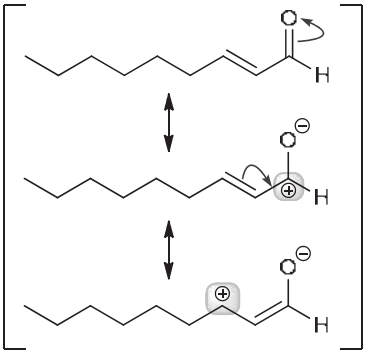


6.29. In this hypothetical compound, the boron atom would have an empty *p* orbital, and would therefore be an electrophilic center. The carbon atom of the C-Li bond withdraws electron density (via induction) from the lithium atom, rendering that carbon atom highly nucleophilic.

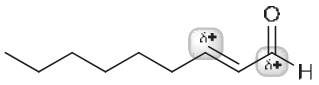


6.30.

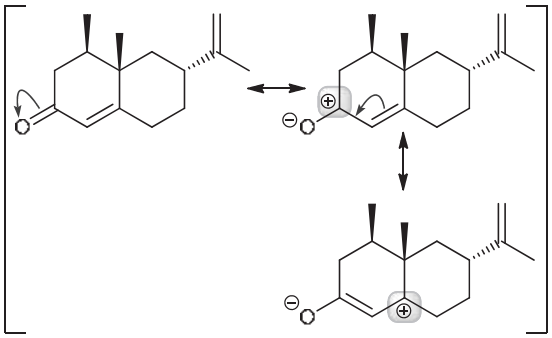
(a) When we draw all significant resonance structures, we find that there are two positions (highlighted) that are deficient in electron density:



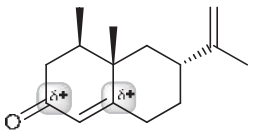
Therefore, these two positions are electrophilic:



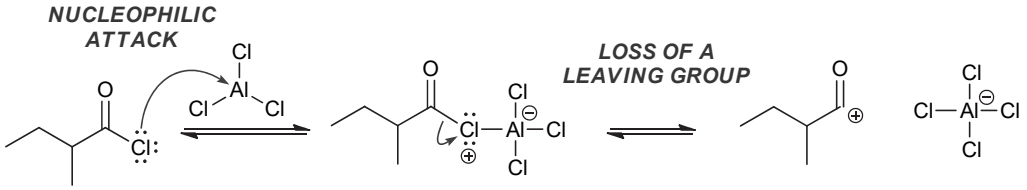
(b) When we draw all significant resonance structures, we find that there are two positions (highlighted) that are deficient in electron density:



Therefore, these two positions are electrophilic:

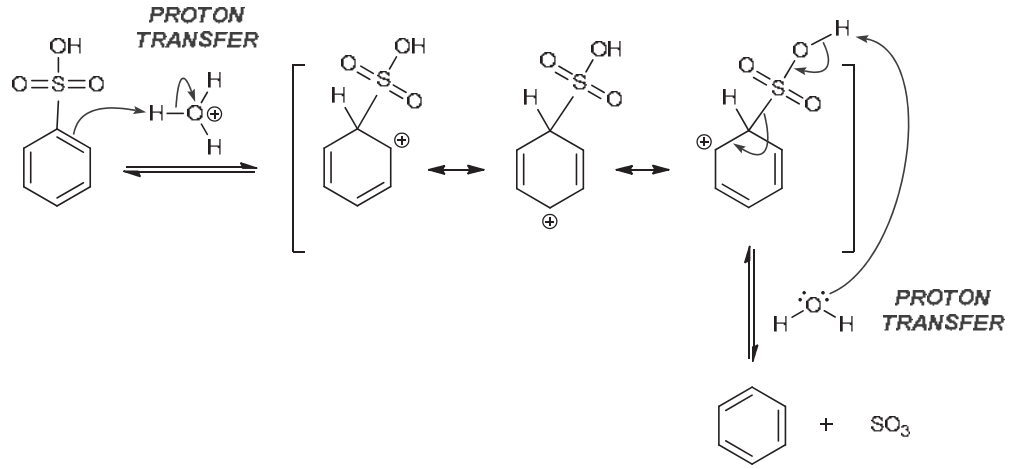


6.31. The sequence of arrow-pushing patterns is as follows:



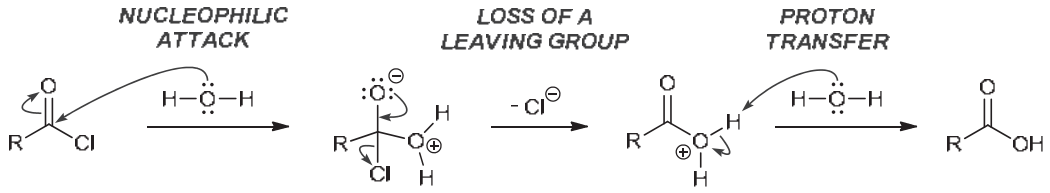
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6.32. The sequence of arrow-pushing patterns is as follows:

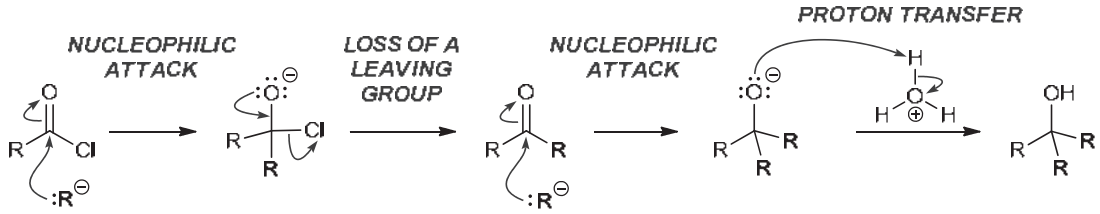


6.33. Both reactions have the same sequence: (i) nucleophilic attack, followed by (ii) loss of a leaving group. In both cases, a hydroxide ion functions as a nucleophile and attacks a compound that can accept the negative charge and store it temporarily. The charge is then expelled as a chloride ion in both cases.

6.34. The sequence of arrow-pushing patterns is as follows:

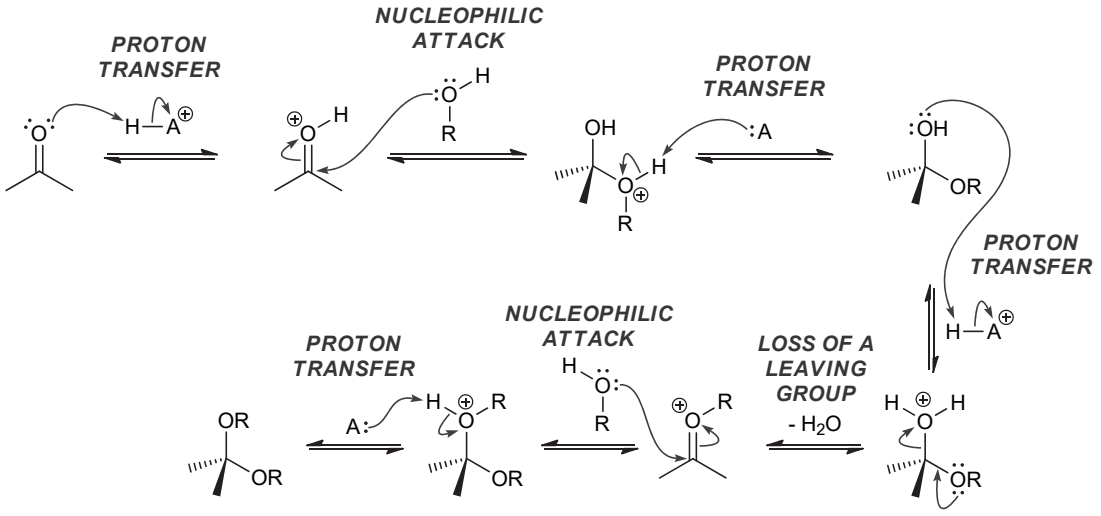


6.35. The sequence of arrow-pushing patterns is as follows:

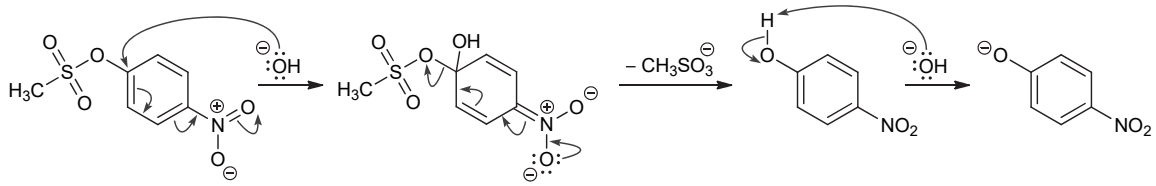


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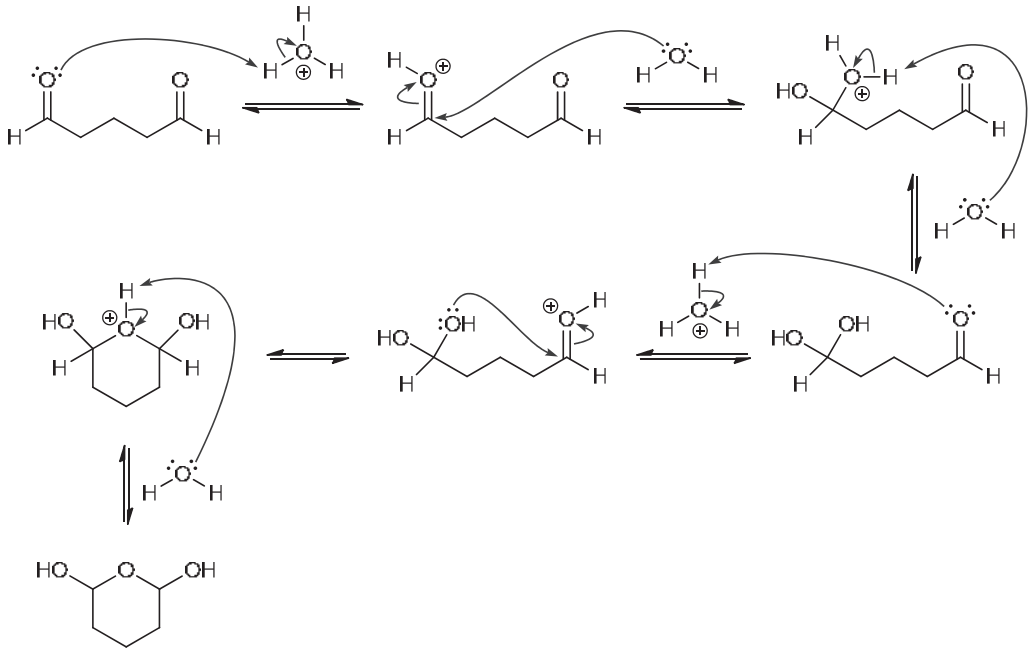
6.36. The sequence of arrow-pushing patterns is as follows:



6.37. The first step is a nucleophilic attack, the second step is loss of a leaving group, and the final step is a proton transfer. In this case, each of the first two steps requires several curved arrows, and the final step requires two curved arrows, as shown:

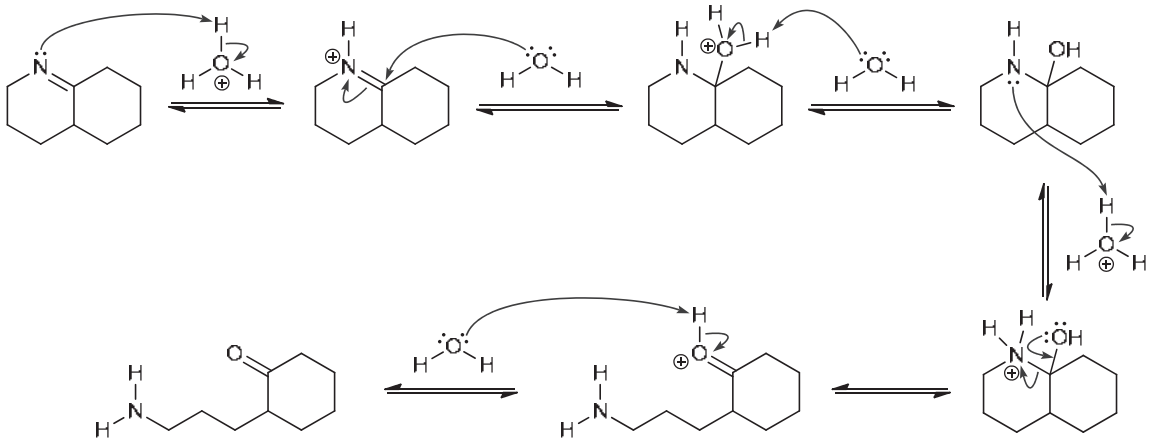


6.38. The following curved arrows show the flow of electrons that achieve the transformation as shown:

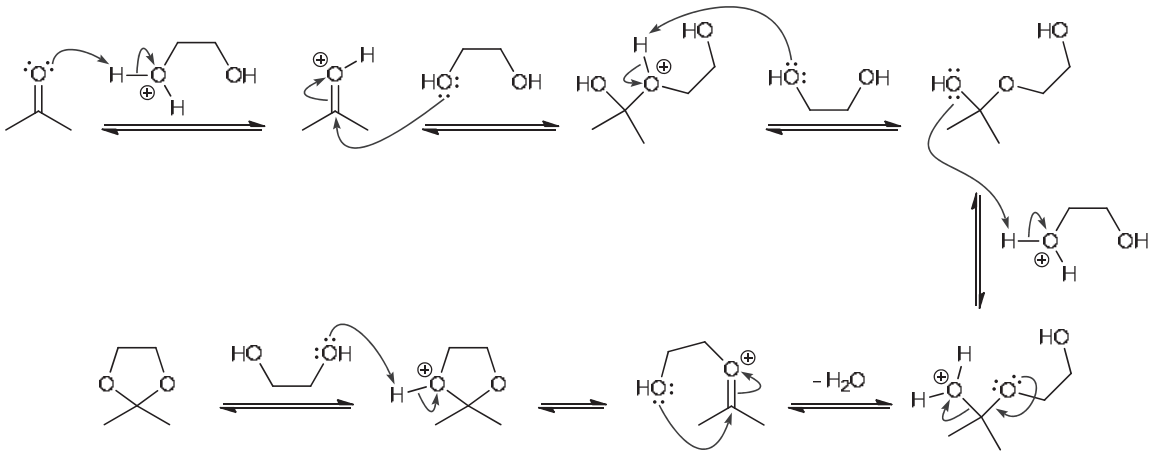


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6.39. The following curved arrows show the flow of electrons that achieve the transformation as shown:



6.40. The following curved arrows show the flow of electrons that achieve the transformation as shown:

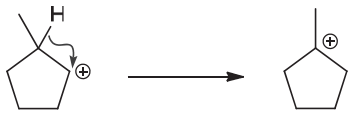


6.41.

(a) This carbocation is secondary, and it can rearrange via a methyl shift (shown below) to give a more stable, tertiary carbocation:

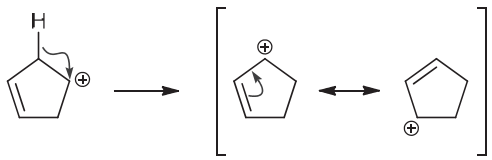


(b) This carbocation is secondary, and it can rearrange via a hydride shift (shown below) to give a more stable, tertiary carbocation:



(c) This carbocation is secondary, but it cannot rearrange to generate a tertiary carbocation.

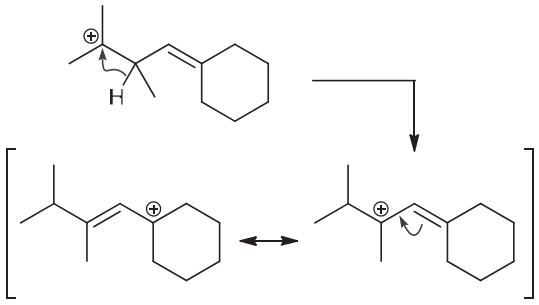
(d) This carbocation is secondary, and it can rearrange via a hydride shift (shown below) to generate a more stable, secondary allylic carbocation, which is resonance stabilized:



(e) This carbocation is tertiary. Yet, in this case, rearrangement via a hydride shift will generate a more

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stable, tertiary allylic carbocation, which is resonance stabilized, as shown below.



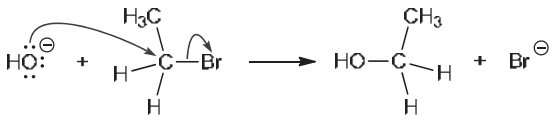
(f) This carbocation is secondary, and it can rearrange via a hydride shift (shown below) to give a more stable, tertiary carbocation:



(g) This carbocation is tertiary and will not rearrange.

6.42.

(a) The C–Br bond is broken, indicating the loss of a leaving group (Br^-), while the C–O bond is formed, indicating a nucleophilic attack. This is, in fact, a concerted process in which nucleophilic attack and loss of the leaving group occur in a simultaneous fashion. One curved arrow is required to show the nucleophilic attack, and another curved arrow is required to show loss of the leaving group:



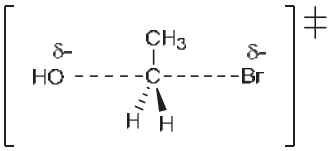
(b) We identify the bond broken (CH_3CH_2—Br), and the bond formed (CH_3CH_2—OH). Using the data in Table 6.1, ΔH for this reaction is expected to be approximately (285 kJ/mol) – (381 kJ/mol). The sign of ΔH is therefore predicted to be negative, which means that the reaction should be exothermic.

(c) Two chemical entities are converted into two chemical entities. Both the reactants and products are acyclic. Therefore, ΔS for this process is expected to be approximately zero.

(d) ΔG has two components: (ΔH) and ($-T\Delta S$). Based on the answers to the previous questions, the first term has a negative value and the second term is insignificant. Therefore, ΔG is expected to have a negative value. This is confirmed by the energy diagram, which shows the products having lower free energy than the reactants.

(e) The position of equilibrium is dependent on the sign and value of ΔG. As mentioned in part e, ΔG is comprised of two terms. The effect of temperature appears in the second term ($-T\Delta S$), which is insignificant because ΔS is approximately zero. Therefore, an increase (or decrease) in temperature is not expected to have a significant impact on the position of equilibrium.

(f) This transition state corresponds with the peak of the curve, and has the following structure:



(g) The transition state in this case is closer in energy to the reactants than the products, and therefore, it is closer in structure to the reactants than the products (the Hammond postulate).

(h) If we inspect the rate equation, we see that the sum of the exponents is two, so this reaction is second order.

(i) According to the rate equation, the rate is linearly dependent on the concentration of hydroxide. Therefore, the rate will be doubled if the concentration of hydroxide is doubled.

(j) At higher temperature, more molecules will have the requisite energy of activation necessary for the reaction to occur, so the rate will increase with increasing temperature.

6.43.

(a) K_{eq} does not affect the rate of the reaction. It only affects the equilibrium concentrations.

(b) ΔG does not affect the rate of the reaction. It only affects the equilibrium concentrations.

(c) Temperature affects the rate of the reaction, by increasing the number of collisions that result in a reaction.

(d) ΔH does not affect the rate of the reaction. It only affects the equilibrium concentrations.

(e) E_a greatly affects the rate of the reaction. Lowering the E_a will increase the rate of reaction.

(f) ΔS does not affect the rate of the reaction. It only affects the equilibrium concentrations.

6.44. In order to determine if reactants or products are favored at high temperature, we must consider the effect of temperature on the sign of ΔG. Recall that ΔG has two components: (ΔH) and ($-T\Delta S$). The reaction is exothermic, so the first term (ΔH) has a negative value, which contributes to a negative value of ΔG. This favors products. At low temperature, the second term will be insignificant and the first term will dominate. Therefore, the process will be thermodynamically favorable, and the reaction will favor the formation of products. However, at high temperature, the second term becomes more significant. In this case, two moles of reactants are converted into one mole of product. Therefore, ΔS for this process is negative, which means that ($-T\Delta S$) is positive. At high enough temperature, the second term ($-T\Delta S$) should dominate over the first term (ΔH), generating a positive value for ΔG. Therefore, the reaction will favor reactants at high temperature.

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6.45. Recall that ΔG has two components:

$$(\Delta H) \text{ and } (-T\Delta S)$$

We must analyze each term separately. The first term is expected to have a negative value, because three π bonds are being converted into one π bond and two σ bonds. A σ bond is stronger (lower in energy) than the π component of a double bond. Therefore, the reaction is expected to release energy to the environment, which means the reaction should be exothermic. In other words, the first term (ΔH) has a negative value, which contributes to a negative value of ΔG. This favors products.

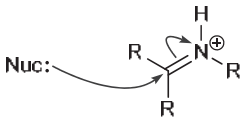
Now let's consider the second term ($-T\Delta S$) contributing to ΔG. In this case, two moles of reactants are converted into one mole of product. Therefore, ΔS for this process is negative, which means that ($-T\Delta S$) is positive. At low temperature, the second term will be insignificant and the first term will dominate. Therefore, the process will be thermodynamically favorable, and the reaction will favor the formation of products. However, at high temperature, the second term becomes more significant. At high enough temperature, the second term ($-T\Delta S$) should dominate over the first term (ΔH), generating a positive value for ΔG. Therefore, the reaction will favor reactants at high temperature.

6.46. The nitrogen atom of an ammonium ion is positively charged, but that does not render it electrophilic. In order to be electrophilic, it must have an empty orbital that can be attacked by a nucleophile. The nitrogen atom in this case does not have an empty orbital, because nitrogen is a second row element and therefore only has four orbitals with which to form bonds. All four orbitals are being used for bonding, leaving none of the orbitals vacant. As a result, the nitrogen atom is not electrophilic, despite the fact that is positively charged.

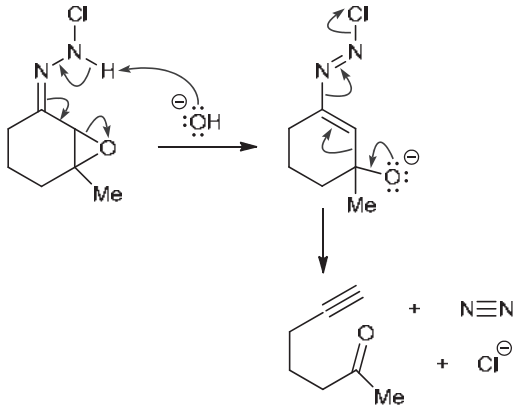
In contrast, an iminium ion is resonance stabilized:



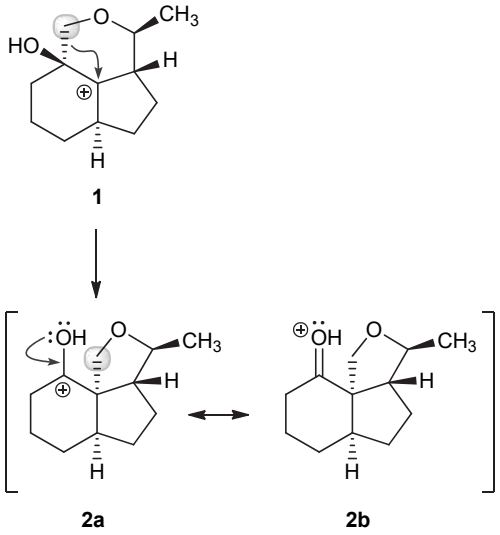
The second resonance structure exhibits a positive charge on a carbon atom, which serves as an electrophilic center. Therefore, an iminium ion is an electrophile and is subject to attack by a nucleophile:



6.47. The following curved arrows show the flow of electrons that achieve the transformation as shown:



6.48. In this case, a six-membered ring is being converted into a five-membered ring (a process called ring-contraction). The migrating carbon atom (highlighted) is bonded to the position that is adjacent to the C+:



1

2a **2b**

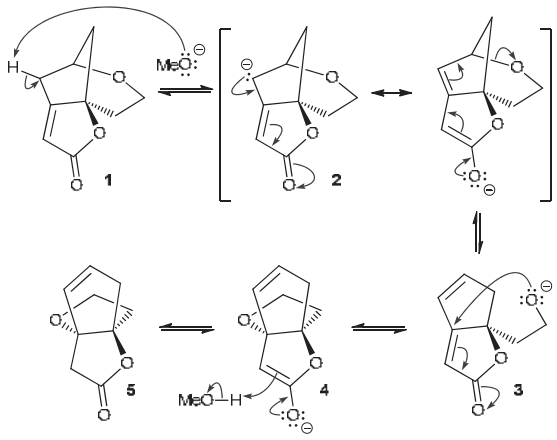
Carbocation **1** is not resonance-stabilized, while carbocation **2** is stabilized by resonance, as shown above. Indeed, the second resonance structure (**2b**) is the more significant contributor to the resonance hybrid of **2**, because all atoms have an octet of electrons. This renders carbocation **2** particularly stable. This additional stability is absent in carbocation **1**.

6.49.

The first step (**1** → **2**) is a proton transfer, in which MeO^- deprotonates **1** to produce **2**, the conjugate base of **1**. The resonance structure of **2** with an anionic oxygen is the greatest contributor to the resonance hybrid due to oxygen being more electronegative than carbon. The transformation of **2** to **3** includes the formation of a C=O

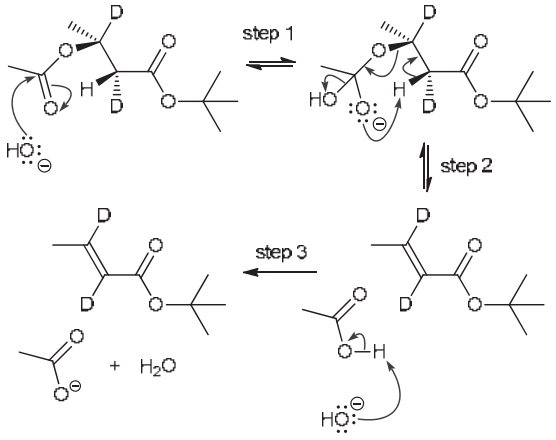
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π bond, the relocation of two C=C π bonds, and the breaking of a C–O σ bond. The resulting anionic oxygen of **3** then serves as a nucleophile, attacking the indicated carbon, pushing electrons up to the oxygen of the C=O bond, as shown. In the final step (**4** → **5**), the C=O π bond is reformed and a proton is transferred from MeOH to the cyclic structure, regenerating MeO^-.



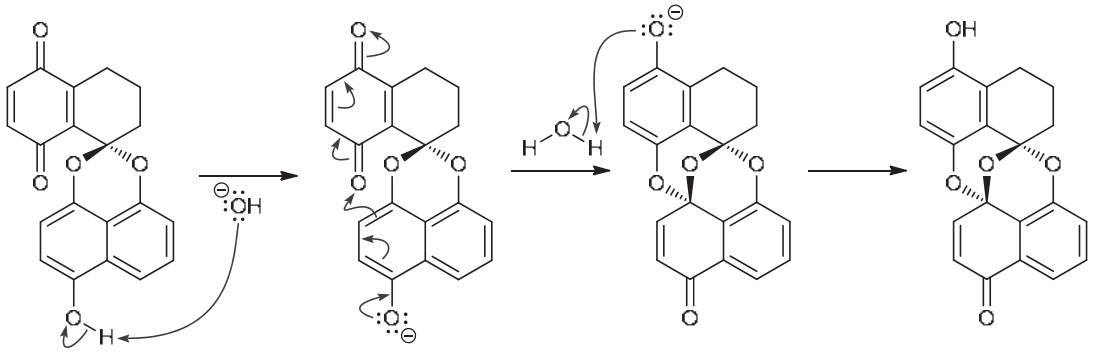
6.50.

In step 1, the hydroxide ion functions as a nucleophile and attacks the carbon atom of the ester group, pushing the π electrons up to the oxygen atom. In step 2, the anionic oxygen atom serves as a base and removes a proton in an intramolecular fashion (proton transfer), as shown. The electrons in the C–H bond form a C=C π bond; the C–O σ bond breaks thus converting the adjacent C–O bond to a double bond, expelling HO^- as a leaving group. Step 3 is a proton transfer to create a resonance-stabilized anion.

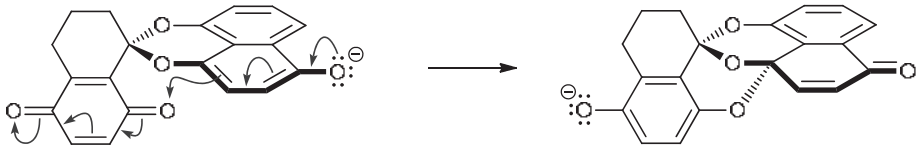


6.51.

(a) The following curved arrows show the flow of electrons that achieve the transformation as shown:



(b) When the second intermediate is redrawn from the following perspective, it becomes clear that the electrons in the carbon-carbon π-bond come from above the carbon-oxygen π bond, allowing for the chiral center to be generated as shown. If you have trouble seeing this, you might find it helpful to build a molecular model.

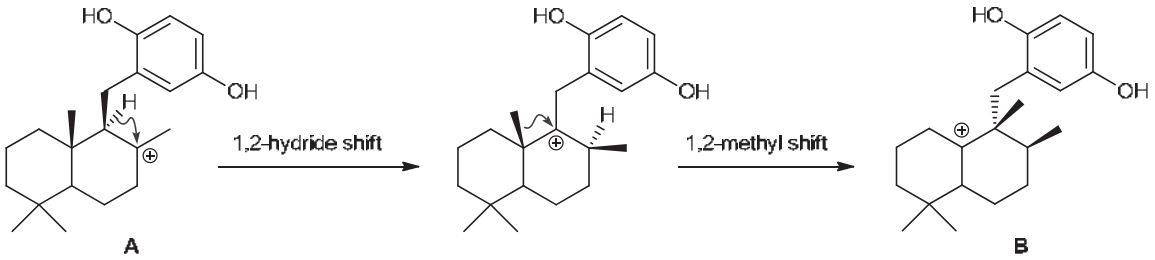


6.52.

The location of C+ appears to have moved two positions, which requires two consecutive carbocation rearrangements. The first rearrangement is a 1,2-hydride shift to give a new 3° carbocation. Notice that the migrating H is on a dash,

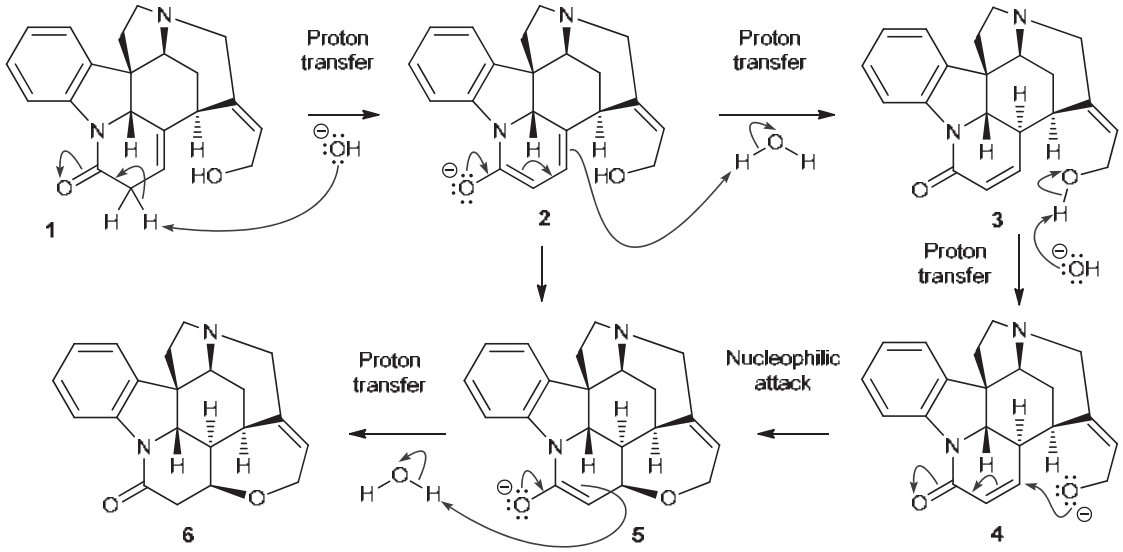
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which means that it is on the face of the molecule pointing away from us. When the 1,2-hydride shift occurs, the H migrates across along the back face of the molecule, so the H remains on a dash in the newly generated carbocation. Then, a 1,2-methyl shift gives another tertiary carbocation **B**. Notice that in this second step, the migrating methyl group is on a solid wedge, which means that it is on the face of the molecule pointing toward us. When the 1,2-methyl shift occurs, the methyl group migrates along the front face of the molecule, so the methyl group remains on a wedge in carbocation **B**.

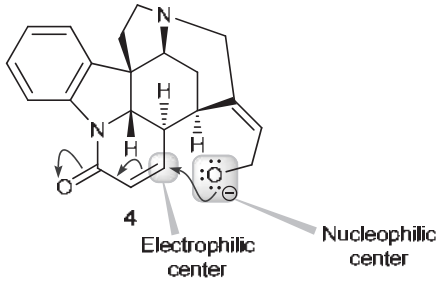


6.53.

(a) The sequence of arrow pushing patterns is shown below, together with all curved arrows:

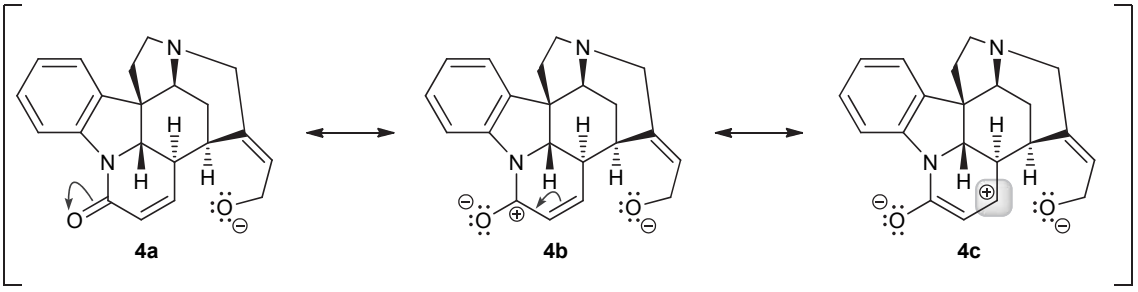


(b) Consider where the nucleophilic attack is occurring. The lone pairs on the oxygen atom (highlighted) are attacking the highlighted carbon atom.

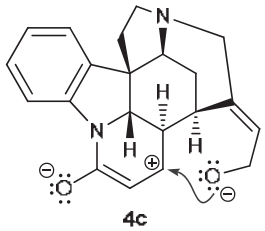


The oxygen atom is the nucleophilic center, and the carbon atom is the electrophilic center. In order to understand why this carbon atom is electron-poor, we draw resonance structures of **4**:

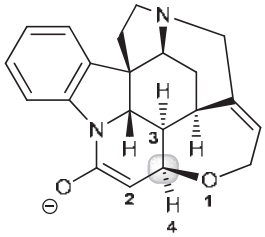
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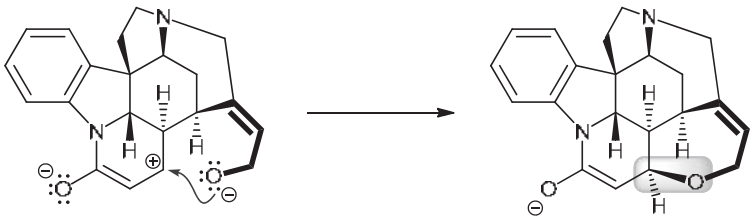
If we inspect resonance structure 4c, we see why the highlighted carbon atom is electrophilic. In fact, when we draw this resonance structure, we can see the nucleophilic attack more clearly:



(c) The new chiral center is highlighted below. The oxygen atom takes priority #1, while the H has priority #4. Between #2 and #3, it is difficult to choose because both are carbon atoms and each of them is connected to C, C, and H. The tie breaker comes when we move farther out, and one of the carbon atoms is connected to O and N, while the other is connected to N. The former wins, giving the *R* configuration:



The newly formed chiral center has the *R* configuration, and not *S*, because the pendant nucleophile is attacking from above, so the O must end up on a wedge:



6.54. The problem statement indicates that the value of ΔG is negative. This does not necessarily indicate whether ΔH is positive or negative. Recall that:

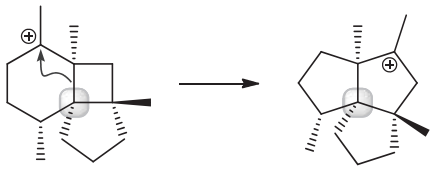
$$\Delta G = \Delta H - T\Delta S$$

We would need to know ΔS and T, in order to know the sign of ΔH. So we don't know whether the reaction is exothermic or endothermic. Therefore, answers (a) and (b) are not correct.
Answer (c) is correct, because an endergonic process is thermodynamically unfavorable, which means that the reactants are favored over the products at equilibrium. That is, $K_{eq} > 1$.

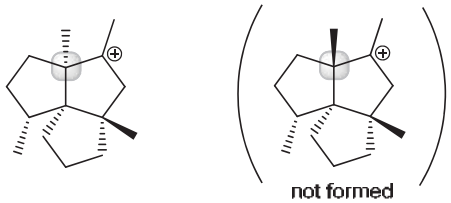
6.55. Compound (a) lacks a lone pair or a pi bond, so it cannot function as a nucleophile. The same is true for compounds (b) and (c). In contrast, the oxygen atom in compound (d) does have lone pairs, which are localized, so water can function as a nucleophile (albeit a weak one).

6.56. Intermediates are represented by local minima (valleys) on an energy diagram. On the energy diagram shown, there are only two local minima (II and IV), so the correct answer is (b).

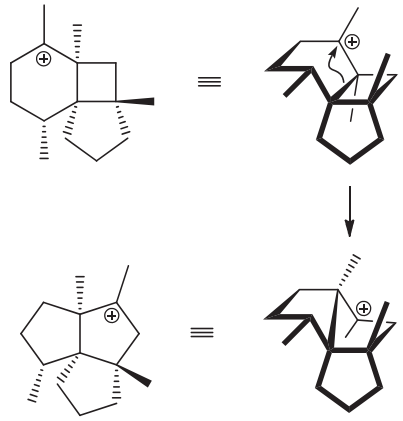
6.57.
(a) The carbon atom highlighted below is migrating, and the following curved arrow shows the migration:



(b) The newly formed chiral center is highlighted below. Notice that the methyl group is on a dash. The diastereomeric cation (not formed) would have its methyl group on a wedge:

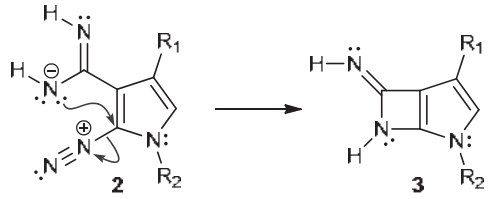


The other configuration is not formed because of the structural rigidity (and lack of conformational freedom) imposed by the tricyclic system. Specifically, only one face of the empty *p* orbital (associated with C+) is accessible to the migrating carbon atom, as seen in the following scheme:

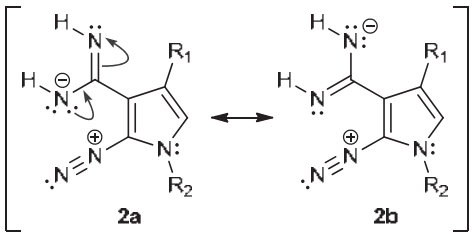


(c) The initial carbocation has three rings. One of them is a four-membered ring. The ring strain associated with this ring is alleviated as a result of the rearrangement. That is, the four-membered ring is converted into a five-membered ring, which has considerably less ring strain. It is true that a six-membered ring (which generally has very little, if any, ring strain) is converted into a five-membered ring, which does possess some ring strain. However, this energy cost is more than off-set by the alleviation of ring strain resulting from enlarging the four-membered ring.

6.58.
(a) The following curved arrows show an intramolecular nucleophilic attack, with the simultaneous loss of a leaving group:

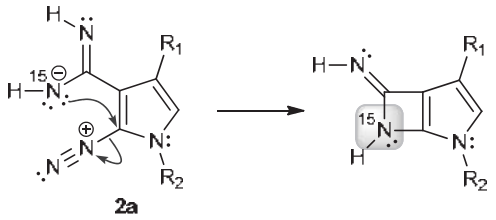


(b) Resonance structures (**2a** and **2b**) can be drawn for intermediate **2**:



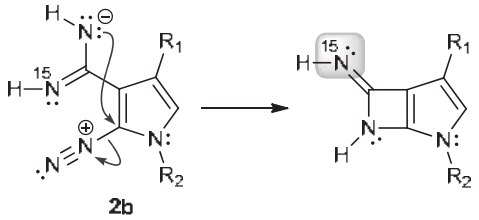
Notice that the negative charge is spread over two nitrogen atoms via resonance. As such, either of these nitrogen atoms can function as the nucleophilic center during the nucleophilic attack. Either the isotopically labeled nitrogen atom can attack, like this:

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2a

or the other nitrogen atom can attack, like this:

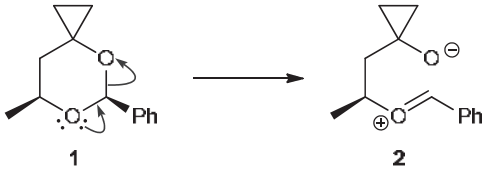


2b

So, if the proposed mechanism were truly operating, we would expect that either nitrogen atom would have an equal probability of forming the four-membered ring, and so only 50% of the ^{15}N atom would be incorporated into the nitrile. That is, both **4a** and **4b** should both be formed. If that had been the case, we would have said that the ^{15}N atom was "scrambled" during the reaction. Since that did not occur, the proposed mechanism was refuted.

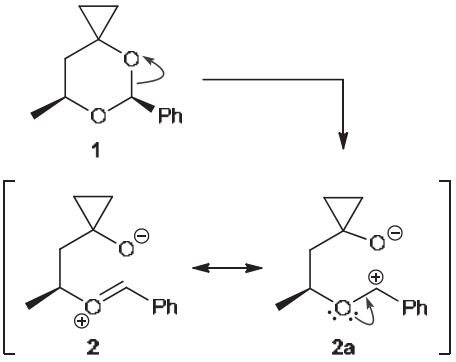
6.59.

(a) Compound **1** is converted to intermediate **2** upon loss of a leaving group.



1 **2**

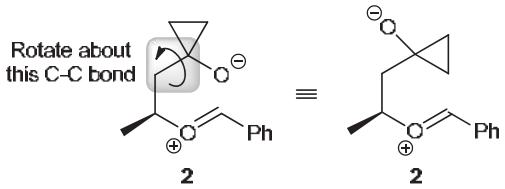
Notice that two curved arrows are employed in this case. The arrow with its tail on a C–O bond represents loss of the leaving group. The other curved arrow (with its tail on a lone pair) can be viewed in two ways: It can be viewed as the electrons coming up from the O to push out the leaving group, as shown above, or it can be viewed as a resonance arrow that allows us to draw resonance structure **2**, thereby bypassing resonance structure **2a**:



1 **2** **2a**

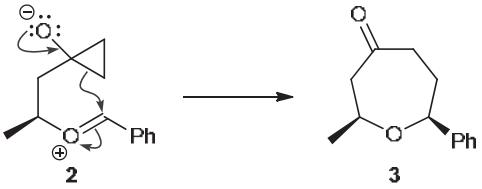
Structure **2** is a greater contributor than **2a** to the overall resonance hybrid because all atoms possess an octet of electrons. That is not the case for **2a** or any of the other resonance structure**s** (not shown) resulting from conjugation with the benzene ring.

(b) In order to draw the curved arrows in this case, it will be helpful if we first rotate about the C–C bond indicated below.



2 **2**

This gives a conformation in which the atoms are all arranged in the proper orientation necessary to show the conversion of **2** into **3**. Three curved arrows are required to show the flow of electrons that correspond with the transformation of **2** into **3**:



2 **3**

Chapter 7
Alkyl Halides: Nucleophilic Substitution and Elimination Reactions

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 7. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Good leaving groups are the conjugate bases of _____ acids.
- S_N2 reactions proceed via _____ **of configuration**, because the nucleophile can only attack from the back side.
- S_N2 reactions cannot be performed with _____ alkyl halides.
- _____ **solvents** contain a hydrogen atom connected directly to an electronegative atom, while _____ **solvents** lack such a hydrogen atom. A _____ solvent will speed up the rate of an S_N2 process by many orders of magnitude.
- In the laboratory, methylation is accomplished via an S_N2 process using methyl iodide. In biological systems, the methylating agent is called _____.
- A *trans* π bond cannot be incorporated into a small ring. When applied to bicyclic systems, this rule is called _____ **rule**, which states that it is not possible for a _____ carbon of a bicyclic system to possess a C=C double bond if it involves a *trans* π bond being incorporated in a small ring.
- E2 reactions are **regioselective** and generally favor the more substituted alkene, called the _____ **product**.
- When both the substrate and the base are sterically hindered, an E2 reaction can favor the less substituted alkene, called the _____ product.
- If the β position has two different protons, the resulting E2 reaction can be stereoselective, because the _____ isomer will be favored.
- If the β position has only one proton, an E2 reaction is said to be _____, because the proton and the leaving group must be _____ to one another.
- **Unimolecular** nucleophilic substitution reactions are called _____ reactions. An S_N1 mechanism is comprised of two core steps: 1) _____ to give a carbocation intermediate, and 2) _____.
- When a solvent molecule functions as the attacking nucleophile, the resulting S_N1 process is called a _____.
- Unimolecular elimination reactions are called _____ reactions.
- S_N1 processes are favored by _____ solvents.
- S_N1 and E1 processes are observed for tertiary alkyl halides, as well as allylic and _____ halides.
- When the α position is a chiral center, an S_N1 reaction gives nearly a racemic mixture. In practice, there is generally a slight preference for _____ of configuration, as a result of the effect of ion pairs.
- If a C–H bond is being broken in the rate-determining step, then a _____ *isotope effect* is observed. If, however, the C-H bond is broken during a step that is not rate-determining, then any measureable effect is said to be a _____ *isotope effect*.
- Substitution and elimination reactions often compete with each other. To predict the products, three steps are required: 1) determine the function of the _____, and 2) analyze the _____ and determine the expected mechanism(s), and 3) consider any relevant regiochemical and stereochemical requirements.
- Alcohols react with HBr to give alkyl halides, either via an _____ pathway (for primary and secondary substrates) or via an _____ pathway (for tertiary substrates).
- When treated with concentrated sulfuric acid, tertiary alcohols are converted into _____ via an E1 process.
- A _____ **analysis** shows the product first, followed by reagents that can be used to make that product.

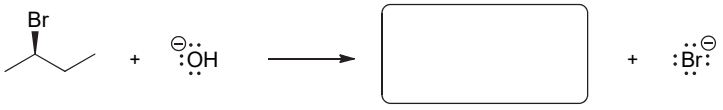
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Review of Skills

Follow the instructions below. To verify that your answers are correct, look in your textbook at the end of Chapter 7. The answers appear in the section entitled *SkillBuilder Review*.

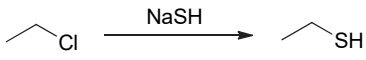
SkillBuilder 7.1 Drawing the Product of an S_N2 Process

REPLACE THE LEAVING GROUP WITH THE NUCLEOPHILE, AND DRAW INVERSION OF CONFIGURATION (IF RELEVANT)



SkillBuilder 7.2 Drawing the Transition State of an S_N2 Process

DRAW THE TRANSITION STATE OF THE FOLLOWING REACTION





SkillBuilder 7.3 Predicting the Regiochemical Outcome of an E2 Reaction

DRAW THE ELIMINATION PRODUCTS OBTAINED WHEN THE COMPOUND BELOW IS TREATED WITH A STRONG BASE.



SkillBuilder 7.4 Predicting the Stereochemical Outcome of an E2 Reaction

PREDICT THE STEREOCHEMICAL OUTCOME OF THE FOLLOWING REACTION. AND DRAW THE PRODUCT.



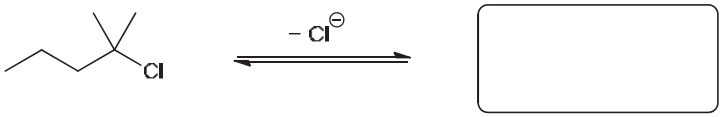
SkillBuilder 7.5 Drawing the Products of an E2 Reaction

PREDICT THE MAJOR AND MINOR PRODUCTS OF THE FOLLOWING REACTION.



SkillBuilder 7.6 Drawing the Carbocation Intermediate of an S_N1 or E1 Process

DRAW THE CARBOCATION THAT WOULD BE FORMED IF A CHLORIDE ION IS EXPELLED FROM THE FOLLOWING COMPOUND

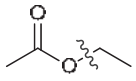
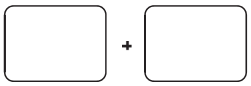
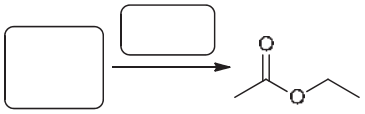


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SkillBuilder 7.7 Predicting the Products of Substitution and Elimination Reactions of Alkyl Halides

FILL IN THE BLANKS BELOW		
STEP 1 *DETERMINE THE FUNCTION OF THE _____*	**STEP 2** *ANALYZE THE _____ AND DETERMINE THE EXPECTED MECHANISM(S).*	**STEP 3** *CONSIDER ANY RELEVANT REGIOCHEMICAL AND _____ REQUIREMENTS*

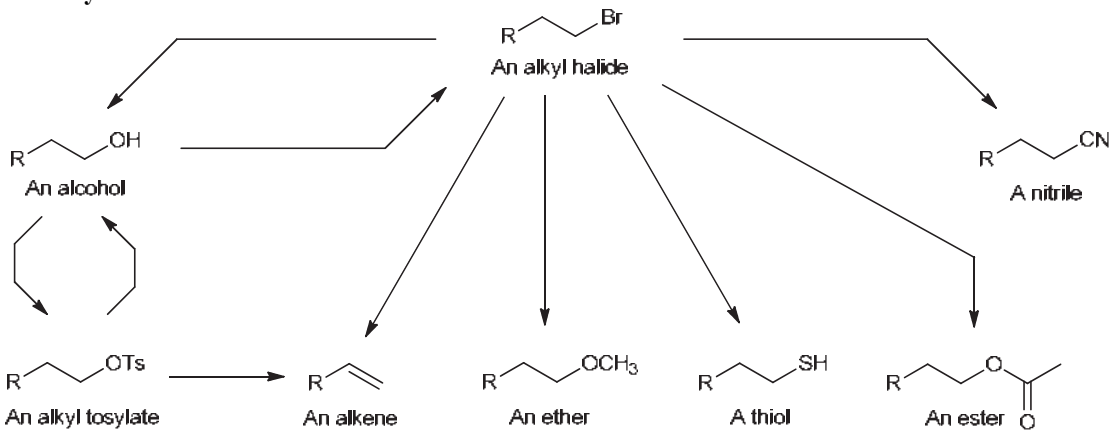
SkillBuilder 7.8 Performing a Retrosynthesis and Providing a Synthesis of a Target Molecule

STEP 1 *USING A WAVY LINE, IDENTIFY A BOND THAT CAN BE MADE VIA KNOWN REACTIONS.*	**STEP 2** *DRAW A SUITABLE NUCLEOPHILE AND ELECTROPHILE THAT WILL REACT TO MAKE THE DESIRED BOND.*	**STEP 3** *VERIFY THAT THE REACTION IS REASONABLE BY DRAWING AND CONSIDERING THE MECHANISM.*	**STEP 4** *DRAW THE FORWARD PROCESS SHOWING ALL REAGENTS.*
			

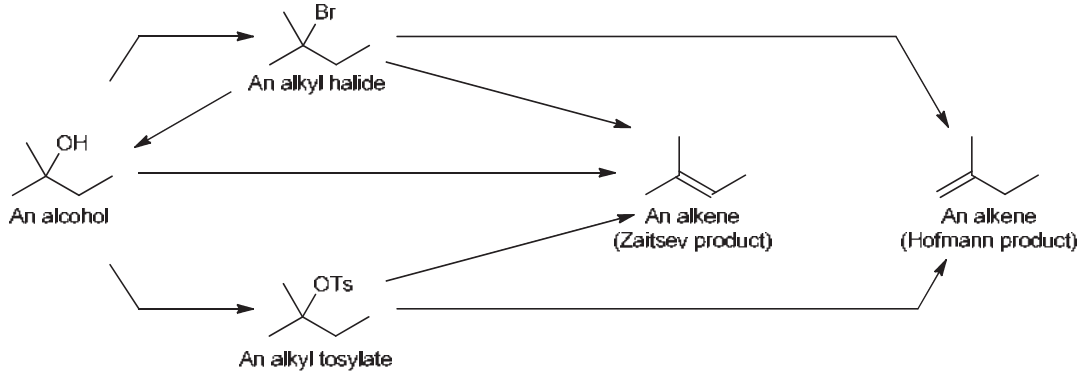
Review of Reactions

Identify reagents that can be used to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 7. The answers appear in the section entitled *Review of Reactions*.

Primary Substrates

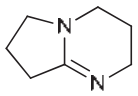
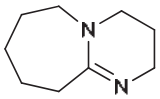


Tertiary Substrates



Useful reagents

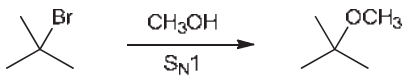
The following is a list of commonly encountered reagents for substitution and elimination reactions:

Reagent	Name	Function
NaCl	Sodium chloride	An ionic salt consisting of Na^+ and Cl^- ions. The former (Na^+) can be ignored in most cases, while the latter (chloride) is a strong nucleophile. NaCl is a source of chloride ions.
NaBr	Sodium bromide	An ionic salt consisting of Na^+ and Br^- ions. The former (Na^+) can be ignored in most cases, while the latter (bromide) is a strong nucleophile. NaBr is a source of bromide ions.
NaI	Sodium iodide	An ionic salt consisting of Na^+ and I^- ions. The former (Na^+) can be ignored in most cases, while the latter (iodide) is a strong nucleophile. NaI is a source of iodide ions.
NaH	Sodium hydride	Hydride is a strong base that can be used in E2 reactions.
	DBN	A strong base that can be used in E2 reactions.
	DBU	A strong base that can be used in E2 reactions.
NaOH	Sodium hydroxide	Hydroxide (HO^-) is both a strong nucleophile AND a strong base, and can therefore be used for either E2 or S_N2 reactions, depending on the substrate (S_N2 is favored for primary substrates, E2 is favored for secondary substrates, and E2 is the exclusive pathway for tertiary substrates).
NaOR	Sodium alkoxide	R is an alkyl group. Examples include sodium methoxide (NaOMe) and sodium ethoxide (NaOEt). Alkoxide ions are both strong nucleophiles and strong bases. They can therefore be used for either E2 or S_N2 reactions, depending on the substrate (S_N2 is favored for primary substrates, E2 is favored for secondary substrates, and E2 is the exclusive pathway for tertiary substrates).
t-BuOK	Potassium *tert*-butoxide	*tert*-Butoxide is both a strong nucleophile and a strong base. But it is sterically hindered, which favors E2 over S_N2 even for primary substrates. For E2 reactions, when more than one regiochemical outcome is possible, *tert*-butoxide will favor formation of the less substituted alkene.
NaSH	Sodium hydrosulfide	HS^- is a strong nucleophile, used in S_N2 reactions.
H_2O	Water	Water is a weak nucleophile and a weak base, used in S_N1 and E1 reactions. Heat will often favor E1 over S_N1.
ROH	An alcohol	Examples include methanol (CH_3OH) and ethanol (CH_3CH_2OH). Alcohols are weak nucleophiles and weak bases, used in S_N1 and E1 reactions. Heat will often favor E1 over S_N1. Alcohols can also serve as substrates for S_N1 or E1 reactions under acidic conditions.
HX (X = Cl, Br, or I)	Hydrogen halides	A strong acid that serves as both a source of H^+ and nucleophilic X^- where X = Cl, Br, or I.
conc. H_2SO_4	Concentrated sulfuric acid	A strong acid, used to convert alcohols into alkenes.

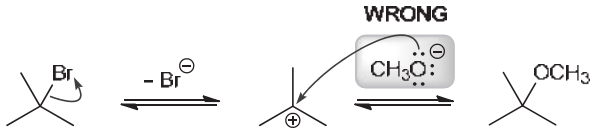
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Common Mistakes to Avoid

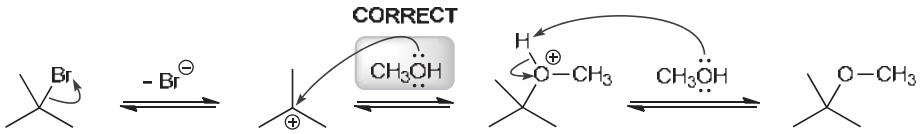
When drawing the mechanism of a reaction, you must always consider what reagents are being used, and your mechanism must be consistent with the conditions employed. As an example, consider the following S_N1 reaction:



The following proposed mechanism is unacceptable, because the reagent employed in the second step is not present:

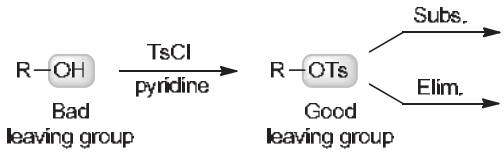


This is a common student error. To see what's wrong, let's look closely at the reagent. Methanol (CH_3OH) is not a strong acid. Rather, it is a weak acid, because its conjugate base, methoxide (CH_3O^-), is a strong base. Therefore, methoxide is not present in substantial quantities, so the mechanism in this case should not employ methoxide. Below is the correct mechanism:

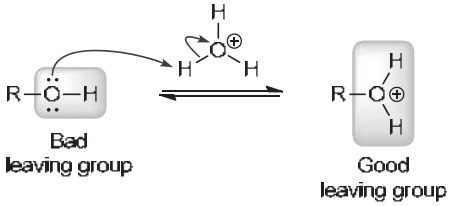


Methanol (rather than methoxide) functions as the nucleophile in the second step, because methoxide was not indicated as a reagent, and it is not expected to be present. The result of the nucleophilic attack is an oxonium ion (an intermediate with a positive charge on an oxygen atom), which is then deprotonated by another molecule of methanol. Once again, in this final step of the mechanism, methanol functions as the base, rather than methoxide, because the latter is not present.
This example is just one illustration of the importance of analyzing the reagent and considering what entities can be used in your mechanism. This will become increasingly important in upcoming chapters.

Now let's consider another reaction, so that we can identity another common student error. We have seen that an OH group is a bad leaving group (because hydroxide is a strong base). Therefore, in order for an alcohol (ROH) to serve as a substrate in a substitution or elimination reaction, the OH group must first be converted into a better leaving group. We have seen two ways to do this. One method involves converting the alcohol into a tosylate:

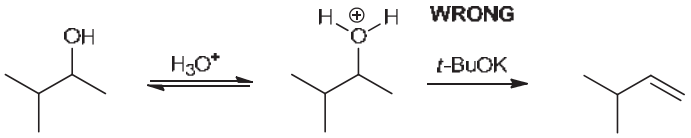


The other method involves protonation of the OH group, as seen in the following example:

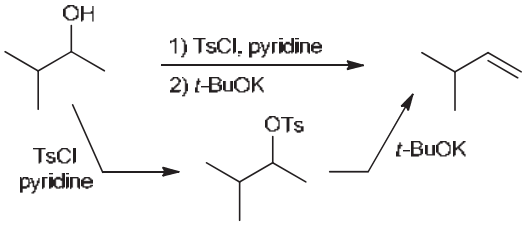


This latter approach (protonation) has a serious limitation. Specifically, it cannot be used if the reagent is a strong base. For example, the following reaction sequence does not work:

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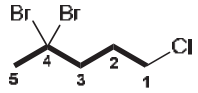
It doesn't work because it is not possible to have a strong acid (H_3O^+) and a strong base (*t*-BuOK) present in the same reaction flask at the same time (they would simply neutralize each other). In order to achieve the desired transformation, the OH group must first be converted to a tosylate (rather than simply being protonated), and then the desired reaction can be performed, as shown here:



Solutions

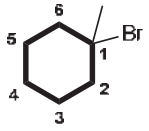
7.1.

(a) The parent is the longest chain, which is five carbon atoms in this case (pentane). There are three substituents (bromo, bromo, and chloro), and their locants are assigned as 4, 4, and 1, respectively. In this case, the parent was numbered from right to left, so as to give the lowest number to the first substituent (**1**,4,4 rather than **2**,2,5). Notice that two locants are necessary (rather than one) to indicate the locations of the two bromine atoms, even though they are connected to the same position (4,4-dibromo rather than 4-dibromo).



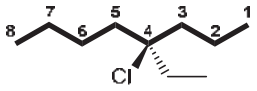
4,4-dibromo-1-chloropentane

(b) The parent is a six-membered ring (cyclohexane). There are two substituents (methyl and bromo), both of which are located at the C1 position. Substituents are alphabetized in the name (bromo precedes methyl).



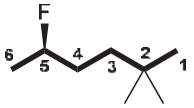
1-bromo-1-methylcyclohexane

(c) The parent is the longest chain, which is eight carbon atoms in this case (octane). There are two substituents (ethyl and chloro), both of which are located at the C4 position. These substituents are alphabetized (chloro precedes ethyl). In this case, there is also a chiral center, so we must assign the configuration (*R*), which must be indicated at the beginning of the name.



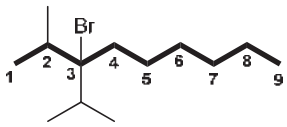
(*R*)-4-chloro-4-ethyloctane

(d) The parent is the longest chain, which is six carbon atoms in this case (hexane). There are three substituents (fluoro, methyl, and methyl), and their locants are assigned as 5, 2, and 2, respectively. In this case, the parent was numbered from right to left, so as to give the lowest number to the second substituent (2,**2**,5 rather than 2,**5**,5). The substituents are arranged alphabetically in the name, so fluoro precedes dimethyl (the former is "f" and the latter is "m"). In this case, there is also a chiral center, so we must assign the configuration (*R*), which must be indicated at the beginning of the name.



(*R*)-5-fluoro-2,2-dimethylhexane

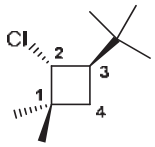
(e) The parent is the longest chain, which is nine carbon atoms in this case (nonane). There are three substituents (methyl, bromo, and isopropyl), and their locants are assigned as 2, 3, and 3, respectively. The substituents are arranged alphabetically in the name (note that isopropyl is alphabetized as "i" rather than as "p", so it comes before methyl). In this case, there is no chiral center (C2 is connected to two methyl groups, and C3 is connected to two isopropyl groups).



3-bromo-3-isopropyl-2-methylnonane

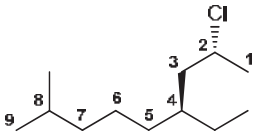
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(f) The parent is a ring of four carbon atoms (cyclobutane). There are four substituents (two methyl groups, a chloro group, and a *tert*-butyl group), and their locants are assigned as 1, 1 ,2, and 3, respectively. In this case, the parent is numbered so as to give the lowest number to the second substituent (1,**1**-dimethyl), and then continuing clockwise. The substituents are arranged alphabetically (note that *tert*-butyl is alphabetized as "b"). In this case, there are also two chiral centers (C2 and C3), so we must assign the configuration of each. Note that C1 is not a chiral center, because it bears two methyl groups.



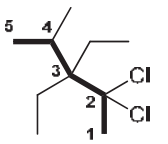
(2*R*,3*R*)-3-*tert*-butyl-2-chloro-1,1-dimethylcyclobutane

(g) The parent is the longest chain, which is nine carbon atoms in this case (nonane). There are three substituents (chloro, ethyl, and methyl), and their locants are assigned as 2, 4, and 8, respectively. In this case, the parent is numbered so as to give the lowest number to the second substituent (2,**4**,8, rather than 2,**6**,8). The substituents are arranged alphabetically. In this case, there are also two chiral centers (C2 and C4), so we must assign the configuration of each.

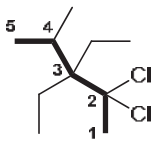


(2*R*,4*S*)-2-chloro-4-ethyl-8-methylnonane

(h) The parent is the longest chain, which is five carbon atoms in this case (pentane). There are several choices for a five-membered parent, so we choose the one with the greatest number of substituents.



There are five substituents (two chloro groups, two ethyl groups, and a methyl group), and their locants are assigned as 2, 2, 3, 3, and 4, respectively. In this case, the parent is numbered so as to give the lowest number to the second substituent (2,2-dichloro). The substituents are arranged alphabetically. In this case, there are no chiral centers.



2,2-dichloro-3,3-diethyl-4-methylpentane

7.2.

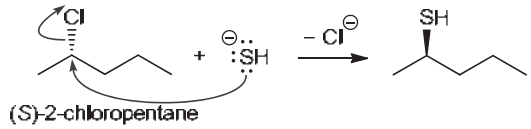
(a) The reaction has a second-order rate equation, and the rate is linearly dependent on the concentrations of two compounds (the nucleophile AND the substrate). If the concentration of the substrate is tripled, the rate should also be tripled.

(b) As described above, the rate is linearly dependent on the concentrations of both the nucleophile and the substrate. If the concentration of the nucleophile is doubled, the rate of the reaction is doubled.

(c) As described above, the rate is linearly dependent on the concentrations of both the nucleophile and the substrate. If the concentration of the substrate is doubled and the concentration of the nucleophile is tripled, then the rate of the reaction will be six times faster (× 2 × 3).

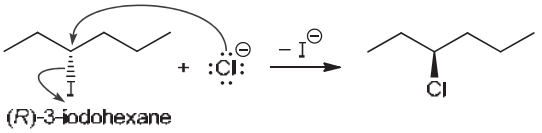
7.3.

(a) The substrate is (*S*)-2-chloropentane, and the nucleophile is HS^-. Chloride is ejected as a leaving group, with inversion of configuration.



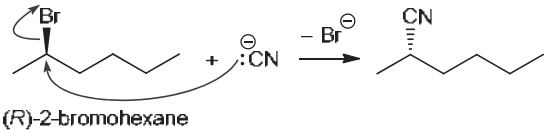
(*S*)-2-chloropentane

(b) The substrate is (*R*)-3-iodohexane, and the nucleophile is chloride (Cl^-). Iodide is ejected as a leaving group, with inversion of configuration.



(*R*)-3-iodohexane

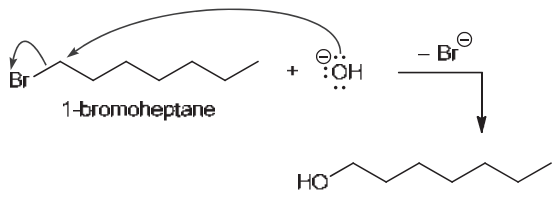
(c) The substrate is (*R*)-2-bromohexane, and the nucleophile is cyanide ($N{\equiv}C^-$). Bromide is ejected as a leaving group, with inversion of configuration.



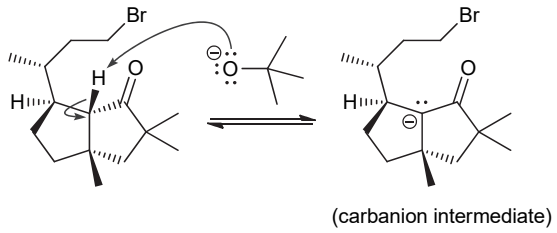
(*R*)-2-bromohexane

(d) The substrate is 1-bromoheptane, and the nucleophile is hydroxide (HO^-). Bromide is ejected as a leaving group. There is no inversion of configuration in this case, because there is no chiral center

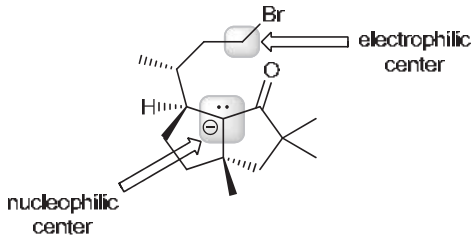
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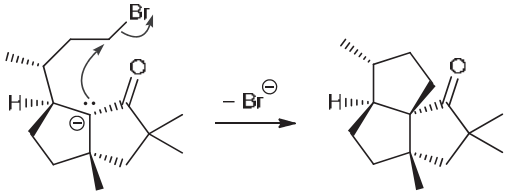
7.4. The problem statement indicates that *tert*-butoxide functions as a base, removing a proton from compound **1** to give the carbanion intermediate. This is a proton transfer step, so it requires two curved arrows, as shown:



This intermediate then undergoes an intramolecular S_N2-type process, because it has both a nucleophilic center and an electrophilic center:

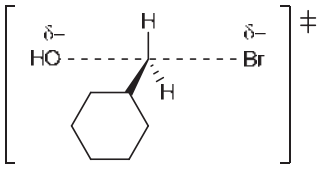


That is, the nucleophile and electrophile are tethered to each other (rather than being separate compounds), and the reaction occurs in an intramolecular fashion, as shown:

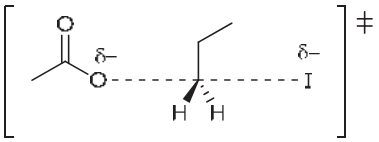


7.5.

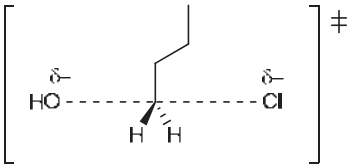
(a) The leaving group is a bromide ion (Br^-) and the nucleophile is a hydroxide ion (HO^-). In the transition state, each of these groups is drawn as being connected to the α position with a dotted line (indicating these bonds are in the process of forming or breaking), and a δ– is placed on each group to indicate that the charge is spread over both locations. Don't forget the brackets and the symbol that indicate the drawing is a transition state.



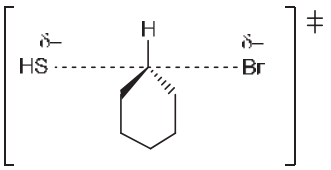
(b) The leaving group is an iodide ion (I^-) and the nucleophile is an acetate ion ($CH_3CO_2^-$). In the transition state, each of these groups is drawn as being connected to the α position with a dotted line (indicating these bonds are in the process of forming or breaking), and a δ– is placed on each group to indicate that the charge is spread over both locations. Don't forget the brackets and the symbol that indicate the drawing is a transition state.



(c) The leaving group is a chloride ion (Cl^-) and the nucleophile is a hydroxide ion (HO^-). In the transition state, each of these groups is drawn as being connected to the α position with a dotted line (indicating these bonds are in the process of forming or breaking), and a δ– is placed on each group to indicate that the charge is spread over both locations. Don't forget the brackets and the symbol that indicate the drawing is a transition state.

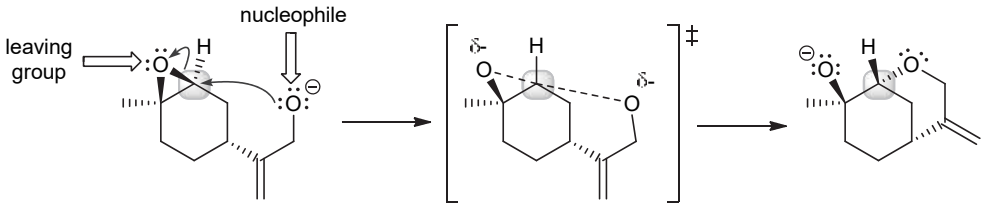


(d) The leaving group is a bromide ion (Br^-) and the nucleophile is HS^-. In the transition state, each of these groups is drawn as being connected to the α position with a dotted line (indicating these bonds are in the process of forming or breaking), and a δ– is placed on each group to indicate that the charge is spread over both locations. Don't forget the brackets and the symbol that indicate the drawing is a transition state.

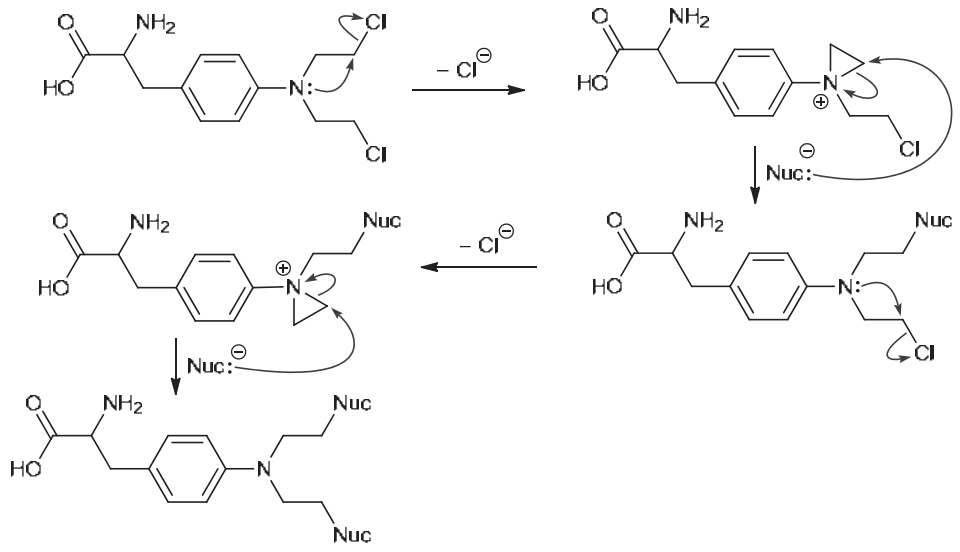


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7.6 The leaving group is the oxygen atom of the three-membered ring, and the nucleophile is the oxygen atom bearing the negative charge. In the transition state, each of these groups is drawn as being connected to the α carbon (highlighted below) with a dotted line (indicating these bonds are in the process of forming or breaking), and a δ– symbol is placed on each group to indicate that the charge is spread over both locations. Notice that the α carbon (highlighted) undergoes inversion of configuration. This can be seen if we compare the location of the hydrogen atom in compound **1** (H is on a dash) and in compound **2** (H is on a wedge). Since the H goes from being on a dash to being on a wedge, it must pass through the plane of the page in the transition state. For this reason, the H is drawn on a straight line (not a wedge or a dash):



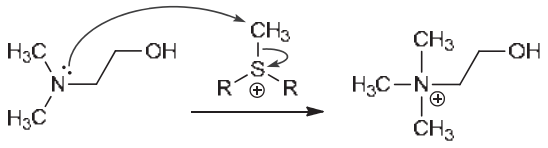
7.7. The lone pair of the nitrogen atom (connected to the aromatic ring) can function as a nucleophile, ejecting the chloride ion in an intramolecular S_N2-type reaction, generating a high-energy intermediate that exhibits a three-membered ring. The ring is opened upon attack of a nucleophile in an S_N2 process. These two steps are then repeated, as shown here.



7.8. The second reaction employs a polar aprotic solvent (DMSO) and is therefore expected to occur at a faster rate.

7.9. The first reaction employs iodide, which is a stronger nucleophile than chloride. With all other factors being the same (the alkyl halide is the same in both reactions, and the solvent is the same for both reactions), the first reaction is expected to occur at a faster rate.

7.10. The nitrogen atom functions as a nucleophilic center and attacks the electrophilic methyl group in SAM, forming an ammonium ion.



7.11.

(a) With a second-order rate equation, the rate is expected to be linearly dependent on the concentrations of the substrate and the base. If the concentration of the substrate is tripled, then the rate is expected to be three times faster.

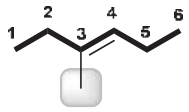
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(b) With a second-order rate equation, the rate is expected to be linearly dependent on the concentrations of the substrate and the base. If the concentration of the base is doubled, then the rate is expected to be two times faster.

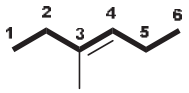
(c) With a second-order rate equation, the rate is expected to be linearly dependent on the concentrations of the substrate and the base. If the concentration of the substrate is doubled and the concentration of the base is tripled, then the rate is expected to be six times faster (×2×3).

7.12.

(a) We begin by identifying the parent. The longest chain is six carbon atoms, so the parent is hexene. There is one substituent (highlighted), which is a methyl group.

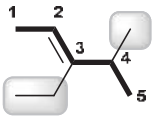


With respect to the π bond, the parent could be numbered from either direction (either way, the double bond will be between C3 and C4), but in this case, we must assign numbers from left to right to give the substituent the lower possible number (C3 rather than C4). We include a locant that identifies the position of the double bond ("3" indicates that the double bond is located between C3 and C4), as well as a locant to identify the position of the substituent. Furthermore, we must include the configuration of the double bond (*E*):

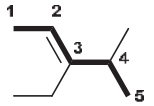


(*E*)-3-methyl-3-hexene

(b) We begin by identifying the parent, which must include the two carbon atoms bearing the double bond. The longest possible chain has five carbon atoms, so the parent is pentene. There is more than one choice for the parent, and we choose the parent with the greater number of substituents:

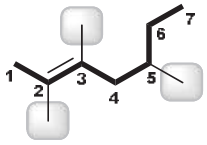


There are two substituents (highlighted): a methyl group and an ethyl group. The parent is numbered to give the double bond the lowest possible number (C2). Therefore, the ethyl group is located at C3, and the methyl group is located at C4. These groups are arranged alphabetically, together with their locants, in the name. Finally, we must include the configuration of the double bond (*E*) at the beginning of the name:



(*E*)-3-ethyl-4-methyl-2-pentene

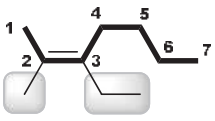
(c) We begin by identifying the parent. The longest chain is seven carbon atoms, so the parent is heptene. There are three substituents (highlighted), all of which are methyl groups. Notice that the parent chain is numbered starting from the side that is closest to the π bond. According to this numbering scheme, the methyl groups are located at C2, C3, and C5. Finally, we use the prefix "tri" to indicate the presence of three methyl groups, and we include a locant that identifies the position of the double bond ("2" indicates that the double bond is located between C2 and C3):



2,3,5-trimethyl-2-heptene

Note that the C2 position is connected to two methyl groups, so the double bond is not stereoisomeric (neither *E* nor *Z*).

(d) We begin by identifying the parent. The longest chain is seven carbon atoms, so the parent is heptene. There are two substituents – a methyl group and an ethyl group (highlighted). Notice that the parent chain is numbered starting from the side that is closest to the π bond. According to this numbering scheme, the methyl group is located at C2, and the ethyl group is located at C3. Finally, we arrange the substituents alphabetically, and we include a locant that identifies the position of the double bond:



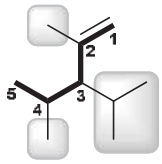
3-ethyl-2-methyl-2-heptene

Note that the C2 position is connected to two methyl groups, so the double bond is not stereoisomeric (neither *E* nor *Z*).

(e) We begin by identifying the parent. The longest chain (containing the double bond) is five carbon atoms, so the parent is pentene. There are three substituents – an isopropyl group and two methyl groups (highlighted). Notice that the parent chain is numbered starting from the side that is closest to the π bond. According to this numbering scheme, the isopropyl group is located at C3, and the methyl groups are located at C2 and C4. Finally, we arrange the substituents alphabetically, and we

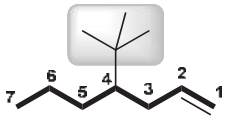
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include a locant that identifies the position of the double bond:



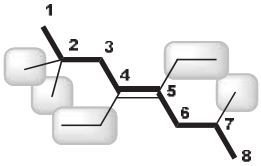
3-isopropyl-2,4-dimethyl-1-pentene

(f) We begin by identifying the parent. The longest chain is seven carbon atoms, so the parent is heptene. There is one substituent – a *tert*-butyl group (highlighted). Notice that the parent chain is numbered starting from the side that is closest to the π bond. According to this numbering scheme, the *tert*-butyl group is located at C4. Finally, we include a locant that identifies the position of the double bond:



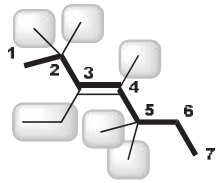
4-*tert*-butyl-1-heptene

(g) We begin by identifying the parent. The longest possible chain has eight carbon atoms, so the parent is octene. There are five substituents (highlighted). With respect to the π bond, the parent could be numbered from either direction (either way, the double bond will be between C4 and C5), but in this case, we must assign numbers from left to right to give the second substituent the lower possible number (2,**2**,7-trimethyl, rather than 2,**7**,7-trimethyl). We include a locant to identify the position of the double bond. Substituents are arranged alphabetically, together with their locants, in the name. Furthermore, we must include the configuration of the double bond (*E*) at the beginning of the name:



(*E*)-4,5-diethyl-2,2,7-trimethyl-4-octene

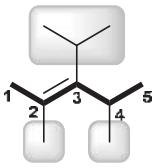
(h) We begin by identifying the parent. The longest possible chain has seven carbon atoms, so the parent is heptene. There are six substituents (highlighted). The parent is numbered from left to right to give the double bond the lower possible number. Substituents are arranged alphabetically (ethyl before methyl), together with their locants, in the name. Furthermore, we must include the configuration of the double bond (*E*) at the beginning of the name:



(*E*)-3-ethyl-2,2,4,5,5-pentamethyl-3-heptene

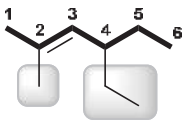
7.13

(a) The parent is five carbon atoms (pentene), with the double bond between C2 and C3. There are three substituents – an isopropyl group at C3, and two methyl groups at C2 and C4:



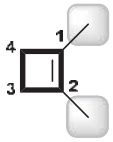
3-isopropyl-2,4-dimethyl-2-pentene

(b) The parent is six carbon atoms (hexene), with the double bond between C2 and C3. There are two substituents – an ethyl group at C4, and a methyl group at C2:



4-ethyl-2-methyl-2-hexene

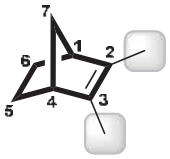
(c) The parent is a four-membered ring (cyclobutene). There are two substituents located at C1 and C2, which are (by definition) the positions bearing the double bond:



1,2-dimethylcyclobutene

7.14. We begin by identifying the parent, which is bicyclic in this case. The parent is bicyclo[2.2.1]heptene. There are two substituents (highlighted), both of which are methyl groups. Notice that the parent chain is numbered starting from one of the bridgeheads, as seen in Section 4.2, which places the double bond between C2 and C3. According to this numbering scheme, the methyl groups are also located at C2 and C3. Finally, we include a locant that identifies the position of the double bond (C2).

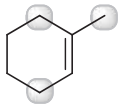
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2,3-dimethylbicyclo[2.2.1]hept-2-ene

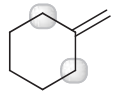
7.15.

(a) This alkene is trisubstituted because there are three groups (highlighted) connected to the double bond:



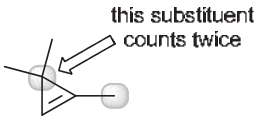
trisubstituted

(b) This alkene is disubstituted because there are two groups (highlighted) connected to the double bond:



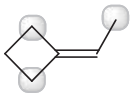
disubstituted

(c) This alkene is trisubstituted because there are three groups (highlighted) connected to the double bond. Notice that one of the groups counts twice because it is connected to both vinylic positions:



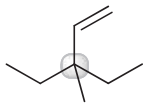
trisubstituted

(d) This alkene is trisubstituted because there are three groups (highlighted) connected to the double bond:



trisubstituted

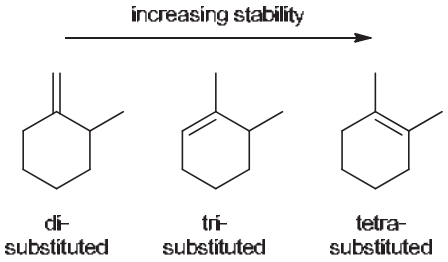
(e) This alkene is monosubstituted because there is only one group (highlighted) connected to the double bond:



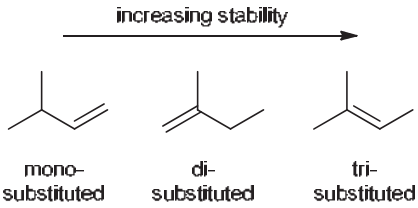
monosubstituted

7.16.

(a) Each alkene is classified according to its degree of substitution. The most highly substituted alkene will be the most stable, and therefore, the following order of stability is expected.



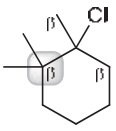
(b) Each alkene is classified according to its degree of substitution. The most highly substituted alkene will be the most stable, and therefore, the following order of stability is expected.



7.17. In the first compound, all of the carbon atoms of the ring are sp^3 hybridized and tetrahedral. As a result, they are supposed to have bond angles of approximately 109.5º, but their bond angles are compressed due to the ring (and are almost 90º). In other words, the compound exhibits angle strain characteristic of small rings. In the second compound, two of the carbon atoms are sp^2 hybridized and trigonal planar. As a result, they are supposed to have bond angles of approximately 120º, but their bond angles are compressed due to the ring (and are almost 90º). The resulting angle strain (120º → 90º) is greater than the angle strain in the first compound (109.5º → 90º). Therefore, the second compound is higher in energy, despite the fact that it has a more highly substituted double bond.

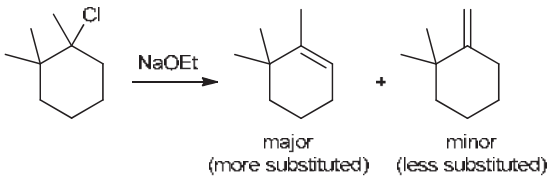
7.18.

(a) This compound has three β positions, but one of them (highlighted) does not bear protons:

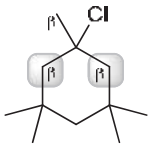


Since there are two β positions bearing protons, there are two possible elimination products. Since the base (ethoxide) is not sterically hindered, we expect that the major product will be the more-substituted alkene, and the minor product will be the less-substituted alkene.

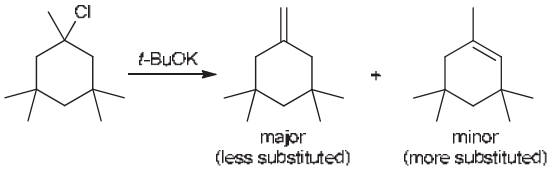
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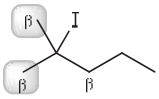
(b) This compound has three β positions that bear protons, but two of them (highlighted) are identical:



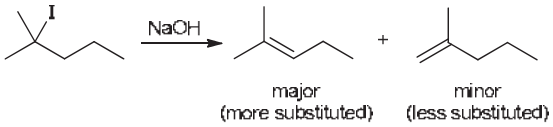
Thus, there are only two unique β positions, giving rise to two possible elimination products, shown below. Since the base (*tert*-butoxide) is sterically hindered, we expect that the major product will be the less-substituted alkene, and the minor product will be the more-substituted alkene.



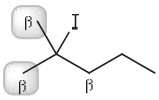
(c) This compound has three β positions that bear protons, but two of them (highlighted) are identical:



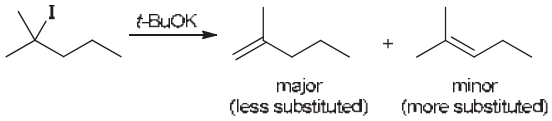
Thus, there are only two unique β positions, giving rise to two possible elimination products, shown below. Since the base (hydroxide) is not sterically hindered, we expect that the major product will be the more-substituted alkene, and the minor product will be the less-substituted alkene.



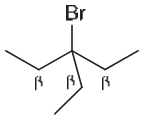
(d) This compound has three β positions that bear protons, but two of them (highlighted) are identical:



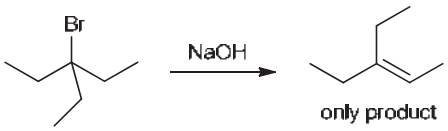
Thus, there are only two unique β positions, giving rise to two possible elimination products. Since the base (*tert*-butoxide) is sterically hindered, we expect that the major product will be the less-substituted alkene, and the minor product will be the more-substituted alkene.



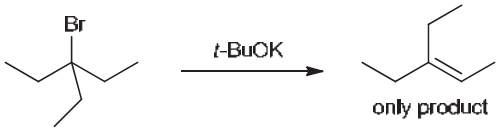
(e) This compound has three β positions that bear protons:



In this case, all three β positions are identical, because removing a proton from any one of these positions will lead to the same product As such, there is only one possible elimination product:

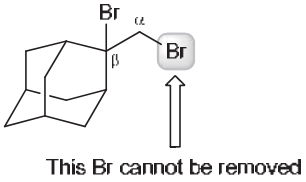


(f) As seen in the solution to part (e), all three β positions are identical, so only one elimination product is possible.



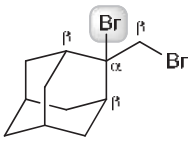
7.19.
(a) The more substituted alkene is desired, so hydroxide (not sterically hindered) should be used.
(b) The less substituted alkene is desired, so *tert*-butoxide (a sterically hindered base) should be used.

7.20. Both bromide leaving groups should be considered for elimination, but the primary bromide cannot be eliminated because it has no beta hydrogen.

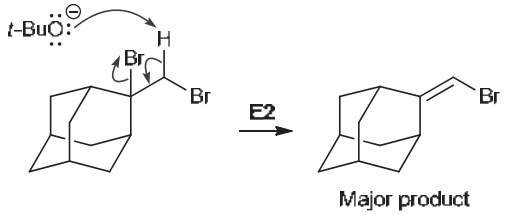


Therefore, the product must be formed via an E2 reaction involving the tertiary bromide.

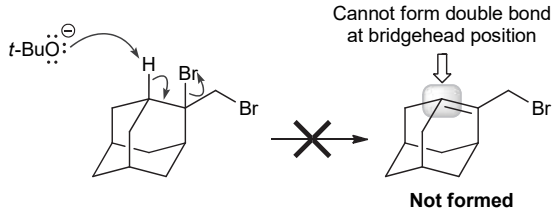
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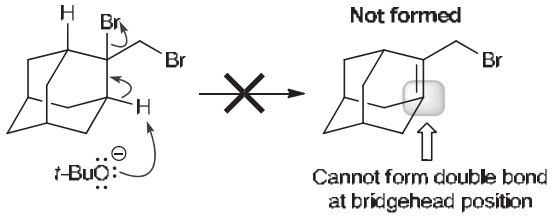
There are many β positions, but the base (*t*-butoxide) is sterically hindered, so we expect the Hofmann product (deprotonation of the less hindered beta hydrogen):



Regarding the other β positions, Bredt's Rule states that it is highly unlikely for a C–C double bond to be formed at a bridgehead carbon of a bicyclic system such as the one shown.



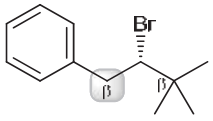
The same is true regarding deprotonation at the other beta position:



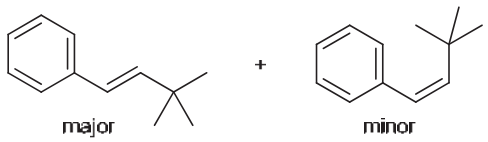
As a result, this reaction affords only one product.

7.21.

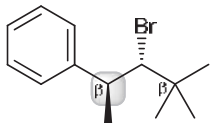
(a) The substrate has two β positions, but only one of these positions (highlighted) bears protons.



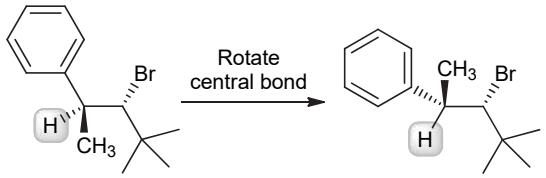
This β position has two protons, so the reaction will be stereoselective. That is, we expect both *cis* and *trans* isomers, with a preference for the *trans* isomer.



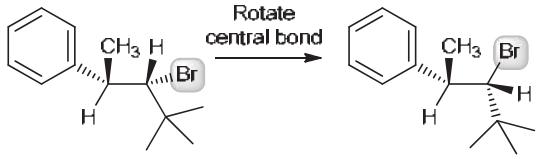
(b) The substrate has two β positions, but only one of these positions (highlighted) bears a proton.



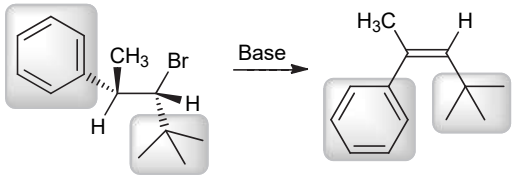
This β position has only one proton, so the reaction will be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we must rotate the central C–C bond so that the β proton is *anti*-periplanar to the leaving group. We will do so in two stages. First, we rotate the central C–C bond in a manner that places the β proton in the plane of the page (rather than on a dash):



Then, we rotate the central C–C bond again, in a manner that places the leaving group (Br) in the plane of the page:

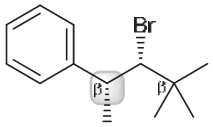


In this conformation, the proton and the leaving group are *anti*-periplanar. To draw the product, use the wedges and dashes as guides. In this case, the *tert*-butyl group and the phenyl group are both on wedges, so they will be *cis* to each other in the product:

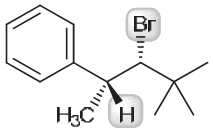


(c) The substrate has two β positions, but only one of these positions (highlighted) bears a proton.

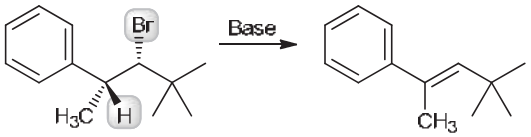
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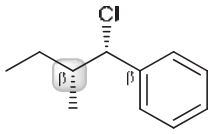
This β position has only one proton, so the reaction will be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we can rotate the central C–C bond so as to place the β proton and the leaving group in the plane of the page. But in this case, that is not necessary, because the β proton and the leaving group are already *anti*-periplanar to one another (one is on a dash and the other is on a wedge):



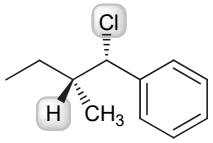
In such a case, it is relatively easy to draw the product, because the carbon skeleton is simply redrawn without the β proton and without the leaving group (with a double instead). Note that a double bond has planar geometry, so the methyl group is on a straight line (not a dash) in the product:



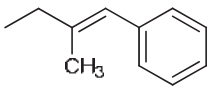
(d) The substrate has two β positions, but only one of these positions (highlighted) bears a proton.



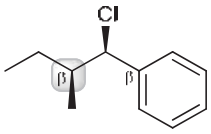
This β position has only one proton, so the reaction will be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we will use the same method employed in the solution to part (c). In this case, the β proton and the leaving group are already *anti*-periplanar to one another (one is on a dash and the other is on a wedge).



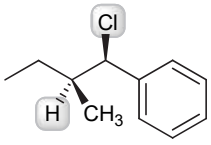
In such a case, the carbon skeleton is simply redrawn without the β proton and without the leaving group (with a double instead). Note that a double bond has planar geometry, so the methyl group is on a straight line (not a dash) in the product:



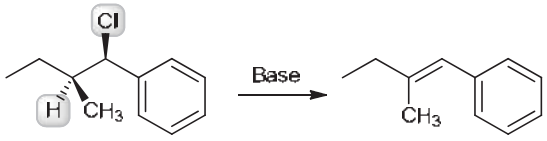
(e) The substrate has two β positions, but only one of these positions (highlighted) bears a proton.



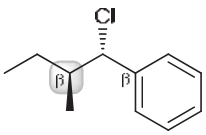
This β position has only one proton, so the reaction will be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we will use the same method employed in the solution to part (c). In this case, the β proton and the leaving group are already *anti*-periplanar to one another (one is on a dash and the other is on a wedge).



In such a case, the carbon skeleton is simply redrawn without the β proton and without the leaving group (with a double instead). Note that a double bond has planar geometry, so the methyl group is on a straight line (not a wedge) in the product:



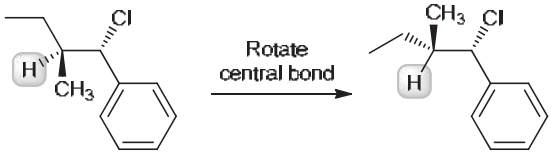
(f) The substrate has two β positions, but only one of these positions (highlighted) bears a proton.



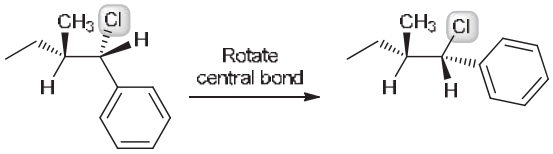
This β position has only one proton, so the reaction will be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we must rotate the central C–C bond so that the β proton is *anti*-periplanar to the leaving group. We will do so in two stages. First, we rotate the

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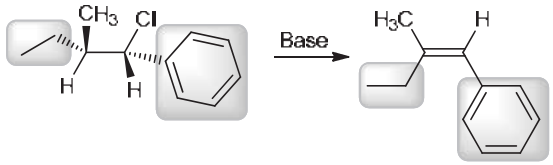
central C–C bond in a manner that places the β proton in the plane of the page (rather than on a dash):



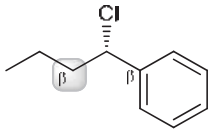
Then, we rotate the central C–C bond again, in a manner that places the leaving group (Cl) in the plane of the page:



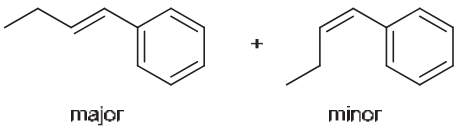
In this conformation, the proton and the leaving group are *anti*-periplanar. To draw the product, use the wedges and dashes as guides. In this case, the ethyl group and the phenyl group are both on dashes, so they will be *cis* to each other in the product:



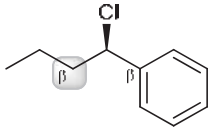
(g) The substrate has two β positions, but only one of these positions (highlighted) bears protons.



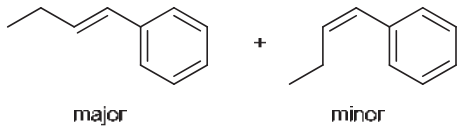
This β position has two protons, so the reaction will be stereoselective. That is, we expect both *cis* and *trans* isomers, with a preference for the *trans* isomer.



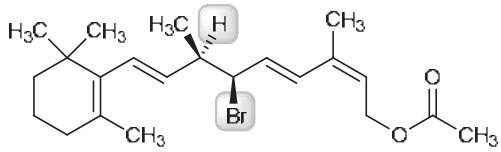
(h) The substrate has two β positions, but only one of these positions (highlighted) bears protons.



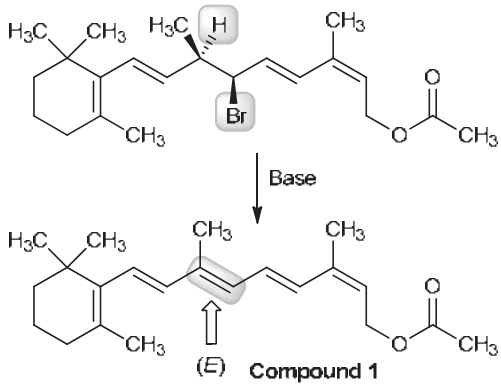
This β position has two protons, so the reaction will be stereoselective. That is, we expect both *cis* and *trans* isomers, with a preference for the *trans* isomer.



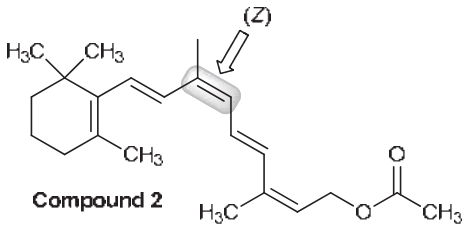
7.22. Since the two alkyl bromides are identical with the exception of the configuration at C6, the stereospecificity of the reaction will dictate the configuration (*E* or *Z*) of the newly formed C=C unit in each case. Let's begin with compound **1**, which can be easily drawn because the β proton and the leaving group are already *anti*-periplanar to one another (one is on a dash and the other is on a wedge):



In such a case, the carbon skeleton is simply redrawn without the β proton and without the leaving group (with a double instead). Note that a double bond has planar geometry, so the methyl group is on a straight line (not a dash) in the product:



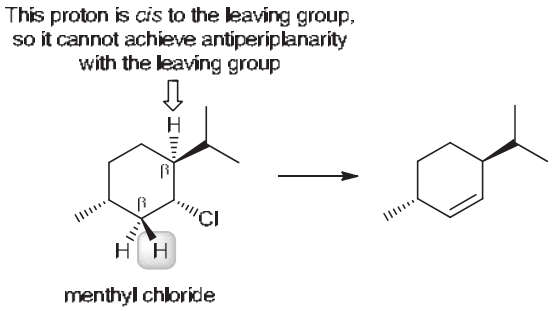
In this case, the *E* product predominates. Since compound **1** has the *E* configuration for the double bond between C6 and C7, compound **2** must have the *Z* configuration for that double bond:



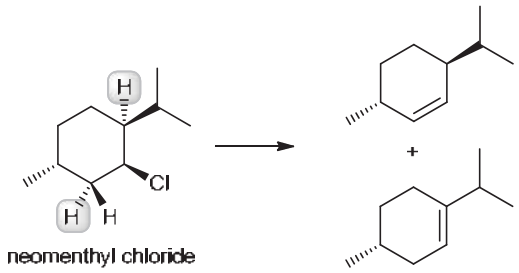
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Compound **1** is expected to be more stable than compound **2**, because of steric considerations (*E* vs. *Z*)

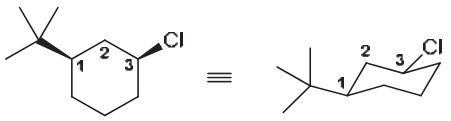
7.23. In the structure of menthyl chloride (shown below), the leaving group (Cl^-) is on a dash. Therefore, we are looking for a β proton that is on a wedge, in order that it should be antiperiplanar with the leaving group. In this case, there is only one β proton on a wedge (highlighted below). Therefore, only one elimination product is observed:



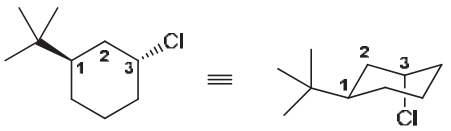
In contrast, the leaving group in neomenthyl chloride is antiperiplanar with two different β protons (highlighted), giving rise to two possible products:



7.24. Because of the bulky *tert*-butyl group, the first compound is essentially locked in a chair conformation in which the leaving group (Cl^-) occupies an equatorial position.



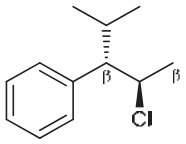
This conformation cannot undergo an E2 reaction because the leaving group is not antiperiplanar with a proton. However, the second compound is locked in a chair conformation in which the leaving group (Cl^-) occupies an axial position.



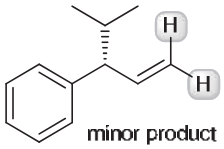
This conformation rapidly undergoes an E2 reaction. Therefore, the second compound is expected to be more reactive towards an E2 process than the first compound.

7.25.

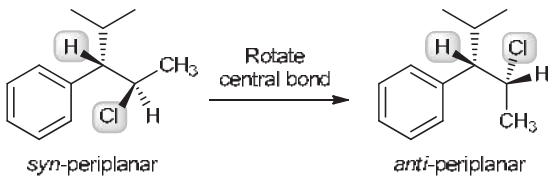
(a) We must determine both the regiochemical outcome and the stereochemical outcome. Let's begin with regiochemistry. There are two β positions in this case, so there are two possible regiochemical outcomes.



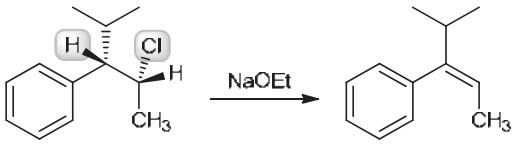
The base (ethoxide) is not sterically hindered, so we expect the major product will be the more-substituted alkene, while the minor product will be the less-substituted alkene. Next, we must identify the stereochemistry of formation of each of the products. Let's begin with the minor product (the less substituted alkene), because its double bond does not exhibit stereoisomerism:



As shown, there are two hydrogen atoms (highlighted) connected to one of the vinylic positions, so this alkene is neither *E* nor *Z*. Now let's turn our attention to the major product of the reaction (the more-substituted alkene). To determine which stereoisomer is obtained, we must first redraw the starting material in a way that shows the β proton and the leaving group in an *anti*-periplanar arrangement:

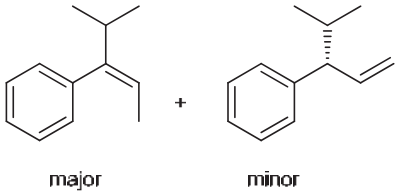


When drawn in an *anti*-periplanar conformation (with the proton on a wedge and the leaving group on a dash), the product can be easily drawn by redrawing the skeleton, with a double bond taking the place of the β proton and the leaving group:

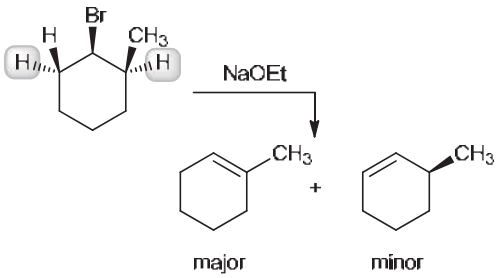


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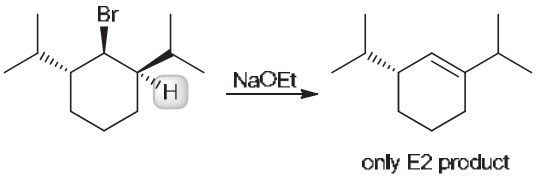
Notice that the isopropyl group is drawn on a straight line (double bonds have planar geometry).
In summary, we expect the following two products:



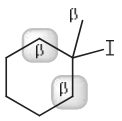
(b) For substituted cyclohexanes, an E2 reaction will occur if the leaving group and the β proton can achieve antiperiplanarity. In order to achieve this, one must be on a wedge and the other must be on a dash. The leaving group (Br^-) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there are two different β protons on a dash (highlighted below), giving rise to two products. Since the base (ethoxide) is not sterically hindered, we expect the more-substituted alkene to be the major product:



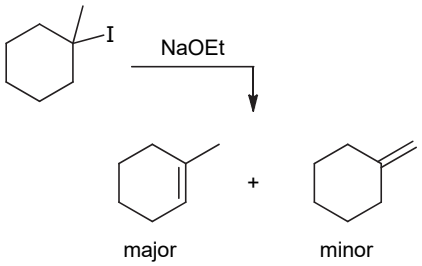
(c) For substituted cyclohexanes, an E2 reaction will occur if the leaving group and the β proton can achieve antiperiplanarity. In order to achieve this, one must be on a wedge and the other must be on a dash. The leaving group (Br^-) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there is only one β proton on a dash (highlighted below), giving rise to only one product:



(d) We must determine both the regiochemical outcome and the stereochemical outcome. Let's begin with regiochemistry. This compound has three β positions, but two of them (highlighted) are identical because deprotonation at either of these locations will result in the same alkene:

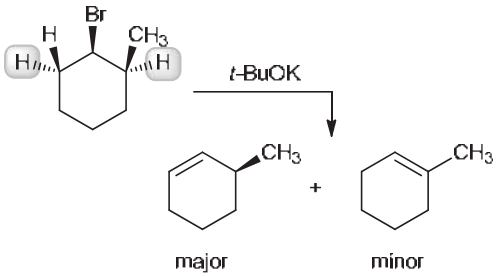


As such, we expect two possible regiochemical outcomes. Since the base (ethoxide) is not sterically hindered, we expect the more-substituted alkene as the major product.

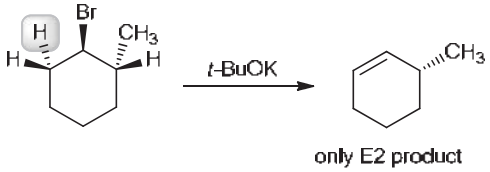


Stereochemisty is not a consideration for either product. The minor product is not stereoisomeric, and the major product cannot exist as an *E* isomer (because the ring makes that impossible).

(e) For substituted cyclohexanes, an E2 reaction will occur if the leaving group and the β proton can achieve antiperiplanarity. In order to achieve this, one must be on a wedge and the other must be on a dash. The leaving group (Br^-) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there are two different β protons on a dash (highlighted below), giving rise to two products. Since the base (*tert*-butoxide) is sterically hindered, we expect the less-substituted alkene to be the major product:

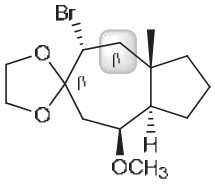


(f) For substituted cyclohexanes, an E2 reaction will occur if the leaving group and the β proton can achieve antiperiplanarity. In order to achieve this, one must be on a wedge and the other must be on a dash. The leaving group (Br^-) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there is only one β proton on a dash (highlighted below), giving rise to only one product:



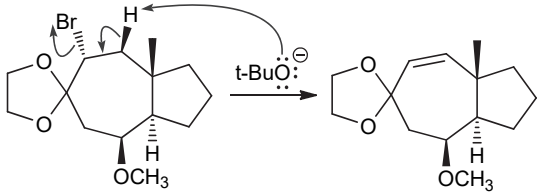
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7.26. Bromide is the best (and only) leaving group in compound **1**, so the carbon atom connected to Br is (by definition) the α carbon. There are two β carbons, but only one of these positions (highlighted) has protons.



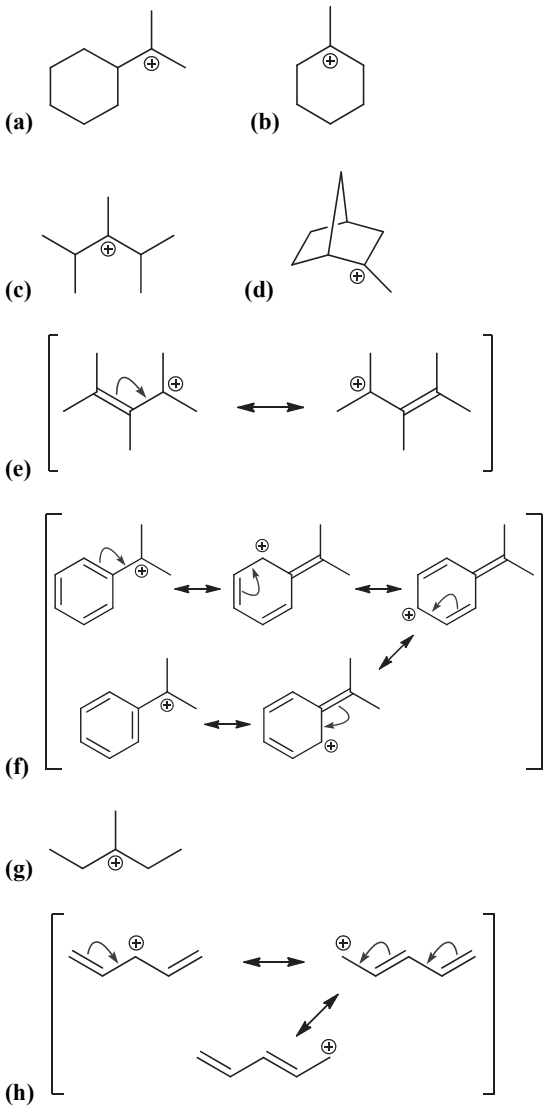
The base (*tert*-butoxide) is sterically hindered; however, there is only one regioisomer possible in this reaction because there is only one β carbon with protons. In this case, *tert*-butoxide was probably chosen as the base (rather than hydroxide, methoxide or some other unhindered base) to favor an E2 reaction over an S_N2 reaction. As we will discover in Section 7.11, substitution and elimination reactions often compete with each other, especially when the substrate is secondary.

Since there are two protons on the β position, we might predict that this reaction would be stereoselective, favoring the *trans* isomer. However, *trans* double bonds are not stable in rings with fewer than eight carbons. Thus, we expect formation of only the *cis* double bond due to the geometric constraints of the seven-membered ring.

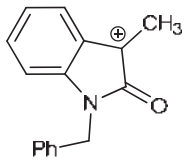


Note that in the mechanism shown above, we remove the beta proton on a wedge (rather than the proton on a dash). This way, the proton and the leaving group are antiperiplanar.

7.27. In each case, the bond between the α position and the leaving group is broken, and the carbon atom obtains a positive charge. Resonance structures are drawn where applicable:

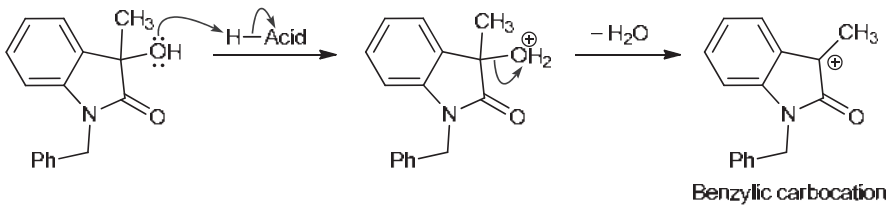


7.28. Notice that the OH group is replaced with a nucleophile. In order for the nucleophile to attack that position, there must have been a carbocation in that position:

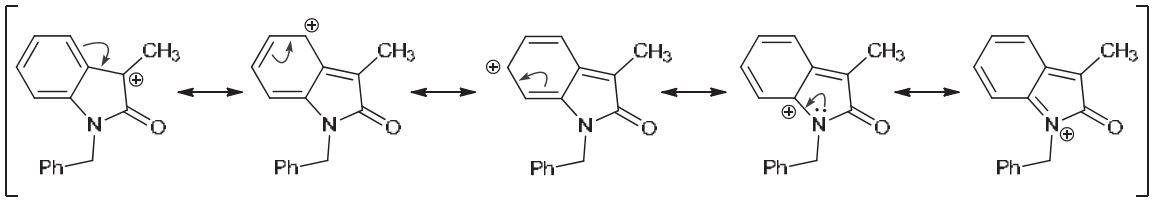


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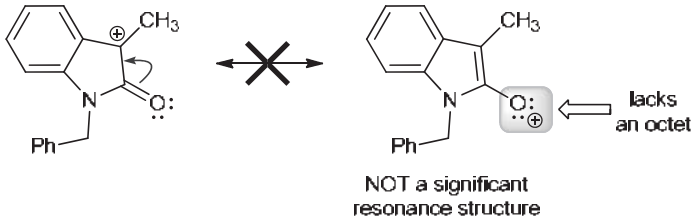
Later in this chapter, we will explore how this carbocation is formed. Specifically, we will see that the OH group can be protonated in the presence of concentrated acid, giving an excellent leaving group. Then, loss of the leaving group (H_2O) gives the carbocation intermediate:



This carbocation is benzylic, so it has extensive resonance stabilization, as shown here:

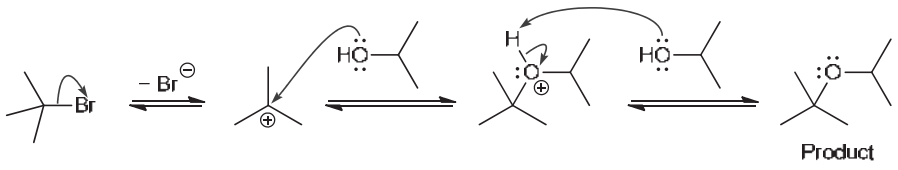


Note that the following resonance structure is not significant because the oxygen atom (highlighted) does not have an octet of electrons:



7.29.

(a) The first step of solvolysis is loss of the leaving group to give a carbocation. If the solvent is isopropanol, $(CH_3)_2CHOH$, then the carbocation will be captured by a molecule of isopropanol, giving an oxonium ion, which is then deprotonated to give the product, shown below:



(b) The rate of solvolysis is dependent on solvent polarity, measured by the dielectric constant of the solvent. A higher dielectric constant corresponds with a faster rate of solvolysis. The dielectric constant of ethanol is 24, while the dielectric constant of isopropanol is only 18. Therefore, solvolysis is expected to occur more rapidly in ethanol than in isopropanol.

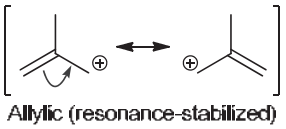
7.30.

(a) The first compound is expected to undergo solvolysis more rapidly because it will proceed via a tertiary benzylic carbocation (resonance-stabilized). In contrast, solvolysis of the second compound will proceed via a tertiary carbocation, which is not resonance-stabilized.



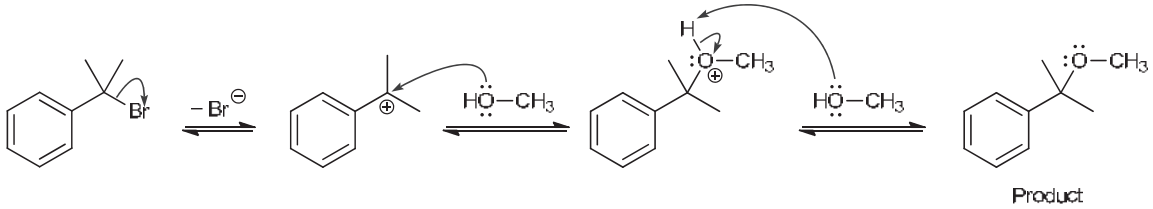
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(b) The first compound is a primary alkyl halide and is therefore not expected to undergo solvolysis at an appreciable rate. In contrast, the second compound is an allylic bromide. Solvolysis of an allylic bromide will proceed via an allylic carbocation, which is resonance-stabilized.

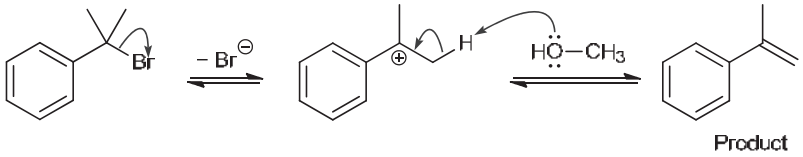


(c) Both compounds have the same carbon skeleton, and therefore give the same carbocation (during solvolysis). Nevertheless, the second compound is expected to undergo solvolysis more rapidly, because the leaving group is bromide, which is a better leaving group than chloride.

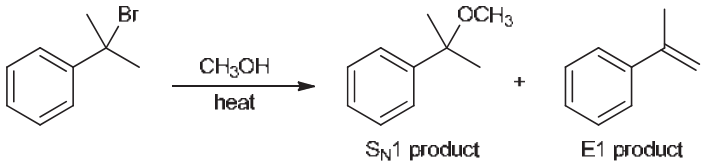
7.31. We expect S_N1 and E1 processes to occur. The S_N1 process gives the following product:



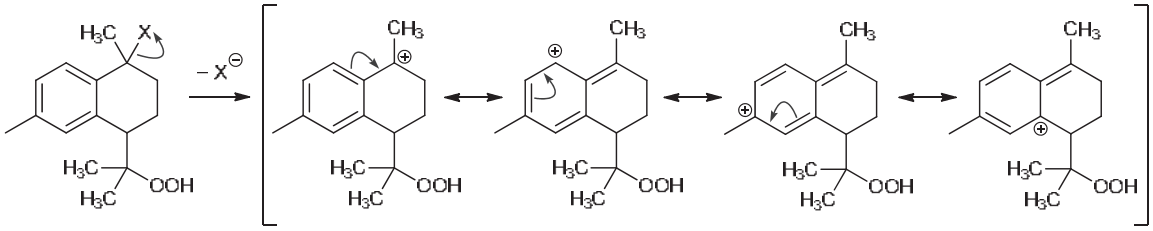
And the E1 process gives the following product:



In summary, solvolysis in methanol should give the following products:

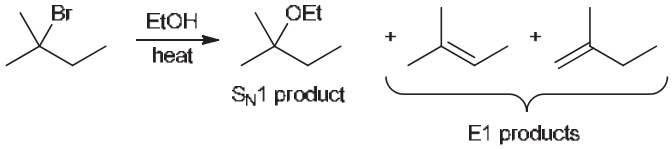


7.32. In each case, the leaving group X is lost in the reaction so the bond between a carbon atom and the leaving group is broken, and a carbocation intermediate is formed. The rate of any S_N1 reaction is dependent on this step of the reaction. More stable carbocations are formed faster because the transition state that leads to them is lower in energy. Ionization of either compound **1** or **3** will result in a tertiary carbocation. Notice, however, that the carbocation that is formed from compound **1** is tertiary AND benzylic. That is, it is resonance-stabilized and therefore should participate in a faster S_N1 reaction.

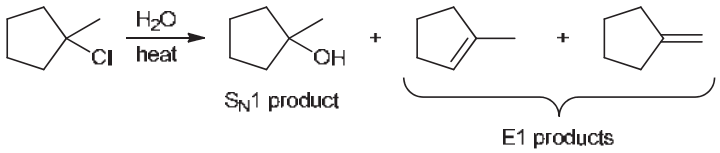


7.33.

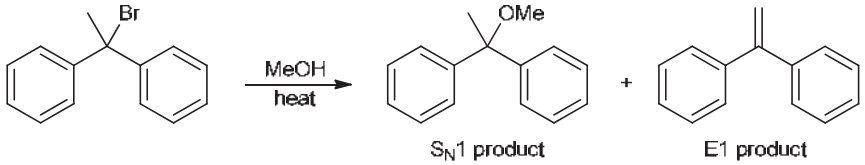
(a) Solvolysis is expected to afford S_N1 and E1 products. In the S_N1 product, an ethoxy group (OEt) has replaced bromide. There are two E1 products (two regiochemical outcomes), although the disubstituted alkene is expected to be a minor product.



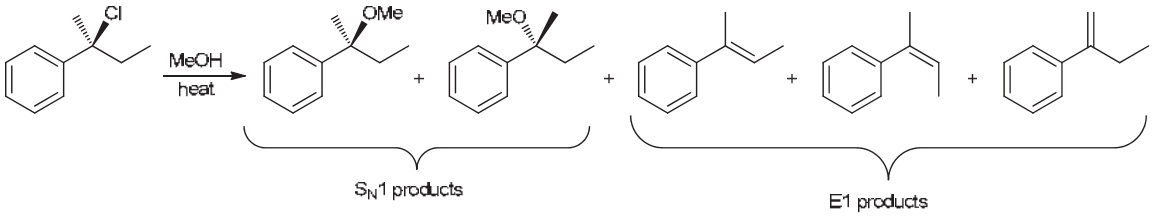
(b) Solvolysis is expected to afford S_N1 and E1 products. In the S_N1 product, an OH group has replaced chloride. There are two E1 products (two regiochemical outcomes), although the disubstituted alkene is expected to be a minor product.



(c) Solvolysis is expected to afford S_N1 and E1 products. In the S_N1 product, a methoxy group (OMe) has replaced bromide. In this case, there is only one E1 product (there is only one possible regiochemical outcome), although the disubstituted alkene is expected to be a minor product.

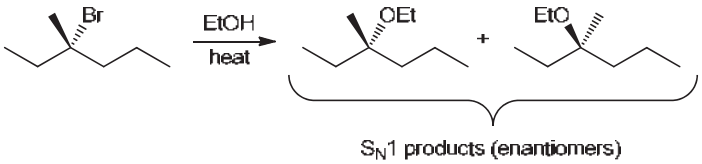


(d) Solvolysis is expected to afford S_N1 and E1 products. In this case, the α position is a chiral center, so we expect a pair of enantiomers (with a small preference for the inverted product, as a result of ion pairs). Both S_N1 products are shown below. There are also three E1 products in this case, shown below as well.

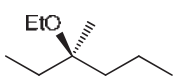


7.34.

(a) In this case, the α position is a chiral center, so we expect a pair of enantiomers:

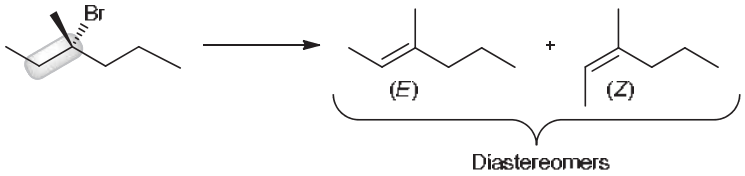


(b) The inverted product is expected to predominate slightly, as a result of ion pairs.

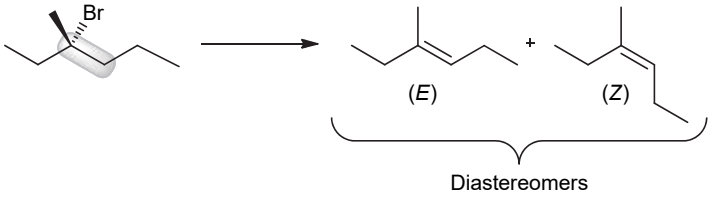


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(c) There are three regiochemical possibilities for an E1 process. Let's explore each of the three possibilities. One regiochemical possibility is to form the double bond in the location highlighted below, which leads to two diastereomeric alkenes.



Another regiochemical possibility is to form the double bond in the location highlighted below, which also leads to two diastereomeric alkenes.



Finally, the third regiochemical possibility leads to a disubstituted alkene, which is not stereoisomeric:



In total, there are five alkene products, all shown above.

(d) For each regiochemical possibility (shown above), the alkene with fewer or weaker steric interactions is favored. In each of these cases, the *E* isomer has weaker steric interactions, and is therefore the favored isomer.

7.35.

(a) In the first compound, the β positions are deuterated. As such, an elimination reaction will involve loss of DBr, which occurs at a slower rate than loss of HBr. Therefore, the second compound is expected to undergo elimination more rapidly.

(b) In the first compound, the β positions are deuterated. In the second compound, the α position is deuterated. Since elimination involves removal of H (or D) from the β position, the rate of reaction for the first compound will be more affected by the presence of deuterium. That is, the first compound is expected to undergo elimination at a slower rate. Therefore, the second compound is expected to undergo elimination more rapidly.

(c) In the first compound, the β position is deuterated. In the second compound, the α position is deuterated. Since elimination involves removal of H (or D) from the β position, the rate of reaction for the first compound will be more affected by the presence of deuterium. That is, the first compound is expected to undergo elimination at a slower rate. Therefore, the second compound is expected to undergo elimination more rapidly.

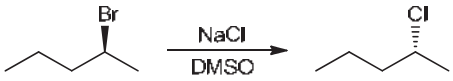
7.36.

(a) Ethoxide is a strong base, so we expect an E2 reaction, which involves deprotonation at the β position. If all of the β protons are replaced with D (as indicated in the problem statement), then the reaction is expected to occur at a slower rate, as a result of a primary isotope effect.

(b) In this case, the reagent is ethanol, which is a weak base. These conditions favor an E1 process. In an E1 process, deprotonation of the β position occurs AFTER the rate determining step (loss of the leaving group). Therefore, we do not expect a primary isotope effect.

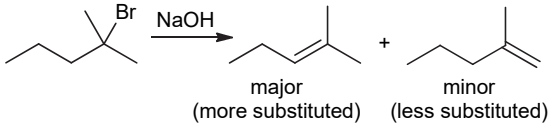
7.37.

(a) The reagent is chloride, which functions as a nucleophile, so we expect a substitution reaction. The substrate is secondary and the solvent (DMSO) is polar aprotic, indicating an S_N2 process. As such, we expect inversion of configuration, as shown:

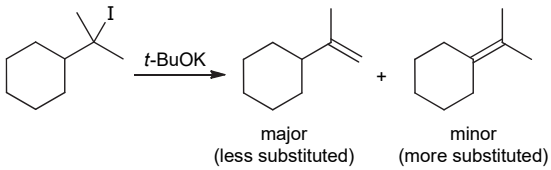


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(b) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is tertiary, so we expect an E2 process. There are three β positions, but two of them are identical, so there are two possible regiochemical outcomes. The more-substituted alkene is the major product, as shown. The products are not stereoisomeric, so stereochemistry is not a consideration.



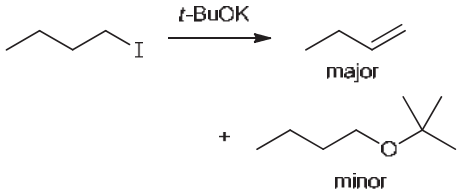
(c) The reagent is *tert*-butoxide, which is a strong, sterically hindered base. The substrate is tertiary, so we expect an E2 process. There are three β positions, but two of them are identical, so there are two possible regiochemical outcomes. Since the base is sterically hindered, we expect that the less-substituted alkene will be the major product, as shown. The products are not stereoisomeric, so stereochemistry is not a consideration.



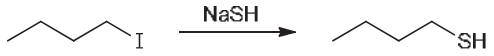
(d) The reagent is DBN, which is a strong base. The substrate is tertiary, so we expect an E2 process. There are two β positions bearing protons, and both of these positions are identical, so there is only one possible regiochemical outcome. The product is not stereoisomeric, so stereochemistry is not a consideration.



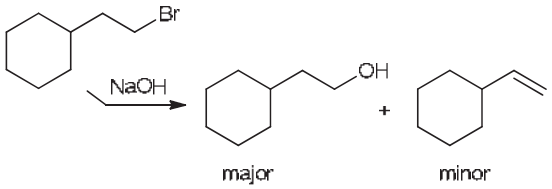
(e) The reagent is *tert*-butoxide, which is a strong base and strong nucleophile. For most reagents in this category, treatment with a primary alkyl halide will give S_N2 as the major pathway and E2 as the minor pathway. However, *tert*-butoxide is sterically hindered, which reduces the rate of the S_N2 process, such that E2 now prevails. Therefore, the major product will result from an E2 process, and the minor product will result from an S_N2 process.



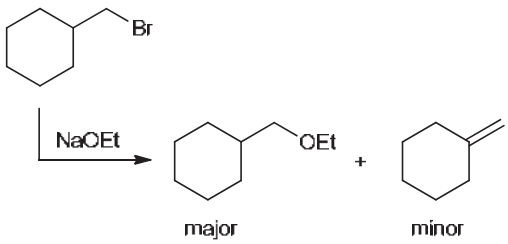
(f) The reagent is HS^-, which is a strong nucleophile and a weak base. The substrate is primary, so we expect an S_N2 process, giving the following product:



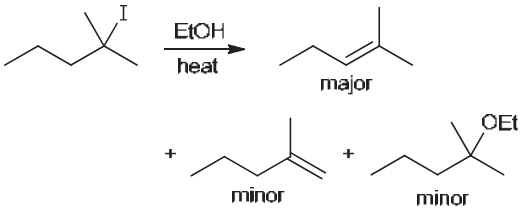
(g) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is primary, so we expect the major product to result from an S_N2 process, and the minor product to result from an E2 process, as shown:



(h) The reagent is ethoxide, which is both a strong base and a strong nucleophile. The substrate is primary, so we expect the major product to result from an S_N2 process, and the minor product to result from an E2 process, as shown:



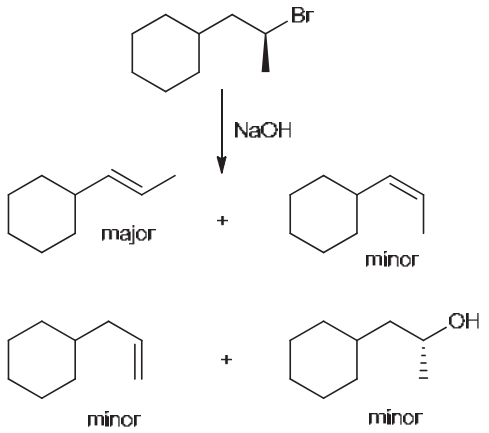
(i) The reagent is ethanol, which is both a weak base and a weak nucleophile. The substrate is tertiary, so we expect E1 and S_N1 processes. One of the alkene products is trisubstituted, so we expect E1 to predominate over S_N1. For the E1 pathway, two regiochemical outcomes are possible. The more-substituted alkene is the major product, while the minor products are the less-substituted alkene and the S_N1 product, shown below:



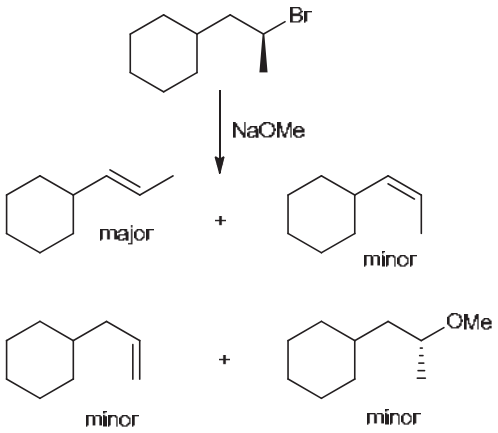
(j) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. Accordingly, the major product is the more substituted alkene, with the *trans* configuration (because the reaction is stereoselective, favoring the *trans* isomer over the *cis*

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isomer). The minor products include the *cis* isomer, as well as the less-substituted alkene and the S_N2 product:

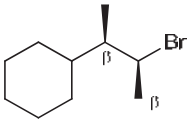


(k) The reagent is methoxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. Accordingly, the major product is the more substituted alkene, with the *trans* configuration (because the reaction is stereoselective, favoring the *trans* isomer over the *cis* isomer). The minor products include the *cis* isomer, as well as the less-substituted alkene and the S_N2 product:

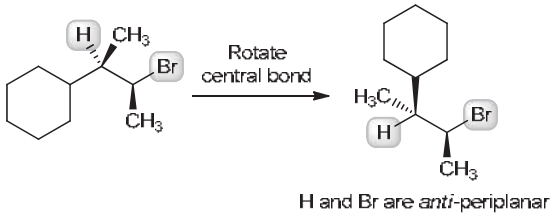


(l) The reagent is methoxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. Let's begin by drawing the major product, and then we will move on to the minor products.

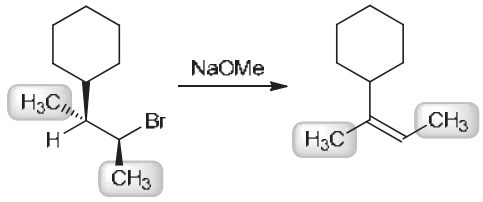
To draw the major product (E2), we note that there are two β positions in this case, so there are two possible regiochemical outcomes.



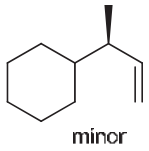
The base is not sterically hindered, so the Zaitsev product (the more substituted alkene) is expected to be the major product. To determine which stereoisomer is obtained, we must first redraw the starting material in a way that shows the β proton and the leaving group in an *anti*-periplanar arrangement:



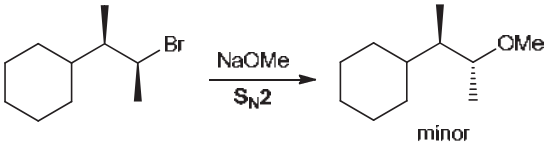
When drawn in an *anti*-periplanar conformation, we can use the dashes and wedges as guides to draw the correct stereoisomer (methyl groups are *trans* to each other in the product):



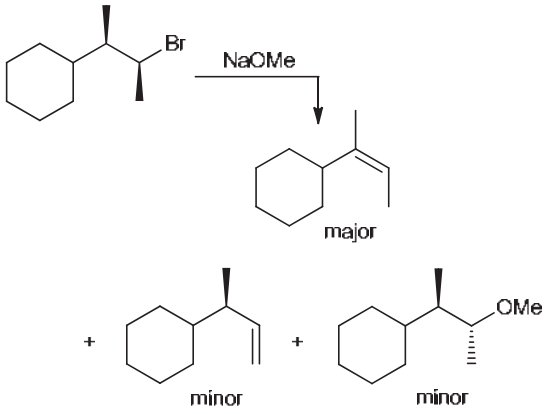
Now let's consider the minor products. We noted before that there are two possible regiochemical outcomes for an E2 process. The Hofmann product (the less substituted alkene) will be a minor product:



Another minor product is obtained via an S_N2 process (with inversion of configuration), as shown:

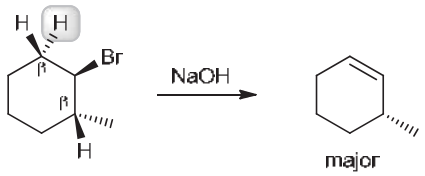


In summary, we expect the following products:

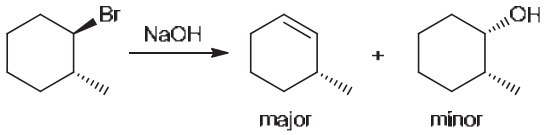


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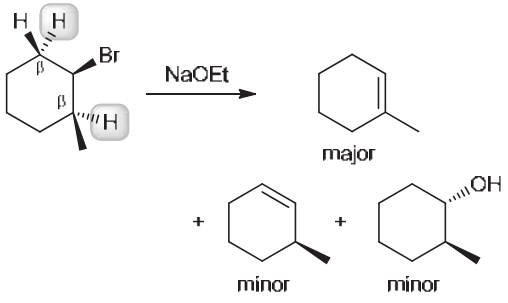
(m) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. For substituted cyclohexanes, an E2 reaction occurs via a conformation in which the leaving group and the β proton are antiperiplanar to one another (one must be on a wedge and the other must be on a dash). The leaving group (Br^-) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there is only one β proton that is on a dash (highlighted below), giving rise to only one elimination product, as shown:



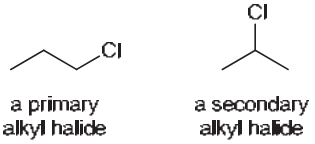
The minor product is generated via an S_N2 pathway (with inversion of configuration, as expected):



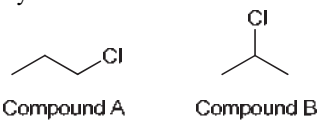
(n) The reagent is ethoxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. For substituted cyclohexanes, an E2 reaction occurs via a conformation in which the leaving group and the β proton are antiperiplanar to one another (one must be on a wedge and the other must be on a dash). The leaving group (Br^-) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there are two such protons (highlighted below), giving rise to two elimination products, as shown. The major product is the more-substituted alkene (because the base is not sterically hindered), while the minor products include the less-substituted alkene and the S_N2 product (with the expected inversion of configuration):



7.38. There are only two constitutional isomers with the molecular formula C_3H_7Cl:

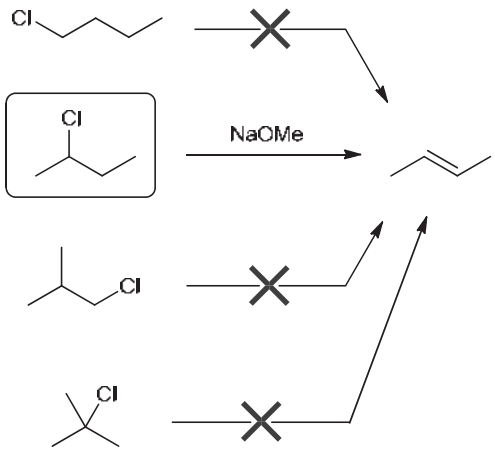


Sodium methoxide is both a strong nucleophile and a strong base. When compound **A** is treated with sodium methoxide, a substitution reaction predominates. Therefore, compound **A** must be the primary alkyl chloride above. When compound **B** is treated with sodium methoxide, an elimination reaction predominates. Therefore, compound **B** must be the secondary alkyl chloride:



7.39.

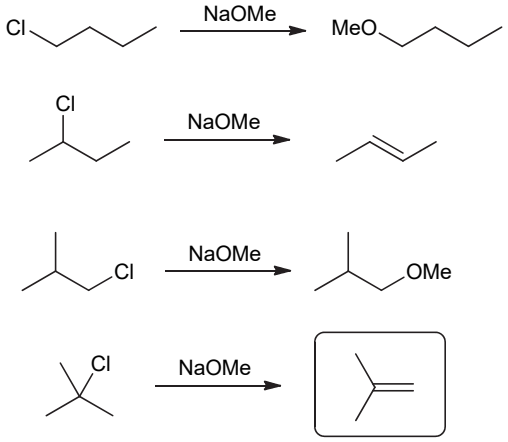
(a) There are four constitutional isomers with the molecular formula C_4H_9Cl, shown below. Only one of them affords the desired product when treated with methoxide:



(b) We saw in the solution to part (a) that there are four constitutional isomers with the molecular formula C_4H_9Cl. Let's consider the **major product** that is expected when each of these isomers is treated with methoxide. Notice that only one of these cases produces

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a disubstituted alkene that is different from the *trans*-2-butene:



Therefore, the following structure must be compound **B**:



7.40. The problem statement indicates that the major product is 2,3-dimethyl-2-butene:

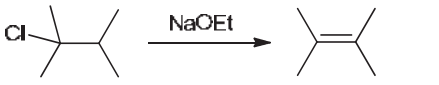


2,3-dimethyl-2-butene

The starting alkyl halide must have the same carbon skeleton as this product, and there are only two such isomers with the molecular formula $C_6H_{13}Cl$.



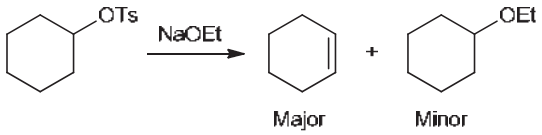
Only one of these isomers gives the desired major product upon treatment with sodium ethoxide:



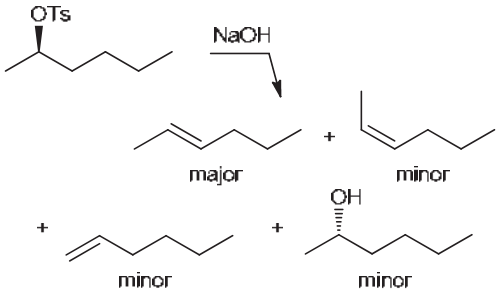
2,3-dimethyl-2-butene

7.41.

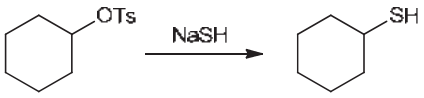
(a) The reagent is ethoxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. There is only one regiochemical outcome for the E2 process, so only one alkene is formed. There is also only one product from the S_N2 process:



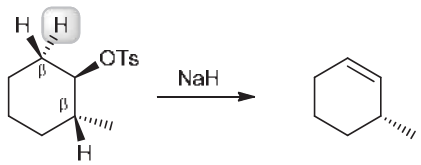
(b) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although the E2 process will be responsible for the major product. There are two regiochemical outcomes for the E2 process. One of these outcomes leads to a disubstituted alkene, which is stereoisomeric. Both stereoisomers are expected, although the *trans* isomer will be favored over the *cis* isomer because the reaction is stereoselective. Indeed, the *trans* isomer is the major product, because the base is not sterically hindered (a sterically hindered base would have favored the monosubstituted alkene). There is also one minor product that is formed via an S_N2 process:



(c) The reagent (HS^-) is a strong nucleophile (not a strong base), and the substrate is secondary, so we expect an S_N2 process, giving the following product:

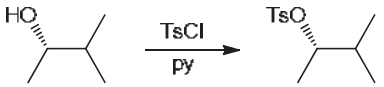


(d) The reagent is hydride (H^-), which is a strong base (not a nucleophile), so we expect an E2 process (no S_N2). For substituted cyclohexanes, an E2 reaction occurs via a conformation in which the leaving group and the β proton are antiperiplanar to one another (one must be on a wedge and the other must be on a dash). The leaving group (OTs) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there is only one β proton that is on a dash (highlighted below), giving rise to only one elimination product, as shown:

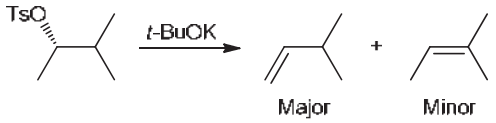


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(e) In the first step, the alcohol is converted into a tosylate:



This tosylate is a secondary substrate. When treated with a strong base, we expect E2 to be favored. The base (*tert*-butoxide) is sterically hindered, so the Hofmann product will be favored. The Zaitsev product is expected to be a minor product:

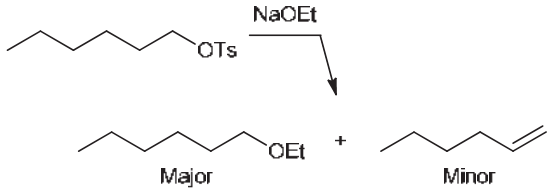


In general, when a secondary substrate is treated with a reagent that is both a strong base and a strong nucleophile, we would expect a minor product from an S_N2 process. However, in this case, the nucleophile (*tert*-butoxide) is sterically hindered, so we would expect there to be very little, if any, of this S_N2 product.

(f) In the first step, the alcohol is converted into a tosylate:



In the next step, the tosylate (a primary substrate) is treated with ethoxide, which is both a strong base and a strong nucleophile. Since the substrate is primary, S_N2 is expected to predominate, giving the major product, shown below. An E2 process is responsible for the minor product, which is an alkene:

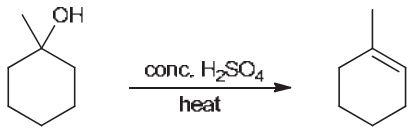


7.42.

(a) A tertiary alcohol will react with HBr to give the corresponding tertiary alkyl bromide via an S_N1 process:

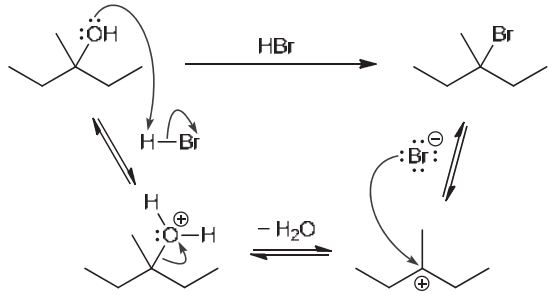


(b) A tertiary alcohol is converted into an alkene upon treatment with concentrated sulfuric acid. The more substituted alkene (Zaitsev product) is favored:

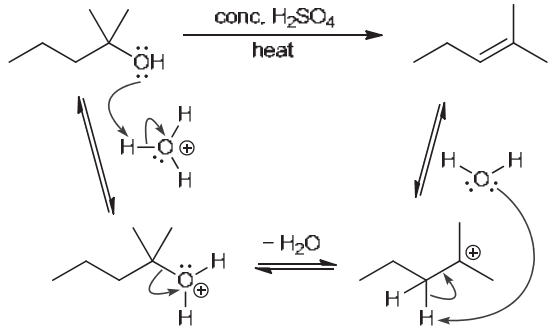


7.43.

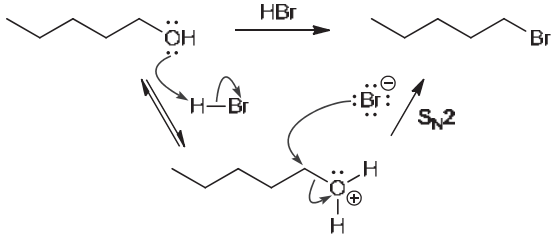
(a) The starting alcohol is tertiary, so we expect the reaction to proceed via an S_N1 process (rather than S_N2). The first step of the process is protonation of the OH group, thereby converting a bad leaving group into an excellent leaving group. Loss of the leaving group gives a carbocation, which is then captured by a bromide ion to give the product:



(b) Upon treatment with concentrated sulfuric acid, a tertiary alcohol is converted into an alkene via an E1 process. The OH group is first protonated, thereby converting a bad leaving group into an excellent leaving group. Loss of the leaving group gives a carbocation, which is then deprotonated by a molecule of the solvent to give the product:

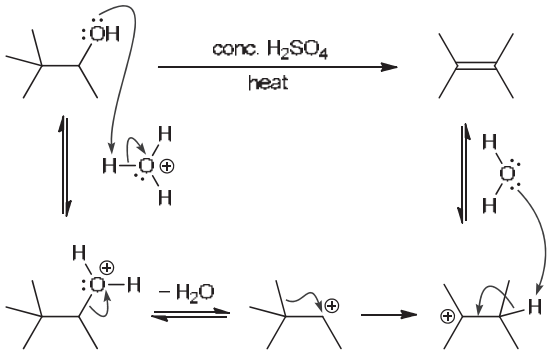


(c) The OH group is first protonated, thereby converting a bad leaving group into an excellent leaving group. This substrate is primary, so an S_N2 process is expected (rather than S_N1) to give the product:

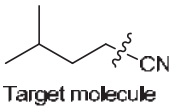


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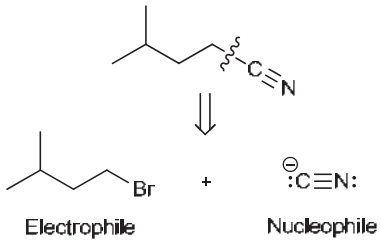
(d) The carbon skeleton has rearranged, which indicates an E1 process. The OH group is first protonated, thereby converting a bad leaving group into an excellent leaving group. Loss of the leaving group gives a secondary carbocation, which can rearrange to give a tertiary carbocation. The tertiary carbocation is then deprotonated by a molecule of the solvent to give the product:



7.44. Our retrosynthesis begins with a disconnection at the cyano group, since we must start with an alkyl halide instead of a cyano substituent:

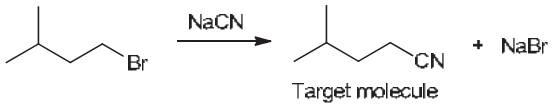


Cyanide ($N{\equiv}C^-$) is a stable and familiar anion, so we will use cyanide as the nucleophile. The other carbon (at the disconnected bond) must have started out as an electrophile, so we draw a leaving group (such as Cl, Br, I or OTs) at that position.

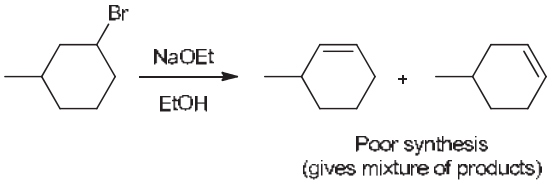


The last step of the planning process is to confirm that the reaction mechanism is favorable. Cyanide is a strong nucleophile but not a strong base, so the S_N2 pathway does not have any significant competition from the E2 pathway. With a primary substrate, we expect an S_N2 process to proceed smoothly to give the desired target molecule.

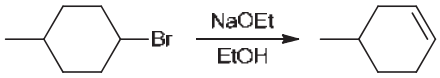
Now we draw the forward process. As shown here, NaCN can be used as a source of cyanide anion:



7.45. Consider the mechanism involved in each possible transformation, and for each one, consider whether or not the target molecule is expected to be the major (or only) product. We begin with the first possibility, which employs an alkyl halide as the starting material. It is true that alkyl halides can be converted to alkenes upon treatment with a strong base (via an E2 process). However, in this case, there are two possible regiochemical outcomes, so we expect a mixture of two alkene products:



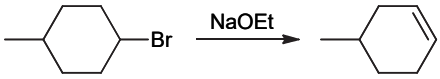
In contrast, treating the second halide with a strong base is expected to give only one product (the desired target molecule):



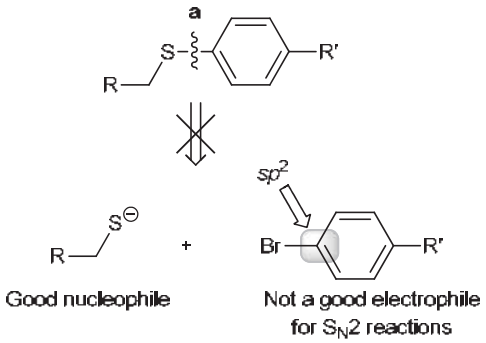
In this case there is only one possible regiochemical outcome:



Therefore, the better synthesis begins with the second alkyl halide shown. Any strong base, such as NaOEt, can be used:

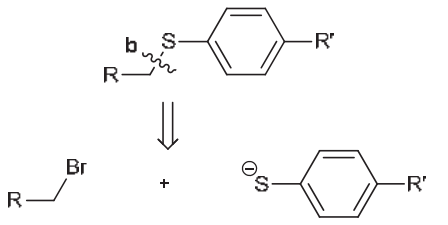


7.46. Let's begin by exploring the retrosynthesis based on disconnection of bond **a**. This retrosynthesis involves a very poor electrophile, because S_N2 reactions generally do not occur at sp^2 hybridized centers:



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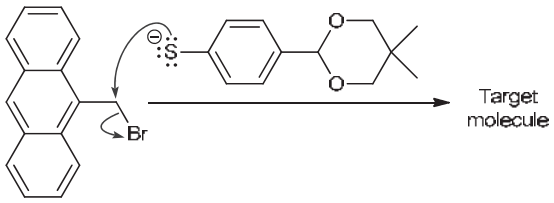
The better retrosynthesis is based on disconnection of bond **b**, because it involves both a good electrophile and a good nucleophile:



Good electrophile for S_N2 (primary alkyl halide)

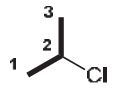
Good nucleophile

The S_N2 process portrayed in retrosynthesis **b** is favorable, because it involves a strong nucleophile and a primary substrate, so this reaction is expected to give the desired target molecule.



7.47.

(a) The parent is the longest chain, which is three carbon atoms in this case (propane). There is only one substituent (chloro), and its locant is assigned as 2 (as shown below), so the systematic name for this compound is 2-chloropropane. The common name is isopropyl chloride.



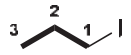
2-chloropropane

(b) The parent is the longest chain, which is three carbon atoms in this case (propane). There are two substituents (bromo and methyl), and their locants are assigned as 2 and 2, as shown below. Substituents are alphabetized in the name (bromo precedes methyl), so the systematic name is 2-bromo-2-methylpropane. The common name is *tert*-butyl bromide.



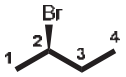
2-bromo-2-methylpropane

(c) The parent is the longest chain, which is three carbon atoms in this case (propane). There is only one substituent (iodo), and its locant is assigned as 1 (as shown), so the systematic name for this compound is 1-iodopropane. The common name is propyl iodide.



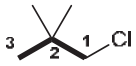
1-iodopropane

(d) The parent is the longest chain, which is four carbon atoms in this case (butane). There is only one substituent (bromo), and its locant is assigned as 2 (as shown below). The compound has a chiral center, so the configuration must be indicated at the beginning of the name: (*R*)-2-bromobutane. The common name is (*R*)-*sec*-butyl bromide.



(*R*)-2-bromobutane

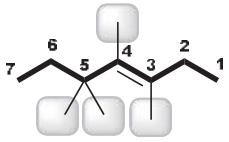
(e) The parent is the longest chain, which is three carbon atoms in this case (propane). There are three substituents (chloro, methyl, and methyl), and their locants are assigned as 1, 2, and 2, respectively, as shown below. Substituents are alphabetized in the name (chloro precedes methyl). Make sure that each methyl group receives a locant (2,2-dimethyl rather than 2-dimethyl). The systematic name is therefore 1-chloro-2,2-dimethylpropane. The common name is neopentyl chloride.



1-chloro-2,2-dimethylpropane

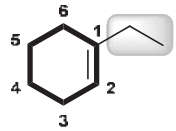
7.48.

(a) We begin by identifying the parent. The longest chain is seven carbon atoms, so the parent is heptene. There are four substituents (highlighted), all of which are methyl groups. Notice that the parent chain is numbered starting from the side that is closest to the π bond. According to this numbering scheme, the methyl groups are located at C3, C4, C5 and C5. Finally, we use the prefix "tetra" to indicate the presence of four methyl groups, and we include a locant that identifies the position of the double bond ("3" indicates that the double bond is located between C3 and C4):



trans-3,4,5,5-tetramethyl-3-heptene

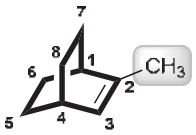
(b) The parent is a six-membered ring (cyclohexene). There is only substituent (located at C1:



1-ethylcyclohexene

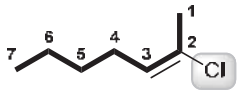
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(c) We begin by identifying the parent, which is bicyclic in this case. The parent is bicyclo[2.2.2]octene. There is only one substituent (a methyl group). Notice that the parent chain is numbered starting from one of the bridgeheads, as seen in Section 4.2, which places the double bond between C2 and C3. According to this numbering scheme, the methyl group is located at C2. Finally, we include a locant that identifies the position of the double bond (C2).



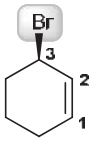
2-methylbicyclo[2.2.2]oct-2-ene

(d) We begin by identifying the parent. The longest chain is seven carbon atoms, so the parent is heptene. There is one substituent (a chloro group). The parent chain is numbered starting from the side that is closest to the π bond. According to this numbering scheme, the chloro group is located at C2. We include a locant that identifies the position of the double bond ("2" indicates that the double bond is located between C2 and C3). In addition, the configuration of the double bond (*E*) must be indicated at the beginning of the name:



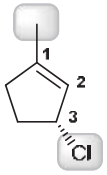
(*E*)-2-chloro-2-heptene

(e) The parent is cyclohexene, which does not require a locant to identify the position of the double bond, because it is assumed to be between C1 and C2. Locants are assigned counter-clockwise, in order to give the substituent (Br) the lowest possible locant (C3 rather than C6). The configuration of the chiral center (*R*) must also be included at the beginning of the name.



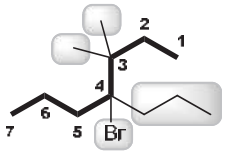
(*R*)-3-bromocyclohexene

(f) The parent is cyclopentene, which does not require a locant to identify the position of the double bond, because it is assumed to be between C1 and C2. Locants are assigned clockwise in this case, in order to give the two substituents (Me and Cl) the lowest possible locants. Substituents are arranged alphabetically in the name. The configuration of the chiral center (*R*) must also be included at the beginning of the name.



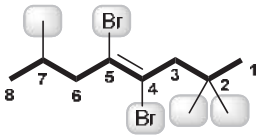
(*R*)-3-chloro-1-methylcyclopentene

(g) We begin by identifying the parent. The longest chain is seven carbon atoms, so the parent is heptane. In this case, there are choices for the parent, and we choose the path that gives the maximum number of substituents. There are four substituents (highlighted). The location of each substituent is indicated with the appropriate locant, and the substituents are alphabetized in the name (note that dimethyl is alphabetized as "m" for methyl, not "d").



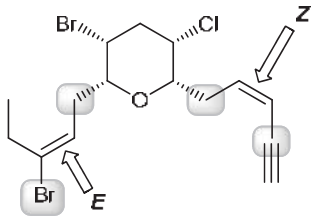
4-bromo-4-ethyl-3,3-dimethylheptane

(h) We begin by identifying the parent. The longest chain is eight carbon atoms, so the parent is octene. There are five substituents (highlighted). The location of each substituent is indicated with the appropriate locant, and the substituents are alphabetized in the name (bromo before methyl). In addition, the configuration of the double bond (*E*) must be indicated at the beginning of the name:

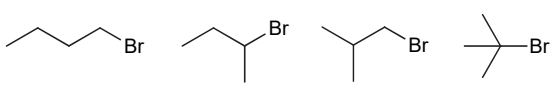


(*E*)-4,5-dibromo-2,2,7-trimethyl-4-octene

7.49. The configuration of each π bond is shown below, together with the priorities (highlighted) that were used to determine the configuration in each case.

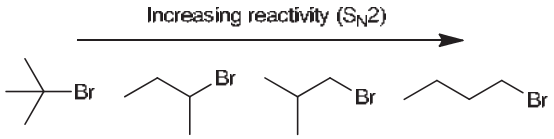


7.50. We begin by drawing all constitutional isomers with the molecular formula C_4H_9Br, shown below. For help, see the solution to Problem 2.51.

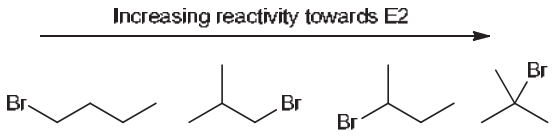


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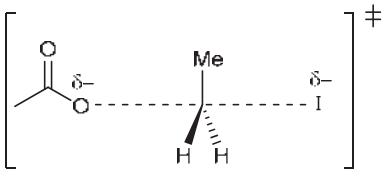
(a) The four constitutional isomers are arranged below in order of increasing reactivity toward S_N2. Notice that the tertiary substrate is the least reactive because it is the most hindered. Among the two primary substrates, butyl bromide is the least sterically hindered (the β position is less substituted). Therefore, butyl bromide is the most reactive toward S_N2.



(b) The four constitutional isomers are arranged below in order of increasing reactivity toward E2. Notice that the tertiary alkyl bromide is the most reactive towards E2, followed by the secondary alkyl bromide. Among the two primary alkyl bromides, the one leading to a disubstituted alkene will be more reactive towards E2 than the one leading to a monosubstituted alkene.

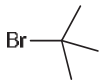


7.51. The leaving group is an iodide ion (I^-) and the nucleophile is an acetate ion ($CH_3CO_2^-$). In the transition state, each of these groups is drawn as being connected to the α position with a dotted line (indicating these bonds are in the process of forming or breaking), and a δ– is placed on each group to indicate that the charge is spread over both locations. Don't forget the brackets and the symbol that indicate the drawing is a transition state.

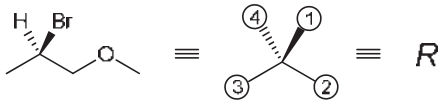


7.52. The substrate is primary, the solvent is DMSO (a polar aprotic solvent), and the nucleophile (iodide) is a very strong nucleophile. All of these factors suggest an S_N2 process. Iodide functions as a nucleophile and attacks (*S*)-2-iodopentane, displacing iodide as a leaving group. Since the reaction is an S_N2 process, we expect inversion of configuration. The product is (*R*)-2-iodopentane. The reaction continues repeatedly until a racemic mixture is eventually obtained.

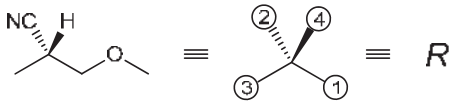
7.53. No. Preparation of this compound via an acetylide ion would require the use of the following tertiary alkyl halide, which will not participate in an S_N2 reaction because of steric crowding.



7.54.
(a) The chiral center in the substrate has the *R* configuration, as shown below.

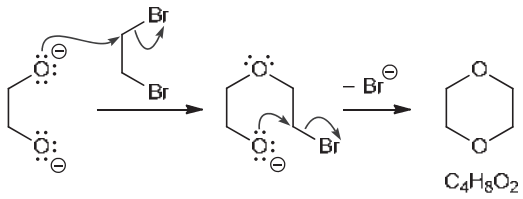


(b) The chiral center in the product has the *R* configuration, as shown below.

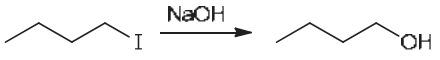


(c) The reaction is an S_N2 process, and it does proceed with inversion of configuration. However, the prioritization scheme changes when the bromo group (#1) is replaced with a cyano group (#2). As a result, the Cahn-Ingold-Prelog system assigns the same configuration to the reactant and the product, even though an inversion has indeed occurred.

7.55. The dianion has two nucleophilic centers, and the electrophile has two electrophilic centers. As such, these compounds can react with each other via two successive S_N2 reactions, as shown below, giving a six-membered ring with the molecular formula $C_4H_8O_2$.



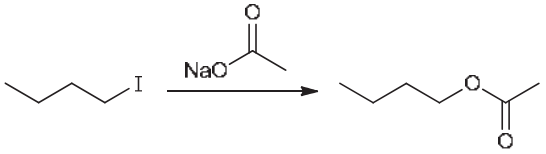
7.56.
(a) The desired compound is a primary alcohol, so we will need to start with the corresponding primary alkyl iodide. The substrate is primary, which dictates that we employ an S_N2 process. Therefore, we must use a strong nucleophile (hydroxide, rather than water).



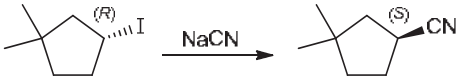
(b) The desired compound can be prepared if we use acetate ($CH_3CO_2^-$) as a nucleophile, and perform an S_N2

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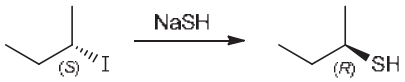
reaction with the corresponding primary alkyl iodide, as shown below.



(c) The desired compound is a nitrile (R–C≡N), so we must use cyanide (N≡C$^-$) as the nucleophile. The product is chiral, and only one enantiomer is desired (not a racemic mixture). This requires an S_N2 process. Since S_N2 processes exhibit inversion of configuration, we will need to start with an alkyl iodide with the *R* configuration in order to produce a nitrile with the *S* configuration.

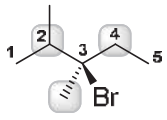


(d) The desired compound is a thiol (RSH), so we must use HS$^-$ as the nucleophile. The product is chiral, and only one enantiomer is desired (not a racemic mixture). This requires an S_N2 process. Since S_N2 processes exhibit inversion of configuration, we will need to start with an alkyl iodide with the *S* configuration in order to produce a thiol with the *R* configuration.



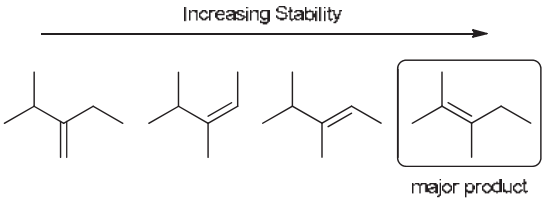
7.57. Each proposed method is a substitution process. In the first method, the nucleophile is a strong nucleophile (methoxide), which favors S_N2, but the substrate is tertiary. S_N2 reactions do not occur at tertiary substrates, so this method will not work (E2 is expected to be the major pathway under these conditions).
The second method should be efficient, because the substrate (methyl iodide) is not sterically hindered, and the nucleophile is a strong nucleophile (*tert*-butoxide). These conditions favor an S_N2 process.

7.58. We begin by drawing the substrate and identifying the β positions (highlighted):

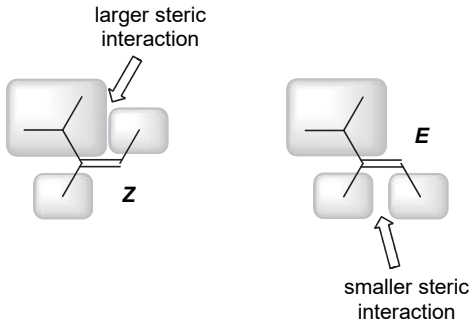


(*R*)-3-Bromo-2,3-dimethylpentane

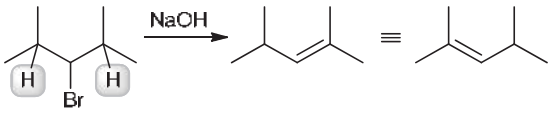
There are three β positions, each of which contains protons, so there are three possible regiochemical outcomes. If the double bond is formed between C3 and C4, then both *cis* and *trans* stereoisomers are possible, giving a total of four alkenes:



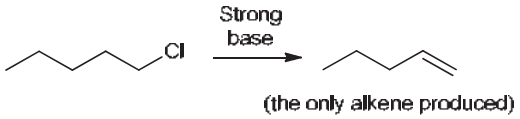
The tetrasubstituted alkene is the most stable, while the disubstituted alkene is the least stable. Among the two trisubstituted alkenes, the *E* isomer is more stable, because it exhibits fewer steric interactions than the *Z* isomer.



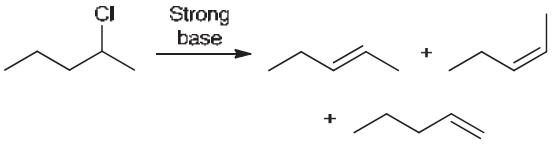
7.59. There are only two β protons to abstract: one at C2 and the other at C4. Abstraction of either proton leads to the same product.



7.60.
(a) There is only one β position, and the resulting alkene is not stereoisomeric, so only one alkene will be produced, as shown:



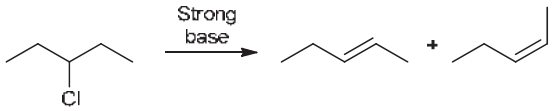
(b) The alkyl halide has two β positions, so there are two possible regiochemical outcomes. The more-substituted alkene can be formed as the E or Z isomer, giving a total of three alkenes, as shown:



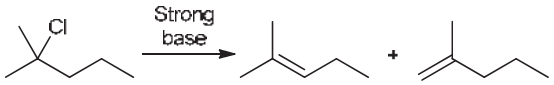
(c) The alkyl halide has two β positions, but they are identical, so there is only one possible regiochemical

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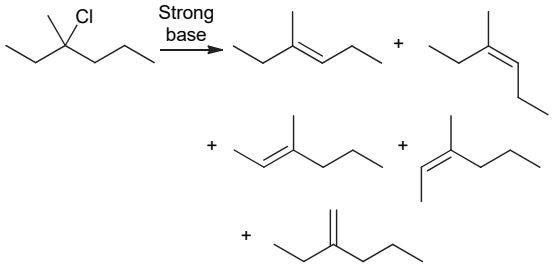
outcome. Two stereoisomers are possible (*cis* and *trans*), giving a total of two alkenes, as shown:



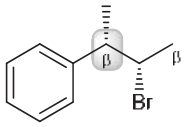
(d) The alkyl halide has three β positions, but two of them are identical. As such, there are two possible regiochemical outcomes, giving the following two alkenes:



(e) There are three different β positions, and each of them has protons, giving rise to three different regiochemical outcomes. For two of these outcomes, both *cis* and *trans* isomers are possible, giving a total of five alkenes, as shown:

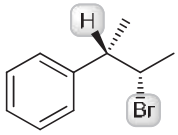


7.61. The substrate is secondary, and the reagent (NaOEt) is both a strong base and a strong nucleophile, so we expect the major product to be obtained via an E2 process. The substrate has two β positions, both of which bear protons, so we must identify the regiochemical outcome of the E2 process. Since the base is not sterically hindered, we expect the Zaitzev product (more substituted alkene). Formation of the Zaitzev product requires deprotonation at the following, highlighted β position:

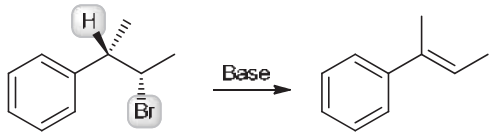


(2*S*,3*S*)-2-bromo-3-phenylbutane

This position bears only one proton, so the reaction is expected to be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we can rotate the central C–C bond so as to place the β proton and the leaving group in the plane of the page. But in this case, that is not necessary, because the β proton and the leaving group are already *anti*-periplanar to one another (one is on a dash and the other is on a wedge):

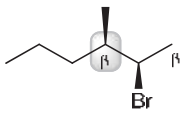


In such a case, it is relatively easy to draw the product, because the carbon skeleton is simply redrawn without the β proton and without the leaving group (with a double instead). Note that a double bond has planar geometry, so the methyl group is on a straight line (not a dash) in the product:

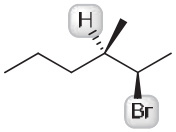


7.62.

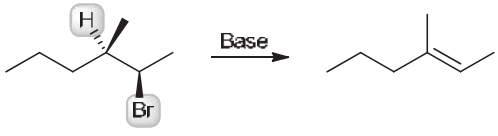
(a) The problem statement indicates that the major product is obtained via an E2 process. The substrate has two β positions, both of which bear protons, so we must identify the regiochemical outcome of the E2 process. Since the base is not sterically hindered, we expect the Zaitzev product (more substituted alkene). Formation of the Zaitzev product requires deprotonation at the following, highlighted β position:



This position bears only one proton, so the reaction is expected to be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we can rotate the central C–C bond so as to place the β proton and the leaving group in the plane of the page. But in this case, that is not necessary, because the β proton and the leaving group are already *anti*-periplanar to one another (one is on a dash and the other is on a wedge):

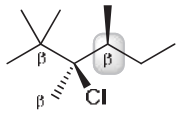


In such a case, it is relatively easy to draw the product, because the carbon skeleton is simply redrawn without the β proton and without the leaving group (with a double instead). Note that a double bond has planar geometry, so the methyl group is on a straight line (not a wedge) in the product:

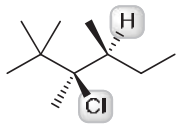


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(b) The problem statement indicates that the major product is obtained via an E2 process. There are three β positions, but only two of them bear protons, so there are two possible regiochemical outcomes. Since the base is not sterically hindered, we expect the Zaitzev product (more substituted alkene). Formation of the Zaitzev product requires deprotonation at the following, highlighted β position:



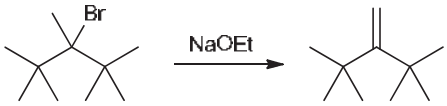
This position bears only one proton, so the reaction is expected to be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we can rotate the central C–C bond so as to place the β proton and the leaving group in the plane of the page. But in this case, that is not necessary, because the β proton and the leaving group are already *anti*-periplanar to one another (one is on a dash and the other is on a wedge):



In such a case, it is relatively easy to draw the product, because the carbon skeleton is simply redrawn without the β proton and without the leaving group (with a double instead). Note that a double bond has planar geometry, so the methyl groups are drawn on straight lines in the product:

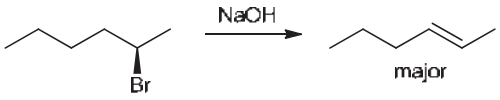


7.63. The reagent is a strong nucleophile and a strong base, so we expect a bimolecular reaction. The substrate is tertiary so only E2 can operate (S_N2 is too sterically hindered to occur). There is only one possible regiochemical outcome for the E2 process, because the other β positions lack protons.

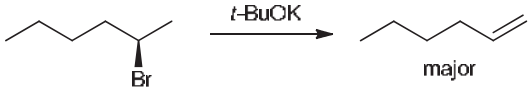


7.64.

(a) The reagent is hydroxide, which is both a strong nucleophile and a strong base. The substrate is secondary, so we expect the E2 pathway to predominate. There are two β positions that bear protons, so there are two possible regiochemical outcomes for an E2 process. The base is not sterically hindered, so the major product will be the more-substituted alkene. Two stereoisomers are possible (*cis* and *trans*), and the *trans* isomer is favored:

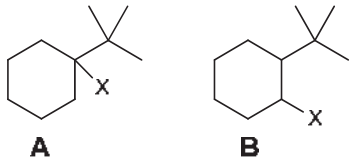


(b) The reagent is *tert*-butoxide, which is a strong, sterically hindered base. The substrate is secondary so we expect E2 processes to predominate (S_N2 is highly disfavored because of steric interactions). There are two β positions that bear protons, so there are two possible regiochemical outcomes. The base is sterically hindered, so the major product will be the less-substituted alkene:



7.65.

(a) Given the location of the π bond, we consider the following two possible alkyl halides as potential starting materials.



Compound **A** has three β positions, but only two of them bear protons, and those two positions are identical. Deprotonation at either location will result in the desired alkene. In contrast, compound **B** has two different β positions that bear protons. Therefore, if compound **B** undergoes an E2 elimination, there will be two possible regiochemical outcomes, so more than one alkene will be formed.

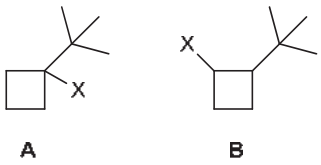
(b) Given the location of the π bond, we consider the following two possible alkyl halides as potential starting materials.



Compound **A** has two β positions, and those two positions are identical. Deprotonation at either location will result in the desired alkene. In contrast, compound **B** has two different β positions that bear protons. Therefore, if compound **B** undergoes an E2 elimination, there will be two possible regiochemical outcomes, so more than one alkene will be formed.

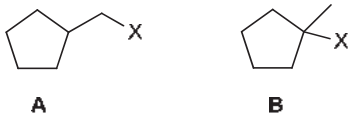
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(c) Given the location of the π bond, we consider the following two possible alkyl halides as potential starting materials.



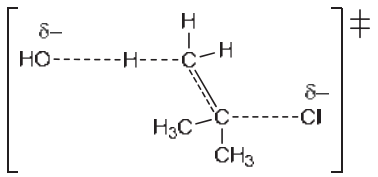
Compound **A** has three β positions, but only two of them bear protons, and those two positions are identical. Deprotonation at either location will result in the desired alkene. In contrast, compound **B** has two different β positions that bear protons. Therefore, if compound **B** undergoes an E2 elimination, there will be two possible regiochemical outcomes, so more than one alkene will be formed.

(d) Given the location of the π bond, we consider the following two possible alkyl halides as potential starting materials.



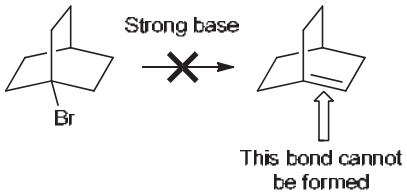
Compound **A** has only one β position, giving rise to only one alkene. In contrast, compound **B** has more than one β position, giving rise to more than one alkene.

7.66. Hydroxide is both a strong nucleophile and a strong base. The substrate is tertiary, so we expect an E2 process only. In the transition state, the hydroxide ion is in the process of removing the proton, the double bond is in the process of forming, and the leaving group is in the process of leaving. We use dotted lines to indicate the bonds that are in the process of being formed or broken, and we use δ– symbols to indicate the distribution of charge. Note that the negative charge is in the process of being transferred from the oxygen atom to the chlorine atom, and the δ– symbols indicate that each location bears partial negative character in the transition state. Finally, brackets are drawn, together with the symbol that indicates that this is a transition state:

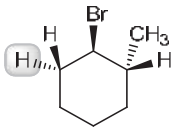


7.67.
(a) The Zaitsev product is desired, so we must a use a base that is not sterically hindered. Sodium ethoxide is the correct choice, because potassium *tert*-butoxide is a sterically hindered base.
(b) The Hofmann product is desired, so a sterically hindered base should be used. The correct choice is potassium *tert*-butoxide.

7.68. π bonds cannot be formed at the bridgehead of a bicyclic compound, unless one of the rings is large (at least eight carbon atoms). This rule is known as Bredt's rule.

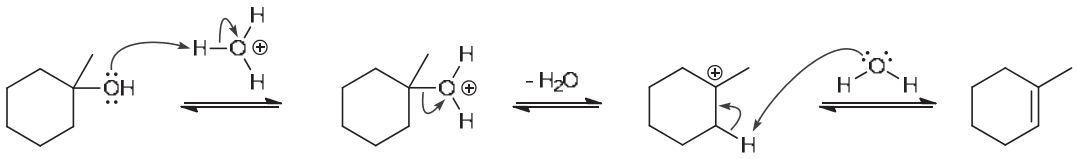


7.69. For substituted cyclohexanes, an E2 reaction will occur if the leaving group and the β proton can achieve antiperiplanarity. In order to achieve this, one must be on a wedge and the other must be on a dash. The leaving group (Br^-) is on a wedge. Therefore, we are looking for a β proton that is on a dash. In this case, there is only one such proton, highlighted below, so there is only one possible regiochemical outcome. In this case, the Hofmann product is formed regardless of the choice of base.

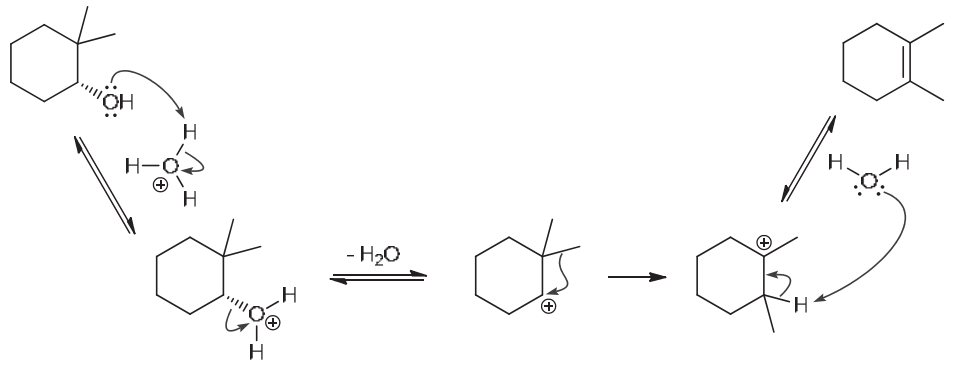


7.70.
(a) In acidic conditions, the OH group is protonated, which converts it from a bad leaving group to a good leaving group. In aqueous sulfuric acid, the acid that is present in solution is H_3O^+ (because of the leveling effect, as explained in Section 3.6), so we use H_3O^+ as the proton source in the first step of the mechanism. The next two steps of the mechanism constitute the core steps of an E1 process: (i) loss of a leaving group (H_2O), which requires one curved arrow, and (ii) proton transfer, which requires two curved arrows, as shown:

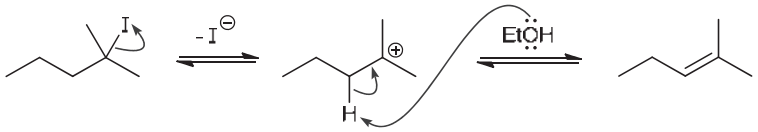
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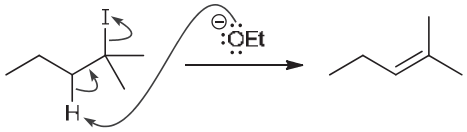
(b) In acidic conditions, the OH group is protonated, which converts it from a bad leaving group to a good leaving group. In aqueous sulfuric acid, the acid that is present in solution is H_3O^+ (because of the leveling effect, as explained in Section 3.6), so we use H_3O^+ as the proton source in the first step of the mechanism. Loss of the leaving group gives a secondary carbocation that can undergo a methyl shift, giving a more stable, tertiary carbocation. Finally, water serves as the base that removes the proton to generate the product:



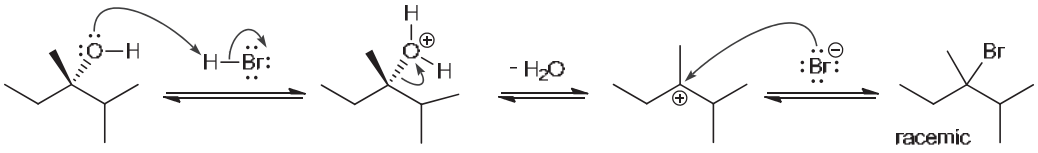
(c) With a weak base (ethanol), the reaction must proceed via an E1 mechanism. The leaving group is iodide. Loss of the leaving group gives a tertiary carbocation that cannot rearrange to become more stable. Finally, ethanol serves as the base that removes the proton to generate the product.



(d) The reagent (ethoxide) is a strong base, and the substrate is tertiary, so the reaction must proceed via an E2 process. Three curved arrows are required. The tail of the first curved arrow is placed on a lone pair of the base (ethoxide) and the head is placed on the proton that is removed. The tail of the second curved arrow is placed on the C–H bond that is breaking, and the head shows formation of the π bond. The third curved arrow shows loss of the leaving group (iodide), as shown here.



7.71. The substrate is an alcohol, so acidic conditions are employed so that the OH group can be protonated, rendering it a better leaving group. Then, loss of a leaving group generates a carbocation, which is then captured by a bromide ion to give the product. Notice that the mechanism is comprised of a proton transfer, followed by the two core steps of an S_N1 process (loss of a leaving group and nucleophilic attack).

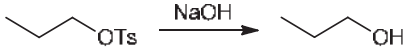


The chiral center is lost when the leaving group leaves to form a carbocation with trigonal planar geometry. The nucleophile can then attack either face of the planar carbocation, leading to a racemic mixture.

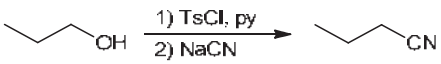
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7.72.

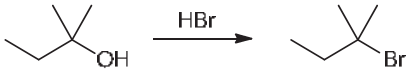
(a) The substrate is primary, so we will need to perform an S_N2 reaction. We must therefore use a strong nucleophile (hydroxide, rather than water).



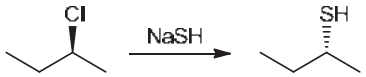
(b) The substrate is a primary alcohol, and the OH group is not a good leaving group. So we first convert the OH group into a better leaving by treating the alcohol with tosyl chloride and pyridine. Then, an S_N2 reaction can be performed (since the substrate is primary) with cyanide as the nucleophile, giving the desired product.



(c) The substrate is tertiary, so we will need to perform an S_N1 reaction. The nucleophile must be bromide, but we cannot simply treat the substrate with bromide, because hydroxide is not a good leaving group. The use of HBr will provide both the nucleophile (bromide) and the proton for converting the bad leaving group to a good leaving group (water).

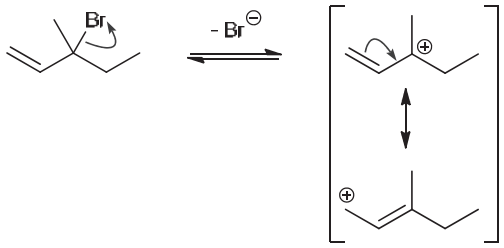


(d) The desired transformation involves inversion of configuration, so we must use an S_N2 process. As such, we want to use a strong nucleophile (HS^-).



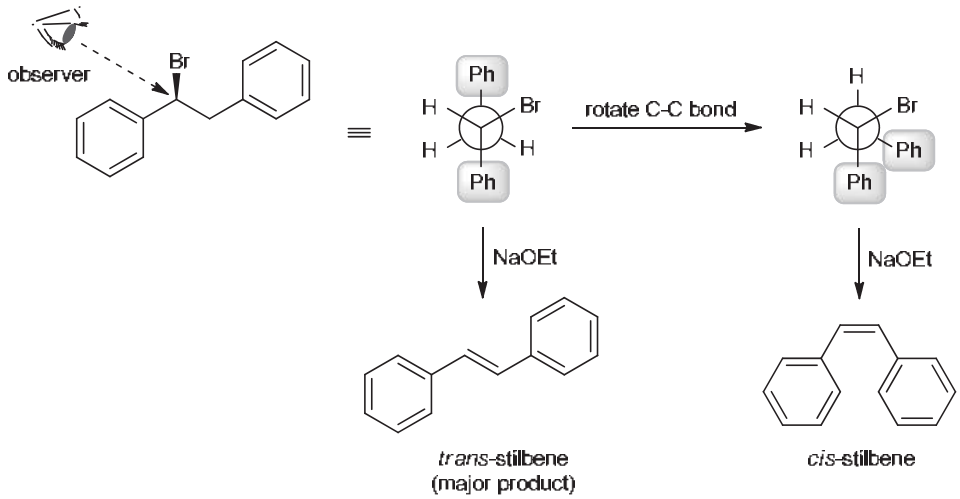
Since the substrate is secondary, the use of a polar aprotic solvent, such as DMSO, will be helpful.

7.73. The first compound is a tertiary substrate. The second compound is a tertiary allylic substrate. The latter will undergo unimolecular solvolysis reactions more rapidly because a tertiary allylic carbocation is more highly stabilized than a tertiary carbocation (because of resonance, shown below).



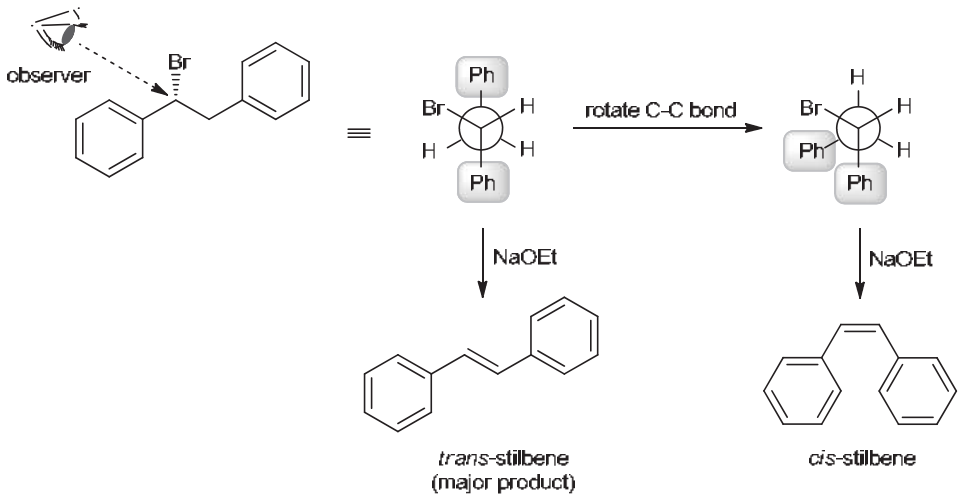
7.74.

(a) We begin by drawing a Newman projection, and we find that the front carbon atom bears the leaving group (bromide), while the back carbon atom bears two β protons, either of which can be removed. The following two Newman projections represent the two conformations in which a β proton is antiperiplanar to the leaving group. In the first Newman projection, the phenyl groups (highlighted) are *anti* to each other, so the transition state is not expected to exhibit a steric interaction between the phenyl groups. In contrast, the second Newman projection exhibits a gauche interaction between the two phenyl groups (highlighted), so the transition state is expected to exhibit a steric interaction. Therefore, *trans*-stilbene is formed at a faster rate than *cis*-stilbene (because formation of the latter involves a higher energy transition state).

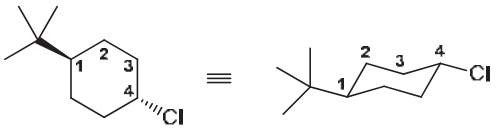


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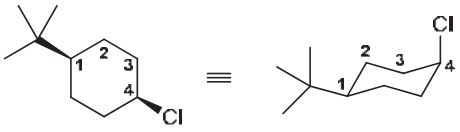
(b) The same argument, as seen in the solution to part (a) of this problem, can be applied again in this case. That is, there are still two β protons that can be abstracted in a β elimination, so both products are still possible, as shown below.



7.75. Because of the bulky *tert*-butyl group, the *trans* isomer is essentially locked in a chair conformation in which the chlorine substituent occupies an equatorial position.



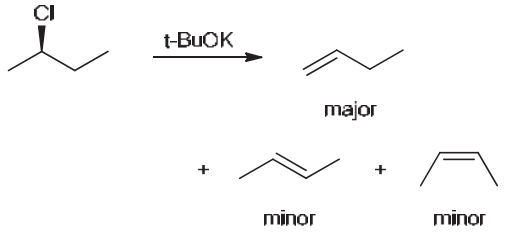
This conformation cannot readily undergo an E2 reaction because the leaving group is not antiperiplanar to a proton. However, the *cis* isomer is locked in a chair conformation in which the chlorine occupies an axial position:



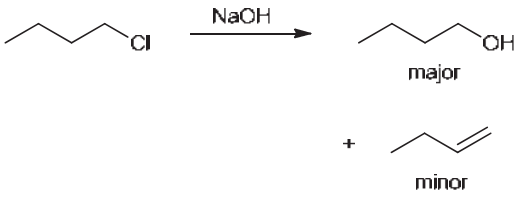
This conformation rapidly undergoes an E2 reaction.

7.76.

(a) The reagent is *tert*-butoxide, which is a strong, sterically hindered base. The substrate is secondary so we expect E2 processes to predominate (S_N2 is highly disfavored because of steric interactions). The major product is the less-substituted alkene. The more-substituted alkene can be formed as either of two stereoisomers (*cis* and *trans*), giving the following three products:

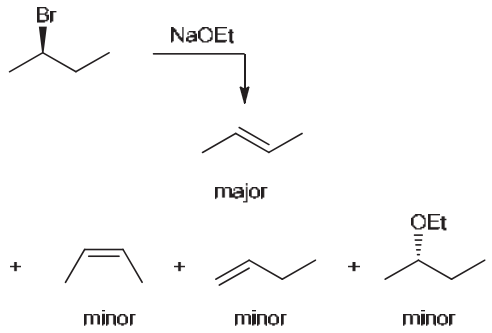


(b) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is primary, so we expect both E2 and S_N2 processes, although S_N2 will be responsible for the major product, as shown here.

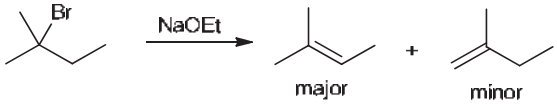


(c) The reagent is ethoxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. Accordingly, the major product is the more substituted alkene, with the *trans* configuration (because the reaction is stereoselective, favoring the *trans* isomer over the *cis* isomer). The minor products include the *cis* isomer, as well as the less-substituted alkene and the S_N2 product (which is formed via inversion of configuration):

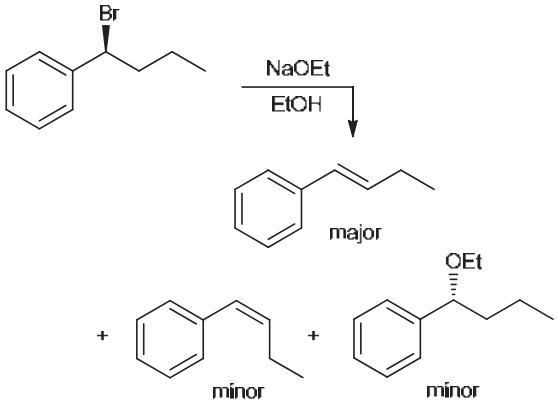
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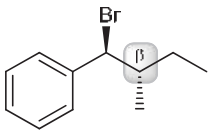
(d) The reagent is ethoxide, which is both a strong base and a strong nucleophile. The substrate is tertiary, so we expect an E2 process. There are three β positions, but two of them are identical, so there are two possible regiochemical outcomes. Since the base is not sterically hindered, we expect that the more-substituted alkene will be the major product, as shown. The less-substituted alkene is the minor product.



(e) The reagent is ethoxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. In this case, there is only one β position that bears protons, so there is only one possible regiochemical outcome. The *trans* isomer is expected to be the major product (because the reaction is stereoselective, favoring the *trans* isomer over the *cis* isomer). The minor products include the *cis* isomer, as well as the S_N2 product (which is formed via inversion of configuration):



(f) The reagent is ethoxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. In this case, there is only one β position that bears a proton,

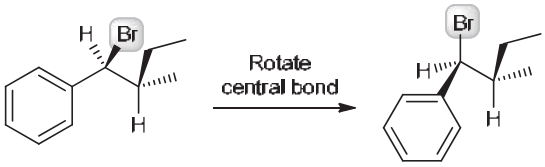


so there is only one possible regiochemical outcome for the E2 process.

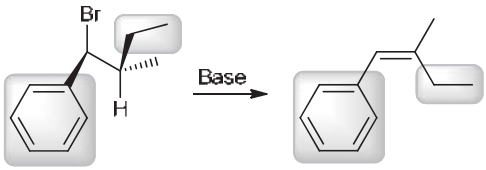
Moreover, since there is only one β proton, the E2 reaction is expected to be stereospecific. That is, only one particular stereoisomeric product will be obtained. To determine which product to expect, we must rotate the central C–C bond so that the β proton is *anti*-periplanar to the leaving group. We will do so in two stages. First, we rotate the central C–C bond in a manner that places the β proton in the plane of the page (rather than on a wedge):



Then, we rotate the central C–C bond again, in a manner that places the leaving group (Br) in the plane of the page:

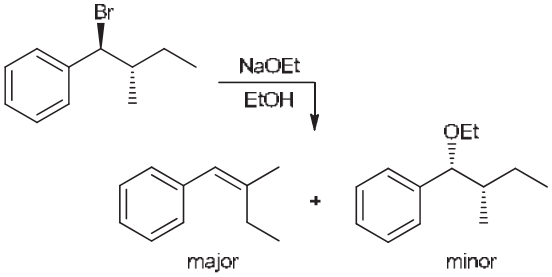


In this conformation, the proton and the leaving group are *anti*-periplanar. To draw the product, use the wedges and dashes as guides. In this case, the phenyl group and the ethyl group are both on wedges, so they will be *cis* to each other in the product:



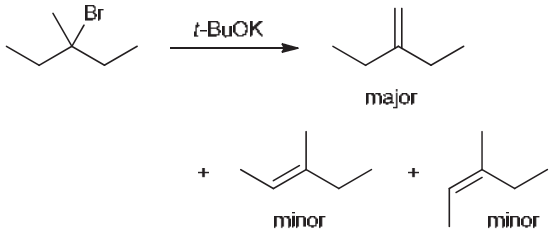
The minor product is formed via an S_N2 process (with inversion of configuration).

In summary, the following products are expected:

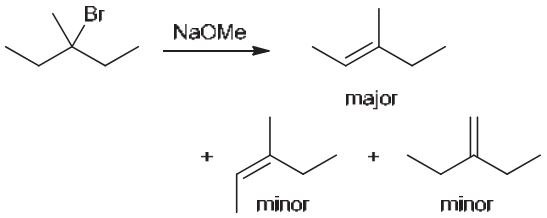


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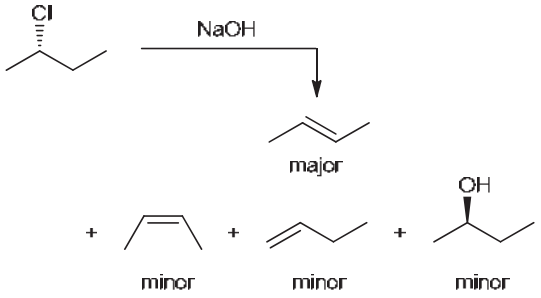
(g) The reagent is *tert*-butoxide, which is both a strong base and a strong nucleophile. The substrate is tertiary so we expect only E2 (no S_N2). The substrate has three β positions that bear protons, but two of them are identical, giving rise to two possible regiochemical outcomes for the E2 process. Since the base (*tert*-butoxide) is sterically hindered, we expect that the major product will be the less-substituted alkene, and the minor product will be the more-substituted alkene. The latter is formed as a mixture of *cis* and *trans* stereoisomers, giving a total of three products, shown here:



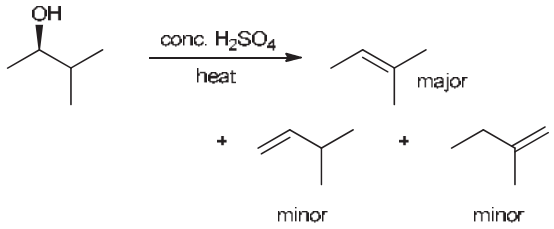
(h) The reagent is methoxide, which is both a strong base and a strong nucleophile. The substrate is tertiary so we expect only E2 (no S_N2). The substrate has three β positions that bear protons, but two of them are identical, giving rise to two possible regiochemical outcomes. Since the base (methoxide) is not sterically hindered, we expect that the major product will be the more-substituted alkene (specifically, the *E* isomer, because the process is stereoselective). The minor products include the *Z* isomer, as well as the less-substituted alkene:



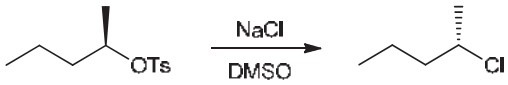
(i) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is secondary so we expect both E2 and S_N2 processes, although E2 will be responsible for the major product. Accordingly, the major product is the more substituted alkene, with the *trans* configuration (because the reaction is stereoselective, favoring the *trans* isomer over the *cis* isomer). The minor products include the *cis* isomer, as well as the less-substituted alkene and the S_N2 product (which is formed via inversion of configuration):



(j) Treatment of an alcohol with concentrated sulfuric acid gives an E1 process to afford an alkene (or a mixture of alkenes). In this case, there are two different β positions that bear protons, so there are two possible regiochemical outcomes. The more-substituted alkene is the major product, and the less-substituted alkene is a minor product. Another minor product can result if the initially formed secondary carbocation undergoes a rearrangement to give a tertiary carbocation, followed by deprotonation to give a disubstituted alkene, shown below:

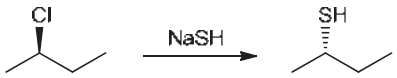


(k) The reagent is chloride, which functions as a nucleophile, so we expect a substitution reaction. The substrate is secondary and the solvent is polar aprotic, indicating an S_N2 process. As such, we expect inversion of configuration, as shown:

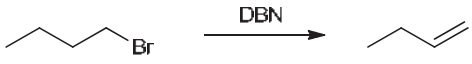


7.77.

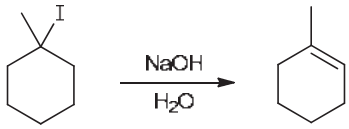
(a) The reagent is HS^-, which is a strong nucleophile, and the substrate is secondary, so we expect an S_N2 process, with inversion of configuration:



(b) The reagent is DBN, which is a strong base, so we expect an E2 process. There is only one β position, so only one regiochemical outcome is possible.



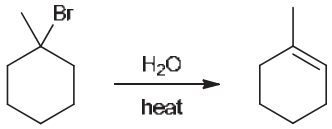
(c) The reagent is hydroxide, which is both a strong base and a strong nucleophile. The substrate is tertiary, so we expect an E2 process. There are three β positions, but two of them are identical, so there are two possible regiochemical outcomes. The more-substituted alkene is the major product, as shown.



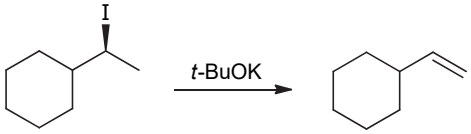
(d) The reagent is water, which is both a weak base and a weak nucleophile. The substrate is tertiary, so we

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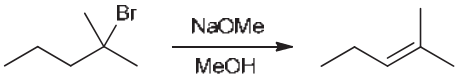
expect E1 and S_N1 processes. One of the alkene products is trisubstituted, so we expect the E1 pathway to predominate. For the E1 pathway, two regiochemical outcomes are possible. The base is not sterically hindered, so the more-substituted alkene is the major product, as shown:



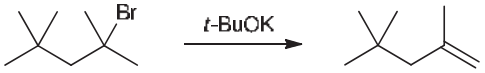
(e) The reagent is *tert*-butoxide, which is a strong, sterically hindered base. The substrate is secondary so we expect E2 processes to predominate (S_N2 is highly disfavored because of steric interactions). There are two β positions bearing protons, so two regiochemical outcomes are possible. Since the base is sterically hindered, the major product is the less-substituted alkene:



(f) The reagent is methoxide, which is both a strong base and a strong nucleophile. The substrate is tertiary, so we expect an E2 process. There are three β positions, but two of them are identical, so there are two possible regiochemical outcomes. The more-substituted alkene is the major product, as shown.



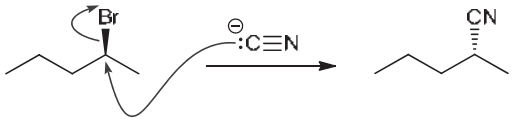
(g) The reagent is *tert*-butoxide, which is a strong, sterically hindered base. The substrate is tertiary, so we expect an E2 process. There are three β positions, but two of them are identical, so there are two possible regiochemical outcomes. Since the base is sterically hindered, we expect that the less-substituted alkene will be the major product, as shown.



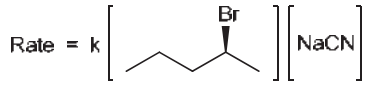
7.78.

(a) A polar aprotic solvent is used, and the reaction occurs with inversion of configuration. These factors indicate an S_N2 process.

In an S_N2 process, nucleophilic attack and loss of the leaving group occur in a concerted fashion (in one step), as shown below.

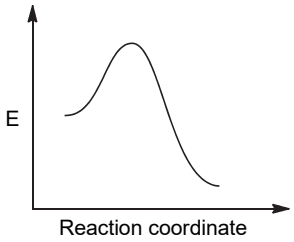


(b) Since the reaction is an S_N2 process, we expect a second-order rate equation that is linearly dependent on both the concentration of the substrate and the concentration of the nucleophile.



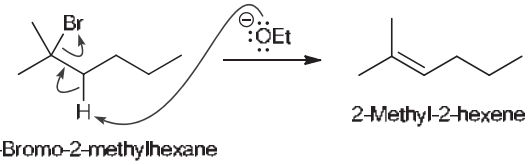
(c) The rate of an S_N2 reaction is linearly dependent on the concentration of the nucleophile. As such, if the concentration of the nucleophile (cyanide) is doubled, the reaction rate is expected to double.

(d) As seen in the solution to part (a) of this problem, the reaction occurs via an S_N2 process, which is comprised of one concerted step (in which the nucleophile attacks with simultaneous loss of the leaving group). As such, the energy diagram will have only one maximum (only one hump).



7.79.

(a) The reagent (ethoxide) is a strong base, and the substrate is tertiary, so the reaction must proceed via an E2 process. Three curved arrows are required. The tail of the first curved arrow is placed on a lone pair of the base (ethoxide) and the head is placed on the proton that is removed. The tail of the second curved arrow is placed on the C–H bond that is breaking, and the head shows formation of the π bond. The third curved arrow shows loss of the leaving group (bromide), as shown here.



(b) For an E2 process, the rate is dependent on the concentrations of the substrate and the base:

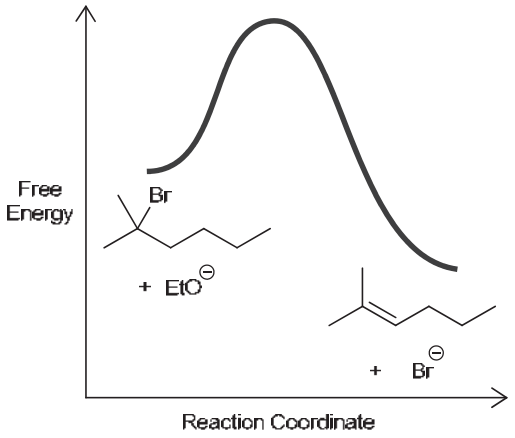
$$\text{Rate} = k\,[\text{substrate}]\,[\text{base}]$$

(c) The rate of an E2 reaction is linearly dependent on the concentration of the base. As such, if the concentration of base is doubled, the rate will be doubled.

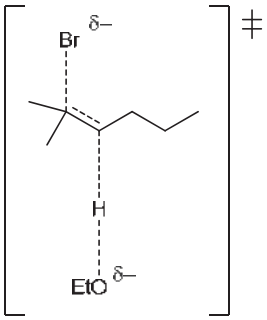
(d) The mechanism has one step, so the energy diagram must have only one maximum (only one hump). The

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products are lower in energy than the reactants, because bromide is more stable than ethoxide.

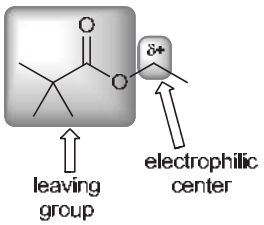


(e) In the transition state, the ethoxide ion is in the process of removing the proton, the double bond is in the process of forming, and the leaving group (bromide) is in the process of leaving. We use dotted lines to indicate the bonds that are in the process of being formed or broken, and we use δ– symbols to indicate the distribution of charge. Note that the negative charge is in the process of being transferred from the oxygen atom to the bromine atom, and the δ– symbols indicate that each location bears partial negative character in the transition state. Finally, brackets are drawn, together with the symbol that indicates that this is a transition state:

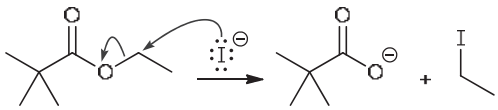


7.80.

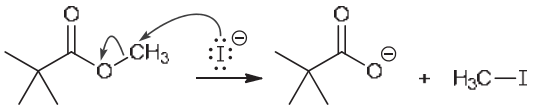
(a) The nucleophile is iodide and the solvent is a polar aprotic solvent (DMF), indicating an S_N2 reaction. The substrate (which is primary) has an electrophilic center shown here.



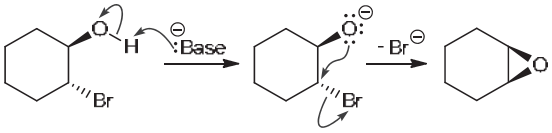
Iodide attacks this electrophilic center in an S_N2 process, ejecting the leaving group (highlighted above), as shown here:



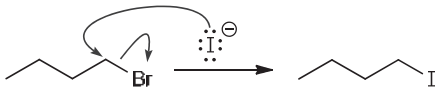
(b) This reaction occurs via an S_N2 process. As such, the rate of the reaction is highly sensitive to the nature of the substrate. The reaction will be faster in this case, because the methyl ester is less sterically hindered than the ethyl ester.



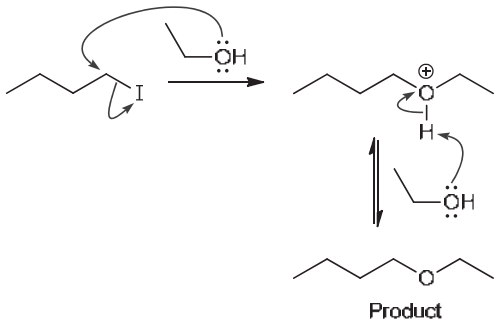
7.81. A strong base will remove the most acidic proton in the starting alcohol (the proton of the OH group), giving an anion that contains both a nucleophilic center and an electrophilic center, allowing for an intramolecular S_N2-type process (bromide is ejected as a leaving group), as shown here.



7.82. Iodide is a much stronger nucleophile than ethanol, so we expect the former to attack butyl bromide (a primary substrate) in an S_N2 reaction to give butyl iodide.

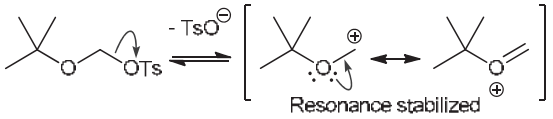


As a result of this initial rapid reaction, the concentration of iodide quickly decreases. Then, the slow rise in concentration of iodide indicates that another nucleophile is slowly ejecting the iodide ions. Indeed, there is a weak nucleophile present (ethanol). In the presence of ethanol, a slow S_N2 process can occur in which butyl iodide functions as the substrate (iodide is an excellent leaving group) and ethanol functions as the nucleophile. The resulting oxonium ion is then deprotonated (by ethanol, this time functioning as a base), giving the product shown below, which is an ether.

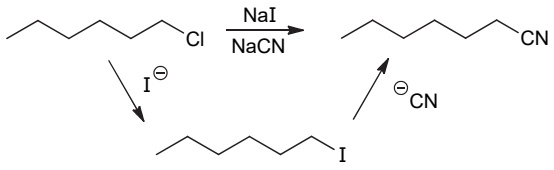


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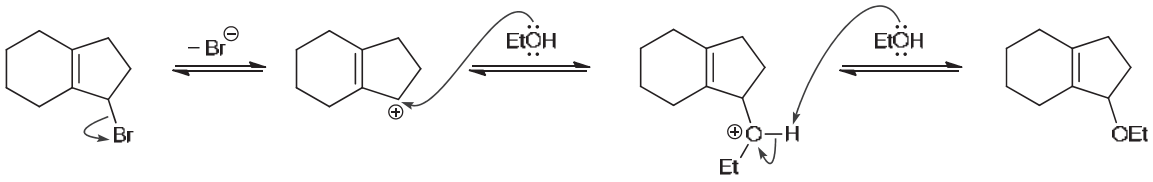
7.83.
Primary substrates generally do not readily undergo S_N1 reactions, because primary carbocations are too high in energy to form at an appreciable rate. However, in this case, loss of the leaving group generates a resonance-stabilized cation. Because this intermediate is stabilized, it can form at an appreciable rate, allowing an S_N1 process to successfully compete, despite the fact that the substrate is primary.



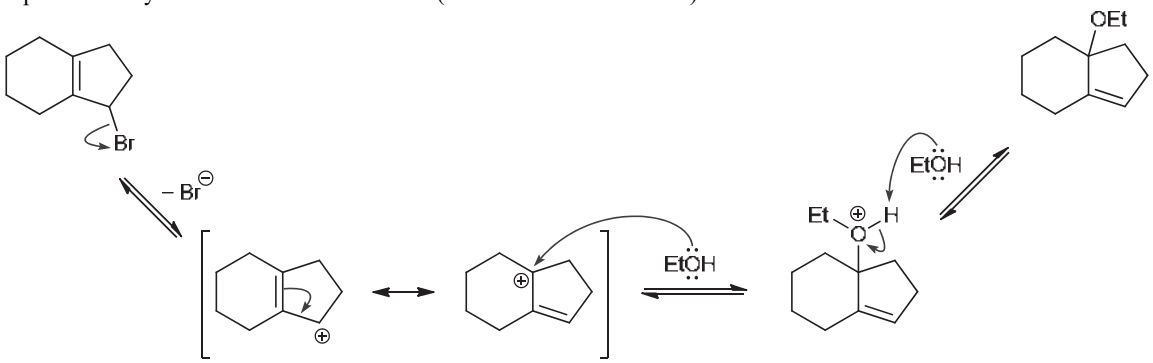
7.84.
Iodide is a very strong nucleophile (because it is highly polarizable), and it is also an excellent leaving group (because it is a very weak base). As such, iodide will function as a nucleophile to displace the chloride ion. Once installed, the iodide group is a better leaving group than chloride, thereby increasing the rate of the reaction.



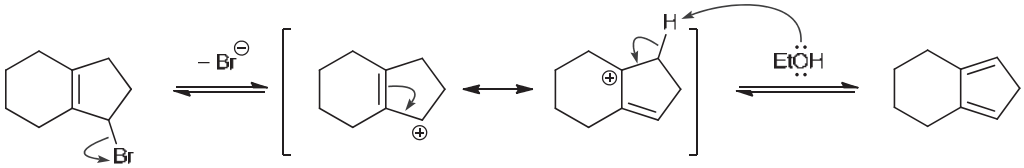
7.85. The conditions (no strong nucleophile or strong base; polar protic solvent) favor unimolecular processes (E1 and S_N1), so we must explain the formation of the products with those mechanisms.
Formation of the first product can be explained with the following S_N1 mechanism, in which the first step is loss of the leaving group to generate a resonance-stabilized cation (resonance structures are not shown here). This carbocation is then captured by ethanol, which functions as a nucleophile; and the resulting oxonium ion is then deprotonated by another molecule of ethanol, which functions as a base:



Formation of the second product can be explained via a similar mechanism (also S_N1). The first step is loss of the leaving group to generate a resonance-stabilized cation (this time, the resonance structures are drawn). This carbocation is then captured by ethanol (which functions as a nucleophile), and the resulting oxonium ion is then deprotonated by another molecule of ethanol (which functions as a base):

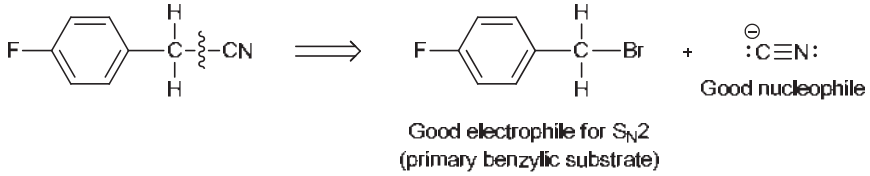


Finally, the third product is formed via an E1 process. In the first step of the mechanism, loss of the leaving group generates a resonance-stabilized cation. Then, in the second (and final) step, ethanol functions as a base and removes a proton, giving the product.



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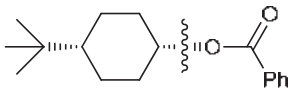
7.86. In this target molecule, the only bond we know how to make (based on reactions covered thus far) is the one next to the cyano group.



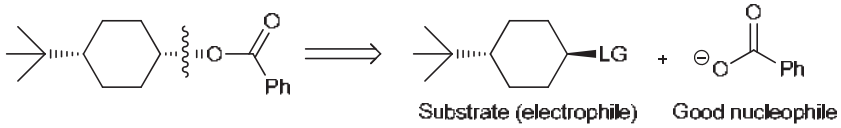
Cyanide is a good nucleophile, and a primary substrate is ideal for an S_N2 process, so these starting materials would lead to a good synthesis of 4-fluorophenylacetonitrile. The forward synthesis is shown here.



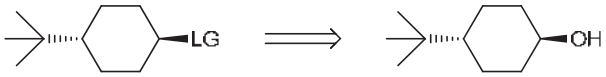
7.87. When comparing the starting compound to the target molecule, we note that the ester group is new, and the configuration of the adjacent chiral center has been inverted. The latter observation indicates that an S_N2 process must be involved. So our retrosynthesis should focus on disconnection of the following bond:



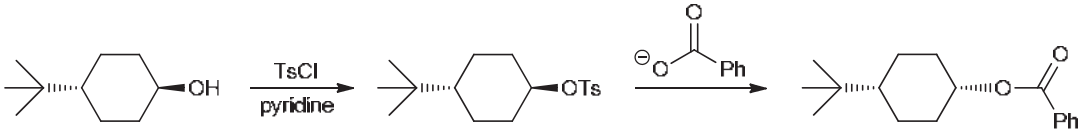
We need a substrate with the opposite configuration (the leaving group should be on a wedge, rather than a dash), as shown here:



This substrate must be made from the starting alcohol:

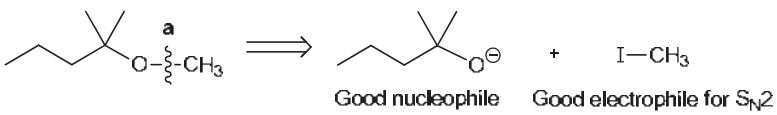


The best way to convert the OH group into a leaving group and retain its stereochemistry is with the use of tosyl chloride to make the tosylate. This tosylate can then function as the substrate in an S_N2 reaction. The forward synthesis is shown here:



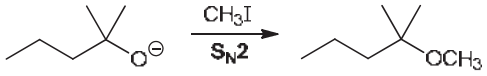
The use of a secondary substrate (for the S_N2 process) is reasonable in this case, since the nucleophile involved is not a strong base (the resonance-stabilized carboxylate anion is the conjugate base of a relatively acidic carboxylic acid), so there is little competition with E2. Backside attack of the nucleophile results in inversion of stereochemistry to give the desired target molecule.

7.88. Disconnection of bond **a** is a logical retrosynthesis that leads to a familiar nucleophile (an alkoxide ion) and a methyl substrate (ideal for S_N2):

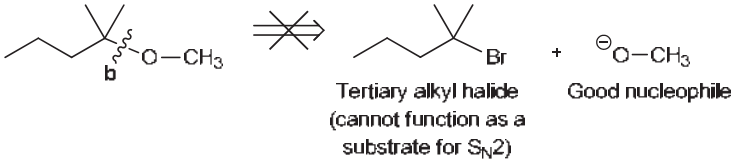


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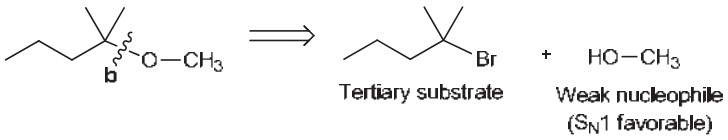
Note that methyl iodide is chosen, rather than methyl bromide or methyl chloride, because methyl iodide is a liquid at room temperature (while methyl bromide and methyl chloride are gases at room temperature, making them more difficult to work with). The forward synthesis is shown here:



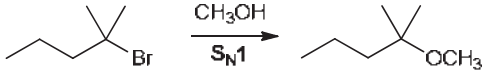
A similar disconnection of bond **b** reveals that a tertiary substrate would be required, and we have seen that S_N2 processes do not occur with tertiary substrates.



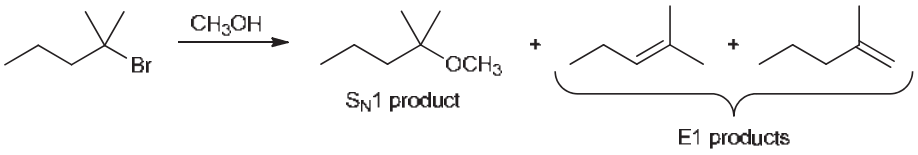
An S_N2 process won't work here. Instead, the alkoxide ion is expected to function as a base, giving E2 products. This issue can be overcome if we employ an S_N1 process instead, by using a weak nucleophile (an alcohol).



This S_N1 process would involve a tertiary carbocation (which would not rearrange), so it is expected to afford the target molecule, as shown:

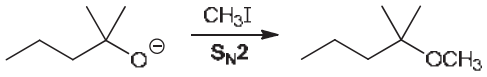


However, this process (solvolysis) is likely to produce competing E1 products, as well:



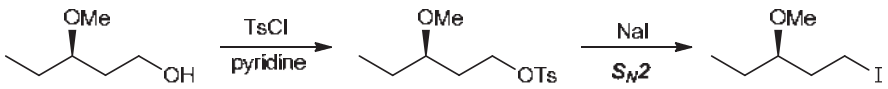
Since one of the E1 products is a trisubstituted alkene, we might even expect for that E1 product to predominate. As such, this synthesis would not be efficient, because it may not provide the desired S_N1 product as the major product.

In summary, our retrosynthetic analysis has uncovered two possible synthetic routes: an S_N2 process and an S_N1 process. The S_N2 process is expected to be more efficient:



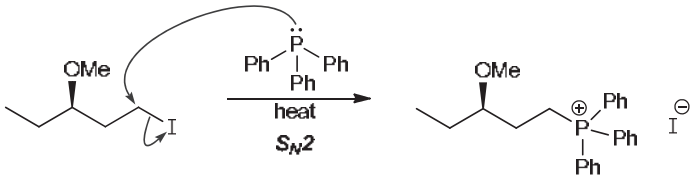
7.89.

(a) The first reaction (with TsCl and pyridine) transforms the OH group into a good leaving group (a tosylate) that undergoes an S_N2 reaction with sodium iodide. The net result of these two steps is the conversion of an alcohol to an alkyl iodide.



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In the final step of the process, the primary alkyl iodide is then treated with triphenylphosphine (PPh_3), which functions as a nucleophile, giving another S_N2 reaction, to afford a phosphonium salt.

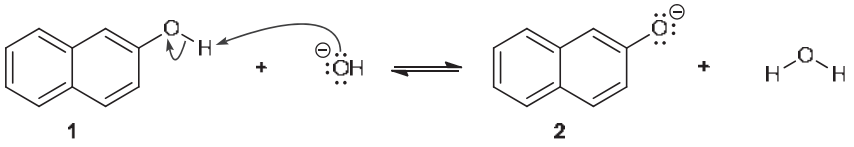


The factors favoring this step are the leaving group and the nucleophile. Let's explore each separately. The leaving group is one of the best leaving groups that could be used (because HI is one of the strongest acids, pK_a = -10). The nucleophile is PPh_3. Why is it such a powerful nucleophile? Phosphorus is in the same column of the periodic table as nitrogen (5A), but it is in the third row, rather than the second row. As such, phosphorus is larger and more polarizable than nitrogen, and therefore more strongly nucleophilic. This argument is similar to the argument we saw in the text when we compared sulfur and oxygen. Recall that sulfur is larger and more polarizable than oxygen, and therefore, sulfur is very strongly nucleophilic (even if it lacks a negative charge). Similarly, PPh_3 is a powerful nucleophile, even though it lacks a negative charge.

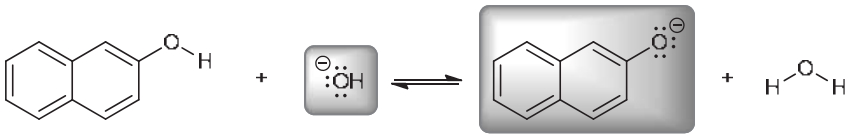
(b) In the second step, one leaving group (tosylate) is replaced with another (iodide). Iodide is a better leaving group than tosylate, which renders step 3 more favorable.

7.90.

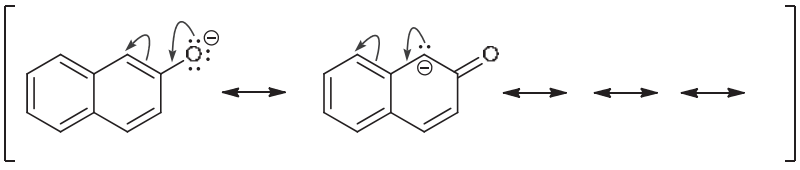
(a) The proton connected to the oxygen atom is the most acidic proton in compound **1**, so it is removed upon treatment with a strong base.



We can justify that hydroxide is a suitable base to achieve the conversion of **1** to **2**, with either a qualitative argument (based on structural comparisons) or with a quantitative argument (based on pK_a values). Let's start with the qualitative argument. Compare the structures of the anions on either side of the reaction.



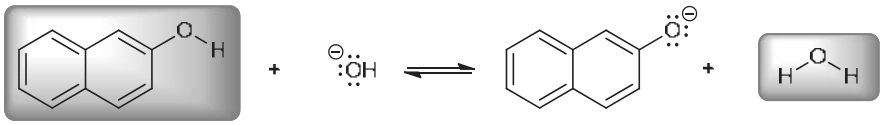
The negative charge in a hydroxide ion is localized on one oxygen atom, while the negative charge in the other anion is delocalized over one oxygen atom and five carbon atoms. As such, we expect the latter anion to be more stabilized (via resonance delocalization).



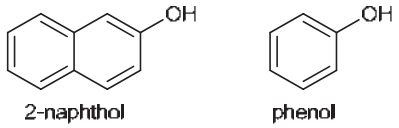
The equilibrium will favor formation of the more stable anion. That is, hydroxide is a sufficiently strong base, because it is stronger (less stable) than anion **2**.

Alternatively, we can use a quantitative argument to justify why hydroxide is an appropriate base to use in this case. Specifically, we compare the pK_a values of the acids on either side of the equilibrium.

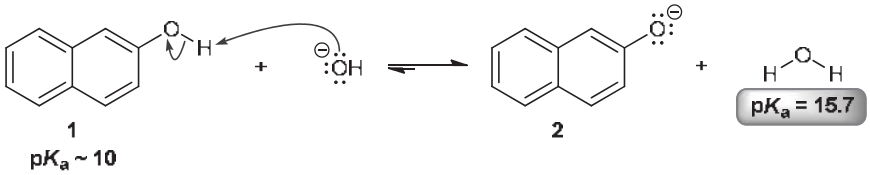
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We know that the pK_a of water is 15.7, but we need a way to assess the pK_a of compound **1**. When we explore Table 3.1, we see that phenol is similar in structure, and has a pK_a of 9.9.

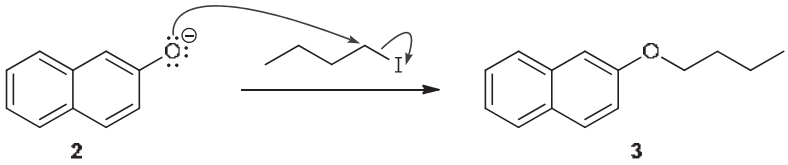


We expect the pK_a of compound **1** (2-naphthol) to be more similar to the pK_a of phenol (than to the pK_a of water). Therefore, we expect the pK_a of compound **1** to be lower than the pK_a of water, and the equilibrium will favor formation of the weaker acid.

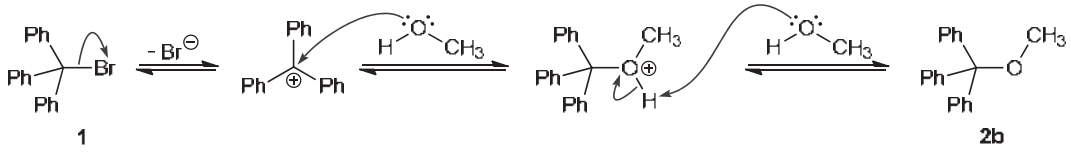


As such, hydroxide is a suitable base to favor deprotonation of compound **1**.

(b) Anion **2** functions as a nucleophile and attacks butyl iodide in an S_N2 reaction, giving compound **3**.

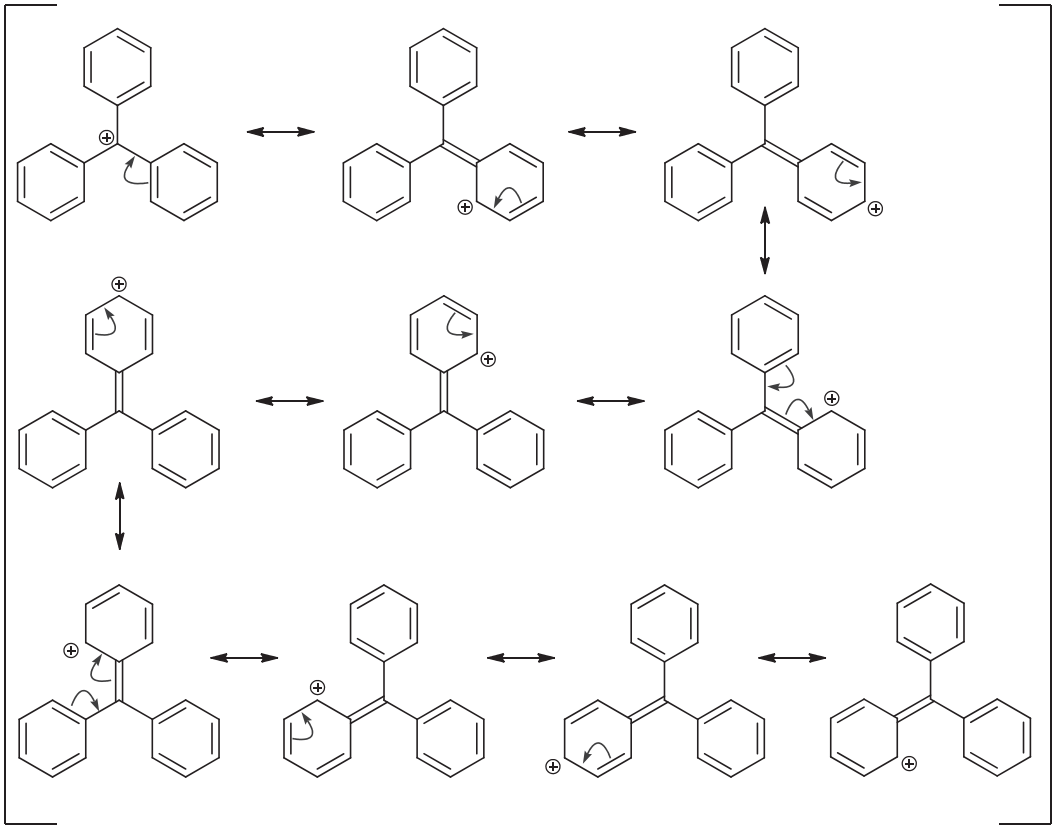


7.91.
(a) The substrate is tertiary, so we expect the reaction to proceed exclusively through an S_N1 pathway (steric crowding prevents S_N2 from competing). The first step involves loss of a bromide to give a carbocation, which is then captured by the nucleophile to produce an oxonium ion. Deprotonation of the oxonium ion gives the product, **2b**.



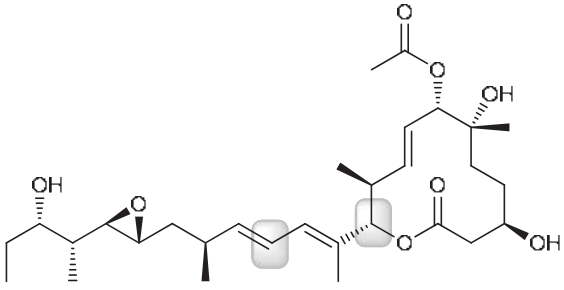
(b) When bromide leaves, the resulting carbocation is benzylic to three different aromatic rings. As such, it is highly stabilized because the positive charge is delocalized over 10 carbon atoms via resonance (as shown). Since this intermediate is so stabilized (low in energy), we can infer that the transition state for formation of the carbocation will also be very low in energy (because any developing charge in the transition state is stabilized by resonance, just as seen in the intermediate carbocation). Since the transition state is low in energy, formation of the carbocation (which is the rate-determining step) will occur very rapidly.

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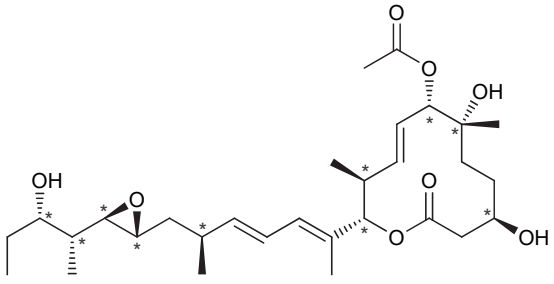


7.92.

(a) The trisubstituted π bond has the *E* configuration. The higher priority groups (highlighted below) are on opposite sides (*E*).

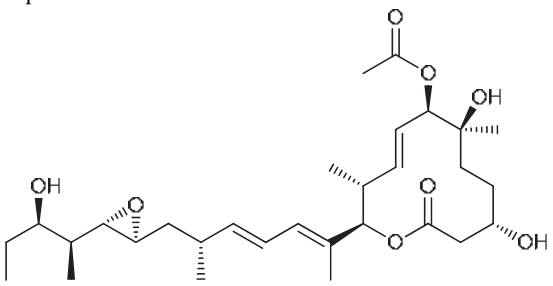


(b) There are 10 chiral centers (indicated below, each of which can be *R* or *S*), and there are three C=C π bonds (each of which can be *E* or *Z*). Thus, the number of possible stereoisomers should be $2^{13} = 8192$.

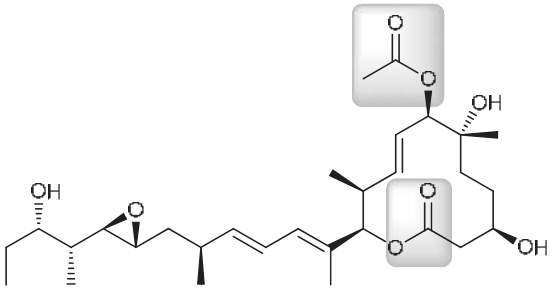


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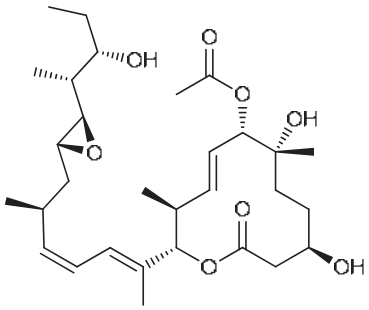
(c) The enantiomer of pladienolide B has the opposite configuration at each and every chiral center, but the configuration of each C=C π bond remains the same as in pladienolide B.



(d) There are two ester groups (highlighted below) in pladienolide B. The following diastereomer is the result of inverting the configuration of the two chiral centers adjacent to the ester groups.

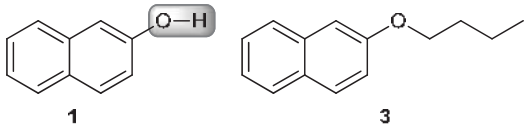


(e) The disubstituted π bond has the *E* configuration. The following is a diastereomer in which the disubstituted π bond has the *Z* configuration.



7.93

(a) If compound **3** was properly dried, then it could be distinguished from compound **1** with IR spectroscopy. Specifically, compound **1** has an O-H bond, so we expect a broad signal in the range 3200-3600 cm^{-1}, while compound **3** lacks such a bond, so its IR spectrum should lack a signal in the same range.

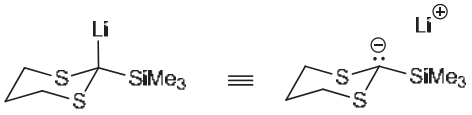


1 **3**

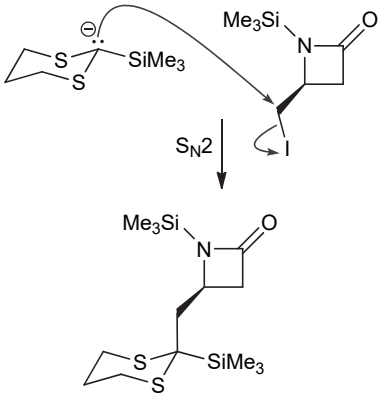
In this way, we can verify whether the reaction has gone to completion, by looking for a signal in the range 3200-3600 cm^{-1} in the IR spectrum of the product. The absence of this signal verifies completion of the reaction. Since we are looking for the absence of an OH stretching signal, it is essential that the product is dried. Otherwise, the water molecules would give a signal exactly in the region of interest (because water has O-H bonds). This would prevent from us from being able to determine whether the reaction had gone to completion.

(b) The conversion of **1** to **2a** involves introduction of an OH group, which should produce a broad, easily detectable signal in the range 3200-3600 cm^{-1}. Therefore, by taking an IR spectrum of the product, we can verify formation of **2a** by looking for a broad signal in the range 3200-3600 cm^{-1}. In contrast, **2b** and **2c** do not have an OH group. As such, it will be difficult to distinguish the diagnostic regions of the IR spectra of compounds **1**, **2b**, and **2c**. The utility of IR in spectroscopy in these cases must rely on analysis of the fingerprint region (C-Br stretch vs. C-O stretch), although fingerprint regions are often more difficult to interpret (except in the hands of a trained expert). Therefore, IR spectroscopy is not the best tool for verifying the conversion of **1** to either **2b** or **2c**. NMR spectroscopy would be a better tool for confirming completion of those reactions.

7.94. Compound **2** is the nucleophile in this S_N2 reaction. To see why, recall from Chapter 1 that a C-Li bond can be viewed as an ionic bond, in which the carbon atom has a lone pair and negative charge.

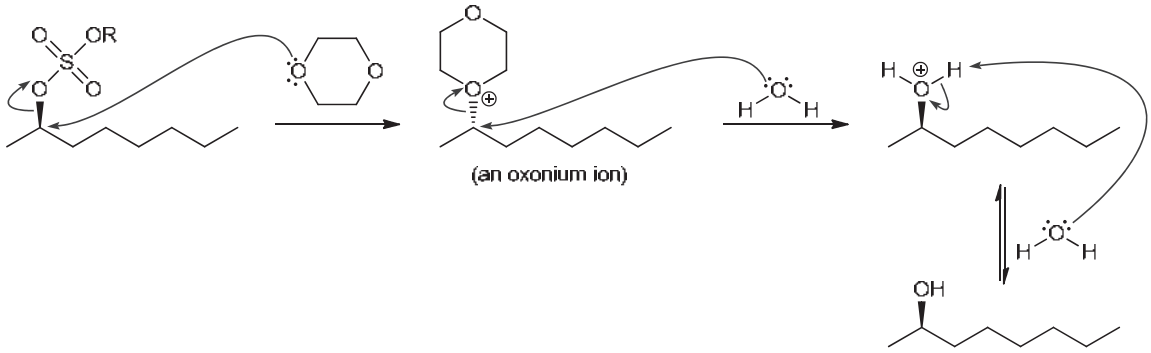


This compound is indeed a very strong nucleophile, and it attacks the alkyl halide in an S_N2 process, as shown here:



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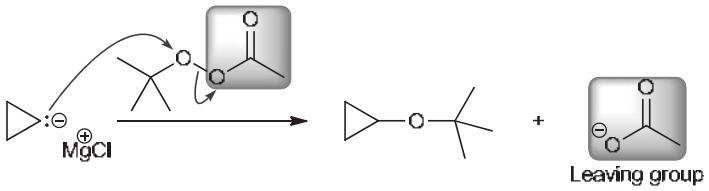
7.95. As described in the problem statement, dioxane can function as a nucleophile and attack 2-octyl sulfonate in an S_N2 reaction, to form an inverted intermediate that can then undergo another S_N2 reaction with water. The product is 2-octanol with an overall retention of stereochemistry, due to two successive S_N2 steps taking place.



Since this process increases in frequency as the concentration of dioxane increases, the optical purity of the resulting 2-octanol decreases as dioxane's concentration is increased.

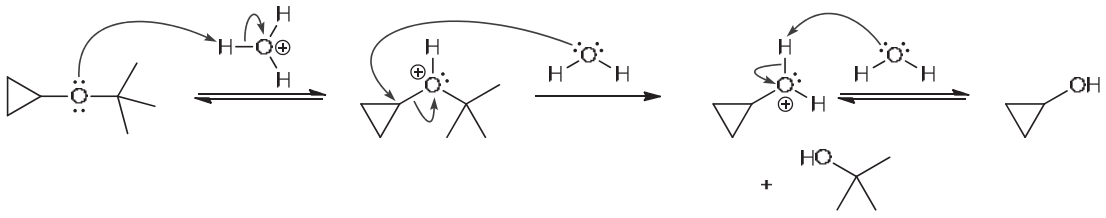
7.96.

(a) Compound **2** functions as a nucleophile, which means that the lone pair on the carbon atom will attack the substrate. Based on the structure of the product, we can deduce that the oxygen atom (next to the *tert*-butyl group) is attacked by the nucleophile. The leaving group is a resonance-stabilized anion (an acetate ion).



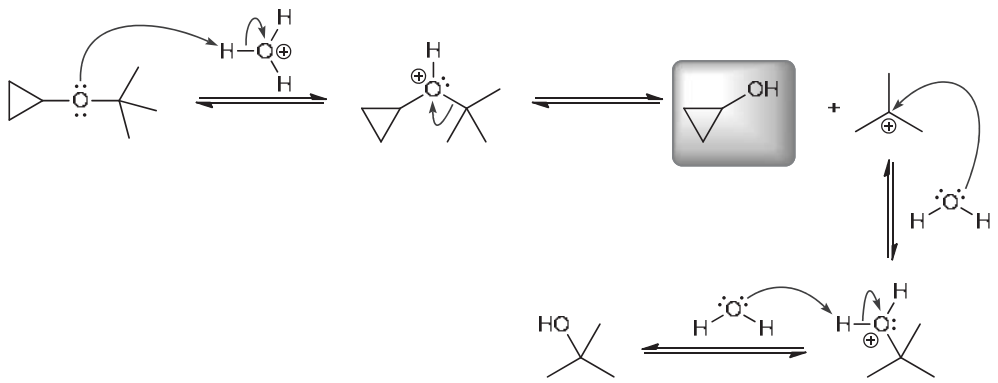
(b) The reverse process would involve an acetate ion functioning as a nucleophile and the expulsion of **2** as a leaving group. That is extremely unlikely to occur, because **2** is not a good leaving group. It is a very strong base, because its conjugate acid is an alkane, which is an extremely weak acid (compare pK_a values of alkanes with other organic compounds). Since **2** is not a weak base, it cannot function as a leaving group. And as a result, the reaction is irreversible.

(c) Since an alkoxide group (RO^-) cannot function as a leaving group, it must be protonated first, in either pathway. The S_N2 pathway involves a *simultaneous* nucleophilic attack and loss of a leaving group. This step is then followed by deprotonation to give the product. As expected for an S_N2 process, the nucleophilic attack occurs at the secondary position, rather than the sterically crowded tertiary position.



The S_N1 pathway also begins with protonation of the oxygen atom to produce a better leaving group. But in this pathway, the leaving group first leaves to generate a carbocation, and only then does the nucleophile attack. As expected for an S_N1 process, loss of the leaving group generates a tertiary carbocation, rather than a secondary carbocation. In this case, the leaving group is the product (cyclopropanol).

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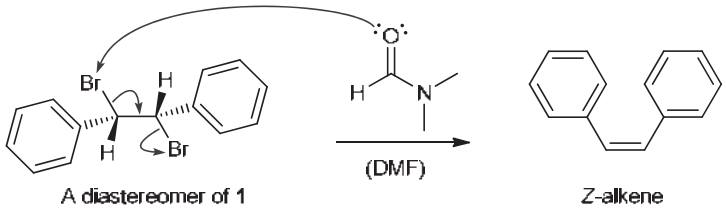


(d) As seen in both the S_N1 and S_N2 pathways, the by-product is *tert*-butanol.



7.97.

(a) The proposed mechanism is a concerted process that very closely resembles an E2 process. As such, we would expect this process to occur when the two bromine atoms are *anti*-periplanar to one another, as shown in the problem statement. If we perform the same reaction with a diastereomer of **1**, we would expect a *Z*-alkene:

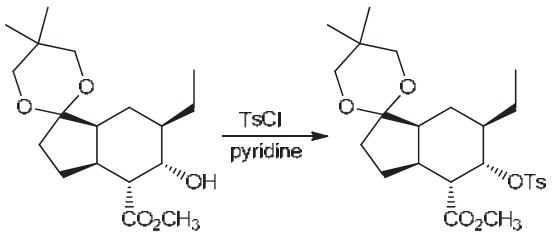


But none of the *Z*-alkene is formed. The *E* isomer is obtained exclusively, which means that the preference for the *E*-isomer is not dependent on the configuration of the starting dibromide. The *E*-alkene is obtained either from **1** or from a diastereomer of **1**. As such, the reaction does not appear to have a requirement for *anti*-periplanarity. This is evidence against a concerted mechanism.

(b) The reaction is not considered to be stereospecific, because the preference for the *E* isomer is not dependent on the configuration of the starting dibromide. The reaction is stereoselective, because one configuration of the alkene product (the *E* isomer) is favored over the other.

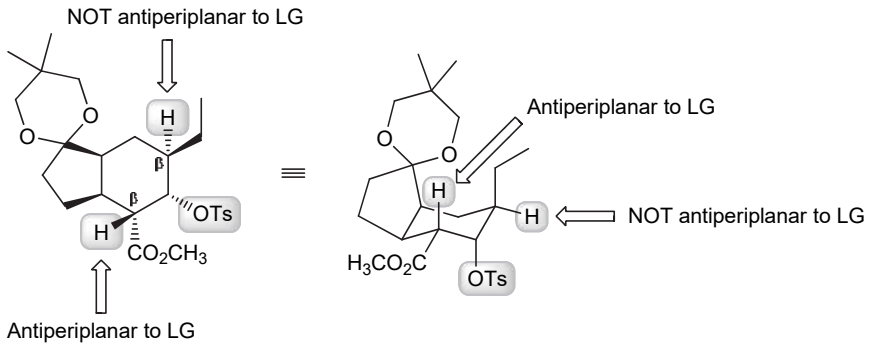
7.98.

In the first reaction, the OH group is converted into a better leaving group. Notice that the configuration of the center bearing the OH group does NOT change in the process (it remains a dash):

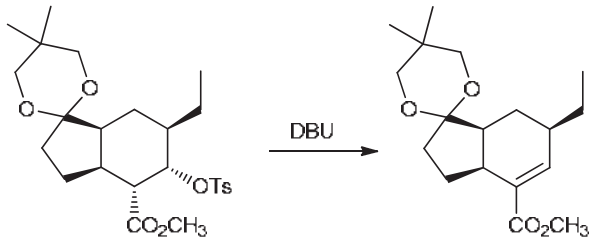


Then, the second reaction employs DBU which is a strong base that generally does not function as a nucleophile. We therefore expect an E2 elimination process to occur. During an E2 process, the base removes a proton that is antiperiplanar to the leaving group. There are two β positions, each of which has one proton, but only one of these protons is anti-periplanar to the leaving group:

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Therefore, we expect the following E2 product:

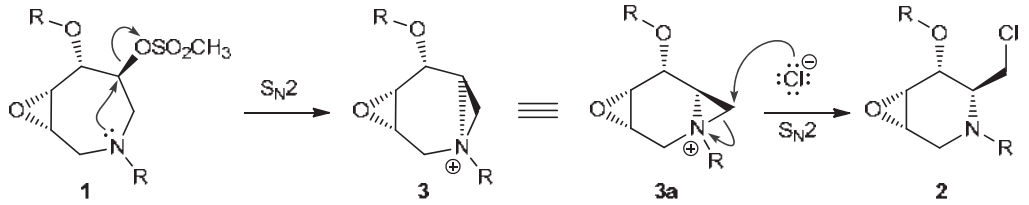


7.99. The substrate is primary and the reagent is a strong nucleophile, so this substitution reaction must occur via an S_N2 pathway. S_N2 reactions are bimolecular processes, so statement (a) is true. In an S_N2 process, the rate is linearly dependent on the concentration of the nucleophile, so statement (b) is also true. Polar aprotic solvents enhance the rate of S_N2 processes, so statement (c) is also true. Therefore, statement (d) must be false, and indeed, it is false. S_N2 reactions do not proceed via carbocation intermediates. Carbocation intermediates are involved in S_N1 reactions, but the alkyl halide is primary in this case, and a primary carbocation is too unstable to form.

7.100. The reagent is both a strong base and a strong nucleophile. With a secondary substrate, the E2 product is favored over the S_N2 product. This rules out option (a). Since the base is not sterically hindered, we expect the Zaitsev product. That is, we expect a disubstituted alkene, rather than a monosubstituted alkene, so we can rule out option (b). Options (c) and (d) are *cis/trans* stereoisomers. Since the E2 process is stereoselective, we expect the *trans* isomer to predominate, so option (d) is the correct answer.

7.101. Option (a) involves a primary substrate being treated with hydroxide (which is both a strong nucleophile and a strong base). Under these conditions, the S_N2 product is expected to predominate over the E2 product. Option (b) would give the more substituted alkene (*trans*-2-butene) as the major product, not 1-butene. Option (d) would also give the more substituted alkene (*trans*-2-butene) as the major product. Only option (c) will give 1-butene.

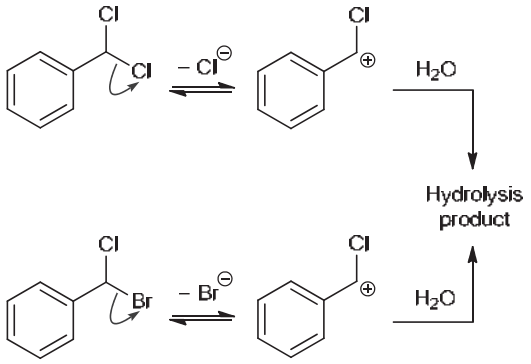
7.102. Compound **1** exhibits a mesylate group (OSO_2CH_3) as a good leaving group (described in Section 7.12). Upon its formation, compound **1** undergoes an intramolecular S_N2-type reaction, in which the nitrogen atom functions as the nucleophile. This results in the formation of a three-membered nitrogen-containing ring fused to a six-membered ring (**3**). Notice the stereochemistry: the nitrogen atom displaced the mesylate from the back face of the molecule, resulting in inversion at the original chiral center. Next, an intermolecular S_N2 reaction occurs: the chloride ion attacks the three-membered ring at the least hindered site, resulting in the formation of the product (**2**). Notice that the configuration of the chiral center (that underwent inversion in the first S_N2-type reaction) does not change during this second S_N2 reaction (in this step, chloride attacks a carbon atom that is not a chiral center).



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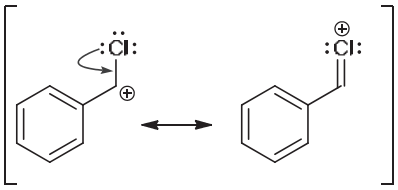
7.103.

(a) Table 7.1 indicates that bromide is expected to be a better leaving group than chloride, because bromide is a more stable base (HBr is a stronger acid than HCl). This is supported by the hydrolysis data, when we compare the rate of hydrolysis for $PhCHCl_2$ and $PhCHBrCl$.



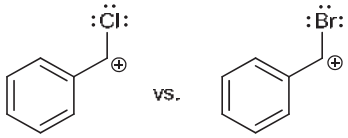
In both cases, the first step involves loss of a leaving group, and in both cases, the intermediate carbocation is the same. The only difference between these two reactions is the identity of the leaving group. According to the data provided, hydrolysis occurs more rapidly when the leaving group is bromide (k = 31.1 x10^4 /min) rather than chloride (k = 2.21 x10^4 /min). This is consistent with the expectation that bromide is a better leaving group than chloride.

(b) If we compare the rates of hydrolysis for $PhCH_2Cl$ and $PhCHCl_2$, we find that the presence of a chloro group (attached to C+) causes an increased rate of hydrolysis. A similar trend is observed if we compare $PhCHCl_2$ and $PhCCl_3$. Therefore, we can conclude that a chloro group will stabilize a carbocation (if the chloro group is attached directly to C+ of the carbocation). This stabilizing effect is unlikely to be caused by induction, because we expect the chloro group to be electron-withdrawing via induction, which would destabilize the carbocation (rather than stabilize it). Instead, the effect must be explained with resonance, which overwhelms the inductive effect. Specifically, the presence of a chloro group stabilizes the carbocation intermediate by spreading the charge via resonance.



(c) If we compare the rates of hydrolysis for $PhCHBr_2$ and $PhCBr_3$, we find that the presence of a bromo group (attached to C+) causes an increased rate of hydrolysis. This is likely explained as a resonance effect, just as we saw in part (b).

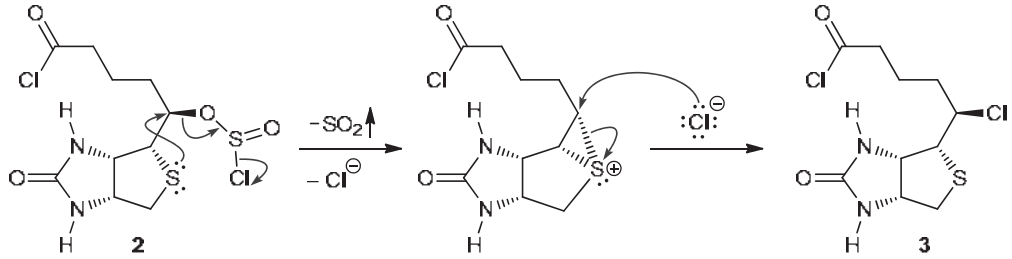
(d) Compare hydrolysis of PhCHBrCl with hydrolysis of $PhCHBr_2$. In both cases, the identity of the leaving group is the same (bromide). But the resulting carbocations are different.



Comparing the rates of hydrolysis indicates that an adjacent chloro group more effectively stabilizes a carbocation than an adjacent bromo group.

(e) Comparison of $PhCHCl_2$ versus $PhCHBr_2$ suggests that the better leaving group ability of the bromide ion is more important than the greater carbocation stability afforded by the chlorine atom via resonance.

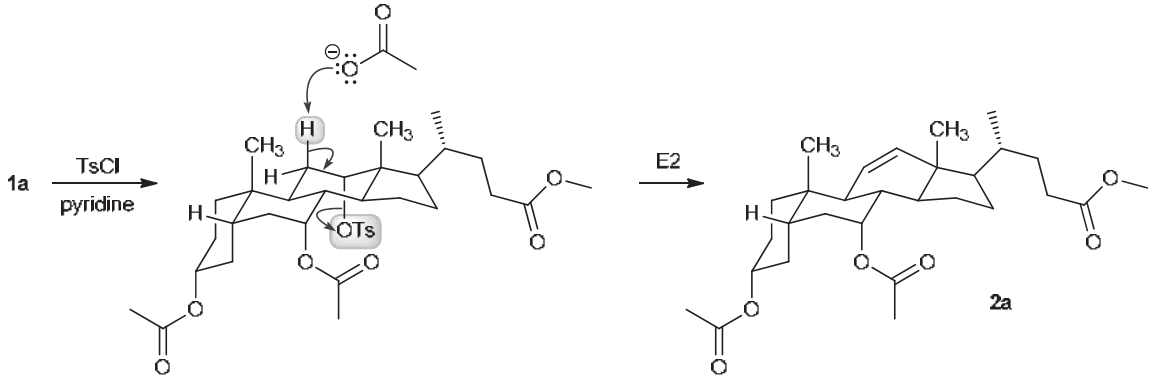
7.104. The sulfur atom provides anchimeric assistance via an intramolecular nucleophilic S_N2-type reaction. That is, a lone pair on the sulfur atom functions as a nucleophile, ejecting the leaving group (causing the liberation of SO_2 gas, as described in the problem statement) to form an intermediate with a positively charged sulfur atom. This intermediate is then attacked by a chloride ion to give **3**. Each of these two steps proceeds with inversion of configuration, as expected, which gives a net overall retention of configuration.



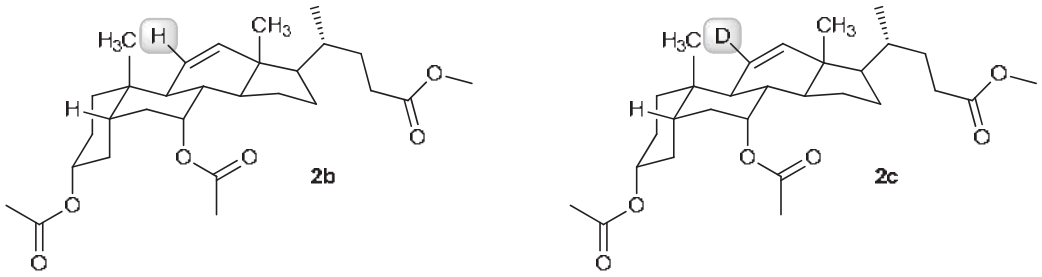
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7.105.

(a) When compound **1a** is treated with TsCl and pyridine, the OH group is converted to OTs (a better leaving group). Then sodium acetate functions as a base and removes a proton to give alkene **2a**. Notice that the axial proton (highlighted) is removed, since that proton is antiperiplanar with the leaving group. The equatorial proton is <u>not</u> antiperiplanar with the leaving group.

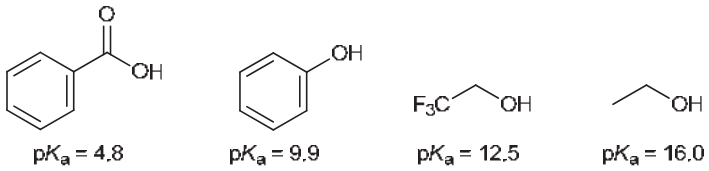


(b) We know that the axial proton (or deuteron) is removed in the elimination step. In compound **1b**, the axial position is occupied by a deuteron, so the deuteron is removed, and the product (**2b**) will not have a deuteron (and thus, **2b** is the same as **2a**). In compound **1c**, the axial position is occupied by a proton, which is removed during the elimination step. The deuteron in **1c** is in an equatorial position, so it survives the reaction. Compound **2c** will be deuterated, as seen below:



7.106.

(a) In order to compare the strength of these four bases, we can compare the pK_a values of their conjugate acids (see the pK_a table on the inside cover of the textbook). Benzoic acid (pK_a = 4.8) is more acidic than phenol (pK_a = 9.9), which is in turn more acidic than trifluoroethanol (pK_a = 12.5), which is more acidic than ethanol (pK_a = 16.0):



Therefore, basicity is expected to increase in the order that the bases were presented. That is, potassium benzoate is the weakest base (among the four bases listed), while ethoxide is the strongest base in the group.

The data indicates that the percentage of 1-butene increases as the basicity of the base increases. This observation can also be stated in the following way: the preference for formation of the more-substituted alkene (2-butene) decreases as the base strength increases. A stronger base is a more reactive base. So we see that there is an inverse relationship between reactivity and selectivity. Specifically, a more-reactive reagent results in lower selectivity, while a less-reactive reagent results in higher selectivity. This is a trend that we will encounter several times throughout the remaining chapters of the textbook, so it would be wise to remember this trend.

(b) Based on the pK_a value of 4-nitrophenol, we can conclude that it is more acidic than phenol, but not quite as acidic as benzoic acid. Based on our answer for part (a), we would expect that the conjugate base of 4-nitrophenol will be a stronger base than potassium benzoate, but a weaker base than potassium phenoxide. As such, we expect the selectivity to be somewhere in between the selectivity of potassium benzoate and potassium phenoxide. So we would expect that the percentage of 1-butene should be somewhere between 7.2% and 11.4%.

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Chapter 8
Addition Reactions of Alkenes

Review of Concepts

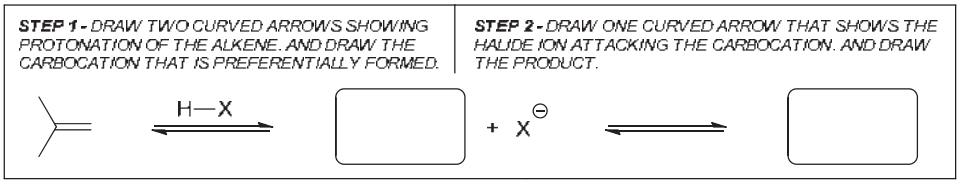
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 8. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Addition reactions are thermodynamically favorable at ____ temperature and disfavored at _____ temperature.
- Hydrohalogenation reactions are **regioselective**, because the halogen is generally installed at the _____ substituted position, called _____ **addition**.
- In the presence of _____, addition of HBr proceeds via an ***anti*-Markovnikov addition**.
- The regioselectivity of an ionic addition reaction is determined by the preference for the reaction to proceed through _____.
- Acid-catalyzed hydration is inefficient when _____ are possible. Dilute acid favors formation of the _____, while concentrated acid favors the _____.
- **Oxymercuration-demercuration** achieves hydration of an alkene without _____.
- _____-_____ can be used to achieve an *anti*-Markovnikov addition of water across an alkene. The reaction is stereospecific and proceeds via a _____ **addition**.
- **Asymmetric hydrogenation** can be achieved with a _____ catalyst.
- Bromination proceeds through a bridged intermediate, called a _____ _____, which is opened by an S_N2 process that produces an _____ **addition**.
- A two-step procedure for *anti* dihydroxylation involves conversion of an alkene to an _____, followed by acid-catalyzed ring opening.
- Ozonolysis can be used to cleave a double bond and produce two _____ groups.
- The position of a leaving group can be changed via _____ followed by _____.
- The position of a π bond can be changed via _____ followed by _____.

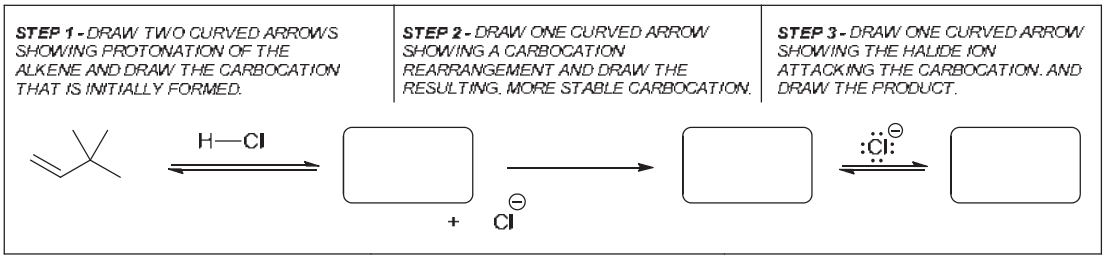
Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 8. The answers appear in the section entitled *SkillBuilder Review*.

8.1 Drawing a Mechanism for Hydrohalogenation

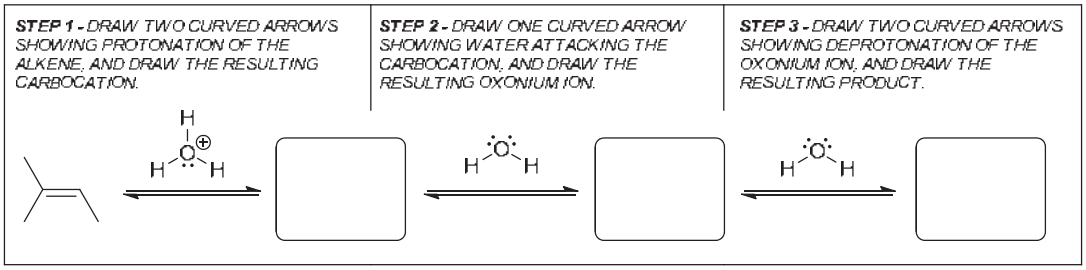


8.2 Drawing a Mechanism for Hydrohalogenation with a Carbocation Rearrangement

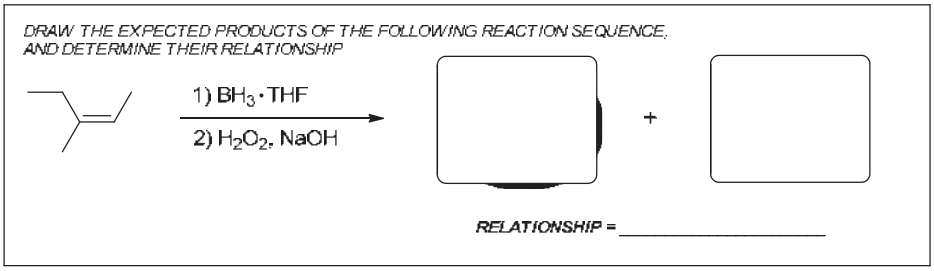


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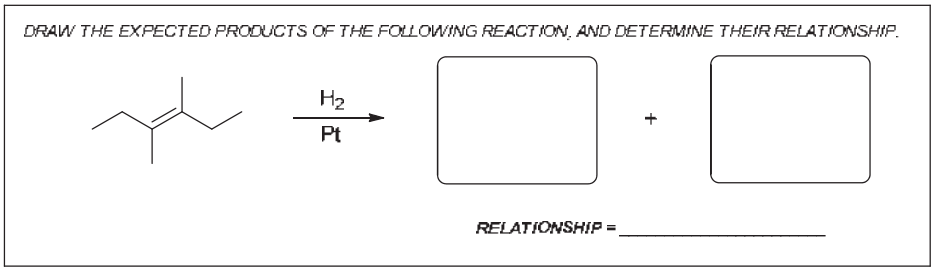
8.3 Drawing a Mechanism for an Acid-Catalyzed Hydration



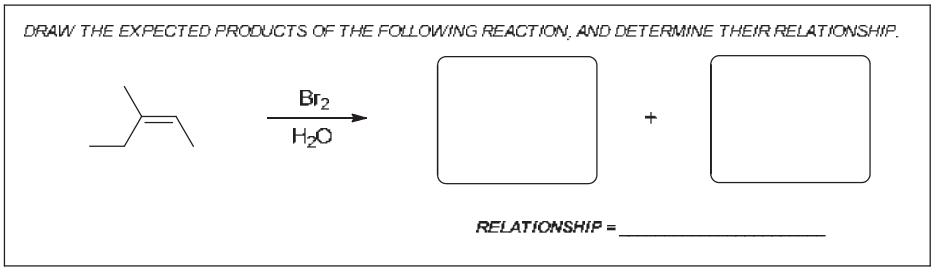
8.4 Predicting the Products of Hydroboration-Oxidation



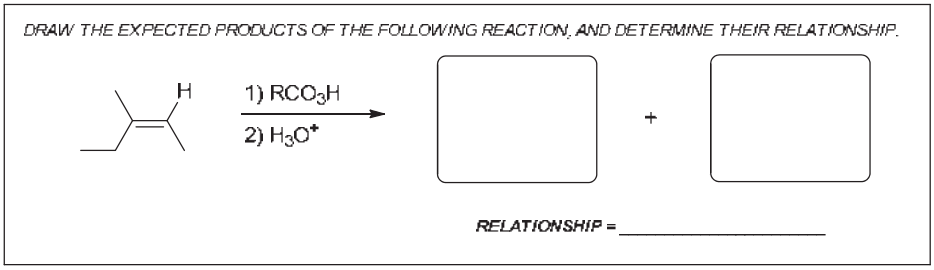
8.5 Predicting the Products of Catalytic Hydrogenation



8.6 Predicting the Products of Halohydrin Formation

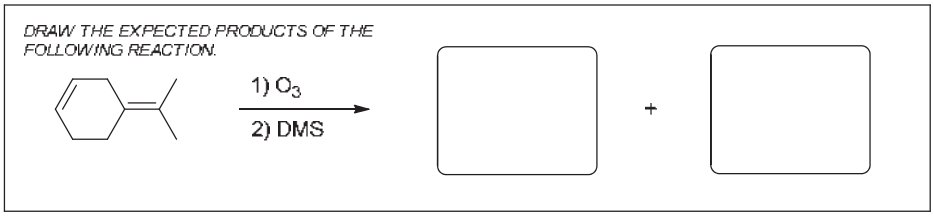


8.7 Drawing the Products of *Anti* Dihydroxylation

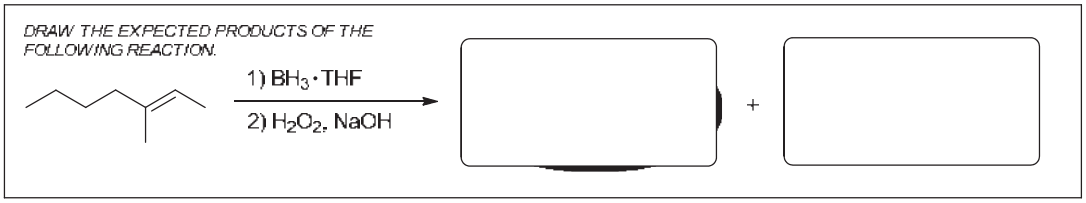


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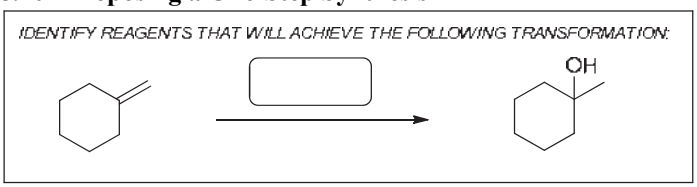
8.8 Predicting the Products of Ozonolysis



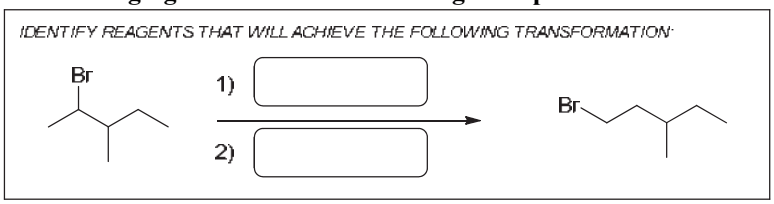
8.9 Predicting the Products of an Addition Reaction



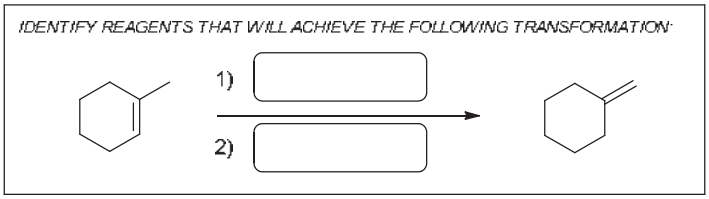
8.10 Proposing a One-Step Synthesis



8.11 Changing the Position of a Leaving Group



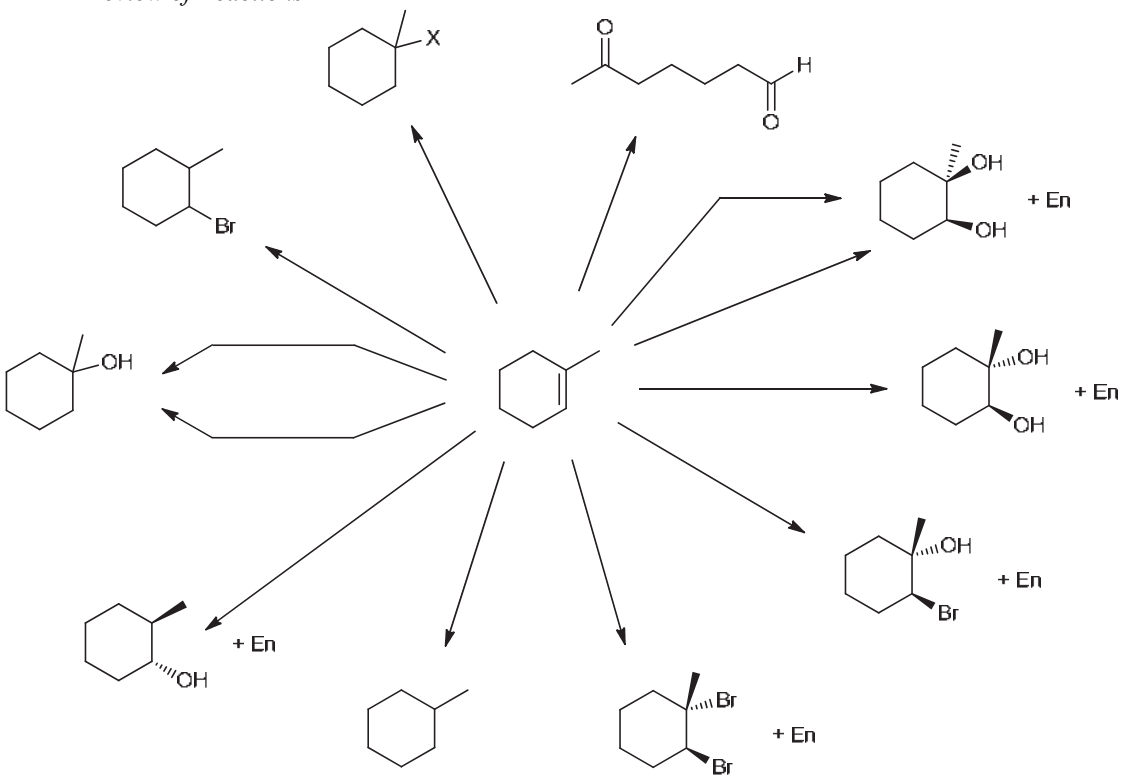
8.12 Changing the Position of a π Bond



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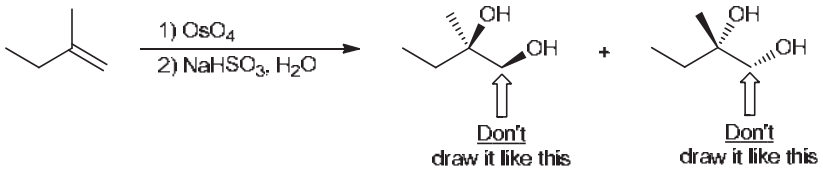
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 8. The answers appear in the section entitled *Review of Reactions*.

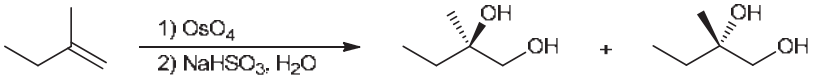


Common Mistakes to Avoid

This chapter introduces several stereospecific addition reactions. Some of them occur exclusively via a *syn* addition (such as hydrogenation or hydroboration-oxidation), while others occur exclusively via an *anti* addition (such as bromination or halohydrin formation). When drawing the products of a stereoscpecific addition reaction, be careful to avoid drawing a wedge or a dash on a location that is not a chiral center. For example, consider the following *syn* dihydroxylation. In such a case, it is tempting for students to draw the products as if they have two chiral centers, like this:



This mistake is understandable – after all, the two OH groups are indeed added in a *syn* fashion. But the product does not contain two chiral centers. It has only one chiral center. As such, the products should be drawn like this:



Notice that the stereochemical requirement for *syn* addition is not relevant in this case, because only one chiral center is formed. As such, both enantiomers are produced, because *syn* addition can occur on either face of the alkene to give either enantiomer.

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Useful reagents

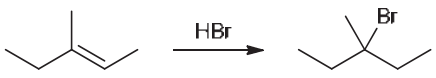
The following is a list of commonly encountered reagents for addition reactions:

Reagents	Name of Reaction	Description
HX	Hydrohalogenation	Treatment with an alkene gives a Markovnikov addition of H and X across the alkene.
HBr, ROOR	Hydrobromination	Treatment with an alkene gives an *anti*-Markovnikov addition of H and Br across the alkene.
H_3O^+	Acid-cat. hydration	Treatment with an alkene gives a Markovnikov addition of H and OH across the alkene.
1) $Hg(OAc)_2$, H_2O 2) $NaBH_4$	Oxymercuration-demercuration	Treatment with an alkene gives a Markovnikov addition of H and OH across the alkene, without any carbocation rearrangements.
1) BH_3 • THF 2) H_2O_2, NaOH	Hydroboration-oxidation	Treatment with an alkene gives an *anti*-Markovnikov addition of H and OH across the alkene. The reaction proceeds exclusively via a *syn* addition.
H_2, Pt	Hydrogenation	Treatment with an alkene gives a *syn* addition of H and H across the alkene.
Br_2	Bromination	Treatment with an alkene gives an *anti* addition of Br and Br across the alkene.
Br_2, H_2O	Halohydrin formation	Treatment with an alkene gives an *anti* addition of Br and OH across the alkene, with the OH group being installed at the more substituted position.
1) RCO_3H 2) H_3O^+	*Anti* Dihydroxylation	Treatment of an alkene with a peroxy acid (RCO_3H) converts the alkene into an epoxide, which is then opened upon treatment with aqueous acid to give a *trans*-diol.
$KMnO_4$, NaOH, cold	*Syn* Dihydroxylation	Treatment with an alkene gives a *syn* addition of OH and OH across the alkene.
1) OsO_4 2) $NaHSO_3$, H_2O	*Syn* Dihydroxylation	Treatment with an alkene gives a *syn* addition of OH and OH across the alkene.
1) O_3 2) DMS	Ozonolysis	Ozonolysis of an alkene causes cleavage of the C=C bond, giving two compounds, each of which possesses a C=O bond.

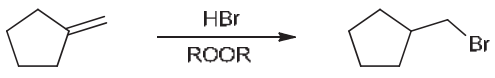
Solutions

8.1.

(a) An alkene is treated with HBr (in the absence of peroxides), so we expect a Markovnikov addition of H and Br across the π bond. That is, Br is installed at the more-substituted position:

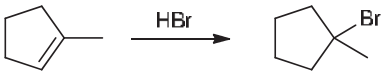


(b) An alkene is treated with HBr in the presence of peroxides, so we expect an *anti*-Markovnikov addition of H and Br across the π bond. That is, Br is installed at the less-substituted position:

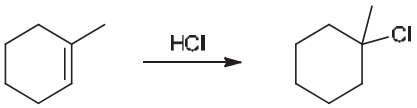


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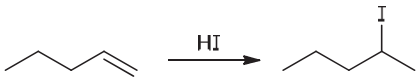
(c) An alkene is treated with HBr (in the absence of peroxides), so we expect a Markovnikov addition of H and Br across the π bond. That is, Br is installed at the more-substituted position:



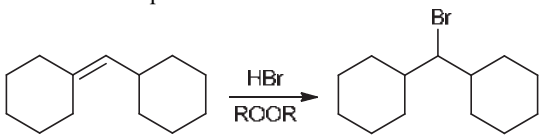
(d) An alkene is treated with HCl, so we expect a Markovnikov addition of H and Cl across the π bond. That is, Cl is installed at the more-substituted position:



(e) An alkene is treated with HI, so we expect a Markovnikov addition of H and I across the π bond. That is, iodine is installed at the more-substituted position:

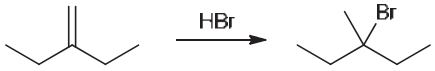


(f) An alkene is treated with HBr in the presence of peroxides, so we expect an *anti*-Markovnikov addition of H and Br across the π bond. That is, Br is installed at the less-substituted position:



8.2.

(a) The desired transformation is a Markovnikov addition of H and Br across the π bond. This can be achieved by treating the alkene with HBr (in the absence of peroxides).

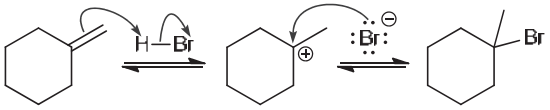


(b) The desired transformation is an *anti*-Markovnikov addition of H and Br across the π bond. This can be achieved by treating the alkene with HBr in the presence of peroxides.

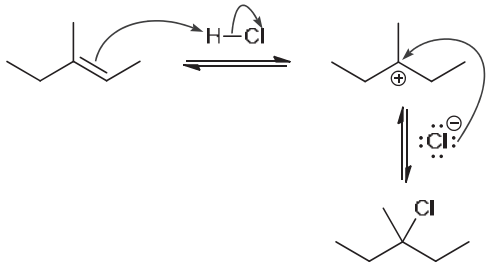


8.3.

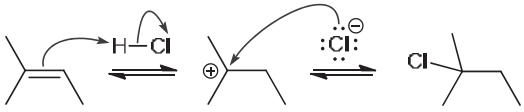
(a) In this reaction, H and Br are added across the alkene in a Markovnikov addition, which indicates an ionic process. There are two mechanistic steps in the ionic addition of HBr across an alkene: 1) proton transfer, followed by 2) nucleophilic attack. In the first step, a proton is transferred from HBr to the alkene, which requires two curved arrows, as shown below. The resulting, tertiary carbocation is then captured by a bromide ion in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile to the electrophile, as shown:



(b) In this reaction, H and Cl are added across the alkene in a Markovnikov addition. There are two mechanistic steps in the ionic addition of HCl across an alkene: 1) proton transfer, followed by 2) nucleophilic attack. In the first step, a proton is transferred from HCl to the alkene, which requires two curved arrows, as shown below. The resulting, tertiary carbocation is then captured by a chloride ion in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile to the electrophile, as shown:

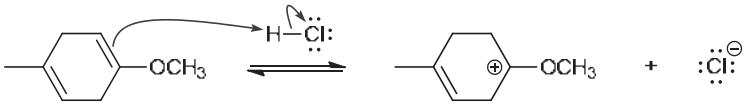


(c) In this reaction, H and Cl are added across the alkene in a Markovnikov addition. There are two mechanistic steps in the ionic addition of HCl across an alkene: 1) proton transfer, followed by 2) nucleophilic attack. In the first step, a proton is transferred from HCl to the alkene, which requires two curved arrows, as shown. The resulting, tertiary carbocation is then captured by a chloride ion in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile to the electrophile, as shown:

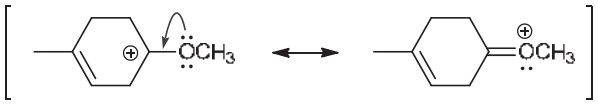


8.4. Compound **1** has two C=C double bonds and each of them can react with HCl in an ionic reaction (Markovnikov addition). Indeed, the molecular formula of compound **2** indicates that two addition reactions must have occurred, because compound **2** has two Cl atoms. We will consider each addition process separately, and in each case, we will focus on the regiochemical outcome. Let's begin by drawing a mechanism for the addition of HCl to the double bond that is adjacent to the methoxy (OCH_3) group). In the first step, a proton is transferred from HCl to the double bond, giving the more stable carbocation. This step requires two curved arrows:

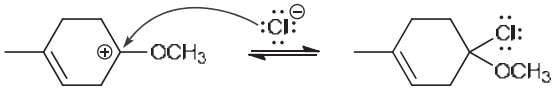
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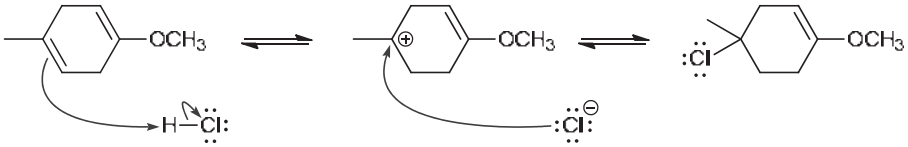
This carbocation is the more stable carbocation because it is stabilized by resonance, as shown:



Indeed, the second resonance structure has completely filled octets, rendering this carbocation particularly stable. Then, in the second step of the process, the carbocation is captured by a chloride ion to generate an alkyl chloride. This step requires one curved arrow:

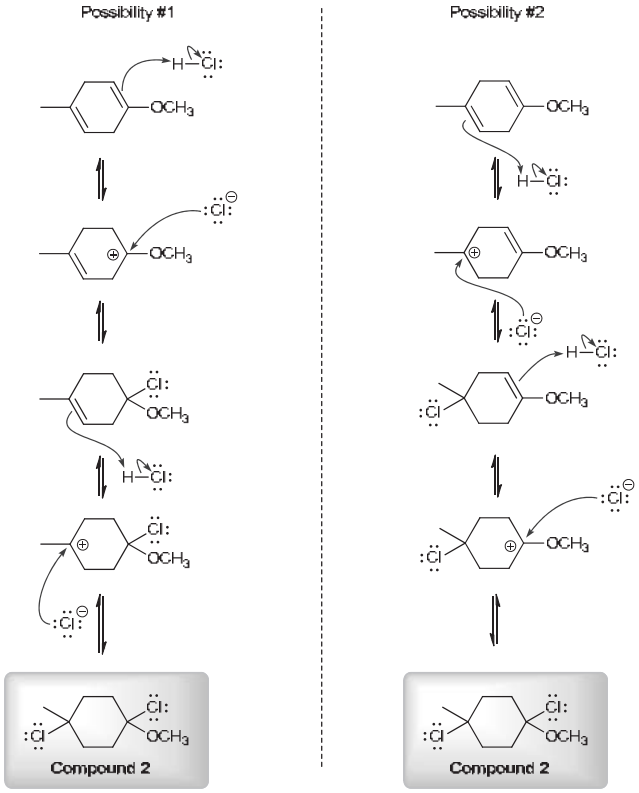


The other C=C bond also reacts with HCl via a similar two-step process:



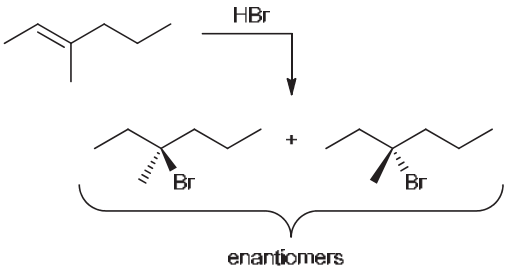
First, a proton is transferred from HCl to the double bond, giving the more stable tertiary carbocation (rather than a secondary carbocation). This carbocation is then captured by a chloride ion to generate a tertiary alkyl chloride.

In summary, there are two addition processes, and each of them occurs, one after the other, to produce an alkyl dichloride with predictable regiochemistry. When drawing a complete mechanism, make sure to draw each step separately. That is, draw one process followed by the other. Either process can be drawn first. Both possibilities are shown below:

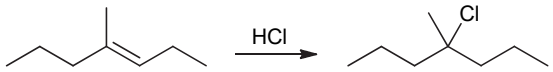


8.5.

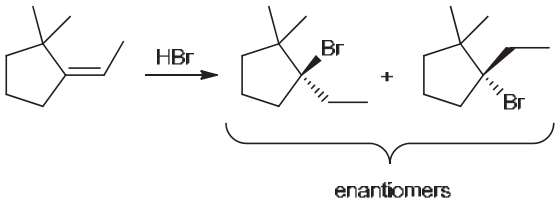
(a) In this case, Markovnikov addition of HBr involves the formation of a new chiral center. As such, we expect both possible stereochemical outcomes. That is, we expect a pair of enantiomers, as shown:



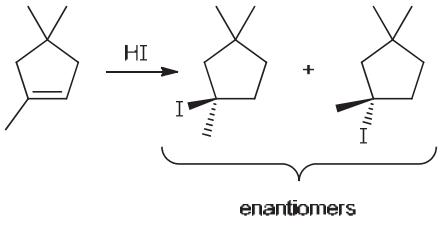
(b) In this case, Markovnikov addition of HCl does not involve the formation of a new chiral center (the α carbon of the resulting alkyl halide bears two propyl groups):



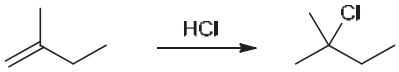
(c) In this case, Markovnikov addition of HBr involves the formation of a new chiral center. As such, we expect both possible stereochemical outcomes. That is, we expect a pair of enantiomers, as shown:



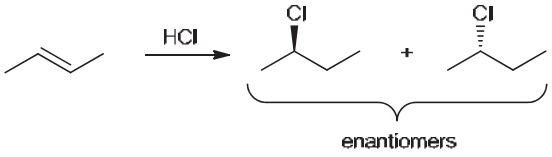
(d) In this case, Markovnikov addition of HI involves the formation of a new chiral center. As such, we expect both possible stereochemical outcomes. That is, we expect a pair of enantiomers, as shown:



(e) In this case, Markovnikov addition of HCl does not involve the formation of a new chiral center (the α carbon of the resulting alkyl halide bears two methyl groups):

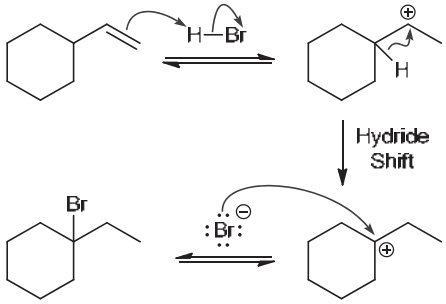


(f) In this case, addition of HCl involves the formation of a new chiral center. As such, we expect both possible stereochemical outcomes. That is, we expect a pair of enantiomers, as shown:

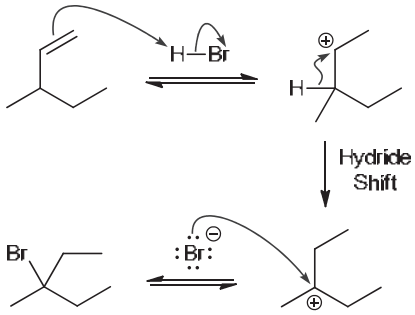


8.6.

(a) Protonation of the alkene requires two curved arrows, as shown, and leads to the more stable, secondary carbocation (rather than a primary carbocation). This secondary carbocation then undergoes a hydride shift, shown with one curved arrow, generating a more stable, tertiary carbocation. In the final step (nucleophilic attack), the carbocation is captured by a bromide ion. This step requires one curved arrow, going from the nucleophile (bromide) to the electrophile (the carbocation), as shown:



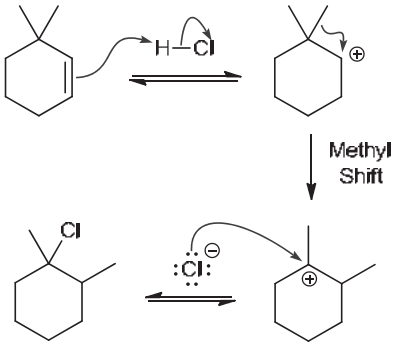
(b) Protonation of the alkene requires two curved arrows, as shown, and leads to the more stable, secondary carbocation (rather than a primary carbocation). This secondary carbocation then undergoes a hydride shift, shown with one curved arrow, generating a more stable, tertiary carbocation. In the final step (nucleophilic attack), the carbocation is captured by a bromide ion. This step requires one curved arrow, going from the nucleophile (bromide) to the electrophile (the carbocation), as shown:



(c) Protonation of the alkene requires two curved arrows, generating a secondary carbocation. This secondary carbocation then undergoes a methyl shift, shown with one curved arrow, generating a more stable,

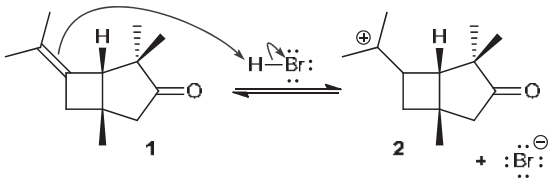
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tertiary carbocation. In the final step of the mechanism (nucleophilic attack), the carbocation is captured by a chloride ion. This step requires one curved arrow, going from the nucleophile (chloride) to the electrophile (the carbocation), as shown:



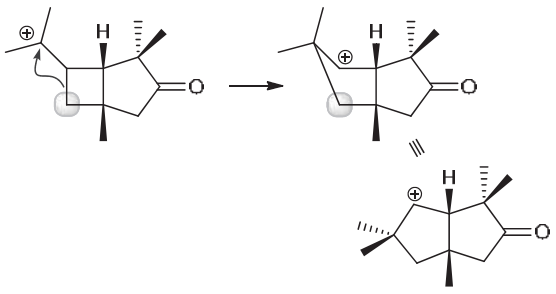
8.7.

(a) The mechanism begins with protonation of the carbon-carbon double bond to form a tertiary carbocation. This step requires two curved arrows:

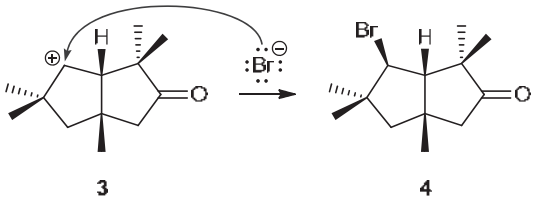


Although both ends of the double bond are doubly substituted, and therefore would yield a tertiary carbocation, only structure **2** can enable the subsequent rearrangement.

Next, the highlighted carbon atom shifts, giving the rearrangement shown. This step requires one curved arrow:



In the final step of the mechanism, a bromide ion (produced in the first step) captures the carbocation to form an alkyl bromide. This step requires one curved arrow:



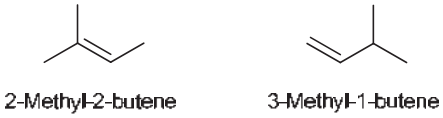
(b) This rearrangement involves a ring expansion, and it is favorable because ring strain is released when a strained four-membered ring becomes a more stable five-membered ring, even though the resulting carbocation is secondary rather than tertiary.

8.8.

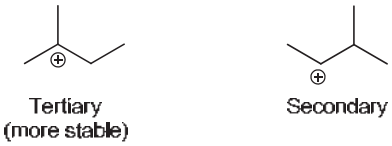
(a) The second compound (highlighted) is expected to be more reactive toward acid-catalyzed hydration than the first compound, because the reaction proceeds via a tertiary carbocation, rather than via a secondary carbocation, as shown.



(b) Begin by drawing the compounds:



The first compound (2-methyl-2-butene) is expected to be more reactive toward acid-catalyzed hydration than the second compound, because the reaction proceeds via a tertiary carbocation, rather than a secondary carbocation.



8.9.

(a) To favor the alcohol, dilute sulfuric acid (mostly water) is used. The presence of a lot of water favors the alcohol, according to Le Châtelier's principle.

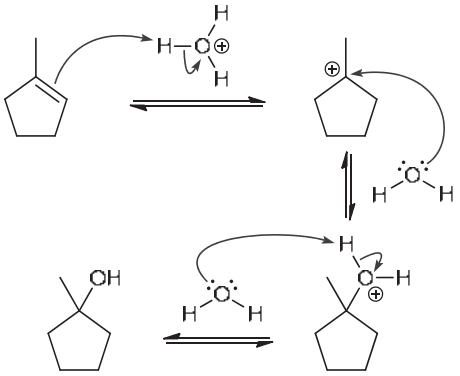
(b) To favor the alkene, concentrated sulfuric acid (which has less water than dilute acid) is used. With less water present, the alkene is favored, according to Le Châtelier's principle.

8.10.

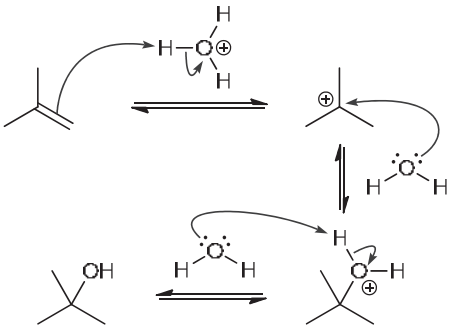
(a) Water (H and OH) is added across the alkene in a Markovnikov fashion. The mechanism is expected to have three steps: 1) proton transfer, 2) nucleophilic attack, and 3) proton transfer. In the first step, a proton is transferred from H_3O^+ to the alkene, which requires two curved arrows, as shown. The resulting tertiary carbocation is then captured by a water molecule in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile (water) to the electrophile (the carbocation). Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product.

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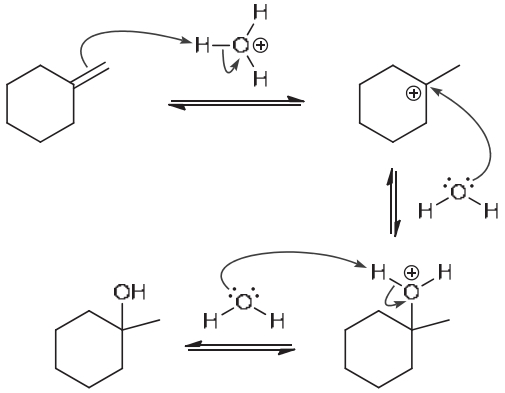
This final step is a proton transfer step, and therefore requires two curved arrows, as shown:



(b) Water (H and OH) is added across the alkene in a Markovnikov fashion. The mechanism is expected to have three steps: 1) proton transfer, 2) nucleophilic attack, and 3) proton transfer. In the first step, a proton is transferred from H_3O^+ to the alkene, which requires two curved arrows, as shown below. The resulting tertiary carbocation is then captured by a water molecule in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile (water) to the electrophile (the carbocation). Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows, as shown:

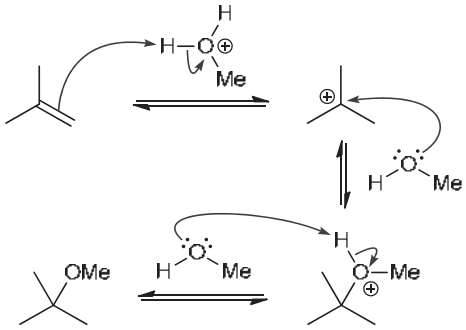


(c) Water (H and OH) is added across the alkene in a Markovnikov fashion. The mechanism is expected to have three steps: 1) proton transfer, 2) nucleophilic attack, and 3) proton transfer. In the first step, a proton is transferred from H_3O^+ to the alkene, which requires two curved arrows, as shown. The resulting tertiary carbocation is then captured by a water molecule in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile (water) to the electrophile (the carbocation). Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows, as shown:

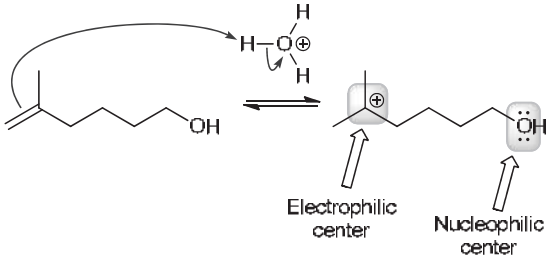


8.11.

(a) Methanol (H and OCH_3) is added across the alkene in a Markovnikov fashion. The reaction is extremely similar to the addition of water across an alkene under acid-catalyzed conditions, so we expect the mechanism to have three steps: 1) proton transfer, 2) nucleophilic attack, and 3) proton transfer. In the first step, a proton is transferred from $CH_3OH_2^+$ to the alkene, which requires two curved arrows, as shown below. The resulting tertiary carbocation is then captured by a molecule of methanol in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile (methanol) to the electrophile (the carbocation). Then, in the final step of the mechanism, a molecule of methanol functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows, as shown:

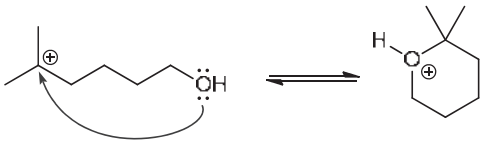


(b) The reactant is acyclic (it does not have a ring), and the product is cyclic, indicating an intramolecular reaction. We can justify an intramolecular reaction if we inspect the cation that is obtained upon protonation of the alkene:

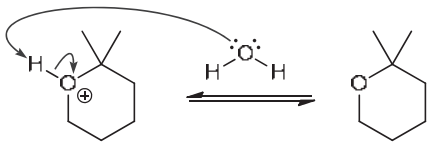


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Notice that this intermediate exhibits both an electrophilic center and a nucleophilic center. That is, the reactive centers are tethered together, via a chain of methylene (CH_2) groups. As such, a ring is formed in the following intramolecular nucleophilic attack, which is shown with one curved arrow:

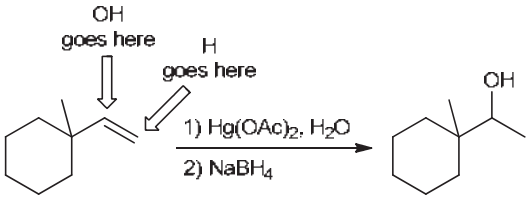


Finally, water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows, as shown:

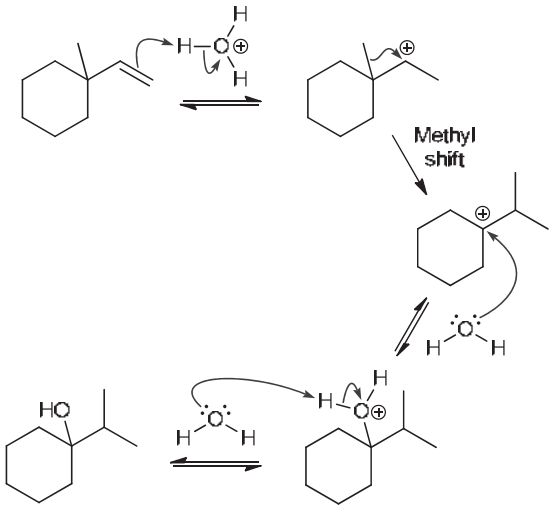


8.12.

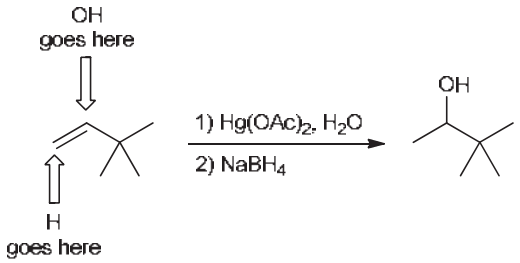
(a) Oxymercuration-demercuration gives Markovnikov addition of water (H and OH) without carbocation rearrangements. That is, the OH group ends up at the more substituted (secondary) position, and the proton ends up at the less substituted (primary) position:



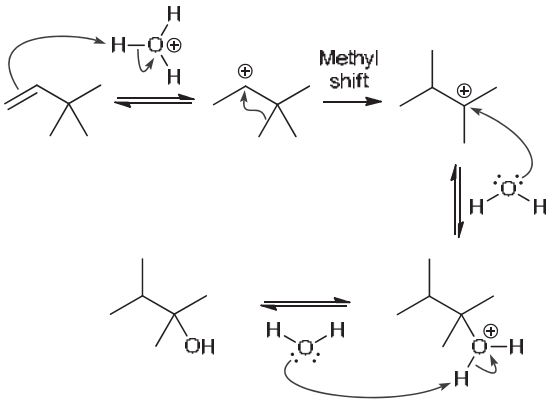
If the same alkene were treated with aqueous acid, the resulting acid-catalyzed hydration would involve a carbocation rearrangement:



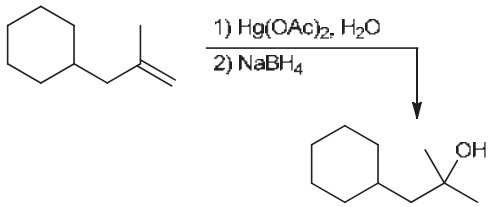
(b) Oxymercuration-demercuration gives Markovnikov addition of water (H and OH) without carbocation rearrangements. That is, the OH group ends up at the more substituted (secondary) position, and the proton ends up at the less substituted (primary) position:



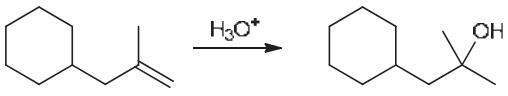
If the same alkene were treated with aqueous acid, the resulting acid-catalyzed hydration would involve a carbocation rearrangement:



(c) Oxymercuration-demercuration gives Markovnikov addition of water (H and OH) without carbocation rearrangements. That is, the OH group ends up at the more substituted (tertiary) position, and the proton ends up at the less substituted (primary) position.



In this case, acid-catalyzed hydration gives the same product, because the intermediate tertiary carbocation does not undergo rearrangement:

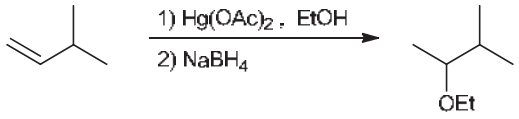


8.13.

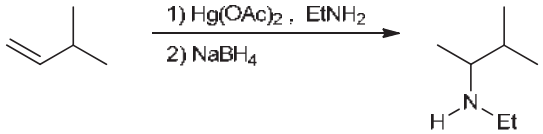
(a) Oxymercuration-demercuration involves the addition of H-Z across the double bond (where Z = OH when

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water, H_2O, is used as the reagent). If ethanol (EtOH) is used as the reagent instead of water, then Z = OEt, so we expect Markovnikov addition of ethanol (H and OEt) across the alkene, with the ethoxy (OEt) group being installed at the more substituted (secondary) position, rather than the less substituted (primary) position.

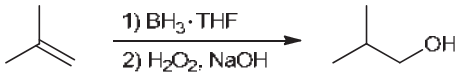


(b) Oxymercuration-demercuration involves the addition of H-Z across the double bond (where Z = OH when water, H_2O, is used as the reagent). If ethylamine ($EtNH_2$) is used as the reagent instead of water, then Z = NHEt, so we expect Markvnikov addition of H and NHEt across the alkene, with the ethylamino group (NHEt) being installed at the more substituted (secondary) position, rather than the less substituted (primary) position.

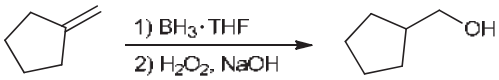


8.14.

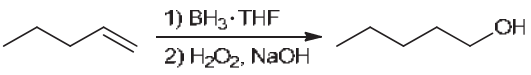
(a) Hydroboration-oxidation results in the *anti*-Markovnikov addition of water (H and OH) across the π bond. That is, the OH group is installed at the less-substituted (primary) position, rather than the more substituted (tertiary) position:



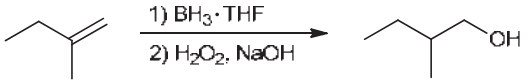
(b) Hydroboration-oxidation results in the *anti*-Markovnikov addition of water (H and OH) across the π bond. That is, the OH group is installed at the less-substituted (primary) position, rather than the more substituted (tertiary) position:



(c) Hydroboration-oxidation results in the *anti*-Markovnikov addition of water (H and OH) across the π bond. That is, the OH group is installed at the less-substituted (primary) position, rather than the more substituted (secondary) position:

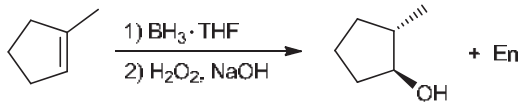


8.15. There is only one alkene that will afford the desired product upon hydroboration-oxidation:

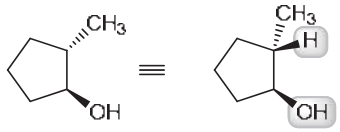


8.16.

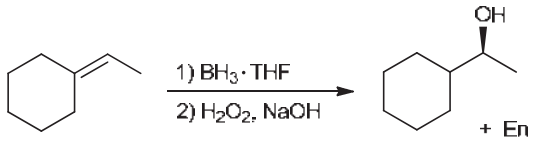
(a) The reagents indicate a hydroboration-oxidation. The net result of this two-step process is the *anti*-Markovnikov addition of H and OH across the π bond. That is, the OH group is installed at the less-substituted position, while the H is installed at the more substituted position. In this case, two chiral centers are created. Therefore, the stereochemical requirement for *syn* addition determines that the H and OH are added on the same face of the alkene, giving the following products:



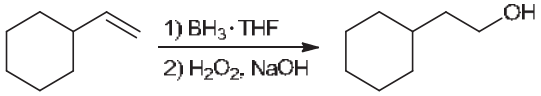
In this case, it might seem as if there was an *anti* addition, rather than a *syn* addition, because we see that the product has one wedge and one dash. But this is an optical illusion. Recall, that most hydrogen atoms are not drawn in bond-line drawings, so the H that was added during the process has not been drawn. However, if we draw that hydrogen atom, we will see that the H and OH were indeed added in a *syn* fashion:



(b) The reagents indicate a hydroboration-oxidation. The net result of this two-step process is the *anti*-Markovnikov addition of H and OH across the π bond. That is, the OH group is installed at the less-substituted position, while the H is installed at the more substituted position. In this case, only one chiral center is created. Since *syn* addition can take place from either face of the alkene with equal likelihood, we expect a pair of enantiomers, as shown:

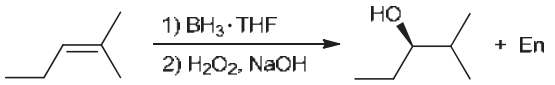


(c) The reagents indicate a hydroboration-oxidation. The net result of this two-step process is the *anti*-Markovnikov addition of H and OH across the π bond. That is, the OH group is installed at the less-substituted position, while the H is installed at the more substituted position. In this case, no chiral centers are created, so the requirement for *syn* addition is irrelevant.

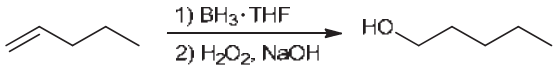


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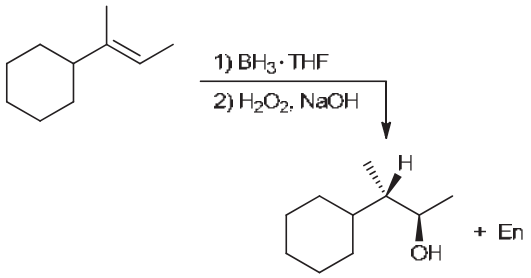
(d) The reagents indicate a hydroboration-oxidation. The net result of this two-step process is the *anti*-Markovnikov addition of H and OH across the π bond. That is, the OH group is installed at the less-substituted position, while the H is installed at the more substituted position. In this case, only one chiral center is created. Since *syn* addition can take place from either face of the alkene with equal likelihood, we expect a pair of enantiomers, as shown:



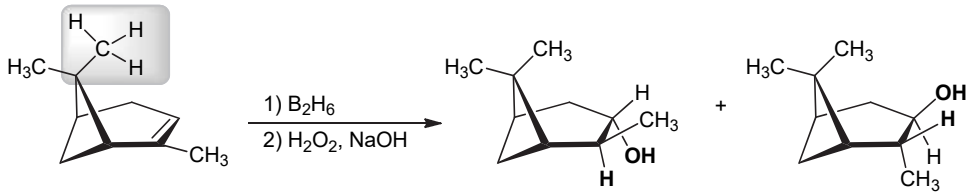
(e) The reagents indicate a hydroboration-oxidation. The net result of this two-step process is the *anti*-Markovnikov addition of H and OH across the π bond. That is, the OH group is installed at the less-substituted position, while the H is installed at the more substituted position. In this case, no chiral centers are created, so the requirement for *syn* addition is irrelevant.



(f) The reagents indicate a hydroboration-oxidation. The net result of this two-step process is the *anti*-Markovnikov addition of H and OH across the π bond. That is, the OH group is installed at the less-substituted position, while the H is installed at the more substituted position. In this case, two chiral centers are created. Therefore, the stereochemical requirement for *syn* addition determines that the H and OH are added on the same face of the alkene, giving the following products:



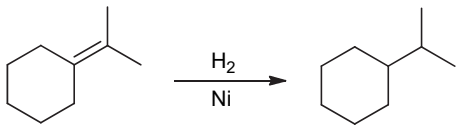
8.17. The problem statement indicates that this is a hydroboration-oxidation sequence, the net result of which is an *anti*-Markovnikov addition of H and OH across the π bond. That is, the OH group is installed at the less-substituted position, while the H is installed at the more substituted position. In this case, two chiral centers are created. Therefore, the stereochemical requirement for *syn* addition determines that the H and OH are added on the same face of the alkene, giving the products shown. Note that the highlighted methyl group creates steric hindrance on the top face of the ring, so the major product arises from hydroboration from the bottom face:



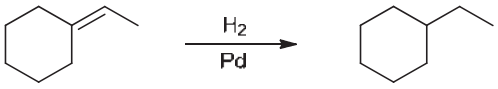
(–)-α-Pinene **Major** **Minor**

8.18.

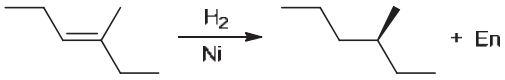
(a) The reagents indicate a catalytic hydrogenation process, so we expect the addition of H and H across the alkene. In this case, the product does not have a chiral center, so stereochemistry is not a relevant consideration.



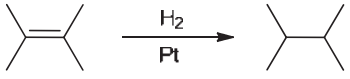
(b) The reagents indicate a catalytic hydrogenation process, so we expect the addition of H and H across the alkene. In this case, the product does not have a chiral center, so stereochemistry is not a relevant consideration.



(c) The reagents indicate a catalytic hydrogenation process, so we expect the addition of H and H across the alkene. In this case, the product has one chiral center, so we expect both possible enantiomers (*syn* addition can occur from either face of the π bond).

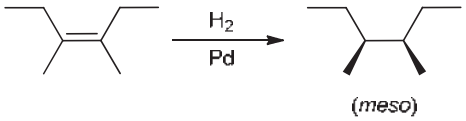


(d) The reagents indicate a catalytic hydrogenation process, so we expect the addition of H and H across the alkene. In this case, the product does not have a chiral center, so stereochemistry is not a relevant consideration.

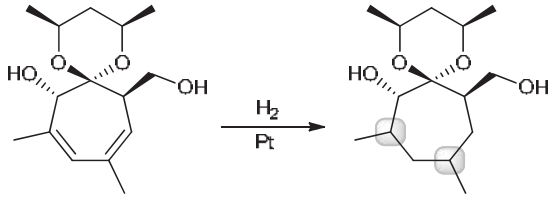


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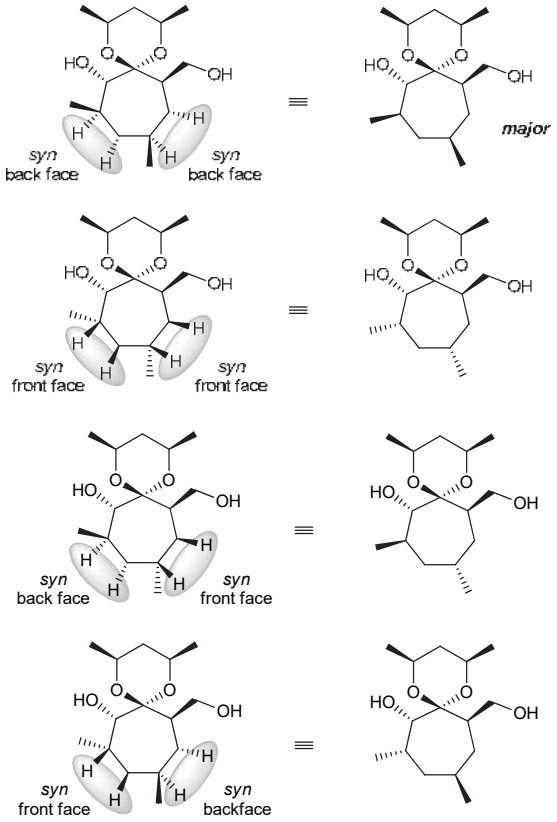
(e) The reagents indicate a catalytic hydrogenation process, so we expect the addition of H and H across the alkene. In this case, the reaction generates two chiral centers. The requirement for *syn* addition results in the formation of a *meso* compound, so there is only one product.



8.19. The starting material has two carbon-carbon π bonds, each of which will undergo hydrogenation when treated with H_2 and a catalyst. This creates two new chiral centers in the product, highlighted below:



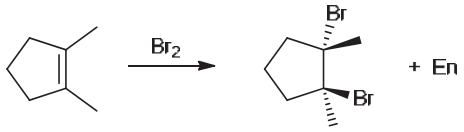
Each individual π bond undergoes a *syn* addition, which can occur either from the top face or from the bottom face of the π bond. Therefore, each of the two new chiral centers can have either the *R* configuration or the *S* configuration, giving four possible products (shown below). These products are all diastereomers of each other (because the starting compound already has other chiral centers).



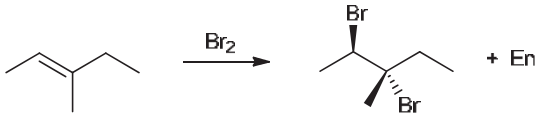
Interestingly, only two stereoisomers are observed in this reaction and the major product results from *syn* addition from the back face of both π bonds. This is an example of an asymmetric catalytic hydrogenation since the chirality of the starting material clearly influences which face undergoes hydrogenation preferentially. Asymmetric catalytic hydrogenation is also possible using a chiral catalyst, as will be discussed later in Section 8.8.

8.20.

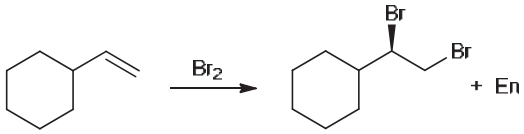
(a) When an alkene is treated with molecular bromine (Br_2), we expect an *anti* addition of Br and Br across the alkene, giving the following pair of enantiomers:



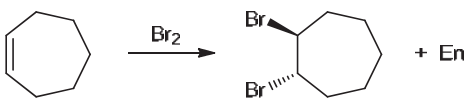
(b) When an alkene is treated with molecular bromine (Br_2), we expect an *anti* addition of Br and Br across the alkene, giving the following pair of enantiomers:



(c) When an alkene is treated with molecular bromine (Br_2), we expect an *anti* addition of Br and Br across the alkene. In this case, only one chiral center is created, so we expect both possible enantiomers (formation of the initial bromonium ion can occur on either face of the π bond with equal likelihood):



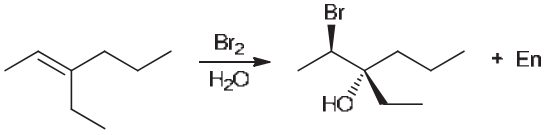
(d) When an alkene is treated with molecular bromine (Br_2), we expect an *anti* addition of Br and Br across the alkene, giving the following pair of enantiomers:



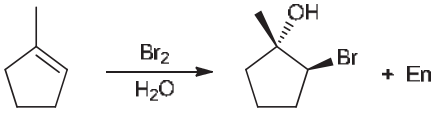
8.21.

(a) Treating an alkene with molecular bromine (Br_2) and water results in the addition of OH and Br across the alkene (halohydrin formation). The OH group is expected to be installed at the more-substituted position, while Br is installed at the less-substituted position. In this case, two new chiral centers are generated, so we

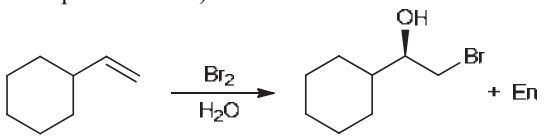
expect only the pair of enantiomers that would result from *anti* addition.



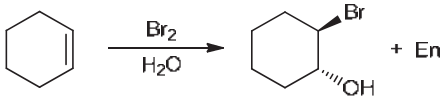
(b) Treating an alkene with molecular bromine (Br_2) and water results in the addition of OH and Br across the alkene (halohydrin formation). The OH group is expected to be installed at the more-substituted position, while Br is installed at the less-substituted position. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition.



(c) Treating an alkene with molecular bromine (Br_2) and water results in the addition of OH and Br across the alkene (halohydrin formation). The OH group is expected to be installed at the more-substituted position, while Br is installed at the less-substituted position. In this case, only one new chiral center is generated, so we expect both possible enantiomers (formation of the initial bromonium ion can occur on either face of the π bond with equal likelihood).

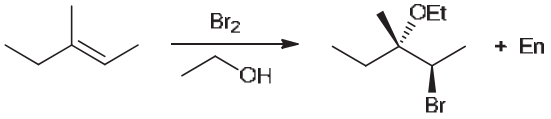


(d) Treating an alkene with molecular bromine (Br_2) and water results in the addition of OH and Br across the alkene (halohydrin formation). In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition.

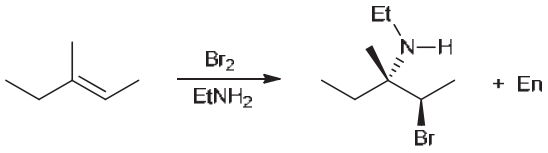


8.22.

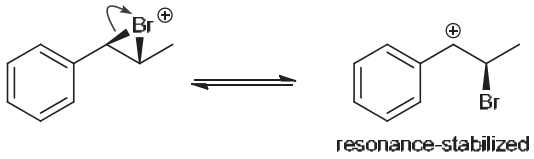
(a) The alkene reacts with molecular bromine to give a bromonium ion, which is then attacked by a molecule of solvent (EtOH, in this case, rather than H_2O). The result is the addition of Br and OEt (rather than the addition of Br and OH). The OEt group is expected to be installed at the more-substituted position, while Br is installed at the less-substituted position. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition:



(b) The alkene reacts with molecular bromine to give a bromonium ion, which is then captured by a molecule of solvent ($EtNH_2$, in this case, rather than H_2O). The result is the addition of Br and NHEt (rather than the addition of Br and OH). The ethylamino group (NHEt) is expected to be installed at the more-substituted position, while Br is installed at the less-substituted position. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition:

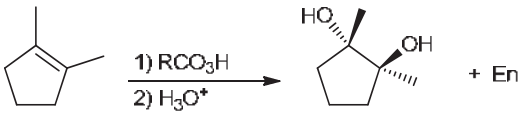


8.23. The bromonium ion can open (before a bromide ion attacks), forming a resonance-stabilized carbocation. This carbocation is trigonal planar and can be attacked from either side:

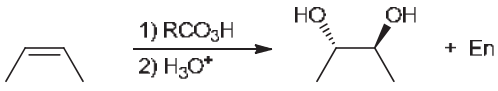


8.24.

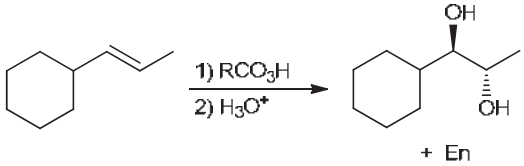
(a) Treating an alkene with a peroxy acid followed by aqueous acid results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition:



(b) Treating an alkene with a peroxy acid followed by aqueous acid results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition:

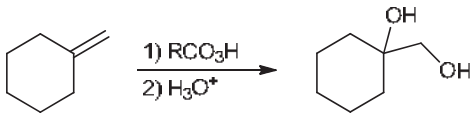


(c) Treating an alkene with a peroxy acid followed by aqueous acid results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition:

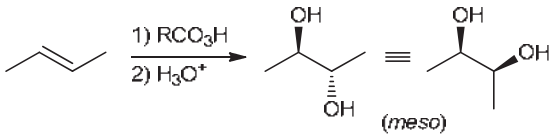


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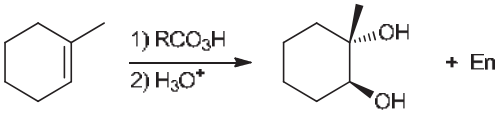
(d) Treating an alkene with a peroxy acid followed by aqueous acid results in the addition of OH and OH across the alkene. In this case, the product has no chiral centers, so stereochemistry is not a relevant consideration.



(e) Treating an alkene with a peroxy acid followed by aqueous acid results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated. However, the *anti* addition results in the formation of a *meso* compound:

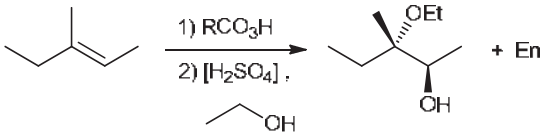


(f) Treating an alkene with a peroxy acid followed by aqueous acid results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *anti* addition:

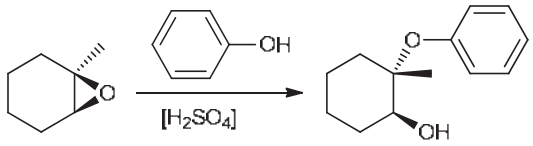


8.25.

(a) Treating an alkene with a peroxy acid results in an epoxide. Further treatment of the epoxide with ethanol under acid conditions results in a ring opening reaction in which ethanol serves as the nucleophile. Nucleophilic attack occurs at the more-substituted (tertiary) position, so the net result is the addition of OH and OEt across the alkene, with the latter being installed at the more-substituted position, as shown:

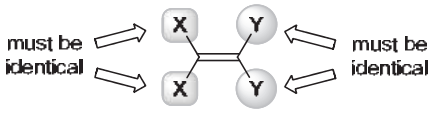


(b) Treatment of the epoxide with phenol (C_6H_5OH) under acid conditions results in a ring opening reaction in which the oxygen atom of phenol serves as the nucleophilic center. Nucleophilic attack occurs at the more-substituted (tertiary) position, so the net result is the addition of OH and OR (where R is C_6H_5) across the alkene, with the latter being installed at the more-substituted position. Since the starting epoxide is enantiomerically pure (we are starting only with the enantiomer shown), we expect an enantiomerically pure product (not a mixture of enantiomers), as shown.

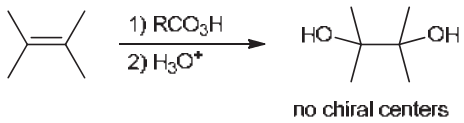


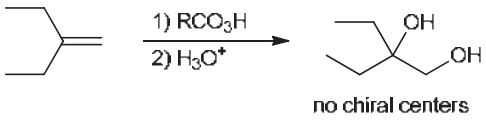
8.26.

(a) Compound **A** is converted to an epoxide upon treatment with a peroxy acid, so compound **A** must be an alkene. There are many alkenes with the molecular formula C_6H_{12}, and it would be time-consuming to try to draw them all. Instead, we notice the following: in order for the product to have no chiral centers, each of the vinylic positions must already contain two identical groups, like this:

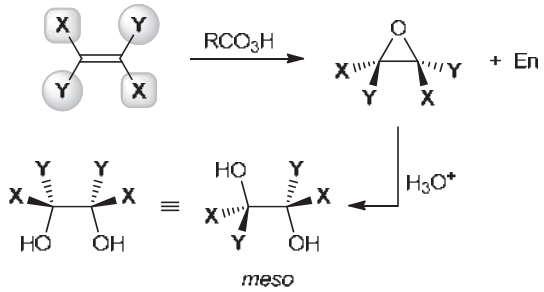


There are only two alkenes with the molecular formula C_6H_{12} that fit this criterion:





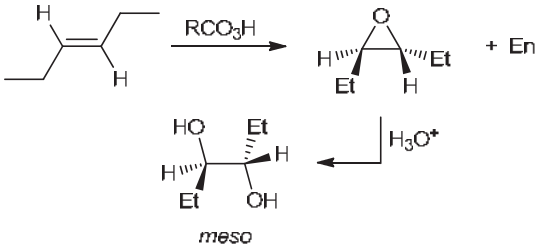
(b) In order to be a *meso* compound, the resulting diol must contain two chiral centers, as well as reflectional symmetry (such as an internal plane of symmetry). In order to achieve this result, the starting alkene must have the following structural features:



The identity of X and Y must be different, or the resulting diol would have no chiral centers. There is

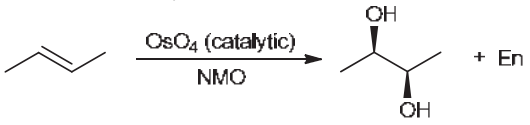
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only one alkene with the molecular formula C_6H_{12} that fits this criterion:

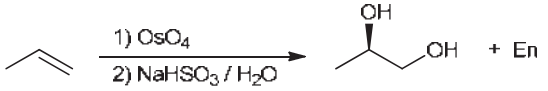


8.27.

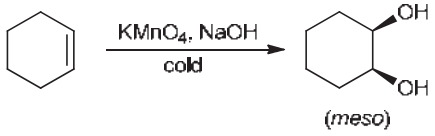
(a) Treating an alkene with catalytic osmium tetroxide and NMO results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *syn* addition:



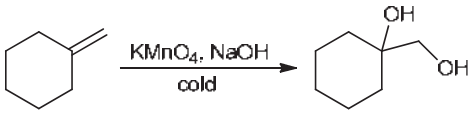
(b) Treating an alkene with osmium tetroxide followed by aqueous sodium bisulfite results in the addition of OH and OH across the alkene. In this case, only one chiral center is created, so we expect both possible enantiomers (formation of the initial cyclic osmate ester can occur on either face of the π bond with equal likelihood):



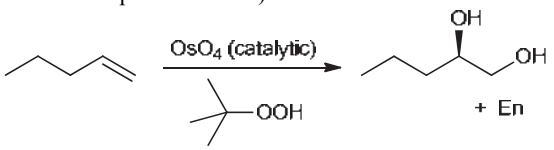
(c) Treating an alkene with cold potassium permanganate and sodium hydroxide results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, and we expect a *syn* addition, giving the following *meso* compound:



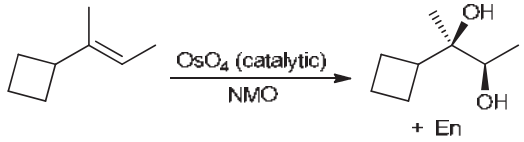
(d) Treating an alkene with cold potassium permanganate and sodium hydroxide results in the addition of OH and OH across the alkene. In this case, the product has no chiral centers, so stereochemistry is not a relevant consideration.



(e) Treating an alkene with catalytic osmium tetroxide and a suitable co-oxidant (*tert*-butyl hydroperoxide) results in the addition of OH and OH across the alkene. In this case, only one chiral center is created, so we expect both possible enantiomers (formation of the initial cyclic osmate ester can occur on either face of the π bond with equal likelihood):

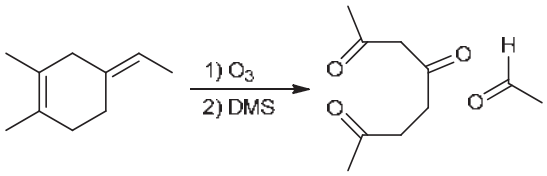


(f) Treating an alkene with catalytic osmium tetroxide and NMO results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *syn* addition:

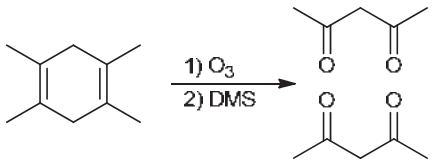


8.28.

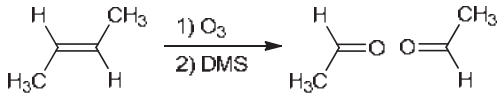
(a) Each C=C bond is split apart and redrawn as two C=O bonds, giving the following products:



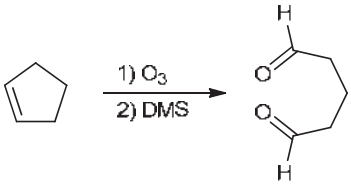
(b) Each C=C bond is split apart and redrawn as two C=O bonds, giving two equivalents of the same product:



(c) The C=C bond is split apart and redrawn as two C=O bonds, giving two equivalents of the same product:

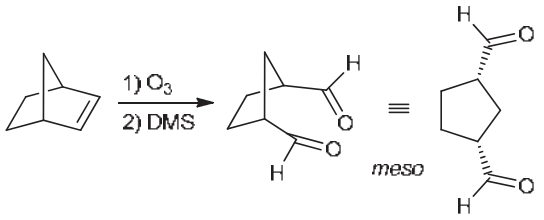


(d) The C=C bond is split apart and redrawn as two C=O bonds, giving the following product:

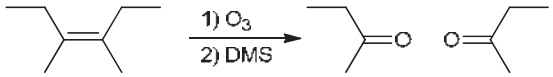


(e) The C=C bond is split apart and redrawn as two C=O bonds, giving the following *meso* compound:

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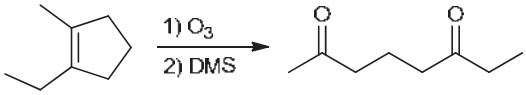


(f) The C=C bond is split apart and redrawn as two C=O bonds, giving two equivalents of the same product:

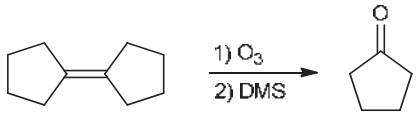


8.29.

(a) We can draw the starting alkene by removing the two oxygen atoms from the product, and connecting the sp^2 hybridized carbon atoms as a C=C bond:

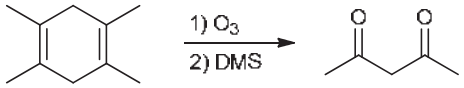


(b) In this case, the starting alkene has ten carbon atoms while the product has only five carbon atoms. Therefore, one equivalent of the starting alkene must produce two equivalents of the product:



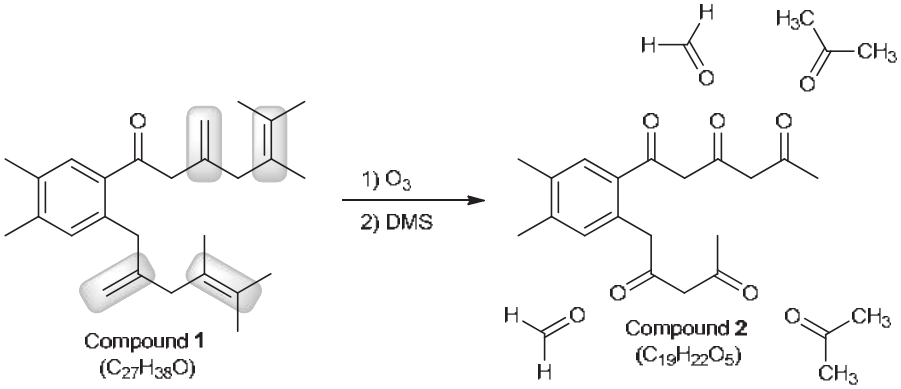
(two equivalents)

(c) In this case, the starting alkene has ten carbon atoms while the product has only five carbon atoms. Therefore, one equivalent of the starting alkene must produce two equivalents of the product:



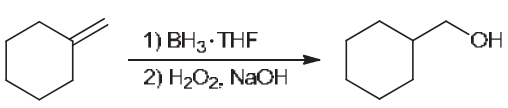
(two equivalents)

8.30. The starting material ($C_{27}H_{38}O$) has only one oxygen atom, while compound **2** ($C_{19}H_{22}O_5$) has five oxygen atoms. The insertion of four oxygen atoms (and the production of four small molecules) indicates that four C=C bonds (highlighted below) undergo ozonolysis. The other three C=C bonds (in the ring) are part of the aromatic system, which is unreactive toward ozonolysis, as mentioned in the problem statement. To draw the products of ozonolysis, each C=C bond is split apart and redrawn as two C=O bonds. This gives compound **2**, shown below, along with two molecules of formaldehyde (CH_2O) and two molecules of acetone ($(CH_3)_2CO$).

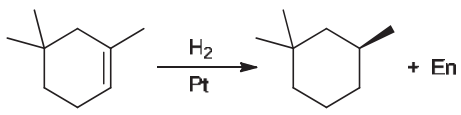


8.31.

(a) The reagents indicate a hydroboration-oxidation, so the net result will be the addition of H and OH across the alkene. For the regiochemical outcome, we expect an *anti*-Markovnikov addition, so the OH group is installed at the less-substituted position. The stereochemical outcome (*syn* addition) is not relevant in this case, because the product has no chiral centers:

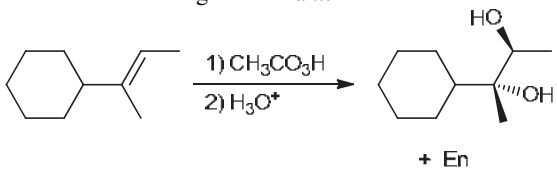


(b) The reagents indicate a hydrogenation reaction, so the net result will be the addition of H and H across the alkene. The regiochemical outcome is not relevant because the two groups added (H and H) are identical. We expect the reaction to proceed via a *syn* addition, but only one chiral center is formed. Therefore, both enantiomers are obtained because *syn* addition can occur from either face of the starting alkene:

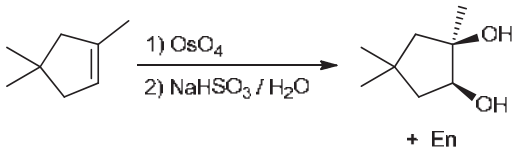


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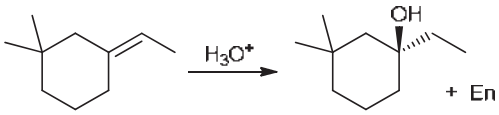
(c) The first reagent is a peroxy acid, indicating formation of an epoxide, which is then opened under aqueous acidic conditions. The net result is expected to be the addition of OH and OH across the alkene. The regiochemical outcome is not relevant because the two groups added (OH and OH) are identical. For the stereochemical outcome, we notice that two chiral centers are formed, and we expect only the pair of enantiomers resulting from an *anti* addition:



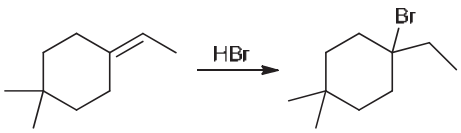
(d) The reagents indicate a dihydroxylation reaction, so the net result will be the addition of OH and OH across the alkene. The regiochemical outcome is not relevant because the two groups added (OH and OH) are identical. We expect the reaction to proceed via a *syn* addition. In this case, two chiral centers are formed, so we expect only the pair of enantiomers resulting from a *syn* addition:



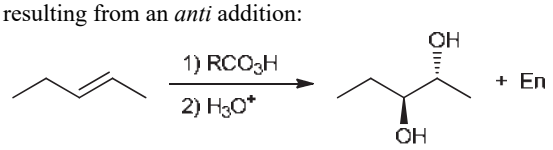
(e) The reagent indicates an acid-catalyzed hydration, so the net result will be the addition of H and OH across the alkene. We expect a Markovnikov addition, so the OH group will be installed at the more-substituted position. Only one chiral center is formed, so we expect the following pair of enantiomers:



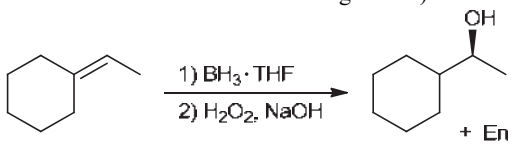
(f) The reagent indicates a hydrobromination reaction, so the net result will be the addition of H and Br across the alkene. We expect a Markovnikov addition, so the Br group will be installed at the more-substituted position. No chiral centers are formed in this case, so stereochemistry is irrelevant:



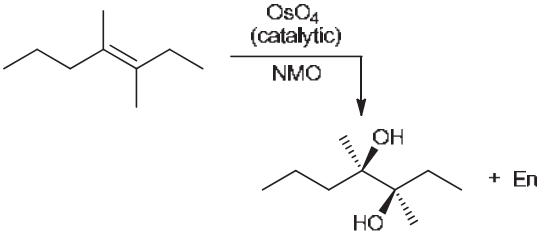
(g) The reagents indicate a dihydroxylation process (via an epoxide), so the net result will be the addition of OH and OH across the alkene. The regiochemical outcome is not relevant because the two groups added (OH and OH) are identical. We expect the reaction to proceed via an *anti* addition. In this case, two chiral centers are formed, so we expect only the pair of enantiomers resulting from an *anti* addition:



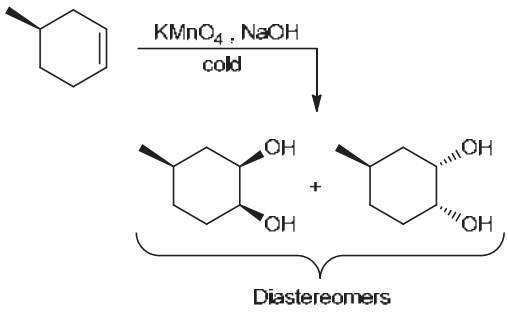
(h) The reagents indicate a hydroboration-oxidation, so the net result will be the addition of H and OH across the alkene. For the regiochemical outcome, we expect an *anti*-Markovnikov addition, so the OH group is installed at the less-substituted position. We expect the reaction to proceed via a *syn* addition, but only one chiral center is formed, so we expect both enantiomers (*syn* addition can occur on either face of the starting alkene):



(i) The reagents indicate a dihydroxylation reaction, so the net result will be the addition of OH and OH across the alkene. The regiochemical outcome is not relevant because the two groups added (OH and OH) are identical. We expect the reaction to proceed via a *syn* addition. In this case, two chiral centers are formed, so we expect only the pair of enantiomers resulting from a *syn* addition:

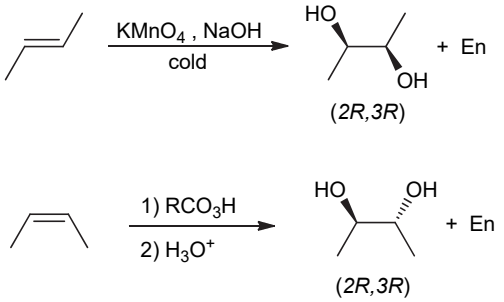


8.32. The net result will be the addition of OH and OH across the alkene. The regiochemical outcome is not relevant because the two groups added (OH and OH) are identical. We expect the reaction to proceed via a *syn* addition. In this case, two chiral centers are formed, so we expect the two products shown below. Because of the presence of a third chiral center, these two products are diastereomers, rather than enantiomers.

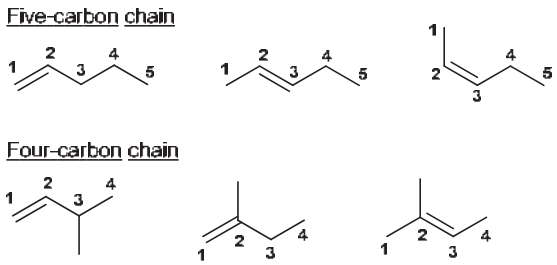


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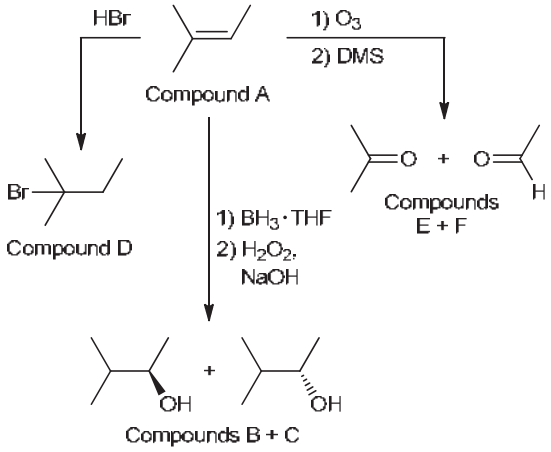
8.33. *syn*-Dihydroxylation of *trans*-2-butene results in the same products as *anti*-dihydroxylation of *cis*-2-butene, as shown below. The configuration of each chiral center has been assigned to demonstrate that the products are indeed the same for these two reaction sequences:



8.34. Compound **A** must be an alkene (because it undergoes reactions that are typically observed for alkenes, such as hydroboration-oxidation, hydrobromination and ozonolysis). So, we begin by drawing all possible alkenes with the molecular formula C_5H_{10} (using a methodical approach similar to the one described in the solution to Problem 4.3):

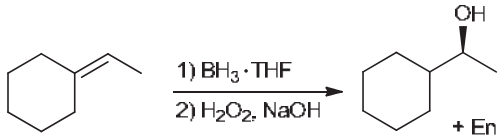


Among these isomers, only the last two will afford a tertiary alkyl halide upon treatment with HBr. And among these two alkenes, only the latter will undergo ozonolysis to produce a compound with three carbon atoms and another compound with two carbon atoms. Now that we have identified the starting alkene, we can draw the products B-F, as shown here:

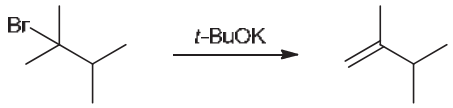


8.35.

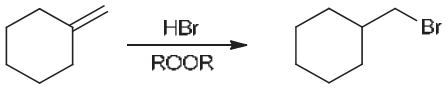
(a) The two groups being added across the alkene are H and OH. The OH group is installed at the less-substituted carbon atom, so we must use conditions that give an *anti*-Markovnikov addition of H and OH. This can be accomplished via hydroboration-oxidation. The reaction proceeds via a *syn* addition, which can occur on either face of the alkene, giving a pair of enantiomers:



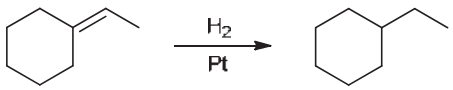
(b) This reaction involves elimination of H and Br to give the less-substituted alkene, so a sterically hindered base (such as *tert*-butoxide) is required:



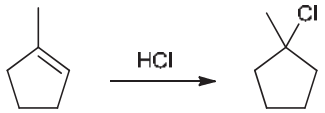
(c) The two groups being added across the alkene are H and Br. The Br group is installed at the less-substituted carbon atom, so we must use conditions that give an *anti*-Markovnikov addition of H and Br. This can be accomplished by treating the alkene with HBr in the presence of peroxides.



(d) The two groups being added across the alkene are H and H, which can be accomplished by treating the alkene with molecular hydrogen (H_2) in the presence of a suitable catalyst.



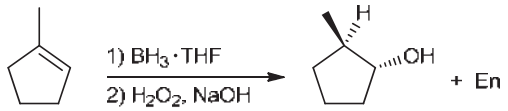
(e) The two groups being added across the alkene are H and Cl. The latter is installed at the more-substituted carbon atom, so we must use conditions that give a Markovnikov addition of H and Cl. This can be accomplished by treating the alkene with HCl.



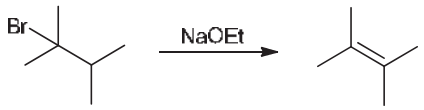
(f) The two groups being added across the alkene are H and OH. The OH group is installed at the less-substituted position, so we must use conditions that give an *anti*-Markovnikov addition of H and OH. Also, the H and OH are added in a *syn* fashion (this can be seen more clearly if you draw the H that was installed, as shown

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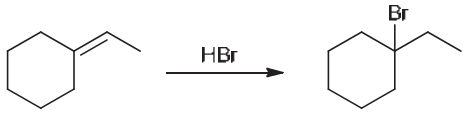
below). This can be accomplished via hydroboration-oxidation:



(g) This reaction involves elimination of H and Br to give the more-substituted alkene, so we must use a strong base that is not sterically hindered. We can use hydroxide, methoxide or ethoxide as the base. All of these bases are suitable, as the substrate is tertiary so S_N2 reactions will not compete.

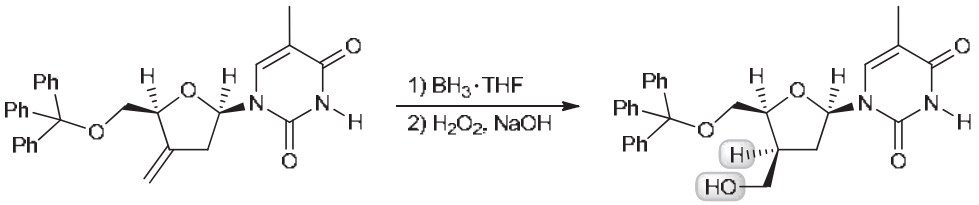


(h) The two groups being added across the alkene are H and Br. The latter is installed at the more-substituted carbon atom, so we must use conditions that give a Markovnikov addition of H and Br. This can be accomplished by treating the alkene with HBr.

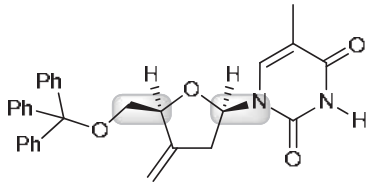


8.36.

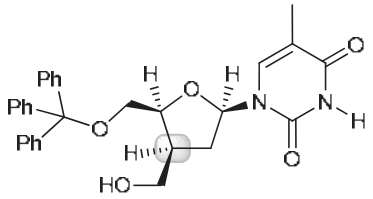
(a) The two groups that are being added across the double bond are OH and H. The OH group must be installed at the less-substituted position, so we must choose reagents that achieve an *anti*-Markovnikov addition. This can be accomplished via hydroboration-oxidation.



(b) The addition of OH and H can occur via a *syn* addition to either face of the π bond. The configuration of the newly formed chiral center (as shown above) results from addition to the back side of the π bond. Hydroboration occurs preferentially on the back face of the π bond in order to minimize steric interactions with the other two very large groups (both on wedges) which are both on the front face.



Although both H and OH are added across the π bond, only the addition of H creates a new chiral center. Addition of H to the back side of the π bond pushes the CH_2OH group forward, as seen in the major product.

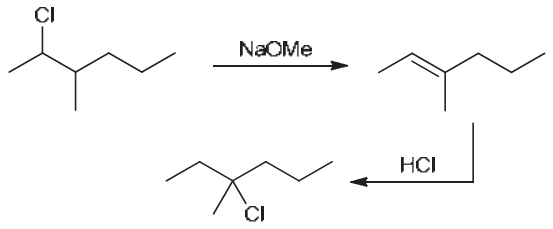


8.37.

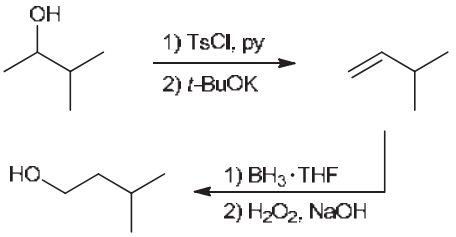
(a) The desired transformation can be achieved via a two-step process (elimination, followed by addition). We must be careful to control the regiochemical outcome of each of these processes. During the elimination process, we want to form the more-substituted alkene, so we must use a strong base that is not sterically hindered (such as hydroxide, methoxide, or ethoxide). Then, during the addition process, we want to add HCl in a Markovnikov fashion (with the Cl being installed at the

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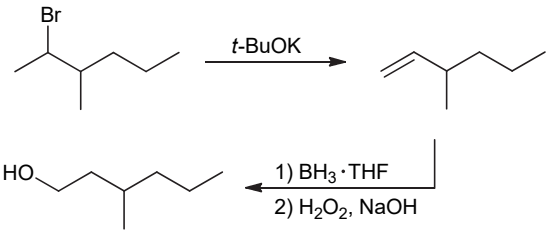
more-substituted position). This can be accomplished by treating the alkene with HCl, as shown here:



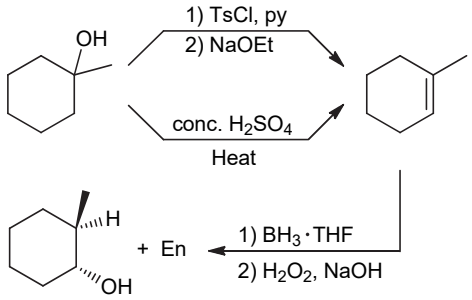
(b) The desired transformation can be achieved via elimination, followed by addition. We must be careful to control the regiochemical outcome of each of these processes. During the elimination process, we want to form the less-substituted alkene, so we must use a strong, sterically hindered base, such as potassium *tert*-butoxide. Notice that the substrate is an alcohol, so we must first convert the OH group (bad leaving group) into a tosylate group (good leaving group) before performing the elimination process. Then, during the addition process, we want to add H and OH in an *anti*-Markovnikov fashion (with the OH being installed at the less-substituted position). This can be accomplished via hydroboration-oxidation, as shown here:



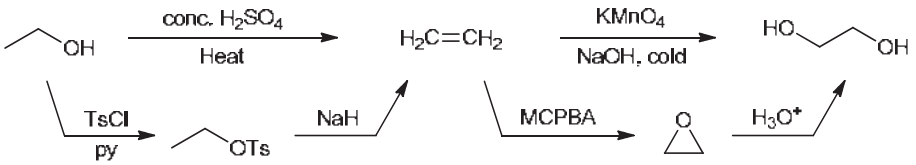
(c) The desired transformation can be achieved via elimination, followed by addition. We must be careful to control the regiochemical outcome of each of these processes. During the elimination process, we want to form the less-substituted alkene, so we must use a strong, sterically hindered base, such as potassium *tert*-butoxide. Then, during the addition process, we want to add H and OH in an *anti*-Markovnikov fashion (with the OH being installed at the less-substituted position). This can be accomplished via hydroboration-oxidation, as shown here:



(d) The desired transformation can be achieved via elimination, followed by addition. We must be careful to control the regiochemical outcome of each of these processes. During the elimination process, we want to form the more-substituted alkene, so we will need a strong base that is not sterically hindered (such as hydroxide, methoxide, or ethoxide). Notice that the substrate is an alcohol, so we must first convert the OH group (bad leaving group) into a tosylate group (good leaving group) before performing the elimination process. Alternatively, we can simply perform the elimination process in one step by treating the alcohol with concentrated aqueous sulfuric acid (via an E1 process, as seen in Section 7.12). Then, during the addition process, we want to add H and OH in an *anti*-Markovnikov fashion (with the OH being installed at the less-substituted position) via a *syn* addition (this can be seen more clearly if you draw the H that is installed, as shown). This can be accomplished via hydroboration-oxidation:



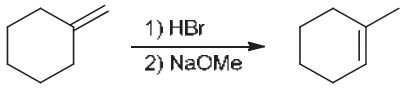
8.38. The desired transformation can be achieved via a two-step process (elimination, followed by addition). Notice that the substrate is an alcohol, so we can simply perform the elimination process by treating the alcohol with concentrated aqueous sulfuric acid. Alternatively, we can first convert the OH group (bad leaving group) into a tosylate group (good leaving group) before performing an elimination process. Treating the resulting ethylene with cold potassium permanganate and sodium hydroxide results in the addition of two OH groups across the alkene, providing the target structure ethylene glycol. Alternatively, the dihydroxylation can be accomplished in a two-step process by epoxide ring-opening. Since there are no chiral centers in the product, *syn*- or *anti*-dihydroxylation of the alkene both give rise to the same diol.



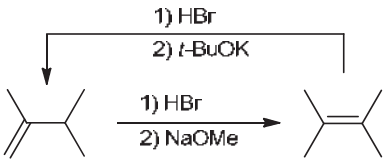
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8.39.

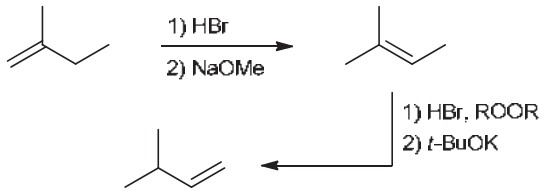
(a) The desired transformation can be achieved via a two-step process (addition, followed by elimination). We must be careful to control the regiochemical outcome of each step of the process. During the addition reaction, we want to install Br at the more-substituted position, so we treat the alkene with HBr (without peroxides). Then, the elimination process must be performed in a way that gives the more-substituted alkene, so we must use a strong base that is not sterically hindered, such as methoxide (hydroxide or ethoxide can also be used).



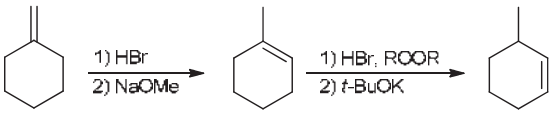
(b) These two alkenes can be interconverted via a two-step process (addition, followed by elimination). We must be careful to control the regiochemical outcome of each step of the process. In one case, a sterically hindered base is required, while in the other case, we must use a base that is not sterically hindered, as shown.



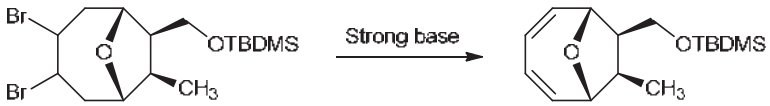
(c) The two-step process (addition followed by elimination) must be used twice in this case. First, we perform a Markovnikov addition of HBr to install Br at the more-substituted position, followed by elimination with a base that is not sterically hindered, thereby giving the more-substituted alkene. Then, we perform the two-step process again. But this time, we begin with an *anti*-Markovnikov addition of HBr (in the presence of peroxides) to install Br at the less-substituted position, followed by elimination with a sterically hindered base to give the less substituted alkene:



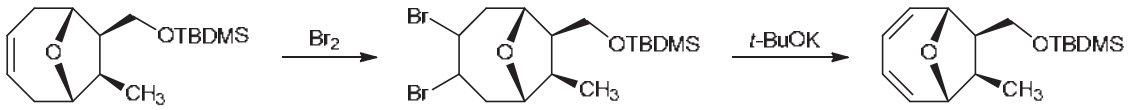
(d) The two-step process (addition followed by elimination) must be used twice in this case. First, we perform a Markovnikov addition of HBr to install Br at the more-substituted position, followed by elimination with a base that is not sterically hindered, thereby giving the more-substituted alkene. Then, we perform the two-step process again. But this time, we begin with an *anti*-Markovnikov addition of HBr (in the presence of peroxides) to install Br at the less-substituted position, followed by elimination with a sterically hindered base to give the less substituted alkene.



8.40. Notice that there are two π bonds in compound **2**, but only one π bond in compound **1**, so we need to add a π bond as well as move one. Each of the π bonds in the product can be made via an elimination reaction, so making both π bonds requires two leaving groups:



Both elimination reactions are favored if we use a bulky base, such as *tert*-butoxide. The necessary dibromide can be made directly from compound **1**, via bromination of the π bond. This gives the following two-step synthesis:

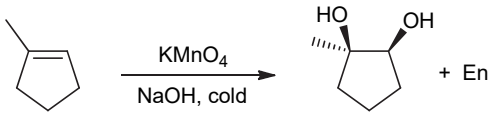


8.41. A reaction is only favorable if ΔG is negative. Recall that ΔG has two components: (ΔH) and ($-T\Delta S$). The first term (ΔH) is positive for this reaction (two σ bonds are converted into one σ bond and one π bond). The second term ($-T\Delta S$) is negative because ΔS is positive (one molecule is converted into two molecules). Therefore, the reaction is only favorable if the second term is greater in magnitude than the first term. This only occurs at high temperature.

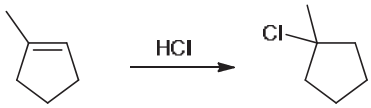
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8.42.

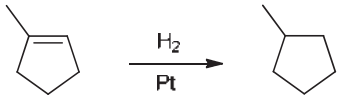
(a) Treating an alkene with cold potassium permanganate and sodium hydroxide results in the addition of OH and OH across the alkene. In this case, two new chiral centers are generated, so we expect only the pair of enantiomers that would result from *syn* addition:



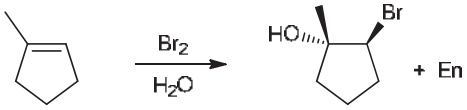
(b) The reagent indicates a hydrochlorination reaction, so the net result will be the addition of H and Cl across the alkene. We expect a Markovnikov addition, so the Cl group will be installed at the more-substituted position. No chiral centers are formed in this case, so stereochemistry is irrelevant:



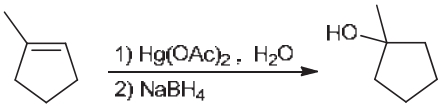
(c) The reagents indicate a hydrogenation reaction, so the net result will be the addition of H and H across the alkene. The regiochemical outcome is not relevant because the two groups added (H and H) are identical. The stereochemical requirement for the reaction (*syn* addition) is not relevant in this case, as no chiral centers are formed:



(d) The reagents indicate bromohydrin formation, so the net result will be the addition of Br and OH across the alkene. The OH group is expected to be installed at the more-substituted position. The reaction proceeds via an *anti* addition, giving the following pair of enantiomers:

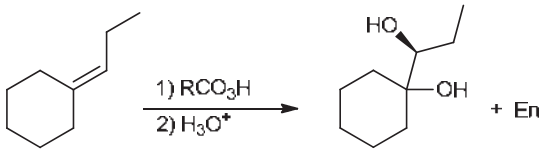


(e) The reagents indicate hydration of the alkene via oxymercuration-demercuration. The net result will be the addition of H and OH across the alkene, with the OH group being installed at the more-substituted position. The product has no chiral centers, so stereochemistry is not a consideration:

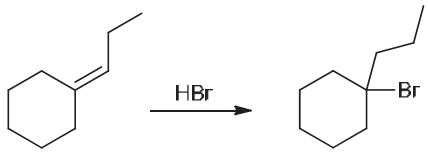


8.43.

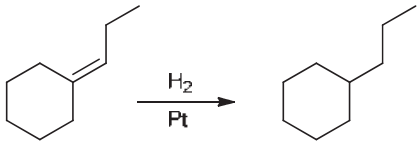
(a) The reagents indicate the addition of OH and OH across the alkene. The regiochemical outcome is not relevant because the two groups added (OH and OH) are identical. We expect the reaction to proceed via an *anti* addition, but only one chiral center is formed, so we expect both enantiomers:



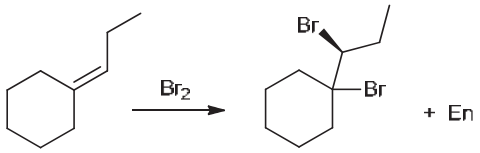
(b) The reagent indicates a hydrobromination reaction, so the net result will be the addition of H and Br across the alkene. We expect a Markovnikov addition, so Br will be installed at the more-substituted position. No chiral centers are formed in this case, so stereochemistry is irrelevant:



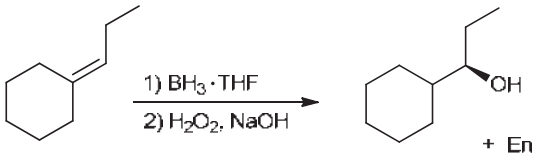
(c) The reagents indicate a hydrogenation reaction, so the net result will be the addition of H and H across the alkene. The regiochemical outcome is not relevant because the two groups added (H and H) are identical. No chiral centers are formed in this case, so stereochemistry is also irrelevant.



(d) The reagent indicates a bromination reaction, so the net result will be the addition of Br and Br across the alkene. The regiochemical outcome is not relevant because the two groups added (Br and Br) are identical. We expect the reaction to proceed via an *anti* addition, but only one chiral center is formed, so we expect both enantiomers:



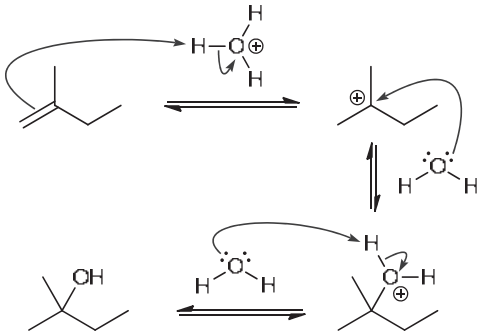
(e) The reagents indicate a hydroboration-oxidation, so the net result will be the addition of H and OH across the alkene. For the regiochemical outcome, we expect an *anti*-Markovnikov addition, so the OH group is installed at the less-substituted (secondary) position. We expect the reaction to proceed via a *syn* addition, but only one chiral center is formed, so we expect both enantiomers (*syn* addition can occur on either face of the alkene):



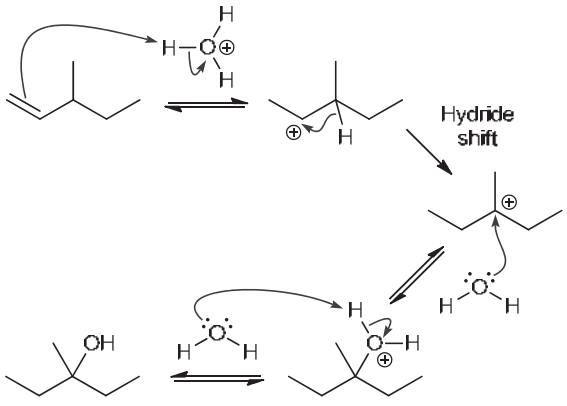
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8.44.

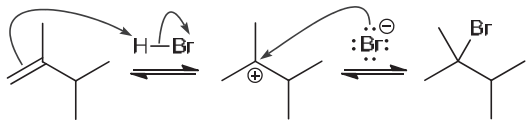
(a) Water (H and OH) is added across the alkene in a Markovnikov fashion. The mechanism is expected to have three steps: 1) proton transfer, 2) nucleophilic attack, and 3) proton transfer. In the first step, a proton is transferred from H_3O^+ to the alkene, which requires two curved arrows, as shown below. The resulting tertiary carbocation is then captured by a water molecule in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile (water) to the electrophile (the carbocation). Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows, as shown:



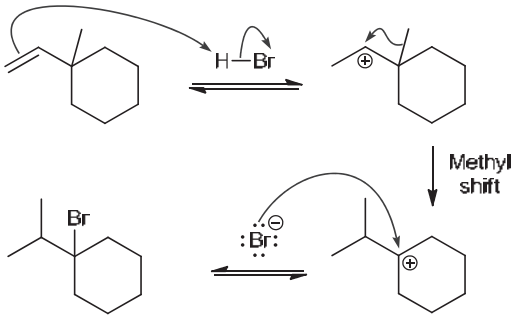
(b) In the first step of the mechanism, a proton is transferred from H_3O^+ to the alkene, which requires two curved arrows, as shown below. The resulting secondary carbocation then rearranges via a hydride shift, giving a more stable, tertiary carbocation. That step is shown with one curved arrow. The tertiary carbocation is then captured by a water molecule, which is shown with one curved arrow, going from the nucleophile (water) to the electrophile (the carbocation). Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows, as shown:



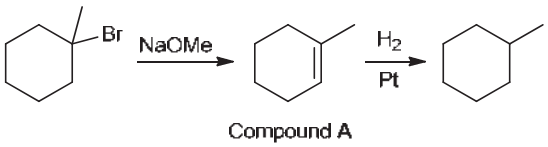
(c) In this reaction, H and Br are added across the alkene in a Markovnikov addition, which indicates an ionic process. There are two mechanistic steps in the ionic addition of HBr across an alkene: 1) proton transfer, followed by 2) nucleophilic attack. In the first step, a proton is transferred from HBr to the alkene, which requires two curved arrows, as shown below. The resulting tertiary carbocation is then captured by a bromide ion in the second step of the mechanism. This step requires one curved arrow, going from the nucleophile to the electrophile, as shown:



(d) Protonation of the alkene requires two curved arrows, as shown, and leads to the secondary carbocation (rather than a primary carbocation). This secondary carbocation then undergoes a methyl shift, shown with one curved arrow, generating a more stable, tertiary carbocation. In the final step of the mechanism (nucleophilic attack), the carbocation is captured by a bromide ion. This step requires one curved arrow, going from the nucleophile (bromide) to the electrophile (the carbocation), as shown:



8.45. The starting material (1-bromo-1-methylcyclohexane) is a tertiary alkyl halide, and will undergo an E2 reaction when treated with a strong base such as methoxide, to give the more substituted alkene (compound **A**). Hydrogenation of compound **A** gives methylcyclohexane:

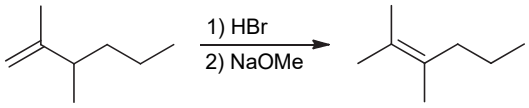


8.46.

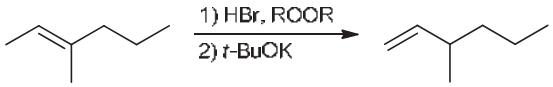
(a) The desired transformation can be achieved via a two-step process (addition, followed by elimination). We must be careful to control the regiochemical outcome of each step of the process. During the addition reaction, we want to install Br at the more-substituted (tertiary) position, so we treat the alkene with HBr (without peroxides present). Then, the elimination process must be performed in a way that gives the more-substituted

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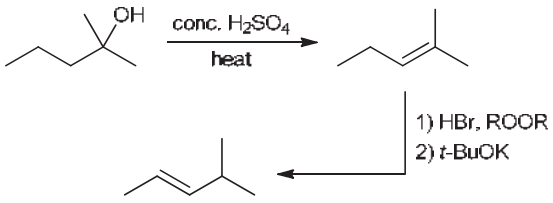
alkene, so we must use a strong base that is not sterically hindered, such as methoxide (hydroxide or ethoxide can also be used).



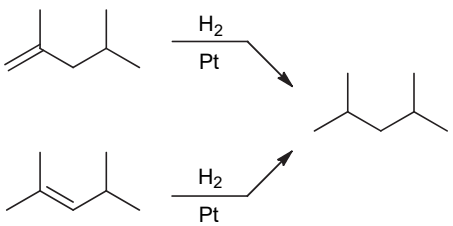
(b) This trisubstituted alkene can be converted into the monosubstituted alkene via a two-step process (addition, followed by elimination). We must be careful to control the regiochemical outcome of each of these steps. During the addition process, we want to install Br at the less-substituted (secondary) position, so we treat the alkene with HBr in the presence of peroxides. Then, the elimination process must be performed in a way that gives the less-substituted alkene, so we must use a strong, sterically hindered base (such as *tert*-butoxide).



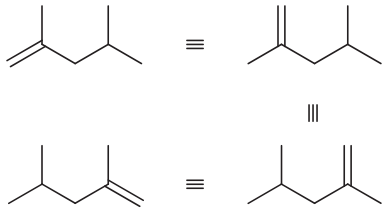
8.47. Treatment of the starting alcohol with concentrated sulfuric acid affords the more substituted alkene. Moving the position of the π bond can then be achieved via a two step-process (addition, followed by elimination). We must be careful to control the regiochemical outcome of each step of the process. During the addition reaction, we want to install Br at the less-substituted (secondary) position, so we treat the alkene with HBr in the presence of peroxides. Then, the elimination reaction must be performed in a way that gives the less-substituted alkene, so we must use a strong, sterically hindered base (such as *tert*-butoxide).



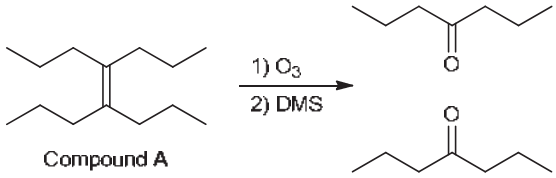
8.48. Two different alkenes will produce 2,4-dimethylpentane upon hydrogenation:



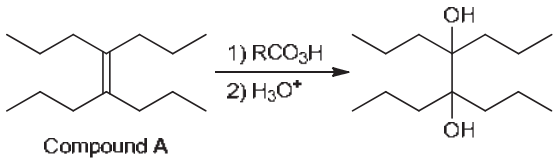
Note that the following four drawings all represent the same compound:



8.49. We must first determine the structure of compound **A**. The necessary information has been provided. Specifically, ozonolysis of compound **A** gives only one product, which has only one C=O bond. Therefore, the starting alkene must be symmetrical, leading to two equivalents of the product:

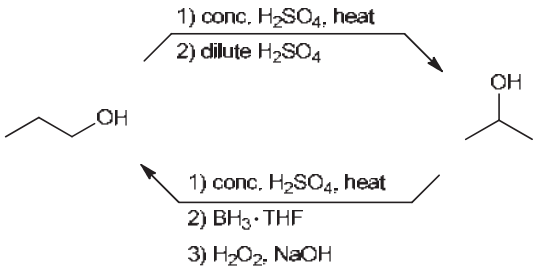


Treatment of compound **A** with a peroxy acid, followed by aqueous acid, affords a diol. No chiral centers are formed, so stereochemistry is not a relevant consideration.



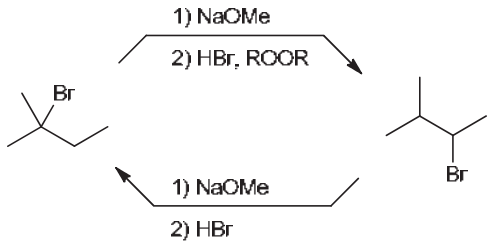
8.50.

(a) Interconversion between the two alcohols requires moving the position of the OH group. In each case, this can be accomplished via a two step-process (elimination followed by addition). In each case, the elimination step can be achieved by treating the alcohol with concentrated sulfuric acid. For the addition step, the regiochemical outcome must be carefully considered. In the first case below, dilute aqueous acid is used to give a Markovnikov addition, while in the second case below, hydroboration-oxidation is employed to give an *anti*-Markovnikov addition.

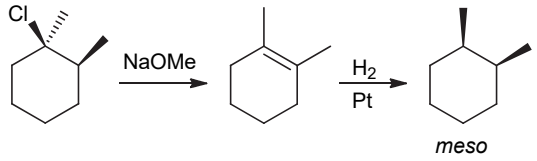


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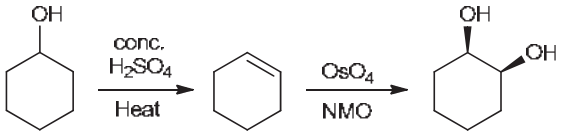
(b) Interconversion between the two alkyl halides requires moving the position of Br. In each case, this can be accomplished via a two step-process (elimination followed by addition). In each case, the elimination step can be achieved via an E2 reaction, using a strong base (such as hydroxide, or methoxide or ethoxide) to give the more substituted alkene. For the addition step, the regiochemical outcome must be carefully considered. In the first case below, HBr and peroxides are used to give an *anti*-Markovnikov addition, while in the second case below, HBr is used to give a Markovnikov addition.



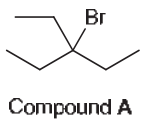
(c) Treating the starting material with a strong base (such as hydroxide, methoxide or ethoxide) gives the more substituted (tetrasubstituted) alkene, which can then be converted to the desired *meso* compound upon hydrogenation.



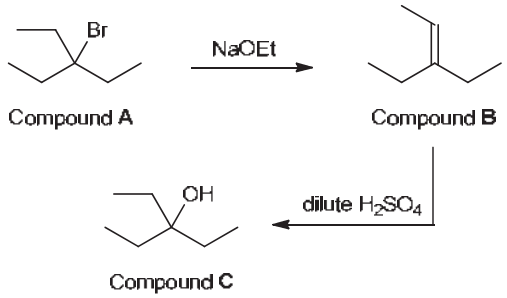
(d) The product is a *cis*-diol which can be prepared via a *syn* dihydroxylation. The necessary alkene (cyclohexene) can be made in one step from the starting alcohol, upon treatment with concentrated sulfuric acid (an E1 reaction):



8.51. Treatment of compound **A** with sodium ethoxide gives no S_N2 products, so the substrate must be tertiary. Only one elimination product is obtained, which means that all β positions are identical. These features indicate the following structure for compound **A**:

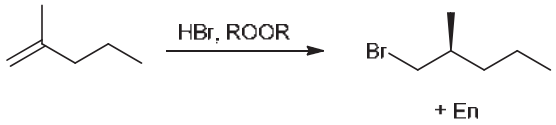


Treatment of compound **A** with ethoxide gives alkene **B**, shown below, which undergoes acid-catalyzed hydration (Markovnikov addition of water) to give alcohol **C**:

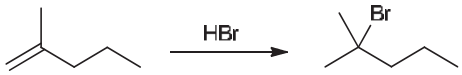


8.52.

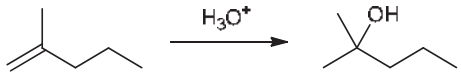
(a) This conversion requires an *anti*-Markovnikov addition of H and Br across the alkene, which can be achieved in just one step, by treating the starting alkene with HBr in the presence of peroxides:



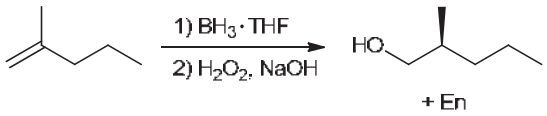
(b) This conversion requires a Markovnikov addition of H and Br across the alkene, which can be achieved in just one step, by treating the starting alkene with HBr:



(c) This conversion requires a Markovnikov addition of H and OH across the alkene, which can be achieved via acid-catalyzed hydration:



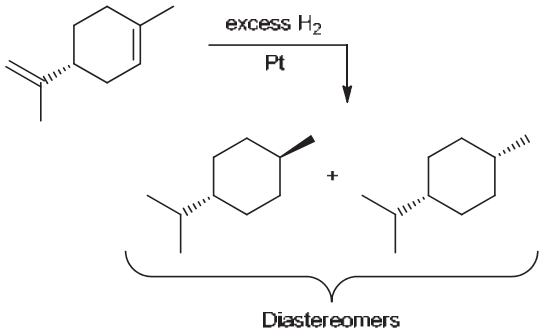
(d) This conversion requires an *anti*-Markovnikov addition of H and OH across the alkene, which can be achieved via hydroboration-oxidation. The process does proceed via *syn* addition, but only one chiral center is formed, and the *syn* addition can take place on either face of the alkene, giving a pair of enantiomers.



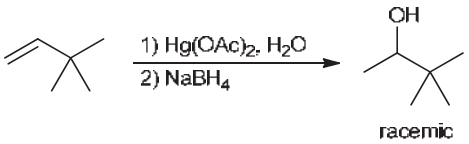
8.53. When treated with excess molecular hydrogen, both π bonds are expected to be reduced. The π bond incorporated in the ring can undergo hydrogenation from either face of the π bond, leading to the following two compounds. These disubstituted cyclohexanes are

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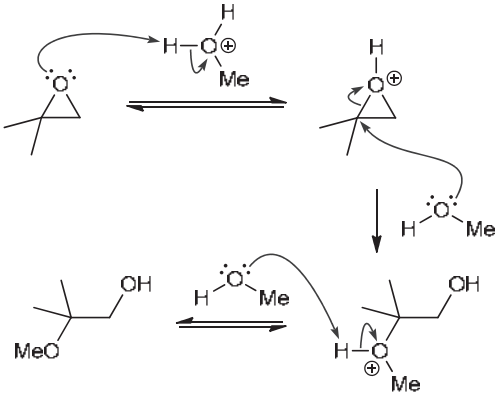
diastereomers because they are stereoisomers that are not mirror images of each other.



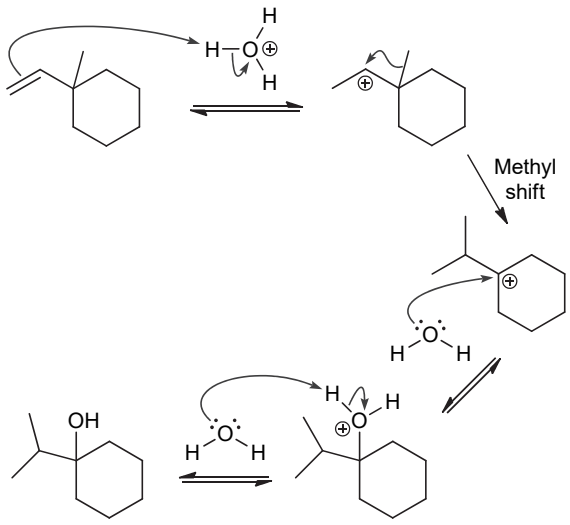
8.54. This conversion requires the Markovnikov addition of water *without* carbocation rearrangement. This can be achieved via oxymercuration-demercuration:



8.55. In the presence of acid, the epoxide is first protonated, which requires two curved arrows, as shown below. The resulting intermediate is then attacked by a molecule of methanol, which functions as a nucleophile. This step requires two curved arrows. Then, in the final step of the mechanism, a molecule of methanol functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows:

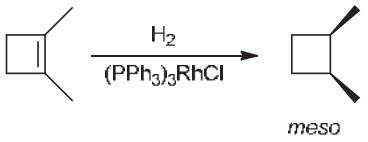


8.56. In the first step of the mechanism, a proton is transferred from H_3O^+ to the alkene, which requires two curved arrows, as shown. The resulting secondary carbocation then rearranges via a methyl shift, giving a more stable, tertiary carbocation. That step is shown with one curved arrow. The tertiary carbocation is then captured by a water molecule, which is shown with one curved arrow, going from the nucleophile (water) to the electrophile (the carbocation). Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows, as shown:

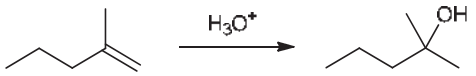


8.57.

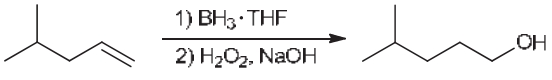
(a) The reagents indicate a hydrogenation reaction, so the net result will be the addition of H and H across the alkene. The regiochemical outcome is not relevant because the two groups added (H and H) are identical. We expect the reaction to proceed via a *syn* addition, giving the following *meso* compound:



(b) The reagents indicate an acid-catalyzed hydration, so the net result will be the addition of H and OH across the alkene. We expect a Markovnikov addition, so the OH group will be installed at the more-substituted position. No chiral centers are formed in the process, so stereochemistry is not a relevant consideration:



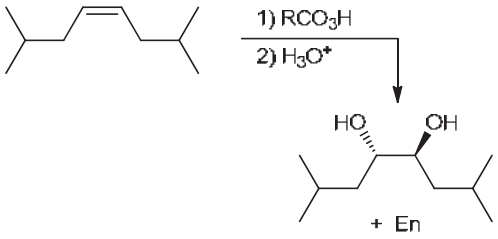
(c) The reagents indicate a hydroboration-oxidation, so the net result will be the addition of H and OH across the alkene. For the regiochemical outcome, we expect an *anti*-Markovnikov addition, so the OH group is installed at the less-substituted position. The stereochemical outcome (*syn* addition) is not relevant in this case, because the product has no chiral centers:



(d) The reagents indicate a dihydroxylation process (via an epoxide), so the net result will be the addition of OH and OH across the alkene. The regiochemical outcome

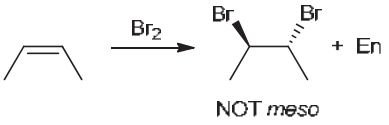
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is not relevant because the two groups added (OH and OH) are identical. We expect the reaction to proceed via an *anti* addition. In this case, two chiral centers are formed, so we expect the pair of enantiomers resulting from an *anti* addition:

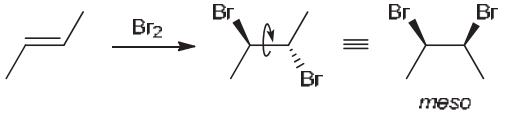


8.58.
(a) Hydroboration-oxidation gives an *anti*-Markovnikov addition. If 1-propene is the starting material, the OH group will not be installed in the correct location. Acid-catalyzed hydration of 1-propene would give the desired product.
(b) Hydroboration-oxidation gives a *syn* addition of H and OH across a double bond. This compound does not have a proton that is *cis* to the OH group, and therefore, hydroboration-oxidation cannot be used to make this compound.
(c) Hydroboration-oxidation gives an *anti*-Markovnikov addition. There is no starting alkene that would yield the desired product via an *anti*-Markovnikov addition.

8.59. Bromination of *cis*-2-butene does NOT give the desired *meso* compound:



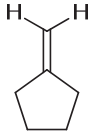
In contrast, *trans*-2-butene gives the desired *meso* compound, as shown:



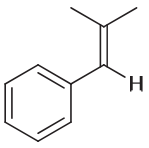
Therefore, compound **X** is *trans*-2-butene.

8.60. In each of the following cases, we draw the necessary alkene by removing the oxygen atoms from the product and connecting the sp^2 hybridized carbon atoms to form a C=C bond:

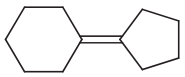
(a)



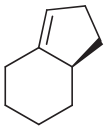
(b)



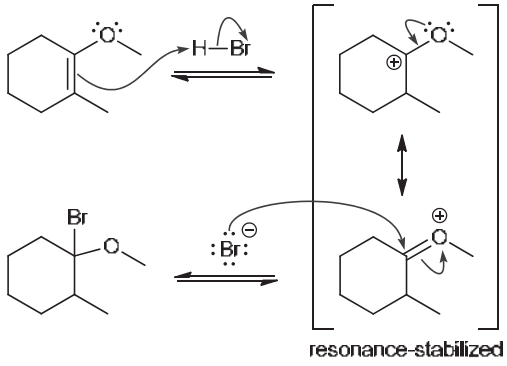
(c)



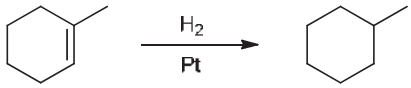
(d)



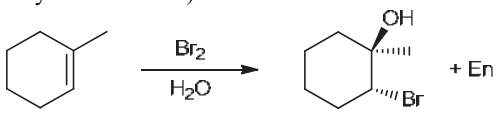
8.61. In the presence of a strong acid, the π bond is protonated to give a resonance-stabilized cation (shown below), which is even lower in energy than a tertiary carbocation. This protonation step determines the regiochemical outcome of the reaction, because the resonance-stabilized cation is captured by a bromide ion to give the product, as shown.



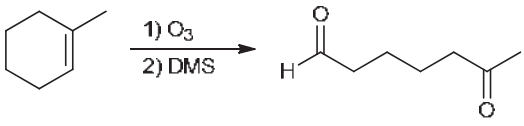
8.62.
(a) The two groups being added across the alkene are H and H, which can be accomplished by treating the alkene with molecular hydrogen (H_2) in the presence of a suitable catalyst.



(b) The two groups being added across the alkene are Br and OH in an *anti* fashion, with the latter being installed at the more substituted position. This can be achieved by treating the alkene with Br_2 in the presence of water (halohydrin formation):



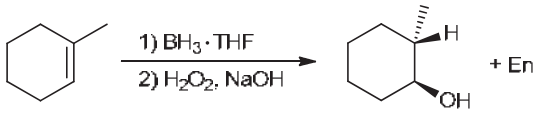
(c) Cleavage of the C=C double bond can be achieved via ozonolysis:



(d) The two groups being added across the alkene are H and OH. The OH group must be installed at the less-substituted carbon atom, so we must use conditions that give an *anti*-Markovnikov addition of H and OH. This

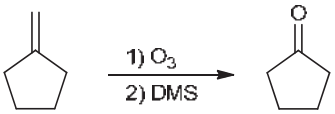
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can be accomplished via hydroboration-oxidation, which proceeds via a *syn* addition:



8.63.

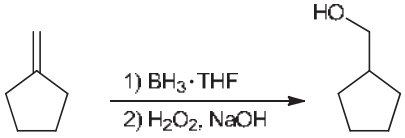
(a) Cleavage of the C=C double bond can be achieved via ozonolysis:



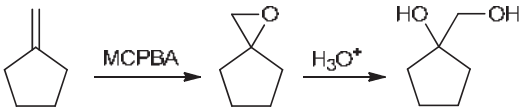
(b) The two groups being added across the alkene are H and Br. The latter is installed at the less-substituted position, so we must use conditions that give an *anti*-Markovnikov addition of H and Br. This can be accomplished by treating the alkene with HBr in the presence of peroxides.



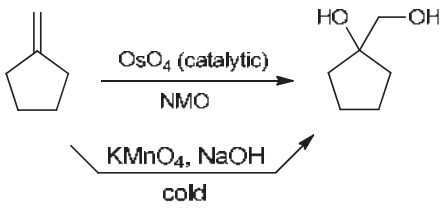
(c) The two groups being added across the alkene are H and OH. The OH group is installed at the less-substituted carbon atom, so we must use conditions that give an *anti*-Markovnikov addition of H and OH. This can be accomplished via hydroboration-oxidation.



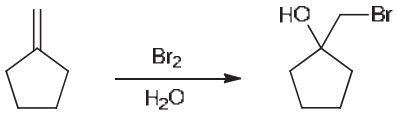
(d) The two groups being added across the alkene are OH and OH. No chiral centers are formed, so stereochemistry is irrelevant. We have learned more than one way to achieve a dihydroxylation. For example, we can convert the alkene to an epoxide and then open the epoxide under aqueous acidic conditions.



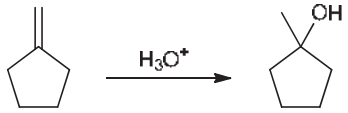
Alternatively, we can treat the alkene with catalytic osmium tetroxide and a suitable co-oxidant, or even with potassium permanganate and NaOH.



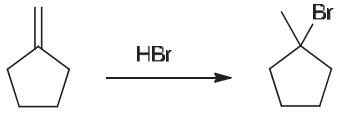
(e) The two groups being added across the alkene are Br and OH, with the latter being installed at the more substituted position. This can be achieved by treating the alkene with Br_2 in the presence of water (halohydrin formation):



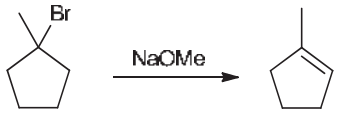
(f) The two groups being added across the alkene are H and OH, with the latter being installed at the more substituted position (Markovnikov addition). This can be achieved via acid-catalyzed hydration:



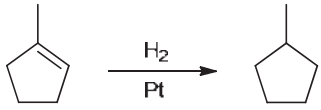
(g) The two groups being added across the alkene are H and Br. The Br group must be installed at the more-substituted, tertiary position, so we must use conditions that give a Markovnikov addition of H and Br. This can be accomplished by treating the alkene with HBr.



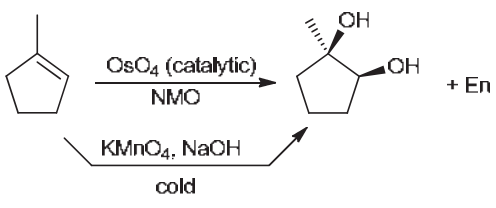
(h) This transformation requires the elimination of H and Br to give the more-substituted alkene, so a strong base is required (such as hydroxide, methoxide, or ethoxide):



(i) The two groups being added across the alkene are H and H, which can be accomplished by treating the alkene with molecular hydrogen (H_2) in the presence of a suitable catalyst.

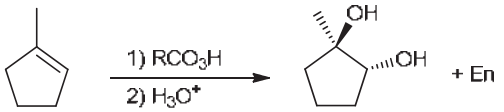


(j) The two groups being added across the alkene are OH and OH, and they must be installed via a *syn* addition. This can be achieved by treating the alkene with catalytic osmium tetroxide and a suitable co-oxidant, or with potassium permanganate:



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(k) The two groups being added across the alkene are OH and OH, and they must be installed via an *anti* addition. This can be achieved by treating the alkene with a peroxy acid, followed by aqueous acid:

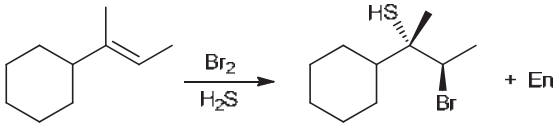


8.64. Let's begin by drawing the structures of the alkenes under comparison:

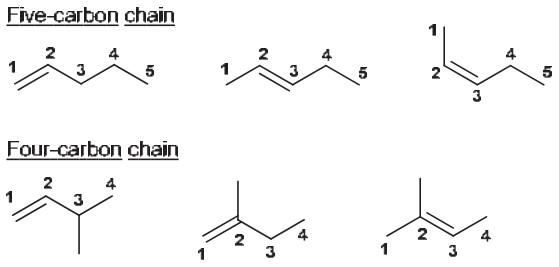


Addition of HBr to 2-methyl-2-pentene should be more rapid because the reaction can proceed via a tertiary carbocation. In contrast, addition of HBr to 4-methyl-1-pentene proceeds via a less stable, secondary carbocation.

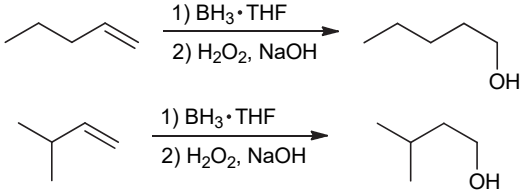
8.65. When treated with molecular bromine (Br_2), the alkene is converted to an intermediate bromonium ion, which is then subject to attack by a nucleophile. We have seen that the nucleophile can be water when the reaction is performed in the presence of water, so it is reasonable that the nucleophile can be H_2S in this case. This should give the installation of an SH group (rather than an OH group) at the more substituted position:



8.66. We begin by drawing all possible alkenes with the molecular formula C_5H_{10} (using a methodical approach similar to the one described in the solution to Problem 4.3):

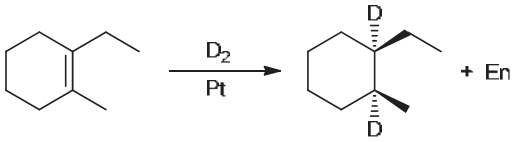


Among these isomers, only two of them will undergo hydroboration-oxidation to afford an alcohol with no chiral centers, shown here:



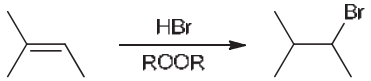
The remaining four isomers will undergo hydroboration-oxidation to produce alcohols that do possess a chiral center.

8.67. We expect a *syn* addition of D and D across the alkene, giving a pair of enantiomers:

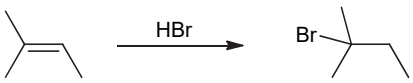


8.68.

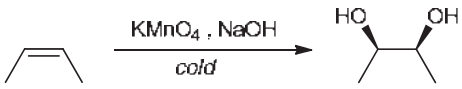
(a) First draw the starting alkene. Treating this alkene with HBr will result in a tertiary alkyl halide. But if peroxides are present, a radical process will occur, resulting in the formation of a secondary alkyl halide, as shown:



(b) First draw the starting alkene. Treating this alkene with HBr will result in a tertiary alkyl halide, as shown:

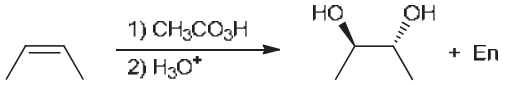


(c) First draw the starting alkene. A *syn* dihydroxylation is required in order to produce a *meso* diol. We have seen several reagents that can be used to accomplish a *syn* dihydroxylation, such as cold potassium permanganate:



Alternatively, we could achieve the same result with catalytic osmium tetroxide and a suitable co-oxidant.

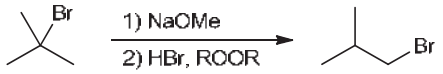
(d) First draw the starting alkene. An *anti* dihydroxylation is required in order to prepare enantiomeric diols. This can be accomplished by converting the alkene into an epoxide, followed by acid-catalyzed ring opening of the epoxide, as shown.



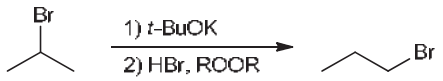
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8.69.

(a) Begin by drawing the starting alkyl halide. This tertiary alkyl halide can be converted into a primary alkyl halide via a two-step process (elimination followed by addition). In each case, we must carefully consider the regiochemical outcome. During the elimination process, there is only one regiochemical outcome, so any strong base will work (even if it is sterically hindered, although that is not necessary). In the addition process, we want to install Br at the less-substituted position, so we will need an *anti*-Markovnikov addition of HBr (using peroxides):

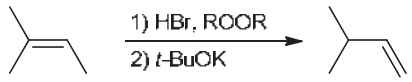


(b) Begin by drawing the starting alkyl halide. This secondary alkyl halide can be converted into a primary alkyl halide via a two-step process (elimination followed by addition). In each case, we must carefully consider the regiochemical outcome. During the elimination process, there is only one regiochemical outcome, so any strong base will work (even if it is sterically hindered). In fact, in this case, there is a distinct advantage to using a sterically hindered base. Specifically, it will suppress the competing S_N2 process (the substrate is secondary, so S_N2 should be a minor product, unless a sterically hindered base is used). During the addition process, we want to install Br at the less-substituted position, so we will need an *anti*-Markovnikov addition of HBr (using peroxides):

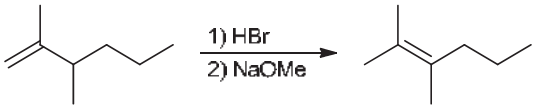


8.70.

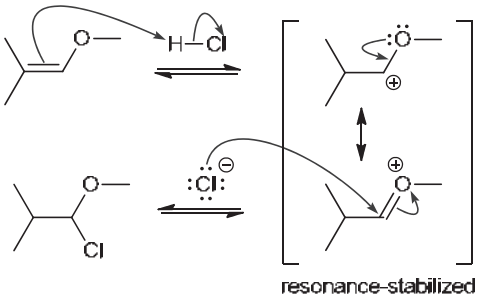
(a) Begin by drawing the starting alkene. This trisubstituted alkene can be converted into a monosubstituted alkene via a two-step process (addition, followed by elimination). We must be careful to control the regiochemical outcome of each step of the process. During the addition reaction, we want to install Br at the less-substituted position, so we treat the alkene with HBr in the presence of peroxides. Then, the elimination reaction must be performed in a way that gives the less-substituted alkene, so we must use a strong, sterically hindered base (such as *tert*-butoxide).



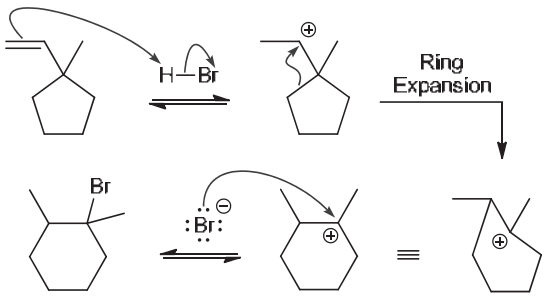
(b) Begin by drawing the starting alkene. This disubstituted alkene can be converted into a tetrasubstituted alkene via a two-step process (addition, followed by elimination). We must be careful to control the regiochemical outcome of each step of the process. During the addition reaction, we want to install Br at the more-substituted position, so we treat the alkene with HBr (without peroxides). Then, the elimination process must be performed in a way that gives the more-substituted alkene, so we must use a strong base that is not sterically hindered, such as methoxide (hydroxide or ethoxide can also be used).



8.71. Since this reaction proceeds through an ionic mechanism, we expect the mechanism to be comprised of two steps: 1) proton transfer, followed by 2) nucleophilic attack. In the first step, a proton is transferred from HCl to the alkene, which requires two curved arrows, as shown below. There are two possible regiochemical outcomes for the protonation step, and we might have expected formation of a tertiary carbocation. However, in this particular case, the other regiochemical outcome is favored because it involves formation of a resonance-stabilized cation. As a result of resonance stabilization, this cation is even more stable than a tertiary carbocation, and the reaction proceeds via the more stable intermediate. This cation is then captured by a chloride ion in the second step of the mechanism, which requires two curved arrows, as shown:

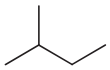


8.72. Protonation of the alkene requires two curved arrows, as shown in the first step of the following mechanism. This leads to the more stable, secondary carbocation (rather than a primary carbocation). This secondary carbocation then undergoes a rearrangement, in which one of the carbon atoms of the ring migrates (as described in the problem statement). This is represented with one curved arrow that shows the formation of a more stable, tertiary carbocation. In the final step of the mechanism (nucleophilic attack), the carbocation is captured by a bromide ion. This step requires one curved arrow, going from the nucleophile (bromide) to the electrophile (the carbocation), as shown:



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8.73.
(a) Compound **X** reacts with H_2 in the presence of a catalyst, so compound **X** is an alkene. The product of hydrogenation is 2-methylbutane, so compound **X** must have the same carbon skeleton as 2-methylbutane:



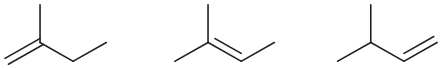
2-methylbutane

We just have to decide where to place the double bond in compound **X**. Keep in mind that the following two positions are identical:

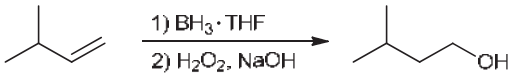


2-methyl-1-butene 2-methyl-1-butene

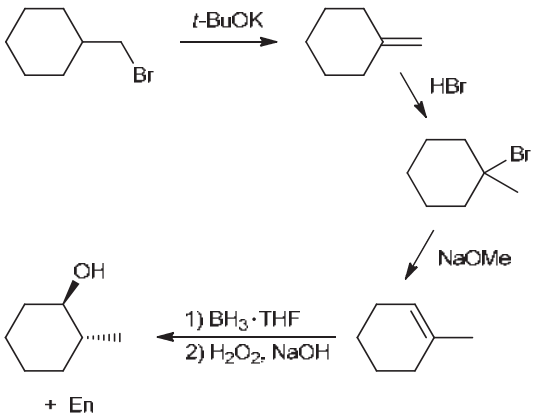
So, there are only three possible locations where we can place the double bond:



(b) Upon hydroboration-oxidation, only one of the three proposed alkenes will be converted to an alcohol without any chiral centers, shown below. Each of the other two compounds will be converted into an alcohol with a chiral center.

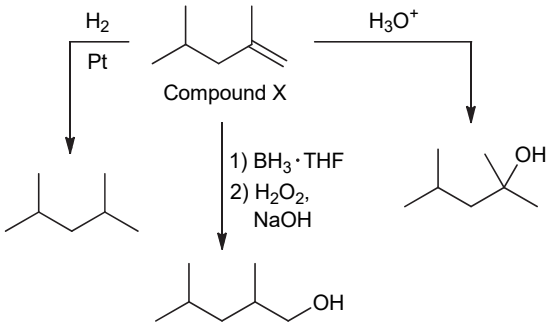


8.74. The following is one possible suggested route:



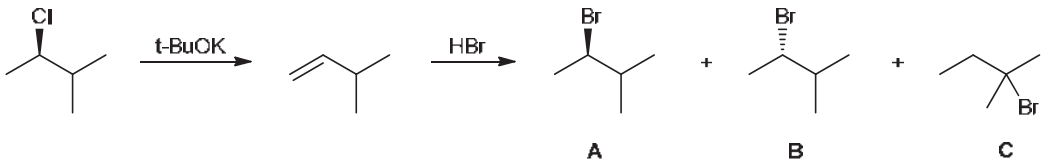
Other acceptable solutions are certainly possible. For example, after the first step (elimination with *tert*-butoxide), the next two steps (addition of HBr, followed by elimination) could be replaced with acid-catalyzed hydration, followed by elimination with conc. H_2SO_4.

8.75. There is only one alkene (compound X, shown below) that can be converted to 2,4-dimethyl-1-pentanol via hydroboration-oxidation. Treatment of that alkene with aqueous acid affords an alcohol (via Markvonikov addition):



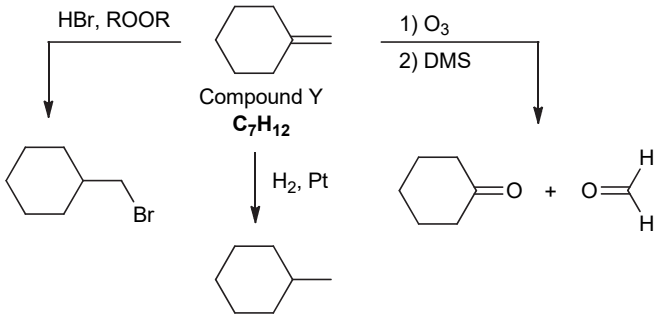
2,4-dimethyl-1-pentanol

8.76. The substrate is a secondary alkyl halide, and treatment with *tert*-butoxide gives the less substituted alkene. When that alkene is treated with HBr, the π bond is protonated to give a secondary carbocation (rather than a primary carbocation). This carbocation can either be captured by a bromide ion, giving products **A** and **B** below, or the carbocation can undergo a rearrangement (hydride shift) to give a tertiary carbocation, which is then captured by a bromide ion, affording product **C**.

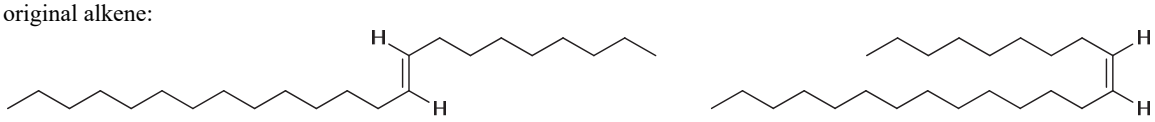


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8.77. There is only one alkene (compound Y, shown below) that is consistent with the information provided in the problem statement. Ozonolysis of that alkene results in cleavage of the C=C bond to give two separate compounds, each of which has a C=O bond, shown below:

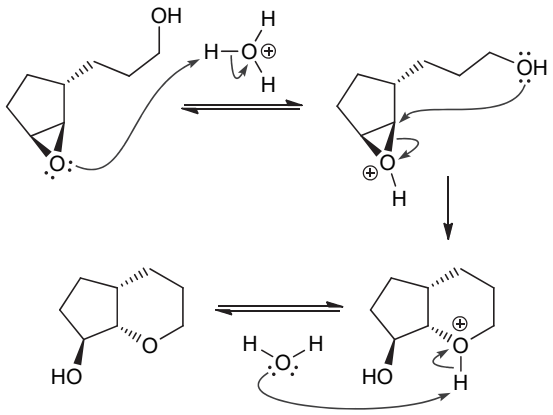


8.78. Each of the products is an aldehyde, and their sp^2 hybridized carbon atoms were once connected to each other as a C=C bond in the original alkene. That gives the following two possibilities (stereoisomers) for the structure of the original alkene:

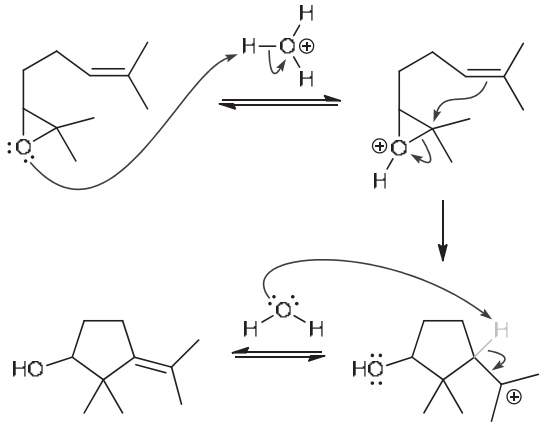


8.79.

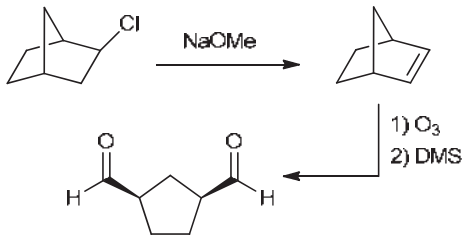
(a) In the presence of aqueous acid, the epoxide is first protonated (two curved arrows), as shown below. The resulting intermediate can then undergo an S_N2-like, intramolecular attack (two curved arrows), in which the OH group functions as the nucleophilic center. Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows:



(b) In the presence of aqueous acid, the epoxide is first protonated (two curved arrows), as shown. The resulting intermediate can then undergo an S_N2-like, intramolecular attack (two curved arrows), in which the π bond functions as the nucleophilic center. Then, in the final step of the mechanism, a molecule of water functions as a base and removes a proton, thereby generating the product. This final step is a proton transfer step, and therefore requires two curved arrows:



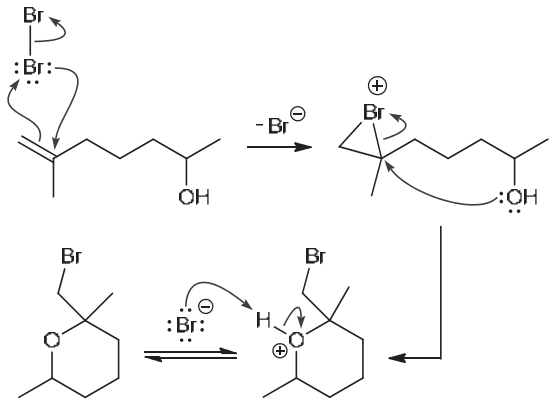
8.80. Treatment of the alkyl halide with a strong base gives an alkene which can then be converted into the desired product via ozonolysis:



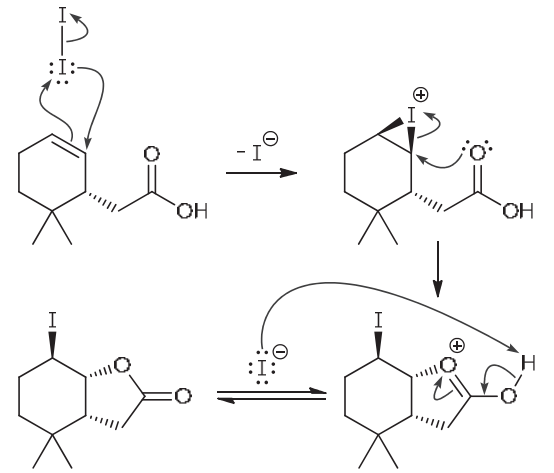
8.81. When the alkene is treated with molecular bromine (Br_2), the π bond functions as a nucleophilic center and attacks Br_2 (three curved arrows), resulting in an intermediate bromonium ion. The bromonium ion is then subject to attack by a nucleophilic center, such as

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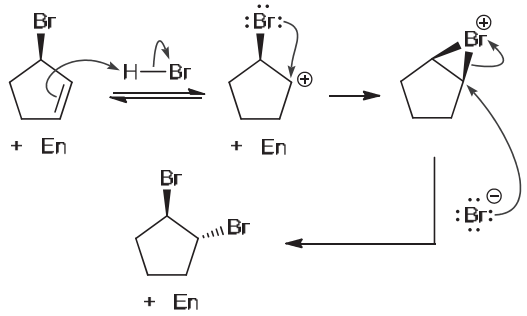
the OH group that is tethered to the bromonium group. The resulting intramolecular nucleophilic attack (two curved arrows) generates an oxonium ion, which then loses a proton (two curved arrows) to give the product.



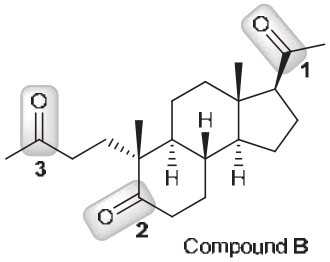
8.82. When the alkene is treated with molecular iodine (I_2), the π bond functions as a nucleophilic center and attacks I_2 (three curved arrows), resulting in an intermediate iodonium ion. The iodonium ion is then subject to attack by a nucleophile, such as the nucleophilic center that is tethered to the iodonium group. The resulting intramolecular nucleophilic attack (two curved arrows) generates an intermediate which then loses a proton (two curved arrows) to give the product.



8.83. The *cis*-dibromide is not obtained, suggesting that the reaction proceeds via an *anti* addition process. This can be explained if we argue that the carbocation (formed upon protonation of the π bond) is converted into a bromonium ion, as shown here. The incoming nucleophile (bromide) would have to attack from the backside of the bromonium bridge, giving a *trans* dibromide:

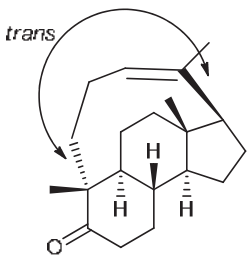


8.84. Inspection of the molecular formula reveals that compound **A** contains the same number of carbon atoms as the product of ozonolysis, compound **B** (21 carbon atoms). Thus, we can predict the structure of compound **A** by choosing any two carbonyl (C=O) groups in the product, removing the oxygen atoms, and connecting the sp^2 hybridized carbon atoms with a double bond. There are three carbonyl groups, so there are three possible alkenes that should be considered.



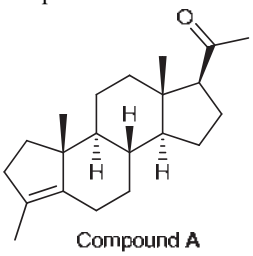
Attachment of carbons **1** and **2** would result in a complex ring system with far too much strain to possibly exist. Carbons **1** and **2** are remotely located on opposite ends of the molecule, pointing in opposite directions. Indeed, we will later learn that this polycyclic skeletal structure is very rigid, and the hypothetical connection of carbons **1** and **2** is impossible.

Similarly, if carbons **1** and **3** were attached it would also result in significant strain (below). Though these carbons are closer than **1** and **2**, and they are linked by a slightly more flexible chain, the *trans* relationship of the two connecting groups creates too much angle strain:

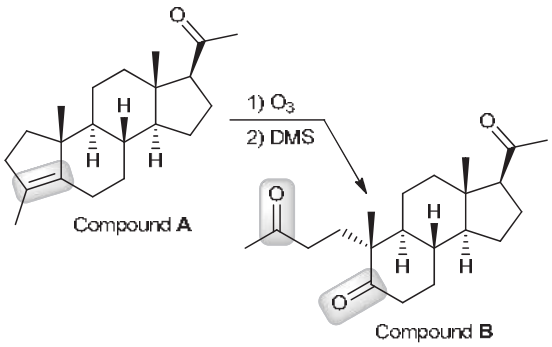


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The only logical reactant is one in which carbons **2** and **3** are connected in a fused cyclopentene precursor. This is the structure of compound **A**.

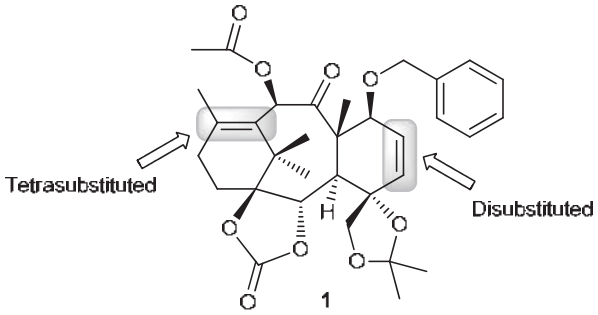


Ozonolysis of compound **A** will produce compound **B**.



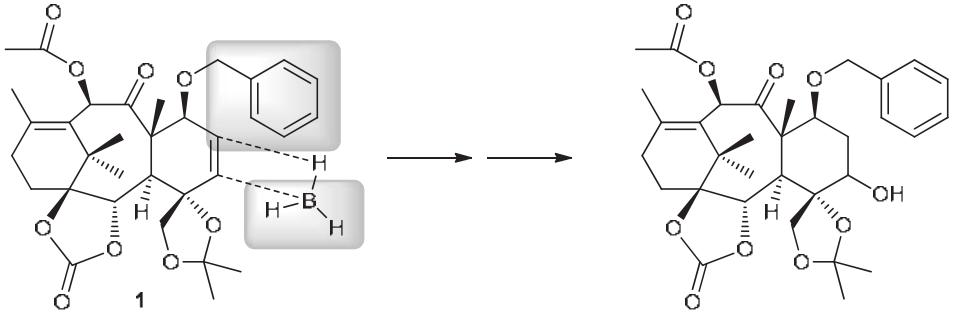
8.85.

(a) The reagents indicate a hydroboration-oxidation, in which an alkene is converted to an alcohol. In compound **1**, there are two alkene groups, so we must choose which one is more likely to react with BH_3. One alkene group is disubstituted, while the other is tetrasubstituted:



Since the rate of hydroboration is particularly sensitive to steric factors, we expect the disubstituted alkene group to undergo hydroboration more readily.

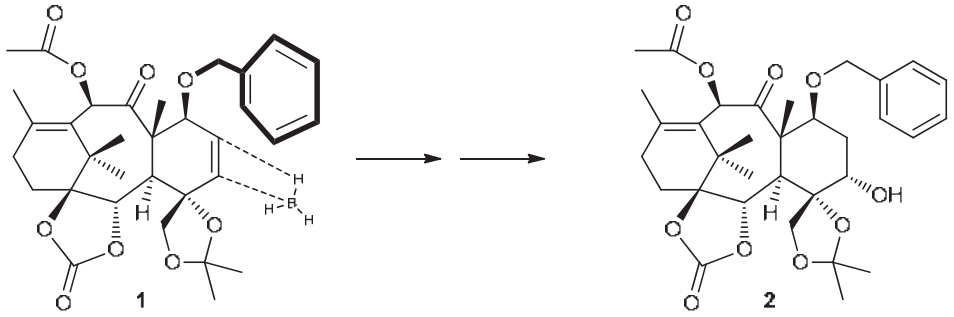
(b) As mentioned in part (a), hydroboration is sensitive to steric considerations. When we inspect both vinylic positions, we find that both are equally substituted. The tie-breaker will likely be the nearby presence of a six-membered, aromatic ring, which provides significant steric crowding that favors the following regiochemical outcome:



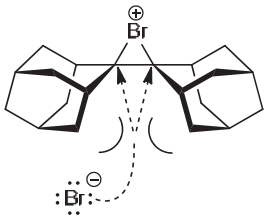
In predicting the stereochemical outcome, we once again invoke the steric bulk of the six-membered, aromatic ring. Specifically, the front face of the alkene group is blocked by the large six-membered, aromatic ring. As a result, the

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back face of the alkene is more accessible, so the reaction occurs more readily on the back face, giving the following expected product:

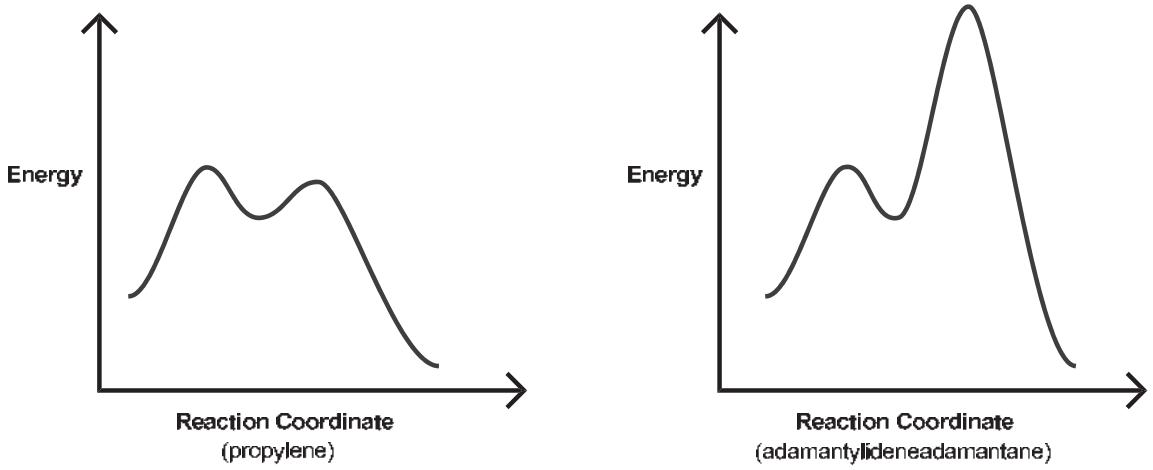


8.86.
The bromonium ion is unusually resistant towards nucleophilic attack by the bromide anion because of significant steric hindrance involved when the anion approaches the electrophilic carbon atoms of the bromonium ion.



Too sterically hindered
for nucleophile to attack

Thus, there is a very large activation energy associated with this bromonium ion being attacked by a nucleophile. This can be illustrated by comparing the following reaction coordinate diagrams.

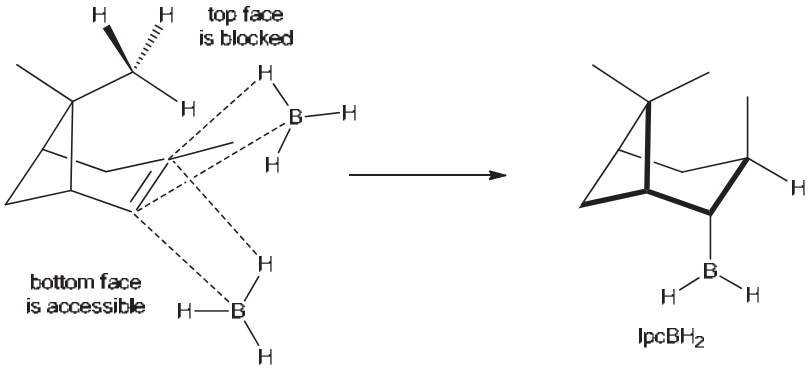


The first figure (left) is the expected energy diagram for bromination of propylene, while the second figure (right) is a proposed energy diagram for bromination of adamantylideneadamantane. The first step in each figure is similar, but compare the second step in each figure (nucleophilic attack of the bromonium ion). For bromination of adamantylideneadamantane, the magnitude of the activation energy for the second step is so large that this step does not take place at an appreciable rate.

8.87.
Hydroboration of an alkene typically occurs with equal probability from both faces of the π-bond. However, in the case of α-pinene, the top face of the π-bond is blocked by one of the methyl substituents, so the approach of borane on this face of the π-bond is severely hindered. Therefore, hydroboration cannot occur at an appreciable rate on the top face of

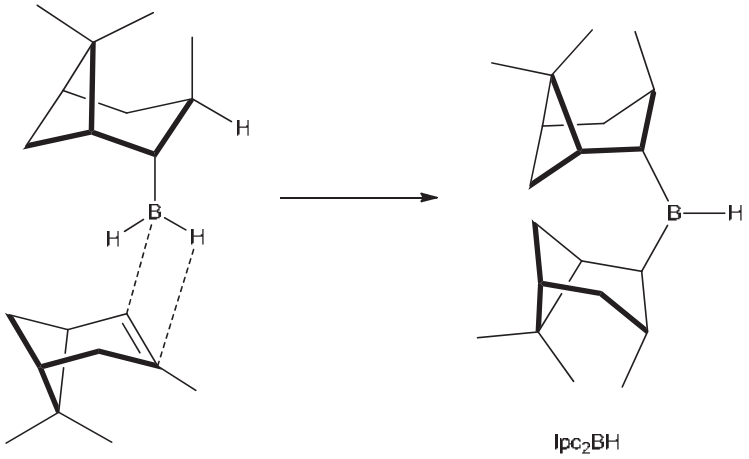
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the π-bond. However, the bottom face of the π-bond is unhindered; it is much more accessible to hydroboration. As a result, boron and hydrogen add in a *syn*-fashion to the bottom face of α-pinene resulting in the $IpcBH_2$ enantiomer shown; as always, boron is added to the less hindered position on the alkene.



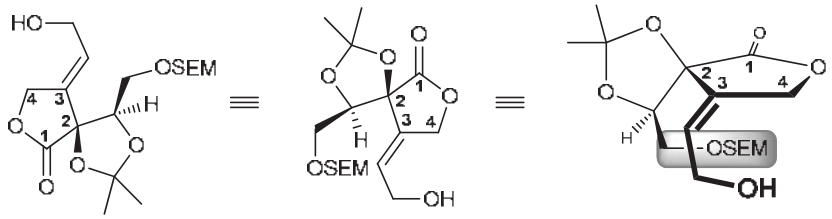
Notice that the methyl group of the alkene is now occupying an axial position in the product.

Next, the π-bond of a second molecule of α-pinene will react with $IpcBH_2$, also from the same face, to produce the observed enantiomer of Ipc_2BH.



8.88.

Building a molecular model is perhaps the best way to see that the bottom face of the π bond is more hindered than the top face. Alternatively, this can be seen if we redraw the compound in a Haworth projection:

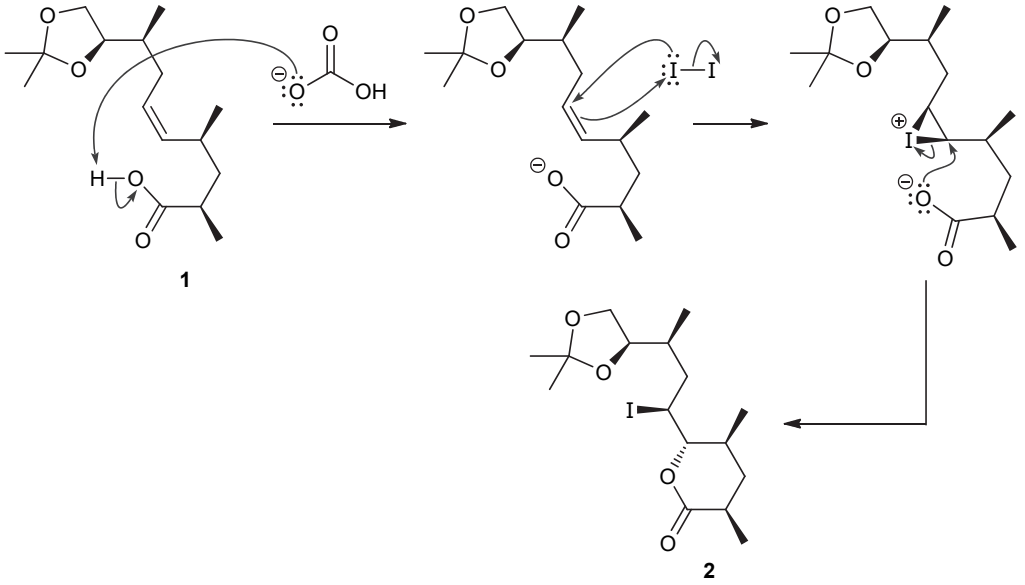


Notice that the π bond is in the plane of the ring, and the large and bulky OSEM group is positioned below the plane of the ring, directly underneath the π bond. As such, the bottom face of the π bond is sterically encumbered, so approach of the oxidizing agent (OsO_4) from that face is blocked (it would involve a transition state that is too high in energy). Attack on the top face is unencumbered, so it involves a lower energy transition state, and as a result, the reaction occurs more readily on this face.

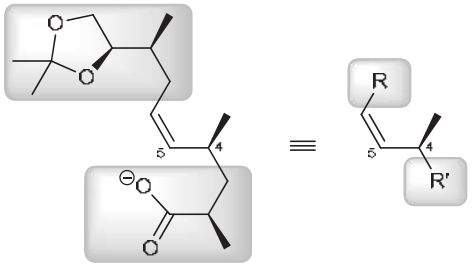
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8.89.

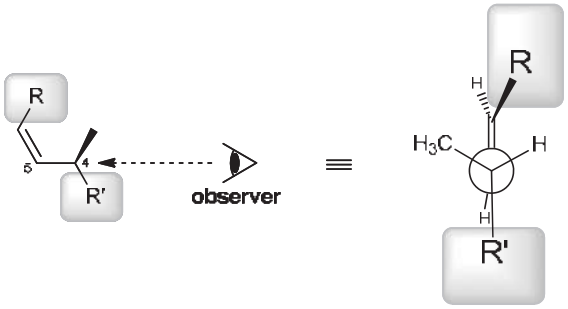
(a) As indicated in the problem statement, sodium bicarbonate functions as a base and deprotonates the carboxylic acid group to give a carboxylate ion. Then, the π bond reacts with I_2 to give an iodonium ion (similar to a bromonium ion), which is then opened via an intramolecular nucleophilic attack to give the product: This process is called iodolactonization, because the product features a newly installed cyclic ester group (a lactone) as well as an iodo group:



(b) Let's simplify our drawings by referring to the following large groups as R and R':

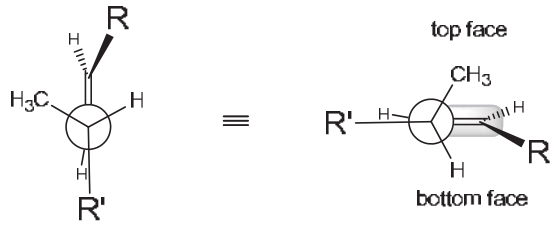


Now we are ready to look down the C4-C5 bond, like this:

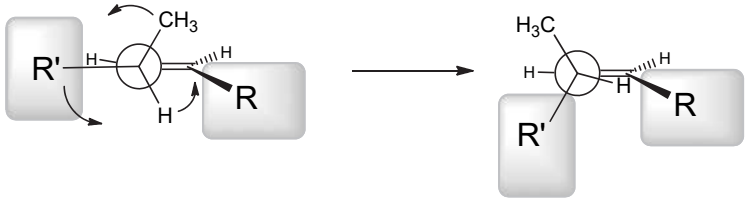


Let's rotate this entire Newman projection by 90° (which does not change the conformation at all) so that we can clearly see the top face and bottom face of the π bond:

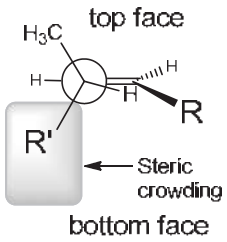
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Notice that the two largest groups (R and R') are farthest away from each other. In our search for the lowest energy conformation, this conformation should be the first one that we examine, because significant steric interactions will be present if R and R' are near each other in space. When we analyze this conformation, we see two additional factors contributing to its overall energy: 1) gauche interactions between the methyl group and the R group, and 2) an eclipsing interaction between R' and a hydrogen atom. The former can be avoided by rotating the front carbon atom counterclockwise, like this:

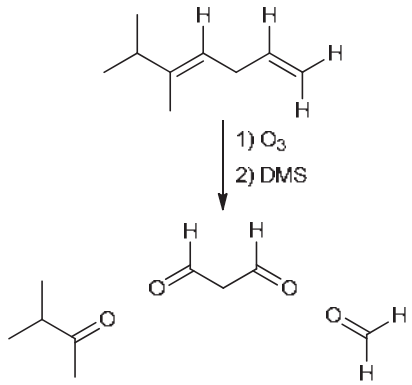


We have traded one eclipsing interaction for another (presumably similar), but notice that we have lost the gauche interaction. Accordingly, we expect this conformation to be the most stable conformation, looking down the C4-C5 bond. This means that the molecule will spend most of its time in this conformation. Notice that, in this lowest energy conformation, the bottom face of the π bond is sterically hindered, while the top face is relatively unhindered:



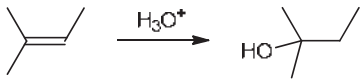
That is, the top face is more accessible (most of the time). As such, if I_2 approaches from the top face of the π bond, the transition state will be lower in energy then if attack occurs from the bottom face. So attack of the top face occurs more readily.

8.90. Each of the double bonds is cleaved, giving the following products:

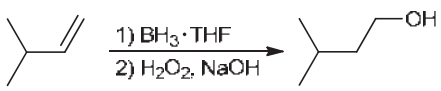


Answer (c) is the only structure that is not among these products.

8.91. Answer (a) is not correct, because the OH group would be installed at the more substituted position, as shown here:

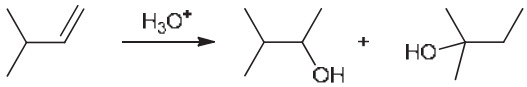


Answer (b) is not correct, because the OH group would be installed at the less substituted position, as shown here:

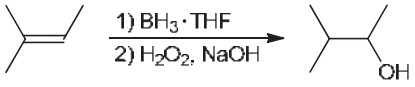


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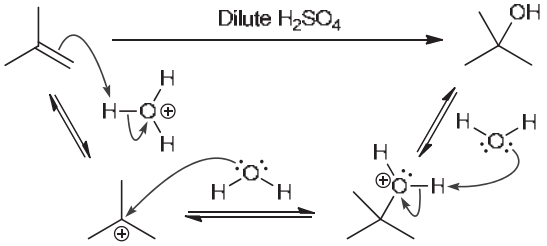
Answer (c) is not correct, because a rearrangement is possible, giving a mixture of products:



Only one of these products is the desired product, so this method is not efficient.
Answer (d) is the correct answer, because hydroboration-oxidation involves installation of an OH group at the less substituted position:



8.92. Acid-catalyzed hydration is believed to occur via the following mechanism:



As shown, this mechanism has two intermediates, which correspond with structures I and II. Therefore, the correct answer is (b).

8.93.
The oxymercuration reaction involves an electrophilic mercuric cation reacting with a nucleophilic π bond of an alkene in an addition reaction. So, as the π bond of the alkene is rendered less nucleophilic due to electron-withdrawing substituent(s), the reaction rate is expected to decrease. Also, steric effects may come into play as the number of substituents around the π bond increases.
Among the alkenes listed, alkene **1** is disubstituted while **4** is trisubstituted. All of the rest are monosubstituted alkenes. Given that alkyl substituents are generally electron-donating groups, we would expect **1** and **4** to be the most reactive. More specifically, compounds **1** and **4** are the only ones capable of having a tertiary carbocation as a resonance contributor in the mercurinium ion intermediate. Therefore, these mercurinium ions are expected to be among the most stable ones, and hence, the oxymercuration reactions of these two alkenes are expected to proceed the fastest. This expectation does not bear itself out for alkene **4** in the relative reactivity data, however, since it is among the slower reacting compounds. This anomaly must be due to the steric repulsion associated when the mercuric cation tries to approach the π bond, or a destabilizing steric effect present in the resulting mercurinium ion intermediate between these substituents and the bound mercury ion.

The monosubstituted alkenes **2**, **3** and **5** are all less reactive than **1** because their corresponding mercurinium ions involve resonance structures with a secondary carbocation, thus resulting in higher energy than the mercurinium ion obtained from compound **1**. Alkene **3** reacts slower than **2** due to electron-withdrawal from the –OMe group, which would destabilize the mercurinium ion by further reducing the electron density of the resulting secondary carbocation resonance contributor. A similar inductive effect would also destabilize the mercurinium ion from alkene **5**, but an additional steric destabilization due to the large chlorine atom may also be in effect to make this alkene the slowest reacting compound among the series.

8.94.
The hydroboration reaction involves an electrophilic borane (or, organoborane such as 9-BBN) reacting with a nucleophilic alkene in an addition reaction. So, as the π bond of the alkene is rendered more nucleophilic due to electron-donating substituent(s), the reaction rate is expected to increase. Steric effects (that arise because of the bulky reagent) are also expected to play an important role in determining the relative rates of reactivity.

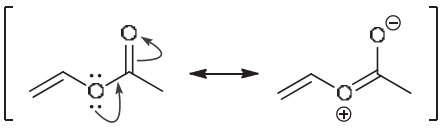
(a) Alkene **1** possesses an alkoxy substituent (OR) in an allylic position. An alkoxy group is expected to be inductively electron-withdrawing, because oxygen is an electronegative atom and will therefore withdraw electron density away from the π bond. This effect should render the π bond less reactive (less nucleophilic). However, the alkoxy group is expected to be electron-donating via resonance, as seen when we draw the resonance structures:



So there are two effects in competition with each other. The alkoxy group is expected to be electron-withdrawing via induction, but it is expected to be electron-donating via resonance. Which effect is stronger? We have seen that, in general, resonance is a stronger effect than induction. As such, we would expect the alkoxy group to be electron-donating, which would render the alkene more nucleophilic (more reactive). This prediction is verified by the high rate of reactivity of compound **1**.
The π bond in compound **2** is adjacent to an alkyl group, rather than an alkoxy group, so there is no resonance effect. The only effect is induction (we have seen that alkyl groups are generally electron donating). As such, the nucleophilicity of the π bond in compound **2** is expected to be enhanced by the presence of the alkyl group, but it is not expected to be quite as nucleophilic as the π bond in compound **1**.
Compounds **3** and **5** both exhibit a CH_2 group in between the π bond and the substituent. As such, the substituents in these compounds do not affect the π bond via resonance effects; only via inductive effects. Both substituents are expected to be inductively electron-

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withdrawing. Therefore, the π bonds in these cases are less electron-rich than in compounds **1** or **2**. The acetoxy group of alkene **5** is expected to be a stronger electron-withdrawing group than the methoxy group of **3** since the carbonyl group in the former compound will enhance the electron-withdrawing ability of the oxygen atom via resonance. Compound **4** is interesting in that the acetoxy oxygen atom is expected to be an electron-donating group with respect to the alkene π bond (via resonance), much like the oxygen atom in compound **1**. From the relative reactivity data, however, the lone pairs on the acetoxy oxygen are apparently less efficient at donating to the carbon-carbon π bond. This can be explained by recognizing that the lone pairs on the acetoxy oxygen are already partially delocalized into the carbonyl group:

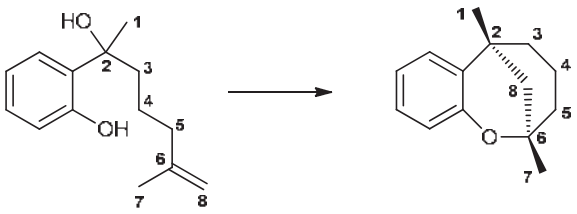


That is, the lone pairs on the acetoxy oxygen are less available to donate electron density to the π bond. Therefore, the acetoxy group of **4** influences the reactivity primarily through its inductive and steric effects, which will be much like that of the substituents in compounds **3** and **5**.

(b) Compound **6** is apparently able to impose the electron-withdrawing effect due to induction of the –CN group on the alkene π bond via the shorter σ bond (due to the sp^3-sp orbital overlap) between the CH_2 and the CN groups, and thus the closer proximity of the partial positive charge to the π electrons of the alkene. This is apparent when comparing the relative rates between compounds **5** and **6**. Here, though the oxygen atom in compound **5** is more electronegative than carbon, the carbon atom of the cyano group apparently possesses a very large partial positive change that effectively renders this carbon atom more electronegative than that of the acetoxy oxygen atom of **5**. The low reactivity associated with compound **7** may be due to both induction and steric effects, since the inductive withdrawal of electron density by the chlorine atom is not expected to exceed the substituent in compound **5**.

(c) Compounds **2**, **8** and **9** illustrate the consequences of steric effects on the hydroboration reaction. Compounds **8** and **9** are the only disubstituted alkenes among the series, and it is not surprising that they have the lowest relative reactivity, due to increased steric effects. They are more than 100 times lower in reactivity than compound **2**, the only monosubstituted alkene with no significant electronic effects (i.e. resonance and induction). In compound **9**, the electron-withdrawing effect of the chlorine atom, which is superimposed upon the increased steric effect, further lowers the reactivity.

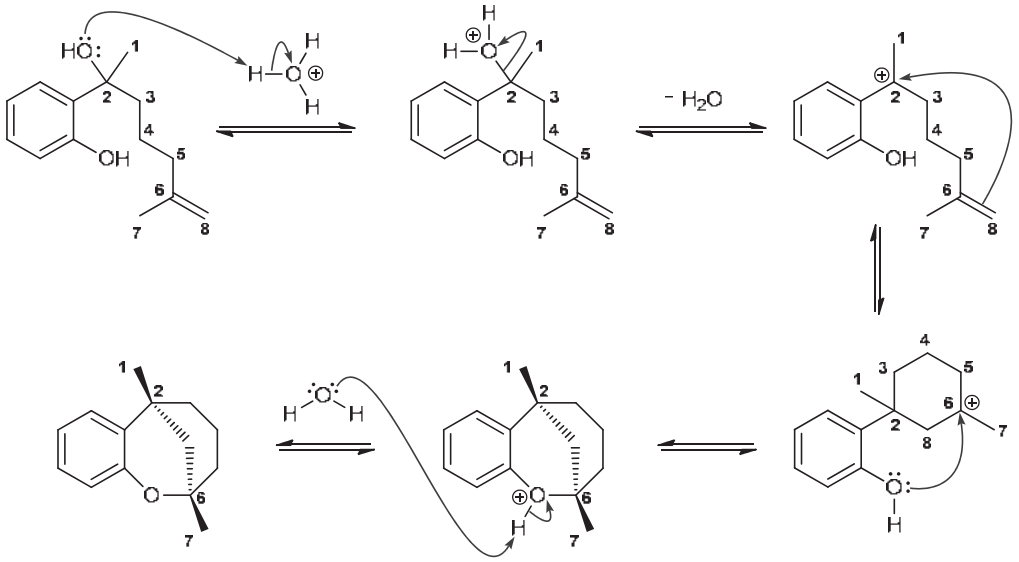
8.95. When approaching this problem, it would be advisable to first label the carbon side chain coming off the benzene ring so that you can determine what new connections have been made. Your numbering system does not need to conform to IUPAC rules for assigning locants. Rather, it is OK to use an arbitrary numbering system, because the goal of the numbering system is to track the fate of all atoms during the transformation:



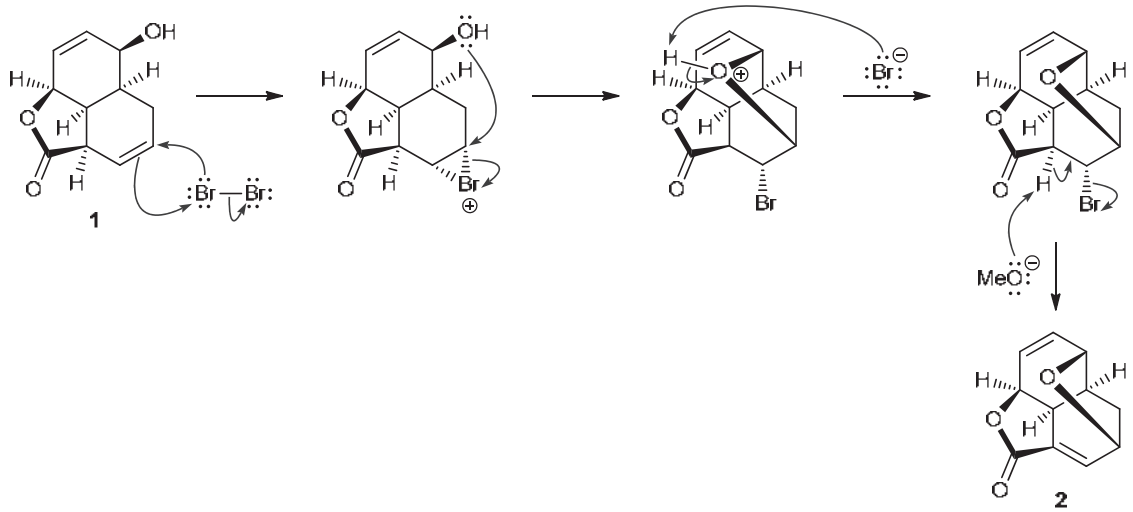
With this numbering system, the benzene ring is attached to C2 of the chain and the phenolic oxygen is attached to C6 of the chain.

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Based on this, a possible mechanism is illustrated below. Protonation of the tertiary alcohol, followed by loss of water, gives the stable tertiary benzylic carbocation (at C2). Markovnikov attack by the terminal alkene (C6 and C8) at the tertiary benzylic carbocation affords a tertiary carbocation at C6. This carbocation is then attacked by the phenolic oxygen to afford the final product after removal of the acidic proton.



8.96.
The first step involves formation of a bromonium ion, which requires three curved arrows (See Mechanism 8.5), followed by an intramolecular nucleophilic attack in which the OH group functions as a nucleophilic center and attacks the bromonium ion. Deprotonation then affords a cyclic ether. In the last step, a methoxide ion functions as a base and removes a proton, which leads to expulsion of bromide in an E2 process.



You might be wondering about the stereochemistry of the last step (the E2 process). In general, E2 processes occur more rapidly when the H and the leaving group are *anti*-periplanar in the transition state. However, it is possible for an E2 process to occur via a transition state in which the H and leaving group are *syn*-periplanar. In general, this is not favored (the transition state is high in energy because all groups are eclipsed rather than staggered), but in this case, the rigid geometry of the polycyclic structure essentially locks the H and the leaving group into a *syn*-periplanar arrangement, where the H and the leaving group are eclipsing each other. As such, the reaction can occur, because the minimum requirement of periplanarity is still met.

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Chapter 9
Alkynes

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 9. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

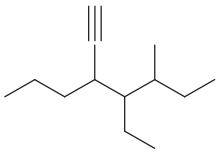
- A triple bond is comprised of three separate bonds: one ____ bond and two ____ bonds.
- Alkynes exhibit _____ geometry and can function either as bases or as _____.
- Monosubstituted acetylenes are **terminal alkynes**, while disubstituted acetylenes are _____ **alkynes**.
- Catalytic hydrogenation of an alkyne yields an _____.
- A **dissolving metal reduction** will convert an alkyne into a _____ alkene.
- Acid-catalyzed hydration of alkynes is catalyzed by mercuric sulfate to produce an _____ that cannot be isolated because it is rapidly converted into a ketone.
- Enols and ketones are _____, which are constitutional isomers that rapidly interconvert via the migration of a proton.
- When treated with ozone, followed by water, internal alkynes undergo oxidative cleavage to produce _____.
- Alkynide ions undergo _____ when treated with an alkyl halide (methyl or primary).

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 9. The answers appear in the section entitled *SkillBuilder Review*.

9.1 Assembling the Systematic Name of an Alkyne

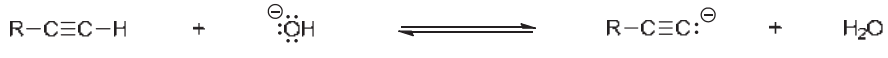
PROVIDE A SYSTEMATIC NAME FOR THE FOLLOWING COMPOUND



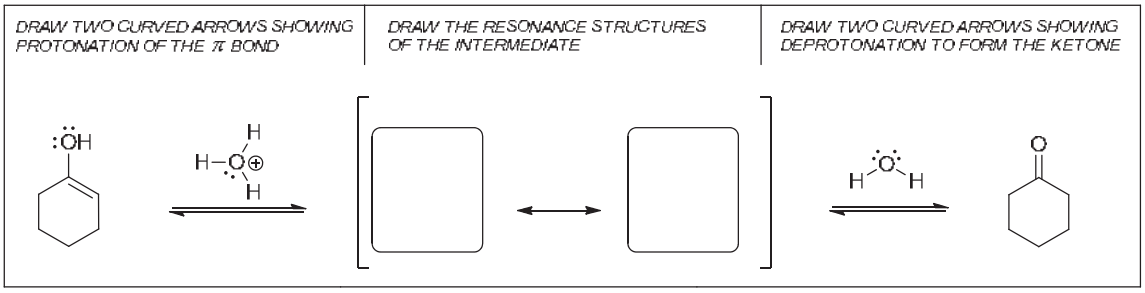
1) IDENTIFY THE PARENT
2) IDENTIFY AND NAME SUBSTITUENTS
3) ASSIGN LOCANTS TO EACH SUBSTITUENT
4) ALPHABETIZE

9.2 Selecting a Base for Deprotonating a Terminal Alkyne

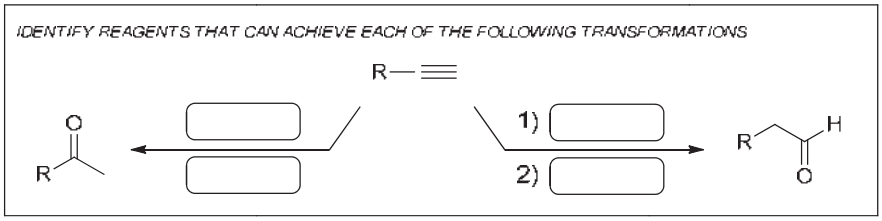
CIRCLE THE SIDE OF THE EQUILIBRIUM THAT IS FAVORED IN THE FOLLOWING ACID-BASE REACTION



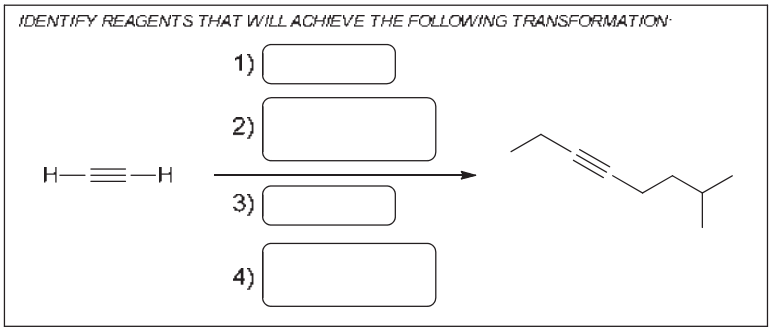
9.3 Drawing a Mechanism for Acid-Catalyzed Keto-Enol Tautomerization



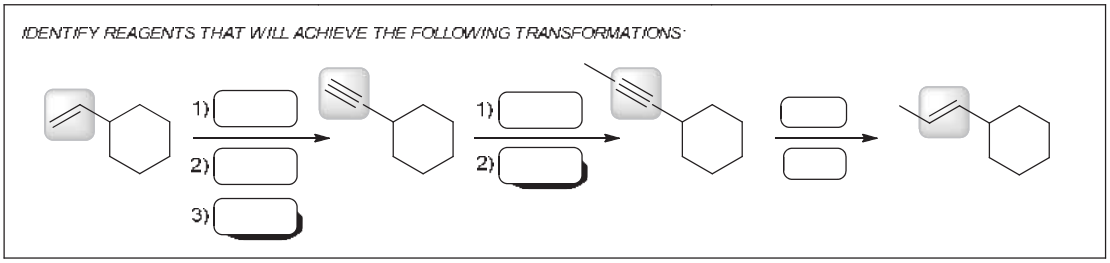
9.4 Choosing the Appropriate Reagents for the Hydration of an Alkyne



9.5 Alkylating Terminal Alkynes



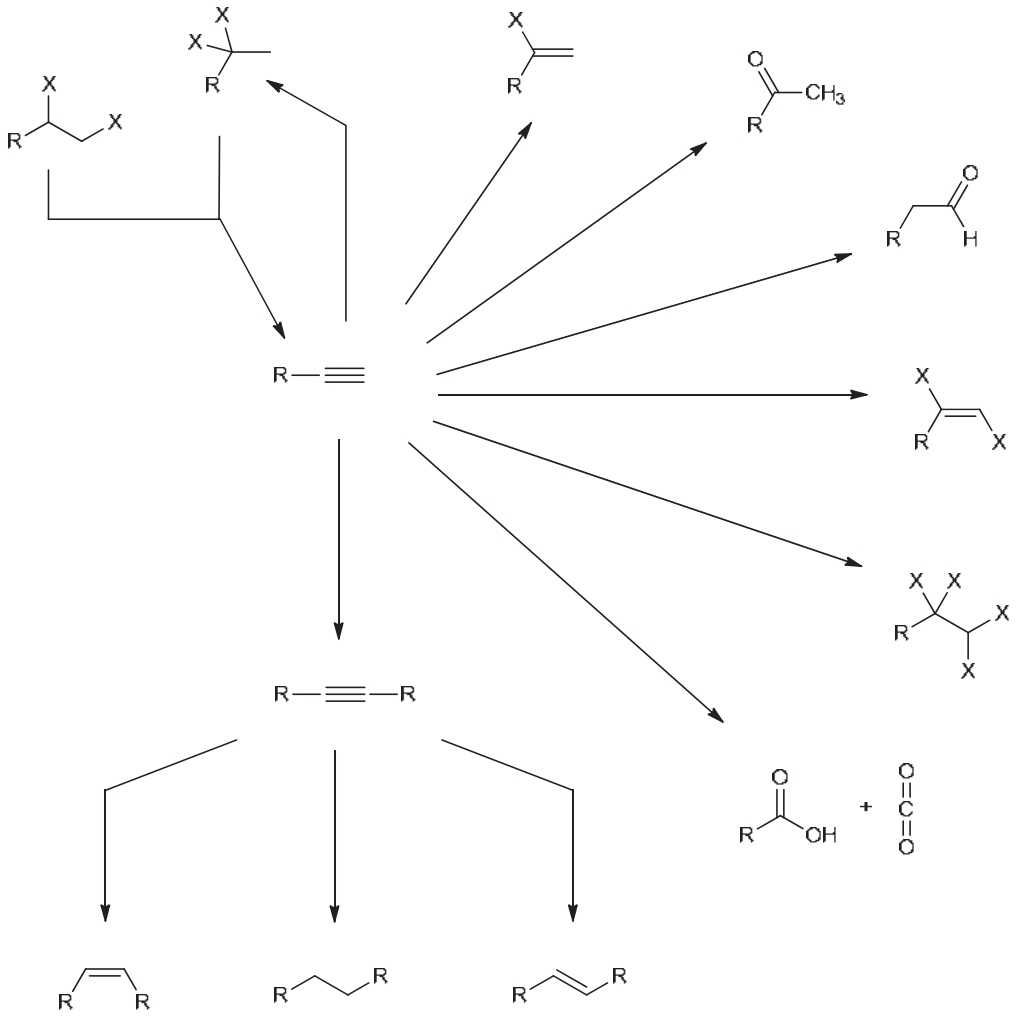
9.6 Interconverting Alkenes and Alkynes



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Review of Reactions

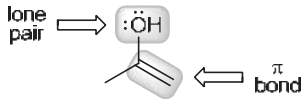
Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 9. The answers appear in the section entitled *Review of Reactions*.



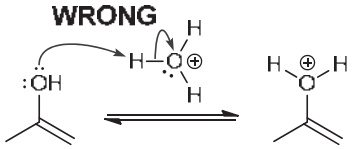
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Common Mistakes to Avoid

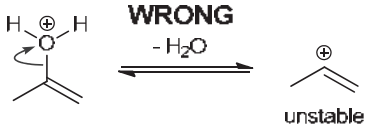
When drawing a mechanism for the acid-catalyzed tautomerization of an enol, the first step is protonation. Students sometimes get confused about where to place the proton during this first step. Indeed, there are two possible locations where protonation could occur (a lone pair or the π bond):



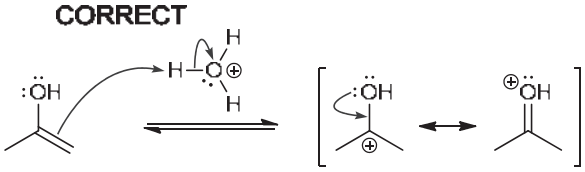
Don't forget that it is the π bond that is protonated during tautomerization of the enol. It is a common student error to protonate the OH group, like this:



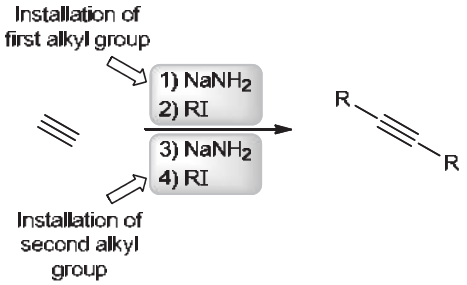
If you make this mistake, you might then be tempted to make another critical mistake - formation of a vinyl carbocation, which is likely too unstable to form (and does not get us any closer to obtaining the ketone).



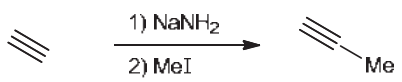
Whenever possible, avoid the formation of high-energy intermediates that are unlikely to form. This is a general rule that should be followed whenever you are drawing a mechanism (exceptions are rare). The correct first step for acid-catalyzed tautomerization of an enol is protonation of the π bond to generate a resonance-stabilized cation:



There is one other (unrelated) common error that should be avoided. When designing a synthesis in which acetylene is alkylated twice, make sure to alkylate each side separately, even if both alkyl groups are the same:



It is a common student error to show the reagents just one time, assuming that alkylation will occur on both sides of acetylene. If the reagents for alkylation are only shown once, then alkylation will only occur once:



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Useful Reagents

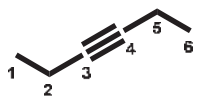
The following is a list of commonly encountered reagents for reactions of alkynes:

Reagents	Name of Reaction	Description of Reaction
1) excess $NaNH_2$ 2) H_2O	Elimination	When treated with these reagents, a vicinal or geminal dibromide is converted to an alkyne.
HX	Hydrohalogenation	When treated with HX, an alkyne undergoes Markovnikov addition (excess HX gives two addition reactions to afford a geminal dihalide).
H_2SO_4, H_2O, $HgSO_4$	Acid-cat. hydration	When treated with these reagents, a terminal alkyne undergoes Markovnikov addition of H and OH to give an enol, which quickly tautomerizes to give a ketone.
1) R_2BH 2) H_2O_2, NaOH	Hydroboration-oxidation	When treated with these reagents, a terminal alkyne undergoes *anti*-Markovnikov addition of H and OH to give an enol, which quickly tautomerizes to give an aldehyde.
X_2	Halogenation	When treated with this reagent, an alkyne undergoes addition of X and X (excess X_2 gives a tetrahalide).
1) O_3 2) H_2O	Ozonolysis	When treated with these reagents, an alkyne undergoes oxidative cleavage of the C≡C bond. Internal alkynes are converted into two carboxylic acids, while terminal alkynes are converted into a carboxylic acid and carbon dioxide.
H_2, Lindlar's catalyst	Hydrogenation	When treated with these reagents, an alkyne is converted to a *cis*-alkene.
H_2, Pt	Hydrogenation	When treated with these reagents, an alkyne is converted to an alkane.
Na, NH_3 (*l*)	Dissolving metal reduction	When treated with these reagents, an internal alkyne is converted to a *trans*-alkene.

Solutions

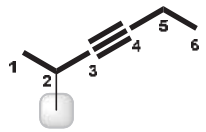
9.1.

(a) We begin by identifying the parent. The longest chain is six carbon atoms, so the parent is hexyne. There are no substituents. We must include a locant that identifies the position of the triple bond ("3" indicates that the triple bond is located between C3 and C4). This is determined by numbering the parent, which can be done in this case either from left to right or vice versa (either way gives the same result).



3-Hexyne

(b) We begin by identifying the parent. The longest chain is six carbon atoms, so the parent is hexyne. There is one substituent – a methyl group (highlighted). In this case, the triple bond is at C3 regardless of which way we number the parent, so the parent chain is numbered starting from the side that gives the substituent the lowest possible number. According to this numbering scheme, the methyl group is located at C2:



2-Methyl-3-hexyne

(c) We begin by identifying the parent. The longest chain is eight carbon atoms, so the parent is octyne. There are no substituents. We must include a locant that identifies the position of the triple bond. The parent chain is numbered so that the triple bond is assigned the

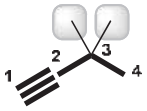
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lowest possible locant ("3" indicates that the triple bond is located between C3 and C4).



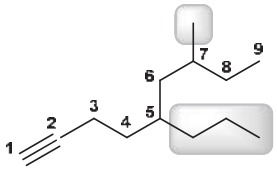
3-Octyne

(d) We begin by identifying the parent. The longest chain is four carbon atoms, so the parent is butyne. There are two substituents – both methyl groups (highlighted). We number the parent so that the triple bond receives the lowest possible locant (C1). According to this numbering scheme, the methyl groups are both located at C3:



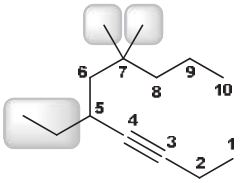
3,3-Dimethyl-1-butyne

(e) We begin by identifying the parent. The longest chain containing the triple bond has nine carbon atoms, so the parent is nonyne. There are two substituents (highlighted) – a methyl group and a propyl group. We number the parent so that the triple bond receives the lowest possible locant (C1). According to this numbering scheme, the propyl group is located at C5 and the methyl group is located at C7. These substituents are arranged alphabetically in the name:



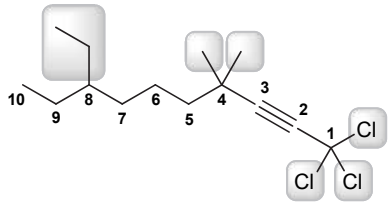
7-methyl-5-propyl-1-nonyne

(f) We begin by identifying the parent. The longest chain containing the triple bond has ten carbon atoms, so the parent is decyne. There are three substituents (highlighted) – two methyl groups and an ethyl group. We number the parent so that the triple bond receives the lowest possible locant (C3). According to this numbering scheme, the ethyl group is located at C5 and the methyl groups are both located at C7. These substituents are arranged alphabetically in the name (ethyl before methyl):



5-ethyl-7,7-dimethyl-3-decyne

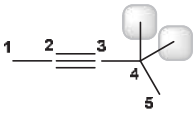
(g) We begin by identifying the parent. The longest chain containing the triple bond has ten carbon atoms, so the parent is decyne. There are many substituents (highlighted). We number the parent so that the triple bond receives the lowest possible locant (C2), and the substituents are arranged alphabetically in the name (chloro, then ethyl, and then methyl):



1,1,1-trichloro-8-ethyl-4,4-dimethyl-2-decyne

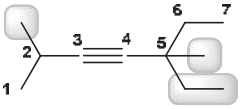
9.2.

(a) The parent (pentyne) indicates a chain of five carbon atoms. The triple bond is between C2 and C3, and there are two methyl groups (highlighted), both located at C4.



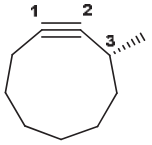
4,4-Dimethyl-2-pentyne

(b) The parent (heptyne) indicates a chain of seven carbon atoms. The triple bond is between C3 and C4, and there are three substituents (highlighted) – two methyl groups (at C2 and C5), as well as an ethyl group at C5.

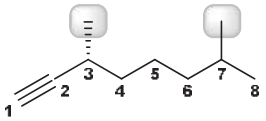


5-Ethyl-2,5-dimethyl-3-heptyne

9.3. The parent is cyclononyne, so we draw a nine-membered ring that incorporates a triple bond. The triple bond is (by definition) between C1 and C2, and a methyl group is located at C3. This position (C3) is a chiral center, with the *R* configuration, shown here:

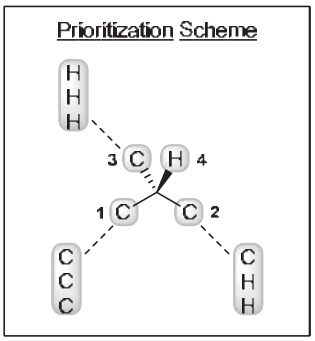


9.4. The parent chain contains eight carbon atoms with two methyl substituents. Numbering so that the triple bond receives the lowest possible locant, the two methyl groups are located at C3 and C7:

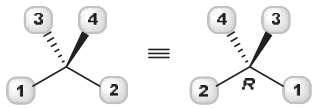


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Notice that there is a chiral center at C3. The complete IUPAC name must include the configuration of this chiral center using the Cahn-Ingold-Prelog system. Priorities are assigned in the following way:



Notice that the low-priority group is in the front rather than the back. So, we rotate the molecule (thereby placing the fourth priority on a dash), and we assign the configuration (*R*):



Putting it all together, the IUPAC name of this alkyne is (*R*)-3,7-dimethyl-1-octyne (using the old IUPAC rules) or (*R*)-3,7-dimethyloct-1-yne (using the new IUPAC rules). Both names are acceptable.

9.5.

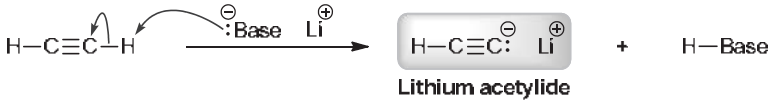
(a) Yes, as seen in Table 9.1, $NaNH_2$ is a sufficiently strong base to deprotonate a terminal alkyne.

(b) Yes, as seen in Table 9.1, NaH is a sufficiently strong base to deprotonate a terminal alkyne.

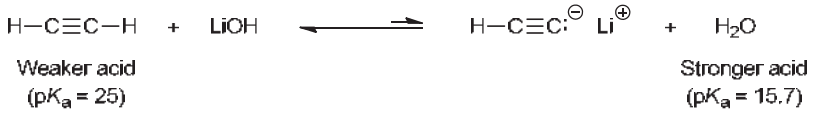
(c) No, as seen in Table 9.1, *t*-BuOK is not a sufficiently strong base to deprotonate a terminal alkyne.

9.6.

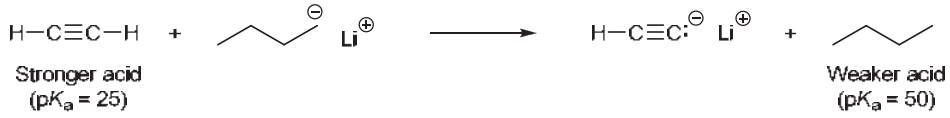
(a) Lithium acetylide is the lithium salt of the conjugate base of acetylene, which is formed when a suitably strong base removes a proton from acetylene:



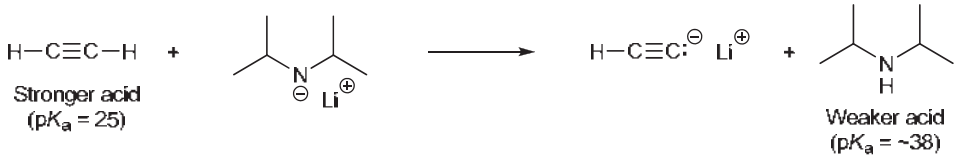
(b) As seen in Table 9.1, hydroxide is not a sufficiently strong base to deprotonate a terminal alkyne. Therefore, LiOH cannot be used to prepare lithium acetylide, since the reverse reaction would be favored:



However, BuLi is a sufficiently strong base to deprotonate a terminal alkyne and can be used to prepare lithium acetylide:



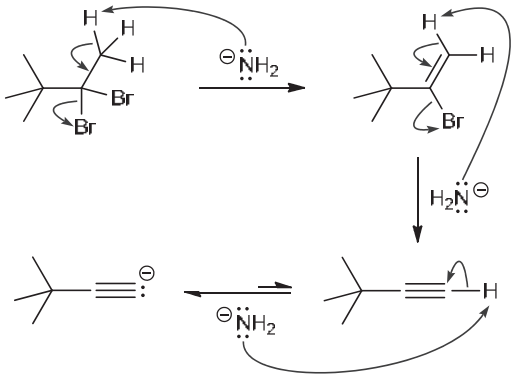
LDA is a base with a negative charge on a nitrogen atom, so we expect that it will be similar (in base strength) to sodium amide ($NaNH_2$). Therefore, LDA will be a sufficiently strong base to deprotonate a terminal alkyne and can be used to prepare lithium acetylide, as shown below. The pK_a value of diisopropyl amine (R_2NH, where R = isopropyl) is not given in Table 9.1, but we can assume that its pK_a is similar in magnitude to the pK_a of NH_3 (~ 38).



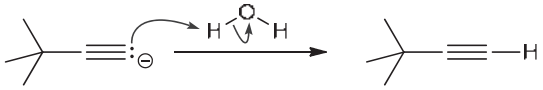
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9.7.

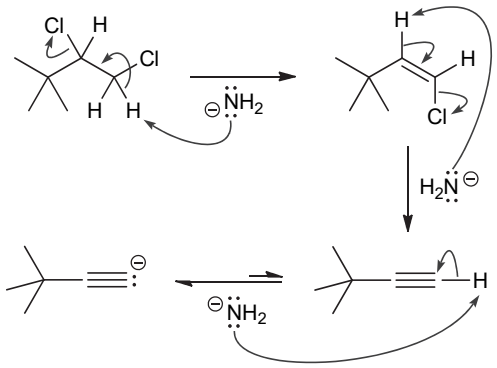
(a) The starting material is a geminal dibromide. When treated with excess sodium amide ($NaNH_2$), two, successive E2 reactions occur (each of which requires three curved arrows, as shown below). The resulting terminal alkyne is then deprotonated to give an alkynide ion:



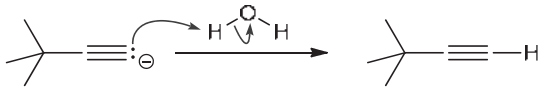
After the reaction is complete, water (H_2O) is introduced into the reaction flask to protonate the alkynide ion, thereby giving the terminal alkyne.



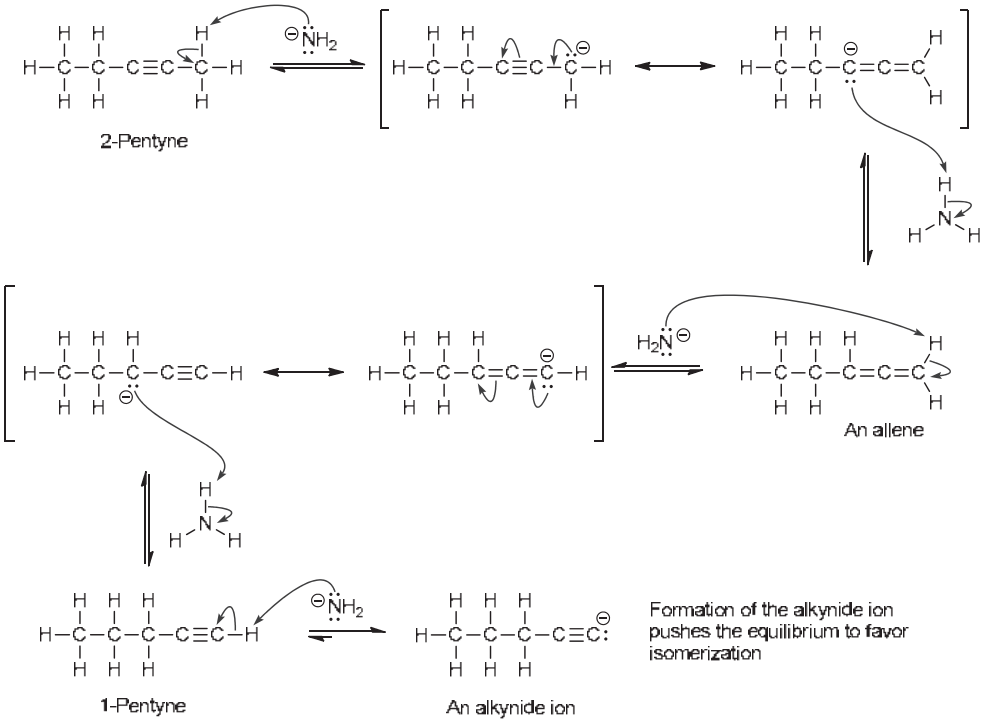
(b) The starting material is a vicinal dichloride. When treated with excess sodium amide ($NaNH_2$), two, successive E2 reactions occur (each of which requires three curved arrows, as shown below). The resulting terminal alkyne is then deprotonated to give an alkynide ion:



After the reaction is complete, water (H_2O) is introduced into the reaction flask to protonate the alkynide ion, thereby giving the terminal alkyne:

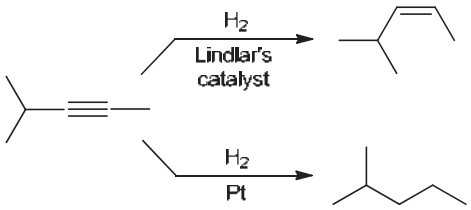


9.8. Deprotonation of 2-pentyne generates a resonance-stabilized anion, which is then protonated by NH_3 to give an allene (a compound featuring a C=C=C unit). The allene is then deprotonated to give a resonance-stabilized anion, which is then protonated by NH_3 to give 1-pentyne. Deprotonation of this terminal alkyne gives an alkynide ion. Formation of this alkynide ion pushes the equilibrium to favor this isomerization process.

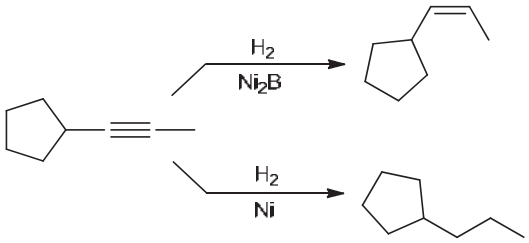


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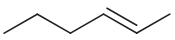
9.9.
(a) When hydrogenation is performed in the presence of a poisoned catalyst (such as Lindlar's catalyst), the alkyne is reduced to a *cis* alkene. When Pt is used as the catalyst, the alkyne is reduced all the way to an alkane, as shown here:



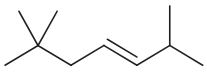
(b) When hydrogenation is performed in the presence of a poisoned catalyst (such as Ni_2B), the alkyne is reduced to a *cis* alkene. When nickel is used as the catalyst, the alkyne is reduced all the way to an alkane, as shown here:



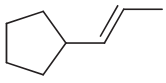
9.10.
(a) When treated with sodium in liquid ammonia, the alkyne is converted to a *trans* alkene:



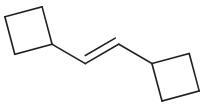
(b) When treated with sodium in liquid ammonia, the alkyne is converted to a *trans* alkene:



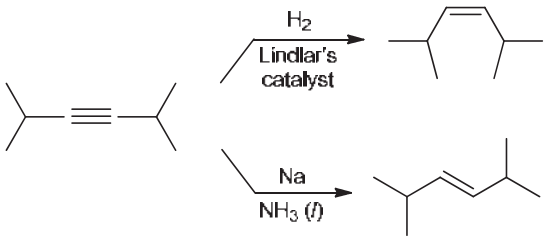
(c) When treated with sodium in liquid ammonia, the alkyne is converted to a *trans* alkene:



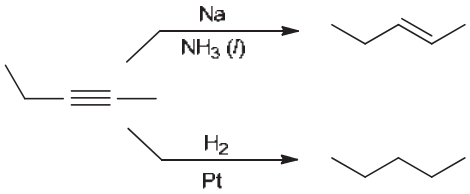
(d) When treated with sodium in liquid ammonia, the alkyne is converted to a *trans* alkene:



9.11.
(a) When the alkyne is treated with molecular hydrogen (H_2) in the presence of a poisoned catalyst (such as Lindlar's catalyst), the alkyne is reduced to a *cis* alkene. If instead, the alkyne is treated with sodium in liquid ammonia, a dissolving metal reduction occurs, giving a *trans* alkene, as shown:



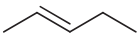
(b) When the alkyne is treated with sodium in liquid ammonia, a dissolving metal reduction occurs, giving a *trans* alkene. If instead, the alkyne is treated with molecular hydrogen (H_2) in the presence of a catalyst such as platinum (NOT a poisoned catalyst), the alkyne is reduced to an alkane, as shown:



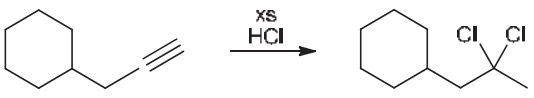
9.12. The product is a disubstituted alkene, so the starting alkyne must be an internal alkyne (rather than a terminal alkyne):



The molecular formula of the alkyne indicates five carbon atoms. Two of those atoms are the *sp* hybridized carbon atoms of the triple bond. The remaining three carbon atoms must be in the R groups. So, one R group must be a methyl group, and the other R group must be an ethyl group:

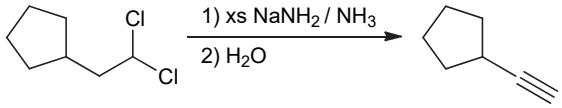


9.13.
(a) The starting alkyne is terminal, and when treated with excess HCl, two successive addition reactions occur, producing a geminal dihalide. The two chlorine atoms are installed at the more substituted, secondary position, rather than the less substituted, primary position:

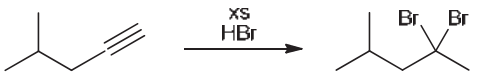


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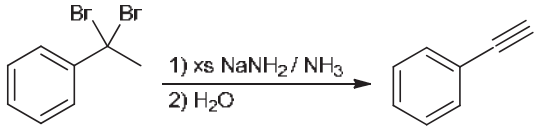
(b) The starting material is a geminal dichloride, and treatment with excess sodium amide (followed by work-up with water) gives a terminal alkyne.



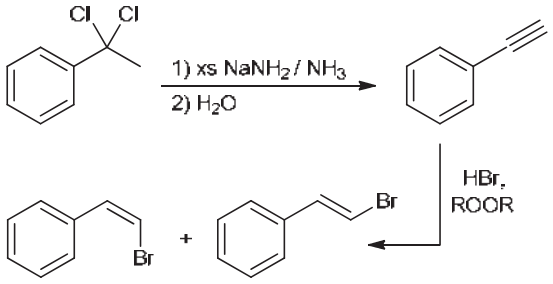
(c) The starting alkyne is terminal, and when treated with excess HBr, two successive addition reactions occur, producing a geminal dibromide. The two bromine atoms are installed at the more substituted, secondary position, rather than the less substituted, primary position:



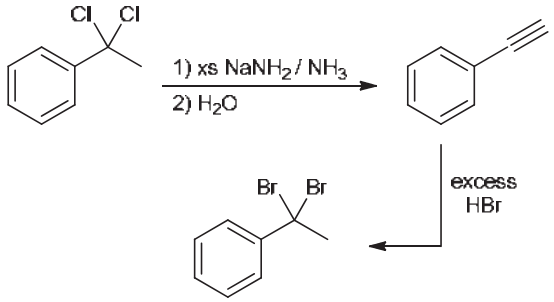
(d) The starting material is a geminal dibromide, and treatment with excess sodium amide (followed by work-up with water) gives a terminal alkyne.



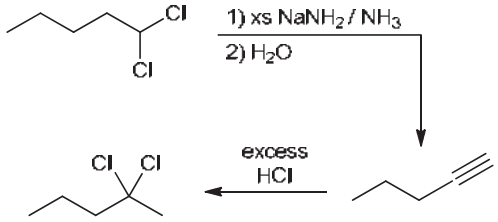
(e) The starting material is a geminal dichloride, and treatment with excess sodium amide (followed by work-up with water) gives a terminal alkyne. When this alkyne is treated with HBr, in the presence of peroxides, an *anti*-Markovnikov addition occurs, in which Br is installed at the less substituted position. This gives rise to two stereoisomers, as shown:



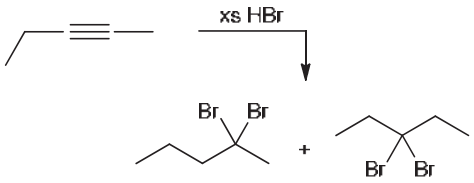
(f) The starting material is a geminal dichloride, and treatment with excess sodium amide (followed by work-up with water) gives a terminal alkyne. When this alkyne is treated with excess HBr, two addition reactions occur, installing two bromine atoms at the more substituted position (Markovnikov addition), as shown:



9.14. The starting material is a geminal dichloride, and the product is also a geminal dichloride. The difference between these compounds is the placement of the chlorine atoms. We did not learn a single reaction that will change the locations of the chlorine atoms. But the desired transformation can be achieved via an alkyne. Specifically, the starting material is treated with excess sodium amide (followed by water work-up) to give the terminal alkyne, which is then treated with excess HCl to give the desired compound:

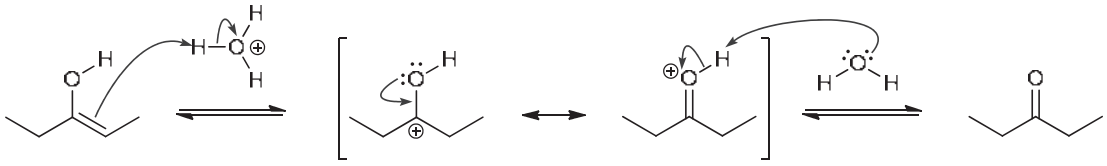


9.15. If two products are obtained, then the alkyne must be internal and unsymmetrical. There is only one such alkyne with the molecular formula C_5H_8 (shown below). The products are also shown:



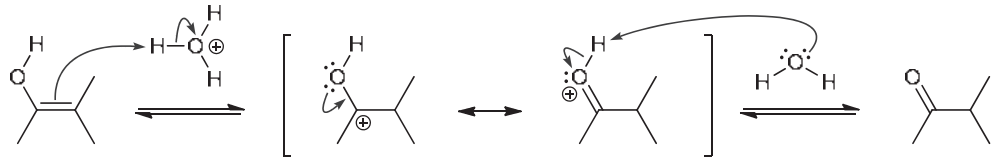
9.16.

(a) Under acid-catalyzed conditions, the enol is first protonated (which requires two curved arrows) to generate a resonance-stabilized cation. Notice that the π bond (of the enol) is protonated in this step (rather than protonating the OH group). The resulting resonance-stabilized cation is then deprotonated by water, which also requires two curved arrows, as shown:

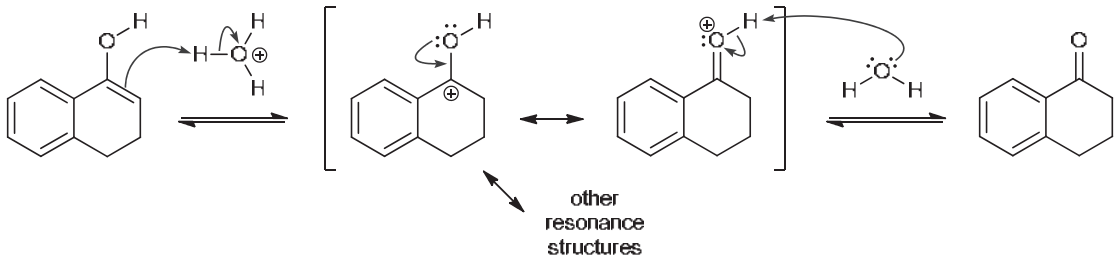


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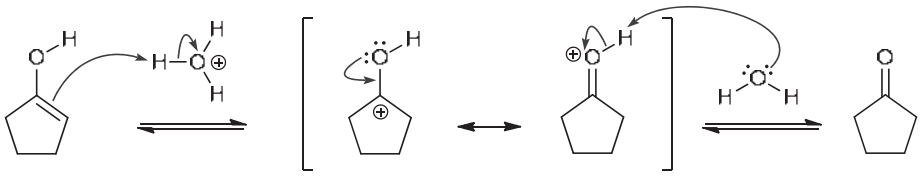
(b) Under acid-catalyzed conditions, the enol is first protonated (which requires two curved arrows) to generate a resonance-stabilized cation. Notice that the π bond (of the enol) is protonated in this step (rather than protonating the OH group). The resulting resonance-stabilized cation is then deprotonated by water, which also requires two curved arrows, as shown:



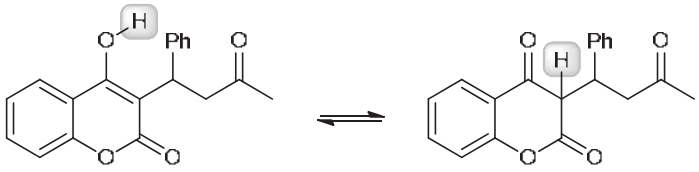
(c) Under acid-catalyzed conditions, the enol is first protonated (which requires two curved arrows) to generate a resonance-stabilized cation. Notice that the π bond (of the enol) is protonated in this step (rather than protonating the OH group). The resulting resonance-stabilized cation is then deprotonated by water, which also requires two curved arrows, as shown:



(d) Under acid-catalyzed conditions, the enol is first protonated (which requires two curved arrows) to generate a resonance-stabilized cation. Notice that the π bond (of the enol) is protonated in this step (rather than protonating the OH group). The resulting resonance-stabilized cation is then deprotonated by water, which also requires two curved arrows, as shown:



9.17. Warfarin has only three oxygen atoms, so in the tri-carbonyl form (three C=O bonds), there must be no OH groups. That is, any enol groups must be converted into C=O bonds. Let's begin by considering the structure of the first tautomer shown in the problem statement. This compound contains one enol group. If this enol group is converted into a ketone, the resulting tautomer would have three carbonyl groups. This tautomerization process involves the change in location of a proton (highlighted):

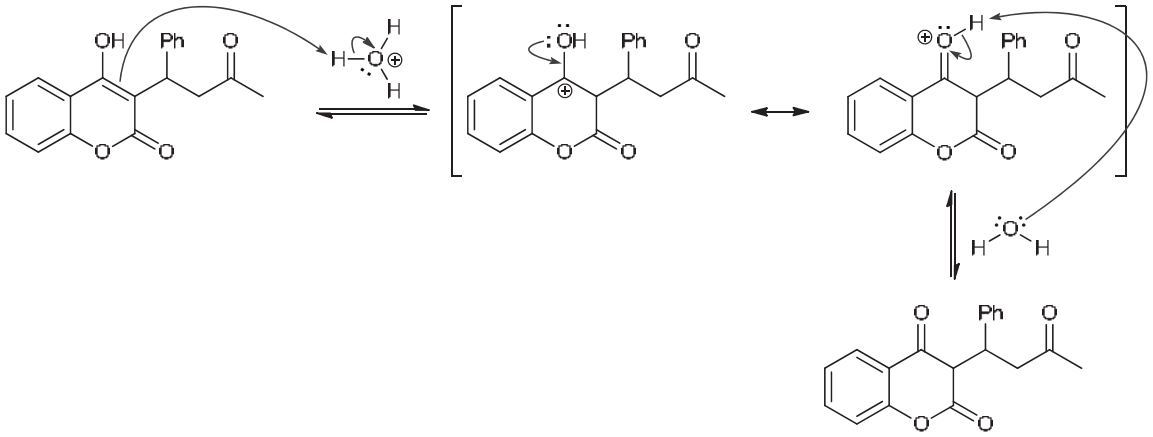


Similarly, the same tri-carbonyl tautomer is obtained if the enol group in the second tautomer (shown in the problem statement) is converted into a C=O bond. Once again, the tautomerization process involves the change in location of a proton (highlighted):

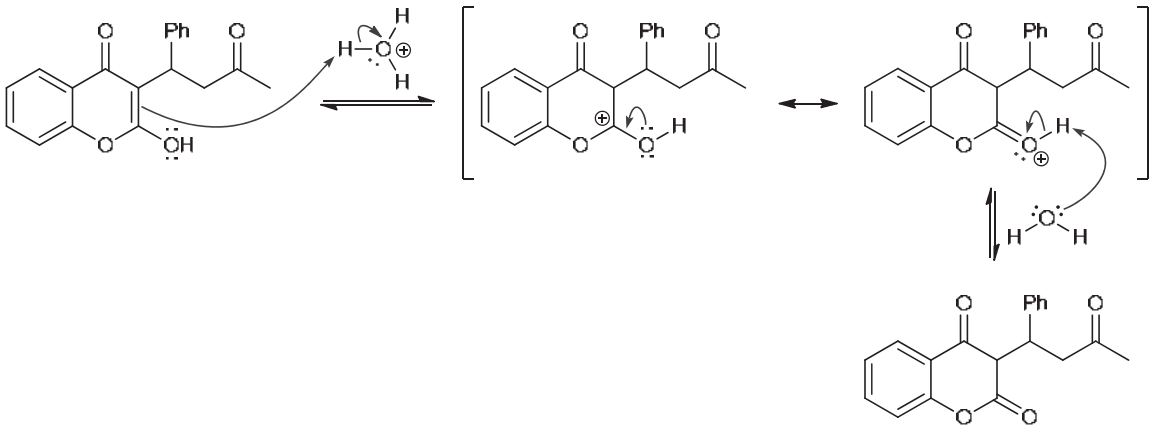


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Under acidic conditions, the tautomerization of either enol tautomer (to give the tri-carbonyl form) occurs via the following steps. First, the C=C π bond is protonated (not the OH group) to give a resonance-stabilized carbocation intermediate. After drawing the resonance structures of the intermediate, deprotonation gives the tri-carbonyl tautomer:

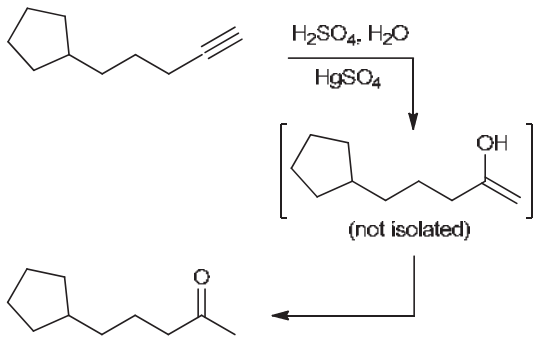


Starting with the other tautomer, we follow the same steps again. First, the π bond is protonated to give a resonance-stabilized carbocation intermediate. After drawing the resonance structures of the intermediate, deprotonation gives the tri-carbonyl tautomer:

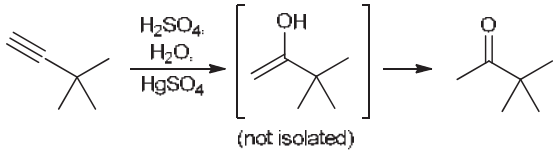


9.18.

(a) When treated with aqueous acid (in the presence of mercuric sulfate), the terminal alkyne undergoes Markovnikov addition of H and OH across the alkyne, giving an enol. The enol is not isolated, because upon its formation, it undergoes tautomerization to give a methyl ketone:



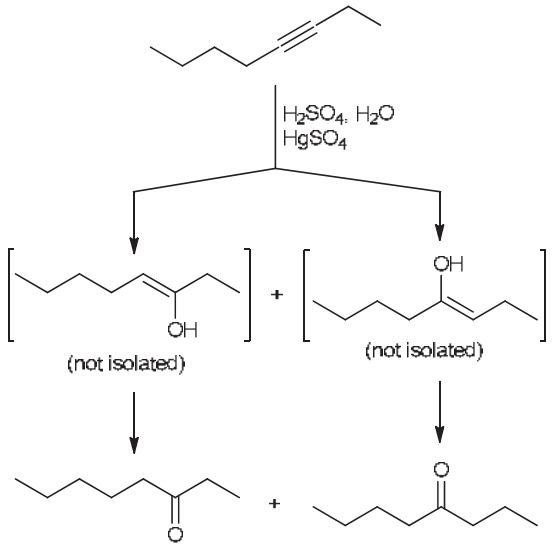
(b) When treated with aqueous acid (in the presence of mercuric sulfate), the terminal alkyne undergoes Markovnikov addition of H and OH across the alkyne, giving an enol. The enol is not isolated, because upon its formation, it undergoes tautomerization to give a methyl ketone:



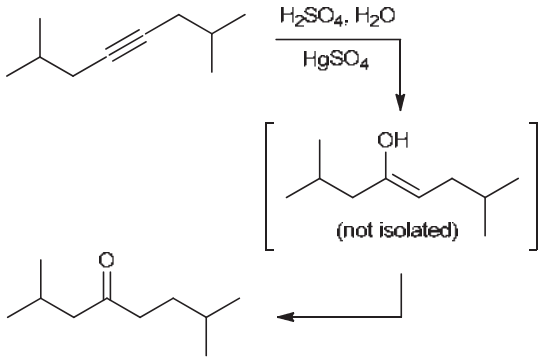
(c) When treated with aqueous acid (in the presence of mercuric sulfate), an alkyne undergoes addition of H and OH across the alkyne. In this case, the starting alkyne is not terminal – it is an internal alkyne. As such, there are two possible regiochemical outcomes, giving rise to two

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possible enols. Neither of these enols is isolated, because upon their formation, they each undergo tautomerization to give a ketone, as shown here:

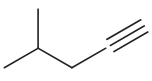


(d) When treated with aqueous acid (in the presence of mercuric sulfate), an alkyne undergoes addition of H and OH across the alkyne. In this case, the starting alkyne is not terminal – it is an internal alkyne, so we might expect two regiochemical outcomes. But look closely at the structure of the alkyne in this case. It is symmetrical (the triple bond is connected to two identical alkyl groups), and as such, there is only one possible enol that can be formed. This enol is not isolated, because upon its formation, it undergoes tautomerization to give a ketone:



9.19.

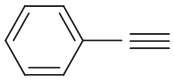
(a) The desired product is a methyl ketone, which can be prepared from the corresponding terminal alkyne, shown here:



(b) The desired product is not a methyl ketone, but it can be made directly from the following internal alkyne. This alkyne is symmetrical, so only one regiochemical outcome is possible:

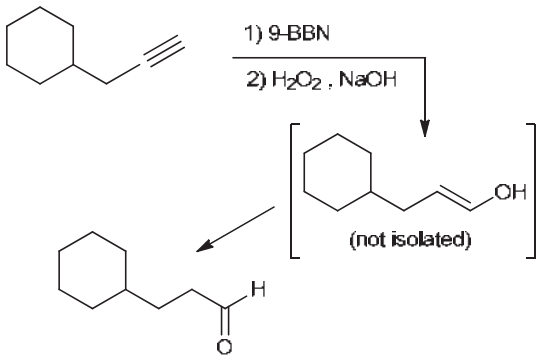


(c) The desired product is a methyl ketone, which can be prepared from the corresponding terminal alkyne, shown here:

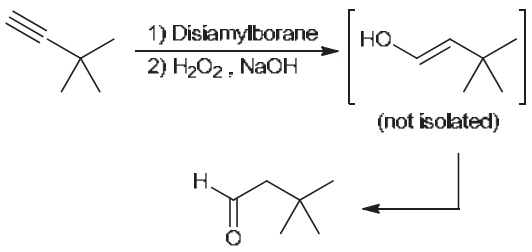


9.20.

(a) The reagents (9-BBN, followed by H_2O_2 and NaOH) indicate hydroboration-oxidation of the terminal alkyne, giving an *anti*-Markovnikov addition of H and OH across the alkyne. The resulting enol is not isolated, because upon its formation, it undergoes tautomerization to give an aldehyde:

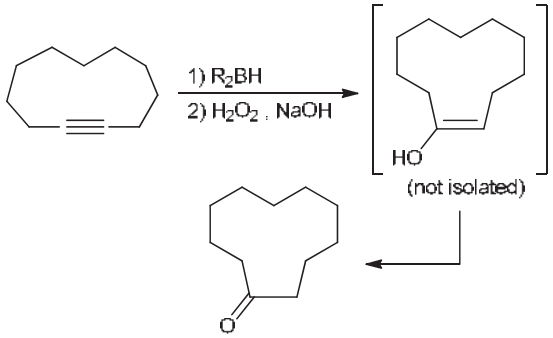


(b) The reagents (disiamylborane, followed by H_2O_2 and NaOH) indicate hydroboration-oxidation of the terminal alkyne, giving an *anti*-Markovnikov addition of H and OH across the alkyne. The resulting enol is not isolated, because upon its formation, it undergoes tautomerization to give an aldehyde:



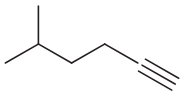
(c) The reagents (R_2BH, followed by H_2O_2 and NaOH) indicate hydroboration-oxidation of the terminal alkyne, giving addition of H and OH. Since the alkyne is symmetrical, regiochemistry is not relevant in this case. The resulting enol is not isolated, because upon its formation, it undergoes tautomerization to give a ketone:

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9.21.

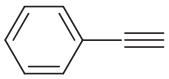
(a) The desired product is an aldehyde, which can be prepared from the corresponding terminal alkyne, shown here:



(b) The desired product is not an aldehyde, but it can be made directly from the following internal alkyne. This alkyne is symmetrical, so only one regiochemical outcome is possible:

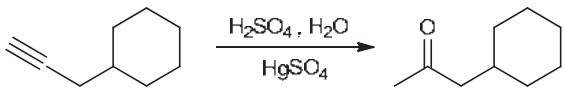


(c) The desired product is an aldehyde, which can be prepared from the corresponding terminal alkyne, shown here:

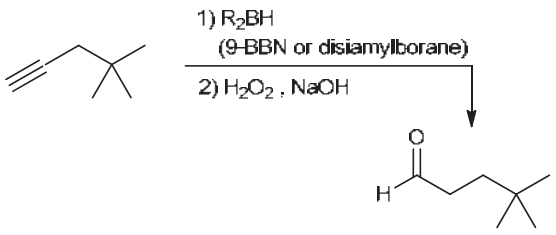


9.22.

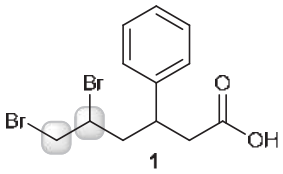
(a) The starting material is a terminal alkyne and the product is a methyl ketone. This transformation requires a Markovnikov addition, which can be achieved via an acid-catalyzed hydration in the presence of mercuric sulfate.



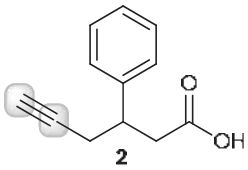
(b) The starting material is a terminal alkyne and the product is an aldehyde. This transformation requires an *anti*-Markovnikov addition, which can be achieved via hydroboration-oxidation.



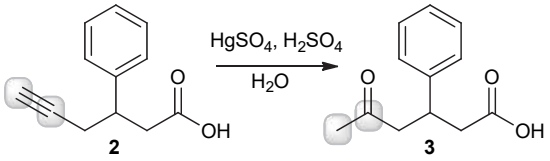
9.23. Compounds **1** and **3** have the same carbon skeleton. Only the identity and location of the functional groups have been changed. In compound **1**, the following two highlighted positions are functionalized (each is attached to Br):



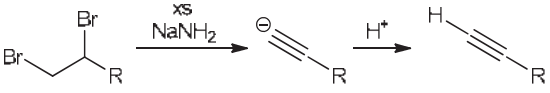
So it is reasonable to propose an alkyne in which the triple bond is between these two carbon atoms:



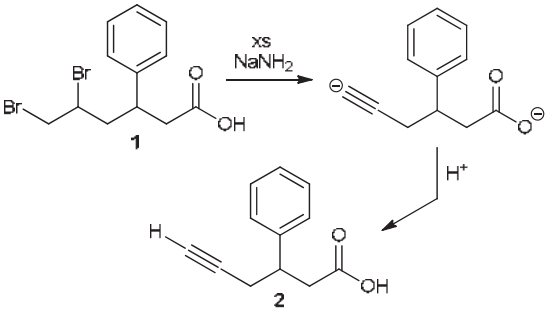
Indeed, we have learned a way to convert this alkyne into the desired methyl ketone (compound **3**), via acid-catalyzed hydration (Markovnikov addition):



To complete the synthesis, we must propose reagents for the conversion of **1** to **2**. As seen earlier in the chapter, this transformation can be achieved via two successive E2 reactions, requiring a strong base such as $NaNH_2$. For this type of process, excess base is generally required. As shown below, the initial product of this general process is an alkynide ion, which is protonated upon treatment with a mild acid to give a terminal alkyne:

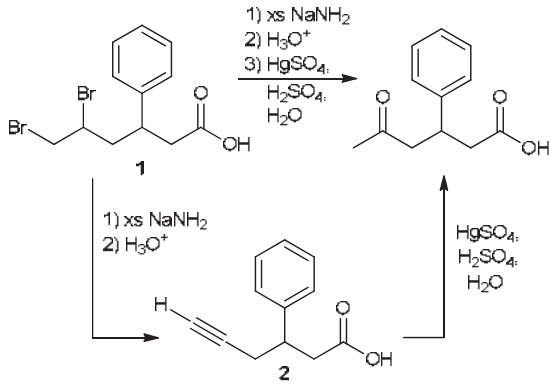


In this case, the strongly basic conditions will also deprotonate the carboxylic acid to give a carboxylate group. This carboxylate group is protonated (together with the alkynide ion) upon treatment with a mild acid:



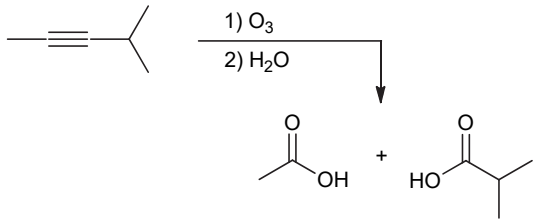
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In summary, the following reagents can be used to convert **1** into **3**:

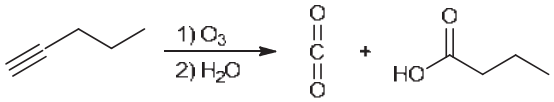


9.24.

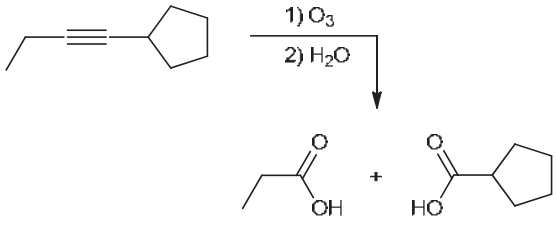
(a) The reagents (O_3, followed by H_2O) indicate ozonolysis. The starting material is an unsymmetrical, internal alkyne, so cleavage of the C≡C bond results in the formation of two carboxylic acids:



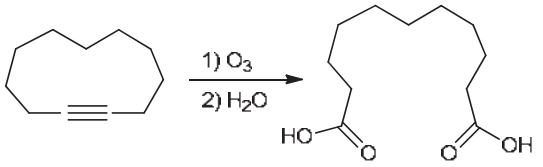
(b) The reagents (O_3, followed by H_2O) indicate ozonolysis. The starting material is a terminal alkyne, so cleavage of the C≡C bond results in the formation of a carboxylic acid and carbon dioxide (CO_2):



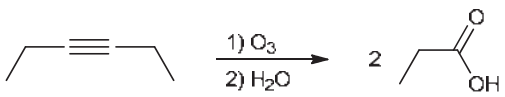
(c) The reagents (O_3, followed by H_2O) indicate ozonolysis. The starting material is an unsymmetrical, internal alkyne, so cleavage of the C≡C bond results in the formation of two carboxylic acids:



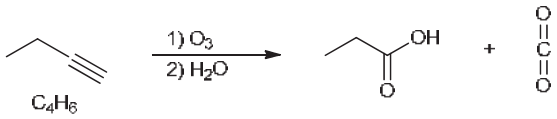
(d) The reagents (O_3, followed by H_2O) indicate ozonolysis. The starting material is a cycloalkyne, so cleavage of the C≡C bond results in the formation of a compound with two carboxylic acid groups:



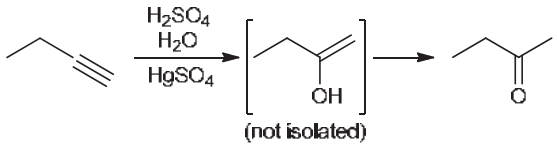
9.25. If ozonolysis produces only one product, then the starting alkyne must be symmetrical. There is only one symmetrical alkyne with the molecular formula C_6H_{10}:



9.26. If ozonolysis produces a carboxylic acid and carbon dioxide, then the starting alkyne must be terminal. There is only one terminal alkyne with the molecular formula C_4H_6:

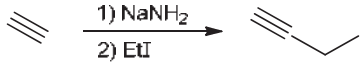


When this alkyne is treated with aqueous acid in the presence of mercuric sulfate, the alkyne is expected to undergo a Markovnikov addition of H and OH, generating an enol. This enol is not isolated, because upon its formation, it undergoes tautomerization to give a methyl ketone:



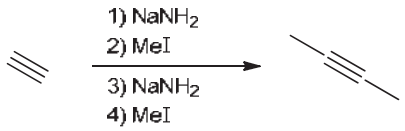
9.27.

(a) We begin by drawing the starting material (acetylene) and the product (1-butyne), which makes it more clear to see that the desired transformation involves a single alkylation process. This can be achieved by treating acetylene with sodium amide, followed by ethyl iodide:

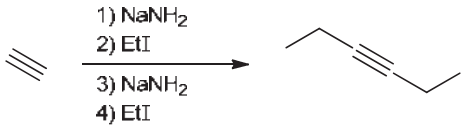


(b) We begin by drawing the starting material (acetylene) and the product (2-butyne), which makes it more clear to see that the desired transformation involves two, successive alkylation processes. The first alkylation is achieved by treating acetylene with sodium amide, followed by methyl iodide. The second alkylation process is then achieved upon further treatment with sodium amide, followed by methyl iodide. Notice that each alkylation process must be performed separately.

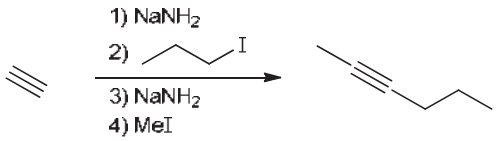
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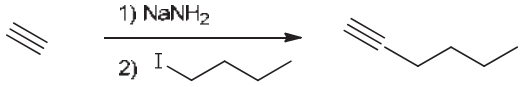
(c) We begin by drawing the starting material (acetylene) and the product (3-hexyne), which makes it more clear to see that the desired transformation involves two, successive alkylation processes. The first alkylation is achieved by treating acetylene with sodium amide, followed by ethyl iodide. The second alkylation process is then achieved upon further treatment with sodium amide, followed by ethyl iodide. Notice that each alkylation process must be performed separately.



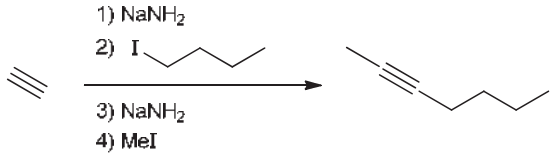
(d) We begin by drawing the starting material (acetylene) and the product (2-hexyne), which makes it more clear to see that the desired transformation involves two, successive alkylation processes. That is, we must install a methyl group and a propyl group. The propyl group is installed by treating acetylene with sodium amide, followed by propyl iodide. And the methyl group is installed in a similar way (upon treatment with sodium amide, followed by methyl iodide). The propyl group can be installed first or last. Either way is acceptable. The following shows installation of the propyl group followed by installation of the methyl group:



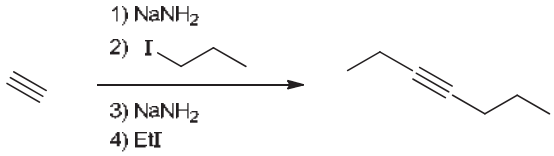
(e) We begin by drawing the starting material (acetylene) and the product (1-hexyne). This makes it more clear to see that the desired transformation involves a single alkylation process, which can be achieved with the following reagents:



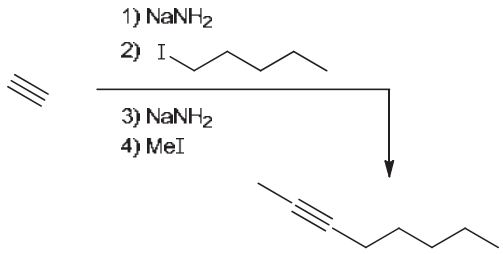
(f) We begin by drawing the starting material (acetylene) and the product (2-heptyne), which makes it more clear to see that the desired transformation involves two, successive alkylation processes. That is, we must install a methyl group and a butyl group. These two groups can be installed in either order. The following shows installation of the butyl group followed by installation of the methyl group:



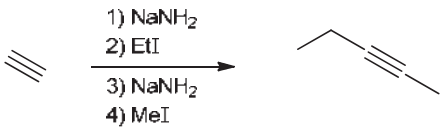
(g) We begin by drawing the starting material (acetylene) and the product (3-heptyne), which makes it more clear to see that the desired transformation involves two, successive alkylation processes. That is, we must install an ethyl group and a propyl group. These two groups can be installed in either order. The following shows installation of the propyl group followed by installation of the ethyl group:



(h) We begin by drawing the starting material (acetylene) and the product (2-octyne), which makes it more clear to see that the desired transformation involves two, successive alkylation processes. That is, we must install a methyl group and a pentyl group. These two groups can be installed in either order. The following shows installation of the pentyl group followed by installation of the methyl group:



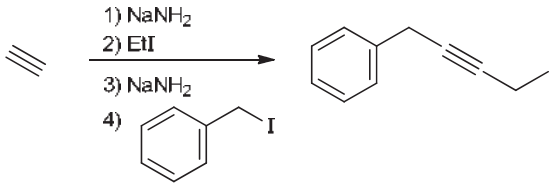
(i) We begin by drawing the starting material (acetylene) and the product (2-pentyne), which makes it more clear to see that the desired transformation involves two, successive alkylation processes. That is, we must install a methyl group and an ethyl group. These two groups can be installed in either order. The following shows installation of the ethyl group followed by installation of the methyl group:



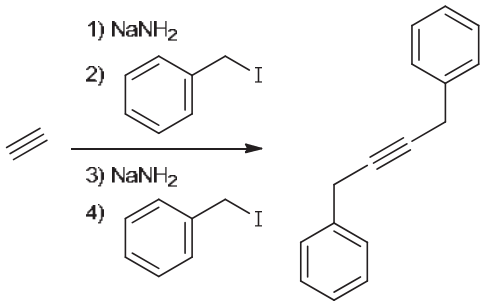
(j) The desired transformation involves two, successive alkylation processes. That is, we must install an ethyl group and a benzyl group. These two groups can be installed in either order. The following shows

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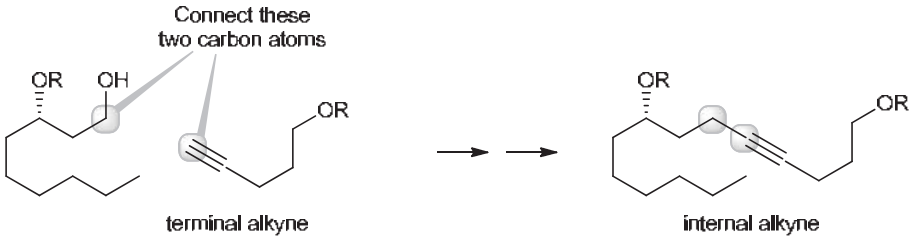
installation of the ethyl group followed by installation of the benzyl group:



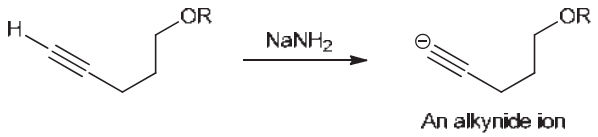
(k) The desired transformation involves two, successive alkylation processes. Each alkylation is achieved by treating the alkyne with sodium amide, followed by benzyl iodide. Notice that each alkylation process must be performed separately.



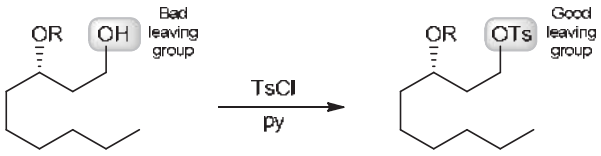
9.28. The carbon atoms present in compounds **1** and **2** completely account for the carbon skeleton of compound **3**, if we can connect the two highlighted carbon atoms:



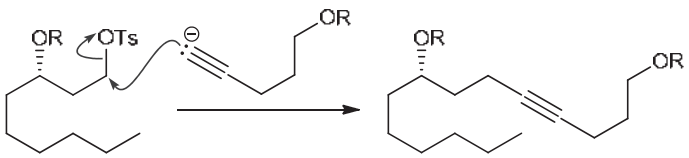
This process involves the conversion of a terminal alkyne (compound **2**) into an internal alkyne (compound **3**), which can be accomplished via an S_N2 process. In order to perform the desired S_N2 reaction, the starting materials must first be modified. The terminal alkyne (compound **2**) must be deprotonated with a strong base to convert it into a good nucleophile (using, for example, $NaNH_2$ to produce an alkynide ion):



Also, the alcohol (compound **1**) must be converted into a substrate that contains a good leaving group, because hydroxide is not a good leaving group. For example, the alcohol can be treated with TsCl and pyridine to give a tosylate (see Section 7.12):



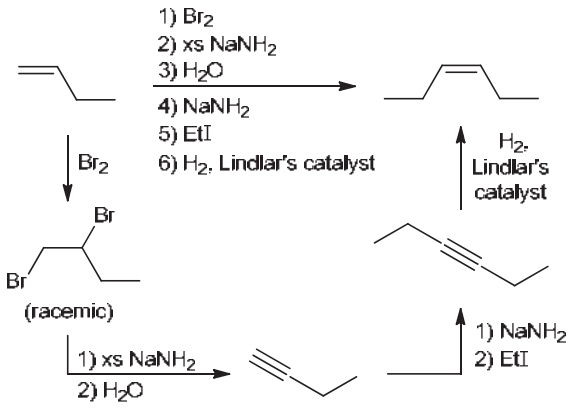
Treating this tosylate with the alkynide ion will result in an S_N2 reaction, giving compound **3**:



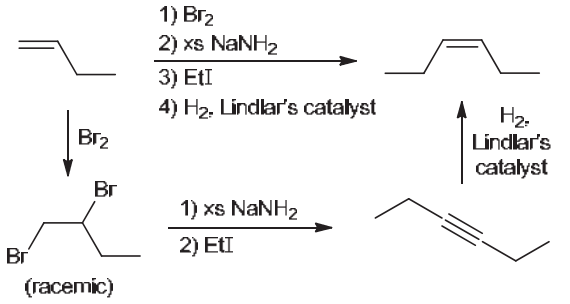
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9.29.

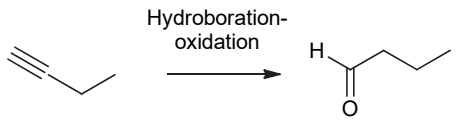
(a) The desired transformation appears to involve installation of an ethyl group. If the starting compound were a terminal alkyne, we could simply perform an alkylation reaction, but unfortunately, the starting compound is an alkene (not an alkyne). Alkenes do not undergo alkylation reactions under the same conditions used for the alkylation of alkynes, and we have not covered the conditions necessary for alkylating an alkene. So, in order to perform the necessary alkylation reaction, we must first convert the alkene into an alkyne. This is accomplished by treating the starting alkene with Br_2, giving a dibromide, followed by treatment with excess sodium amide (and then water work-up). At this point, the alkylation step can be performed with ease, and the resulting alkyne can then be reduced with molecular hydrogen (H_2) in the presence of Lindlar's catalyst to generate the desired *cis* alkene.



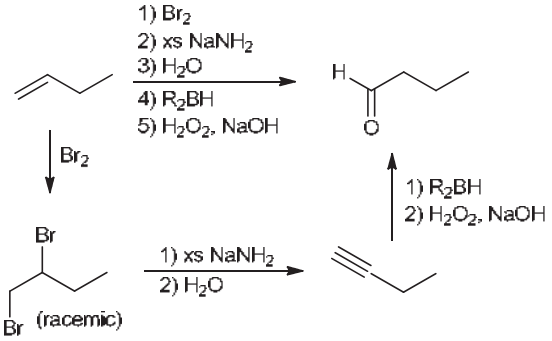
Note: The alkyne produced after step 3 does not need to be isolated and purified, and therefore, steps 3 and 4 can be omitted. That is, the synthesis can be presented like this:



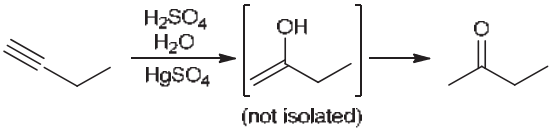
(b) The desired product is an aldehyde, which can be made from the following alkyne (1-butyne) via hydroboration-oxidation:



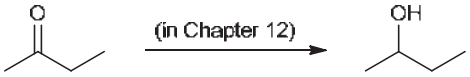
This alkyne can be prepared from the starting alkene by brominating the alkene to give a dibromide, followed by elimination with excess sodium amide:



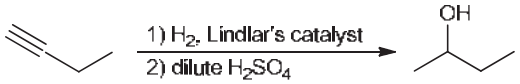
(c) We see an OH group at the more substituted position, indicating a Markovnikov addition. But there is a problem. If we try to perform Markovnikov addition of H and OH across the alkyne, the resulting enol will immediately tautomerize to give a ketone:



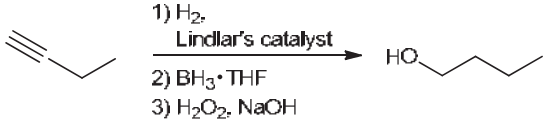
And we have not yet learned a way to convert the ketone into the desired product, although we will learn how to achieve this transformation in Chapter 12:



So, we must find another route. Instead of performing acid-catalyzed hydration first, we could first reduce the alkyne (in the presence of a poisoned catalyst), giving an alkene. This alkene can then be treated with dilute aqueous acid to give Markovnikov addition of H and OH, resulting in the desired product:

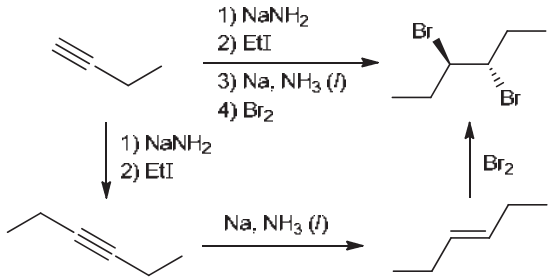


(d) Much as we saw in the solution to the previous problem, the desired product can be made by first reducing the alkyne in the presence of a poisoned catalyst (to give an alkene), followed by addition of H and OH across the alkene. In this case, we need an *anti*-Markovnikov addition, so we employ a hydroboration-oxidation procedure:

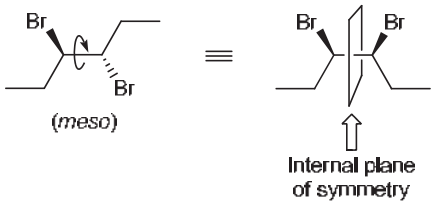


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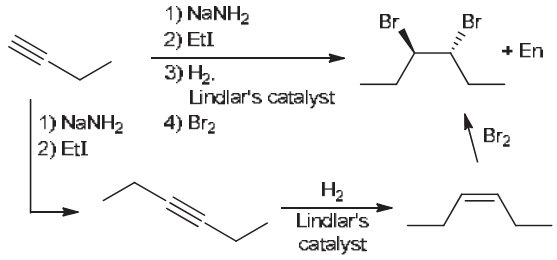
(e) The starting alkyne has only four carbon atoms, while the desired product has six carbon atoms. So we must install an ethyl group. This can be achieved by alkylating the starting alkyne. After the alkylation, the resulting, symmetrical alkyne can be reduced to an alkene, followed by bromination. Since the last step (bromination) proceeds via an *anti* addition, the desired stereoisomer can only be obtained if the previous step (reduction of the alkyne) is performed in an *anti* fashion. That is, we must use a dissolving metal reduction, rather than hydrogenation with a poisoned catalyst.



Notice that the product is a *meso* compound, which can be seen more clearly if we rotate about the central C-C bond, like this:



(f) The starting alkyne has only four carbon atoms, while the desired product has six carbon atoms. So we must install an ethyl group. This can be achieved by alkylating the starting alkyne. After the alkylation, the resulting, symmetrical alkyne can be reduced to an alkene, followed by bromination. Since the last step (bromination) proceeds via an *anti* addition, the desired stereoisomer can only be obtained if the previous step (reduction of the alkyne) is performed in a *syn* fashion. That is, we must perform a hydrogenation reaction with a poisoned catalyst, rather than using a dissolving metal reduction.



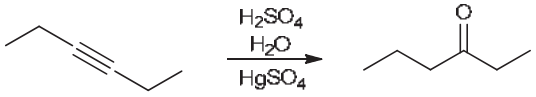
9.30. The starting material has two carbon atoms, and the desired product has six carbon atoms:



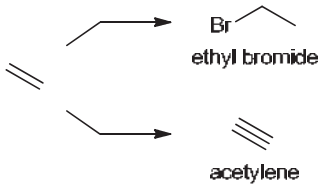
So, we must form C-C bonds. This can be achieved with acetylene and two equivalents of ethyl bromide:



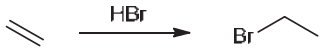
And the resulting alkyne can be converted into the product in just one step:



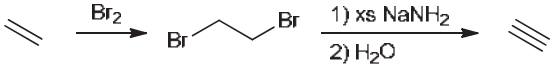
So, our goal is to convert ethylene into acetylene and ethyl bromide:



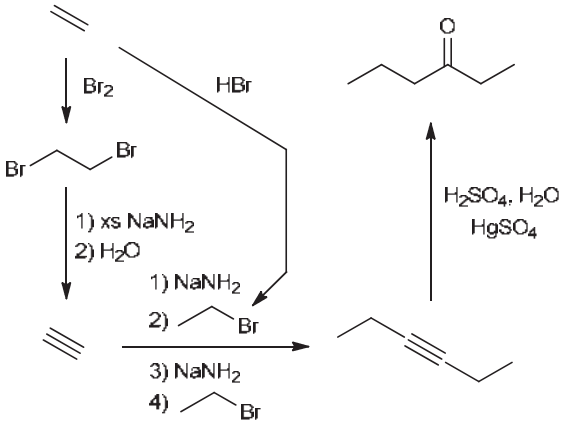
The former can be achieved in just one step, by treating ethylene with HBr:



Acetylene can be made from ethylene via the following two step process:

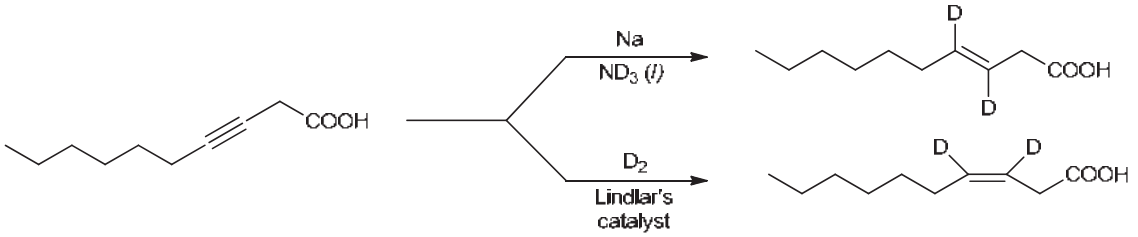


In summary, the following synthetic route converts ethylene into 3-hexanone:

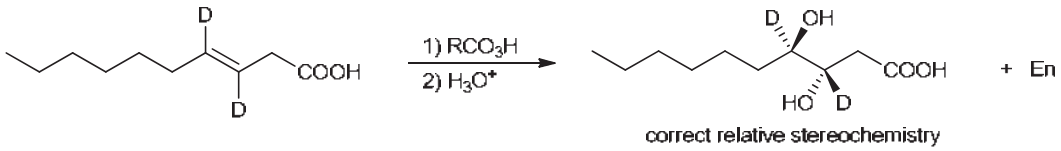


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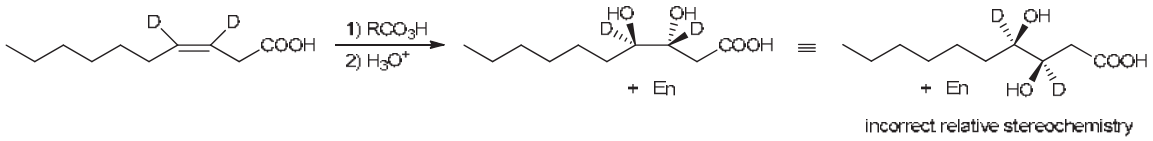
9.31. In this overall transformation, we need to add two hydrogen atoms and two hydroxyl groups to the two π bonds of the alkyne. We have also been told that an alkene is made and then used in each synthesis. It is reasonable to begin, therefore, by reducing the carbon-carbon triple bond to a carbon-carbon double bond. Use of a dissolving metal reduction will generate a *trans* alkene (using deuterium instead of protium), while hydrogenation with a poisoned catalyst will generate a *cis* alkene (again, using deuterium instead of protium).



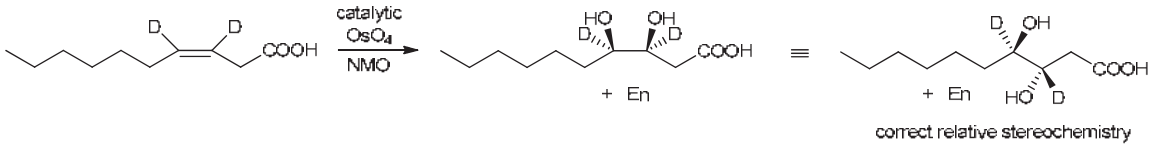
Dihydroxylation of these alkenes will provide diols; however, care must be taken to produce the desired stereochemical outcome. An *anti* addition to the *trans* alkene will produce the desired product (as a mixture of enantiomers). This can be accomplished upon treatment with a peroxyacid, to generate an epoxide intermediate, followed by aqueous acid to generate the diol.



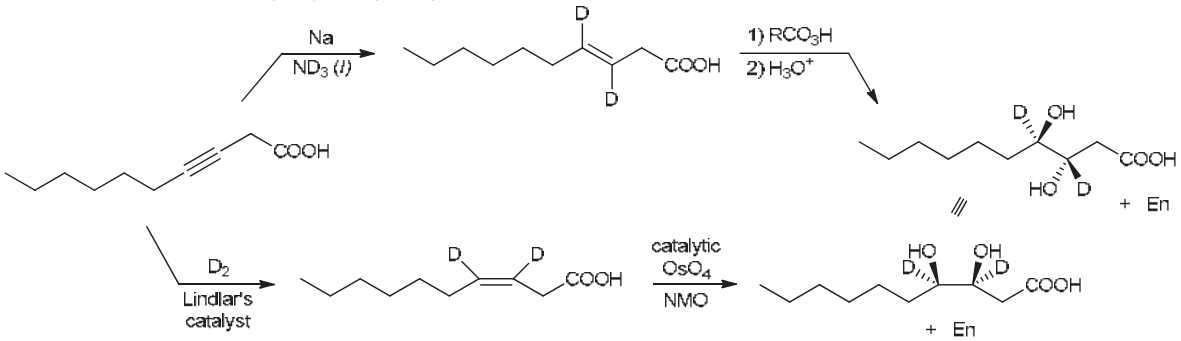
However, the same reagents will not provide the proper stereochemical outcome when used with the *cis* alkene. This is more apparent after rotating the newly formed single bond in the product.



A *syn* addition to the *cis* alkene does provide the appropriate stereochemical outcome (again a single bond rotation in the product makes this easier to see). This can be accomplished using NMO and catalytic OsO_4.



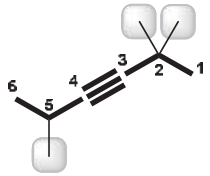
In summary, there are two ways to accomplish this overall transformation with the appropriate stereochemical outcome. One reduces the alkyne to the *trans* alkene, followed by an *anti* dihydroxylation. The other reduces the alkyne to the *cis* alkene, followed by a *syn* dihydroxylation.



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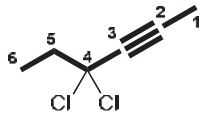
9.32.

(a) We begin by identifying the parent. The longest chain is six carbon atoms, so the parent is hexyne. There are three substituents – all methyl groups (highlighted). Numbering the parent chain from either direction will place the triple bond at C3 (between C3 and C4), so we number in the direction that gives the lower number to the second substituent (2,2,5 rather than 2,5,5):



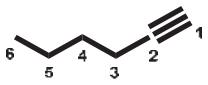
2,2,5-Trimethyl-3-hexyne

(b) We begin by identifying the parent. The longest chain is six carbon atoms, so the parent is hexyne. There are two substituents – both chloro groups. The parent chain is numbered to give the triple bond the lower possible number, C2 (because it is between C2 and C3). According to this numbering scheme, the chlorine atoms are both at C4:



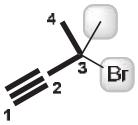
4,4-Dichloro-2-hexyne

(c) We begin by identifying the parent. The longest chain is six carbon atoms, so the parent is hexyne. There are no substituents. We must include a locant that identifies the position of the triple bond. The parent chain is numbered so that the triple bond is assigned the lowest possible locant ("1" indicates that the triple bond is located between C1 and C2).



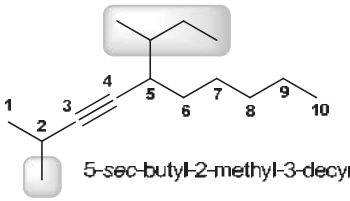
1-Hexyne

(d) We begin by identifying the parent. The longest chain is four carbon atoms, so the parent is butyne. There are two substituents (highlighted) – a methyl group and a bromo group. The parent chain is numbered so that the triple bond is assigned the lowest possible locant ("1" indicates that the triple bond is located between C1 and C2). According to this numbering scheme, both substituents are located at C3. They are alphabetized in the name, so "bromo" precedes "methyl."



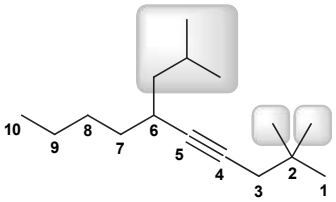
3-Bromo-3-methyl-1-butyne

(e) We begin by identifying the parent. The longest chain containing the triple bond has ten carbon atoms, so the parent is decyne. There are two substituents (highlighted) – a methyl group and a *sec*-butyl group. We number the parent so that the triple bond receives the lowest possible locant (C3). According to this numbering scheme, the *sec*-butyl group is located at C5 and the methyl group is located at C2. These substituents are arranged alphabetically in the name (butyl before methyl):



5-sec-butyl-2-methyl-3-decyne

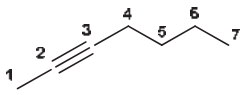
(f) We begin by identifying the parent. The longest chain containing the triple bond has ten carbon atoms, so the parent is decyne. There are three substituents (highlighted) – two methyl groups and an isobutyl group. We number the parent so that the triple bond receives the lowest possible locant (C4). According to this numbering scheme, the isobutyl group is located at C6 and the two methyl groups are located at C2. These substituents are arranged alphabetically in the name (isobutyl before methyl):



6-isobutyl-2,2-dimethyl-4-decyne

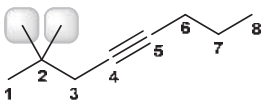
9.33.

(a) The parent (heptyne) indicates a chain of seven carbon atoms. The triple bond is between C2 and C3, and there are no substituents.



2-Heptyne

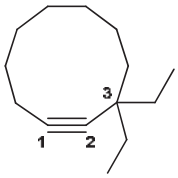
(b) The parent (octyne) indicates a chain of eight carbon atoms, with the triple bond located between C4 and C5. There are two methyl groups (highlighted), both located at position C2.



2,2-Dimethyl-4-octyne

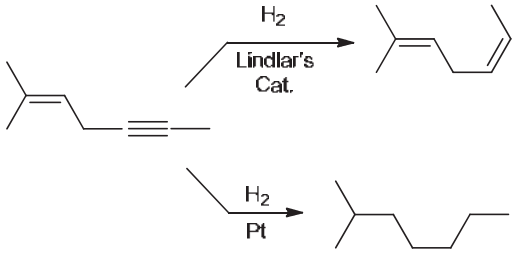
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(c) The parent (cyclodecyne) indicates a ring of ten carbon atoms. The numbering system is assigned such that the triple bond is between C1 and C2. There are two substituents (ethyl groups), each of which is located at position C3:



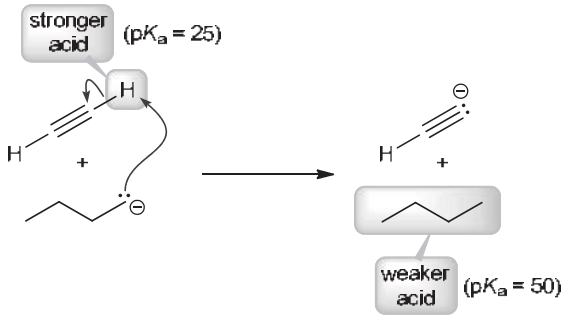
3,3-Diethylcyclodecyne

9.34. The starting material has both a double bond and a triple bond. When hydrogenation is performed in the presence of a poisoned catalyst (such as Lindlar's catalyst), only the triple bond is reduced (via *syn* addition to give a *cis* alkene). However, when Pt is used as the catalyst, both the double bond and the triple bond are reduced, giving an alkane:

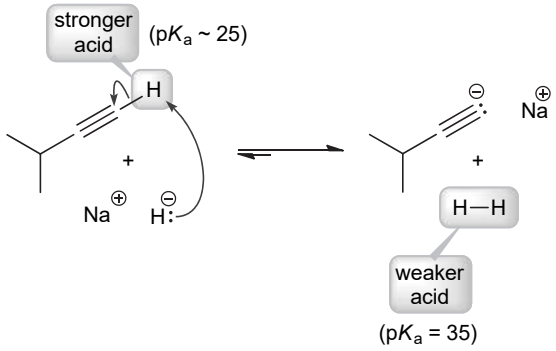


9.35.

(a) The starting carbanion (C^-) is a strong base, and acetylene has an acidic proton. The resulting proton transfer step gives an acetylide ion and butane. When we compare the acids (highlighted below), we find a massive difference in pK_a values (See Table 9.1). The difference between acetylene (pK_a = 25) and butane (pK_a = 50) is 25 units, which represents a difference of 25 orders of magnitude. That is, acetylene is 10^{25} times more acidic than butane. With such a large difference in pK_a values, the reaction is considered to be irreversible.



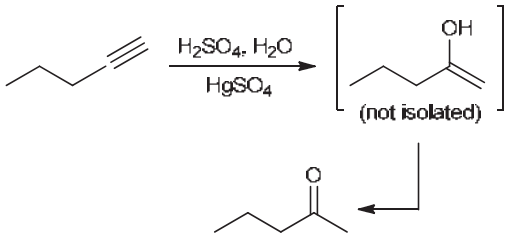
(b) Hydride (H^-) is a strong base, and the terminal alkyne has an acidic proton. The resulting proton transfer step gives an alkynide ion and hydrogen gas (H_2). We compare the pK_a values of the acids (highlighted below) using the values given in Table 9.1. Acetylene (pK_a = 25) is more acidic than H_2 (pK_a = 35). As such, the equilibrium favors the weaker acid (H_2).



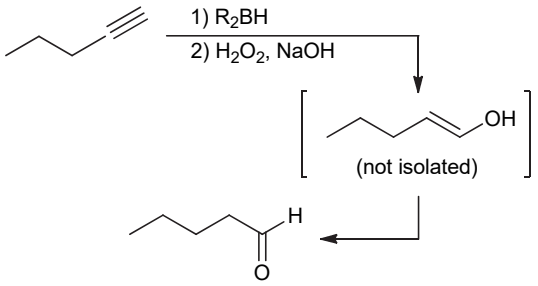
In practice, H_2 bubbles out of solution as a gas, and as a result, the reaction proceeds to completion (Le Chatelier's principle).

9.36.

(a) When treated with aqueous acid (in the presence of mercuric sulfate), the terminal alkyne undergoes Markovnikov addition of H and OH across the alkyne, giving an enol. The enol is not isolated, because upon its formation, it undergoes tautomerization to give a methyl ketone:



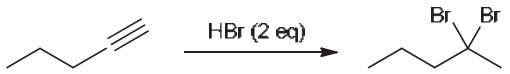
(b) The reagents (R_2BH, followed by H_2O_2 and NaOH) indicate hydroboration-oxidation of the terminal alkyne, giving an *anti*-Markovnikov addition of H and OH across the alkyne. The resulting enol is not isolated, because upon its formation, it undergoes tautomerization to give an aldehyde:



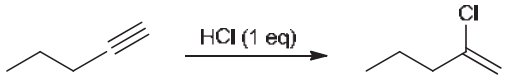
(c) When treated with two equivalents of HBr, a terminal alkyne undergoes two, successive addition

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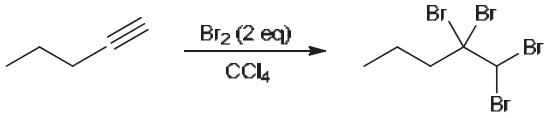
reactions, each of which proceeds in a Markovnikov fashion, giving the following geminal dibromide:



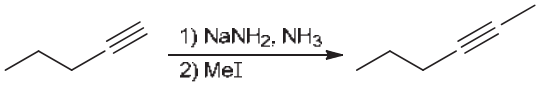
(d) When treated with one equivalent of HCl, a terminal alkyne undergoes an addition reaction that proceeds in a Markovnikov fashion, giving the following vinyl chloride:



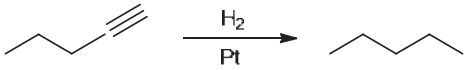
(e) When treated with two equivalents of Br_2, the alkyne undergoes two, successive addition reactions, giving the following tetrabromide:



(f) These reagents indicate an alkylation process. In step 1, the alkyne is deprotonated by the strong base (H_2N^-) to give an alkynide ion. In step 2, this alkynide ion is used as a nucleophile to attack methyl iodide in an S_N2 reaction), thereby installing a methyl group:

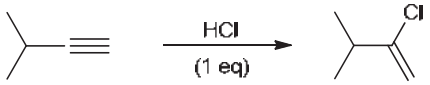


(g) Since platinum is used as the catalyst (rather than a poisoned catalyst), hydrogenation of the alkyne gives an alkane:

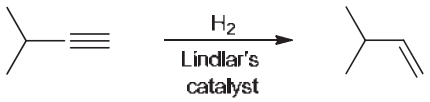


9.37.

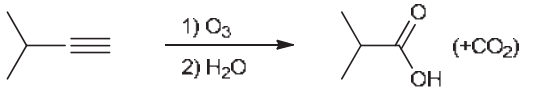
(a) Markovnikov addition of addition of H and Cl can be achieved by treating the alkyne with one equivalent of HCl:



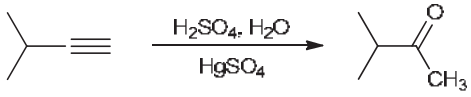
(b) Reduction of the alkyne to an alkene can be achieved by performing a hydrogenation reaction in the presence of a poisoned catalyst, such as Lindlar's catalyst:



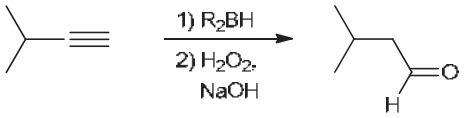
(c) Ozonolysis of the alkyne achieves cleavage of the C≡C bond to give a carboxylic acid (and carbon dioxide as a by-product):



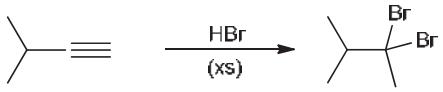
(d) A terminal alkyne can be converted into a methyl ketone upon treatment with aqueous acid in the presence of mercuric sulfate. These conditions allow for Markovnikov addition of H and OH, giving an enol, which tautomerizes to the methyl ketone:



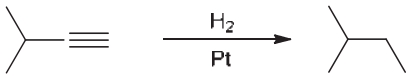
(e) A terminal alkyne can be converted into an aldehyde via hydroboration-oxidation. These conditions allow for an *anti*-Markovnikov addition of H and OH, giving an enol, which tautomerizes to the aldehyde:



(f) An alkyne can be converted to a geminal dibromide via two successive addition reactions with HBr. Markovnikov addition is required, so we use excess HBr without peroxides.



(g) Reduction of the alkyne to an alkane can be achieved by performing hydrogenation in the presence of a catalyst, such as platinum (not a poisoned catalyst):



9.38.

(a) As seen in Table 9.1, methoxide is not a sufficiently strong base to deprotonate a terminal alkyne, because the conjugate acid of methoxide (methanol, $pK_a = 16$) is a stronger acid than a terminal alkyne ($pK_a \sim 25$).

(b) As seen in Table 9.1, hydride (H^-) is a sufficiently strong base to deprotonate a terminal alkyne, because the conjugate acid of hydride (H_2, $pK_a = 35$) is a weaker acid than a terminal alkyne ($pK_a \sim 25$).

(c) As seen in Table 9.1, butyllithium is a sufficiently strong base to deprotonate a terminal alkyne, because the conjugate acid (butane, $pK_a = 50$) is a weaker acid than a terminal alkyne ($pK_a \sim 25$).

(d) As seen in Table 9.1, hydroxide is not a sufficiently strong base to deprotonate a terminal alkyne, because the conjugate acid of hydroxide (water, $pK_a = 15.7$) is a stronger acid than a terminal alkyne ($pK_a \sim 25$).

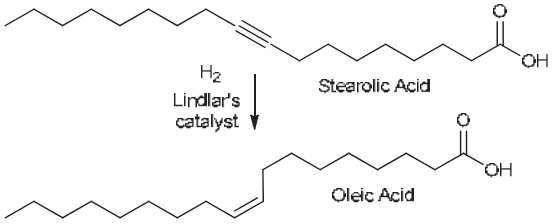
(e) As seen in Table 9.1, the amide ion (H_2N^-) is a sufficiently strong base to deprotonate a terminal alkyne,

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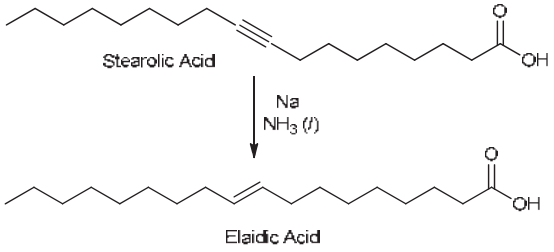
because the conjugate acid (NH_3, pK_a = 38) is a weaker acid than a terminal alkyne (pK_a ~ 25).

9.39.
(a) Yes, these compounds represent a pair of keto-enol tautomers.
(b) Yes, these compounds represent a pair of keto-enol tautomers.

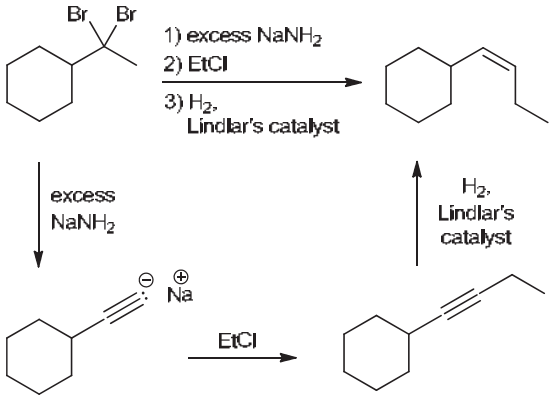
9.40. The difference between oleic acid and elaidic acid is the configuration of the C=C double bond. Oleic acid has the *cis* configuration, while elaidic acid has the *trans* configuration. Each of these stereoisomers can be obtained via reduction of the corresponding alkyne. Hydrogenation in the presence of a poisoned catalyst affords the *cis* alkene,



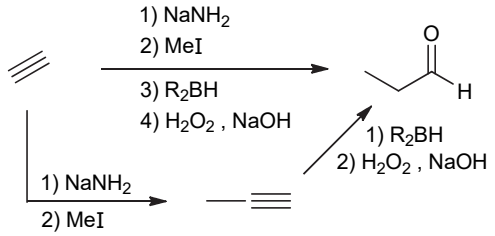
while a dissolving metal reduction gives the *trans* alkene:



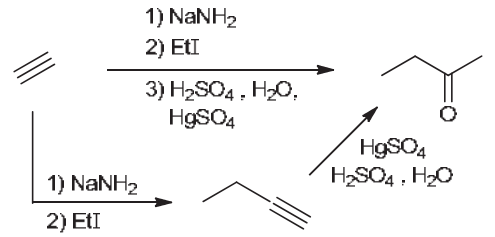
9.41.
(a) Upon treatment with excess sodium amide, the geminal dibromide undergoes elimination (twice) followed by deprotonation, to give an alkynide ion. This alkynide ion then undergoes alkylation when treated with ethyl chloride. Finally, hydrogenation in the presence of a poisoned catalyst affords the *cis* alkene:



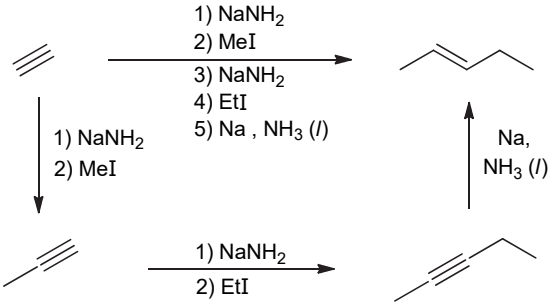
(b) Acetylene undergoes alkylation upon treatment with sodium amide, followed by methyl iodide. The resulting alkyne (1-propyne) then undergoes hydroboration-oxidation when treated with a dialkylborane (R_2BH) followed by H_2O_2 and NaOH, giving an aldehyde:



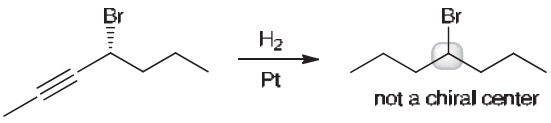
(c) Acetylene undergoes alkylation upon treatment with sodium amide, followed by ethyl iodide. The resulting alkyne (1-butyne) then undergoes acid-catalyzed hydration when treated with aqueous acid in the presence of mercuric sulfate, giving a methyl ketone:



(d) Acetylene undergoes alkylation upon treatment with sodium amide, followed by methyl iodide. The resulting alkyne (1-propyne) then undergoes alkylation, once again, upon treatment with sodium amide, followed by ethyl iodide. The first alkylation process installs a methyl group, while the second process installs an ethyl group. Finally, a dissolving metal reduction converts the alkyne to a *trans* alkene:

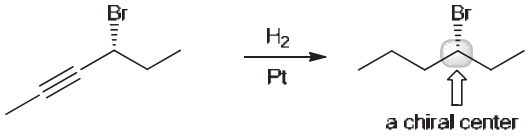


9.42. When *(R)*-4-bromohept-2-yne is treated with H_2 in the presence of Pt, the asymmetry is destroyed and C4 is no longer a chiral center:

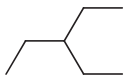


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This is not the case for *(R)*-4-bromohex-2-yne:

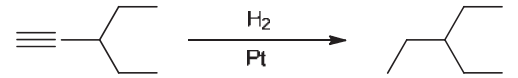


9.43. We are looking for an alkyne that will undergo hydrogenation to give the following alkane:



3-Ethylpentane

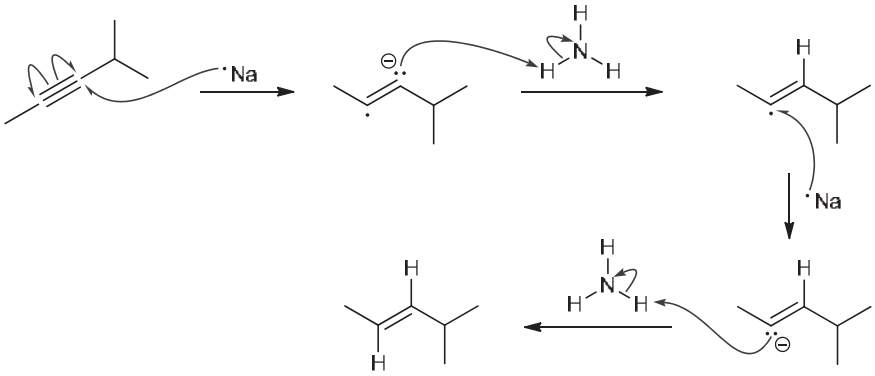
In order to produce this alkane, the starting alkyne must have the same carbon skeleton as this alkane. There is only one such alkyne (3-ethyl-1-pentyne, shown below), because the triple bond cannot be placed between C2 and C3 of the skeleton (as that would make the C3 position pentavalent, and carbon cannot accommodate more than four bonds):



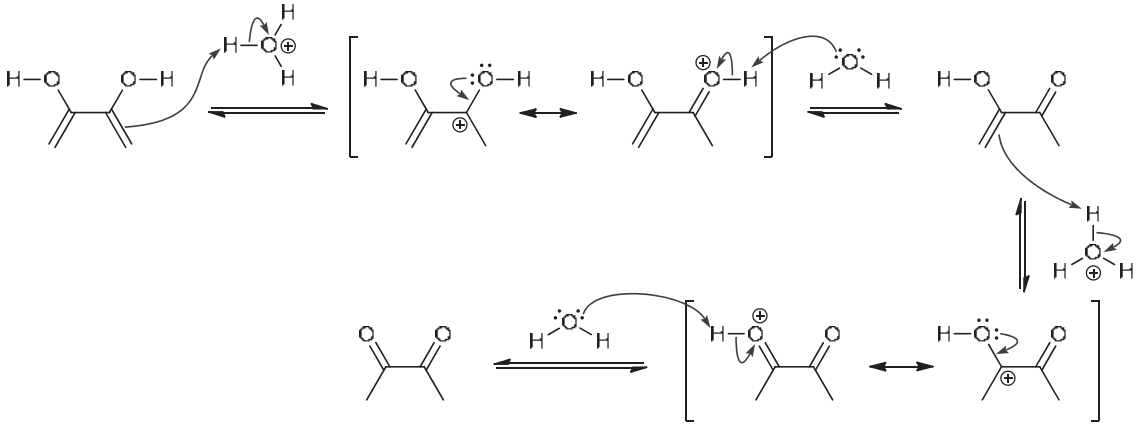
3-Ethyl-1-pentyne 3-Ethylpentane

9.44.

(a) This process is a dissolving metal reduction, so it follows the four steps shown in Mechanism 9.1. In the first step, a single electron is transferred from the sodium atom to the alkyne, generating a radical anion intermediate. This intermediate is then protonated (ammonia is the proton source), generating a radical intermediate. A single electron is transferred once again from a sodium atom to the radical intermediate, generating an anion, which is then protonated in the final step of the mechanism:

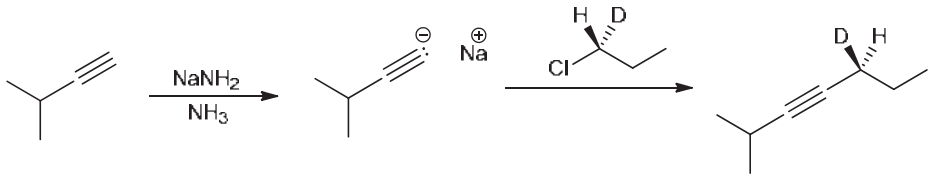


(b) The starting material has two enol groups, and the product has two ketone groups. As such, this transformation represents two tautomerization processes. Each tautomerization process must be shown separately, with two steps. In the first step, a double bond of one of the enol groups is protonated, generating a resonance-stabilized cation, which is then deprotonated (with water serving as the base) to generate the ketone. These two steps are then repeated for the other enol group, as shown:



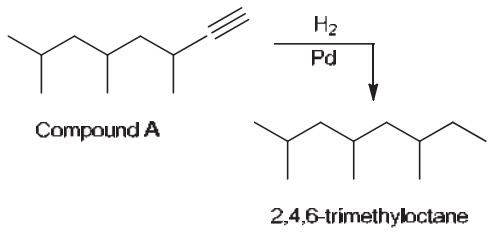
9.45. Treatment of the terminal alkyne with sodium amide results in the formation of alkynide ion, which then functions as a nucleophile in an S_N2 reaction. The stereochemical requirement for inversion determines the configuration of the chiral center in the product.

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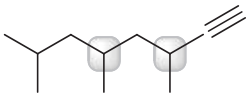


9.46.

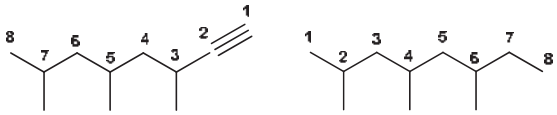
(a) In order to produce 2,4,6-trimethyloctane, the starting alkyne must have the same carbon skeleton as this alkane. There is only one such alkyne (shown below), because the triple bond cannot be placed in any other location (as that would give a pentavalent carbon atom, which is not possible):



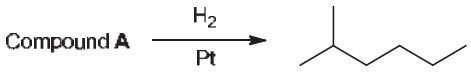
(b) Compound **A** has two chiral centers, highlighted below:



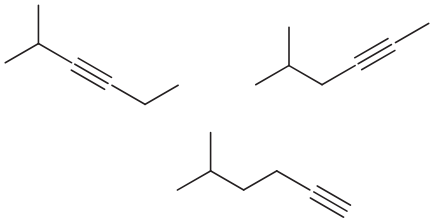
(c) The locants for the methyl groups in compound **A** are 3, 5, and 7, because locants are assigned in a way that gives the triple bond the lower possible number (1 rather than 7). In the alkane, the numbering scheme goes in the other direction, so as to give the first substituent the lower possible number (2 rather than 3)



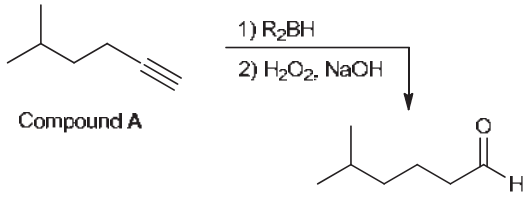
9.47. Hydrogenation of compound **A** produces 2-methylhexane:



There are several alkynes that can undergo hydrogenation to yield 2-methylhexane.

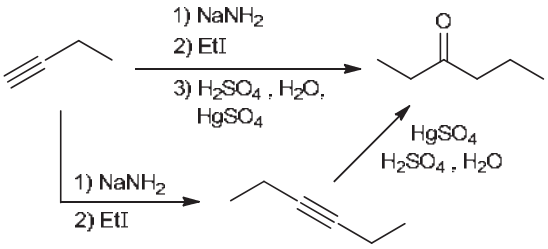


However, only one of these three possibilities will undergo hydroboration-oxidation to give an aldehyde. Specifically, the alkyne must be terminal in order to generate an aldehyde upon hydroboration-oxidation:



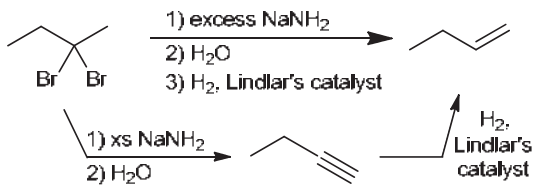
9.48.

(a) The starting material has four carbon atoms, while the product has six carbon atoms. Therefore, two carbon atoms must be introduced. This can be achieved via alkylation of the terminal alkyne, as seen in the first two steps of the following synthesis. The resulting, symmetrical alkyne can then undergo acid-catalyzed hydration to give the desired ketone. Alternatively, the alkyne can be converted into the desired ketone via hydroboration-oxidation.

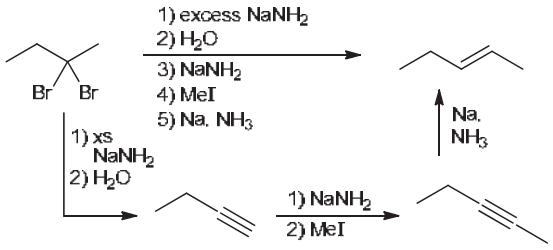


(b) The starting material is a geminal dihalide, and we have not learned a way to convert a geminal dihalide directly into an alkene. However, we have learned how to convert a geminal dihalide into a terminal alkyne, upon treatment with excess sodium amide (followed by water workup). The alkyne can then be reduced by hydrogenation with a poisoned catalyst, such as Lindlar's catalyst.

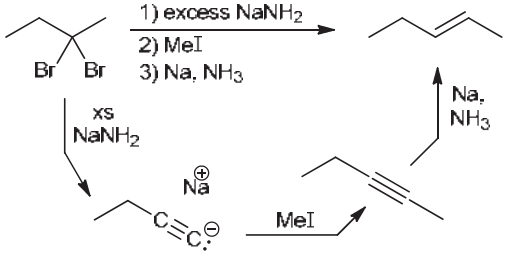
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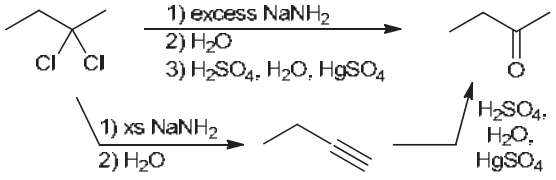
(c) This problem is similar to the previous problem, but an additional methyl group must be installed. We have not seen a way to alkylate an alkene (only an alkyne). So, the extra alkylation process must be performed before the alkyne is reduced to an alkene in the last step of the synthesis:



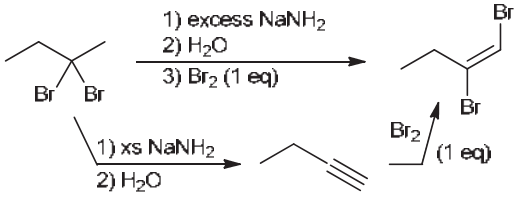
Note: The alkyne produced after step 2 does not need to be isolated and purified, and therefore, steps 2 and 3 can be omitted, like this:



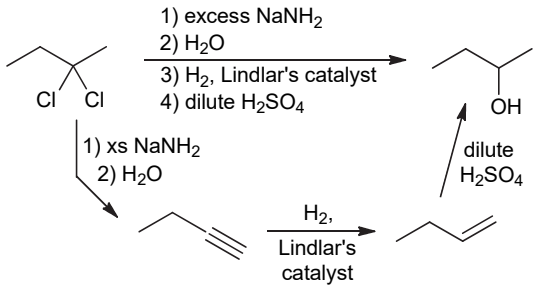
(d) The starting material is a geminal dihalide, which can be converted to a terminal alkyne upon treatment with excess sodium amide (followed by water workup). The terminal alkyne can then undergo acid-catalyzed hydration in the presence of mercuric sulfate to give a methyl ketone:



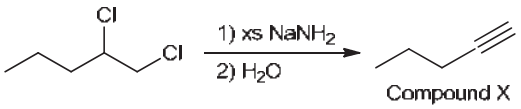
(e) The starting material is a geminal dihalide, which can be converted to a terminal alkyne upon treatment with excess sodium amide (followed by water workup). The terminal alkyne can then undergo bromination to give the dibromide, as shown:



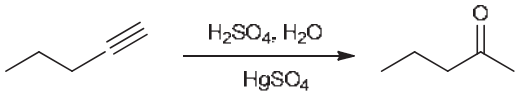
(f) The starting material is a geminal dihalide, which can be converted to a terminal alkyne upon treatment with excess sodium amide (followed by water workup). The terminal alkyne can then be reduced to give an alkene, which can then be treated with aqueous acid to give a Markvonikov addition of water, affording the desired product:



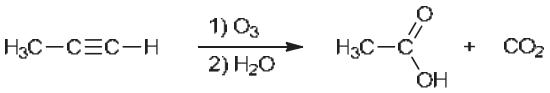
9.49. Treatment of 1,2-dichloropentane with excess sodium amide (followed by water-workup) gives 1-pentyne (compound X).



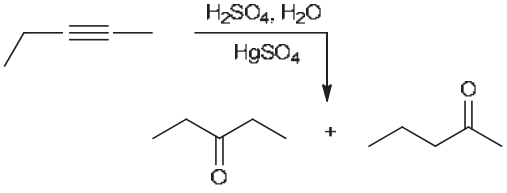
Compound X undergoes acid-catalyzed hydration to give a methyl ketone, shown below:



9.50. Acetic acid has two carbon atoms, and carbon dioxide has one, so our starting alkyne has three carbon atoms:



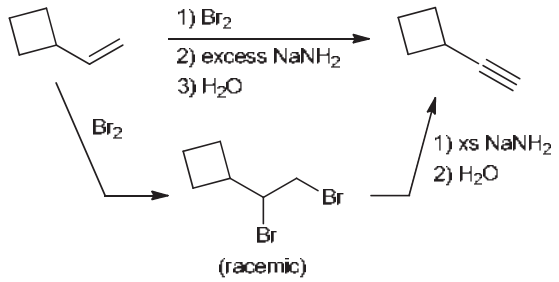
9.51. If two products are obtained, then the alkyne must be internal and unsymmetrical. There is only one such alkyne with the molecular formula C_5H_8:



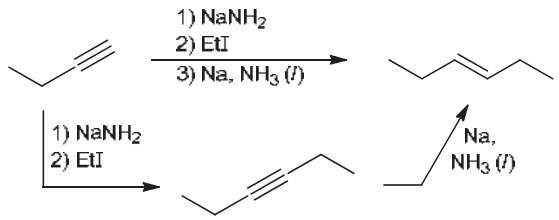
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9.52.

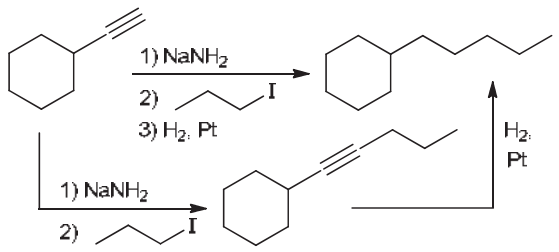
(a) As seen in Figure 9.7, a double bond can be converted into a triple bond via bromination, followed by two successive elimination reactions (with excess $NaNH_2$). Under these conditions, the resulting terminal alkyne is deprotonated, so water is introduced to protonate the alkynide ion, generating the alkyne:



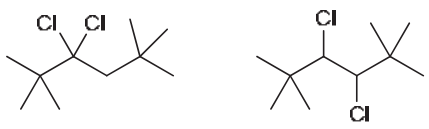
(b) The starting material has four carbon atoms, and the product has six carbon atoms, so two carbon atoms must be installed. This can be accomplished by alkylating the terminal alkyne. After the alkylation process, a dissolving metal reduction will convert the alkyne into the desired *trans* alkene:



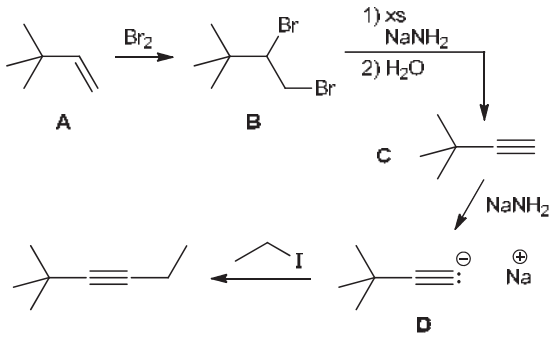
(c) The starting material has eight carbon atoms, and the product has eleven carbon atoms, so three carbon atoms must be installed. This can be accomplished by alkylating the terminal alkyne. After the alkylation process, the resulting internal alkyne can be converted to the desired alkane upon hydrogenation:



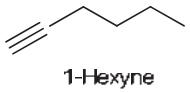
9.53. The starting material can either be a geminal dichloride or a vicinal dichloride:



9.54. In order to determine the structures of compounds A-D, we must work backwards. The last step is an alkylation process that installs an ethyl group, so compound D must be an alkynide ion, which is prepared from the dibromide (compound B) formed in the first step when an alkene (compound A) is treated with Br_2:



9.55. Terminal alkynes have the structure R–C≡C–H. The molecular formula indicates six carbon atoms, so the R group must be comprised of four carbon atoms. There are four different ways to connect these carbon atoms. They can be connected in a linear fashion, like this:



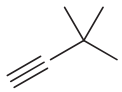
1-Hexyne

or there can be one methyl branch, which can be placed in either of two locations (C3 or C4), shown here:



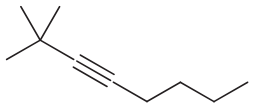
3-Methyl-1-pentyne 4-Methyl-1-pentyne

or there can be two methyl branches, as shown here:



3,3-Dimethyl-1-butyne

9.56. Formation of 2,2-dimethyl-3-octyne (shown below) from acetylene would require two alkylation processes. That is, we must install a butyl group and a *tert*-butyl group. The former can be readily achieved, but the latter cannot, because installation of a *tert*-butyl group would require the use of a tertiary substrate, which will not undergo an S_N2 process:

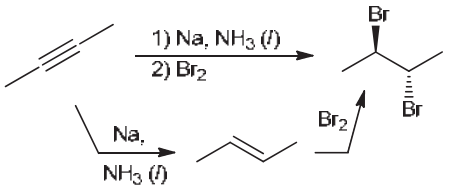


2,2-Dimethyl-3-octyne

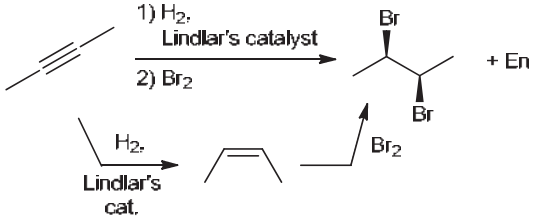
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9.57.

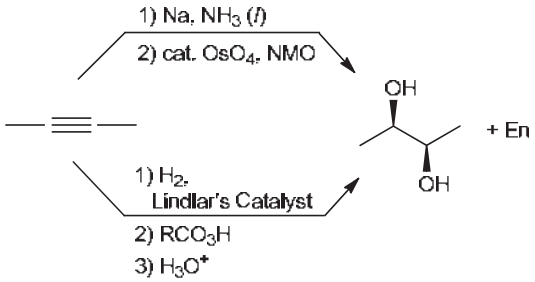
(a) The alkyne can be reduced to an alkene, followed by bromination. Since the last step (bromination) proceeds via an *anti* addition, the desired stereoisomer can only be obtained if the previous step (reduction of the alkyne) is performed in an *anti* fashion as well. That is, we must perform a dissolving metal reduction:



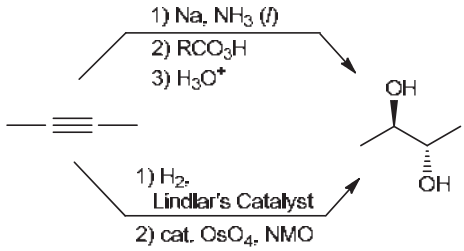
(b) The alkyne can be reduced to an alkene, followed by bromination. Since the last step (bromination) proceeds via an *anti* addition, the desired stereoisomer can only be obtained if the previous step (reduction of the alkyne) is performed in a *syn* fashion. That is, we must perform a hydrogenation reaction with a poisoned catalyst, rather than using a dissolving metal reduction.



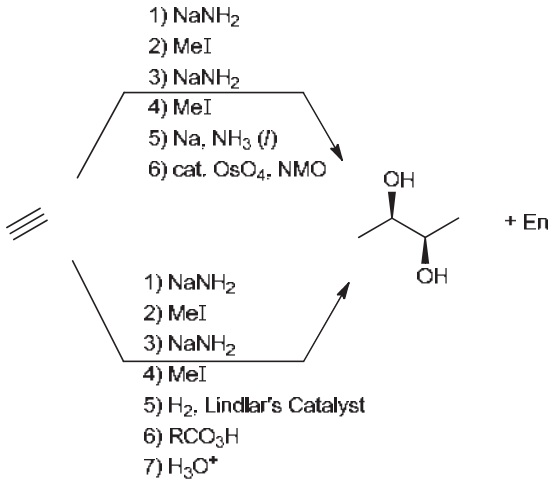
(c) This transformation requires two processes: 1) reduction of the alkyne to give an alkene, and 2) dihydroxylation to give a diol. In order to achieve the desired stereochemical outcome, we must perform one process in an *anti* fashion, and the other in a *syn* fashion. In the first answer below, the reduction is performed in an *anti* fashion, while the dihydroxylation process is performed in a *syn* fashion. In the second answer below, the reduction is performed in a *syn* fashion, while the dihydroxylation process is performed in an *anti* fashion. Both answers are acceptable.



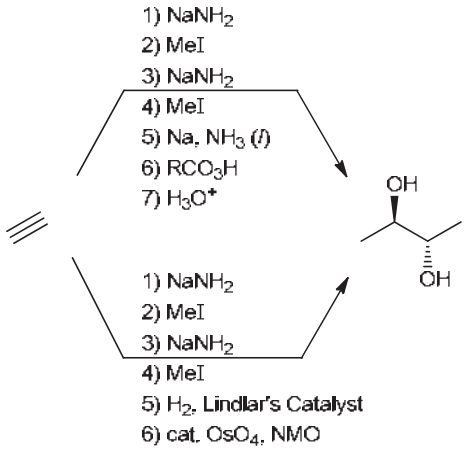
(d) This transformation requires two processes: 1) reduction of the alkyne to give an alkene, and 2) dihydroxylation to give a diol. In order to achieve the desired stereochemical outcome, we must either perform each process in an *anti* fashion (as shown in the first answer below), or we must perform each process in a *syn* fashion (as shown in the second answer below). Both answers are acceptable.



(e) This problem is similar to part (c), but the starting alkyne is acetylene, which must first be alkylated twice:



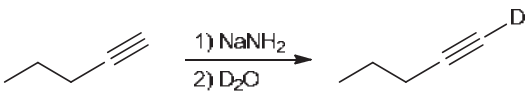
(f) This problem is similar to part (d), but the starting alkyne is acetylene, which must first be alkylated twice:



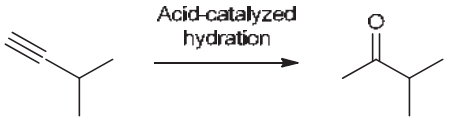
9.58. Treatment of the alkyne with sodium amide results in an alkynide ion. If the alkynide ion is treated with water (H_2O), the alkynide ion will be protonated again to regenerate the starting alkyne. If, however, the alkynide

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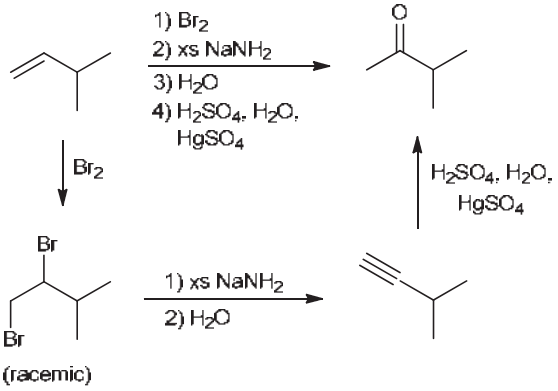
ion is treated with a source of deuterons (D_2O), then the desired deuterated compound will be produced:



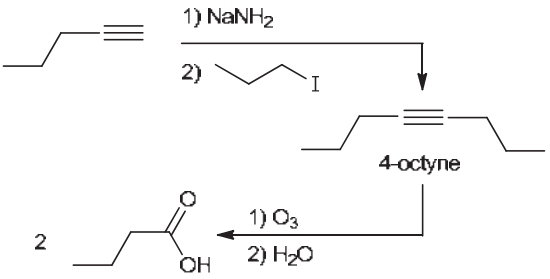
9.59. The product is a methyl ketone, and the starting material is an alkene. We have not seen a method for directly converting an alkene into a ketone. However, we have seen a way of converting a terminal alkyne into a methyl ketone.



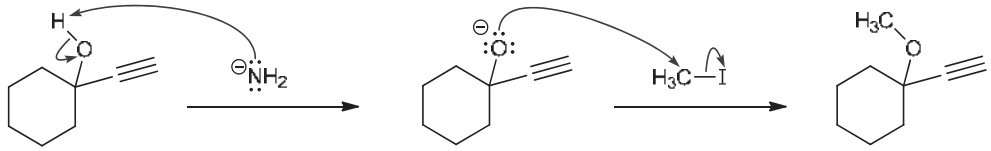
Completing the synthesis requires that we first prepare the alkyne above from the starting alkene, shown in the problem statement. This can be accomplished via a two-step procedure. The alkene is treated with molecular bromine (Br_2) to give a vicinal dibromide, which is then treated with excess $NaNH_2$ (followed by water work-up) to give an alkyne. And as mentioned earlier, the alkyne can be converted into the desired methyl ketone via acid-catalyzed hydration in the presence of mercuric sulfate:



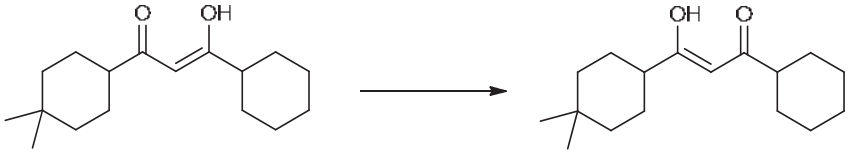
9.60. Since ozonolysis of the internal alkyne leads to only one carboxylic acid (rather than two), we can deduce that the internal alkyne must be symmetrical. If it has to be symmetrical, then it must be 4-octyne, since we installed a propyl group ourselves (that is, the starting alkyne already had one propyl group).



9.61. The acetylenic proton ($pK_a \sim 25$) is not the most acidic proton in the compound. The OH group bears a more acidic proton ($pK_a \sim 18$), so treatment with a strong base (such as sodium amide) will result in deprotonation of the OH group. The resulting alkoxide ion then serves as a nucleophile when treated with methyl iodide, giving an S_N2 reaction to generate the following product:

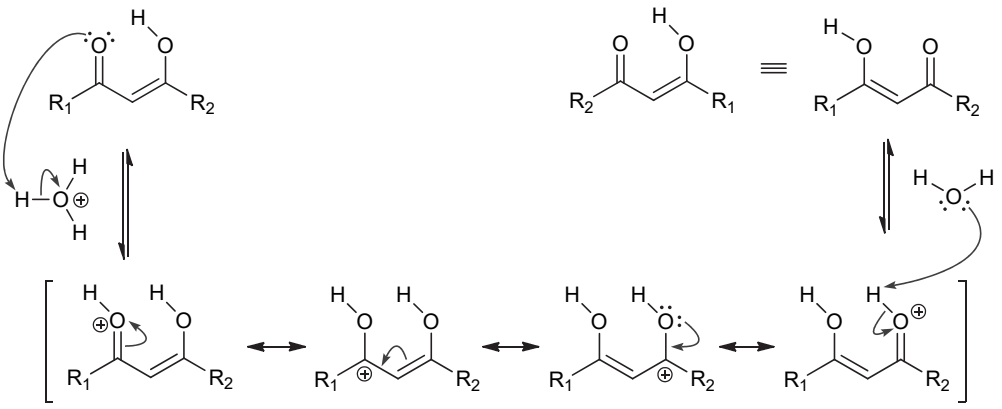


9.62. The key to solving this problem is to recognize that the methyl groups are not actually migrating. We can see this more clearly, if we flip the product horizontally, and then compare it to the starting material:

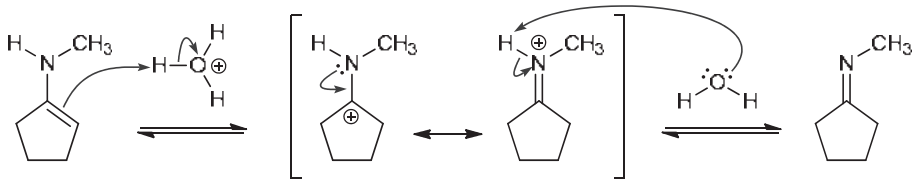


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When drawn in this way, we can see more clearly that it is just a tautomerization process. Protonation of the C=O bond gives an intermediate that is highly resonance stabilized. Deprotonation then gives the product:

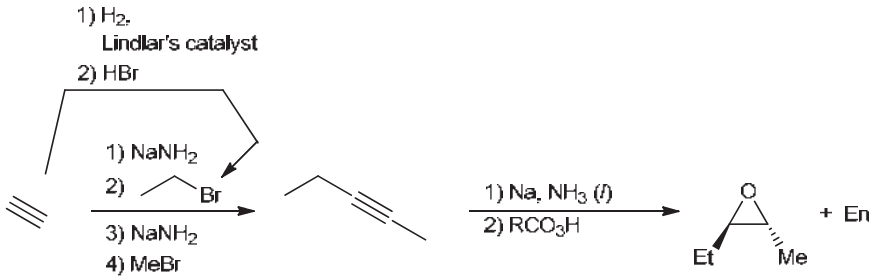


9.63. Much like an enol, the starting material in this case (called an enamine) also undergoes tautomerization via a similar mechanism. That is, the double bond is first protonated to generate a resonance-stabilized cation, which is then deprotonated. Notice that, in the first step, the double bond is protonated, rather than the nitrogen atom. Protonation of the nitrogen atom does not result in a resonance-stabilized cation.

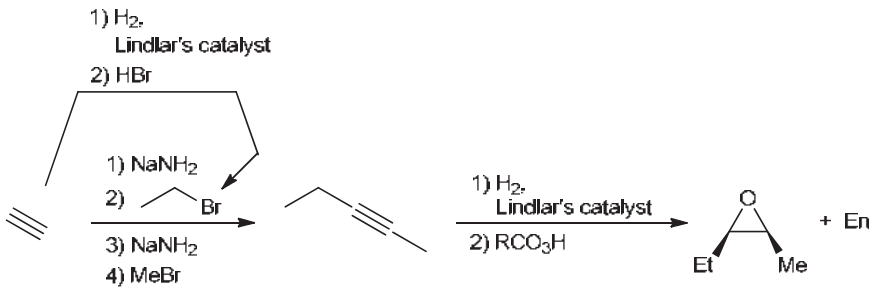


9.64.

(a) The desired epoxide can be made from 2-pentyne via a dissolving metal reduction, followed by epoxidation. The necessary alkyne (2-pentyne) can be made through two successive alkylation processes, shown here:

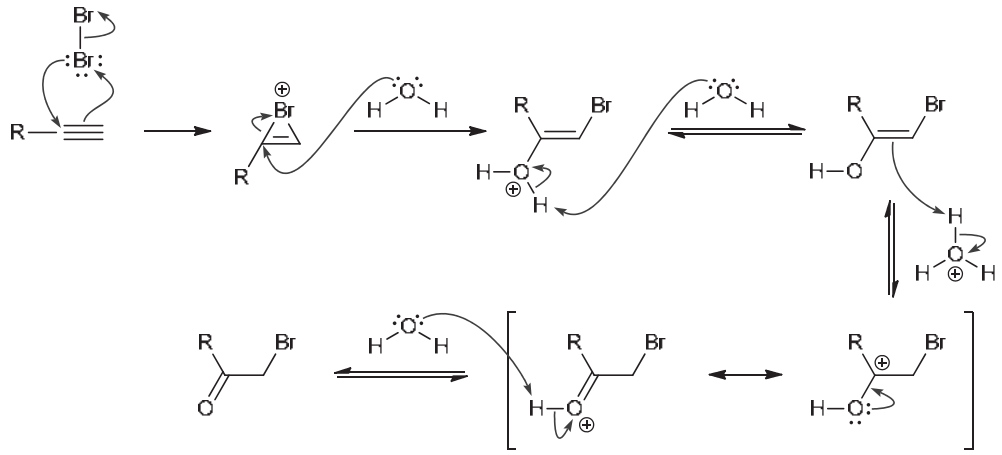


(b) The desired epoxide can be made from 2-pentyne via hydrogenation (with a poisoned catalyst), followed by epoxidation. The necessary alkyne (2-pentyne) can be made through two successive alkylation processes, shown here:

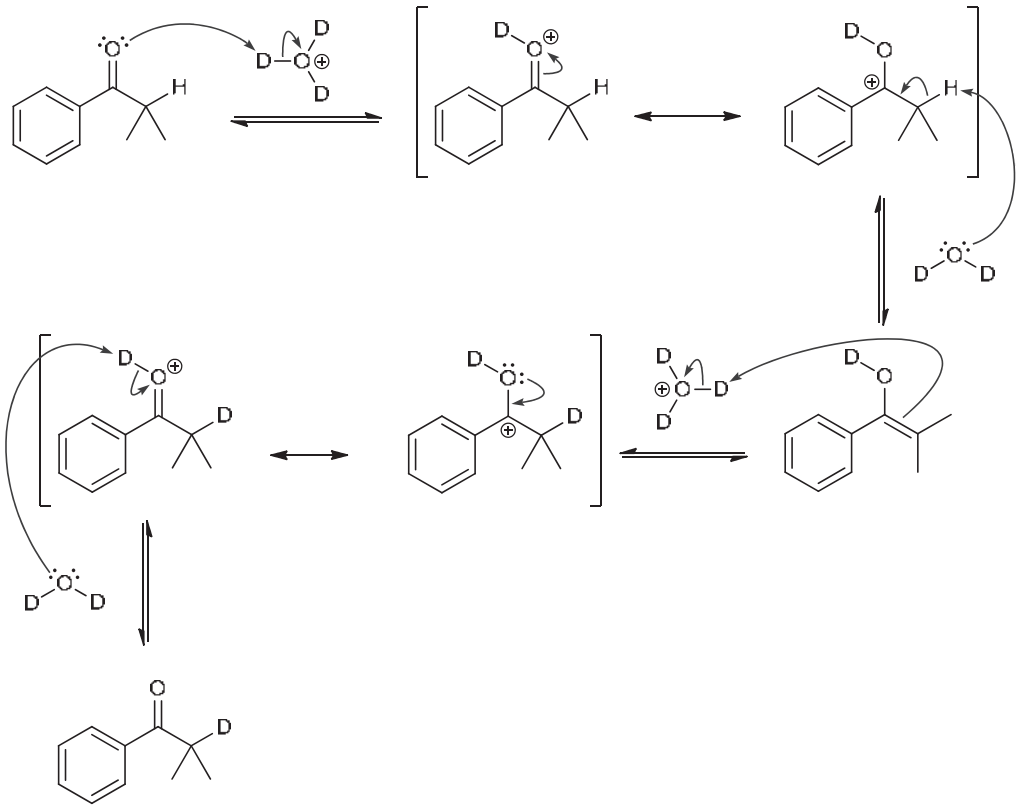


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9.65. In the presence of Br_2, the alkyne is converted to a bromonium ion, which can be opened with water. The resulting oxonium ion is deprotonated to reveal an enol, which undergoes tautomerization to give the desired product:

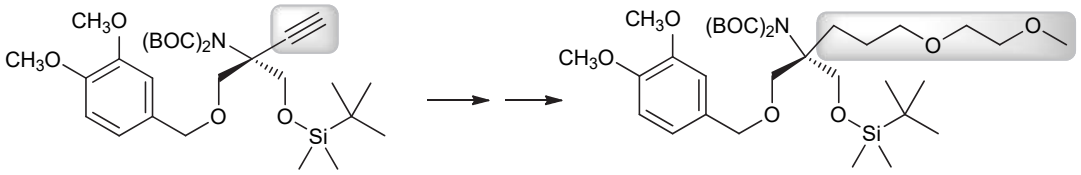


9.66. D_3O^+ is directly analogous to H_3O^+, but the protons have been replaced with deuterons. In the presence of D_3O^+, tautomerization processes can occur. Below are two, successive tautomerization processes that can successfully explain formation of the deuterated product:

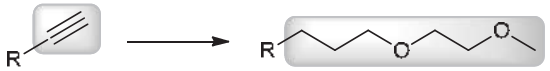


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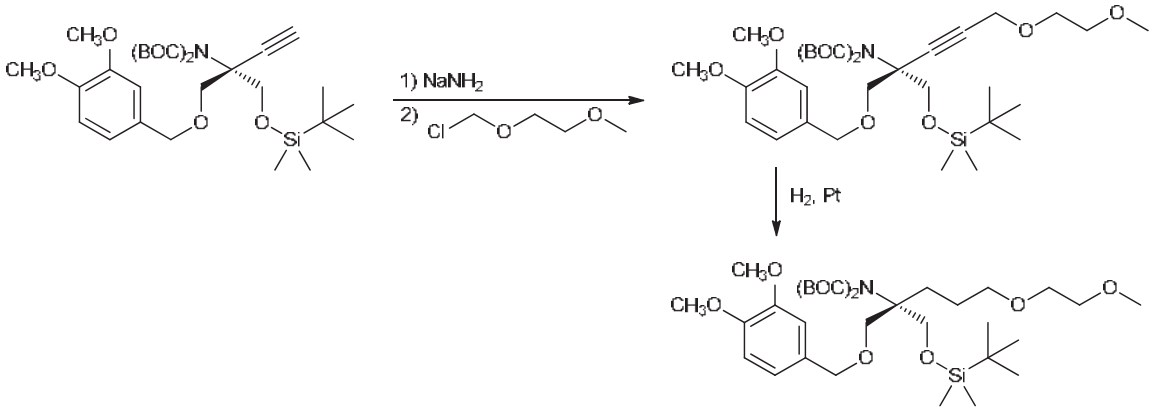
9.67.
(a) Compare the structures of the starting material and product, and identify the part of the structure that must be modified:



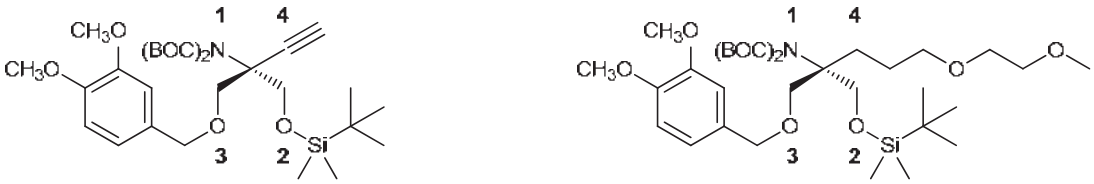
The rest of the structure remains unchanged. If we represent that part of the structure with an R group, the desired transformation can be shown as follows:



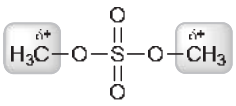
This transformation can be achieved by deprotonation of the terminal alkyne (with $NaNH_2$) and subsequent treatment with an appropriate electrophile (in this case the electrophile is $ClCH_2OCH_2CH_2OCH_3$, called methoxy ethoxymethyl chloride or MEM chloride), followed by reduction of the alkyne group via hydrogenation.



(b) The chiral center has the *S* configuration in both the starting material and the final product (the priorities, shown below, do not change as a result of the transformation).

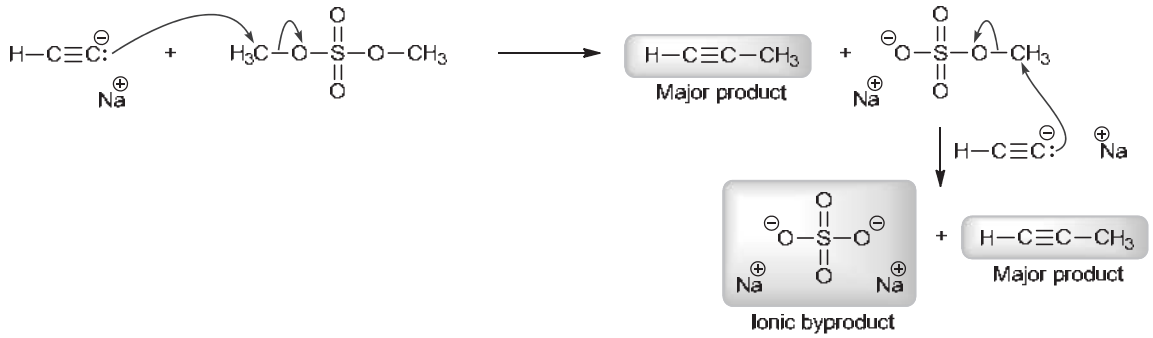


9.68.
(a) Dimethyl sulfate has two electrophilic methyl groups, each of which can be transferred to an acetylide ion:

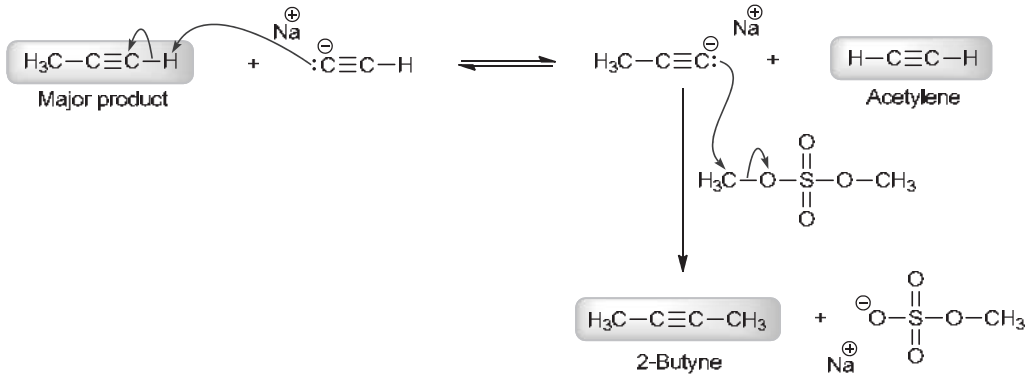


A mechanism is shown here. First, an acetylide ion functions as a nucleophile and attacks one of the methyl groups of dimethyl sulfate, thereby methylating the acetylide ion, giving propyne. Then, another acetylide ion attacks the remaining methyl group, to give a second equivalent of propyne. The ionic byproduct is Na_2SO_4 (sodium sulfate), as shown.

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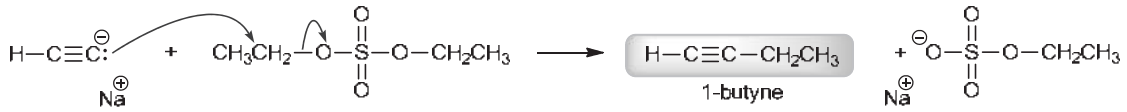


(b) During the course of the reaction, propyne molecules are being generated in the presence of acetylide ions. Under these conditions, propyne is deprotonated to give an alkynide ion which can then function as a nucleophile and attack a methyl group of dimethyl sulfate, giving 2-butyne:

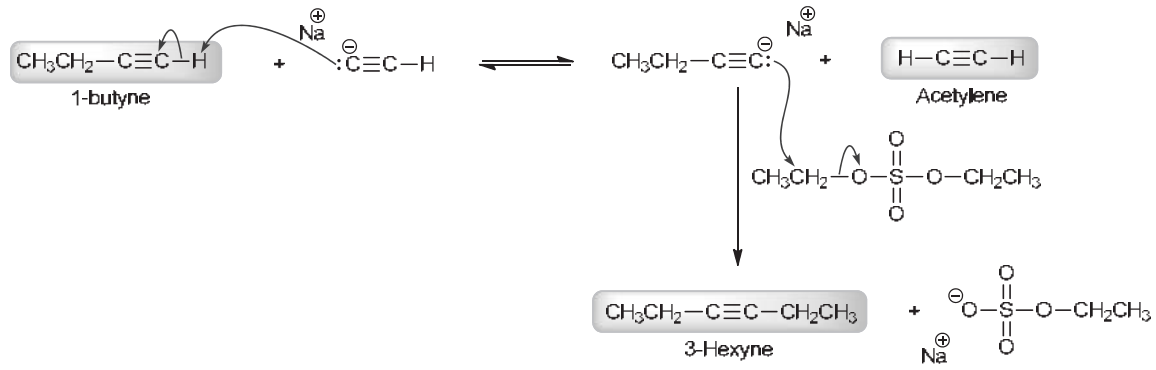


Notice that in the first step of this process, an acetylide ion is converted to acetylene. This mechanism is therefore consistent with the observation that acetylene is present among the reaction products.

(c) With diethyl sulfate, an ethyl group is transferred (rather than a methyl group). Therefore, the major product would be 1-butyne, as shown below:

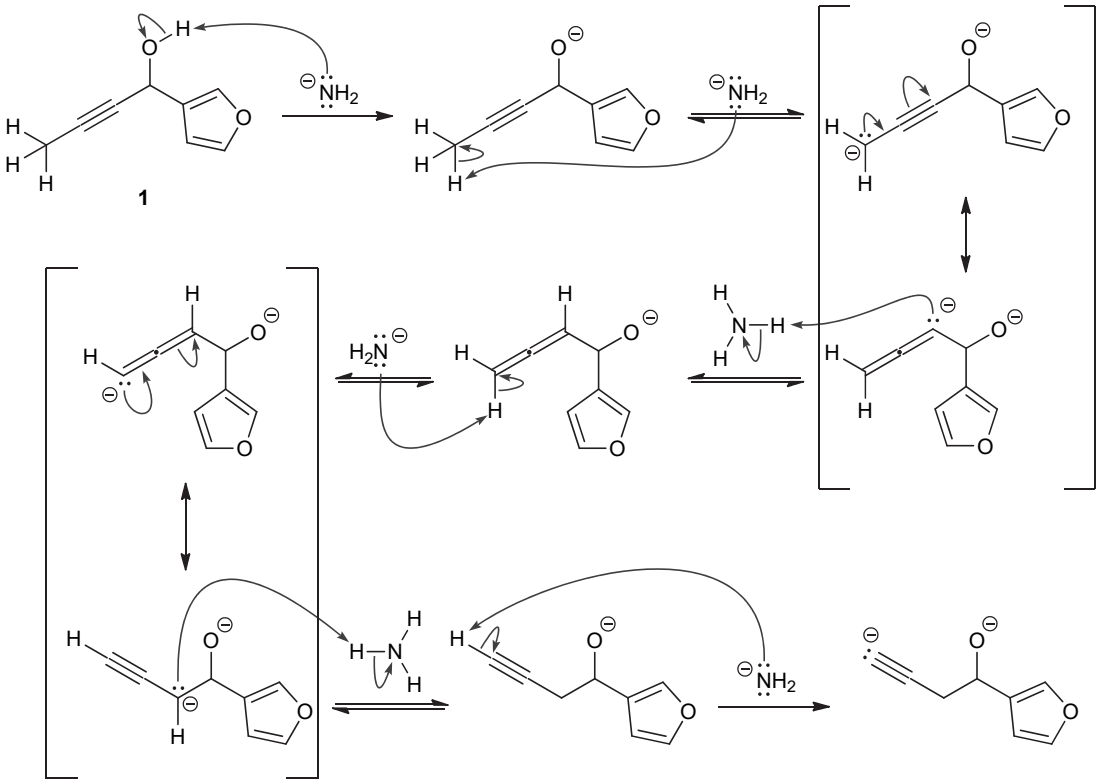


The minor product would be 3-hexyne, as shown below:

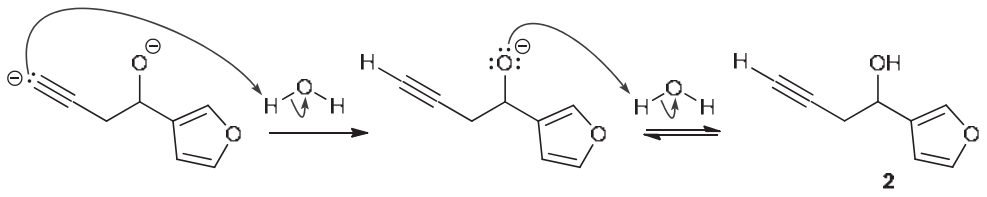


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9.69. Sodium amide is a strong base; before the alkyne isomerization occurs, the alcohol group in **1** will be deprotonated to form an alkoxide ion (a negative charge on an oxygen atom) which is carried through until the final reprotonation event (when H_2O is introduced, which takes place *after* the transformation below is complete).

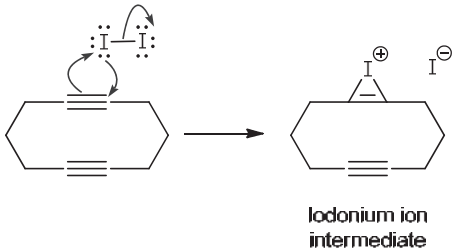


The formation of an alkynide ion (stabilized by having the lone pair on the carbon atom in an *sp* hybridized orbital) serves as a driving force for the reaction (See solution to problem 9.8). After the transformation above is complete, water is introduced as a proton source, giving **2**. The more strongly basic position is likely protonated first, followed by protonation of the alkoxide:



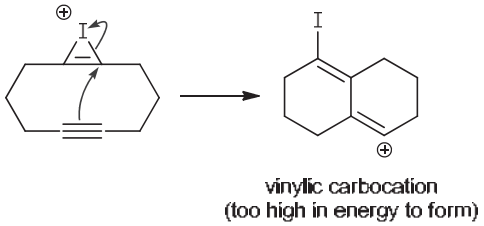
9.70.

(a) The problem statement indicates that the first mechanistic step for iodination of an alkyne is formation of a bridged iodonium intermediate, as shown below. This intermediate is analogous to the intermediate that we saw during halogenation of alkenes, although notice that the three-membered ring has a double bond (because the starting material was an alkyne, rather than an alkene).

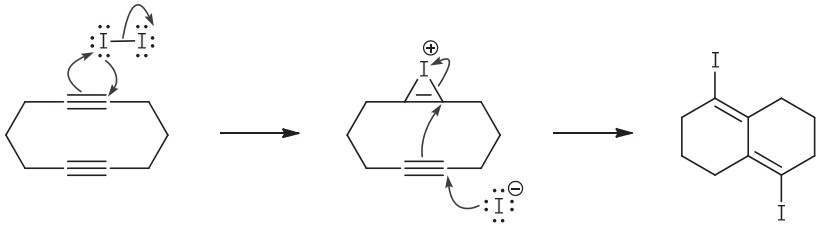


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(b) As shown, the resulting carbocation would be vinylic, and we have seen that vinylic carbocations are generally too high in energy to form:

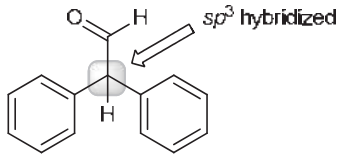


(c) The problem statement describes the following two-step mechanism, which avoids the formation of a vinylic carbocation intermediate. After the initial formation of the iodonium ion, the iodide anion can attack the second alkyne group, causing the π-electrons to attack the iodonium ion, giving the final product.

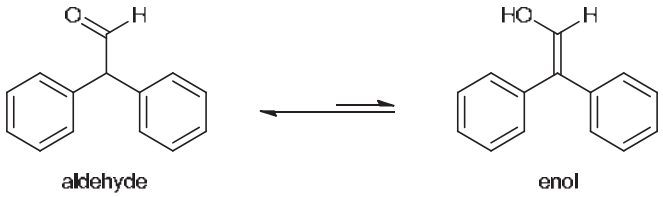


9.71.

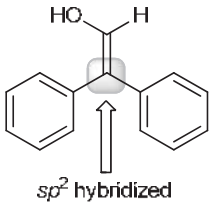
(a) The highlighted carbon atom has four σ bonds, and is therefore sp^3 hybridized. As a result, the geometry around this carbon atom is expected to be tetrahedral, with approximate bond angles of 109.5°.



(a) Compound **1** is an aldehyde, and its enol is shown here:

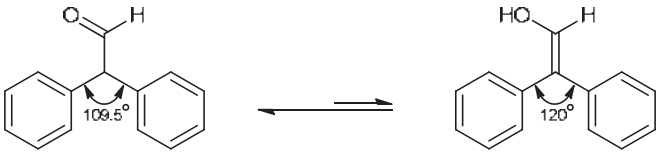


If we explore the same carbon atom that we analyzed in part (a), we find that this carbon atom (highlighted below) is sp^2 hybridized, with approximate bond angles of 120°.



(c) As we noted in the solutions to parts (a) and (b), we expect the bond angles to change when compound **1** is converted into its enol form. Specifically, there is an increase in the bond angles from 109.5° to 120°, as shown:

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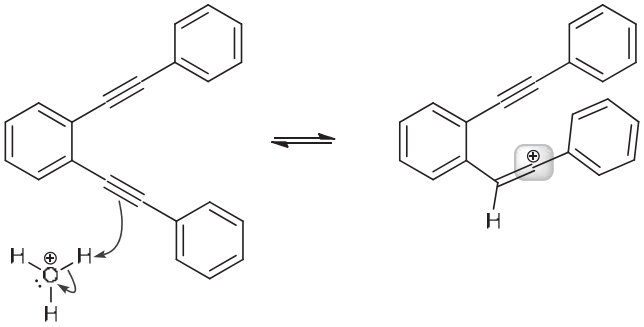
As such, the sterically demanding (bulky) aromatic rings are able to alleviate some steric strain in the enol form, relative to the aldehyde. In the aldehyde form, the aromatic rings are forced to be closer together in space. This steric effect causes the enol form to be particularly stable, and its concentration is significant (9.1%).

(d) For compound **2**, the following equilibrium is established between the aldehyde and the enol:

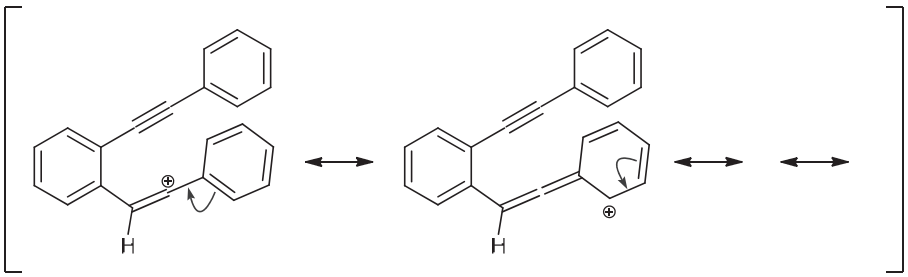


Once again, there is a change in hybridization state for the central carbon atom, and once again there is a steric effect. But in this case, the steric effect is more pronounced. The presence of the methyl groups causes the steric effect to be much greater, and as a result, the enol form is actually more stable than the aldehyde, because the enol form alleviates much of the significant steric strain present in the aldehyde form.

9.72.
(a) Begin by drawing the carbocation intermediate in this case:



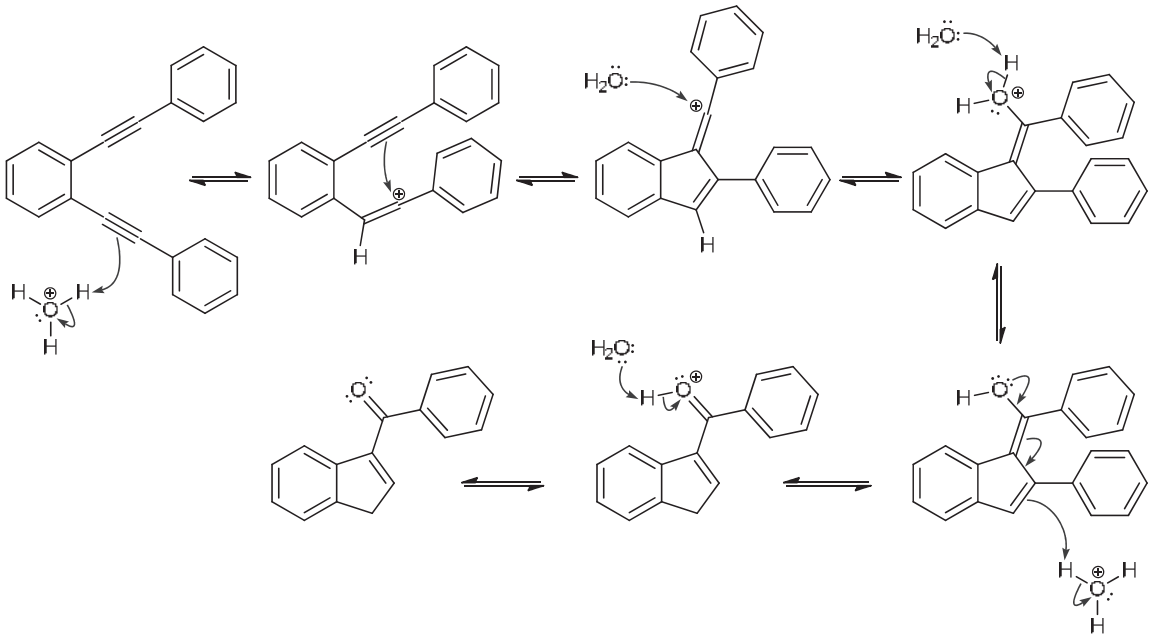
This particular carbocation is stabilized by resonance, as shown below.



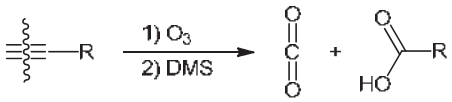
(b) The mechanism described in the problem statement is shown. One of the alkyne groups is protonated resulting in the formation of a new C-H bond, and a resonance-stabilized vinyl carbocation. The π electrons from the other alkyne

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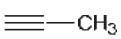
attack this carbocation, resulting in the formation of a new C-C bond, and a new vinyl carbocation. Nucleophilic attack of water, followed by deprotonation gives the enol, which tautomerizes to form the ketone, as shown:



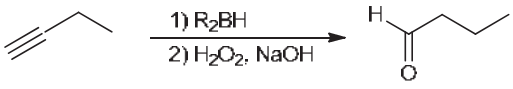
9.73. The products are carbon dioxide and a carboxylic acid, so we must be dealing with a terminal alkyne:



In this case, R = CH_3, so the correct answer is (a):



9.74. Answer (c) involves hydroboration-oxidation of a terminal alkyne, which would give an aldehyde (not a ketone):

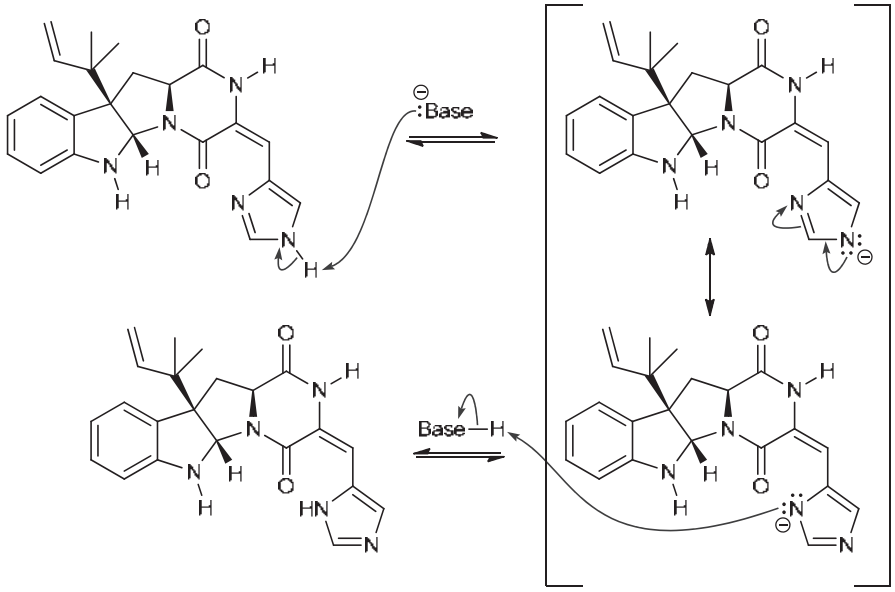


9.75. The reaction shows the conversion of an internal alkyne into a *trans* alkene. This can be accomplished via a dissolving metal reduction, which employs sodium in liquid ammonia. The answer is (c).

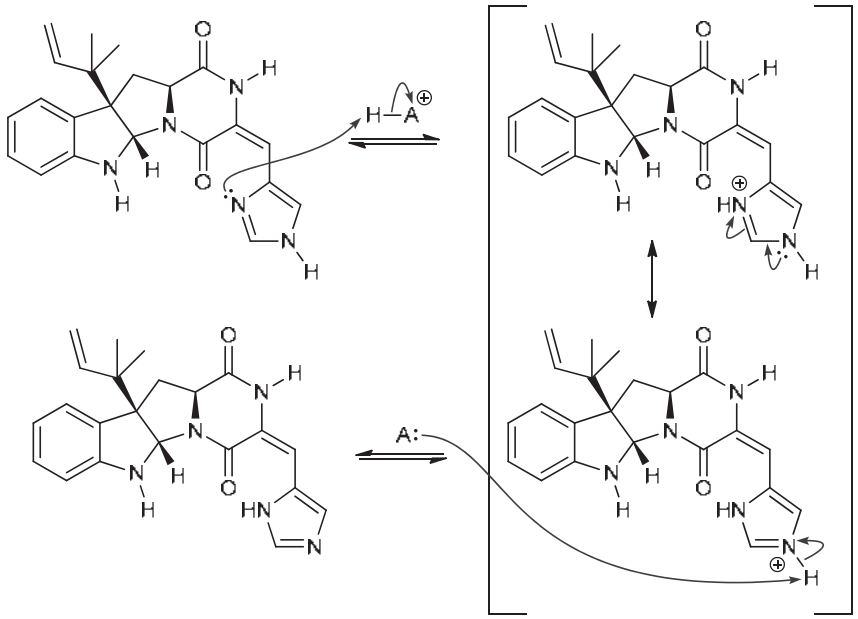
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9.76.

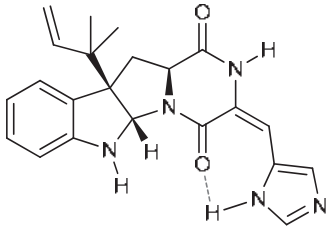
(a) If the tautomerization process is base-catalyzed, then the first step will be deprotonation to give a resonance stabilized anion, which is then protonated to give the tautomer.



(b) If the tautomerization process is acid-catalyzed, then the first step will be protonation to give a resonance stabilized cation, which is then deprotonated to give the tautomer.



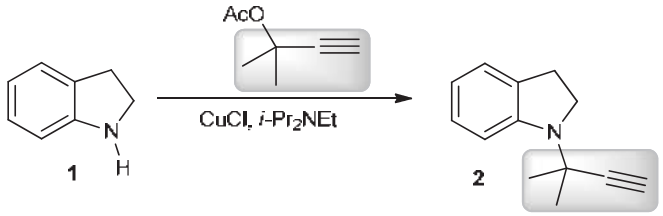
(c) The more stable tautomer is likely the one that can form an intramolecular hydrogen bonding interaction:



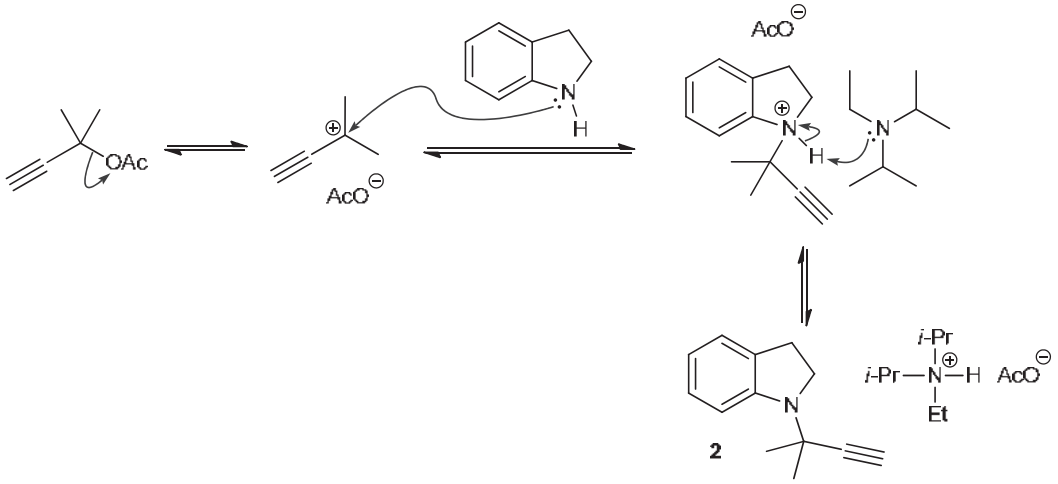
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9.77.

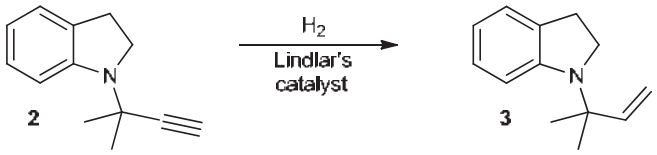
(a) The molecular formula of compound **2** indicates that five carbon atoms have been installed (compound **1** contains only eight carbon atoms, while compound **2** contains thirteen carbon atoms). The lack of oxygen atoms in the molecular formula of compound **2** also indicates that the acetate group (OAc) has been completely removed, but the nitrogen atom is still present. These observations are consistent with the following structure, which can be formed via a substitution reaction in which the nitrogen atom of the indoline ring functions as the nucleophilic center, and the acetate group functions as a leaving group.



Since the substrate is tertiary, an S_N2 pathway is too slow to be viable, as the result of steric hindrance. As such, the reaction must proceed via an S_N1 pathway:

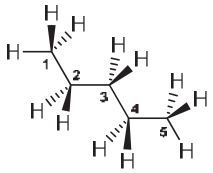


(b) The reduction of the alkyne group to an alkene group can be accomplished by treating compound **2** with H_2 and Lindlar's catalyst.



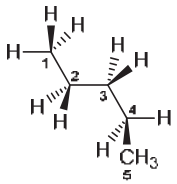
9.78.

(a) The following is a wedge-and-dash structure for the *anti-anti* conformation of pentane. Notice that C1 and C4 are *anti* to each other (when looking down the C2-C3 bond), while C2 and C5 are also *anti* to each other (when looking down the C3-C4 bond).

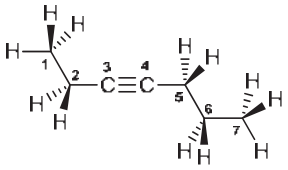


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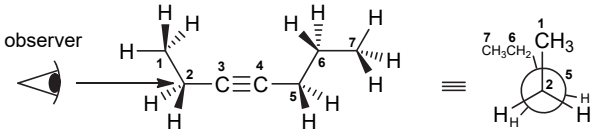
The following is a wedge-and-dash structure for the *anti-gauche* conformation of pentane. Notice that C1 and C4 are *anti* to each other (when looking down the C2-C3 bond), while C2 and C5 are *gauche* to each other (when looking down the C3-C4 bond).



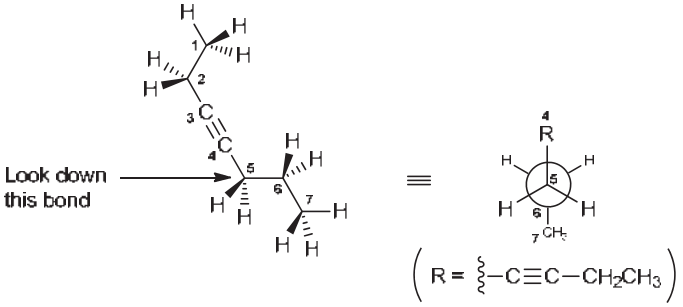
(b) The following conformer of 3-heptyne is analogous to the *anti-anti* conformer of pentane. Notice that C1 and C6 are *anti* to each other (when looking down the alkyne group), while C4 and C7 are also *anti* to each other (when looking down the C5-C6 bond).



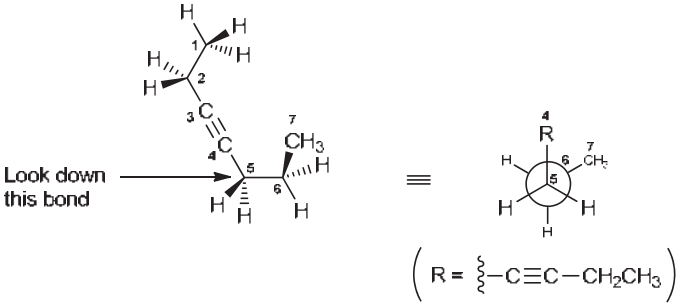
(c) In each of the lowest energy conformations of 3-heptyne, C1 and C6 are eclipsing each other (when looking down the alkyne group), as shown below. Note that the wedge-and-dash structure below is one of the two low-energy conformations, where C4 and C7 are *anti*:



(d) The difference between the two lowest energy conformations of 3-heptyne can be seen when looking down the C5-C6 bond. In one conformation, C4 and C7 are *anti* to each other, as shown below.



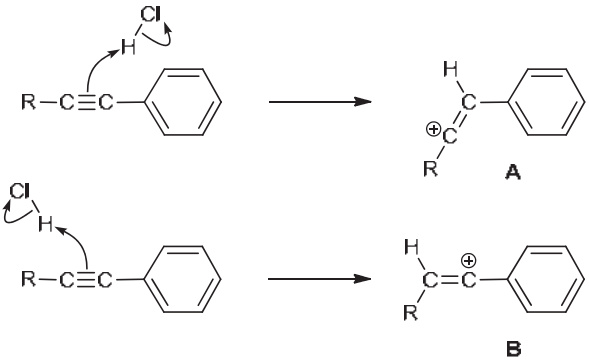
In the other conformation, C4 and C7 are *gauche*, as shown here:



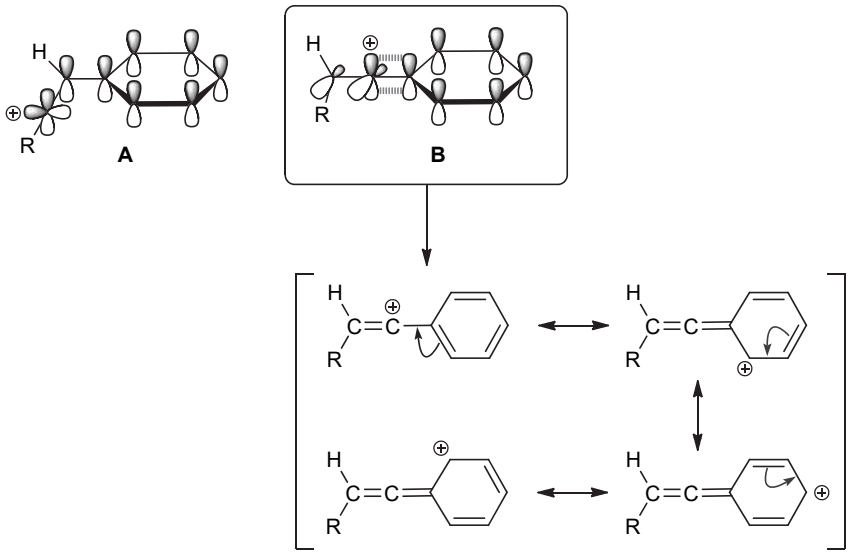
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9.79.

(a) The following are the two possible vinyl cations (**A** and **B**) that can be produced when phenyl-substituted acetylenes (**1a-d**) are treated with HCl:



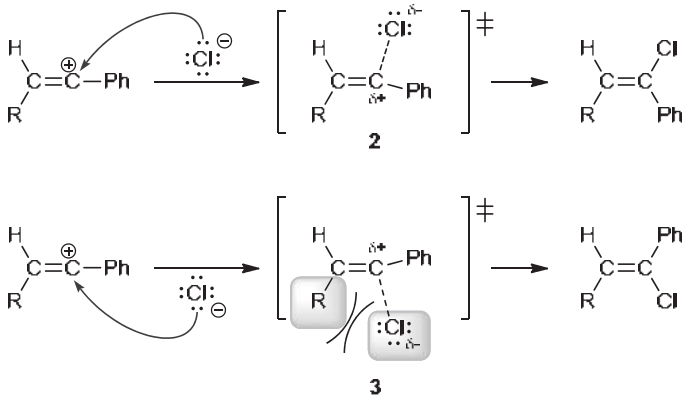
The empty 2*p* orbital (of the C+ atom) in cation **A** cannot be stabilized via resonance interaction with the aromatic ring, so we expect this cation to be highly unstable (as is the case for most vinyl carbocations). In contrast, the empty *p*-orbital of cation **B** *can* overlap effectively with the π system of the aromatic ring:



Since cation **B** is resonance-stabilized, it is much more stable than a typical vinyl carbocation. That is, cation **B** is more stable than cation **A**, explaining the regioselectivity observed in this series of hydrohalogenation reactions. This explains why Cl is installed at the benzylic position (the position next to the aromatic ring), because that is the location of the most stable carbocation.

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(b) The stereoselectivity can be explained by considering the steric effects involved in the two competing transition states:



Attack of chloride on the vinyl carbocation via transition state **2** gives the *E* isomer, while transition state **3** results in the *Z* isomer. The latter involves a steric interaction between the alkyl group and the chloro group. For a small R group (such as R = Me), the preference for the *E* isomer is relatively small (70:30). As the size of the R group increases, the preference for the *E* isomer is enhanced. When R is a *t*-butyl group, the *E* isomer is the exclusive product.

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Chapter 10
Radical Reactions

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 10. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Radical mechanisms utilize **fishhook arrows**, each of which represents the flow of _____.
- Every step in a radical mechanism can be classified as **initiation**, _____, or **termination**.
- A **radical initiator** is a compound with a weak bond that readily undergoes _____.
- A _____, also called a radical scavenger, is a compound that prevents a chain process from either getting started or continuing.
- _____ is more selective than chlorination.
- When a new chiral center is created during a radical halogenation process, a _____ mixture is obtained.
- _____ can undergo **allylic bromination**, in which bromination occurs at the allylic position.
- Organic compounds undergo oxidation in the presence of atmospheric oxygen to produce **hydroperoxides**. This process, called _____, is believed to proceed via a _____ mechanism.
- **Antioxidants**, such as BHT and BHA, are used as food preservatives to prevent autooxidation of _____ oils.
- When vinyl chloride is polymerized, _____ is obtained.
- Radical halogenation provides a method for introducing _____ into an alkane.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 10. The answers appear in the section entitled *SkillBuilder Review*.

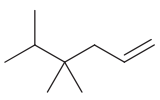
10.1 Drawing Resonance Structures of Radicals

DRAW A RESONANCE STRUCTURE OF THE RADICAL BELOW, AS WELL AS THE FISHHOOK ARROWS THAT SHOW ITS FORMATION:



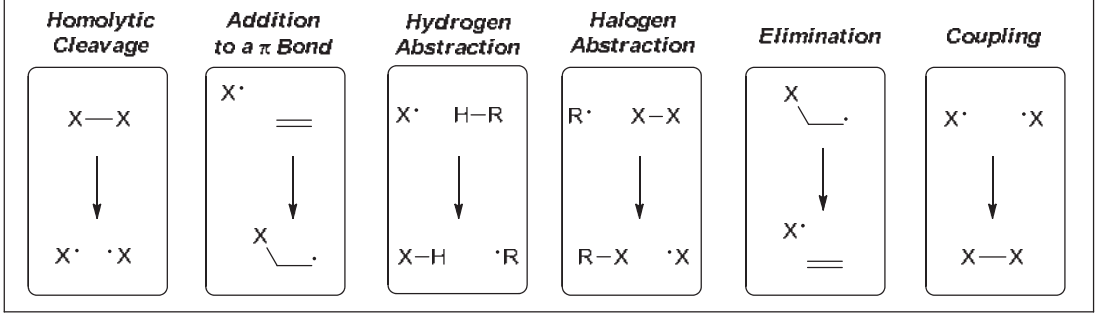
10.2 Identifying the Weakest C-H Bond in a Compound

IDENTIFY THE WEAKEST C-H BOND IN THE FOLLOWING COMPOUND:



10.3 Identifying a Radical Pattern and Drawing Fishhook Arrows

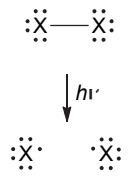
DRAW THE FISHHOOK ARROWS FOR EACH OF THE SIX PATTERNS SHOWN BELOW:



10.4 Drawing a Mechanism for Radical Halogenation

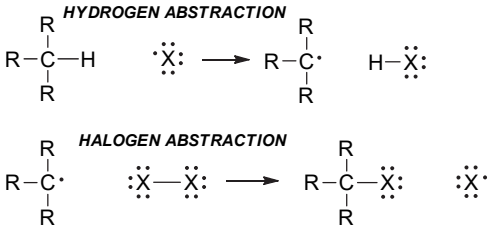
INITIATION

DRAW FISHHOOK ARROWS FOR THE INITIATION STEP BELOW:



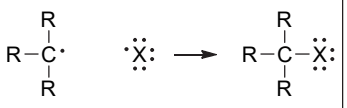
PROPAGATION

DRAW FISHHOOK ARROWS FOR THE PROPAGATION STEPS BELOW:



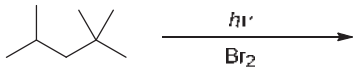
TERMINATION

DRAW FISHHOOK ARROWS FOR THE TERMINATION STEP BELOW:



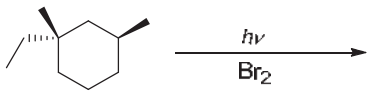
10.5 Predicting the Selectivity of Radical Bromination

DRAW THE EXPECTED MAJOR PRODUCT OF THE FOLLOWING MONOBROMINATION REACTION:



10.6 Predicting the Stereochemical Outcome of Radical Bromination

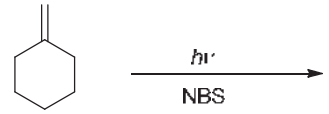
DRAW THE EXPECTED PRODUCTS OF THE FOLLOWING REACTION:



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10.7 Predicting the Products of Allylic Bromination

DRAW THE EXPECTED PRODUCTS OF THE FOLLOWING REACTION:



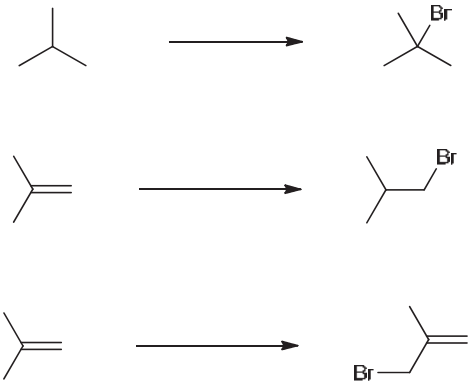
10.8 Predicting the Products for Radical Addition of HBr

DRAW THE EXPECTED PRODUCTS OF THE FOLLOWING REACTION:



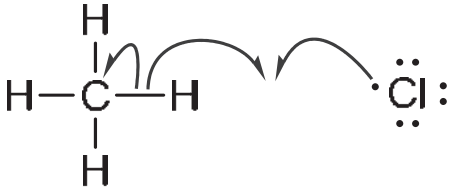
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 10. The answers appear in the section entitled *Review of Synthetically Useful Radical Reactions*.



Common Mistakes to Avoid

When drawing a mechanism for a radical process, make sure that all curved arrows are single-barbed (called fishhook arrows), rather than double-barbed. For example, look closely at the head of each of the following fishhook arrows:



Each of these single-barbed arrows indicates the motion of one electron, while double-barbed arrows indicate the motion of two electrons. All of the mechanisms presented in this chapter utilize single-barbed arrows. Make sure to draw them properly.

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Useful Reagents

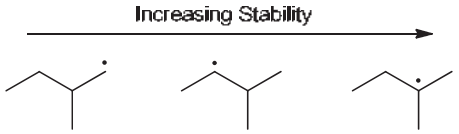
The following is a list of common reagents covered in this chapter:

Reagents	Name of Reaction	Description of Reaction
Br_2, $h\nu$	Radical bromination	Under these conditions, an alkane undergoes bromination, with installation of the Br at the most substituted position.
Cl_2, $h\nu$	Radical chlorination	Under these conditions, an alkane undergoes chlorination. This reaction is less selective than bromination (but faster), and as such, it is generally most useful in situations where only one regiochemical outcome is possible (such as chlorination of cyclohexane or chlorination of 2,2-dimethylpropane).
HBr, ROOR	Hydrobromination	When treated with HBr in the presence of peroxides, an alkene undergoes *anti*-Markovnikov addition of H and Br.
NBS, $h\nu$	Allylic bromination	NBS, or *N*-bromosuccinimide, is a reagent that can be used to install a bromine atom at the allylic position of an alkene.

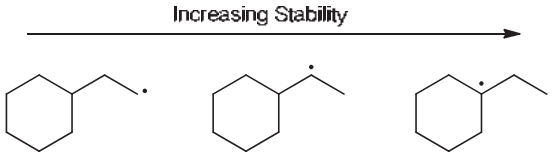
Solutions

10.1.

(a) The tertiary radical is the most stable, because alkyl groups stabilize the unpaired electron via a delocalization effect, called hyperconjugation. The primary radical is the least stable, because it lacks the stabilizing effect provided by multiple alkyl groups.

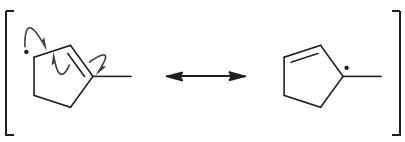


(b) The tertiary radical is the most stable, because alkyl groups stabilize the unpaired electron via a delocalization effect, called hyperconjugation. The primary radical is the least stable, because it lacks the stabilizing effect provided by multiple alkyl groups.

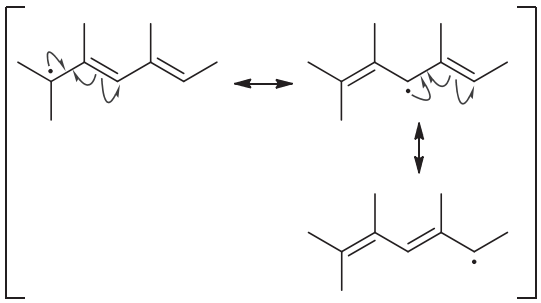


10.2.

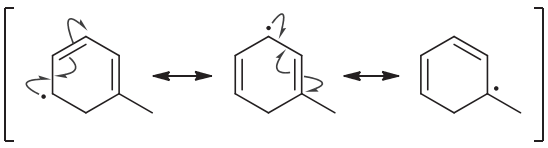
(a) The unpaired electron occupies an allylic position, so it is resonance-stabilized. Three fishhook arrows are required, as shown:



(b) The unpaired electron occupies an allylic position, so it is resonance-stabilized. Three fishhook arrows are required, as shown below. The resulting resonance structure exhibits an unpaired electron that is allylic to another π bond, so again we draw three fishhook arrows to arrive at another resonance structure:

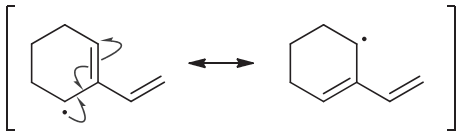


(c) The unpaired electron occupies an allylic position, so it is resonance-stabilized. Three fishhook arrows are required, as shown below. The resulting resonance structure exhibits an unpaired electron that is allylic to another π bond, so again we draw three fishhook arrows to arrive at another resonance structure:



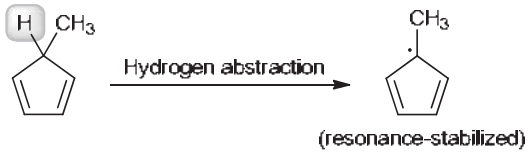
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(d) The unpaired electron occupies an allylic position, so it is resonance-stabilized. Three fishhook arrows are required, as shown:

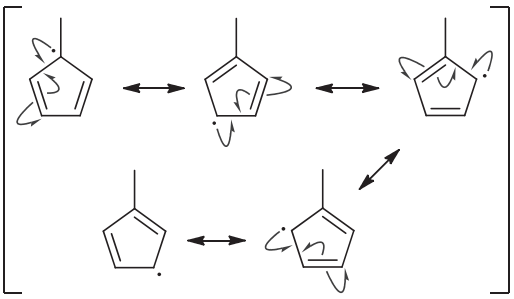


Note that the other π bond does not participate in resonance, because the unpaired electron is not allylic to that π bond.

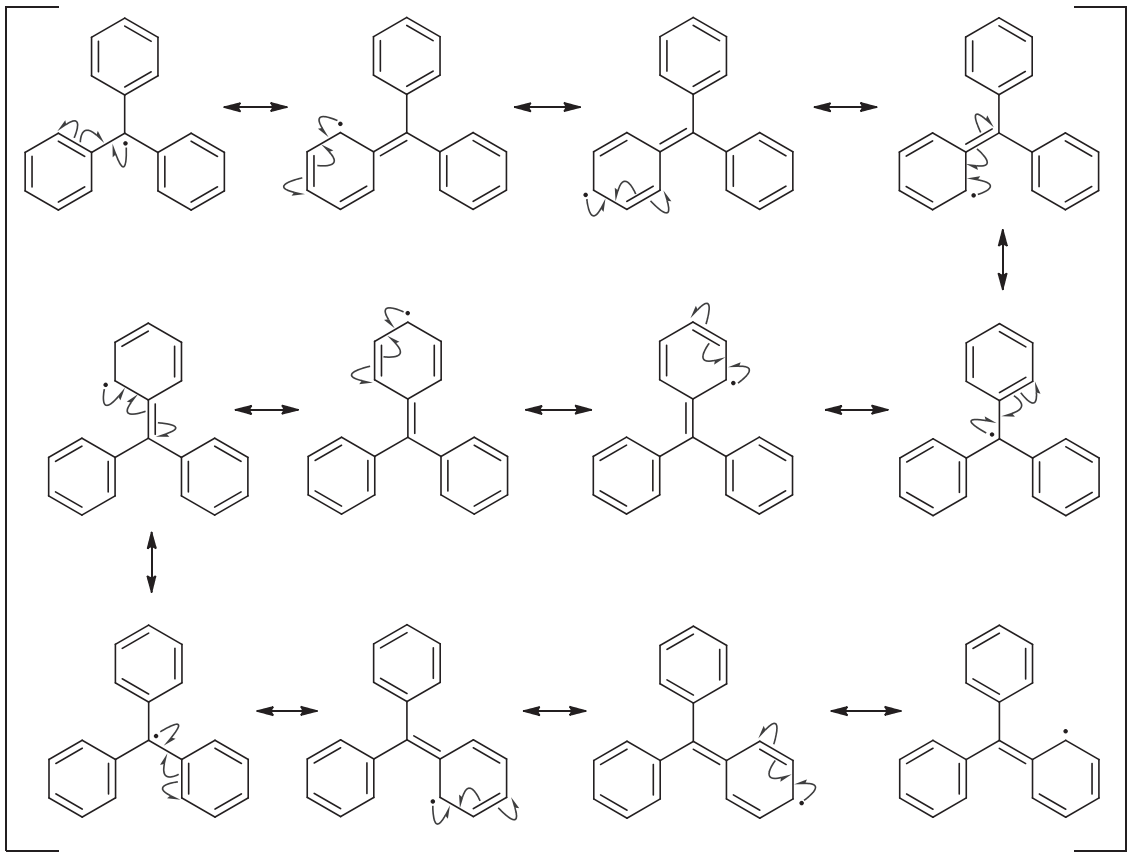
10.3. The following hydrogen atom (highlighted) is connected to an allylic position, and its removal will generate a resonance-stabilized radical:



To draw the resonance structures for this radical, we begin by drawing three fishhook arrows. The resulting resonance structure also exhibits an unpaired electron that is allylic to a π bond, so again we draw three fishhook arrows as well as the resulting resonance structure. This process continues until we have drawn all five resonance structures, shown here:



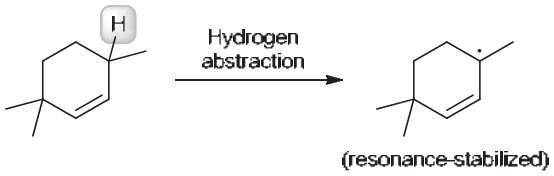
10.4. This radical is unusually stable, because it has a large number of resonance structures, so the unpaired electron is highly delocalized. As shown below, three fishhook arrows are required in order to draw each resonance structure:



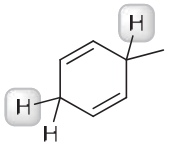
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10.5.

(a) We consider each of the C-H bonds in the compound, and in each case, we imagine the radical that would result from homolytic cleavage of that C-H bond. Among all the C-H bonds, only one of them can undergo homolytic cleavage to generate a resonance-stabilized radical. Specifically, removal of the highlighted hydrogen atom will result in an allylic radical. And therefore, this C-H bond is the weakest C-H bond in the compound:



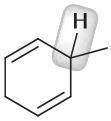
(b) We consider each of the C-H bonds in the compound, and in each case, we imagine the radical that would result from homolytic cleavage of that C-H bond. There are only two different kinds of C-H bonds that can undergo homolytic cleavage to generate a resonance-stabilized radical. Specifically, removing either of the highlighted hydrogen atoms will result in a resonance-stabilized intermediate (with three resonance structures):



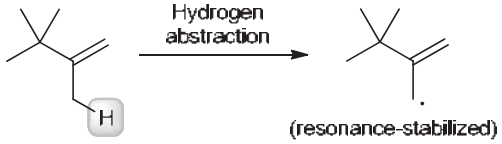
These two locations represent the two weakest C-H bonds in the compound. Between the two of them, the weaker C-H bond is the one that gives a tertiary allylic radical upon removal of the hydrogen atom (rather than a secondary allylic radical):



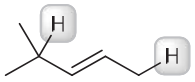
A tertiary allylic radical is more stable than a secondary allylic radical, so the following C-H bond is the weakest C-H bond in the compound:



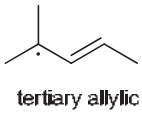
(c) We consider each of the C-H bonds in the compound, and in each case, we imagine the radical that would result from homolytic cleavage of that C-H bond. Among all the different types of C-H bonds, only one location can undergo homolytic cleavage to generate a resonance-stabilized radical. Specifically, removal of the highlighted hydrogen atom will result in an allylic radical. And therefore, this C-H bond is the weakest C-H bond in the compound:



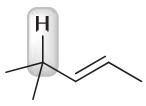
(d) We consider each of the C-H bonds in the compound, and in each case, we imagine the radical that would result from homolytic cleavage of that C-H bond. There are only two different kinds of C-H bonds that can undergo homolytic cleavage to generate a resonance-stabilized radical. Specifically, removing either of the highlighted hydrogen atoms will result in a resonance-stabilized intermediate (with two resonance structures):



These two locations represent the two weakest C-H bonds in the compound. Between the two of them, the weaker C-H bond is the one that gives a tertiary allylic radical upon removal of the hydrogen atom:

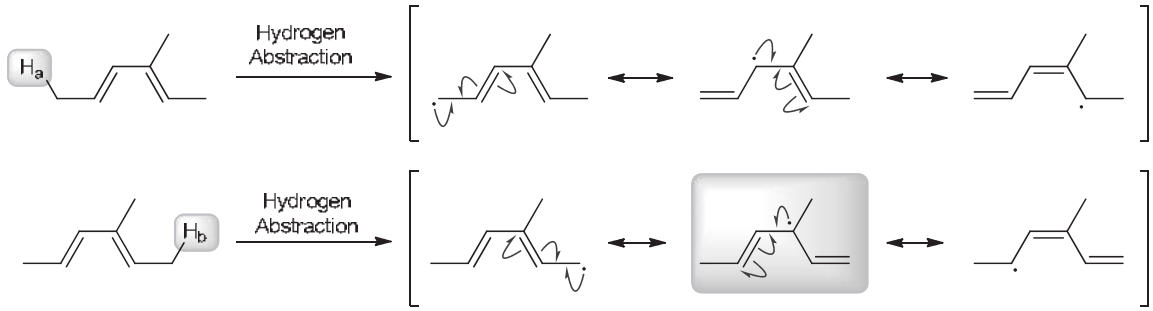


Therefore, the following C-H bond is the weakest C-H bond in the compound:



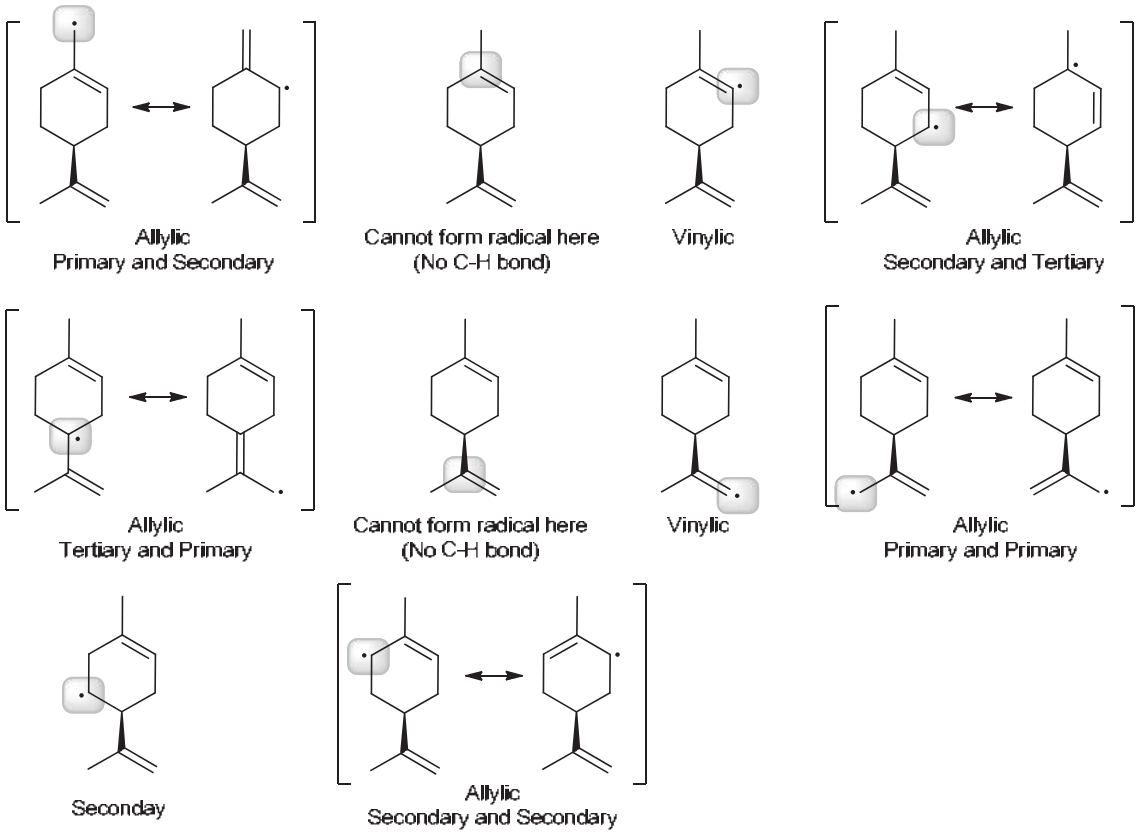
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10.6. We begin by drawing the resonance structures of the radical that is formed when H_a is abstracted, as well as the resonance structures of the radical that is formed when H_b is abstracted:



Compare the resonance structures in each case. Specifically, look at the middle resonance structure in each case. When H_b is abstracted, the middle resonance structure is tertiary, and the effect of the methyl group is to stabilize the radical. This stabilizing factor is not present when H_a is abstracted. Therefore, we expect the C-H_b bond to be slightly weaker than the C-H_a bond.

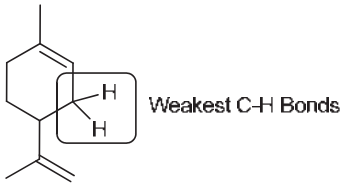
10.7. Imagine homolytically breaking each different type of C-H bond in the compound and then evaluate the stability of the resulting radical. There are ten locations to consider. Starting with the methyl group at the top, and proceeding methodically clockwise around the structure, gives the following analysis:



Two positions have no H atoms attached and therefore cannot react. Loss of a hydrogen atom at each of the remaining eight positions yields the eight radicals as shown. Two are vinylic, one is secondary and five are allylic. Each of the allylic radicals has two resonance forms and we must consider those forms when evaluating their relative stability. It appears that the most stable allylic radical has the unpaired electron delocalized over a secondary and a tertiary

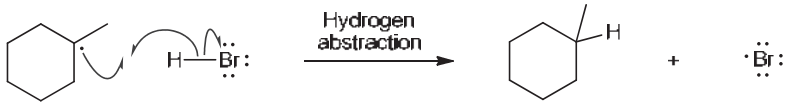
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position, while the other allylic radicals are less substituted. Based on this, we conclude that the following C-H bonds are the weakest, since removal of a hydrogen atom from this location yields the most stable radical.

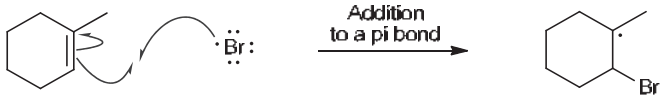


10.8.

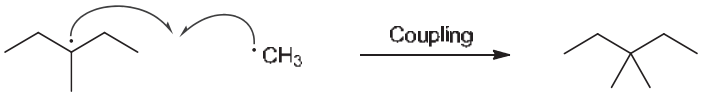
(a) This step is a *hydrogen abstraction*, which requires a total of three fishhook arrows. In order to place the fishhook arrows properly, we must identify any bonds being formed (C–H) and any bonds being broken (H–Br). Formation of the C–H bond is shown with two fishhook arrows: one coming from the carbon radical and the other coming from the H–Br bond. The latter, together with the third fishhook arrow, shows the breaking of the H–Br bond:



(b) This step is *addition to a π bond*, which requires a total of three fishhook arrows. In order to place the fishhook arrows properly, we must identify any bonds being formed (C–Br) and any bonds being broken (C═C π bond). Formation of the C–Br bond is shown with two fishhook arrows: one coming from the π bond and the other coming from the bromine radical. The former, together with the third fishhook arrow, shows the breaking of the C═C π bond:



(c) This step is a *coupling* process, which requires a total of two fishhook arrows, showing formation of a bond (in this case, a C–C bond is formed):



(d) This step is a *hydrogen abstraction*, which requires a total of three fishhook arrows. In order to place the fishhook arrows properly, we must identify any bonds being formed (H–Br) and any bonds being broken (C–H). Formation of the H–Br bond is shown with two fishhook arrows: one coming from the bromine radical and the other coming from the C–H bond. The latter, together with the third fishhook arrow, shows the breaking of the C–H bond:

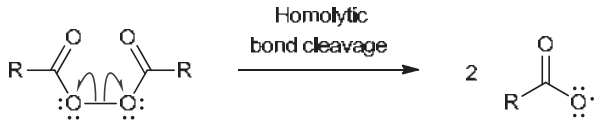


(e) This step is an *elimination*, which requires a total of three fishhook arrows. In order to place the fishhook arrows properly, we must identify any bonds being formed (a C═C π bond) and any bonds being broken (C–C). Formation of the C═C π bond is shown with two fishhook arrows: one coming from the carbon radical and the other coming from the neighboring C–C bond. The latter, together with the third fishhook arrow, shows the breaking of the C–C bond:

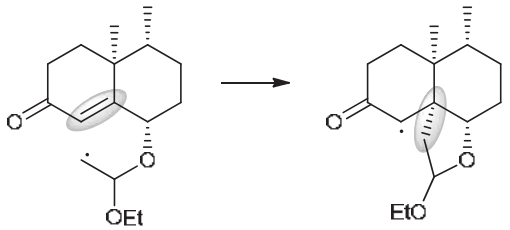


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(**f**) This step is a *homolytic bond cleavage*, which requires a total of two fishhook arrows, showing breaking of a bond (in this case, an O–O bond is broken):

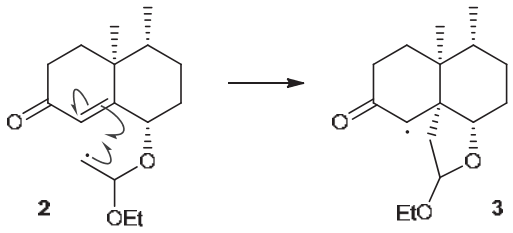


10.9. In this intramolecular process, a radical is reacting with a π bond. One π bond is broken and one σ bond is formed in this step – these bonds are highlighted below:



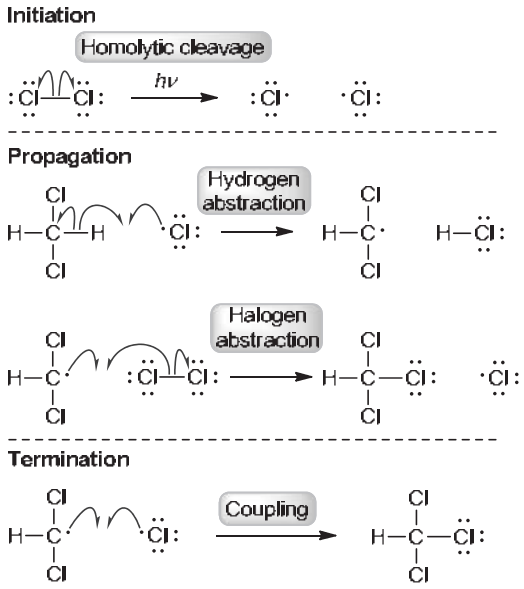
π bond broken σ bond formed

This step is an example of addition to a π bond, which requires three fishhook arrows. Two of these arrows show formation of the new σ bond, and the other arrow shows where the unpaired electron will be located in intermediate **3**.



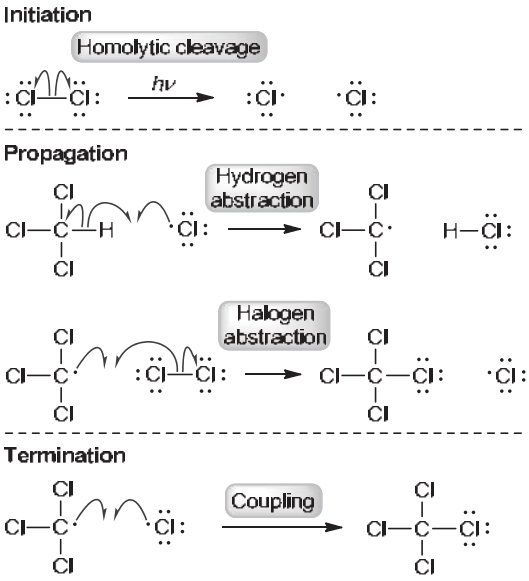
10.10.

(a) The mechanism will have three distinct stages. The first stage is initiation, in which the Cl–Cl bond is broken to generate chlorine radicals. This step requires two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). Finally, there are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown here is a termination step that generates the desired product, but it is still considered to be a termination step because this step reduces the number of radicals present in the reaction flask (two radicals are destroyed, without generating new radicals):

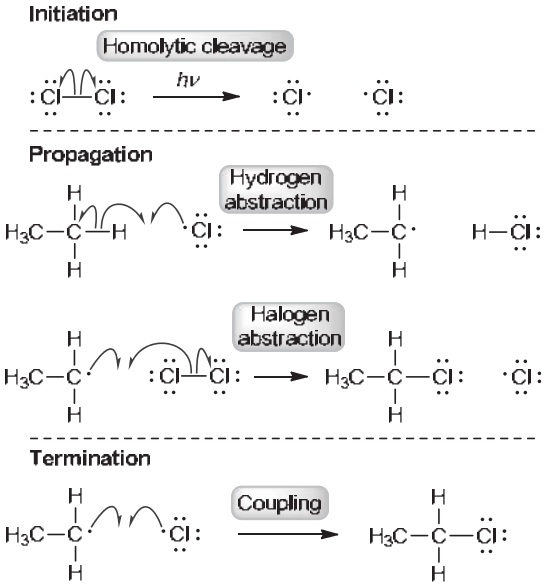


(b) The mechanism will have three distinct stages. The first stage is initiation, in which the Cl–Cl bond is broken to generate chlorine radicals. This step requires two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). Finally, there are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown here is a termination step that generates the desired product, but it is still considered to be a termination step because this step reduces the number of radicals present in the reaction flask (two radicals are destroyed, without generating new radicals):

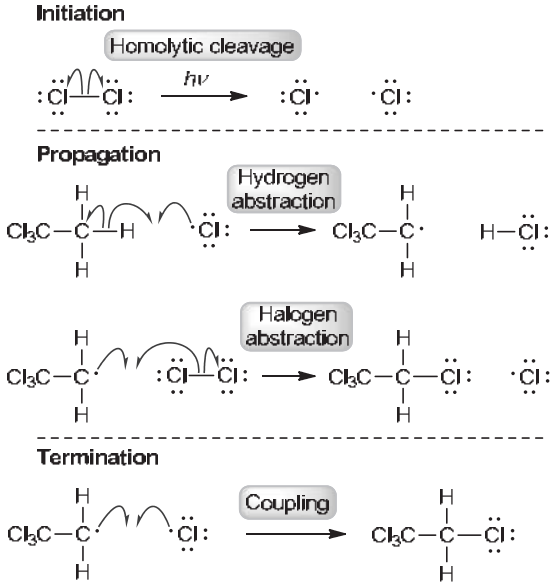
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(c) The mechanism will have three distinct stages. The first stage is initiation, in which the Cl–Cl bond is broken to generate chlorine radicals. This step requires two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). Finally, there are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown below is a termination step that generates the desired product, but it is still considered to be a termination step because this step reduces the number of radicals present in the reaction flask (two radicals are destroyed, without generating new radicals):

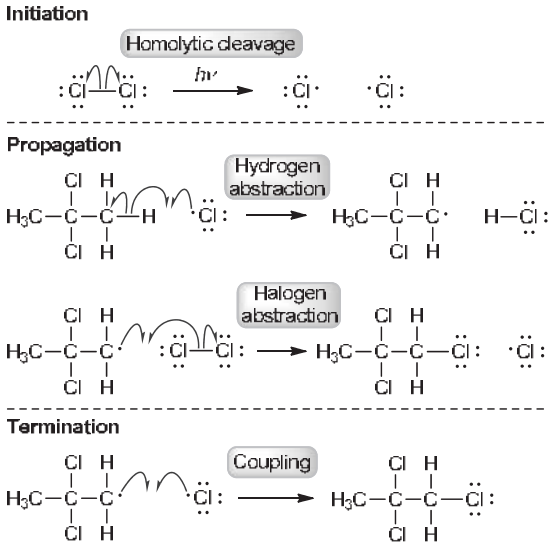


(d) The mechanism will have three distinct stages. The first stage is initiation, in which the Cl–Cl bond is broken to generate chlorine radicals. This step requires two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). Finally, there are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown below is a termination step that actually generates the desired product, but it is still considered to be a termination step because this step reduces the number of radicals present in the reaction flask (two radicals are destroyed, without generating new radicals):



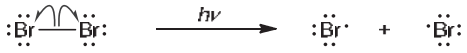
(e) The mechanism will have three distinct stages. The first stage is initiation, in which the Cl–Cl bond is broken to generate chlorine radicals. This step requires two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). Finally, there are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown here is a termination step that actually generates the desired product, but it is still considered to be a termination step because this step reduces the number of radicals present in the reaction flask (two radicals are destroyed, without generating new radicals):

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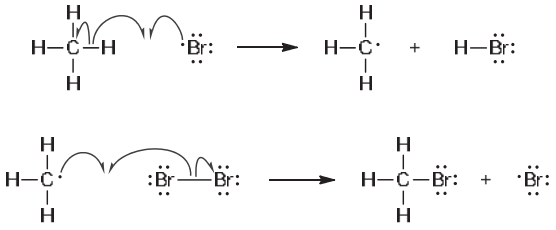


10.11.

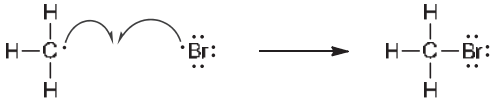
(a) The mechanism for radical bromination of methane will have three distinct stages. The first stage is initiation, which creates bromine radicals. This initiation step involves homolytic bond cleavage (using Br_2 and either heat or light) and should employ two fishhook arrows.



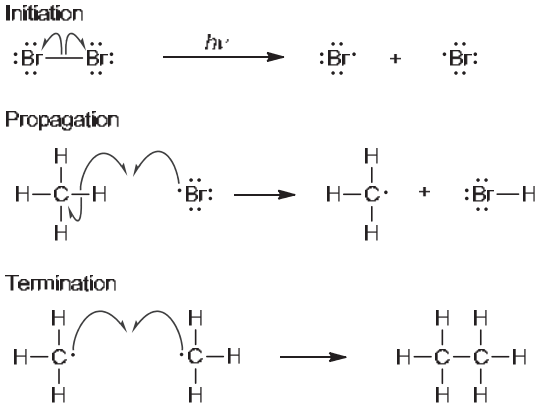
The next stage involves propagation steps. There are two propagation steps: hydrogen abstraction to remove a hydrogen atom, followed by halogen abstraction to attach a bromine atom. Each of these steps should have three fishhook arrows. These two steps together represent the core reaction. They show how the product is formed.



There are a number of possible termination steps to end the process. When drawing a mechanism for a radical reaction it is generally not necessary to draw all possible termination steps unless specifically asked to do so. It is sufficient to draw one termination step. Shown here is one termination step that also happens to produce the desired product.

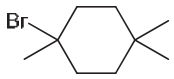


(b) During the bromination of methane, methyl radicals are produced. If two of these methyl radicals combine in a termination step, ethane is produced:

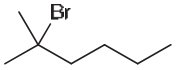


10.12.

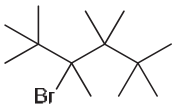
(a) The tertiary position is expected to undergo selective bromination, giving the following alkyl bromide:



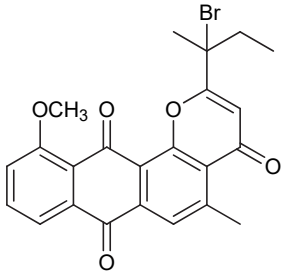
(b) The tertiary position is expected to undergo selective bromination, giving the following alkyl bromide:



(c) The tertiary position is expected to undergo selective bromination, giving the following alkyl bromide:



10.13. The tertiary allylic position is expected to undergo selective bromination, giving the following alkyl bromide as the major product:

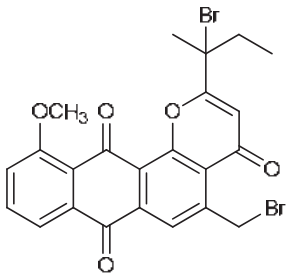


Major

Bromination at the benzylic position is also favorable because it proceeds via a resonance-stabilized, benzylic

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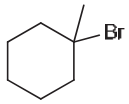
radical intermediate. The minor product thus has a second bromine atom attached at the benzylic position:



Minor

10.14.

(a) The starting compound contains only one tertiary position, so bromination occurs at this position. The product does not contain a chiral center:



no chiral center

(b) The starting compound contains only one tertiary position, so bromination occurs at this position. This position is an existing chiral center, so we expect loss of configuration to produce both possible enantiomers:



(c) The starting compound contains only one tertiary position, so bromination occurs at this position. This position is an existing chiral center, so we expect loss of configuration to produce both possible enantiomers:

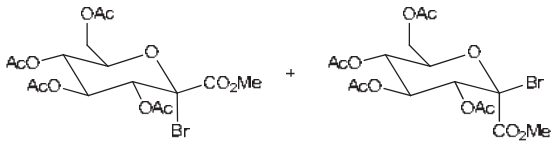


(d) The starting compound contains only one tertiary position, so bromination occurs at this position. This position is an existing chiral center, so we expect loss of configuration to produce both possible stereoisomers:



Notice that the other chiral center was unaffected by the reaction. The products are diastereomers.

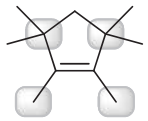
10.15. The position undergoing halogenation is an existing chiral center, so we expect loss of configuration to produce both possible stereoisomers:



Notice that the other chiral centers are unaffected by the reaction. The products are diastereomers so they are not expected to be formed in equal amounts.

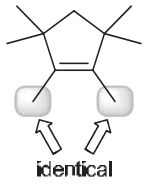
10.16.

(a) We begin by identifying allylic positions. There are four:



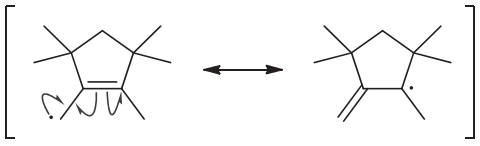
allylic positions

But two of these positions (the top two positions in the structure above) lack hydrogen atoms. So those positions cannot undergo radical bromination (a C–H bond is necessary because a key step in the mechanism is a hydrogen abstraction step). The remaining two allylic positions are identical (the molecule has a plane of symmetry that renders these two positions identical):

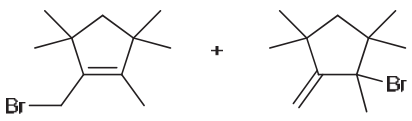


identical

So, we only need to consider allylic bromination occurring at one of these positions. To do that, we remove a hydrogen atom from the allylic position and draw the resonance structures of the resulting allylic radical:

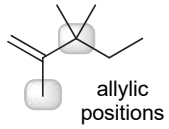


Finally, we use these resonance structures to determine the products, by placing a bromine atom at the position of the unpaired electron in each resonance structure:

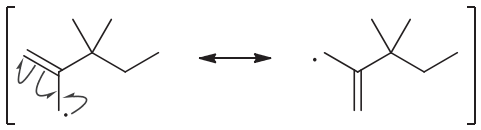


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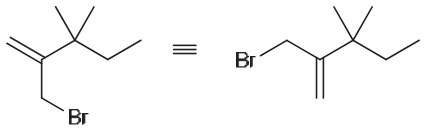
(b) We begin by identifying the allylic positions. There are two:



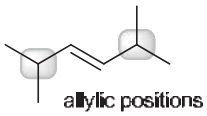
But one of these positions (the top position in the structure above) lacks a hydrogen atom. So this position cannot undergo radical bromination (a C–H bond is necessary because a key step in the mechanism is a hydrogen abstraction step). So, we only need to consider allylic bromination occurring at one position. To do that, we remove a hydrogen atom from the allylic position and draw the resonance structures of the resulting allylic radical:



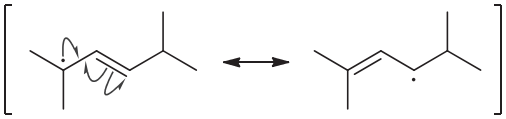
Finally, we use these resonance structures to determine the products, by placing a bromine atom at the position of the unpaired electron in each resonance structure. In this case, our methodical approach has produced two structures that are identical compounds, so this reaction has only one product:



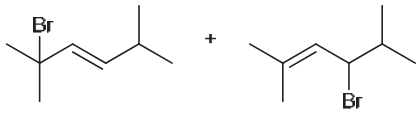
(c) We begin by identifying allylic positions. There are two:



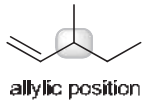
But these two positions are identical (symmetry). So, we only need to consider allylic bromination occurring at one of these positions. To do that, we remove a hydrogen atom from the allylic position and draw the resonance structures of the resulting allylic radical:



Finally, we use these resonance structures to determine the products, by placing a bromine atom at the position of the unpaired electron in each resonance structure:



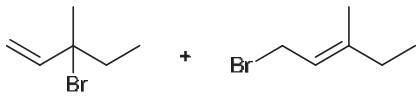
(d) We begin by identifying allylic positions. There is only one in this case:



Next, we remove a hydrogen atom from the allylic position and draw the resonance structures of the resulting allylic radical:

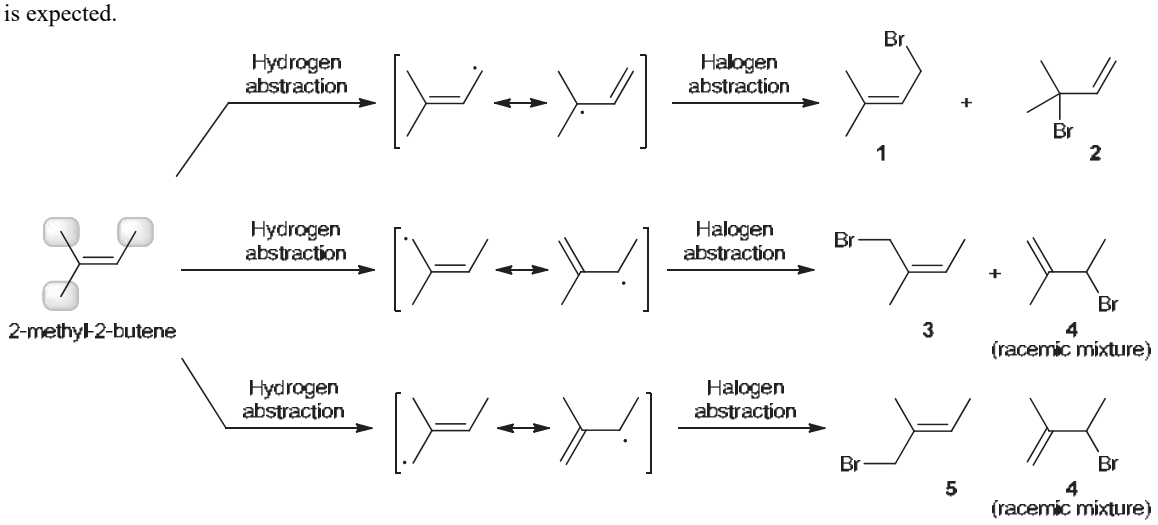


Finally, we use these resonance structures to determine the products, by placing a bromine atom at the position of the unpaired electron in each resonance structure:

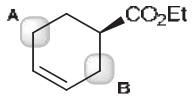


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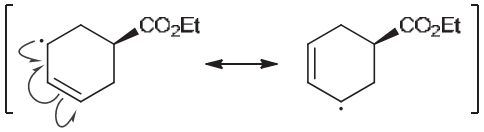
10.17. We begin by drawing the starting compound (2-methyl-2-butene) and identifying the allylic positions (highlighted below). Each of these three positions can undergo hydrogen abstraction to give a resonance-stabilized radical, shown below. The resulting products are also shown. Notice that there are a total of five products, labeled **1** – **5**. Notice that compound **4** is the only product that exhibits a chiral center. As such, a racemic mixture of compound **4** is expected.



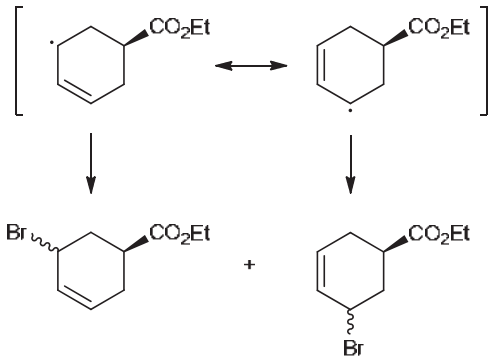
10.18. This compound has two allylic positions (highlighted below, A and B). Each allylic position has hydrogen atoms that can be abstracted, so we will need to consider products resulting from abstraction at each allylic position.



First, draw the resonance structures that result from abstracting a hydrogen atom from position **A** (in the first propagation step).

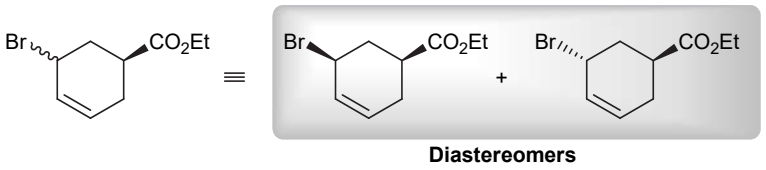


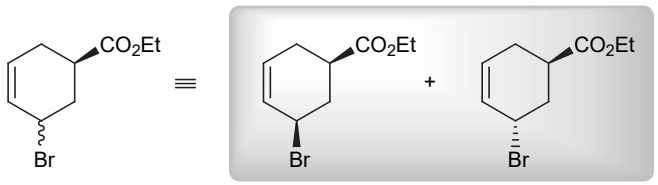
Then, halogen abstraction (in the second propagation step) can occur from either resonance structure, resulting in two possible regiochemical outcomes:



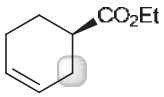
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Now consider the stereochemical outcome in each of these cases. As described in Section 10.6, the bromine atom can be installed on either face (front or back) of the radical. This gives four isomers, which represent two pairs of diastereomers, as shown:

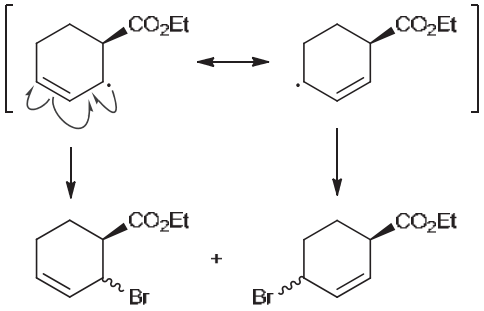




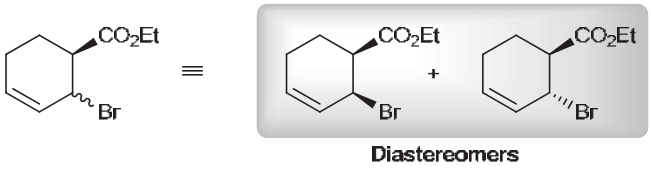
Now let's start over again, and draw the resonance structures that result from abstracting a hydrogen atom from the other allylic position (in the first propagation step):

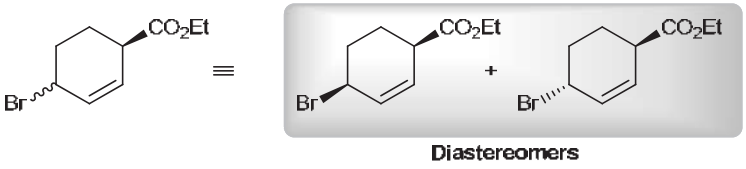


Once again, halogen abstraction (in the second propagation step) can occur from either resonance structure, resulting in two more constitutional isomers:



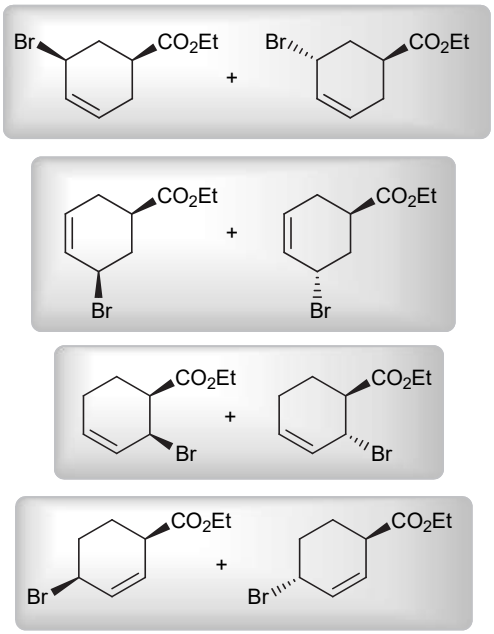
And once again, the bromine atom can be installed on either face (front or back) of the radical. This gives four isomers, which represent two pairs of diastereomers, as shown:



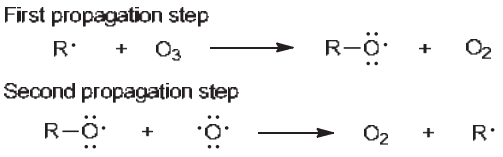


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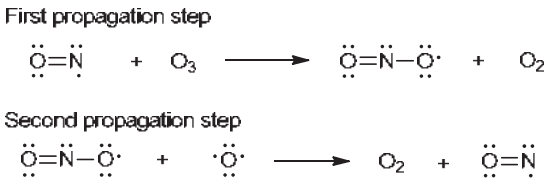
In summary, there are four possible isomeric products that result from hydrogen abstraction at position **1** and four possible isomeric products that result from hydrogen abstraction at position **2**. This gives a total of eight isomeric products, which represent four pairs of diastereomers:



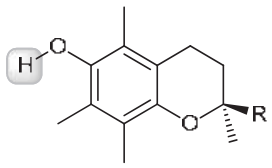
10.19. As seen in Section 10.8, destruction of ozone in the atmosphere occurs via the following two propagation steps (where R• represents a radical, such as Cl•, that is responsible for destroying ozone):



If we redraw this mechanism with nitric oxide serving as the radical that destroys ozone, we get the following:



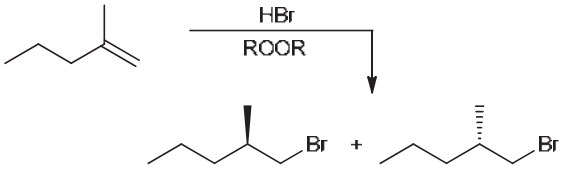
10.20. Radicals will react with BHT and BHA because each of these compounds has a hydrogen atom that can be readily abstracted, thereby generating a resonance-stabilized radical. In each case, the phenolic hydrogen atom is abstracted (the hydrogen atom of the OH group connected to the aromatic ring). Similarly, vitamin E also exhibits a phenolic hydrogen atom. Abstraction of this hydrogen atom (highlighted below) gives a resonance-stabilized radical.



Vitamin E

10.21.

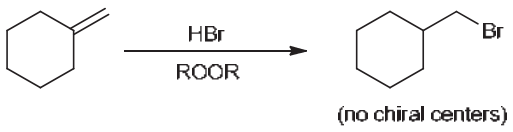
(a) The reagent (HBr) indicates that H and Br are added across the π bond. In the presence of peroxides (ROOR), we expect an *anti*-Markovnikov addition. That is, the bromine atom is installed at the less substituted position. In this case, one new chiral center is created, which results in a racemic mixture of the two possible enantiomers.



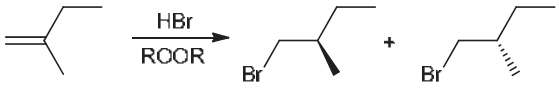
(b) The reagent (HBr) indicates that H and Br are added across the π bond. In the presence of peroxides (ROOR),

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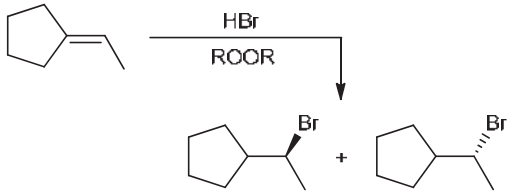
we expect an *anti*-Markovnikov addition. That is, the bromine atom is installed at the less substituted position. In this case, no new chiral centers are formed:



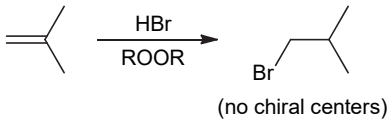
(c) The reagent (HBr) indicates that H and Br are added across the π bond. In the presence of peroxides (ROOR), we expect an *anti*-Markovnikov addition. That is, the bromine atom is installed at the less substituted position. In this case, one new chiral center is created, which results in a racemic mixture of the two possible enantiomers.



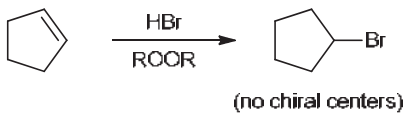
(d) The reagent (HBr) indicates that H and Br are added across the π bond. In the presence of peroxides (ROOR), we expect an *anti*-Markovnikov addition. That is, the bromine atom is installed at the less substituted position. In this case, one new chiral center is created, which results in a racemic mixture of the two possible enantiomers.



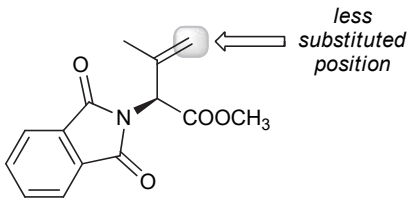
(e) The reagent (HBr) indicates that H and Br are added across the π bond. In the presence of peroxides (ROOR), we expect an *anti*-Markovnikov addition. That is, the bromine atom is installed at the less substituted position. In this case, no new chiral centers are formed:



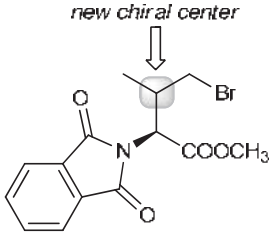
(f) The reagent (HBr) indicates that H and Br are added across the π bond. In the presence of peroxides (ROOR), we expect an *anti*-Markovnikov addition, although that is irrelevant in this case, because the alkene is symmetrical. No new chiral centers are formed:



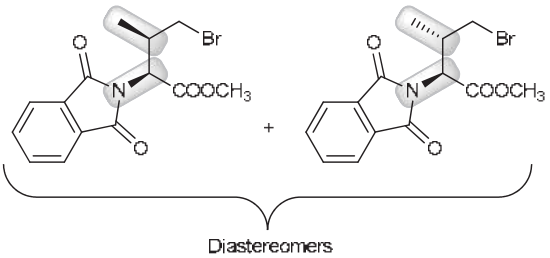
10.22. The use of HBr indicates the addition of H and Br across the π bond. The problem statement indicates a radical process (caused by the use of light, rather than ROOR, in this case), so we expect *anti*-Markovnikov addition of HBr across the π bond. That is, the bromine atom will be installed at the less substituted position.



In this case, one new chiral center is created:

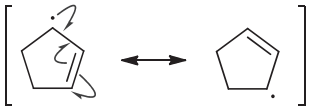


Since there was already one chiral center present, the products are diastereomers.

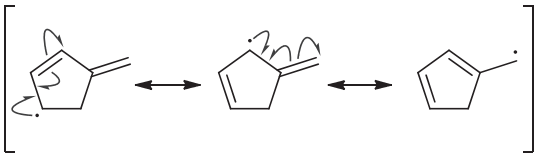


10.23.

(a) The unpaired electron occupies an allylic position, so it is resonance-stabilized. Three fishhook arrows are required, as shown:

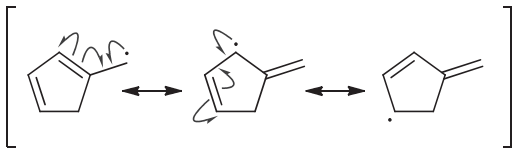


(b) The unpaired electron occupies an allylic position, so it is resonance-stabilized. Three fishhook arrows are required, as shown below. The resulting resonance structure exhibits an unpaired electron that is allylic to another π bond, so again we draw three fishhook arrows to arrive at another resonance structure:

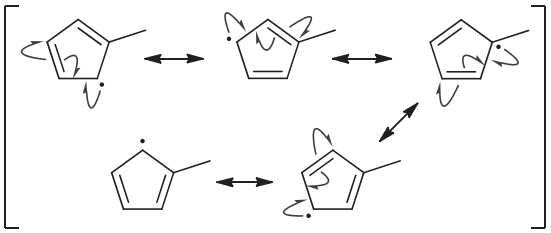


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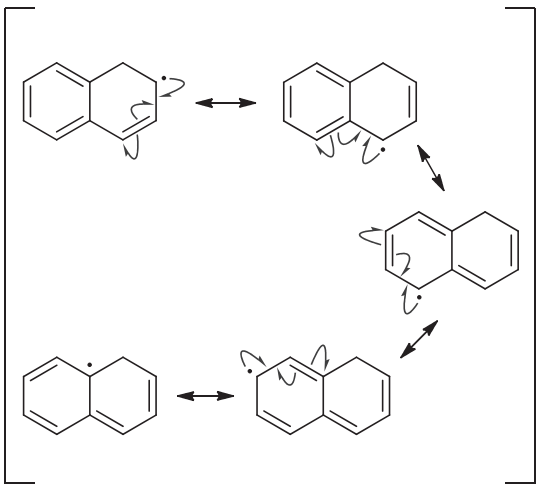
(c) The unpaired electron occupies an allylic position, so it is resonance-stabilized. Three fishhook arrows are required, as shown below. The resulting resonance structure exhibits an unpaired electron that is allylic to another π bond, so again we draw three fishhook arrows to arrive at another resonance structure:



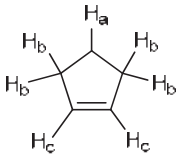
(d) The unpaired electron is allylic to a π bond, so it is resonance-stabilized. Three fishhook arrows are required, as shown below. The resulting resonance structure also exhibits an unpaired electron that is allylic to a π bond, so again we draw three fishhook arrows as well as the resulting resonance structure. This process continues until we have drawn five resonance structures, shown here:



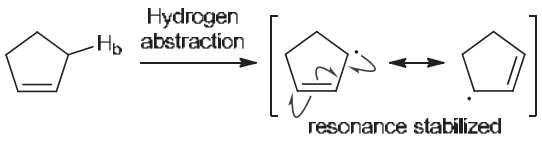
(e) The unpaired electron is allylic to a π bond, so it is resonance-stabilized. Three fishhook arrows are required, as shown below. The resulting resonance structure also exhibits an unpaired electron that is allylic to a π bond, so again we draw three fishhook arrows as well as the resulting resonance structure. This process continues until we have drawn five resonance structures, shown here:



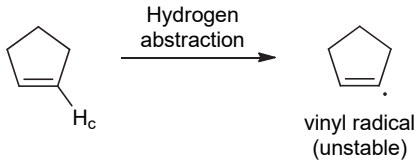
10.24. There are three different hydrogen atoms to consider, labeled H_a, H_b and H_c:



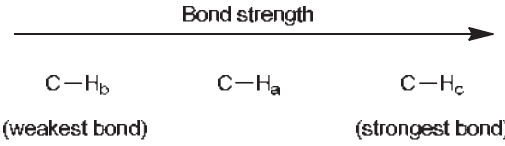
The weakest C–H bond is C–H_b, because abstraction of H_b generates a radical that is stabilized by resonance:



The strongest C–H bond is C–H_c, because abstraction of H_c generates an unstable vinyl radical:

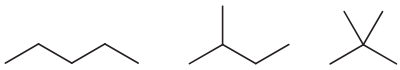


We therefore expect the C–H bonds of cyclopentene to exhibit the following order of increasing bond strength:



10.25.

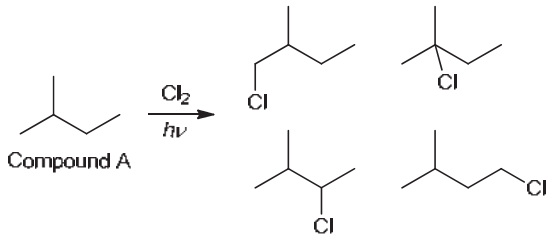
(a) We must first draw all structures with the molecular formula C_5H_{12}. To do this, we employ the same methodical approach that was used in the solution to Problem 4.3, giving the following three compounds:



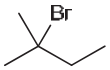
The middle compound above must be compound **A**, because monochlorination of the first compound above gives only three constitutionally isomeric alkyl chlorides (1-chloropentane, 2-chloropentane, or 3-chloropentane), while monochlorination of the last compound above gives only one regiochemical outcome. The middle compound is 2-methylbutane.

(b) Among the possibilities that we explored in part (a), we found that compound **A** is 2-methylbutane. This compound undergoes monochlorination to produce four constitutionally isomeric alkyl chlorides, shown here:

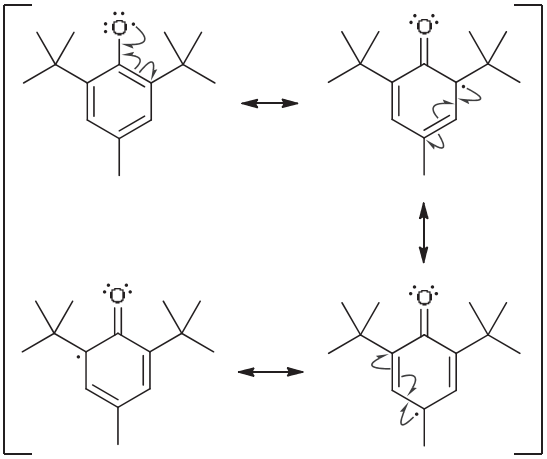
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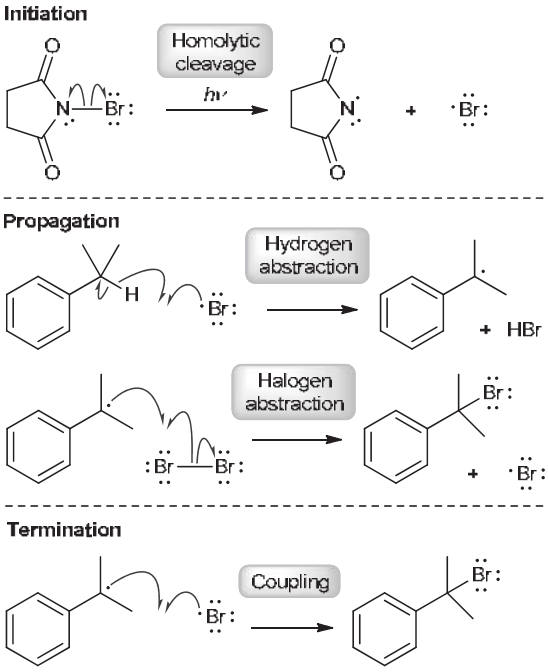
(c) The tertiary position undergoes selective bromination, giving the following tertiary alkyl bromide:



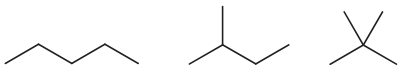
10.26. The unpaired electron is allylic to a π bond, so it is resonance-stabilized. Three fishhook arrows are required, as shown below. The resulting resonance structure exhibits an unpaired electron that is allylic to another π bond, so again we draw three fishhook arrows to arrive at another resonance structure. This pattern appears one more time, giving a fourth resonance structure. This radical is particularly stable, because it has many resonance structures, so the unpaired electron is highly delocalized.



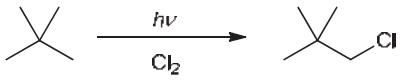
10.27. The benzylic hydrogen atom is the only hydrogen atom that can be abstracted to generate a resonance-stabilized radical. As such, the benzylic position is selectively brominated. The mechanism will have three distinct stages. The first stage is initiation, in which the N–Br bond (of NBS) is broken to generate a bromine radical. This step requires two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). Finally, there are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown here is a termination step that generates the desired product:



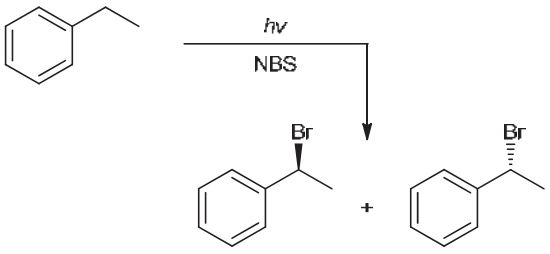
10.28. We must first draw all structures with the molecular formula C_5H_{12}. To do this, we employ the same methodical approach that was used in the solution to Problem 4.3, giving the following three compounds:



Monochlorination of the first compound above gives three constitutionally isomeric chloroalkanes (1-chloropentane, 2-chloropentane, or 3-chloropentane), while monochlorination of the second compound gives four constitutionally isomeric chloroalkanes. The last compound above (2,2-dimethylpropane) gives only one monochlorination product:



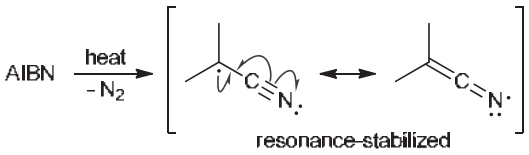
10.29. Selective bromination at the benzylic position generates a new chiral center. The intermediate benzylic radical is expected to be attacked from either face of the planar radical with equal likelihood, giving rise to a racemic mixture of enantiomers:



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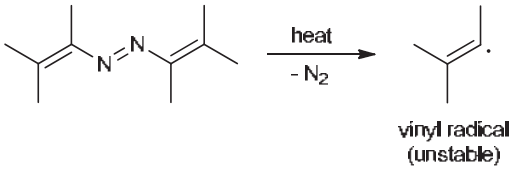
10.30.

(a) Heating AIBN generates a radical that is resonance-stabilized (the unpaired electron is delocalized via resonance, which is a stabilizing effect):



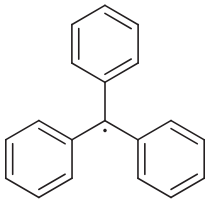
In addition, the radical is further stabilized by the presence of methyl groups, which are capable of stabilizing the unpaired electron via a delocalization effect, called hyperconjugation.

(b) Loss of nitrogen gas would result in the formation of vinyl radicals, which are too unstable to form under normal conditions:

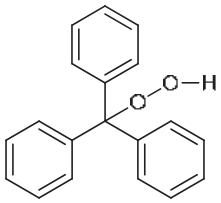


10.31.

(a) The central carbon atom is benzylic to three aromatic rings. As such, that C–H bond is expected to be extremely weak. Hydrogen abstraction (which initiates the autooxidation process) occurs at this location, generating a radical that is highly stabilized by resonance (see solution to Problem 10.3 for resonance structures):

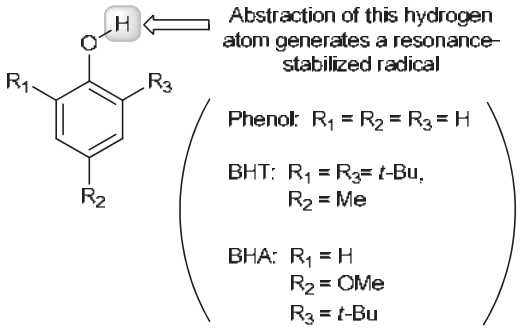


Autooxidation at this location gives the following hydroperoxide:



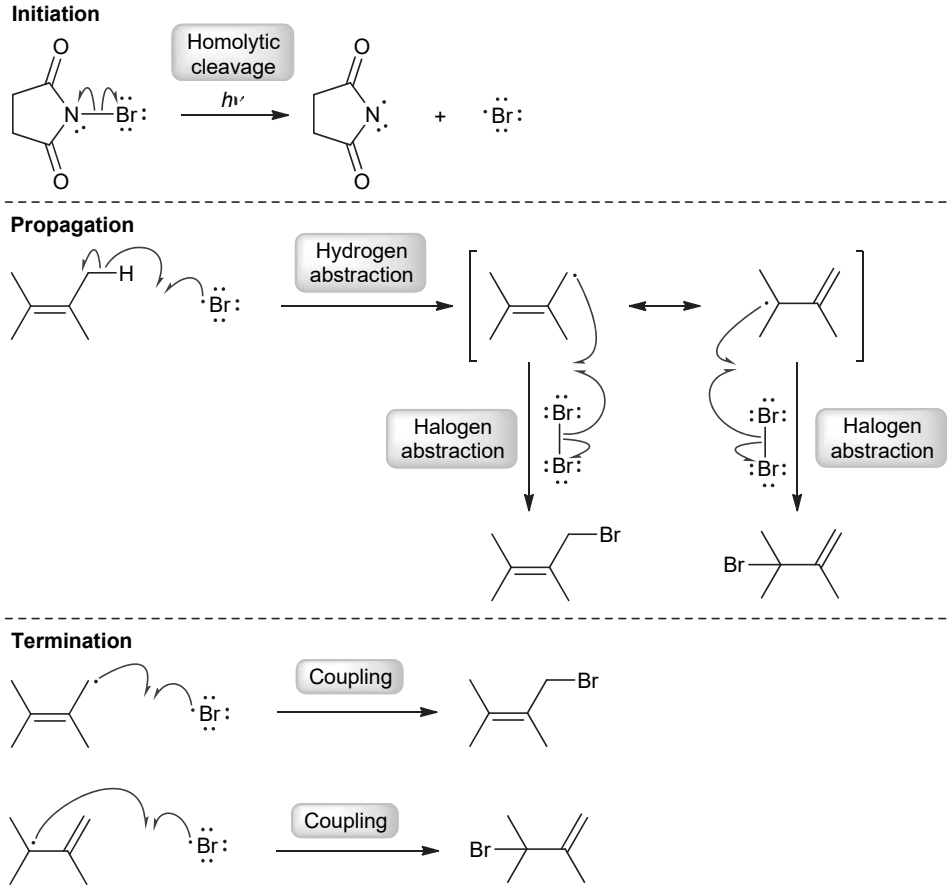
(b) As explained in the solution to part (a) of this problem, hydrogen abstraction leads to an exceptionally stable radical, with many, many resonance structures (see solution to Problem 10.3).

(c) Phenol acts as a radical scavenger (much like BHA and BHT), thereby preventing the chain process from beginning.



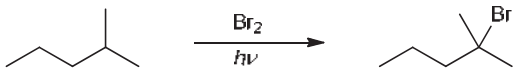
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10.32. A radical mechanism will have three distinct stages. The first stage is initiation, in which the N–Br bond (of NBS) is broken to generate a bromine radical. This step requires two fishhook arrows, as shown. The next stage is propagation. There are two propagation steps. The first is hydrogen abstraction, which requires three fishhook arrows and generates a resonance-stabilized radical. The second propagation step (halogen abstraction) also requires three fishhook arrows. Notice that this step can occur in either of two locations, as shown. The final stage is termination, and there are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown below are termination steps that generate the desired products:

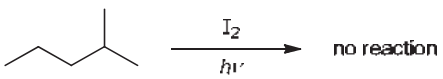


10.33.

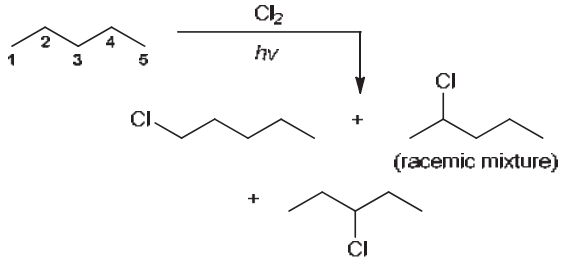
(a) The reagents indicate a radical bromination process. The starting material has only one tertiary position, which undergoes selective bromination, giving the following tertiary alkyl bromide.



(b) As seen in Section 10.4, radical iodination is not thermodynamically favorable. We expect no reaction in this case:



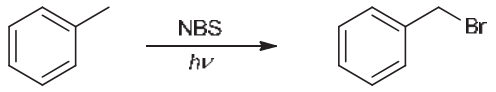
(c) The reagents indicate a radical chlorination process. Radical chlorination is less selective than radical bromination, so we expect a mixture of products. That is, we expect chlorination to occur at each of the unique locations: C1, C2, or C3. Chlorination at C2 generates a product with a chiral center, so a racemic mixture is expected:



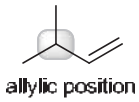
Chlorination at C4 yields the same product as chlorination at C2. Similarly, chlorination at C5 yields the same product as chlorination at C1.

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(d) The reagents indicate a radical bromination process. Bromination is expected to occur selectively at the benzylic position (because hydrogen abstraction occurs at that position to generate a resonance-stabilized radical):



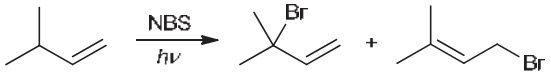
(e) The reagents indicate a radical bromination process. Bromination is expected to occur selectively at the allylic position (because hydrogen abstraction occurs at that position to generate a resonance-stabilized radical). In this case, there is only one allylic position:



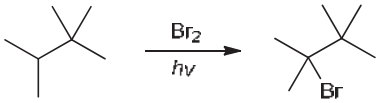
We remove a hydrogen atom from the allylic position and draw the resonance structures of the resulting allylic radical:



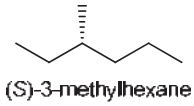
Finally, we use these resonance structures to determine the products, by placing a bromine atom at the position of the unpaired electron in each resonance structure:



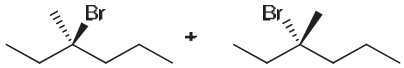
(f) The reagents indicate a radical bromination process. The starting material has only one tertiary position, which undergoes selective bromination, giving the following tertiary alkyl bromide.



10.34. We begin by drawing the starting material, (*S*)-3-methylhexane:

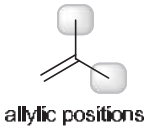


This compound has only one tertiary position, so bromination will occur selectively at that site. In this case, the reaction is occurring at a chiral center, so we expect a racemic mixture:

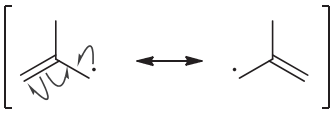


10.35.

(a) We begin by identifying allylic positions. There are two:



But these two positions are identical (symmetry). So, we only need to consider allylic bromination occurring at one of these positions. To do that, we remove a hydrogen atom from the allylic position and draw the resonance structures of the resulting allylic radical:

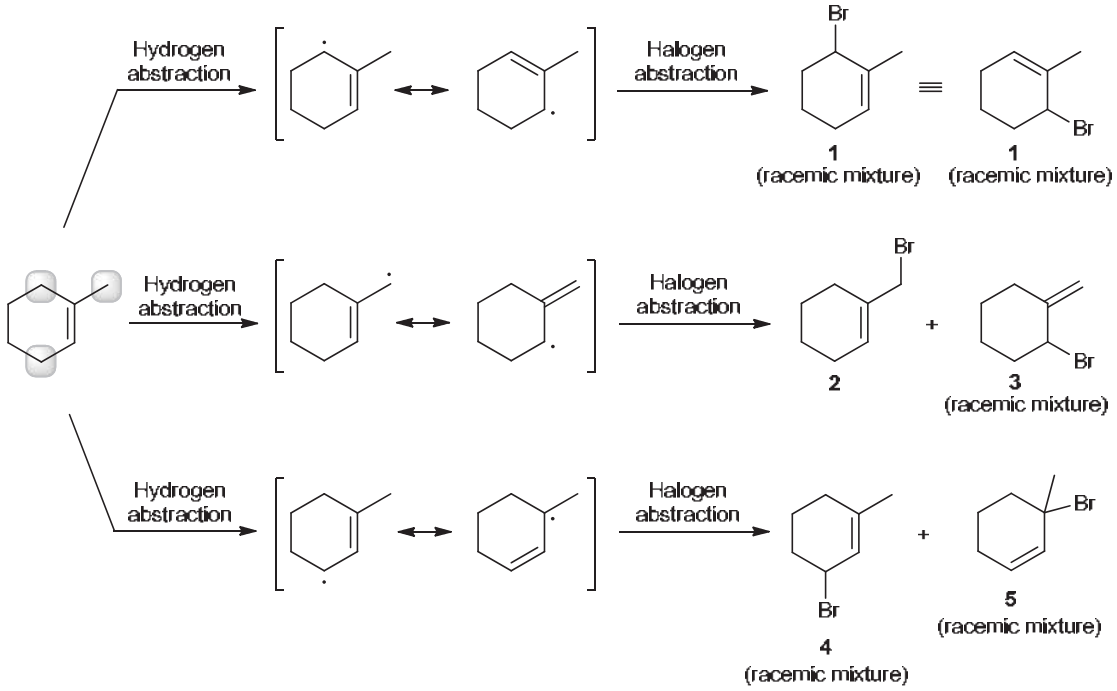


Finally, we use these resonance structures to determine the products, by placing a bromine atom at the position of the unpaired electron in each resonance structure. In this case, the two resulting structures represent the same compound, so only one product is obtained:

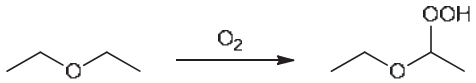


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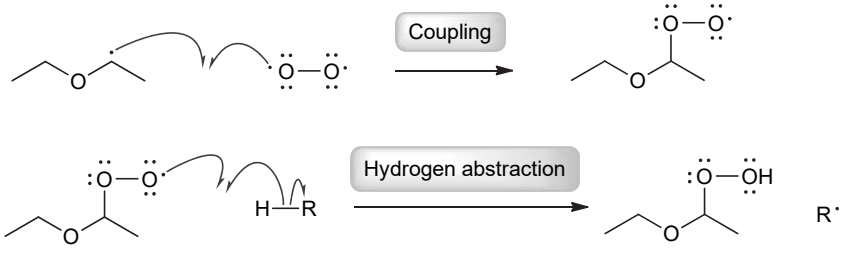
(b) We begin by identifying the allylic positions. There are three of them (highlighted below), each of which can undergo hydrogen abstraction to give a resonance-stabilized radical, shown below. The resulting products are also shown. Notice that there are a total of five products, labeled **1** – **5**. Notice that many of the products exhibit a chiral center, and a racemic mixture is expected in each case.



10.36. As seen in Section 10.9, diethyl ether undergoes autooxidation to give the following hydroperoxide:

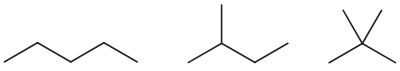


As seen in Mechanism 10.2, autooxidation is believed to occur via two propagation steps. The first is a coupling step, and the second is a hydrogen abstraction, as shown here:



10.37.

(a) Compound **A** has the molecular formula C_5H_{12}, so it must be one of the following three constitutional isomers:

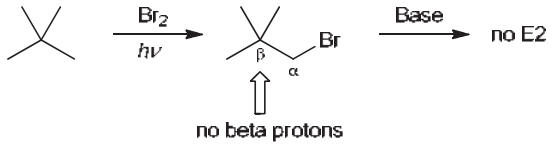


The first compound has no tertiary positions, so we would expect bromination to occur at one of the secondary positions. While there are three such positions in pentane (C2, C3, and C4), two of these positions are identical (C2 = C4). So there are two unique positions that are likely to be brominated: C2 and C3. That is, monobromination of pentane should produce a mixture of 2-bromopentane and 3-bromopentane. So, compound **A** cannot be pentane, because the problem statement indicates that monobromination would result in only one product. The

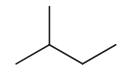
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other two constitutional isomers above are candidates, because each of them would give one alkyl halide as the product. The second compound above (2-methylbutane) will undergo bromination selectively at the tertiary position. For the last compound above (2,2-dimethylpropane), all of the methyl groups are identical, so only one regiochemical outcome is possible.

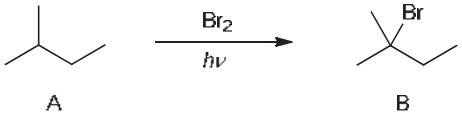
To determine which isomer is compound **A**, we must interpret the other piece of information provided in the problem statement. When compound **B** is treated with a strong base, two products are obtained. This would not be true if compound **A** were 2,2-dimethylpropane, as then, compound B would not undergo elimination at all (it would have no β protons):



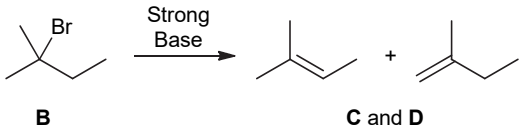
Therefore, compound **A** must be 2-methylbutane:



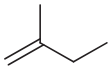
As mentioned, compound **A** undergoes mono-bromination selectively at the tertiary position, giving the corresponding tertiary alkyl halide (compound **B**):



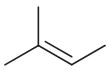
When compound **B** is treated with a strong base, an E2 reaction is expected. Two regiochemical outcomes are possible, so we expect a mixture of both products (the major product is determined by the choice of base, as seen in the remaining parts of this problem):



(b) When compound **B** is treated with *tert*-butoxide (a sterically hindered base), the Hofmann product is favored.



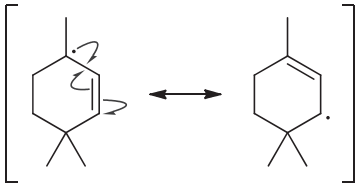
(c) When compound B is treated with sodium ethoxide, the Zaitsev product is favored:



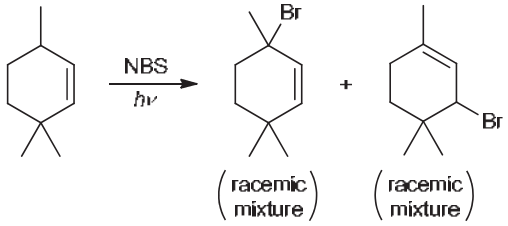
10.38. We begin by identifying the allylic positions. There are two:



But one of these positions (the lower position in the structure above) lacks a hydrogen atom. So this position cannot undergo radical bromination (a C–H bond is necessary because a key step in the mechanism is a hydrogen abstraction step). So, we only need to consider allylic bromination occurring at one position. To do that, we remove a hydrogen atom from that allylic position and draw the resonance structures of the resulting allylic radical:

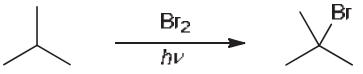


Finally, we use these resonance structures to determine the products, by placing a bromine atom at the position of the unpaired electron in each resonance structure. Notice that each product has a chiral center and is therefore expected to be produced as a racemic mixture:

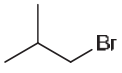


10.39.

(a) Bromination occurs selectively at the tertiary position, giving the following *tert*-butyl bromide:



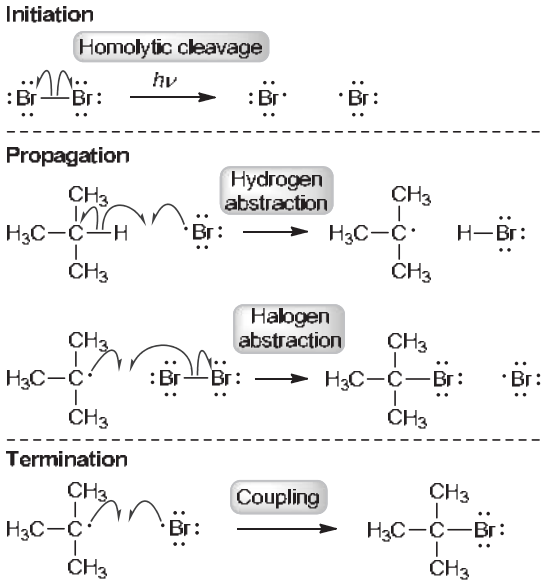
(b) The minor product occurs via bromination at the primary position:



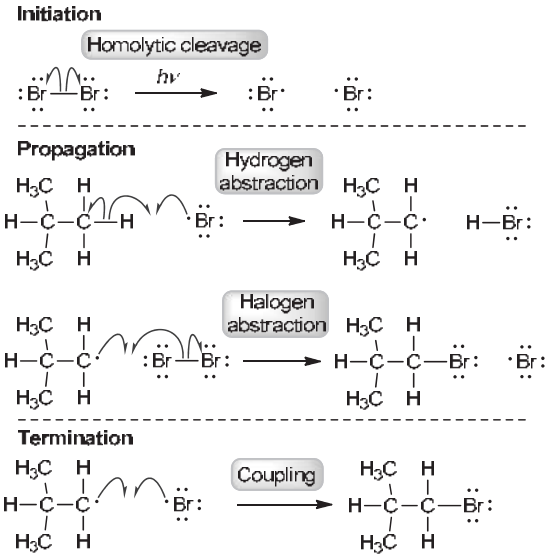
(c) The mechanism will have three distinct stages. The first stage is initiation, in which the Br–Br bond is broken to generate bromine radicals. This step requires

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two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). In the first propagation step, a hydrogen atom is abstracted to give the more stable tertiary radical. In the second step, this radical undergoes halogen abstraction to give the product. There are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown below is a termination step that generates the desired product:



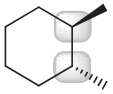
(d) The mechanism will have three distinct stages. The first stage is initiation, in which the Br–Br bond is broken to generate bromine radicals. This step requires two fishhook arrows, as shown. There are two propagation steps (hydrogen abstraction and halogen abstraction), each of which requires three fishhook arrows (to show the bonds being broken and formed). In the first propagation step, a hydrogen atom is abstracted to give the less stable primary radical (we are drawing the mechanism that leads to the minor product). In the second step, this radical undergoes halogen abstraction to give the product. There are many steps that can serve as termination steps, because there are many radicals that can couple together under these conditions. Shown here is a termination step that generates the desired product:



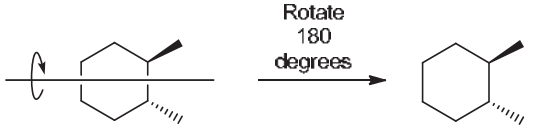
(e) The minor product is only formed via a primary radical, which does not readily form under bromination conditions. Indeed, in this case, the minor product represents less than 1% of the product distribution (as seen in the textbook, just before SkillBuilder 10.5). The tertiary radical is selectively formed, which leads to the tertiary alkyl bromide as the major product.

10.40.

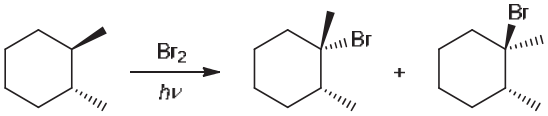
(a) There are two tertiary positions in this case, highlighted here:



But these positions are identical, because they can be interchanged by an axis of symmetry, shown here (when we rotate 180 degrees about this axis, the same image is regenerated – you might want to build a molecular model to prove this to yourself):



So we only need to consider bromination at one of these positions (either one will lead to the same products). Since the reaction occurs at a chiral center, we expect monobromination to give both possible configurations (*R* and *S*) for that chiral center. The configuration of the other chiral center (not involved in the reaction) is retained. Therefore, the products are diastereomers:

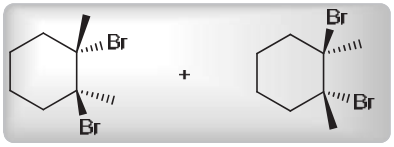


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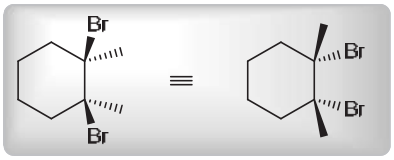
(b) The starting compound has two tertiary positions, so dibromination will install one bromine atom at each of the tertiary positions:



Each chiral center can be produced with either the *R* or *S* configuration, so all possible stereoisomers are expected. With two chiral centers, we might expect four stereoisomers (2^n, where n = # of chiral centers = 2). However, in this case, there are only three stereoisomers, because one of them is a *meso* compound, shown here. (For a review of *meso* compounds, see Section 5.6)



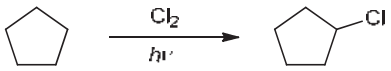
enantiomers



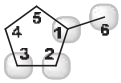
a *meso* compound

10.41. Methyl radicals are less stable than *tert*-butyl radicals so the former react with each other more rapidly than the latter. Also, methyl radicals are less hindered than *tert*-butyl radicals, so the former react with each other more rapidly than the latter.

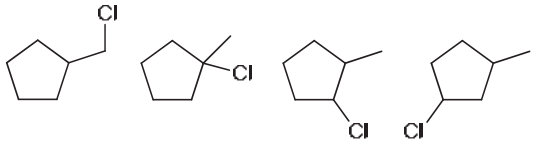
10.42.
(a) Monochlorination of cyclopentane gives only one product, because a reaction at any position generates the same product as a reaction at any other position:



(b) This compound has six carbon atoms, but there are only four unique positions (highlighted) where chlorination can occur:

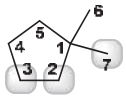


Chlorination at C4 produces the same result as chlorination at C3, and chlorination at C5 produces the same result as chlorination at C2. Therefore, the following four constitutional isomers are expected:

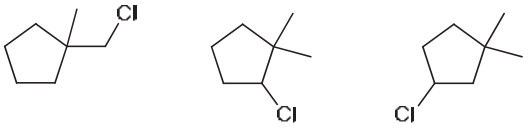


The last two structures have chiral centers and are therefore produced as mixtures of stereoisomers. But this can be ignored for purposes of solving this problem, because the problem statement asks for the number of *constitutional isomers* that are obtained.

(c) This compound has seven carbon atoms, but there are only three unique positions (highlighted) where chlorination can occur:

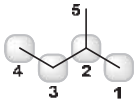


Chlorination cannot occur at C1, because that position does not have a C–H bond (which is necessary, because hydrogen abstraction is the first step of the chlorination process). Chlorination at C4 produces the same result as chlorination at C3; chlorination at C5 produces the same result as chlorination at C2; and chlorination at C6 produces the same result as chlorination at C7. Therefore, the following three constitutional isomers are expected:

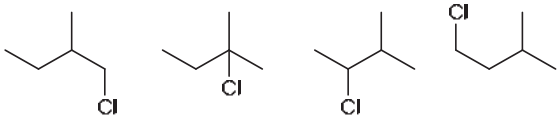


Each of the last two structures has a chiral center and is therefore produced as a mixture of enantiomers. But this can be ignored for purposes of solving this problem, because the problem statement asks for the number of *constitutional isomers* that are obtained.

(d) This compound has five carbon atoms, but there are only four unique positions (highlighted) where chlorination can occur:



Chlorination at C5 produces the same result as chlorination at C1. Therefore, the following four constitutional isomers are expected:

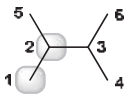


The first structure has a chiral center and is therefore produced as a racemic mixture of enantiomers. The same is true of the third structure above. But this can be

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ignored for purposes of solving this problem, because the problem statement asks for the number of *constitutional isomers* that are obtained.

(e) This compound has six carbon atoms, but there are only two unique positions (highlighted) where chlorination can occur:

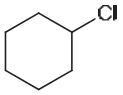


Chlorination at C3 produces the same result as chlorination at C2. Similarly, chlorination at C4, C5, or C6 produces the same result as chlorination at C1. Therefore, the following two constitutional isomers are expected:

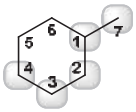


The first structure has a chiral center and is therefore produced as a racemic mixture of enantiomers. But this can be ignored for purposes of solving this problem, because the problem statement asks for the number of *constitutional isomers* that are obtained.

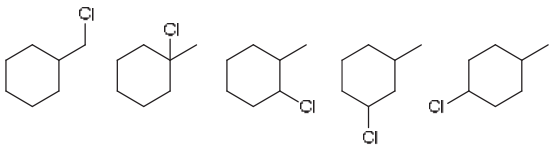
(f) Monochlorination of cyclohexane gives only one product, because a reaction at any position generates the same product as a reaction at any other position:



(g) This compound has seven carbon atoms, but there are only five unique positions (highlighted) where chlorination can occur:



Chlorination at C5 produces the same result as chlorination at C3, and chlorination at C6 produces the same result as chlorination at C2. Therefore, the following five constitutional isomers are expected:

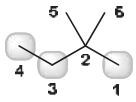


Each of the last three structures is produced as a mixture of stereoisomers. But this can be ignored for purposes of solving this problem, because the problem statement asks for the number of *constitutional isomers* that are obtained.

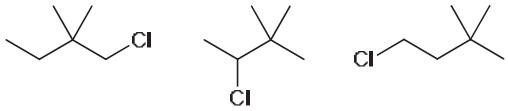
(h) This compound has eight carbon atoms, but two of them (the two central carbon atoms) cannot undergo chlorination because they lack a C–H bond. The remaining six carbon atoms (the methyl groups) all are identical, because a reaction at any position generates the same product as a reaction at any other position.



(i) This compound has six carbon atoms, but there are only three unique positions (highlighted) where chlorination can occur:

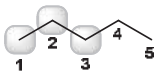


Chlorination cannot occur at C2, because that position lacks a C–H bond. Chlorination at C5 or C6 produces the same result as chlorination at C1. Therefore, the following three constitutional isomers are expected:

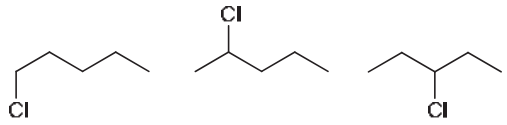


The middle structure has a chiral center and is therefore produced as a racemic mixture of enantiomers. But this can be ignored for purposes of solving this problem, because the problem statement asks for the number of *constitutional isomers* that are obtained.

(j) This compound has five carbon atoms, but there are only three unique positions (highlighted) where chlorination can occur:



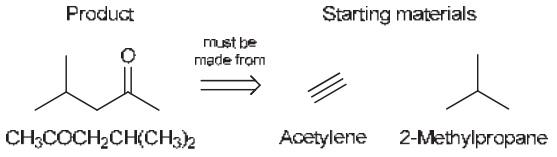
Chlorination at C4 produces the same result as chlorination at C2, and chlorination at C5 produces the same result as chlorination at C1. Therefore, the following three constitutional isomers are expected:



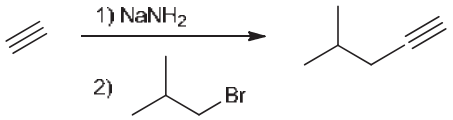
The middle structure has a chiral center and is therefore produced as a racemic mixture of enantiomers. But this can be ignored for purposes of solving this problem, because the problem statement asks for the number of *constitutional isomers* that are obtained.

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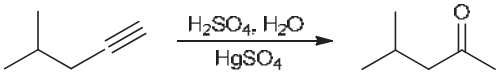
10.43. Let's begin by drawing our product and starting materials, so that we can see them more clearly:



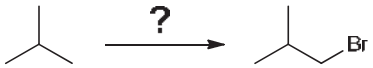
The starting materials have two carbon atoms and four carbon atoms, respectively, while the product has six carbon atoms. Therefore, we must find a way to join the starting materials. So far, we have only seen one way to make a carbon-carbon bond. Specifically, acetylene can undergo alkylation, as shown here:



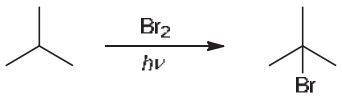
The resulting terminal alkyne can then be converted into the desired product via acid-catalyzed hydration in the presence of mercuric sulfate:



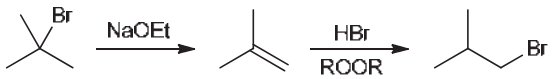
All that remains is to show how the starting alkane (2-methylpropane) can be converted into the necessary primary alkyl halide:



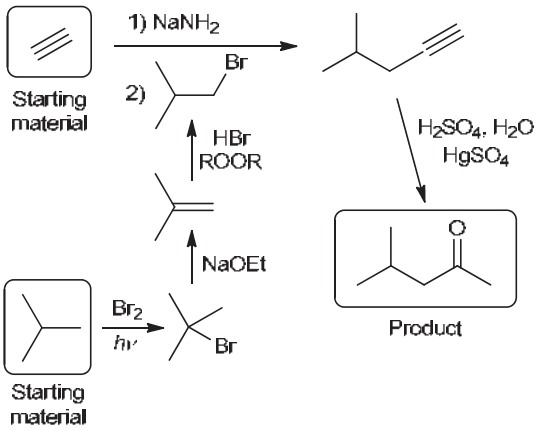
Radical bromination will indeed install a bromine atom, but this occurs selectively at the tertiary position:



This tertiary alkyl bromide must now be converted into the desired primary alkyl bromide. That is, we must move the position of the bromine atom, which can be accomplished via elimination, followed by *anti*-Markovnikov addition of HBr:

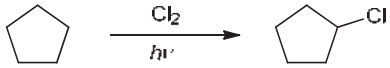


In summary, the entire synthesis is shown here:

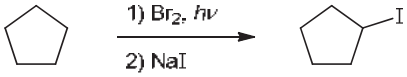


10.44.

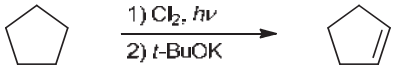
(a) This transformation can be achieved via radical chlorination (under conditions that favor monochlorination):



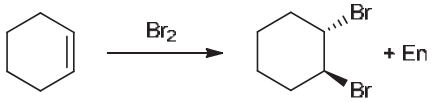
(b) Radical iodination is not a feasible process (it is not thermodynamically favorable), so we cannot directly iodinate the starting cycloalkane. However, radical bromination can be performed, followed by an S_N2 reaction in which iodide replaces bromide:



(c) We have not seen a way to convert an alkane into an alkene in one step. However, it can be achieved in two steps. First, radical chlorination or bromination can be performed, thereby installing a leaving group, which then allows for an E2 process with a strong base to give the desired product. Any strong base can be used (there is only one regiochemical outcome, so a sterically hindered base is not required). It is acceptable to use hydroxide, methoxide or ethoxide for the E2 process. That being said, in this particular case, *tert*-butoxide will likely be more efficient, as it will suppress the competing S_N2 process (we would expect S_N2 to give a minor product if the base is not sterically hindered).

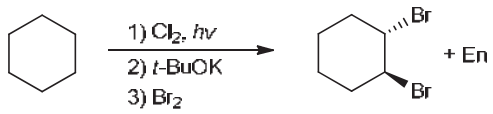


(d) The product is a *trans*-dibromide, so the last step of the synthesis is likely to be addition of Br_2 across a π bond:

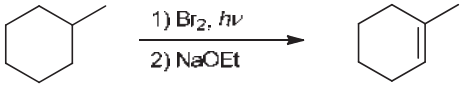


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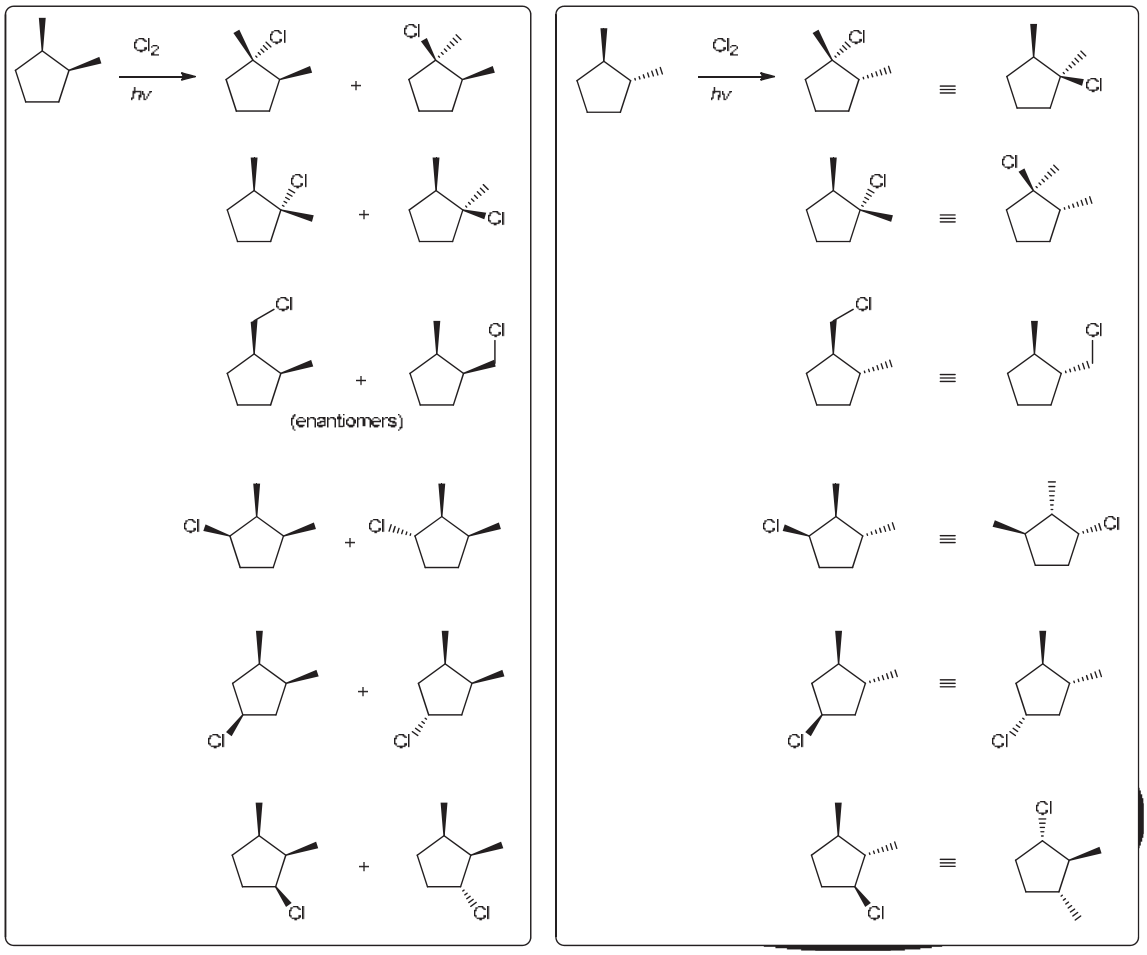
To make the desired alkene (cyclohexene) from the starting compound (cyclohexane), we use the same approach taken in the solution to part (c). That is, we perform radical chlorination or bromination to install a leaving group, which then allows for an E2 process with a strong base to give the desired product. Once again, *tert*-butoxide will likely be more efficient, as it will suppress the competing S_N2 process. In summary, the desired transformation can be achieved via the following three-step synthesis:



(e) Radical bromination installs a bromine atom selectively at the tertiary position. Then, a strong base is used to give an E2 reaction (Zaitsev product, since the base employed is not sterically hindered):



10.45. *cis*-1,2-Dimethylcyclopentane produces six pairs of compounds, where each pair have a diastereomeric relationship (except for one pair, which is enantiomeric, indicated below). In contrast, *trans*-dimethylcyclopentane produces only six different compounds, as shown below:



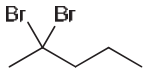
10.46.

(a) Recall that ΔG has two components: (ΔH) and (-TΔS). The first term is positive, so the second term must have a large negative value in order for ΔG to be negative (which is necessary in order for the process to be thermodynamically favorable). This will be the case if ΔS and T are both large and positive (T cannot be negative). At high T, both of these terms are indeed large. ΔS is large and positive because one chemical entity is being converted into two chemical entities, which significantly increases the entropy of the system.

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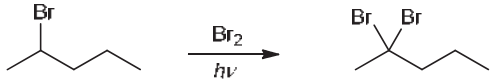
(b) Recall that ΔG has two components: (ΔH) and (-TΔS). The magnitude of the latter term is dependent on the temperature. At high temperature, the latter term dominates over the former, and the reaction is thermodynamically favorable. However, at low temperature, the first term (enthalpy) dominates, and the reaction is no longer thermodynamically favored.

10.47. Bromination of compound **A** gives 2,2-dibromopentane:



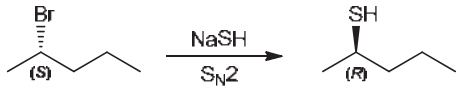
2,2-dibromopentane

So compound **A** must be 2-bromopentane:



Compound A

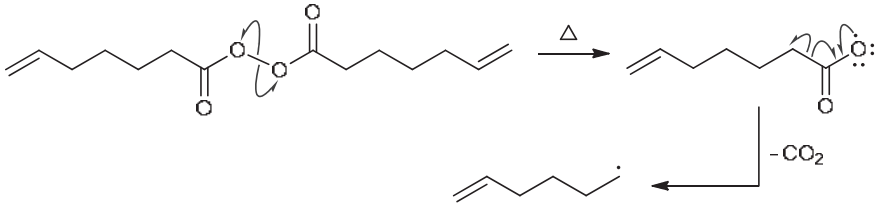
Compound **A** exhibits one chiral center. The problem statement provides the information that is necessary to determine the configuration of this chiral center. Specifically, we are told that treating compound **A** with a strong nucleophile (S_N2 conditions) results in a product with the *R* configuration. Since S_N2 reactions proceed via inversion of configuration, the chiral center must have the *S* configuration in compound **A**:



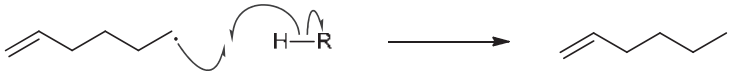
Compound A
(*S*)-2-bromopentane

10.48. The first propagation step in a bromination process is generally slow. In fact, this is the source of the selectivity for bromination processes. A pathway via a secondary radical will be significantly lower in energy than a pathway via a primary radical. As a result, bromination occurs predominantly at the more substituted (secondary) position. However, when chlorine is present, chlorine radicals can perform the first propagation step (hydrogen abstraction) very rapidly, and with little selectivity. Under these conditions, primary radicals are formed almost as readily as secondary radicals. The resulting radicals then react with bromine in the second propagation step to yield monobrominated products. Therefore, in the presence of chlorine, the selectivity normally observed for bromination is lost.

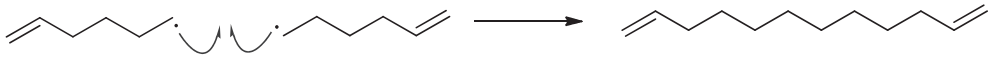
10.49. As shown in the problem statement, an acyl peroxide will undergo cleavage to give a radical that can then lose carbon dioxide:



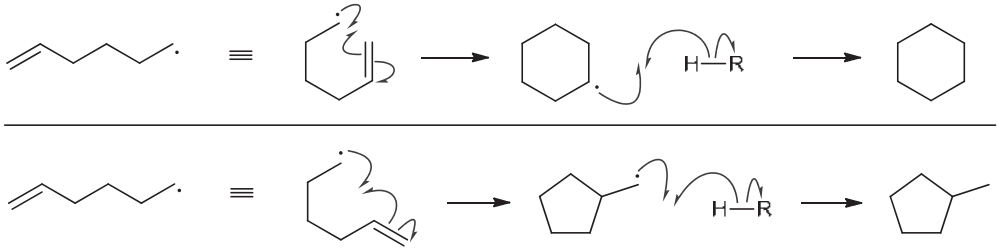
This radical is responsible for the formation of each of the reported products. The first product is formed when the radical undergoes hydrogen abstraction:



The second product is formed when two of the radicals couple with each other, as shown:



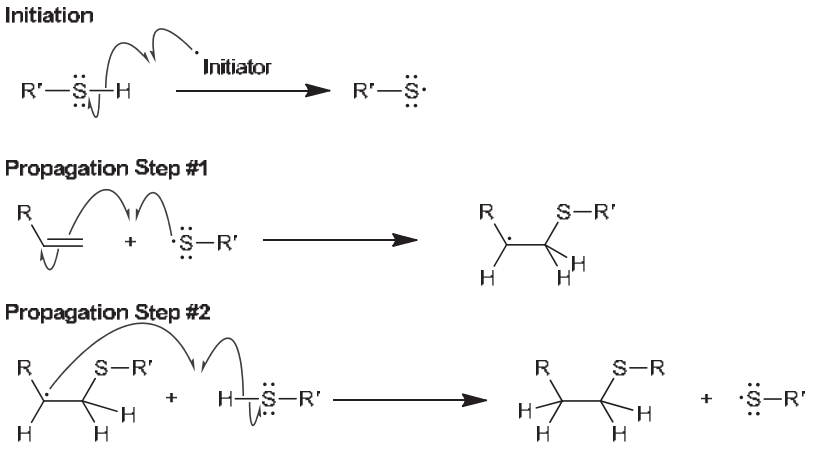
And finally, each of the cyclic products is formed via addition to a π bond (in an intramolecular fashion), followed by hydrogen abstraction:



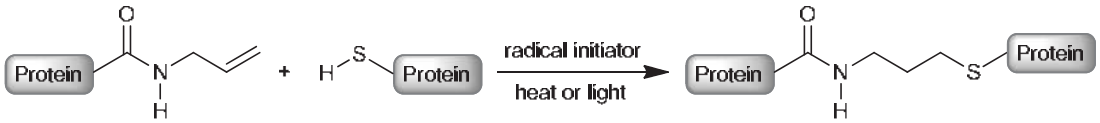
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10.50.

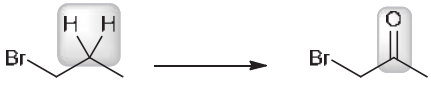
(a) In this reaction, two groups (R′S and H) are being added across the π bond in an *anti*-Markovnikov fashion. This reaction resembles the *anti*-Markovnikov addition of HBr across a π bond (Section 10.10). Using that reaction as a guide, we can draw the following initiation and propagation steps. In the initiation step, an R′S radical is formed. The first propagation step is an addition to a π bond, and the second propagation step is a hydrogen abstraction to regenerate an R′S radical.



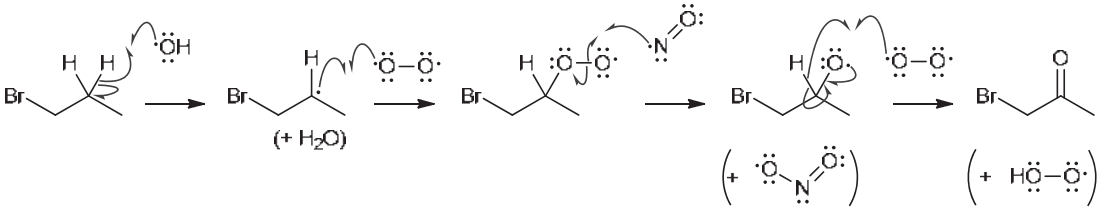
(b) We expect an *anti*-Markovnikov addition of R′S and H across the π bond, as follows:



10.51. Overall, in this oxidation reaction, the two C-H bonds on the central carbon atom are replaced with a C=O double bond, as shown below. It is useful to keep this in mind as we draw our mechanism.

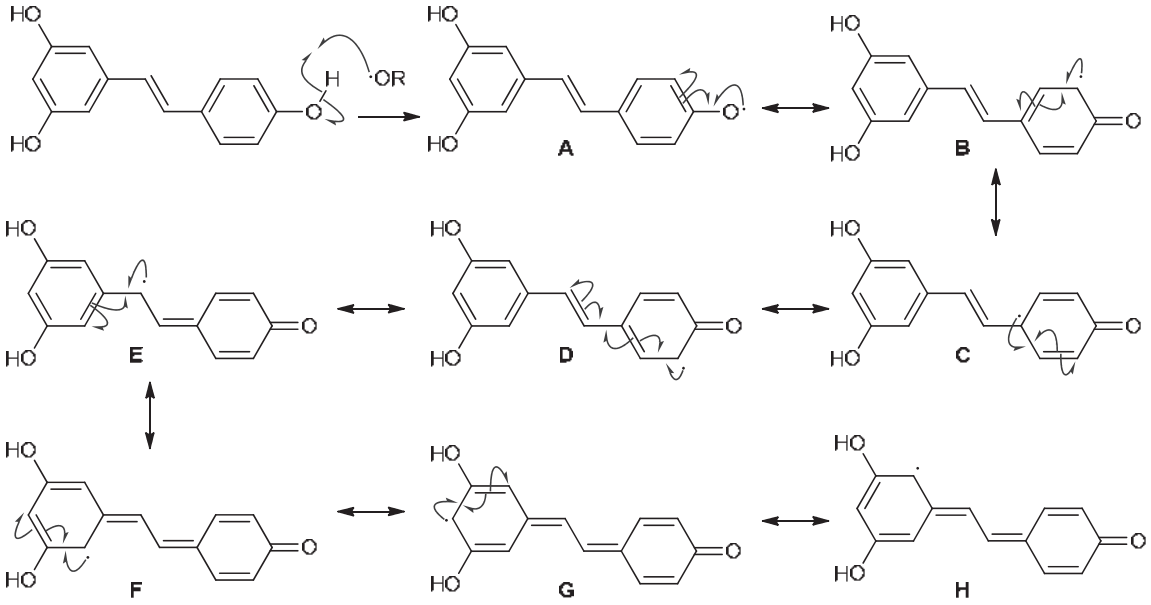


The following mechanism is described in the problem statement.

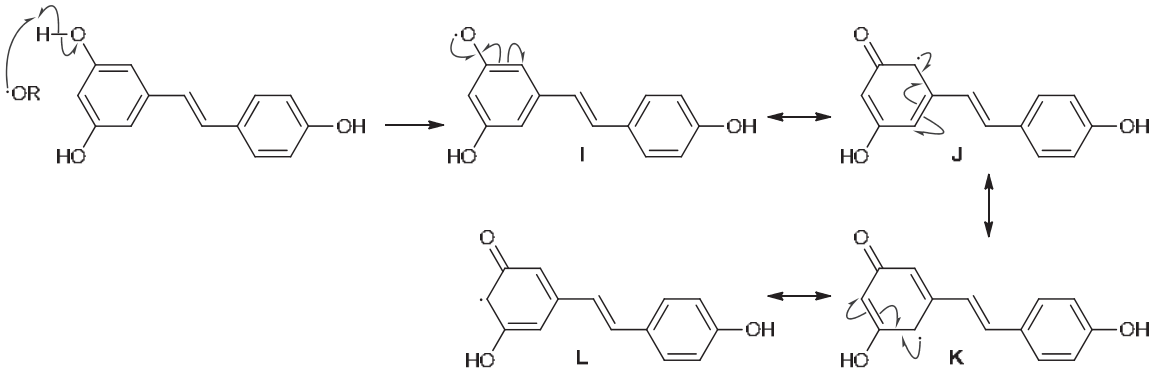


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10.52.
Abstraction of any of the hydrogen atoms attached to carbon leads to a vinyl radical that is not resonance stabilized. Abstraction of any of the hydrogen atoms attached to oxygen leads to a resonance-stabilized radical. Thus, we should focus our attention on the three hydroxyl groups.
Abstraction of a hydrogen atom from the hydroxyl group on the right side of the molecule leads to a radical with eight reasonable resonance structures, as shown below (**A-H**).



Abstraction of a hydrogen atom from either of the hydroxyl groups on the left side of the molecule leads to a radical with four reasonable resonance structures, as shown here (**I-L**).

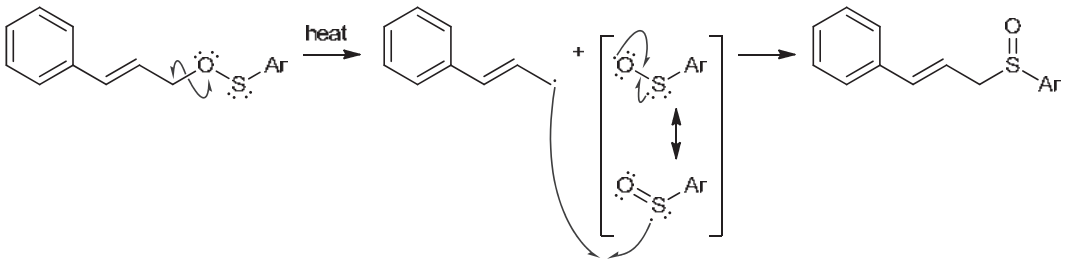


This suggests that the hydrogen atom of the hydroxyl group on the right side of the molecule is more susceptible to abstraction because it leads to the formation of a more stable radical.

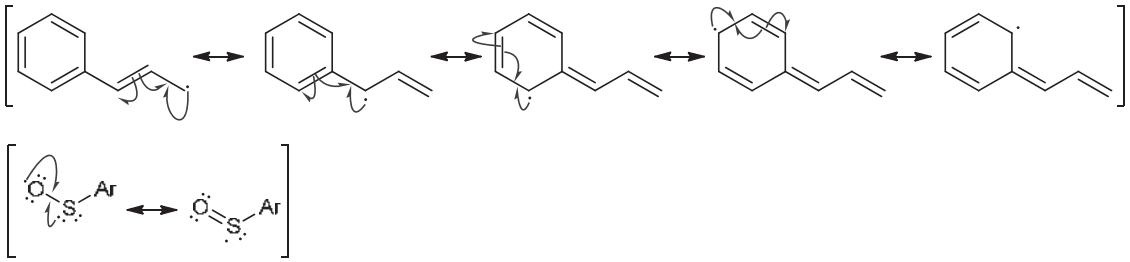
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10.53.

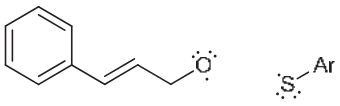
(a) In the first step, the C-O bond undergoes homolytic cleavage, yielding the two radicals shown. A resonance structure of the sulfoxide radical demonstrates that the unpaired electron is delocalized over the oxygen and sulfur atoms, as shown. Recombination of the radicals then provides the product, as shown.



(b) To propose an explanation for the scission of the C-O bond over the O-S bond, we must analyze the radicals formed from each of these homolytic cleavages. The radicals formed from cleavage of the C-O bond are both resonance stabilized, as shown below. Note that the sulfoxide radical is also further resonance-stabilized by the adjacent aromatic ring (not shown). The formation of these resonance-stabilized radicals is consistent with facile bond cleavage.

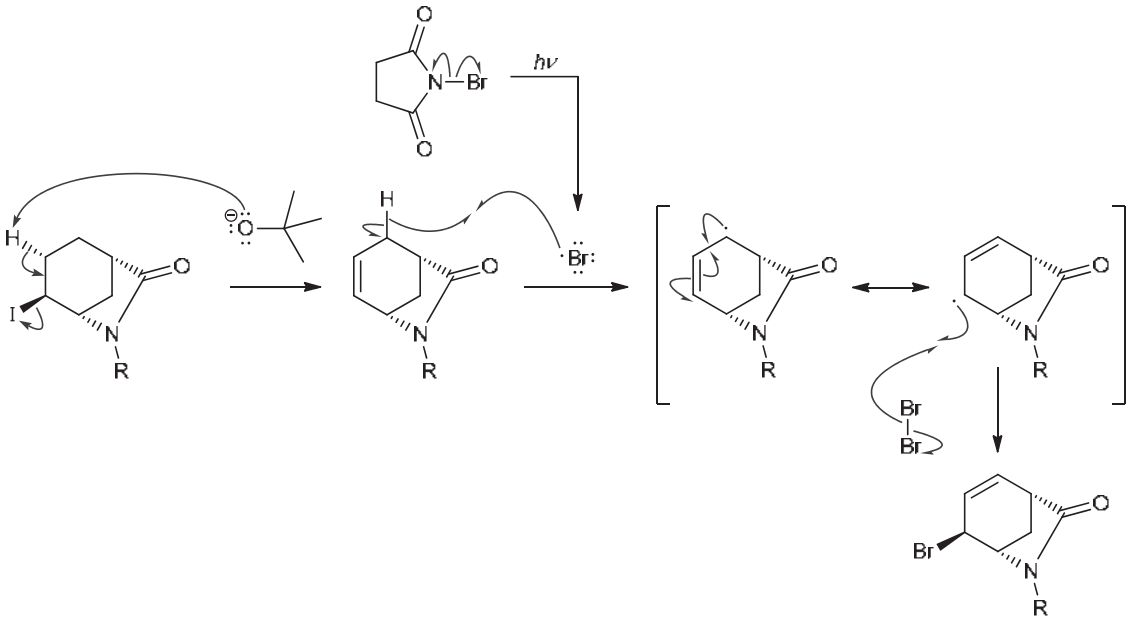


The radicals formed from homolytic cleavage of the O-S bond are shown below. The oxygen radical is not resonance-stabilized. The sulfur radical is resonance-stabilized due to being adjacent to an aromatic ring. However, analogous resonance stabilization is also present in the sulfoxide radical shown above, so this does not provide any additional relative stabilization.

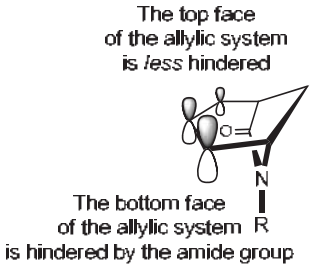


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10.54.
In the first step, *tert*-butoxide is a strong, sterically hindered base, so we expect an E2 process, generating an alkene. Then, when treated with NBS under radical conditions, the alkene undergoes hydrogen abstraction to give a resonance stabilized radical, followed by halogen abstraction to generate the product.



To rationalize the observed stereochemical outcome, consider the two faces of the allylic system (which are essentially the two faces of the six-membered ring). Notice that the bottom face is blocked by the amide. As a result, it would be difficult for bromine to react on this face of the molecule. This steric consideration can successfully explain why bromine traps the carbon radical on the top face of the molecule, leading to the observed stereochemical outcome.



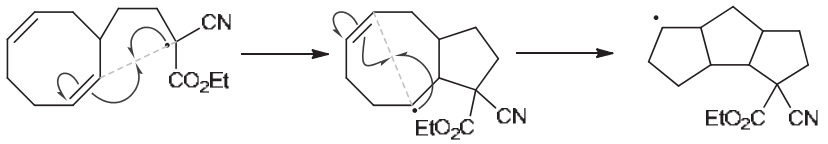
10.55 When an aromatic compound bearing an alkyl side chain is treated with excess NBS, all benzylic hydrogen atoms will be replaced with bromine atoms. The correct answer is therefore (c).

10.56 Iodination is the only reaction that is expected to be thermodynamically unfavorable (positive ΔG). Fluorination, chlorination and bromination are all expected to be thermodynamically favorable (negative ΔG), although fluorination will be too violent to be practically useful. The correct answer is (b).

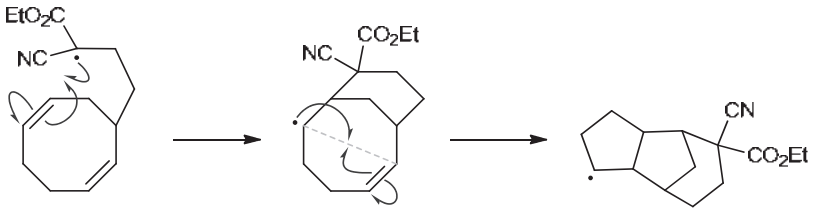
10.57 Hydrogen abstraction is the first propagation step in radical bromination. The weakest C-H bond (the one with the smallest BDE) will be broken during this step. For a simple alkene, like 1-butene, an allylic C-H bond will be the weakest C-H bond, giving an allylic radical intermediate after bond cleavage. The correct answer is (c). The first two possibilities, (a) and (b), are vinylic radicals which are too high in energy to form. The fourth possibility (d) is a primary radical and is significantly less stable than an allylic radical.

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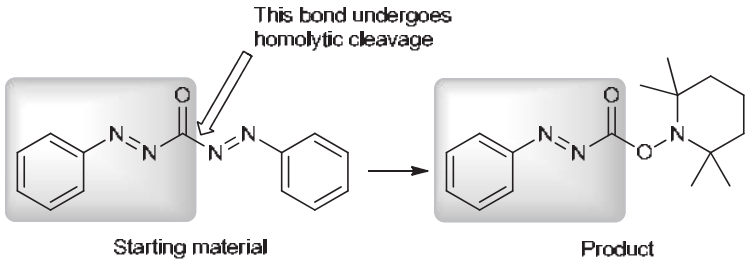
10.58. The first tricyclic radical can be formed with the following two steps. First, the initial radical undergoes an intramolecular addition to a π bond, generating a 5-membered ring and a new radical. This radical once again undergoes addition to a π bond, destroying the second π bond and resulting in the formation of two 5-membered rings and a new radical.



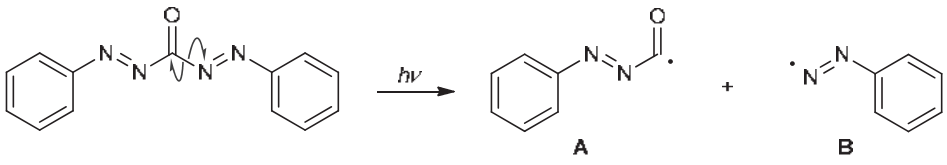
The second tricyclic radical can be formed if the initial radical undergoes addition with the π bond that is farther away, followed by another addition with the remaining π bond.



10.59. A comparison of the first product with the starting material reveals which bond in the starting material undergoes homolytic cleavage:

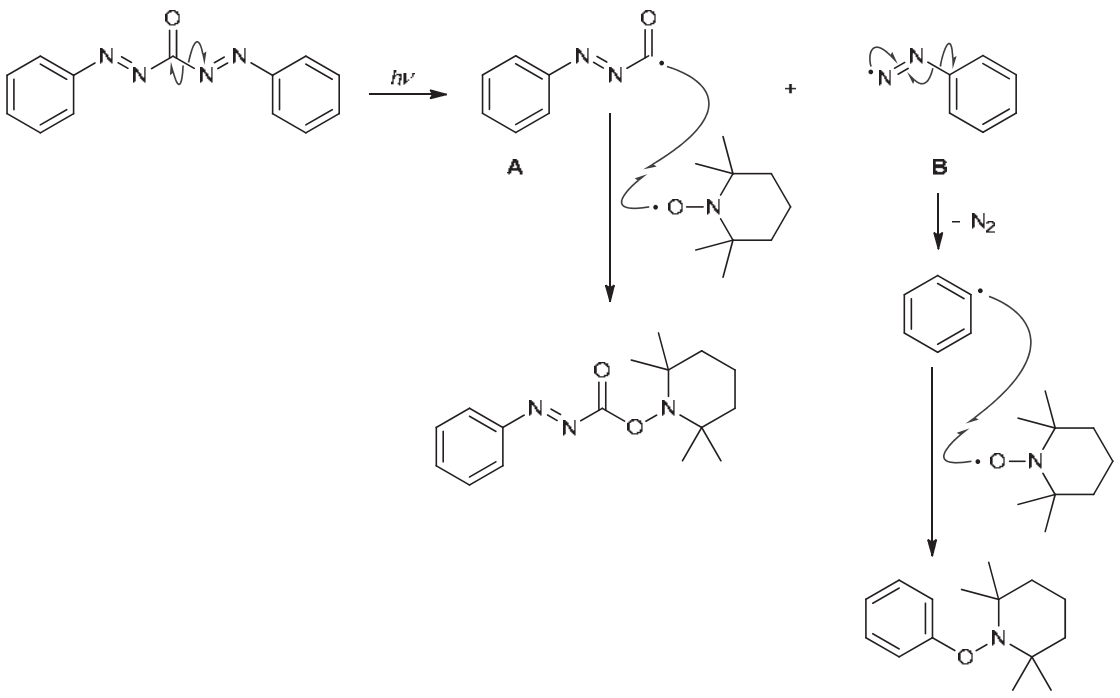


So we begin our mechanism by drawing homolytic cleavage of that bond, giving two radicals (**A** and **B**):



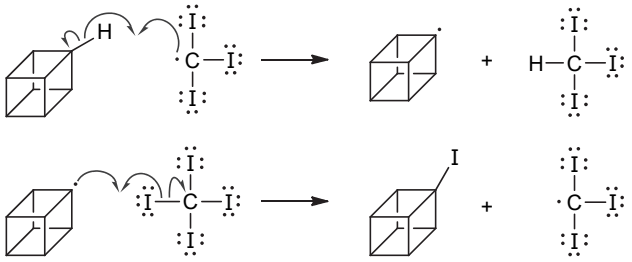
Radical **A** then reacts with TEMPO to give the first product, while radical **B** undergoes further homolytic cleavage to give nitrogen gas and a phenyl radical, which reacts with TEMPO to give the second product.

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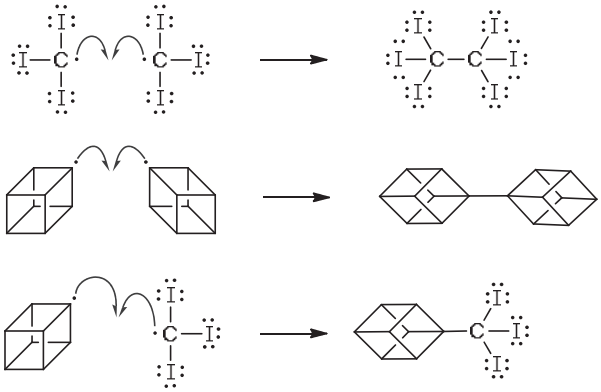


10.60.

(a) The first step of the propagation cycle is abstraction of a proton from cubane, generating a cubyl radical. In the second step of the propagation cycle, halogen abstraction gives the product (iodocubane) and also regenerates the triiodomethyl radical.

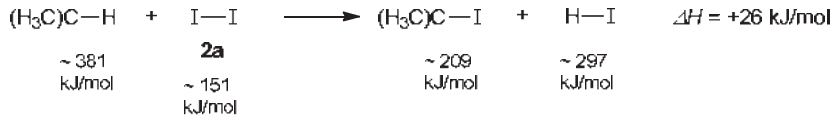


(b) Termination steps generally involve the coupling of two radicals. The following coupling reactions are all possible termination steps.



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(c) Recall (Section 10.4) that for radical halogenation reactions, $\Delta G \approx \Delta H$. For the iodination of an alkane with I_2 (compound **2a**), ΔH will have a positive value:

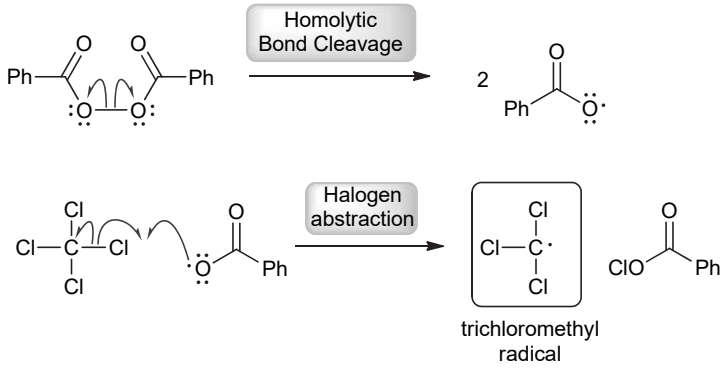


Since ΔH for the reaction is positive, ΔG for the reaction will also be positive. Therefore, the reaction is thermodynamically unfavorable. This argument is expected to hold true for cubane as well, assuming that the BDE for the C–H bond in cubane is not too different from the BDE for the C–H bond in $(CH_3)_3CH$. That is, iodination of cubane with molecular iodine (**2a**) is unfavorable.

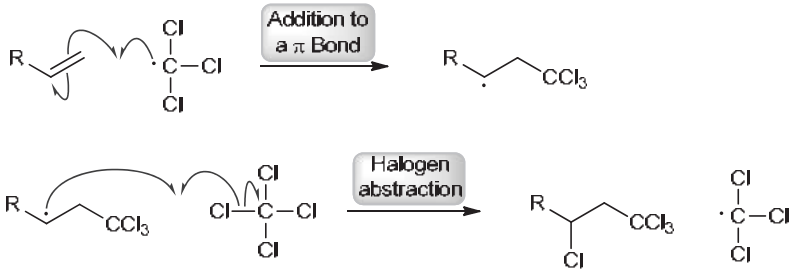
In contrast, when **2b** is used as the reagent for iodination, ΔH for the reaction will be negative, which gives a negative value for ΔG. This can be rationalized by comparing the BDE values for **4a** and **4b**. The BDE of **4a** is 297 kJ/mol, while the BDE of **4b** is 423 kJ/mol. This significant difference in BDE values causes ΔH for the reaction to be negative when **2b** is used rather than **2a**. Recall that bonds broken require an input of energy, contributing to a positive value of ΔH, while bonds formed release energy when they are formed, contributing to a negative value of ΔH. Since the bonds in **4a** and **4b** are being formed during the process, a large BDE (such as that of **4b**) will contribute to a negative value of ΔH, while a small BDE (such as that of **4a**) will contribute to a positive value of ΔH.

10.61.

(a) Benzoyl peroxide is a radical initiator, and upon heating, it readily undergoes homolytic bond cleavage, giving resonance-stabilized radicals. These radicals can then abstract a halogen from CCl_4 in a halogen abstraction step to give a trichloromethyl radical ($Cl_3C\bullet$), shown below.



There are two propagation steps, shown below. In the first propagation step, the π bond reacts with a trichloromethyl radical to give the more stable secondary radical (rather than the less stable primary radical). This step explains the regiochemical outcome of the process. Then, in the second propagation step, a halogen abstraction gives the product and regenerates the reactive intermediate ($Cl_3C\bullet$), as expected for a propagation cycle.

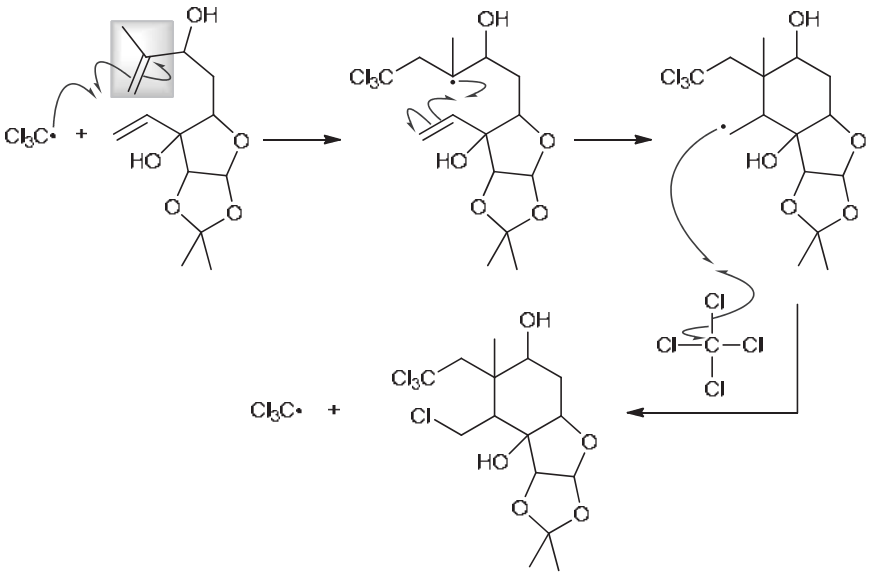


(b) The initiation steps are the same as those for a standard Kharasch reaction [see the initiation steps in part (a) of this problem]

Based on our answer to part (a), we expect the first propagation step to involve addition of $Cl_3C\bullet$ across a π bond. In this case, there are two π bonds. The $Cl_3C\bullet$ radical can react with either π bond, but reaction with the more substituted alkene (di-substituted) affords the more stable 3° radical. This intermediate radical can then add to the other π bond

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(mono-substituted) to afford a primary radical that quickly reacts with CCl_4 to give the desired product. Once again, notice that the final propagation step involves regeneration of the reactive intermediate, $Cl_3C\bullet$, as expected for a propagation cycle.



Chapter 11
Synthesis

Review of Concepts

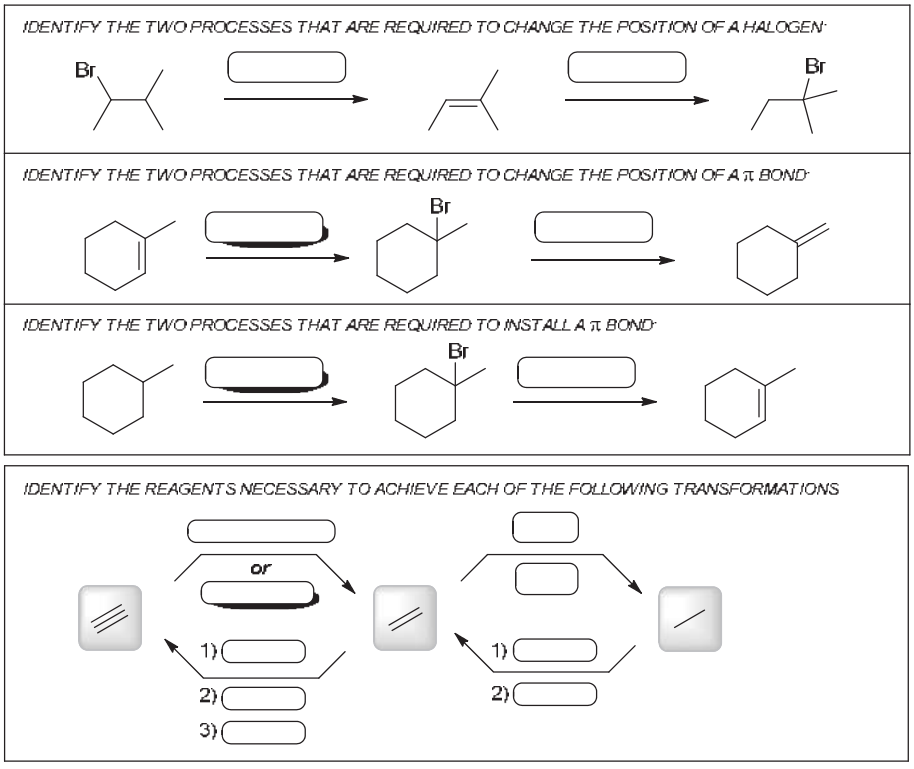
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 11. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- The position of a halogen can be moved by performing _____ followed by _____.
- The position of a π bond can be moved by performing _____ followed by _____.
- An alkane can be functionalized via radical _____.
- Every synthesis problem should be approached by asking the following two questions:
  1. Is there any change in the _____?
  2. Is there any change in the identity or location of the _____?
- In a _____ **analysis**, the last step of the synthetic route is first established, and the remaining steps are determined, working backwards from the product.

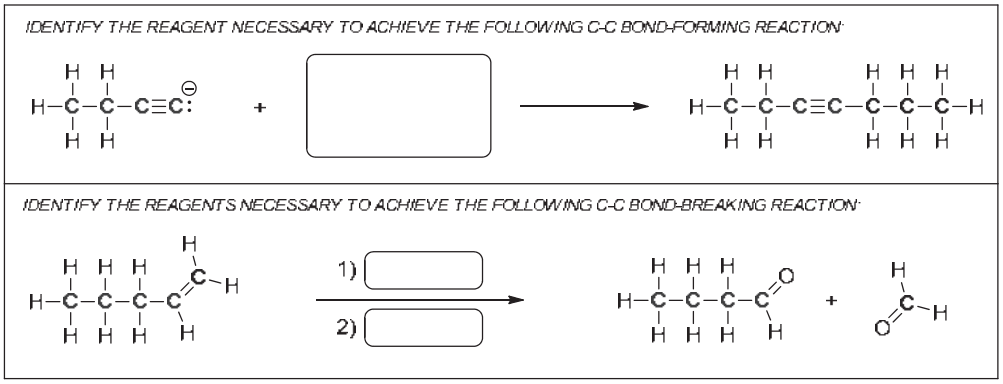
Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 11. The answers appear in the section entitled *SkillBuilder Review*.

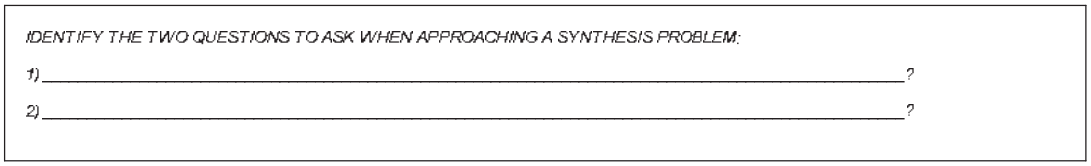
11.1 Changing the Identity or Position of a Functional Group



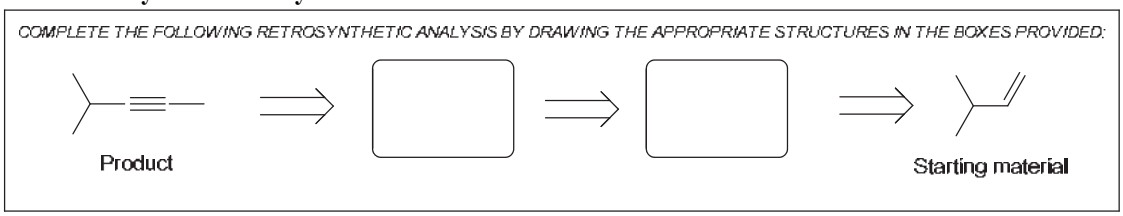
11.2 Changing the Carbon Skeleton



11.3 Approaching a Synthesis Problem by Asking Two Questions



11.4 Retrosynthetic Analysis



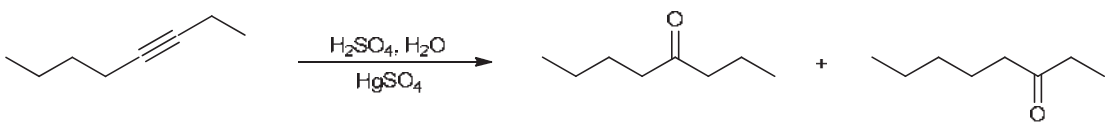
Useful Reagents:

This chapter does not cover any new reactions. As such, there are no new reagents in this chapter. The problems in this chapter require the use of the reagents covered in previous chapters (specifically, Chapter 3 and Chapters 7-10). For each of those chapters, a summary of reagents can be found in the corresponding chapters of this solutions manual.

Common Mistakes to Avoid

When proposing a synthesis, avoid drawing curved arrows (unless the problem statement asks you to draw a mechanism). So often, students will begin drawing mechanism, rather than a synthesis, when asked to propose a synthesis. If you look through all of the solutions to the problems in this chapter, you will find that none of the solutions exhibit curved arrows.

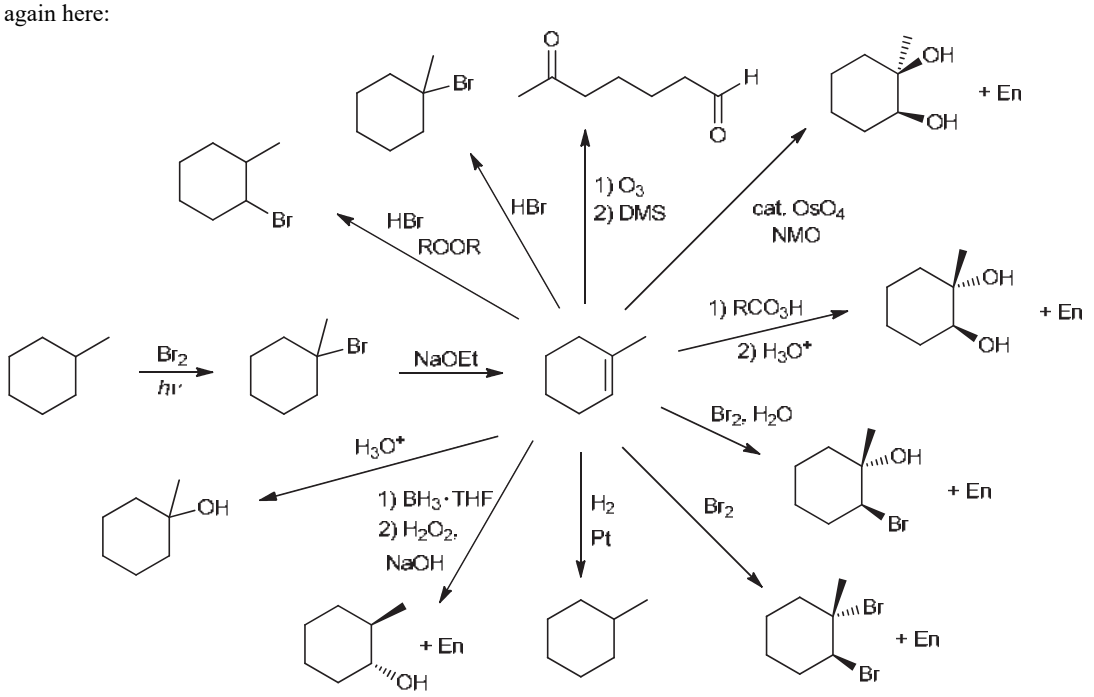
Also, avoid using steps for which you have no control over the regiochemical outcome or the stereochemical outcome. For example, acid-catalyzed hydration of the following alkyne will produce two different ketones.



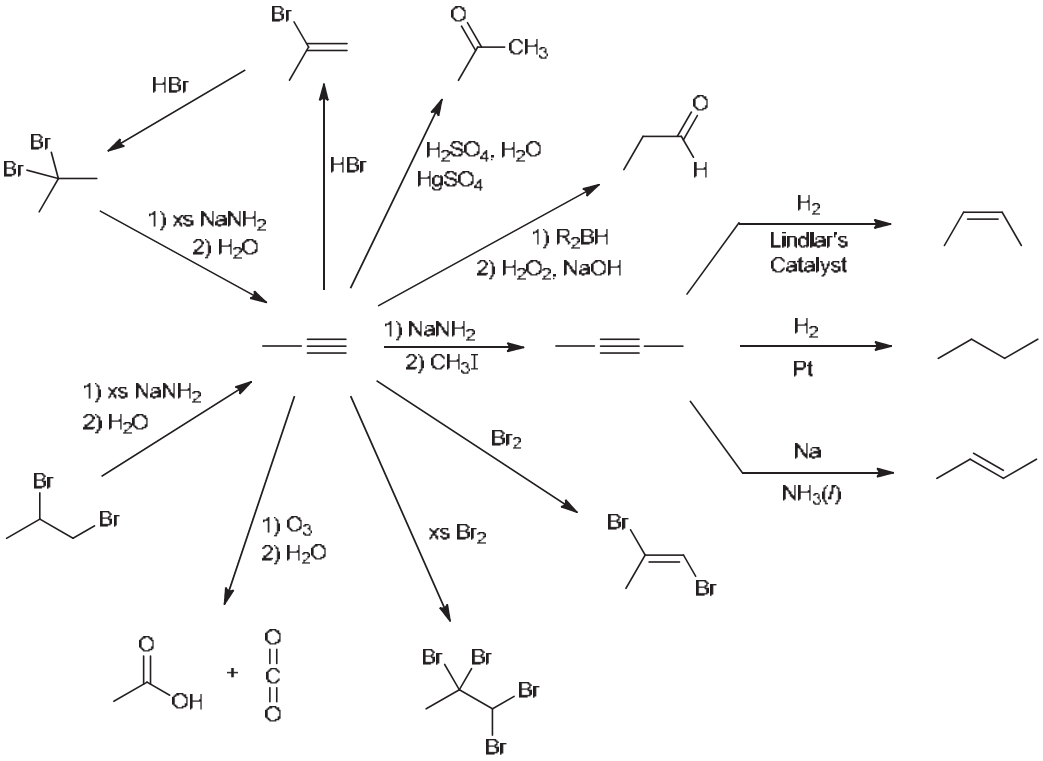
This process should not be used if only one of these ketones is desired.

Solutions

11.1. The reagents for these reactions can be found in the summary material at the end of Chapter 8. They are shown again here:



11.2. The reagents for these reactions can be found in the summary material at the end of Chapter 10. They are shown again here:



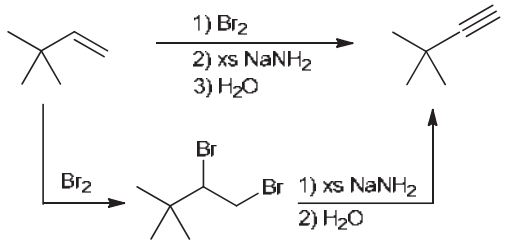
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11.3.

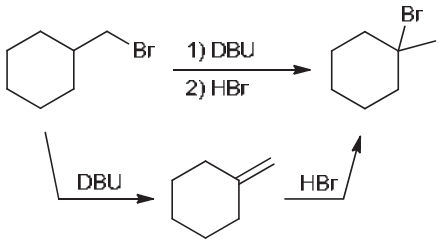
(a) We begin by analyzing the identity and location of the functional group in both the starting material and the product:



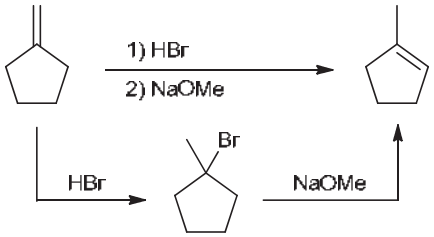
The identity of the functional group has changed (double bond → triple bond), but its location has not changed (it remains between C1 and C2). The conversion of a double bond to a triple bond can be accomplished via the following two-step process (bromination, followed by elimination):



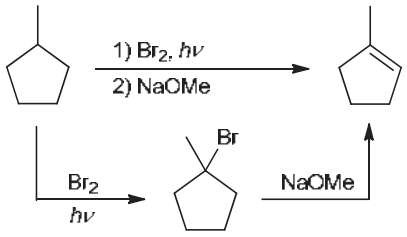
(b) We begin by analyzing the identity and location of the functional group in both the starting material and the product. The identity of the functional group (Br) has not changed, but its location has changed. We have seen that this transformation can be accomplished via a two-step process (elimination, followed by addition). For the elimination process, there is only one possible regiochemical outcome; nevertheless, we must carefully choose a base. We need a strong base that will not function as a nucleophile (with a primary substrate, substitution would predominate over elimination if we use a base such as hydroxide, methoxide, or ethoxide). Appropriate bases are DBN or DBU. Alternatively, *tert*-butoxide can be used, because it is sterically hindered, thereby suppressing the competing S_N2 reaction. For the next step of our synthesis, Markovnikov addition is required, so we use HBr without peroxides.



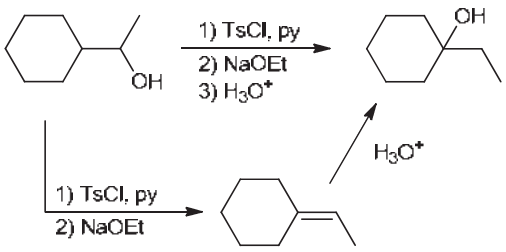
(c) We begin by analyzing the identity and location of the functional group in both the starting material and the product. The identity of the functional group (a π bond) has not changed, but its location has changed. We have seen that this transformation can be accomplished via a two-step process (addition, followed by elimination). For the first step of our synthesis, Markovnikov addition is required, so we use HBr without peroxides. For the next step of our synthesis, the more substituted alkene is desired (trisubstituted rather than disubstituted), so the base cannot be sterically hindered. Appropriate choices include hydroxide, methoxide, and ethoxide.



(d) We begin by analyzing the identity and location of the functional group in both the starting material and the product. In doing so, we immediately realize that the starting material has no functional group (it is an alkane), so the first step of our synthesis must be the installation of a functional group. This can be accomplished via radical bromination, which selectively installs a bromine atom at the tertiary position. The resulting tertiary alkyl halide can then be converted into the product via an elimination process. The more substituted alkene is desired (trisubstituted rather than disubstituted), so the base cannot be sterically hindered. Appropriate choices include hydroxide, methoxide, and ethoxide.

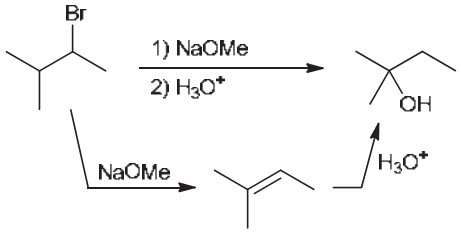


(e) The identity of the functional group (OH) has not changed, but its location has changed. We have seen that this transformation can be accomplished via a two-step process (elimination, followed by addition). Elimination can be achieved by converting the alcohol to a tosylate followed by treatment with a strong base (E2). The resulting alkene can then be converted to the desired product via an addition process. Specifically, a hydration reaction must be performed (addition of H and OH) in a Markovnikov fashion. This can be achieved by treating the alkene with dilute acid (acid-catalyzed hydration):

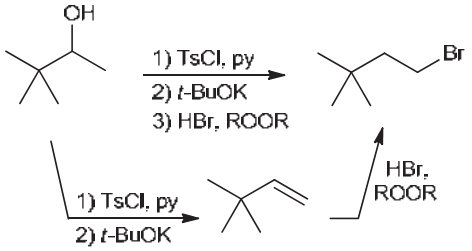


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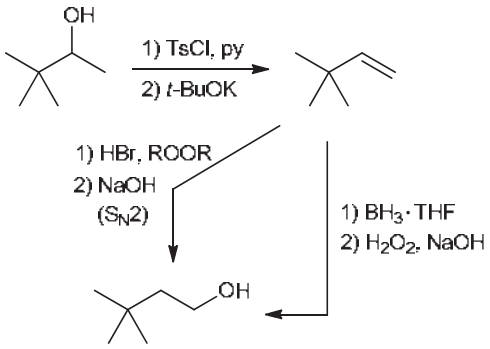
(f) We begin by analyzing the identity and location of the functional group in both the starting material and the product. The identity of the functional group has changed (Br → OH), and its location has changed as well. We have seen that this type of transformation can be accomplished via a two-step process (elimination of H and Br, followed by addition H and OH). For the first step of our synthesis, the more substituted alkene is desired (trisubstituted rather than monosubstituted), so the base cannot be sterically hindered. Appropriate choices include hydroxide, methoxide, and ethoxide. A hydration reaction must be performed (addition of H and OH) in a Markovnikov fashion. This can be achieved by treating the alkene with dilute acid (acid-catalyzed hydration):



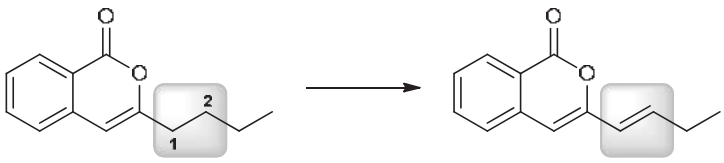
(g) We begin by analyzing the identity and location of the functional group in both the starting material and the product. The identity of the functional group has changed (OH → Br), and its location has changed as well. We have seen that this type of transformation can be accomplished via a two-step process (elimination of H and OH, followed by addition H and Br). For the first part of our synthesis (elimination), we must first convert the alcohol to a tosylate before treating with a strong base. The use of a sterically hindered base is not required (E2 = major product; while S_N2 = minor product). Nevertheless, a sterically hindered base will be helpful here as it will suppress the competing S_N2 reaction. So *tert*-butoxide is used in the synthesis shown. Alternatively, DBU or DBN could be used. Note that an E1 process should be avoided, because heating the alcohol with concentrated sulfuric acid will likely involve a carbocation rearrangement (methyl shift). For the second part of our synthesis, we must perform an *anti*-Markovnikov addition of H and Br, so we use HBr in the presence of peroxides.



(h) We begin by analyzing the identity and location of the functional group in both the starting material and the product. The identity of the functional group (OH) has not changed, but its location has changed. We have seen that this type of transformation can be accomplished via a two-step process (elimination, followed by addition). For the first part of our synthesis (elimination), we must first convert the alcohol to a tosylate before treating with a strong base. The use of a sterically hindered base is not required (E2 = major product; while S_N2 = minor product). Nevertheless, a sterically hindered base will be helpful here as it will suppress the competing S_N2 reaction. So *tert*-butoxide is used in the synthesis below. Alternatively, DBU or DBN could be used. For the second part of our synthesis, we must perform an *anti*-Markovnikov addition of H and OH. This can be achieved via hydroboration-oxidation, or alternatively, it can be achieved by *anti*-Markovnikov addition of HBr followed by an S_N2 process to give the desired alcohol:



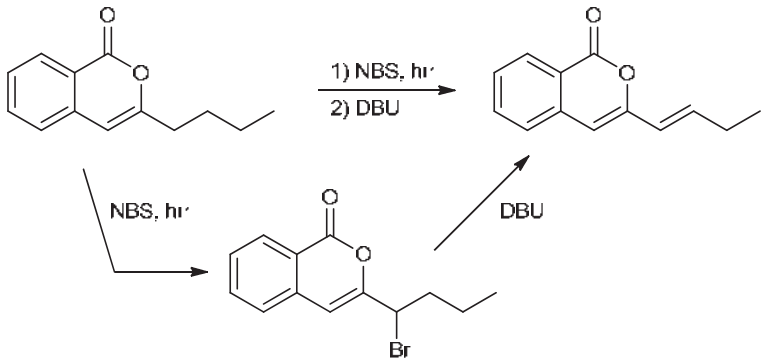
11.4. We begin by analyzing the identity and location of the functional groups in both the starting material and the product, and we look for a difference. In this case, a double bond is introduced at the locations labeled C1 and C2 below:



Neither of these positions is functionalized, so we must first install a functional group at one of these locations. This can be accomplished by allylic bromination, which installs a bromine atom at position C1 (an allylic position). The

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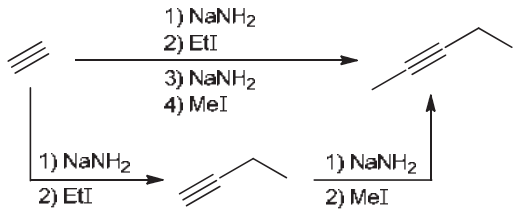
resulting secondary bromide can then be converted into the product via an elimination process. A non-nucleophilic base can be used to favor elimination over substitution. The desired *E* isomer is thermodynamically favored over the *Z* isomer.



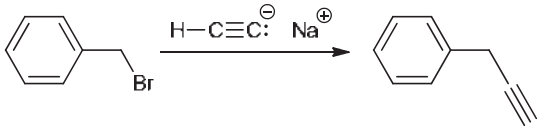
The only constitutional isomer observed in the first step (allylic bromination) is the one shown, because it maintains the conjugated π bonds of the starting material (recall from Chapter 2 that π bonds are conjugated when they are separated from each other by one σ bond). We will explore conjugated π systems in more detail in Chapters 16 and 17.

11.5.

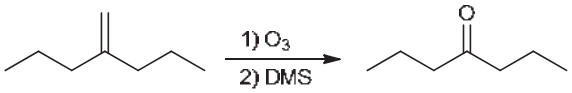
(a) The starting material (acetylene) has two carbon atoms, and the product has five carbon atoms. Therefore, we must change the carbon skeleton by forming carbon-carbon bonds. Specifically, we must install a methyl group and an ethyl group. Each of these alkylation reactions can be achieved upon treatment of the alkyne with sodium amide followed by the appropriate alkyl halide. Notice that each alkyl group must be installed separately, and it does not matter which alkyl group is installed first and which is installed second.



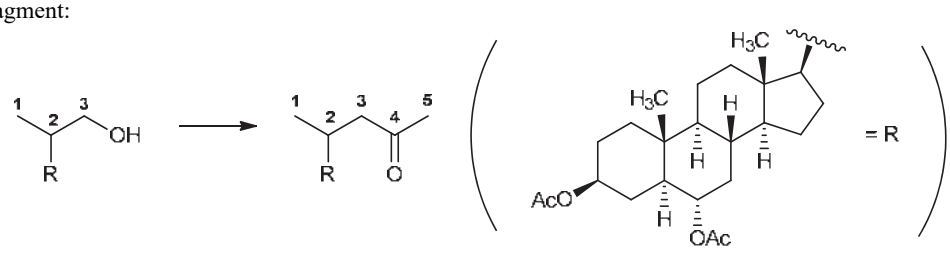
(b) The starting material (benzyl bromide) has seven carbon atoms, and the product has nine carbon atoms. Therefore, we must install two carbon atoms. This alkylation process can be achieved in one step, by treating the starting material with sodium acetylide:



(c) The starting material has eight carbon atoms, and the product has only seven carbon atoms. One carbon atom must be removed, which can be achieved via ozonolysis:



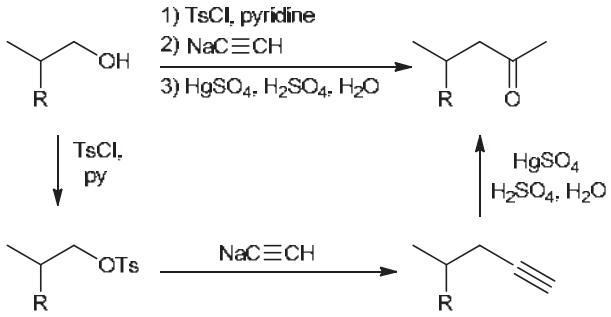
11.6. Let's begin by counting the number of carbons atoms in each of the side chains. There are three carbon atoms in the side chain of compound **1**, and there are five carbon atoms in the side chain of compound **2**, so the carbon skeleton is changing. This requires a reaction in which a C-C bond is formed, thereby achieving the installation of a two carbon-fragment:



The only reaction we know (so far) that can install carbon atoms on an existing carbon skeleton is the reaction of an alkynide anion with an appropriate substrate bearing a good leaving group. An alcohol is not a good substrate for the

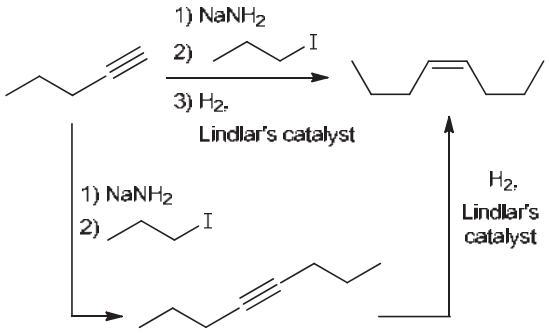
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required S_N2 reaction; however, conversion of the alcohol to a tosylate creates a good leaving group. Addition of an alkynide anion (specifically the acetylide anion) makes a new carbon-carbon bond and gives the desired five-carbon skeleton of the substituent. The resulting alkylation product (a terminal alkyne) can then be subjected to Markovnikov hydration to produce the desired methyl ketone.

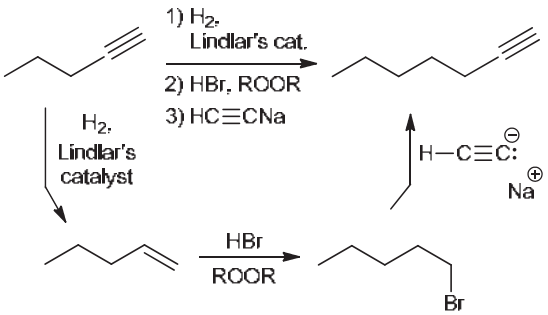


11.7.

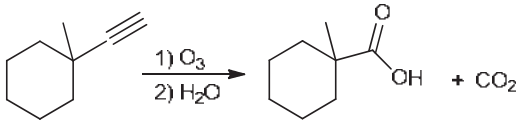
(a) The starting material has five carbon atoms, and the product has eight carbon atoms. So our synthesis must involve the installation of three carbon atoms. In addition, the identity of the functional group must be changed (from a triple bond to a double bond). Reduction of the alkyne (to give an alkene) must be the last step of our synthesis, because if we first reduce the triple bond, then we would not be able to perform the alkylation step. The alkylation step must be performed first, followed by reduction of the alkyne (with a poisoned catalyst), as shown here:



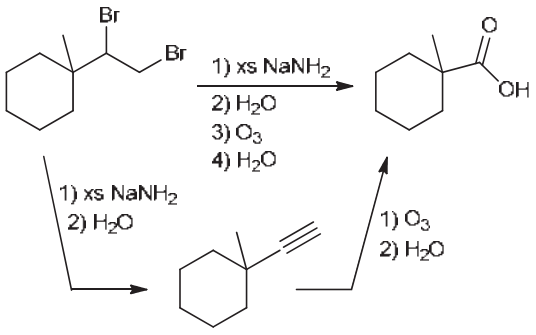
(b) The starting material has five carbon atoms, and the product has seven carbon atoms. So our synthesis must involve the installation of two carbon atoms. If we simply alkylate the starting alkyne (by treating with sodium amide followed by ethyl iodide), then we will need to move the location of the triple bond. Instead, we can convert the starting alkyne into an alkyl halide (via hydrogenation with a poisoned catalyst followed by an *anti*-Markovnikov addition of HBr). If this alkyl halide is treated with acetylide, the desired product is formed:



(c) The starting material has one more carbon atom than the product. Therefore, our synthesis must employ an ozonolysis process. Since the product is a carboxylic acid (rather than an aldehyde or ketone), we can conclude that the last step of our process must involve ozonolysis of an *alkyne*, rather than ozonolysis of an *alkene*:

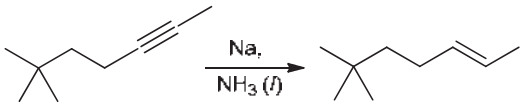


This alkyne can be prepared directly from the starting material upon treatment with excess sodium amide (followed by water workup). The complete synthesis is shown here:

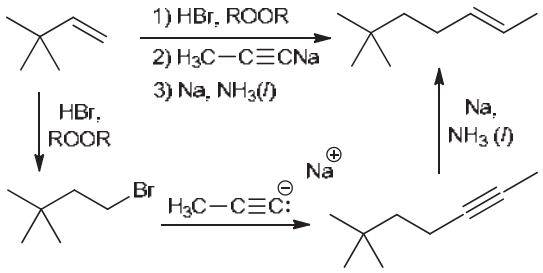


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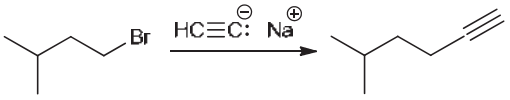
(d) The starting material has six carbon atoms, and the product has nine carbon atoms. So our synthesis must involve the installation of three carbon atoms. Also, the location of the functional group has been changed. The product is a *trans* alkene, which can be made if the last step of our synthesis is a dissolving metal reduction:



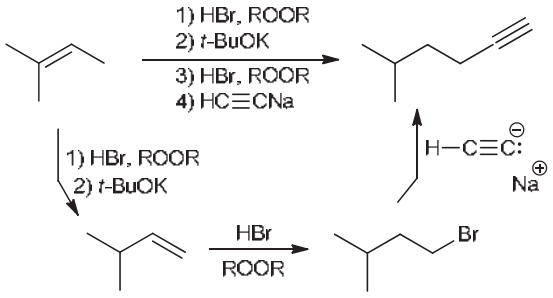
This alkyne can be made from the starting alkene via an *anti*-Markovnikov addition of HBr, followed by treatment with the appropriate alkynide ion, as shown here:



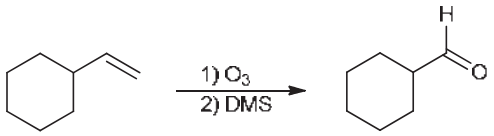
(e) The product has two more carbon atoms than the starting material. The installation of two carbon atoms can be achieved via an alkylation process. In fact, the desired product is a terminal alkyne, which can be made from the following alkyl halide in just one step:



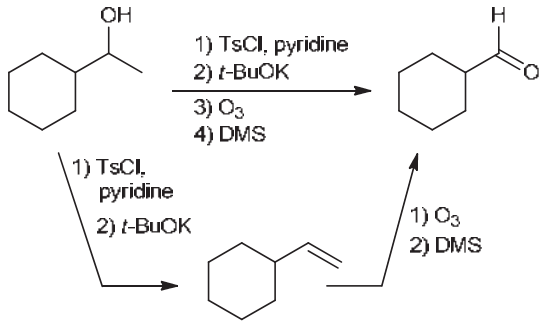
This alkyl halide can be made from the starting material by first moving the location of the π bond, followed by *anti*-Markovnikov addition:



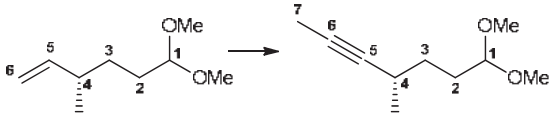
(f) The starting material has one more carbon atom than the product. Therefore, our synthesis must employ an ozonolysis process. Since the product is an aldehyde, we can conclude that the last step of our process must involve ozonolysis of an alkene:



This alkene can be prepared from the starting material by converting the alcohol to a tosylate, and then performing an E2 reaction with a sterically hindered base (giving the less substituted alkene):

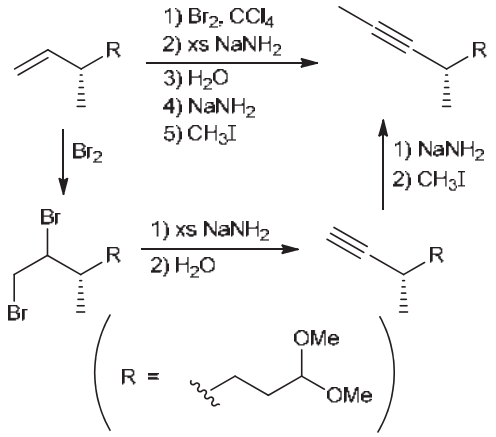


11.8. As with all synthesis problems, we must consider the following two questions:
1) Is there is a change in the carbon skeleton?
2) Is there a change in the identity or location of any functional groups?
To answer the first question, we can assign numbers to the carbon atoms from right to left, and we see that one carbon atom (a methyl group) must be installed during this transformation. To answer the second question, there is a change in the identity of a functional group, because the carbon-carbon double bond in the starting material has been replaced by a carbon-carbon triple bond in the product.

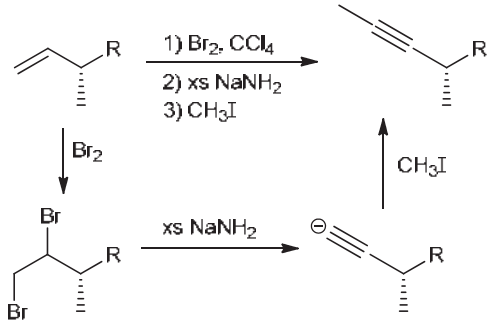


So far, the only way that we have learned to make a new carbon-carbon bond is by alkylation of an alkynide ion; this provides us with a way to convert terminal alkynes into internal alkynes. This suggests that we should first convert the alkene into an alkyne, and then address the change in the carbon skeleton. We have not yet learned a way to convert an alkene into an alkyne in a single step; however, we can achieve this conversion using a two-step process: bromination followed by elimination (which requires aqueous workup to produce a neutral product). Alkylation of the resulting terminal alkyne can then be accomplished using a strong base and an appropriate methyl substrate, such as methyl iodide.

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Notice that steps 3 and 4 are unnecessary. The purpose of the water in step 3 is simply to protonate the alkynide ion (after both eliminations have occurred) that is reformed in step 4 by reaction with an excess of $NaNH_2$. Thus, a more efficient synthesis would omit these steps, as shown here:



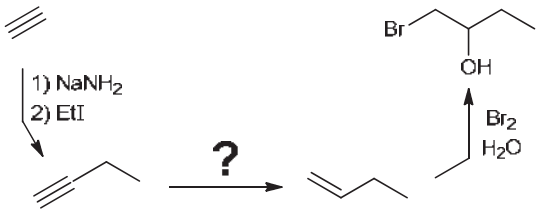
11.9.

(a) The product is a halohydrin, which can be made from an alkene:

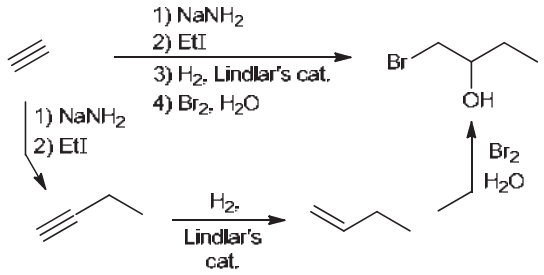


So the last step of our synthesis will likely be conversion of the alkene into the halohydrin.

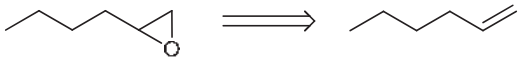
Now let's work forward from the starting material. The starting material has only two carbon atoms, while the product has four carbon atoms, so two carbon atoms must be installed. This can be achieved via an alkylation process:



Now we must bridge the gap (between the terminal alkyne and the alkene). This can be achieved in one step, via hydrogenation with a poisoned catalyst. In summary, the desired transformation can be achieved with the following synthesis:

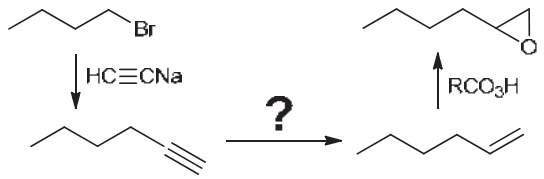


(b) The product is an epoxide, which can be made from an alkene:

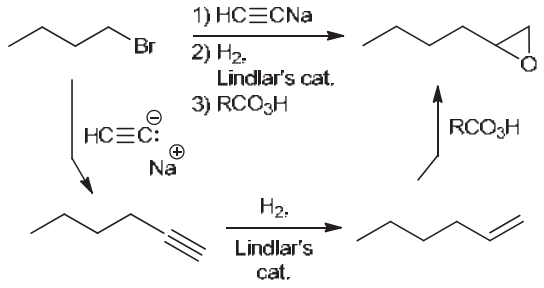


So the last step of our synthesis will likely be conversion of the alkene into the epoxide.

Now let's work forward from the starting material. The starting material has only four carbon atoms, while the product has six carbon atoms, so two carbon atoms must be installed. This can be achieved via an alkylation process:



Now we must bridge the gap (between the terminal alkyne and the alkene). This can be achieved in one step, via hydrogenation with a poisoned catalyst. In summary, the desired transformation can be achieved with the following synthesis:



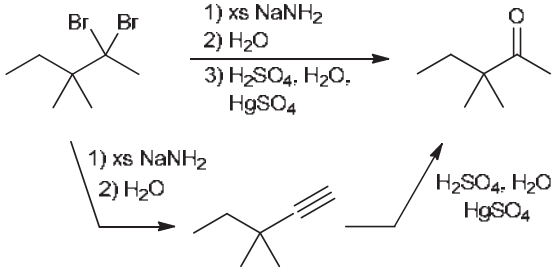
(c) The product is a methyl ketone, and we have seen that a methyl ketone can be prepared from an alkyne (via acid-catalyzed hydration):



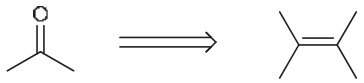
This alkyne can be prepared directly from the starting material upon treatment with excess sodium amide (followed by water workup). In summary, the desired

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transformation can be achieved with the following synthesis:

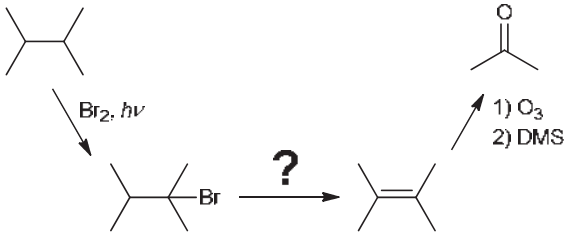


(d) The starting material has six carbon atoms and the product has three carbon atoms, indicating that an ozonolysis reaction will be necessary. The product can be made from the following alkene:

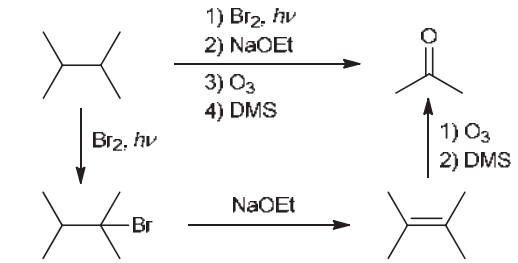


So the last step of our synthesis will likely be ozonolysis of this alkene.

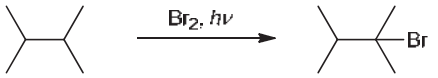
Now let's work forward from the starting material. The starting material is an alkane (no functional group), so we must first install a functional group. Radical bromination will selectively install a bromine atom at a tertiary position:



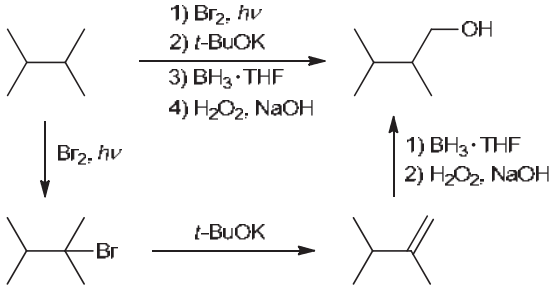
Now we must bridge the gap (between the alkyl halide and the alkene). This can be achieved in one step, via an E2 reaction with a strong base (such as hydroxide, methoxide, or ethoxide). In summary, the desired transformation can be achieved with the following synthesis:



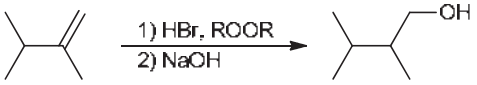
(e) The starting material is an alkane (no functional group), so we must first install a functional group. Radical bromination will selectively install a bromine atom at a tertiary position:



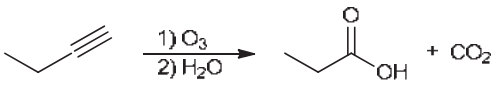
Converting this compound into the product requires changing both the identity and the location of the functional group. This can be achieved via a two-step process, involving elimination followed by addition. The elimination process must be performed with a sterically hindered base so that the less substituted alkene is produced, and the addition process must be performed in an *anti*-Markovnikov fashion (via hydroboration-oxidation):



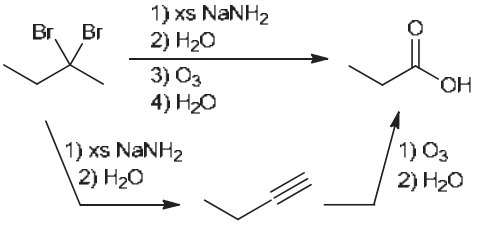
It should be noted that there are other acceptable answers. As one example, the last part of our synthesis (hydroboration-oxidation) could be replaced with *anti*-Markovnikov addition of HBr to give a primary alkyl bromide, followed by an S_N2 process with hydroxide as the nucleophile:



(f) The starting material has one more carbon atom than the product. Therefore, our synthesis must employ an ozonolysis process. Since the product is a carboxylic acid (rather than an aldehyde or ketone), we can conclude that the last step of our process must involve ozonolysis of an *alkyne*, rather than ozonolysis of an *alkene*:

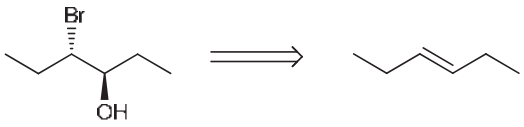


This alkyne can be prepared directly from the starting material upon treatment with excess sodium amide (followed by water workup). The complete synthesis is shown here:



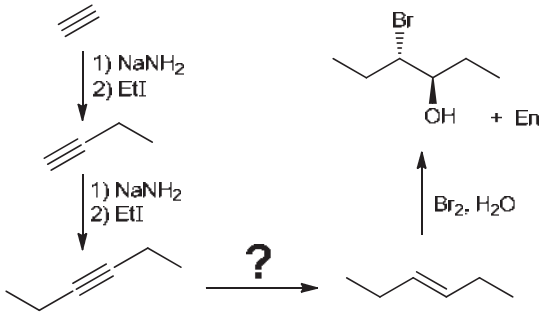
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(g) The product is a halohydrin, which can be made from the following *trans* alkene:

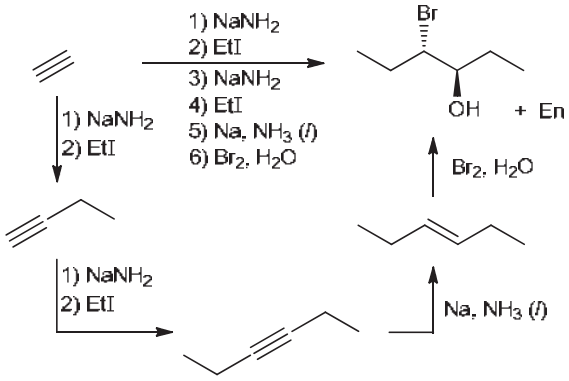


So the last step of our synthesis will likely be conversion of this alkene into the halohydrin.

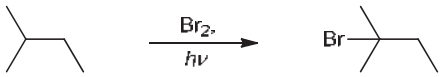
Now let's work forward from the starting material. The starting material has only two carbon atoms, while the product has six carbon atoms. Two alkylation processes are required:



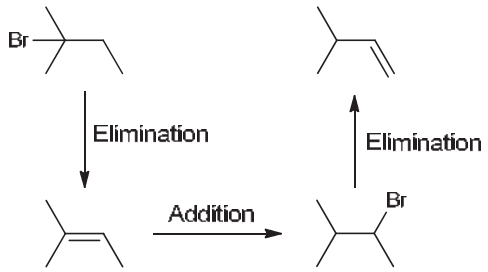
Now we must bridge the gap (between the internal alkyne and the *trans* alkene). This can be achieved in one step, via a dissolving metal reduction. In summary, the desired transformation can be achieved with the following synthesis:



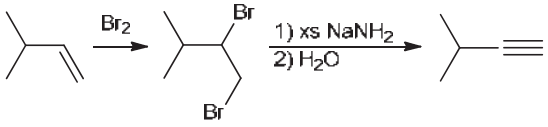
(h) In this case, the carbon skeleton remains the same. The starting material is an alkane (no functional group) so we must begin our synthesis by installing a functional group. Radical bromination will selectively install a bromine atom at the tertiary position, giving the following tertiary alkyl halide:



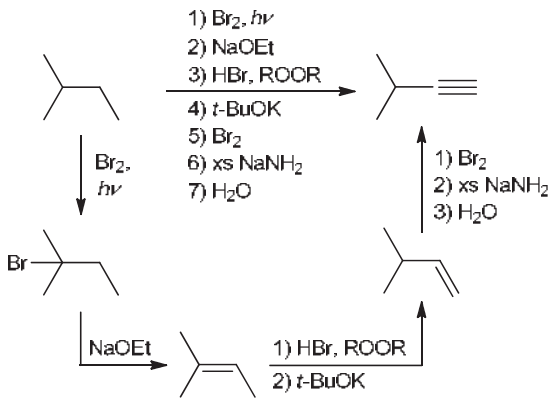
Now we must change both the location and the identity of the functional group. We can move the functional group into the right location through the following series of reactions:



And then finally, the double bond can be converted to the triple bond via the following two-step process:

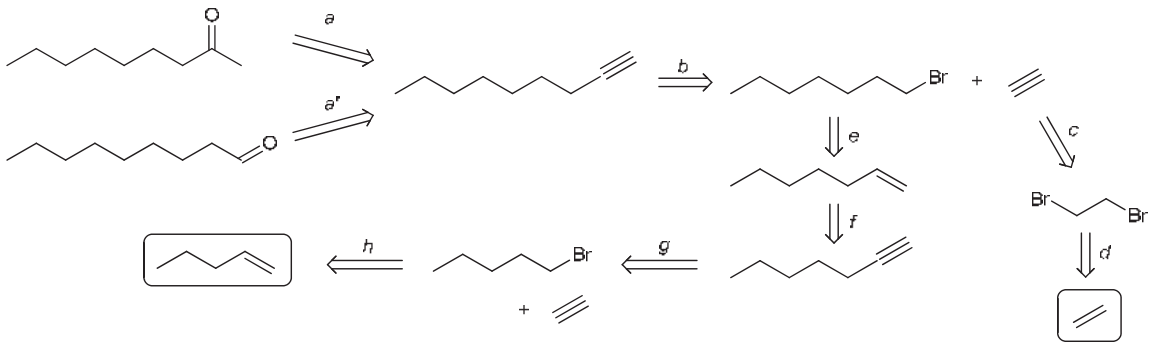


In summary, the desired transformation can be achieved with the following synthesis:



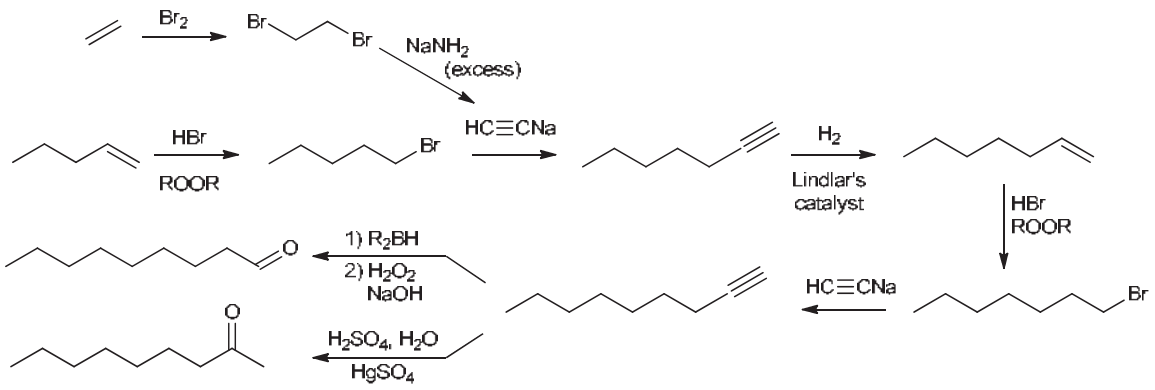
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11.10. Each of the following syntheses is one suggested synthetic pathway. There are likely many other acceptable approaches that accomplish the same goals.
Each of the target compounds has a nine carbon linear chain, and our reagents must be alkenes with fewer than six carbon atoms. Thus, it is clear that we will be forming new C-C bonds in the course of this synthesis. The figure below outlines a retrosynthetic analysis for our target compound. An explanation of each of the steps (*a*-*h*) follows.



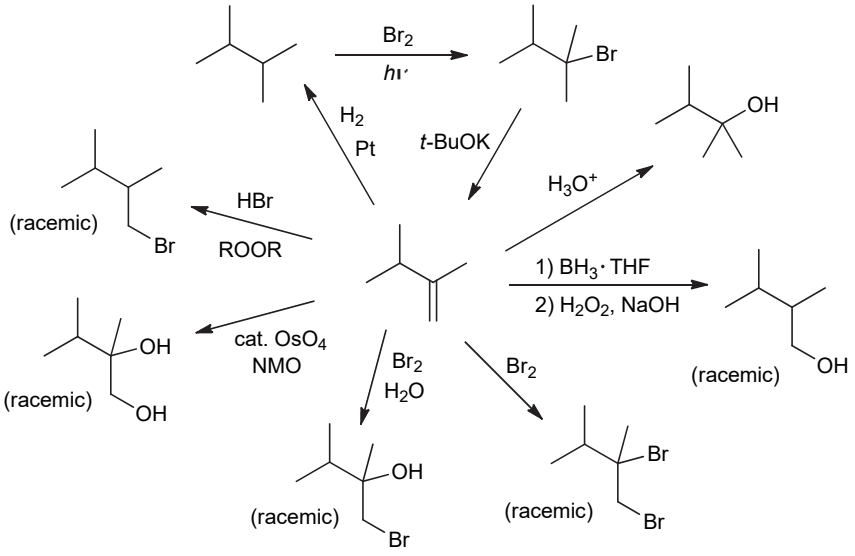
a. Either of the products can be prepared from a common synthetic intermediate, 1-nonyne, by hydration of the alkyne via (*a*) Markovnikov addition, or (a') *anti*-Markovnikov addition.
b. The terminal alkyne can be prepared via reaction of 1-bromoheptane with an acetylide anion (formed by deprotonating acetylene).
c. Acetylene is prepared via a double elimination from 1,2-dibromoethane.
d. 1,2-Dibromoethane is prepared via bromination of ethylene.
e. 1-Bromoheptane is prepared via *anti*-Markovnikov addition of HBr across 1-heptene.
f. 1-Heptene is prepared via hydrogenation of 1-heptyne in the presence of a poisoned catalyst.
g. 1-Heptyne is prepared via reaction of 1-bromopentane with an acetylide anion.
h. 1-Bromopentane is prepared via *anti*-Markovnikov addition of HBr across 1-pentene.

Now, let's draw the forward scheme. In the presence of peroxides, the reaction of 1-pentene with HBr produces 1-bromopentane (via *anti*-Markovnikov addition). Subsequent reaction with acetylide [produced from ethylene as shown by bromination (Br_2), double elimination and deprotonation (excess $NaNH_2$)] provides 1-heptyne. Reduction to the alkene (H_2 / Lindlar's catalyst) followed by *anti*-Markovnikov addition (HBr / peroxides) yields 1-bromoheptane. This primary alkyl bromide can then undergo an S_N2 reaction when treated with acetylide (prepared above), giving the common intermediate, 1-nonyne. A hydroboration / oxidation protocol (R_2BH then H_2O_2, NaOH) produces the target aldehyde. Acid and mercury catalyzed hydration gives the target ketone.

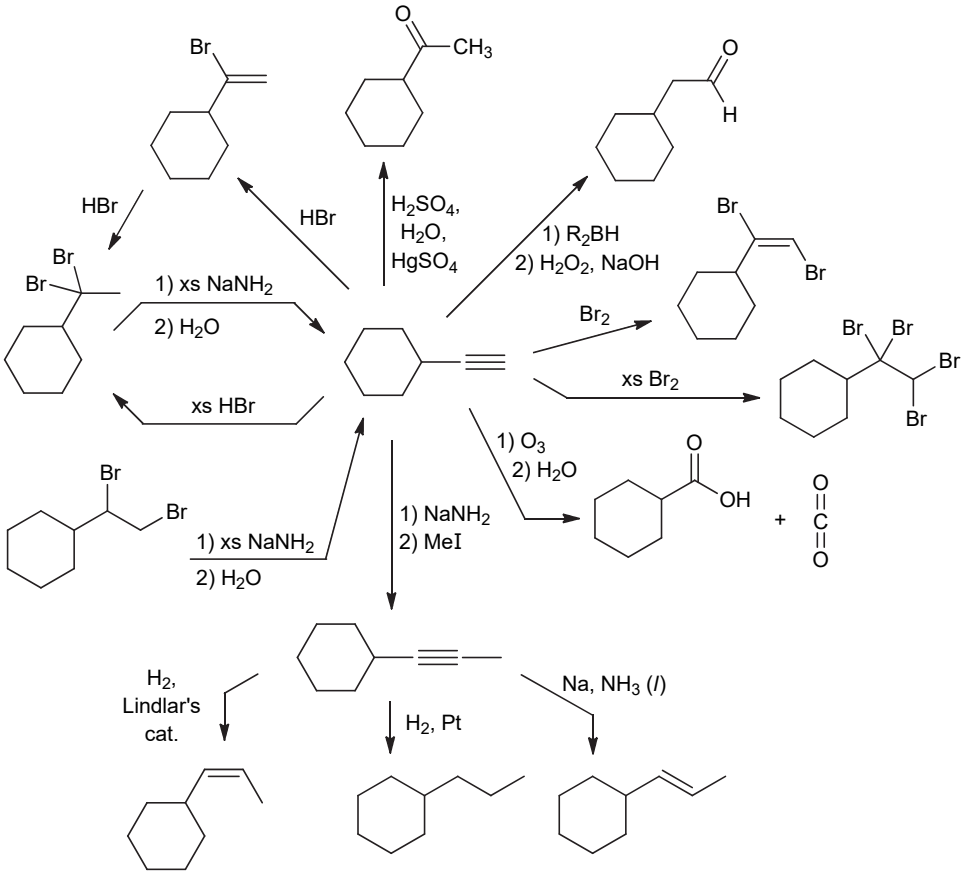


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11.11. Most of the following reactions are addition reactions, which can be found in Chapter 8. The following reagents can be used to achieve each of the transformations shown:

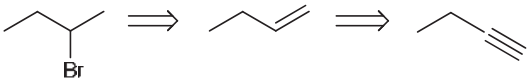


11.12. Most of the following reactions involve alkynes, which can be found in Chapter 10. The following reagents can be used to achieve each of the transformations shown:

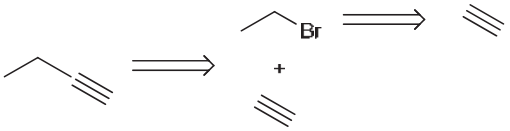


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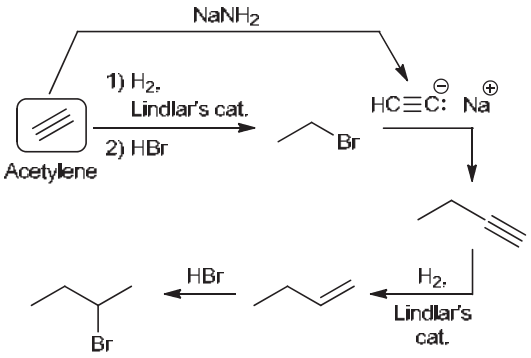
11.13. The product can be made from 1-butene, which can be made from 1-butyne:



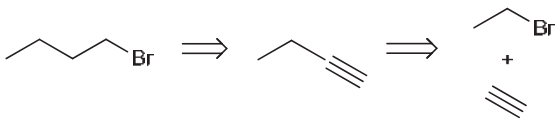
1-Butyne can be made from acetylene and ethyl bromide via an alkylation process. And ethyl bromide can be made from acetylene:



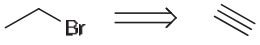
In summary, the desired transformation can be achieved with the following synthesis:



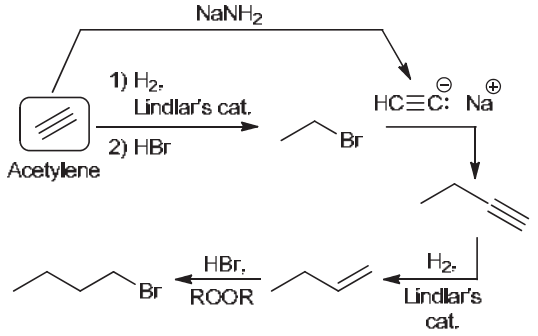
11.14. 1-Bromobutane can be made from 1-butyne, which can be made from acetylene and ethyl bromide via an alkylation process:



And ethyl bromide can be made from acetylene:

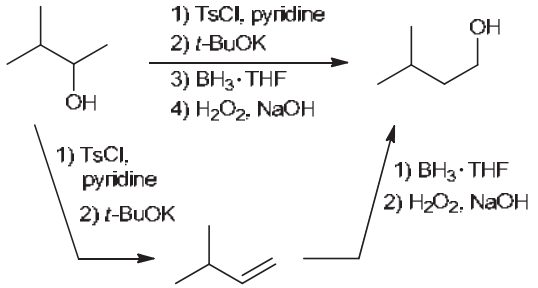


In summary, the desired transformation can be achieved with the following synthesis:

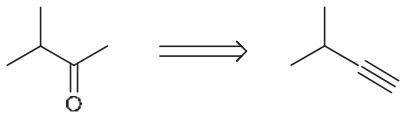


11.15.

(a) The identity of the functional group (OH) has not changed, but its location has changed. We have seen that this type of transformation can be accomplished via a two-step process (elimination, followed by addition). For the first part of our synthesis (elimination), we must first convert the alcohol to a tosylate before performing the elimination process. Then, for the elimination, we must use a sterically hindered base, *tert*-butoxide, in order to obtain the less-substituted alkene. For the second part of our synthesis, we must perform an *anti*-Markovnikov addition of H and OH. This can be achieved via hydroboration-oxidation, or alternatively, it can be achieved by *anti*-Markovnikov addition of HBr followed by an S_N2 process (with hydroxide as a nucleophile) to give the desired alcohol:

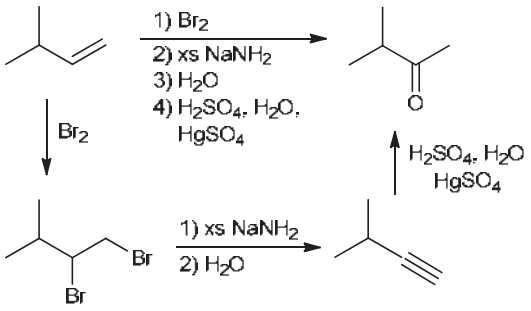


(b) The product is a methyl ketone, which can be made from an alkyne (via acid-catalyzed hydration):

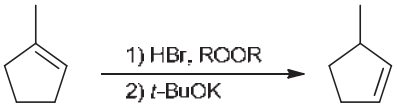


This alkyne can be made from the starting alkene via a two-step process (bromination, followed by elimination with excess sodium amide):

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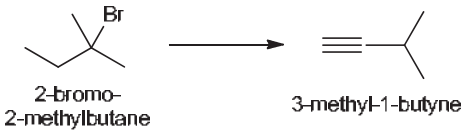


11.16. We must move the location of the π bond, and we have seen that this can be achieved via a two-step process (addition, followed by elimination). The addition step must occur in an *anti*-Markovnikov fashion, which can be achieved by treating the starting material with HBr in the presence of peroxides. The elimination process must give the less substituted alkene, so a sterically hindered base is required:

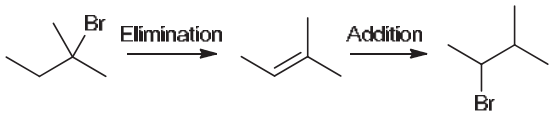


Alternatively, the addition of HBr can be replaced with hydroboration-oxidation (addition of H and OH), which is also an *anti*-Markovnikov addition. In that scenario, the resulting alcohol must first be converted to a tosylate before the elimination step can be performed.

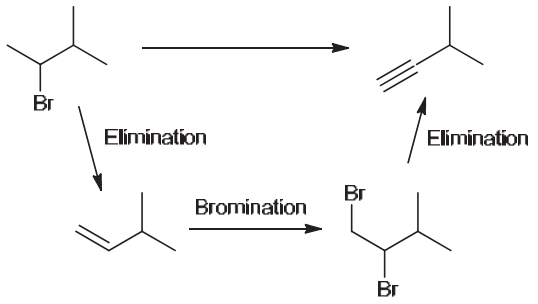
11.17. Let's begin by drawing the starting material and the product, so that we can see the desired transformation more clearly:



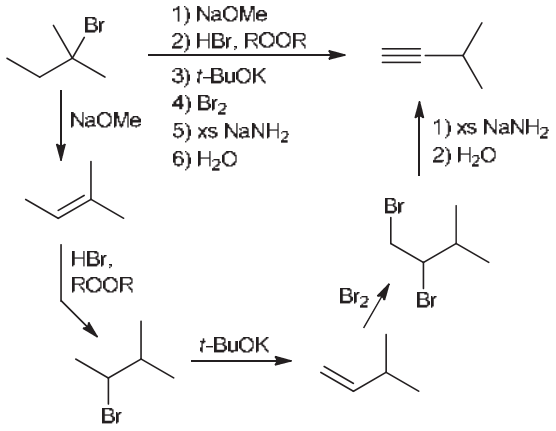
In this case, the identity and the location of the functional group have changed. During our synthesis, the functional group (Br) must be relocated, AND it must be converted into a triple bond. Moving the functional group can be achieved via elimination (to give the Zaitsev product) followed by addition (in an *anti*-Markovnikov fashion).



Then, changing the identity of the functional group can be achieved via the following three-step process:

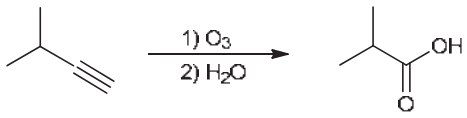


The necessary reagents are shown here:

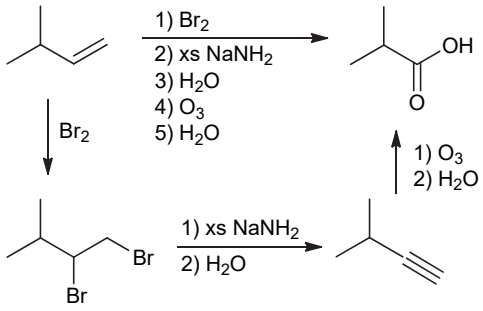


11.18.

(a) The starting material has one more carbon atom than the product. Therefore, our synthesis must employ an ozonolysis process. Since the product is a carboxylic acid (rather than an aldehyde or ketone), we can conclude that the last step of our process must involve ozonolysis of an *alkyne*, rather than ozonolysis of an *alkene*:

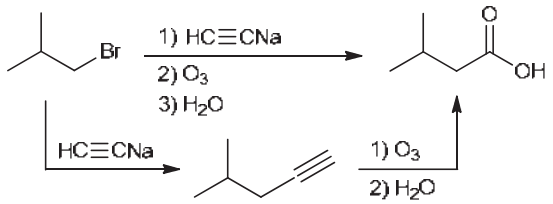


This alkyne can be made from the starting alkene via a two-step process (bromination, followed by elimination with excess sodium amide):

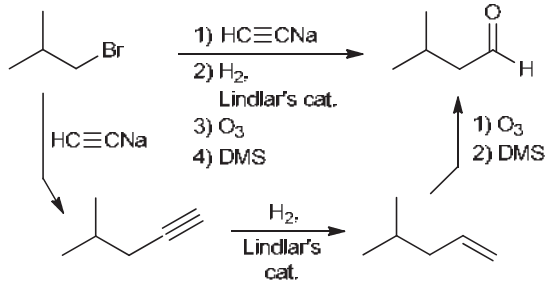


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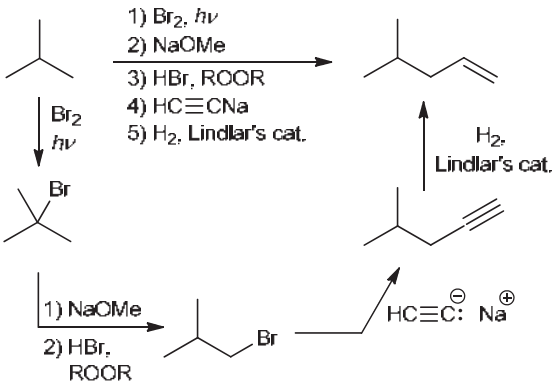
(b) We have not learned a direct way of installing only one carbon atom. That is, two carbon atoms are installed (not one) if we use the alkyl halide in an alkylation process (with sodium acetylide). However, after installing two carbon atoms, we can remove one of them with an ozonolysis procedure, giving the desired product:



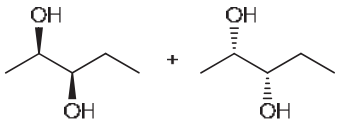
(c) We have not learned a direct way of installing only one carbon atom. That is, two carbon atoms are installed (not one) if we use the alkyl halide in an alkylation process (with sodium acetylide). However, after installing two carbon atoms, we can remove one of them with an ozonolysis procedure. In order to obtain an aldehyde, the last step must be ozonolysis of an alkene, so the penultimate step must be reduction of the alkyne to an alkene in the presence of a poisoned catalyst:



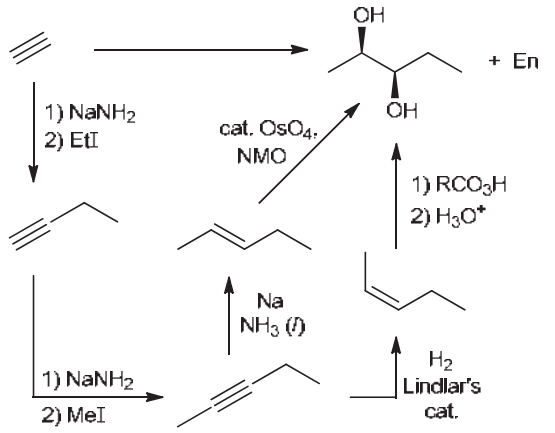
(d) The starting material has four carbon atoms, and the product has six carbon atoms. Therefore, our synthesis must employ an alkylation process. The starting material (2-methylpropane) cannot be converted into an alkyne without giving five bonds to the central carbon atom (which is impossible). Therefore, the starting material must be converted into an alkyl halide (so that it can be treated with sodium acetylide to give an alkylation process). Radical bromination provides a tertiary alkyl halide, which must be converted to a primary alkyl halide. That is, the position of the functional group must be moved, which can be accomplished via a two-step process (elimination followed by *anti*-Markovnikov addition). The primary alkyl halide is then treated with sodium acetylide to give an alkylation process. The resulting terminal alkyne can be reduced in the presence of a poisoned catalyst to give the desired alkene:



11.19. We begin by drawing the desired products:

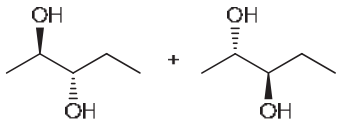


These compounds have five carbon atoms, but our starting materials can contain no more than two carbon atoms. So our synthesis must involve the formation of carbon-carbon bonds. This can be accomplished via the alkylation of acetylene (a compound with two carbon atoms). The location of the functional groups (C2 and C3) indicates that we need two alkylation processes (one to install a methyl group and the other to install an ethyl group). This places the triple bond between C2 and C3, which enables the installation of the functional groups at those locations. Conversion of the internal alkyne into the desired product requires the addition of H and H to give an alkene, followed by the addition of OH and OH. In order to achieve the correct stereochemical outcome, one of these addition processes must be performed in a *syn* fashion, while the other must be performed in an *anti* fashion. That is, we can perform an *anti* addition of H and H, followed by a *syn* addition of OH and OH, or we can perform a *syn* addition of H and H, followed by an *anti* addition of OH and OH, as shown:

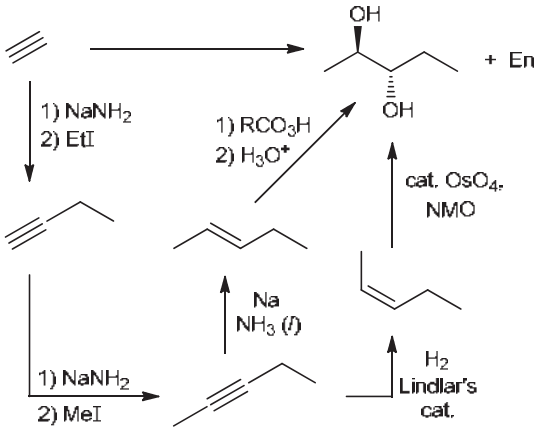


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11.20. We begin by drawing the desired products:

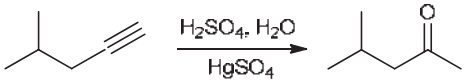


These compounds have five carbon atoms, but our starting materials can contain no more than two carbon atoms. So our synthesis must involve the formation of carbon-carbon bonds. This can be accomplished via the alkylation of acetylene (a compound with two carbon atoms). The location of the functional groups (C2 and C3) indicates that we need two alkylation processes (one to install a methyl group and the other to install an ethyl group). This places the triple bond between C2 and C3, which enables the installation of the functional groups at those locations. Conversion of the internal alkyne into the desired product requires the addition of H and H to give an alkene, followed by the addition of OH and OH. In order to achieve the correct stereochemical outcome, both of these addition processes must be performed in an *anti* fashion, or both must be performed in a *syn* fashion. That is, we can perform an *anti* addition of H and H, followed by an *anti* addition of OH and OH, or we can perform a *syn* addition of H and H, followed by a *syn* addition of OH and OH, as shown:

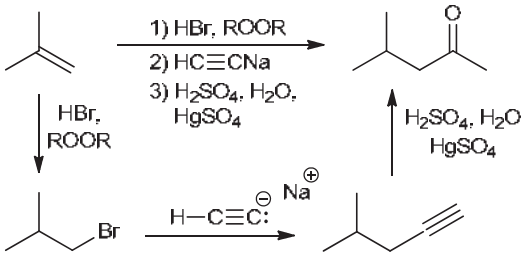


11.21.

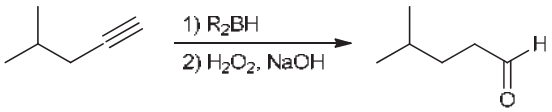
(a) The starting material has four carbon atoms, and the product has six carbon atoms. So our synthesis must involve the installation of two carbon atoms. Also, the location of the functional group has been changed. The product is a methyl ketone, which can be made from a terminal alkyne (via acid catalyzed hydration):



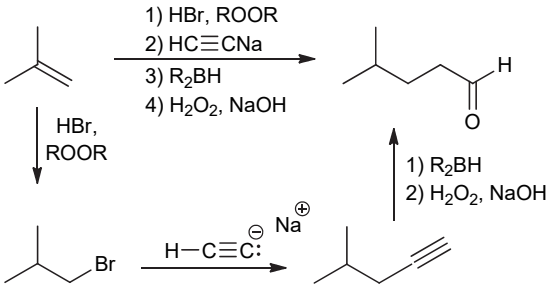
This alkyne can be made from the starting alkene via an *anti*-Markovnikov addition of HBr, followed by treatment with sodium acetylide, as shown here:



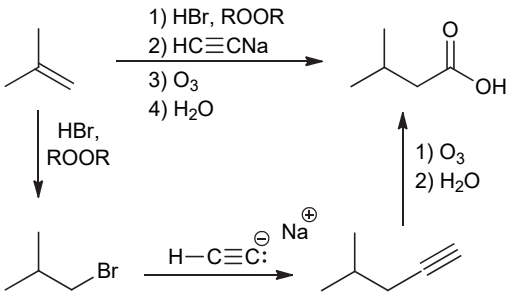
(b) The starting material has four carbon atoms, and the product has six carbon atoms. So our synthesis must involve the installation of two carbon atoms. Also, the location of the functional group has been changed. The product is an aldehyde, which can be made from a terminal alkyne (via hydroboration-oxidation):



As seen in the solution to part (a), this alkyne can be made from the starting alkene via an *anti*-Markovnikov addition of HBr, followed by treatment with sodium acetylide, as shown here:

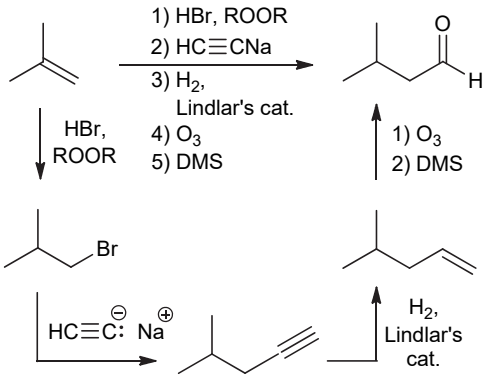


(c) The starting material has four carbon atoms, and the product has five carbon atoms. We have not learned a direct way of installing only one carbon atom. That is, two carbon atoms are installed (not one) if we convert the starting alkene into an alkyl halide (via an *anti*-Markovnikov addition), and then treat the alkyl halide with sodium acetylide. However, after installing two carbon atoms, we can remove one of them with ozonolysis, giving the product:

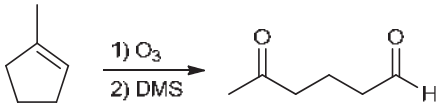


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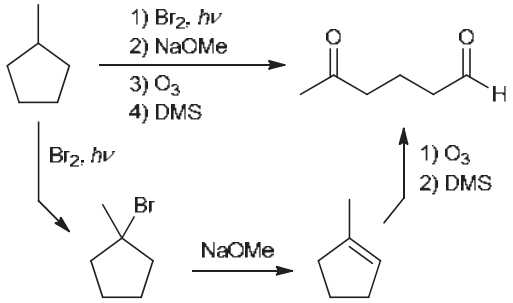
(d) We have not learned a direct way of installing only one carbon atom. The synthesis below involves installing two carbon atoms, followed by removing one of them with an ozonolysis procedure. In order to obtain an aldehyde, the last step must be ozonolysis of an alkene, so the second-to-last step (called the penultimate step) must be reduction of the alkyne to an alkene in the presence of a poisoned catalyst:



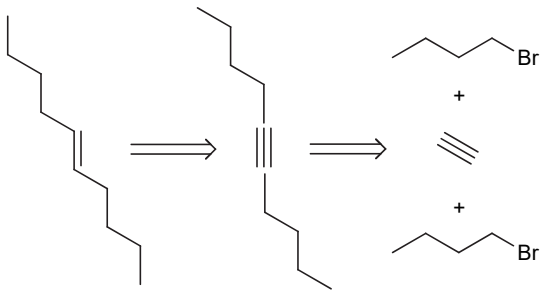
(e) The starting material is cyclic (it contains a ring) and the product is acyclic (it lacks a ring). So, we must break one of the carbon-carbon bonds of the ring. We have only learned one way (ozonolysis) to break a carbon-carbon bond. So, the last step of our synthesis is likely the following reaction:



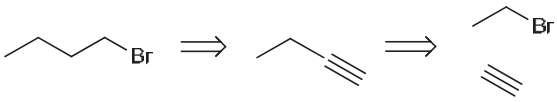
This cycloalkene can be prepared from the starting material in just two steps. First, radical bromination can be used to selectively install a bromine atom at the tertiary position. And then, the resulting alkyl halide can be treated with a strong base (such as hydroxide, methoxide, or ethoxide) to give an E2 reaction:



11.22. The product is a *trans* alkene, which can be made from an alkyne. So the last step of our synthesis might be a dissolving metal reduction to convert the alkyne into the product. This alkyne can be made from acetylene and 1-bromobutane via alkylation processes:



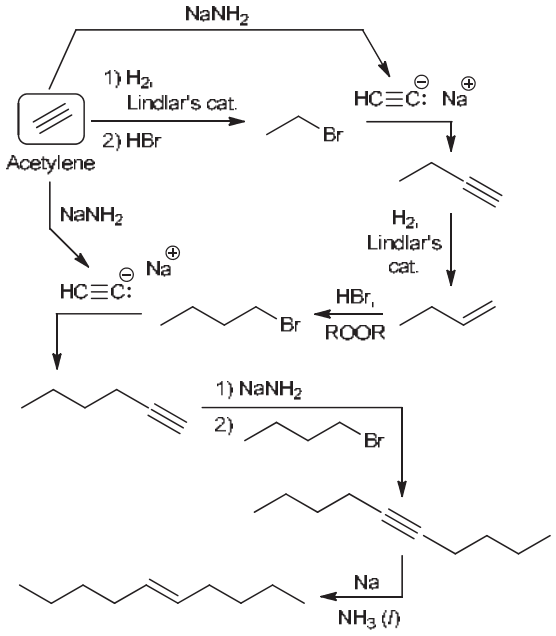
1-Bromobutane can be made from 1-butyne, which can be made from acetylene and ethyl bromide via an alkylation process:



And ethyl bromide can be made from acetylene:

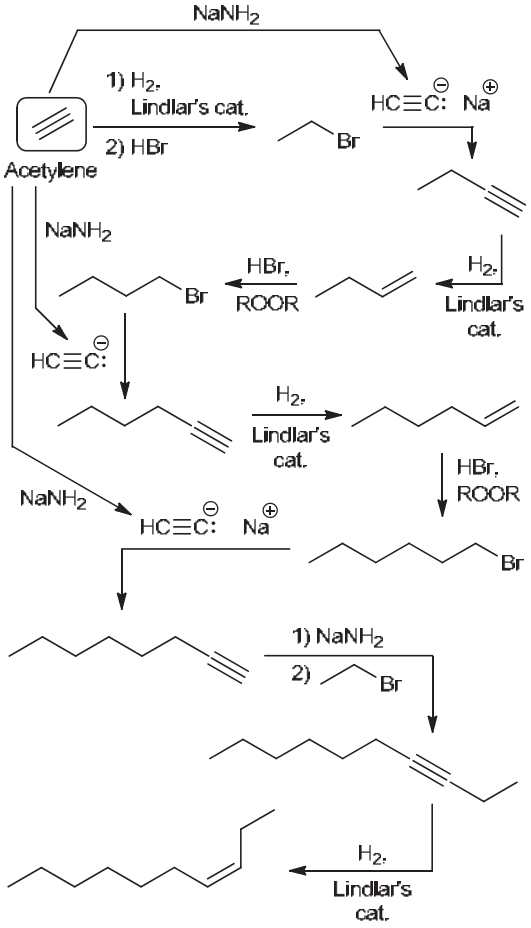


In summary, the desired transformation can be achieved with the following synthesis:

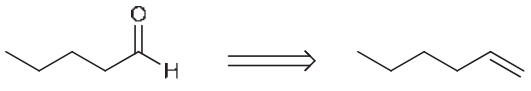


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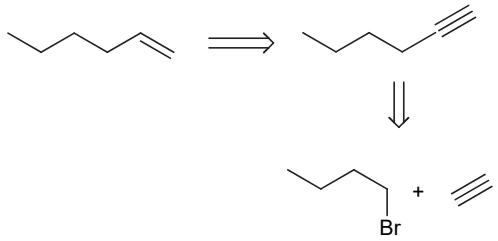
11.23. We use the same approach taken in the previous problem. All carbon-carbon bonds are prepared via alkylation of an alkynide ion with the appropriate alkyl halide. Each alkyl halide must be prepared from acetylene. The last step of the synthesis is the reduction of an alkyne to a *cis* alkene via hydrogenation with a poisoned catalyst:



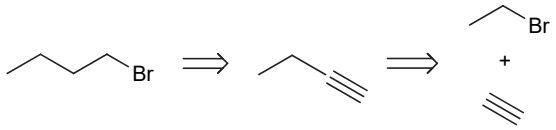
11.24. The starting material has two carbon atoms, and the product has five carbon atoms. So, we must join three fragments together (each of which has two carbon atoms), and then we must remove one of the carbon atoms. The latter process can be achieved via ozonolysis. Since the product is an aldehyde, it is reasonable to explore using ozonolysis as the last step of our synthesis:



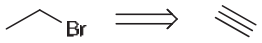
This alkene can be prepared from an alkyne, which can be prepared from acetylene and 1-bromobutane:



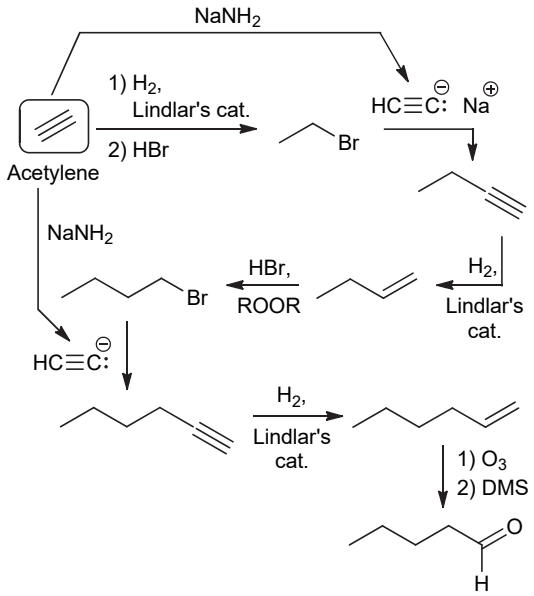
1-Bromobutane can be made from 1-butyne, which can be made from acetylene and ethyl bromide via an alkylation process:



And ethyl bromide can be made from acetylene:



In summary, the desired transformation can be achieved with the following synthesis:

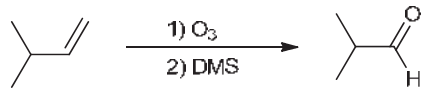


This synthesis represents just one correct answer to the problem. There are certainly other acceptable answers to this problem.

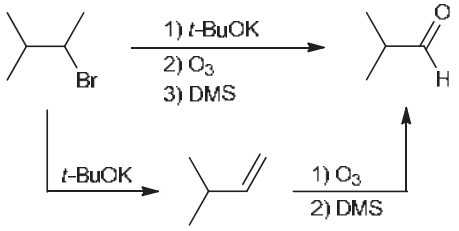
11.25.

(a) The starting material has five carbon atoms, and the product has only four carbon atoms. One carbon atom must be removed, which can be achieved via ozonolysis of an alkene:

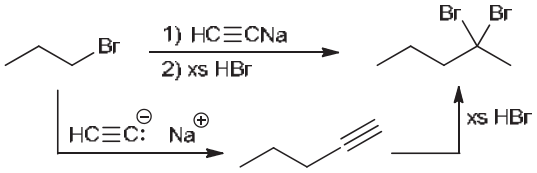
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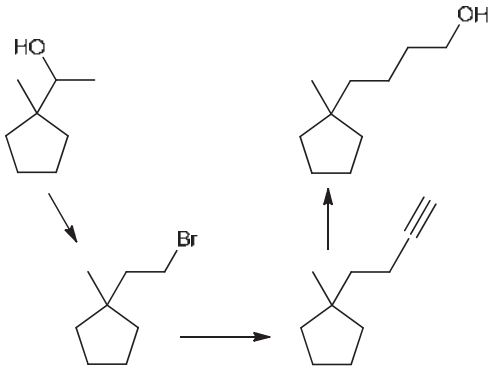
The alkene can be prepared from the starting material via an elimination reaction with a sterically hindered base (giving the less substituted alkene):



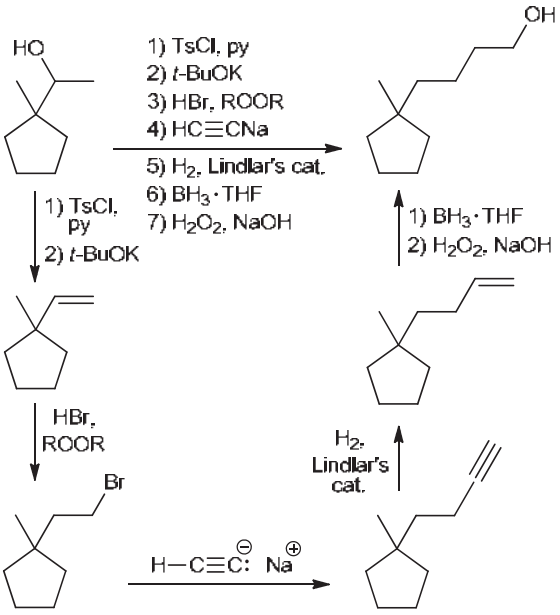
(b) The starting material has three carbon atoms, and the product has five carbon atoms. We can install two carbon atoms by treating the starting material with sodium acetylide. The resulting alkylation product (a terminal alkyne) can then be converted to the desired product (a geminal dihalide) upon treatment with excess HBr:



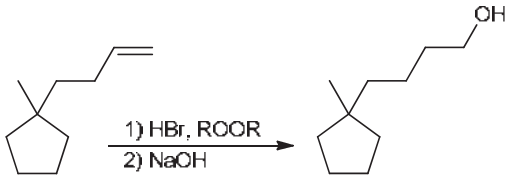
11.26. The desired transformation involves the installation of two carbon atoms, as well as a change in the location of the functional group. This can be achieved by converting the alcohol into a primary alkyl bromide, performing an alkylation process and then converting the triple bond into the desired alcohol:



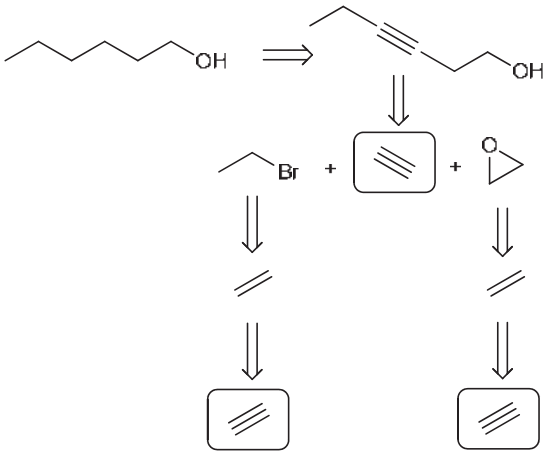
The following reagents can be used to achieve the desired transformations:



It should be noted that there are other acceptable answers. As one example, the last part of our synthesis (hydroboration-oxidation) could be replaced with *anti*-Markovnikov addition of HBr to give a primary alkyl bromide, followed by an S_N2 process with hydroxide as the nucleophile:

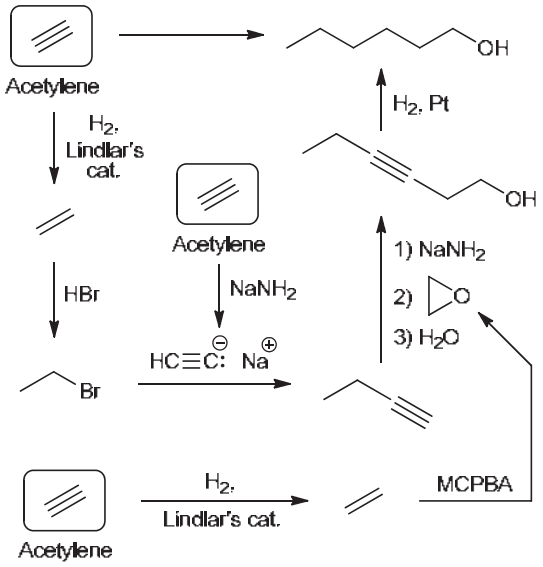


11.27. There are certainly many acceptable answers to this problem. The following retrosynthetic analysis employs the technique described in the problem statement:

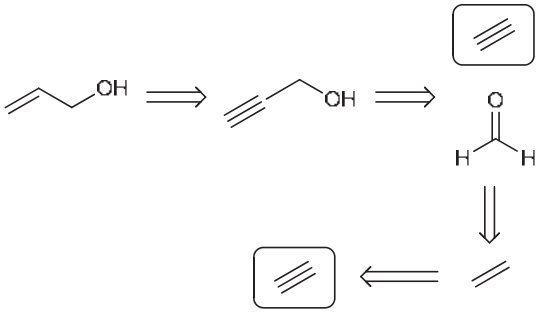


This retrosynthetic analysis gives the following synthesis:

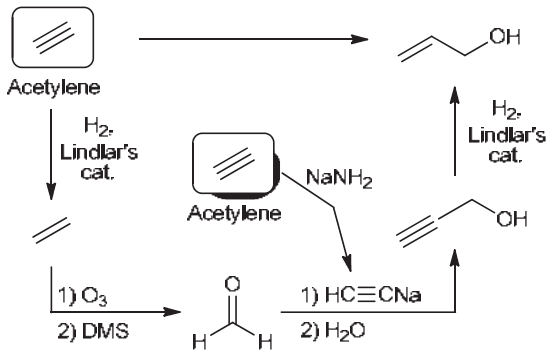
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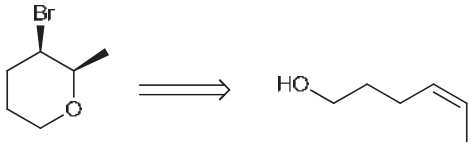
11.28. There are certainly many acceptable answers to this problem. The following retrosynthetic analysis employs the technique described in the problem statement:



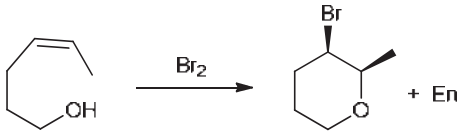
This retrosynthetic analysis gives the following synthesis:



11.29. The key to solving this problem is recognizing that the cyclic product can be made from the following acyclic compound (which can be prepared from the starting material in just one step):

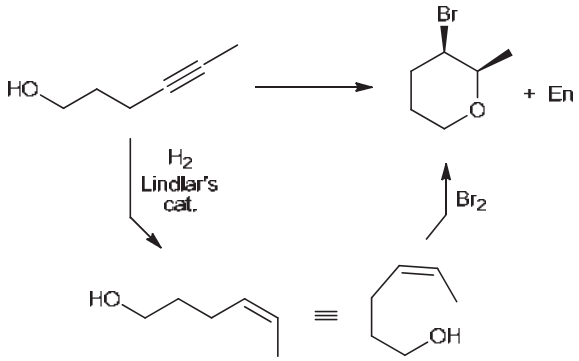


This reaction is similar to halohydrin formation:



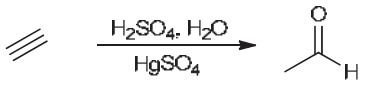
The π bond reacts with molecular bromine to give a bromonium ion, which is then attacked by the OH group in an intramolecular process. You may find it helpful to build molecular models to help visualize the stereochemistry of the ring-closing step.

According to the retrosynthetic analysis above, the desired transformation can be achieved in just two steps, shown here:



11.30.

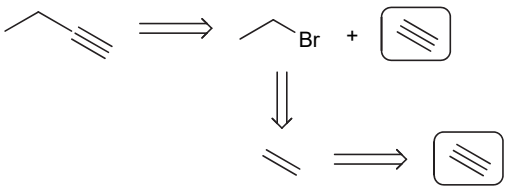
(a) The desired compound can be prepared from acetylene in just one step (via acid-catalyzed hydration):



Alternatively, this transformation can also be achieved via hydroboration-oxidation of acetylene.

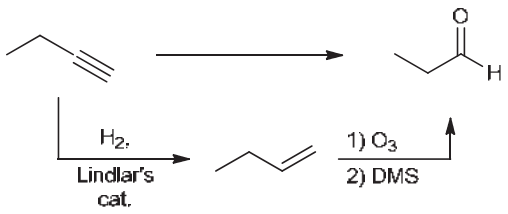
(b) The following synthesis represents just one correct answer to the problem. There are certainly other acceptable answers to this problem.

We have seen in previous problems that 1-butyne can be prepared from two equivalents of acetylene:

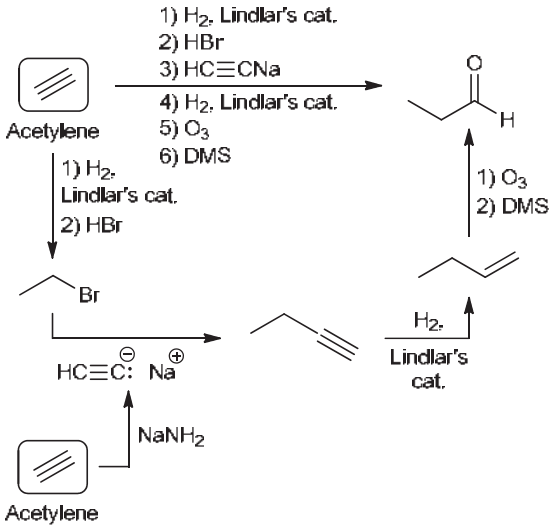


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And 1-butyne can be converted into the product in just two steps (hydrogenation, followed by ozonolysis):

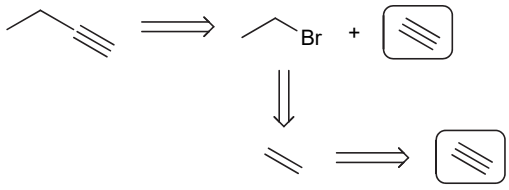


In summary, the following synthesis can be used to make the desired compound from acetylene:

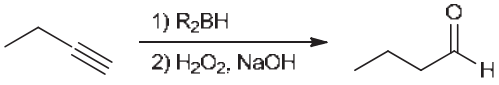


(c) The synthesis developed below is only one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.

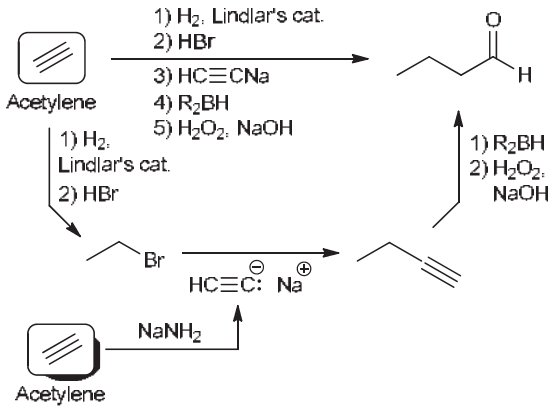
We have seen in previous problems that 1-butyne can be prepared from two equivalents of acetylene:



And 1-butyne can be converted into the product via hydroboration-oxidation:

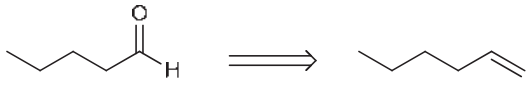


In summary, the following synthesis can be used to make the desired compound from acetylene:

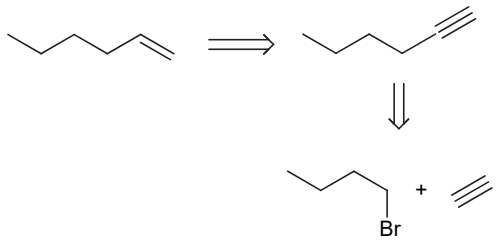


(d) The synthesis developed below is only one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.

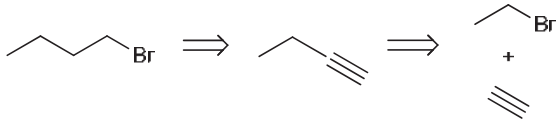
The starting material has two carbon atoms, and the product has five carbon atoms. So, we must join three fragments together (each of which has two carbon atoms), and then we must remove one of the carbon atoms. The latter process can be achieved via ozonolysis. Since the product is an aldehyde, it is reasonable to explore using ozonolysis as the last step of our synthesis:



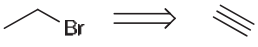
This alkene can be prepared from an alkyne, which can be prepared from acetylene and 1-bromobutane:



1-Bromobutane can be made from 1-butyne, which can be made from acetylene and ethyl bromide via an alkylation process:

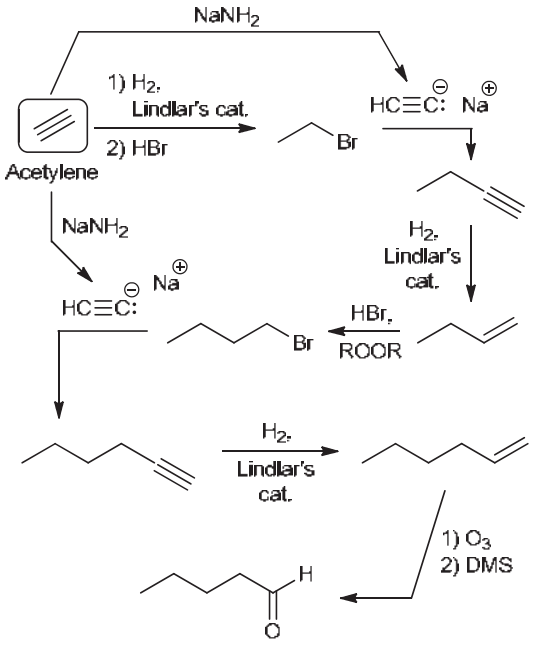


And ethyl bromide can be made from acetylene:

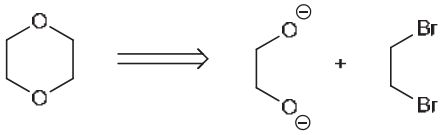


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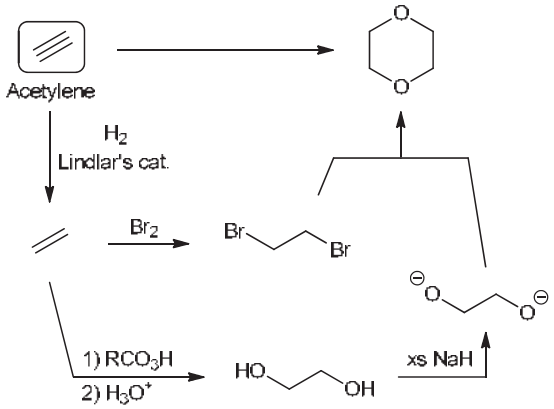
In summary, the desired transformation can be achieved with the following synthesis:



11.31. The key to solving this problem is recognizing that the cyclic product can be made from the following acyclic compounds via two S_N2 reactions:

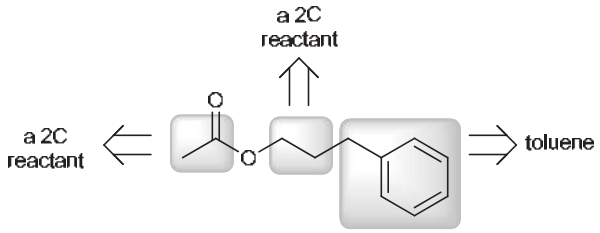


Each of these starting materials can be made from acetylene, as seen in the following synthesis:

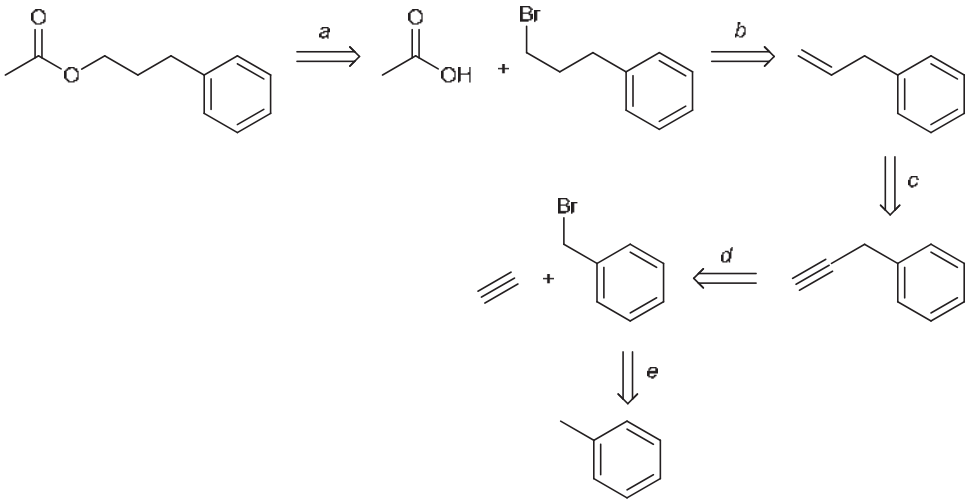


11.32.
The synthesis developed below is only one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.

An analysis of the structure of the product suggests the following origins of each of the carbon atoms in the product.

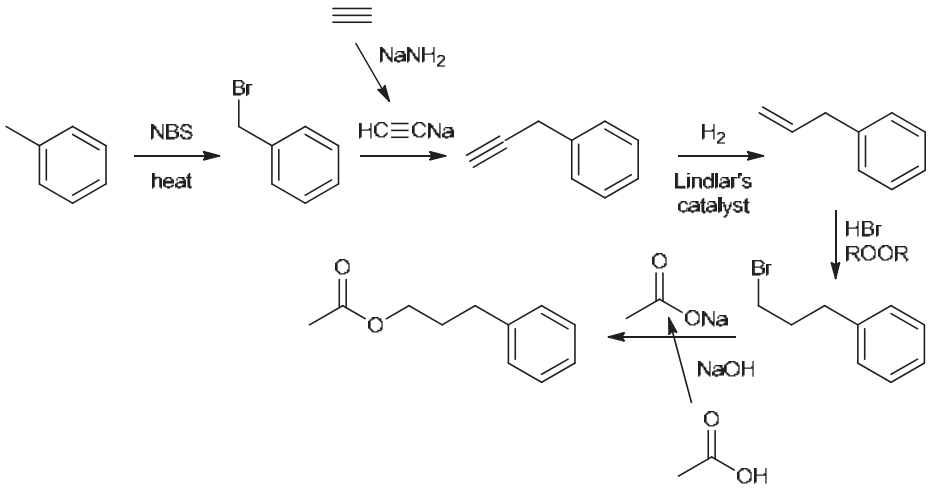


The following figure outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a-f*) follows.

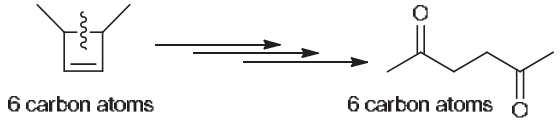


a. The product 3-phenylpropyl acetate can be made via an S_N2 reaction between the carboxylic acid (after deprotonation to make a competent nucleophile) and the primary alkyl bromide.
b. The primary alkyl bromide can be made by *anti*-Markovnikov addition of HBr to the monosubstituted alkene.
c. The alkene is made by reduction of the corresponding terminal alkyne.
d. The terminal alkyne is made by alkylating acetylene (using sodium amide to deprotonate) with benzyl bromide.
e. Benzyl bromide is made via radical bromination of toluene. (The carbon adjacent to the aromatic ring is activated toward bromination due to the resonance-stabilized radical intermediate that forms.)

Now, let's draw the forward scheme. Toluene is brominated using NBS and heat. Reaction with sodium acetylide (made by deprotonating acetylene with sodium amide) produces the terminal alkyne. The alkyne is reduced to the alkene using molecular hydrogen and Lindlar's catalyst. *Anti*-Markovnikov addition of HBr in the presence of peroxides produces the primary alkyl halide. S_N2 substitution with the conjugate base of acetic acid (made by deprotonating acetic acid with sodium hydroxide) produces the desired product.

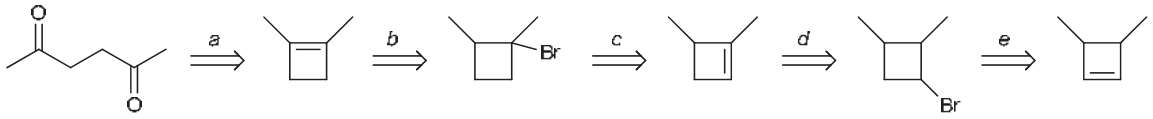


11.33.
The following synthesis is one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.
Take note that the reactant and product each have six carbon atoms. This suggests that our synthetic plan will not necessarily involve any C-C bond-forming reactions. However, there is a change in the carbon skeleton, and we will need a C-C bond-*breaking* reaction to convert the cyclic starting material into an acyclic product.



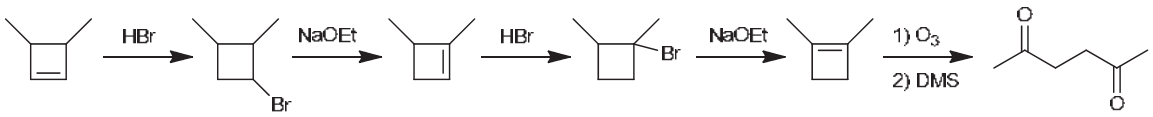
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The product contains two ketone groups, which is suggestive of an ozonolysis. The figure below outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a*-*e*) follows.



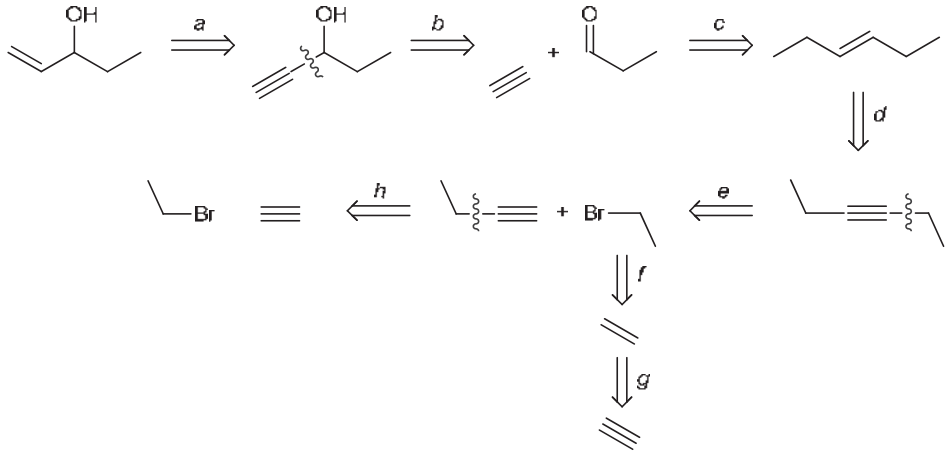
a. The two ketone groups can be prepared via ozonolysis of 1,2-dimethylcyclobutene. This is a key disconnection as it brings us to a synthetic intermediate with the same basic connectivity as the provided reactant (3,4-dimethylcyclobutene). The remaining steps involve reactions to move the position of the double bond.
b. 1,2-dimethylcyclobutene is prepared via elimination from a suitable alkyl halide (*e.g.*, 1-bromo-1,2-dimethylcyclobutane).
c. The tertiary alkyl bromide is prepared via Markovnikov addition of HBr to 1,4-dimethylcyclobutene.
d. This alkene can be prepared via Zaitsev elimination of 1-bromo-2,3-dimethylcyclobutane.
e. This secondary alkyl bromide can be made via addition of HBr to 3,4-dimethylcyclobutene (our provided reactant).

Now, let's draw out the forward scheme. HBr converts 3,4-dimethylcyclobutene to 1-bromo-2,3-methylcyclobutane. Zaitsev elimination using sodium ethoxide affords 1,4-dimethylcyclobutene, which is subsequently converted to 1-bromo-1,2-dimethylcyclobutane using HBr (Markovnikov addition). Elimination, followed by azonolysis of the resulting alkene gives the product, 2,5-hexanedione.



11.34.
The synthesis developed below is only one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.

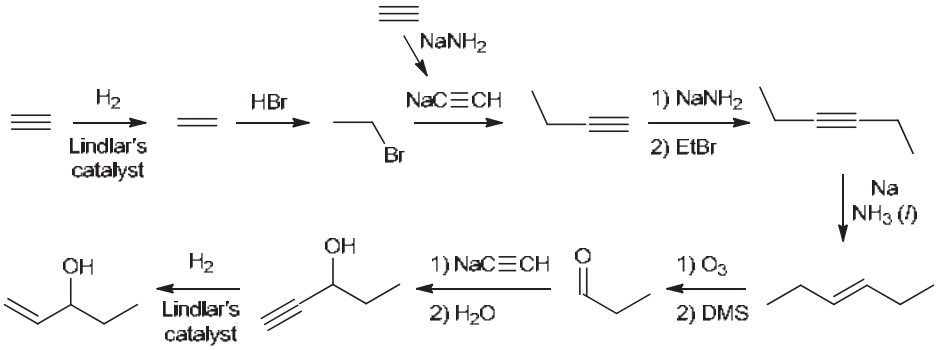
The following figure outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a*-*h*) follows.



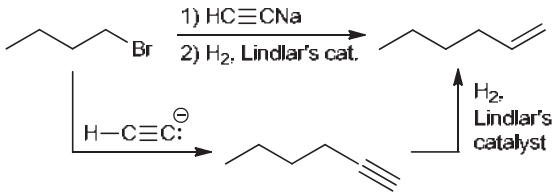
a. 1-Penten-3-ol can be made by reduction of the corresponding terminal alkyne.
b. The terminal alkyne can be made from acetylene (after deprotonation to form a nucleophile) and the aldehyde shown.
c. The aldehyde can be made by ozonolysis of (*E*)-3-hexene.
d. (*E*)-3-Hexene is prepared via reduction of 3-hexyne.
e. 3-Hexyne is made by alkylating 1-butyne with bromoethane.
f. Bromoethane is made by HBr addition to ethylene.
g. Ethylene is made by reduction of acetylene.
h. 1-Butyne is made by alkylation of acetylene using bromoethane (made as described above in steps *f*-*g*).

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Now, let's draw the forward scheme. Acetylene is reduced to ethylene using molecular hydrogen and Lindlar's catalyst. Addition of HBr affords bromoethane. Reaction with sodium acetylide (prepared from acetylene and sodium amide) gives 1-butyne. Deprotonation with sodium amide followed by reaction with bromoethane produces 3-hexyne, which is subsequently reduced to (*E*)-3-hexene using a dissolving metal reduction. Alternatively, hydrogenation in the presence of Lindlar's catalyst will provide the *Z* alkene, which will also lead to the product via the same steps. Ozonolysis produces two equivalents of the desired aldehyde. Reaction with sodium acetylide gives the alkyne/alcohol which is reduced to the product using molecular hydrogen and Lindlar's catalyst.



11.35. The starting material has four carbon atoms, and the product has six carbon atoms. The installation of two carbon atoms can be achieved by treating the starting primary alkyl bromide with sodium acetylide. The resulting alkylation product (a terminal alkyne) can then be reduced to an alkene via hydrogenation with a poisoned catalyst, such as Lindlar's catalyst:



Therefore, the correct answer is therefore (c).

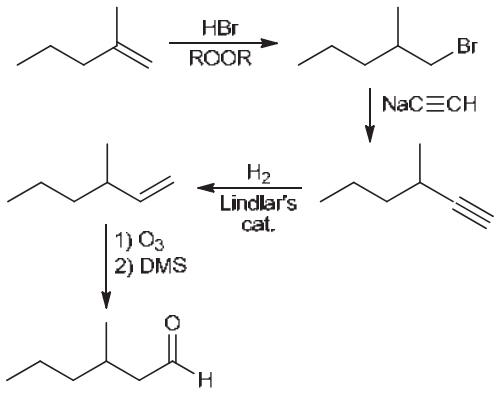
11.36. Option (a) does not work, because the OH group is not a good leaving group. Upon treatment with a strong base, such as NaOEt, the OH group will simply be deprotonated to give an alkoxide ion. The elimination product will not be obtained.

Option (b) does not work, because the second step (elimination) employs a sterically hindered base. As a result, that process will give the Hofmann product, not the Zaitsev product.

Option (c) is the correct answer. In the first step, the bromine atom is installed at the tertiary position. Then, in the second step, a strong base will give the Zaitsev elimination reaction, affording the desired product.

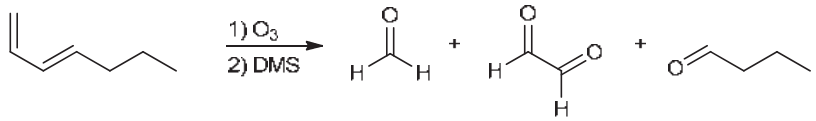
Option (d) does not work, because alkenes do not have an acidic proton like terminal alkynes.

11.37. Option (a) does not work because, in the second step, and OH group cannot function as a leaving group. Option (b) does not work because the final step (ozonolysis of an alkyne) will give a carboxylic acid, rather than an aldehyde. Option (c) does not work because the product will have too many carbon atoms (the starting material has six carbon atoms, and the product has seven carbon atoms, not eight). Option (d) is the correct answer, as shown below. *Anti*-Markovnikov addition of HBr gives a primary alkyl bromide, which is then converted into a terminal alkyne upon treatment with sodium acetylide. The terminal alkyne is then reduced to an alkene, followed by ozonolysis to give the desired aldehyde:



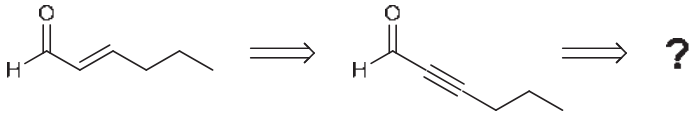
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11.38.
The following synthesis is one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.
The target molecule, (*E*)-2-hexenal, is bifunctional - containing both an alkene group and an aldehyde group. We have learned two ways to make aldehydes: (i) ozonolysis of alkenes and (ii) *anti*-Markovnikov hydration of terminal alkynes. In this case, it is not immediately apparent which of these methods we should use. For example, ozonolysis of the compound below would not be a good approach, as both C=C bonds are susceptible to cleavage, yielding the following three products.

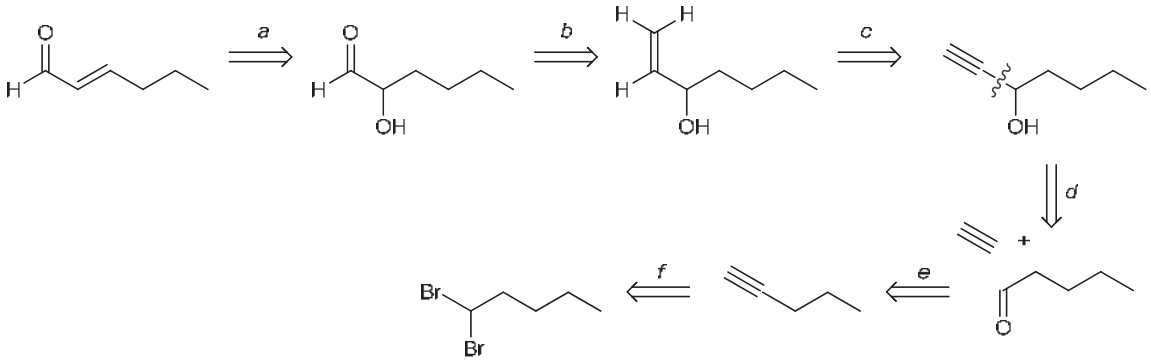


Anti-Markovnikov hydration of a terminal alkyne also does not appear to be a viable approach, as there is no obvious precursor that would allow installation of the C=C double bond adjacent to the aldehyde group.

Likewise, we know two ways to make an alkene: (i) reduction of an alkyne and (ii) elimination. We could potentially make the target molecule from the corresponding alkyne, but it is unclear what the next retrosynthetic step should be. (Note that in Chapter 13, we will learn reactions to make this approach possible.)



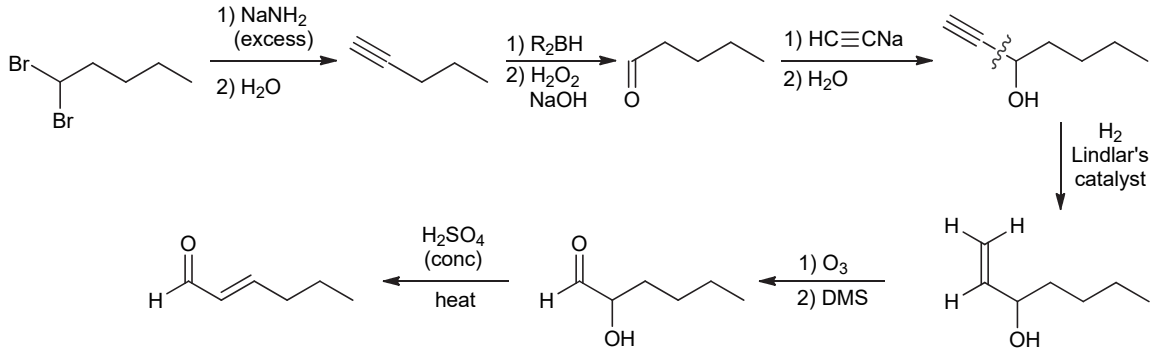
Installing the alkene group by elimination turns out to be a viable approach in this case, as described below.
The figure below outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a-f*) follows.



a. The target compound can be made via elimination of the alcohol under acidic conditions.
b. The aldehyde can be made by ozonolysis of the alkene shown here. Note that this compound only has one C=C double bond, so we avoid the problem described above with ozonolysis of a diene.
c. The alkene can be made by partial reduction of the corresponding alkyne.
d. This compound can be made from the reaction between an acetylide ion and the aldehyde shown (see problem 11.28).
e. The aldehyde is made from *anti*-Markovnikov addition of water to 1-pentyne.
f. 1-Pentyne is made from 1,1-dibromopentane by double elimination.

Now let's draw the forward scheme. 1,1-Dibromopentane is converted to 1-pentyne by reaction with excess sodium amide (to afford double elimination followed by deprotonation of the resulting alkyne), followed by aqueous workup to protonate the terminal alkynide. 1-Pentyne is converted to the aldehyde via hydroboration/oxidation. Subsequent reaction with sodium acetylide, followed by aqueous workup, produces an alcohol. Reduction with H_2 and Lindlar's catalyst converts the alkyne group to an alkene group. Ozonolysis converts the alkene to an aldehyde. Reaction with concentrated acid allows for elimination of the alcohol, producing the target compound.

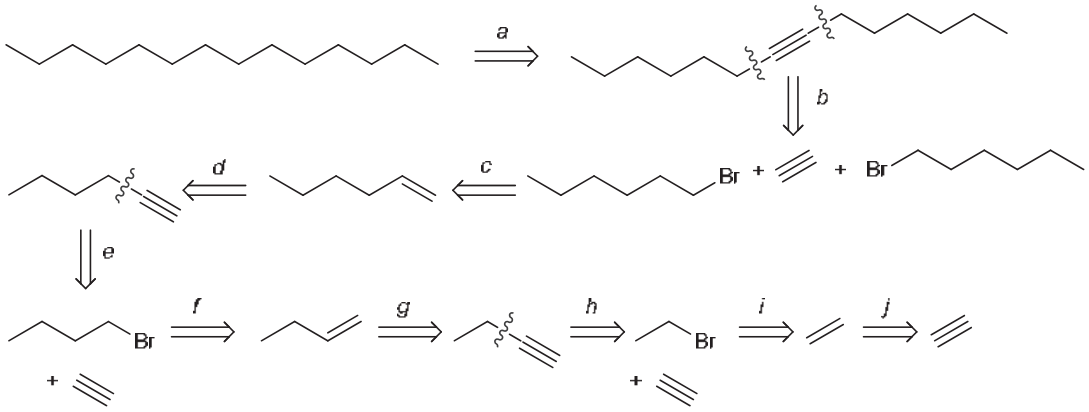
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11.39.
The synthesis developed below is only one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.

As seen in Table 4.1, tetradecane is a saturated hydrocarbon with 14 carbon atoms (with no branching), and our source of carbon (acetylene) has two carbon atoms, so we will likely use 7 equivalents of acetylene in this synthesis. There are a number of different approaches to complete this synthesis, including connecting two carbon atoms at a time sequentially from one end, or disconnecting it symmetrically from the center. The retrosynthesis below takes the latter of these two tactics.

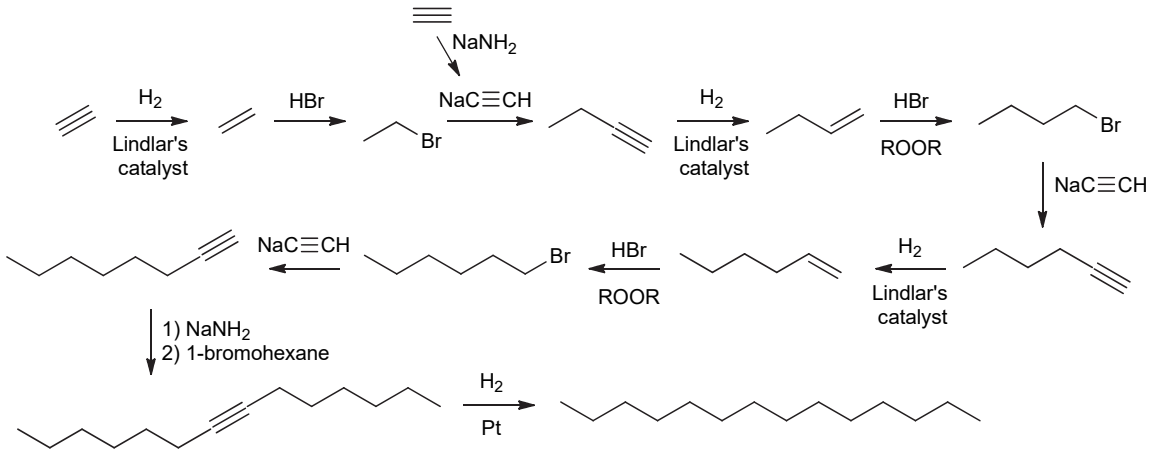
The figure below outlines a retrosynthetic analysis for our target molecule, employing squiggly lines to indicate C-C bonds that are disconnected in the retrosynthetic direction. An explanation of each of the steps (*a-j*) follows.



a. Tetradecane can be made via hydrogenation of 7-tetradecyne.
b. 7-Tetradecyne can be made by sequentially alkylating both sides of acetylene with 1-bromohexane.
c. 1-Bromohexane is made via an *anti*-Markovnikov addition of HBr across 1-hexene.
d. 1-Hexene is made by reduction of 1-hexyne using H_2 and Lindlar's catalyst.
e. 1-Hexyne can be produced from acetylene (after deprotonation to make a nucleophile) and 1-bromobutane.
f. 1-Bromobutane is made via an *anti*-Markovnikov addition of HBr across 1-butene.
g. 1-Butene is made by reduction of 1-butyne using H_2 and Lindlar's catalyst.
h. 1-Butyne is made from acetylene (after deprotonation) and 1-bromoethane.
i. 1-Bromoethane is made by addition of HBr across ethylene.
j. Ethylene is made by reduction of acetylene using H_2 and Lindlar's catalyst.

Now, let's draw out the forward scheme. Acetylene is reduced to ethylene using H_2 and Lindlar's catalyst. HBr addition, followed by S_N2 substitution with an acetylide nucleophile (made by deprotonation of acetylene with sodium amide) gives 1-butyne. Reduction to 1-butene with H_2 and Lindlar's catalyst followed by *anti*-Markovnikov addition of HBr in the presence of peroxide produces 1-bromobutane. A substitution reaction with sodium acetylide gives 1-hexyne. Another round of hydrogenation (H_2, Lindlar's catalyst), *anti*-Markovnikov addition (HBr, peroxide) and substitution (sodium acetylide) lengthens the chain by two more carbons, giving 1-octyne. Deprotonation of this terminal alkyne, followed by alkylation with another equivalent of 1-bromohexane yields 7-tetradecyne. Hydrogenation with H_2 and Pt produces the desired product, tetradecane.

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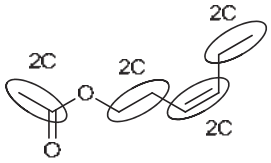


11.40.
The synthesis developed below is only one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.

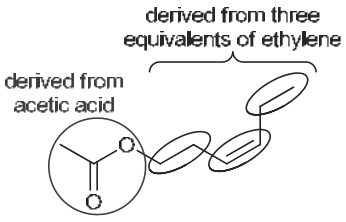
Acetic acid and ethylene each have two carbon atoms, and our product has eight carbon atoms. So our synthesis will need to involve a total of *four* equivalents of starting materials in order to produce a product with eight carbon atoms.



A more detailed look at the product allows us to hypothesize where each of the two-carbon components will ultimately end up in the product (below). This is helpful in that it may allow us to determine which new bonds will be formed in the course of the reaction (*i.e.*, those connecting each of the 2C components).



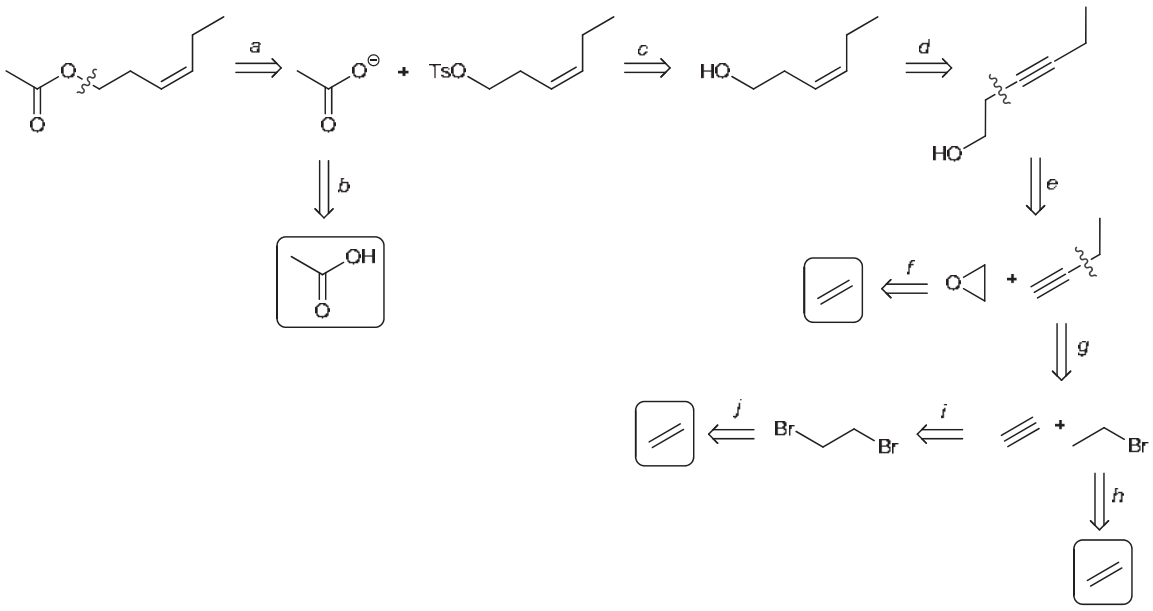
By comparing the structures of the reactants and product, we can also make an initial guess on the origins of each of the 2C components (shown below). It seems reasonable to assume that the ester will be derived from acetic acid (as both of these have a carbonyl flanked by a methyl group and an oxygen), and the other three 2C components will be derived from ethylene (with appropriate functional group modification).



When considering which types of reactions to use, we will connect these pieces using a number of substitution reactions. Also, the only way we have learned to produce a *cis* alkene is via hydrogenation of an alkyne using H_2 and Lindlar's catalyst, so this will clearly be one of our steps.

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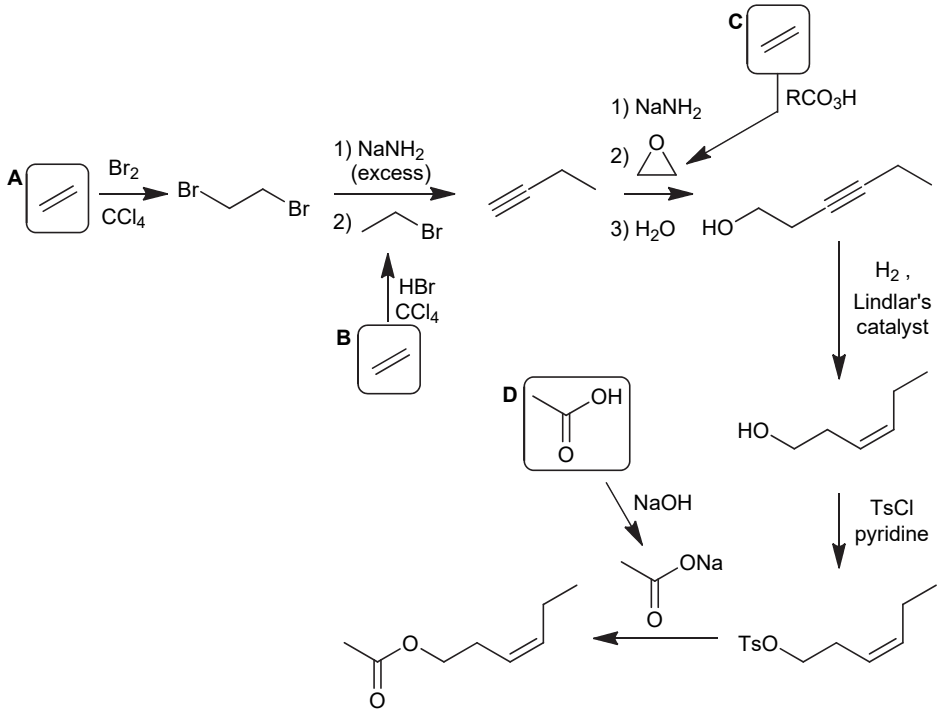
The figure below outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a-j*) follows.



a. The indicated C-O bond (wavy line) can be made via an S_N2 reaction between a carboxylate (the conjugate base of a carboxylic acid) and a substrate with an appropriate leaving group (*e.g.*, tosylate).
b. The carboxylate can be prepared from acetic acid (one of our given reactants) by treatment with a suitable base, such as NaOH.
c. The tosylate can be prepared from the corresponding alcohol.
d. The *cis* alkene can be produced from the corresponding alkyne (H_2 / Lindlar's catalyst).
e. This retrosynthetic step is the key disconnection that utilizes the reaction described in the problem statement. We can make this internal alkyne/alcohol by the reaction of an alkynide ion (formed by deprotonating 1-butyne) and an epoxide.
f. The epoxide is prepared from ethylene via epoxidation.
g. 1-Butyne is prepared by alkylating the conjugate base of acetylene using bromoethane.
h. Bromoethane is prepared via HBr addition to ethylene.
i. Acetylene is prepared via a double elimination from 1,2-dibromoethane.
j. 1,2-Dibromoethane is prepared via bromination of ethylene.

Now, let's draw out the forward scheme. This multi-step synthesis uses three equivalents of ethylene (labeled **A**, **B**, **C** in the scheme shown) and one equivalent of acetic acid (labeled **D**). Ethylene (**A**) is converted to 1,2-dibromoethane upon treatment with bromine. Subsequent reaction with excess sodium amide produces an acetylide anion which is then treated with bromoethane [made from ethylene (**B**) and HBr] to produce 1-butyne. Deprotonation with sodium amide, followed by reaction with an epoxide [prepared by epoxidation of ethylene (**C**)] and water workup, produces a compound with an alkyne group and an alcohol group. Reduction of the alkyne to the *cis* alkene is accomplished with H_2 and Lindlar's catalyst, after which the alcohol is converted to a tosylate with tosyl chloride. Reaction with the conjugate base of acetic acid [produced by treating acetic acid (**D**) with NaOH] allows for an S_N2 reaction, thus yielding the desired product, *Z*-hexenyl acetate.

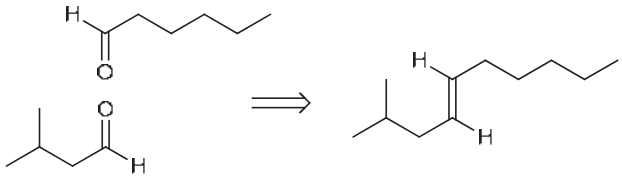
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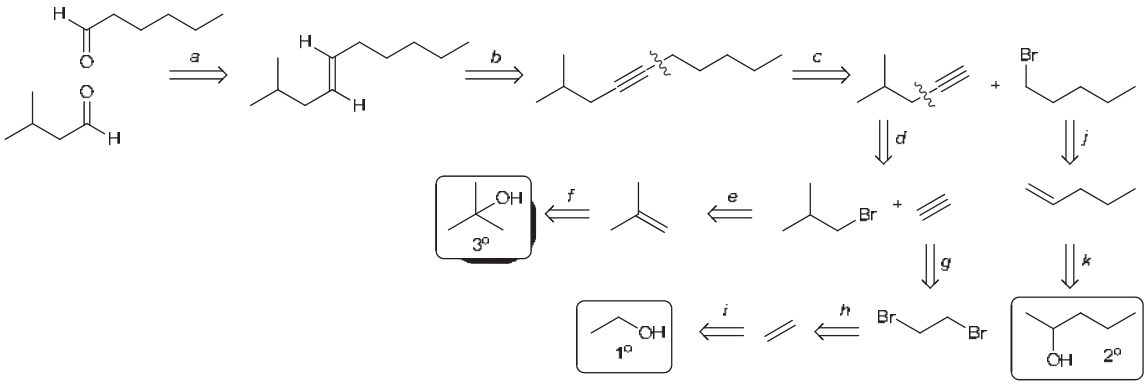
11.41.

The following synthesis is one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.

Thus far, we have learned two ways to make aldehydes: (i) *anti*-Markovnikov hydration of a terminal alkyne or (ii) ozonolysis of an alkene, either of which is potentially reasonable here. However, in order to produce both of these compounds from a single synthetic protocol, a key recognition is that they can be produced from ozonolysis of the following disubstituted alkene.



The following figure outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a*-*k*) follows.



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a. The mixture of aldehydes can be made by ozonolysis of this disubstituted alkene (*trans*-2-methyl-4-decene), as described above. (Note that the *E* alkene is shown here, but ozonolysis of the *Z* alkene would also produce the same two aldehydes.)

b. Thus far, we have learned two methods to make an alkene: 1) reduction of an alkyne or 2) elimination. In this case, the better choice to make this alkene is by reduction of the corresponding internal alkyne. The reason for this is explained in the next step.

c. We have to start our synthesis with compounds with fewer than six carbons, so this alkyne is a useful intermediate because we know how to make bonds between *sp* and sp^3 hybridized carbon atoms. This internal alkyne can thus be made from 4-methyl-1-pentyne (which must be deprotonated to produce a nucleophile) and 1-bromopentane.

d. The terminal alkyne can be made from acetylene (which must be deprotonated to produce a nucleophile) and 1-bromo-2-methylpropane.

e. Recall that we need to start with one 1°, one 2° and one 3° alcohol. The synthetic intermediate 1-bromo-2-methylpropane is the only one with a 3° carbon, so it follows that this compound is the one produced from a 3° alcohol. With this in mind, the alkyl halide can be produced from *anti*-Markovnikov addition of HBr to an alkene.

f. The alkene can be made from acid-catalyzed dehydration of the 3° alcohol.

g. Acetylene has only two carbons, so the only type of alcohol that can be used to make it is a 1° alcohol. Acetylene is thus made from double elimination of 1,2-dibromoethane.

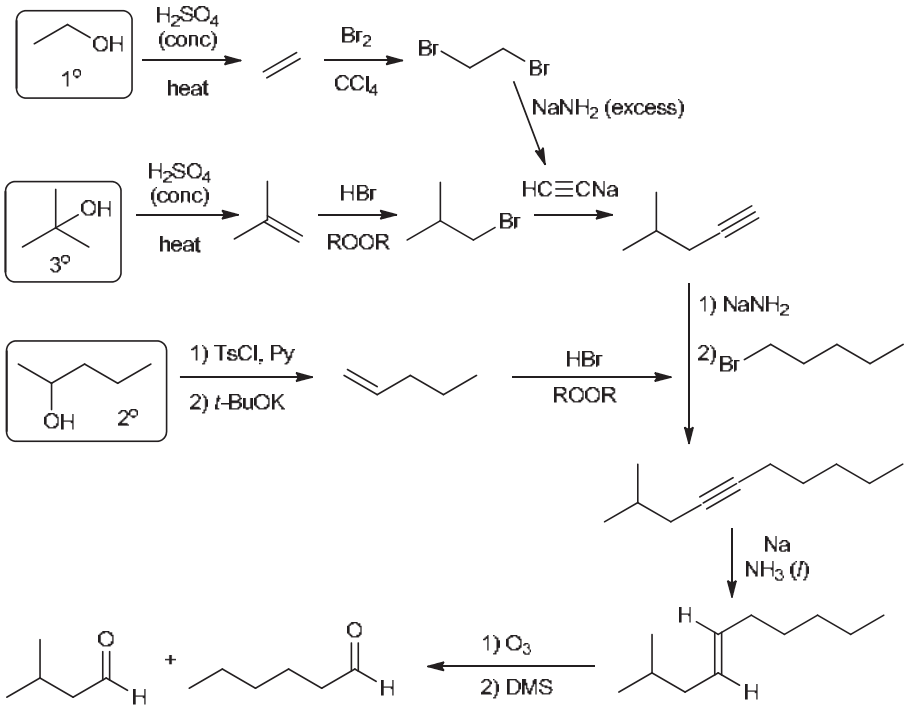
h. 1,2-Dibromoethane is produced by bromination of ethylene.

i. Ethylene is produced by acid-catalyzed elimination from ethanol, a 1° alcohol.

j. 1-Bromopentane is made by *anti*-Markovnikov addition of HBr to 1-pentene.

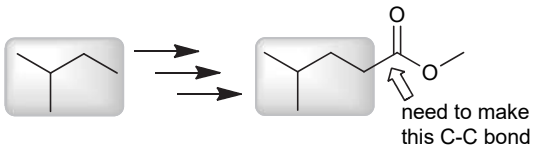
k. 1-Pentene is made from the 2° alcohol by tosylation followed by reaction with a bulky base to give the less substituted product.

Now let's draw the forward scheme. The 3° alcohol is converted to 2-methylpropene using strong acid. *Anti*-Markovnikov addition of HBr (with peroxides) produces 1-bromo-2-methylpropane. Subsequent reaction with sodium acetylide (produced from the 1° alcohol by dehydration, bromination and double elimation/deprotonation as shown) produces 4-methyl-1-pentyne. Deprotonation with sodium amide followed by reaction with 1-bromopentane (made from the 2° alcohol by tosylation, elimination and *anti*-Markovnikov addition) yields 2-methyl-4-decyne. Reduction using sodium in liquid ammonia produces the *E* alkene. Ozonolysis followed by treatment with dimethylsulfide produces an equimolar ratio of the two products, 3-methylbutanal and hexanal.

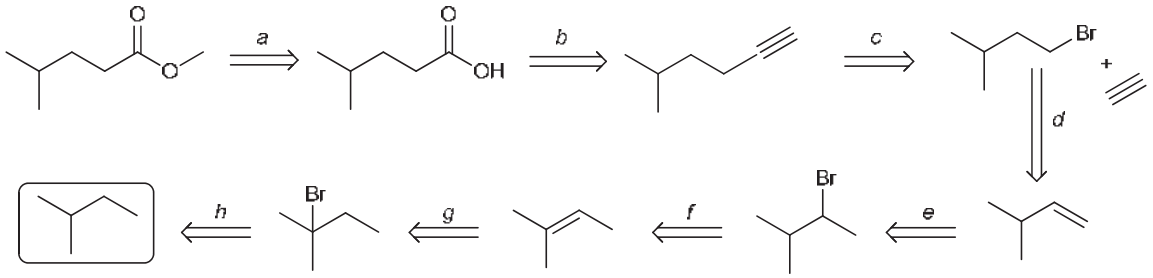


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11.42.
The following synthesis is one suggested synthetic pathway. There are likely other acceptable approaches that accomplish the same goal.
An analysis of the structure of the product reveals that the five-carbon alkyl group (highlighted below) matches the skeletal structure of 2-methylbutane, the given starting material. This indicates which C-C bond (arrow) must be made in the course of the synthesis.

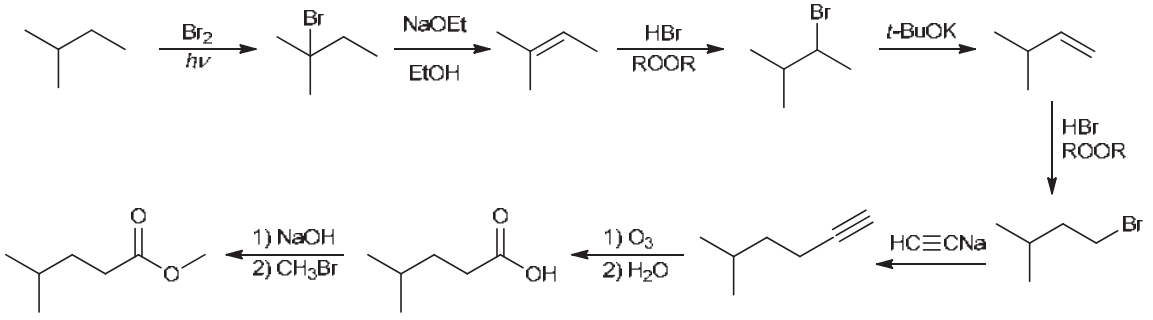


The figure below outlines a retrosynthetic analysis for our target compound. An explanation of each of the steps (*a*-*h*) follows.



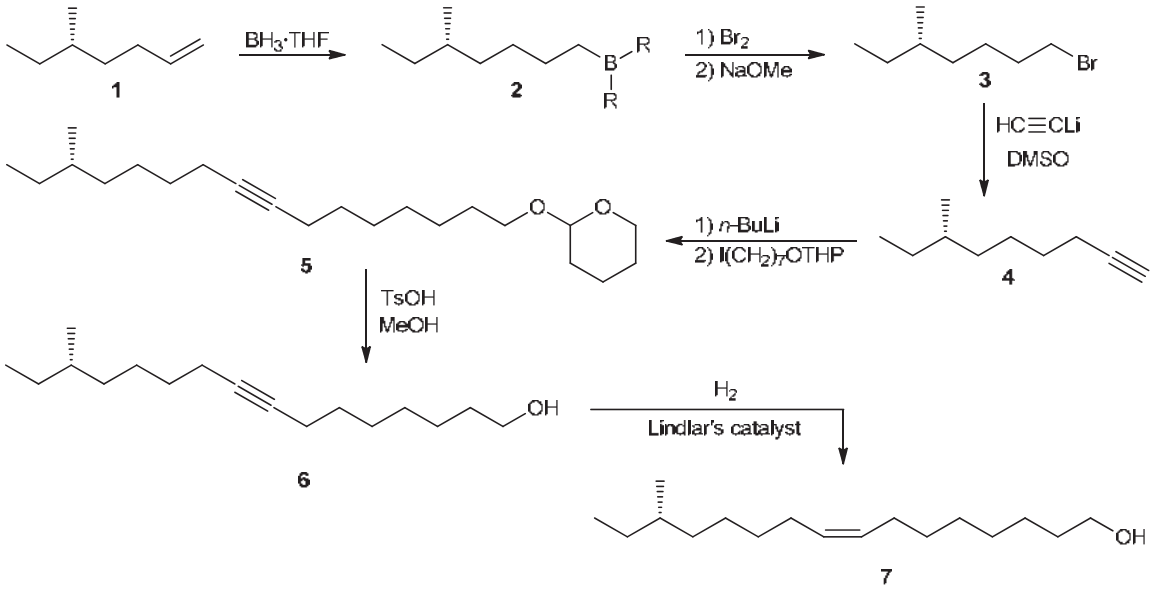
a. The only way we have learned to make an ester (so far) is via a reaction of a carboxylate nucleophile (the conjugate base of a carboxylic acid) and an alkyl halide (in this case, bromomethane).
b. The only way we have learned to make a carboxylic acid (so far) is by ozonolysis of an alkyne. An alternative intermediate to the terminal alkyne shown would be the symmetric internal alkyne, 2,9-dimethyl-5-decyne (not shown), which would produce two equivalents of the target carboxylic acid upon ozonolysis.
c. The alkyne is prepared from the reaction of 1-bromo-3-methylbutane with an acetylide anion (formed by deprotonating acetylene). This alkyl halide has the same carbon skeleton as our given starting material (2-methylbutane), so our remaining steps involve primarily functional group manipulation.
d. Knowing that the first synthetic step must be radical halogenation of 2-methylbutane to produce the tertiary alkyl halide (the only useful reaction of alkanes), we need to migrate the functionality back toward the tertiary carbon in this retrosynthetic analysis. Thus, 1-bromo-3-methylbutane can be prepared via *anti*-Markovnikov addition of HBr to 3-methyl-1-butene.
e. 3-Methyl-1-butene is prepared via elimination (with a sterically hindered base) from 2-bromo-3-methylbutane.
f. 2-Bromo-3-methylbutane is prepared via *anti*-Markovnikov addition of HBr to 2-methyl-2-butene.
g. 2-Methyl-2-butene is prepared via Zaitsev elimination from 2-bromo-2-methylbutane.
h. 2-bromo-2-methylbutane is made from our given starting material, 2-methylbutane, via radical bromination.

Now, let's draw the forward scheme. Radical bromination of 2-methylbutane produces the tertiary alkyl halide, selectively. Then, elimination with NaOEt, followed by *anti*-Markovnikov addition (HBr / peroxides), and then elimination with *tert*-butoxide, followed by another *anti*-Markovnikov addition (HBr / peroxides) produces 1-bromo-3-methylbutane. This alkyl halide will then undergo an S_N2 reaction when treated with an acetylide ion to give 5-methyl-1-hexyne. Ozonolysis of this terminal alkyne cleaves the CC triple bond, producing the carboxylic acid. Deprotonation (with NaOH) produces a carboxylate nucleophile that subsequently reacts with bromomethane in an S_N2 reaction to give the desired ester.



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11.43. Treatment of compound **1** with BH_3 affords a chiral organoborane (**2**). Compound **3** is an alkyl halide, which is expected to react with an acetylide ion in an S_N2 reaction, to give compound **4**. Upon treatment with the strong base BuLi, compound **4** is deprotonated to give an alkynide ion, which then serves as a nucleophile in an S_N2 reaction to give compound **5**. As described in the problem statement, treatment of compound **5** with TsOH in methanol gives an alcohol (**6**). In the final step of the sequence, the triple bond in compound **6** is reduced to give a *cis* alkene (compound **7**).



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Chapter 12
Alcohols

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 12. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

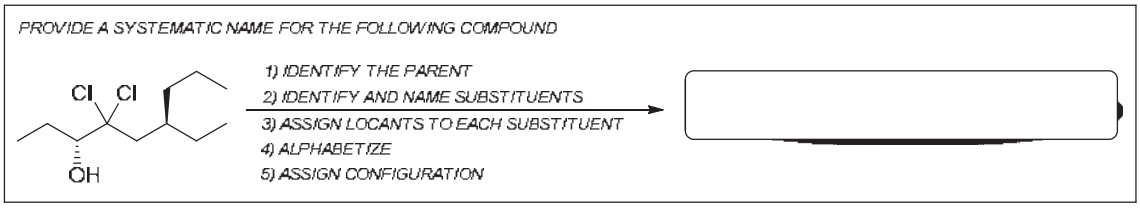
- When naming an alcohol, the parent is the longest chain containing the _____ group.
- The conjugate base of an alcohol is called an _____ ion.
- Several factors determine the relative acidity of alcohols, including _____, _____, and _____.
- The conjugate base of phenol is called a _____, or _____ ion.

- When preparing an alcohol via a substitution reaction, primary substrates will require S_N___ conditions, while tertiary substrates will require S_N___ conditions.
- Alcohols can be formed by treating a _____ **group** (C=O bond) with a _____ **agent**.
- **Grignard reagents** are carbon nucleophiles that are capable of attacking a wide range of _____, including the carbonyl group of ketones or aldehydes, to produce an alcohol.
- _____ **groups**, such as the trimethylsilyl group, can be used to circumvent the problem of Grignard incompatibility and can be easily removed after the desired Grignard reaction has been performed.
- Tertiary alcohols will undergo an S_N___ reaction when treated with a hydrogen halide.
- Primary and secondary alcohols will undergo an S_N___ process when treated with either HX, $SOCl_2$, PBr_3, or when the hydroxyl group is converted into a tosylate group followed by nucleophilic attack.
- Tertiary alcohols undergo E1 elimination when treated with _____.
- Primary alcohols undergo **oxidation** twice to give a _____.
- Secondary alcohols are oxidized only once to give a _____
- PCC can be used to convert a primary alcohol into an _____. Alternatively, primary alcohols can be converted into _____ with a _____ oxidation or a DMP-based oxidation.
- NADH is a biological reducing agent that functions as a _____ delivery agent (very much like $NaBH_4$ or $LiAlH_4$), while NAD^+ is an _____ agent.
- There are two key issues to consider when proposing a synthesis:
    1. A change in the _____.
    2. A change in the _____.

Review of Skills

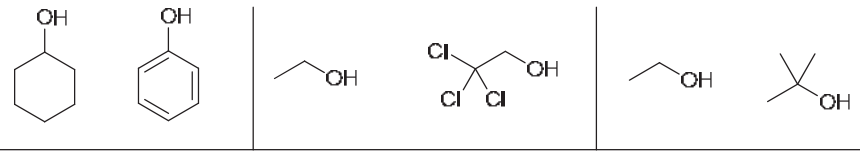
Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 12. The answers appear in the section entitled *SkillBuilder Review*.

12.1 Naming an Alcohol



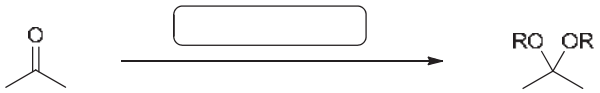
12.2 Comparing the Acidity of Alcohols

FOR EACH PAIR OF COMPOUNDS BELOW, CIRCLE THE COMPOUND THAT IS MORE ACIDIC:



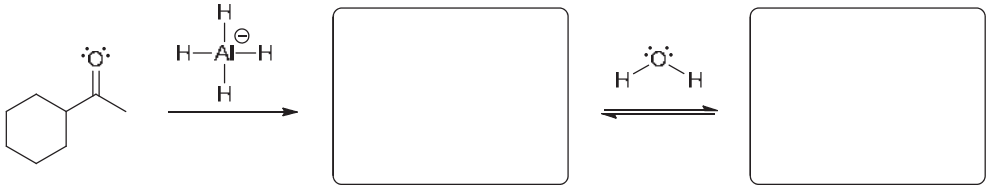
12.3 Identifying Oxidation and Reduction Reactions

IN THE FOLLOWING REACTION, DETERMINE WHETHER THE STARTING MATERIAL HAS BEEN OXIDIZED, REDUCED, OR NEITHER:



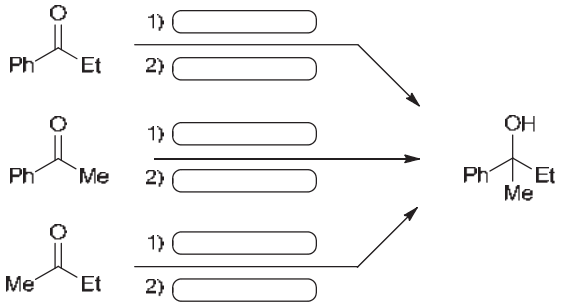
12.4 Drawing a Mechanism, and Predicting the Products of Hydride Reductions

COMPLETE THE MECHANISM BELOW BY DRAWING ALL CURVED ARROWS, INTERMEDIATES AND PRODUCTS.



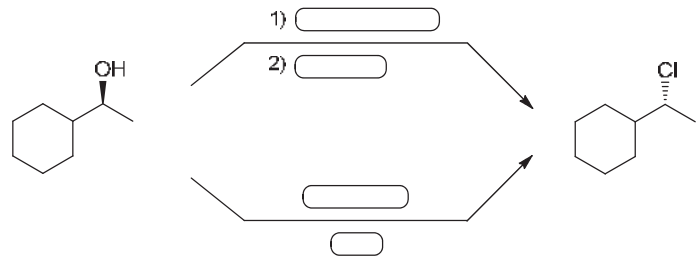
12.5 Preparing an Alcohol via a Grignard Reaction

IDENTIFY REAGENTS THAT CAN ACHIEVE EACH OF THE FOLLOWING TRANSFORMATIONS



12.6 Proposing Reagents for the Conversion of an Alcohol into an Alkyl Halide

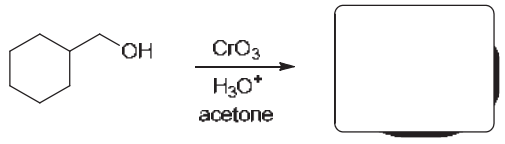
IDENTIFY REAGENTS THAT CAN ACHIEVE EACH OF THE FOLLOWING TRANSFORMATIONS



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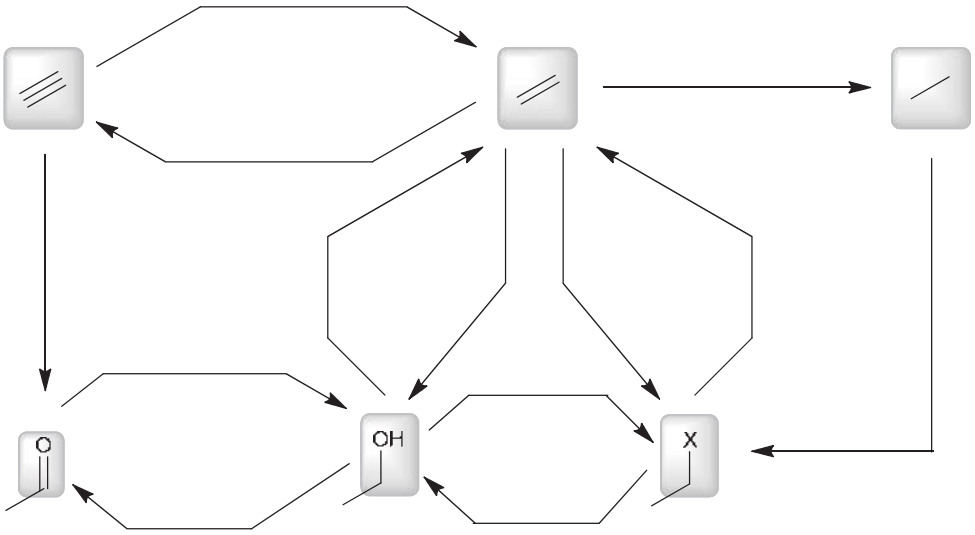
12.7 Predicting the Products of an Oxidation Reaction

DRAW THE EXPECTED PRODUCT OF THE FOLLOWING REACTION



12.8 Converting Functional Groups

IDENTIFY REAGENTS THAT CAN ACHIEVE EACH OF THE FOLLOWING FUNCTIONAL GROUP TRANSFORMATIONS



12.9 Proposing a Synthesis

AS A GUIDE FOR PROPOSING A SYNTHESIS, ASK THE FOLLOWING TWO QUESTIONS:

1) IS THERE A CHANGE IN THE _____ SKELETON?

2) IS THERE A CHANGE IN THE LOCATION OR IDENTITY OF THE _____?

AFTER PROPOSING A SYNTHESIS, USE THE FOLLOWING TWO QUESTIONS TO ANALYZE YOUR ANSWER:

1) IS THE _____ OUTCOME OF EACH STEP CORRECT?

2) IS THE _____ OUTCOME OF EACH STEP CORRECT?

Review of Reactions

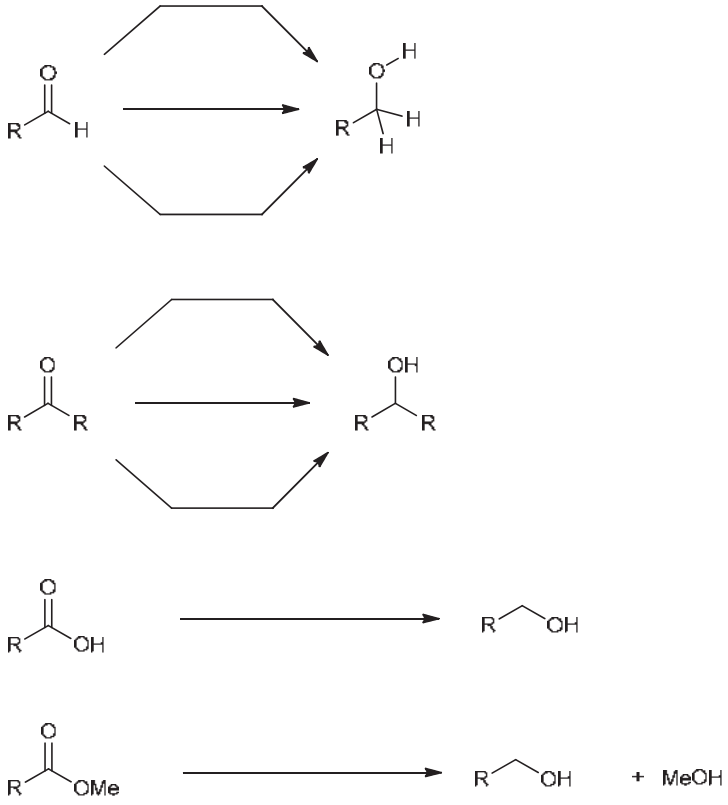
Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 13. The answers appear in the section entitled *Review of Reactions*.

Preparation of Alkoxides

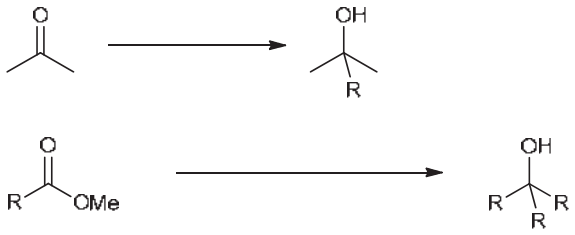


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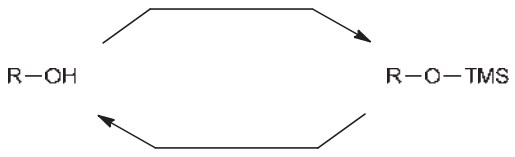
Preparation of Alcohols via Reduction



Preparation of Alcohols via Grignard Reagents



Protection and Deprotection of Alcohols

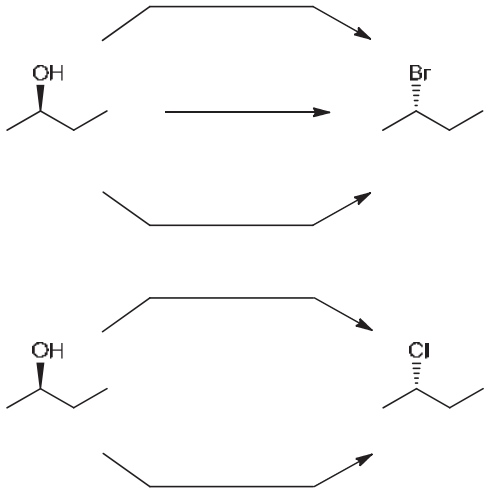


S_N1 Reactions with Alcohols

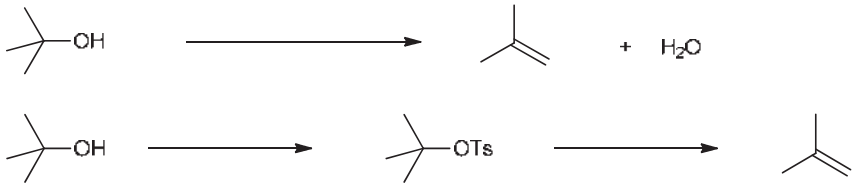


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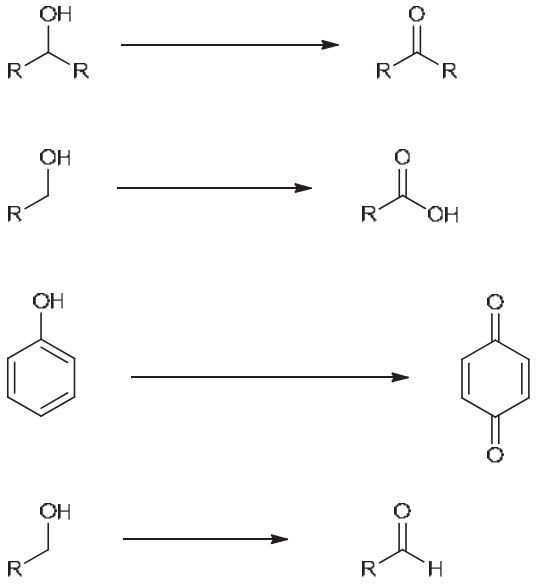
S_N2 Reactions with Alcohols



E1 and E2 Reactions with Alcohols



Oxidation of Alcohols and Phenols



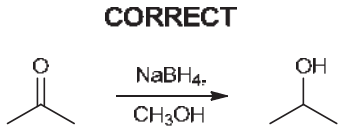
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Common Mistakes to Avoid

If you are proposing a synthesis that involves reduction of a ketone or aldehyde with $LiAlH_4$, make sure that the water workup is shown as a separate step:



This is important because $LiAlH_4$ is incompatible with the proton source. In contrast, $NaBH_4$ is used in the presence of a proton source:



So, when using $NaBH_4$ as a reducing agent, do not show the proton source (MeOH) as a separate step.

Also, when drawing a mechanism for the reduction of a ketone, aldehyde, or ester, make sure that the first curved arrow is placed on the Al–H bond, rather than on the negative charge:



In previous chapters, we have seen that it is generally acceptable to place the tail of a curved arrow on a negative charge, but this is an exceptional case. The negative charge in this case is not associated with a lone pair, so the tail of the curved arrow cannot be placed on the negative charge. It must be placed on the bond. This is true for reductions involving $NaBH_4$ as well:



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Useful reagents

The following is a list of reagents that were new in this chapter:

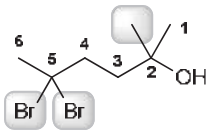
Reagents	Function
NaH	A very strong base, used to deprotonate an alcohol to give an alkoxide ion.
Na	Will react with an alcohol to liberate hydrogen gas, giving an alkoxide ion.
$NaBH_4$, MeOH	A reducing agent. Can be used to reduce ketones or aldehydes to alcohols. Will not reduce esters or carboxylic acids.
1) $LiAlH_4$ 2) H_2O	A strong reducing agent. Can be used to reduce ketones, aldehydes, esters, or carboxylic acids to give an alcohol.
H_2, Pt	Reducing agent. Generally used to reduce alkenes to alkanes, but in some cases, it can also be used to reduce ketones to alcohols.
Mg	Can be used to convert an alkyl halide (RX) into a Grignard reagent (RMgX).
RMgX	A Grignard reagent. Examples include MeMgBr, EtMgBr and PhMgBr. These reagents are very strong nucleophiles (and very strong bases as well), and they will react with aldehydes or ketones. Aldehydes are converted into secondary alcohols (except for formaldehyde which is converted to a primary alcohol), while ketones are converted to tertiary alcohols. Esters are converted to tertiary alcohols when treated with excess Grignard.
TMSCl, Et_3N	Trimethylsilyl chloride, in the presence of a base (such as triethylamine), will protect an alcohol.
TBAF	Tetrabutyl ammonium fluoride. Used for deprotection of alcohols with silyl protecting groups.
HX	HBr and HCl are strong acids that also provide a source of a strong nucleophile. Can be used to convert an alcohol into an alkyl halide.
TsCl, pyridine	Will convert an alcohol into a tosylate. This is important because it converts a bad leaving group (HO^-) into a good leaving group (TsO^-).
PBr_3	Can be used to convert a primary or secondary alcohol into an alkyl bromide. If the OH group is connected to a chiral center, we expect inversion of configuration (typical for an S_N2 process).
$SOCl_2$, pyridine	Can be used to convert a primary or secondary alcohol into an alkyl chloride. If the OH group is connected to a chiral center, we expect inversion of configuration (typical for an S_N2 process).
HCl, $ZnCl_2$	Can be used to convert an alcohol into an alkyl chloride.
$Na_2Cr_2O_7$, H_2SO_4, H_2O	A mixture of sodium dichromate and sulfuric acid gives chromic acid, which is a strong oxidizing agent. Primary alcohols are oxidized to give carboxylic acids, while secondary alcohols are oxidized to give ketones. Tertiary alcohols are generally unreactive.
PCC, CH_2Cl_2	A mild oxidizing agent that will oxidize a primary alcohol to give an aldehyde, rather than a carboxylic acid. Secondary alcohols are oxidized to give ketones.
DMP, CH_2Cl_2	A mild oxidizing agent that will oxidize a primary alcohol to give an aldehyde, rather than a carboxylic acid. Secondary alcohols are oxidized to give ketones.
1) DMSO, $(COCl)_2$, 2) Et_3N	The Swern oxidation will oxidize a primary alcohol to give an aldehyde, rather than a carboxylic acid. Secondary alcohols are oxidized to give ketones.

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Solutions

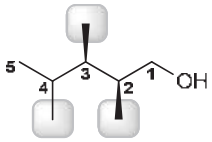
12.1.

(a) We begin by identifying the parent. The carbon atom connected to the OH group must be included in the parent. The longest chain that includes this carbon atom is six carbon atoms in length, so the parent is hexanol. There are three substituents (highlighted). Notice that the parent chain is numbered starting from the side that is closest to the OH group (the OH group is at C2 rather than C5). According to this numbering scheme, the methyl group is located at C2, and the bromine atoms are both at C5. Finally, we assemble the substituents alphabetically. The compound does not contain any chiral centers.



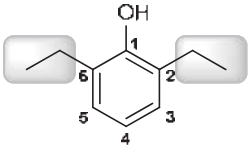
5,5-dibromo-2-methylhexan-2-ol

(b) We begin by identifying the parent. The carbon atom connected to the OH group must be included in the parent. The longest chain that includes this carbon atom is five carbon atoms in length, so the parent is pentanol. There are three substituents (highlighted), all of which are methyl groups. Notice that the parent chain is numbered starting from the side that is closest to the OH group (thereby placing the OH group at C1). According to this numbering scheme, the methyl groups are at C2, C3 and C4. We use the prefix "tri" to indicate three methyl groups. Finally, we assign a configuration to each chiral center.



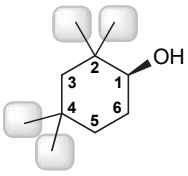
(2*S*,3*R*)-2,3,4-trimethylpentan-1-ol

(c) We begin by identifying the parent (phenol). There are two substituents (highlighted), both of which are ethyl groups. Notice that the ring is numbered starting from the carbon atom bearing the OH group (it is not necessary to indicate a locant for the OH group, because in a ring, it is assumed to be at C1, by definition). According to this numbering scheme, the ethyl groups are at C2 and C6. We use the prefix "di" to indicate two ethyl groups. The compound does not contain any chiral centers.



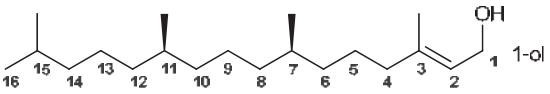
2,6-diethylphenol

(d) We begin by identifying the parent. The carbon atom connected to the OH group must be included in the parent. That carbon atom is part of a six-membered ring, so the parent is cyclohexanol. There are four substituents (highlighted), all of which are methyl groups. Notice that the parent chain is numbered starting from the carbon atom bearing the OH group (it is not necessary to indicate a locant for the OH group, because in a ring, it is assumed to be at C1, by definition). The numbers go counterclockwise, so as to give the lowest number to the first substituents (C2). According to this numbering scheme, the methyl groups are at C2, C2, C4 and C4. We use the prefix "tetra" to indicate four methyl groups. Finally, we assign a configuration to the chiral center.



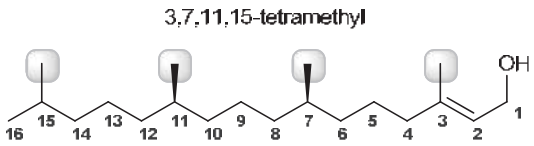
(*S*)-2,2,4,4-tetramethylcyclohexanol

12.2. The longest carbon chain contains 16 carbon atoms, and the chain is numbered to give the hydroxyl group the lowest number possible. Without the hydroxyl group, the alkene parent would be 2-hexadecene or hexadec-2-ene. To indicate the presence of the hydroxyl group, we drop the "e" and add the "ol" suffix.

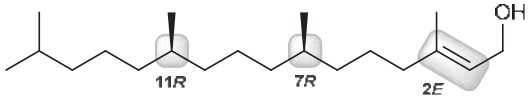


Hexadec-2-en-1-ol 2-en

Then identify the substituents and assign their locations.



Finally, assign the configuration of each chiral center, as well as the configuration of the alkene unit:



Putting it all together, the complete IUPAC name for phytol is:

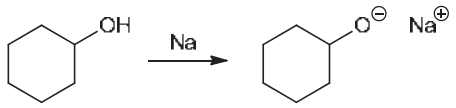
(2*E*,7*R*,11*R*)-3,7,11,15-tetramethylhexadec-2-en-1-ol.

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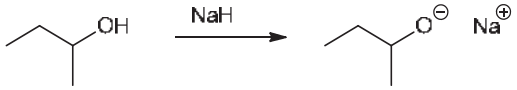
12.3. Nonyl mandelate has a longer alkyl chain than octyl mandelate and is therefore more effective at penetrating cell membranes, rendering it a more potent agent. Nonyl mandelate has a shorter alkyl chain than decyl mandelate and is therefore more water-soluble, enabling it to be transported through aqueous media and to reach its target destination more effectively.

12.4.

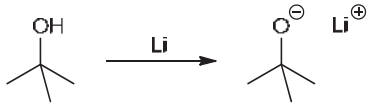
(a) When an alcohol is treated with elemental sodium (Na), the OH group is deprotonated, giving the corresponding alkoxide ion.



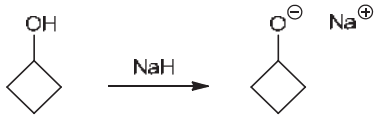
(b) When an alcohol is treated with sodium hydride (NaH), the OH group is deprotonated, giving the corresponding alkoxide ion.



(c) When an alcohol is treated with elemental lithium (Li), the OH group is deprotonated, giving the corresponding alkoxide ion.

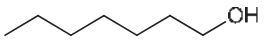


(d) When an alcohol is treated with sodium hydride (NaH), the OH group is deprotonated, giving the corresponding alkoxide ion.

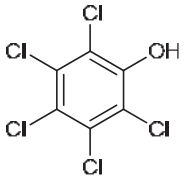


12.5.

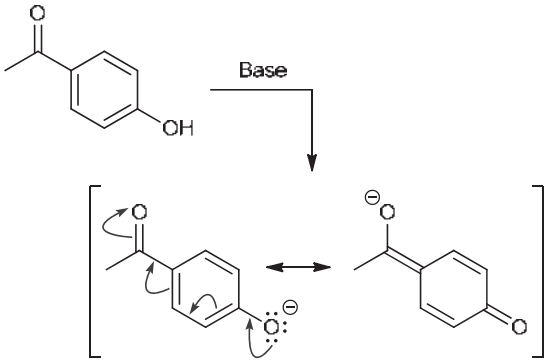
(a) The first compound is more acidic because the conjugate base of a primary alcohol will be more easily solvated than the conjugate base of a tertiary alcohol.



(b) The first compound is more acidic because the electron-withdrawing effects of the chlorine atoms stabilize the conjugate base.

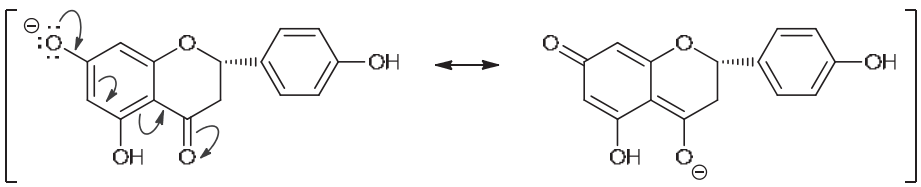


(c) The second compound is more acidic because its conjugate base is more stabilized by resonance, with the negative charge spread over two oxygen atoms, rather than just one oxygen atom.



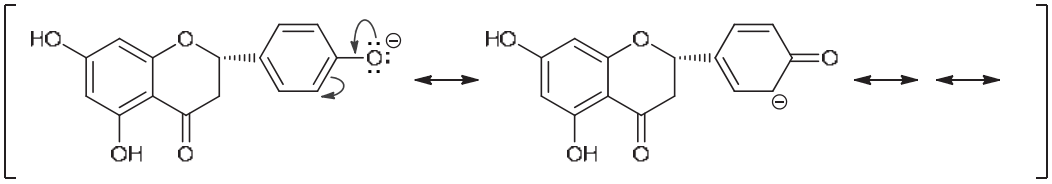
(d) The second compound is more acidic because its conjugate base is stabilized by resonance. In contrast, the conjugate base of the first compound is not resonance-stabilized.

12.6. The hydroxyl group on the benzene ring on the left is expected to be more acidic (lower pK_a) because its conjugate base has a resonance structure in which the negative charge is spread onto an oxygen atom of the carbonyl group, as shown below:



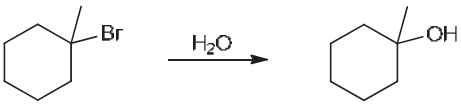
In contrast, the hydroxyl corresponding to pK_{a2} does not have such a resonance structure and can only spread its negative charge onto carbon atoms.

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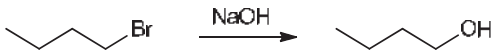


12.7.

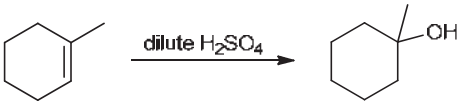
(a) The starting material is an alkyl halide, and the product is an alcohol, so we need a substitution reaction. The substrate (the alkyl halide) is tertiary, so we must use an S_N1 process. That is, we must use a weak nucleophile (water rather than hydroxide, as the latter would give E2).



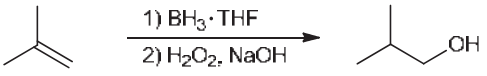
(b) The starting material is an alkyl halide, and the product is an alcohol, so we need a substitution reaction. The substrate (the alkyl halide) is primary, so we must use an S_N2 process. Therefore, we use a strong nucleophile (hydroxide).



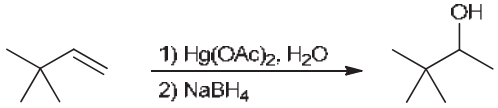
(c) The starting material is an alkene, and the product is an alcohol, so we need an addition process. The OH group must be installed at the more substituted position, so we need to perform a Markovnikov addition of H and OH across the alkene. Carbocation rearrangements are not a concern in this case (protonation of the alkene generates a tertiary carbocation which cannot rearrange), so acid-catalyzed hydration will give the desired product.



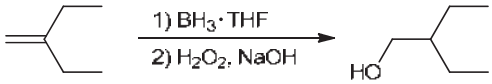
(d) The starting material is an alkene, and the product is an alcohol, so we need an addition process. The OH group must be installed at the less substituted position, so we need to perform an *anti*-Markovnikov addition of H and OH across the alkene. This can be achieved via hydroboration-oxidation.



(e) The starting material is an alkene, and the product is an alcohol, so we need an addition process. The OH group must be installed at the more substituted position, so we need to perform a Markovnikov addition of H and OH across the alkene. Carbocation rearrangements are a concern in this case (protonation of the alkene generates a secondary carbocation which can rearrange to give a more stable, tertiary carbocation), so acid-catalyzed hydration cannot be used. Instead, the desired product can be obtained via oxymercuration-demercuration, which will install the OH group at the more substituted position without carbocation rearrangements.

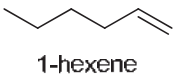


(f) The starting material is an alkene, and the product is an alcohol, so we need an addition process. The OH group must be installed at the less substituted position, so we need to perform an *anti*-Markovnikov addition of H and OH across the alkene. This can be achieved via hydroboration-oxidation.

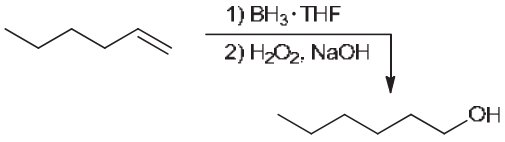


12.8.

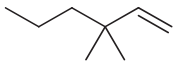
(a) Let's begin by drawing the starting material.



Addition of H and OH across this alkene will provide an alcohol. Markovnikov addition will give a secondary alcohol, so we must perform an *anti*-Markovnikov addition in order to obtain a primary alcohol. This can be achieved via hydroboration-oxidation.



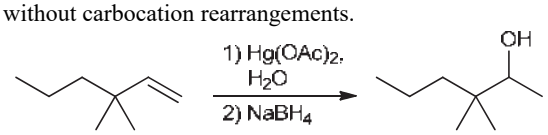
(b) Let's begin by drawing the starting material.



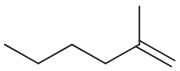
Addition of H and OH across this alkene will provide an alcohol. Markovnikov addition will give a secondary alcohol, but we must be careful. Protonation of the alkene will generate a secondary carbocation which can rearrange (via a methyl shift) to give a more stable, tertiary carbocation. Therefore, acid-catalyzed hydration cannot be used. Instead, the desired product can be

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obtained via oxymercuration-demercuration, which will install the OH group at the more substituted position without carbocation rearrangements.

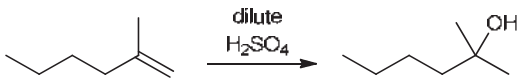


(c) Let's begin by drawing the starting material.



2-methyl-1-hexene

Addition of H and OH across this alkene will provide an alcohol. Specifically, Markovnikov addition will give a tertiary alcohol. Carbocation rearrangements are not a concern in this case (protonation of the alkene generates a tertiary carbocation which cannot rearrange), so acid-catalyzed hydration will give the desired product.



12.9.

(a) We focus on the carbon atom that undergoes a change in bonding as a result of the transformation. In the starting material, that carbon atom (the central carbon atom) has an oxidation state of +2. In the product, the same carbon atom has an oxidation state of +2. Since the oxidation state does not change, the starting material is neither oxidized nor reduced.

(b) We focus on the carbon atom that undergoes a change in bonding as a result of the transformation. In the starting material, that carbon atom has an oxidation state of +1. In the product, the same carbon atom has an oxidation state of +3. Since the oxidation state increases as a result of the transformation, the starting material is oxidized.

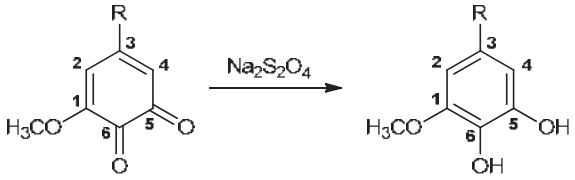
(c) We focus on the carbon atom that undergoes a change in bonding as a result of the transformation. In the starting material, that carbon atom has an oxidation state of +3. In the product, the same carbon atom has an oxidation state of -1. Since the oxidation state decreases as a result of the transformation, the starting material is reduced.

(d) We focus on the carbon atom that undergoes a change in bonding as a result of the transformation. In the starting material, that carbon atom has an oxidation state of +3. In the product, the same carbon atom has an oxidation state of +3. Since the oxidation state does not change, the starting material is neither oxidized nor reduced.

(e) We focus on the carbon atom that undergoes a change in bonding as a result of the transformation. In the starting material, that carbon atom has an oxidation state of 0. In the product, the same carbon atom has an oxidation state of +2. Since the oxidation state increases as a result of the transformation, the starting material is oxidized.

(f) We focus on the carbon atom that undergoes a change in bonding as a result of the transformation. In the starting material, that carbon atom has an oxidation state of +2. In the product, the same carbon atom has an oxidation state of +3. Since the oxidation state increases as a result of the transformation, the starting material is oxidized.

12.10. The carbon atoms in the ring have been numbered for ease of analysis. Let's consider each one separately.



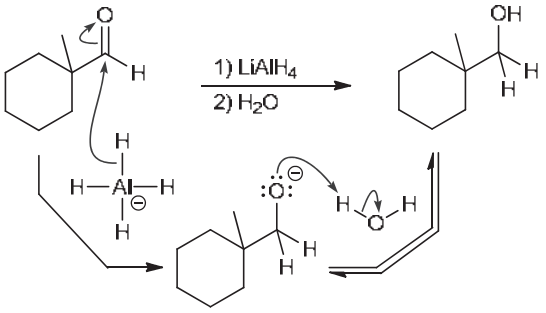
Carbon Atom	Starting Material Oxidation State	Product Oxidation State	Change in Oxidation State
1	+1	+1	0
2	-1	-1	0
3	0	0	0
4	-1	-1	0
5	+2	+1	Decrease by 1
6	+2	+1	Decrease by 1

Carbon atoms 1-4 do not undergo a change in oxidation state. Carbon atoms 5 and 6 both exhibit a decrease in oxidation state, so they are both reduced. This makes sense because both carbon atoms have lost a bond to oxygen.

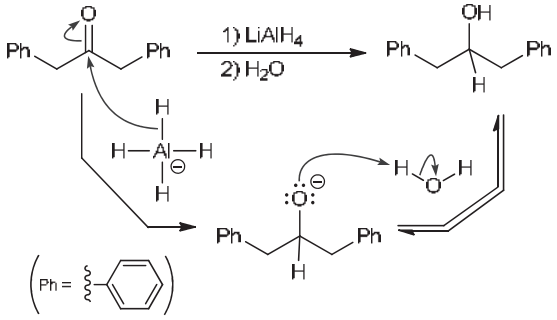
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12.11.

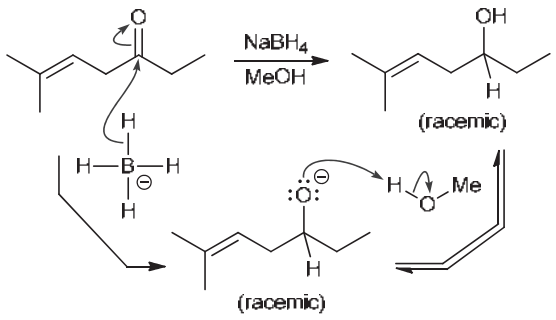
(a) Two curved arrows are used to show hydride delivery. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting alkoxide ion is then protonated upon treatment with water. This protonation step requires two curved arrows, as shown.



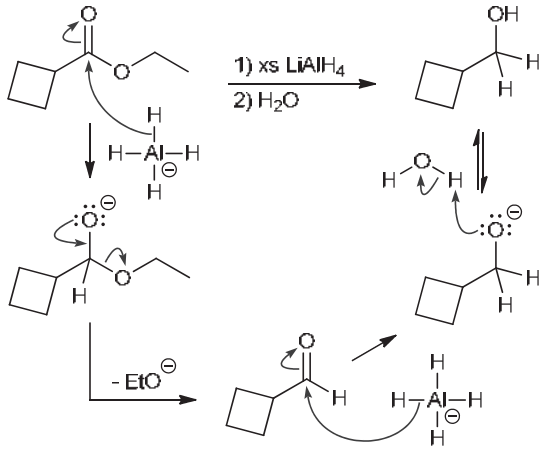
(b) Two curved arrows are used to show hydride delivery. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting alkoxide ion is then protonated upon treatment with water. This protonation step requires two curved arrows, as shown.



(c) Two curved arrows are used to show hydride delivery. Note that the tail of the first curved arrow is placed on the bond between B and H (it is NOT placed on the negative charge). The resulting alkoxide ion is then protonated, which requires two curved arrows, as shown.

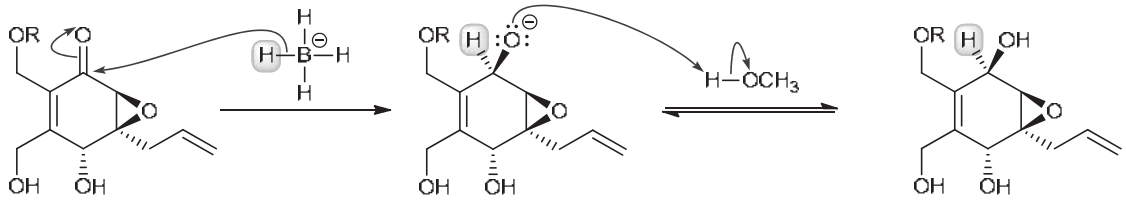


(d) Two curved arrows are used to show hydride delivery to the ester. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting intermediate then ejects ethoxide as a leaving group, which requires two curved arrows. The resulting aldehyde is then further reduced by another equivalent of $LiAlH_4$. Once again, two curved arrows are used to show hydride delivery. The resulting alkoxide ion is then protonated upon treatment with water. This protonation step requires two curved arrows, as shown.



12.12.

(a) Two curved arrows are used to show hydride delivery. Note that the tail of the first arrow is placed on the bond between B and H (it is NOT placed on the negative charge). The resulting alkoxide is then protonated, which also requires two curved arrows.

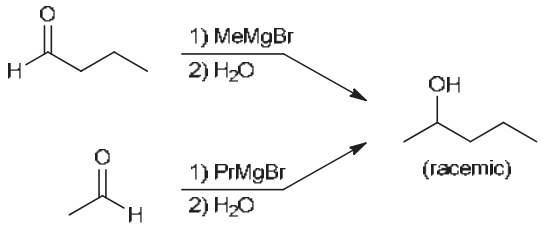


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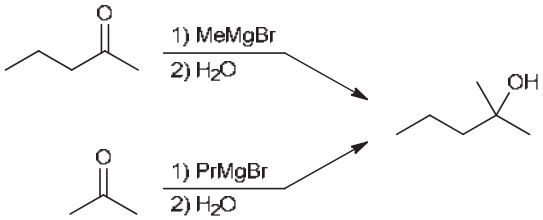
(b) The stereoisomer that is formed is the result of hydride delivery to the bottom face of the C=O bond, so that the newly installed hydrogen atom is on a dash, and the oxygen atom ends up on a wedge. This indicates that the borohydride ion approaches preferentially from the bottom face of the carbonyl group.

12.13.

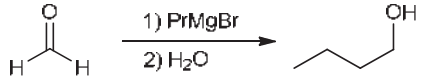
(a) The desired product has only two groups connected to the α position. Either one of these groups could have been installed via a Grignard reaction with the appropriate aldehyde, as shown.



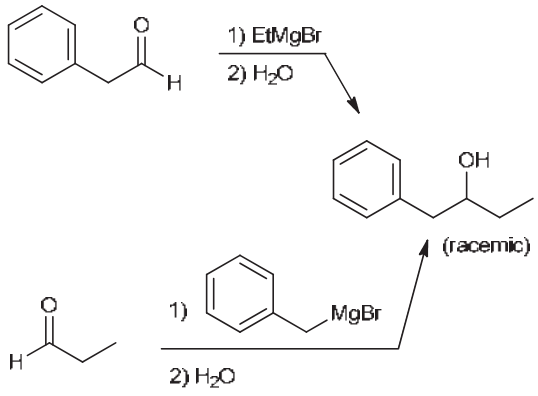
(b) The desired product has three groups connected to the α position, although two of them are identical. So there are only two different groups that could have been installed via a Grignard reaction, shown here.



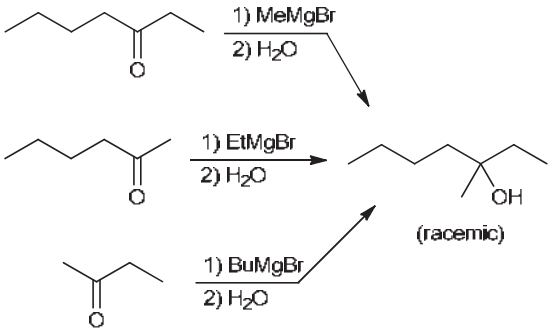
(c) The desired product has only one group connected to the α position. That group could have been installed via a Grignard reaction with formaldehyde, as shown.



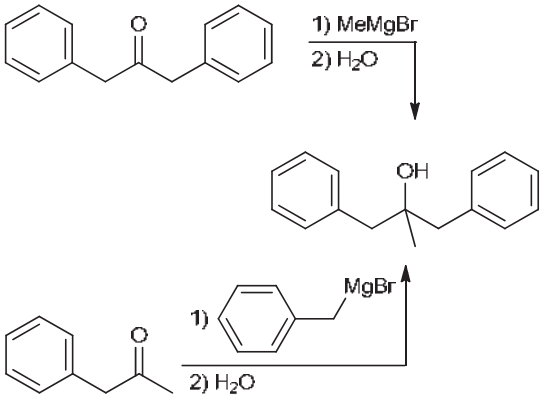
(d) The desired product has only two groups connected to the α position. Either one of these groups could have been installed via a Grignard reaction with the appropriate aldehyde, as shown.



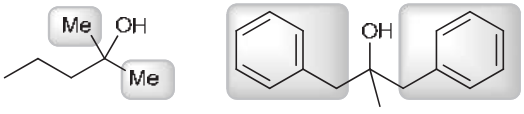
(e) The desired product has three groups connected to the α position. Any one of these groups could have been installed via a Grignard reaction with the appropriate ketone, as shown.



(f) The desired product has three groups connected to the α position, although two of them are identical. So there are only two different groups that could have been installed via a Grignard reaction, shown here.



12.14. Each of the following two compounds can be prepared from the reaction between a Grignard reagent and an ester, because each of these compounds has two identical R groups connected to the α position:

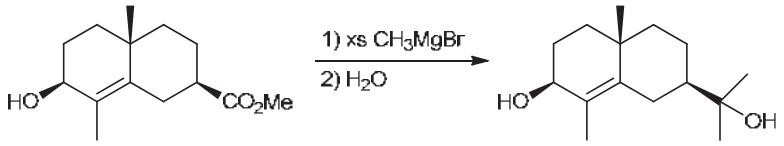


The other four compounds from Problem 12.13 do not contain two identical R groups connected to the α position, and cannot be prepared from the reaction between an ester and a Grignard reagent.

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12.15.

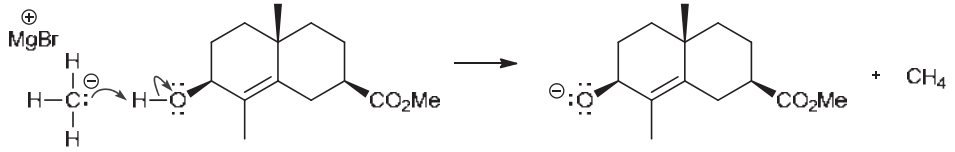
(a) This synthetic transformation converts an ester to an alcohol with the installation of two new methyl groups. Both methyl groups can be installed in the same Grignard reaction, using CH_3MgBr (MeMgBr), since two equivalents of a Grignard reagent will react with an ester. After the reaction is complete, an aqueous workup then gives the desired product.



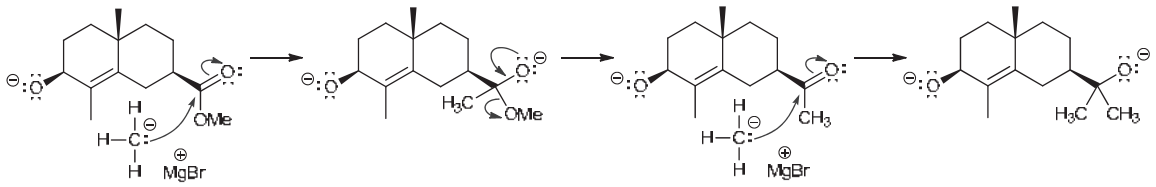
1 2

(b) In this case, a third equivalent of the Grignard reagent is required because of the presence of the alcohol functional group. The acidic proton of the alcohol will react with one equivalent of the Grignard reagent.

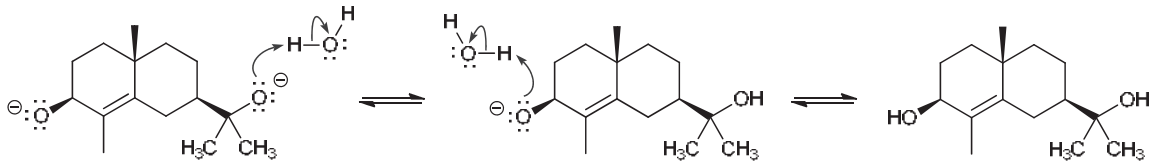
(c) In the first step of the mechanism, a proton-transfer reaction occurs. One equivalent of the Grignard reagent (methyl magnesium bromide) functions as a base and removes the proton of the alcohol. This step requires two curved arrows.



In the second step of the mechanism, a second equivalent of the Grignard reagent functions as a nucleophile and attacks the C=O bond of the ester. This step requires two curved arrows. The resulting intermediate then ejects a leaving group to give a ketone, which also requires two curved arrows. The ketone is then further attacked by a third equivalent of the Grignard reagent. Once again, two curved arrows are used to show the nucleophilic attack, resulting in a dianion.

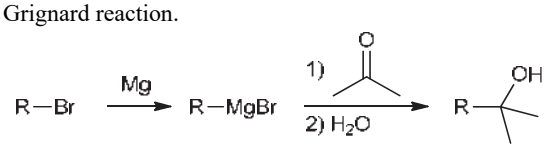


Finally, the dianion is then protonated upon treatment with water. There are two locations that are protonated, each of which requires two curved arrows, as shown. Notice that each anion is protonated in a separate step (this should not be drawn as one step with four curved arrows, because there are two distinct processes occurring, and it is unlikely that they occur precisely at the same moment).



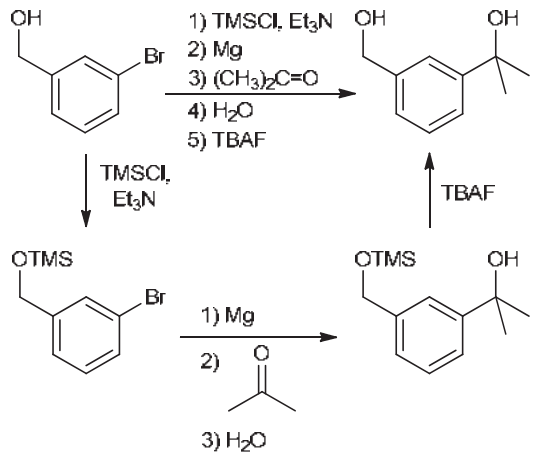
12.16.

(a) This type of transformation can be achieved via a Grignard reaction.

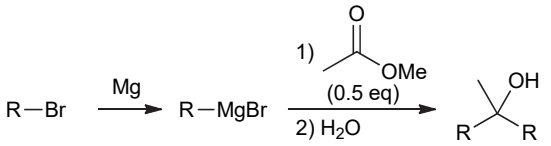


However, the starting material has an OH group, which is incompatible with a Grignard reaction. To resolve this issue, we must first protect the OH group and then perform the desired Grignard reaction. Deprotection then gives the desired product, as shown.

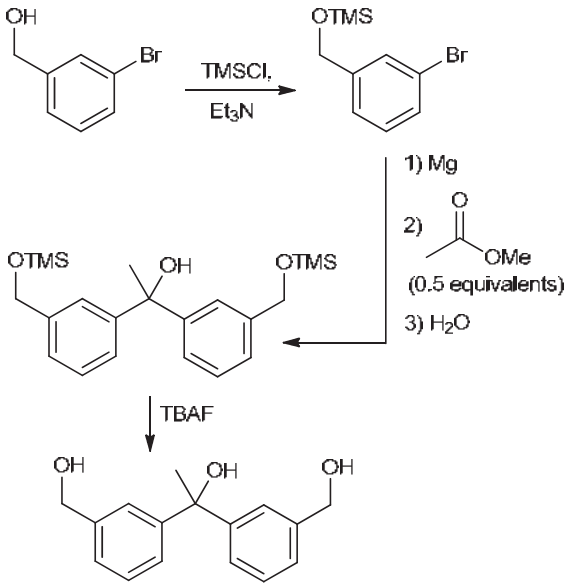
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(b) This type of transformation can be achieved via a Grignard reaction in which the Grignard reagent is treated with 0.5 equivalents of an ester.

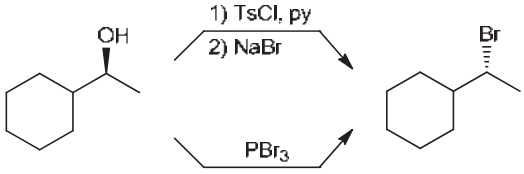


However, the starting material has an OH group, which is incompatible with a Grignard reaction. To resolve this issue, we must first protect the OH group and then perform the desired Grignard reaction. Deprotection then gives the desired product, as shown (next page).



12.17.

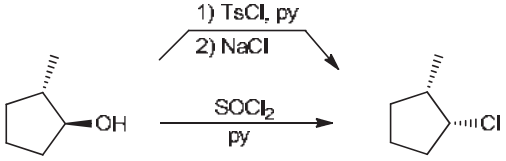
(a) We must convert a secondary alcohol into a secondary alkyl bromide, with inversion of configuration, so an S_N2 process is required. However, the OH group is a bad leaving group. One way around this issue is to convert the OH group into a tosylate (by treating the alcohol with tosyl chloride and pyridine). The tosylate can then be treated with bromide to give the desired product. Alternatively, the alcohol can be treated with PBr_3 to give the desired product.



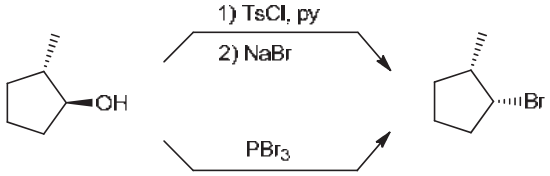
(b) We must convert a tertiary alcohol into a tertiary alkyl bromide. This can be achieved upon treatment with HBr.



(c) We must convert a secondary alcohol into a secondary alkyl chloride, with inversion of configuration, so an S_N2 process is required. However, the OH group is a bad leaving group. One way around this issue is to convert the OH group into a tosylate (by treating the alcohol with tosyl chloride and pyridine). The tosylate can then be treated with chloride to give the desired product. Alternatively, the alcohol can be treated with thionyl chloride and pyridine.



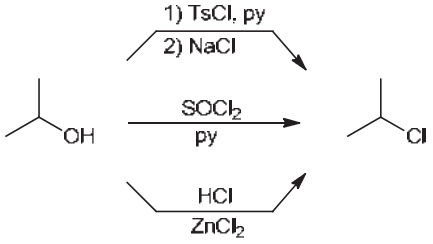
(d) We must convert a secondary alcohol into a secondary alkyl bromide, with inversion of configuration, so an S_N2 process is required. However, the OH group is a bad leaving group. One way around this issue is to convert the OH group into a tosylate (by treating the alcohol with tosyl chloride and pyridine). The tosylate can then be treated with bromide to give the desired product. Alternatively, the alcohol can be treated with PBr_3 to give the desired product.



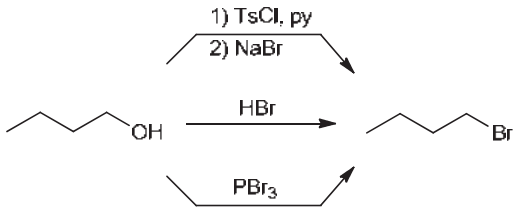
(e) We must convert a secondary alcohol into a secondary alkyl chloride, so a substitution process is required. However, the OH group is a bad leaving group. One way around this issue is to convert the OH group into a tosylate (by treating the alcohol with tosyl

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chloride and pyridine). The tosylate can then be treated with chloride to give the desired product. Alternatively, the alcohol can be treated with thionyl chloride and pyridine, or with HCl and $ZnCl_2$.

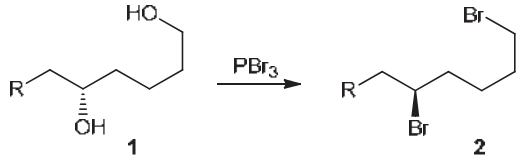


(f) We must convert a primary alcohol into a primary alkyl chloride, so an S_N2 process is required. However, the OH group is a bad leaving group. One way around this issue is to convert the OH group into a tosylate (by treating the alcohol with tosyl chloride and pyridine). The tosylate can then be treated with bromide to give the desired product. Alternatively, the alcohol can be treated with HBr or with PBr_3.

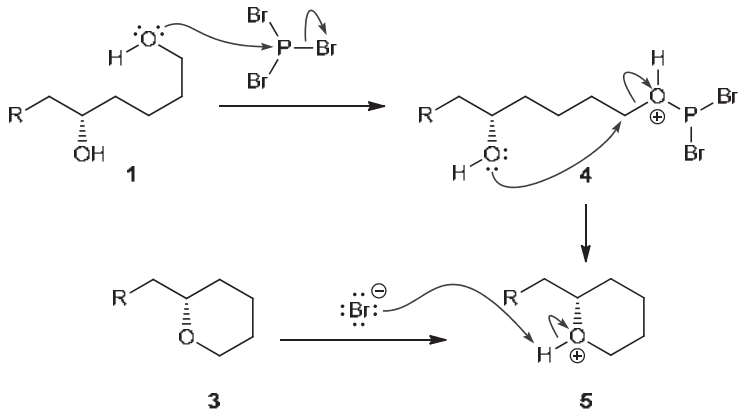


12.18.

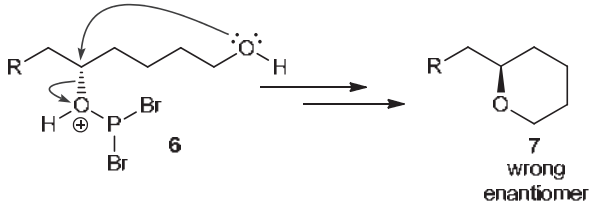
(a) When diol **1** is treated with PBr_3, each of the two OH groups can separately react with the reagent to produce dibromide **2**. Notice that the configuration of the chiral center is now inverted, since the mechanism for bromide displacement involves an S_N2 reaction.



(b) The byproduct can be formed via the following process. First, the terminal alcohol is converted into a good leaving group upon treatment with PBr_3. However, before a bromide ion can attack this intermediate, an intramolecular S_N2-type reaction occurs – the internal OH group can displace the good leaving group of **4** to form cyclic ether **5** which can be deprotonated to produce byproduct **3**.



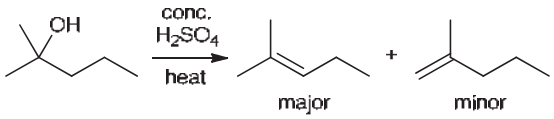
Notice that the primary OH group is converted into a good leaving group, and the secondary OH group functions as a nucleophile. If instead the secondary OH group had reacted with PBr_3 (**6**), and the primary OH group had functioned as a nucleophile, then compound **7** would have been produced, which is not the byproduct (it is the enantiomer of the byproduct).



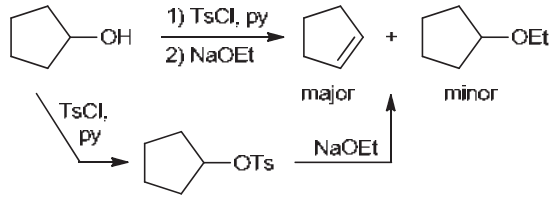
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12.19.

(a) An alcohol is converted to an alkene upon treatment with concentrated sulfuric acid. In this case, there are two possible regiochemical outcomes, and we expect that the more substituted alkene will be the major product.

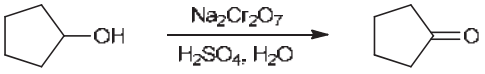


(b) An alcohol is converted to a tosylate upon treatment with tosyl chloride and pyridine. This tosylate is a secondary substrate, and ethoxide is both a strong nucleophile and a strong base. Recall from Chapter 7 that a secondary substrate is expected to react with ethoxide via an E2 process to give the major product (while S_N2 gives the minor product).

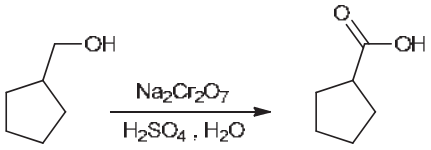


12.20.

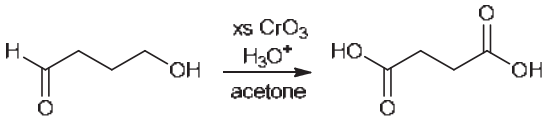
(a) The alcohol in this case is secondary. Chromic acid will oxidize the alcohol to give a ketone.



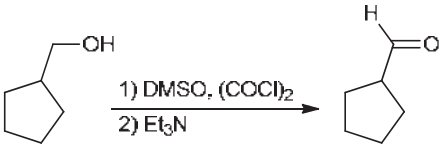
(b) The alcohol in this case is primary. Chromic acid will oxidize the alcohol to give a carboxylic acid.



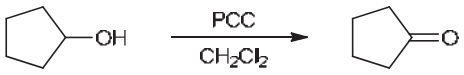
(c) The alcohol in this case is primary. This alcohol is oxidized upon treatment with chromic acid to give a carboxylic acid group, and the aldehyde group (already present) also undergoes oxidation to give a carboxylic acid group as well.



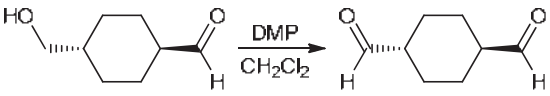
(d) The alcohol in this case is primary. A Swern oxidation will oxidize the alcohol to give an aldehyde. Appears



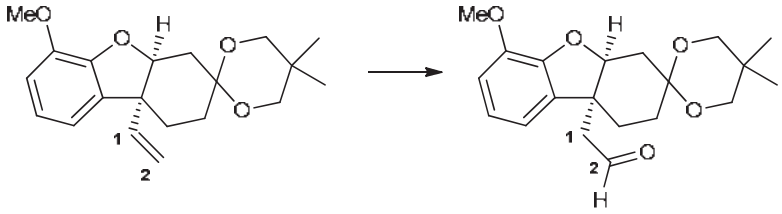
(e) The alcohol in this case is secondary. PCC will oxidize the alcohol to give a ketone.



(f) The alcohol in this case is primary. Dess-Martin periodinane (DMP) will oxidize the alcohol to give an aldehyde, and the other aldehyde group (already present) is unaffected under these conditions.

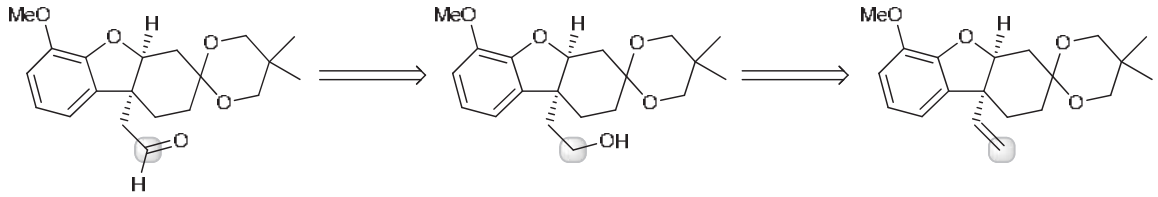


12.21. As with all synthesis problems, we must determine: 1) if there is a change in the carbon skeleton, and 2) if there is a change in the functional groups. By numbering the carbon atoms of the galanthamine side chain, we see that the number of carbon atoms has remained the same. We can also observe that the carbon-carbon double bond of the starting material has been replaced by a carbon-carbon single bond, along with the installation of a carbon-oxygen double bond at the position labelled as C2.

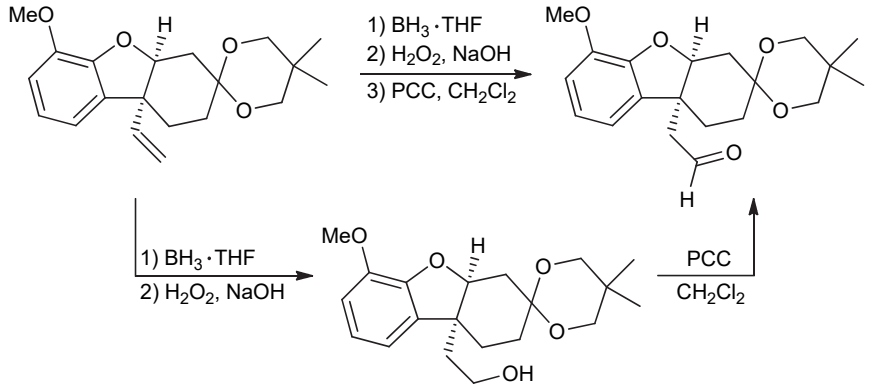


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The following retrosynthesis shows that the aldehyde can be made from the corresponding alcohol via an oxidation reaction. This alcohol can be made from the alkene via a hydration reaction. The C2 position is highlighted in the retrosynthetic scheme shown below:

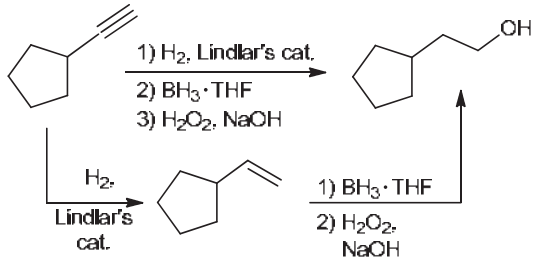


Now let's draw the forward process. The hydration step requires *anti*-Markovnikov regioselectivity, so a hydroboration-oxidation reaction is appropriate. Since the alcohol is primary, care must be used to select a reagent that will produce the aldehyde and not a carboxylic acid in the oxidation reaction. The following reaction sequence would produce the desired product:

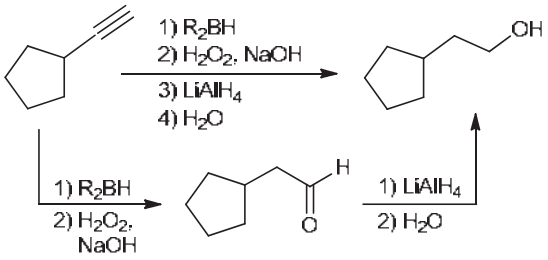


12.22.

(a) The desired transformation can be achieved by converting the alkyne into an alkene, followed by *anti*-Markovnikov addition of H and OH.

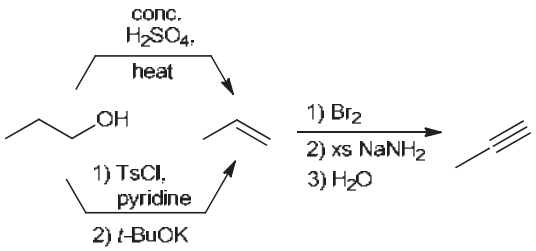


As is the case with most synthesis problems that you will encounter, there is usually more than one way to achieve the desired transformation using the reactions that we have learned so far. For example, the following alternative synthesis is perfectly acceptable. The alkyne is converted to an aldehyde via hydroboration-oxidation, followed by reduction with $LiAlH_4$.



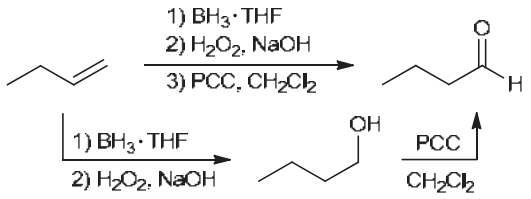
There are likely other acceptable answers as well.

(b) The desired transformation can be achieved by converting the alcohol into an alkene, and then converting the alkene into an alkyne, as shown.

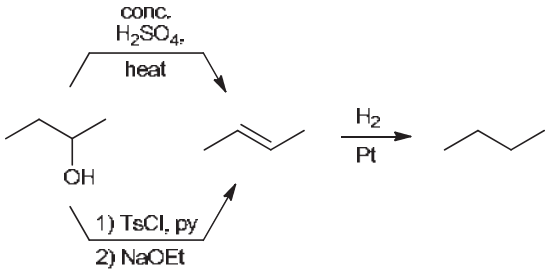


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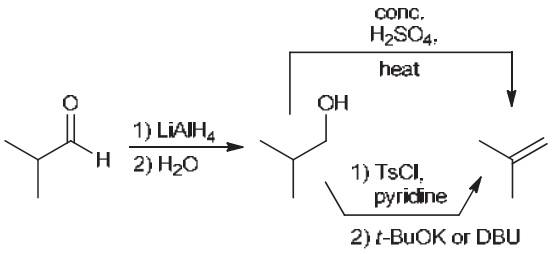
(c) The desired transformation can be achieved by converting the alkene into an alcohol, and then oxidizing the alcohol with PCC to give the aldehyde, as shown.



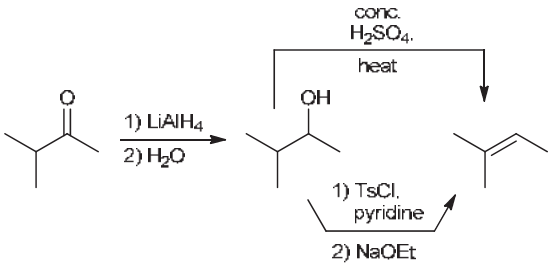
(d) The desired transformation can be achieved by converting the alcohol into an alkene, and then reducing the alkene to an alkane, as shown.



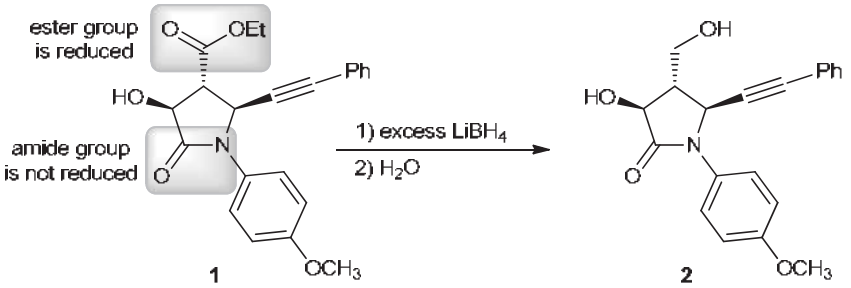
(e) The desired transformation can be achieved by reducing the aldehyde, and then converting the resulting alcohol into an alkene, as shown. If the second process is performed by converting the alcohol to a tosylate, followed by treatment with a strong base, then it is important that the base is sterically hindered (*tert*-butoxide). With a primary substrate, S_N2 will likely predominate over E2 if the base is not sterically hindered. Alternatively, a non-nucleophilic base, such as DBU, can be used



(f) The desired transformation can be achieved by reducing the ketone, and then converting the resulting secondary alcohol into an alkene, as shown. If the second process is performed by converting the alcohol to a tosylate, followed by treatment with a strong base, then it is important that the base is not sterically hindered. A sterically hindered base would give the less substituted alkene as the major product, and we need the more substituted alkene. Appropriate bases include hydroxide, methoxide and ethoxide (ethoxide is shown in the following synthesis).

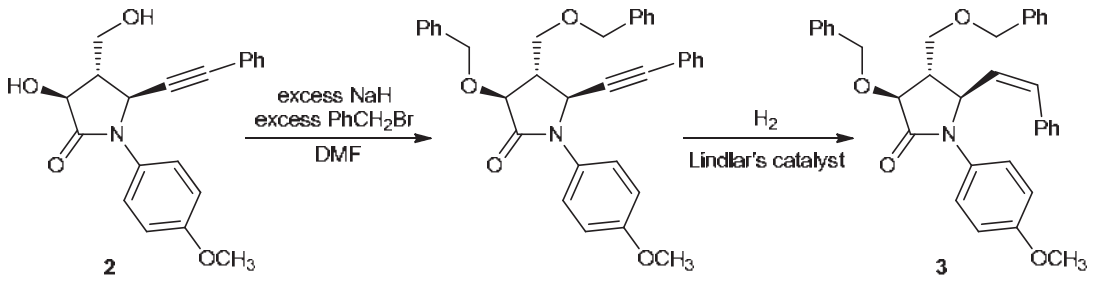


12.23. Compound **1** contains both an ester group and an amide group. As described in the problem statement, treatment of compound **1** with $LiBH_4$ is expected to result in reduction of the ester group, while the amide group will remain unchanged.



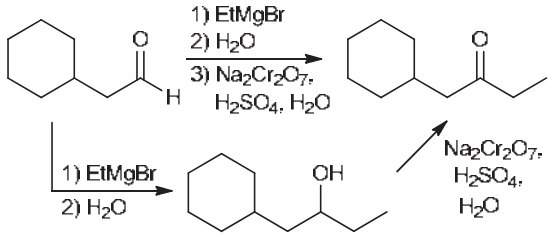
Treatment of compound **2** with excess NaH, followed by excess benzyl bromide, converts both hydroxyl groups into ether groups. Finally, partial reduction of the alkyne affords the *cis*-alkene:

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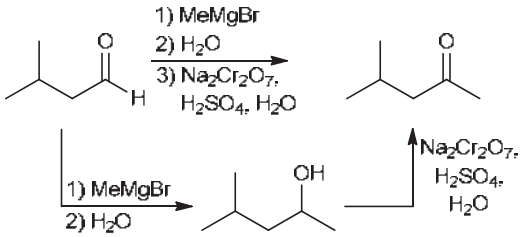


12.24.

(a) The product has more carbon atoms than the starting material, so we must form a carbon-carbon bond. This can be achieved with a Grignard reaction (using ethyl magnesium bromide to install an ethyl group). The resulting alcohol can then be oxidized to give the desired product.



(b) The product has one more carbon atom than the starting material, so we must form a carbon-carbon bond. This can be achieved with a Grignard reaction (using methyl magnesium bromide to install a methyl group). The resulting alcohol can then be oxidized to give the desired product.



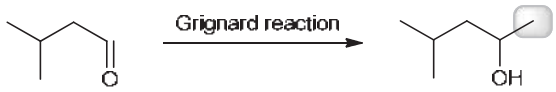
12.25.

(a) We begin by asking the following two questions:

1) *Is there a change in the carbon skeleton?* Yes, the carbon skeleton is increasing in size by one carbon atom.

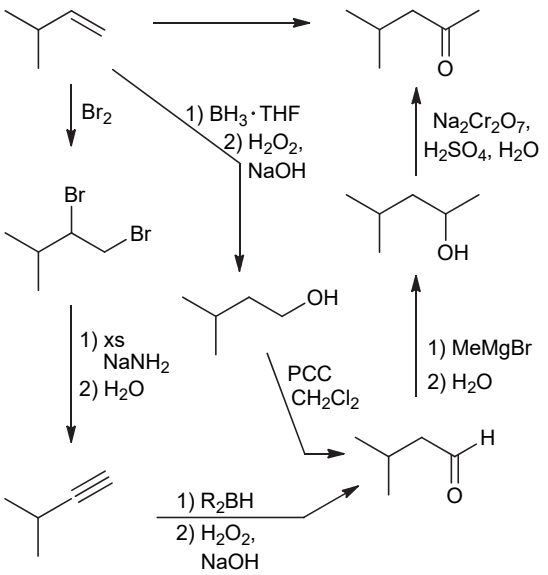
2) *Is there a change in the functional groups?* Yes, the starting material has a carbon-carbon double bond, while the product has an OH group.

Now we must propose a strategy for achieving these changes. If we use a Grignard reaction to install the methyl group, we would need to use the aldehyde shown here:

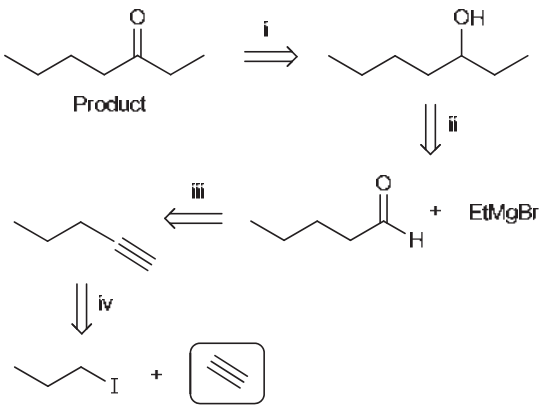


The resulting alcohol has the correct carbon skeleton, and it can be converted directly into the product via oxidation. So we only need to determine if the aldehyde above can be made from the starting material. Indeed, there are at least two methods for converting the starting alkene into the necessary aldehyde. One method is to convert the alkene into an alkyne (via bromination followed by elimination) and then to perform hydroboration-oxidation to obtain the aldehyde. Another method is to perform hydroboration-oxidation with the starting alkene, followed by oxidation with PCC to give the aldehyde.

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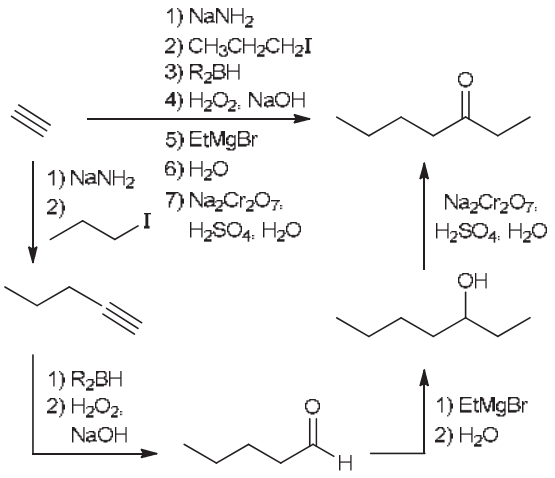


(b) The starting material has two carbon atoms, while the product has seven carbon atoms, so we will need to create carbon-carbon bonds. The starting functional group is a triple bond, and the product is a ketone. There are certainly many acceptable answers to this problem. One such answer can be rationalized with the following retrosynthetic analysis.

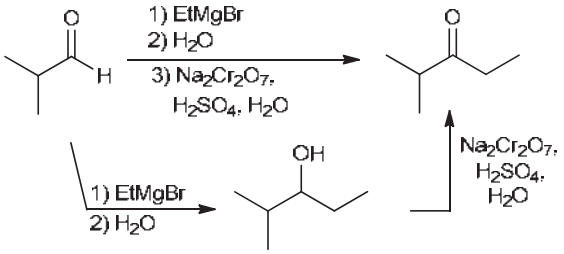


i. The product is a ketone, which can be made via oxidation of the corresponding secondary alcohol.
ii. The secondary alcohol can be made by treating the appropriate aldehyde with ethyl magnesium bromide.
iii. The aldehyde can be made from the corresponding terminal alkyne (via hydroboration-oxidation).
iv. The terminal alkyne can be made from the starting material via alkylation (to install a propyl group).

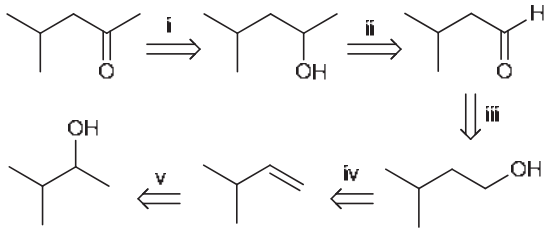
The reagents for this synthetic strategy are shown here.



(c) The product has more carbon atoms than the starting material, so we must form a carbon-carbon bond. This can be achieved with a Grignard reaction (using ethyl magnesium bromide to install an ethyl group). The resulting alcohol can then be oxidized to give the desired product.



(d) The starting material has five carbon atoms, while the product has six carbon atoms, so we will need to install a methyl group. The starting functional group is an alcohol, and the product is a ketone. There are certainly many acceptable answers to this problem. One such answer can be rationalized with the following retrosynthetic analysis.

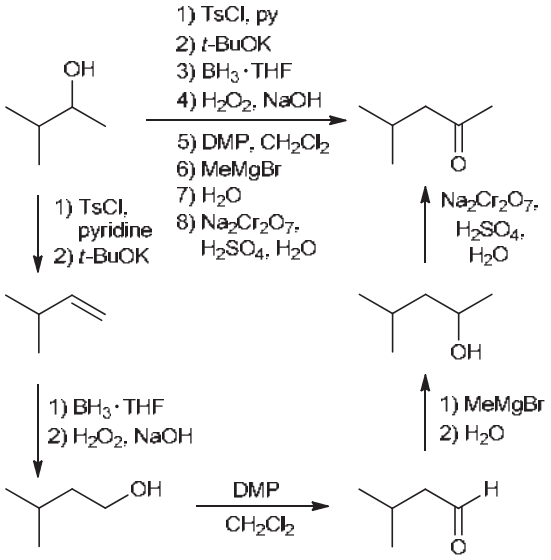


i. The ketone can be made via oxidation of the corresponding secondary alcohol.
ii. The alcohol can be made by treating the appropriate aldehyde with methyl magnesium bromide.

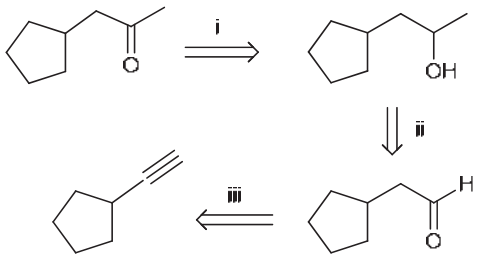
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iii. The aldehyde can be made from the corresponding primary alcohol and a suitable oxidizing agent (such as PCC, Swern, or DMP).
iv. The alcohol can be made from an alkene via hydroboration-oxidation (*anti*-Markovnikov addition of H and OH)
v. The alkene can be made from the starting alcohol via an elimination process. Since OH is a bad leaving group, it must first be converted into a tosylate in order to perform an E2 reaction. A sterically hindered base is then used to favor the less-substituted alkene.

Reagents for this synthetic strategy are shown here:

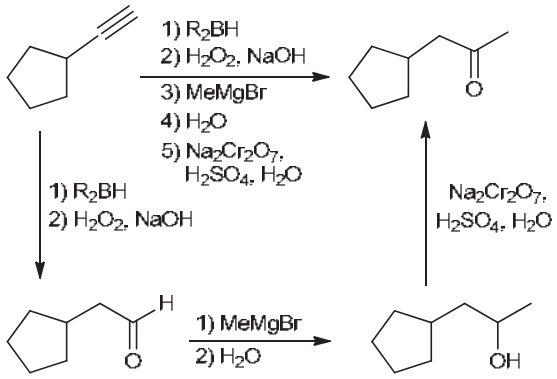


(e) The product has one more carbon atom than the starting material, so we will need to install a methyl group. The starting functional group is a triple bond, and the product is a ketone. There are certainly many acceptable answers to this problem. One such answer can be rationalized with the following retrosynthetic analysis.

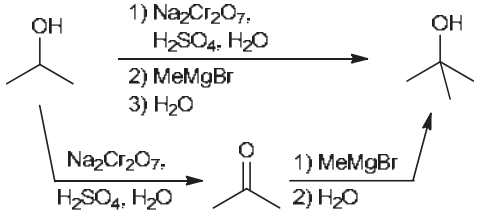


i. The product is a ketone, which can be made via oxidation of the corresponding secondary alcohol.
ii. The secondary alcohol can be made by treating the appropriate aldehyde with methyl magnesium bromide.
iii. The aldehyde can be made from the corresponding terminal alkyne (via hydroboration-oxidation).

The reagents for this synthetic strategy are shown here.

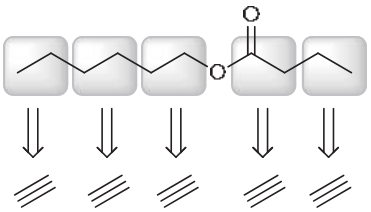


(f) The functional group has not changed, but the product has an additional methyl group. This methyl group can be installed with a Grignard reaction, if the starting alcohol is first converted to a ketone (oxidation). Then, a Grignard reaction with methyl magnesium bromide will give the desired product.

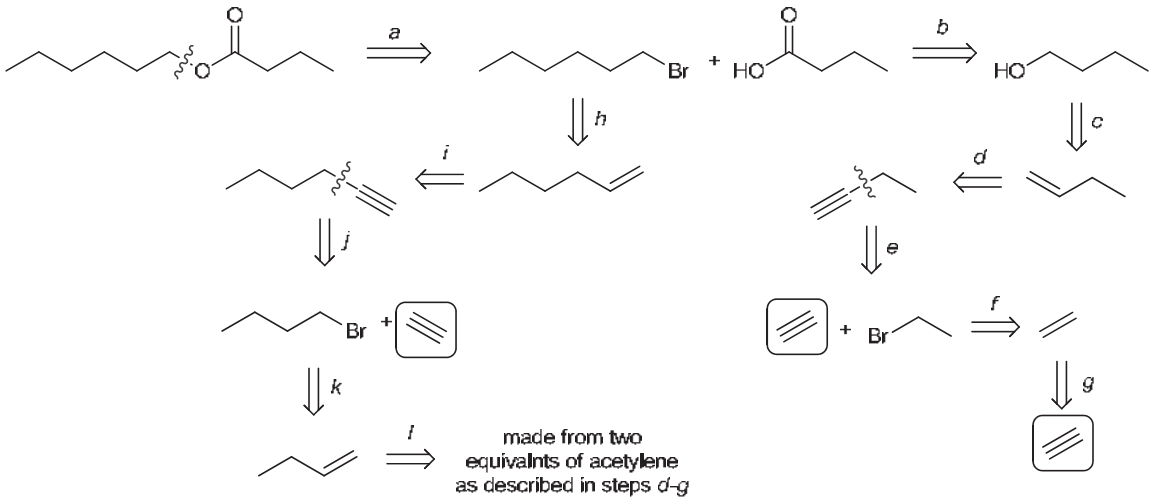


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12.26. The following synthesis is one suggested approach. There are certainly other acceptable synthetic pathways that accomplish the same goal.
The product (hexyl butanoate) has a total of 10 carbons, all of which must be ultimately derived from acetylene (which has two carbon atoms). Thus, we will likely use five equivalents of acetylene in this synthesis. We can map each two-carbon fragment of the product back to acetylene as shown below.



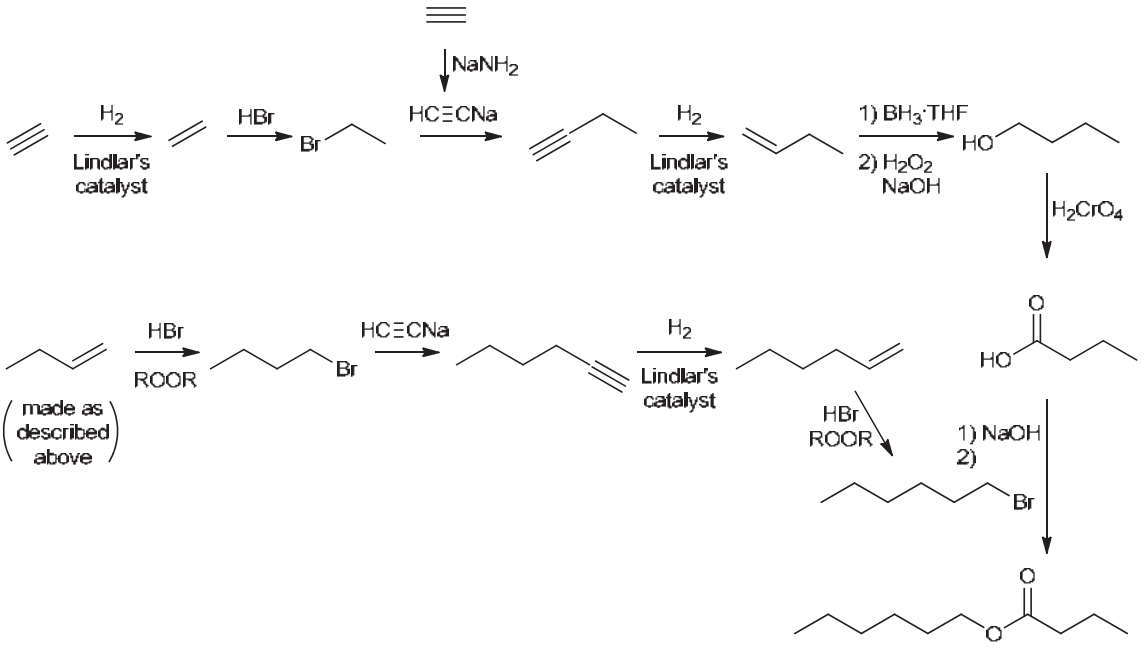
The figure below outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a*-*l*) follows.



a. Hexyl butanoate is made from an S_N2 reaction between 1-bromohexane and the carboxylic acid shown (after deprotonation of the carboxylic acid to make a good nucleophile).
b. The carboxylic acid is made by oxidation of 1-butanol.
c. 1-Butanol is made by *anti*-Markovnikov hydration of 1-butene.
d. 1-Butene is made by partial reduction of 1-butyne.
e. 1-Butyne is made from an S_N2 reaction between acetylene (which must be deprotonated to form an acetylide ion) and bromoethane.
f. Bromoethane is made by addition of HBr to ethylene.
g. Ethylene is made by partial reduction of acetylene.
h. 1-Bromohexane is made by *anti*-Markovnikov addition of HBr to 1-hexene.
i. 1-Hexene is made by partial reduction of 1-hexyne.
j. 1-Hexyne is made from an S_N2 reaction between acetylene (which must be deprotonated to form an acetylide ion) and 1-bromobutane.
k. 1-Bromobutane is made by *anti*-Markovnikov addition of HBr to 1-butene.
l. 1-Butene is made as described in steps *d*-*g*.

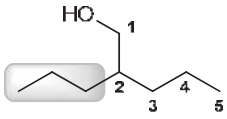
Now let's draw the forward scheme. Acetylene is converted to bromoethane in two steps by hydrogenation with Lindlar's catalyst followed by addition of HBr to the resulting alkene. Reaction with sodium acetylide (made from acetylene and sodium amide) produces 1-butyne, which is then treated with H_2 and Lindlar's catalyst to furnish 1-butene. *Anti*-Markovnikov addition of water (via hydroboration / oxidation) gives 1-butanol, which is subsequently oxidized to the carboxylic acid using chromic acid. Deprotonation with sodium hydroxide followed by reaction with 1-bromohexane produces the product, hexyl butanoate. (1-Bromohexane is made in four steps from 1-butene, as shown. *Anti*-Markovnikov addition using HBr and peroxides gives 1-bromobutane. Reaction with sodium acetylide gives 1-hexyne, which is subsequently reduced to 1-hexene with H_2 and Lindlar's catalyst. *Anti*-Markovnikov addition using HBr and peroxides gives 1-bromohexane.)

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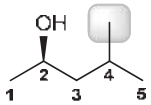
12.27.

(a) We begin by identifying the parent. The carbon atom connected to the OH group must be included in the parent. The longest chain that includes this carbon atom is five carbon atoms in length. So the parent is pentanol. There is only one substituent (highlighted) – a propyl group, located at C2. A locant is included to indicate the location of the OH group.



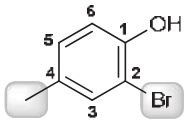
2-propyl-1-pentanol

(b) We begin by identifying the parent. The carbon atom connected to the OH group must be included in the parent. The longest chain that includes this carbon atom is five carbon atoms in length. So the parent is pentanol. There is only one substituent (highlighted) – a methyl group, located at C4. Finally, we assign a configuration to the chiral center.



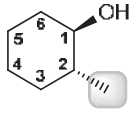
(*R*)-4-methyl-2-pentanol

(c) We begin by identifying the parent (phenol). There are two substituents (highlighted) – a bromo group and a methyl group. Notice that the ring is numbered starting from the carbon atom bearing the OH group (it is not necessary to indicate a locant for the OH group, because in a ring, it is assumed to be at C1, by definition). We then number in the direction that gives the second substituent the lowest possible number (C2 rather than C4). According to this numbering scheme, the bromo group is at C2 and the methyl group is at C4. The substituents are arranged alphabetically in the name.



2-bromo-4-methylphenol

(d) We begin by identifying the parent. The carbon atom connected to the OH group must be included in the parent. That carbon atom is part of a six-membered ring, so the parent is cyclohexanol. There is only one substituent (highlighted) – a methyl group. Notice that the parent chain is numbered starting from the carbon atom bearing the OH group (it is not necessary to indicate a locant for the OH group, because in a ring, it is assumed to be at C1, by definition). The numbers go clockwise, so as to give the lowest number to the substituent (C2 rather than C6). Finally, we assign a configuration to each chiral center.



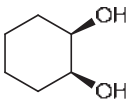
(*1R,2R*)-2-methylcyclohexanol

12.28.

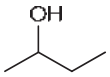
(a) Cyclohexanediol is a six-membered ring containing two OH groups. The locants for the OH groups (C1 and

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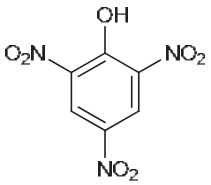
C2) indicate that they are on adjacent carbon atoms, and the name of the compound indicates a *cis* configuration. That is, the OH groups are on the same side of the ring, giving the following *meso* compound.



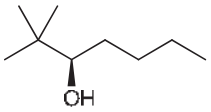
(b) Isobutanol is the common name for 2-butanol. The parent is a chain of four carbon atoms with the OH group connected to the C2 position.



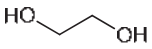
(c) The parent is phenol and there are three substituents (all of which are nitro groups) located at C2, C4 and C6.



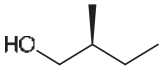
(d) The parent (3-heptanol) is a chain of seven carbon atoms containing an OH group at the C3 position. The name indicates that there are two substituents (both methyl groups) at the C2 position. The C3 position is a chiral center, and it has the *R* configuration.



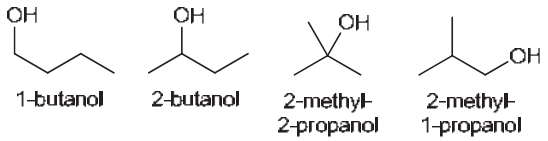
(e) Ethylene glycol is the common name for the following diol.



(f) The parent (1-butanol) is a chain of four carbon atoms with an OH group connected to the C1 position. The name indicates that there is one substituent (a methyl group) at C2. The C2 position is a chiral center, and it has the *S* configuration.

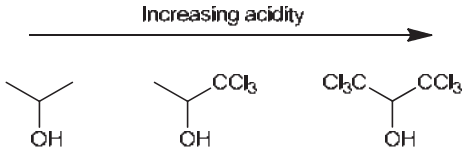


12.29. The solution to Problem 1.1d shows all constitutional isomers with the molecular formula $C_4H_{10}O$. Four of these isomers are alcohols, and have the following systematic names:

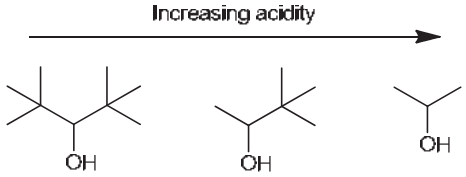


12.30.

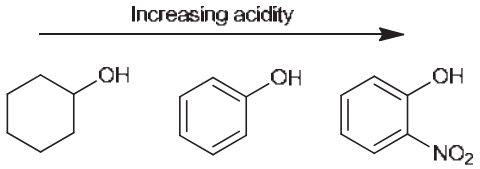
(a) The trichloromethyl group (CCl_3) is powerfully electron-withdrawing because of the combined inductive effects of the three chlorine atoms. As a result, the presence of a trichloromethyl group stabilizes the conjugate base (alkoxide ion) that is formed when the OH group is deprotonated. So the presence of the trichloromethyl group (in close proximity to the OH group) renders the alcohol more acidic. The compound with two such groups is the most acidic.



(b) The following order is based on a solvating effect, as described in Section 3.7. Specifically, the presence of *tert*-butyl groups will destabilize the conjugate base that is formed when the OH group is deprotonated. As such, the compound with two *tert*-butyl groups will be the least acidic.

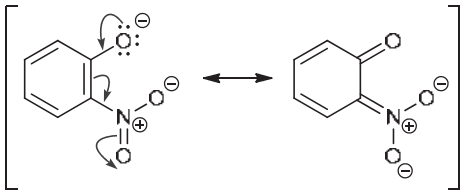


(c) These compounds are expected to have the following relative acidity.



Cyclohexanol is the least acidic because its conjugate base is not resonance stabilized. The other two compounds are much more acidic, because each of them generates a resonance stabilized phenolate ion upon deprotonation. Among these two compounds, 2-nitrophenol is more acidic, because its conjugate base has an additional resonance structure in which the negative charge is placed on an oxygen atom of the nitro group.

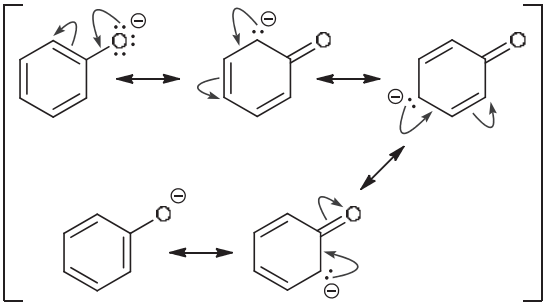
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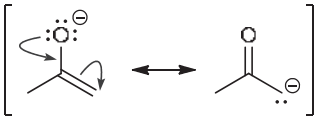
Note: This conjugate base has other resonance structures not shown here.

12.31.

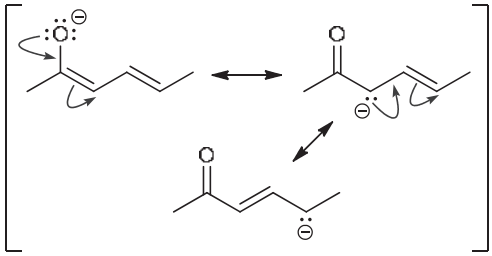
(a) This structure exhibits a lone pair next to a π bond, so we draw the two curved arrows associated with that pattern (see Section 2.10). The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair. The resulting resonance structure also exhibits a lone pair next to a π bond, so again we draw the two curved arrows associated with that pattern. This is continued until we have drawn all of the resonance structures, shown here.



(b) This structure exhibits a lone pair next to a π bond, so we draw the two curved arrows associated with that pattern (see Section 2.10). The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair.

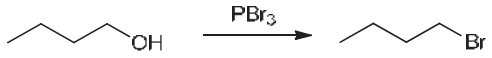


(c) This structure exhibits a lone pair next to a π bond, so we draw the two curved arrows associated with that pattern (see Section 2.10). The first curved arrow is drawn showing a lone pair becoming a π bond, while the second curved arrow shows a π bond becoming a lone pair. The resulting resonance structure also exhibits a lone pair next to a π bond, so again we draw the two curved arrows associated with that pattern, giving the third and final resonance structure.

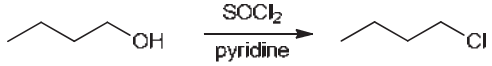


12.32.

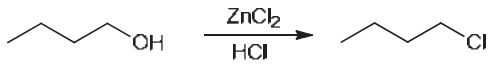
(a) 1-Butanol is a primary alcohol. When treated with PBr_3, the OH group is replaced with Br, so the product is 1-bromobutane.



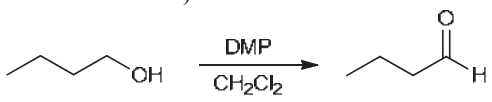
(b) 1-Butanol is a primary alcohol. When treated with $SOCl_2$ and pyridine, the OH group is replaced with Cl, so the product is 1-chlorobutane.



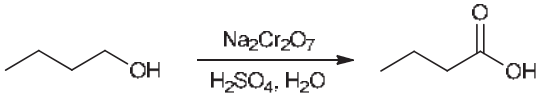
(c) 1-Butanol is a primary alcohol. When treated with HCl and $ZnCl_2$, the OH group is replaced with Cl, so the product is 1-chlorobutane.



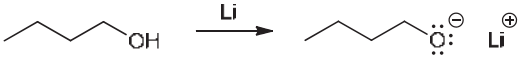
(d) When treated with Dess-Martin periodinane (DMP), a primary alcohol is oxidized to give an aldehyde (which is not further oxidized).



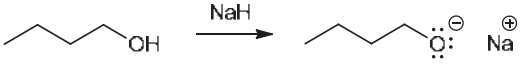
(e) When treated with chromic acid, a primary alcohol is oxidized to give a carboxylic acid.



(f) When treated with lithium, an alcohol is deprotonated to give an alkoxide ion.

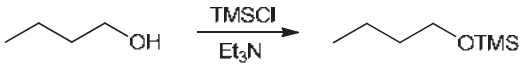


(g) When treated with sodium hydride (a strong base), an alcohol is deprotonated to give an alkoxide ion.

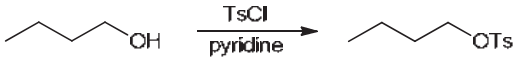


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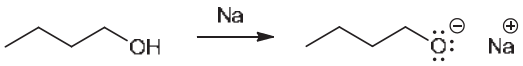
(h) When treated with TMSCl and a base (Et_3N), the OH group is protected (it is converted to OTMS).



(i) When treated with tosyl chloride and a base (pyridine), the OH group is converted to a tosylate group.



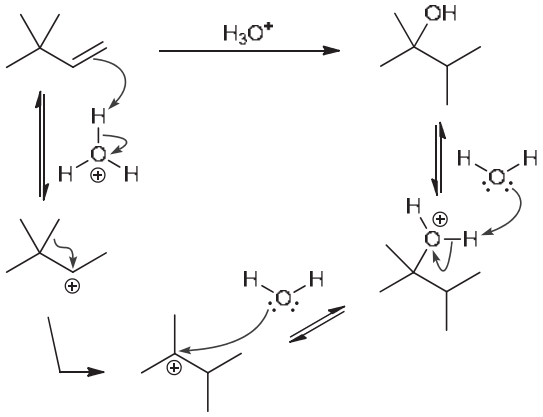
(j) When treated with sodium, an alcohol is deprotonated to give an alkoxide ion.



(k) When treated with *tert*-butoxide (a strong base), an alcohol is deprotonated to give an alkoxide ion.

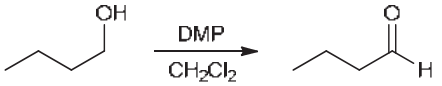


12.33. When treated with aqueous acid, the π bond is protonated, giving a secondary carbocation (rather than a primary carbocation). This secondary carbocation can then rearrange via a methyl shift to give a more stable, tertiary carbocation, which is then captured by a water molecule. The resulting oxonium ion is then deprotonated by a molecule of water to give the product:

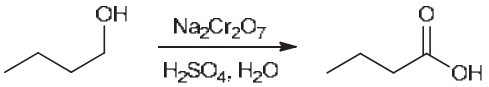


12.34.

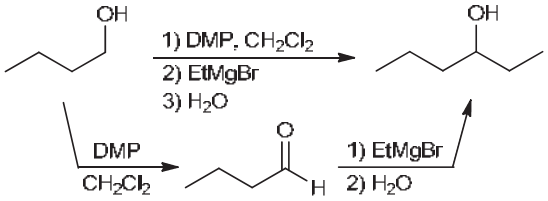
(a) The desired aldehyde can be prepared in one step, using PCC, or DMP, or the Swern oxidation. One of these is shown below.



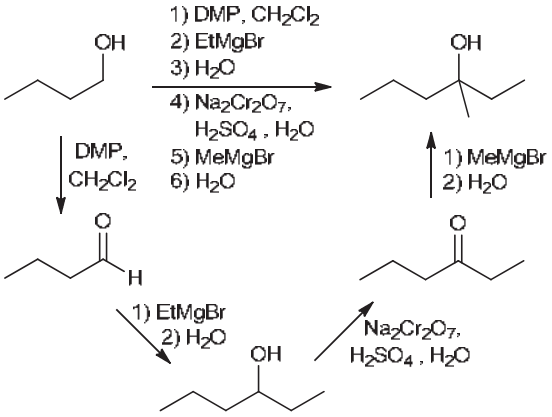
(b) The desired carboxylic acid can be prepared in one step, using chromic acid as the oxidizing agent.



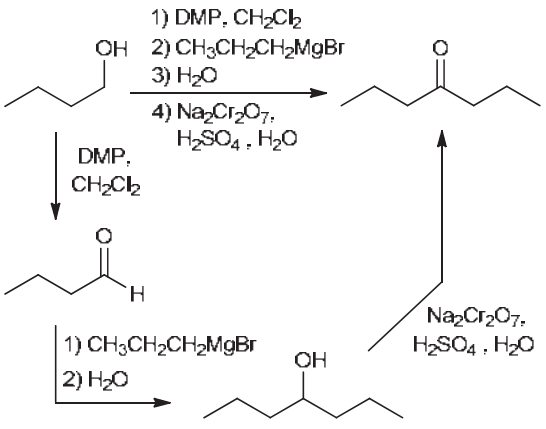
(c) The desired alcohol can be prepared by first converting the starting alcohol into an aldehyde (with DMP, or with PCC, or via Swern oxidation) followed by a Grignard reaction with ethyl magnesium bromide.



(d) This problem is similar to the previous problem, but two alkyl groups must be installed (an ethyl group and a methyl group). Each alkyl group can be installed using the same procedure from the previous problem (oxidation, followed by a Grignard reaction). The first oxidation procedure can be performed with DMP (or PCC, or Swern oxidation) to give the aldehyde. The second oxidation procedure can also be achieved with a variety of oxidizing agents, including chromic acid.



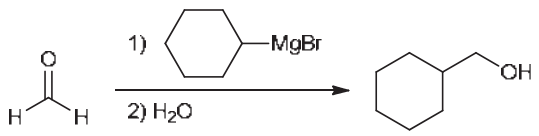
(e) Oxidation with DMP (or PCC, or Swern oxidation) gives an aldehyde, which can then be treated with a Grignard reagent to give a secondary alcohol. Oxidation of this alcohol gives the desired ketone.



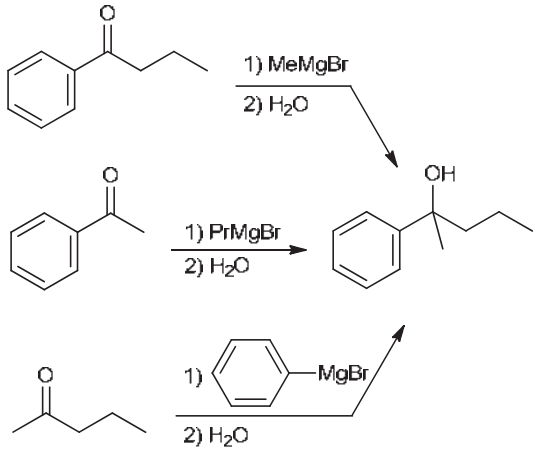
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12.35.

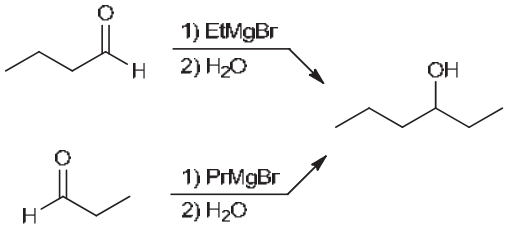
(a) The desired product has only one group connected to the α position. That group could have been installed via a Grignard reaction with formaldehyde, as shown.



(b) The desired product has three groups connected to the α position. Any one of these groups could have been installed via a Grignard reaction with the appropriate ketone, as shown.

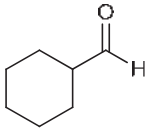


(c) The desired product has only two groups connected to the α position. Either one of these groups could have been installed via a Grignard reaction with the appropriate aldehyde, as shown.

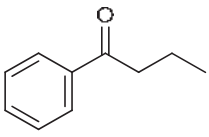


12.36.

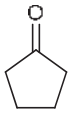
(a) Reduction of the following aldehyde will afford the desired product.



(b) Reduction of the following ketone will afford the desired product.

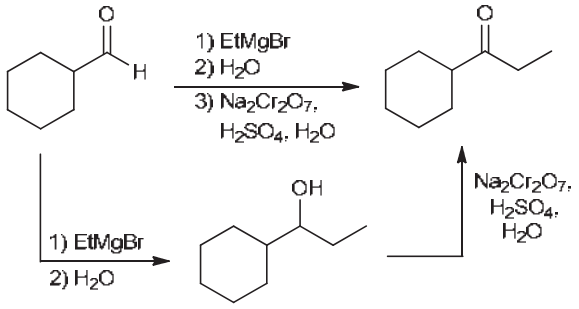


(c) Reduction of the following ketone will afford the desired product.

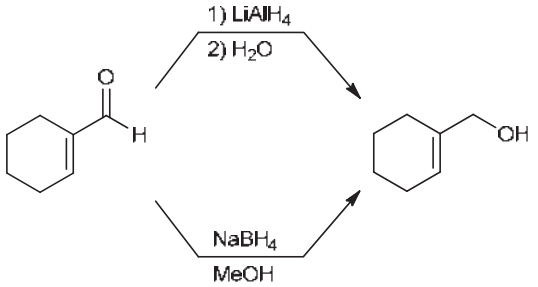


12.37.

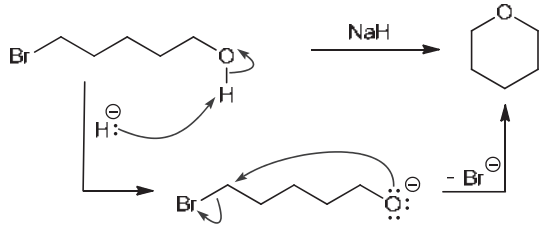
(a) The product has more carbon atoms than the starting material, so we must form a carbon-carbon bond. This can be achieved with a Grignard reaction (using ethyl magnesium bromide to install an ethyl group). The resulting alcohol can then be oxidized to give the desired product.



(b) Reduction of the aldehyde can be achieved with either $LiAlH_4$ or $NaBH_4$. This transformation cannot be achieved via catalytic hydrogenation, as that process would also reduce the carbon-carbon π bond.

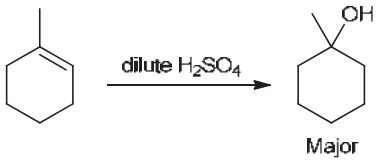


12.38. Hydride functions as a base and removes a proton from the alcohol, giving an alkoxide ion. This intermediate has both a nucleophilic region (the negatively charged oxygen atom) and an electrophilic region (the position that is α to the bromine atom). As such, an intramolecular, S_N2-type process can occur, giving a cyclic product.



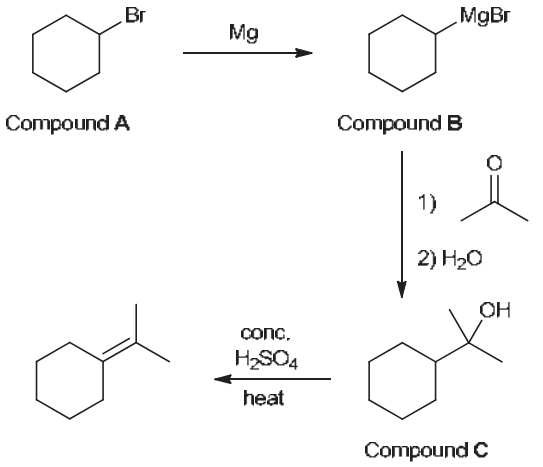
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12.39. The major product is 1-methylcyclohexanol (resulting from Markovnikov addition), which is a tertiary alcohol.

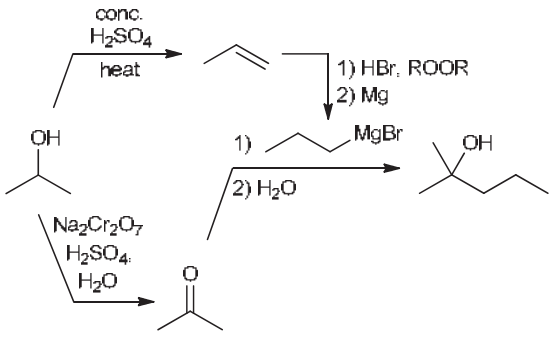


Tertiary alcohols do not generally undergo oxidation. In contrast, the minor product (2-methylcyclohexanol) is a secondary alcohol and can undergo oxidation to yield a ketone.

12.40. The conversion of compound **B** to compound **C** is achieved via a Grignard reaction that employs acetone as the electrophile. Therefore, the Grignard reagent (compound **B**) must be cyclohexyl magnesium bromide, as shown.

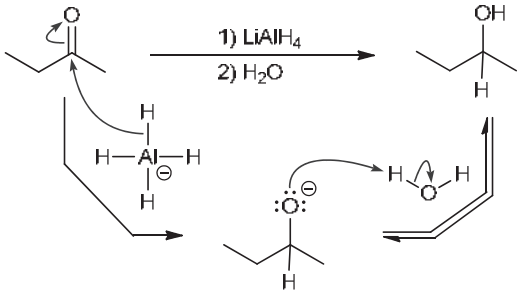


12.41. The starting material has three carbon atoms, and the product has six carbon atom, so we must form a carbon-carbon bond. This can be achieved with a Grignard reaction. The reagents for this Grignard reaction (acetone and propyl magnesium bromide) can both be prepared from the starting alcohol, as shown here.

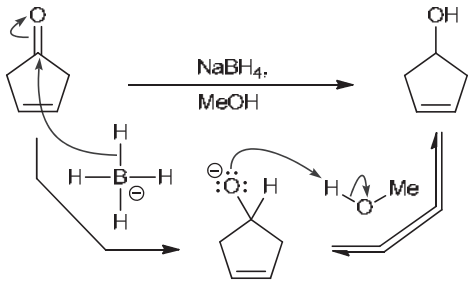


12.42.

(a) Two curved arrows are used to show hydride delivery. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting alkoxide ion is then protonated upon treatment with water. This protonation step requires two curved arrows, as shown.

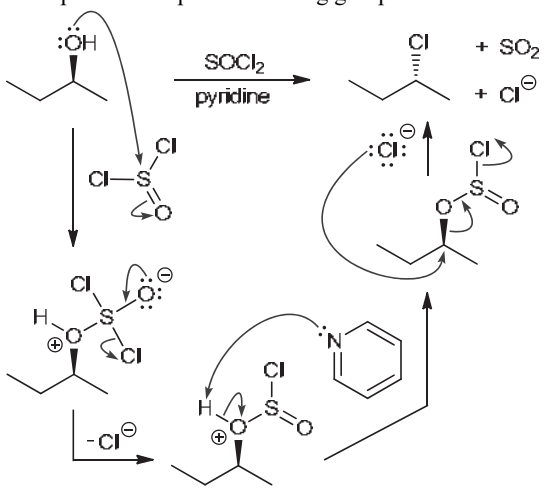


(b) Two curved arrows are used to show hydride delivery. Note that the tail of the first curved arrow is placed on the bond between B and H (it is NOT placed on the negative charge). The resulting alkoxide ion is then protonated, which requires two curved arrows, as shown.



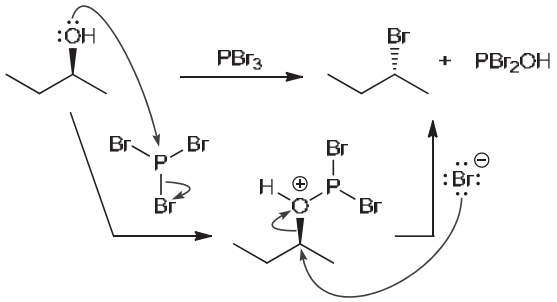
12.43.

(a) As seen in Mechanism 12.6, the OH group is transformed into a better leaving group (through a series of steps shown below), and then chloride attacks as a nucleophile and expels the leaving group.

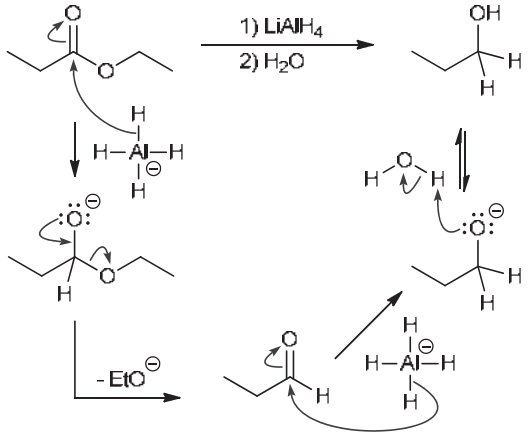


(b) As seen in Mechanism 12.7, the OH group is transformed into a better leaving group, and then bromide attacks as a nucleophile and expels the leaving group.

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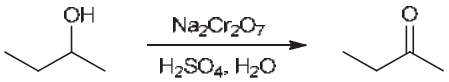


(c) Two curved arrows are used to show hydride delivery to the ester. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting intermediate then ejects ethoxide as a leaving group, which requires two curved arrows. The resulting aldehyde is then further reduced by another equivalent of $LiAlH_4$. Once again, two curved arrows are used to show hydride delivery. The resulting alkoxide ion is then protonated upon treatment with water. This protonation step requires two curved arrows.

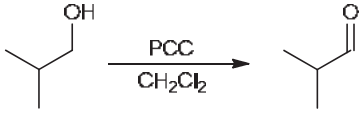


12.44.

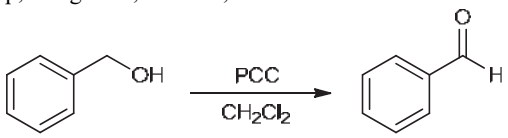
(a) The starting material is an alcohol, and the product is a ketone. This transformation can be achieved in one step, using chromic acid as the oxidizing agent.



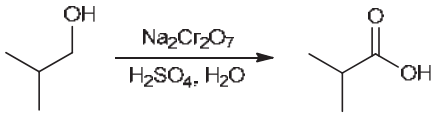
(b) The starting material is an alcohol and the product is an aldehyde. This transformation can be achieved in one step, using PCC, or DMP, or a Swern oxidation.



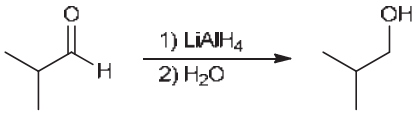
(c) The starting material is an alcohol, and the product is an aldehyde. This transformation can be achieved in one step, using PCC, or DMP, or a Swern oxidation.



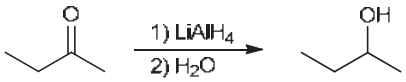
(d) The starting material is an alcohol and the product is a carboxylic acid. This transformation can be achieved in one step, using chromic acid as the oxidizing agent.



(e) The starting material is an aldehyde, and the product is an alcohol. This transformation can be achieved in one step, using $LiAlH_4$ or $NaBH_4$ as a reducing agent.

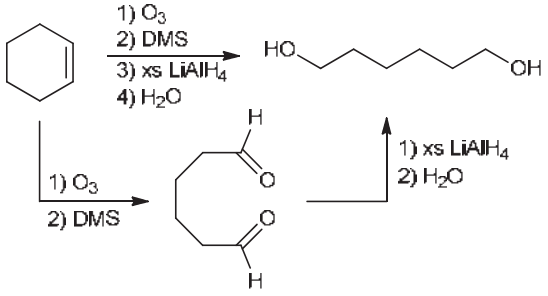


(f) The starting material is a ketone and the product is an alcohol. This transformation can be achieved in one step, using $LiAlH_4$ or $NaBH_4$ as a reducing agent.



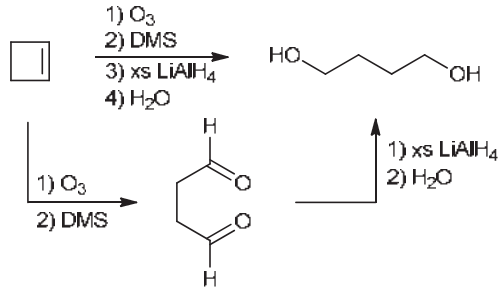
12.45.

(a) Ozonolysis of the alkene gives a dialdehyde, which is then reduced when treated with excess $LiAlH_4$ to give a diol.

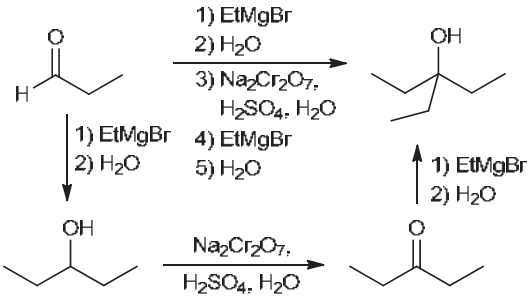


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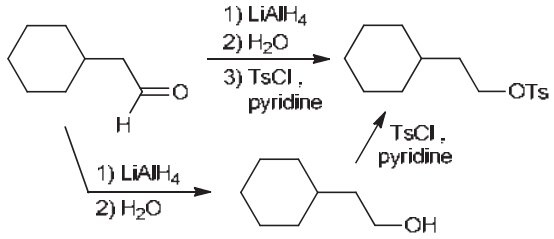
(b) Ozonolysis of the alkene gives a dialdehyde, which is then reduced when treated with excess $LiAlH_4$ to give a diol.



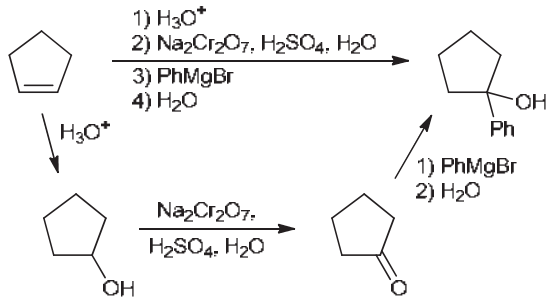
(c) Treating the aldehyde with ethyl magnesium bromide (followed by water work-up) gives a secondary alcohol, which is then oxidized to give a ketone upon treatment with chromic acid. Finally, the ketone is converted to a tertiary alcohol when treated with ethyl magnesium bromide (followed by water work-up).



(d) The aldehyde is reduced upon treatment with $LiAlH_4$ to give an alcohol. Treating the alcohol with tosyl chloride and pyridine converts the alcohol into a tosylate.

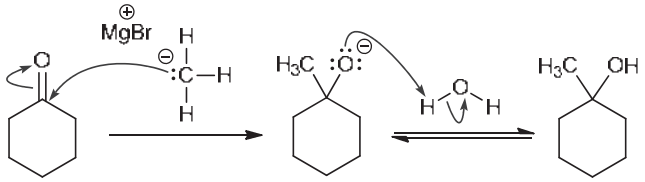


(e) Acid-catalyzed hydration of the alkene gives a secondary alcohol, which is then oxidized to a ketone upon treatment with chromic acid. Finally, the ketone is converted to a tertiary alcohol when treated with a Grignard reagent (followed by water work-up).

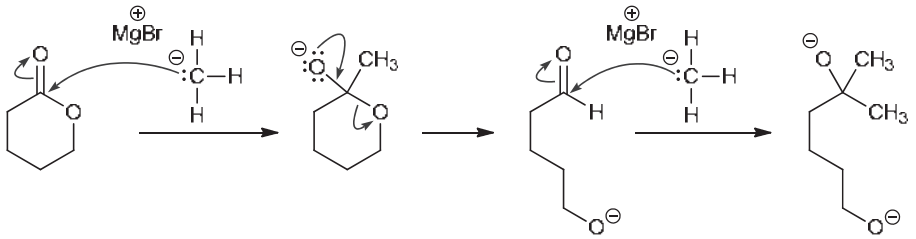


12.46.

(a) In the first step of the mechanism shown below, the Grignard reagent (methyl magnesium bromide) functions as a nucleophile and attacks the C=O bond of the ketone. This step requires two curved arrows. The resulting alkoxide ion is then protonated upon treatment with water. This proton transfer step also requires two curved arrows, as shown.

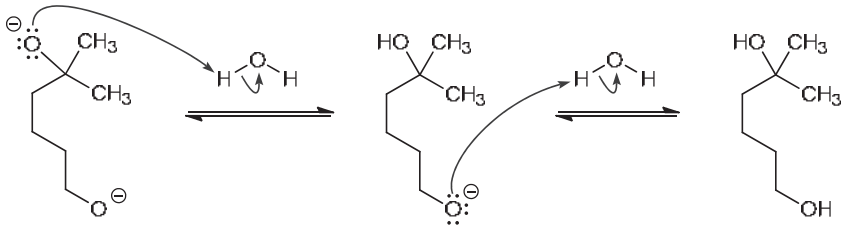


(b) In the first step of the mechanism shown below, the Grignard reagent (methyl magnesium bromide) functions as a nucleophile and attacks the C=O bond of the ester. This step requires two curved arrows. The resulting intermediate then ejects a leaving group to give a ketone, which requires two curved arrows. The ketone is then further attacked by another equivalent of the Grignard reagent. Once again, two curved arrows are used to show the nucleophilic attack, resulting in a dianion.



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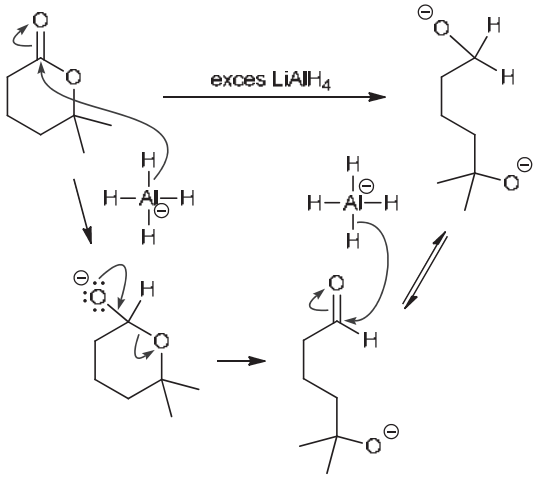
The resulting dianion is then protonated upon treatment with water. There are two locations that are protonated, each of which requires two curved arrows, as shown. Notice that each anion is protonated in a separate step (this should not be drawn as one step with four curved arrows, because there are two distinct processes occurring, and it is unlikely that they occur precisely at the same moment).



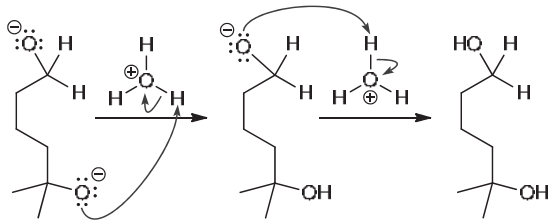
12.47. One carbon atom is reduced from an oxidation state of 0 to an oxidation state of -1, while the other carbon atom is oxidized from an oxidation state of 0 to an oxidation state of +1. Overall, the starting material does not undergo a net change in oxidation state and is, therefore, neither reduced nor oxidized.

12.48. One carbon atom is reduced from an oxidation state of 0 to an oxidation state of -2, while the other carbon atom is oxidized from an oxidation state of 0 to an oxidation state of +2. Overall, the starting material does not undergo a net change in oxidation state and is, therefore, neither reduced nor oxidized.

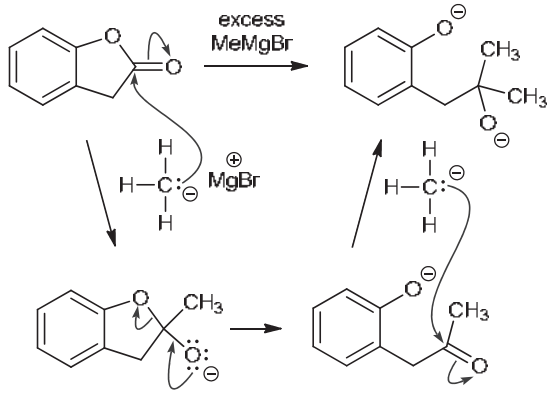
12.49. Two curved arrows are used to show delivery of hydride to the ester. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting intermediate then ejects a leaving group, which requires two curved arrows. The resulting aldehyde is then further reduced by another equivalent of $LiAlH_4$. Once again, two curved arrows are used to show hydride delivery, resulting in a dianion.



The dianion is then protonated upon treatment with aqueous acid. There are two locations that are protonated, each of which requires two curved arrows, as shown. Notice that each protonation step is drawn separately. The less stable negative charge (the stronger base) is protonated first (see Section 3.7 to determine which negative charge is less stable).

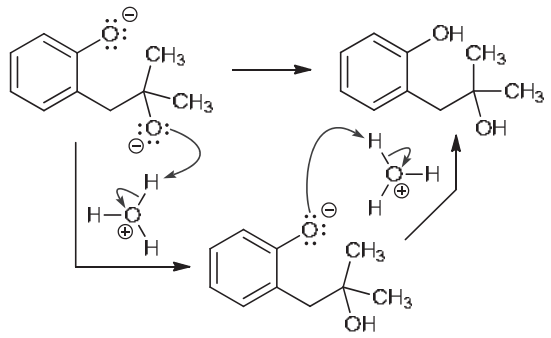


12.50. In the first step of the mechanism, the Grignard reagent (methyl magnesium bromide) functions as a nucleophile and attacks the C=O bond of the ester. This step requires two curved arrows. The resulting intermediate then ejects a leaving group to give a ketone, which requires two curved arrows. The ketone is then further attacked by another equivalent of the Grignard reagent. Once again, two curved arrows are used to show the nucleophilic attack, resulting in a dianion.



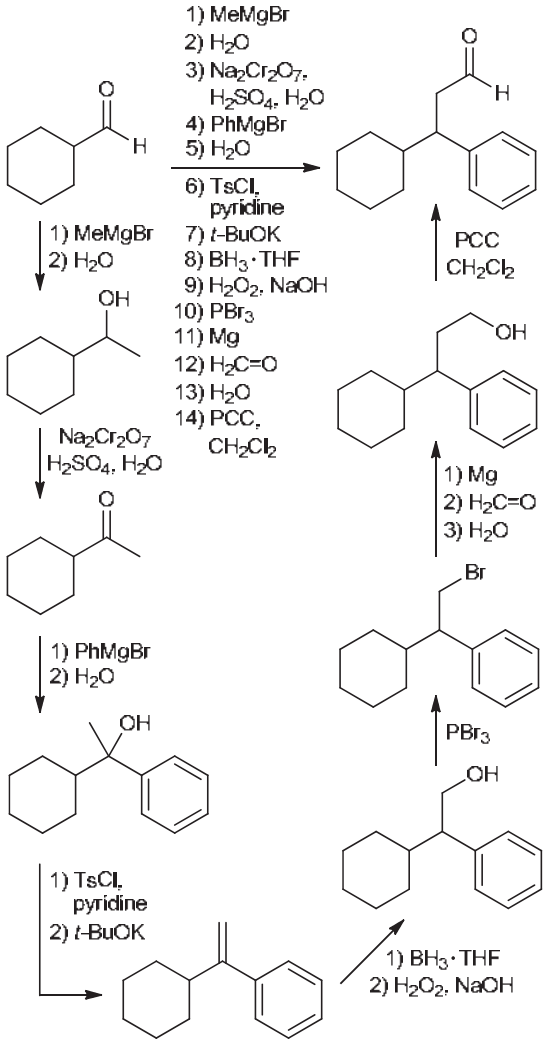
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The resulting dianion is then protonated upon treatment with aqueous acid. There are two locations that are protonated, each of which requires two curved arrows, as shown.

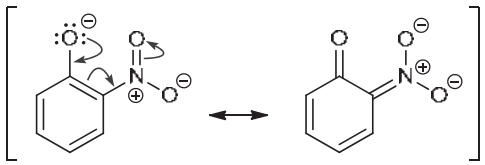


Notice that each protonation step is drawn separately. The less stable negative charge (the alkoxide) is protonated first (rather than phenolate, which is more stable because it is resonance-stabilized). In fact, the phenolate anion is even more stable than a hydroxide ion, which explains why the proton source must be H_3O^+ rather than water. Water is not sufficiently acidic to protonate a phenolate ion (see Section 12.2, Acidity of Alcohols and Phenols).

12.51. Treating the aldehyde with methyl magnesium bromide (followed by water work-up) gives the secondary alcohol, which can then be oxidized with chromic acid to give a ketone. Treatment of the ketone with phenyl magnesium bromide gives a tertiary alcohol. Converting this alcohol to the less substituted alkene (disubstituted, rather than trisubstituted) requires that we first convert the OH group to a tosylate group, and then perform an E2 reaction with a sterically hindered base, such as *tert*-butoxide. Conversion of this alkene into a primary alcohol requires an *anti*-Markovnikov addition of H and OH across the alkene, which can be achieved via hydroboration-oxidation. Treatment with PBr_3 then converts the primary alcohol to a primary bromide. This alkyl bromide is then converted to a Grignard reagent (upon treatment with Mg) and then treated with formaldehyde. The resulting alcohol can then be oxidized to an aldehyde with PCC (or DMP, or Swern oxidation).



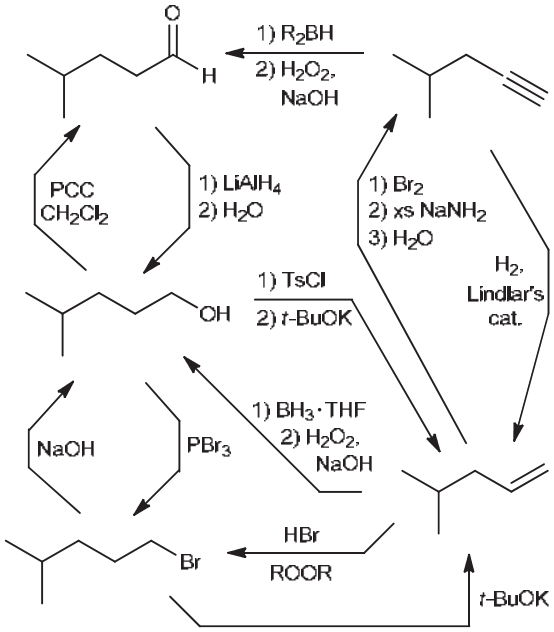
12.52. 2-Nitrophenol is expected to be more acidic (lower pK_a) because its conjugate base has a resonance structure in which the negative charge is spread onto an oxygen atom of the nitro group:



In contrast, 3-nitrophenol does not have such a resonance structure.

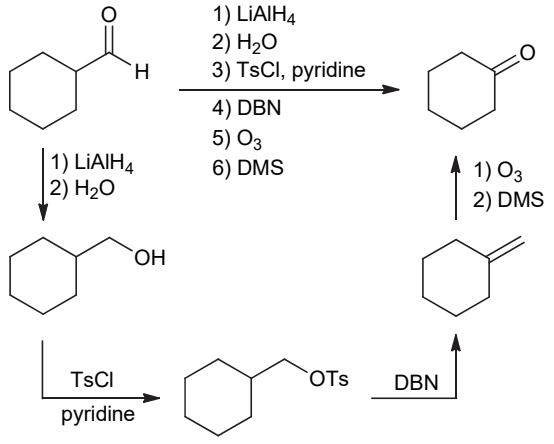
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12.53. Most of the reagents for these transformations can be found in Figure 12.11.

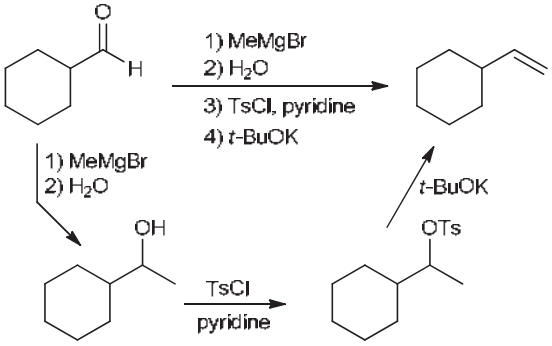


12.54.

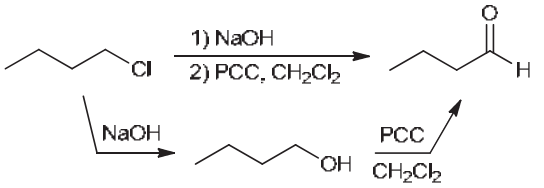
(a) The product has one less carbon atom then the starting material, so we must break a carbon-carbon bond. Therefore, the last step of our synthesis must be ozonolysis of an alkene to give the desired ketone. With this in mind, preparation of the alkene can be achieved by reducing the starting material (with $LiAlH_4$ or $NaBH_4$), followed by converting the OH group to a tosylate and then treating the tosylate with a non-nucleophilic base.



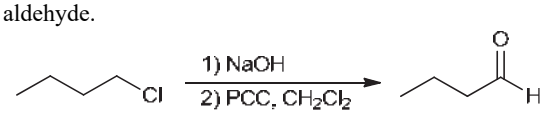
(b) The product has one more carbon atom than the starting material, so we must make a carbon-carbon bond. This can be achieved with a Grignard reaction, using methyl magnesium bromide to install a methyl group. The resulting alcohol can then be converted to the desired alkene via a two-step process. First, the alcohol is converted to a tosylate (because OH is a bad leaving group), and then the tosylate is treated with a sterically hindered base to give the less substituted alkene.



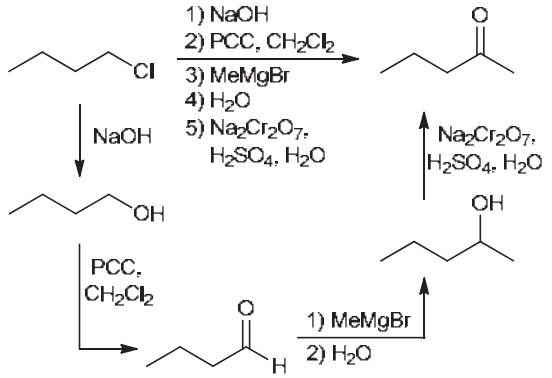
(c) The starting material and the product have the same carbon skeleton. The identity of the functional group must be changed. This can be achieved in two steps. The alkyl chloride can first be converted to a primary alcohol via an S_N2 process, and then the alcohol can be oxidized with PCC (or DMP or Swern oxidation) to give the desired product.



(d) In the previous problem, we saw a two-step procedure for converting the starting material into an aldehyde.

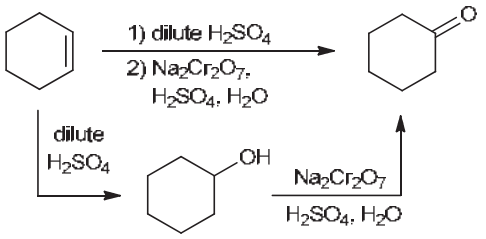


This aldehyde can then be converted into the desired product via a two-step process (a Grignard reaction to install a methyl group, followed by oxidation).

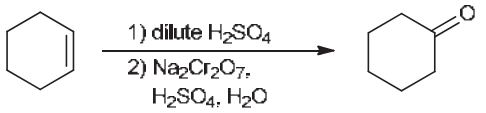


(e) The starting material and the product have the same carbon skeleton. The identity of the functional group must be changed. This can be achieved in two steps. The alkene is first converted to an alcohol via acid-catalyzed hydration, and then the alcohol can be oxidized with chromic acid to give the desired product.

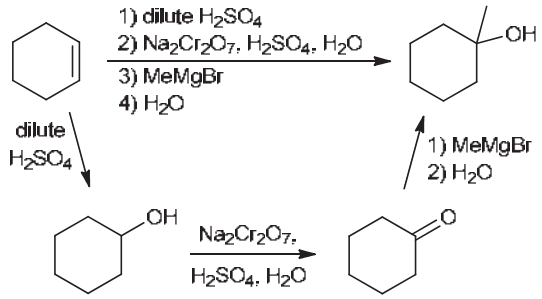
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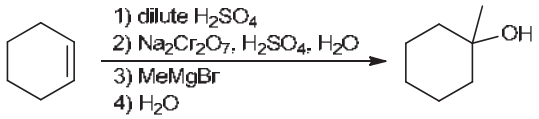
(f) In the previous problem, we saw that the starting material can be converted into a ketone in just two steps.



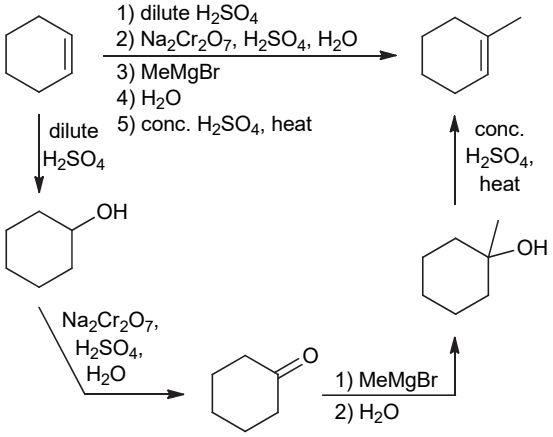
This ketone can be converted into the desired product with a Grignard reaction.



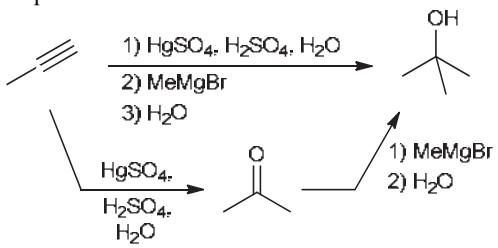
(g) In the previous problem, we saw that the starting material can be converted into a tertiary alcohol.



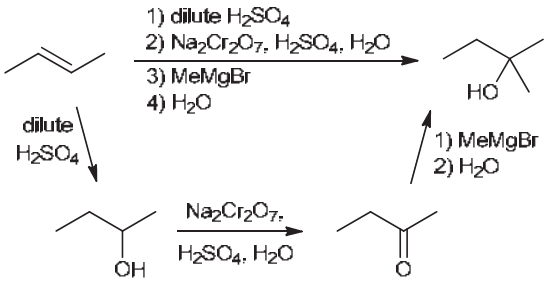
This alcohol can be converted into the desired product in just one step (upon treatment with concentrated sulfuric acid).



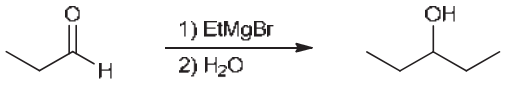
(h) The product has one more carbon atom than the starting material, so we must make a carbon-carbon bond. This can be achieved with a Grignard reaction, using methyl magnesium bromide to install a methyl group. In order to perform the desired Grignard reaction, we must first convert the starting alkyne into a ketone, which can be accomplished via acid-catalyzed hydration in the presence of mercuric sulfate.



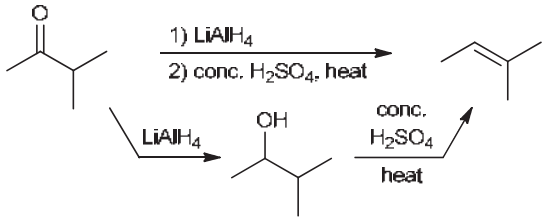
(i) The product has one more carbon atom than the starting material, so we must make a carbon-carbon bond. This can be achieved with a Grignard reaction, using methyl magnesium bromide to install a methyl group. In order to perform the desired Grignard reaction, we must first convert the starting alkene into a ketone, which can be accomplished via a two-step process (acid-catalyzed hydration, followed by oxidation).



(j) The desired transformation can be achieved in one step, using a Grignard reaction.



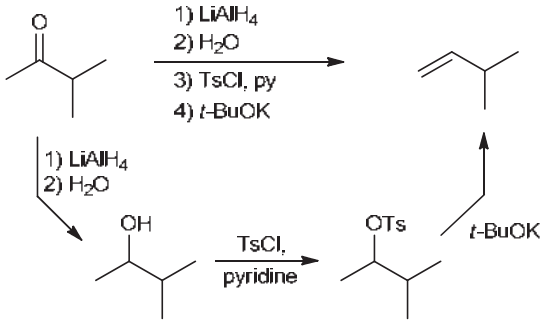
(k) The starting material and the product have the same carbon skeleton. The identity of the functional group must be changed. This can be achieved in two steps. The ketone is first converted to an alcohol via reduction (using either $LiAlH_4$ or $NaBH_4$), and then the alcohol can be treated with concentrated sulfuric acid to give the desired alkene.



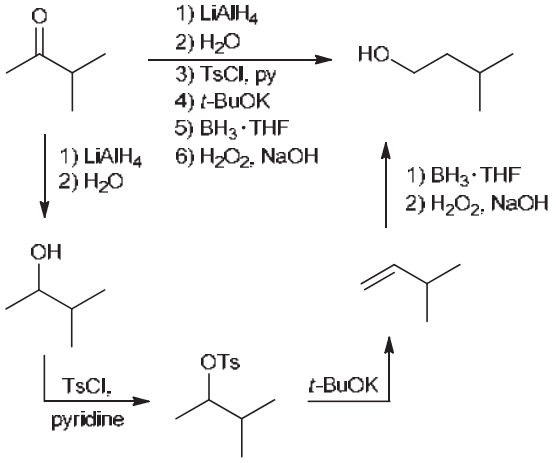
(l) The starting material and the product have the same carbon skeleton. The identity of the functional group

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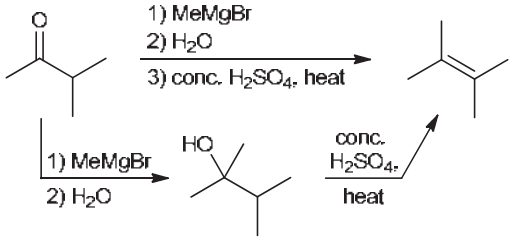
must be changed. The ketone is first converted to an alcohol via reduction (using either $LiAlH_4$ or $NaBH_4$), and then we must perform an elimination process. Since the less substituted alkene is desired, we must use a sterically hindered base. Since OH is a bad leaving group, it must first be converted to a good leaving group. This can be accomplished by treating the alcohol with tosyl chloride and the resulting tosylate can then be treated with *tert*-butoxide to give the desired product.



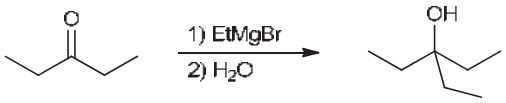
(m) The starting material and the product have the same carbon skeleton. The identity and location of the functional group must be changed. The answer to the previous problem allows us to convert the starting material into an alkene, which can be then converted into the product via hydroboration-oxidation.



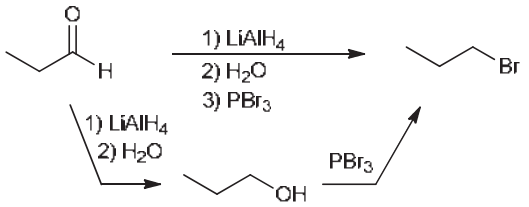
(n) The product has one more carbon atom than the starting material, so we must make a carbon-carbon bond. This can be achieved with a Grignard reaction, using methyl magnesium bromide to install a methyl group. The resulting alcohol can then be converted to the desired product upon treatment with concentrated sulfuric acid (an E1 process).



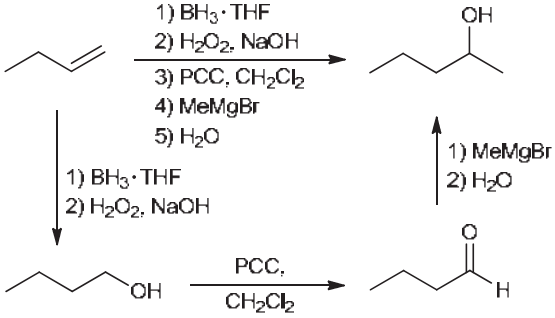
(o) The desired transformation can be achieved in one step, using a Grignard reaction.



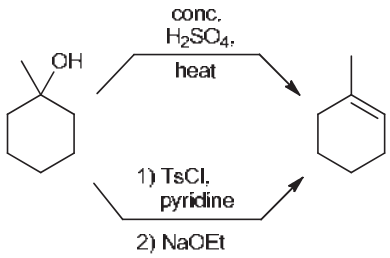
(p) The starting material and the product have the same carbon skeleton. The identity of the functional group must be changed. This can be achieved by reducing the aldehyde (with either $LiAlH_4$ or $NaBH_4$) followed by treatment with PBr_3 to give the desired alkyl bromide.



(q) The product has one more carbon atom than the starting material, so we must make a carbon-carbon bond. This can be achieved with a Grignard reaction, using methyl magnesium bromide to install a methyl group. In order to perform the desired Grignard reaction, we must first convert the starting alkene into an aldehyde, which can be accomplished via hydroboration-oxidation, followed by oxidation with PCC (or DMP or Swern).

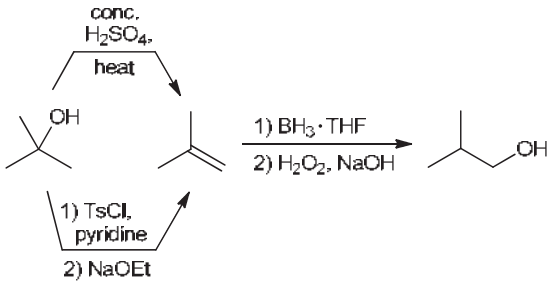


12.55. The alcohol can be converted to an alkene via either of the two processes shown below. Notice that the second method involves converting the alcohol into a tosylate, followed by treatment with a strong base. If this method is used, it is important that the base is not sterically hindered. A sterically hindered base might give the less substituted alkene as the major product, and we need the more substituted alkene. Appropriate bases include hydroxide, methoxide and ethoxide (ethoxide is shown below).



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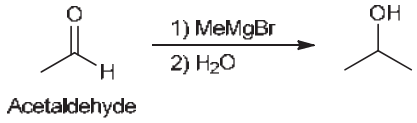
12.56. The desired transformation can be achieved by converting the alcohol to an alkene (via either of the two methods discussed in the previous problem), followed by *anti*-Markovnikov addition of H and OH to give the product.



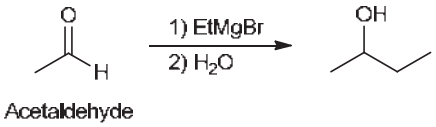
There are certainly other acceptable answers. For example, conversion of the alkene to the desired alcohol can be achieved via *anti*-Markovnikov addition of HBr (in the presence of peroxides) followed by an S_N2 process in which hydroxide functions a nucleophile and replaces bromide.

12.57.

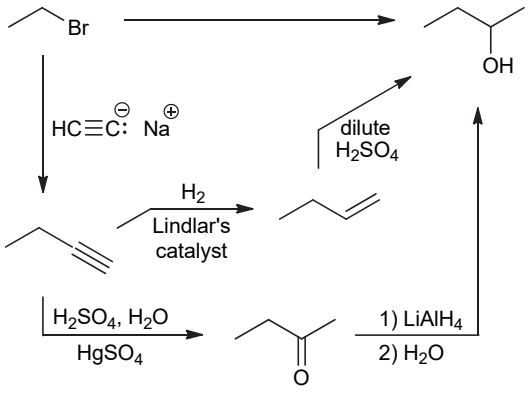
(a) The desired product can be made in just one step (via a Grignard reaction) from acetaldehyde (two carbon atoms).



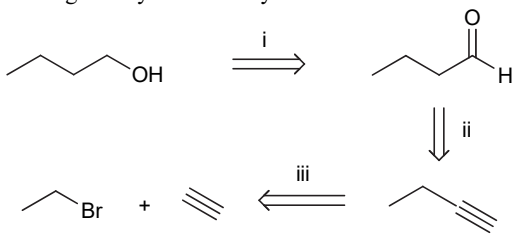
(b) The desired transformation can be achieved via a Grignard reaction in which acetaldehyde (two carbon atoms) is treated with ethyl magnesium bromide (two carbon atoms):



Certainly, there are other acceptable answers, two of which are shown below. In both of these pathways, the starting material is ethyl bromide (two carbon atoms):

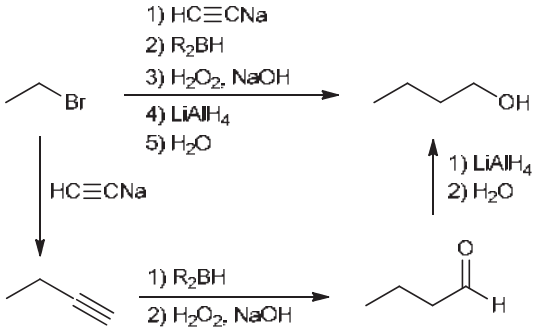


(c) There are certainly many acceptable answers to this problem. One such answer can be rationalized with the following retrosynthetic analysis.

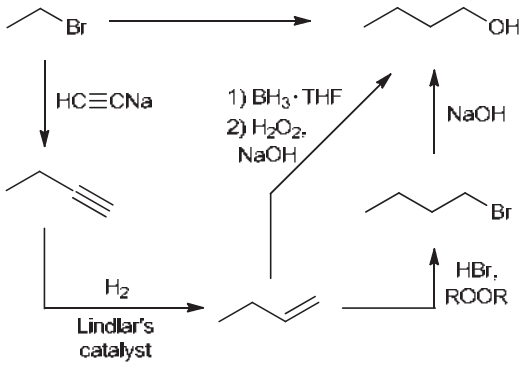


i. The product is an alcohol, which can be made from the corresponding aldehyde via reduction.
ii. The aldehyde can be made from a terminal alkyne via hydroboration-oxidation.
iii. The terminal alkyne can be made via an alkylation process.

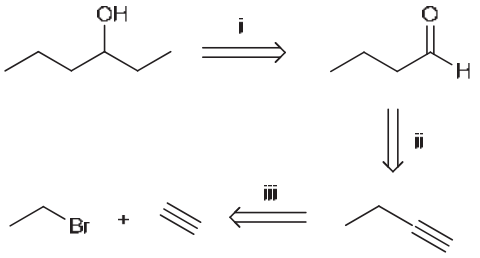
Reagents for this synthetic strategy are shown here.



The following are alternative synthetic pathways that also achieve the desired transformation:



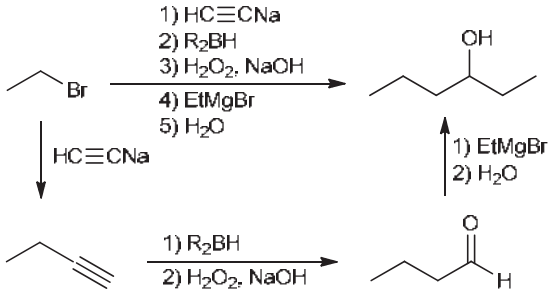
(d) There are certainly many acceptable answers to this problem. One such answer can be rationalized with the following retrosynthetic analysis.



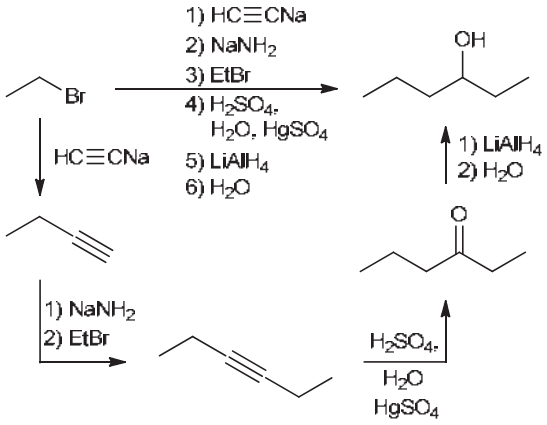
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i. The alcohol can be made by treating the appropriate aldehyde with ethyl magnesium bromide.
ii. The aldehyde can be made from a terminal alkyne (via hydroboration-oxidation).
iii. The terminal alkyne can be made via an alkylation process.

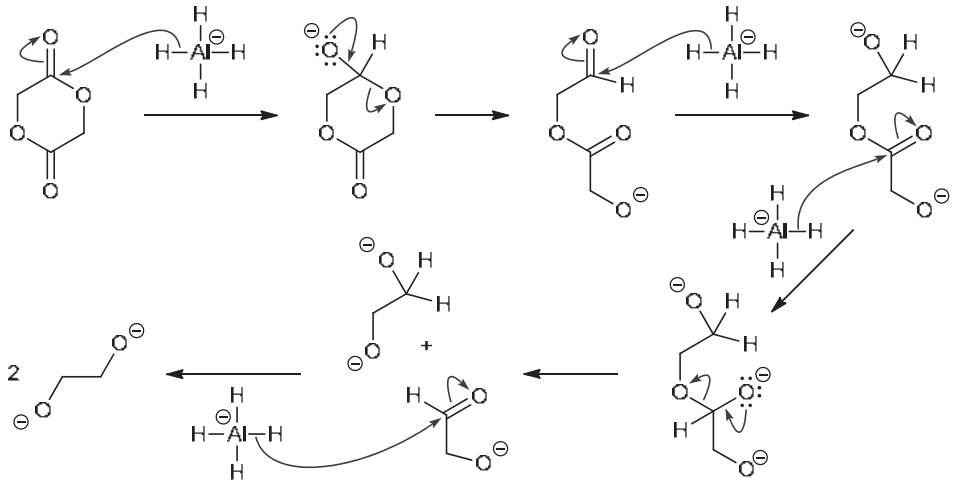
Reagents for this synthetic strategy are shown here.



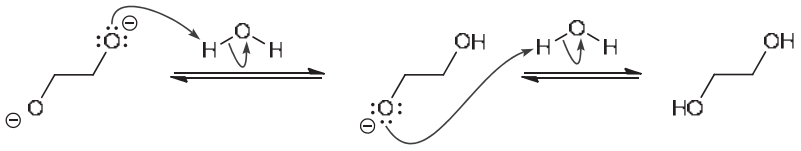
The following is an alternative synthetic pathway that also achieves the desired transformation:



12.58. Two curved arrows are used to show hydride delivery to one of the ester groups. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting intermediate then ejects a leaving group, which requires two curved arrows. The resulting aldehyde is then further reduced by another equivalent of $LiAlH_4$. Once again, two curved arrows are used to show hydride delivery. This entire process is then repeated again for the other ester group, giving two equivalents of the dianion.



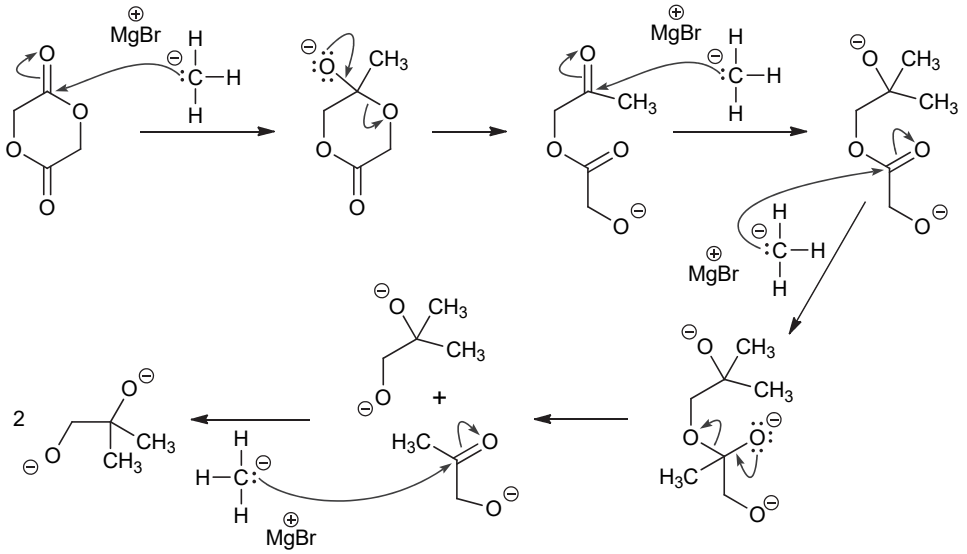
The resulting dianion is then protonated upon treatment with water. Notice that each protonation step is drawn separately.



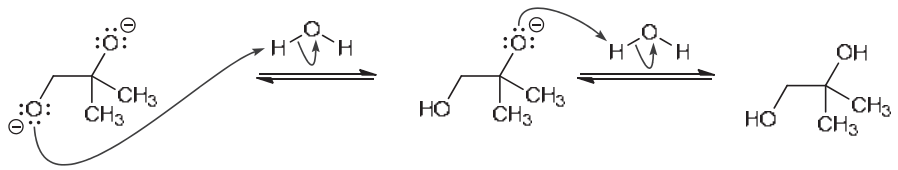
12.59. Two curved arrows are used to show a Grignard reagent attacking one of the ester groups. The resulting intermediate then ejects a leaving group, which requires two curved arrows. The resulting ketone is then further attacked by another equivalent of the Grignard reagent. Once again, two curved arrows are used to show the

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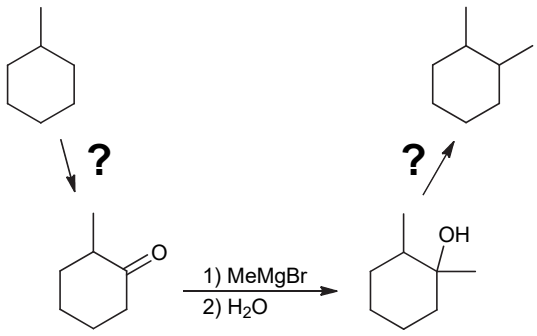
nucleophilic attack. This entire process is then repeated again for the other ester group, giving two equivalents of the dianion.



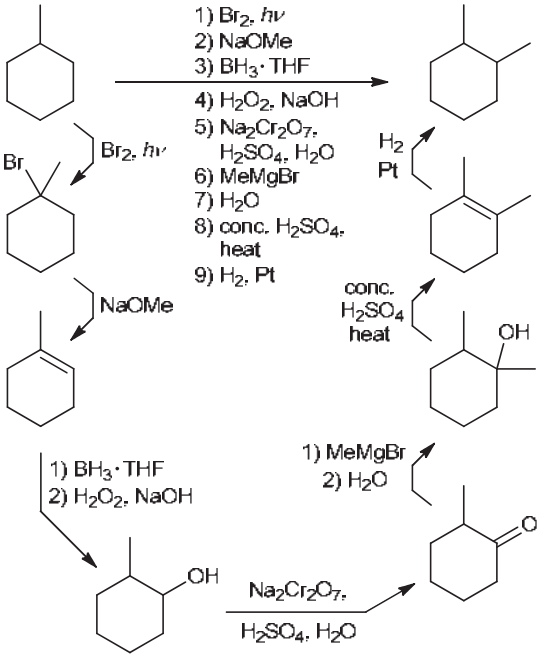
The resulting dianion is then protonated upon treatment with water. Notice that each protonation step is drawn separately.



12.60. The product has one more carbon atom than the starting material. This extra methyl group can be installed using a Grignard reaction, as shown here:

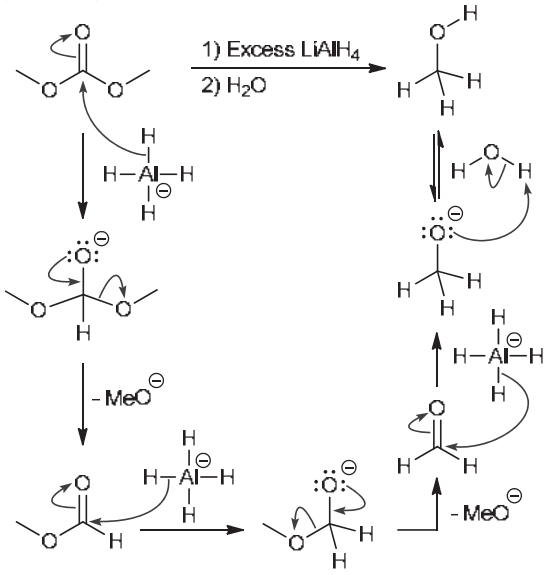


If we are going to use this Grignard reaction to form the critical carbon-carbon bond, then we must first convert the starting cycloalkane into the necessary ketone, AND we must convert the product of the Grignard reaction (a tertiary alcohol) into the desired product. There are certainly many acceptable synthetic routes that can be used. One such route is shown here. The starting material does not have a functional group, but one can be introduced via radical bromination. Elimination followed by hydroboration-oxidation gives an alcohol that can be oxidized to give the ketone necessary for the Grignard reaction. Then, after the Grignard reaction is complete, the resulting tertiary alcohol can be converted into the product in just two steps (E1 elimination followed by catalytic hydrogenation):

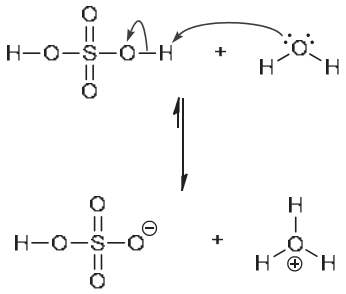


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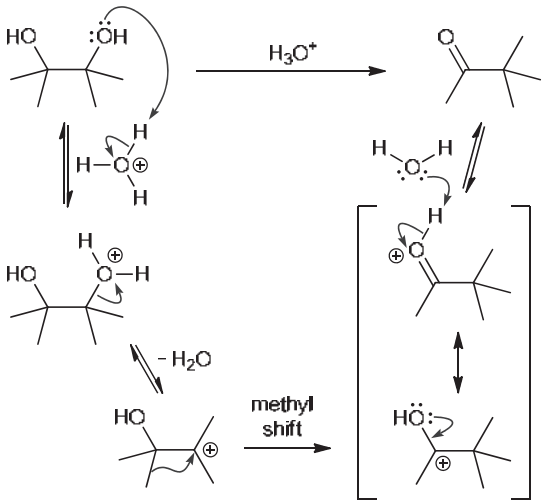
12.61. Two curved arrows are used to show delivery of hydride to the C=O bond. Note that the tail of the first curved arrow is placed on the bond between Al and H (it is NOT placed on the negative charge). The resulting intermediate then ejects methoxide as a leaving group, which requires two curved arrows. The resulting compound is then further reduced by another equivalent of $LiAlH_4$. Once again, two curved arrows are used to show hydride delivery, resulting in an intermediate that ejects methoxide as a leaving group, which requires two curved arrows, to give formaldehyde. Formaldehyde is then reduced one last time by a third equivalent of $LiAlH_4$ (and once again, two curved arrows are required). The resulting alkoxide ion is then protonated upon treatment with water to give the product (methanol).



12.62. When sulfuric acid is used, the actual proton source is more likely to be H_3O^+, rather than H_2SO_4, because aqueous sulfuric acid contains water (even when concentrated), and the equilibrium favors H_3O^+ over H_2SO_4, as shown here.

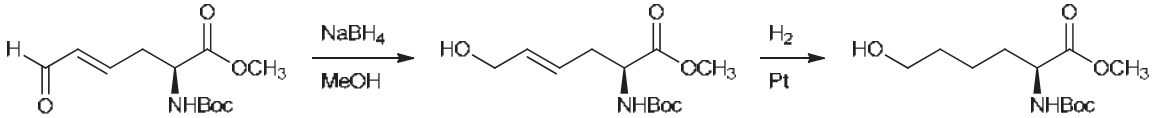


Therefore, our mechanism will show H_3O^+ as the proton source. In the first step of the mechanism, one of the OH groups is protonated to give a good leaving group. Loss of the leaving group then generates a tertiary carbocation. In this case, the tertiary carbocation can rearrange to produce a more stable cation that is resonance-stabilized. Water then functions as a base to remove a proton, giving the product. Notice that the last step employs water as the base. You cannot show hydroxide functioning as a base because the concentration of hydroxide is negligible in acidic conditions.



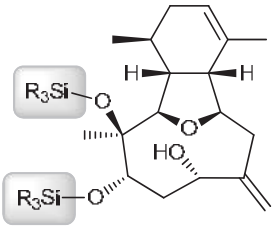
12.63. One carbon atom is oxidized from an oxidation state of +1 to an oxidation state of +2, while the other carbon atom is reduced from an oxidation state of +1 to an oxidation state of 0. Overall, the starting material does not undergo a net change in oxidation state and is, therefore, neither reduced nor oxidized.

12.64. Analysis of the starting material and the product shows that the aldehyde and alkene groups have been reduced. Secondly, the aldehyde is selectively reduced in the presence of the ester. Selective reduction of the aldehyde with $NaBH_4$, followed by reduction of the alkene (H_2, Pt), affords the desired product. Note that $LiAlH_4$ cannot be used in this case, because $LiAlH_4$ would reduce the ester group as well.

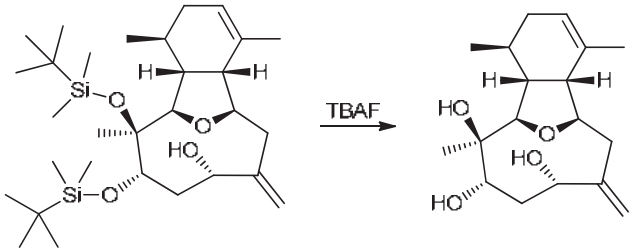


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12.65. We have seen that tetrabutylammonium fluoride (TBAF) can be used to remove silyl protecting groups. In this case, there are two such groups:



We learned about the trimethylsilyl protecting group (TMS), and the protecting groups employed in this case are very similar (in each case, one of the methyl (R) groups has been replaced with a *tert*-butyl group). This protecting group is called the *tert*-butyldimethyl silyl group (TBDMS, or just TBS for short), and it is removed upon treatment with TBAF, in much the same way that the TMS group is removed under similar conditions. The rest of the compound is expected to remain unchanged.

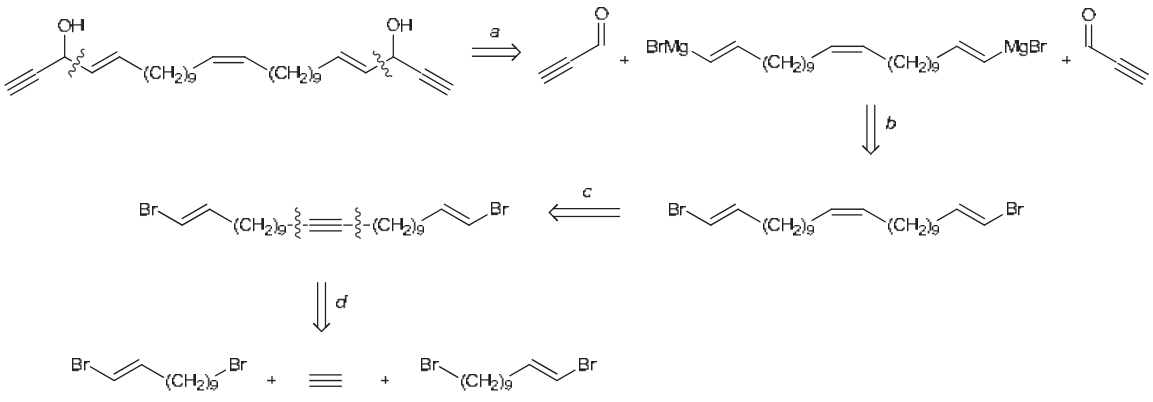


12.66. The following synthesis is one suggested synthetic pathway. There are certainly other acceptable approaches that accomplish the same goal.

Let's start with a few general observations:

1. Our starting materials cannot have more than eleven carbon atoms, and the target compound has thirty carbon atoms, so we will need to form more than one C-C bond.
2. The molecule is symmetric, so it makes sense to propose equivalent reactions on each side of the molecule.
3. The central C=C bond has the *cis* configuration, which we can make via reduction of an internal alkyne using H_2 and Lindlar's catalyst. This, however, cannot be the final step of our proposed synthesis, because these conditions would also reduce the two terminal alkyne groups. Thus, the two terminal alkyne groups need to be installed *after* reduction of the central alkyne group.

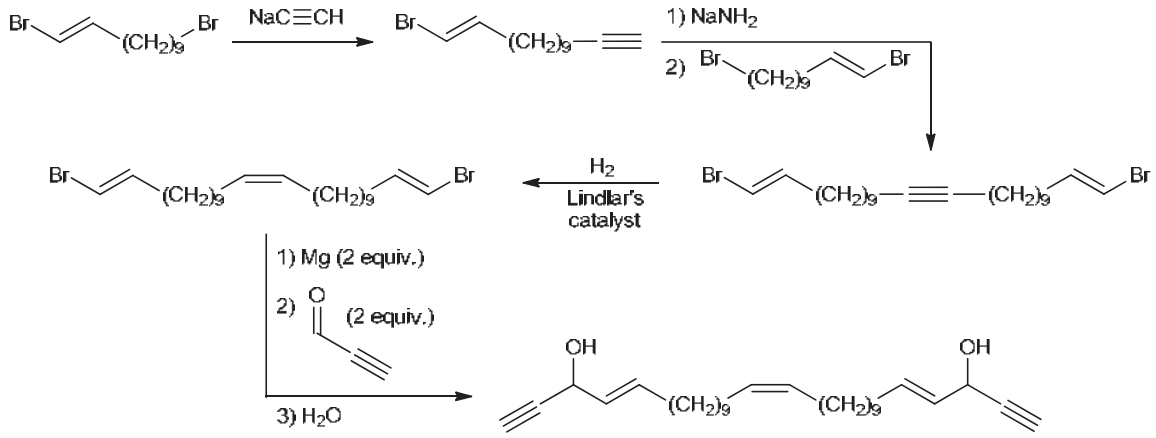
The figure below outlines a retrosynthetic analysis for our target molecule. An explanation of each of the steps (*a-d*) follows.



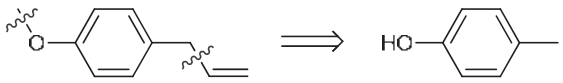
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a. Duryne can be made from the reaction between the bis-vinyl Grigard reagent (a dianion) and two equivalents of the aldehyde shown.
b. The bis-vinyl Grignard is made from the bis-vinyl bromide and two equivalents of magnesium.
c. The *cis* alkene is produced via reduction of the corresponding internal alkyne.
d. The alkyne is made by sequentially alkylating each carbon of acetylene with *E*-1,11-dibromo-1-undecene. Note that while there are two bromines on this molecule, only the bromide attached to the sp^3 hybridized atom carbon can serve as a leaving group in an S_N2 reaction.

Now let's draw the forward scheme. The starting material, *E*-1,11-dibromo-1-undecene, is treated with sodium acetylide to produce a terminal alkyne. Deprotonation with sodium amide, followed by treatment with a second equivalent of *E*-1,11-dibromo-1-undecene gives the internal alkyne. Reduction of the alkyne with H_2 and Lindlar's catalyst affords the *cis* alkene. Further treatment with two equivalents of magnesium yields the bis-vinyl Grignard, which reacts with two equivalents of the aldehyde. Aqueous workup produces the target molecule, duryne.

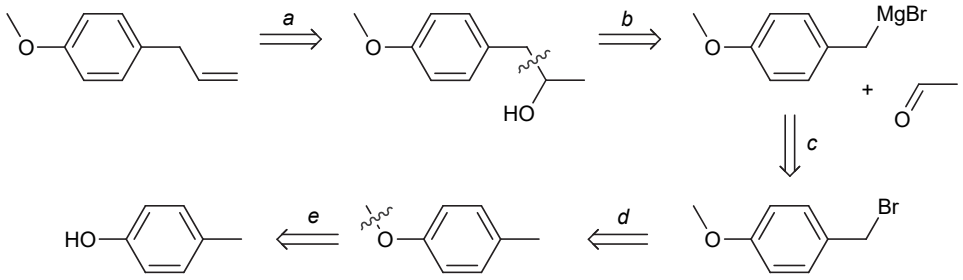


12.67. The following synthesis is one suggested synthetic pathway. There are certainly other acceptable approaches that accomplish the same goal.
By comparing the structures of the starting material (4-methylphenol) and the product, it is clear that the following bonds (indicated by wavy lines below) need to be made in this synthesis.



The left bond (C-O) can be made via an S_N2 process, while the right bond (C-C) can be made by either a Grignard reaction or by using an acetylide ion as a nucleophile. It is important that we make the ether bond early in our scheme to avoid an acid/base reaction between the phenolic proton ($pK_a \approx 10$) and the Grignard reagent or acetylide (both of which are strong bases). If the phenolic proton is subjected to a Grignard reagent, the latter would be destroyed via protonation. The same fate would occur for an acetylide ion that is treated with a compound bearing a phenolic proton.

The following is a retrosynthetic analysis for our target compound. An explanation of each of the steps (*a-e*) follows.

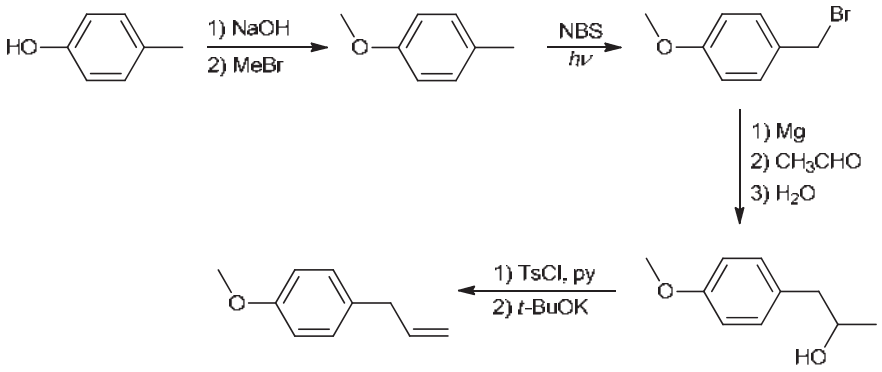


a. We can make the monosubstituted alkene by converting the OH group into a tosylate group and then performing an elimination reaction with a sterically hindered base.

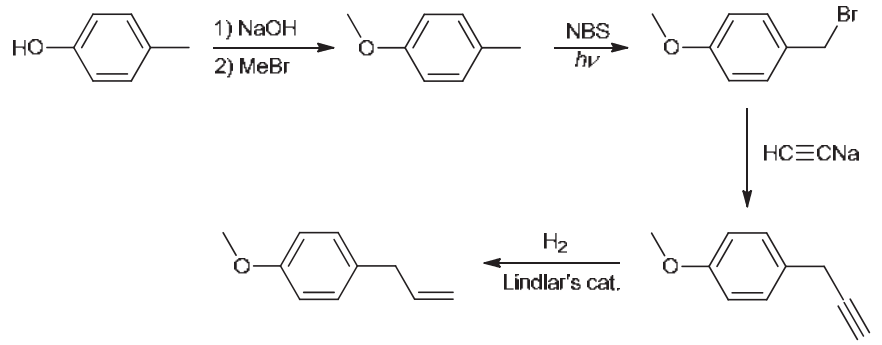
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b. The alcohol can be made via a Grignard reaction between the benzylic Grignard reagent and the aldehyde shown.
c. The Grignard reagent is made from the corresponding benzylic bromide.
d. The bromine atom can be installed via radical bromination at the benzylic position.
e. The methyl ether can be produced via an S_N2 reaction from the starting material.

Now let's draw the forward scheme. The starting material, 4-methylphenol, is deprotonated with sodium hydroxide and the resulting phenoxide serves as a nucleophile in an S_N2 reaction with bromomethane. The bromine atom is installed using *N*-bromosuccinimide and light. This compound is then converted into a Grignard reagent using magnesium. The Grignard reagent reacts with the appropriate aldehyde (CH_3CHO), followed by a water workup to produce the alcohol. Conversion to the tosylate and subsequent reaction with *tert*-butoxide produces the less-substituted elimination product, estragole.

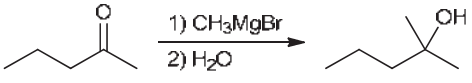


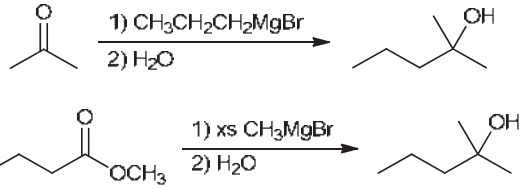
As mentioned, the synthetic route above is not the only method for making estragole. For example, the following alternative synthesis involves an acetylide ion, rather than a Grignard reaction:



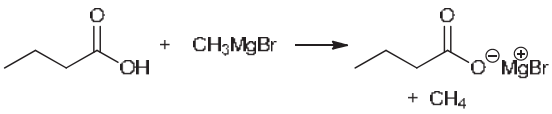
12.68. The starting material has two OH groups, one of which is primary, and the other is secondary. The secondary alcohol must be oxidized to a ketone, which can be achieved with a variety of reagents, but the primary alcohol must be oxidized to an aldehyde (and not a carboxylic acid). Only option (c) will achieve the desired transformation.

12.69. Options (a), (b), and (c) will achieve the desired transformation via a Grignard reaction.



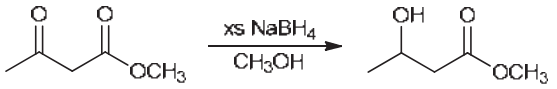


Option (d) is the answer, because option (d) will NOT achieve the desired transformation. A Grignard reagent will simply deprotonate the carboxylic acid, to give a carboxylate ion, thereby destroying the Grignard reagent.

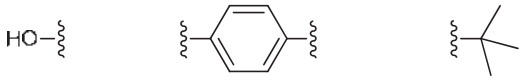


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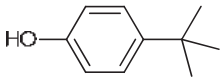
12.70. Sodium borohydride is a reducing agent that will reduce ketones and aldehydes, but not esters. In this case, the ketone group will be reduced to a secondary alcohol, but the ester group will not undergo reduction. Therefore, the correct answer is (b).



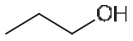
12.71. The singlet with an integration of 9 is characteristic of a *tert*-butyl group. The signals near 7 ppm (with a total integration of 4) indicate a disubstituted aromatic ring. The splitting pattern of these signals indicates that the compound is *para*-disubstituted (because of symmetry). The signal at 5 ppm with an integration of 1 is likely an OH group. Our analysis produces the following three fragments:



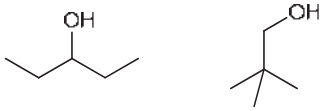
These three fragments can only be assembled in one way:



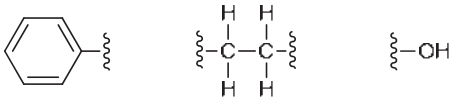
12.72. The ^{13}C NMR spectrum indicates that all three carbon atoms are in different environments. One of these signals appears between 50 and 100 ppm, indicating that one carbon atom is connected to an oxygen atom (the molecular formula indicates the presence of an oxygen atom). Now we turn to the ^{1}H NMR spectrum. The signal at 1 ppm has an integration of 3, indicating a CH_3 group. Since this signal is a triplet, the CH_3 group must be adjacent to a CH_2 group. The signal at 3.6 ppm indicates a CH_2 group (integration = 2) that is neighboring an oxygen atom (thus it is shifted downfield, as expected for protons that are α to an OH group). The singlet at 2.4 ppm is likely an OH group, and the signal at 1.6 ppm results from the CH_2 group that is being split by two sets of neighbors. Using all of this information, we can arrive at the following structure.



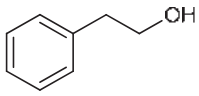
12.73. In the IR spectrum, the broad signal between 3200 and 3600 cm^{-1} indicates an OH group. The NMR spectrum indicates that there are only three different kinds of carbon atoms, yet the molecular formula indicates that the compound has five carbon atoms. Therefore, we must draw structures that possess enough symmetry such that there are only three unique kinds of carbon atoms. The following two structures are consistent with this analysis.



12.74. There is a multiplet just above 7 ppm, indicating an aromatic ring. Since the integration of this signal is 5, we expect the aromatic ring to be monosubstituted. The two triplets (at 2.8 ppm and 3.8 ppm) indicate two CH_2 groups that are neighboring each other, and the singlet at 2 ppm (with an integration of 1) is likely an OH group. Our analysis produces the following three fragments:



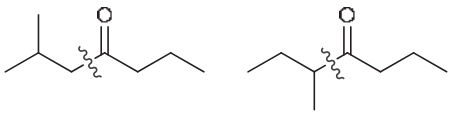
These three fragments can only be assembled in one way:



Notice that the signals for the CH_2 groups (the triplets) are shifted downfield. The signal at 3.8 ppm represents the CH_2 group next to the oxygen atom, and the signal at 2.8 ppm represents the CH_2 group next to the aromatic ring.

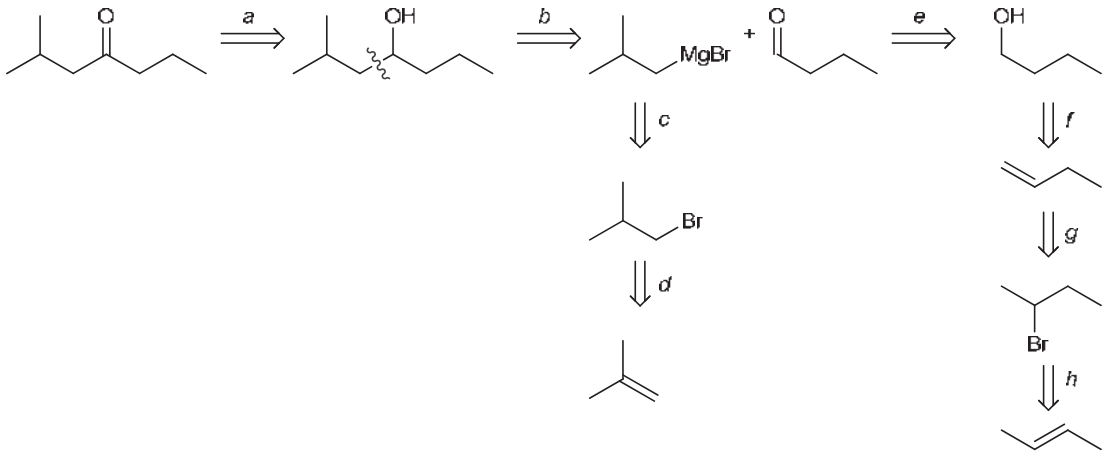
12.75. The following two syntheses are suggested synthetic pathways. There are certainly other acceptable approaches that accomplish the same goal.

Each of the target compounds has eight carbon atoms, suggesting the following disconnections, which break each carbon skeleton into two four-carbon fragments.



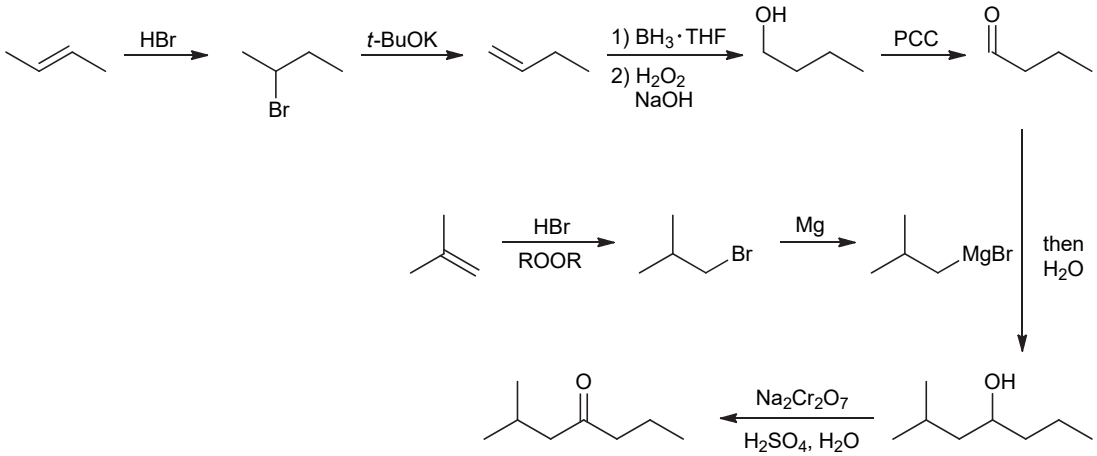
The following figure outlines a retrosynthetic analysis for our first target molecule. An explanation of each of the steps (*a*-*h*) follows.

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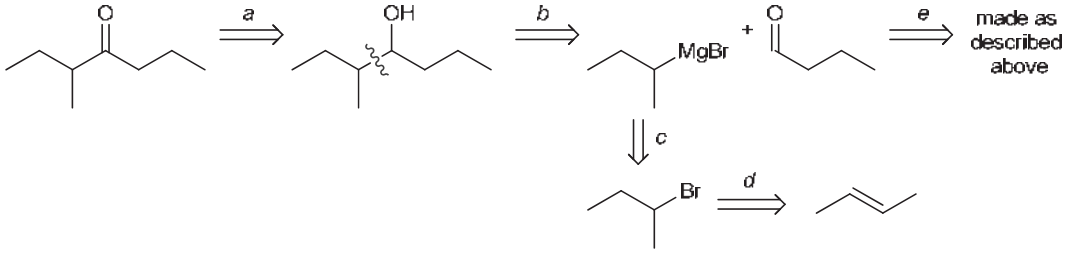


a. The target ketone is made by oxidation of the corresponding alcohol, 2-methyl-4-heptanol.
b. The alcohol is produced via a Grignard reaction between the Grignard reagent and aldehyde shown.
c. The Grignard reagent is made from the corresponding alkyl halide, 1-bromo-2-methylpropane.
d. 1-Bromo-2-methylpropane is produced via an *anti*-Markovnikov addition of HBr to 2-methylpropene.
e. The aldehyde is made from oxidation of 1-butanol.
f. 1-Butanol is made from 1-butene via hydroboration/oxidation.
g. 1-Butene is made from 2-bromobutane using a sterically hindered base to produce the less substituted alkene.
h. 2-Bromobutane is made from HBr addition to *trans*-2-butene. (Note: *Cis*-2-butene also produces the same product.)

Now let's draw the forward scheme. Addition of HBr to *trans*-2-butene produces 2-bromobutane, which is subsequently treated with *tert*-butoxide to give 1-butene. *Anti*-Markovnikov addition of water (via hydroboration/oxidation) followed by PCC (or DMP or Swern oxidation) gives the aldehyde. Reaction with the Grignard reagent (produced by *anti*-Markovnikov addition of HBr to 2-methylpropene, then magnesium, as shown) gives 2-methyl-4-heptanol after water workup. Oxidation produces the target ketone.



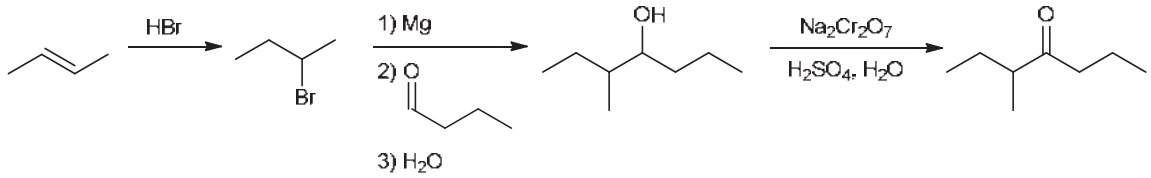
The following figure outlines a retrosynthetic analysis for our second target molecule. An explanation of each of the steps (*a*-*e*) follows.



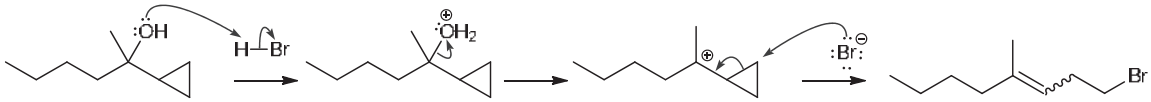
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a. The target ketone is made by oxidation of the corresponding alcohol, 3-methyl-4-heptanol.
b. The alcohol is produced via a Grignard reaction between the Grignard reagent and aldehyde shown.
c. The Grignard reagent is made from the corresponding alkyl halide, 2-bromobutane.
d. 2-bromobutane is produced via addition of HBr to *trans*-2-butene. (Note: *Cis*-2-butene also produces the same product.)
e. The aldehyde is made as described in the synthesis of the first target ketone.

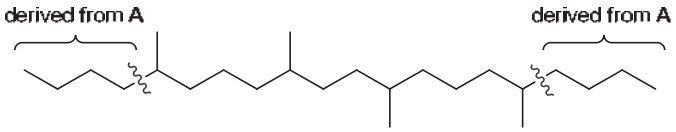
Now let's draw the forward scheme. Addition of HBr to *trans*-2-butene produces 2-bromobutane. 2-Bromobutane is converted to a Grignard reagent which is subsequently treated with the aldehyde (made as described above), followed by water workup, to produce 3-methyl-4-heptanol. Oxidation gives the target ketone.



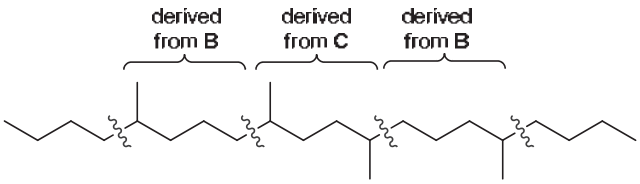
12.76.
(a) The alcohol is protonated by HBr, converting it into a good leaving group. Water leaves, producing a tertiary carbocation intermediate. Bromide attacks the indicated carbon atom of the cyclopropyl group, thus opening up the ring to produce the product. The last step of the mechanism is aided by the relief of ring strain present in the three-membered ring.



(b) The following synthesis is one suggested synthetic pathway. There are certainly other acceptable approaches that accomplish the same goal.
Let's start by looking at the product and attempting to map out the destinations of the carbon atoms in each of our given starting materials. The product is symmetric, which suggests that the groups from the left and right halves will have analogous origins. Compounds **A**, **B**, and **C** have four, five, and six carbon atoms, respectively. Both of the four-carbon linear termini of the product likely originate from the two equivalents of 1-bromobutane, which also has a linear four-carbon chain.

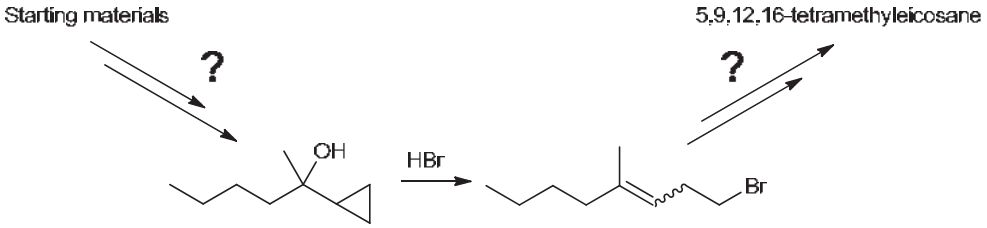


This leaves 16 carbon atoms in the central portion of the target structure (between the two wavy lines in the figure above). A careful analysis of this fragment (and keeping in mind the symmetry of the product) suggests that the six central carbon atoms are from **C**, while the two five-carbon units flanking this portion are derived from two equivalents of **B**.

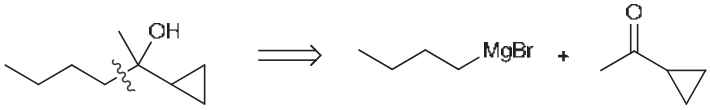


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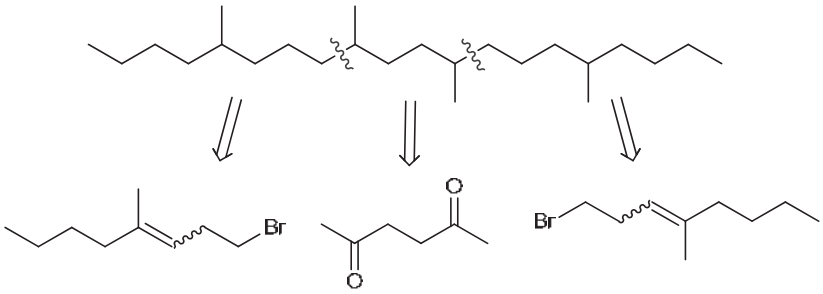
Now let's consider the key step (described in the problem statement) and how it will fit into our synthesis. We need to fill in the gap between the starting materials and the key step, as well as the gap between the key step and the final product.



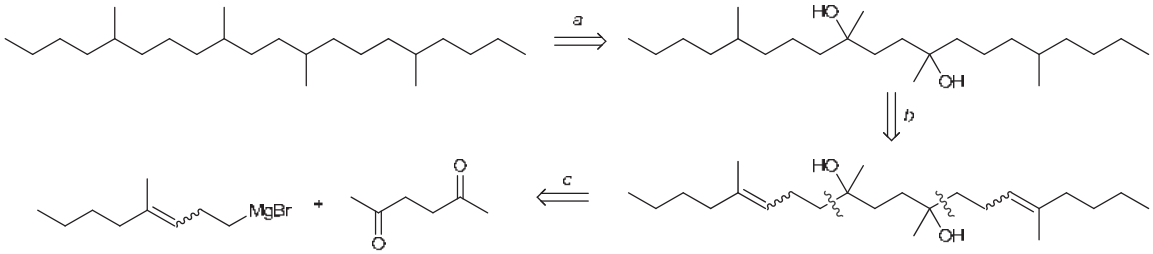
The tertiary alcohol above can be prepared via a Grignard reaction between butyl Grignard (prepared from **A**) and ketone **B**.



Now let's focus on the steps following the key step. The carbon atoms in the product can be mapped on to two equivalents of the alkenyl bromide and one equivalent of the diketone as shown in the figure below.



This suggests the following retrosynthetic approach.

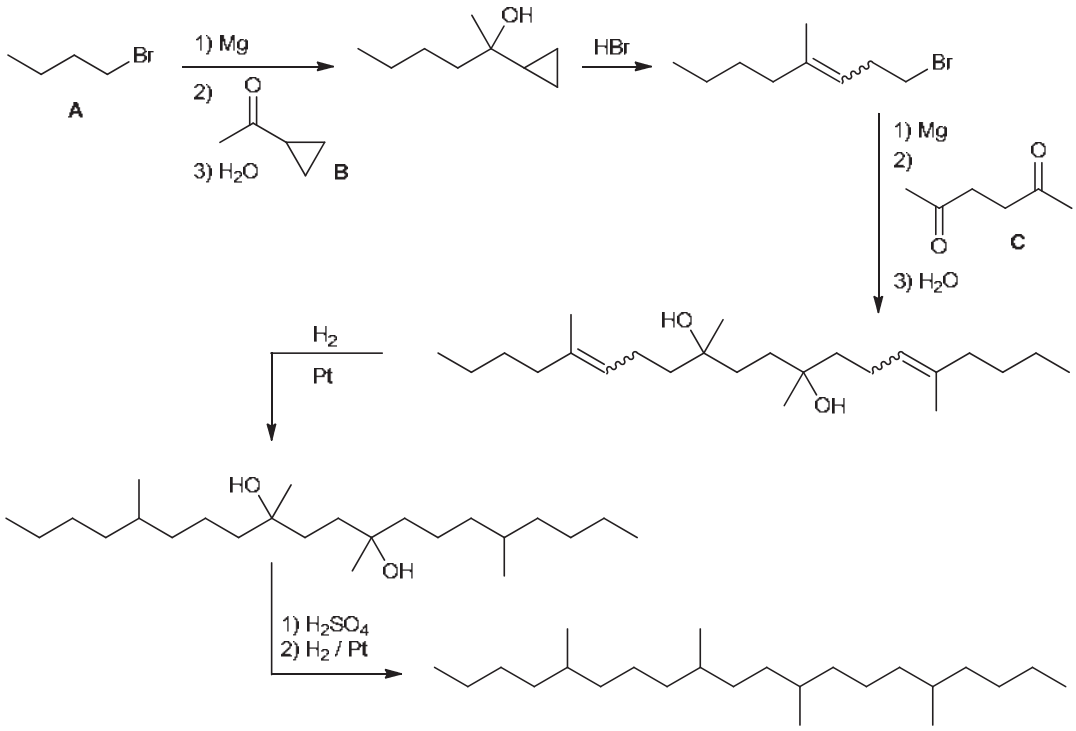


a. The product can be prepared in two steps from the diol: acid-catalyzed elimination followed by hydrogenation of the resulting diene.
b. The two double bonds can be removed via hydrogenation.
c. A double Grignard reaction of two equivalents of the Grignard reagent and one equivalent of the diketone allows for the formation of the indicated bonds.

Now, let's draw out the forward scheme. 1-Bromobutane (**A**) is treated with magnesium to give a Grignard reagent, and subsequently reacted with ketone **B**. Aqueous workup produces the tertiary alcohol. Reaction with HBr drives the ring-

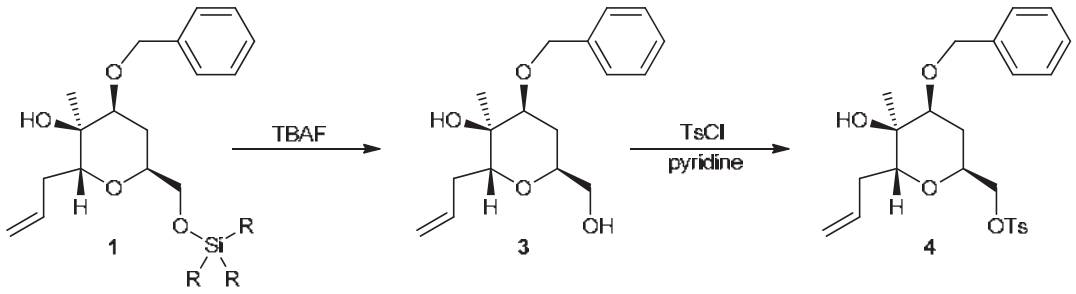
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opening reaction to give the alkenyl bromide. Conversion to the Grignard (Mg), followed by addition of diketone **C** (2:1 ratio) and a water workup, yields the dialkenyl diol, which is converted to the diol via hydrogenation. Acid-catalyzed elimination followed by hydrogenation affords the product, 5,9,12,16-tetramethyleicosane.



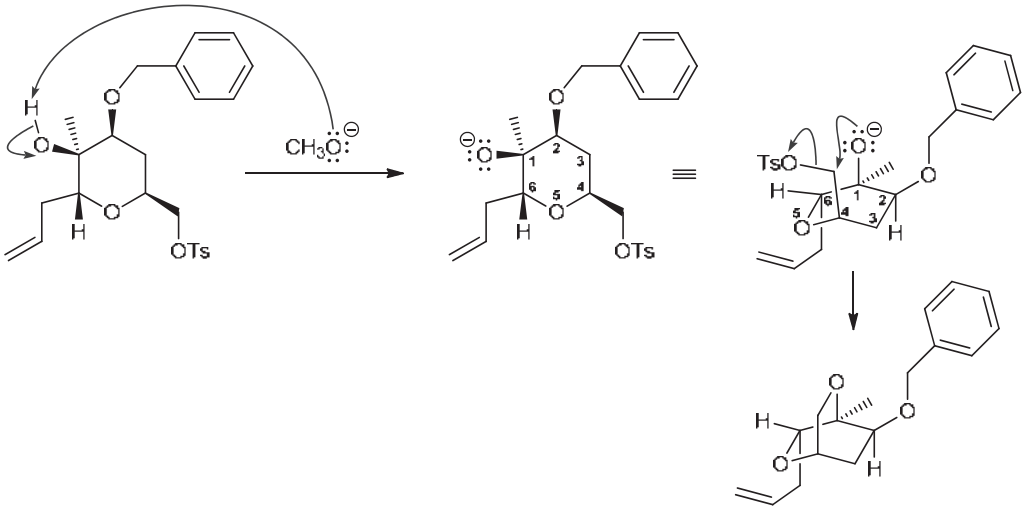
12.77.

(a) TBAF removes the silyl protecting group to give compound **3**, which then undergoes selective tosylation of the primary hydroxyl group (as mentioned in the problem statement) to give compound **4**:



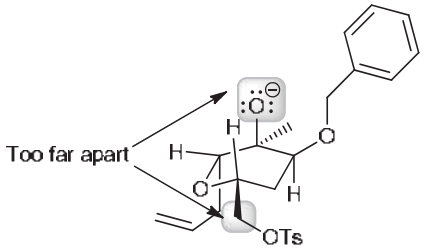
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(b) Methoxide functions as a base and deprotonates the tertiary hydroxyl group. The resulting alkoxide functions as a nucleophile and attacks the primary tosylate in an intramolecular, S_N2-type process. Locants have been assigned to help redraw the alkoxide ion.



Note that these locants do not necessarily adhere to IUPAC guidelines for assigning locants, but rather, they are simply tools that are used to verify that the alkoxide ion has been drawn correctly (it enables you to compare the configurations in each drawing, and prove to yourself that these drawings are the same). The use of locants can be especially helpful in situations like this.

(c) The *syn* relationship places the negatively charged oxygen atom in close proximity with the carbon atom bearing the tosylate group, thereby enabling an intramolecular attack. The *syn* relationship is necessary in order for the reaction to occur. The following structure lacks the *syn* relationship, so the reactive centers are too far apart for an intramolecular reaction to occur:



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Chapter 13
Ethers and Epoxides; Thiols and Sulfides

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 13. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

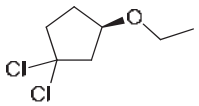
- Ethers are often used as _____ for organic reactions.
- Cyclic polyethers, or _____ **ethers**, are capable of solvating metal ions in organic (nonpolar) solvents.
- Ethers can be readily prepared from the reaction between an alkoxide ion and an _____, a process called a **Williamson ether synthesis**. This process works best for _____ or _____ alkyl halides. _____ alkyl halides are significantly less efficient, and _____ alkyl halides cannot be used.
- When treated with a strong acid, an ether will undergo **acidic** _____ in which it is converted into two alkyl halides.
- When a phenyl ether is cleaved under acidic conditions, the products are _____ and an alkyl halide.
- Ethers undergo autooxidation in the presence of atmospheric oxygen to form _____.
- Substituted oxiranes are also called _____.
- _____ can be converted into epoxides by treatment with peroxy acids or via halohydrin formation and subsequent epoxidation.
- _____ catalysts can be used to achieve the enantioselective epoxidation of allylic alcohols.
- Epoxides will undergo **ring-opening reactions** in: 1) conditions involving a strong nucleophile, or under 2) _____-catalyzed conditions. When a strong nucleophile is used, the nucleophile attacks at the _____-substituted position.
- Sulfur analogs of alcohols contain an SH group rather than an OH group, and are called _____.
- Thiols can be prepared via an S_N2 reaction between sodium hydrosulfide (NaSH) and a suitable _____.
- The sulfur analogs of ethers (thioethers) are called _____.
- Sulfides can be prepared from thiols in a process that is essentially the sulfur analog of the Williamson ether synthesis, involving a _____ ion, rather than an alkoxide.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 13. The answers appear in the section entitled *SkillBuilder Review*.

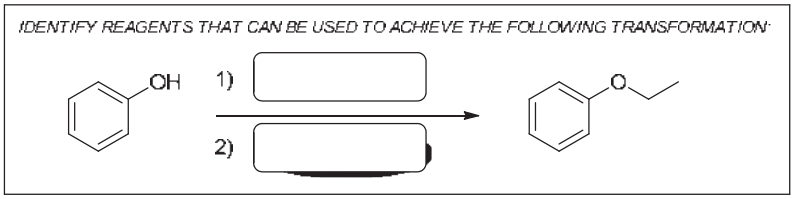
13.1 Naming an Ether

PROVIDE A SYSTEMATIC NAME FOR THE FOLLOWING COMPOUND

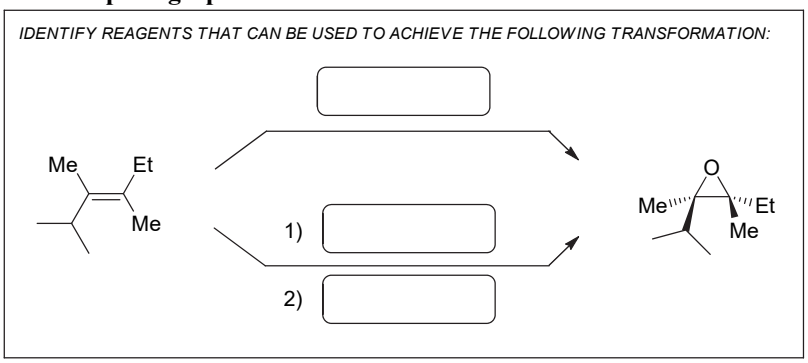


1) IDENTIFY THE PARENT
2) IDENTIFY AND NAME SUBSTITUENTS
3) ASSIGN LOCANTS TO EACH SUBSTITUENT
4) ALPHABETIZE
5) ASSIGN CONFIGURATION

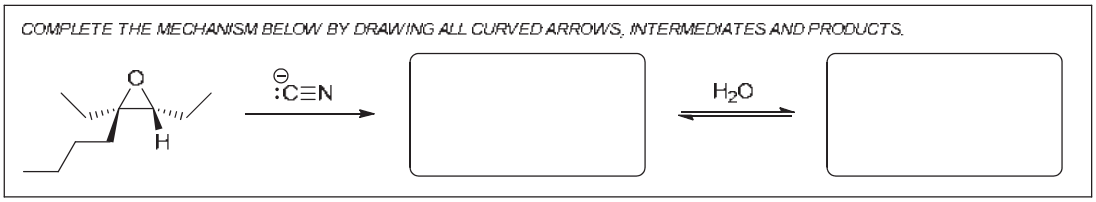
13.2 Preparing an Ether via a Williamson Ether Synthesis



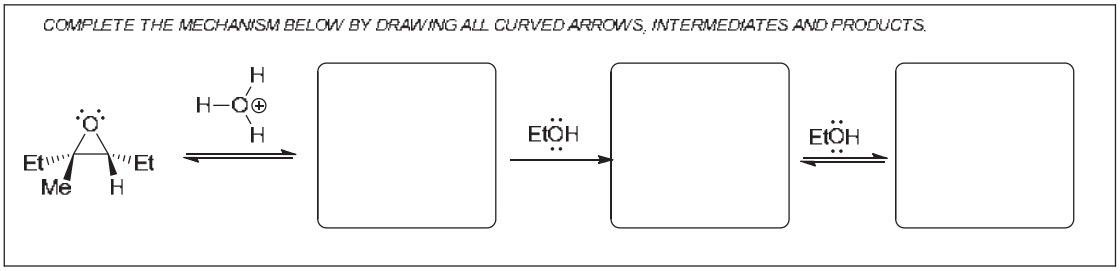
13.3 Preparing Epoxides



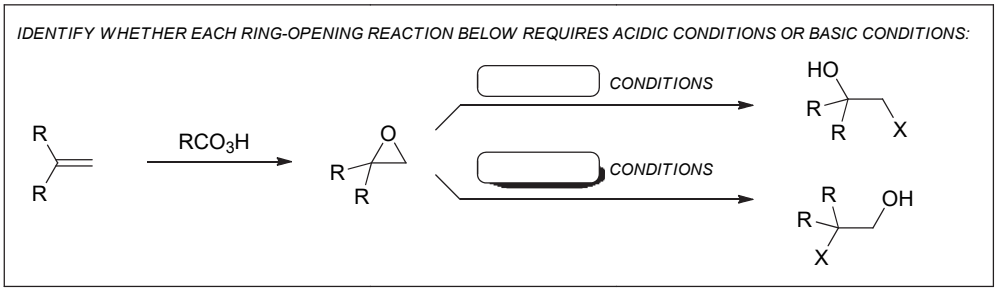
13.4 Drawing the Mechanism and Predicting the Product of the Reaction between a Strong Nucleophile and an Epoxide



13.5 Drawing the Mechanism and Predicting the Product of Acid-Catalyzed Ring-Opening

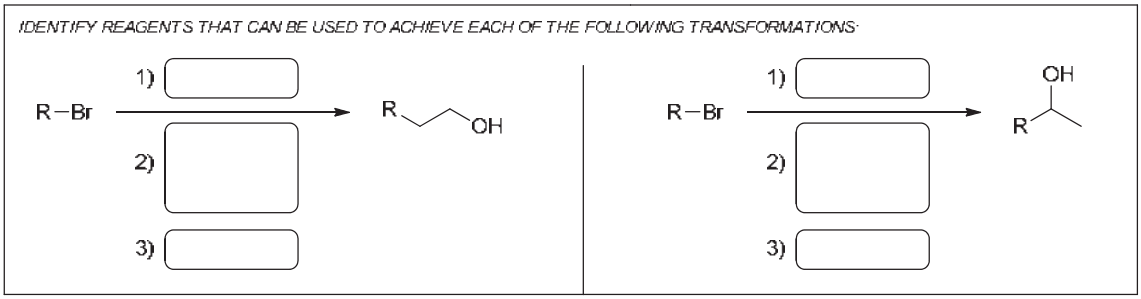


13.6 Installing Two Adjacent Functional Groups



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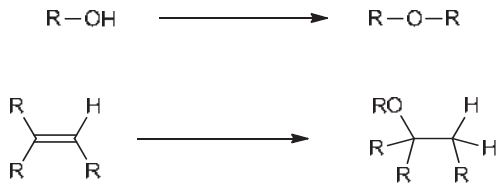
13.7 Choosing the Appropriate Grignard Reaction



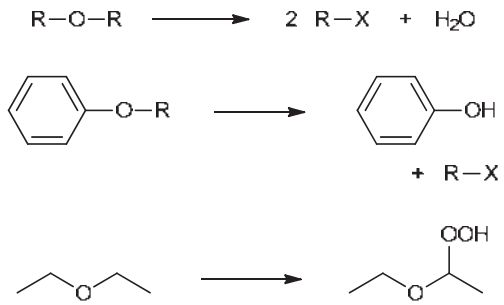
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 13. The answers appear in the section entitled *Review of Reactions*.

Preparation of Ethers



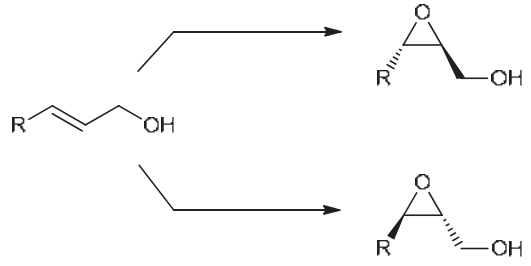
Reactions of Ethers



Preparation of Epoxides

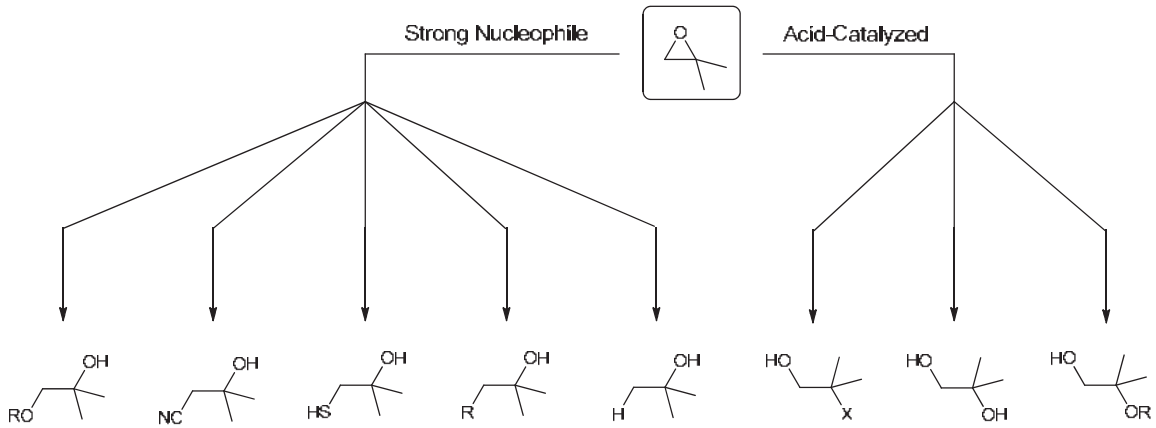


Enantioselective Epoxidation



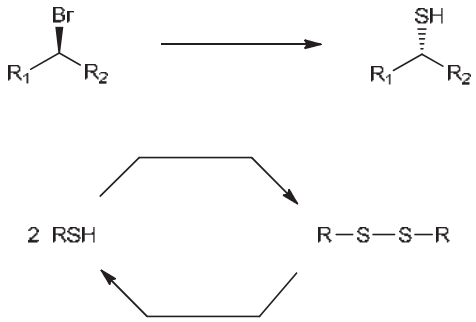
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Ring-Opening Reactions of Epoxides

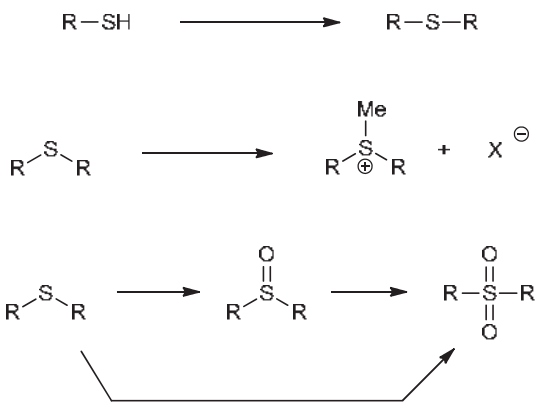


Thiols and Sulfides

Thiols



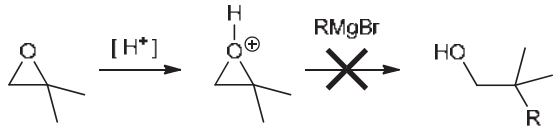
Sulfides



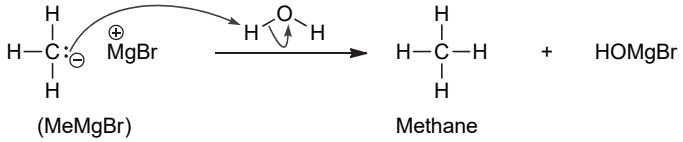
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Common Mistakes to Avoid

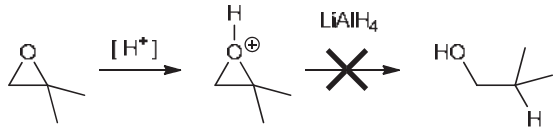
We have seen that epoxides will react with a wide variety of nucleophiles (causing ring-opening reactions), either under acidic conditions or under basic conditions. If the attacking nucleophile is itself a strong base, such as a Grignard reagent, then acidic conditions cannot be used. That is, the following transformation is not possible to achieve, so avoid trying to do something like this:



This doesn't work because Grignard reagents are not only strong nucleophiles, but they are also strong bases. And strong bases are incompatible with acidic conditions. If a Grignard reagent is subjected to a source of acid (even a relatively weak acid, such as H_2O), the Grignard reagent is irreversibly protonated to give an alkane, for example:



In summary, never use a Grignard reagent in the presence of an acid. The same rule applies to the use of $LiAlH_4$ (lithium aluminum hydride), which is both a strong nucleophile and a strong base. Therefore, much like a Grignard reagent, $LiAlH_4$ also cannot be used to open an epoxide under acidic conditions:



Once again, this doesn't work because $LiAlH_4$ is incompatible with acidic conditions. Avoid making this mistake.

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Useful reagents

The following is a list of commonly encountered reagents for reactions involving ethers, epoxides, thiols, and sulfides:

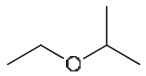
Reagents	Description
RX	An alkyl halide. Used for the alkylation of alcohols or thiols. First, the alcohol or thiol is deprotonated with a base, such as NaH or NaOH, and the resulting anion is then treated with the alkyl halide, thereby installing an alkyl group.
1) $Hg(OAc)_2$, ROH 2) $NaBH_4$	These reagents will achieve alkoxymercuration-demercuration of an alkene. This process adds H and OR in a Markovnikov fashion across the alkene.
HX	Will convert dialkyl ethers into alkyl halides via cleavage of the C–O bonds. Will also react with an epoxide, thereby opening the ring, and installing a halogen at the more substituted position.
MCPBA	*meta*-Chloro-peroxybenzoic acid. An oxidizing agent that will convert an alkene into an epoxide.
RCO_3H	A peroxy acid. An oxidizing agent that will convert an alkene into an epoxide. MCPBA is an example of a peroxy acid.
1) Br_2, H_2O 2) NaOH	Alternative reagents for converting an alkene into an epoxide.
$(CH_3)_3COOH$, $Ti[OCH(CH_3)_2]_4$. (+)-DET or (–)-DET	Reagents for enantioselective (Sharpless) epoxidation
NaOR (or RONa)	An alkoxide ion is both a strong nucleophile and a strong base. It can be used to open an epoxide under basic conditions (the alkoxide ion attacks the less substituted position).
NaCN	A good nucleophile that will react with an epoxide in a ring-opening reaction.
NaSH	A very strong nucleophile that will react with an epoxide in a ring-opening reaction. NaSH can also be used to prepare thiols from alkyl halides.
RMgBr	A Grignard reagent. A strong base and a strong nucleophile. Will react with an epoxide in a ring-opening reaction, to attack the less substituted side (it is not possible to use acidic conditions and have the Grignard reagent attack the more substituted side – see the previous section on common mistakes to avoid).
$LiAlH_4$	Lithium aluminum hydride is a source of nucleophilic hydride ions. It will react with an epoxide in a ring-opening reaction, to attack the less substituted side (it is not possible to use acidic conditions and have a hydride ion attack the more substituted side – see the previous section on common mistakes to avoid).
$[H^+]$, H_2O	Aqueous acidic conditions. Under these conditions, an epoxide is opened to give a diol.
$[H^+]$, ROH	Under these conditions, an epoxide is opened, with a molecule of the alcohol attacking a protonated epoxide at the more substituted position.
$NaOH/H_2O$, Br_2	Reagents for converting thiols into disulfides.
HCl, Zn	Reagents for converting thiols into disulfides.
H_2O_2	Strong oxidizing agent, used to oxidize sulfides to sulfoxides, and then further to sulfones.
$NaIO_4$	Oxidizing agent, used to oxidize sulfides to sulfoxides.

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Solutions

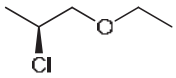
13.1.

(a) The oxygen atom has two groups attached to it. One group has two carbon atoms and the other group has three carbon atoms. The parent is named after the larger group, so the parent is propane. The smaller group (together with the oxygen atom) is treated as an ethoxy substituent, and a locant is included to identify the location (C2) of the substituent on the parent chain.



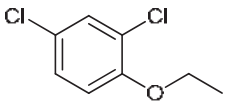
2-Ethoxypropane

(b) The oxygen atom has two groups attached to it. One group has three carbon atoms and the other group has two carbon atoms. The parent is named after the larger group, so the parent is propane. The smaller group (together with the oxygen atom) is treated as an ethoxy substituent, and a locant is included to identify the location (C1) of the substituent on the parent chain. The parent chain also has a chloro substituent, located at C2 of the parent. That position is a chiral center, so a stereodescriptor is required to identify the configuration (*S*). When assembling the name, the substituents are arranged alphabetically (chloro precedes ethoxy).



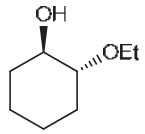
(*S*)-2-Chloro-1-ethoxypropane

(c) The oxygen atom has two groups attached to it. The parent is named after the larger group, so the parent is benzene. The smaller group (together with the oxygen atom) is treated as an ethoxy substituent, and a locant (C1) is included to identify the location of the substituent on the parent chain. The parent chain also has two chloro substituents, located at C2 and C4 of the parent. The parent is numbered to give the substituents the lowest possible numbers (1,2,4 instead of 1,3,4). When assembling the name, the substituents are arranged alphabetically (chloro precedes ethoxy).



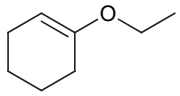
2,4-Dichloro-1-ethoxybenzene

(d) The parent is cyclohexanol, and the ethoxy group is listed as a substituent. A locant (C2) is included to indicate the location of the ethoxy group on the cyclohexanol parent, and stereodescriptors are included to indicate the configuration of each chiral center:



(*1R,2R*)-2-Ethoxycyclohexanol

(e) The parent is cyclohexene, and the ethoxy group is listed as a substituent. A locant (C1) is included to indicate the location of the ethoxy group on the cyclohexene parent:



1-Ethoxycyclohexene

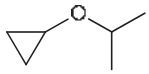
13.2.

(a) The parent (cyclobutane) is a four-membered ring, and there is an ethoxy group connected to the ring (which is defined as position C2 of the ring). This position is a chiral center, and it has the *R* configuration. There are two methyl groups, both located at C1.



(*R*)-2-Ethoxy-1,1-dimethylcyclobutane

(b) This name has the format of a common name. It is an ether in which the oxygen atom is connected to a cyclopropyl group (a three-membered ring) and an isopropyl group (a three-membered chain, connected at the middle carbon atom).

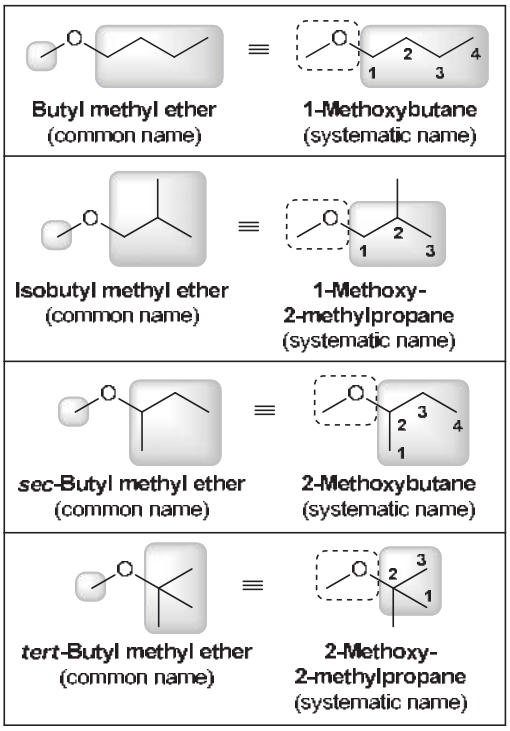


Cyclopropyl isopropyl ether

13.3. Recall that the general structure of an ether is R–O–R′ where R and R′represent alkyl, aryl, or vinyl groups. For an ether with the molecular formula $C_5H_{12}O$, both groups must be alkyl groups. Further, if R has one carbon atom, then R′must have four carbon atoms; and if R has two carbon atoms, then R′must have three carbon atoms. These are the only options. Let's first consider the possibilities when R has one carbon atom and R′has four carbon atoms. There is only one way to have a one-carbon substituent (CH_3), but there are

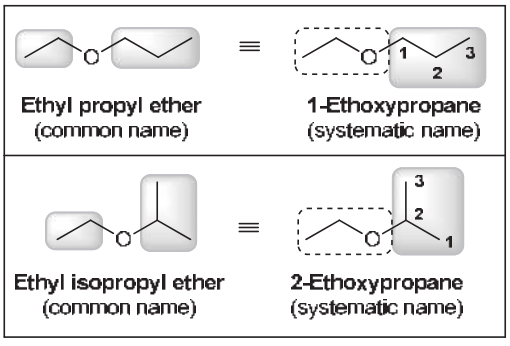
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four ways to assemble a four-carbon substituent. These options result in four possible ethers, shown below, along with their common and systematic names.



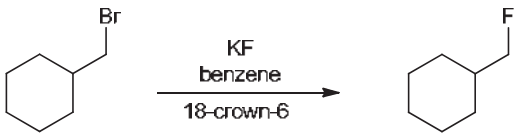
The common names of the four butyl groups were discussed in Section 4.2. The systematic name of each compound uses the longest continuous carbon chain as the parent and treats the methoxy group as a substituent in all four cases.

Now let's consider the possibilities when R has two carbon atoms and R′has three carbon atoms. There is only one way to have a two-carbon substituent, but there are two ways to assemble a three-carbon substituent (propyl or isopropyl). These options result in two possible ethers, shown below, along with their common and systematic names. The common names of the two propyl groups were discussed in Section 4.2. Each systematic name uses the longest continuous carbon chain as the parent (propane) and treats the ethoxy group as a substituent.

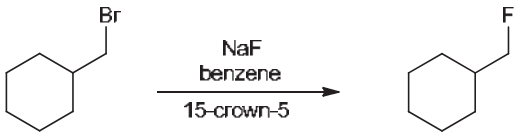


13.4.

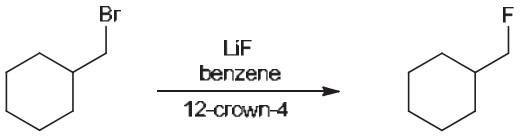
(a) The cation is potassium, so we must use 18-crown-6, which solvates potassium ions.



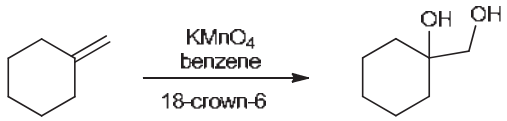
(b) The cation is sodium, so we must use 15-crown-5, which solvates sodium ions.



(c) The cation is lithium, so we must use 12-crown-4, which solvates lithium ions.

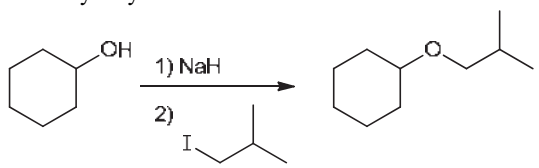


(d) The cation is potassium, so we must use 18-crown-6, which solvates potassium ions.

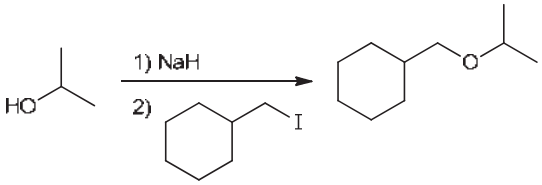


13.5.

(a) A Williamson ether synthesis will be more efficient with a less sterically hindered substrate, since the process involves an S_N2 reaction. Therefore, in this case, it is better to start with a secondary alcohol and a primary alkyl halide, rather than a primary alcohol and a secondary alkyl halide:

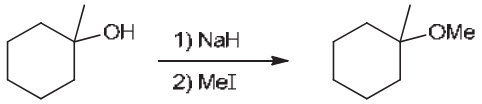


(b) In this case, it is better to start with a secondary alcohol and a primary alkyl halide, rather than a primary alcohol and a secondary alkyl halide:

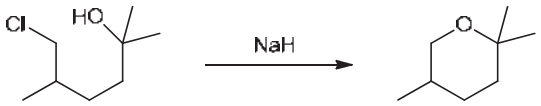


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(c) In this case, it is better to start with a tertiary alcohol and a methyl halide, rather than methanol and a tertiary alkyl halide:

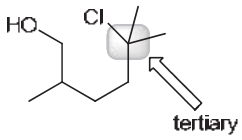


(d) In order to perform an intramolecular Williamson ether synthesis, we must choose a starting compound that contains both an OH group and a halogen, as shown here:

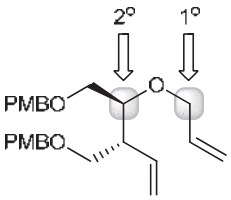


The OH group is deprotonated upon treatment with NaH (a strong base). The resulting alkoxide ion can then function as a nucleophile in an intramolecular, S_N2-type reaction, expelling chloride as a leaving group, and giving a six-membered ring.

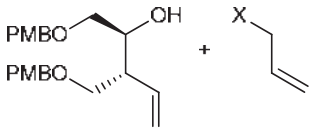
The alternative starting compound, shown below, cannot be used, because the leaving group is attached to a tertiary position, so an S_N2-type process cannot occur at that location.



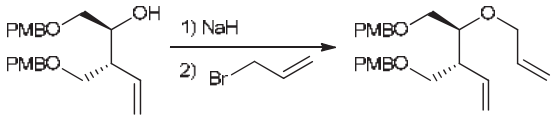
13.6. We begin by classifying the carbon atoms on either side of the oxygen atom. One is secondary and the other is primary:



A Williamson ether synthesis will be more efficient with a less sterically hindered substrate. Therefore, a primary halide and a secondary alcohol should be used, rather than a secondary halide and a primary alcohol:

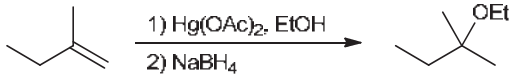


The following reagents can be used to make the ether group of compound **1**:

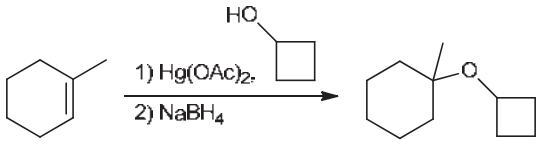


13.7.

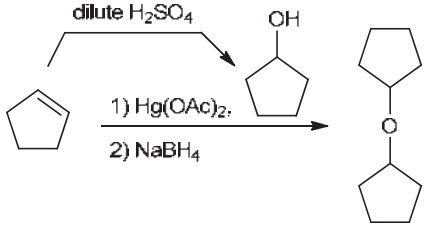
(a) The desired transformation involves the Markovnikov addition of H and OEt across the π bond. This can be accomplished via alkoxymercuration-demercuration, where EtOH is used during the oxymercuration process.



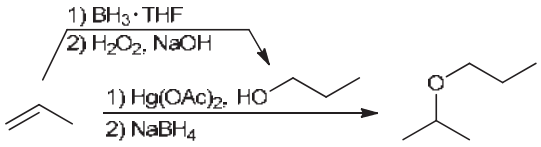
(b) The desired transformation involves the Markovnikov addition of H and OR across the π bond. This can be accomplished via alkoxymercuration-demercuration, where ROH (cyclobutanol) is used in the first step of the process.



13.8. Cyclopentene can be converted to cyclopentanol via acid-catalyzed hydration (upon treatment with dilute aqueous H_2SO_4). Cyclopentanol can then be used for the alkoxymercuration of cyclopentene, giving the desired product.



13.9. Propene can be converted to 1-propanol via an *anti*-Markovnikov addition of H and OH across the π bond, which can be achieved with hydroboration-oxidation. This alcohol can then be used for the alkoxymercuration of propene, giving the desired product.

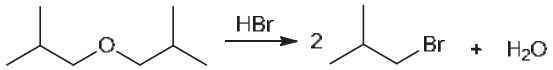


13.10.

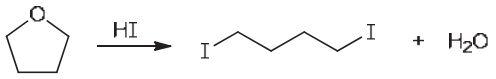
(a) The oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. As such, treatment with HBr is expected to cleave each of the C–O bonds and replace them with C–Br bonds. Because the starting ether is symmetrical, the resulting two alkyl bromides

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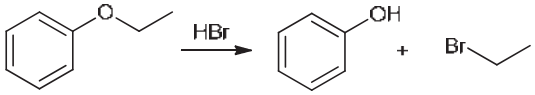
are identical. Therefore, two equivalents of this alkyl bromide are expected.



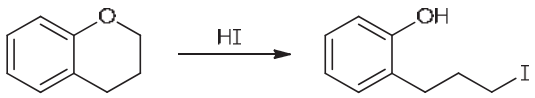
(b) The oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. As such, treatment with HI is expected to cleave each of the C–O bonds and replace them with C–I bonds, giving the following diiodide.



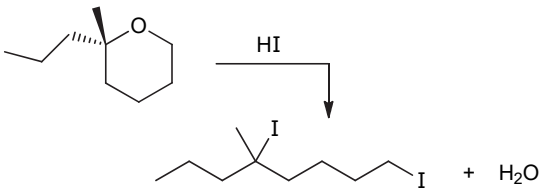
(c) The oxygen atom is connected to two carbon atoms. One of these carbon atoms (left) is sp^2 hybridized, while the other (right) is sp^3 hybridized. As such, treatment with HBr is expected to cleave only the C–O bond involving the sp^3 hybridized carbon atom. The other C–O bond is not cleaved. This gives phenol and ethyl bromide as products.



(d) The oxygen atom is connected to two carbon atoms. One of these carbon atoms (left) is sp^2 hybridized, while the other (right) is sp^3 hybridized. As such, treatment with HI is expected to cleave only the C–O bond involving the sp^3 hybridized carbon atom. The other C–O bond is not cleaved, giving the following product.

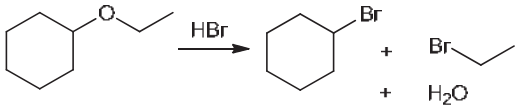


(e) The oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. As such, treatment with HI is expected to cleave each of the C–O bonds and replace them with C–I bonds. One of these carbon atoms is a chiral center. Since this position is tertiary, cleavage will occur via an S_N1 process, so we expect racemization.



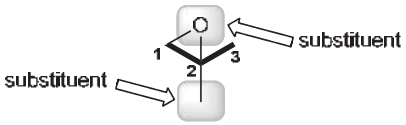
(racemic mixture)

(f) The oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. As such, treatment with HBr is expected to cleave each of the C–O bonds and replace them with C–Br bonds, giving cyclohexyl bromide and ethyl bromide as products.



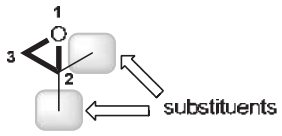
13.11.

(a) There are two methods for naming epoxides. In one method, the parent will be propane, and the oxygen atom is considered to be an epoxy substituent connected to the parent at C1 and C2. In addition, there is a methyl substituent at C2.



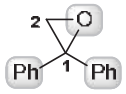
2-Methyl-1,2-epoxypropane

According to the second method for naming epoxides, the parent is considered to be the oxirane ring, which has two methyl groups attached to it, both located at the 2 position.



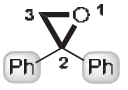
2,2-Dimethyloxirane

(b) There are two methods for naming epoxides. In one method, the parent will be ethane, and the oxygen atom is considered to be an epoxy substituent connected to the parent at C1 and C2. In addition, there are two phenyl substituents at C1.



1,1-Diphenyl-1,2-epoxyethane

According to the second method for naming epoxides, the parent is considered to be the oxirane ring, which has two phenyl groups attached to it, both located at the 2 position.

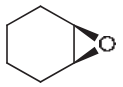


2,2-Diphenyloxirane

(c) There are two methods for naming epoxides, although one of these methods will be less helpful because the two substituents (connected to the oxirane ring) are actually closed in a ring. This makes it difficult to name the compound as an oxirane. According to the first method for naming ethers, the parent is

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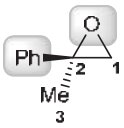
cyclohexane, and the oxygen atom is considered to be an epoxy substituent connected to the parent at C1 and C2.



1,2-Epoxycyclohexane

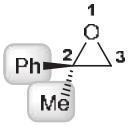
13.12.

(a) There are two methods for naming epoxides. In one method, the parent will be propane, and the oxygen atom is considered to be an epoxy substituent connected to the parent at C1 and C2. In addition, there is a phenyl substituent at C2, and the configuration of the chiral center is indicated.



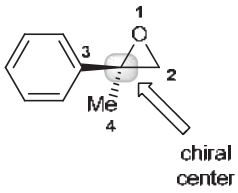
(*R*)-2-Phenyl-1,2-epoxypropane

According to the second method for naming epoxides, the parent is considered to be the oxirane ring. The methyl group and the phenyl group are both considered to be substituents, and their locations are identified with locants. Finally, the configuration of the chiral center is indicated (at the beginning of the name).



(*R*)-2-Methyl-2-phenyloxirane

In this case, the chiral center has the *R* configuration, as a result of the following prioritization scheme.

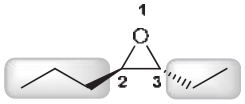


(b) There are two methods for naming epoxides. In one method, the parent will be heptane, and the oxygen atom is considered to be an epoxy substituent connected to the parent at C3 and C4. The configuration of each chiral center is indicated.



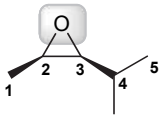
(3*R*,4*R*)-3,4-Epoxyheptane

According to the second method for naming epoxides, the parent is considered to be the oxirane ring, which is connected to two substituents (a propyl group and an ethyl group). Their locations are identified with locants, and the configuration of each chiral center is indicated (at the beginning of the name).



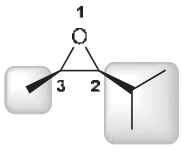
(2*R*,3*R*)-3-Ethyl-2-propyloxirane

(c) There are two methods for naming epoxides. In one method, the parent will be pentane, and the oxygen atom is considered to be an epoxy substituent connected to the parent at C2 and C3. There is also a methyl substituent located at C4. The configuration of each chiral center is indicated.



(2*R*,3*S*)-4-Methyl-2,3-epoxypentane

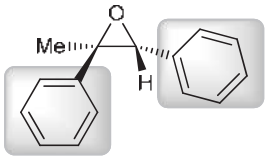
According to the second method for naming epoxides, the parent is considered to be the oxirane ring, which is connected to two substituents (a methyl group and an isopropyl group). Their locations are identified with locants, and the configuration of each chiral center is indicated (at the beginning of the name).



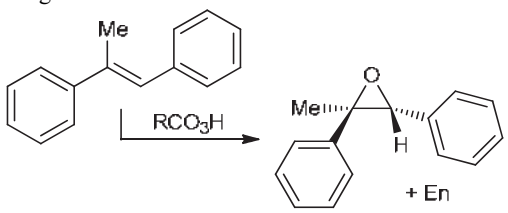
(2*S*,3*R*)-2-Isopropyl-3-methyloxirane

13.13.

(a) We begin by identifying the four groups attached to the epoxide ring. On the left, there is a methyl group and a phenyl group. On the right, there is a phenyl group and a hydrogen atom. Notice that the two phenyl groups are *trans* to each other:



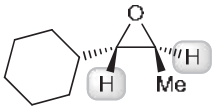
These two groups must be *trans* to each other in the starting alkene.



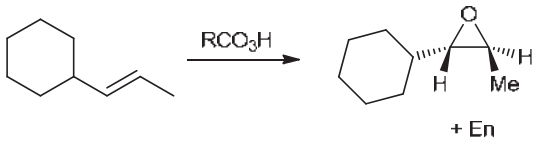
(b) We begin by identifying the four groups attached to the epoxide ring. On the left, there is a cyclohexyl group

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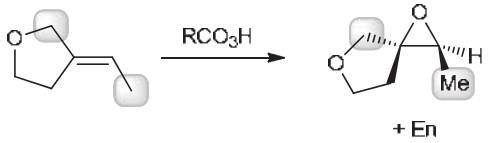
and a hydrogen atom. On the right, there is a methyl group and a hydrogen atom. Notice that the two hydrogen atoms are *trans* to each other.



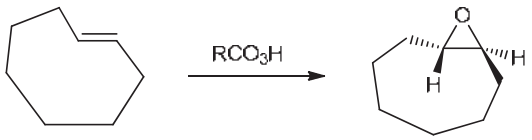
These two hydrogen atoms must be *trans* to each other in the starting alkene.



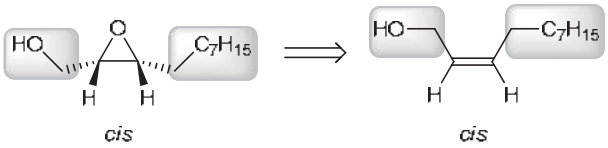
(c) The starting alkene must have the *E* configuration in order to obtain the desired epoxide, as shown.



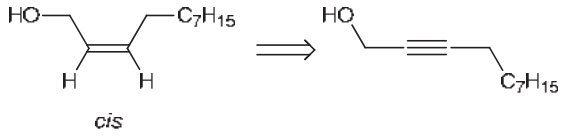
(d) The starting alkene must have the *E* configuration in order to obtain the desired epoxide, as shown.



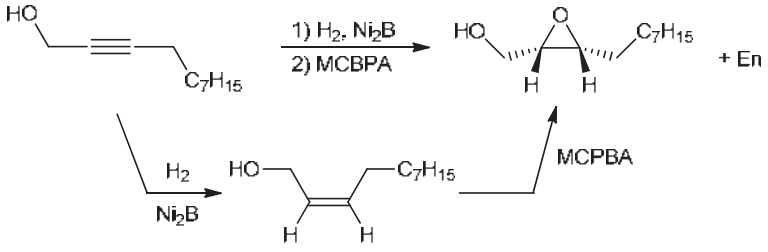
13.14. Compounds **1** and **3** have the same carbon skeleton. Only the identity of a functional group has changed. The epoxide product is *cis*-disubstituted, so we can deduce that the carbon-carbon double bond of alkene **2** must also be *cis*-disubstituted (because the epoxidation process is stereospecific).



The carbon-carbon double bond of the alkene can be made via reduction of the alkyne.



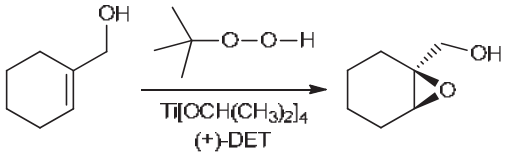
Now let's draw the forward process. Conversion of alkyne **1** to alkene **2** requires the use of H_2 and a poisoned catalyst to generate the *cis*-disubstituted alkene. In this particular case, the investigators used Ni_2B (also called the P-2 catalyst), but Lindlar's catalyst would also be acceptable. Conversion of alkene **2** into epoxide **3** can be accomplished using a peroxy acid, such as MCPBA, and results in a racemic mixture of epoxide **3**, because the epoxidation reaction can occur on either face (top or bottom) of the C=C bond.



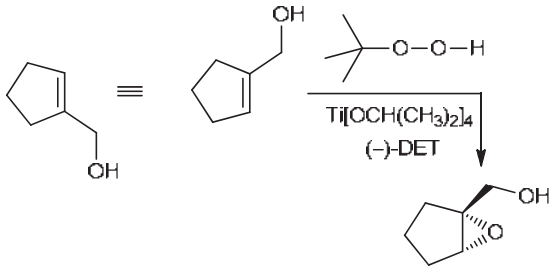
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13.15.

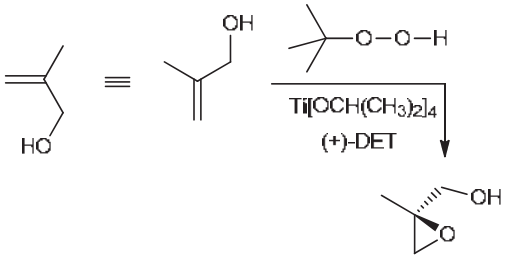
(a) The allylic hydroxyl group appears in the upper right corner, so a Sharpless epoxidation with (+)-DET will generate an epoxide ring above the plane of the π bond, giving the following enantiomer.



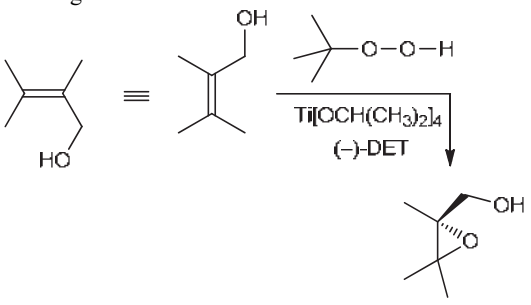
(b) We begin by redrawing the compound so that the allylic hydroxyl group appears in the upper right corner. A Sharpless epoxidation with (–)-DET will generate an epoxide ring below the plane of the π bond, giving the following enantiomer.



(c) We begin by redrawing the compound so that the allylic hydroxyl group appears in the upper right corner. A Sharpless epoxidation with (+)-DET will generate an epoxide ring above the plane of the π bond, giving the following enantiomer.

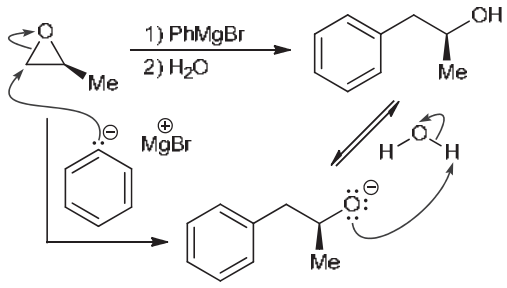


(d) We begin by redrawing the compound so that the allylic hydroxyl group appears in the upper right corner. A Sharpless epoxidation with (–)-DET will generate an epoxide ring below the plane of the π bond, giving the following enantiomer.

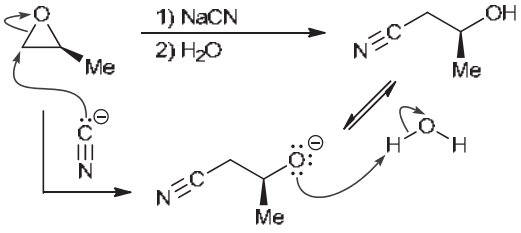


13.16.

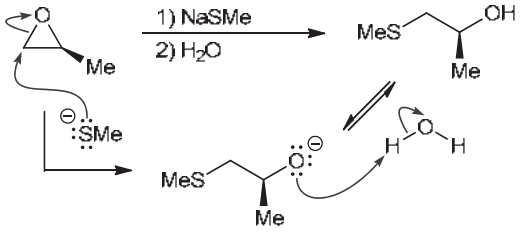
(a) The Grignard reagent (PhMgBr) is a strong nucleophile, and it attacks the epoxide at the less substituted position. The epoxide is opened, resulting in an alkoxide ion. This alkoxide is then protonated upon treatment with water.



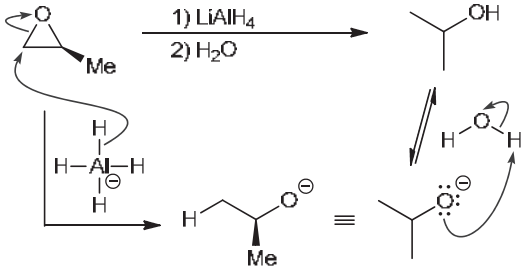
(b) Cyanide (NC^-) is a good nucleophile, and it attacks the epoxide at the less substituted position. This opens the epoxide, resulting in an alkoxide ion, which is then protonated upon treatment with water.



(c) MeS^- is a very strong nucleophile, and it attacks the epoxide at the less substituted position. This opens the epoxide, resulting in an alkoxide ion, which is then protonated upon treatment with water.

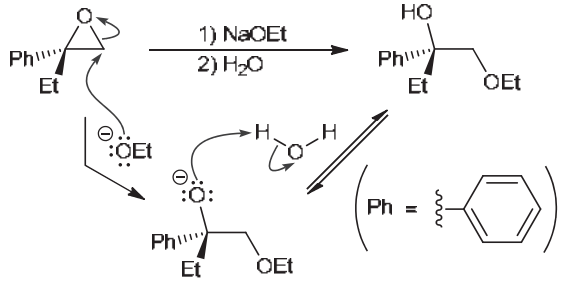


(d) $LiAlH_4$ is a source of nucleophilic hydride (H^-), and it attacks the epoxide at the less substituted position. This opens the epoxide, resulting in an alkoxide ion, which is then protonated upon treatment with water.

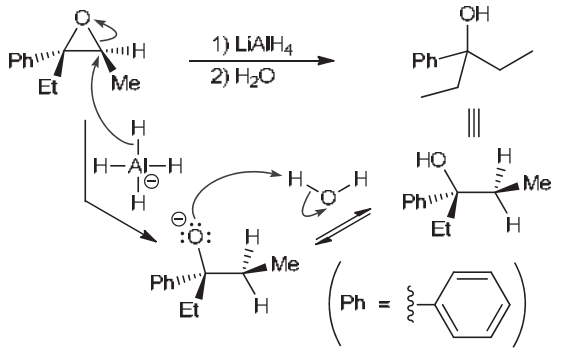


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(e) EtO^- is a strong nucleophile, and it attacks the epoxide at the less substituted position. That position is not a chiral center. The other chiral center does not participate in the reaction and therefore does not experience an inversion of configuration. The resulting alkoxide ion is then protonated upon treatment with water.



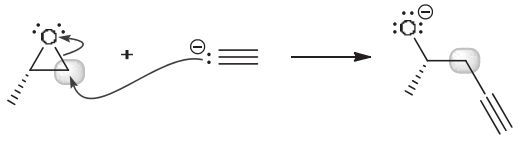
(f) $LiAlH_4$ is a source of nucleophilic hydride (H^-), and it attacks the epoxide at the less substituted position. That position is a chiral center, so we expect an inversion of configuration at that center. The resulting alkoxide ion is then protonated upon treatment with water.



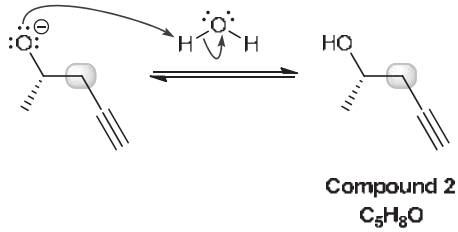
13.17. The reagent, lithium acetylide, has a C–Li bond. Since carbon is more electronegative than lithium, there is a partial negative (δ–) charge on the carbon atom. The difference in electronegativity is significant (carbon = 2.5 and lithium = 1.0), so the bond is sufficiently polar that it can be treated as ionic:



With negative character on the carbon atom, lithium acetylide is a strong nucleophile that will attack the less substituted side of the epoxide (highlighted below). The less substituted side of the epoxide is not a chiral center, so even though the mechanism proceeds with back-side attack, there will not be an observable inversion of configuration at that location. The more substituted side will retain its original configuration since there are no bonds being made or broken at that position.

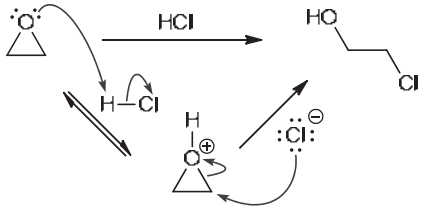


The resulting alkoxide ion is then protonated upon treatment with water, to give the following alcohol (compound **2**):

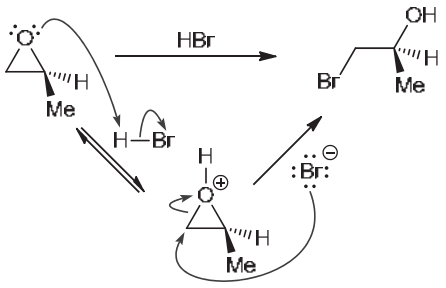


13.18.

(a) Under acidic conditions, the epoxide is protonated, thereby generating a very powerful electrophile (a protonated epoxide). Since the starting epoxide is symmetrical, regiochemistry is not a concern in this case. That is, the nucleophile can attack the epoxide at either position, giving the same product either way. Stereochemistry is also not an issue in this case, because the product does not contain any chiral centers.



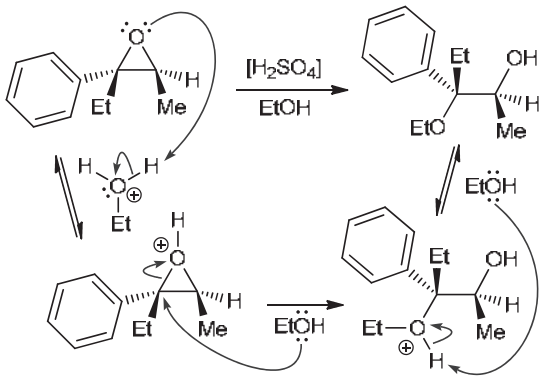
(b) Under acidic conditions, the epoxide is protonated, thereby generating a very powerful electrophile (a protonated epoxide). To determine where the nucleophile (bromide) attacks, we must decide whether steric or electronic effects dominate. In this case, one position (left) is primary and the other position (right) is secondary. Under these conditions, steric effects will dominate, and the attack is expected to occur at the less substituted position. The position being attacked is not a chiral center. There is an existing chiral center, but that center is not attacked, so we do not expect the configuration of that chiral center to change.



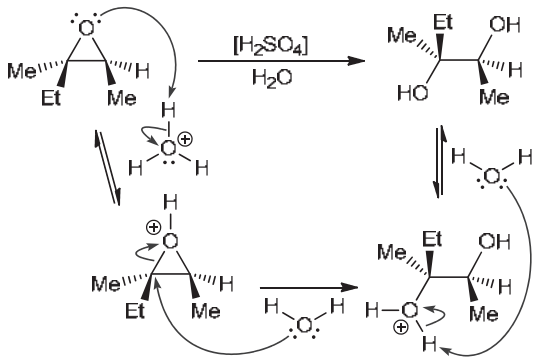
(c) Under acidic conditions, the epoxide is protonated, thereby generating a very powerful electrophile (a protonated epoxide). Ethanol (EtOH) is a weak nucleophile, and we must decide which position will be attacked. In this case, one position (left) is tertiary, and the other position (right) is secondary. When the

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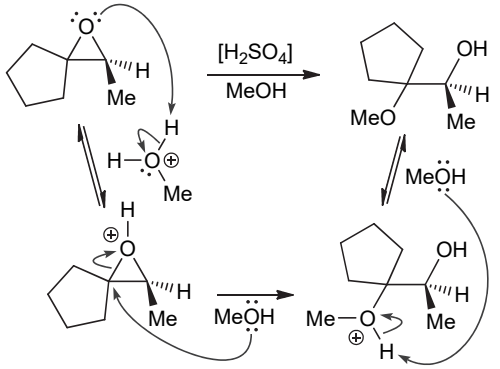
competition is between a secondary position and a tertiary position, electronic factors dominate and the tertiary position is attacked. Back-side attack causes inversion of configuration at the chiral center being attacked. Finally, a proton is removed (the most likely base is the solvent, ethanol).



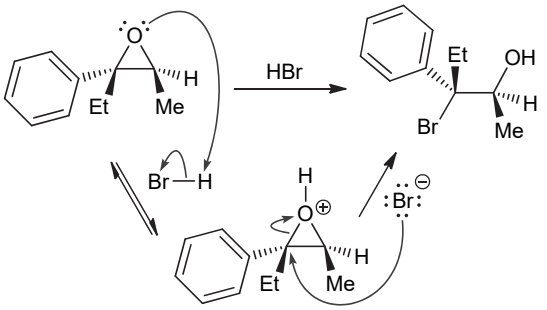
(d) Under acidic conditions, the epoxide is protonated, thereby generating a very powerful electrophile (a protonated epoxide). Water (H_2O) is a weak nucleophile, and we must decide which position will be attacked. In this case, one position (left) is tertiary, and the other position (right) is secondary. When the competition is between a secondary position and a tertiary position, electronic factors dominate and the tertiary position is attacked. Back-side attack causes inversion of configuration at the chiral center being attacked. Finally, a proton is removed (the most likely base is the solvent, water).



(e) Under acidic conditions, the epoxide is protonated, thereby generating a very powerful electrophile (a protonated epoxide). Methanol (CH_3OH) is a weak nucleophile, and we must decide which position will be attacked. In this case, one position (left) is tertiary, and the other position (right) is secondary. When the competition is between a secondary position and a tertiary position, electronic factors dominate and the tertiary position is attacked. Back-side attack causes inversion of configuration at the chiral center being attacked. Finally, a proton is removed (the most likely base is the solvent, methanol).

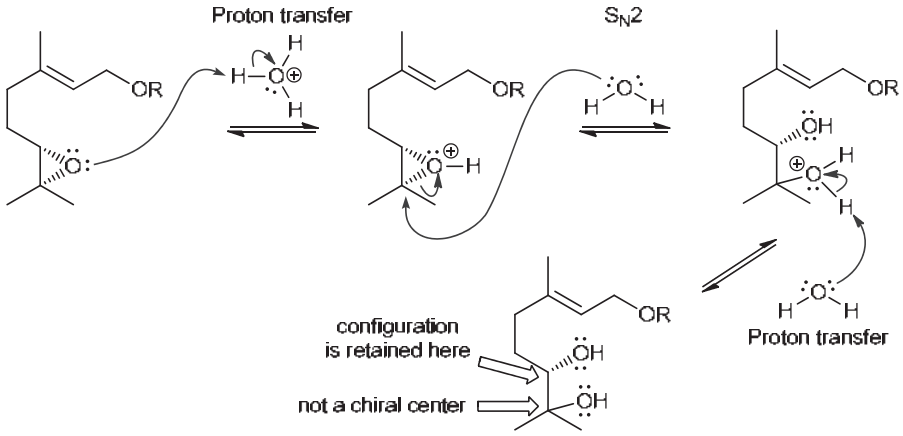


(f) Under acidic conditions, the epoxide is protonated, thereby generating a very powerful electrophile (a protonated epoxide). Bromide is a nucleophile, and we must decide which position will be attacked. In this case, one position (left) is tertiary, and the other position (right) is secondary. When the competition is between a secondary position and a tertiary position, electronic factors dominate and the tertiary position is attacked. Back-side attack causes inversion of configuration at the chiral center being attacked.

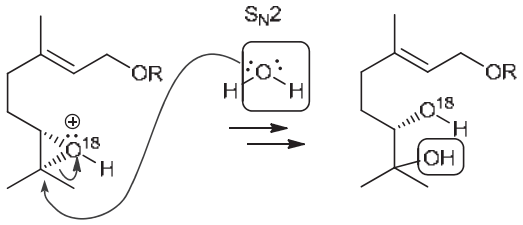


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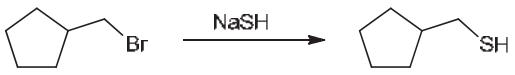
13.19.
(a) In this acid-catalyzed reaction, we expect the nucleophile (H_2O) to attack the more substituted (tertiary) position of the protonated epoxide. The S_N2 backside attack would result in inversion of stereochemistry, but this is not a chiral center so no stereochemistry needs to be shown at the position where the S_N2 attack occurred. The existing chiral center of the epoxide retains its configuration in the diol product.



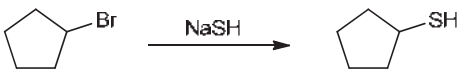
(b) The regiochemical outcome of the ring-opening reaction is determined at the S_N2 step of the mechanism, so let's look closely at that step. Since the nucleophile (water) attacks the more substituted position in this acid-catalyzed reaction, the labeled oxygen of the epoxide remains attached to the less-substituted position, as shown here:



13.20.
(a) The desired thiol can be prepared by treating an appropriate alkyl halide (shown below) with sodium hydrosulfide (NaSH).



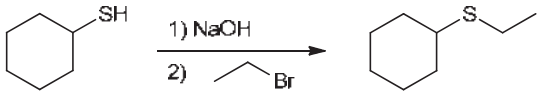
(b) The desired thiol can be prepared by treating an appropriate alkyl halide (shown below) with sodium hydrosulfide (NaSH).



(c) The desired thiol can be prepared by treating an appropriate alkyl halide (shown) with sodium hydrosulfide (NaSH). Notice that inversion of configuration is expected, so the starting alkyl halide must have a different configuration than the desired product.



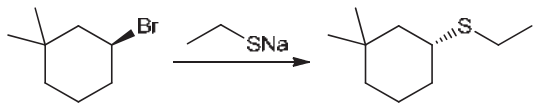
13.21.
(a) Treating a thiol with sodium hydroxide results in deprotonation of the thiol to give a thiolate ion. This thiolate ion is a very strong nucleophile, and it will attack a primary alkyl halide to give an S_N2 reaction. The product is a sulfide.



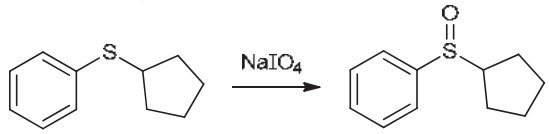
(b) A secondary alkyl bromide will serve as a substrate (electrophile) in an S_N2 reaction, upon treatment with a

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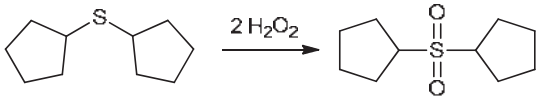
thiolate ion. The reaction occurs at a chiral center, so we expect inversion of configuration, which is characteristic of S_N2 processes.



(c) A sulfide is oxidized to give a sulfoxide upon treatment with sodium *meta*-periodate. This oxidizing agent does not further oxidize the sulfoxide (the sulfone is not obtained).

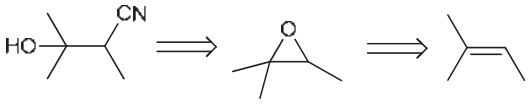


(d) A sulfide is oxidized all the way to a sulfone upon treatment with two equivalents of hydrogen peroxide. The first equivalent is responsible for oxidizing the sulfide to a sulfoxide, and the second equivalent oxidizes the sulfoxide to a sulfone.

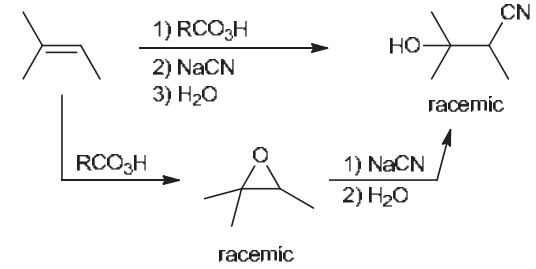


13.22.

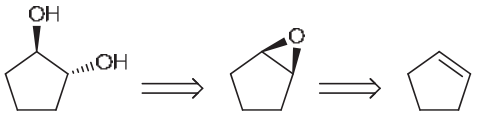
(a) The desired product can be made from an epoxide, which can be made from the starting alkene, as illustrated in the following retrosynthetic analysis:



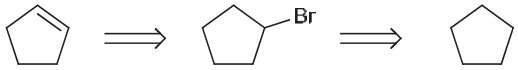
Now let's consider the reagents necessary for each step of the synthesis. First, the alkene must be converted into an epoxide, which can be achieved upon treatment with a peroxy acid. Notice that the resulting epoxide contains one chiral center. Since the epoxide can form on either face of the π bond with equal likelihood, we expect a racemic mixture of the epoxide. Basic conditions are required (NaCN, rather than HCN) during the ring opening step, in order to ensure that the nucleophile (cyanide) attacks the less substituted position. If acidic conditions were employed (HCN), the nucleophile (cyanide) would attack the more substituted position.



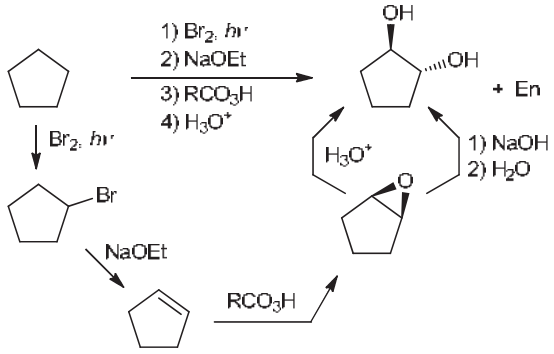
(b) The desired *trans*-diol can be made from an epoxide, which can be made from the corresponding alkene.



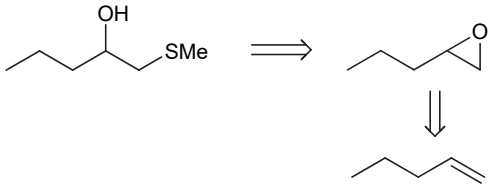
And the alkene can be prepared in two steps from the starting material.



Now let's consider the reagents necessary for each step of the synthesis, going forward. The starting material has no functional group, so one must be installed, which can be achieved via radical bromination. The resulting alkyl bromide is a secondary substrate, and treatment with a strong base will give an alkene via an E2 process. Treatment of the alkene with a peroxy acid gives an epoxide, which can then be opened either under aqueous acidic conditions or under aqueous basic conditions to give the desired *trans*-diol.

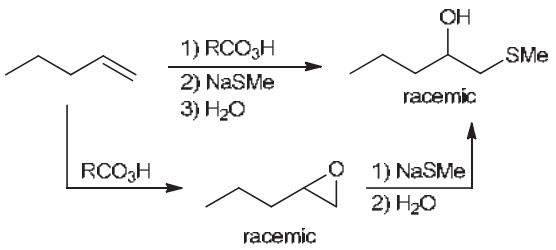


(c) The desired product can be made from an epoxide, which can be made from the starting alkene, as illustrated in the following retrosynthetic analysis:

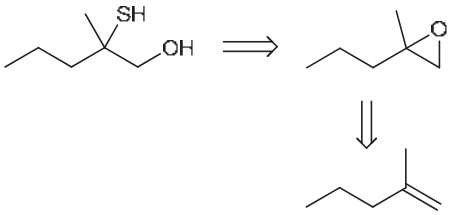


Now let's consider the reagents necessary for each step of the synthesis. First, the alkene must be converted into an epoxide, which can be achieved upon treatment with a peroxy acid. Notice that the resulting epoxide contains one chiral center. Since the epoxide can form on either face of the π bond with equal likelihood, we expect a racemic mixture of the epoxide. NaSMe must be used as the reagent, rather than MeSH and sulfuric acid) during the ring opening step, in order to ensure that the nucleophile (MeS^-) attacks the less substituted position.

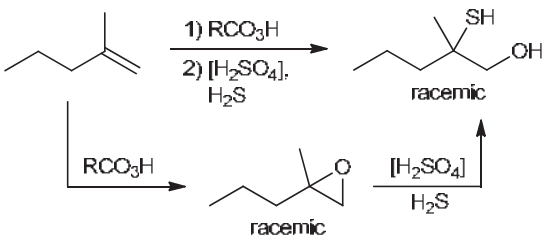
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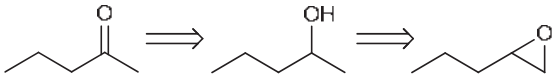
(d) The desired product can be made from an epoxide, which can be made from the starting alkene, as illustrated in the following retrosynthetic analysis:



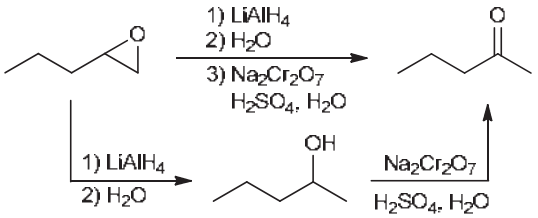
Now let's consider the reagents necessary for each step of the synthesis. First, the alkene must be converted into an epoxide, which can be achieved upon treatment with a peroxy acid. Notice that the resulting epoxide contains one chiral center. Since the epoxide can form on either face of the π bond with equal likelihood, we expect a racemic mixture of the epoxide. Acidic conditions are required (H_2S and sulfuric acid, rather than NaSH) during the ring opening step, in order to ensure that the nucleophile (H_2S) attacks the more substituted position.



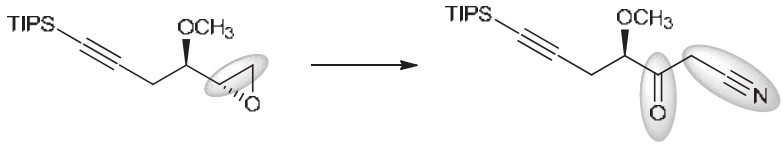
(e) The desired product (a ketone) can be made via oxidation of a secondary alcohol, which can be made from the starting epoxide, as illustrated in the following retrosynthetic analysis:



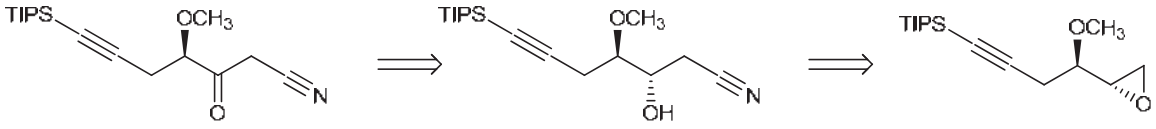
Now let's consider the reagents necessary for each step of the synthesis. First, the epoxide must be converted into an alcohol, which can be achieved upon treatment with $LiAlH_4$, followed by water work-up. The resulting alcohol is then oxidized to give the desired ketone.



13.23. We always approach a synthesis problem by asking two questions.
1) Is there a change in the carbon skeleton? Yes, there is one more carbon atom in the product than in the starting material.
2) Is there a change in the functional group(s)? Yes, the starting material has an epoxide that is missing in the product. The product has two new functional groups, a ketone and a nitrile



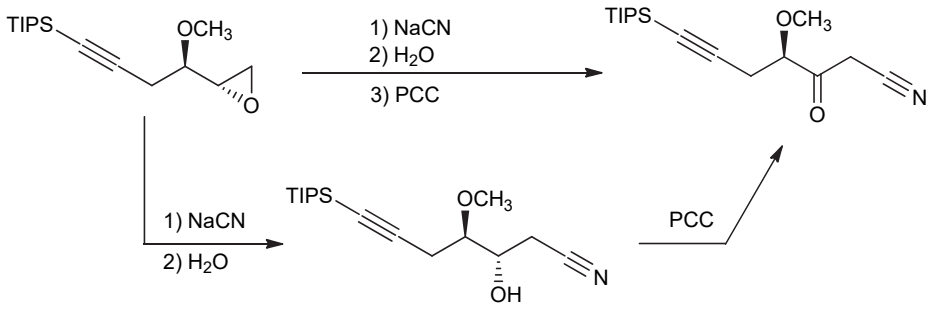
The product ketone can be made via oxidation of a secondary alcohol, which can be made by opening the starting epoxide with a cyanide nucleophile, as shown in the following retrosynthesis:



Let's write out the steps in the forward direction. The epoxide-opening requires a strong nucleophile to achieve the desired regiochemistry (the less hindered position must be attacked). Use of NaCN, followed by water to protonate the

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resulting alkoxide, accomplishes this and forms a new carbon-carbon bond in the process. Oxidation of the secondary alcohol to a ketone can be accomplished by a variety of reagents; one such option is shown below:

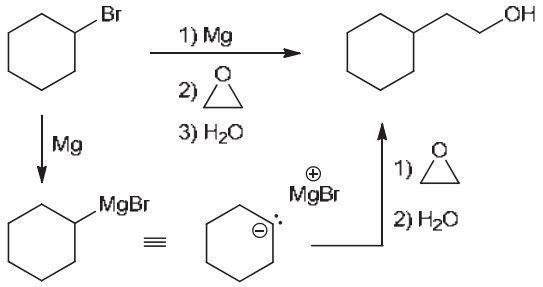


13.24.

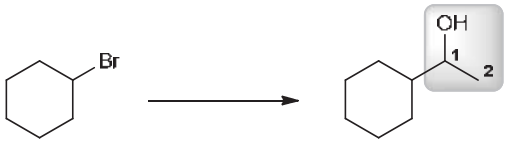
(a) This transformation involves the installation of two carbon atoms, with an OH group placed at the second carbon atom.



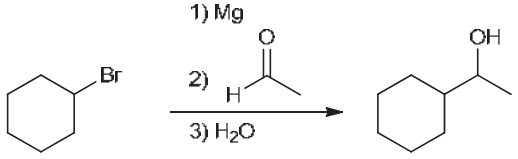
This can be achieved by converting the starting alkyl halide into a Grignard reagent, and then treating the Grignard reagent with an epoxide (followed by water work-up).



(b) This transformation involves the installation of two carbon atoms, with an OH group placed at the first carbon atom.



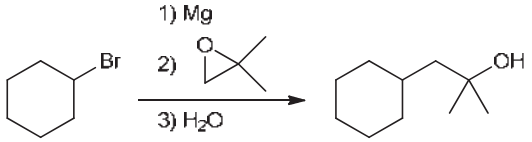
This can be achieved by converting the starting alkyl halide into a Grignard reagent, and then treating the Grignard reagent with an aldehyde (followed by water work-up).



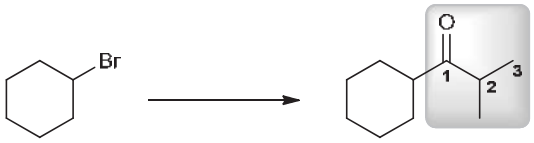
(c) This transformation involves the installation of an alkyl chain, with an OH group placed at the second carbon atom of the chain.



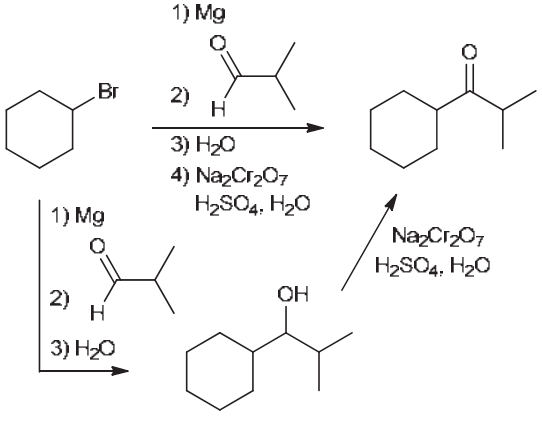
This can be achieved by converting the starting alkyl halide into a Grignard reagent, and then treating the Grignard reagent with the appropriate epoxide (followed by water work-up).



(d) This transformation involves the installation of several carbon atoms, with a functional group at the first carbon atom of the chain.



This can be achieved by converting the starting alkyl halide into a Grignard reagent, treating the Grignard reagent with an aldehyde (followed by water work-up) to give an alcohol, and then oxidizing the alcohol to a ketone.

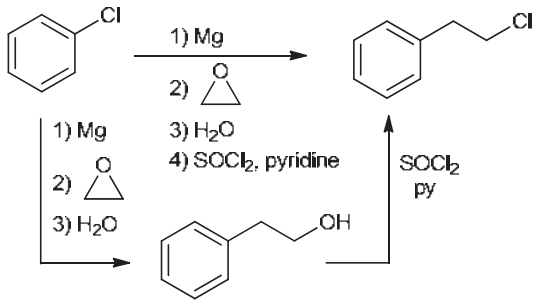


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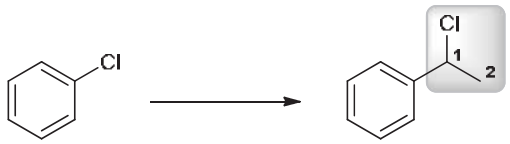
(e) This transformation involves the installation of two carbon atoms, with a functional group placed at the second carbon atom.



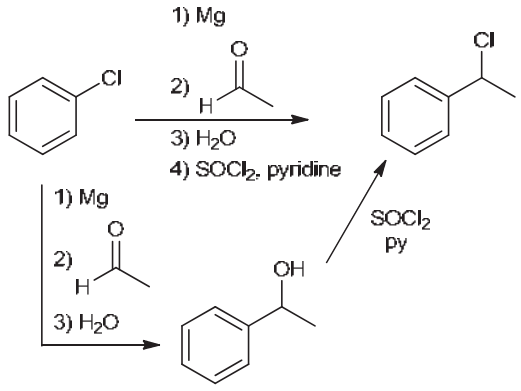
This can be achieved by converting the starting alkyl halide into a Grignard reagent, treating the Grignard reagent with an epoxide (followed by water work-up), and then converting the resulting alcohol into an alkyl chloride (via an S_N2 process).



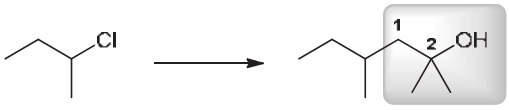
(f) This transformation involves the installation of two carbon atoms, with a functional group placed at the first carbon atom.



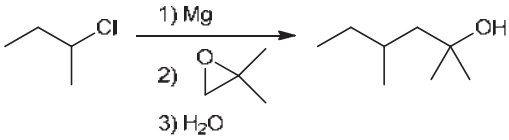
This can be achieved by converting the starting alkyl halide into a Grignard reagent, treating the Grignard reagent with an aldehyde (followed by water work-up), and then converting the resulting alcohol into an alkyl chloride.



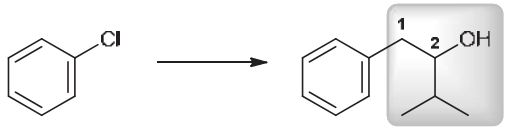
(g) This transformation involves the installation of an alkyl chain, with an OH group placed at the second carbon atom of the newly installed chain.



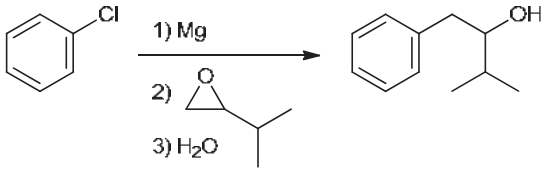
This can be achieved by converting the starting alkyl halide into a Grignard reagent, and then treating the Grignard reagent with the appropriate epoxide (followed by water work-up).



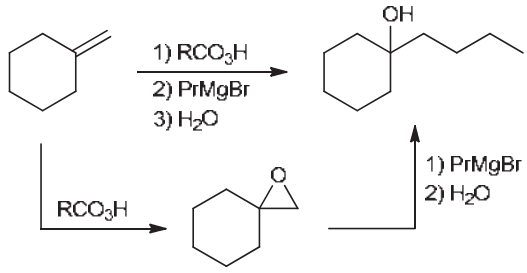
(h) This transformation involves the installation of an alkyl chain, with an OH group placed at the second carbon atom of the chain.



This can be achieved by converting the starting alkyl halide into a Grignard reagent, and then treating the Grignard reagent with the appropriate epoxide (followed by water work-up).



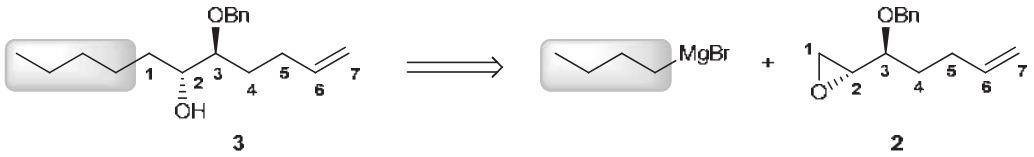
(i) The desired transformation can be achieved by converting the alkene into an epoxide, and then attacking the epoxide with a Grignard reagent, as shown here:



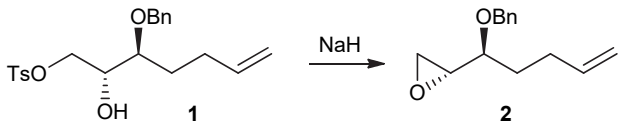
13.25. A Grignard reagent with four carbon atoms is reacting with compound **2** to give compound **3** (which has eleven carbon atoms in the longest chain). Therefore, compound **2** must have seven carbon atoms in the longest chain. Additionally, the four-carbon chain is installed on the carbon atom that is adjacent to the carbon atom bearing the hydroxyl (OH) group; this is consistent with a reaction between a Grignard reagent and an epoxide. The configurations

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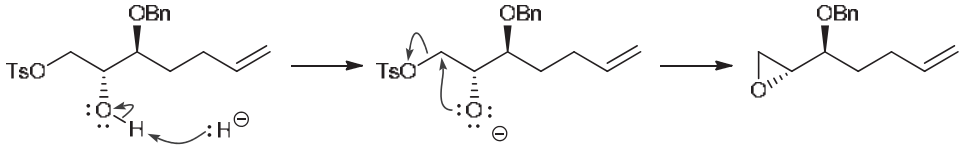
of the chiral centers in compounds **2** and **3** will remain the same, since these carbon atoms are not undergoing bond-making or bond-breaking.



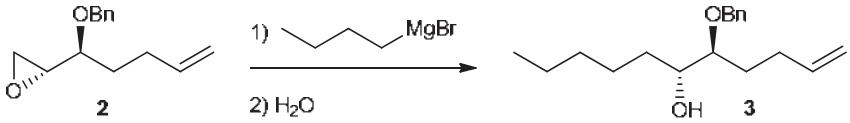
Now that we have drawn the structure of compound **2**, we need to provide mechanisms for each step of this overall transformation. Let's start with the conversion of compound **1** to compound **2**:



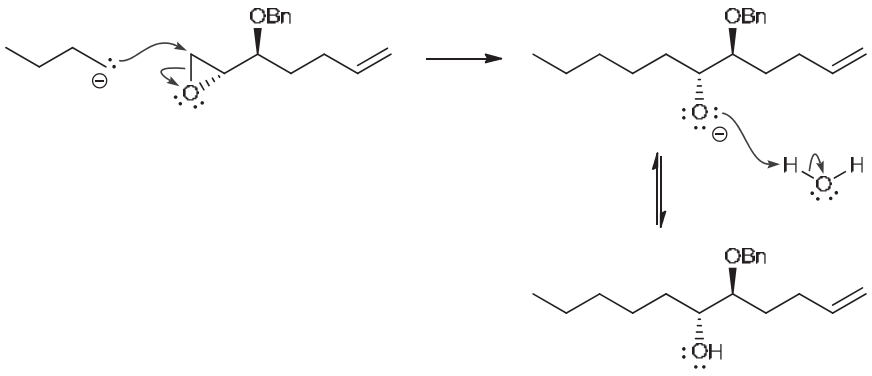
Recall that NaH is a strong, non-nucleophilic base. The mechanism begins with a proton transfer, as NaH deprotonates the alcohol. This is followed by an intramolecular S_N2-type reaction in which the tosylate group is the leaving group (this is an intramolecular Williamson ether synthesis). Note that the configuration at the alcohol carbon atom is unaffected in this reaction because no bonds are being made or broken with that carbon atom.



Now, let's consider the conversion of compound **2** to compound **3**:

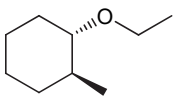


Recall that the Grignard reagent is characterized by a C-Mg bond that is very polar, and can be treated as an ionic bond. This carbanion is a strong nucleophile that attacks the less substituted carbon atom of the epoxide to form a new carbon-carbon bond and an alkoxide ion. Subsequent protonation of the alkoxide with water produces an alcohol as the product. Note that the configuration at the more substituted carbon atom of the epoxide is unaffected in this reaction because no bonds are being made or broken with that carbon atom.



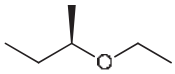
13.26.

(a) The oxygen atom has two groups attached to it. The parent is named after the larger group (cyclohexane). The smaller group (together with the oxygen atom) is treated as an ethoxy substituent. Locants are used to identify the positions of the ethoxy group and of the methyl group. The compound has two chiral centers, each of which is assigned a configuration in the beginning of the name, placed in parentheses.



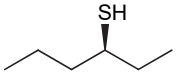
(*1S,2S*)-1-Ethoxy-2-methylcyclohexane

(b) The oxygen atom has two groups attached to it. One group has two carbon atoms and the other group has four carbon atoms. The parent is named after the larger group, so the parent is butane. The smaller group (together with the oxygen atom) is treated as an ethoxy substituent, and a locant (2) is included to identify the location of the substituent on the parent chain. The configuration of the chiral center is indicated at the beginning of the name, placed in parentheses.



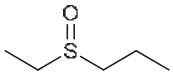
(*R*)-2-Ethoxybutane

(c) The compound is named in the same way that we would name an alcohol (if the SH group were an OH group), except that the term "thiol" is used in the suffix of the name. In this case, the parent is hexane, and the location of the SH group is at C3, which must be indicated with a locant. The configuration of the chiral center is indicated at the beginning of the name, placed in parentheses.



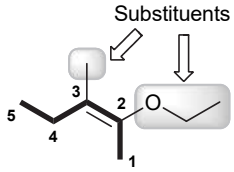
(*S*)-3-Hexanethiol

(d) This compound is a sulfoxide (S=O group) with an ethyl group and a propyl group. The groups are alphabetized in the name, so ethyl precedes propyl.

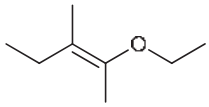


Ethyl propyl sulfoxide

(e) The oxygen atom has two groups attached to it. The parent is named after the larger group. In this case, the parent is pentene (an alkene), and the smaller group (together with the oxygen atom) is treated as an ethoxy substituent.

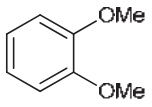


Locants are used to identify the positions of the ethoxy group and of the methyl group. The configuration of the alkene is indicated in the beginning of the name, placed in parentheses.



(*E*)-2-Ethoxy-3-methyl-2-pentene

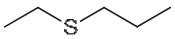
(f) The parent is benzene, and the two methoxy groups are treated as substituents. Locants are used to indicate the relative placement of the methoxy groups on the ring.



1,2-Dimethoxybenzene

Alternatively, the parent can be named as anisole (the common name for methoxybenzene), in which case the compound would be called 2-methoxyanisole. Both of these names are acceptable IUPAC names.

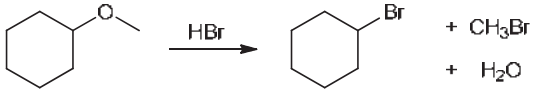
(g) This compound is a sulfide (R–S–R), and it is named very much like an ether. The sulfur atom is connected to two groups, ethyl and propyl, which are arranged alphabetically in the name.



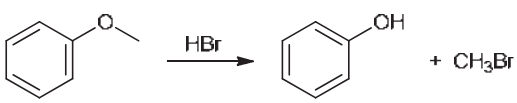
Ethyl propyl sulfide

13.27.

(a) The oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. Therefore, each of the C–O bonds is cleaved, giving two alkyl bromides.

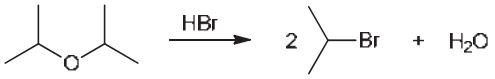


(b) The oxygen atom is connected to two carbon atoms, but only one of them is sp^3 hybridized. Therefore, only one C–O bond is cleaved. The other C–O bond (where the C is sp^2 hybridized) is not cleaved. The products are phenol and methyl bromide.

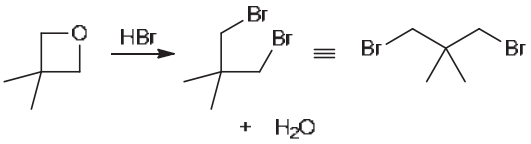


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(c) The oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. Therefore, each of the C–O bonds is cleaved, giving two equivalents of 2-bromopropane.



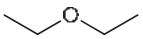
(d) The oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. Therefore, each of the C–O bonds is cleaved. As a result, the ring is opened, giving a dibromide, as shown.



13.28. Ethers have the following structure:

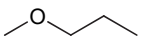


We are looking for ethers with the molecular formula $C_4H_{10}O$, which means that the four carbon atoms must be contained in the two R groups of the ether. One possibility is that each R group has two carbon atoms.

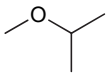


ethoxyethane
(diethyl ether)

Alternatively, one R group can have three carbon atoms and the other R group can have one carbon atom. The R group containing three carbon atoms can either be a propyl group or an isopropyl group, giving the following two additional isomers:



1-methoxypropane
(methyl propyl ether)

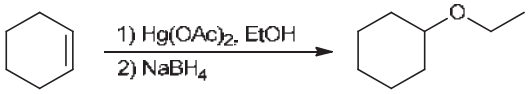


2-methoxypropane
(isopropyl methyl ether)

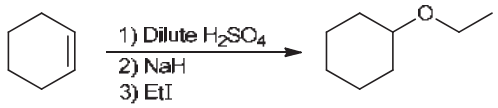
In total, there are three constitutionally isomeric ethers with the molecular formula $C_4H_{10}O$.

13.29.

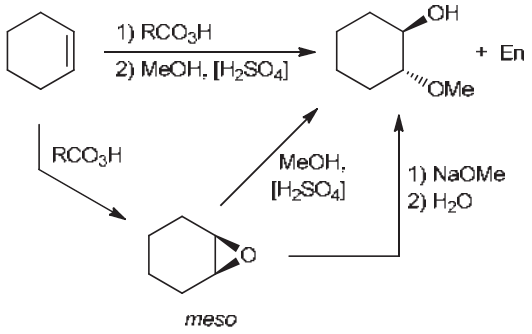
(a) The desired transformation involves addition of H and OEt across a π bond. This can be achieved via alkoxymercuration-demercuration, where EtOH is used as the alcohol during the alkoxymercuration step:



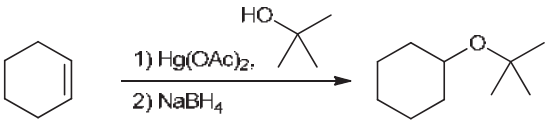
Alternatively, cyclohexene can be treated with dilute sulfuric acid to give cyclohexanol, which can then be used in a Williamson ether synthesis, together with ethyl iodide, to give the desired product:



(b) The desired transformation involves an *anti* addition of OH and OMe across a π bond. This can be achieved by converting cyclohexene into an epoxide (upon treatment with a peroxy acid), followed by a ring opening reaction. The second step of this process (opening the ring) can be performed under either acidic conditions or basic conditions.

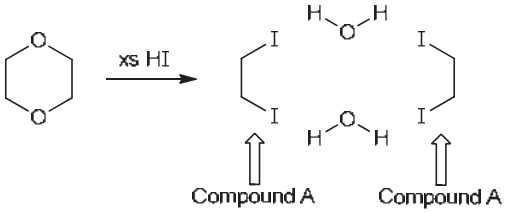


(c) The desired transformation involves addition of H and OR across a π bond. This can be achieved via alkoxymercuration-demercuration, where $(CH_3)_3COH$ is used as the alcohol during the alkoxymercuration step.



13.30.

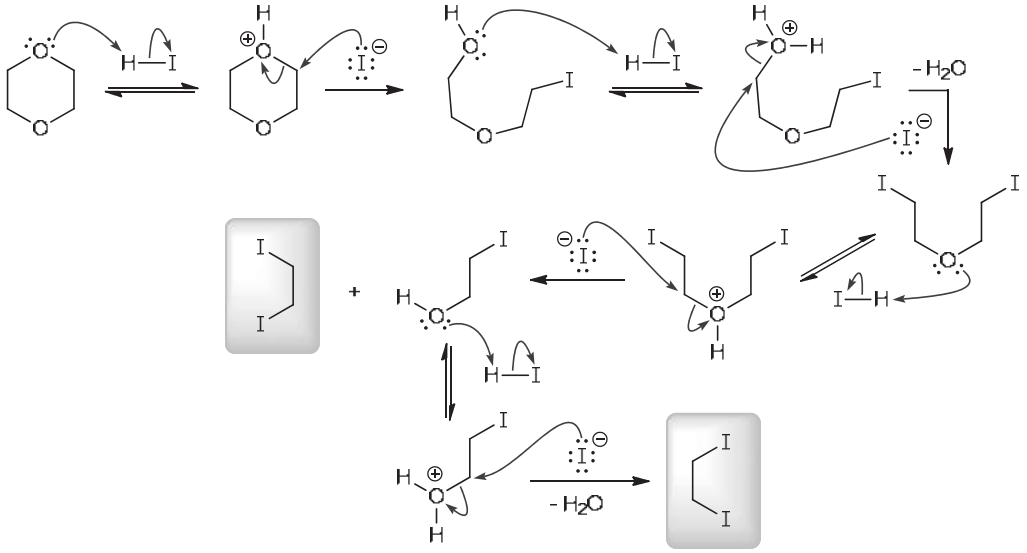
(a) There are four C–O bonds, and each of them is cleaved under acidic conditions and replaced with a C–I bond, giving two moles of compound **A** and two moles of water.



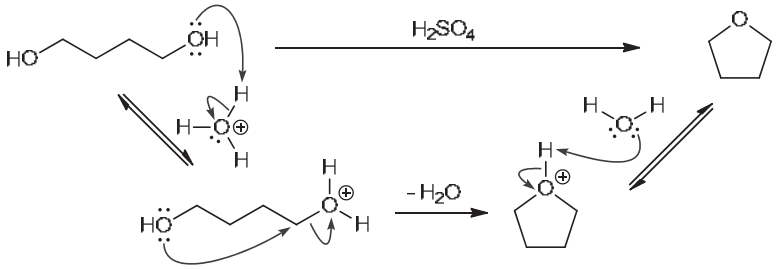
(b) As seen in the previous solution (14.34a), two moles of compound **A** are produced for every one mole of 1,4-dioxane.

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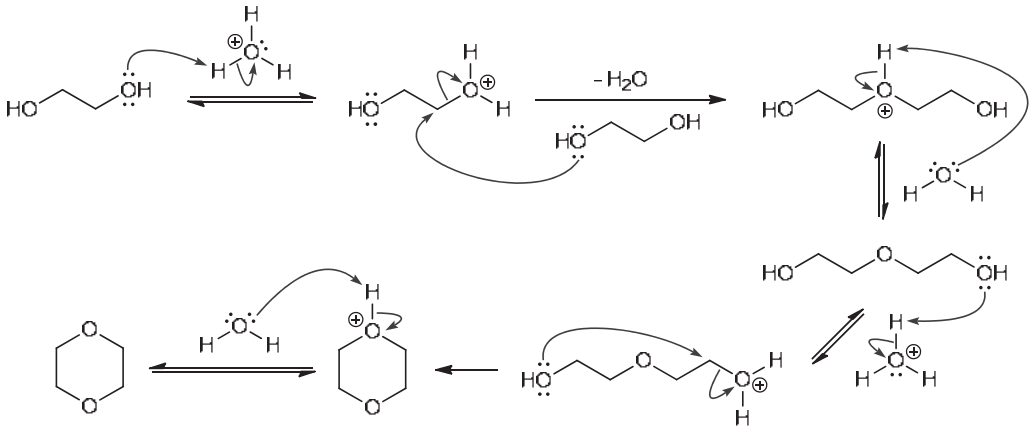
(c) Each of the C–O bonds is cleaved via a two-step process: (i) protonation of the oxygen atom to give an oxonium ion, and (ii) an S_N2 reaction, in which iodide functions as a nucleophile and attacks the primary substrate. Each of these two steps requires two curved arrows, as shown. Since there are four C–O bonds that undergo cleavage, our mechanism will have a total of eight steps, where each step utilizes two curved arrows, as shown.



13.31. In the presence of an acid catalyst, an OH group is protonated to give an oxonium ion, thereby converting a bad leaving group into a good leaving group. Then, the other OH group (that was not protonated) functions as a nucleophilic center in an S_N2-type process, forming a ring. Finally, deprotonation gives the product. Notice that water (not hydroxide) functions as the base in the deprotonation step (because there is virtually no hydroxide present in acidic conditions).



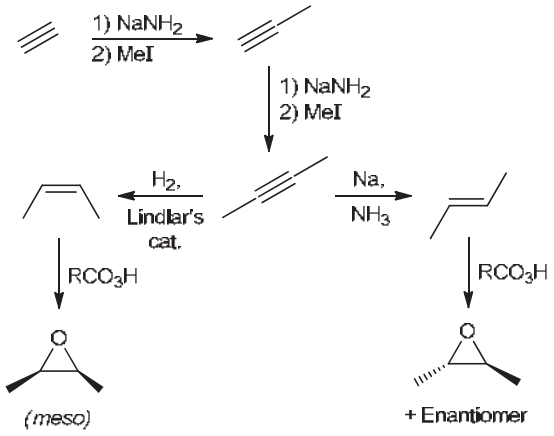
13.32. In the presence of an acid catalyst, an OH group is protonated to give an oxonium ion, thereby converting a bad leaving group into a good leaving group. Then, one molecule of the diol (that was not yet protonated) can function as a nucleophile and attack the oxonium ion in an S_N2 process, expelling water as a leaving group. The resulting oxonium ion is then deprotonated. The previous three steps are then repeated (proton transfer, S_N2, and then proton transfer), giving the cyclic product. Notice that each of the deprotonation steps is shown with water functioning as the base (not hydroxide), because there is virtually no hydroxide present in acidic conditions.



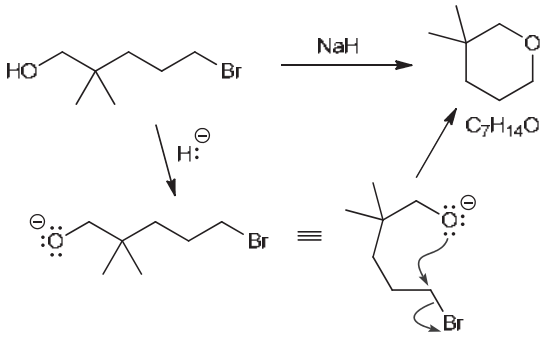
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13.33. Ethylene oxide has a high degree of ring strain, and readily functions as an electrophile in an S_N2 reaction. The reaction opens the ring and alleviates the ring strain. Oxetane has less ring strain and is, therefore, less reactive as an electrophile towards S_N2. The reaction can still occur, albeit at a slower rate, to alleviate the ring strain associated with the four-membered ring. THF has almost no ring strain and does not function as an electrophile in an S_N2 reaction.

13.34. Acetylene undergoes alkylation when treated with a strong base (such as $NaNH_2$) followed by an alkyl halide. This process is then repeated to install a second methyl group, giving 2-butyne. This alkyne can be reduced either via hydrogenation with a poisoned catalyst to give a *cis* alkene, or via a dissolving metal reduction to give a *trans* alkene. Treatment of these alkenes with a peroxy acid gives the epoxides shown.

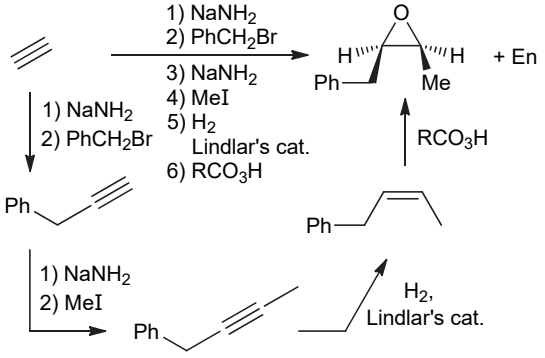


13.35. Upon treatment with NaH (a strong base), the hydroxyl proton is removed, giving an alkoxide ion. This alkoxide ion is tethered to a leaving group (bromide), so an intramolecular, S_N2-type process can occur, forming the cyclic product shown here.

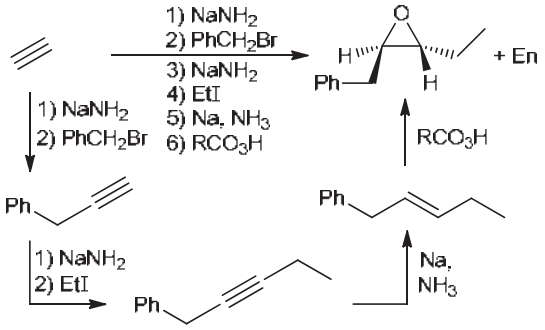


13.36.

(a) Acetylene can be treated with $NaNH_2$ followed by $PhCH_2Br$ to install a benzyl group ($PhCH_2$). This process is then repeated (with methyl iodide as the alkyl halide) to install a methyl group. These two alkylation processes could have been performed in reverse order (with installation of the methyl group first, followed by installation of the benzyl group). The resulting alkyne can then be reduced via hydrogenation with a poisoned catalyst to give a *cis* alkene, which gives the desired epoxide upon treatment with a peroxy acid.



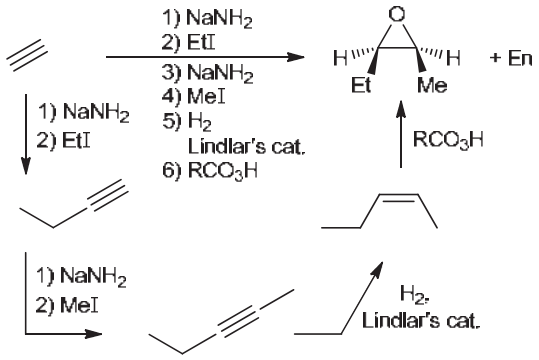
(b) Acetylene can be treated with $NaNH_2$ followed by $PhCH_2Br$ to install a benzyl group ($PhCH_2$). This process is then repeated (with ethyl iodide as the alkyl halide) to install an ethyl group. These two alkylation processes could have been performed in reverse order (with installation of the ethyl group first, followed by installation of the benzyl group). The resulting alkyne can then be reduced via a dissolving metal reduction to give a *trans* alkene, which gives the desired epoxide upon treatment with a peroxy acid.



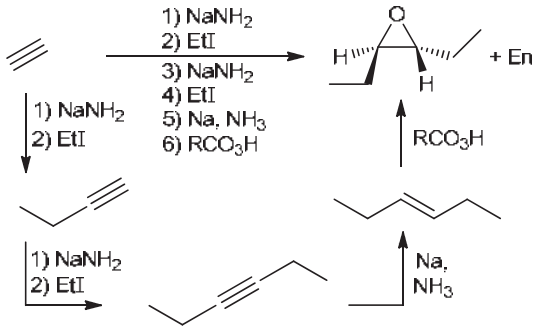
(c) Acetylene can be treated with $NaNH_2$ followed by ethyl iodide to install an ethyl group. This process is then repeated (with methyl iodide as the alkyl halide) to install a methyl group. These two alkylation processes could have been performed in reverse order (with installation of the methyl group first, followed by installation of the ethyl group). The resulting alkyne can then be reduced via hydrogenation with a poisoned

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catalyst to give a *cis* alkene, which gives the desired epoxide upon treatment with a peroxy acid.

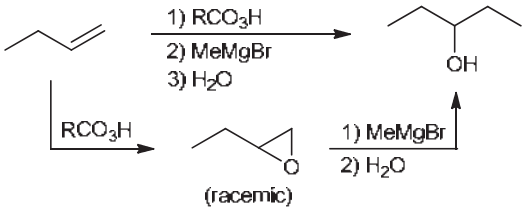


(d) Acetylene can be treated with $NaNH_2$ followed by ethyl iodide to install the first ethyl group. This process is then repeated (again with ethyl iodide as the alkyl halide) to install the second ethyl group. Notice that two alkylation processes are required, even though the same group is being installed on both sides of acetylene. The reagents ($NaNH_2$ followed by ethyl iodide) will install only one ethyl group. So these reagents must be repeated to install the second ethyl group (treating acetylene with two equivalents of $NaNH_2$ followed by two equivalents of ethyl iodide will NOT produce the desired internal alkyne). The resulting alkyne can then be reduced via a dissolving metal reduction to give a *trans* alkene, which gives the desired epoxide upon treatment with a peroxy acid.

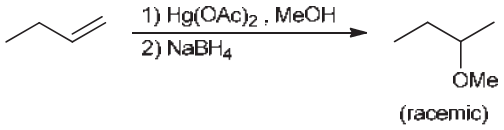


13.37.

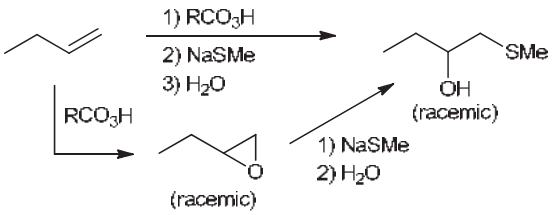
(a) Treating the alkene with a peroxy acid generates an epoxide. This epoxide has one chiral center, so we expect a racemic mixture of enantiomers (epoxide formation can occur on either face of the π bond with equal likelihood). Then, the epoxide is treated with methyl magnesium bromide, a strong nucleophile, resulting in a ring-opening reaction. Attack occurs at the less substituted position, giving an alkoxide ion, which is then protonated upon treatment with water to give a secondary alcohol as the product. Notice that this product does not have a chiral center.



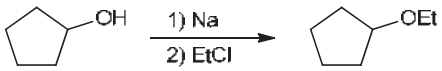
(b) The starting material is an alkene, and the reagents indicate an alkoxymercuration-demercuration, resulting in the Markovnikov addition of H and OMe across the π bond. One chiral center is generated in the process, so we expect a racemic mixture of enantiomers.



(c) Treating the alkene with a peroxy acid generates an epoxide. This epoxide has one chiral center, so we expect a racemic mixture of enantiomers (epoxide formation can occur on either face of the π bond with equal likelihood). Then, the epoxide is treated with a strong nucleophile (MeS^-), resulting in a ring-opening reaction. Nucleophilic attack occurs at the less substituted position, giving an alkoxide ion, which is then protonated upon treatment with water to give the product shown here.



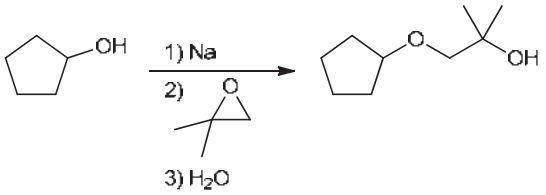
(d) Upon treatment with elemental sodium, an alcohol is deprotonated to give an alkoxide ion. The alkoxide then functions as a nucleophile when treated with ethyl chloride, giving an S_N2 reaction that affords the following ether:



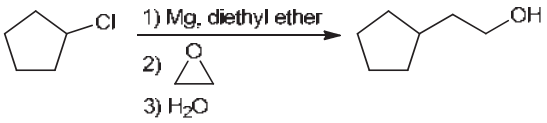
(e) Upon treatment with elemental sodium, an alcohol is deprotonated to give an alkoxide ion. The alkoxide then functions as a nucleophile and attacks the epoxide, giving a ring-opening reaction. Nucleophilic attack occurs at the less substituted position, giving another

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alkoxide ion, which is then protonated upon treatment with water to give the following product:

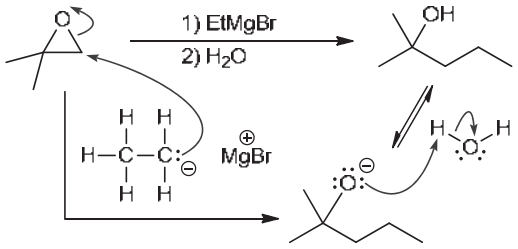


(f) Upon treatment with magnesium (Mg), the starting alkyl halide is converted into a Grignard reagent, which is a very strong nucleophile. When this Grignard reagent is treated with an epoxide, a ring-opening reaction occurs. The resulting alkoxide ion is then protonated upon treatment with water to give the product shown:

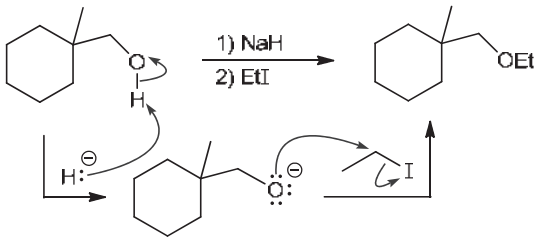


13.38.

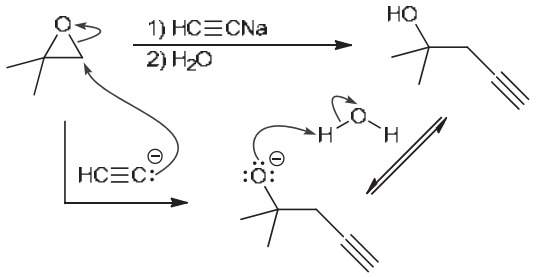
(a) Ethyl magnesium bromide is a strong nucleophile, so it can attack the epoxide at the less substituted position, giving a ring-opening reaction. The resulting alkoxide ion is then protonated upon treatment with water to give the tertiary alcohol as the product.



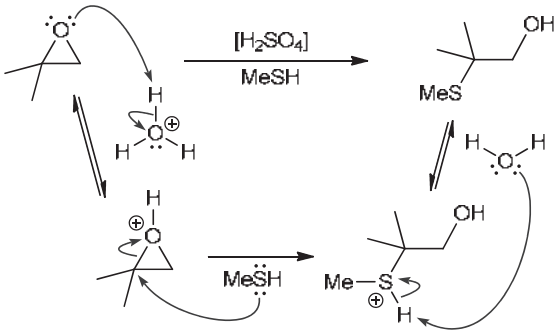
(b) Sodium hydride is a strong base, and it will deprotonate an alcohol to give an alkoxide ion. This alkoxide ion will then function as a nucleophile when treated with a primary alkyl halide, giving an S_N2 reaction, as shown here:



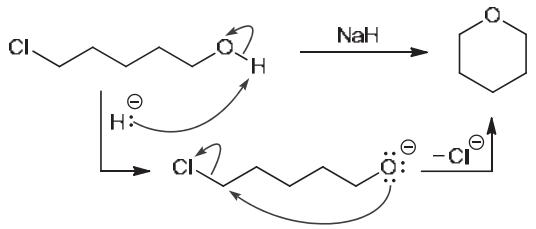
(c) The acetylide ion is a strong nucleophile and it will attack the epoxide at the less substituted position, giving a ring-opening reaction. The resulting alkoxide ion is then protonated upon treatment with water, as shown:



(d) Upon treatment with a strong acid, the epoxide is protonated. The resulting protonated epoxide is then attacked by MeSH (a good nucleophile). Nucleophilic attack occurs at the more substituted position, as a result of electronic effects (the tertiary position bears more partial carbocationic character than the primary position). In the final step, a proton is removed to give the product shown:



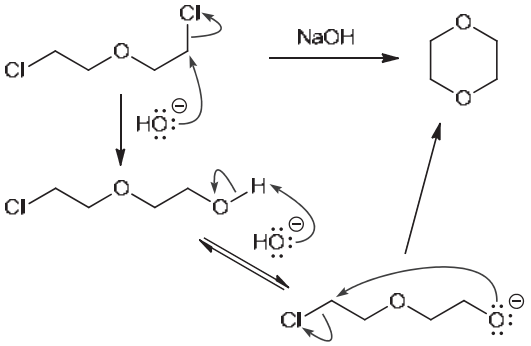
(e) Sodium hydride is a strong base, and it will deprotonate the alcohol to give an alkoxide ion. This alkoxide ion contains a built-in leaving group, so it can undergo an intramolecular S_N2-type process in which a chloride ion is ejected as a leaving group, giving the cyclic product shown:



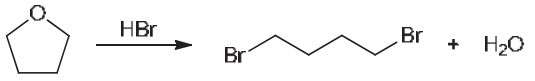
(f) Hydroxide functions as a nucleophile in an S_N2 reaction, ejecting chloride as a leaving group. The resulting alcohol is then deprotonated by hydroxide, giving an alkoxide ion. This alkoxide ion contains a built-in leaving group, so it can undergo an intramolecular S_N2-type process in which a chloride ion is

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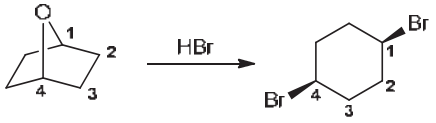
ejected as a leaving group, giving the cyclic product shown:



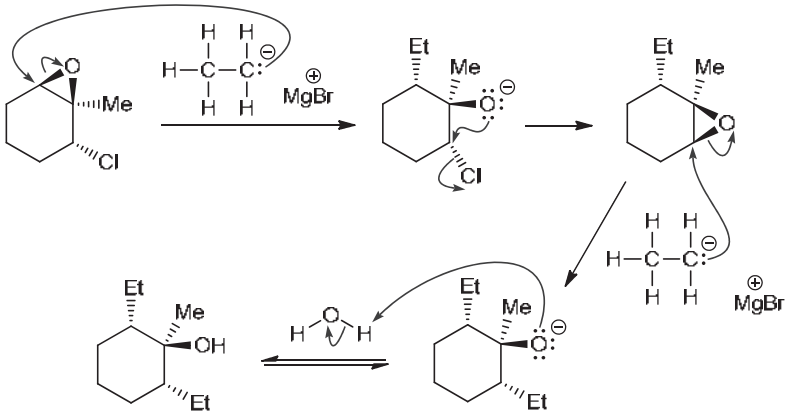
13.39. The starting material is a cyclic ether, in which the oxygen atom is connected to two carbon atoms, each of which is sp^3 hybridized. As such, treatment with HBr is expected to cleave each of the C–O bonds and replace them with C–Br bonds, giving the following dibromide:



13.40. The starting material has six carbon atoms, and the product has six carbon atoms. So, the starting material must be some sort of cyclic ether, which opens to give a dibromide. By inspecting the dibromide product, we can determine which two carbon atoms must have been connected to the oxygen atom in the starting cyclic ether.

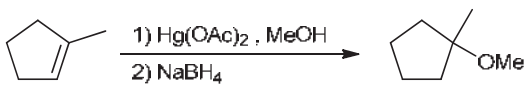


13.41. Ethyl magnesium bromide is a strong nucleophile, and can attack the epoxide at the less substituted position, in a ring-opening process, with inversion of configuration at the position that is attacked. The resulting alkoxide ion can then undergo an intramolecular S_N2-type process, expelling a chloride ion and generating a new epoxide. This epoxide can be attacked once again by ethyl magnesium bromide, once again at the less substituted position, and once again with inversion of configuration. The resulting alkoxide ion is then protonated upon treatment with water, to give the observed product.

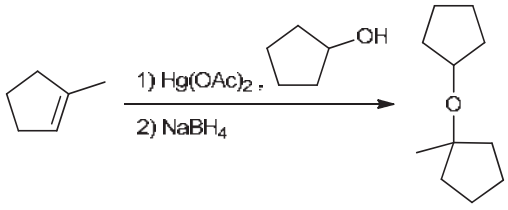


13.42.

(a) The starting material is an alkene, and the reagents indicate an alkoxymercuration-demercuration, resulting in the Markovnikov addition of H and OMe across the π bond.



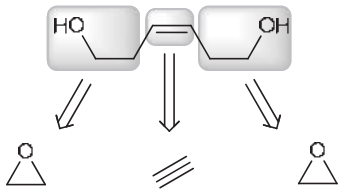
(b) The starting material is an alkene, and the reagents indicate an alkoxymercuration-demercuration, resulting in the Markovnikov addition of H and OR across the π bond.



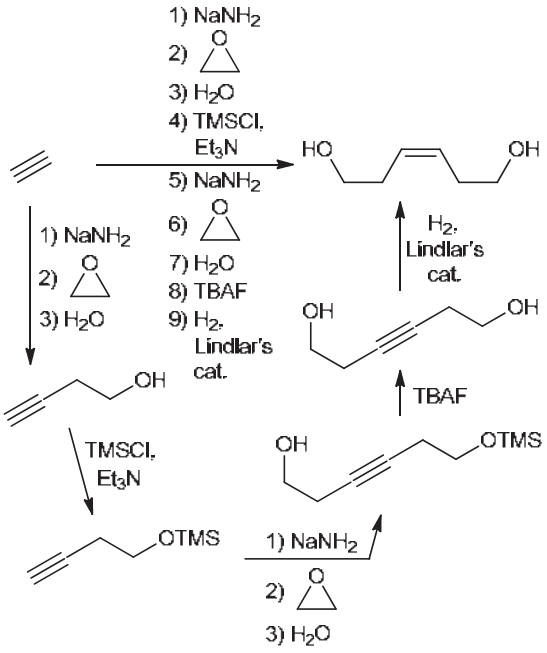
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13.43.

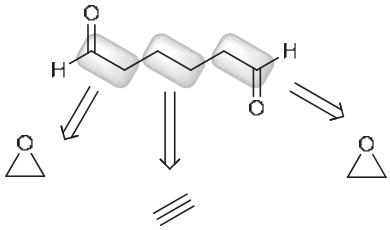
(a) There are certainly many ways to prepare the target compound. The following strategy represents just one possible synthetic approach.



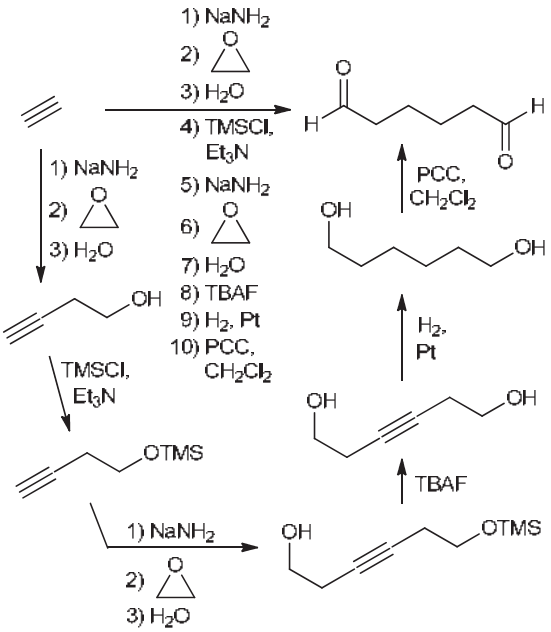
The central two carbon atoms (C3 and C4) come from acetylene, and the bonds at C2-C3 and C4-C5 are formed via the reaction between an acetylide ion and an epoxide. The forward process is shown below. Notice that after the first carbon-carbon bond is formed, the resulting compound is an alcohol. As such, the OH group must be protected before treating the terminal alkyne with a strong base (a strong base would simply deprotonate the alcohol, rather than the alkyne, if the OH group were not protected). The protecting group can be removed after the second carbon-carbon bond is formed. Finally, the desired product is obtained upon reduction of the alkyne via hydrogenation in the presence of a poisoned catalyst, to give the *cis* alkene.



(b) There are certainly many ways to prepare the target compound. The following strategy represents just one possible synthetic approach.

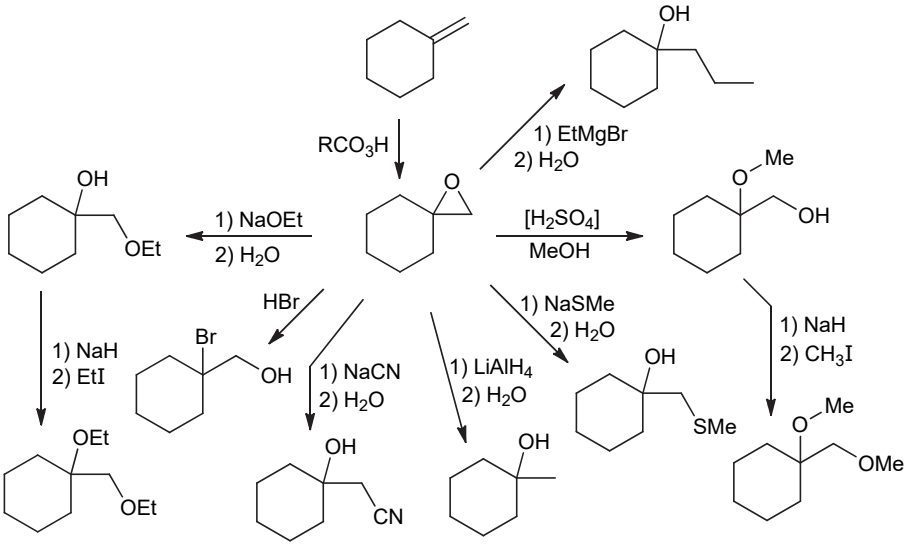


The central two carbon atoms (C3 and C4) come from acetylene, and the bonds at C2-C3 and C4-C5 are formed via the reaction between an acetylide ion and an epoxide. The forward process is shown below. Notice that after the first carbon-carbon bond is formed, the resulting compound is an alcohol. As such, the OH group must be protected before treating the terminal alkyne with a strong base (a strong base would simply deprotonate the alcohol, rather than the alkyne, if the OH group were not protected). The protecting group can be removed after the second carbon-carbon bond is formed. Finally, the desired product is obtained via hydrogenation of the alkyne followed by oxidation of the primary alcohol groups to aldehyde groups (using PCC, or DMP, or a Swern oxidation):

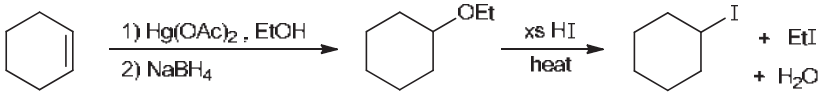


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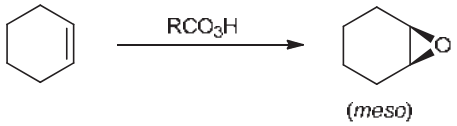
13.44. The following reagents can be used to achieve the desired transformations:



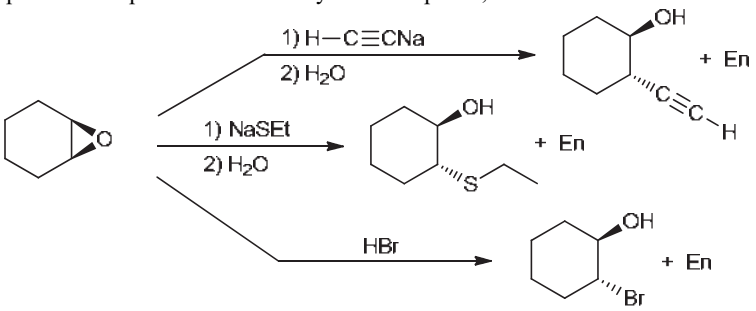
13.45. Alkoxymercuration-demercuration converts the alkene into an ether, which is then cleaved into two alkyl halides upon treatment with excess HI:



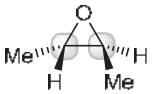
Treatment of the alkene with a peroxy acid results in an epoxide, which is a *meso* compound in this case:



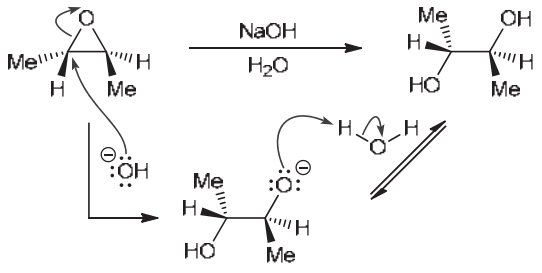
The epoxide can be opened in the presence of a variety of nucleophiles, as shown:



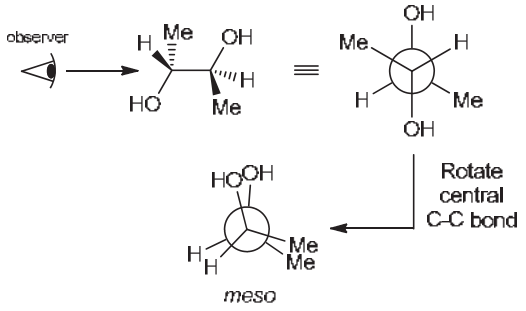
13.46. Hydroxide is a strong nucleophile, and it can attack the epoxide at either of two locations, highlighted here:



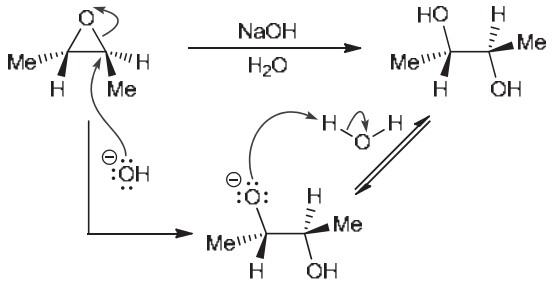
Let's first consider the ring-opening reaction occurring at the position on the left. The resulting alkoxide ion is protonated by water to give a diol:



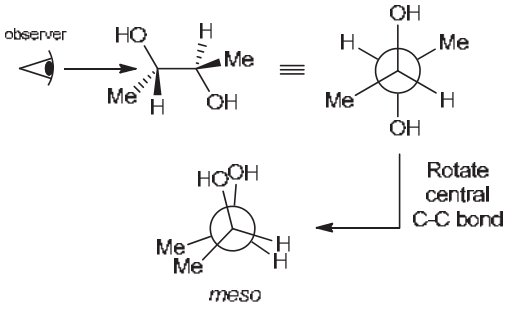
This diol is a *meso* compound, which can be seen more clearly if we draw a Newman projection and then rotate about the central C–C bond:



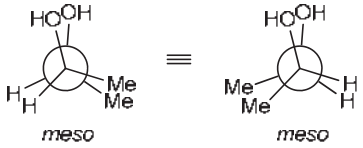
Now let's consider the product that is obtained if the ring-opening reaction occurs at the position on the right:



Once again, notice that the resulting diol is a *meso* compound:



In fact, this *meso* compound is the same *meso* compound that was obtained earlier (when the attack occurred at the position on the left).

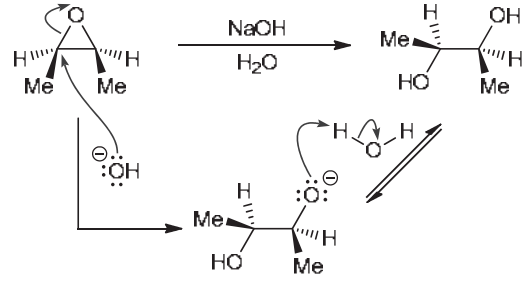


That is, the same product is obtained, regardless of which electrophilic position is attacked by hydroxide.

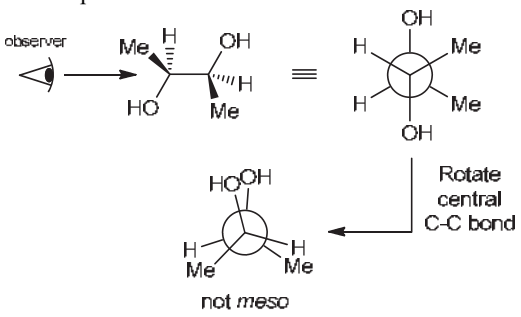
13.47. We begin by drawing the structure of *meso*-2,3-epoxybutane.



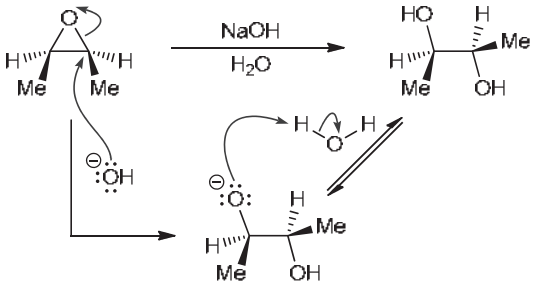
Hydroxide is a strong nucleophile, and it can attack the epoxide at either of two locations, just as we saw in the previous problem. Let's first consider the ring-opening reaction occurring at the position on the left. The resulting alkoxide ion is protonated by water to give a diol:



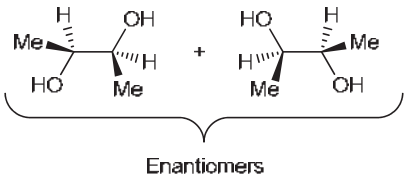
If we draw a Newman projection of the diol, as we did in the previous problem, we will see that this diol is **not** a *meso* compound.



Now let's consider the product that is obtained if the ring-opening reaction occurs at the position on the right:

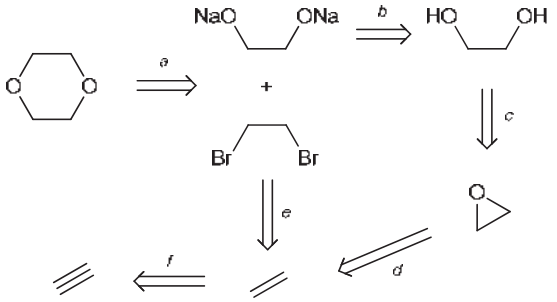


Once again, the resulting diol is ***not*** a *meso* compound. If we compare the two possible diols, we find that they are non-superimposable mirror images of each other, and therefore, they are enantiomers:



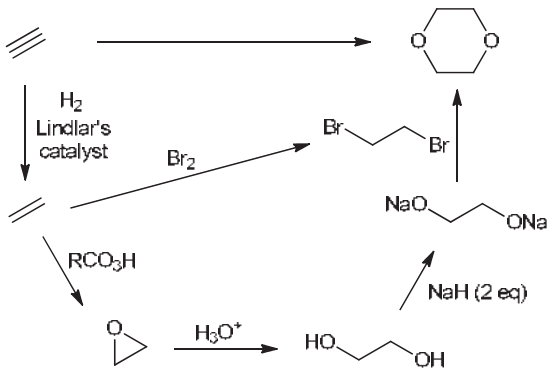
13.48. There are certainly many acceptable methods for achieving the desired transformation. The following

retrosynthetic analysis represents one such method. An explanation of each of the steps (*a-f*) follows.

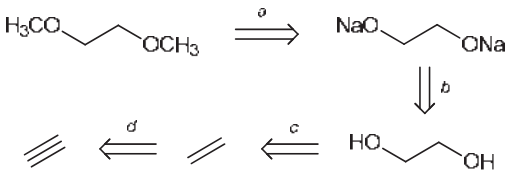


a. The cyclic product can be made by treating a dianion with a dihalide (via two successive S_N2 reactions).
b. The dianion can be made by treating the corresponding diol with two equivalents of a strong base (such as NaH).
c. The diol can be made from an epoxide, via a ring-opening reaction (either under acidic conditions or under basic conditions).
d. The epoxide can be made by treating the corresponding alkene with a peroxy acid.
e. The dibromide can be made via bromination of the corresponding alkene.
f. The alkene can be made via hydrogenation of the corresponding alkyne, in the presence of Lindlar's catalyst.

Now let's draw the forward scheme. Acetylene undergoes hydrogenation in the presence of Lindlar's catalyst to afford ethylene, which can be converted to an epoxide upon treatment with a peroxy acid. Acid-catalyzed ring-opening of the epoxide gives a diol (base-catalyzed conditions can also be used). Treatment of the diol with two equivalents of a strong base, such as NaH, gives a dianion. The dianion will react with 1,2-dibromoethane (formed from bromination of ethylene) to give the desired cyclic product via two successive S_N2 reactions.

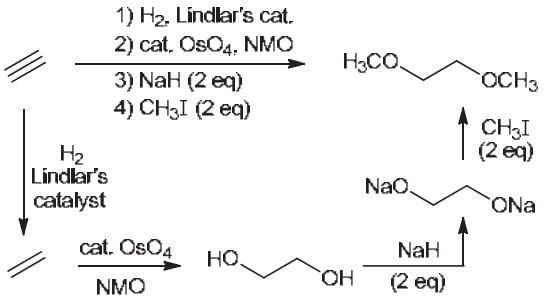


13.49. There are certainly many acceptable methods for achieving the desired transformation. The following retrosynthetic analysis represents one such method. An explanation of each of the steps (*a-d*) follows.

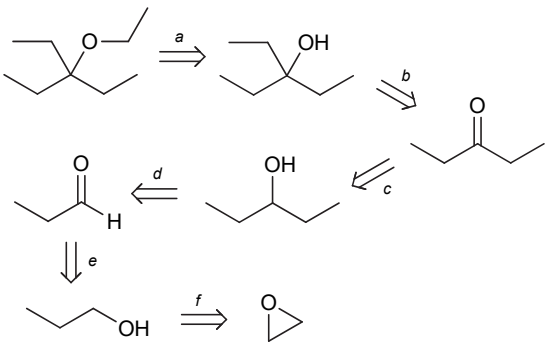


a. The product has two ether groups, each of which can be formed via a Williamson ether synthesis, from the dianion shown.
b. The dianion can be made by treating the corresponding diol with two equivalents of a strong base (such as NaH).
c. The diol can be made from an alkene, via a dihydroxylation process.
d. The alkene can be made via hydrogenation of the corresponding alkyne, in the presence of Lindlar's catalyst.

Now let's draw the forward scheme. Acetylene undergoes hydrogenation in the presence of Lindlar's catalyst to afford ethylene, which can be converted to a diol via a dihydroxylation process. Treatment of the diol with two equivalents of a strong base, such as NaH, gives a dianion. The dianion will react with two equivalents of methyl iodide giving the product (via a Williamson ether synthesis, twice).



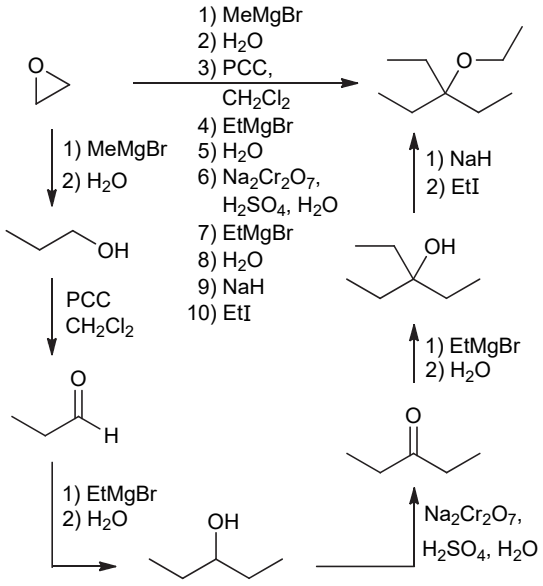
13.50. There are certainly many acceptable methods for achieving the desired transformation. The following retrosynthetic analysis represents one such method. An explanation of each of the steps (*a-f*) follows.



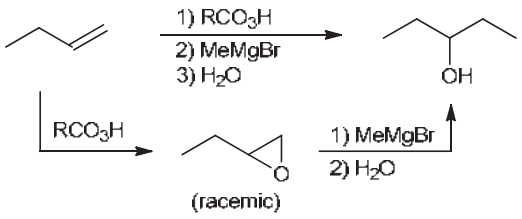
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a. The product can be made via a Williamson ether synthesis, by treating the alcohol shown with base followed by ethyl iodide.
b. The alcohol can be made by treating a ketone with a Grignard reagent.
c. The ketone can be made via oxidation of the corresponding secondary alcohol.
d. The secondary alcohol can be made by treating an aldehyde with a Grignard reagent.
e. The aldehyde can be made via oxidation of the primary corresponding primary alcohol.
f. The alcohol can be made by treating an epoxide with a Grignard reagent.

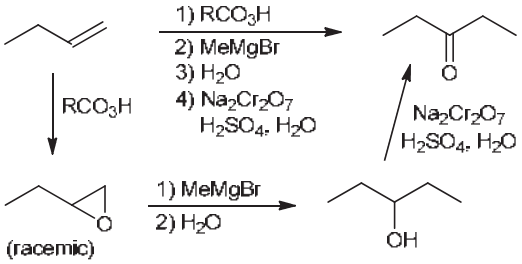
Now let's draw the forward scheme. The epoxide is opened with methyl magnesium bromide, followed by water work-up, to give 1-propanol. 1-Propanol is then oxidized to an aldehyde with PCC (or with DMP, or with a Swern oxidation). Treating the aldehyde with a Grignard reagent gives a secondary alcohol. Oxidation of the alcohol gives a ketone, which can be treated with ethyl magnesium bromide to give a tertiary alcohol. This alcohol is then deprotonated upon treatment with a strong base, such as NaH. The resulting anion then functions as a nucleophile in an S_N2 reaction with ethyl iodide to give the desired product.



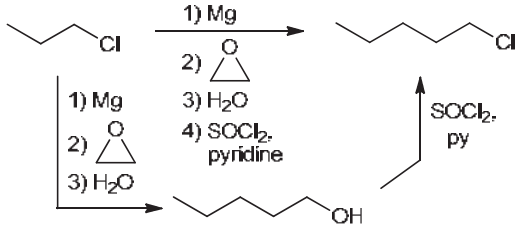
13.51.
(a) Treating the alkene with a peroxy acid gives an epoxide. This epoxide undergoes a ring-opening reaction when treated with methyl magnesium bromide (a strong nucleophile), to give an alkoxide ion which is protonated upon treatment with water to give the desired product.



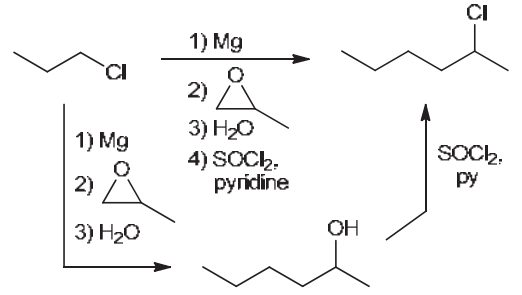
(b) The following synthesis builds on the synthesis in the previous solution (**13.51a**). The product of that synthesis is treated with an oxidizing agent, such as chromic acid, to give the desired ketone:



(c) Two carbon atoms are installed, with a functional group on the second carbon atom of the newly installed chain. This indicates a reaction involving a Grignard reagent and an epoxide. The starting alkyl halide is converted into a Grignard reagent, which is then treated with ethylene oxide, followed by water work-up. This installs the two carbon atoms, and simultaneously installs a functional group at the second carbon atom of the newly installed chain. This functional group (OH) is then converted into the desired functional group upon treatment with thionyl chloride and pyridine:

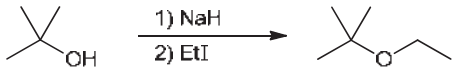


(d) The solution to this problem is a slight modification of the solution to the previous problem (**13.51c**). The only change is the structure of the starting epoxide:

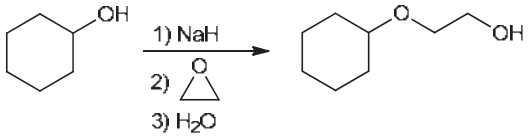


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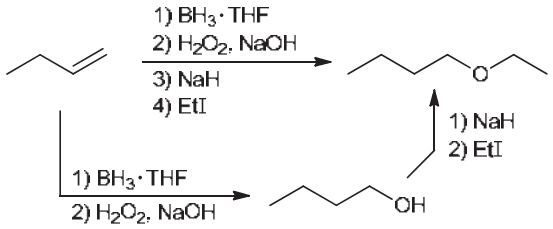
(e) The starting material is an alcohol and the product is an ether. This transformation can be achieved via a Williamson ether synthesis. The alcohol is first deprotonated with a strong base (such as NaH) to give an alkoxide ion, which is then treated with ethyl iodide to give an S_N2 reaction (with iodide serving as the leaving group):



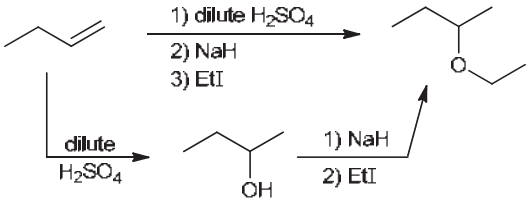
(f) Two carbon atoms are installed, with a functional group on the second carbon atom of the newly installed chain. This indicates a reaction involving an epoxide. The alcohol is first deprotonated with a strong base (such as NaH) to give an alkoxide ion, which is then treated with ethylene oxide to give a ring-opening reaction. The resulting alkoxide ion is protonated upon aqueous work-up to give the desired product:



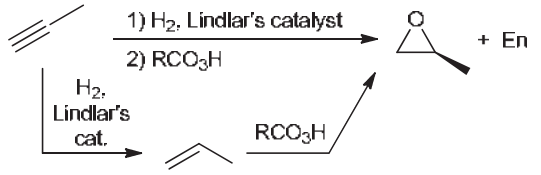
(g) The starting alkene will undergo hydroboration-oxidation (*anti*-Markovnikov addition of H and OH) to give the primary alcohol. A Williamson ether synthesis can then be used to convert the alcohol into the desired ether.



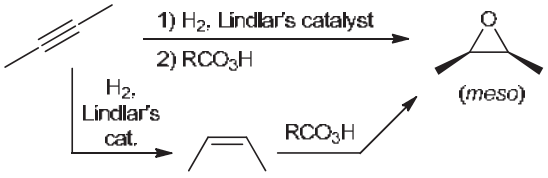
(h) The starting alkene will undergo acid-catalyzed hydration (Markovnikov addition of H and OH) to give the secondary alcohol. A Williamson ether synthesis can then be used to convert the alcohol into the desired ether.



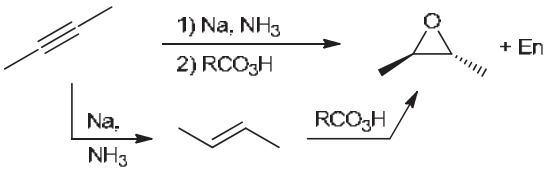
(i) Reduction of the alkyne in the presence of a poisoned catalyst affords an alkene, which is converted to the epoxide upon treatment with a peroxy acid.



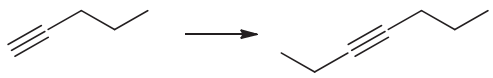
(j) Reduction of the alkyne in the presence of a poisoned catalyst affords a *cis*-alkene, which is converted to the desired epoxide upon treatment with a peroxy acid.



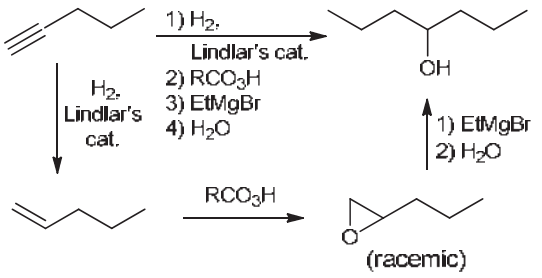
(k) Reduction of the alkyne via a dissolving metal reduction affords a *trans*-alkene, which is converted to the desired epoxide upon treatment with a peroxy acid.



(l) The starting material has five carbon atoms and the product has seven carbon atoms. There are several ways to install two carbon atoms, but we must carefully consider where we want the functional group to be in the product. For example, if we try to alkylate the alkyne, we will obtain an unsymmetrical internal alkyne.

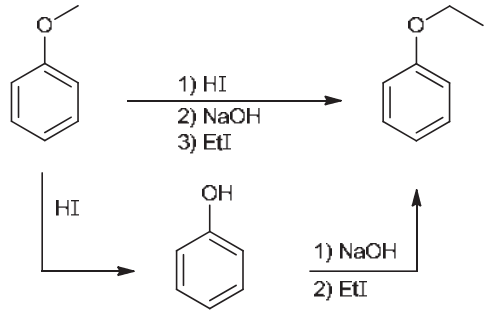


As such, we won't be able to control the regiochemical outcome of hydration of this internal alkyne (two products would be obtained, which is inefficient).
Instead, we can convert the alkyne into an epoxide, and then open the epoxide with a Grignard reagent. This strategy installs the two carbon atoms while simultaneously installing a functional group in the desired location.

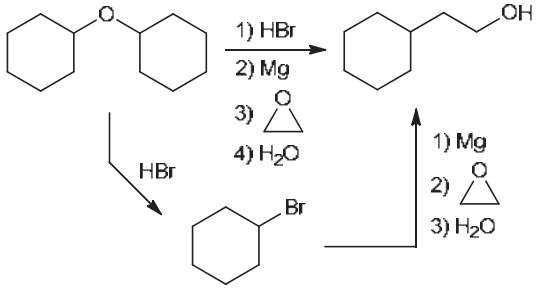


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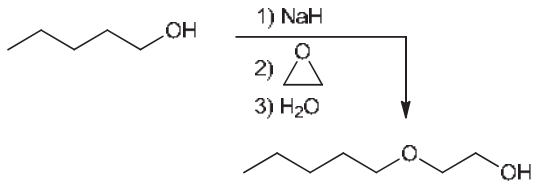
(m) We did not learn a way to alkylate an ether. However, we did learn a way to cleave a phenyl ether to give phenol. A Williamson ether synthesis can then be used to reinstall the alkyl group (this time an ethyl group, rather than a methyl group):



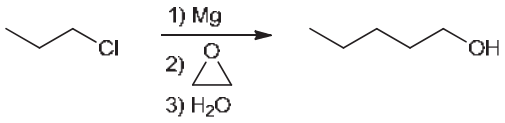
(n) The starting material is an ether, which will undergo cleavage when treated with HBr to give bromocyclohexane. Conversion of this alkyl halide into a Grignard reagent, followed by treatment with ethylene oxide (and aqueous work-up), gives the desired product.



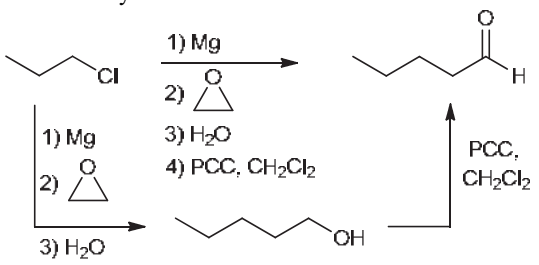
(o) Two carbon atoms are installed, with a functional group on the second carbon atom of the newly installed chain. This indicates a reaction involving an epoxide. The alcohol is first deprotonated with a strong base (such as NaH) to give an alkoxide ion, which is then treated with ethylene oxide to give a ring-opening reaction. The resulting alkoxide ion is protonated upon aqueous work-up to give the desired product:



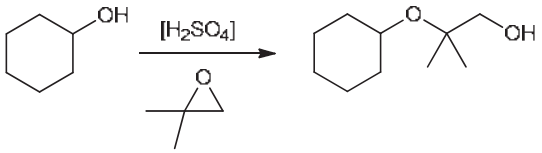
(p) Two carbon atoms are installed, with a functional group on the second carbon atom of the newly installed chain. This indicates a reaction involving an epoxide. The starting alkyl halide is converted into a Grignard reagent, which is then treated with ethylene oxide, followed by water work-up. This installs the two carbon atoms, and simultaneously installs the correct functional group in the correct location (at the second carbon atom of the newly installed chain):



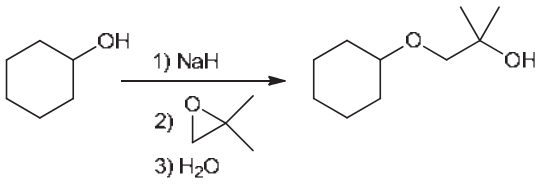
(q) Two carbon atoms are installed, with a functional group on the second carbon atom of the newly installed chain. This indicates a reaction involving an epoxide. The starting alkyl halide is converted into a Grignard reagent, which is then treated with ethylene oxide, followed by water work-up. This installs the two carbon atoms, and simultaneously installs a functional group in the correct location (at the second carbon atom of the newly installed chain). Oxidation of the primary alcohol with PCC (or DMP, or with a Swern oxidation) gives the desired aldehyde:



(r) This conversion can be achieved in one step, by treating the starting material with the epoxide shown, in the presence of acid catalysis. Under these conditions, the alcohol functions as a nucleophile and attacks a protonated epoxide to give a ring-opening reaction in which the nucleophile attacks the more substituted tertiary position (due to an electronic effect).

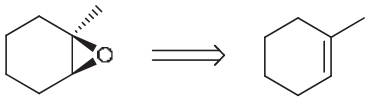


(s) This transformation is similar to the previous problem (**13.51r**), although in this case, the nucleophilic attack must occur at the less substituted position. This requires treating an epoxide with a strong nucleophile in basic conditions. The starting alcohol is first deprotonated with a strong base (such as NaH), and the resulting alkoxide ion is treated with the epoxide shown below. The resulting ring-opening reaction, followed by aqueous work-up, gives the desired product.

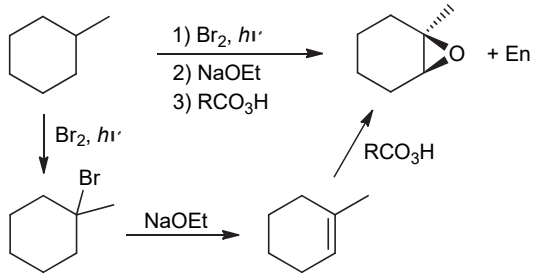


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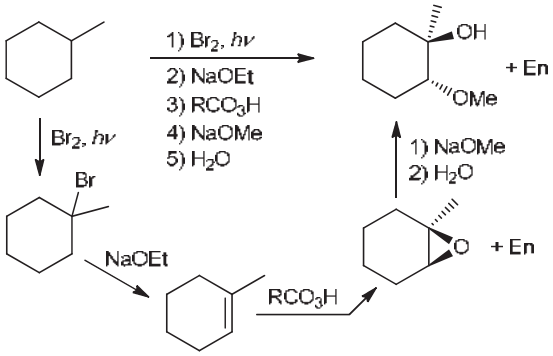
(t) The epoxide can be made from the following alkene, so we must find a way to make this alkene:



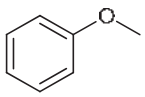
This alkene can be made from the starting alkane in two steps (radical bromination, followed by elimination), giving the following synthesis:



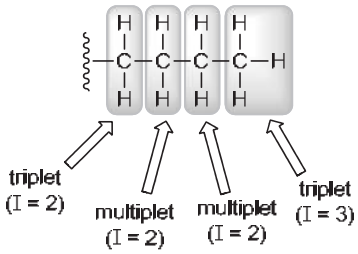
(u) The following synthesis builds on the synthesis in the previous solution (**13.51t**). The product of that synthesis is opened by a strong nucleophile (methoxide), which attacks the less substituted position. Aqueous work-up gives the desired product.



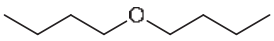
13.52. The molecular formula indicates that there are seven carbon atoms, but the spectrum has only five signals, indicating symmetry. With four degrees of unsaturation (see Section 14.16), we suspect an aromatic ring. There are four signals in the aromatic region of the spectrum, so we expect a monosubstituted ring, which explains the symmetry. The fifth signal appears above 50 ppm, indicating that it is next to an electronegative atom. We see in the molecular formula that there is an oxygen atom, so we propose the following structure, called methoxybenzene (also called anisole).



13.53. The ^{1}H NMR spectrum has four signals, and the total integration of those four signals is 2+2+2+3 = 9. However, the molecular formula indicates eighteen hydrogen atoms, so we expect a high degree of symmetry (one half of the molecule mirrors the other half). The compound has no degrees of unsaturation (see Section 14.16), so we expect an acyclic compound with no π bonds. The integration values of the signals in the proton NMR spectrum indicate the presence of three CH_2 groups and one CH_3 group, which appear to be connected to each other in a chain:



We therefore propose the following structure:

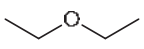


This structure is consistent with the carbon NMR spectrum as well. Notice that there are four different kinds of carbon atoms, thus giving rise to four signals. Only one of the four signals is above 50 ppm, indicating that it is next to an electronegative atom. This is consistent with the structure above.

13.54. The molecular formula indicates that there are four carbon atoms, but the carbon NMR spectrum has only two signals, indicating symmetry. With one degree of unsaturation (see Section 14.16), the structure must contain either a ring or a double bond. The following structure has a ring and would indeed produce only two signals in the carbon NMR spectrum (because of symmetry). The IR spectrum contains no signals in the diagnostic region (other than C-H signals just below 3000 cm^{-1}), which is consistent with the proposed structure.

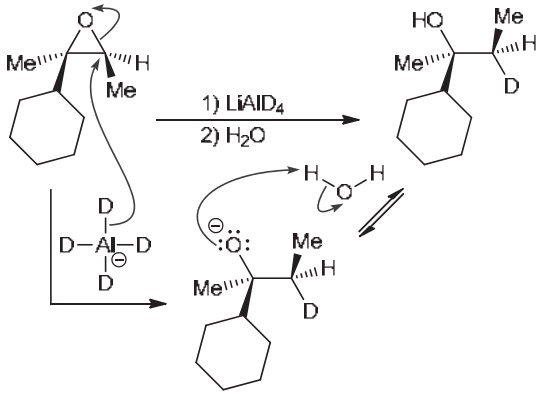


13.55. The spectrum has two signals, and the total integration of those two signals is 2+3 = 5. However, the molecular formula indicates ten hydrogen atoms, so we expect a high degree of symmetry (one half of the molecule mirrors the other half). The compound has no degrees of unsaturation (see Section 14.16), so we expect an acyclic compound with no π bonds. The signals in the spectrum are consistent with an ethyl group (a quartet with an integration of 2, and a triplet with an integration of 3). The molecular formula indicates the presence of an oxygen atom, so we propose the following structure in which the two ethyl groups mirror each other:

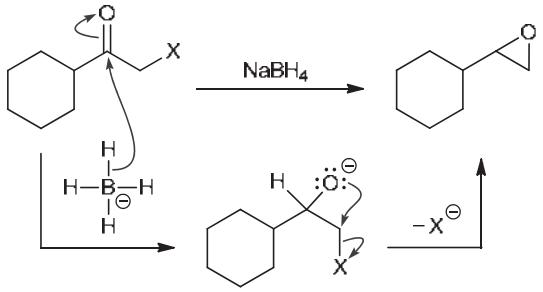


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13.56. $LiAlD_4$ is expected to function very much like $LiAlH_4$. That is, it is expected to be a delivery agent of D^- (rather than H^-), which attacks the less hindered position (secondary rather than tertiary), with inversion of configuration at that position. The resulting alkoxide ion is then protonated upon treatment with water, to give the product shown.

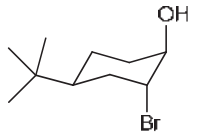


13.57. $NaBH_4$ is expected to serve as a delivery agent of H^-, which attacks the electrophilic carbonyl group (that carbon atom is electrophilic because of both resonance and induction). The resulting alkoxide ion can then undergo an intramolecular S_N2-type reaction, expelling a halide as a leaving group, and generating the epoxide, as shown:

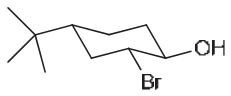


13.58 When methyloxirane is treated with HBr, the regiochemical outcome is determined by a competition between steric and electronic factors, with steric factors prevailing – bromide attacks the less substituted position. However, when phenyloxirane is treated with HBr, electronic factors prevail in controlling the regiochemical outcome. Specifically, the position next to the phenyl group is a benzylic position and can stabilize a large partial positive charge. In such a case, electronic factors are more powerful than steric factors, and bromide attacks the more substituted position.

13.59. This process for epoxide formation involves deprotonation of the hydroxyl group, followed by an intramolecular S_N2-type attack. Recall that S_N2 processes occur via back-side attack, which can only be achieved when both the hydroxyl group and the bromine occupy axial positions on the ring. Due to the steric bulk of a *tert*-butyl group, compound **A** spends most of its time in a chair conformation that has the *tert*-butyl group in an equatorial position. In this conformation, the OH and Br are indeed in axial positions, so the reaction can occur quite rapidly. In contrast, compound **B** spends most of its time in a chair conformation in which the OH and Br occupy equatorial positions. The S_N2 process cannot occur from this conformation.



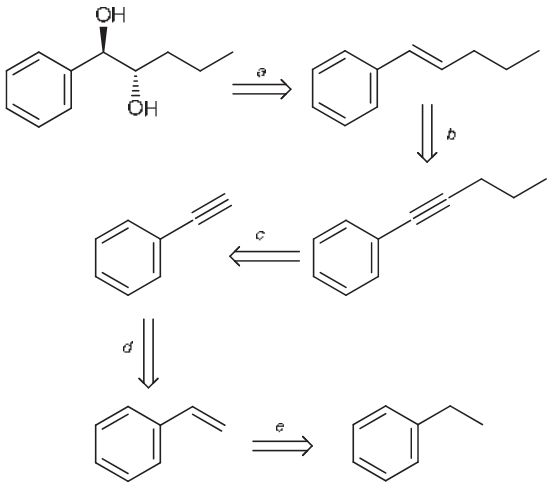
Most stable conformation of compound **A**



Most stable conformation of compound **B**

When compound **A** is treated with NaOH, the hydroxyl group in compound **A** is deprotonated, giving an alkoxide ion which can serve as a nucleophile in an intramolecular S_N2-type attack that gives an epoxide.

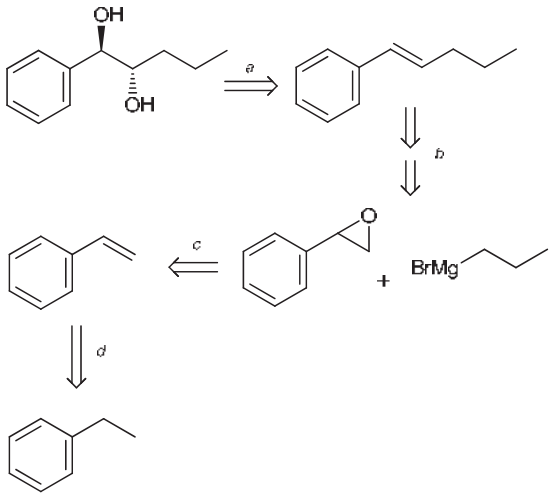
13.60. There are certainly many acceptable methods for achieving the desired transformation. The following retrosynthetic analysis represents one such method. An explanation of each of the steps (*a*-*e*) follows.



a. The diol can be made from the *trans* alkene, by converting the alkene into an epoxide and then opening under aqueous acidic conditions (or under basic conditions).
b. The alkene can be made from the corresponding alkyne via a dissolving metal reduction.
c. The alkyne can be made via alkylation of a terminal alkyne.
d. The terminal alkyne can be made from the corresponding alkene via bromination followed by elimination with $NaNH_2$.
e. The alkene can be made from the alkane via bromination, followed by elimination with a strong base, such as NaOEt.

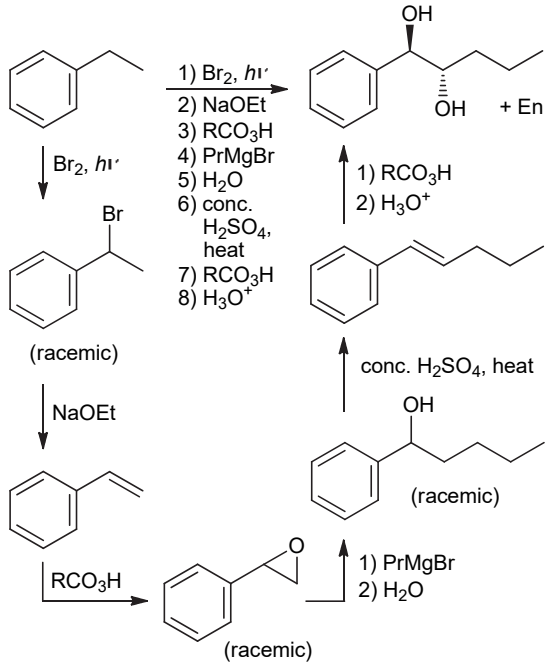
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Here is an alternative strategy. An explanation of each of the steps (*a*-*d*) follows.:

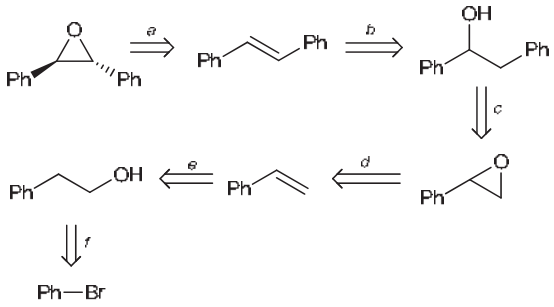


a. The diol can be made from the *trans* alkene, by converting the alkene into an epoxide and then opening under aqueous acidic conditions (or under basic conditions).
b. The alkene can be made from the corresponding alcohol, which can be made from the corresponding epoxide via a Grignard reaction.
c. The epoxide can be made from the corresponding alkene (called styrene)
d. The alkene can be made from the alkane via bromination, followed by elimination with a strong base, such as NaOEt.

The forward synthetic scheme for the second pathway is illustrated here:

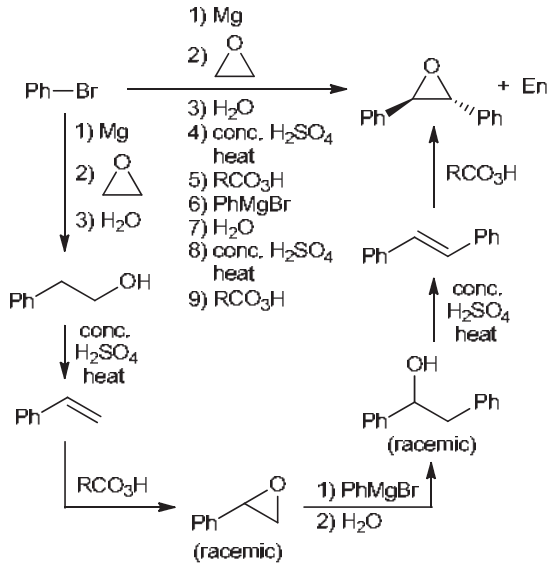


13.61. There are certainly many acceptable methods for achieving the desired transformation. The following retrosynthetic analysis represents one such method. An explanation of each of the steps (*a*-*e*) follows.



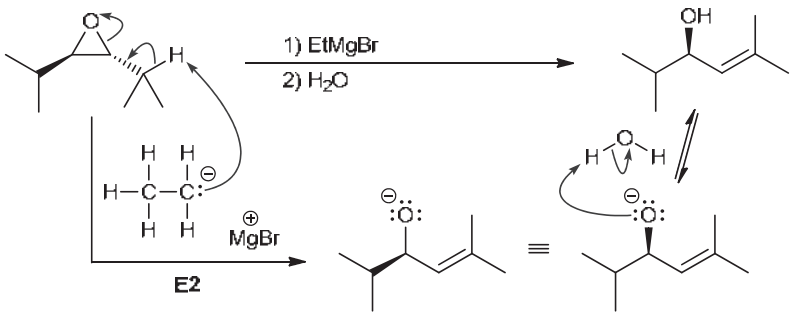
a. The epoxide can be made from the corresponding *trans* alkene.
b. The *trans* alkene can be made from the corresponding alcohol via a dehydration reaction (upon treatment with concentrated sulfuric acid).
c. The alcohol can be made from the reaction between a Grignard reagent (PhMgBr) and an epoxide, thereby installing a phenyl group.
d. The epoxide can be made from the corresponding alkene upon treatment with a peroxy acid.
e. The alkene can be made from the corresponding primary alcohol.
f. The primary alcohol can be made via Grignard reaction involving an epoxide.

The forward synthetic scheme is illustrated here:

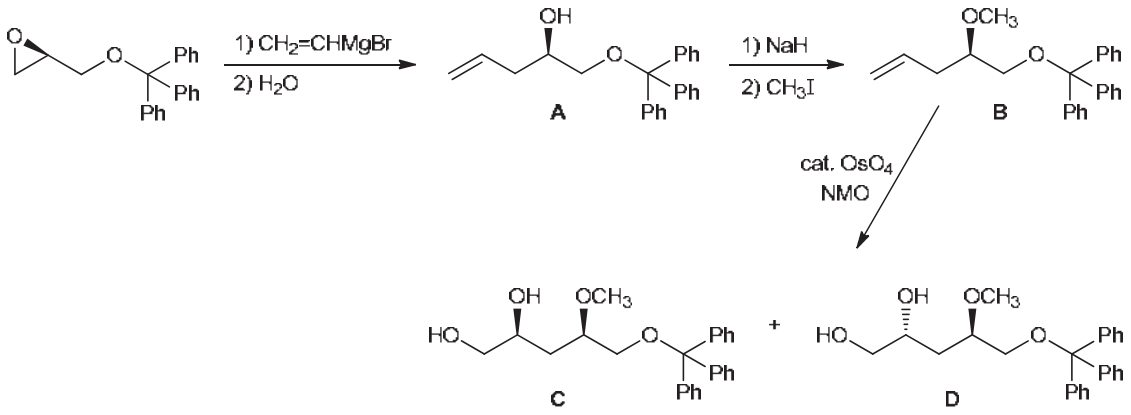


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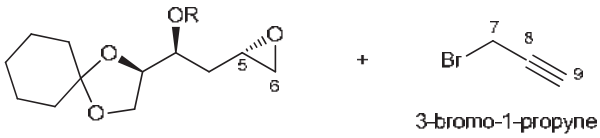
13.62. Since the Grignard reagent is both a strong base and a strong nucleophile, substitution and elimination can both occur. Indeed, they compete with each other. As we discussed in Chapter 7, elimination will be favored when the substrate is secondary. Both electrophilic positions in this epoxide are secondary, and so, elimination predominates:



13.63. In the first step, vinylmagnesium bromide is a powerful nucleophile and can attack the epoxide in a ring-opening reaction (attacking the less substituted carbon) to afford an alcohol. This alcohol is subsequently converted to an ether via a Williamson ether synthesis. Dihydroxylation of the terminal alkene with catalytic OsO_4 in the presence of NMO gives a mixture of diastereomeric diols.

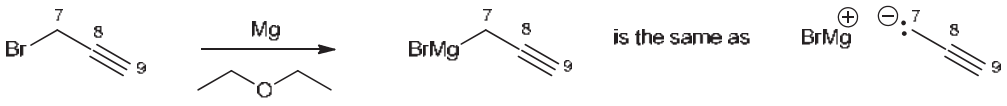


13.64. A new carbon-carbon bond must be made between C6 and C7:

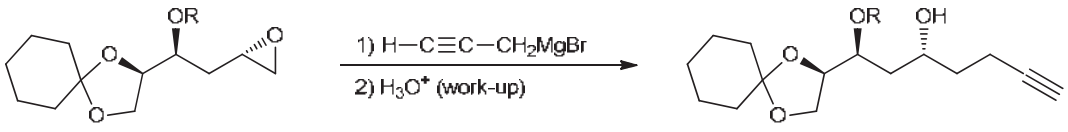


Epoxides are electrophilic functional groups and are subject to attack by a nucleophile. In order for the OH group to be ultimately positioned at C5, the nucleophile must attack the less substituted side of the epoxide (C6), which requires basic conditions (rather than acidic conditions, which often favors attack at the more substituted carbon).

The nucleophile for this reaction must be made from 3-bromo-1-propyne, which can be achieved by treatment with magnesium, thereby forming the Grignard reagent:

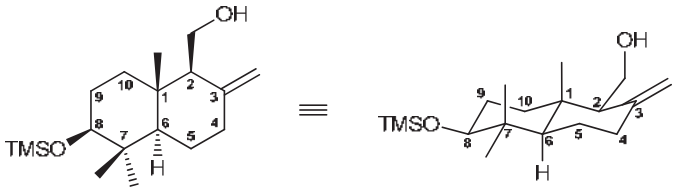


The desired transformation can therefore be achieved in the following way:



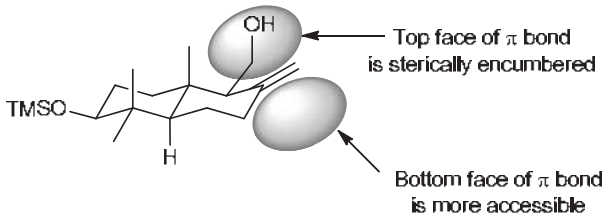
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13.65. Let's begin by drawing the *trans*-decalin system in a way that illustrates the chair conformation of each six-membered ring (as instructed by the problem statement). Assigning locants can be helpful in this situation, since they make it easier to place all of the substituents in the correct locations and in the correct configurations:

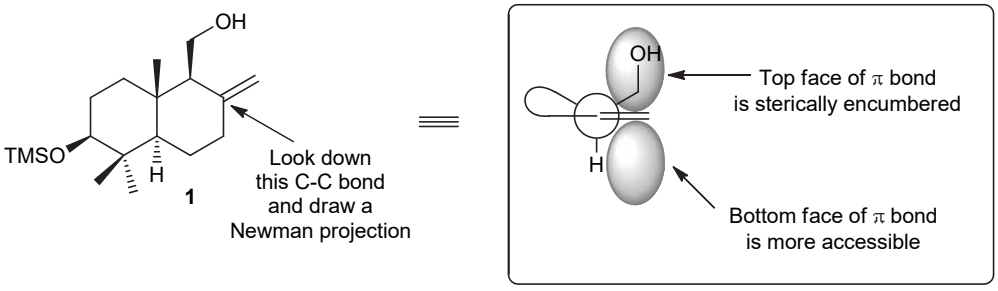


The *trans*-decalin structure imposes structural rigidity and limits the conformational freedom available to the compound.

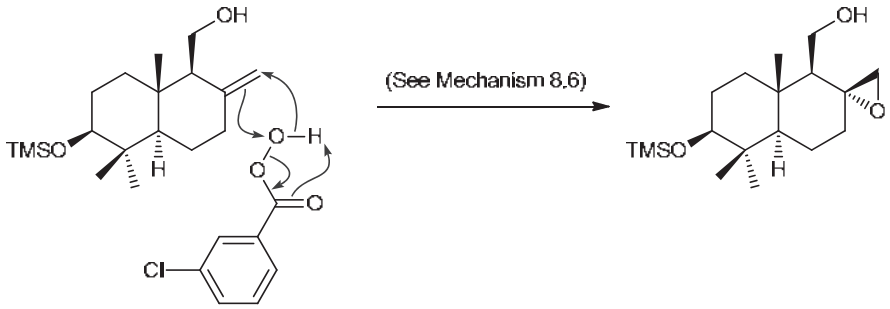
Now let's consider the two faces of the π bond (the top face and the bottom face):



These two faces of the π bond are not equally accessible. That is, the compound is confined to a conformation in which one face of the π bond is more sterically encumbered than the other. This steric consideration is difficult to see in the drawing above, and can be visualized more clearly if we draw a Newman projection, looking down the C2-C3 bond.

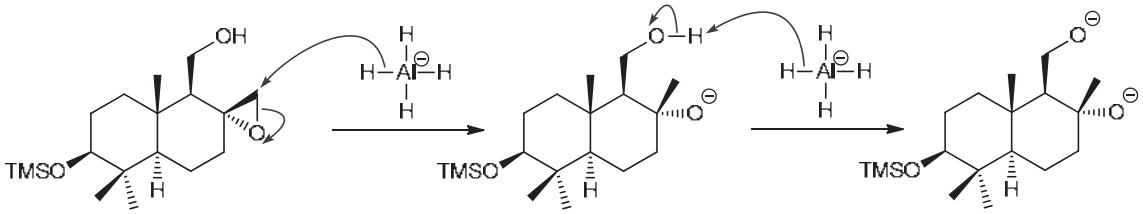


Since the bottom face of the π bond is more accessible, the epoxidation process will occur on that face, giving the following epoxide:

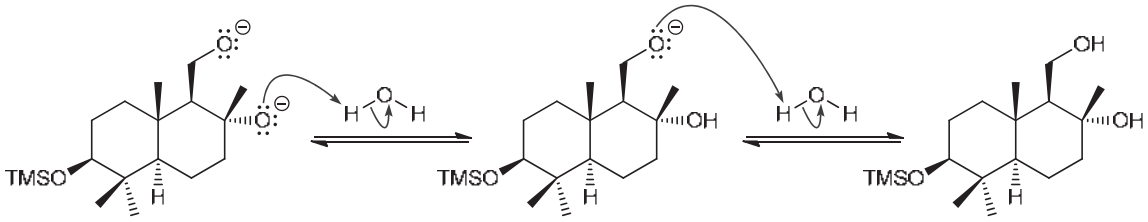


This epoxide is then opened with $LiAlH_4$, and under these conditions, it is likely that the primary OH group will be deprotonated, giving a dianion:

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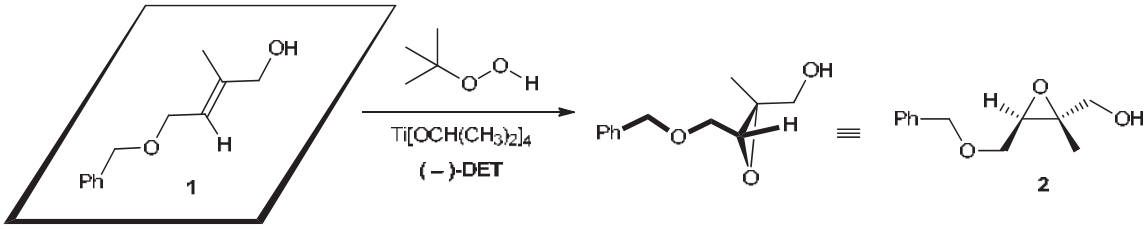


This dianion is then protonated upon aqueous work-up to give the following diol:



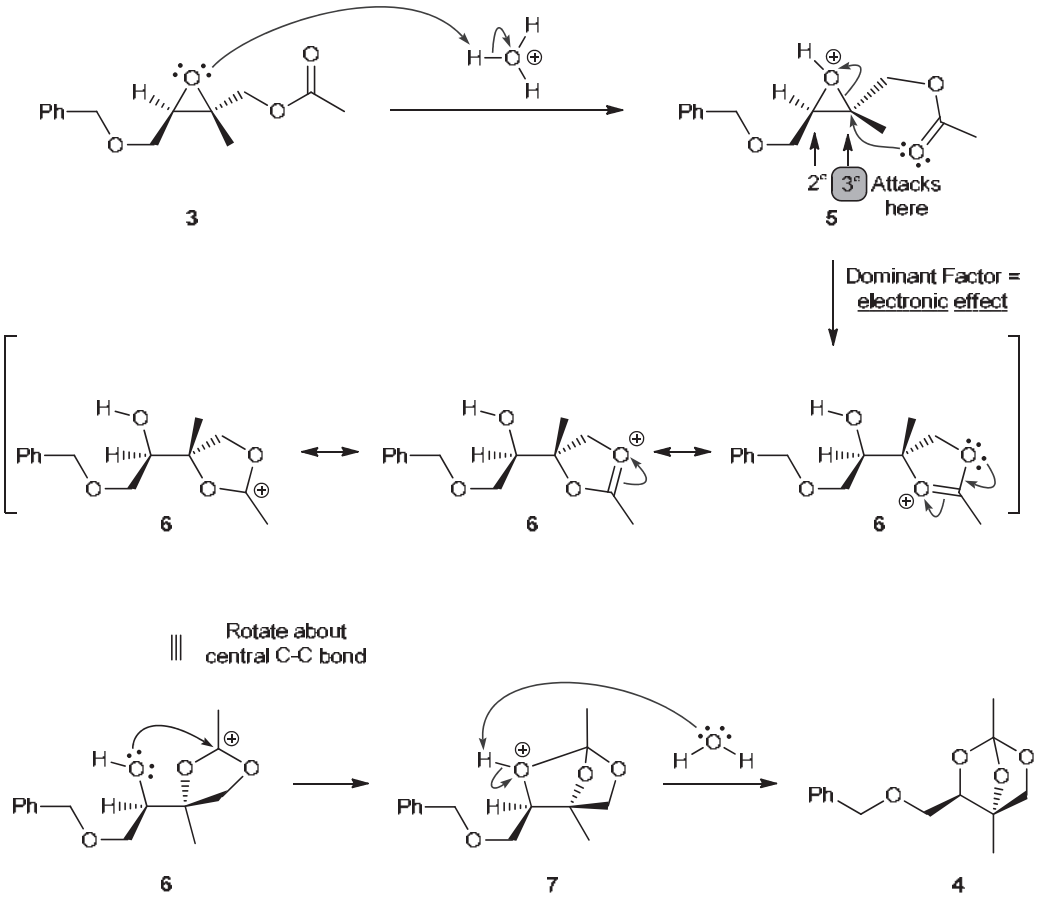
13.66.

(a) Epoxide **2** can be generated from allylic alcohol **1** via a Sharpless asymmetric epoxidation. The reagents for this reaction are: *tert*-butyl hydroperoxide, titanium tetraisopropoxide, and one enantiomer of diethyl tartrate (DET), depending on which epoxide enantiomer is required. In Figure 13.3, we saw a predictive tool for determining which enantiomer of DET would be required to afford epoxide **2**. Allylic alcohol **1** is orientated so that the allylic hydroxyl group appears in the upper right corner, and then we can see that (–)-DET is required in order for the epoxide ring to be formed on the bottom face of the molecule, corresponding to compound **2**.



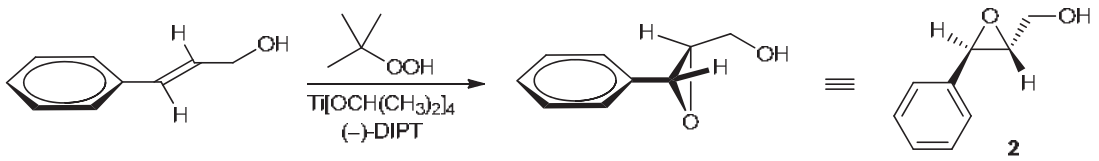
(b) In the first step, the epoxide group in compound **3** is protonated to form intermediate **5**. Notice that the epoxide is unsymmetrical; on the left side, the epoxide carbon is secondary, and on the right side, it is tertiary. Under acidic conditions, and when the epoxide has a tertiary carbon, the dominant effect is electronic (more important than steric considerations), and a nucleophile will attack at this site (Section 13.10). In this example, the nucleophile that opens the epoxide is the oxygen atom of the pendant ester group, generating a resonance-stabilized intermediate (**6**) which exhibits a 5-membered ring. At this stage, the alcohol on the 2° carbon, which was generated from the epoxide opening, can attack to generate intermediate **7**. And finally, deprotonation of **7** generates compound **4**.

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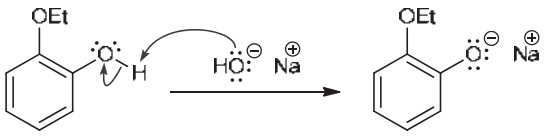


13.67.

(a) The conversion of **1** to **2** utilizes a Sharpless asymmetric epoxidation, so the product is expected to be an epoxide. The stereochemical outcome can be deduced by applying the paradigm provided in Figure 13.3. Since the chiral catalyst was formed using (–)-DIPT, which affords the same stereochemical outcome as (–)-DET, we can conclude that the epoxide forms "below the plane" of the alkene:

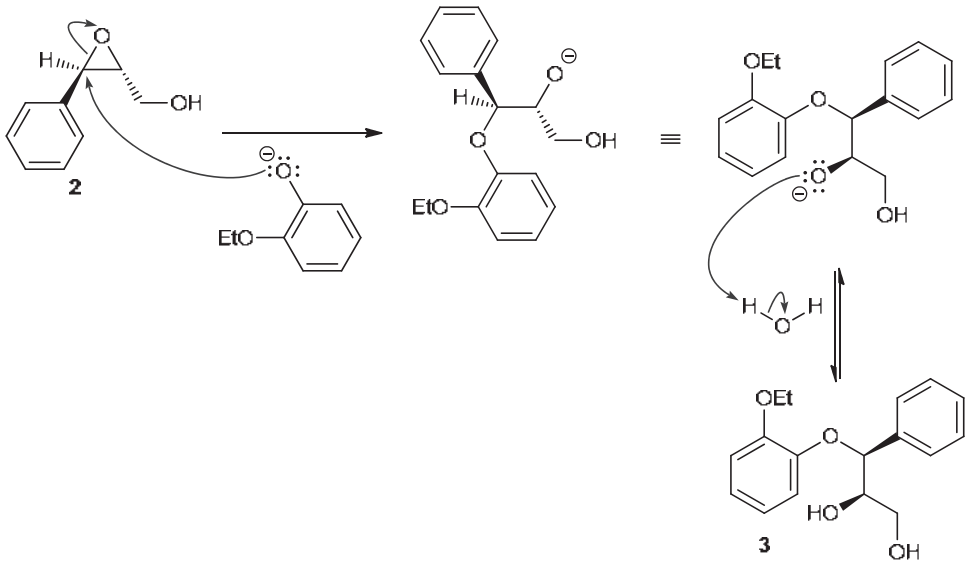


(b) First consider the reagents. Sodium hydroxide will deprotonate 2-ethoxyphenol to give a phenolate ion.

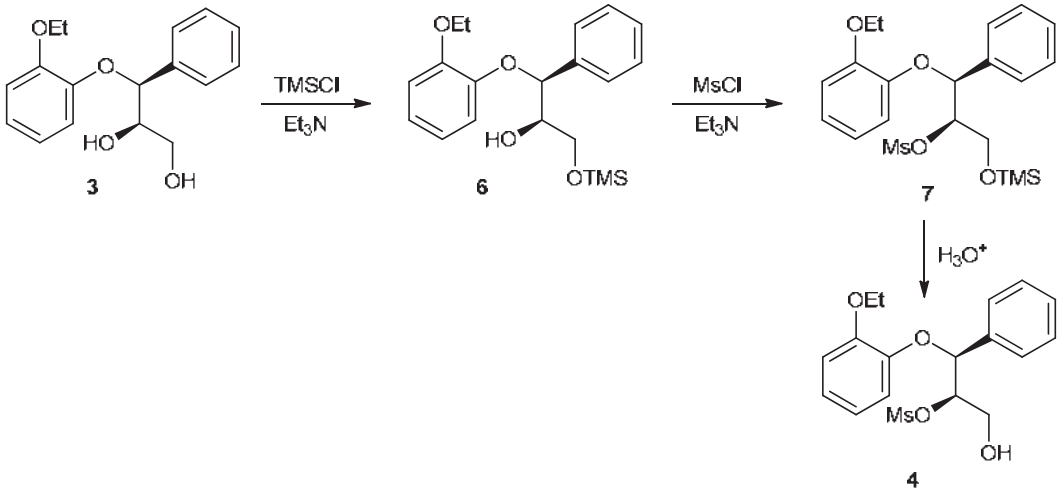


The phenolate ion can serve as a nucleophile and attack epoxide **2** in a ring-opening reaction. Nucleophilic attack occurs at the benzylic position (the carbon atom attached to the benzene ring) to form an alkoxide intermediate, that is protonated to give diol **3**.

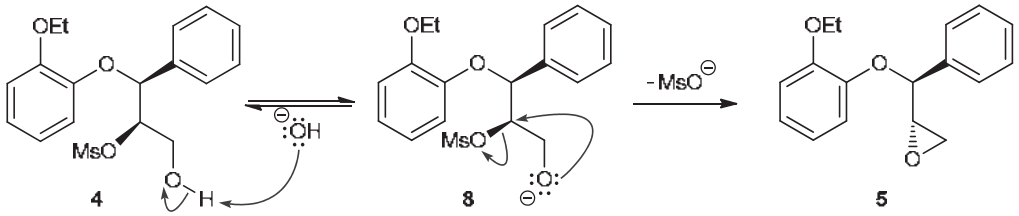
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(c) Treatment of **3** with TMSCl in Et_3N results in the selective protection of the less sterically hindered primary alcohol (rather than the secondary alcohol) to give **6**. The secondary OH group of **6** is then converted to the mesylate with MsCl, thereby converting it into a good leaving group, as seen in compound **7**. Subjecting **7** to aqueous acid results in the removal of the silyl protecting group to form **4** in which the primary alcohol group is revealed. The net result of these three reactions is the selective mesylation of the secondary OH group.



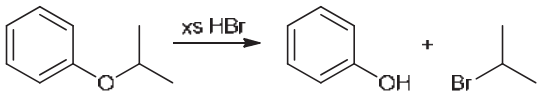
(d) Treatment of **4** with aqueous NaOH results in deprotonation of the primary alcohol to give alkoxide **8**, a strong nucleophile. This facilitates an intramolecular ring-forming reaction, with inversion of configuration at the carbon atom bearing the mesylate leaving group, to give compound **5**.



13.68 The desired product is an ether (ROR) in which one R group is a phenyl group and the other R group is a tertiary alkyl group. A Williamson ether synthesis requires the use of an alkoxide ion and an alkyl halide, but the alkyl halide cannot be a tertiary alkyl halide or a phenyl halide. Therefore, this compound cannot be made via a Williamson ether synthesis, so options (a), (c), and (d) are not viable. The correct answer is option (b), which is an alkoxymercuration-demercuration. This process adds H and OPh across the alkene in a Markovnikov fashion, giving the desired product.

13.69 Acidic options are employed, so none of the intermediates should contain alkoxide ions, which are strong bases and therefore inconsistent with acidic conditions. So options (b) and (c) are not correct. Option (a) is a primary carbocation, which is too high in energy to form. The correct answer is (d). This is an example of an acid-catalyzed ring-opening reaction, with ethanol functioning as the nucleophile that opens the ring. In the first step of the mechanism, the epoxide is protonated, just as we would expect under acidic conditions. Then, this protonated epoxide is attacked by ethanol, opening the ring, and giving the intermediate shown in option (d). This intermediate is then deprotonated by ethanol to give the product.

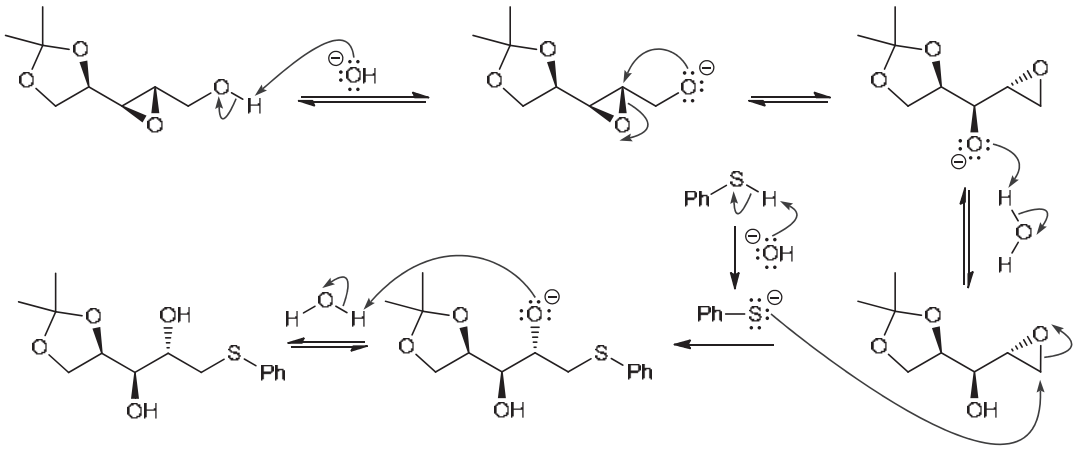
13.70 The starting material is an alkyl phenyl ether. The alkyl group is expected to be cleaved under these acidic conditions, giving an alkyl bromide, but the phenyl group (sp^2) is not cleaved:



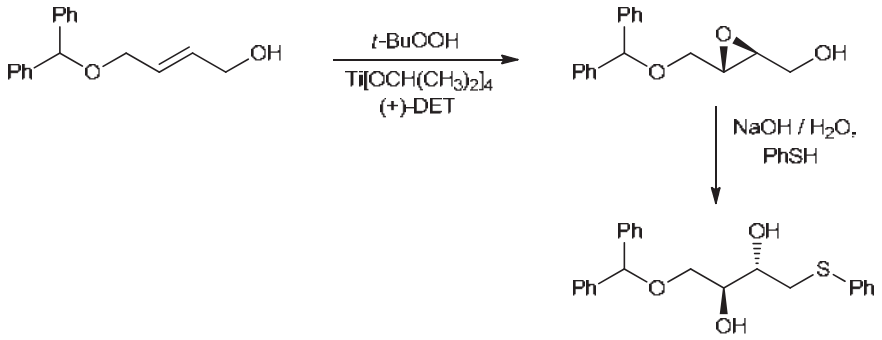
The correct answer is (a).

13.71.

(a) As described in the problem statement, the hydroxyl group is first deprotonated to give an alkoxide ion, which functions as a nucleophile and participates in an intramolecular S_N2-type process in which the epoxide is opened and a new epoxide is formed (notice that back-side attack places the oxygen atom of the new epoxide on a dash). After protonation of the resulting alkoxide, the epoxide group can then be opened with a thiophenolate ion (PhS^-) to give another alkoxide, which is then protonated to give the observed product.

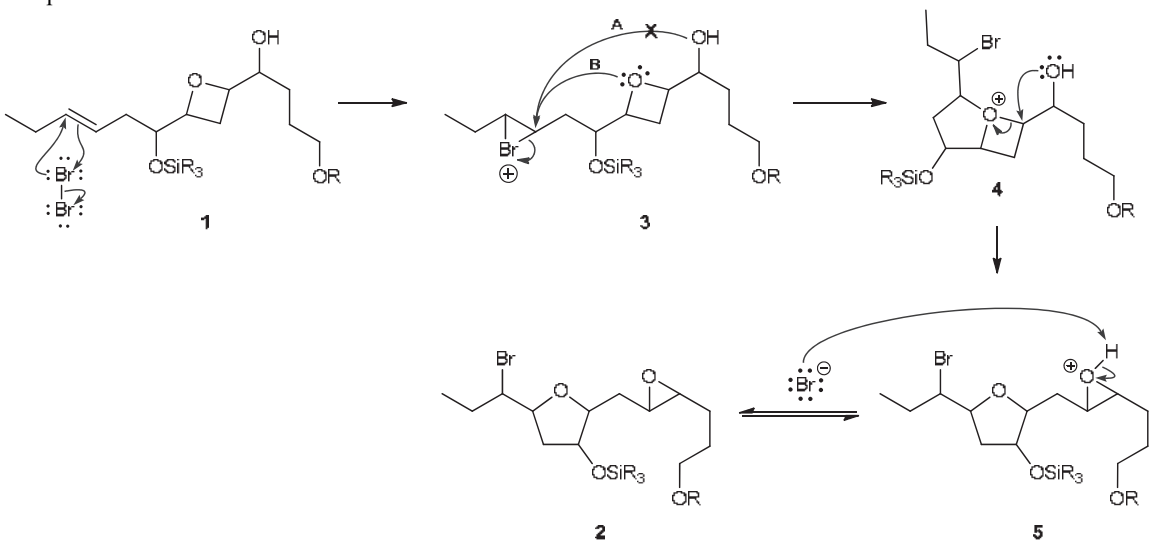


(b) The allylic alcohol undergoes a Sharpless asymmetric epoxidation to give the following epoxide, which then undergoes the reaction explored in part (a).



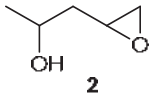
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13.72. When compound **1** is treated with an electrophilic source of bromine, the alkene will readily react to form bromonium ion **3**. At this stage there are two possibilities for further reactivity. Typically, with an OH group present in the compound, the OH group can function as a nucleophile and attack the bromonium ion to form an ether. For example, consider path A. If this were to occur, an 8-or 9-membered ring would be formed, depending on which side of the bromonium ion is attacked by the alcohol. However, since we do not see the formation of a medium-sized ring in the product, a different reaction pathway must be occurring. Consider the lone pairs on the oxygen atom which is part of the 4-membered cyclic ether. If one of these lone pairs were to attack the bromonium ion (path B), the result would be a 5-membered ring fused to the 4-membered ring (compound **4**). However, this intermediate is not stable – the ring oxygen has 3 bonds and is positively charged. At this stage, if the free OH group reacts in an S_N2 fashion to open the 4-membered ring, followed by the loss of a proton, the product formed will have both the 5-membered cyclic ether and the epoxide:

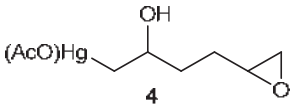


13.73.

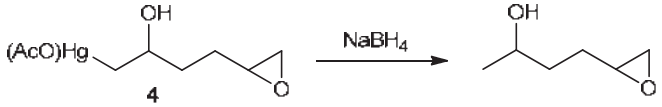
(a) Oxymercuration-demercuration of an alkene affords an alcohol, via a Markovnikov addition. As such, we expect that compound **2** is the following hydration product:



(b) Oxymercuration of compound **3** results in the addition of OH and HgOAc across the π bond, with the OH group being positioned at the more substituted position. Thus, compound **4** is the initial product of oxymercuration:

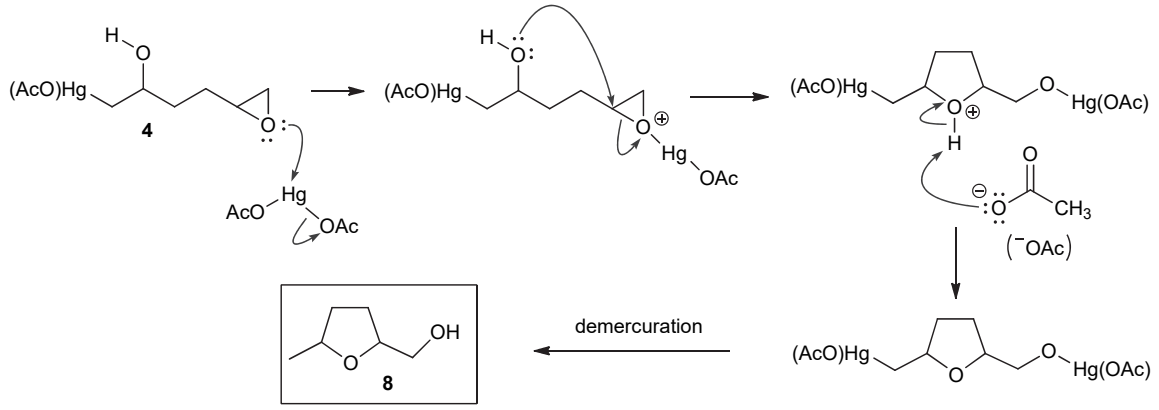


This intermediate can theoretically be converted into the Markovnikov hydration product via demercuration.

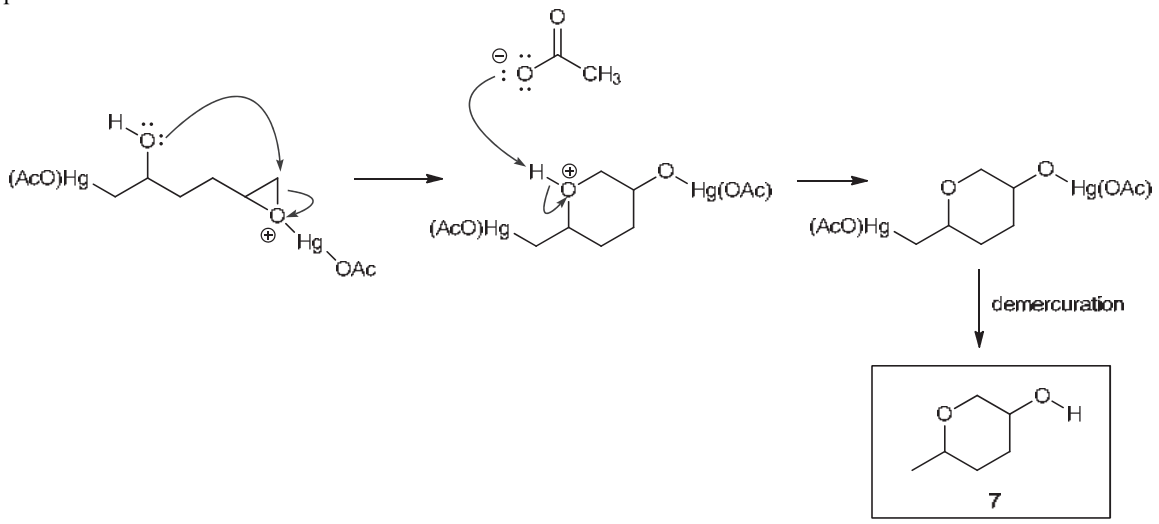


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However, before $NaBH_4$ is introduced, **4** can also continue to react under the oxymercuration conditions, where $Hg(OAc)_2$ can behave as a Lewis acid. As shown, the $Hg(OAc)_2$ can interact with the oxygen atom of the epoxide group, much like an epoxide interacts with a proton, to facilitate the intramolecular nucleophilic attack by the nearby hydroxyl group. This intramolecular cyclization reaction forms a five-membered ring. A final proton transfer step, followed by the demercuration step, results in one of the major cyclization products, **8**.



The other cyclization product, **7**, is a result of an alternative cyclization reaction in which a six-membered ring is the product:

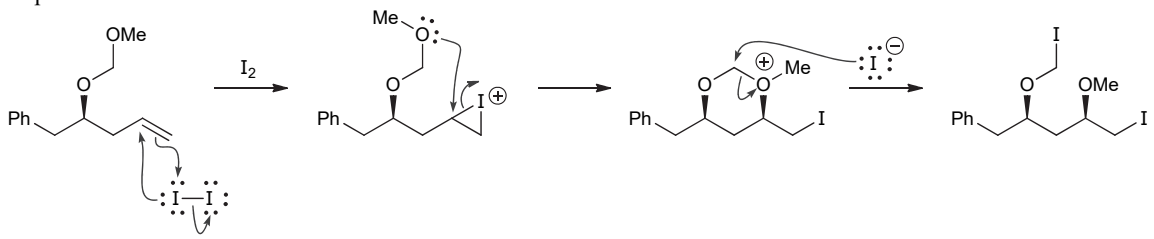


(c) Oxymercuration-demercuration of **1** can only result in a cyclic product if a four-membered ring is formed. Four-membered rings exhibit significant ring strain so their formation is slow under these conditions.

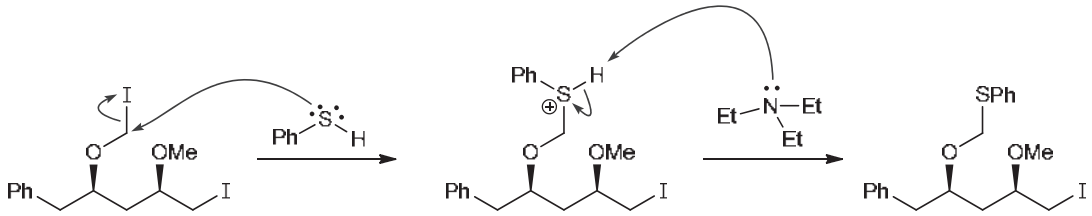
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13.74. In the first step, iodine (the electrophile) adds to the terminal alkene to form an iodonium ion. Once formed, intramolecular attack of this intermediate by the pendant methoxy group occurs, resulting in the formation of a 6-membered ring. This intermediate, however, is not stable and is quickly trapped by the iodide ion, resulting in ring opening to form a stable product. In the second step, phenylsulfide displaces the iodide in an S_N2 fashion, followed by deprotonation of the resulting intermediate using triethylamine as a base.

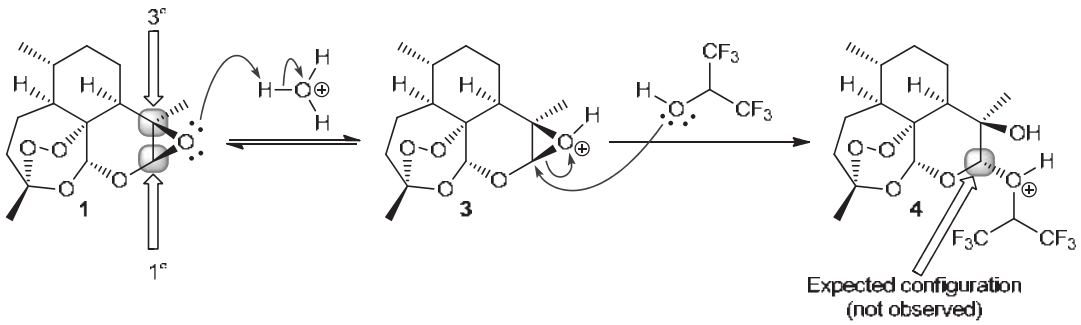
Step 1



Step 2

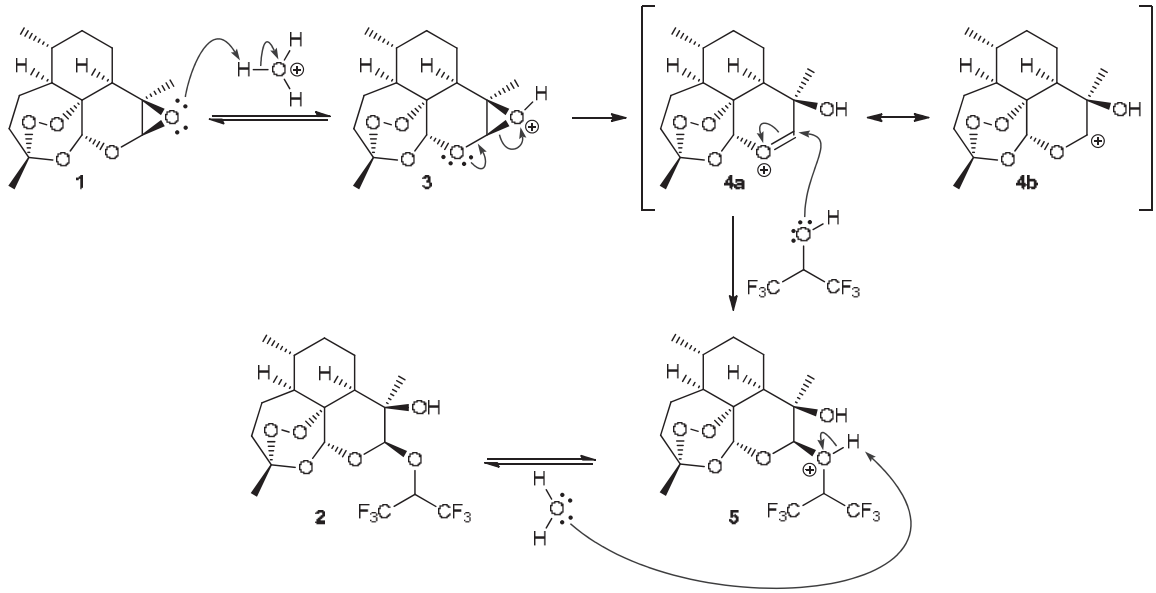


13.75. The epoxide in compound **2** has a tertiary carbon on the top side, and a primary carbon on the bottom side. Under acidic conditions, we saw that electronic effects override steric effects when there is a tertiary carbon on one side of the epoxide. If this line of reasoning were to govern product formation in this example, the alcohol should have attacked the top carbon. However, we know from looking at the structure of compound **2** that the alcohol must have attacked the primary carbon. Also of note is the stereochemistry at the ring opening site. After epoxide **1** is protonated, hexafluoro-2-propanol is expected to approach intermediate **3** from the bottom face of the molecule, resulting in compound **4**. Again, this is not what we observe.



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As it turns out, when the epoxide is protonated, the neighboring oxygen atom is able to open the epoxide ring intramolecularly, resulting in a resonance-stabilized cation (**4a** and **4b**). This oxonium ion can then be trapped by hexafluoro-2-propanol, which approaches from the top face of the molecule (the bottom face is blocked by the nearby methyl group, and peroxide bridge), producing compound **5**. Finally, loss of a proton forms alcohol **2**.



Notice that this example does not violate the principles underlying electronic trends. Specifically, when there is an oxygen atom attached directly to one side of the epoxide, under acidic conditions, ring opening can occur at this site, *because it results in a more stable (resonance-stabilized) cation.*

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Chapter 14
Infrared Spectroscopy and Mass Spectrometry

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 14. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- **Spectroscopy** is the study of the interaction between _____ and _____.
- The difference in energy (ΔE) between vibrational energy levels is determined by the nature of the bond. If a photon of light possesses exactly this amount of energy, the bond can absorb the photon to promote a **_____ excitation**.
- IR spectroscopy can be used to identify which _____ are present in a compound.
- The location of each signal in an IR spectrum is reported in terms of a frequency-related unit called _____.
- The wavenumber of each signal is determined primarily by bond _____ and the _____ of the atoms sharing the bond.
- The intensity of a signal is dependent on the _____ of the bond giving rise to the signal.
- _____ C=C bonds do not produce signals.
- Primary amines exhibit two signals resulting from **_____ stretching** and **_____ stretching**.
- **Mass spectrometry** is used to determine the _____ and _____ of a compound.
- **Electron impact ionization** (**EI**) involves bombarding the compound with high energy _____, generating a radical cation that is symbolized by $(M)^{+\bullet}$ and is called the **molecular ion**, or the **_____ ion**.
- Only the molecular ion and the cationic fragments are deflected, and they are then separated by their _____ (*m/z*).
- The tallest peak in a mass spectrum is assigned a relative value of 100% and is called the **_____ peak**.
- The relative heights of the $(M)^{+\bullet}$ peak and the $(M+1)^{+\bullet}$ peak indicates the number of _____.
- A signal at M–15 indicates the loss of a _____ group; a signal at M–29 indicates the loss of an _____ group.
- **_____** alkanes have a molecular formula of the form C_nH_{2n+2}.
- Each double bond and each ring represents one **degree of _____**.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 14. The answers appear in the section entitled *SkillBuilder Review*.

14.1 Analyzing an IR Spectrum

STEP 1 *- LOOK FOR _____ BONDS BETWEEN 1600 AND 1850 cm^{-1}* ***GUIDELINES:*** *C=O BONDS PRODUCE _____ SIGNALS* *C=C BONDS GENERALLY PRODUCE _____ SIGNALS. SYMMETRICAL C=C BONDS DO NOT APPEAR AT ALL*	***STEP 2*** *- LOOK FOR _____ BONDS BETWEEN 2100 AND 2300 cm^{-1}* ***GUIDELINES:*** *_____ TRIPLE BONDS DO NOT PRODUCE SIGNALS*	***STEP 3*** *- LOOK FOR _____ BONDS BETWEEN 2750 AND 4000 cm^{-1}* ***GUIDELINES:*** *DRAW A LINE AT 3000 cm^{-1}, AND LOOK FOR _____ OR _____ C-H BONDS TO THE LEFT OF THE LINE* *THE SHAPE OF AN O-H SIGNAL IS AFFECTED BY _____ (DUE TO H-BONDING)* *PRIMARY AMINES EXHIBIT TWO N-H SIGNALS (_____ AND _____ STRETCHING)*

14.2 Distinguishing Between Two Compounds Using IR Spectroscopy

STEP 1 - WORK METHODICALLY THROUGH THE EXPECTED _____ OF EACH COMPOUND	**STEP 2** - DETERMINE IF ANY _____ WILL BE PRESENT FOR ONE COMPOUND BUT ABSENT FOR THE OTHER	**STEP 3** - FOR EACH EXPECTED SIGNAL, COMPARE FOR ANY POSSIBLE DIFFERENCES IN _____, _____, OR _____.

14.3 Using the Relative Abundance of the $(M+1)^{+\bullet}$ Peak to Propose a Molecular Formula

STEP 1 - FILL IN THE BOXES BELOW TO COMPLETE THE FORMULA THAT CAN BE USED TO DETERMINE THE NUMBER OF CARBON ATOMS IN A COMPOUND USING MASS SPECTROMETRY: $\left(\frac{\text{Abundance of } \square \text{ peak}}{\text{Abundance of } \square \text{ peak}}\right) \times 100\% \Big/ 1.1\,\%$	**STEP 2** - ANALYZE THE MASS OF THE MOLECULAR ION TO DETERMINE IF ANY _____ ARE PRESENT.

14.4 Calculating HDI

STEP 1 - REWRITE THE MOLECULAR FORMULA "AS IF" THE COMPOUND HAD NO ELEMENTS OTHER THAN C AND H. USING THE FOLLOWING RULES: - ADD ONE H FOR EACH _____ - IGNORE ALL _____ ATOMS - SUBTRACT ONE H FOR EACH _____	**STEP 2** - DETERMINE WHETHER ANY H'S ARE MISSING. EVERY TWO H'S REPRESENT ONE DEGREE OF UNSATURATION: C_xH_yCl ⟶ HDI = _____ C_xH_yO ⟶ HDI = _____ C_xH_yN ⟶ HDI = _____

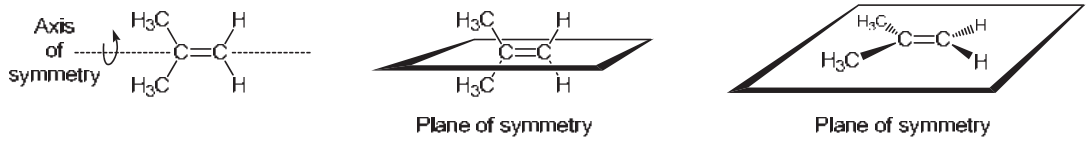
Mistakes to Avoid

We have seen that the IR spectrum of an alkene will exhibit a signal near 1650 cm^{-1} (the characteristic signal for a C=C bond) if there is a dipole moment associated with the C=C bond. In such a case, the dipole moment changes as the C=C bond vibrates, creating an oscillating electric field that serves as an antenna to absorb the appropriate frequency of IR radiation. If the C=C bond does not have a dipole moment, then it cannot efficiently absorb IR radiation, and the signal near 1650 cm^{-1} will be absent. For example, consider the following two compounds:

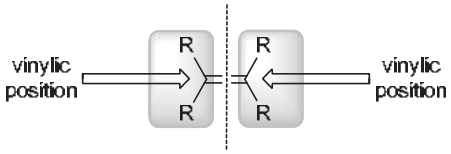


will produce a signal near 1650 cm^{-1} | will NOT produce a signal near 1650 cm^{-1}

Don't be confused by the terms 'symmetrical alkene' and 'unsymmetrical alkene'. We might refer to the first compound as an unsymmetrical alkene (in reference to the dipole moment), but the truth is that this alkene still does possess some symmetry (an axis of symmetry, as well as two planes of symmetry).



But these symmetry elements are not relevant for determining whether a C=C bond has a dipole moment, and therefore, they are not relevant for determining whether or not a C=C bond will produce a signal in an IR spectrum. When we refer to a symmetrical alkene, we are referring to the symmetry of the two vinylic positions:



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With this in mind, let's consider the following alkene:

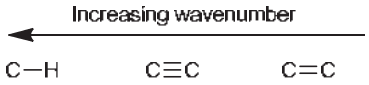


While this molecule does possess some symmetry, you should avoid falling into the trap of calling it a symmetrical alkene and erroneously deciding that the C=C double bond will not produce a signal. In fact, the dipole moment for this C=C bond is expected to be quite large (because of the combined inductive effects of the chlorine atoms. One vinylic position (the one connected to the two chlorine atoms) is more electron-deficient (δ+) than the other vinylic position. As a result, this C=C bond is expected to produce a rather strong signal in the IR spectrum.

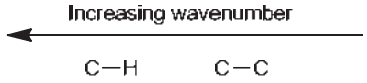
Solutions

14.1.

(a) The C–H bond is expected to produce the signal with the largest wavenumber, because bonds to H typically produce high-energy signals (due to the low mass of the hydrogen atom). Among the remaining two bonds, the triple bond is stronger than the double bond, so we expect the double bond to produce the signal with lowest wavenumber.

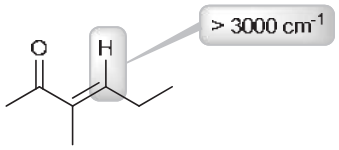


(b) Each of the bonds in this case is a single bond. The C–H bond is expected to produce the signal with the larger wavenumber, because bonds to H typically produce high-energy signals (due to the low mass of the hydrogen atom).



14.2.

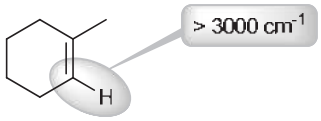
(a) This compound exhibits an sp^2 hybridized carbon atom that is connected to a hydrogen atom. As such, this C–H bond (highlighted) should produce a signal above 3000 cm^{-1} (at approximately 3100 cm^{-1}).



(b) This compound has three sp^2 hybridized carbon atoms, but none of them are connected to hydrogen atoms. And there are no *sp* hybridized carbon atoms. Therefore, we do not expect a signal above 3000 cm^{-1}.

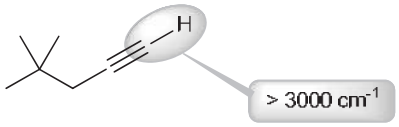
(c) This compound has two *sp* hybridized carbon atoms, but neither of them are connected to hydrogen atoms. And there are no sp^2 hybridized carbon atoms. Therefore, we do not expect a signal above 3000 cm^{-1}.

(d) This compound exhibits an sp^2 hybridized carbon atom that is connected to a hydrogen atom. As such, this C-H bond (highlighted) should produce a signal above 3000 cm^{-1} (at approximately 3100 cm^{-1}).



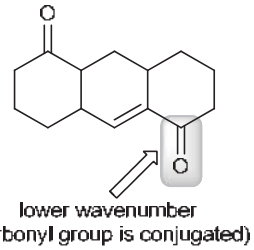
(e) This compound has two sp^2 hybridized carbon atoms, but neither of them are connected to hydrogen atoms. And there are no *sp* hybridized carbon atoms. Therefore, we do not expect a signal above 3000 cm^{-1}.

(f) This compound exhibits an *sp* hybridized carbon atom that is connected to a hydrogen atom. As such, this C-H bond (highlighted) should produce a signal above 3000 cm^{-1} (at approximately 3300 cm^{-1}).



14.3.

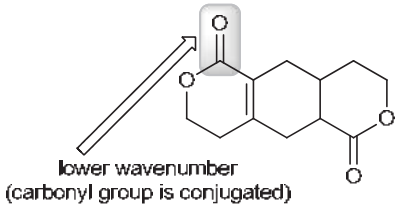
(a) One of the carbonyl groups (upper left) is not conjugated, so it is expected to produce a signal at approximately 1720 cm^{-1}. The other carbonyl group (bottom right) is conjugated to a C=C π bond, so it is expected to produce a signal at approximately 1680 cm^{-1}.



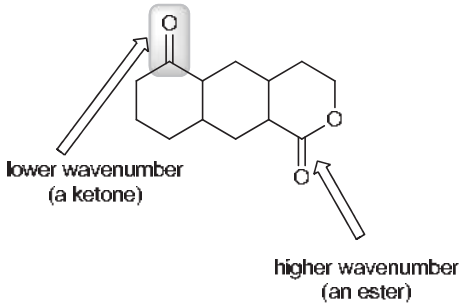
(b) One of the ester groups (bottom right) is not conjugated, so it is expected to produce a signal at

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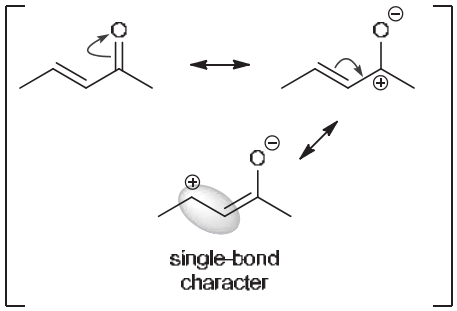
approximately 1740 cm^{-1}. The other carbonyl group (upper left) is conjugated to a C=C π bond, so it is expected to produce a signal at approximately 1710 cm^{-1}.



(c) The carbonyl group of a ketone is expected to produce a signal at approximately 1720 cm^{-1}, while the carbonyl group of an ester is expected to produce a signal at approximately 1740 cm^{-1}.

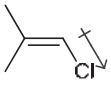


14.4. The C=C π bond in the conjugated compound produces a signal at lower wavenumber (1600 cm^{-1}) because it has some single bond character, as seen in the third resonance structure below. This additional single bond character renders the C=C π bond weaker (relative to the C=C π bond of the other compound, which does not exhibit any single bond character).



14.5.

(a) The second compound has an electronegative chlorine atom, which withdraws electron density via induction.

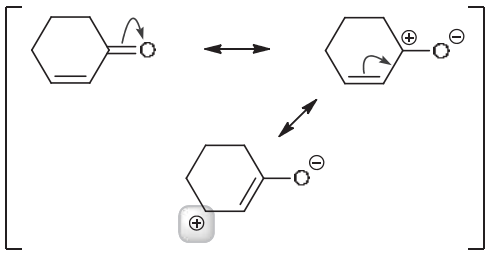


This causes the two vinylic positions to experience different electronic environments. The vinylic position connected directly to the chlorine atom is expected to be more electron-poor (δ+) than the other vinylic position (which is not directly connected to the chlorine atom). Therefore, the C=C bond in this compound has a larger dipole moment than the C=C bond in the other compound. As a result, we expect the chloroalkene to be more efficient at absorbing IR radiation (thereby producing a stronger signal).

(b) The C=C bond in the compound shown below will have a larger dipole moment because one vinylic position is connected to two chlorine atoms while the other vinylic position is not directly connected to any chlorine atoms. As a result, the two vinylic positions are in very different electronic environments, giving rise to a large dipole moment. We therefore expect this C=C bond to be more efficient at absorbing IR radiation (and therefore produce a stronger signal).



14.6. If we draw all significant resonance structures of 2-cyclohexenone, we see that one of the vinylic positions is electron-deficient (highlighted in the third resonance structure):



As a result, the two vinylic positions experience very different electronic environments, giving rise to a large dipole moment. With a large dipole moment, this C=C bond is expected to be very efficient at absorbing IR radiation, thereby producing a strong signal.

14.7. The vinylic C–H bond should produce a signal at approximately 3100 cm^{-1}.



14.8. The narrow signal is produced by the O–H stretching in the absence of a hydrogen bonding effect. The broad signal is produced by O–H stretching when hydrogen bonding is present. Hydrogen bonding effectively lowers the bond strength of the O–H bonds, because each hydrogen atom is slightly pulled away from the oxygen atom to which it is connected. A longer bond length (albeit temporary) corresponds with a weaker bond, which corresponds with a lower wavenumber.

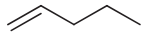
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14.9.
(a) The broad signal between 3200 and 3600 cm^{-1} is characteristic of an alcohol (ROH).
(b) This spectrum lacks broad signals above 3000 cm^{-1}, so the compound is neither an alcohol nor a carboxylic acid (both of which produce broad signals that reach as high as 3600 cm^{-1}).
(c) The extremely broad signal that extends from 2200 to 3600 cm^{-1} is characteristic of the O-H stretching of a carboxylic acid (RCO_2H). The signal just above 1700 cm^{-1} is also consistent with a carboxylic acid (for the C=O bond of the carboxylic acid).
(d) This spectrum lacks broad signals above 3000 cm^{-1}, so the compound is neither an alcohol nor a carboxylic acid (both of which produce broad signals that reach as high as 3600 cm^{-1}).
(e) The broad signal between 3100 and 3600 cm^{-1} is characteristic of an alcohol (ROH).
(f) The extremely broad signal that extends from 2200 to 3600 cm^{-1} is characteristic of the O–H stretching of a carboxylic acid (RCO_2H). The signal around 1700 cm^{-1} is also consistent with a carboxylic acid (for the C=O bond of the carboxylic acid).

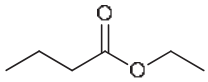
14.10.
(a) The strong signal just above 1700 cm^{-1} is consistent with the stretching of the carbonyl group (C=O) of a ketone.
(b) The extremely broad signal that extends from 2200 to 3600 cm^{-1} is characteristic of the O–H stretching of a carboxylic acid (RCO_2H). The signal just above 1700 cm^{-1} is also consistent with a carboxylic acid (for the C=O bond of the carboxylic acid).
(c) The signal at approximately 3400 cm^{-1} is consistent with the stretching of the N–H bond of a secondary amine.
(d) The two signals at 3350 and 3450 cm^{-1} are consistent with the stretching of the N–H bond (symmetric and asymmetric) of a primary amine.
(e) The strong signal just above 1700 cm^{-1} is consistent with the stretching of the carbonyl group (C=O) of a ketone.
(f) The broad signal between 3200 and 3600 cm^{-1} is characteristic of an alcohol (ROH).

14.11. The C_{sp^3}–H bonds can stretch symmetrically, asymmetrically, or in a variety of ways with respect to each other. Each one of these possible stretching modes is associated with a different wavenumber of absorption, giving a large number of overlapping peaks.

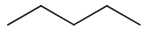
14.12.
(a) Begin by drawing a line at 1500 cm^{-1} and ignoring everything to the right (the fingerprint region). Then, look for any signals associated with double bonds (1600–1850 cm^{-1}) or triple bonds (2100–2300 cm^{-1}). In this case, there is a weak signal between 1600 and 1700 cm^{-1}, consistent with an alkene. Finally, we draw a line at 3000 cm^{-1}, and we look for signals to the left of this line. In this case, there is a signal at approximately 3100 cm^{-1}, which is consistent with a C_{sp^2}–H bond of an alkene. Among the possible structures, the alkene is the structure that is consistent with the signals in the spectrum.



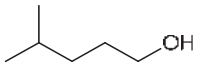
(b) Begin by drawing a line at 1500 cm^{-1} and ignoring everything to the right (the fingerprint region). Then, look for any signals associated with double bonds (1600–1850 cm^{-1}) or triple bonds (2100–2300 cm^{-1}). In this case, there is a strong signal between 1700 and 1800 cm^{-1}, consistent with a carbonyl group. Among the possible structures, only two of them exhibit C=O bonds. One of these structures has carboxylic acid groups, and the spectrum does not match that compound (because that compound is expected to give a broad signal from 2200-3600 cm^{-1}, which is absent in our spectrum). The following structure (an ester) is consistent with the IR spectrum.



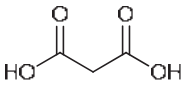
(c) Begin by drawing a line at 1500 cm^{-1} and ignoring everything to the right (the fingerprint region). Then, look for any signals associated with double bonds (1600–1850 cm^{-1}) or triple bonds (2100–2300 cm^{-1}). In this case, there are none. Next, we draw a line at 3000 cm^{-1}, and we look for signals to the left of this line. In this case, there are none. With no characteristic signals for any functional groups, this spectrum is consistent with an alkane.



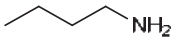
(d) The broad signal between 3200 and 3600 cm^{-1} is characteristic of an alcohol (ROH). There is only one alcohol among the possible structures given.



(e) The extremely broad signal that extends from 2200 to 3600 cm^{-1} is characteristic of the O–H stretching of a carboxylic acid (RCO_2H). The signal just above 1700 cm^{-1} is also consistent with a carboxylic acid (for the C=O bond of a carboxylic acid group). Notice that this signal appears to be comprised of two overlapping signals, which can likely be attributed to symmetric and asymmetric stretching of the two carboxylic acid groups.



(f) The two signals at 3350 and 3450 cm^{-1} are consistent with the stretching of the N–H bonds (symmetric and asymmetric) of a primary amine. There is only one primary amine among the possible structures given.



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14.13. The following five signals are expected (presented in order of increasing wavenumber):
1) The C=C bond (expected to be ~ 1650 cm^{-1})
2) The C=O bond of the carboxylic acid group (expected to be ~ 1720 cm^{-1})
3) All C_{sp^3}–H bonds (expected to be <3000 cm^{-1})
4) The C_{sp^2}–H bond (expected to be ~ 3100 cm^{-1})
5) The O–H bond of the carboxylic acid group (expected to be 2200 - 3600 cm^{-1})

14.14.
(a) The starting material is an alcohol and is expected to produce a typical signal for an O–H stretch (a broad signal between 3200 and 3600 cm^{-1}). In contrast, the product is a carboxylic acid and is expected to produce an even broader O–H signal (2200-3600 cm^{-1}) as a result of more extensive hydrogen bonding. Alternatively, the product can be differentiated from the starting material by looking for a signal at around 1720 cm^{-1}. The product has a C=O bond and should exhibit this signal. The starting material lacks a C=O bond and will not show a signal at 1720 cm^{-1}.

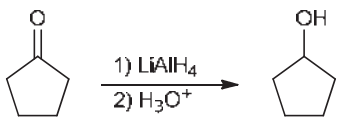
(b) The starting material is an unsymmetrical alkyne and is expected to produce a signal at around 2200 cm^{-1}. In contrast, the product is an unsymmetrical alkene and is expected to produce a signal at around 1600 cm^{-1}. Also, the product has C_{sp^2}–H bonds that are absent in the starting material. The product is expected to have signals at around 3100 cm^{-1}, and the starting material will have no signal in that region.

(c) The C≡C bond in the starting material and the C=C bond in the product are each symmetrical and will not produce signals. However, the product has C_{sp^2}–H bonds that are absent in the starting material. The product is expected to have a signal at around 3100 cm^{-1}, and the starting material will have no signal in that region.

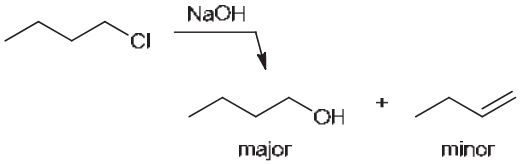
(d) The starting material will have two signals in the double-bond region: one for the C=O bond and one for the C=C bond. The product only has one signal in the double-bond region. It only has the signal for the C=O bond, which should be at a higher wavenumber (because the C=O bond is not conjugated in the product).

14.15. The starting material has a cyano group (C≡N) and is expected to produce a signal at approximately 2200 cm^{-1}. In contrast, the product is a carboxylic acid and is expected to produce a broad signal from 2200–3600 cm^{-1}, as well as a signal at 1720 cm^{-1} for the C=O bond.

14.16. The starting material should have a C=O signal at 1720 cm^{-1}, while the product should have an O–H signal at 3200 – 3600 cm^{-1}.



14.17. 1-Chlorobutane is a primary substrate. When treated with sodium hydroxide, substitution is expected to dominate over elimination (see Chapter 7), but both products are expected to be obtained:



The substitution product is an alcohol and should have a broad signal from 3200 to 3600 cm^{-1}. The elimination product is an unsymmetrical alkene and is expected to give a C=C signal at approximately 1650 cm^{-1}, as well as a C_{sp^2}–H signal at 3100 cm^{-1}.

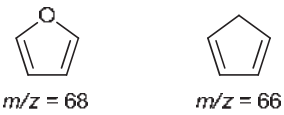
14.18.
(a) The first compound (called furan) has four carbon atoms, four hydrogen atoms and one oxygen atom, so it has the following molecular weight:

$$MW = (4\times12) + (4\times1) + (16) = 68$$

In contrast, the second compound (called cyclopentadiene) has five carbon atoms and six hydrogen atoms, so it has the following molecular weight:

$$MW = (5\times12) + (6\times1) = 66$$

These compounds have different molecular weights, so mass spectrometry can be used to distinguish between them. Specifically, the mass spectrum of furan is expected to have a molecular ion peak at m/z = 68, while the mass spectrum of cyclopentadiene is expected to have a molecular ion peak at m/z = 66.



(b) The first compound (benzene) has six carbon atoms and six hydrogen atoms, so it has the following molecular weight:

$$MW = (6\times12) + (6\times1) = 78$$

In contrast, the second compound (pyridine) has five carbon atoms, five hydrogen atoms, and one nitrogen atom, so it has the following molecular weight:

$$MW = (5\times12) + (5\times1) + (14) = 79$$

These compounds have different molecular weights, so mass spectrometry can be used to distinguish between them. Specifically, the mass spectrum of benzene is expected to have a molecular ion peak at m/z = 78, while the mass spectrum of pyridine is expected to have a molecular ion peak at m/z = 79.

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m/z = 78



m/z = 79

14.19.

(a) This compound does not have any nitrogen atoms. According to the nitrogen rule, this compound should have an even molecular weight.
With five carbon atoms, ten hydrogen atoms and one oxygen atom, the molecular weight is calculated as follows:

$$MW = (5\times12) + (10\times1) + (16) = 86$$

Therefore, we expect the molecular ion peak to appear at *m/z* = 86.

(b) This compound does not have any nitrogen atoms. According to the nitrogen rule, this compound should have an even molecular weight.
With five carbon atoms, eight hydrogen atoms and two oxygen atoms, the molecular weight is calculated as follows:

$$MW = (5\times12) + (8\times1) + (2\times16) = 100$$

Therefore, we expect the molecular ion peak to appear at *m/z* = 100.

(c) This compound has one nitrogen atom. According to the nitrogen rule, this compound should have an odd molecular weight.
With six carbon atoms, fifteen hydrogen atoms and one nitrogen atom, the molecular weight is calculated as follows:

$$MW = (6\times12) + (15\times1) + (14) = 101$$

Therefore, we expect the molecular ion peak to appear at *m/z* = 101.

(d) This compound has two nitrogen atoms. According to the nitrogen rule, this compound should have an even molecular weight.
With five carbon atoms, fourteen hydrogen atoms and two nitrogen atoms, the molecular weight is calculated as follows:

$$MW = (5\times12) + (14\times1) + (2\times14) = 102$$

Therefore, we expect the molecular ion peak to appear at *m/z* = 102.

14.20.

(a) In order to determine the number of carbon atoms in the compound, we compare the relative heights of the $(M+1)^{+\bullet}$ peak and the $(M)^{+\bullet}$ peak, like this:

$$\frac{1.7\%}{38.3\ \%} \times 100\ \% = 4.4\%$$

This means that the $(M+1)^{+\bullet}$ peak is 4.4% as tall as the $(M)^{+\bullet}$ peak. Recall that each carbon atom in the compound contributes 1.1% to the height of the $(M+1)^{+\bullet}$ peak, so we must divide by 1.1% to determine the number of carbon atoms in the compound:

$$\text{Number of C} = \frac{4.4\ \%}{1.1\ \%} = 4$$

The compound contains four carbon atoms, which account for 4 × 12 = 48 amu (atomic mass units), but the molecular weight is 72 amu. So we must account for the remaining 72 – 48 = 24 amu. The molecular formula cannot be C_4H_{24}, because a compound with four carbon atoms cannot have that many hydrogen atoms.
Therefore, there must be another element present. It cannot be a nitrogen atom as that would give an odd molecular weight (the nitrogen rule). So we try oxygen (16 amu), leaving only 8 amu for hydrogen atoms. This gives the following proposed molecular formula: C_4H_8O.

(b) In order to determine the number of carbon atoms in the compound, we compare the relative heights of the $(M+1)^{+\bullet}$ peak and the $(M)^{+\bullet}$ peak, like this:

$$\frac{4.3\%}{100\ \%} \times 100\ \% = 4.3\%$$

This means that the $(M+1)^{+\bullet}$ peak is 4.3% as tall as the $(M)^{+\bullet}$ peak. Recall that each carbon atom in the compound contributes 1.1% to the height of the $(M+1)^{+\bullet}$ peak, so we must divide by 1.1% to determine the number of carbon atoms in the compound:

$$\text{Number of C} = \frac{4.3\ \%}{1.1\ \%} = 4$$

The compound contains four carbon atoms, which account for 4 × 12 = 48 amu (atomic mass units), but the molecular weight is 68 amu. So we must account for the remaining 68 – 48 = 20 amu. The molecular formula cannot be C_4H_{20}, because a compound with four carbon atoms cannot have that many hydrogen atoms.
Therefore, there must be another element present. It cannot be a nitrogen atom as that would give an odd molecular weight (the nitrogen rule). So we try oxygen (16 amu), leaving only 4 amu for hydrogen atoms. This gives the following proposed molecular formula: C_4H_4O.

(c) In order to determine the number of carbon atoms in the compound, we compare the relative heights of the $(M+1)^{+\bullet}$ peak and the $(M)^{+\bullet}$ peak, like this:

$$\frac{4.6\%}{100\ \%} \times 100\ \% = 4.6\%$$

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This means that the $(M+1)^{+\bullet}$ peak is 4.6% as tall as the $(M)^{+\bullet}$ peak. Recall that each carbon atom in the compound contributes 1.1% to the height of the $(M+1)^{+\bullet}$ peak, so we must divide by 1.1% to determine the number of carbon atoms in the compound:

$$\text{Number of C} = \frac{4.6\ \%}{1.1\ \%} = 4.15 \sim 4$$

The compound cannot have 4.15 carbon atoms. It must be a whole number, so we round to the nearest whole number, which is 4. That is, the compound contains four carbon atoms, which account for $4 \times 12 = 48$ amu (atomic mass units), but the molecular weight is 54 amu. So we must account for the remaining $54 - 48 = 6$ amu. This indicates six hydrogen atoms, giving the following proposed molecular formula: C_4H_6.

(d) In order to determine the number of carbon atoms in the compound, we compare the relative heights of the $(M+1)^{+\bullet}$ peak and the $(M)^{+\bullet}$ peak, like this:

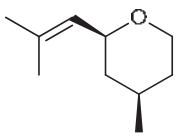
$$\frac{1.5\ \%}{19.0\ \%} \times 100\ \% = 7.9\ \%$$

This means that the $(M+1)^{+\bullet}$ peak is 7.9% as tall as the $(M)^{+\bullet}$ peak. Recall that each carbon atom in the compound contributes 1.1% to the height of the $(M+1)^{+\bullet}$ peak, so we must divide by 1.1% to determine the number of carbon atoms in the compound:

$$\text{Number of C} = \frac{7.9\ \%}{1.1\ \%} = 7.2 \sim 7$$

The compound cannot have 7.2 carbon atoms. It must be a whole number, so we round to the nearest whole number, which is 7. That is, the compound contains seven carbon atoms, which account for $7 \times 12 = 84$ amu (atomic mass units), but the molecular weight is 96 amu. So we must account for the remaining $96 - 84 = 12$ amu. This indicates twelve hydrogen atoms, giving the following proposed molecular formula: C_7H_{12}.

14.21. The molecular formula of the first structure is $C_{10}H_{18}O$, while the molecular formula of the second structure is $C_9H_{14}O_2$. Each compound is expected to exhibit a parent ion at *m/z* = 154, so the location of the parent signal cannot be used to differentiate these compounds. Instead, we can use the relative abundance of the $(M+1)^{+\bullet}$ peak. The following calculations show that the observed data are more consistent with a compound containing 10 carbon atoms, rather than 9.



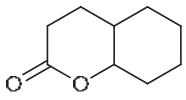
10 carbon atoms

expected abundance of $(M+1)^{+\bullet}$

10 x 1.1% = 11% of $(M)^{+\bullet}$

$(M+1)^{+\bullet}$ = 0.11 x 17.8%

$(M+1)^{+\bullet}$ = 2.0%



9 carbon atoms

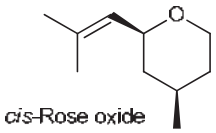
expected abundance of $(M+1)^{+\bullet}$

9 x 1.1% = 9.9% of $(M)^{+\bullet}$

$(M+1)^{+\bullet}$ = 0.099 x 17.8%

$(M+1)^{+\bullet}$ = 1.8%

The first structure is expected to give an $(M+1)^{+\bullet}$ peak with a relative abundance of 2.0%. Therefore, we conclude that the first structure is *cis*-rose oxide:



cis-Rose oxide

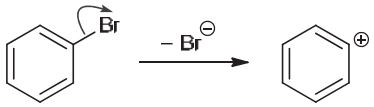
When comparing the relative abundance of the $(M+1)^{+\bullet}$ peaks in this particular case, the expected difference is quite small (1.8% vs. 2.0%), so other techniques will be more useful for differentiating these compounds, including high-resolution mass spectrometry (Section 14.13).

As a side note, these compounds can be easily distinguished by their strong odors: *cis*-rose oxide smells like roses, and the other compound (bicyclononalactone) smells like coconuts!

14.22.

(a) This fragment is M – 79, which is formed by loss of a Br. So the fragment does not contain Br. Also, the fragment has a smaller mass than a single bromine atom (77 < 79).

(b) Loss of bromide generates a phenyl cation, as shown:



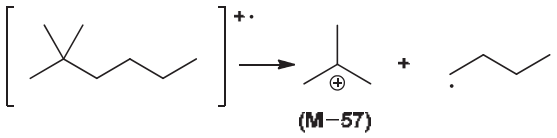
m/z = 77

Note: This type of process readily occurs under the high energy conditions in a mass spectrometer, but this process is generally not otherwise observed, because phenyl carbocations are generally too high in energy to form at an appreciable rate during reactions performed in the laboratory.

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14.23.
(a) There is not a significant $(M+2)^{+\bullet}$ peak, so neither bromine nor chlorine is present.
(b) There is not a significant $(M+2)^{+\bullet}$ peak, so neither bromine nor chlorine is present.
(c) The $(M+2)^{+\bullet}$ peak is approximately equivalent in height to the molecular ion peak, indicating the presence of a bromine atom.
(d) The $(M+2)^{+\bullet}$ peak is approximately one-third as tall as the molecular ion peak, indicating the presence of a chlorine atom.

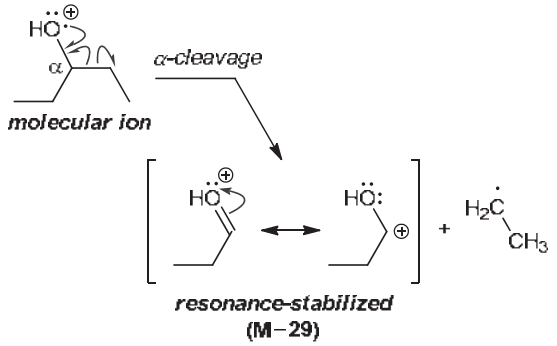
14.24.
(a) A peak at M–57 indicates the loss of a four-carbon radical fragment, which can result in the formation of a tertiary carbocation, as shown. This tertiary carbocation is the fragment responsible for the peak at M–57:



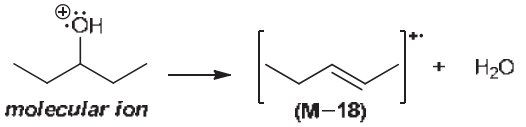
Remember that the radical fragment (the butyl radical) is not detected by the mass spectrometer.

(b) This carbocation is tertiary, and its formation is favored over the other possible secondary and primary carbocations.
(c) They readily fragment to produce tertiary carbocations.
(d) M–15 corresponds to loss of a methyl group. Indeed, loss of a methyl group would also produce a tertiary carbocation, but that pathway is less favorable because it involves formation of a methyl radical (which is less stable than a primary radical).

14.25. A fragment at M–29 should result from α cleavage:



and a fragment at M–18 should result from dehydration:



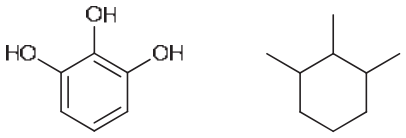
14.26. A peak at M–43 indicates the loss of a three-carbon radical fragment, which can result in the formation of a tertiary carbocation, as shown. This tertiary carbocation is the fragment responsible for the peak at M–43:



Notice that this fragmentation results in a tertiary carbocation as well as a secondary radical. No other possible fragmentation results in more stable fragments, so we expect this fragmentation to occur more often than any other possible fragmentation. As a result, the signal at M–43 is expected to be the most abundant signal in the spectrum (the base peak).

14.27. In the first spectrum, the base peak appears at M–29, signifying the loss of an ethyl group. This spectrum is likely the mass spectrum of ethylcyclohexane. The second spectrum has a peak at M–15, signifying the loss of a methyl group. The second spectrum is likely the mass spectrum of 1,1-dimethylcyclohexane.

14.28.
(a) If atomic masses are rounded to the nearest whole number, then both of these compounds have the same molecular weight (126 amu). However, when measured to four decimal places, these compounds do *not* have the same mass, and the difference is detectable via high-resolution mass spectrometry.

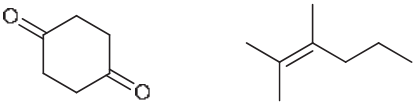


The calculation for each compound is shown here:

$C_6H_6O_3 = (6\times12.0000) + (6\times1.0078) + (3\times15.9949) =$ **126.0315** amu

$C_9H_{18} = (9\times12.0000) + (18\times1.0078) =$ **126.1404** amu

(b) If atomic masses are rounded to the nearest whole number, then both of these compounds have the same molecular weight (112 amu). However, when measured to four decimal places, these compounds do *not* have the same mass, and the difference is detectable via high-resolution mass spectrometry:



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The calculation for each compound is shown here:

$C_6H_8O_2 = (6\times12.0000) + (8\times1.0078) + (2\times15.9949) =$ **112.0522 amu**

$C_8H_{16} = (8\times12.0000) + (16\times1.0078) =$ **112.1248 amu**

14.29.
(a) The first compound should have a broad signal between 3200 and 3600 cm^{-1}, corresponding with O–H stretching. The second compound will not have such a signal.
(b) The first compound should have a pair of strong signals around 1720 cm^{-1}, corresponding with symmetric and asymmetric stretching of the C=O bonds. In contrast, the second compound will have a weak signal at around 1650 cm^{-1}, corresponding to the C=C bond.

14.30.
(a) A compound with six carbon atoms would require (2×6) + 2 = 14 hydrogen atoms to be fully saturated. This compound has only ten hydrogen atoms, so four hydrogen atoms are missing. The compound therefore has two degrees of unsaturation (HDI = 2).

(b) A compound with five carbon atoms would require (2×5) + 2 = 12 hydrogen atoms to be fully saturated (the presence of the oxygen atom does not affect this calculation). This compound has only ten hydrogen atoms, so two hydrogen atoms are missing. Therefore, the compound has one degree of unsaturation (HDI = 1).

(c) A compound with the molecular formula C_5H_9N is expected to have the same HDI as a compound with the molecular formula C_5H_8. With five carbon atoms, the compound would need to have twelve hydrogen atoms to be fully saturated. With only eight hydrogen atoms, four are missing, representing two degrees of unsaturation (HDI = 2).

(d) A compound with the molecular formula C_3H_5ClO is expected to have the same HDI as a compound with the molecular formula C_3H_6 (Cl is treated like H, while O is ignored). With three carbon atoms, the compound would need to have eight hydrogen atoms to be fully saturated. With only six hydrogen atoms, two are missing, representing one degree of unsaturation (HDI = 1).

(e) A compound with ten carbon atoms would require (2 × 10) + 2 = 22 hydrogen atoms to be fully saturated. This compound has only twenty hydrogen atoms, so two hydrogen atoms are missing. The compound therefore has one degree of unsaturation (HDI = 1).

(f) A compound with the molecular formula $C_4H_6Br_2$ is expected to have the same HDI as a compound with the molecular formula C_4H_8 (each Br is treated like an H). With four carbon atoms, the compound would need to have ten hydrogen atoms to be fully saturated. With only eight hydrogen atoms, two are missing, representing one degree of unsaturation (HDI = 1).

(g) A compound with six carbon atoms would require (2×6) + 2 = 14 hydrogen atoms to be fully saturated. This compound has only six hydrogen atoms, so eight hydrogen atoms are missing. The compound therefore has four degrees of unsaturation (HDI = 4).

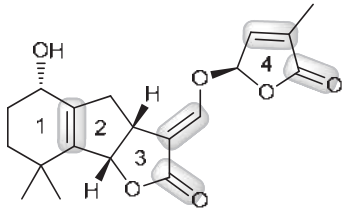
(h) A compound with the molecular formula C_2Cl_6 is expected to have the same HDI as a compound with the molecular formula C_2H_6 (each Cl is treated like an H). With two carbon atoms, the compound would need to have six hydrogen atoms to be fully saturated. No hydrogen atoms are missing, representing zero degrees of unsaturation (HDI = 0).

(i) A compound with the molecular formula $C_2H_4O_2$ is expected to have the same HDI as a compound with the molecular formula C_2H_4 (the oxygen atoms can be ignored for purposes of calculating HDI). With two carbon atoms, the compound would need to have six hydrogen atoms to be fully saturated. With only four hydrogen atoms, two are missing, representing one degree of unsaturation (HDI = 1).

(j) A compound with the molecular formula $C_{100}H_{200}Cl_2O_{16}$ is expected to have the same HDI as a compound with the molecular formula $C_{100}H_{202}$ (each Cl is treated like an H, and all of the oxygen atoms are ignored). No hydrogen atoms are missing, representing zero degrees of unsaturation (HDI = 0).

14.31. A compound with the molecular formula $C_3H_5ClO_2$ is expected to have the same HDI as a compound with the molecular formula C_3H_6 (the Cl is treated like an H, and both oxygen atoms are ignored). Both $C_3H_5ClO_2$ and C_3H_6 have one degree of unsaturation.

14.32. Strigol has four rings (numbered below) and five double bonds (highlighted below), for a total hydrogen deficiency index of nine:

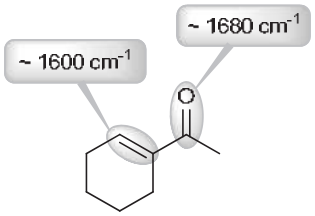


If saturated, a compound with 19 carbon atoms would have 40 hydrogen atoms (19x2 + 2), but an HDI of nine means that 18 hydrogen atoms are missing. So there must be 22 hydrogen atoms in the formula (40-18=22). Inspection of the structure also reveals six oxygen atoms, so the molecular formula of strigol must be $C_{19}H_{22}O_6$.

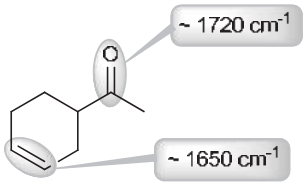
14.33. The range between 1600 and 1850 cm^{-1} is associated with the stretching of double bonds. Each of the compounds in this problem exhibits at least one double bond, if not two.
(a) The carbonyl group is conjugated so it is expected to produce a signal near 1680 cm^{-1}. The C=C double bond

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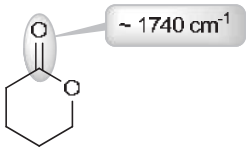
is conjugated so it is expected to produce a signal near 1600 cm^{-1}.



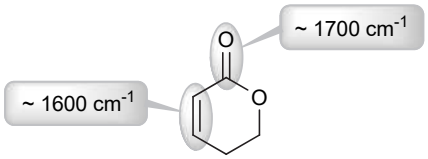
(b) The carbonyl group is isolated (not conjugated) so it is expected to produce a signal near 1720 cm^{-1}. The C=C double bond is also isolated so it is expected to produce a signal near 1650 cm^{-1}.



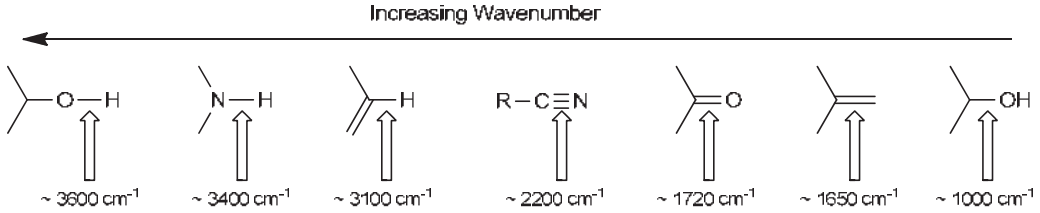
(c) The carbonyl group of an ester will typically produce a signal near 1740 cm^{-1}.



(d) The carbonyl group of the ester is conjugated so it is expected to produce a signal near 1710 cm^{-1}. The C=C double bond is conjugated so it is expected to produce a signal near 1600 cm^{-1}.



14.34. The signals at highest wavenumber are expected to be associated with X–H bonds (because hydrogen has the lowest atomic mass). Among the list of bonds in the problem statement, there are three bonds that belong to this category (O–H, N–H, and C–H). These three bonds are expected to produce signals at approximately 3600, 3400, and 3100 cm^{-1}, respectively. Among the remaining bonds, the triple bond has the next highest wavenumber, followed by the double bonds (the C=O bond has a higher wavenumber than the C=C bond), followed by the C–O single bond.



14.35.

(a) In addition to the C_{sp^3}–H stretching signals that are expected to appear just below 3000 cm^{-1}, the C=N bond and the C=O bond should each produce a signal in the double bond region (1600 – 1850 cm^{-1}).

(b) In addition to the C_{sp^3}–H stretching signals that are expected to appear just below 3000 cm^{-1}, the C_{sp^2}–H bond should produce a signal near 3100 cm^{-1}, and the C=C bond should produce a signal in the double bond region (1600 – 1850 cm^{-1}).

(c) In addition to the C_{sp^3}–H stretching signals that are expected to appear just below 3000 cm^{-1}, the C_{sp^2}–H bonds should produce a signal near 3100 cm^{-1}, and the C=C bond and the C=O bond should each produce a signal in the double bond region (1600 – 1850 cm^{-1}). The two C≡C bonds should also produce two signals around 2200 cm^{-1}, and the C_{sp}–H bond should produce a signal around 3300 cm^{-1}.

(d) In addition to the C_{sp^3}–H stretching signals that are expected to appear just below 3000 cm^{-1}, the C=O bond should produce a signal in the double bond region around 1720 cm^{-1}, and the O–H of the carboxylic acid group should produce a very broad signal from 2200 – 3600 cm^{-1}.

14.36.

(a) The IR spectrum of the reactant should have a signal near 1650 cm^{-1} (for the C=C bond) and a signal near 3100 cm^{-1} (for the C_{sp^2}–H bond). In contrast, the IR spectrum of the product should not exhibit either of these signals.

(b) The IR spectrum of the reactant should have a broad signal from 3200 – 3600 cm^{-1} (for the O–H bond), while the IR spectrum of the product should not exhibit this signal, and instead should have a strong signal near 1720 cm^{-1} (for the C=O bond).

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(c) The C=O bond of an ester should produce a signal at higher wavenumber (~1740 cm^{-1}) than the signal associated with the C=O bond of a ketone (~1720 cm^{-1}).

(d) The IR spectrum of the reactant should have a signal near 1650 cm^{-1} (for the C=C bond) and a signal near 3100 cm^{-1} (for the C_{sp^2}–H bonds). In contrast, the IR spectra of the products should not exhibit either of these signals. Instead, they should have signals near 1720 cm^{-1} (for the C=O bonds).

(e) The IR spectrum of the product should have a signal near 1650 cm^{-1} (for the C=C bond) and a signal near 3100 cm^{-1} (for the C_{sp^2}–H bond). In contrast, the IR spectrum of the reactant should not exhibit either of these signals.

14.37.
(a) The IR spectrum of this compound is expected to exhibit C_{sp^3}–H signals just below 3000 cm^{-1}, and a C=O signal near 1720 cm^{-1}.
(b) The IR spectrum of this compound is expected to exhibit C_{sp^3}–H signals just below 3000 cm^{-1}, and a C=O signal near 1680 cm^{-1} (conjugated), and a C=C signal near 1600 cm^{-1} (conjugated), and a C_{sp^2}–H signal near 3100 cm^{-1}.
(c) The IR spectrum of this compound is expected to exhibit C_{sp^3}–H signals just below 3000 cm^{-1}, and a C=O signal near 1720 cm^{-1} and a C=C signal near 1650 cm^{-1} and a C_{sp^2}–H signal near 3100 cm^{-1}.
(d) The IR spectrum of this compound is expected to exhibit C_{sp^3}–H signals just below 3000 cm^{-1}, and a C=C signal near 1650 cm^{-1} and a broad O-H signal in the range of 3200 – 3600 cm^{-1} and a C_{sp^2}–H signal near 3100 cm^{-1}.
(e) The IR spectrum of this compound is expected to exhibit C_{sp^3}–H signals just below 3000 cm^{-1}, and a C=O signal near 1720 cm^{-1} and an extremely broad O-H signal in the range of 2200 – 3600 cm^{-1}.
(f) The IR spectrum of this compound is expected to exhibit C_{sp^3}–H signals just below 3000 cm^{-1}, and a C=O signal near 1720 cm^{-1} and a broad O-H signal in the range of 3200 – 3600 cm^{-1}.

14.38. The molecular ion peak appears at m/z = 86, so the compound must have a molecular weight of 86 amu. Each carbon atom contributes 12 amu, and each hydrogen atom contributes 1 amu. So, we begin by considering the following possibilities, each of which has one degree of unsaturation (as required by the problem statement).

$$C_4H_8 = (4\times12) + (8\times1) = 56 \text{ amu}$$
$$C_5H_{10} = (5\times12) + (10\times1) = 70 \text{ amu}$$
$$C_6H_{12} = (6\times12) + (12\times1) = 84 \text{ amu}$$

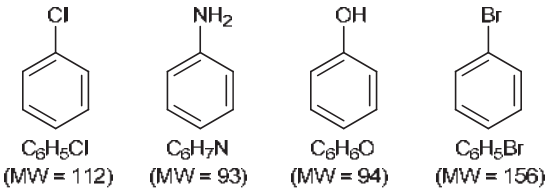
None of these possibilities exhibits the correct molecular weight. The closest is C_6H_{12}, but we are short by two amu (86 – 84 = 2 amu). If we add two hydrogen atoms (to give C_6H_{14}) then the compound will no longer have one degree of unsaturation (it would be fully saturated). So, we consider C_5H_{10}, which has a molecular weight of 70 amu. In order to get this number up to 86, we are missing 16 amu, which is exactly the weight of an oxygen atom. So, a compound with the molecular formula $C_5H_{10}O$ will have a molecular weight of 86 amu (and still has one degree of unsaturation, because the insertion of an oxygen atom does not affect the HDI).
There are certainly many acceptable answers to this problem. For example, a compound with the molecular formula $C_4H_{10}N_2$ will have a molecular weight of 86 amu and its structure will have one degree of unsaturation.

14.39. The problem statement indicates that the $(M+1)^{+\bullet}$ peak is 10% as tall as the $(M)^{+\bullet}$ peak. Recall that each carbon atom in the compound contributes 1.1% to the height of the $(M+1)^{+\bullet}$ peak, so we must divide by 1.1% to determine the number of carbon atoms in the compound:

$$\text{Number of C} = \frac{10\ \%}{1.1\ \%} = 9.1 \sim 9$$

The compound cannot have 9.1 carbon atoms. It must be a whole number, so we round to the nearest whole number, which is nine. That is, the compound contains nine carbon atoms.

14.40. We begin by determining the molecular formula and molecular weight of each compound:



Each of these compounds has a different molecular weight, so we should be able to use match each compound with its spectrum if we focus on the molecular ion peak in each case.
Chlorobenzene (C_6H_5Cl) is consistent with spectrum (b) which has an $(M)^{+\bullet}$ peak at m/z = 112, as well as an $(M+2)^{+\bullet}$ peak that is one-third the height of the $(M)^{+\bullet}$ peak (characteristic of an organochloride).
Aniline (C_6H_7N) is consistent with spectrum (c) which has an $(M)^{+\bullet}$ peak at m/z = 93 (which is an odd number, consistent with the nitrogen rule).
Phenol (C_6H_6O) is consistent with spectrum (a) which has an $(M)^{+\bullet}$ peak at m/z = 94.
Bromobenzene (C_6H_5Br) is consistent with spectrum (d) which has an $(M)^{+\bullet}$ peak at m/z = 156, as well as an $(M+2)^{+\bullet}$ peak that is approximately the same height as the $(M)^{+\bullet}$ peak (characteristic of an organobromide).

14.41.
(a) The broad signal between 3200 and 3600 cm^{-1} indicates the presence of an OH group. The signals between 1600 and 1700 cm^{-1} indicate the presence of double bonds.

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(b) In order to determine the number of carbon atoms in the compound, we compare the relative heights of the $(M+1)^{+\bullet}$ peak and the $(M)^{+\bullet}$ peak, like this:

$$\frac{3.9\ \%}{27.2\ \%} \times 100\ \% = 14.3\ \%$$

This means that the $(M+1)^{+\bullet}$ peak is 14.3% as tall as the $(M)^{+\bullet}$ peak. Recall that each carbon atom in the compound contributes 1.1% to the height of the $(M+1)^{+\bullet}$ peak, so we must divide by 1.1% to determine the number of carbon atoms in the compound:

$$\text{Number of C} = \frac{14.3\ \%}{1.1\ \%} = 13$$

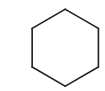
Our analysis reveals that the compound likely has thirteen carbon atoms.

(c) The molecular ion peak appears at *m/z* = 196, so the compound must have a molecular weight of 196 amu. Each carbon atom contributes 12 amu, and each hydrogen atom contributes 1 amu. So, we begin by considering the following possibilities, each of which has two degrees of unsaturation (as required by the problem statement).

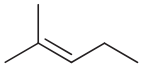
$C_{12}H_{22} = (12\times12) + (22\times1) = 166$ amu
$C_{13}H_{24} = (13\times12) + (24\times1) = 180$ amu
$C_{14}H_{26} = (14\times12) + (26\times1) = 194$ amu

None of these possibilities exhibits the correct molecular weight. The closest is $C_{14}H_{26}$, but we are short by two amu (196 – 194 = 2 amu). If we add two hydrogen atoms (to give $C_{14}H_{28}$), then the compound will no longer have two degrees of unsaturation (it would only have one degree of unsaturation). So, we consider $C_{13}H_{24}$, which has a molecular weight of 180 amu. In order to get this number up to 196, we are missing 16 amu, which is exactly the weight of an oxygen atom. So, a compound the molecular formula $C_{13}H_{24}O$ will have a molecular weight of 196 amu (and still has two degrees of unsaturation, because the insertion of an oxygen atom does not affect the HDI).
There are certainly many acceptable answers to this problem. For example, a compound with the molecular formula $C_{12}H_{24}N_2$ will have a molecular weight of 196 amu and its structure will have two degrees of unsaturation.

14.42.
(a) Each of these compounds has the molecular formula C_6H_{12}.



Cyclohexane
(C_6H_{12})



2-methyl-2-pentene
(C_6H_{12})

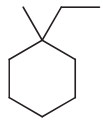
(b) A compound with six carbon atoms would require (6×2) + 2 = 14 hydrogen atoms to be fully saturated. Each of these compounds has only twelve hydrogen atoms, so each compound is missing two hydrogen atoms. Therefore, each of these compounds has one degree of unsaturation (HDI = 1).

(c) No. Both compounds have exactly six carbon atoms and twelve hydrogen atoms, so each of these compounds will produce an $(M)^{+\bullet}$ peak with the same *m/z,* even with high resolution mass spectrometry.

$C_6H_{12} = (6\times12.0000) + (12\times1.0078) =$ **84.0936 amu**

(d) The IR spectrum of the alkene would have a signal near 1650 cm^{-1} for the C=C bond and another signal near 3100 cm^{-1} for the C_{sp^2}–H bond. The IR spectrum of cyclohexane lacks both of these signals.

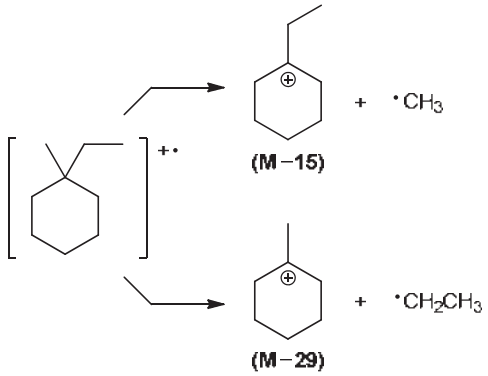
14.43. The parent ion for 1-ethyl-1-methylcyclohexane is expected to appear at *m/z* = 126 (calculation below).



1-Ethyl-1-methylcyclohexane
(C_9H_{18})

MW of $C_9H_{18} = (9\times12) + (18\times1) = 126$ amu

If the parent ion appears at *m/z* = 126, then the signal that appears at *m/z* = 111 is at (M–15), which corresponds with the loss of a methyl group. The signal at *m/z* = 97 is at (M–29), which corresponds with the loss of an ethyl group. Both fragmentations lead to a tertiary carbocation:



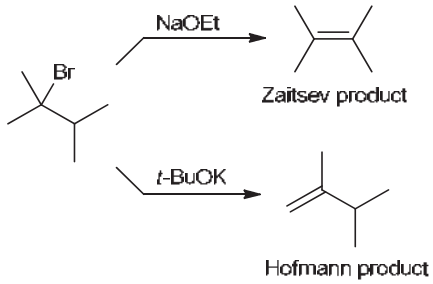
14.44.
(a) This fragment appears at (M–15), which corresponds with the loss of a methyl group. Therefore, this fragment still contains the bromine atom. As such, we do expect a signal at M–13 that is equal in height to the M–15 peak (because there are two isotopes of bromine in roughly equal abundance).

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(b) This fragment appears at (M–29), which corresponds with the loss of an ethyl group. Therefore, this fragment still contains the bromine atom. As such, we do expect a signal at M–27 that is equal in height to the M–29 peak (because there are two isotopes of bromine in roughly equal abundance).

(c) This fragment appears at M–79, which corresponds with the loss a bromine atom. Therefore, the fragment no longer contains bromine. As such, we do not expect a signal at M–77 (which we would only observe if the fragment still contained the bromine atom).

14.45. As seen in Chapter 7, the choice of base affects the regiochemical outcome. Ethoxide favors the more-substituted (Zaitsev) product, while *tert*-butoxide favors the less-substituted (Hofmann) product.



The Zaitsev product is a symmetrical alkene, and as such, its IR spectrum will not exhibit a signal at 1650 cm^{-1} (where the signals for C=C bonds typically appear) or a signal at 3100 cm^{-1} (because this compound contains no C_{sp^2}–H bonds). In contrast, the Hofmann product will display both of these signals in its IR spectrum.

14.46.
(a)
The molecular ion peak appears at *m/z* = 66, so the compound must have a molecular weight of 66 amu. Each carbon atom contributes 12 amu, and each hydrogen atom contributes 1 amu. Five carbon atoms will account for 60 amu, leaving 6 amu for hydrogen atoms.

$$C_5H_6 = (5\times12) + (6\times1) = 66 \text{ amu}$$

The compound cannot have six carbon atoms, because that would exceed the known molecular weight (6×12 = 72 amu). And the compound cannot have four carbon atoms, because then we would not reach 66 amu even if the compound is fully saturated:

$$C_4H_{10} = (4\times12) + (10\times1) = 58 \text{ amu}$$

A hydrocarbon with four carbon atoms cannot have more than ten hydrogen atoms.

(b) The molecular ion peak appears at *m/z* = 70, so the compound must have a molecular weight of 70 amu. Each carbon atom contributes 12 amu, and each hydrogen atom contributes 1 amu. The signal in the IR spectrum indicates the presence of a carbonyl group (C=O), so we must also account for at least one oxygen atom, which contributes 16 amu. If we start with four carbon atoms (4 × 12 = 48), and one oxygen atom (16), we get a total of 48 + 16 = 64 amu, which is just 6 amu short of the known molecular weight (70 amu). Six hydrogen atoms will supply the remaining 6 amu, giving the molecular formula C_4H_6O.

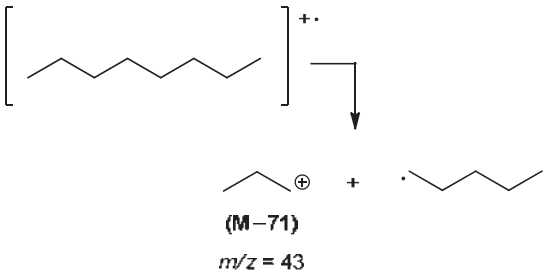
14.47.
(a) Octane is a saturated alkane with the molecular formula C_8H_{18}. The molecular weight of octane is calculated here:

$$C_8H_{18} = (8\times12) + (18\times1) = 114 \text{ amu}$$

Therefore, the molecular ion peak is expected to appear at *m/z* = 114, and indeed, that peak can be seen in the spectrum.

(b) The base peak is (by definition) the tallest peak in the spectrum, which appears at *m/z* = 43.

(c) The base peak (at *m/z* = 43) corresponds with the loss of a radical fragment that is 114 – 43 = 71 amu. That is, the base peak is at (M–71), which corresponds with the loss of a pentyl radical to give a propyl cation, as shown here.



14.48.
(a) A compound with four carbon atoms would require (2×4) + 2 = 10 hydrogen atoms to be fully saturated. This compound has only six hydrogen atoms, so four hydrogen atoms are missing. The compound therefore has two degrees of unsaturation (HDI = 2).

(b) A compound with five carbon atoms would require (2×5) + 2 = 12 hydrogen atoms to be fully saturated. This compound has only eight hydrogen atoms, so four hydrogen atoms are missing. The compound therefore has two degrees of unsaturation (HDI = 2).

(c) A compound with 40 carbon atoms would require (2×40) + 2 = 82 hydrogen atoms to be fully saturated. This compound has only 78 hydrogen atoms, so four hydrogen atoms are missing. The compound therefore has two degrees of unsaturation (HDI = 2).

(d) A compound with 72 carbon atoms would require (2×72) + 2 = 146 hydrogen atoms to be fully saturated. This compound has only 74 hydrogen atoms, so 72

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hydrogen atoms are missing. The compound therefore has 36 degrees of unsaturation (HDI = 36).

(e) A compound with the molecular formula $C_6H_6O_2$ is expected to have the same HDI as a compound with the molecular formula C_6H_6 (the oxygen atoms can be ignored for purposes of calculating HDI). With six carbon atoms, the compound would need to have fourteen hydrogen atoms to be fully saturated. With only six hydrogen atoms, eight are missing, representing four degrees of unsaturation (HDI = 4).

(f) A compound with the molecular formula $C_7H_9NO_2$ is expected to have the same HDI as a compound with the molecular formula C_7H_8 (the oxygen atoms can be ignored, and we subtract one H because of the presence of an N). With seven carbon atoms, the compound would need to have sixteen hydrogen atoms to be fully saturated. With only eight hydrogen atoms (in C_7H_8), eight are missing, representing four degrees of unsaturation (HDI = 4).

(g) A compound with the molecular formula $C_8H_{10}N_2O$ is expected to have the same HDI as a compound with the molecular formula C_8H_8 (the oxygen atom can be ignored, and we subtract one H for each N). With eight carbon atoms, the compound would need to have eighteen hydrogen atoms to be fully saturated. With only eight hydrogen atoms (in C_8H_8), ten are missing, representing five degrees of unsaturation (HDI = 5).

(h) A compound with the molecular formula $C_5H_7Cl_3$ is expected to have the same HDI as a compound with the molecular formula C_5H_{10} (each Cl is treated like an H). With five carbon atoms, the compound would need to have twelve hydrogen atoms to be fully saturated. With only ten hydrogen atoms (in C_5H_{10}), two are missing, representing one degree of unsaturation (HDI = 1).

(i) A compound with the molecular formula C_6H_5Br is expected to have the same HDI as a compound with the molecular formula C_6H_6 (Br is treated like H). With six carbon atoms, the compound would need to have fourteen hydrogen atoms to be fully saturated. With only six hydrogen atoms, eight are missing, representing four degrees of unsaturation (HDI = 4).

(j) A compound with the molecular formula $C_6H_{12}O_6$ is expected to have the same HDI as a compound with the molecular formula C_6H_{12} (the oxygen atoms can be ignored for purposes of calculating HDI). With six carbon atoms, the compound would need to have fourteen hydrogen atoms to be fully saturated. With only twelve hydrogen atoms, two are missing, representing one degree of unsaturation (HDI = 1).

14.49. The compound contains only carbon atoms and hydrogen atoms, and there is a signal in the IR spectrum at 3300 cm^{-1}, indicating a C_{sp}–H bond. That is, the compound is a terminal alkyne. There are only two terminal alkynes with the molecular formula C_5H_8, shown here:

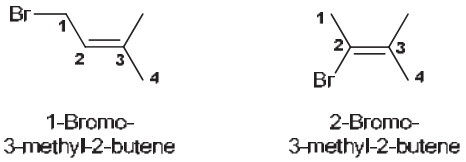


14.50. Limonene is a hydrocarbon, which means that it contains only carbon atoms and hydrogen atoms. That is, we must account for the entire molecular weight (136 amu) with only carbon atoms (12 amu) and hydrogen atoms (1 amu). With two double bonds and one ring, the compound has three degrees of unsaturation. So, we begin by considering the following possibilities, each of which has three degrees of unsaturation (as required by the problem statement).

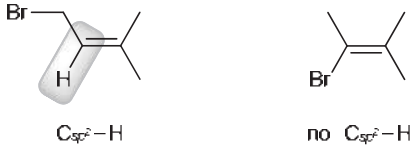
$$C_9H_{14} = (9 \times 12) + (14 \times 1) = 122 \text{ amu}$$
$$C_{10}H_{16} = (10 \times 12) + (16 \times 1) = 136 \text{ amu}$$
$$C_{11}H_{18} = (11 \times 12) + (18 \times 1) = 150 \text{ amu}$$

The middle possibility ($C_{10}H_{16}$) matches exactly (136 amu).

14.51. Let's begin by drawing the structures of the compounds that must be distinguished:



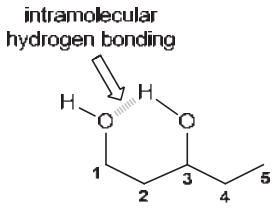
Both of these compounds contain an unsymmetrical C=C bond that is expected to produce a signal in the range between 1600 and 1700 cm^{-1}, so we cannot use that signal to distinguish the compounds. Next we consider any other signals that are expected to appear in the diagnostic region (1600 – 4000 cm^{-1}). Neither compound has a triple bond so the region between 2100 and 2300 cm^{-1} won't be helpful. So we look to the region of the spectrum that has signals from X–H bonds. The first compound does indeed have a C_{sp^2}–H bond that is absent in the second compound:



As such, the IR spectrum of the first compound is expected to exhibit a signal near 3100 cm^{-1}, while the IR spectrum of the second compound is not expected to have any signals above 3000 cm^{-1}. These compounds can therefore be distinguished by looking for a signal at 3100 cm^{-1} in the IR spectrum of each compound.

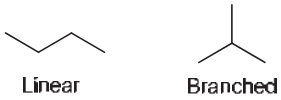
14.52. The compound can exhibit intramolecular hydrogen bonding even in dilute solutions, as shown here:

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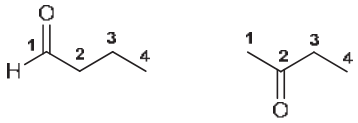


14.53. Each nitrogen atom in the molecular formula of a compound should contribute 0.37% to the $(M+1)^{+\bullet}$ peak. Three nitrogen atoms therefore contribute the same amount (1.1%) as one carbon atom. A compound with the molecular formula $C_8H_{11}N_3$ should have an $(M+1)^{+\bullet}$ peak that is 9.9% as tall as the molecular ion peak. If the molecular ion peak is 24% of the base peak, then the $(M+1)^{+\bullet}$ peak must be 2.4% of the base peak.

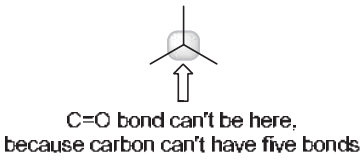
14.54. A compound with the molecular formula C_4H_8O is expected to have the same HDI as a compound with the molecular formula C_4H_8 (the oxygen atom can be ignored for purposes of calculating HDI). With four carbon atoms, the compound would need to have ten hydrogen atoms to be fully saturated. With only eight hydrogen atoms, two are missing, representing one degree of unsaturation (HDI = 1). A compound with one degree of unsaturation must contain either one double bond or one ring (but not both). The IR spectrum indicates the presence of a C=O bond, which accounts for the one degree of unsaturation (this means that the compound does NOT have a ring).
In the absence of a ring, there are only two ways to connect four carbon atoms (linear or branched):



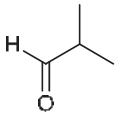
Let's begin with the linear skeleton. There are two unique locations on the linear skeleton where a C=O bond can be placed (either at C1 or at C2):



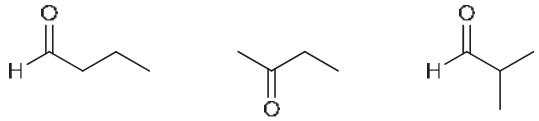
Placing the C=O bond at C3 would be the same as placing it at C2. Similarly, placing the C=O bond at C4 would be the same as placing it at C1.
Next we turn to the branched skeleton. We cannot place a C=O bond at the central position, because that would violate the octet rule:



And the remaining three positions are all identical. Placing the C=O bond at any of these three positions will give the same aldehyde:



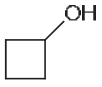
In summary, there are only three possible structures that have the molecular formula C_4H_8O and contain a C=O bond:



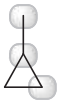
14.55. A compound with the molecular formula C_4H_8O is expected to have the same HDI as a compound with the molecular formula C_4H_8 (the oxygen atom can be ignored for purposes of calculating HDI). With four carbon atoms, the compound would need to have ten hydrogen atoms to be fully saturated. With only eight hydrogen atoms, two are missing, representing one degree of unsaturation (HDI = 1). A compound with one degree of unsaturation must contain either one double bond or one ring (but not both). The IR spectrum does not have signals between 1600 and 1850 cm^{-1}, which indicates the absence of either a C=O bond or an unsymmetrical C=C bond (and a symmetrical double bond is not possible because the compound has only one oxygen atom). Therefore, the structure likely contains a ring. With four carbon atoms, there are only two different types of rings that are possible (a four-membered ring or a three-membered ring):



The broad signal between 3200-3600 cm^{-1} indicates an OH group, so our structure must include an OH group. There is only one unique location where an OH group can be placed on a four-membered ring:

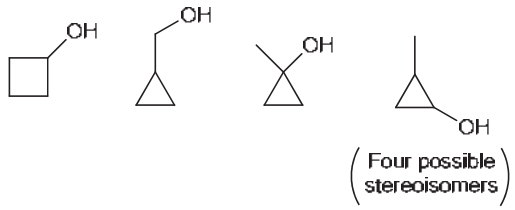


Placement of the OH group at any other location would give the same compound (cyclobutanol). However, there are three unique locations where the OH group can be placed on the other skeleton (containing the three-membered ring):



Our methodical analysis has revealed that there are four constitutional isomers with the molecular formula C_4H_8O that contain one ring and an OH group:

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14.56. A signal at 2200 cm^{-1} signifies the presence of a C≡C bond. There are only two possible constitutional isomers: 1-butyne or 2-butyne. The latter is symmetrical and would not produce a signal at 2200 cm^{-1}. The compound must be 1-butyne.

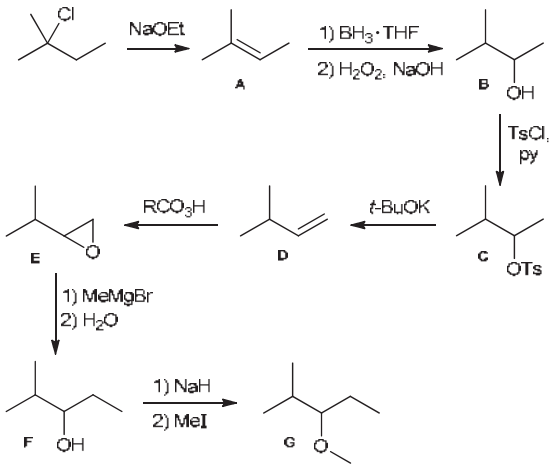
14.57. The IR spectrum has a strong signal just above 1700 cm^{-1}, which indicates that the compound has a C=O bond. The mass spectrum has a molecular ion peak at m/z = 86, which indicates a molecular weight of 86. The base peak is at M–43, indicating the loss of a propyl group. The compound likely has a three carbon chain (either a propyl group or isopropyl group) as shown in the following two structures.



14.58. The IR spectrum has a narrow signal near 2100 cm^{-1}, which indicates the presence of a triple bond. In addition, the signal at 3300 cm^{-1} is consistent with a C_{sp}–H bond, which indicates that the compound is a terminal alkyne. The mass spectrum has a molecular ion peak at m/z = 68, which indicates a molecular weight of 68 amu. So we are looking for terminal alkynes with a molecular weight of 68 amu. Recall that each carbon atom contributes 12 amu, so five carbon atoms contribute 60 amu to the molecular weight, leaving just 8 amu left for hydrogen atoms (each hydrogen atom is 1 amu). That is, compounds with the molecular formula C_5H_8 will have a molecular weight of 68 amu. This molecular formula is consistent with two degrees of unsaturation (a triple bond).
There are two terminal alkynes with the molecular formula C_5H_8, shown here:

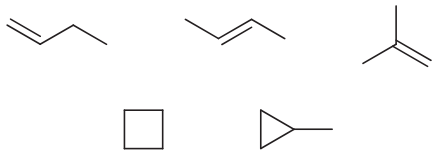


14.59. All of the reactions in the following sequence were covered in previous chapters. The starting alkyl chloride is a tertiary substrate and will undergo an E2 reaction when treated with a strong base. With a base like ethoxide (which is not sterically hindered), the major product is the more-substituted alkene (the Zaitsev product), compound **A**. Hydroboration-oxidation of compound **A** gives an *anti*-Markovnikov addition of H and OH, affording alcohol **B**. When treated with tosyl chloride and pyridine, the alcohol is turned into the corresponding tosylate (compound **C**). Treatment of the tosylate with a sterically hindered base gives another E2 reaction, this time giving the less substituted alkene (the Hofmann product), compound **D**. Treating **D** with a peroxy acid gives epoxide **E**. When the epoxide is treated with a Grignard reagent (such as MeMgBr), followed by an aqueous workup, a ring-opening reaction occurs in which the Grignard reagent attacks the less substituted side of the epoxide, to afford alcohol **F**. The last step of the sequence is a Williamson ether synthesis, in which a methyl group is installed to give compound **G**.



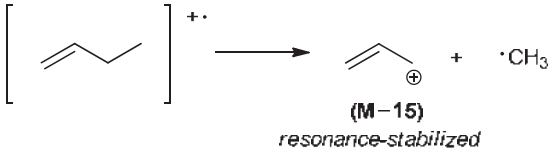
(a) Compound **F** is an alcohol and its IR spectrum will exhibit a broad signal between 3200 and 3600 cm^{-1}. Compound **G** is an ether and its IR spectrum will not exhibit the same signal.
(b) Compound **D** is an alkene and its IR spectrum will exhibit a signal near 1650 cm^{-1} (for the C=C bond), as well as a signal near 3100 cm^{-1} (for the C_{sp^2}–H bond). Compound **E** is an epoxide, and its IR spectrum will not have these two signals.
(c) IR spectroscopy would not be helpful to distinguish these two compounds because they are both alcohols. Mass spectrometry could be used to differentiate these two compounds because they have different molecular weights.
(d) No, they both have the same molecular formula, although a trained expert might be able to distinguish these compounds based on their fragmentation patterns.

14.60. The molecular formula C_4H_8 indicates an HDI of 1. As such, every constitutional isomer of C_4H_8 must contain either one ring or one double bond. The following structures are consistent with this description. Each of the first three constitutional isomers (shown here) exhibits a double bond, while each of the last two constitutional isomers exhibits a ring.

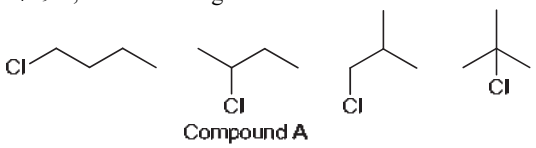


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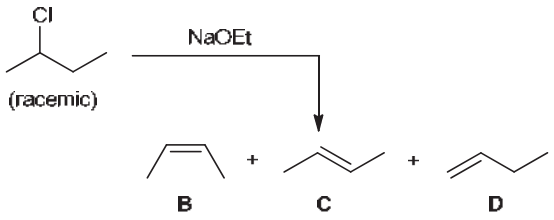
From among these isomers, only one of them (1-butene) can lose a methyl group to form a resonance stabilized carbocation at (M–15):



14.61. As seen in the solution to Problem **2.51**, there are four constitutional isomers with the molecular formula C_4H_9Cl, shown here again:

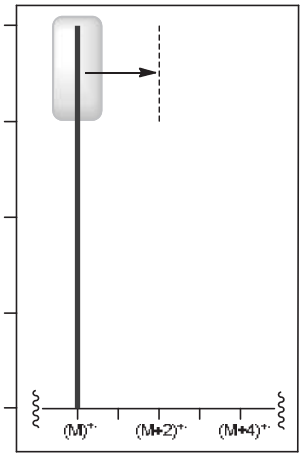


Only one of these four isomers, compound **A**, exhibits a chiral center. When compound **A** is treated with a strong base, the following three alkenes are formed (**B**, **C**, and **D**):

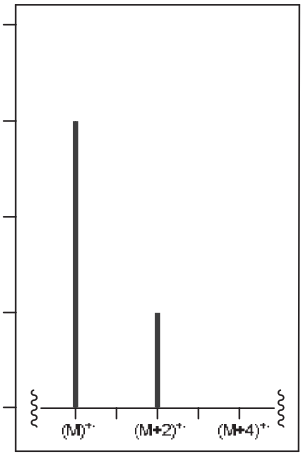


Compounds **B** and **C** are diastereomers (*cis* vs. *trans*), with the *trans* alkene being favored. That leaves the minor product **D**, which is an unsymmetrical alkene. Accordingly, we do expect that the C=C bond will have a small dipole moment, so there should be a signal near 1650 cm^{-1} in the IR spectrum of compound **D**.

14.62. In order to determine the pattern of signals that we expect in the mass spectrum of a compound with two chlorine atoms, we must quickly review the reason for the pattern of signals that are observed for a compound with only one chlorine atom. Let's first imagine that all chlorine atoms had the same mass (35 amu). In such a hypothetical world, we would see the $(M)^{+\bullet}$ peak, but we would not observe a significant $(M+2)^{+\bullet}$ peak. However, all chlorine atoms are not the same mass, because there are two naturally abundant isotopes: ^{35}Cl and ^{37}Cl. The latter represents approximately ¼ of all chlorine atoms in the world. As such, approximately ¼ of the parent ions (for a compound with one chlorine atom) will contain an atom of ^{37}Cl instead of ^{35}C. This causes ¼ of the signal to be moved from $(M)^{+\bullet}$ to $(M+2)^{+\bullet}$.

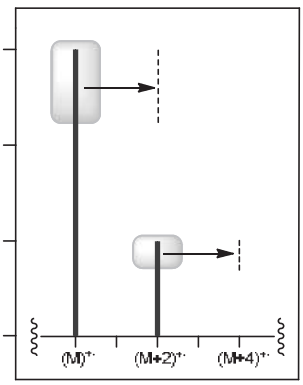


This gives the following familiar pattern of signals, in which the $(M+2)^{+\bullet}$ peak is approximately 1/3 the height of the $(M)^{+\bullet}$ peak:



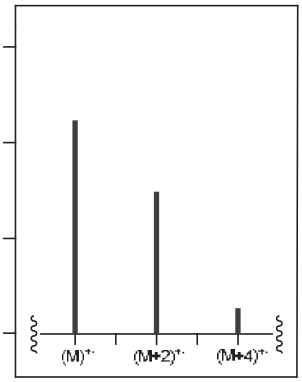
This is the characteristic pattern of signals for a compound with one chlorine atom.

Now let's consider a compound with *two* chlorine atoms. We will begin with the pattern of signals above, and determine how this pattern changes if the parent ion has two chlorine atoms, rather than just one. Once again, ¼ of each peak is moved up by two *m/z* units, because in ¼ of all of those ions, the second chlorine atom will be ^{37}Cl rather than ^{35}Cl.

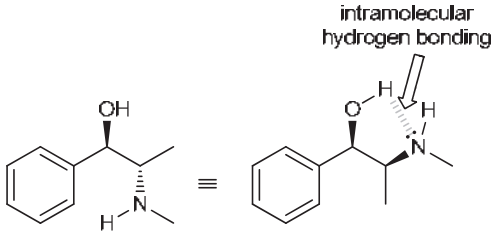


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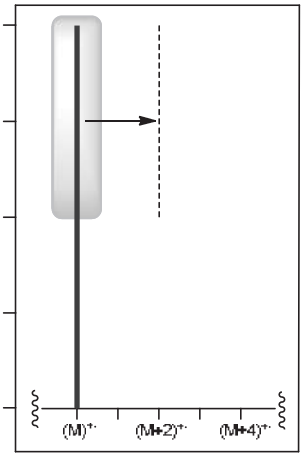
This gives the following pattern of signals at M, M+2, and M+4.



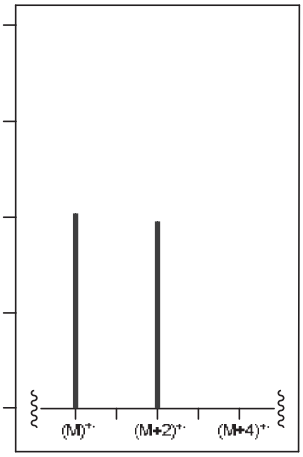
14.63. The OH group in ephedrine can engage in intramolecular hydrogen bonding, even in dilute solutions.



14.64. In order to determine the pattern of signals that we expect in the mass spectrum of a compound with two bromine atoms, we must quickly review the reason for the pattern of signals that are observed for a compound with only one bromine atom. Let's first imagine that all bromine atoms had the same mass (79 amu). In such a hypothetical world, we would see the $(M)^{+\bullet}$ peak, but we would not observe a significant $(M+2)^{+\bullet}$ peak. However, all bromine atoms do not have the same mass, because there are two naturally abundant isotopes: ^{79}Br and ^{81}Br. Each isotope represents approximately half of all bromine atoms in the world. As such, approximately half of the parent ions (for a compound with one bromine atom) will contain an atom of ^{81}Br instead of ^{79}Br. This causes approximately half of the signal to be moved from $(M)^{+\bullet}$ to $(M+2)^{+\bullet}$.

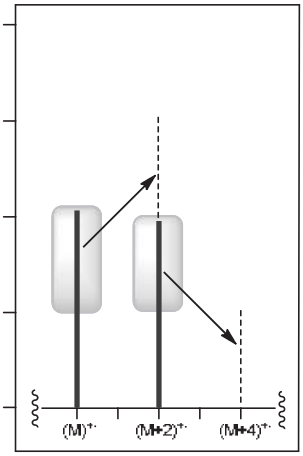


This gives the following familiar pattern of signals, in which the $(M+2)^{+\bullet}$ peak is approximately the same height as the $(M)^{+\bullet}$ peak:

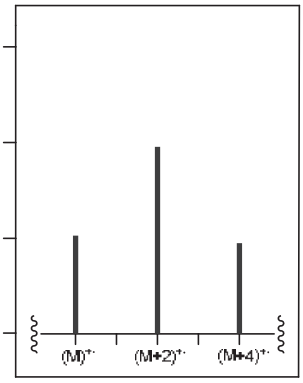


This is the characteristic pattern of signals for a compound with one bromine atom.

Now let's consider a compound with *two* bromine atoms. We will begin with the pattern of signals above, and determine how this pattern changes if the parent ion has two bromine atoms, rather than just one. Once again, half of each peak is moved up by two *m/z* units, because in half of all of those ions, the second bromine atom will be ^{81}Br rather than ^{79}Br.

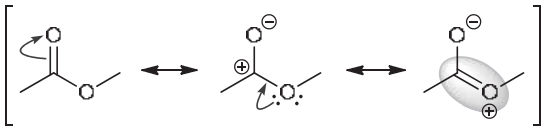


This gives the following pattern of signals at M, M+2, and M+4.

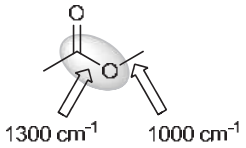


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14.65.
Explanation #1) Outside of the carbonyl group, one of the C–O bonds of the ester has some double bond character, as can be seen in the third resonance structure below:

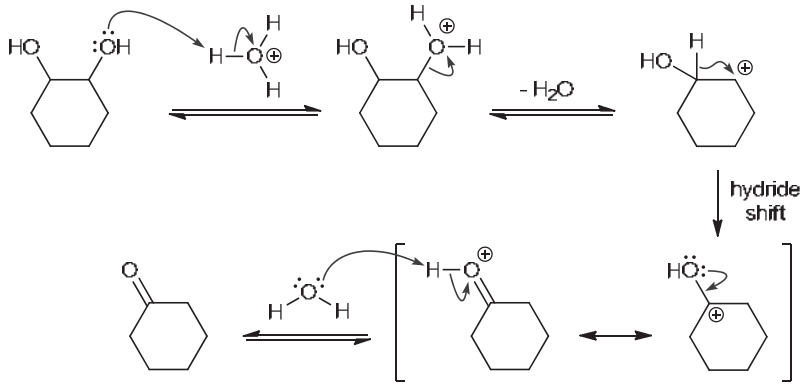


This C–O bond is a stronger bond than the other C–O single bond, which does not have any double bond character. As a result, the stronger C–O bond (highlighted) produces a signal at higher wavenumber.

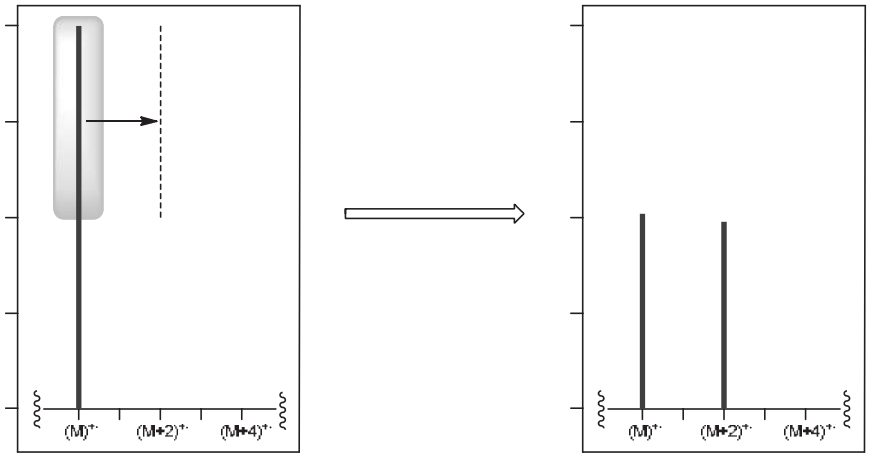


Explanation #2) The C–O bond at 1300 cm^{-1} involves an sp^2 hybridized carbon atom, rather than an sp^3 hybridized carbon atom. The former has more *s*-character and holds its electrons closer to the positively charged nucleus. A C_{sp^2}–O bond is therefore shorter and stronger than a C_{sp^3}–O bond, so the former should produce a signal at higher wavenumber.

14.66. A signal at 1720 cm^{-1} indicates the presence of a C=O bond. The following mechanism justifies the formation of a C=O bond. In the first step, one of the OH groups is protonated to give an oxonium ion, which then loses a leaving group (H_2O) to give a secondary carbocation. This carbocation then rearranges to give a more-stable, resonance-stabilized cation, which is deprotonated to give the product (a ketone), consistent with the signal at 1720 cm^{-1}.

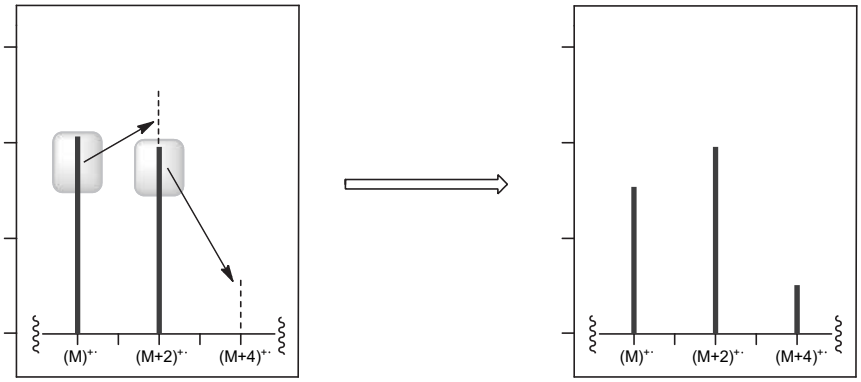


14.67. In the solution to Problem **14.64**, we explained the source of the characteristic peaks that are observed in the mass spectrum for a compound containing a bromine atom. Specifically, the $(M+2)^{+\bullet}$ peak is approximately the same height as the $(M)^{+\bullet}$ peak, because approximately half of the bromine atoms are ^{81}Br, rather than ^{79}Br.

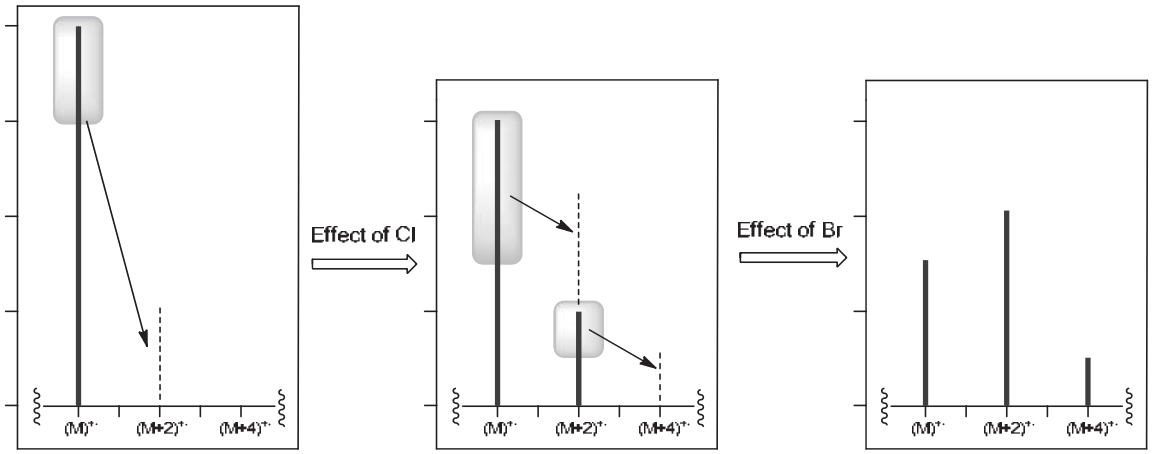


Now let's consider what happens if the parent ion also has a chlorine atom. In the solution to Problem **14.62**, we saw that the effect of a chlorine atom is to move ¼ of each peak by two *m/z* units, which gives the following pattern.

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Incidentally, we would arrive at the same characteristic pattern if we had started our analysis by first considering the effect of the chlorine atom and only then considering the effect of the bromine atom, as illustrated here:



14.68.

(a) The molecular formula for the dye is $C_{21}H_{15}N_2O_6S^-$. Using the values in Table 14.5 for C, H, N and O, and the values given in the question for S, we can calculate the expected mass for the parent ion using the most abundant isotope of each element (^1H, ^{12}C, ^{14}N, ^{16}O, ^{32}S) as follows.

$C_{21}H_{15}N_2O_6S^-$ =
(21 × 12.000) + (15 × 1.0078) + (2 × 14.0031) + (6 × 15.9949) + (1 × 31.9721)
= **423.0647**

This is consistent with reported base peak of the spectrum [(M^-), 100% relative intensity].
Now we must consider the other two peaks – the peak at 424.0681 is nominally 1 amu higher than the parent molecular ion, while the peak at 425.0605 is nominally two amu higher. Considering the relative natural isotopic abundances of C, H, N, O and S, the two elements that have the highest percentage of a second isotope are carbon (^{12}C = 98.93%, ^{13}C = 1.07%) and sulfur (^{32}S = 95.02%, ^{34}S = 4.21%). With this in mind, the peak at *m/z* = 424.0681 is consistent with an ion where one of the ^{12}C atoms is replaced with a ^{13}C.

$^{12}C_{20}{}^{13}C_1H_{15}N_2O_6S^-$ =
(20 × 12.000) + (1 × 13.0034) + (15 × 1.0078) + (2 × 14.0031) + (6 × 15.9949) + (1 × 31.9721)
= **424.0681**

The peak with a nominal mass of 425 is consistent with an ion with one ^{34}S, as demonstrated by the calculation below:

$C_{21}H_{15}N_2O_6{}^{34}S^-$ =
(21 × 12.000) + (15 × 1.0078) + (2 × 14.0031) + (6 × 15.9949) + (1 × 33.9679)
= **425.0605**

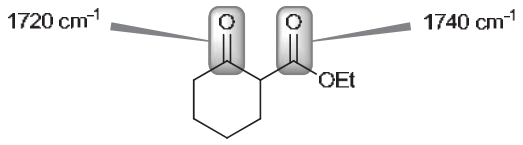
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Now, we must consider the relative abundances of each peak. The peak at *m/z* = 423.0647 is the base peak, because it has a relative abundance of 100% (it is, by definition, the most abundant ion). The peak at 424.0681 has an abundance of 22.5%, relative to the most abundant ion. This is consistent with an ion having 21 carbon atoms, because the natural abundance of ^{13}C is 1.07%. [21 × 1.07% = 22.5%]
The peak at 425.0605 has an abundance of 4.21%, relative to the most abundant ion. This is consistent with an ion having one sulfur atom, because the natural abundance of ^{34}S is 4.21%. [1 × 4.21% = 4.21%]

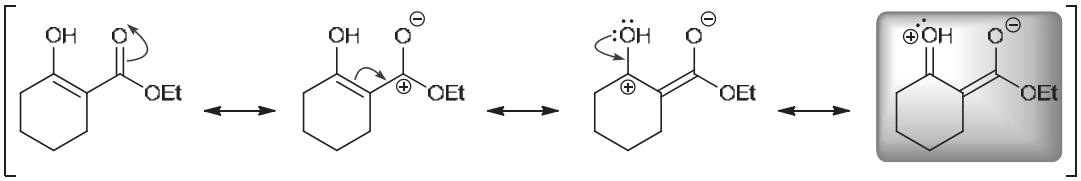
(b) The peak at *m/z* = 425.0605 is consistent with an ion in which two of the ^{12}C atoms are replaced with two ^{13}C atoms:

$^{12}C_{19}{}^{13}C_2H_{15}N_2O_6S^-$ =
(19 × 12.000) + (2 × 13.0034) + (15 × 1.0078) + (2 × 14.0031) + (6 × 15.9949) + (1 × 31.9721)
= **425.0715**

14.69.
(a) Tautomerization occurs rapidly (and is difficult to prevent) so an IR spectrum of **A** is essentially an IR spectrum of a mixture of **A** and **B**. The signal at 1740 cm^{-1} corresponds to the nonconjugated C=O bond of the ester group in **A**, and the signal at 1720 cm^{-1} corresponds to the nonconjugated C=O bond of the ketone group in **A**, just as we would expect.

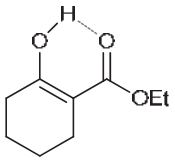


The C=O bond in compound **B** is part of a conjugated ester, so it appears at a lower wavenumber than a typical C=O bond of an ester. This must be the signal at 1660 cm^{-1}. This might be initially surprising, as we might have expected a conjugated ester to produce a signal around 1700 cm^{-1}. But on further inspection, we recognize that this conjugated system has an OH group, whose lone pairs are participating in resonance.



As such, there is one additional resonance structure (highlighted above); this additional resonance structure gives the C=O bond additional single bond character (relative to other conjugated esters).
Finally, the signal at 1620 cm^{-1} corresponds with the conjugated C=C bond in **B**.

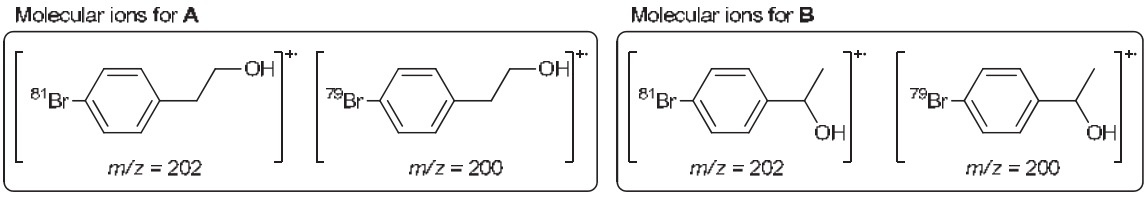
(b) Compound **B** is capable of forming an intramolecular hydrogen bonding interaction, which lowers the energy of that tautomer. As such, it has a more significant presence at equilibrium.



There is one additional factor that favors the enol in this case, which we will discuss in Chapter 16. Specifically, we will see that conjugation is a source of stabilization. Compound **B** possesses this type of stabilization, while compound **A** does not.

14.70.
The two compounds are isomers (both have the molecular formula C_8H_9BrO) so we expect the molecular ion from each of them to have the same *m/z* value. Recall that there are two isotopes of bromine with approximately equivalent natural abundance (^{81}Br and ^{79}Br), which results in two molecular ion peaks for each compound:

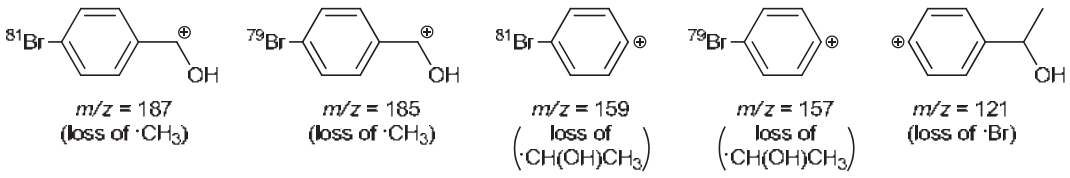
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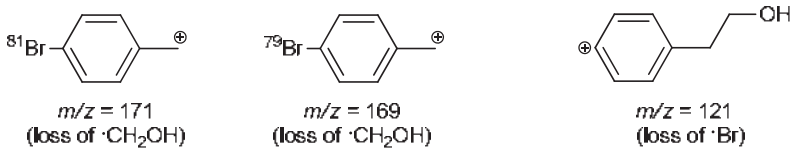
These molecular ions correspond to the two highest *m/z* peaks in each spectrum. Now we have to consider fragmentation patterns to match each spectrum to the correct isomer. Note that in each spectrum, there are several pairs of peaks separated by two mass units. This is consistent with the presence of bromine in these fragments, with the two peaks corresponding to fragments with ^{79}Br and ^{81}Br, respectively, just as observed for the molecular ion. In the peak list below, pairs separated by two mass units are shown in brackets.

Sample **X**, *m/z* = [202, 200], [187, 185], [159, 157], 121
Sample **Y**, *m/z* = [202, 200], [171, 169], 121

Focusing on sample **X**, the peaks at 187 and 185 represent a loss of 15 from the molecular ions 202 and 200, respectively. This is consistent with the loss of a $\bullet CH_3$ radical fragment. Compound **B** has a methyl group, while compound **A** does not, suggesting that this spectrum is from compound **B**. The peaks at 159 and 157 represent a loss of 43 from the molecular ions 202 and 200, respectively. This is consistent with the loss of a $\bullet CH(OH)CH_3$ radical fragment. The peak at 121 represents a loss of $^{81}Br\bullet$ radical from the heavier molecular ion (202-81=121) or a loss of $^{79}Br\bullet$ radical from the lighter molecular ion (200-79=121). These data are consistent with the structure of compound **B**, and the ions below.

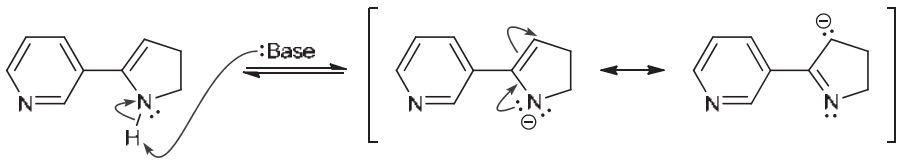


Focusing on sample **Y**, the peaks at 171 and 169 represent a loss of 31 from the molecular ions 202 and 200, respectively. This is consistent with the loss of a $\bullet CH_2OH$ radical fragment. The peak at 121 represents a loss of $^{81}Br\bullet$ radical from the heavier molecular ion (202-81=121) or a loss of $^{79}Br\bullet$ radical from the lighter molecular ion (200-79=121), analogous to the corresponding peak in sample **X**. These data are consistent with the structure of compound **A** and with the ions shown below.



14.71.
(a) The structure contains an N-H bond, which is expected to produce a broad signal above 3300 cm^{-1}, but that signal is absent from the spectrum.

(b) Recall that tautomers are constitutional isomers that can rapidly interconvert via the migration of a proton. We know that the tautomer of the proposed structure must not exhibit an N-H bond, so it is clear that this is the proton that must migrate. To determine where it migrates, we remove the proton (this is how tautomerization occurs under base-catalyzed conditions) and draw the conjugate base, which is resonance stabilized:



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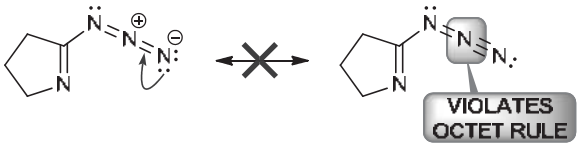
The second resonance structure indicates where the proton is likely to migrate. Specifically, protonation of the negatively charged carbon atom leads to the following compound:



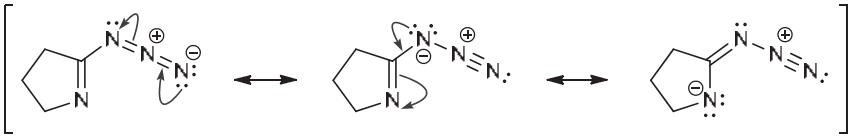
This compound lacks an N-H bond and is therefore consistent with the IR spectrum.

(c) The tautomer of the proposed structure exhibits a C=N bond, which is likely to be the source of the signal at 1621 cm^{-1} (this is the region of the spectrum where double bonds generally appear). An unconjugated C=N bond would likely appear at a higher wavenumber than 1621 cm^{-1}, but this C=N bond is conjugated, so the location of the signal is appropriate if the source of the signal is indeed the C=N bond.

14.72. Notice that the azido group in compound **2** exhibits charge separation. If we try to draw a resonance structure without charge separation, we find that we cannot do so without violating the octet rule:



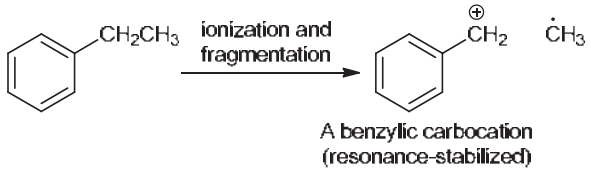
We see that the structure of the azido group cannot be drawn without charge separation (much like a nitro group, which also cannot be drawn without charge separation). Nevertheless, the azido group is still stabilized by resonance, as seen here:



Notice that the second and third resonance structures exhibit a nitrogen-nitrogen triple bond. We therefore expect that this bond will have significant triple bond character. Indeed, azido groups typically produce a characteristic signal in the triple bond region of an IR spectrum (2120-2160 cm^{-1}). The absence of this signal indicates that compound **2** is not present in substantial quantities.

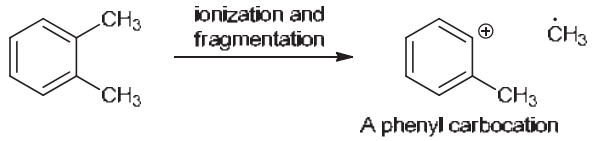
14.73. The IR spectrum shows a very broad signal in the range of 2200–3600 cm^{-1}, as well as a strong signal at 1700 cm^{-1}, indicating the presence of a carboxylic acid group. Carboxylic acids can only be made via oxidation of primary alcohols (not secondary or tertiary). The correct answer is (a). Choice (d) is not correct because the compound may or may be acyclic or cyclic (we lack the information necessary to make such a determination).

14.74. All of these isomers have the molecular formula C_8H_{10} (molecular weight = 106 amu), so we expect the molecular ion to be at *m/z* = 106. A peak at *m/z* = 91 corresponds with M-15, which indicates the loss of a methyl group. All of the isomers have methyl groups, but only option (a) gives a relatively stable benzylic carbocation upon loss of a methyl radical:



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All of the other options lead to unstable phenyl carbocations, for example:



Since the most abundant peak is expected to result from formation of the most stable carbocation, the correct answer is (a).

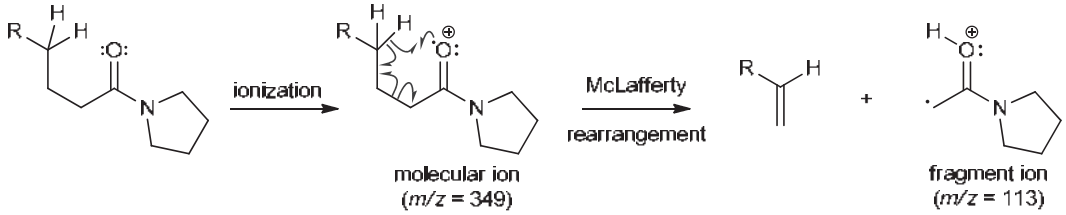
14.75 The mass spectrum shows a molecular ion at *m/z* 78. This corresponds with option (a) which has the molecular formula C_6H_6 (MW = 78). Option (b) has the molecular formula C_6H_8 (MW = 80), option (c) has the molecular formula C_6H_{12} (MW = 84), and option (d) has the molecular formula C_6H_4 (MW = 76). Only option (a) has the correct molecular weight.

14.76. The molecular ion for cyclohexanone is expected at *m/z* = 98, so the two peaks at *m/z* = 55 must be due to ionic fragments. Considering the atoms present in cyclohexanone ($C_6H_{10}O$), we must consider all possible ionic formula with a nominal *m/z* = 55.
One approach to this is to start with the heavier elements (carbon, oxygen) to come up with a formula close to (but not greater than) 55 and then adding in hydrogens to make up the difference. For example, an ion with 4 carbon atoms (nominal mass = 48) would require 7 hydrogen atoms (nominal mass = 7) to give the correct total mass [48+7=55]. Alternatively, we can start with one oxygen atom (nominal mass = 16), add three carbon atoms (nominal mass = 36), and 3 hydrogen atoms (nominal mass = 3) [16+36+3=55]. Thus, our two possible ionic formulas that fit are $C_3H_3O^+$ and $C_4H_7^+$.
Using the values in Table 15.5, we can calculate the high resolution masses:

$C_3H_3O^+ = (3 \times 12.000) + (3 \times 1.0078) + (1 \times 15.9949) =$ **55.0183** amu
$C_4H_7^+ = (4 \times 12.000) + (7 \times 1.0078) =$ **55.0546** amu

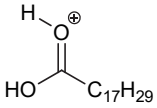
The peak at *m/z* = 55.0183 (with a relative intensity of 86.7) is thus assigned to $C_3H_3O^+$, and the peak at *m/z* = 55.0546 (with a relative intensity of 13.3) is assigned to $C_4H_7^+$.

14.77.
Using the nitrogen rule, we can quickly determine that the molecular mass of the parent compound is an odd number since there is one nitrogen atom in the structure. Thus, the difference in mass between the expected molecular ion (an odd number) and the fragment of interest (*m/z* = 113, which is also an odd number) is an even number. This suggests the possibility of a McLafferty rearrangement. [This can be confirmed by calculating the molecular mass using the molecular formula ($C_{23}H_{43}NO$), resulting in a difference between the expected molecular ion (*m/z* = 349) and the fragment of interest (*m/z* = 113) of 236.] This amide has the structural feature required for such a rearrangement: a hydrogen atom that is gamma to a C=O group (analogous to the ketones and aldehydes discussed in section 14.12). The resulting ion (*m/z* = 113) and its mechanism of formation are presented below.



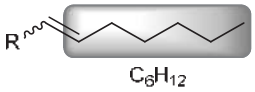
14.78.
(a) The mass of pinolenic acid (based on its given chemical formula) is 278 amu. The significant peak at 279 in positive ion mode is likely due to the addition of a proton, as this experiment is performed under conditions facilitating protonation. We can refer to this ion as the $(M+1)^+$ ion.

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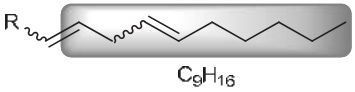


Next, we need to determine the positions of the three *cis* double bonds. The peaks at 211, 171 and 117 (which only appear when ozone is present) are likely due to ozonolysis products of each of the three alkenes. In each case, the C=C is replaced with C=O bonds. These three peaks represent losses of 68, 108, and 162 from the $(M+1)^+$ ion. The change in mass between the $(M+1)^+$ ion and each of the ozonolysis products corresponds to the loss of carbon atoms and hydrogen atoms (from the chain terminus to each sp^2 hybridized carbon atom) as well as the gain of an oxygen atom. Accounting for the additional mass of oxygen (16) in each ionic fragment, the portions of the molecule cleaved by ozonolysis have masses of **84** (=68+16), **124** (=108+16) and **178** (=162+16).

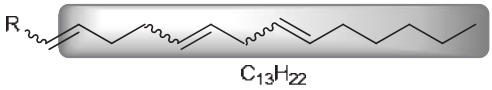
With this information, we can reconstruct the chain starting from the end distal to the carboxylic acid. A loss of 84 is consistent with the loss of a C_6H_{12} fragment.



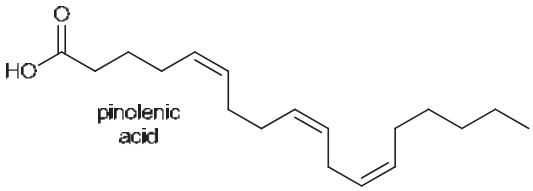
Continuing up the chain, a loss of 124 is consistent with the loss of a C_9H_{16} fragment.



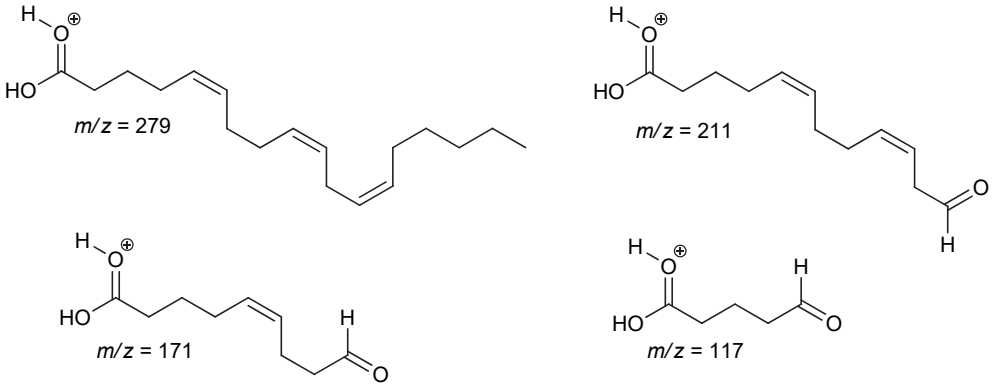
A loss of 178 is consistent with the loss of a $C_{13}H_{22}$ fragment.



With all of this information in hand, along with the knowledge that all of the double bonds have the *cis* configuration, we can propose the following structure for pinolenic acid:

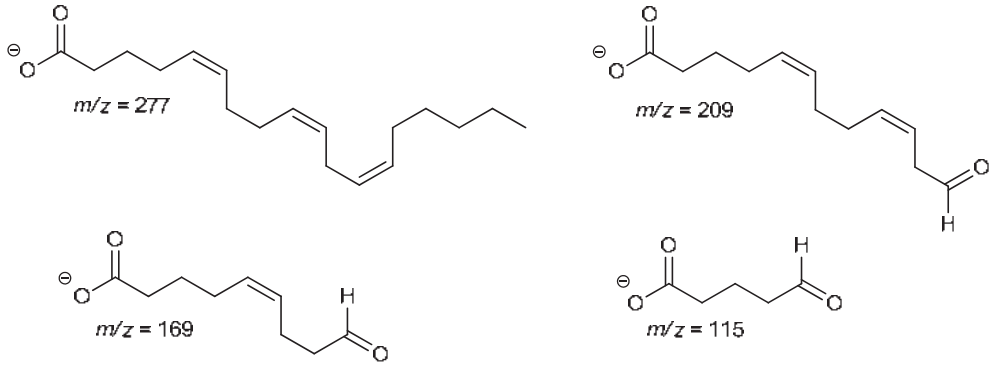


And we can propose the following structures for the four indicated fragments in positive ion mode.

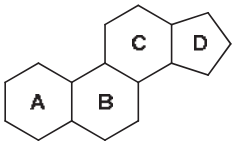


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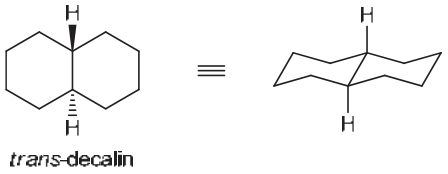
(b) In negative ion mode, under conditions facilitating deprotonation, we expect to form the conjugate base of the carboxylic acid instead of the conjugate acid, thus giving the following ions, each with two mass units lower than the corresponding ions in positive ion mode.



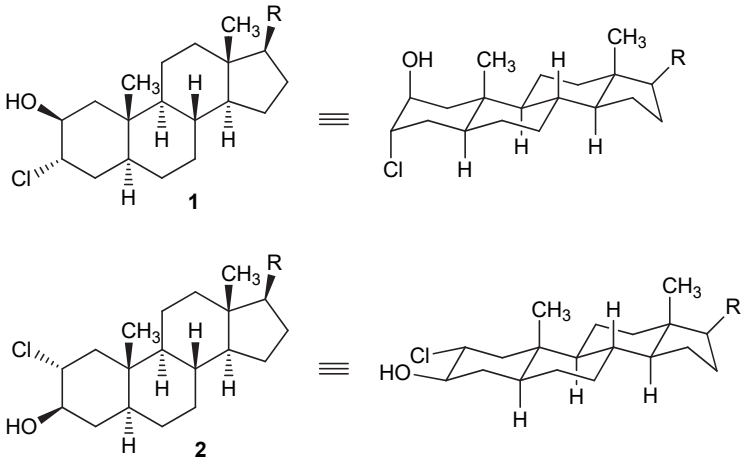
14.79.
(a) Each of these compounds has four rings, which we can label A-D:



Notice that the A-B ring fusion resembles a *trans*-decalin system, which we explored at the end of Chapter 4:



But in our cases here, there four rings. Building on the decalin system as a foundation, can we redraw our compounds (starting with the A-B ring fusion), in a way that shows the conformation of each ring:



These polycyclic systems are conformationally rigid, because none of the six-membered rings can undergo a ring flip (you might find it helpful to build a model to prove to yourself that this is the case). Notice that in compound **2**, the

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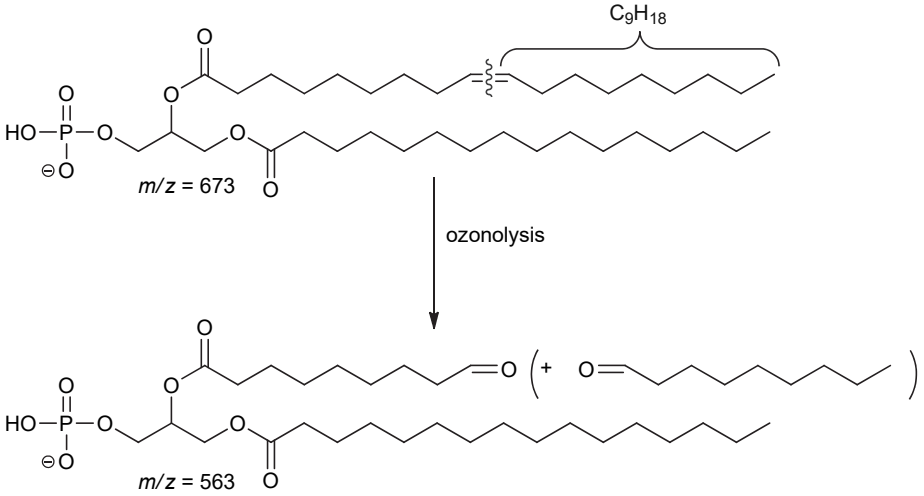
OH group and the Cl group are in close proximity and can therefore participate in an intramolecular hydrogen-bonding interaction (which weakens the existing O-H bond in **2**, giving a lower wavenumber of absorption). In contrast, the OH group and the Cl group are far apart from each other in compound **1**, and cannot participate in an intramolecular hydrogen-bonding interaction.

(b) The problem statement specifies that dilute solutions were investigated. As such, the effects of *inter*molecular hydrogen bonds are negligible and can be ignored. Compound **2** is capable of forming an *intra*molecular hydrogen bonding interaction (while compound **1** is not), so the signal for the OH group in compound **2** is expected to be broader.

14.80.

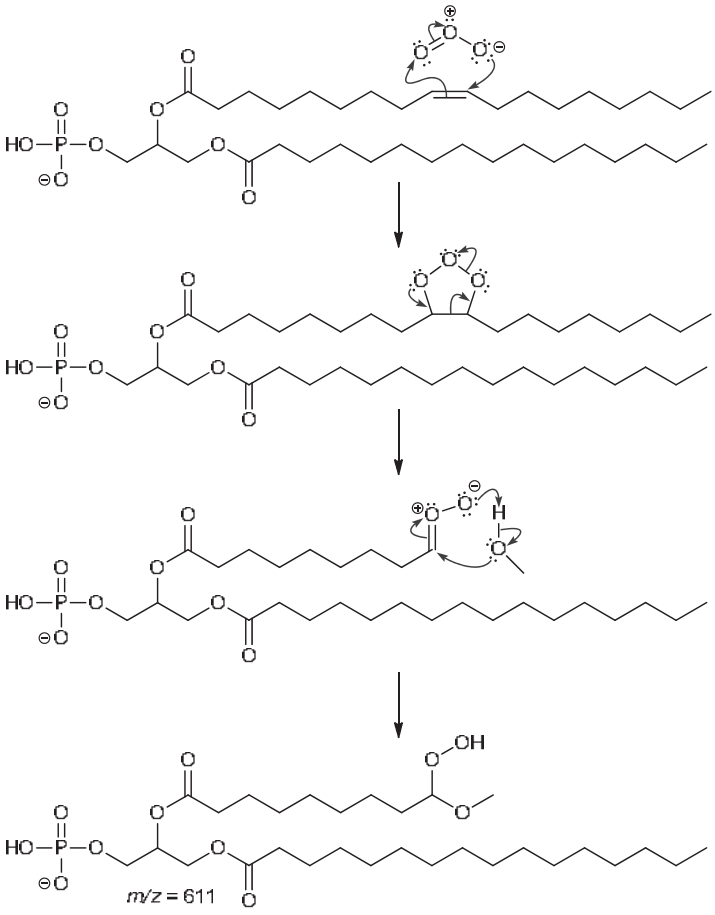
(a) The problem statement indicates that one of the two hydrocarbon chains contains a *cis* alkene group. To determine which of these two chains contains the double bond, consider the relative numbers of carbon atoms and hydrogen atoms in each chain. One of these chains ($-C_{15}H_{31}$) is fully saturated, because there are two hydrogen atoms for every carbon atom in the chain, except for the terminal methyl group which has three hydrogen atoms. In contrast, the other chain ($-C_{17}H_{33}$) must be unsaturated, because a saturated chain with 17 carbon atoms would be expected to have 35 hydrogen atoms (16 C with two H's and one C with three H's). Since it has only 33 hydrogen atoms, this chain must contain the double bond.

Now that we know which chain contains the double bond, we can determine the position of the double bond by analyzing the mass spectrometry data. The introduction of ozone allows for ozonolysis of the alkene, breaking the C=C bond and producing two new C=O bonds. The peak at *m/z* = 563 provides the information needed to determine the position of the double bond. The change in mass between the parent ion and the product of ozonolysis (110 mass units) corresponds to the loss of carbon atoms and hydrogen atoms (from the chain terminus to the first sp^2 hybridized carbon) as well as the gain of an oxygen atom. Accounting for the additional mass of oxygen (16), the portion of the molecule that was cleaved by ozonolysis has a mass of 126. This is consistent with the loss of a fragment with the formula C_9H_{18}, as shown here:



(b) The difference between the new peak in methanol (611) and the new peak in ethanol (625) is 14 mass units. This is equivalent to the difference in mass between the two alcohols (methanol = 32, ethanol = 46), suggesting that the new peak arises from incorporation of solvent. Focusing on the methanol experiment, the difference between the peak for the ozonolysis product (563) and the second peak (611) is 48, suggesting that the mystery product incorporates methanol (mass = 32) plus an extra oxygen (mass = 16) [32+16=48]. Likewise, when ethanol is used the new peak at 625 (which is 62 larger than 563) is due to incorporation of ethanol (mass = 46) plus an extra oxygen (mass = 16) [46+16=62]. This is consistent with the incorporation of the alcohol solvent by reacting with one of the intermediates of the ozonolysis reaction, as shown here.

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Chapter 15
Nuclear Magnetic Resonance Spectroscopy

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 15. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

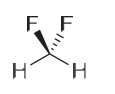
- A spinning proton generates a **magnetic** _____, which must align either with or against an imposed external magnetic field.
- All protons do not absorb the same frequency because of _____, a weak magnetic effect due to the motion of surrounding electrons that either **shield** or **deshield** the proton.
- _____ solvents are generally used for acquiring NMR spectra.
- In a ^{1}H NMR spectrum, each signal has three important characteristics: _____, _____ and _____.
- When two protons are interchangeable by rotational symmetry, the protons are said to be _____.
- When two protons are interchangeable by reflectional symmetry, the protons are said to be _____.
- The left side of an NMR spectrum is described as _____**field**, and the right side is described as _____**field**.
- In the absence of inductive effects, a methyl group (CH_3) will produce a signal near _____ppm, a **methylene group** (CH_2) will produce a signal near _____, and a _____ **group** (CH) will produce a signal near _____. The presence of nearby groups increases these values somewhat predictably.
- The _____, or area under each signal, indicates the number of protons giving rise to the signal.
- _____represents the number of peaks in a signal. A _____has one peak, a _____has two, a _____has three, a _____has four, and a _____has five.
- Multiplicity is the result of **spin-spin splitting**, also called _____, which follows the **n+1 rule**.
- When signal splitting occurs, the distance between the individual peaks of a signal is called the **coupling constant**, or _____ **value**, and is measured in hertz.
- Complex splitting occurs when a proton has two different kinds of neighbors, often producing a _____.
- ^{13}C is an _____of carbon, representing _____% of all carbon atoms.
- All ^{13}C-^{1}H splitting is suppressed with a technique called **broadband** _____, causing all of the ^{13}C signals to collapse to _____.

Review of Skills

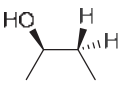
Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 15. The answers appear in the section entitled *SkillBuilder Review*.

15.1 Determining the Relationship between Two Protons in a Compound

FOR EACH OF THE FOLLOWING COMPOUNDS, IDENTIFY THE RELATIONSHIP BETWEEN THE TWO INDICATED PROTONS (ARE THEY HOMOTOPIC, ENANTIOTOPIC OR DIASTEREOTOPIC?) AND DETERMINE WHETHER THEY ARE CHEMICALLY EQUIVALENT.









RELATIONSHIP

CHEMICALLY EQUIVALENT?

15.2 Identifying the Number of Expected Signals in a ^{1}H NMR Spectrum

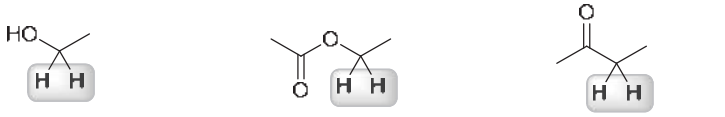
FOR EACH OF THE FOLLOWING COMPOUNDS, DETERMINE WHETHER THE INDICATED PROTONS ARE CHEMICALLY EQUIVALENT.



CHEMICALLY EQUIVALENT? ☐ ☐ ☐ ☐

15.3 Predicting Chemical Shifts

FOR EACH OF THE FOLLOWING COMPOUNDS, PREDICT THE EXPECTED CHEMICAL SHIFT OF THE INDICATED PROTONS.



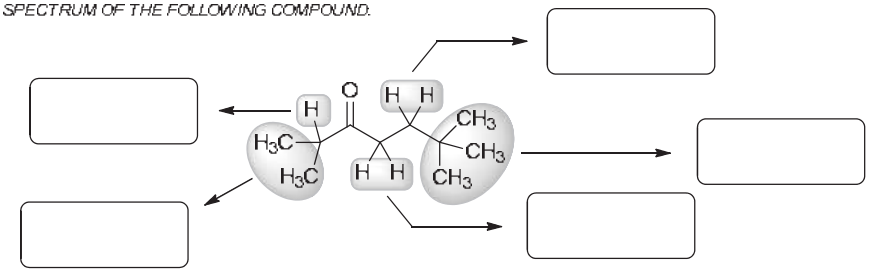
☐ ppm ☐ ppm ☐ ppm

15.4 Determining the Number of Protons Giving Rise to a Signal

STEP 1 - COMPARE THE RELATIVE _____ VALUES, AND CHOOSE THE LOWEST NUMBER.	**STEP 2 -** DIVIDE ALL INTEGRATION VALUES BY THE NUMBER FROM STEP #1, WHICH GIVES THE RATIO OF _____.	**STEP 3 -** IDENTIFY THE NUMBER OF PROTONS IN THE COMPOUND (FROM THE MOLECULAR FORMULA) AND THEN ADJUST THE RELATIVE INTEGRATION VALUES SO THAT THE SUM TOTAL EQUALS THE NUMBER OF _____.

15.5 Predicting the Multiplicity of a Signal

IDENTIFY THE EXPECTED MULTIPLICITY FOR EACH SIGNAL IN THE PROTON NMR SPECTRUM OF THE FOLLOWING COMPOUND.



15.6 Drawing the Expected ^{1}H NMR Spectrum of a Compound

STEP 1 - IDENTIFY THE NUMBER OF _____.	**STEP 2** - PREDICT THE _____ _____ OF EACH SIGNAL.	**STEP 3** - DETERMINE THE _____ OF EACH SIGNAL BY COUNTING THE NUMBER OF _____ GIVING RISE TO EACH SIGNAL.	**STEP 4** - PREDICT THE _____ OF EACH SIGNAL.	**STEP 5** - DRAW EACH SIGNAL.

15.7 Using ^{1}H NMR Spectroscopy to Distinguish Between Compounds

STEP 1 - IDENTIFY THE NUMBER OF _____ THAT EACH COMPOUND WILL PRODUCE.	**STEP 2** - IF EACH COMPOUND IS EXPECTED TO PRODUCE THE SAME NUMBER OF SIGNALS, THEN DETERMINE THE _____, _____, AND _____ OF EACH SIGNAL IN BOTH COMPOUNDS.	**STEP 3** - LOOK FOR DIFFERENCES IN THE CHEMICAL SHIFTS, MULTIPLICITIES OR INTEGRATION VALUES OF THE EXPECTED SIGNALS.

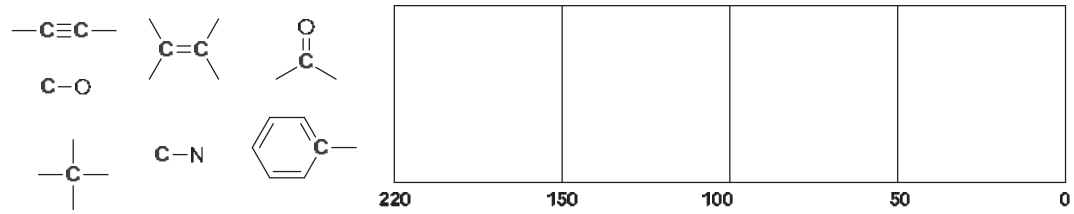
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15.8 Analyzing a ^{1}H NMR Spectrum and Proposing the Structure of a Compound

STEP 1 - *USE THE _____ _____ TO DETERMINE THE HDI. AN HDI OF _____ INDICATES THE POSSIBILITY OF AN AROMATIC RING.*	**STEP 2 -** *CONSIDER THE NUMBER OF SIGNALS AND INTEGRATION OF EACH SIGNAL (GIVES CLUES ABOUT THE _____ OF THE COMPOUND).*	**STEP 3 -** *ANALYZE EACH SIGNAL (____, ____, AND ____), AND THEN DRAW FRAGMENTS CONSISTENT WITH EACH SIGNAL. THESE FRAGMENTS BECOME OUR PUZZLE PIECES THAT MUST BE ASSEMBLED TO PRODUCE A MOLECULAR STRUCTURE.*	**STEP 4 -** *ASSEMBLE THE FRAGMENTS.*	**STEP 5 -** *VERIFY THAT THE PROPOSED STRUCTURE IS CONSISTENT WITH ALL OF THE SPECTRAL DATA.*

15.9 Predicting the Number of Signals and Approximate Location of Each Signal in a ^{13}C NMR Spectrum

BELOW ARE SEVEN DIFFERENT TYPES OF CARBON ATOMS. EACH OF THEM IS EXPECTED TO PRODUCE A SIGNAL IN ONE OF FOUR POSSIBLE REGIONS IN A CARBON NMR SPECTRUM. IDENITFY THE EXPECTED REGION FOR EACH TYPE OF CARBON ATOM.



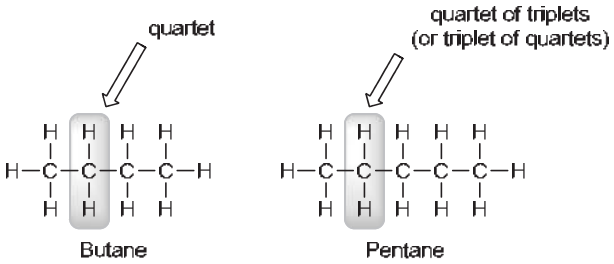
15.10 Determining Molecular Structure using DEPT ^{13}C NMR Spectroscopy

COMPLETE THE FOLLOWING CHART BY DRAWING THE EXPECTED SHAPE OF EACH SIGNAL:

	CH_3	CH_2	CH	C
BROADBAND DECOUPLED				
DEPT-90				
DEPT-135				

Mistakes to Avoid

In ^{1}H NMR spectroscopy, two neighboring CH_2 groups will only split each other if they are not chemically equivalent. For example compare the structures of butane and pentane, and in particular, compare the CH_2 group at the C2 position in each structure, highlighted below:

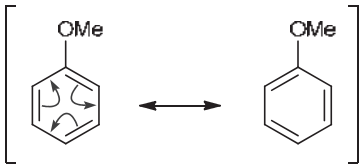


In the case of butane, the signal for the highlighted CH_2 group is expected to be a quartet as a result of the neighboring methyl group. Notice that the signal is not further split by the neighboring CH_2 group (C3), because the CH_2 groups at C2 and C3 are chemically equivalent and therefore, they don't split each other. In contrast, the signal for the highlighted CH_2 group in pentane has a more complex multiplicity. In the case of pentane, the C2 and C3 positions are not identical. The C2 position is next to a methyl group, while the C3 position is not. They occupy different electronic environments, and they are not interchangeable by symmetry. As a result, the signal for the highlighted CH_2 group (C2) is expected to be split into a quartet of triplets (or into a triplet of quartets, depending on which *J* value is larger). When analyzing a ^1H NMR spectrum, make sure to take this into account, as students will often misinterpret a spectrum as a result of failing to take this into account.

Solutions

15.1.

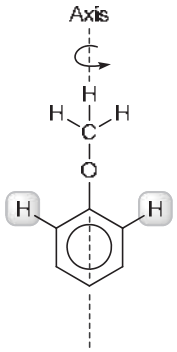
(a) When looking for symmetry, don't be confused by the position of the double bonds in the aromatic ring. Recall that we can draw the following two resonance structures:



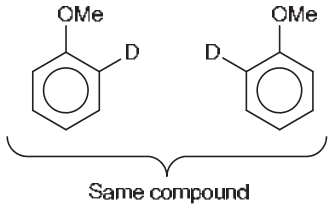
Neither resonance structure is more correct than the other. For purposes of looking for symmetry, it will be less confusing to draw the compound like this:



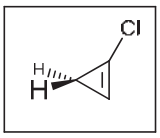
When drawn in this way, we can see that the two highlighted protons can be interchanged by rotational symmetry (the axis of symmetry is shown below). Therefore, the protons are homotopic.



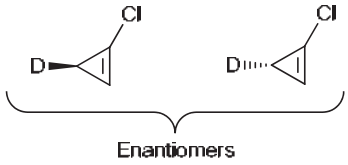
This conclusion can be verified by the replacement test. Specifically, each proton is replaced with deuterium, and the resulting compounds are found to be the same. Therefore, the compounds are homotopic:



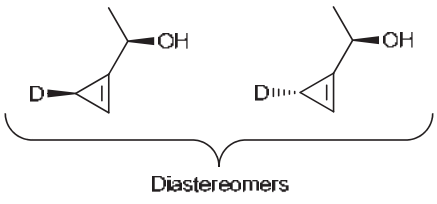
(b) These protons cannot be interchanged by rotational symmetry, so they are not homotopic. They can be interchanged by reflectional symmetry (the plane of symmetry is the plane of the page). Therefore, the protons are enantiotopic.



This conclusion can be verified by the replacement test. Specifically, each proton is replaced with deuterium, and the resulting compounds are found to be enantiomers. Therefore, the compounds are enantiotopic:

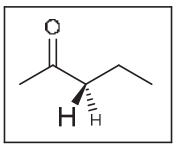


(c) These protons cannot be interchanged by rotational symmetry, so they are not homotopic. They also cannot be interchanged by reflectional symmetry so they are not enantiotopic either. To determine if they are diastereotopic, we use the replacement test. Specifically, each proton is replaced with deuterium, and the resulting compounds are found to be diastereomers. Therefore, the compounds are diastereotopic:

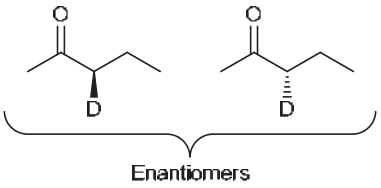


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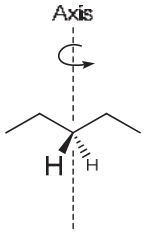
(d) These protons cannot be interchanged by rotational symmetry, so they are not homotopic. They can be interchanged by reflectional symmetry (the plane of symmetry is the plane of the page). Therefore, the protons are enantiotopic.



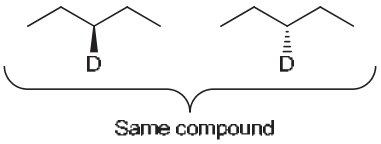
This conclusion can be verified by the replacement test. Specifically, each proton is replaced with deuterium, and the resulting compounds are found to be enantiomers. Therefore, the compounds are enantiotopic:



(e) These protons can be interchanged by rotational symmetry (the axis of symmetry is shown below). Therefore, the protons are homotopic.



This conclusion can be verified by the replacement test. Specifically, each proton is replaced with deuterium, and the resulting compounds are found to be the same. Therefore, the compounds are homotopic:

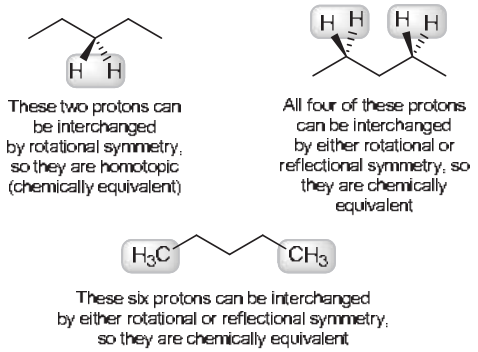


15.2.

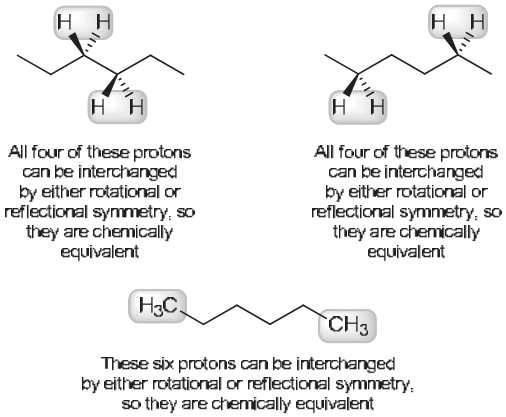
(a) All four protons shown in red can be interchanged either via rotation or reflection, so they are all chemically equivalent.

(b) The three protons of a methyl group are always equivalent (as we will soon see, immediately after the SkillBuilder), and in this case, the two methyl groups are equivalent to each other because they can be interchanged by rotation. Therefore, all six protons shown in blue are equivalent.

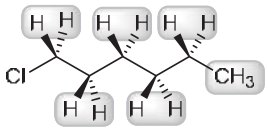
(c) Pentane has three different kinds of protons, shown here:



(d) Hexane has three different kinds of protons, shown here:



(e) The presence of a chlorine atom creates six different environments (in terms of proximity to the Cl), so there are six different kinds of protons, highlighted here:



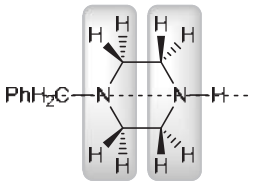
15.3. The compound must have a high degree of symmetry in order to have only one kind of proton. The molecular formula indicates that there are twelve protons. The equivalence of twelve protons can be achieved by four methyl groups in identical environments. Four methyl groups account for four of the five carbon atoms in the compound. So, we can draw a structure in which the fifth carbon atom is connected to each of the methyl groups (shown below), providing the necessary symmetry:



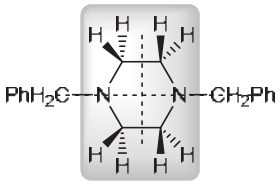
15.4. In BZP, the two protons on each CH_2 group are equivalent, because they can be interchanged by reflectional symmetry (the plane of symmetry is the plane of the page). In addition, a second plane of

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symmetry passing through both nitrogen atoms in the ring makes the CH_2 groups on one half of the molecule equivalent to the corresponding CH_2 groups on the other half of the molecule. Overall, BZP has two signals for the piperazine CH_2 protons, as shown below:

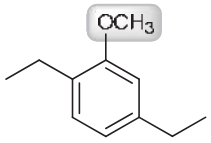


DBZP has an additional plane of symmetry (slicing top to bottom in the structure shown), so all eight CH_2 protons are equivalent, and only one signal is expected for these eight protons.

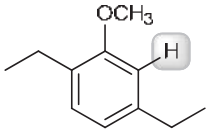


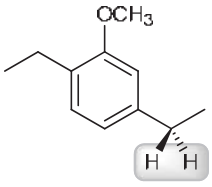
15.5.

(a) This compound has eight different kinds of protons (highlighted below), giving rise to eight signals.

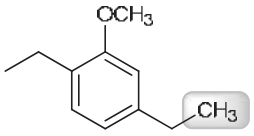


The three protons of a methyl group are always equivalent

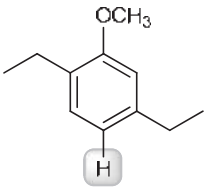


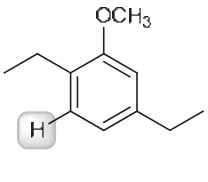


These two protons can be interchanged by reflectional symmetry, so they are enantiotopic

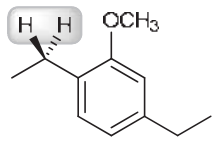


The three protons of a methyl group are always equivalent

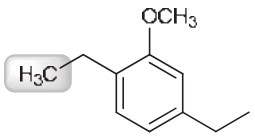




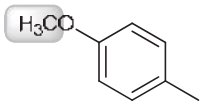
(b) This compound has four different kinds of protons (highlighted below), giving rise to four signals.



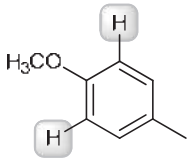
These two protons can be interchanged by reflectional symmetry, so they are enantiotopic



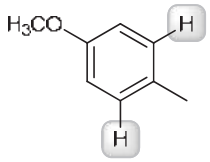
The three protons of a methyl group are always equivalent



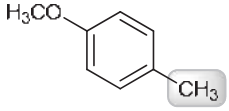
The three protons of a methyl group are always equivalent



These two protons can be interchanged by rotational symmetry, so they are homotopic

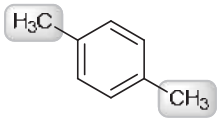


These two protons can be interchanged by rotational symmetry, so they are homotopic

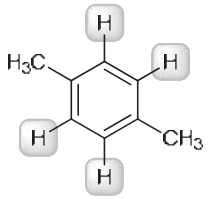


The three protons of a methyl group are always equivalent

(c) This compound has two different kinds of protons (highlighted below), giving rise to two signals.

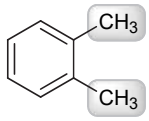


These two methyl groups can be interchanged by rotational symmetry, so all six protons are homotopic

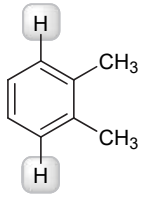


These four protons can all be interchanged by rotational symmetry, so they are all equivalent

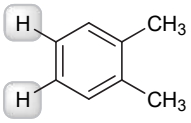
(d) This compound has three different kinds of protons (highlighted below), giving rise to three signals.



These two methyl groups can be interchanged by rotational symmetry, so all six protons are homotopic



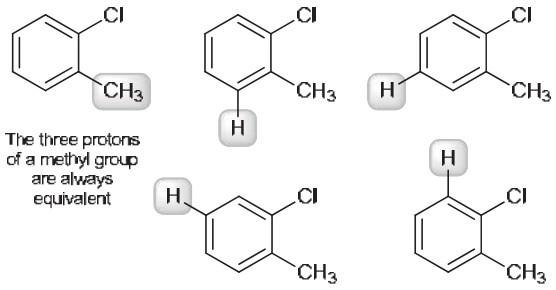
These two protons can be interchanged by rotational symmetry, so they are homotopic



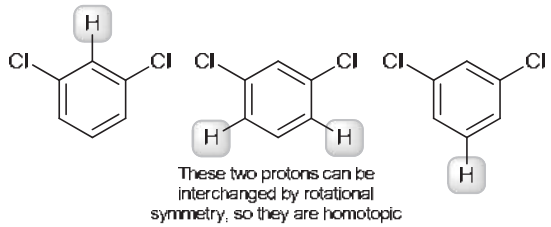
These two protons can be interchanged by rotational symmetry, so they are homotopic

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(e) This compound has five different kinds of protons (highlighted below), giving rise to five signals.

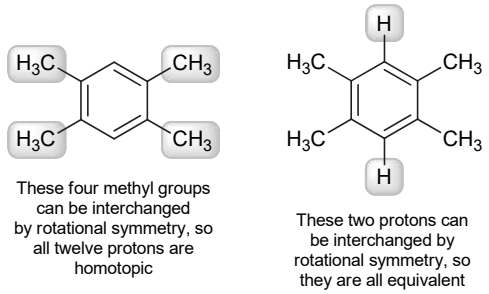


(f) This compound has three different kinds of protons (highlighted below), giving rise to three signals.



(g) This compound has four protons and none of them can be interchanged by rotational or reflectional symmetry. Each of the four protons occupies a unique electronic environment, giving rise to four signals.

(h) This compound has two different kinds of protons (highlighted below), giving rise to two signals.

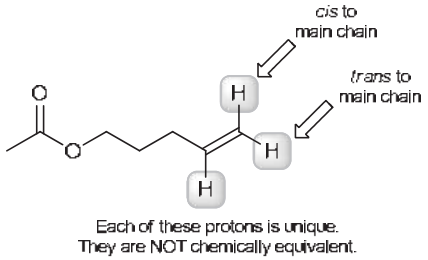


(i) Due to the location of the two bromine atoms, each CH_2 group occupies a unique electron environment, giving rise to two separate signals (one for each CH_2 group). In addition, the two methyl groups are also in different electronic environments, giving two separate signals. In total, we expect four signals.

(j) Each of the protons in each CH_2 group is in a unique electronic environment, as a result of the presence of a chiral center. That is, each CH_2 group gives rise to two separate signals, so the two CH_2 groups collectively give rise to four different signals. The two methyl groups are also different from each other (because of their proximity to the bromine atom), giving two more signals. In addition, there is one signal from the proton attached to the carbon bearing the bromine atom. In total, we expect seven signals.

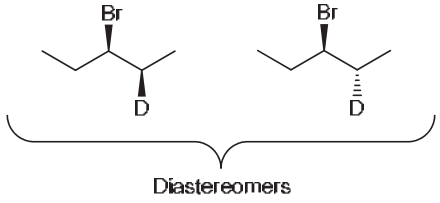
(k) As we saw in the solution to Problem **15.2c**, pentane is expected to produce three signals in its ^1H NMR spectrum. A similar analysis of heptane indicates that its ^1H NMR spectrum should contain four signals.

(l) Each of the three vinylic protons occupies a unique electronic environment, giving rise to three separate signals:

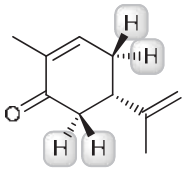


The two vinylic protons at the very end are different from each other because one is *cis* to the main chain and the other is *trans* to the main chain, as shown. Each of the CH_2 groups provides one signal (because each CH_2 group occupies a unique electronic environment), and the CH_3 provides one more signal, giving a total of seven signals.

15.6. The presence of the bromine atom does not render C3 a chiral center because there are two ethyl groups connected to C3. Nevertheless, the presence of the bromine atom does prevent the two protons at C2 from being interchangeable by reflection. The replacement test gives a pair of diastereomers, so the protons are diastereotopic (which means that they are not chemically equivalent).

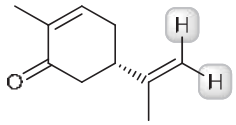


15.7. Each of the protons in the following highlighted CH_2 groups is in a unique electronic environment, as a result of the presence of the chiral center. That is, each CH_2 group will give rise to two separate signals, because one H is on the same face as (*cis* to) the propenyl substituent, while the other H is further away from it, on the opposite face as (*trans* to) the propenyl substituent. Therefore, these two CH_2 groups collectively give rise to four different signals:

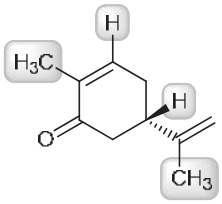


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In addition, the following highlighted protons are also diastereotopic:



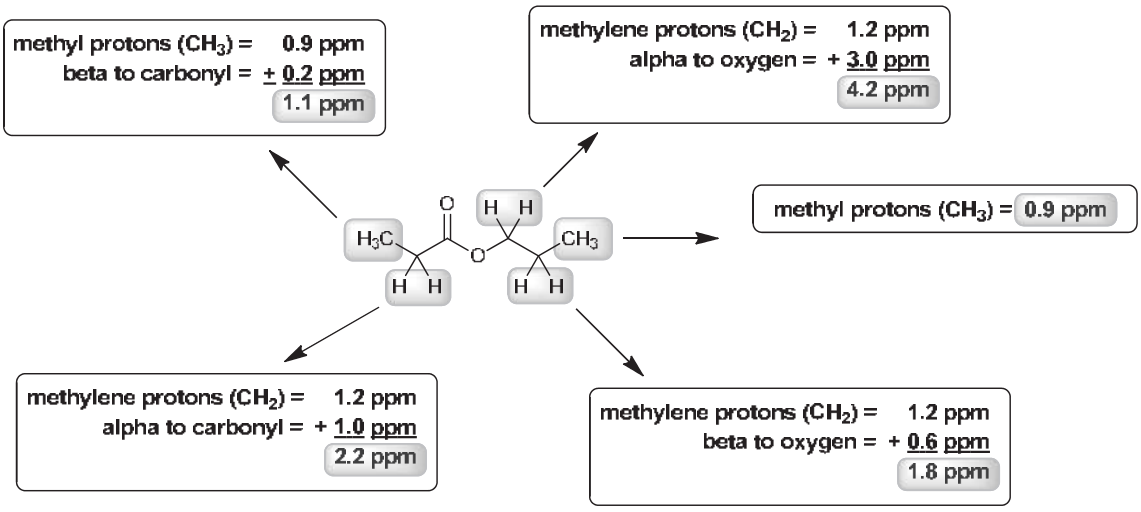
Furthermore, there are four more signals arising from the two methyl groups and the two CH groups, as shown:



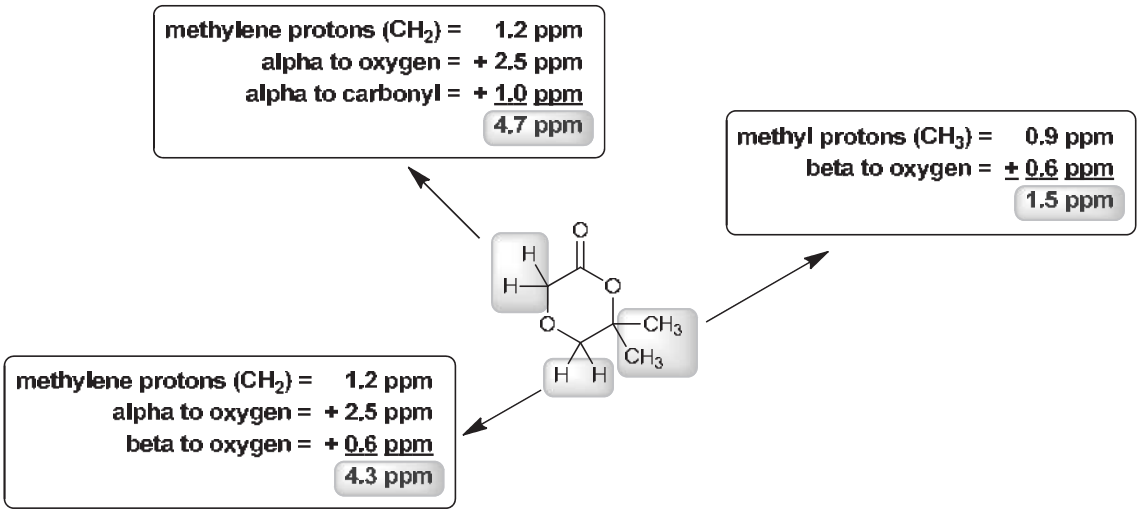
Therefore, we have seen that (*S*)-carvone has a total of ten different kinds of protons, giving rise to ten signals.

15.8.

(a) The ^{1}H NMR spectrum of this compound is expected to exhibit five signals. The calculation for the estimated chemical shift of each signal is shown here:

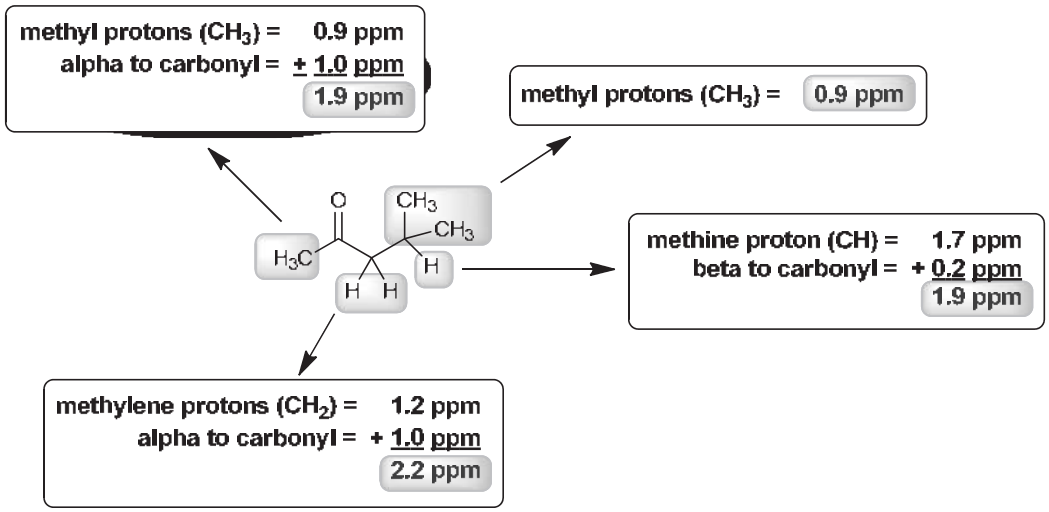


(b) The ^{1}H NMR spectrum of this compound is expected to exhibit three signals. The calculation for the estimated chemical shift of each signal is shown here:

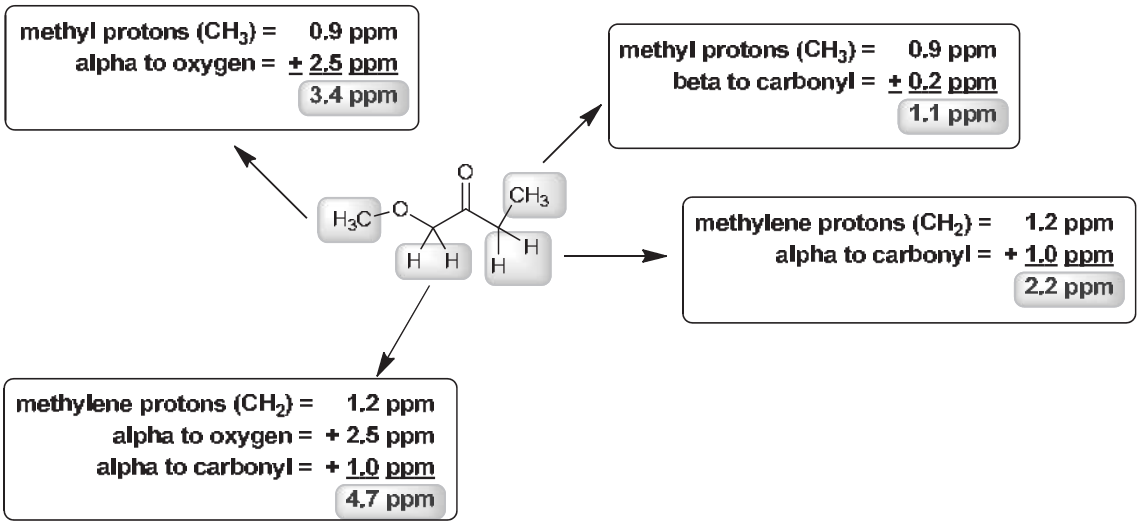


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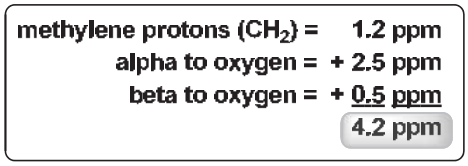
(c) The ^{1}H NMR spectrum of this compound is expected to exhibit four signals. The calculation for the estimated chemical shift of each signal is shown here:



(d) The ^{1}H NMR spectrum of this compound is expected to exhibit four signals. The calculation for the estimated chemical shift of each signal is shown here:



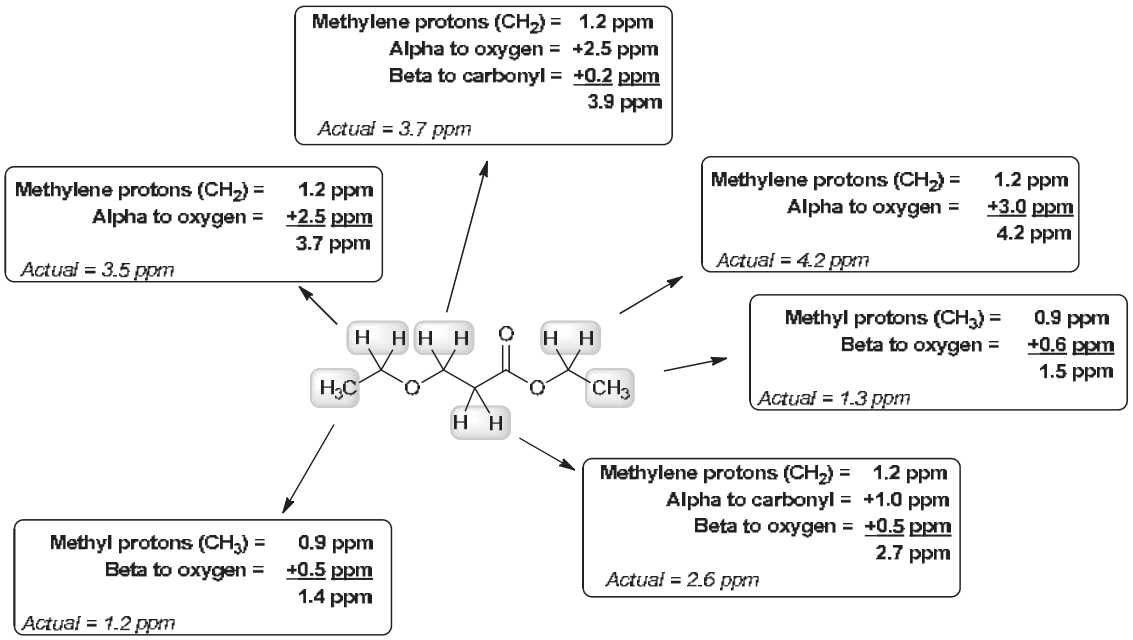
(e) All four methylene groups are equivalent, so the compound will have only one signal in its ^{1}H NMR spectrum. That signal is expected to appear at approximately (1.2 + 2.5 + 0.5) = 4.2 ppm.



15.9. First determine the number of expected signals. In this compound there are six different kinds of protons giving rise to six distinct signals. For each type of signal, identify whether it represents a methyl group (0.9 ppm), a methylene group (1.2 ppm), or a methine group (1.7 ppm). Finally, modify each of these values based on proximity to the oxygen

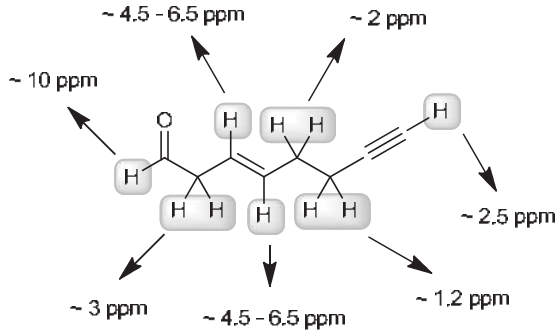
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atoms and the carbonyl group, as shown. These values are only estimates and the actual chemical shifts might differ slightly from the predicted values. The actual values are also shown, and they are fairly close to the estimated values.

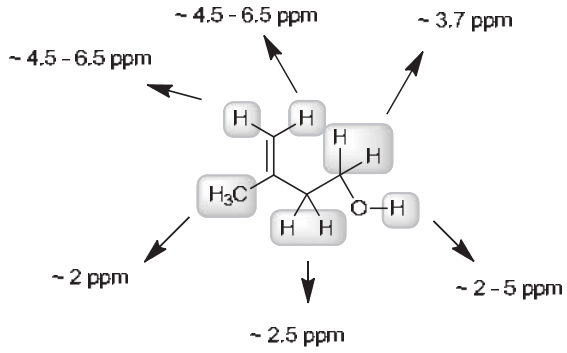


15.10.

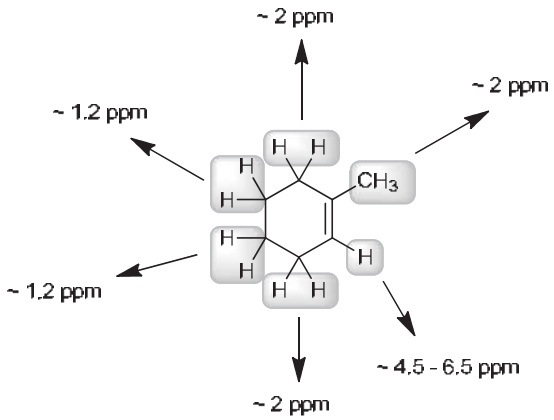
(a) Using the values provided in Tables 15.1 and 15.2, we expect the following chemical shifts:



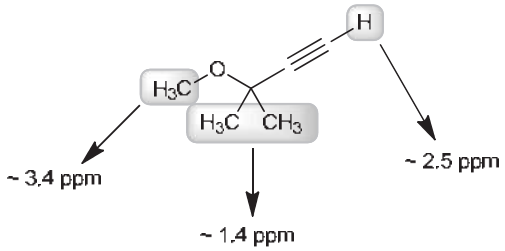
(b) Using the values provided in Tables 15.1 and 15.2, we expect the following chemical shifts:



(c) Using the values provided in Tables 15.1 and 15.2, we expect the following chemical shifts:



(d) Using the values provided in Tables 15.1 and 15.2, we expect the following chemical shifts:



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15.11. Among the integration values provided, the lowest number is 33.2, so we divide all integration values by 33.2, giving the following ratio:

1 : 1.5 : 1 : 1.5

Since there is no such thing as a half of a proton, these numbers must represent 2, 3, 2, and 3 protons, respectively. This is confirmed by the molecular formula, which indicates that the compound has ten hydrogen atoms.

Therefore,

The signal at 4.0 ppm represents two protons.
The signal at 2.0 ppm represents three protons.
The signal at 1.6 ppm represents two protons.
The signal at 0.9 ppm represents three protons.

15.12. Among the integration values provided, the lowest number is 17.1, so we divide all integration values by 17.1, giving the following ratio:

1 : 5 : 1 : 3

The molecular formula indicates that the compound has ten hydrogen atoms, so the numbers above are not only relative values, but they are also exact values.

Therefore,

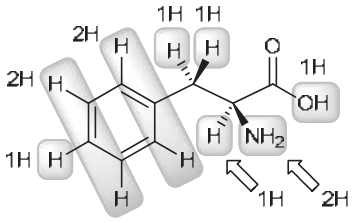
The signal at 9.6 ppm represents one proton.
The signal at 7.5 ppm represents five protons.
The signal at 7.3 ppm represents one proton.
The signal at 2.1 ppm represents three protons.

15.13. Among the integration values provided, the lowest number is 18.92, so we divide all integration values by 18.92, giving the following ratio:

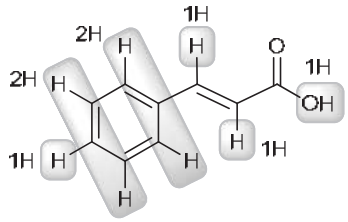
1 : 1 : 1

The molecular formula indicates that the compound has six hydrogen atoms (not just three), so the numbers above are only relative values. Each signal must actually represent two protons.

15.14. We expect a total of eight signals in the ^{1}H NMR spectrum of phenylalanine; note the symmetry in the benzene ring and the nonequivalent diastereotopic protons next to the chiral center bearing the NH_2 group.

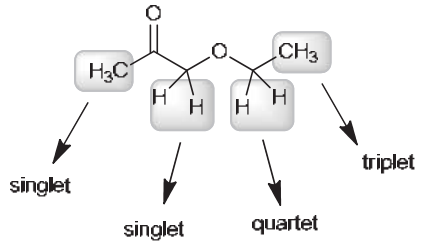


Cinnamic acid has a simpler ^{1}H NMR spectrum with only six signals.

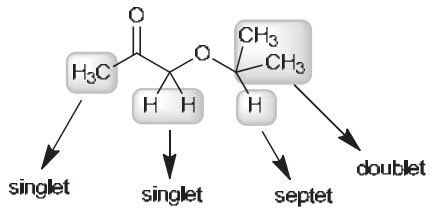


15.15.

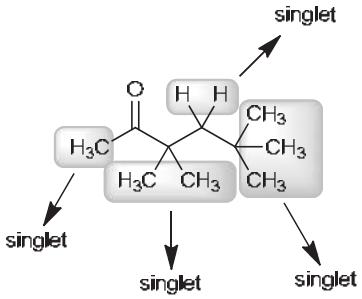
(a) This compound has four different kinds of protons, highlighted here. In each case, we apply the n+1 rule, giving the multiplicities shown:



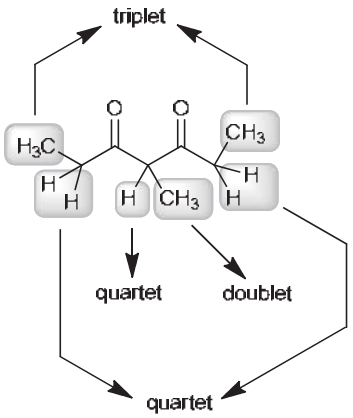
(b) This compound has four different kinds of protons, highlighted here. In each case, we apply the n+1 rule, giving the multiplicities shown:



(c) This compound has four different kinds of protons, highlighted here. In each case, we apply the n+1 rule, giving the multiplicities shown:

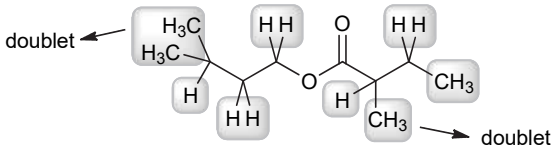


(d) This compound has six different kinds of protons, highlighted here. In each case, we apply the n+1 rule, giving the multiplicities shown:



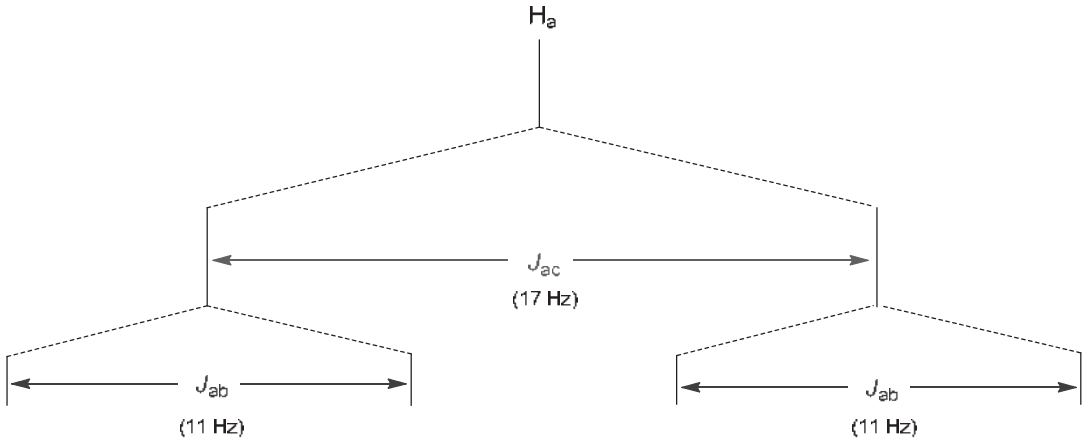
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15.16. Considering the n+1 rule, we recognize that a doublet must have only one neighboring proton. This compound has eight different kinds of protons, but only the two indicated below are each expected to give rise to a doublet signal:

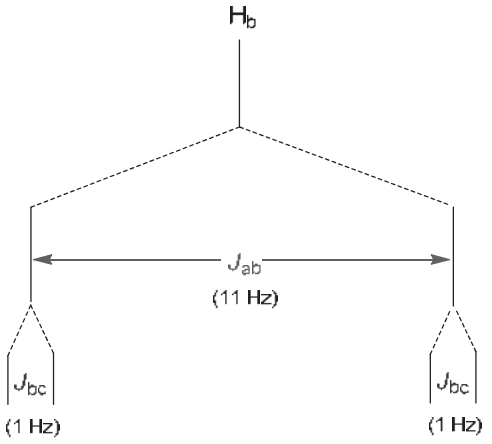


15.17.
(a) The spectrum exhibits the characteristic pattern of an isopropyl group (a septet with an integration of one, and a doublet with an integration of six).
(b) The spectrum exhibits the characteristic pattern of an isopropyl group (a septet with an integration of one, and a doublet with an integration of six) as well as the characteristic pattern of an ethyl group (a quartet with an integration of two, and a triplet with an integration of three).
(c) The spectrum exhibits a singlet with a relative integration of 9 (because 55.0 / 6.0 ≈ 9), which is the characteristic pattern of a *tert*-butyl group.
(d) The spectrum does not exhibit the characteristic pattern of an ethyl group, an isopropyl group, or a *tert*-butyl group.

15.18.
(a) To determine the expected splitting pattern for the signal corresponding to H_a, we must consider the effects of the two non-equivalent neighbors, H_b and H_c, The former is coupled to H_a with a coupling constant J_{ab} (11 Hz), and the latter is coupled to H_a with a coupling constant J_{ac} (17 Hz). We begin with the larger coupling constant (J_{ac} in this case), which splits the signal into a doublet. Then, each peak of this doublet is then further split into a doublet because of the effect of H_b. The result is a doublet of doublets. It can be distinguished from a quartet because all four peaks should have roughly equivalent integrations values (if integrated individually), as opposed to a quartet, in which the individual peaks have a relative integration of 1 : 3 : 3 : 1.

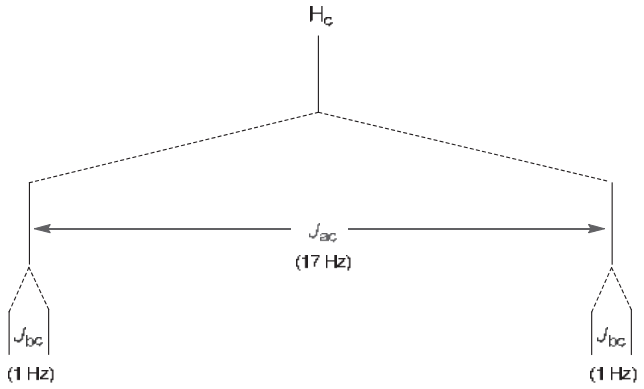


(b) To determine the expected splitting pattern for the signal corresponding to H_b, we must consider the effects of the two non-equivalent neighbors, H_a and H_c, The former is coupled to H_b with a coupling constant J_{ab} (11 Hz), and the latter is coupled to H_b with a coupling constant J_{bc} (1 Hz). We begin with the larger coupling constant (J_{ab} in this case), which splits the signal into a doublet. Then, each peak of this doublet is then further split into a doublet because of the effect of H_c. The result is a doublet of doublets.



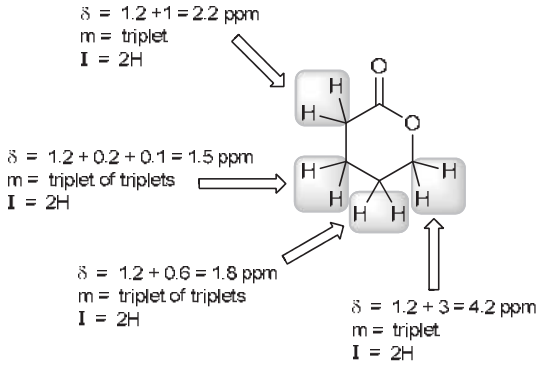
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(c) To determine the expected splitting pattern for the signal corresponding to H_c, we must consider the effects of the two non-equivalent neighbors, H_a and H_b, The former is coupled to H_c with a coupling constant J_{ac} (17 Hz), and the latter is coupled to H_c with a coupling constant J_{bc} (1 Hz). We begin with the larger coupling constant (J_{ac} in this case), which splits the signal into a doublet. Then, each peak of this doublet is then further split into a doublet because of the effect of H_b. The result is a doublet of doublets.

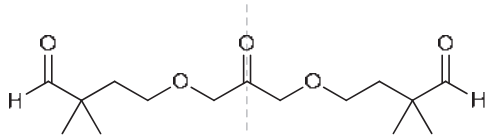


15.19.

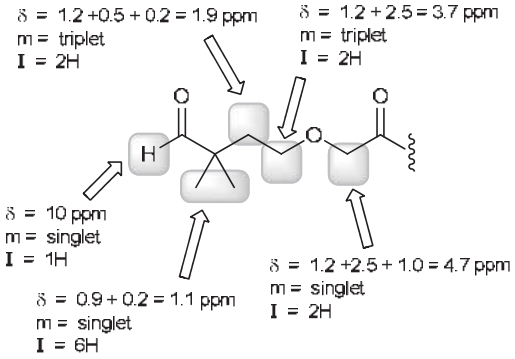
(a) This compound is expected to produce four signals in its ^{1}H NMR spectrum. For each signal, its expected chemical shift, multiplicity, and integration are shown.



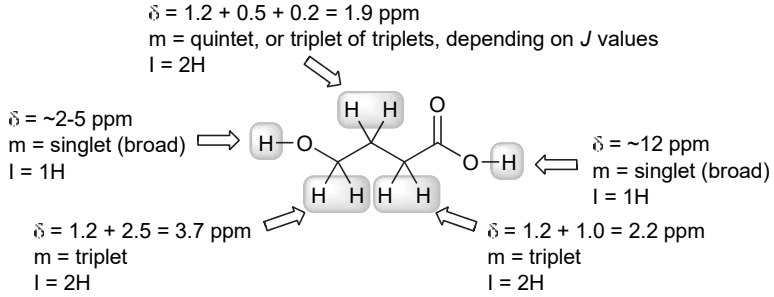
(b) This compound has rotational and reflectional symmetry:



So we expect its ^{1}H NMR spectrum to exhibit only five signals, corresponding with the following highlighted protons. For each signal, its expected chemical shift, multiplicity, and integration are shown.



15.20. GHB is expected to produce five signals in its ^{1}H NMR spectrum. For each signal, its expected chemical shift, multiplicity, and integration are shown below. Note that OH protons typically do not couple with neighboring protons, and as a result, no splitting occurs. Furthermore, OH signals generally appear as broad singlets.



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15.21.

(a) The first compound will have only three signals in its ^{1}H NMR spectrum, while the second compound will have six signals.

(b) Both compounds will exhibit ^{1}H NMR spectra with only two singlets. In each spectrum, the relative integration of the two singlets is 1:3. In the first compound, the singlet with the smaller integration value will be at approximately 2 ppm. In the second compound, the singlet with the smaller integration value will be at approximately 4 ppm.

(c) The first compound will have only two signals in its ^{1}H NMR spectrum, while the second compound will have three signals.

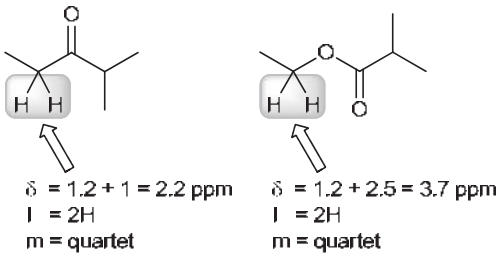
(d) The first compound will have five signals in its ^{1}H NMR spectrum, while the second compound will have only three signals.

(e) The first compound will have only two signals in its ^{1}H NMR spectrum, while the second compound will have four signals.

(f) The first compound will have only one signal in its ^{1}H NMR spectrum, while the second compound will have two signals.

15.22.

(a) Both compounds will have very similar ^{1}H NMR spectra, with the same number of signals, splitting patterns and integration values. The only difference will be the location of the 2H quartet signal. For the first structure, this signal is expected to appear near 2.2 ppm, because it is a methylene group (benchmark value = 1.2 ppm) next to a carbonyl group (+1). For the second structure, this signal will appear at approximately 4.2 ppm, because it is a methylene group next to an oxygen atom (+3):



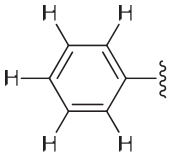
Likewise, the adjacent methyl group, β to the ester oxygen, would be expected to exhibit a different shift (though less pronounced than observed for the α–methylene) than the corresponding methyl group that is β to the ketone carbonyl.

(b) These compounds are indeed expected to exhibit a different number of signals in their ^{1}H NMR spectra. However, most of the signals will appear in the region 1-2 ppm (in each spectrum), and may overlap, making it difficult to count the number of signals. The only distinctive peaks will be the vinyl and aldehyde signals. In fact, the presence or absence of a signal near 10 ppm is the easiest way to differentiate these compounds. The second compound is an aldehyde so it is expected to produce a signal near 10 ppm. The first compound will lack such a signal.

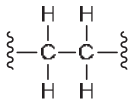
15.23.

(a) The molecular formula ($C_8H_{10}O$) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring. To determine the relative integration values, we divide each of the integration values by 9.1, giving a ratio of approximately 5 : 2 : 2 : 1. Since the compound has ten protons, the numbers above are not only relative values, but they are also exact values. Now let's analyze each of the signals individually.

The signal just above 7 ppm confirms our suspicion of an aromatic ring. This signal has an integration of 5H, indicating a monosubstituted aromatic ring:



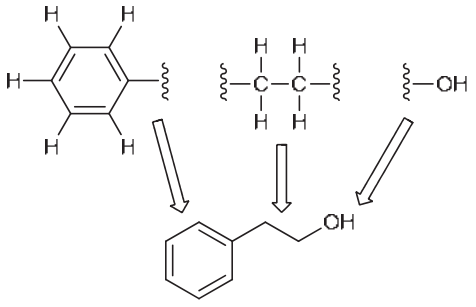
The spectrum also exhibits two triplets (just below 3 ppm and just below 4 ppm), indicating two methylene groups connected to each other:



Each of these signals appears more downfield than we might expect for a methylene group (1.2 ppm), so each of these methylene groups must be connected to a group that causes a deshielding effect. This must be taken into account in our final structure.

If we inspect the two fragments that we have determined thus far (the monosubstituted aromatic ring and the methylene groups that neighbor each other), we will find that these two fragments account for nearly all of the atoms in the molecular formula ($C_8H_{10}O$). We only need to account for one more proton and one oxygen atom. The singlet at 2 ppm has an integration of 1, so this signal corresponds with only one proton (with no neighbors), so we conclude that the compound has an OH group.

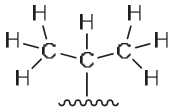
There is only one way to assemble the three fragments:



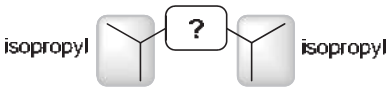
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This structure is consistent with all of the signals, including the chemical shifts of the two triplets, which can be explained by the electron withdrawing effect of the oxygen atom as well as the local magnetic field established by the aromatic ring.

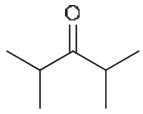
(b) The molecular formula ($C_7H_{14}O$) indicates one degree of unsaturation (see Section 14.16), which means that the compound must possess either a double bond or a ring. To determine the relative integration values, we divide each of the integration values by 10.8, giving a ratio of approximately 1 : 6. This spectrum has the characteristic pattern of an isopropyl group (a doublet with a relative integration of 6 and a septet with a relative integration of 1).



An isopropyl group only contains seven protons, but there are fourteen protons in the compound ($C_7H_{14}O$). We therefore conclude that the compound must contain two isopropyl groups, which are interchangeable by symmetry:



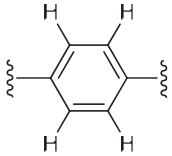
Notice that the two isopropyl groups account for all but one of the carbon atoms in the compound. Therefore, there can only be one carbon atom in between the two isopropyl groups. This carbon atom cannot have any protons, since we don't see any other signals in the ^1H NMR spectrum. Also, we must still account for one oxygen atom ($C_7H_{14}O$), and we said that the compound must contain one degree of unsaturation. This all points to a carbonyl group at the central position:



This structure is indeed consistent with the observed chemical shift at 2.7 ppm for the methine (CH) protons (1.7 + 1 = 2.7 ppm).

(c) The molecular formula ($C_{10}H_{14}O$) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring.

The signals near 7 ppm are likely a result of aromatic protons. Notice that the combined integration of these two signals is 4H. This, together with the distinctive splitting pattern (a pair of doublets), suggests a 1,4-disubstituted aromatic ring:

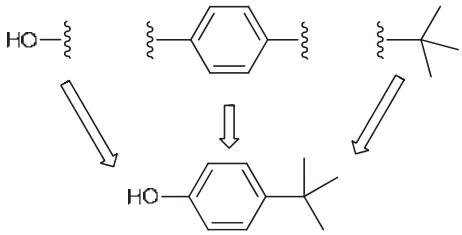


The spectrum also exhibits a singlet with an integration of 9H (at approximately 1.4 ppm) which is characteristic of a *tert*-butyl group.



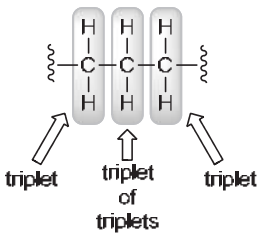
If we inspect the two fragments that we have determined thus far (the disubstituted aromatic ring and the *tert*-butyl group), we will find that these two fragments account for nearly all of the atoms in the molecular formula ($C_{10}H_{14}O$). We only need to account for one more proton and one oxygen atom. The peak just under 5 ppm has an integration of 1, so this signal corresponds with only one proton (with no neighbors), so we conclude that the compound has an OH group. This signal is broad, which is often (although not always) the case for signals arising from OH groups.

There is only one way to assemble the three fragments:



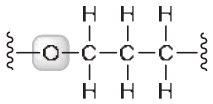
(d) The molecular formula ($C_4H_6O_2$) indicates two degrees of unsaturation (see Section 14.16), which means that the compound must possess either two double bonds, or two rings, or one ring and one double bond, or a triple bond.

To determine the relative integration values, we divide each of the integration values by 19.46, giving a ratio of approximately 1 : 1 : 1. The molecular formula indicates six protons (rather than three), so the relative integration values must correspond with two protons for each signal. That is, the spectrum indicates the presence of three different methylene groups. From the splitting patterns (a triplet, a triplet, and a triplet of triplets), we can conclude that the three methylene groups are connected to each other:

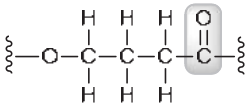


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Now let's focus on the chemical shifts of the triplets (2.4 ppm and 4.3 ppm). Both signals are shifted downfield (relative to 1.2 ppm for a typical methylene group). One of these signals is significantly shifted downfield, perhaps because it is next to an oxygen atom (after all, the molecular formula indicates that there are two oxygen atoms in the compound):

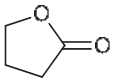


The other triplet is also shifted downfield, but the effect is weaker. This seems consistent with the effect of a carbonyl group:



The central methylene group is beta to both the oxygen atom and the carbonyl group, and it feels the distant effects of both (explaining why that signal is shifted somewhat downfield itself).

The fragment above accounts for ALL of the atoms in the molecular formula, yet we are still missing one degree of unsaturation (the product must contain two degrees of unsaturation, but the fragment above has only one degree of unsaturation). Therefore, we close the ends together, giving the following structure:



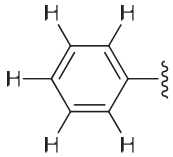
(e) The molecular formula ($C_9H_{10}O$) indicates five degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring, in addition to either one double bond or one ring.

To determine the relative integration values, we divide each of the integration values by 13.9, giving a ratio of approximately 1 : 1.5 : 1 : 1.5. Since the compound has ten protons, the numbers above must correspond with:

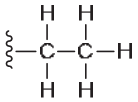
2 : 3 : 2 : 3

Now let's analyze each of the signals individually.

The signals near 7 ppm are likely a result of aromatic protons. Notice that the combined integration of these signals is 5H, indicating a monosubstituted aromatic ring:



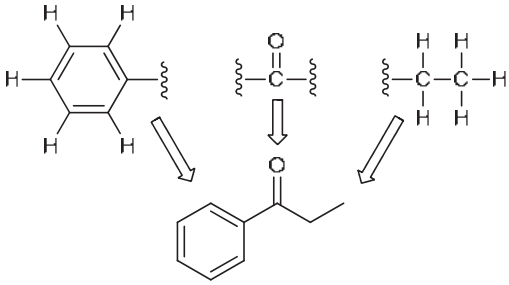
The spectrum also exhibits the characteristic pattern of an ethyl group (a quartet with an integration of 2 and a triplet with an integration of 3):



If we inspect the two fragments that we have determined thus far (the monosubstituted aromatic ring and the ethyl group), we will find that these two fragments account for nearly all of the atoms in the molecular formula ($C_9H_{10}O$). We only need to account for one more carbon atom and one oxygen atom. And let's not forget that our structure still needs one more degree of unsaturation, suggesting a carbonyl group:



There is only one way to connect these three fragments.

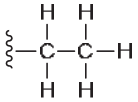


(f) The molecular formula ($C_5H_{12}O$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound does not have a π bond or a ring.

To determine the relative integration values, we divide each of the integration values by 13.6, giving a ratio of approximately 1 : 2 : 6 : 3. Since the compound has twelve protons, the numbers above are not only relative values, but they are also exact values.

Now let's analyze each of the signals individually.

Let's begin with the two signals that represent the characteristic pattern for an ethyl group (a quartet with an integration of 2 and a triplet with an integration of 3).



The singlet at 1.2 ppm has an integration of 6, indicating two methyl groups that can be interchanged via symmetry (and they cannot have any neighboring protons).

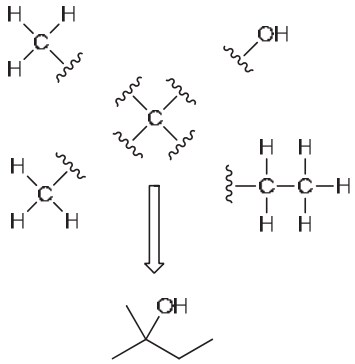


The singlet at 2.2 ppm has an integration of 1, so this signal corresponds with only one proton (with no

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neighbors), so we conclude that this likely represents an OH group (the molecular formula indicates the presence of an oxygen atom).

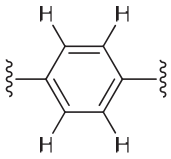
If we inspect the fragments that we have determined thus far (an ethyl group, two methyl groups and an OH group), we will find that these fragments account for all of the atoms in the molecular formula ($C_5H_{10}O$) except for one carbon atom. Indeed, this carbon atom is necessary to connect all of the fragments, as shown:



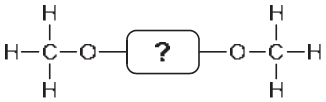
15.24. The molecular formula ($C_{10}H_{10}O_4$) indicates six degrees of unsaturation (see Section 14.16), which suggests an aromatic ring as well as two other degrees of unsaturation.

To determine the relative integration values, we divide each of the integration values by 52, giving a ratio of approximately 1 : 1.5. Since the compound has ten protons ($C_{10}H_{10}O_4$), the numbers above must correspond to four protons and six protons, respectively.

Now let's analyze each of the signals individually. The signal at 8.1 ppm is significantly downfield, and likely represents aromatic protons. Since it is a singlet with an integration of 4, it must correspond with a 1,4-disubstituted aromatic ring in which both substituents are identical (therefore rendering all four aromatic protons equivalent).



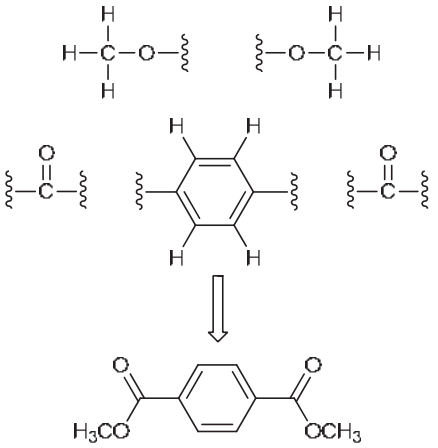
The other signal has an integration of 6, which likely represents two equivalent methyl groups (interchangeable by symmetry). Since the signal is a singlet, these methyl groups must not have any neighbors. The chemical shift is consistent with these methyl groups being connected to oxygen atoms:



If we inspect the fragments that we have determined thus far (a 1,4-disubstituted aromatic ring, and two methoxy groups), we will find that these fragments account for all of the atoms in the molecular formula ($C_{10}H_{10}O_4$) except for two carbon atoms and two oxygen atoms. Recall that the compound must have six degrees of unsaturation, and the fragments above only account for four degrees of unsaturation. Therefore, the remaining two carbon atoms and two oxygen atoms are likely carbonyl groups:



There are certainly a few different ways to connect all of these fragments, but there is only one way to connect them without breaking the symmetry necessary to keep all four aromatic protons identical:

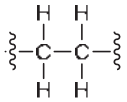


15.25. Begin by calculating the HDI. The molecular formula indicates 9 carbon atoms and 1 nitrogen atom. These would require 21 hydrogen atoms in order to be fully saturated. There are only 13 hydrogen atoms, so 8 hydrogen atoms are missing. Therefore, the HDI is 4. This is a relatively large number, and it would be inefficient to think about all of the possible ways to have 4 degrees of unsaturation. Anytime we encounter an HDI of 4 or more, we should be on the lookout for an aromatic ring. Keep this in mind when analyzing the spectrum, which we expect to exhibit aromatic protons (near 7 ppm).

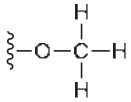
Next, consider the number of signals and the integration value for each signal. Be on the lookout for integration values that suggest the presence of symmetry. For example, a signal with an integration of 4 would suggest two equivalent CH_2 groups.

The spectral data indicates a total of 6 signals. Let's begin with the pair of triplets just below 3 ppm, each of which has an integration of 2. This suggests that there are two adjacent methylene groups.

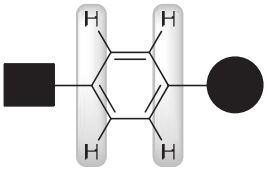
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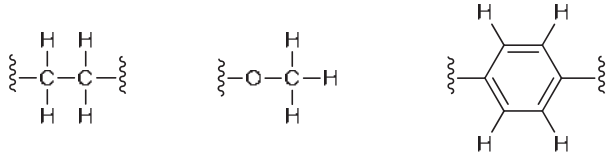
The singlet near 4 ppm has an integration of 3 which suggests an isolated methyl group, likely connected to an electronegative oxygen atom. A methoxy fragment, OCH_3, seems likely.



Moving downfield, there are 2 doublets near 7 ppm, each of which has an integration of 2. This pattern is characteristic of a 1,4-disubstituted benzene ring, bearing two different substituents (with different electronic demands). In such a case, there are two types of aromatic protons, each of which has an integration of 2 and is split into a doublet by its one neighbor:

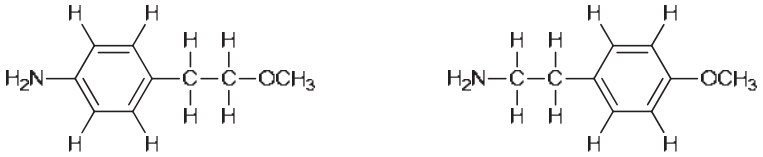


So far, we have the following three fragments:

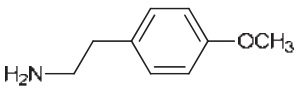


These fragments collectively account for 9 carbon atoms, 11 hydrogen atoms, and 1 oxygen atom. If we inspect the molecular formula, we see that we have accounted for all of the carbon atoms and the oxygen atom, but we must still account for 2 more hydrogen atoms and 1 nitrogen atom. Therefore, we conclude that the broad singlet near 1 ppm is likely to be an NH_2 group. We will see later (Chapter 22) that NH_2 protons generally appear as broad signals between 0.5 and 5.0 ppm.

Next, we assemble the fragments. There are two reasonable ways to connect the fragments in this case.



To distinguish between these two options, we consider chemical shifts. Note that the adjacent methylene groups appear fairly close to one another, near 3 ppm, indicating that neither is attached to the highly electronegative and deshielding oxygen atom. The first compound above shows a CH_2 group connected to oxygen, and we expect that compound to produce a triplet somewhere near 4 ppm, which is absent from the spectral data. The second compound above has the two CH_2 groups connected to an aromatic ring and an NH_2 group, respectively, which is consistent with the observed chemical shifts of these triplets. The structure is redrawn here in conventional bond-line notation.



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15.26.

(a) The two methyl groups occupy identical environments (there is a conformation of this molecule in which the two methyl groups are interchangeable by reflectional symmetry), so the methyl groups are chemically equivalent. All of the other carbon atoms are unique, giving rise to a total of four signals. Three of the signals are produced by sp^3 hybridized carbon atoms (not connected to electronegative atoms), and are therefore expected to appear in the region 0 – 50 ppm. The fourth signal is produced by the carbon atom of the carbonyl group (C=O), which is expected to appear in the region 150 – 220 ppm.

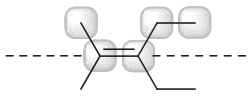
(b) This compound exhibits symmetry, rendering the two methyl groups equivalent. Similarly, the ring has only four unique signals, because of symmetry. In total, the ^{13}C NMR spectrum of this compound should exhibit five signals. All five are produced by sp^3 hybridized carbon atoms (not connected to electronegative atoms) and are therefore expected to appear in the region 0 – 50 ppm.

(c) Monosubstituted aromatic rings exhibit symmetry, giving only four unique carbon atoms in the aromatic ring. These four signals will appear in the region 100-150 ppm. Each of the carbon atoms of the ethyl group is unique, giving a total of six signals. The two signals of the ethyl group are produced by sp^3 hybridized carbon atoms (not connected to electronegative atoms) and are therefore expected to appear in the region 0 – 50 ppm.

(d) The compound has no symmetry. Each of the carbon atoms is unique, giving a total of nine signals. Two signals appear in the region 0 – 50 ppm (sp^3 hybridized), one signal appears in the region 50 – 100 ppm (the sp^3 hybridized carbon atom attached to an oxygen atom), and six signals appear in the region 100 – 150 ppm (sp^2 hybridized).

(e) The aromatic ring is 1,4-disubstituted so it exhibits symmetry, giving four unique carbon atoms in the aromatic ring (four signals). These four signals will appear in the region 100-150 ppm. In addition, there will be a signal for the carbon atom of the methoxy group, which will appear in the region 50 – 100 ppm (as expected for an sp^3 hybridized carbon atom attached to an oxygen atom). And finally there will be two signals in the region 0 – 50 ppm (for the sp^3 hybridized carbon atoms of the ethyl group). In total, there are seven signals.

(f) This compound has symmetry, giving only five unique positions (highlighted):



So the ^{13}C NMR spectrum should have five signals. Three of them should appear in the region 0 – 50 ppm (sp^3 hybridized), and two signals should appear in the region 100 – 150 ppm (sp^2 hybridized).

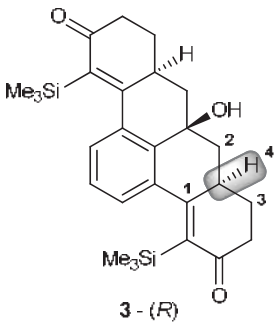
(g) None of the carbon atoms in this compound can be interchanged with any of the other carbon atoms in this compound via either reflection or rotation. All of the carbon atoms are unique, giving rise to seven signals. Five of them should appear in the region 0 – 50 ppm (sp^3 hybridized), and two signals should appear in the region 100 – 150 ppm (sp^2 hybridized).

(h) This compound exhibits a high degree of symmetry. All four methyl groups are interchangeable by either rotation or reflection, and therefore, all four methyl groups give rise to one signal, appearing in the region 0 – 50 ppm (sp^3 hybridized). The two vinylic carbon atoms are also chemically equivalent, giving rise to one signal in the region 100 – 150 ppm (sp^2 hybridized). In total, there are only two signals.

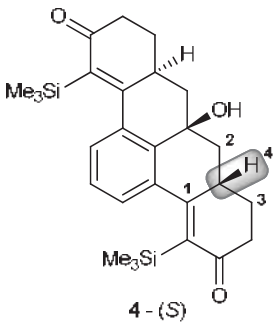
(i) This compound exhibits a high degree of symmetry. All four carbon atoms are interchangeable by either rotation or reflection, and therefore, all four carbon atoms give rise to one signal, appearing in the region 50 – 100 ppm (as expected for an sp^3 hybridized carbon atom attached to an oxygen atom).

(j) None of the carbon atoms in this compound can be interchanged with any of the other carbon atoms in this compound via either reflection or rotation. All of the carbon atoms are unique, giving rise to five signals. Among the two sp^3 hybridized carbon atoms, one of them should produce a signal in the region 0 – 50 ppm, and the other sp^3 hybridized carbon atom (connected to an oxygen atom) should appear in the region 50 – 100 ppm. In addition, the two vinylic carbon atoms will each produce a signal in the region 100 – 150 ppm (sp^2 hybridized). And finally, the carbonyl group (C=O) will produce a signal in the region 150 – 220 ppm.

15.27. Let's first determine which diastereomer has the *R* configuration and which has the *S* configuration. When we place the hydrogen on a dash, the three substituents will be arranged such that the sequence of priorities (1–2–3) is clockwise; therefore, compound **3** (having the *R* configuration) will have the H on a dash. Since compound **4** has the *S* configuration, we would simply need to invert the configuration at that center, meaning the H should be placed on a wedge.



3 - (*R*)

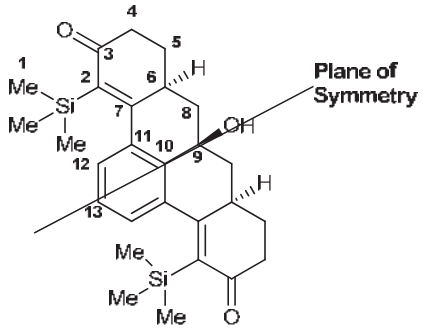


4 - (*S*)

Upon close inspection, compound **3** has a plane of symmetry that compound **4** lacks. In fact, compound **3** is

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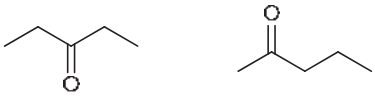
a *meso* compound. As a result, compound **3** should exhibit only thirteen signals in its ^{13}C NMR spectrum, while compound **4** should have twenty-three signals in its ^{13}C NMR spectrum. This would be an easy way to distinguish between these compounds.



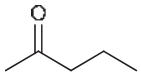
3 - (*R*)

15.28. The molecular formula ($C_5H_{10}O$) indicates one degree of unsaturation (see Section 14.16), which means that the compound must either have a double bond or a ring. The signal above 200 ppm (in the broadband-decoupled spectrum) indicates the source of the degree of unsaturation (C=O). The four signals in the range 0 – 50 ppm represent four unique sp^3 hybridized carbon atoms. Two of them are upside-down in the DEPT-135 spectrum, indicating that they are methylene groups. Based on the number of protons in the compound ($C_5H_{10}O$), the other two signals must be methyl groups (to give a total of ten protons).

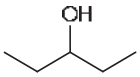
Now we must connect a carbonyl group, two methylene groups and two methyl groups. There are only two ways to do that:



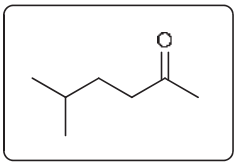
The first possibility cannot be correct because it has too much symmetry, and would have fewer signals. The latter structure is the only structure that is consistent with the data.



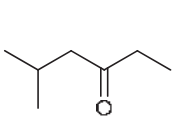
15.29. The molecular formula ($C_5H_{12}O$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound cannot have either a double bond or a ring. The signal at 73.8 δ must be produced by the carbon atom that is connected to the oxygen atom. Notice that only one signal can be found in the range 50 – 100 ppm, which is consistent with the compound being an alcohol, as indicated in the problem statement. There are only two other signals, indicating symmetry. Both of those signals represent sp^3 hybridized carbon atoms. The following structure meets these requirements:



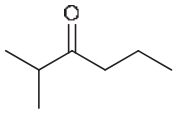
15.30. The molecular formula ($C_7H_{14}O$) indicates one degree of unsaturation (see Section 14.16), which means that the compound must possess either a double bond or a ring. The signal above 200 ppm (in the broadband-decoupled spectrum) indicates the source of the degree of unsaturation (C=O). The five signals in the range 0 – 50 ppm represent five unique sp^3 hybridized carbon atoms. As such, the spectrum has a total of six signals for a compound with seven carbon atoms. That means that one of the signals in the range 0 – 50 ppm must represent two carbon atoms (for example, two equivalent methyl groups – the ^1H NMR data confirms the two equivalent methyl groups). Also notice that two of the signals are upside-down in the DEPT-135 spectrum, indicating that they are methylene groups. Based on the DEPT-90 spectrum, we can see that one of the signals is a CH group, while the last two signals must be methyl groups. There are several possible structures that are consistent with the information above, but only one of them is consistent with the ^1H NMR spectrum. Specifically, the singlet at 1.9 ppm (with an integration of 3) indicates a methyl ketone.



Consistent with
^1H NMR and ^{13}C NMR spectra



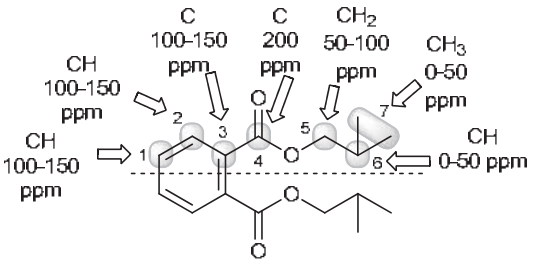
Consistent only with
^{13}C NMR spectrum



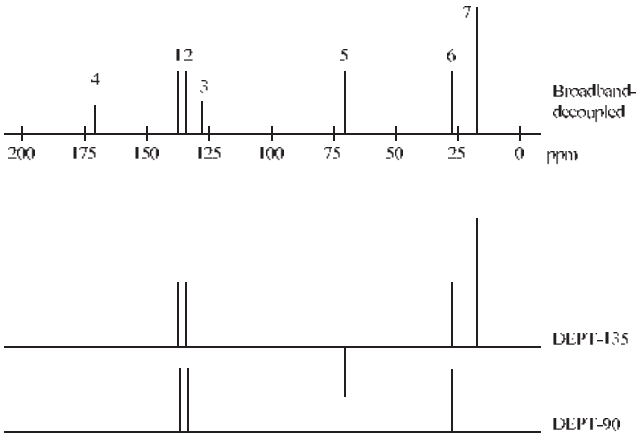
Consistent only with
^{13}C NMR spectrum

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15.31. Diisobutyl phthalate has an internal plane of symmetry, so the two isobutyl groups are chemically equivalent (since they can be interchanged by rotational symmetry); the symmetry also bisects the aromatic ring. Although there are 16 carbon atoms in DIBP, only 7 signals are thus expected in its broadband-decoupled ^{13}C NMR spectrum. Using the values provided in Figure 15.22, we expect the following approximate chemical shifts:



The DEPT-90 spectrum exhibits three signals for the CH groups: two in the sp^2 hybridized region 100-150 (C1 and C2), and one in the 0-50 ppm region (C6). The DEPT-135 spectrum exhibits five signals (only the quaternary carbon atoms, C3 and C4, are missing); there is one signal in the 50-100 ppm region that is a negative signal, indicating the presence of a methylene group (CH_2) attached to an oxygen atom, C5.

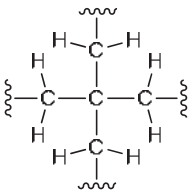


15.32.

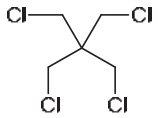
(a) The molecular formula (C_5H_{10}) indicates one degree of unsaturation (see Section 14.16), which means that the compound must possess either a double bond or a ring. With only one signal in the spectrum, the structure must have a high degree of symmetry, such that all ten protons are equivalent. This is indeed the case for a five-membered ring (cyclopentane). There is no alkene with the molecular formula C_5H_{10} in which all ten protons occupy identical electronic environments. So cyclopentane is the only structure consistent with the spectral data:



(b) The molecular formula ($C_5H_8Cl_4$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound cannot have any double bonds, triple bonds, or rings. That is, the structure must be acyclic and cannot have any π bonds. With only one signal in the spectrum, the structure must have a high degree of symmetry, such that all eight protons are equivalent. This can be achieved with four equivalent methylene (CH_2) groups. Four CH_2 groups will be chemically equivalent if they are all attached to the same carbon atom (provided that all four CH_2 groups are connected to identical groups):

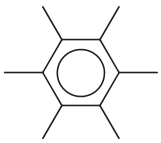


The molecular formula indicates five carbon atoms (which are now all accounted for) and four chlorine atoms, which can serve to cap the four loose ends shown above, like this:

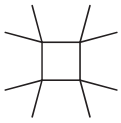


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(c) The molecular formula ($C_{12}H_{18}$) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring. With only one signal in the spectrum, the structure must have a high degree of symmetry, such that all eighteen protons are equivalent. This can be achieved with six equivalent methyl groups, as seen in the following structure:

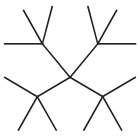


15.33. The molecular formula ($C_{12}H_{24}$) indicates one degree of unsaturation (see Section 14.16), which means that the compound must possess either a double bond or a ring. With only one signal in the ^{1}H NMR spectrum, the structure must have a high degree of symmetry, such that all twenty-four protons are equivalent. This can be accomplished with either twelve equivalent methylene (CH_2) groups or eight equivalent methyl (CH_3) groups. Since the former would use up all of the carbon atoms in the structure (all twelve), it is tempting to explore that possibility first. Indeed, a twelve-membered ring is comprised of twelve equivalent methylene groups, which should give rise to one signal in the ^{1}H NMR spectrum. And this compound (cyclododecane) also exhibits the correct degree of unsaturation (HDI = 1). However, this structure would give only one signal in its ^{13}C NMR spectrum, and the problem statement indicates that the ^{13}C NMR spectrum has two signals. So, we consider our other alternative (eight equivalent methyl groups). If the structure has eight equivalent methyl groups, then we still need to account for four more carbon atoms, as well as one degree of unsaturation. We can account for all four carbon atoms in a four-membered ring (HDI = 1). In the following structure, all eight methyl groups are equivalent.



This structure has a high degree of symmetry, and it will indeed give rise to two signals in its ^{13}C NMR spectrum (one signal for all of the methyl groups, and another signal for all four carbon atoms of the ring).

15.34. The molecular formula ($C_{17}H_{36}$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound cannot have any double bonds, triple bonds, or rings. That is, the structure must be acyclic and cannot have any π bonds. With only one signal in the ^{1}H NMR spectrum, the structure must have a high degree of symmetry, such that all thirty-six protons are equivalent. If all of these protons were methylene groups, then we would need at least eighteen carbon atoms, but the molecular formula indicates fewer than eighteen carbon atoms. So the thirty-six protons must be twelve equivalent methyl groups. Twelve methyl groups cannot all be attached to the same carbon atom, because the central carbon atom cannot have twelve bonds. However, twelve methyl groups will be equivalent if they comprise four equivalent *tert*-butyl groups, attached to one carbon atom.



This structure is consistent with all of the available data, and it is expected to give rise to three signals in its ^{13}C NMR spectrum (one signal for the central carbon atom, another signal for the four carbon atoms connected to the central carbon atom, and then one last signal for all twelve, equivalent methyl groups).

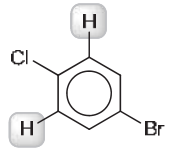
15.35.

(a) All six methyl groups are equivalent (giving rise to one signal), while all four aromatic protons are also equivalent (giving rise to another signal). In total, we expect two signals.

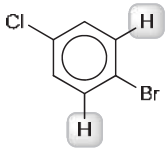
(b) All four aromatic protons are in unique environments (because of their proximity to the two substituents). Therefore, we expect four signals.

(c) All four aromatic protons are in unique environments (because of their proximity to the two substituents). Therefore, we expect four signals.

(d) This compound has two different kinds of protons (highlighted below), giving rise to two signals.



These two protons are homotopic (they produce one signal)



These two protons are homotopic (they produce one signal)

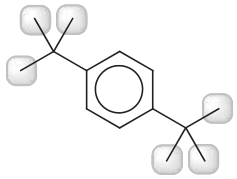
(e) The methine (CH) proton gives one signal, while the two methyl groups collectively give one signal (with an integration of 6). In total, we expect two signals.

(f) The replacement test indicates that the two protons of the methylene group are diastereotopic. Therefore, each of these protons will produce its own signal. That is, the methylene group will give rise to two signals (because of the presence of the chiral center). The structure also has two methyl groups which are not equivalent to each other (because of their proximity to the Cl) so they also produce two different signals. Finally, the methine (CH) proton gives a signal, for a total of five signals.

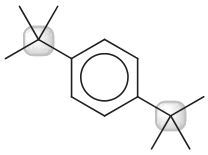
15.36.

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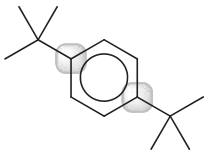
(a) This compound has four different kinds of carbon atoms (highlighted below), giving rise to four signals.



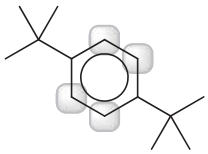
These six methyl groups are all equivalent (giving one signal)



These two carbon atoms are equivalent (giving one signal)



These two carbon atoms are equivalent (giving one signal)

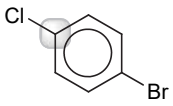


These four carbon atoms are all equivalent (giving one signal)

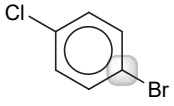
(b) Each of the six carbon atoms is in a unique environment (because of its unique proximity to the two substituents). Therefore, we expect six signals.

(c) Each of the six carbon atoms is in a unique environment (because of its unique proximity to the two substituents). Therefore, we expect six signals.

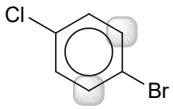
(d) This compound has four different kinds of carbon atoms (highlighted below), giving rise to four signals.



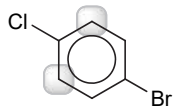
This carbon atom gives one signal



This carbon atom gives one signal



These two carbon atoms are equivalent (giving one signal)



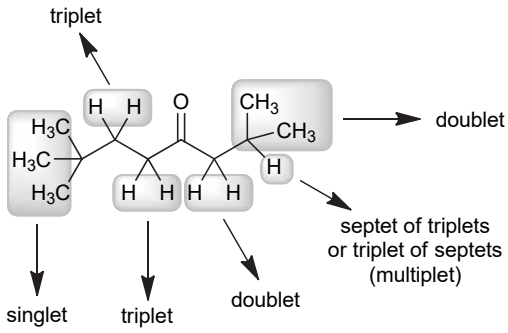
These two carbon atoms are equivalent (giving one signal)

(e) The carbon atom of the methine (CH) group gives one signal, and the two methyl groups give one signal, for a total of two signals.

(f) Each of the four carbon atoms is in a unique environment, because of its proximity to the substituent. Therefore, we expect four signals.

15.37. The first compound exhibits symmetry that causes some of the carbon atoms to be equivalent (similar to the symmetry present in 15.36d). As such, the first compound will have five signals in its ^{13}C NMR spectrum. In contrast, the second compound lacks this symmetry. Each carbon atom occupies a unique environment, so the second compound is expected to produce seven signals in its ^{13}C NMR spectrum.

15.38. This compound has six different kinds of protons, highlighted here. In each case, we apply the n+1 rule, giving the multiplicities shown:



15.39.

(a) The first compound has a very high degree of symmetry, and will produce only four only signals in its ^{13}C NMR spectrum, while the second compound will produce twelve signals.

Also, the first compound will produce only two signals in its ^{1}H NMR spectrum, while the second compound will produce eight signals.

(b) The first compound is a *meso* compound. Two of the protons are enantiotopic (the protons that are alpha to the chlorine atoms) and are therefore chemically equivalent. As such, the first compound will only have two signals in its ^{1}H NMR spectrum, while the second compound will have three signals. For a similar reason, the first compound will only have two signals in its ^{13}C NMR spectrum, while the second compound will have three signals.

(c) The ^{13}C NMR spectrum of the second compound will have one more signal than the ^{13}C NMR spectrum of the first compound. The ^{1}H NMR spectra will differ in the following way: the OH group in the first compound will produce a singlet somewhere between 2 and 5 ppm with an integration of 1, while the methoxy group in the second compound will produce a singlet at approximately 3.4 ppm with an integration of 3.

(d) The first compound has symmetry that is not present in the second compound. As such, the first compound will have three signals in its ^{13}C NMR spectrum, while the second compound will have five signals.

For similar reasons, the first compound will have two signals in its ^{1}H NMR spectrum, while the second compound will have four signals.

15.40. The molecular formula (C_8H_{18}) indicates no degrees of unsaturation (see Section 14.16), which means that the compound does not have a π bond or a ring. With only one signal in its ^{1}H NMR spectrum, the structure must have a high degree of symmetry, such that

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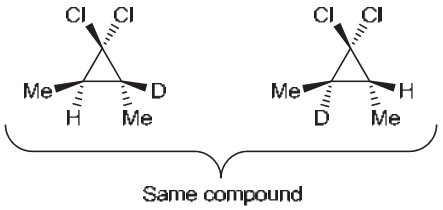
all eighteen protons are equivalent. This can be achieved with six equivalent methyl groups, which account for six of the eight carbon atoms. The remaining two carbon atoms can be placed at the center of the structure, rendering all six methyl groups equivalent, like this:



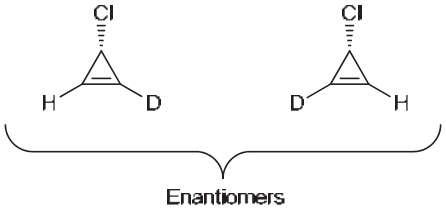
This compound will exhibit two signals in its ^{13}C NMR spectrum (one signal for the two central carbon atoms, and another signal for the six methyl groups).

15.41.

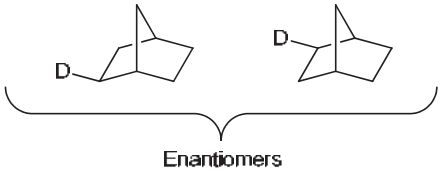
(a) The replacement test gives the same compound, so the protons are homotopic:



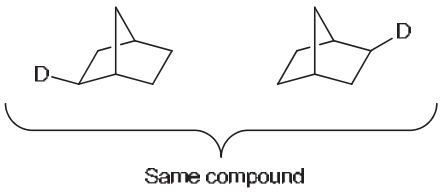
(b) The replacement test gives enantiomers, so the protons are enantiotopic:



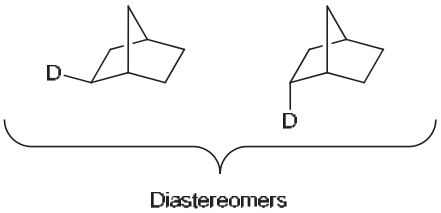
(c) The replacement test gives enantiomers, so the protons are enantiotopic:



(d) The replacement test gives the same compound, so the protons are homotopic:

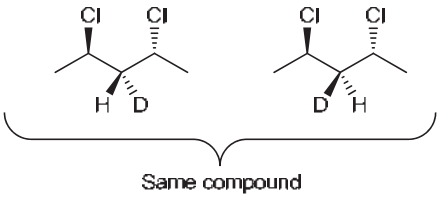


(e) The replacement test gives diastereomers, so the protons are diastereotopic:

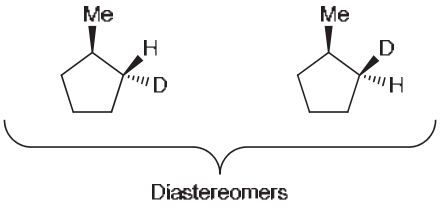


These compounds are diastereomers because they are stereoisomers that are not mirror images of each other. If it seems to you like they should be enantiomers, keep in mind that each of these compounds has three chiral centers, and these compounds differ only in the configuration of one of the three chiral centers (each of the bridgehead positions is a chiral center).

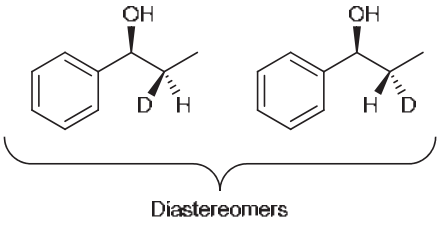
(f) The replacement test gives the same compound, so the protons are homotopic:



(g) The replacement test gives diastereomers, so the protons are diastereotopic:

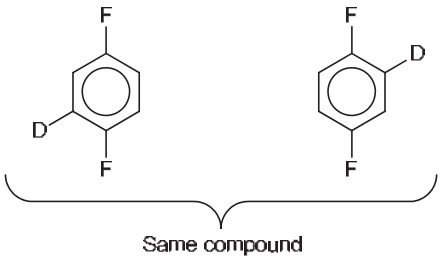


(h) The replacement test gives diastereomers, so the protons are diastereotopic:

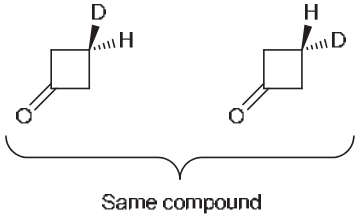


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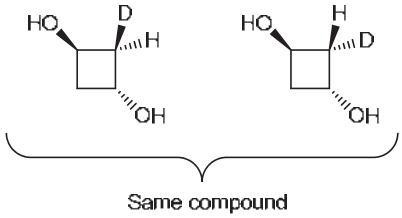
(i) The replacement test gives the same compound, so the protons are homotopic:



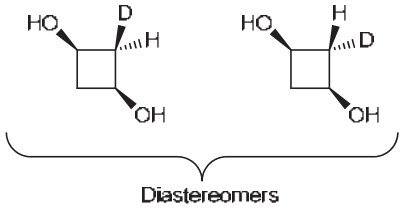
(j) The replacement test gives the same compound, so the protons are homotopic:



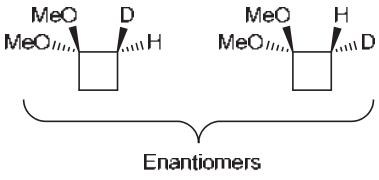
(k) The replacement test gives the same compound, so the protons are homotopic:



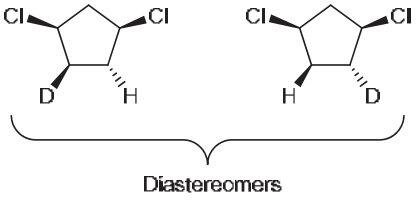
(l) The replacement test gives diastereomers, so the protons are diastereotopic:



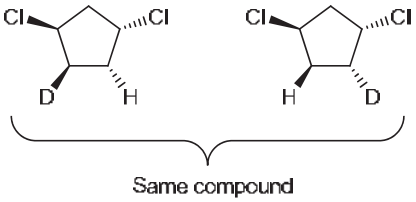
(m) The replacement test gives enantiomers, so the protons are enantiotopic:



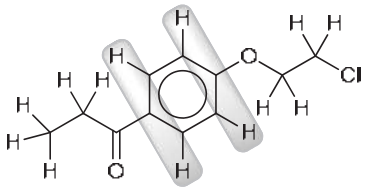
(n) The replacement test gives diastereomers, so the protons are diastereotopic:



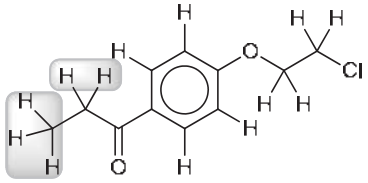
(o) The replacement test gives the same compound, so the protons are homotopic:



15.42. This compound has four aromatic protons. Because of their relationship with the respect to the ring (symmetry), we expect two types of protons, giving rise to a pair of doublets between 7 and 8 ppm:

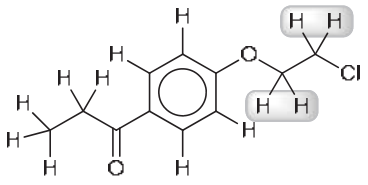


The structure also has an ethyl group, so we expect the characteristic pattern of signals for an ethyl group. Specifically, we expect a triplet with an integration of 3 (corresponding to the CH_3 of the ethyl group) and a quartet with an integration of 2 (corresponding to the CH_2 of the ethyl group).



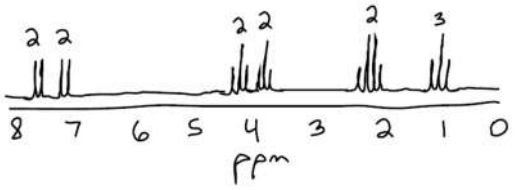
The signal for the CH_2 of the ethyl group is expected to appear at 1.2 + 1 = 2.2 ppm, while the signal for the CH_3 of the ethyl group is expected to appear at 0.9 + 0.2 = 1.1 ppm.

Finally, there are two neighboring methylene groups, shown here:



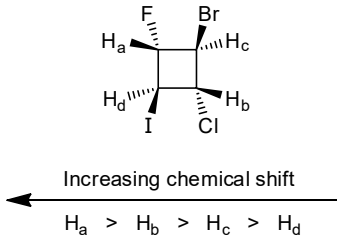
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Each of these signals is expected to be a triplet with an integration of 2. And each of these signals is expected to be shifted downfield, because of the electron-withdrawing effects of the chlorine atom and oxygen atom. As seen in Section 16.5, each Cl adds approximately +2, and oxygen adds approximately +2.5 ppm. The CH_2 next to the oxygen atom should produce a signal near 1.2 + 2.5 + 0.4 = 4.1 ppm. The last term (+0.4) was for the effect of the distant Cl (one-fifth of 2.0). The CH_2 next to the Cl should produce a signal near 1.2 + 2.0 + 0.5 = 3.7 ppm.
The following hand-drawn spectrum shows all of the signals described above.



15.43.
(a) Each of the protons occupies a unique environment, and therefore, we expect four signals in the ^{1}H NMR spectrum of this compound.

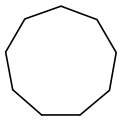
(b) All of the halogens withdraw electron density from the neighboring proton, causing a downfield shift. But the effect will be strongest for fluorine (the most electronegative) and weakest for iodine (the least electronegative of the halogens in this compound).



(c) Each of the carbon atoms occupies a unique environment, and therefore, we expect four signals in the ^{13}C NMR spectrum of this compound.

(d) The carbon atoms follow the same trend exhibited by the protons.

15.44. The molecular formula (C_9H_{18}) indicates one degree of unsaturation (see Section 14.16), which means that the compound must possess either a double bond or a ring. With only one signal in the ^{1}H NMR spectrum, the structure must have a high degree of symmetry, such that all eighteen protons are equivalent. This can be accomplished with either nine equivalent methylene (CH_2) groups or six equivalent methyl (CH_3) groups. Since the former would use up all of the carbon atoms in the structure (all nine), it is tempting to explore that possibility first. Indeed, a nine-membered ring is comprised of nine equivalent methylene groups, which should give rise to one signal in the ^{1}H NMR spectrum:



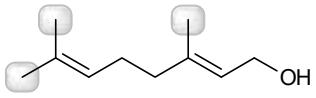
And this compound (cyclononane) also exhibits the correct degree of unsaturation (HDI = 1). However, this structure would give only one signal in its ^{13}C NMR spectrum, and the problem statement indicates that the ^{13}C NMR spectrum has two signals. So, we consider our other alternative (six equivalent methyl groups). If the structure has six equivalent methyl groups, then we still need to account for three more carbon atoms, as well as one degree of unsaturation. We can account for all three carbon atoms in a three-membered ring (HDI = 1). In the following structure, all six methyl groups are equivalent.



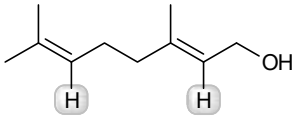
This structure has a high degree of symmetry, and it will indeed give rise to two signals in its ^{13}C NMR spectrum (one signal for all of the methyl groups, and another signal for all three carbon atoms of the ring).

15.45.
(a) This compound has three different methylene (CH_2) groups, giving rise to three separate signals.

In addition, each of the three methyl groups gives its own unique signal, as none of the methyl groups are in identical electronic environments (the two methyl groups on the left side of the structure are not in identical environments, because one is *trans* to the main chain, while the other is *cis* to the main chain):



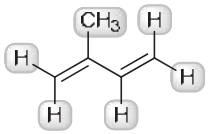
Each of the vinylic CH groups are different, giving rise to two more signals:



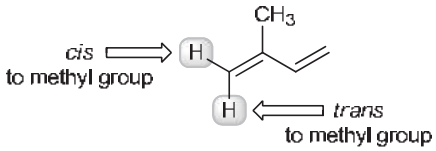
And finally, the proton of the OH group gives one last signal, for a total of 3 + 3 + 2 + 1 = 9 signals.

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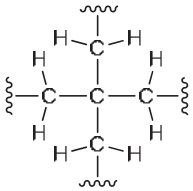
(b) The methyl group gives one signal, and then each of the remaining protons gives rise to its own signal, for a total of six signals:



Note that all of the vinylic protons are different from each other. For example, the following two vinylic protons are different from each other even though they are connected to the same carbon atom:



15.46. Four CH_2 groups can be chemically equivalent if they are all attached to the same carbon atom (provided that the four CH_2 groups are all connected to identical groups:

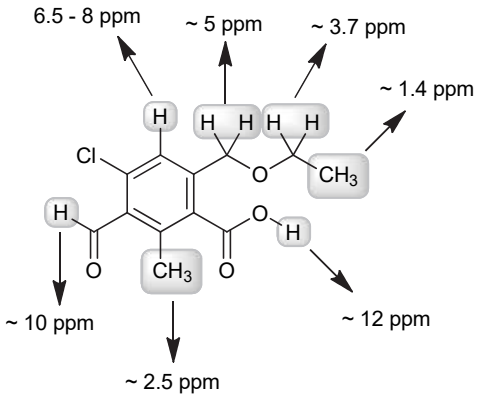


The molecular formula indicates a total of nine carbon atoms and twenty hydrogen atoms, but the structure above only accounts for five carbon atoms and eight hydrogen atoms. We must still account for another four carbon atoms and twelve hydrogen atoms. This can be accomplished if we simply connect a methyl group to each of the CH_2 groups, giving the following structure:



The four methyl groups are chemically equivalent, giving rise to only signal. As such, the ^1H NMR spectrum of this compound is expected to exhibit only two signals (one for the CH_2 groups and the other for the CH_3 groups).

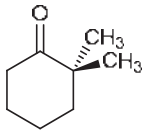
15.47. Below are the expected chemical shifts for each of the seven signals in this compound:



15.48.

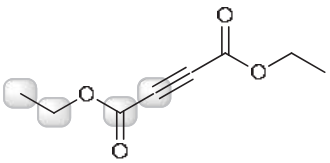
(a) Symmetry in the ring gives four different signals for the carbon atoms of the ring, in addition to two signals for the vinylic carbon atoms. So in total, we expect six signals, all of which result from sp^2 hybridized carbon atoms, and therefore, we expect all six signals to appear in the region 100 – 150 ppm.

(b) Each of the carbon atoms of the ring occupies a unique environment, giving six signals. The two methyl groups occupy identical environments (they are interchangeable by reflectional symmetry), so they produce one signal. This can be seen more clearly if we draw wedges and dashes to illustrate the 3D orientation of the methyl groups:



This gives a total of seven signals. The signal resulting from the carbon atom of the carbonyl group is expected to appear in the region 150 – 220 ppm, while the remaining six signals should appear in the region 0 – 50 ppm.

(c) The compound is symmetrical, so we only need to consider half of the structure. We expect a total of four signals, corresponding with the following unique positions:

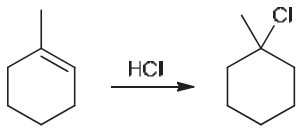


The signal from the carbon atom of the methyl group (sp^3 hybridized) will appear in the region 0 – 50 ppm. The carbon atom of the methylene (CH_2) group is also sp^3 hybridized, but it is next to an oxygen atom. So we expect that signal to appear in the region 50 – 100 ppm,

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together with the signal from the *sp* hybridized carbon. Finally, the signal from the carbonyl group is expected to appear in the region 150 – 220 ppm.

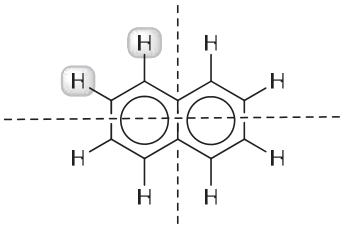
15.49. Let's begin by drawing the reaction described in the problem statement:



The Markovnikov product has symmetry that the *anti*-Markovnikov product lacks. As such, a ^{1}H NMR spectrum of the Markovnikov product should have fewer signals than a ^{1}H NMR spectrum of the *anti*-Markovnikov product.

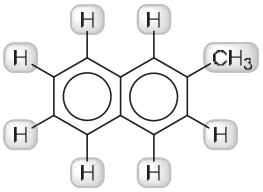
15.50.

(a) The compound has a high degree of symmetry, and there are only two unique aromatic protons, highlighted below, giving rise to two signals.

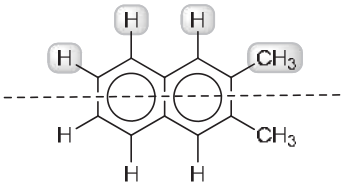


Each of the remaining aromatic protons can be interchanged with one of these positions (via either rotational or reflectional symmetry).

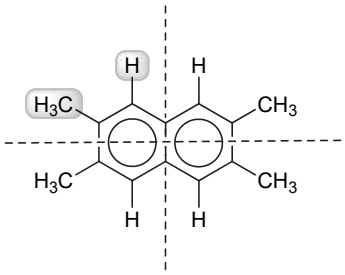
(b) The presence of the methyl group renders all of the aromatic protons different from each other (because of their proximity to the methyl group). As such, we expect eight signals:



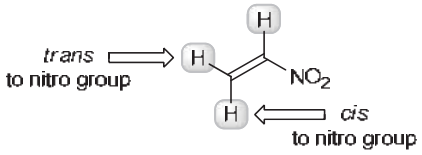
(c) The compound has symmetry that renders some positions identical to other positions. As such, there are only four unique types of protons, highlighted below, giving rise to four signals.



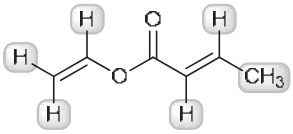
(d) The compound has a high degree of symmetry that renders some positions identical to other positions. As such, there are only two unique types of protons, highlighted below, giving rise to two signals.



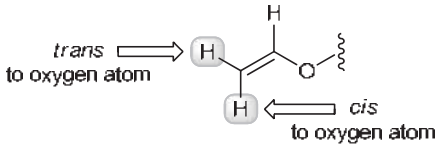
(e) All three vinylic protons are in unique environments, so we expect three signals.



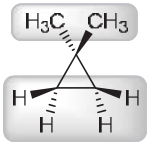
(f) Each of the highlighted protons occupies a unique environment, giving rise to six signals:



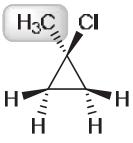
Note that the following positions are different from each other:



(g) The compound has a high degree of symmetry. As such, the two methyl groups occupy identical environments and collectively give rise to one signal. Similarly, all four protons of the two methylene (CH_2) can be interchanged by either rotational or reflection symmetry, so these four protons will collectively give rise to one signal. In total, we expect only two signals:

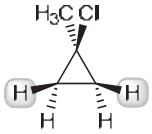


(h) The methyl group will produce one signal.

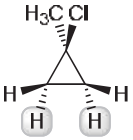


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Now let's consider the remaining four protons. The two protons on wedges (highlighted below) are interchangeable via reflectional symmetry, so they are enantiotopic and therefore chemically equivalent.

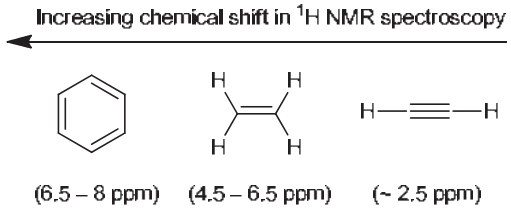


Similarly, the two protons on dashes (highlighted below) are also interchangeable via reflectional symmetry, so they too are enantiotopic and therefore chemically equivalent.



In summary, we expect this compound to produce three signals in its ^{1}H NMR spectrum.

15.51. Among these three compounds, the first one (benzene) has aromatic protons, which are expected to produce a signal the farthest downfield (between 6.5 and 8 ppm). Acetylenic protons give signals that are relatively upfield (near 2.5 ppm) while vinylic protons are expected to produce a signal in the range of 4.5 – 6.5 ppm.



15.52. In Section 15.5, the term "chemical shift" was defined in the following way:

$$\delta = \frac{\text{observed shift from TMS (in Hz)}}{\text{operating frequency of the instrument (in Hz)}}$$

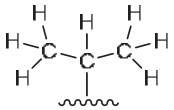
The problem statement indicates that the chemical shift of the proton is 1.2 ppm and the operating frequency of the spectrometer is 300-MHz. We then plug these values into the equation above, as shown:

$$1.2 \times 10^{-6} = \frac{\text{observed shift from TMS (in Hz)}}{300 \times 10^{6}\ \text{Hz}}$$

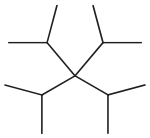
which gives the following observed shift from TMS (in Hz):

$$\text{observed shift from TMS (in Hz)} = \left(1.2 \times 10^{-6}\right) \times \left(300 \times 10^{6}\ \text{Hz}\right) = 360\ \text{Hz}$$

15.53. The molecular formula ($C_{13}H_{28}$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound does not have a π bond or a ring. The ^{1}H NMR spectrum exhibits the characteristic pattern of an isopropyl group (a septet with an integration of 1 and a doublet with an integration of 6):



However, there are no other signals in this spectrum, and the molecular formula indicates that there are 28 protons (not just 7 protons, as we would expect for an isopropyl group). So the compound must be highly symmetrical, with four equivalent isopropyl groups (to account for all 28 protons). This also accounts for 12 of the 13 carbon atoms in this compound. The remaining carbon atom must be at the center, connected to all four isopropyl groups:



15.54. The molecular formula (C_8H_{10}) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring. This accounts for six of the eight carbon atoms in the structure. The other two carbon atoms must be connected to the ring, either as an ethyl group or as two methyl groups. Ethylbenzene would give an ^{1}H NMR spectrum with four signals and a ^{13}C NMR spectrum with six signals. The problem statement indicates fewer signals in each of these spectra, which means that the compound must have more symmetry than ethylbenzene. If we explore the three possible ways to connect two methyl groups to a ring (1,2 or 1,3 or 1,4), we will find that only 1,4-dimethylbenzene has the necessary symmetry to give only two signals in the ^{1}H NMR spectrum and three signals in the ^{13}C NMR spectrum.

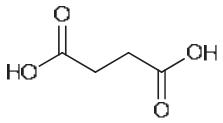


15.55. The molecular formula (C_3H_8O) indicates no degrees of unsaturation (see Section 14.16), which means that the compound does not have a π bond or a ring. The broad signal between 3200 and 3600 cm^{-1} indicates the presence of an OH group. The molecular formula indicates that the structure has three carbon atoms, yet the ^{13}C NMR spectrum exhibits only two signals (not three), indicating the presence of symmetry. This is only true for 2-propanol (not for 1-propanol):



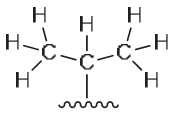
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15.56. The molecular formula ($C_4H_6O_4$) indicates two degrees of unsaturation (see Section 14.16), which means that the compound must possess either two double bonds, or two rings, or one ring and one double bond, or a triple bond. The very broad signal (2500 – 3600 cm^{-1}) in the IR spectrum indicates the presence of a carboxylic acid group. The ^1H NMR spectrum has only two signals, with a total integration of 3, however the molecular formula indicates the presence of 6 protons. Therefore, the actual integration values for the signals are 2H and 4H, respectively. The singlet at 12.1 ppm is characteristic of a carboxylic acid group (COOH), as suggested by the IR spectrum, and since this signal has an integration value of 2H, we conclude that the compound must have two carboxylic acid groups. This accounts for both degrees of unsaturation, which means that the compound does not possess a ring. In order for the remaining four protons to be identical, they must be interchangeable by symmetry, which is indeed the case when we place two methylene (CH_2) groups in between the two carboxylic acid groups, like this:

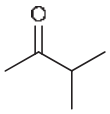


15.57.

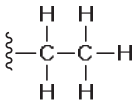
(a) The molecular formula ($C_5H_{10}O$) indicates one degree of unsaturation (see Section 14.16), which means that the compound must possess either a double bond or a ring. The ^1H NMR spectrum exhibits the characteristic pattern of an isopropyl group (a doublet with an integration of 6, and a septet with an integration of 1):



There is also a singlet with an integration of 3, indicating a methyl group. Notice that the signal for the methyl group appears at 2.12 ppm rather than 0.9 ppm, so it has been shifted downfield by just over 1 ppm, which is consistent with being adjacent to a C=O group (accounting for the one degree of unsaturation). The same downfield shift is true for the chemical shift of the CH of the isopropyl group. This gives the following structure:



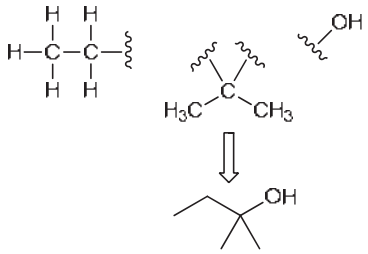
(b) The molecular formula ($C_5H_{12}O$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound does not have a π bond or a ring. The ^1H NMR spectrum exhibits the characteristic pattern of an ethyl group (a quartet with an integration of 2, and a triplet with an integration of 3):



In addition, the singlet with an integration of 6 indicates two equivalent methyl groups:



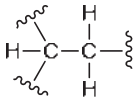
And the singlet with an integration of 1 is suggestive of an OH group. These pieces account for all of the atoms in the compound except for one carbon atom, which we place in between the two methyl groups. The three fragments can then only be connected in one way, giving the following structure:



(c) The molecular formula ($C_4H_{10}O$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound does not have a π bond or a ring. The ^1H NMR spectrum exhibits a signal with an integration of 6, which indicates two equivalent methyl groups:

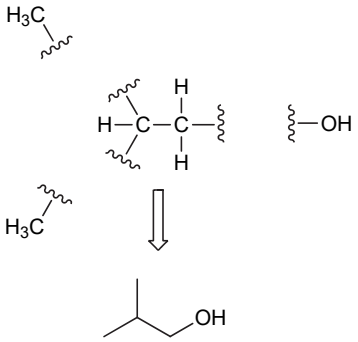


The singlet with an integration of 1 is suggestive of an OH group. The doublet with an integration of 2 indicates a methylene group with only one neighboring proton:

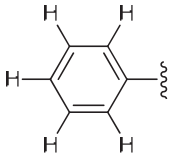


The CH (methine) proton is responsible for the last remaining signal, which is a multiplet, indicating that this CH group is adjacent to the CH_2 group as well as the methyl groups, like this:

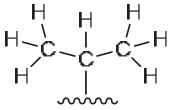
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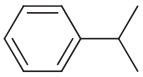
15.58. The molecular formula (C_9H_{12}) indicates four degrees of unsaturation (see Section 15.16), which is highly suggestive of an aromatic ring. This is confirmed by the multiplet just above 7 ppm in the ^{1}H NMR spectrum. This signal has an integration of 5, indicating that the ring is monosubstituted:



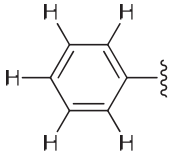
The ^{1}H NMR spectrum also shows the characteristic pattern of signals for an isopropyl group (a septet with an integration of 1 and a doublet with an integration of 6):



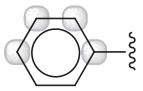
These two fragments (the monosubstituted aromatic ring and the isopropyl group) account for the entire structure:



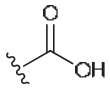
15.59. The molecular formula ($C_9H_{10}O_2$) indicates five degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring, in addition to either one double bond or one ring. The multiplet just above 7 ppm in the ^{1}H NMR spectrum corresponds with aromatic protons, which confirms the presence of an aromatic ring. The integration of this signal is 5, which indicates that the ring is monosubstituted:



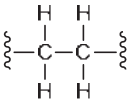
The presence of a monosubstituted ring is confirmed by the four signals between 100 and 150 ppm in the ^{13}C NMR spectrum (the region associated with sp^2 hybridized carbon atoms), just as expected for a monosubstituted aromatic ring:



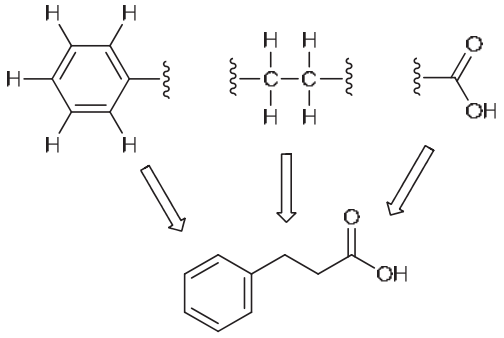
In the ^{1}H NMR spectrum, the signal near 12 ppm (with an integration of 1) indicates the presence of a carboxylic acid group, which is confirmed by the signal near 180 ppm in the ^{13}C NMR spectrum (the region associated with carbonyl groups):



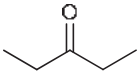
In the ^{1}H NMR spectrum, the pair of triplets (each with an integration of 2) indicates a pair of neighboring methylene groups:



These methylene groups account for the two signals between 0 and 50 ppm in the ^{13}C NMR spectrum.
We have now analyzed all of the signals in both spectra, and we have uncovered three fragments, which can only be connected to each other in the following way:

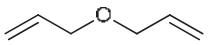


15.60.
(a) The molecular formula ($C_5H_{10}O$) indicates one degree of unsaturation (see Section 14.16), which means that the compound must possess either a double bond or a ring. One of the signals in the ^{13}C NMR spectrum appears above 200 ppm, indicating the presence of a carbonyl group (C=O), which accounts for the one degree of unsaturation.
In total, the ^{13}C NMR spectrum exhibits only three signals, while the molecular formula indicates the presence of five carbon atoms. Therefore, the structure must possess symmetry, giving only three different kinds of carbon atoms (one of which is a carbonyl group), as seen in the following structure:

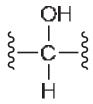


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(b) The molecular formula ($C_6H_{10}O$) indicates two degrees of unsaturation (see Section 14.16), which means that the compound must possess either two double bonds, or two rings, or one double bond and one ring, or a triple bond. The ^{13}C NMR spectrum exhibits only three signals, while the molecular formula indicates the presence of six carbon atoms. Therefore, the structure must possess symmetry, giving only three different kinds of carbon atoms. Two of these types of carbon atoms must be sp^2 hybridized (because two signals appear between 100 and 150 ppm), while the third signal indicates a carbon atom attached to an oxygen atom. The following structure accounts for all of the observations above:

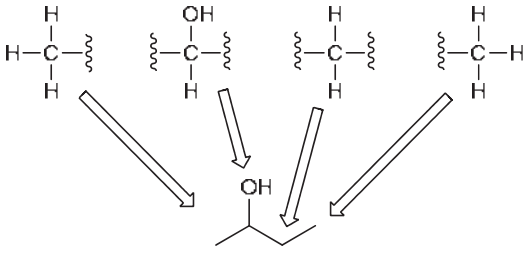


15.61. The problem statement indicates that the compound is an alcohol, so it must contain an OH group. The molecular formula ($C_4H_{10}O$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound cannot have any double bonds, triple bonds, or rings. That is, the structure must be acyclic and cannot have any π bonds. The broadband decoupled spectrum has four signals, one of which appears above 50 ppm (this signal accounts for the carbon atom attached directly to the OH group). The other three signals in the broadband decoupled spectrum are all below 50 ppm, indicating that all of the carbon atoms are sp^3 hybridized (although we already knew that because HDI = 0). The DEPT-90 spectrum has only one signal, which means the compound has only one methine (CH) group. Furthermore, this signal is above 50 ppm, which indicates that this CH group is connected to directly to the OH group:

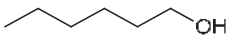


The DEPT-135 spectrum indicates that the other three signals (below 50 ppm) correspond with one methylene group (upside-down signal) and two methyl groups (right-side up signals that did not appear in the DEPT-90).

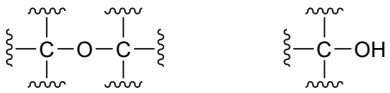
We have now analyzed all of the signals in all of the spectra, and we have uncovered four fragments, which can only be connected to each other in the following way:



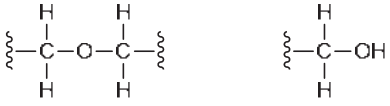
15.62. The problem statement indicates that the compound is an alcohol, so it must contain an OH group. The molecular formula ($C_6H_{14}O$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound cannot have any double bonds, triple bonds, or rings. That is, the structure must be acyclic and cannot have any π bonds. The DEPT-135 spectrum exhibits five signals that are upside-down, indicating the presence of five methylene groups. One of these methylene groups must be connected to the OH group, because one of the upside-down signals appears above 50 ppm. The five methylene groups and the OH group account for 11 of the 14 protons in this compound. Therefore, the signal pointing up must correspond with a methyl group (rather than a CH group). There is only one way to connect a methyl group, five methylene groups, and an OH group, as shown here:



15.63. The molecular formula ($C_6H_{14}O_2$) indicates no degrees of unsaturation (see Section 14.16), which means that the compound cannot have any double bonds, triple bonds, or rings. That is, the structure must be acyclic and cannot have any π bonds. The IR spectrum has a broad signal between 3200 and 3600 cm^{-1}, indicating the presence of an OH group. The ^{13}C NMR spectrum has six signals, and the molecular formula indicates there are six carbon atoms, which means that the compound lacks symmetry that would interchange any of the carbon atoms. Since the compound has no degrees of unsaturation, all of the signals must arise from sp^3 hybridized carbon atoms. Indeed, three of the signals appear between 0 and 50 ppm, as expected for sp^3 hybridized carbon atoms. But the other three signals appear between 50 and 100 ppm, indicating that three carbon atoms are connected to an oxygen atom. We can therefore draw the following fragments (since the compound has an OH group, and since the molecular formula indicates only two oxygen atoms):

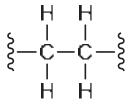


Now we explore the ^1H NMR spectrum. Let's begin with the signals downfield. There are three signals that appear between 3.5 and 4 ppm. One of these signals is clearly a triplet, but the other two signals are overlapping so it is difficult to determine their multiplicity (perhaps they are doublets that appear very close to each other, or perhaps they are overlapping triplets). We will revisit the multiplicity of these signals later. For now, let's focus on the chemical shifts and integration values for these signals. These signals are certainly from the three groups connected to oxygen atoms (because of their chemical shifts), and we notice that each of these signals has an integration of 2H, which allows us to modify the fragments above as follows:



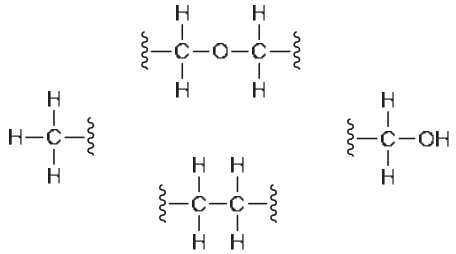
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The singlet at 2.4 ppm has an integration of 1, which can be attributed to the OH group. Each of the multiplets near 1.5 ppm has an integration of 2H, indicating methylene groups that have complex splitting:

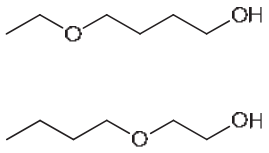


The triplet at 1.0 ppm has an integration of 3H, indicating a methyl group that is connected to a neighboring CH_2 group.

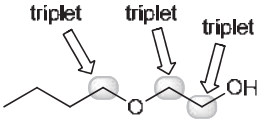
In summary, we have the following fragments:



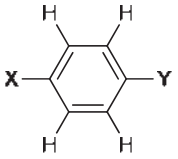
There are only two ways to connect these four fragments:



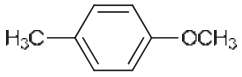
The first structure contains an ethyl group, which should produce a quartet with an integration of 2 (for the CH_2 portion of the ethyl group). If we inspect the three signals between 3.5 and 4 ppm, it is difficult to argue that any of these signals is a quartet. While it is difficult to be certain, because two of these signals overlap with each other, it looks more like each of these signals is a triplet, which would be consistent with the second structure:



15.64. The molecular formula ($C_8H_{10}O$) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring. This is confirmed by the presence of signals just above 3000 cm^{-1} in the IR spectrum, and signals at approximately 1600 cm^{-1}. In the ^1H NMR spectrum, the signals near 7 ppm are likely a result of aromatic protons, which also confirms the presence of an aromatic ring. Notice that the combined integration of these two signals (near 7 ppm) is 4H. This, together with the distinctive splitting pattern (a pair of doublets), suggests a 1,4-disubstituted aromatic ring:

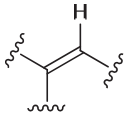


The spectrum also exhibits two singlets, each of which has an integration of 3H, indicating methyl groups. Notice that both signals are shifted downfield (relative the benchmark value for a methyl group of 0.9 ppm). One of them is shifted much more than other, indicating that it is likely next to an oxygen atom. This gives the following structure:

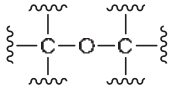


This structure is consistent with the ^{13}C NMR spectrum. Specifically, there are four signals for the aromatic ring, one of which is shifted downfield because it is next to an oxygen atom. And the other two signals are for the methyl groups, one of which appears above 50 ppm because the carbon atom giving rise to this signal is next to an oxygen atom.

15.65. The molecular formula ($C_5H_{10}O$) indicates one degree of unsaturation (see Section 14.16), which means that the compound must either have a double bond or a ring. The IR spectrum has a signal at approximately 3100 cm^{-1}, indicating the presence of a Csp^2–H bond:

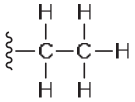


This is consistent with the weak signal at 1600 cm^{-1}, indicating the presence of a C=C double bond (which accounts for the one degree of unsaturation).
The ^{13}C NMR spectrum has two signals between 100 and 150 ppm, confirming the presence of a C=C double bond. In addition, there are three other signals, two of which appear between 50 and 100 ppm. These latter two signals are characteristic of carbon atoms connected to an oxygen atom. Since there is only one oxygen atom in the structure ($C_5H_{10}O$), these two carbon atoms must be connected to it:

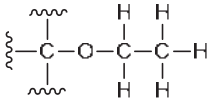


In the ^1H NMR spectrum, we see the characteristic pattern of an ethyl group (a triplet with an integration of 3 and a quartet with an integration of 2):

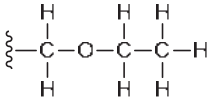
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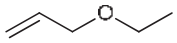
Notice that the quartet appears at 3.5 ppm, indicating that the ethyl group is one of the two groups that is connected to the oxygen atom:



The signal at 4.0 ppm has an integration of 2, which represents a CH_2 group connected to the other side of the oxygen, like this:



Remember that our structure must include a double bond, which completes the structure, and accounts for all of the atoms in the molecular formula ($C_5H_{10}O$):



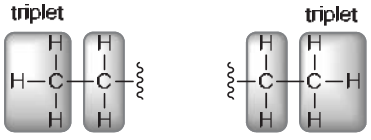
The signals above 5.0 correspond with the vinylic protons. There are three signals, and they are all splitting each other. Two of them are overlapping, to give an apparent integration of 2.

15.66. The molecular formula ($C_8H_{14}O_3$) indicates that the compound has two degrees of unsaturation, so the structure must either have two rings, or two double bonds, or a ring and a double bond, or a triple bond.

In the IR spectrum, there are two signals that are suggestive of C=O groups, which would account for both degrees of unsaturation.

In the ^{1}H NMR spectrum, there are three signals. By comparing the heights of the S-curves, we can see that the *relative* integration values are 2:2:3. With a total of 14 protons (as seen in the molecular formula), these relative integration values must correspond to 4:4:6. This indicates a high level of symmetry in the compound.

The signal at approximately 1 ppm has an integration of 6, indicating two methyl groups that are identical because of symmetry. This signal is a triplet, which means that each of these CH_3 groups is neighboring a methylene (CH_2) group.

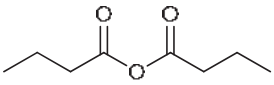


Based on the integration and multiplicities of the remaining two signals (at 1.7 ppm and 2.5 ppm), we can assemble the following two fragments, which must be identical by symmetry:



Each of the central methylene groups is being split by a neighboring methyl group and a neighboring methylene group. This could lead to a complex splitting pattern (either a triplet of quartets or a quartet of triplets). In this case, we are not seeing such a complex pattern. As mentioned in the textbook, this can happen when the J-values are fortuitously similar. In such a case, the system behaves as if it has five neighbors, and the n+1 rule gives a sextet, which is what we see in this case.

Thus far, we have identified the presence of two, symmetrically positioned propyl groups, and there are two C=O bonds. Since the molecular formula indicates that there are three oxygen atoms in this compound, we can deduce the following structure:



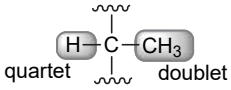
The IR spectrum is consistent with this structure, in that the two signals (at 1755 and 1820 cm^{-1}) represent symmetrical and unsymmetrical stretching of the anhydride unit.

The ^{13}C NMR spectrum is also consistent with this structure. We see a carbon atom (of a C=O bond) at 180 ppm - notice that there is only one signal at 180 ppm, because the two carbonyl groups are identical by symmetry. As expected, three signals appear between 0 and 50 ppm, corresponding to the three carbon atoms of the propyl group (once again, the two propyl groups are identical to each other, giving rise to three signals rather than six). We can see from the DEPT-135 spectrum that two of these signals are methylene groups (because the signals are upside down), which is also consistent with the structure that we deduced above.

15.67. A compound with the molecular formula $C_6H_{10}O_4$ has two degrees of unsaturation, so any proposed structure must either have two rings, or two double bonds, or a ring and a double bond, or a triple bond.

The signal at 1747 cm^{-1} is likely a C=O bond of an ester, which accounts for one of the degrees of unsaturation.

In the proton NMR spectrum, there are four signals. The signal just above 5 ppm has an integration of 1, indicating a methine proton (CH), and it is a quartet, which indicates a neighboring methyl group. The signal for the methyl group should be a doublet (since it is next to the methine proton). That signal appears at 1.5ppm.

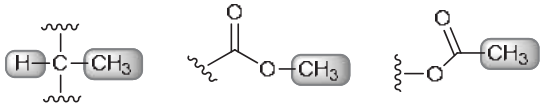


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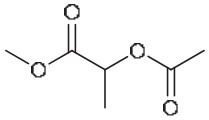
The quartet is significantly downfield (5 ppm), which indicates that it is neighbored by an oxygen atom, as well as some other group which can also shift the signal further downfield. The remaining two signals, just above 2 ppm and just below 4 ppm, are methyl groups (each has an integration of 3). Based on their chemical shifts, the former is likely to have a neighboring C=O group, while the latter is likely to be next to an oxygen atom:



The carbon NMR spectrum reveals that there are actually two carbonyl groups in this compound, and the molecular formula indicates four oxygen atoms, so it is likely that there are two ester groups that are overlapping in the IR spectrum (both at approximately 1747 cm^{-1}). This gives us three pieces that must be assembled:



The following structure can be assembled from these three pieces:

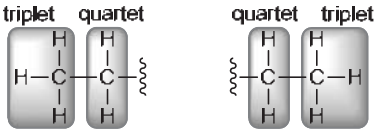


15.68. The molecular formula ($C_8H_{14}O_4$) indicates that the compound has two degrees of unsaturation, so the structure must either have two rings, or two double bonds, or a ring and a double bond, or a triple bond.

The signal at 1736 cm^{-1} is likely a C=O bond of an ester, which accounts for one of the degrees of unsaturation.

In the proton NMR spectrum, there are three signals. By comparing the heights of the S-curves, we can see that the *relative* integration values are 2:2:3. With a total of 14 protons (as seen in the molecular formula), these relative integration values must correspond to 4:4:6. This indicates a high level of symmetry in the compound.

The signal just above 4 ppm has an integration of 4, indicating two methylene (CH_2) groups that are identical because of symmetry. This signal is a quartet, which means that each of these two CH_2 groups is neighboring a methyl group. The signal for these methyl groups should be a triplet with an integration of 6. That signal appears just above 1 ppm.

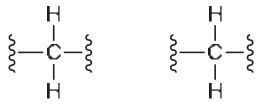


The quartet is significantly downfield (4 ppm), which indicates that it is neighboring an oxygen atom.



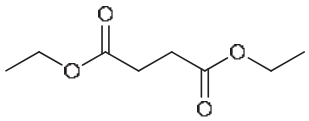
These two groups cannot be connected to each other, as that would not give us an opportunity to connect the remaining atoms in the compound.

The remaining signal, just below 3 ppm, is a singlet with an integration of 4, indicating two methylene groups that are equivalent by symmetry, with no neighboring protons:



These two groups may or may not be connected to each other, but we know that they must be equivalent by symmetry, and they cannot have any neighbors.

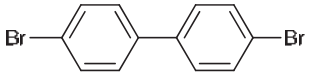
The molecular formula indicates two degrees of unsaturation and the presence of four oxygen atoms, but so far, we have only accounted for one degree of unsaturation (C=O) and only three oxygen atoms. The fourth oxygen atom, as well as the extra degree of unsaturation can be accounted for in the following structure which has the necessary symmetry, and is consistent with all of the spectra:



Notice that, because of symmetry, there are only four different kinds of carbon atoms in this compound, giving four signals in the carbon NMR spectrum. Two of these signals correspond to methylene (CH_2) groups, as confirmed by the presence of two upside-down signals in the DEPT-135 spectrum.

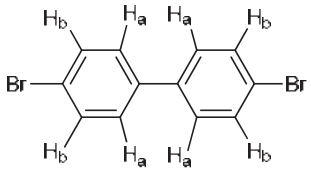
15.69. The molecular formula ($C_{12}H_8Br_2$) indicates that the compound has eight degrees of unsaturation, so the structure likely contains two aromatic rings (each of which represents four degrees of unsaturation).

In the proton NMR spectrum, there are only two signals, with the same relative integration. Since the molecule has eight protons (as seen in the molecular formula), we must conclude that each signal corresponds to four protons. Each of these signals is a doublet indicating only one neighboring proton. The following structure is consistent with this information:

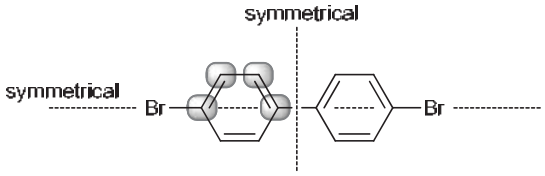


In this structure, there are only two different kinds of protons, labeled H_a and H_b:

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This structure is consistent with the carbon NMR spectrum, in which there are only four signals, all of which are aromatic:



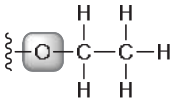
15.70.

(a) The height of the $(M+1)^{+\bullet}$ peak indicates that the compound has four carbon atoms (1.1% for each carbon atom). Since the parent ion appears at *m/z* = 104, we know that nearly half of the molecular weight is due to carbon atoms (12 x 4 = 48). The rest of the molecular weight (104 – 48 = 56) must be attributed to oxygen atoms and hydrogen atoms. There is a limit to how many hydrogen atoms there can be, since there are only four carbon atoms. Even if the compound is fully saturated, it could not have more than 10 protons (2n+2, where n is the number of carbon atoms). Oxygen has an atomic weight of approximately 16. Therefore, the compound must contain at least three oxygen atoms (otherwise we could not account for the rest of the compound using hydrogen atoms alone). But the compound cannot contain *more* than three oxygen atoms, because four oxygen atoms have a combined atomic weight of 64, which already blows our budget, even before we place any hydrogen atoms (remember that our budget for O and H atoms is a total mass of 56). So, we conclude that the compound must have exactly three oxygen atoms. The remaining weight is accounted for with hydrogen atoms, giving the following molecular formula: $C_4H_8O_3$.

(b) The molecular formula ($C_4H_8O_3$) indicates that the compound has one degree of unsaturation, so the structure must either have a ring or a double bond.

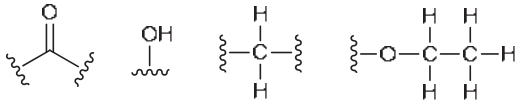
In the IR spectrum, the broad signal between 3200 and 3600 cm^{-1} is characteristic of an O-H bond, and the signal at 1742 cm^{-1} is likely a C=O group of an ester.

In the proton NMR spectrum, there are four signals. By comparing the heights of the S-curves, we can see that the relative integration values are 2:2:1:3. With a total of eight protons (as seen in the molecular formula), these relative integration values correspond precisely to the number of protons giving rise to each peak. The signal just above 1 ppm corresponds to three protons, and is therefore a methyl group. Since this signal is a triplet, it must be next to a methylene (CH_2) group. The signal for that methylene group appears as a quartet, just as expected (since it is next to the methyl group) above 4 ppm. The location of this signal indicates that the methylene group is likely next to an oxygen atom (since it is shifted downfield). So far, we have the following fragment:

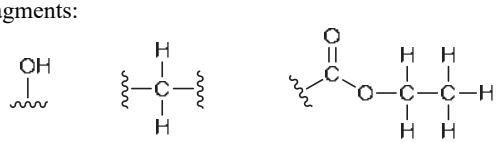


Now let's explore the remaining two signals in the proton NMR spectrum. The signal at approximately 3.6 ppm (with an integration of 1) vanishes in D_2O, indicating that it is the proton of the OH group (confirming our analysis of the IR spectrum). The singlet just above 4 ppm has an integration of 2, and therefore corresponds with an isolated methylene group (no neighbors). This methylene group is shifted significantly downfield, and our structure will have to take this into account.

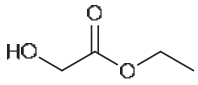
In summary, we have the following fragments, which must be assembled.



Since the C=O bond is likely part of an ester (based on the IR spectrum), we can redraw the following three fragments:

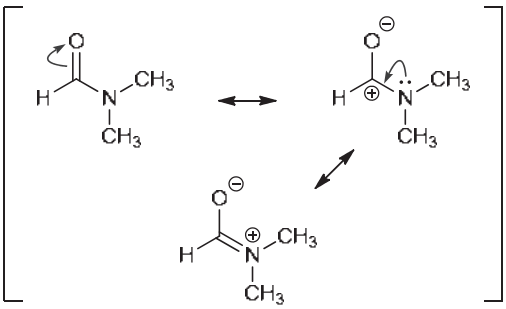


These fragments can only be assembled in one way:



This structure is consistent with the carbon NMR spectrum, in which there is one signal for the C=O unit, two signals between 50 and 100 ppm (both of which must be methylene groups, based on the DEPT spectrum), and one signal between 0 and 50 ppm (representing the methyl group).

15.71. *N,N*-dimethylformamide (DMF) has three resonance structures:



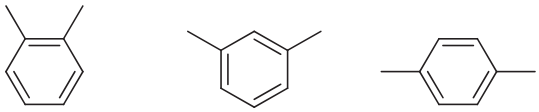
Consider the third resonance structure, in which the C-N bond is a double bond. This indicates that this bond is expected to have some double bond character. As such, there is an energy barrier associated with rotation about

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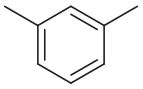
this bond, such that rotation of this bond occurs at a rate that it slower than the timescale of the NMR spectrometer. Therefore, the two methyl groups will appear as distinct signals in a ^{1}H NMR spectrum. At high temperature, more molecules will have the requisite energy to undergo free rotation about the C-N bond, so the process can occur on a timescale that is faster than the timescale of the NMR spectrometer. For this reason, the signals are expected to collapse into one signal at high temperature.

15.72. The first compound lacks a chiral center. The two methyl groups are enantiotopic and are therefore chemically equivalent. The second compound has a chiral center (the position bearing the OH group). As such, the two neighboring methyl groups are diastereotopic and are therefore not chemically equivalent. For this reason, the ^{13}C NMR spectrum of the second compound exhibits six signals, rather than five.

15.73. The molecular formula (C_8H_{10}) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring. The aromatic ring accounts for six of the eight carbon atoms, so we must account for the other two carbon atoms, which must be sp^3 hybridized. However, only one signal appears in the region 0 – 50 ppm, suggesting that the two sp^3 hybridized carbon atoms are interchangeable by symmetry. This can be achieved in any of these three compounds:

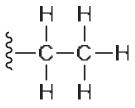


However, only one of these compounds, shown below, will exhibit four signals in the region 100 – 150 ppm.

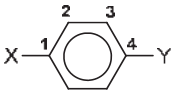


15.74. The methyl group on the right side is located in the shielding region of the π bond, so the signal for this proton is moved upfield to 0.8 ppm.

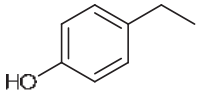
15.75. The two signals farthest upfield are a quartet with an integration of 2 and a triplet with an integration of 3. Together, these two signals indicate the presence of an ethyl group:



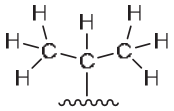
The signals near 7 ppm represent aromatic protons. Note that the total integration of the aromatic region is 2H + 2H = 4H, which means that the ring is disubstituted. Furthermore, the aromatic signals are a pair of doublets, indicating symmetry, which is achieved with a 1,4-disubstituted aromatic ring.



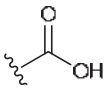
Therefore, the answer is (a), and the signal at 4.7 ppm (with an integration of 1H) represents the phenolic proton:



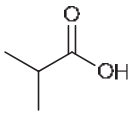
15.76 The molecular formula ($C_4H_8O_2$) indicates one degree of unsaturation, which means that the compound must possess either a double bond or a ring. The ^{1}H NMR spectrum exhibits the characteristic pattern of an isopropyl group (a doublet with an integration of 6, and a septet with an integration of 1):



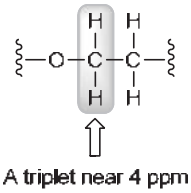
There is also a singlet with an integration of 1 at 11.38 ppm, indicating a carboxylic acid group (which accounts for the one degree of unsaturation).



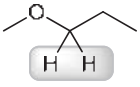
These two fragments account for all of the atoms that appear in the molecular formula, so we connect these fragments together to give structure (b):



15.77. A triplet indicates protons that are adjacent to a methylene (CH_2) group. The chemical shift of this signal (4 ppm) indicates that the protons giving rise to the signal are adjacent to some powerful electron-withdrawing group, such as an oxygen atom. So, we are looking for a compound that contains the following structural features:

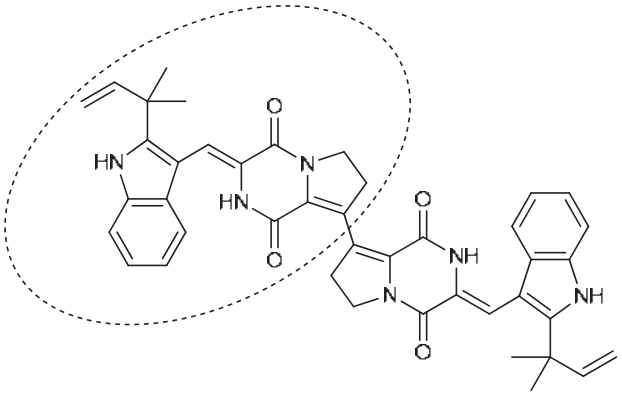


Only structure (b) has these features:

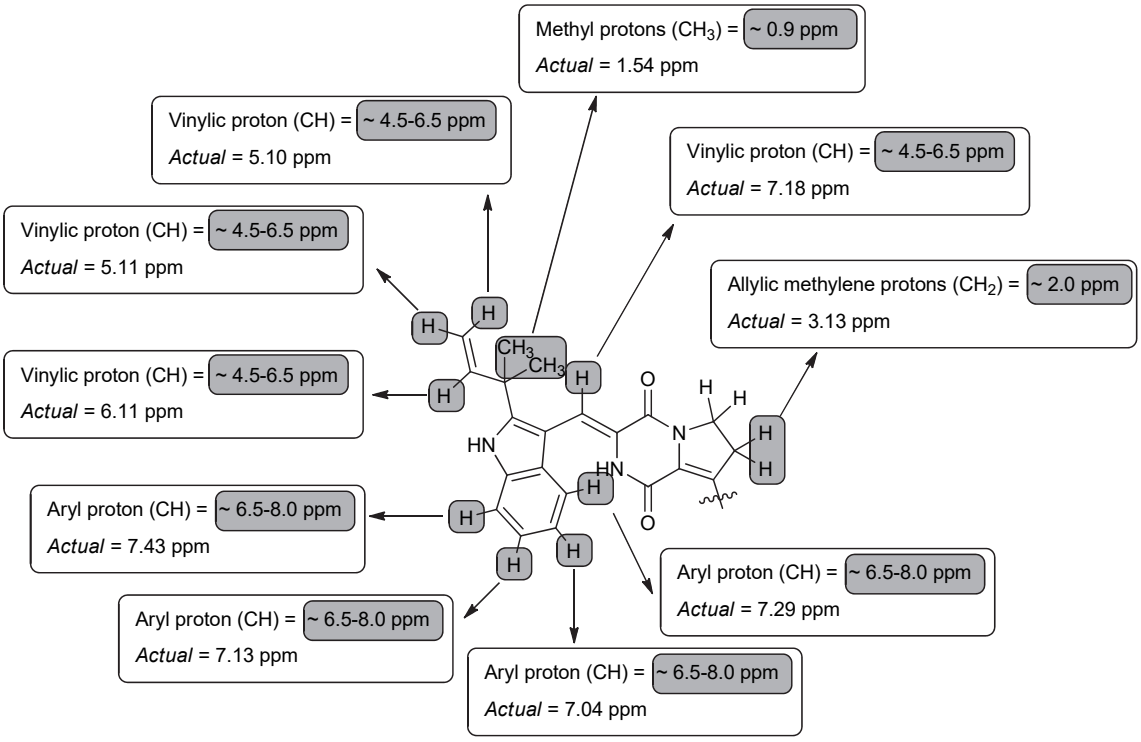


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15.78. Brevianamide S has a high degree of symmetry. In fact, there is a rotational axis of symmetry that runs right through the molecule. Therefore, only half of the molecule will need to be analyzed.

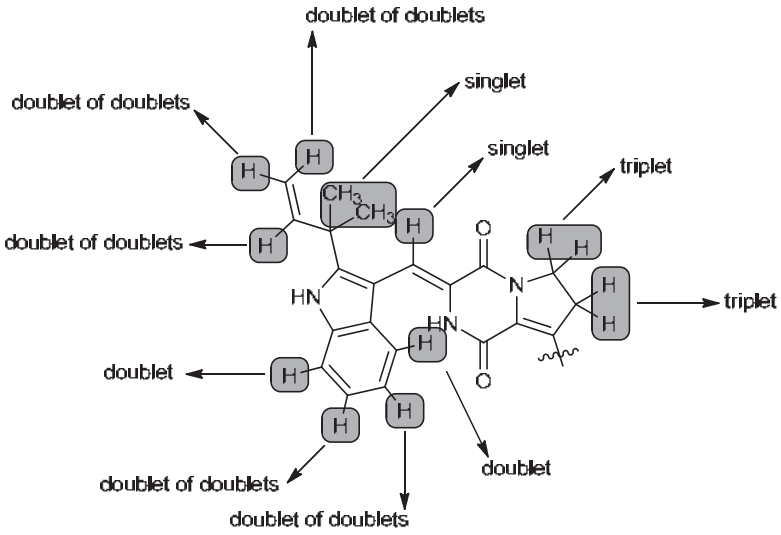


The compound lacks a chiral center and is achiral. As a result, the two protons for any methylene (CH_2) group will be equivalent to each other. There are two unique methylene groups, giving rise to two unique signals. In addition, the methyl groups will all be equivalent, giving rise to one signal. The predicted chemical shift for all signals is shown below:



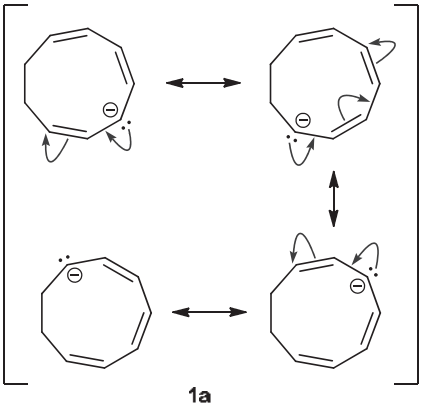
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The multiplicity of each proton is determined with the n+1 rule, as shown below. Note: complex splitting is observed for two of the protons on the aromatic ring, as well as all three protons of the terminal olefin.



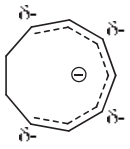
15.79.

(a) The two most acidic protons are at C9 and C5. Deprotonation at C9 leads to a resonance-stabilized anion in which the negative charge is delocalized over three carbon atoms, while deprotonation at C5 leads to a resonance-stabilized anion in which the negative charge is delocalized over *four* carbon atoms. The latter anion is more stable than the former (since the negative charge is more highly delocalized). As such, the proton at C5 is the most acidic proton. Deprotonation at C5 yields the following anion, with four resonance structures:

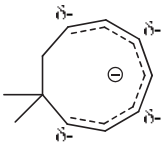


1a

(b) In an attempt to capture the nature of the resonance hybrid for each anion, **1a** and **2a** can be drawn in the following way:

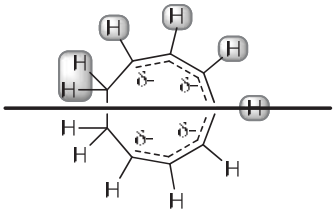


1a



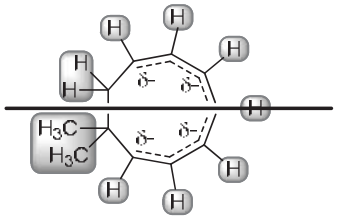
2a

When viewed in this way, we can see that anion **1a** possesses symmetry, rendering positions C8 and C9 equivalent. Similarly, C1 and C7 are equivalent. Therefore, we expect only five signals in the proton NMR spectrum of **1a**.



1a

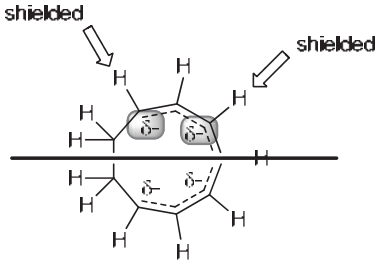
In contrast, anion **2a** does not possess the same symmetry, as a result of the presence of the methyl groups. That is, each and every position is unique (for example, C1 is not equivalent to C7). Therefore, we expect nine signals for anion **2a**, shown below:



2a

Note that the two methyl groups of **2a** are identical and give one signal.

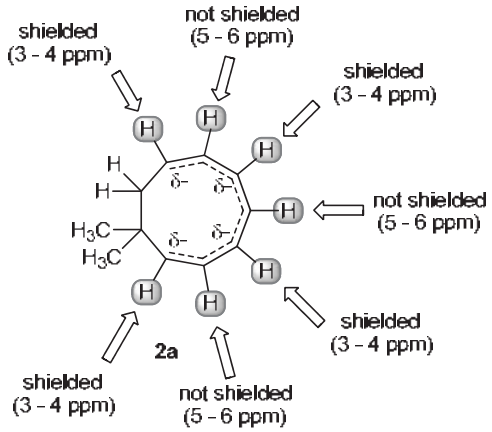
(c) Once again, we can use the resonance hybrid to explain this effect:



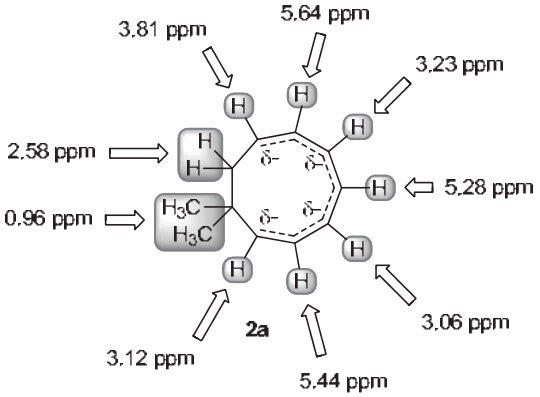
1a

The protons at positions C1 and C3 are shielded by the electron density that is distributed over those positions via resonance. The protons at positions C2 and C4 are less shielded, and they produce signals farther downfield.

(d) Inspecting the resonance hybrid, we expect four signals in the range of 3 – 4 ppm, and three signals in the range 5 – 6 ppm, as shown below:

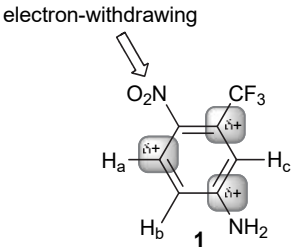


The following are the actual data from the proton NMR spectrum of **2a**, which supports our prediction.

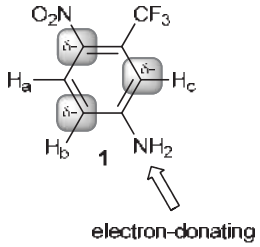


15.80.

(a) The nitro group is a powerful electron-withdrawing group (primarily due to resonance), which renders the *ortho* and *para* positions electron-poor (highlighted below). This effect should cause H_a to be deshielded:



The amino group is a powerful electron-donating group (via resonance), which renders the *ortho* and *para* positions electron-rich (highlighted below). This effect should cause H_b and H_c to be shielded:



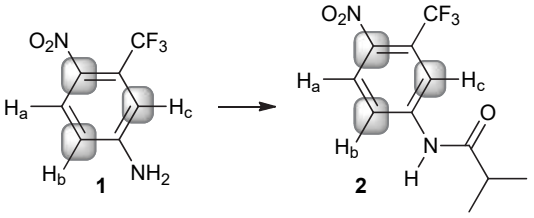
Based on these effects alone, we expect H_a to be downfield (deshielded) relative to H_b and H_c, and we expect that H_b and H_c will be upfield (shielded) relative to H_a. That is, based solely on the resonance effects of the nitro group and the amino group, we expect H_a to give the signal farthest downfield.

There is, however, one other group on the aromatic ring. The trifluoromethyl group is a powerful electron-withdrawing group, via induction (rather than resonance). As such, we expect its effect to diminish with distance, so H_a should be affected less than H_c. While this effect deshields H_c more than H_a, we would not expect this inductive effect to overwhelm the two resonance effects that suggest that H_a gives the most downfield signal. After all, there are two different

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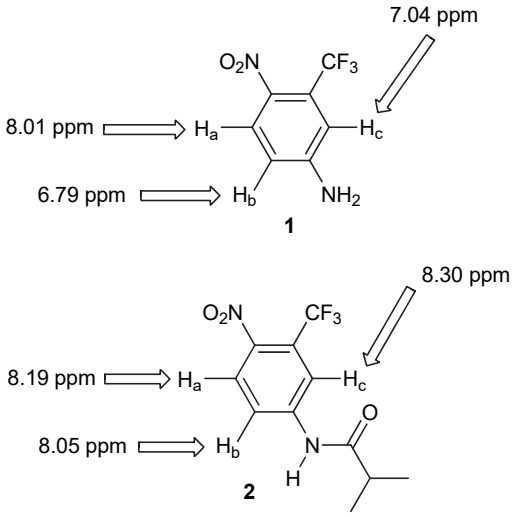
resonance effects suggesting H_a is the most downfield signal, AND resonance is generally a stronger effect than induction.

(b) This transformation involves conversion of the amino group (a strong activator) into an amide group (a moderate activator). This can be rationalized by considering the lone pair on the nitrogen atom of the amine/amide; in **1** it is completely available for resonance into the ring, but in **2**, the adjacent carbonyl group involves this lone pair in resonance, pulling it away from the ring. As such, the *ortho* and *para* positions are the most affected, highlighted below:



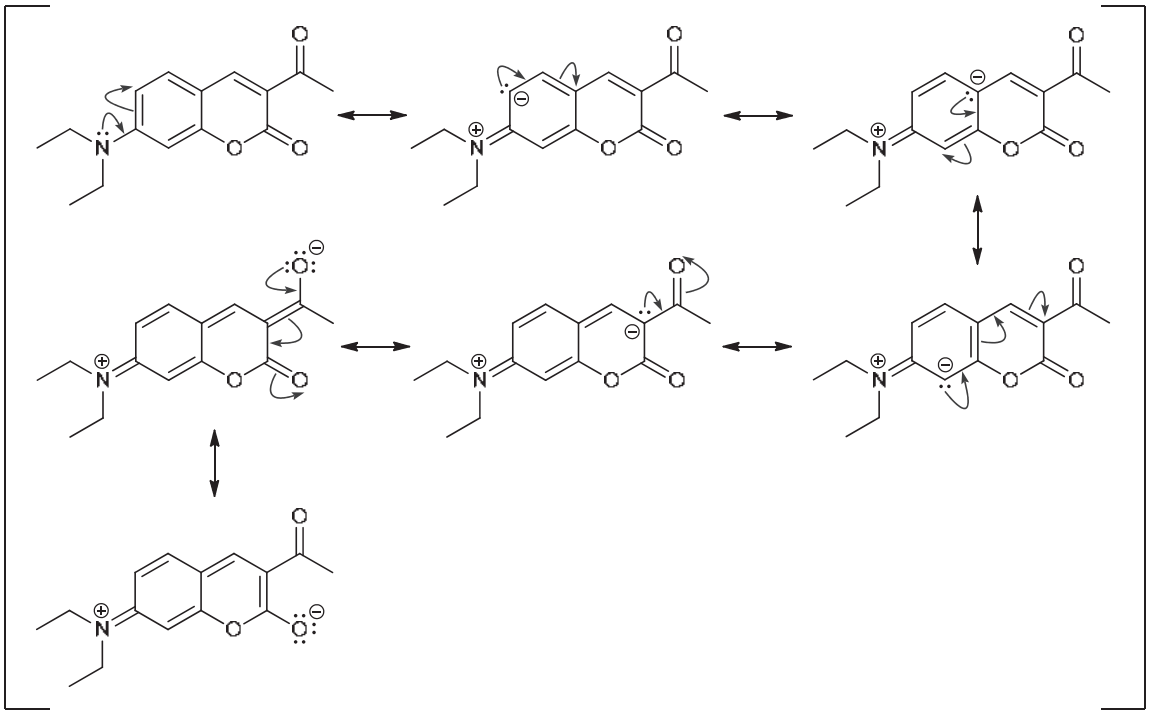
In both compound **1** and compound **2**, these three positions are shielded. But the shielding effect is greater in compound **1** than in compound **2**. In other words, these three positions become less shielded. As a result, we expect the signals for H_b and H_c to be more affected by this transformation than the signal for H_a. Specifically, H_b and H_c become less shielded as a result of this transformation, so we expect those two signals to move farther downfield.

The actual chemical shifts (shown below) support our predictions.



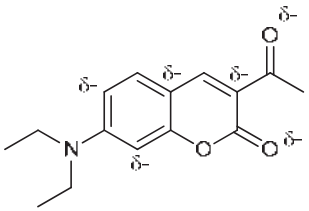
15.81.

(a) We are looking for the proton that is expected to be the most deshielded. In other words, we must identify the proton that resides in the most electron-deficient environment. Let's begin by considering resonance effects of the diethyl amino group:

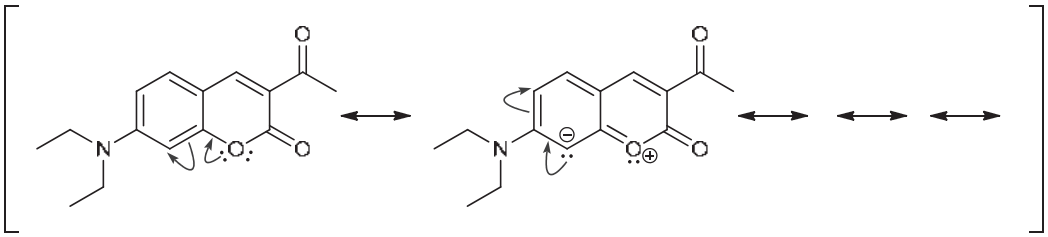


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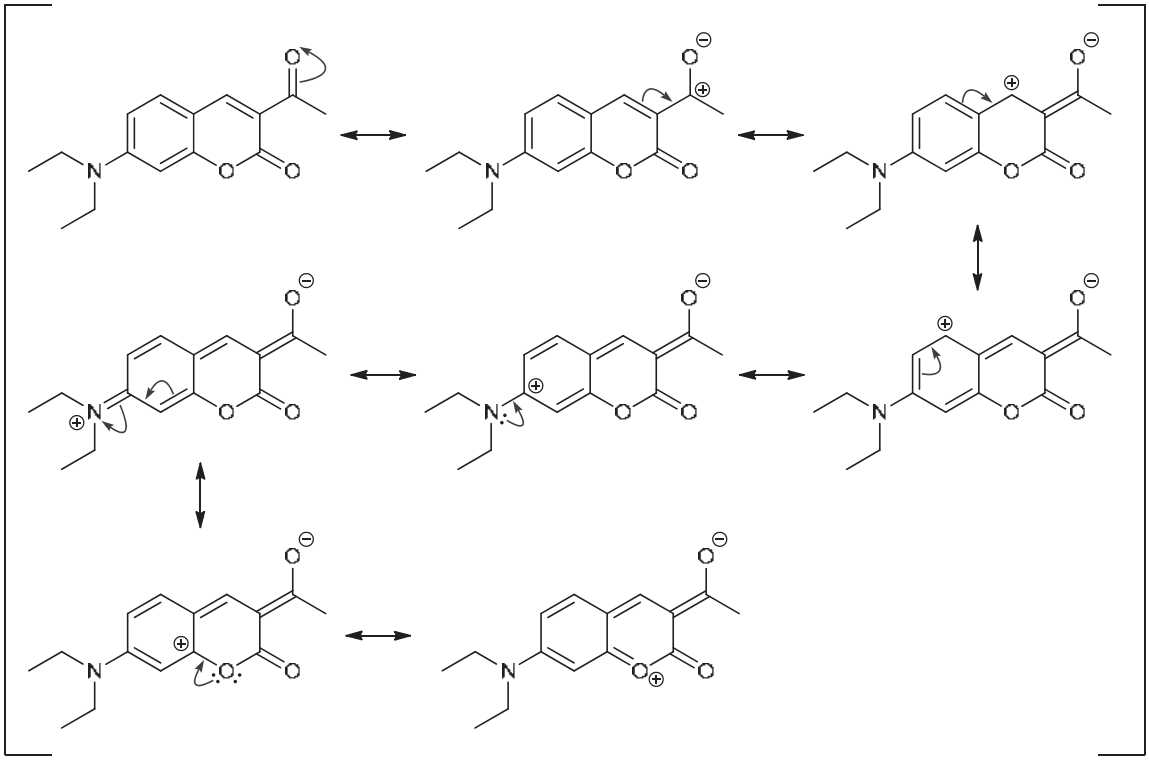
These resonance structures indicate that the diethylamino group donates electron density, so it has the opposite effect of what we are looking for; that is, the diethylamino group renders the following positions electron-rich:



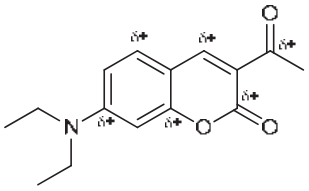
The oxygen atom incorporated in the ring has a similar effect on the same positions:



So we explore the effect of the ketone group, and we draw the following resonance structures:

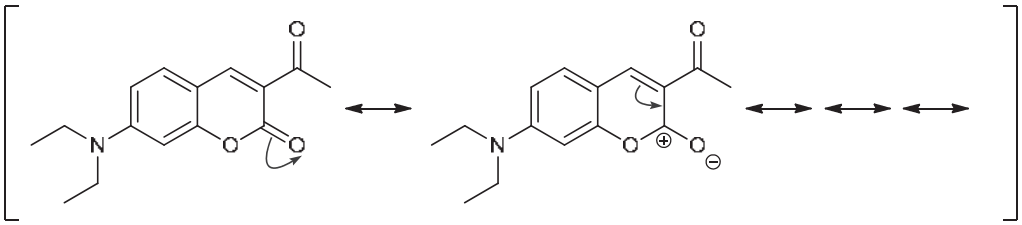


Notice that these resonance structures indicate that several positions are electron-deficient.

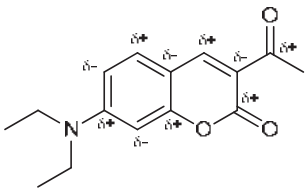


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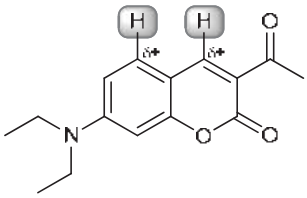
A similar effect is expected from the ester group:



In summary, if we take into account *all* resonance effects (described above), the following picture emerges:

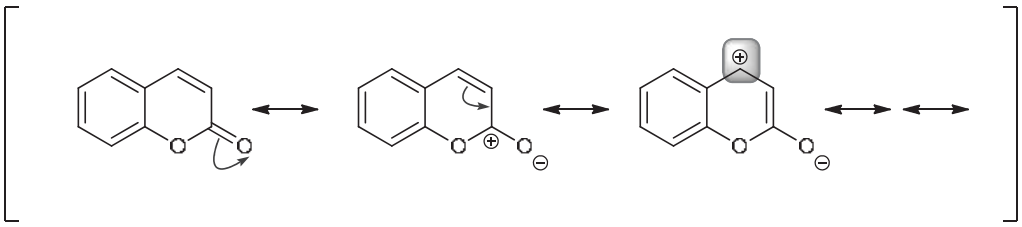


Notice that only two protons are directly attached to electron-deficient centers:

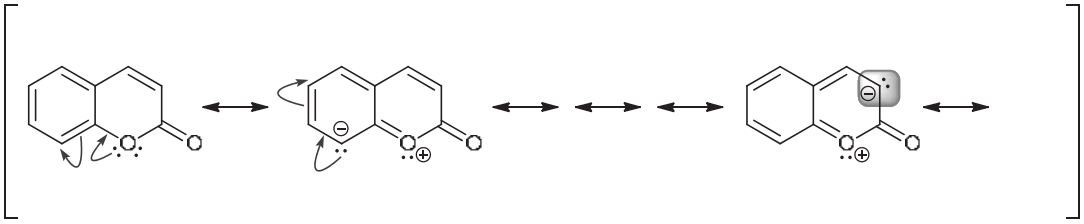


These are the two protons that are expected to produce the two signals farthest downfield in the proton NMR spectrum.

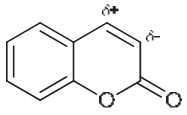
(b) In compound **1**, the C4 position is electron-deficient, as seen in the third resonance structure below:



and the C3 position is electron-rich, as highlighted below:

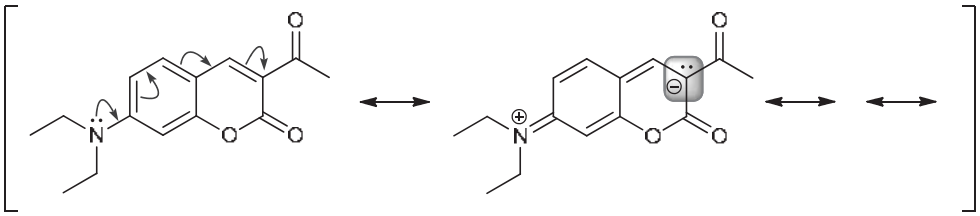


As a result, the C3-C4 π bond is highly polarized and is expected to produce a strong signal.

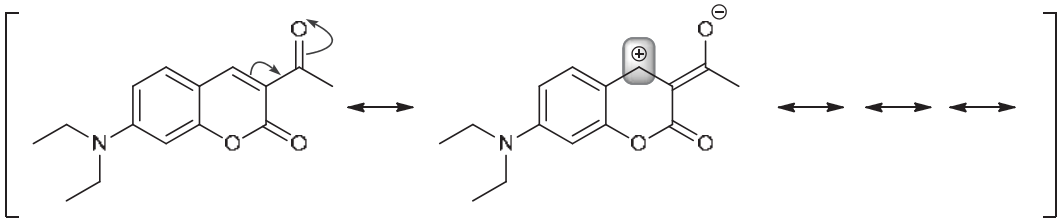


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A similar effect is expected in compound **2**, but the effect should be much stronger, because the presence of the diethylamino group renders C3 even more electron-rich:



And the presence of the ketone renders C4 even more electron-deficient, as highlighted below:



Therefore, the C3-C4 bond in compound **2** is expected to be even more polarized than the C3-C4 bond in compound **1**. So the former is expected to produce a stronger (more intense) signal.

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Chapter 16
Conjugated Pi Systems and Pericyclic Reactions

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 16. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Conjugated dienes experience free-rotation about the C2-C3 bond, giving rise to two important conformations**: *s*-**_____ and ***s*-**_____. The _____ conformation is lower in energy.
- The _____ and _____ are referred to as **frontier orbitals**.
- An _____ **state** is produced when a π electron in the HOMO absorbs a photon of light bearing the appropriate energy necessary to promote the electron to a higher energy orbital.
- Reactions induced by light are called _____ **reactions**.
- When butadiene is treated with HBr, two major products are observed, resulting from _____**-addition** and _____**-addition**.
- Conjugated dienes that undergo addition at low temperature are said to be under _____ **control.** Conjugated dienes that undergo addition at elevated temperature are said to be under _____ **control**.
- _____ **reactions** proceed via a concerted process with a cyclic transition state, and they are classified as **cycloaddition reactions**, _____ **reactions**, and **sigmatropic rearrangements.**
- The Diels–Alder reaction is a **[_____] cycloaddition** in which two C-C bonds are formed simultaneously.
- High temperatures can often be used to achieve the reverse of a Diels–Alder reaction, called a _____ **Diels–Alder**.
- The starting materials for a Diels–Alder reaction are a diene, and a _____.
- The Diels–Alder reaction only occurs when the diene adopts an ____ conformation.
- When cyclopentadiene is used as the starting diene, a bridged bicyclic compound is obtained, and the _____ cycloadduct is favored over the _____ cycloadduct.
- Conservation of orbital symmetry determines whether an electrocyclic reaction occurs in a _____ fashion or a _____ fashion.
- A [_____] sigmatropic rearrangement is called a **Cope rearrangement** when all six atoms of the cyclic transition state are carbon atoms.
- Compounds that possess a conjugated π system will absorb UV or visible light to promote an electronic excitation called a _____ transition.
- The most important feature of the absorption spectrum is the _____, which indicates the wavelength of maximum absorption.
- When a compound exhibits a λ_{max} between 400 and 700 nm, the compound will absorb _____ light, rather than UV light.

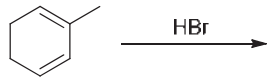
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Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 16. The answers appear in the section entitled *SkillBuilder Review*.

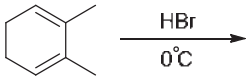
16.1 Proposing a Mechanism and Predicting the Products of Electrophilic Addition to Conjugated Dienes

IN THE SPACE PROVIDED, DRAW THE MECHANISM OF THE REACTION THAT IS EXPECTED TO OCCUR WHEN THE FOLLOWING COMPOUND IS TREATED WITH HBr. MAKE SURE TO DRAW ALL POSSIBLE PRODUCTS.



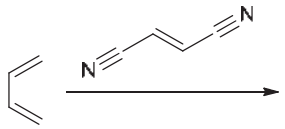
16.2 Predicting the Major Product of an Electrophilic Addition to Conjugated Dienes

DRAW THE MAJOR PRODUCT OF THE FOLLOWING REACTION:



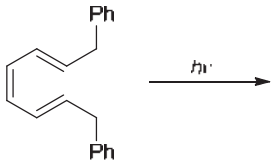
16.3 Predicting the Product of a Diels–Alder Reaction

DRAW THE MAJOR PRODUCT OF THE FOLLOWING REACTION:



16.4 Predicting the Product of an Electrocyclic Reaction

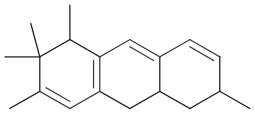
DRAW THE MAJOR PRODUCT OF THE FOLLOWING REACTION:



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16.5 Using Woodward–Fieser Rules to Estimate λ_{max}

USE WOODWARD-FIESER RULES TO ESTIMATE λ_{max} FOR THE FOLLOWING COMPOUND:



BASE VALUE =

ADDITIONAL DOUBLE BONDS =

AUXOCHROMIC ALKYL GROUPS =

EXOCYCLIC DOUBLE BOND =

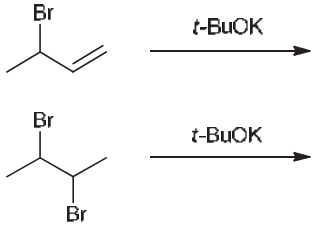
HOMOANNULAR DIENE =

TOTAL =

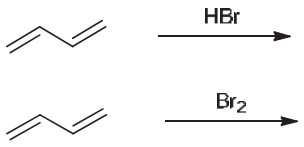
Review of Reactions

Predict the Products for each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 16. The answers appear in the section entitled *Review of Reactions*.

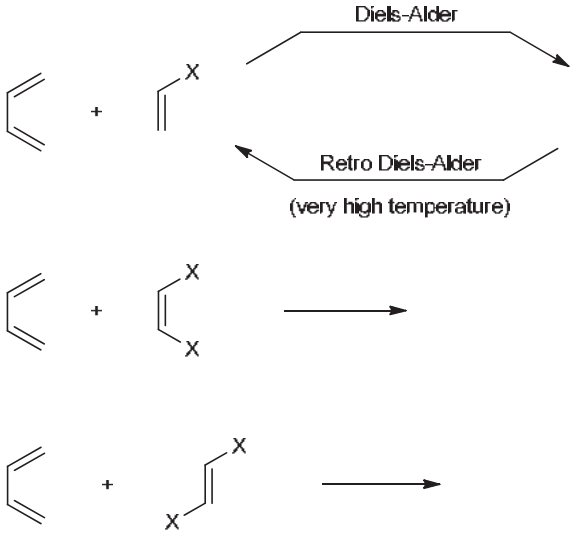
Preparation of Dienes



Electrophilic Addition

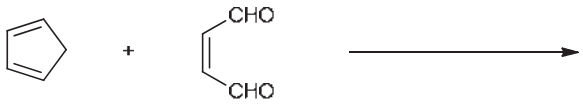


Diels–Alder Reaction

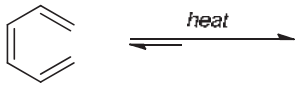


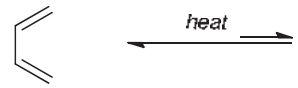
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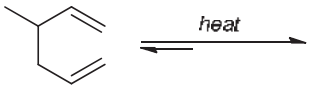
Electrocyclic Reactions



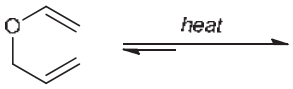


Sigmatropic Rearrangements

Cope Rearrangement

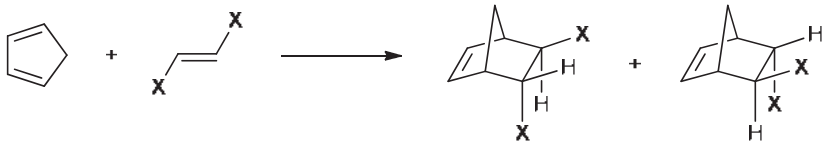


Claisen Rearrangement



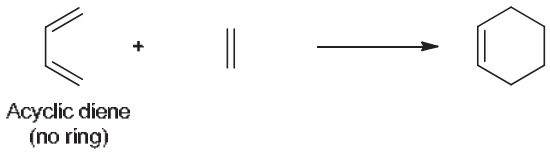
Mistakes to Avoid

Many students have trouble drawing the product(s) of a Diels-Alder reaction when bicyclic structures are involved:

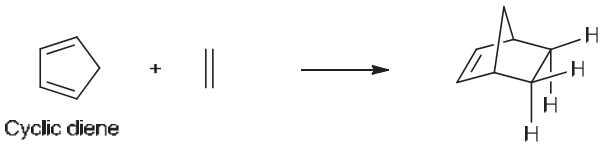


You might have trouble visualizing these structures, drawing them, or knowing where to place the substituents. The following are a few guidelines that might help you avoid making mistakes.
In a Diels-Alder reaction, an acyclic diene will give a product with a cyclohexene ring:

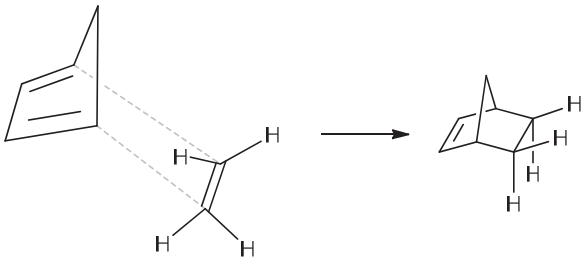
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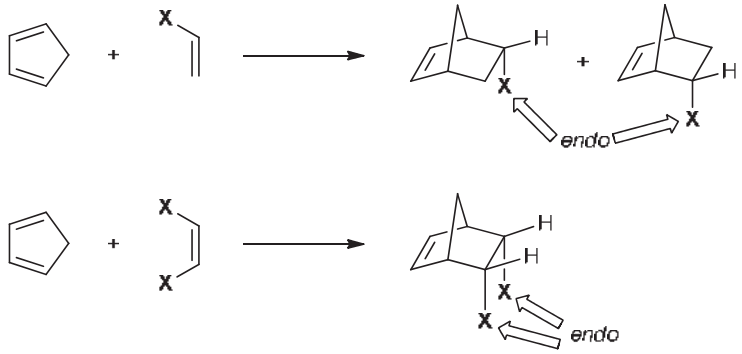
However, if the diene is cyclic (both π bonds are contained in the ring), then the product is a bicyclic structure:



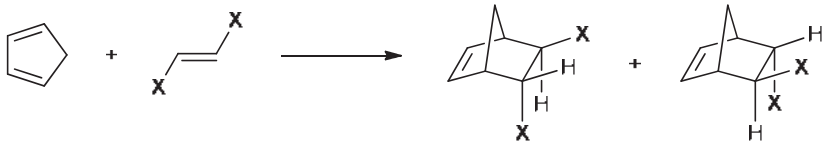
Formation of the bicyclic structure can be seen more clearly if we redraw the cyclic diene with distorted bond angles, like this:



The dotted lines indicate the locations where σ bonds are forming as a result of the reaction. When the dienophile is monosubstituted or *cis*-disubstituted, the *endo* rule determines the product(s) obtained:



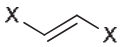
However, when a *trans*-disubstituted dienophile is used, the *endo* rule is not relevant. Two stereoisomeric products are obtained (in this case, enantiomers), and in each product, one group occupies an *endo* position while the other group occupies an *exo* position (because the *trans* configuration of the dienophile is preserved during a Diels-Alder reaction):



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Useful reagents

The following is a list of reagents used in this chapter:

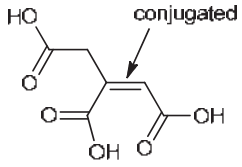
Reagents	Function
t-BuOK	A strong, sterically hindered base, used to convert a dibromide into a diene.
HBr	Will add across a conjugated π system to give two products: a 1,2 adduct and a 1,4 adduct.
Br_2	Will add across a conjugated π system to give two products: a 1,2 adduct and a 1,4 adduct.
	1,3-Butadiene. Can serve as a diene in a Diels-Alder reaction.
	1,3-Cyclopentadiene. Can serve as a diene in a Diels-Alder reaction.
	Can serve as a dienophile in a Diels-Alder reaction, if the substituents (X) are electron-withdrawing groups. The *cis* configuration of the dienophile is preserved in the product.
	Can serve as a dienophile in a Diels-Alder reaction, if the substituents (X) are electron-withdrawing groups. The *trans* configuration of the dienophile is preserved in the product.
	Can serve as a dienophile in a Diels-Alder reaction, if the substituents (X) are electron-withdrawing groups.
heat	When you see "heat" without any other reagents indicated, consider the possibility of a pericyclic reaction (cycloaddition, electrocyclic reaction, or a sigmatropic rearrangement).
hν	When you see this term, or "light", without any other reagents indicated, consider the possibility of an electrocyclic reaction.

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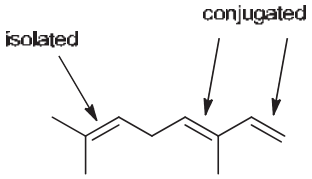
Solutions

16.1.

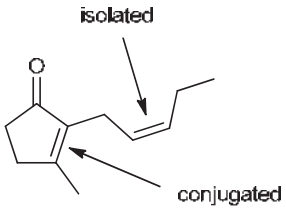
(a) The C=C bond in this compound is conjugated to two of the carboxylic acid groups:



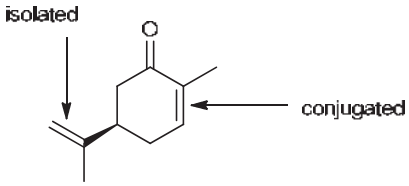
(b) The C=C bond on the left is isolated, while the other two C=C bonds are conjugated to each other.



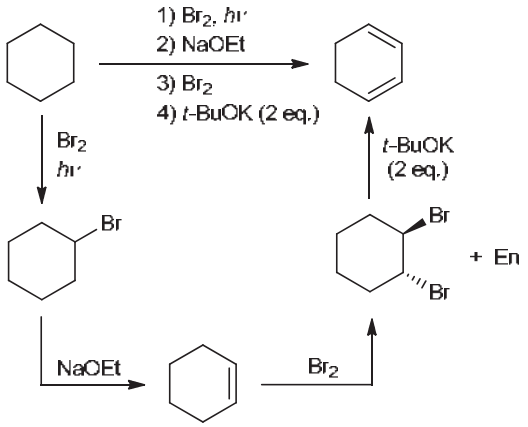
(c) One of C=C bonds is conjugated to the carbonyl (C=O) group, and the other C=C bond is isolated:



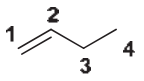
(d) One of C=C bonds is conjugated to the carbonyl group, and the other C=C bond is isolated:



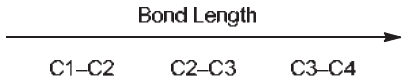
16.2. Radical bromination can be employed to install a functional group. The resulting alkyl halide can then be treated with a strong base to give an alkene. Bromination of the alkene will give a dibromide, which can then be converted into the product upon treatment with a strong, sterically hindered base, such as *t*-butoxide. This final step involves two elimination reactions, giving the desired diene:



16.3. The C1–C2 bond length is expected to be the shortest because it is a double bond (comprised of both a σ bond and a π bond):

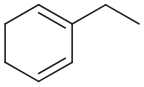


Among the other two bonds, C2–C3 is expected to be shorter than C3–C4 because the former is a C_{sp^2}–C_{sp^3} bond, while the latter is a C_{sp^3}–C_{sp^3} bond (sp^2 hybridized orbitals are closer to the nucleus than sp^3 hybridized orbitals, and therefore form shorter bonds).



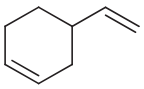
16.4.

(a) All three of these compounds will yield the same product (ethylcyclohexane) upon hydrogenation with two moles of hydrogen gas. Yet only one of these compounds is a conjugated diene, shown below.



The other two compounds exhibit isolated π bonds. The conjugated diene will liberate the least heat because it is the most stable of the three compounds (lowest in energy).

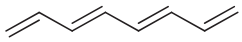
(b) The following compound is expected to liberate the most heat upon hydrogenation with two moles of hydrogen gas:



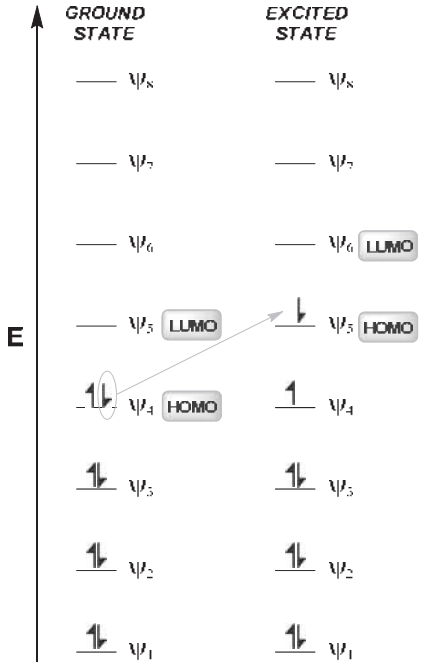
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This isolated diene will liberate more heat than the other isolated diene, because the π bonds in this compound are not as highly substituted (one π bond is monosubstituted and the other is disubstituted). In the other isolated diene, the π bonds are disubstituted and trisubstituted (and therefore more stable).

16.5. This compound is comprised of eight, consecutive, overlapping, *p* orbitals, giving rise to eight molecular orbitals:

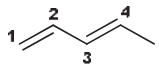


There are eight π electrons, which occupy the four lower energy MO's (the bonding MO's). In the ground state, ψ_4 is the HOMO and ψ_5 is the LUMO, as shown. Photochemical excitation causes one electron to be promoted from ψ_4 to ψ_5. In the excited state, the HOMO is ψ_5 and the LUMO is ψ_6:

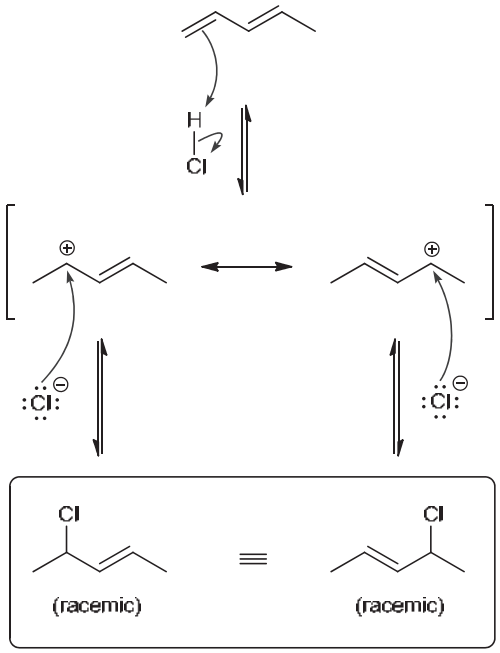


16.6.

(a) We first identify the locations where protonation can occur. There are four unique positions where protonation can occur, labeled C1 through C4:

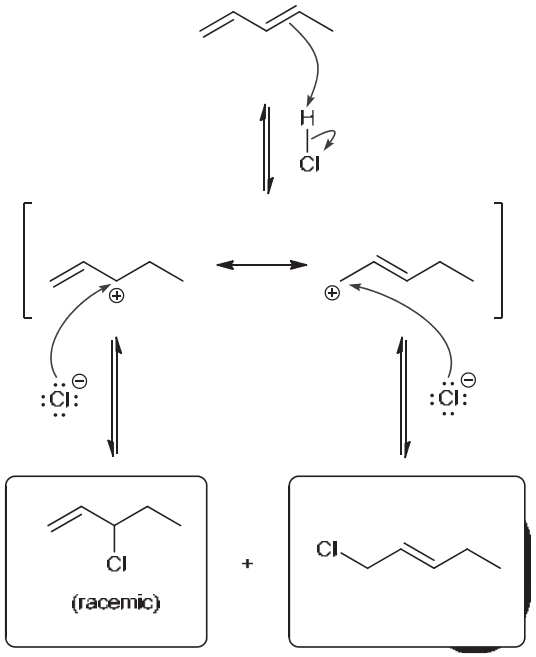


Among these four positions, only protonation at C1 or at C4 will generate a resonance-stabilized carbocation. So, we must explore protonation at each of these positions. Let's begin with protonation at C1, which leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, although the product is the same in either case, leading to only one product:



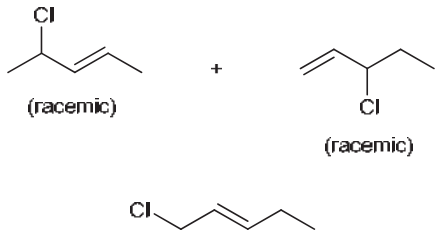
Notice that the product possesses a chiral center and is therefore produced as a racemic mixture (because the chloride ion can attack either face of the allylic carbocation with equal likelihood).

Now let's consider protonation at C4. Once again, protonation leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, giving two possible products, as shown:

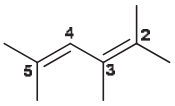


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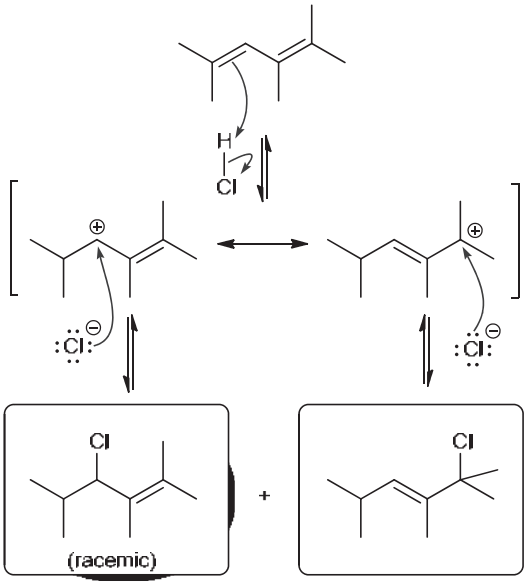
In summary, we expect the following possible products:



(b) We first identify the locations where protonation can occur. There are four unique positions where protonation can occur, labeled C2, C3, C4, and C5:

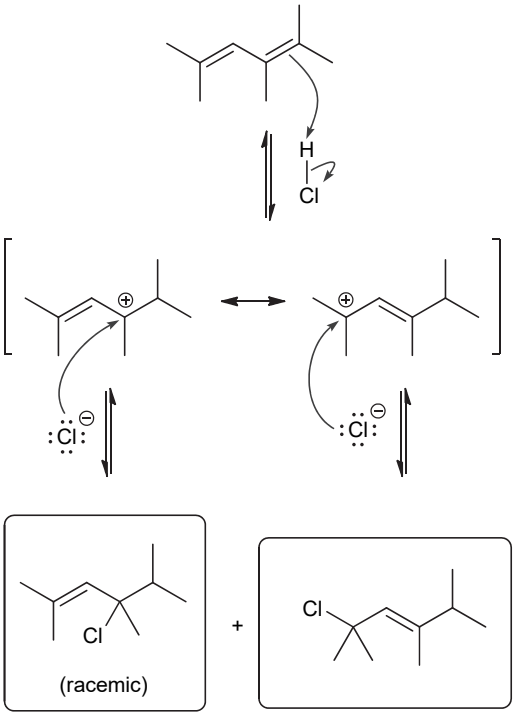


Among these four positions, only protonation at C2 or at C5 will generate a resonance-stabilized carbocation. So, we must explore protonation at each of these positions. Let's begin with protonation at C5, which leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, giving rise to two products:

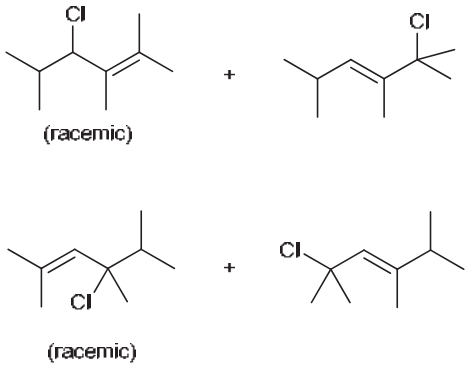


Notice that one of the products possesses a chiral center and is therefore produced as a racemic mixture (because the chloride ion can attack either face of the allylic carbocation with equal likelihood).

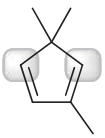
Now let's consider protonation at C2. Once again, protonation leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, giving two possible products, as shown:



In summary, we expect the following possible products:

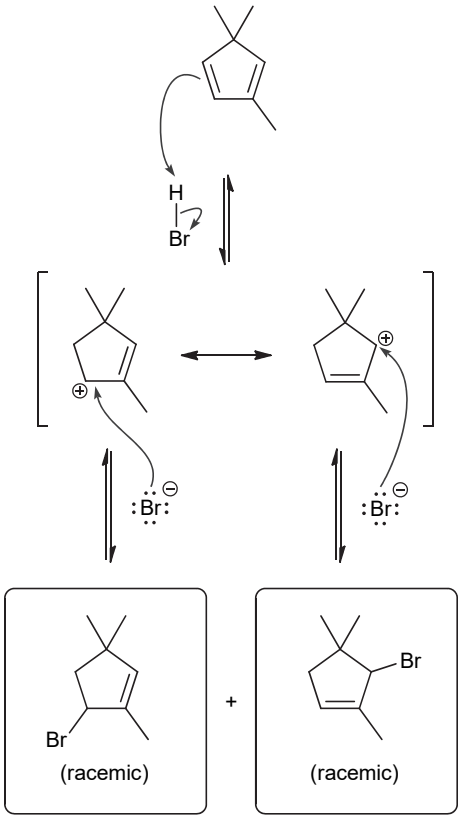


(c) We first identify the locations where protonation can occur. There are four unique positions where protonation can occur, although a resonance-stabilized intermediate can only be obtained upon protonation of one of the ends of the conjugated π system, highlighted below:



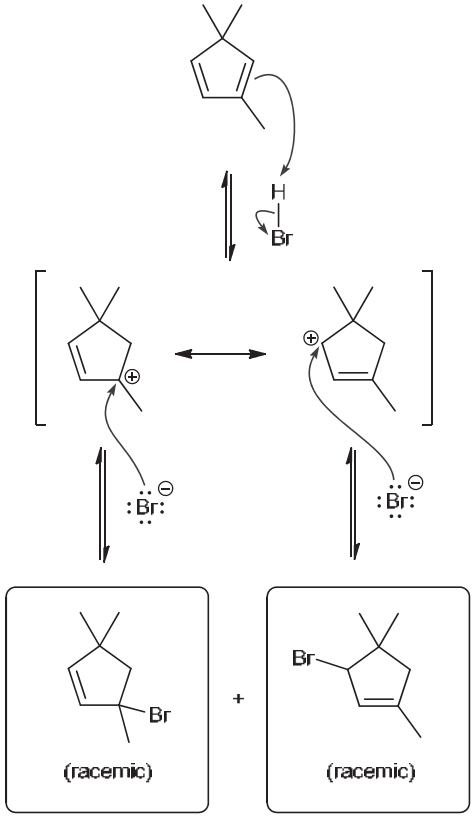
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We must explore protonation at each of these positions. Let's begin with protonation of the position on the left, which leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, giving rise to two products:

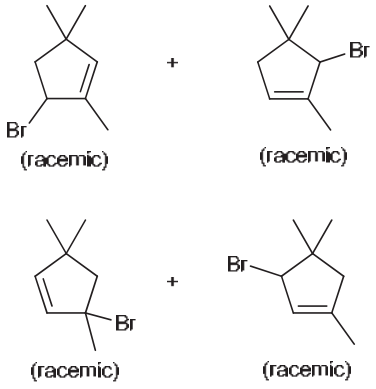


Notice that each of the products possesses a chiral center and is therefore produced as a racemic mixture (because the bromide ion can attack either face of the allylic carbocation with equal likelihood).

Now let's consider protonation at the position on the right. Once again, protonation leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, giving two possible products, as shown:



In summary, we expect the following possible products:

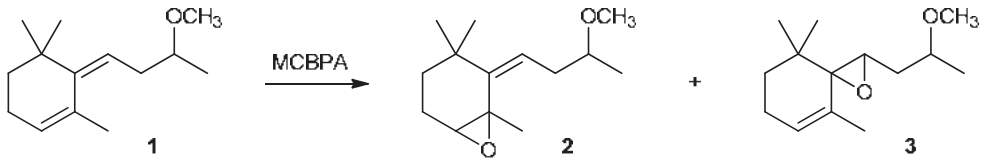


16.7. The first diene can be protonated either at C1 or at C4. Each of these pathways produces a resonance-stabilized carbocation. And each of these carbocations can be attacked in two positions, giving rise to four possible products.

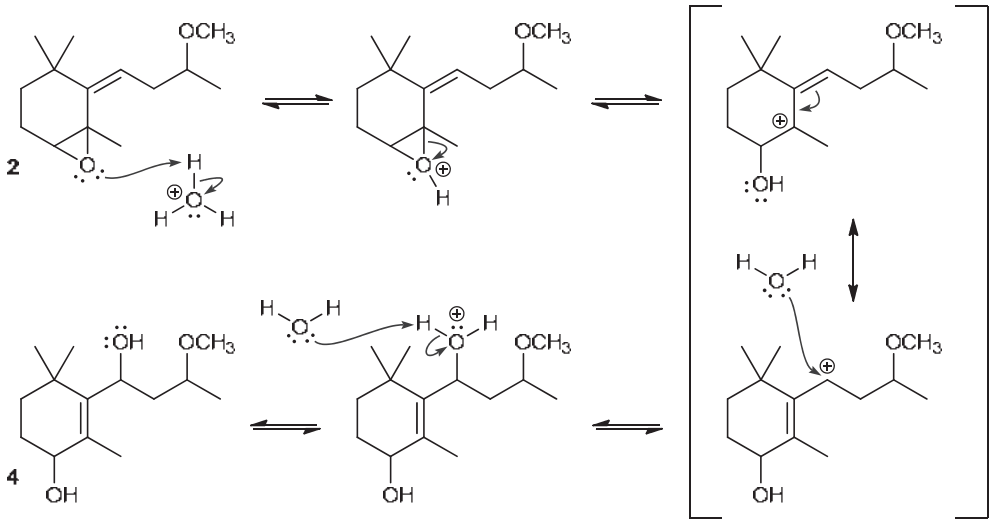
In contrast, the second diene yields the same carbocation regardless of whether protonation occurs at C1 or at C4. This resonance-stabilized carbocation can be attacked in two positions, giving rise to two products (not four).

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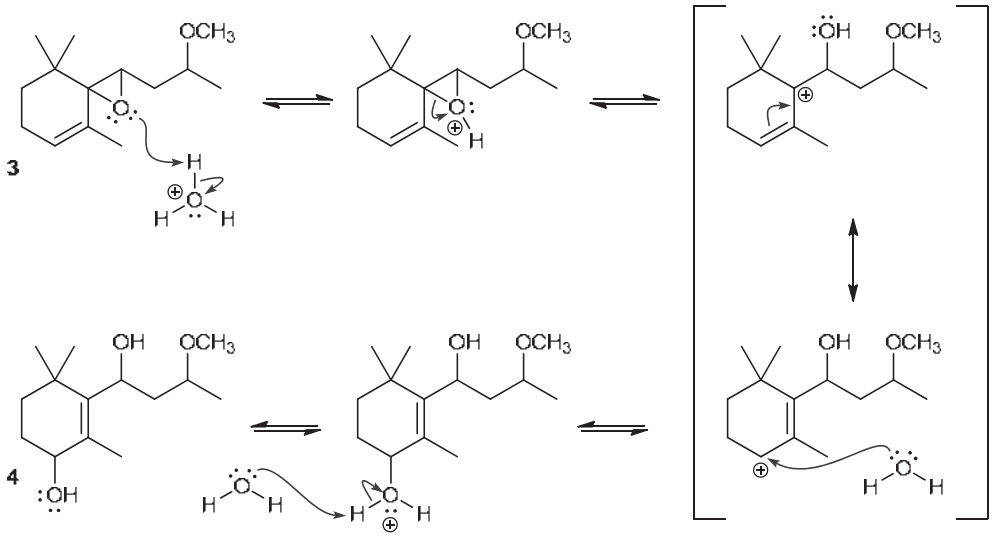
16.8. Recall that MCPBA produces an epoxide when it reacts with a carbon-carbon double bond. Compound **1** has two double bonds, so there are two possible epoxides that can be produced. These constitutional isomers are compounds **2** and **3** (it does not matter which epoxide is labeled **2** and which is labeled **3**).



In the conversion of compound **2** into compound **4**, the mechanism begins with a proton transfer to give a protonated epoxide. Then, as indicated in the problem statement, the epoxide can open to give a resonance-stabilized allylic cation. After drawing the resonance structures of this allylic carbocation, nucleophilic attack by water, followed by a proton transfer, generates compound **4**.



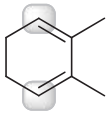
Likewise, the mechanism for the conversion of compound **3** into compound **4** begins with a proton transfer to create a protonated epoxide. The epoxide then opens to give a resonance-stabilized allylic cation. Nucleophilic attack by water, followed by a proton transfer, generates compound **4**.



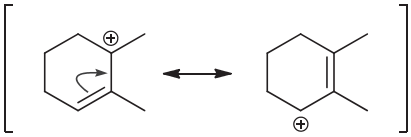
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16.9.

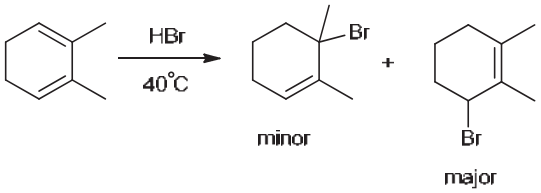
(a) The diene is symmetrical, so protonation at one end of the conjugated system is the same as protonation at the other end of the conjugated system:



Therefore, we only need to consider protonation at one of these locations, which gives a resonance-stabilized cation:

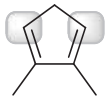


This cation has two electrophilic positions and can be attacked at either of these two positions to give the following two possible products, as shown.

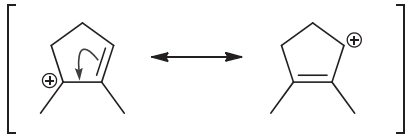


At elevated temperature, the thermodynamic product (the compound with the more substituted π bond) is expected to predominate.

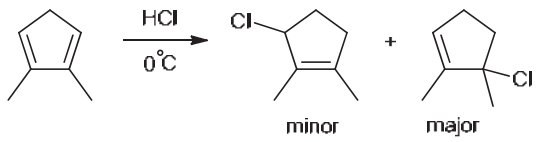
(b) The diene is symmetrical, so protonation at one end of the conjugated system is the same as protonation at the other end of the conjugated system:



Therefore, we only need to consider protonation at one of these locations, which gives a resonance-stabilized cation:

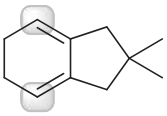


This cation has two electrophilic positions and can be attacked at either of these two positions to give the following two possible products, as shown.

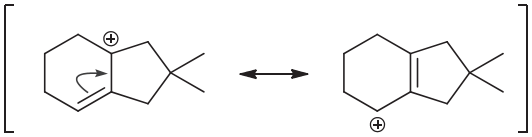


At reduced temperature, the kinetic product (resulting from 1,2-addition) is expected to predominate.

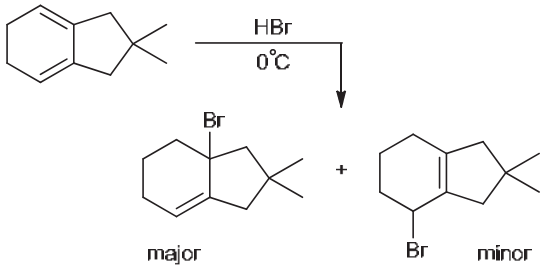
(c) The diene is symmetrical, so protonation at one end of the conjugated system is the same as protonation at the other end of the conjugated system:



Therefore, we only need to consider protonation at one of these locations, which gives a resonance-stabilized cation:



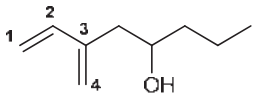
This cation has two electrophilic positions and can be attacked at either of these two positions to give the following two possible products, as shown.



At reduced temperature, the kinetic product (resulting from 1,2-addition) is expected to predominate.

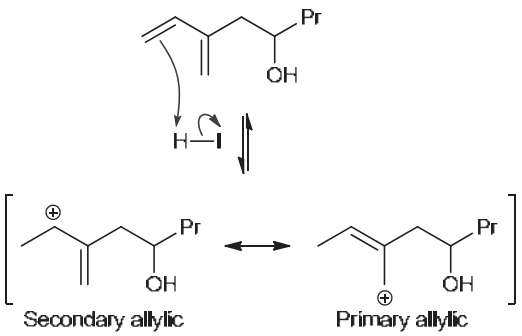
16.10. In this case, the π bond in the 1,2-adduct is more substituted than the π bond in the 1,4-adduct (trisubstituted rather than disubstituted). As a result, the 1,2-adduct predominates at either low temperature or high temperature.

16.11. We first identify the locations where protonation can occur. There are four unique positions where protonation can occur, labeled C1 through C4:

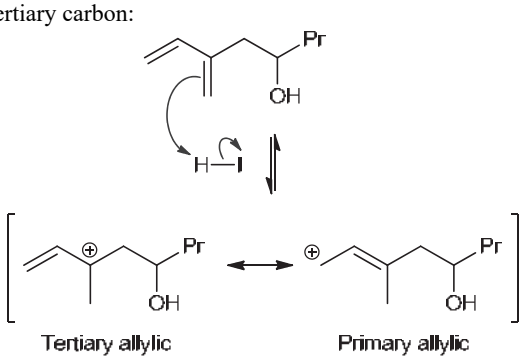


Among these four positions, only protonation at C1 or at C4 will generate a resonance-stabilized carbocation. So, we must explore protonation at each of these positions. Protonation at C1 leads to a resonance-stabilized intermediate with carbocations located at secondary and primary carbons.

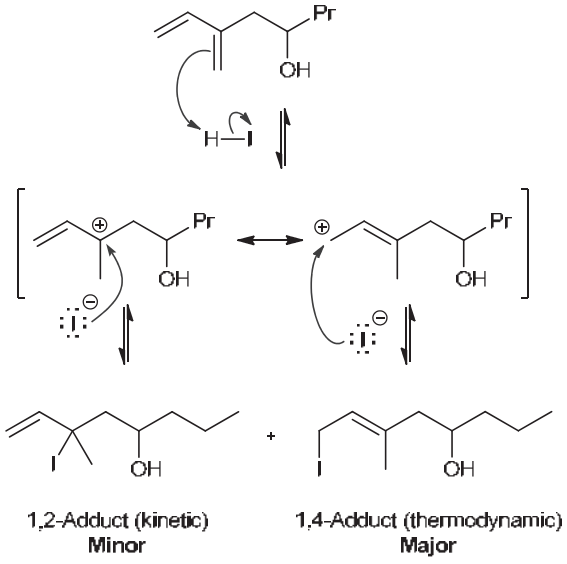
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Protonation at C4, however, leads to a resonance-stabilized intermediate with a carbocation located at a tertiary carbon:

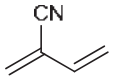


As observed with Markovnikov's Rule, protonation of a π bond will occur in the position that leads to the more stable carbocation intermediate, so the reaction begins with protonation at C4. When both resonance structures of the resulting carbocation intermediate are drawn, we can see that two positions are electrophilic. Nucleophilic attack of the iodide ion can occur at either of these locations, giving rise to two products. Under thermodynamic control, the major product is the more stable compound with the more substituted π bond, as shown below:

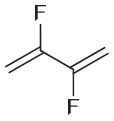


16.12.

(a) This polymer is similar in structure to neoprene, but the chloro group has been replaced with a cyano group. So the starting material should be similar in structure to chloroprene (the monomer of neoprene), except that the chloro group is replaced with a cyano group:

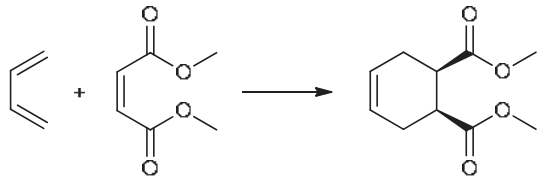


(b) This polymer is comprised of repeating units that bear two substituents (both fluoro groups). The following monomer is necessary.

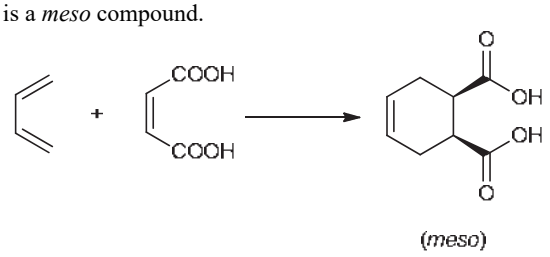


16.13.

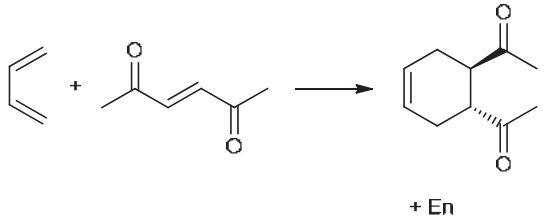
(a) The dienophile has a *cis* configuration, which is preserved in the product. This product is superimposable on its mirror image, so it does not have an enantiomer. It is a *meso* compound.



(b) The dienophile has a *cis* configuration, which is preserved in the product. This product is superimposable on its mirror image, so it does not have an enantiomer. It is a *meso* compound.

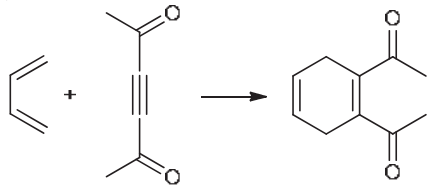


(c) The dienophile has a *trans* configuration, which is preserved in the product. This product is not superimposable on its mirror image (its enantiomer), and both enantiomers are expected to be formed.

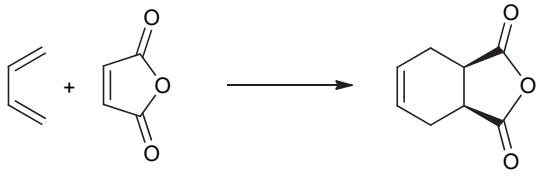


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(d) The dienophile is an alkyne, and therefore, the product does not have any chiral centers (no wedges or dashes).

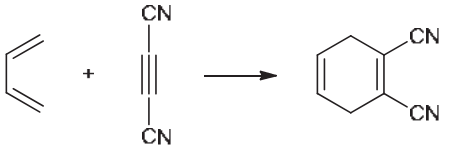


(e) The dienophile has a *cis* configuration, which is preserved in the product. This product is superimposable on its mirror image, so it does not have an enantiomer. It is a *meso* compound.

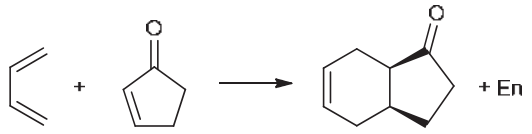


(*meso*)

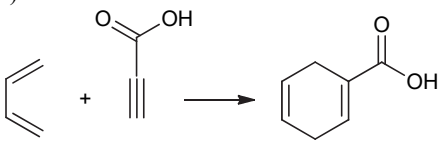
(f) The dienophile is an alkyne, and therefore, the product does not have any chiral centers (no wedges or dashes).



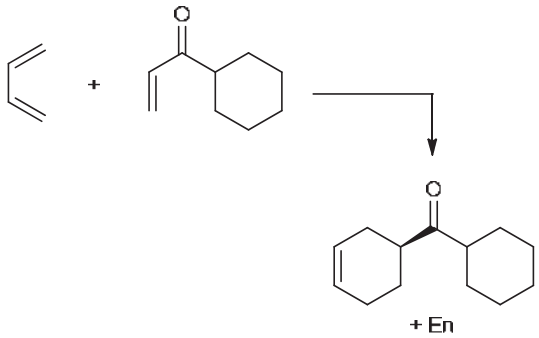
(g) The dienophile has a *cis* configuration, which is preserved in the product. This product is not superimposable on its mirror image (its enantiomer), and both enantiomers are expected to be formed.



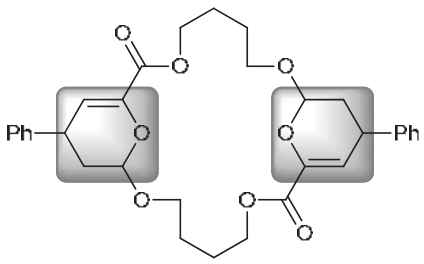
(h) The dienophile is an alkyne, and therefore, the product does not have any chiral centers (no wedges or dashes).



(i) The dienophile is a monosubstituted alkene, giving a cycloadduct with one chiral center. This product is not superimposable on its mirror image (its enantiomer), and both enantiomers are expected to be formed.

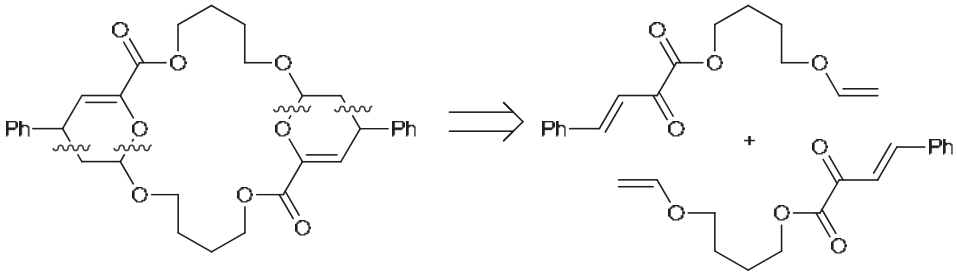


16.14. A Diels-Alder reaction produces a cyclohexene adduct. It follows that a hetero-Diels-Alder reaction should produce a cyclohexene-type product in which one or more of the carbon atoms of the cyclohexene ring are replaced with nitrogen or oxygen. Analysis of the macrocyclic product reveals two such moieties, highlighted below.

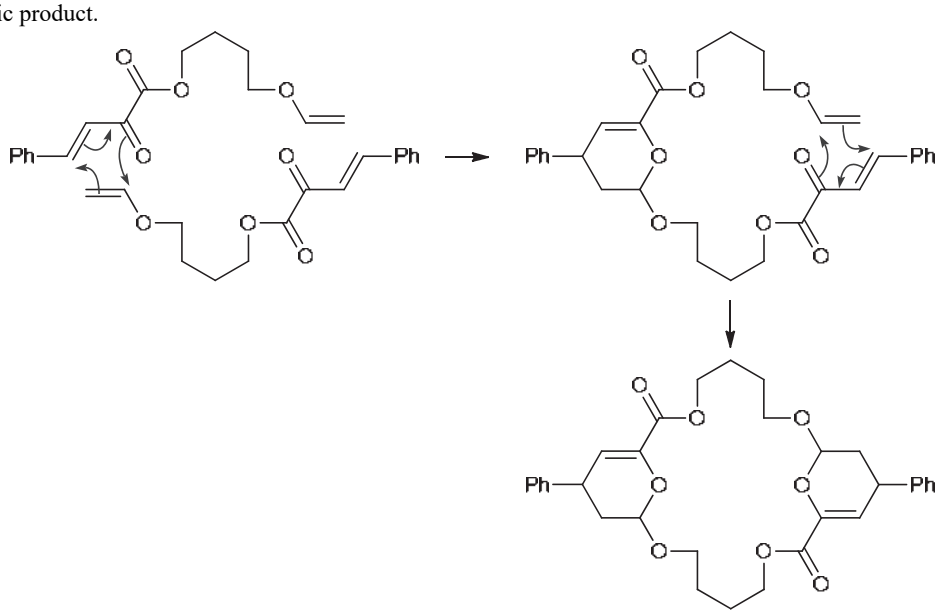


A retrosynthetic analysis, shown here, demonstrates that this product can be produced from two equivalents of the acyclic reactant, arranged head-to-tail, where the four bonds with the wavy lines are produced in two hetero-Diels-Alder reactions.

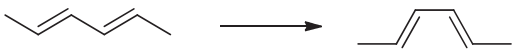
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A mechanism consistent with this reaction is presented below. In the first step, the terminal alkene group of the bottom molecule serves as the "dienophile". On the top molecule, the alkene group next to the phenyl group and the adjacent, conjugated ketone serve the role of the "diene" (although in this case it is not formally a diene since one of the carbon atoms has been replaced by oxygen). This hetero-Diels-Alder reaction produces the first six-membered ring as shown. A second hetero-Diels-Alder reaction then proceeds at the other terminus of the molecule, thus producing the macrocyclic product.

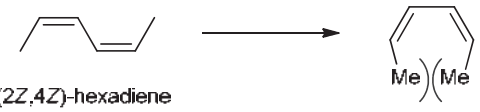


16.15. The 2*E*,4*E* isomer is expected to react more rapidly as a diene in a Diels–Alder reaction, because it can readily adopt an *s-cis* conformation.



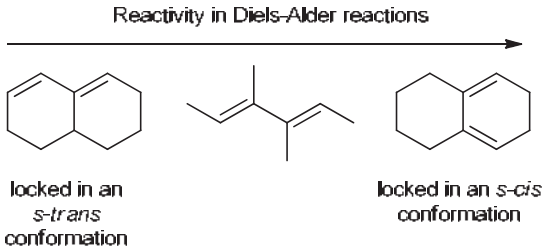
(2*E*,4*E*)-hexadiene

In contrast, the 2*Z*,4*Z* isomer is expected to react more slowly as a diene in a Diels–Alder reaction, because it cannot readily adopt an *s-cis* conformation, as a result of steric interactions.



(2*Z*,4*Z*)-hexadiene

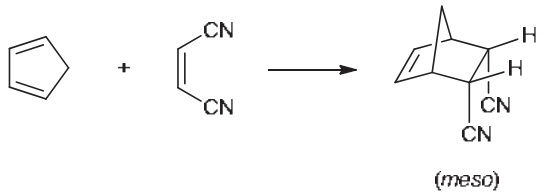
16.16. One compound is locked in an *s-cis* conformation and will therefore be the most reactive in a Diels-Alder reaction. Another compound is locked in an *s-trans* conformation and will therefore be the least reactive in a Diels-Alder reaction:



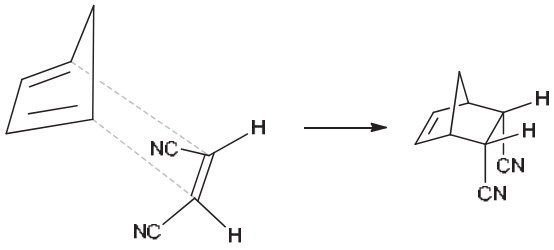
16.17.

(a) The diene is cyclic and the dienophile has a *cis* configuration, so we must consider the *endo* rule. Specifically, we draw the cycloadduct in which the cyano groups occupy *endo* positions. This product has an internal plane of symmetry and is a *meso* compound.

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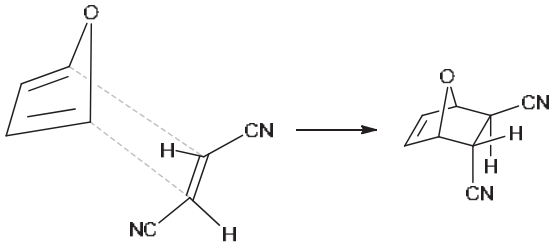


If you have trouble seeing how the bicyclic framework is produced by this reaction, consider the following drawing in which the bond angles have been distorted to show how the bicyclic structure is formed:

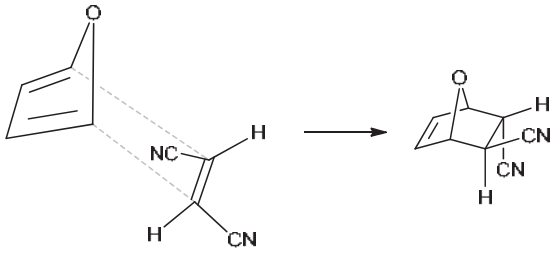


In this drawing, the dotted lines indicate the new σ bonds that are formed during the Diels-Alder reaction.

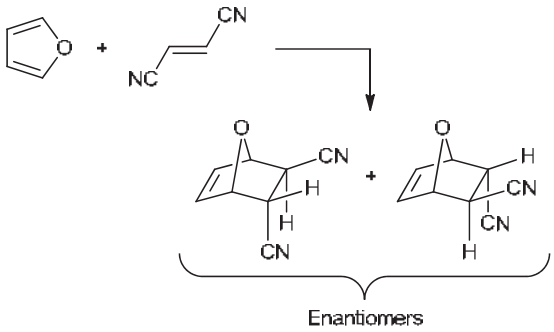
(b) The diene is cyclic, but the dienophile has a *trans* configuration. Therefore, the *endo* rule is not relevant in this case. Two products are expected, because the reaction can either occur like this,



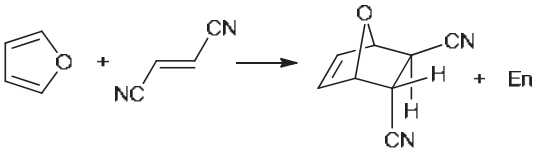
or the reaction can occur like this:



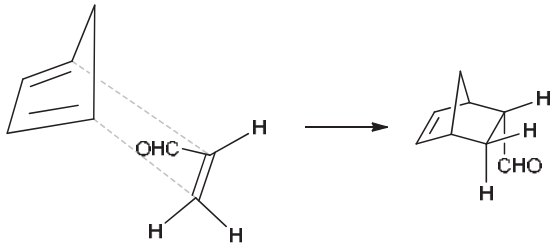
Either way, one group will occupy an *endo* position and the other group will occupy an *exo* position, because the configuration of the dienophile is preserved during a Diels-Alder reaction. Notice that the two possible products are non-superimposable mirror images of each other, so they represent a pair of enantiomers:



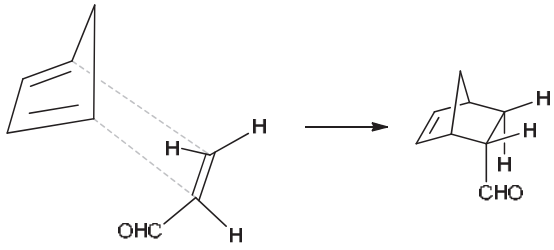
This can also be indicated in the following way:



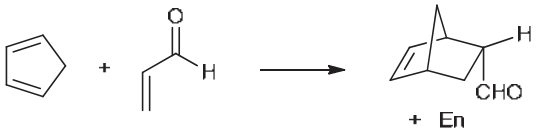
(c) The diene is cyclic, and the *endo* rule indicates that the substituent should occupy an *endo* position in the product. With this restriction in mind, the reaction can either occur like this,



or the reaction can occur like this:

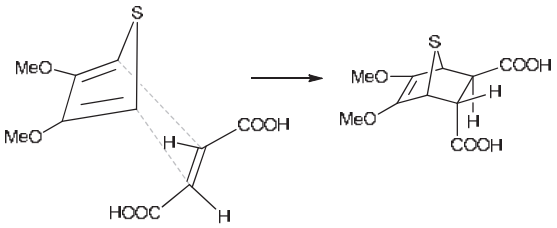


These two products represent a pair of enantiomers, and both are expected.

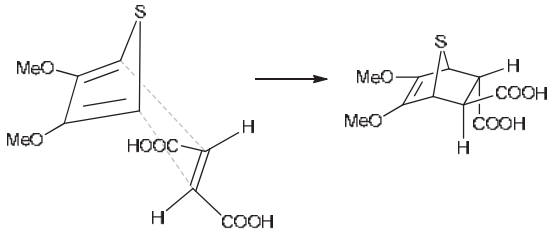


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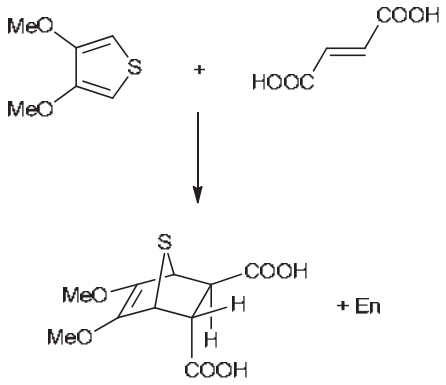
(d) The diene is cyclic, but the dienophile has a *trans* configuration. Therefore, the *endo* rule is not relevant in this case. Two products are expected, because the reaction can either occur like this,



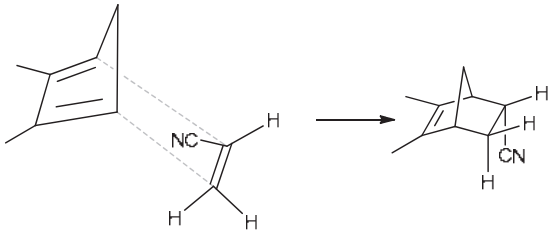
or the reaction can occur like this:



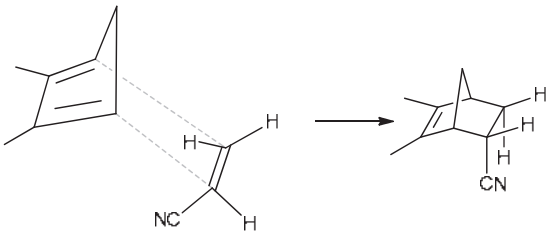
Either way, one group will occupy an *endo* position and the other group will occupy an *exo* position, because the configuration of the dienophile is preserved during a Diels-Alder reaction. Notice that the two possible products are non-superimposable mirror images of each other, so they represent a pair of enantiomers:



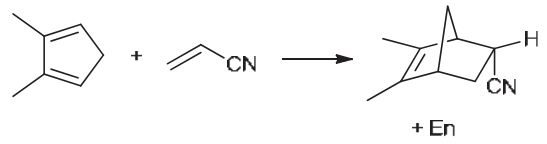
(e) The diene is cyclic, and the *endo* rule indicates that the substituent should occupy an *endo* position in the product. With this restriction in mind, the reaction can either occur like this,



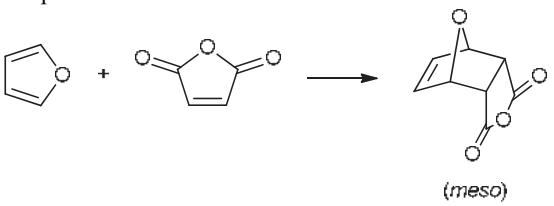
or the reaction can occur like this:



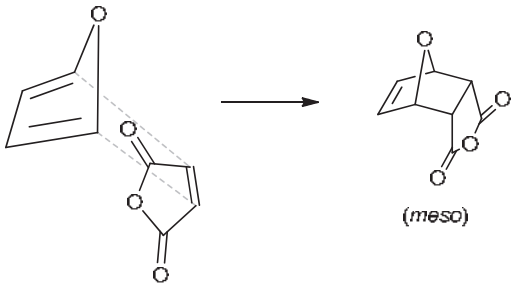
These two products represent a pair of enantiomers, and both are expected.



(f) The diene is cyclic and the dienophile has a *cis* configuration, so we must consider the *endo* rule. Specifically, we draw the *endo* product, which has an internal plane of symmetry in this case, so it is a *meso* compound.



If you have trouble seeing how the bicyclic framework is produced by this reaction, consider the following drawing in which the bond angles have been distorted to show how the bicyclic structure is formed:

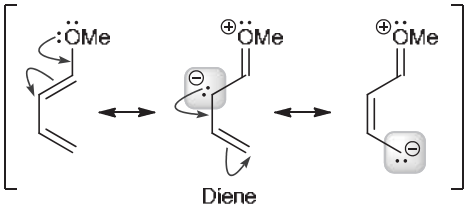


In this drawing, the dotted lines indicate the new σ bonds that are formed during the Diels-Alder reaction.

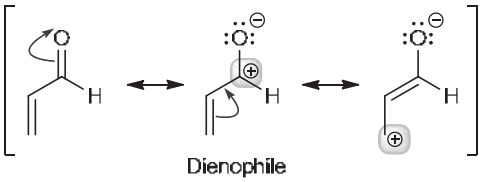
16.18.

(a) Both the diene and the dienophile are unsymmetrical, so there are two possible regiochemical outcomes. The major product can be predicted by considering resonance structures for the diene,

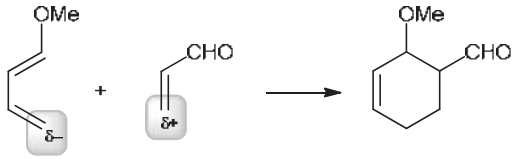
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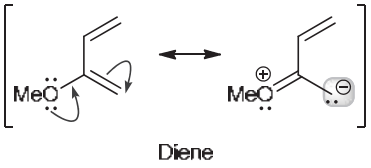
and resonance structures for the dienophile:



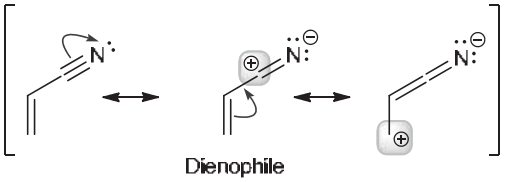
Notice that the diene is electron-rich, because of the electron-donating effect of the methoxy group; while the dienophile is electron-poor, because of the electron-withdrawing effect of the aldehyde group. The major product results when the regions of δ+ and δ– (highlighted) are aligned:



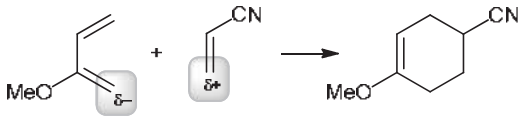
(b) Both the diene and the dienophile are unsymmetrical, so there are two possible regiochemical outcomes. The major product can be predicted by considering resonance structures for the diene,



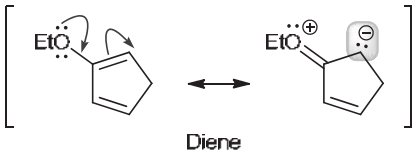
and resonance structures for the dienophile:



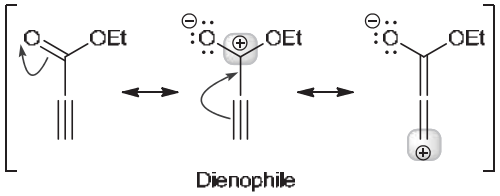
Notice that the diene is electron-rich, because of the electron-donating effect of the methoxy group; while the dienophile is electron-poor, because of the electron-withdrawing effect of the cyano group. The major product results when the regions of δ+ and δ– (highlighted) are aligned:



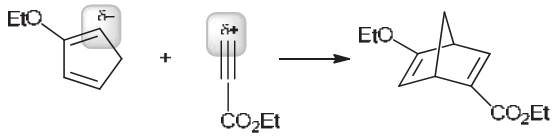
(c) Both the diene and the dienophile are unsymmetrical, so there are two possible regiochemical outcomes. The major product can be predicted by considering resonance structures for the diene,



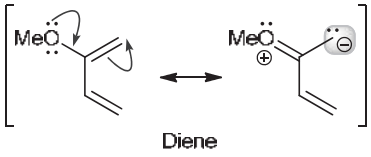
and resonance structures for the dienophile:



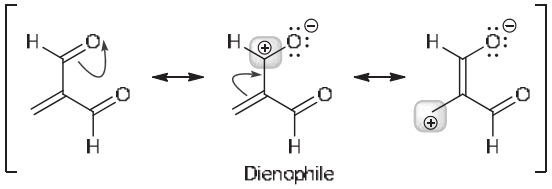
Notice that the diene is electron-rich, because of the electron-donating effect of the ethoxy group; while the dienophile is electron-poor, because of the electron-withdrawing effect of the ester group. The major product results when the regions of δ+ and δ– (highlighted) are aligned:



(d) Both the diene and the dienophile are unsymmetrical, so there are two possible regiochemical outcomes. The major product can be predicted by considering resonance structures for the diene,



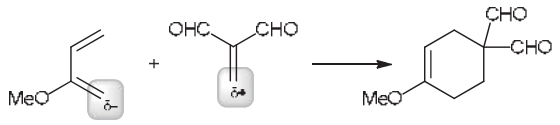
and resonance structures for the dienophile:



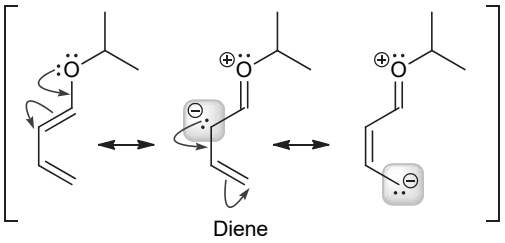
Notice that the diene is electron-rich, because of the electron-donating effect of the methoxy group; while the dienophile is electron-poor, because of the electron-withdrawing effects of the aldehyde groups. The major

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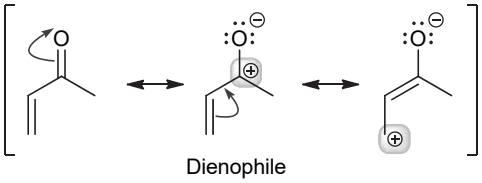
product results when the regions of δ+ and δ– (highlighted) are aligned:



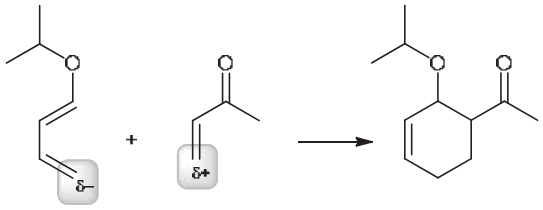
(e) Both the diene and the dienophile are unsymmetrical, so there are two possible regiochemical outcomes. The major product can be predicted by considering resonance structures for the diene,



and resonance structures for the dienophile:



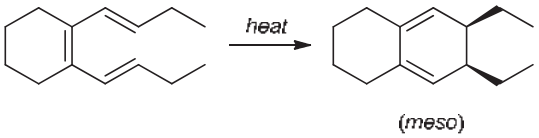
Notice that the diene is electron-rich, because of the electron-donating effect of the isopropoxy group; while the dienophile is electron-poor, because of the electron-withdrawing effect of the aldehyde group. The major product results when the regions of δ+ and δ– (highlighted) are aligned:



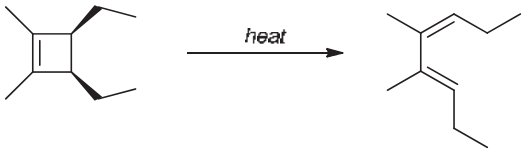
16.19. We first consider the HOMO of one molecule of butadiene and the LUMO of another molecule of butadiene (see Figure 16.17 for the HOMO and LUMO of butadiene). The phases of these MOs do not align, so a thermal reaction is symmetry-forbidden. However, if one molecule is photochemically excited, the HOMO and LUMO of that molecule are redefined. The phases of the frontier orbitals will align under these conditions, so the reaction is expected to occur photochemically.

16.20.

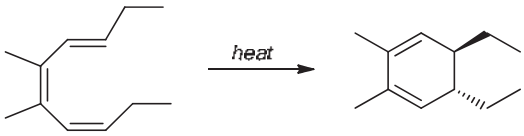
(a) This system has six π electrons, so an electrocyclic reaction is expected to occur under thermal conditions to give disrotatory ring closure. The resulting product has an internal plane of symmetry and is therefore a *meso* compound.



(b) In this reaction, the four-membered ring is opening (this is the reverse of an electrocyclic ring closure). If we look at the product, we see that four π electrons are involved in the process. Under thermal conditions, this electrocyclic process is expected be conrotatory, giving the following product.

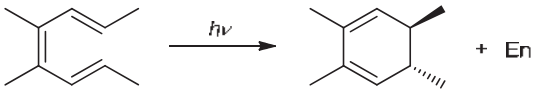


(c) This system has six π electrons, so an electrocyclic reaction is expected to occur under thermal conditions to give disrotatory ring closure. The resulting product is chiral, and both enantiomers are expected (one ethyl group rotates clockwise and the other rotates counterclockwise, or vice versa, leading to both possible enantiomers).



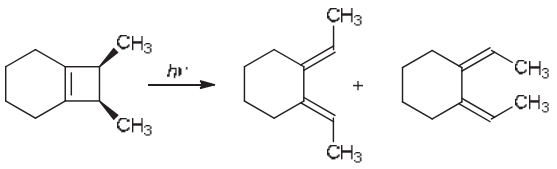
16.21.

(a) This system has six π electrons, so an electrocyclic reaction is expected to occur under photochemical conditions to give conrotatory ring closure. The resulting product is chiral, and both enantiomers are expected (either both methyl groups rotate clockwise or both methyl groups rotate counterclockwise).

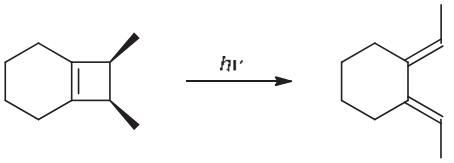


(b) In this reaction, the four-membered ring is opening (this is the reverse of an electrocyclic ring closure). If we look at the product, we see that four π electrons are involved in the process. Under photochemical conditions, this electrocyclic process is expected be disrotatory. In theory, two products can be produced from disrotatory ring-opening (one methyl group rotates clockwise and the other rotates counterclockwise, or vice versa, leading to two possible products):

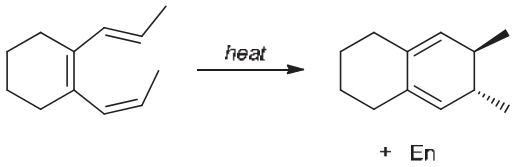
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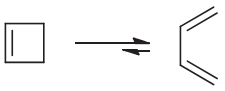
But the second product exhibits a severe steric interaction (the protons of the methyl groups are forced to occupy the same region of space), and this product is therefore not likely to be formed in substantial quantities. We therefore predict the following product for this reaction.



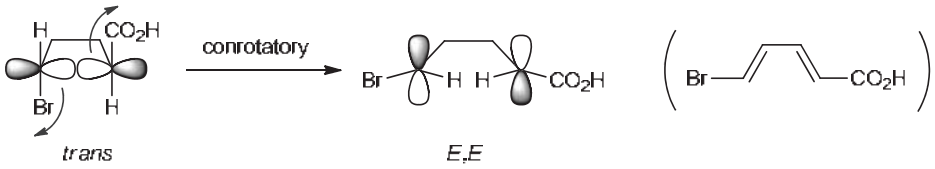
(c) This system has six π electrons, so an electrocyclic reaction is expected to occur under thermal conditions to give disrotatory ring closure. The resulting product is chiral, and both enantiomers are expected (one methyl group rotates clockwise and the other rotates counterclockwise, or vice versa, leading to both possible enantiomers).



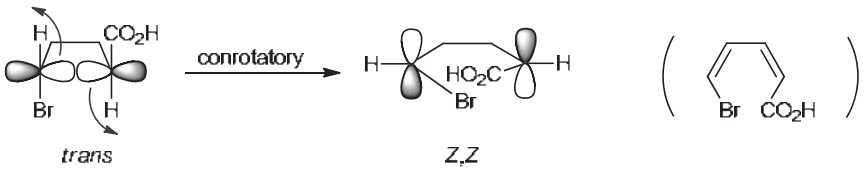
16.22. We begin by determining the number of π electrons that are involved in the reaction. Electrocyclic ring-opening and ring-closing reactions are equilibrium processes; in this case, a cyclobutene ring is in equilibrium with a diene. (In fact, ring opening is favored because it alleviates ring strain). From this equilibrium, we can see that 4 π electrons are involved in this electrocyclic reaction.



Since the reaction was done under thermal conditions (heat), the Woodward-Hoffmann rules predict a conrotatory ring opening. Thus, both ends of the π system will rotate clockwise or both will rotate counterclockwise. If they both rotate clockwise, the initial *trans* stereochemistry of the ring will lead to double bonds that both have the *E* configuration.



If they both rotate counterclockwise, the initial *trans* stereochemistry of the ring will lead to double bonds that both have the *Z* configuration.

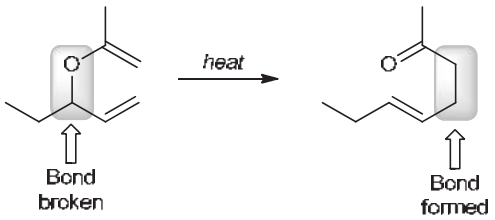


The Woodward-Hoffmann rules allow either the *E,E* isomer or the *Z,Z* isomer. It is not possible to get the *E,Z* or *Z,E* isomer under these conditions. Practically, only the *E,E* isomer is formed because the steric strain between the Br and CO_2H groups in the *Z,Z* isomer prevent its formation.

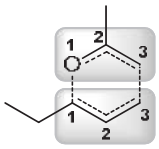
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16.23.

(a) We begin by identifying the σ bond that is broken and the σ bond that is formed, highlighted here:

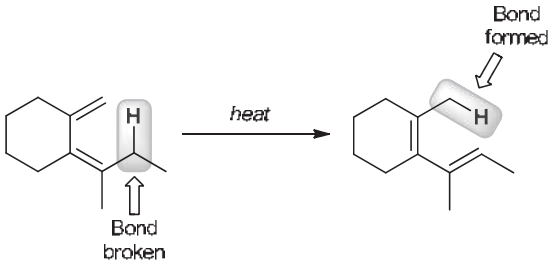


In the transition state, the bond that is breaking and the bond that is forming are separated by two different pathways, each of which is comprised of three atoms:

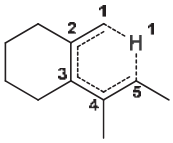


Therefore, this reaction is a [3,3] sigmatropic rearrangement.

(b) We begin by identifying the σ bond that is broken and the σ bond that is formed, highlighted here:



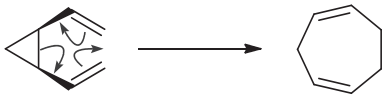
In the transition state, the bond that is breaking and the bond that is forming are separated by two different pathways: one is comprised of five atoms and the other is comprised of only one atom:



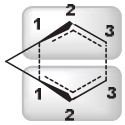
Therefore, this reaction is a [1,5] sigmatropic rearrangement.

16.24.

(a) This transformation can be achieved via the following sigmatropic rearrangement:



(b) We identify the σ bond that is broken and the σ bond that is formed, and then determine the pathways (highlighted below) that separate these bonds.

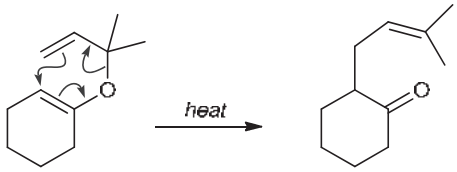


Each pathway is comprised of three atoms, so the reaction is a [3,3] sigmatropic rearrangement.

(c) The ring strain associated with the three-membered ring is alleviated. The reverse process would involve forming a high-energy, three-membered ring. The equilibrium disfavors the reverse process.

16.25.

(a) This compound is an allylic vinylic ether, and it can therefore undergo a Claisen rearrangement to give the following product:



(b) This compound has two π bonds that are separated from each other by exactly three σ bonds. As such, this compound can undergo a Cope rearrangement to give the following product:

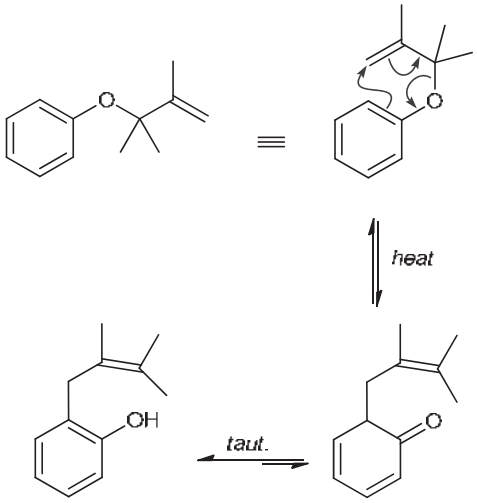


(c) This compound has two π bonds that are separated from each other by exactly three σ bonds. As such, this compound can undergo a Cope rearrangement to give the following product:

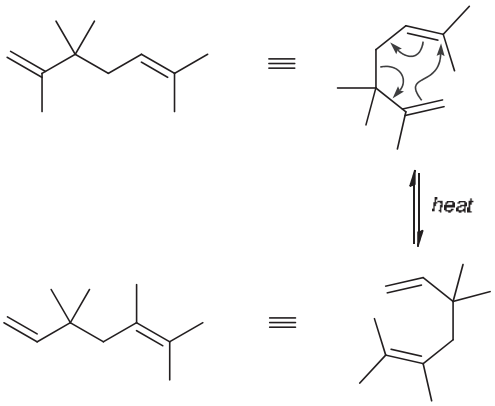


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(d) This compound is an allylic vinylic ether, and it can therefore undergo a Claisen rearrangement to give a ketone, which tautomerizes to give the enol, thereby re-establishing aromaticity:

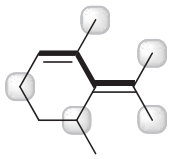


16.26. This compound has two π bonds that are separated from each other by exactly three σ bonds. As such, this compound can undergo a Cope rearrangement. To draw the product of this reaction, it is helpful to redraw the starting material, as shown below, so that it is easier to see the ring of electrons responsible for the transformation:

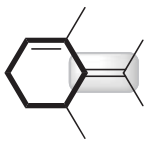


16.27.

(a) This conjugated system (comprised of two π bonds) has five auxochromic alkyl groups, highlighted here:



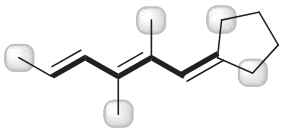
and one exocyclic double bond:



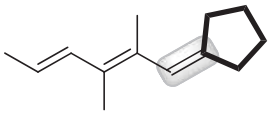
The calculation for λ_{max} is shown here:

Base	=	217
Additional double bonds	=	0
Auxochromic alkyl groups	=	+25
Exocyclic double bond	=	+5
Homoannular diene	=	0
Total	=	247 nm

(b) This conjugated system (comprised of three π bonds) has five auxochromic alkyl groups, highlighted here:



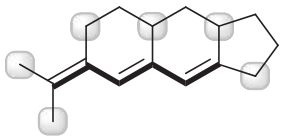
and one exocyclic double bond:



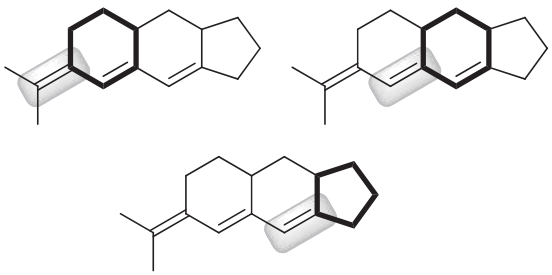
The calculation for λ_{max} is shown here:

Base	=	217
Additional double bonds	=	+30
Auxochromic alkyl groups	=	+25
Exocyclic double bond	=	+5
Homoannular diene	=	0
Total	=	277 nm

(c) This conjugated system (comprised of three π bonds) has six auxochromic alkyl groups, highlighted here:



and three exocyclic double bonds (each of the double bonds is exocyclic to a ring), shown here:

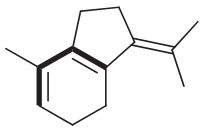


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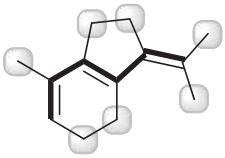
The calculation for λ_{max} is shown here:

Base	=	217
Additional double bonds	=	+30
Auxochromic alkyl groups	=	+30
Exocyclic double bonds	=	+15
Homoannular diene	=	0
Total	=	292 nm

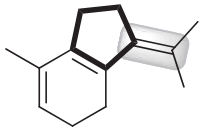
(d) This conjugated system (comprised of three π bonds) has two of the double bonds in the same ring (homoannular):



In addition, there are seven auxochromic alkyl groups, highlighted here:



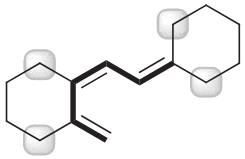
and one exocyclic double bond:



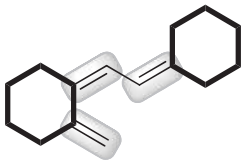
The calculation for λ_{max} is shown here:

Base	=	217
Additional double bonds	=	+30
Auxochromic alkyl groups	=	+35
Exocyclic double bonds	=	+5
Homoannular diene	=	+39
Total	=	326 nm

16.28. Focusing on the chromophore, we see that the conjugated system (comprised of three π bonds) has four auxochromic alkyl groups, highlighted here:



and three exocyclic double bonds:



We therefore predict that this compound will have a λ_{max} near 282 nm, as shown in the calculation below:

Base	=	217
Additional double bonds (1)	=	+ 30
Auxochromic alkyl groups (4)	=	+ 20
Exocyclic double bond (3)	=	+ 15
Homoannular dienes (0)	=	+ 0
Total	=	282 nm

Incidentally, the actual value is 265nm. This demonstrates that our prediction was not exact, but is nevertheless reasonably close to the actual value.

16.29.

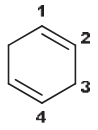
(a) As seen in Figure 16.37 (the color wheel), the complementary color of orange is blue. Therefore, a compound that absorbs orange light will appear to be blue.

(b) As seen in Figure 16.37 (the color wheel), the complementary color of blue-green is red-orange. Therefore, a compound that absorbs blue-green light will appear to be red-orange.

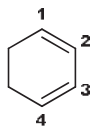
(c) As seen in Figure 16.37 (the color wheel), the complementary color of orange-yellow is blue-violet. Therefore, a compound that absorbs orange-yellow light will appear to be blue-violet.

16.30.

(a) The parent ("cyclohex") indicates a six-membered ring, and the suffix ("diene") indicates the presence of two C=C bonds. The locants (1 and 4) indicate the positions of the two double bonds.



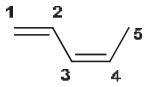
(b) The parent ("cyclohex") indicates a six-membered ring, and the suffix ("diene") indicates the presence of two C=C bonds. The locants (1 and 3) indicate the positions of the two double bonds.



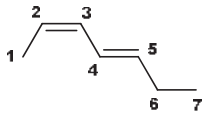
(c) The parent ("pent") indicates a five-carbon chain, and the suffix ("diene") indicates the presence of two C=C bonds. The locants (1 and 3) indicate the positions

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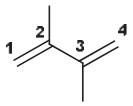
of the two double bonds, and the stereodescriptor (*Z*) indicates the configuration of the C=C bond between C3 and C4.



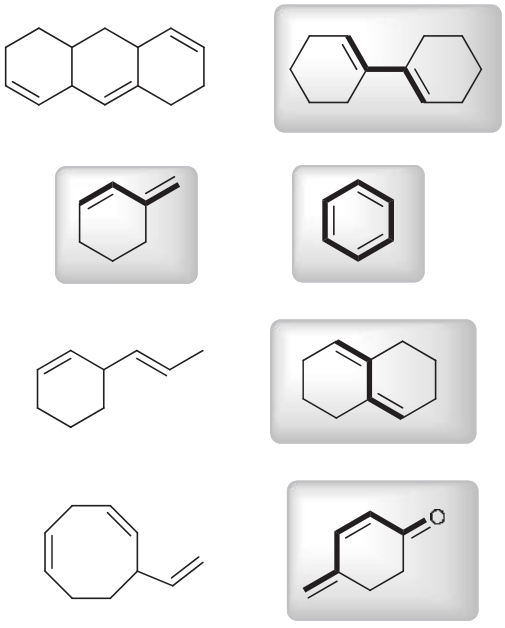
(d) The parent ("hept") indicates a seven-carbon chain, and the suffix ("diene") indicates the presence of two C=C bonds. The locants (2 and 4) indicate the positions of the two double bonds, and the stereodescriptors indicate the configurations of the double bonds.



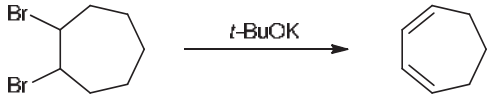
(e) The parent ("but") indicates a four-carbon chain, and the suffix ("diene") indicates the presence of two C=C bonds. The locants (1 and 3) indicate the positions of the two double bonds. There are two methyl substituents, at positions C2 and C3.



16.31. Each of the highlighted compounds possesses a conjugated π system, which is shown with darker bonds.



16.32. Potassium tert-butoxide is a strong, sterically hindered base, and the starting material will react with two equivalents of this base to undergo two successive elimination (E2) reactions, producing a conjugated, homoannular diene, as shown.

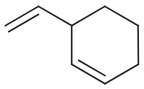


16.33.
(a) The non-conjugated isomer (shown below) will be higher in energy than the conjugated isomer.



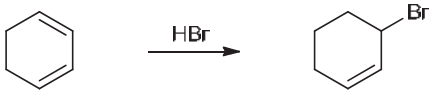
As a result, this compound will liberate more heat upon hydrogenation.

(b) The non-conjugated isomer (shown below) will be higher in energy than the conjugated isomer.

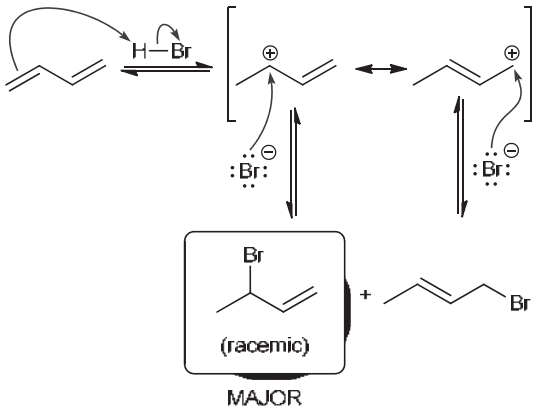


As a result, this compound will liberate more heat upon hydrogenation.

16.34. Treatment of 1,3-cyclohexadiene with HBr produces only one product (because 1,2 addition and 1,4 addition give the same product).



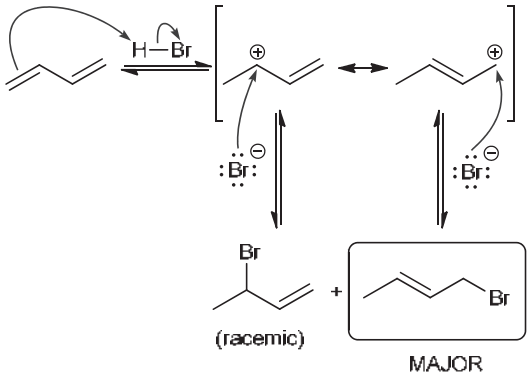
16.35. The diene is protonated to give a resonance stabilized cation, which can then be attacked in one of two locations, leading to the 1,2-adduct and the 1,4-adduct. At low temperature, the kinetic product (the 1,2-adduct) dominates.



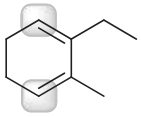
16.36. The diene is protonated to give a resonance stabilized cation, which can then be attacked in one of

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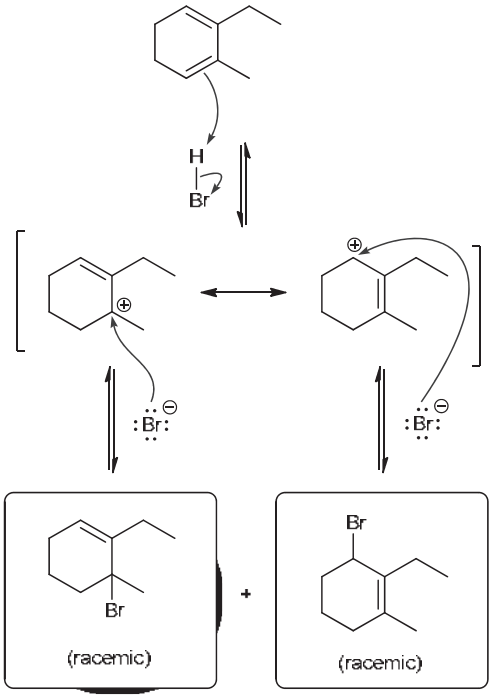
two locations, leading to the 1,2-adduct and the 1,4-adduct. At elevated temperature, the thermodynamic product (the 1,4-adduct) dominates.



16.37. We first identify the locations where protonation can occur. There are four unique positions where protonation can occur, although a resonance-stabilized intermediate can only be obtained upon protonation of one of the ends of the conjugated π system, highlighted below:

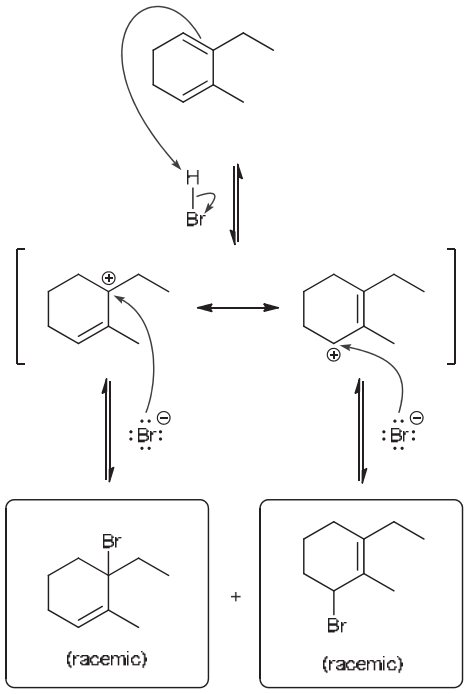


We must explore protonation at each of these positions. Let's begin with protonation of the bottom position, which leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, giving rise to two products:

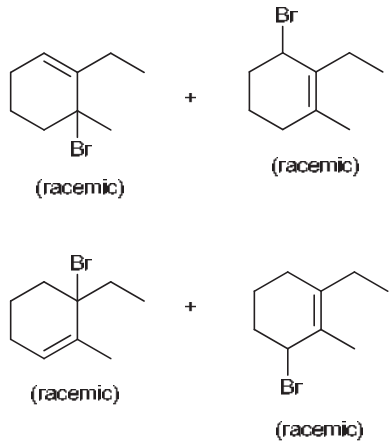


Notice that each of the products possesses a chiral center and is therefore produced as a racemic mixture (because the bromide ion can attack either face of the allylic carbocation with equal likelihood).

Now let's consider protonation at the position on top. Once again, protonation leads to a resonance–stabilized intermediate. When we draw both resonance structures, we can see that two positions are electrophilic. Nucleophilic attack can occur at either of these locations, giving two possible products, as shown:



In summary, we expect the following possible products:

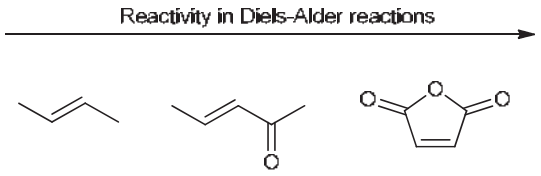


16.38. An increase in temperature allowed the system to reach equilibrium concentrations, which are determined by the relative stability of each product. Under these conditions, the 1,4-adducts predominate. Once at equilibrium, lowering the temperature will not cause a decrease in the concentration of the 1,4-adducts.

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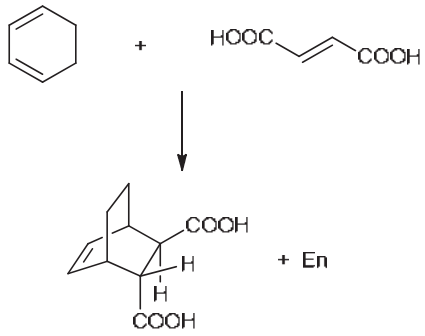
16.39.
(a) The *tert*-butyl groups provide significant steric interactions that prevent the compound from adopting an *s-cis* conformation.
(b) This diene is not conjugated.
(c) The methyl groups provide a significant steric interaction in the *s-cis* conformation that prevents the compound from adopting this conformation.
(d) This diene cannot adopt an *s-cis* conformation.

16.40. The most reactive dienophile is the one connected to two electron-withdrawing C=O groups. Then, the dienophile with only one C=O group is the next most reactive. And finally, the least reactive dienophile is the one that lacks an electron-withdrawing substituent altogether.

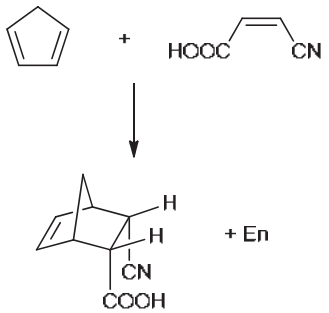


16.41. The π bonds in 1,2-butadiene are not conjugated, and λ_{max} is therefore lower than 217 nm. In fact, it is below 200 nm, which is beyond the range used by most UV-Vis spectrometers.

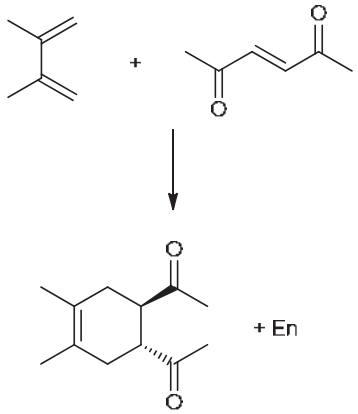
16.42.
(a) In a Diels-Alder reaction, the configuration of the dienophile (in this case, *trans*) is preserved in the product, giving a pair of enantiomers:



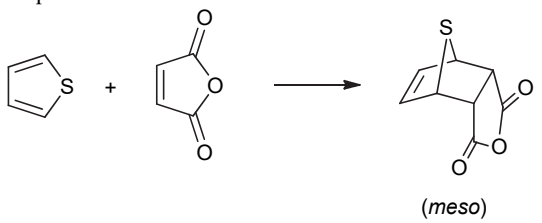
(b) In a Diels-Alder reaction, the configuration of the dienophile (in this case, *trans*) is preserved in the product, giving a pair of enantiomers. Notice that both substituents occupy *endo* (rather than *exo*) positions:



(c) In a Diels-Alder reaction, the configuration of the dienophile (in this case, *trans*) is preserved in the product, giving a pair of enantiomers:



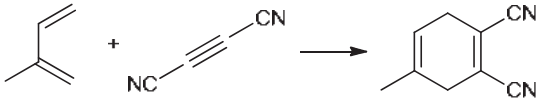
(d) The diene is cyclic and the dienophile has a *cis* configuration, so we must consider the *endo* rule. Specifically, we draw the *endo* product, which has an internal plane of symmetry in this case, so it is a *meso* compound.



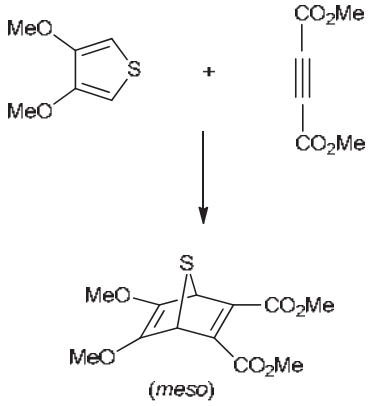
(*meso*)

If you have trouble seeing how the bicyclic framework is produced by this reaction, see the solution to Problem **16.17f**, which is very similar.

(e) The dienophile is an alkyne, and the product does not have any chiral centers (no wedges or dashes).



(f) The starting material is a cyclic diene, but the *endo* rule is not relevant in this case, because an alkyne is used as the dienophile, so there are no *endo* positions. The product is a *meso* compound.

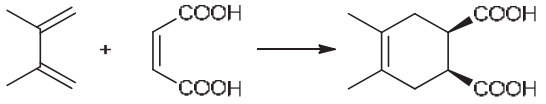


(*meso*)

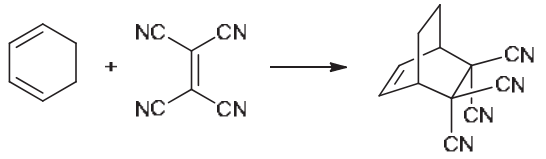
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16.43.

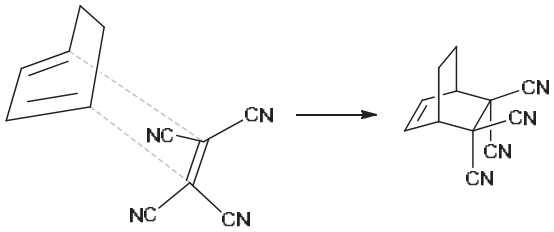
(a) The product exhibits a *cis* orientation of the carboxylic acid groups, so the dienophile must have the *cis* configuration as well.



(b) The following diene and dienophile can be used to produce the desired product.

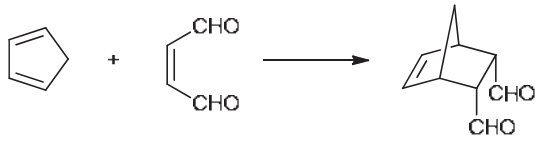


If you have trouble seeing how the bicyclic framework is produced by this reaction, consider the following drawing in which the bond angles have been distorted to show how the bicyclic structure is formed:

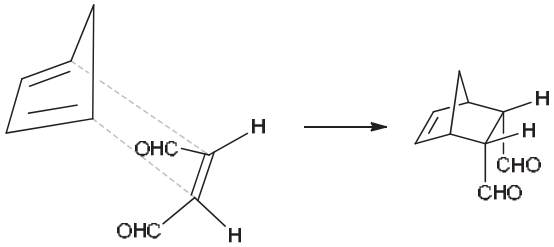


In this drawing, the dotted lines indicate the new σ bonds that are formed during the Diels-Alder reaction.

(c) The product exhibits a *cis* orientation of the aldehyde (CHO) groups, so the dienophile must have the *cis* configuration as well. Notice that the *endo* rule ensures formation of the desired product.

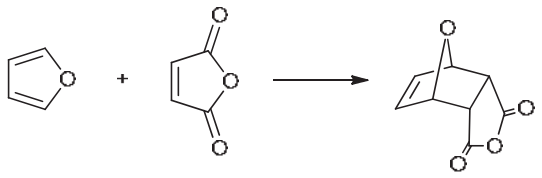


If you have trouble seeing how the bicyclic framework is produced by this reaction, consider the following drawing in which the bond angles have been distorted to show how the bicyclic structure is formed:



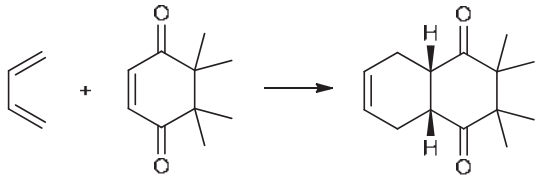
In this drawing, the dotted lines indicate the new σ bonds that are formed during the Diels-Alder reaction.

(d) The following diene and dienophile can be used to produce the desired product.

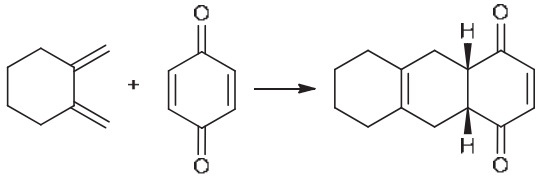


Notice that the *endo* rule ensures formation of the desired product.

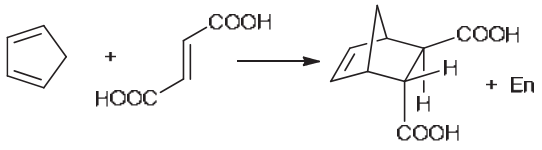
(e) The product exhibits a *cis* configuration, so the dienophile must have the *cis* configuration as well (although in this case, a *trans* configuration is not possible in a six-membered ring).



(f) The product exhibits a *cis* configuration, so the dienophile must have the *cis* configuration as well (although in this case, a *trans* configuration is not possible in a six-membered ring).

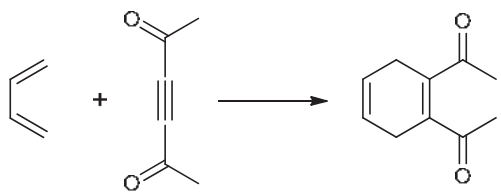


(g) The product exhibits a *trans* configuration, so the dienophile must have the *trans* configuration as well



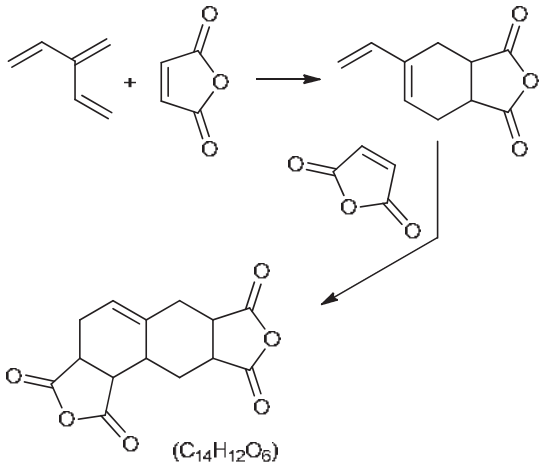
If you have trouble seeing why a pair of enantiomers is produced, see the solution to Problem **16.17b**, which is very similar to this problem (just replace the cyano groups with carboxylic acid groups)

(h) The product has a cyclohexadiene ring, so the starting dienophile must be an alkyne:

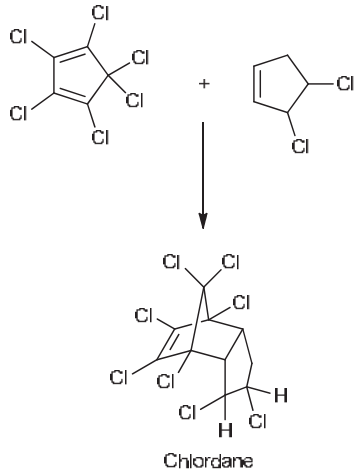


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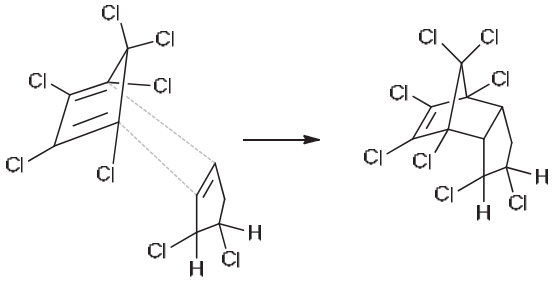
16.44. A product with the molecular formula $C_{14}H_{12}O_6$ can be formed via two successive Diels-Alder reactions, as shown here:



16.45. The following diene and dienophile would be necessary in order to produce the desired compound via a Diels-Alder reaction:



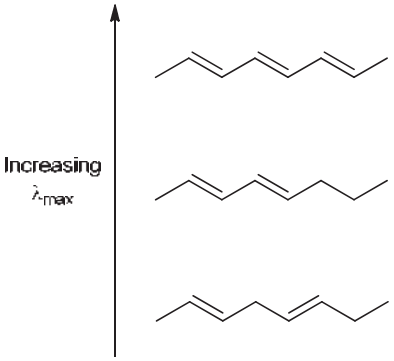
If you have trouble seeing how the bicyclic framework is produced by this reaction, consider the following drawing in which the bond angles have been distorted to show how the bicyclic structure is formed:



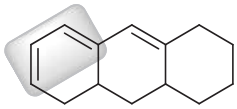
In this drawing, the dotted lines indicate the new σ bonds that are formed during the Diels-Alder reaction.

16.46. The two ends of the conjugated system are much farther apart in a seven-membered ring than they are in a five-membered ring.

16.47. One of the compounds has three π bonds in conjugation. That compound has the most extended conjugated system, so that compound is expected to have the longest λ_{max}. Of the remaining two compounds, one of them exhibits conjugation (two π bonds separated by exactly one σ bond), so it will have the next longest λ_{max}. The compound with two isolated C=C bonds will have the shortest λ_{max}:

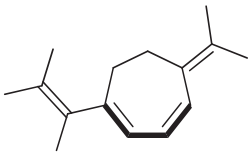


16.48. Each of these compounds has three π bonds that comprise one extended conjugated system. However, in the first compound (shown below), two of the π bonds are in the same ring (homoannular), which adds +39 nm to the estimate for λ_{max}.

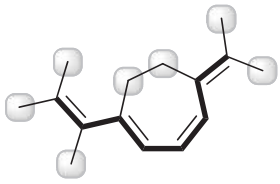


We therefore expect this compound to have the longer λ_{max}.

16.49. This conjugated system (comprised of four π bonds) has two of the double bonds in the same ring (homoannular):

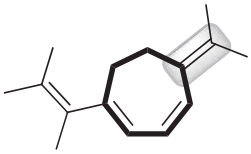


In addition, there are seven auxochromic alkyl groups, highlighted here:



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and one exocyclic double bond:



The calculation for λ_{max} is shown here:

Base	=	217
Additional double bonds	=	+60
Auxochromic alkyl groups	=	+35
Exocyclic double bonds	=	+5
Homoannular diene	=	+39
Total	=	356 nm

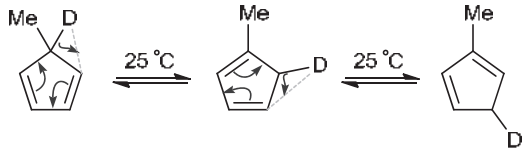
16.50. Notice that the carbon skeleton does not change during these reactions. It is the location of the deuteron, as well as the location of the π bonds, that changes. This is indeed characteristic of [1,5] sigmatropic rearrangements, as seen in the following general reaction mechanism:



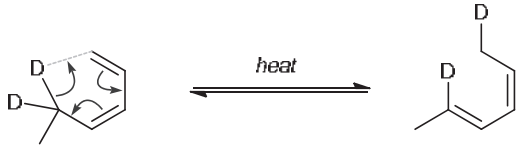
Notice that the position of the proton changes, as well as the position of the π bonds. And we can certainly envision this process occurring with a deuteron, in place of the proton:



Much like the previous example, the position of the deuteron changes, as well as the position of the π bonds. This is exactly the type of transformation taking place in the reactions shown in the problem statement. It is therefore reasonable to explain each of these transformations with a [1,5] sigmatropic rearrangement, as shown:

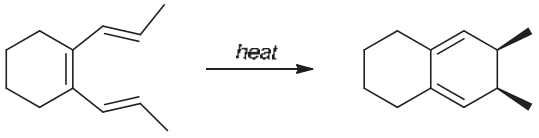


16.51. Notice that the carbon skeleton does not change during these reactions. It is the location of a deuteron, as well as the location of the π bonds, that changes. As described in the solution to the previous problem, these changes are characteristic of a [1,5] sigmatropic rearrangement:

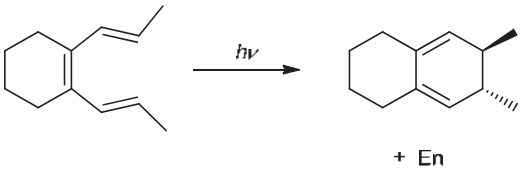


16.52.

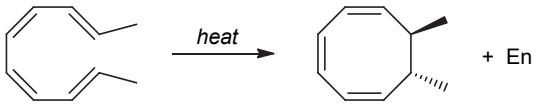
(a) This system has six π electrons, so an electrocyclic reaction is expected to occur under thermal conditions to give disrotatory ring closure. The resulting product is a *meso* compound because it is superimposable on its mirror image:



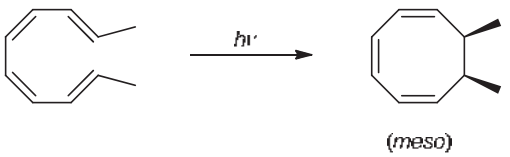
(b) This system has six π electrons, so an electrocyclic reaction is expected to occur under photochemical conditions to give conrotatory ring closure. The resulting product is chiral, and both enantiomers are expected (the methyl groups can both rotate in a clockwise fashion, or they can both rotate in a counterclockwise fashion, giving both possible enantiomers).



(c) This system has eight π electrons, so an electrocyclic reaction is expected to occur under thermal conditions to give conrotatory ring closure. The resulting product is chiral, and both enantiomers are expected (the methyl groups can both rotate in a clockwise fashion, or they can both rotate in a counterclockwise fashion, giving both possible enantiomers).



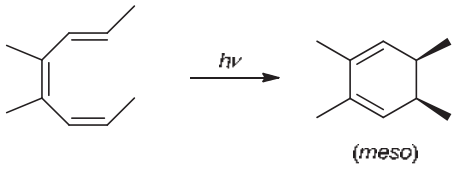
(d) This system has eight π electrons, so an electrocyclic reaction is expected to occur under photochemical conditions to give disrotatory ring closure. The resulting product is a *meso* compound because it is superimposable on its mirror image:



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16.53.

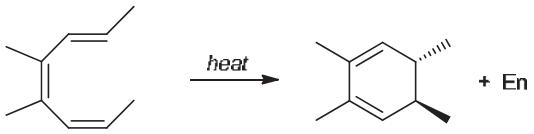
(a) This system has six π electrons, so an electrocyclic reaction is expected to occur under photochemical conditions to give conrotatory ring closure. The resulting product is a *meso* compound because it is superimposable on its mirror image:



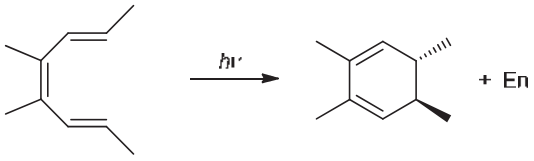
This product is obtained whether both methyl groups rotate in a clockwise fashion, or whether both methyl groups rotate in a counterclockwise fashion:



(b) This system has six π electrons, so an electrocyclic reaction is expected to occur under thermal conditions to give disrotatory ring closure. The resulting product is chiral, and both enantiomers are expected (one methyl group rotates clockwise and the other rotates counterclockwise, or vice versa, leading to both possible enantiomers):

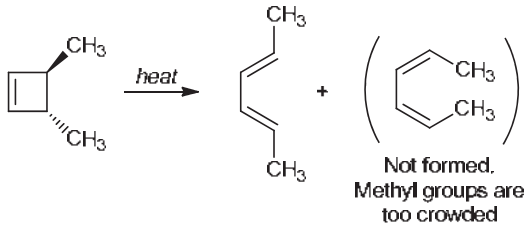


(c) This system has six π electrons, so an electrocyclic reaction is expected to occur under photochemical conditions to give conrotatory ring closure. The resulting product is chiral, and both enantiomers are expected (either both methyl groups can rotate clockwise or both can rotate counterclockwise, leading to both possible enantiomers):

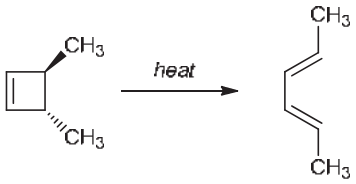


16.54. The compound on the right has a π bond in conjugation with the aromatic ring, while the compound on the left does not. Therefore, the compound on the right side of the equilibrium is expected to be more stable, and the equilibrium will favor this compound because it is lower in energy.

16.55. In this reaction, the four-membered ring is opening (this is the reverse of an electrocyclic ring closure). If we look at the product, we see that four π electrons are involved in the process. Under thermal conditions, this electrocyclic process is expected be conrotatory. In theory, two products can be produced from conrotatory ring-opening (the methyl groups can both rotate in a clockwise fashion, or they can both rotate in a counterclockwise fashion):

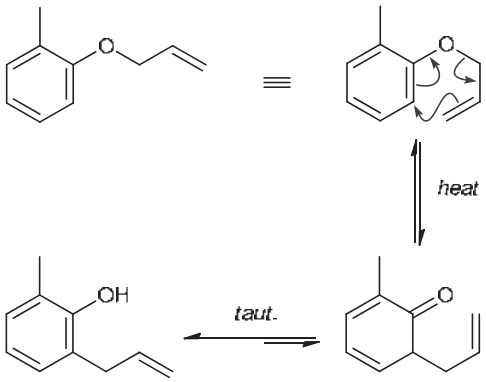


However, the second possible product exhibits a severe steric interaction (the protons of the methyl groups are forced to occupy the same region of space), and this product is therefore not likely formed in substantial quantities. We therefore predict the following product for this reaction.



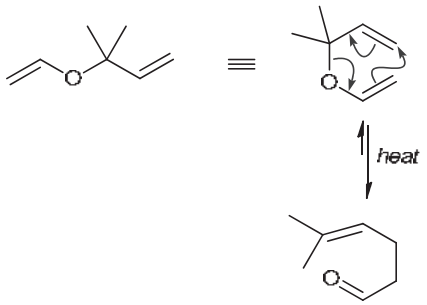
16.56.

(a) This compound is an allylic vinylic ether, and it can therefore undergo a Claisen rearrangement to give a ketone, which tautomerizes to give the enol, thereby re-establishing aromaticity. Note that it is helpful to redraw the starting material, as shown below, so that it is easier to see the ring of electrons responsible for the transformation:

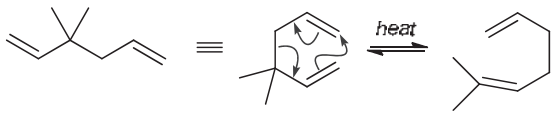


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(b) This compound is an allylic vinylic ether, and it can therefore undergo a Claisen rearrangement to give an aldehyde, as shown. Note that it is helpful to redraw the starting material, as shown below, so that it is easier to see the ring of electrons responsible for the transformation:

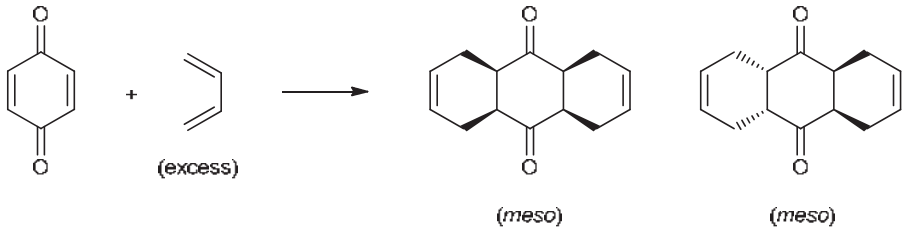


(c) This compound has two π bonds that are separated from each other by exactly three σ bonds. As such, this compound can undergo a Cope rearrangement. To draw the product of this reaction, it is helpful to redraw the starting material, as shown below, so that it is easier to see the ring of electrons responsible for the transformation:

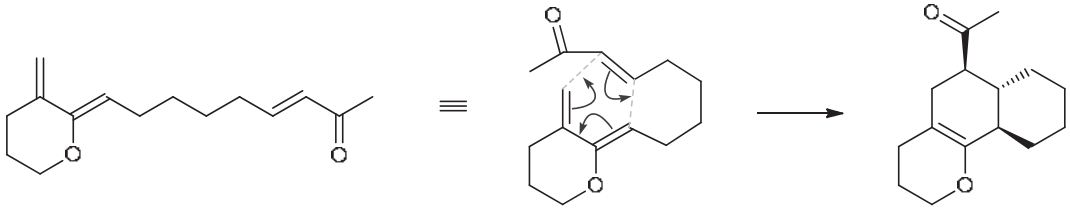


The product has a trisubstituted π bond, and is therefore more stable than the starting material. As such, the equilibrium will favor formation of the product.

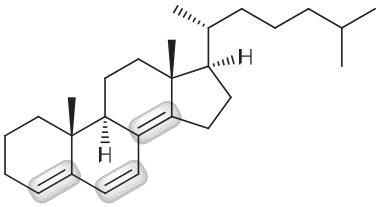
16.57. Benzoquinone has two C=C π bonds, each of which can function as a dienophile in a Diels-Alder reaction. Two successive Diels-Alder reactions will afford a tricyclic structure. The tricyclic products are diastereomers, and are formed because the second Diels-Alder reaction need not occur on the same face as the first Diels-Alder reaction.



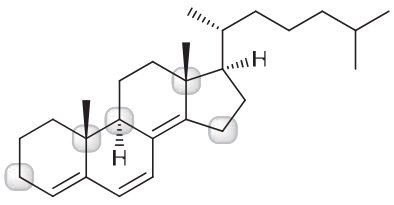
16.58. This transformation can occur via an intramolecular Diels-Alder reaction, in which a portion of the compound functions as the diene, while another portion of the compound functions as the dienophile. The result is a polycyclic compound (which is expected to be formed as a racemic mixture).



16.59. First count the number of conjugated double bonds. This compound has three. Two of them count toward the base value of 217 nm and the other will add +30.

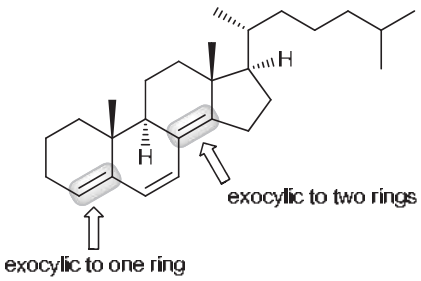


Next, look for any auxochromic alkyl groups. These are the carbon atoms connected directly to the chromophore. This compound has five auxochromic alkyl groups each of which adds +5, giving another +25.



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Next, look for exocyclic double bonds. In this case, two double bonds (highlighted below) are exocyclic. One of the double bonds is exocyclic to two rings giving a total of three exocyclic relationships that each add +5 for a total of +15.



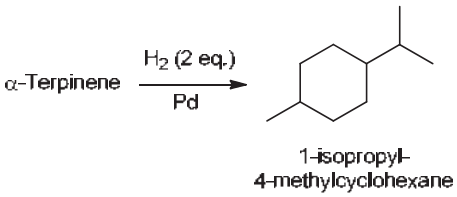
Finally, look for a homoannular diene. There appears to be no ring that has two double bonds contained wholly within it, so no adjustment is required for this compound. In summary, the following calculation predicts a λ_{max} of approximately 287 nm:

Base =	217
Additional double bond (1) =	+30
Auxochromic alkyl groups (5) =	+25
Exocyclic double bonds (3) =	+15
Homoannular diene (0) =	0
Total =	287 nm

This prediction is in fairly good agreement with the experimentally observed value of 283 nm.

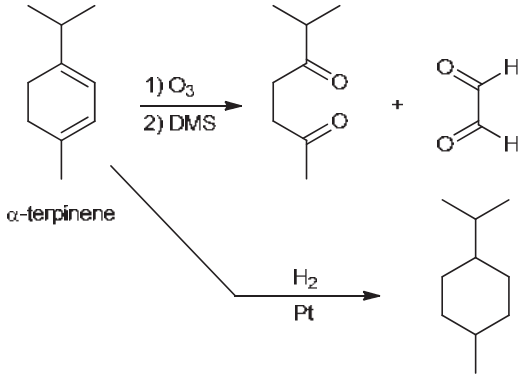
16.60.

(a) α-Terpinene reacts with two equivalents of molecular hydrogen, so it must have two π bonds. These π bonds must be associated with two C=C double bonds (rather than being associated with a C≡C triple bond), because the carbon skeleton (which does not change during hydrogenation) cannot support a triple bond:

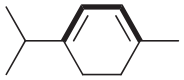


A triple bond could not have been in the ring, because a six-membered ring cannot support the linear geometry required by the *sp* hybridized carbon atoms of a triple bond. The other C-C bonds (outside the ring) can also not support a triple bond (without violating the octet rule by giving a carbon atom with five bonds). Therefore, α-terpinene must have two double bonds.

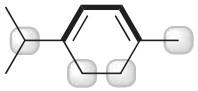
(b) The ozonolysis products indicate how the molecule must have been constructed, because ozonolysis breaks C=C bonds into C=O bonds:



(c) This conjugated system is a homoannular diene:



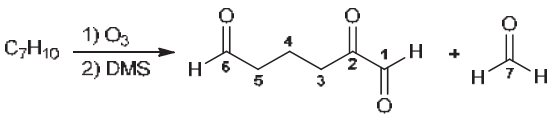
In addition, there are four auxochromic alkyl groups, highlighted here:



The calculation for λ_{max} is shown here:

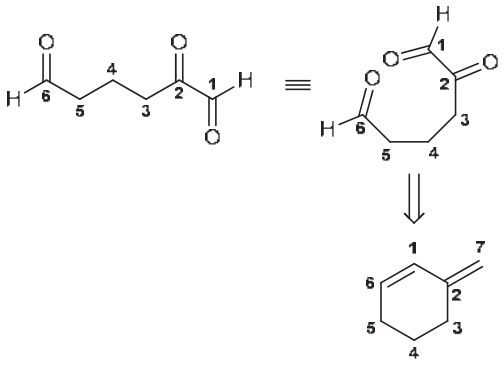
Base	=	217
Additional double bonds	=	0
Auxochromic alkyl groups	=	+20
Exocyclic double bonds	=	0
Homoannular diene	=	+39
Total	=	276 nm

16.61. The molecular formula (C_7H_{10}) indicates three degrees of unsaturation (see Section 14.16). The problem statement indicates that compound **A** will react with two equivalents of molecular hydrogen (H_2). Therefore, we can conclude that compound **A** has two π bonds, which accounts for two of the three degrees of unsaturation. The remaining degree of unsaturation must be a ring. Ozonolysis yields two products, which together account for all seven carbon atoms:

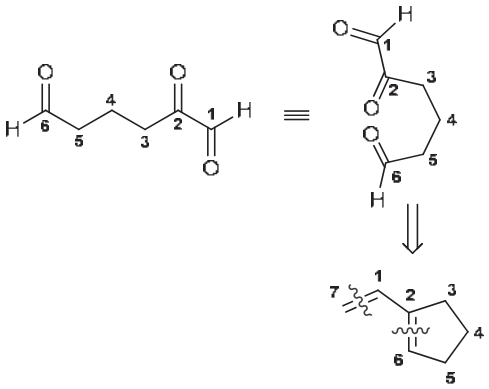


Focus on the product with three carbonyl groups. Two of them must have been connected to each other in compound **A** (as a C=C bond), and the third carbonyl group must have been connected to the carbon atom of formaldehyde (CH_2O). This gives two possibilities: Either C1 was connected to C6 (and C2 was connected to C7):

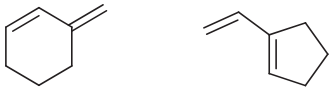
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or C2 was connected to C6, and C1 was connected to C7:



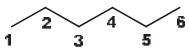
In summary, we have found two possible structures for compound **A,** both of which are conjugated dienes:



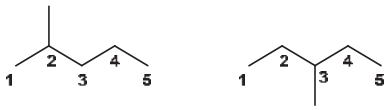
16.62. The molecular formula (C_6H_{10}) indicates two degrees of unsaturation (see Section 14.16). The problem statement indicates that all proposed structures must be conjugated dienes, which accounts for both degrees of unsaturation. That is, the proposed structures cannot have any rings. All structures must be acyclic.

To draw all possible conjugated dienes with the molecular formula C_6H_{10}, we must first consider all of the different ways in which six carbon atoms can be connected to each other.

We begin with a linear chain (parent = hexane):



Next, we look for any skeletons where the parent is pentane (five carbon atoms). There are only two such skeletons. Specifically, we can either connect the extra CH_3 group to positions C2 or C3 of the pentane chain:



We cannot connect the CH_3 group to positions C1 or C5, as that would simply give us the linear chain (hexane), which we already drew (above). We also cannot connect the CH_3 group to position C4 as that would generate the same structure as placing the CH_3 group at the C2 position:



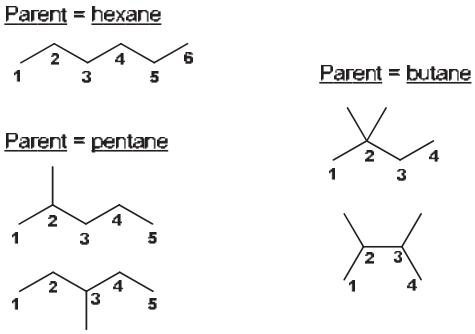
Next, we look for any skeletons where the parent is butane (four carbon atoms). There are only two such skeletons. Specifically, we can either connect two CH_3 groups to adjacent positions (C2 and C3) or the same position:



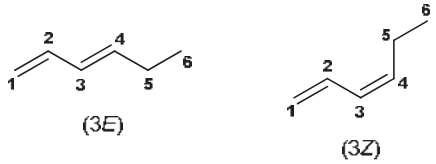
If we try to connect a CH_3CH_2 group to a butane chain, we end up with a pentane chain (which was has already been drawn earlier):



In summary, there are five different ways in which six carbon atoms can be connected:



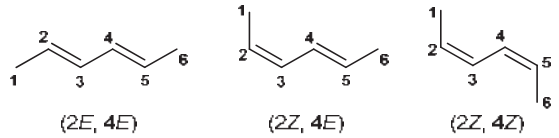
For each one of these skeletons, we must consider all of the different unique positions where the double bonds can be placed (keeping in mind that they must remain conjugated). For the first skeleton (hexane), there are many different locations where the double bonds can be placed. For example, the double bonds can be at C1 and C3 (giving two stereoisomeric options, because the double bond at C3 can have either the *E* configuration or the *Z* configuration):



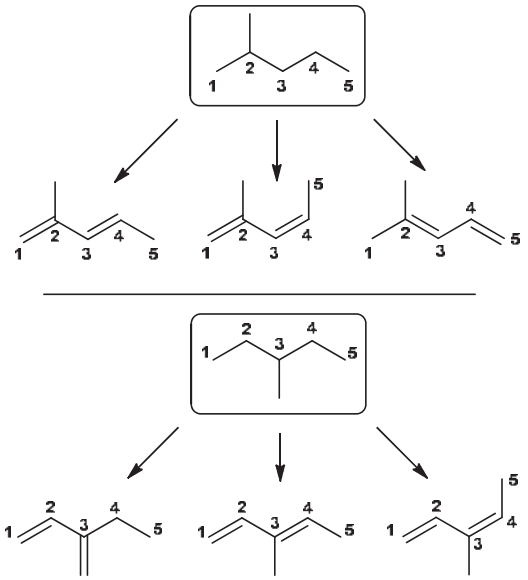
or the double bonds can be placed at C2 and C4 of the hexane skeleton, in which case each of the double bonds

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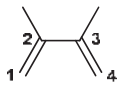
can either have the *E* or *Z* configuration, giving three more possible structures:



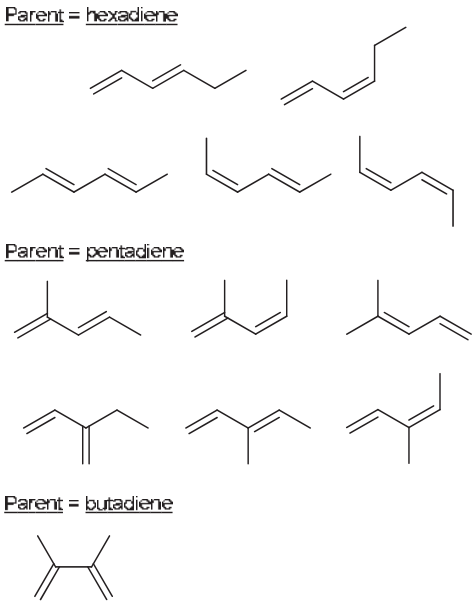
Next we move on to the skeletons that have only five carbon atoms in a linear chain, and for each of these skeletons, we consider all possible locations where the double bonds can be placed (including stereoisomers):



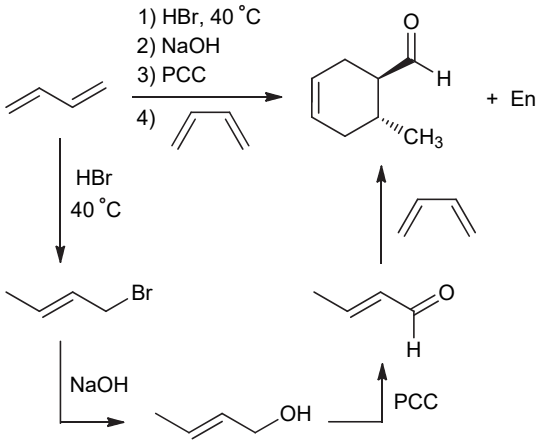
Next we move on to the skeletons that have only four carbon atoms in a linear chain. There are two such skeletons, and the first of them cannot accommodate two π bonds (without violating the octet rule by giving more the four bonds to a carbon atom). The other skeleton with only four carbon atoms in a linear chain CAN accommodate conjugated C=C bonds, but there is only such way, shown here:



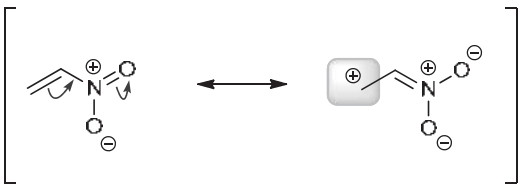
In summary, we have revealed twelve different conjugated dienes with the molecular formula C_6H_{10}, shown here:



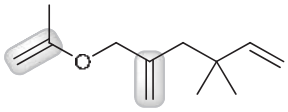
16.63. Treating 1,3-butadiene with HBr at elevated temperature gives the 1,4-adduct, which can be treated with sodium hydroxide to give an S_N2 process in which Br is replaced with a hydroxyl group. Oxidation with PCC (or DMP or Swern) converts the alcohol into an aldehyde, which can then be treated with another equivalent of 1,3-butadiene to give a Diels-Alder reaction that affords the product.



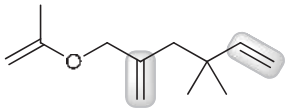
16.64. Nitroethylene should be more reactive than ethylene in a Diels–Alder reaction, because the nitro group is electron-withdrawing, via resonance:



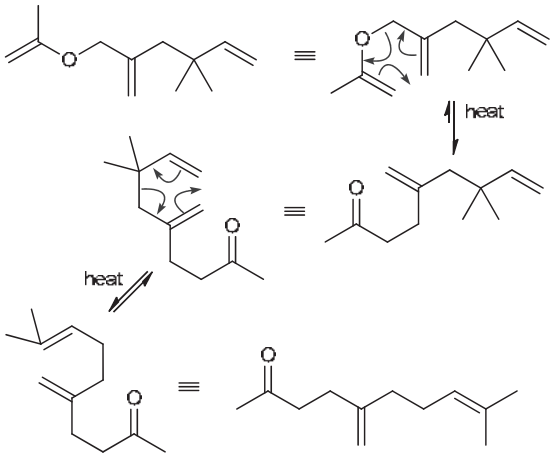
16.65. The starting material is an allylic vinylic ether, so it can undergo a Claisen rearrangement.



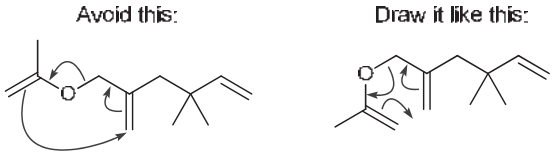
Alternatively, we also note that the starting material has two C=C bonds that are separated from each other by exactly three σ bonds, so it can undergo a Cope rearrangement:



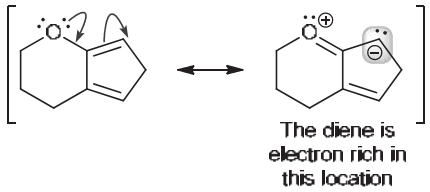
We will ultimately end up drawing both processes, and it does not matter the order in which we draw these two processes. Below, the Claisen rearrangement is drawn first, followed by the Cope rearrangement. If instead, the Cope rearrangement was drawn first, followed by the Claisen rearrangement, the same product would be obtained.



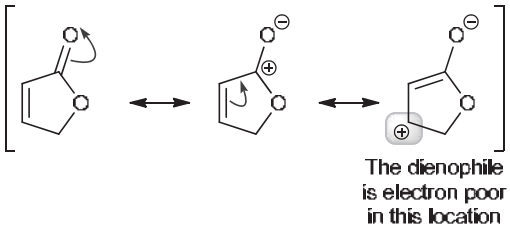
Note that for each of the sigmatropic processes above (the Claisen rearrangement and the Cope rearrangement), the compound is redrawn in such a way that enables us to clearly see the motion of the electrons that cause the reaction. You are likely to make a mistake if you try to draw the curved arrows without first redrawing the structure. That is, avoid doing this:



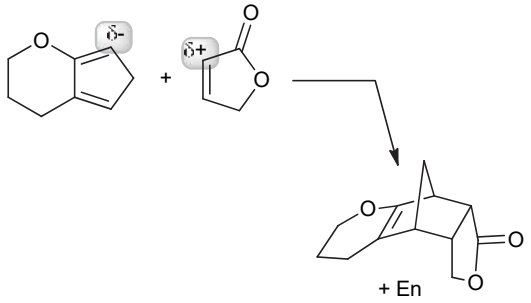
16.66. First we determine the regiochemical outcome. The diene is electron-rich, as seen in the second resonance structure below:



And the dienophile is electron-poor, as seen in the third resonance structure below:

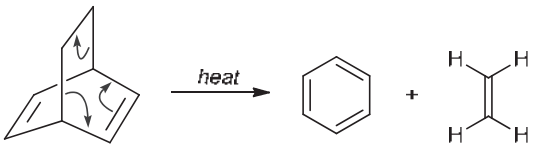


These two compounds will join in such a way that the electron-poor center lines up with the electron-rich center:

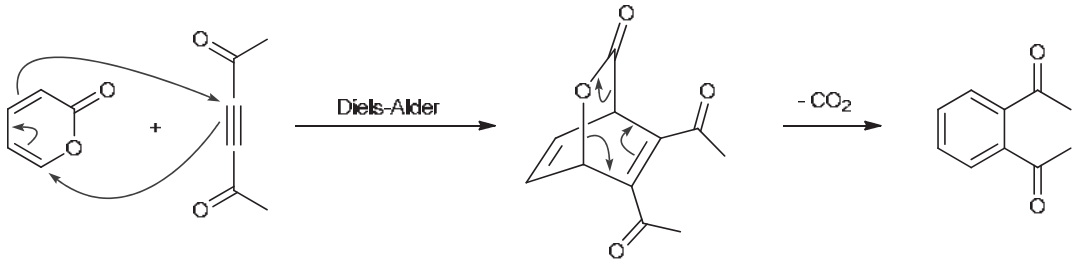


Notice that the endo product is obtained, rather than the exo product, as is expected for Diels-Alder reactions.

16.67. This transformation can be achieved via a retro Diels-Alder reaction (shown below), which requires elevated temperature, as described in Section 16.7.

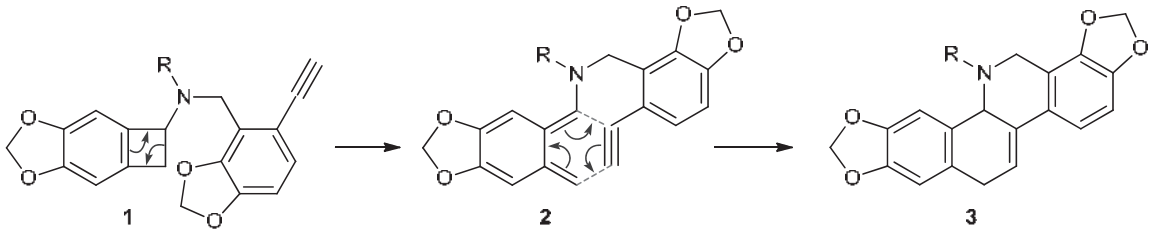


16.68. A Diels-Alder reaction, followed by a retro Diels-Alder reaction, can account for formation of the aromatic product, as shown here:

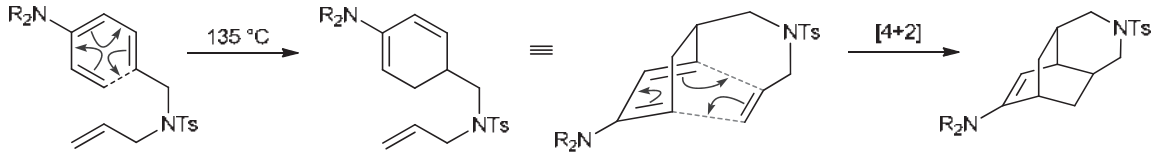


16.69. The nitrogen atom in divinyl amine is sp^2 hybridized. The lone pair is delocalized, and joins the two neighboring π bonds into one conjugated system. As such, the compound absorbs light above 200 nm (UV light). In contrast, 1,4-pentadiene has two isolated double bonds and therefore does not absorb UV light in the region between 200 and 400 nm.

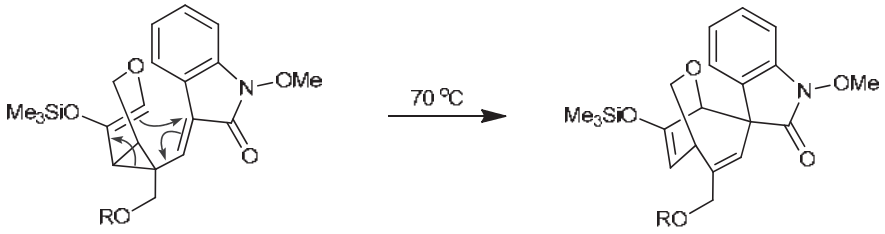
16.70. Notice that compound **1** contains a strained, four-membered ring. When this compound is heated to 120 °C, it will undergo a thermal electrocyclic reaction to form compound **2**, which possesses significantly less ring strain. The newly generated diene can then undergo a thermal, intramolecular Diels-Alder reaction with the alkyne, re-establishing aromaticity, and forming the hexacyclic product.



16.71. The first step involves a 6-π electrocyclic reaction that closes the first ring to form a cyclohexadiene. When this intermediate is redrawn, we can clearly see that the pendant alkene is in close enough proximity with the newly generated diene to induce an intramolecular [4+2] Diels-Alder cycloaddition, which will result in the formation of the tricyclic product.

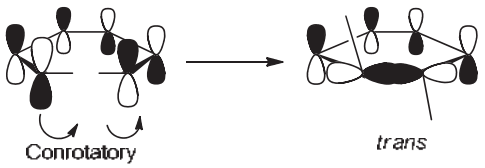


16.72. The divinylcyclopropane unit is converted to a cycloheptadiene in this 3,3-sigmatropic rearrangement. Interestingly, this rearrangement also opens one ring (cyclopropane) and forms a new ring (cycloheptadiene).

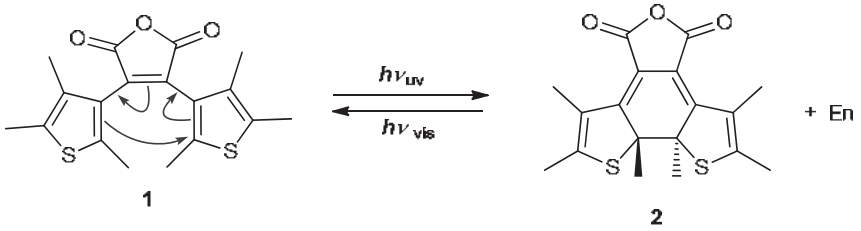


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16.73. Compound **1** undergoes an electrocyclic reaction involving 6π-electrons. The reaction occurs with light, rather than heat, so we expect ring-closure to occur in a conrotatory fashion:

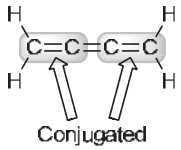


We therefore expect the two methyl groups to be *trans* to each other in the product:



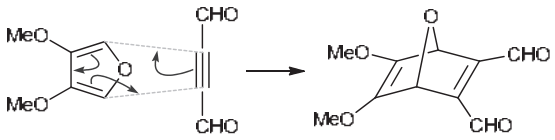
Compound **2** has rotational symmetry, but it lacks reflectional symmetry (see Section 5.6). As such, it is chiral, in much the same way that *trans*-1,2-dimethylcyclohexane is chiral.

16.74. Recall that two double bonds are conjugated if they are separated from each other by exactly one sigma bond (no more and no less). The double bonds at the periphery are separated by a C-C bond that has one sigma bond and one pi bond. Therefore, these two double bonds are conjugated:

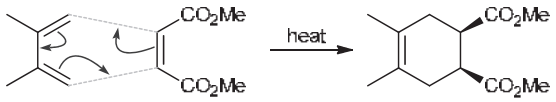


The central double bond is not conjugated to either of the other double bonds, because there is no sigma bond separating them. Therefore, the correct answer is (c).

16.75. A Diels-Alder reaction would be ideal to prepare the target. The product is a substituted cyclohexadiene (rather than a substituted cyclohexene), so the dienophile must be a disubstituted alkyne, rather than a disubstituted alkene. The correct answer is (d):

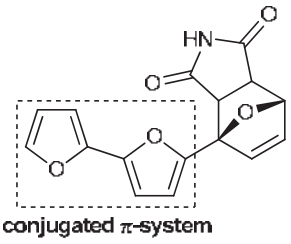


16.76. This is a Diels-Alder reaction. We begin by redrawing the diene in its *s*-cis conformation, and aligning it with the dienophile, as shown here:



The correct answer is (b). Note that the *cis* relationship of the ester groups is maintained in the product.

16.77. Oligofurans are highly conjugated materials. When treated with maleimide, only one product results – the [4+2] addition to the terminal furan. Notice that this product is still conjugated – there are two furans that share resonance stabilization.

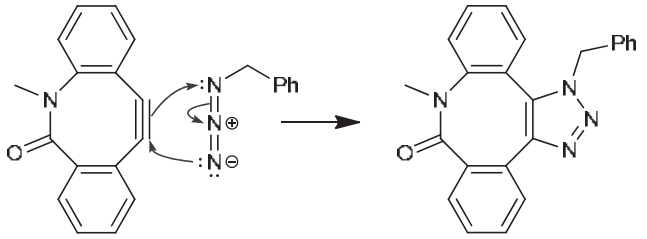


If the internal furan were to react, the conjugation between furans would be broken, leaving behind two isolated furans. This molecule would be much higher in energy because of the loss of conjugation. Since the product distribution of a Diels-Alder reaction is determined by thermodynamic considerations, the higher energy product is not obtained.

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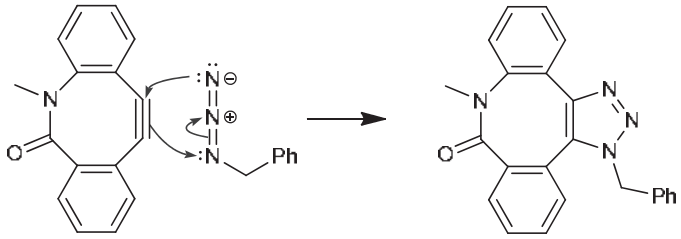
16.78.

(a) The reaction is a cycloaddition process, so we expect a concerted process. The following curved arrows represent a concerted process that would give the product:



A B

(b) Depending on the relative orientation of the azide and alkyne during the reaction, the following compound can also be formed.

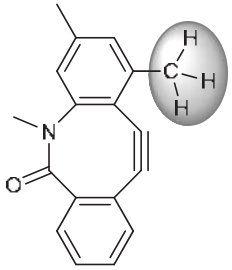


A C

(c) Recall from Chapter 9 that the smallest isolatable cycloalkyne is cyclooctyne, which experiences significant angle strain due to the incorporation of the two adjacent *sp* hybridized carbon atoms (that should have linear geometry) into an 8-membered ring. As such, compound **A** has significant angle strain. We can infer that this strain plays an important role in the click reaction, because alkyne **D** (which is free of this strain) is unreactive under these conditions. This angle strain increases the energy of the starting alkyne, thus decreasing the activation energy of the reaction (since it is now closer in energy to the transition state). Considering the geometry of the atoms involved in the reaction, the angle strain forces the alkyne to have bond angles closer to the angles required in the transition state leading to the sp^2 hybridized carbon atoms in the product. In other words, there is a higher activation energy associated with distorting an unstrained alkyne (180°) to an alkene (120°), compared to the analogous conversion of a strained alkyne (<180°) to an alkene (120°).

Alkyne **E** is less reactive because the non-alkyne atoms in the ring are all sp^3 hybridized; this eases some of the angle strain due to their relative conformational flexibility. The multiple sp^2 hybridized atoms in the ring of alkyne **A** increase the strain on the alkyne, thus increasing the reaction rate.

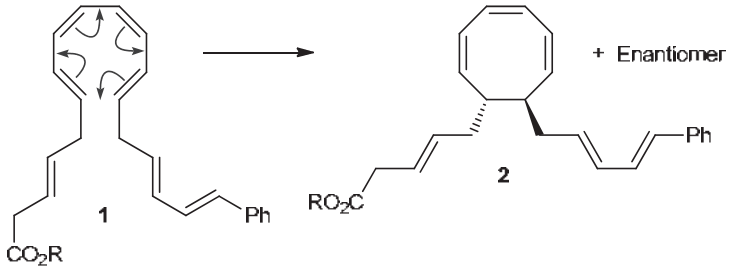
Alkyne **F** is less reactive because one of the methyl groups (on the aromatic ring) sterically hinders the approach of the benzyl azide.



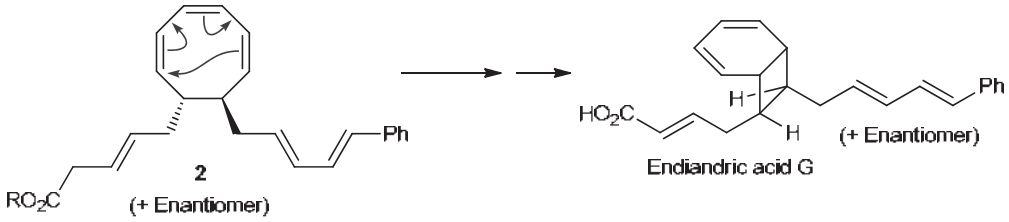
16.79.

(a) The following electrocyclic reaction will produce an eight-membered ring. Since the reaction involves eight π electrons, under thermal conditions, we expect conrotatory ring-closure, producing the *trans*-configuration seen in compound **2**. This ring-closing reaction can occur if either: (1) both ends of the forming ring rotate clockwise, or 2) both ends rotate counter-clockwise. These two possibilities can occur with equal likelihood, resulting in a racemic mixture of compound **2**.

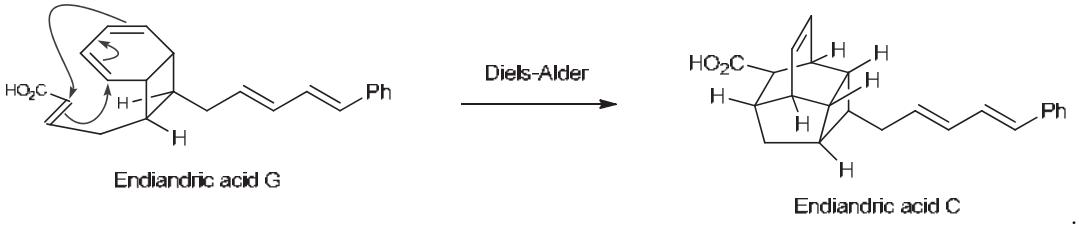
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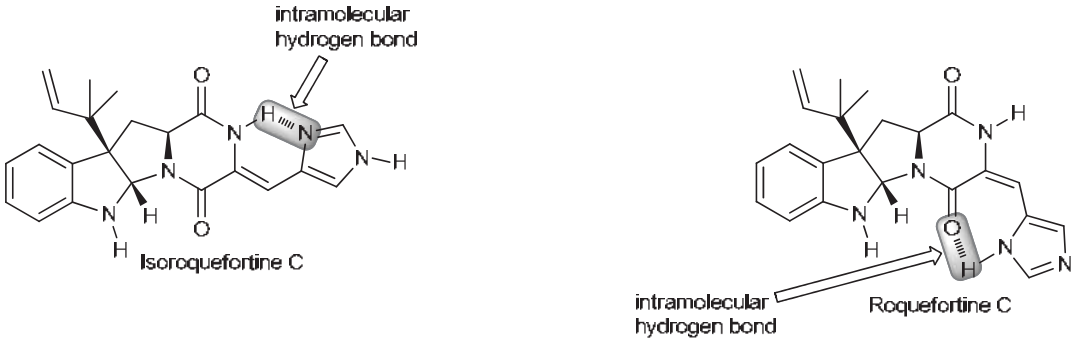
(b) The conversion of compound **2** to endiandric acid G occurs via an electrocyclic reaction involving six π electrons.



(c) Endiandric acid G contains two diene groups, but only one of them is in close proximity with the dienophile. An intramolecular Diels-Alder reaction, as shown below, gives endiandric acid C:

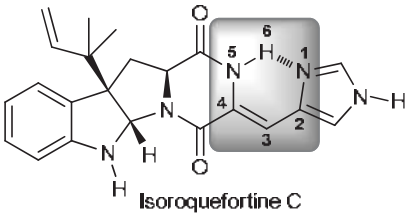


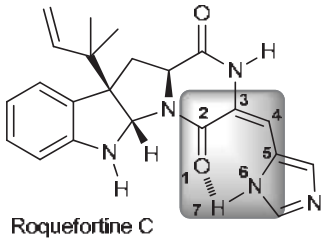
16.80. Both compounds exhibit intramolecular hydrogen bonding interactions, as shown below:



However, the hydrogen bonding interaction in isoroquefortine C involves a "ring" comprised of six atoms, while the hydrogen bonding interaction in roquefortine C involves a "ring" comprised of seven atoms.

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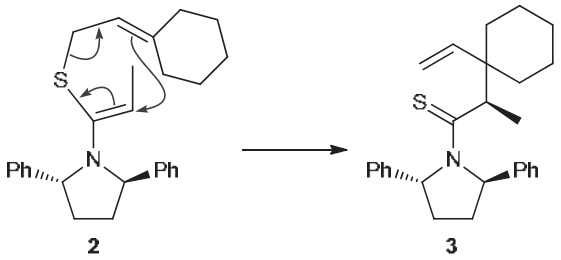


Both are expected to prefer a coplanar arrangement of all atoms in the "ring," because any deviations from coplanarity will diminish the stabilizing effect of conjugation. If confined to a coplanar arrangement, roquefortine C will have a more difficult time adopting the ideal bond angles for sp^2 hybridized centers (120°), because there are seven atoms in the "ring" rather than six. In contrast, isoroquefortine C (with its six atoms in the "ring") will not experience as much strain as it attempts to adopt the ideal bond angles in a coplanar arrangement. Deviation from the ideal bond angles or from coplanarity will cause an increase in energy. While both compounds will deviate (to a certain extent) from the ideal bond angles and from coplanarity, the deviation is expected to be more significant for roquefortine C. Therefore, roquefortine C is higher in energy than isoroquefortine C.

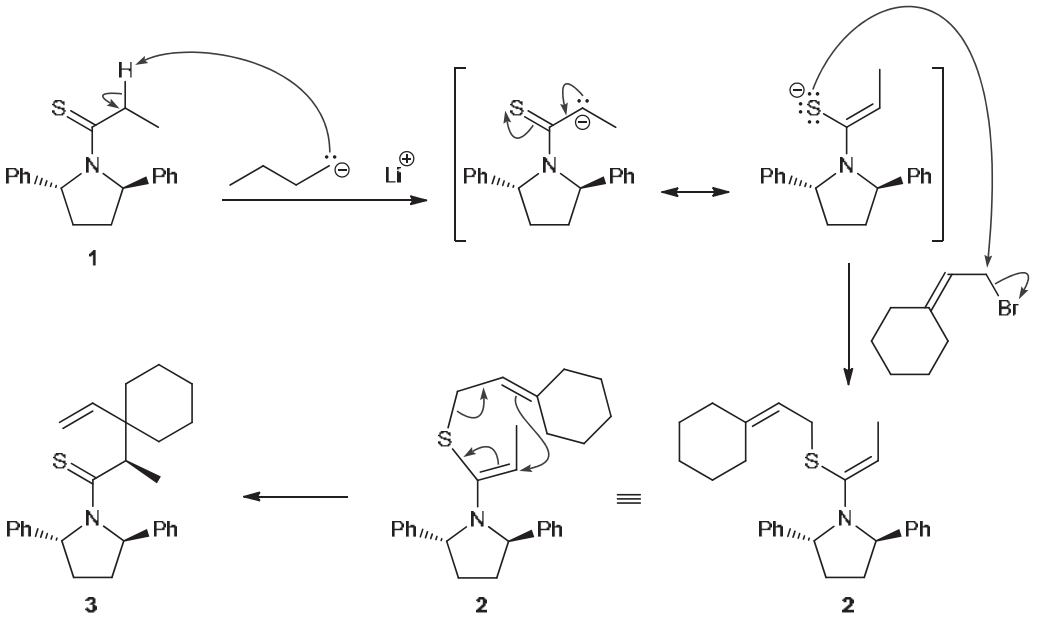
This explanation is verified by the experimentally determined bond angles for roquefortine C (largest bond angle is 134°) and isoroquefortine C (largest bond angle is 127°).

16.81.

(a) The problem statement indicates that compound **3** is formed from a thio-Claisen rearrangement of compound **2**. This allows us to determine the structure of compound **2,** as shown below (notice that the carbon-carbon π bond is shown in the *Z* configuration, as indicated in the problem statement):

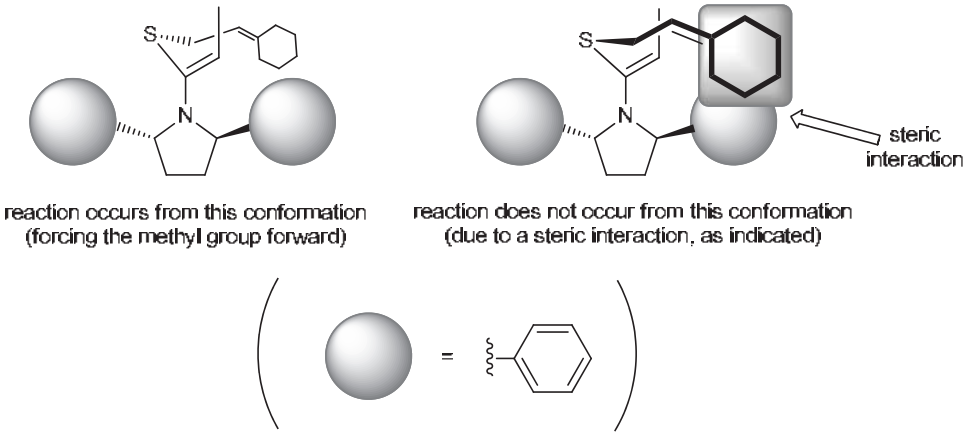


(b) Butyl lithium is a strong base, which removes the most acidic proton from compound **1**, generating a resonance-stabilized anion. This anion can then function as a nucleophile and attack the alkyl bromide in an S_N2 reaction, generating compound **2**, which then undergoes a thio-Claisen rearrangement to afford compound **3**:



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(c) The existing chiral centers have an influence on the stereochemical outcome of this reaction. Specifically, one of the phenyl groups provides steric hindrance that forces the reaction to occur in a stereospecific manner, so that the phenyl group and the cyclohexyl group remain far apart from one other:



The reaction will proceed via the lowest energy transition state, which is most likely achieved from the first conformation above, rather than from the second conformation, in which there is a large steric interaction (highlighted).

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Chapter 17
Aromatic Compounds

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 17. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

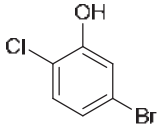
- When a benzene ring is a substituent, it is called a _____ **group**.
- Disubstituted derivatives of benzene can be differentiated by the use of the descriptors _____, ***meta*** and _____**,** or by the use of locants.
- Benzene is comprised of a ring of six identical C-C bonds, each of which has a bond order of _____.
- The **stabilization energy** of benzene can be measured by comparing _____ of hydrogenation.
- The stability of benzene can be explained with MO theory. The six π electrons all occupy _____ MOs.
- The presence of a fully conjugated ring of π electrons is not the sole requirement for aromaticity. The requirement for an odd number of electron pairs is called _____ **rule**.
- **Frost circles** accurately predict the relative energy levels of the _____ in a conjugated ring system.
- A compound is aromatic if it contains a ring comprised of _____ _____ and if it has a _____ number of π electrons in the ring.
- Compounds that fail the first criterion are called _____.
- Compounds that satisfy the first criterion, but have 4n electrons (rather than 4*n*+2) are _____.
- Cyclic compounds containing heteroatoms, such as S, N, O, are called _____.
- Any carbon atom attached directly to a benzene ring is called a _____ **position**.
- Alkyl benzenes are oxidized at the benzylic position by _____ or _____.
- In a **Birch reduction**, the aromatic moiety is reduced to give a nonconjugated diene. The carbon atom connected to _____ is not reduced, while the carbon atom connected to _____ is reduced.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 17. The answers appear in the section entitled *SkillBuilder Review*.

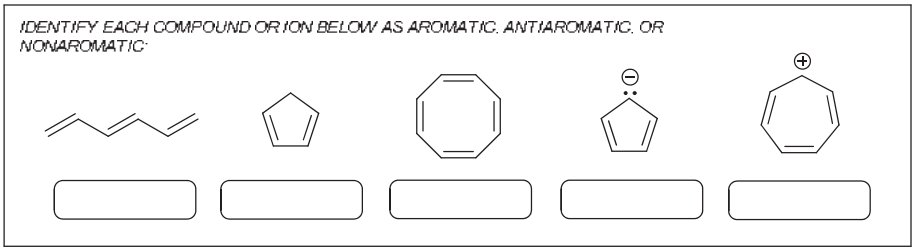
17.1 Naming a Polysubstituted Benzene

PROVIDE A SYSTEMATIC NAME FOR THE FOLLOWING COMPOUND

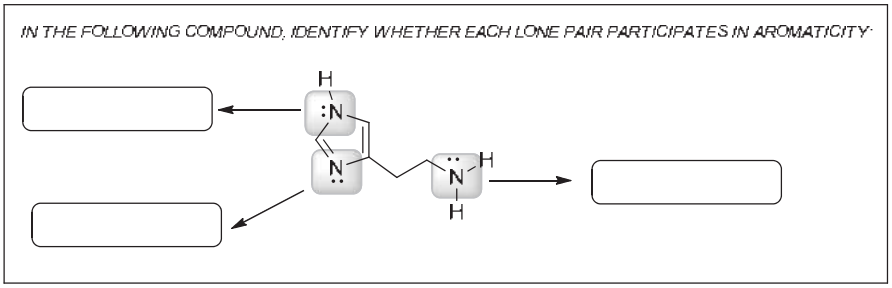


1) IDENTIFY THE PARENT
2) IDENTIFY AND NAME SUBSTITUENTS
3) ASSIGN LOCANTS TO EACH SUBSTITUENT
4) ALPHABETIZE

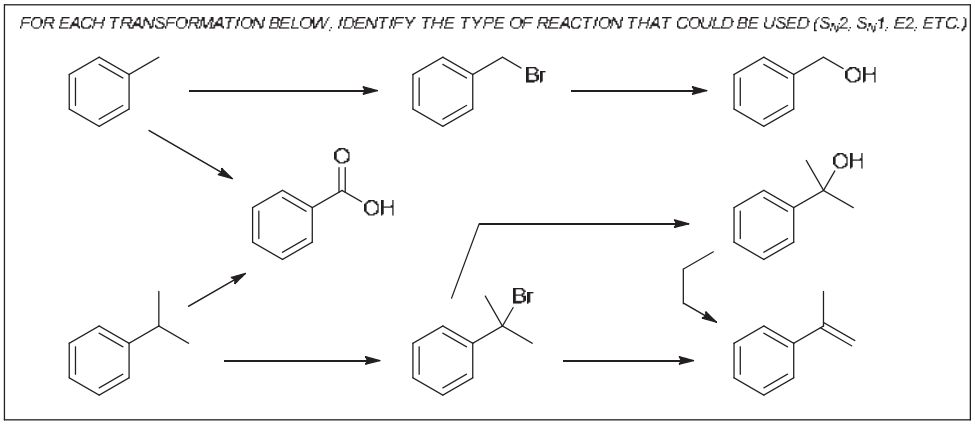
17.2 Determining Whether a Structure is Aromatic, Nonaromatic, or Antiaromatic



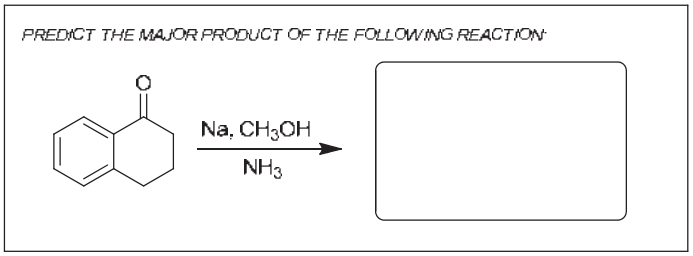
17.3 Determining Whether a Lone Pair Participates in Aromaticity



17.4 Manipulating the Side Chain of an Aromatic Compound



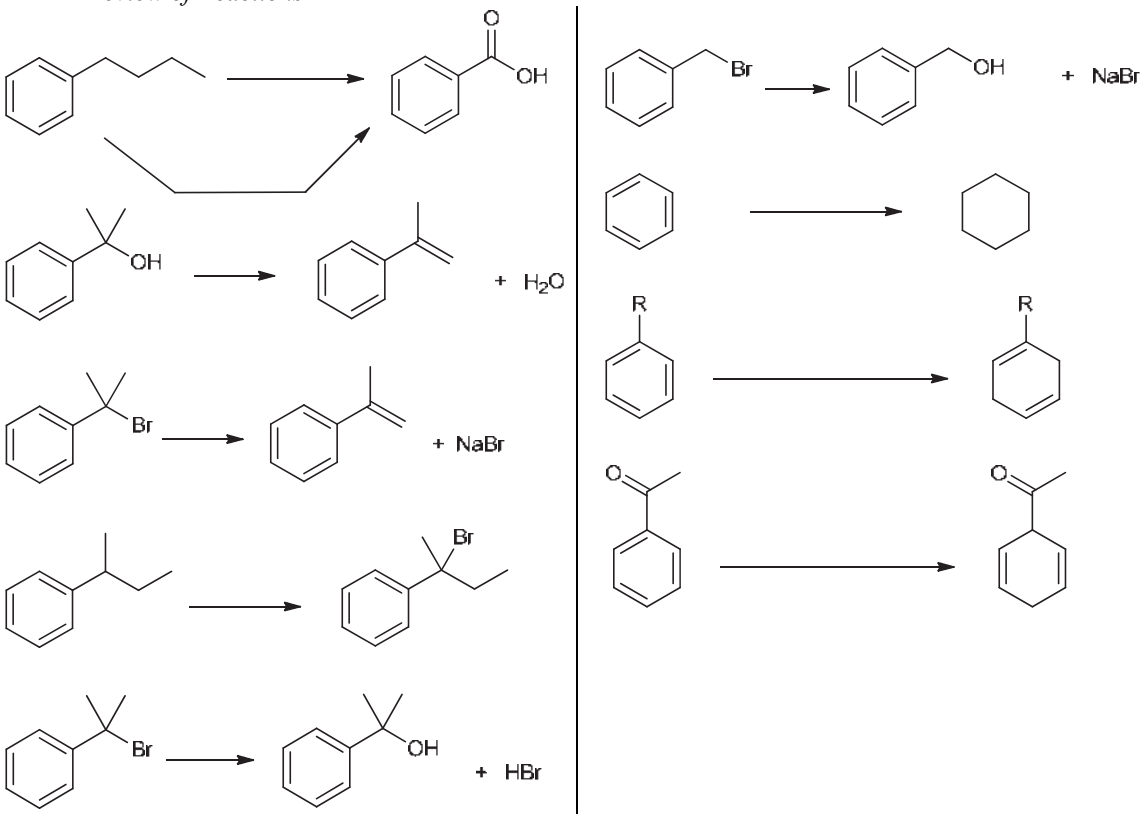
17.5 Predicting the Product of a Birch Reduction



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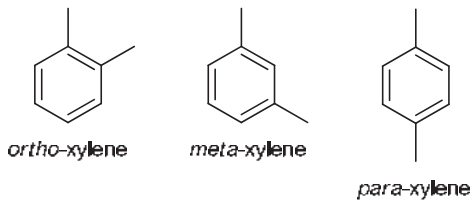
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 17. The answers appear in the section entitled *Review of Reactions*.



Mistakes to Avoid

When analyzing an NMR spectrum (^{1}H or ^{13}C), we must always consider the role of symmetry in affecting the number of signals in the spectrum. For example, consider the number of signals in the ^{1}H NMR spectrum of each of the following constitutional isomers:



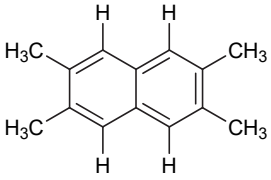
Each of these compounds exhibits a different number of signals in its ^{1}H NMR spectrum (3 signals, 4 signals, and 2 signals, respectively). Similarly, each of these compounds exhibits a different number of signals in its ^{13}C NMR spectrum (4 signals, 5 signals, and 3 signals, respectively).

When analyzing an NMR spectrum of an aromatic compound, always make sure that the substitution pattern (i.e. monosubstituted, *ortho*-disubstituted, etc.) is fully consistent with all signals in the spectrum (taking symmetry into account). When doing so, avoid being distracted by the positions of the double bonds. After all, the π electrons are delocalized, and there are resonance structures in which the double bonds are drawn in different locations. The best way to avoid being distracted is to draw a circle to represent the aromatic ring, like this:

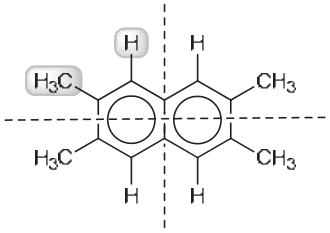


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To see the value of this approach, consider the following structure and determine how many signals are expected in the ^{1}H NMR and ^{13}C NMR spectra of this compound:

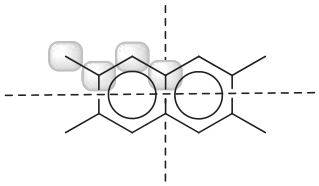


By redrawing the structure with circles to represent aromatic rings (rather than alternating single and double bonds), it becomes easier to see that there are only two unique kinds of protons in this structure (highlighted below):



This compound will have only two signals in its ^{1}H NMR spectrum.

Similarly, the compound will have only four signals in its ^{13}C NMR spectrum:



Throughout the solutions presented in this chapter, we will often represent aromatic rings with circles (particularly when symmetry is relevant to the discussion).

Useful reagents

The following is a list of reagents encountered in this chapter, as well as their specific function in the context of this chapter:

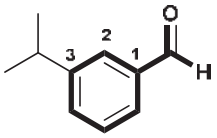
Reagents	Description
$Na_2Cr_2O_7$, H_2SO_4, H_2O	Sodium dichromate and sulfuric acid give chromic acid, which is a strong oxidizing agent that can be used to oxidize a benzylic position, provided that the benzylic position has at least one benzylic proton. The alkyl group (connected to the aromatic ring) is converted into a carboxylic acid group.
1) $KMnO_4$, H_2O, heat 2) H_3O^+	Potassium permanganate. A strong oxidizing agent that can be used to oxidize a benzylic position, provided that the benzylic position has at least one benzylic proton. The alkyl group (connected to the aromatic ring) is converted into a carboxylic acid group.
NBS, heat	N-Bromosuccinimide. A reagent that is used for radical bromination at the benzylic position.
H_2O	Water is a weak nucleophile that can be used in an S_N1 reaction with a benzylic halide.
NaOH	Hydroxide is a strong nucleophile that can be used in an S_N2 reaction with a primary benzylic halide.
conc. H_2SO_4	A strong acid that can be used to achieve acid-catalyzed dehydration to give an alkene.
NaOEt	Sodium ethoxide is a strong base that can be used to convert secondary or tertiary halides into alkenes (via an E2 process)
$3H_2$, 100 atm, 150 ºC	Conditions for complete hydrogenation of benzene to give cyclohexane.
Na, CH_3OH, NH_3	Reagents for a Birch reduction, which reduces a benzene ring to give a 1,4-cyclohexadiene ring.

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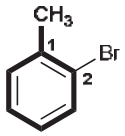
Solutions

17.1.

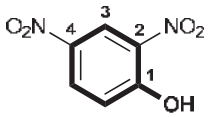
(a) The parent is benzaldehyde, shown in bold. An isopropyl group is located at C3 (also called the *meta* position), so the compound is 3-isopropylbenzaldehyde, (also called *meta*-isopropylbenzaldehyde):



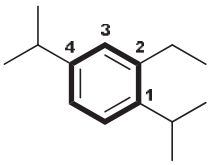
(b) The parent is toluene, shown in bold. A bromo group is located at C2 (also called the *ortho* position), so the compound is 2-bromotoluene (also called *ortho*-bromotoluene):



(c) The parent is phenol, shown in bold. Two nitro groups are located at C2 and C4, so the compound is called 2,4-dinitrophenol:

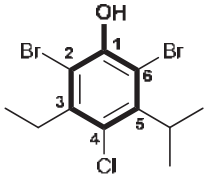


(d) The parent is benzene, shown in bold. There are three substituents (two isopropyl groups and one ethyl group). The assignment of locants, shown below, achieves the lowest numbers for all three substituents:



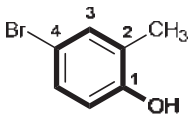
Therefore, the name of the compound is:
2-ethyl-1,4-diisopropylbenzene

(e) The parent is phenol, shown in bold. The substituents are each named and assigned a locant, as shown below. The locants start at the carbon atom connected to the OH group, and are then assigned counter-clockwise. This way, the ethyl group ("e") is assigned a lower locant than the isopropyl group ("i"), since there are no other differentiating factors that would allow us to decide which way to assign the locants.

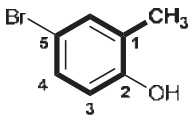


2,6-dibromo-4-chloro-3-ethyl-5-isopropylphenol

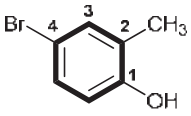
17.2. When naming this compound, there are three choices for the parent. The compound can be named as a disubstituted phenol, as a disubstituted toluene, or as a trisubstituted benzene. For each of these possibilities, the assignment of locants is shown:



Parent = phenol



Parent = toluene



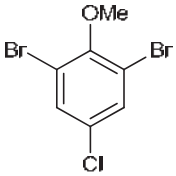
Parent = benzene

This gives the following three possible names:

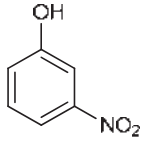
(a) 4-bromo-2-methylphenol
(b) 5-bromo-2-hydroxytoluene
(c) 4-bromo-1-hydroxy-2-methylbenzene

17.3.

(a) The parent is anisole (methoxybenzene), and there are three other substituents (Br, Br, and Cl), in the following locations:



(b) The parent is phenol (hydroxybenzene), and there is one nitro group, located at C3 (the *meta* position):

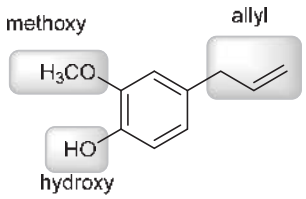


17.4. When naming this compound, there are three choices for the parent. The compound can be named as a disubstituted benzene, as a monosubstituted toluene, or as xylene. This gives the following possible names, all of which are acceptable IUPAC names:

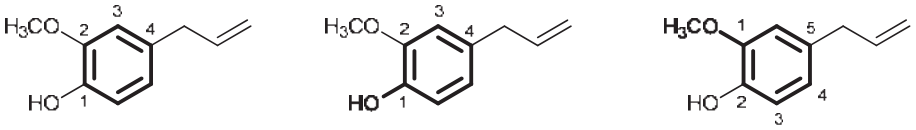
(a) *meta*-xylene
(b) *meta*-dimethylbenzene
(c) 1,3-dimethylbenzene
(d) *meta*-methyltoluene
(e) 3-methyltoluene

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17.5.
(a) Eugenol contains three substituents: an allyl group, a hydroxy group, and a methoxy group.

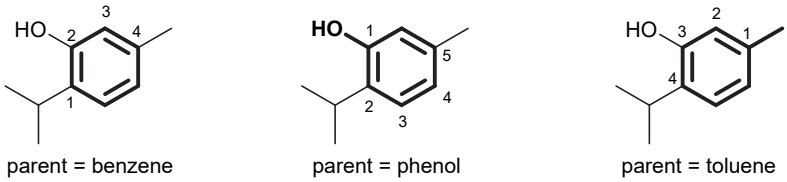


All benzene derivatives can be named with benzene as the parent. In this case, the parent could also be either phenol (hydroxybenzene) or anisole (methoxybenzene). So there are three choices for the parent. For each possibility, the assignment of locants is shown by numbering to give the lowest possible number to each consecutive substituent:



The last step is to arrange the substituents alphabetically so the three names for eugenol are as follows:
As a benzene derivative: 4-allyl-1-hydroxy-2-methoxybenzene
As a phenol derivative: 4-allyl-2-methoxyphenol
As an anisole derivative: 5-allyl-2-hydroxyanisole

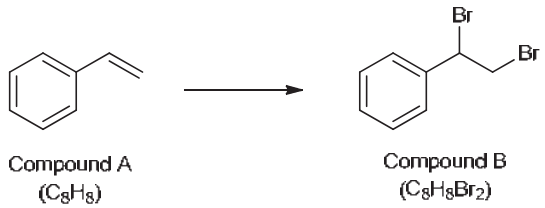
Thymol contains three substituents as well: a methyl group, a hydroxy group, and an isopropyl group. Each can be named based on benzene, phenol, or toluene as the parent. These possibilities are shown below, with the corresponding locants shown:



Arranging the substituents we obtain the following three possible IUPAC names:
As a benzene derivative: 2-hydroxy-1-isopropyl-4-methylbenzene
As a phenol derivative: 2-isopropyl-5-hydroxyphenol
As a toluene derivative: 3-hydroxy-4-isopropyltoluene

(b) This name violates two of the rules for naming polysubstituted aromatic compounds. First, the substituents are not listed alphabetically. Second, if named with benzene as the parent, the methyl group needs to have the first locant in order to minimize the number of the third locant. Thus, a correct name would be 2-hydroxy-4-isopropyl-1-methylbenzene.

17.6. The molecular formula (C_8H_8) indicates five degrees of unsaturation (see Section 14.16), four of which are accounted for by the aromatic ring, so the structure must also contain either a ring or a double bond (in addition to the aromatic ring). If compound **A** undergoes bromination to produce a dibromide, then it must contain a C=C double bond (outside of the aromatic ring, which does not react with Br_2). This C=C double bond accounts for the last degree of unsaturation, described above. The structure of compound **A,** as well as the structure of the resulting dibromide (compound **B**) are shown here:

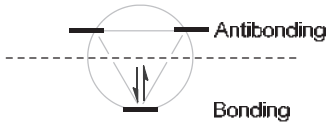


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17.7.
(a) According to Figure 17.1, the conversion from cyclohexane to cyclohexene is uphill in energy (ΔH has a positive value).
(b) According to Figure 17.1, the conversion from cyclohexene to benzene is uphill in energy (ΔH has a positive value).
(c) According to Figure 17.1, the conversion from cyclohexadiene to benzene is downhill in energy (ΔH has a negative value).

17.8.
(a) This compound has six π bonds, for a total of twelve π electrons. Twelve is not a Hückel number, so the compound is not expected to be aromatic.
(b) This compound has seven π bonds, for a total of fourteen π electrons. Fourteen is a Hückel number. In Section 17.5, we saw that [14]annulene is somewhat destabilized by a steric interaction between the hydrogen atoms positioned inside the ring. Although [14]annulene is nonplanar, it does indeed exhibit aromatic stabilization, because the deviation from planarity is not too great.
(c) This compound has eight π bonds, for a total of sixteen π electrons. Sixteen is not a Hückel number, so the compound is not expected to be aromatic.

17.9. We draw a circle and inscribe a triangle inside the circle, with one of the points of the triangle at the bottom of the circle. Each location where the triangle touches the circle represents an energy level. The energy level on the bottom of the circle is a bonding MO, and the two energy levels on top are antibonding MOs. The structure has two π electrons, which both occupy the bonding MO. This Frost circle indicates that there is only one bonding MO and it is filled, while the antibonding MOs are empty. This structure is expected to exhibit aromatic stabilization.



17.10. This structure exhibits a ring of continuously overlapping *p* orbitals, and there are 22 π electrons (a Hückel number). Therefore, the compound is expected to exhibit aromatic stabilization.

17.11.
(a) This structure exhibits a ring of continuously overlapping *p* orbitals, but there are four π electrons, rendering the structure antiaromatic. This anion is expected to be very high in energy (very unstable).
(b) This structure exhibits a ring of continuously overlapping *p* orbitals (C+ represents a carbon atom with an empty *p* orbital), and there are two π electrons, rendering the structure aromatic.
(c) This structure exhibits a ring of continuously overlapping *p* orbitals, but there are four π electrons, rendering the structure antiaromatic.
(d) This structure exhibits a ring of continuously overlapping *p* orbitals (the lone pair occupies a *p* orbital because it is resonance stabilized). There are ten π electrons, rendering the structure aromatic.

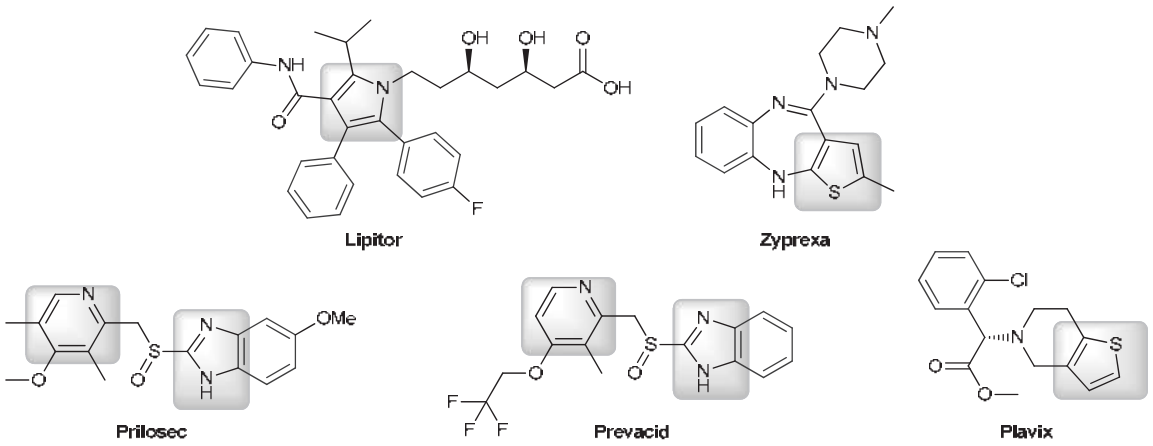
17.12. In order to predict whether this dianion is aromatic, we must determine if the following two criteria have been met:
1. Does the compound contain a ring comprised of continuously overlapping *p* orbitals?
2. Is there a Hückel number of π electrons in the ring?

The lone pairs can occupy *p* orbitals providing for continuous overlap of *p* orbitals around the ring, so the first criterion has been met. To determine if the second criterion has been met, we must count the number of π electrons. Each π bond counts as two electrons, and each lone pair counts as two electrons, for a total of 10 π electrons. Ten is a Hückel number, so the dianion is aromatic. All ten π electrons are thus completely delocalized around the eight-membered ring.

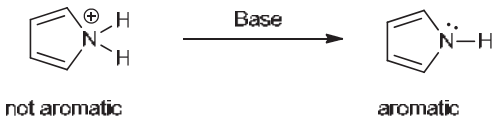
17.13.
(a) One of the lone pairs occupies a *p* orbital, thereby rendering the compound aromatic (six π electrons). The other lone pair will occupy an sp^2 hybridized orbital, in the plane of the ring, extending away from the ring.
(b) One of the lone pairs occupies a *p* orbital, thereby rendering the compound aromatic (six π electrons). The other lone pair will occupy an sp^2 hybridized orbital, in the plane of the ring, extending away from the ring.
(c) If the lone pair were to occupy a *p* orbital, there would be a continuous system of overlapping *p* orbitals with eight π electrons (antiaromatic). To avoid the instability associated with antiaromaticity, the lone pair is expected to occupy an sp^3 hybridized orbital.
(d) One of the lone pairs on the sulfur atom occupies a *p* orbital, thereby rendering the compound aromatic (six π electrons). The lone pair on the nitrogen atom occupies an sp^2 hybridized orbital that is in the plane of the ring (because the nitrogen atom is already using a *p* orbital to establish aromaticity).
(e) There is only one lone pair (on oxygen) and it is not participating in aromaticity. That oxygen atom is already using a *p* orbital to establish aromaticity.
(f) Each nitrogen atom has one lone pair, and neither is participating in aromaticity. In each case, the nitrogen atom is already using a *p* orbital to establish aromaticity.
(g) The compound is not aromatic. In order to achieve a continuous system of overlapping *p* orbitals, each oxygen atom would need to contribute a lone pair in a *p* orbital, and that would give 8 π electrons (not a Hückel number).
(h) One of the lone pairs on the oxygen atom occupies a *p* orbital, thereby rendering the compound aromatic (six π electrons). The lone pair on the nitrogen atom occupies an sp^2 hybridized orbital that is in the plane of the ring (because the nitrogen atom is already using a *p* orbital to establish aromaticity).

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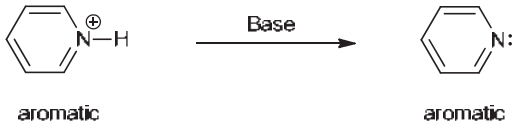
17.14. In addition to the aromatic rings indicated in the structures of the best-selling drugs (Section 17.1), each of the highlighted rings also has a continuous system of overlapping *p* orbitals, with six π electrons, and is therefore aromatic:



17.15. The first compound is expected to be more acidic (has a lower pK_a), because deprotonation restores aromaticity to the ring.

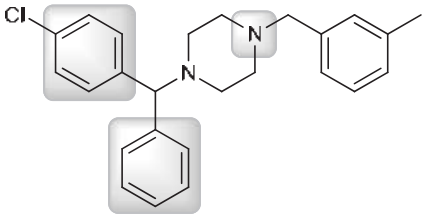


The second compound is already aromatic, even before deprotonation.



In this case, the driving force for losing the proton is not as great.

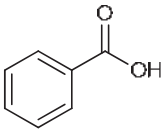
17.16.
(a) Yes, it has the required pharmacophore (two aromatic rings separated by one carbon atom, and a tertiary amine).



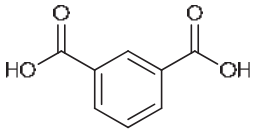
(b) Meclizine is mostly nonpolar, so it crosses the blood-brain barrier and binds with receptors in the central nervous system, causing sedation.

(c) Introduce polar functional groups (such as OH groups or COOH groups) that reduce the ability of the compound to cross the blood-brain barrier.

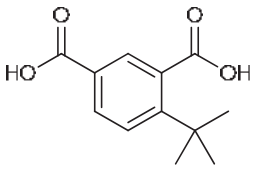
17.17.
(a) The benzylic position undergoes oxidation, giving a carboxylic acid:



(b) Each of the benzylic positions undergoes oxidation. Notice that oxidation of the ethyl group involves cleavage of a C-C bond to give a diacid with one less carbon atom than the starting material.



(c) There are three benzylic positions, but one of these positions (the *tert*-butyl group) lacks a benzylic proton, and as such, that position does not undergo oxidation. The other two benzylic positions undergo oxidation, giving the following diacid.



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17.18.

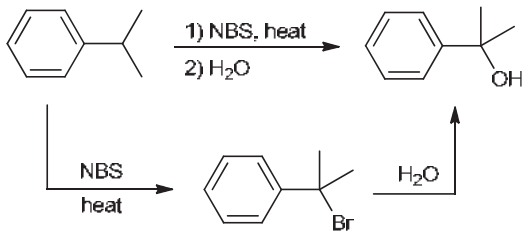
(a) There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

In this case, there is no change in the carbon skeleton:



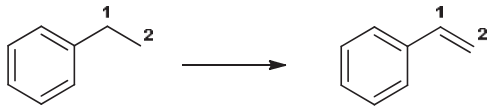
but there is a change in the functional group. Specifically, an OH group must be installed in the benzylic position. We did not encounter a one-step method for achieving this transformation. However, we can achieve the desired transformation in two steps (bromination at the benzylic position, followed by an S_N1 process in which water is used as a nucleophile).



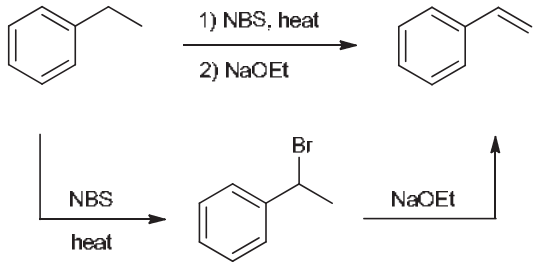
(b) There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

In this case, there is no change in the carbon skeleton.



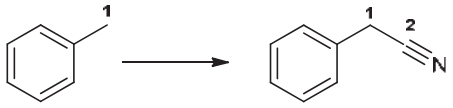
but there is a change in the functional group. Specifically, a π bond must be installed. We did not encounter a one-step method for achieving this transformation. However, we can achieve the desired transformation in two steps:
1) bromination at the benzylic position, followed by
2) elimination (E2) upon treatment with a strong base, such as sodium ethoxide:



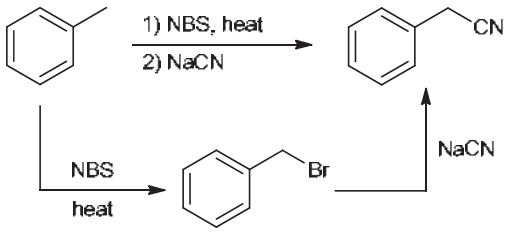
(c) There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

In this case, there is a change in the carbon skeleton. The product has one more carbon atom than the starting material:



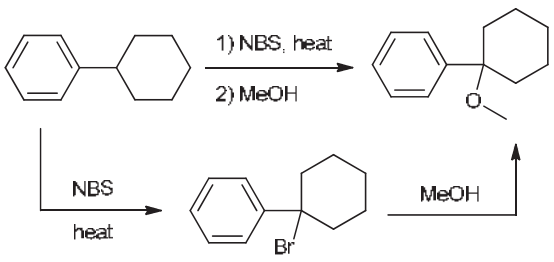
Also, a functional group (cyano group) must be installed at the benzylic position. We did not encounter a one-step method for achieving this transformation. However, we can achieve the desired transformation in two steps:
1) bromination at the benzylic position, followed by
2) substitution (S_N2), in which a cyanide ion functions as the nucleophile:



(d) There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

In this case, there is no change in the carbon skeleton, but there is a change in the functional group. Specifically, a methoxy group (OMe) must be installed in the benzylic position. We did not encounter a one-step method for achieving this transformation. However, we can achieve the desired transformation in two steps:
1) bromination at the benzylic position, followed by
2) substitution (S_N1), in which methanol functions as the nucleophile:

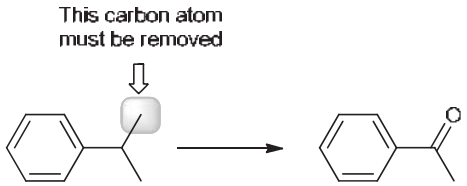


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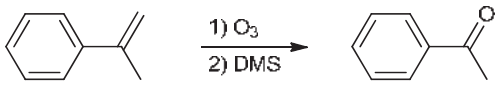
(e) There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

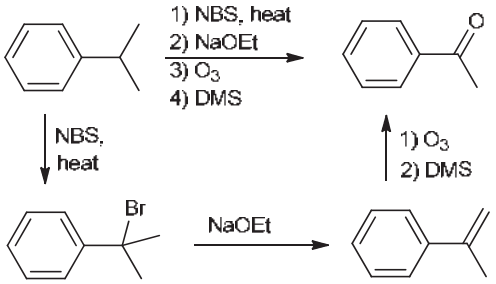
In this case, there is a change in the carbon skeleton. The product has one less carbon atom than the starting material:



Also, a functional group (a C=O bond) must be installed. Let's begin with the change in the carbon skeleton. We have only learned one way (ozonolysis) to remove a carbon atom from the carbon skeleton. Ozonolysis would indeed install the necessary functional group in the correct location:



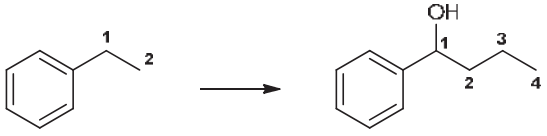
This strategy requires that we first form the alkene above, which can be accomplished via bromination of the benzylic position, followed by elimination (E2) upon treatment with a strong base (such as sodium ethoxide):



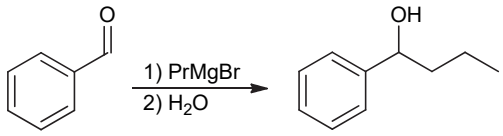
(f) There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

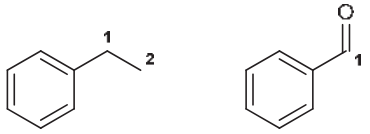
In this case, there is a change in the carbon skeleton. The product has two additional carbon atoms that are absent in the starting material:



Also, a functional group (an OH group) must be installed at the benzylic position. Both of these goals (the change in carbon skeleton and installation of the functional group) can be accomplished via a Grignard reaction. That is, the following Grignard reaction can create the necessary C–C bond, while leaving an OH group in the desired location.



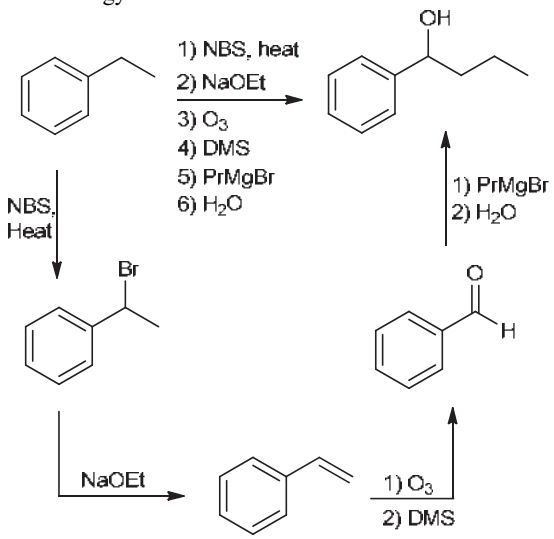
However, the necessary aldehyde does not have the same number of carbon atoms as the starting material:



Nevertheless, we can easily convert the starting material into the desired aldehyde via the following three step process:

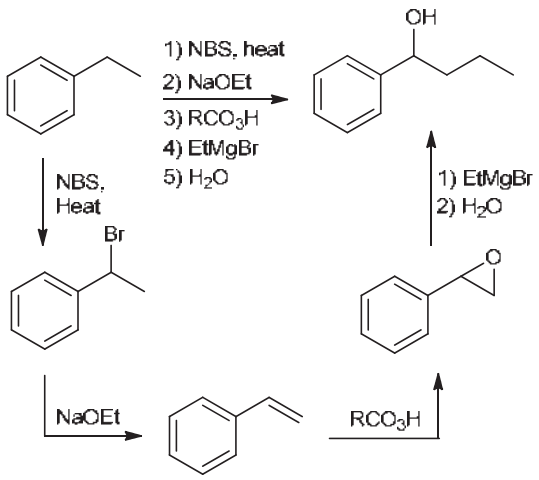
1) bromination at the benzylic position,
2) elimination (E2) upon treatment with a strong base,
3) ozonolysis

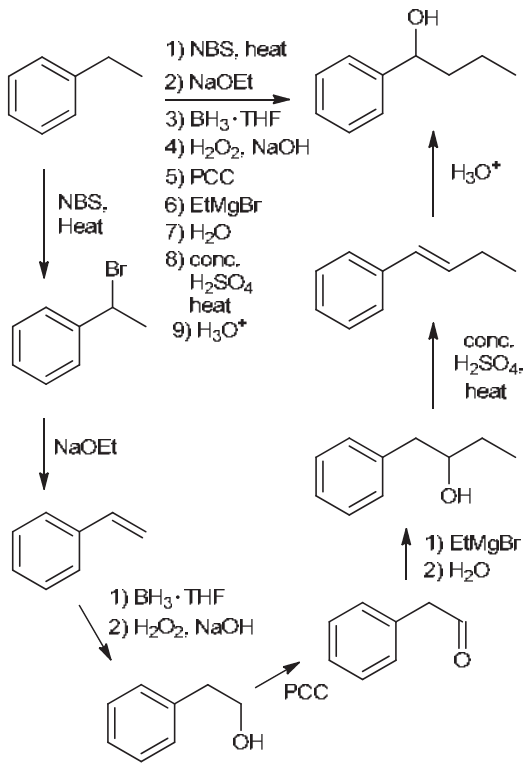
This strategy is shown here:



There are certainly other acceptable solutions to this problem. The solution above represents just one approach. For example, the following is another acceptable approach:

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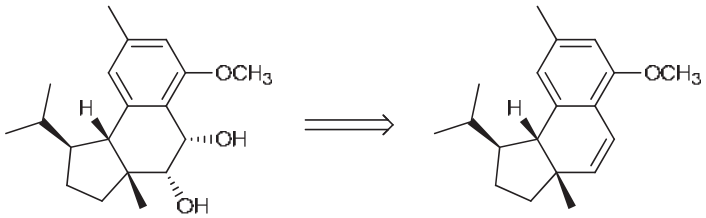


And here is yet one further way to achieve the desired transformation. In the following proposed synthesis, the regiochemical outcome of the final step is controlled by the preference for formation of a benzylic carbocation intermediate, and the regiochemical outcome of the penultimate step is controlled by the preference for formation of a conjugated π bond.

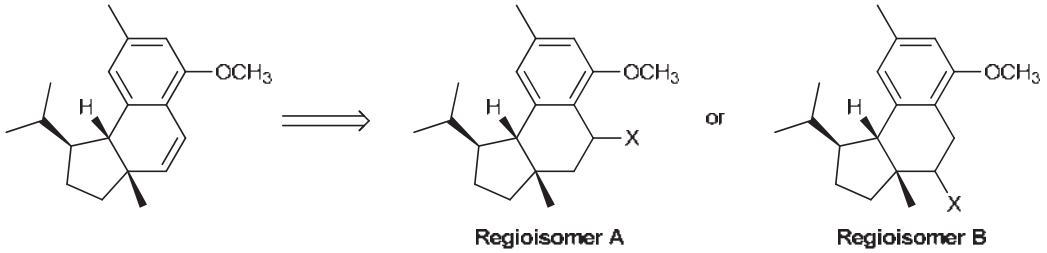
17.19. We begin by asking the following two questions:

1) Is there is a change in the carbon skeleton?
2) Is there is a change in the identity and/or location of the functional group(s)?

In this example, the carbon skeleton has not changed; however, two carbon atoms have been functionalized (the benzylic carbon atom and the carbon atom adjacent to it). Approaching this synthesis from a retrosynthetic perspective, we know that the diol can be made via dihydroxylation of a carbon-carbon double bond; given our recent study of the stability of aromatic systems, it is reasonable to expect that the aromatic π bonds will not undergo dihydroxylation:

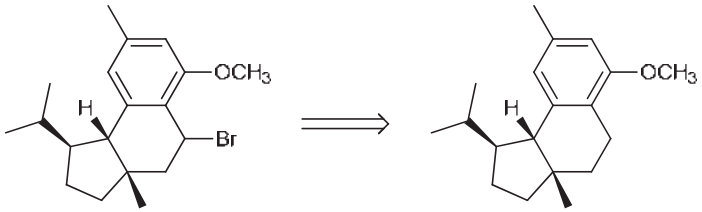


The carbon-carbon double bond can be made via an elimination reaction, using a suitable leaving group, from either of two regioisomers:



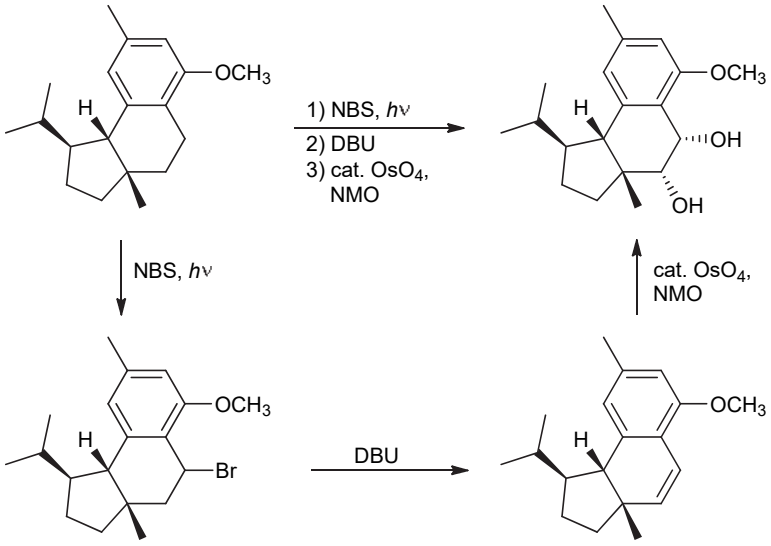
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In particular, regioisomer A allows us to make use of the reactivity of the benzylic position to install a bromide via benzylic bromination.



Regioisomer A

Now let's draw the entire synthesis in the forward direction. Our synthesis begins with benzylic bromination, using NBS and light. As mentioned in the problem statement, formation of the secondary benzylic bromide is favored. Elimination is accomplished using a strong base, such as DBU. The desired *cis*-diol can then be obtained using OsO_4/NMO to affect a stereospecific *syn* addition. This addition reaction can theoretically occur on either face of the alkene, although there is an observed preference for formation of the diastereomer shown (with the two OH groups on dashes, rather than on wedges), as a result of steric effects:

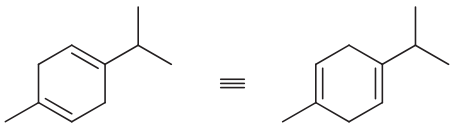


17.20.

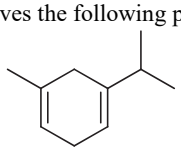
(a) The ring bears one substituent (an alkyl group), which is electron donating. The carbon atom next to the alkyl group will not be reduced. In a Birch reduction, only two positions are reduced, and they must be 1,4 to each other. This gives the following product (note: the two structures below represent the same compound):



(b) The ring bears two substituents (alkyl groups), which are both electron donating. The carbon atoms next to the alkyl groups will not be reduced. In a Birch reduction, only two positions are reduced, and they must be 1,4 to each other. This gives the following product (note: the two structures below represent the same compound):

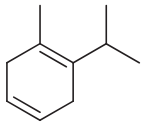


(c) The ring bears two substituents (alkyl groups), which are both electron donating. The carbon atoms next to the alkyl groups will not be reduced. In a Birch reduction, only two positions are reduced, and they must be 1,4 to each other. This gives the following product:

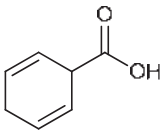


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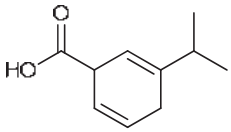
(d) The ring bears two substituents (alkyl groups), which are both electron donating. The carbon atoms next to the alkyl groups will not be reduced. In a Birch reduction, only two positions are reduced, and they must be 1,4 to each other. This gives the following product:



(e) The ring bears one substituent (a carboxylic acid group), which is electron withdrawing. The carbon atom next to the carboxylic acid group will be reduced. In a Birch reduction, only two positions are reduced, and they must be 1,4 to each other. This gives the following product:

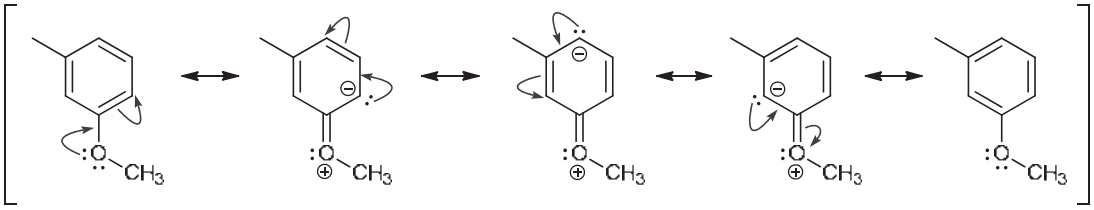


(f) The ring bears two substituents. The alkyl group is electron donating, so the carbon atom next to the alkyl group is not reduced. The carboxylic acid group is electron withdrawing, so the carbon atom next to the carboxylic acid group is reduced. In a Birch reduction, only two positions are reduced, and they must be 1,4 to each other. This gives the following product:

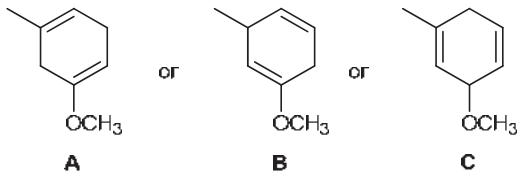


17.21.

(a) Compound **1** contains a lone pair (on the methoxy oxygen) next to a π-bond, so we draw two curved arrows associated with that characteristic pattern (see Chapter 2). The resulting resonance structure also exhibits a lone pair next to a π-bond, so once again, we draw the resulting resonance structure. This pattern is continued, until the final resonance structure differs from the first resonance structure only in the position of the double bonds (that is, in fact, one of the other characteristic patters seen in Chapter 2 – conjugated π-bonds enclosed in a ring).



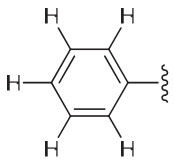
(b) There are three possible products that could result from a Birch Reduction of **1**. Let's call them **A**, **B**, and **C**.



We know that alkyl groups are electron donating and they direct the reduction away from the point of attachment of the alkyl group. Thus, option **B** is unlikely because the carbon atom attached to the methyl group is reduced. If the methoxy substituent was predominantly electron-donating, **A** would be the major product; and if the methoxy substituent was predominantly electron-withdrawing, then **C** would be the major product. Since **A** is the major product, we deduce that the methoxy group must be electron-donating, and resonance must be the major factor. Indeed, this fact will be further discussed in the next chapter.

17.22.

(a) The molecular formula (C_8H_8O) indicates five degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring, in addition to either one double bond or one ring. The aromatic ring is confirmed by the presence of a signal just above 3000 cm^{-1} in the IR spectrum, as well a signal at 1646 cm^{-1}. In the ^1H NMR spectrum, the multiplet at 7.5 ppm also confirms the aromatic ring. Notice that this multiplet has an integration of 5, which indicates that the aromatic ring is monosubstituted:

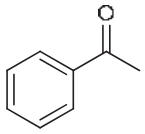


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The singlet with an integration of 3 indicates a methyl group, and its chemical shift suggests it might be near a C=O bond:

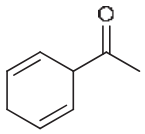


Indeed, a C=O bond will account for the signal at 1686 cm^{-1} in the IR spectrum as well as the fifth degree of unsaturation described earlier. The signal at 1686 cm^{-1} is consistent with a conjugated carbonyl group, as seen in the following structure:



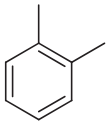
(b) As seen in Section 17.2, the common name for this compound is acetophenone.

(c) The reagents indicate a Birch reduction. The ring bears one substituent (a carbonyl group), which is electron withdrawing via resonance. The carbon atom next to the carbonyl group will be reduced. In a Birch reduction, only two positions are reduced, and they must be 1,4 to each other. This gives the following product:



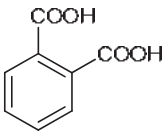
17.23.

(a) The molecular formula (C_8H_{10}) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring. The presence of an aromatic ring is confirmed by the signals just above 3000 cm^{-1} in the IR spectrum, as well as the signal near 1600 cm^{-1}. In the ^1H NMR spectrum, the multiplet at 7.1 ppm further confirms the presence of an aromatic ring. The integration of this signal is 4, indicating that the aromatic ring is disubstituted. The aromatic ring accounts for six of the eight carbon atoms in the compound (C_8H_{10}), so there must be two methyl groups attached to the ring (dimethyl benzene). To determine the substitution pattern (*ortho*, *meta* or *para*), we note that the ^{13}C NMR spectrum exhibits three signals in the region of 100-150 ppm, which indicates the *ortho* substitution pattern:



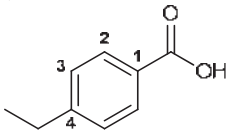
(b) As seen in Section 17.2, the common name for *ortho*-dimethylbenzene is *ortho*-xylene.

(c) When treated with chromic acid (a strong oxidizing agent), both benzylic positions are oxidized, giving the following diacid:

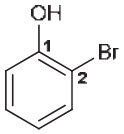


17.24.

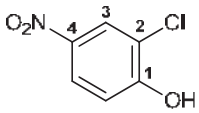
(a) The parent is benzoic acid. An ethyl group is located at C4 (also called the *para* position), so the compound is 4-ethylbenzoic acid, (also called *para*-ethylbenzoic acid):



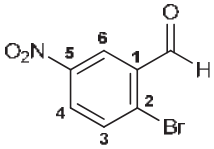
(b) The parent is phenol. A bromine atom is located at C2 (also called the *ortho* position), so the compound is 2-bromophenol, (also called *ortho*-bromophenol):



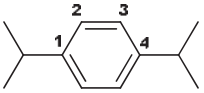
(c) The parent is phenol. A chlorine atom is located at C2 and a nitro group is located at C4, so the compound is 2-chloro-4-nitrophenol:



(d) The parent is benzaldehyde. A bromine atom is located at C2 and a nitro group is located at C5 (as shown), so the compound is 2-bromo-5-nitrobenzaldehyde:



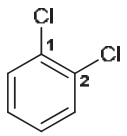
(e) The parent is benzene. There are two substituents, both isopropyl groups, located at C1 and C4, so the compound is 1,4-diisopropylbenzene, (also called *para*-diisopropylbenzene):



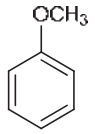
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17.25.

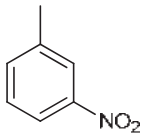
(a) The parent is benzene, and there are two chlorine atoms that are *ortho* to each other (C1 and C2).



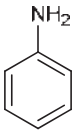
(b) As seen in Section 17.2, anisole is the common name for methoxybenzene:



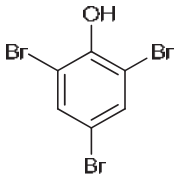
(c) The parent is toluene (methylbenzene), and there is a nitro group in the *meta* position (C3).



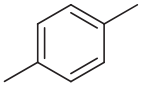
(d) As seen in Section 17.2, aniline is the common name for aminobenzene:



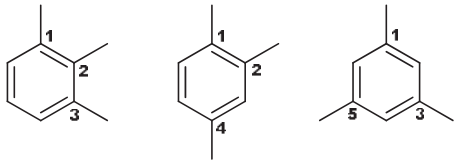
(e) The parent is phenol (hydroxybenzene), and there are three bromine atoms, connected to positions C2, C4, and C6.



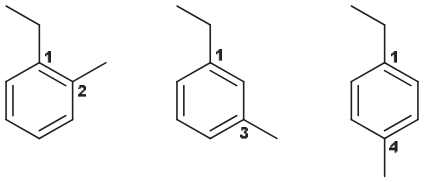
(f) As seen in Section 17.2, *para*-xylene is the common name for *para*-dimethylbenzene:



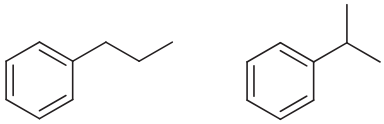
17.26. The molecular formula (C_9H_{12}) indicates four degrees of unsaturation (see Section 14.16), and the benzene ring accounts for all four degrees of unsaturation. The ring contains six carbon atoms, so the remaining three carbon atoms must be attached to the aromatic ring without any additional π bonds or rings. There are several ways to attach three carbon atoms to an aromatic ring without introducing any additional π bonds or rings. The carbon atoms can be attached as three individual methyl groups, for which there are three unique constitutional isomers:



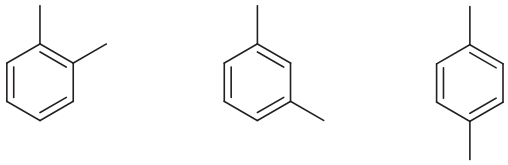
or there can be one ethyl group and one methyl group, for which there are also three constitutional isomers:



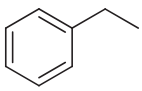
Finally, all three carbon atoms can be connected to the ring as a single substituent, and there are two ways to accomplish that, as shown here:



17.27. The molecular formula (C_8H_{10}) indicates four degrees of unsaturation (see Section 14.16), and the aromatic ring accounts for all four degrees of unsaturation. The ring contains six carbon atoms, so the remaining two carbon atoms must be attached to the aromatic ring without any additional π bonds or rings. There are several ways to attach two carbon atoms to an aromatic ring without introducing any additional π bonds or rings. The carbon atoms can be attached as two individual methyl groups, for which there are three unique constitutional isomers:



or there can simply be one ethyl group:

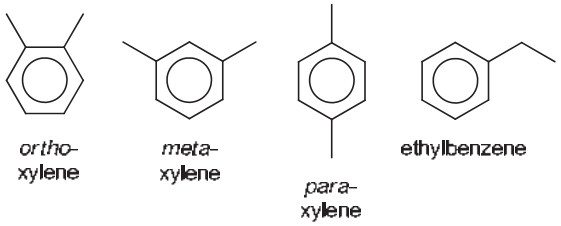


In total, we have seen four constitutional isomers.

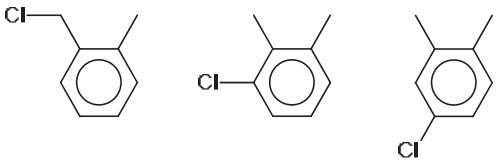
17.28. The molecular formula (C_8H_9Cl) is similar to the molecular formula in the previous problem (C_8H_{10}), but one of the hydrogen atoms has been replaced with a chlorine atom. So, we begin our analysis by redrawing all four skeletons shown in the solution to the previous problem. In each case, we will draw a circle for the

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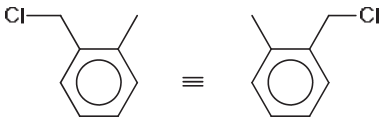
aromatic ring, rather than drawing π bonds, as it will be easier to identify symmetry without being distracted by the arbitrary locations of the double bonds:



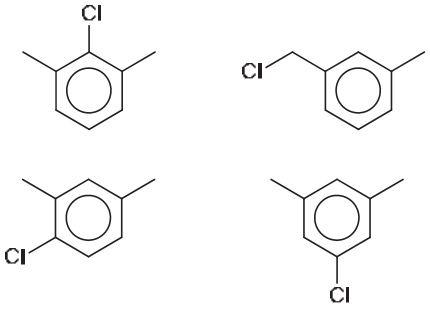
For each one of these skeletons, we must consider all of the unique locations where a chlorine atom can be placed. Let's begin with the first skeleton (*ortho*-xylene), for which there are three unique locations where the chlorine atom can be placed:



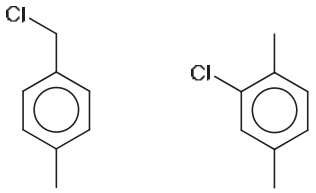
Placing the chlorine atom in any other location on this skeleton will result in one of the compounds above. For example:



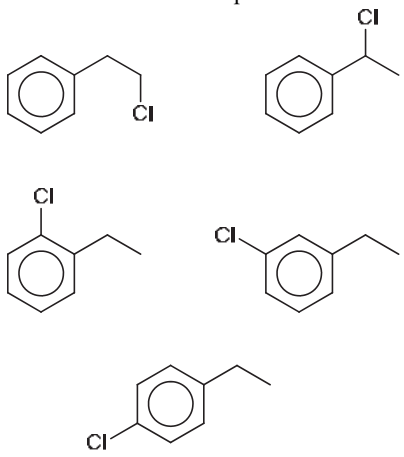
Next, we consider the second skeleton (*meta*-xylene), for which there are four unique locations where the chlorine atom can be placed:



Next, we consider the third skeleton (*para*-xylene), for which there are only two unique locations where the chlorine atom can be placed:

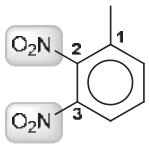


And finally, we consider the last skeleton (ethylbenzene), for which there are five unique locations where the chlorine atom can be placed:

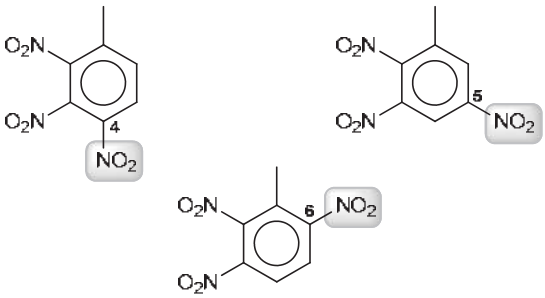


In total, we have seen fourteen constitutional isomers.

17.29. We begin by placing the first two nitro groups at positions C2 and C3:

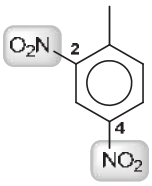


There are now three choices of where to place the third nitro group (C4, C5, or C6), giving rise to the following three constitutional isomers:

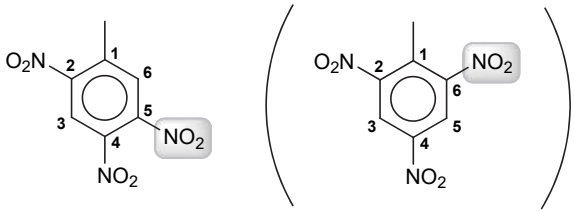


We have now exhausted all possibilities in which the first two nitro groups occupy positions C2 and C3. Next, we place the first two nitro groups at C2 and C4:

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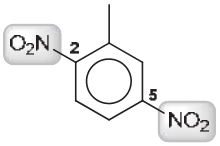


There are now two choices of where to place the third nitro group (C5 or C6), giving rise to the following two constitutional isomers, although the second isomer is the one described in the problem statement (so we will not count that one):

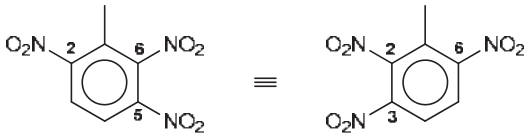


We do not count this isomer, as per the instructions in the problem statement

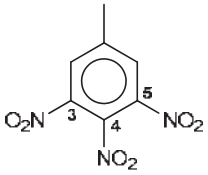
We have now exhausted all possibilities in which the first two nitro groups occupy positions C2 and C4. Next, we place the first two nitro groups at C2 and C5:



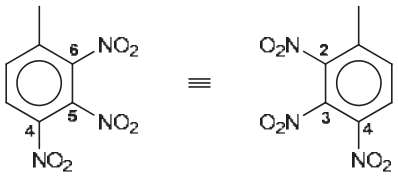
This leaves only one option for the third nitro group (C6), and this isomer has already been drawn earlier:



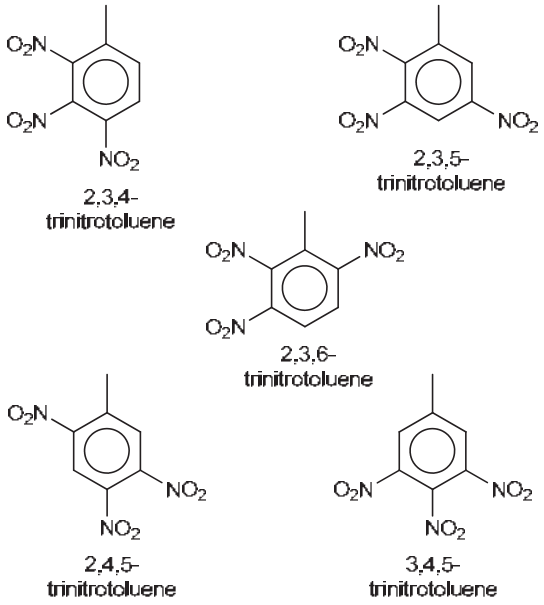
We have now considered all options for which the first nitro group is placed at C2. Now we continue our analysis by placing the first nitro group at C3. If we place the remaining two nitro groups at C4 and C5, then we obtain the following isomer:



Any other arrangement of nitro groups will be identical to one of the arrangements already drawn. For example:



In summary, the following five isomers are consistent with the requirements described in the problem statement:



17.30.

(a) Each π bond counts as two π electrons, and the lone pair also counts as two π electrons, giving a total of ten π electrons.

(b) Each π bond counts as two π electrons. In addition, one of the lone pairs on the sulfur atom is participating in resonance (it occupies a *p* orbital and is delocalized) and therefore contributes two more π electrons. This gives a total of six π electrons.

(c) Each π bond counts as two π electrons, giving a total of ten π electrons.

(d) Each π bond counts as two π electrons, giving a total of four π electrons. The lone pair on the nitrogen atom does not occupy a *p* orbital, because the nitrogen atom is already using a *p* orbital to form a π bond. The lone pair occupies an sp^2 hybridized orbital and does not contribute any π electrons.

(e) Each π bond counts as two π electrons, giving a total of six π electrons. The carbocation represents an empty *p* orbital and does not contribute any π electrons.

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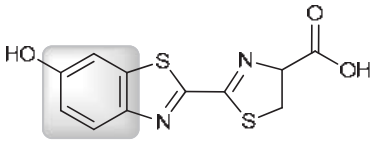
17.31. The terms used in reference to cyclohexane were discussed in Chapter 4, while the terms used in reference to benzene were discussed in Chapter 17.
(a) The term *meta* refers to a 1,3-disubstituted benzene ring.
(b) A Frost circle is used to draw an energy diagram showing the relative energy levels of the MOs associated with a ring comprised of a continuous conjugated π system, such as benzene.
(c) All six carbon atoms in benzene are sp^2 hybridized, with trigonal planar geometry.
(d) A chair conformation is one of the conformations that a cyclohexane ring can adopt. Benzene is flat and does not adopt the conformations that are accessible to cyclohexane.
(e) The term *ortho* refers to a 1,2-disubstituted benzene ring.
(f) All six carbon atoms in cyclohexane are sp^3 hybridized, with tetrahedral geometry.
(g) Benzene is resonance stabilized (while cyclohexane possesses no π electrons, and therefore has no resonance structures).
(h) Benzene has π electrons, while cyclohexane does not.
(i) The term *para* refers to a 1,4-disubstituted benzene ring.
(j) Cyclohexane undergoes a conformational change called ring flipping. In contrast, benzene is planar and does not undergo ring flipping.
(k) A boat conformation is one of the conformations that a cyclohexane ring can adopt. Benzene is flat and does not adopt the conformations that are accessible to cyclohexane.

17.32.
(a) Each of the rings is comprised of a continuous system of overlapping *p* orbitals with a total of six π electrons. As such, each ring is aromatic. The compound would be aromatic if either ring alone were aromatic. This compound is most certainly aromatic. Notice that, in determining aromaticity, each ring is considered individually.
(b) As described in Section 17.5, the hydrogen atoms positioned inside the ring experience a steric interaction that forces this compound, called [10]annulene, out of planarity. Since the molecule cannot adopt a planar conformation, the *p* orbtials cannot continuously overlap with each other to form one system, and as a result, [10]annulene does not meet the criteria for aromaticity. It is not aromatic.
(c) In order for this five-membered ring to exhibit a continuous system of overlapping *p* orbitals, each oxygen atom would have to be sp^2 hybridized (thereby placing a lone pair in a *p* orbital). If this were in fact to be the case, the ring would have eight π electrons (two π electrons for the π bond and two π electrons for each lone pair that occupies a *p* orbital). This would make the ring antiaromatic. Therefore, not all of the oxygen atoms will adopt sp^2 hybridization. At least one of them will adopt sp^3 hybridization to avoid antiaromaticity. As such, the compound does not have a continuous system of *p* orbitals, and is therefore not aromatic.
(d) One of the lone pairs on the oxygen atom occupies a *p* orbital, thereby rendering the compound aromatic (six π electrons). The lone pair on the nitrogen atom occupies an sp^2 hybridized orbital that is in the plane of the ring (because the nitrogen atom is already using a *p* orbital to establish aromaticity).
(e) One of the carbon atoms in the ring is sp^3 hybridized (highlighted):

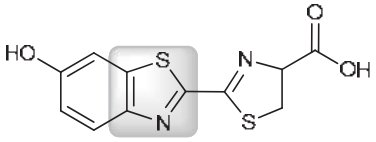


So the structure does not possess a continuous system of overlapping *p* orbitals. Therefore, it is not aromatic.

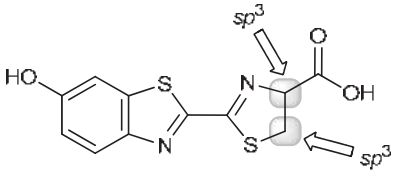
17.33.
(a) The six-membered ring is aromatic because it is comprised of a continuous system of overlapping *p* orbitals with six π electrons:



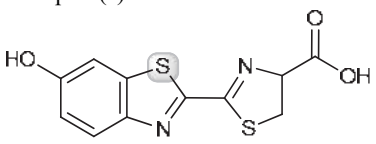
In addition, the adjacent five-membered ring is also aromatic:



In this five-membered ring, one of the lone pairs on the sulfur atom occupies a *p* orbital, thereby rendering the ring aromatic (six π electrons). The lone pair on the nitrogen atom occupies an sp^2 hybridized orbital that is in the plane of the ring (because the nitrogen atom is already using a *p* orbital to establish aromaticity).
The other five-membered ring (not highlighted above) is not aromatic because the ring contains sp^3 hybridized atoms and is therefore not a continuous system of overlapping *p* orbitals:



(b) Many of the lone pairs are delocalized by resonance (one lone pair on each of the sulfur atoms, as well as one lone pair on each of the OH groups). However, only one of these lone pairs (on the atom highlighted below) is participating in establishing aromaticity, as explained in the solution to part (a):



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17.34.

(a) If the oxygen atom adopts sp^2 hybridization so that the lone can occupy a *p* orbital (to give a continuous system of overlapping *p* orbitals), then there would be a total of eight π electrons (six π electrons from the double bonds and two π electrons from the lone pair that occupies a *p* orbital). This compound would therefore be antiaromatic and extremely high in energy. To avoid the huge energy cost associated with antiaromaticity, the oxygen atom likely adopts sp^3 hybridization, so that the lone pair occupies an sp^3 hybridized orbital. This hybridization state destroys the continuous system of overlapping *p* orbitals, rendering the compound nonaromatic. As such, the lone pairs on the oxygen atom are expected to be localized (to avoid anti-aromaticity).

(b) If the nitrogen atom adopts sp^2 hybridization so that the lone can occupy a *p* orbital (to give a continuous system of overlapping *p* orbitals), then there would be a total of eight π electrons (six π electrons from the double bonds and two π electrons from the lone pair that occupies a *p* orbital). This compound would therefore be antiaromatic and extremely high in energy. To avoid the huge energy cost associated with antiaromaticity, the nitrogen atom likely adopts sp^3 hybridization, so that the lone pair occupies an sp^3 hybridized orbital. This hybridization state destroys the continuous system of overlapping *p* orbitals, rendering the compound nonaromatic. As such, the lone pair on the nitrogen atom is expected to be localized (to avoid anti-aromaticity).

(c) Aromatic. One of the lone pairs of the sulfur atom occupies a *p* orbital, thereby establishing a continuous system of overlapping *p* orbitals, containing six π electrons. The lone pair on the nitrogen atom occupies an sp^2 hybridized orbital that is in the plane of the ring (because the nitrogen atom is already using a *p* orbital to establish aromaticity).

(d) This compound is aromatic, much like benzene. Each nitrogen possesses a lone pair that occupies an sp^2 hybridized orbital (they do not participate in establishing aromaticity).

(e) The ring is aromatic because it is comprised of a continuous system of overlapping *p* orbitals with six π electrons, just like benzene.

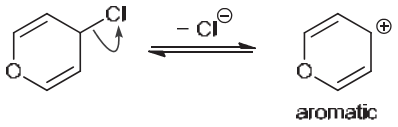
(f) The nitrogen atom does not have a *p* orbital, so there is not a continuous system of overlapping *p* orbitals. Therefore, this structure is not aromatic.

(g) The lone pair of the oxygen atom occupies a *p* orbital, thereby establishing a continuous system of overlapping *p* orbitals, containing six π electrons. Therefore, this structure is aromatic.

(h) Each of the nitrogen atoms possesses a lone pair. If each of these nitrogen atoms adopts sp^2 hybridization so that each lone pair can occupy a *p* orbital, then there would be a continuous system of overlapping *p* orbitals, with a total of six π electrons (two π electrons from the double bond, and then two more π electrons from each lone pair that occupies a *p* orbital). Therefore, this compound is expected to exhibit aromatic stabilization.

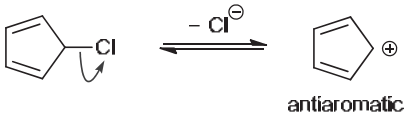
17.35.

(a) The following compound is expected to undergo an S_N1 reaction most readily, because loss of the leaving group generates an aromatic cation, as shown:



This cation is aromatic because the oxygen atom can adopt sp^2 hybridization, thereby placing a lone pair in a *p* orbital. The positive charge represents an empty *p* orbital, so there is a continuous system of overlapping *p* orbitals. Each π bond contributes two π electrons, and the oxygen atom contributes two more π electrons, for a total of six π electrons.

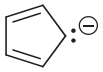
(b) The following compound is expected to undergo an S_N1 reaction least readily, because loss of the leaving group generates an antiaromatic cation.



17.36. The following compound is the most acidic from among the group,

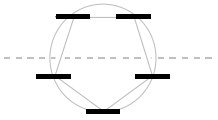


because deprotonation of this compound generates an aromatic ion (a continuous system of overlapping *p* orbitals containing six π electrons).



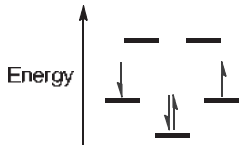
17.37. The second compound is a stronger base, because the lone pair on the nitrogen atom is localized and available to function as a base. In contrast, the nitrogen atom in the first compound is delocalized and is participating in aromaticity. This lone pair is unavailable to function as a base, because that would destroy aromaticity.

17.38. In order to draw a Frost circle, we begin by drawing a circle, and then we place a pentagon inside the circle, with all five corners touching the circle, such that one of the corners points to the bottom of the circle, as shown here:

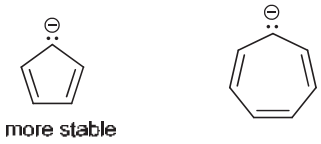


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Each position where a corner touches the circle represents the relative energy level of a molecular orbital. If we draw a horizontal line through the center of the circle, we see that there are three MOs in the bottom half of the circle, and two MOs in the top half. The former represent the bonding MOs, while the latter represent the antibonding MOs. With three bonding MOs, we expect that six π electrons are required in order to achieve aromaticity. This cation only has four π electrons. Two of them occupy the lowest energy MO (at the bottom of the circle), but the remaining are split between the two degenerate bonding MOs. As such, this system is not a closed-shell electron configuration, giving rise to instability.



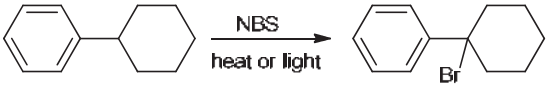
17.39. Cyclopentadiene is more acidic because its conjugate base is highly stabilized. Deprotonation of cyclopentadiene generates an anion that is aromatic, because it is a continuous system of overlapping *p* orbitals containing six π electrons. In contrast, deprotonation of cycloheptatriene gives an anion with eight π electrons, expected to be highly unstable (antiaromatic).



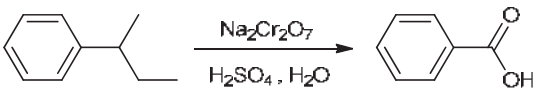
17.40. Yes. The lone pairs on the nitrogen atoms do not contribute to aromaticity. They occupy sp^2 hybridized orbitals. One of the lone pairs on the oxygen atom (in the ring) occupies a *p* orbital, giving a continuous system of overlapping *p* orbitals containing six π electrons (two π electrons from each double bond, as well as two more π electrons from the lone pair that occupies a *p* orbital).

17.41. Benzene does not have three C-C single bond and three C-C double bonds. In fact, all six C-C bonds of the ring have the same bond order and are the same length. However, cyclooctatetraene has four isolated π bonds. The molecule adopts a tub shape to avoid antiaromaticity. Some of the C-C bonds are double bonds (shorter in length), and some of the C-C bonds are single bonds (longer in length). Therefore, the two methyl groups can either be separated by a C-C single bond or a C=C double bond. And those two possibilities represent different compounds.

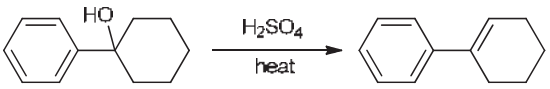
17.42.
(a) The starting material has a benzylic proton, so treatment with NBS is expected to result in bromination at the benzylic position to give the following product.



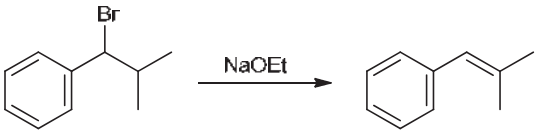
(b) The starting material has a benzylic proton, so treatment with chromic acid is expected to result in oxidation of the benzylic position. Note that only the benzylic carbon atom survives, while the other carbon atoms of the alkyl substituent are removed (characteristic of oxidation reactions at benzylic positions).



(c) The starting material is an alcohol in which the OH group occupies a benzylic position. Upon treatment with sulfuric acid, we expect an E1 process to form a conjugated π bond, as shown:



(d) The starting material is a secondary, benzylic bromide. Upon treatment with a strong base, such as ethoxide, we expect an E2 process to form a conjugated π bond, as shown:



17.43.
(a) A monosubstituted aromatic ring is expected to produce four signals in the region between 100 and 150 ppm in the ^{13}C NMR spectrum. In addition, the isopropyl group is expected to produce two signals (because the methyl groups are equivalent) in the region between 0 and 50 ppm. In total, we expect six signals in the ^{13}C NMR spectrum.

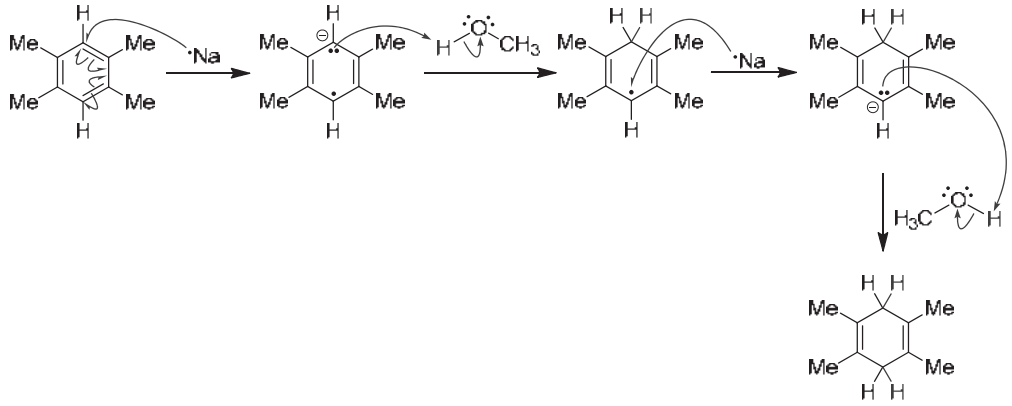
(b) A *para*-disubstituted aromatic ring (where the two substituents are different from each other) is expected to produce four signals in the region between 100 and 150 ppm in the ^{13}C NMR spectrum. In addition, the methyl group is expected to produce one more signal in the region between 0 and 50 ppm. In total, we expect five signals in the ^{13}C NMR spectrum.

(c) The aromatic ring is 1,3,5-trisubstituted, and all three substituents are identical (methyl groups). Because of symmetry, there are only two unique kinds of aromatic carbon atoms, giving rise to two signals in the region between 100 and 150 ppm in the ^{13}C NMR spectrum. In addition, the three methyl groups are all equivalent and will collectively give rise to one signal in the region between 0 and 50 ppm. In total, we expect three signals in the ^{13}C NMR spectrum.

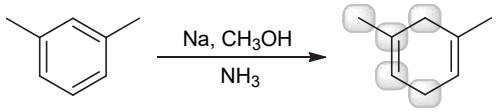
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(d) The aromatic ring is 1,2,4-trisubstituted, and it lacks the symmetry necessary to render any of the carbon atoms identical. All six carbon atoms of the ring occupy unique environments, and similarly, all three methyl groups also occupy unique environments. We therefore expect six signals in the region between 100 and 150 ppm, and we expect three more signals in the region between 0 and 50 ppm, for a total of nine signals in the ^{13}C NMR spectrum.

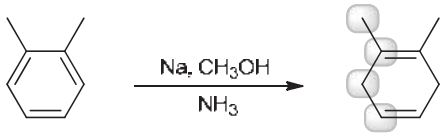
17.44. The reagents indicate a Birch reduction, which is believed to occur via a four-step mechanism (as seen in Mechanism 17.1). In the first step, an electron is transferred to the aromatic ring, generating a radical anion, which is then protonated (with methanol functioning as the proton source). Another electron transfer process, followed by a proton transfer, results in the formation of 1,2,4,5-tetramethyl-1,4-cyclohexadiene, as shown. Notice that the four positions bearing the electron-donating alkyl groups are not reduced. The two positions without electron-donating substituents are reduced.



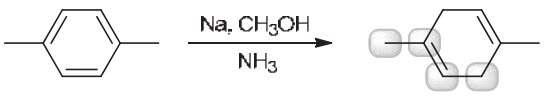
17.45. The reagents indicate a Birch reduction, and *meta*-xylene is expected to undergo a Birch reduction to produce a compound that will exhibit five signals in its ^{13}C NMR spectrum. The five unique carbon atoms are highlighted in the product:



The answer cannot be *ortho*-xylene, because a Birch reduction of *ortho*-xylene would produce a compound that exhibits only four signals in its ^{13}C NMR spectrum:

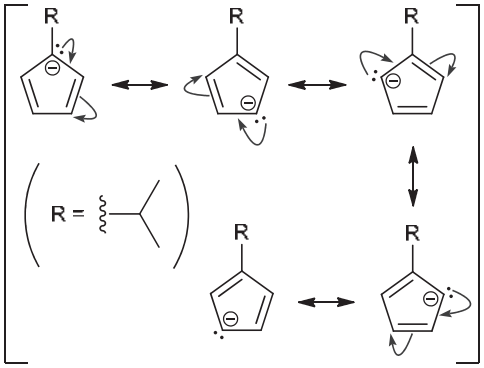


And the answer cannot be *para*-xylene, because a Birch reduction of *para*-xylene produces a compound that also exhibits only four signals in its ^{13}C NMR spectrum:



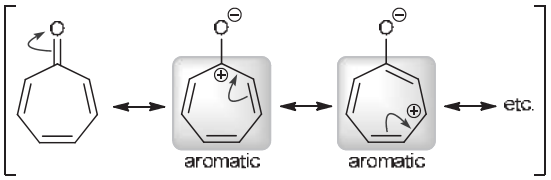
17.46.
(a) The first compound would lack C-H stretching signals just above 3000 cm^{-1}, while the second compound will have C-H stretching signals just above 3000 cm^{-1}.
(b) The ^{1}H NMR spectrum of the first compound will have only one signal, while the ^{1}H NMR spectrum of the second compound will have two signals.
(c) The ^{13}C NMR spectrum of the first compound will have only two signals, while the ^{13}C NMR spectrum of the second compound will have three signals.

17.47. When either compound is deprotonated, an aromatic anion is generated, which can be drawn with five resonance structures. The resulting anion is the same in either case:

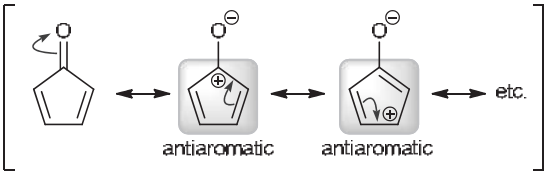


17.48. In cycloheptatrienone, the significant resonance structures with C^{+} and O^{-} contribute significant character to the overall resonance hybrid, because these forms are aromatic:

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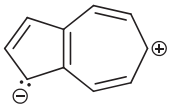


Therefore, the oxygen atom of this C=O bond is particularly electron rich. A similar analysis of cyclopentadienone reveals resonance structures with antiaromatic character:



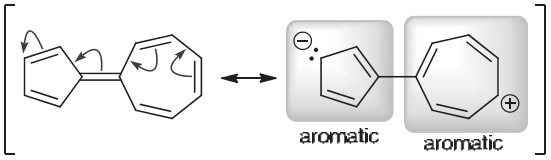
These resonance structures contribute very little character to the overall resonance hybrid, and as a result, the oxygen atom of this C=O bond is less electron rich as compared with most C=O bonds.

17.49.
(a) Each of the rings in the following resonance structure is aromatic.



Therefore, this resonance structure contributes significant character to the overall resonance hybrid, which gives azulene a considerable dipole moment.

(b) The following compound has resonance structures in which both rings are aromatic, as shown here:



Therefore, this compound will have a significant dipole moment.
In contrast, the other compound does not have resonance structures in which both rings are aromatic, and is not expected to exhibit a dipole moment.

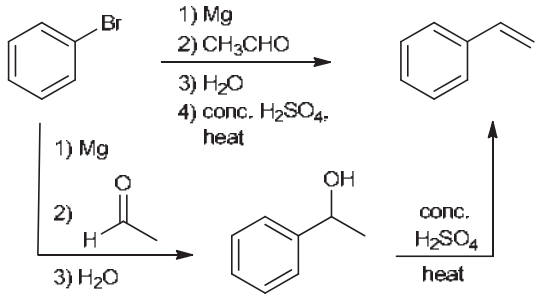
17.50. There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

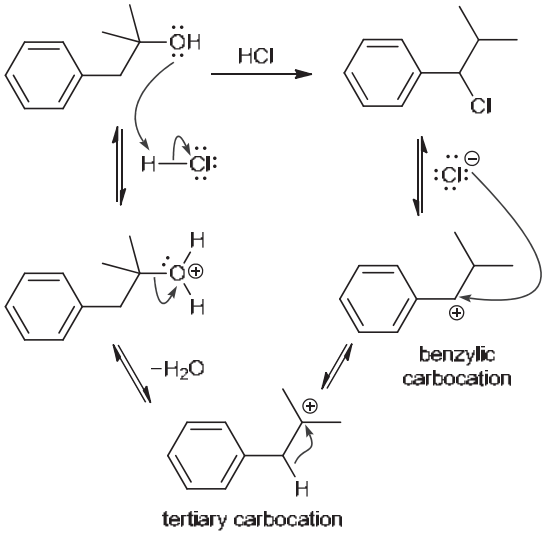
In this case, there is a change in the carbon skeleton. The product has two more carbon atoms than the starting material:



Also, a functional group (a π bond) must be installed. Let's begin with the change in the carbon skeleton. In order to increase the size of the carbon skeleton, we must form a C–C bond. A Grignard reaction will allow us to form the critical C–C bond, and the resulting alcohol can then be converted into the desired alkene via an E1 process, as shown below.



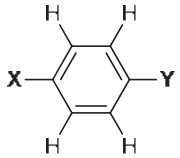
17.51. In acidic conditions, the OH group is protonated, thereby generating a better leaving group (H_2O). Loss of the leaving group generates a tertiary carbocation, which can rearrange via a hydride shift to generate a resonance-stabilized benzylic carbocation. This benzylic carbocation is then captured by a chloride ion (generated in the first step of the mechanism) to give the product, as shown.



17.52. The molecular formula ($C_9H_{10}O_2$) indicates five degrees of unsaturation (see Section 14.16), which is strongly suggestive of an aromatic ring, as well as one additional double bond or ring. The signal just above 3000 cm^{-1} in the IR spectrum confirms the aromatic ring, as does the signal just above 1600 cm^{-1}. The ^1H NMR spectrum exhibits two doublets between 6.9 and 7.9

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ppm, each with an integration of 2. This is the characteristic pattern of a disubstituted aromatic ring, in which the two substituents are different from each other:



The singlet at 3.9 ppm (with an integration of 3) represents a methyl group. The chemical shift is downfield from the expected benchmark value of 0.9 ppm for a methyl group, indicating that it is likely next to an oxygen atom:

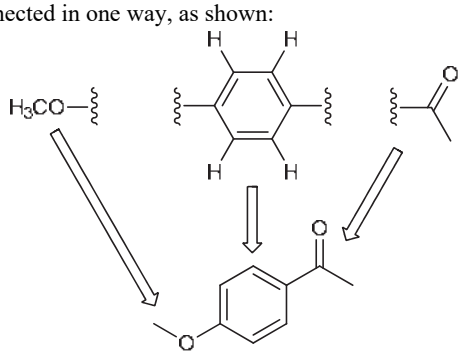


The singlet at 2.6 ppm (with an integration of 3) represents an isolated methyl group. The chemical shift of this signal suggests that the methyl group is neighboring a carbonyl group:



The carbonyl group accounts for one degree of unsaturation, and together with the aromatic ring, this would account for all five degrees of unsaturation. The presence of a carbonyl group is also confirmed by the signal at 196.6 ppm in the ^{13}C NMR spectrum.

We have uncovered three pieces, which can only be connected in one way, as shown:

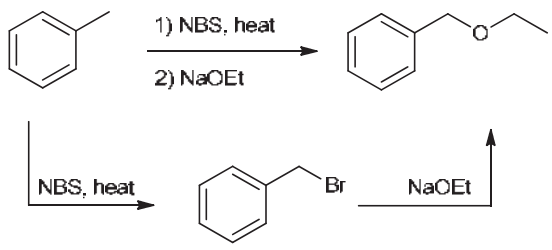


This structure is consistent with the ^{13}C NMR data: four signals for the sp^2 hybridized carbon atoms of the aromatic ring, and two signals for the sp^3 hybridized carbon atoms (one of which is above 50 ppm because it is next to an oxygen atom).

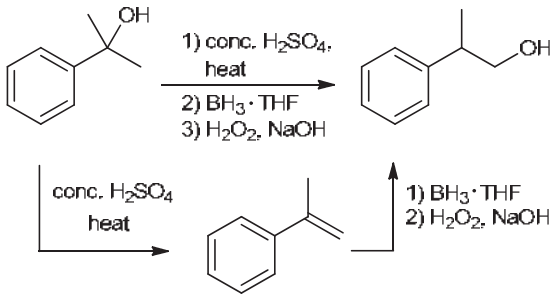
Also notice that the carbonyl group is conjugated to the aromatic ring, which explains why the signal for the C=O bond in the IR spectrum appears at 1676 cm^{-1}, rather than 1720 cm^{-1}.

17.53.

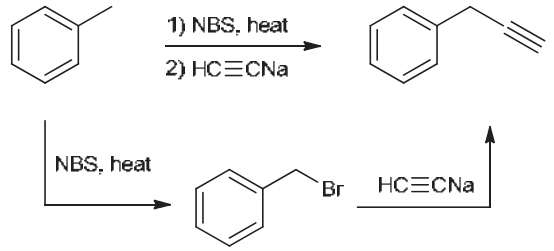
(a) If we functionalize the benzylic position (via bromination), the product can be obtained in just one more step, via a Williamson ether synthesis, as shown:



(b) This transformation requires that we move the position of the OH group. This was a strategy that was covered in Chapter 11. Specifically, we saw that the location of an OH group can be moved via elimination followed by addition. The first step is to convert the alcohol into an alkene via acid-catalyzed dehydration (E1). Then, hydroboration-oxidation will convert the alkene into the desired alcohol, via an *anti*-Markovnikov addition of H and OH across the π bond:



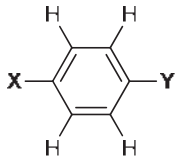
(c) The carbon skeleton is getting larger, so we must form a C–C bond. In addition, we must install a triple bond. Both of these goals can be achieved via bromination at the benzylic position, followed by an S_N2 reaction in which an acetylide ion is used as the nucleophile, as shown:



17.54. The molecular formula ($C_{11}H_{14}O_2$) indicates five degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring, as well as either one double bond or one ring.

In the ^1H NMR spectrum, the signals near 7 ppm are likely a result of aromatic protons. Notice that the combined integration of these two signals is 4H. This, together with the distinctive splitting pattern (a pair of doublets), suggests a 1,4-disubstituted aromatic ring, in which the two substituents are different:

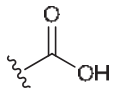
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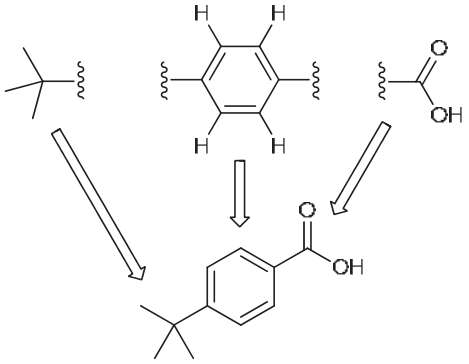
The spectrum also exhibits a singlet with an integration of 9H (at approximately 1.4 ppm) which is characteristic of a *tert*-butyl group.



The ^{1}H NMR spectrum has only one other signal, very far downfield, characteristic of a carboxylic acid:



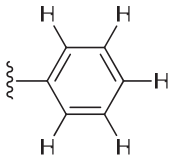
The presence of a carboxylic acid group is confirmed by the IR spectrum, which has a broad signal between 2200 and 3600 cm^{-1}. The carboxylic acid group also accounts for one degree of unsaturation, and together with the aromatic ring, they collectively account for all five degrees of unsaturation.
We have uncovered three fragments, which account for all of the atoms in the molecular formula. These three fragments can only be connected in one way, as shown:



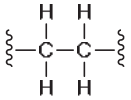
The ^{13}C NMR spectrum confirms this structure. The signal at 172.6 ppm corresponds to the carbon atom of the carbonyl group. The next four signals on the spectrum (above 100 ppm) are characteristic of a disubstituted aromatic ring, and finally, there are two signals between 0 and 50 ppm for the *tert*-butyl group (all three methyl groups are equivalent and give one signal, in addition to the signal from the benzylic carbon atom).

17.55. The molecular formula ($C_9H_{10}O$) indicates five degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring, as well as either one double bond or one ring.

In the ^{1}H NMR spectrum, the multiplet near 7 ppm is likely a result of aromatic protons. The integration of this multiplet is 5H, indicating a monosubstituted aromatic ring:



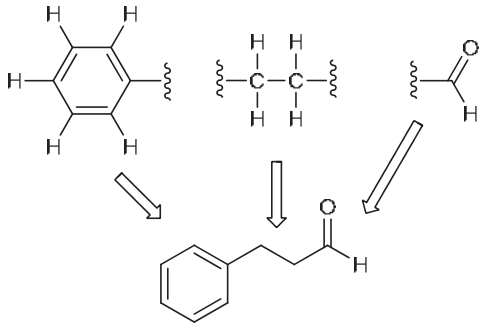
The spectrum also exhibits two triplets (near 3 ppm), indicating two methylene groups connected to each other:



Each of these signals appears more downfield than we might expect for a methylene group (1.2 ppm), so each of these methylene groups must be connected to a group that causes a deshielding effect. This must be taken into account in our final structure.
The singlet near 10 ppm is characteristic of an aldehyde group:



We have uncovered three fragments, which account for all of the atoms in the molecular formula. These three fragments can only be connected in one way, as shown:



Notice that the structure explains why the two triplets appear downfield. One is shifted downfield primarily as a result of its proximity to the carbonyl group, while the other is shifted primarily as a result of its proximity to the aromatic ring.
The ^{13}C NMR spectrum confirms the structure above. The signal near 200 ppm corresponds to the carbon atom of the carbonyl group. The next four signals on the spectrum (above 100 ppm) are characteristic of a monosubstituted aromatic ring, and finally, there are two signals between 0 and 50 ppm for the methylene groups. In addition, the IR spectrum also confirms this structure. The strong signal just above 1700 cm^{-1} corresponds with the C=O bond, and the signals between 3000 and 3100 cm^{-1} correspond with the aromatic ring. Curiously, there is a signal between 3200 and 3600 which is reminiscent

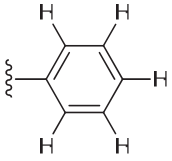
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of an O-H signal, although a bit weaker than normal (the signal for an OH group is typically much stronger). This is perhaps due to some concentration of the tautomeric enol that is present at equilibrium (which exhibits an OH group).

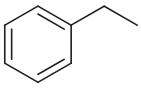
17.56.
(a) The second compound holds greater promise as a potential antihistamine, because it possesses two planar aromatic rings separated from each other by one carbon atom. The first compound has only one aromatic ring. The ring with the oxygen atom is not aromatic and not planar.
(b) Yes, because it lacks polar functional groups that would prevent it from crossing the blood-brain barrier, as described in the Medically Speaking application (that appears at the end of Section 17.5).

17.57. No, this compound possesses an allene group (C=C=C). The *p* orbitals of one C=C bond of the allene group do not overlap with the *p* orbitals of the other C=C bond. This prevents the compound from having one continuous system of overlapping *p* orbitals.

17.58. The molecular formula (C_8H_{10}) indicates four degrees of unsaturation (see Section 14.16), consistent with an aromatic ring. The ^{1}H NMR spectrum of compound **A** has a multiplet near 7 ppm with an integration of 5H, indicating a monosubstituted aromatic ring:

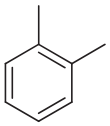


The aromatic ring accounts for six of the eight carbon atoms in the structure. If the ring is monosubstituted, then the other two carbon atoms must be an ethyl group, which is consistent with the two upfield signals in the ^{1}H NMR spectrum:



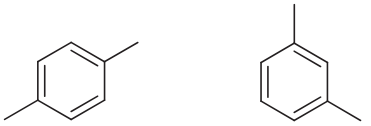
Compound A

Compound **B** is a constitutional isomer of **A** and exhibits four signals in its ^{13}C NMR spectrum, which is consistent with *ortho*-xylene (*meta*-xylene would produce five signals, while *para*-xylene would produce three signals in its ^{13}C NMR spectrum):



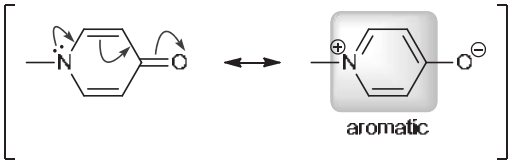
Compound B

Compound **C** is a constitutional isomer of **A** and **B**, and it exhibits three signals in its ^{13}C NMR spectrum, which is consistent with *para*-xylene. Compound **D** is a constitutional isomer of **A**, **B**, and **C**, and it must be *meta*-xylene:



Compound **C** Compound D

17.59. The lone pair on the nitrogen atom in compound **A** is localized and is not participating in resonance. It is free to function as a base. The lone pair on the nitrogen atom in compound **B** is delocalized, allowing the compound to achieve aromatic stabilization via resonance:

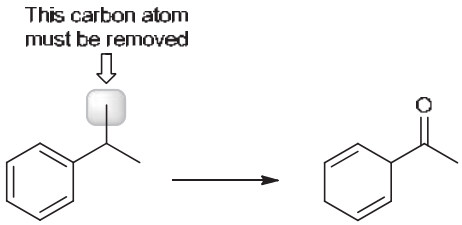


In compound **B**, the lone pair on the nitrogen atom is participating in establishing aromaticity, and therefore, it is not available to function as a base.

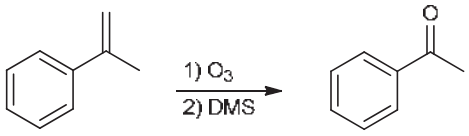
17.60. There are two questions to ask when approaching a synthesis problem.

1) Is there a change in the carbon skeleton?
2) Is there a change in the position or identity of the functional groups?

In this case, there is a change in the carbon skeleton. The product has one less carbon atom than the starting material:

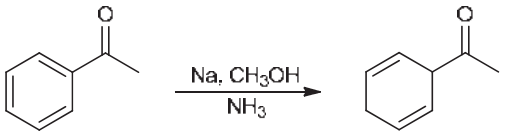


Also, a functional group (a C=O bond) must be installed, and the aromatic ring must be reduced to a diene.
Let's begin with the change in the carbon skeleton. We have only learned one way (ozonolysis) to remove a carbon atom from the carbon skeleton. Ozonolysis would indeed install the necessary functional group in the correct location:



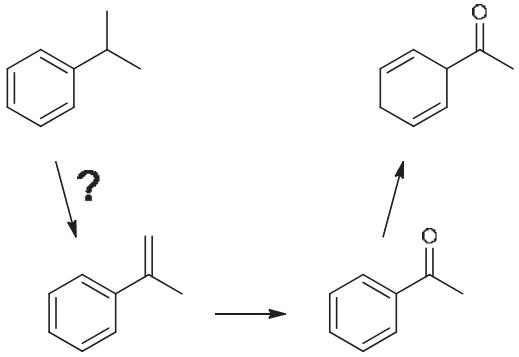
And the ketone above can be treated with Birch conditions to give the desired product:

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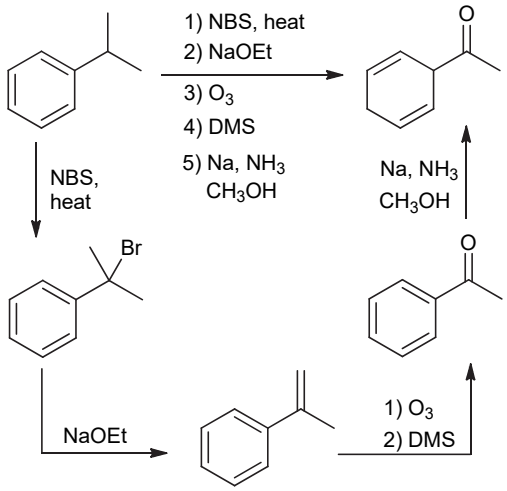


Notice that the regiochemical outcome of the Birch reduction is controlled by the carbonyl group, giving the desired product.

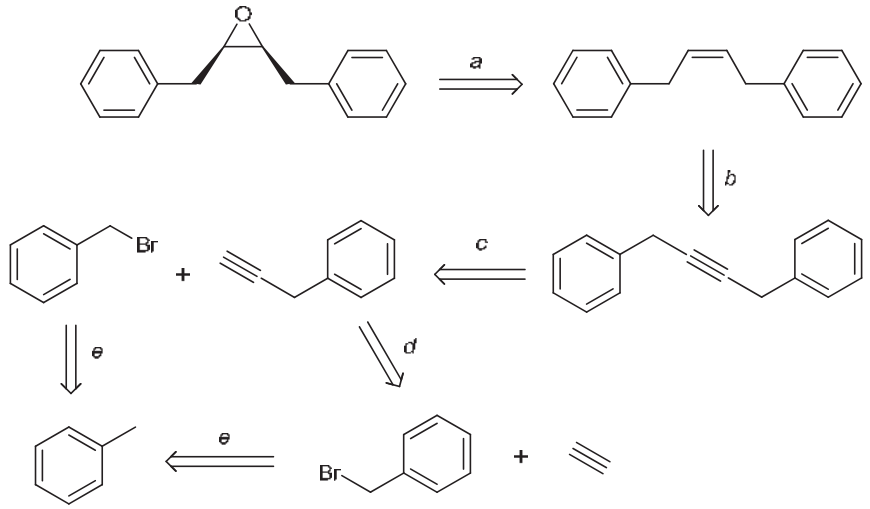
The strategy above requires that we first form the alkene from the starting material:



This can be accomplished via bromination of the benzylic position, followed by elimination (E2) upon treatment with a strong base (such as sodium ethoxide). The entire synthesis is summarized here:



17.61. The following retrosynthetic analysis (and subsequent explanation) represents one strategy for preparing the desired compound from the given starting materials (acetylene and toluene):



a. The *cis* epoxide can be made from the corresponding *cis* alkene, via epoxidation with a peroxy acid.

b. The *cis* alkene can be made from the corresponding alkyne, via a *syn* addition of molecular hydrogen (H_2) in the presence of a poisoned catalyst, such as Lindlar's catalyst.

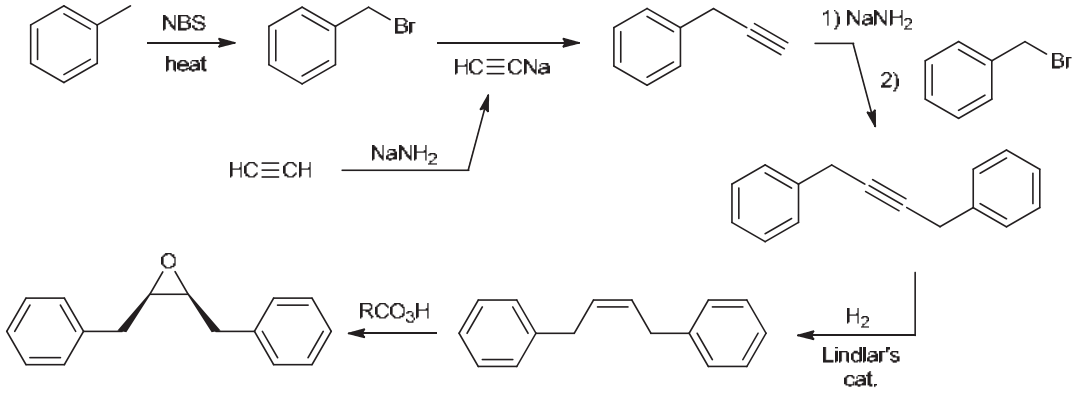
c. The internal alkyne can be made from a terminal alkyne and benzyl bromide. The terminal alkyne is first deprotonated to give an alkynide ion, which is then treated with benzyl bromide (in an S_N2 reaction).

d. The terminal alkyne can be made from acetylene and benzyl bromide. Acetylene is first deprotonated to give an acetylide ion, which is then treated with benzyl bromide (in an S_N2 reaction).

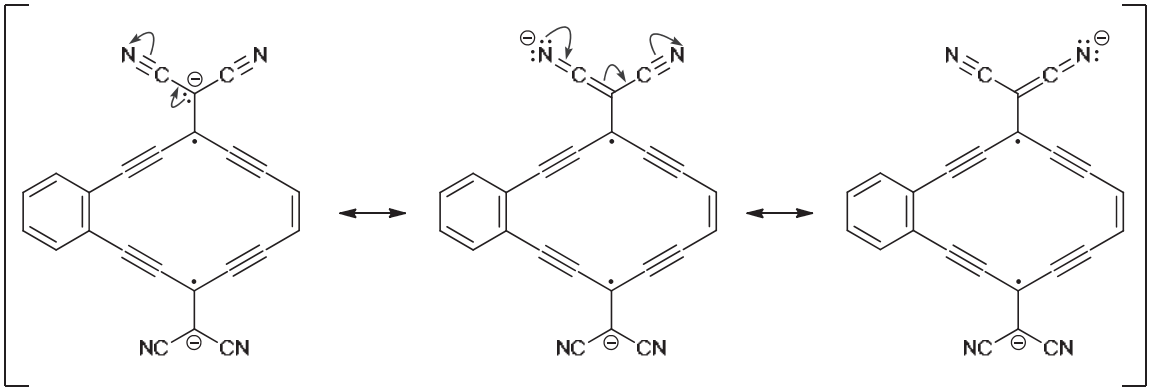
e. Benzyl bromide can be made from toluene via radical bromination at the benzylic position.

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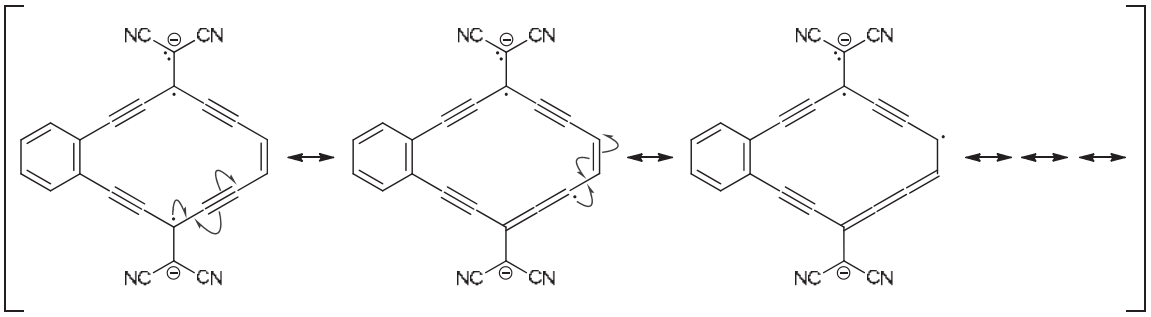
The forward process is shown here:



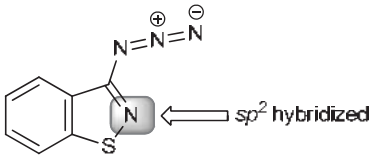
17.62.
(a) Each of the double bonds and triple bonds contributes two π electrons, and each of the unpaired electrons counts as one electron. This gives a total of 14 π electrons, so the large ring in **B** is aromatic.
(b) Each of the negative charges is delocalized over three positions, as seen in the following three resonance structures:



(c) Each of the unpaired electrons is highly delocalized, as seen in the following resonance structures:



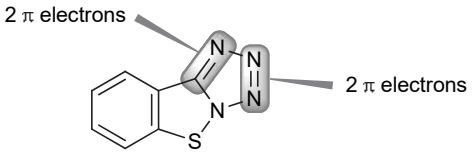
17.63. The nitrogen atom incorporated in the ring in compound **2** (highlighted below) possesses a double bond and is clearly sp^2 hybridized.



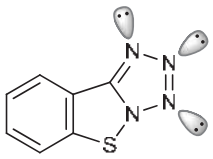
So, we must determine the hybridization state of the same nitrogen atom in compound **1**. This requires that we determine whether the tetrazole ring is aromatic. That is, the lone pair on the nitrogen atom will occupy a *p* orbital (rendering the nitrogen atom sp^2 hybridized) if doing so establishes aromaticity. However, if doing so establishes antiaromaticity, then the nitrogen atom would adopt sp^3 hybridization to avoid antiaromaticity.

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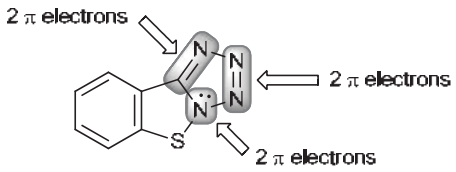
To determine if the tetrazole ring is aromatic, we count the π electrons. The atoms highlighted below contribute a total of four π electrons (two for each π bond).



The lone pairs on those atoms must reside in sp^2 hybridized orbitals (rather than *p* orbitals) in the plane of the ring, and cannot contribute to aromaticity:



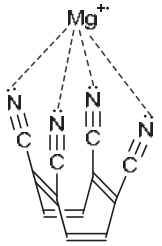
The lone pair on the remaining nitrogen atom therefore occupies a *p* orbital, giving a total of 6 π electrons.



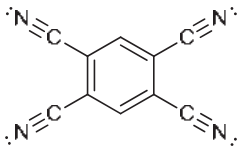
With a Hückel number of π electrons, the tetrazole ring is indeed aromatic, and as such, this nitrogen atom is sp^2 hybridized. Therefore, this nitrogen atom does not undergo a change in hybridization state during the isomerization process. It is sp^2 hybridized in both constitutional isomers.

17.64.

(a) If planar, the cyclooctatetraene ring would be antiaromatic (4n π electrons, where n = 2). It instead adopts a more stable tub conformation that is non-planar, thus avoiding the energetic cost of antiaromaticity. The tub conformation allows all four cyano groups to be oriented approximately in the same direction such that they can coordinate to a single $Mg^{+\bullet}$ ion as shown.

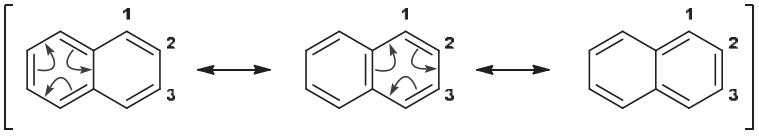


(b) The four nitriles on 1,2,4,5-tetracyanobenzene are oriented away from each other due to benzene's planar (aromatic) structure. Due to this, the four cyano groups cannot be simultaneously coordinated to the same $Mg^{+\bullet}$ ion.



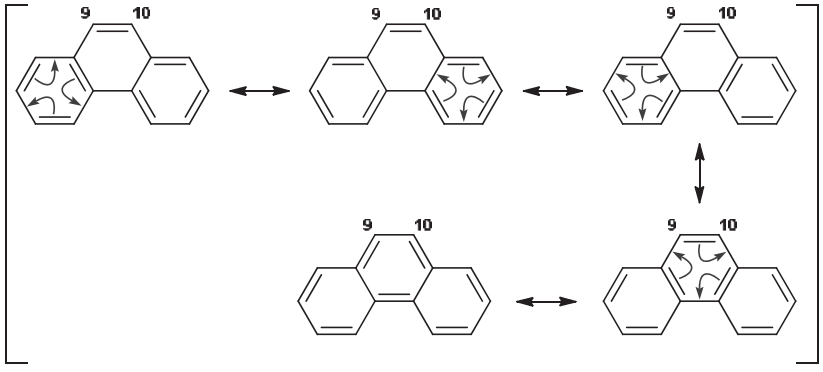
17.65.

(a) Consider the three resonance structures for naphthalene, and focus in particular on the C1-C2 bond and the C2-C3 bond:



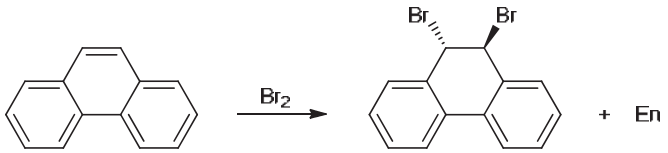
Notice that the C1-C2 bond is a double bond in two of the three resonance structures, while the C2-C3 bond is a double bond in only one of the resonance structures. As such, the former has more double-bond character than the latter, so the C1-C2 bond will have a shorter bond length. Recall that double bonds are shorter than single bonds (see Table 1.2).

(b) Begin by drawing all of the resonance structures:

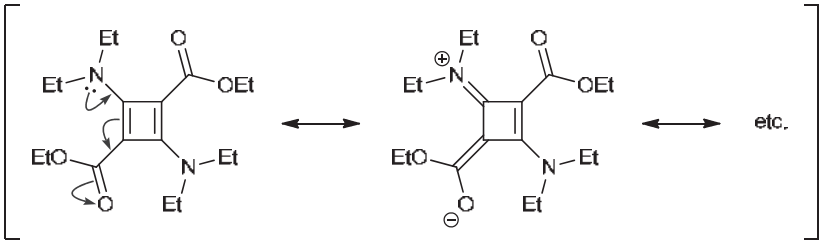


Notice that the C9-C10 bond is a double bond in four of the five resonance structures. No other bond in phenanthrene has this feature. As such, the C9-C10 bond is expected to have the most double-bond character, and consequently, the shortest bond length.

(c) In part (b), we determined that the C9-C10 bond has the most double-bond character, and in fact, this bond functions very much like a regular π bond. It will undergo addition with Br_2 to give a dibromide which retains aromaticity on two of the rings:



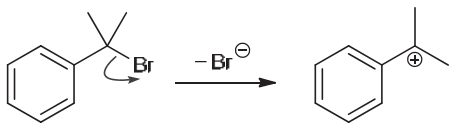
17.66.
(a) We know that *tert*-butyl groups are sterically bulky, so it is reasonable to suggest that the presence of three *tert*-butyl groups provides enough steric hindrance to slow the rate of the Diels-Alder process substantially, allowing the compound to be stable at room temperature.
(b) With these particular substituents, it is possible to draw resonance structures in which the double bonds are not positioned inside the ring, thereby diminishing the destabilizing effect of antiaromaticity.



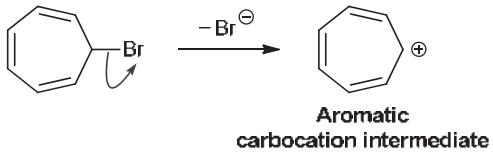
(c) Unlike systems with 4n π electrons, which exhibit destabilization associated with antiaromaticity, systems with 4n+2 π electrons exhibit aromatic stabilization. For these systems, the presence of resonance structures that diminish the aromatic stabilization will have a destabilizing effect.

17.67. In structure (a), the nitrogen atom has four sigma bonds, so it must be sp^3 hybridized. It does not have a *p* orbital, so the ring is NOT a continuous system of overlapping *p* orbitals. Therefore, structure (a) is nonaromatic. Structures (b), (c), and (d) are all aromatic.

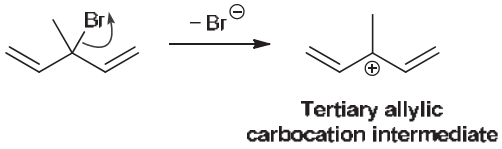
17.68. Structure (a) is a tertiary benzylic bromide, and it is therefore expected to undergo an S_N1 reaction in ethanol, because the intermediate carbocation is highly stabilized:



Similarly, structure (b) is also expected to undergo an S_N1 reaction, because the intermediate carbocation is aromatic and therefore highly stabilized:



Structure (c) is also expected to undergo an S_N1 reaction, because the intermediate carbocation is tertiary and allylic (twice), so it is highly stabilized as well:



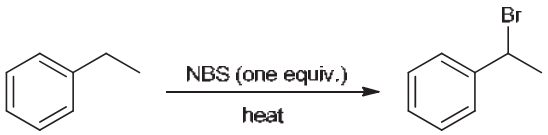
Only structure (d) gives an unstable carbocation upon loss of a leaving group:



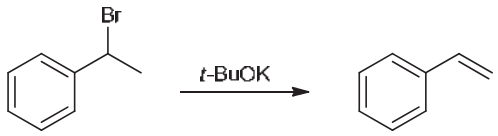
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This cation is unstable because it is antiaromatic. Therefore, structure (d) is not expected to undergo an S_N1 reaction. The answer is (d).

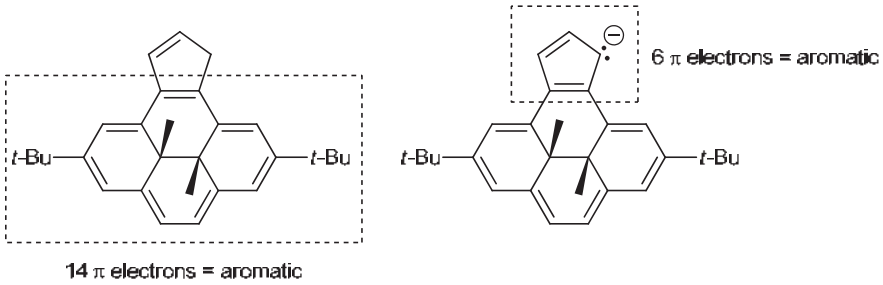
17.69. In the first step, one equivalent of NBS will install one Br (not two) at the benzylic position:



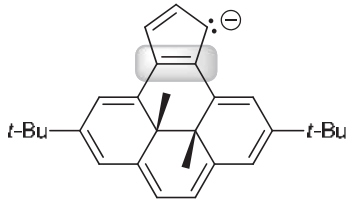
The resulting secondary benzylic halide is expected to undergo an E2 reaction upon treatment with a strong, sterically hindered base, giving structure (b).



17.70. In Chapter 15, we learned about magnetic anisotropy, and how aromatic ring currents have a shielding effect on substituents located at the interior of large aromatic rings. The starting material has an aromatic [14]annulene ring, which causes the two methyl groups to be shielded from the external magnetic field (even more so than the protons in TMS), hence their chemical shift of –3.9 ppm. When treated with a base, deprotonation occurs to generate a new aromatic system - notice that the five-membered ring now has 6 π electrons:

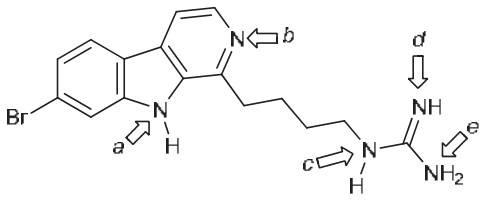


The aromatic stabilization associated with the five membered ring will cause the following highlighted π electrons (fused to the [14]annulene system) to be less available to the larger ring for conjugation, therefore resulting in a diminished ring current:

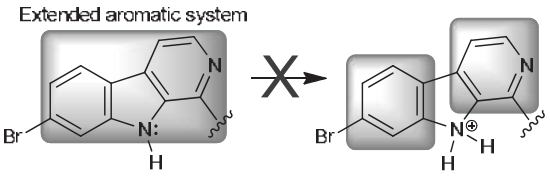


As a result, the local magnetic field established by the [14]annulene system opposes the external magnetic less significantly, causing the methyl groups to become less shielded. Being less shielded is equivalent to being more deshielded, so the signals for the methyl protons are shifted slightly downfield from –3.9 ppm to –1.8 ppm.

17.71. First, let's consider the relative basicity of each nitrogen atom in the structure.



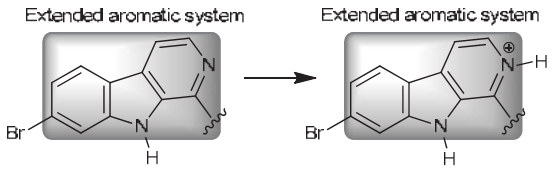
(a) The lone pair on this nitrogen atom occupies a *p*-orbital, thereby including the central ring in the aromatic stabilization of this compound. Protonation of this nitrogen is thus unlikely, as it would disrupt this extended aromatic system. Each of the two six-membered rings of the product below is still aromatic, but the extended aromatic system would be lost.



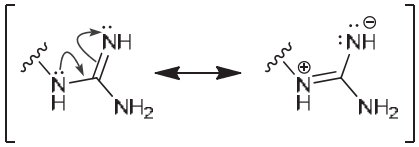
(b) The lone pair on this nitrogen atom occupies an sp^2 hybridized orbital that is orthogonal to the conjugated π system of the ring. Protonation of this nitrogen is thus

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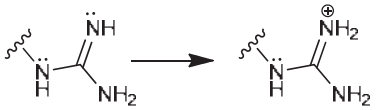
reasonable, as the extended aromaticity of the resulting conjugate acid remains intact.



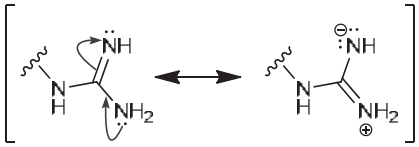
(c) The lone pair on this nitrogen atom is delocalized, as can be demonstrated by the following resonance structure. Thus, protonation of this nitrogen atom is not likely.



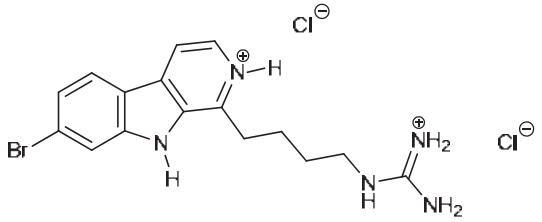
(d) The lone pair on this nitrogen atom is localized, and not involved in any resonance structures. Protonation of this site is therefore reasonable.



(e) The lone pair on this nitrogen atom is delocalized in a fashion analogous to location *c*. Protonation of this site is thus unlikely.



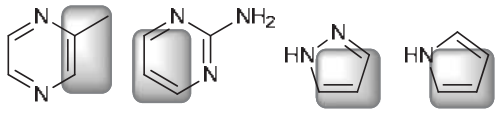
Based on the above analysis, treatment of the natural product with two equivalents of HCl is expected to afford the following structure:



17.72. In order to propose a structure for the fragment at *m/z* = 39, we should consider all of the possible combinations of atoms that will provide a mass-to-charge ratio of 39. Considering the atoms present (C, H, N) in each of the analytes, there are two possible ionic formulas that fit: C_2NH^+ or $C_3H_3^+$. Considering the fact that the fragment is very common (found in 17 of 20 samples), and relatively abundant (5-84% of the base peak), it is reasonable to assume that this fragment is a relatively stable cation. While there is no obvious stable cation with a formula of C_2NH^+, we can draw an aromatic cation with a formula of $C_3H_3^+$, called a cyclopropenium cation.

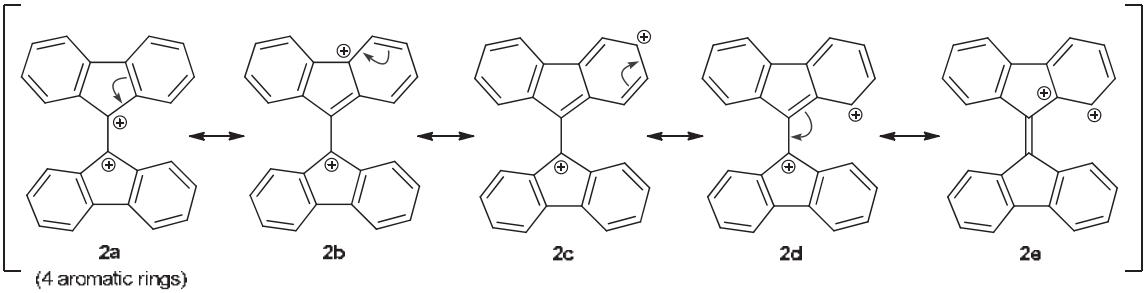


Now we must consider why the compounds in the top row produce this fragment, while those in the bottom row do not. Each of the compounds in the top row contains at least three contiguous carbon atoms with at least three hydrogen atoms among them (these six atoms are necessary for formation of the cyclopropenium cation), as highlighted below.



This is a structural feature that the three compounds in the bottom row lack. Thus, it is reasonable to propose that the cyclopropenium fragment results from rearrangements of the fragments from the molecules in the top row.

17.73. Many resonance structures can be drawn for dication **2**. The following are just a few of them:

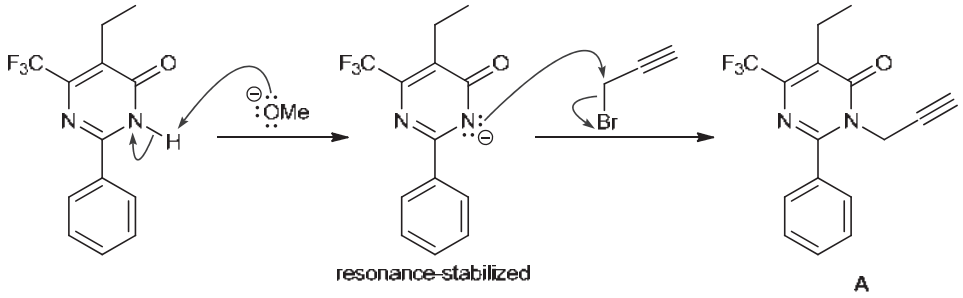


Notice that only resonance structure **2a** has four complete aromatic rings. The extra stabilization associated with this structure means that this resonance structure will contribute more character to the overall resonance hybrid, and as a result, the two neighboring central carbon atoms in dication **2** will both exhibit a large degree of carbocationic character.

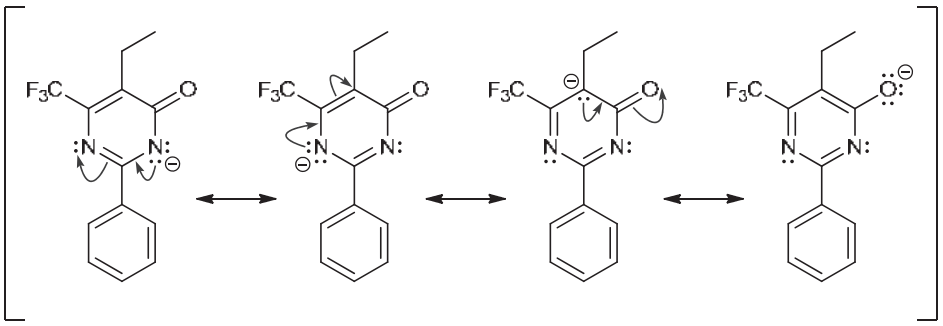
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17.74.

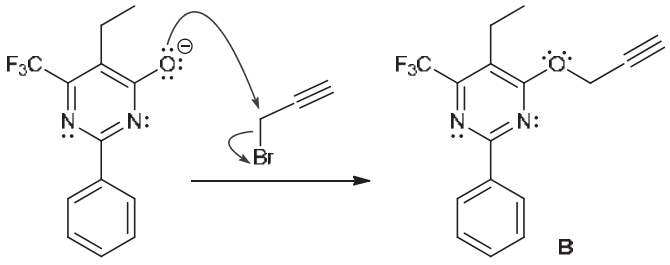
(a) Sodium methoxide is a strong base, which removes the most acidic proton in the starting material. The resulting resonance-stabilized anion can then function as a nucleophile and attack 3-bromo-1-propyne in an S_N2 process, giving **A**.



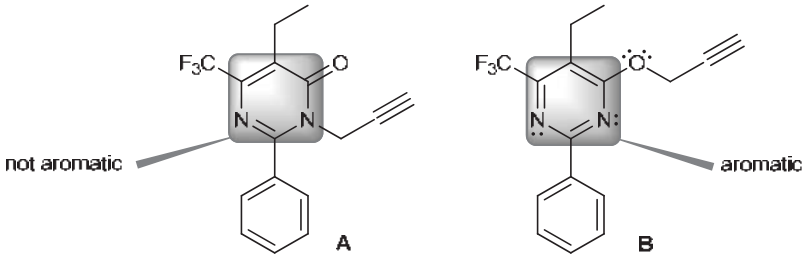
(b) As mentioned in the solution to part (a), the anionic intermediate is resonance-stabilized, so we draw the resonance structures:



Among these resonance structures, the last one is expected to contribute the most character to the overall resonance hybrid, for two reasons: 1) the negative charge is placed on an oxygen atom (rather than on a nitrogen atom or on a carbon atom), and 2) this resonance structure exhibits a benzene-like ring. In fact, this anionic intermediate is indeed aromatic, and we expect the oxygen atom to bear the majority of the delocalized negative charge. Based on this, we can propose the following structure and mechanism of formation for **B**:



(c) Compound **B** has aromatic stabilization that is absent in **A**. As such, **B** is expected to be lower in energy, so the product mixture will have more of **B** than **A**.



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Chapter 18
Aromatic Substitution Reactions

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 18. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- In the presence of iron, an _____ **aromatic substitution** reaction is observed between benzene and bromine.
- Iron tribromide is a _____ acid that interacts with Br_2 and generates Br^+, which is sufficiently electrophilic to be attacked by benzene.
- Electrophilic aromatic substitution involves two steps:
  - Formation of the _____ **complex**, or **arenium ion.**
  - Deprotonation, which restores _____.
- Sulfur trioxide (SO_3) is a very powerful _____ that is present in fuming sulfuric acid. Benzene reacts with SO_3 in a reversible process called _____.
- A mixture of sulfuric acid and nitric acid produces the **nitronium ion** (NO_2^+). Benzene reacts with the nitronium ion in a process called _____.
- A nitro group can be reduced to an _____group.
- **Friedel–Crafts alkylation** enables the installation of an alkyl group on _____. When choosing an alkyl halide, the carbon atom connected to the halogen must be _____hybridized.
- When treated with a Lewis acid, an acyl chloride will generate an _____ **ion**, which is resonance stabilized and not susceptible to _____ rearrangements.
- When a Friedel–Crafts acylation is followed by a **Clemmensen reduction**, the net result is the installation of an _____ group.
- A methyl group is said to **activate** an aromatic ring and is an _____**-**_____ **director**.
- All activators are _____-_____directors.
- A nitro group **deactivates** an aromatic ring and is a _____director.
- Most deactivators are _____directors.
- **Strong activators** are characterized by the presence of a _____ immediately adjacent to the aromatic ring.
- **Strong deactivators** are powerfully electron withdrawing, either by _____or _____.
- When multiple substituents are present, the more powerful _____ dominates the directing effects.
- In a **nucleophilic aromatic substitution** reaction, the aromatic ring is attacked by a _____. This reaction has three requirements: 1) the ring must contain a powerful electron-withdrawing group (typically a _____group) 2) the ring must contain a _____, and 3) the leaving group must be either _____or _____to the electron-withdrawing group.
- An **elimination-addition** reaction occurs via a _____intermediate.

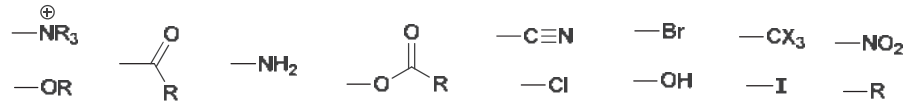
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Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 18. The answers appear in the section entitled *SkillBuilder Review*.

18.1 Identifying the Effects of a Substituent

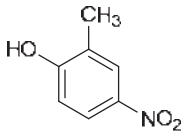
PLACE EACH OF THE FOLLOWING GROUPS IN THE CORRECT CATEGORY BELOW.



ACTIVATORS			DEACTIVATORS		
STRONG	MODERATE	WEAK	WEAK	MODERATE	STRONG

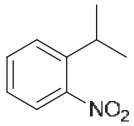
18.2 Identifying Directing Effects for Disubstituted and Polysubstituted Benzene Rings

IN THE FOLLOWING COMPOUND, IDENTIFY THE POSITION THAT IS MOST REACTIVE TOWARDS ELECTROPHILIC AROMATIC SUBSTITUTION.



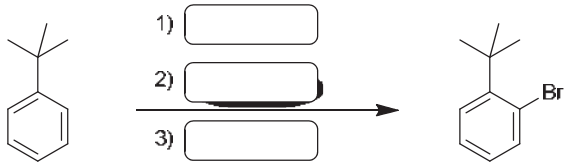
18.3 Identifying Steric Effects for Disubstituted and Polysubstituted Aromatic Benzene Rings

IN THE FOLLOWING COMPOUND, IDENTIFY THE POSITION THAT IS MOST REACTIVE TOWARDS ELECTROPHILIC AROMATIC SUBSTITUTION.



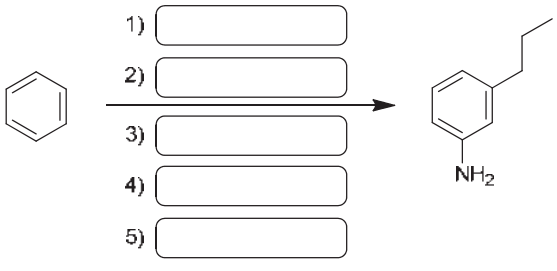
18.4 Using Blocking Groups to Control the Regiochemical Outcome of an Electrophilic Aromatic Substitution Reaction

IDENTIFY REAGENTS THAT WILL ACHIEVE THE FOLLOWING TRANSFORMATION.



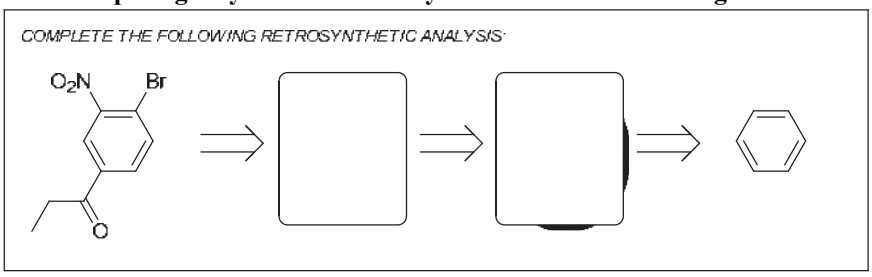
18.5 Proposing a Synthesis for a Disubstituted Benzene Ring

IDENTIFY REAGENTS THAT CAN BE USED TO ACHIEVE THE FOLLOWING TRANSFORMATION.

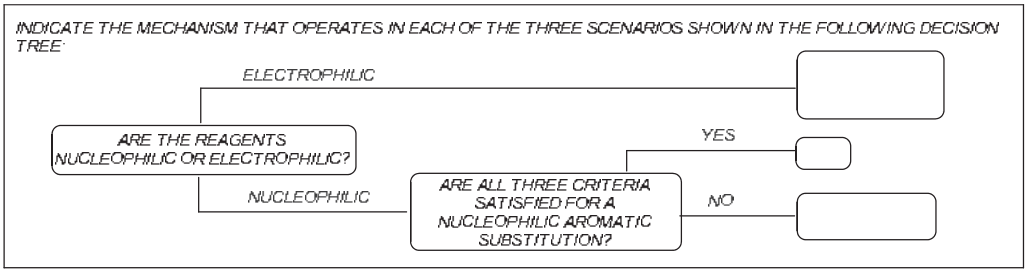


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18.6 Proposing a Synthesis for a Polysubstituted Benzene Ring



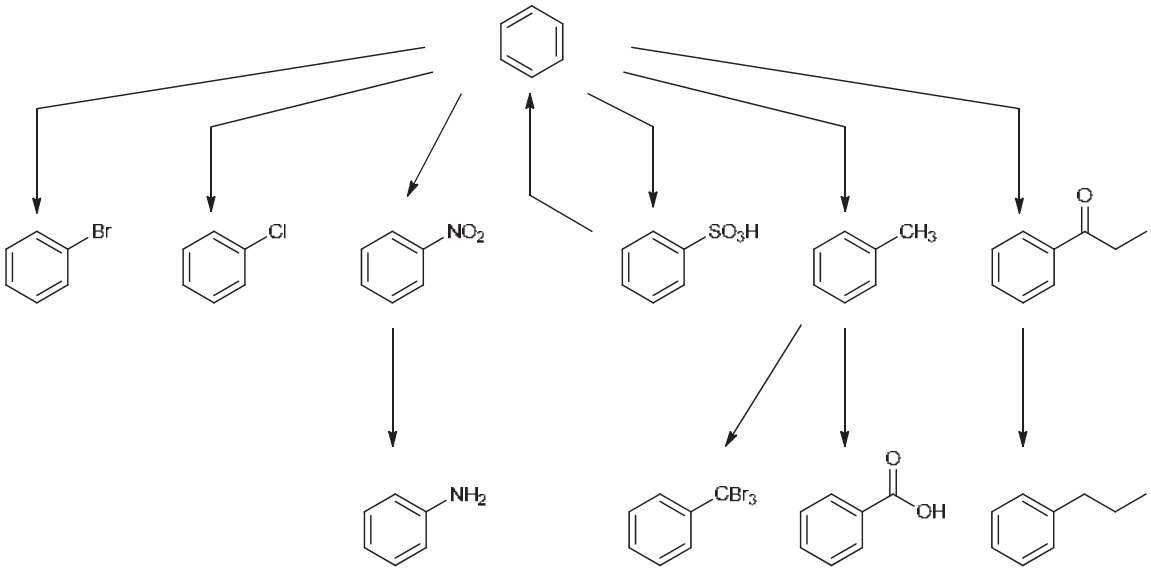
18.7 Determining the Mechanism of an Aromatic Substitution Reaction



Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 18. The answers appear in the section entitled *Review of Reactions*.

Electrophilic Aromatic Substitution

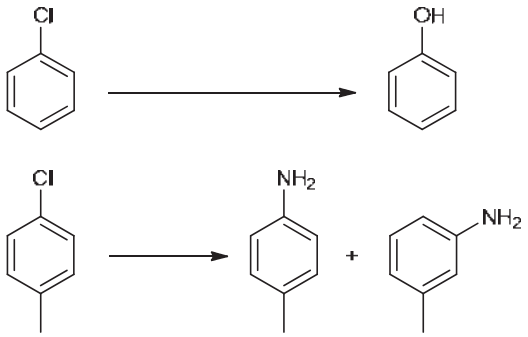


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Nucleophilic Aromatic Substitution

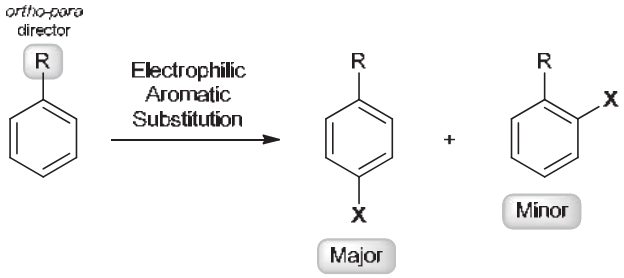


Elimination-Addition

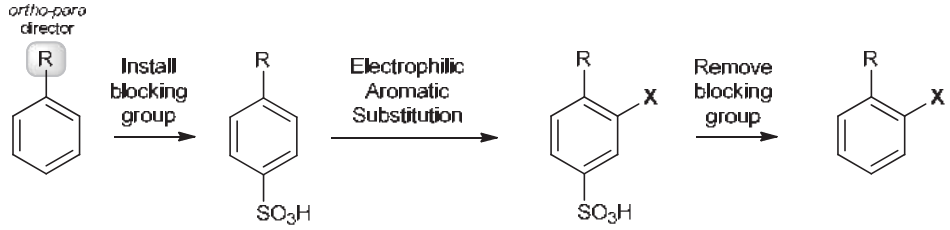


Common Mistakes to Avoid

For most *ortho-para* directors, we can rely on steric effects that will favor substitution at the *para* position rather than the *ortho* position:



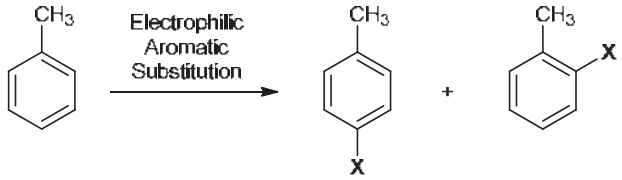
The major product results from *para* attack, and the minor product results from *ortho* attack. If we want to achieve substitution at the *ortho* position, then we must employ a blocking group:



With this technique, we use the *para*-directing effects of the substituent to block (temporarily) the *para* position. This allows us to perform the desired reaction at the *ortho* position, followed by removal of the blocking group.

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When designing a synthesis that involves the directing effects of an *ortho-para* director, you can generally rely on a preference for *para* attack (at the expense of *ortho* attack). A notable exception is toluene, which exhibits a very small group (a methyl group). The steric bulk provided by a methyl group is small enough to give a nearly equal mixture of *ortho* and *para* products:



It is often difficult to predict which product will predominate, and the product distribution will be dependent on the conditions employed. When toluene undergoes an electrophilic aromatic substitution reaction, a mixture of *ortho* and *para* products is unavoidable. Therefore, it would be inefficient to rely on the directing effects (to favor *para* attack over *ortho* attack) of a methyl group. Avoid making this mistake, as there are many ways that this mistake can manifest itself in a synthesis problem. For example, if you are designing a synthesis for a polysubstituted aromatic ring (where one of the substituents is a methyl group), consider installing the methyl group last, rather than first. Consider the following transformation, which requires two successive Friedel-Crafts alkylation reactions:



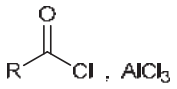
This transformation is best achieved if the *tert*-butyl group is installed prior to the methyl group. After the *tert*-butyl group is installed, subsequent methylation is forced to occur almost exclusively at the *para* position (because of the steric bulk of the *tert*-butyl group). In contrast, if methylation is performed first, then installation of the *tert*-butyl group will not proceed with the same degree of regioselectivity.

Useful reagents

The following is a list of reagents encountered in this chapter:

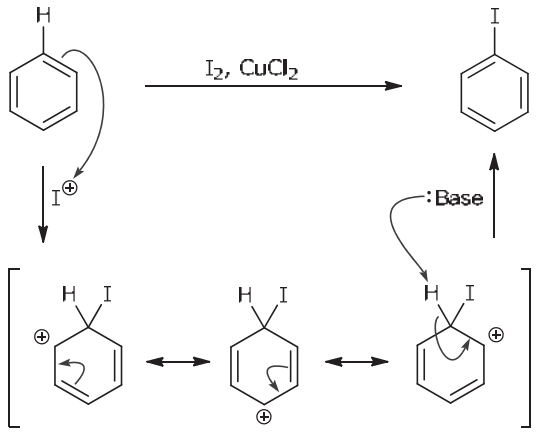
Reagents	Name of Reaction	Description
Br_2, $AlBr_3$ or $FeBr_3$	Bromination	Installation of a bromine atom on an aromatic ring.
Br_2	Bromination	Installation of a bromine atom on a moderately or strongly activated aromatic ring.
Cl_2, $AlCl_3$ or $FeCl_3$	Chlorination	Installation of a chlorine atom on an aromatic ring.
Cl_2	Chlorination	Installation of a chlorine atom on a moderately or strongly activated aromatic ring.
HNO_3, H_2SO_4	Nitration	Installation of a nitro group on an aromatic ring. Cannot be performed if an amino group is already present on the aromatic ring.
Fuming H_2SO_4	Sulfonation	Installation of a sulfonic acid group, often used as a blocking group.
Dilute H_2SO_4	Desulfonation	Removes a sulfonic acid group.
RCl, $AlCl_3$	Friedel-Crafts alkylation	Installation of an alkyl group on an aromatic ring. This process is limited to R groups that are not susceptible to carbocation rearrangements. Unless otherwise indicated, assume conditions will favor monoalkylation. This reaction cannot be performed on a moderately or strongly deactivated aromatic ring.

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	Friedel-Crafts acylation	Installation of an acyl group on an aromatic ring. Cannot be performed on a moderately or strongly deactivated aromatic ring.
1) Fe or Zn, HCl 2) NaOH	Reduction	Reduction of a nitro group to give an amino group.
Excess NBS	Benzylic bromination	Exhaustive bromination of the benzylic position.
1) $KMnO_4$, H_2O, heat 2) H_3O^+	Benzylic oxidation	Oxidation of the benzylic position to give a carboxylic acid.
Zn(Hg), HCl, heat	Clemmensen reduction	Reduction of a carbonyl group to give a methylene (CH_2) group.
NaOH	S_NAr or elimination-addition	A strong nucleophile used in nucleophilic aromatic substitution reactions as well as elimination-addition reactions.
$NaNH_2$	elimination-addition	A very strong base (and strong nucleophile) used in elimination-addition reactions.

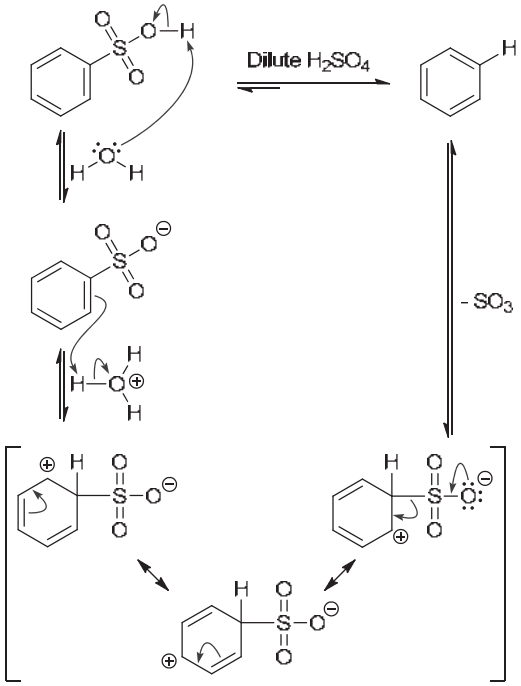
Solutions

18.1. In the first step, the aromatic ring functions as a nucleophile and attacks the electrophile (I^+), giving a resonance-stabilized intermediate (called a sigma complex). The sigma complex then loses a proton to restore aromaticity, affording the product:



The problem statement has not provided enough information for us to determine the identity of the base that removes the proton in the last step of the process. This type of situation is extremely rare. In nearly all cases that you encounter throughout this course, you should be able to determine the identity of the base.

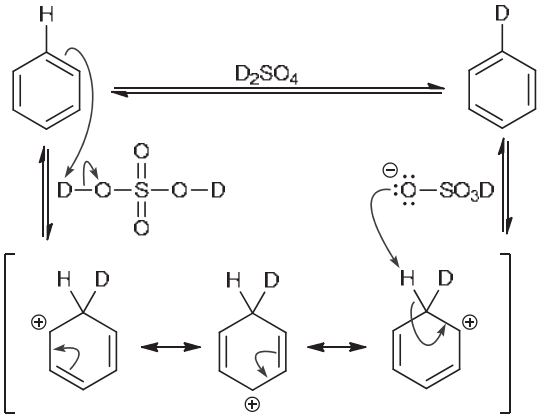
18.2. If we consider the fact that desulfonation is the reverse process of sulfonation, then the first step of desulfonation should be a proton transfer (since that was the last step of sulfonation). The aromatic ring is then protonated to give a resonance-stabilized intermediate (sigma complex), which then loses SO_3 to regenerate aromaticity.



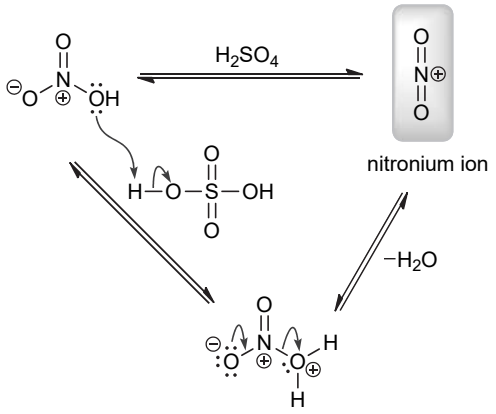
18.3. The aromatic ring functions as a base and removes a deuteron from D_2SO_4, giving an intermediate sigma

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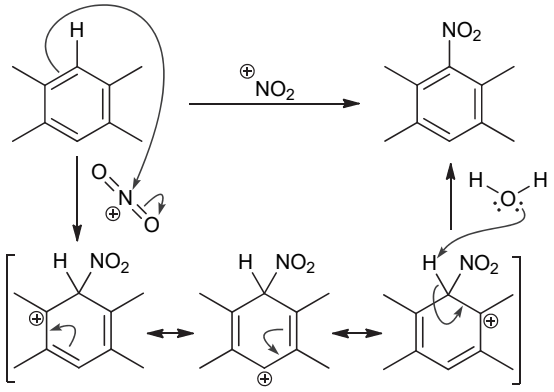
complex, which then loses a proton to restore aromaticity.



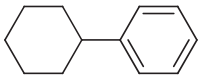
18.4.
In the presence of sulfuric acid, nitric acid can be protonated, followed by loss of water to give a nitronium ion (highlighted):



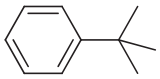
The aromatic ring then functions as a nucleophile and attacks the nitronium ion to give an intermediate sigma complex, which then loses a proton to restore aromaticity. Water is the likely base for the final deprotonation step, since water is present in large quantities (and there are no strong bases present in strongly acidic conditions).



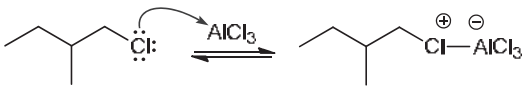
18.5.
(a) When benzene is treated with R–Cl in the presence of a Lewis acid, an R group is installed on the aromatic ring. In this case, the R group is a cyclohexyl group, so we expect a cyclohexyl group to be installed on the aromatic ring, giving the following product:



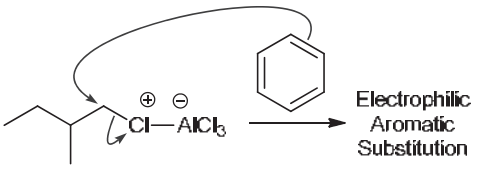
(b) When benzene is treated with R–Cl in the presence of a Lewis acid, an R group is installed on the aromatic ring. In this case, the R group is a *tert*-butyl group, so we expect a *tert*-butyl group to be installed on the aromatic ring. No rearrangement is expected, since the carbocation formed upon chloride departure is tertiary.



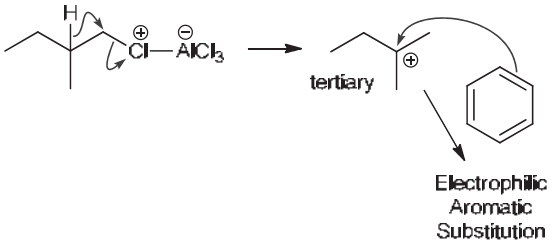
(c) When benzene is treated with R–Cl in the presence of a Lewis acid, an R group is installed on the aromatic ring. In this case, consider the complex that is formed when R–Cl interacts with the Lewis acid:



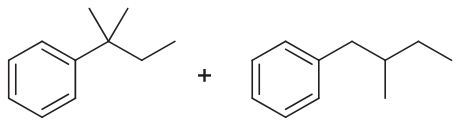
This complex can either be attacked by benzene,



or the complex can rearrange, via a hydride shift, to give a tertiary carbocation, which can then react with benzene:

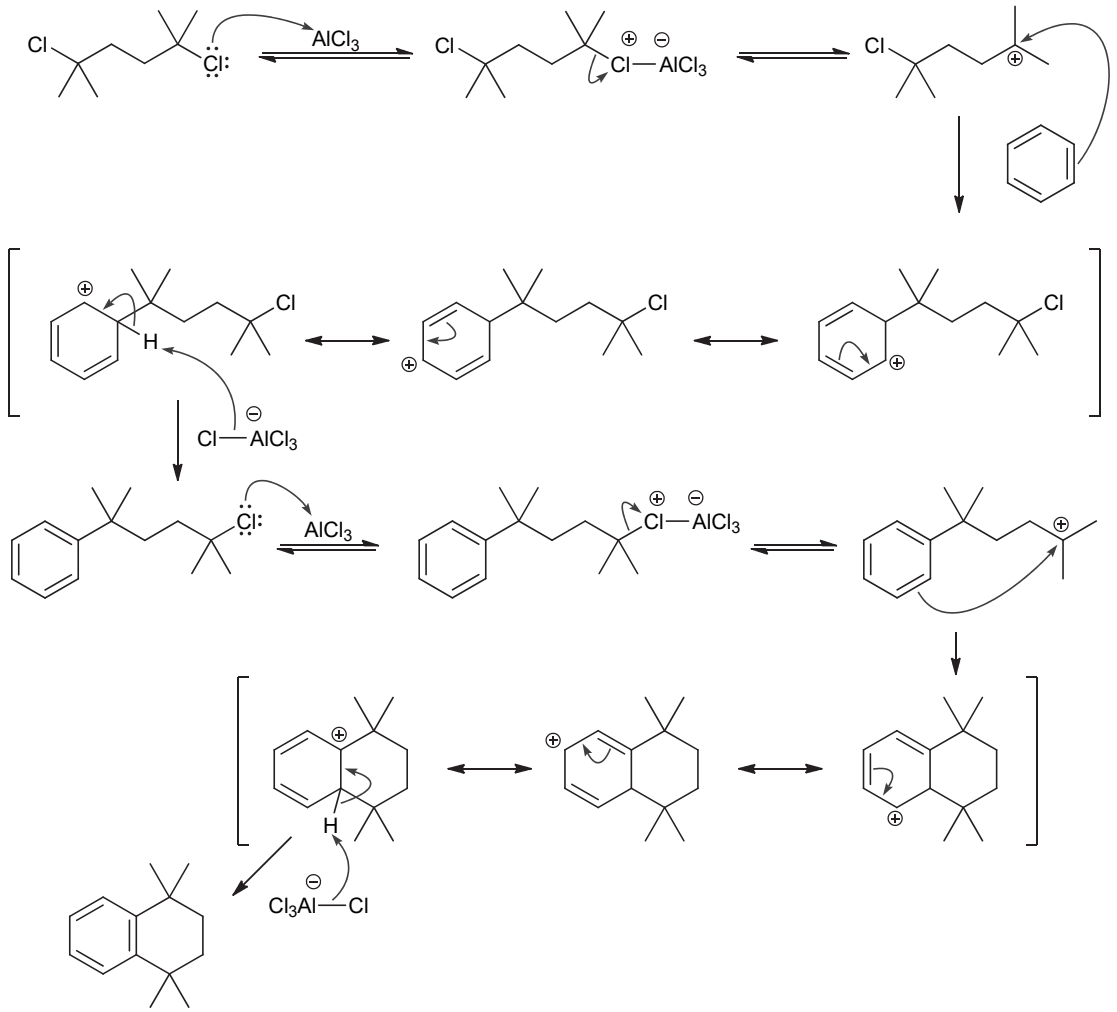


As such, there are two possible products for this electrophilic aromatic substitution reaction:



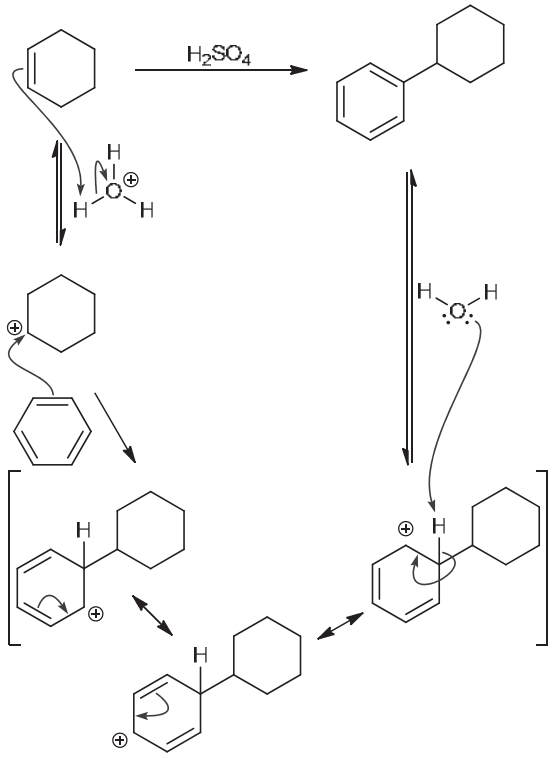
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18.6. An interaction between a lone pair (on one of the chlorine atoms) and the Lewis acid generates a complex that can lose a leaving group ($AlCl_4^-$) to give a tertiary carbocation. This carbocation then functions as an electrophile in an electrophilic aromatic substitution reaction. That is, benzene attacks the carbocation to give an intermediate sigma complex, which then loses a proton to restore aromaticity. All of the steps above are then repeated once again to close the ring, except this time, the electrophilic aromatic substitution reaction occurs in an intramolecular fashion. A lone pair on the chlorine atom interacts with the Lewis acid to generate a complex that can lose a leaving group ($AlCl_4^-$) to give a tertiary carbocation. This carbocation then functions as an electrophile in an *intramolecular* electrophilic aromatic substitution reaction. That is, the aromatic ring attacks the carbocation to give an intermediate sigma complex, which then loses a proton to restore aromaticity:



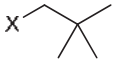
18.7. Sulfuric acid is used as an aqueous solution, so we indicate H_3O^+ as the proton source in our mechanism, rather than H_2SO_4 (because H_2SO_4 is a stronger acid than H_3O^+, so mixing H_2SO_4 and water causes the protons to be transferred from H_2SO_4 to H_2O, giving H_3O^+). In these acidic conditions, the alkene is protonated to give a carbocation. This carbocation then serves as an electrophile in an electrophilic aromatic substitution reaction. The aromatic ring attacks the electrophile to give an intermediate sigma complex, which is then deprotonated to restore aromaticity, thereby giving the product. Water is the likely base for the final deprotonation step, since water is present in a solution of sulfuric acid (and there are no strong bases present in strongly acidic conditions).

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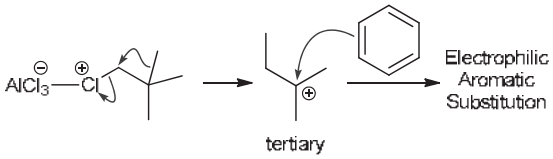


18.8.

(a) Making the desired product via a Friedel–Crafts alkylation process would require the use of the following type of alkyl halide:

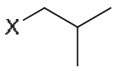


This alkyl halide will interact with a Lewis acid to give a complex that can undergo a methyl shift:

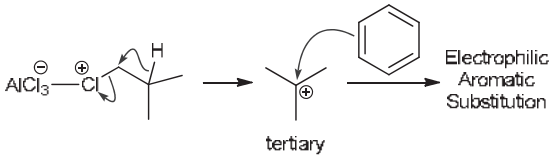


Therefore, it is necessary to perform an acylation followed by a Clemmensen reduction to avoid carbocation rearrangements.

(b) Making the desired product via a Friedel–Crafts alkylation process would require the use of the following type of alkyl halide:

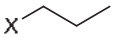


This alkyl halide will interact with a Lewis acid to give a complex that can undergo a hydride shift:

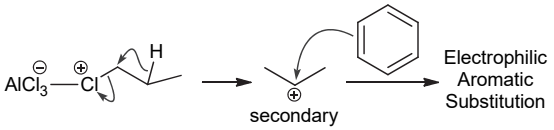


Therefore, it is necessary to perform an acylation followed by a Clemmensen reduction to avoid carbocation rearrangements.

(c) Making the desired product via a Friedel–Crafts alkylation process would require the use of the following type of alkyl halide:



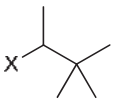
This alkyl halide will interact with a Lewis acid to give a complex that can undergo a hydride shift:



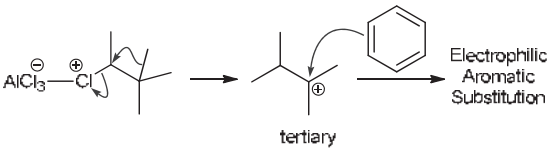
Therefore, it is necessary to perform an acylation followed by a Clemmensen reduction to avoid carbocation rearrangements.

(d) Making the desired product via a Friedel–Crafts alkylation process would require formation of a Lewis acid/base complex that would not undergo carbocation rearrangement. Therefore, the compound can be made using a direct Friedel–Crafts alkylation.

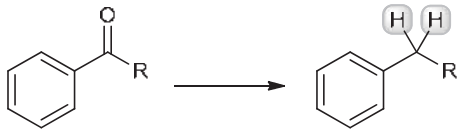
18.9. Making the desired product via a Friedel–Crafts alkylation process would require the use of the following type of alkyl halide:



This alkyl halide will interact with a Lewis acid to give a complex that can undergo a methyl shift:



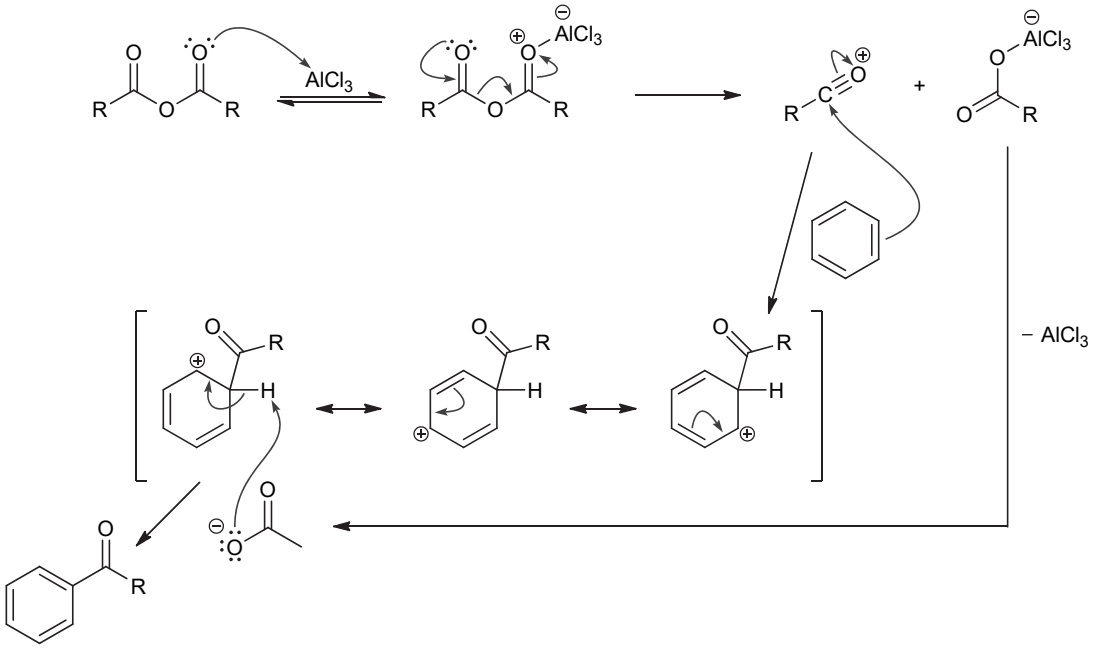
The desired product also cannot be made via acylation followed by a Clemmensen reduction, because the product of a Clemmensen reduction has two benzylic protons:



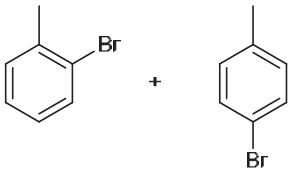
The desired product has only one benzylic proton, which means that it cannot be made via a Clemmensen reduction.

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18.10. The anhydride interacts with the Lewis acid to give a complex which loses a leaving group to produce an acylium ion. This acylium ion then serves as an electrophile in an electrophilic aromatic substitution reaction. The aromatic ring attacks the electrophile to give an intermediate sigma complex, which is then deprotonated to restore aromaticity, thereby giving the product. An acetate ion is the likely base for the final deprotonation step, since acetate is a by-product of the reaction. Acetate is formed when the leaving group (of the second step of mechanism) breaks apart into $AlCl_3$ and acetate (as shown).

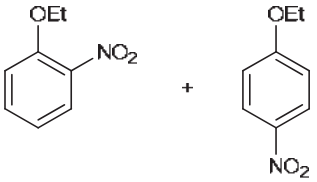


18.11. The methyl group is an activator, which directs the incoming electrophile (Br^+) to the *ortho* and *para* positions:

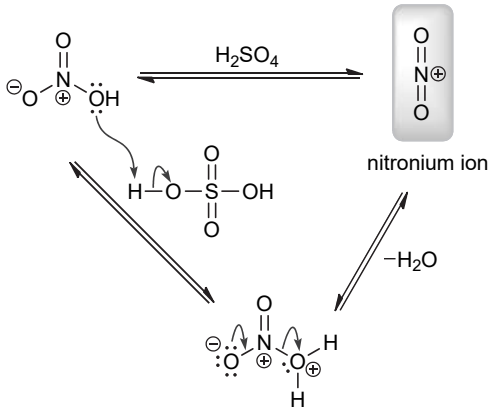


18.12.

(a) The ethoxy group is an activator, which directs the incoming electrophile (NO_2^+) to the *ortho* and *para* positions:

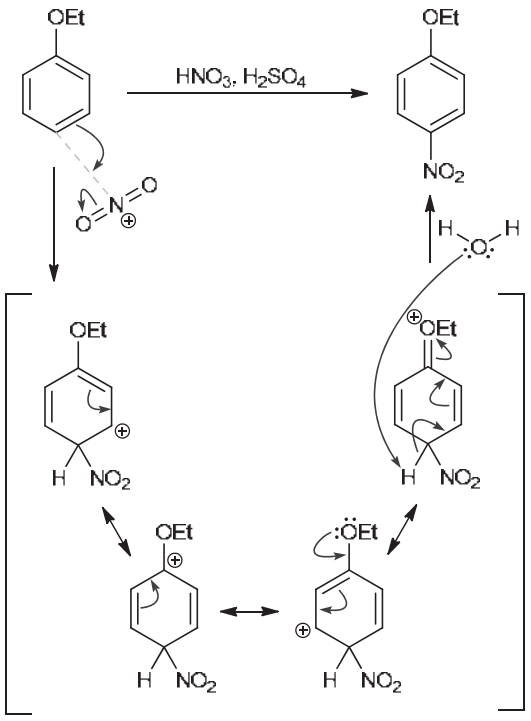


(b) In the presence of sulfuric acid, nitric acid can be protonated, followed by loss of water to give a nitronium ion:



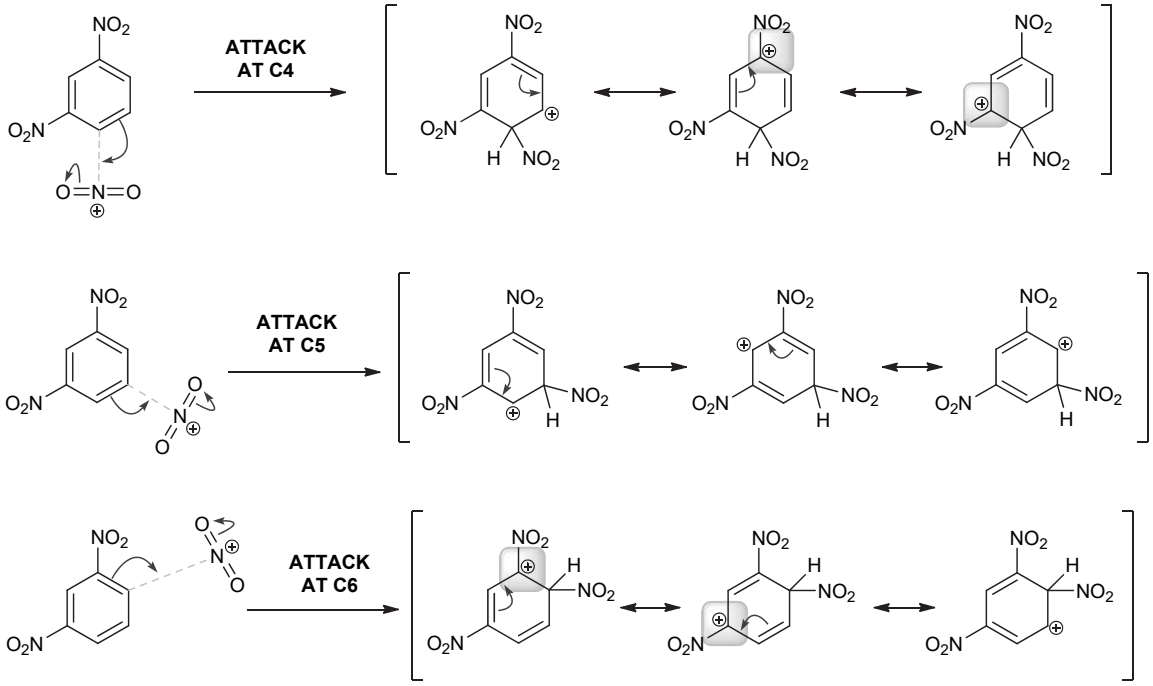
The aromatic ring then functions as a nucleophile and attacks the nitronium ion. We will draw the attack occurring at the *para* position because the problem statement asked for a mechanism of formation of the major product (the *para* product predominates over the *ortho* product as a result of steric factors). The resulting intermediate sigma complex then loses a proton to restore aromaticity.

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Water is the likely base for the final deprotonation step, since water is present (and there are no strong bases present in strongly acidic conditions).

18.13. As shown below, attack at C4 or C6 produces a sigma complex in which two of the resonance structures have a positive charge next to an electron-withdrawing group (NO_2). These resonance structures are less contributing to the resonance hybrid, thereby destabilizing the sigma complex. In contrast, attack at C5 produces a sigma complex for which none of the resonance structures have a positive charge next to a nitro group.

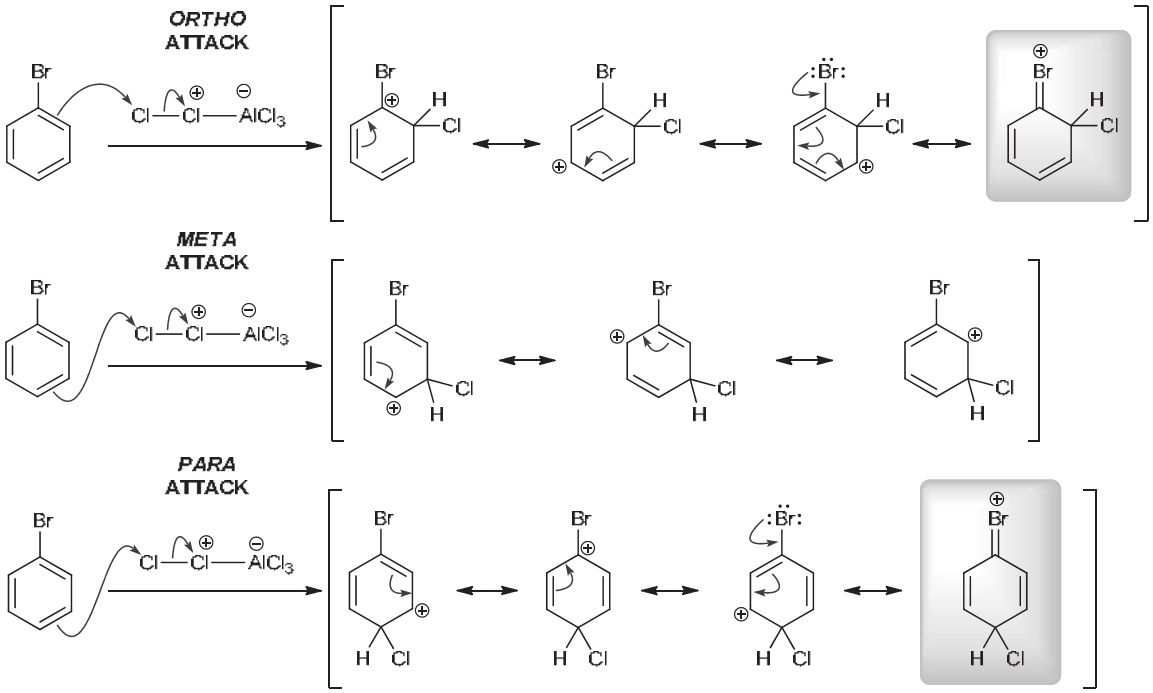


Attack at C2 is identical to attack at C4 because the starting material has symmetry that renders C2 and C4 identical.

18.14. The chlorine atom in chlorobenzene deactivates the ring relative to benzene. If benzene requires a Lewis acid for chlorination, than chlorobenzene should certainly require a Lewis acid for chlorination.

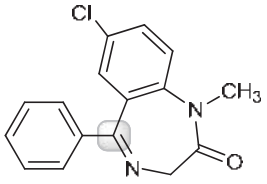
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18.15. *Ortho* attack and *para* attack are preferred because each of these pathways involves a sigma complex with four resonance structures (shown below). Attack at the *meta* position involves formation of a sigma complex with only three resonance structures, which is not as stable as a sigma complex with four resonance structures. The reaction will proceed more rapidly via the lower energy sigma complex, so attack takes place at the *ortho* and *para* positions in preference to the *meta* position.



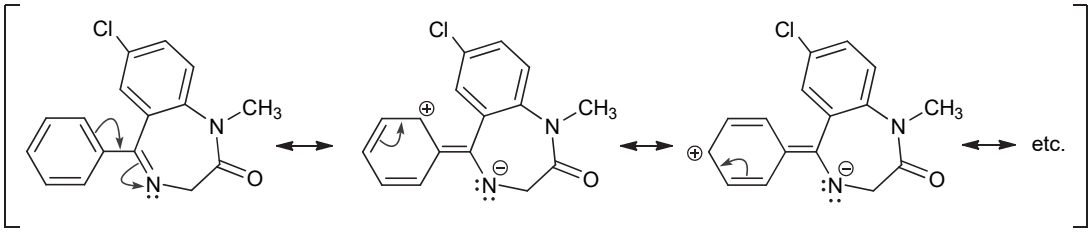
18.16.
(a) As seen in Table 18.1, the nitro is strongly deactivating and *meta*-directing.
(b) As seen in Table 18.1, an acyl group is moderately deactivating and *meta*-directing.
(c) As seen in Table 18.1, a bromine atom is weakly deactivating and *ortho, para*-directing.
(d) This aromatic ring exhibits a C=N bond (a π bond to a heteroatom) conjugated to the ring and is therefore similar to a C=O bond that is conjugated to the ring. This group is moderately deactivating and *meta*-directing.
(e) In this compound the carbonyl group of the ester is connected directly to the ring. As seen in Table 18.1, a carbonyl group is moderately deactivating and *meta*-directing.
(f) As seen in Table 18.1, the oxygen atom of an ester (connected directly to an aromatic ring) is moderately activating and *ortho, para*-directing.

18.17. There are two aromatic rings in the structure, but we are evaluating only the monosubstituted ring. Don't be distracted by the size of the substituent connected to that ring. First check if there is a lone pair immediately adjacent to the ring. In this case, there isn't one. The atom directly attached to the benzene ring is a carbon atom.



Next, check for a π bond to an electronegative atom, where the π bond is conjugated with the ring. The C=N bond is conjugated with the ring allowing for electron withdrawal via resonance, as shown here:

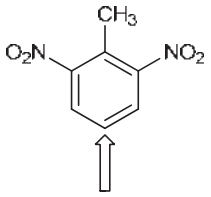
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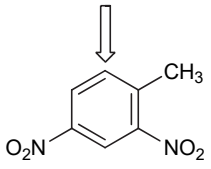
We therefore expect the monosubstituted ring to be moderately deactivated. Note the effect of the substituent. The resonance structures indicate that the *ortho* and *para* positions should be electron-poor (δ+). We therefore predict those positions to be the least likely to react with an electrophile. The deactivating substituent is (as usual) a *meta* director.

18.18.

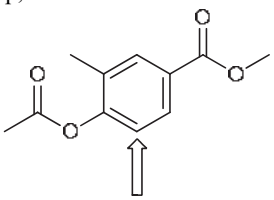
(a) The methyl group is weakly activating and the nitro groups are strongly deactivating. The directing effects are controlled by the most strongly activating group. Therefore, in this case, the methyl group controls the directing effects. As an activator, the methyl group is an *ortho-para* director. However, the two *ortho* positions are both already occupied (by the nitro groups). Therefore, an electrophilic aromatic substitution reaction is most likely to occur at the position that is *para* to the methyl group, shown here:



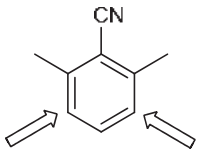
(b) The methyl group is weakly activating and the nitro groups are strongly deactivating. The directing effects are controlled by the most strongly activating group. Therefore, in this group controls the directing effects. As an activator, the methyl group is an *ortho-para* director. However, the *para* position and one of the *ortho* positions are already occupied (by the nitro groups). Therefore, an electrophilic aromatic substitution reaction is most likely to occur at the position that is *ortho* to the methyl group, shown here:



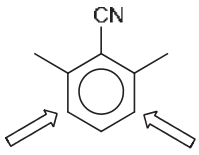
(c) This aromatic ring has three substituents. The methyl group is weakly activating. The other two groups are both esters, but they differ in the way they are connected to the ring. One group is moderately activating (the oxygen atom connected to the ring) and the other is moderately deactivating (the carbonyl group connected to the ring). The directing effects are controlled by the most strongly activating group. Therefore, in this case, the ester group (connected to the ring by its oxygen atom) controls the directing effects. As an activator, this group is an *ortho-para* director. However, the *para* position and one of the *ortho* positions are already occupied (by the other substituents). Therefore, an electrophilic aromatic substitution reaction is most likely to occur at the position that is *ortho* to the moderately activating group, shown here:



(d) The methyl groups are weakly activating and the cyano group is moderately deactivating. The directing effects are controlled by the most strongly activating group(s). Therefore, in this case, the methyl groups control the directing effects. Both of the methyl groups are directing to the same two locations (*ortho* and *para* to the methyl groups), shown here.



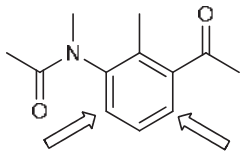
These two locations are identical because of symmetry. Don't be confused by the arbitrary location of the double bonds. Perhaps it is less distracting if we draw the structure like this:



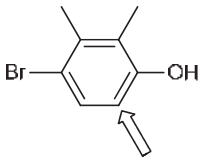
(e) This aromatic ring has three substituents. The methyl group is weakly activating. The carbonyl group (C=O) is moderately deactivating, and the amide group is moderately activating (see Table 18.1). The directing effects are controlled by the most strongly activating group. Therefore, in this case, the amide group controls the directing effects. As an activator, this group is an

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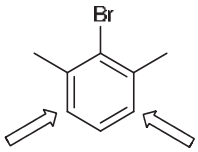
ortho-para director. However, one of the *ortho* positions is already occupied (by the methyl group). Therefore, an electrophilic aromatic substitution reaction is most likely to occur at the following positions, which are *ortho* and *para* to the amide group:



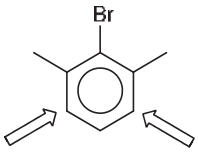
(f) The directing effects are controlled by the most strongly activating group. Therefore, in this case, the OH group (a strong activator) controls the directing effects. As an activator, this group is an *ortho-para* director. However, the *para* position and one of the *ortho* positions are already occupied (by the other substituents). Therefore, an electrophilic aromatic substitution reaction is most likely to occur at the position that is *ortho* to the OH group, shown here:



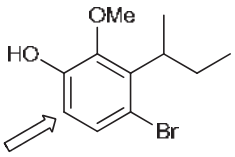
(g) The methyl groups are weakly activating and the bromo group is weakly deactivating. The directing effects are controlled by the most strongly activating group(s). Therefore, in this case, the methyl groups control the directing effects. Both of the methyl groups are directing to the same two locations (*ortho* and *para* to the methyl groups), shown here.



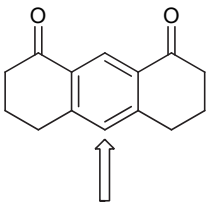
These two locations are identical because of symmetry. Don't be confused by the arbitrary location of the double bonds. It is less distracting if we draw the structure like this:



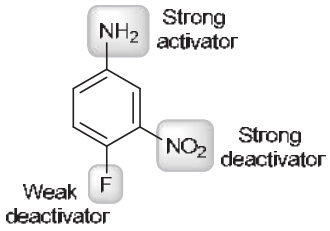
(h) The directing effects are controlled by the most strongly activating group. Therefore, in this case, the OH group (a strong activator) controls the directing effects (rather than the methoxy group, which is only a moderate activator). As an activator, the OH group is an *ortho-para* director. However, the *para* position and one of the *ortho* positions are already occupied (by the other substituents). Therefore, an electrophilic aromatic substitution reaction is most likely to occur at the position that is *ortho* to the OH group, shown here:



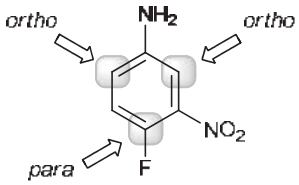
(i) This ring has four substituents (two electron-donating alkyl groups and two electron-withdrawing carbonyl groups). The directing effects are controlled by the most strongly activating group(s). Therefore, in this case, the alkyl substituents control the directing effects. Both of the alkyl substituents are directing to the same location (*ortho* to the alkyl substituents), shown here.



18.19. Begin by identifying the effect of each group on the aromatic ring.

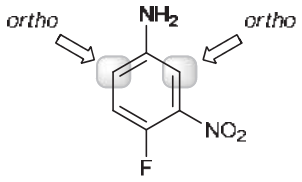


The most powerful activator will dominate the directing effects. In this case the NH_2 group is the strongest activator so we consider the positions that are *ortho* and *para* to the NH_2 group.

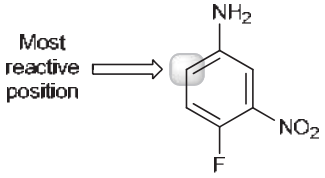


The *para* position is already occupied by F. There are two positions that are *ortho* to the NH_2 group, and both are available. Therefore, we expect that the reaction should occur primarily at these two positions:

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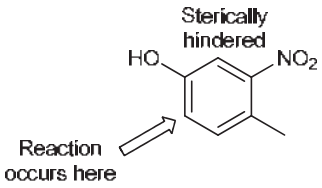


However, we will soon see (immediately after this SkillBuilder) that the *ortho* position on the left is more accessible for steric reasons, so substitution at this position leads to the major product.

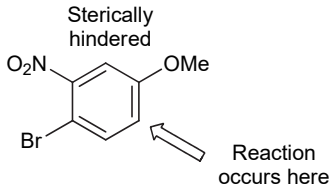


18.20.

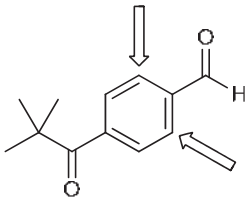
(a) The directing effects are controlled by the most strongly activating group. Therefore, in this case, the OH group (a strong activator) controls the directing effects. As an activator, the OH group is an *ortho-para* director. However, the *para* position is already occupied (by the methyl group). Therefore, an electrophilic aromatic substitution reaction should occur at an *ortho* position. Among the two *ortho* positions, one of them (top) is sterically hindered and we do not expect the reaction to occur at that location. Therefore, the reaction is most likely to occur at the following position:



(b) The directing effects are controlled by the most strongly activating group. Therefore, in this case, the methoxy group (a moderate activator) controls the directing effects. As an activator, the methoxy group is an *ortho-para* director. However, the *para* position is already occupied (by the bromine atom). Therefore, an electrophilic aromatic substitution reaction should occur at an *ortho* position. Among the two *ortho* positions, one of them (top) is sterically hindered and we do not expect the reaction to occur at that location. Therefore, the reaction is most likely to occur at the following position:

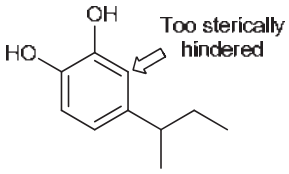


(c) This aromatic ring lacks an activating substituent. Both substituents are deactivators, and they are competing with each other (each group directs to the positions that are *meta* to itself). So electronically, the four aromatic positions are equally likely to undergo an electrophilic aromatic substitution reaction. The positions are differentiated from each other when we consider steric effects. The larger group (left) is more sterically bulky, and therefore blocks the positions closest to it. The reaction therefore occurs at one of the following locations.

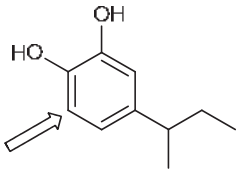


These two locations are identical because of symmetry.

(d) The directing effects are controlled by the most strongly activating group(s). Therefore, in this case, the OH groups (strong activators) control the directing effects. However, each OH group directs to different locations (*ortho* and *para* to itself), so all available positions are activated. To differentiate between them, we note that the following position is too sterically hindered for a reaction to occur at this location:

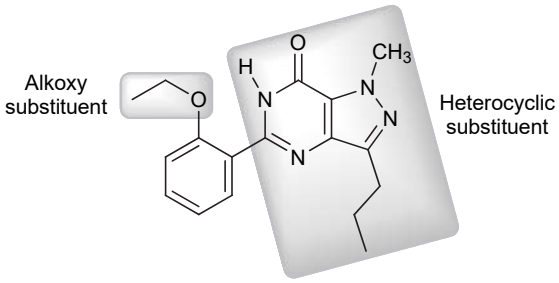


Among the other two locations, one of them is more sterically accessible than the other, so the reaction is expected to occur at this location:

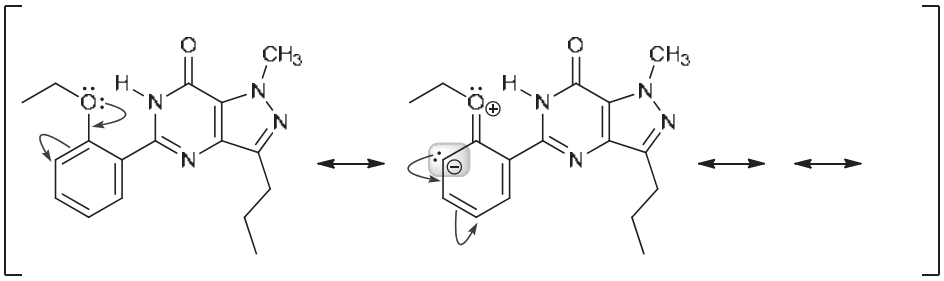


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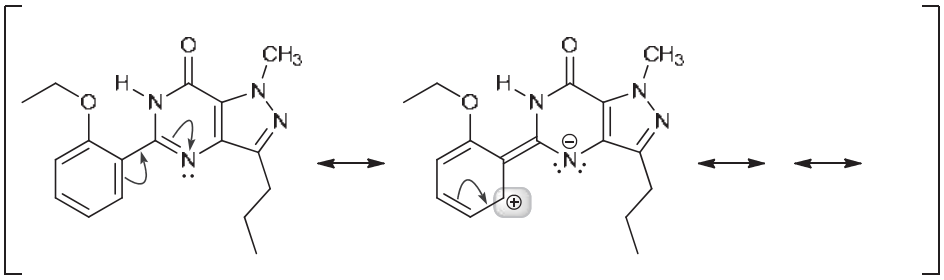
18.21. As mentioned in the problem statement, the benzene ring has two substituents. One is an alkoxy group, and the other is a heterocyclic substituent (it contains nitrogen atoms incorporated in rings):



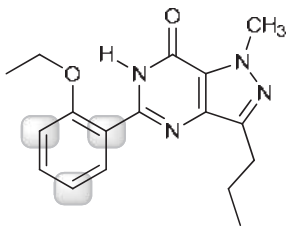
Let's begin with the ethoxy group. With its lone pairs on oxygen, the ethoxy group is a moderate activator capable of donating electrons toward the ring, as expected for an alkoxy substituent:



The heterocyclic substituent contains a π-bond conjugated with the benzene ring which can withdraw electron density from the ring via resonance:



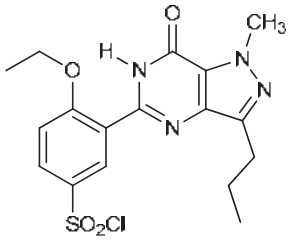
This makes the heterocycle a moderate deactivator.
Recall that the most powerful activator will dominate the directing effects, so we must consider the positions that are *ortho* and *para* to the ethoxy group (highlighted):



One of these positions is already occupied, leaving only two choices. Since the *ortho* position is more sterically hindered by the ethoxy substituent than the *para* position, we expect substitution to take place primarily at the *para* position. Though the conditions for this reaction are new, the resulting electrophilic aromatic substitution is similar to

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the reactions we have encountered. Specifically, the site of attack exchanges its proton for the electrophilic group, in this case -SO_2Cl. Substitution occurs to afford the following product:

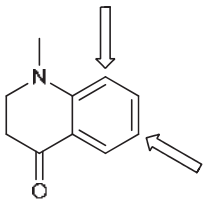


18.22.

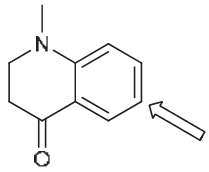
(a) This aromatic ring has only one substituent (an alkyl group). Alkyl groups are weak activators and therefore *ortho-para* directors. An isopropyl group is sterically bulky, and we therefore expect a nitration reaction to occur predominantly at the *para* position. In order to install a nitro group at the *ortho* position, a blocking group will be required.

(b) This aromatic ring has only one substituent (an alkyl group). Alkyl groups are weak activators and therefore *ortho-para* directors. An isopropyl group is sterically bulky, and we therefore expect a bromination reaction to occur predominantly at the *para* position. Therefore, a blocking group is not required. Direct bromination will give the desired product.

(c) The aromatic ring has two substituents: an amino group and a carbonyl group. The former is a strong activator and the latter is a moderate deactivator. The directing effects are controlled by the more strongly activating group. Therefore, in this case, the amino group controls the directing effects. As an activator, the amino group is an *ortho-para* director. However, one of the *ortho* positions is already occupied (by the other substituent). Therefore, there are only two locations where bromination can occur (*ortho* or *para* to the amino group):

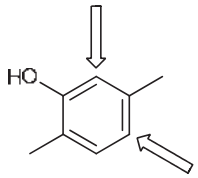


Among these two locations, one of them (top) is more sterically hindered than the other. Bromination is therefore expected to occur at the location that is more sterically accessible.



In order to install the bromine atom at the other location (*ortho* rather than *para*), a blocking group will be required.

(d) The directing effects for the desired nitration process are controlled by the most strongly activating group. Therefore, in this case, the OH group (a strong activator) controls the directing effects. As an activator, this group is an *ortho-para* director. However, one of the *ortho* positions is already occupied (by a methyl group). This leaves only two locations where the reaction can occur:

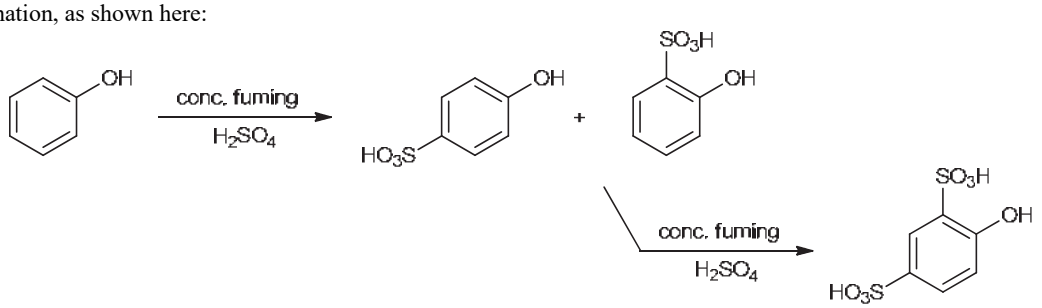


One of these locations (bottom right) is more accessible than the other, and this is exactly the position where a nitro group must be installed. Therefore, a blocking group will not be required.

18.23. Analyze the starting material. The OH group is a strong activator and an *ortho*/*para*-director. Indeed, it is such a strong activator that bromination conditions will likely give a tribrominated product (with bromination occurring at the *para* position and both *ortho* positions), even at room temperature. Also, even if monobromination could be carried out cleanly, the product mixture would likely contain only some of the more sterically hindered (desired) product along with a substantial amount of the *para* isomer that would likely be the major product. Our strategy will be to block

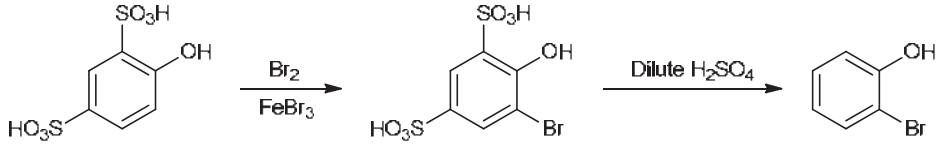
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some reactive positions, brominate, and then unblock. As we have seen, reactive positions can be blocked via sulfonation, as shown here:



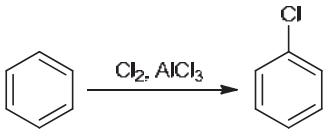
The first sulfonic acid group is installed quickly, and it deactivates the ring somewhat, so the second sulfonation is expected to occur more slowly (and possibly require a higher temperature). A third sulfonation would require an even higher temperature, so there is likely an optimum temperature at which the disulfonated product can be obtained in high yield (and indeed, this is the case!). The regiochemistry of the second sulfonation is controlled by the *o*/*p*-directing effect of the OH group (although the *meta*-directing SO_3H group also directs to the same location). This double blocking can be carried out in one synthetic step with excess fuming sulfuric acid, but is shown stepwise above for clarity.

Bromination at the only remaining reactive site, followed by desulfonation to remove the two blocking groups, yields the desired product:

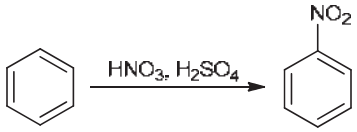


18.24.

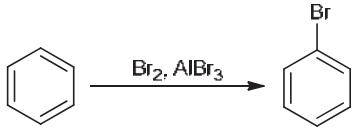
(a) The aromatic ring will undergo chlorination upon treatment with molecular chlorine (Cl_2) and a Lewis acid ($AlCl_3$).



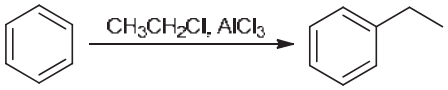
(b) The aromatic ring will undergo nitration upon treatment with a mixture of nitric acid and sulfuric acid.



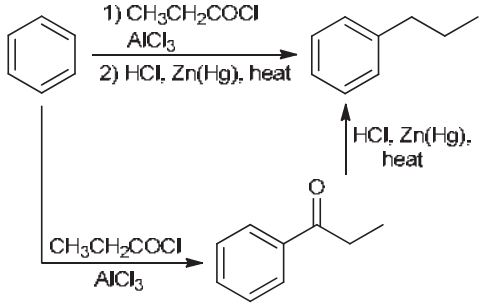
(c) The aromatic ring will undergo bromination upon treatment with molecular bromine (Br_2) and a Lewis acid ($AlBr_3$ or $FeBr_3$).



(d) The aromatic ring will undergo a Friedel-Crafts alkylation upon treatment with ethyl chloride and a Lewis acid ($AlCl_3$), to give ethylbenzene.

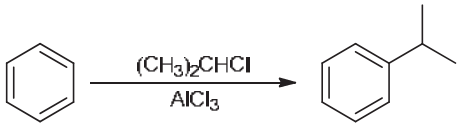


(e) A propyl group cannot be installed via a Friedel-Crafts alkylation, as a carbocation rearrangement is likely to occur. In order to install a propyl group (without rearrangement), we can first perform a Friedel-Crafts acylation, followed by a Clemmensen reduction, as shown:



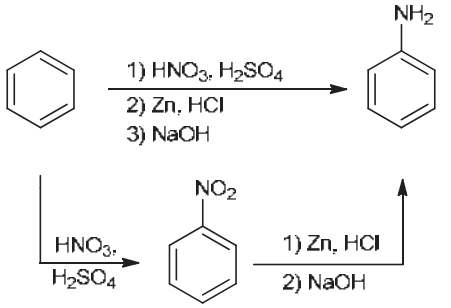
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(f) An isopropyl group can be installed via a Friedel-Crafts alkylation in which isopropyl chloride is used as the alkyl halide:

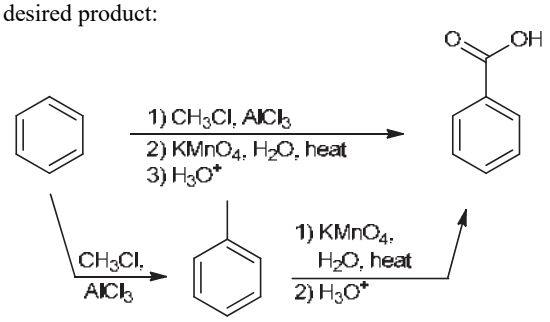


Notice that we use isopropyl chloride to install an isopropyl group, rather than using propyl chloride and relying on a carbocation rearrangement (which would be inefficient because it would likely yield a mixture of products).

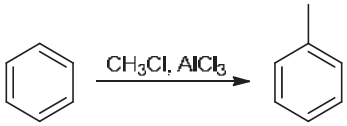
(g) We did not learn a one-step method for installing an amino group on an aromatic ring, but we did learn a two-step method for achieving that transformation. Specifically, we first install a nitro group, and then we reduce the nitro group to an amino group, as shown here:



(h) We did not learn a one-step method for installing a carboxylic acid group on an aromatic ring, but we did learn a multi-step method for achieving that transformation. Specifically, we first install a methyl group, and then we oxidize the methyl group to give the desired product:

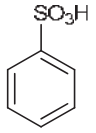


(i) The aromatic ring will undergo a Friedel-Crafts alkylation upon treatment with methyl chloride and a Lewis acid ($AlCl_3$), to give toluene.

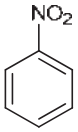


18.25.

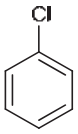
(a) These reagents will install a sulfonic acid group on the aromatic ring (a process called sulfonation), giving benzenesulfonic acid:



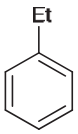
(b) These reagents will install a nitro group on the aromatic ring (a process called nitration), giving nitrobenzene:



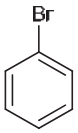
(c) These reagents will install a chlorine atom on the aromatic ring (a process called chlorination), giving chlorobenzene:



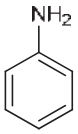
(d) These reagents will install an ethyl group on the aromatic ring (via a Friedel-Crafts alkylation), giving ethylbenzene:



(e) These reagents will install a bromine atom on the aromatic ring (a process called bromination), giving bromobenzene:



(f) These reagents will achieve the installation of a nitro group on the aromatic ring, followed by reduction of the nitro group to give aminobenzene (also called aniline):



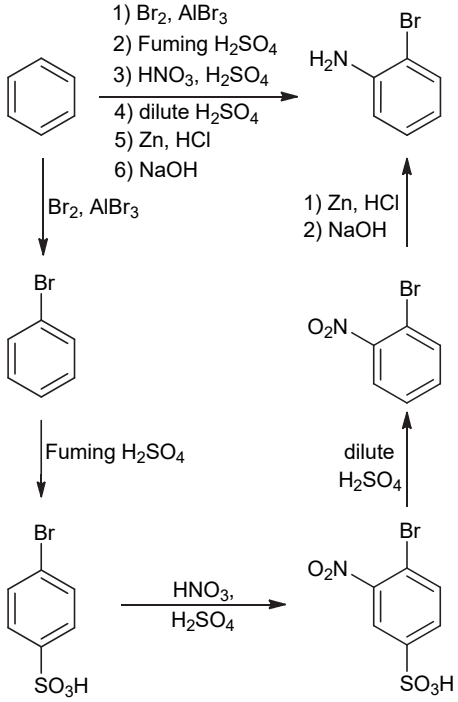
18.26.

(a) Installation of the amino group requires a two-step process (nitration, followed by reduction), while installation of the bromine atom can be achieved in just one step. Therefore, our synthesis must have at least those three steps.

Now let's consider the order of events. These two groups must be installed in an *ortho* fashion. Both

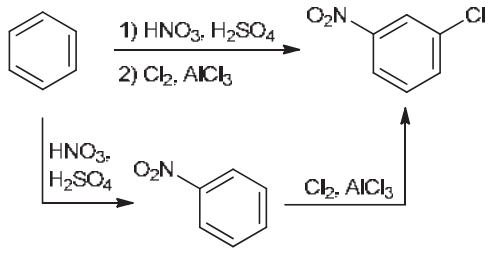
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groups are *ortho-para* directing, so we could theoretically install either one first, and then use a blocking technique to install the second group in the correct location (*ortho*, rather than *para*). However, if we install the amino group first, there is a concern of polybromination, since aminobenzene (also called aniline) is highly activated. To avoid this problem, we first install the bromine atom (which does not activate the ring). Then, we perform a sulfonation to block the *para* position. Nitration then installs the nitro group in the desired location (*ortho*). Then, after removing the blocking group, the nitro group is reduced to give the desired product.



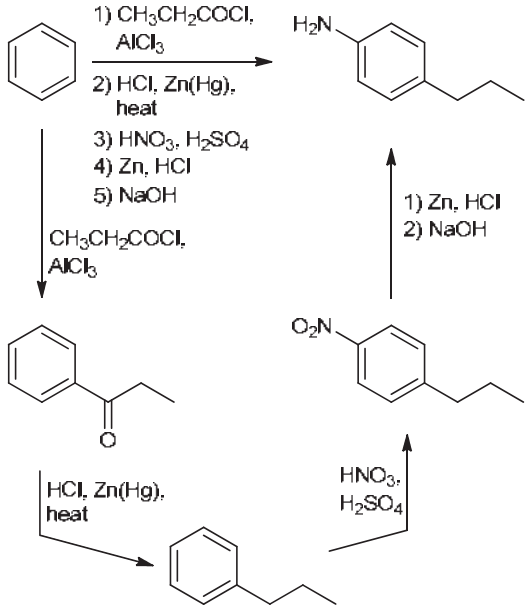
(b) Installation of the nitro group can be achieved in just one step (nitration), and installation of the chlorine atom can also be achieved in just one step.

Now let's consider the order of events. These two groups must be installed in a *meta* fashion. Only the nitro group is a *meta* director, so it must be installed first, followed by chlorination in the presence of a Lewis acid.



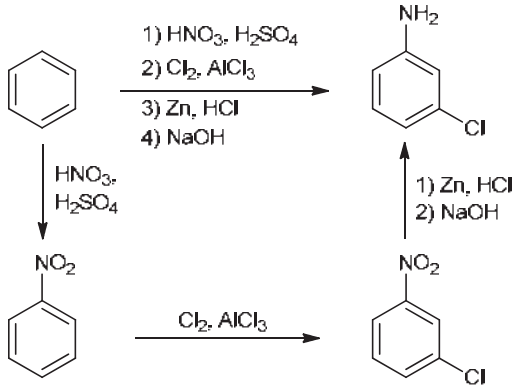
(c) Installation of the amino group requires a two-step process (nitration, followed by reduction), and installation of the propyl group also requires a two-step process (Friedel-Crafts acylation, followed by Clemmensen reduction).

Now let's consider the order of events. These two groups must be installed in a *para* fashion. Both groups are *ortho-para* directors, so we might think that either group could be installed first. However, to favor the *para* product over the *ortho* product, we must capitalize on the steric bulk of the propyl group. That is, we install the propyl group first, followed by installation of the amino group. Also, the amino group is too highly activating and cannot be installed first.



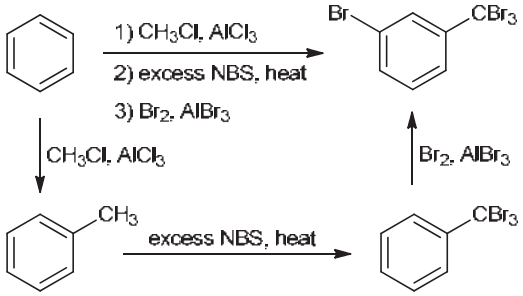
(d) Installation of the amino group requires a two-step process (nitration, followed by reduction), while installation of the chlorine atom can be achieved in just one step.

Now let's consider the order of events. These two groups must be installed in a *meta* fashion, but both groups are *ortho-para* directors. Installation of these two groups (in either order) does not appear to give the desired *meta* substitution pattern. However, recall that installation of the amino group requires two steps. The first step is nitration, and a nitro group is a *meta*-director. So, we can achieve the desired transformation by performing the chlorination process after the nitration process but before the reduction process, as shown here:

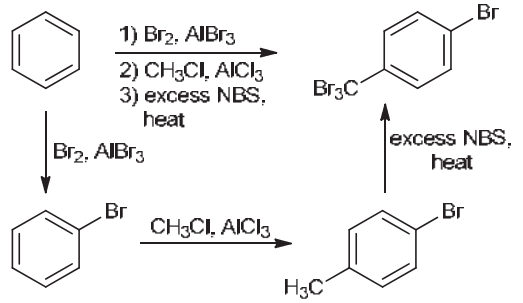


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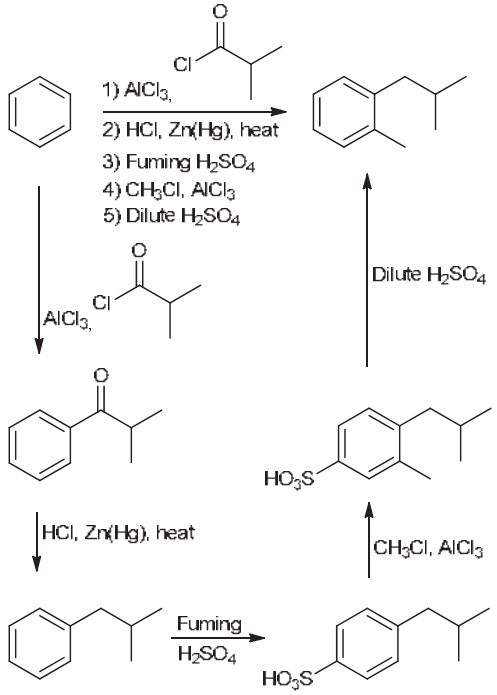
(e) Installation of the tribromomethyl group requires a two-step process (Friedel-Crafts alkylation, followed by benzylic bromination), while installation of the bromine atom can be achieved in just one step.
Now let's consider the order of events. These two groups must be installed in a *meta* fashion. Only the tribromomethyl group is a *meta* director, so it must be installed first (via the required two-step process), followed by bromination in the presence of a Lewis acid:



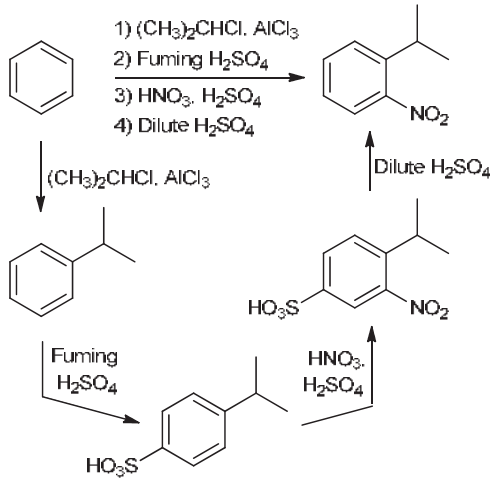
(f) Installation of the tribromomethyl group requires a two-step process (Friedel-Crafts alkylation, followed by benzylic bromination), while installation of the bromine atom can be achieved in just one step.
Now let's consider the order of events. These two groups must be installed in a *para* fashion. Only the bromo group is an *ortho-para* director, so we install that group first, followed by installation of the tribromomethyl group (which requires two steps), as shown:



(g) This aromatic ring has two substituents, both of which are alkyl groups, although only the methyl group can be installed via a Friedel-Crafts alkylation process. The other alkyl group must be installed via a two-step process (Friedel-Crafts acylation, followed by Clemmensen reduction), because direct alkylation would result in a mixture of products (due to carbocation rearrangements).
Now let's consider the order of events. These two groups must be installed in an *ortho* fashion. Both groups are *ortho-para* directing, so we could theoretically install either one first, and then use a blocking technique to install the second group in the desired location (*ortho*, rather than *para*). However, if we install the methyl group first, then subsequent sulfonation is likely to produce a mixture of *ortho* and *para* products, since the methyl group is not very sterically demanding. To circumvent this lack of regiochemical control, it is best to install the bulky alkyl group first (using a Friedel-Crafts acylation, followed by a Clemmensen reduction), and then continue with a sulfonation step. This provides for much better selectivity during the sulfonation step, and therefore, a better yield of the final product.

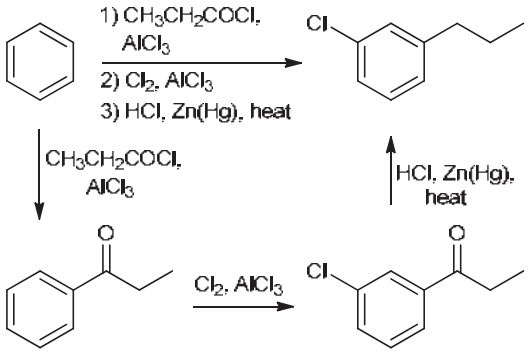


(h) Installation of the nitro group can be achieved in just one step (nitration), and installation of the isopropyl group can also be achieved in just one step (Friedel-Crafts alkylation with isopropyl chloride and aluminum trichloride).
Now let's consider the order of events. These two groups must be installed in an *ortho* fashion. Only the alkyl group is an *ortho-para* director, so it must be installed first. Then, in order to install a nitro group in the *ortho* position (rather than the *para* position), a blocking group must be used. After the blocking group is installed, nitration will install a nitro group in the desired location. Desulfonation then affords the desired product.

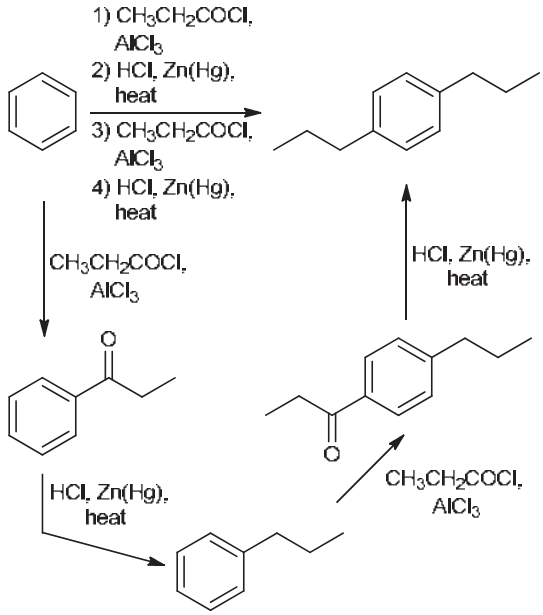


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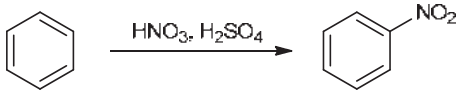
(i) Installation of the propyl group requires a two-step process (Friedel-Crafts acylation, followed by Clemmensen reduction), while installation of the chlorine atom can be achieved in just one step.
Now let's consider the order of events. These two groups must be installed in a *meta* fashion, but both groups are *ortho-para* directors. Installation of these two groups (in either order) does not appear to give the desired *meta* substitution pattern. However, as mentioned above, installation of the propyl group requires two steps. The first step is acylation, and the resulting acyl group is a *meta*-director. So, we can achieve the desired transformation by performing the chlorination process after the acylation process but before the reduction process, as shown here:



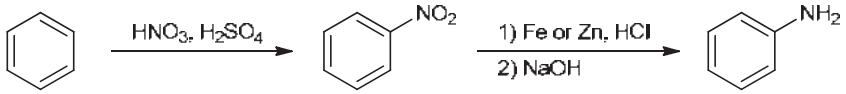
(j) Installation of each propyl group requires a two-step process (Friedel-Crafts acylation, followed by Clemmensen reduction). These two groups must be installed in a *para* fashion. Propyl groups are *ortho-para* directors, and their steric bulk is expected to cause a preference for *para*-substitution. So we simply install one propyl group (via Friedel-Crafts acylation followed by reduction), followed by the second propyl group, as shown here:



18.27. The synthesis of 2-nitroaniline from benzene requires the installation of a nitro group and an amino group on a benzene ring. The nitro group can be installed in one step,



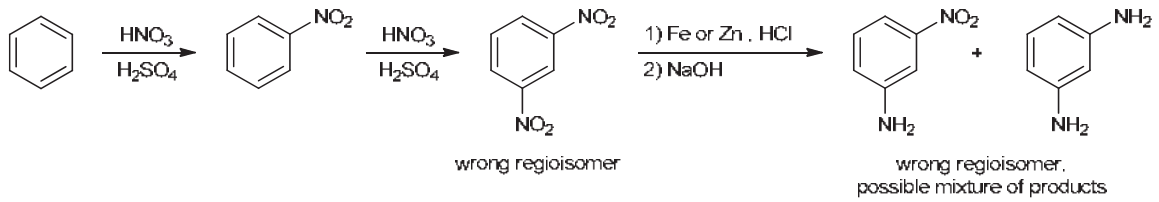
while installation of the amino group can be achieved in two steps (nitration followed by reduction), as shown:



Notice that each of these groups is installed via nitration of benzene, so nitration must be the first step of the synthesis. We must therefore decide whether to perform the second nitration before or after the reduction. Consider what will happen if the second nitration is attempted before the reduction. Since the existing nitro group is *meta*-directing, the

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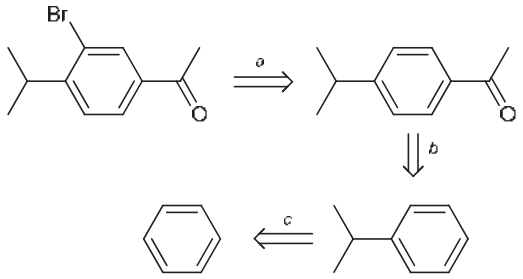
1,3-regioisomer will be produced, leading to 3-nitroaniline as the product. Additionally, the subsequent reduction may affect either one or both of the nitro groups.



Now consider what will happen if the reduction is performed before the second nitration. The reduction will likely proceed smoothly; however, the following nitration step will be problematic. Under the acidic conditions employed during nitration, the amino group (an *ortho/para*-directing group) will be protonated to give an ammonium group, which is a *meta*-directing group. Therefore, nitration of aniline is not expected to give the desired regiochemical outcome

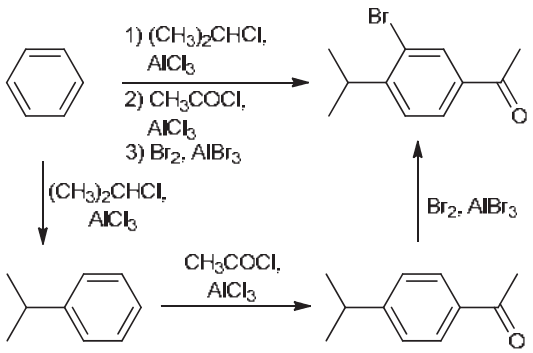
18.28.

(a) The following retrosynthetic analysis represents one strategy for preparing the desired compound. An explanation of each of the steps (*a-c*) follows.



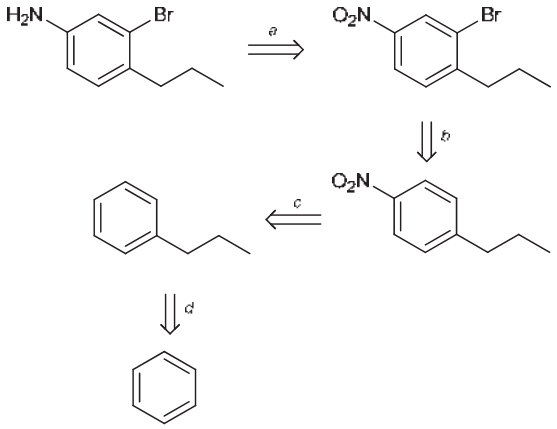
a. The product can be prepared via bromination of the disubstituted ring shown.
b. The disubstituted ring can be prepared via a Friedel-Crafts acylation.
c. The monosubstituted ring (isopropylbenzene) can be prepared via a Friedel-Crafts alkylation.

Now, let's draw the forward scheme. First, an isopropyl group is installed via a Friedel-Crafts alkylation. Then, an acyl group is installed via a Friedel-Crafts acylation. During this acylation step, the isopropyl group directs the incoming acyl group into the *para* position. And finally, bromination will install the bromine atom in the correct location (*ortho* to the isopropyl group).



This strategy represents just one method for making the desired the compound. There are often other acceptable solutions. For example, after installation of the isopropyl group, the acyl group and the bromo group can be installed in the opposite order (first the bromo group and then the acyl group), although this would require a blocking group (to help direct the incoming bromo group into the *ortho* position). The first method (shown above) avoids the need for a blocking group.

(b) The following retrosynthetic analysis represents one strategy for preparing the desired compound. An explanation of each of the steps (*a-d*) follows.

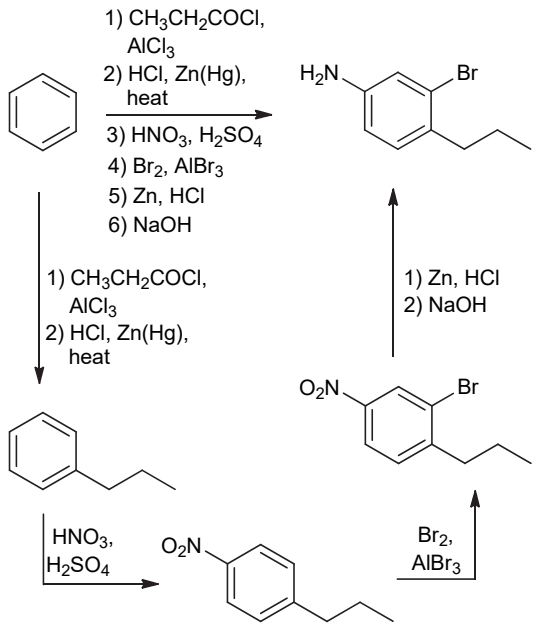


a. The product can be prepared via reduction of the nitro group.
b. The bromo group can be installed in the correct location based on the directing effects of the propyl group.
c. The nitro group is installed in the *para* position via nitration.
d. A propyl group is installed onto the ring via Friedel-Crafts acylation, followed by reduction.

Now, let's draw the forward scheme. First, a propyl group is installed via a Friedel-Crafts acylation, followed by a Clemmensen reduction. This transformation could

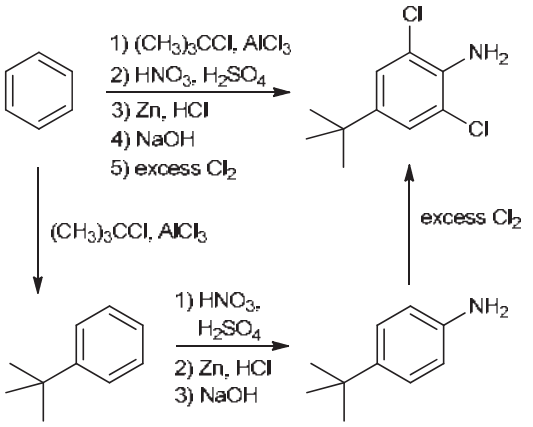
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not have been achieved via direct alkylation (due to the problem of carbocation rearrangements). Then, a nitro group is installed in the *para* position because of the directing effects (and steric effects) of the propyl group. Bromination then installs the bromine atom in the correct location (*ortho* to the activating group), and finally, reduction of the nitro group gives the product.

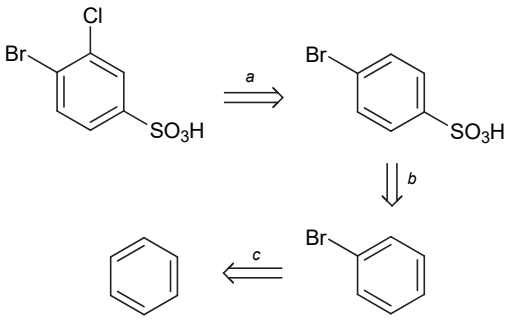


The strategy above represents just one method for making the desired the compound. There are often other acceptable solutions. For example, the nitro group and the bromo group can be installed in the opposite order (first the bromo group and then the nitro group), although this would require a blocking group (to help direct the incoming bromo group into the *ortho* position). The first method (shown above) avoids the need for a blocking group.

(c) While there is more than one way to achieve the desired transformation, the following strategy is perhaps the most efficient, as it avoids the need for a blocking group. The *tert*-butyl group is first installed, and its directing effects are exploited to install an amino group in the *para* position (installation of the amino group requires a two-step process – nitration, followed by reduction). Finally, chlorination in the presence of excess Cl_2 gives the desired product ($AlCl_3$ is not used because the ring is highly activated). The regiochemical outcome of the final step is controlled by the electronic effects of the amino group (in concert with the steric effects of the *tert*-butyl group).

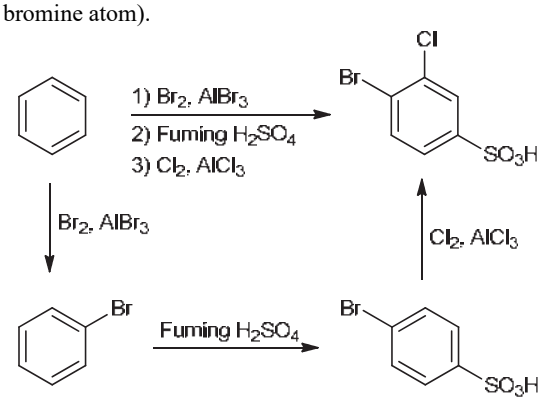


(d) The following retrosynthetic analysis represents one strategy for preparing the desired compound. An explanation of each of the steps (*a*-*c*) follows.



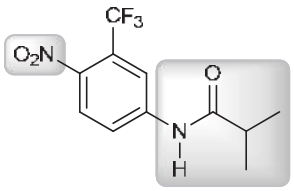
a. The product can be prepared via chlorination of the disubstituted ring shown.
b. The disubstituted ring can be prepared via sulfonation.
c. The monosubstituted ring (bromobenzene) can be prepared from benzene.

Now, let's draw the forward scheme. First, a bromine atom is installed via bromination in the presence of a Lewis acid. Then, a sulfonic acid group is installed. During this sulfonation step, the bromine atom directs the incoming sulfonic acid group into the *para* position. And finally, chlorination will install the bromine atom in the correct location (*ortho* to the *ortho-para* directing bromine atom).

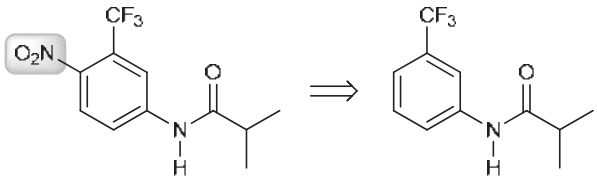


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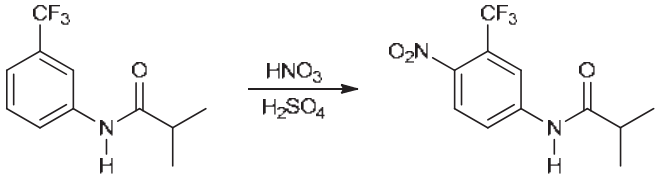
18.29. This transformation requires the installation of two groups, highlighted here:



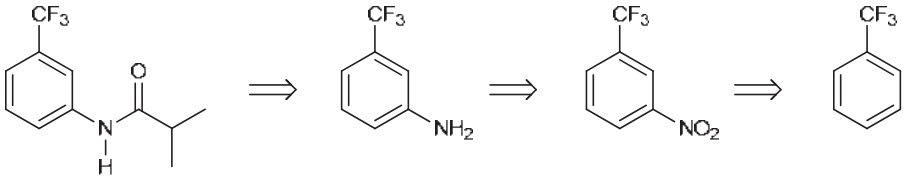
We begin by considering which of these two groups should be installed last. The nitro group is an electron-withdrawing substituent and a *meta*-director. The amide group is an electron-donating substituent and an *ortho,para*-director. Therefore, it makes sense for the last step of our synthesis to be nitration:



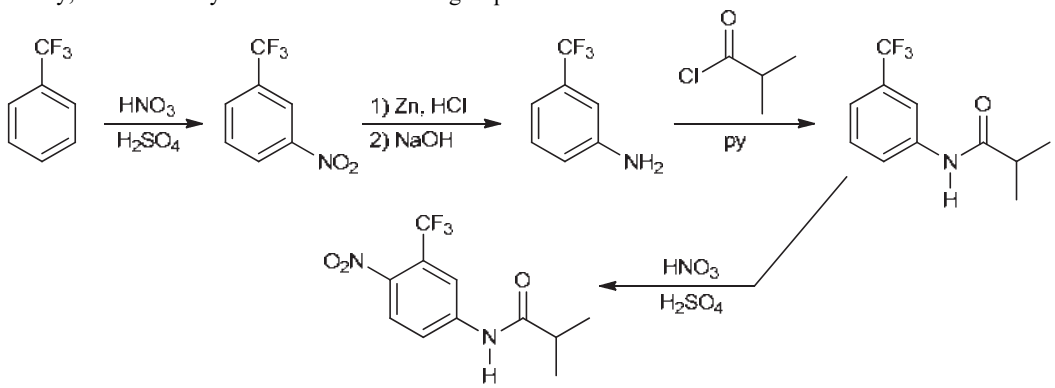
In this way, the amide group directs the final nitration step to occur in the desired location (*para* to the large amide group):



Continuing the retrosynthetic analysis, the amide group can be prepared from the corresponding aniline derivative which, in turn, can be made from reduction of a nitro group, as shown here:



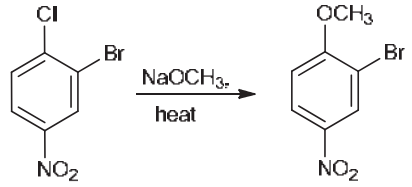
In summary, our forward synthesis has the following sequence of events.



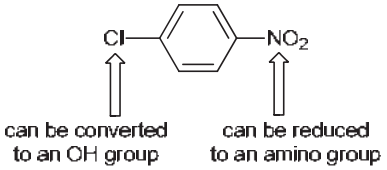
18.30. The ring contains a nitro group, as well as two leaving groups (chloride and bromide), and the reagent is a strong base (methoxide). As such, a nucleophilic aromatic substitution reaction can occur, but only if the leaving group is *ortho* or *para* to the nitro group. The bromine atom is *meta* to the nitro group, so the reaction

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does not occur there. Instead, chloride functions as the leaving group, because it is *para* to the nitro group.

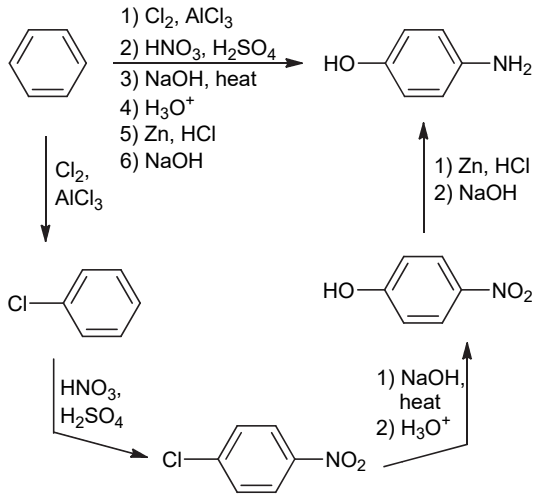


18.31. This transformation involves the installation of two groups: NH_2 and OH. Thus far, we have only seen one way (S_NAr) to install an OH group on an aromatic ring (we will see one other way in Section 18.14, and yet another method in Chapter 22). In order to install an OH group via an S_NAr reaction, the ring must exhibit both a nitro group and a leaving group:



The chlorine atom can be replaced with an OH group, and the nitro group can be reduced to an amino group, giving the product. And the key intermediate above can be made in just two steps (chlorination, followed by nitration)

The entire synthesis is shown below. Benzene is first treated with chlorine in the presence of a Lewis acid to give chlorobenzene, which is then treated with sulfuric acid and nitric acid, to give the key intermediate. The chlorine atom is then replaced with an OH group upon treatment with hydroxide, followed by aqueous acid work-up. Reduction of the nitro group affords the desired product.

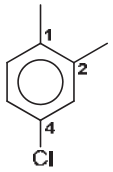


18.32.

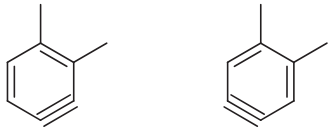
(a) Each additional nitro group serves as a reservoir of electron density and provides for an additional resonance structure in the Meisenheimer complex, thereby stabilizing the Meisenheimer complex and lowering the energy of activation for the reaction.

(b) No, a fourth nitro group would not be *ortho* or *para* to the leaving group, and would not provide resonance stabilization for the Meisenheimer complex. Therefore, we do not expect the temperature requirement to be significantly lowered.

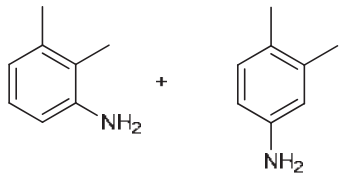
18.33. The starting material is 4-chloro-2-methyltoluene, shown here:



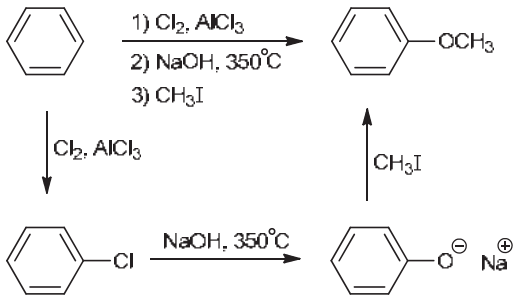
Upon treatment with sodium amide, two possible benzyne intermediates can form:



Then, for each of these benzyne intermediates, the amide ion can attack either side of the triple bond, which means that the NH_2 group is ultimately positioned at either C3, C4, or C5. Substitution at C4 yields the same product as substitution at C5 (because of symmetry), giving rise to only two products (rather than three):



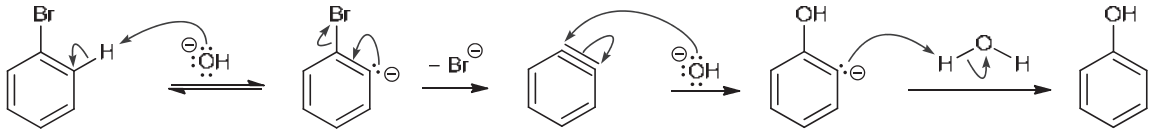
18.34. We have not yet seen a direct method for installing a methoxy group on an aromatic ring, however, we have seen a way to install an OH group (via chlorination, followed by elimination-addition). A Williamson ether synthesis can then be used to methylate the oxygen atom, giving the product.



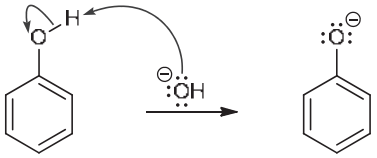
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18.35.

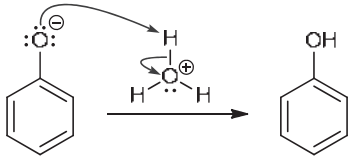
(a) The reagent is hydroxide, which is both a strong nucleophile and a strong base. However, the three criteria for S_NAr are not met (the aromatic ring lacks a nitro group), and therefore, the reaction must occur via an elimination-addition mechanism (as seen in Mechanism 18.9). The elimination-addition mechanism is also indicated by the high temperature (350°C).



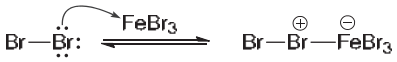
Under the basic conditions employed, the resulting product (phenol) is deprotonated to give a phenolate ion:



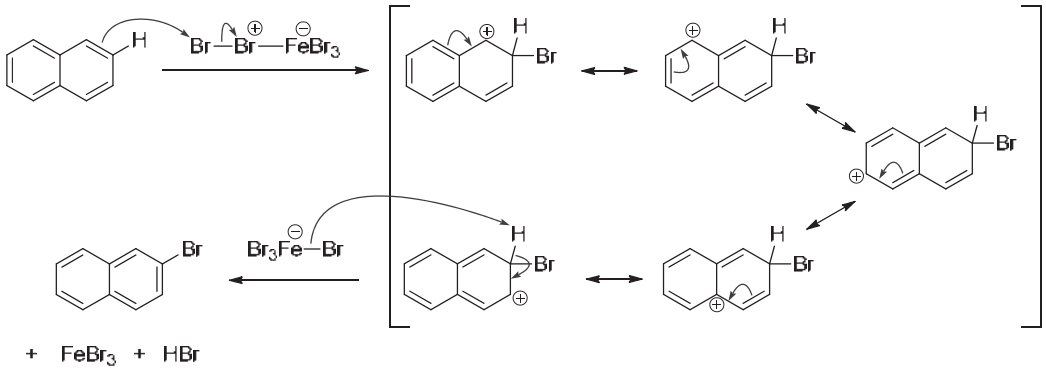
This is why aqueous acid must be introduced into the reaction flask after the reaction is complete, in order to serve as a proton source to regenerate phenol:



(b) These reagents provide a powerful electrophile, so the reaction must be an electrophilic aromatic substitution reaction. The first step of an electrophilic aromatic substitution reaction is formation of the electrophile that will react with the aromatic ring. This occurs when molecular bromine interacts with the Lewis acid to form a complex:



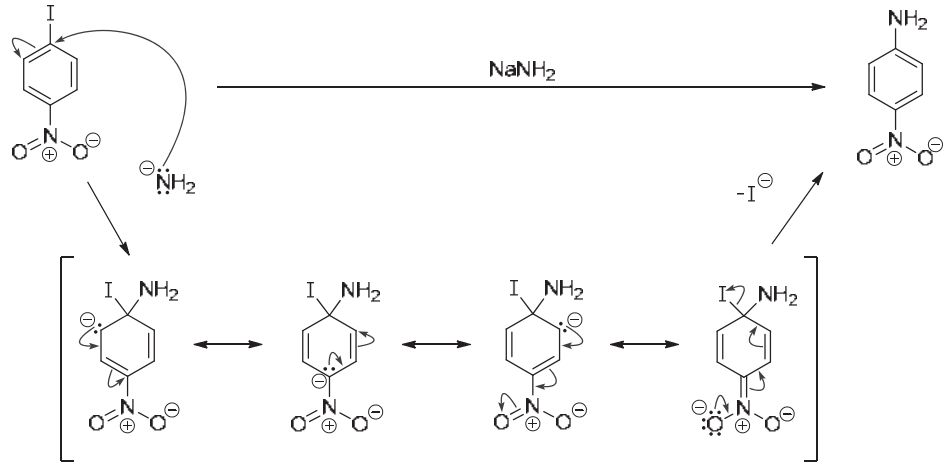
Then, one of the rings attacks the complex to give a resonance stabilized intermediate (a sigma complex), which then loses a proton to restore aromaticity (electrophilic aromatic substitution):



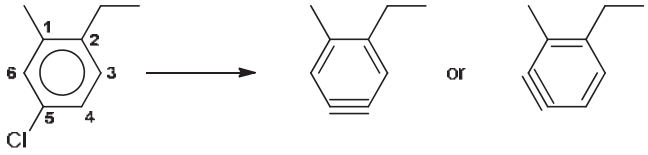
(c) The reagent (sodium amide) is a powerful nucleophile, and the three criteria for S_NAr are met (a nitro group and a leaving group that are *para* to each other), so we expect an S_NAr mechanism. In an S_NAr reaction, the first step

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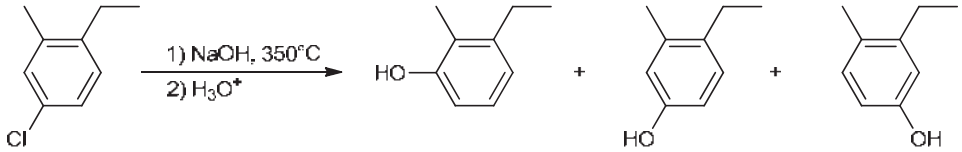
involves the nucleophile attacking the aromatic ring to generate a resonance stabilized intermediate (a Meisenheimer complex). Loss of a leaving group then gives the product, as shown:



18.36. The reagent (hydroxide) is a strong nucleophile and a strong base, and the three criteria for S_NAr are not met (the aromatic ring does not have a nitro group), so we expect an elimination-addition reaction. Upon treatment with sodium hydroxide, two possible benzyne intermediates are initially formed:



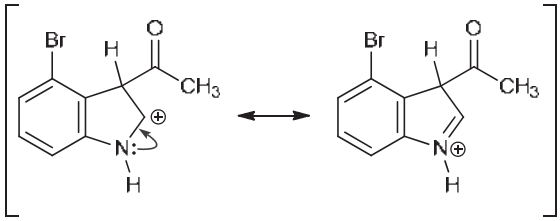
Then, for each of these benzyne intermediates, the hydroxide ion can attack either side of the triple bond, which means that the OH group is ultimately positioned at either C4, C5, or C6, giving rise to the following three products:



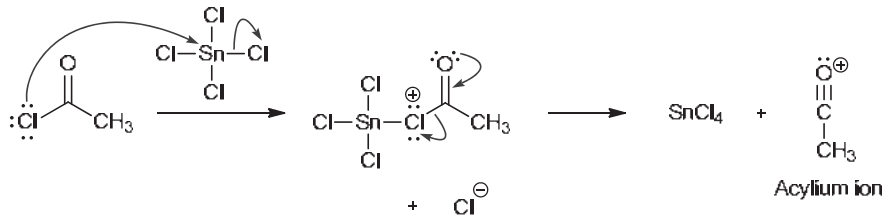
18.37.

(a) First look at the reagents. Both the acid chloride and $SnCl_4$ are electrophiles, so we can rule out S_NAr and elimination-addition. Additionally, the reaction involves the substitution of an H in an aromatic ring (pyrrole) with another group so this must be an electrophilic aromatic substitution. Since a methyl ketone results from the substitution, this is a Friedel-Crafts acylation.

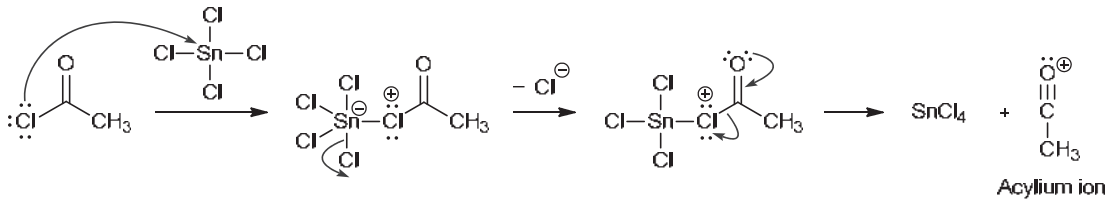
Since the reaction is an electrophilic aromatic substitution, the intermediate formed must have a positive charge, as shown below.



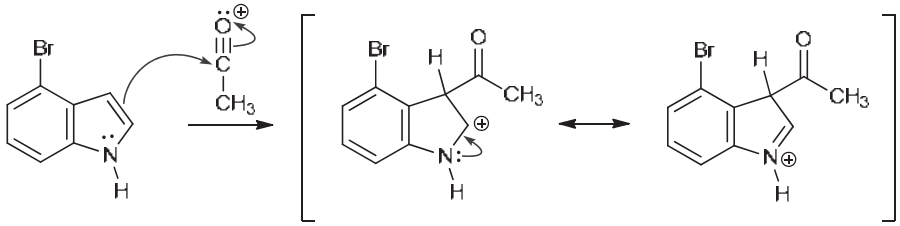
(b) The Friedel-Crafts acylation first involves the formation of an acylium ion when the acid chloride displaces a chloride anion from the Lewis acid followed by the loss of $SnCl_4$ leaving group.



Alternatively, the formation of the acylium could be drawn using a stepwise addition-elimination mechanism where the tin atom becomes pentavalent and then loses a chloride:

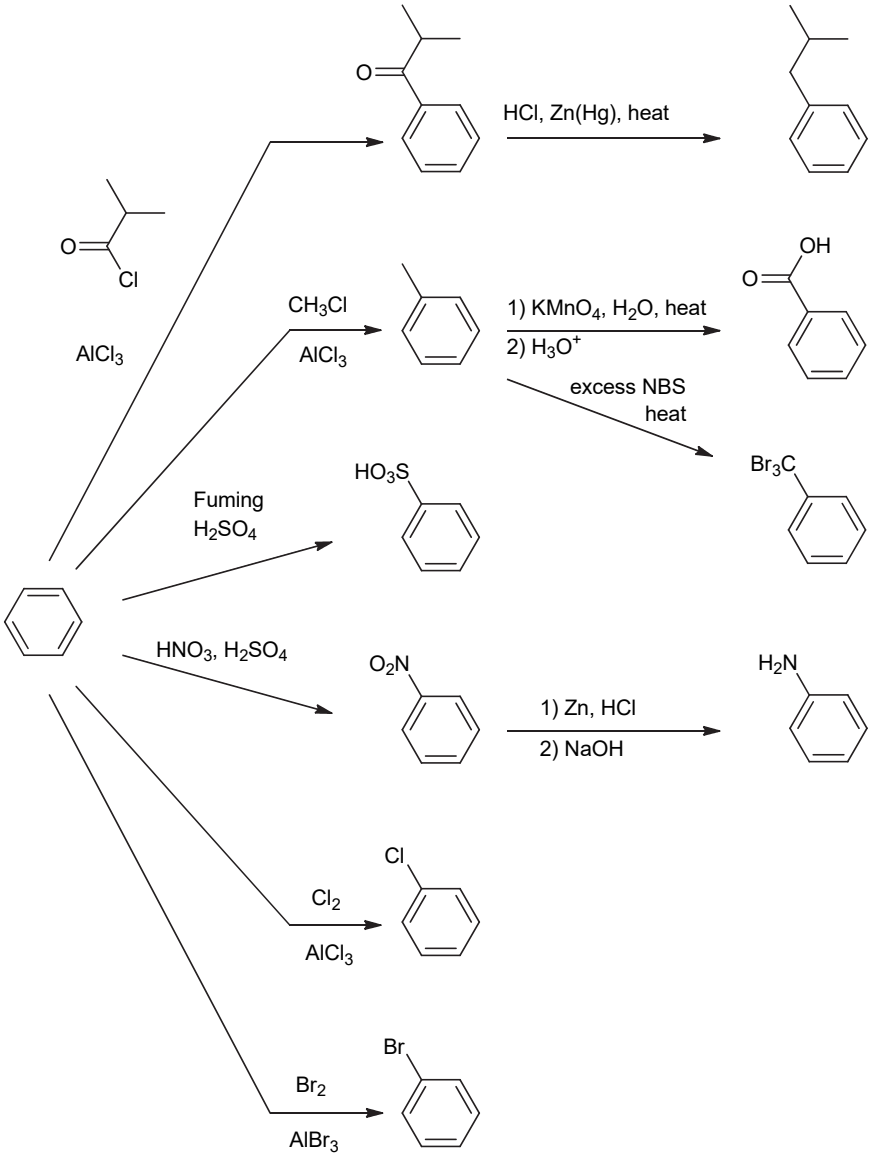


This acylium ion is then attacked by the pyrrole ring to form a sigma complex:

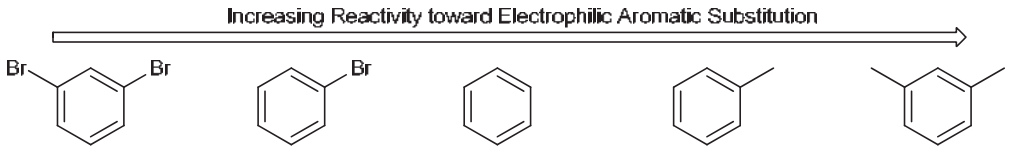


(c) Friedel-Crafts reactions frequently fail when amines are present due to the reaction of the nucleophilic amine and the Lewis acid. Since the lone pair of the nitrogen is part of an aromatic system, it is very non-nucleophilic and does not interfere with the formation of the acylium ion.

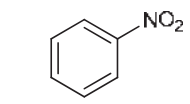
18.38. The reagents for these reactions can be found in the Review of Reactions at the end of the chapter. They are shown again here:



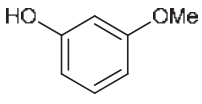
18.39. Alkyl groups are activating while halogens are deactivating toward electrophilic aromatic substitution. As such, the compound with two alkyl groups will be the most activated toward electrophilic aromatic substitution, while the compound with two halogens will be the least activated:



18.40. A nitro group is a strong deactivator. Therefore, among the four compounds, nitrobenzene is the least activated toward electrophilic aromatic substitution. The most activated ring is the one that exhibits two activators (OH and OMe).



least activated

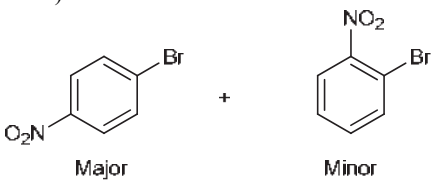


most activated

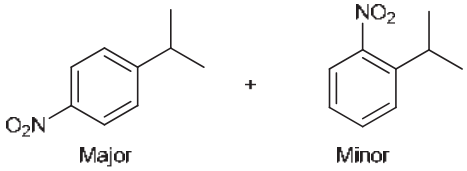
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18.41.

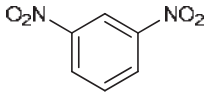
(a) The reagents indicate a nitration reaction, so we must decide where the nitro group will be installed. The aromatic ring has one substituent (Br) which is an *ortho-para* director, so we expect nitration to occur at the *ortho* and *para* positions. Because of the size of the bromine atom, the *para* product is expected to predominate (a steric effect).



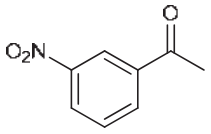
(b) The reagents indicate a nitration reaction, so we must decide where the nitro group will be installed. The aromatic ring has one substituent (an isopropyl group) which is an *ortho-para* director, so we expect nitration to occur at the *ortho* and *para* positions. Because of the size of the isopropyl group, the *para* product is expected to predominate (a steric effect).



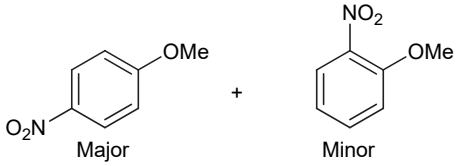
(c) The reagents indicate a nitration reaction, so we must decide where the nitro group will be installed. The aromatic ring has one substituent (a nitro group) which is a *meta* director, so we expect nitration to occur at the *meta* position.



(d) The reagents indicate a nitration reaction, so we must decide where the nitro group will be installed. The aromatic ring has one substituent (a carbonyl group) which is a *meta* director, so we expect nitration to occur at the *meta* position.

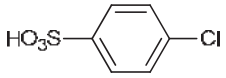


(e) The reagents indicate a nitration reaction, so we must decide where the nitro group will be installed. The aromatic ring has one substituent (a methoxy group) which is an *ortho-para* director, so we expect nitration to occur at the *ortho* and *para* positions. The *para* product is likely to predominate (because of a steric effect).

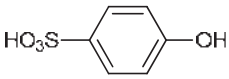


18.42.

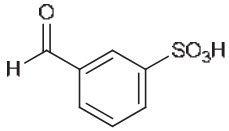
(a) These reaction conditions indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has one substituent (Cl) which is an *ortho-para* director, so we expect sulfonation to occur at the *ortho* and *para* positions. For steric considerations, the *para* product (shown here) is likely to predominate over the *ortho* product.



(b) These reaction conditions indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has one substituent (OH) which is an *ortho-para* director, so we expect sulfonation to occur at the *ortho* and *para* positions. For steric considerations, perhaps the *para* product (shown here) predominates over the *ortho* product, although it is a close call in this case. The OH group is similar in steric bulk to a methyl group, and we know that a methyl group provides little steric bulk (for example, sulfonation of toluene is expected to produce a mixture of *ortho* and *para* products, and the major product is difficult to predict).

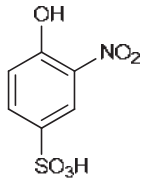


(c) These reaction conditions indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has one substituent (a carbonyl group) which is a *meta* director, so we expect sulfonation to occur at the *meta* position.

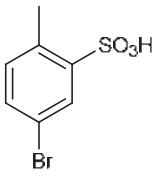


(d) These reaction conditions indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has two substituents (OH and NO_2). The directing effects are controlled by the more highly activating group, which is the OH group. As an activator, this group is an *ortho-para* director, so we expect sulfonation to occur at the *ortho* and *para* positions. For steric considerations, the *para* product (shown here) is likely to predominate over the *ortho* product.

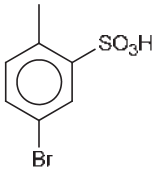
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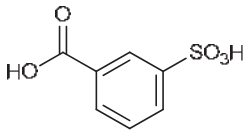
(e) These reaction conditions indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has two substituents (Br and Me). The directing effects are controlled by the more highly activating group, which is the methyl group. As an activator, this group is an *ortho-para* director, so we expect sulfonation to occur at the *ortho* and *para* positions. However, the *para* position is already occupied (by the bromine atom). Therefore, sulfonation can only take place at the *ortho* positions.



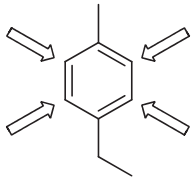
In this case, sulfonation at either *ortho* position leads to the same product. The two *ortho* positions are identical because of symmetry. Don't be confused by the arbitrary location of the double bonds. It is less distracting if we draw the structure like this:



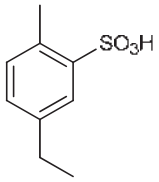
(f) These reaction conditions indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has one substituent (a carboxylic acid group) which is a *meta* director, so we expect sulfonation to occur at the *meta* position.



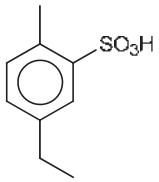
(g) These reaction conditions indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has two substituents (methyl and ethyl). Both groups are weak activators, so all unoccupied aromatic positions are equally activated:



These positions are differentiated from each because of steric factors. The ethyl group is larger than the methyl group, so the reaction is expected to occur *ortho* to the methyl group, rather than *ortho* to the more sterically bulky ethyl group.



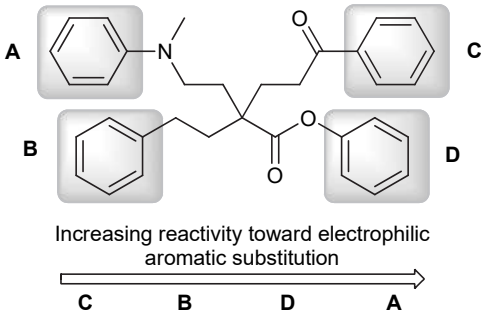
In this case, sulfonation at either *ortho* position leads to the same product. The two *ortho* positions are identical because of symmetry. Don't be confused by the arbitrary location of the double bonds. It is less distracting if we draw the structure like this:



18.43. Each of these substituents appears in Table 18.1.
(a) This group is an activator and an *ortho-para* director.
(b) This group is an activator and an *ortho-para* director.
(c) This group is an activator and an *ortho-para* director.
(d) This group is a deactivator and an *ortho-para* director.
(e) This group is a deactivator and a *meta*-director.
(f) This group is a deactivator and a *meta*-director.
(g) This group is a deactivator and a *meta*-director.
(h) This group is a deactivator and a *meta*-director.
(i) This group is a deactivator and an *ortho-para* director.
(j) This group is a deactivator and a *meta*-director.

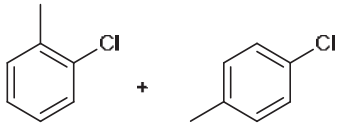
18.44. There are four aromatic rings, labeled **A** – **D**. Ring **A** is the most activated, because it exhibits a group that is a strong activator (an amino group). Ring **D** is moderately activated because it is connected to the oxygen atom of an ester. Ring **B** is weakly activated because it is connected to an alkyl group. And finally, ring **C** is deactivated because it is connected to a carbonyl group (a moderate deactivator).

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18.45.

(a) The reagents indicate a Friedel-Crafts alkylation reaction (methylation), so we must decide where the methyl group will be installed. The aromatic ring has one substituent (Cl) which is an *ortho-para* director, so we expect methylation to occur at the *ortho* and *para* positions.

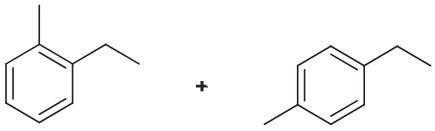


The latter is likely the major product because of steric considerations.

(b) This aromatic ring is moderately deactivated and will therefore not undergo a Friedel-Crafts alkylation.

(c) This aromatic ring is strongly deactivated and will therefore not undergo a Friedel-Crafts alkylation.

(d) The reagents indicate a Friedel-Crafts alkylation reaction (methylation), so we must decide where the methyl group will be installed. The aromatic ring has one substituent (Et) which is an *ortho-para* director, so we expect methylation to occur at the *ortho* and *para* positions.



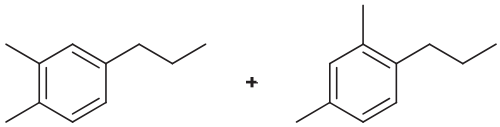
The latter is expected to be the major product because of steric considerations.

(e) The reagents indicate a Friedel-Crafts alkylation reaction (methylation), so we must decide where the methyl group will be installed. The aromatic ring has two substituents (I and Me). The directing effects are controlled by the most strongly activating group. Therefore, in this case, the methyl group controls the directing effects. As an activator, this group is an *ortho-para* director. However, one of the *ortho* positions is already occupied (by the other substituent). Therefore, methylation will occur at the position that is *ortho* or *para* to the methyl group, shown here:



The former is expected to be the major product because of steric considerations.

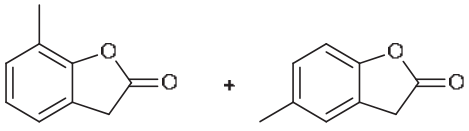
(f) The reagents indicate a Friedel-Crafts alkylation reaction (methylation), so we must decide where the methyl group will be installed. The aromatic ring has two substituents (propyl and methyl). Both groups are weak activators, and *ortho-para* directors. Therefore, we expect the following two products:



The former is expected to be the major product because of steric considerations.

(g) This aromatic ring has two substituents, and both are moderately deactivating. As such, the ring is too deactivated to undergo a Friedel-Crafts alkylation.

(h) The reagents indicate a Friedel-Crafts alkylation reaction (methylation), so we must decide where the methyl group will be installed. The aromatic ring has two substituents (the oxygen atom of an ester, and an alkyl group). The directing effects are controlled by the most strongly activating group. Therefore, in this case, the ester group controls the directing effects. As an activator, this group is an *ortho-para* director. However, one of the *ortho* positions is already occupied (by the other substituent). Therefore, methylation will occur at the positions that are *ortho* and *para* to the ester group, shown here:

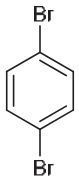


The latter is expected to be the major product because of steric considerations.

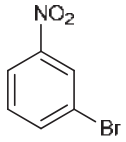
18.46.

(a) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed.

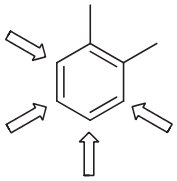
The aromatic ring has one substituent (Br) which is an *ortho-para* director, so we expect bromination to occur at the *ortho* and *para* positions. For steric considerations, the *para* product (shown here) is likely to predominate over the *ortho* product.



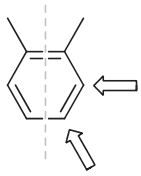
(b) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has one substituent (NO_2) which is a *meta* director, so we expect bromination to occur at the *meta* position:



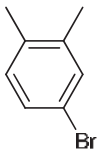
(c) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has two substituents (both methyl groups). Both groups are *ortho-para* directors, so all four unoccupied positions are activated:



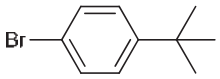
Because of symmetry, there are only two unique locations where bromination can occur:



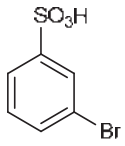
For steric considerations, the following product is expected to predominate.



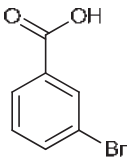
(d) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has one substituent (a *tert*-butyl group) which is an *ortho-para* director. The *tert*-butyl group is sterically bulky, so we expect the *para* product (shown here) to predominate over the *ortho* product.



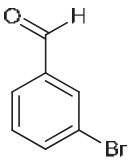
(e) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has one substituent (a sulfonic acid group) which is a *meta* director, so we expect bromination to occur at the *meta* position:



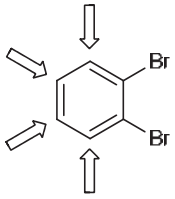
(f) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has one substituent (a carboxylic acid group) which is a *meta* director, so we expect bromination to occur at the *meta* position:



(g) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has one substituent (a carbonyl group) which is a *meta* director, so we expect bromination to occur at the *meta* position:

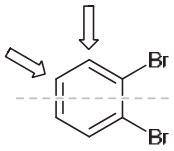


(h) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has two substituents (two bromine atoms). Both groups are *ortho-para* directors, so we expect these groups to direct to all four positions:

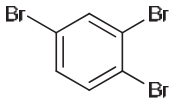


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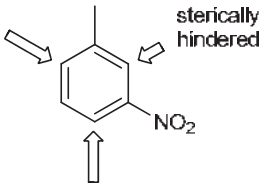
Because of symmetry, there are only two unique locations where bromination can occur:



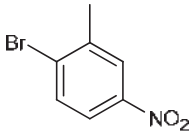
For steric considerations, the following product is expected to predominate.



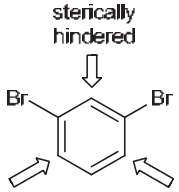
(i) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has two substituents: a methyl group (activator) and a nitro group (deactivator). The directing effects are controlled by the most strongly activating group. Therefore, in this case, the methyl group controls the directing effects. As an activator, this group is an *ortho-para* director, thereby activating the following three locations, one of which is sterically hindered:



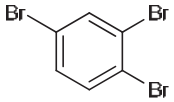
Among the remaining two positions, the position next to the nitro group is probably more hindered than the position next to the methyl group. So, we predict that bromination will occur predominantly near the methyl group:



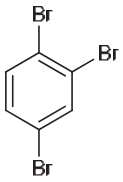
(j) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has two substituents (two bromine atoms). Both groups are *ortho-para* directors, so we expect these groups to direct to the following three positions, one of which is too sterically hindered:



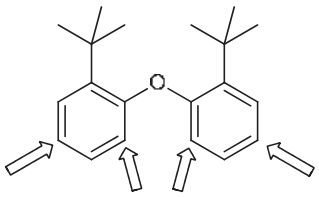
The remaining two positions are identical by symmetry. That is, bromination at either position will generate the same product:



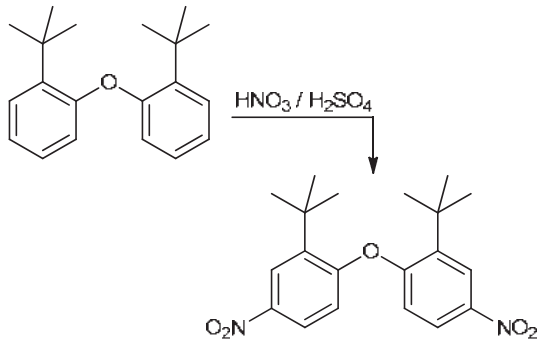
(k) The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has two substituents (two bromine atoms), both of which are *ortho-para* directors, so we expect these groups to direct to all four positions (all of which of which are *ortho* to one of the halogens). Indeed, all four positions are equivalent by symmetry anyway. Bromination will install a third bromine atom which can be drawn in any of the four unoccupied positions (all are identical):



18.47. There are two aromatic rings, and each ring has two substituents. For each ring, the directing effects are controlled by the most strongly activating group. Therefore, in this case, the OR group (a moderate activator) controls the directing effects for each ring (rather than the *tert*-butyl groups, which are weak activators). As an activator, the OR group is an *ortho-para* director. However, in each ring, one of the *ortho* positions is already occupied (by the *tert*-butyl group). Therefore, nitration can occur at the following locations:

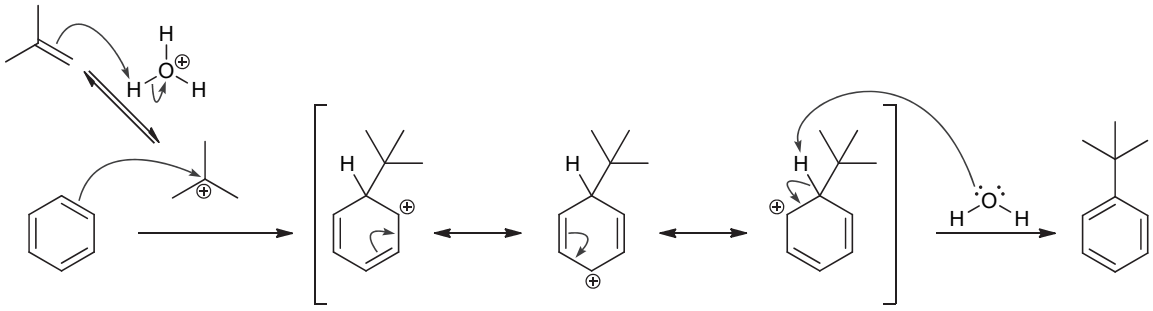


However, two of these locations are sterically hindered, so we only expect nitration at the remaining two (unencumbered) positions:



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18.48. In acidic conditions, 2-methylpropene is protonated to give a tertiary carbocation, which can function as an electrophile in an electrophilic aromatic substitution reaction. The aromatic ring attacks the carbocation to give a resonance stabilized intermediate (sigma complex), followed by deprotonation which restores aromaticity. In aqueous acidic conditions, the proton source is H_3O^+ (in the beginning of the mechanism), and the base is H_2O (at the end of the mechanism).

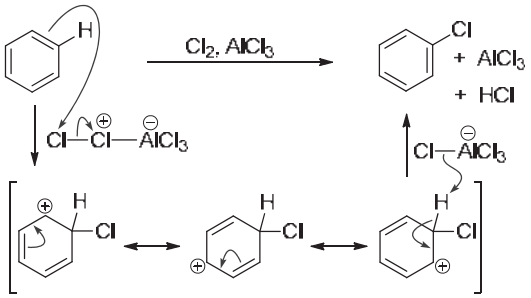


18.49.

(a) This is an electrophilic aromatic substitution reaction, and before we can draw the two steps of the process, we must begin by drawing formation of the electrophilic complex that will react with the aromatic ring. This occurs when molecular chlorine (Cl_2) attacks the Lewis acid, forming an electrophilic complex.

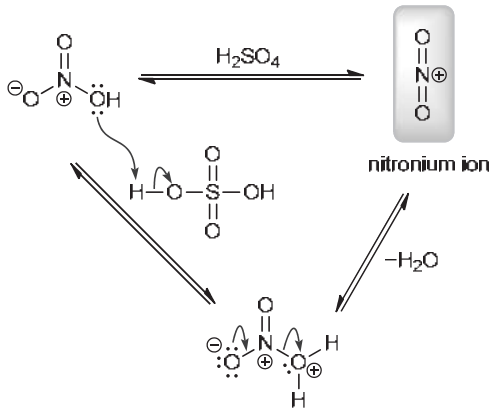


This complex serves as a delivery agent of Cl^+ (a powerful electrophile). The aromatic ring then functions as a nucleophile and attacks the electrophilic complex. The resulting intermediate sigma complex then loses a proton to restore aromaticity.

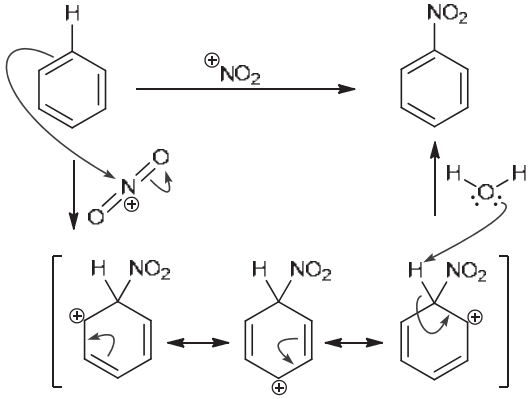


The base for the final step is $AlCl_4^-$. When it removes a proton, thereby re-establishing aromaticity, HCl is generated as a byproduct and the Lewis acid ($AlCl_3$) is regenerated (its function is catalytic).

(b) In the presence of sulfuric acid, nitric acid can be protonated, followed by loss of water to give a nitronium ion:

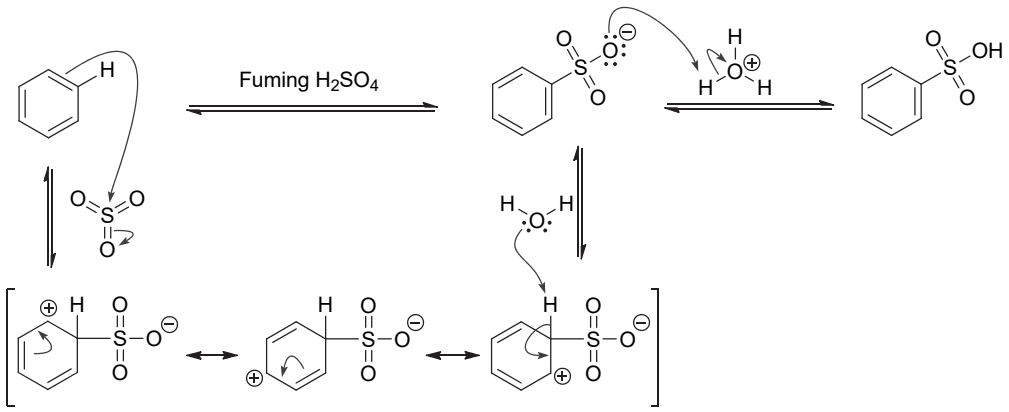


The aromatic ring then functions as a nucleophile and attacks the nitronium ion. The resulting intermediate sigma complex then loses a proton to restore aromaticity. Water is the likely base for the final deprotonation step, since water is present (and there are no strong bases present in strongly acidic conditions).

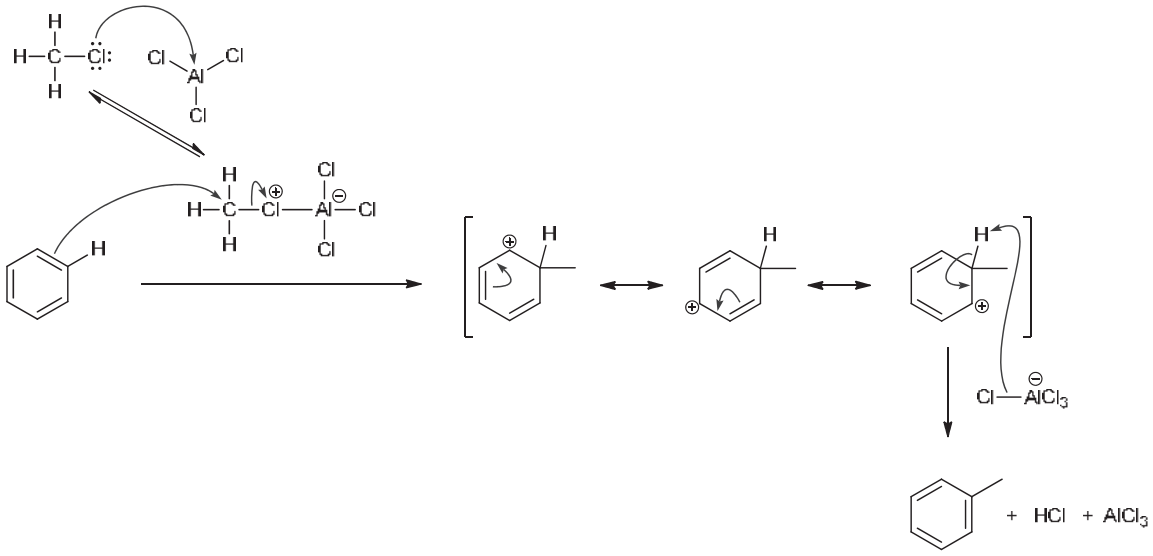


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(c) This is an electrophilic aromatic substitution reaction (called sulfonation). As for all electrophilic aromatic substitution reactions, there are two key steps. First, the aromatic ring functions as a nucleophile and attacks the electrophilic species (SO_3). Then, the resulting intermediate sigma complex loses a proton to restore aromaticity. Notice that the product is an anion, which is protonated under these acidic conditions, as shown:



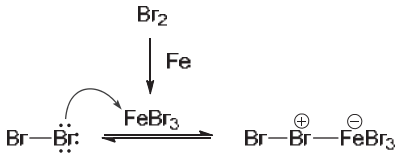
(d) This is a Friedel-Crafts alkylation process, which begins with the formation of the electrophilic complex that will react with the aromatic ring. Methyl chloride attacks the Lewis acid, forming an electrophilic complex. This complex serves as a delivery agent of H_3C^+. The aromatic ring functions as a nucleophile and attacks the electrophilic complex. The resulting intermediate sigma complex then loses a proton to restore aromaticity, as shown:



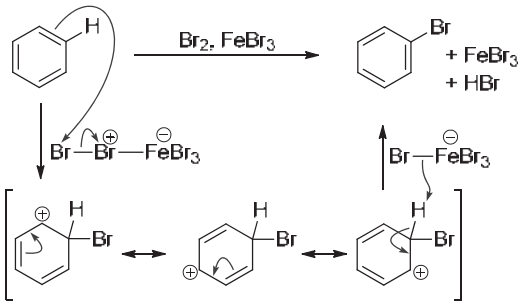
The base for the final step is $AlCl_4^-$. When it removes a proton, thereby re-establishing aromaticity, HCl is generated as a byproduct and the Lewis acid ($AlCl_3$) is regenerated (its function is catalytic).

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(e) This is an electrophilic aromatic substitution reaction, and before we can draw the two steps of the process, we must begin by drawing formation of the electrophilic complex that will react with the aromatic ring. This occurs when molecular bromine (Br_2) attacks the Lewis acid, forming an electrophilic complex.



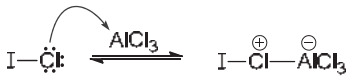
This complex serves as a delivery agent of Br^+ (a powerful electrophile). The aromatic ring then functions as a nucleophile and attacks the electrophilic complex. The resulting intermediate sigma complex then loses a proton to restore aromaticity.



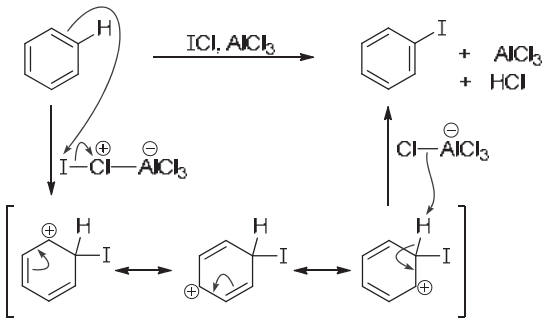
The base for the final step is $FeBr_4^-$. When it removes a proton, thereby re-establishing aromaticity, HBr is generated as a byproduct and the Lewis acid ($FeBr_3$) is regenerated (its function is catalytic).

18.50.

(a) This is an electrophilic aromatic substitution reaction, and before we can draw the two steps of the process, we must begin by drawing formation of the electrophilic complex that will react with the aromatic ring. This occurs when I–Cl attacks the Lewis acid, forming an electrophilic complex.



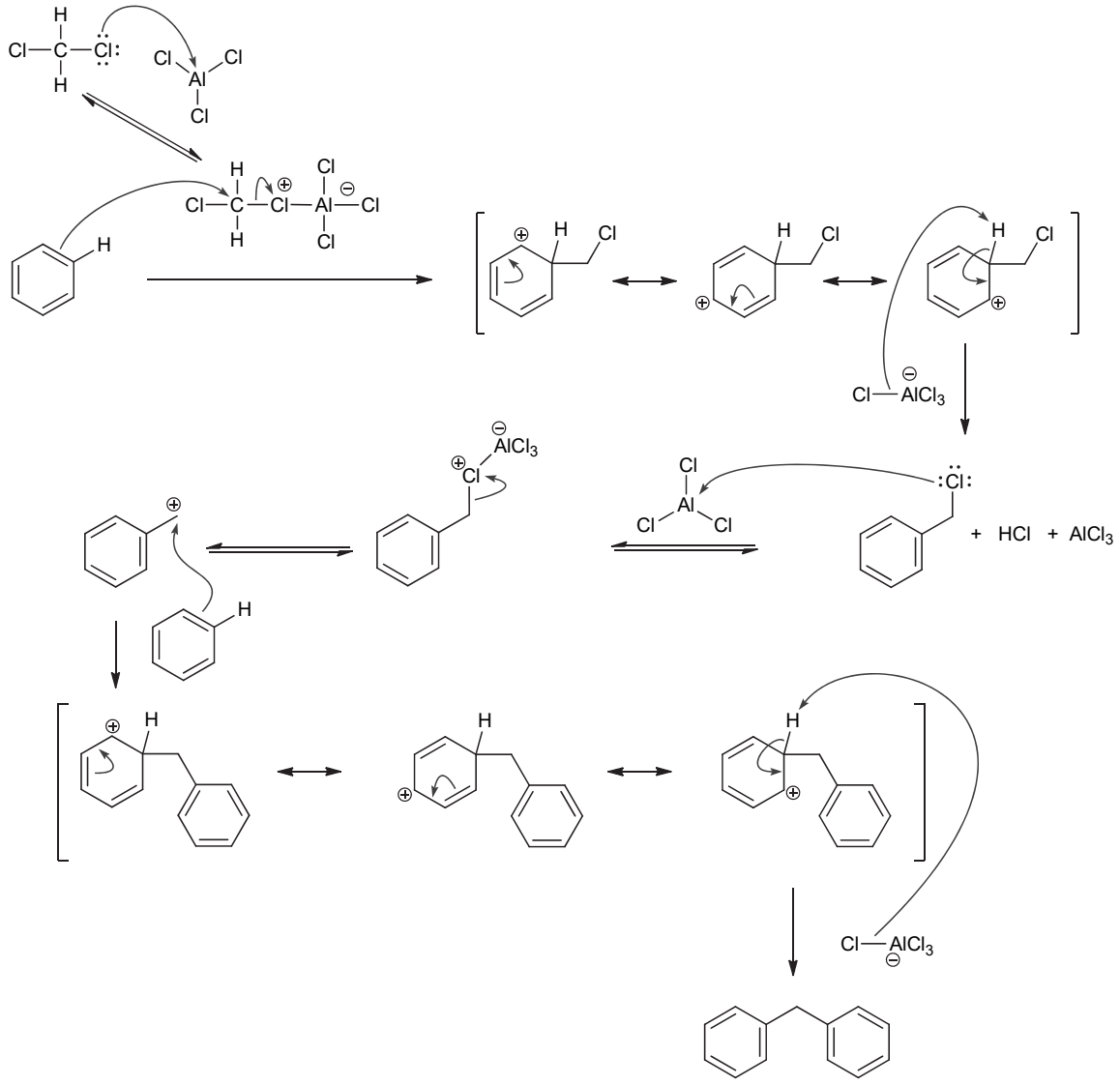
This complex serves as a delivery agent of I^+. The aromatic ring then functions as a nucleophile and attacks the electrophilic complex. The resulting intermediate sigma complex then loses a proton to restore aromaticity.



The base for the final step is $AlCl_4^-$. When it removes a proton, thereby re-establishing aromaticity, HCl is generated as a byproduct and the Lewis acid ($AlCl_3$) is regenerated (its function is catalytic).

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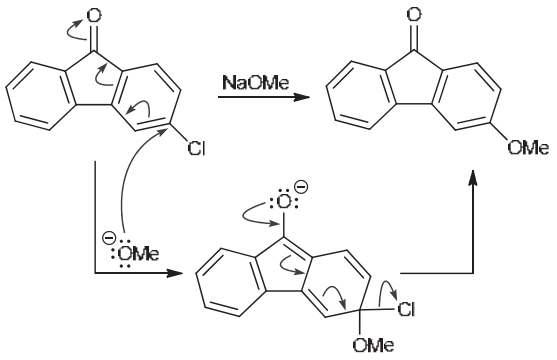
(b) This transformation occurs via two successive electrophilic aromatic substitution reactions. The process begins with formation of the electrophilic complex that will react with the first aromatic ring. Methylene chloride (CH_2Cl_2) attacks the Lewis acid, forming an electrophilic complex. This complex serves as a delivery agent of ClH_2C^+. The aromatic ring functions as a nucleophile and attacks the electrophilic complex. The resulting intermediate sigma complex then loses a proton to restore aromaticity, giving benzyl chloride. Then, all of the previous steps (formation of the electrophilic complex, followed by the two steps of an electrophilic aromatic substitution reaction) are repeated again, as shown, giving the product (diphenylmethane). Notice that, for each deprotonation step, the base is $AlCl_4^-$. When it removes a proton, HCl is generated as a byproduct and the Lewis acid ($AlCl_3$) is regenerated (its function is catalytic):



18.51. The substituent (Cl) is replaced with a different substituent (OMe). Therefore, this is an aromatic substitution reaction. The reagent (methoxide) is nucleophilic, so we must determine whether this reaction occurs via an S_NAr mechanism or via an elimination-addition mechanism. All three criteria for an S_NAr mechanism are met: 1) there is a leaving group (chloride), and 2) there is an electron-withdrawing group (the carbonyl group is electron withdrawing via resonance), and 3) the leaving group is *para* to the electron-withdrawing group. Therefore, we draw an S_NAr mechanism. In the first step, methoxide functions as a nucleophile and attacks the aromatic ring at the position bearing the leaving group, thereby forming an

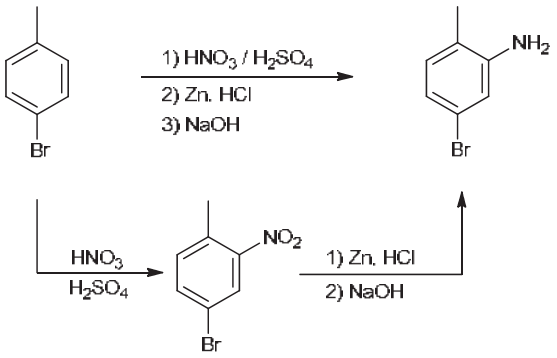
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intermediate Meisenheimer complex. Then, a leaving group (chloride) is ejected, restoring aromaticity, and giving the product, as shown.

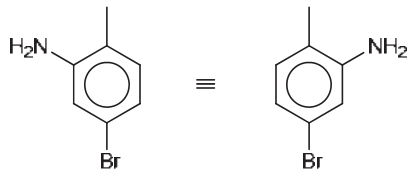


18.52.

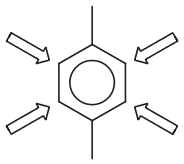
(a) The reagents indicate the installation of a nitro group, followed by its reduction to an amino group. To determine where this group is installed, recall that the directing effects are controlled by the most strongly activating group. In this case, the methyl group is the only activating group (albeit weakly activating), so it controls the directing effects. As an activator, this group is an *ortho-para* director. However, the *para* position is already occupied (by the other substituent). Therefore, the group is installed in a position that is *ortho* to the methyl group.



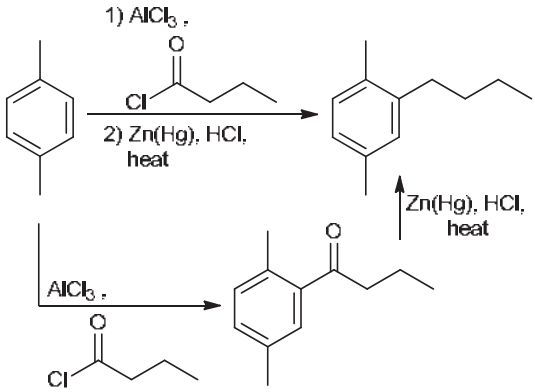
In this case, both *ortho* positions are equivalent because of symmetry, so the group can be drawn in either ortho position (don't be distracted by the arbitrary placement of the double bonds in the aromatic ring):



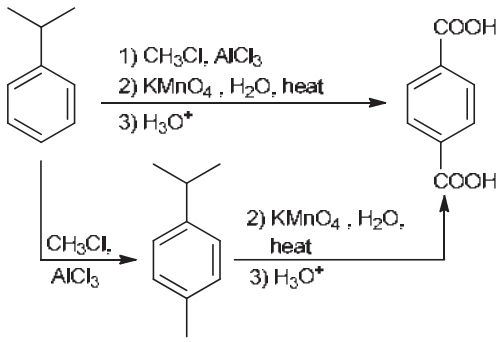
(b) The starting material is *para*-xylene, in which the following four positions are identical (because of symmetry):



Therefore, installation of a third group leads to only one regiochemical outcome. Each group weakly activates the ring, so this compound will readily undergo a Friedel-Crafts acylation reaction, thereby installing an acyl group on the ring. Then, in the second step, the carbonyl group is reduced, giving the product shown:



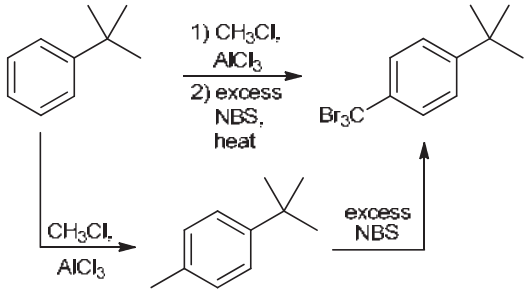
(c) The aromatic ring has only one substituent (an isopropyl group), which is an activator and therefore an *ortho-para* director. The *ortho* positions are sterically hindered (by their proximity to the bulky isopropyl group), so an electrophilic aromatic substitution reaction is expected to occur predominantly at the *para* position. In the first step, a Friedel-Crafts alkylation is used to install a methyl group in the *para* position. Then, both alkyl groups are oxidized to give a diacid, as shown:



(d) The aromatic ring has only one substituent (a *tert*-butyl group), which is an activator and therefore an *ortho-para* director. The *ortho* positions are very sterically hindered (by their proximity to the bulky *tert*-butyl group), so an electrophilic aromatic substitution reaction is expected to occur almost exclusively at the *para* position. In the first step, a Friedel-Crafts alkylation is used to install a methyl group in the *para* position. Then, in the next step, the benzylic protons are replaced with bromine atoms. The *tert*-butyl group does

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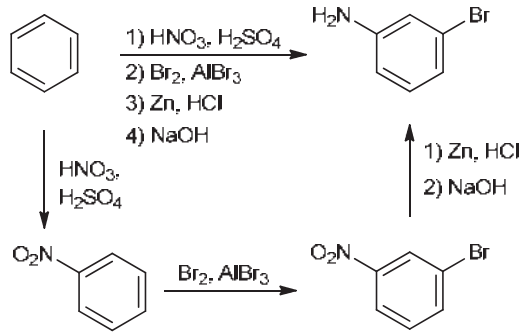
not have any benzylic protons, so no bromine atoms are installed in that location. Only the methyl group undergoes benzylic bromination (exhaustively), as shown:



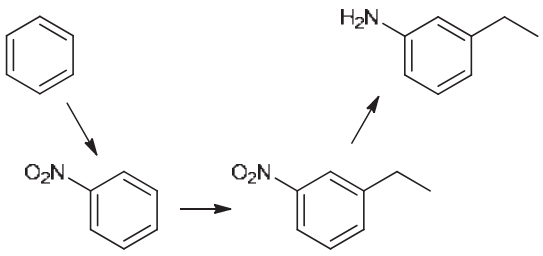
18.53.

(a) Installation of the amino group requires a two-step process (nitration, followed by reduction), while installation of the bromine atom can be achieved in just one step.

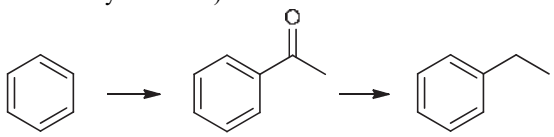
Now let's consider the order of events. These two groups must be installed in a *meta* fashion, but both groups are *ortho-para* directors. Installation of these two groups (in either order) does not appear to give the desired *meta* substitution pattern. However, recall that installation of the amino group requires two steps. The first step is nitration, and a nitro group is a *meta*-director. So, we can achieve the desired transformation by performing the bromination process after the nitration process but before the reduction process, as shown here:



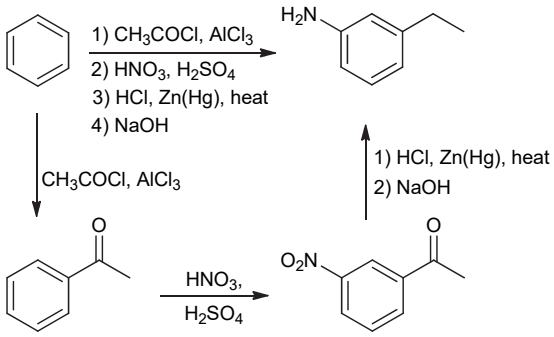
(b) Installation of the amino group requires two steps (nitration, followed by reduction), while installation of the ethyl group can be achieved in just one step (via a Friedel-Crafts alkylation). The substituents must be installed in a *meta* fashion, yet both substituents are *ortho-para* directors. To circumvent the problem, we consider utilizing the *meta*-directing effects of the nitro group to achieve the desired regiochemical outcome:



However, this strategy will not succeed because the middle step is flawed. Specifically, a Friedel-Crafts alkylation cannot be performed on a strongly deactivated ring (such as nitrobenzene). Therefore, we must find another way to install the two groups in a *meta* fashion. The trick that we used in the solution to Problem 19.57a can be used here again. That is, we install the ethyl group via a two-step process (Friedel-Crafts acylation, followed by reduction):



By installing the ethyl group in this way, we can capitalize on the directing effects of the carbonyl group, before reducing it. As seen below, a Friedel-Crafts acylation installs an acyl group, which is a *meta*-director. Subsequent nitration allows for the installation of a nitro group in the *meta* position. And finally, reduction (of both groups) gives the product, as shown.



18.54.

(a) The second step of the synthesis will not work, because a strongly deactivated ring will not undergo a Friedel-Crafts alkylation. The product of the first step, nitrobenzene, will be unreactive in the second step.

(b) The second step of the synthesis will not efficiently install a propyl group, because a carbocation rearrangement can occur, which can result in the installation of an isopropyl group. A mixture of products is expected.

(c) The second step of the synthesis will not install the acyl group in the *meta* position. It will be installed in a position that is either *ortho* or *para* to the bromine atom.

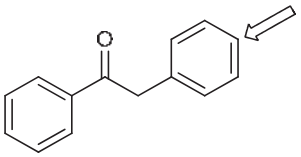
(d) The second step of the synthesis will not install the bromine atom in the *ortho* position, because of steric hindrance from the *tert*-butyl group. Bromination will occur primarily at the *para* position.

18.55.

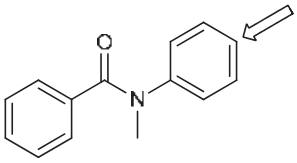
(a) This compound has two aromatic rings, each of which is monosubstituted. One aromatic ring (left) is connected directly to a carbonyl group and is therefore deactivated. The other aromatic ring (right) is connected to a methylene group (CH_2) and is therefore activated (the substituent is treated like an alkyl group). So, we expect monobromination to occur on the activated ring.

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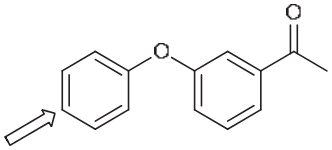
Since the substituent is an activator, it must also be an *ortho-para* director. The *ortho* positions are sterically hindered (by the large substituent), so the reaction is expected to occur predominantly at the *para* position, indicated here:



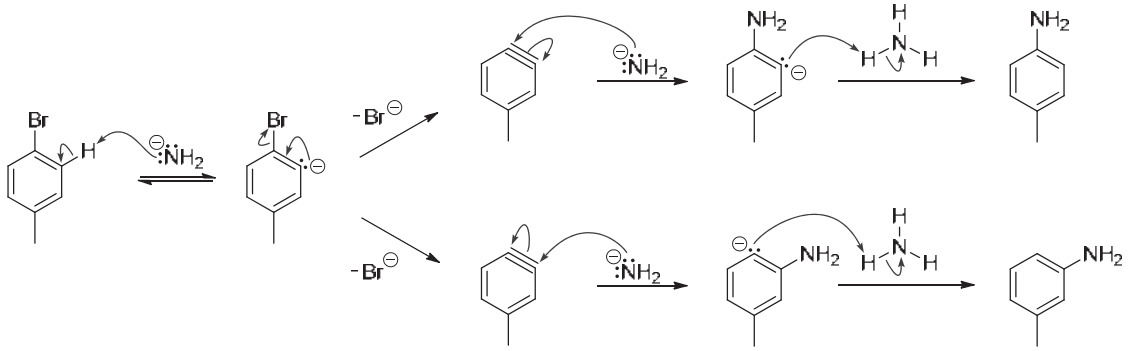
(b) This compound has two aromatic rings, each of which is monosubstituted. One aromatic ring (left) is connected directly to a carbonyl group and is therefore deactivated. The other aromatic ring (right) is connected to a nitrogen atom and is therefore activated. So, we expect monobromination to occur on the activated ring. Since the substituent is an activator, it must also be an *ortho-para* director. The *ortho* positions are sterically hindered (by the large substituent), so the reaction is expected to occur predominantly at the *para* position, indicated here:



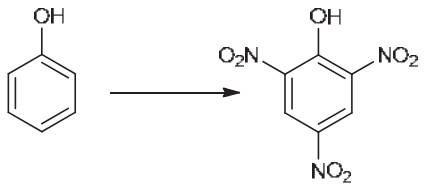
(c) This compound has two aromatic rings. The ring on the left has one only substituent, which is an activator. The ring on the right has two substituents: an activator and a deactivator. As such, we expect monobromination to occur on the left ring, which is more activated. Since the substituent (on the left ring) is an activator, it must also be an *ortho-para* director. The *ortho* positions are sterically hindered (by the large substituent), so the reaction is expected to occur predominantly at the *para* position, indicated here:



18.56. The reagent is sodium amide, which is strongly nucleophilic and strongly basic. The three criteria for S_NAr are not met (the aromatic ring lacks a nitro group), and therefore, the reaction must occur via an elimination-addition mechanism (as seen in Mechanism 18.9), shown here. The benzyne intermediate can be attacked on either side of the triple bond, leading to the two products shown:



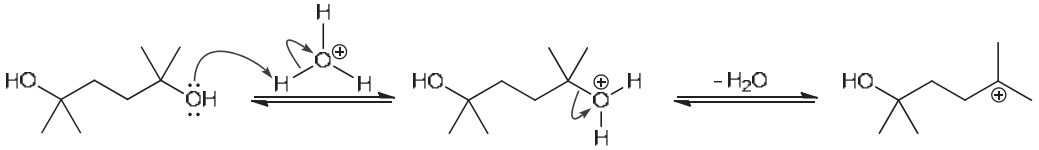
18.57. Phenol has only one substituent (OH) connected to the aromatic ring. This group is a strong activator, and is therefore an *ortho-para* director. If conditions are controlled such that three nitro groups are installed, then we expect the three nitro groups to be installed at the *ortho* and *para* positions, as shown:



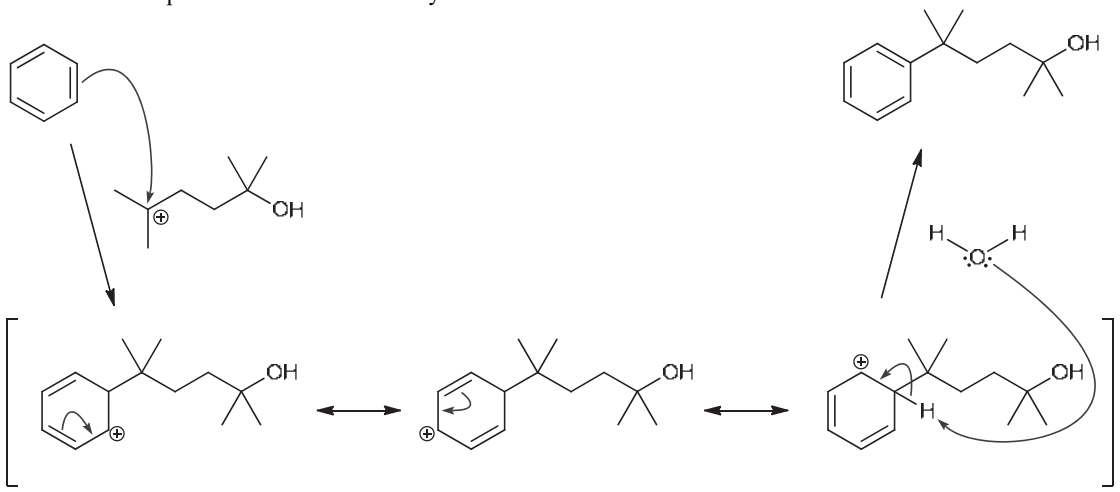
2,4,6-trinitrophenol
(picric acid)

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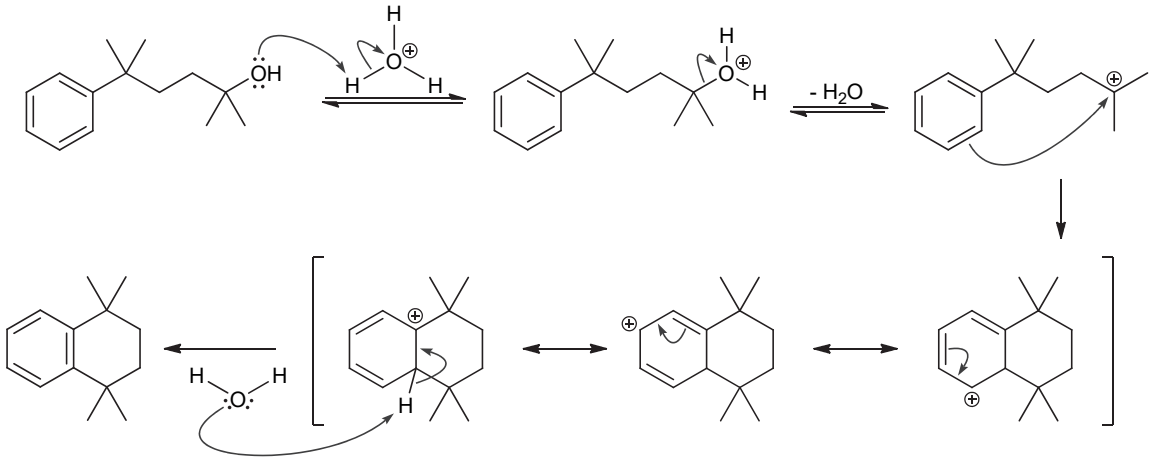
18.58. The starting material is benzene, and the product exhibits a disubstituted aromatic ring. This will require two successive aromatic substitution reactions. The reagent (the diol) is not a very strong nucleophile, nor is it a very strong electrophile. However, in acidic conditions, the diol exists in equilibrium with a very powerful electrophile (a carbocation), as shown:



As seen above, one of the OH groups can be protonated, giving an excellent leaving group, which can leave to give a tertiary carbocation. Since the reagent is electrophilic, we expect that the reaction will proceed via electrophilic aromatic substitution. Accordingly, the aromatic ring attacks the carbocation to give an intermediate sigma complex, which then loses a proton to restore aromaticity:



The entire process is then repeated again, except this time, the reaction will proceed in an *intramolecular* fashion, closing a ring. The OH group is protonated to give an excellent leaving group, which can leave to give a tertiary carbocation. The aromatic ring attacks the carbocation in an intramolecular process to give an intermediate sigma complex, which then loses a proton to restore aromaticity:



Since aqueous acidic conditions are employed (H_2SO_4 is generally dissolved in water), the proton source throughout the mechanism has been H_3O^+, and the base has always been H_2O, to be consistent with acidic conditions.

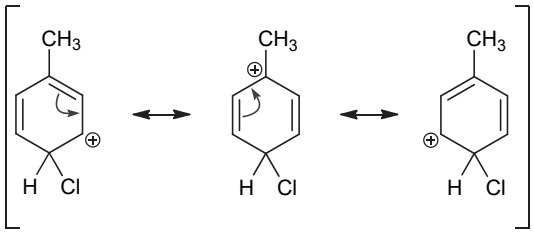
18.59. These reagents will achieve the installation of an isopropyl group on the aromatic ring. The problem statement indicates that conditions will favor dialkylation, which means that two isopropyl groups are installed. After installation of the first isopropyl group, the second isopropyl is expected to be installed

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predominantly in the *para* position (because alkyl groups are *ortho-para* directors, and the *ortho* positions are sterically hindered by their proximity to the isopropyl group):

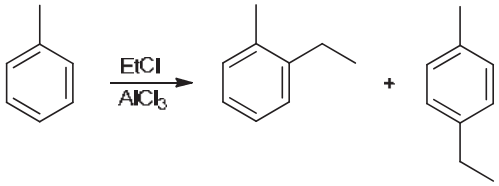


18.60. A chlorine atom is placed at the *para* position, and a resonance-stabilized positive charge is formed, as shown:



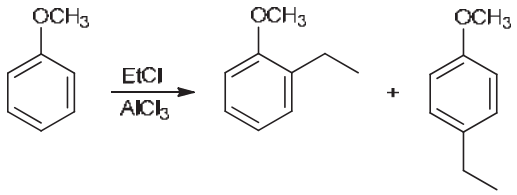
18.61.

(a) Toluene is the only compound with an activated ring, and it is expected to undergo a Friedel-Crafts reaction most rapidly. The methyl group is an *ortho-para* director, so we expect a mixture of *ortho* and *para* products (*ortho*-ethyltoluene and *para*-ethyltoluene):

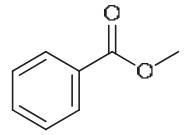


Generally, *para* substitution products are favored over *ortho* substitution products because of steric factors, However, a methyl group provides only a small amount of steric hindrance, and therefore, the product distribution is difficult to predict. That is, we cannot predict which product will predominate, and it will likely be sensitive to the conditions employed.

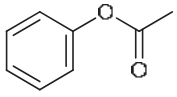
(b) Anisole (methoxybenzene) exhibits the most activated ring, and it is therefore expected to undergo a Friedel-Crafts reaction most rapidly. The methoxy group is an *ortho-para* director, so we expect a mixture of *ortho* and *para* products, although the *para* product is expected to predominate because of steric factors:



18.62. The molecular formula indicates five degrees of unsaturation, which accounts for the aromatic ring (four degrees) and the ester group (1 degree). The aromatic ring accounts for six of the eight carbon atoms, so the ester group can only have two carbon atoms. The following two structures fit this description:



Compound A

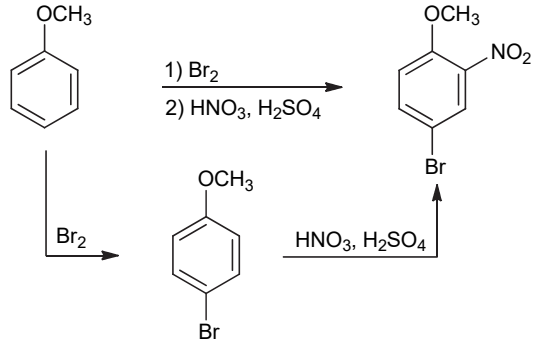


Compound B

Compound **A** must be the compound in which the carbonyl group is connected directly to the aromatic ring, because bromination of compound **A** leads to only one product. Recall that the carbonyl group is a *meta* director, and both *meta* positions are identical, which explains why there is only one monobromination product. In contrast, compound **B** exhibits an activating group, which is an *ortho-para* director. As such, we expect two monobromination products (bromination can occur at either the *ortho* position or the *para* position).

18.63.

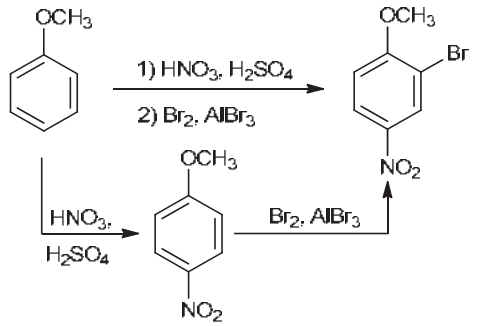
(a) The starting material is methoxybenzene (anisole) and the product has two additional substituents, located at the *ortho* and *para* positions. The bromine atom is installed in just one step (bromination), and the nitro group can also be installed in just one step (nitration). The methoxy group is an *ortho-para* director, although substitution at the *para* position will likely predominate because of steric factors. Therefore, we must first perform the bromination reaction, thereby installing the bromine atom in the correct location. Note that no Lewis acid is required, as the ring is moderately activated; just one equivalent of Br_2 would be used. And finally, we perform a nitration reaction which installs the nitro group in the position that is *ortho* to the moderately activating methoxy group.



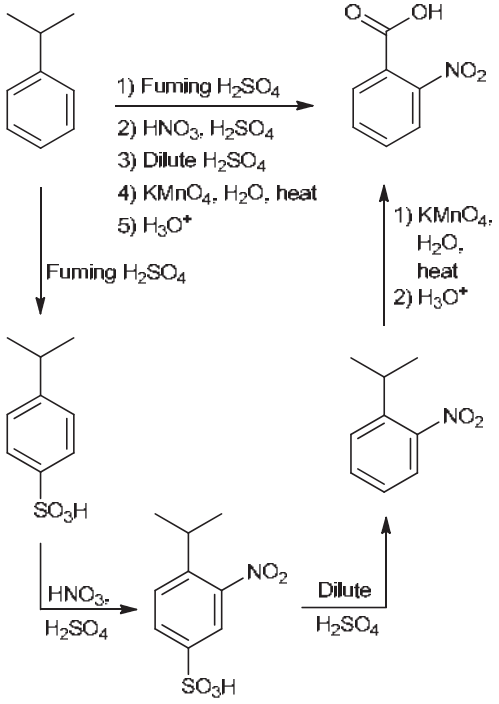
(b) The starting material is methoxybenzene (anisole) and the product has two additional substituents, located at the *ortho* and *para* positions. The bromine atom is installed in just one step (bromination), and the nitro group can also be installed in just one step (nitration). The methoxy group is an *ortho-para* director, although substitution at the *para* position will likely predominate because of steric factors. Therefore, we must first perform the nitration reaction, thereby installing the nitro

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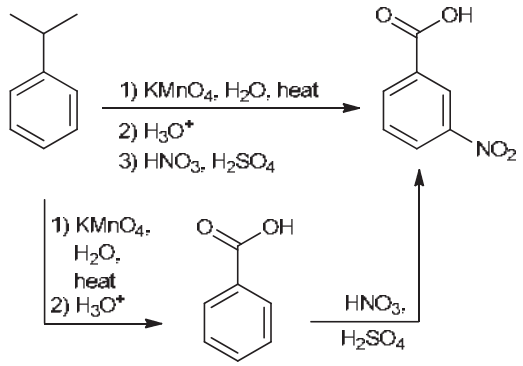
group in the correct location. And then, we perform a bromination reaction which installs the bromine atom in the position that is *ortho* to the moderately activating methoxy group.



(c) The starting material exhibits an aromatic ring with only one substituent (an isopropyl group). In the product, the isopropyl group has been converted into a carboxylic acid, which can be achieved via benzylic oxidation with a strong oxidizing agent. In addition, a nitro group must be installed. Now we must determine the order of events. Both substituents (in the product) are *meta* directors, yet they are *ortho* to each other. Therefore, we must install the nitro group before the isopropyl group is oxidized, thereby relying on the *ortho-para* directing effects of an isopropyl group. A blocking group must be used because the isopropyl group provides steric bulk that would otherwise favor nitration at the *para* position, rather than the *ortho* position. By blocking the *para* position, we can perform a nitration reaction, thereby installing the nitro group in the desired location. Removing the blocking group, followed by oxidation of the benzylic position, gives the desired product.



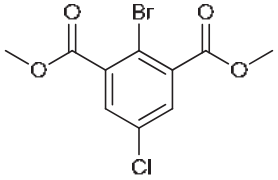
(d) The starting material exhibits an aromatic ring with only one substituent (an isopropyl group). In the product, the isopropyl group has been converted into a carboxylic acid, which can be achieved via benzylic oxidation with a strong oxidizing agent. In addition, a nitro group must be installed. Now we must determine the order of events. Both substituents (in the product) are *meta* directors, and they are indeed *meta* to each other. Therefore, we simply oxidize the benzylic position, and then perform a nitration reaction to give the desired product.



Note that an isopropyl group is an *ortho-para* director, but the desired nitration reaction must occur at the *meta* position, so nitration cannot be the first step of our synthesis. We must first convert the alkyl group (which is an *ortho-para* director) into a carboxylic acid group (which is a *meta* director).

18.64.

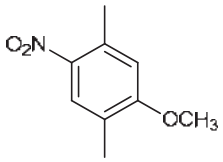
(a) The reagents indicate a chlorination reaction, so we must decide where the chlorine atom will be installed. The directing effects are controlled by the most strongly activating group. In this case, none of the groups are activators, but the halogen is at least an *ortho-para* director, and therefore controls the directing effects (rather than the ester groups, which are *meta*-directing). The two *ortho* positions are already occupied (by the other substituents). Therefore, chlorination is expected to occur at the position that is *para* to the bromine atom. This is consistent with the directing effects of the ester groups as well.



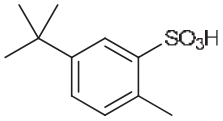
(b) The reagents indicate a nitration reaction, so we must decide where the nitro group will be installed. The directing effects are controlled by the most strongly activating group. Therefore, in this case, the methoxy group controls the directing effects. As an activator, this group is an *ortho-para* director. However, one of the *ortho* positions is already occupied (by a methyl

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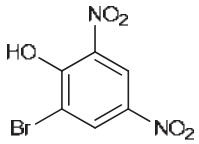
substituent). That leaves two possible locations: the remaining *ortho* position and the *para* position. The former is too sterically hindered and the reaction is not likely to occur there. Therefore, we expect nitration to occur in the *para* position, giving the following product.



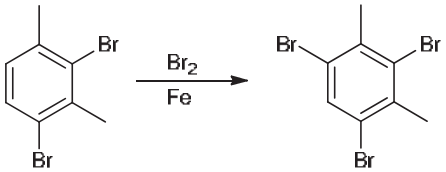
(c) The reagents indicate a sulfonation reaction, so we must decide where the sulfonic acid group will be installed. The aromatic ring has two substituents (*tert*-butyl and methyl). Both groups are weak activators, and *ortho-para* directors. Because of steric factors, we expect the sulfonic acid group to be installed *ortho* to the methyl group, rather than *ortho* to the large *tert*-butyl group.



(d) The reagents indicate a nitration reaction, so we must decide where the nitro group will be installed. The directing effects are controlled by the most strongly activating group. Therefore, in this case, the OH group controls the directing effects. As an activator, this group is an *ortho-para* director. However, one of the *ortho* positions and the *para* position are already occupied (by the other substituents). Therefore, nitration can only occur in the remaining position that is *ortho* to the OH group, giving the following product.

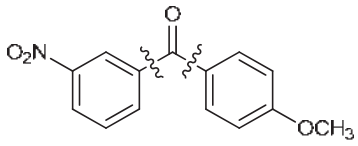


18.65. The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The directing effects are controlled by the most strongly activating group(s). The methyl groups are weakly activating and the bromo groups are weakly deactivating. Therefore, in this case, the methyl groups control the directing effects. Both of the methyl groups are directing to the same location (*ortho* and *para* to the methyl groups):

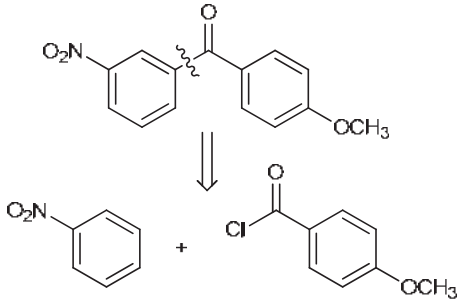


18.66.

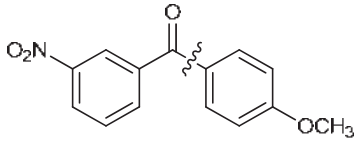
(a) There are two possible pathways to consider, based on which C–C bond is to be formed:



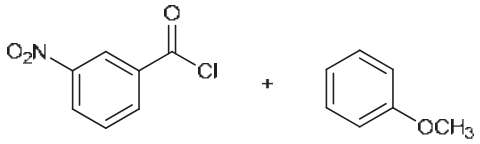
Let's consider one of these pathways (forming the bond on the left). Forming this bond via a Friedel-Crafts acylation would require the following starting materials:



Indeed, the nitro group of nitrobenzene is *meta*-directing, so the regiochemistry is correct. However, we must remember that a Friedel-Crafts acylation cannot be performed on an aromatic ring that is strongly deactivated. Since nitrobenzene is strongly deactivated, this pathway is not feasible. So, we must explore the other possible pathway, forming this bond:

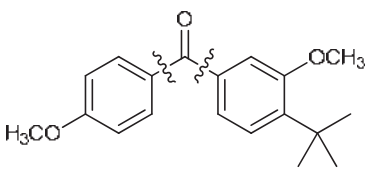


Forming this bond via a Friedel-Crafts acylation would require the following starting materials:



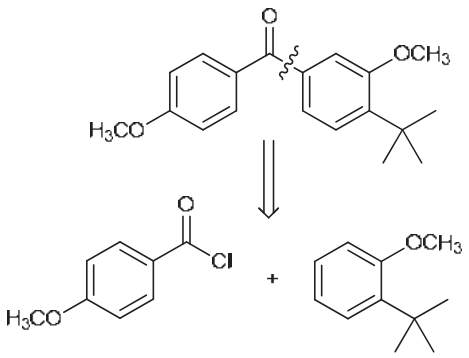
The methoxy group is an *ortho-para* director, and *para* substitution is expected to predominate (because of steric factors), giving rise to the desired product.

(b) There are two possible pathways to consider, based on which C–C bond is to be formed:

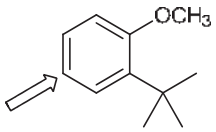


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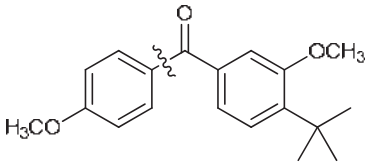
Let's consider one of these pathways (forming the bond on the right). Forming this bond via a Friedel-Crafts acylation would require the following starting materials:



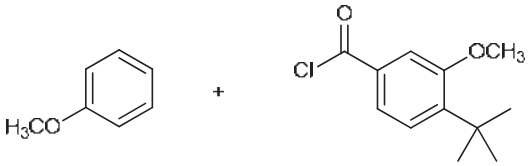
Let's consider the regiochemical outcome of a Friedel-Crafts acylation with these starting materials. The methoxy group controls the directing effects, so substitution is expected to occur at the position that is *para* to the methoxy group (not *meta* to the methoxy group).



Therefore, this pathway is not feasible, because it would not give the correct product. So we must explore the other possible pathway, forming this bond:



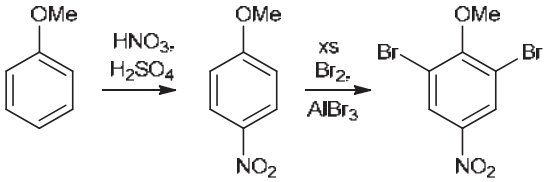
Forming this bond via a Friedel-Crafts acylation would require the following starting materials:



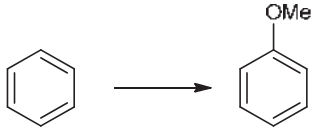
The methoxy group is an *ortho-para* director, and *para* substitution is expected to predominate (because of steric factors), giving rise to the desired product.

18.67.

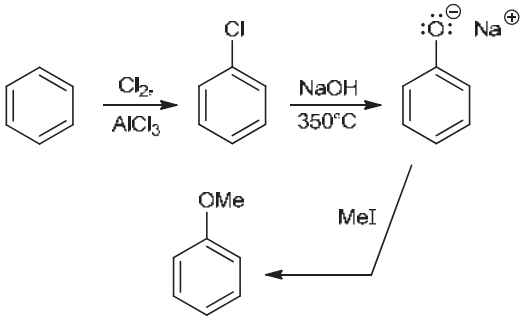
(a) The product has four substituents. One of them is a methoxy group, which is an *ortho-para* director. The directing effects of this substituent, if installed first, can be used to install the other groups in the correct locations:



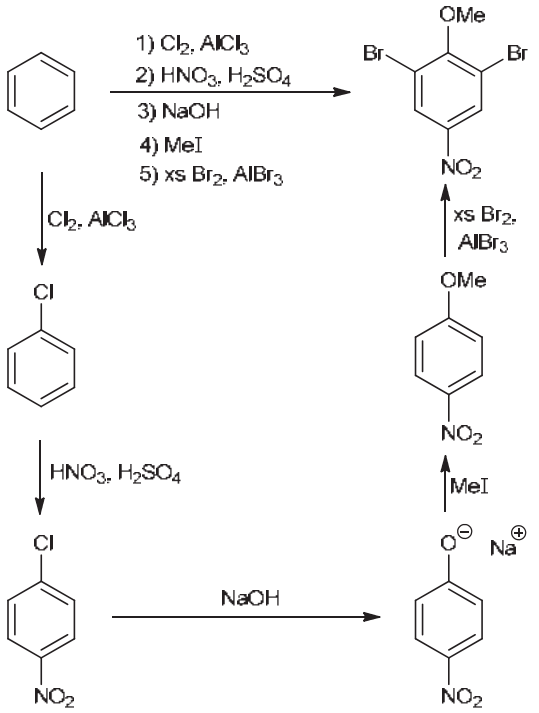
So the key to solving this problem is to convert benzene into methoxybenzene (anisole):



This can be achieved via the following three-step process.



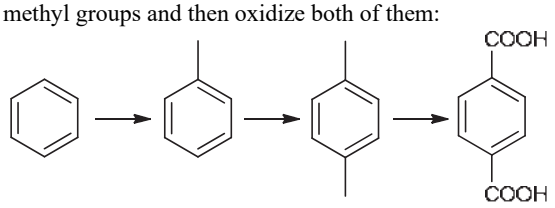
There are certainly other acceptable methods for achieving the desired transformation. Once such alternative is shown here:



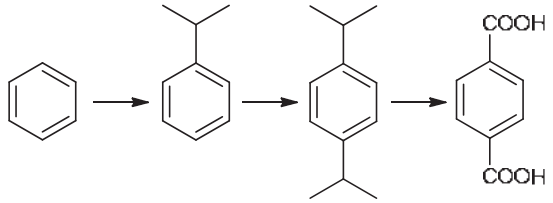
(b) The product has three substituents (a nitro group, and two carboxylic acid groups). Each of the carboxylic acid groups must be installed via a two-step method

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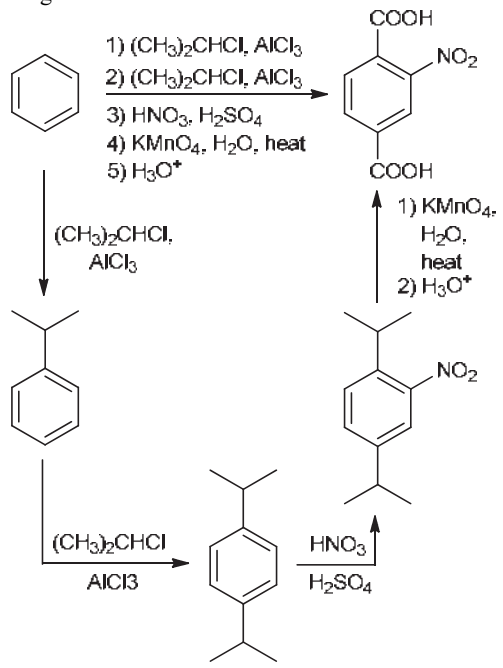
(Friedel-Crafts alkylation, followed by oxidation of the benzylic position). We could certainly install two methyl groups and then oxidize both of them:



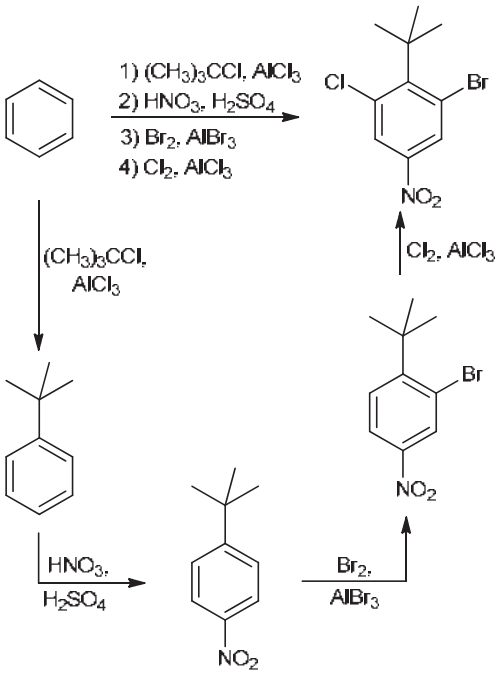
However, the second alkylation step would not proceed with good regiochemical control. Methyl groups do not provide significant steric hindrance, so we would expect a mixture of *ortho* and *para* products (difficult to predict which will predominate). If, however, we install isopropyl groups (rather than methyl groups), then the second alkylation step will occur predominantly at the *para* position, as desired. Then, both benzylic positions can be oxidized to give the diacid:



In the synthesis shown below, the nitration step is performed prior to oxidation of the benzylic groups, because nitration of an activated ring is likely to proceed more readily than nitration of a deactivated ring. Nitration of *para*-diisopropylbenzene gives only one nitration product, because all unoccupied positions on the ring are identical.

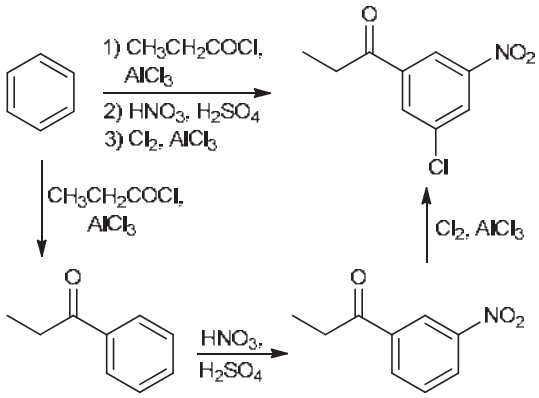


(c) If we install the *tert*-butyl group first, we can use its directing effects to install all of the other groups in the correct locations. The *tert*-butyl group is installed via a Friedel-Crafts alkylation. The directing effects of the *tert*-butyl group cause the next group to be installed in the *para* position, so the next step of our synthesis must be a nitration step. Subsequent halogenation steps are forced to proceed at the positions that are *ortho* to the *tert*-butyl group. These positions are indeed sterically hindered, but the position that is *para* to the *tert*-butyl group is already occupied (by the nitro group). So any subsequent reactions must take place at the *ortho* positions.



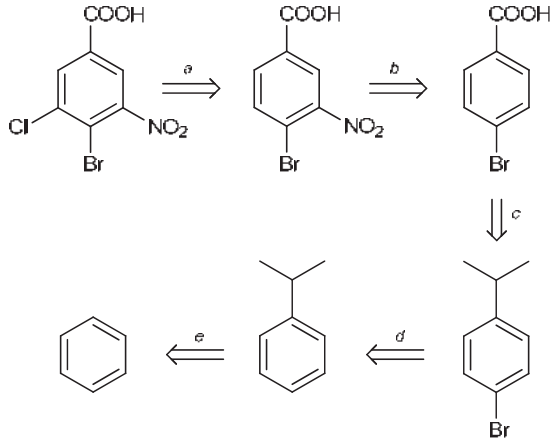
(d) We must install three groups (a chlorine atom, an acyl group, and a nitro group). Two of these groups are *meta* directors (the nitro group and the acyl group), while the other group (Cl) is an *ortho*-*para* director. The groups are all *meta* to each other in the product, so the Cl group must be installed last.

The first two steps of the synthesis must install the acyl group (via Friedel-Crafts acylation) and the nitro group (via nitration). These two steps cannot be performed in either order. The nitro group cannot be installed first, because nitrobenzene is too deactivated to undergo a Friedel-Crafts alkylation. Therefore, the order of events must be: 1) Friedel-Crafts alkylation, 2) nitration, and 3) chlorination. This synthesis is shown here:



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(e) There is likely more than one way to achieve the desired transformation. The following retrosynthetic analysis represents one strategy for preparing the desired compound. An explanation of each of the steps (*a*-*e*) follows.



a. The product can be prepared by installing the Cl group last. None of the three groups (on the ring) are activators, but all three groups direct to the same location.

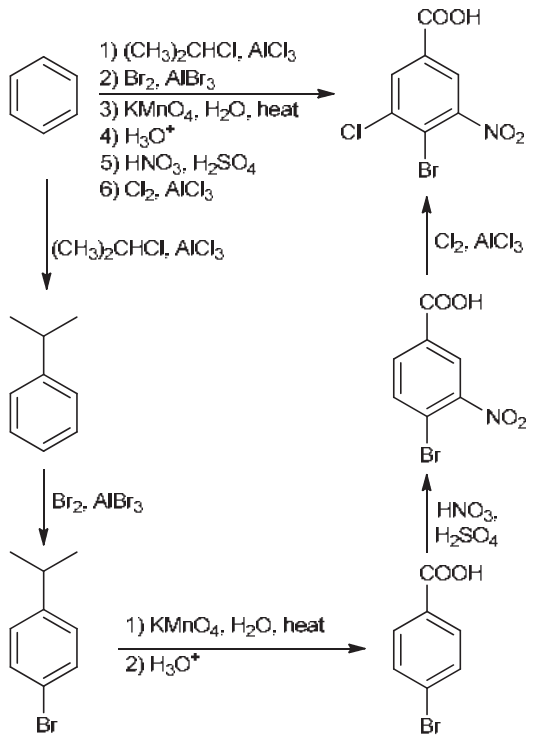
b. Installation of the nitro group would occur in the position that is *ortho* to the *ortho-para* directing group (and *meta* to the *meta*-directing group).

c. The carboxylic acid group can be made via oxidation of the benzylic position. A methyl group can certainly be oxidized to a carboxylic acid group, however, we choose a larger, sterically hindered alkyl group, as will soon be explained.

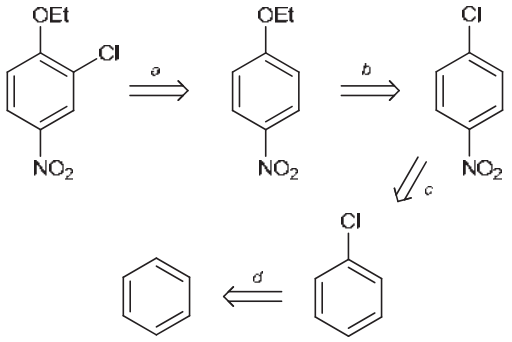
d. Bromination will occur predominantly in the *para* position, because the *ortho* positions are sterically hindered. This is indeed the reason why we chose an isopropyl group rather than a methyl group. With a methyl group, we would expect a mixture of *ortho* and *para* products.

e. Installation of an isopropyl group can be achieved via a Friedel-Crafts alkylation.

Now, let's draw the forward scheme. Note that in the first step (Friedel-Crafts alkylation), it would be inefficient to use propyl chloride and then rely on a carbocation rearrangement, as that would likely give a mixture of products (propylbenzene and isopropylbenzene).



(f) The following retrosynthetic analysis represents one strategy for preparing the desired compound. An explanation of each of the steps (*a*-*d*) follows.



a. Chlorination will install a chlorine atom in the position that is *ortho* to the activator (OEt) because the *para* position is already occupied (by the nitro group).

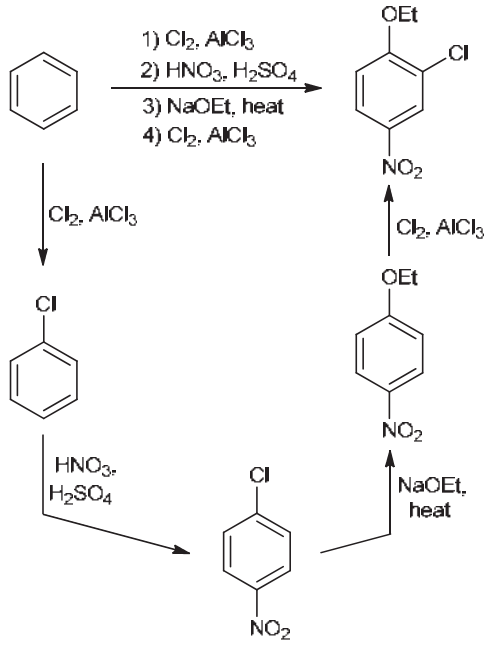
b. An S_NAr reaction will replace the chlorine atom with an ethoxy group.

c. Installation of the nitro group would occur predominantly in the position that is *para* to the *ortho-para* directing Cl group.

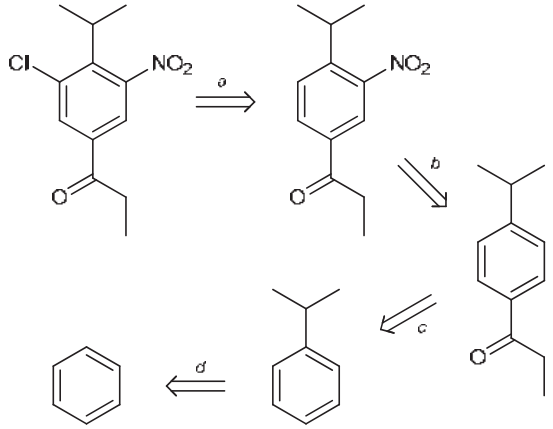
d. Chlorination gives chlorobenzene.

Now, let's draw the forward scheme, as described above:

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(g) The following retrosynthetic analysis represents one strategy for preparing the desired compound. An explanation of each of the steps (*a*-*d*) follows.



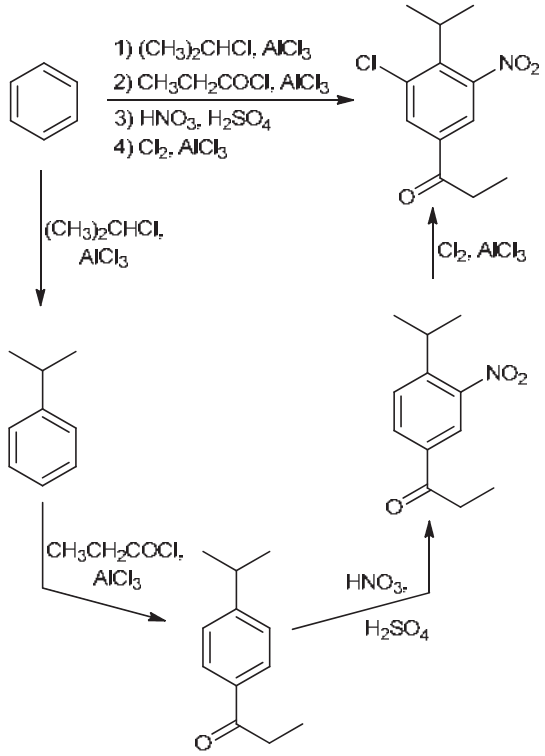
a. Chlorination will install a chlorine atom in the position that is *ortho* to the activator (isopropyl group) because the *para* position and the other *ortho* position are already occupied (by the acyl group and nitro group, respectively).

b. Nitration will occur in the position that is *ortho* to the activator (isopropyl group) because the *para* position is already occupied (by the acyl group).

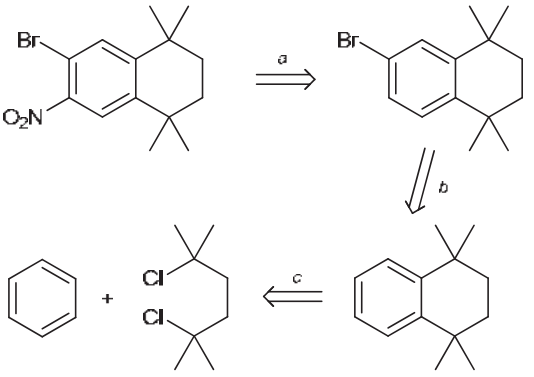
c. Friedel-Crafts acylation will occur predominantly in the position that is *para* to the isopropyl group, because the isopropyl group is an *ortho-para* director, and it is sterically bulky.

d. Friedel-Crafts alkylation can be used to install an isopropyl group.

Now, let's draw the forward scheme. Note that in the first step (Friedel-Crafts alkylation), it would be inefficient to use propyl chloride and then rely on a carbocation rearrangement, as that would likely give a mixture of products (propylbenzene and isopropylbenzene).



(h) The following retrosynthetic analysis represents one strategy for preparing the desired compound. An explanation of each of the steps (*a*-*c*) follows.



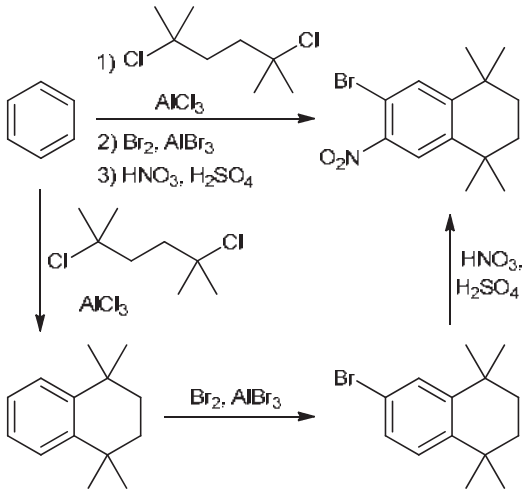
a. Nitration will occur in the correct location because of steric factors.

b. Bromination will install a bromine atom in the correct location since the branching on the non-aromatic ring provides significant steric bulk.

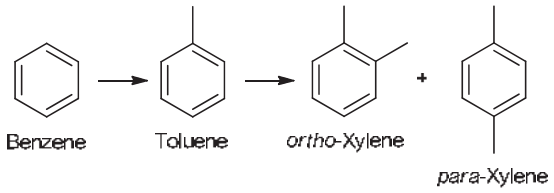
c. Two successive Friedel-Crafts alkylation reactions (the first intermolecular and the second intramolecular) will form the desired additional ring.

Now, let's draw the forward scheme, as described above:

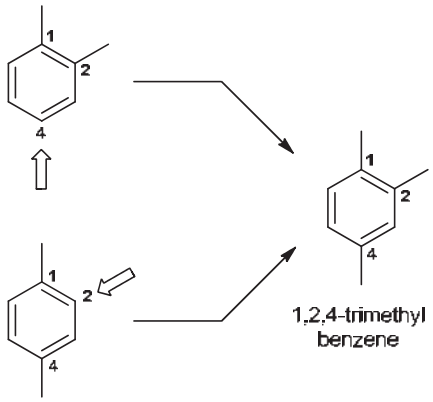
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18.68. These reagents will install a methyl group, and the problem statement indicates that three methyl groups are installed. Installation of the first methyl group gives toluene. Methylation of toluene gives a mixture of *ortho*-xylene and *para*-xylene.

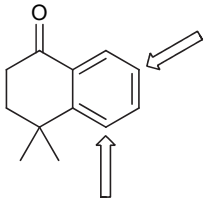


ortho-Xylene undergoes methylation at C4 because of steric factors, while *para*-xylene undergoes methylation at C2 (because all four positions are equivalent). Either way, the product is the same: 1,2,4-trimethylbenzene

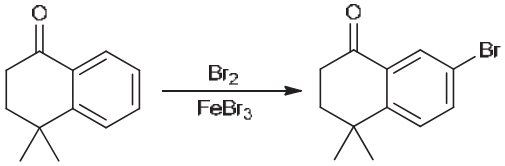


18.69. All three available positions are sterically hindered.

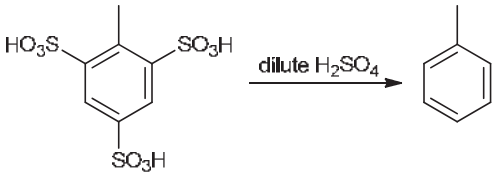
18.70. The reagents indicate a bromination reaction, so we must decide where the bromine atom will be installed. The aromatic ring has two substituents: an alkyl group and a carbonyl group. The former is a weak activator and the latter is a moderate deactivator. The directing effects are controlled by the more strongly activating group. Therefore, in this case, the alkyl group controls the directing effects. As an activator, the alkyl group is an *ortho-para* director. However, one of the *ortho* positions is already occupied (by the other substituent). Therefore, there are only two locations where bromination can occur (*ortho* or *para* to the alkyl group):



Among these two locations, one of them is more sterically hindered than the other. The reaction is expected to occur at the location that is more sterically accessible:



18.71. The reaction conditions (dilute H_2SO_4) will remove each of the sulfonic acid groups, giving toluene as the major product:



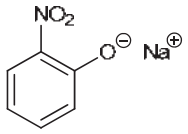
18.72.

(a) The reagent (hydroxide) is a strong nucleophile, and the three criteria for S_NAr are met (there is a nitro group and a leaving group that are *ortho* to each other), so we expect an S_NAr mechanism. In an S_NAr reaction, the nucleophile (hydroxide) replaces the leaving group (bromide) and maintains the same location:

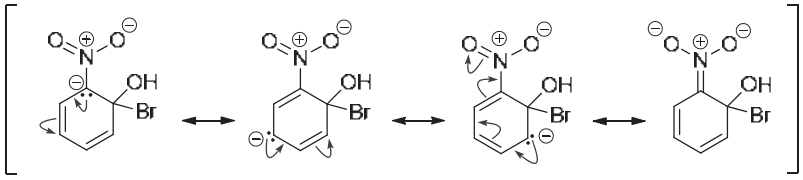


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Under these basic conditions, the product (*ortho*-nitrophenol) is deprotonated upon its formation (because the resulting resonance stabilized anion is more stable than hydroxide). In order to return the proton and regenerate *ortho*-nitrophenol, we must introduce a proton source into the reaction flask after the reaction is complete (aqueous acidic work-up). The problem statement did not mention an acidic workup, so the product is the following salt (the conjugate base of *ortho*-nitrophenol):



(b) In an S_NAr mechanism, the nucleophile (hydroxide) attacks the ring at the position bearing the leaving group, giving the following resonance-stabilized intermediate (called a Meisenheimer complex):

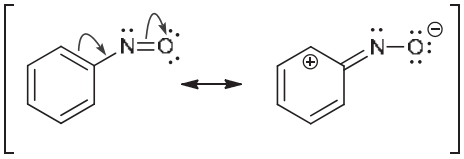


(c) No. In order for an S_NAr reaction to occur, the leaving group must be *ortho* or *para* to the nitro group. If the leaving group is *meta* to the nitro group, then the nitro group cannot function as a reservoir for electron density to stabilize the intermediate Meisenheimer complex. The Meisenheimer complex is therefore too high in energy to form at an appreciable rate.

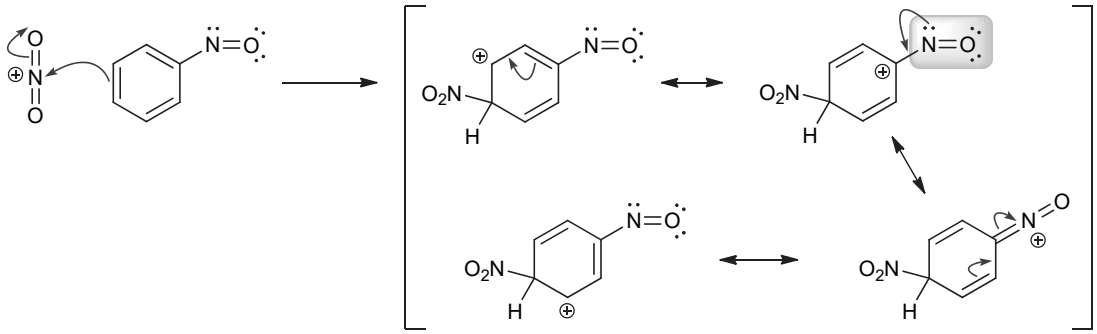
(d) Yes. This example meets all three criteria for an S_NAr mechanism. The aromatic starting material exhibits a nitro group and a leaving group (bromide) that are *para* to each other.

18.73.

(a) The nitroso group is a strong deactivator due to both resonance and induction. Considering induction, both the nitrogen and oxygen atoms withdraw electrons. More importantly, the pi-bond conjugated with the benzene ring withdraws electron density via resonance, moving electron density toward the highly electronegative oxygen as shown below.

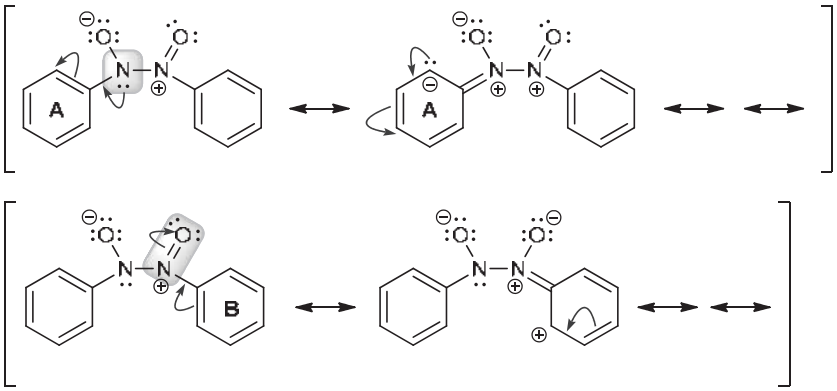


(b) Given the lone pair of electrons on the nitrogen atom, the sigma complex may be further stabilized through extra resonance when the electrophile adds to the *ortho* or *para* position. The *para*-substituted sigma-complex is shown below for a nitration reaction, with the participation of the nitrogen lone pair highlighted.



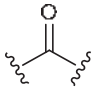
(c) Ring **A** is substituted with a nitrogen atom bearing a lone pair of electrons, and is therefore capable of donating electron density to the benzene ring via resonance. Thus, it is an activator and an *ortho*/*para* director. The nitrogen atom that is a substituent on ring **B** contains a positive charge along with a pi-bond to oxygen that strongly withdraws electrons from the benzene ring through both induction and resonance. This nitrogen atom on **B** is structurally analogous to a nitro group (positive charge on N) and would be expected to be a strong deactivator and *meta* director.

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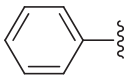
Since ring **A** is weakly activated and ring **B** is strongly deactivated, electrophilic aromatic substitution occurs on ring **A** in either the *ortho* or *para* position. Given that there is significant steric hindrance at the *ortho* position because of the large substituent, it makes sense that the major product occurs via *para* substitution on ring **A**.

18.74. The molecular formula indicates five degrees of unsaturation. One of these degrees of unsaturation must account for the signal in the double bond region of the IR spectrum (1680 cm^{-1}). The wavenumber of this signal indicates that it is likely a C=O bond that is conjugated:



(conjugated)

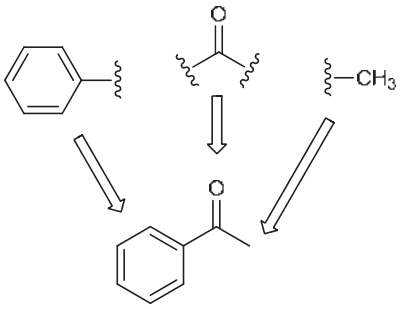
In the ^1H NMR spectrum of compound **A**, the signals between 7.5 and 8 ppm indicate the presence of an aromatic ring, which account for the remaining four degrees of unsaturation. This signal has an integration of 5, indicating a monosubstituted aromatic ring:



The upfield signal has an integration of 3, which indicates a methyl group:

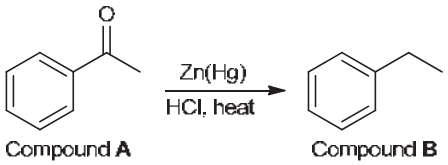


These three fragments can only be connected in one way:



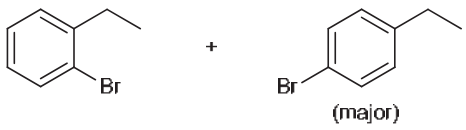
Compound A

Indeed, the C=O bond is conjugated in this structure. A Clemmensen reduction of compound **A** gives ethyl benzene (compound **B**):



Compound **A** Compound **B**

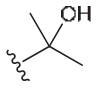
When compound **B** is treated with Br_2 and $AlBr_3$, an electrophilic aromatic substitution reaction occurs, in which a bromine atom is installed on the ring. The reaction at the *para* position is expected to occur more rapidly because *ortho* attack is sterically hindered by the ethyl group:



(major)

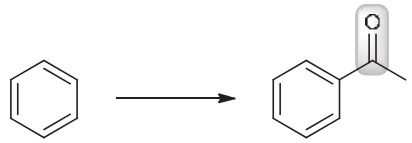
18.75.

(a) We did not learn a direct method for installing the following group on an aromatic ring:



So we must identify a group that can be installed and then converted into the group above. Notice that the atom connected to the aromatic ring is a carbon atom, which means that the reaction requires the formation of a C-C bond. Therefore, we must use either a Friedel-Crafts alkylation or a Friedel-Crafts acylation. The former will install an alkyl group, *without* a functional group. In contrast, acylation will form the C-C bond and install a functional group in the desired location:

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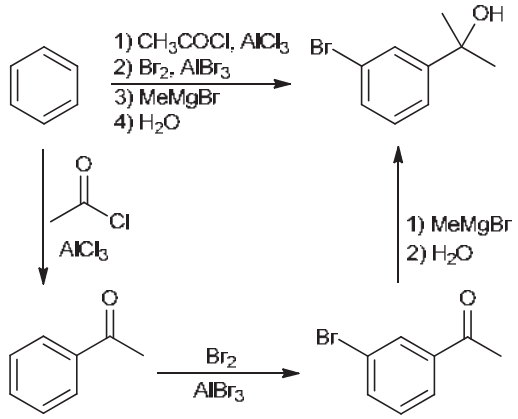


To convert this ketone into the desired product, we must introduce a methyl group in a way that converts the ketone into an alcohol:



This can be achieved with a Grignard reaction, using methyl magnesium bromide.

Finally, we must consider the order of events. Notice that the product has two substituents that are *meta* to each other. This can be achieved if we take advantage of the *meta*-directing effects of the intermediate that possesses a carbonyl group. That is, our synthesis would begin with a Friedel-Crafts acylation, thereby installing the *meta*-directing acyl group. Bromination then installs a bromine atom in the *meta* position. And finally, a Grignard reaction affords the desired product:



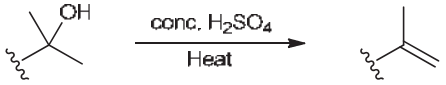
(b) We did not learn a direct method for installing the following group on an aromatic ring:



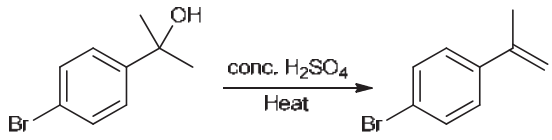
However, in the solution to part (a), we saw how to install the following functional group:



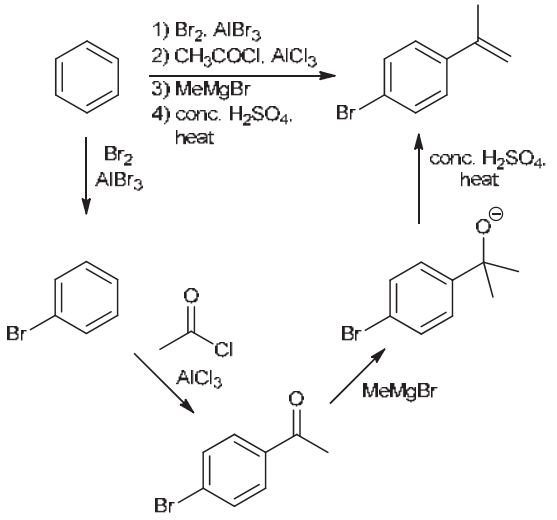
This functional group can be converted into the desired functional group in just one step:



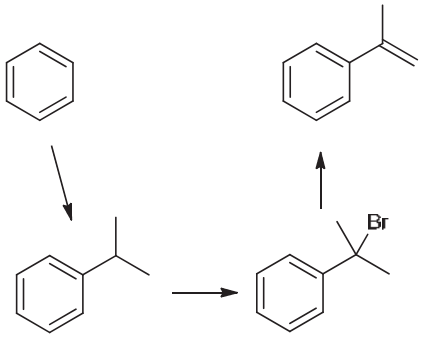
Therefore, we can perform a synthesis similar to the one described in the solution to Problem 18.75a, followed by this reaction:



The complete synthesis is shown here. Notice that bromination is performed prior to acylation, in order to install the groups in a *para* fashion:



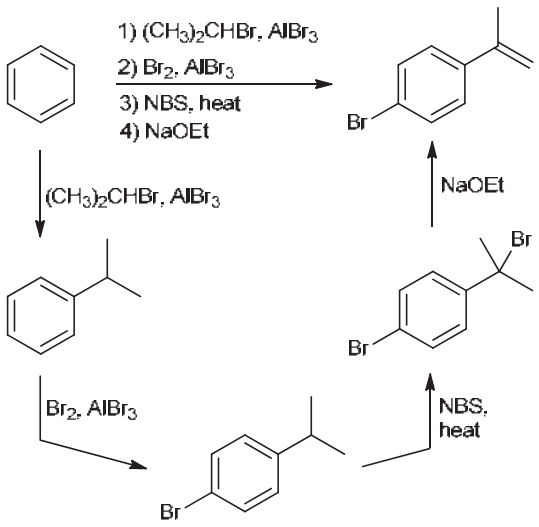
Alternatively, we can install the desired group in an entirely different way. Rather than performing a Friedel-Crafts acylation, we can perform a Friedel-Crafts alkylation to install an isopropyl group, which can then be functionalized via benzylic bromination, followed by elimination:



With this strategy, bromination of the aromatic ring is performed after installation of the isopropyl group, which allows us to employ the directing effects of the isopropyl group to install the bromine atom in the *para* position.

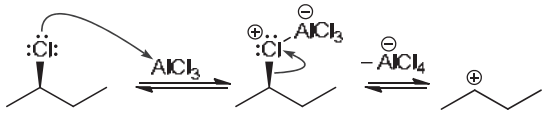
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This alternative synthesis is summarized here:

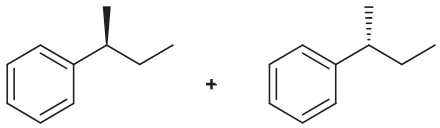


18.76.

(a) The alkyl halide can interact with the Lewis acid to produce a carbocation:



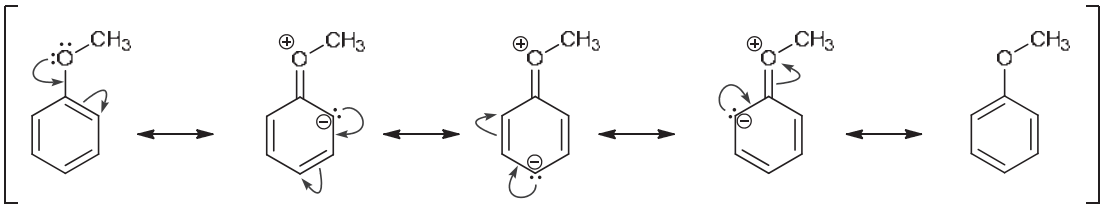
The carbocation is planar, so the aromatic ring can attack either face of the carbocation, with equal likelihood. As a result, a Friedel-Crafts alkylation with this optically active alkyl halide is expected to produce a racemic pair of enantiomeric products:



(b) As explained in the solutions to part (a), the reaction proceeds via a carbocation intermediate, which can be attacked from either face, leading to a racemic mixture. Therefore, the product mixture is optically inactive.

18.77.

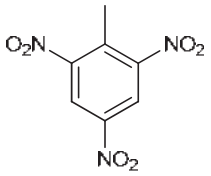
The OH group activates the ring toward electrophilic aromatic substitution because the OH group donates electron density via resonance.



This effect gives electron density primarily to the *ortho* and *para* positions, as seen in the resonance structures above. These positions are shielded, and the protons at these positions are expected to produce signals farther upfield than protons at the *meta* position. According to this reasoning, the *meta* protons correspond with the signal at 7.2 ppm.

18.78. The upfield signal has an integration of 3, and must correspond with the methyl group that is attached to the ring. The other signal (downfield) must correspond with aromatic protons. Since that signal has an integration of 2, the ring must bear two protons, which means that three nitro groups must have been installed.

The methyl group of toluene is an *ortho-para* director, and as such, nitration is expected to occur at the *ortho* and *para* positions. Each successive nitro group deactivates the ring, thereby requiring a higher temperature in order to install the next nitro group. At high enough temperature, all three positions will undergo nitration, giving 2,4,6-trinitrotoluene (also called TNT):



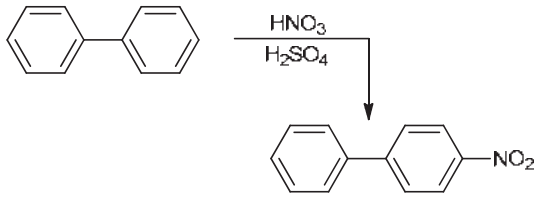
2,4,6-trinitrotoluene

18.79.

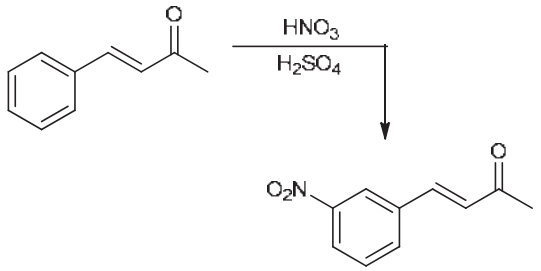
(a) A phenyl group is an *ortho-para* director, because the sigma complex formed from *ortho* attack or *para* attack is highly stabilized by resonance (the positive charge is spread over both rings). The *ortho* position is sterically

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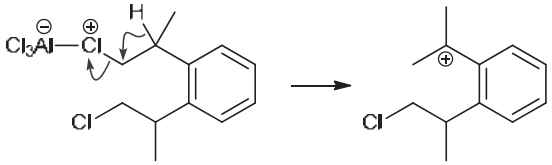
hindered while the *para* position is not, so we expect nitration to occur predominantly at the *para* position:



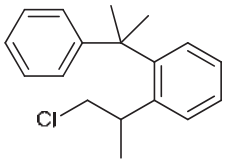
(b) This group withdraws electron density form the ring via resonance (many of the resonance structures of this compound exhibit a positive charge in the ring). As a result, this group is a moderate deactivator, and therefore a *meta*-director:



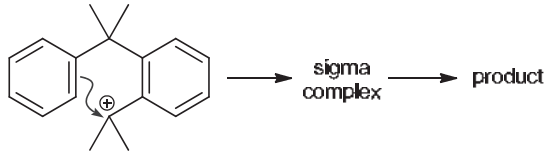
18.80. Each of the chlorine atoms in the dichloride can interact with $AlCl_3$ and initiate a Friedel-Crafts alkylation process. During the first alkylation process, a tertiary benzylic carbocation can form via a hydride shift:



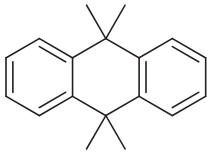
This carbocation is then attacked by benzene in an electrophilic aromatic substitution reaction, giving the following:



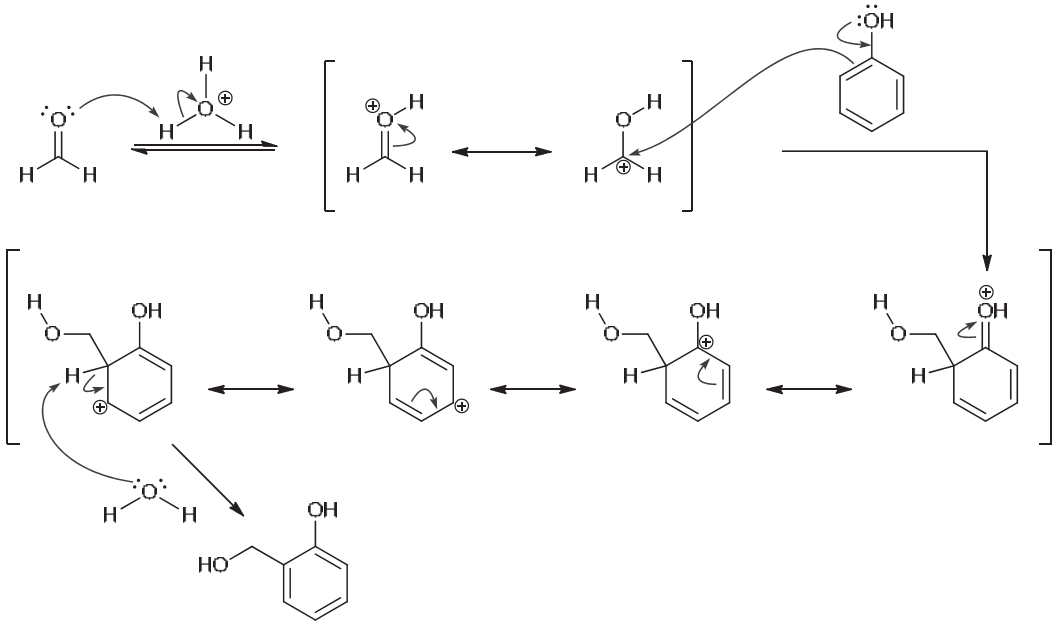
This compound still has one more chlorine atom, allowing for the second alkylation process. Once again, the second alkylation occurs in a similar fashion (via a tertiary, benzylic carbocation), but this time, the electrophilic aromatic substitution reaction proceeds in an intramolecular fashion:



The following product is therefore expected:

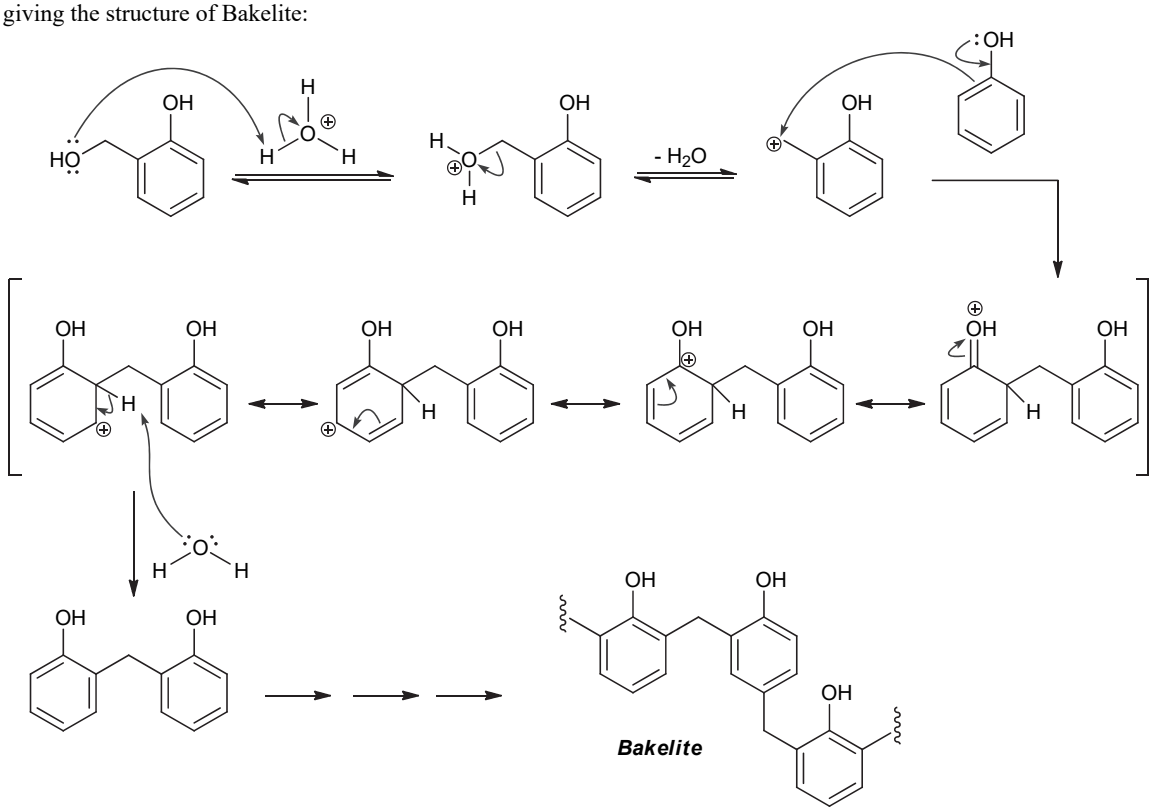


18.81. Formaldehyde is protonated to give a resonance-stabilized cation that can serve as an electrophile in an electrophilic aromatic substitution reaction. Phenol functions as the nucleophile and attacks the electrophile, giving a resonance-stabilized intermediate (sigma complex). Water can then serve as a base and remove a proton from the sigma complex, thereby restoring aromaticity:

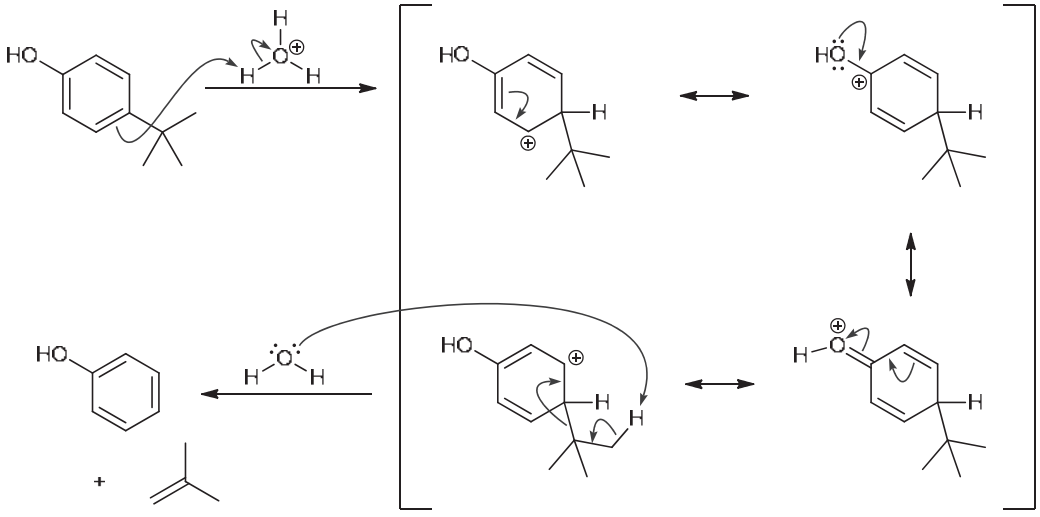


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The resulting compound bears an OH group connected to a benzylic position. This OH can be protonated under acidic conditions, followed by loss of a leaving group to give a resonance-stabilized, benzylic carbocation. This carbocation can then serve as an electrophile in an electrophilic aromatic substitution reaction. Phenol functions as the nucleophile and attacks the electrophile, giving a resonance-stabilized intermediate (sigma complex). Water can then serve as a base and remove a proton from the sigma complex, thereby restoring aromaticity. This process continues, ultimately giving the structure of Bakelite:

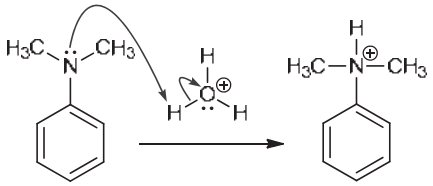


18.82. A *tert*-butyl group is removed from the ring and replaced with a proton, in what appears to be the reverse of an electrophilic aromatic substitution reaction. As such, we expect the reaction to proceed via an intermediate sigma complex. The aromatic ring is protonated to give a sigma complex. Water then functions as a base and removes a proton in an elimination-type reaction, where the leaving group is an aromatic ring. This step restores aromaticity, and produces isobutylene as a byproduct:

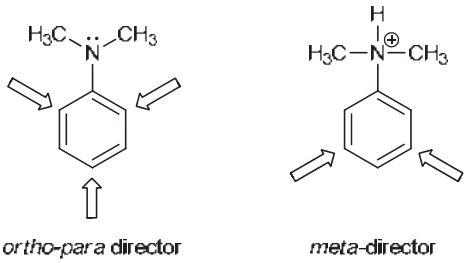


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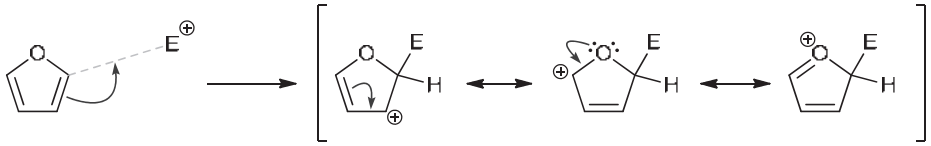
18.83. The amino group in *N,N*-dimethylaniline is a strong activator, and therefore, an *ortho-para* director. For this reason, bromination occurs at the *ortho* and *para* positions. However, in acidic conditions, the amino group is protonated to give an ammonium ion:



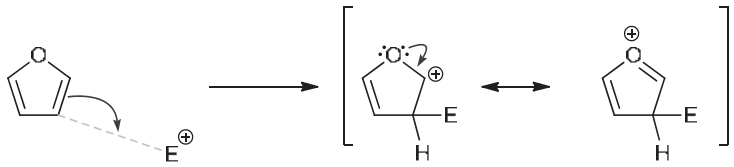
Unlike the amino group, an ammonium ion is a strong deactivator and a *meta* director. Under these conditions, nitration occurs primarily at the *meta* position.



18.84. Attack at the C2 position proceeds via an intermediate with three resonance structures:



In contrast, attack at the C3 position proceeds via an intermediate with only two resonance structures:



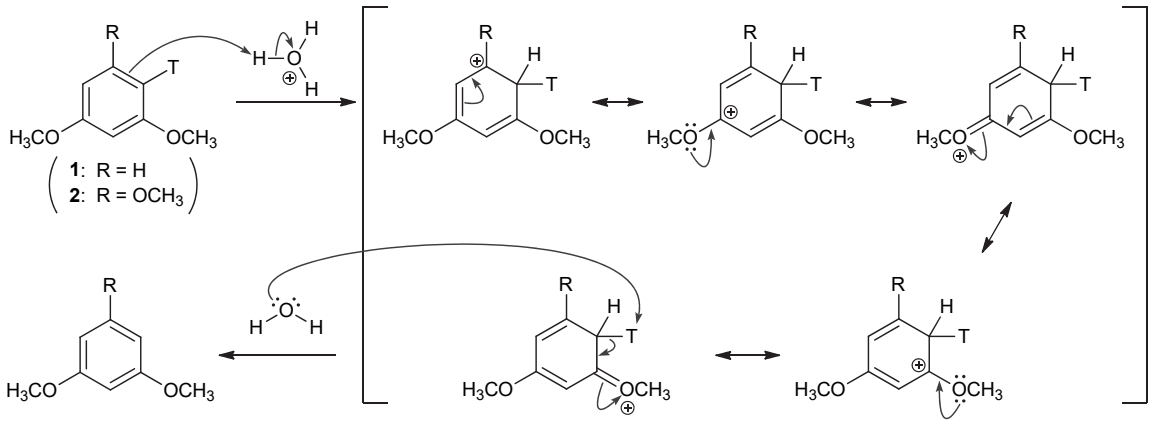
The intermediate for C2 attack is lower in energy than the intermediate for C3 attack. The transition state leading to the intermediate of C2 attack will therefore be lower in energy than the transition state leading to the intermediate of C3 attack. As a result, C2 attack occurs more rapidly.d r

18.85. In all cases, the X substituent is a methoxy group. It is the Y substituent that varies in identity. It is difficult to imagine that there could be a steric effect here, since the Y substituent is far away from the alkene π bond. The trend is more easily explained when we consider the electronic effect of the Y substituent. Specifically, the methoxy group (a powerful activator) can donate electron density via resonance into the alkene π bond, making it the most nucleophilic π bond among the disubstituted stilbenes. A methyl group is only weakly activating, so its effect should be smaller than the effect of a methoxy group (giving a smaller rate constant). A chloro group is a weak deactivator, which means that the net effect of the chloro group is to withdraw electron density from the aromatic ring and the conjugated alkene π bond. As a result, when Y = Cl, the rate constant is smaller than the rate constant when Y = Me. Finally, the nitro group is powerfully electron-withdrawing, via resonance, and it will significantly reduce the nucleophilicity of the alkene π bond, rendering it the least reactive double bond towards molecular bromine.

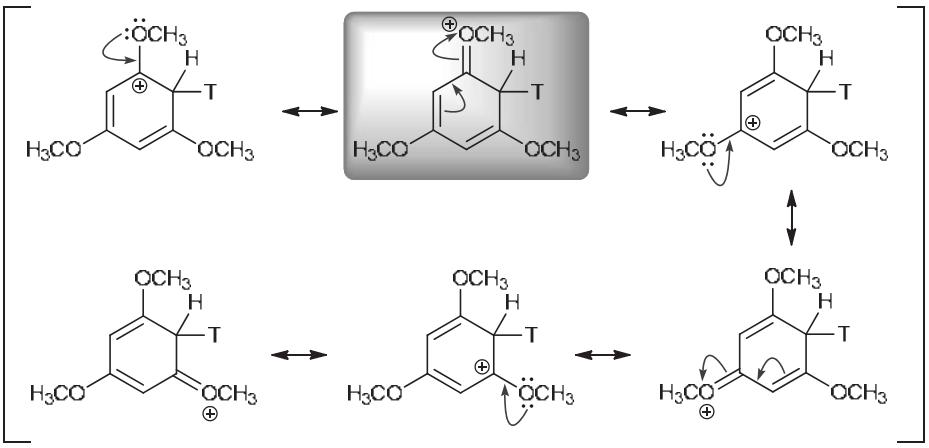
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18.86.

(a) In aqueous acidic conditions, compounds **1** and **2** lose tritium via an electrophilic aromatic substitution reaction. First, the aromatic ring is protonated to give a resonance-stabilized sigma complex, which then undergoes loss of T^+ (rather than H^+) to re-establish aromaticity. Notice that the methoxy groups render the sigma complex particularly stable, because the positive charge is spread over the oxygen atoms as well (via resonance).



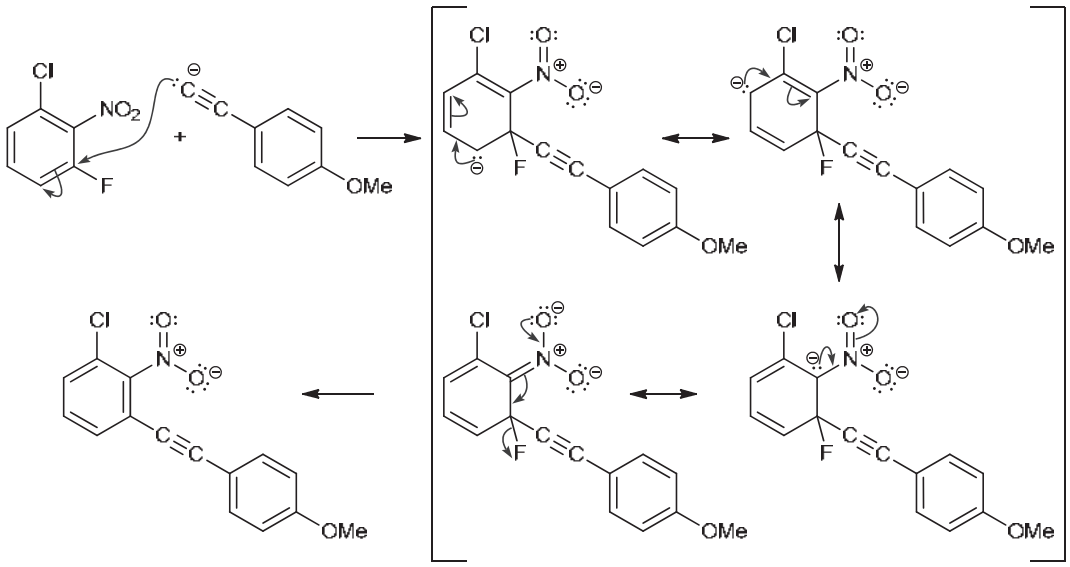
(b) Compound **2** has an extra methoxy group that is absent in compound **1**. This group further stabilizes the intermediate sigma complex by introducing one more resonance structure (highlighted below). That is, the positive charge is further delocalized:



When compound **2** undergoes an electrophilic aromatic substitution reaction, the intermediate sigma complex exhibits a positive charge that is spread over three carbon atoms and three oxygen atoms. This intermediate is more stable than the intermediate formed when compound **1** undergoes an electrophilic aromatic substitution reaction. It is therefore expected that compound **2** will lose tritium at a faster rate than compound **1**.

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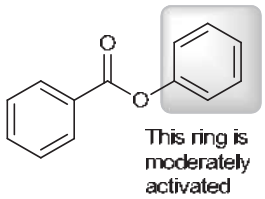
18.87.
(a) This is a reaction between a strong nucleophile (the terminal alkynide ion) and an electron-poor arene, from which a halide is expelled. This satisfies the criteria for a nucleophilic aromatic substitution mechanism, as shown below. The alkynide ion attacks the carbon atom attached to fluorine, producing a resonance-stabilized Meisenheimer complex, which loses a fluoride leaving group to give the product.



(b) The observed regiochemical outcome (that the fluoride is substituted and not the chloride, even though chloride is a better leaving group) indicates that the departure of the leaving group does not occur in the rate determining step. The leaving group leaves in step 2, so step 1 must be rate determining. In other words, the poor ability of fluoride to serve as a leaving group does not affect the rate of the reaction, since this occurs in the step that is not rate determining.
In the first step, the nucleophile prefers to attack the carbon atom attached to fluorine because of its greater electrophilicity (due to fluorine's greater electronegativity) relative to the carbon next to chlorine.

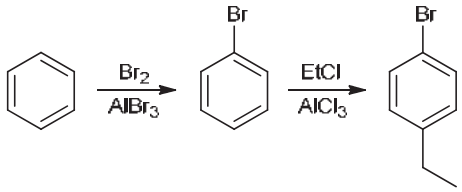
18.88. Friedel-Crafts reactions cannot be performed with aromatic rings that are strongly or moderately deactivated. Options (a) and (d) are both activated aromatic rings, and option (c) has a halogen, which is a weak deactivator. All three of these compounds will undergo Friedel-Crafts reactions. Only nitrobenzene is strongly deactivated and therefore, it will not undergo Friedel-Crafts reactions. The correct answer is (b).

18.89. One aromatic ring is connected to a carbonyl group (C=O), while the other aromatic ring is connected to an oxygen atom. The former is moderately deactivated, while the latter is moderately activated (as seen in Table 18.1).

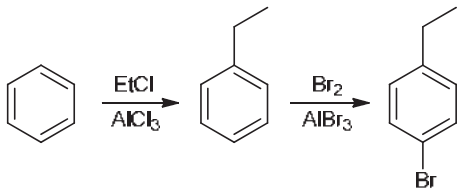


As an activated ring, we expect *ortho-para* directing effects. The reaction will occur predominantly at the *para* position, rather than the *ortho* positions, because of steric factors. Therefore, the answer is (c).

18.90. Option (a) would install a bromine substituent and an ethyl substituent, as desired, but the regiochemical outcome would not be correct. The two groups would be installed in a *para*-disubstituted fashion, rather than *meta*-disubstituted:

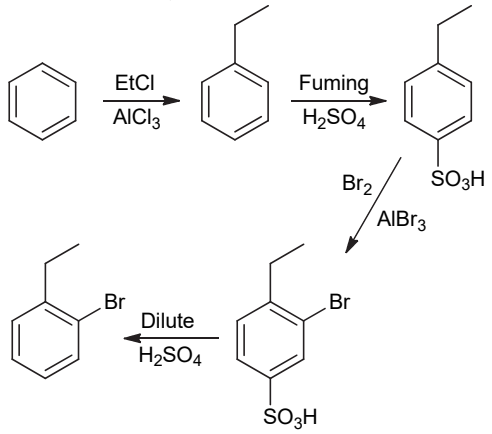


Similarly, option (b) would also install the two groups in a *para*-disubstituted fashion:

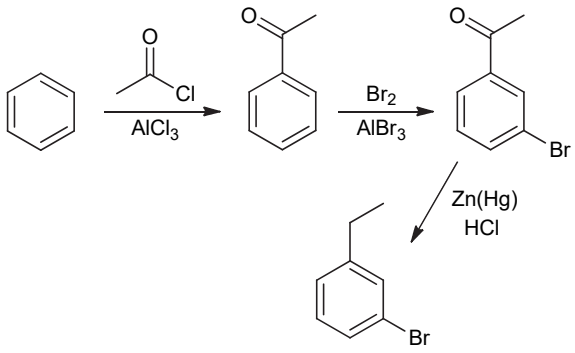


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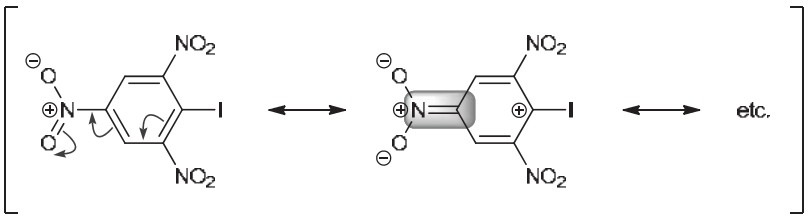
Option (c) employs a blocking technique, which would install the two groups in an *ortho*-disubstituted fashion (not *meta*, as desired):



Option (d) employs a Friedel-Crafts acylation, followed by bromination at the *meta* position, followed by a Clemmensen reduction, giving the desired product. The correct answer is (d):



18.91. Each of the three nitro groups is conjugated with the aromatic ring, and as a result, each of the C-N bonds has some double-bond character. The following resonance structure illustrates this for one of the nitro groups:

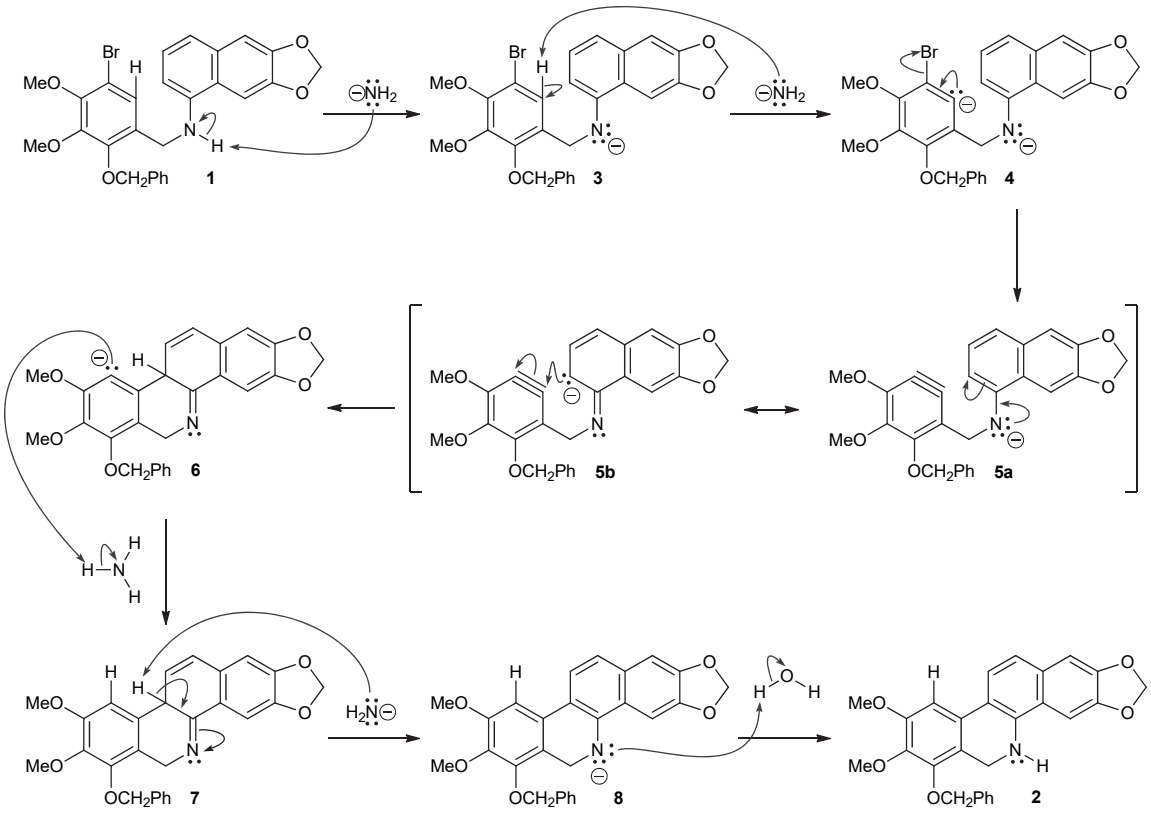


There are three nitro groups. Two of them are *ortho* to the very large iodo group. The size of the electron cloud associated with the iodo group offers steric strain that forces these two nitro groups out of planarity with the ring, in order to alleviate some of the strain. This results in reduced overlap of the *p* orbitals, and consequently, the resonance effect is diminished. As such, the C-N bonds of these two nitro groups will have less double-bond character. In contrast, the nitro group that is *para* to the iodo group is coplanar with the ring, and its C-N bond has significant double bond character – see the resonance structure above. This additional C=N character leads to a shorter bond, as is characteristic of double bonds.

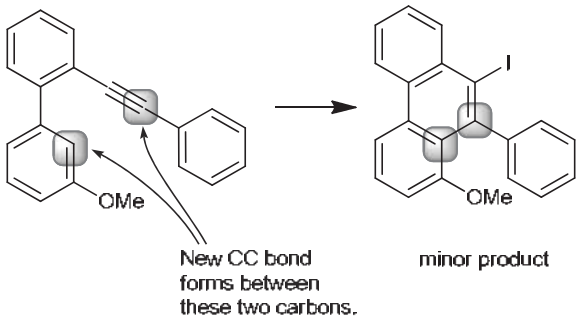
18.92. Sodium amide ($NaNH_2$) is a strong base, and under these conditions, a proton is abstracted from the nitrogen atom of **1** ($pK_a \sim 30$) to generate anion **3**. This proton will be re-introduced during the reprotonation event (work-up with water). It might seem unnecessary to draw this deprotonation step (only to protonate this location at the end of the mechanism), but this step must be drawn to indicate that you understand that this proton is sufficiently acidic that it will not survive under these conditions (because anion **3** is resonance-stabilized). Next, deprotonation will produce **4**, which loses a bromide ion to form benzyne **5**. This intermediate is then trapped by the nearby aromatic ring to form

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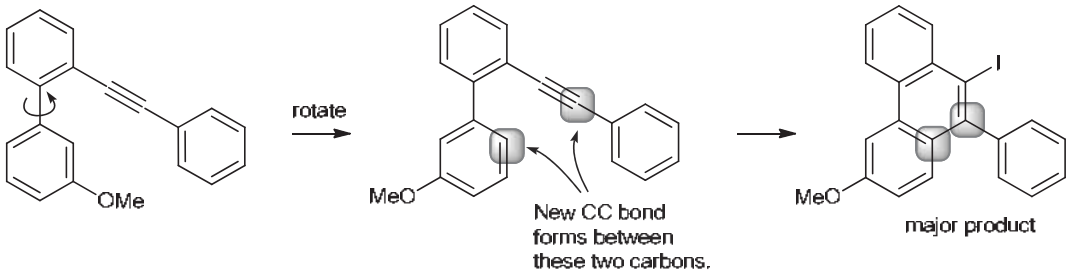
anion **6**. Proton transfer will produce imine **7**, which can be rearomatized by the loss of a proton to form anion **8**. In the final step, protonation of **8** will form compound **2**.



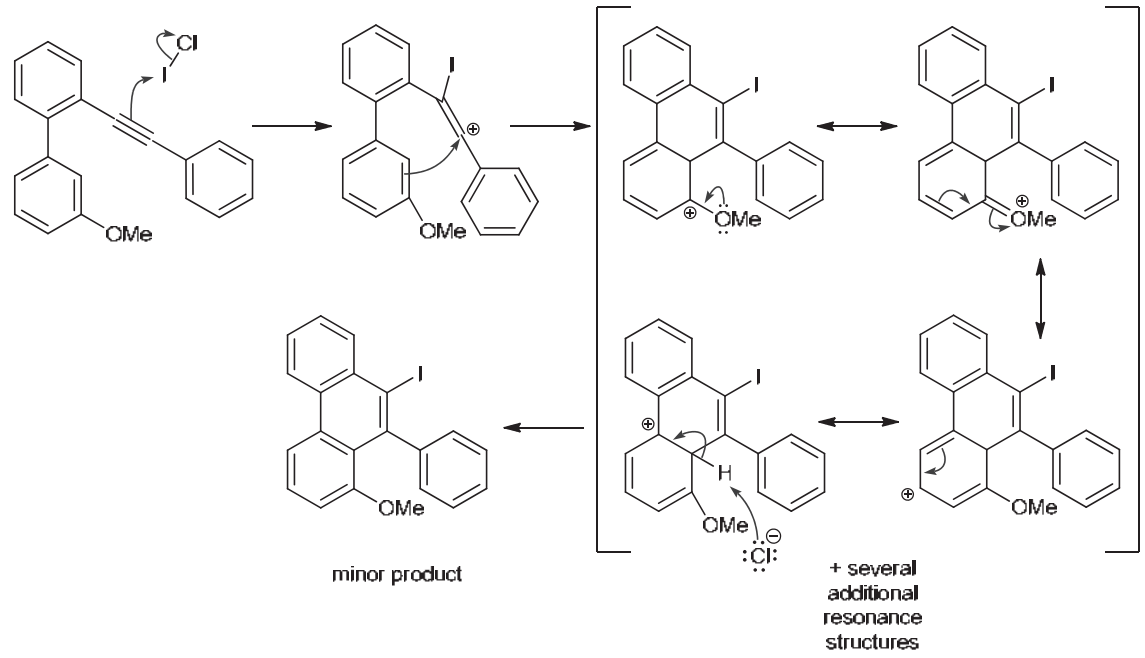
18.93.
(a) An analysis of the reactant and the minor product reveals that during the course of the reaction, a new C-C bond forms between the two carbon atoms indicated below.



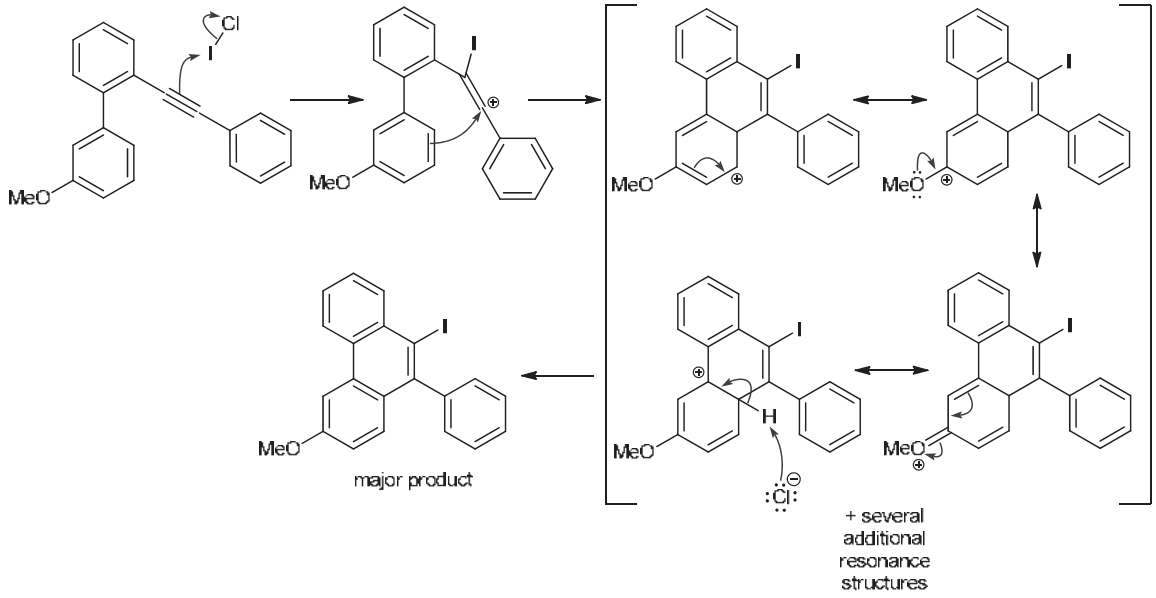
Likewise, in the formation of the major product, an analogous new C-C bond forms after rotation around the C-C bond indicated below.



A mechanism for the formation of the minor product is presented below. The alkyne attacks ICl, resulting in the formation of a new C-I bond, and a vinyl carbocation (see below for a justification for formation of a vinyl carbocation in this case). This carbocation then serves as an electrophile in an electrophilic aromatic substitution. The π electrons from the methoxyarene attack this carbocation, resulting in the formation of a new C-C bond, and a resonance-stabilized sigma complex. This intermediate is highly conjugated and has at least seven reasonable resonance structures in addition to the four shown. Deprotonation of the sigma complex restores aromaticity, thus yielding the product.

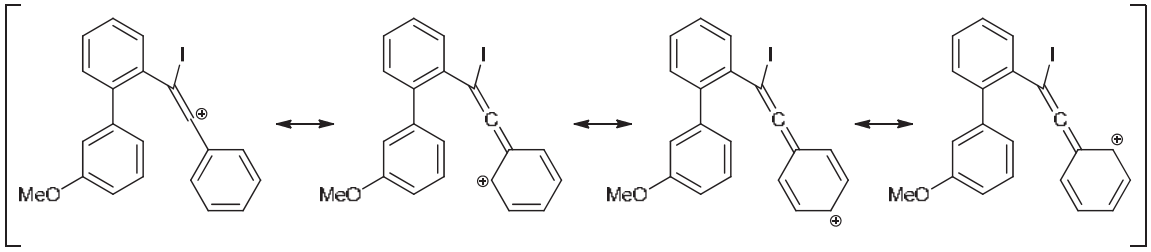


A mechanism to account for the formation of the major product is below. Each step is analogous to the mechanism presented above.

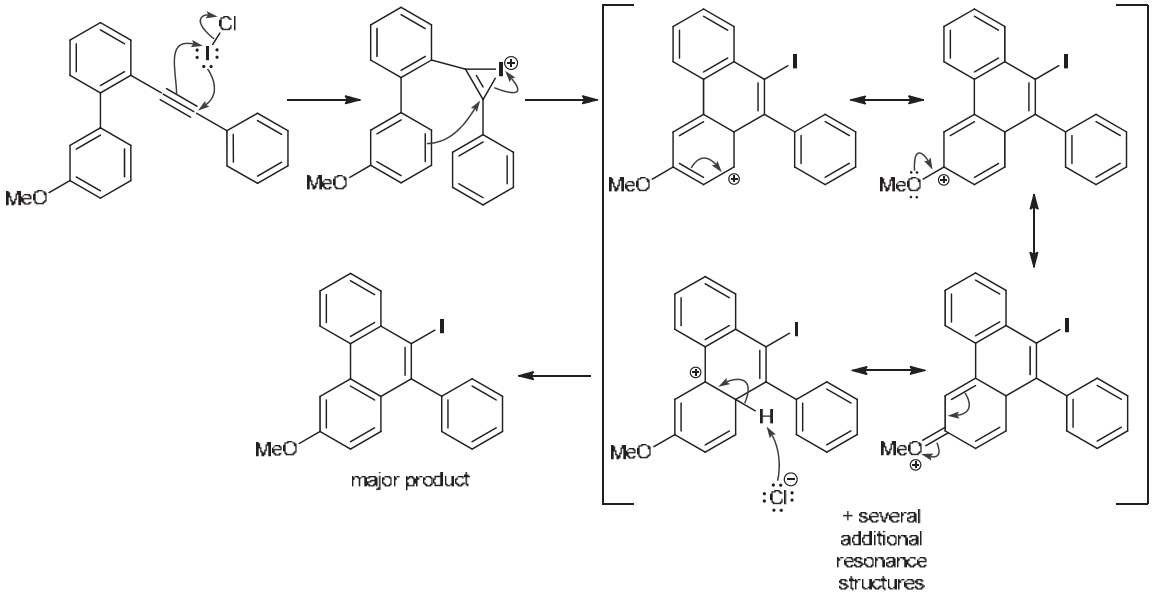


In Chapter 9, we noted that vinyl carbocations are not very stable, and thus we should consider whether or not our first intermediate is a reasonable one. In this case, the vinyl carbocation is not an unreasonable intermediate, because it is stabilized by the adjacent aromatic ring, as demonstrated by the following resonance structures.

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Alternatively, it would also be plausible to suggest a mechanism involving an iodonium ion, rather than a vinyl carbocation. In that case, the mechanism for formation of the major product would be as follows:



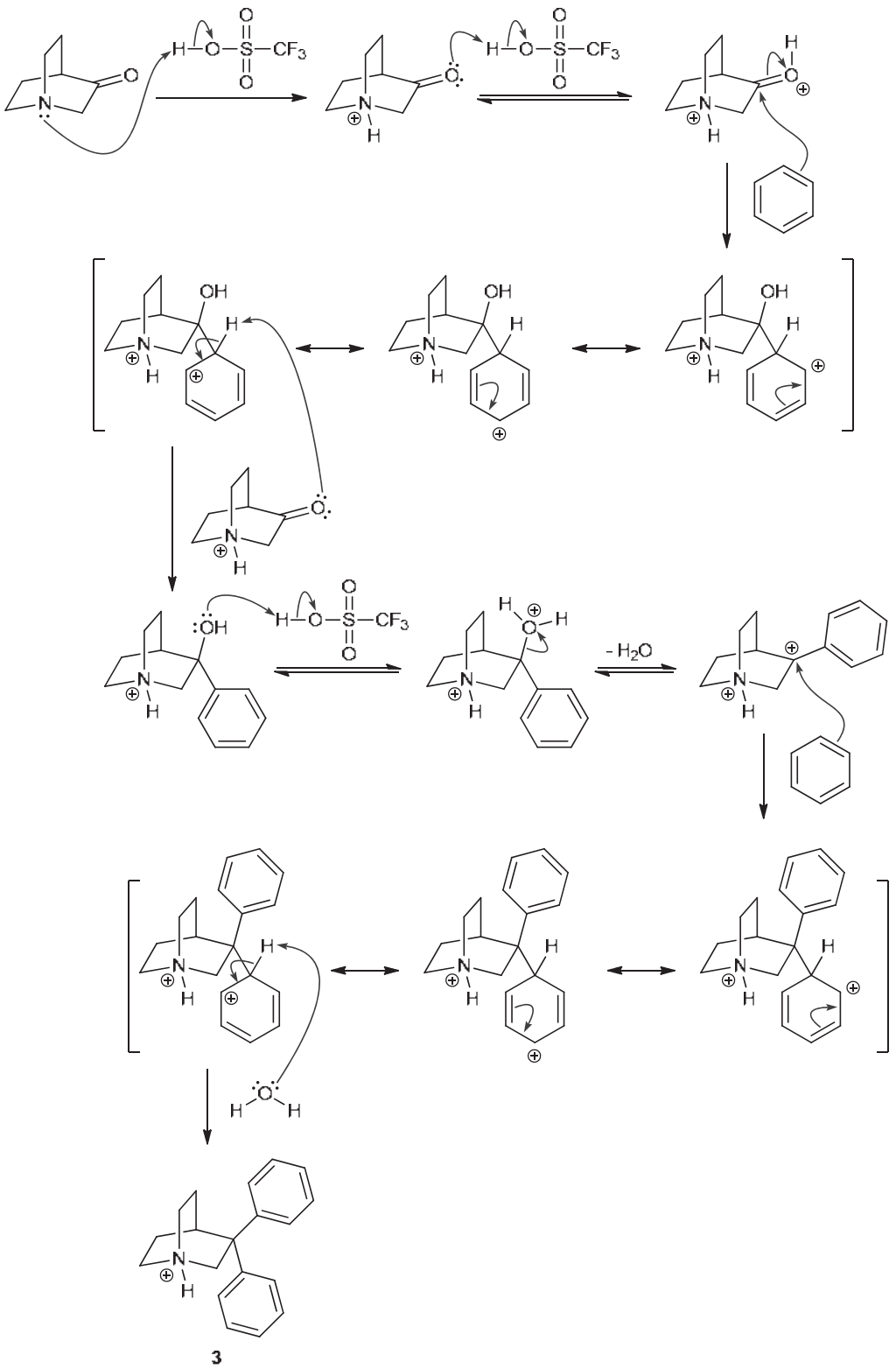
Formation of the minor product might also occur in this way, via an iodonium ion, rather than a vinyl carbocation.

(b) In the formation of each of the products, we should take into account both electronic and steric considerations. In the formation of the minor product, the new C-C bond is *ortho* to the methoxy group. In contrast, the new C-C bond is *para* to the methoxy in the formation of the major product. Both of these products are thus consistent with the methoxy group serving as an *ortho-para* director. The predominance of the major product can be explained by the increased steric accessibility of electrophilic carbocation to the position *para* to the methoxy group.

18.94. The first steps of the mechanism are two successive, proton transfers to form the dication **2**. In each of these steps, triflic acid is the source of the proton. The amine is protonated first, to give an ammonium ion. If we compare the pK_a values of triflic acid (-14) and a typical ammonium ion (~10), we see that this proton transfer step is effectively irreversible, thus the irreversible reaction arrow for that step. Then, another proton transfer step generates the dication. Notice that protonation of the carbonyl group occurs as the second step, *after* protonation of the amine, because a protonated carbonyl group is a highly acidic species (p$K_a \approx -7$), relative to an ammonium ion.

Once the highly electrophilic dication intermediate is formed, an electrophilic aromatic substitution reaction occurs, in which benzene functions as the nucleophile. The resulting intermediate sigma complex is deprotonated to restore aromaticity. Under these acidic conditions, the hydroxyl group is protonated, generating an excellent leaving group, which leaves to give a resonance-stabilized benzylic carbocation (resonance structures not shown). This benzylic carbocation then functions as an electrophile in another electrophilic aromatic substitution reaction. The resulting sigma complex is then deprotonated to restore aromaticity, thereby producing ammonium ion **3**.

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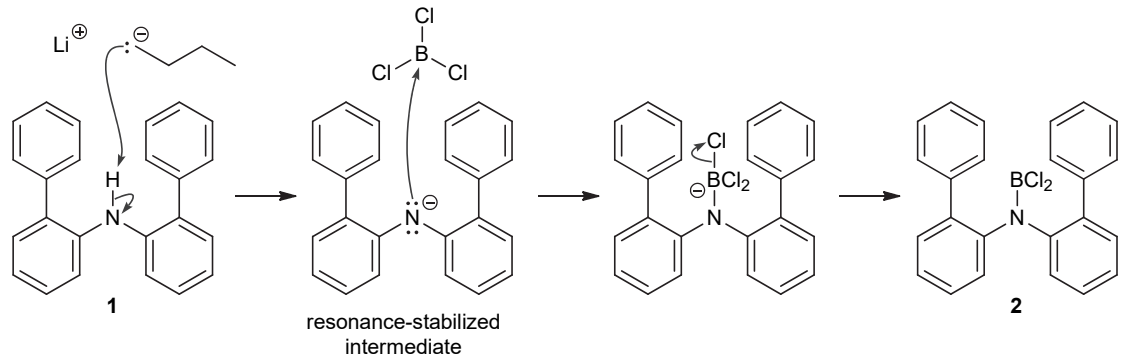


3

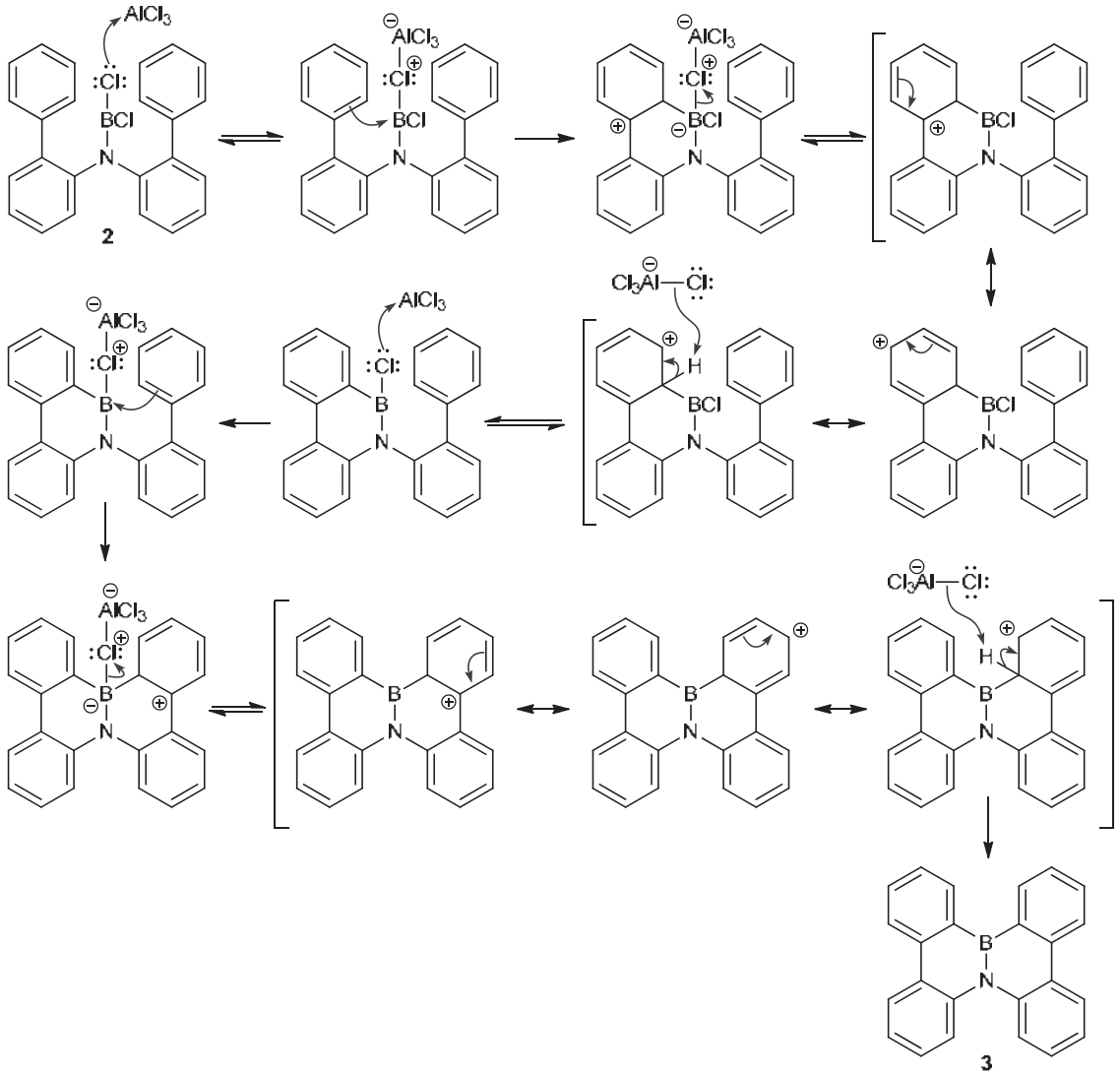
18.95.

(a) A reasonable mechanism for the conversion of **1** to **2** is shown. In the first step, butyllithium functions as a base and deprotonates the amine to produce a resonance-stabilized anion (resonance structures not shown). Boron trichloride serves as a Lewis acid in the next step, accepting an electron pair from the nucleophilic nitrogen atom, giving the Lewis acid – Lewis base complex. Subsequent loss of a chloride ion gives the compound **2**.

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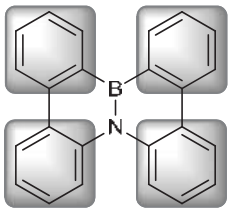


A mechanism for the final step is shown below. Overall, this step constitutes two subsequent electrophilic aromatic substitution reactions, resulting in the formation of two new B-C bonds. Addition of aluminum trichloride, a Lewis acid, serves to enhance the electrophilicity of the boron by forming a complex with one of the chlorine atoms. The boron is then attacked by one of the pendant arenes, with subsequent loss of $AlCl_4^-$ and formation of a resonance-stabilized sigma complex (several, but not all, of the many resonance structures are shown). Deprotonation with $AlCl_4^-$ restores aromaticity, giving a neutral intermediate. An identical sequence of mechanistic steps (complexation with $AlCl_3$, attack of the arene, loss of $AlCl_4^-$ and deprotonation) results in the formation of the second B-C bond, thus producing compound **3**.

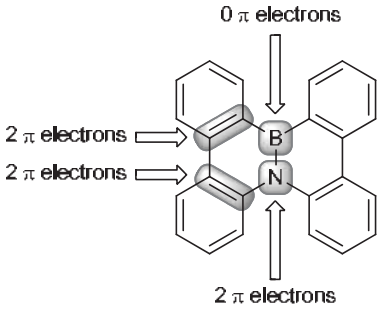


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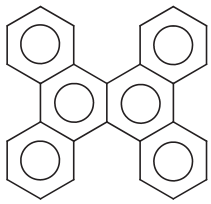
(b) Each of the four peripheral rings is clearly aromatic.



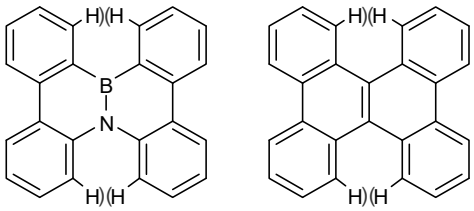
For the two central rings, the boron and nitrogen are both expected to be sp^2-hybridized, with boron having an empty *p*-orbital and nitrogen holding its lone pair in a *p*-orbital. As such, each central ring exhibits a continuous system of overlapping *p* orbitals with a total of 6 π electrons, thus fulfilling the criteria for aromaticity:



Therefore, all six rings are aromatic, providing for one extended aromatic system that is electronically similar to the following polycyclic aromatic compound:



(c) In part b, we determined that we expect both central rings in **3** to be aromatic, and as such, we would expect the entire molecule to be planar. The observation that the central two rings are twisted (non-planar) indicates that the central rings actually have limited aromatic character, despite the fact that they have the right number of π electrons to be aromatic. There must be something causing the rings to twist out of planarity. This can be explained by the steric repulsion between the indicated hydrogen atoms shown in the structures below. A slightly twisted structure avoids this repulsive interaction.



This steric interaction is very similar to the steric interaction in diphenylmethane, causing it to adopt a non-coplanar conformation, as seen in the Medically Speaking application at the end of section 17.5 (The Development of Non-Sedating Antihistamines).

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Chapter 19
Ketones and Aldehydes

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 19. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

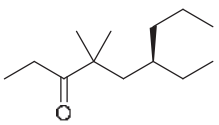
- The suffix "_____" indicates an aldehydic group, and the suffix "_____" is used for ketones.
- The electrophilicity of a carbonyl group derives from _____ effects, as well as _____ effects.
- A general mechanism for nucleophilic addition under basic conditions involves two steps
  1) nucleophilic attack
  2) _____
- The position of equilibrium is dependent on the ability of the nucleophile to function as a _____.
- In acidic conditions, an aldehyde or ketone will react with two molecules of alcohol to form an _____.
- The reversibility of acetal formation enables acetals to function as _____ groups for ketones or aldehydes. Acetals are stable under strongly _____ conditions.
- In acidic conditions, an aldehyde or ketone will react with a primary amine to form an _____.
- In acidic conditions, an aldehyde or ketone will react with a secondary amine to form an _____.
- In the **Wolff-Kishner reduction**, a hydrazone is reduced to an _____ under strongly basic conditions.
- _____ of acetals, imines, and enamines under acidic conditions produces ketones or aldehydes.
- In acidic conditions, an aldehyde or ketone will react with two equivalents of a thiol to form a _____.
- When treated with Raney nickel, thioacetals undergo **desulfurization** to yield a _____ group.
- When treated with a hydride reducing agent, such as lithium aluminum hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$), aldehydes and ketones are reduced to _____.
- The reduction of a carbonyl group with $LiAlH_4$ or $NaBH_4$ is not a reversible process, because hydride does not function as a _____.
- When treated with a Grignard reagent, aldehydes and ketones are converted into alcohols, accompanied by the formation of a new _____ bond.
- Grignard reactions are not reversible, because carbanions do not function as _____.
- When treated with hydrogen cyanide (HCN), aldehydes and ketones are converted into _____. For most aldehydes and unhindered ketones, the equilibrium favors formation of the _____.
- The **Wittig reaction** can be used to convert a ketone to an _____.
- A **Baeyer-Villiger oxidation** converts a ketone to an _____ by inserting _____ next to the carbonyl group. Cyclic ketones produce cyclic esters called _____.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 19. The answers appear in the section entitled *SkillBuilder Review*.

19.1: Naming Aldehydes and Ketones

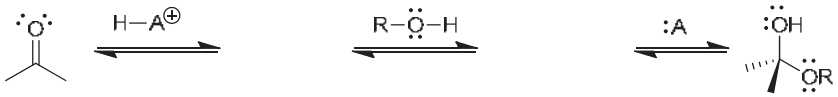
PROVIDE A SYSTEMATIC NAME FOR THE FOLLOWING COMPOUND



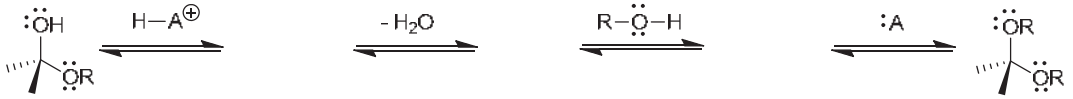
1) IDENTIFY THE PARENT
2) IDENTIFY AND NAME SUBSTITUENTS
3) ASSIGN LOCANTS TO EACH SUBSTITUENT
4) ALPHABETIZE
5) ASSIGN CONFIGURATION

19.2: Drawing the Mechanism of Acetal Formation

DRAW A MECHANISM FOR THE ACID-CATALYZED CONVERSION OF A KETONE TO A HEMIACETAL. MAKE SURE TO DRAW ALL CURVED ARROWS AND INTERMEDIATES.

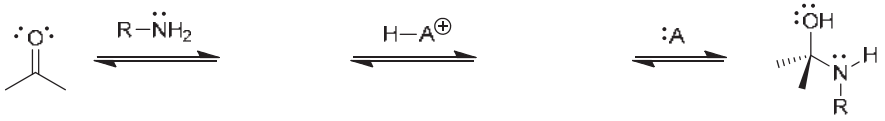


DRAW A MECHANISM FOR THE ACID-CATALYZED CONVERSION OF A HEMIACETAL TO AN ACETAL. MAKE SURE TO DRAW ALL CURVED ARROWS AND INTERMEDIATES.

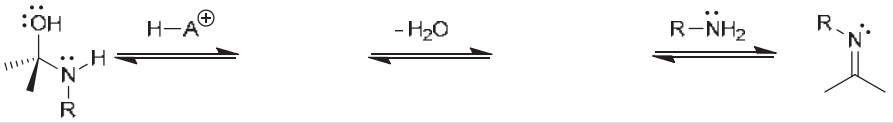


19.3: Drawing the Mechanism of Imine Formation

DRAW A MECHANISM FOR THE ACID-CATALYZED CONVERSION OF A KETONE TO A CARBINOLAMINE. MAKE SURE TO DRAW ALL CURVED ARROWS AND INTERMEDIATES.

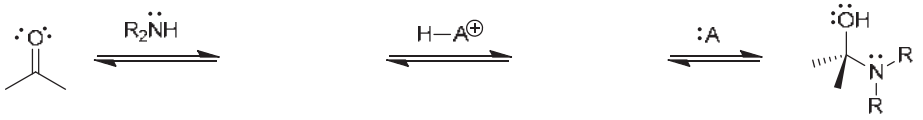


DRAW A MECHANISM FOR THE ACID-CATALYZED CONVERSION OF A CARBINOLAMINE TO AN IMINE. MAKE SURE TO DRAW ALL CURVED ARROWS AND INTERMEDIATES.

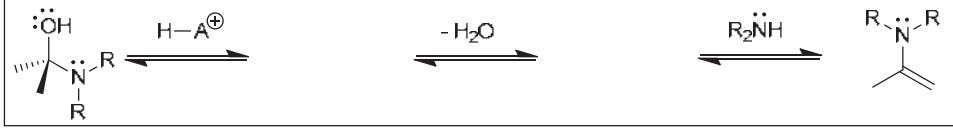


19.4: Drawing the Mechanism of Enamine Formation

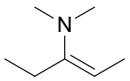
DRAW A MECHANISM FOR THE ACID-CATALYZED CONVERSION OF A KETONE TO A CARBINOLAMINE. MAKE SURE TO DRAW ALL CURVED ARROWS AND INTERMEDIATES.



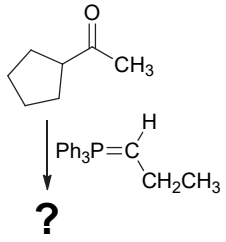
DRAW A MECHANISM FOR THE ACID-CATALYZED CONVERSION OF A CARBINOLAMINE TO AN ENAMINE. MAKE SURE TO DRAW ALL CURVED ARROWS AND INTERMEDIATES.



19.5: Drawing the Products of a Hydrolysis Reaction

DRAW THE EXPECTED PRODUCTS WHEN THE FOLLOWING COMPOUND IS TREATED WITH AQUEOUS ACID	***STEP 1 -*** *IDENTIFY THE BOND(S) EXPECTED TO UNDERGO CLEAVAGE*	***STEP 2 -*** *IDENTIFY THE CARBON ATOM THAT WILL BECOME A CARBONYL GROUP*	***STEP 3 -*** *DETERMINE THE IDENTITY OF THE OTHER FRAGMENT(S)*
			

19.6: Predicting the Major Product of a Wittig or HWE Reaction

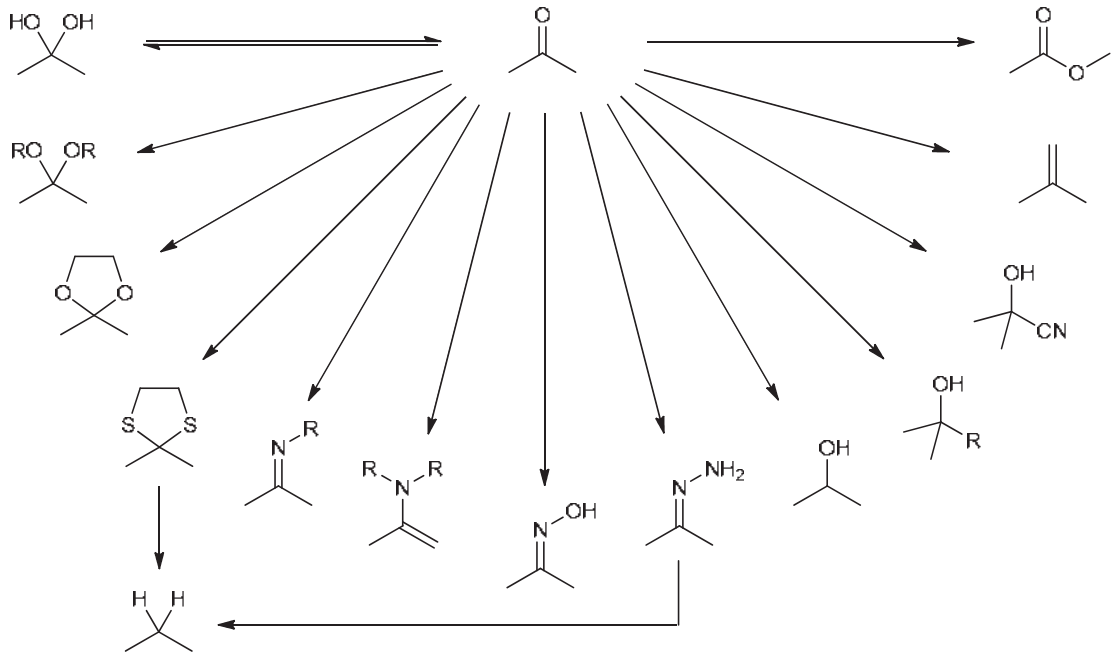
EXAMPLE	***STEP 1 -*** *IDENTIFY THE NUCLEOPHILE AND ELECTROPHILE*	***STEP 2 -*** *DETERMINE WHETHER THE WITTIG REAGENT IS STABILIZED*	***STEP 3 -*** *DRAW THE ALKENE PRODUCT WITH THE APPROPRIATE STEREOCHEMISTRY*
			

19.7: Proposing a Synthesis

BEGIN BY ASKING THE FOLLOWING TWO QUESTIONS: *1) IS THERE A CHANGE IN THE _____?* *2) IS THERE A CHANGE IN THE _____?*	*IF THERE IS A CHANGE IN THE CARBON SKELETON, CONSIDER ALL OF THE C-C BOND FORMING REACTIONS AND ALL OF THE C-C BOND BREAKING REACTIONS THAT YOU HAVE LEARNED SO FAR.* *C-C BOND-FORMING REACTIONS IN THIS CHAPTER:* *-_____* *-_____* *-_____* *C-C BOND-BREAKING REACTIONS IN THIS CHAPTER:* *-_____*

Review of Reactions

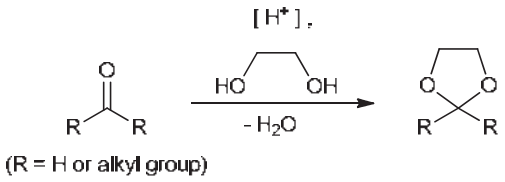
Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 19. The answers appear in the section entitled *Review of Reactions*.



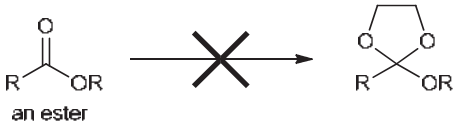
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Common Mistakes to Avoid

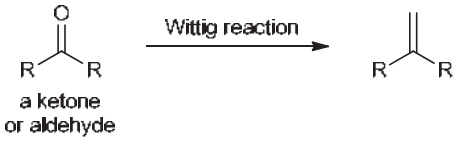
This chapter covers many reactions, including the formation of acetals:



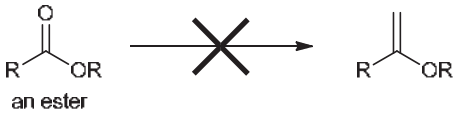
This reaction is covered in the context of the reactivity of ketones and aldehydes. The same reaction does not occur for other compounds containing a carbonyl group, such as esters:



Students often make this mistake, assuming that acetal formation will work for esters, just as it does for ketones. It does not. This is a common mistake, and it should be avoided.
As another example of a reaction that is often applied in the wrong context, consider the Wittig reaction.



Once again, Chapter 19 covers this reaction in the context of the reactivity of ketones and aldehydes. You cannot assume that the same reaction will occur for other compounds containing a carbonyl group, such as esters:



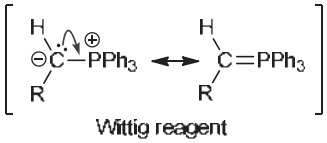
Students often make this type of mistake, by applying a reaction outside of the scope in which it was discussed. Try to avoid doing this. Whenever we cover a reaction that applies to ketones and aldehydes, you cannot assume that it will apply to esters (or any other functional group for that matter).

Useful reagents

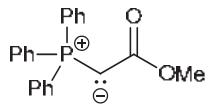
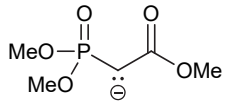
The following is a list of reagents encountered in this chapter:

Reagents	Type of Reaction	Description
H_3O^+	Hydrate formation	Conversion of a carbonyl group to a hydrate. This process is only efficient for formaldehyde and some simple aldehydes. For ketones, the equilibrium generally does not favor formation of the hydrate.
$[H^+]$, 2 ROH,	Acetal formation	Conversion of an aldehyde or ketone into an acetal. The acetal group can be used to

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(– H_2O)		protect aldehydes and ketones. The acetal group is stable to basic conditions, but is removed when subjected to aqueous acidic conditions to regenerate the carbonyl group (a process called hydrolysis).
[H^+], $HOCH_2CH_2OH$, – H_2O	Cyclic acetal formation	Ethylene glycol can be used to convert an aldehyde or ketone into an acetal. The acetal group can be used to protect aldehydes and ketones. The acetal group is stable to basic conditions, but is removed when subjected to aqueous acidic conditions to regenerate the carbonyl group (a process called hydrolysis).
[H^+], $HSCH_2CH_2SH$, (– H_2O)	Cyclic thioacetal formation	Ethylene thioglycol can be used to convert an aldehyde or ketone into a cyclic thioacetal.
Raney Nickel	Desulfurization	Converts a thioacetal (or cyclic thioacetal) to an alkane.
[H^+], RNH_2, (– H_2O)	Imine formation	Converts an aldehyde or ketone into an imine. The imine group is removed when subjected to aqueous acidic conditions to regenerate the carbonyl group (a process called hydrolysis).
[H^+], R_2NH, (– H_2O)	Enamine formation	Converts an aldehyde or ketone into an enamine. The enamine group is removed when subjected to aqueous acidic conditions to regenerate the carbonyl group (a process called hydrolysis).
[H^+], NH_2OH, (– H_2O)	Oxime formation	Converts an aldehyde or ketone into an oxime.
[H^+], NH_2NH_2, (– H_2O)	Hydrazone formation	Converts an aldehyde or ketone into a hydrazone.
NaOH, H_2O, heat	Wolff-Kishner reduction	Reduces a hydrazone to an alkane.
1) $LiAlH_4$ 2) H_2O	Reduction	Reduces an aldehyde or ketone to an alcohol.
1) RMgBr 2) H_2O	Grignard reaction	When an aldehyde or ketone is treated with a Grignard reagent (followed by water work-up), a carbon-carbon bond-forming reaction occurs, giving an alcohol that exhibits the newly formed C-C bond.
HCN, KCN	Cyanohydrin formation	Converts an aldehyde or ketone into a cyanohydrin.
 Wittig reagent	Wittig reaction	When an aldehyde or ketone is treated with a Wittig reagent, a carbon-carbon bond-forming reaction occurs, giving an alkene that exhibits the newly formed C=C bond in the location of the former carbonyl group. If R is a simple alkyl group, such as methyl or ethyl, then the (*Z*) alkene is generally observed to be the major product.

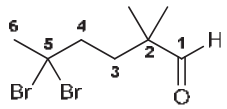
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	Wittig reaction	A stabilized Wittig reagent that will react with an aldehyde or ketone to give the (*E*) alkene as the major product.
	HWE reaction (Horner-Wadsworth-Emmons)	A HWE reagent functions like a stabilized Wittig reagent. It will react with an aldehyde or ketone to give the (*E*) alkene as the major product.
RCO_3H	Baeyer-Villiger oxidation	Converts a ketone into an ester (via insertion of an oxygen atom). Converts an aldehyde into a carboxylic acid (via insertion of an oxygen atom).

Solutions

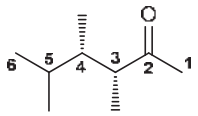
19.1.

(a) We begin by identifying the longest chain that includes the carbon atom of the carbonyl group. In this case, the parent is a chain of six carbon atoms, with the carbonyl group at C1, so the parent is hexanal. Next, we identify the substituents. There are four: two methyl groups (both at C2) and two bromine atoms (both at C5). Finally, we assemble the substituents alphabetically, giving the following name:



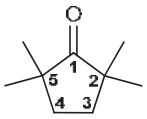
5,5-dibromo-2,2-dimethylhexanal

(b) We begin by identifying the longest chain that includes the carbon atom of the carbonyl group. In this case, the parent is a chain of six carbon atoms, with the carbonyl group at C2, so the parent is 2-hexanone. Next, we identify the substituents. There are three, all of which are methyl groups, located at C3, C4 and C5. We then assign a configuration to each of the chiral centers, giving the following name:



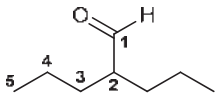
(3*R*,4*S*)-3,4,5-trimethyl-2-hexanone

(c) We begin by identifying the parent. In this case, the carbonyl group is part of a five-membered ring, so the parent is cyclopentanone. In a cyclic ketone, the carbonyl group is at C1 (by definition). Next, we identify the substituents. There are four, all of which are methyl groups (two at C2 and two at C5), giving the following name:



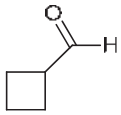
2,2,5,5-tetramethylcyclopentanone

(d) We begin by identifying the longest chain that includes the carbon atom of the carbonyl group. In this case, the parent is a chain of five carbon atoms, with the carbonyl group at C1, so the parent is pentanal. Next, we identify the substituents. There is only one substituent: a propyl group at C2, giving the following name:



2-propylpentanal

(e) A cyclic compound containing an aldehyde adjacent to the ring is named as a cycloalkane carbaldehyde. In this case, the aldehyde group is connected to a four-membered ring (cyclobutane), giving the following name:



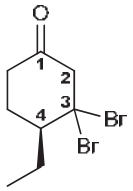
cyclobutanecarbaldehyde

19.2.

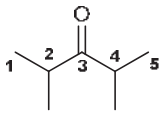
(a) The name indicates that the parent (cyclohexanone) is a six-membered ring, with a carbonyl group incorporated in the ring (a cyclic ketone). There are three

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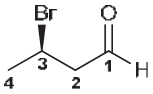
substituents: two bromine atoms (both at C3) and an ethyl group (at C4). The chiral center at C4 has the *S* configuration:



(b) The name indicates that the parent (3-pentanone) is a chain of five carbon atoms, with the carbonyl group at C3. There are two substituents (both methyl groups), located at C2 and C4, as shown:

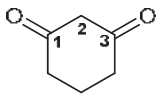


(c) The name indicates that the parent (butanal) is a chain of four carbon atoms, with the carbonyl group at C1 (by definition). There is only one substituent (Br), located at C3, which exhibits the *R* configuration, as shown:



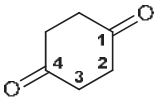
19.3.

(a) The parent is a six-membered ring with two carbonyl groups (a dione). The locants indicate the relative positions of the carbonyl groups (C1 and C3):



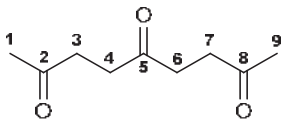
1,3-cyclohexanedione

(b) The parent is a six-membered ring with two carbonyl groups (a dione). The locants indicate the relative positions of the carbonyl groups (C1 and C4):



1,4-cyclohexanedione

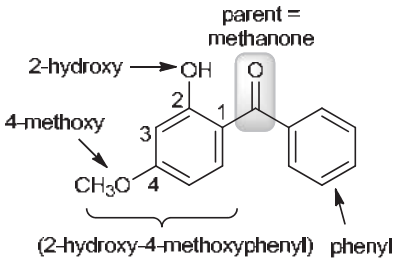
(c) The parent is a chain of nine carbon atoms, for which three of the carbon atoms are carbonyl groups (a trione). The locants indicate the relative positions of the carbonyl groups (C2, C5, and C8):



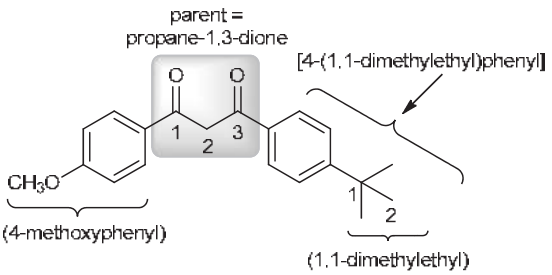
2,5,8-nonanetrione

19.4.

(a) To draw a complex molecule when given a complex name, it helps to start at the end and work backwards. First, draw the parent compound (methanone = a one-carbon ketone). Next, draw the substituents. There are two substituents in this case: phenyl and (2-hydroxy-4-methoxyphenyl). Draw the complex substituent by starting with a phenyl group and then adding the hydroxy and methoxy groups at the appropriate positions (recall that the point of attachment to the parent chain is defined as carbon #1 of the substituent). You may recognize that another possible name for this compound is 2-hydroxy-4-methoxybenzophenone.

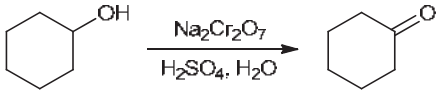


(b) Following the same approach, we begin by drawing the parent, propane-1,3-dione, a three-carbon ketone with carbonyl groupss at positions 1 and 3. Next to the carbonyl group, we place a phenyl substituent with a methoxy group on carbon 4. Next to the other carbonyl group, we draw a phenyl substituent with a 1,1-dimethylethyl group (also known as a *t*-butyl group) at carbon 4. Note: the systematic use of the parentheses should clarify the position of the entire *tert*-butylphenyl substituent on the parent diketone compound (e.g. "3") as well as the position of the tert-butyl "sub-substituent" on the phenyl substituent (the "4" or *para* position).



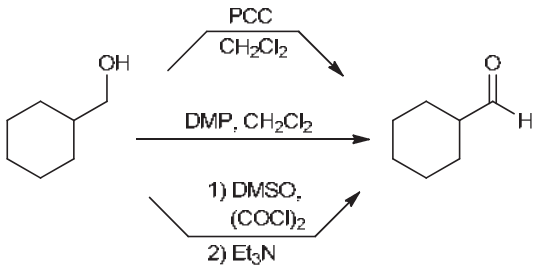
19.5.

(a) Oxidation of a secondary alcohol (to give a ketone) can be achieved with chromic acid (H_2CrO_4), which is prepared by mixing sodium dichromate ($Na_2Cr_2O_7$) and aqueous sulfuric acid. Alternatively, PCC or DMP can affect this transformation.

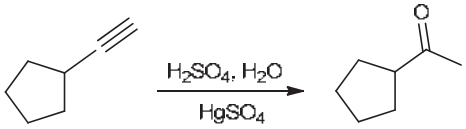


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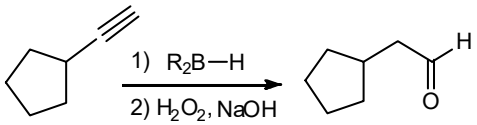
(b) Oxidation of a primary alcohol (to give an aldehyde) can be achieved upon treatment with PCC, or upon treatment with DMP, or via a Swern oxidation:



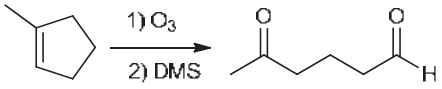
(c) A terminal alkyne can be converted into a methyl ketone upon acid-catalyzed hydration in the presence of mercuric sulfate:



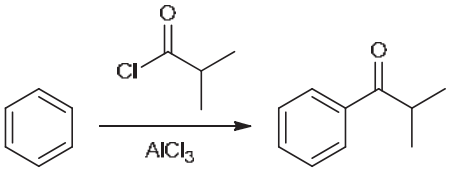
(d) A terminal alkyne can be converted into an aldehyde via hydroboration-oxidation:



(e) A C=C bond can be cleaved into two carbonyl groups via ozonolysis. In this case, the ring is opened to give an acyclic product.

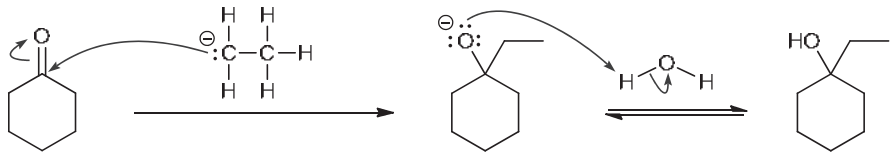


(f) An acyl group can be installed via a Friedel-Crafts acylation, using the appropriate acyl halide, as shown:

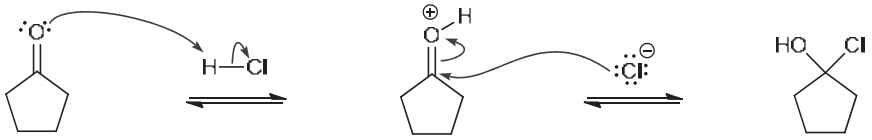


19.6.

(a) As seen in Section 12.6, a Grignard reagent is a strong nucleophile that will attack a carbonyl group to give an alkoxide ion. After the reaction is complete, water is introduced into the reaction flask, thereby serving as a proton source to protonate the alkoxide ion, giving an alcohol:



(b) Under acidic conditions, the carbonyl group is first protonated to give a resonance-stabilized cation. This cation is a strong electrophile that is then captured by a chloride ion to give the addition product shown. The equilibrium likely favors the ketone.



19.7. The carbonyl group in hexafluoroacetone is flanked by two very powerful electron-withdrawing groups (CF_3). These groups withdraw electron density from the carbonyl group, thereby increasing the electrophilicity of the carbonyl group. The resulting increase in energy of the reactant causes the equilibrium to favor the product (the hydrate, which is now lower in energy by comparison).

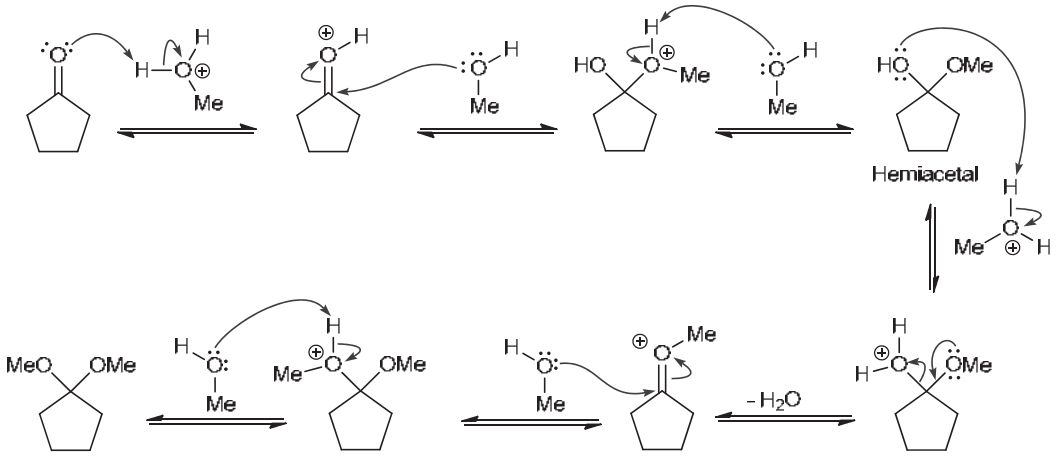
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19.8.

(a) Acid-catalyzed acetal formation proceeds via a seven-step process, which can be divided into two parts:

Part one is conversion of the ketone into a hemiacetal. In the first step of the following mechanism, a proton transfer generates a protonated carbonyl group, which is an excellent electrophile and is subject to attack by a nucleophile. The alcohol functions as the nucleophile, attacking the protonated carbonyl group to give an oxonium ion that loses a proton to give the hemiacetal.

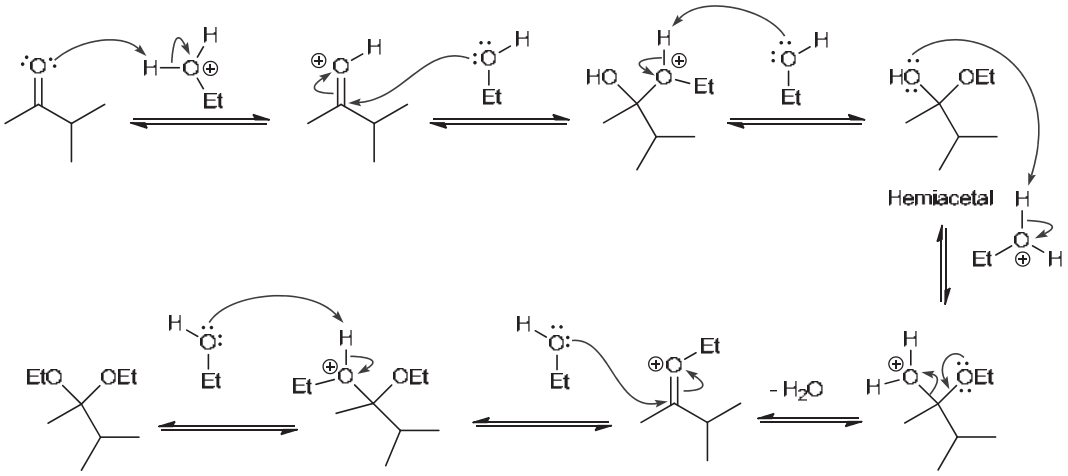
Part two of the mechanism is conversion of the hemiacetal into an acetal, which requires four steps. First a proton transfer step converts a bad leaving group (hydroxide) into an excellent leaving group (water). Loss of water gives an intermediate that can be attacked by another molecule of the alcohol. The resulting oxonium ion is then deprotonated to give an acetal. Note that in all steps of the mechanism, the proton source is a protonated alcohol, and the base is the alcohol (MeOH). No strong bases are employed or formed at any point during the mechanism.



(b) Acid-catalyzed acetal formation proceeds via a seven-step process, which can be divided into two parts:

Part one is conversion of the ketone into a hemiacetal. In the first step of the following mechanism, a proton transfer generates a protonated carbonyl group, which is an excellent electrophile and is subject to attack by a nucleophile. The alcohol functions as the nucleophile, attacking the protonated carbonyl group to give an oxonium ion that loses a proton to give the hemiacetal.

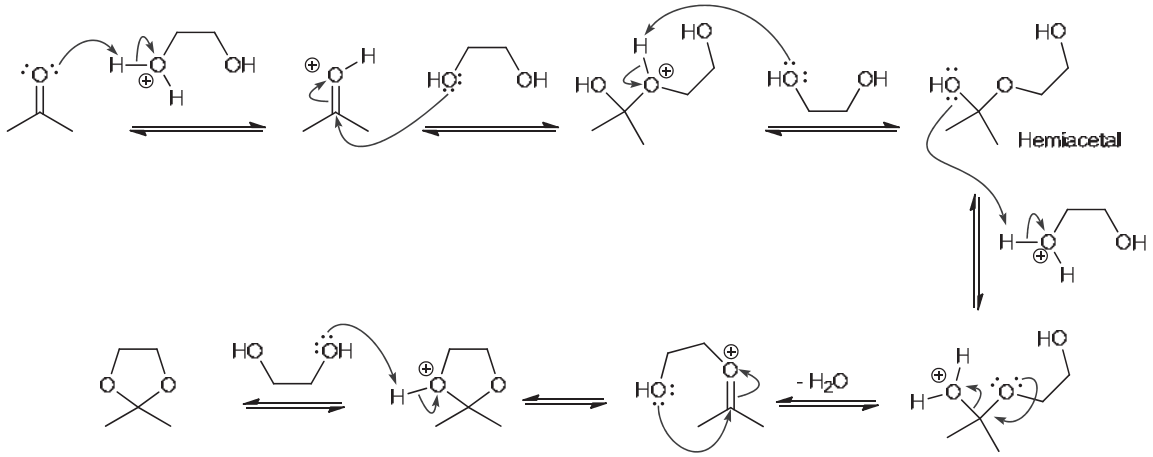
Part two of the mechanism is conversion of the hemiacetal into an acetal, which requires four steps. First a proton transfer step converts a bad leaving group (hydroxide) into an excellent leaving group (water). Loss of water gives an intermediate that can be attacked by another molecule of the alcohol. The resulting oxonium ion is then deprotonated to give an acetal. Note that in all steps of the mechanism, the proton source is a protonated alcohol, and the base is the alcohol (EtOH). No strong bases are employed or formed at any point during the mechanism.



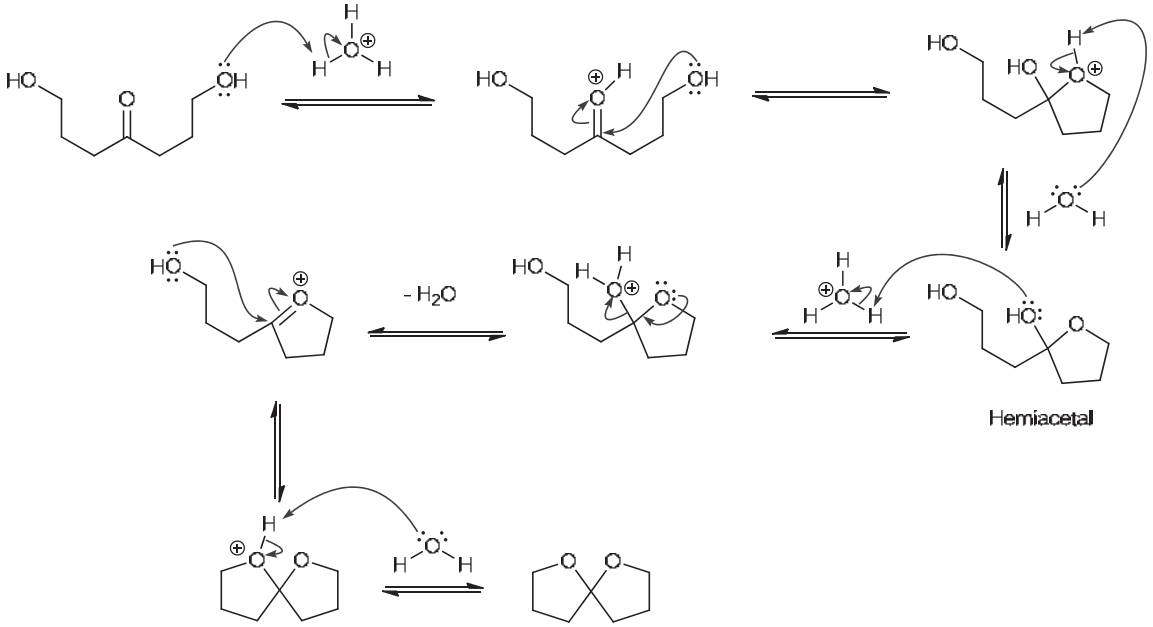
(c) Conversion of the ketone to an acetal occurs via a seven-step process. First the ketone is converted to a hemiacetal via the following three steps: 1) proton transfer, 2) nucleophilic attack, and then 3) proton transfer. And then the hemiacetal is converted into an acetal via the following four steps: 4) proton transfer, 5) loss of a leaving group, 6)

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nucleophilic attack, and 7) proton transfer. There is a subtle difference between this mechanism and the mechanisms shown in the solutions to part (a) and part (b) of this problem. The difference can be seen in step 6 (the second nucleophilic attack). In this case, step 6 occurs in an *intramolecular* fashion, giving a cyclic acetal:

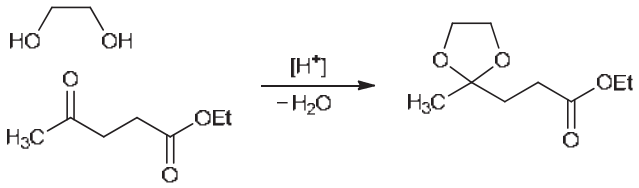


(d) Acid-catalyzed acetal formation proceeds via a seven-step process, which can be divided into two parts:
Part one is conversion of the ketone into a hemiacetal. In the first step of the following mechanism, a proton transfer generates a protonated carbonyl group, which is an excellent electrophile and is subject to attack by a nucleophile. In this case, the nucleophilic attack occurs in an *intramolecular* fashion to give a five-membered ring. This oxonium ion then loses a proton to give the hemiacetal.
Part two of the mechanism is conversion of the hemiacetal into an acetal, which requires four steps. First, a proton transfer step converts a bad leaving group (hydroxide) into an excellent leaving group (water). Loss of water gives an intermediate that can be attacked by another nucleophile. Once again, an intramolecular attack generates another five-membered ring. This oxonium ion is then deprotonated to give an acetal. Note that in all steps of the mechanism, the proton source is H_3O^+, and the base is water (H_2O). No strong bases are employed or formed at any point during the mechanism.



19.9.
(a) The reaction shows the formation of a cyclic acetal from a ketone. Since the reactant is a ketone, the reagent must be a diol and catalytic acidic conditions are required. Since the two oxygen atoms (in the acetal) are attached by two methylene (CH_2) groups, the diol reagent must also be attached by two methylene groups.

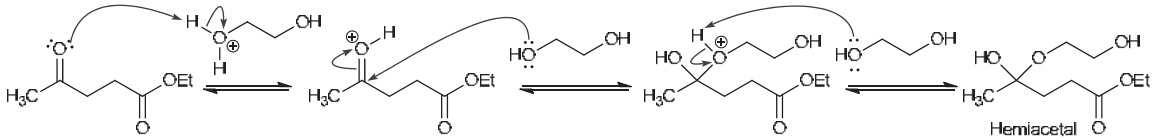
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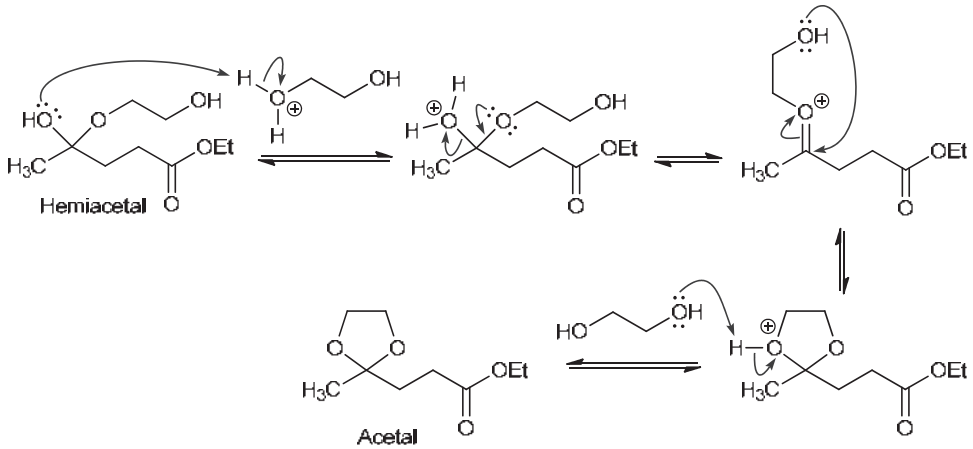
A strong acid must be used, typically H_2SO_4 or TsOH.

(b) The mechanism shown below is very similar to the mechanisms drawn in the solutions to problems 19.8a-d. Specifically, it involves a seven-step process that can be divided into two parts: (1) formation of the hemiacetal (three steps) and (2) formation of the acetal (four steps).

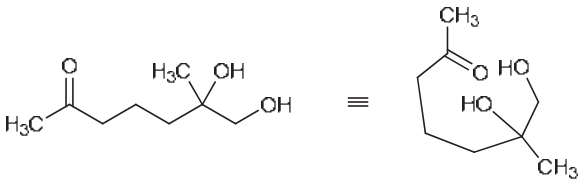
Formation of the hemiacetal involves three mechanistic steps: 1) proton transfer, 2) nucleophilic attack, and then 3) proton transfer.



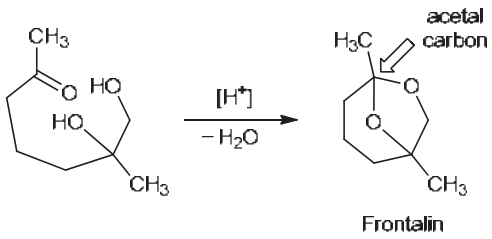
From the hemiacetal, the acetal forms in four mechanistic steps: 1) proton transfer, 2) loss of a leaving group, 3) nucleophilic attack, and then 4) proton transfer.



(c) First, redraw the keto-diol in a conformation where the ketone is placed near each of the hydroxyl groups.



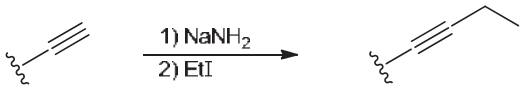
Next make a bond between the carbonyl carbon and each of the hydroxyl oxygen atoms. This produces a bicyclic acetal, as shown.



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19.10.

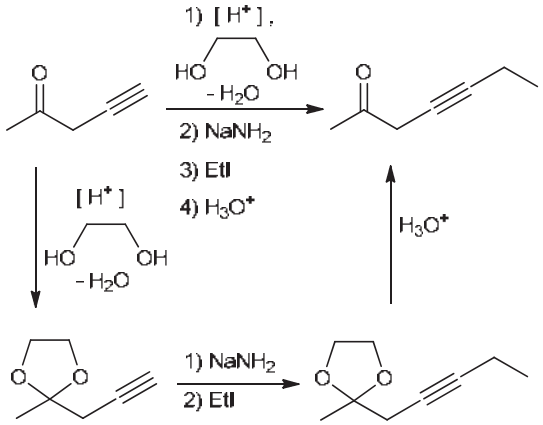
(a) This type of transformation can be achieved via alkylation of a terminal alkyne, as seen in Section 9.10:



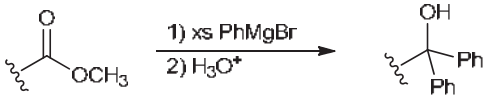
However, the starting material has a carbonyl group, which is a good electrophile. In the presence of the nucleophilic alkynide ion, the following undesired reaction can occur:



To avoid this undesired reaction, the carbonyl group is first converted into an acetal, which serves as a protecting group. The desired reaction is then performed, and finally, the protecting group (the acetal group) is removed with aqueous acid to give the product:



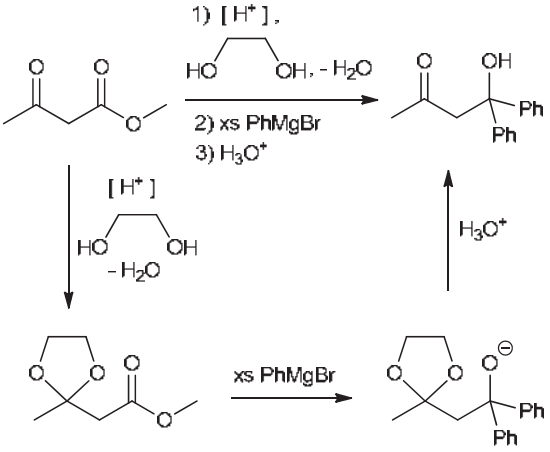
(b) This type of transformation can be achieved by treating the ester with excess phenyl magnesium bromide (see Mechanism 12.5):



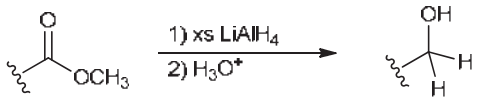
However, the starting material has another carbonyl group, which is also a good electrophile. In the presence of a powerful nucleophile (the Grignard reagent), the following undesired reaction can occur:



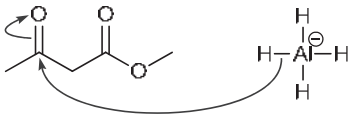
To avoid this undesired reaction, the ketone is first converted into an acetal, which serves as a protecting group. Installation of the protecting group occurs exclusively at the carbonyl group of the ketone, rather than the ester group, because the ketone carbonyl is more reactive than the ester carbonyl group (esters are ***not*** converted to their corresponding acetals). Once the ketone has been protected, the desired reaction is then performed, and finally, the protecting group is removed with aqueous acid to give the product. This final step also protonates the alkoxide ion which was formed by the Grignard reaction:



(c) This type of transformation can be achieved by treating the ester with excess $LiAlH_4$ (see Mechanism 12.3):

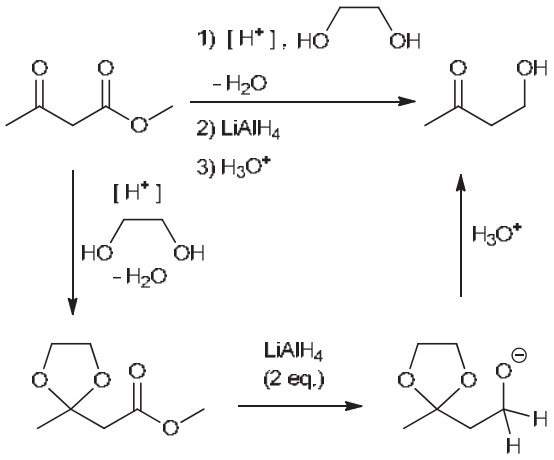


However, the starting material has another carbonyl group, which is also a good electrophile. In the presence of $LiAlH_4$, the following undesired reaction can occur:

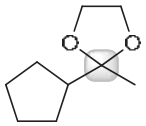


To avoid this undesired reaction, the ketone is first converted into an acetal, which serves as a protecting group. Installation of the protecting group occurs exclusively at the carbonyl group of the ketone, rather than the ester group, because the ketone carbonyl is more reactive than the ester carbonyl group (esters are ***not*** converted to their corresponding acetals). Once the ketone has been protected, the desired reaction is then performed, and finally, the protecting group is removed with aqueous acid to give the product. This final step also protonates the alkoxide ion which was formed by reduction of the ester group:

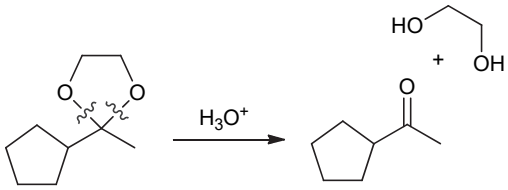
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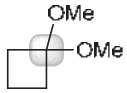
19.11.
(a) Begin by identifying the carbon atom that is connected to two oxygen atoms (highlighted):



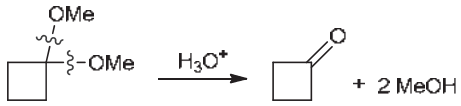
This carbon atom bears an acetal group, and will ultimately be converted into a carbonyl group in the product. The C-O bonds are cleaved, giving a ketone. Since these C-O bonds are contained in a ring, a diol is released.



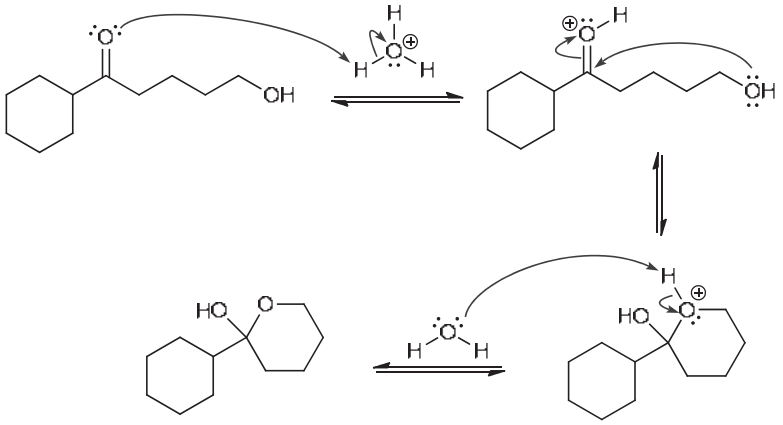
(b) Begin by identifying the carbon atom that is connected to two oxygen atoms (highlighted):



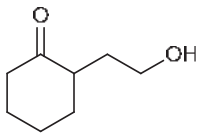
This carbon atom bears an acetal group, and will ultimately be converted into a carbonyl group in the product. The C-O bonds are cleaved, giving a ketone. Since these C-O bonds are not contained in a ring, two molecules of methanol are released.



19.12. The starting material contains both a carbonyl group and an OH group, and the product is a hemiacetal. As seen in Mechanism 19.5, formation of a hemiacetal requires three steps. First, the carbonyl is protonated, rendering it more electrophilic. Then, the alcohol group attacks the protonated carbonyl group (in an intramolecular fashion), giving an oxonium ion, which is deprotonated to give the hemiacetal, as shown:



19.13. The molecular formula indicates two degrees of unsaturation. Since the product is a hemiacetal, the starting material must contain both a carbonyl group and an OH group. The carbon atom of the acetal group must have been the location of the carbonyl group. The OH group (that attacks the carbonyl group to form the hemiacetal) must be contained in the structure of compound A, which explains why a cyclic hemiacetal is formed.

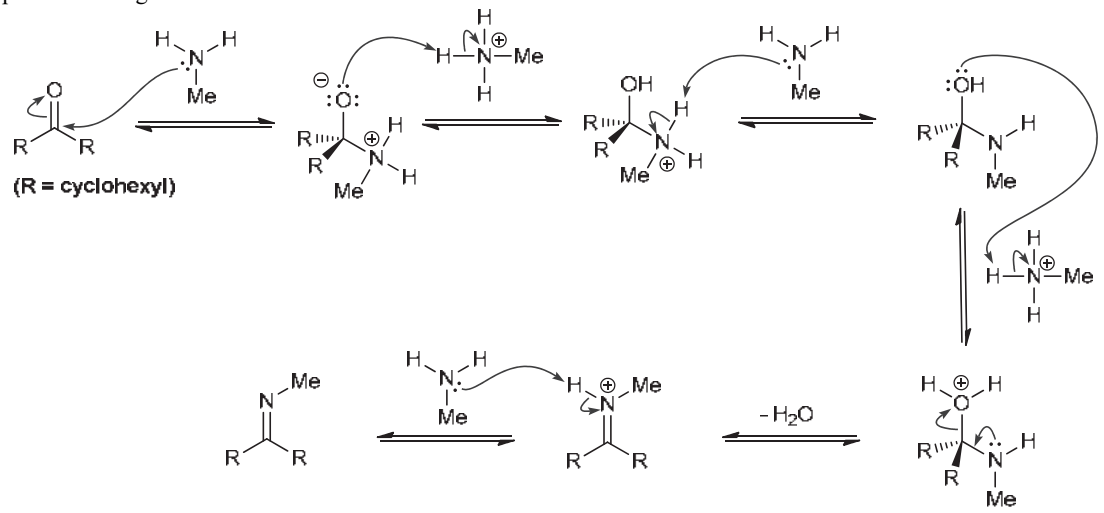


Compound A

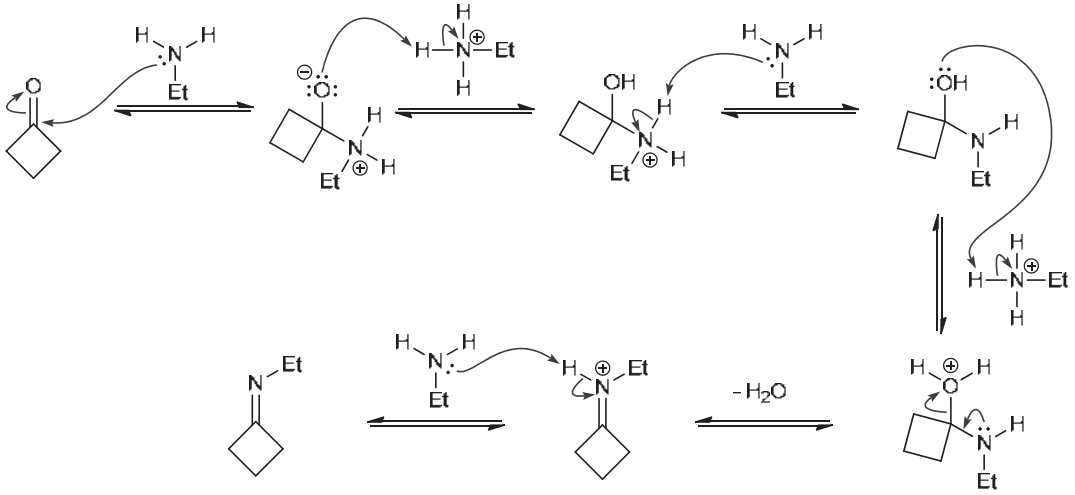
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19.14.

(a) As seen in Mechanism 19.6, imine formation proceeds via six steps. First, the amine functions as a nucleophile and attacks the ketone. The resulting intermediate is then protonated to remove the negative charge (note that the likely proton source under these conditions is a protonated amine, called an ammonium ion). Proton transfer then gives a carbinolamine (note that the likely base for this step is a molecule of the amine). Protonation then converts the bad leaving group (hydroxide) into a good leaving group (water). Loss of water then gives an iminium ion, which is deprotonated to give an imine.

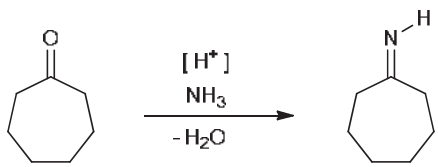


(b) As seen in the solution to part (a) of this problem, imine formation proceeds via six steps. The same six steps are drawn again here: 1) nucleophilic attack, 2) proton transfer, 3) proton transfer, 4) proton transfer, 5) loss of a leaving group, and 6) proton transfer.



19.15.

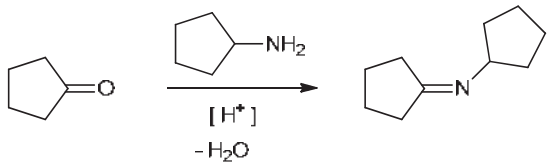
(a) When treated with ammonia under acid-catalyzed conditions (with removal of water), a ketone is converted to an imine. In this case, ammonia (NH_3) is used as the nucleophile (rather than a primary amine, RNH_2), and as a result, the product will not have an R group connected to the nitrogen atom of the imine group. Instead, there will be a proton in that location (two of the protons from NH_3 are removed during imine formation, while the third proton remains connected to the nitrogen atom in the product).



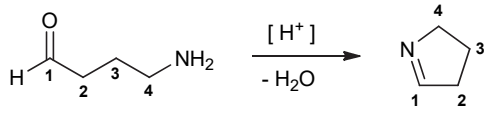
(b) Upon treatment with a primary amine under acid-catalyzed conditions (with removal of water), a ketone is converted to an imine. The carbon atom of the carbonyl group ends up being connected to the nitrogen atom (with a double bond). The oxygen atom is removed, together with the two protons connected to the nitrogen

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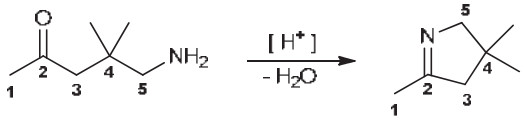
atom of the amine (thus, loss of water), to give the following product:



(c) Under acid-catalyzed conditions (with removal of water), an aldehyde will react with a primary amine to give an imine. In this case, the aldehyde group and the amino group are tethered to each other (in the same molecule), and the reaction therefore occurs in an intramolecular fashion. The carbon atom of the carbonyl group ends up being connected to the nitrogen atom (with a double bond), thereby closing a five-membered ring (four carbon atoms and one nitrogen atom). The oxygen atom is removed, together with the two protons connected to the nitrogen atom of the amino group (thus, loss of water), to give the product shown. Note that locants have been assigned to help draw the product. This problem illustrates how useful locants can be when drawing the products of a reaction, especially when the reaction involves formation of a ring.

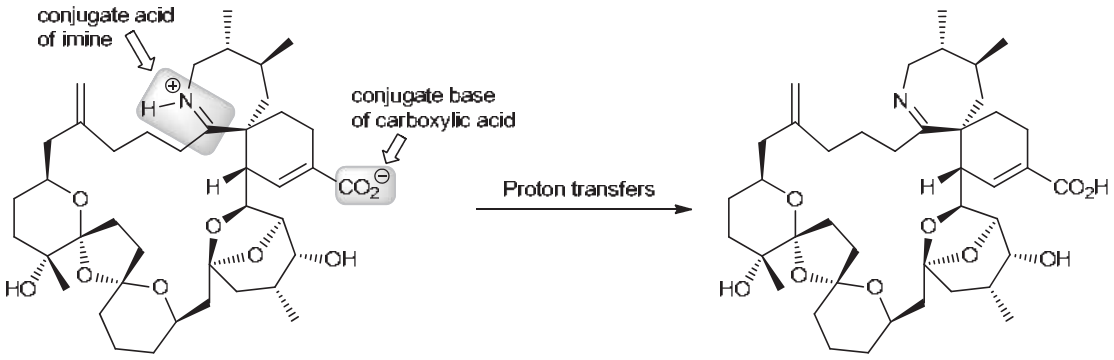


(d) This problem is very similar to the previous problem, although there is a ketone group (rather than an aldehyde group), and there are two other methyl groups connected to the middle of the chain. To ensure that all substituents are drawn in the correct locations, we assign locants, much as we did in the previous solution. This allows us to see that the methyl groups are placed at C4 in the product. Remember that the carbon atom of the carbonyl group ends up being connected to the nitrogen atom (with a double bond).

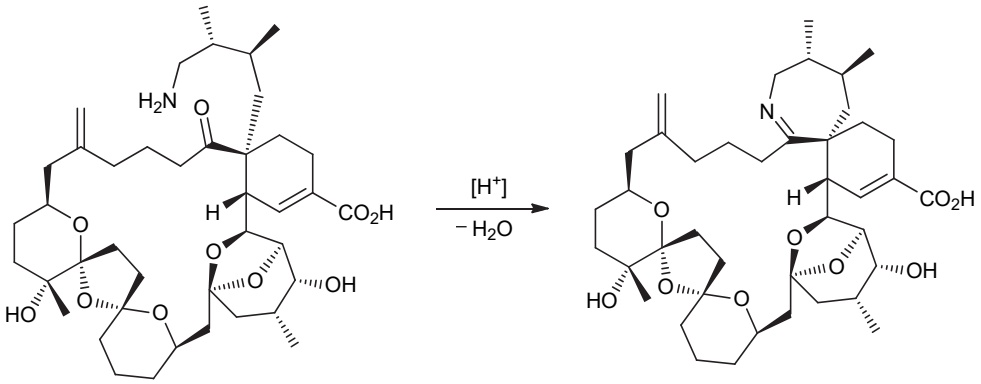


19.16.

(a) An iminium ion is the conjugate acid of an imine. Notice that pinnatoxin A also contains the conjugate base of a carboxylic acid, called a carboxylate ion. Transferring the proton from the iminium group to the carboxylate ion gives a neutral structure with the imine and carboxylic acid functional groups in their uncharged forms.

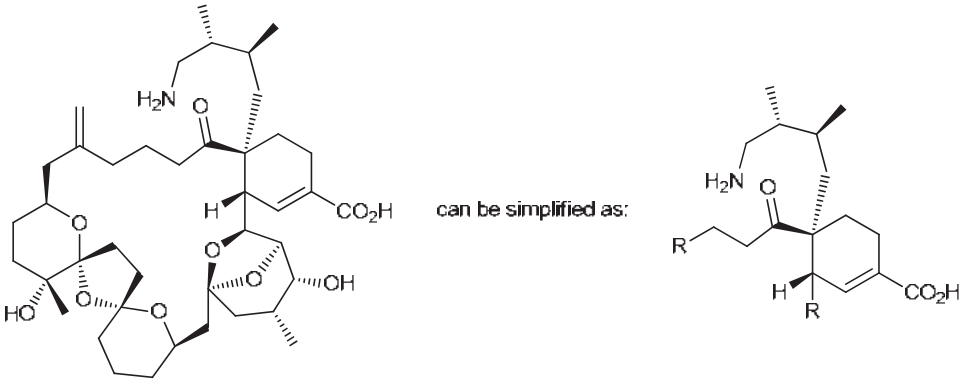


(b) To draw the amino ketone precursor, we consider the location of the C=N bond in the imine. The carbon atom of this bond must have been the carbonyl group in the starting ketone, and the nitrogen atom must have been connected to two protons in the starting amine. Thus, the following amino ketone reactant should give the desired imine (under acid-catalyzed conditions with the removal of water).

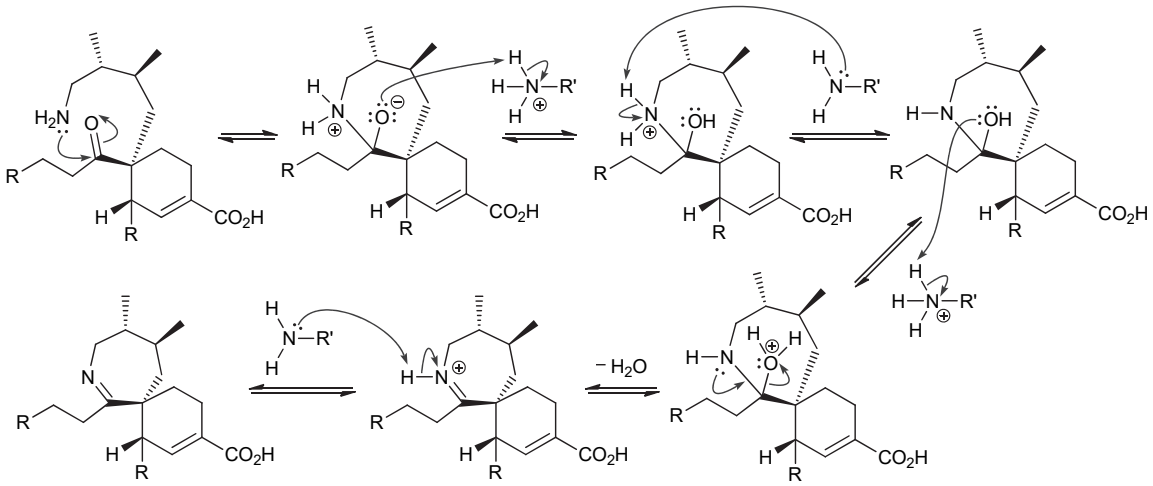


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(c) Given the complexity of the structure, let's simplify the molecule by representing the macrocycle with R groups.

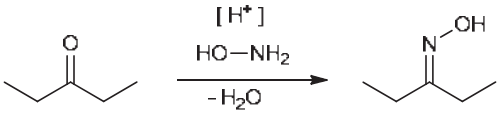


Imine formation proceeds via six steps. First, the amino group functions as a nucleophile and attacks the carbonyl group. The next three steps are a series of proton transfers assisted by a general acid ($R'—NH_3^+$) or base ($R'—NH_2$). For the entire mechanism, the general acid is likely the protonated amine of pinnatoxin (or related intermediates) and the general base is likely the free amine of pinnatoxin (or related intermediates). Expulsion of water affords the iminium ion that is deprotonated to give the imine.

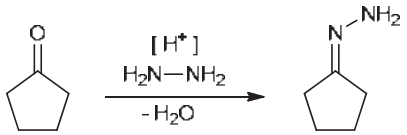


19.17.

(a) Treating a ketone with hydroxylamine under acidic conditions (with removal of water) gives an oxime ($R_2C{=}NOH$). During this process, the oxygen atom of the starting ketone is replaced with a nitrogen atom connected to an OH group:

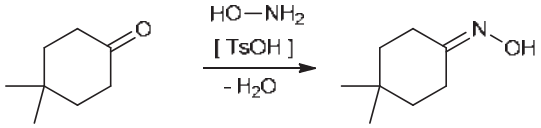


(b) Treating a ketone with hydrazine under acidic conditions (with removal of water) gives a hydrazone ($R_2C{=}NNH_2$). During this process, the oxygen atom of the starting ketone is replaced with a nitrogen atom connected to an NH_2 group:



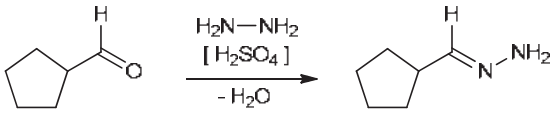
19.18.

(a) An oxime can be made by treating the corresponding ketone with hydroxyl amine, in acid catalyzed conditions (with removal of water), as shown.



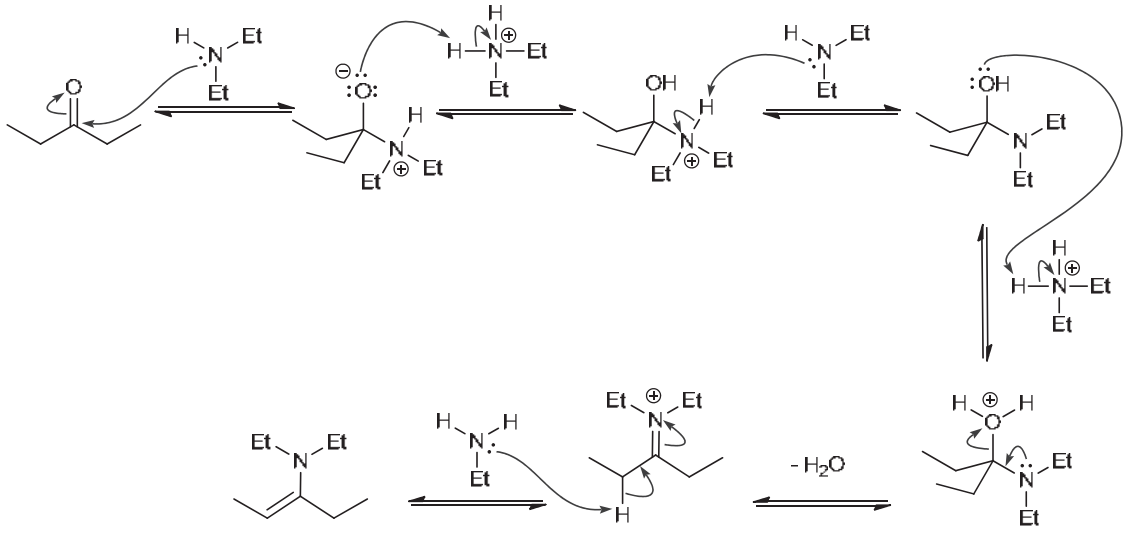
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(b) Treating a ketone with hydrazine under acidic conditions (with removal of water) gives a hydrazone ($R_2C{=}NNH_2$). During this process, the oxygen atom of the starting ketone is replaced with a nitrogen atom connected to an NH_2 group:

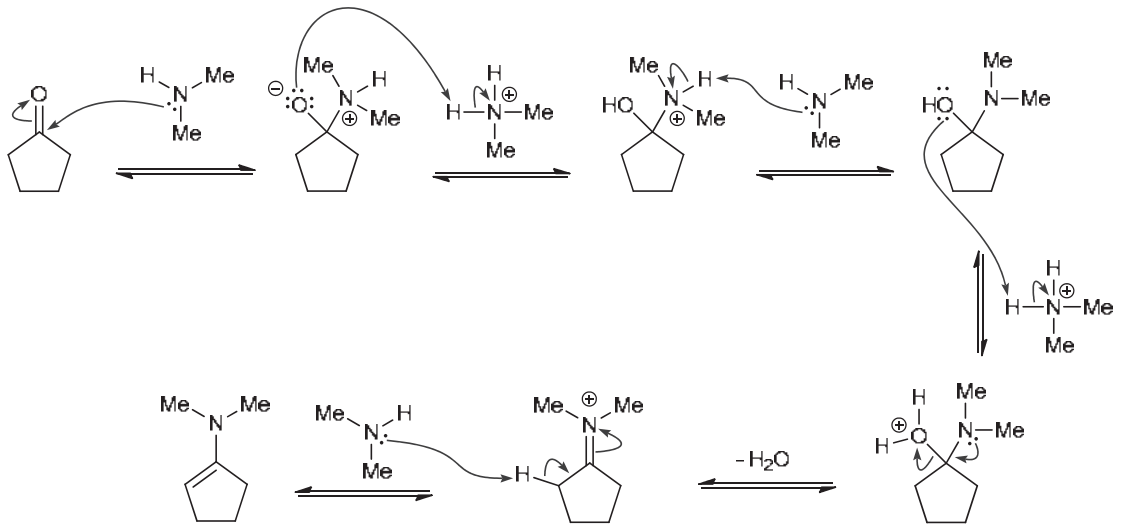


19.19.

(a) As seen in Mechanism 19.7, enamine formation proceeds via six steps. First, the amine functions as a nucleophile and attacks the ketone. The resulting intermediate is then protonated to remove the negative charge (note that the likely proton source under these conditions is a protonated amine, or ammonium ion). Proton transfer then gives a carbinolamine (note that the likely base for this step is a molecule of the amine). Protonation then converts the bad leaving group (hydroxide) into a good leaving group (water). Loss of water then gives an iminium ion, which is deprotonated to give an enamine.



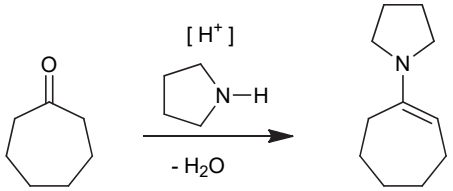
(b) As seen in Mechanism 19.7, enamine formation proceeds via six steps. First, the amine functions as a nucleophile and attacks the ketone. The resulting intermediate is then protonated to remove the negative charge (note that the likely proton source under these conditions is a protonated amine, or ammonium ion). Proton transfer then gives a carbinolamine (note that the likely base for this step is a molecule of the amine). Protonation then converts the bad leaving group (hydroxide) into a good leaving group (water). Loss of water then gives an iminium ion, which is deprotonated to give an enamine.



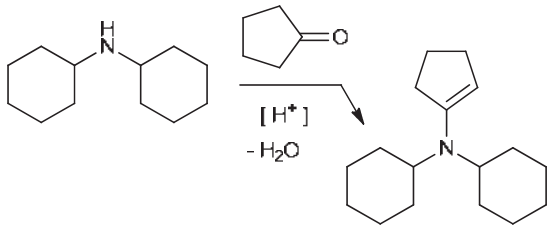
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19.20.

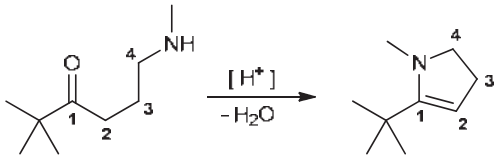
(a) Upon treatment with a secondary amine under acid-catalyzed conditions (with removal of water), a ketone is converted to an enamine. The carbon atom of the carbonyl group ends up being connected to the nitrogen atom (with a single bond), and that same carbon atom ends up having a double bond to a neighboring carbon atom, as shown. In the process, the oxygen atom is removed altogether, as well as two protons (one from the nitrogen atom and the other from a carbon atom) to give loss of water.



(b) Upon treatment with a secondary amine under acid-catalyzed conditions (with removal of water), a ketone is converted to an enamine. The carbon atom of the carbonyl group ends up being connected to the nitrogen atom (with a single bond), and that same carbon atom ends up having a double bond to a neighboring carbon atom, as shown. In the process, the oxygen atom is removed altogether, as well as two protons (one from the nitrogen atom and the other from a carbon atom) to give loss of water.

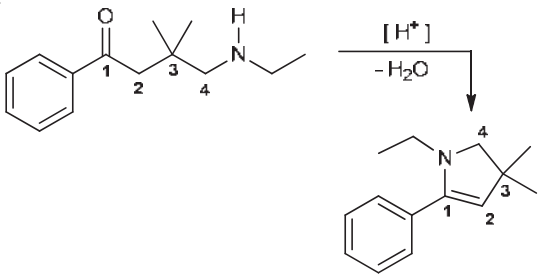


(c) Under acid-catalyzed conditions (with removal of water), a ketone will react with a secondary amine to give an enamine. In this case, the carbonyl group and the amino group are tethered to each other (in the same molecule), and therefore, the reaction occurs in an intramolecular fashion, forming a five-membered ring (four carbon atoms and one nitrogen atom). The carbon atom of the carbonyl group ends up being connected to the nitrogen atom (with a single bond). That same carbon atom ends up having a double bond to a neighboring carbon atom. The oxygen atom is removed altogether, as well as two protons (one from the nitrogen atom and the other from a carbon atom) to give loss of water.



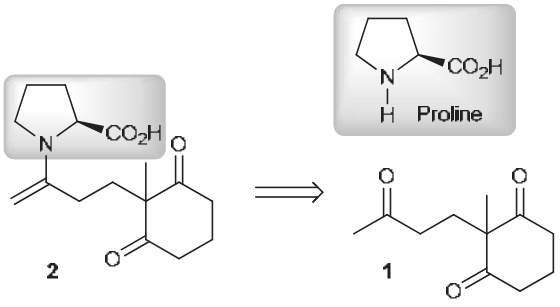
Note that locants have been assigned to help draw the product. These locants do not have to conform to IUPAC rules, as they are just helpful tools that we are using to draw the product correctly. The starting material above is not numbered according to IUPAC rules but that is OK, as long as we don't name the starting material using these incorrect locants.

(d) Under acid-catalyzed conditions (with removal of water), a ketone will react with a secondary amine to give an enamine. In this case, the carbonyl group and the amino group are tethered to each other (in the same molecule), and therefore, the reaction occurs in an intramolecular fashion, forming a five-membered ring (four carbon atoms and one nitrogen atom). The carbon atom of the carbonyl group ends up being connected to the nitrogen atom (with a single bond). That same carbon atom ends up having a double bond to a neighboring carbon atom. The oxygen atom is removed altogether, as well as two protons (one from the nitrogen atom and the other from a carbon atom) to give loss of water. Locants have been assigned to help draw the product.



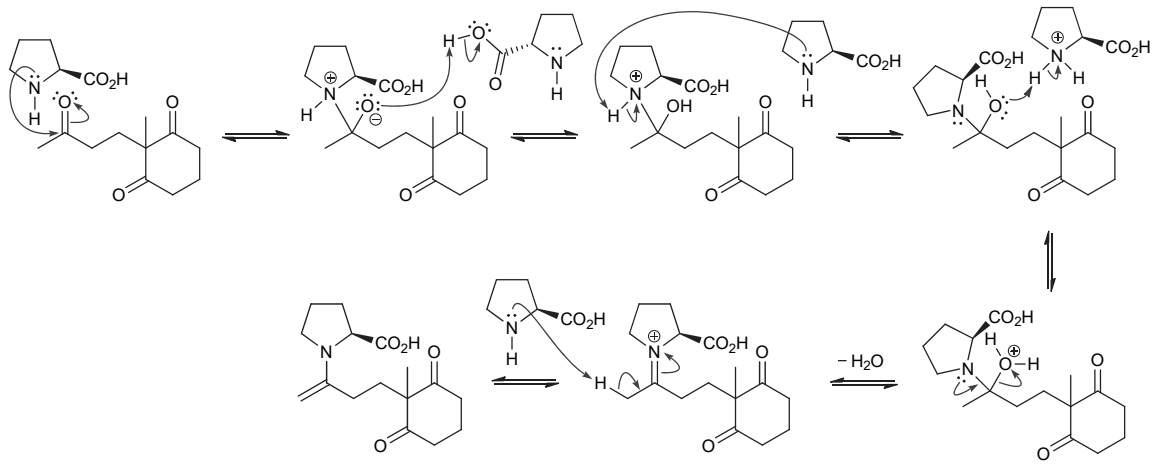
19.21.

(a) Enamines are formed from secondary amines. Since compound 2 is an enamine, proline must be a secondary amine. If we analyze the structure of **2**, we can see that proline must contain a 5-membered ring, as shown:



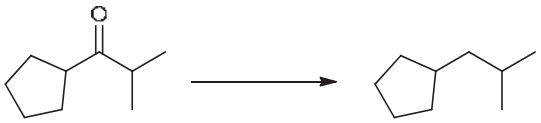
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(b) The formation of the enamine intermediate proceeds via six steps. First the nitrogen atom in proline attacks a carbonyl group. The next three steps are a series of proton transfers assisted by a general acid or general base. Expulsion of water affords an iminium ion, followed by deprotonation to yield the enamine.

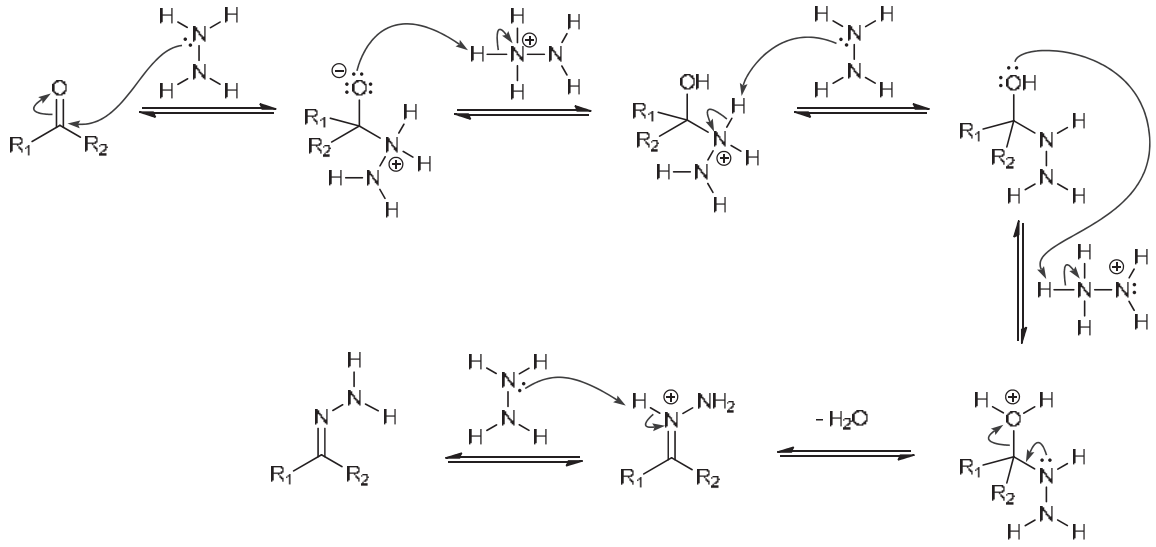


For the entire mechanism, the general acid is likely the carboxylic acid or the protonated amine on proline (R—CO_2H or R—NH_3^+) and the general base is likely the free amine on proline (R—NH_2).

19.22. The starting material is a ketone, and the reagents indicate formation of a hydrazone, followed by a Wolff-Kishner reduction. The net result is complete reduction of the carbonyl group to a methylene group (CH_2):

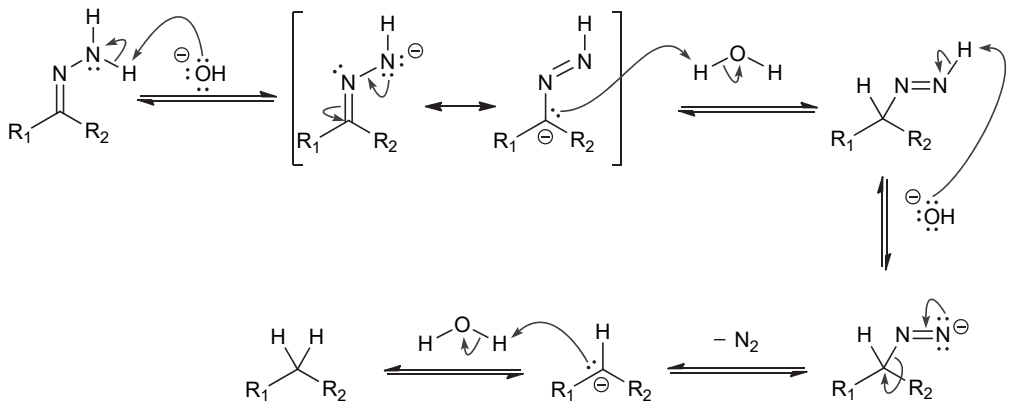


Formation of the hydrazone occurs via a six-step process (Mechanism 19.6). First, hydrazine functions as a nucleophile and attacks the ketone. The resulting intermediate is then protonated to remove the negative charge (note that the likely proton source under these conditions is a protonated hydrazine). Proton transfer then gives a carbinolamine (note that the likely base for this step is hydrazine). Protonation then converts the bad leaving group (hydroxide) into a good leaving group (water). Loss of water then gives an iminium ion, which is deprotonated to give the hydrazone.



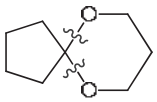
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And then, under basic conditions, the hydrazone is reduced via the process shown here. As seen in Mechanism 19.8, three successive proton transfer steps, followed by loss of nitrogen gas, gives a carbanion, which is protonated by water to give the product:

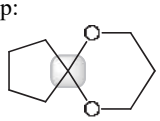


19.23.

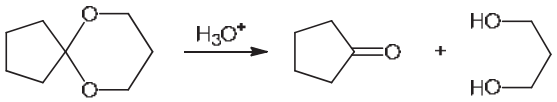
(a) The starting compound is an acetal, and it is being treated with aqueous acid, so a hydrolysis reaction is expected. We first identify the bonds that will undergo cleavage. When an acetal undergoes hydrolysis, cleavage occurs for the C-O bonds of the acetal group:



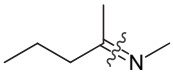
Therefore, the following carbon atom will be converted into a carbonyl group:



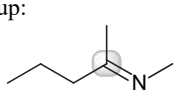
In the process, a diol is released, as shown:



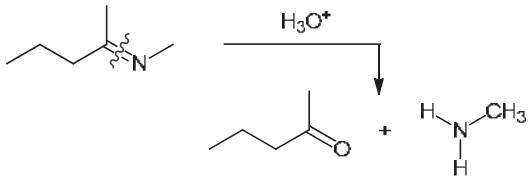
(b) The starting compound is an imine, and it is being treated with aqueous acid, so a hydrolysis reaction is expected. We first identify the bond that will undergo cleavage. When an imine undergoes hydrolysis, cleavage occurs for the C=N bond:



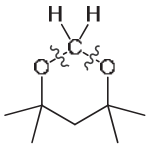
Therefore, the following carbon atom will be converted into a carbonyl group:



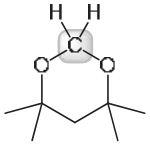
As a result of cleavage of the C=N bond, the carbon atom becomes a carbonyl group, and the nitrogen atom will accept two protons to generate a primary amine:



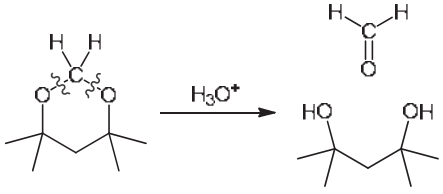
(c) The starting compound is an acetal, and it is being treated with aqueous acid, so a hydrolysis reaction is expected. We first identify the bonds that will undergo cleavage. When an acetal undergoes hydrolysis, cleavage occurs for the C-O bonds of the acetal group:



Therefore, the following carbon atom will be converted into a carbonyl group:

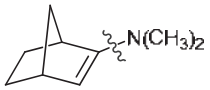


In the process, a diol is released, as shown:

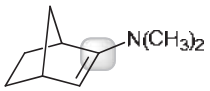


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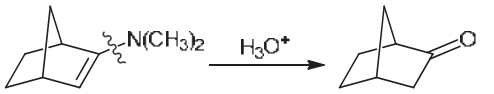
(d) The starting compound is an enamine, and it is being treated with aqueous acid, so a hydrolysis reaction is expected. We first identify the bond that will undergo cleavage. When an enamine undergoes hydrolysis, cleavage occurs for the bond between the nitrogen atom and the sp^2-hybridized carbon atom to which it is attached:



Therefore, the following carbon atom will be converted into a carbonyl group:

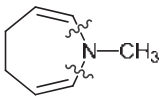


As a result of the C-N bond cleavage, the carbon atom becomes a carbonyl group, and the nitrogen atom will accept a proton to generate a secondary amine:

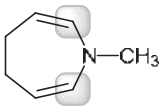


+ $(CH_3)_2NH$

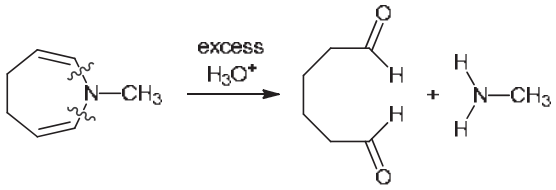
(e) In the starting compound, the nitrogen atom is connected to two different vinylic positions. As such, there are two C-N bonds that will undergo hydrolysis:



Each of these C-N bonds will be cleaved in the same way that the C-N bond of an enamine group can be cleaved. That is, each of the following carbon atoms (highlighted) will be converted into a carbonyl group:



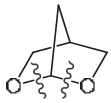
In the process, an amine is released, as shown:



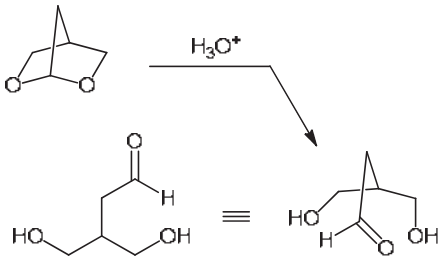
(f) The starting compound exhibits a carbon atom that is connected to two oxygen atoms, as shown, and is therefore an acetal:



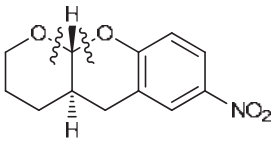
When an acetal is treated with aqueous acid, it is expected to undergo hydrolysis. We first identify the bonds that will undergo cleavage. When an acetal undergoes hydrolysis, cleavage occurs for the C-O bonds of the acetal group:



Each of these bonds is broken, thereby converting the carbon atom of the acetal group into a carbonyl group. In the process, each of the oxygen atoms will accept a proton to become an OH group, giving the following product, which exhibits a carbonyl group, as well as two OH groups:

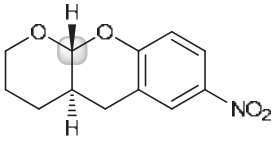


19.24. First identify which bond(s) are susceptible to acid-catalyzed hydrolysis. Compound **1** contains a carbon atom flanked by two ether-like oxygen atoms and is therefore an acetal. These two C-O bonds can undergo hydrolytic cleavage upon reaction with excess water and catalytic acid.

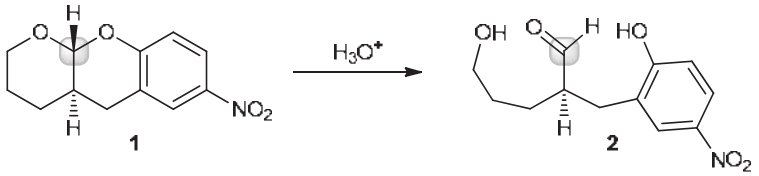


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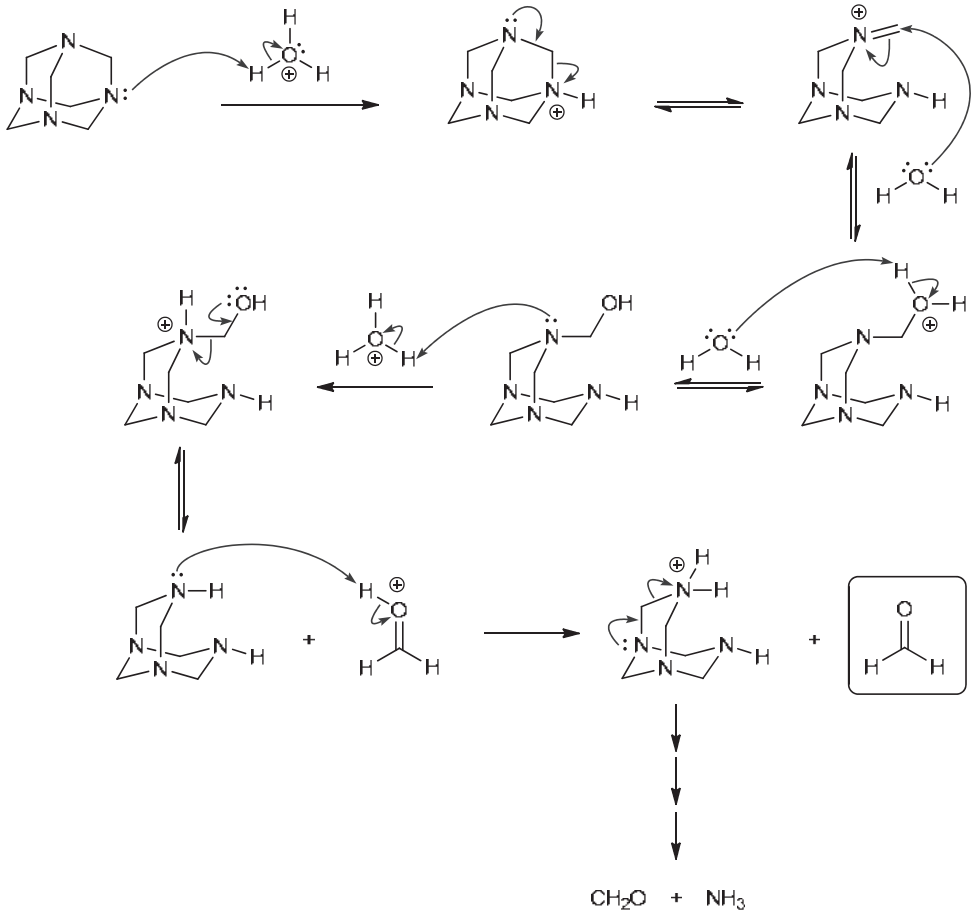
Next, identify the carbon atom that is converted into a carbonyl group.



Note that the acetal carbon bears a hydrogen atom, and will therefore yield an aldehyde upon hydrolysis. Hydrolysis of this acetal leads to two ring-openings, so the "fragments" will still be tethered to the rest of the molecule in the final product. The two acetal oxygen atoms will become OH groups. The acetal carbon of **1** was a chiral center, and it has been converted into a planar aldehyde group (not a chiral center). The other chiral center in compound **1** was not affected by hydrolysis, so it retains its configuration (H is still on a dash).

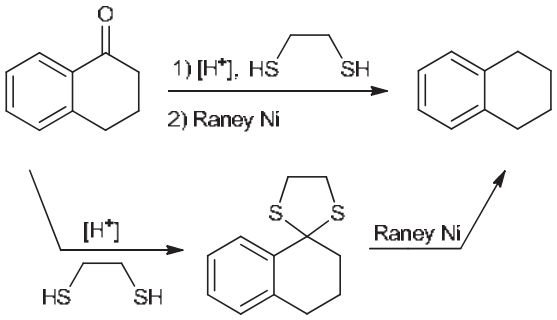


19.25. In aqueous acidic conditions, one of the nitrogen atoms is protonated to give an ammonium ion. Loss of a leaving group then generates an iminium ion, which is attacked by water to give an oxonium ion. Loss of a proton then gives an alcohol (the likely base is water). Protonation of the neighboring nitrogen atom gives a leaving group, which leaves, thereby expelling a fragment with one carbon atom. A proton transfer provides the first equivalent of formaldehyde. The other equivalents are formed in a similar way.

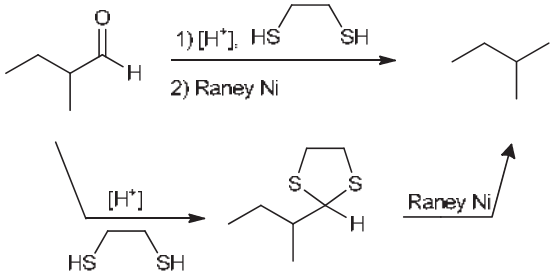


19.26.

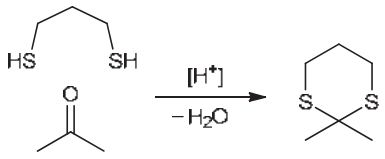
(a) The starting material is a ketone, and the reagents indicate the formation of a cyclic thioacetal, followed by desulfurization with Raney nickel. The net result is conversion of the carbonyl group into a methylene (CH_2) group, as shown.



(b) The starting material is an aldehyde, and the reagents indicate the formation of a cyclic thioacetal, followed by desulfurization with Raney nickel. The net result is the reduction of the carbonyl group to give an alkane.

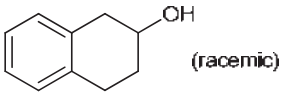


19.27. When a ketone is treated with a dithiol in the presence of an acid catalyst, a cyclic thioacetal is formed. The carbonyl group is replaced with C-S bonds, as shown:

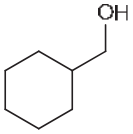


19.28.

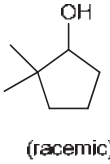
(a) The starting material is a ketone, and $LiAlH_4$ is a hydride reducing agent. Upon treatment with $LiAlH_4$, followed by water work-up, the ketone is reduced to give the following secondary alcohol. A new chiral center is formed in the process, so we expect a racemic mixture of enantiomers:



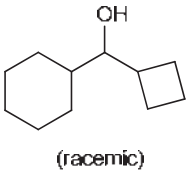
(b) The starting material is an aldehyde, and $NaBH_4$ is a hydride reducing agent. Upon treatment with $NaBH_4$ and methanol, the aldehyde is reduced to give the following primary alcohol:



(c) The starting material is a ketone, and $LiAlH_4$ is a hydride reducing agent. Upon treatment with $LiAlH_4$, followed by water work-up, the ketone is reduced to give the following secondary alcohol. A new chiral center is formed in the process, so we expect a racemic mixture of enantiomers:

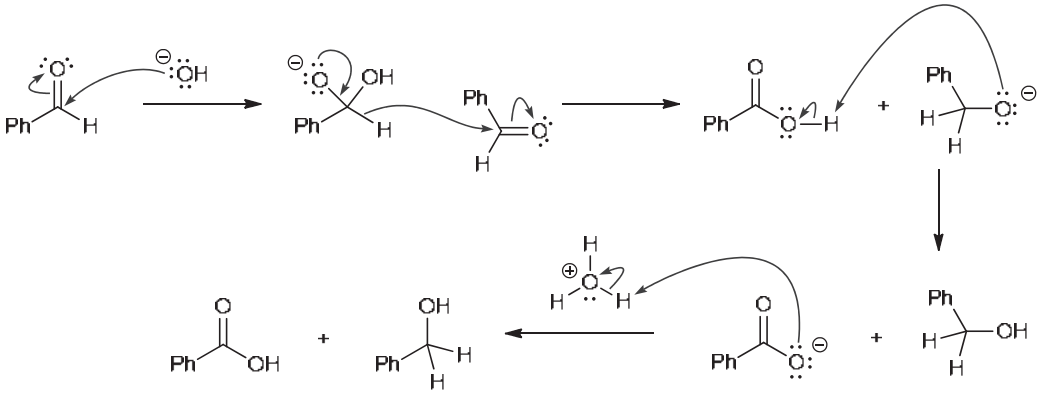


(d) The starting material is a ketone, and $NaBH_4$ is a hydride reducing agent. Upon treatment with $NaBH_4$ and methanol, the ketone is reduced to give the following secondary alcohol. A new chiral center is formed in the process, so we expect a racemic mixture of enantiomers:



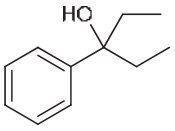
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19.29.
(a) The following mechanism is consistent with the description given in the problem statement. After a hydroxide ion attacks one molecule of benzaldehyde, the resulting intermediate functions as a hydride delivery agent to attack another molecule of benzaldehyde, giving a carboxylic acid and an alkoxide ion. The alkoxide ion then deprotonates the carboxylic acid, generating a more stable carboxylate ion. When the reaction is complete, aqueous acid is added to the reaction flask in order to protonate the carboxylate ion, giving benzoic acid.

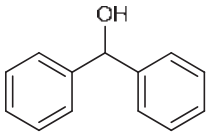


(b) The function of H_3O^+ in the second step is to serve as a proton source to protonate the carboxylate ion, giving benzoic acid.
(c) Water is only a weak acid (pK_a = 15.7), and is not sufficiently strong to serve as a proton source for a carboxylate ion (pK_a of PhCOOH is 4.2). See Section 3.5 for a discussion of this topic.

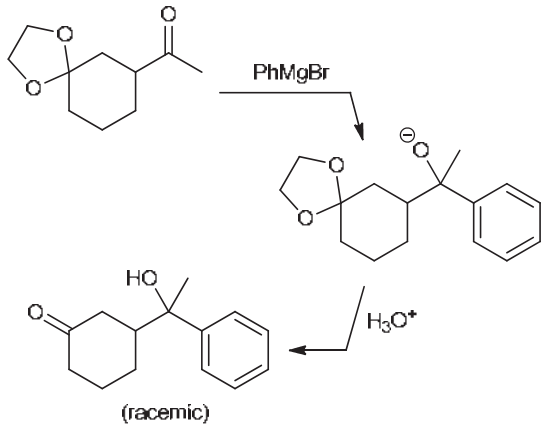
19.30.
(a) The starting material is a ketone, and ethyl magnesium bromide is a Grignard reagent (a strong nucleophile). Upon treatment with a Grignard reagent, followed by water work-up, the ketone is converted to a tertiary alcohol (with installation of an ethyl group):



(b) The starting material is an aldehyde, and phenyl magnesium bromide is a Grignard reagent (a strong nucleophile). Upon treatment with a Grignard reagent, followed by water work-up, the aldehyde is converted to a secondary alcohol (with installation of a phenyl group):



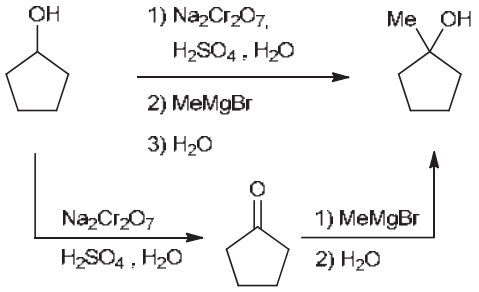
(c) The starting material is a ketone, and phenyl magnesium bromide is a Grignard reagent (a strong nucleophile). Upon treatment with a Grignard reagent, followed by water work-up, the ketone is attacked, giving the alkoxide ion shown. Treatment with aqueous acid then protonates the alkoxide ion (giving a tertiary alcohol) and also hydrolyzes the acetal group, giving a ketone group. During this process, a chiral center is formed, so we expect a racemic mixture of enantiomers:



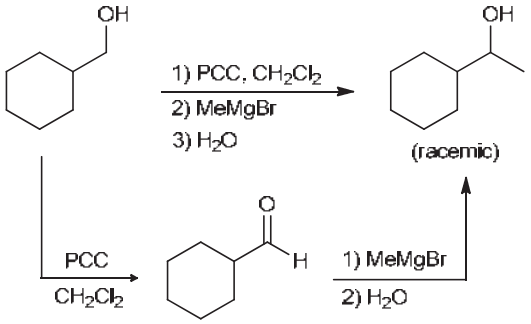
19.31.
(a) This transformation requires installation of a methyl group at the α position of an alcohol. We have not learned a direct way to achieve this transformation. However, if we first oxidize the alcohol to give a ketone,

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then treatment with methyl magnesium (followed by water work-up) will install the methyl group and simultaneously reduce the ketone back to an alcohol. The net result is the conversion of a secondary alcohol into a tertiary alcohol, as shown. A variety of oxidizing agents can be used for the oxidation step, including chromic acid (formed by mixing sodium dichromate with aqueous sulfuric acid).

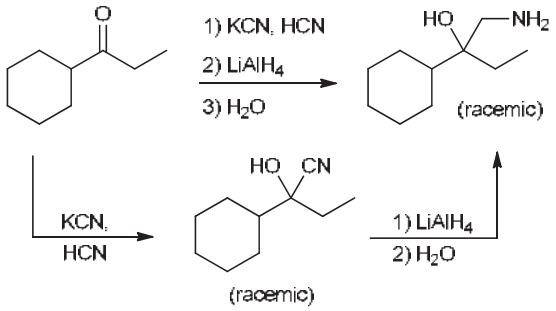


(b) This transformation requires installation of a methyl group at the α position of an alcohol. We have not learned a direct way to achieve this transformation. However, if we first oxidize the alcohol to give an aldehyde, then treatment with methyl magnesium (followed by water work-up) will install the methyl group and simultaneously reduce the aldehyde back to an alcohol. This final step creates a new chiral center, so a racemic mixture of enantiomers is expected. The net result is the conversion of a primary alcohol into a secondary alcohol, as shown. The oxidation step can be performed with PCC (or DMP or Swern), to give an aldehyde. The use of chromic acid would result in formation of a carboxylic acid, rather than an aldehyde.

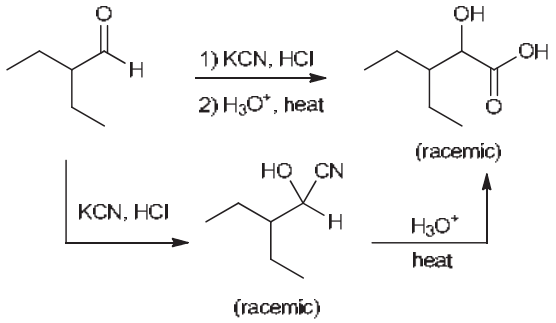


19.32.

(a) The starting material is a ketone, and the reagents indicate cyanohydrin formation, followed by reduction to give an amino alcohol. During cyanohydrin formation, a new chiral center is formed, so a racemic mixture is expected.

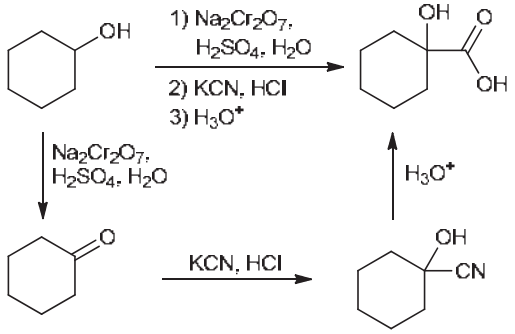


(b) The starting material is an aldehyde, and the reagents indicate cyanohydrin formation, followed by hydrolysis of the cyano group to give a carboxylic acid group. During cyanohydrin formation, a new chiral center is formed, so a racemic mixture is expected.



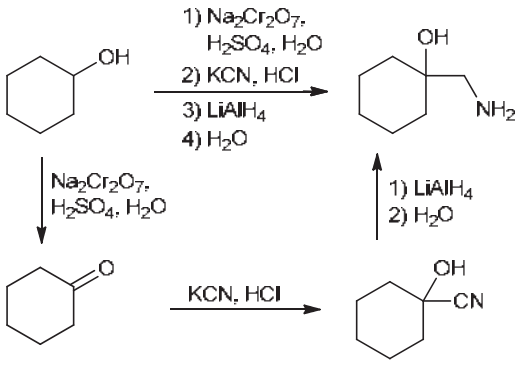
19.33.

(a) This transformation requires installation of a carboxylic acid group at the α position of an alcohol. We have not learned a direct way to achieve this transformation. However, if we first oxidize the alcohol to give a ketone, then treatment with KCN and HCl will convert the ketone into a cyanohydrin (thereby installing the extra carbon atom in the correct location, while simultaneously converting the carbonyl group back into an alcohol). Hydrolysis of the cyano group then gives the desired product. A variety of oxidizing agents can be used for the oxidation step, including chromic acid (formed by mixing sodium dichromate with aqueous sulfuric acid).



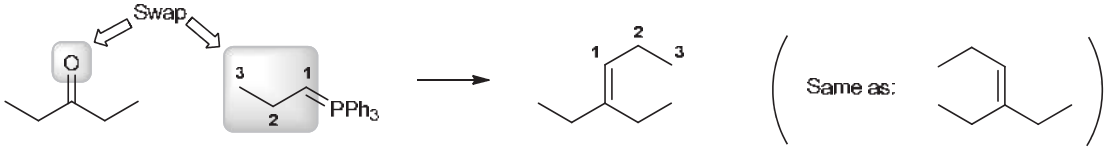
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(b) This transformation requires installation of a CH_2NH_2 group at the α position of an alcohol. We have not learned a direct way to achieve this transformation. However, if we first oxidize the alcohol to give a ketone, then treatment with KCN and HCl will convert the ketone into a cyanohydrin (thereby installing the extra carbon atom in the correct location, while simultaneously converting the carbonyl group back into an alcohol). Reduction of the cyano group (with $LiAlH_4$, followed by water work-up) then gives the desired product. A variety of oxidizing agents can be used for the oxidation step, including chromic acid (formed by mixing sodium dichromate with aqueous sulfuric acid).

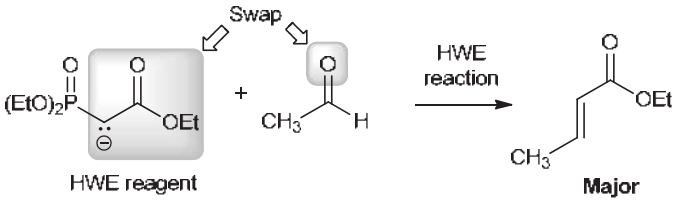


19.34.

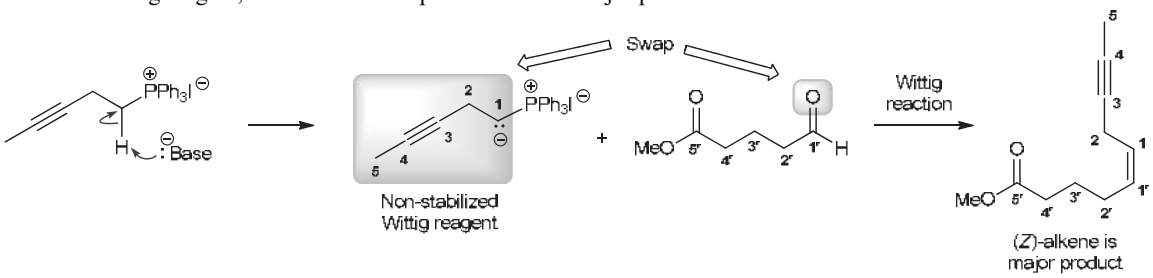
(a) This is a reaction between a ketone and a non-stabilized Wittig reagent. Stereochemistry is not relevant in this case since there is only one stereoisomer possible, so the oxygen atom of the carbonyl group is replaced with the propyl group of the Wittig reagent, giving an alkene product. Numbering the carbon atoms on the Wittig reagent can help you draw the correct number of carbon atoms in the product.



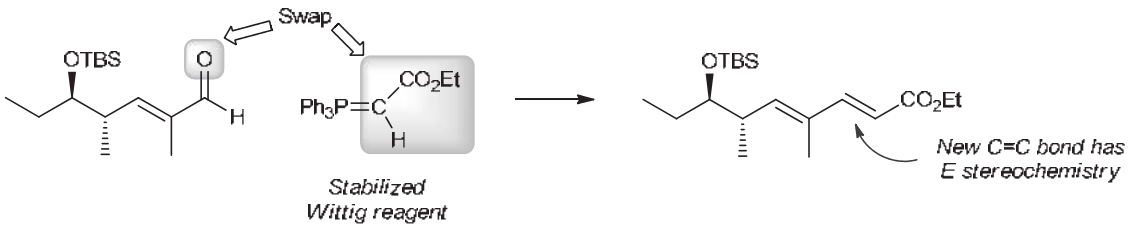
(b) Reaction of the HWE reagent with acetaldehyde will give the *E* alkene as the major product:



19.35. After deprotonation, the newly formed Wittig reagent will react with the aldehyde. Because this is a non-stabilized Wittig reagent, the *Z* isomer is expected to be the major product.

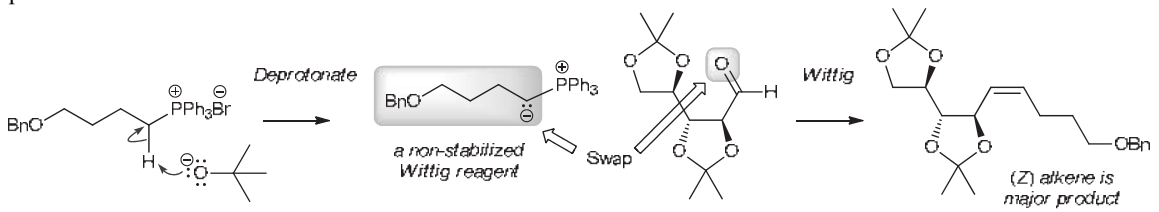


19.36. The presence of the ester group makes this a stabilized Wittig reagent, so the alkene with *E* stereochemistry will predominate as the major product.



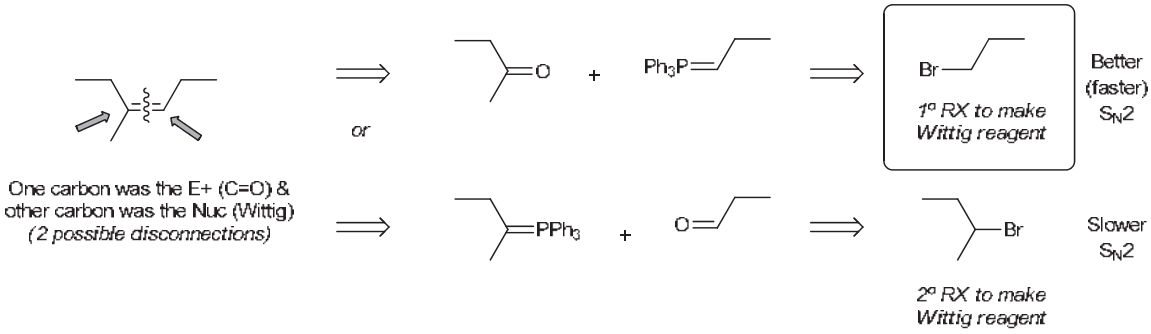
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19.37. First, the Wittig reagent must be prepared by deprotonation of the phosphonium salt with the given base, *t*-butoxide. The resulting non-stabilized Wittig reagent will react with the aldehyde to form a Z alkene as the major product.

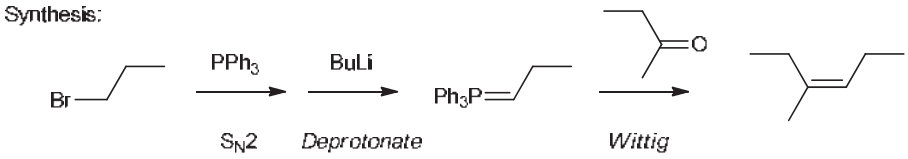


19.38.

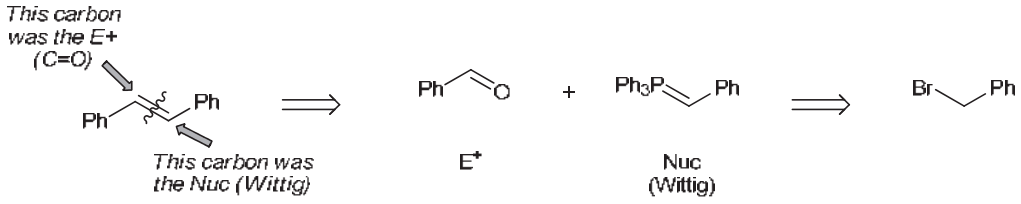
(a) There are two possible disconnections for the alkene target molecule.

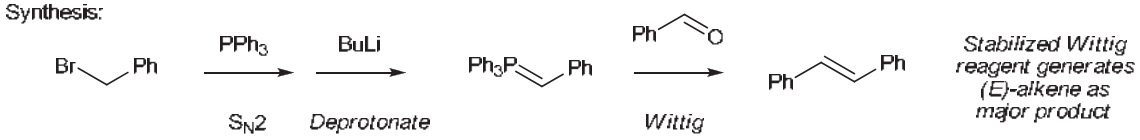


When comparing the two possible Wittig reagents, the one derived from the primary alkyl halide is preferred since it would be a faster and higher yielding S_N2 substitution with PPh_3. This non-stabilized Wittig reagent reacts with 2-butanone to give the target molecule, a *Z* alkene.



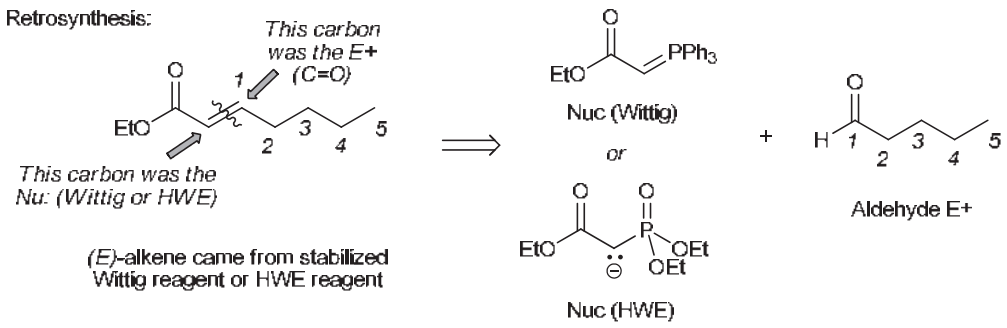
(b) There is only one possible disconnection for this symmetrical alkene target molecule. The stabilized Wittig reagent (due to resonance with phenyl group) is prepared from benzyl bromide and reacts with benzaldehyde to give the target molecule, an *E* alkene.



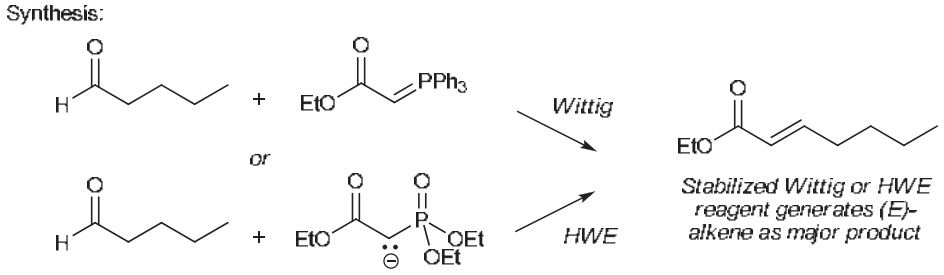


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(c) The best disconnection for this alkene target molecule is to align the ester group with the nucleophilic carbon (resulting in either a stabilized Wittig or HWE reagent); this will ensure the *E* configuration in the resulting alkene. The other component is a 5-carbon aldehyde.

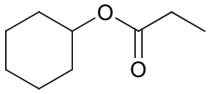


Reaction of pentanal with either the Wittig or HWE reagent shown will afford the desired target molecule, with *E* stereochemistry.

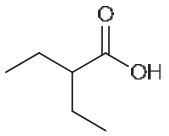


19.39.

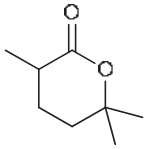
(a) The starting material is a ketone, and the reagent is a peroxy acid, which indicates a Baeyer-Villiger oxidation. The ketone is unsymmetrical, so we must decide where to insert the oxygen atom (i.e., which side of the carbonyl group). According to the trends of migratory aptitude that we encountered, we would expect the oxygen atom to be inserted on the left side (secondary) rather than the right side (primary), giving the following product:



(b) The starting material is an aldehyde, and the reagent is a peroxy acid, which indicates a Baeyer-Villiger oxidation. Aldehydes are oxidized to carboxylic acids with this process, giving the following product:



(c) The starting material is a ketone, and the reagent is a peroxy acid, which indicates a Baeyer-Villiger oxidation. The ketone is unsymmetrical, so we must decide where to insert the oxygen atom (i.e., which side of the carbonyl group). According to the trends of migratory aptitude that we encountered, we would expect the oxygen atom to be inserted on the right side (tertiary) rather than the left side (secondary), giving the following product:



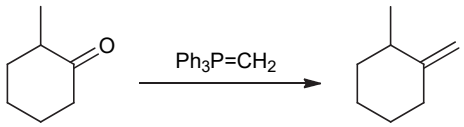
19.40.

(a) We begin by asking the following two questions:

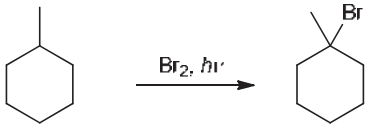
1) *Is there a change in the carbon skeleton?* Yes, the carbon skeleton is increasing in size by one carbon atom.
2) *Is there a change in the functional groups?* Yes, the starting material lacks a functional group, and the product has an exocyclic double bond (extending from the ring).

Now we must propose a strategy for achieving these changes. Since the carbon skeleton is increasing in size by one carbon atom, we know that we must form a carbon-carbon bond. We have seen several ways to make carbon-carbon bonds, and there are certainly many acceptable solutions to this problem. Since the extra carbon atom bears a double bond, we consider using a Wittig reaction as the last step of our synthesis:

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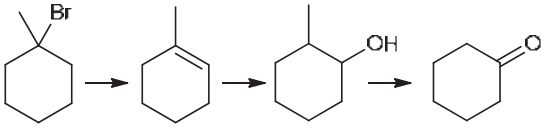
This step will install the extra carbon atom while simultaneously installing a double bond in the desired location. In order for this strategy to work, we must find a way to convert the starting material into the ketone above. Since the starting material lacks a functional group, the first step our synthesis must be a radical bromination:



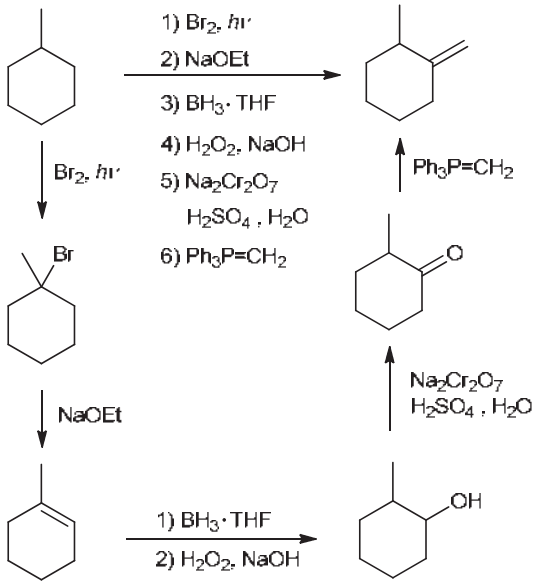
In order to complete the synthesis, we must bridge the following gap:



This transformation requires that we change both the location and the identity of the functional group. This can be achieved via elimination to give an alkene, followed by hydroboration-oxidation to give an alcohol, followed by oxidation:



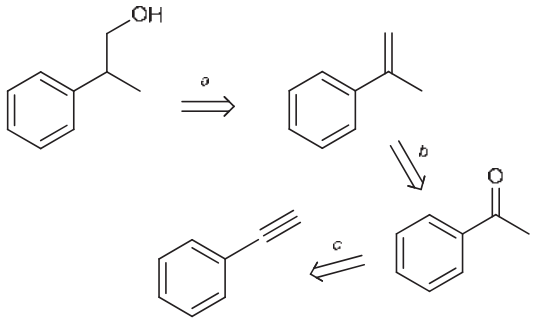
The entire proposed synthesis is summarized here:



(b) We begin by asking the following two questions:

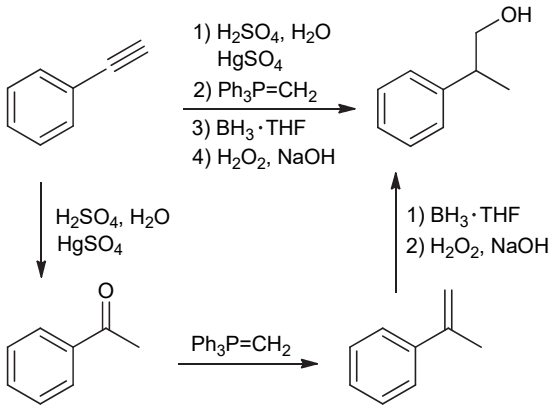
1) *Is there a change in the carbon skeleton?* Yes, the carbon skeleton is increasing in size by one carbon atom.
2) *Is there a change in the functional groups?* Yes, the starting material has a triple bond, and the product is an alcohol.

Now we must propose a strategy for achieving these changes. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.



a. The desired product is a primary alcohol, which can be made via hydroboration-oxidation of an alkene.
b. The alkene can be made from a ketone via a Wittig reaction.
c. The ketone can be made from the starting alkyne (via acid-catalyzed hydration).

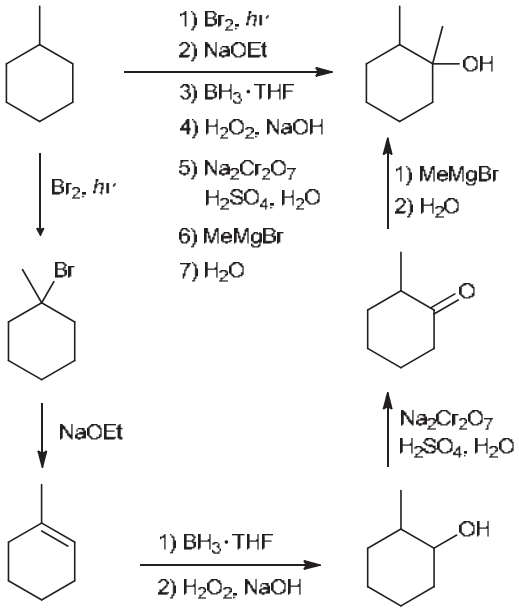
Now let's draw the forward scheme. The starting alkyne is treated with aqueous acid in the presence of mercuric sulfate to give a hydration reaction (the initially formed enol rapidly tautomerizes to give a methyl ketone). This ketone is then treated with a Wittig reagent, thereby forming the crucial carbon-carbon bond. The resulting alkene is then expected to undergo hydroboration-oxidation to give *anti*-Markovnikov addition of H and OH across the double bond, affording the desired alcohol.



(c) There are certainly many acceptable solutions to this problem. One such solution is virtually identical to the

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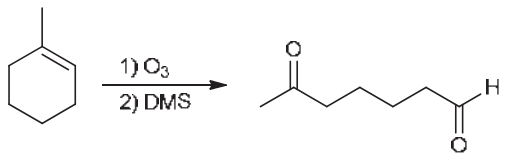
solution presented for Problem **19.40a**, except that the last step has been replaced with a Grignard reaction:



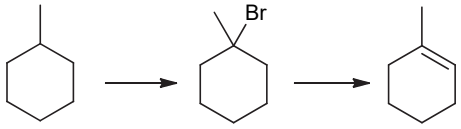
(d) We begin by asking the following two questions:

1) *Is there a change in the carbon skeleton?* Yes, the starting material is cyclic and the product is acyclic. In addition, the starting material has seven carbon atoms, while the product has nine. Two carbon atoms must be installed and the ring must be opened.
2) *Is there a change in the functional groups?* Yes, the starting material lacks a functional group, and the product has two functional groups (C=O and OH).

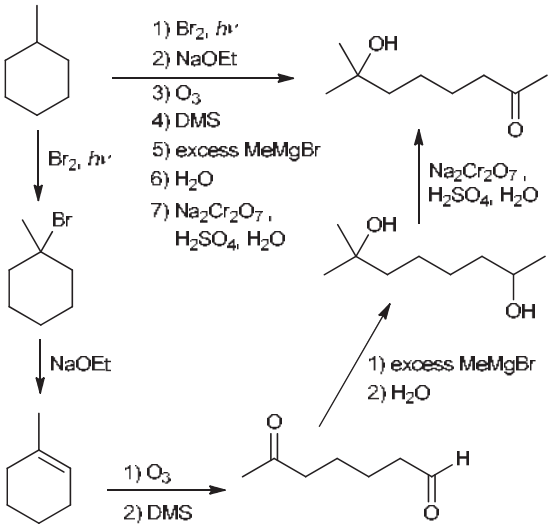
Now we must propose a strategy for achieving these changes. The ring can be opened via ozonolysis, but only if we first install a double bond in the ring:



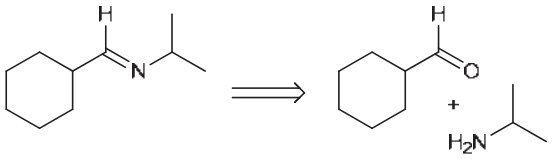
The necessary cycloalkene can be generated from the starting material in just two steps: 1) radical bromination installs a bromine atom in the tertiary position, and 2) subsequent treatment of the resulting tertiary alkyl halide with a strong base (such as sodium ethoxide) gives the cycloalkene above:



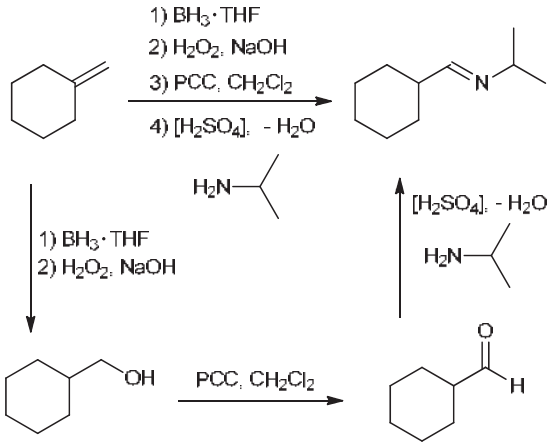
This cycloalkene then undergoes ozonolysis to open the ring. After ozonolysis has been performed, the resulting dicarbonyl compound can be converted into the product in just two steps. First, treatment with excess methyl magnesium bromide installs two methyl groups, giving a diol. When treated with a strong oxidizing agent, the tertiary OH group is unaffected, while the secondary OH group is oxidized to a ketone.



(e) The product is an imine, which can be made from the corresponding aldehyde and primary amine:

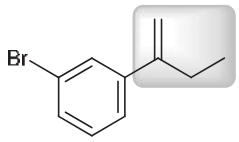


This aldehyde can be made from the starting material via hydroboration-oxidation, followed by oxidation with PCC (or DMP or Swern), as shown:

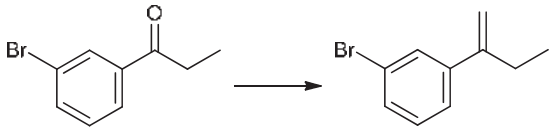


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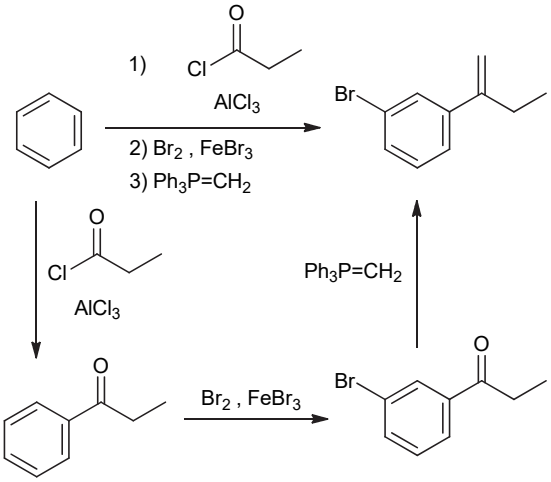
(f) While we certainly learned a way to install a bromine atom on a ring (bromination) we did not learn a way to install the other substituent (highlighted):



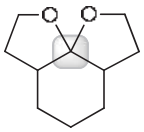
However, this substituent can be made from the following ketone, using a Wittig reaction:



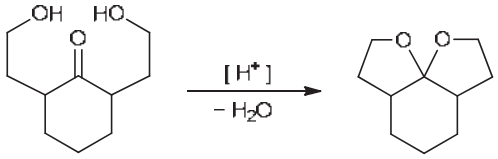
And we have indeed seen a way to install an acyl group on a ring (Friedel-Crafts acylation). The two substituents are *meta* to each other, so we must utilize the directing effects of the acyl group to install the bromine atom in the correct location (Br is an *ortho-para* director, so it cannot be installed first). After the acyl group has been installed, the product can be obtained via bromination (which installs a bromine atom in the *meta* position), followed by a Wittig reaction, as shown:



(g) The desired product has a carbon atom (highlighted) connected to two oxygen atoms, so this compound is an acetal:

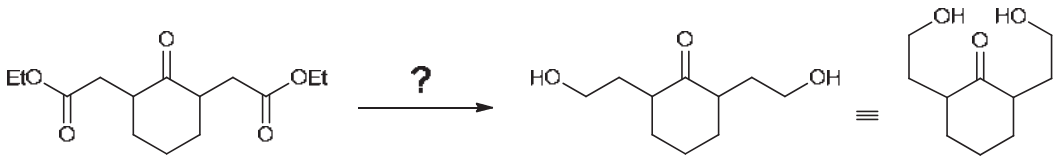


As such, the last step of our synthesis might be formation of the acetal group from the following precursor:



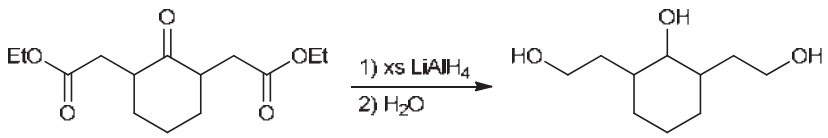
Notice that the reaction occurs in an intramolecular fashion because the two OH groups and the carbonyl group are tethered together.

Now we must determine how to make the precursor above from the starting material:

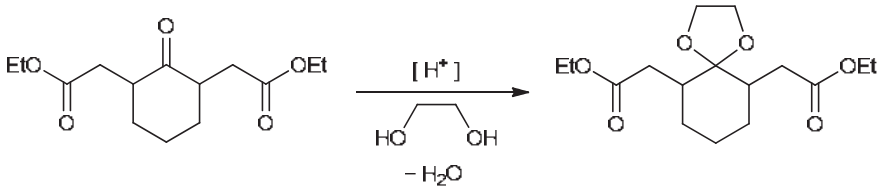


It might be tempting to treat the starting material with a reducing agent, such as $LiAlH_4$ (xs), so it will reduce the two ester groups. Unfortunately, excess $LiAlH_4$ will also reduce the ketone:

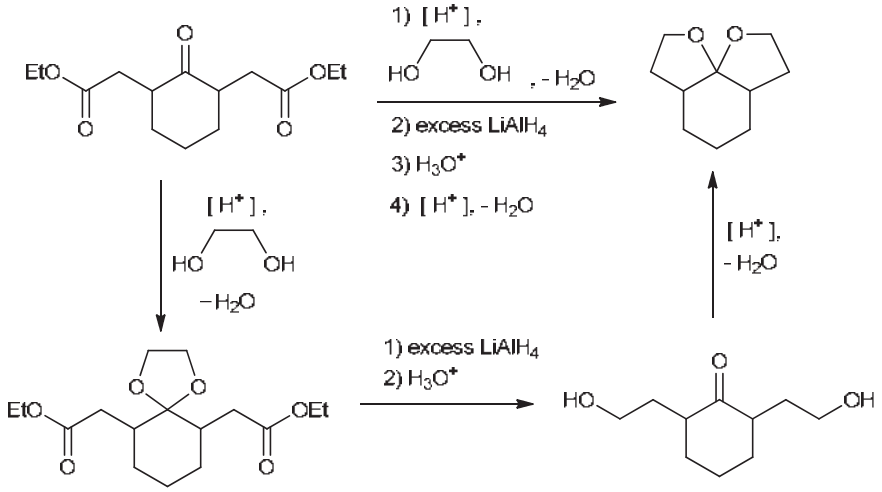
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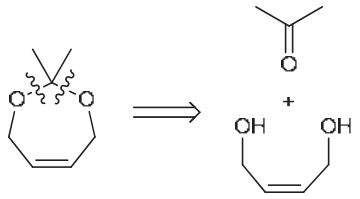
And once all three functional groups are reduced to a triol, we are stuck, because we have not learned a way to selectively oxidize the secondary OH group. This problem can be circumvented by using a protecting group first. That is, the ketone can be converted into an acetal group, thereby protecting it prior to the reduction step:



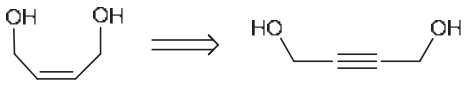
Notice that the ester groups are NOT converted into acetals. Only the ketone group is converted to an acetal. Subsequent reaction with xs $LiAlH_4$ causes reduction of both ester groups (the acetal group is stable under these conditions). Treatment with aqueous acid will then protonate the dianion (each ester group is reduced to an alkoxide when treated with xs $LiAlH_4$). In addition, aqueous acid will also remove the acetal group, converting it back into a ketone. This allows us to perform the final step of the synthesis (intramolecular acetal formation) to give the product. The complete synthesis is shown here:



19.41. The product shown is a cyclic acetal, which can be made from a diol and acetone:

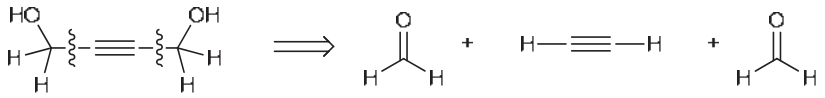


The alkene-diol can be prepared from the corresponding alkyne-diol:

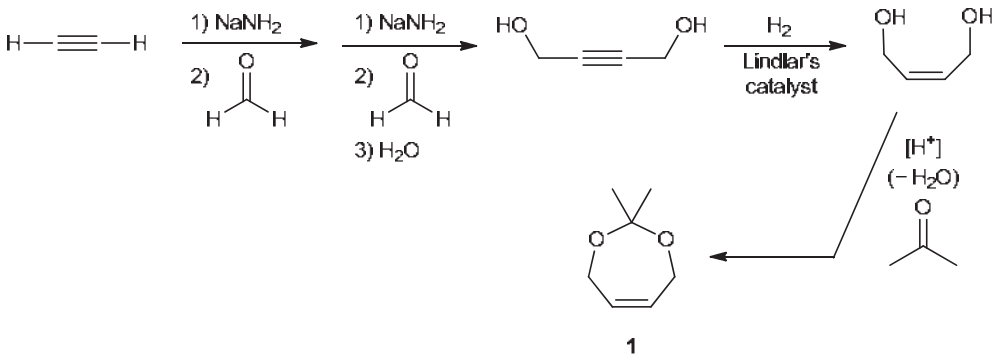


And the alkyne diol can be prepared from acetylene and two equivalents of formaldehyde:

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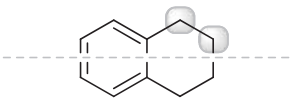


The forward synthesis begins with deprotonation of acetylene and treatment with formaldehyde. Repeating this process gives an alkyne-diol, which can be reduced to a *cis*-alkene-diol. That diol then reacts with acetone under acidic conditions (and removal of water) to give the cyclic acetal, **1**.

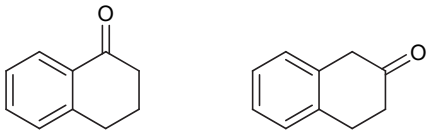


1

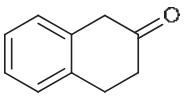
19.42. The signal at 1720 cm^{-1} indicates the presence of a carbonyl group. That carbonyl group is reduced to a methylene (CH_2) group upon treatment with 1,2-ethanedithiol followed by Raney nickel. Therefore, the position of the carbonyl group (in compound **A**) must correspond with one of the methylene groups in the product. Because of symmetry, there are only two unique methylene positions in the product.



Therefore, compound **A** must be one of the following two structures:



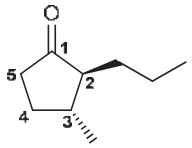
We can differentiate between these two structures based on the nature of the carbonyl group. In the first structure, the carbonyl group is conjugated to the aromatic ring. In the second structure, the carbonyl group is isolated. The signal at 1720 cm^{-1} indicates an isolated carbonyl group (a conjugated carbonyl group would produce a signal near 1680 cm^{-1}). Therefore, compound **A** must be the structure with the isolated carbonyl group.



Compound **A**

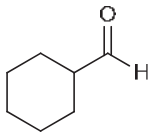
19.43.

(a) We begin by identifying the parent. In this case, the carbonyl group is part of a five-membered ring, so the parent is cyclopentanone. In a cyclic ketone, the carbonyl group is at C1 (by definition). Next, we identify the substituents. There are two (a propyl group at C2 and a methyl group at C3), which are organized alphabetically in the name (methyl precedes propyl). We then assign a configuration to each of the chiral centers, giving the following name:



(2*S*,3*R*)-3-methyl-2-propylcyclopentanone

(b) A cyclic compound containing an aldehyde adjacent to the ring is named as a cycloalkane carbaldehyde. In this case, the aldehyde group is connected to a six-membered ring (cyclohexane), giving the following name:

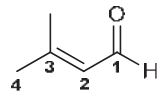


cyclohexanecarbaldehyde

(c) This compound is an aldehyde with a parent of four carbon atoms, so we might think the parent should be butanal. But this parent also contains a double bond, which is indicated by changing "an" to "en" (as in propane vs. propene). Therefore, in this case, it is 2-butenal. Notice that the location of the double bond

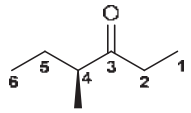
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(between C2 and C3) is indicated with a single locant (2). The location of the aldehyde group is at C1 (by definition) and need not be specified. The methyl group at C3 must be indicated the name. The name does not have a stereodescriptor (*E* or *Z*) because the C=C bond is not stereoisomeric (one of the vinylic positions is connected to two identical groups).



3-methyl-2-butenal

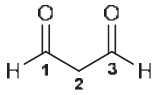
(d) The parent is a chain of six carbon atoms, with the carbonyl group at C3, so the parent is 3-hexanone. Next, we identify the substituents. There is only one: a methyl group at C4. We then assign a configuration to the chiral center, giving the following name:



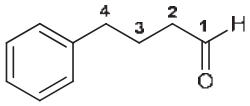
(*S*)-4-methyl-3-hexanone

19.44.

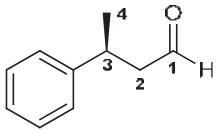
(a) The parent indicates three carbon atoms, and the suffix "dial" indicates two aldehyde groups at either end of the parent chain:



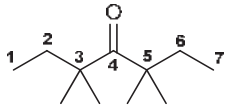
(b) The parent ("butanal") indicates four carbon atoms, and the suffix "al" indicates an aldehyde group (which is at C1, by definition). A phenyl substituent is located at C4:



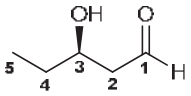
(c) The parent ("butanal") indicates four carbon atoms, and the suffix "al" indicates an aldehyde group (which is at C1, by definition). A phenyl substituent is located at C3, which is a chiral center with the *S* configuration:



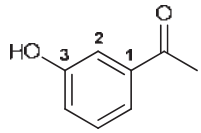
(d) The parent ("heptanone") indicates seven carbon atoms, and the suffix "one" indicates a ketone. The carbonyl group is located at C4, and there are four methyl groups (two at C3 and two at C5):



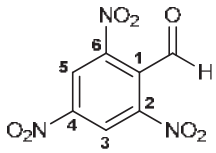
(e) The parent ("pentanal") indicates five carbon atoms, and the suffix "al" indicates an aldehyde group (which is at C1, by definition). An OH group is located at C3, which is a chiral center with the *R* configuration:



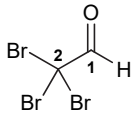
(f) The parent is acetophenone, and there is an OH group in the *meta* position (C3 of the ring):



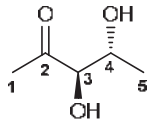
(g) The parent is benzaldehyde, and there are three nitro groups, located at C2, C4, and C6:



(h) The parent is acetaldehyde (which is the common name for ethanal), and there are three bromine atoms. Since C1 must be connected to an H (in order to be an aldehyde), there are only three positions where the bromine atoms can be placed, and they occupy all three of those positions. This is why locants were not necessary in the name.



(i) The parent ("pentanone") indicates five carbon atoms, and the suffix "one" indicates a ketone. The carbonyl group is located at C2, and there are two OH groups, located at C3 and C4, both of which are chiral centers with the *R* configuration:



19.45. We begin by identifying the parent chain, which is a bicyclic structure. Using the skills covered in SkillBuilder 4.5, we assign the parent name for this structure and we assign a locant for the position of the carbonyl group (C2). The configurations of the two chiral centers (the bridgeheads, C1 and C4) are assigned and included in the name, as shown:



(*1S,4R*)bicyclo[2.2.1]heptan-2-one

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19.46. The molecular formula (C_4H_8O) indicates one degree of unsaturation (see Section 14.16), which accounts for the carbonyl group of an aldehyde:



Since there is only one degree of unsaturation (which has now been accounted for), the remaining three carbon atoms do not comprise a ring and do not possess any π bonds. There are only two ways to connect three carbon atoms (without a ring or a π bond), shown here:



Therefore, there are only two aldehydes with the molecular formula C_4H_8O, shown here:

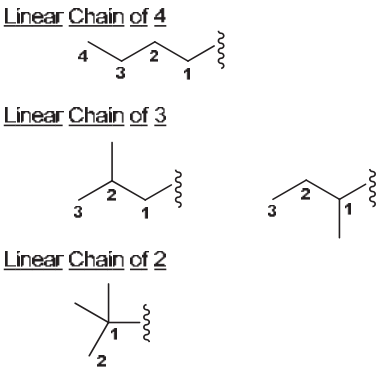


butanal 2-methylpropanal

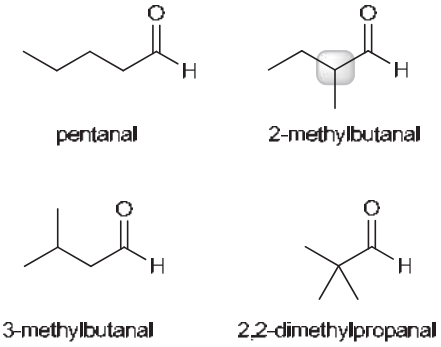
19.47. The molecular formula ($C_5H_{10}O$) indicates one degree of unsaturation (see Section 14.16), which accounts for the carbonyl group of an aldehyde:



Since there is only one degree of unsaturation (which has now been accounted for), the remaining four carbon atoms do not comprise a ring and do not possess any π bonds. There are only four ways to connect four carbon atoms (without a ring or a π bond), shown here:



Therefore, there are only four aldehydes with the molecular formula $C_5H_{10}O$, shown here. One of these aldehydes exhibits a chiral center (highlighted):



pentanal 2-methylbutanal

3-methylbutanal 2,2-dimethylpropanal

19.48. The molecular formula ($C_6H_{12}O$) indicates one degree of unsaturation (see Section 14.16), which accounts for the carbonyl group of a ketone:

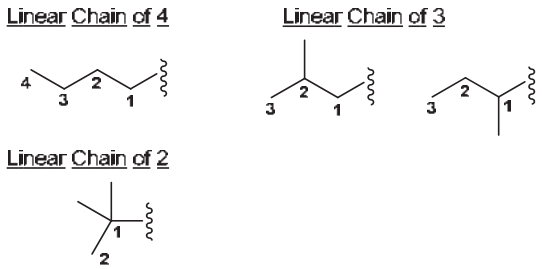


Since there is only one degree of unsaturation (which has now been accounted for), the remaining five carbon atoms do not comprise a ring and do not possess any π bonds. Now let's consider all of the different unique ways of connecting five carbon atoms around a carbonyl group. We can immediately rule out any isomers for which we place all five carbon atoms on one side of the carbonyl group, as that would generate an aldehyde, not a ketone. So, either there are four carbon atoms on one side of the carbonyl group and one carbon atom on the other side, OR, there are two carbon atoms on one side and three carbon atoms on the other side. We must explore each of these possibilities.

If we first consider having two carbon atoms on one side and three carbon atoms on the other side, there are only two such isomers, shown here:

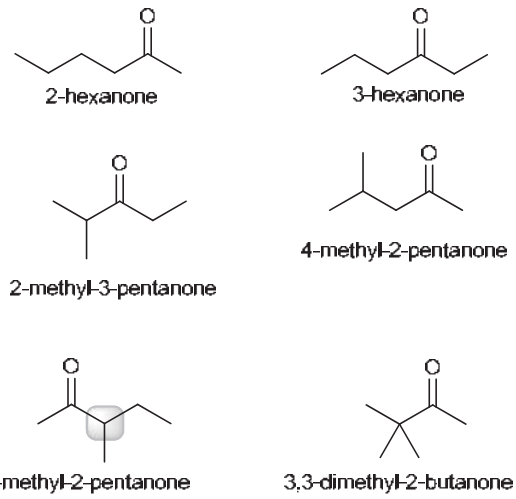


Now we consider having four carbon atoms on one side of the carbonyl group and one carbon atom on the other side. The side with four carbon atoms can be arranged in one of four possible ways, shown here, giving rise to four more isomers:



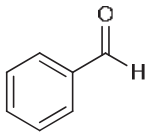
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In total, there are six different isomeric ketones with the molecular formula $C_6H_{12}O$, shown here. One of these ketones exhibits a chiral center (highlighted):

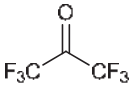


19.49.

(a) The following compound is expected to react with a nucleophile more rapidly, because aldehydes are more reactive than ketones toward nucleophiles, as a result of electronic effects (aldehydes are more electrophilic than ketones) as well as steric effects (See Section 19.4).

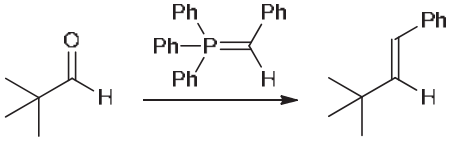


(b) The following compound is expected to react with a nucleophile more rapidly, because each of the trifluoromethyl groups is very powerfully electron-withdrawing, thereby rendering the carbonyl group even more electrophilic.

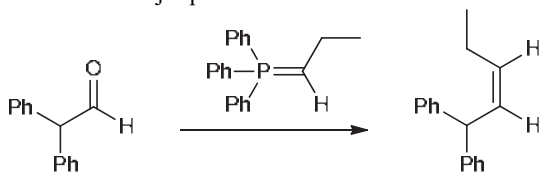


19.50.

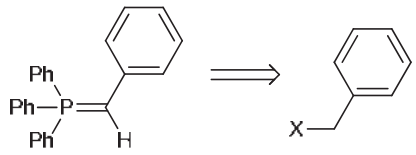
(a) The Wittig reagent attacks the carbonyl group, thereby forming a C=C bond between the carbon atom of the carbonyl group and the carbon atom attached to phosphorus (in the Wittig reagent). In this case, the Wittig reagent is stabilized by the presence of the phenyl group, so we expect the product to have the *E* configuration.

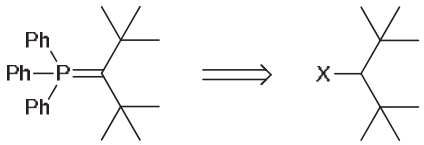


(b) The Wittig reagent attacks the carbonyl group, thereby forming a C=C bond between the carbon atom of the carbonyl group and the carbon atom attached to phosphorus (in the Wittig reagent). In this case, the Wittig reagent is not stabilized, so we expect the *Z* alkene as the major product:



19.51. Each of the Wittig reagents can be made from the corresponding alkyl halide, as shown:

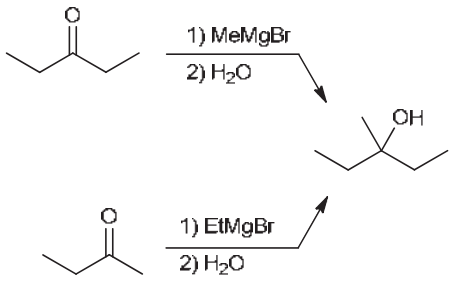




In the first case, the alkyl halide is primary, while in the second case, the alkyl halide is secondary (although this secondary alkyl halide is likely to behave much like a tertiary alkyl halide in that it exhibits significant steric hindrance). The latter alkyl halide will be more difficult to convert into a Wittig reagent, because it is too sterically hindered to undergo an S_N2 attack.

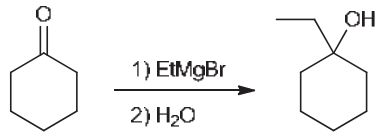
19.52.

(a) A Grignard reagent will attack the carbonyl group of a ketone, thereby forming a C-C bond and giving a tertiary alcohol. In this case, there are two possible routes that can be used to form the product via a Grignard reaction (the Grignard reaction can be used to install either a methyl group or an ethyl group), as shown:

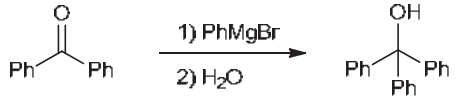


(b) A Grignard reagent will attack the carbonyl group of a ketone, thereby forming a C-C bond and giving an alcohol. In this case, treating cyclohexanone with ethyl magnesium bromide (followed by water work-up) gives the desired product:

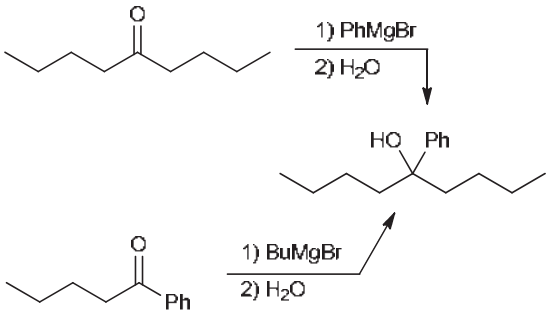
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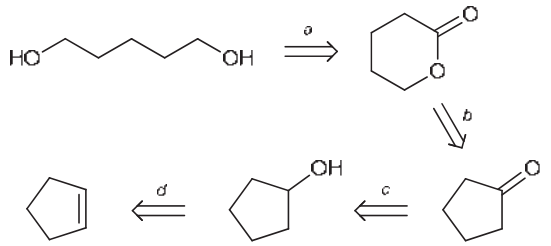
(c) Treating benzophenone with phenyl magnesium bromide (followed by water work-up) will afford the desired product via a Grignard reaction:



(d) A Grignard reagent will attack the carbonyl group of a ketone, thereby forming a C-C bond and giving an alcohol. In this case, there are two possible routes that can be used to form the product via a Grignard reaction (the Grignard reaction can be used to install either a phenyl group or a butyl group), as shown:

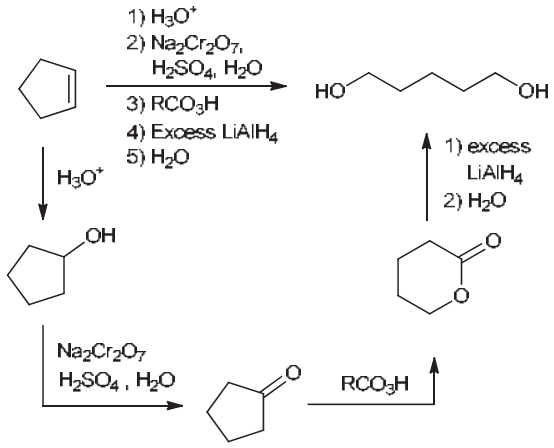


19.53. The following retrosynthetic analysis relies on a different strategy for opening the ring (rather than ozonolysis). Specifically, the final step might involve opening a cyclic ester (called a lactone) into the desired diol via reduction with $LiAlH_4$ (as seen in Section 12.4). This ester can be made from the starting material, as shown. An explanation of each of the steps (*a-d*) follows.



a. The diol can be made from the lactone shown, upon reduction with xs $LiAlH_4$.
b. The lactone can be made from the corresponding ketone (cyclopentanone).
c. Cyclopentanone can be made via oxidation of the corresponding secondary alcohol (cyclopentanol).
d. Cyclopentanol can be made from cyclopentene via acid-catalyzed hydration.

Now let's draw the forward scheme. Cyclopentene is treated with aqueous acid to give cyclopentanol, which is then oxidized with chromic acid to give cyclopentanone. A Baeyer-Villiger oxidation converts the ketone into a lactone (a cyclic ester), which can then be converted into the product upon treatment with excess $LiAlH_4$ followed by water work-up:



19.54.

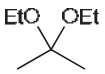
(a) A ketone is converted into an imine upon treatment with ammonia in acid catalyzed conditions (with removal of water).



(b) A ketone is converted into an imine upon treatment with a primary amine in acid catalyzed conditions (with removal of water).



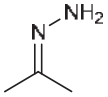
(c) A ketone is converted into an acetal upon treatment with two equivalents of an alcohol in acid catalyzed conditions (with removal of water).



(d) A ketone is converted into an enamine upon treatment with a secondary amine in acid catalyzed conditions (with removal of water).

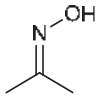


(e) A ketone is converted into a hydrazone upon treatment with hydrazine in acid catalyzed conditions (with removal of water).



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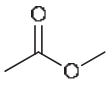
(f) A ketone is converted into an oxime upon treatment with hydroxylamine in acid catalyzed conditions (with removal of water).



(g) A ketone is reduced to a secondary alcohol upon treatment with a reducing agent such as $NaBH_4$ (methanol serves as a proton source during the reaction).



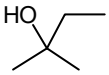
(h) A ketone is converted into an ester upon treatment with a peroxyacid. This process is called a Baeyer-Villiger oxidation.



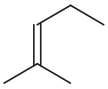
(i) A ketone is converted into a cyanohydrin upon treatment with HCN and KCN.



(j) Ethyl magnesium bromide is a Grignard reagent (a very strong nucleophile) and it will attack a ketone to give a tertiary alcohol (with installation of the ethyl group at the α position to the OH group):



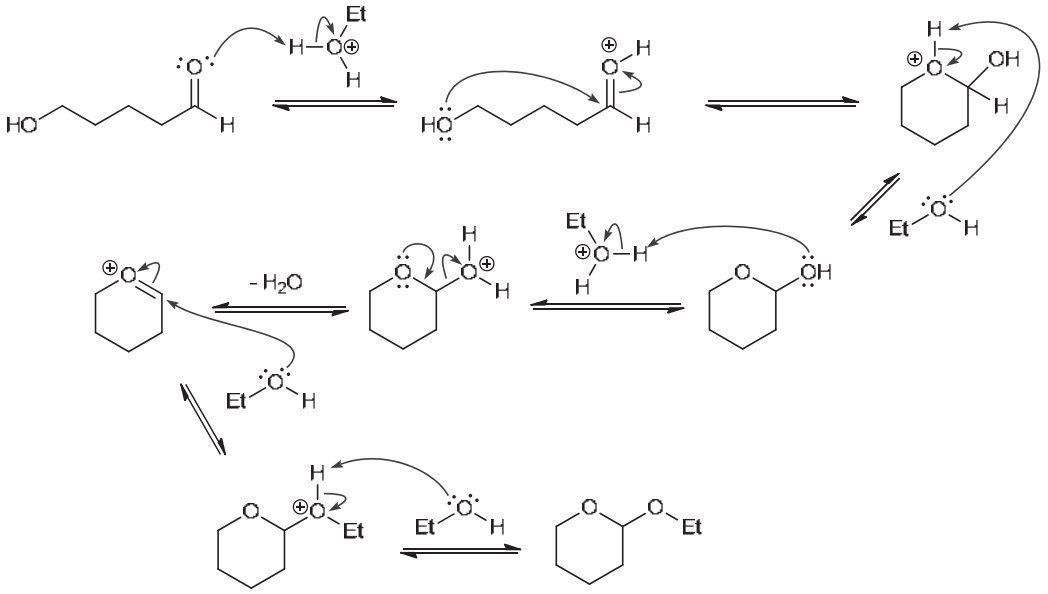
(k) A ketone is converted into an alkene when treated with a Wittig reagent. This particular Wittig reagent installs three carbon atoms, to give the following product:



(l) A ketone is reduced to a secondary alcohol upon treatment with $LiAlH_4$ followed by water work-up.

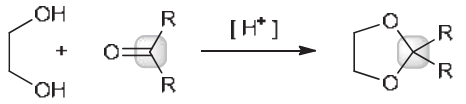


19.55. Under acid-catalyzed conditions, the carbonyl group can be protonated, rendering it more electrophilic, and subject to attack by a nucleophile. There are two options for the attacking nucleophile in the second step of the mechanism: 1) the protonated carbonyl group is tethered to an OH group that can function as a nucleophile and attack the protonated carbonyl group in an intramolecular fashion, or 2) the reagent (ethanol) can serve as a nucleophile and attack the protonated carbonyl group. Indeed, both of these processes will occur, as the product is an acetal. But we must decide which one is likely to occur first. As a general rule, intramolecular reactions will occur more rapidly than intermolecular reactions. As such, the second step of the mechanism will show the OH group attacking the protonated carbonyl group in an intramolecular fashion to give an oxonium ion, which then loses a proton to give a hemiacetal (the base for this step is likely a molecule of ethanol). Protonation of the hemiacetal gives a good leaving group (water) which leaves to give a resonance-stabilized cation that is attacked by ethanol. The resulting oxonium ion is then deprotonated to afford the product.

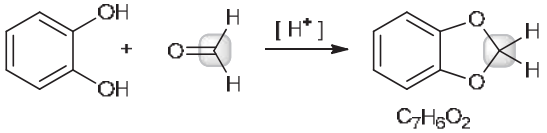


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19.56. When ethylene glycol is treated with a ketone or aldehyde in acidic conditions, a cyclic acetal is formed:



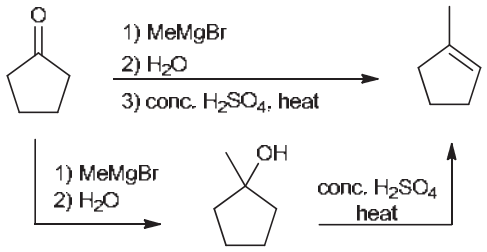
Catechol also has two OH groups (like ethylene glycol). So, when treated with a ketone or aldehyde in acidic conditions, catechol can behave much like ethylene glycol, giving formation of a cyclic acetal:



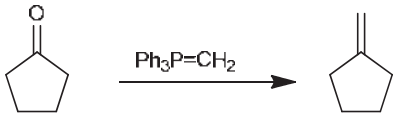
$C_7H_6O_2$

19.57.

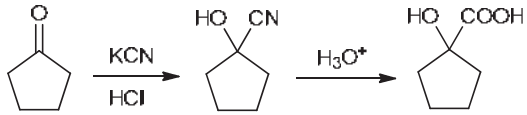
(a) This transformation requires installation of a methyl group, which can be achieved with a Grignard reaction (by treating the starting material with methyl magnesium bromide, followed by aqueous work-up). The resulting tertiary alcohol can then be heated with concentrated sulfuric acid to give an E1 process, generating the desired alkene.



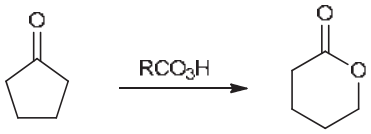
(b) This transformation requires installation of a carbon atom, while converting the carbonyl group into a C=C bond. This can be achieved in just one step, via a Wittig reaction:



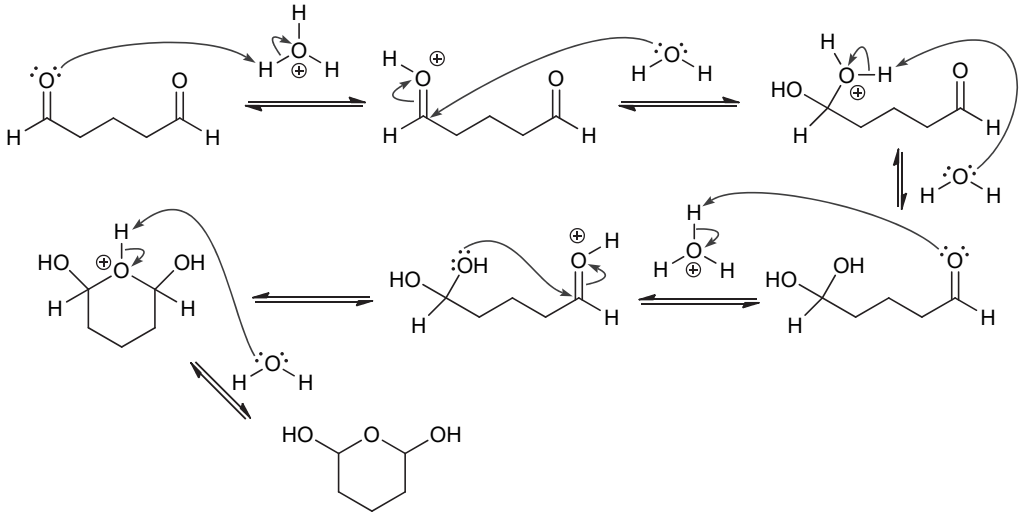
(c) This transformation can be achieved in just two steps: 1) conversion of the ketone to a cyanohydrin, followed by 2) hydrolysis of the cyano group to give a carboxylic acid:



(d) This transformation involves insertion of an oxygen atom next to the carbonyl group of a ketone, thereby converting the ketone into a cyclic ester. This can be accomplished with a Baeyer-Villiger oxidation, which requires the use of a peroxyacid.



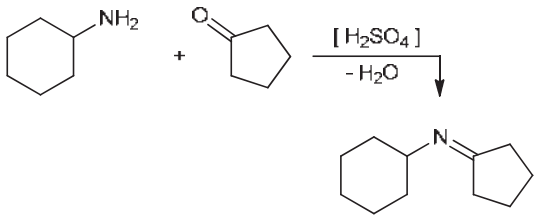
19.58. Under acid-catalyzed conditions, one of the carbonyl groups can be protonated, rendering it more electrophilic, and subject to attack by a nucleophile. Water serves as a nucleophile, attacking the protonated carbonyl group to give an oxonium ion, which then loses a proton (the base for this deprotonation step is likely a molecule of water). Under these conditions, the other carbonyl group can be protonated, rendering it more electrophilic (just as we saw with the first carbonyl group), and subject to attack by a nucleophile. One of the OH groups (present in the intermediate), can then function as a nucleophile and attack the protonated carbonyl group, giving an oxonium ion, which is deprotonated to give the product.



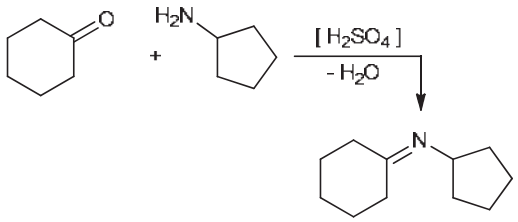
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19.59.

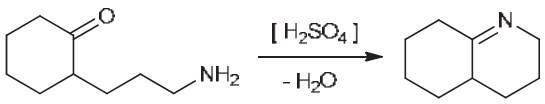
(a) An imine can be prepared from a ketone (or aldehyde) and a primary amine. To determine the starting ketone and starting amine that must be used, we consider the location of the C=N bond in the imine. The carbon atom of this bond must have been a carbonyl group in the starting ketone, and the nitrogen atom must have been connected to two protons in the starting amine. So, the following starting materials should give the desired imine (under acid-catalyzed conditions with removal of water):



(b) An imine can be prepared from a ketone (or aldehyde) and a primary amine. To determine the starting ketone and starting amine that must be used, we consider the location of the C=N bond in the imine. The carbon atom of this bond must have been a carbonyl group in the starting ketone, and the nitrogen atom must have been connected to two protons in the starting amine. So, the following starting materials should give the desired imine (under acid-catalyzed conditions with removal of water):

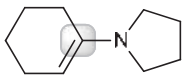


(c) An imine can be prepared from a ketone (or aldehyde) and a primary amine. To determine the starting ketone and starting amine that must be used, we consider the location of the C=N bond in the imine. The carbon atom of this bond must have been a carbonyl group in the starting ketone, and the nitrogen atom must have been connected to two protons in the starting amine. In this case, the C=N bond is incorporated into a ring, which means that the starting ketone and the starting amine must have been tethered to each other in the starting material (thereby closing into a cyclic imine). That is, imine formation must occur in an intramolecular fashion (under acid-catalyzed conditions with removal of water):

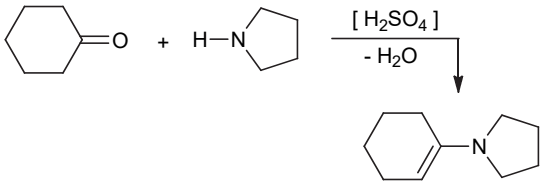


19.60.

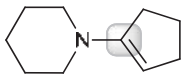
(a) An enamine can be prepared from a ketone (or aldehyde) and a secondary amine. To determine the starting ketone and starting amine that must be used, we consider the location of the vinylic carbon atom (highlighted) connected directly to nitrogen:



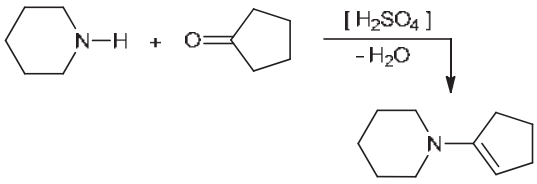
This carbon atom must have been a carbonyl group in the starting ketone, and the nitrogen atom must have been connected to one proton in the starting amine. So, the following starting materials should give the desired enamine (under acid-catalyzed conditions with removal of water):



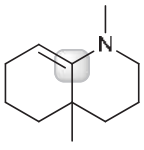
(b) An enamine can be prepared from a ketone (or aldehyde) and a secondary amine. To determine the starting ketone and starting amine that must be used, we consider the location of the vinylic carbon atom (highlighted) connected directly to nitrogen:



This carbon atom must have been a carbonyl group in the starting ketone, and the nitrogen atom must have been connected to one proton in the starting amine. So, the following starting materials should give the desired enamine (under acid-catalyzed conditions with removal of water):

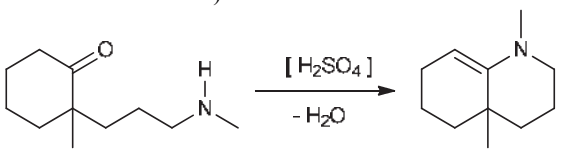


(c) An enamine can be prepared from a ketone (or aldehyde) and a secondary amine. To determine the starting ketone and starting amine that must be used, we consider the location of the vinylic carbon atom (highlighted) connected directly to nitrogen:



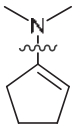
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This carbon atom must have been a carbonyl group in the starting ketone, and the nitrogen atom must have been connected to one proton in the starting amine. In this case, the C-N bond of the enamine group is incorporated into a ring, which means that the starting ketone and the starting amine must have been tethered to each other in the starting material (thereby closing into a cyclic enamine). That is, enamine formation must occur in an intramolecular fashion (under acid-catalyzed conditions with removal of water):



19.61.

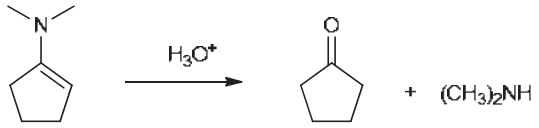
(a) To determine the products of hydrolysis of an enamine, we must first identify the bond that will undergo cleavage. Bond cleavage is expected for the bond between the nitrogen atom and the sp^2-hybridized carbon atom to which it is attached:



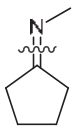
Therefore, the following carbon atom will be converted into a carbonyl group:



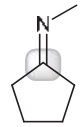
As a result of the C-N bond cleavage, the carbon atom becomes a carbonyl group, and the nitrogen atom will accept a proton to generate a secondary amine (dimethyl amine):



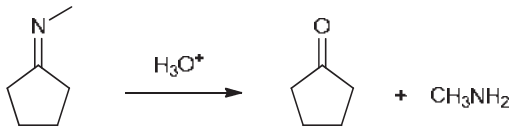
(b) To determine the products of hydrolysis of an imine, we must first identify the bond that will undergo cleavage. Bond cleavage is expected for the C=N bond:



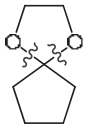
Therefore, the following carbon atom will be converted into a carbonyl group:



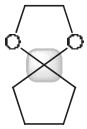
As a result of cleavage of the C=N bond, the carbon atom becomes a carbonyl group, and the nitrogen atom will accept two protons to generate a primary amine (methyl amine):



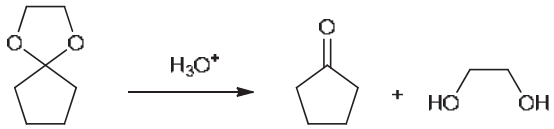
(c) To determine the products of hydrolysis of an acetal, we must first identify the bonds that will undergo cleavage. Bond cleavage is expected for the C-O bonds of the acetal group:



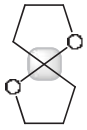
Therefore, the following carbon atom will be converted into a carbonyl group:



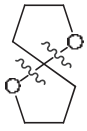
In the process, a diol is released, as shown:



(d) The starting compound exhibits a carbon atom that is connected to two oxygen atoms, as shown, and is therefore an acetal:

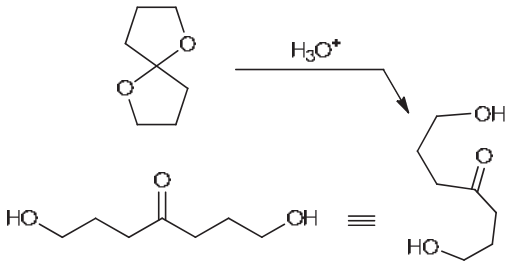


When an acetal is treated with aqueous acid, it will undergo hydrolysis. During acetal hydrolysis, cleavage occurs for the C-O bonds of the acetal group:

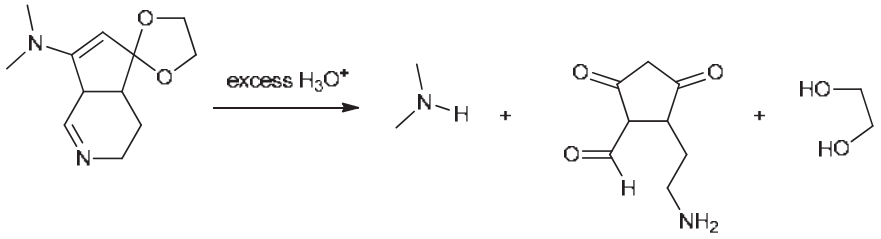


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Each of these bonds is broken, thereby converting the carbon atom of the acetal group into a carbonyl group. In the process, each of the oxygen atoms will accept a proton to become an OH group, giving the following product, which exhibits a carbonyl group, as well as two OH groups:

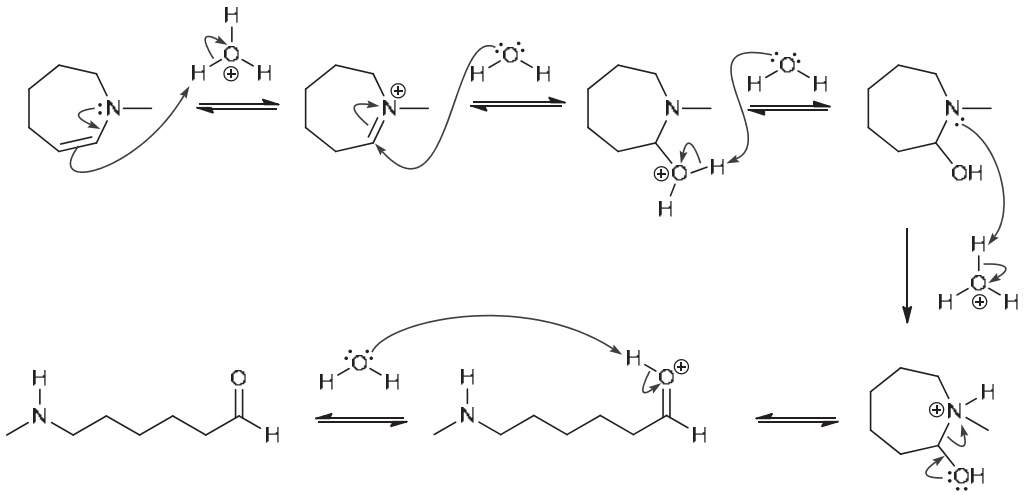


19.62. This compound contains three different functional groups that will each undergo hydrolysis. The enamine (upper left corner) is hydrolyzed to give a ketone and a secondary amine. The imine (bottom left) is hydrolyzed to give an aldehyde and an amino group (tethered together). And finally, the cyclic acetal is hydrolyzed to give a ketone and ethylene glycol, as shown:



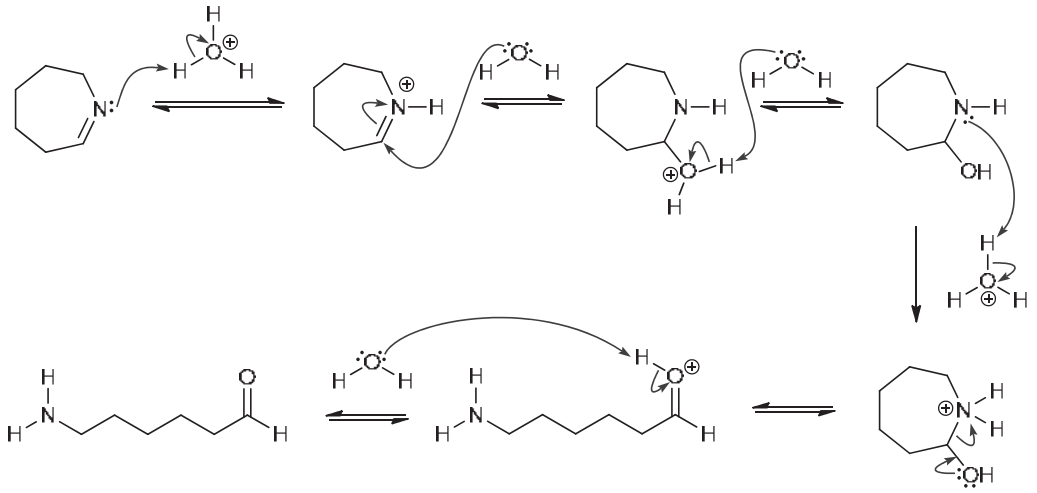
19.63.

(a) This transformation involves hydrolysis of an enamine under acidic conditions, and therefore, we propose a mechanism that is the reverse of the mechanism for enamine formation (all of the same intermediates, but in reverse order). Under acid-catalyzed conditions, the π bond of the enamine can be protonated, giving an iminium ion which is then attacked by water to give an oxonium ion. Loss of a proton gives a carbinolamine intermediate. Protonation of the amino group gives a good leaving group, which leaves to give a resonance-stabilized cation that is deprotonated to give the product.

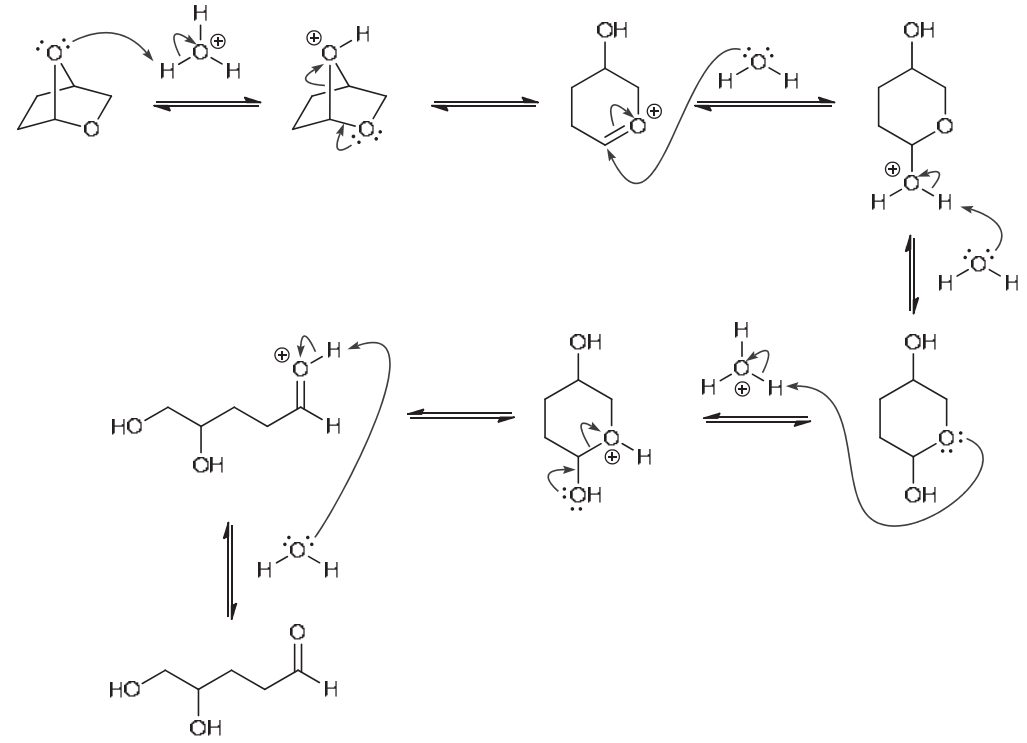


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(b) This transformation involves hydrolysis of an imine under acidic conditions, and therefore, we propose a mechanism that is the reverse of the mechanism for imine formation (all of the same intermediates, but in reverse order). Under acid-catalyzed conditions, the imine is protonated, giving an iminium ion which is then attacked by water to give an oxonium ion. Loss of a proton gives a carbinolamine intermediate. Protonation of the amino group gives a good leaving group, which leaves to give a resonance-stabilized cation that is deprotonated to give the product.



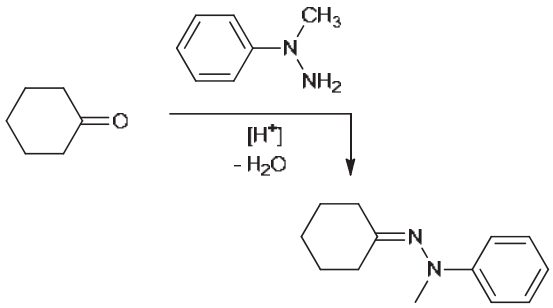
(c) This transformation involves hydrolysis of an acetal under acidic conditions, and therefore, we propose a mechanism that is the reverse of the mechanism for acetal formation (all of the same intermediates, but in reverse order). Under acid-catalyzed conditions, one of the oxygen atoms can be protonated (we can protonate either oxygen atom, and the end result will be the same), giving an oxonium ion. Loss of leaving group gives a resonance-stabilized cation that can be attacked by water to give another oxonium ion. Deprotonation gives a hemiacetal (water likely functions as the base for this step). Protonation, followed by loss of a leaving group gives a protonated aldehyde, which is deprotonated to give the product.



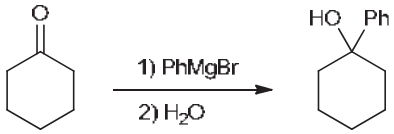
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19.64.

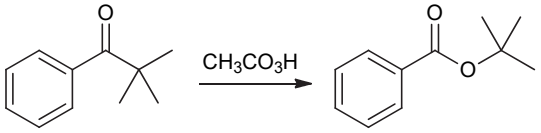
(a) The starting material is a ketone, and the reagent is a substituted derivative of hydrazine. We therefore expect the following substituted hydrazone as a product:



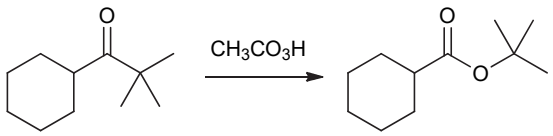
(b) The starting material is a ketone, and the reagent is phenyl magnesium bromide (a Grignard reagent, which is a very strong nucleophile). The Grignard reagent will attack the ketone to give a tertiary alcohol (with installation of the phenyl group at the α position):



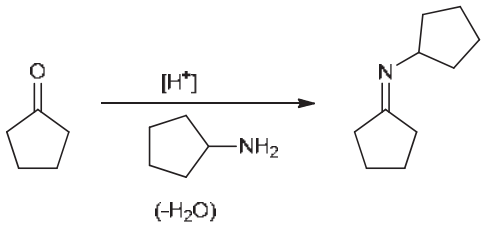
(c) The starting material is a ketone, and the reagent (CH_3CO_3H) is a peroxy acid, which indicates a Baeyer-Villiger reaction, thereby converting the ketone into an ester. We expect that the oxygen atom will be inserted on the right side (tertiary) rather than left side (phenyl), because of differences in migratory aptitude (tertiary > phenyl).



(d) The starting material is a ketone, and the reagent (CH_3CO_3H) is a peroxy acid, which indicates a Baeyer-Villiger reaction, thereby converting the ketone into an ester. We expect that the oxygen atom will be inserted on the right side (tertiary) rather than left side (secondary), because of differences in migratory aptitude (tertiary > secondary).

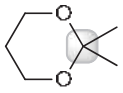


(e) A ketone is converted into an imine upon treatment with a primary amine in acid catalyzed conditions (with removal of water). In the process, the C=O bond is replaced a C=N bond.

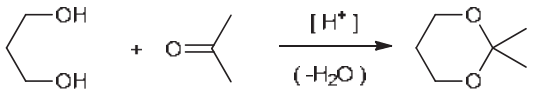


19.65.

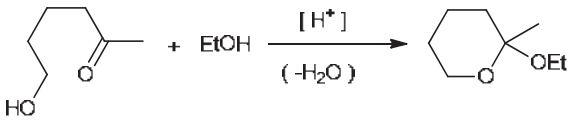
(a) The desired product is a cyclic acetal, which will require a diol and the appropriate ketone or aldehyde. To determine the identity of the starting ketone or aldehyde, we find the carbon atom that is connected to two oxygen atoms (highlighted):



This carbon atom bears the acetal group, so this carbon atom must have been the carbonyl group in the starting materials, as shown. The starting materials are 1,3-propanediol and acetone.



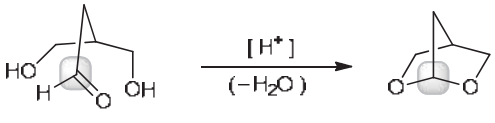
(b) This compound is a cyclic acetal, which can be made from the corresponding hydroxy-ketone and ethanol, as shown:



(c) The product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:

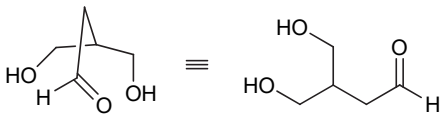


This carbon atom must have been the carbonyl group in the starting material, as shown:

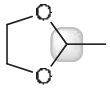


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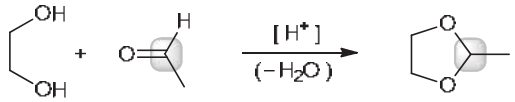
The starting material exhibits a carbonyl group, as well as two OH groups, and can be redrawn like this:



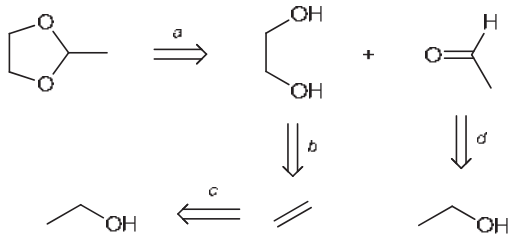
19.66. The desired product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:



This carbon atom must have been the carbonyl group in the starting material, as shown:

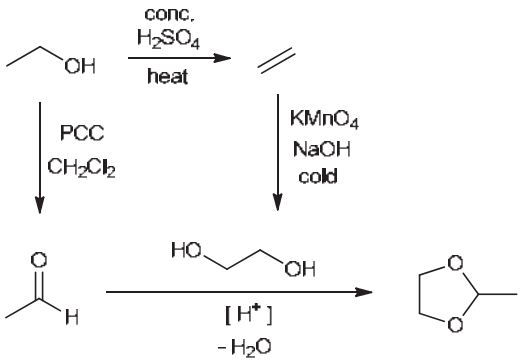


The diol and aldehyde shown above (ethylene glycol and acetaldehyde) can both be prepared from ethanol, as shown in the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

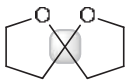


a. The acetal can be made from ethylene glycol and acetaldehyde.
b. Ethylene glycol can be made from ethylene via dihydroxylation.
c. Ethylene can be made from ethanol via acid-catalyzed dehydration.
d. Acetaldehyde can be prepared from ethanol via oxidation (with PCC)

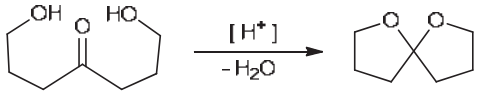
Now let's draw the forward scheme. Ethanol is heated with concentrated sulfuric acid to give ethylene. Subsequent treatment with potassium permanganate (or osmium tetroxide) gives ethylene glycol.
Another equivalent of ethanol is oxidized with PCC (or DMP or Swern) to give an aldehyde, which is then treated with ethylene glycol in acid-catalyzed conditions (with removal of water) to give the desired acetal, as shown.



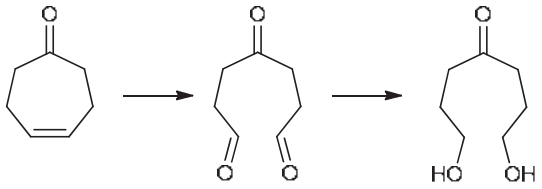
19.67.
(a) The desired product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:



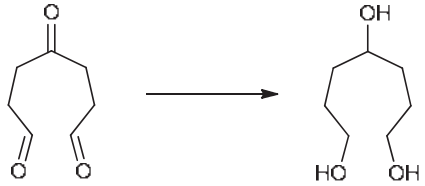
Therefore, this acetal can be made (via acetal formation) from the following dihydroxyketone:



Now we must find a way to convert the starting material into the dihydroxyketone above. It might be tempting to perform ozonolysis on the starting material, followed by reduction:

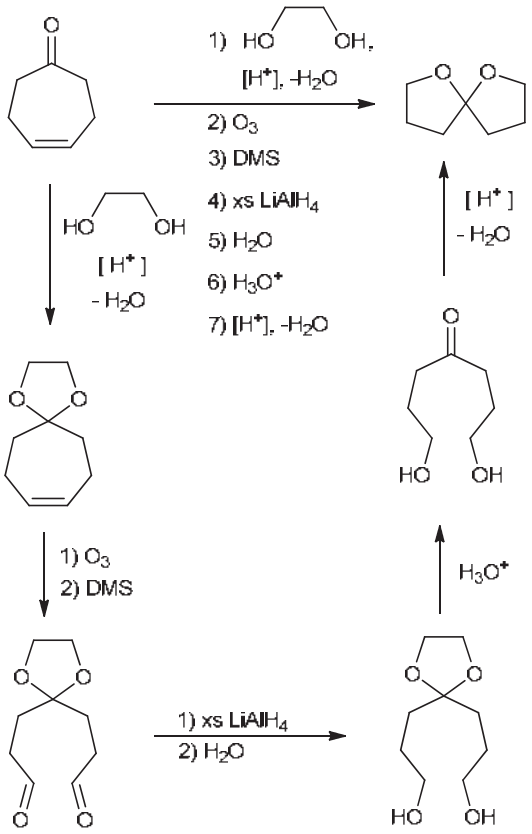


However, the reduction step is problematic, because we don't know a way to selectively reduce the aldehyde groups in the presence of a ketone. Therefore, treatment with a reducing agent (such as $LiAlH_4$) would result in a triol:

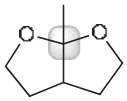


To circumvent this problem, we must first protect the ketone, before opening the ring with ozonolysis.
The entire synthesis is summarized here:

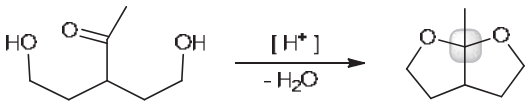
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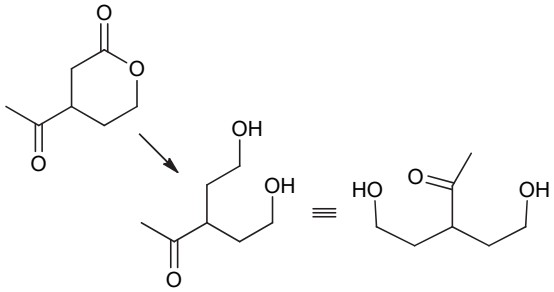
(b) The desired product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:



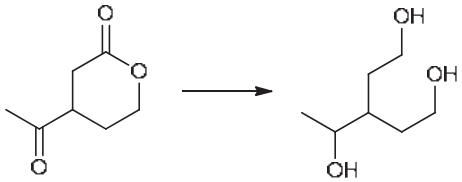
Therefore, this acetal can be made (via acetal formation) from the following dihydroxyketone:



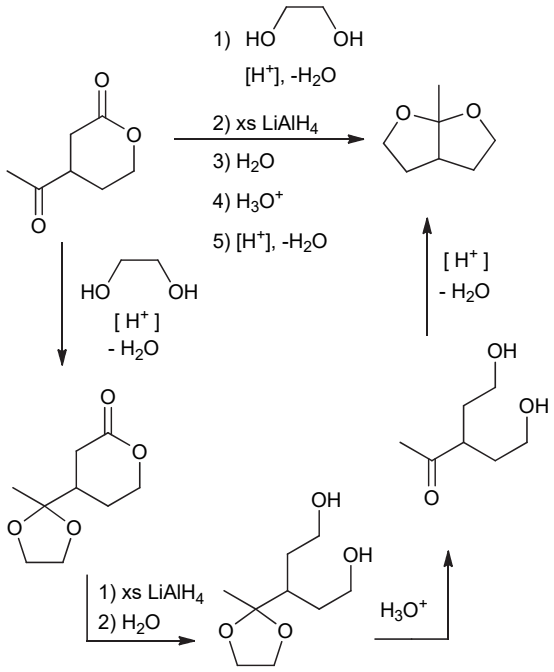
Now we must find a way to convert the starting material into the dihydroxyketone above. It might be tempting to simply reduce the cyclic ester with xs $LiAlH_4$:



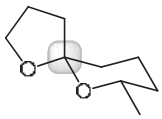
However, this reduction step is problematic, because treatment with a reducing agent (such as $LiAlH_4$) would result in a triol:



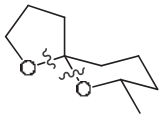
To circumvent this problem, we must first protect the ketone, before opening the ring with reduction. The entire synthesis is summarized here:



19.68. The starting compound exhibits a carbon atom that is connected to two oxygen atoms, as shown, and is therefore an acetal:



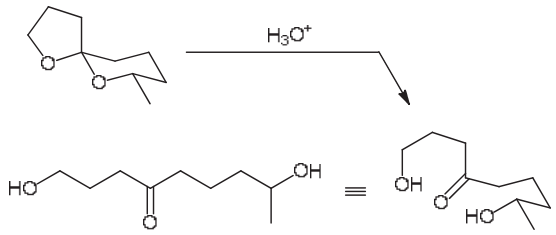
When an acetal is treated with aqueous acid, it is expected to undergo hydrolysis. We first identify the bonds that will undergo cleavage. When an acetal undergoes hydrolysis, cleavage occurs for the C-O bonds of the acetal group:



Each of these bonds is broken, thereby converting the carbon atom of the acetal group into a carbonyl group.

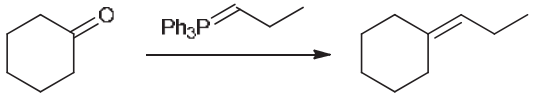
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In the process, each of the oxygen atoms will accept a proton to become an OH group, giving the following product, which exhibits a carbonyl group, as well as two OH groups:

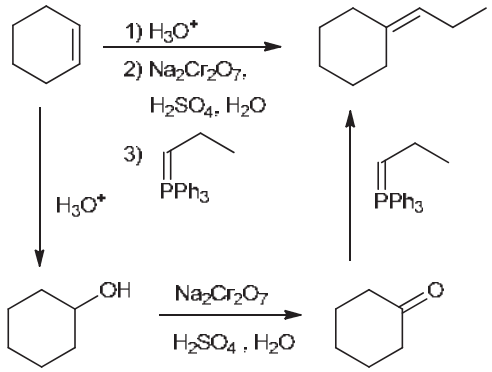


19.69.

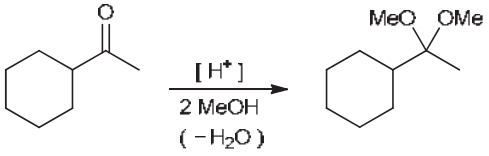
(a) The product has three more carbon atoms than the starting material, which requires a C-C bond-forming reaction. Also, the position of the double bond must be moved. The extra three carbon atoms and the double bond can both be installed in the correct location if the last step of our synthesis is a Wittig reaction:



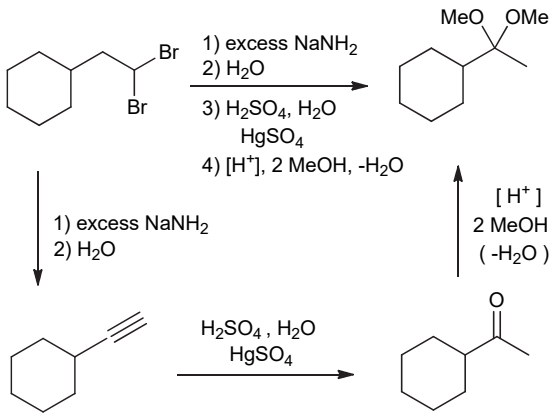
This strategy requires converting the starting alkene (cyclohexene) into the ketone shown above (cyclohexanone), which can be achieved in two steps (via acid-catalyzed hydration, followed by oxidation with chromic acid). A Wittig reaction then gives the final product:



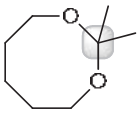
(b) The product is an acetal, which can be made from the corresponding ketone:



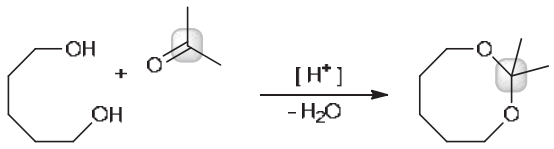
This ketone can be made from the starting material in just two steps. First, the dibromide is converted to an alkyne upon treatment with excess sodium amide (via two successive E2 reactions), followed by water work-up (to protonate the resulting alkynide ion). The terminal alkyne is then treated with aqueous acid, in the presence of mercuric sulfate, giving a hydration reaction. The initially formed enol will rapidly tautomerize to give a ketone. Conversion of the ketone to an acetal then gives the desired product.



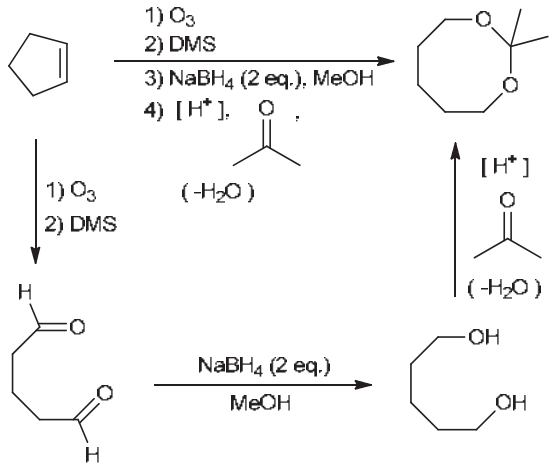
(c) The desired product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:



Therefore, this acetal can be made (via acetal formation) from the following ketone and diol:

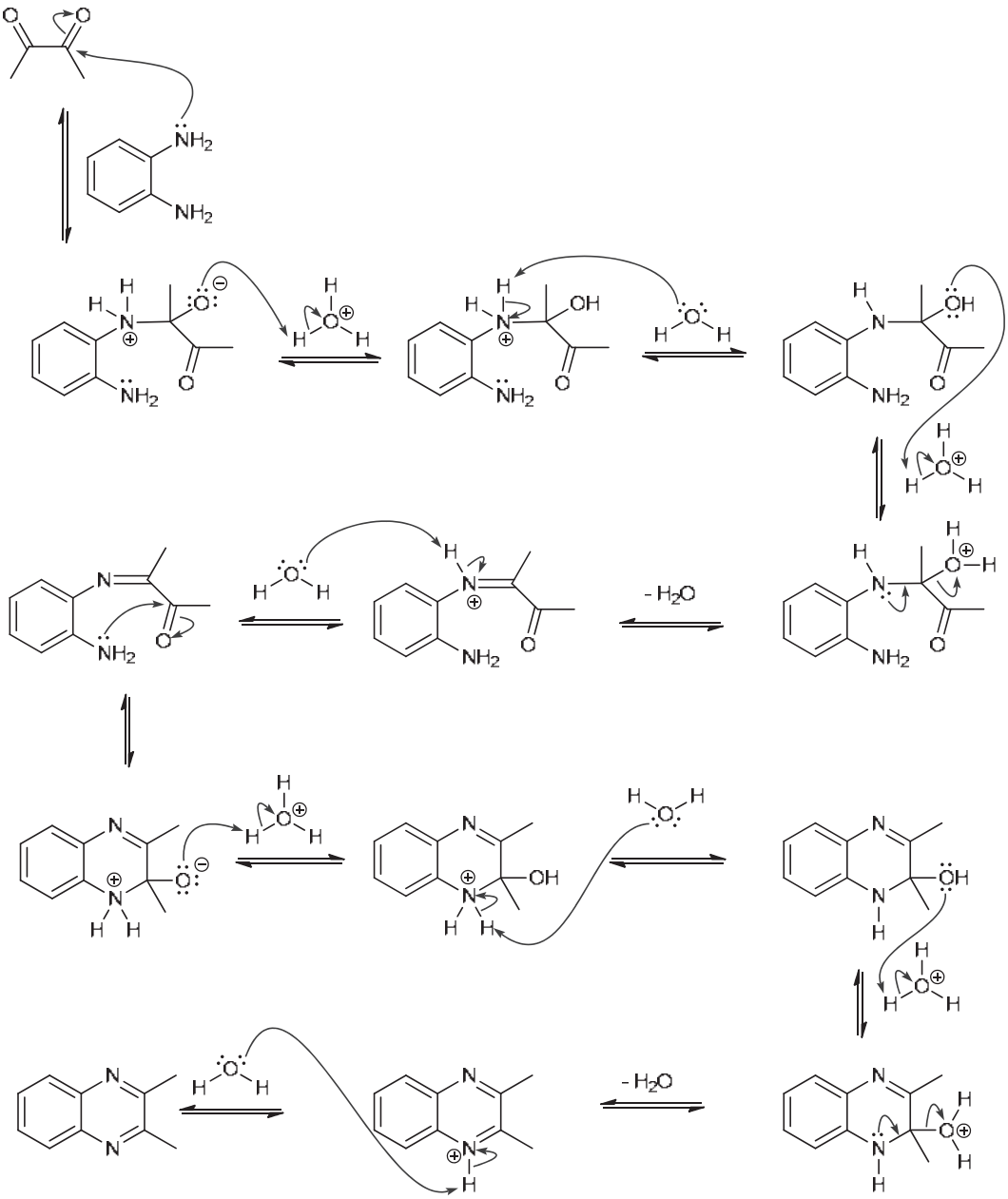


Now we must find a way to convert the starting cycloalkene into the diol shown above. This can be achieved in just two steps. First, the ring is opened with an ozonolysis reaction to produce a dialdehyde. Then, the dialdehyde is reduced to a diol upon treatment with two equivalents of a reducing agent. Acetal formation then gives the final product.



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19.70. The steps of the following mechanism are based on the steps found in Mechanism 19.6 (imine formation). A lone pair on the nitrogen atom attacks one of the carbonyl groups, giving an intermediate that is protonated (under acidic conditions). The resulting cation is then deprotonated, followed by protonation of the OH group, thereby converting a bad leaving group into a good leaving group (water). Loss of the leaving group gives a cation, which is then deprotonated. The second carbonyl group is then attacked by a nucleophile, this time in an intramolecular fashion. The NH_2 group functions as a nucleophile and attacks the carbonyl group, closing a ring. The resulting intermediate is then protonated to remove the negative charge, followed by deprotonation. Protonation of the OH group converts a bad leaving group into a good leaving group (water), which then leaves. The resulting cation is then deprotonated to give the product.

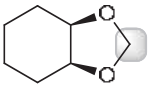


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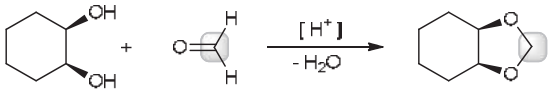
19.71. Cyclopropanone exhibits significant ring strain, with bond angles of approximately 60º. Some of this ring strain is relieved upon conversion to the hydrate, because an sp^2-hybridized carbon atom (that must be 120º to be strain free) is replaced by an sp^3-hybridized carbon atom (that must be only 109.5º to be strain free). In contrast, cyclohexanone is a larger ring and exhibits only minimal ring strain. Conversion of cyclohexanone to its corresponding hydrate does not alleviate a significant amount of ring strain.

19.72. 1,2-dioxane has two adjacent oxygen atoms and is therefore a peroxide. Like other peroxides, it is extremely unstable and potentially explosive.
1,3-dioxane has two oxygen atoms separated by one carbon atom. This compound is therefore an acetal. Like other acetals, it is only stable under basic conditions, but undergoes hydrolysis under mildly acidic conditions.
1,4-dioxane is neither a peroxide nor an acetal. It is therefore stable under basic conditions as well as mildly acidic conditions (like other ethers), and is used as a common solvent because of its inert behavior.

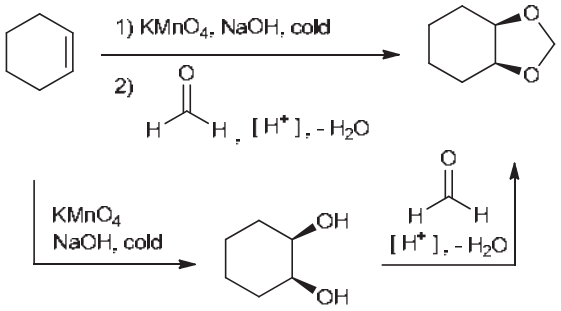
19.73.
(a) The desired product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:



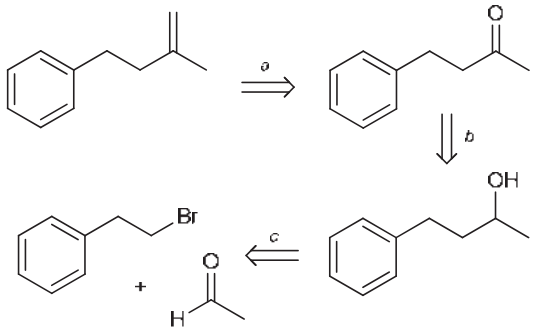
Therefore, this acetal can be made (via acetal formation) from the following diol and formaldehyde:



The diol can be made from the starting alkene in just one step, giving the following two-step synthesis:

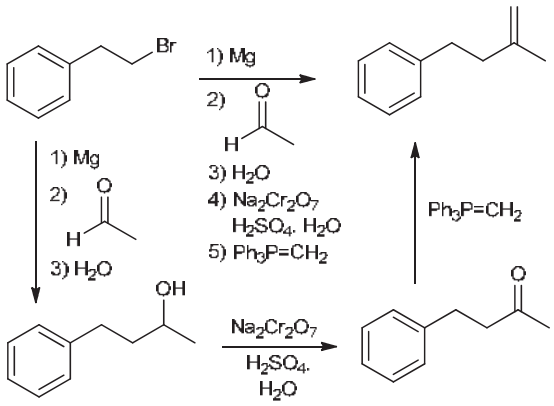


(b) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

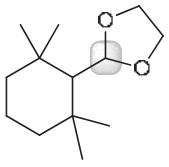


a. The desired alkene can be made from a ketone via a Wittig reaction.
b. The ketone can be made via oxidation of the corresponding secondary alcohol.
c. The alcohol can be made from the starting material via a Grignard reaction.

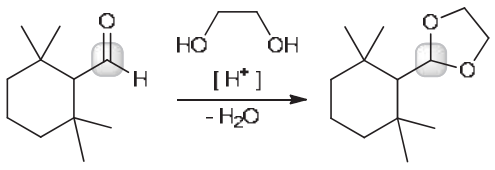
Now let's draw the forward scheme. Treating the starting material with magnesium gives a Grignard reagent, which is then treated with acetaldehyde (to give a Grignard reaction), followed by water work-up, to give the alcohol. Oxidation of the alcohol with chromic acid gives a ketone, which can then be converted into the desired product upon treatment with a Wittig reagent:



(c) The desired product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:

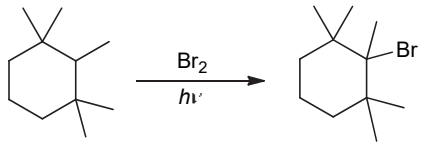


Therefore, this acetal can be made (via acetal formation) from the following aldehyde:

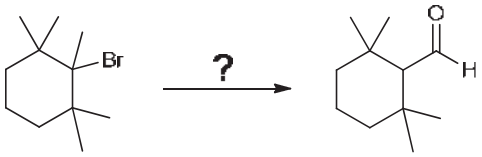


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So we will need to make this aldehyde from the starting material. But the starting material lacks a functional group, so the first step of our synthesis must be a radical bromination process in order to install a functional group:



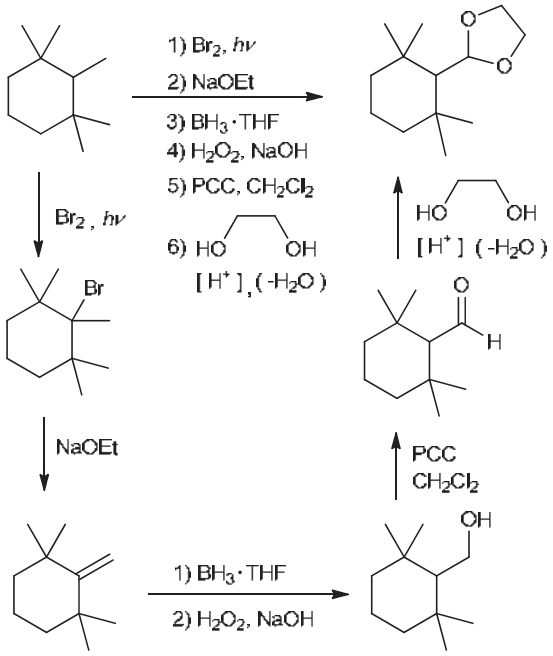
With the functional group installed, we must now bridge the gap between the first and last steps of the synthesis:



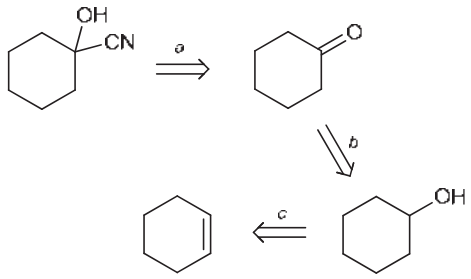
This transformation does not involve a change in the carbon skeleton, but it does involve a change in both the location and the identity of the functional group. This can be achieved in just a few steps:

1) elimination to give an alkene (upon treatment with a strong base),
2) hydroboration-oxidation to convert the alkene into a primary alcohol via *anti*-Markovnikov addition of H and OH, and
3) oxidation of the primary alcohol to an aldehyde (with PCC or DMP or Swern).

The entire synthesis is summarized here:

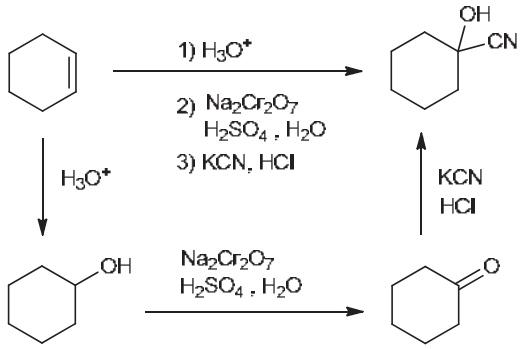


(d) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

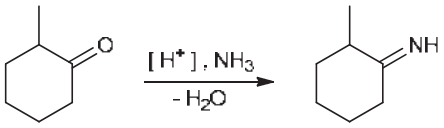


a. The product is a cyanohydrin, which can be made from the corresponding ketone.
b. The ketone can be made via oxidation of the corresponding secondary alcohol.
c. The alcohol can be made from the starting alkene via acid-catalyzed hydration.

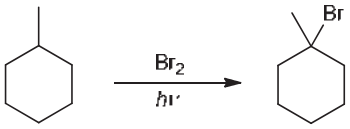
Now let's draw the forward scheme. The starting alkene is converted to an alcohol upon treatment with aqueous acid. Oxidation of the alcohol with chromic acid gives a ketone, which can then be converted into the desired cyanohydrin upon treatment with KCN and HCl:



(e) The desired product is an imine, which can be made from the corresponding ketone:

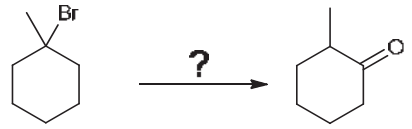


So we will need to make this ketone from the starting material. But the starting material lacks a functional group, so the first step of our synthesis must be a radical bromination process in order to install a functional group:



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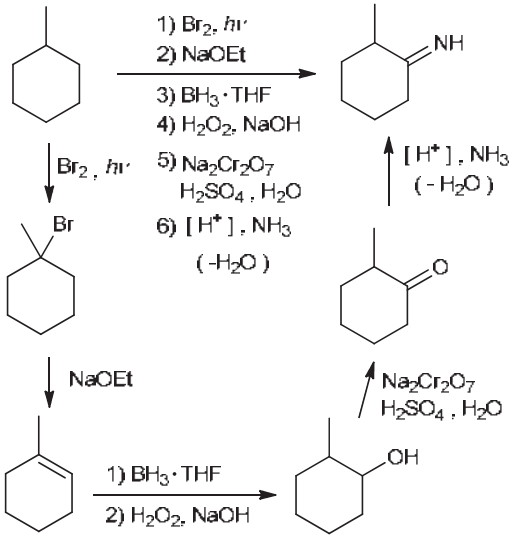
With the functional group installed, we must now bridge the gap between the first and last steps of the synthesis:



This transformation does not involve a change in the carbon skeleton, but it does involve a change in both the location and the identity of the functional group. This can be achieved in just a few steps:

1) elimination to give an alkene (upon treatment with a strong base),
2) hydroboration-oxidation to convert the alkene into a secondary alcohol via *anti*-Markovnikov addition of H and OH, and
3) oxidation of the secondary alcohol to a ketone (with chromic acid).

The entire synthesis is summarized here:

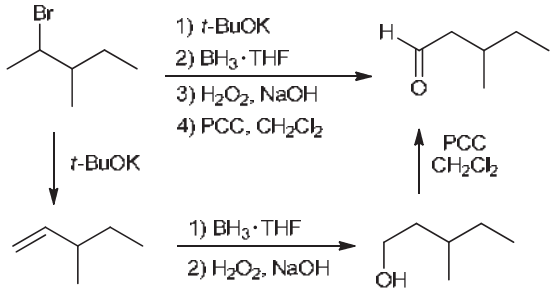


(f) This transformation does not involve a change in the carbon skeleton, but it does involve a change in both the location and the identity of the functional group:

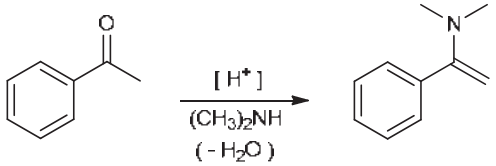


This can be achieved in just a few steps:

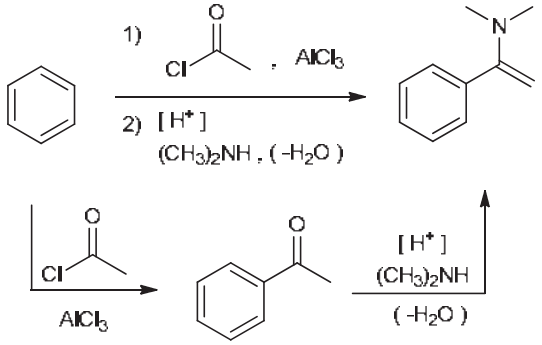
1) elimination with a strong, sterically hindered base to give the less substituted alkene,
2) hydroboration-oxidation to convert the alkene into a primary alcohol via *anti*-Markovnikov addition of H and OH, and
3) oxidation of the primary alcohol to an aldehyde (with PCC or DMP or Swern):



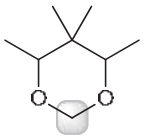
(g) The product is an enamine, which can be prepared from the corresponding ketone:



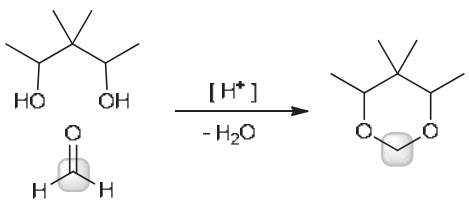
This ketone can be made from benzene via a Friedel-Crafts acylation:



(h) The desired product is an acetal, because the following (highlighted) carbon atom is connected to two oxygen atoms:



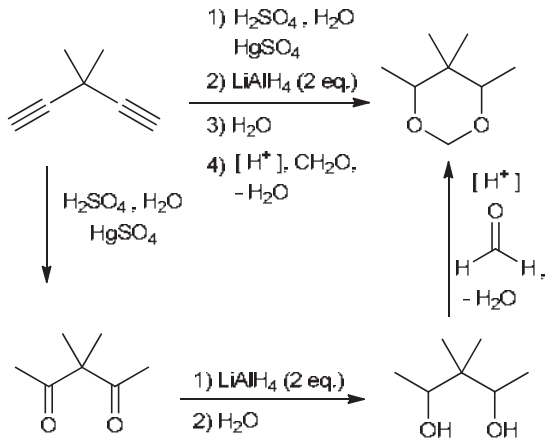
Therefore, this acetal can be made (via acetal formation) from the following diol and formaldehyde, as shown:



So we will need to make this diol from the starting material. This can be achieved in just two steps. First, the starting diyne is treated with sulfuric acid, in the

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presence of mercuric sulfate, to give a dione. Then, the dione can be reduced with two equivalents of $LiAlH_4$, followed by water work-up, to give the diol, which is then converted into the desired acetal.

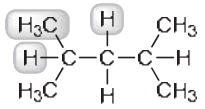


19.74. The molecular formula ($C_7H_{14}O$) indicates one degree of unsaturation (see Section 14.16). Therefore, the compound must have either one double bond or one ring. Treating compound **A** with a reducing agent ($NaBH_4$) gives an alcohol, so compound **A** is a ketone or aldehyde (accounting for the one degree of unsaturation). The ^1H NMR spectrum of compound **A** exhibits only two signals (for 14 protons). Therefore, the structure must be symmetrical. The two signals in the ^1H NMR spectrum are characteristic of an isopropyl group, which means that compound **A** must be diisopropyl ketone (or 2,4-dimethyl-3-pentanone). Conversion of compound **A** into a thioacetal, followed by desulfurization with Raney nickel, gives compound **B**. Notice that the carbonyl group has been reduced to a methylene (CH_2) group.



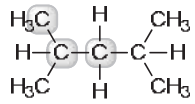
Compound A Compound B

(a) Compound **B** is symmetrical, much like compound **A**, giving rise to only three signals in its ^1H NMR spectrum, corresponding with the following protons:



Compound B

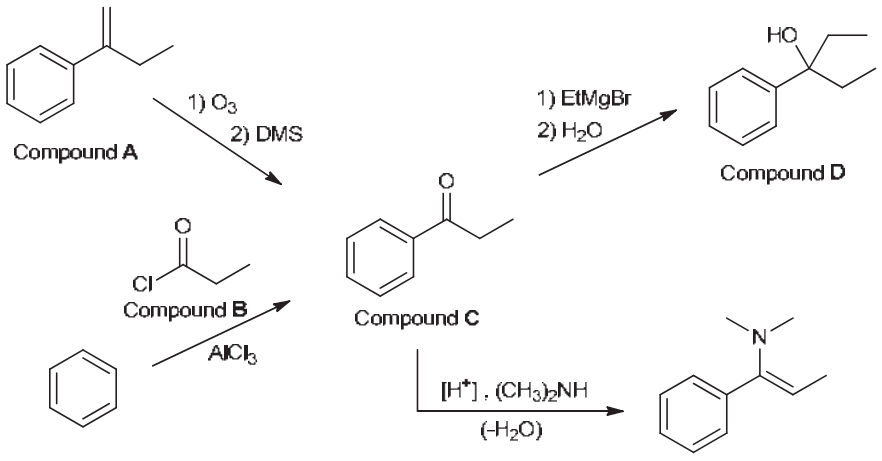
(b) Compound **B** is symmetrical, giving rise to only three signals in its ^{13}C NMR spectrum, corresponding with the following three unique locations:



Compound B

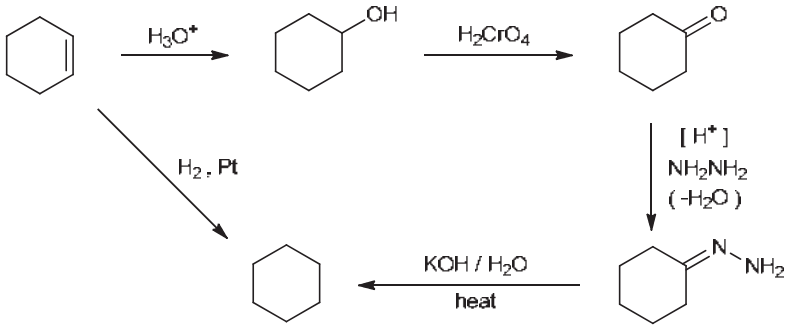
(c) Compound **A** is a ketone, while compound **B** is an alkane. Therefore, compound **A** will exhibit a strong signal near 1715 cm^{-1}, while compound **B** will not exhibit a signal in the same region.

19.75. Compound **C** is converted to an enamine upon treatment with a secondary amine under acid-catalyzed conditions, so compound **C** must be the corresponding ketone. Once we know the structure of compound **C**, the other structures can be identified. Compound **A** must be an alkene, because ozonolysis gives a ketone (we know that only one carbon atom is lost during this process, because the molecular formula of compound **A** indicates 10 carbon atoms, while the resulting ketone has only nine carbon atoms). Compound **B** must be an acyl halide with three carbon atoms, in order to install an acyl group on the aromatic ring via a Friedel-Crafts acylation. Compound **D** is formed when a Grignard reagent (ethyl magnesium bromide) attacks the ketone to give an alkoxide ion which is then protonated (via aqueous work-up) to give a tertiary alcohol, as shown:

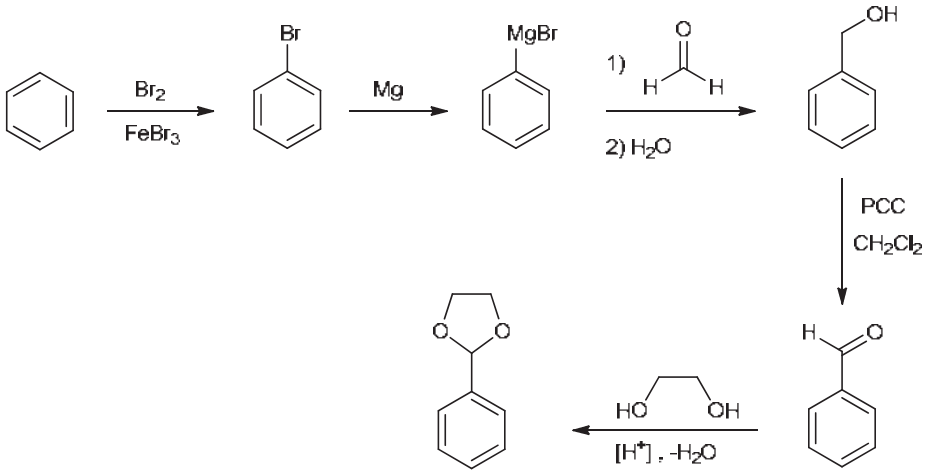


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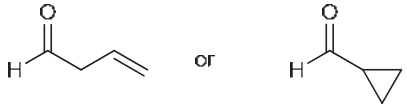
19.76. Cyclohexene is converted to cyclohexanol upon treatment with aqueous acid (acid-catalyzed hydration). Cyclohexanol is oxidized to cyclohexanone upon treatment with a strong oxidizing agent. Upon treatment with hydrazine in acid-catalyzed conditions, cyclohexanone is converted into the corresponding hydrazone. A Wolff-Kishner reduction then gives cyclohexane.
The conversion of cyclohexene to cyclohexane can be achieved more directly, in one step, via hydrogenation:



19.77. Benzene undergoes an electrophilic aromatic substitution reaction when treated with Br_2 and a Lewis acid, such as $FeBr_3$, to give bromobenzene. Subsequent treatment with magnesium gives a Grignard reagent (phenyl magnesium bromide), which reacts with formaldehyde to give benzyl alcohol (after aqueous work-up). This alcohol is oxidized by PCC to give benzaldehyde, which is then converted into an acetal upon treatment with ethylene glycol under acid-catalyzed conditions.

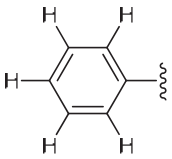


19.78.
(a) The problem statement indicates that the compound is an aldehyde. The molecular formula (C_4H_6O) indicates two degrees of unsaturation (see Section 14.16), but the aldehyde group only accounts for one of the degrees of unsaturation. The signal at 1715 cm^{-1} (stretching of the carbonyl group) indicates that the carbonyl group is NOT conjugated. If it were conjugated, the signal would be expected to appear at lower wavenumber (below 1700 cm^{-1}).
The following two structures are consistent with the requirements described above. The first aldehyde is acyclic and exhibits a double bond that is not conjugated to the carbonyl group, while the second aldehyde is cyclic:



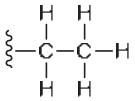
(b) The acyclic aldehyde would exhibit four signals in its ^{13}C NMR spectrum, while cyclopropyl carbaldehyde would exhibit only three signals in its ^{13}C NMR spectrum (two of the carbon atoms of the cyclopropyl group are identical).

19.79. The molecular formula ($C_9H_{10}O$) indicates five degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring, in addition to either one double bond or one ring.
In the ^1H NMR spectrum, the signals near 7 ppm are likely a result of aromatic protons. Notice that the combined integration of these signals is 5H, indicating a monosubstituted aromatic ring:



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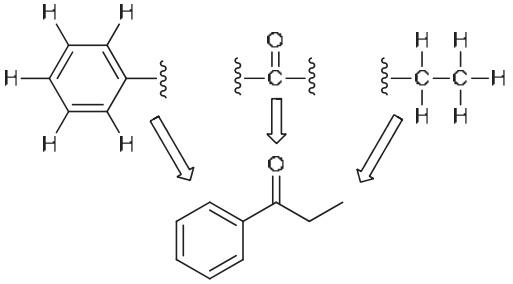
The spectrum also exhibits the characteristic pattern of an ethyl group (a quartet with an integration of 2 and a triplet with an integration of 3):



If we inspect the two fragments that we have determined thus far (the monosubstituted aromatic ring and the ethyl group), we will find that these two fragments account for nearly all of the atoms in the molecular formula ($C_9H_{10}O$). We only need to account for one more carbon atom and one oxygen atom. And let's not forget that our structure still needs one more degree of unsaturation, suggesting a carbonyl group:

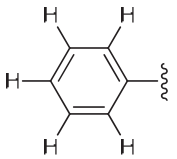


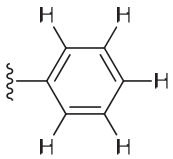
There is only one way to connect these three fragments.



This structure is consistent with the ^{13}C NMR spectrum. The signal near 200 ppm corresponds with the carbon atom of the carbonyl group. A monosubstituted aromatic ring gives four signals between 100 and 150 ppm, and there are two signals between 0 and 50 ppm, corresponding to the carbon atoms of the ethyl group. The signal in the IR spectrum (at 1687 cm^{-1}) is consistent with a conjugated carbonyl group.

19.80. The molecular formula ($C_{13}H_{10}O$) indicates nine degrees of unsaturation (see Section 14.16), which is highly suggestive of two aromatic rings, in addition to either one double bond or one ring. The ^{13}C NMR spectrum exhibits only five signals, which must account for all thirteen carbon atoms in the compound. Therefore, many of the carbon atoms are identical, as a result of symmetry. There are four signals between 100 and 150 ppm, indicating a monosubstituted aromatic ring. To account for so many degrees of unsaturation, as well as the symmetry that must be present, we propose two monosubstituted aromatic rings, rather than just one:

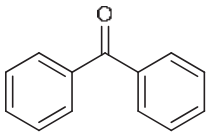




If we inspect these two fragments, we will find that they account for nearly all of the atoms in the molecular formula ($C_{13}H_{10}O$). We only need to account for one more carbon atom and one oxygen atom. And let's not forget that our structure still needs one more degree of unsaturation, suggesting a carbonyl group:



There is only one way to connect these fragments, as shown:

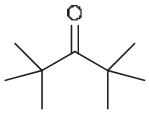


The carbonyl group in this compound (benzophenone) is conjugated to each of the rings, which explains why it produces a signal at a relatively low wavenumber (1660 cm^{-1}) for a carbonyl group of a ketone.

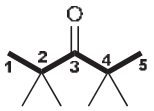
19.81. The molecular formula ($C_9H_{18}O$) indicates one degree of unsaturation (see Section 14.16). The problem statement indicates that the compound is a ketone, which accounts for the one degree of unsaturation:



With only one signal in the ^1H NMR spectrum, the structure must have a high degree of symmetry, such that all eighteen protons are equivalent. This can be achieved with two tert-butyl groups:



This compound is a ketone with a parent chain of five carbon atoms. The carbonyl group is located at C3, and there are four methyl groups (two at C2 and two at C4):



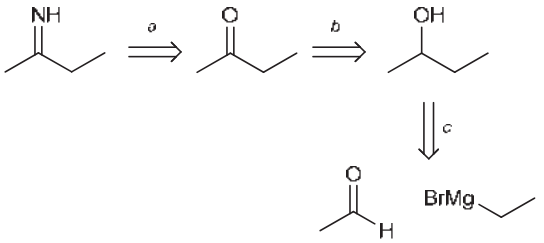
2,2,4,4-Tetramethyl-3-pentanone

19.82.

(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following

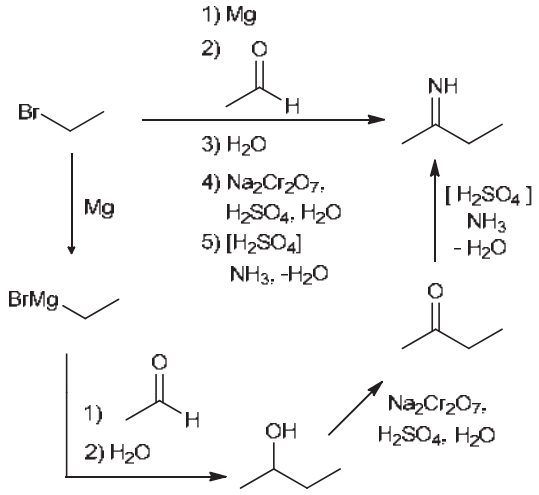
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retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

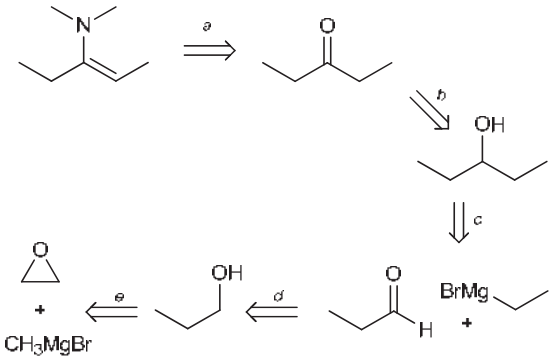


a. The desired product is an imine, which can be made from the corresponding ketone.
b. The ketone can be made via oxidation of the corresponding secondary alcohol.
c. The secondary alcohol can be made via a Grignard reaction from compounds containing no more than two carbon atoms.

Now let's draw the forward scheme. Ethyl bromide is converted into ethyl magnesium bromide (a Grignard reagent), which is then treated with acetaldehyde (to give a Grignard reaction), followed by water work-up, to give 2-butanol. Oxidation gives 2-butanone, which can then be converted into the desired imine upon treatment with ammonia in acid-catalyzed conditions (with removal of water):

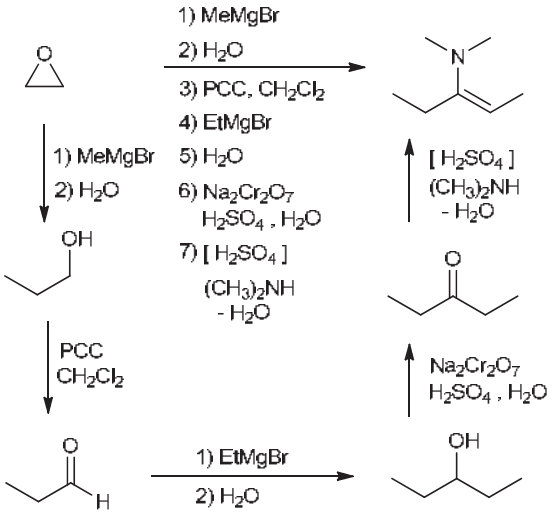


(b) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*e*) follows.



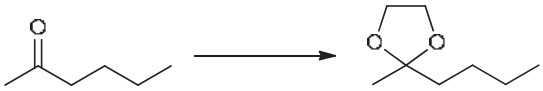
a. The desired product is an enamine, which can be made from the corresponding ketone (3-pentanone).
b. The ketone can be made via oxidation of the corresponding secondary alcohol (3-pentanol).
c. The secondary alcohol can be made via a Grignard reaction between ethyl magnesium bromide and an aldehyde (propanal).
d. Propanal can be made via oxidation of the corresponding alcohol (1-propanol).
e. 1-Propanol can be made by treating ethylene oxide with methyl magnesium bromide.

Now let's draw the forward scheme. Ethylene oxide is treated with methyl magnesium bromide, followed by water work-up to give 1-propanol. This alcohol is then oxidized to an aldehyde with PCC (or DMP or Swern), and the resulting aldehyde is then treated with ethyl magnesium bromide, followed by water work-up, to give 3-pentanol. Oxidation with chromic acid gives 3-pentanone, which is then converted to the corresponding enamine upon treatment with dimethylamine and acid catalysis (with removal of water):

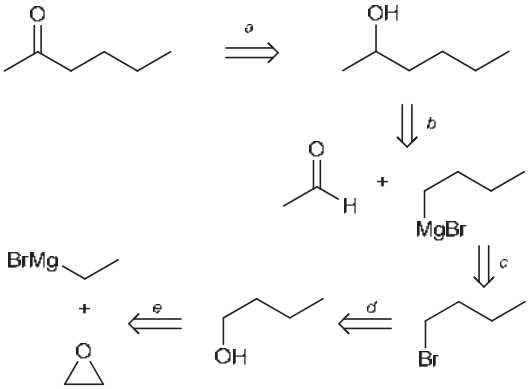


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(c) The product is a cyclic acetal, which can be made from the corresponding ketone:

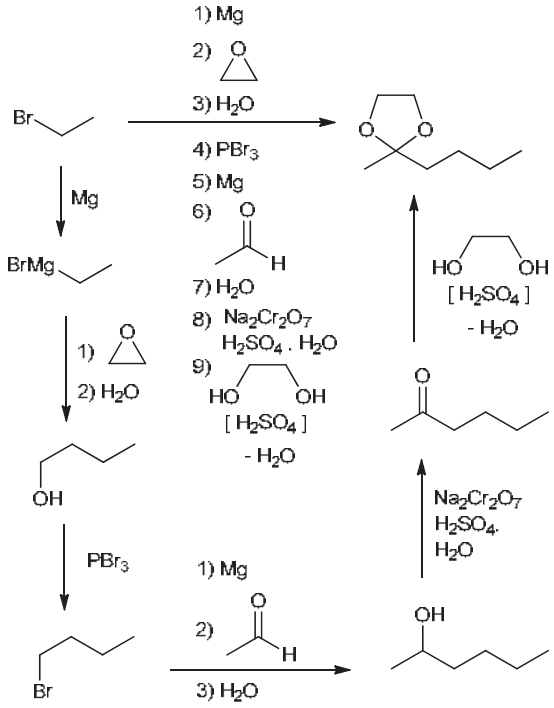


This ketone can be prepared in a variety of ways, so there are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*e*) follows.



a. The ketone can be made via oxidation of the corresponding secondary alcohol (2-hexanol).
b. 2-Hexanol can be made via a Grignard reaction between acetaldehyde and butyl magnesium bromide.
c. Butyl magnesium bromide can be made from 1-bromobutane.
d. 1-Bromobutane can be made from 1-butanol via a substitution process.
e. 1-Butanol can be made by treating ethylene oxide with ethyl magnesium bromide.

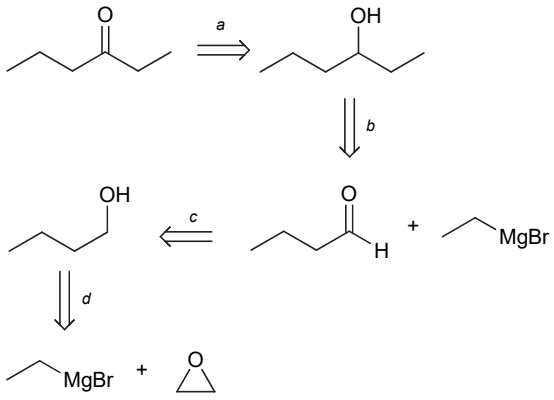
Now let's draw the forward scheme. Bromoethane is converted into a Grignard reagent and then treated with ethylene oxide, followed by water work-up to give 1-butanol. This alcohol is then converted to the corresponding alkyl bromide upon treatment with PBr_3. The alkyl bromide is then converted into a Grignard reagent (via insertion of Mg), and then treated with acetaldehyde, followed by water work-up to give 2-hexanol. Oxidation with chromic acid gives 2-hexanone, which is then converted to the corresponding acetal upon treatment with ethylene glycol and acid catalysis (with removal of water):



(d) The product is a cyclic acetal, which can be made from the corresponding ketone:



This ketone can be prepared in a variety of ways, so there are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

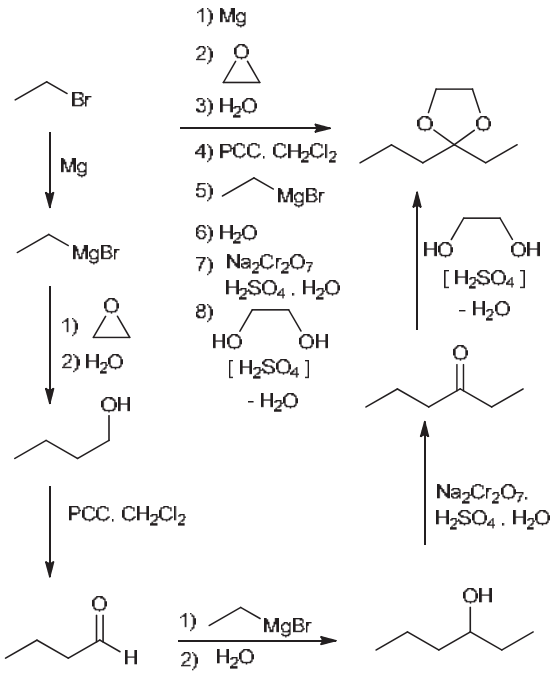


a. The ketone can be made via oxidation of the corresponding secondary alcohol (3-hexanol).
b. 3-Hexanol can be made via a Grignard reaction between butanal and ethyl magnesium bromide.
c. Butanal can be via oxidation of 1-butanol.

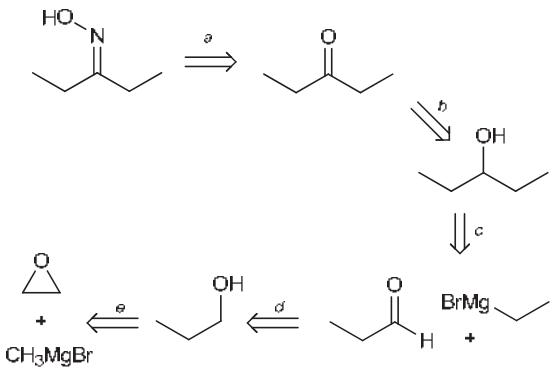
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d. 1-Butanol can be made by treating ethylene oxide with ethyl magnesium bromide.

Now let's draw the forward scheme. Bromoethane is converted into a Grignard reagent and then treated with ethylene oxide, followed by water work-up to give 1-butanol. This alcohol is then oxidized with PCC (or DMP or Swern) to give butanal, which is then treated with ethyl magnesium bromide (followed by water work-up) to give 3-hexanol. Oxidation with chromic acid gives 3-hexanone, which is then converted to the corresponding acetal upon treatment with ethylene glycol and acid catalysis (with removal of water):

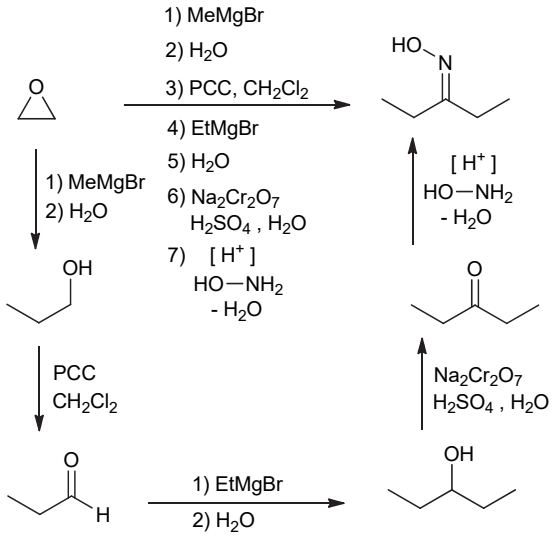


(e) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*e*) follows.

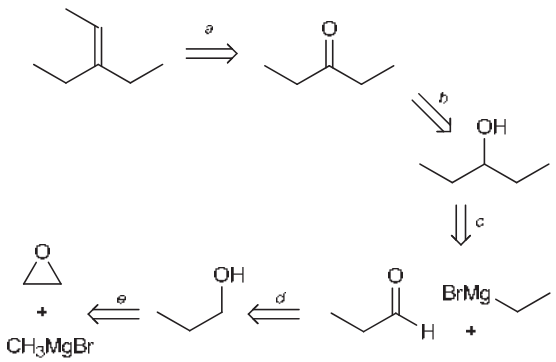


a. The desired product is an oxime, which can be made from the corresponding ketone (3-pentanone).
b. The ketone can be made via oxidation of the corresponding secondary alcohol (3-pentanol).
c. The secondary alcohol can be made via a Grignard reaction between ethyl magnesium bromide and an aldehyde (propanal).
d. Propanal can be made via oxidation of the corresponding alcohol (1-propanol).
e. 1-Propanol can be made by treating ethylene oxide with methyl magnesium bromide.

Now let's draw the forward scheme. Ethylene oxide is treated with methyl magnesium bromide, followed by water work-up to give 1-propanol. This alcohol is then oxidized to an aldehyde with PCC (or DMP or Swern), and the resulting aldehyde is then treated with ethyl magnesium bromide, followed by water work-up, to give 3-pentanol. Oxidation with chromic acid gives 3-pentanone, which is then converted to the corresponding oxime upon treatment with hydroxylamine and acid catalysis (with removal of water):

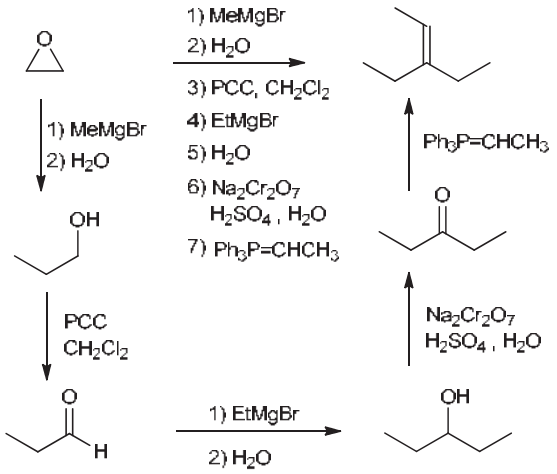


(f) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*e*) follows.

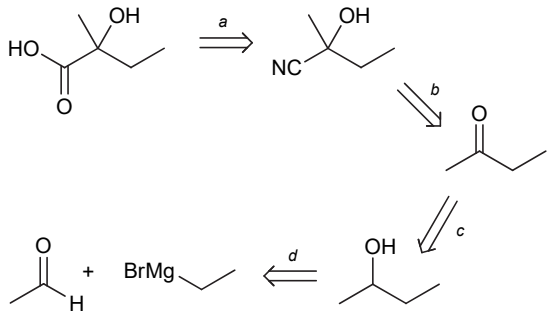


a. The desired product is an alkene, which can be made from a ketone (3-pentanone) via a Wittig reaction.
b. The ketone can be made via oxidation of the corresponding secondary alcohol (3-pentanol).
c. The secondary alcohol can be made via a Grignard reaction between ethyl magnesium bromide and an aldehyde (propanal).
d. Propanal can be made via oxidation of the corresponding alcohol (1-propanol).
e. 1-Propanol can be made by treating ethylene oxide with methyl magnesium bromide.

Now let's draw the forward scheme. Ethylene oxide is treated with methyl magnesium bromide, followed by water work-up to give 1-propanol. This alcohol is then oxidized to an aldehyde with PCC (or DMP or Swern), and the resulting aldehyde is then treated with ethyl magnesium bromide, followed by water work-up, to give 3-pentanol. Oxidation with chromic acid gives 3-pentanone, which is then converted to the product upon treatment with the appropriate Wittig reagent, thereby installing two carbon atoms and a double bond in the correct location:

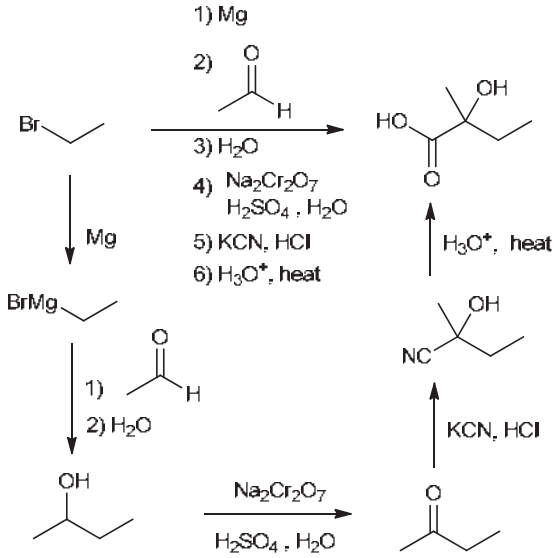


(g) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

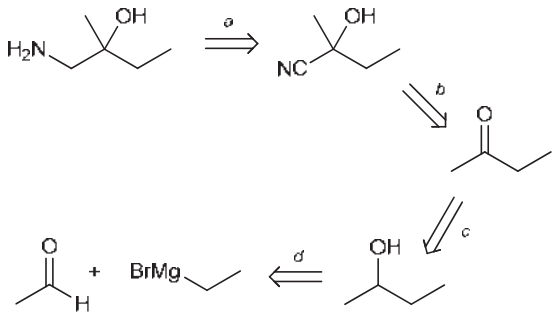


a. The product can be made from a cyanohydrin, via hydrolysis of the cyano group.
b. The cyanohydrin can be made from the corresponding ketone (2-butanone).
c. 2-Butanone can be made via oxidation of the corresponding secondary alcohol (2-butanol).
d. 2-Butanol can be made via a Grignard reaction between acetaldehyde and ethyl magnesium bromide.

Now let's draw the forward scheme. Ethyl bromide is converted into ethyl magnesium bromide, which is then treated with acetaldehyde (to give a Grignard reaction), followed by water work-up, to give 2-butanol. Oxidation of 2-butanol with chromic acid gives 2-butanone, which can then be converted into a cyanohydrin upon treatment with KCN and HCl. And finally, hydrolysis of the cyano group gives the desired product:



(h) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

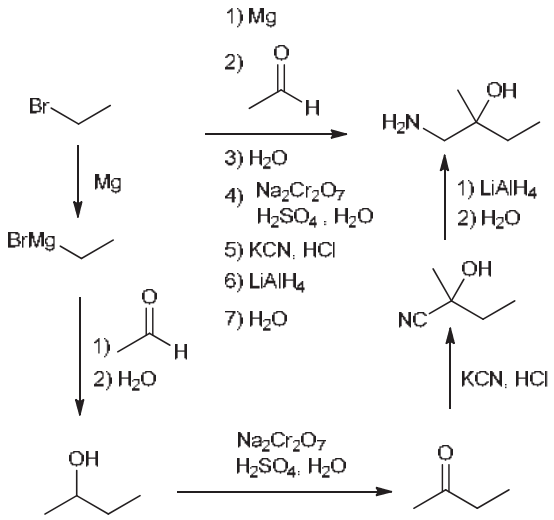


a. The product can be made from a cyanohydrin, via reduction of the cyano group.
b. The cyanohydrin can be made from the corresponding ketone (2-butanone).

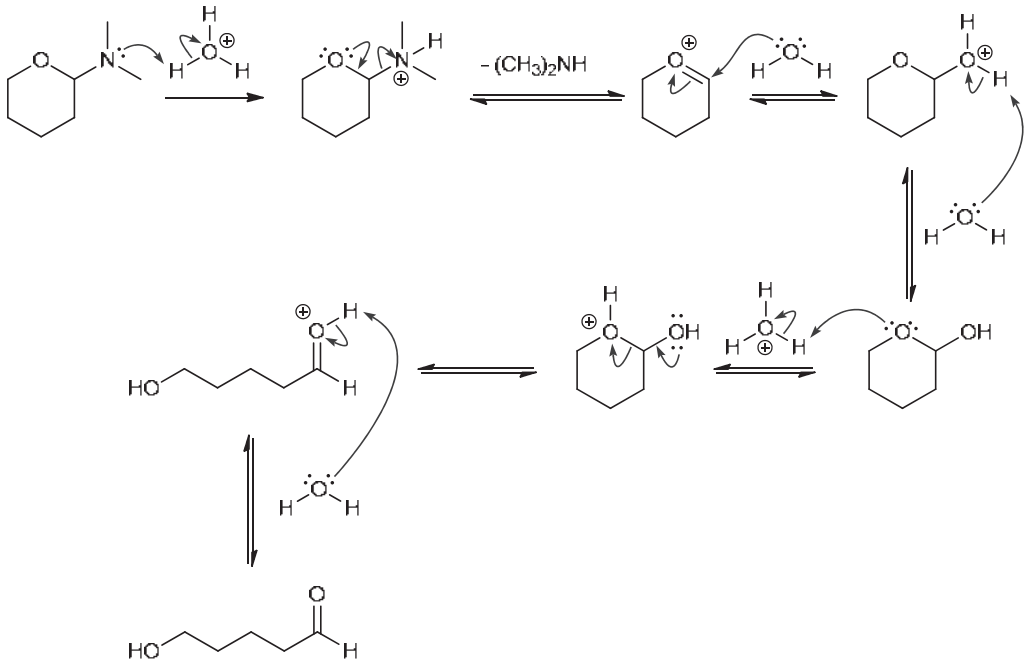
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c. 2-Butanone can be made via oxidation of the corresponding secondary alcohol (2-butanol).
d. 2-Butanol can be made via a Grignard reaction between acetaldehyde and ethyl magnesium bromide.

Now let's draw the forward scheme. Ethyl bromide is converted into ethyl magnesium bromide, which is then treated with acetaldehyde (to give a Grignard reaction), followed by water work-up, to give 2-butanol. Oxidation of 2-butanol with chromic acid gives 2-butanone, which can then be converted into a cyanohydrin upon treatment with KCN and HCl. And finally, reduction of the cyano group gives the desired product:

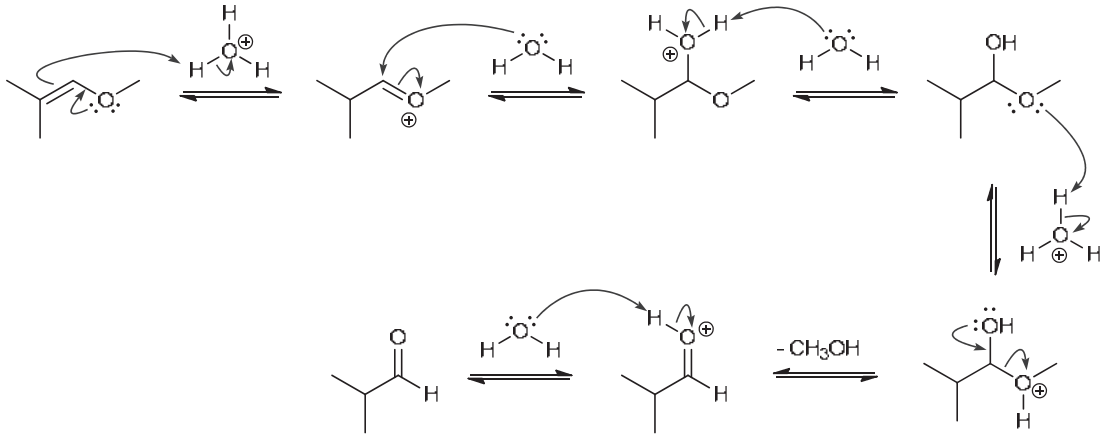


19.83.
(a) In acid-catalyzed conditions, the starting material is protonated. There are two locations where protonation can occur (the lone pair of the nitrogen atom, or a lone pair of the oxygen atom). The nitrogen atom is more likely protonated first, because it is a stronger base (a protonated amine, called an ammonium ion, is a much weaker acid than a protonated ether, called an oxonium ion, as seen in the pK_a table on the inside cover of the textbook). Loss of a leaving group (dimethyl amine) gives a resonance-stabilized cation, which is then attacked by water. The resulting oxonium ion is then deprotonated to give a cyclic hemiacetal. Protonation, followed by loss of a leaving group gives a protonated carbonyl group, which then loses a proton to give the product. Notice that water functions as the base in each deprotonation step.



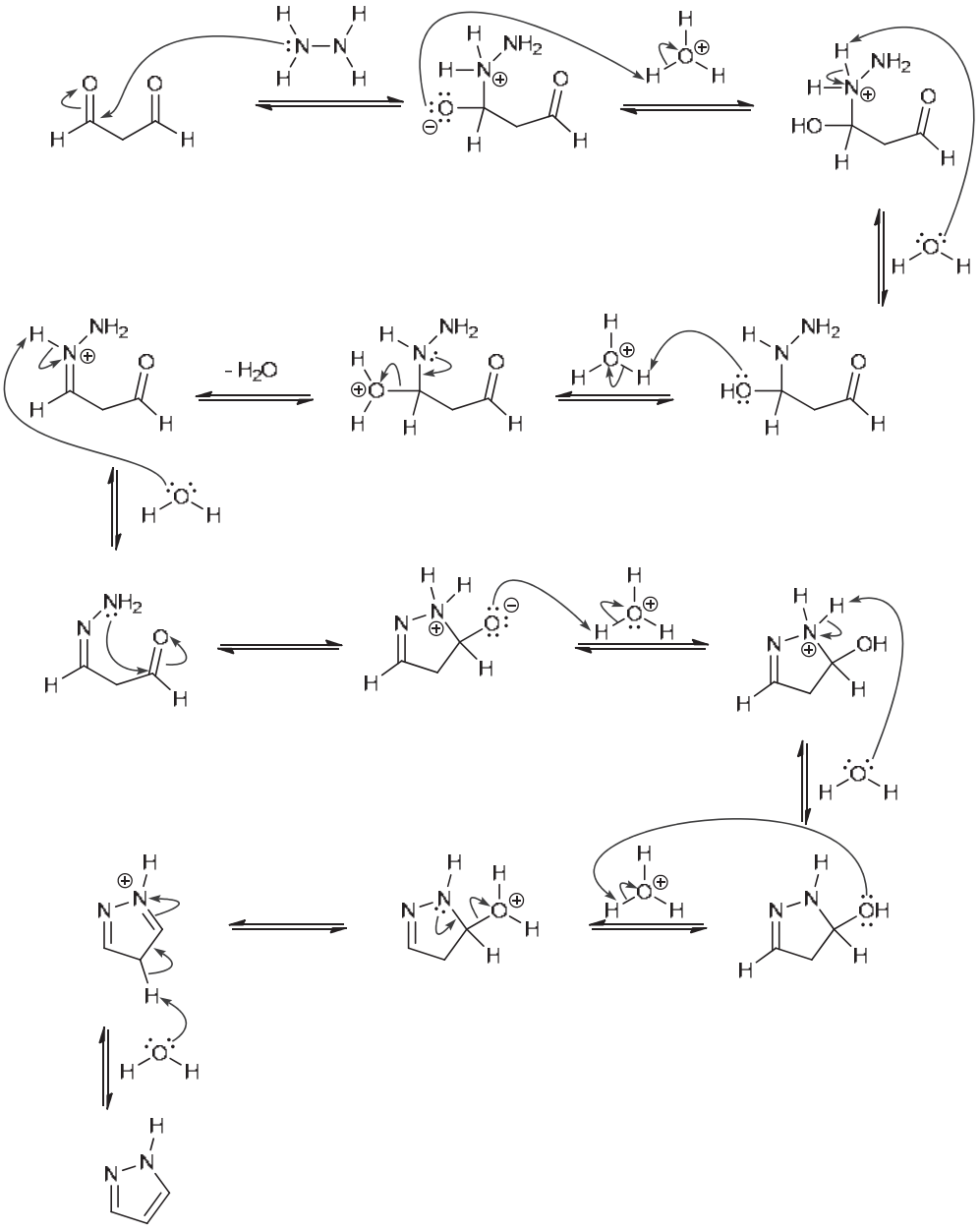
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(b) The starting material is a vinyl ether, and it is being subjected to aqueous acidic conditions. This indicates that protonation is likely the first step of the mechanism. There are two locations to consider for protonation: the oxygen atom or the π bond. Protonation of the oxygen atom does not result in a resonance-stabilized cation, while protonation of the π bond does indeed result in a resonance-stabilized cation. As such, the first step is protonation of the π bond. The resulting intermediate is then attacked by water to give an oxonium ion, which is then deprotonated to give a hemiacetal. Protonation, followed by loss of a leaving group gives a protonated carbonyl group, which then loses a proton to give the product. Notice that water functions as the base in each deprotonation step.

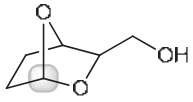


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(c) Hydrazine is sufficiently nucleophilic to attack a carbonyl group directly (without prior activation of the carbonyl group via protonation). The resulting intermediate undergoes two successive proton transfer steps, giving an intermediate that is free of formal charges. Protonation of the OH group converts a bad leaving group into a good one (water). Loss of the leaving group gives a resonance-stabilized cation, which then loses a proton to give a hydrazone. An intramolecular nucleophilic attack gives an intermediate that undergoes two proton transfer steps to give an intermediate free of formal charges. Protonation of the OH group converts a bad leaving group into a good one (water). Loss of the leaving group gives a resonance-stabilized cation, which then loses a proton to give the product, which is aromatic.

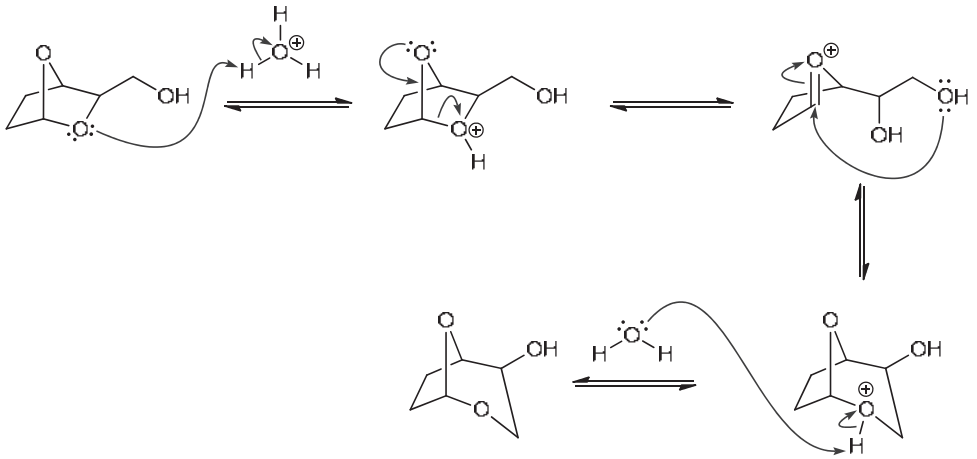


(d) The starting material exhibits a carbon atom that is connected to two oxygen atoms, so this compound is an acetal:

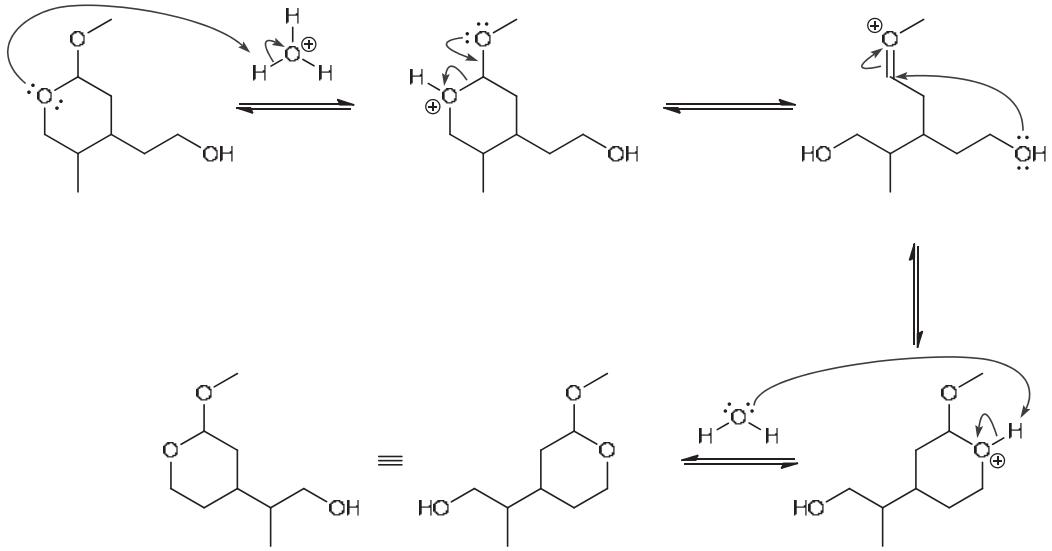


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Protonation of the acetal (specifically at the oxygen atom in the bottom right corner of the structure) results in an oxonium ion that can lose a leaving group to give a resonance-stabilized cation. This intermediate has two OH groups. If the more distant OH group attacks the C=O bond, the resulting oxonium ion can lose a proton to give the product. Notice that the base for the deprotonation step is water.



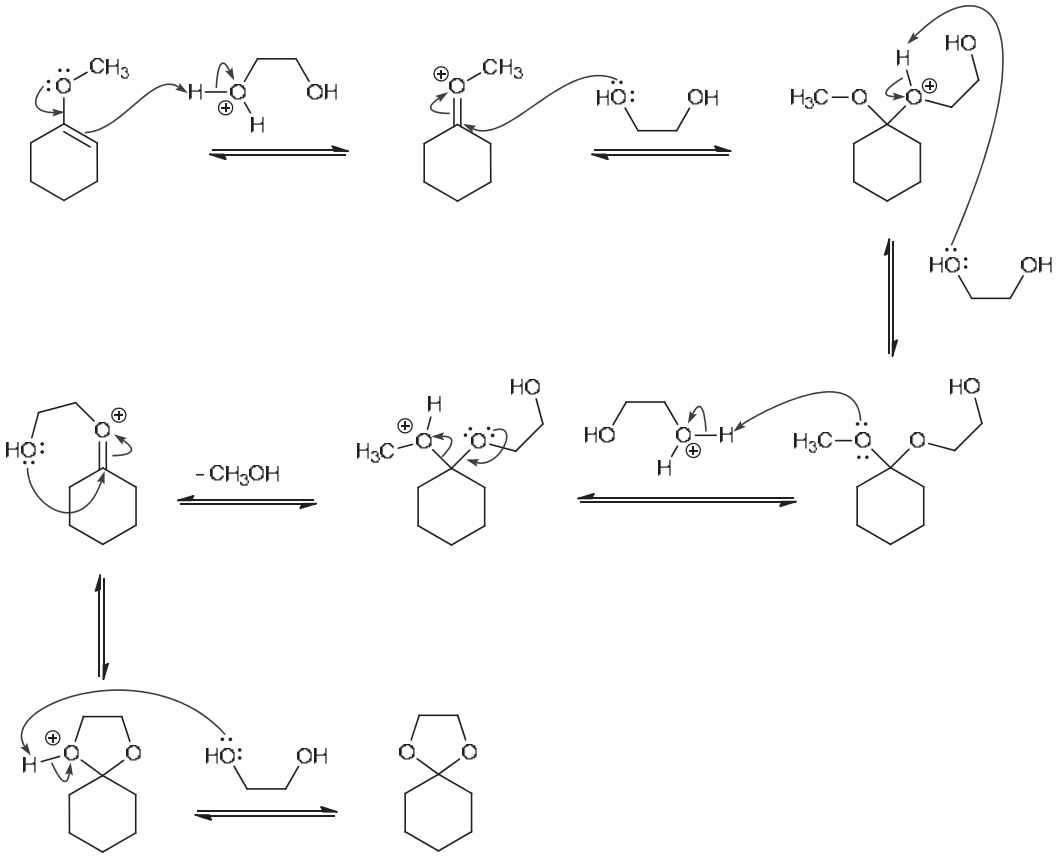
(e) The starting material exhibits a carbon atom that is connected to two oxygen atoms, so this compound is an acetal. Protonation of the acetal (specifically at the oxygen atom on the left) results in an oxonium ion that can lose a leaving group to give a resonance-stabilized cation. This intermediate has two OH groups. If the one on the right side attacks the C=O bond, the resulting oxonium ion can lose a proton to give the product. Notice that the base for the deprotonation step is water.



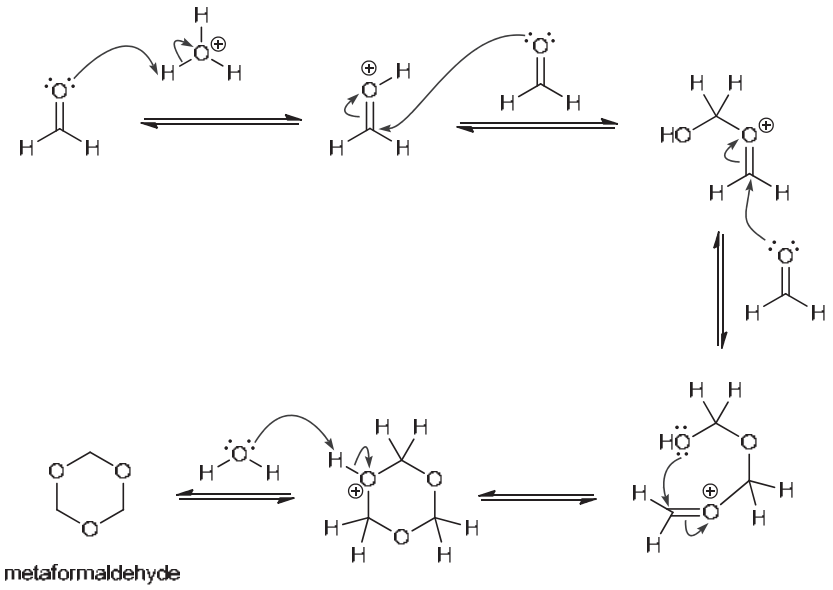
(f) The starting material is a vinyl ether, and it is being subjected to acidic conditions. This indicates that protonation is likely the first step of the mechanism. There are two locations to consider for protonation: the oxygen atom or the π bond. Protonation of the oxygen atom does not result in a resonance-stabilized cation, while protonation of the π bond does indeed result in a resonance-stabilized cation. As such, the first step is protonation of the π bond. The likely proton source is the conjugate acid of ethylene glycol, which received its proton from the acid (TsOH). Protonation results in a resonance-stabilized cation, which can then attacked by ethylene glycol to give an oxonium ion, followed by deprotonation to give a hemiacetal. Protonation of the methoxy group, followed by loss of a leaving group (methanol) gives a protonated carbonyl group, which then functions as an electrophile in an intramolecular nucleophilic attack. Deprotonation then gives the product.

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Notice that ethylene glycol functions as the base in each deprotonation step.

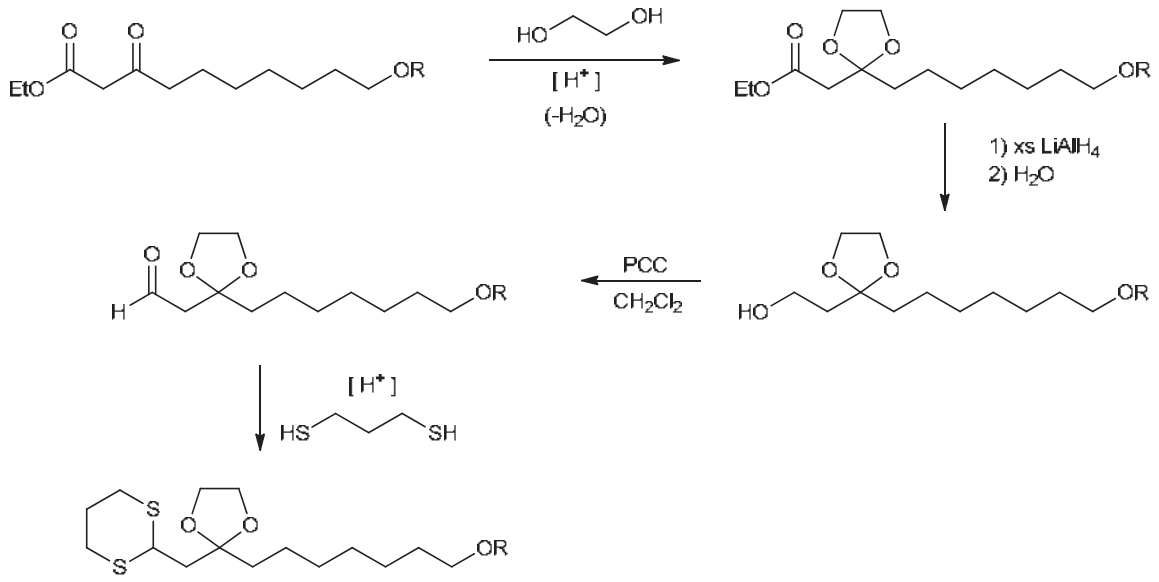


19.84. In aqueous acidic conditions, the carbonyl group of formaldehyde is protonated, thereby rendering it more electrophilic. Another molecule of formaldehyde (that has not been protonated) can function as a nucleophile and attack the protonated carbonyl group. The resulting resonance-stabilized cation functions as an electrophile and is attacked by another molecule of formaldehyde, giving yet another resonance-stabilized cation. An intramolecular attack gives an oxonium ion, which is then deprotonated to give the product.



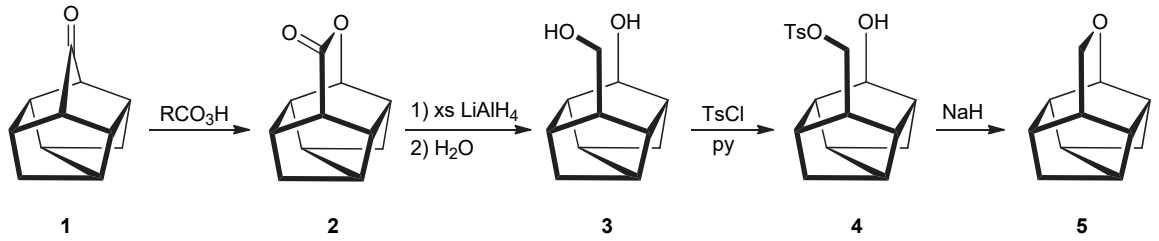
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19.85. The ketone group (the more reactive carbonyl) must first be protected by converting it into an acetal. Then, the ester can be reduced with xs $LiAlH_4$ to give an alcohol (if the ketone had not been protected, it would have also been reduced by $LiAlH_4$). Mild oxidation of the alcohol with PCC (or DMP or Swern) gives an aldehyde, which is then converted to the corresponding thioacetal.

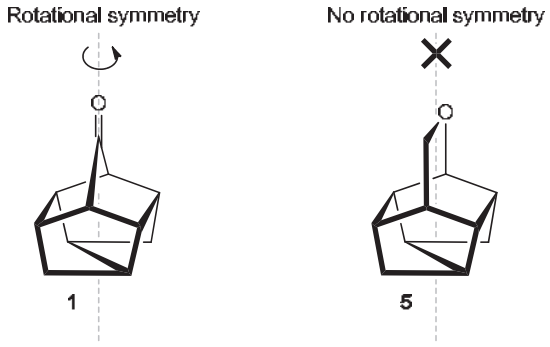


19.86.

(a) Compound **1** is a ketone, while compound **2** is an ester. This transformation from **1** to **2** can be achieved with a peroxy acid (RCO_3H). Then, compound **2** can be converted into diol **3** upon treatment with excess lithium aluminum hydride. Finally, compound 5 can be obtained if compound **4** is treated with a strong base, such as NaH. Under these conditions, the hydroxyl group is deprotonated to give an alkoxide ion, which functions as a nucleophilic center in an intramolecular S_N2-type process, giving an ether (compound **5**):

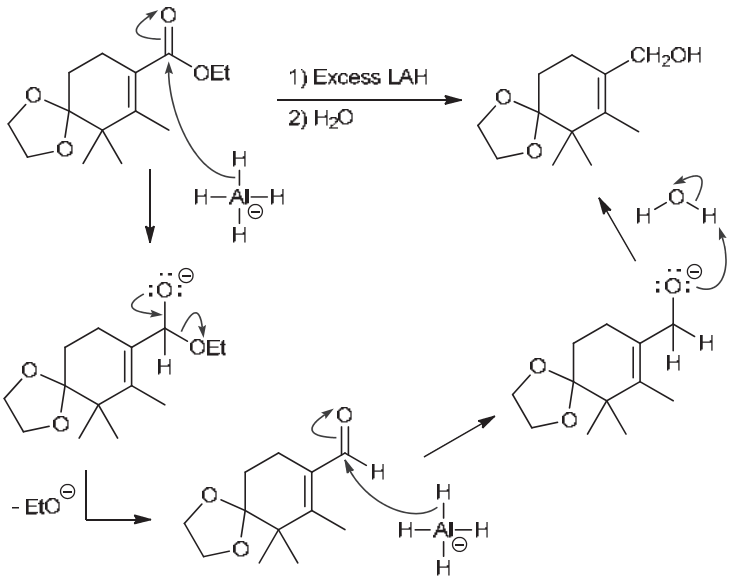


(b) Compound **1** has rotational symmetry, which compound **5** lacks. Therefore, compound **1** has fewer signals in its NMR spectrum.

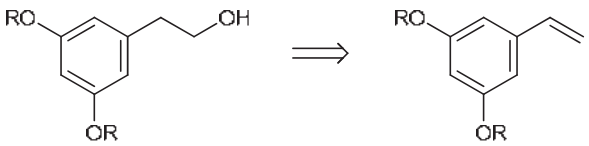


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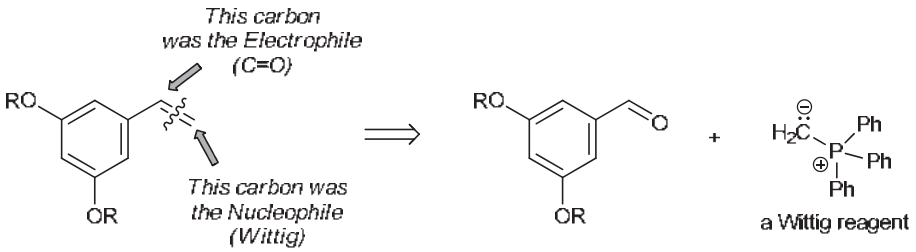
19.87. First, two curved arrows are used to show delivery of hydride to the ester. In the next step, two curved arrows show collapse of the charged tetrahedral intermediate and ejection of the leaving group, which in this case is ethoxide. The resulting aldehyde is then further reduced by another equivalent of hydride from LAH. Once again, two curved arrows are used to show hydride delivery. Finally, the resulting alkoxide ion is protonated upon treatment with water, and two curved arrows are needed to show this proton transfer step. Therefore, the net reaction is the reduction of the ester functional group to generate an alcohol.



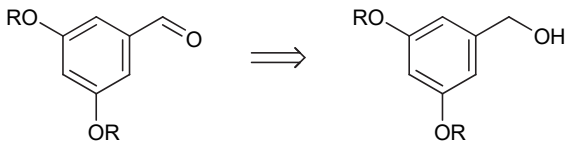
19.88. The carbon chain must be extended by adding a single additional carbon atom, and we are given a clue that a Wittig reaction is involved, so we know there is an alkene intermediate at some point. Using a retrosynthetic analysis, the target molecule (compound **2**) can be made from an alkene, via an *anti*-Markovnikov addition of H and OH:



This alkene can be made from an aldehyde via a Wittig reaction:

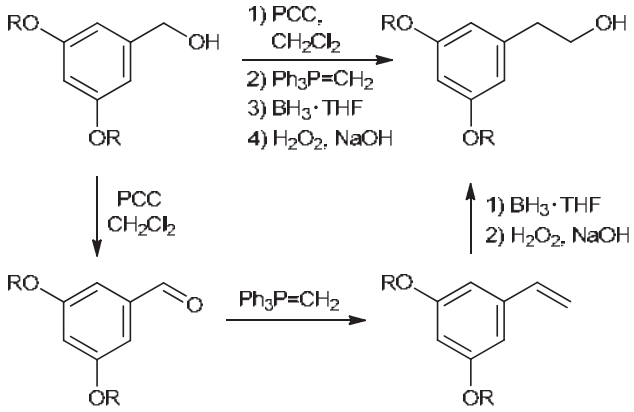


And the aldehyde can be made from the corresponding alcohol (compound **1**) via oxidation:



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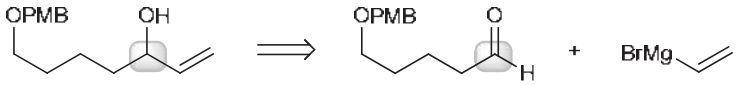
Now that we have completed the retrosynthetic planning, we can draw the forward process, as shown below. PCC oxidation of the primary alcohol gives an aldehyde, and reaction with a Wittig reagent affords the alkene. Hydroboration-oxidation adds H and OH in an *anti*-Markovnikov fashion, giving the desired alcohol.



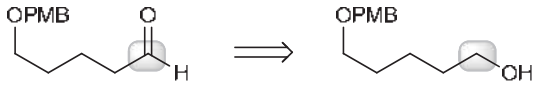
19.89. As with all synthesis problems, we must determine 1) if there is a change in the carbon skeleton, and 2) if there is a change in identity or location of the functional group(s). Numbering the carbon atoms from left to right, we see that two carbon atoms are being introduced during this transformation. We also see that the alcohol functional group (OH) is in the same location in both the starting material and the product.



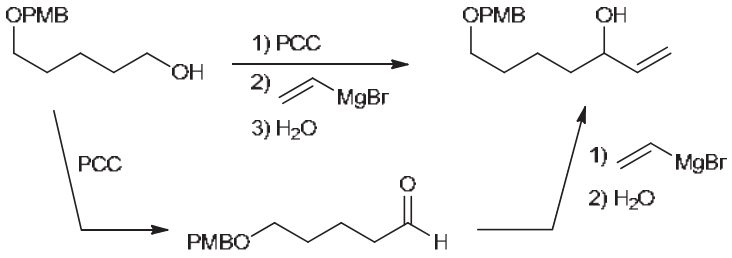
Importantly, a new C-C bond must be formed at the same location as the OH group (carbon 5 in our labeling scheme above, also the highlighted carbon below). This suggests a synthetic route involving a Grignard reagent attacking a C=O bond. That is, the product can be made from the following aldehyde, as shown in the following retrosynthetic scheme:



The starting material does not have the aldehyde group needed to react with a Grignard reagent. However, the required aldehyde can be made via oxidation of the primary alcohol, as shown in the following retrosynthetic scheme:

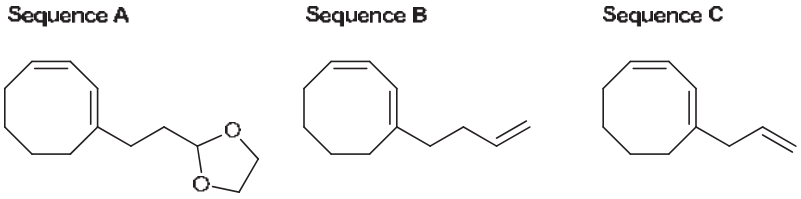


Now let's draw the forward process. There are many reagents that can be used to convert a primary alcohol into an aldehyde; one such reagent is PCC. The resulting aldehyde can then be treated with vinyl magnesium bromide (CH_2=CHMgBr), followed by protonation with water, to produce the desired product:



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19.90. In all three reaction sequences, the first two steps involve the addition of a Grignard reagent to the ketone, followed by alcohol dehydration using concentrated sulfuric acid and heat. The products of each of these operations are shown below:

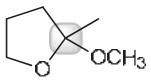


In sequence A, the final step is acetal deprotection using acetic acid and water, which will produce the desired product, aldehyde **2**. Under these conditions no undesired side reactions are expected to occur. In sequence B, ozonolysis of the terminal alkene will certainly produce an aldehyde, however the molecule also contains two additional alkenes within the 8-membered ring. Since ozone is a non-selective oxidant, if this compound were subjected to O_3/DMS, all three alkene groups would react! Therefore, the major product of the reaction will not be aldehyde **2**, but a compound with three different carbonyl groups (as well as two other fragments). In sequence C, hydroboration/oxidation will convert the terminal alkene to a primary alcohol, which will then be transformed into the desired product via oxidation with PCC. However, just like we saw in sequence B, the two other π bonds will react under the hydroboration/oxidation conditions; the product isolated will not be aldehyde **2**. In conclusion, after a thorough analysis, only sequence A will lead to the desired product.

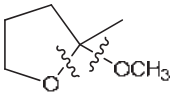
19.91. A ketone will react with a secondary amine (in the presence of an acid catalyst) to give an enamine. The answer is (a).

19.92. This process occurs under acid-catalyzed conditions. Under these conditions, option (d) is unlikely to form, because it has a negative charge on an oxygen atom, which is a strong base. Strong bases are unlikely to form in acidic conditions, so the answer is (d).

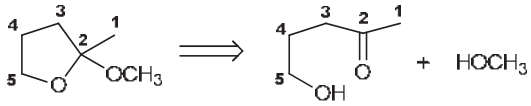
19.93. The desired compound is an acetal, because the highlighted carbon atom is connected to two OR groups:



Acetal formation involves formation of the following bonds:



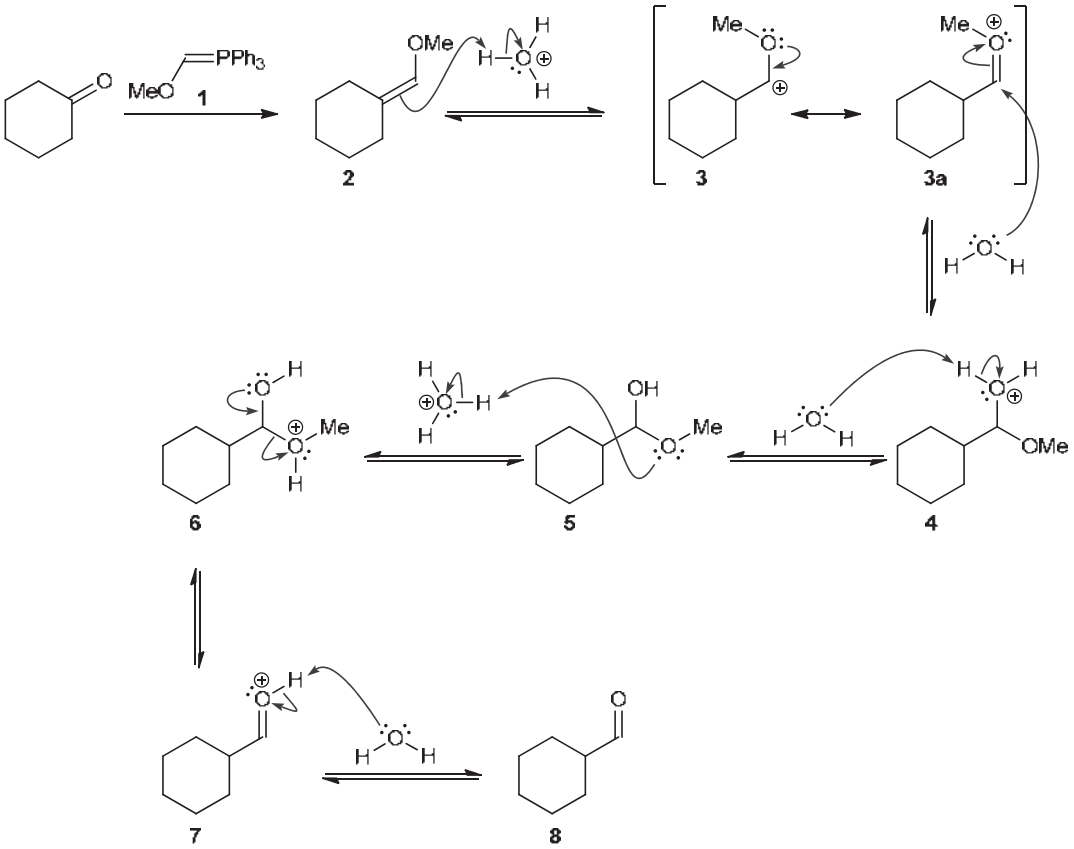
This acetal can be formed from the following reactants:



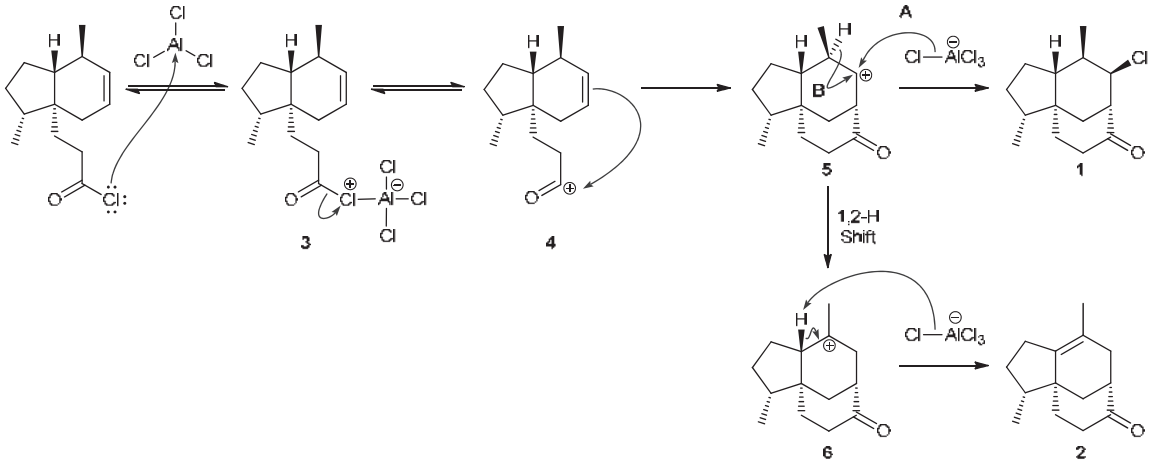
These reactants correspond with option (b).

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19.94. The product of the Wittig reaction is alkene **2**. The mechanism for acid-catalyzed hydration of this alkene begins with protonation of the π bond to generate **3**, a resonance-stabilized intermediate. Note that this intermediate is similar to the type of intermediate that we encountered during acetal formation/cleavage. Water then attacks to generate a tetrahedral intermediate (**4**) which can be deprotonated to form hemiacetal **5**. Protonation, followed by regeneration of the carbonyl group via loss of methanol, will produce protonated aldehyde **7**, which is deprotonated in the final step to afford aldehyde **8**.



19.95. In the first step, the acid chloride reacts with $AlCl_3$ to form a resonance-stabilized acylium ion (**4**). In the absence of an aromatic ring, the C=C π bond will function as a nucleophile and trap the acylium ion to produce a carbocation (**5**). This carbocation is transformed into compound **1** if $AlCl_4^-$ transfers a chloride ion to the carbocation (path **A**). Alternatively, carbocation **5** is transformed into compound **2** via a 1,2-hydride shift to form tertiary carbocation **6** (path **B**), followed by deprotonation.



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19.96.

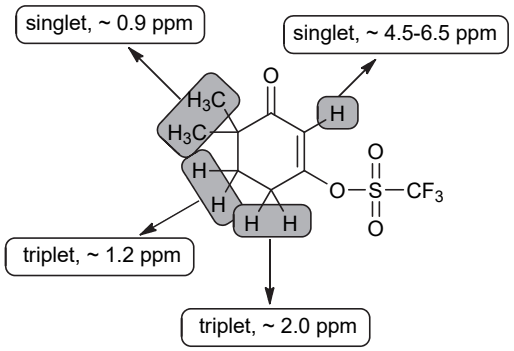
(a) We begin by determining the HDI for compound **B**, as shown here:

HDI = ½ (2C + 2 + N – H – X)
= ½ (2•8 + 2 + 0 – 14 – 0)
= ½ (4)
= 2

Therefore, compound **B** has two degrees of unsaturation. Now let's consider the IR data. Only two peaks are given, but they are important bands: a broad band around 3300 cm^{-1} is typical for an alcohol group, and 2117 cm^{-1} is diagnostic for a triple bond – either an alkyne (C≡C) or a nitrile (C≡N). Since nitrogen is absent from the molecular formula, the band at 2117 cm^{-1} must correspond with a C≡C triple bond. This accounts for both degrees of unsaturation.

At this stage consider the ^{1}H NMR data. Also, take into consideration the structure of the starting material; we know that the product should have at least some degree of similarity. The ^{1}H NMR data shows six types of protons; the easiest to assign is the broad singlet at 1.56 **δ** which is likely a proton of an alcohol; this is further confirmed by the IR band at 3305 cm^{-1}.

To assign the remaining signals, let's look at the starting material and consider what its ^{1}H NMR must look like.



The starting material has no chiral centers, and only 4 unique protons. The two methyl groups will appear as a singlet near 0.9 ppm, the allylic methylene group is expected to appear as a triplet near 2.0 ppm, the methylene next to the gem-dimethyl group is expected to be a triplet near 1.2 ppm, and finally, the vinyl proton should be a singlet in the range 4.5-6.5 ppm.

Now let's take another look at the ^{1}H NMR data for compound B.

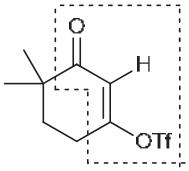
0.89 **δ** (6H, singlet)
~~1.49 **δ** (1H, broad singlet)~~
1.56 **δ** (2H, triplet)
1.95 **δ** (1H, singlet)
2.19 **δ** (2H, triplet)
3.35 **δ** (2H, singlet)

We've already assigned the 1.49 ppm broad singlet as an OH proton, so we can cross it off. We can also make the assumption that the 0.89 ppm singlet that integrates for 6 protons must be the gem-dimethyl group, and the two triplets at 1.56 ppm and 2.19 ppm are the two methylene groups from the starting material. Let's cross them out as well.

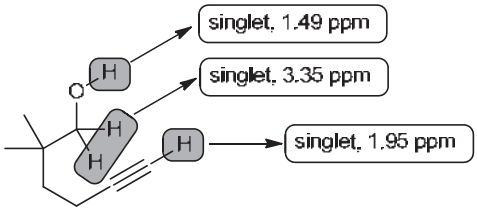
~~0.89 **δ** (6H, singlet)~~
~~1.49 **δ** (1H, broad singlet)~~
~~1.56 **δ** (2H, triplet)~~
1.95 **δ** (1H, singlet)
~~2.19 **δ** (2H, triplet)~~
3.35 **δ** (2H, singlet)

The vinyl proton of the starting material (4.5 – 6.5 ppm) is absent in Compound **B**. In its place, there are two signals: a singlet at 3.35 ppm, which (because of chemical shift and integration) is likely a methylene group alpha to an OH group, and the singlet at 1.95 which integrates to 1 proton.

Let's take a look at the starting material again:



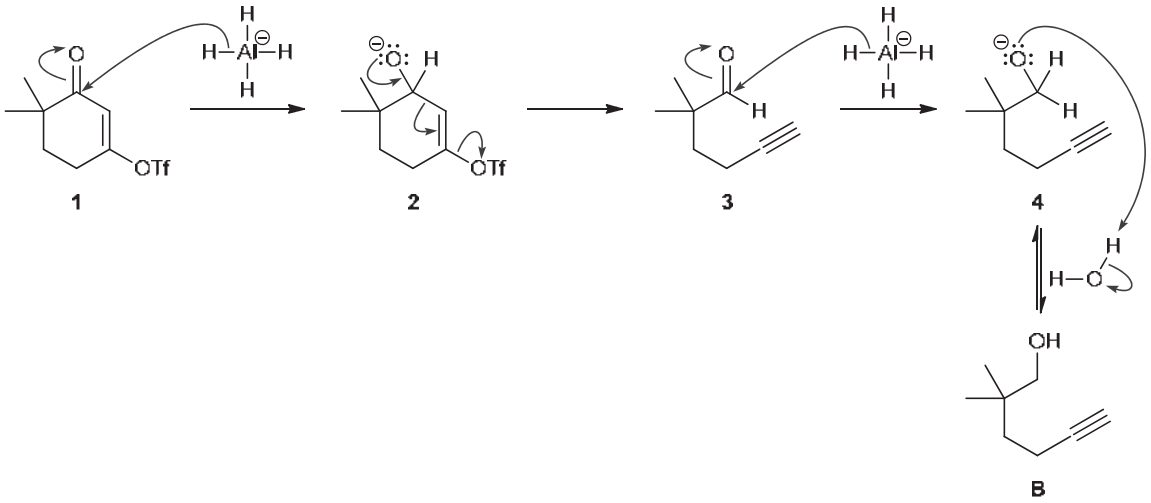
It seems that the left half is represented in compound **B**, however the right half has changed dramatically. From the molecular formula we know that there is no longer any sulfur in the molecule, so the triflate group must be gone. We also know that Compound B must exhibit an OH group and a C≡C triple bond (from the IR spectral data). If we were to take an eraser and eliminate the triflate, form an alkyne where the alkene once was, and reduce the ketone to an alcohol we would arrive at this structure:



Does this structure fit the data left over for compound B? The methylene group alpha to the OH group should be a singlet with an integration of 2. The chemical shift of 3.35 ppm is also in the acceptable range for a proton next to oxygen. And the proton of the alkyne should also be a singlet, with an integration of 1. The chemical shift is slightly less than what the table in chapter 16 shows (~2.5 ppm), but it is certainly within a margin of error. The molecular formula also matches.

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(b) In the first step, $LiAlH_4$ delivers hydride to the carbonyl group to form tetrahedral intermediate **2**. Next, the carbonyl group is regenerated which induces carbon-carbon bond cleavage to simultaneously generate the alkyne via the expulsion of the triflate leaving group, producing aldehyde **3**. The *anti* orientation of the electrons in the carbon-carbon single bond and the triflate leaving group facilitated this E2-like process. In the presence of $LiAlH_4$, another hydride ion can be delivered once more, to attack the aldehyde. This forms tetrahedral intermediate **4**, which is protonated upon workup to form compound **B**.



Chapter 20
Carboxylic Acids and Their Derivatives

Review of Concepts

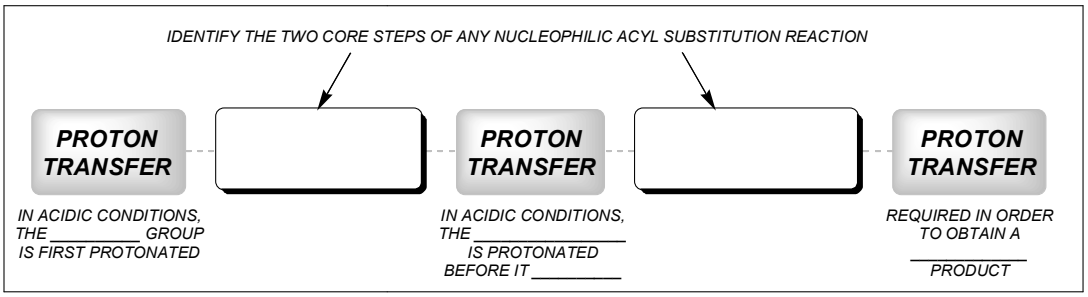
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 20. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Treatment of a carboxylic acid with a strong base yields a _____ salt.
- The pK_a of most carboxylic acids is between ____ and _____.
- Using the **Henderson-Hasselbalch equation**, it can be shown that carboxylic acids exist primarily as _____ at **physiological pH**.
- Electron-_____ substituents can increase the acidity of a carboxylic acid.
- When treated with aqueous acid, a nitrile will undergo _____**,** yielding a carboxylic acid.
- Carboxylic acids are reduced to _____ upon treatment with lithium aluminum hydride or borane.
- Carboxylic acid derivatives exhibit the same _____ state as carboxylic acids.
- Carboxylic acid derivatives differ in reactivity, with _____ being the most reactive and _____ the least reactive.
- When drawing a mechanism, avoid formation of a strong _____ in acidic conditions, and avoid formation of a strong _____ in basic conditions.
- When a nucleophile attacks a carbonyl group to form a tetrahedral intermediate, always reform the carbonyl group if possible, but avoid expelling _____ or _____.
- When treated with an alcohol, acid chlorides are converted into _____.
- When treated with ammonia, acid chlorides are converted into _____.
- When treated with a _____ reagent, acid chlorides are converted into alcohols with the introduction of two alkyl groups.
- The reactions of anhydrides are the same as the reactions of _____ except for the identity of the leaving group.
- When treated with a strong base followed by an alkyl halide, carboxylic acids are converted into _____.
- In a process called the **Fischer esterification**, carboxylic acids are converted into esters when treated with an _____ in the presence of _____.
- Esters can be hydrolyzed to yield carboxylic acids upon treatment with either aqueous base or aqueous _____. Hydrolysis under basic conditions is also called _____.
- When treated with lithium aluminum hydride, esters are reduced to yield _____. If the desired product is an aldehyde, then _____ is used as a reducing agent instead of $LiAlH_4$.
- When treated with a _____ reagent, esters are reduced to yield alcohols, with the introduction of two alkyl groups.
- When treated with excess $LiAlH_4$, amides are converted into _____.
- Nitriles are converted to amines when treated with _____.

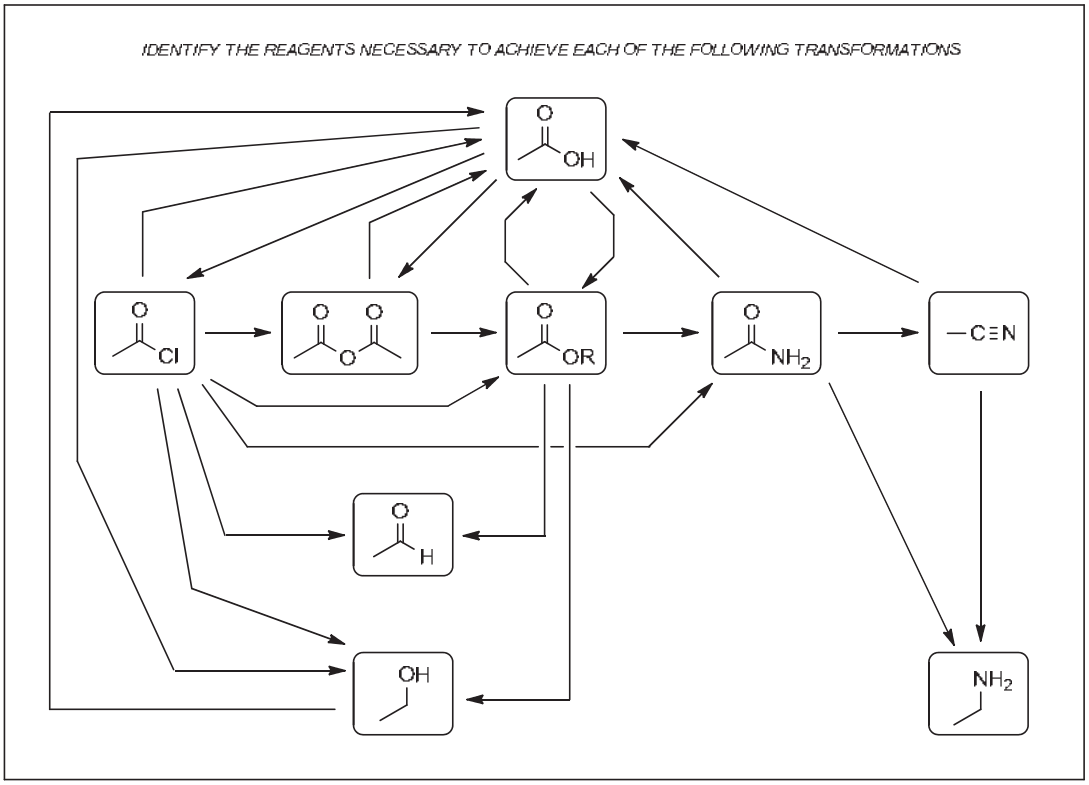
Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 20. The answers appear in the section entitled *SkillBuilder Review*.

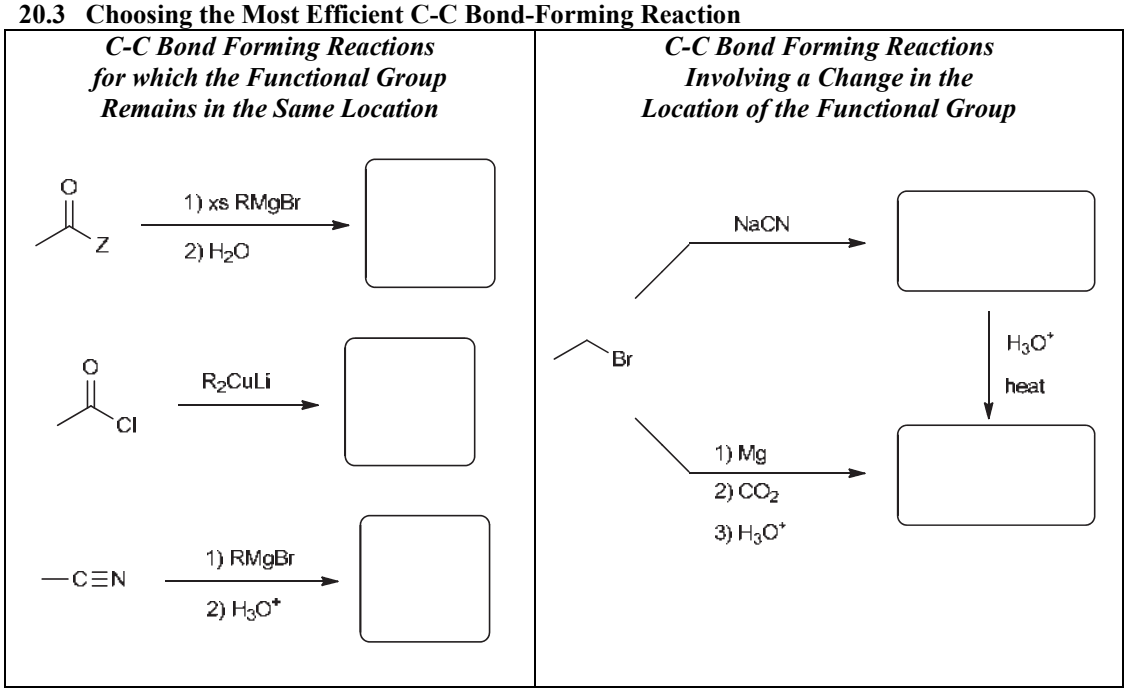
20.1 Drawing the Mechanism of a Nucleophilic Acyl Substitution Reaction



20.2 Interconverting Functional Groups



20.3 Choosing the Most Efficient C-C Bond-Forming Reaction

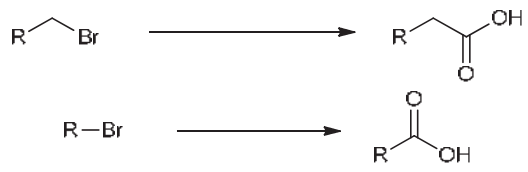


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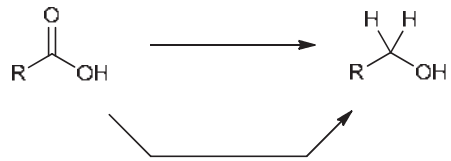
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 20. The answers appear in the section entitled *Review of Reactions*.

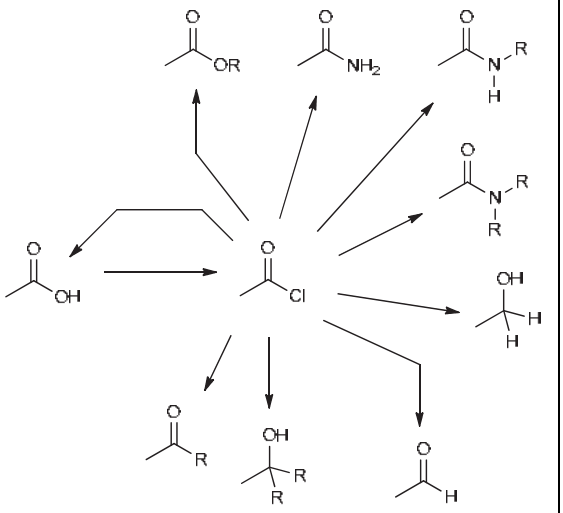
Preparation of Carboxylic acids



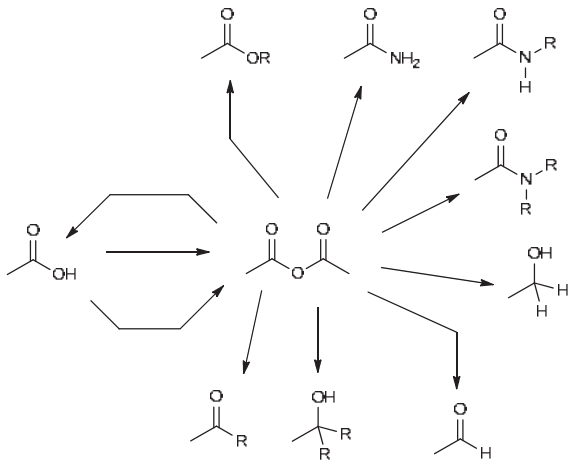
Reactions of Carboxylic Acids



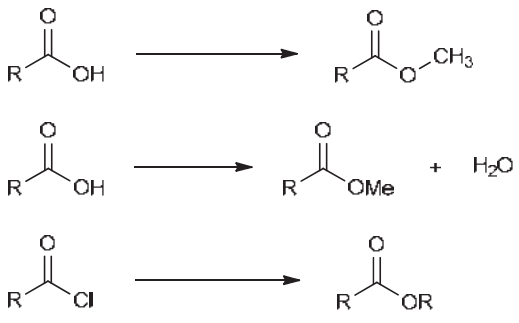
Preparation and Reactions of Acid Chlorides



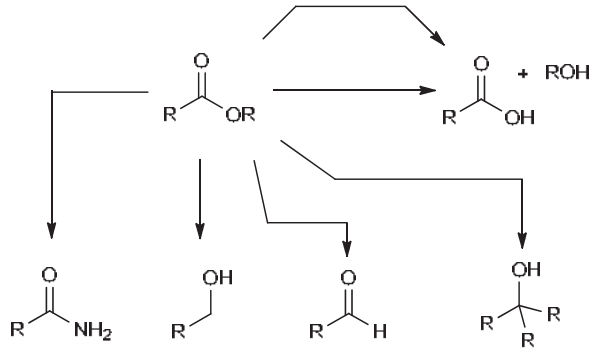
Preparation and Reactions of Acid Anhydrides

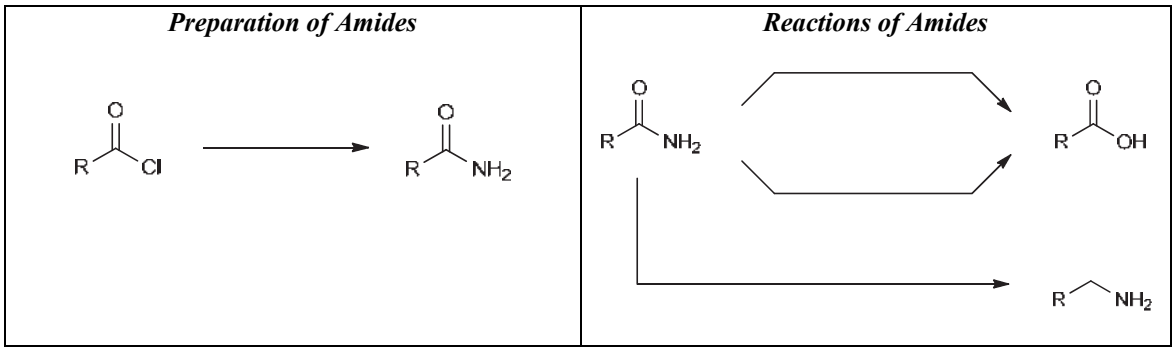


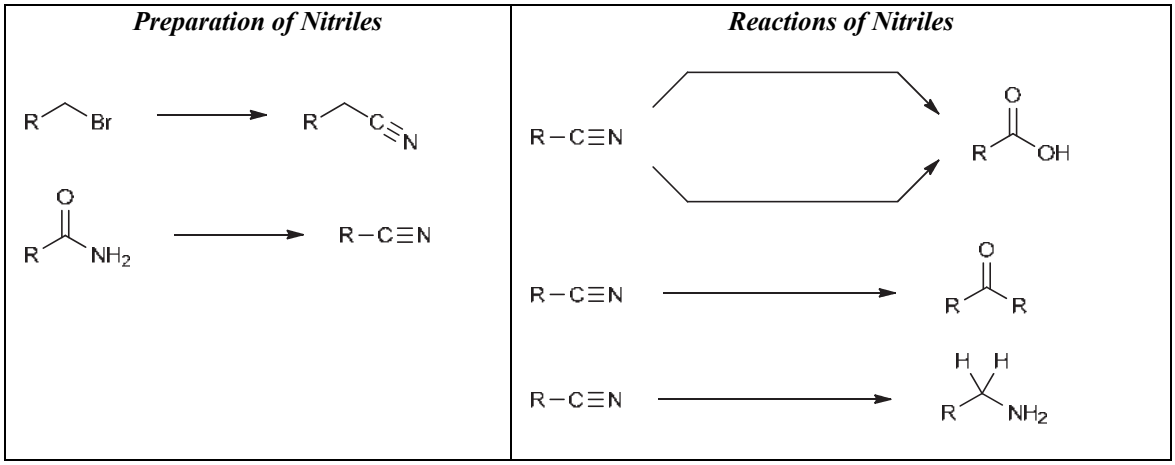
Preparation of Esters



Reactions of Esters

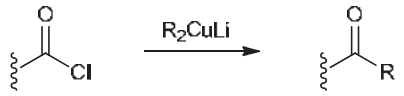




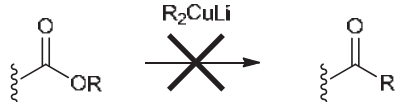


Common Mistake to Avoid

This chapter covers many reactions. One of these reactions is between an acid chloride and a lithium dialkyl cuprate, giving a ketone as the product:



The resulting ketone is not further attacked by the lithium dialkyl cuprate (unlike a Grignard reagent, which would attack the ketone). For some reason, students commonly propose a similar reaction between an ester and a lithium dialkyl cuprate:



This reaction will not work. If a lithium dialkyl cuprate will not attack a ketone, then it certainly won't attack an ester (which is less electrophilic than a ketone). Students often make this type of mistake, by applying a reaction outside of the scope in which it was discussed. Try to avoid doing this. Whenever we cover a reaction that applies to a particular functional group, you cannot assume that it will apply to other, less reactive, functional groups as well.

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Useful reagents

The following is a list of reagents encountered in this chapter:

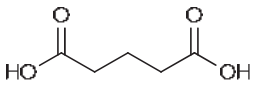
Reagents	Description
NaCN	This reagent will react with an alkyl halide to give a nitrile. Subsequent hydrolysis of the nitrile gives a carboxylic acid, with one more carbon atom than the starting alkyl halide.
1) Mg 2) CO_2 3) H_3O^+	These reagents can be used to convert an alkyl halide into a carboxylic acid, with the introduction of one carbon atom. Insertion of magnesium gives a Grignard reagent, which then attacks carbon dioxide to give a carboxylate ion, which is the protonated upon acid work-up.
1) $LiAlH_4$ 2) H_2O	Lithium aluminum hydride is a powerful hydride reducing agent. It will reduce ketone, aldehydes, esters and carboxylic acids to give alcohols. Reduction of esters and carboxylic acids requires the use of excess $LiAlH_4$. Reduction of an amide (with $LiAlH_4$) gives an amine.
	Pyridine is a weak base that is often used as an "acid sponge," for reactions that produce a strong acid as a by-product.
$SOCl_2$	Thionyl chloride can be used to convert a carboxylic acid into an acid halide. This reagent can also be used to dehydrate an amide to give a nitrile.
ROH	Alcohols are weak nucleophiles and weak bases. An alcohol can be used to convert an acid chloride or an acid anhydride into an ester.
NH_3	Ammonia is both a base and a nucleophile. Excess ammonia can be used to convert an acid chloride or an acid anhydride into an amide.
RNH_2	Primary amines are bases and nucleophiles. Excess amine can be used to convert an acid chloride or an acid anhydride into an amide.
R_2NH	Secondary amines are bases and nucleophiles. Excess amine can be used to convert an acid chloride or an acid anhydride into an amide.
1) xs RMgBr 2) H_2O	A Grignard reagent is a strong nucleophile. Two equivalents of a Grignard reagent will react with an acid chloride, with an anhydride, or with an ester, followed by water work-up, to give an alcohol (with the introduction of two R groups). A Grignard reagent will also react with a nitrile, followed by water work-up, to give a ketone.
R_2CuLi	A lithium dialkyl cuprate is a weak nucleophile. It will react with an acid chloride to give a ketone, but it will not react with ketones or esters.
1) $LiAl(OR)_3H$ 2) H_2O	Lithium trialkoxy aluminum hydrides are reducing agents that will convert an acid chloride or an acid anhydride into an aldehyde, without subsequent reduction of the resulting aldehyde.
1) DIBAH 2) H_2O	Diisobutyl aluminum hydride is a hydride reducing agent that will convert an ester into an aldehyde.
H_3O^+	Aqueous acid will cause hydrolysis of an acid chloride, an anhydride, an ester, an amide, or a nitrile to give a carboxylic acid.
$[H^+]$, ROH	Under acidic conditions, an alcohol will react with a carboxylic acid via a Fischer esterification, giving an ester.

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Solutions

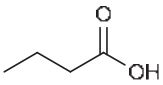
20.1.

(a) In this molecule, the longest chain that contains both carboxylic acid groups is comprised of five carbon atoms, so the parent name (pentane) is given the suffix "–dioic acid", resulting in the IUPAC name pentanedioic acid. The common name is glutaric acid.



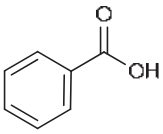
IUPAC name = pentanedioic acid
Common name = glutaric acid

(b) In this molecule, the longest chain that contains the carboxylic acid group is comprised of four carbon atoms, so the "e" in the parent name (butane) is replaced with the suffix "-oic acid", resulting in the IUPAC name butanoic acid. The common name is butyric acid.



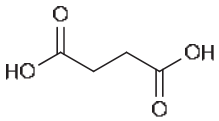
IUPAC name = butanoic acid
Common name = butyric acid

(c) The carboxylic acid group is attached to a ring, so the IUPAC name for this compound uses the name of the ring followed by the suffix "-carboxylic acid"; thus this compound is benzenecarboxylic acid. The common name is benzoic acid.



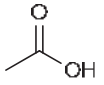
IUPAC name = benzenecarboxylic acid
Common name = benzoic acid

(d) In this molecule, the longest chain that contains both carboxylic acid groups is comprised of four carbon atoms, so the parent name (butane) is given the suffix "–dioic acid", resulting in the IUPAC name butanedioic acid. The common name is succinic acid.



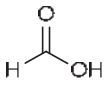
IUPAC name = butanedioic acid
Common name = succinic acid

(e) In this molecule, the parent chain is comprised of two carbon atoms, and the "e" in the parent name (ethane) is replaced with the suffix "-oic acid", resulting in the IUPAC name ethanoic acid. The common name is acetic acid.



IUPAC name = ethanoic acid
Common name = acetic acid

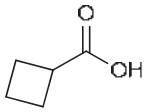
(f) In this molecule, which contains only one carbon atom, the "e" in the parent name (methane) is replaced with the suffix "-oic acid", resulting in the IUPAC name methanoic acid. The common name is formic acid.



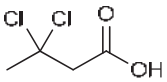
IUPAC name = methanoic acid
Common name = formic acid

20.2.

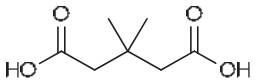
(a) This molecule has a four-membered ring (cyclobutane) connected to a carboxylic acid group.



(b) The parent (butyric acid) has a four-carbon chain with a carboxylic acid at one terminus. The name indicates that there are two substituents (both chlorine atoms) at the C3 position.



(c) The parent (glutaric acid) has a five-carbon chain with a carboxylic acid at each terminus. The name indicates that there are two substituents (both methyl groups) at the C3 position.

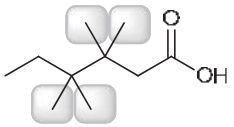


20.3.

(a) We begin by identifying the parent. The carbon atom of the carboxylic acid group must be included in the parent. The longest chain that includes this carbon atom is six carbon atoms in length, so the parent is hexanoic acid. There are four substituents (highlighted), all of which are methyl groups. Notice that the parent chain is numbered starting from the carbonyl carbon (defined as C1). According to this numbering scheme, two methyl

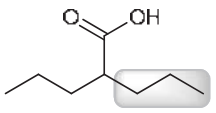
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groups are at C3, and two are at C4. We use the prefix "tetra" to indicate four methyl groups.



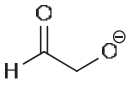
3,3,4,4-tetramethylhexanoic acid

(b) We begin by identifying the parent. The carbon atom of the carboxylic acid must be included in the parent. The longest chain that includes this carbon atom is five carbon atoms in length, so the parent is pentanoic acid. There is one substituent: a propyl group (highlighted). Notice that the parent chain is numbered starting from the carbonyl carbon (defined as C1). According to this numbering scheme, the propyl group is at C2.

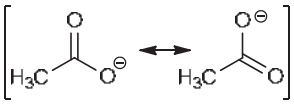


2-propylpentanoic acid

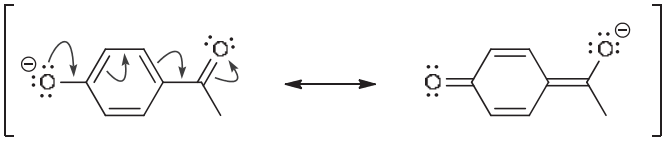
20.4. The conjugate base of the first compound is not resonance stabilized.



The second compound is more acidic because its conjugate base is resonance-stabilized:



20.5. The conjugate base is resonance stabilized, with the negative charge spread over two oxygen atoms (much like the conjugate base of a carboxylic acid), as shown below. Note: there are three additional resonance structures that have not been drawn (each of which exhibits the negative charge on a carbon atom).



20.6. The first step is to draw the conjugate base of each molecule, including all relevant resonance structures. *meta*-Hydroxyacetophenone is expected to be less acidic than *para*-hydroxyacetophenone, because in the conjugate base of the former, the negative charge is spread over only one oxygen atom (and three carbon atoms). In contrast, the conjugate base of *para*-hydroxyacetophenone has the negative charge spread over two oxygen atoms (and three carbon atoms). The additional resonance structure of the latter conjugate base renders it more stable.

20.7. The first step is to identify the acid (formic acid) and base (hydroxide). When drawing a mechanism for an acid-base reaction, two curved arrows are required, as shown below. The tail of the first arrow is placed on a lone pair of the hydroxide oxygen atom, and the head is placed on the acidic hydrogen atom of formic acid. The tail of the second arrow is placed on the O-H bond, and the head is placed on the oxygen atom. The resulting carboxylate salt is named starting with the inorganic cation (potassium) followed by replacing the "-ic acid" suffix from formic acid to "-ate" giving the name potassium formate.



formic acid potassium formate

20.8. To determine the relative amounts of acetic acid and its conjugate base (acetate), we plug the pK_a of acetic acid (4.76) and the pH (5.76) into the rearranged Henderson-Hasselbach equation as shown below:

$$\frac{[\text{conjugate base}]}{[\text{acid}]} = 10^{(\text{pH} - \text{p}K_a)} = 10^{(5.76 - 4.76)} = 10^1 = 10$$

The result shows that the conjugate base predominates under these conditions (at a ratio of 10:1).

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20.9. For each set of acids, we need to assess the relative stability of each of the conjugate bases. A more stable conjugate base means that the corresponding acid is more acidic. When comparing the structures, we need to consider the nature of the substituents and their position relative to the carboxylic acid functional group. Electron-withdrawing groups stabilize the conjugate base while electron-donating groups destabilize the conjugate base. Substituents that are closer to the carboxylic acid have a greater effect on acidity.

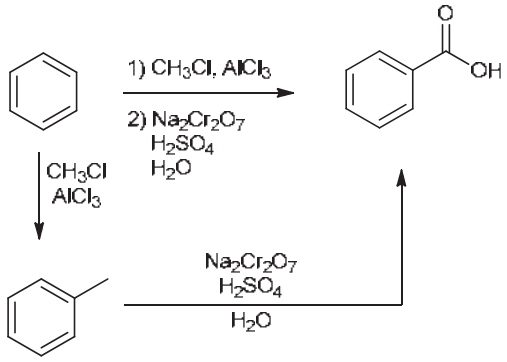
(a) Each of the three acids has the same four-carbon parent: butyric acid. The first two molecules have two electron-withdrawing chlorine substituents each, rendering them more acidic than the third molecule, which has two electron-donating methyl groups. The difference between the first two molecules is in the relative positions of the two chlorine atoms. The compound with the two chlorine atoms on positions C2 and C3 is more acidic than the compound with the chlorine atoms on positions C2 and C4. The chlorine atom on C3 has a greater effect than the chlorine atom on C4. The correct order, in increasing acidity, is thus: 3,4-dimethylbutyric acid < 2,4-dichlorobutyric acid < 2,3-dichlorobutyric acid.

(b) Each of the three acids has the same three-carbon parent: propionic acid. The first molecule has an electron-withdrawing bromine substituent on C3 and the other two molecules have two bromine substituents each. The compound with two bromine atoms on C2 is the most acidic because the two bromine atoms are closest to the carboxylic acid group. The compound with two bromine atoms on C3 is more acidic than the compound with one carbon atom on C3 due to the additive effect of the two bromine atoms. The correct order, in increasing acidity, is thus: 3-bromopropionic acid < 3,3-dibromopropionic acid < 2,2-dibromo-propionic acid.

20.10.
(a) The starting material is an alcohol (ethanol) and the product is the corresponding carboxylic acid with two carbon atoms (acetic acid). Reagents that accomplish this oxidation reaction are: $Na_2Cr_2O_7$, H_2SO_4, H_2O.

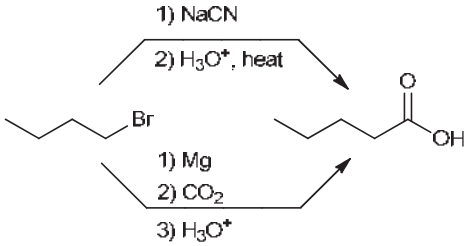
(b) The conversion of toluene to benzoic acid requires oxidation of the methyl group to give a carboxylic acid group. Recall that an alkyl group attached to an aromatic ring is oxidized to a carboxylic acid by a strong oxidizing agent, as long as the alkyl group has at least one benzylic hydrogen atom. This conversion can thus be accomplished using: $Na_2Cr_2O_7$, H_2SO_4, H_2O.

(c) The conversion of benzene to benzoic acid requires the installation of a carbon atom on the carbon skeleton of the starting material. One approach to accomplish this transformation is to install a methyl group using a Friedel-Crafts alkylation (CH_3Cl, $AlCl_3$) followed by an oxidation of the methyl group using strongly oxidizing conditions, as shown.



There are certainly other acceptable solutions. For example, bromination of benzene, followed by treatment of the resulting bromobenzene with magnesium, gives phenyl magnesium bromide. This Grignard reagent can then be treated with CO_2, followed by acid work-up, to give benzoic acid. This alternate solution illustrates an important point. For most of the synthesis problems that you will encounter, there is rarely only one correct approach. Most often, there are multiple correct ways to approach the problem.

(d) The starting material (1-bromobutane) has four carbon atoms, and the product (pentanoic acid) has five carbon atoms, so we need to propose a synthesis that involves installation of the fifth carbon atom. We can use NaCN to convert the four-carbon starting material to a five-carbon synthetic intermediate (a nitrile) via an S_N2 process. Hydrolysis of this intermediate (H_3O^+, heat) converts the nitrile to a carboxylic acid, giving the desired product. An alternate approach is to convert the starting alkyl halide to the corresponding Grignard reagent using Mg, followed by reaction with CO_2 to produce a carboxylate. Protonation with aqueous acid gives the desired carboxylic acid.

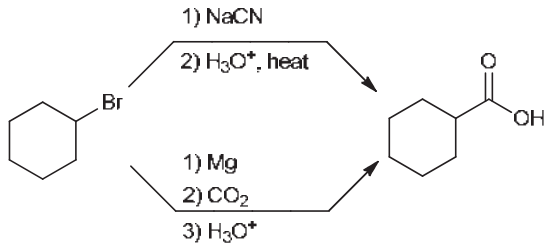


(e) The conversion of ethylbenzene to benzoic acid requires an oxidation of the benzylic carbon atom of the starting material to form a carboxylic acid group. Recall that an alkyl group attached to an aromatic ring is oxidized to a carboxylic acid by a strong oxidizing agent, as long as the alkyl group has at least one benzylic hydrogen atom. This conversion can thus be accomplished using: $Na_2Cr_2O_7$, H_2SO_4, H_2O.

(f) The starting material (bromocyclohexane) has six carbon atoms, and the product (cyclohexanecarboxylic acid) has seven carbon atoms, so we need to propose a synthesis that includes the installation of the seventh

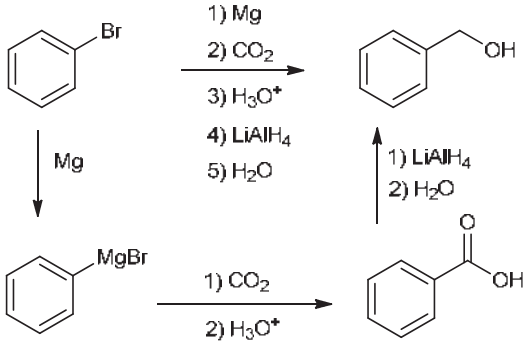
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carbon atom. We can use NaCN to convert the six-carbon starting material to a seven-carbon synthetic intermediate via an S_N2 process. Hydrolysis of this intermediate (H_3O^+, heat) converts the nitrile to a carboxylic acid, giving the desired product. An alternate approach is to convert the starting alkyl halide to the corresponding Grignard reagent using Mg, followed by reaction with CO_2 to produce a carboxylate. Protonation with aqueous acid gives the desired carboxylic acid.

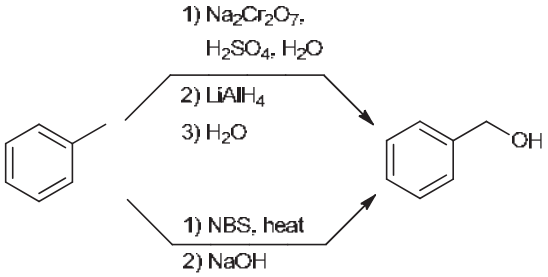


20.11.

(a) This synthesis requires the conversion of a six-carbon starting material (bromobenzene) to a seven-carbon product (benzyl alcohol), so we must include a reaction to form a new C-C bond. There are certainly multiple solutions to this problem. One such solution involves conversion of the starting material into a Grignard reagent, which can then be treated with CO_2 followed by acidic workup (H_3O^+) to produce benzoic acid. Reduction of the carboxylic acid using lithium aluminum hydride, followed by protonation with water, produces the desired product (benzyl alcohol) as shown.

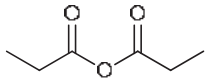


(b) The starting material (toluene) and product (benzyl alcohol) have seven carbon atoms each. Oxidation of the starting material to benzoic acid can be accomplished with a suitable oxidizing agent to give benzoic acid. Reduction of the resulting carboxylic acid using lithium aluminum hydride followed by protonation with water produces the desired product (benzyl alcohol) as shown. Alternatively, a bromine atom can be installed in the benzylic position using NBS/heat. Subsequent reaction with NaOH produces the desired product via an S_N2 reaction, as shown:



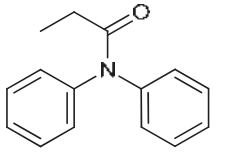
20.12.

(a) This symmetric anhydride is named by replacing "acid" from the corresponding carboxylic acid (propionic acid) with the suffix "anhydride", giving the name propionic anhydride.



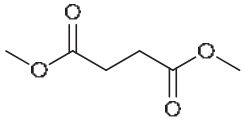
propionic anhydride

(b) This amide is named as a derivative of the carboxylic acid "propionic acid" by replacing the "-ic acid" suffix with "-amide". The two phenyl groups attached to the nitrogen atom are listed as substituents. Their position is indicated by the locant "*N*" thus giving the name *N*,*N*-diphenylpropionamide.



N,*N*-diphenylpropionamide

(c) This diester is named as a derivative of the parent dicarboxylic acid "succinic acid" by replacing the "-ic acid" suffix with "-ate". The two methyl groups attached to the oxygen atoms are indicated at the beginning, thus giving the name dimethyl succinate.

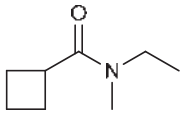


dimethyl succinate

(d) This amide is named as a derivative of "cyclobutanecarboxylic acid" by replacing "-carboxylic acid" with "-carboxamide". The two alkyl groups attached to the nitrogen atom (ethyl and methyl) are listed in alphabetical order as substituents. Their

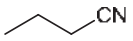
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position is indicated with the locant "*N*" thus giving the name *N*-ethyl-*N*-methylcyclobutanecarbox-amide.



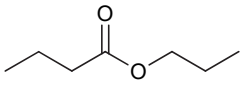
N-ethyl-*N*-methylcyclobutanecarboxamide

(e) This nitrile is named as a derivative of the carboxylic acid "butyric acid" by replacing the "-ic acid" suffix with "-onitrile" giving the name butyronitrile.



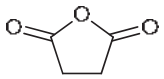
butyronitrile

(f) This ester is named as a derivative of the parent carboxylic acid "butyric acid" by replacing the "-ic acid" suffix with "-ate". The propyl group attached to the oxygen atom is indicated at the beginning, thus giving the name propyl butyrate.



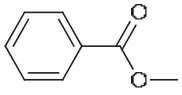
propyl butyrate

(g) This cyclic anhydride is named as a derivative of the parent dicarboxylic acid "succinic acid" by replacing "acid" with "anhydride", giving the name succinic anhydride.



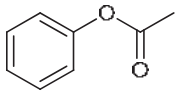
succinic anhydride

(h) This ester is named as a derivative of the parent carboxylic acid "benzoic acid" by replacing the "-oic acid" suffix with "-ate". The methyl group attached to the oxygen atom is indicated at the beginning, thus giving the name methyl benzoate.



methyl benzoate

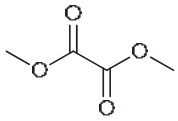
(i) This ester is named as a derivative of the parent carboxylic acid "acetic acid" by replacing the "-ic acid" suffix with "-ate". The phenyl group attached to the oxygen atom is indicated at the beginning, thus giving the name phenyl acetate.



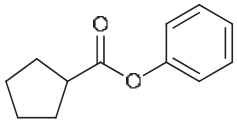
phenyl acetate

20.13.

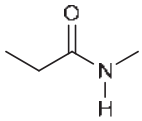
(a) The parent (oxalic acid) is a dicarboxylic acid with two carbon atoms. The suffix "-ic acid" is replaced with "-ate", indicating that this is a diester. The name indicates that the two alkyl groups attached to the oxygen atoms are methyl groups.



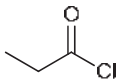
(b) The parent (cyclopentanecarboxylic acid) is a ring with five carbon atoms attached to a carboxylic acid. The suffix "-ic acid" is replaced with "-ate", indicating that this is an ester. The name indicates that the group attached to the oxygen atom is a phenyl group.



(c) The parent (propionic acid) is a carboxylic acid with three carbon atoms. The suffix "-ic acid" is replaced with "-amide", indicating that this compound is an amide. The name indicates that there is one methyl group attached to the nitrogen atom.



(d) The parent (propionic acid) is a carboxylic acid with three carbon atoms. The suffix "-ic acid" is replaced with "-yl chloride", indicating that this compound is an acid chloride.

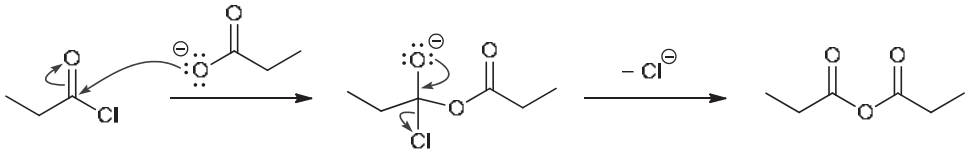


20.14.

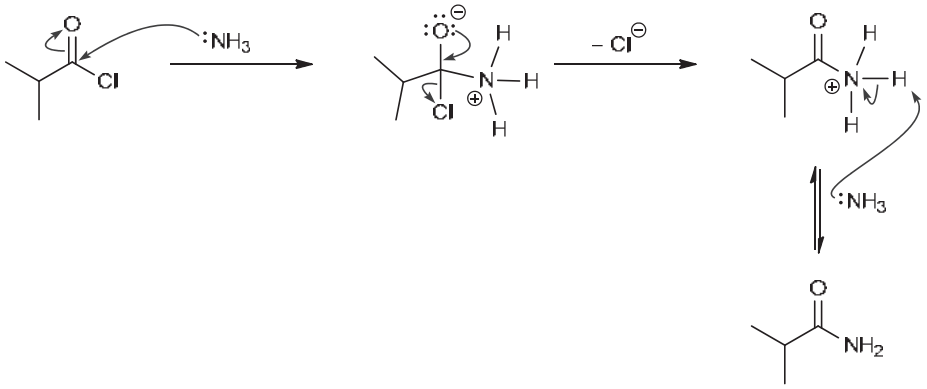
(a) This mechanism has two steps: 1) nucleophilic attack, and 2) loss of a leaving group. The first step (nucleophilic attack), requires two curved arrows, which show the carboxylate ion functioning as a nucleophile and attacking the electrophilic carbonyl group, resulting in a tetrahedral intermediate. In step two (loss of a leaving group), the carbonyl

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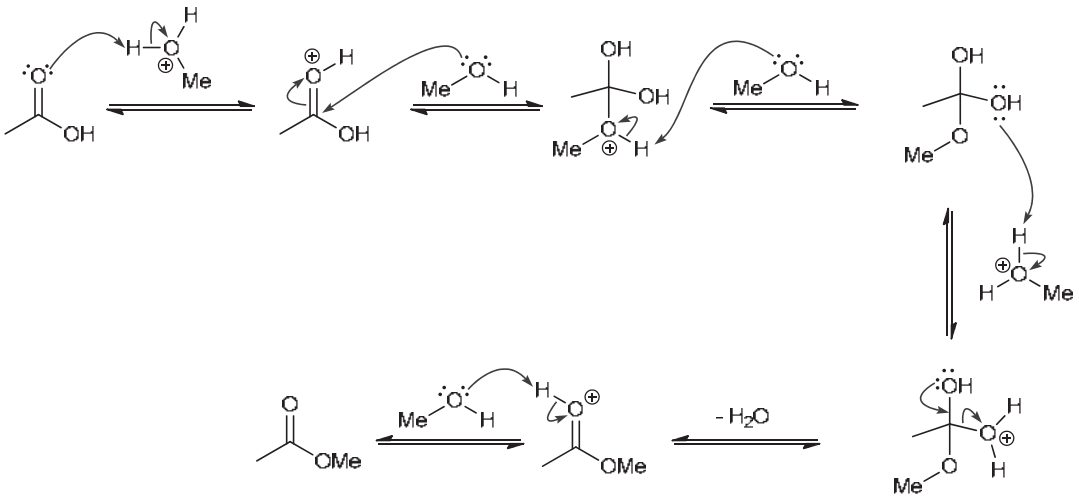
group is reformed and chloride leaves, as shown with two curved arrows, resulting in the formation of an anhydride, as shown.



(b) This mechanism has three steps: 1) nucleophilic attack, 2) loss of a leaving group and 3) proton transfer. The first step (nucleophilic attack) requires two curved arrows, which show ammonia functioning as a nucleophile and attacking the electrophilic carbonyl group, resulting in a tetrahedral intermediate. In step two (loss of a leaving group), the carbonyl group is reformed and chloride leaves, as shown with two curved arrows. In the third step (proton transfer), a second equivalent of ammonia serves as a base, deprotonating the cationic intermediate, resulting in the formation of an amide, as shown.

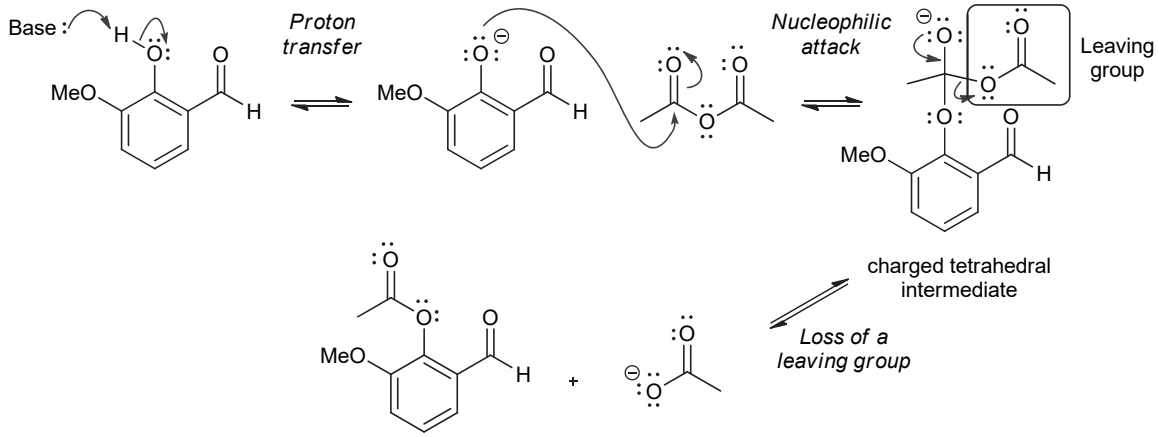


(c) This reaction occurs under acidic conditions, so we must avoid formation of a strong base. Thus, proton transfers are required at multiple stages in the mechanism. The mechanism shown below has six steps: 1) proton transfer, 2) nucleophilic attack, 3) proton transfer, 4) proton transfer, 5) loss of a leaving group and 6) proton transfer. The first step (proton transfer) requires two curved arrows to show the transfer of a proton from $MeOH_2^+$ to the carbonyl group, resulting in the formation of an activated electrophile. In step two (nucleophilic attack), methanol serves as a nucleophile attacking the protonated carbonyl group, producing a cationic tetrahedral intermediate. We cannot immediately expel the OH group at this stage, as this would result in the formation of a strong base (hydroxide). This must be avoided in acidic conditions. In step 3 (proton transfer), methanol serves as a base, resulting in a neutral intermediate. Subsequently, in step 4 (proton transfer) a proton is transferred from $MeOH_2^+$ to the uncharged oxygen atom, as shown. In step 5 (loss of leaving group), the carbonyl group is reformed and water serves as the leaving group. In step 6 (proton transfer), methanol serves as a base which deprotonates the cationic intermediate, resulting in formation of the ester.

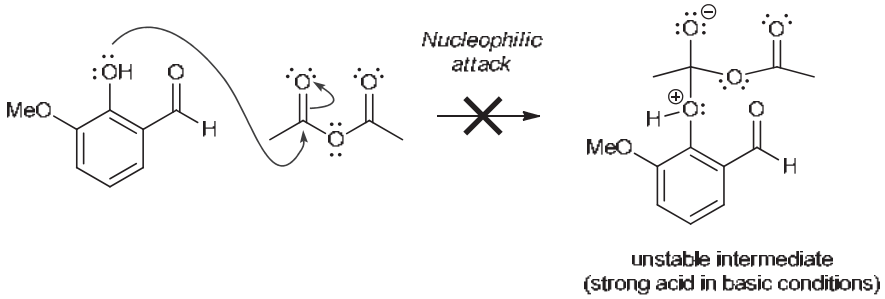


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20.15. Since the reaction conditions are basic, we begin the mechanism with a deprotonation of the acidic phenol proton. The resulting phenolate ion is a good nucleophile that can attack the carbonyl group of the anhydride. Loss of the leaving group from the charged tetrahedral intermediate completes the nucleophilic acyl substitution.



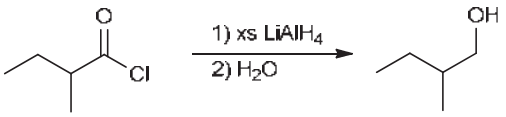
Note that unlike with an amine nucleophile, it is unacceptable to attack with a neutral alcohol (or phenol) nucleophile because that would result in formation of a strong acid (oxygen atom with a localized positive charge) in basic conditions.



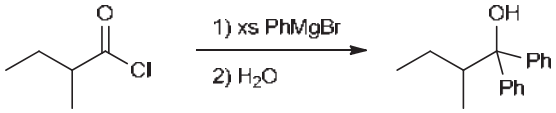
Instead, deprotonation of the alcohol occurs first, before nucleophilic attack.

20.16.

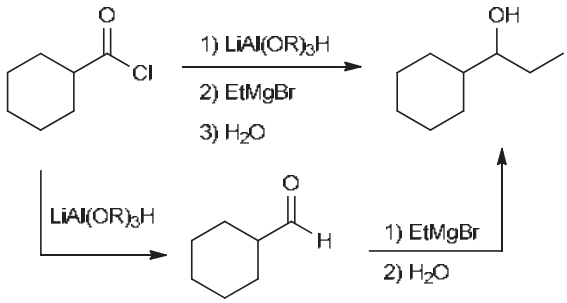
(a) The reaction of an acid chloride with excess $LiAlH_4$, followed by water work-up, results in the formation of the corresponding alcohol shown below.



(b) The reaction of an acid chloride with excess phenyl magnesium bromide, followed by water work-up, results in the incorporation of two phenyl groups, giving a tertiary alcohol.



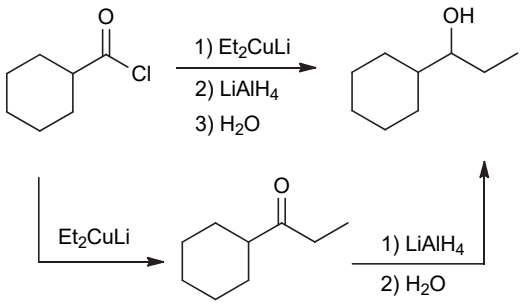
(c) The reaction of an acid chloride with the selective hydride-reducing agent, $LiAl(OR)_3H$, produces an aldehyde. Subsequent reaction with a Grignard reagent, followed by water work-up, gives a secondary alcohol.



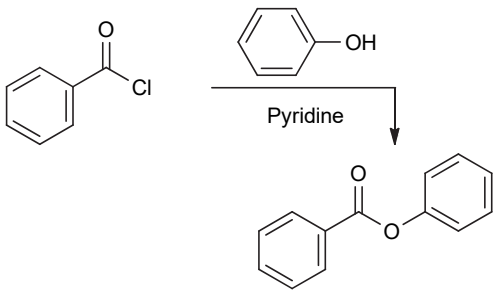
(d) The reaction of an acid chloride with a lithium dialkyl cuprate (a selective carbon nucleophile) produces

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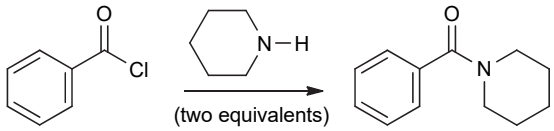
a ketone. Subsequent reaction with $LiAlH_4$, followed by water work-up, gives a secondary alcohol.



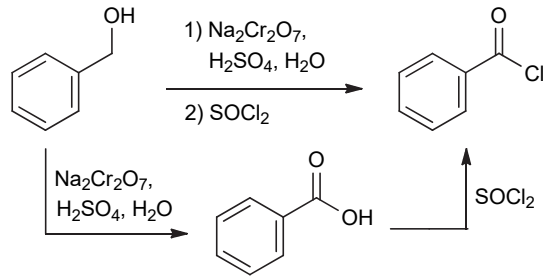
(e) The reaction of an acid chloride with phenol (in the presence of pyridine) results in the replacement of the chlorine atom with the phenol oxygen atom, producing an ester, as shown.



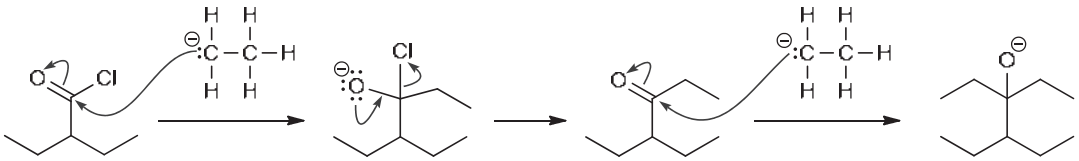
(f) The reaction of an acid chloride with two equivalents of an amine results in the replacement of the chlorine atom with the amine nitrogen atom, producing an amide, as shown.



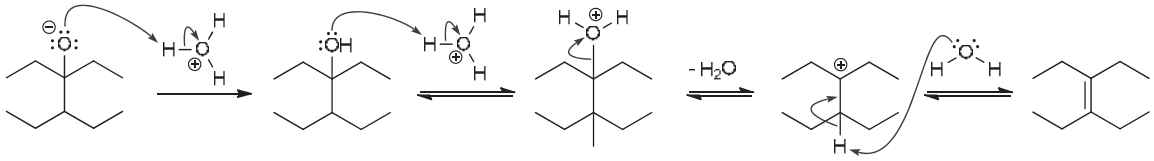
20.17. The conversion of benzyl alcohol to benzoyl chloride requires oxidation of the benzylic carbon atom. Subsequent reaction with thionyl chloride results in the conversion of the carboxylic acid to the desired acid chloride.



20.18. The reaction between an acid chloride and a Grignard reagent occurs via the following mechanism. In the first step (nucleophilic attack), the anionic carbon atom of the Grignard reagent serves as a nucleophile and attacks the electrophilic carbonyl group, resulting in a tetrahedral intermediate. In step two (loss of a leaving group), the carbonyl group is reformed and chloride leaves, shown with two curved arrows. In step three (nucleophilic attack), a second equivalent of the Grignard reagent attacks the carbonyl group of the intermediate ketone, resulting in the formation of another tetrahedral intermediate.



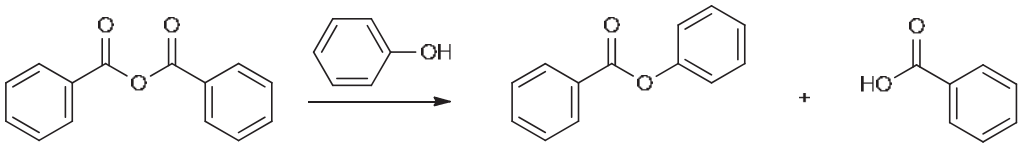
Once this reaction is complete, concentrated acid is added to the reaction flask. H_3O^+ serves as an acid, protonating the alkoxide ion and producing an alcohol. Under these strongly acidic conditions, the alcohol is further protonated, giving an oxonium ion. Loss of water generates a tertiary carbocation, which can then be deprotonated (an E1 process). Note that removal of this proton results in the more substituted alkene (the Zaitsev product).



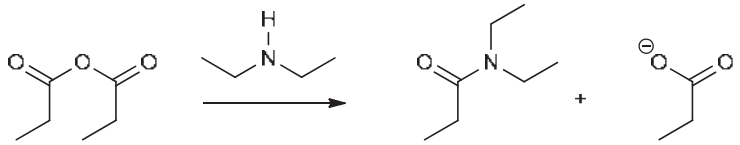
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20.19.

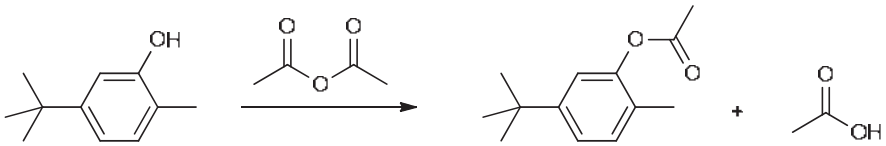
(a) The reaction of an acid anhydride with phenol results in replacement of the carboxylate leaving group with the phenol oxygen atom. After a proton transfer, the following ester and carboxylic acid are produced.



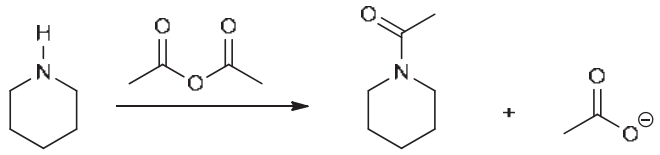
(b) The reaction of an acid anhydride with diethylamine results in replacement of the carboxylate leaving group with the amine nitrogen atom. After a proton transfer, the following amide and a carboxylate ion are produced. You might be wondering why a carboxylate ion is drawn rather than a carboxylic acid. This will be discussed in Chapter 23, but here is a preview: In the presence of excess diethylamine, the resulting carboxylic acid is deprotonated to give a carboxylate ion (compare the pK_a values of an ammonium ion and a carboxylic acid, which can be found in the pK_a table on the inside cover of the textbook).



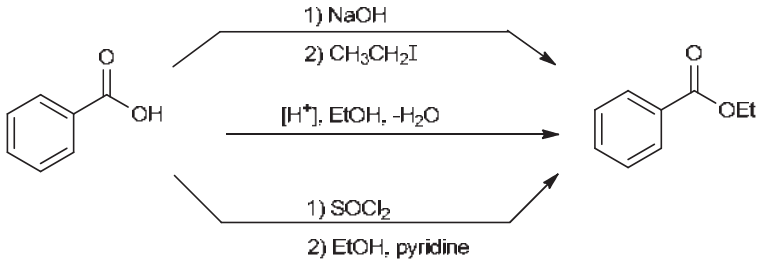
(c) The reaction of a phenol derivative with acetic anhydride results in the replacement of the carboxylate leaving group with the phenol oxygen atom. After a proton transfer, the following ester and carboxylic acid are produced.



(d) The reaction of an acid anhydride with a cyclic secondary amine results in the replacement of the carboxylate leaving group with the amine nitrogen atom. After a proton transfer, the following amide and carboxylic acid are produced. You might be wondering why a carboxylate ion is drawn rather than a carboxylic acid. This will be discussed in Chapter 23, but here is a preview: In the presence of excess amine, the resulting carboxylic acid is deprotonated to give a carboxylate ion (compare the pK_a values of an ammonium ion and a carboxylic acid, which can be found in the pK_a table on the inside cover of the textbook).



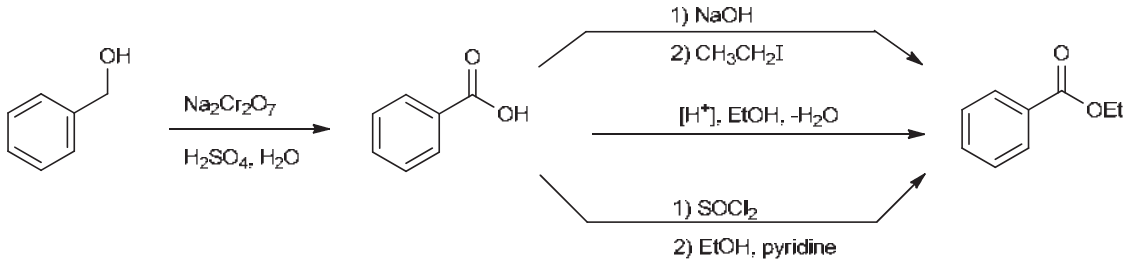
20.20. Three methods of converting benzoic acid to ethyl benzoate are shown below. In the first method, benzoic acid is deprotonated by NaOH. The intermediate salt (sodium benzoate) serves as a nucleophile in a subsequent S_N2 reaction with ethyl iodide. The second method is a Fischer esterification process, in which ethanol serves as both the solvent and a weak nucleophile. In the third method, benzoic acid is first converted to benzoyl chloride, and subsequently treated with ethanol (in the presence of pyridine) to produce the desired ester.



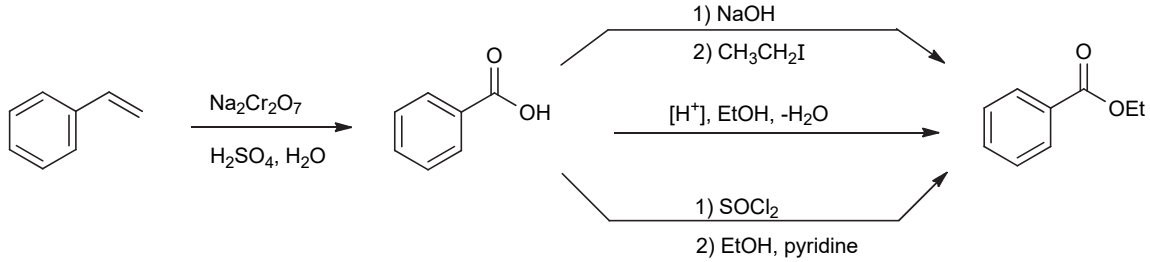
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20.21.

(a) Oxidation of benzyl alcohol to benzoic acid is accomplished using strongly oxidizing conditions, as shown below. Subsequent conversion to the corresponding ethyl ester can be accomplished by any of the three methods shown, as described above in the solution to problem 20.20.

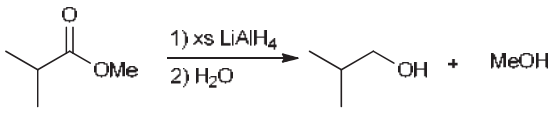


(b) Oxidation of styrene to benzoic acid is accomplished using strongly oxidizing conditions, as shown below. Subsequent conversion to the corresponding ethyl ester can be accomplished by any of the three methods shown, as described above in the solution to problem 20.20.



20.22.

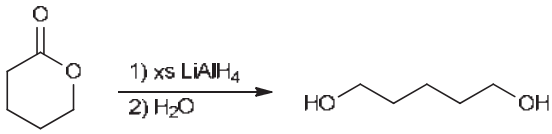
(a) The first equivalent of lithium aluminum hydride reduces the ester to an aldehyde in two mechanistic steps (nucleophilic attack of $LiAlH_4$, then loss of methoxide). A second equivalent further reduces the aldehyde to the corresponding alkoxide, which is subsequently protonated by water. Overall, $LiAlH_4$ supplies two equivalents of hydride that are incorporated into the product.



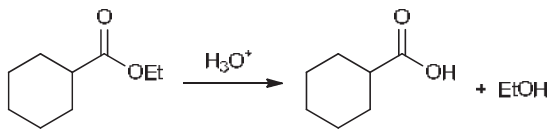
(b) The first equivalent of the Grignard reagent attacks the carbonyl group, thereby converting the ester into a ketone in two mechanistic steps (nucleophilic attack of EtMgBr, followed by loss of methoxide). A second equivalent of the Grignard reagent then attacks the carbonyl group of the ketone intermediate to produce an alkoxide ion, which is subsequently protonated by water. Overall, two ethyl substituents are incorporated into the product.



(c) The first equivalent of lithium aluminum hydride reduces the ester to an aldehyde in two mechanistic steps (nucleophilic attack of $LiAlH_4$, followed by loss of a leaving group, which remains tethered to the aldehyde group via the alkyl chain). A second equivalent of lithium aluminum hydride further reduces the aldehyde to the corresponding alkoxide. The resulting dianion is protonated upon treatment with water. Overall, $LiAlH_4$ supplies two equivalents of hydride that are incorporated into the product.

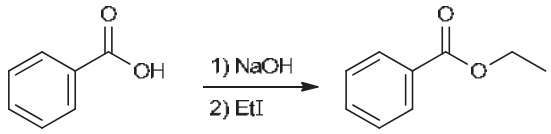


(d) Upon treatment with aqueous acid, an ethyl ester is hydrolyzed to the corresponding carboxylic acid and ethanol. The reaction occurs under acid-catalyzed conditions, in which an OH group ultimately replaces the OEt group of the ester.

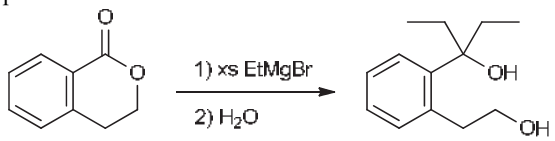


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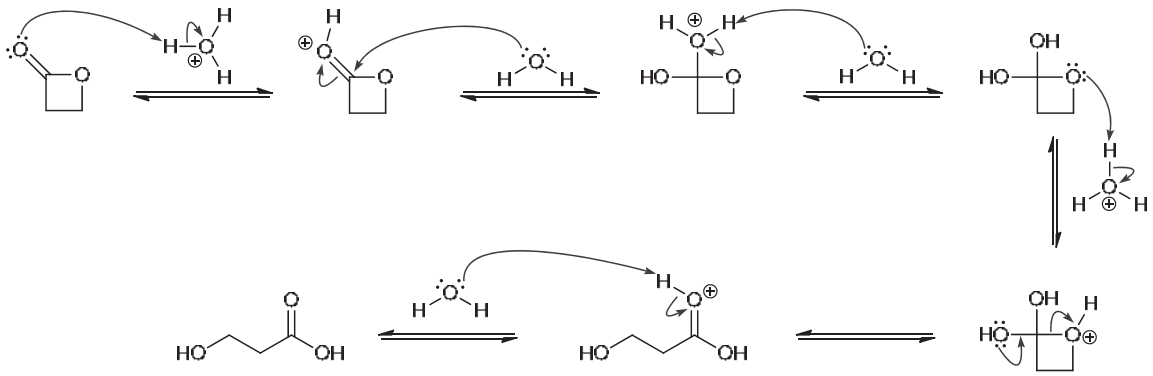
(e) In step 1, benzoic acid is deprotonated by NaOH. The intermediate salt (sodium benzoate) serves as a nucleophile in a subsequent S_N2 reaction with ethyl iodide, giving an ester, as shown.



(f) The first equivalent of the Grignard reagent attacks the carbonyl group, thereby converting the cyclic ester into an acyclic ketone in two mechanistic steps (nucleophilic attack of EtMgBr, followed by loss of the leaving group, which remains tethered to the molecule via the alkyl chain attached to the aromatic ring). A second equivalent of the Grignard reagent attacks the carbonyl group of the ketone intermediate to produce an alkoxide ion, which is subsequently protonated by water. Overall, two ethyl substituents are incorporated into the product.

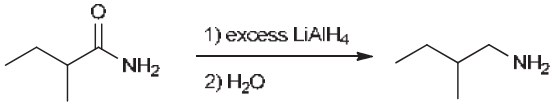


20.23. This reaction occurs under acidic conditions, so we must avoid formation of a strong base. Thus, proton transfers are required at multiple stages in the mechanism. The mechanism shown below has six steps: 1) proton transfer, 2) nucleophilic attack, 3) proton transfer, 4) proton transfer, 5) loss of a leaving group and 6) proton transfer. The first step (proton transfer), requires two curved arrows to show the transfer of a proton from H_3O^+ to the carbonyl group, resulting in formation of an activated electrophile. In step two (nucleophilic attack), water serves as a nucleophile, attacking the protonated carbonyl group, producing a cationic tetrahedral intermediate. We cannot immediately expel the alkoxy group at this stage, as this would result in the formation of a strong base (an alkoxide ion). This must be avoided in acidic conditions. This oxygen atom must first be protonated. However, protonation at this stage would result in an intermediate with two positive charges, which should be avoided, if possible. Therefore, in the next step (step 3), water serves as a base, resulting in a neutral intermediate. Subsequently, in step 4 (proton transfer) a proton is transferred from H_3O^+ to the oxygen atom, as shown. In step 5 (loss of leaving group), the carbonyl group is reformed and an alcohol serves as the leaving group, resulting in the opening of the ring. In step 6 (proton transfer), water serves as a base which deprotonates the cationic intermediate, resulting in formation of a bifunctional product.

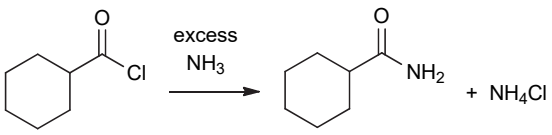


20.24.

(a) An amide is converted to the corresponding amine upon treatment with lithium aluminum hydride, followed by water work-up.

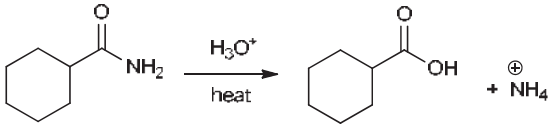


(b) The reaction of an acid chloride with excess ammonia results in replacement of the chloride leaving group with an NH_2 group.

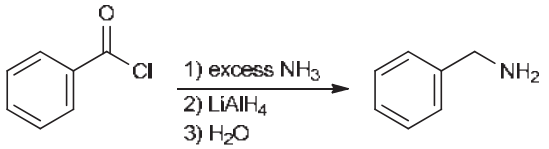


(c) An amide is hydrolyzed to give a carboxylic acid upon treatment with aqueous acid at elevated temperature. Under these acidic conditions, the by-product (ammonia) is protonated, resulting in formation of an ammonium ion.

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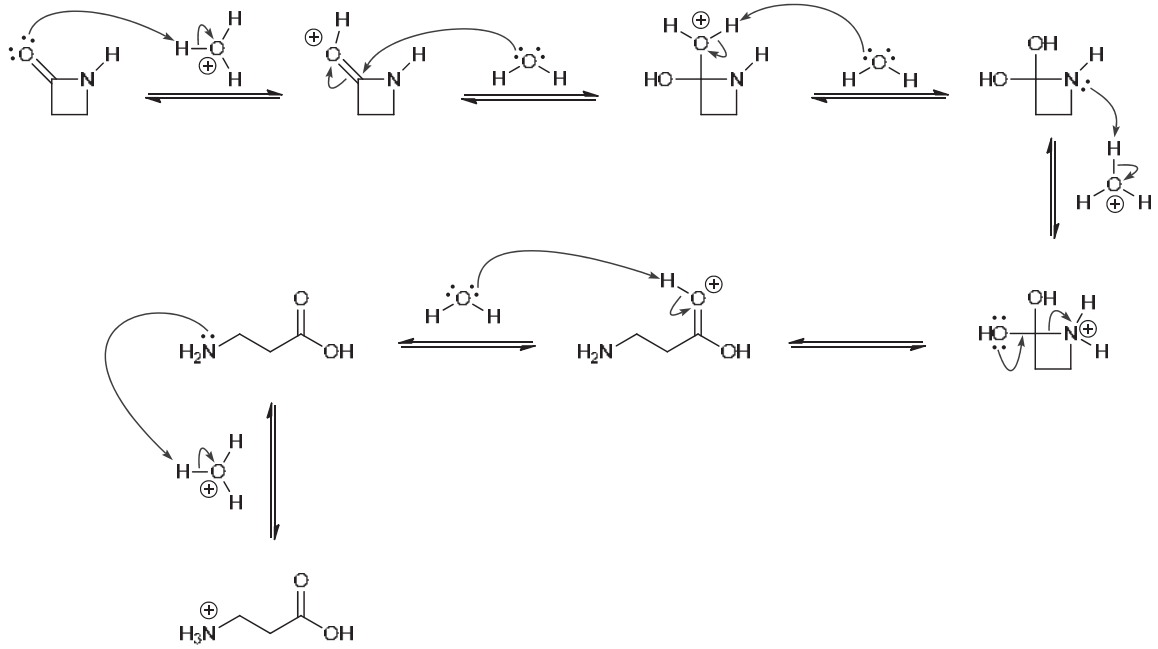


20.25. An acid chloride can be converted to an amine in two steps. First, the acid chloride is treated with excess ammonia to produce the corresponding amide. Subsequent reduction with lithium aluminum hydride, followed by protonation with water, produces benzyl amine, as shown.



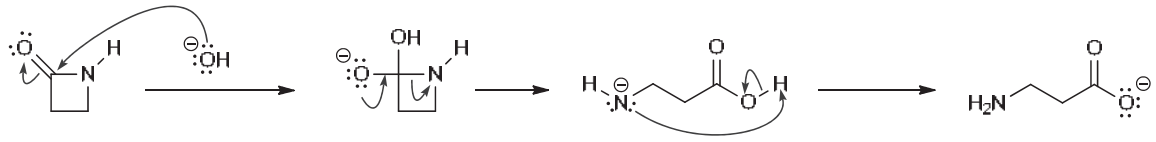
20.26.

(a) This reaction occurs under acidic conditions, so we must avoid formation of a strong base. Thus, proton transfers are required at multiple stages in the mechanism. The first step (proton transfer), requires two curved arrows to show the transfer of a proton from H_3O^+ to the carbonyl group, resulting in formation of an activated electrophile. In step two (nucleophilic attack), water serves as a nucleophile attacking the protonated carbonyl group, producing a cationic tetrahedral intermediate. We cannot immediately expel the amine group at this stage, as this would result in the formation of a strong base. This must be avoided in acidic conditions. This nitrogen atom must first be protonated. However, protonation at this stage would result in an intermediate with two positive charges, which should be avoided, if possible. Therefore, in the next step (step 3), water serves as a base, resulting in a neutral intermediate. Subsequently, in step 4 (proton transfer), a proton is transferred from H_3O^+ to the nitrogen atom, as shown. In step 5 (loss of leaving group), the carbonyl group is reformed and the amine serves as the leaving group, resulting in the opening of the ring. In step 6 (proton transfer), water serves as a base which deprotonates the cationic intermediate, resulting in formation of a bifunctional product. Under these acidic conditions, the amino group in the product is protonated to give an ammonium ion.



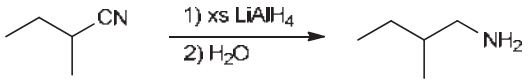
(b) This mechanism has three steps: 1) nucleophilic attack, 2) loss of a leaving group and 3) proton transfer. The first step (nucleophilic attack) requires two curved arrows, which show hydroxide functioning as a nucleophile and attacking the electrophilic carbonyl group, resulting in an anionic tetrahedral intermediate. In step two (loss of a leaving group), the carbonyl group is reformed as a result of cleavage of the carbon-nitrogen bond, thereby opening up the ring and resulting in formation of a bifunctional anionic intermediate containing a carboxylic acid group and a deprotonated amine. In the third step (proton transfer) the anionic nitrogen atom serves as a base, deprotonating the carboxylic acid group in an intramolecular process, resulting in the formation of a carboxylate ion.

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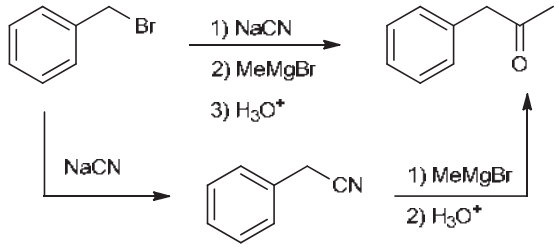


20.27.

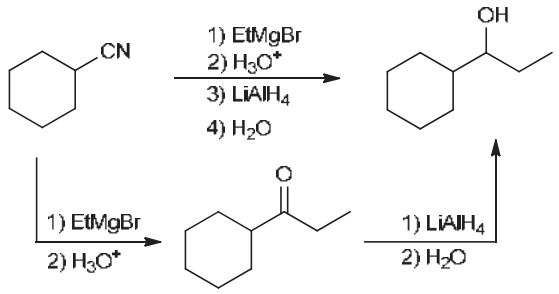
(a) $LiAlH_4$ reduces the C≡N triple bond to a single bond via incorporation of two equivalents of hydride, producing the primary amine shown.



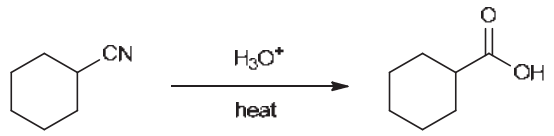
(b) Treating benzyl bromide with sodium cyanide results in the formation of an intermediate nitrile (shown) via an S_N2 reaction. Subsequent attack by a Grignard reagent produces an anionic intermediate which is then protonated and hydrolyzed with H_3O^+ to form the corresponding ketone.



(c) Reaction of a nitrile with a Grignard reagent produces an anionic intermediate which is subsequently protonated and hydrolyzed with H_3O^+ to form a ketone, as shown. Reduction with $LiAlH_4$, followed by water, converts the ketone to the corresponding secondary alcohol.

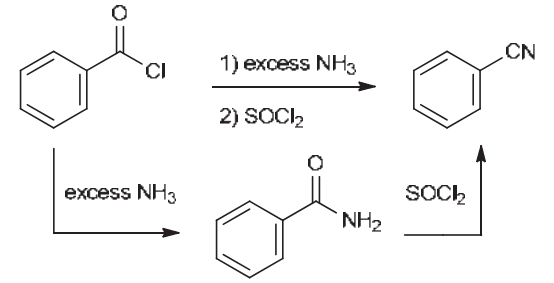


(d) A nitrile undergoes hydrolysis to give a carboxylic acid upon prolonged treatment with aqueous acid at elevated temperature.



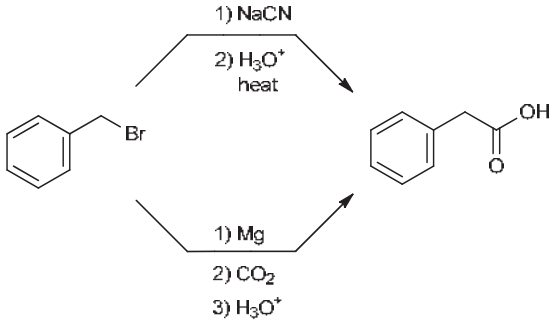
20.28.

(a) Reaction of the acid chloride with excess ammonia results in substitution of chloride with the nitrogen atom from ammonia. Thionyl chloride serves to dehydrate the resulting amide thus producing the desired nitrile as shown.



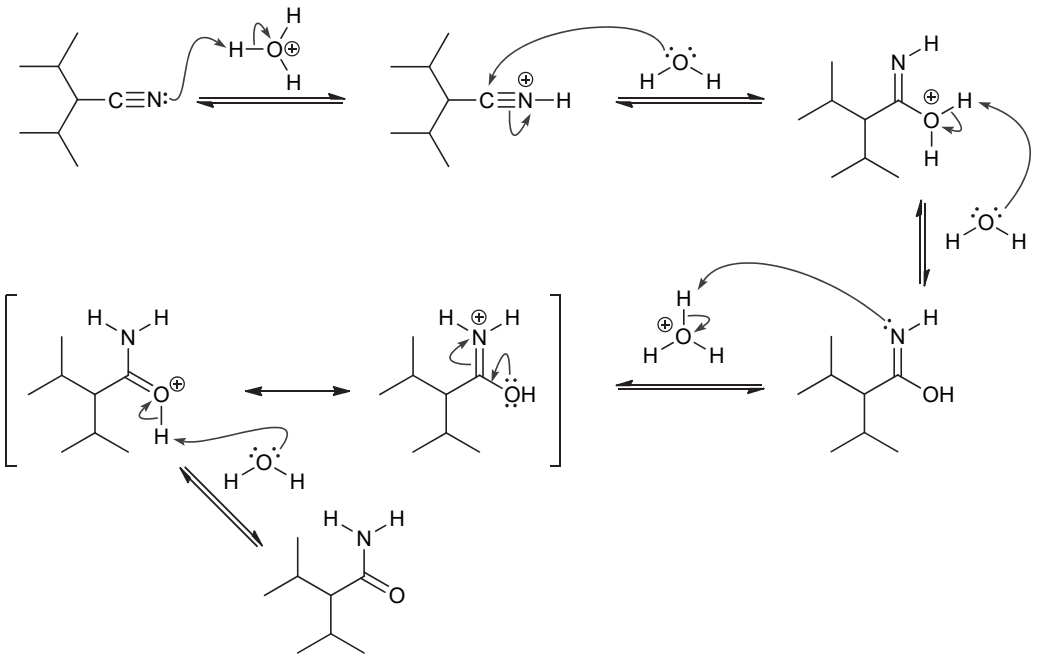
(b) Two approaches for this transformation are shown. Note that each approach incorporates an extra carbon atom to convert the starting material (which has seven carbon atoms) into the product (which has eight carbon atoms). In the first approach, sodium cyanide serves as a nucleophile in an S_N2 reaction, displacing the bromide to produce a nitrile. The nitrile is subsequently hydrolyzed upon heating with aqueous acid, to produce the desired carboxylic acid.

In the second approach, benzyl bromide is converted to benzyl magnesium bromide (a Grignard reagent), which serves as a nucleophile in a subsequent reaction with carbon dioxide. The resulting carboxylate ion is then protonated with H_3O^+ to produce the desired carboxylic acid.



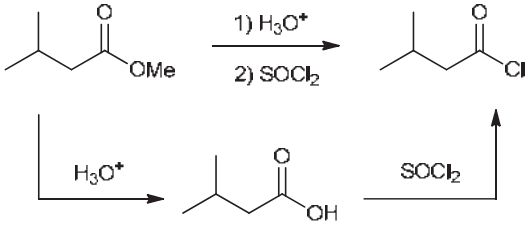
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20.29. This reaction occurs under acidic conditions, so we must avoid formation of a strong base. Thus, proton transfers are required at multiple stages in this mechanism. The following mechanism has five steps: 1) proton transfer, 2) nucleophilic attack, 3) proton transfer, 4) proton transfer and 5) proton transfer. The first step (proton transfer), requires two curved arrows to show the transfer of a proton from H_3O^+ to the nitrogen atom, resulting in the formation of an activated electrophile. In step two (nucleophilic attack), water serves as a nucleophile attacking the activated electrophilic carbon atom of the protonated nitrile, producing a cationic intermediate. In step 3 (proton transfer), water serves as a base, resulting in a neutral intermediate. Subsequently, in step 4 (proton transfer), a proton is transferred from H_3O^+ to the nitrogen atom to produce a cationic intermediate (two key resonance structures are shown). In step 5 (proton transfer), water serves as a base which deprotonates the cationic intermediate, resulting in the formation of an amide.

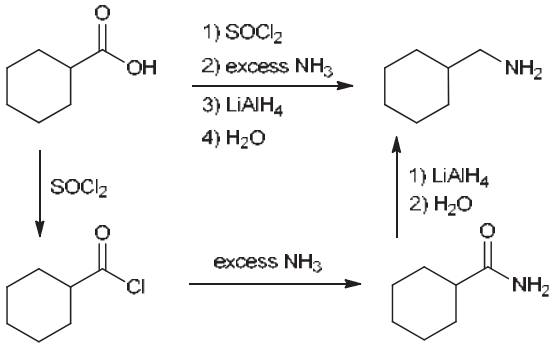


20.30.

(a) Acid catalyzed hydrolysis of the ester produces the carboxylic acid, which can then be converted to the acid chloride upon treatment with thionyl chloride.

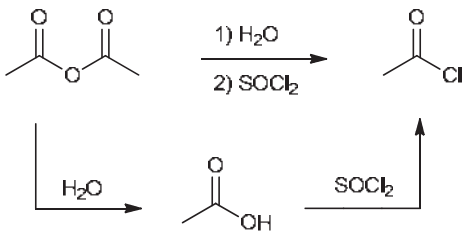


(b) Upon treatment with thionyl chloride, a carboxylic acid is converted to the corresponding acid chloride, which can then be treated with excess ammonia to produce an amide. Reduction of the amide with $LiAlH_4$, followed by protonation with water, yields the desired primary amine.

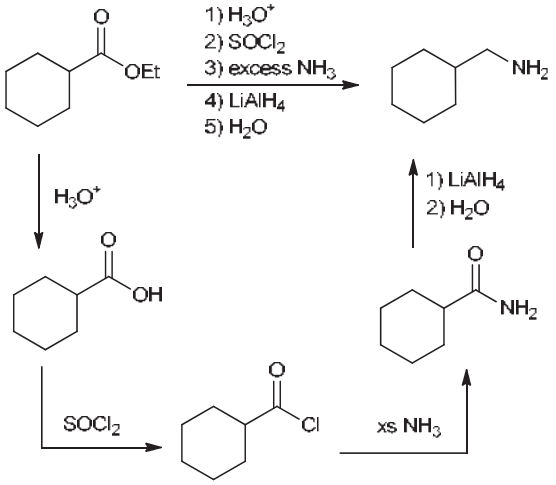


(c) Hydrolysis of acetic anhydride with water produces acetic acid, which can be converted to the desired product (acetyl chloride) upon treatment with thionyl chloride.

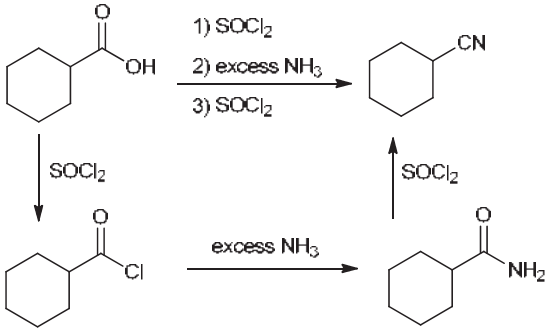
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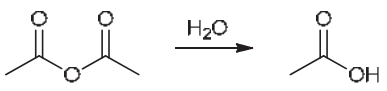
(d) The transformation requires conversion of an ester to an amine (with no change in the carbon skeleton). One way to achieve this transformation involves initial hydrolysis of the ester. The resulting carboxylic acid is converted to the acid chloride with thionyl chloride, which subsequently reacts with excess ammonia to produce the amide. Reduction of the amide with $LiAlH_4$, followed by water work-up, yields the desired primary amine.



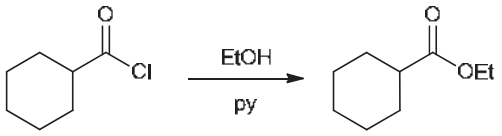
(e) A carboxylic acid can be converted to an acid chloride upon treatment with thionyl chloride. The acid chloride will then react with excess ammonia to produce an amide. Dehydration of the amide with thionyl chloride yields the desired nitrile.



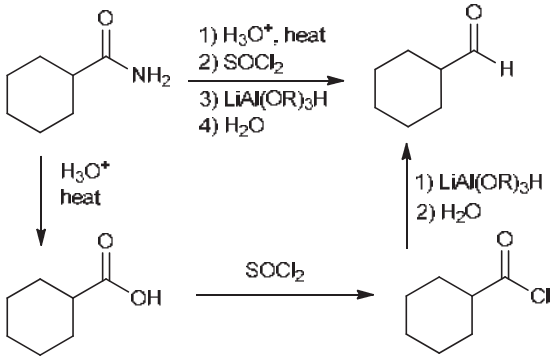
(f) This transformation involves hydrolysis of acetic anhydride to give acetic acid, which can be achieved in a single step, upon treatment with water.



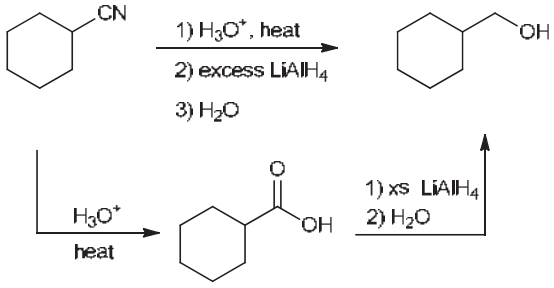
(g) An acid chloride can be converted to the corresponding ethyl ester in a single step, as shown.



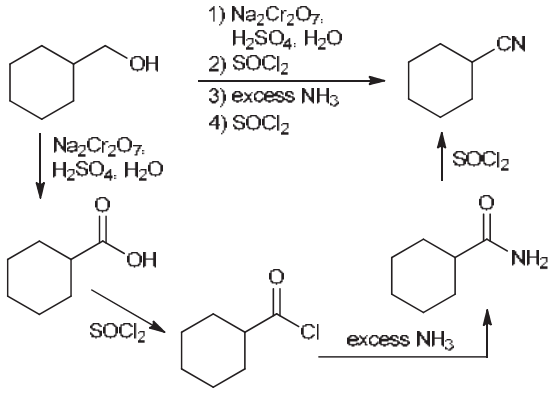
(h) Hydrolysis of the amide with H_3O^+ (and heat) produces a carboxylic acid, which can be converted to an acid chloride upon treatment with thionyl chloride. Subsequent reaction with a sterically hindered lithium trialkoxy aluminum hydride reagent, followed by water work-up, produces the desired aldehyde.



(i) Hydrolysis of the nitrile produces the carboxylic acid, which can be subsequently reduced to the primary alcohol with $LiAlH_4$, followed by water.



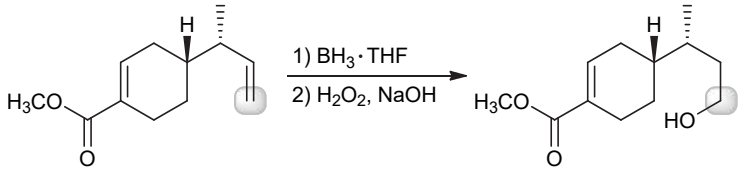
(j) Oxidation of a primary alcohol with a strong oxidizing agent yields a carboxylic acid, which can be subsequently converted to an acid chloride. Reaction with excess ammonia gives an amide, which can be dehydrated with thionyl chloride to give the desired nitrile.



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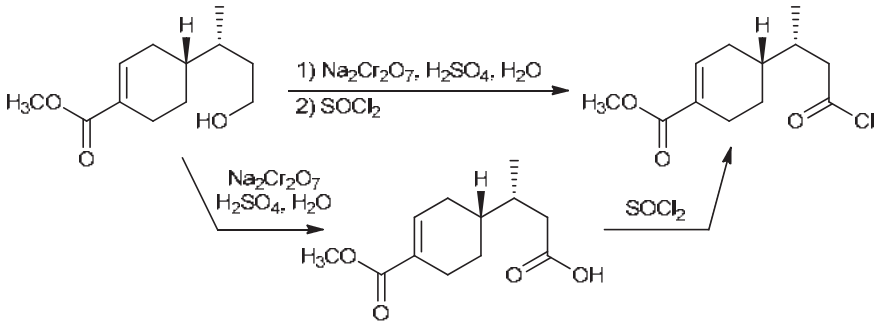
20.31.

(a) In this transformation, an alkene is being converted into an alcohol. Since the OH group is installed at the less substituted carbon, we need an *anti*-Markovnikov addition. This can be accomplished using a hydroboration- oxidation reaction sequence.



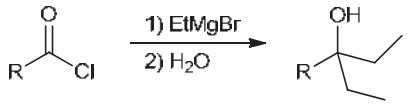
It is reasonable to assume that the unhindered monosubstituted alkene will react more rapidly than the hindered trisubstituted alkene. In practice, the investigators enhanced the selectivity of the hydroboration process by using R_2BH (where R = alkyl) in place of BH_3.

(b) In this transformation, a primary alcohol is being converted to an acid chloride. This can be accomplished via a two-step process. The primary alcohol is first oxidized to a carboxylic acid, so we must choose an appropriate oxidizing agent. This is followed by conversion of the carboxylic acid to the acid chloride, using $SOCl_2$, as shown.

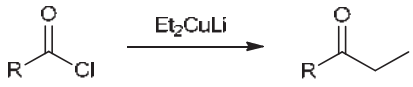


20.32.

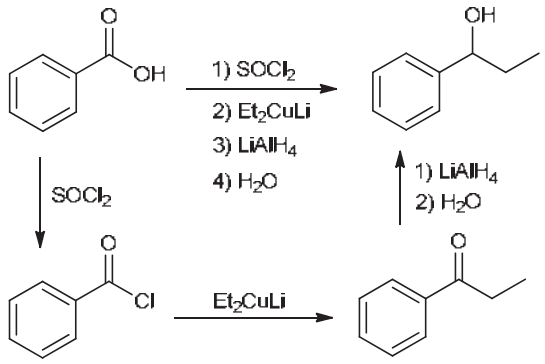
(a) The starting material has seven carbon atoms, and the product has nine carbon atoms. This requires installation of an ethyl group via a carbon-carbon bond-forming reaction. There are certainly several ways to achieve the installation of a single ethyl group. Let's first consider one way that will NOT work. Specifically, we cannot install the ethyl group via the reaction between an acid chloride and a Grignard reagent, as that would install two ethyl groups:



This reaction cannot be controlled to install a single ethyl group. However, a lithium dialkyl cuprate will attack an acid chloride just once, installing just one ethyl group:



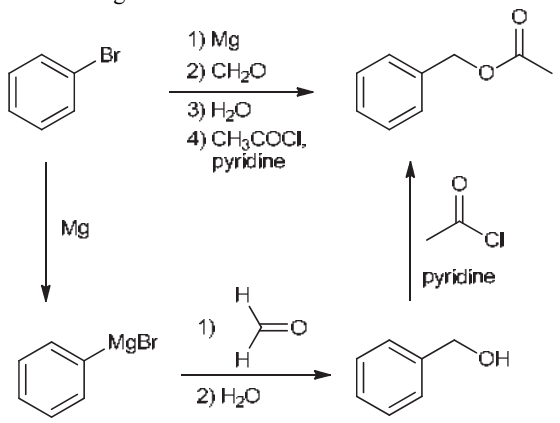
In order to use this method to install an ethyl group, we must first convert the starting material into an acid halide (which can be accomplished by treating the acid with thionyl chloride). Then, after installation of the ethyl group, we must convert the ketone into the final product (which can be achieved via reduction):



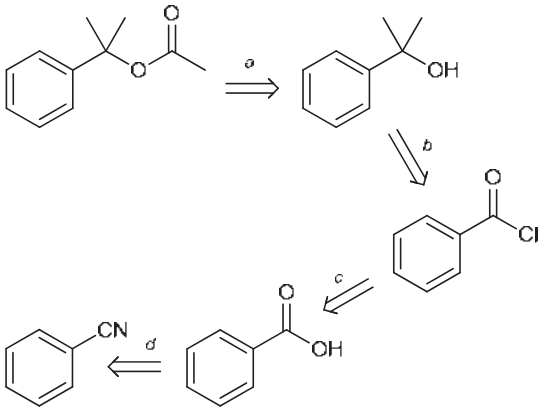
Alternatively, a single ethyl group can be installed via the reaction between an aldehyde and a Grignard reagent. This strategy gives the following synthesis: The carboxylic acid is first converted to an acid halide, followed by subsequent treatment with $LiAl(OR)_3H$ to give an aldehyde. The aldehyde can then be treated with ethyl magnesium bromide, followed by aqueous work-up, to give the desired product. This alternative strategy demonstrates that there is rarely only one correct way to approach a synthesis problem. THIS IS TRUE FOR NEARLY ALL OF THE SYNTHESIS PROBLEMS THAT WE ENCOUNTER.

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(b) One solution to this problem is shown here (there are certainly other acceptable solutions). Bromobenzene is converted to phenyl magnesium bromide (a Grignard reagent) and then treated with formaldehyde, followed by water work-up, to give benzyl alcohol, which serves as a nucleophile in a subsequent reaction with acetyl chloride to give the desired ester.

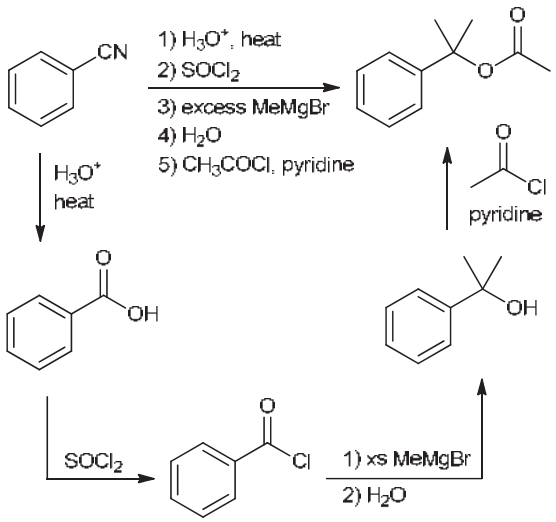


(c) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

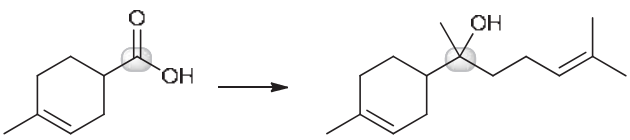


a. The desired product is an ester, which can be made via acetylation of the appropriate tertiary alcohol.
b. The tertiary alcohol can be made from an acid halide upon treatment with excess Grignard reagent.
c. The acid halide can be made from the corresponding carboxylic acid (benzoic acid).
d. Benzoic acid can be made from the starting material via hydrolysis.

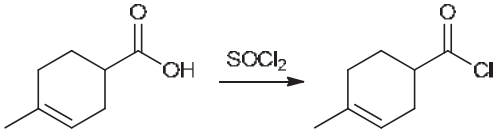
Now let's draw the forward scheme. Hydrolysis of the nitrile to the carboxylic acid, followed by reaction with thionyl chloride, produces the acid chloride. Reaction with excess methyl magnesium bromide, followed by water work-up, results in the formation of a tertiary alcohol, with the incorporation of two new methyl groups. The tertiary alcohol can then serve as a nucleophile in an acetylation reaction (upon treatment with acetyl chloride) to give the desired ester.



20.33. In this transformation, two new C-C bonds are being formed. Note that the two new groups are different. One is a simple methyl group and the other is a branched six-carbon group containing a double bond. The identity, *but not the position*, of the functional group is also changing.

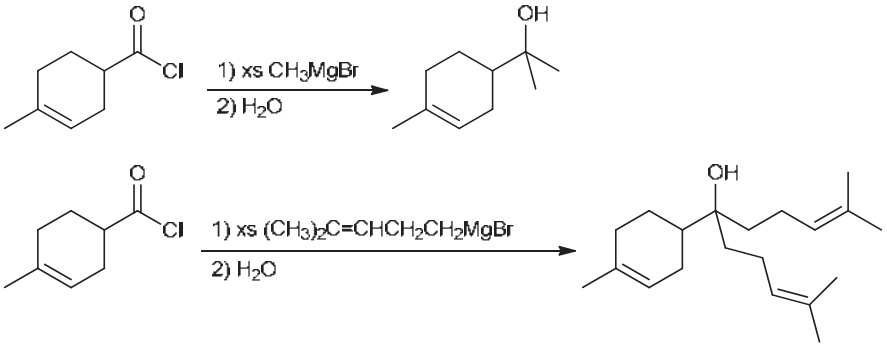


A reasonable first step is to convert the carboxylic acid into an acid chloride.

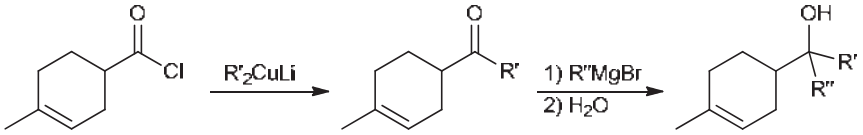


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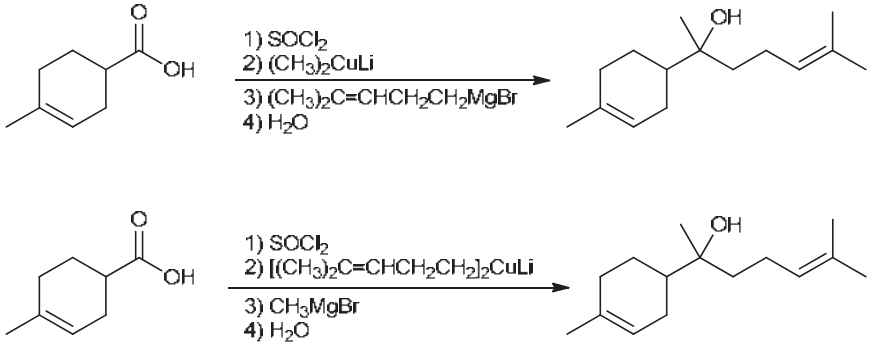
The desired product is a tertiary alcohol, and we know that tertiary alcohols can be made from acid chlorides using excess Grignard reagent. This approach will not work in this case, because we must install two different groups. Consider what would happen if we treated the acid chloride above with excess Grignard reagent:



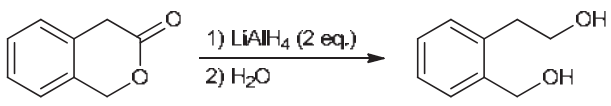
In each case shown above, the product would be a tertiary alcohol in which two identical groups have been installed. This is a noteworthy limitation to the use of excess Grignard for making tertiary alcohols from acid chlorides. Our synthesis must install two different groups, one at a time. Use of a Gilman reagent would allow the installation of one group, forming a ketone; subsequent addition of a Grignard reagent to the ketone, followed by protonation, installs the second group, giving a tertiary alcohol.



Putting it all together, there are two variations of this synthesis that differ only in the order in which the two groups are installed:



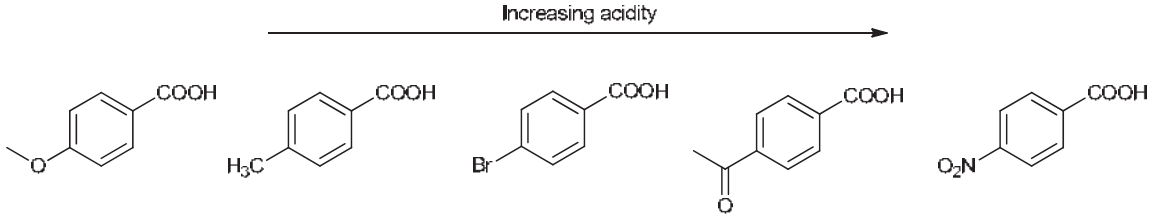
20.34. The signal at 1740 cm^{-1} indicates the presence of a carbonyl group (likely of an ester group) that is not conjugated with the aromatic ring (it would be at a lower wavenumber if it was conjugated). The cyclic ester (lactone) below fits the description provided and would indeed result in the diol shown upon reduction with two equivalents of $LiAlH_4$, followed by water work-up.



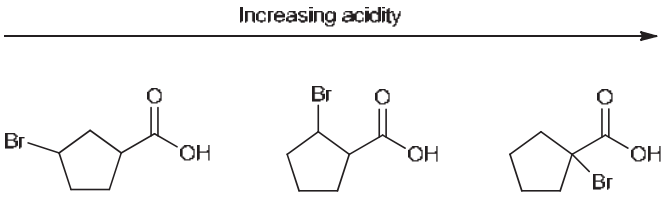
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20.35.

(a) Each of these acids is a *para*-substituted benzoic acid. Relative acid strength depends on the electron withdrawing (or electron donating) capacity of the substituent. Electron withdrawing groups pull electron density away from the ring, thus stabilizing the anionic charge on the conjugate base, thus giving a stronger acid. Electron donating groups have the opposite effect: they donate electron density into the ring, thus destabilizing the anionic charge on the conjugate base, resulting in a weaker acid. Accordingly, the acids below are arranged in order of increasing acid strength. As seen in Table 18.1, a methoxy group is strongly electron-donating; a methyl group is weakly electron-donating; a bromine atom is weakly electron-withdrawing; a carbonyl group is a moderate electron-withdrawing group; a nitro group is a strong electron-withdrawing group.



(b) When comparing the acids below, the difference in acidity is related to the proximity of the electron-withdrawing bromine atom to the carboxylic acid group. The closer the bromine atom is to the carboxylic acid, the more it stabilizes the anionic charge on the conjugate base. Accordingly, the strongest acid in this series has the bromine atom *alpha* to the carboxylic acid, followed by the isomer with the bromine atom on a *beta* position, and then the isomer with the bromine atom on a *gamma* position, as shown below.

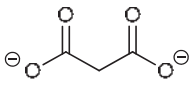


20.36.

(a) The second carboxylic acid group is electron withdrawing, and stabilizes the conjugate base that is formed when the first proton is removed.

(b) The carboxylate ion is electron rich and it destabilizes the conjugate base that is formed when the second proton is removed.

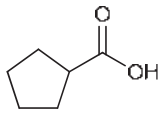
(c) Since both pK_1 and pK_2 are lower than 7.3, they are both expected to be largely deprotonated at physiological pH, resulting in the dianion shown below.



(d) The number of methylene (CH_2) groups separating the carboxylic acid groups is greater in succinic acid than in malonic acid. Therefore, the inductive effects described above in parts (a) and (b) are not as strong.

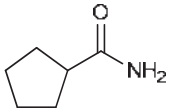
20.37.

(a) When a carboxylic acid group is attached to a ring, it is named as an alkanecarboxylic acid. This compound (with a ring composed of five carbon atoms) is thus cyclopentanecarboxylic acid.



cyclopentanecarboxylic acid

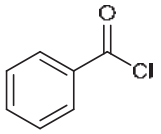
(b) An amide is named by replacing the suffix "ic acid" or "oic acid" with "amide". The corresponding carboxylic acid is named cyclopentanecarboxylic acid. Replacement of "ic acid" with "amide" produces the name cyclopentanecarboxamide.



cyclopentanecarboxamide

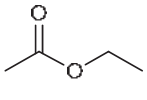
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(c) This acid chloride is named by replacing the "ic acid" from the parent (benzoic acid) with "yl chloride" to produce benzoyl chloride.



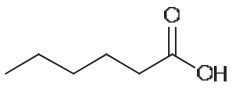
benzoyl chloride

(d) An ester is named by indicating the alkyl group (in this case, ethyl) attached to the oxygen atom of the ester, followed by the parent name of the corresponding carboxylic acid in which the "ic acid" is replaced by "ate". That is, the parent carboxylic acid (acetic acid) becomes acetate, giving the name ethyl acetate.



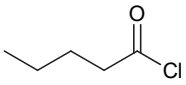
ethyl acetate

(e) The chain that contains the carboxylic acid group is comprised of six carbon atoms, so the "e" in the parent name (hexane) is replaced with the suffix "-oic acid", resulting in the IUPAC name hexanoic acid.



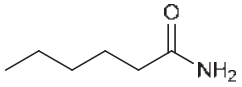
hexanoic acid

(f) The chain that contains the acid chloride group is comprised of five carbon atoms, so the "e" in the parent name (pentane) is replaced with the suffix "-oyl chloride", resulting in the IUPAC name pentanoyl chloride.



pentanoyl chloride

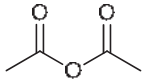
(g) The chain that contains the amide group is comprised of six carbon atoms, so the "e" in the parent name (hexane) is replaced with the suffix "-amide", resulting in the IUPAC name hexanamide.



hexanamide

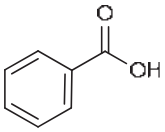
20.38. The common name for each molecule is shown below:

(a)



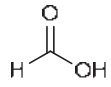
acetic anhydride

(b)



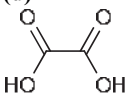
benzoic acid

(c)



formic acid

(d)

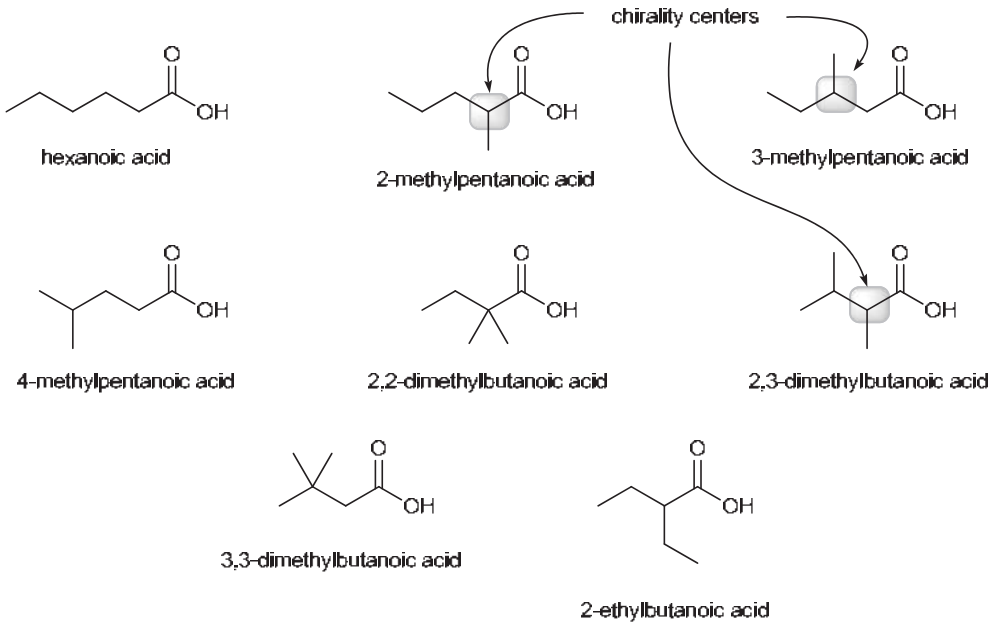


oxalic acid

20.39. A molecular formula of $C_6H_{12}O_2$ corresponds with one degree of unsaturation (see Section 14.16), which accounts for the carboxylic acid group. Since there are no other degrees of unsaturation, all of the isomers must be acyclic, saturated carboxylic acids. There are eight isomers that fit this description, shown here. These isomers are identified by methodically considering each possible parent chain. There is only one isomer with a parent chain of six carbon atoms (the first isomer shown). Then, there are three isomers that have a parent chain of five carbon atoms (with one methyl substituent). The methyl group can be located at C2, C3 or C4 (it cannot be at C5, because that would simply generate a parent chain of six carbon atoms, and we have already accounted for that isomer). Then, there are several isomers with a parent chain of only four carbons (with either two methyl groups or with one ethyl group). Once again, these isomers are drawn methodically. The two methyl groups can both be at C2, or they can be at C2 and C3, or both can be at C3. And finally, there can be an ethyl group at C2. Notice that, for a four-carbon chain, an ethyl group cannot be placed at C3, as that would generate a structure with a parent of five carbon atoms (and we have already accounted for that isomer).

Each carboxylic acid is named by identifying the longest chain containing the carboxylic acid group and replacing the "e" at the end of the alkane name with "oic acid". Each chain is numbered with the carboxylic acid carbon atom being C1, and the substituents are identified accordingly. Three of the isomers exhibit chiral centers (highlighted).

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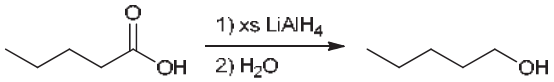


20.40. There are only two constitutional isomers, shown below. Each one is named by identifying the longest chain containing the acid chloride group and replacing the "e" in the parent name with the suffix "-oyl chloride". The first isomer is thus named butanoyl chloride. In the second (branched) isomer, the chain is numbered so that the carbonyl group is C1, which puts the methyl substituent on C2, resulting in the IUPAC name 2-methylpropanoyl chloride.

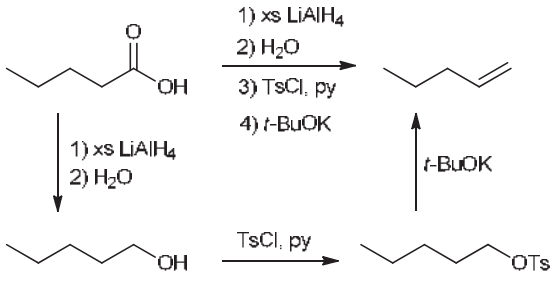


20.41.

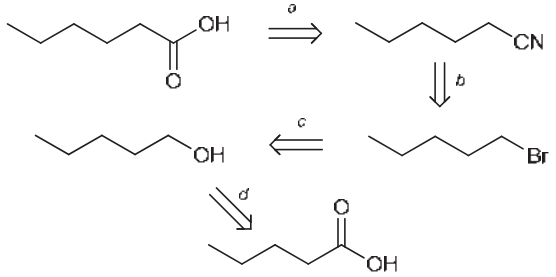
(a) Pentanoic acid is converted to 1-pentanol using a strong reducing agent ($LiAlH_4$), followed by water work-up, as shown.



(b) Pentanoic acid is initially converted to 1-pentanol using a strong reducing agent ($LiAlH_4$), followed by water work-up, as shown. Conversion to the tosylate followed by reaction with a strong, sterically hindered base produces 1-pentene via an E2 reaction. Note that a sterically hindered base is required in the last step because a non-sterically hindered base (*i.e.*, NaOEt) would result in the formation of the S_N2 product as the major product.



(c) Conversion of pentanoic acid to hexanoic acid requires the installation of an extra carbon atom. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

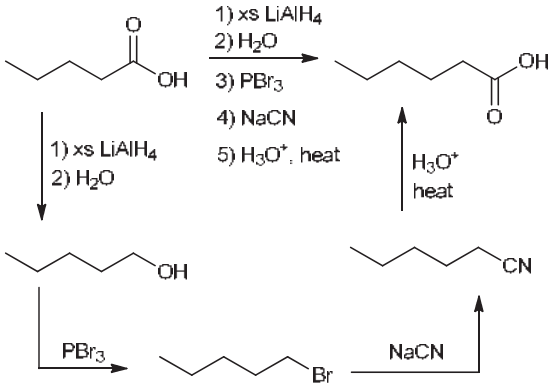


a. The desired product can be made via hydrolysis of a nitrile.
b. The nitrile can be made from 1-bromopentane (via an S_N2 process).
c. 1-Bromopentane can be made from 1-pentanol (upon treatment with PBr_3).

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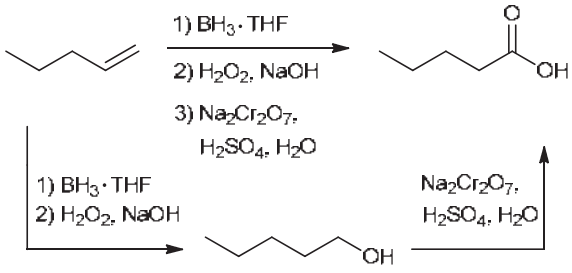
d. 1-Pentanol can be made from pentanoic acid via reduction.

Now let's draw the forward scheme. Reduction of pentanoic acid gives 1-pentanol. Treating this alcohol with PBr_3 produces 1-bromopentane. Subsequent S_N2 substitution with sodium cyanide installs an extra carbon atom, producing a nitrile, which can be hydrolyzed to the desired product under acidic conditions:

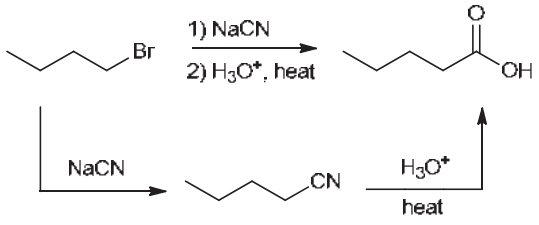


20.42.

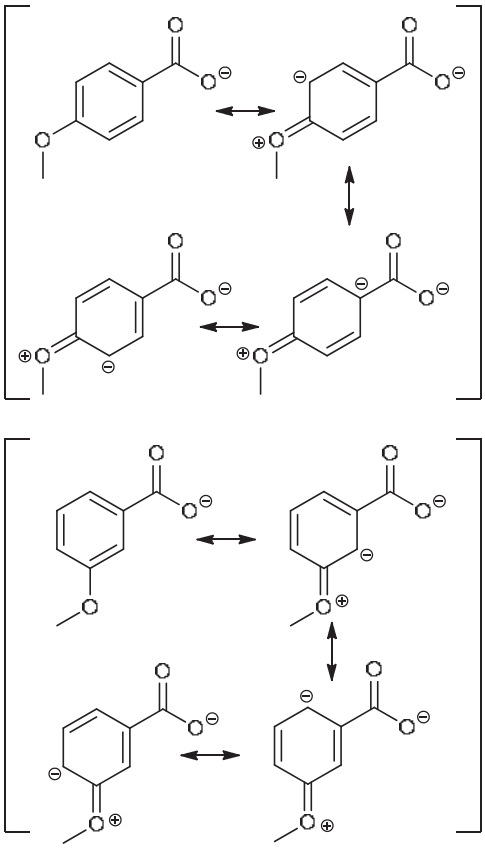
(a) *Anti*-Markovnikov addition of water (via hydroboration / oxidation) produces 1-pentanol, which is subsequently oxidized to pentanoic acid using a strong oxidizing agent.



(b) Conversion of 1-bromobutane to pentanoic acid requires the installation of an extra carbon atom. This extra carbon atom can be installed via an S_N2 process in which bromide is replaced with cyanide, thereby converting the alkyl halide into a nitrile. Subsequent acid-catalyzed hydrolysis produces the desired carboxylic acid, pentanoic acid.

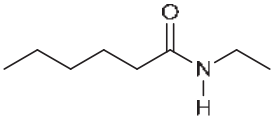


20.43. As discussed in Chapter 18, the methoxy group is electron donating via resonance, but electron withdrawing via induction. The resonance donation effect is stronger, but only significantly affects the acidity when the methoxy group is in an *ortho* or *para* position relative to the carboxylic acid. Note that in the third resonance structure for the conjugate base of the *para* derivative below, there is a negative charge next to the carboxylate group (a destabilizing effect). In contrast, none of the resonance structures of the corresponding *meta* derivative have this destabilizing feature, and as such, the conjugate base of the *meta* derivative is more stable than the conjugate base of the *para* derivative. In fact, the conjugate base of the *meta* derivative is even more stable than the conjugate base of benzoic acid, because of the electron withdrawing effect of the methoxy group (in the absence of strong resonance effects that are present in the *ortho* or *para* derivative).



20.44.

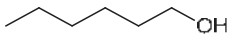
(a) Reaction of hexanoyl chloride with an excess of ethyl amine produces the corresponding amide, where the chloride leaving group has been replaced with the nitrogen atom of the amine, as shown.



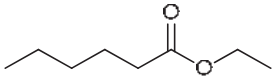
(b) Reaction of hexanoyl chloride with an excess of $LiAlH_4$, followed by water work-up, reduces the

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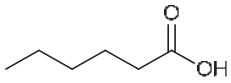
carboxylic acid group to the corresponding primary alcohol.



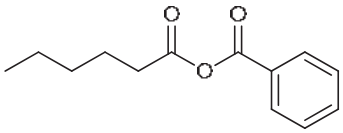
(c) Reaction of hexanoyl chloride with ethanol and pyridine produces the corresponding ester, where the chloride leaving group has been replaced with an ethoxy group.



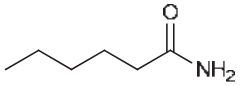
(d) Reaction of hexanoyl chloride with water (in the presence of pyridine) produces the parent carboxylic acid, where the chloride leaving group has been replaced with an OH group.



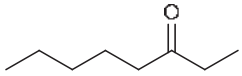
(e) Reaction of hexanoyl chloride with sodium benzoate produces the corresponding anhydride, where the chloride leaving group has been replaced with an oxygen atom of sodium benzoate, as shown.



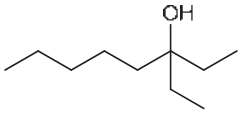
(f) Reaction of hexanoyl chloride with excess ammonia produces the corresponding amide, where the chloride leaving group has been replaced with an NH_2 group.



(g) Reaction of hexanoyl chloride with lithium diethyl cuprate produces a ketone, where the chloride leaving group has been replaced with the ethyl group from the diethyl cuprate, as shown.

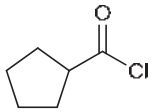


(h) Reaction of hexanoyl chloride with excess ethyl magnesium bromide, followed by water work-up, produces a tertiary alcohol, where two new ethyl groups have been incorporated into the product. The first equivalent of ethyl magnesium bromide attacks the carbonyl group of the acid chloride to give a ketone (nucleophilic attack of EtMgBr, followed by loss of chloride). A second equivalent of ethyl magnesium bromide then attacks the carbonyl group of the ketone intermediate to produce an alkoxide ion, which is subsequently protonated during work-up to give the following tertiary alcohol.

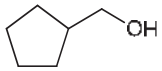


20.45.

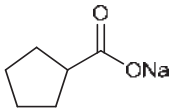
(a) Reaction with thionyl chloride converts a carboxylic acid into the corresponding acid chloride, shown here.



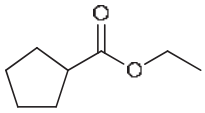
(b) A carboxylic acid is reduced to the corresponding alcohol upon treatment with $LiAlH_4$, followed by water work-up.



(c) Reaction with sodium hydroxide deprotonates the carboxylic acid to yield the sodium carboxylate.

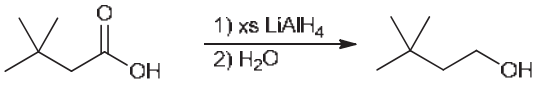


(d) Reaction with ethanol and catalytic acid converts the carboxylic acid to the ethyl ester shown, via a Fischer esterification.

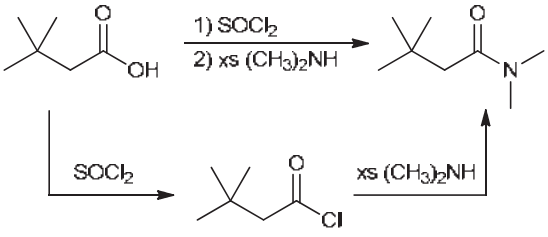


20.46.

(a) A carboxylic acid is reduced to the corresponding alcohol upon treatment with $LiAlH_4$, followed by water work-up.

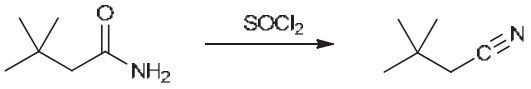


(b) Reaction with thionyl chloride converts the carboxylic acid to the corresponding acid chloride. Subsequent reaction with dimethylamine (in the presence of pyridine) converts the acid chloride to the corresponding dimethylamide.

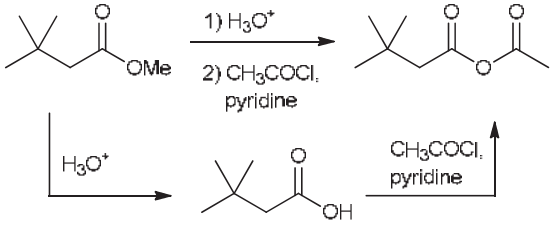


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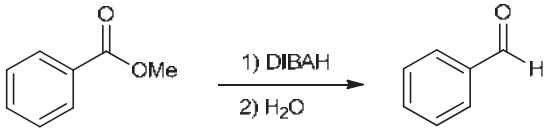
(c) An amide is converted into the corresponding nitrile upon treatment with thionyl chloride.



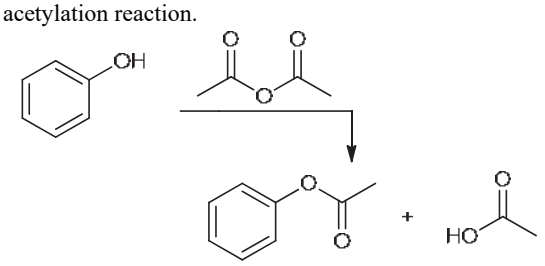
(d) Acid catalyzed hydrolysis of an ester gives a carboxylic acid. Subsequent reaction with acetyl chloride and pyridine causes an acetylation reaction that gives the following anhydride as the product.



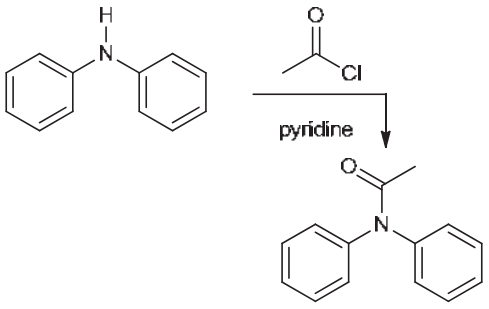
(e) An ester is converted into an aldehyde upon treatment with DIBAH, followed by water work-up.



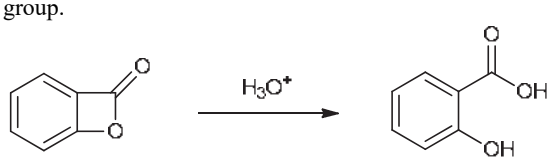
(f) Phenol serves as a nucleophile in this reaction. Phenol replaces the acetate leaving group on acetic anhydride resulting in the formation of a phenyl ester and acetic acid, as shown. This process is called an acetylation reaction.



(g) Diphenylamine serves as a nucleophile in this reaction. Diphenylamine replaces the chloride leaving group on acetyl chloride resulting in the formation of the diphenylamide shown here:

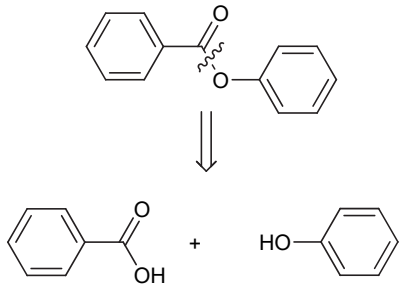


(h) Acid-catalyzed hydration of the cyclic ester (lactone) results in formation of a bifunctional molecule containing both a carboxylic acid group and a phenol group.

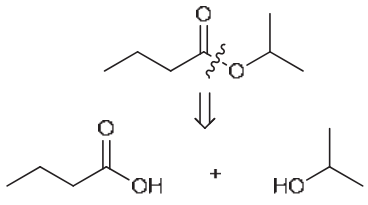


20.47.

(a) The new bond that forms as a result of a Fischer esterification is the σ bond between the carbonyl group and the oxygen atom connected to it, as shown. Making this disconnection, it becomes evident that benzoic acid and phenol would produce the desired ester under acidic conditions.

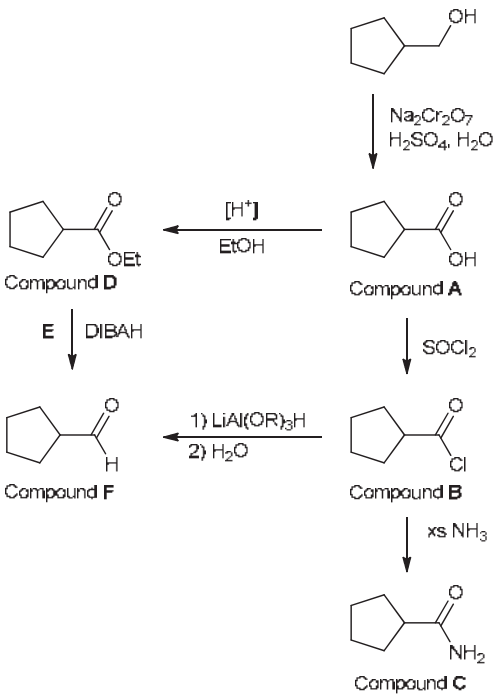


(b) The new bond that forms as a result of a Fischer esterification is the σ bond between the carbonyl group and the oxygen atom connected to it, as shown. Making this disconnection, it becomes evident that butyric acid and isopropanol would produce the desired ester under acidic conditions.



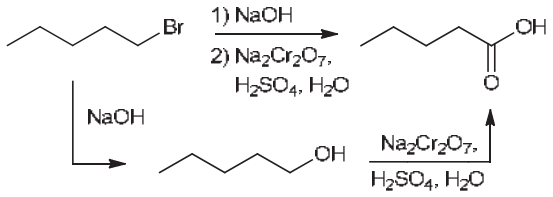
20.48. Oxidation of the primary alcohol gives the corresponding carboxylic acid (**A**). Reaction of **A** with thionyl chloride converts the carboxylic acid to the acid chloride (**B**). Reaction of **B** with excess ammonia produces the amide (**C**). Carboxylic acid (**A**) undergoes Fischer esterification upon reaction with ethanol and catalytic acid to produce the ethyl ester (**D**). Reaction of acid chloride **B** with a lithium trialkoxyaluminum hydride produces aldehyde **F**, which can also be made from ester **D** by reaction with DIBAH (**E**).

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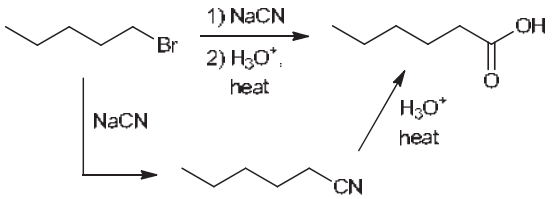


20.49.

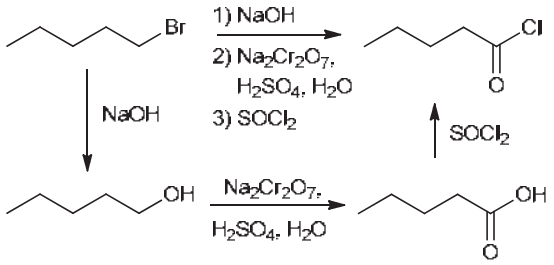
(a) This transformation does not involve a change in the carbon skeleton. Only the identity of the functional group must be changed. To accomplish this transformation, the starting material can be treated with NaOH to give 1-pentanol via an S_N2 reaction. Subsequent oxidation of the primary alcohol gives the desired carboxylic acid.



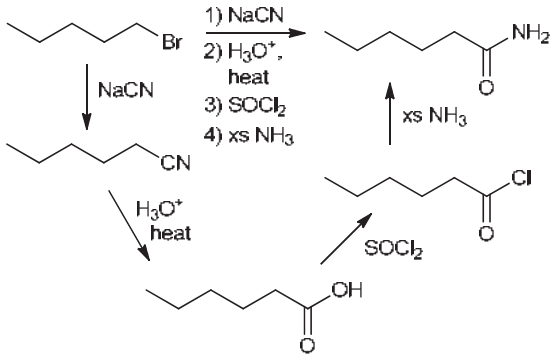
(b) This transformation involves a change in the carbon skeleton (one extra carbon atom must be inserted), as well as a change in the identity and location of the functional group. To accomplish this transformation, the starting material can be treated with NaCN, thereby converting 1-bromopentane into hexanenitrile via an S_N2 reaction. Subsequent acid catalyzed hydrolysis of the nitrile (upon treatment with aqueous acid) gives hexanoic acid.



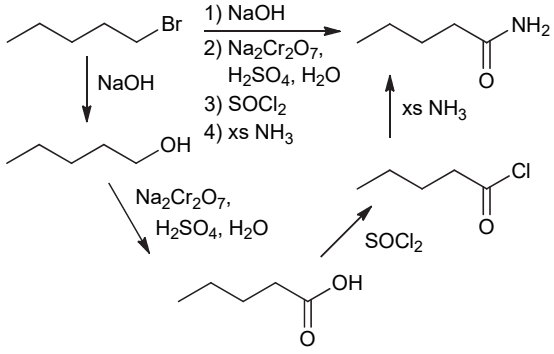
(c) First, 1-bromopentane can be converted into pentanoic acid in just two steps, as shown in the solution to part (a) of this problem. Then, treating this carboxylic acid with $SOCl_2$ will give the desired acid chloride.



(d) First, 1-bromopentane can be converted into hexanoic acid in just two steps, as shown in the solution to part (b) of this problem. Then, this carboxylic acid can be converted into an acid halide, followed by treatment with excess ammonia to give the desired product:



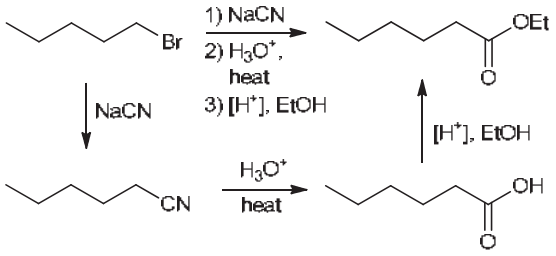
(e) First, 1-bromopentane can be converted into pentanoic acid in just two steps, as shown in the solution to part (a) of this problem. This carboxylic acid can then be converted into an acid halide, followed by treatment with excess ammonia to give the desired product:



(f) First, 1-bromopentane can be converted into hexanoic acid in just two steps, as shown in the solution to part (b) of this problem. Upon treatment with ethanol in acid-catalyzed conditions, the carboxylic acid can be

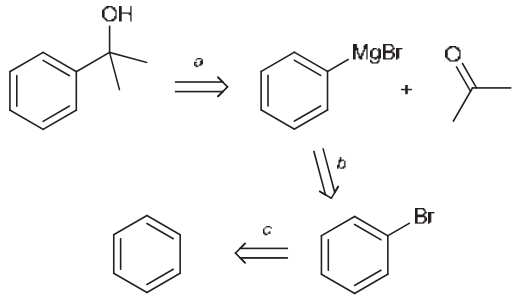
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converted into an ester via a Fischer esterification process:



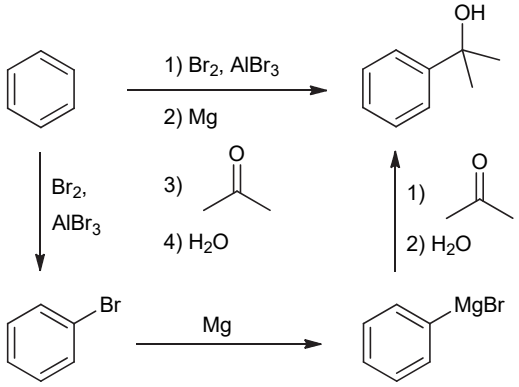
20.50.

(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

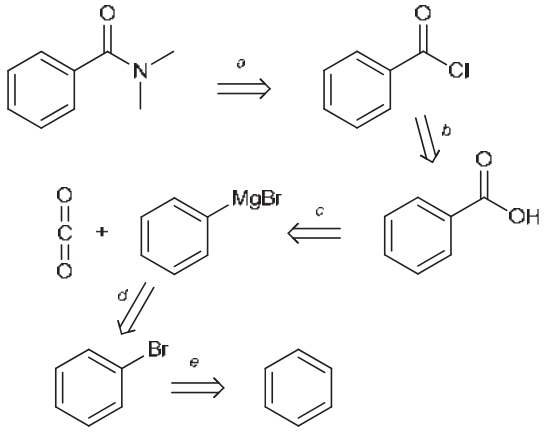


a. The desired product can be made via a Grignard reaction between phenyl magnesium bromide and acetone.
b. Phenyl magnesium bromide can be made from bromobenzene via insertion of magnesium.
c. Bromobenzene can be made from benzene via bromination.

Now let's draw the forward scheme. Benzene is converted into bromobenzene upon treatment with Br_2 and $AlBr_3$ (via an electrophilic aromatic substitution reaction). Bromobenzene is subsequently converted into phenyl magnesium bromide, which is then treated with acetone (in a Grignard reaction), followed by water work-up, to give the desired tertiary alcohol.

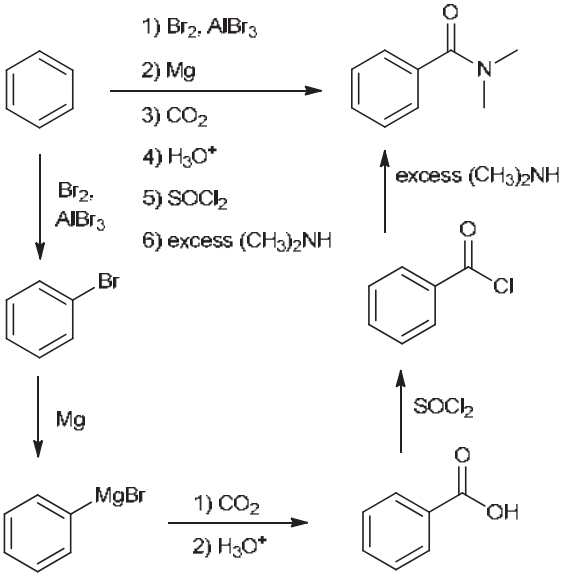


(b) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*e*) follows.



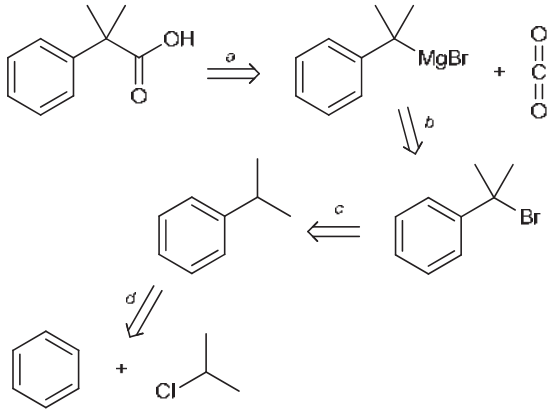
a. The desired amide can be made from the corresponding acid chloride (benzoyl chloride).
b. Benzoyl chloride can be made from benzoic acid upon treatment with thionyl chloride.
c. Benzoic acid can be made from the reaction between phenyl magnesium bromide and carbon dioxide.
d. Phenyl magnesium bromide can be made from bromobenzene via insertion of magnesium.
e. Bromobenzene can be made from benzene via bromination.

Now let's draw the forward scheme. Benzene is converted into bromobenzene upon treatment with Br_2 and $AlBr_3$ (via an electrophilic aromatic substitution reaction). Bromobenzene is subsequently converted into phenyl magnesium bromide, which is then treated with carbon dioxide, followed by an acidic workup, to give benzoic acid. Conversion to the acid chloride, followed by reaction with dimethylamine, yields the desired amide.



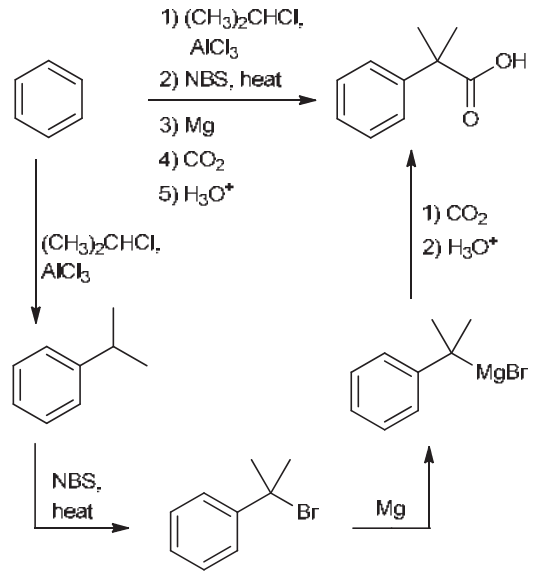
As mentioned, there are many alternative solutions. For example, benzoic acid can be made from benzene via Friedel-Crafts methylation, followed by benzylic oxidation.

(c) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

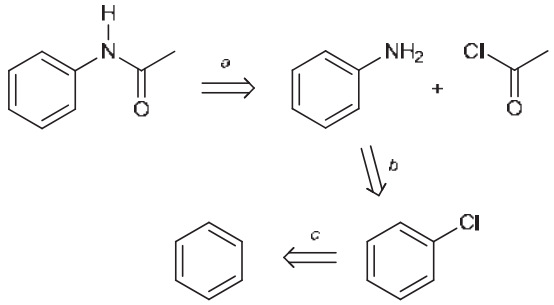


a. The desired carboxylic acid can be made from the reaction between a Grignard reagent and CO_2.
b. The Grignard reagent can be made from the corresponding tertiary benzylic halide.
c. The benzylic halide can be made from isopropyl benzene via benzylic bromination.
d. Isopropylbenzene can be made from benzene via a Friedel-Crafts alkylation.

Now let's draw the forward scheme. Benzene is converted into isopropyl benzene upon treatment with 2-chloropropane and a Lewis acid (via a Friedel-Crafts alkylation). Benzylic bromination replaces the benzylic hydrogen atom with a bromine atom. Conversion to a Grignard reagent, followed by reaction with carbon dioxide and subsequent acidification, gives the desired carboxylic acid.

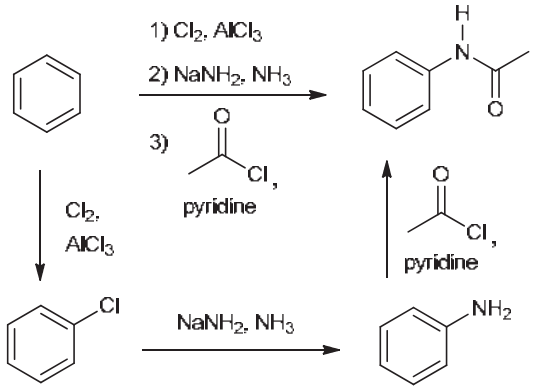


(d) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.



a. The desired amide can be made from aniline via an acetylation reaction.
b. Aniline can be made from chlorobenzene via an elimination-addition process.
c. Chlorobenzene can be made from benzene via chlorination of the aromatic ring.

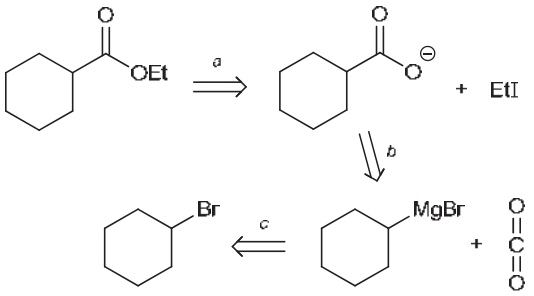
Now let's draw the forward scheme. Benzene is converted into chlorobenzene upon treatment with Cl_2 and $AlCl_3$ (via an electrophilic aromatic substitution reaction). Chlorobenzene is then converted to aniline via an elimination-addition reaction. Reaction with acetyl chloride (in the presence of pyridine) converts aniline to the desired amide.



As mentioned, there are many alternative solutions. For example, aniline can be made from benzene via nitration (upon treatment with sulfuric acid and nitric acid), followed by reduction (with Zn and HCl).

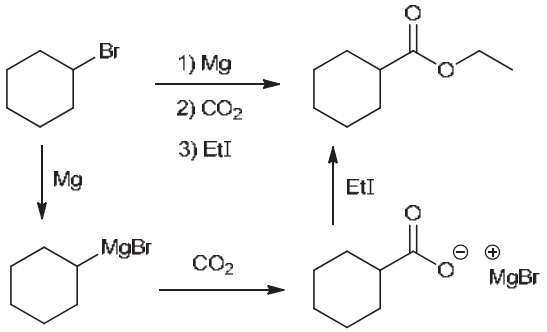
20.51.
(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

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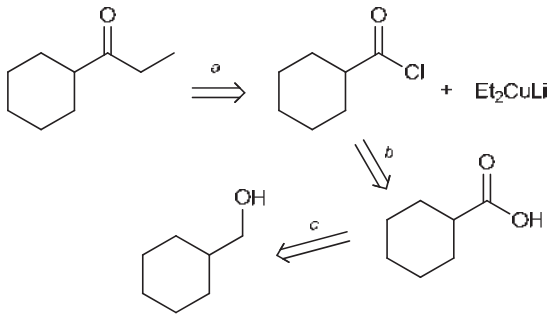


a. The desired ester can be made from a reaction between the corresponding carboxylate ion and ethyl iodide (S_N2).
b. The carboxylate ion can be made from the reaction between a Grignard reagent and CO_2.
c. The Grignard reagent can be made from the corresponding secondary bromide.

Now let's draw the forward scheme. Bromocyclohexane is converted to a Grignard reagent, which subsequently reacts with carbon dioxide to produce a carboxylate ion. This anion then serves as a nucleophile in an S_N2 reaction with iodoethane, giving the desired product.

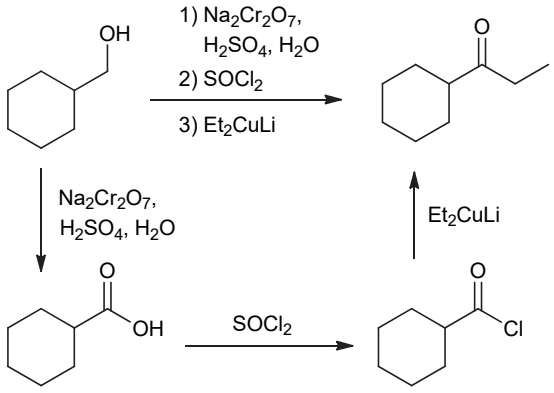


(b) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

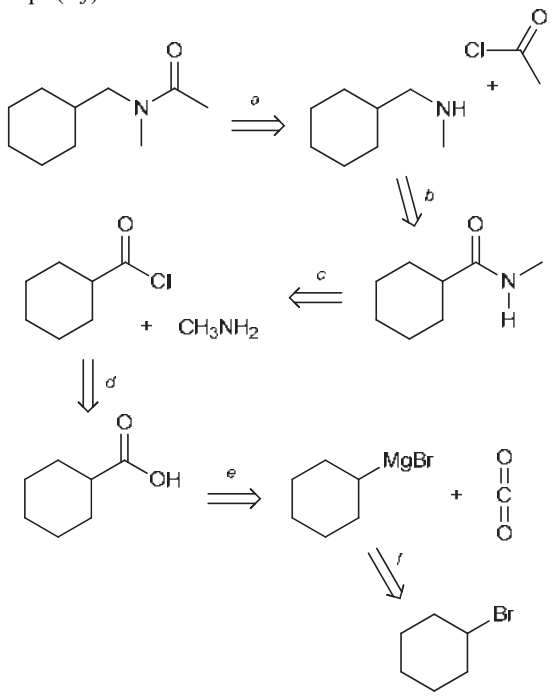


a. The desired ketone can be made from a reaction between an acid chloride and lithium diethyl cuprate.
b. The acid chloride can be made from the corresponding carboxylic acid.
c. The carboxylic acid can be made from the corresponding primary alcohol via oxidation.

Now let's draw the forward scheme. The primary alcohol is oxidized to the carboxylic acid, and subsequently converted to the acid chloride upon treatment with thionyl chloride. Reaction with lithium diethyl cuprate then produces the desired ketone.



(c) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*f*) follows.

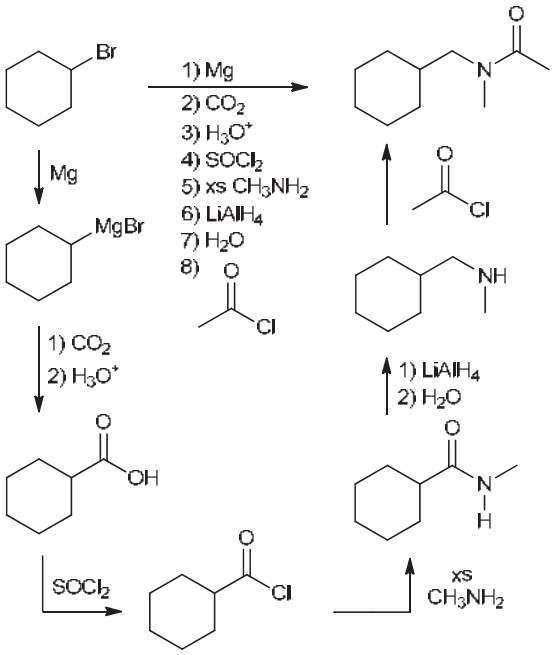


a. The desired amide can be made via acetylation of the corresponding secondary amine.
b. The secondary amine can be made via reduction of the corresponding amide.
c. The amide can be made from the corresponding acid halide (upon treatment with excess methyl amine).
d. The acid halide can be made from the corresponding carboxylic acid, upon treatment with thionyl chloride.

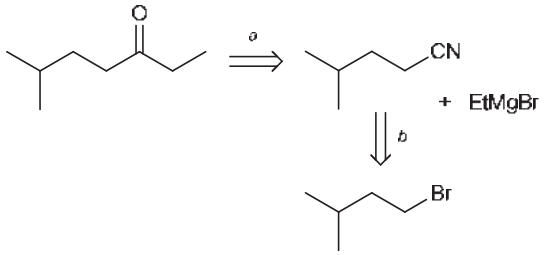
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e. The carboxylic acid can be made from the reaction between a Grignard reagent and CO_2.
f. The Grignard reagent can be made from the corresponding secondary alkyl bromide.

Now let's draw the forward scheme. Bromocyclohexane is converted to a Grignard reagent, which subsequently reacts with carbon dioxide to produce the carboxylic acid (after acid work-up). Conversion to the acid chloride, followed by reaction with methylamine, yields an intermediate amide. This intermediate is then reduced to the corresponding amine. Finally, reaction with acetyl chloride (upon treatment with excess amine) produces the desired product.

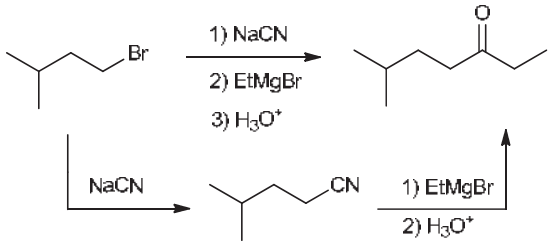


(d) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*b*) follows.



a. The desired ketone can be made from the reaction between a Grignard reagent and a nitrile.
b. The nitrile can be made from the corresponding primary bromide via an S_N2 process.

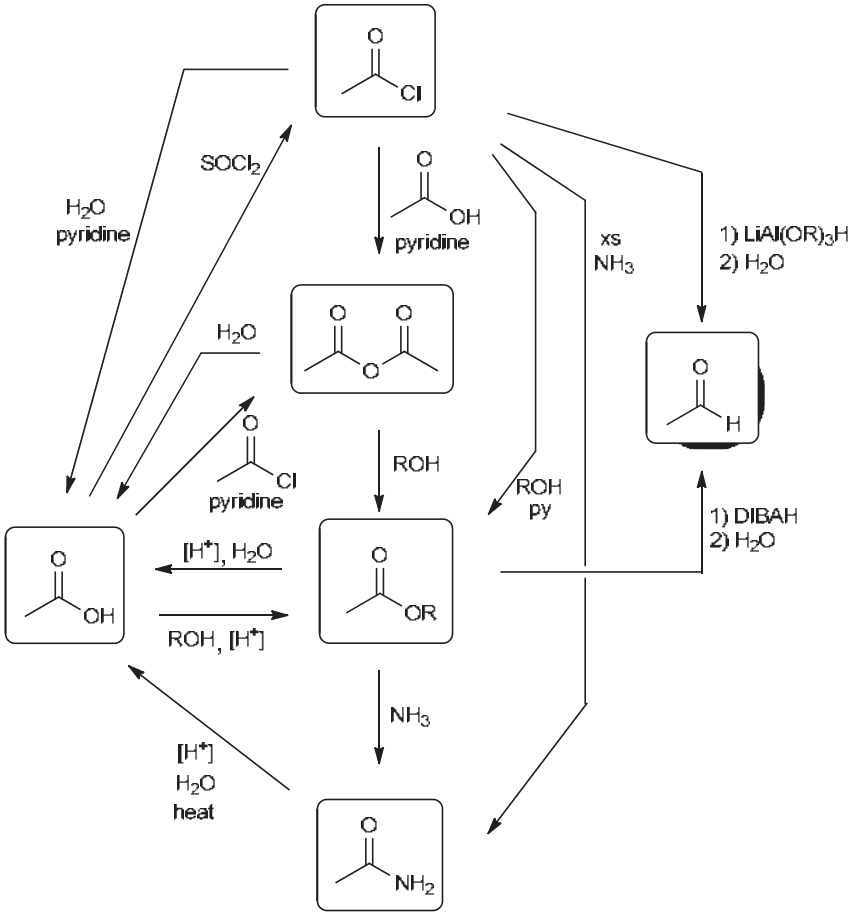
Now let's draw the forward scheme. Reaction of 1-bromo-3-methylbutane with sodium cyanide produces the nitrile, which is subsequently converted to the desired ketone upon treatment with ethyl magnesium bromide, followed by aqueous acid, as shown.



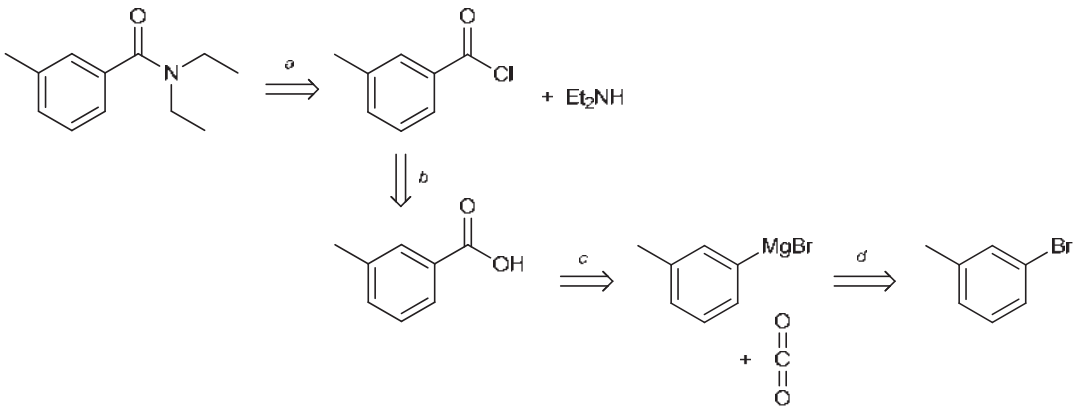
20.52. A methoxy group is electron donating, thereby decreasing the electrophilicity of the ester group. A nitro group is electron withdrawing, thereby increasing the electrophilicity of the ester group.

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20.53. The reagents for each of these transformations can be found in Figure 20.11.



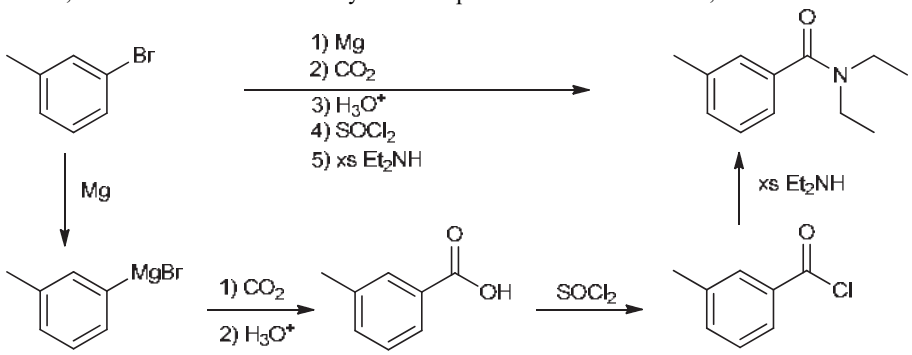
20.54. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a-d*) follows.



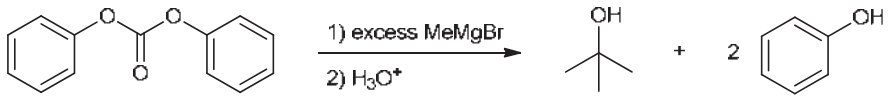
a. The desired amide can be made from the corresponding acid halide (upon treatment with excess diethylamine).
b. The acid halide can be made from the corresponding carboxylic acid, upon treatment with thionyl chloride.
c. The carboxylic acid can be made from the reaction between a Grignard reagent and CO_2.
d. The Grignard reagent can be made from the starting material, via insertion of magnesium.

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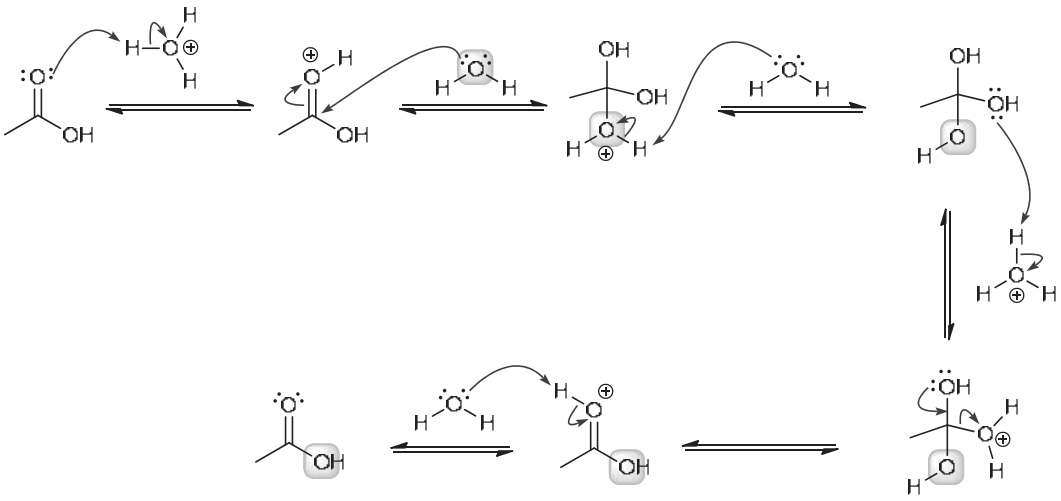
Now let's draw the forward scheme. Conversion of *meta*-bromotoluene to a Grignard reagent, followed by reaction with carbon dioxide and subsequent acidification, produces *meta*-methylbenzoic acid. The carboxylic acid is converted to the acid chloride, which then reacts with diethylamine to produce the desired amide, DEET.



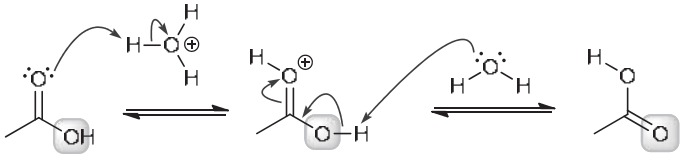
20.55. The carbonyl group of diphenyl carbonate has two phenoxide groups attached to it. Each of these groups can serve as a leaving group in a nucleophilic acyl substitution reaction. Accordingly, the first equivalent of methyl magnesium bromide replaces one phenoxide leaving group in the first two steps of the mechanism (nucleophilic attack, followed by loss of the leaving group) to produce an ester intermediate. The second equivalent of methyl magnesium bromide then replaces the second phenoxide group in an analogous manner (nucleophilic attack, followed by loss of the leaving group) to produce a ketone intermediate (acetone). A third equivalent of methyl magnesium bromide then attacks the carbonyl group of the ketone to produce *tert*-butoxide. Work-up with aqueous acid (H_3O^+) protonates *tert*-butoxide, as well as the phenoxide ions, giving *tert*-butanol and two equivalents of phenol.



20.56. A mechanism for this reaction is shown below, in which the isotopically labeled ^{18}O atom is highlighted with a gray box. Protonation of the carbonyl group activates it toward nucleophilic attack by $^{18}OH_2$. Two successive proton transfers, followed by expulsion of the non-labeled oxygen atom (as a leaving group, H_2O) and another proton transfer, result in the formation of acetic acid with one labeled oxygen atom.



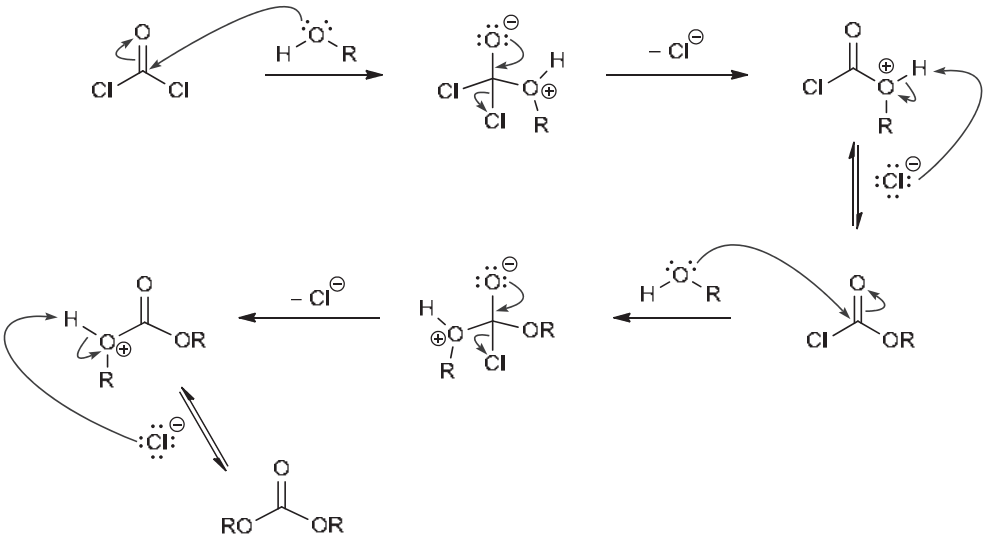
Two successive proton transfer steps (protonation, followed by deprotonation) give a molecule of acetic acid in which the labeled oxygen atom is incorporated in the carbonyl group, as shown.



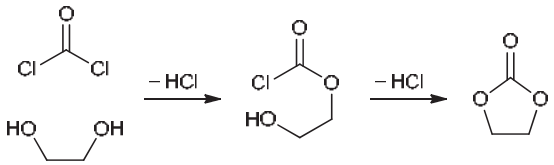
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20.57.

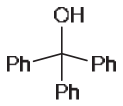
(a) An alcohol (ROH) is used as a representative nucleophile in the mechanism below, which has six steps: 1) nucleophilic attack, 2) loss of a leaving group, 3) proton transfer, 4) nucleophilic attack, 5) loss of a leaving group and 6) proton transfer. ROH attacks the carbonyl group of phosgene to form a tetrahedral intermediate which subsequently expels a chloride ion. A proton transfer produces the neutral, monochlorinated intermediate shown below. A second round of these three steps (nucleophilic attack by ROH, loss of chloride and proton transfer) results in the overall substitution of the second chloride ion with the oxygen atom from the alcohol, thereby producing a carbonate ester, as shown.



(b) The molecule below is produced from the reaction between phosgene and ethylene glycol via a mechanism analogous to the one in part (a) above. In this case, the second nucleophilic attack (step 4) is an intramolecular reaction, leading to the cyclic product shown here.

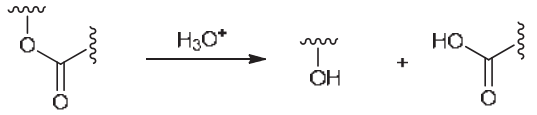


(c) Excess phenyl magnesium bromide reacts with phosgene to produce a tertiary alcohol (shown below), which results from the incorporation of three molar equivalents of the Grignard reagent. The first equivalent attacks the carbonyl group to produce a tetrahedral anionic intermediate; subsequent expulsion of a chloride ion gives an acid chloride intermediate. Likewise, a second equivalent of the Grignard reagent attacks the carbonyl group, producing a second anionic tetrahedral intermediate. Subsequent expulsion of a chloride leaving group gives a ketone intermediate, which is attacked by a third equivalent of phenyl magnesium bromide. Protonation of the resulting alkoxide ion (by H_2O) gives the tertiary alcohol, shown here.

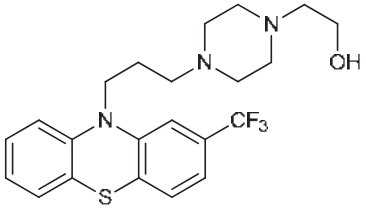


20.58.

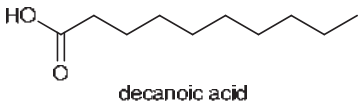
(a) Hydrolysis of an ester group produces an alcohol and a carboxylic acid.



As such, hydrolysis of fluphenazine decanoate releases the hydrophobic chain as a carboxylic acid, giving the following primary alcohol:

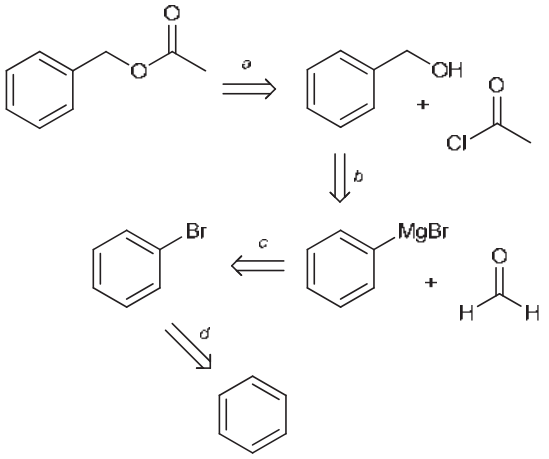


(b) The by-product of the reaction is a carboxylic acid containing ten carbon atoms. The "e" at the end of the parent alkane name (decane) is replaced with the suffix "-oic acid" to give the IUPAC name decanoic acid.



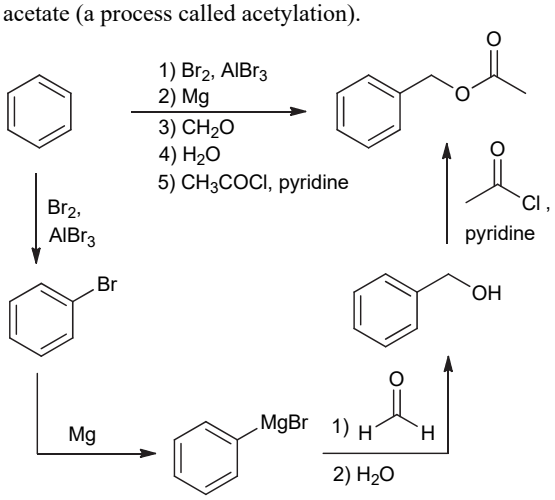
decanoic acid

20.59. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

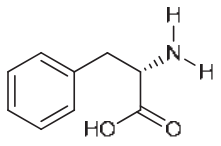


a. The ester can be made via acetylation of the corresponding alcohol (benzyl alcohol).
b. The alcohol can be made from the reaction between phenyl magnesium bromide and formaldehyde.
c. Phenyl magnesium bromide can be made from bromobenzene, via insertion of magnesium.
d. Bromobenzene can be made from benzene via bromination of the aromatic ring.

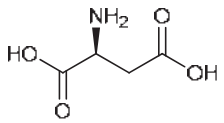
Now let's draw the forward scheme. Benzene is converted into bromobenzene upon treatment with Br_2 and $AlBr_3$ (via an electrophilic aromatic substitution reaction). Bromobenzene is then converted to phenyl magnesium bromide (a Grignard reagent), which is then treated with formaldehyde, followed by water work-up, to give benzyl alcohol. This alcohol then serves as a nucleophile in a subsequent acyl substitution reaction with acetyl chloride and pyridine to produce benzyl acetate (a process called acetylation).



20.60. Hydrolysis of aspartame hydrolyzes both the amide group and the ester group in the molecule. Hydrolysis of the ester group produces methanol and the carboxylic acid group in phenylalanine, shown below. Hydrolysis of the amide group converts this group to an amine (shown below on phenylalanine) and a carboxylic acid (on the left side of aspartic acid below). Note that the stereochemistry at both chiral centers is retained because none of the bonds to the chiral centers are broken in this transformation.



phenylalanine

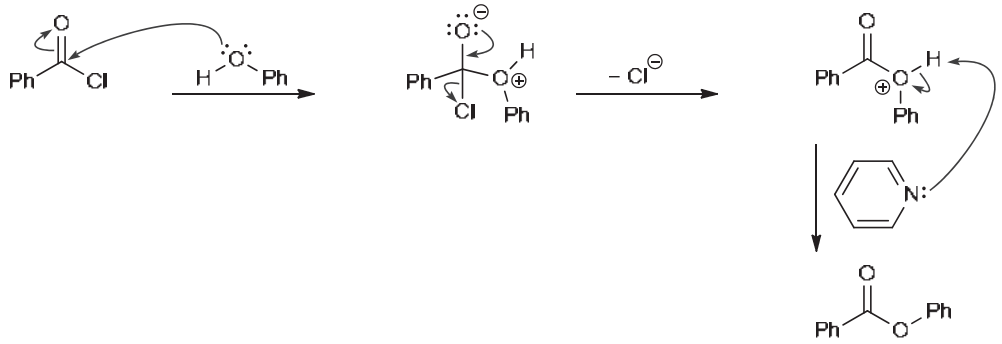


aspartic acid

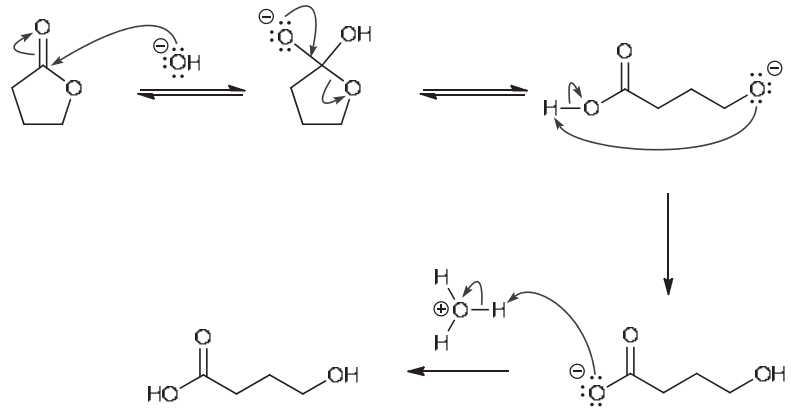
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20.61.

(a) The mechanism shown below has three steps: 1) nucleophilic attack, 2) loss of a leaving group and 3) proton transfer. Phenol serves as a nucleophile in the first step, attacking the carbonyl group of the acid chloride to produce a tetrahedral intermediate. Reformation of the carbonyl group and expulsion of the leaving group (chloride) produces a cationic intermediate which is subsequently deprotonated by pyridine to give an ester.

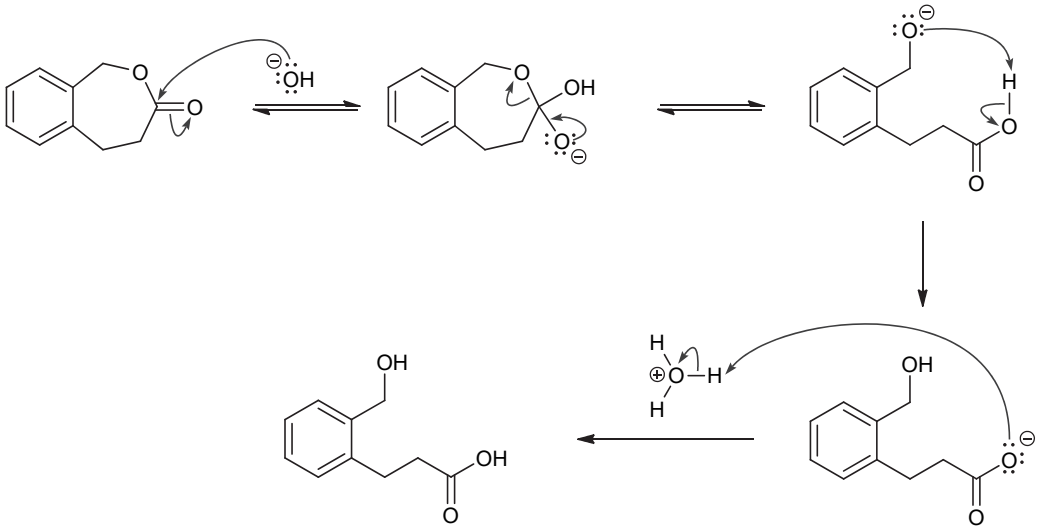


(b) The first part of this reaction (saponification) has three mechanistic steps: 1) nucleophilic attack, 2) loss of a leaving group and 3) proton transfer. The first step (nucleophilic attack) requires two curved arrows, which show hydroxide functioning as a nucleophile and attacking the electrophilic carbonyl group, resulting in an anionic tetrahedral intermediate. In step two (loss of a leaving group), the carbonyl group is reformed with loss of an alkoxide ion, resulting in opening of the ring and formation of a carboxylic acid. In the third step (proton transfer), the tethered alkoxide ion serves as a base, deprotonating the carboxylic acid intermediate, resulting in the formation of a carboxylate ion. This third step (in which a strong base deprotonates the carboxylic acid) is the driving force of the reaction. Subsequent work-up with aqueous acid protonates the carboxylate ion, regenerating the carboxylic acid.

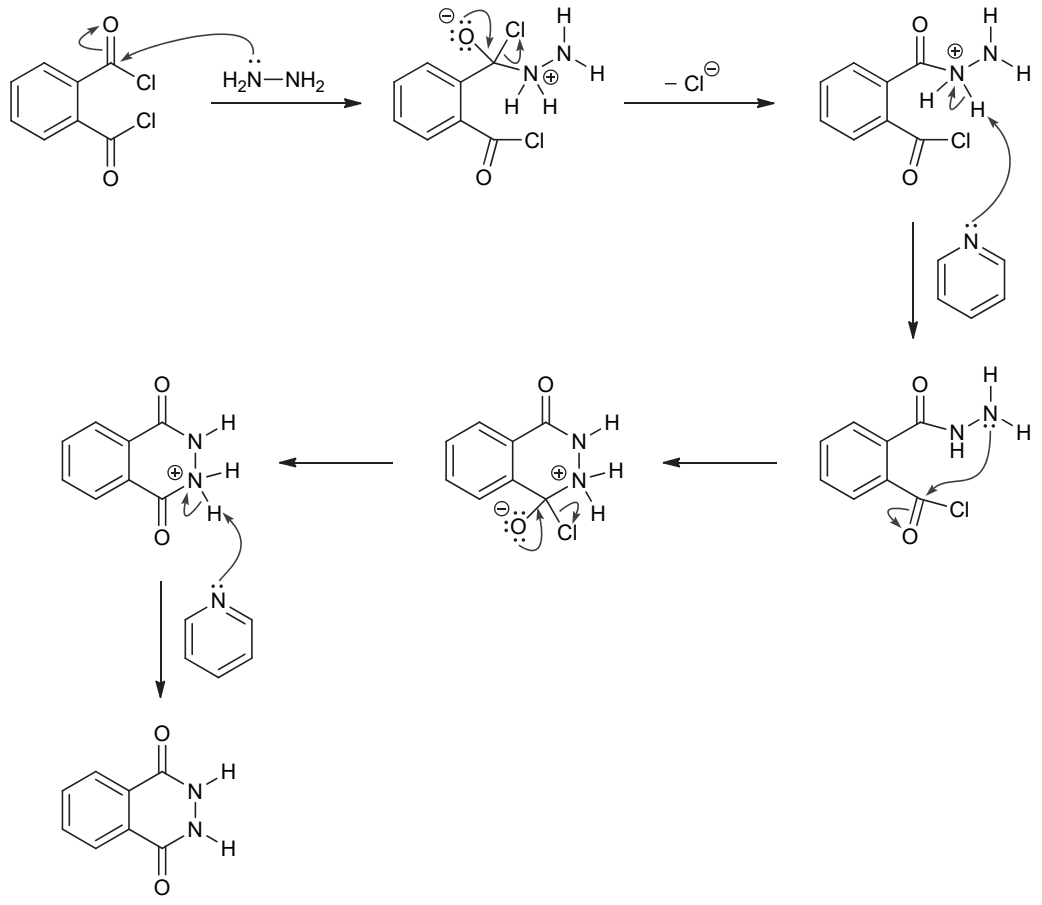


(c) The first part of this reaction (saponification) has three mechanistic steps: 1) nucleophilic attack, 2) loss of a leaving group and 3) proton transfer. The first step (nucleophilic attack) requires two curved arrows, which show hydroxide functioning as a nucleophile and attacking the electrophilic carbonyl group, resulting in an anionic tetrahedral intermediate. In step two (loss of a leaving group), the carbonyl group is reformed with loss of an alkoxide ion, resulting in opening of the ring and formation of a carboxylic acid. In the third step (proton transfer), the tethered alkoxide ion serves as a base, deprotonating the carboxylic acid intermediate, resulting in the formation of a carboxylate ion. This third step (in which a strong base deprotonates the carboxylic acid) is the driving force of the reaction. Subsequent work-up with aqueous acid protonates the carboxylate ion, regenerating the carboxylic acid.

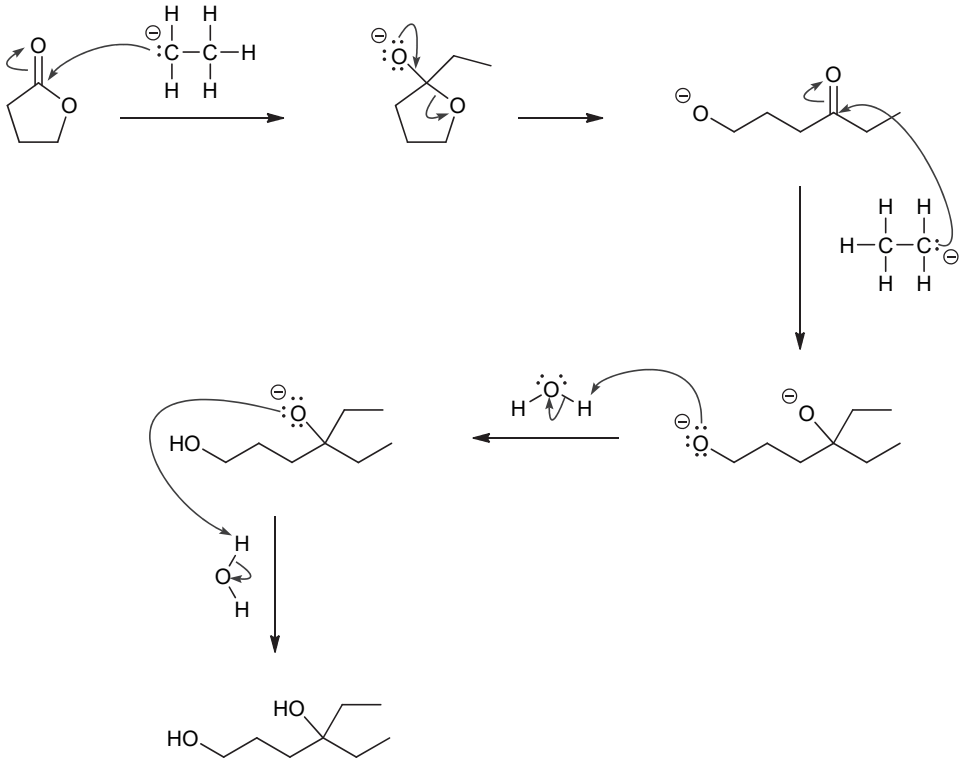
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(d) The mechanism shown below has six steps: 1) nucleophilic attack, 2) loss of a leaving group, 3) proton transfer, 4) nucleophilic attack, 5) loss of a leaving group and 6) proton transfer. Hydrazine (NH_2NH_2) has two nucleophilic centers (each nitrogen atom has a lone pair), each of which can attack an acid chloride group. In the first step, hydrazine attacks one of the acid chloride groups to form a tetrahedral intermediate which subsequently expels a leaving group (chloride). Pyridine then functions as a base and removes a proton, giving an intermediate that bears no formal charges. Subsequent intramolecular nucleophilic attack by the second nitrogen atom on the second acid chloride group, followed by loss of chloride, results in an intermediate that is deprotonated to give the product. Once again, pyridine functions as the base for deprotonation.

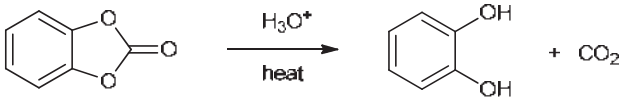


(e) The mechanism shown below has five steps: 1) nucleophilic attack, 2) loss of a leaving group, 3) nucleophilic attack, 4) proton transfer and 5) proton transfer. In the first step (nucleophilic attack), the anionic carbon atom of ethyl magnesium bromide serves as a nucleophile and attacks the electrophilic carbonyl group, resulting in a tetrahedral intermediate. In step two (loss of a leaving group), the carbonyl group is reformed with loss of an alkoxide ion, resulting in opening of the ring. In step three (nucleophilic attack) a second equivalent of ethyl magnesium bromide attacks the carbonyl group of the intermediate ketone, resulting in the formation of another tetrahedral intermediate. After the reaction is complete, a proton source (water) is introduced into the reaction flask, thereby protonating the dianion. Each anion is protonated separately, so two separate steps are required.



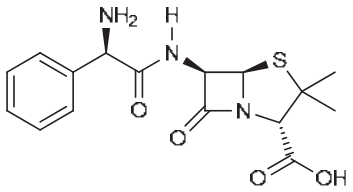
20.62. The three chlorine atoms withdraw electron density via induction. This effect renders the carbonyl group more electrophilic, and thus more reactive toward hydrolysis.

20.63. When treated with aqueous acid, each of the C-O bonds (on either side of the carbonyl group) is expected to undergo cleavage via an acid-catalyzed nucleophilic acyl substitution reaction. This produces a diol, shown below:



20.64.

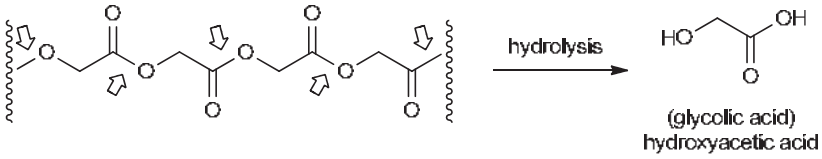
(a) When treated with aqueous acid, the ester group is hydrolyzed via a nucleophlic acyl substitution reaction in which water functions as a nucleophile, giving the active drug shown below. Note that the configuration of each chiral center is conserved, because the bonds to those chiral centers were not involved in the reaction.



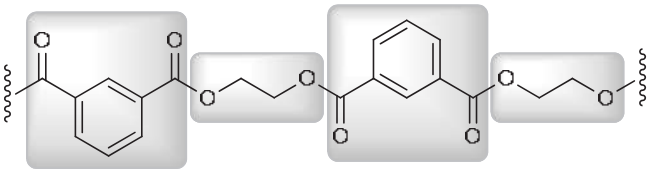
(b) The active drug is ampicillin, as indicated in the Medically Speaking box.

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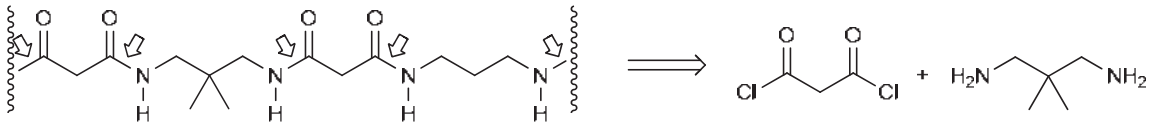
20.65. Hydrolysis of the ester groups in Dexon™ results in cleavage of the bonds indicated by the arrows in the figure below. This results in the formation of glycolic acid. The IUPAC name is based on a parent carboxylic acid called acetic acid, with indication of an alcohol (hydroxy group) at C2. Since acetic acid only has one location that can bear a substituent, a locant is not required to indicate the position of the OH group. The IUPAC name is thus hydroxyacetic acid.



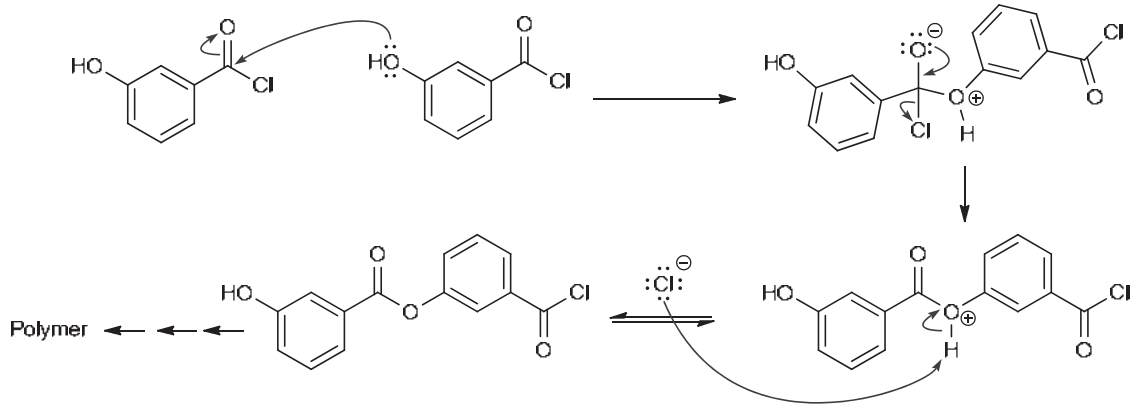
20.66. Each of the monomers bears two identical functional groups. The first monomer has two acid chloride groups, each of which can serve as an electrophile in the polymerization reaction. The second monomer has two OH groups, each of which can serve as a nucleophile. Reaction of the two monomers thus produces the polymer below via a series of nucleophilic acyl substitution reactions. The monomeric origins of each section of the polymer are highlighted below.



20.67. A retrosynthetic analysis of the polymer is shown below, where each of the bonds made during polymerization is indicated by an arrow. Each of these bonds can be made from a nucleophilic acyl substitution reaction between an amine and an acid chloride. Reaction of one monomer (bearing two electrophilic acid chloride groups) with the other monomer (bearing two nucleophilic amino groups) will produce the desired polymer.



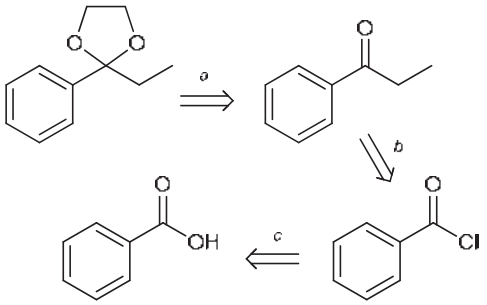
20.68. *meta*-Hydroxybenzoyl chloride (structure below) has a nucleophilic center (the OH group) as well as a strong electrophilic center (the acid chloride group) in a single molecule, thus making it susceptible to facile polymerization via the mechanism below. Each nucleophilic acyl substitution reaction has three steps: 1) nucleophilic attack, 2) loss of a leaving group and 3) proton transfer. In the first step (nucleophilic attack), the phenol oxygen atom of one molecule attacks the electrophilic carbonyl group on a second molecule resulting in the formation of a tetrahedral intermediate. A chloride leaving group is expelled in step 2 (loss of a leaving group), along with reformation of the carbonyl group. A proton transfer gives an intermediate that does not bear any formal charges. This intermediate (like the reactant) has a nucleophilic center (phenol oxygen atom) and a strong electrophilic center (the acid chloride group), thus allowing further reactions via an analogous pathway to produce a polymer.



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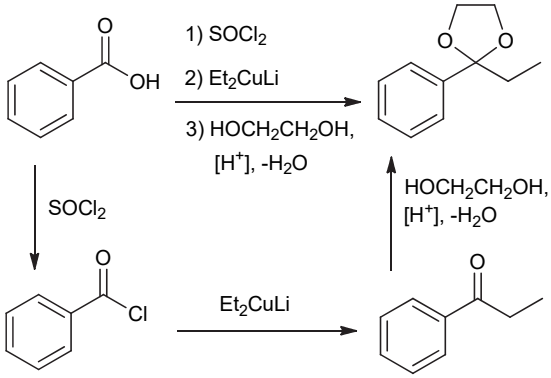
\20.69.

(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

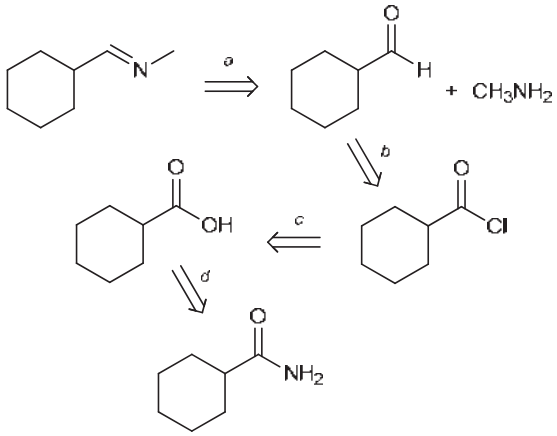


a. The desired cyclic acetal can be made from the corresponding ketone (via acetal formation).
b. The ketone can be made from benzoyl chloride, upon treatment with lithium diethyl cuprate.
c. The acid halide can be prepared from benzoic acid.

Now let's draw the forward scheme. Benzoic acid is converted to benzoyl chloride upon treatment with thionyl chloride. Subsequent reaction with lithium diethyl cuprate installs an ethyl group, giving a ketone. An acid-catalyzed reaction with ethylene glycol (with removal of water) produces the desired cyclic acetal.

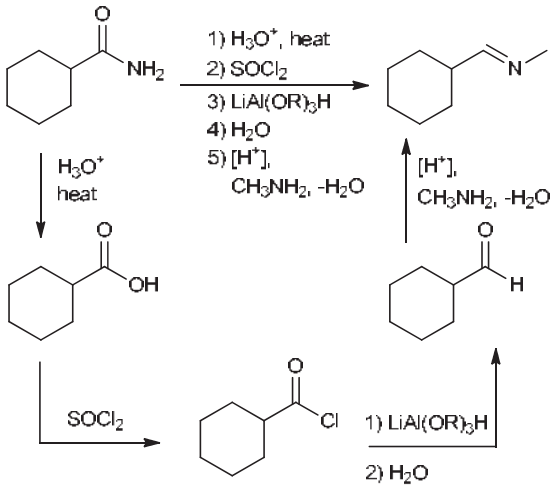


(b) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.



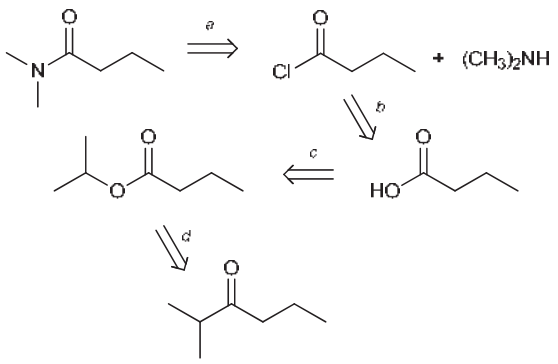
a. The desired imine can be made from the corresponding aldehyde.
b. The aldehyde can be made from the corresponding acid chloride, upon treatment with $LiAl(OR)_3H$, followed by water work-up.
c. The acid chloride can be prepared from the corresponding carboxylic acid, upon treatment with thionyl chloride.
d. The carboxylic acid can be made via hydrolysis of the starting amide.

Now let's draw the forward scheme. Acid catalyzed hydrolysis of the amide gives a carboxylic acid which is then converted to the acid chloride upon treatment with thionyl chloride. Reaction with a lithium trialkoxyaluminum hydride, followed by water, produces the aldehyde. Subsequent treatment of the aldehyde with methylamine under acid-catalyzed conditions (with removal of water) gives the desired imine.



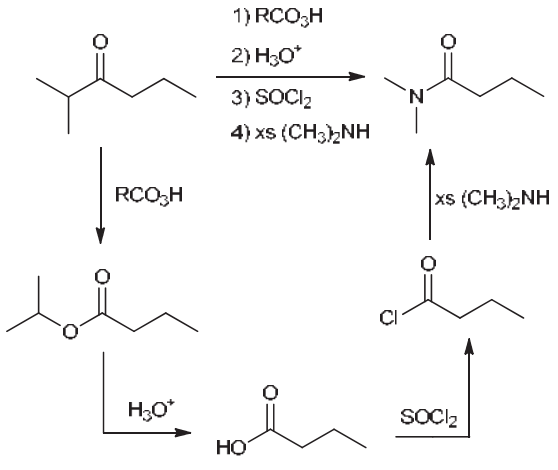
(c) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

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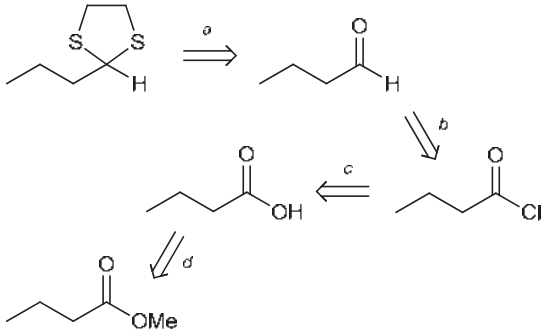


a. The desired amide can be made from the corresponding acid halide upon treatment with excess dimethylamine.
b. The acid halide can be made from the corresponding carboxylic acid, upon treatment with thionyl chloride.
c. The carboxylic acid can be prepared via hydrolysis of an ester.
d. The ester can be made from the starting ketone via a Baeyer-Villiger oxidation.

Now let's draw the forward scheme. Baeyer-Villiger oxidation of the starting ketone achieves the insertion of an oxygen atom between the carbonyl group and the more substituted alkyl group, thereby giving an ester. Acid-catalyzed hydrolysis of the ester gives butyric acid, which is then converted to the acid chloride upon treatment with thionyl chloride. The acid chloride is then converted into the desired product upon treatment with excess dimethyl amine (via a nucleophilic acyl substitution reaction).

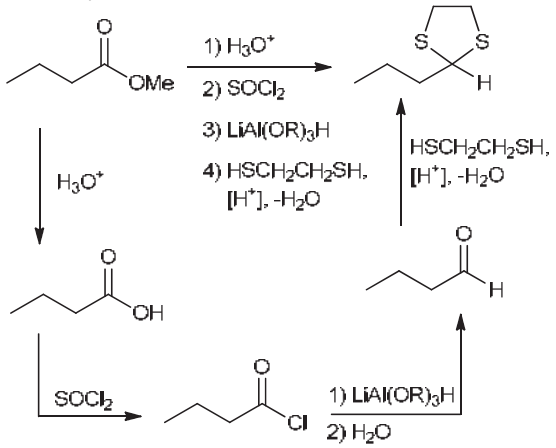


(d) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

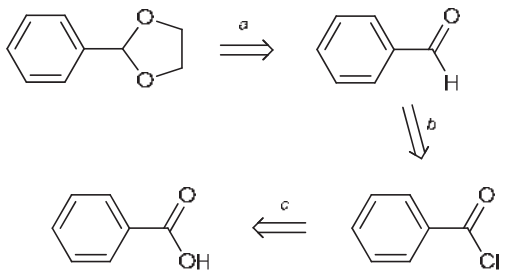


a. The cyclic thioacetal can be made from the corresponding aldehyde.
b. The aldehyde can be made from the corresponding acid halide, upon treatment with $LiAl(OR)_3H$, followed by water work-up.
c. The acid halide can be made from the corresponding carboxylic acid, upon treatment with thionyl chloride.
d. The carboxylic acid can be made from the starting ester via hydrolysis.

Now let's draw the forward scheme. The ester undergoes hydrolysis upon treatment with aqueous acid, giving butyric acid, which is subsequently converted to an acid chloride upon treatment with thionyl chloride. Reaction with a lithium trialkoxyaluminum hydride produces an aldehyde, which is then converted into the desired cyclic thioacetal.

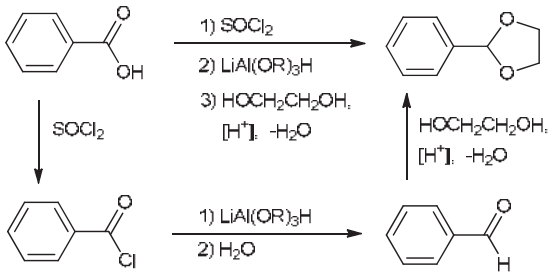


(e) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

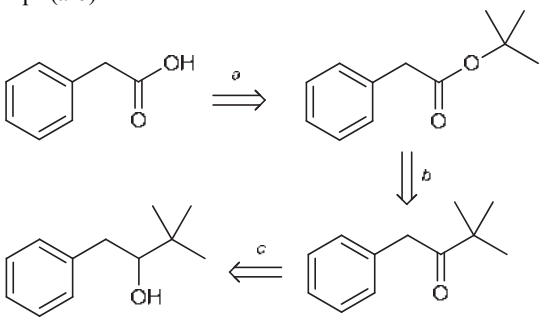


a. The cyclic acetal can be made from the corresponding aldehyde (benzaldehyde) via acetal formation.
b. Benzaldehyde can be made from the corresponding acid halide (benzoyl chloride).
c. Benzoyl chloride can be made from benzoic acid.

Now let's draw the forward scheme. Benzoic acid is converted to benzoyl chloride upon treatment with thionyl chloride. Benzoyl chloride is then converted into an aldehyde upon treatment with a lithium trialkoxyaluminum hydride. The aldehyde is then treated with ethylene glycol under acid-catalyzed conditions (with removal of water), giving the desired cyclic acetal.

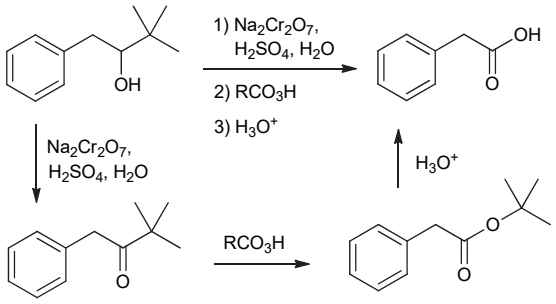


(f) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

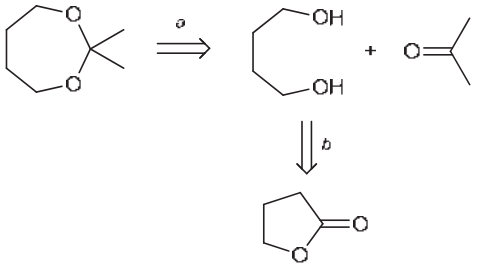


a. The carboxylic acid can be made from an ester, via hydrolysis.
b. The ester can be made from a ketone via a Baeyer-Villiger oxidation.
c. The ketone can be made from the starting material via oxidation of the starting alcohol.

Now let's draw the forward scheme. Oxidation of a secondary alcohol gives a ketone, which is then converted into an ester via a Baeyer-Villiger oxidation (this process inserts an oxygen atom between the carbonyl group and the more substituted alkyl group). Finally, acid-catalyzed hydrolysis of the ester gives the desired carboxylic acid.

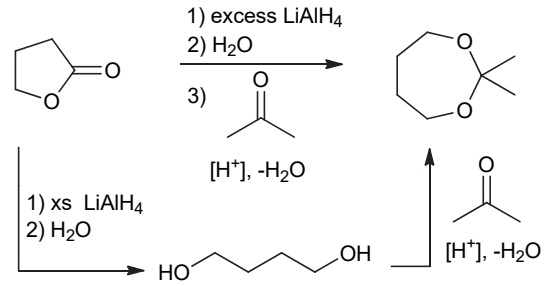


(g) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of both steps follows.



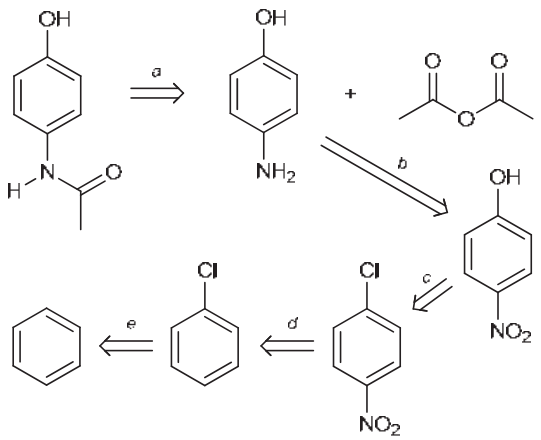
a. The product is a cyclic acetal, which can be made from a diol and a ketone (via acetal formation).
b. The diol can be made from the starting material via reduction with excess $LiAlH_4$.

Now let's draw the forward scheme. Reduction of the cyclic ester (lactone) with excess $LiAlH_4$, followed by water work-up, causes the ring to open, giving 1,4-butanediol. This diol can then be treated with acetone under acid-catalyzed conditions (with removal of water) to give the desired cyclic acetal.



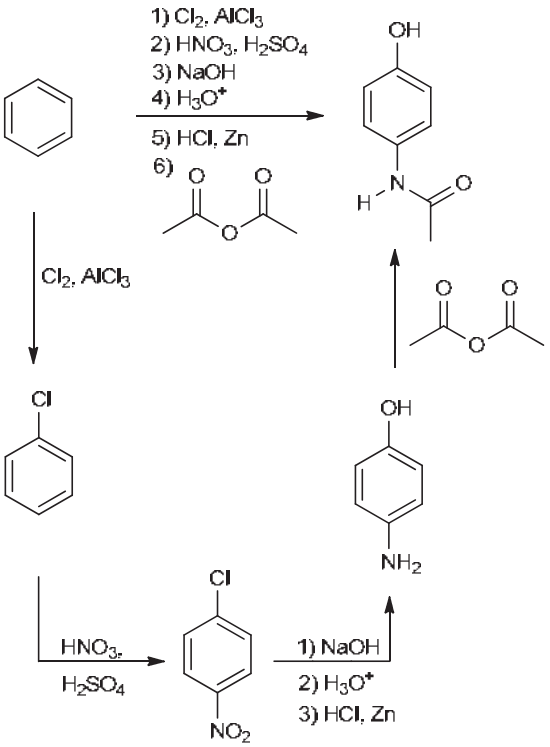
20.70. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

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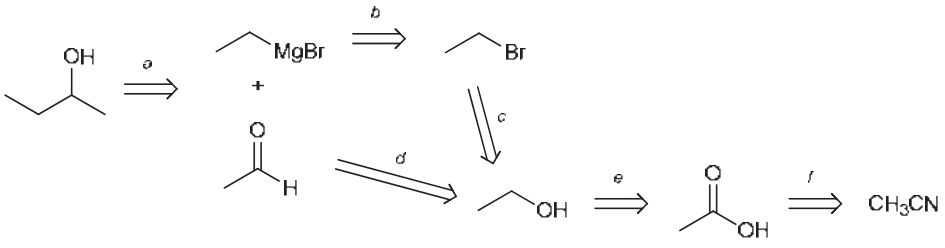


a. The product can be made via acetylation of *para*-aminophenol.
b. *para*-Aminophenol can be made from *para*-nitrophenol via reduction of the nitro group.
c. *para*-Nitrophenol can be made from *para*-chloronitrobenzene via an S_NAr process.
d. *para*-Chloronitrobenzene can be made via the nitration of chlorobenzene.
e. Chlorobenzene can be made from benzene via chlorination of the aromatic ring.

Now let's draw the forward scheme. Benzene is converted into chlorobenzene via an electrophilic aromatic substitution (upon treatment with Cl_2 and $AlCl_3$). The chlorine substituent is an *ortho-para* director, thus allowing subsequent nitration to install a nitro group in the *para* position. This intermediate exhibits a leaving group (chloride) that is *para* to a strong electron withdrawing group (nitro), so this compound is susceptible to nucleophilic aromatic substitution upon treatment with hydroxide, to produce *para*-nitrophenol (after acid work-up). Subsequent reduction of the nitro group with zinc and HCl gives *para*-aminophenol. Exposure to one molar equivalent of acetic anhydride produces the desired product, acetominophen. Note that the nitrogen atom of *para*-aminophenol is a stronger nucleophile than the oxygen atom, thus allowing the appropriate selectivity for production of the desired product.



20.71.
(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a-f*) follows.

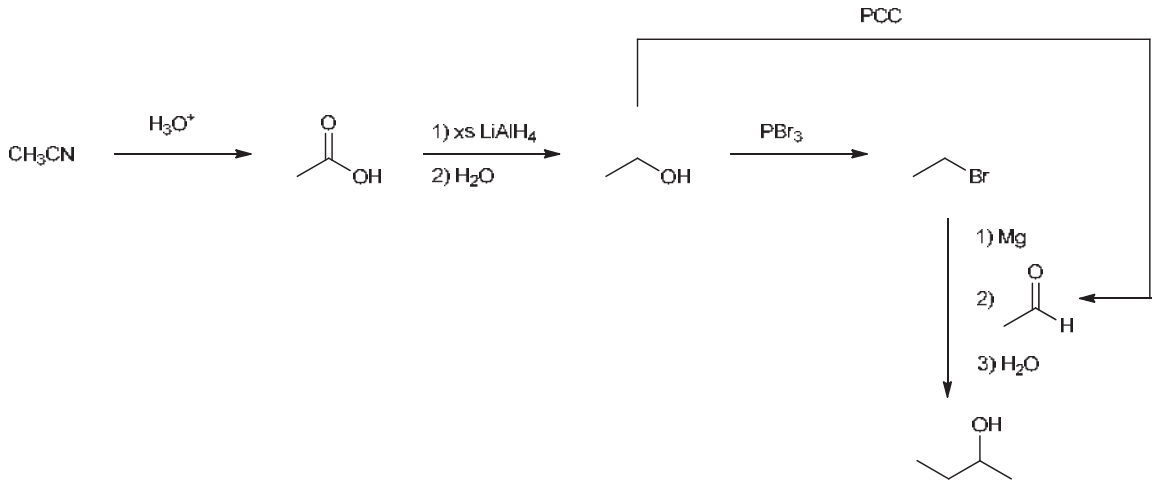


a. The desired alcohol can be made from a Grignard reaction between acetaldehyde and ethyl magnesium bromide.
b. Ethyl magnesium bromide is made from ethyl bromide, by insertion of magnesium.
c. Ethyl bromide can be made from ethanol upon treatment with PBr_3.

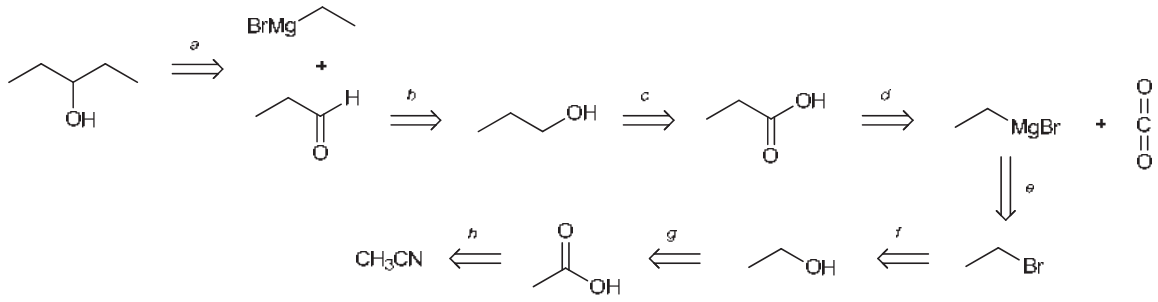
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d. Acetaldehyde can be made from ethanol via oxidation with PCC.
e. Ethanol can be made via reduction of acetic acid.
f. Acetic acid can be made via hydrolysis of acetonitrile.

Now let's draw the forward scheme. Hydrolysis of acetonitrile gives acetic acid which is subsequently reduced to ethanol upon treatment with excess $LiAlH_4$, followed by water work-up. Upon treatment with PBr_3, ethanol is converted to ethyl bromide which is then converted to ethyl magnesium bromide (a Grignard reagent). A Grignard reaction with acetaldehyde (produced by PCC oxidation of ethanol, as shown), followed by water work-up, produces the desired alcohol, 2-butanol.



(b) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*g*) follows.

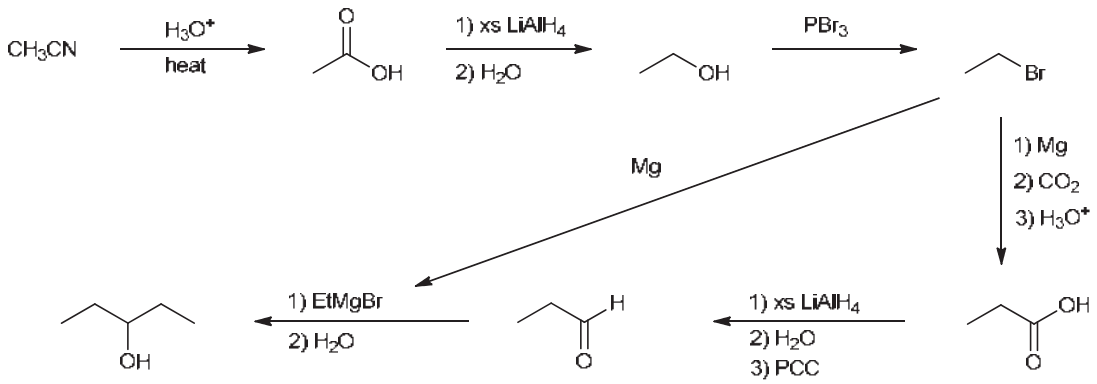


a. The desired alcohol can be made from a Grignard reaction between propanal and ethyl magnesium bromide (formed in step *d*).
b. Propanal can be made from 1-propanol, upon treatment with PCC.
c. 1-Propanol can be made from propanoic acid, upon treatment with excess $LiAlH_4$, followed by water work-up.
d. Propanoic acid can be made from a reaction between ethyl magnesium bromide and carbon dioxide.
e. Ethyl magnesium bromide is made from ethyl bromide, by insertion of magnesium.
f. Ethyl bromide can be made from ethanol upon treatment with PBr_3.
g. Ethanol can be made via reduction of acetic acid.
h. Acetic acid can be made via hydrolysis of acetonitrile.

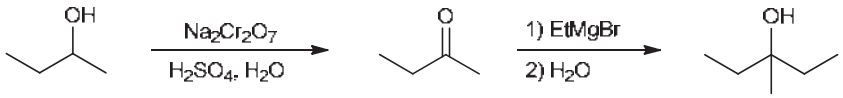
Now let's draw the forward scheme. Hydrolysis of acetonitrile gives acetic acid which is subsequently reduced to ethanol upon treatment with excess $LiAlH_4$, followed by water work-up. Upon treatment with PBr_3, ethanol is

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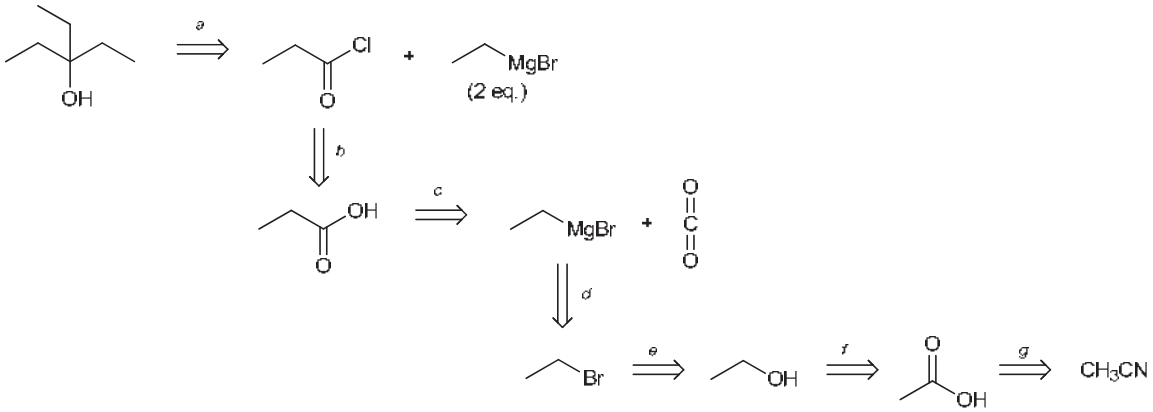
converted to ethyl bromide which is then converted to ethyl magnesium bromide (a Grignard reagent). A Grignard reaction with carbon dioxide, followed by protonation with H_3O^+, gives propanoic acid. This acid is converted into propanal via reduction (with excess $LiAlH_4$) followed by oxidation with PCC. Reaction with ethyl magnesium bromide (prepared as described above), followed by water work-up, gives the desired alcohol, 3-pentanol.



(c) The desired product can be made from the product of **20.71(a)** in just two steps. Therefore, we would first perform the synthesis described in the solution to **20.71(a)**, followed by these two reactions:



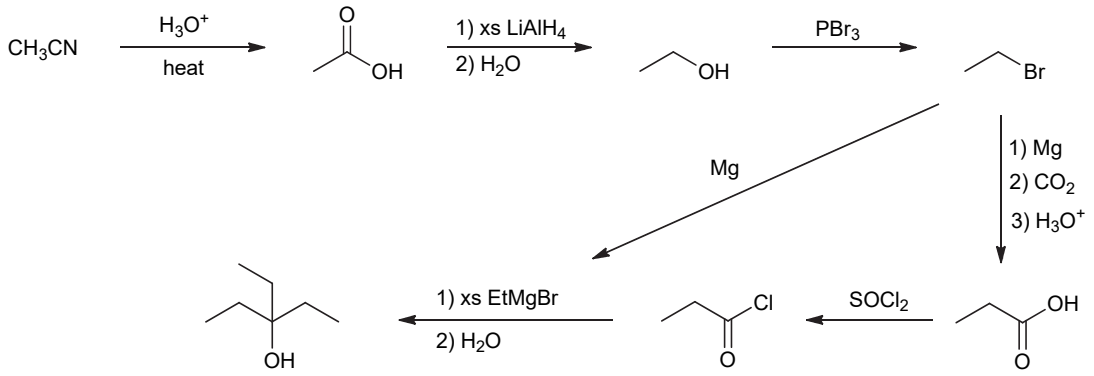
(d) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*g*) follows.



a. The desired alcohol can be made from a Grignard reaction between propanoyl chloride and two equivalents of ethyl magnesium bromide (formed in step *d*).
b. Propanoyl chloride can be made from propanoic acid, upon treatment with thionyl chloride.
c. Propanoic acid can be made from a reaction between ethyl magnesium bromide and carbon dioxide.
d. Ethyl magnesium bromide is made from ethyl bromide, by insertion of magnesium.
e. Ethyl bromide can be made from ethanol upon treatment with PBr_3.
f. Ethanol can be made via reduction of acetic acid.
g. Acetic acid can be made via hydrolysis of acetonitrile.

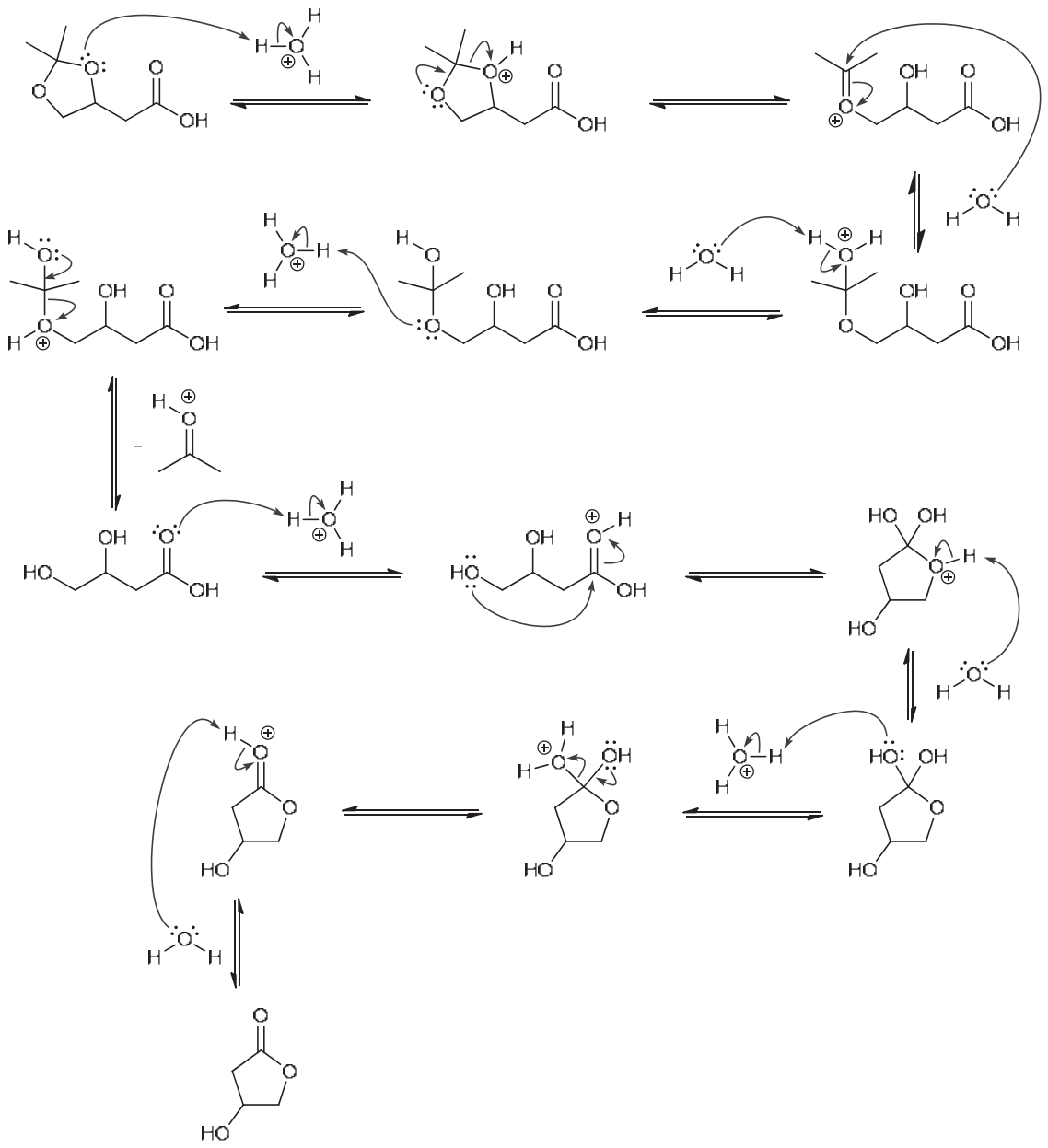
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Now let's draw the forward scheme. Hydrolysis of acetonitrile gives acetic acid which is subsequently reduced to ethanol upon treatment with excess $LiAlH_4$, followed by water work-up. Upon treatment with PBr_3, ethanol is converted to ethyl bromide which is then converted to ethyl magnesium bromide (a Grignard reagent). A Grignard reaction with carbon dioxide followed by protonation with H_3O^+ gives propanoic acid. Conversion to the acid chloride, followed by reaction with excess ethyl magnesium bromide (prepared as described above) produces the desired tertiary alcohol, 3-ethyl-3-pentanol.

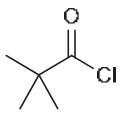


20.72. The mechanism shown below has 12 steps: 1) proton transfer, 2) loss of a leaving group, 3) nucleophilic attack, 4) proton transfer, 5) proton transfer, 6) loss of a leaving group, 7) proton transfer, 8) nucleophilic attack, 9) proton transfer, 10) proton transfer, 11) loss of a leaving group and 12) proton transfer. In step 1 (proton transfer), one of the acetal oxygen atoms is protonated by H_3O^+, activating it as a leaving group (either oxygen atom can be protonated, which will ultimately lead to the same product). In step 2, an alcohol group leaves as a leaving group. Water then attacks the activated carbonyl group in step 3 (nucleophilic attack). In step 4 (proton transfer), water deprotonates the cationic oxygen atom, and in step 5 (proton transfer), the other oxygen atom in the hemiacetal is protonated by H_3O^+, producing a cationic intermediate. In step 6, an alcohol serves as a leaving group. Protonation of the carbonyl group (step 7, proton transfer) activates this carbonyl group for intramolecular attack by one of the tethered alcohol groups (step 8, nucleophilic attack), thus forming a ring (a five-membered ring is more likely formed than a more strained, four-membered ring). Deprotonation by water (step 9, proton transfer) followed by protonation by H_3O^+ (step 10, proton transfer) produces a cationic intermediate with an activated leaving group (water). In step 11, water serves as a leaving group. In step 12 (proton transfer), water serves as a weak base to deprotonate the cationic oxygen atom, resulting in the formation of the final product (a lactone).

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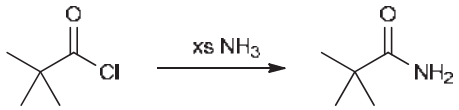


20.73. The carboxylic acid has a molecular formula of $C_5H_{12}O_2$. Thionyl chloride replaces the OH group on the carboxylic acid with a chlorine atom, thus the molecular formula of the resulting acid chloride is $C_5H_{11}ClO$. Considering the possible acid chloride isomers with this molecular formula, only one (compound **A**) gives a single signal in its ^1H NMR spectrum



Compound **A**

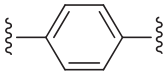
When compound **A** is treated with excess ammonia, a nucleophilic acyl substitution reaction occurs, producing the amide shown.



20.74. The molecular formula ($C_{10}H_{10}O_4$) indicates six degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring (which accounts for four degrees of unsaturation) plus two more degrees of unsaturation (either two rings, or two double bonds, or a ring and a double bond, or a triple bond).

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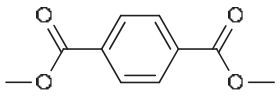
There are two signals (both singlets) in the ^{1}H NMR spectrum, with integration values of 3H (4.0 ppm) and 2H (8.1 ppm). There are a total of 10 hydrogen atoms in the molecule, so the ratio of the integration values (3:2) must represent a 6H:4H ratio of the hydrogen atoms in the molecule (6H + 4H = 10H total). This indicates a high degree of symmetry in the structure.
The signal at 8.1 ppm (with an integration of 4H) is consistent with the chemical shift expected for aromatic protons. The integration (4H) indicates a disubstituted ring, and the multiplicity of this signal (it is a singlet) suggests a *para*-disubstituted aromatic ring with two equivalent substituents, thereby rendering all four aromatic protons equivalent (thus giving rise to a singlet):



The signal at 4.0 ppm (with an integration of 6H) is consistent with two identical methyl groups, each of which must be next to an oxygen atom to justify the downfield shift of the signal:



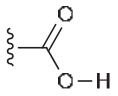
The two methoxy fragments and the aromatic ring account for all of the atoms in the molecular formula except for two carbon atoms and two oxygen atoms. Since we still need to account for two more degrees of unsaturation, and since the proposed structure must retain its high degree of symmetry, we propose the following structure:



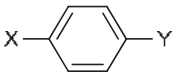
20.75. An IR spectrum of butyric acid should have a broad signal between 2200 and 3600 cm^{-1} due to the O-H stretch of the carboxylic acid. An IR spectrum of ethyl acetate will not have this signal.

20.76. The ^{1}H NMR spectrum of *para*-chlorobenzaldehyde should have a signal at approximately 10 ppm corresponding to the aldehydic proton. The ^{1}H NMR spectrum of benzoyl chloride should not have a signal near 10 ppm.

20.77. The molecular formula ($C_8H_8O_3$) indicates five degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring (which accounts for four degrees of unsaturation) plus either one ring or one double bond.
The broad signal between 2200 cm^{-1} and 3600 cm^{-1} in the IR spectrum is consistent with the O-H stretch of a carboxylic acid.



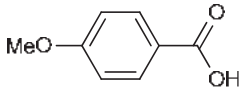
The ^{1}H NMR spectrum exhibits a signal at approximately 12 ppm, confirming the presence of a carboxylic acid group. The pair of doublets (with a combined integration of 4H) appearing between 7 and 8 ppm is characteristic of a *para*-disubstituted aromatic ring (with two different substituents):



The singlet near 4 ppm has an integration of 3H, indicating a methyl group. The downfield chemical shift of this signal indicates that the methyl group is likely attached to an oxygen atom:



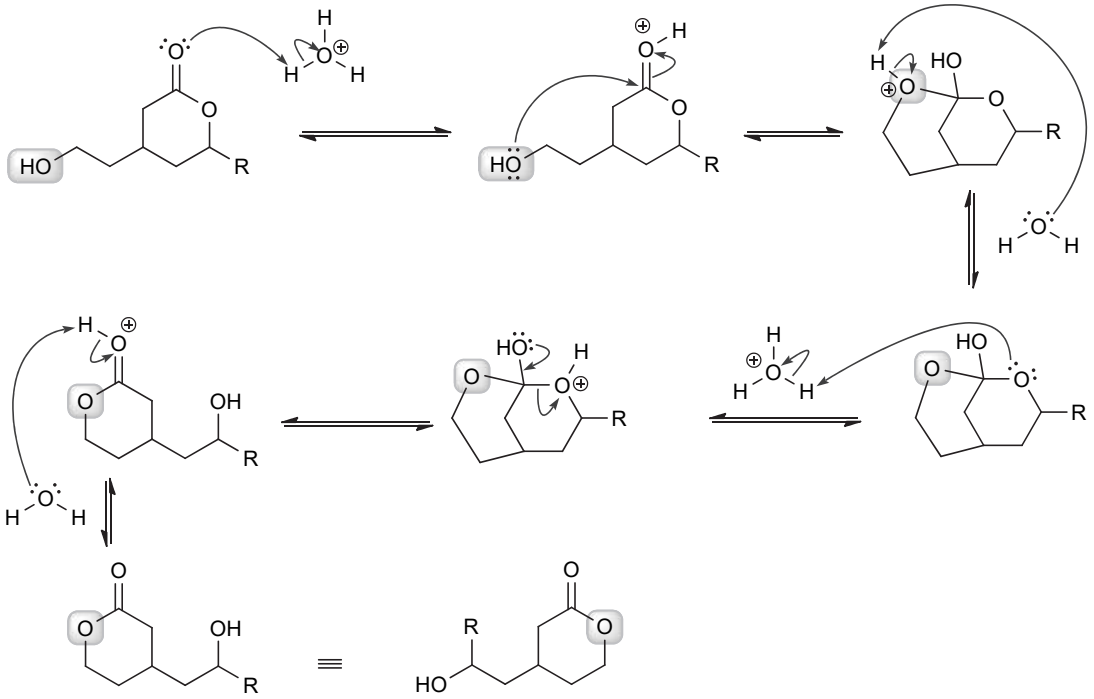
There is only one way to connect the three fragments:



The ^{13}C NMR spectrum is consistent with this structure. The most downfield signal (172.8 ppm) is consistent with the carbonyl group. A disubstituted aromatic ring (bearing two different substituents) is expected to produce four signals between 100 and 150 ppm. We do in fact see four signals, although one of them is above 150 ppm, which likely corresponds with the carbon atom connected to the methoxy group (an oxygen atom is electron-withdrawing, causing a deshielding effect). Finally, the signal between 50 and 100 ppm is consistent with the carbon atom of the methoxy group (an sp^3 hybridized carbon atom attached to an electronegative atom).

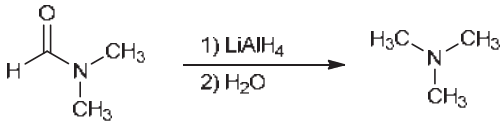
20.78. The mechanism shown below has 6 steps: 1) proton transfer, 2) nucleophilic attack, 3) proton transfer, 4) proton transfer, 5) loss of a leaving group and 6) proton transfer. In step 1 (proton transfer), the carbonyl group is protonated by H_3O^+, activating it as an electrophile. In step 2 (nucleophilic attack), the tethered alcohol group serves as a nucleophile in an intramolecular nucleophilic attack. In step 3 (proton transfer), water deprotonates the oxonium ion, and in step 4 (proton transfer), a different oxygen atom is protonated by H_3O^+, activating it as a leaving group. In step 5 (loss of a leaving group), an alcohol serves as a leaving group. Deprotonation (step 6) gives the final, rearranged product. If the oxygen atom of the OH group in the starting material is an isotopic label (as indicated by the highlighted boxes), then we would expect the label to be incorporated into the ring of the product, as shown.

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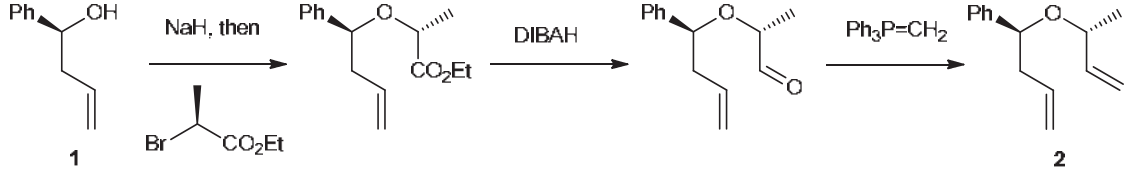
20.79. The lone pair of the nitrogen atom (of the amide group) is participating in aromaticity and is therefore unavailable to donate electron density into the carbonyl group. As a result, the carbonyl group is more electrophilic than the carbonyl group of a regular amide (where the lone pair contributes significant electron density to the carbonyl group via resonance). Also, when this compound functions as an electrophile in a nucleophilic acyl substitution reaction, the leaving group is particularly stable because it is an aromatic anion in which the negative charge is spread over all five atoms of the aromatic ring. With such a good leaving group, this compound more closely resembles the reactivity of an acid halide than an amide.

20.80.
(a) DMF, like most amides, exhibits restricted rotation about the bond between the carbonyl group and the nitrogen atom, due to the significant contribution of the resonance form with a C=N double bond. This restricted rotation causes the methyl groups to be in different electronic environments. They are not chemically equivalent, and will therefore produce two different signals (in addition to the signal from the other proton in the compound). Upon treatment with excess $LiAlH_4$, followed by water work-up, DMF is reduced to an amine:



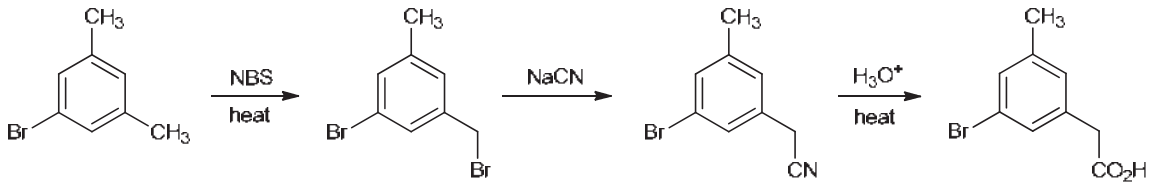
This amine does not exhibit restricted rotation. As such, all of the methyl groups are now chemically equivalent and will together produce only one signal.
(b) Restricted rotation causes the methyl groups to be in different electronic environments. As a result, the ^{13}C NMR spectrum of DMF should have three signals.

20.81. The first step of the synthesis involves deprotonation of the alcohol group in compound **1** using NaH, generating an alkoxide ion. This alkoxide ion is then treated with the chiral 2-bromo ethyl ester, to give an S_N2 reaction (note the inversion of configuration of the chiral center bearing the methyl group). Reduction of the ester with DIBAH provides an aldehyde, which is transformed into the terminal olefin (compound **2**) using a Wittig reaction.



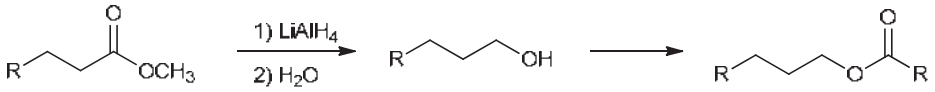
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20.82. Notice that the product has one more carbon atom than the starting material, and therefore, we must introduce a carbon atom. This can be accomplished by first installing a leaving group at one of the benzylic positions, followed by an S_N2 process in which the leaving group is replaced with cyanide. Acid-catalyzed hydrolysis of the resulting nitrile affords the desired carboxylic acid. This route is preferable to the formation of a Grignard reagent followed by condensation with CO_2, as there are two bromine atoms in the molecule.



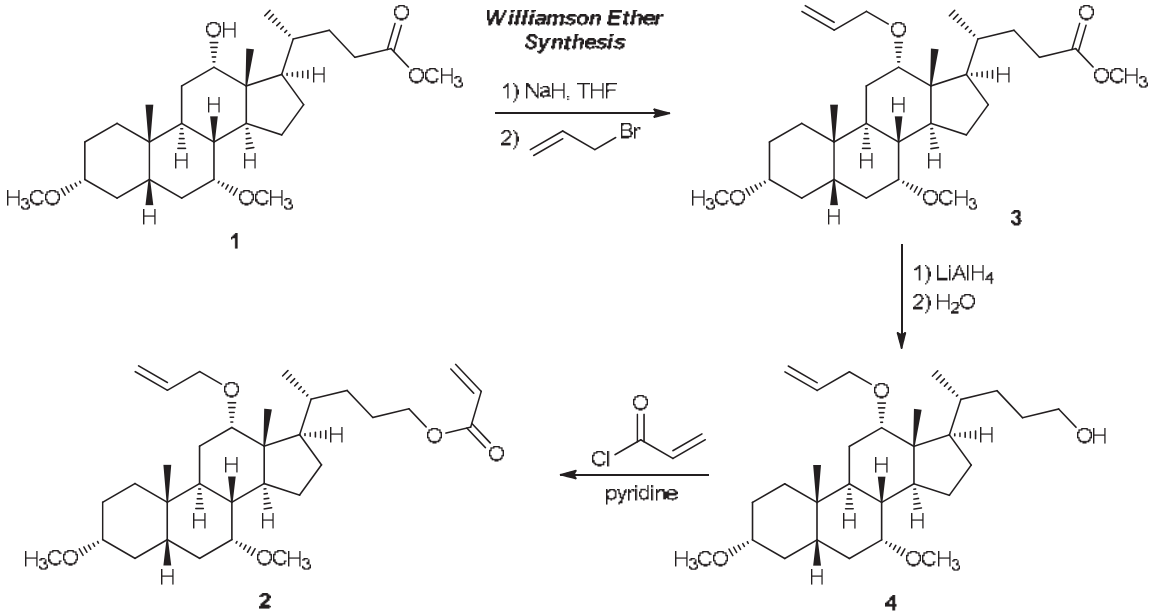
20.83. A possible synthesis is shown below. When analyzing the starting material, **1**, and the product, **2**, it can be seen that the alcohol is transformed into an ether and that the ester is converted to a different ester. So first determine a method to make an ether; the Williamson ether synthesis (base + RX) is a convenient method for ether formation.

For the conversion of the ester to a different ester, notice that the carbonyl carbon of ester **1** is still part of the side chain, but it is now a methylene (CH_2) and therefore the ester must be reduced at some point ($LiAlH_4$ is known to reduce esters). Reduction of the ester affords a 1° alcohol, which can then be converted to the new ester:



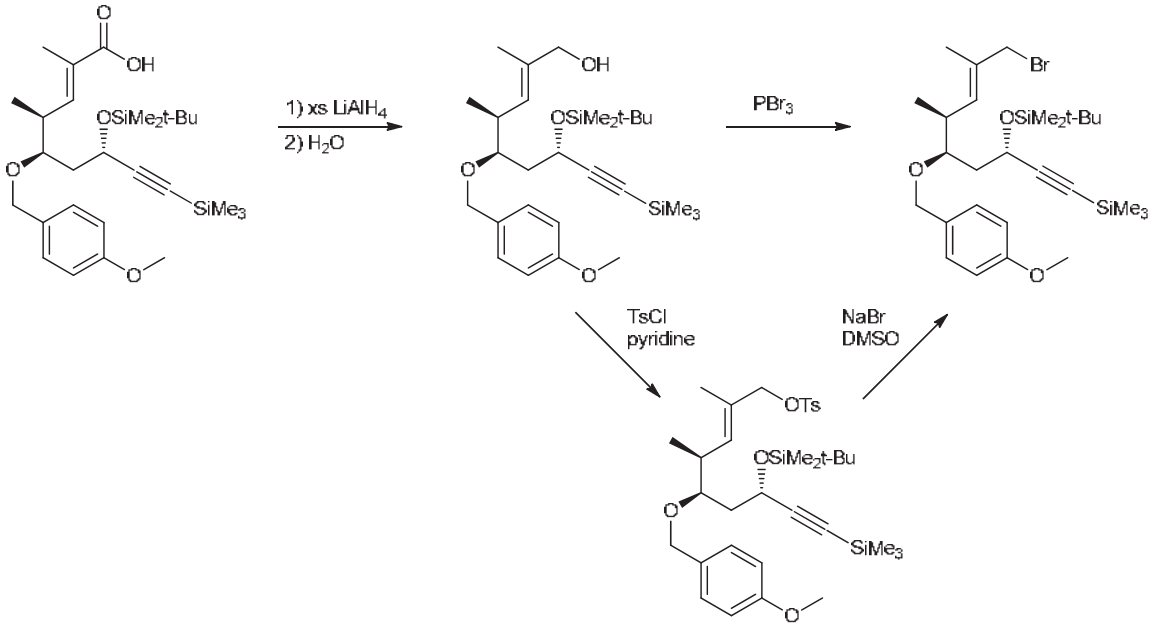
Conversion of the alcohol into the ester could be achieved either via an acid-catalyzed Fischer esterification (ROH + RCO_2H) or the via addition of an alcohol to an acid chloride (ROH + RCOCl). The latter method is preferable, because acidic conditions (employed by the first method) could produce undesired side reactions with other functional groups present.

Finally, the order of addition of these reagents is important so that you don't get an undesired product. See the correct order below, which shows the formation of ether **3** first (Williamson ether synthesis), followed by reduction of the ester to give alcohol **4**, and finally, conversion of alcohol **4** to the desired ester **2** using the corresponding acid chloride.

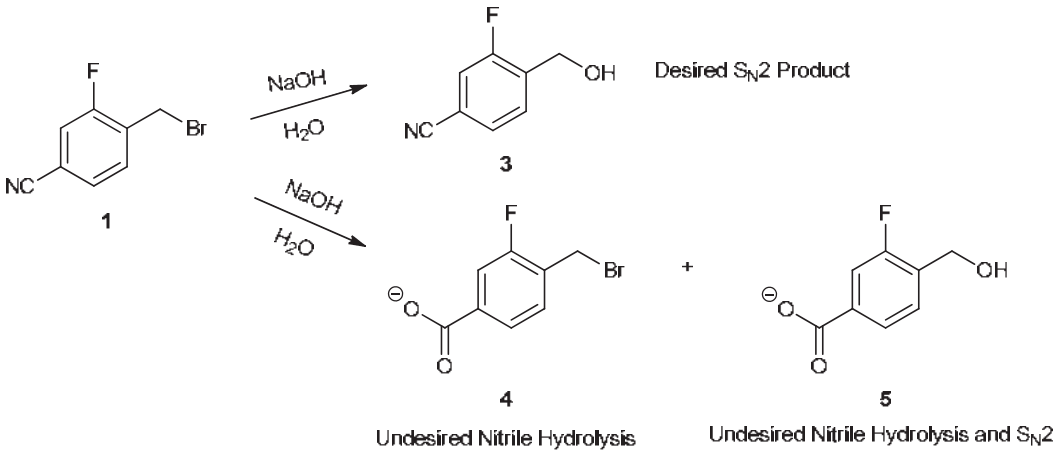


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20.84.
The desired transformation can be achieved via reduction of the carboxylic acid, followed by substitution. Direct conversion of the resultant alcohol may be accomplished using PBr_3, or one can utilize a two-step method involving: 1) tosylate formation using TsCl and pyridine followed by, 2) S_N2 displacement using sodium bromide in DMSO:

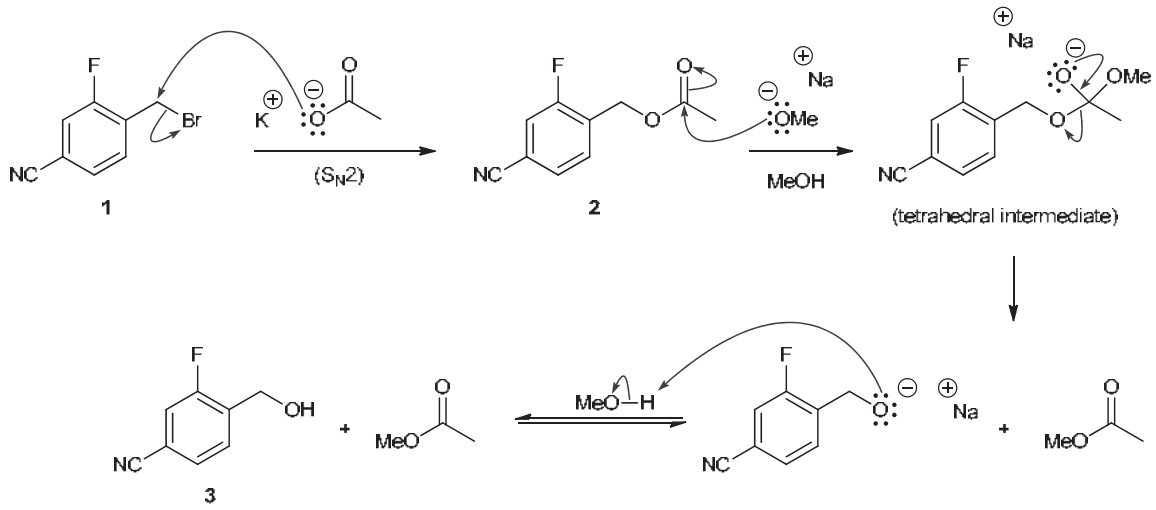


20.85.
(a) Compound 1 is a nitrile (it contains a cyano group), which can undergo hydrolysis under these reaction conditions. This gives rise to three possible products, only one of which is the desired product:

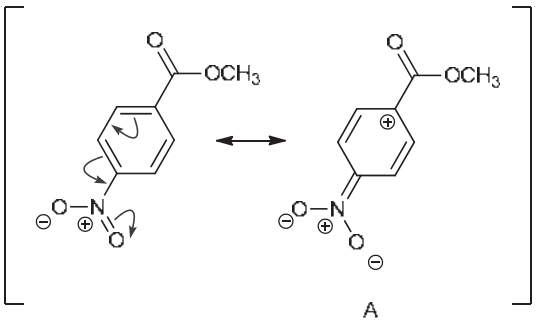


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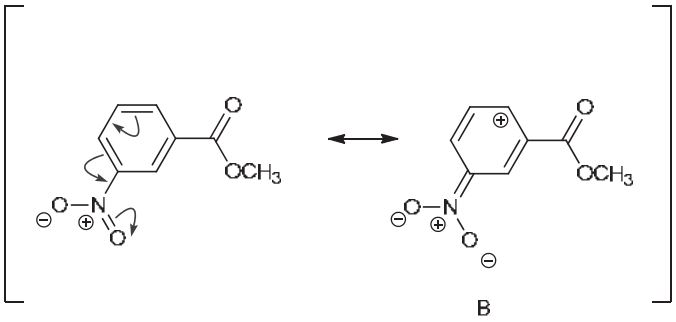
(b) A possible mechanism for the reaction sequence is shown here. The conversion of compound **1** to compound **2** is an S_N2 displacement of the bromide with acetate ($CH_3CO_2^-$). The reaction of the ester with NaOMe/MeOH is expected to proceed via a mechanism in which methoxide (CH_3O^-) attacks the carbonyl carbon of the ester (just as hydroxide would during hydrolysis). This generates a tetrahedral intermediate that collapses back down to give a new ester and alkoxide, which is protonated by the solvent to give the desired alcohol, compound **3**.



20.86. Note that methyl benzoate is the reference compound among the series of compounds examined. So, benzoates with rate constants larger in value than 1.7 $M^{-1}min^{-1}$ are more reactive while those with lower values are less reactive than the reference compound. The aromatic ring of methyl *p*-nitrobenzoate is considerably lower in electron density due to resonance interaction between the nitro group and the ring. However, in one of the resonance forms (structure A below), the electron deficient carbon atom of the ring is adjacent to the carbonyl carbon atom. Thus, the electrophilicity at the carbonyl functional group is the largest, making its reactivity towards nucleophilic attack by hydroxide anion the largest in this compound.



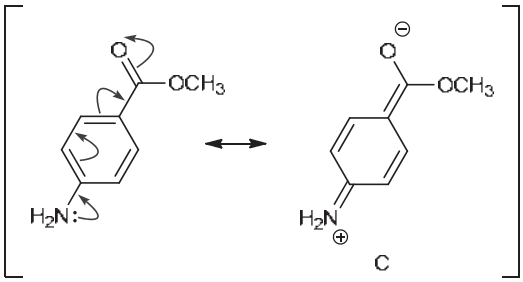
While the aromatic ring of methyl *m*-nitrobenzoate is also expected to be just as deficient in electron density as that of the *para* isomer, the positive charge on the ring never occupies the carbon atom adjacent to the carbonyl carbon atom (structure B). So, the electron deficiency (electrophilicity) at the carbonyl carbon atom is not as large as that of the *para* isomer. Thus, the reaction rate is not as large as that of the *para* isomer.



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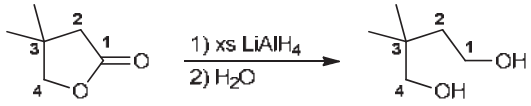
The main electronic interaction between the halogen atoms and the aromatic ring is induction by which both chlorine and bromine are expected to withdraw electron density from the ring. Since chlorine is more electronegative than bromine, the *m*-chlorophenyl ring is more electron deficient than the *m*-bromophenyl ring, and thus more reactive.

The remaining three benzoates are less reactive than the reference compound. This suggests that the substituents found in these compounds are all electron-donating so as to increase the electron density at the carbonyl group. The increased electron density lowers the electrophilicity at the carbonyl group and thus lowers their reactivity towards hydroxide ion. The methyl group is only weakly electron-donating, so it raises the electron density the least. According to electronegativity trends, since a nitrogen atom is more electron-donating than oxygen, the amino group is the best electron donor via resonance and thus lowers the reactivity of the carbonyl carbon the most (structure C).

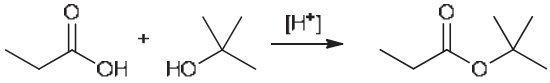


In this problem, we see that the influence of the resonance effects dominates those of induction. We also learn that the precise resonance forms involved can make a difference in the overall reactivity (*p*- vs *m*-nitrobenzoates).

20.87. An ester will react with two equivalents of lithium aluminum hydride to give a diol, so we can rule out options (a) and (b). Between the remaining two options, (c) has the correct skeleton, which we can see more easily if we assign numbers to the skeleton, and then track the location of the methyl groups:

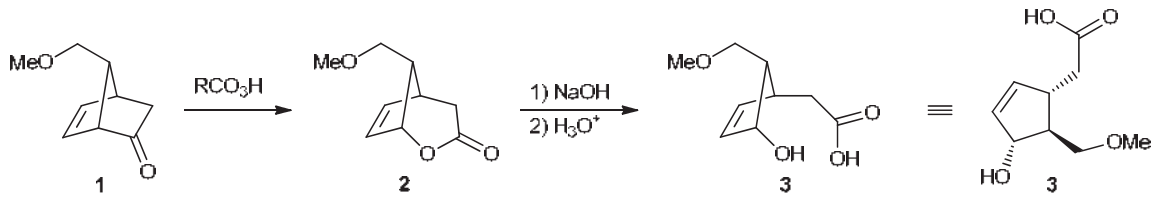


20.88. A Fischer esterification requires a carboxylic acid and an alcohol, so we can rule out options (a) and (c). Additionally, (b) has too many carbon atoms (3+5=8); the product has only seven carbon atoms. The correct answer is (d):



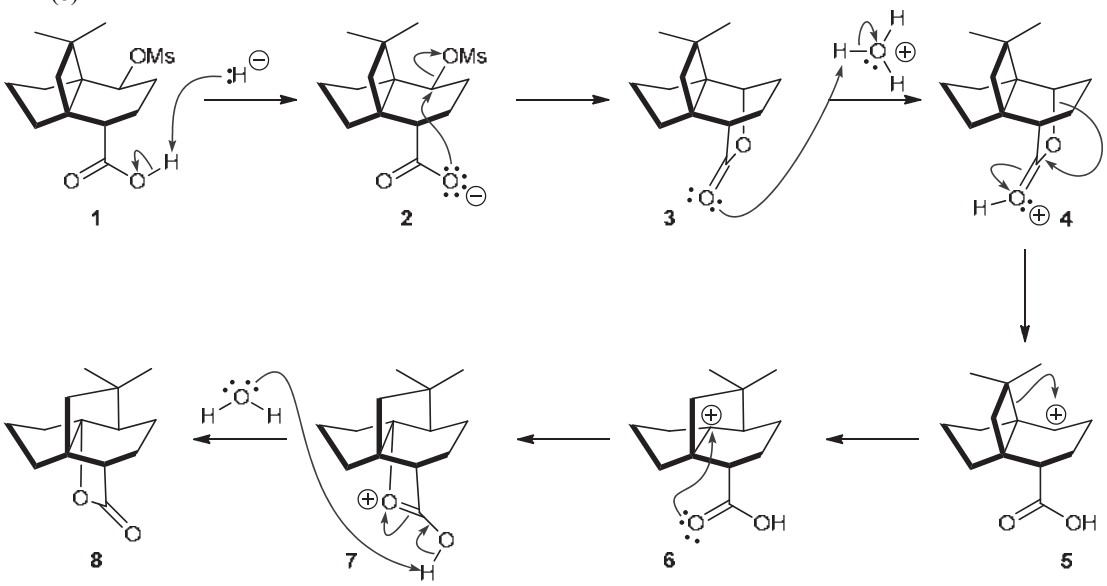
20.89. Option (d) is the correct answer because a negatively charged nitrogen atom is too strongly basic to be formed in acidic conditions. The other three structures (a-c) are all intermediates in the expected mechanism for amide hydrolysis.

20.90. Compound **1** is a ketone, so treatment with a peroxy acid will give the corresponding lactone (cyclic ester). Notice that the oxygen atom is inserted between the carbonyl group and the bridgehead position (because that position is more substituted than the other side of the carbonyl group). Hydrolysis of the lactone gives compound **3**. In Corey's synthesis, this hydrolysis step was performed under basic conditions (saponification), and under those conditions, the product (compound **3**) would be deprotonated to give a carboxylate ion. Acid workup is necessary in order to protonate the carboxylate ion and regenerate the carboxylic acid (compound **3**).

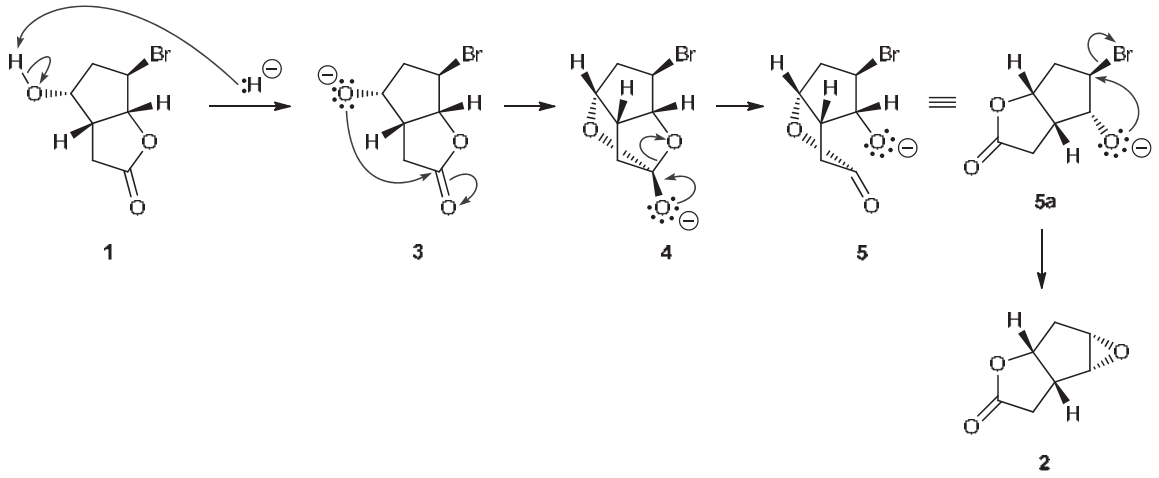


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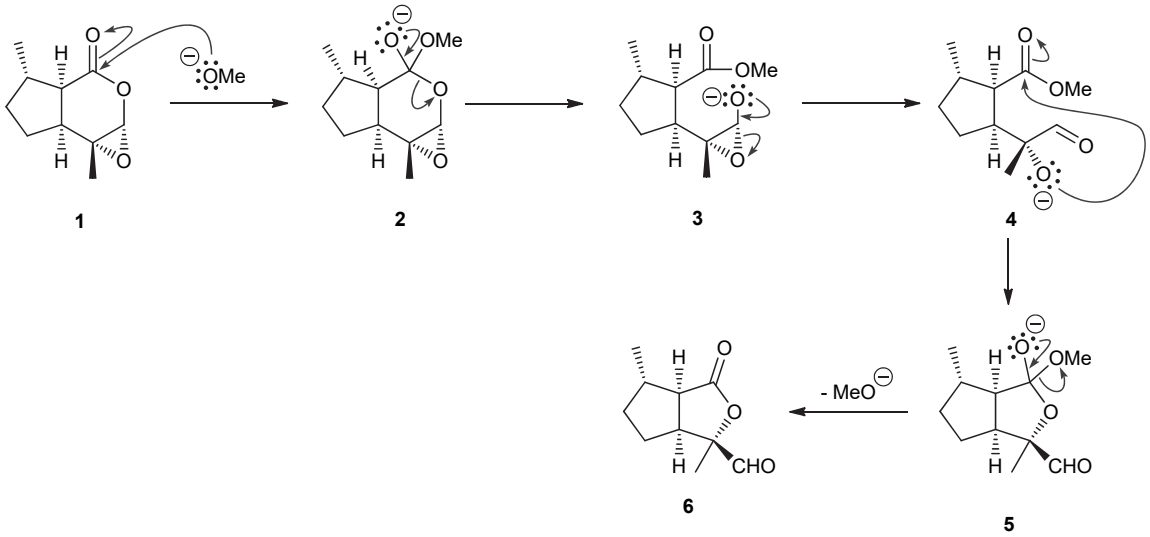
20.91. The first step of the synthesis involves deprotonation of the carboxylic acid with sodium hydride, followed by intramolecular esterification of **2** via loss of the mesylate group, giving **3**. Note that the newly formed ring is on the bottom face of the molecule. Next, protonation of the ester with aqueous acid will generate an activated carbonyl (**4**) that spontaneously leaves as a neutral carboxylic acid, generating a secondary carbocation (**5**). Next, a 1,2-carbon migration occurs so that the four-membered ring opens and the pair of electrons in the C-C σ-bond moves over one carbon to satisfy the carbocation, which in turn will generate a new, tertiary carbocation (**6**). In the next step, the carboxylic acid will form a new C-O bond with the carbocation, on the bottom face of the molecule, to generate a resonance-stabilized intermediate (**7**). In the final step of the mechanism, **7** is deprotonated to produce the desired ring system (**8**).



20.92. Deprotonation of alcohol **1** with sodium hydride will produce an alkoxide (**3**) that can easily react at the lactone carbonyl to form intermediate **4** (note: the bond angles in **4** have been exaggerated). Once formed, the unstable tetrahedral intermediate quickly decomposes to generate a new 5-membered lactone via the expulsion of an alkoxide leaving group. While it may be difficult to see in its current form, intermediate **5** can be redrawn as **5a**, which clearly shows the desired fused 5,5-ring system of the product with the proper stereochemistry at the ring junction. In the final step, the alkoxide in **5a** reacts at the carbon-bromine bond in an S_N2 fashion to produce epoxide **2**.



20.93. In the first step, methoxide attacks the lactone carbonyl to produce tetrahedral intermediate **2**. In the second step, the carbonyl is reformed via the loss of a leaving group, which in this case is the oxygen atom that was part of the 6-membered ring, leading to alkoxide **3**. Alpha to this newly formed alkoxide is an epoxide; generation of a new carbonyl via alkoxide opening of the epoxide will produce aldehyde **4**. Finally, the alkoxide that was generated from the epoxide opening can now attack the ester carbonyl to form tetrahedral intermediate **5**, which quickly loses methoxide to form lactone **6**.



Chapter 21
Alpha Carbon Chemistry: Enols and Enolates

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 21. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

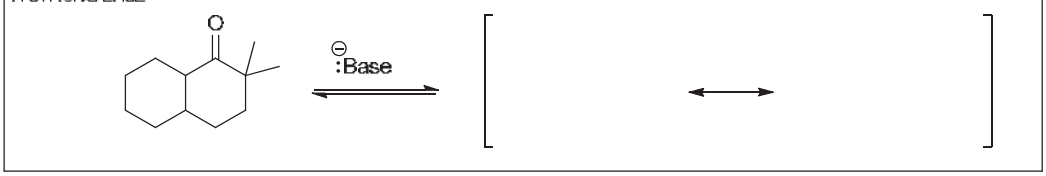
- In the presence of catalytic acid or base, a ketone will exist in equilibrium with an _____. In general, the equilibrium will significantly favor the _____.
- When treated with a strong base, the α position of a ketone is deprotonated to give an _____.
- _____ or _____ will irreversibly and completely convert an aldehyde or ketone into an enolate.
- In the **haloform reaction**, a _____ ketone is converted into a carboxylic acid upon treatment with excess base and excess halogen followed by acid workup.
- When an aldehyde is treated with sodium hydroxide, an **aldol addition reaction** occurs, and the product is a _____.
- For most simple aldehydes, the position of equilibrium favors the aldol product. For most ketones, the reverse process, called a **_____-aldol reaction** is favored.
- When an aldehyde is heated in aqueous sodium hydroxide, an **aldol _____ reaction** occurs, and the product is an _____. Elimination of water occurs via an **_____ mechanism**.
- **Crossed aldol,** or **mixed aldol reactions** are aldol reactions that occur between different partners and are only efficient if one partner lacks _____ or if a **directed aldol addition** is performed.
- Intramolecular aldol reactions show a preference for formation of _____ and ____-membered rings.
- When an ester is treated with an alkoxide base, a **Claisen condensation reaction** occurs, and the product is a _____.
- The α position of a ketone can be alkylated by forming an enolate and treating it with an _____.
- For unsymmetrical ketones, reactions with _____ at low temperature favor formation of the kinetic enolate, while reactions with _____ at room temperature favor the thermodynamic enolate.
- When LDA is used with an unsymmetrical ketone, alkylation occurs at the _____ position.
- The _____ **synthesis** enables the conversion of an alkyl halide into a carboxylic acid with the introduction of two new carbon atoms.
- The _____ **synthesis** enables the conversion of an alkyl halide into a methyl ketone with the introduction of two new carbon atoms.
- Aldehydes and ketones that possess _____-unsaturation are susceptible to nucleophilic attack at the β position. This reaction is called a _____ **addition,** or *1,4-addition***,** or a **Michael reaction**.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 21. The answers appear in the section entitled *SkillBuilder Review*.

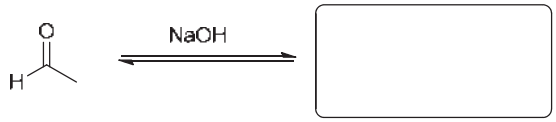
21.1 Drawing Enolates

DRAW THE RESONANCE STRUCTURES OF THE ENOLATE THAT IS FORMED WHEN THE KETONE BELOW IS TREATED WITH A STRONG BASE:



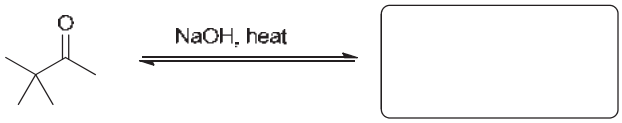
21.2 Predicting the Products of an Aldol Addition Reaction

PREDICT THE PRODUCT OF THE ALDOL ADDITION REACTION THAT OCCURS WHEN THE FOLLOWING ALDEHYDE IS TREATED WITH SODIUM HYDROXIDE:



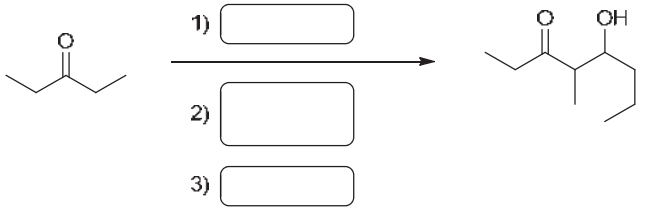
21.3 Drawing the Product of an Aldol Condensation

DRAW THE PRODUCT OF THE ALDOL CONDENSATION REACTION THAT OCCURS WHEN THE FOLLOWING COMPOUND IS HEATED WITH SODIUM HYDROXIDE:



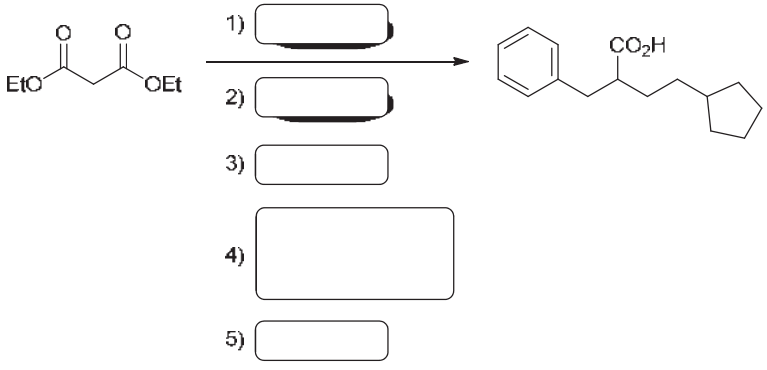
21.4 Identifying the Reagents Necessary for a Crossed Aldol Reaction

IDENTIFY REAGENTS THAT WILL ACHIEVE THE FOLLOWING TRANSFORMATION:

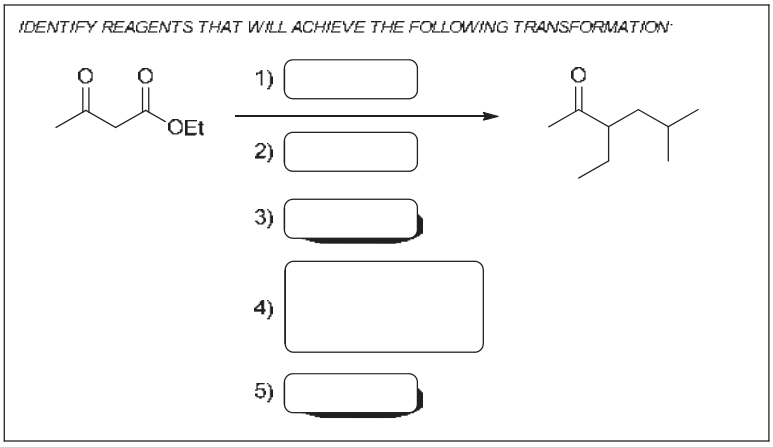


21.5 Using the Malonic Ester Synthesis

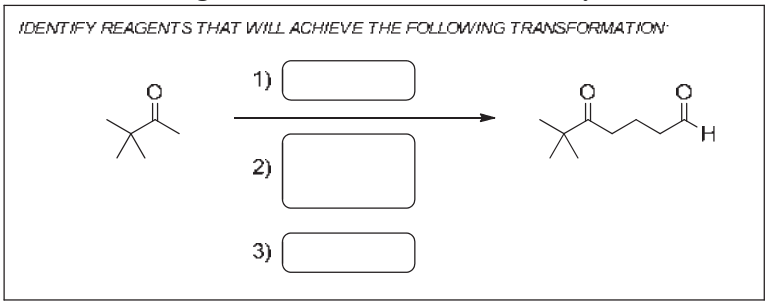
IDENTIFY REAGENTS THAT WILL ACHIEVE THE FOLLOWING TRANSFORMATION:



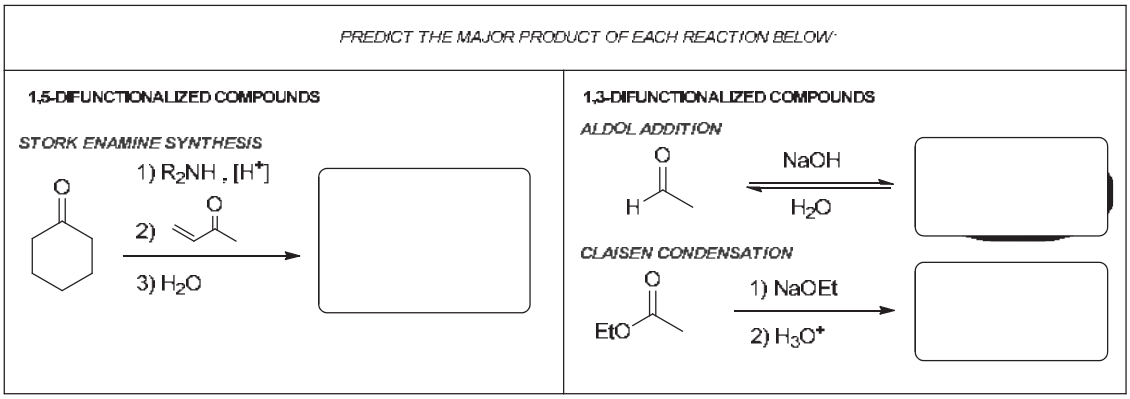
21.6 Using the Acetoacetic Ester Synthesis



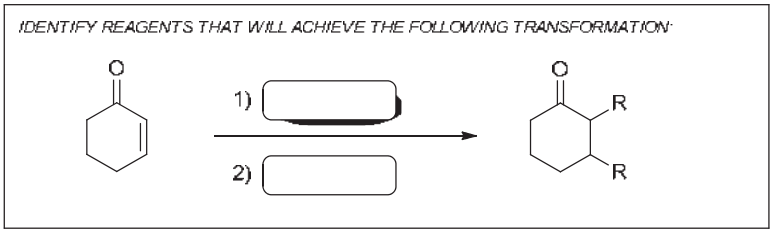
21.7 Determining When to Use a Stork Enamine Synthesis



21.8 Determining which Addition or Condensation Reaction to Use



21.9 Alkylating the α and β Positions

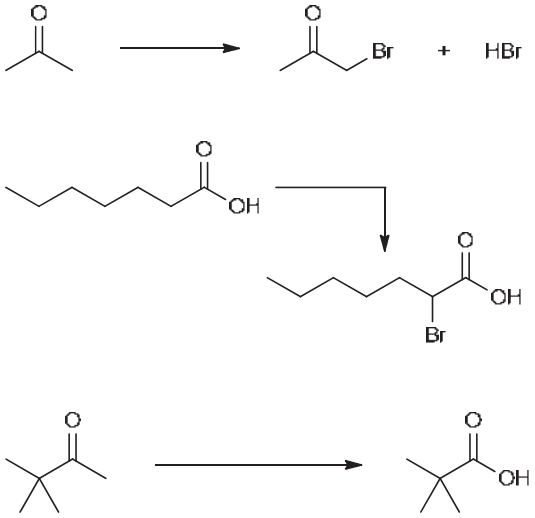


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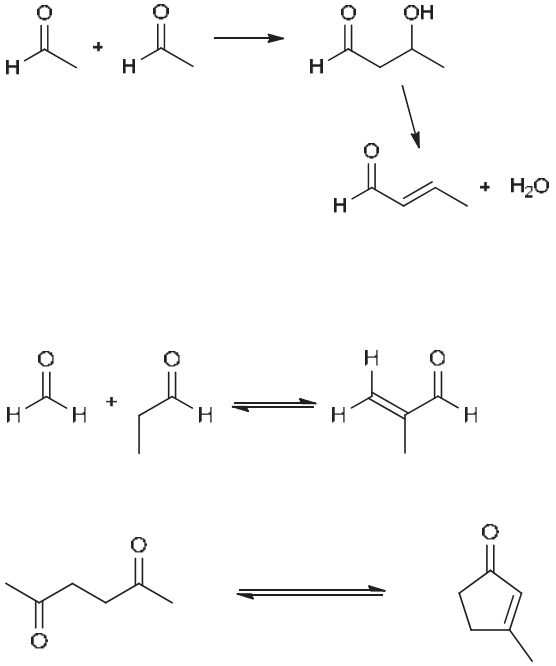
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 22. The answers appear in the section entitled *Review of Reactions*.

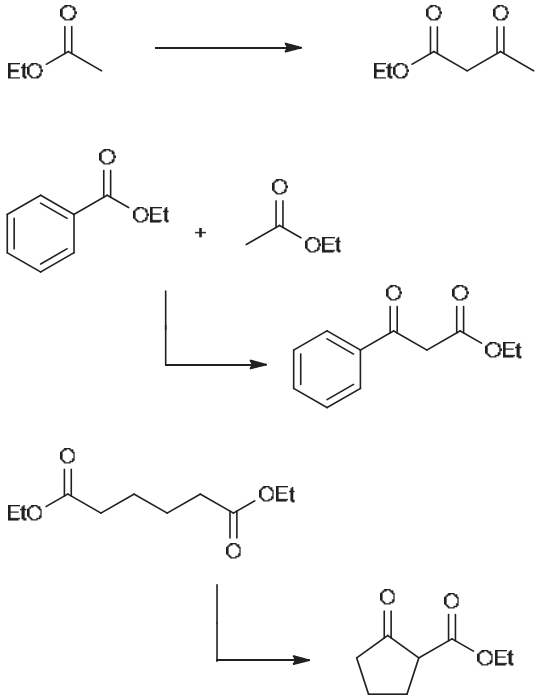
Alpha Halogenation



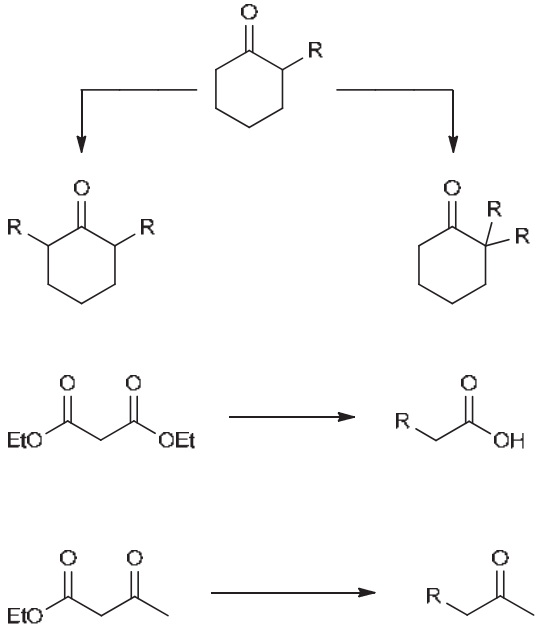
Aldol Reactions



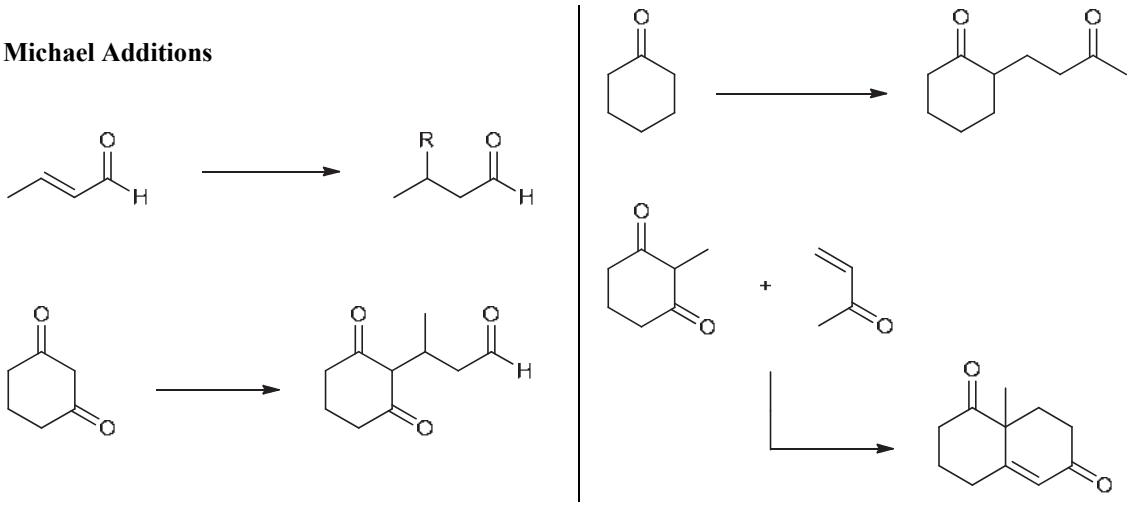
Claisen Condensation



Alkylation

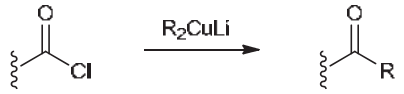


Michael Additions

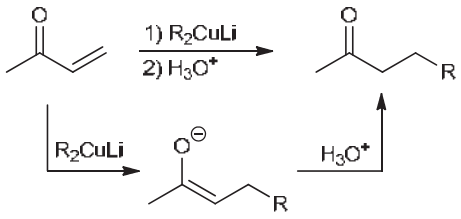


Common Mistake to Avoid

This chapter covers many reactions. Some of them require aqueous work-up, some require aqueous acidic work-up, while others require no work-up at all. Students often confuse the appropriate work-up conditions by associating the work-up conditions with the reagents, rather than the reaction occurring. For example, consider the following reaction:



This reaction (covered in Section 20.8) involves a lithium dialkyl cuprate being used as a nucleophile, giving a ketone as a product. In contrast, consider the following reaction (from Chapter 21), which also employs a lithium dialkyl cuprate as a nucleophile:

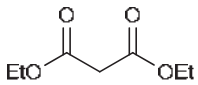
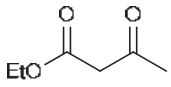


In this case, the initial product of the reaction is an enolate, which must be protonated, thereby requiring acidic work-up. This was not the case for the reaction between an acid chloride and a lithium dialkyl cuprate. It would therefore be a mistake to memorize that lithium dialkyl cuprates always require aqueous acidic work-up (or to memorize the opposite), because it depends on the situation. Rather than memorizing arbitrary rules that don't always apply, it would be wiser to focus on understanding *why* certain reactions require work-up while others do not. Your understanding will be facilitated by a strong focus on reaction mechanisms.

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Useful reagents

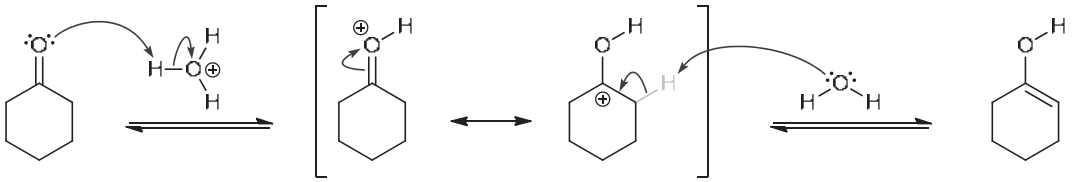
The following is a list of reagents encountered in this chapter:

Reagents	Type of Reaction	Description
$[H_3O^+]$, Br_2	α-Bromination	These reagents can be used to install a bromine atom at the α position of a ketone (or aldehyde). Subsequent treatment of the resulting α-bromoketone with pyridine gives an α,β-unsaturated ketone. This two-step process can be used to introduce α,β-unsaturation into a ketone or aldehyde.
1) Br_2, PBr_3 2) H_2O	Hell-Volhard-Zelinsky reaction	These reagents can be used to install a bromine atom at the α position of a carboxylic acid.
1) NaOH, Br_2 2) H_3O^+	Haloform reaction	These reagents can be used to convert a methyl ketone into a carboxylic acid. This process is most efficient when the other α position (of the starting ketone) bears no protons.
NaOH, H_2O	Aldol addition reaction	Aqueous sodium hydroxide will cause an aldol addition reaction between two equivalents of an aldehyde or ketone to give a β-hydroxyaldehyde (or a β-hydroxyketone).
NaOH, H_2O, heat	Aldol condensation	Aqueous sodium hydroxide and heat will cause an aldol condensation between two equivalents of an aldehyde or ketone to give an α,β-unsaturated aldehyde (or an α,β-unsaturated ketone).
1) NaOEt 2) H_3O^+	Claisen condensation	These reagents will cause two equivalents of an ester to undergo a condensation reaction, giving a β-ketoester.
1) LDA, -78ºC 2) RX	Alkylation	These conditions can be used to install an alkyl group at the less-substituted α position of an unsymmetrical ketone (via the kinetic enolate).
1) NaH, 25ºC 2) RX	Alkylation	These conditions can be used to install an alkyl group at the more-substituted α position of an unsymmetrical ketone (via the thermodynamic enolate).
	Malonic ester synthesis	Diethyl malonate can be converted into a substituted carboxylic acid upon treatment with ethoxide, followed by an alkyl halide, followed by aqueous acid.
	Acetoacetic ester synthesis	Ethyl acetoacetate can be converted into a derivative of acetone upon treatment with ethoxide, followed by an alkyl halide, followed by aqueous acid.
1) R_2CuLi 2) H_3O^+	Michael reaction	A lithium dialkyl cuprate is a weak nucleophile and can serve as a Michael donor. It will react with a suitable Michael acceptor (see Table 21.2).

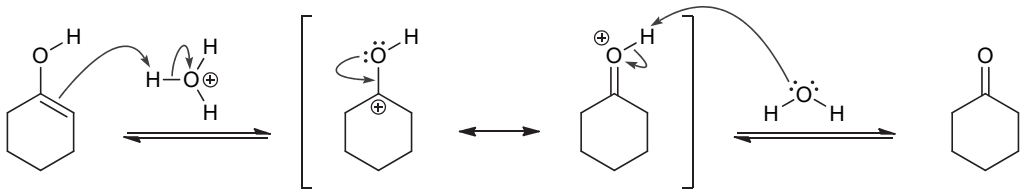
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Solutions

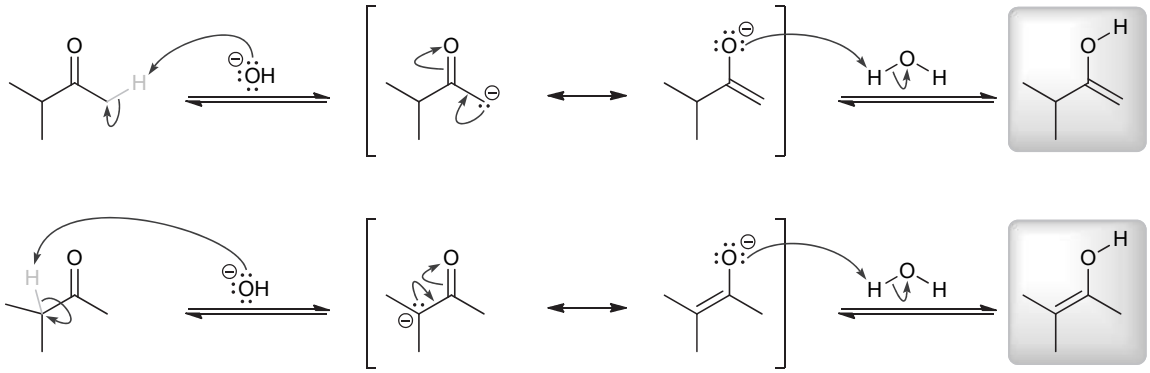
21.1. Under acid-catalyzed conditions, the carbonyl group is first protonated, generating a resonance-stabilized intermediate, which is then deprotonated at the α position to give an enol. Notice that the acid for the protonation step is a hydronium ion, and the base for the deprotonation step is water, consistent with acidic conditions.



21.2. If we carefully inspect the solution to the previous problem, we find that the final step of the mechanism is deprotonation of the α position, thereby converting the resonance-stabilized cationic intermediate into an enol. Therefore, the reverse of this process must begin with protonation of the α position, thereby converting the enol into a resonance-stabilized cationic intermediate. Subsequent deprotonation of this intermediate gives the ketone. Notice that the acid for the protonation step is a hydronium ion, and the base for the deprotonation step is water, consistent with acidic conditions.

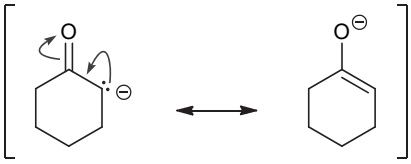


21.3. Under base-catalyzed conditions, the α position is first deprotonated, generating a resonance-stabilized anionic intermediate. The oxygen atom in this intermediate is then protonated to give an enol. Since the ketone is unsymmetrical, the two α positions are not equivalent. Therefore, the enol can be formed at either α position, as shown below. Notice that, in each case, the base for the deprotonation step is a hydroxide ion, and the acid for the protonation step is water, consistent with basic conditions.

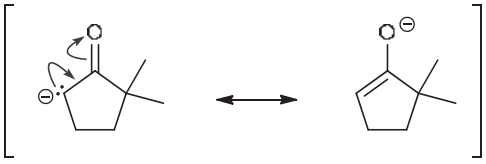


21.4.

(a) This compound has two α positions, although they are identical because the ketone is symmetrical. Deprotonation at either location will lead to the same enolate ion, which has the following resonance structures:

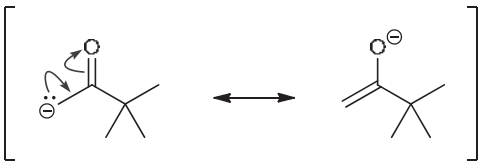


(b) This compound has two α positions, although only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion with the following resonance structures:

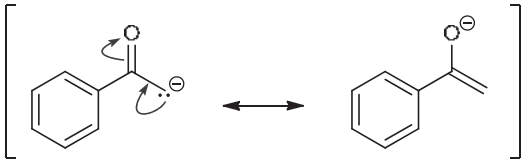


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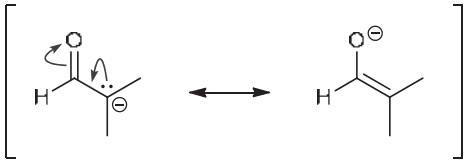
(c) This compound has two α positions, although only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion with the following resonance structures:



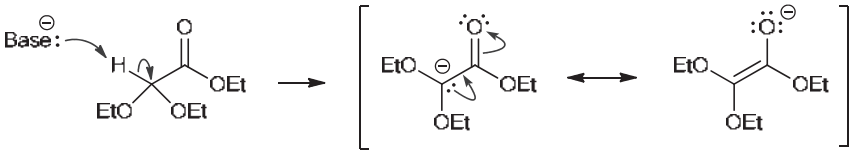
(d) This compound has two α positions, although only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion with the following resonance structures:



(e) This compound is an aldehyde and therefore has only one α position. Deprotonation at that location will lead to an enolate ion with the following resonance structures:

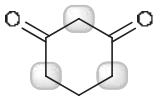


21.5. The ester has only one alpha carbon, and the proton at that position will be removed when treated with a strong base. Just as we would expect for the enolate of an aldehyde or a ketone, the resulting ester enolate has two resonance structures.

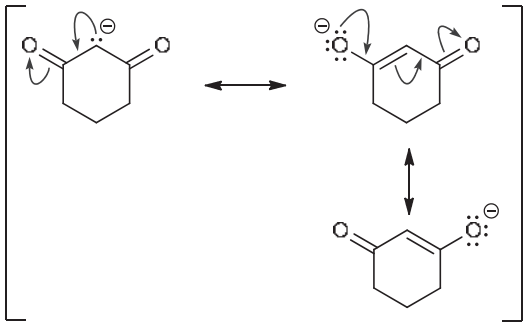


21.6.

(a) This compound has three α positions:

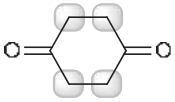


Among these positions, the central position is α to both carbonyl groups, and therefore, deprotonation occurs at this location. The resulting anion is a doubly stabilized enolate ion, which is particularly stable:

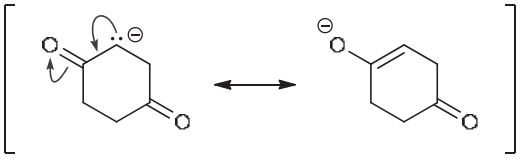


If ethoxide is used as the base to form the enolate, then enolate formation can be treated as nearly complete. That is, there will not be a substantial amount of diketone present after the equilibrium has been established.

(b) This compound has four α positions:



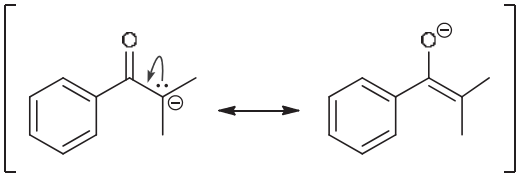
All four of these positions are identical because of symmetry (the structure has been rotated to make the symmetry more apparent). Therefore, deprotonation at any one of these positions results in the same enolate, which has the following two resonance structures:



Notice that the negative charge is delocalized over only one oxygen atom (not two). As such, deprotonation of the diketone with ethoxide will result in a mixture containing both the enolate and the starting diketone. That is, there will be a substantial amount of diketone present after the equilibrium has been established.

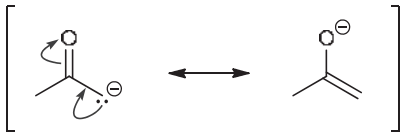
(c) This compound has two α positions, although only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion with the following resonance structures:

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Notice that the negative charge is delocalized over only one oxygen atom. As such, deprotonation of the ketone with ethoxide will result in a mixture containing both the enolate and the starting ketone. That is, there will be a substantial amount of ketone present after the equilibrium has been established.

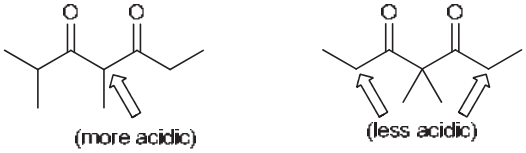
(d) This compound has two α positions, although they are identical because the ketone is symmetrical. Deprotonation at either location will lead to the same enolate ion, which has the following resonance structures:



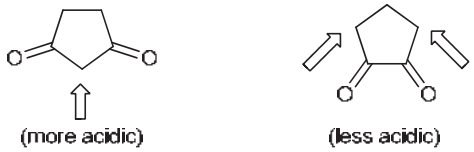
Notice that the negative charge is delocalized over only one oxygen atom. As such, deprotonation of the ketone with ethoxide will result in a mixture containing both the enolate and the starting ketone. That is, there will be a substantial amount of ketone present after the equilibrium has been established.

21.7.

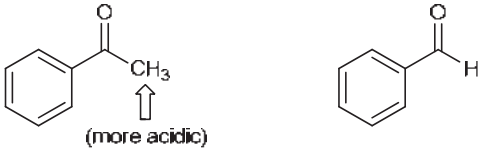
(a) 2,4-Dimethyl-3,5-heptanedione is more acidic because its conjugate base is a doubly stabilized enolate. The other compound (4,4-dimethyl-3,5-heptanedione) cannot form a doubly stabilized enolate because there are no protons connected to the carbon atom that is in between both carbonyl groups.



(b) 1,3-Cyclopentanedione is more acidic because its conjugate base is a doubly stabilized enolate. The other compound (1,2-cyclopentanedione) cannot form a doubly stabilized enolate because the carbonyl groups are adjacent to each other.

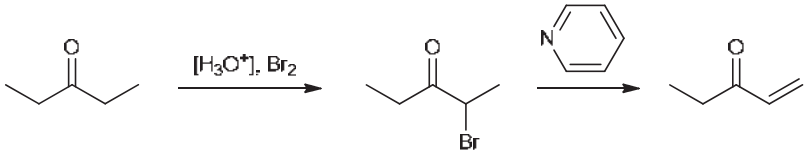


(c) Acetophenone is more acidic than benzaldehyde because the former has α protons and the latter does not.



21.8.

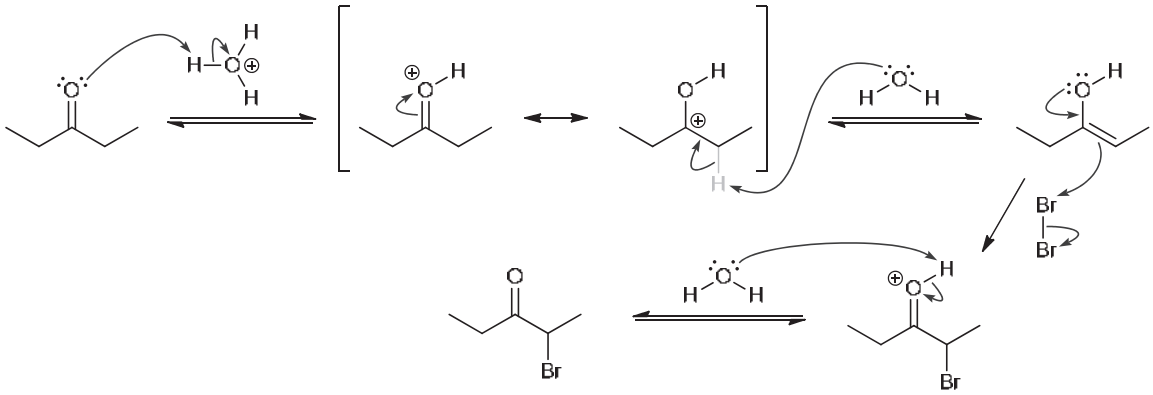
(a) These reagents indicate bromination at the α position, followed by elimination to give an α,β-unsaturated ketone:



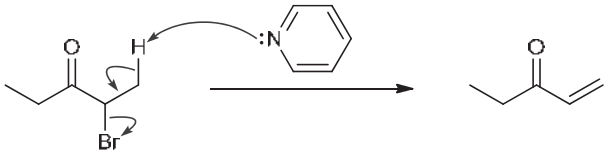
The following is a mechanism accounting for the entire transformation. Under acid-catalyzed conditions, the carbonyl group is protonated, giving a resonance-stabilized intermediate, which can then be deprotonated to give an enol. There

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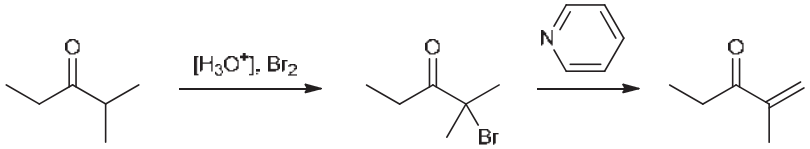
is only a small amount of enol present at equilibrium, but its steady presence is responsible for the bromination process (as the enol is consumed by reacting with Br_2, the equilibrium is adjusted to replenish the small concentration of enol). The enol is a nucleophile and can attack molecular bromine (Br_2) to give an intermediate which is then deprotonated by water to give the product of the first reaction.



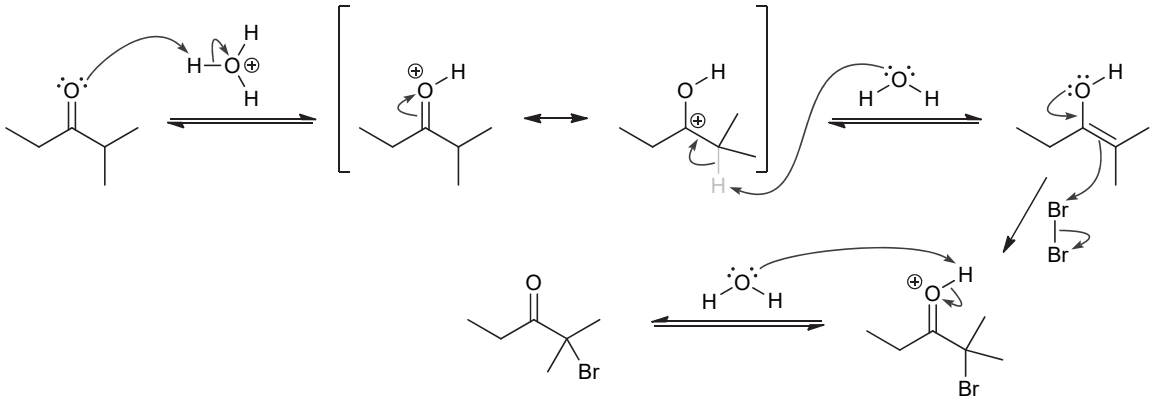
When this α-bromoketone is subsequently treated with pyridine, an E2 reaction gives the product:



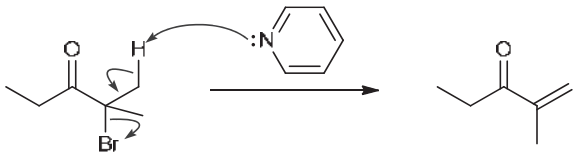
(b) These reagents indicate bromination at the more substituted α position, followed by elimination to give an α,β-unsaturated ketone:



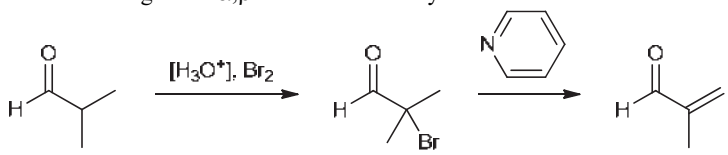
Below is a mechanism accounting for the entire transformation. Under acid-catalyzed conditions, the carbonyl group is protonated, giving a resonance-stabilized intermediate, which can then be deprotonated to give an enol (the more substituted enol is favored over the less substituted enol at equilibrium). There is only a small amount of enol present at equilibrium, but its steady presence is responsible for the bromination process (as the enol is consumed by reacting with Br_2, the equilibrium is adjusted to replenish the small concentration of enol). The enol is a nucleophile and can attack molecular bromine (Br_2) to give an intermediate which is then deprotonated by water to give the product of the first reaction.



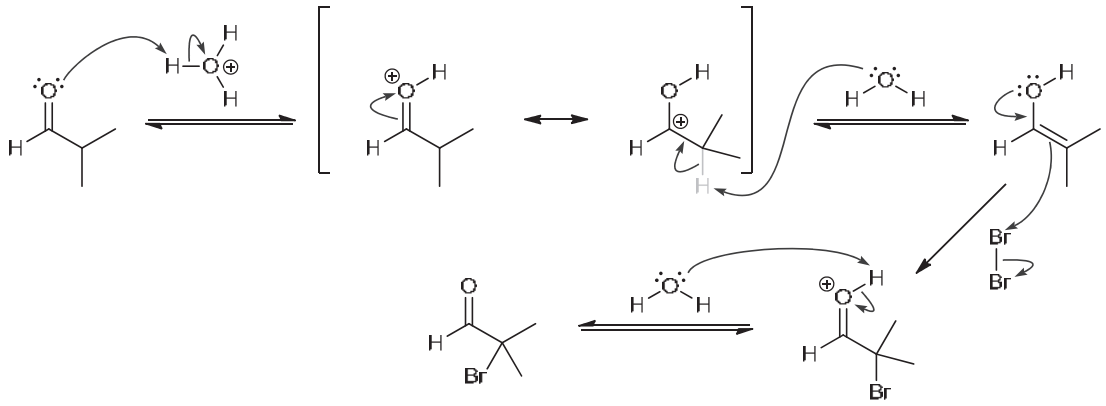
When this α-bromoketone is subsequently treated with pyridine, an E2 reaction gives the product:



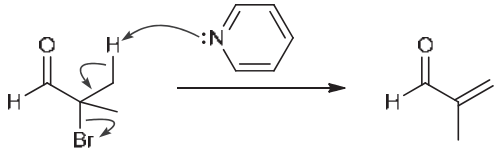
(c) The starting material is an aldehyde, which has only one α position. These reagents indicate bromination at the α position, followed by elimination to give an α,β-unsaturated aldehyde:



Below is a mechanism accounting for the entire transformation. Under acid-catalyzed conditions, the carbonyl group is protonated, giving a resonance-stabilized intermediate, which can then be deprotonated to give an enol. There is only a small amount of enol present at equilibrium, but its steady presence is responsible for the bromination process (as the enol is consumed by reacting with Br_2, the equilibrium is adjusted to replenish the small concentration of enol). The enol is a nucleophile and can attack molecular bromine (Br_2) to give an intermediate which is then deprotonated by water to give the product of the first reaction.

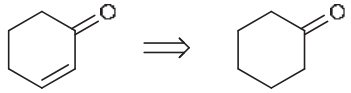


When this α-bromoaldehyde is subsequently treated with pyridine, an E2 reaction gives the product:



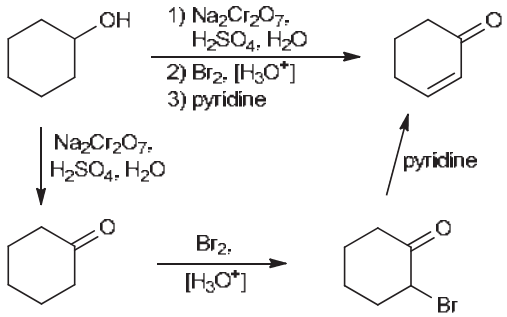
21.9.

(a) The product is an α,β-unsaturated ketone, which can be prepared from the corresponding saturated ketone (via acid-catalyzed halogenation followed by elimination),



and this saturated ketone can be prepared from the starting secondary alcohol via oxidation.

The complete synthesis is shown here. The first step employs chromic acid as the oxidizing agent. Alternatively, PCC can be used to affect the same transformation.

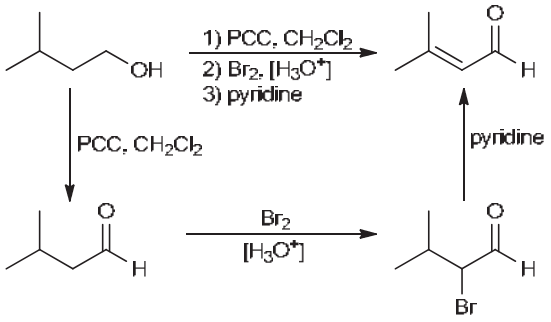


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(b) The product is an α,β-unsaturated aldehyde, which can be prepared from the corresponding saturated aldehyde (via acid-catalyzed halogenation followed by elimination):

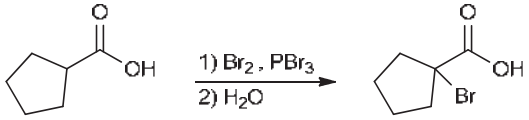


The saturated aldehyde can be prepared from the starting primary alcohol via oxidation with PCC (or with DMP or via a Swern oxidation).

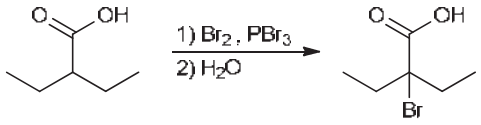


21.10.

(a) The starting material is a carboxylic acid, and the reagents indicate a Hell-Volhard-Zelinsky reaction. This process installs a bromine atom at the α position, as shown:

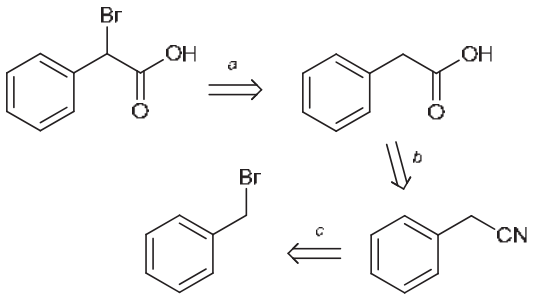


(b) The starting material is a carboxylic acid, and the reagents indicate a Hell-Volhard-Zelinsky reaction. This process installs a bromine atom at the α position, as shown:



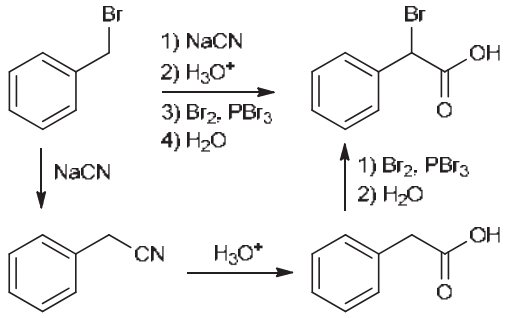
21.11.

(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

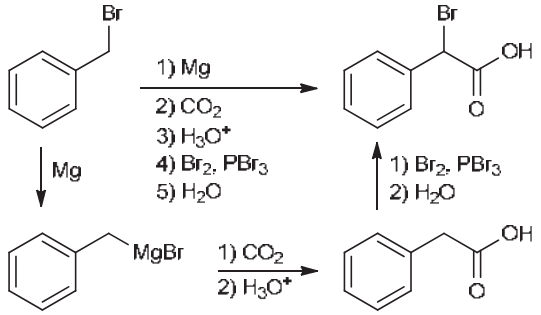


a. The product can be made from the corresponding carboxylic acid via bromination at the α position.
b. The carboxylic acid can be prepared via hydrolysis of the corresponding nitrile.
c. The nitrile can be made from the starting material (benzyl bromide) via an S_N2 process in which cyanide is used as a nucleophile.

Now let's draw the forward scheme. Benzyl bromide is treated with sodium cyanide, giving an S_N2 reaction that results in formation of a nitrile. Upon treatment with aqueous acid, the nitrile is hydrolyzed to give a carboxylic acid. Bromination at the α position then gives the product, as shown.

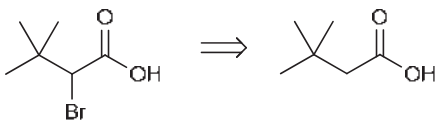


Alternatively, the carboxylic acid can be prepared via a Grignard reaction between benzyl magnesium bromide and carbon dioxide, followed by acid work-up, as shown:



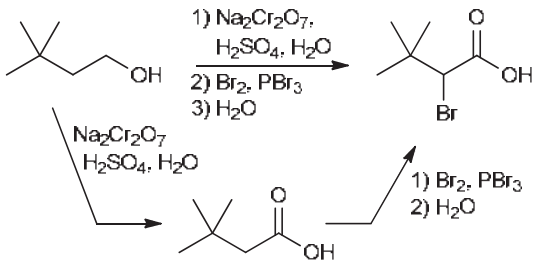
This alternate synthesis demonstrates an important point that has been stressed several times throughout this solutions manual. Specifically, synthesis problems will generally have multiple correct solutions. There is rarely only one correct solution to a synthesis problem.

(b) The product is an α-bromo carboxylic acid, which can be prepared from the corresponding carboxylic acid (via a Hell-Volhard-Zelinsky reaction):



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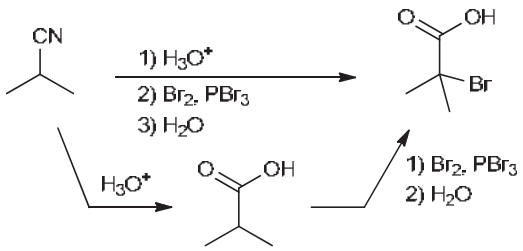
This carboxylic acid can be prepared from the starting primary alcohol via oxidation with chromic acid:



(c) The product is an α-bromo carboxylic acid, which can be prepared from the corresponding carboxylic acid (via a Hell-Volhard-Zelinsky reaction):

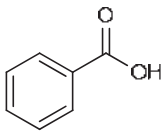


This carboxylic acid can be prepared from the starting nitrile via hydrolysis with aqueous acid, as shown:

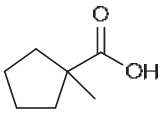


21.12.

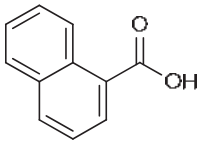
(a) The starting material is a methyl ketone, which is converted into the corresponding carboxylic acid (shown here) via the haloform reaction:



(b) The starting material is a methyl ketone, which is converted into the corresponding carboxylic acid (shown here) via the haloform reaction:

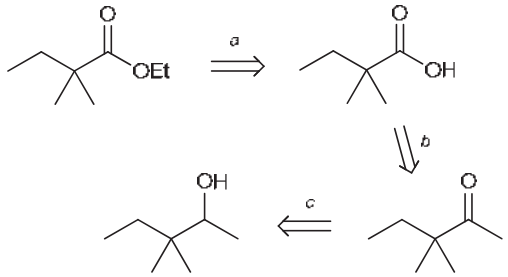


(c) The starting material is a methyl ketone, which is converted into the corresponding carboxylic acid (shown here) via the haloform reaction:



21.13.

(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

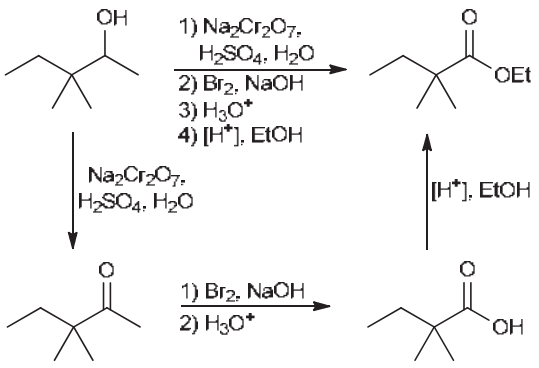


a. The product is an ester, so it can be made from the corresponding carboxylic acid via a Fischer esterification.

b. The carboxylic acid can be prepared from the corresponding methyl ketone via a haloform reaction.

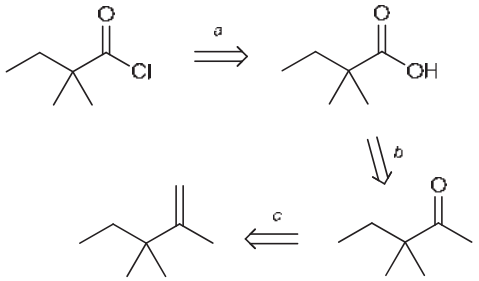
c. The ketone can be made via oxidation of the corresponding secondary alcohol.

Now let's draw the forward scheme. The starting alcohol is oxidized upon treatment with chromic acid (alternatively, PCC can be used for this step). The resulting ketone is then treated with molecular bromine (Br_2) and sodium hydroxide, followed by aqueous acid, to give a carboxylic acid (via a haloform reaction). Finally, the carboxylic acid is treated with ethanol in the presence of an acid catalyst, giving the desired ester (via a Fischer esterification).



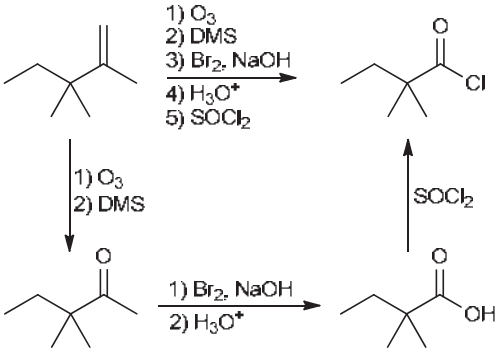
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(b) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

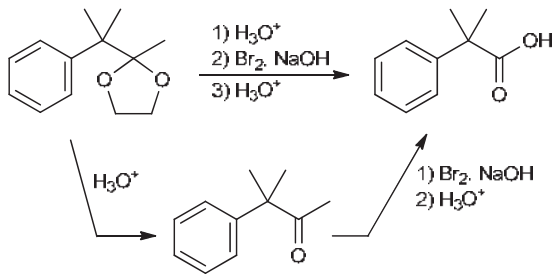


a. The product is an acid chloride which can be made from the corresponding carboxylic acid.
b. The carboxylic acid can be prepared from the corresponding methyl ketone via a haloform reaction.
c. The ketone can be made from the starting alkene via ozonolysis.

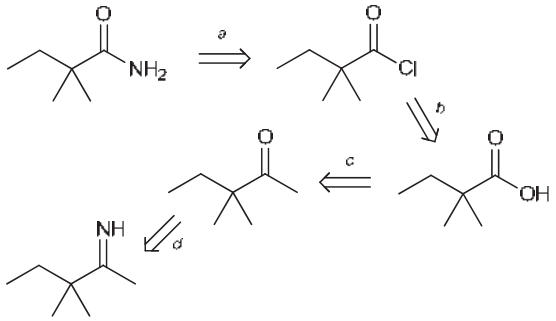
Now let's draw the forward scheme. Ozonolysis converts the starting alkene into a ketone (with loss of a carbon atom). The resulting ketone is then treated with molecular bromine (Br_2) and sodium hydroxide, followed by aqueous acid, to give a carboxylic acid (via a haloform reaction). Finally, the carboxylic acid is converted into an acid chloride upon treatment with thionyl chloride.



(c) The starting material is an acetal. Upon treatment with aqueous acid, the acetal is converted to a ketone, which can then be converted into the desired carboxylic acid via a haloform reaction.

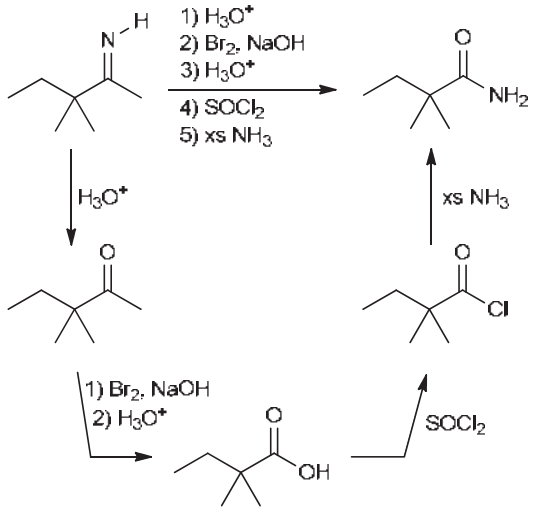


(d) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.



a. The product is an amide, which can be made from the corresponding acid chloride.
b. The acid chloride can be made from the corresponding carboxylic acid upon treatment with thionyl chloride.
c. The carboxylic acid can be prepared from the corresponding methyl ketone via a haloform reaction.
d. The ketone can be made via hydrolysis of the starting imine.

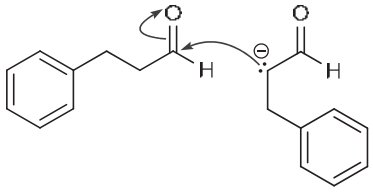
Now let's draw the forward scheme. The starting imine is hydrolyzed upon treatment with aqueous acid to give a ketone. The ketone is then treated with molecular bromine (Br_2) and sodium hydroxide, followed by aqueous acid, to give a carboxylic acid (via a haloform reaction). The carboxylic acid is then converted into an acid chloride upon treatment with thionyl chloride. Finally, the acid chloride is converted into the desired amide upon treatment with excess ammonia (via a nucleophilic acyl substitution reaction).



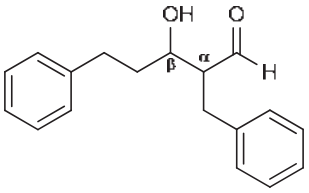
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21.14.

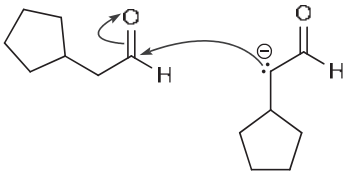
(a) The α position of one molecule of the aldehyde is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the aldehyde:



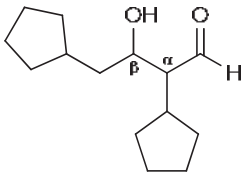
As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give the following β-hydroxy aldehyde:



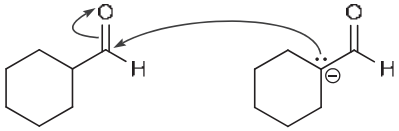
(b) The α position of one molecule of the aldehyde is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the aldehyde:



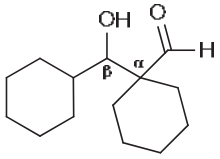
As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give the following β-hydroxy aldehyde:



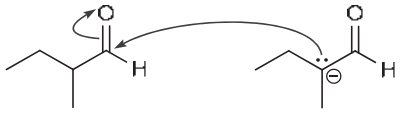
(c) The α position of one molecule of the aldehyde is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the aldehyde:



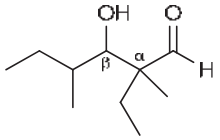
As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give the following β-hydroxy aldehyde:



(d) The α position of one molecule of the aldehyde is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the aldehyde:

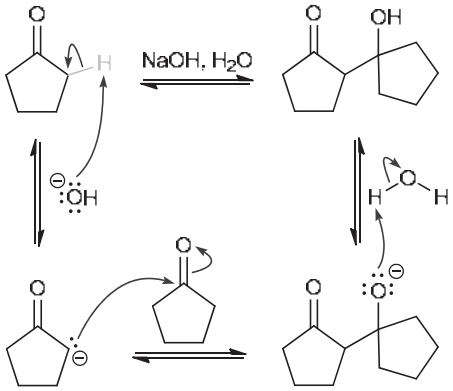


As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give the following β-hydroxy aldehyde:

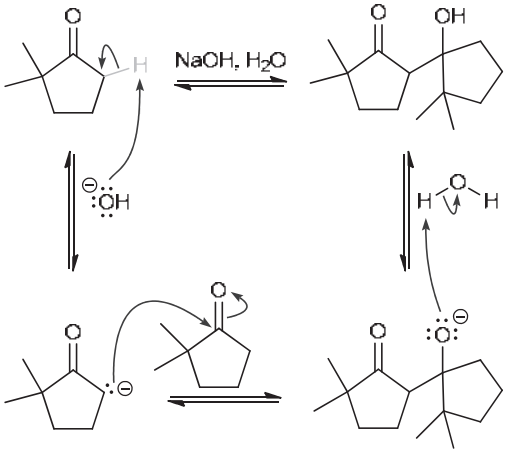


21.15.

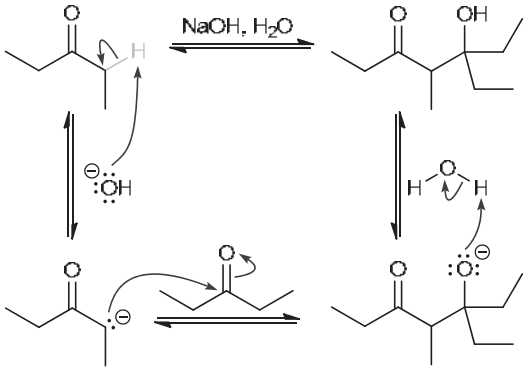
(a) This compound has two α positions, although they are identical because the ketone is symmetrical. That is, deprotonation at either location will lead to the same enolate. This enolate can then function as a nucleophile and attack the carbonyl group of another molecule of the ketone. As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give a β-hydroxy ketone, as shown:



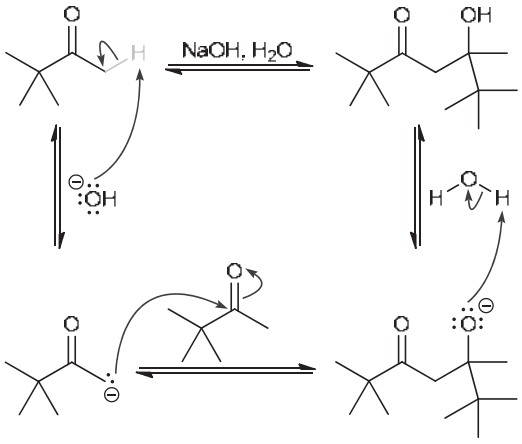
(b) This compound has two α positions, although only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion that can function as a nucleophile and attack the carbonyl group of another molecule of the ketone. As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give a β-hydroxy ketone, as shown:



(c) This compound has two α positions, although they are identical because the ketone is symmetrical. That is, deprotonation at either location will lead to the same enolate. This enolate can then function as a nucleophile and attack the carbonyl group of another molecule of the ketone. As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give a β-hydroxy ketone, as shown:

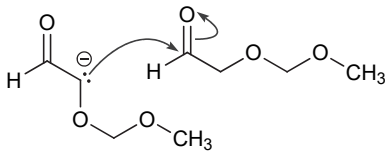


(d) This compound has two α positions, although only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion that can function as a nucleophile and attack the carbonyl group of another molecule of the ketone. As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give a β-hydroxy ketone, as shown:

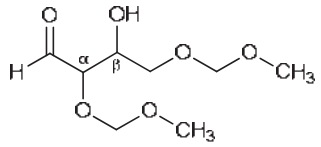


21.16.

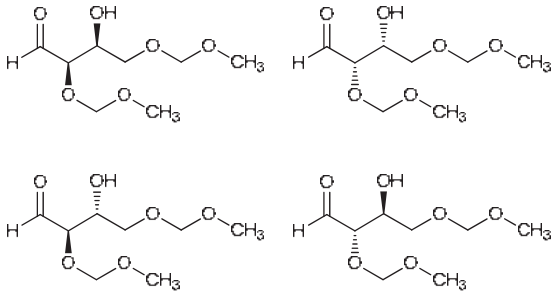
(a) The α position of one molecule of the aldehyde is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the aldehyde:



As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give the following β-hydroxy aldehyde:



(b) The α and β positions are both chiral centers, so we expect $2^2 = 4$ stereoisomers, shown below:

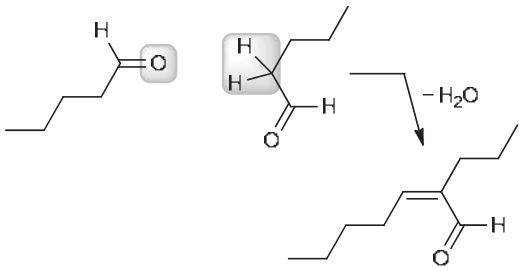


21.17.

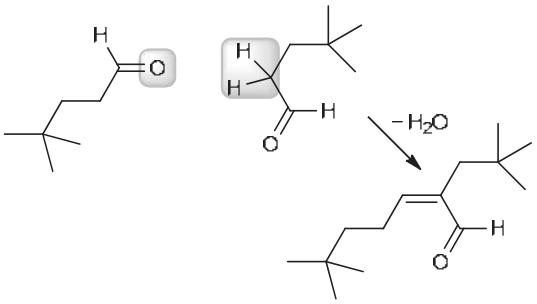
(a) Two molecules of the aldehyde are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). When drawn in this way, it is easier to predict the product without having to draw the entire mechanism.

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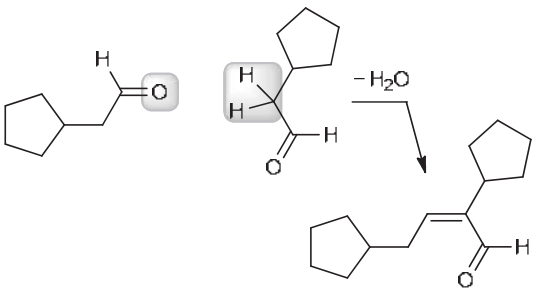
We simply remove the two α protons and the oxygen atom, and we replace them with a double bond. In this case, two stereoisomers are possible, so we draw the product that is likely to have fewer steric interactions:



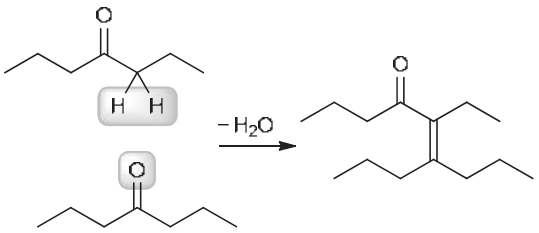
(b) Two molecules of the aldehyde are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond. In this case, two stereoisomers are possible, so we draw the product that is likely to have fewer steric interactions:



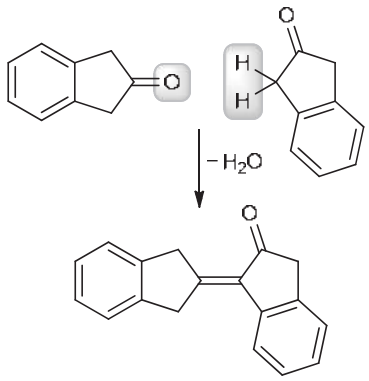
(c) Two molecules of the aldehyde are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond. In this case, two stereoisomers are possible, so we draw the product that is likely to have fewer steric interactions:



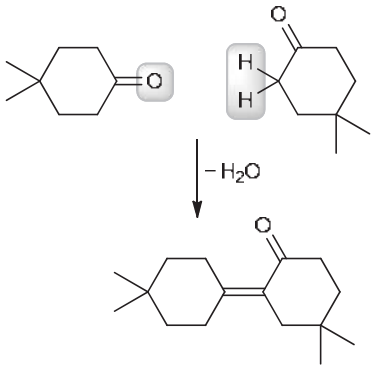
(d) This compound has two α positions, although they are identical because the ketone is symmetrical, so we only need to consider the reaction occurring at one of these locations.
Two molecules of the ketone are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond:



(e) This compound has two α positions, although they are identical because the ketone is symmetrical, so we only need to consider the reaction occurring at one of these locations.
Two molecules of the ketone are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond:

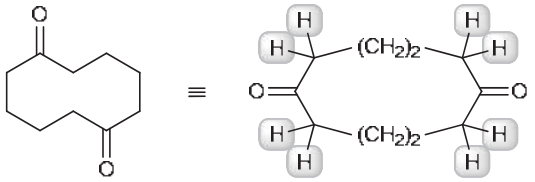


(f) This compound has two α positions, although they are identical because the ketone is symmetrical, so we only need to consider the reaction occurring at one of these locations.
Two molecules of the ketone are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond:

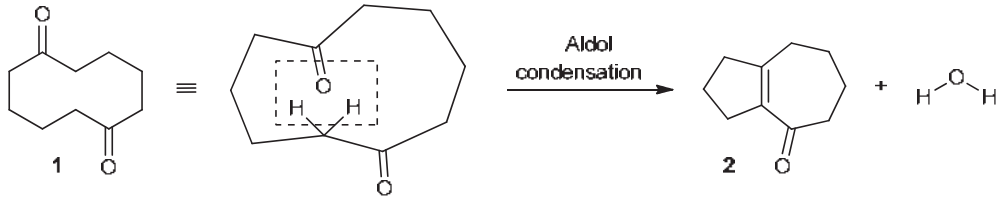


21.18. Compound **1** has 8 equivalent alpha protons, highlighted below:

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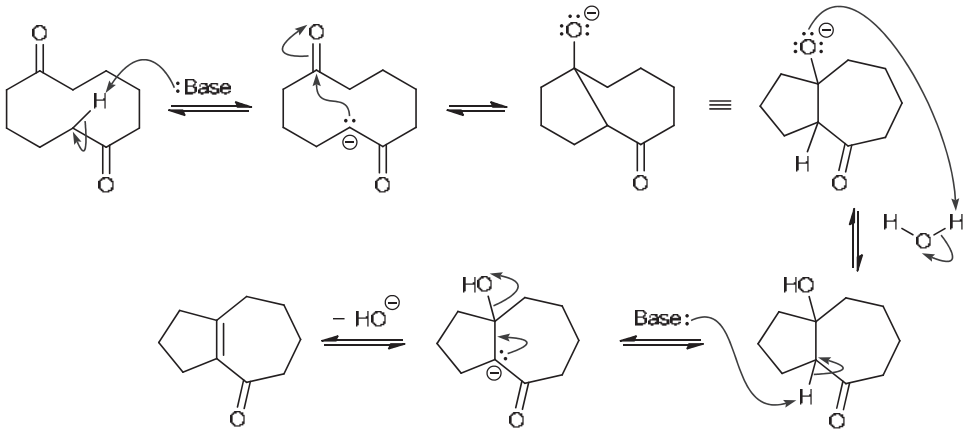


Removal of any one of these protons with a base will yield the same enolate and ultimately lead to the same final aldol condensation product. To draw the aldol condensation product, we redraw compound **1** to show one set of alpha protons directly facing the other carbonyl group. Removing the carbonyl group and the two alpha protons (in the box below) gives the structure of the final product, compound **2**, which has the molecular formula $C_{10}H_{14}O$.



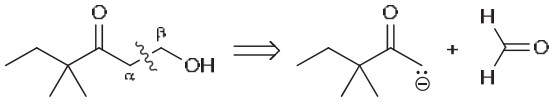
Note that in this case the bicyclic structure limits the product to only one possible stereoisomer around the newly-formed C=C unit.

The above is only a bookkeeping trick for predicting the product. It is beneficial to think about the mechanism as shown below. After deprotonation, the resulting enolate ion attacks the carbonyl group, giving an alkoxide ion. After protonation of the alkoxide, a base-catalyzed elimination process gives an α,β−unsaturated ketone:

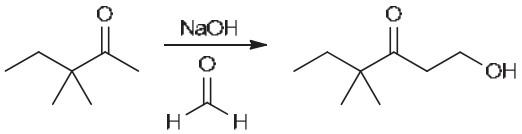


21.19.

(a) We first identify the α and β positions, and then apply a retrosynthetic analysis:

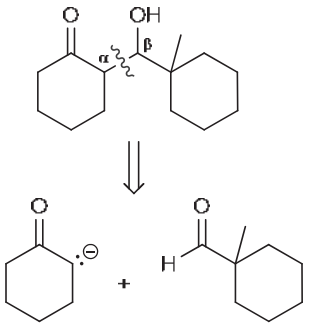


This transformation can be achieved with an aldol reaction between two different partners. One of the partners (the ketone) only has one α position that can be deprotonated (giving only one possible enolate), and the other partner (formaldehyde) lacks α protons and is more electrophilic than the ketone. As such, LDA is not required as a base for this directed aldol addition. Sodium hydroxide can be used, as shown:

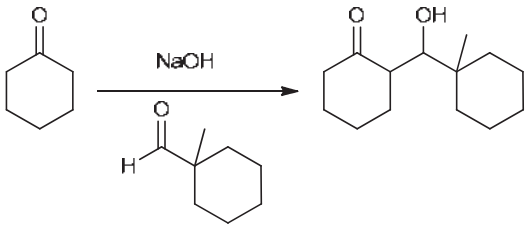


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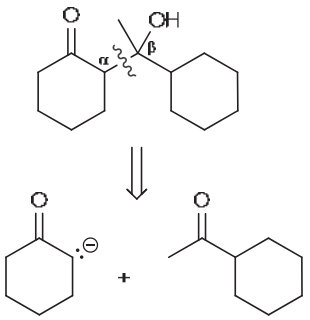
(b) We first identify the α and β positions, and then apply a retrosynthetic analysis:



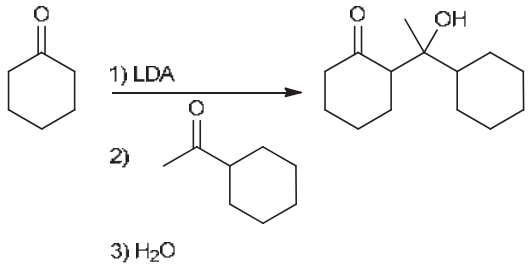
This transformation can be achieved with an aldol reaction between two different partners. One of the partners (the ketone) only has one α position that can be deprotonated (giving only one possible enolate), and the other partner (the aldehyde) lacks α protons and is more electrophilic than the ketone. As such, LDA is not required as a base for this directed aldol addition. Sodium hydroxide can be used, as shown:



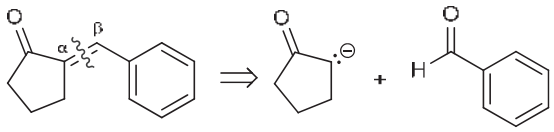
(c) We first identify the α and β positions, and then apply a retrosynthetic analysis:



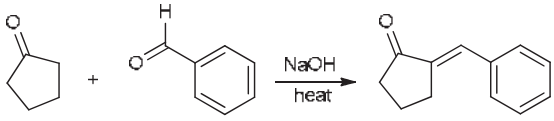
Two different partners are required, each of which can be deprotonated to give an enolate. Therefore, this transformation must be achieved with a directed aldol reaction, using LDA as the base, followed by water work-up, as shown:



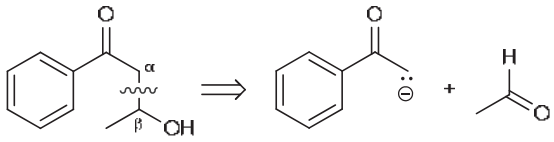
(d) We first identify the α and β positions, and then apply a retrosynthetic analysis to identify the starting materials:



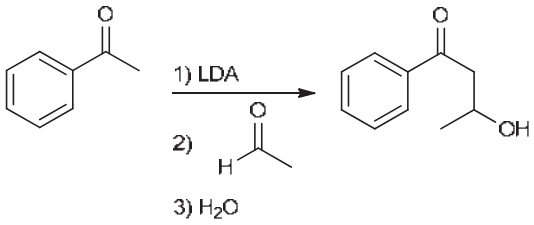
This transformation can be achieved with an aldol reaction between two different partners. One of the partners (the ketone) only has one α position that can be deprotonated (giving only one possible enolate), and the other partner (the aldehyde) lacks α protons and is more electrophilic than the ketone. As such, LDA is not required as a base for this directed aldol addition. Sodium hydroxide can be used, as shown:



(e) We first identify the α and β positions, and then apply a retrosynthetic analysis:

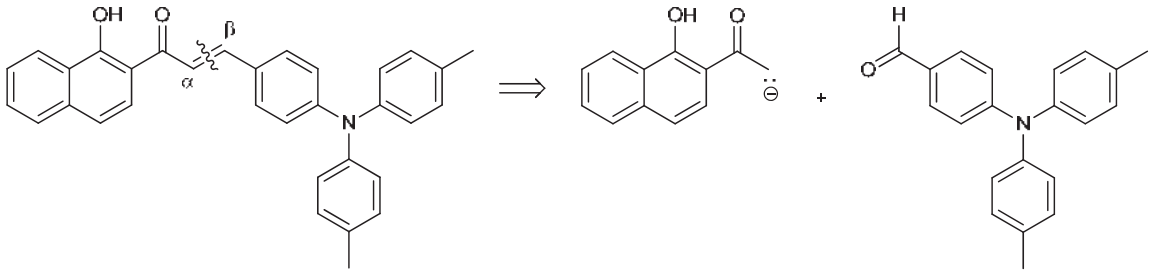


Two different partners are required, each of which can be deprotonated to give an enolate. Therefore, this transformation must be achieved with a directed aldol reaction, using LDA as the base, followed by water work-up, as shown:

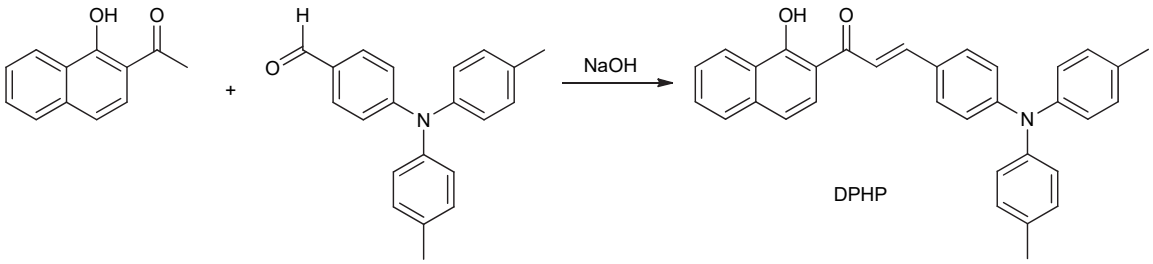


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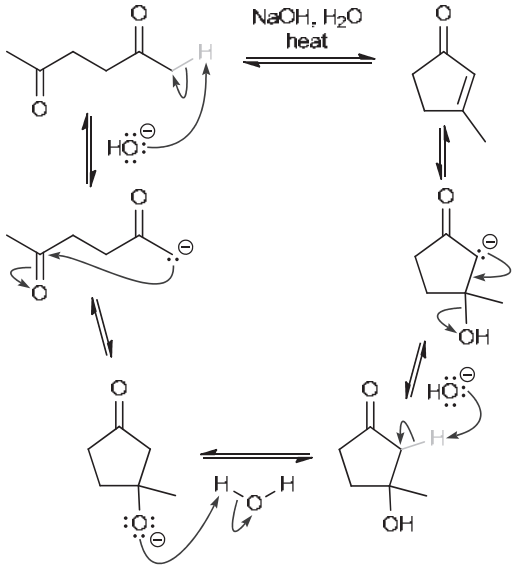
21.20. We first identify the part of the structure of DPHP that is produced by an aldol reaction, and look for either a β–hydroxy carbonyl or an α,β-unsaturated carbonyl. We do see in DPHP an α,β-unsaturated carbonyl. After identifying the α and β positions, we then apply a retrosynthetic analysis to identify the starting materials:



A strong base, such as LDA, is not needed for this crossed aldol reaction since only one of the compounds (the ketone) has an α position that can be deprotonated (giving only one possible enolate) and the other partner (the aldehyde) lacks α protons and is more electrophilic that the ketone. Sodium hydroxide can be used, as shown:

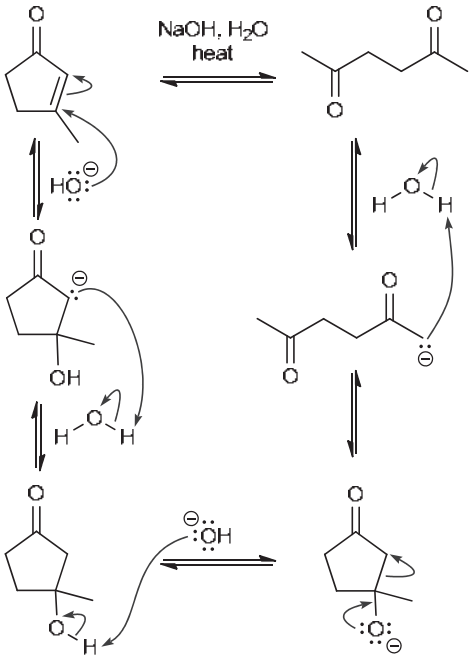


21.21. This process is an intramolecular aldol condensation reaction. As such, we draw a mechanism with the same mechanistic steps found in Mechanism 21.6. First, hydroxide functions as a base and deprotonates the starting dione to give an enolate. This enolate ion is a nucleophilic center, and it will attack the carbonyl group present in the same structure (an intramolecular process), thereby closing a five-membered ring. The resulting alkoxide ion is then protonated to give a β-hydroxy ketone. Hydroxide then functions as a base again, deprotonating the α position. The resulting enolate then ejects a hydroxide ion, giving the condensation product, as shown:



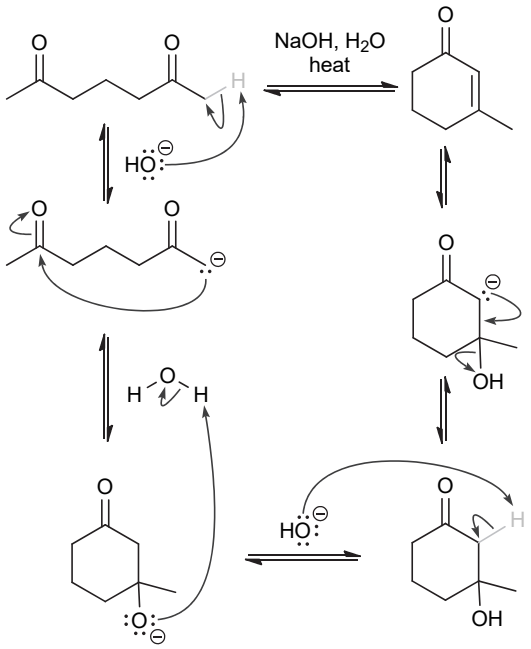
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21.22. The following process is the reverse of the mechanism shown in the previous problem. As such, all of the intermediates are identical to the intermediates in the previous problem, but they appear in reverse order. First, hydroxide attacks the β position of the α,β-unsaturated ketone, giving an enolate. The enolate is then protonated to give a β-hydroxyketone, which is subsequently deprotonated to give an alkoxide ion. The carbonyl group is then reformed, with loss of an enolate as a leaving group (this is a retro-aldol process). The resulting enolate is then protonated to give the dione. Notice that each of the protonation steps employs water as an acid, consistent with basic conditions (strong acids are not measurably present under these conditions).



21.23. This process is an intramolecular aldol condensation reaction, and is similar to Problem **21.21**, with one additional methylene (CH_2) group in between the two carbonyl groups. As such, a six-membered ring is formed, rather than a five-membered ring. Other than this small difference, this mechanism is identical to the mechanism shown in the solution to Problem **21.21**.

First, hydroxide functions as a base and deprotonates the starting dione to give an enolate. This enolate ion is a nucleophilic center, and it will attack the carbonyl group present in the same structure (an intramolecular process), thereby closing a six-membered ring. The resulting alkoxide ion is then protonated to give a β-hydroxy ketone. Hydroxide then functions as a base again, deprotonating the α position. The resulting enolate then ejects a hydroxide ion, giving the condensation product, as shown:



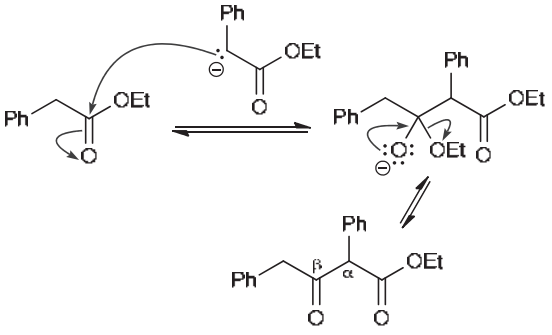
21.24.

(a) The starting material is an ester, and the product is a β-ketoester. Therefore, this process is a Claisen condensation. In this case, two identical partners will react with each other (this is not a crossed Claisen condensation). Since the alkoxy group of the ester is an ethoxy group, we must use sodium ethoxide as the base, in order to avoid transesterification.

(b) The starting material is an ester, and the product is a β-ketoester. Therefore, this process is a Claisen condensation. In this case, two identical partners will react with each other (this is not a crossed Claisen condensation). Since the alkoxy group of the ester is a *tert*-butoxy group, we must use potassium *tert*-butoxide as the base, in order to avoid transesterification.

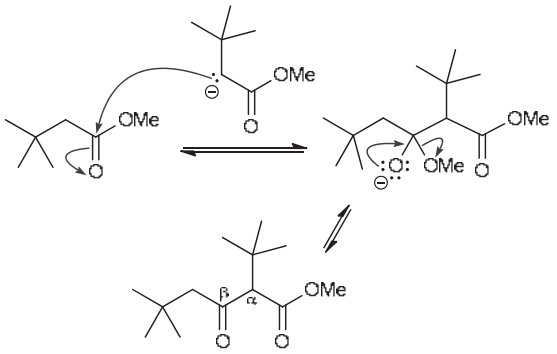
21.25.

(a) The α position of one molecule of the ester is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the ester. As a result, a carbon-carbon bond is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, affording a β-ketoester, as shown:



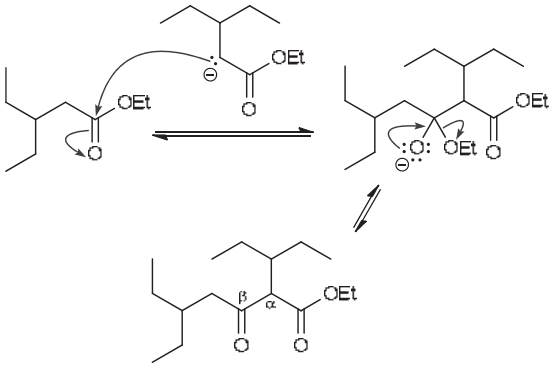
This product is deprotonated under the conditions of its formation, which is the reason for acid work-up (H_3O^+) after the reaction is complete (to return the proton).

(b) The α position of one molecule of the ester is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the ester. As a result, a carbon-carbon bond is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of a methoxide ion, affording a β-ketoester, as shown:



This product is deprotonated under the conditions of its formation, which is the reason for acid work-up (H_3O^+) after the reaction is complete (to return the proton).

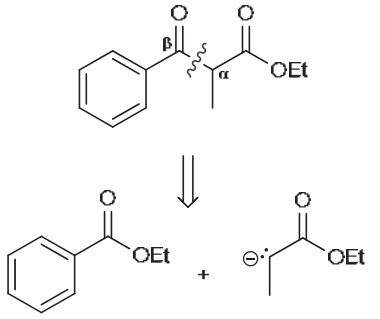
(c) The α position of one molecule of the ester is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the ester. As a result, a carbon-carbon bond is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, affording a β-ketoester, as shown:



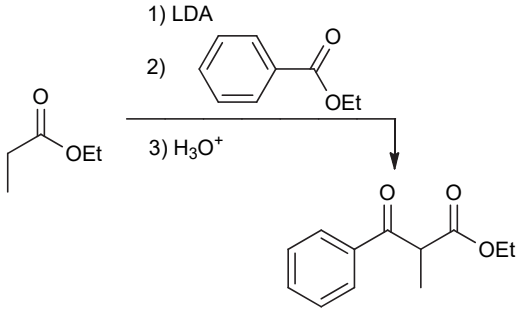
This product is deprotonated under the conditions of its formation, which is the reason for acid work-up (H_3O^+) after the reaction is complete (to return the proton).

21.26.

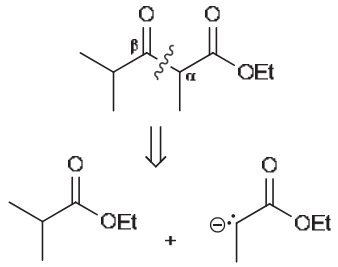
(a) We first identify the α and β positions, and then apply a retrosynthetic analysis. The α position is the location between the two carbonyl groups, and the β position bears the keto group:



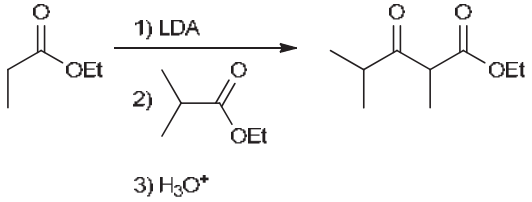
Since the two partners are different, we use a crossed Claisen condensation. LDA is used as the base in the first step, and the final step of the process is aqueous acidic work-up, as shown:



(b) We first identify the α and β positions, and then apply a retrosynthetic analysis. The α position is the location between the two carbonyl groups, and the β position bears the keto group:

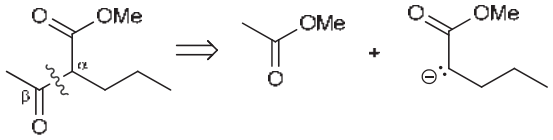


Since the two partners are different, we use a crossed Claisen condensation. LDA is used as the base in the first step, and the final step of the process is aqueous acidic work-up, as shown:

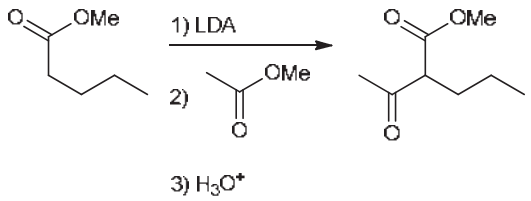


(c) We first identify the α and β positions, and then apply a retrosynthetic analysis. The α position is the

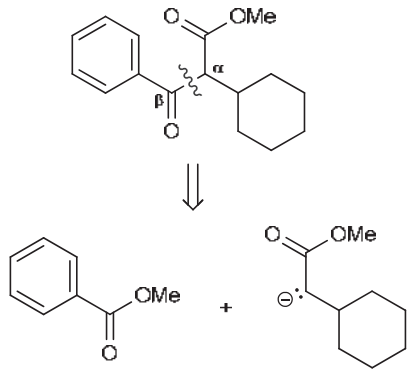
location between the two carbonyl groups, and the β position bears the keto group:



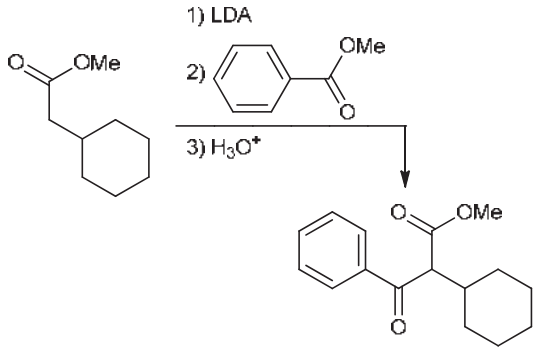
Since the two partners are different, we use a crossed Claisen condensation. LDA is used as the base in the first step, and the final step of the process is aqueous acidic work-up, as shown:



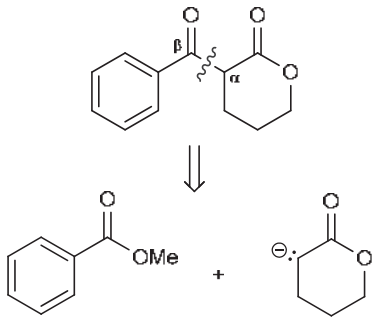
(d) We first identify the α and β positions, and then apply a retrosynthetic analysis. The α position is the location between the two carbonyl groups, and the β position bears the keto group:



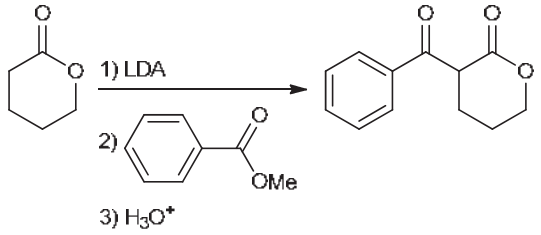
Since the two partners are different, we use a crossed Claisen condensation. LDA is used as the base in the first step, and the final step of the process is aqueous acidic work-up, as shown:



(e) We first identify the α and β positions, and then apply a retrosynthetic analysis. The α position is the location between the two carbonyl groups, and the β position bears the keto group:

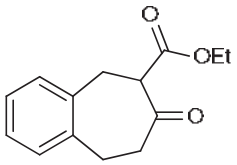


Since the two partners are different, we use a crossed Claisen condensation. LDA is used as the base in the first step, and the final step of the process is aqueous acidic work-up, as shown:



21.27.

(a) This is an example of an intramolecular Claisen condensation (called a Dieckmann cyclization). The α position of one ester group is deprotonated, and the resulting enolate functions as a nucleophile and attacks the other carbonyl group within the same structure. As a result, a ring is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, giving a β-ketoester:

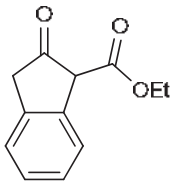


Under these basic conditions, the β-ketoester is deprotonated to give a doubly-stabilized enolate, requiring acidic work-up in order to regenerate the β-ketoester above.

(b) This is an example of an intramolecular Claisen condensation (called a Dieckmann cyclization). The α position of one ester group is deprotonated, and the resulting enolate functions as a nucleophile and attacks the other carbonyl group within the same structure. As a

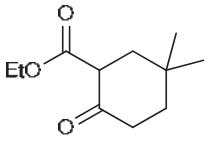
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result, a ring is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, giving a β-ketoester:



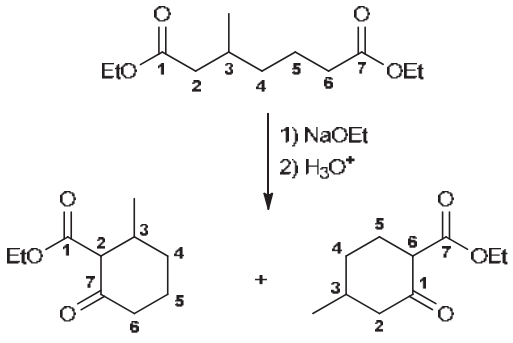
Under these basic conditions, the β-ketoester is deprotonated to give a doubly-stabilized enolate, requiring acidic work-up in order to regenerate the β-ketoester above.

(c) This is an example of an intramolecular Claisen condensation (called a Dieckmann cyclization). The α position of one ester group is deprotonated, and the resulting enolate functions as a nucleophile and attacks the other carbonyl group within the same structure. As a result, a ring is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, giving a β-ketoester:



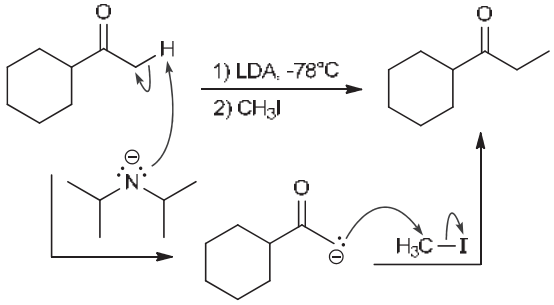
Under these basic conditions, the β-ketoester is deprotonated to give a doubly-stabilized enolate, requiring acidic work-up in order to regenerate the β-ketoester above.

21.28. There are two α positions which are not identical (because of the presence of the methyl group at C3). Therefore, either α position (C2 or C6) can be deprotonated, followed by an intramolecular attack, leading to the following two possible condensation products. That is, the cyclization process can either result in a bond between C2 and C7 or between C6 and C1:

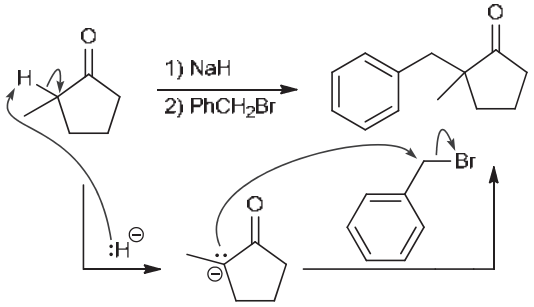


21.29.

(a) The starting material is a ketone, which has two α positions. With LDA as the base (at low temperature), we expect deprotonation to occur at the less substituted site, giving the kinetic enolate. This enolate is then treated with methyl iodide to give an S_N2 reaction, thereby installing the methyl group at the less substituted α position, as shown.

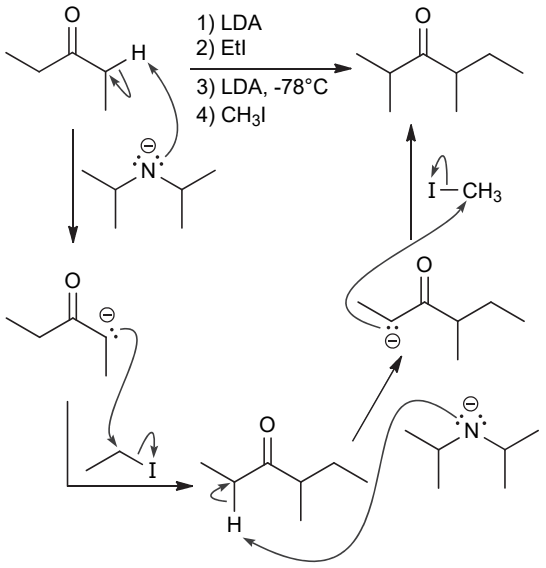


(b) The starting material is a ketone, which has two α positions. With NaH as the base, we expect deprotonation to occur at the more substituted site, giving the thermodynamic enolate. This enolate is then treated with benzyl bromide to give an S_N2 reaction, thereby installing the benzyl group at the more substituted α position, as shown.

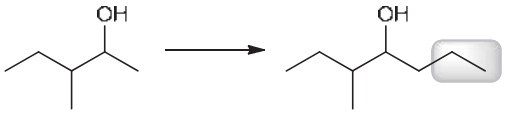


(c) The starting material is a ketone, which has two α positions, although they are identical because the ketone is symmetrical. Deprotonation at either location will lead to the same enolate ion. In the first step, LDA functions as a base and deprotonates the ketone to give an enolate. This enolate is then treated with ethyl iodide to give an S_N2 reaction, thereby installing an ethyl group. Subsequent treatment with LDA (at low tempereature), followed by methyl iodide, installs a methyl group at the other (less substituted) α position via the kinetic enolate. The net result is the installation of an ethyl group at one α position and the installation of a methyl group at the other α position:

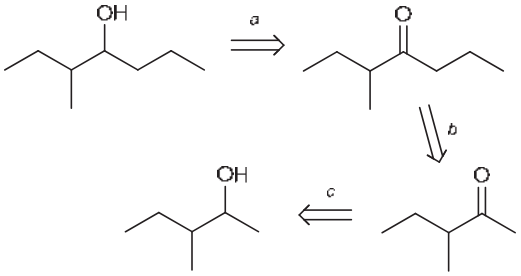
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21.30. This transformation does not involve a change in the identity or location of the functional group (a hydroxyl group), but it does involve a change in the carbon skeleton:

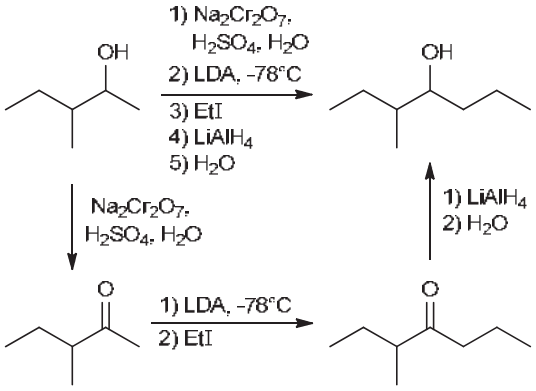


An ethyl group must be installed, although we have not learned a way to do this in one step. A multi-step strategy is necessary. One strategy for achieving this transformation derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

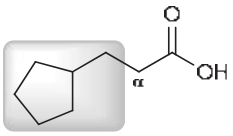


a. The alcohol can be made via reduction of the corresponding ketone.
b. The ethyl group can be installed through alkylation of 3-methyl-2-pentanone (via the kinetic enolate).
c. 3-Methyl-2-pentanone can be made from the starting alcohol via oxidation.

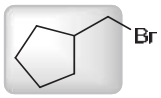
Now let's draw the forward scheme. The starting alcohol is oxidized with chromic acid to give 3-methyl-2-pentanone. Alternatively, PCC can be used to affect the same transformation. The ketone is then treated with LDA at low temperature to deprotonate the less substituted α position, giving the kinetic enolate. Upon treatment with ethyl iodide, an ethyl group is installed in the desired location. The resulting ketone is then reduced with $LiAlH_4$, followed by water work-up, to give the product.



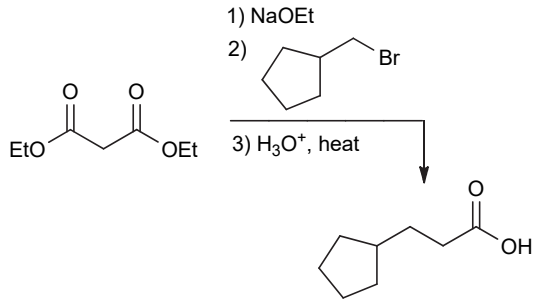
21.31.
(a) The product is a carboxylic acid that has the following (highlighted) group connected to the α position:



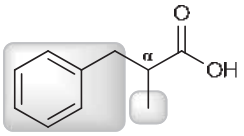
This group can be installed via a malonic ester synthesis, using the following alkyl halide:



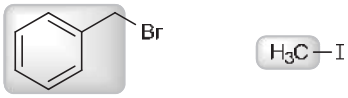
A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with the alkyl halide above, thereby installing the alkyl group. Subsequent hydrolysis and decarboxylation give the product, as shown:



(b) The product is a carboxylic acid that has the following two (highlighted) groups connected to the α position:

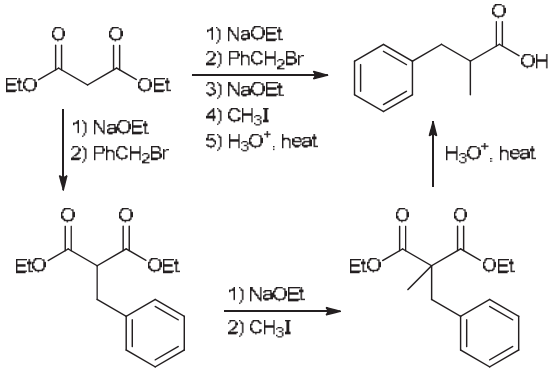


Both of these groups can be installed via a malonic ester synthesis, using the following halides:

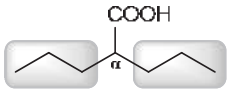


You might notice that methyl iodide has been chosen, rather than methyl bromide. There is a practical reason for this choice (methyl iodide is a liquid at room temperature, while methyl bromide is a gas, rendering the latter more difficult to work with).

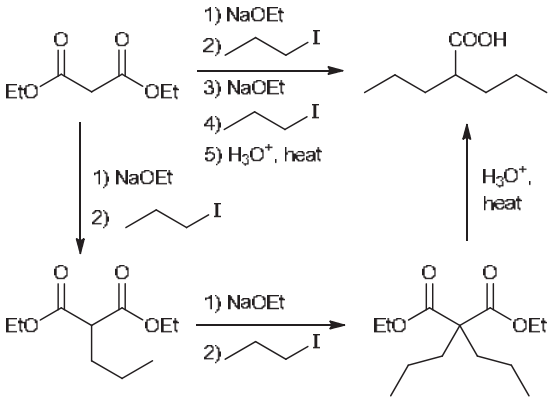
A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with the one of the halides above (either one), thereby installing the first group. The second group is installed in a similar way (deprotonation, followed by treatment with the second alkyl halide). Subsequent hydrolysis and decarboxylation give the product, as shown:



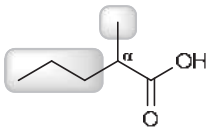
(c) The product is a carboxylic acid that has two propyl groups (highlighted) connected to the α position:



Both of these groups can be installed via a malonic ester synthesis, using propyl iodide. A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with propyl iodide, thereby installing the first propyl group. The second propyl group is installed in a similar way (deprotonation, followed by treatment with propyl iodide). Subsequent hydrolysis and decarboxylation give the product, as shown:

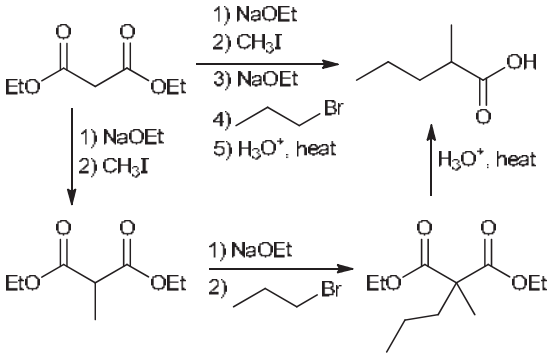


(d) The product is a carboxylic acid that has the following two (highlighted) groups connected to the α position:

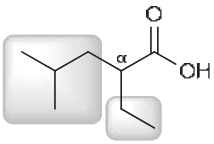


Both of these groups can be installed via a malonic ester synthesis, using propyl bromide and methyl iodide, respectively. The reason for using methyl iodide (rather than methyl bromide) was discussed in the solution to part (b).

A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with the one of the alkyl halides above (either one), thereby installing the first alkyl group. The second alkyl group is installed in a similar way (deprotonation, followed by treatment with the second alkyl halide). Subsequent hydrolysis and decarboxylation give the product, as shown:

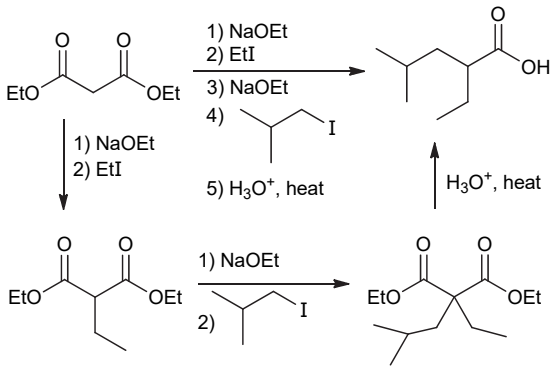


(e) The product is a carboxylic acid that has the following two (highlighted) groups connected to the α position:

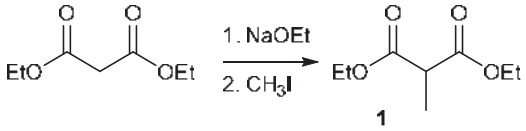


Both of these groups can be installed via a malonic ester synthesis, using ethyl iodide and isobutyl iodide, respectively.

A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with the one of the alkyl halides above (either one), thereby installing the first alkyl group. The second alkyl group is installed in a similar way (deprotonation, followed by treatment with the second alkyl halide). Subsequent hydrolysis and decarboxylation give the product, as shown:

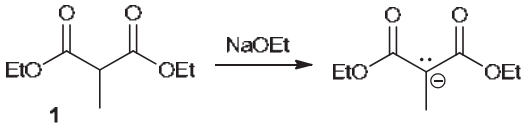


21.32. Product **1** is simply the alkylation product of diethylmalonate. Therefore, treatment of diethylmalonate with base (typically sodium ethoxide) followed by methyl iodide affords compound **1**.



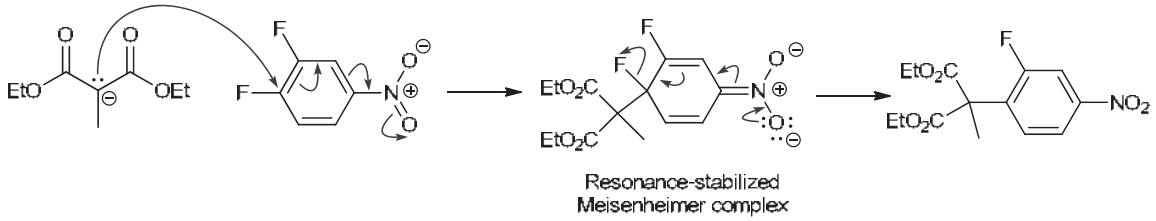
1

The steps leading from **1** to **2** constitute a malonic ester synthesis, where an aryl halide is used instead of an alkyl halide, giving a nucleophilic aromatic substitution. This effectively installs an aryl group onto the malonate derivative (**1**) rather than installing an alkyl group. Sodium ethoxide serves as the base to deprotonate **1** making a nucleophilic enolate.



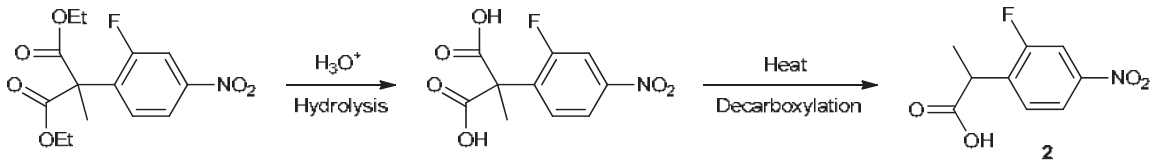
1

1,2-Difluoro-4-nitrobenzene is a very electron-deficient arene that can be attacked by the enolate of **1**. Recall that for an S_NAr reaction to take place, there must be (1) a powerful electron withdrawing group on the aromatic ring (in this case the nitro group), (2) a leaving group (in this case a fluoride) and (3) the leaving group must be either *ortho* or *para* to the electron withdrawing group. This third point dictates which fluoride is expelled (the one that is *para* to the nitro group).



You may note that fluoride is not typically a good leaving group. For the S_NAr reaction, it turns out that the attack of the benzene ring (which breaks aromaticity) is the rate determining step. For this reason, the leaving group ability is much less relevant for S_NAr. In fact, the electron withdrawing nature of fluoride actually *increases* the rate of S_NAr (relative to Cl and Br) due to making the benzene ring more electrophilic.

Finally, the last step uses H_3O^+ and heat to invoke a hydrolysis and subsequent decarboxylation of the arylated malonate product. Product **2** is a mono-carboxylic acid as shown below:

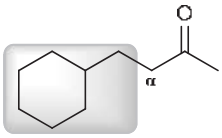


2

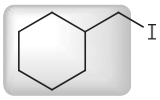
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21.33.

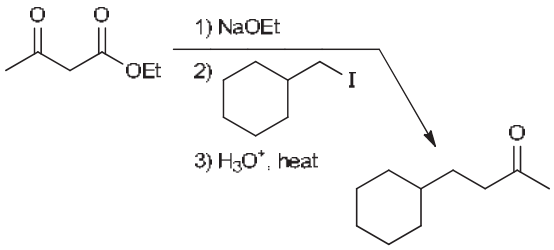
(a) The product is a methyl ketone that has the following (highlighted) group connected to the α position:



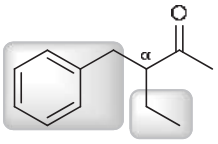
This group can be installed via an acetoacetic ester synthesis, using the following alkyl halide:



An acetoacetic ester synthesis begins with the deprotonation of ethyl acetoacetate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with the alkyl halide above, thereby installing the alkyl group. Subsequent hydrolysis and decarboxylation give the product, as shown:



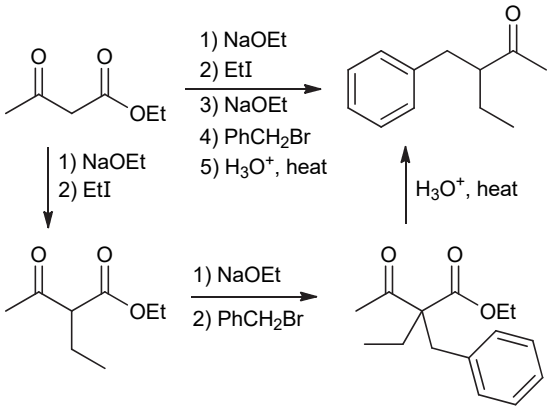
(b) The product is a methyl ketone that has the following two (highlighted) groups connected to the α position:



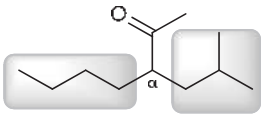
Each of these groups can be installed via an acetoacetic ester synthesis, using the following halides:



An acetoacetic ester synthesis begins with the deprotonation of ethyl acetoacetate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with one of the halides above, to install one of the two groups. The other group is installed in a similar way (deprotonation with a base, followed by alkylation). Subsequent hydrolysis and decarboxylation give the product, as shown:



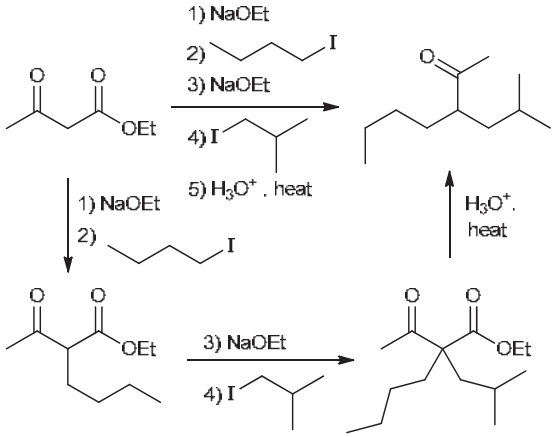
(c) The product is a methyl ketone that has the following two (highlighted) groups connected to the α position:



Each of these groups can be installed via an acetoacetic ester synthesis, using the following alkyl halides:

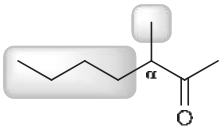


An acetoacetic ester synthesis begins with the deprotonation of ethyl acetoacetate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with one of the alkyl halides above, thereby installing one of the two alkyl groups. The other alkyl group is installed in a similar way (deprotonation with a base, followed by alkylation). Subsequent hydrolysis and decarboxylation give the product, as shown:



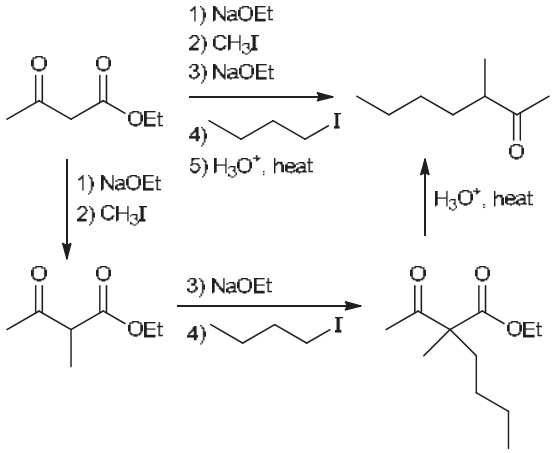
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(d) The product is a methyl ketone that has the following two (highlighted) groups connected to the α position:



Each of these groups can be installed via an acetoacetic ester synthesis, using methyl iodide and butyl iodide, respectively.

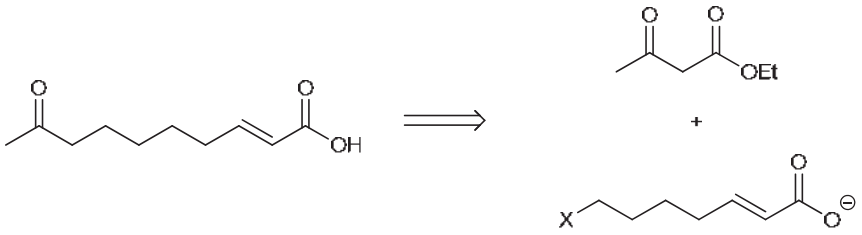
An acetoacetic ester synthesis begins with the deprotonation of ethyl acetoacetate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with one of the alkyl halides above, thereby installing one of the two alkyl groups. The other alkyl group is installed in a similar way (deprotonation with a base, followed by alkylation). Subsequent hydrolysis and decarboxylation give the product, as shown:



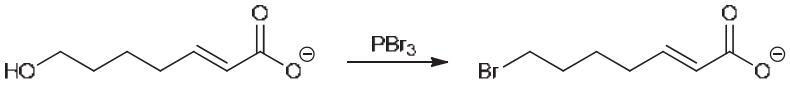
21.34. Comparison of carbon skeletons reveals that three carbon atoms have been introduced in this transformation; specifically, carbon atoms 8-10 look like acetone and can be installed using an acetoacetic ester synthesis.



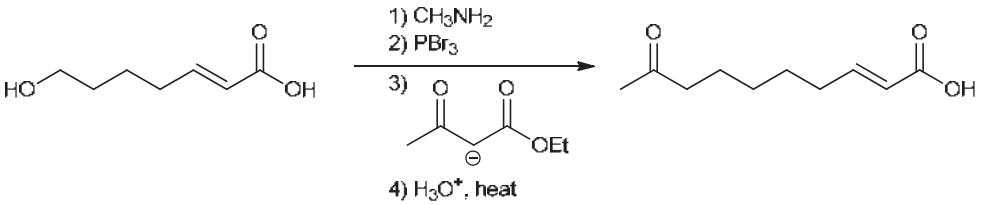
That makes carbon 8 the α carbon, so carbon 7 will need to have a leaving group. The necessary alkyl halide will be a primary halide and a good substrate for the acetoacetic acid synthesis, provided that the COOH group is deprotonated, as indicated in the problem statement.



The alkyl halide must be made from the alcohol starting material. The mild reagent PBr_3 can be used to convert the primary alcohol to a primary bromide.



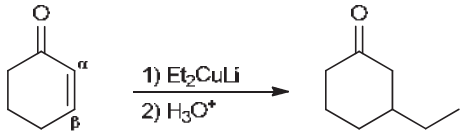
Putting it all together, we have the following sequence:



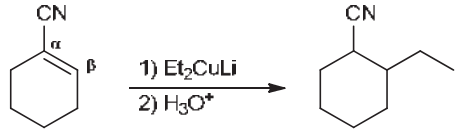
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21.35.

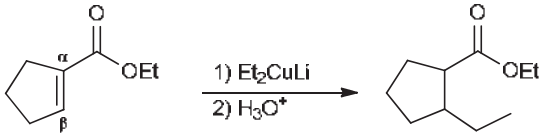
(a) The starting material is an α,β-unsaturated ketone, which can function as a Michael acceptor (see Table 21.2), and the reagent (lithium diethyl cuprate) can function as a Michael donor. As such, we expect a Michael reaction, thereby installing an ethyl group at the β position:



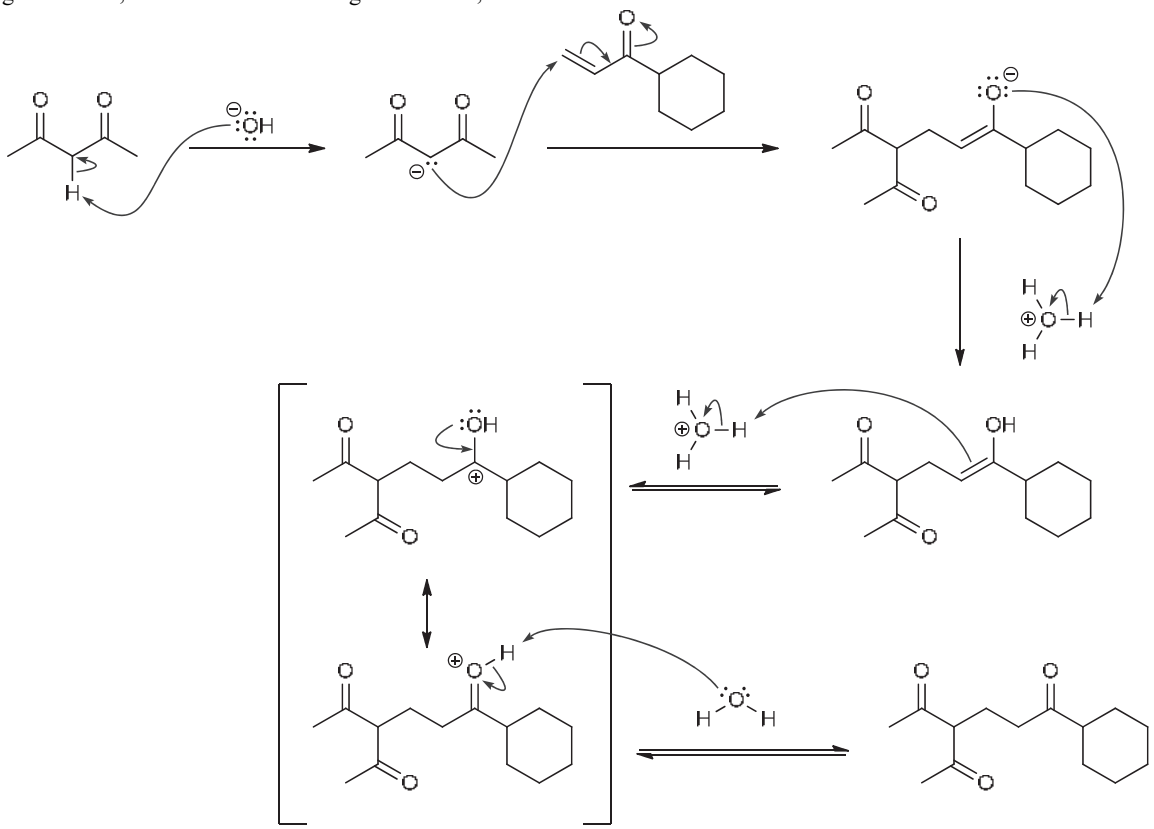
(b) The starting material is an α,β-unsaturated nitrile, which can function as a Michael acceptor (see Table 21.2), and the reagent (lithium diethyl cuprate) can function as a Michael donor. As such, we expect a Michael reaction, thereby installing an ethyl group at the β position:



(c) The starting material is an α,β-unsaturated ester, which can function as a Michael acceptor (see Table 21.2), and the reagent (lithium diethyl cuprate) can function as a Michael donor. As such, we expect a Michael reaction, thereby installing an ethyl group at the β position:

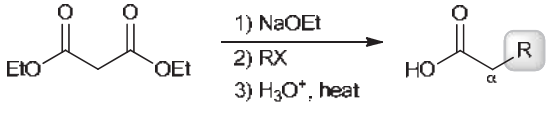


21.36. The starting material has an acidic proton, which is removed upon treatment with a strong base, such as hydroxide. The resulting resonance-stabilized conjugate base (a doubly-stabilized enolate) functions as a Michael donor and attacks the Michael acceptor (an α,β-unsaturated ketone). Subsequent acid work-up causes protonation to give an enol, which tautomerizes to give a ketone, as shown.



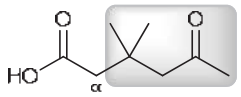
21.37.

(a) Recall that the malonic ester synthesis is useful for creating carboxylic acids that possess either one or two alkyl groups at the α position:

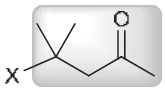


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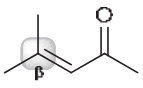
Therefore, making the desired product via a malonic ester synthesis would require installation of the following highlighted group:



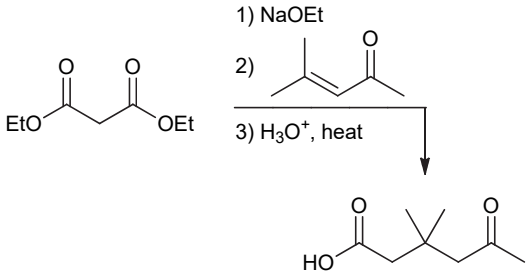
Installation of this group via alkylation (as seen in Section 21.5) would require a tertiary alkyl halide:



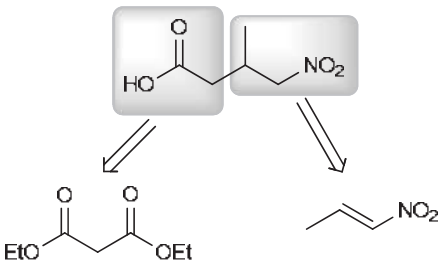
However, a tertiary alkyl halide will not undergo an S_N2 reaction because it is too sterically hindered. So this method will not work. The problem statement indicates that a Michael reaction can be used to achieve the desired transformation. That is, we would use an electrophile with the same carbon skeleton as the alkyl halide above, but the electrophilic position will be the β position of an α,β-unsaturated ketone:



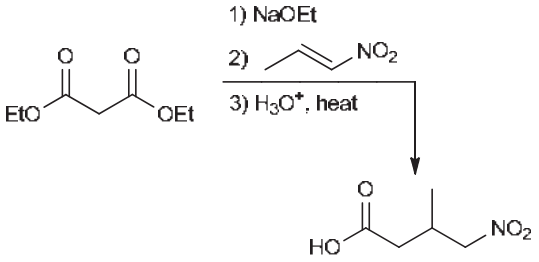
This compound can function as a Michael acceptor, thereby allowing the desired transformation, as seen in the following synthesis:



(b) As described in the solution to part (a), the conjugate base of diethyl malonate can function as a Michael donor. So we must identify the appropriate Michael acceptor, shown here:

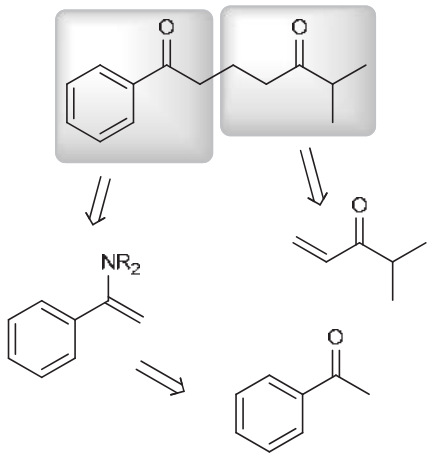


The forward scheme is shown here:

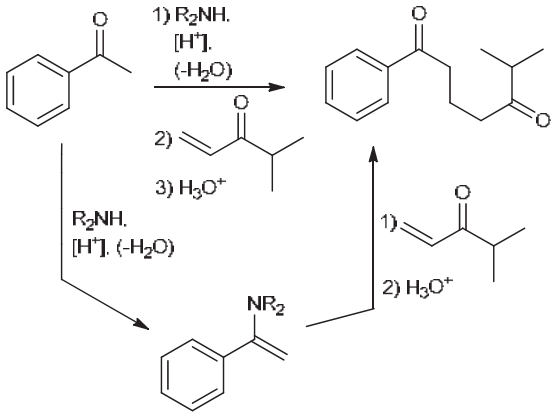


21.38.

(a) With the following retrosynthetic analysis, we can identify the starting reagents necessary to prepare this product via a Stork enamine synthesis:

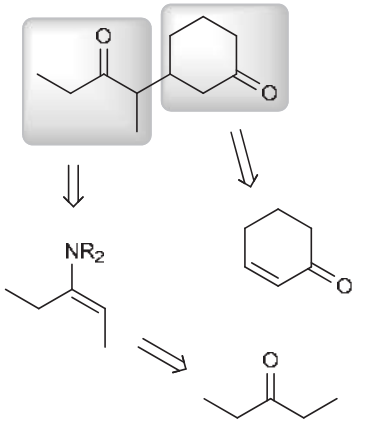


The forward scheme is shown here. The starting ketone is first treated with a secondary amine in acidic conditions (with removal of water) to give an enamine. This enamine is then used as a Michael donor in a Michael reaction with an α,β-unsaturated ketone. Aqueous acidic work-up gives the desired product.

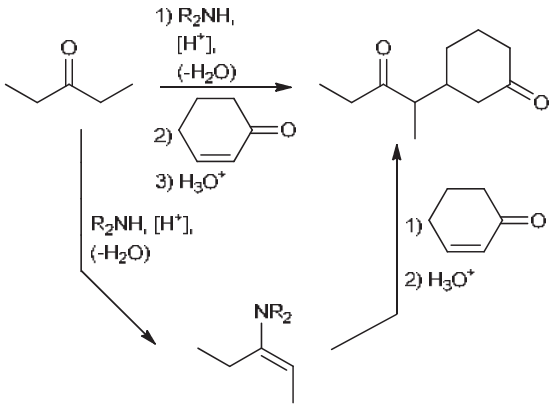


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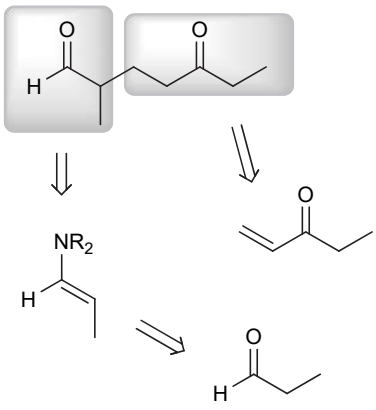
(b) With the following retrosynthetic analysis, we can identify the starting reagents necessary to prepare this product via a Stork enamine synthesis:



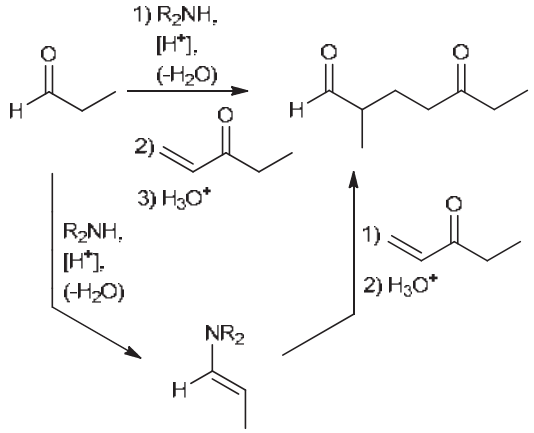
The forward scheme is shown here. The starting ketone is first treated with a secondary amine in acidic conditions (with removal of water) to give an enamine. This enamine is then used as a Michael donor in a Michael reaction with an α,β-unsaturated ketone. Aqueous acidic work-up gives the desired product.



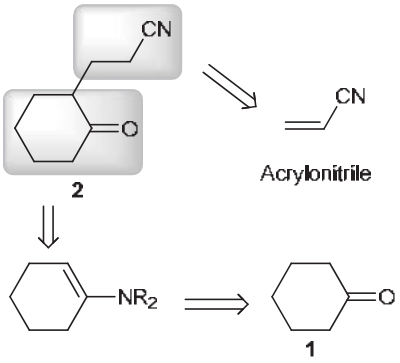
(c) With the following retrosynthetic analysis, we can identify the starting reagents necessary to prepare this product via a Stork enamine synthesis:



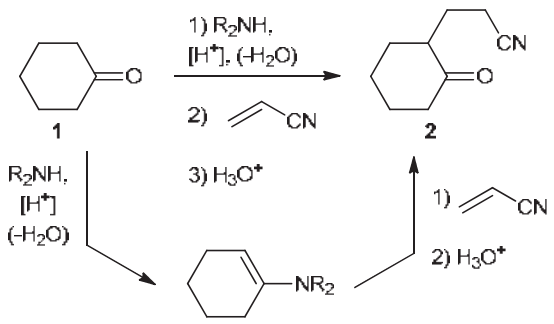
The forward scheme is shown here. The starting ketone is first treated with a secondary amine in acidic conditions (with removal of water) to give an enamine. This enamine is then used as a Michael donor in a Michael reaction with an α,β-unsaturated ketone. Aqueous acidic work-up gives the desired product.



21.39. With the following retrosynthetic analysis, we can identify the starting reagents necessary to prepare compound **2** via a Stork enamine synthesis:

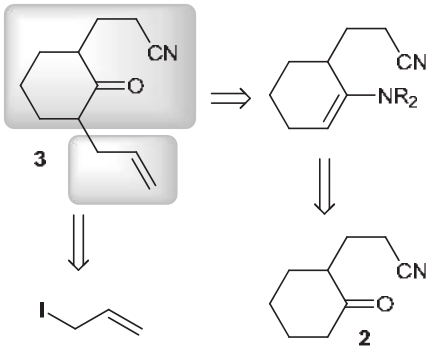


The forward scheme is shown here. The starting ketone **1** is first treated with a secondary amine in acidic conditions (with removal of water) to give an enamine. This enamine is then used as a Michael donor in a Michael reaction with an α,β-unsaturated compound, acrylonitrile, as the Michael acceptor. Aqueous acidic work-up gives the desired product **2**.

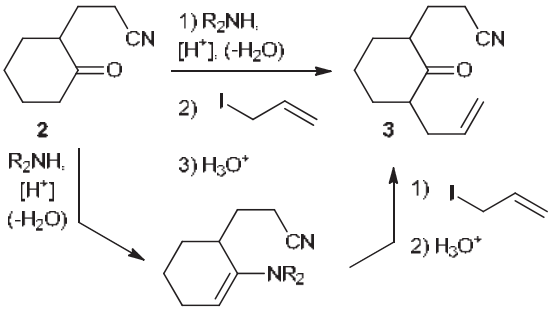


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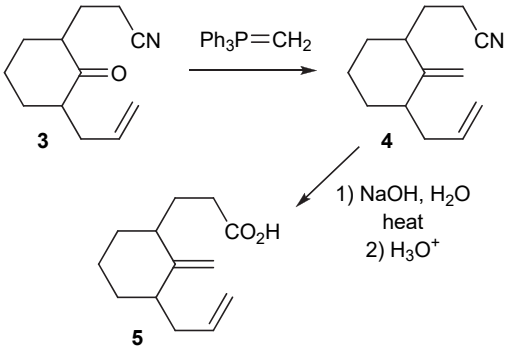
Now let's consider the conversion of **2** to **3**. You might be wondering why a Stork enamine synthesis is used, rather than treating compound **2** with LDA, followed by an allyl halide. This won't work, because LDA can deprotonate the position that is alpha to the cyano group. Therefore, a Stork enamine synthesis is required to convert **2** to **3**. We can identify the starting reagents necessary to prepare compound **3** via a Stork enamine as a nucleophile and an alkyl halide as an electrophile.



The forward scheme is shown here. The starting ketone **2** is first treated with a secondary amine in acidic conditions (with removal of water) to give an enamine. Note that deprotonation at the less hindered alpha carbon is favored to give the less substituted enamine. This enamine is then used as a nucleophile in an S_N2 reaction with allyl iodide. Aqueous acidic work-up gives the desired product **3**.

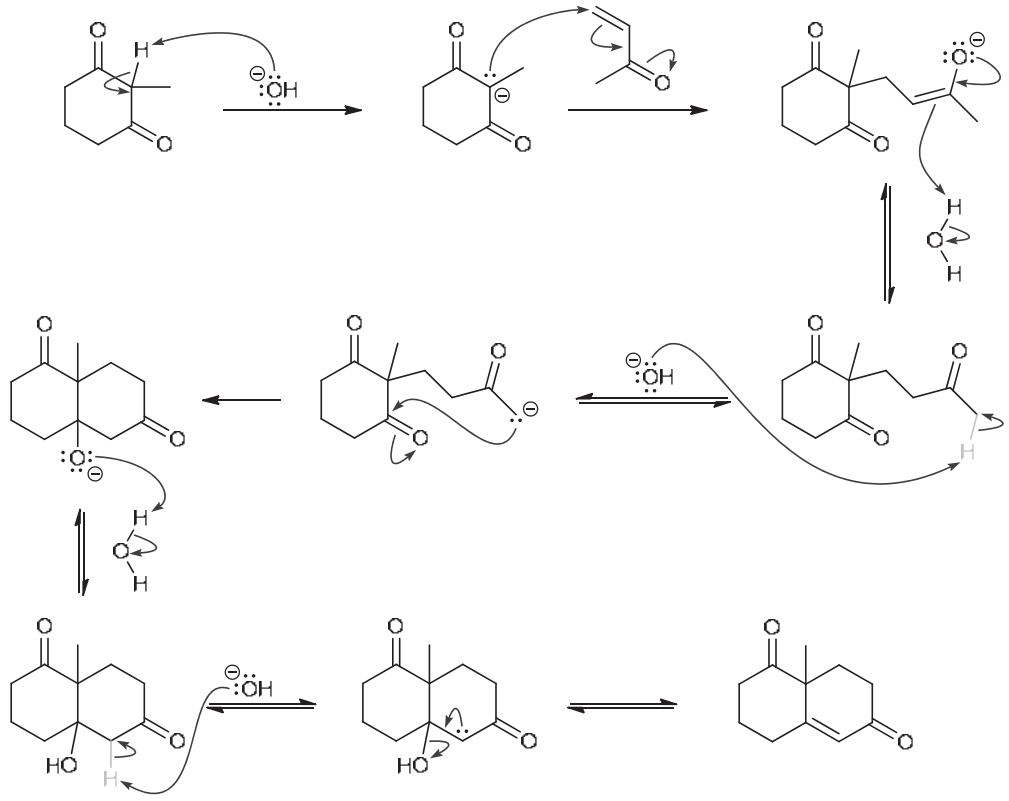


Ketone **3** can be converted into alkene **4** upon treatment with a Wittig reagent, and hydrolysis of the cyano group gives the desired carboxylic acid product **5**. In the literature synthesis, this hydrolysis step was performed under basic conditions (like saponification), and under those conditions, the product would be deprotonated to give a carboxylate ion. Acid workup is necessary in order to protonate the carboxylate ion and regenerate the carboxylic acid.

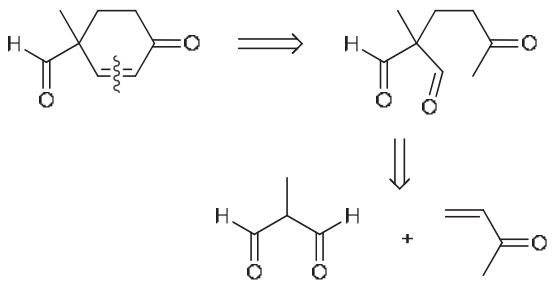


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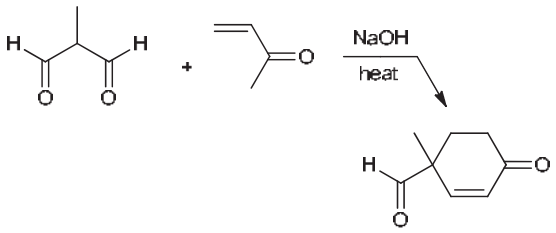
21.40. In the presence of a strong base, the β-dicarbonyl compound is deprotonated, giving a resonance-stabilized intermediate (doubly stabilized enolate) which then functions as a Michael donor, attacking the β position of the α,β-unsaturated ketone in a Michael reaction. The resulting enolate is then protonated, and then subsequently deprotonated to give a different enolate (these two steps represent equilibration of the enolates). The new enolate then attacks one of the carbonyl groups to initiate an aldol condensation. The resulting alkoxide ion is then protonated by water. Subsequent deprotonation and loss of hydroxide gives the product. Notice that water functions as the acid for all protonation steps, consistent with basic conditions (strong acids are not measurably present under these conditions).



21.41. A Robinson annulation is comprised of a Michael reaction, followed by an intramolecular aldol condensation. To determine the starting materials necessary to prepare the desired product via a Robinson annulation, we draw the following retrosynthetic analysis:

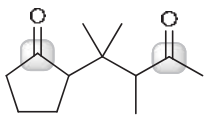


These two steps do not represent two separate reactions. A Robinson annulation can be performed in one reaction flask, as shown in the following forward scheme:

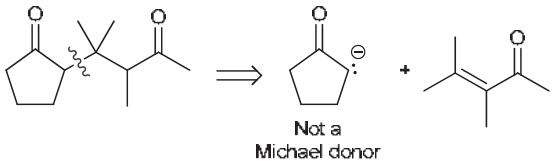


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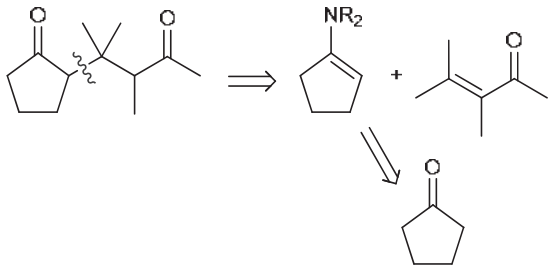
21.42.
(a) The product is 1,5-difunctionalized:



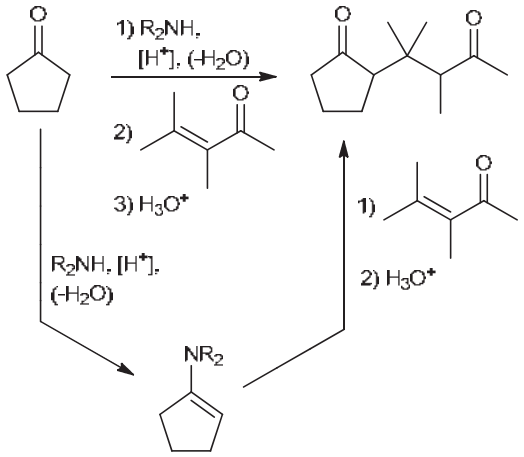
Therefore, we consider preparing the product via a Michael reaction, which would require the following starting materials:



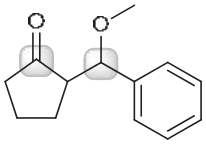
Since enolates are not efficient Michael donors, we must consider a Stork enamine synthesis (in which we use an enamine, rather than an enolate, as a Michael donor). The enamine can be made directly from cyclopentanone.



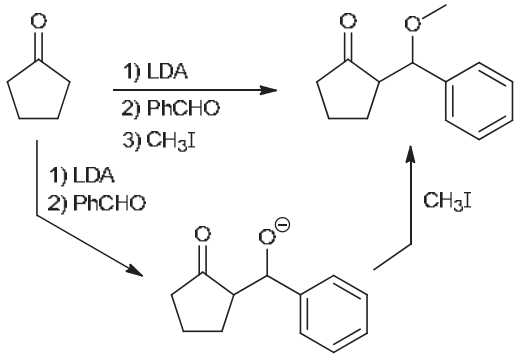
The forward scheme is shown here:



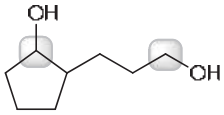
(b) The product is 1,3-difunctionalized:



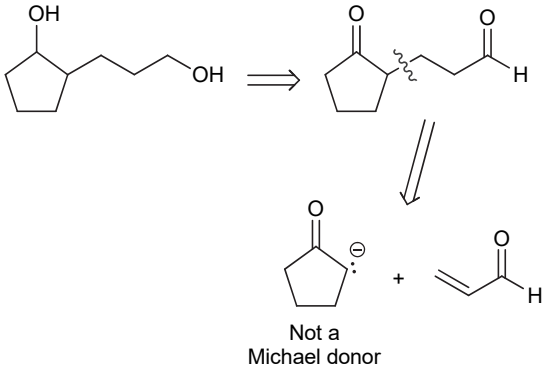
Therefore, we consider preparing the product via either an aldol reaction or a Claisen condensation. In this case, a directed aldol addition, followed by methylation of the resulting alkoxide ion (in a Williamson ether synthesis), gives the desired product:



(c) The product is 1,5-difunctionalized:

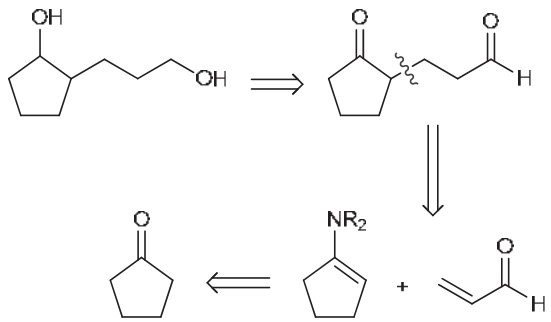


Therefore, we consider preparing the product via a Michael reaction:

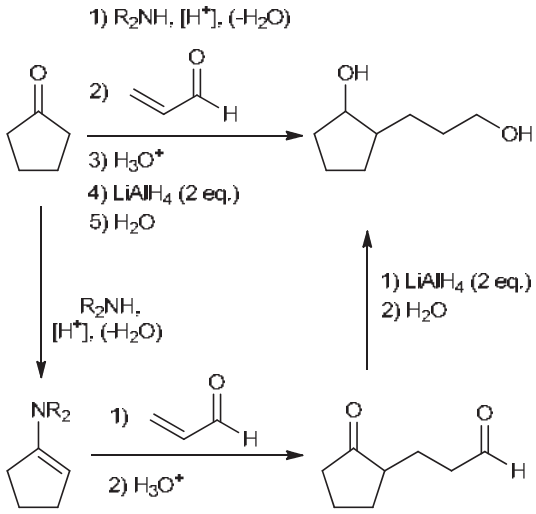


This strategy will not work, because it involves the use of an enolate, which is not an efficient Michael donor. Therefore, we consider a Stork enamine synthesis (in which we use an enamine, rather than an enolate, as a Michael donor). The enamine can be made directly from cyclopentanone.

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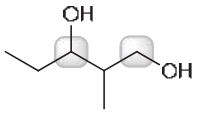


The forward scheme is shown here:

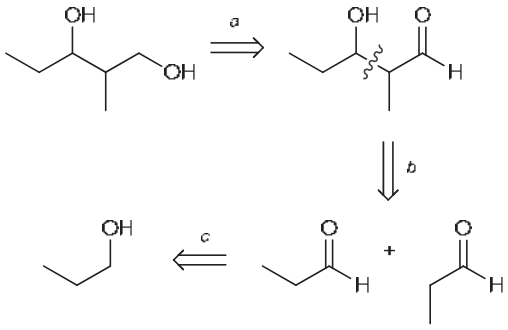


21.43.

(a) The product is 1,3-difunctionalized:

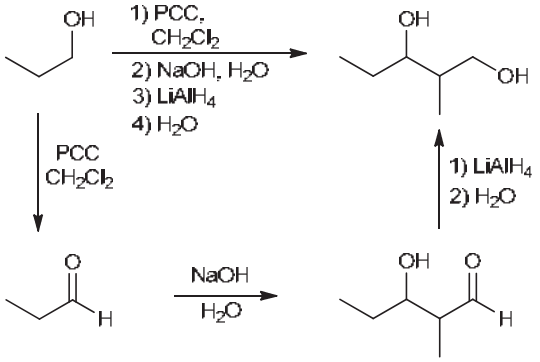


Therefore, we consider preparing the product via either an aldol reaction or a Claisen condensation. In this case, an aldol addition reaction can be employed, as shown in the following retrosynthetic analysis.

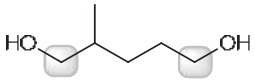


a. The product can be made via reduction of a β-hydroxyaldehyde.
b. The β-hydroxyaldehyde can be made via an aldol addition reaction between two molecules of propanal.
c. Propanal can be made via oxidation of 1-propanol with PCC (or DMP or via a Swern oxidation).

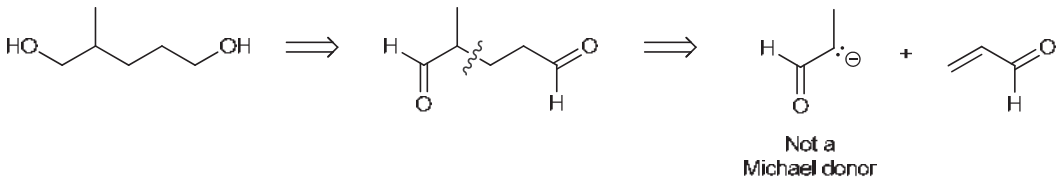
Now let's draw the forward scheme. Upon treatment with PCC, 1-propanol is oxidized to give propanal. Treating propanal with sodium hydroxide then gives a β-hydroxyaldehyde (via an aldol addition reaction between two molecules of propanal). Reduction with $LiAlH_4$, followed by water work-up, gives the product.



(b) The product is 1,5-difunctionalized:



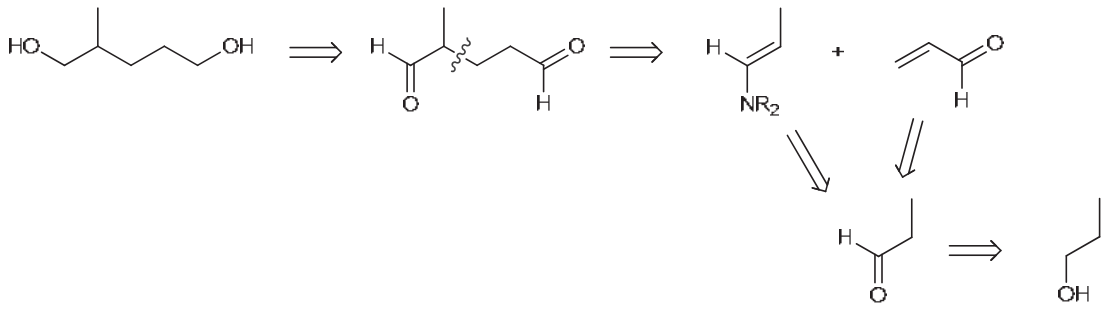
Therefore, we consider preparing the product via a Michael reaction:



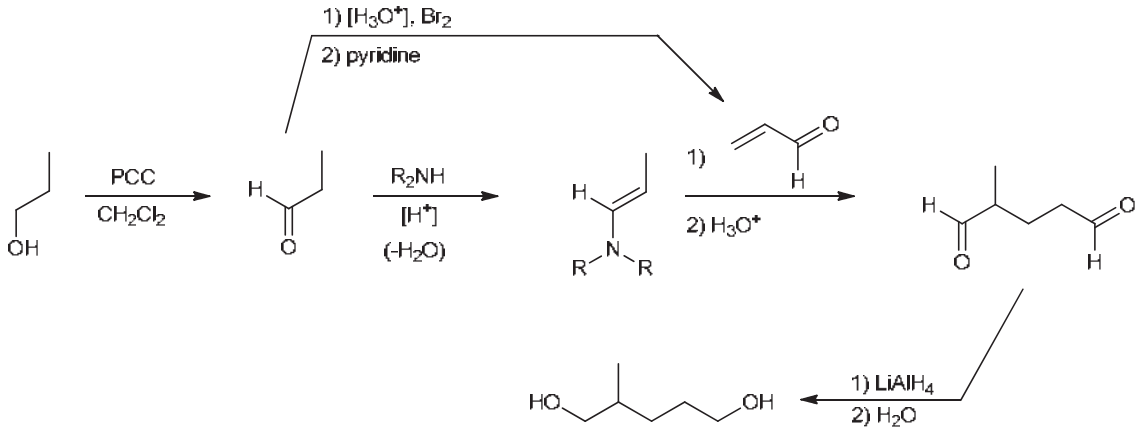
This strategy will not work, because it involves the use of an enolate, which is not an efficient Michael donor. Therefore, we consider a Stork enamine synthesis (in which we use an enamine, rather than an enolate, as a Michael

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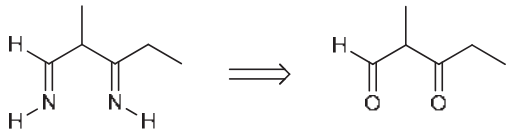
donor). Both the Michael donor and the Michael acceptor can be made from propanal, which can be made from 1-propanol via oxidation with PCC (or DMP or via a Swern oxidation):



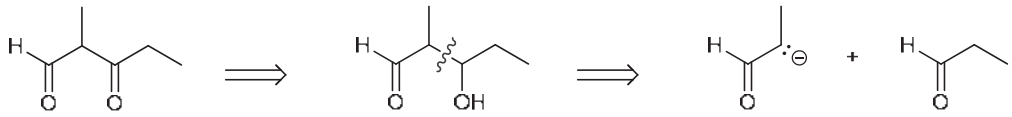
The forward scheme is shown here:



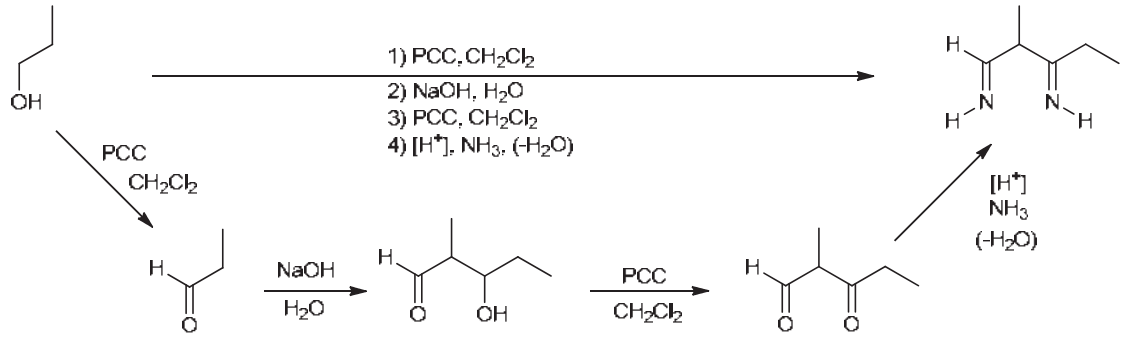
(c) The product has two imine groups which can be made from the corresponding dicarbonyl compound upon treatment with ammonia in acid-catalyzed conditions (with removal of water):



This dicarbonyl compound is 1,3-difunctionalized and can be made from a β-hydroxyaldehyde, which can be made from propanal via an aldol addition reaction:

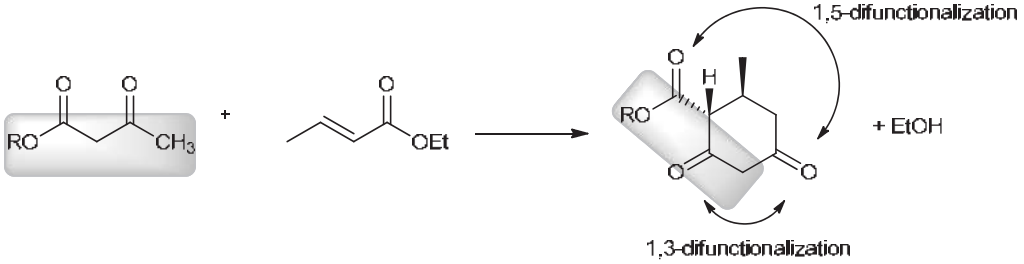


And propanal can be made from 1-propanol via oxidation with PCC (or DMP or via a Swern oxidation). The forward scheme is shown here. Notice that the third step of this synthesis employs PCC, rather than chromic acid, to avoid oxidation of the aldehyde group.

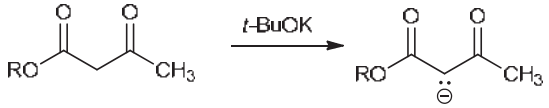


21.44.

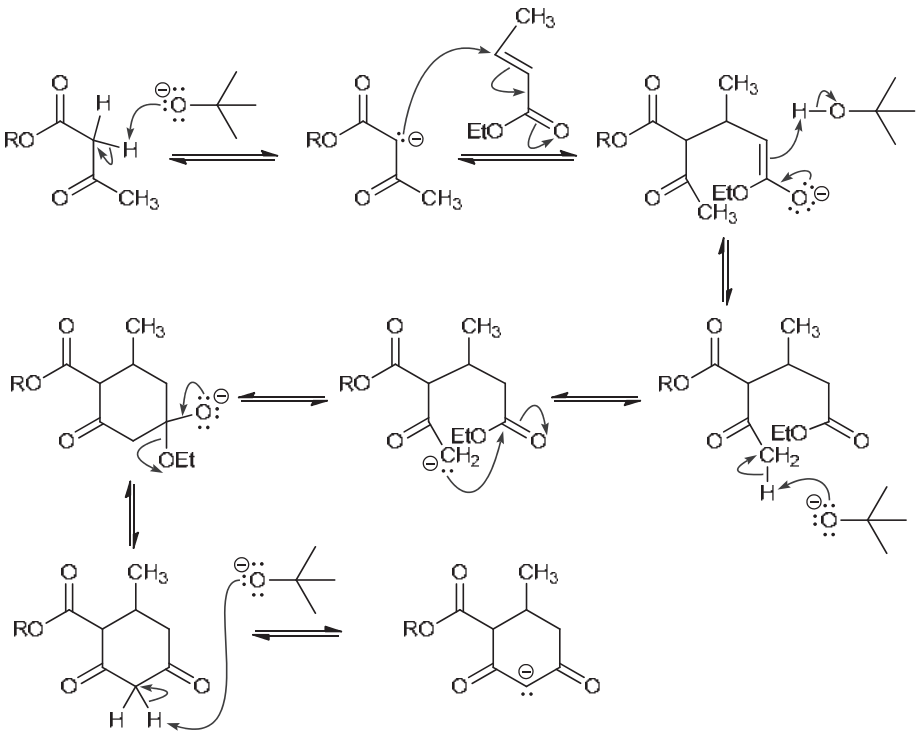
(a) Begin by analyzing (1) the C—C framework of both the reactants and the product and (2) the location and identity of the functional groups in the product. Notice that the product exhibits 1,5-functionalization resulting from the Michael reaction, as well as 1,3-functionalization resulting from the Claisen-type reaction.



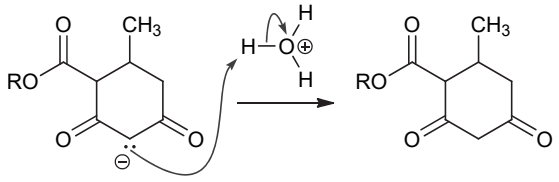
The first reactant is a 1,3-dicarbonyl compound which contains an acidic proton that is removed upon treatment with a strong base, such as *tert*-butoxide, to give a doubly-stabilized enolate.



Due to the stability of this enolate, the first step is 1,4-addition (a Michael reaction). The other reactant contains an α,β-unsaturated ester capable of participating as a Michael acceptor, giving 1,5-difunctionalization, as shown below. Next, notice that a stable 6-membered ring could result if the ketone $-CH_3$ group were deprotonated and the resulting enolate attacked the ethyl ester. This is consistent with a Claisen-type condensation (1,2-addition) which would afford 1,3-difunctionalization. As a final step, deprotonation gives a doubly-stabilized enolate (there is another location where deprotonation could also occur to give a doubly-stabilized enolate):



Then, upon acidic work-up (H_3O^+), the doubly-stabilized enolate is protonated to give the observed product:

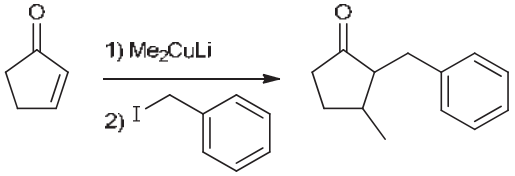


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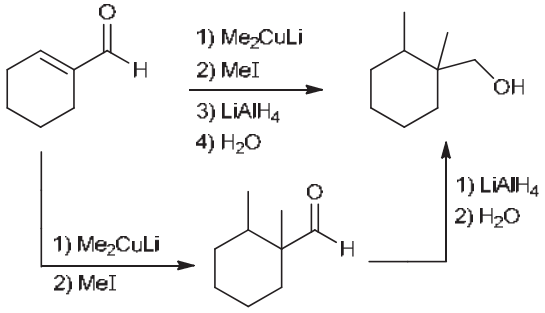
(b) Claisen condensations are nucleophilic acyl substitution reactions where the nucleophile is an ester enolate and the electrophile is an ester; intramolecular versions are known as Dieckmann condensations. This reaction, however, involves a ketone enolate (rather than an ester enolate) attacking an ester in a nucleophilic acyl substitution, so neither of these names strictly apply.

21.45.

(a) This transformation requires the installation of two groups (one at the α position and the other at the β position). This can be achieved by treating the α,β-unsaturated ketone with lithium dimethyl cuprate, thereby installing a methyl group and generating an enolate, which is then treated with benzyl iodide to install a benzyl group:

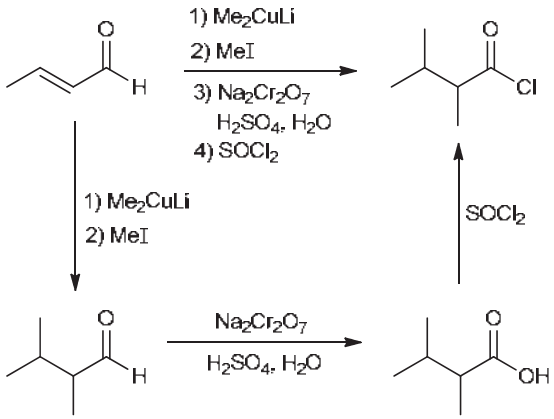


(b) This transformation requires the installation of two methyl groups (one at the α position and the other at the β position), as well as reduction of the aldehyde group. Installation of the two methyl groups can be achieved by treating the α,β-unsaturated ketone with lithium dimethyl cuprate, followed by methyl iodide. Reduction is then achieved with $LiAlH_4$, followed by water work-up.

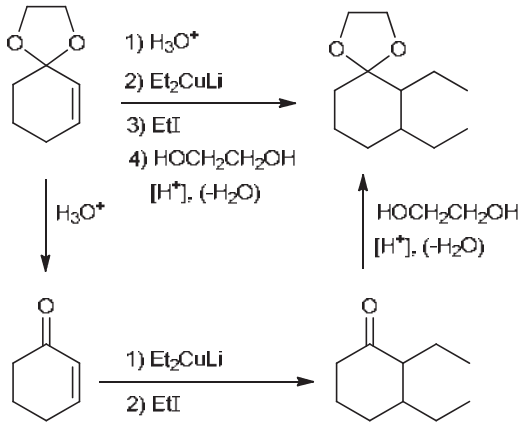


(c) This transformation requires the installation of two methyl groups (one at the α position and the other at the β position), as well as conversion of the aldehyde group into an acid halide. Installation of the two methyl groups can be achieved by treating the α,β-unsaturated aldehyde with lithium dimethyl cuprate, followed by methyl iodide. The aldehyde is then converted into an acid halide via oxidation with chromic acid (to give a carboxylic acid) followed by treatment with thionyl chloride.

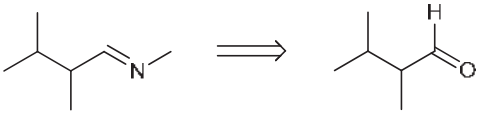
Note than the acid chloride group is formed at the end of the synthesis, because if it were formed in the beginning of the synthesis, then lithium dimethyl cuprate would react with the acid chloride group.



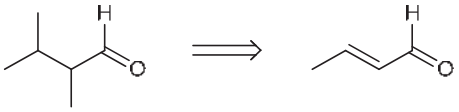
(d) If the acetal is hydrolyzed with aqueous acid, the resulting α,β-unsaturated ketone can be treated with lithium diethyl cuprate, followed by ethyl iodide, to install the two ethyl groups in the correct locations. The ketone can then be converted back into an acetal upon treatment with ethylene glycol under acidic conditions (with removal of water).



(e) The imine can be prepared from the corresponding aldehyde:

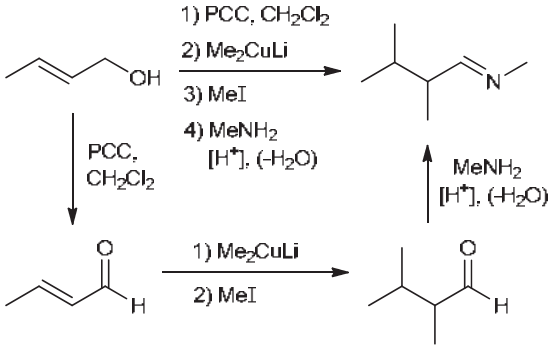


This aldehyde can be made from an α,β-unsaturated aldehyde, with installation of two methyl groups (one at the α position and the other at the β position):

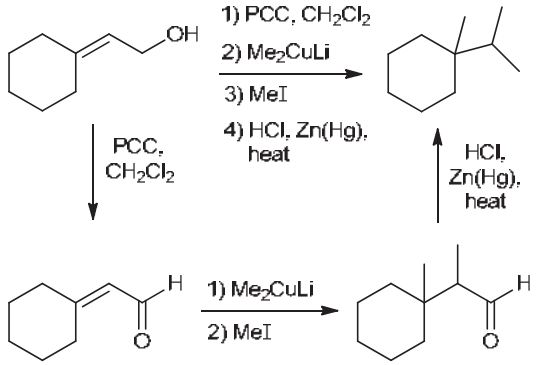


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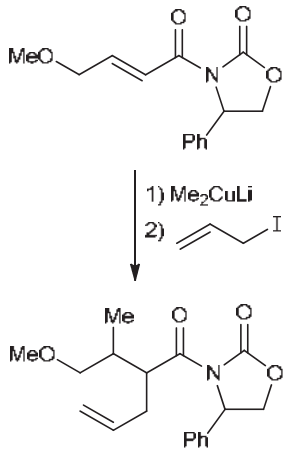
The α,β-unsaturated aldehyde can be made from the starting material via oxidation with PCC (or DMP or via a Swern oxidation). The entire synthesis is summarized here:



(f) This problem is very similar to the previous problem, although the final step is reduction of the aldehyde with a Clemmensen reduction to give an alkane.

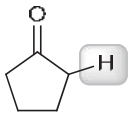


21.46. This transformation requires the installation of two groups (one at the α position and the other at the β position). This can be achieved by treating the α,β-unsaturated carbonyl with lithium dimethyl cuprate, thereby installing a methyl group and generating an enolate, which can then be treated with allyl iodide to install an allyl group at the α position, as shown below:

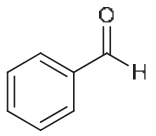


21.47.

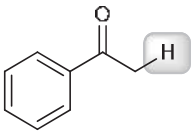
(a) Deprotonation (of the highlighted proton) results in a resonance-stabilized enolate ion. Therefore, the highlighted proton is the most acidic proton (with a pK_a just below 20), because its removal leads to a stabilized conjugate base.



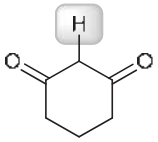
(b) This compound does not have an acidic proton, and is expected to have a pK_a above 20.



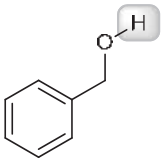
(c) Deprotonation (of the highlighted proton) results in a resonance stabilized enolate ion. Therefore, the highlighted proton is the most acidic proton (with a pK_a just below 20), because its removal leads to a stabilized conjugate base.



(d) Deprotonation (of the highlighted proton) results in a resonance stabilized conjugate base (a doubly-stabilized enolate). Therefore, the highlighted proton is the most acidic proton (with a pK_a just below 20), because its removal leads to the most stable conjugate base possible.

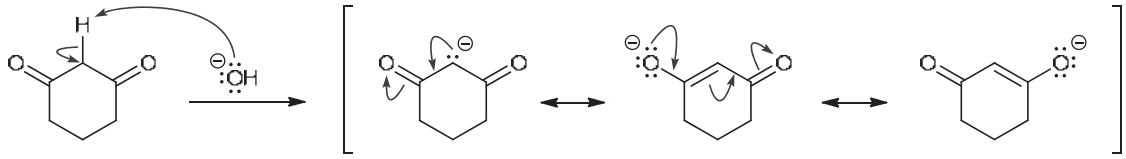


(e) Deprotonation (of the highlighted proton) results in an alkoxide ion. As such, the compound below is expected to have a pK_a lower than 20 (see the pK_a table on the inside cover of the textbook).



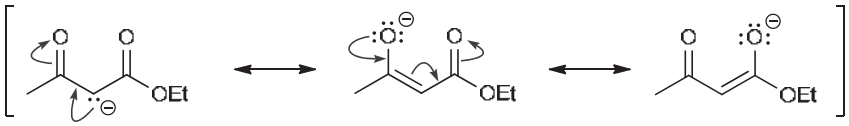
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21.48. The most acidic proton is connected to the position that is α to two carbonyl groups (in between both carbonyl groups). Deprotonation at this location leads to a resonance stabilized conjugate base in which the negative charge is spread over two oxygen atoms and one carbon atom).

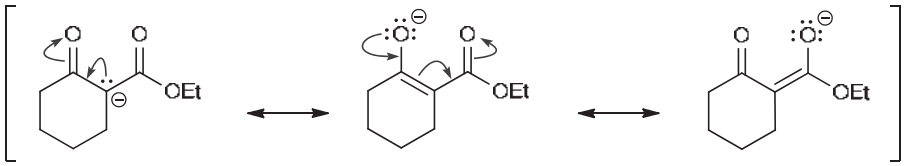


21.49.

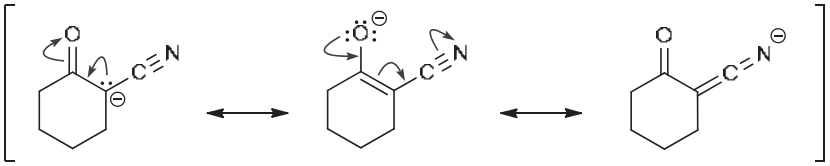
(a) The most acidic proton is connected to the position that is α to both carbonyl groups (in between both carbonyl groups). Deprotonation at this location leads to a resonance stabilized conjugate base in which the negative charge is spread over two oxygen atoms and one carbon atom).



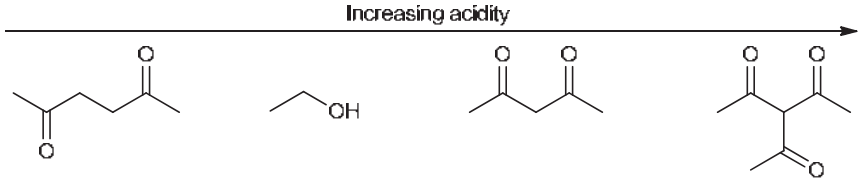
(b) The most acidic proton is connected to the position that is α to both carbonyl groups (in between both carbonyl groups). Deprotonation at this location leads to a resonance stabilized conjugate base in which the negative charge is spread over two oxygen atoms and one carbon atom).



(c) The most acidic proton is connected to the position that is α to the carbonyl group as well as the cyano group (in between both groups). Deprotonation at this location leads to a resonance stabilized conjugate base in which the negative charge is spread over an oxygen atom, a nitrogen atom and a carbon atom).

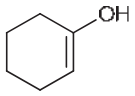


21.50. The most acidic compound is the one that exhibits a position that is α to three carbonyl groups (deprotonation of this compound gives a conjugate base in which the negative charge is spread over three oxygen atoms and one carbon atom). The next most acidic compound is the one that exhibits a position that is α to two carbonyl groups (deprotonation of this compound gives a conjugate base in which the negative charge is spread over two oxygen atoms and one carbon atom). Of the remaining two compounds, an alcohol is generally more acidic than a ketone (see the pK_a table on the inside cover of the textbook).

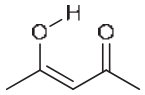


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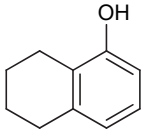
21.51.
(a) This enol does not exhibit a significant presence at equilibrium. Ketones are generally favored at equilibrium.



(b) The following enol does exhibit a significant presence at equilibrium because it exhibits conjugation as well as intramolecular hydrogen bonding (between the oxygen atom of the carbonyl group and the proton of the OH group):

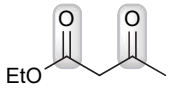


(c) The following enol does indeed exhibit a significant presence at equilibrium, because it is aromatic.

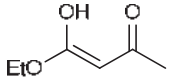


In fact, in this case, the ketone does not exhibit a significant presence at equilibrium. The aromatic ring is so strongly favored, that we cannot detect the ketone present in the mixture.

21.52. Ethyl acetoacetate has two carbonyl groups:



One of them (left) has only one α position and can therefore only form one enol:

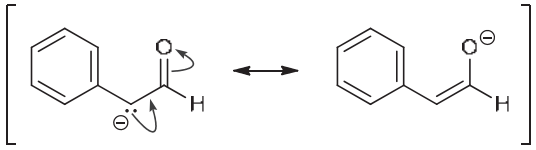


The other carbonyl group (right) has two α positions and can therefore form two different enols:

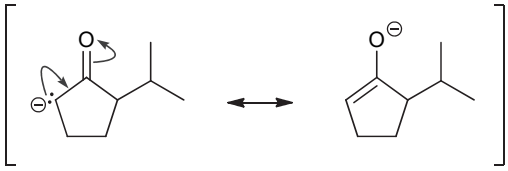


In total, there are three enol isomers.

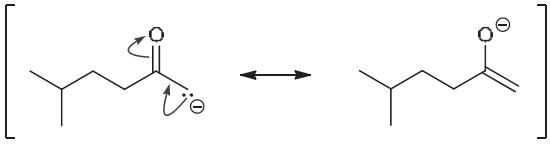
21.53.
(a) This compound has only one α position. LDA is a strong base and it will deprotonate the compound (at the α position), resulting in the following enolate.



(b) This compound has two α positions. LDA is a strong, sterically hindered base, so deprotonation will occur at the less substituted position. Deprotonation at that position results in the following kinetic enolate:

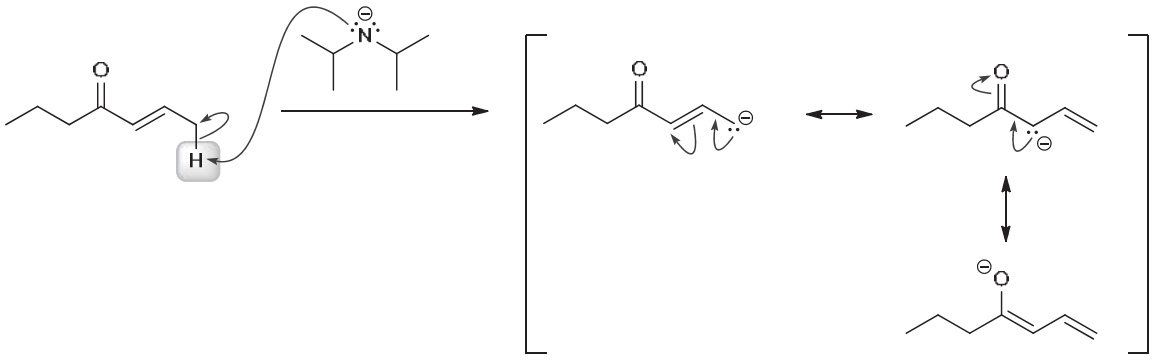


(c) This compound has two α positions. LDA is a strong, sterically hindered base, so deprotonation will occur at the less substituted position. Deprotonation at that position results in the following kinetic enolate:

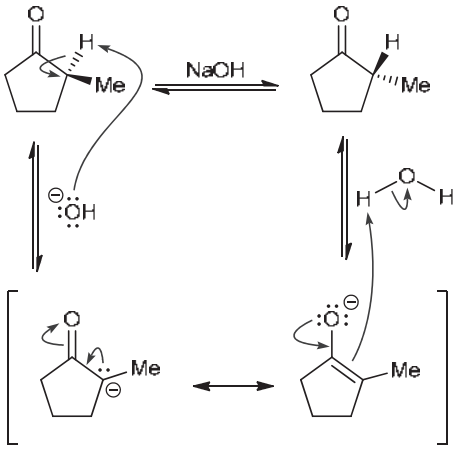


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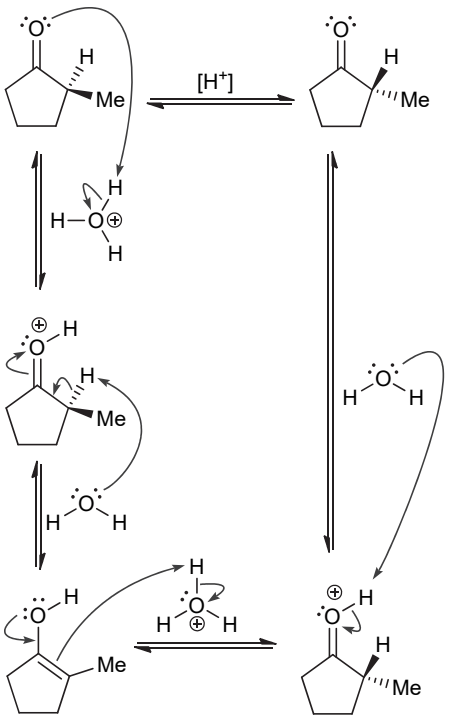
21.54. Deprotonation at the highlighted γ position results in an anion that has three resonance structures. The negative charge is spread over one oxygen atom and two carbon atoms:



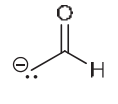
21.55. Deprotonation at the α carbon changes the hybridization state of the α carbon from sp^3 (tetrahedral) to sp^2 (planar). When the α position is protonated once again, the proton can be placed on either side of the planar α carbon, resulting in racemization:



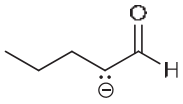
21.56. In acidic conditions, the carbonyl group is first protonated, resulting in a resonance-stabilized cation that is deprotonated at the α position to give an enol. The enol is then protonated at the α position, followed by deprotonation. Once again, racemization occurs because the chiral center becomes planar (achiral) when the enol is formed. Subsequent tautomerization back to the ketone allows for protonation to occur on either face of the planar enol, giving a racemic mixture.



21.57. Each of the starting aldehydes has an α position that can be deprotonated, giving two possible enolates:

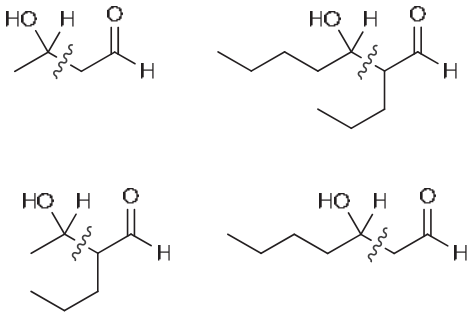


Enolate of acetaldehyde

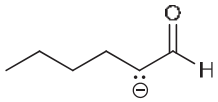


Enolate of pentanal

So, there are two nucleophiles in solution, as well as two electrophiles (acetaldehyde and pentanal), giving rise to the following four possible products. In each case, a wavy line is used to indicate the bond that was formed as a result of the aldol addition reaction:

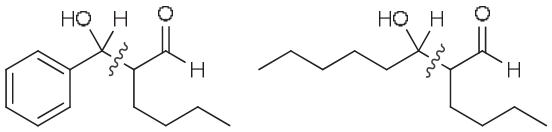


21.58. Hexanal has an α position that bears protons, but the α position of benzaldehyde does not bear any protons. As such, only one enolate can form under these conditions:



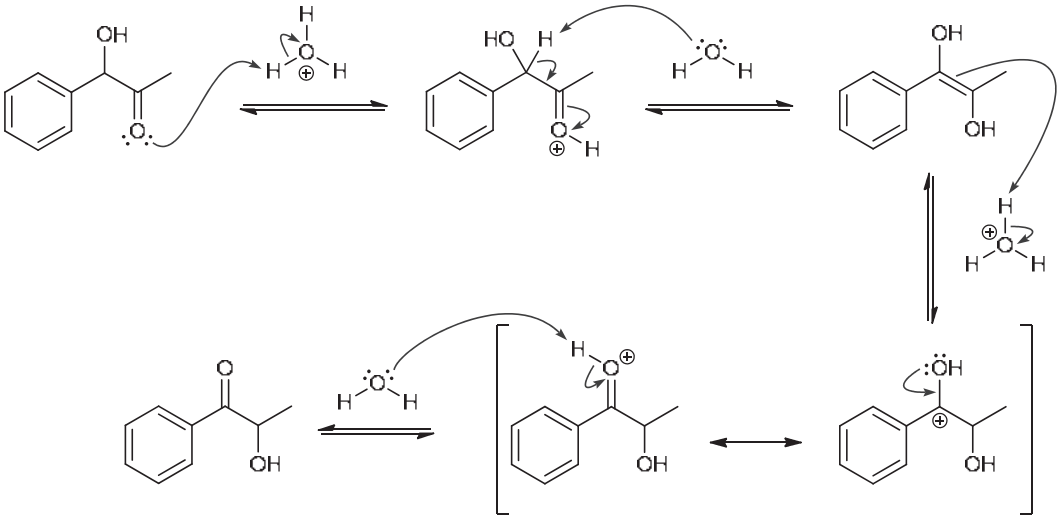
Enolate of hexanal

This enolate is present in solution together with two electrophiles (hexanal and benzaldehyde), giving rise to the following two possible products. In each case, a wavy line is used to indicate the bond that was formed as a result of the aldol addition reaction:

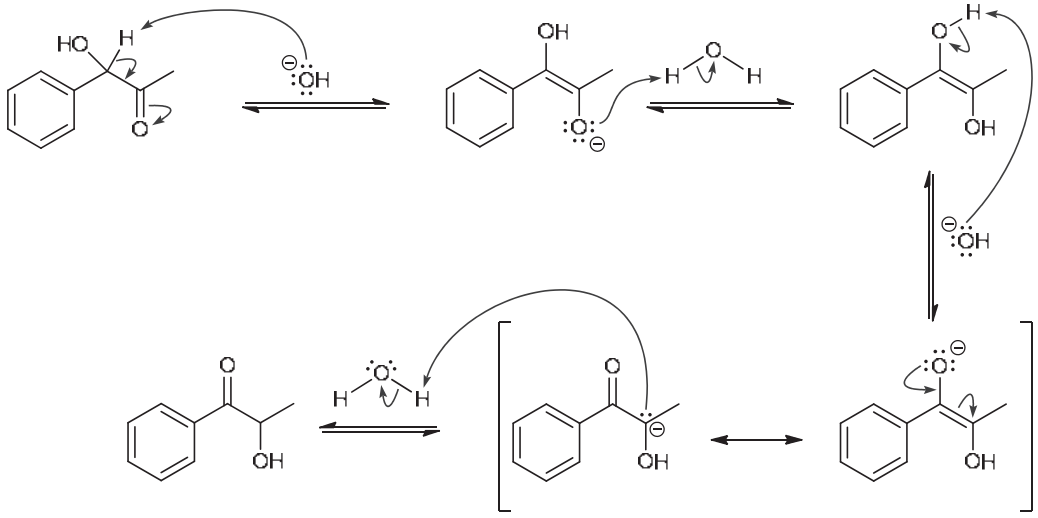


21.59. The carbonyl group is protonated, giving a resonance-stabilized intermediate that is then deprotonated to give an enol. Protonation of the enol results in a resonance-stabilized, benzylic carbocation intermediate that is then deprotonated to give the product.

In the product, the carbonyl group and the aromatic ring are conjugated. However, in the starting material, the carbonyl group and the aromatic ring are *not* conjugated. Formation of conjugation results in a decrease in energy which serves as a driving force for formation of the product.

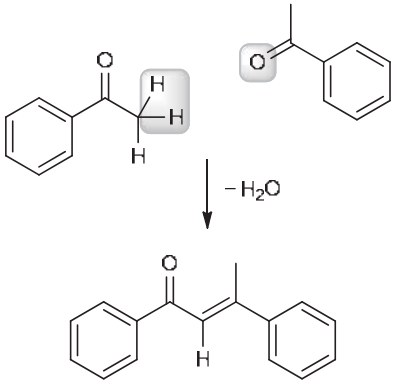


21.60. Hydroxide functions as a base and deprotonates the α position, giving a resonance-stabilized enolate (only the more significant resonance structure is drawn below) that is protonated to give an enol. The enol is then deprotonated to give another enolate ion, which is then protonated to give the product.

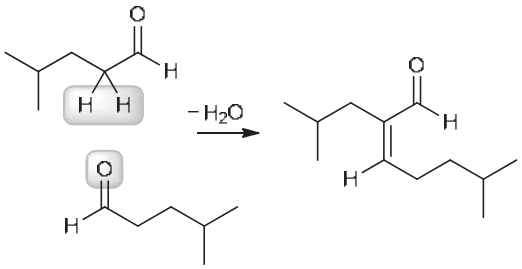


21.61.

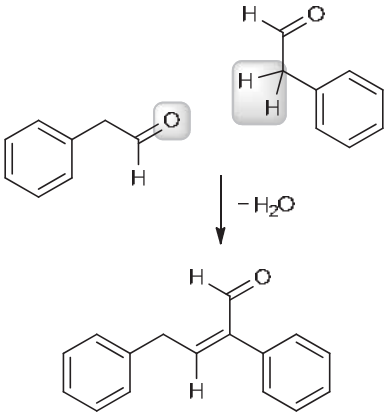
(a) This compound (acetophenone) has only one α position that bears protons. Two molecules of the ketone are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond. In this case, two stereoisomeric products are possible, and we draw the *E* isomer, rather than the *Z* isomer, because the former has fewer steric interactions.



(b) This compound is an aldehyde, so there is only one α position. Two molecules of the aldehyde are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond. In this case, two stereoisomeric products are possible, and we draw the isomer that exhibits fewer steric interactions.

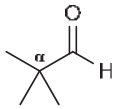


(c) This compound is an aldehyde, so there is only one α position. Two molecules of the aldehyde are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond. In this case, two stereoisomeric products are possible, and we draw the isomer that exhibits fewer steric interactions.



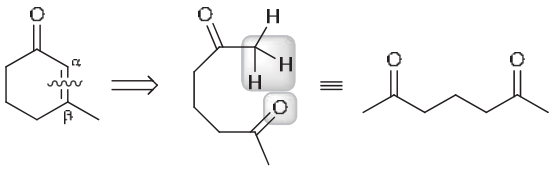
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21.62. Trimethylacetaldehyde does not have any α protons, and therefore, a base cannot deprotonate the α position (the first step of an aldol reaction). As such, this compound cannot undergo an aldol reaction.

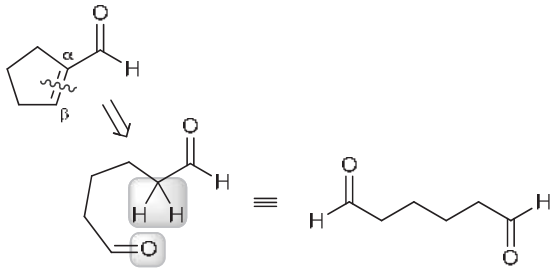


21.63.

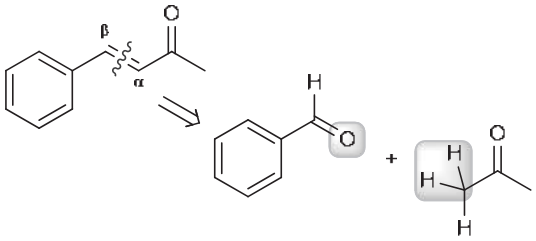
(a) First identify the carbon-carbon bond (indicated with a wavy line below) that is formed as a result of an aldol condensation. This double bond must have been formed via the loss of two hydrogen atoms and an oxygen atom. The β position of the condensation product must have originally been a carbonyl group in the starting material:



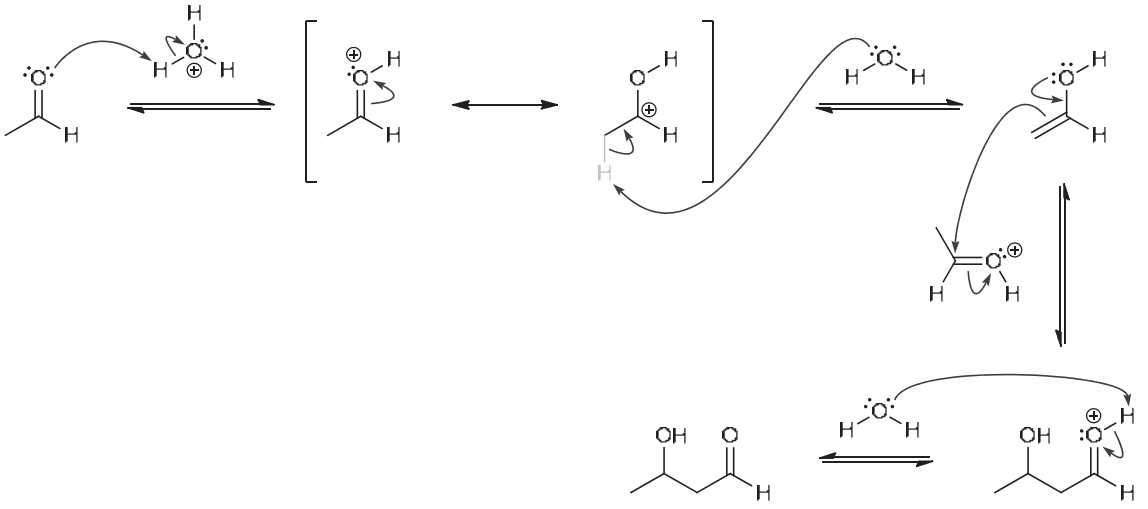
(b) First identify the carbon-carbon bond (indicated with a wavy line below) that is formed as a result of an aldol condensation. This double bond must have been formed via the loss of two hydrogen atoms and an oxygen atom. The β position of the condensation product must have originally been a carbonyl group in the starting material:



(c) First identify the carbon-carbon bond (indicated with a wavy line below) that is formed as a result of an aldol condensation. This double bond must have been formed via the loss of two hydrogen atoms and an oxygen atom. The β position of the condensation product must have originally been a carbonyl group in the starting material:



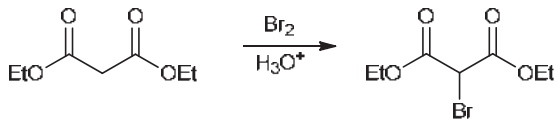
21.64. In acidic conditions, the nucleophilic agent must be an enol, rather than an enolate, because enolate ions are fairly basic and are therefore incompatible with acidic conditions. In the first step, the carbonyl group is protonated, giving a resonance-stabilized intermediate, which is then deprotonated at the α position to give an enol. The enol then functions as a nucleophile and attacks another protonated carbonyl group. The resulting resonance-stabilized cation is then deprotonated to give the aldol addition product.



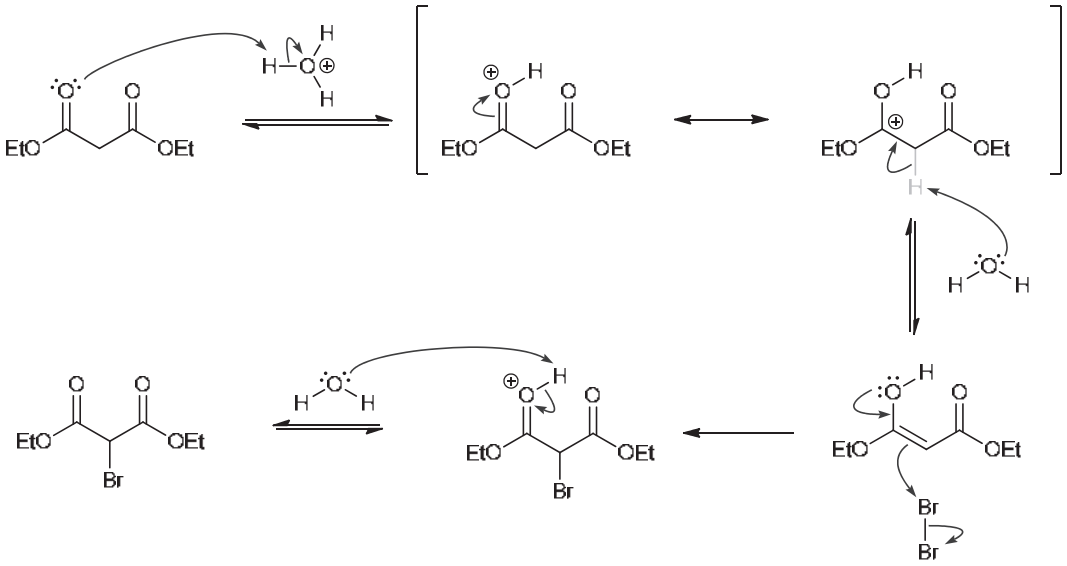
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21.65.

(a) In acidic conditions, the nucleophilic agent must be an enol, rather than an enolate, because enolate ions are fairly basic and are therefore incompatible with acidic conditions. The reaction still occurs at the α position, installing a bromine atom at that position (α-halogenation), giving the following product.

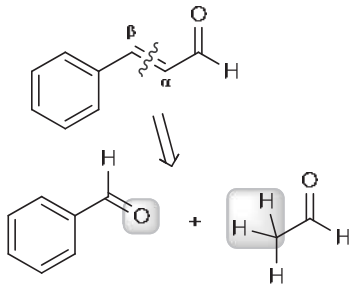


(b) In the first step, the carbonyl group is protonated, giving a resonance-stabilized intermediate, which is then deprotonated at the α position to give an enol. The enol then functions as a nucleophile and attacks molecular bromine (Br_2). The resulting resonance-stabilized cation is then deprotonated to give the product.

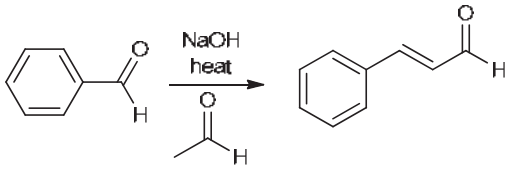


(c) The product should be more acidic than diethyl malonate because of the inductive effect of the bromine atom, which stabilizes the conjugate base.

21.66. Cinnamaldehyde is an α,β-unsaturated aldehyde, so it can be made via an aldol condensation. To determine the starting materials necessary, first identify the carbon-carbon bond (indicated with a wavy line below) that is formed as a result of an aldol condensation. This double bond must have been formed via the loss of two hydrogen atoms and an oxygen atom. The β position of the condensation product must have originally been a carbonyl group in the starting material:



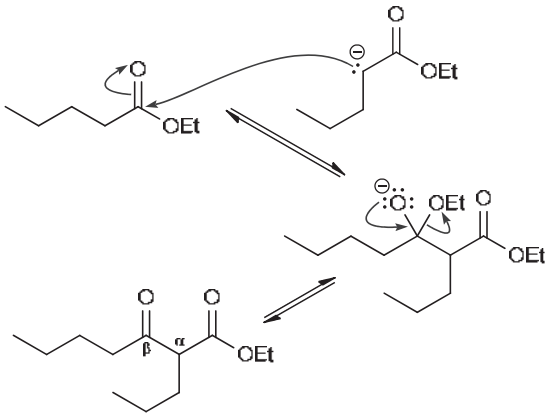
Therefore, cinnamaldehyde can be made from benzaldehyde and acetaldehyde, as shown:



21.67.

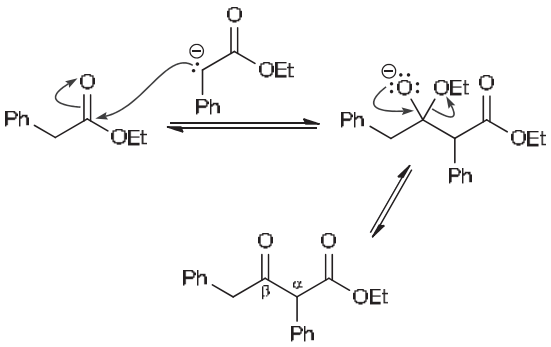
(a) The α position of one molecule of the ester is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the ester. As a result, a carbon-carbon bond is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, affording a β-ketoester, as shown:

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This product is deprotonated under the conditions of its formation, which is the reason for the acid work-up after the reaction is complete (to return the proton).

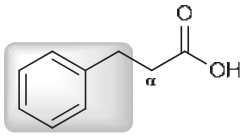
(b) The α position of one molecule of the ester is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the ester. As a result, a carbon-carbon bond is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, affording a β-ketoester, as shown:



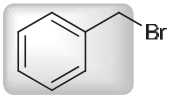
This product is deprotonated under the conditions of its formation, which is the reason for the acid work-up after the reaction is complete (to return the proton).

21.68.

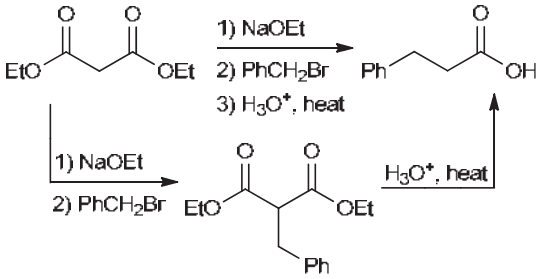
(a) The product is a carboxylic acid that has the following (highlighted) group connected to the α position:



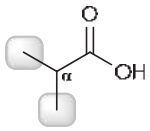
This group can be installed via a malonic ester synthesis, using benzyl bromide:



A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with benzyl bromide, thereby installing the alkyl group. Subsequent hydrolysis and decarboxylation give the product, as shown:

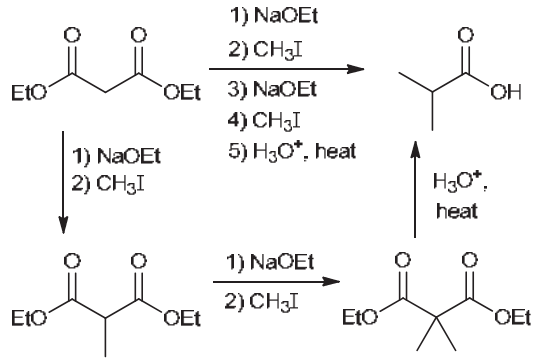


(b) The product is a carboxylic acid that has two methyl groups (highlighted) connected to the α position:

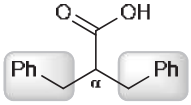


Each of these groups can be installed via a malonic ester synthesis, using methyl iodide. The reason for using methyl iodide (rather than methyl bromide) was discussed in the solution to Problem **21.31b**.

A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with methyl iodide, thereby installing the first methyl group. The second methyl group is installed in a similar way (deprotonation, followed by treatment with methyl iodide). Subsequent hydrolysis and decarboxylation give the product, as shown:

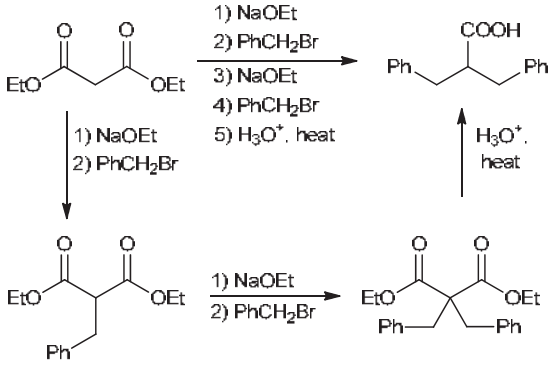


(c) The product is a carboxylic acid that has two benzyl groups (highlighted) connected to the α position:

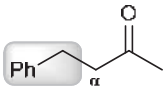


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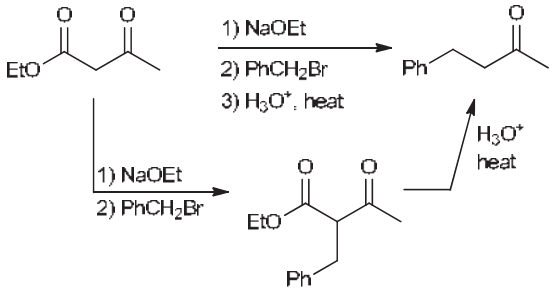
Each of these groups can be installed via a malonic ester synthesis, using benzyl bromide.
A malonic ester synthesis begins with the deprotonation of diethyl malonate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with benzyl bromide, thereby installing the first benzyl group. The second benzyl group is installed in a similar way (deprotonation, followed by treatment with benzyl bromide). Subsequent hydrolysis and decarboxylation give the product, as shown:



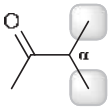
21.69.
(a) The product is a methyl ketone that has a benzyl group (highlighted) connected to the α position:



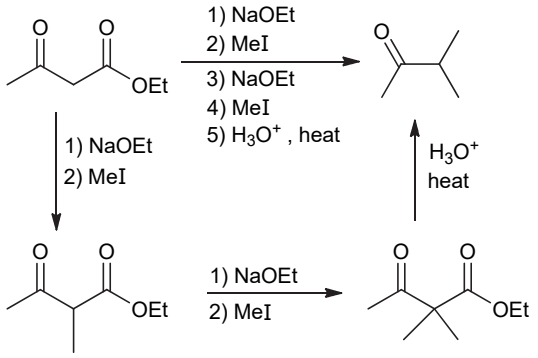
This group can be installed via an acetoacetic ester synthesis, using benzyl bromide.
An acetoacetic ester synthesis begins with the deprotonation of ethyl acetoacetate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with benzyl bromide, thereby installing a benzyl group. Subsequent hydrolysis and decarboxylation give the product, as shown:



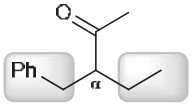
(b) The product is a methyl ketone that has two methyl groups (highlighted) connected to the α position:



Each of these groups can be installed via an acetoacetic ester synthesis, using methyl iodide to install each methyl group.
An acetoacetic ester synthesis begins with the deprotonation of ethyl acetoacetate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with methyl iodide, thereby installing the first methyl group. The second methyl group is installed in a similar way (deprotonation with a base, followed by alkylation). Subsequent hydrolysis and decarboxylation give the product, as shown:



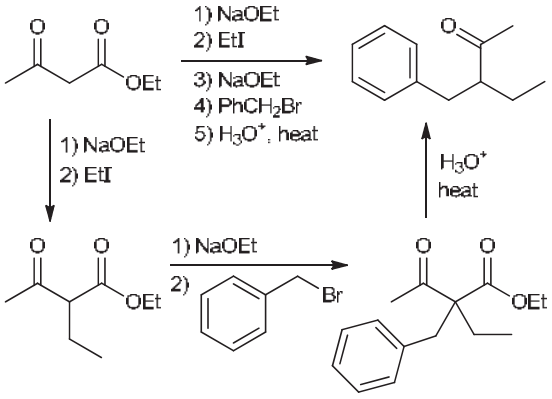
(c) The product is a methyl ketone that has the following two (highlighted) groups connected to the α position:



Each of these groups can be installed via an acetoacetic ester synthesis, using the following halides:

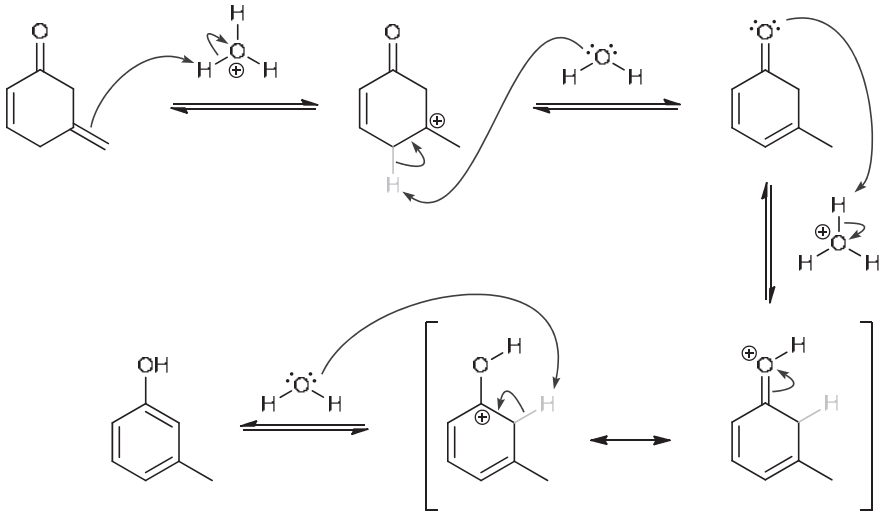


An acetoacetic ester synthesis begins with the deprotonation of ethyl acetoacetate (using ethoxide as a base). The resulting resonance-stabilized conjugate base is then treated with one of the halides above, to install one of the two groups. The other group is installed in a similar way (deprotonation with a base, followed by alkylation). Subsequent hydrolysis and decarboxylation give the product, as shown:



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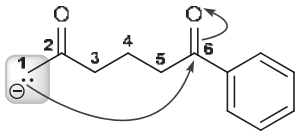
21.70. Protonation of the isolated π bond gives a tertiary carbocation, which is then deprotonated to give a fully conjugated system. Protonation of the carbonyl group then gives a resonance stabilized cation (there are two additional significant resonance structures that have not been drawn). This intermediate is then deprotonated to generate aromaticity, which is the driving force for this process.



21.71. The reaction conditions suggest an aldol condensation. This compound has three α positions. During an aldol condensation, one of the α positions must be deprotonated to give an enolate, which will attack the other carbonyl group (in an intramolecular process). But we must decide which of the three possible enolates gives rise to the product, as all three possible enolates are expected to be present at equilibrium. If either of the interior α positions is deprotonated to give an enolate ion, the resulting intramolecular attack would generate a four-membered ring:

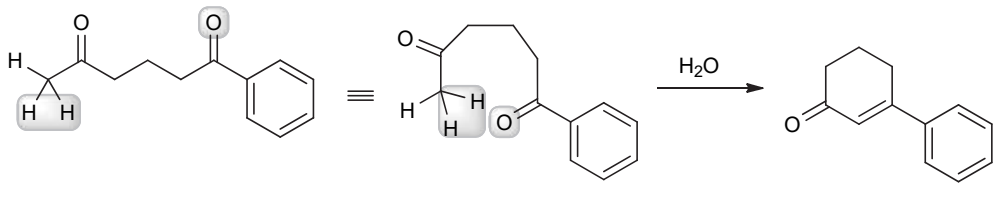


However, the third enolate can participate in an intramolecular attack that gives a six-membered ring:



Formation of a six-membered ring is favored over formation of a four-membered ring, because the former is relatively strain-free, while the latter is not (and therefore higher in energy).

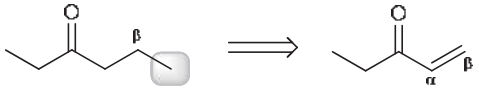
Now that we have identified which carbon-carbon bond will be formed during an intramolecular aldol condensation, we can draw the product by removing the following two highlighted α protons and the oxygen atom, and we replace them with a double bond, giving a product with the molecular formula $C_{12}H_{12}O$:



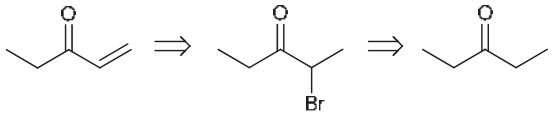
21.72. This transformation requires the installation of a methyl group at a β position:



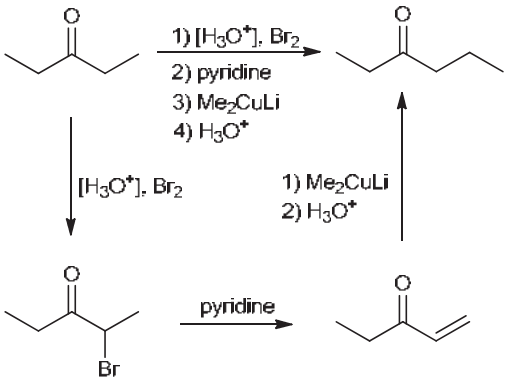
We did not learn a way to install a group at the β position of a saturated ketone, however, we did learn a way to install a methyl group at the β position of an α,β-unsaturated ketone:



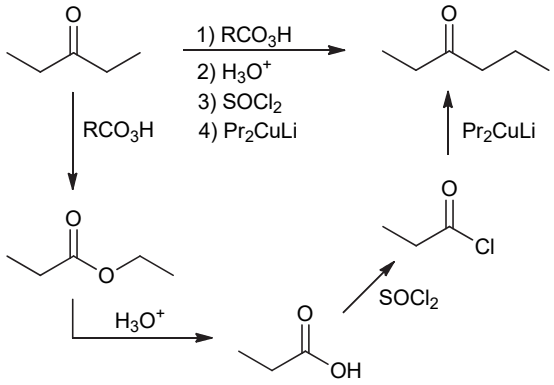
This α,β-unsaturated ketone can be prepared from the starting material via bromination at the α position under acidic conditions, thereby installing a leaving group, which can then be removed in an elimination process upon treatment with a base (pyridine):



The forward scheme is shown here:

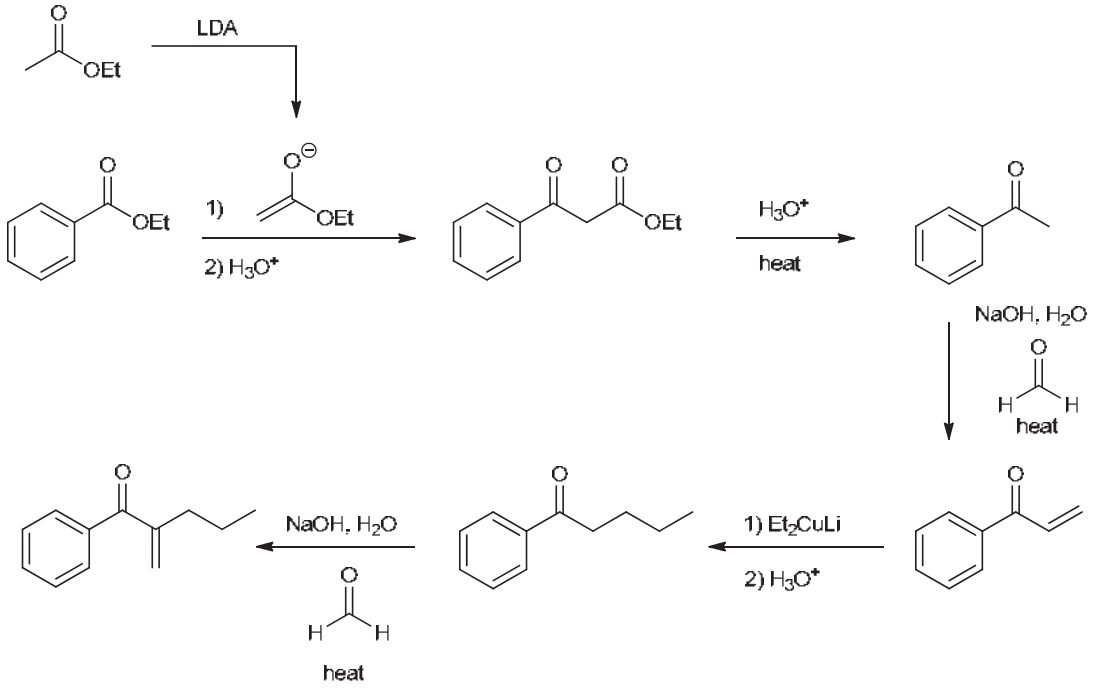


As mentioned so many times throughout this entire course, there are almost always multiple correct solutions to a synthesis problem. For example, in this case, the desired transformation can be achieved using several reactions from previous chapters. The starting ketone can be converted into an ester via a Baeyer-Villiger oxidation, followed by hydrolysis to give propanoic acid. This acid can then be converted to an acid chloride upon treatment with thionyl chloride, followed by conversion to the product upon treatment with lithium dipropyl cuprate:



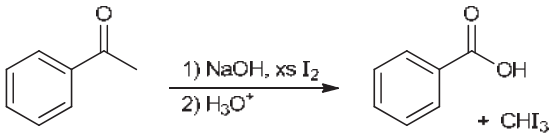
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21.73. The ester is converted into a β-ketoester via a crossed Claisen condensation. Upon treatment with aqueous acid at elevated temperature, the ester group is hydrolyzed and the resulting β-ketoacid (not drawn below) undergoes decarboxylation to give acetophenone. A crossed aldol condensation (with formaldehyde) gives an α,β-unsaturated ketone. Treating the α,β-unsaturated ketone with lithium diethyl cuprate, followed by water work-up, installs an ethyl group at the β position, and removes the unsaturation between the α and β positions. Another crossed aldol condensation (with formaldehyde again) gives the final product.

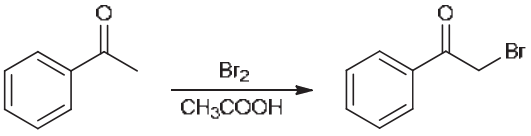


21.74.

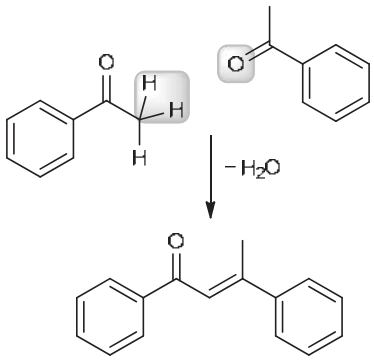
(a) The starting material is a methyl ketone, and the reagents indicate a haloform reaction, giving a carboxylic acid:



(b) The starting material is a ketone, and the reagents indicate α-bromination, which will only occur at an α position that bears protons. In this case, there is only one such position. Under these conditions, a bromine atom is installed at this α position, to give the following product:



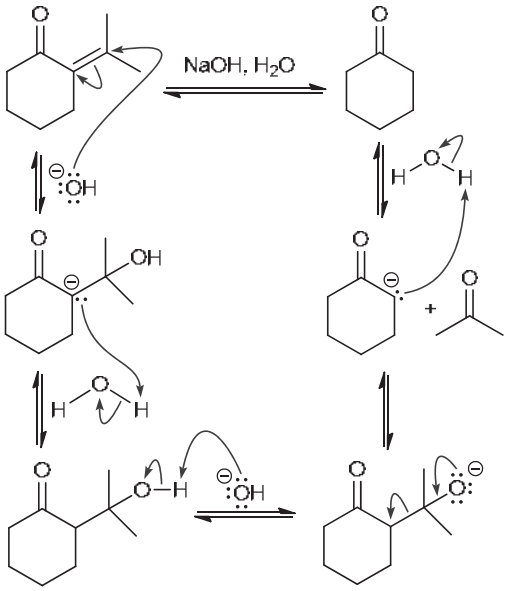
(c) The starting material is a ketone, and the reagents indicate an aldol condensation. The starting ketone has only one α position that bears protons, and the reaction occurs at this location. To draw the product, two molecules of the ketone are redrawn such that two α protons of one molecule are directly facing the carbonyl group of another molecule (highlighted). We then remove the two α protons and the oxygen atom, and we replace them with a double bond. In this case, two stereoisomers are possible, so we draw the product with fewer steric interactions:



21.75. This transformation represents a retro-aldol reaction, which occurs via a mechanism that is the reverse of an aldol condensation (all the same intermediates, but in reverse order). First a hydroxide ion functions as a nucleophile and attacks the electrophilic β position of the α,β-unsaturated ketone. The resulting enolate is then protonated to give a β-hydroxyketone. Deprotonation gives an alkoxide ion, which then reforms a carbonyl group by expelling an

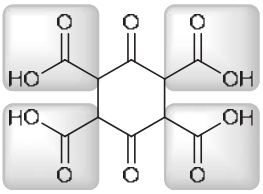
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enolate ion as a leaving group. This enolate ion is then protonated to give cyclohexanone. Notice that water is the proton source for the protonation steps, consistent with basic conditions (strong acids, such as hydronium ions, are not measurably present under these conditions).

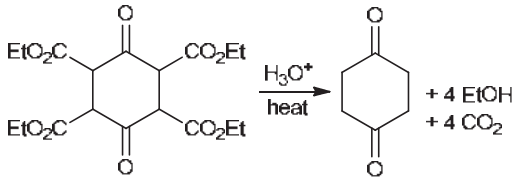


21.76.

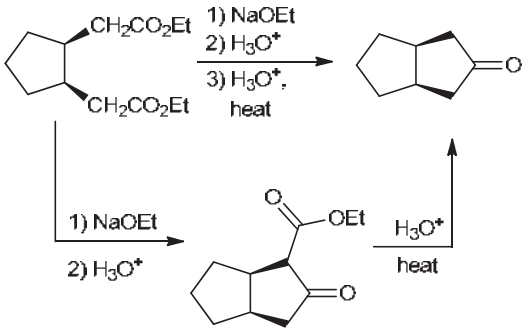
(a) Upon treatment with aqueous acid, each of the four ester groups is hydrolyzed, giving a compound with four carboxylic acid groups, shown here:



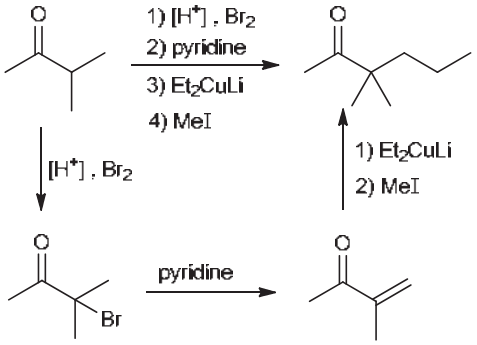
Each of these four carboxylic acid groups is β to a carbonyl group, and will therefore undergo decarboxylation upon heating. This gives the dione shown below, as well as four equivalents of ethanol (from hydrolysis) and four equivalents of carbon dioxide (from decarboxylation):



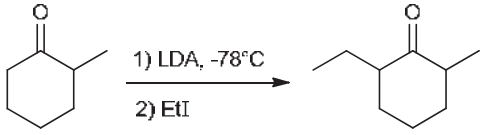
(b) The starting material is a diester. Upon treatment with ethoxide, an intramolecular Claisen condensation (followed by acid work-up) gives a β-ketoester via formation of a ring. Upon heating with aqueous acid, the β-ketoester is hydrolyzed to a β-ketoacid (not shown), which then undergoes decarboxylation (under the conditions of its formation) to give the ketone shown below. Notice that the configuration of each chiral center remains unchanged because the chiral centers are not involved in the reaction.



(c) The starting material is an unsymmetrical ketone. Treatment with bromine in aqueous acidic conditions gives α-bromination, which is expected to occur at the more substituted position. Subsequent treatment of the resulting α-bromoketone with pyridine (a base) gives an elimination reaction to afford an α,β-unsaturated ketone. Treatment of the α,β-unsaturated ketone with lithium diethyl cuprate, followed by methyl iodide, achieves the installation of an ethyl group at the β position and a methyl group at the α position:



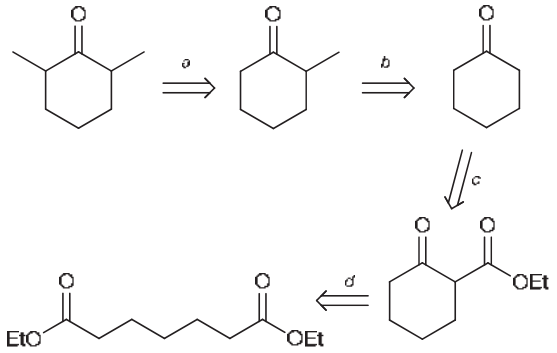
(d) The starting material is an unsymmetrical ketone, and LDA is a strong, sterically hindered base. At low temperature, LDA will irreversibly deprotonate the ketone at the less substituted α position to give the kinetic enolate. Subsequent treatment of the enolate with ethyl iodide will install an ethyl group at this α position:



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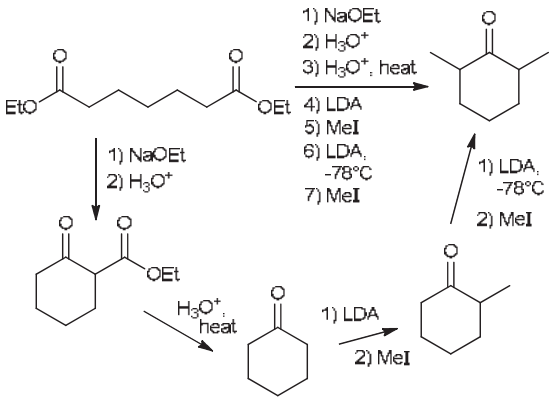
21.77.

(a) One strategy for achieving the desired transformation derives from the following retrosynthetic analysis. An explanation of each of the steps (*a-d*) follows.

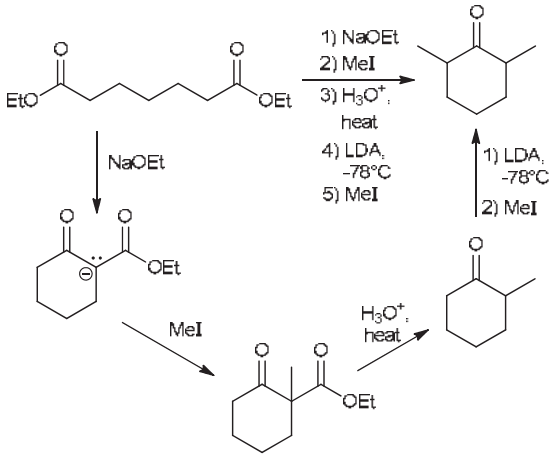


a. The product can be made from 2-methylcyclohexanone via alkylation of an α position (with LDA as the base, to control the regiochemical outcome).
b. 2-Methylcyclohexanone can be made from cyclohexanone via alkylation of an α position.
c. Cyclohexanone can be made from a β-ketoester via hydrolysis and subsequent decarboxylation.
d. The β-ketoester can be made from the starting material via a Dieckmann cyclization.

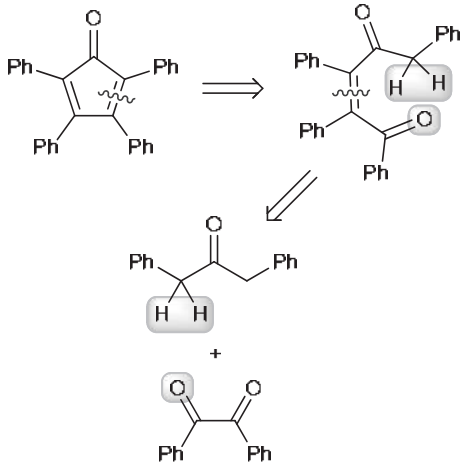
Now let's draw the forward scheme. Treating the starting diester with ethoxide, followed by acid work-up, gives a β-ketoester via a Dieckmann cyclization. Upon treatment with aqueous acid and heat, the β-ketoester is hydrolyzed to give a β-keto acid, which then undergoes decarboxylation to give cyclohexanone. Two subsequent alkylation processes will install the two methyl groups. The choice of base in the first alkylation is not so critical, because cyclohexanone is symmetrical (both α positions are identical). But during the second alkylation process, LDA must be used at low temperature, in order to install the methyl group at the less substituted α position (via the kinetic enolate).



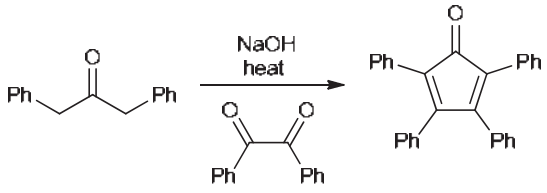
Alternatively, and perhaps more efficiently, installation of the first methyl group can be performed immediately after the Dieckmann cyclization (before hydrolysis and decarboxylation). In this way, the anionic product of the Dieckmann cyclization (without acid work-up) is used as a nucleophile to attack methyl iodide in an S_N2 process, thereby installing the first methyl group, as shown.



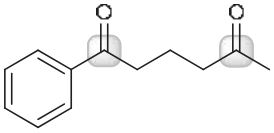
(b) The product can be made via two successive aldol condensation reactions, one of which is intramolecular and the other is intermolecular:



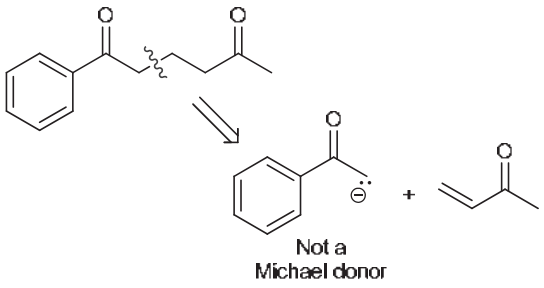
The entire transformation can be achieved in one reaction flask, by treating the starting material with the dione above in basic conditions.



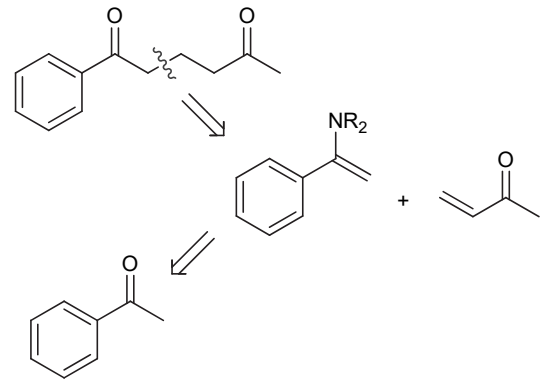
(c) The product is 1,5-difunctionalized:



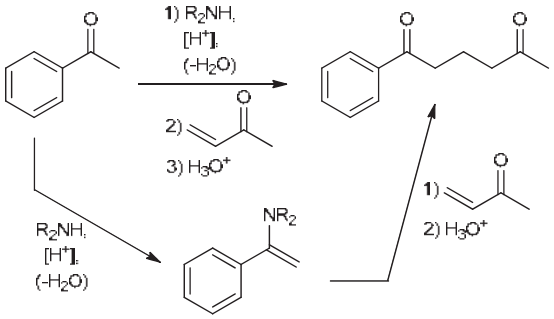
Therefore, we consider preparing the product via a Michael reaction:



This strategy will not work, because it involves the use of an enolate, which is not an efficient Michael donor. Therefore, we consider a Stork enamine synthesis (in which we use an enamine, rather than an enolate, as a Michael donor). The enamine can be made directly from the starting material (acetophenone).

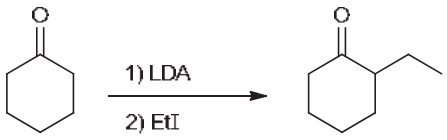


The forward scheme is shown here:

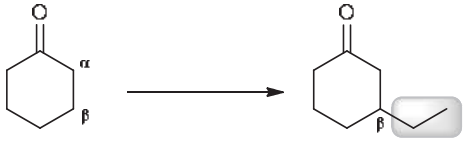


21.78.

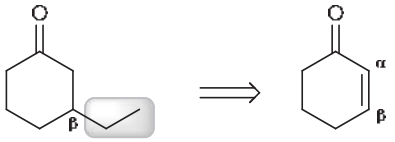
(a) This transformation involves installation of an ethyl group at the α position of a ketone. A strong base is used to deprotonate the α position, giving an enolate, which is then treated with ethyl iodide to give the product via an S_N2 reaction.



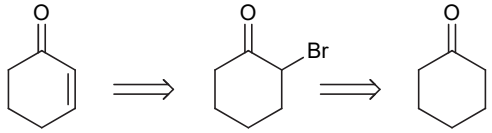
(b) This transformation requires the installation of an ethyl group at a β position:



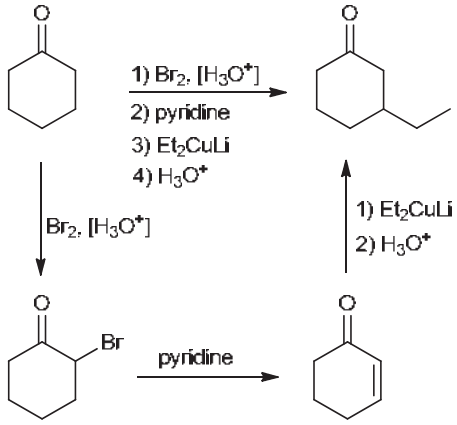
We did not learn a way to install an alkyl group at the β position of a saturated ketone, however, we did learn a way to install an alkyl group at the β position of an α,β-unsaturated ketone:



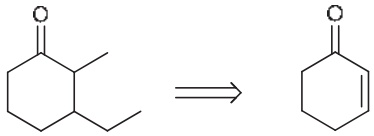
This α,β-unsaturated ketone can be prepared from the corresponding α-bromoketone upon treatment with a base (pyridine). And the α-bromoketone can be made from the starting material via α-bromination under acidic conditions:



The forward scheme is shown here:

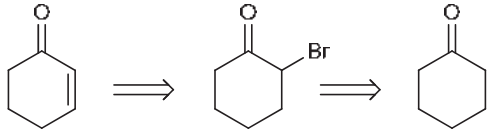


(c) The product is a ketone with alkyl groups at the α and β positions, which could have been installed by treating the following α,β-unsaturated ketone with lithium diethyl cuprate, followed by methyl iodide:

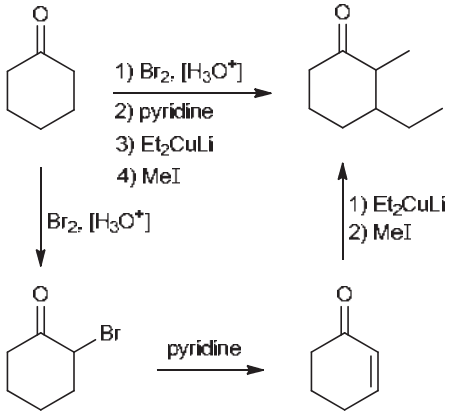


This α,β-unsaturated ketone can be prepared from the corresponding α-bromoketone upon treatment with a base (pyridine). And the α-bromoketone can be made

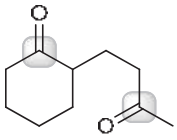
from the starting material via α-bromination under acidic conditions:



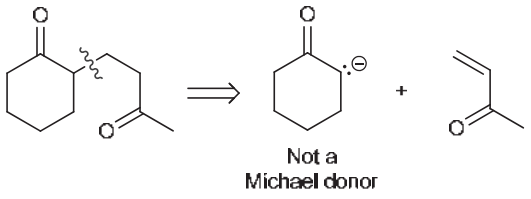
The forward scheme is shown here:



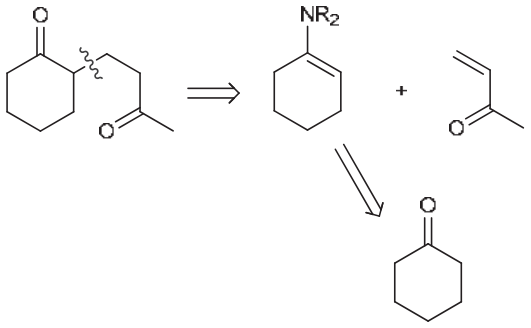
(d) The product is 1,5-difunctionalized:



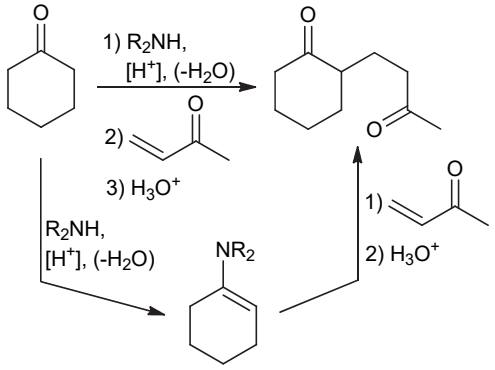
Therefore, we consider preparing the product via a Michael reaction:



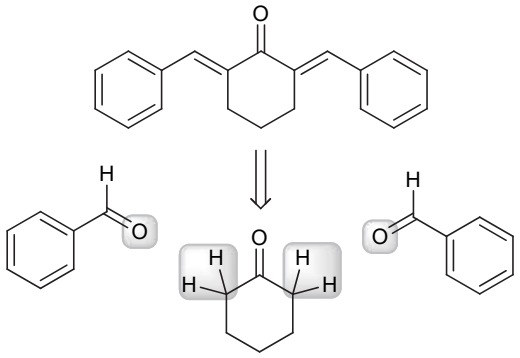
This strategy will not work, because it involves the use of an enolate, which is not an efficient Michael donor. Therefore, we consider a Stork enamine synthesis (in which we use an enamine, rather than an enolate, as a Michael donor). The enamine can be made from the starting ketone upon treatment with a secondary amine under acid-catalyzed conditions (with removal of water):



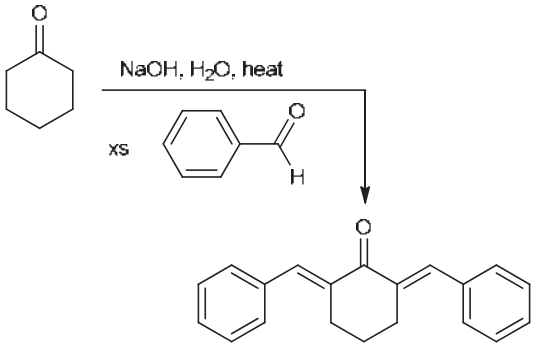
The forward scheme is shown here:



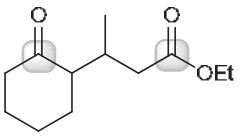
(e) The product is a ketone that exhibits α,β-unsaturation on either side of the carbonyl group. This suggests two aldol condensation reactions, one at each α position of the starting ketone (cyclohexanone):



Both aldol condensation reactions can be performed in a single reaction flask, by treating cyclohexanone with excess benzaldehyde under basic conditions:

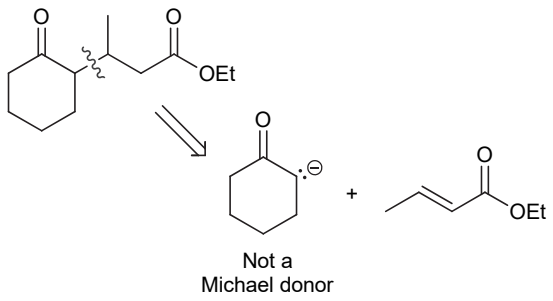


(f) The product is 1,5-difunctionalized:

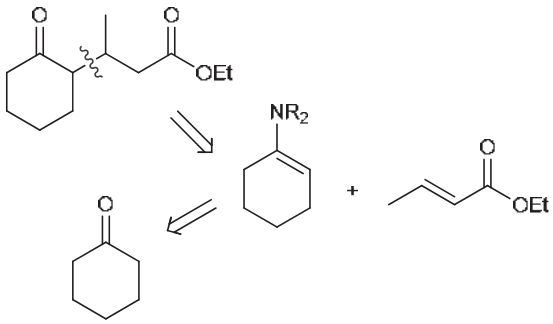


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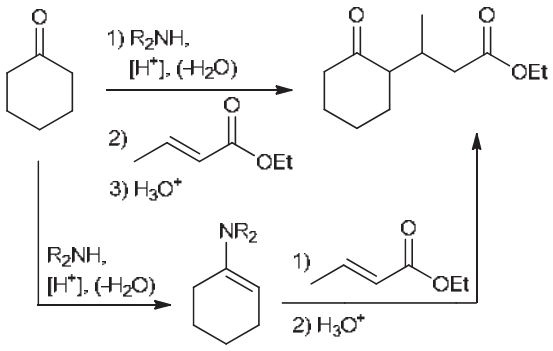
Therefore, we consider preparing the product via a Michael reaction:



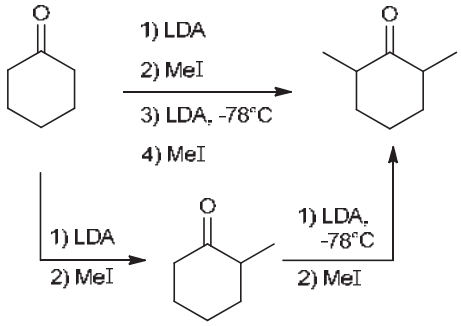
This strategy will not work, because it involves the use of an enolate, which is not an efficient Michael donor. Therefore, we consider a Stork enamine synthesis (in which we use an enamine, rather than an enolate, as a Michael donor). The enamine can be made from the starting ketone upon treatment with a secondary amine under acid-catalyzed conditions (with removal of water):



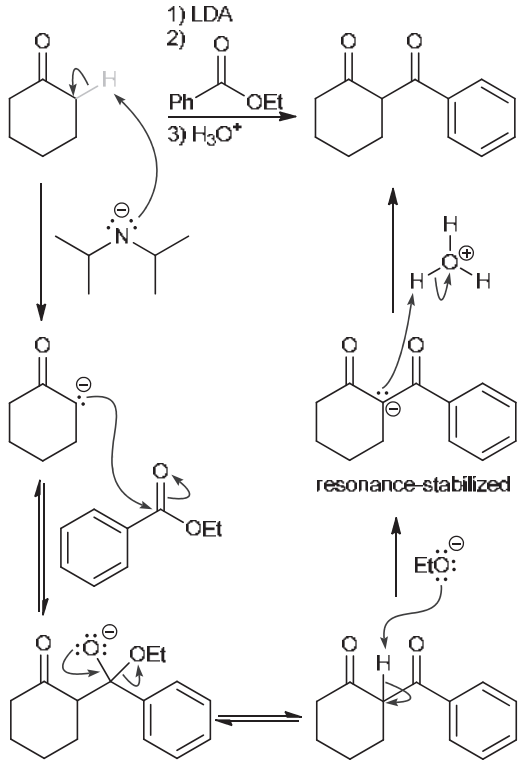
The forward scheme is shown here:



(g) Two subsequent alkylation processes will install the two methyl groups. The choice of base in the first alkylation is not so critical, because cyclohexanone is symmetrical (both α positions are identical). But during the second alkylation process, LDA must be used at low temperature, in order to install the methyl group at the less substituted α position (via the kinetic enolate).



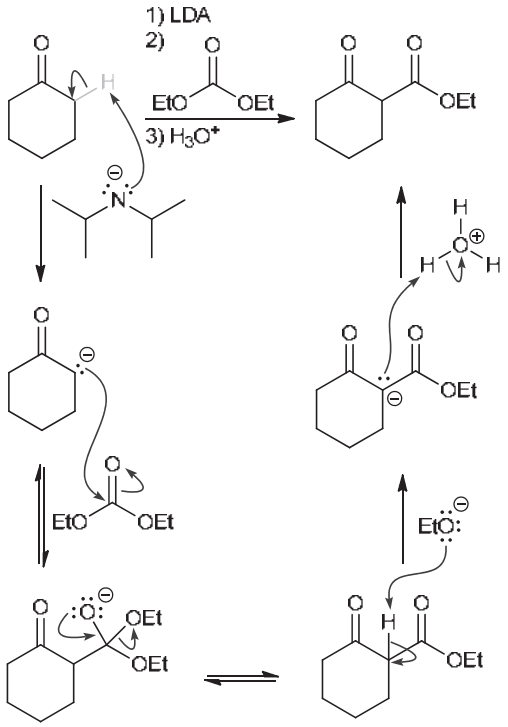
21.79. LDA is a strong, sterically hindered base, and it will irreversibly deprotonate the cyclohexanone (at the α position) to give an enolate. The ketone is symmetrical, so deprotonation at either α position leads to the same enolate ion. When treated with an ester, the enolate ion will attack the ester, to give a tetrahedral intermediate, which reforms the carbonyl group by expelling ethoxide. The resulting β-dicarbonyl compound is then deprotonated to give a doubly-stabilized enolate. Indeed, the formation of this resonance-stabilized anion is a driving force for this reaction. After the reaction is complete, an acid is required to protonate this anion.



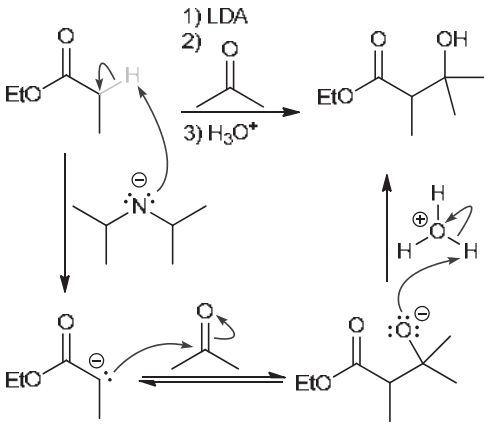
21.80. LDA is a strong, sterically hindered base, and it will irreversibly deprotonate the cyclohexanone (at the α position) to give an enolate. The ketone is symmetrical, so deprotonation at either α position leads to the same enolate ion. When treated with a carbonate, the enolate ion will attack the carbonate, to give a tetrahedral

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intermediate, which reforms the carbonyl group by expelling ethoxide. The resulting β-ketoester is then deprotonated to give a doubly-stabilized enolate. Indeed, the formation of this resonance-stabilized anion is a driving force for this reaction. After the reaction is complete, an acid is required to protonate this anion.

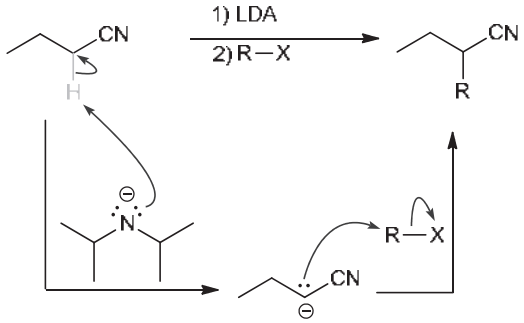


21.81. LDA is a strong, sterically hindered base, and it will irreversibly deprotonate the ester (at the α position) to give an ester enolate. When treated with a ketone, the enolate ion will attack the ketone, to give an alkoxide ion. After the reaction is complete, an acid is required to protonate this alkoxide ion.

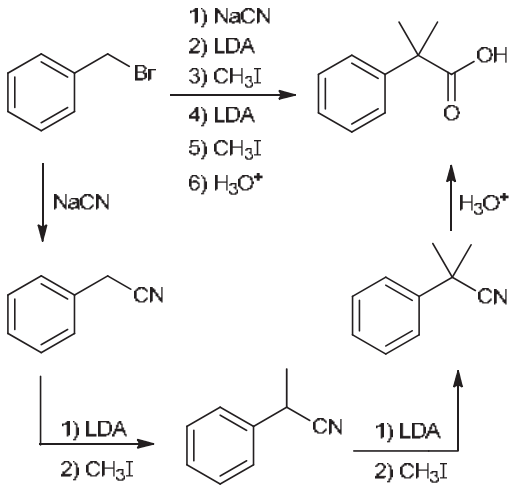


21.82.

(a) The following mechanism is consistent with the description in the problem statement.

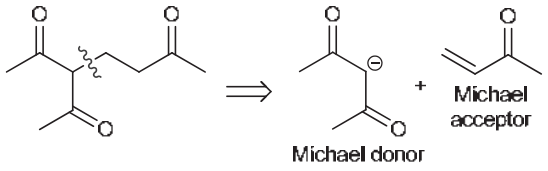


(b) Benzyl bromide is converted into a nitrile (via an S_N2 reaction in which cyanide functions as a nucleophile). This nitrile can then undergo two successive alkylation processes, installing two methyl groups at the α position. Hydrolysis of the nitrile then gives a carboxylic acid.

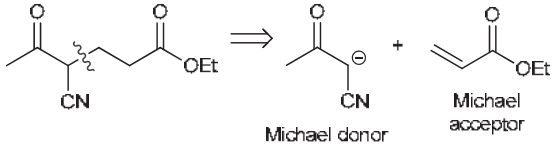


21.83.

(a) A retrosynthetic analysis reveals the Michael donor (stabilized nucleophile) and Michael acceptor that are responsible for formation of the carbon-carbon bond that is indicated with a wavy line:

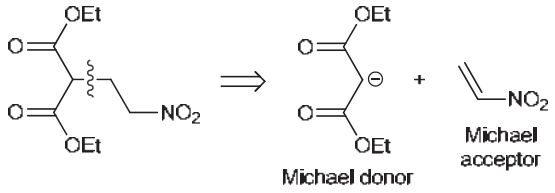


(b) A retrosynthetic analysis reveals the Michael donor (stabilized nucleophile) and Michael acceptor that are responsible for formation of the carbon-carbon bond that is indicated with a wavy line:

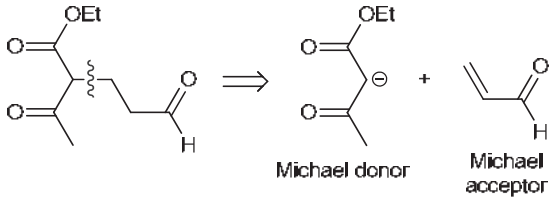


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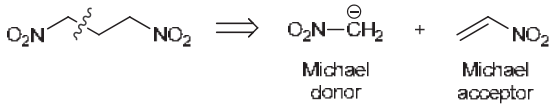
(c) A retrosynthetic analysis reveals the Michael donor (stabilized nucleophile) and Michael acceptor that are responsible for formation of the carbon-carbon bond that is indicated with a wavy line:



(d) A retrosynthetic analysis reveals the Michael donor (stabilized nucleophile) and Michael acceptor that are responsible for formation of the carbon-carbon bond that is indicated with a wavy line:

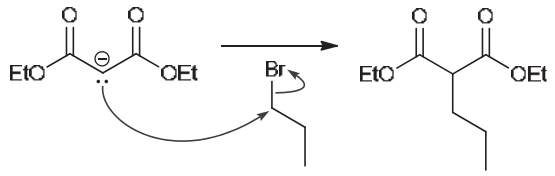


(e) A retrosynthetic analysis reveals the Michael donor (stabilized nucleophile) and Michael acceptor that are responsible for formation of the carbon-carbon bond that is indicated with a wavy line:

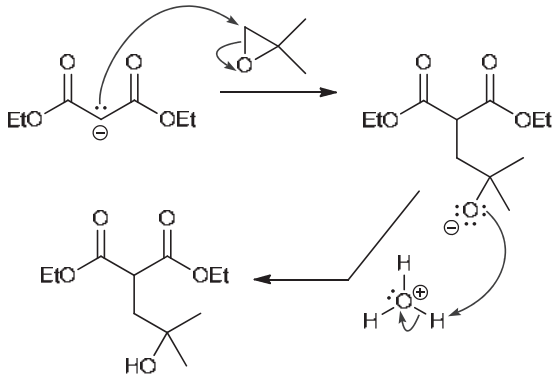


21.84.

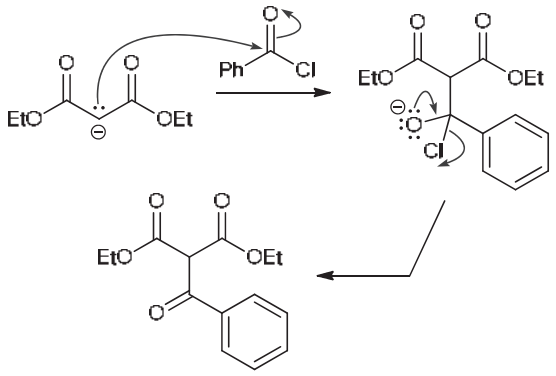
(a) The conjugate base of diethyl malonate functions as a nucleophile and attacks propyl bromide in an S_N2 process, expelling bromide as a leaving group, and giving the following product:



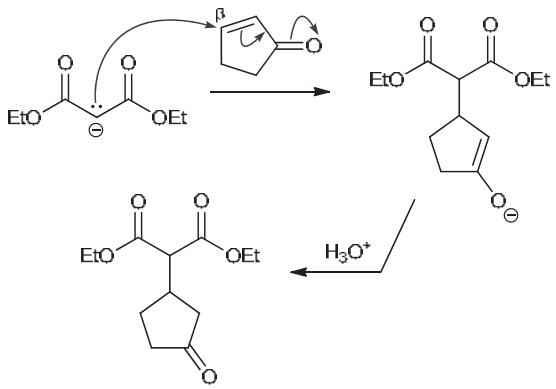
(b) The conjugate base of diethyl malonate functions as a nucleophile and attacks the epoxide at the less substituted (more accessible) position, thereby opening the epoxide and forming an alkoxide ion. Acid work-up converts the alkoxide ion into an alcohol, as shown:



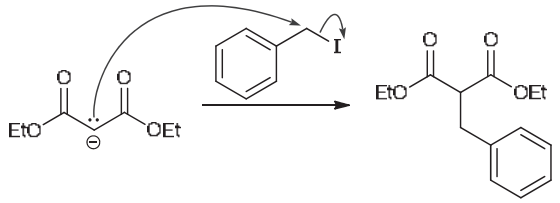
(c) The conjugate base of diethyl malonate functions as a nucleophile and attacks the acid chloride to give a tetrahedral intermediate, which expels a chloride ion to reform a carbonyl group (via a nucleophilic acyl substitution reaction):



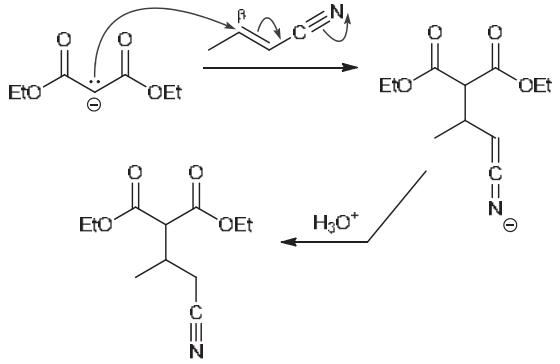
(d) The conjugate base of diethyl malonate functions as a nucleophile and attacks the β position of the α,β-unsaturated ketone. The resulting enolate is converted back into a ketone upon treatment with aqueous acid, giving the following product:



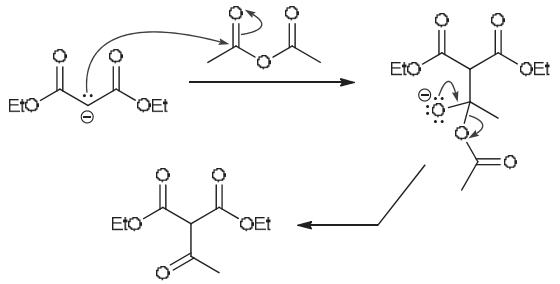
(e) The conjugate base of diethyl malonate functions as a nucleophile and attacks benzyl iodide in an S_N2 process, expelling iodide as a leaving group, and giving the following product:



(f) The conjugate base of diethyl malonate functions as a nucleophile and attacks the β position of the α,β-unsaturated nitrile. The resulting intermediate is converted back into a nitrile upon acid work-up, giving the following product:

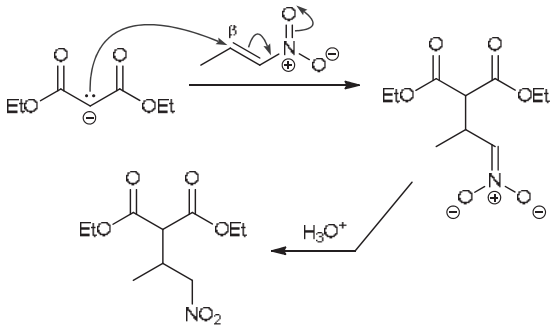


(g) The conjugate base of diethyl malonate functions as a nucleophile and attacks the acid anhydride to give a tetrahedral intermediate, which expels an acetate ion to reform a carbonyl group (via a nucleophilic acyl substitution reaction):

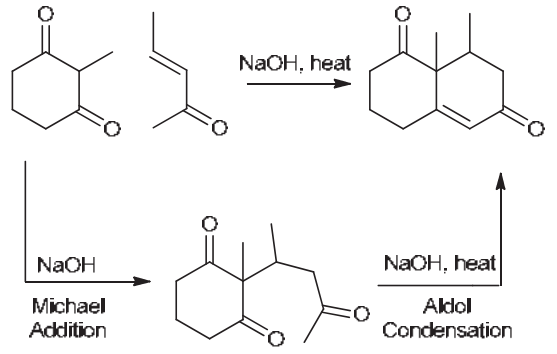


This compound is deprotonated under these conditions (by the acetate ion, which can function as a base), which serves as a driving forced to push the reaction to completion. Then, acid workup gives the proton back, regenerating the product shown above.

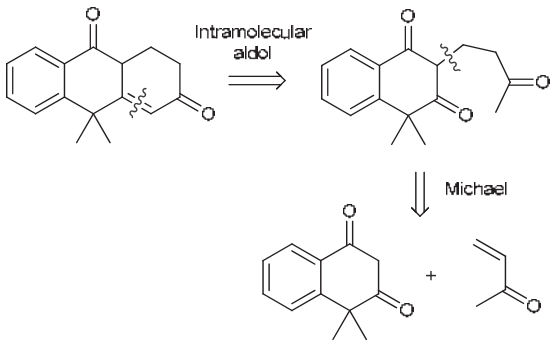
(h) The conjugate base of diethyl malonate functions as a nucleophile and attacks the β position of the α,β-unsaturated nitro compound. The resulting intermediate is converted back into a nitro compound upon acid work-up, giving the following product:



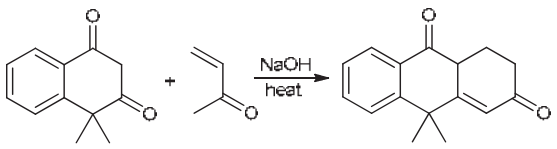
21.85. A Robinson annulation is comprised of a Michael addition, followed by an intramolecular aldol condensation, as shown:



21.86. A Robinson annulation is comprised of a Michael reaction, followed by an intramolecular aldol condensation. To determine the starting materials necessary to prepare the desired product via a Robinson annulation, we draw the following retrosynthetic analysis:

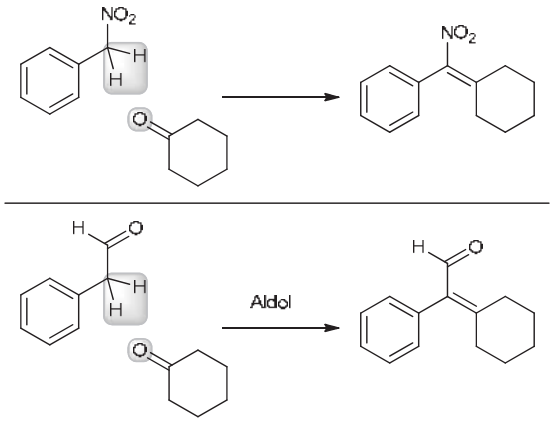


These two steps do not represent two separate reactions. A Robinson annulation can be performed in one reaction flask, as shown in the following forward scheme:

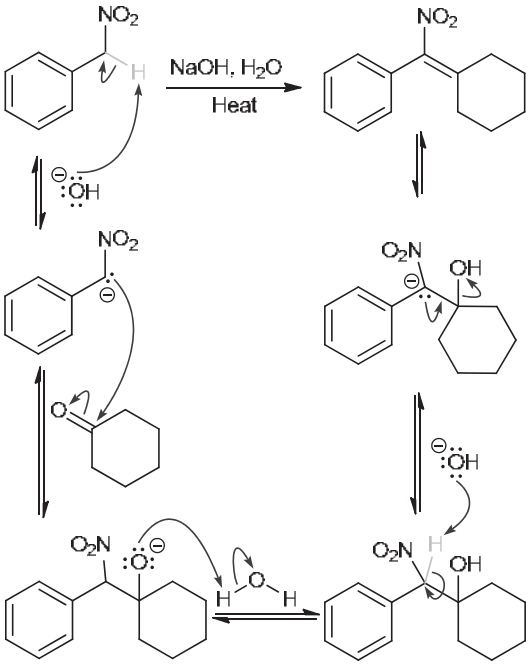


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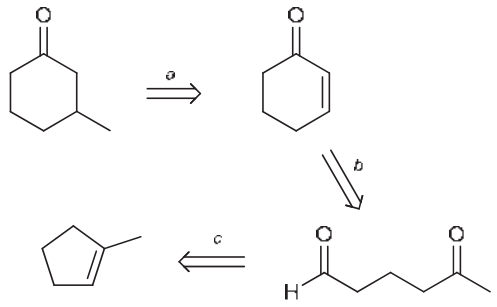
21.87. Notice the similarity between this transformation and an aldol condensation:



Indeed, we will draw a mechanism (below) that is extremely similar to the mechanism of an aldol condensation. In the first step, hydroxide functions as a base and deprotonates the position adjacent to the nitro group, giving a resonance-stabilized conjugate base (much like an enolate). This conjugate base can function as a nucleophile and attack cyclohexanone, giving an alkoxide ion. Protonation of the alkoxide ion gives an alcohol. Deprotonation, followed by loss of hydroxide, gives the product. Notice that the protonation step employs water as the proton source, consistent with basic conditions (strong acids, such as hydronium, are not measurably present):



21.88. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

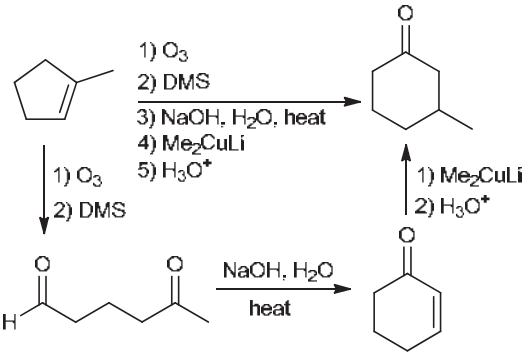


a. The product has seven carbon atoms, while the starting material only has six carbon atoms. The extra carbon atom can be installed in the last step of the synthesis, via a Michael addition (between a lithium dialkyl cuprate and an α,β-unsaturated ketone).

b. The α,β-unsaturated ketone can be made via an intramolecular aldol condensation, starting the appropriate dicarbonyl compound.

c. The dicarbonyl compound can be made from the starting material via ozonolysis.

Now let's draw the forward scheme:

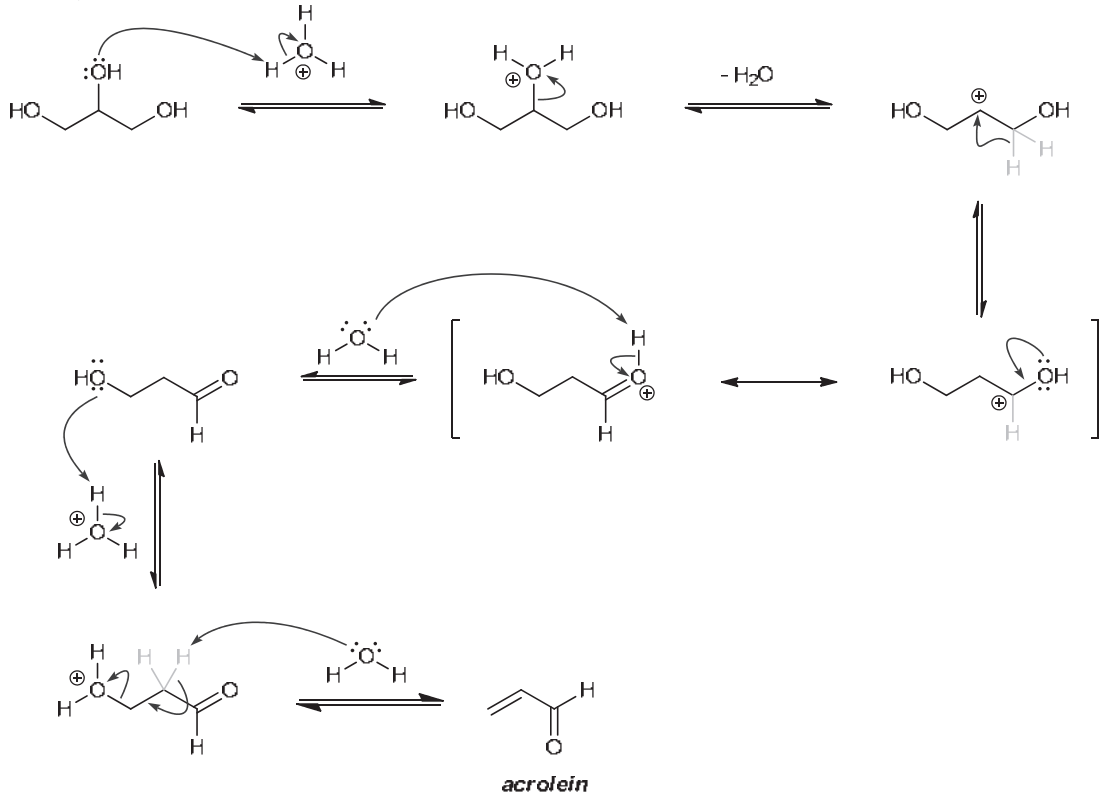


21.89. A ketone generally produces a strong signal at approximately 1720 cm^{-1} (C=O stretching), while an alcohol produces a broad signal between 3200 and 3600 cm^{-1} (O-H stretching). These regions of an IR spectrum can be inspected to determine whether the ketone or the enol predominates.

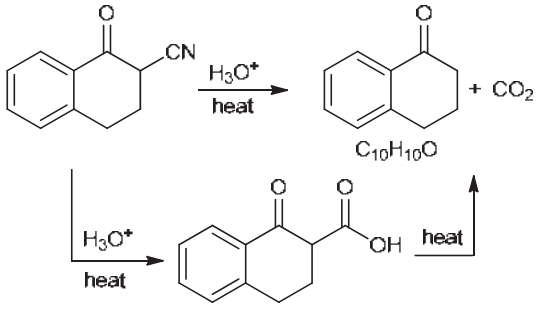
21.90. Under acidic conditions, one of the OH groups is protonated. If the middle OH group is protonated, the resulting leaving group (water) can leave to give a secondary carbocation. A hydride shift then gives a resonance-stabilized cation that is deprotonated to give a hydroxyaldehyde. Protonation of the OH group (to give a good leaving group), followed by an E2 process, gives the product. In this last step, an E2 process is more likely than an E1 process,

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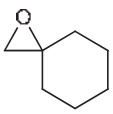
because the latter would involve formation of a primary carbocation. Notice that water is the base for the deprotonation steps, consistent with acidic conditions (strong bases, such as hydroxide, are not measurably present under these conditions).



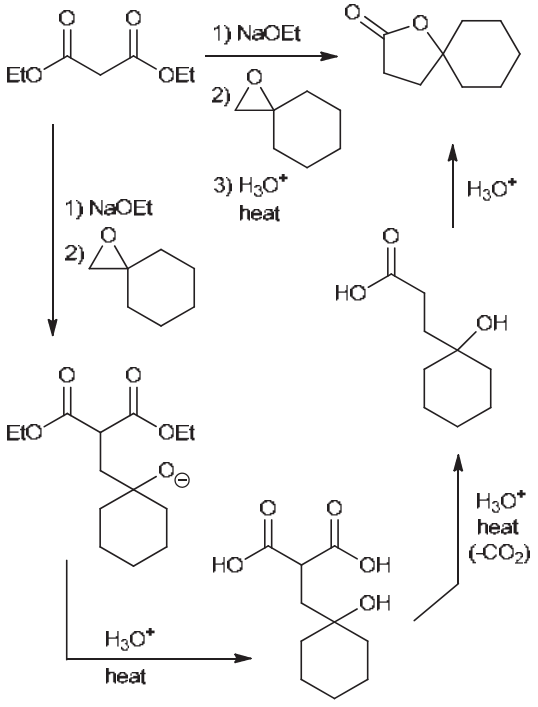
21.91. Upon treatment with aqueous acid, the nitrile is hydrolyzed to give a β-ketoacid, which undergoes decarboxylation at elevated temperature to give the following ketone:



21.92. Using the strategy described in the problem statement, the desired lactone can be made if we use the following epoxide, instead of ethylene oxide:

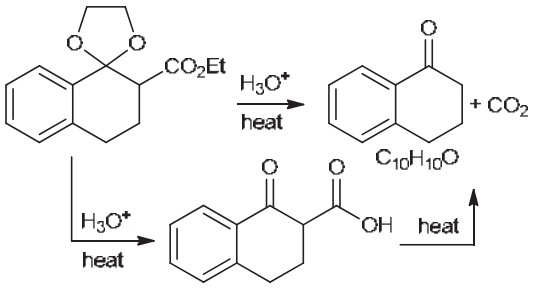


The synthesis, as described in the problem statement, is shown here (follow the location of the cyclohexyl group):



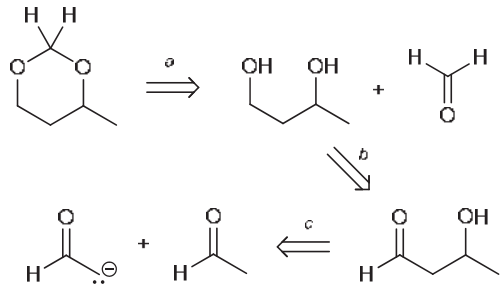
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21.93. Upon treatment with aqueous acid at elevated temperature, the ester group is hydrolyzed to a carboxylic acid group, and the acetal is hydrolyzed to a ketone. Under these conditions, the resulting β-keto acid undergoes decarboxylation to give the ketone shown below:



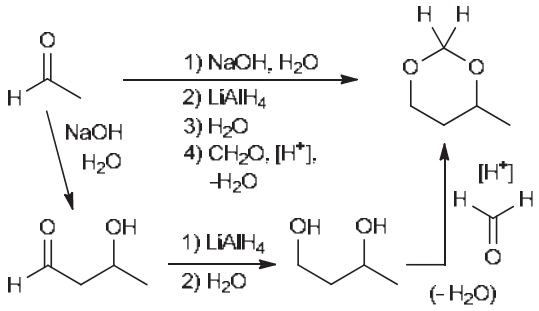
21.94.

(a) One strategy for achieving the desired transformation derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.

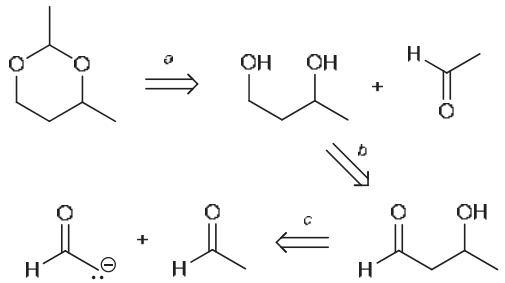


a. The product is a cyclic acetal, which can be prepared from a diol and formaldehyde.
b. The diol can be made via reduction of a β-hydroxyaldehyde.
c. The β-hydroxyaldehyde can be made via an aldol addition reaction between two molecules of acetaldehyde.

Now let's draw the forward scheme. Upon treatment with sodium hydroxide, acetaldehyde will undergo an aldol addition reaction, giving a β-hydroxyaldehyde. Reduction with $LiAlH_4$, followed by water work-up, gives a diol, which can be then be converted into the desired acetal upon treatment with formaldehyde in acid-catalyzed conditions (with removal of water).

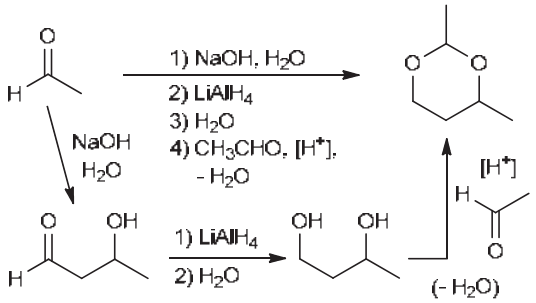


(b) One strategy for achieving the desired transformation derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*c*) follows.



a. The product is a cyclic acetal, which can be prepared from a diol and acetaldehyde.
b. The diol can be made via reduction of a β-hydroxyaldehyde.
c. The β-hydroxyaldehyde can be made via an aldol addition reaction between two molecules of acetaldehyde.

Now let's draw the forward scheme. Upon treatment with sodium hydroxide, acetaldehyde will undergo an aldol addition reaction, giving a β-hydroxyaldehyde. Reduction with $LiAlH_4$, followed by water work-up, gives a diol, which can be then be converted into the desired acetal upon treatment with acetaldehyde in acid-catalyzed conditions (with removal of water).



21.95.

When treated with aqueous acid, both compound **A** and compound **B** undergo racemization at the α position (via the enol as an intermediate). Each of these compounds establishes an equilibrium between *cis* and *trans* isomers. But the position of equilibrium is very different for

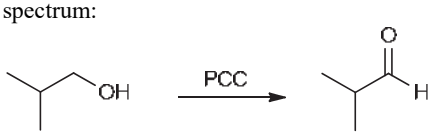
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compound **A** than it is for compound **B**. The equilibrium for compound **A** favors a *cis* configuration, because that is the configuration for which the compound can adopt a chair conformation in which both groups occupy equatorial positions. The equilibrium for compound **B** favors a *trans* configuration, because that is the configuration for which that compound can adopt a chair conformation in which both groups occupy equatorial positions.

21.96. The problem statement indicates that oxidation of the alcohol with PCC gives an aldehyde, which indicates that the alcohol must be primary. There are only two primary alcohols with the molecular formula $C_4H_{10}O$:



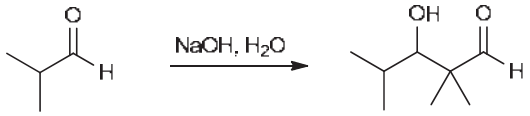
Oxidation of the first compound (1-butanol) gives 1-butanal, which is expected to produce four signals in its ^{1}H NMR spectrum. In contrast, oxidation of the second compound (2-methyl-1-propanol) is expected to produce an aldehyde that exhibits only three signals in its ^{1}H NMR spectrum:



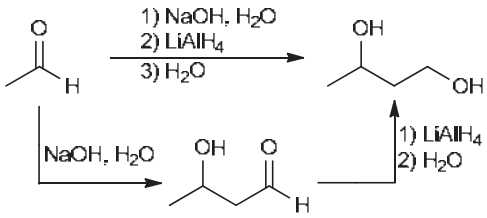
Upon treatment with aqueous sodium hydroxide, this aldehyde is deprotonated to give an enolate ion that can function as a nucleophile and attack the carbonyl group of another molecule of the aldehyde:



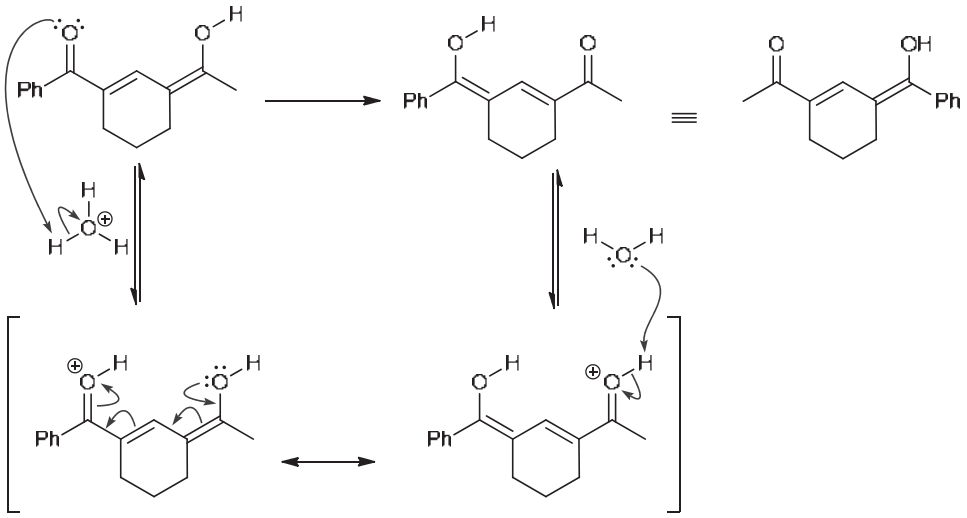
As a result, a carbon-carbon bond is formed. The resulting alkoxide ion is then protonated to give a β-hydroxy aldehyde, as shown:



21.97. Treatment of acetaldehyde with aqueous sodium hydroxide results in a β-hydroxy aldehyde that can be converted into the desired diol via reduction with $LiAlH_4$, followed by water work-up, as shown:

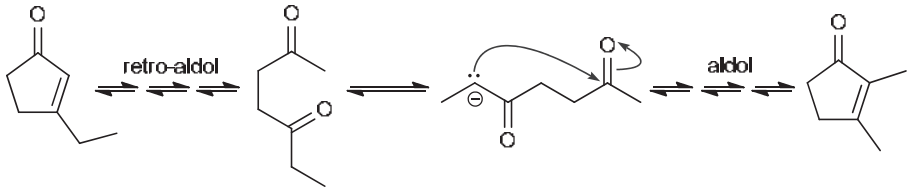


21.98. Protonation of the carbonyl group gives a resonance-stabilized cation, which is then deprotonated to give the product. This process is an example of tautomerization:

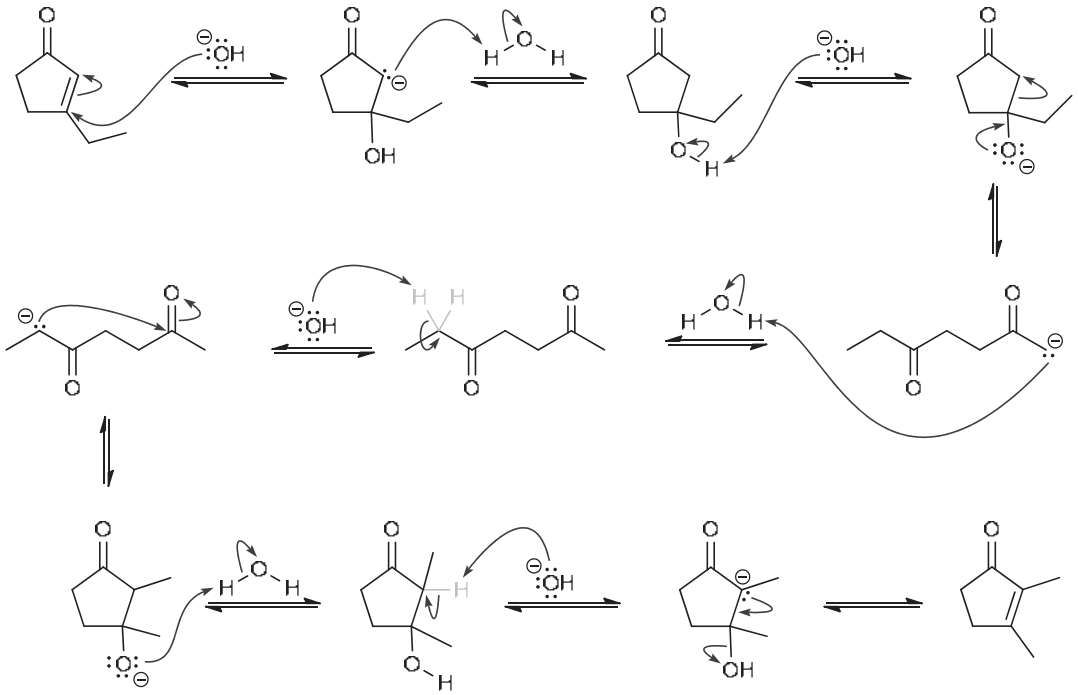


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21.99. A retro-aldol reaction opens the ring into an acyclic diketone, which then closes up again via an intramolecular aldol condensation:



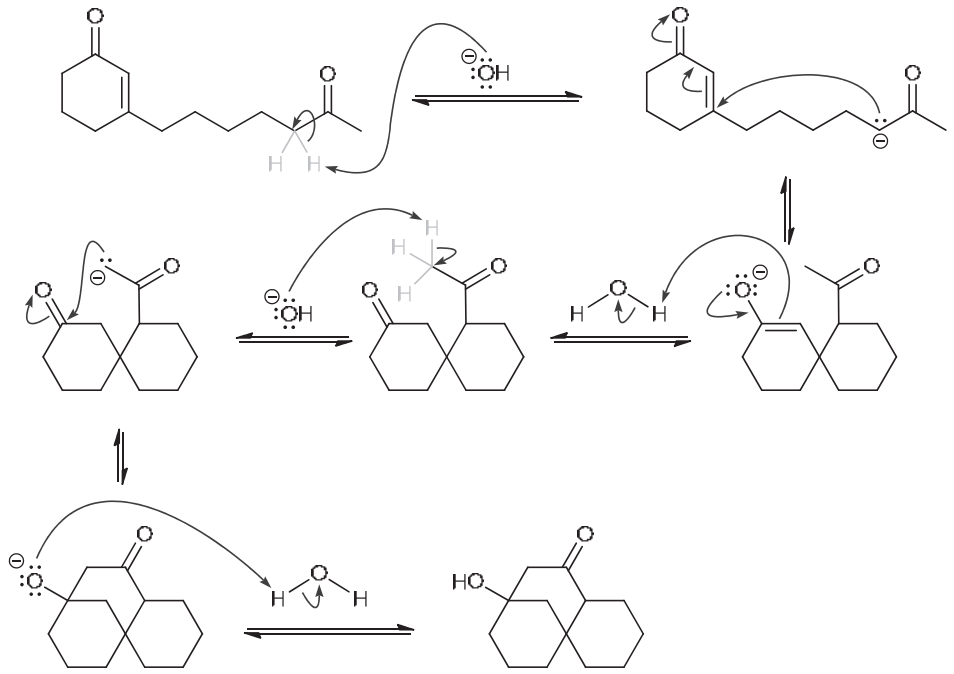
The retro-aldol process proceeds via a mechanism similar to the mechanism seen in the solution to Problem **21.22**. In the first step, hydroxide attacks the β position of the α,β-unsaturated ketone, giving an enolate. The enolate is then protonated to give a β-hydroxyketone, which is subsequently deprotonated to give an alkoxide ion. The carbonyl group is then formed, with loss of an enolate as a leaving group. The resulting enolate is then protonated to give the diketone. Then, an intramolecular aldol reaction occurs, thereby closing a six-membered ring. First, hydroxide functions as a base, giving a new enolate. This enolate ion is a nucleophilic center, and it will attack the carbonyl group present in the same structure (an intramolecular process), thereby closing a five-membered ring. The resulting alkoxide ion is then protonated to give a β-hydroxy ketone. Hydroxide then functions as a base again, deprotonating the α position. The resulting enolate then ejects a hydroxide ion, giving the condensation product, as shown. Notice that each of the protonation steps employs water as the proton source, consistent with basic conditions (strong acids are not measurably present under these conditions).



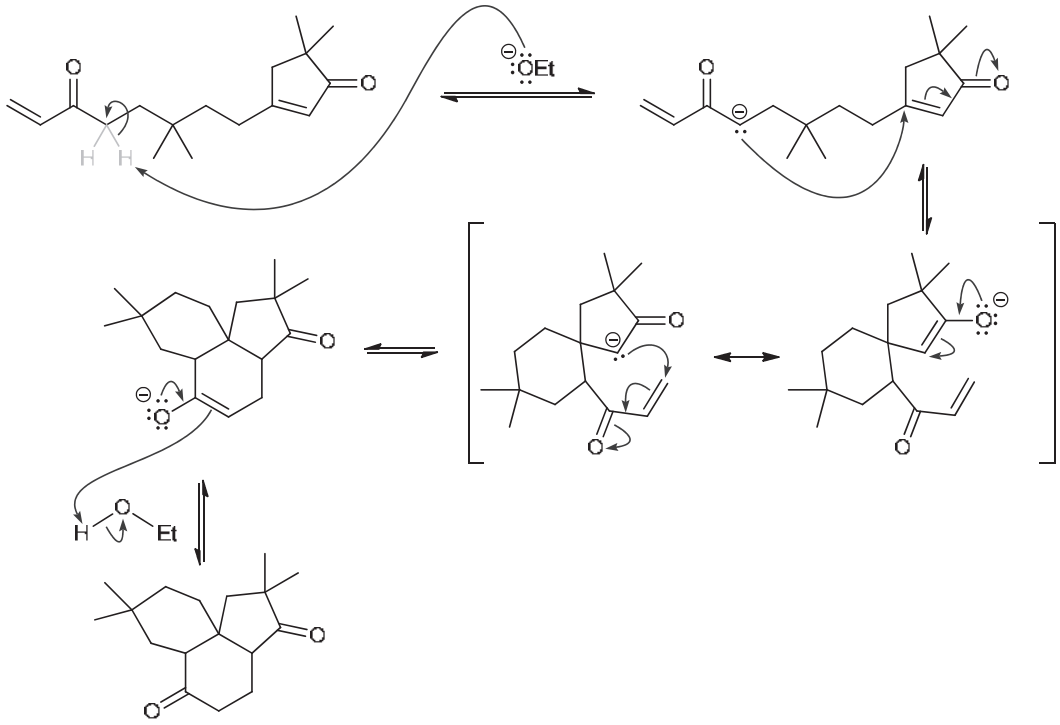
21.100.

(**a)** Hydroxide functions as a base and deprotonates the α position of the ketone, giving an enolate. The enolate then functions as a nucleophile in an intramolecular Michael addition, attacking the β position of the α,β-unsaturated ketone. The resulting enolate ion is then protonated to give a ketone, which is then further deprotonated to give a new enolate (all possible enolates are present at equilibrium). This enolate then attacks the other carbonyl group in an intramolecular attack, giving an alkoxide ion, which is then protonated to give the product. Notice that each of the protonation steps employs water as the proton source, consistent with basic conditions (strong acids are not measurably present under these conditions).

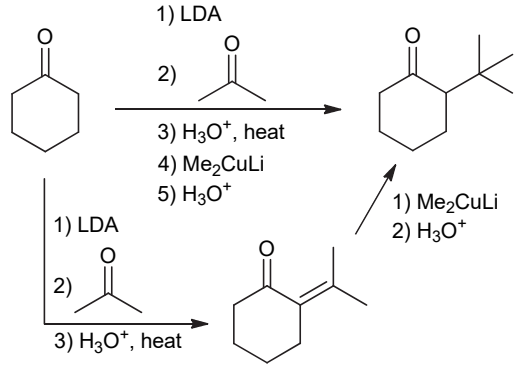
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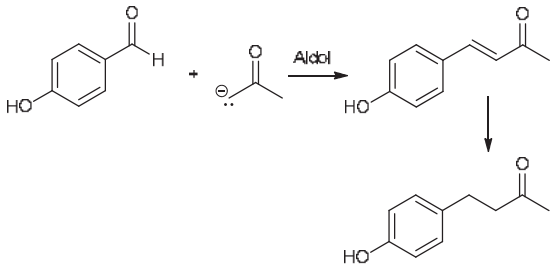
(**b)** Ethoxide functions as a base and deprotonates an α position, giving an enolate. The enolate then functions as a nucleophile in an intramolecular Michael addition, attacking the β position of the other α,β-unsaturated ketone. The resulting enolate ion is then functions as a nucleophile in another intramolecular Michael addition, attacking the β position of the α,β-unsaturated ketone. The resulting enolate is then protonated to give the product. Notice that each of the protonation steps employs ethanol as the proton source, consistent with basic conditions (strong acids are not measurably present under these conditions).



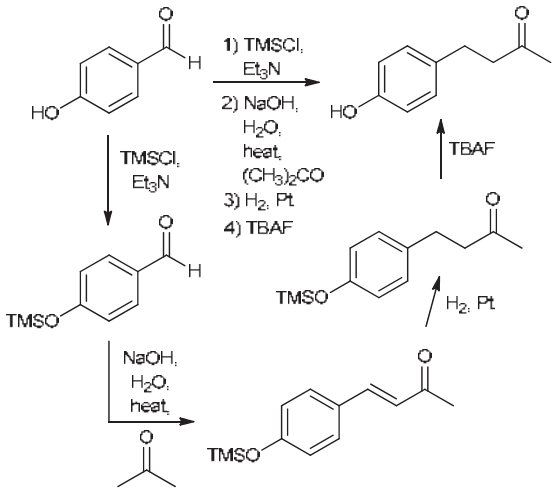
21.101. Direct alkylation would require performing an S_N2 reaction on a tertiary substrate, which will not occur. Instead the enolate would function as a base and E2 elimination would be observed instead of S_N2. The desired transformation can be achieved via a directed aldol condensation, followed by a Michael addition, as shown:



21.102. There are certainly many ways to achieve this transformation, which involves a change in the carbon skeleton. We begin by considering a directed aldol condensation, followed by reduction:



This strategy suffers from a fatal flaw. The phenolic OH group is more acidic than acetone. Therefore, it is not possible to form the enolate of acetone without first deprotonating the phenolic OH group. And deprotonation in that location would generate a resonance stabilized anion, in which the negative charge is spread over several positions including the oxygen atom of the carbonyl group, thereby deactivating the aldehyde group as an electrophile. This obstacle can be circumvented by protecting the OH group before the desired transformation is performed, and then deprotecting with TBAF at the end of the synthesis (see Section 12.7).

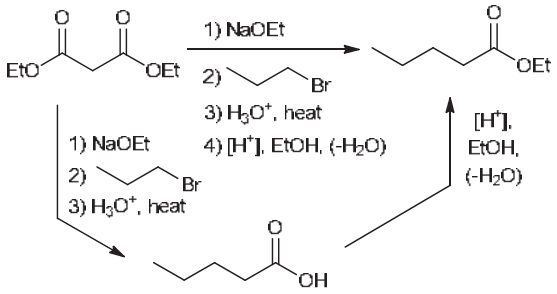


21.103.

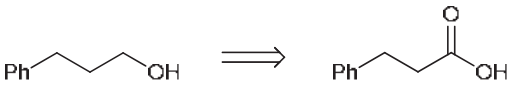
(a) The desired product is an ester, which can be made from the corresponding carboxylic acid via a Fischer esterification:



The carboxylic acid can be made with a malonic ester synthesis, as shown in the following scheme:

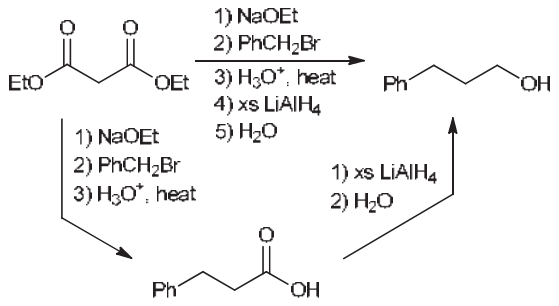


(b) The desired product is a primary alcohol, which can be made from the corresponding carboxylic acid via reduction:

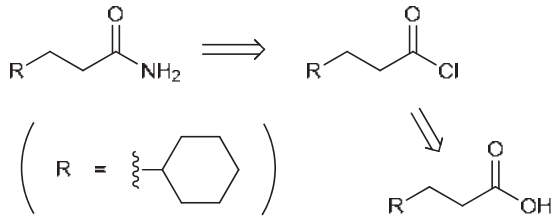


This carboxylic acid can be made with a malonic ester synthesis, as shown in the following scheme:

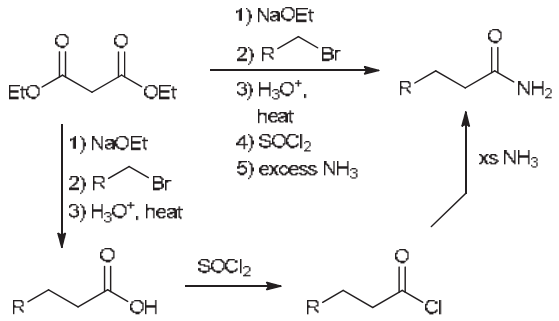
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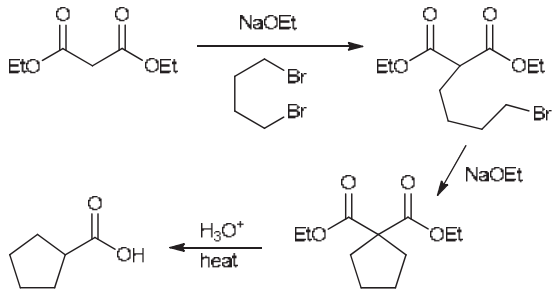
(c) The desired product is an amide, which can be made from the corresponding carboxylic acid (via an acid halide), as shown:



This carboxylic acid can be made with a malonic ester synthesis, as shown in the following scheme:

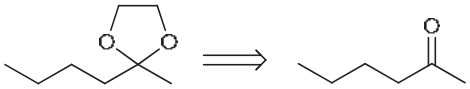


21.104. When a dibromide is used (rather than two separate alkyl halides), a cyclic product is expected, as shown:

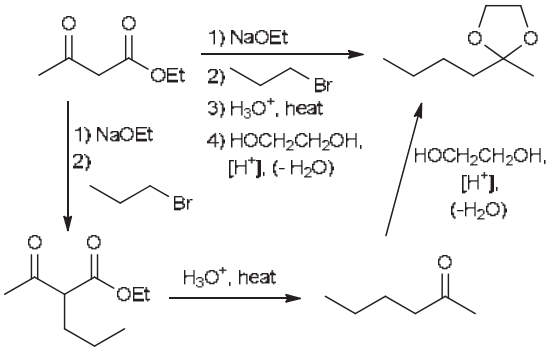


21.105.

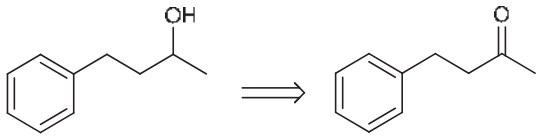
(a) The desired product is an acetal, which can be made from the corresponding ketone:



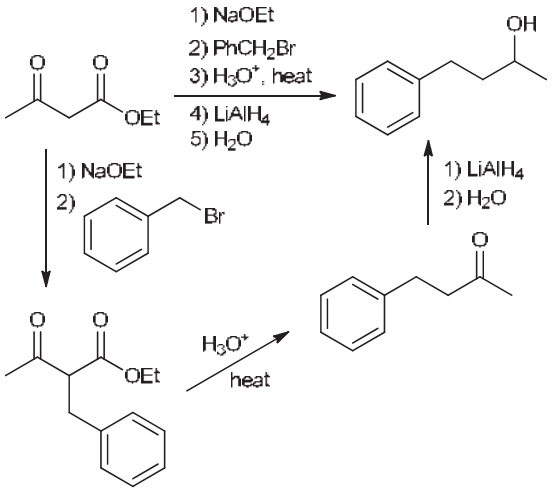
This ketone can be made from ethyl acetoacetate via an acetoacetic ester synthesis, as shown in the following scheme:



(b) The desired product is an alcohol, which can be made from the corresponding ketone via a reduction process:

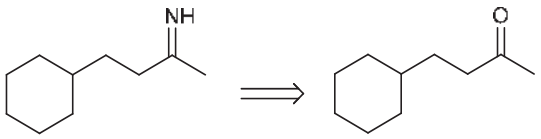


This ketone can be made from ethyl acetoacetate via an acetoacetic ester synthesis, as shown in the following scheme:

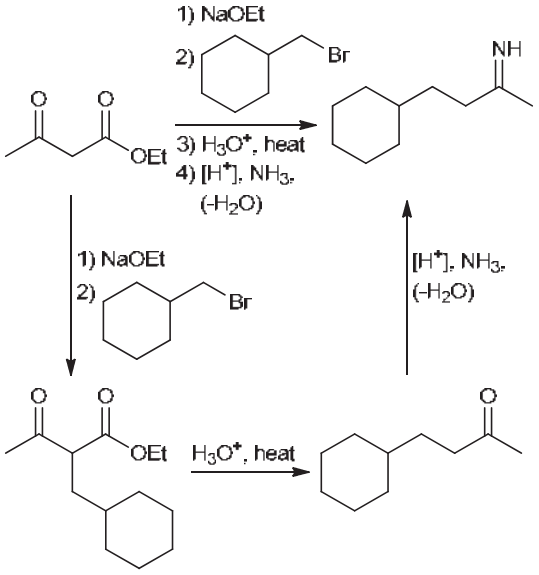


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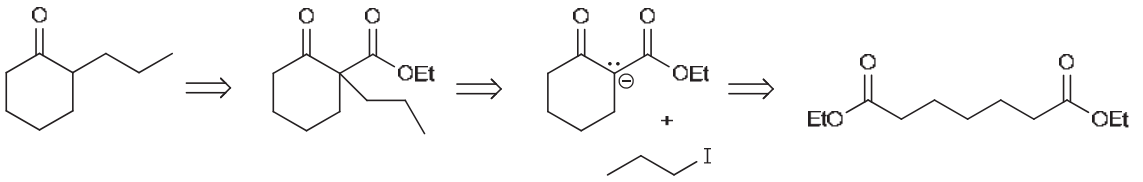
(c) The desired product is an imine, which can be made from the corresponding ketone:



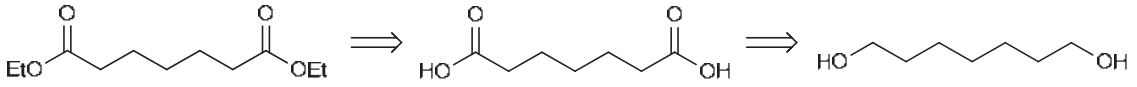
This ketone can be made from ethyl acetoacetate via an acetoacetic ester synthesis, as shown in the following scheme:



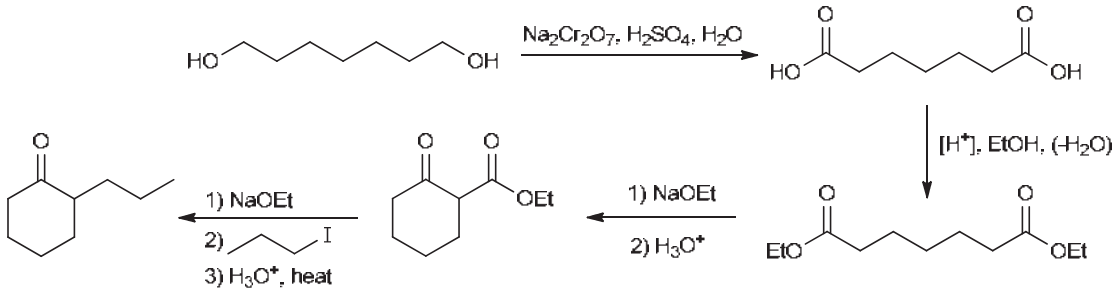
21.106. Using the approach described in the problem statement, the product can be made from an acyclic diester, as shown in the following retrosynthetic analysis:



The diester can be made from the corresponding diacid (via Fischer esterification of both carboxylic acid groups), and the diacid can be made via oxidation of the starting diol:



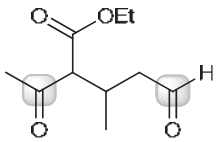
Now let's draw the forward scheme. The starting diol is converted to a diacid upon treatment with chromic acid. This diacid is then converted to a diester upon treatment with ethanol and an acid catalyst (with removal of water). The resulting diester will undergo a Dieckmann cyclization upon treatment with sodium ethoxide, followed by aqueous acid work-up. Alkylation, followed by hydrolysis and decarboxylation, gives the product, as shown.



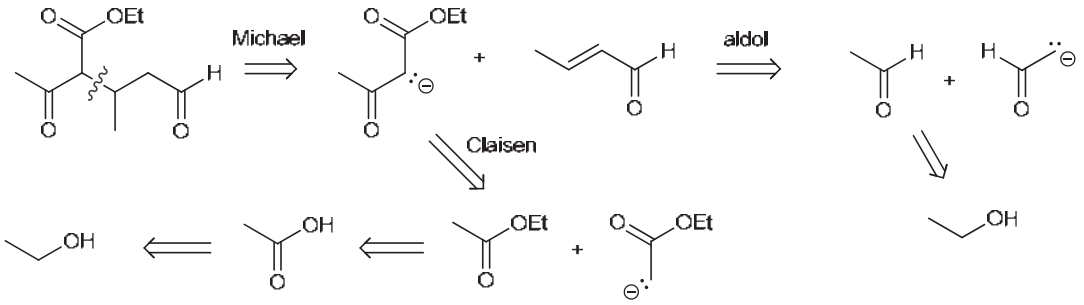
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21.107.

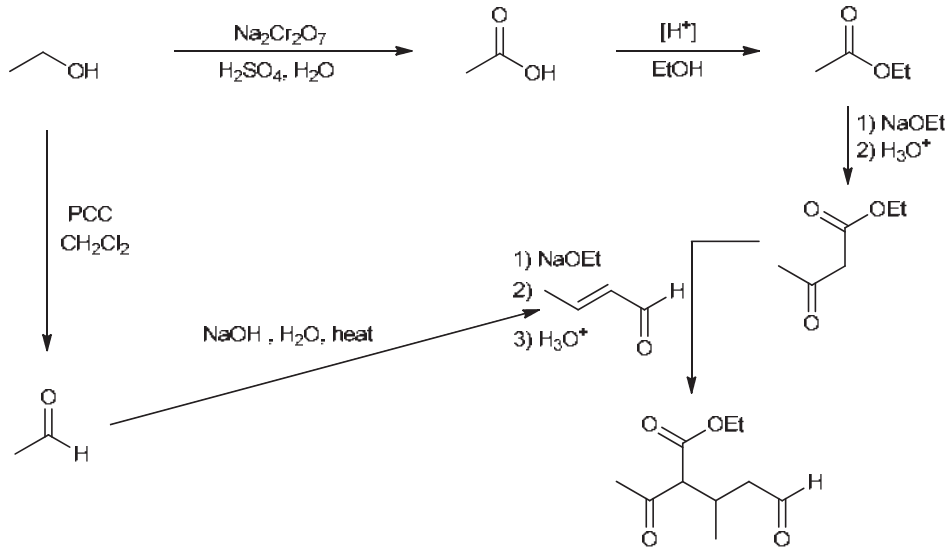
(a) The compound possesses three functional groups, and can be assembled in a variety of ways. One method capitalizes on the 1,5-arrangement of two of the functional groups (highlighted):



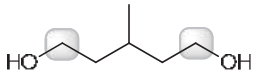
Therefore, we consider preparing the product via a Michael reaction. The following retrosynthetic analysis is based on assembly of the carbon skeleton via a Michael reaction, as well as an aldol condensation reaction to prepare the Michael acceptor, and a Claisen condensation to prepare the Michael donor:



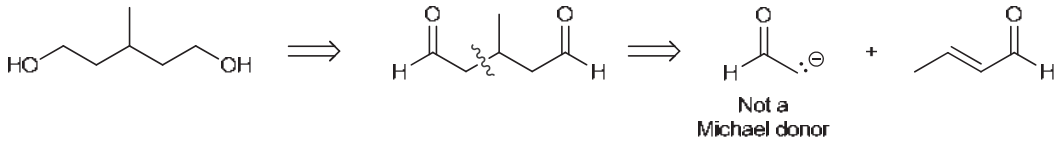
Now let's show the forward scheme for this strategy. One equivalent of ethanol is oxidized with PCC to give acetaldehyde, which is then heated with aqueous sodium hydroxide to give an α,β-unsaturated aldehyde (via an aldol condensation reaction). Another equivalent of ethanol is oxidized with chromic acid to give a carboxylic acid, which is then treated with ethanol under acidic conditions to give an ester (via Fischer esterification). The ester is then converted into a β-ketoester (via a Claisen condensation). The β-ketoester is then deprotonated with ethoxide to give a doubly stabilized enolate which then attacks the α,β-unsaturated aldehyde to give a Michael reaction:



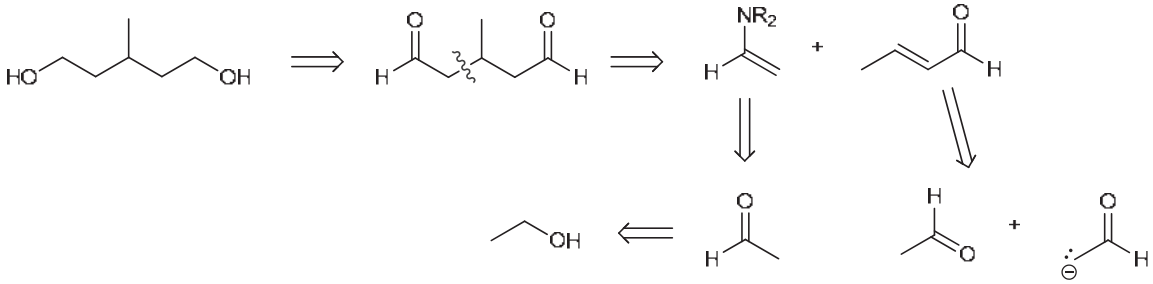
(b) The product is 1,5-difunctionalized:



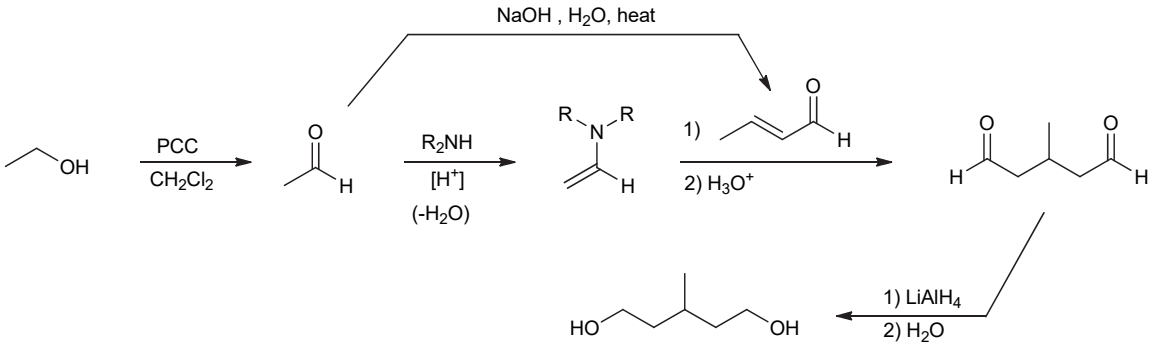
Therefore, we consider preparing the product via a Michael reaction:



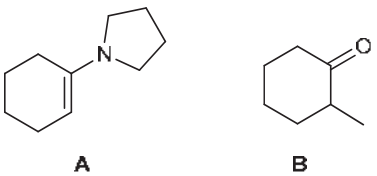
This strategy will not work, because it involves the use of an enolate, which is not an efficient Michael donor. Therefore, we consider a Stork enamine synthesis (in which we use an enamine, rather than an enolate, as a Michael donor). The Michael donor can be made from acetaldehyde, which can be made from ethanol via oxidation with PCC (or DMP or via a Swern oxidation). The Michael acceptor can be made from two equivalents of acetaldehyde via an aldol condensation:



The forward scheme is shown here:

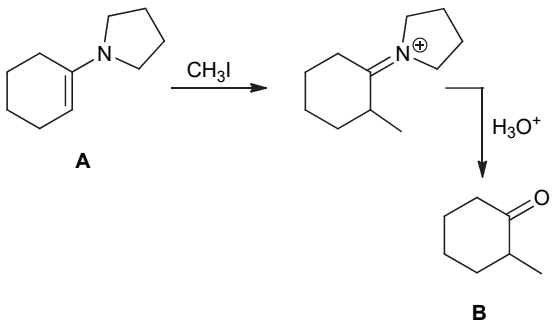


21.108. Intermediate **A** is the corresponding enamine, while the alkylation product **B** is 2-methylcyclohexanone:



A **B**

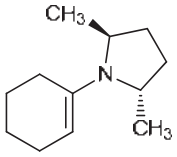
Product **B** is a result of the hydrolysis of the iminium ion shown here, which forms after alkylation of enamine **A** by methyl iodide:



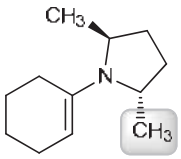
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21.109.

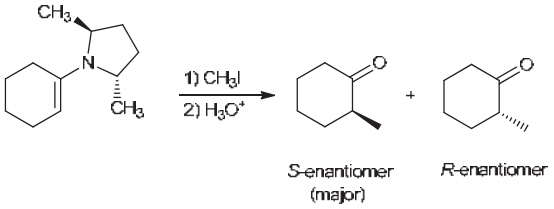
(a) Only one isomer of the enamine forms due to rotational symmetry possessed by the secondary amine. Due to this symmetry property, the two possible conformational isomers for this enamine are equivalent.



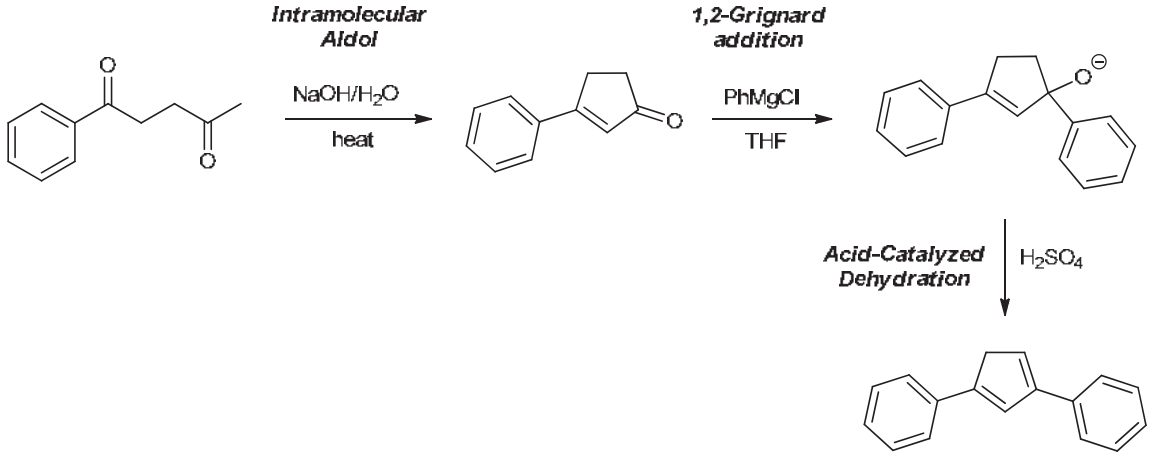
(b) When the enamine in part (a) reacts with methyl iodide, the methyl group closer to the α carbon atom of the enamine is oriented below the plane of the page.



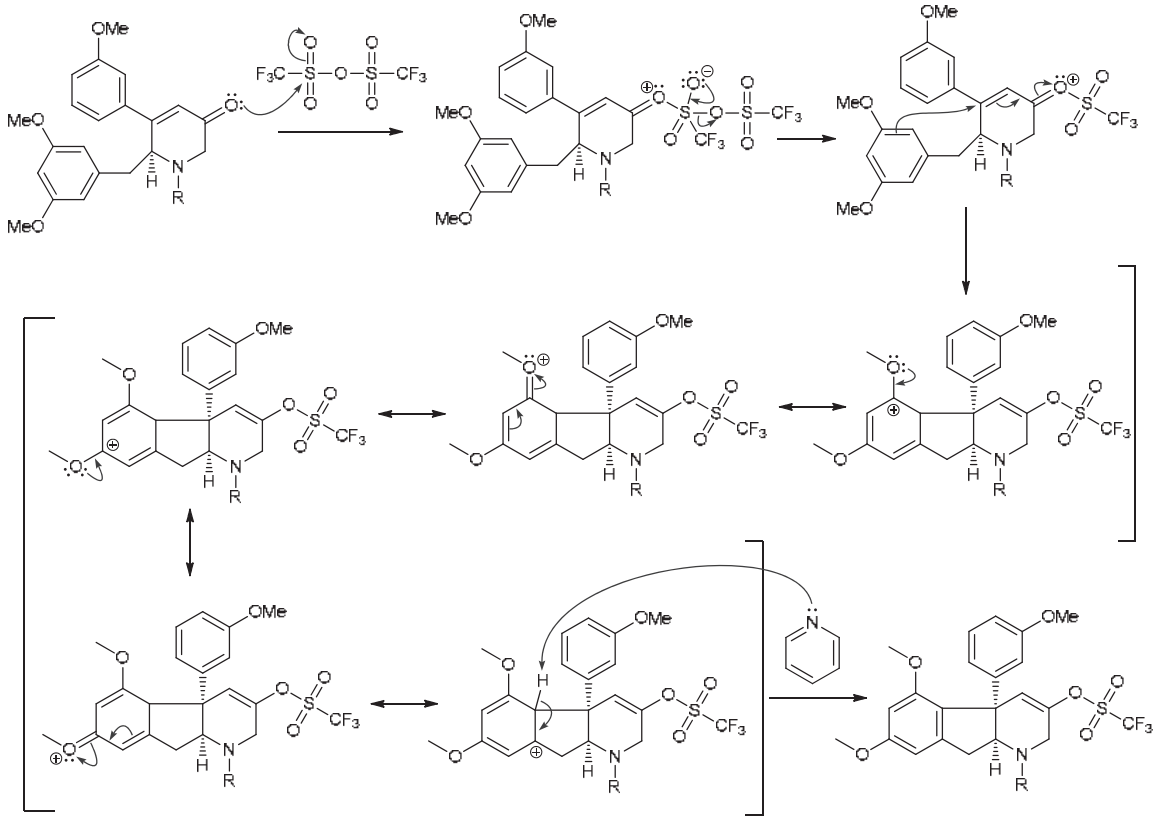
So, approach by the electrophile from that direction is hindered, resulting in (*R*)-2-methylcyclohexanone being the minor product. In contrast, since the approach of methyl iodide from the top face of the page is unimpeded by this substituent, (*S*)-2-methylcyclohexanone is the major product. And since this is the only isomer of the enamine undergoing alkylation, the *S*-enantiomer is the major product formed. This means that the rotational symmetry of the starting secondary amine is responsible for the % *ee* achieved.



21.110. While there are three alpha positions in the molecule, deprotonation at only one of them (the terminal methyl group) will lead to the formation of a 5-membered ring. The first reaction is a base-catalyzed, intramolecular aldol condensation reaction, affording an α,β-unsaturated ketone. Addition of the Grignard reagent phenylmagnesium chloride gives an alkoxide ion. Treatment with sulfuric acid causes protonation of the alkoxide ion, followed by acid-catalyzed dehydration to afford the highly conjugated diene shown below.

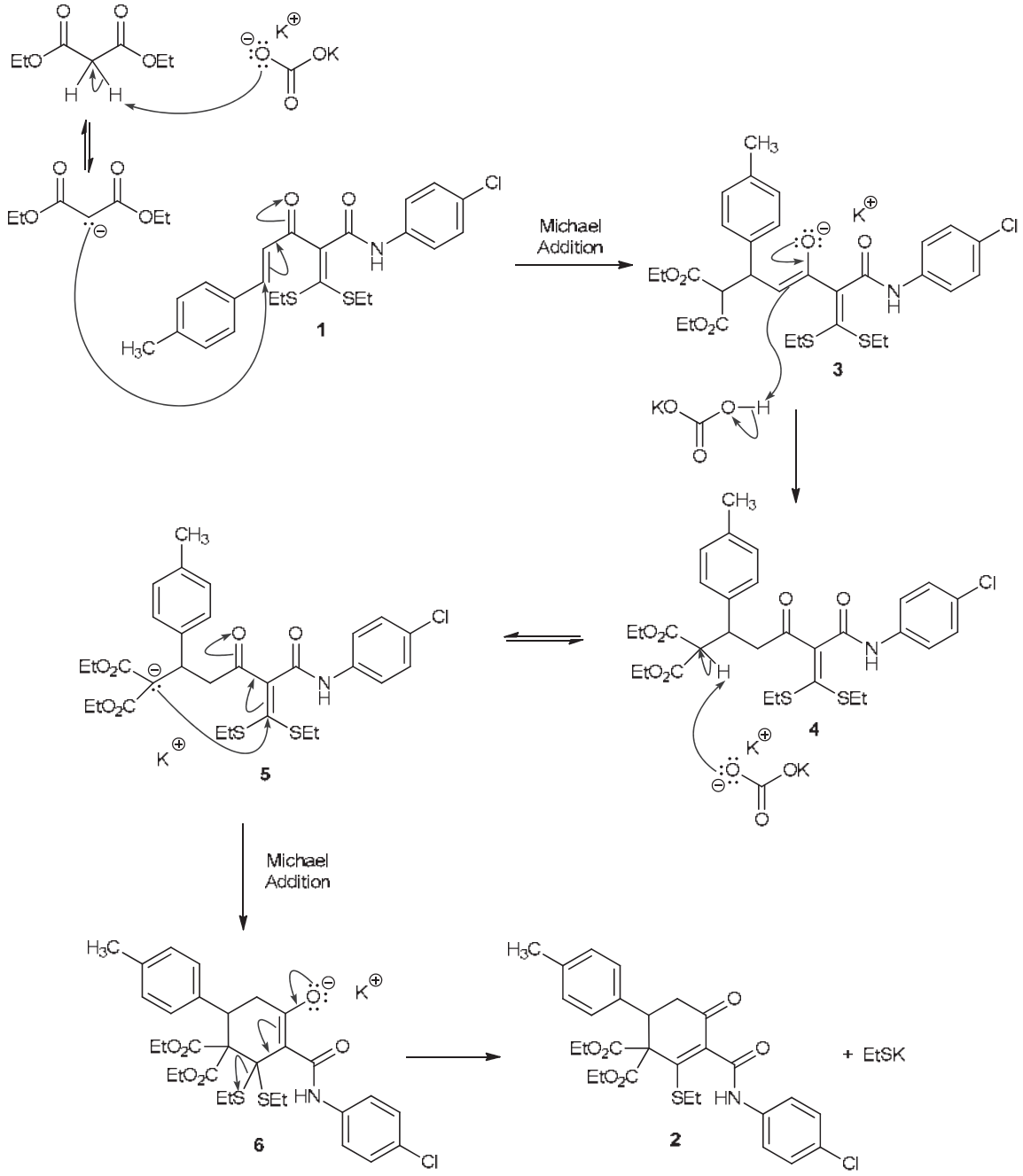


21.111. In the starting material, the dimethoxybenzyl group is in the "up" position on the chiral carbon, from the perspective drawn. This group thus attacks the β carbon of the α,β-unsaturated ketone from the top face, pushing the other aromatic ring "down", so that it ends up *cis* to the hydrogen on the adjacent chiral center.



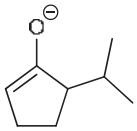
21.112. This transformation involves two successive Michael addition reactions. The sequence begins with the deprotonation of diethylmalonate with potassium carbonate to give a stabilized anion (Michael donor) that attacks the α,β-unsaturated ketone **1** (Michael acceptor) in a Michael fashion to afford enolate **3**. After protonation of enolate **3** to give compound **4**, the β-diester moiety is then deprotonated to give the resonance-stabilized anion **5**. At this point a second Michael addition occurs as the anion (Michael donor) attacks the carbon containing the two thioethers (Michael acceptor) in a conjugate fashion to give enolate **6**. Finally, the electrons of the enolate come back down to make the ketone and the α,β-unsaturation by expelling the ethanethiolate anion as a leaving group to afford the final product **2**.

Alternatively, the reverse order of these two Michael additions will likewise afford the product.

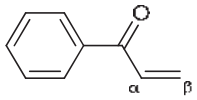


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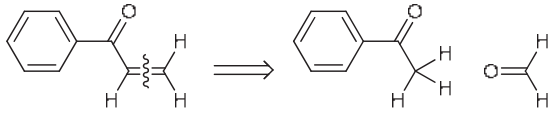
21.113. Options (c) and (d) are enols, not enolates, so they can be ruled out. The base (diisopropylamide) is sterically hindered, so we expect formation of the less substituted (kinetic) enolate, which corresponds with option (b).



21.114. The product is an α,β-unsaturated ketone:

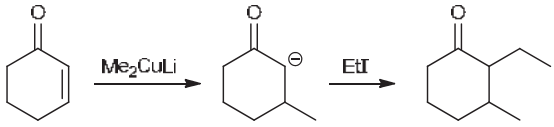


Therefore, it can be prepared via an aldol condensation, using the following starting materials:



These compounds correspond with option (c).

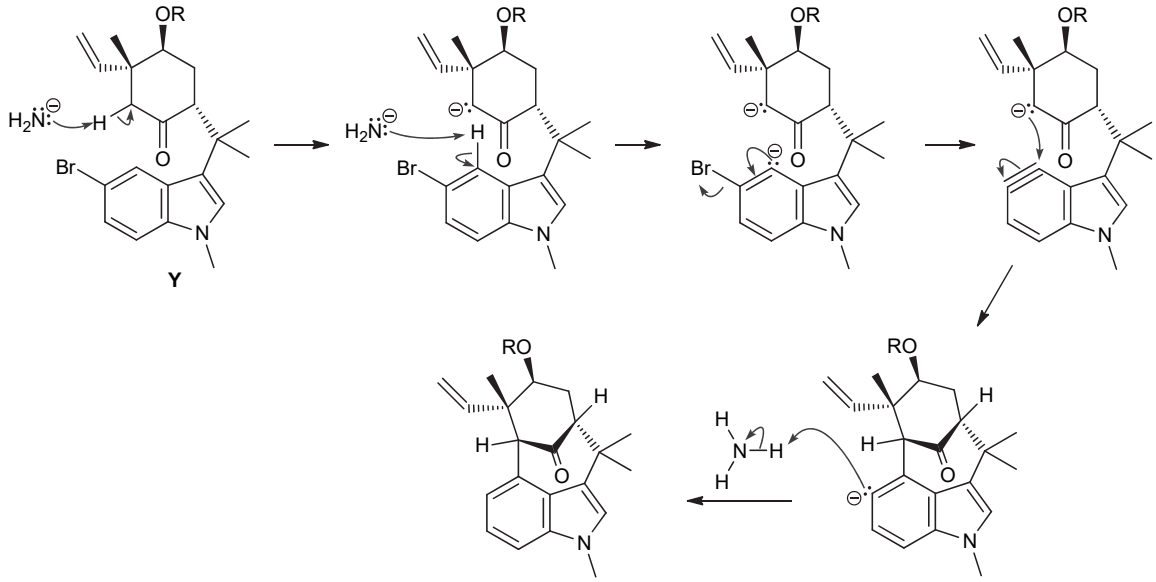
21.115. This process involves the installation of two alkyl groups bear a carbonyl group: an ethyl group at the alpha position and a methyl group at the beta position. This can be achieved by first installing the methyl group at the beta position, by treating the starting compound with Me_2CuLi, to give an enolate, followed by alkylation with ethyl iodide to give the desired product:



Therefore, the answer is (d).

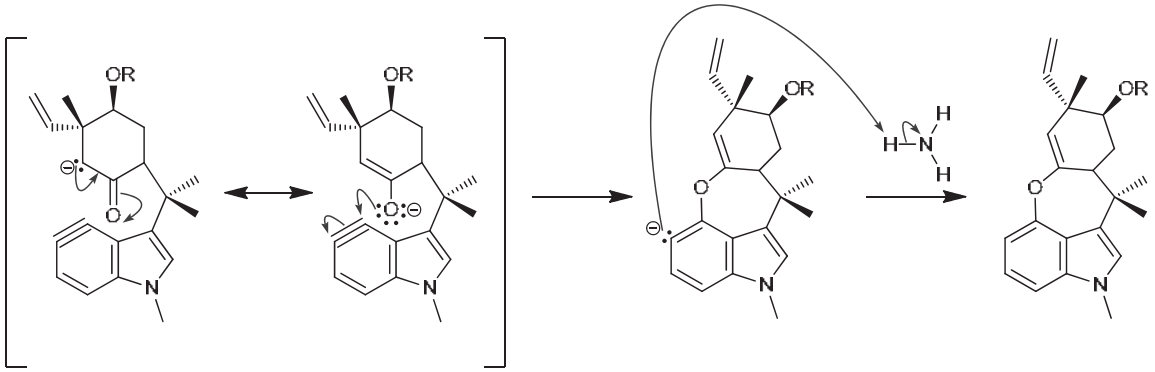
21.116.

(a) Under strongly basic conditions, an enolate is formed. Then, under these conditions, an elimination-addition reaction can occur (Section 18.14), in which the nucleophilic enolate attacks the tethered benzyne in a ring-forming reaction, followed by protonation.



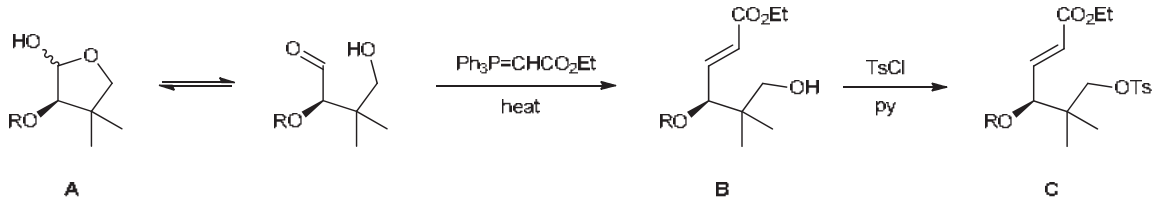
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(b) The enolate ion is an ambident nucleophile, which means that it can attack from the oxygen, as well as from the alpha carbon atom. If the oxygen atom of the enolate functions as the nucleophile and attacks the benzyne unit, the following side product is formed:

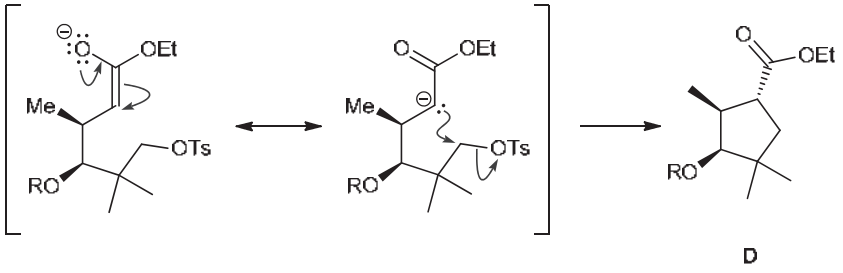


21.117.

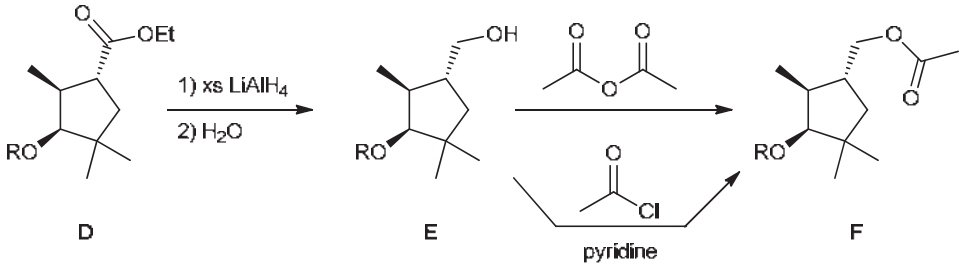
(a) Cyclic hemiacetal **A** is in equilibrium with its open chain form, which has an aldehyde group and a hydroxyl group. The aldehyde group can undergo a Wittig reaction when treated with a stabilized ylide ($Ph_3P{=}CHCO_2Et$), giving an α,β-unsaturated ester. Then, the hydroxyl group is converted to a tosylate group upon treatment with tosyl chloride:



(b) The conversion of compound **C** to **D** begins with a Michael addition reaction, in which Me_2CuLi functions as a Michael donor and attacks the α,β-unsaturated ester (the Michael acceptor) to afford an enolate. This enolate can then function as a nucleophile in an intramolecular S_N2-type process (shown below), in which the enolate undergoes α-alkylation to close the cyclopentyl ring system, giving compound **D**:

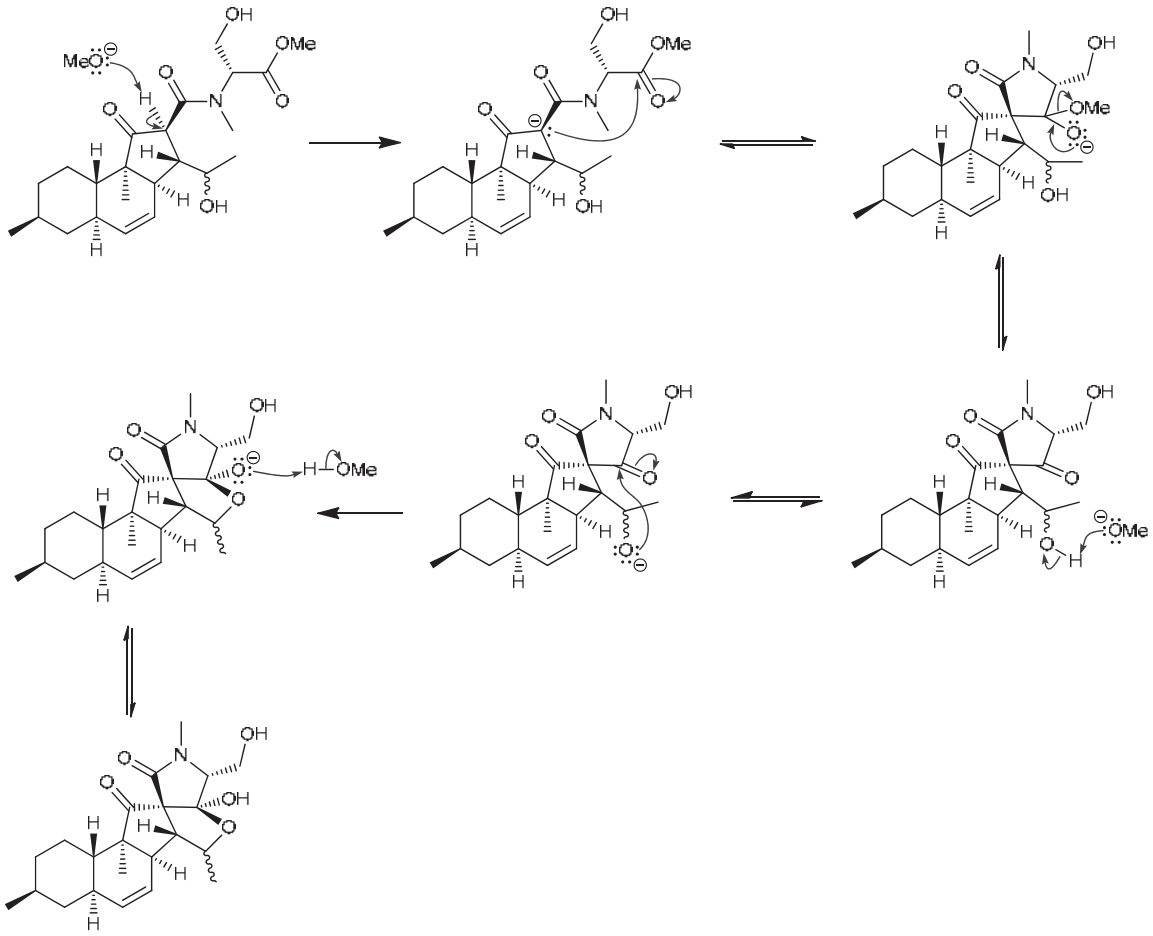


(c) The ester is first reduced to an alcohol (compound **E**), which can be acylated, using either acetic anhydride or acetyl chloride and pyridine:



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21.118. Methoxide functions as a base and deprotonates the most acidic position, leading to a doubly-stabilized enolate. This enolate then functions as a nucleophile and attacks the ester in an intramolecular nucleophilic acyl substitution reaction. The resulting tetrahedral intermediate loses methoxide to reform the carbonyl group. The OH group is then deprotonated to give an alkoxide ion, which then attacks the newly formed carbonyl group to give another alkoxide ion, which is protonated to give the product.



Chapter 22
Amines

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 22. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

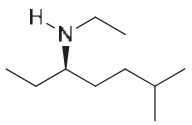
- Amines are _____, _____, or _____, depending on the number of groups attached to the nitrogen atom.
- The lone pair on the nitrogen atom of an amine can function as a _____ or _____.
- The basicity of an amine can be quantified by measuring the pK_a of the corresponding _____.
- Aryl amines are less basic than alkyl amines, because the lone pair is _____.
- Pyridine is a stronger base than pyrrole, because the lone pair in pyrrole participates in _____.
- An amine group exists primarily as _____ at physiological pH.
- The **azide synthesis** involves treating an _____ with sodium azide, followed by _____.
- The _____ **synthesis** generates primary amines upon treatment of potassium phthalimide with an alkyl halide, followed by hydrolysis or reaction with N_2H_4.
- Amines can be prepared via **reductive amination**, in which a ketone or aldehyde is converted into an imine in the presence of a _____ agent, such as **sodium cyanoborohydride** ($NaBH_3CN$).
- Amines react with acyl halides to produce _____.
- In the **Hofmann elimination**, an amino group is converted into a better leaving group which is expelled in an ____ process to form an _____.
- Primary amines react with a nitrosonium ion to yield a _____ **salt** in a process called **diazotization**.
- **Sandmeyer reactions** utilize copper salts (CuX), enabling the installation of a halogen or a _____ group.
- In the **Schiemann reaction**, an aryl diazonium salt is converted into a fluorobenzene by treatment with _____.
- Aryldiazonium salts react with activated aromatic rings in a process called _____ **coupling**, to produce colored compounds called _____ **dyes**.
- A _____ is a ring that contains atoms of more than one element.
- Pyrrole undergoes electrophilic aromatic substitution reactions, which occur primarily at C__.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 22. The answers appear in the section entitled *SkillBuilder Review*.

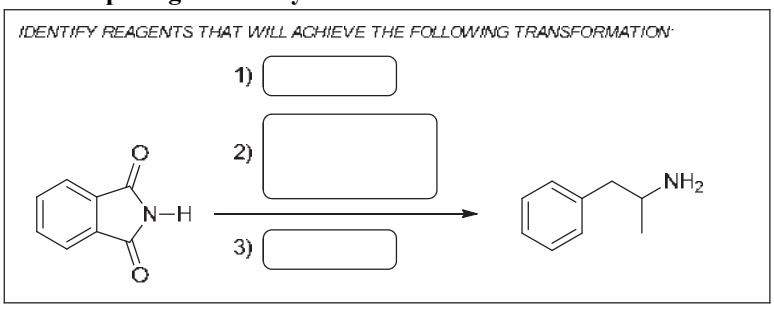
22.1 Naming an Amine

PROVIDE A SYSTEMATIC NAME FOR THE FOLLOWING COMPOUND:

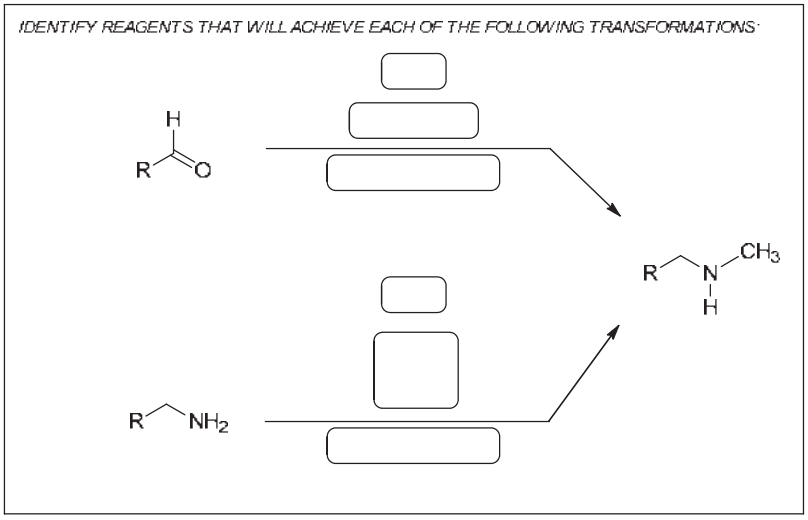


1) IDENTIFY THE PARENT
2) IDENTIFY AND NAME SUBSTITUENTS
3) ASSIGN LOCANTS TO EACH SUBSTITUENT
4) ALPHABETIZE
5) ASSIGN CONFIGURATION

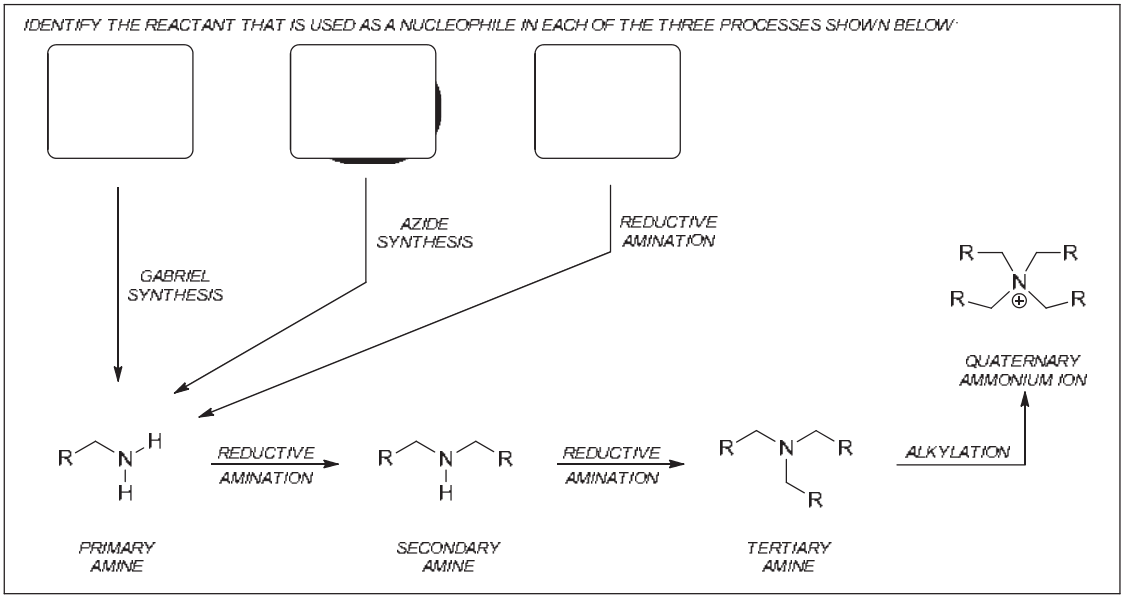
22.2 Preparing a Primary Amine via the Gabriel Reaction



22.3 Preparing an Amine via a Reductive Amination

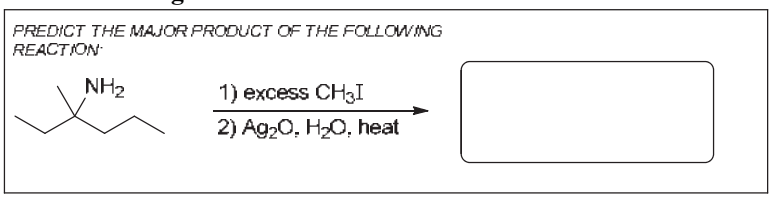


22.4 Synthesis Strategies

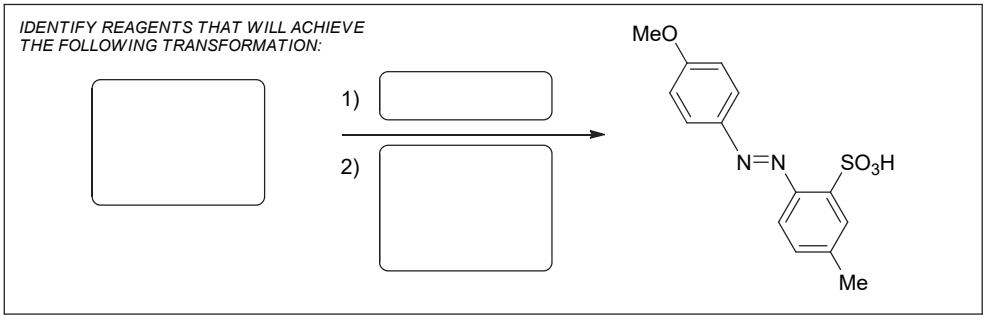


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22.5 Predicting the Product of a Hofmann Elimination



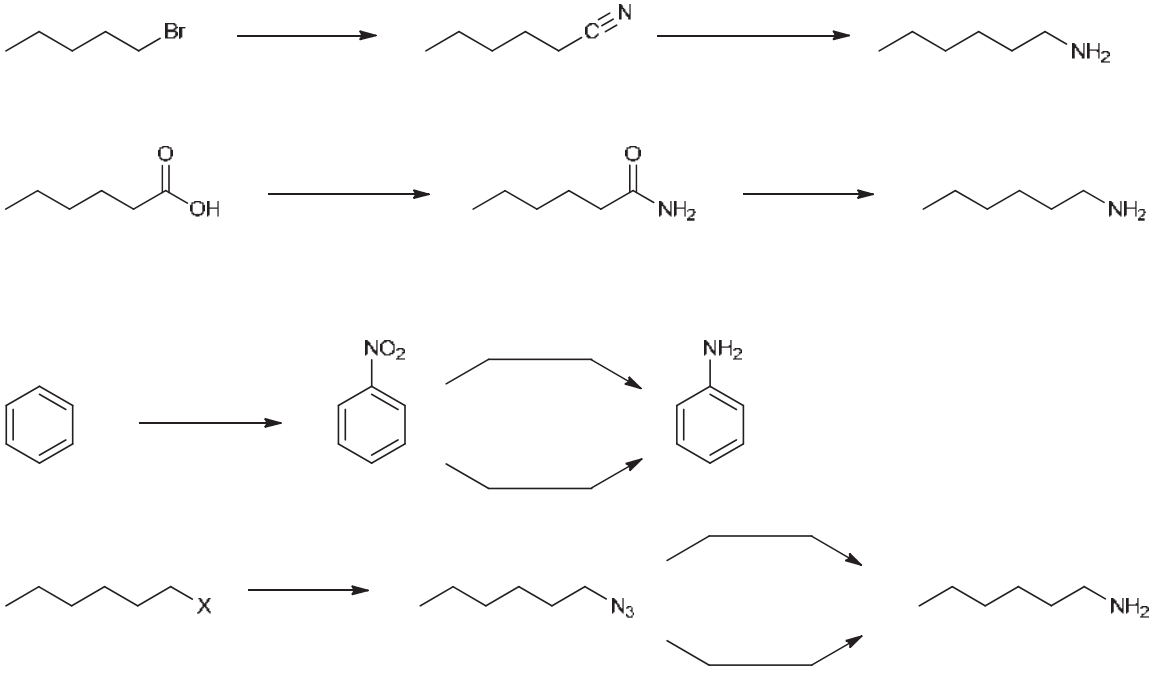
22.6 Determining the Reactants for Preparing an Azo Dye

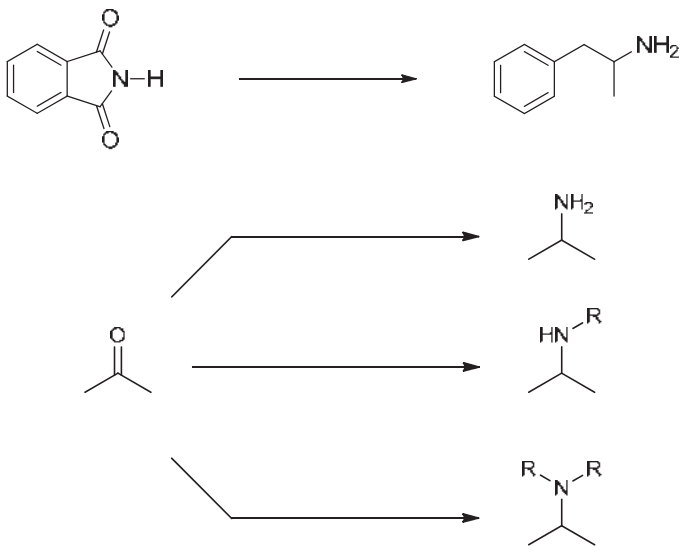


Review of Reactions

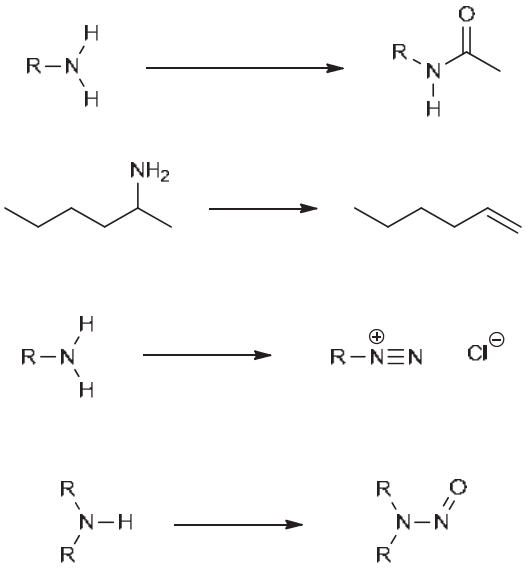
Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 22. The answers appear in the section entitled *Review of Reactions*.

Preparation of Amines

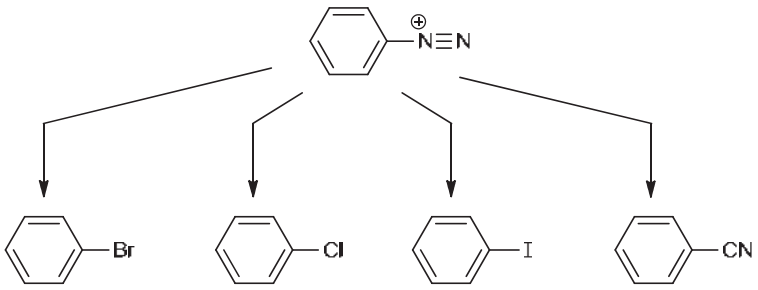


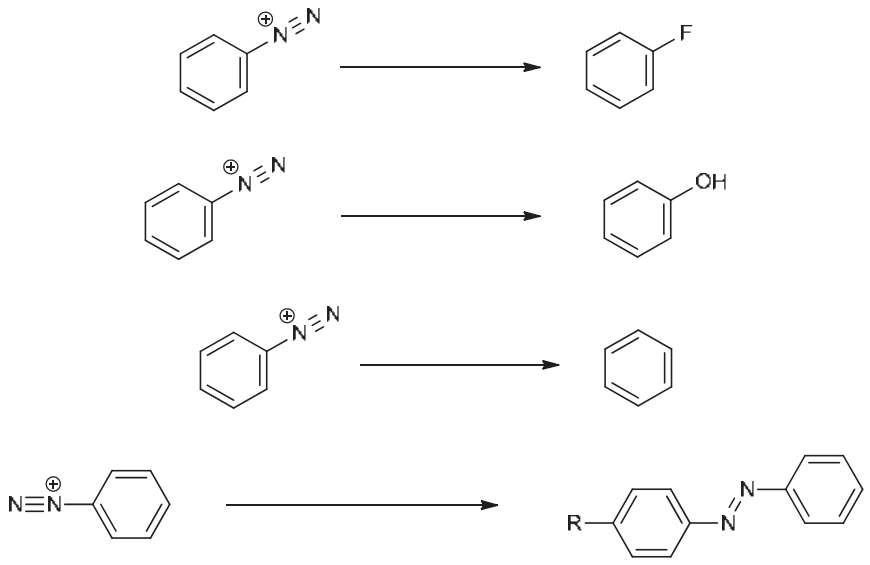


Reactions of Amines

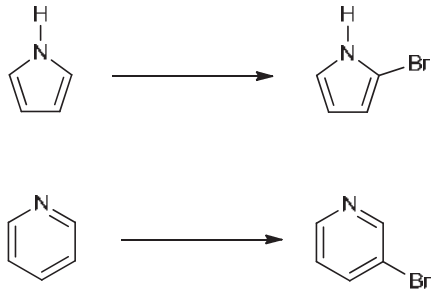


Reactions of Aryldiazonium Salts



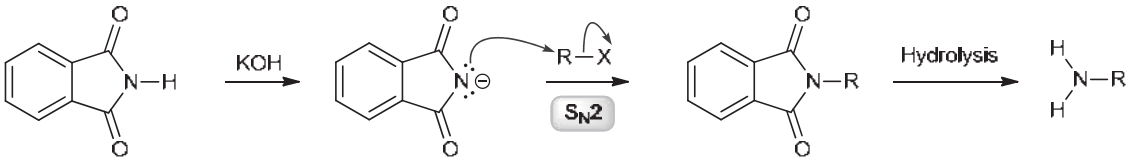


Reactions of Nitrogen Heterocycles



Common Mistake to Avoid

Whenever you learn a new reaction, pay close attention to any restrictions that may apply. For example, the Gabriel synthesis employs an S_N2 process to create the critical C–N bond of a primary amine:

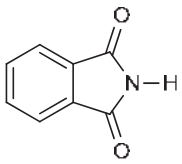


Since an S_N2 process is employed, a tertiary alkyl halide cannot be used, because tertiary alkyl halides are too sterically hindered to undergo an S_N2 process. It is a common mistake to attempt to use a tertiary alkyl halide in a Gabriel synthesis, because it is easy to forget the restrictions that apply. Keep this in mind for all reactions that you study. Make sure that you understand the circumstances under which each reaction can or cannot be used.

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Useful reagents

The following is a list of reagents encountered in this chapter:

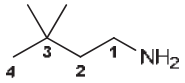
Reagents	Type of Reaction	Description
1) NaCN 2) xs $LiAlH_4$ 3) H_2O	Preparation of an amine (from an alkyl halide)	These reagents can be used to convert an alkyl halide into an amine with the introduction of one carbon atom (from the cyano group).
1) $SOCl_2$ 2) xs NH_3 3) xs $LiAlH_4$ 4) H_2O	Preparation of an amine (from a carboxylic acid)	These reagents can be used to convert a carboxylic acid into an amine, without a change in the carbon skeleton.
1) Fe, H_3O^+ 2) NaOH	Reduction	These reagents can be used to reduce an aryl nitro group into an amino group. The first step employs acidic conditions, so the amine is protonated (under the conditions of its formation) to give an ammonium ion. The ammonium ion is then deprotonated upon basic work-up, giving the amine.
1) NaN_3 2) $LiAlH_4$ 3) H_2O	Azide synthesis	These reagents can be used to convert an alkyl halide into an amine, without a change in the carbon skeleton. The last two steps (reduction and water work-up) can be replaced with hydrogenation in the presence of a metal catalyst (H_2, Pt)
	Gabriel synthesis	Phthalimide is the starting material for the Gabriel synthesis, which can be used to prepare primary amines. Phthalimide is treated with KOH to give potassium phthalimide, which is then treated with an alkyl halide, giving an S_N2 reaction. The product of the S_N2 process is then hydrolyzed (upon treatment with hydrazine or aqueous acid) to release the amine.
$NaBH_3CN$	Reductive amination	In the presence of an acid catalyst, sodium cyanoborohydride can be used to achieve a reductive amination. The reaction occurs between a ketone (or aldehyde) and an amine (or ammonia). This process can be used to convert a primary amine into a secondary amine. Similarly, a secondary amine is converted into a tertiary amine.
	Acetylation	An amine will undergo acetylation (giving an amide) when treated with acetyl chloride.
1) Excess CH_3I 2) Ag_2O, H_2O, heat	Hofmann elimination	These reagents can be used to achieve elimination of H and NH_2 to give an alkene. When there are two possible regiochemical outcomes for the elimination process, the less substituted alkene predominates.
$NaNO_2$, HCl	Reactions with nitrous acid	A mixture of sodium nitrite and HCl will convert a primary amine into a diazonium salt. Under the same conditions, a secondary amine is converted into an *N*-nitrosamine.
CuBr	Sandmeyer reaction	When an aryldiazonium salt is treated with CuBr, the diazonium group is replaced with a bromine atom.
CuCl	Sandmeyer reaction	When an aryldiazonium salt is treated with CuCl, the diazonium group is replaced with a chlorine atom.
CuI	Sandmeyer reaction	When an aryldiazonium salt is treated with CuI, the diazonium group is replaced with an iodine atom.
CuCN	Sandmeyer reaction	When an aryldiazonium salt is treated with CuCN, the diazonium group is replaced with a cyano group.
HBF_4	Fluorination (Schiemann reaction)	When an aryldiazonium salt is treated with HBF_4, the diazonium group is replaced with a fluorine atom.
H_2O, heat	Preparation of phenol	When an aryldiazonium salt is treated with water and heat, the diazonium group is replaced with an OH group.
H_3PO_2	Reduction	When an aryldiazonium salt is treated with H_3PO_2, the diazonium group is replaced with a hydrogen atom.

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Solutions

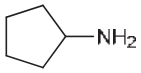
22.1.

(a) This compound is an amine that has only one alkyl group connected to the nitrogen atom. Since this alkyl group is complex, we must name the compound as an alkanamine (rather than an alkyl amine). The parent is comprised of four carbon atoms (thus, butanamine), and the amino group is located at C1. There are two methyl groups, both located at C3.



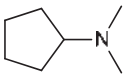
3,3-dimethyl-1-butanamine

(b) This compound is an amine that has only one simple alkyl group (a cyclopentyl group) connected to the nitrogen atom, so we can name this compound as an alkyl amine, rather than an alkanamine. Therefore, this compound is cyclopentylamine.



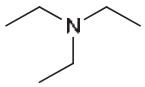
cyclopentylamine

(c) This compound is an amine that has three simple alkyl groups (two methyl groups and a cyclopentyl group) connected to the nitrogen atom, so we can name this compound as a trialkyl amine, rather than an alkanamine. The alkyl groups are listed in alphabetical order:



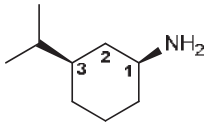
cyclopentyldimethylamine

(d) This compound is an amine that has three simple alkyl groups (all ethyl groups) connected to the nitrogen atom, so we can name this compound as a trialkyl amine, rather than an alkanamine:



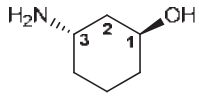
triethylamine

(e) This compound is an amine that has only one alkyl group connected to the nitrogen atom. Since this alkyl group is complex, we must name the compound as an alkanamine (rather than an alkyl amine). The parent is a six-membered ring (thus, cyclohexanamine), and there is an isopropyl group located at C3. There are two chiral centers, and the configuration of each is listed at the beginning of the name:



(1*S*,3*R*)-3-isopropylcyclohexanamine

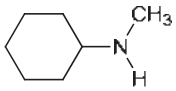
(f) This compound has two functional groups (an OH group and an NH_2 group). The OH group takes priority, so the compound is named as an alcohol (cyclohexanol), with the amino group listed as a substituent, located at C3. There are two chiral centers, and the configuration of each is listed at the beginning of the name:



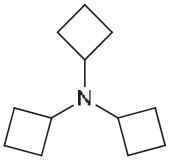
(1*S*,3*S*)-3-aminocyclohexanol

22.2.

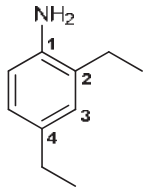
(a) The name indicates a dialkyl amine, in which both alkyl groups are simple groups (a cyclohexyl group and a methyl group):



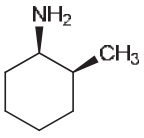
(b) The name indicates a trialkyl amine, in which all three alkyl groups are cyclobutyl groups:



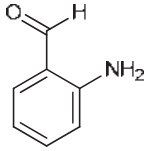
(c) The parent is aniline (or aminobenzene), and there are two ethyl groups (one at C2 and the other at C4):



(d) The parent is a six-membered ring that bears an amino group (thus, cyclohexanamine). There is a methyl group at C2, and the configuration of each chiral center (C1 and C2) is indicated in the name:

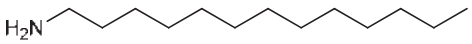


(e) The parent is benzaldehyde, and there is an amino substituent in the *ortho* position.



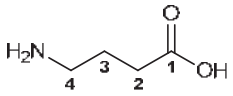
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22.3.
(a) This compound is an amine that has only one simple alkyl group (13 carbons is a tridecyl group) connected to the nitrogen atom, so we can name this compound as an alkyl amine or an alkanamine. Therefore, this compound can be named tridecylamine or 1-tridecanamine.



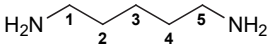
Tridecylamine *or*
1-tridecanamine

(b) The parent is a four-carbon carboxylic acid (butanoic acid). The NH_2 group is called an amino group. The carboxylic acid functionality has a higher suffix priority than amines, therefore, this compound is named 4-aminobutanoic acid.



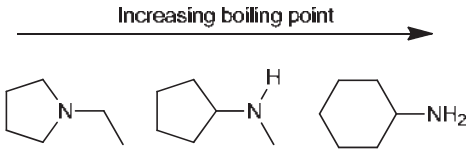
4-Aminobutanoic acid

(c) This compound has two amine groups and is named as a diamine (similar to a compound with two hydroxyl groups being named as a diol). The amino groups are at positions 1 and 5 of a five-carbon chain so it is named pentane-1,5-diamine.



Pentane-1,5-diamine

22.4. The primary amine has two N-H bonds and is expected to exhibit the highest extent of hydrogen bonding, and therefore, the highest boiling point. The tertiary amine lacks N-H bonds, and is therefore expected to have the lowest boiling point.



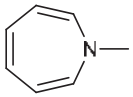
22.5.
(a) This amine has more than five carbon atoms per amino group (there are eight carbon atoms and only one amino group). Therefore, this compound is not expected to be water soluble.
(b) This amine has fewer than five carbon atoms per amino group (there are only three carbon atoms and one amino group). Therefore, this compound is expected to be water soluble.
(c) This diamine has fewer than five carbon atoms per amino group (there are six carbon atoms and two amino groups). Therefore, this compound is expected to be water soluble.

22.6.
(a) The following compound is expected to be a stronger base because the lone pair is localized, and therefore more available to function as a base.



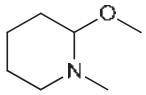
The other compound exhibits a delocalized lone pair, and is therefore a weaker base.

(b) The following compound is expected to be a stronger base because the lone pair is not participating in aromaticity. It is available to function as a base.



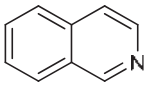
In contrast, the other compound is aromatic, and the lone pair is delocalized (in order to establish aromaticity), so it is unavailable to function as base.

(c) The following compound is expected to be a stronger base because the nitrogen atom has a lone pair that is localized, and therefore more available to function as a base.



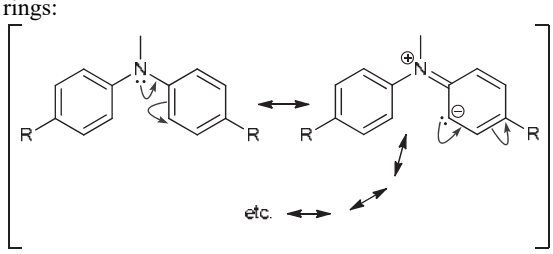
The other compound exhibits a nitrogen atom with a delocalized lone pair, and is therefore a weaker base.

(d) The following compound is expected to be a stronger base because the lone pair is not participating in aromaticity. The lone pair occupies an sp^2 hybridized orbital (directed away from the ring, in the plane of the ring) and is available to function as a base.



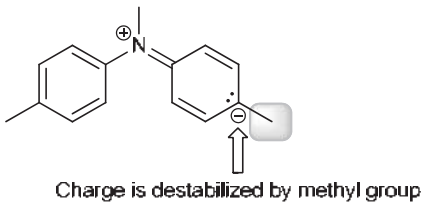
In contrast, the other compound (shown in the problem statement) exhibits a nitrogen atom with a lone pair that is highly delocalized (in order to establish aromaticity in the five-membered ring), so it is unavailable to function as base.

22.7. In all of these compounds, the lone pair (on the nitrogen atom) is delocalized throughout two aromatic rings:



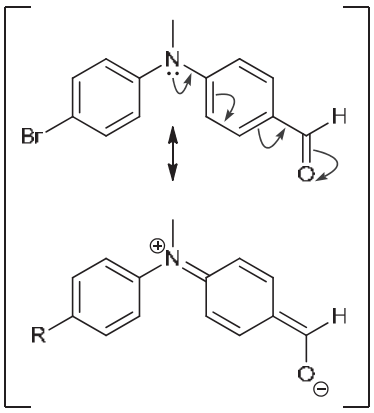
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One of the three compounds (shown in the problem statement) has two methyl groups (electron-donating), which destabilize the delocalized charge:

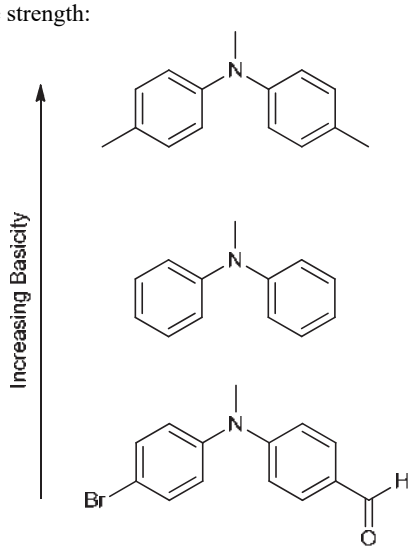


This compound is the strongest base, because the delocalization effect is diminished by the effect of the alkyl groups.

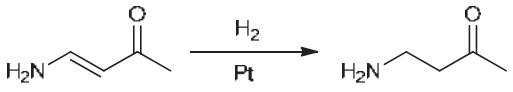
In contrast, the following compound has an aldehyde group. This group is electron-withdrawing, and a resonance structure can be drawn in which the nitrogen atom bears a positive charge, and the oxygen atom bears a negative charge:



This resonance contributor is significant, and it renders the lone pair highly delocalized, and therefore a very poor base. In summary, we predict the following order of base strength:

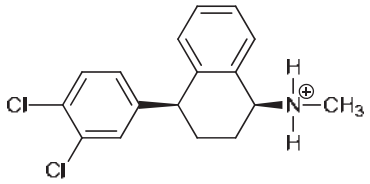


22.8. In the reactant, the lone pair of the amino group is delocalized via resonance. In the product, the lone pair of the amino group is localized, and is therefore more available to function as a base.

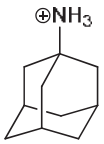


22.9.

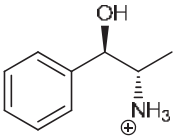
(a) At physiological pH, the amino group exists primarily as a charged ammonium ion:



(**b**) At physiological pH, the amino group exists primarily as a charged ammonium ion:

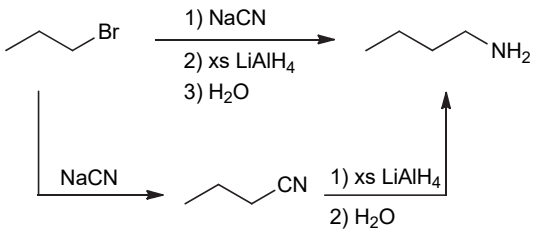


(c) At physiological pH, the amino group exists primarily as a charged ammonium ion:



22.10.

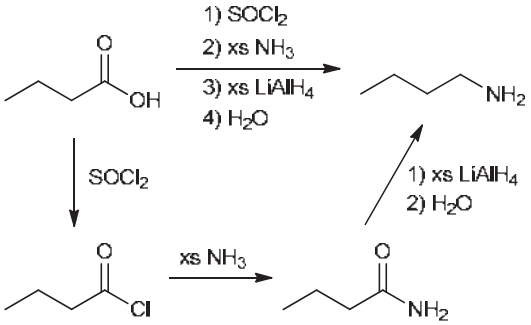
(a) Butylamine can be made from 1-bromopropane, as shown. Treatment with sodium cyanide gives a nitrile (via an S_N2 reaction). Reduction of the nitrile with excess lithium aluminum hydride, followed by water work-up, gives the product:



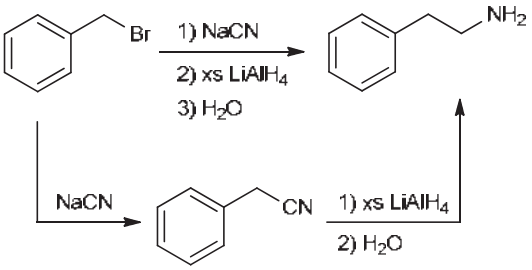
Alternatively, butylamine can be made from butanoic acid, as shown. Treatment with thionyl chloride gives an acid chloride, which can be treated with excess ammonia to give an amide. The amide is then reduced with excess

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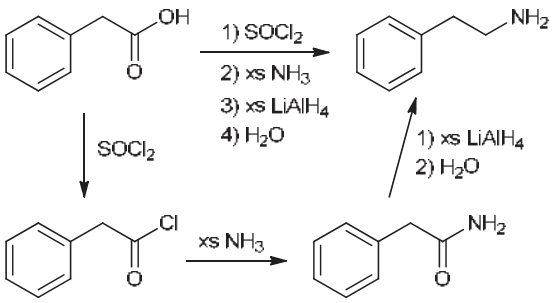
lithium aluminum hydride, followed by water work-up, to give the product:



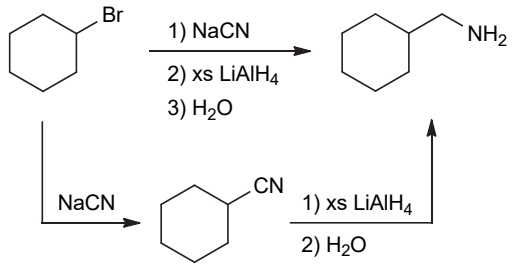
(b) The desired amine can be made from benzyl bromide, as shown. Treatment with sodium cyanide gives a nitrile (via an S_N2 reaction). Reduction of the nitrile with excess lithium aluminum hydride, followed by water work-up, gives the product:



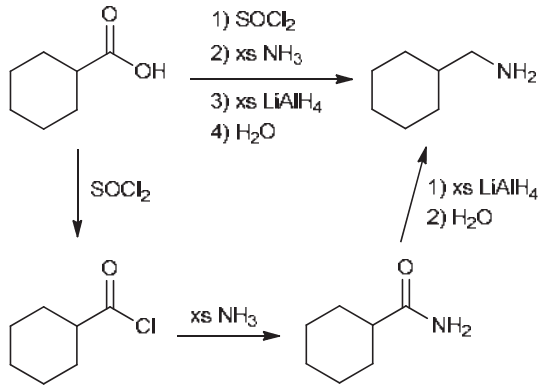
Alternatively, the desired amine can be made from the corresponding carboxylic acid, as shown below. Treatment with thionyl chloride gives an acid chloride, which can then be treated with excess ammonia to give an amide. The amide is then reduced with excess lithium aluminum hydride, followed by water work-up, to give the product:



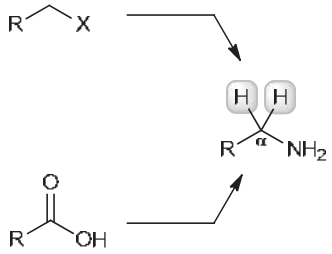
(c) The desired amine can be made from bromocyclohexane, as shown. Treatment with sodium cyanide gives a nitrile (via an S_N2 reaction). Reduction of the nitrile with excess lithium aluminum hydride, followed by water work-up, gives the product:



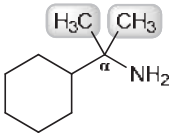
Alternatively, the desired amine can be made from the corresponding carboxylic acid, as shown below. Treatment with thionyl chloride gives an acid chloride, which can then be treated with excess ammonia to give an amide. The amide is then reduced with excess lithium aluminum hydride, followed by water work-up, to give the product:



22.11. This compound cannot be prepared from an alkyl halide or a carboxylic acid, using the methods described in this section, because both methods produce an amine with two alpha protons:



The desired product has two methyl groups at the alpha position:

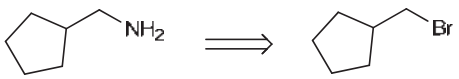


So this product cannot be made with either of the synthetic methods above.

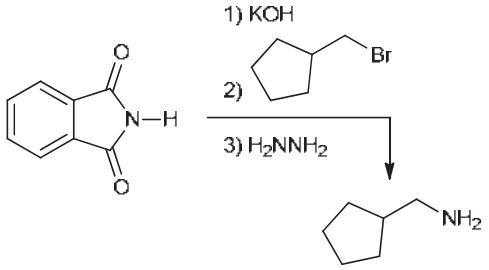
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22.12.

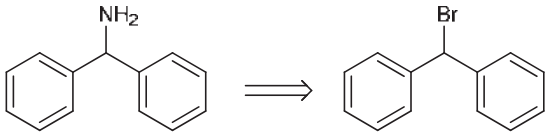
(a) We begin by identifying an alkyl halide that can serve as a precursor:



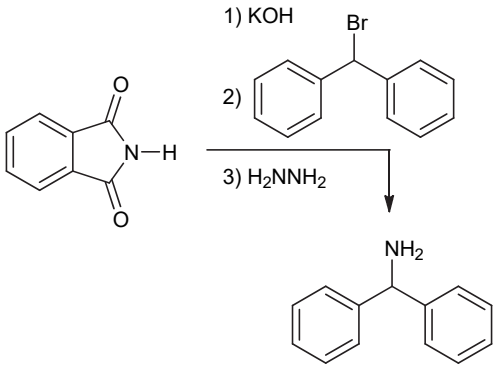
In the Gabriel synthesis, phthalimide is the starting material, and three steps are required. In the first step, phthalimide is deprotonated by hydroxide to give potassium phthalimide, which can serve as a nucleophile and attack the alkyl halide above in an S_N2 process. Subsequent treatment with hydrazine (or aqueous acid) releases the desired amine:



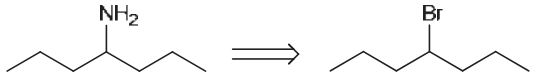
(b) We begin by identifying a halide that can serve as a precursor:



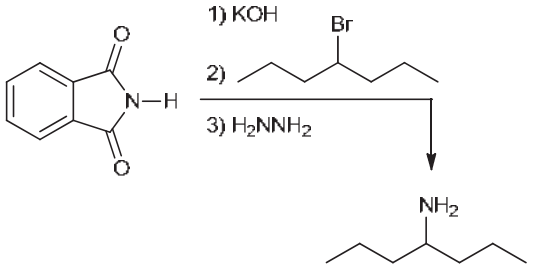
In the Gabriel synthesis, phthalimide is the starting material, and three steps are required. In the first step, phthalimide is deprotonated by hydroxide to give potassium phthalimide, which can serve as a nucleophile and attack the halide above in an S_N2 process. Subsequent treatment with hydrazine (or aqueous acid) releases the desired amine:



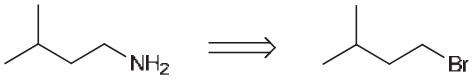
(c) We begin by identifying an alkyl halide that can serve as a precursor:



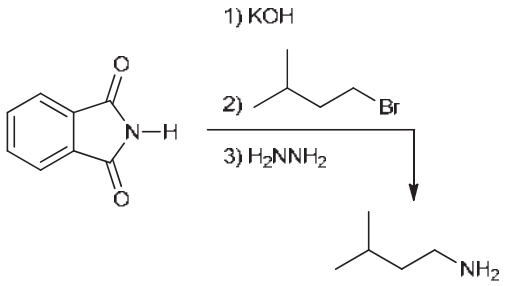
In the Gabriel synthesis, phthalimide is the starting material, and three steps are required. In the first step, phthalimide is deprotonated by hydroxide to give potassium phthalimide, which can serve as a nucleophile and attack the alkyl halide above in an S_N2 process. Subsequent treatment with hydrazine (or aqueous acid) releases the desired amine:



(d) We begin by identifying an alkyl halide that can serve as a precursor:

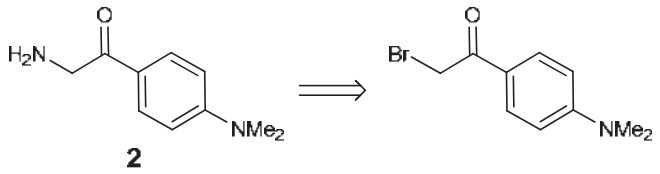


In the Gabriel synthesis, phthalimide is the starting material, and three steps are required. In the first step, phthalimide is deprotonated by hydroxide to give potassium phthalimide, which can serve as a nucleophile and attack the alkyl halide above in an S_N2 process. Subsequent treatment with hydrazine (or aqueous acid) releases the desired amine:

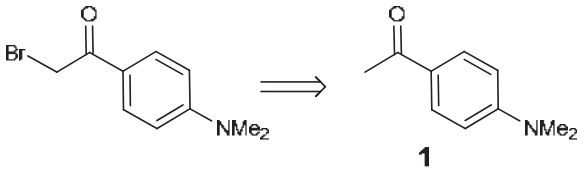


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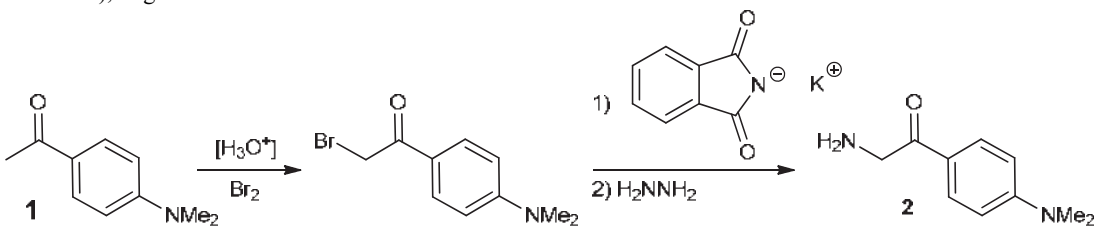
22.13. The problem statement dictates that a Gabriel synthesis be employed, so we begin by identifying a suitable alkyl halide that can be converted into compound **2** via a Gabriel synthesis.



Since the bromine atom is attached to the alpha carbon, this halide can be installed by an alpha-halogenation of **1**.

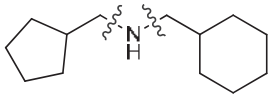


Enolization of **1** under basic conditions would lead to tribromination of the alpha carbon, followed by a C-C bond cleaving reaction (the haloform reaction). The proper way to mono-brominate **1** involves the use of acidic conditions. Treatment of the ketone (**1**) with Br_2 under catalytic acidic conditions affords the alpha bromo ketone. Once the necessary alkyl halide has been prepared, it can be treated with potassium phthalimide, followed by hydrazine (or aqueous acid), to give the desired amine as shown:

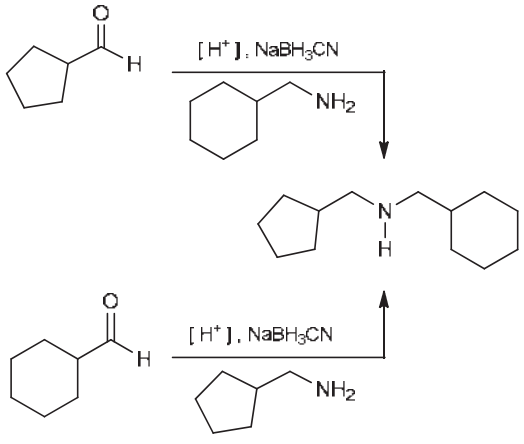


22.14.

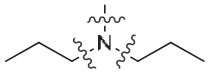
(a) The compound has two C-N bonds:



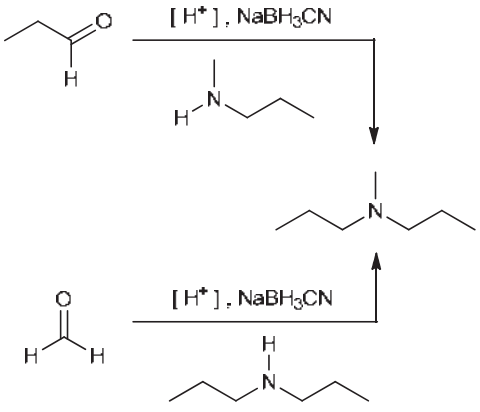
Each of these bonds can be made via a reductive amination, giving two possible synthetic routes, shown here:



(b) The compound has three C-N bonds:

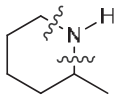


Each of these bonds can be made via a reductive amination. However, two of them are identical (because of symmetry), giving two possible synthetic routes, shown here:

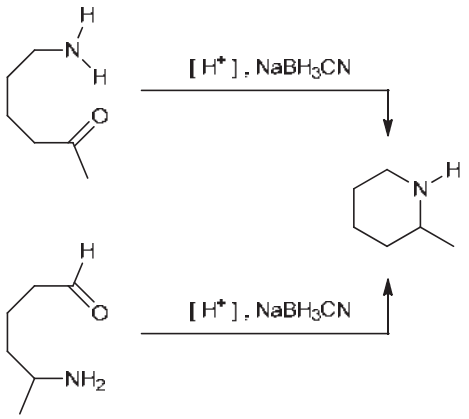


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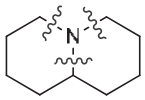
(c) The compound has two C-N bonds:



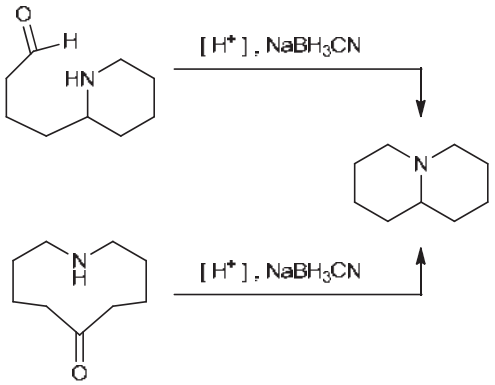
Each of these bonds can be made via a reductive amination, giving two possible synthetic routes, shown here:



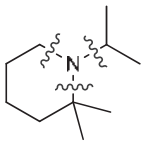
(d) The compound has three C-N bonds:



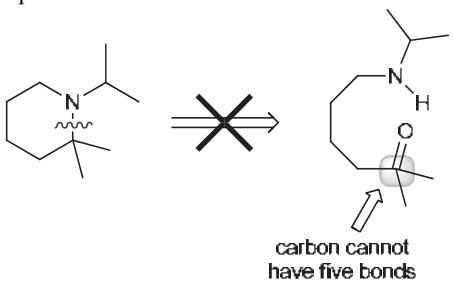
Each of these bonds can be made via a reductive amination. However, two of them are identical (because of symmetry), giving two possible synthetic routes, shown here:



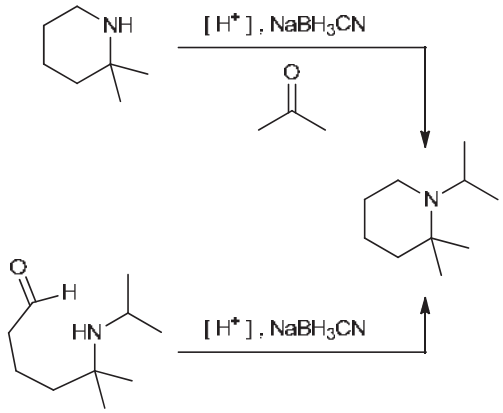
(e) The compound has three C-N bonds:



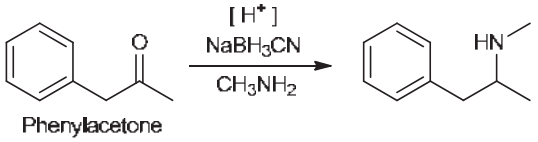
However, one of these bonds cannot be made via a reductive amination, because the starting material cannot have a pentavalent carbon atom:



Each of the other two C-N bonds can be made via reductive amination, giving two possible synthetic routes, shown here:

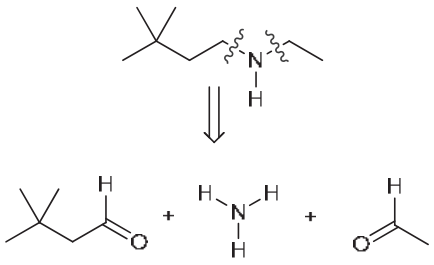


22.15. Phenylacetone is expected to give a secondary amine upon treatment with methyl amine in the presence of sodium cyanoborohydride and an acid catalyst, as shown:

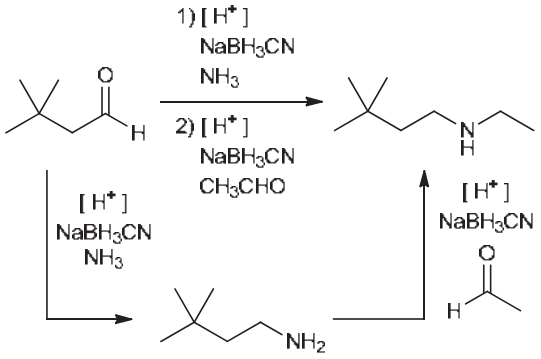


22.16.

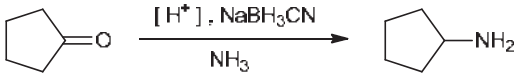
(a) This amine is secondary (it bears two alkyl groups). The source of nitrogen is ammonia, which dictates that each group must be installed via a reductive amination process. The following retrosynthetic analysis reveals the necessary starting materials:



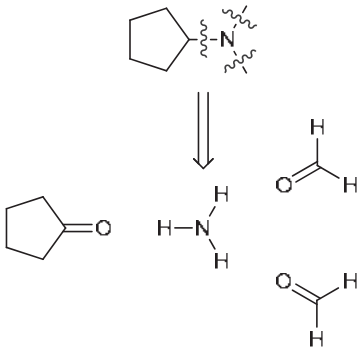
Each C-N bond can be formed via a reductive amination, as shown in the following forward scheme:



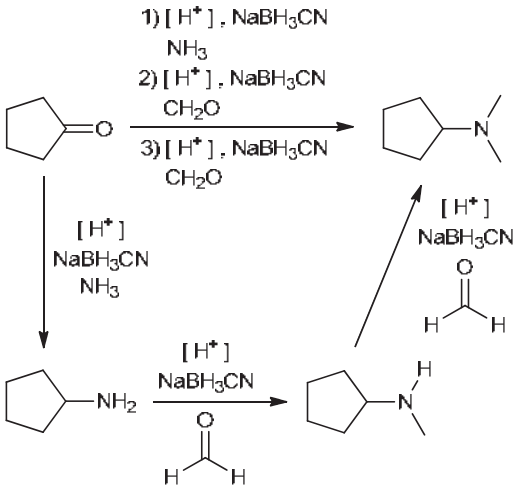
(b) Cyclopentyl amine can be made from cyclopentanone and ammonia, via a reductive amination, as shown:



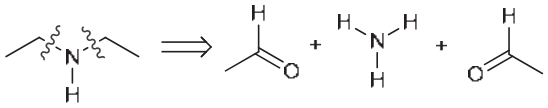
(c) This amine is tertiary (it bears three alkyl groups). The source of nitrogen is ammonia, which dictates that each group must be installed via a reductive amination process. The following retrosynthetic analysis reveals the necessary starting materials:



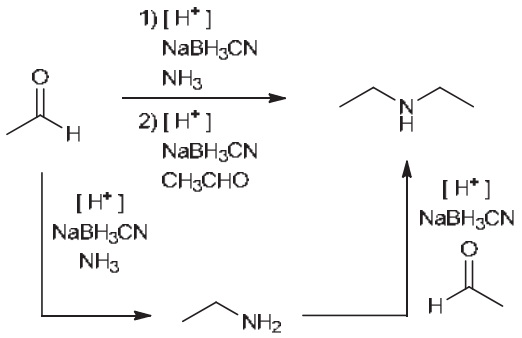
Each C-N bond can be formed via a reductive amination, as shown in the following forward scheme:



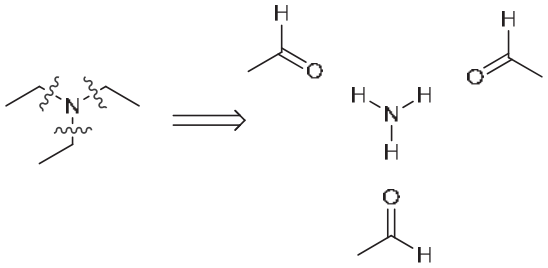
(d) This amine is secondary (it bears two ethyl groups). The source of nitrogen is ammonia, which dictates that each group must be installed via a reductive amination process. The following retrosynthetic analysis reveals the necessary starting materials:



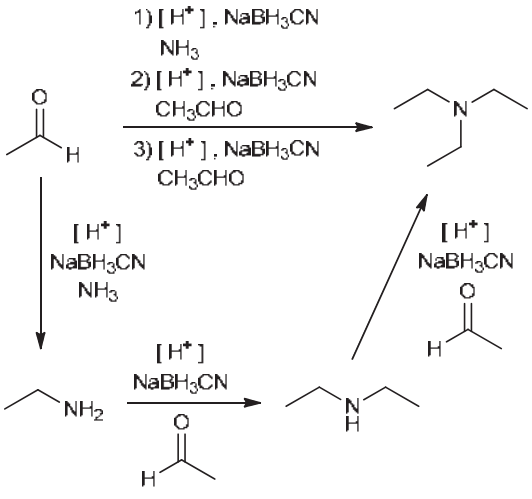
Each C-N bond can be formed via a reductive amination, as shown in the following forward scheme:



(e) This amine is tertiary (it bears three ethyl groups). The source of nitrogen is ammonia, which dictates that each group must be installed via a reductive amination process. The following retrosynthetic analysis reveals the necessary starting materials:

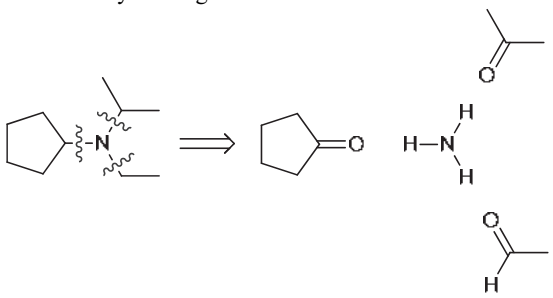


Each C-N bond can be formed via a reductive amination, as shown in the following forward scheme:

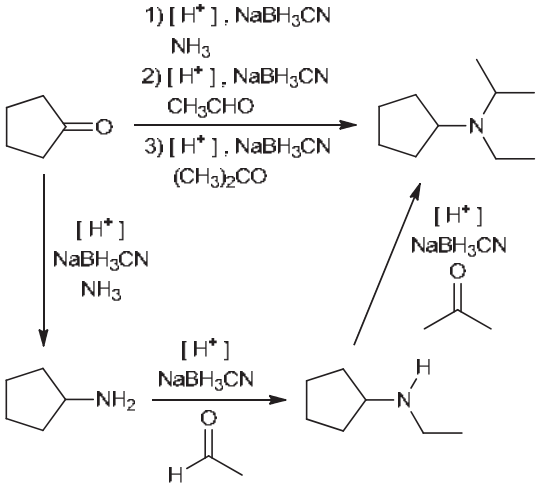


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(f) This amine is tertiary (it bears three alkyl groups). The source of nitrogen is ammonia, which dictates that each group must be installed via a reductive amination process. The following retrosynthetic analysis reveals the necessary starting materials:

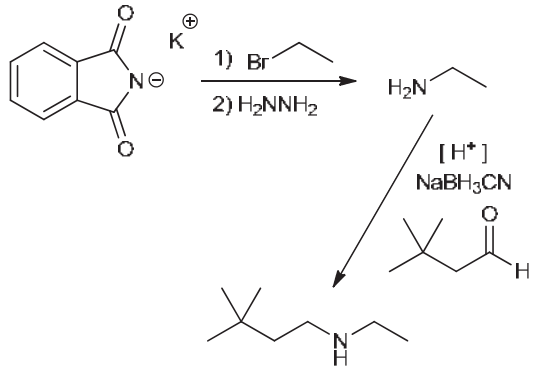


Each C-N bond can be formed via a reductive amination, as shown in the following forward scheme:

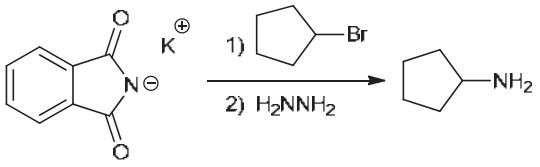


22.17.

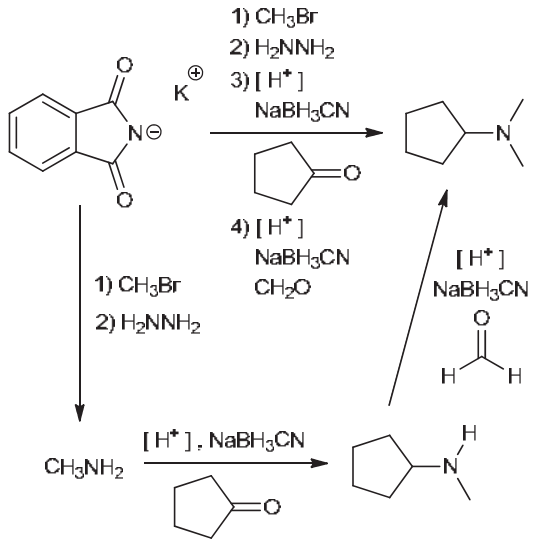
(a) The desired amine is secondary, so we must install two alkyl groups. The first alkyl group is installed via a Gabriel synthesis, and the remaining alkyl group is installed via a reductive amination process. There is a choice regarding which group to install via the initial Gabriel synthesis, so we choose the least sterically hindered group (the group whose installation involves the least hindered alkyl halide):



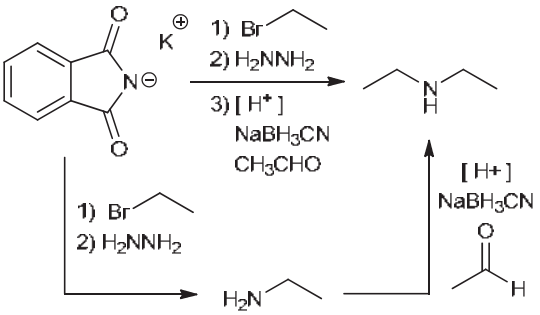
(b) The desired amine is primary, so we only need to install one alkyl group, which can be achieved with a Gabriel synthesis, as shown:



(c) The desired amine is tertiary, so we must install three alkyl groups. The first alkyl group is installed via a Gabriel synthesis, and the remaining alkyl groups are installed via reductive amination processes. There is a choice regarding which group to install via the initial Gabriel synthesis, so we choose the least sterically hindered group (one of the methyl groups):

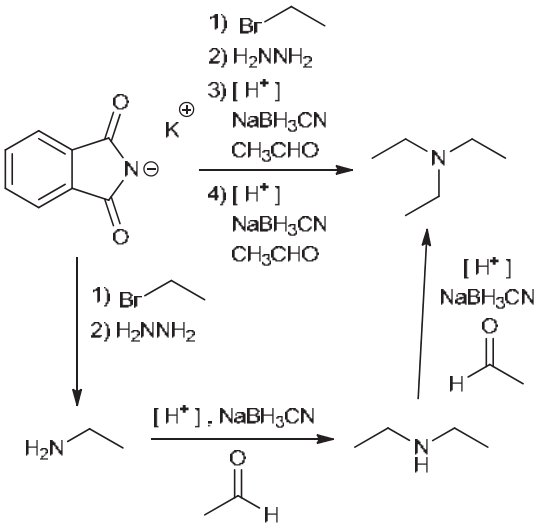


(d) The desired amine is secondary, so we must install two alkyl groups. The first ethyl group is installed via a Gabriel synthesis, and the remaining ethyl group is installed via a reductive amination process:

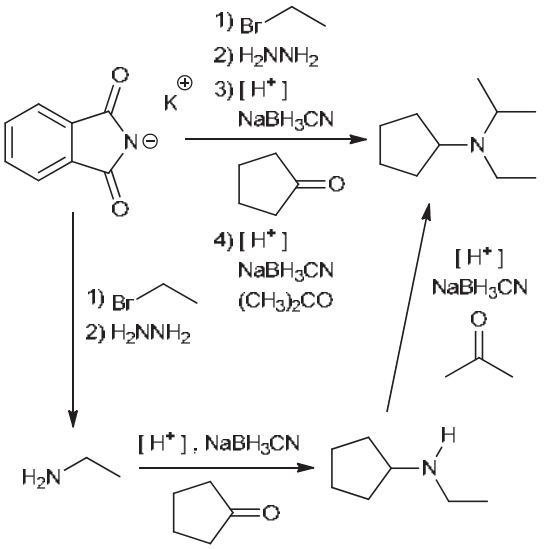


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(e) The desired amine is tertiary, so we must install three alkyl groups (all ethyl groups). The first ethyl group is installed via a Gabriel synthesis, and the remaining ethyl groups are installed via reductive amination processes.

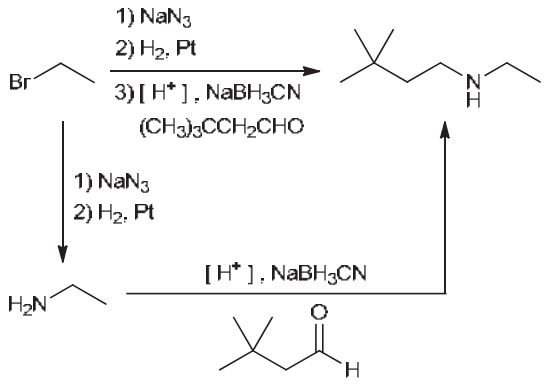


(f) The desired amine is tertiary, so we must install three alkyl groups. The first alkyl group is installed via a Gabriel synthesis, and the remaining alkyl groups are installed via reductive amination processes. There is a choice regarding which group to install via the initial Gabriel synthesis, so we choose the least sterically hindered group (the ethyl group):

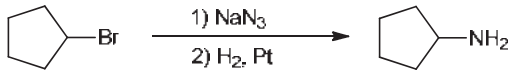


22.18.

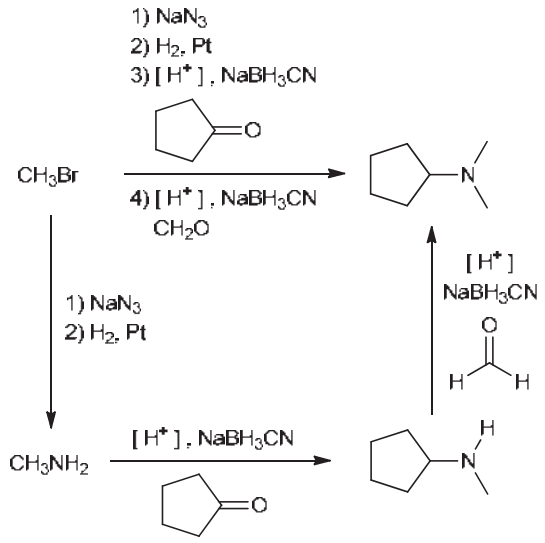
(a) The desired amine is secondary, so we must install two alkyl groups. The first alkyl group is installed via an azide synthesis, and the remaining alkyl group is installed via a reductive amination process. There is a choice regarding which group to install via the initial azide synthesis, so we choose the least sterically hindered group (the group whose installation involves the least hindered alkyl halide):



(b) The desired amine is primary, so we only need to install one alkyl group, which can be achieved via an azide synthesis, as shown:

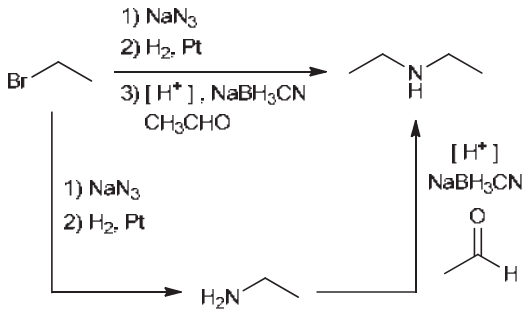


(c) The desired amine is tertiary, so we must install three alkyl groups. The first alkyl group is installed via an azide synthesis, and the remaining alkyl groups are installed via reductive amination processes. There is a choice regarding which group to install via the initial azide synthesis, so we choose the least sterically hindered group (one of the methyl groups):

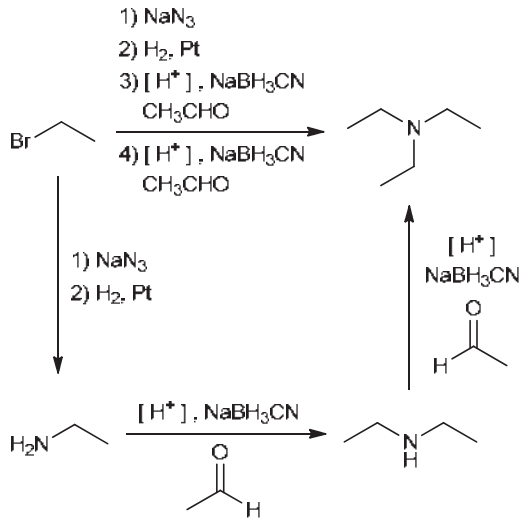


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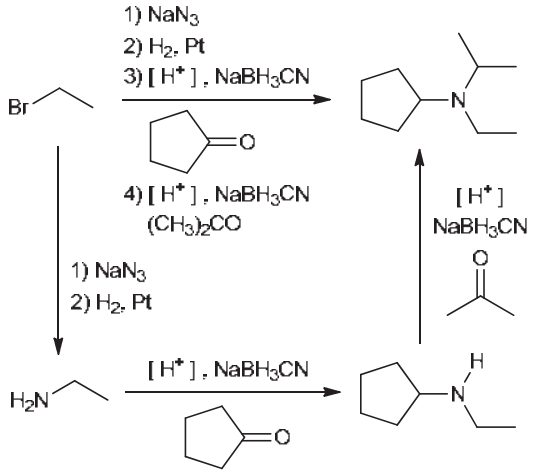
(d) The desired amine is secondary, so we must install two alkyl groups. The first ethyl group is installed via an azide synthesis, and the remaining ethyl group is installed via a reductive amination process:



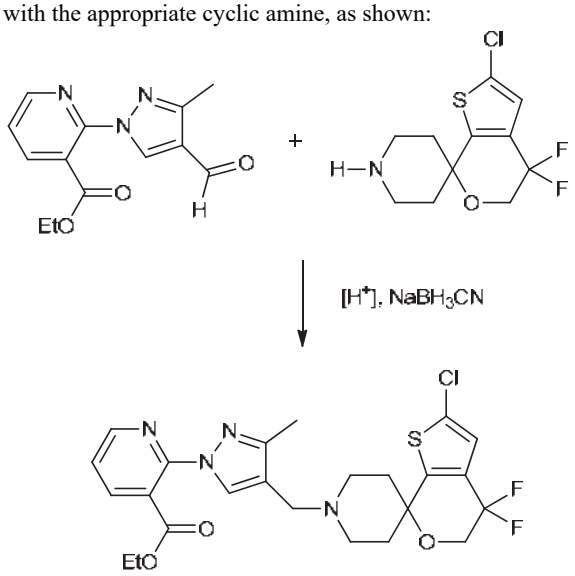
(e) The desired amine is tertiary, so we must install three alkyl groups (all ethyl groups). The first ethyl group is installed via an azide synthesis, and the remaining ethyl groups are installed via reductive amination processes.



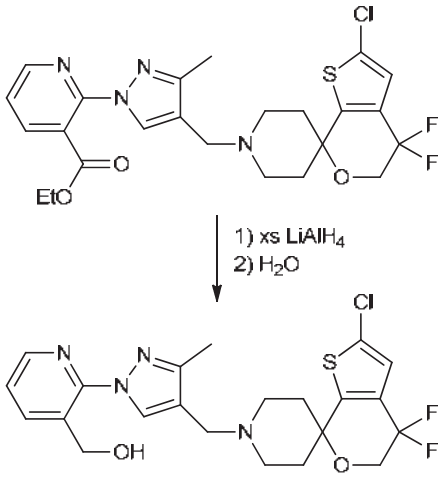
(f) The desired amine is tertiary, so we must install three alkyl groups. The first alkyl group is installed via an azide synthesis, and the remaining alkyl groups are installed via reductive amination processes. There is a choice regarding which group to install via the initial azide synthesis, so we choose the least sterically hindered group (the ethyl group):



22.19. For the conversion of **1** to **2**, the desired C-N bond can be installed via a reductive amination process, with the appropriate cyclic amine, as shown:

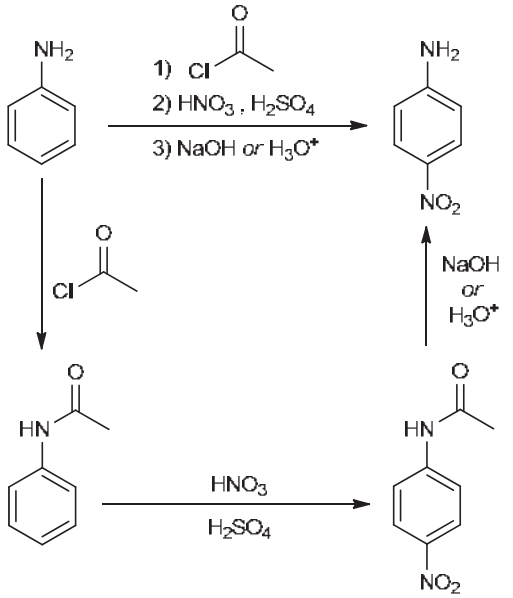


Then, conversion of **2** to **3** requires reduction of an ester group, which can generally be achieved with excess $LiAlH_4$:

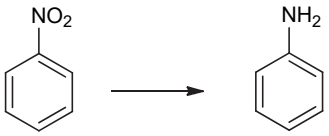


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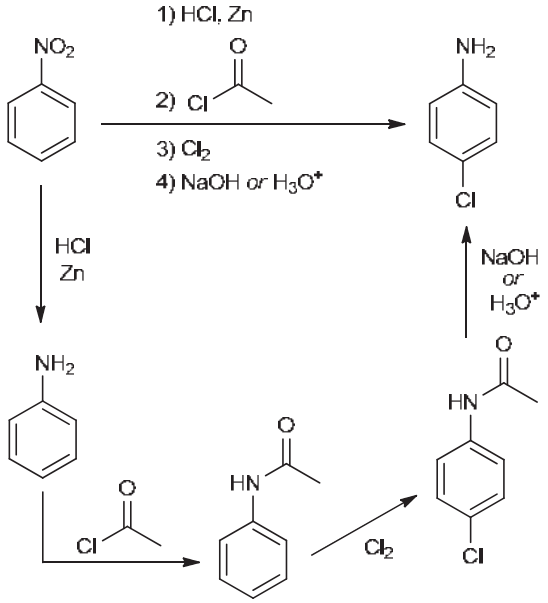
22.20. Acetylation of the amino group allows for direct nitration of the ring (in the *para* position). After nitration is complete, the acetyl group can be removed in aqueous basic or acidic conditions:



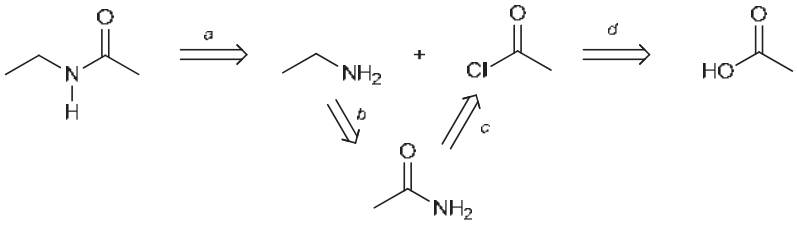
22.21. Direct chlorination of nitrobenzene would result in a *meta*-disubstituted product (because the nitro group is *meta*-directing). So we must first reduce the nitro group into an amino group, thereby converting a *meta* director into an *ortho-para* director:



Monochlorination of aniline (in the *para* position) will then give the product. Unfortunately, aniline will not efficiently undergo monochlorination (the ring is too highly activated to install just one chlorine atom). However, the strongly activating effect of the amino group can be temporarily diminished via acetylation. Then, after monochlorination has been performed, the acetyl group can be removed in aqueous basic or acidic conditions. The entire synthesis is shown here:



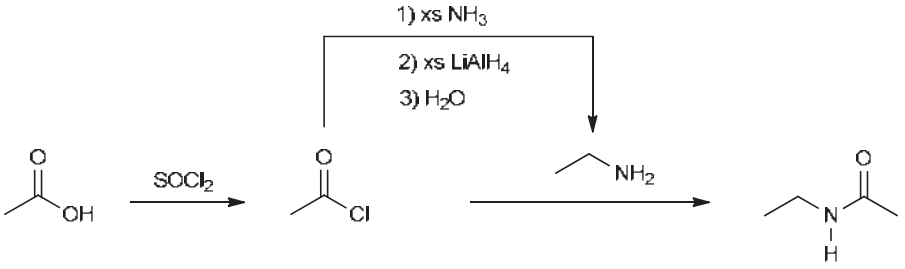
22.22. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a-d*) follows.



a. The product can be made from ethyl amine and acetyl chloride, via a nucleophilic acyl substitution reaction.
b. Ethyl amine can be made from acetamide via reduction with $LiAlH_4$, followed by water work-up.
c. Acetamide can be made from acetyl chloride, via a nucleophilic acyl substitution reaction.
d. Acetyl chloride can be made from acetic acid upon treatment with thionyl chloride.

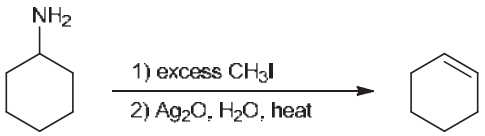
Now let's draw the forward scheme. Acetic acid is treated with thionyl chloride to give acetyl chloride. One equivalent of acetyl chloride is converted into ethyl amine (via aminolysis, followed by reduction), which is then treated with another equivalent of acetyl chloride to give the product:

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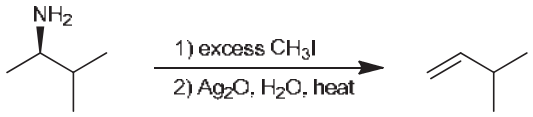


22.23.

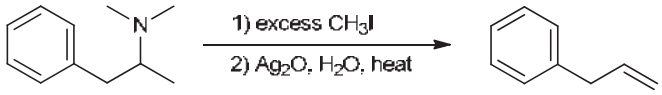
(a) The starting material is an amine, and the reagents indicate a Hofmann elimination. There are two β positions, but they are identical because of symmetry. As such, there is only one possible regiochemical outcome for the elimination process:



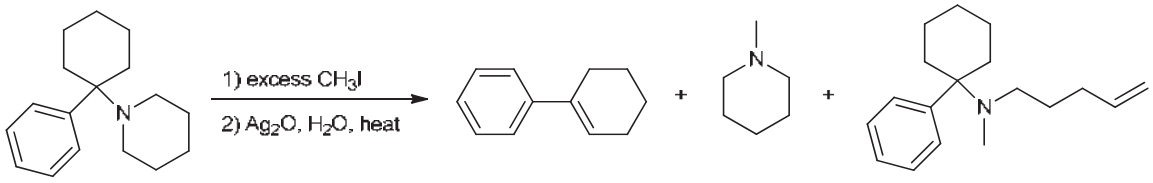
(b) The starting material is an amine, and the reagents indicate a Hofmann elimination. There are two β positions, and we expect elimination to occur at the β position that leads to the less substituted alkene:



(c) The starting material is an amine, and the reagents indicate a Hofmann elimination. There are two β positions, and we expect elimination to occur at the β position that leads to the less substituted alkene:

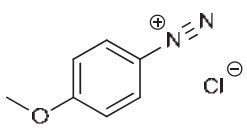


22.24. The third product is perhaps the most revealing. It indicates that the structure of PCP must contain an aromatic ring for which the benzylic position is connected to a nitrogen atom, and the same benzylic position is also part of a cyclohexyl ring. This justifies formation of the first product shown. The second product indicates that the nitrogen atom in PCP must be incorporated in a six-membered ring. This ring is opened during formation of the third product.

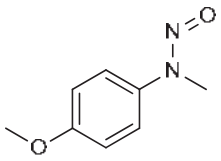


22.25.

(a) The starting material is a primary amine, so it is converted into the corresponding diazonium salt upon treatment with sodium nitrite and HCl:

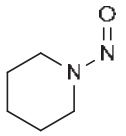


(b) The starting material is a secondary amine, so it is converted into the corresponding *N*-nitrosamine upon treatment with sodium nitrite and HCl:

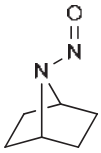


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(c) The starting material is a secondary amine, so it is converted into the corresponding *N*-nitrosamine upon treatment with sodium nitrite and HCl:



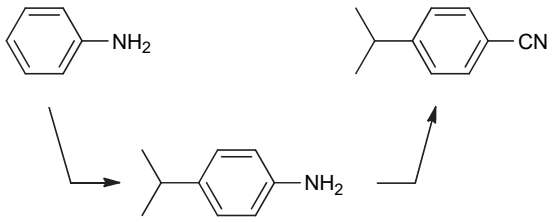
(d) The starting material is a secondary amine, so it is converted into the corresponding *N*-nitrosamine upon treatment with sodium nitrite and HCl:



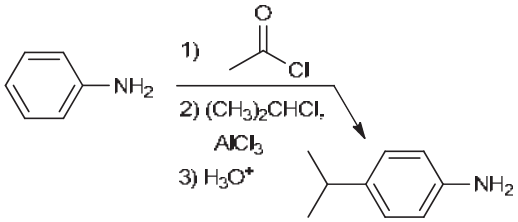
22.26.

(a) The desired transformation requires installation of an isopropyl group in the *para* position, as well as conversion of the NH_2 group into a cyano group. The former can be achieved via a Friedel-Crafts alkylation, while the latter can be achieved with a Sandmeyer reaction (via a diazonium ion).

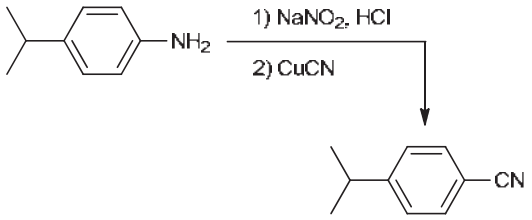
Now let's consider the order of events. An amino group is a strong activator, and therefore an *ortho-para* director, while a cyano group is a *meta* director. Therefore, in order to achieve *para*-disubstitution, the isopropyl group must be installed before conversion of the amino group into a cyano group:



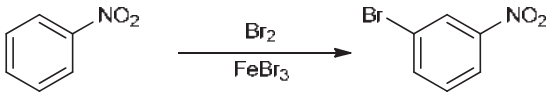
However, this strategy has one flaw. A Friedel-Crafts alkylation requires the use of a Lewis acid ($AlCl_3$), which can interact with the lone pair of the amino group, thereby converting the activating amino group into a deactivating group (see Section 22.8). As such, a Friedel-Crafts alkylation will not work. This issue can be avoided by acetylating the amino group first, thereby reducing the nucleophilicity of the lone pair on the nitrogen atom. The desired Friedel-Crafts alkylation is then performed (installing an isopropyl group), followed by hydrolysis to restore the amino group:



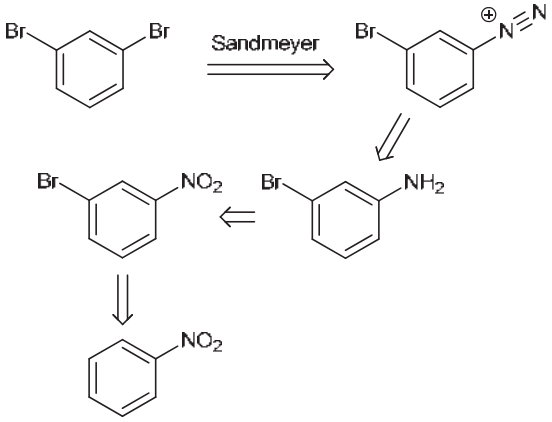
And finally, conversion of the amino group into a cyano group is achieved in two steps. First, *para*-isopropylaniline is treated with sodium nitrite and HCl, giving an aromatic diazonium ion, which is then treated with CuCN to give a Sandmeyer reaction that affords the desired product:



(b) The *meta*-directing effect of the nitro group enables installation of a bromine atom in the correct location (the *meta* position):

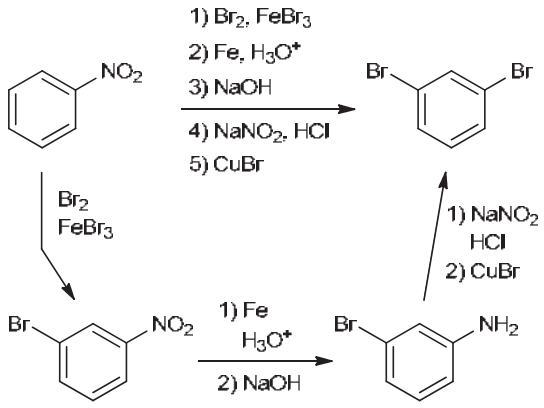


Now we must replace the nitro group with a bromine atom. One method for accomplishing this transformation involves the use of a Sandmeyer reaction, as seen in the following retrosynthetic analysis:

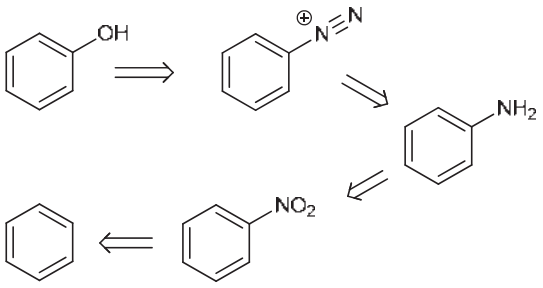


Now let's draw the forward scheme. The starting material is treated with Br_2 and a Lewis acid, thereby installing a bromine atom in the *meta* position. Reduction of the nitro group gives *meta*-bromoaniline, which is then converted into an aromatic diazonium ion upon treatment with sodium nitrite and HCl. The aromatic diazonium ion is then treated with CuBr to give a Sandmeyer reaction that affords the desired product, as shown:

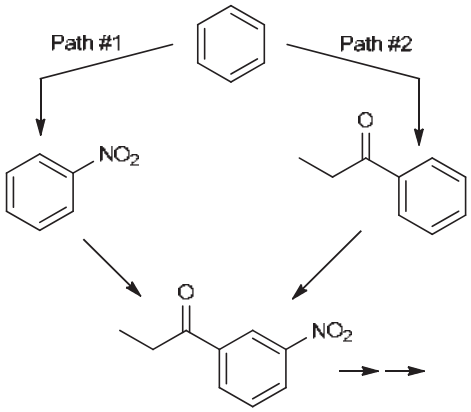
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(c) The starting material is benzene and the product is disubstituted. Specifically, we must install a propyl group and a hydroxyl group. Installation of a propyl group can be achieved with a Friedel-Crafts acylation (followed by reduction). Installation of a hydroxyl group can be achieved via a diazonium ion, as shown in the following retrosynthetic analysis:

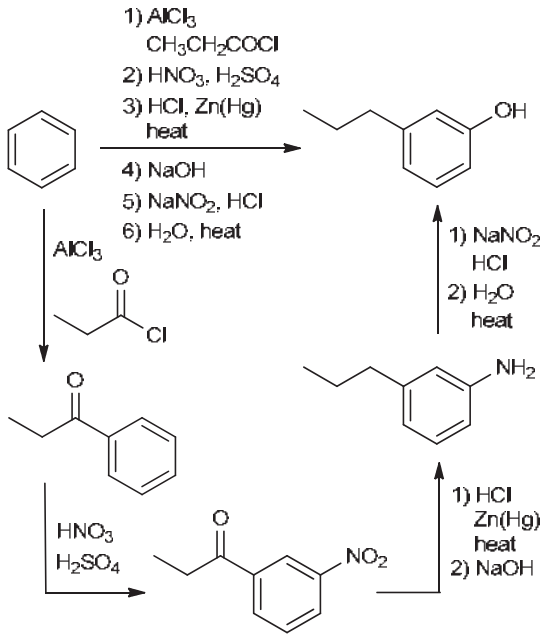


Now let's consider the order of events. In order to achieve *meta*-disubstitution, we must capitalize either on the *meta*-directing effects of a nitro group, or on the *meta*-directing effects of an acyl group:

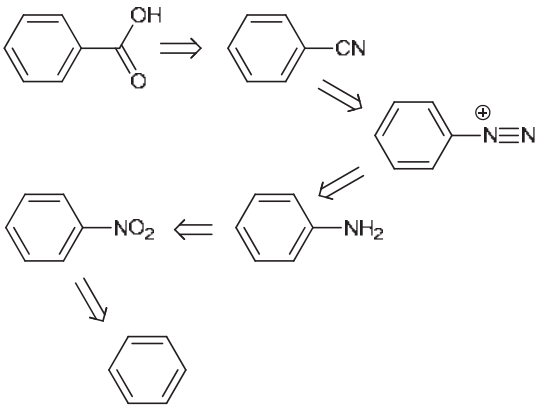


The first path is flawed, because it involves a Friedel-Crafts acylation process on a strongly deactivated ring, which will not occur. Therefore, only the second pathway is viable.

Now let's draw the forward scheme. A Friedel-Crafts acylation will install an acyl group, which is *meta*-directing. Upon treatment with nitric acid and sulfuric acid, a nitro group is then installed in the *meta* position. The conditions that reduce the acyl group are likely to reduce the nitro group as well, followed by basic work-up, to give *meta*-propylaniline, which is then converted into an aromatic diazonium ion upon treatment with sodium nitrite and HCl. The aromatic diazonium ion is then treated with H_2O and heat to afford the desired product, as shown:

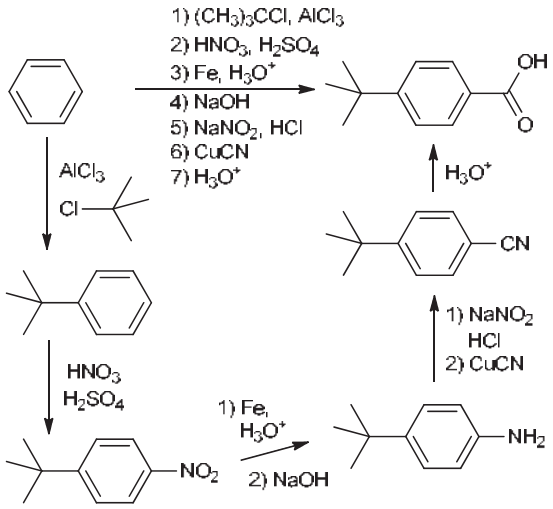


(d) Installation of a *tert*-butyl group can be achieved with a Friedel-Crafts alkylation. Installation of a carboxylic acid group can be achieved via a diazonium ion, as shown in the following retrosynthetic analysis:



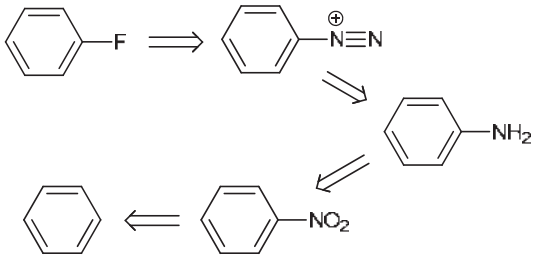
Now let's consider the order of events. The desired product is *para*-disubstituted, which can be achieved by installing the *tert*-butyl group first. This group is very large and will favor nitration at the *para* position, as seen in the following forward scheme:

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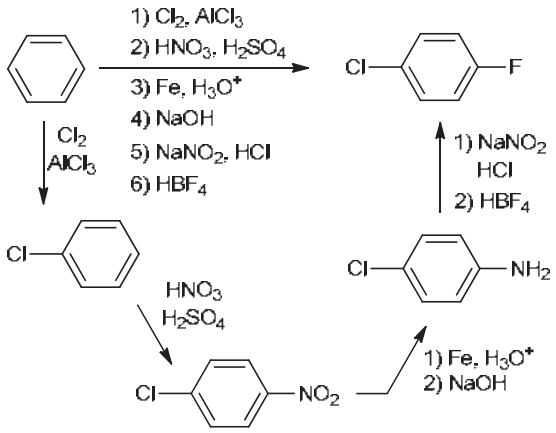
Alternatively, the first step of the synthesis above can be followed by a Friedel-Crafts alkylation (with MeCl and $AlCl_3$), followed by oxidation of the benzylic position with chromic acid to give the desired product.

(e) Installation of a chlorine atom can be achieved by treating benzene with Cl_2 and $AlCl_3$ (via an electrophilic aromatic substitution reaction). Installation of a fluorine atom cannot be achieved via a similar process, but it can be achieved via a diazonium ion, as shown in the following retrosynthetic analysis:

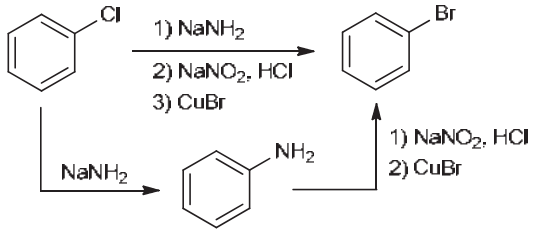


Now let's consider the order of events. Chlorine is larger than fluorine, so it is reasonable to install the chlorine atom first (thereby favoring the *para*-disubstituted product over the *ortho*-disubstituted product). In fact, we cannot install the fluorine atom first, because the directing effects of a fluorine substituent were not discussed in Chapter 18 (beyond scope of course).

Now let's draw the forward scheme. The starting material is treated with Cl_2 and a Lewis acid, thereby installing a chlorine atom. A nitro group is then installed in the *para* position, upon treatment with nitric acid and sulfuric acid. Reduction of the nitro group gives *para*-chloroaniline, which is then converted into an aromatic diazonium ion upon treatment with sodium nitrite and HCl. The aromatic diazonium ion is then treated with HBF_4 (a Schiemann reaction) to give the desired product, as shown:

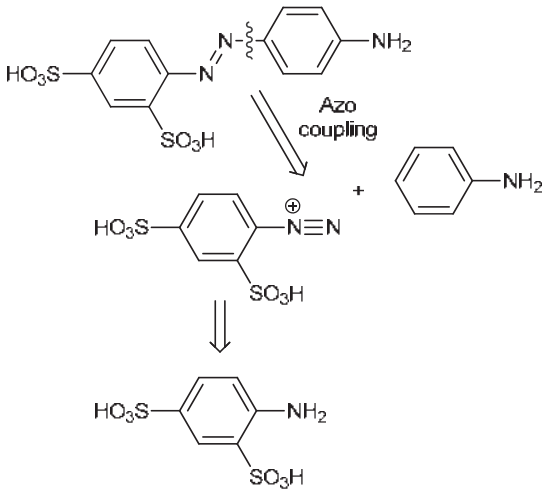


(f) This transformation can be achieved by replacing the chlorine atom with an amino group (via elimination-addition), followed by conversion of aniline into a diazonium ion, followed by subsequent treatment with CuBr (via a Sandmeyer reaction):



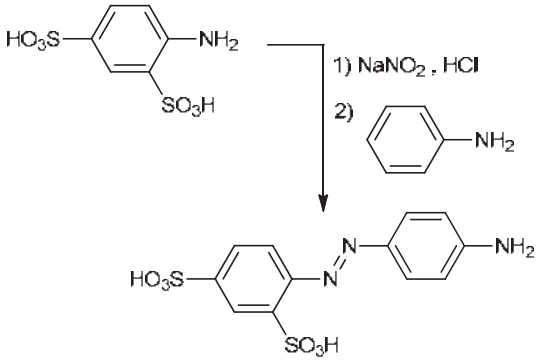
22.27.

(a) The starting material has two aromatic rings. The ring bearing the amino group is more highly activated. During the azo coupling process, the activated ring functions as the nucleophile, and the other ring must function as the diazonium ion, as shown in the following retrosynthetic analysis:

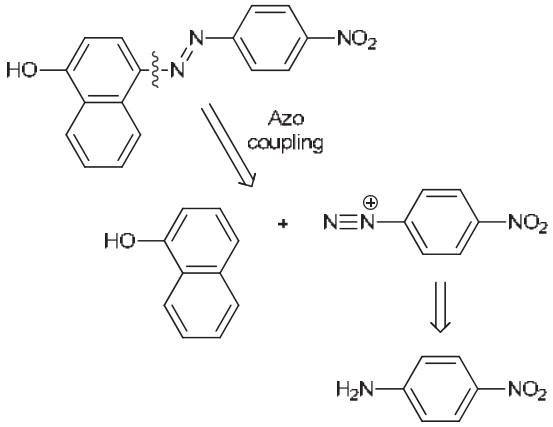


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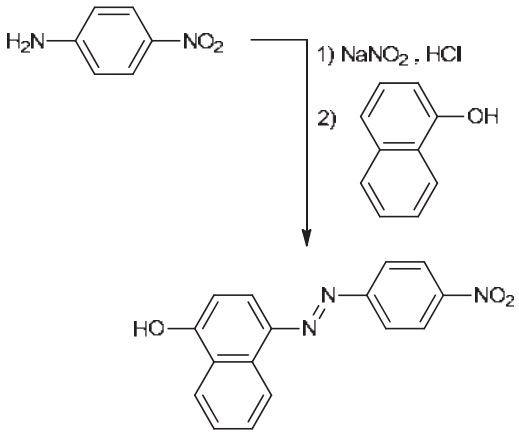
The forward scheme is shown here:



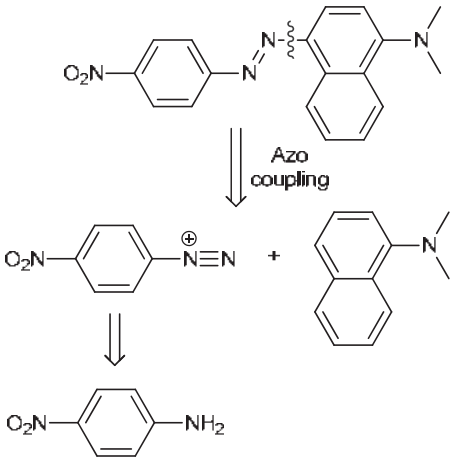
(b) The ring bearing the hydroxyl group is more highly activated ring. During the azo coupling process, the activated ring functions as the nucleophile, and the other ring must function as the diazonium ion, as shown in the following retrosynthetic analysis:



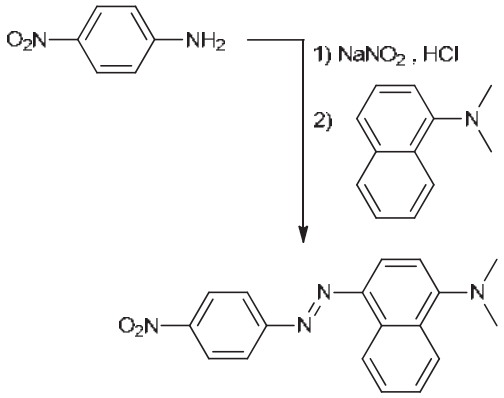
The forward scheme is shown here:



(c) The ring bearing the dimethylamino group is the more highly activated ring. During the azo coupling process, the activated ring functions as the nucleophile, and the other ring must function as the diazonium ion, as shown in the following retrosynthetic analysis:

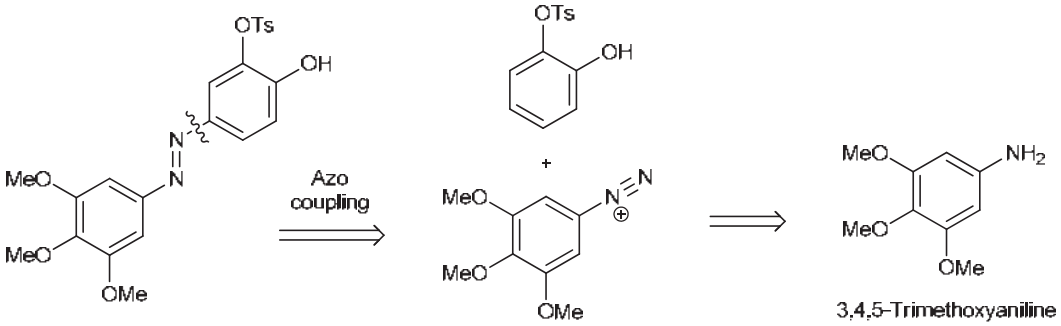


The forward scheme is shown here:

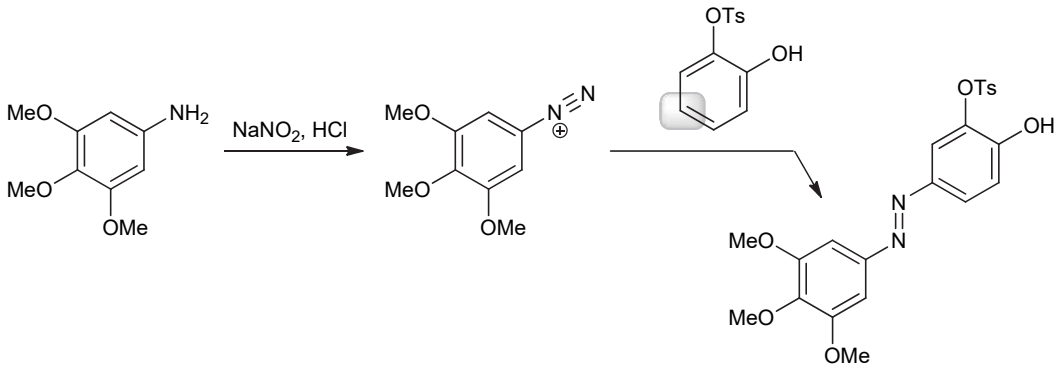


22.28.

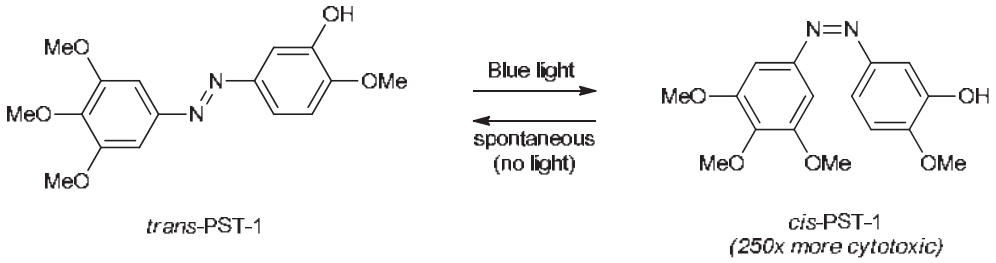
(a) The retrosynthesis is guided by the instructions that the synthesis must begin with 3,4,5-trimethoxyaniline. Disconnection at the appropriate location leads to the required diazonium salt (prepared from 3,4,5-trimethoxyaniline) and the dihydroxybenzene derivative shown (called 2-hydroxyphenyl-*para*-toluenesulfonate).



Note that the electrophilic aromatic substitution reaction takes place at the position that is *para* to the more strongly activating OH group (the sulfonate ester is only a moderate activator, similar to a regular ester). The forward scheme is shown here:



(b) The *trans* isomer has the two aromatic rings on opposite sides of the N=N double bond. To draw the *cis* isomer, we need to place both groups on the same side of the double bond:

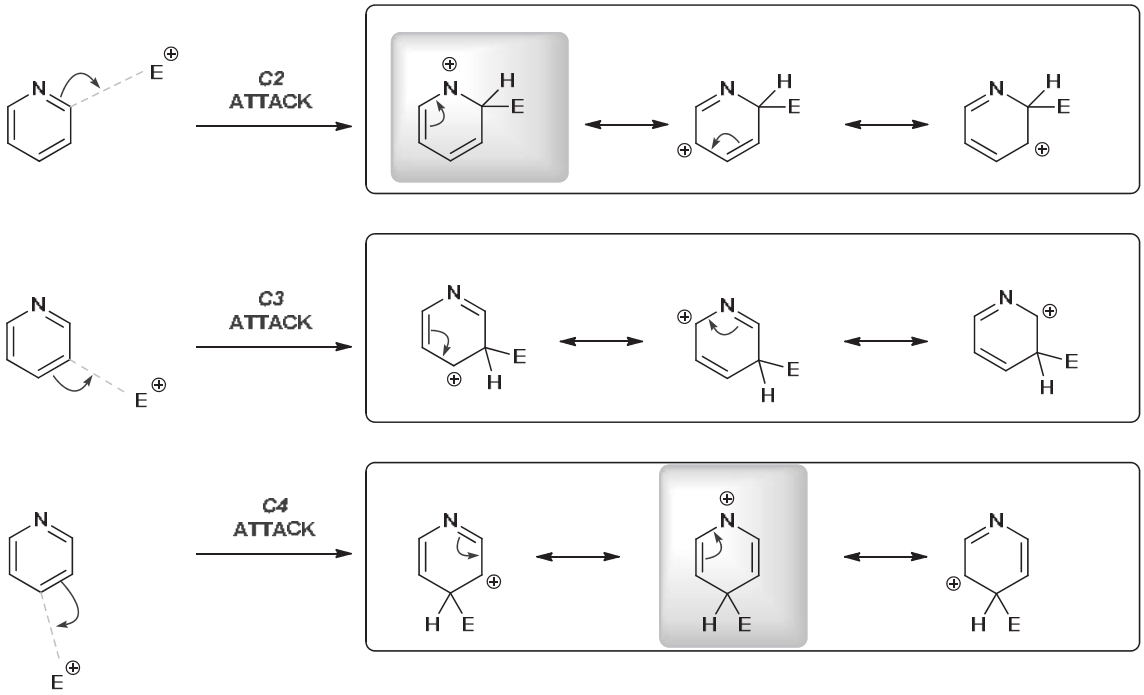


trans-PST-1

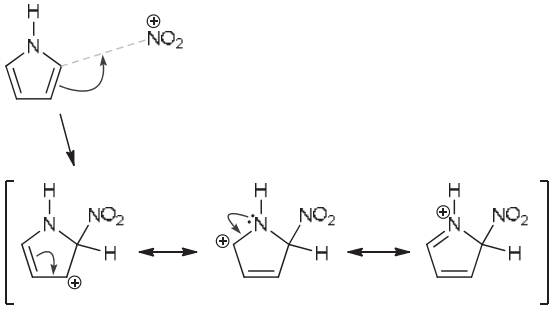
cis-PST-1
(250x more cytotoxic)

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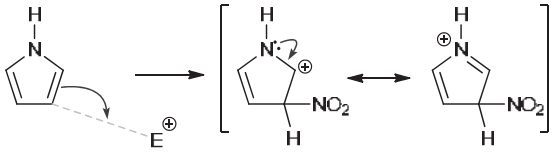
22.29. Attack at either C2 or C4 generates an intermediate that exhibits a resonance structure with a nitrogen atom that bears a positive charge and lacks an octet (highlighted below). Attack at C3 generates a more stable intermediate (carbon is more electropositive than nitrogen so a carbon atom can better stabilize a positive charge associated with an unfilled octet):



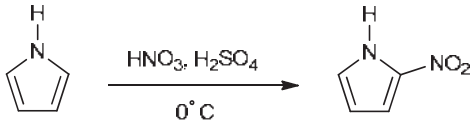
22.30. Attack at the C2 position proceeds via an intermediate with three resonance structures:



In contrast, attack at the C3 position proceeds via an intermediate with only two resonance structures:



The intermediate for C2 attack is lower in energy than the intermediate for C3 attack. The transition state leading to the intermediate of C2 attack will therefore be lower in energy than the transition state leading to the intermediate of C3 attack. As a result, C2 attack occurs more rapidly, giving the following product:



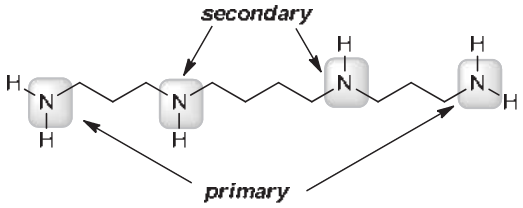
22.31.
(a) The second compound will have an N-H stretching signal between 3300 and 3500 cm^{-1}. The first compound will not have such a signal.
(b) When treated with HCl, the first compound will be protonated to form an ammonium salt that will produce an IR signal between 2200 and 3000 cm^{-1}. The second compound is not an amine and will not exhibit the same behavior.

22.32.
(a) The ^1H NMR spectrum of the first compound will have a singlet resulting from the N-methyl group. The ^1H NMR spectrum of the second compound is not expected to exhibit any singlets.
(b) The ^1H NMR spectrum of the first compound will have six signals, while the ^1H NMR spectrum of the second compound will have only three signals.

22.33. The designation "primary" indicates that two hydrogen atoms are attached to the nitrogen atom, while

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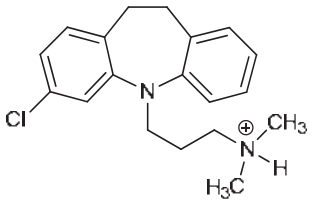
the designation "secondary" indicates that one hydrogen atom is attached to the nitrogen atom:



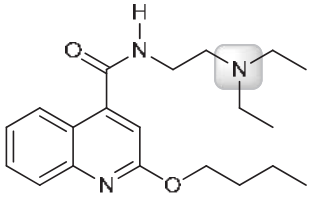
22.34.

(a) The lone pair that is farther away from the rings is the most basic, because that lone pair is localized. The lone pair of the other nitrogen atom is delocalized via resonance.

(b) The dimethylamino group exhibits a localized lone pair, and as such, it is expected to exist primarily as a charged ammonium ion ($pK_a \sim 10$; see pK_a table on inside cover of textbook) at physiological pH. In contrast, the other nitrogen atom exhibits a delocalized lone pair, and it is not expected to be protonated at physiological pH (see discussion of the Henderson-Hasselbalch equation in Section 20.3).



22.35. The nitrogen atom of the amide group exhibits a delocalized lone pair, so this lone pair will certainly not be the most basic. Indeed, amides do not function as bases. Each of the remaining two nitrogen atoms exhibits a localized lone pair. The nitrogen atom of the aromatic system has the localized lone pair in an sp^2 hybridized orbital (in the plane of the ring, and going away from the ring). In contrast, the other nitrogen atom (highlighted) has the localized lone pair in an sp^3 hybridized orbital. The sp^3 hybridized nitrogen atom (highlighted) is expected to be a better base than the sp^2 hybridized nitrogen atom, because the former has a lone pair that is farther away from the nucleus (held less tightly) and is therefore more available to function as a base. Also, a comparison of pK_a values (see inside cover of textbook) indicates that pyridine is a weaker base than triethyl amine (compare the pK_a values of the corresponding ammonium ions).



22.36.

(a) Pyridine is a weaker base than trimethylamine because the lone pair of pyridine occupies an sp^2 hybridized orbital, rather than an sp^3 hybridized orbital. By occupying an sp^2 hybridized orbital, the electrons of the lone pair have more *s* character and are therefore closer to the positively charged nucleus, rendering them less basic. As such, trimethylamine is a stronger base than pyridine:

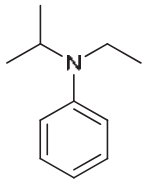


(b) The nitrogen atom of an amide group exhibits a lone pair that is highly delocalized and is therefore not expected to function as a base. Pyridine is a stronger base because the lone pair is localized (the lone pair occupies an sp^2 hybridized orbital):

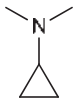


22.37.

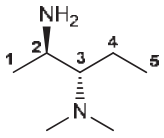
(a) The parent is aniline (aminobenzene), and there are two alkyl groups connected to the nitrogen atom (an ethyl group and an isopropyl group):



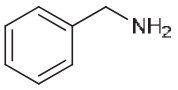
(b) The name indicates a three-membered ring connected to a nitrogen atom, as well as two substituents (both methyl groups) connected to the nitrogen atom.



(c) The parent is a five-membered chain (pentane) that bears an amino group at C2. In addition, there is a dimethyl amino group located at C3. The configuration of each chiral center (C2 and C3) is indicated in the name:

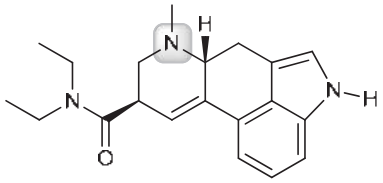


(d) The name indicates a primary amine in which the nitrogen atom is connected to a benzyl ($PhCH_2$–) group:



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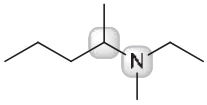
22.38. Only one of the nitrogen atoms (highlighted) has a localized lone pair.



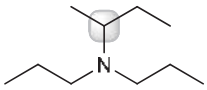
As such, this nitrogen atom is significantly more basic than the other two nitrogen atoms, each of which exhibits a highly delocalized lone pair. The nitrogen atom on the left is part of an amide group, and is not expected to function as a base, while the nitrogen atom on the right is using its lone pair to establish aromaticity. So that lone pair is also unavailable to serve as a base.

22.39.

(a) Recall that an atom bearing four different groups is a chiral center. There are two chiral centers (highlighted) in this compound. Notice that, in this case, the nitrogen atom is a chiral center because it is connected to four different groups (one of which is a lone pair).

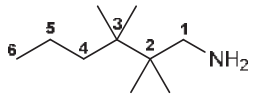


(b) Recall that an atom bearing four different groups is a chiral center. There is only one chiral center (highlighted) in this compound. Notice that, in this case, the nitrogen atom is not a chiral center because it is connected to two identical groups (two propyl groups).



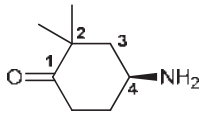
22.40.

(a) This compound is an amine that has only one alkyl group connected to the nitrogen atom. Since this alkyl group is complex, we must name the compound as an alkanamine (rather than an alkyl amine). The parent is comprised of six carbon atoms (thus, hexanamine), and the amino group is connected to C1. There are four methyl groups (two at C2 and two at C3), resulting in the following name:



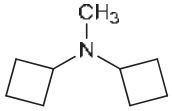
2,2,3,3-tetramethyl-1-hexanamine

(b) This compound has two functional groups (a carbonyl group and an NH_2 group). The carbonyl group takes priority, so the compound is named as a ketone (cyclohexanone), with the amino group listed as a substituent, located at C4. In addition, there are two methyl groups, both located at C2. The configuration of the chiral center is listed at the beginning of the name:



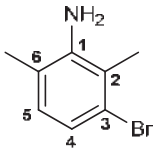
(*S*)-4-amino-2,2-dimethylcyclohexanone

(c) This compound is an amine in which the nitrogen atom is connected to three alkyl groups (two cyclobutyl groups and a methyl group) connected to the nitrogen atom, so we can name this compound as a trialkyl amine, rather than an alkanamine. The alkyl groups are listed in alphabetical order:



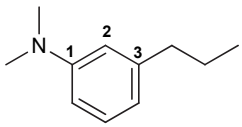
dicyclobutylmethylamine

(d) The parent is aniline, and there are two methyl groups (one at C2 and the other at C6), as well as one bromine atom located at C3:



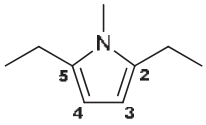
3-bromo-2,6-dimethylaniline

(e) The parent is aniline, and there are three substituents: a propyl group at C3 and two methyl groups (both connected to the nitrogen atom).



N,*N*-dimethyl-3-propylaniline

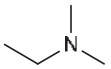
(f) The parent is pyrrole, and there are three substituents: a methyl group connected to the nitrogen atom, and two ethyl groups at C2 and C5.



2,5-diethyl-*N*-methyl pyrrole

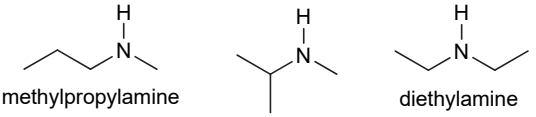
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22.41. The molecular formula ($C_4H_{11}N$) indicates no degrees of unsaturation (see Section 14.16), so all of the isomers must be acyclic amines. We will methodically consider all possible primary, secondary, and tertiary amines. Let's begin our analysis with tertiary amines. There is only one isomer that is a tertiary amine:



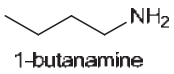
ethyldimethylamine

And there are three isomers that are all secondary amines:

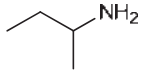


methylpropylamine isopropylmethylamine diethylamine

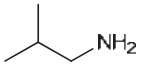
And finally, there are four isomers that are all primary amines:



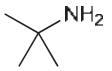
1-butanamine



2-butanamine



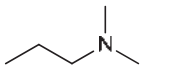
2-methyl-1-propanamine



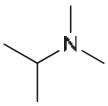
2-methyl-2-propanamine

In total, there are eight constitutional isomers with the molecular formula $C_4H_{11}N$.

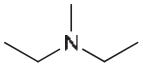
22.42. The molecular formula ($C_5H_{13}N$) indicates no degrees of unsaturation (see Section 14.16), so all of the isomers must be acyclic amines. The following three isomers are all tertiary amines (acyclic and fully saturated), and none of them have a chiral center:



dimethylpropylamine



isopropyldimethylamine



diethylmethylamine

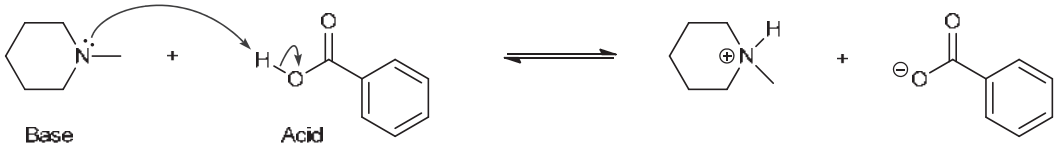
22.43.

(a) The lone pair on pyridine functions as a base and deprotonates acetic acid, giving a pyridinium ion and an acetate ion, as shown. Two curved arrows must be drawn. The first curved arrow shows the base attacking the proton, and the second curved arrow shows heterolytic cleavage of the O-H bond:



Base Acid

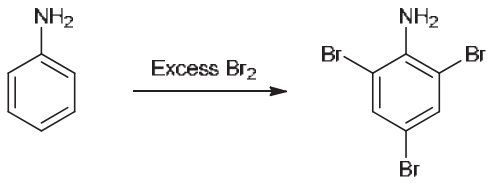
(b) The tertiary amine functions as a base and deprotonates the carboxylic acid (benzoic acid), giving an ammonium ion and a benzoate ion, as shown. Two curved arrows must be drawn. The first curved arrow shows the base attacking the proton, and the second curved arrow shows heterolytic cleavage of the O-H bond:



Base Acid

22.44.

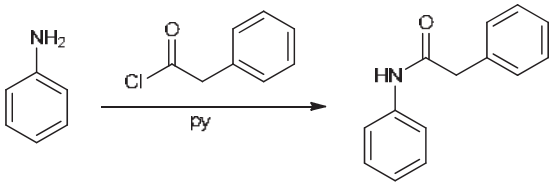
(a) The amino group of aniline is an *ortho-para* director and it strongly activates the ring toward electrophilic aromatic substitution. When treated with excess Br_2, we expect bromination to occur in the two *ortho* positions and the *para* position, giving 2,4,6-tribromoaniline:



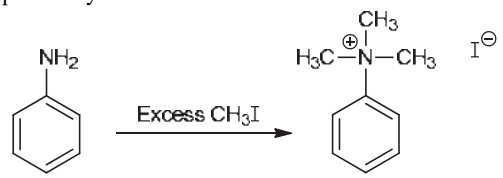
Excess Br_2

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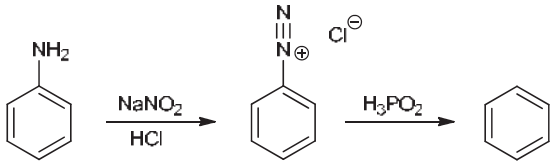
(b) Aniline is a strong nucleophile. When treated with an acid chloride, the amino group undergoes acylation, giving the following product. Pyridine functions as an acid sponge to neutralize the HCl that is produced as a by-product of the reaction.



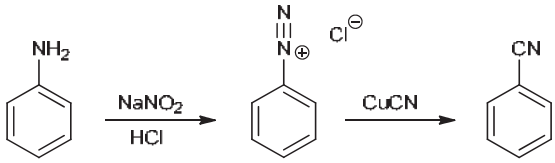
(c) When treated with excess methyl iodide, the amino group of aniline undergoes exhaustive alkylation to give a quaternary ammonium salt:



(d) Treating aniline with sodium nitrite and HCl gives a diazonium ion, which is then converted into benzene upon treatment with H_3PO_2:

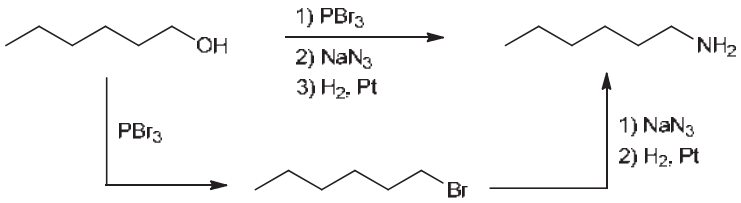


(e) Treating aniline with sodium nitrite and HCl gives a diazonium ion, which is then converted into benzonitrile via a Sandmeyer reaction (upon treatment with CuCN):

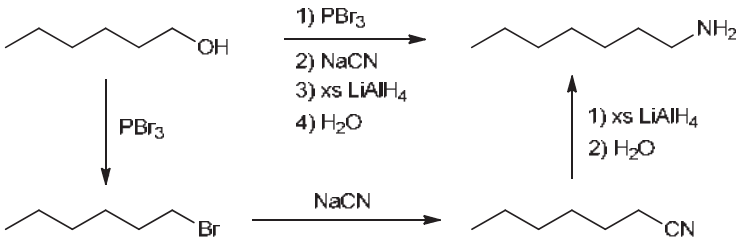


22.45.

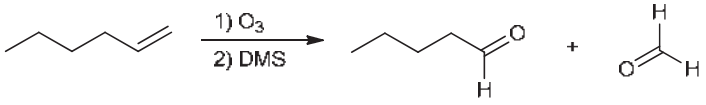
(a) This transformation does not involve a change in the carbon skeleton. Only the identity of the functional group must be changed. This can be achieved by converting the alcohol into an alkyl halide (upon treatment with PBr_3), followed by an azide synthesis, as shown below. Alternatively, the alkyl halide can be converted into the desired amine via a Gabriel synthesis.



(b) This transformation involves a change in the carbon skeleton, as well as a change in the identity and location of the functional group. There are certainly many ways to install the extra carbon atom and manipulate the functional group as necessary. One method involves converting the alcohol into an alkyl halide (upon treatment with PBr_3), followed by an S_N2 reaction with cyanide as the nucleophile, thereby giving a nitrile. Reduction of the nitrile with excess lithium aluminum hydride, followed by water work-up, gives the product:

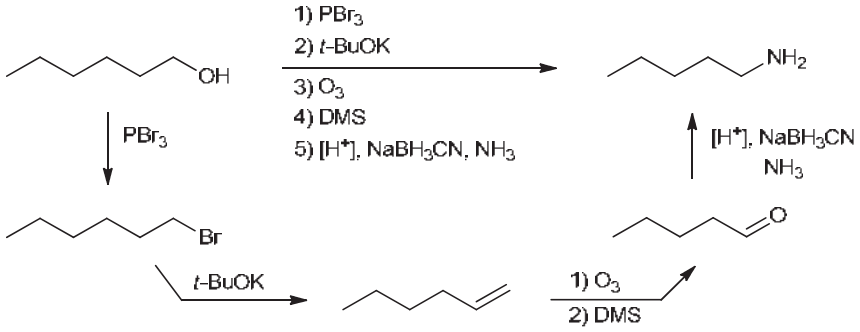


(c) The starting material has six carbon atoms, while the product has only five carbon atoms. In order to remove a carbon atom, a carbon-carbon bond must be broken, which can be accomplished via ozonolysis:



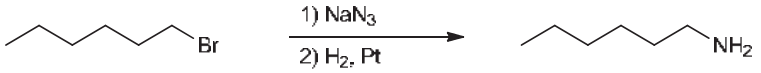
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This strategy requires that we first convert the starting alcohol into the alkene above, which can be achieved by treating the alcohol with PBr_3, giving an alkyl halide, followed by elimination with a strong, sterically hindered base (such as *tert*-butoxide) to give an alkene. Ozonolysis of the alkene gives pentanal, which can be converted into the product via reductive amination, as shown:

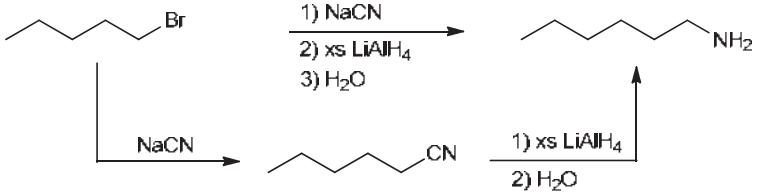


22.46.

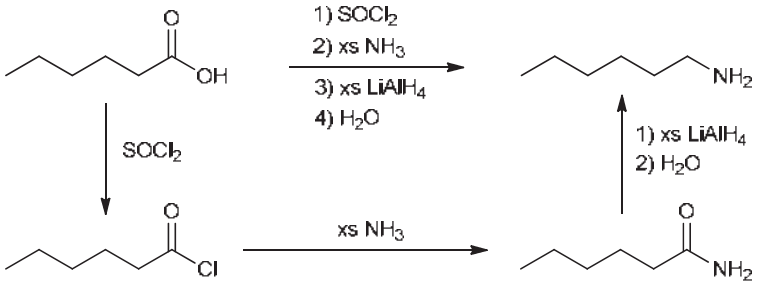
(a) This transformation does not involve a change in the carbon skeleton. Only the identity of the functional group must be changed. This can be achieved via an azide synthesis, as shown below. Alternatively, the alkyl halide can be converted into the desired amine via a Gabriel synthesis.



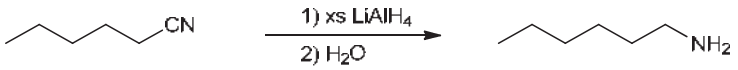
(b) This transformation involves a change in the carbon skeleton, as well as a change in the identity and location of the functional group. There are certainly many ways to install the extra carbon atom and manipulate the functional group as necessary. One method involves an S_N2 reaction with cyanide as the nucleophile, thereby converting the alkyl bromide into a nitrile. Reduction of the nitrile with excess lithium aluminum hydride, followed by water work-up, gives the product:



(c) This transformation does not involve a change in the carbon skeleton, although the identity of the functional group must be changed. There are certainly many ways to change the identity of the functional group. One method involves conversion of the carboxylic acid to the corresponding amide (upon treatment with thionyl chloride to give an acid chloride, followed by treatment with excess NH_3). Reduction of the amide with excess lithium aluminum hydride, followed by water work-up, gives the product:



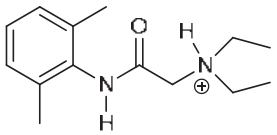
(d) This transformation does not involve a change in the carbon skeleton, although the identity of the functional group must be changed. This can be accomplished via reduction of the nitrile (upon treatment with excess lithium aluminum hydride, followed by water work-up):



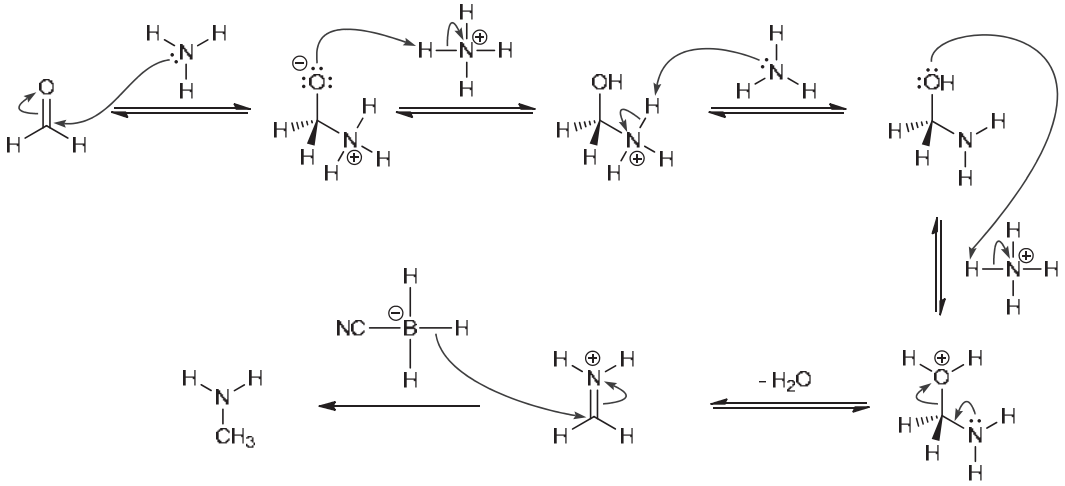
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22.47. Aziridine has significant ring strain, and this strain will increase significantly during pyramidal inversion (as the bond angle must increase during the geometric change associated with pyramidal inversion; see Figure 22.3). This provides a significant energy barrier for pyramidal inversion at room temperature.

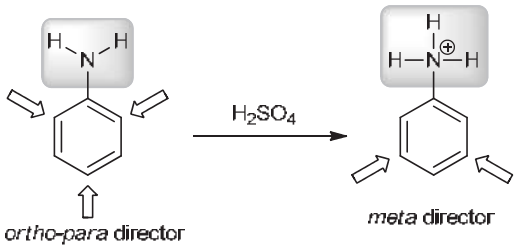
22.48. The diethylamino group exhibits a localized lone pair, and as such, it is expected to exist primarily as a charged ammonium ion (pK_a ~ 10; see pK_a table on inside cover of textbook) at physiological pH. In contrast, the other nitrogen atom exhibits a highly delocalized lone pair, and it is not expected to be protonated at physiological pH (see discussion of the Henderson-Hasselbalch equation in Section 20.3).



22.49. The following mechanism is based on Mechanism 19.6 (imine formation), although the final step is reduction, rather than a proton transfer step. In the first step, ammonia is a strong nucleophile and will attack the aldehyde directly. The resulting intermediate is then protonated, followed by subsequent deprotonation to give a carbinolamine. Protonation of the carbinolamine gives an excellent leaving group (H_2O), which leaves to give an iminium ion. Finally, sodium cyanoborohydride is a delivery agent of a hydride ion, which reduces the iminium ion to give methyl amine, as shown.

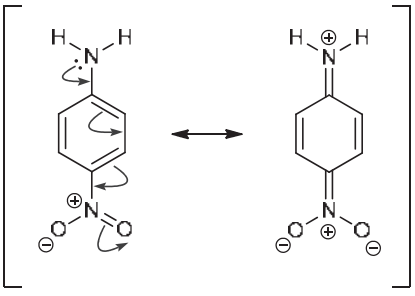


22.50. In acidic conditions, the amino group is protonated to give an ammonium ion. The ammonium group is a powerful deactivator and a *meta*-director.



22.51.

(a) In each compound, the lone pair of the amino group is delocalized because it is adjacent to the aromatic ring. However, the lone pair is more strongly delocalized for the compound that exhibits a nitro group in the *para* position (rather than the *meta* position). This extra delocalization is a result of the following additional resonance structure, in which electron density is delocalized onto the nitro group:

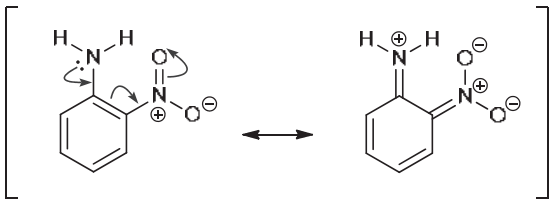


A similar resonance structure (in which electron density is delocalized onto the nitro group) cannot be drawn for *meta*-nitroaniline. As such, the lone pair in *meta*-nitroaniline is less delocalized and is therefore a stronger

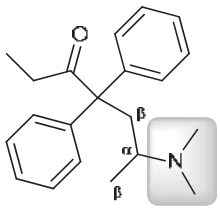
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base. This explains why *para*-nitroaniline is a weaker base than *meta*-nitroaniline.

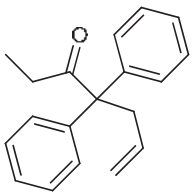
(b) The basicity of *ortho*-nitroaniline should be closer in value to *para*-nitroaniline, because a resonance structure can be drawn in which the lone pair is delocalized onto the nitro group:



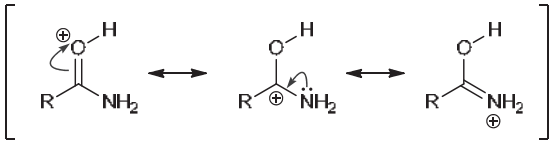
22.52. The starting amine exhibits two positions that are β to the dimethyl amino group:



During a Hofmann elimination, the amino group is removed, and a double bond is formed between the α position and the less substituted β position, giving the following product:

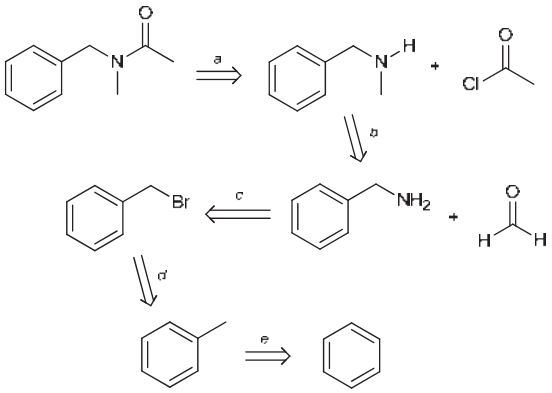


22.53. Protonation of the oxygen atom gives a cation in which the positive charge is delocalized over three locations:



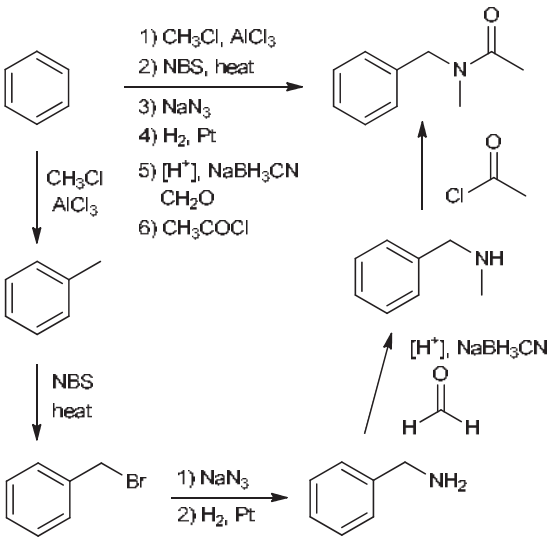
In contrast, protonation of the nitrogen atom gives a cation in which the charge is localized (on the nitrogen atom).

22.54.
(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*e*) follows.

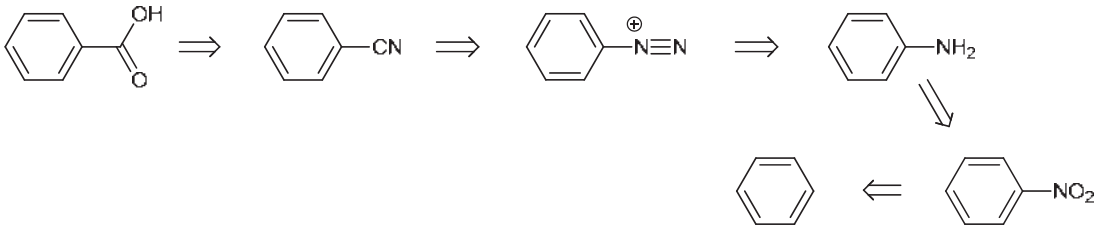


a. The product can be made via acetylation of the corresponding secondary amine.
b. The secondary amine can be made from the corresponding primary amine (benzyl amine) via a reductive amination.
c. Benzyl amine can be made from benzyl bromide via an azide synthesis.
d. Benzyl bromide can be made from toluene via radical bromination at the benzylic position.
e. Toluene can be made from benzene via a Friedel-Crafts alkylation.

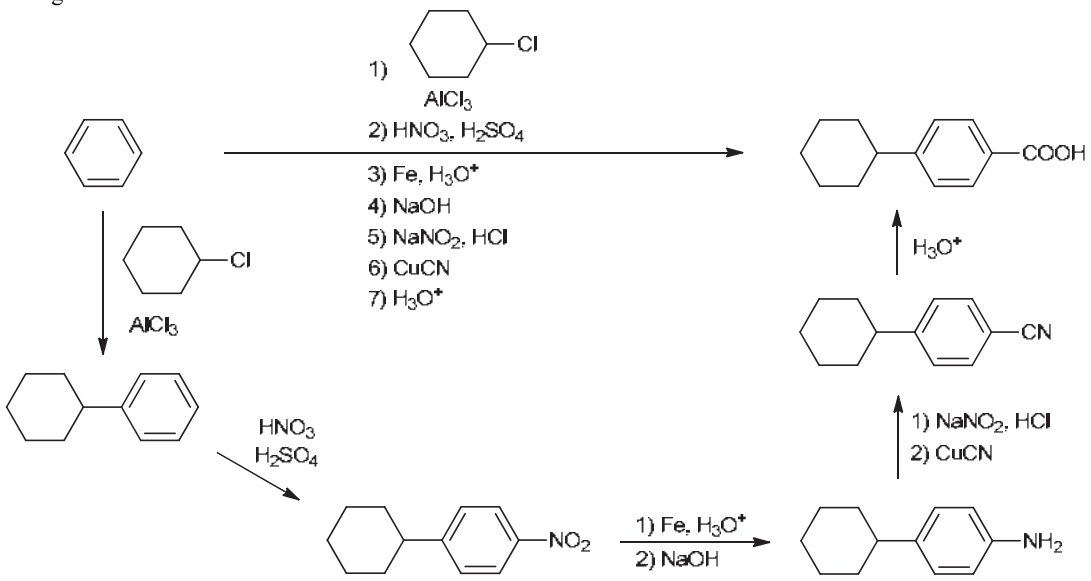
The forward scheme is shown here. Benzene is first converted into toluene upon treatment with methyl chloride and aluminum trichloride (via a Friedel-Crafts alkylation). Upon treatment with NBS and heat, a bromine atom is installed at the benzylic position, giving benzyl bromide. An azide synthesis then converts benzyl bromide into benzyl amine. A reductive amination then installs a methyl group, followed by acetylation with acetyl chloride to give the product:



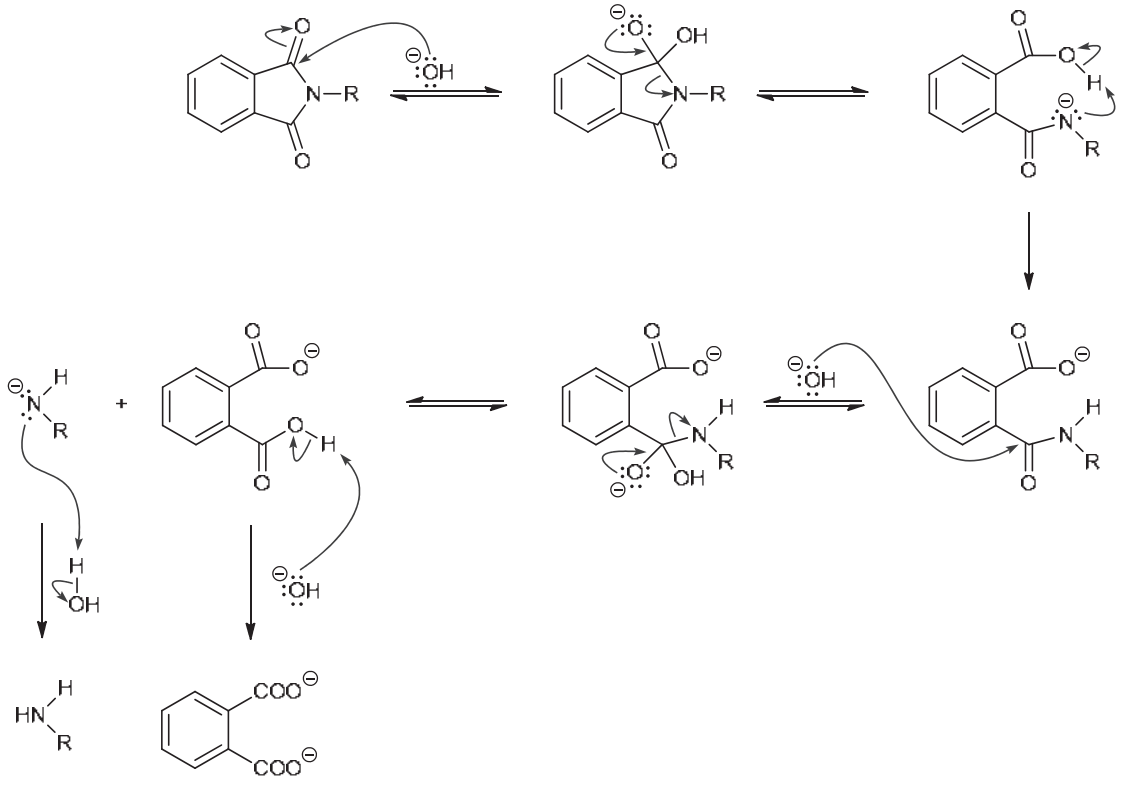
(b) This transformation requires the installation of a cyclohexyl group as well as a carboxylic acid group. Installation of the cyclohexyl group can be achieved with a Friedel-Crafts alkylation, using chlorocyclohexane and $AlCl_3$. Installation of a carboxylic acid group can be achieved via a diazonium ion, as shown in the following retrosynthetic analysis:



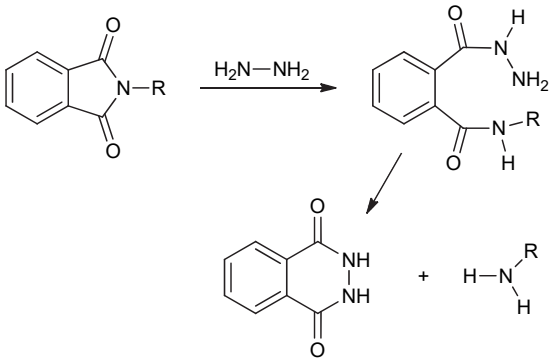
Now let's consider the order of events. The desired product is *para*-disubstituted, which can be achieved by installing the cyclohexyl group first. This group is very large and will favor nitration at the *para* position, as seen in the following forward scheme:



22.55. In Chapter 20, we learned that an amide linkage can be hydrolyzed under aqueous basic conditions. In this case, the compound has two amide linkages, each of which is hydrolyzed via a nucleophilic acyl substitution process. Hydroxide functions as a nucleophile and attacks one of the carbonyl groups to give a tetrahedral intermediate that reforms the carbonyl group by expelling a negatively charge nitrogen atom as a leaving group. The resulting anion then undergoes an intramolecular proton transfer step, giving a more stable carboxylate ion. Then, the remaining amide group undergoes hydrolysis in a similar way. Specifically, hydroxide attacks the carbonyl group to give a tetrahedral intermediate that reforms the carbonyl group by expelling a negatively charged nitrogen atom as a leaving group. Under these conditions, the carboxylic acid group is deprotonated to give a carboxylate ion, and the amide ion is protonated (by water) to give an amine:

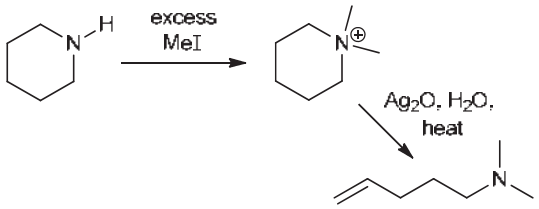


22.56. Hydrazine releases the amine via two successive nucleophilic acyl substitution reactions (as shown), giving the following by-product:

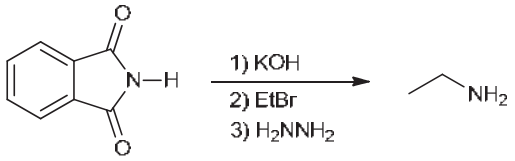


22.57.

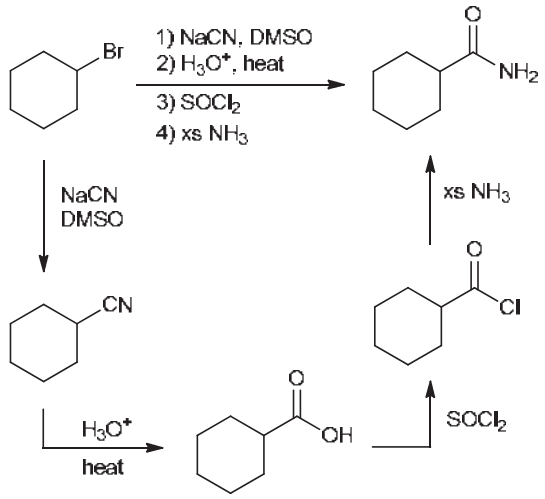
(a) The starting material is a secondary amine and the reagents indicate a Hofmann elimination. In the first step, two methyl groups are installed, converting the secondary amine into a quaternary ammonium ion. Then, treatment with aqueous silver oxide and heat results in cleavage of a C-N bond (thereby opening the ring) and formation of a double bond, as shown:



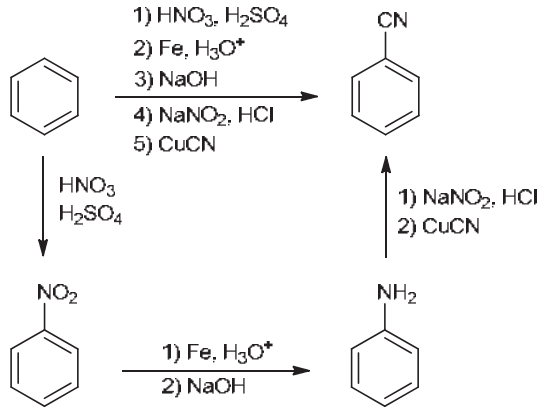
(b) This is a Gabriel synthesis. Since the alkyl halide is ethyl bromide, the product is ethylamine:



(c) The starting alkyl halide is converted into a nitrile upon treatment with sodium cyanide in a polar aprotic solvent (via an S_N2 process). Hydrolysis of the nitrile with aqueous acid and heat gives a carboxylic acid, which is then converted into an acid chloride upon treatment with thionyl chloride. The acid chloride is then converted into an amide upon treatment with excess ammonia, via a nucleophilic acyl substitution reaction.



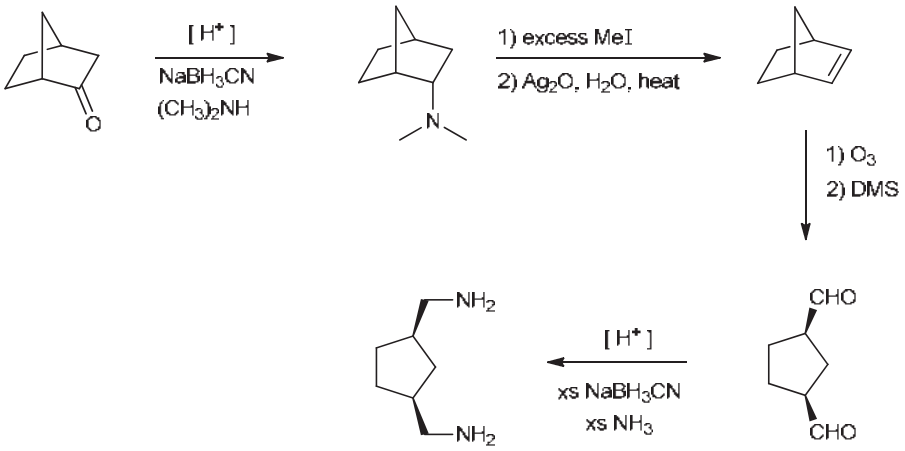
(d) Treating benzene with a mixture of nitric and sulfuric acid results in nitration of the aromatic ring, giving nitrobenzene. Subsequent treatment of nitrobenzene with iron in aqueous acid (followed by basic work-up) results in reduction of the nitro group, giving aniline. Aniline is converted into a diazonium ion upon treatment with sodium nitrite and HCl, and the diazonium ion is converted into benzonitrile via a Sandmeyer reaction (with CuCN):



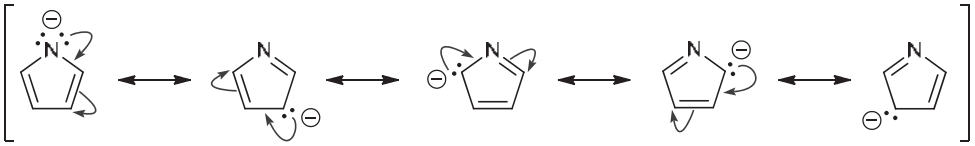
22.58. The carbonyl group is converted into a dimethyl amino group via a reductive amination process. A Hofmann elimination then gives an alkene. The double bond cannot be formed at a bridgehead position (Bredt's rule), so there is

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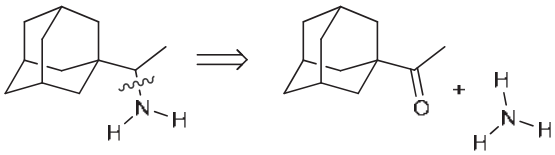
only one possible regiochemical outcome for the elimination process. Ozonolysis of the alkene gives a dialdehyde (in a *cis* configuration), which is then converted into a diamine via reductive amination of each carbonyl group.



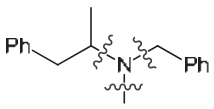
22.59. The conjugate base of pyrrole is highly stabilized because it is an aromatic anion and it is resonance stabilized, spreading the negative charge over all five atoms of the ring, as shown below. Pyrrole is relatively acidic (compared with other amines) because its conjugate base is so highly stabilized.



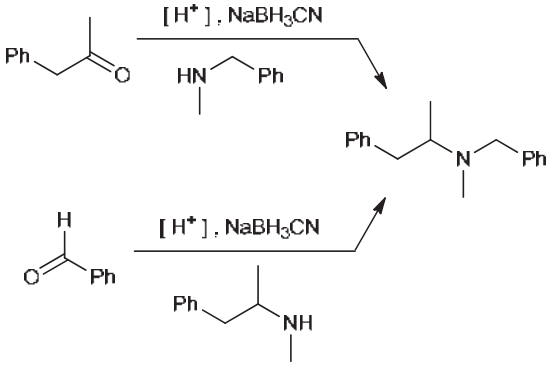
22.60. The desired amine is primary (it has only one C–N bond), and it can be made from the following ketone and ammonia via a reductive amination:



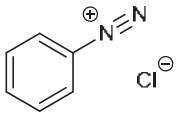
22.61.
The compound has three C-N bonds:



Each of these bonds can be made via a reductive amination, giving three possible synthetic routes. Two are shown here (the third route begins with formaldehyde):

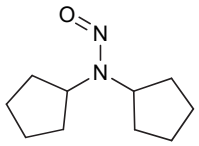


22.62.
(a) The starting amine is primary, so it is converted into the following diazonium salt upon treatment with sodium nitrite and HCl:

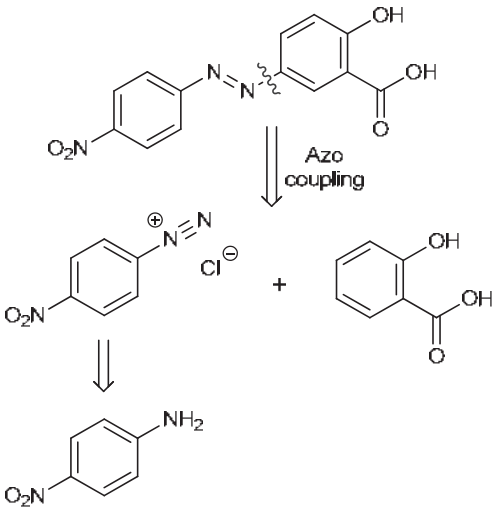


(b) The starting amine is secondary, so it is converted into the following *N*-nitrosamine upon treatment with sodium nitrite and HCl:

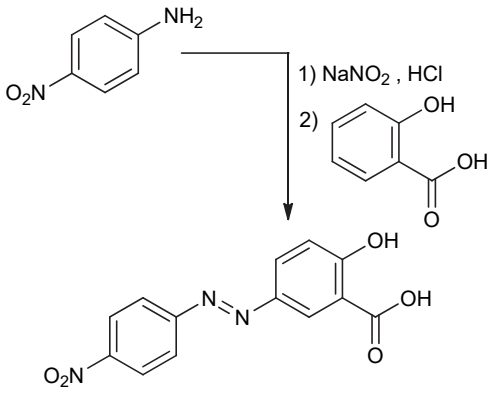
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22.63. The starting material has two aromatic rings. The ring bearing the hydroxyl group is more highly activated. During the azo coupling process, the activated ring functions as the nucleophile, and the other ring must function as the diazonium ion, as shown in the following retrosynthetic analysis:

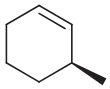


The forward scheme is shown here:

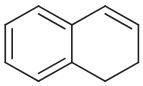


22.64.

(a) The starting material is a primary amine, and the reagents indicate a Hofmann elimination. There are two β positions, and we expect elimination to occur at the β position that leads to the less substituted alkene:

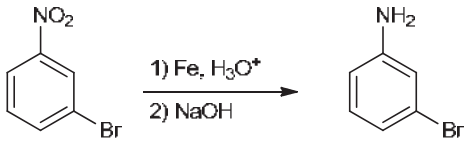


(b) The starting material is a primary amine, and the reagents indicate a Hofmann elimination. There are two β positions, but only one of these positions bears a proton (which is necessary for elimination to occur). So, there is only one possible regiochemical outcome for this Hofmann elimination, giving the following alkene:

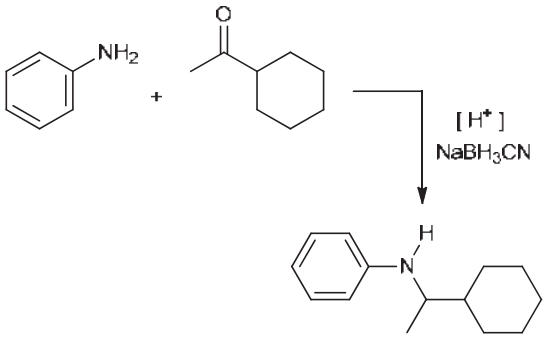


22.65.

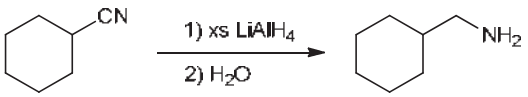
(a) Reduction of the nitro group, followed by basic work-up, gives *meta*-bromoaniline:



(b) The starting materials are a primary amine and a ketone, and the reagents (sodium cyanoborohydride and an acid catalyst) indicate a reductive amination process, giving the following secondary amine:

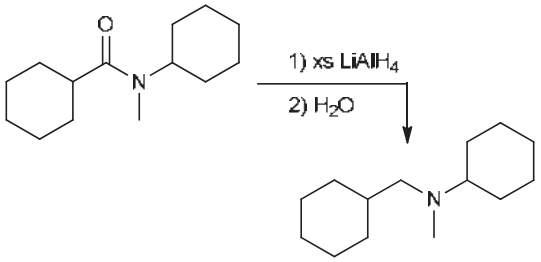


(c) A nitrile is reduced to an amine upon treatment with excess lithium aluminum hydride, followed by water work-up:



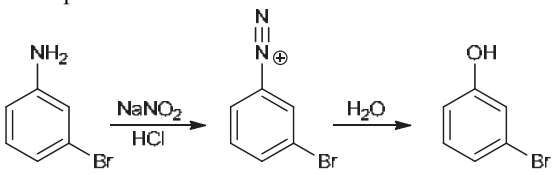
(d) An amide is reduced to an amine upon treatment with excess lithium aluminum hydride, followed by water work-up:

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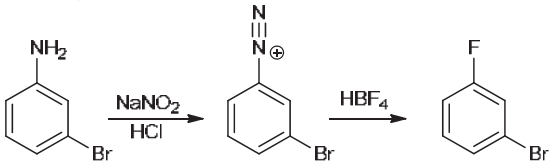


22.66.

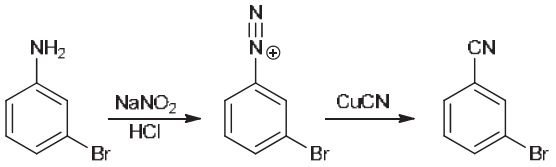
(a) Upon treatment with water, the diazonium group is replaced with a hydroxyl group, giving *meta*-bromophenol:



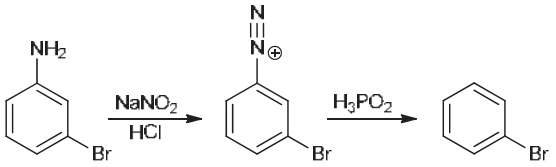
(b) Upon treatment with HBF_4, the diazonium group is replaced with a fluorine atom (via a Schiemann reaction), as shown:



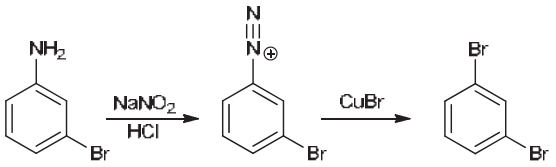
(c) Upon treatment with CuCN, the diazonium group is replaced with a cyano group via a Sandmeyer reaction:



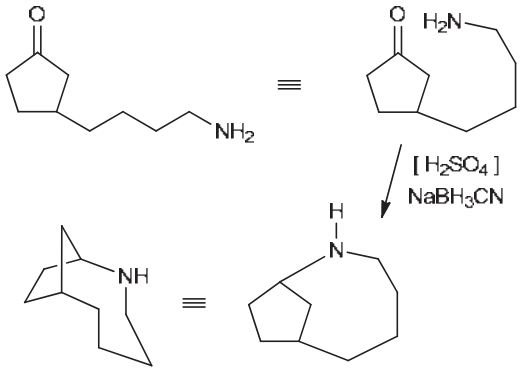
(d) Upon treatment with H_3PO_2, the diazonium group is replaced with a hydrogen atom, giving bromobenzene:



(e) Upon treatment with CuBr, the diazonium group is replaced with a bromine atom via a Sandmeyer reaction:

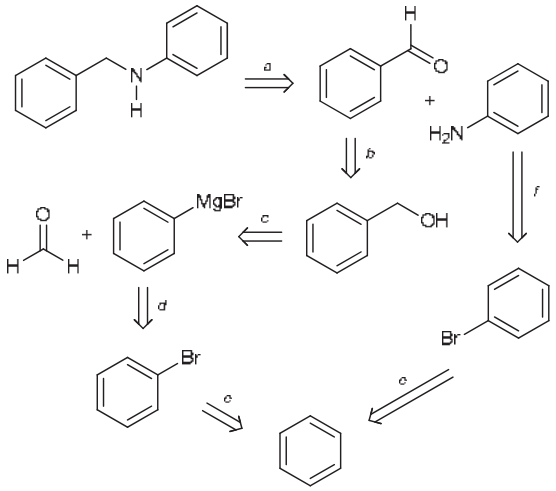


22.67. In this case, the carbonyl group and the amino group are tethered together (both functional groups are present in one compound), so we expect an *intramolecular* reductive amination to occur, thereby forming a new ring to give a bicyclic product, as shown:



22.68.

(a) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a-f*) follows.



a. The product is a secondary amine, which can be made from benzaldehyde and aniline via a reductive amination.

b. Benzaldehyde can be made from benzyl alcohol via oxidation (with PCC or with DMP or via a Swern oxidation).

c. Benzyl alcohol can be made from phenyl magnesium bromide and formaldehyde, via a Grignard reaction.

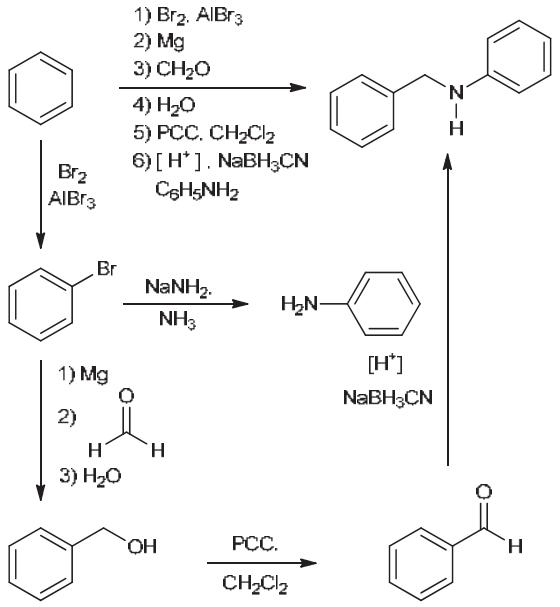
d. Phenyl magnesium bromide can be made from bromobenzene, upon treatment with magnesium.

e. Bromobenzene can be made from benzene via an electrophilic aromatic substitution reaction.

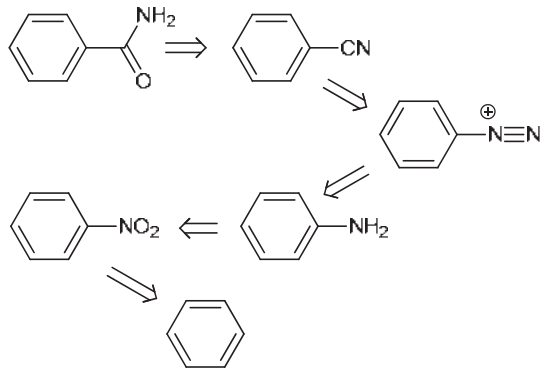
f. Aniline can be made from bromobenzene via elimination-addition.

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The forward scheme is shown here. Benzene is first converted into bromobenzene upon treatment with bromine in the presence of a Lewis acid ($AlBr_3$). Treating bromobenzene with magnesium gives a Grignard reagent, which can be further treated with formaldehyde, followed by water work-up, to give benzyl alcohol (via Grignard reaction). Oxidation with PCC (or DMP or via a Swern oxidation) gives benzaldehyde, which is then treated with aniline in a reductive amination process to give the product. Aniline can be made from bromobenzene upon treatment with sodium amide in ammonia (via elimination-addition):

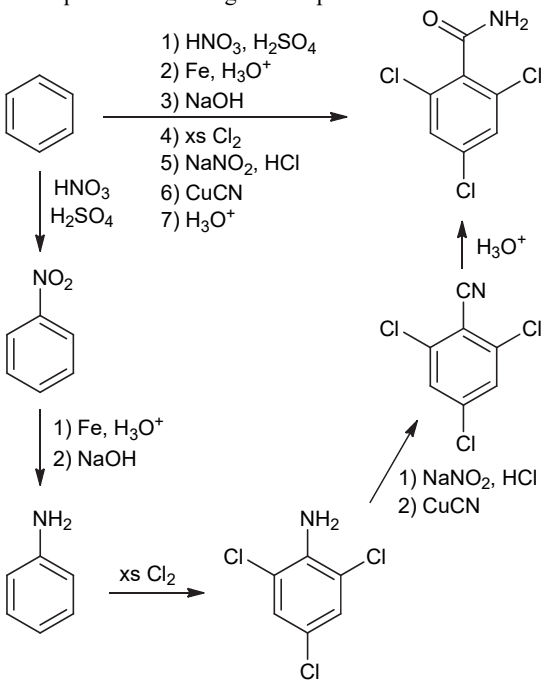


(b) This transformation requires the installation of an amide group and three chlorine atoms (in the *ortho* and *para* positions). Installation of the amide group can be achieved via a diazonium ion, as shown here:

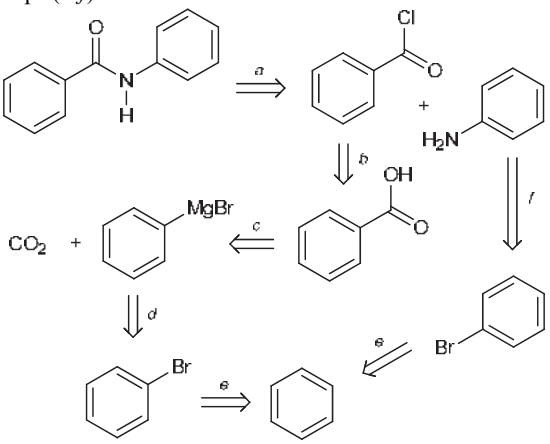


In order to install three chlorine atoms (in the positions that are *ortho* and *para* to the amide group), we must perform chlorination (with excess chlorine) during a stage in the process when the ring is highly activated (thereby giving trichlorination). This can be accomplished immediately prior to making the diazonium ion, because aniline is strongly activated toward electrophilic aromatic substitution, giving trichlorination, as desired.

The forward scheme is shown here. Benzene is first treated with a mixture of sulfuric acid and nitric acid, giving nitrobenzene. Reduction, followed by basic work-up, gives aniline, which will undergo trichlorination when treated with excess chlorine to give 2,4,6-trichloroaniline. Treatment with sodium nitrite and HCl converts the substituted aniline into a diazonium ion, which can then be treated with CuCN to give a nitrile (via a Sandmeyer reaction). Treating the nitrile with aqueous acid then gives the product.



(c) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a-f*) follows.



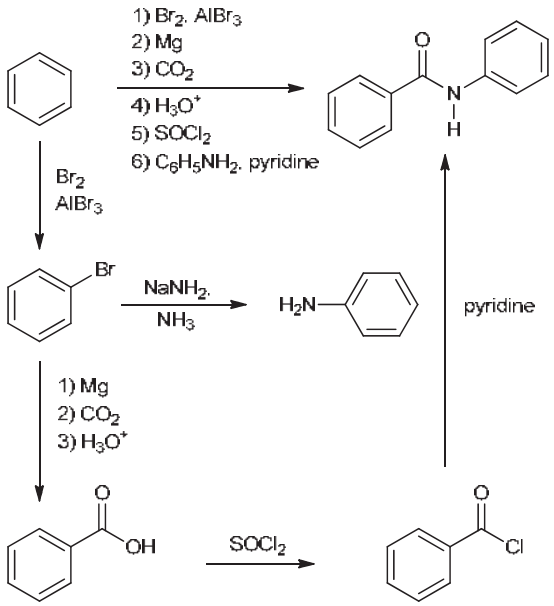
a. The product is an amide, which can be made from benzoyl chloride and aniline via a nucleophilic acyl substitution reaction.

b. Benzoyl chloride can be made from benzoic acid upon treatment with thionyl chloride.

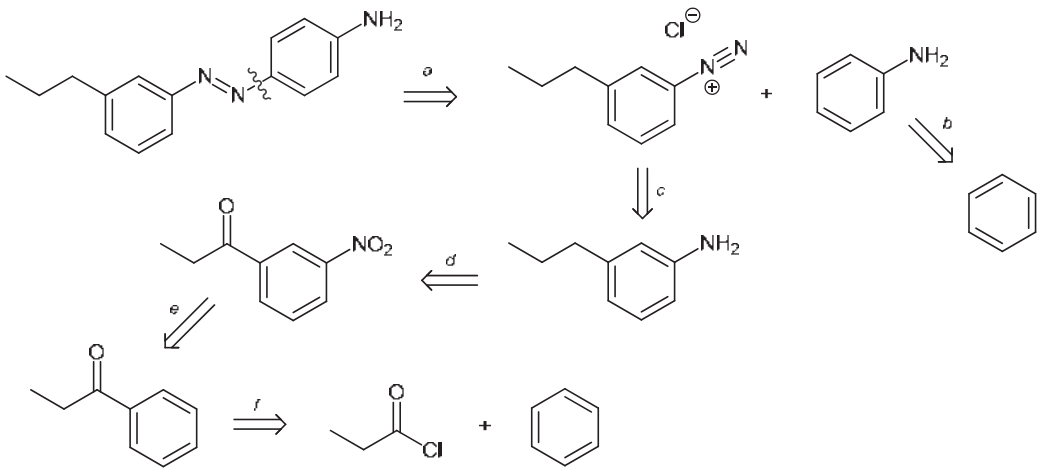
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c. Benzoic acid can be made from phenyl magnesium bromide and carbon dioxide, via a Grignard reaction.
d. Phenyl magnesium bromide can be made from bromobenzene, upon treatment with magnesium.
e. Bromobenzene can be made from benzene via an electrophilic aromatic substitution reaction.
f. Aniline can be made from bromobenzene via elimination-addition.

The forward scheme is shown here. Benzene is first converted into bromobenzene upon treatment with bromine in the presence of a Lewis acid ($AlBr_3$). Treating bromobenzene with magnesium gives a Grignard reagent, which can be further treated with carbon dioxide, followed by acidic work-up, to give benzoic acid. Treating benzoic acid with thionyl chloride gives benzoyl chloride, which is then treated with aniline in a nucleophilic acyl substitution to give the product. Aniline can be made from bromobenzene upon treatment with sodium amide in ammonia (via elimination-addition):



(d) There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a-f*) follows.

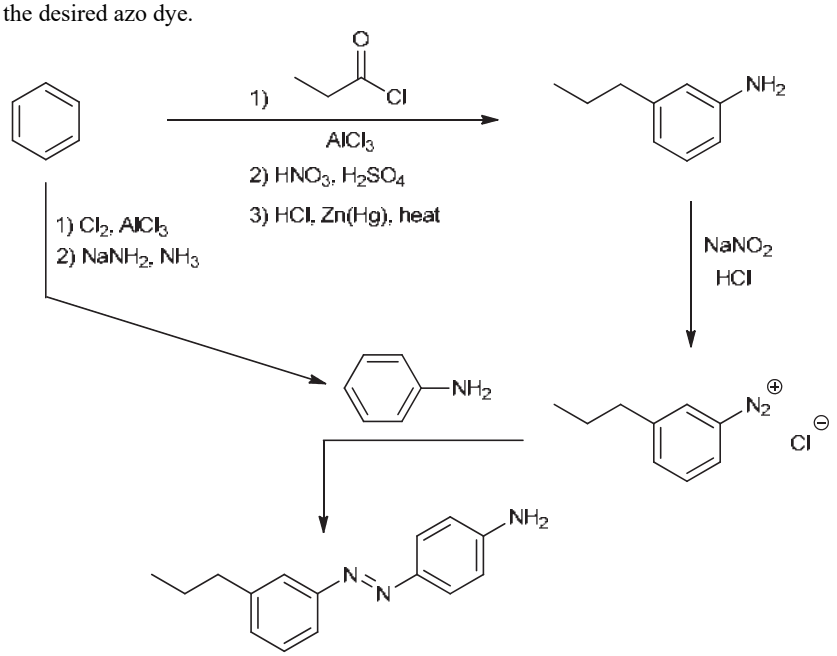


a. The product is an azo dye, which can be made via azo coupling from a diazonium ion and an activated aromatic ring.
b. Aniline can be made from benzene via chlorination followed by treatment with sodium amide in liquid ammonia (elimination-addition).
c. The diazonium ion can be made from *meta*-propylaniline, upon treatment with sodium nitrite and HCl.
d. *meta*-Propylaniline can be made via reduction of the disubstituted ring shown.
e. The disubstituted ring can be prepared via nitration of an aromatic ketone (giving nitration at the *meta* position).
f. The aromatic ketone can be made via a Friedel-Crafts acylation.

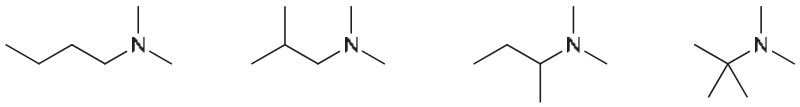
The forward scheme is shown here. One equivalent of benzene is converted into aniline via chlorination (with Cl_2 and $AlCl_3$) followed by elimination-addition (with sodium amide in liquid ammonia). Another equivalent of benzene is subjected to a Friedel-Crafts acylation (thereby installing an acyl group), followed by nitration (in the *meta* position),

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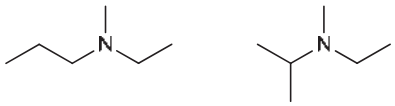
followed by conditions that will reduce both the carbonyl group and the nitro group, giving *meta*-propylaniline. Treatment with sodium nitrite and HCl gives a diazonium ion, which is then treated with aniline (in an azo compling process) to give the desired azo dye.



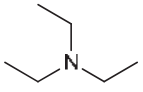
22.69. The molecular formula ($C_6H_{15}N$) indicates no degrees of unsaturation (see Section 14.16), so all of the isomers must be saturated, acyclic amines. The IR data indicates that we are looking for structures that lack an N-H bond (i.e., tertiary amines). Let's first consider all tertiary amines in which the nitrogen atom is connected to two methyl groups. Since there must be a total of six carbon atoms in each structure (and the two methyl groups only account for two carbon atoms), we must consider all of the different ways in which the remaining four carbon atoms can be connected. There are four ways, shown here (butyl, isobutyl, *sec*-butyl, and *tert*-butyl):



Now let's consider all isomers in which the nitrogen atom is connected to one methyl group and one ethyl group. Since there must be a total of six carbon atoms in each structure (while one methyl group and one ethyl group only account for three carbon atoms), we must consider all of the different ways in which the remaining three carbon atoms can be connected. There are only two ways, shown here (propyl and isopropyl):



And finally, there is only one isomer in which the nitrogen atom has two ethyl groups. In this structure, the third group is also an ethyl group, giving triethylamine:

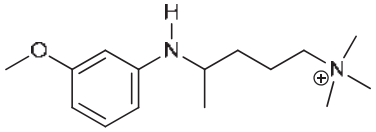


In total, we have seen seven different tertiary amines with the molecular formula $C_6H_{15}N$.

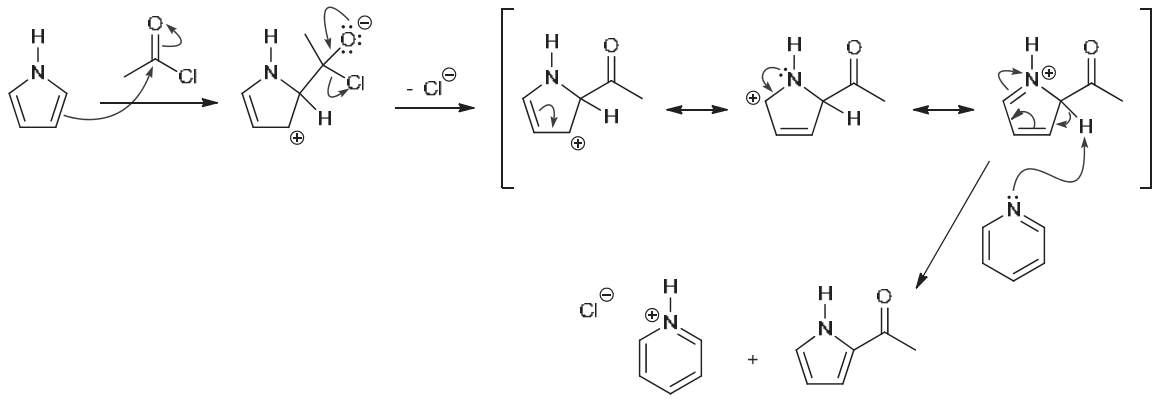
22.70. The compound has two nitrogen atoms. One of the nitrogen atoms (adjacent to the aromatic ring) exhibits a delocalized lone pair, while the other nitrogen atom (of the NH_2 group) exhibits a localized lone pair. The localized

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lone pair is more nucleophilic than the delocalized lone pair, so only the NH_2 group is converted into a quaternary ammonium ion, as shown here:

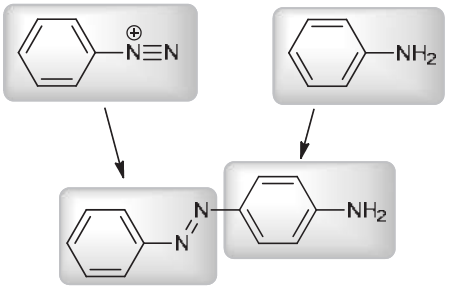


22.71. Pyrrole functions as a nucleophile (preferentially at C2, as discussed in Section 22.12) and attacks acetyl chloride, giving a tetrahedral intermediate that can then expel a chloride ion (as a leaving group), thereby regenerating a carbonyl group. The resulting cation is resonance-stabilized, much like a sigma complex. Pyridine then functions as a base and removes a proton, thereby restoring aromaticity and generating the product:

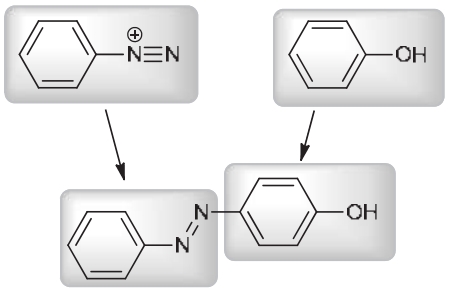


22.72.

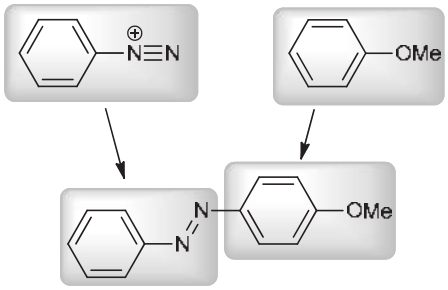
(a) An azo coupling reaction will give the following product:



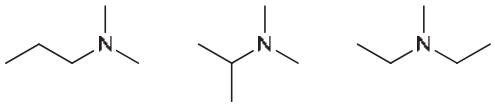
(b) An azo coupling reaction will give the following product:



(c) An azo coupling reaction will give the following product:

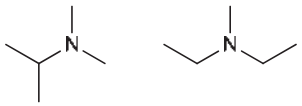


22.73. The molecular formula ($C_5H_{13}N$) indicates no degrees of unsaturation (see Section 14.16), so all of the isomers must be saturated, acyclic amines. The IR data indicates that we are looking for structures that lack an N-H bond (i.e., tertiary amines). As seen in the solution to Problem **22.42**, there are three isomers that fit this description:

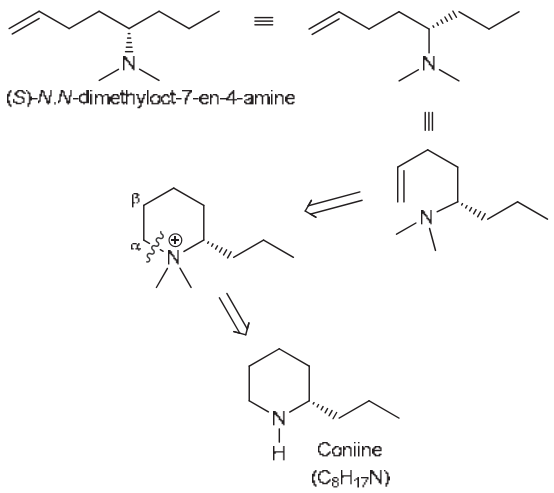


The first compound above is expected to exhibit four signals in its ^1H NMR spectrum. Only the latter two isomers are expected to produce three signals in their ^1H NMR spectra:

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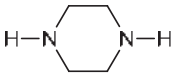


22.74. The molecular formula ($C_8H_{17}N$) indicates one degree of unsaturation (see Section 14.16), so the structure must contain either one double bond or one ring (but not both). We are given the product obtained when coniine is subjected to a Hofmann elimination, which allows us to determine the structure of coniine, as shown in the following retrosynthetic analysis:



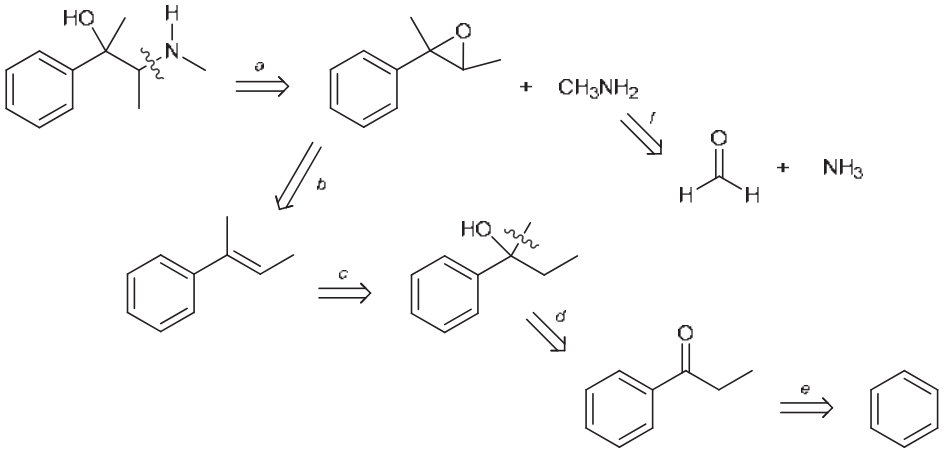
The N-H bond in coniine is responsible for the one peak above 3000 cm^{-1} in the IR spectrum.

22.75. The molecular formula ($C_4H_{10}N_2$) indicates one degree of unsaturation (see Section 14.16), so the structure must contain either one double bond or one ring (but not both). The ^1H NMR spectrum has only two signals, indicating a high degree of symmetry. One of these signals vanishes in D_2O, indicating a labile proton, consistent with an N-H bond. The other signal must account for all of the other protons. The following structure accounts for all of the observations:



The two N-H protons are identical (because of symmetry), and they produce one signal in the ^1H NMR spectrum. The four methylene (CH_2) groups are all identical, giving rise to the second signal in the ^1H NMR spectrum.

22.76. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis, in which the final step of the synthesis employs the strategy described in the problem statement (opening an epoxide with an amine functioning as the nucleophile). An explanation of each of the steps (*a-f*) follows.

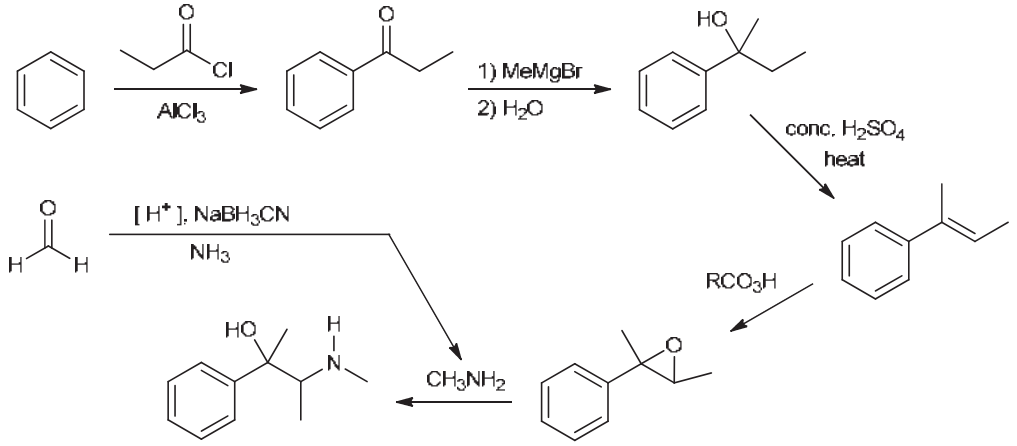


a. The product can be made by treating the appropriate epoxide with methyl amine, as described in the problem statement.
b. The epoxide can be made from the corresponding alkene, upon treatment with a peroxy acid.
c. The alkene can be made from an alcohol, via acid-catalyzed dehydration.
d. The alcohol can be made from a ketone, via a Grignard reaction (with methyl magnesium bromide, followed by water work-up).

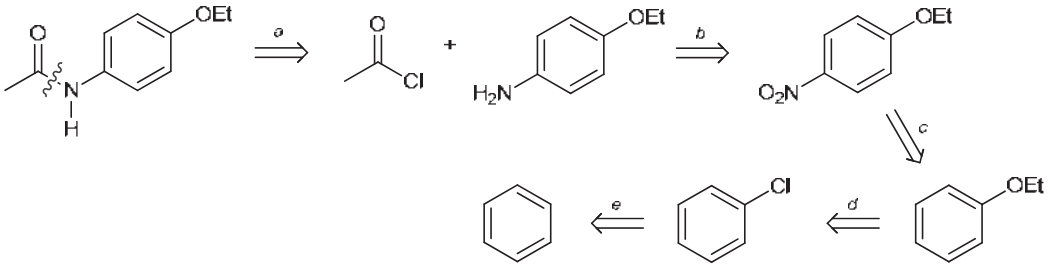
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e. The ketone can be made from benzene via a Friedel-Crafts acylation.
f. Methylamine can be made from formaldehyde and ammonia via a reductive amination.

The forward scheme is shown here. Benzene is treated with an acyl chloride and $AlCl_3$, thereby installing an acyl group via a Friedel-Crafts acylation. The resulting ketone is then treated with methyl magnesium bromide, followed by water work-up, to give a tertiary alcohol. This alcohol undergoes dehydration upon treatment with concentrated sulfuric acid and heat, giving an alkene. Treating the alkene with a peroxy acid gives an epoxide. The epoxide is then converted into the desired product upon treatment with methyl amine (which can be made from formaldehyde and ammonia via a reductive amination process).



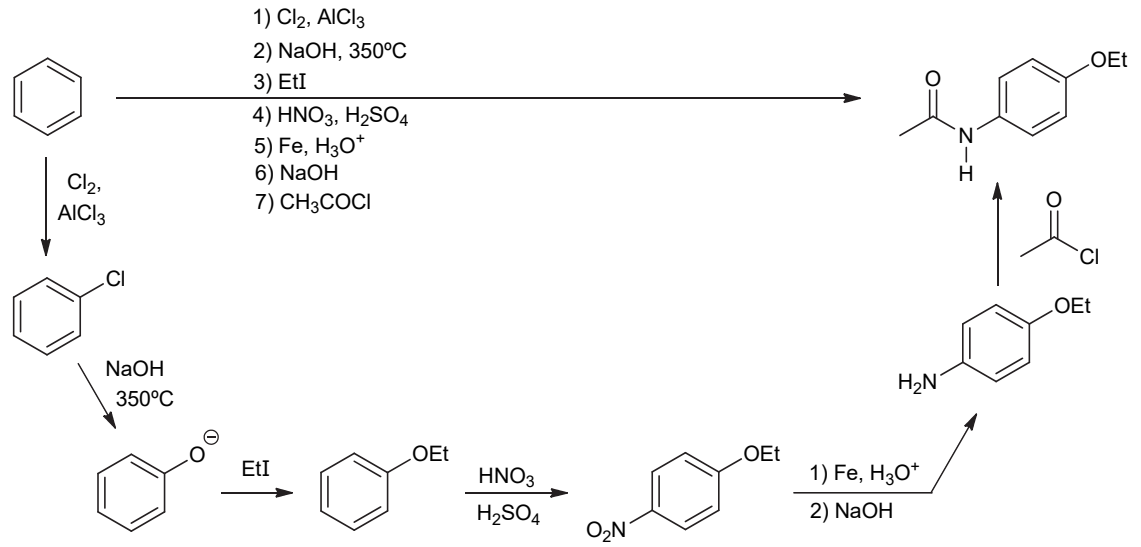
22.77. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*e*) follows.



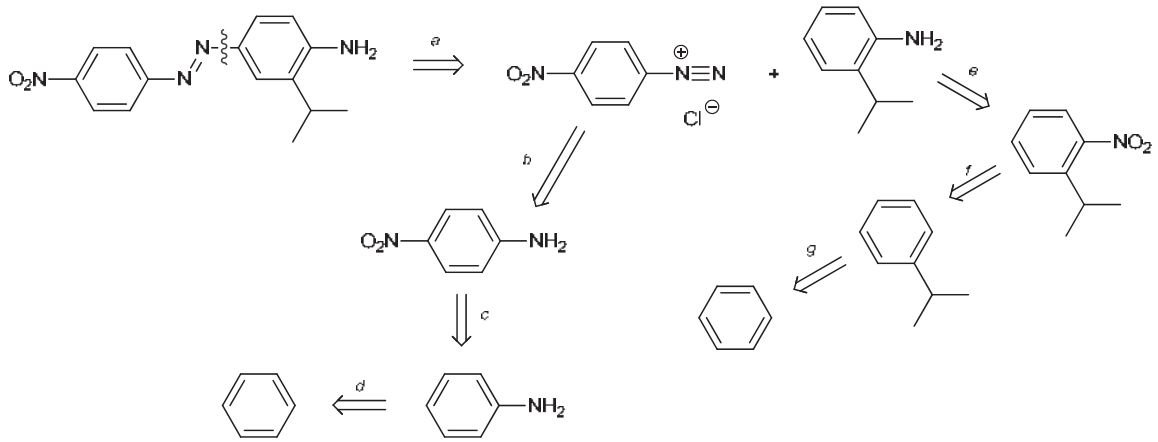
a. The product has an amide group, which can be made via acetylation of the amino group in 4-ethoxyaniline.
b. 4-Ethoxyaniline can be made from the corresponding nitro compound via reduction.
c. The nitro compound can be made from ethoxybenzene, via nitration of the aromatic ring (in the *para* position).
d. Ethoxybenzene can be made from chlorobenzene, via elimination-addition (upon treatment with hydroxide at high temperature), followed by a Williamson ether synthesis.
e. Chlorobenzene can be made from benzene via an electrophilic aromatic substitution reaction.

The forward scheme is shown here. Benzene is treated with Cl_2 and $AlCl_3$, thereby installing a chlorine atom. Heating chlorobenzene (at 350ºC) in the presence of hydroxide gives an elimination-addition process that gives a phenolate ion as the product. Rather than protonating the phenolate ion to give phenol, we can treat the phenolate ion with ethyl iodide, giving ethoxybenzene via an S_N2 process. When ethoxybenzene is treated with a mixture of sulfuric acid and nitric acid, nitration occurs at the *para* position (the ethoxy group is an *ortho-para* director, and the *para* position is favored because of steric factors). Reduction of the nitro group, followed by acetylation of the resulting amino group, gives the desired product.

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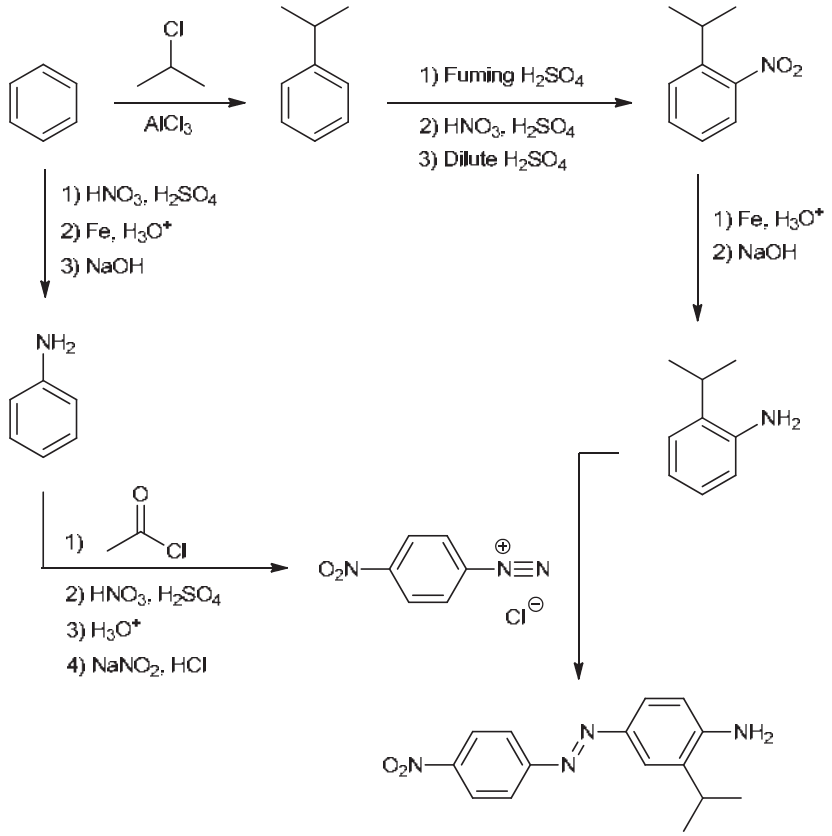
22.78. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*g*) follows.



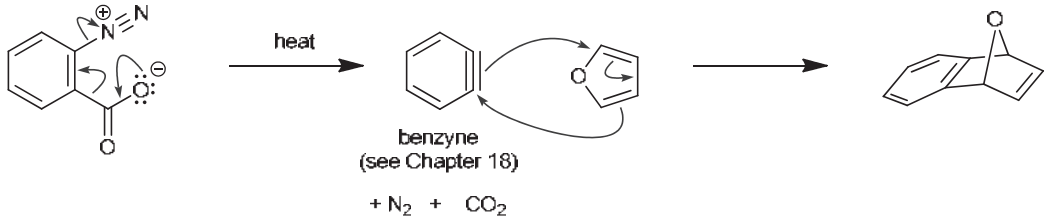
a. The product is an azo dye, which can be made via azo coupling from a diazonium ion and an activated aromatic ring.
b. The diazonium ion can be made from *para*-nitroaniline, upon treatment with sodium nitrite and HCl.
c. *para*-Nitroaniline can be made from aniline via nitration. This process requires acetylation prior to nitration, and removal of the acetyl group after nitration (because aniline will not directly undergo nitration to give *para*-nitroaniline).
d. Aniline can be made from benzene via nitration followed by reduction of the nitro group.
e. The substituted aniline can be made via reduction of the corresponding nitro compound.
f. The nitro compound can be made via nitration. This process requires sulfonation prior to nitration, so that nitration will occur at the *ortho* position (rather than the *para* position). Desulfonation is then required after nitration (to remove the sulfonic acid group).
g. Isopropyl benzene can be made from benzene via a Friedel-Crafts alkylation.

The forward scheme is shown here:

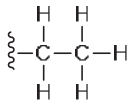
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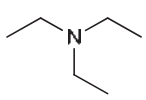
22.79. The starting material can lose both carbon dioxide and nitrogen gas, as shown below, to give a very reactive benzyne intermediate. This intermediate can then react with furan in a Diels-Alder reaction, as first described in Section 18.14, to give the cycloadduct shown.



22.80. The molecular formula ($C_6H_{15}N$) indicates no degrees of unsaturation (see Section 14.16), so the structure does not contain a π bond or a ring. That is, the structure must be a saturated, acyclic amine. The ^{1}H NMR spectrum exhibits the characteristic pattern of an ethyl group (a quartet with an integration of 2 and a triplet with an integration of 3).



There are no other signals in the ^{1}H NMR spectrum, indicating a high degree of symmetry. That is, these two signals must account for all fifteen protons in the compound, indicating that there are three equivalent ethyl groups. The compound is therefore triethylamine:

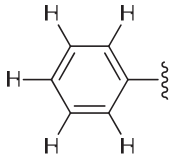


This analysis is confirmed by the ^{13}C NMR spectrum, which has only two signals (one signal for the three equivalent methyl groups and another signal for the three equivalent methylene groups).

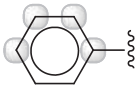
22.81. The molecular formula ($C_8H_{11}N$) indicates four degrees of unsaturation (see Section 14.16), which is highly suggestive of an aromatic ring. The multiplet just above 7 ppm in the ^{1}H NMR spectrum corresponds with aromatic protons, which confirms the presence of an

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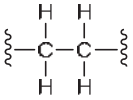
aromatic ring. The integration of this signal is 5, which indicates that the ring is monosubstituted:



The presence of a monosubstituted ring is confirmed by the four signals between 100 and 150 ppm in the ^{13}C NMR spectrum (the region associated with sp^2 hybridized carbon atoms), just as expected for a monosubstituted aromatic ring:



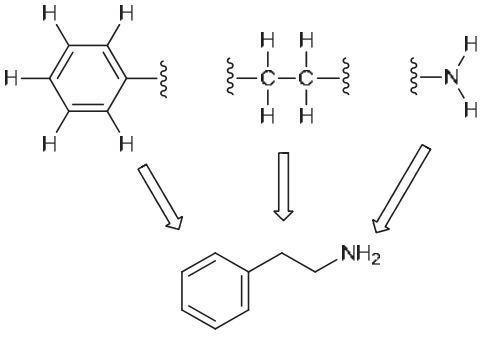
In the ^1H NMR spectrum, the pair of triplets (each with an integration of 2) indicates a pair of neighboring methylene groups:



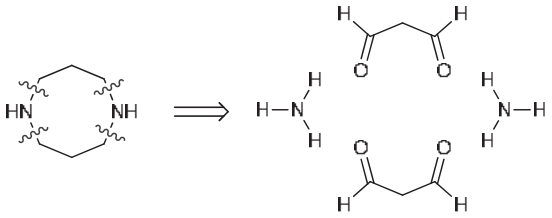
These methylene groups account for the two upfield signals in the ^{13}C NMR spectrum.

Thus far, we have accounted for all of the atoms in the molecular formula, except for one nitrogen atom and two hydrogen atoms, suggesting an amino group. This would indeed explain the singlet in the ^1H NMR spectrum with an integration of 2.

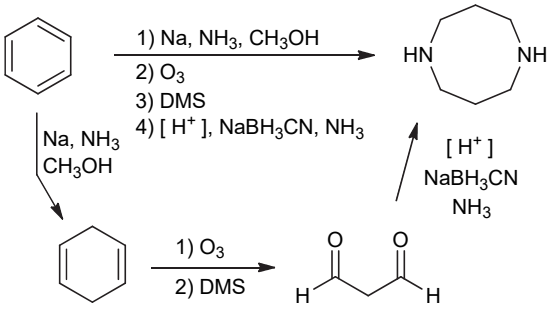
We have now analyzed all of the signals in both spectra, and we have uncovered the following three fragments, which can be connected to each other in only one way:



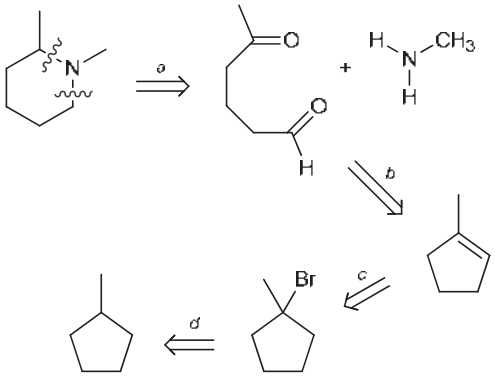
22.82. The product has four C-N bonds, each of which can be prepared via a reductive amination process. As such, the product can be made from the following starting materials (two equivalents of ammonia and two equivalents of a dialdehyde):



The necessary dialdehyde has only three carbon atoms, but the starting material (benzene) has six carbon atoms. This suggests that we must somehow break apart the aromatic ring into two fragments. This might seem impossible at first, as we have seen that aromatic rings are particularly stable. We did, however, cover a reaction that destroys aromaticity (a Birch reduction will convert benzene into 1,4-cyclohexadiene). If a Birch reduction is followed by ozonolysis, the resulting dialdehyde can then be treated with ammonia and sodium cyanoborohydride (with an acid catalyst) to give the product:

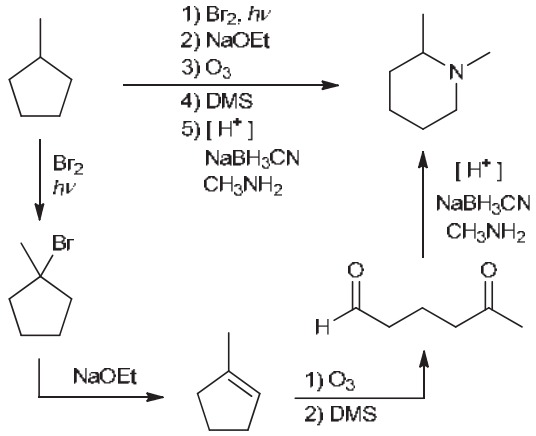


22.83. The starting material exhibits a five-membered ring, while the product exhibits a six-membered ring that contains a nitrogen atom. Since we have not learned a way to insert a nitrogen atom into an existing ring, we must consider opening the ring, and then closing it back up again (in a way that incorporates the nitrogen atom into the ring). There are certainly many acceptable synthetic routes. One such route derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

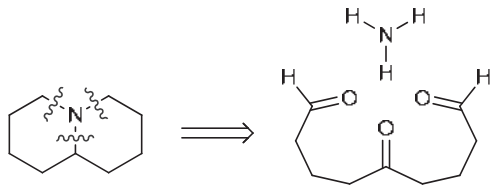


a. The product is a tertiary amine, and it can be made from a dicarbonyl compound and methyl amine, via two reductive amination processes.
b. The dicarbonyl compound can be made via ozonolysis of 1-methylcyclopentene.
c. 1-Methylcyclopentene can be made from 1-bromo-1-methylcyclopentane via an elimination reaction.
d. 1-Bromo-1-methylcyclopentane can be made from methylcyclopentane via radical bromination.

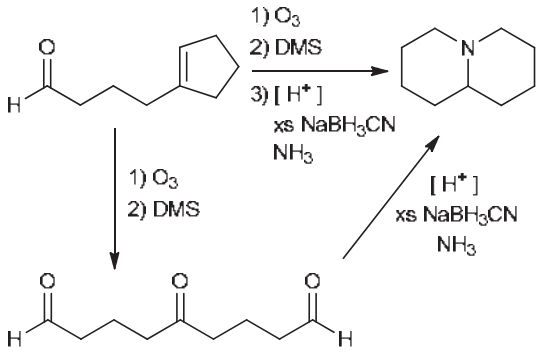
The forward scheme is shown here. Methylcyclopentane will undergo radical bromination selectively at the tertiary position, giving a tertiary alkyl bromide. This alkyl bromide will undergo an elimination reaction upon treatment with a strong base, such as sodium ethoxide. Ozonolysis of the resulting alkene gives a dicarbonyl compound, which can then be converted into the product upon treatment with methyl amine and sodium cyanoborohydride (with acid catalysis):



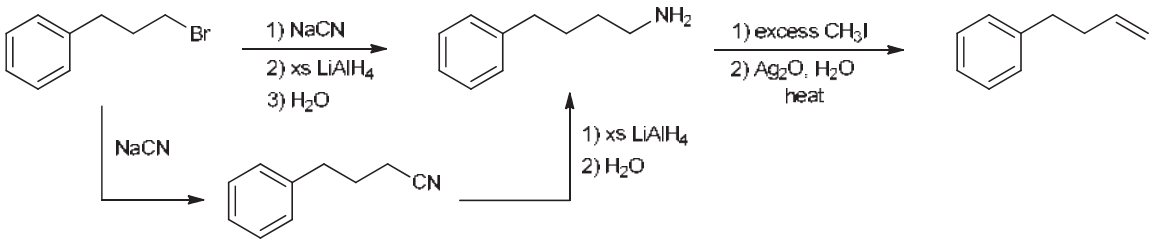
22.84. This amine is tertiary, and each C-N bond can be made via a reductive amination process, as shown in the following retrosynthetic analysis:



The necessary tricarbonyl compound can be made from the starting material via ozonolysis, as shown in the following forward scheme:



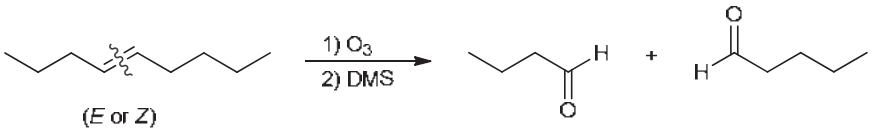
22.85. The starting material has nine carbon atoms, while the product has ten. The identity of the functional group has also changed, so we must propose a synthesis that introduces the tenth carbon atom and installs a π bond in the appropriate location. There are certainly many ways to achieve the desired transformation. One method involves introduction of the tenth carbon atom via conversion of the starting alkyl halide into a nitrile upon treatment with cyanide (an S_N2 reaction). Reduction of the nitrile with excess $LiAlH_4$, followed by water work-up, gives an amine, which can then be converted into the desired alkene via a Hofmann elimination, as shown:



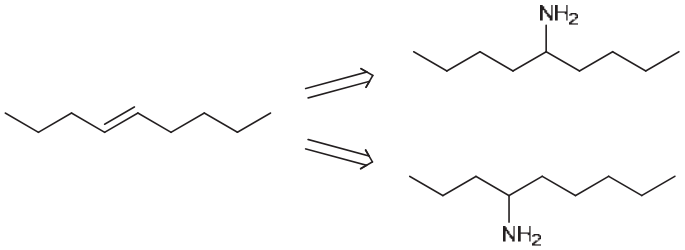
As an alternate approach, the starting alkyl halide can be treated with NaOH to give an alcohol, which can be oxidized (with PCC or with DMP or via a Swern oxidation) to give an aldehyde. This aldehyde can then be converted directly into the product with a Wittig reaction.

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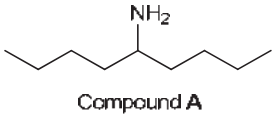
22.86. The structure of the intermediate alkene can be determined from the products of ozonolysis (butanal and pentanal). Based on the ozonolysis products alone, we cannot determine the configuration of the alkene (*E* or *Z*):



The *E* alkene can be made via a Hofmann elimination from two possible amines:



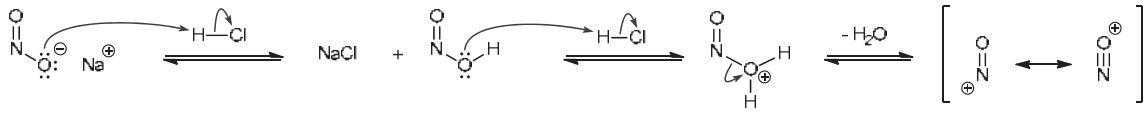
But only one of these amines lacks a chiral center, as shown below (due to symmetry):



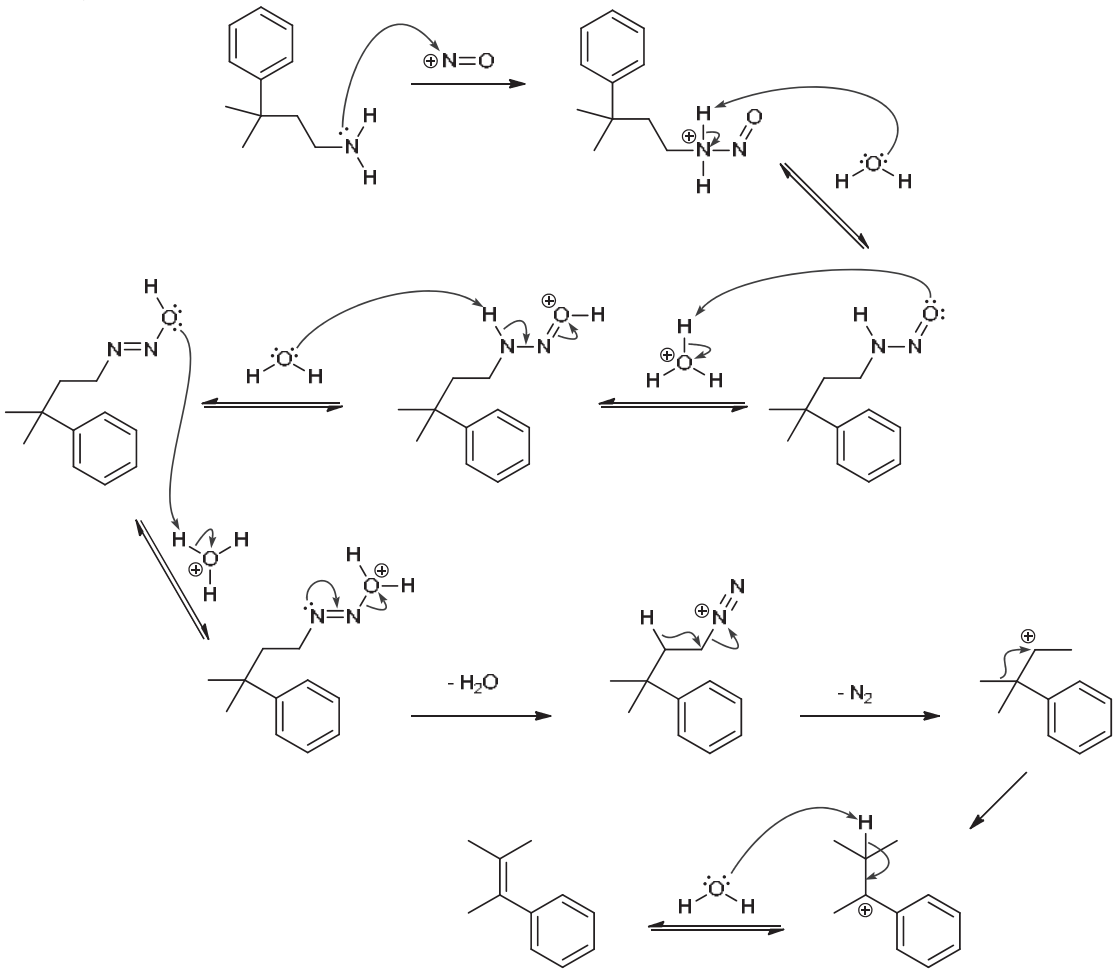
Compound **A**

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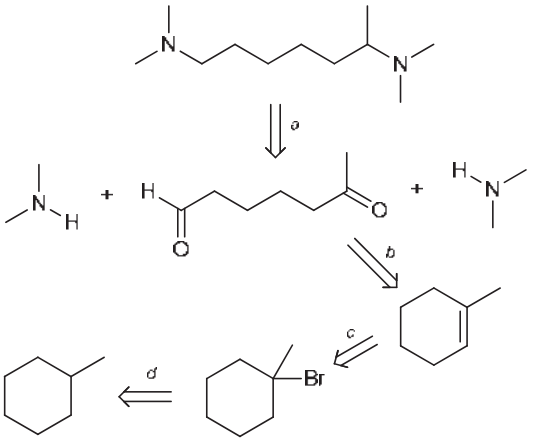
22.87. Sodium nitrite is protonated upon treatment with HCl, giving nitrous acid (HONO), which can be further protonated under these acidic conditions. The resulting cation can lose water (an excellent leaving group), giving a nitrosonium ion, as shown:



The amino group attacks the nitrosonium ion, giving a cation, which then loses a proton to give an intermediate *N*-nitrosamine. Protonation, followed by deprotonation, gives a tautomer of the *N*-nitrosamine. Protonation of this tautomer, followed by loss of a leaving group (water) gives a diazonium ion. Loss of the diazonium group (as N_2 gas) would generate a primary carbocation, which is unlikely to occur because of the high energy cost associated with primary carbocations. However, a hydride shift can occur at the same time as the leaving group leaves (see the discussion at the very end of Section 7.9), giving a secondary carbocation. A subsequent methyl shift generates a more stable, tertiary benzylic carbocation. Finally, deprotonation gives the product. Notice that in acidic conditions, water functions as the base for all deprotonation steps, rather than hydroxide (which is not measurably present in acidic conditions).



22.88. There are certainly many acceptable solutions to this problem. One such solution derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.



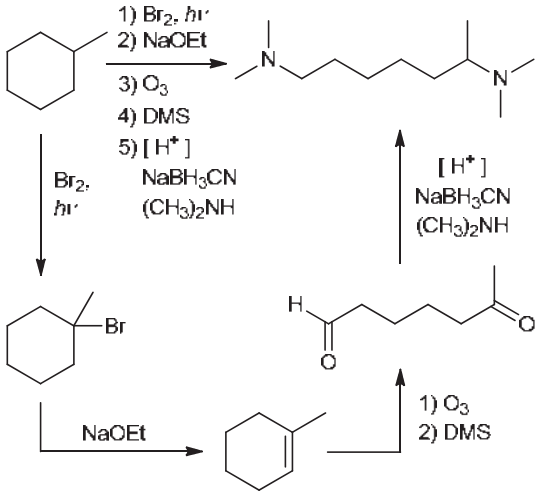
a. The product can be made from the corresponding dicarbonyl compound via reductive amination with excess dimethyl amine (thereby converting each carbonyl group into a dimethyl amino group).

b. The dicarbonyl compound can be made via ozonolysis of 1-methylcyclohexene.

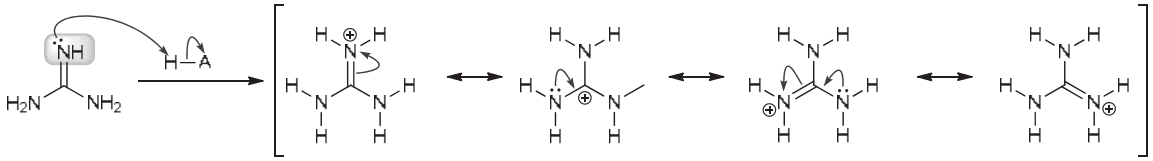
c. 1-Methylcyclohexene can be made from 1-bromo-1-methylcyclohexane via elimination with a strong base.

d. 1-Bromo-1-methylcyclohexane can be made from the starting material via radical bromination at the tertiary position.

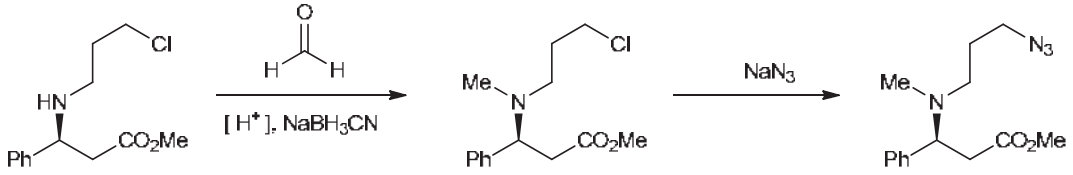
Now let's draw the forward scheme. Radical bromination of the starting cycloalkane gives a tertiary alkyl bromide, which is then converted into an alkene upon treatment with a strong base, such as ethoxide. Ozonolysis causes cleavage of the C=C bond, thereby opening the ring and giving a dicarbonyl compound, which can then be converted into the product via reductive amination, upon treatment with excess dimethylamine and sodium cyanoborohydride with acid catalysis.



22.89. Protonation of the highlighted nitrogen atom results in a cation that is highly resonance stabilized. Protonation of either of the other nitrogen atoms would not result in a resonance-stabilized cation.



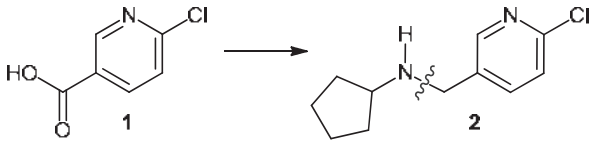
22.90. Two steps are required. The secondary amine must be methylated to give a tertiary amine, and the halogen (Cl) must be replaced with azide. The first step can be achieved via a reductive amination (the nitrogen atom cannot simply be methylated by using MeI, because that would result in over-alkylation, giving the quaternary salt, $R_4N^+ I^-$). Then, in the second step, Cl can function as a leaving group in an S_N2 reaction with sodium azide, to afford compound **2**.



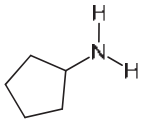
1 **2**

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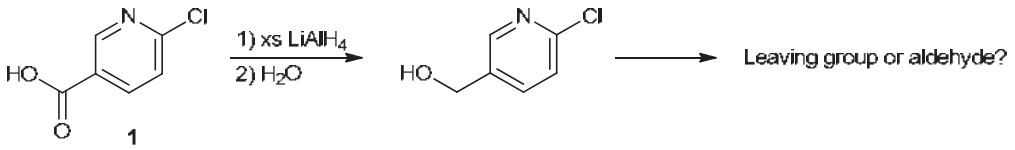
22.91. We begin by identifying the bond that must be made:



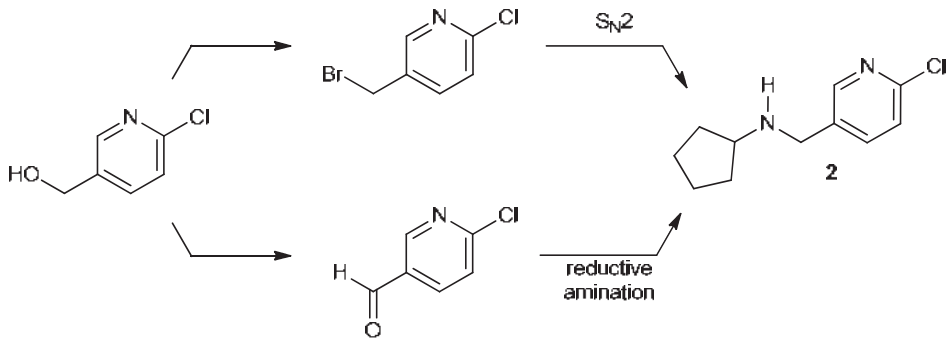
Forming this C-N bond will require the use of cyclopentyl amine:



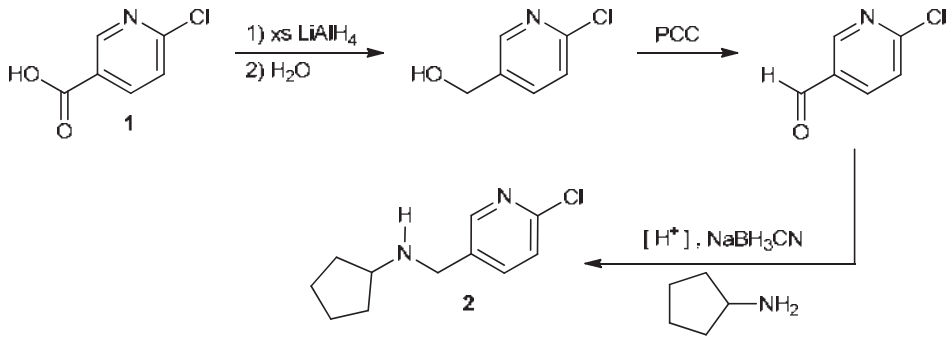
In order to form the desired C-N bond, the carboxylic acid can be reduced to an alcohol (which can be achieved with $LiAlH_4$), but then we must decide what to do with the alcohol.



We can either convert the alcohol into a leaving group (OTs, Cl, Br) and then treat it with cyclopentyl amine in an S_N2 reaction, or we can convert the alcohol into an aldehyde and then perform a reductive amination with cyclopentyl amine:

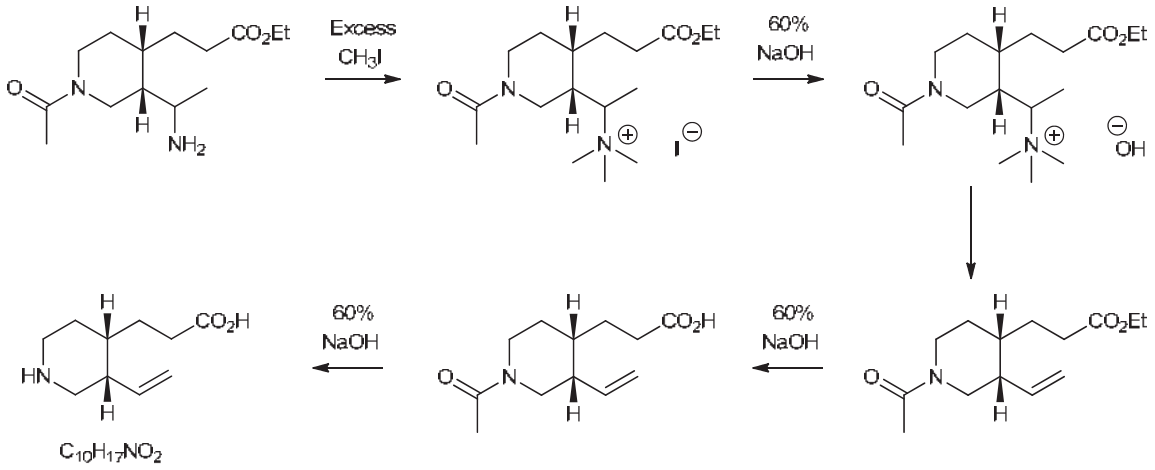


The first path is expected to be inefficient, because it will be difficult to achieve monoalkylation. More likely, polyalkylation will occur, especially with the activated benzylic leaving group. The second path is expected to be more efficient, which gives the following synthesis:

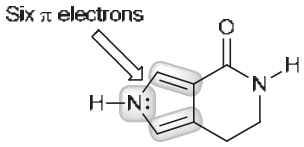


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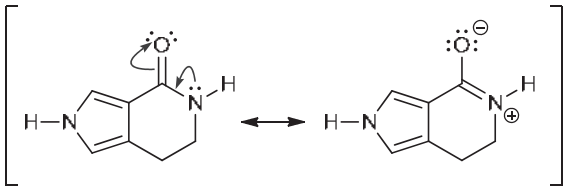
22.92. The starting material has a primary amino group. When treated with excess methyl iodide, it will undergo exhaustive methylation to produce a quaternary ammonium salt. When this salt is treated with NaOH, first an anion exchange occurs, followed by an E2 elimination to produce an alkene (Hofmann elimination). At this stage it would be useful to take inventory of the other functional groups in the molecule. Compound **5** also contains an ethyl ester. We saw in Section 20.11 that esters will undergo saponification when treated with aqueous sodium hydroxide. We also learned in Section 20.12 that amides undergo hydrolysis when treated with aqueous sodium hydroxide, to afford a carboxylic acid as well as an amine. In this case, the product has the molecular formula $C_{10}H_{17}NO_2$.



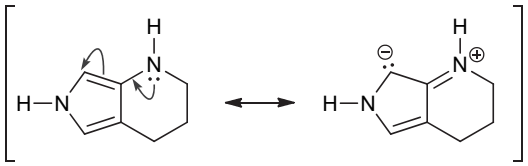
22.93. Option (a) has two nitrogen atoms, although both are expected to be weakly basic. The nitrogen atom on the left is not a strong base because its lone pair is involved in aromaticity and is therefore not available to function as a base (not even as a weak base):



The nitrogen atom on the right is also not basic, because its lone pair is delocalized by resonance:



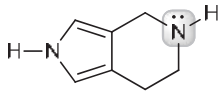
In option (b), the nitrogen atom on the right has a lone pair that is delocalized,



but the delocalization is not as pronounced as it is in the case of an amide (because a resonance structure with C^- is less significant than a resonance structure with O^-). This compound might function as a base, although it would not be expected to be a very strong base, so we continue our analysis of the remaining two options.

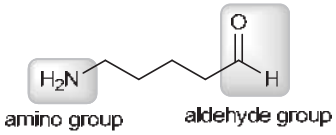
Option (c) has only one nitrogen atom, and its lone pair is involved in aromaticity.

Option (d) is the correct answer, because it has a nitrogen atom (on the right side) with a localized lone pair:



This compound is the strongest base among the four options.

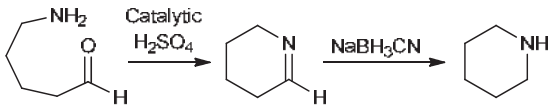
22.94. The reactant has both an amino group and an aldehyde group:



In the presence of catalytic acid, these two functional groups are expected to react with each other, in an intramolecular fashion, to give an imine. Since the imine

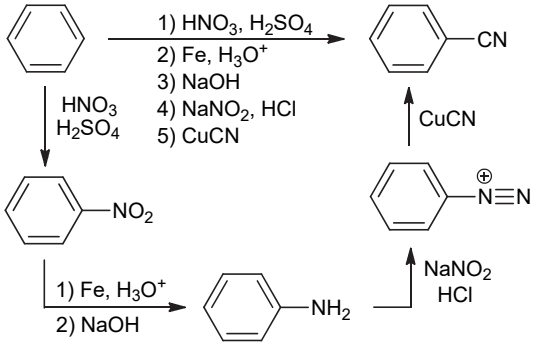
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is formed in the presence of $NaBH_3CN$, the imine is reduced to give a cyclic amine:



Therefore, option (a) is the correct answer.

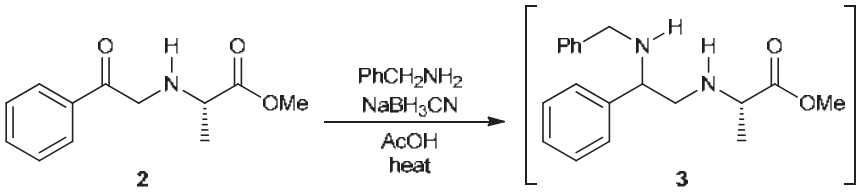
22.95. Option (a) is not a known reaction. Benzene is not expected to react with HCN. Option (b) gives the desired product:



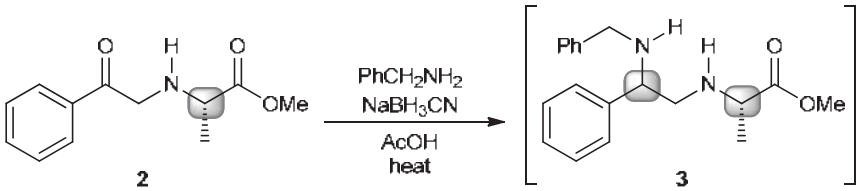
Nitration of the ring gives nitrobenzene, which is then reduced to give aniline. Aniline is then converted into a diazonium ion, followed by reaction with CuCN to give the product. In options (c) and (d), the second step (in each case) is not a viable reaction.

22.96.

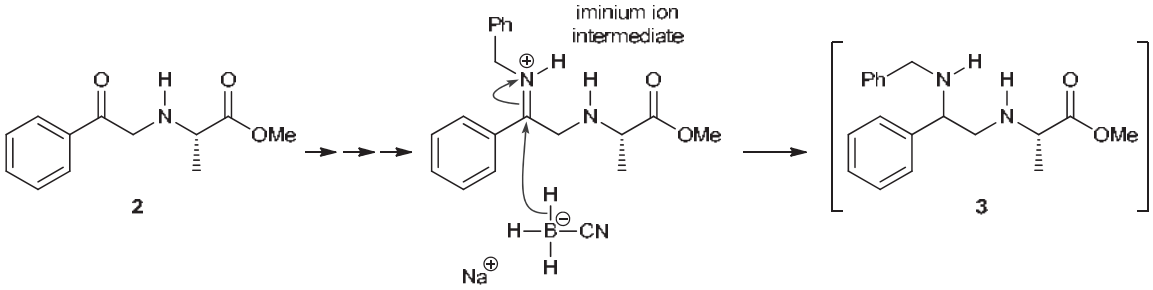
(a) The ketone group of compound **2** undergoes reductive amination (the ester group is unreactive under these conditions) to give compound **3**, as shown below:



Notice that compound **2** has only one chiral center (highlighted below), and its configuration is not affected during the conversion of **2** to **3**. Compound **3** has two chiral centers (highlighted below), because a new chiral center is created during the conversion of **2** to **3**:



This new chiral center is formed when an iminium ion (formed from compound **2**) is reduced by the hydride reducing agent ($NaBH_3CN$) to give **3**:

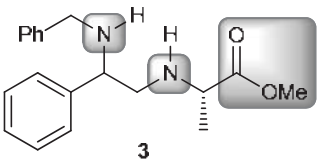


Focus carefully on the reduction step above, in which the new chiral center is created. Since the reducing agent can approach from either face of the C=N π bond, we would expect the following two diastereomeric products:



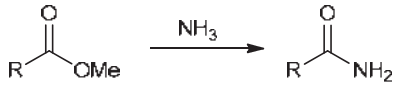
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(b) The problem statement indicates that compound **3** undergoes a reaction that produces a cyclic amide. So we inspect the structure of **3** to determine which functional groups can react with each other to produce a cyclic amide. Compound **3** has two amine groups and one ester group:



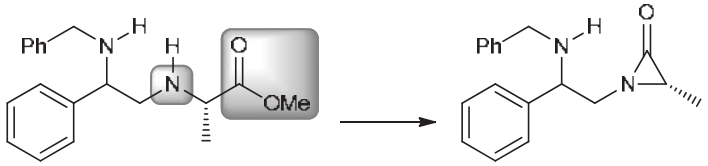
3

And we learned in Section 20.11 that an amide can be formed from an amine and an ester:

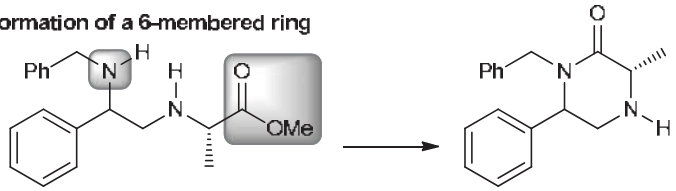


This type of reaction is generally slow and inefficient, but in our case, the reaction is intramolecular, so it can occur more rapidly. The reaction can occur in two possible ways, either forming a 3-membered ring or a 6-membered ring, depending on which amine group reacts with the ester group:

Formation of a 3-membered ring

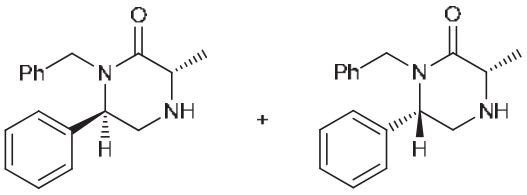


Formation of a 6-membered ring



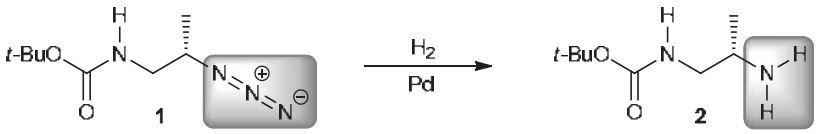
The 3-membered ring will be higher in energy than the 6-membered ring as a result of significant ring strain which is present in the former and absent in the latter. As such, the 6-membered ring will be formed as the product.

Since compound **3** was formed as a diastereomeric mixture, we expect that compound **4** will also be produced as a diastereomeric mixture:



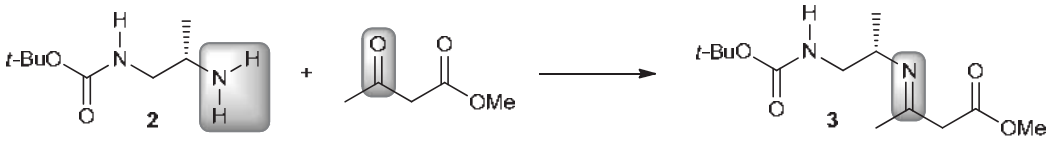
22.97.

(a) Hydrogenation of an azide is expected to give an amine.



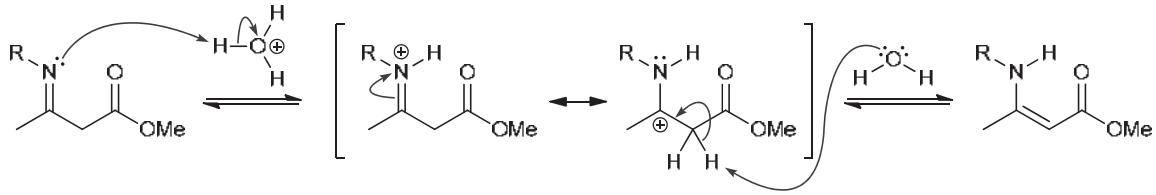
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Compound **2** is a primary amine, and the problem statement indicates that it reacts with methyl acetoacetate to give an imine. We saw in Chapter 19 that an imine is the product generated when a primary amine is treated with a ketone. Methyl acetoacetate does have a ketone group, so we expect that compound **3** will have the following structure:



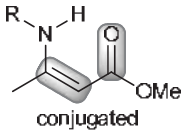
In Chapter 19, we saw that the process was catalyzed by acid, but in this case, the problem statement indicates that acid catalyst was not employed, and the reaction proceeded without it.

(b) Tautomerization can occur either in acid-catalyzed conditions or in base-catalyzed conditions. In fact, even if we do not introduce either acid or base, there should be sufficient quantities of either (adsorbed to the surface of the glassware) to catalyze the tautomerization process. The problem statement asks us to draw an acid-catalyzed mechanism. Much like keto-enol tautomerization, the process should require two steps (protonation and deprotonation). In acidic conditions, protonation occurs first, to give a resonance stabilized cation, which then undergoes deprotonation:

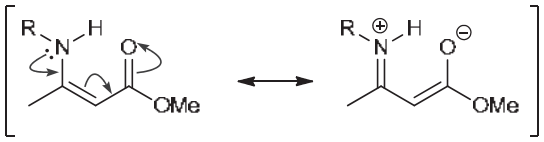


(c) The following are three reasons why the enamine is particularly stable in this case:

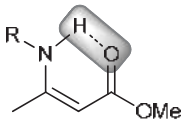
(1) The presence and proximity of the ester group allows for conjugation with the C=C bond, which is a stabilizing factor:



(2) The lone pair of this enamine is particularly delocalized, as a result of the resonance structure shown below. This delocalization contributes to the stability of this enamine.



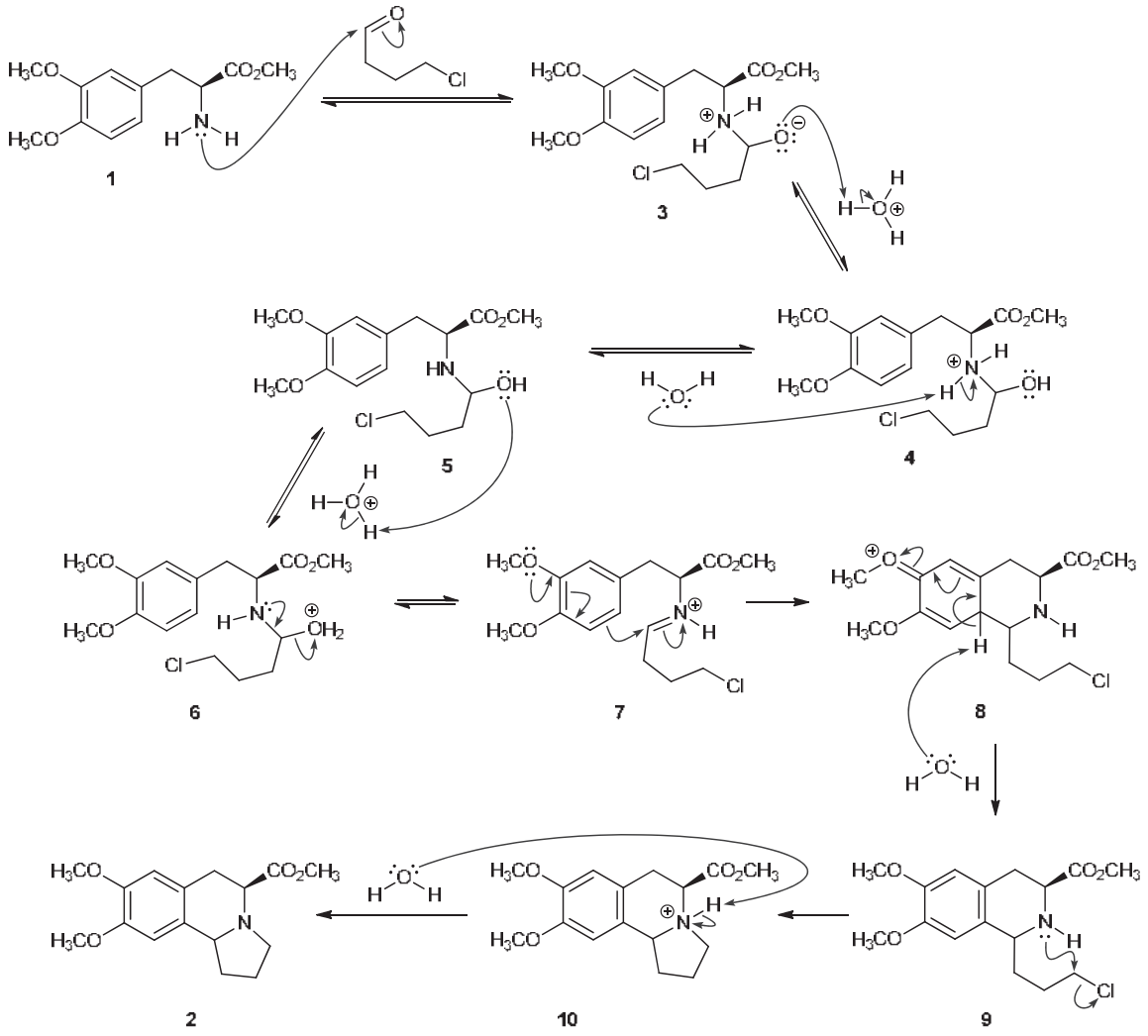
(3) The presence and proximity of the ester group enables intramolecular hydrogen bonding, which is also a stabilizing factor.



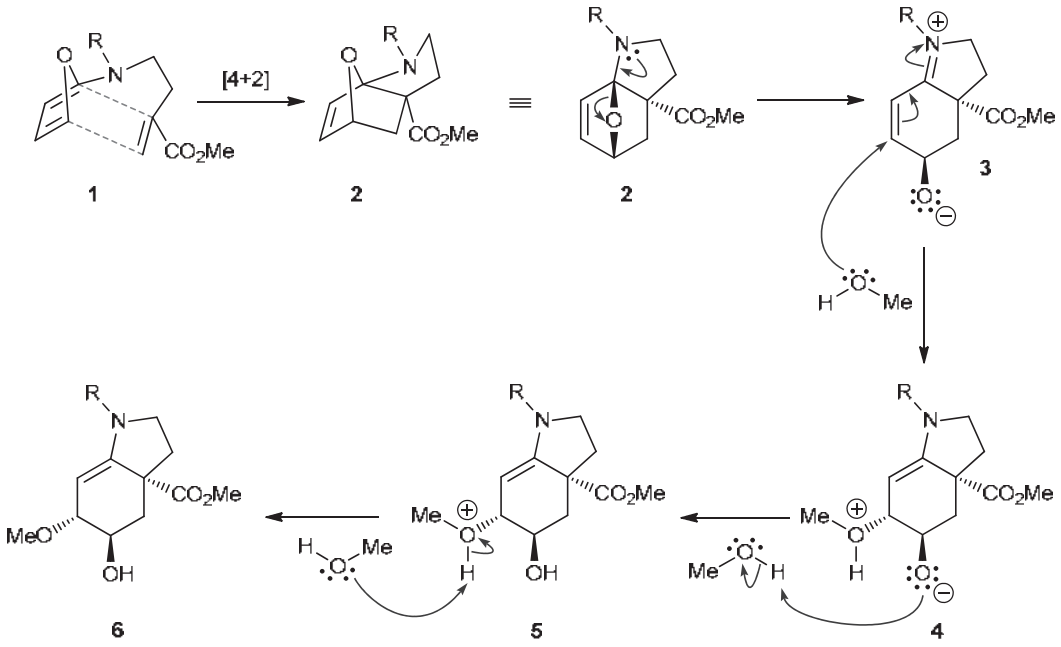
All three factors (described above) contribute to the enhanced stability of the enamine in this particular case, and as such, the equilibrium favors formation of the enamine.

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22.98. The amino group of compound **1** attacks the carbonyl group of the aldehyde to produce intermediate **3**. After three successive proton transfer steps, water is lost, producing iminium ion **7**. In section 22.6, we saw that iminium ions are sufficiently activated (electrophilic) to be reduced by sodium cyanoborohydride. In the absence of a hydride source, they can also be trapped by a nucleophile. In this example, the nucleophile is the attached aromatic ring. In Chapter 18, we learned about electrophilic aromatic substitution reactions (such as the Friedel-Crafts acylation); we know that the two methoxy groups in **7** sufficiently activate the aromatic ring, enabling the ring to function as a nucleophile and attack an electrophile. Nucleophilic attack by the aromatic ring will produce intermediate **8**, in which the electrophilic group has been added *para* to one of the methoxy groups. Next, rearomatization will produce compound **9**. This process is known as the Pictet-Spengler condensation reaction. In the final stage of the synthesis, the lone pair on the nitrogen atom will function as a nucleophile and attack, via S_N2, the 1° alkyl chloride to form the 5-membered ring. A final proton transfer produces desired product, compound **2**.



22.99. If we redraw the starting material so that the pendant π bond is in close proximity to the diene, we can envision a thermal [4+2] Diels Alder reaction occurring. Notice that the dienophile will approach the diene, resulting in the oxo-bridge on one face and the ester group on the other face of the newly formed system. After cyclization, compound **2** can undergo a nitrogen-induced fragmentation that will result in the formation of a C-N π-bond via the breakage of the C-O σ-bond. Compound **3** has a highly electrophilic α,β-unsaturated iminium ion that can be trapped by methanol to produce intermediate **4**. Because the top face of the six-membered ring is hindered by the alkoxide, methanol will approach from the bottom face, thereby installing the methoxy group on a dash. The final two steps of the mechanism are proton transfer steps, producing the desired compound (**6**).



Chapter 23
Organometallic Compounds

Review of Concepts

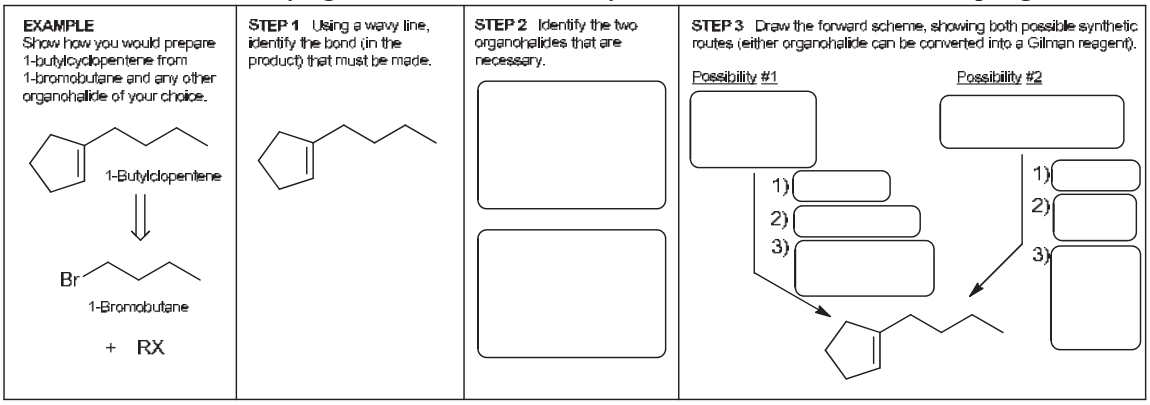
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 23. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Organolithium (RLi) and organomagnesium (RMgX) compounds are strong bases and strong _____.
- Alkenes will react with ICH_2ZnI to form a three-membered ring, in a process called _____.
- Stille coupling, which occurs in the presence of a suitable palladium catalyst, is the reaction between an _____ and an organic electrophile to form a new C–C σ bond. The coupling process is stereospecific. It is observed to proceed with _____ of configuration at each of the C=C units.
- Suzuki coupling, which occurs in the presence of a suitable palladium catalyst and a base, is the reaction between an _____ and an organic electrophile to form a new C–C σ bond. The coupling process is stereospecific. It is observed to proceed with _____ of configuration at each of the C=C units.
- Negishi coupling, which occurs in the presence of a suitable palladium catalyst, is the reaction between an organic electrophile (R′X) and an organometallic species containing _____, to form a new C–C σ bond. The coupling process is stereospecific. It is observed to proceed with _____ of configuration at each of the C=C units.
- The Heck reaction is a coupling reaction that occurs between an aryl, vinyl or benzyl halide (RX) and an _____ in the presence of an appropriate Pd catalyst and a base.
- Alkene _____ is a process that is characterized by the redistribution (changing of position) of carbon-carbon double bonds.
- When terminal alkenes are used, the evolution of _____ gas drives the reaction toward the formation of one alkene with excellent yields.
- When the starting material is a diene and the reaction is conducted in dilute solutions (thereby favoring an intramolecular process over intermolecular processes), alkene metathesis can serve as a method for ring-formation. This process is called _____ metathesis. Similarly, ring-opening metathesis can be achieved in the presence of _____.

Review of Skills

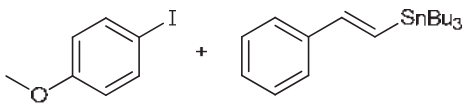
Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 23. The answers appear in the section entitled *SkillBuilder Review*.

SkillBuilder 23.1 Identifying the Partners for a Corey-Posner/Whitesides-House Coupling Reaction



SkillBuilder 23.2 Predicting the Product of a Stille Coupling Reaction

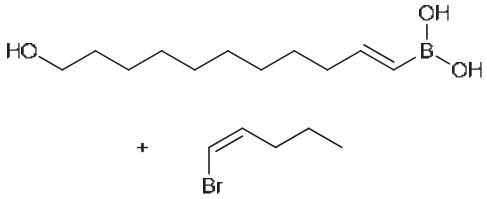
STEP 1 Consider a Stille coupling reaction between the following two coupling partners. Circle the carbon atoms that will be joined via a new σ bond.



STEPS 2 and 3 Rotate the coupling partners and draw the product, making sure to retain the configuration of any C=C units.

SkillBuilder 23.3 Predicting the Product of a Suzuki Coupling Reaction

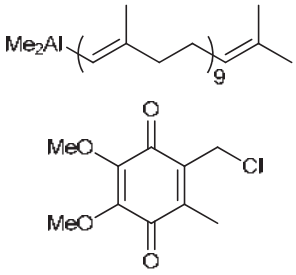
STEP 1 Consider a Suzuki coupling reaction between the following two coupling partners. Circle the carbon atoms that will be joined via a new σ bond.



STEPS 2 and 3 Rotate the coupling partners and draw the product, making sure to retain the configuration of any C=C units.

SkillBuilder 23.4 Predicting the Product of a Negishi Coupling Reaction

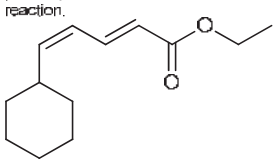
STEP 1 Consider a Negishi coupling reaction between the following two coupling partners. Circle the carbon atoms that will be joined via a new σ bond.



STEPS 2 and 3 Orient the coupling partners and draw the product, making sure to retain the configuration of any C=C units.

SkillBuilder 23.5 Identifying the Partners for a Heck Reaction

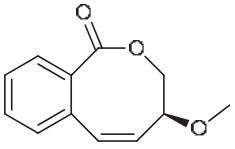
STEP 1 Using a wavy line, identify the bond (in the following desired product) that can be made via a Heck reaction.



STEP 2 Identify the organohalide and alkene necessary. Keep in mind that Heck reactions are stereoselective with respect to the starting alkene, and stereospecific with respect to the organohalide (if it is a vinyl halide, as in this case).

SkillBuilder 23.6 Identifying the Starting Material for a Ring-Closing Metathesis

STEP 1 Identify the C=C unit that can be made via a ring-closing metathesis.



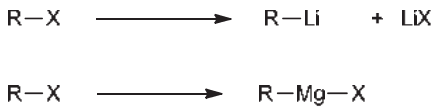
STEP 2 Break the C=C unit apart, and attach a methylene (CH_2) group to each of the two vinyl positions of the broken C=C unit.

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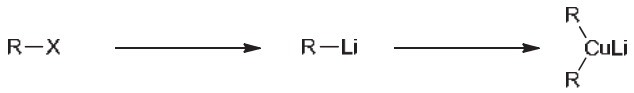
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 23. The answers appear in the section entitled *Review of Reactions*.

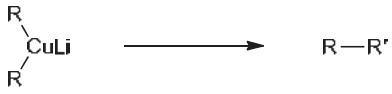
Preparation of Organolithium and Organomagnesium Compounds



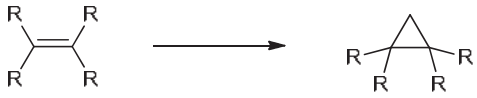
Preparation of Gilman Reagents



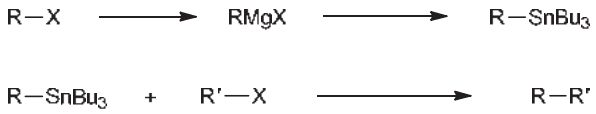
Coupling Reaction of a Gilman Reagent with an Organohalide



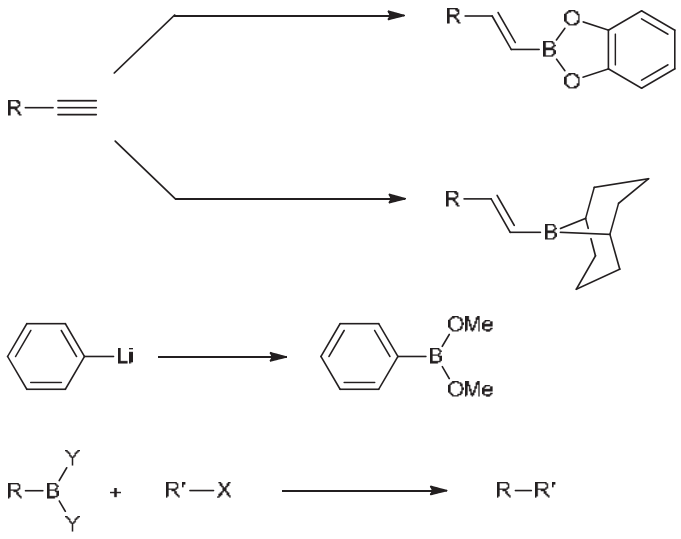
Simmons-Smith Reaction



Stille Coupling

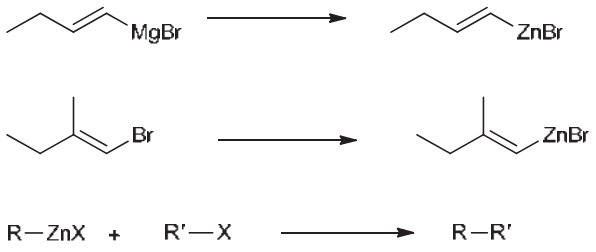


Suzuki Coupling

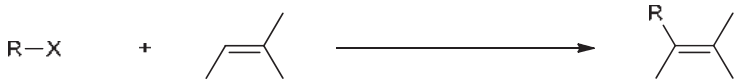


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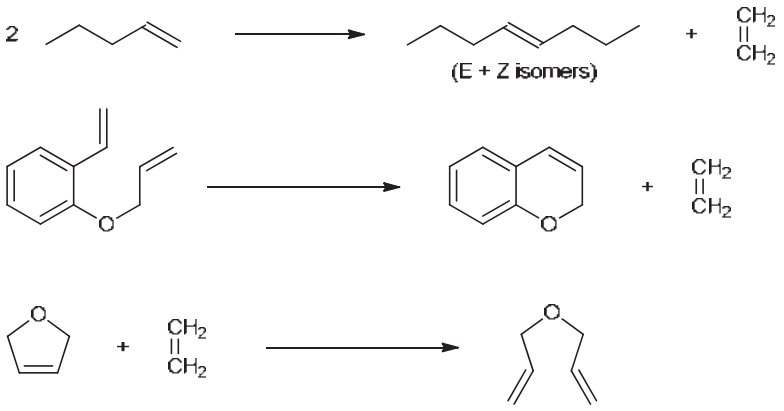
Negishi Coupling



Heck Reaction

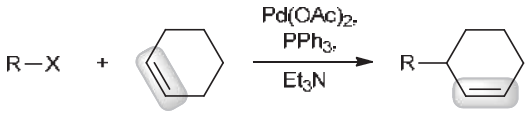


Alkene Metathesis

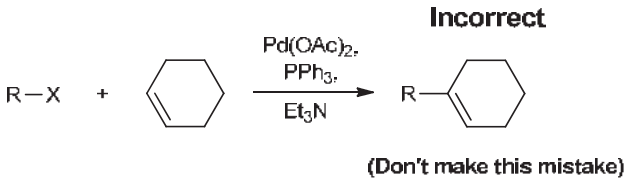


Common Mistake to Avoid

When a cyclic alkene is used in a Heck reaction, make sure to move the position of the C=C unit when drawing the product:



It is a common mistake to forget to move the C=C unit:

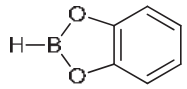
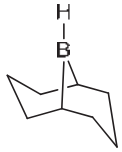


Recall that the C=C unit moves because this is the only regiochemical outcome that accommodates *syn* elimination. This is the case whenever a cyclic alkene is used as a starting material in a Heck reaction, so make sure to take this into account when drawing the product of a Heck reaction.

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Useful reagents

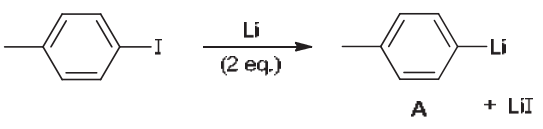
The following is a list of reagents that appear in this chapter:

Reagents	Function
Li (2 eq.)	Used to convert an organohalide into an organolithium compound.
RLi	An organolithium reagent. A very strong nucleophile and a very strong base.
Mg, Et_2O	Reagents for converting an organohalide into a Grignard reagent.
RMgX	A Grignard reagent. A very strong nucleophile and a very strong base.
CuX (0.5 eq.)	Used to convert an organolithium compound into a Gilman reagent.
CH_2I_2, Zn-Cu, Et_2O	Reagents for a Simmons-Smith cyclopropanation.
Bu_3SnCl	Used to convert an organolithium or organomagnesium compound into an organostannane.
$Pd(PPh_3)_4$	A catalyst used for coupling reactions, including Stille coupling, Suzuki coupling, Negishi coupling, and the Heck reaction.
$Pd(OAc)_2$	A catalyst used for coupling reactions, including Stille coupling, Suzuki coupling, Negishi coupling, and the Heck reaction.
	Catechol borane. Used to convert an alkyne into a vinyl boronic ester. Also used to convert an alkene into an alkyl boronic ester.
	9-BBN. Used to convert an alkyne into a vinyl borane. Also used to convert an alkene into an alkyl borane.
$B(OMe)_3$	Trimethylborate. Used to convert an aryllithium compound into an aryl boronic ester.
$ZnBr_2$	Zinc dibromide. Used to convert an organolithium or organomagnesium compound into an organozinc compound.
Zn, Et_2O	Zinc and diethyl ether. Used to convert an organolithium or organomagnesium compound into an organozinc compound.
Grubbs catalyst	Used to achieve alkene metathesis, including ring-opening metathesis and ring-closing metathesis.

Solutions

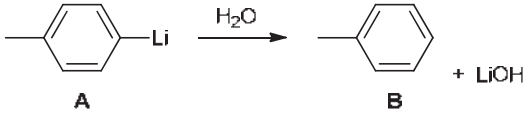
23.1. The first compound is an organomagnesium compound (C–Mg bond), while the second compound is an organozinc reagent (C–Zn bond). We must compare these two C–M bonds to determine which bond has greater ionic character. The difference in electronegativity between C (2.5) and Mg (1.2) is greater than the difference in electronegativity between C (2.5) and Zn (1.6). Therefore, the carbon atom of a C–Mg bond is expected to have a greater partial negative character, and thus be more nucleophilic than the carbon atom of the C–Zn bond. That is, organomagnesium compounds are expected be more nucleophilic than organozinc compounds. Indeed, they are.

23.2. Compound **A** is formed when the iodide group (in 4-iodotoluene) is replaced with a lithium atom, giving an organolithium compound:

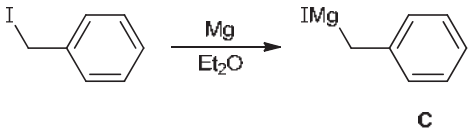


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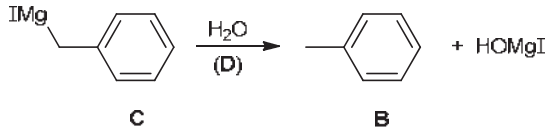
Upon treatment with H_2O, compound **A** functions as a base and removes a proton from H_2O, giving toluene (compound **B**):



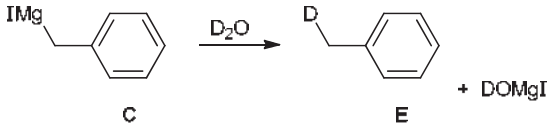
Compound **C** is formed via insertion of magnesium, as shown:



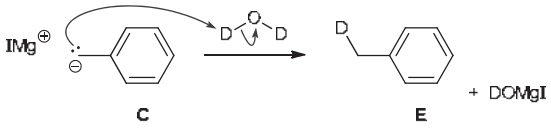
Compound **C** is converted into compound **B** upon treatment with a proton source, such as H_2O (compound **D**):



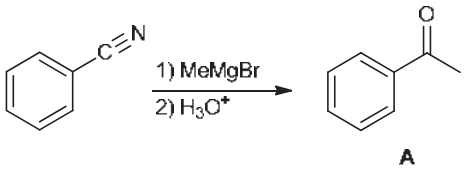
Upon treatment with D_2O, compound **C** functions as a base and removes a deuteron from D_2O, giving a deuterated product (compound **E**), as shown:



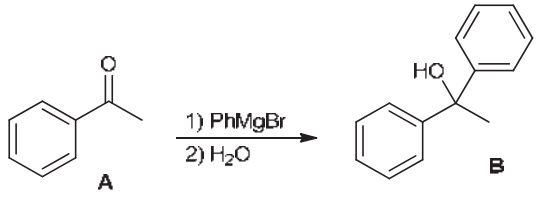
23.3. Compound **C** functions as a base and removes a deuteron, which requires two curved arrows, as shown:



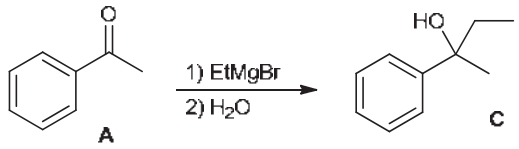
23.4. Treating a nitrile with a Grignard reagent, followed by aqueous acid, gives ketone **A** (Section 21.13):



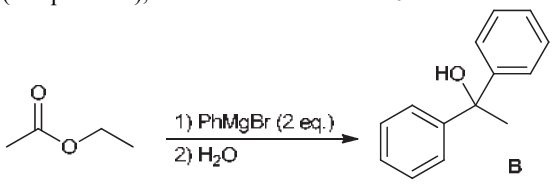
When a ketone (compound **A**) is treated with PhMgBr, followed by aqueous workup, a phenyl group is installed and the product is alcohol **B** (Section 12.6):



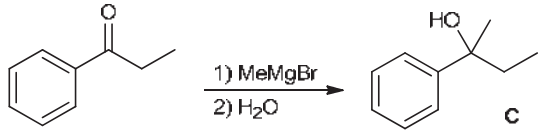
When compound **A** is treated with EtMgBr, followed by aqueous workup, an ethyl group is installed and the product is alcohol **C** (Section 12.6):



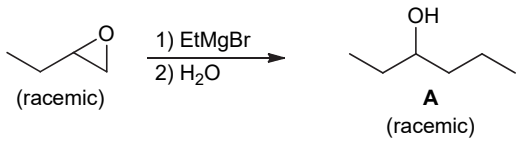
The starting ester can be converted into compound **B** upon treatment with two equivalents of PhMgBr (compound **D**), as described in Section 20.11:



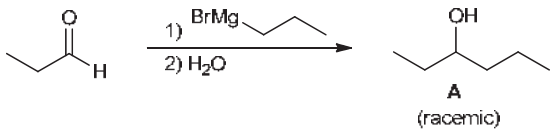
The starting ketone can be converted into compound **C** upon treatment with one equivalent of MeMgBr (compound **E**), followed by aqueous workup, as described in Section 20.11:



23.5. When the racemic epoxide is treated with ethyl magnesium bromide, followed by aqueous workup, an ethyl group is installed at the less substituted side of the epoxide, and the three-membered ring is opened to give a racemic alcohol (compound **A**):

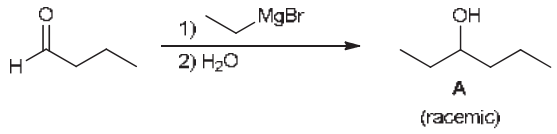


Propanal can be converted into compound **A** upon treatment with propyl magnesium bromide (compound **B**), followed by water workup, as shown:

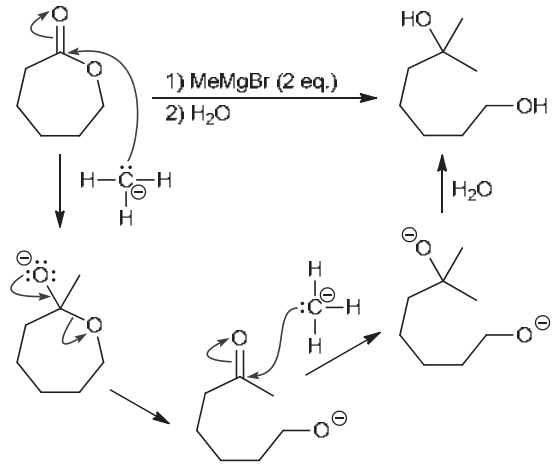


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Butanal can be converted into compound **A** upon treatment with ethyl magnesium bromide (compound **C**), followed by water workup, as shown:

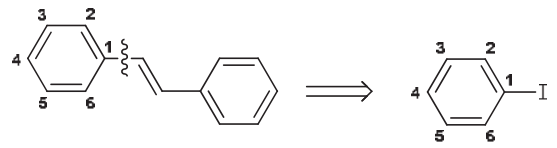


23.6. The first equivalent of the Grignard reagent attacks the carbonyl group, followed by loss of the leaving group to give a ketone (note that the leaving group is still tethered to the ketone). A second equivalent of the Grignard reagent attacks the carbonyl group of the ketone intermediate to produce a dianion, which is subsequently protonated by water to give a diol. Overall, the ring has been opened, and two methyl substituents are incorporated into the product:

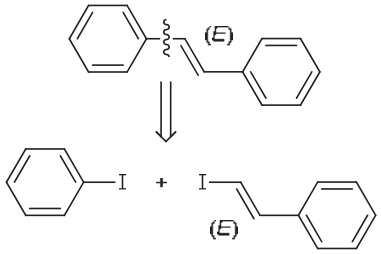


23.7.

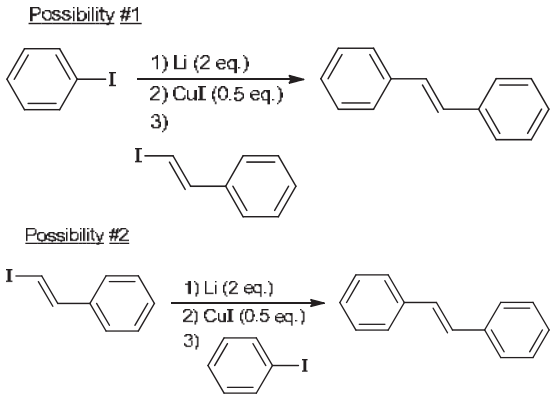
(a) First determine which bond (in the product) will be made via a coupling process:



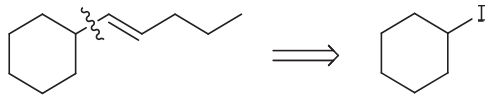
Next, draw the two organohalides that are necessary for the coupling process. One of the organohalides has already been identified in the problem statement (iodobenzene). The other organohalide (of our choice) must be a vinyl halide, so we draw an iodide (because iodides are more reactive than bromides or chlorides). This vinyl iodide must have an *E* configuration, because that C=C unit has the *E* configuration in the product:



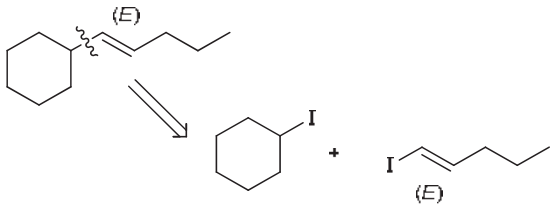
One of these organohalides must be converted into a Gilman reagent and then treated with the other organohalide. This leads to two possible synthetic routes, both of which are viable:



(b) First determine which bond (in the product) will be made via a coupling process:

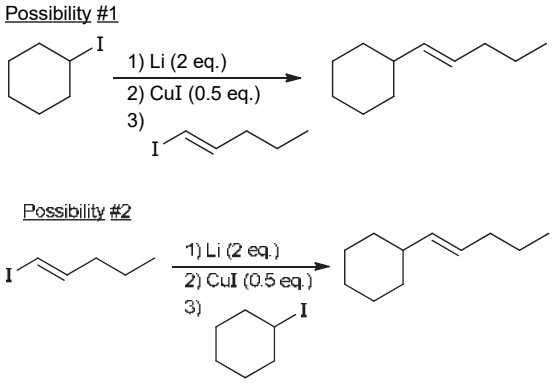


Next, draw the two organohalides that are necessary for the coupling process. One of the organohalides has already been identified in the problem statement (cyclohexyl iodide). The other organohalide (of our choice) must be a vinyl halide, so we draw an iodide. This vinyl iodide must have an *E* configuration, because that C=C unit has the *E* configuration in the product:

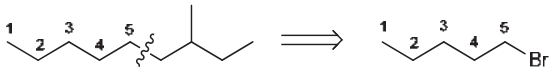


One of these organohalides must be converted into a Gilman reagent and then treated with the other organohalide. This leads to two possible synthetic routes, both of which are viable:

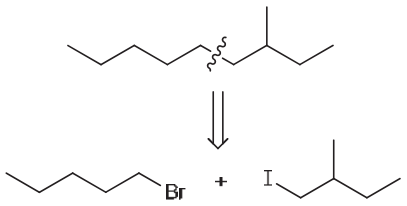
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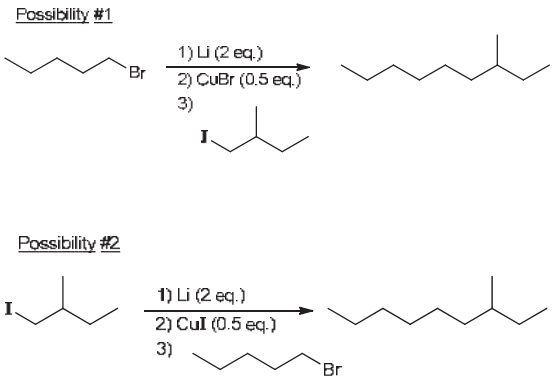
(c) First determine which bond (in the product) will be made via a coupling process:



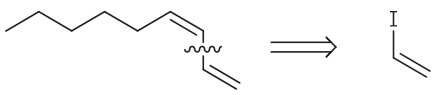
Next, draw the two organohalides that are necessary for the coupling process. One of the organohalides has already been identified in the problem statement (1-bromopentane). The other organohalide (of our choice) must be an alkyl halide, so we draw an iodide:



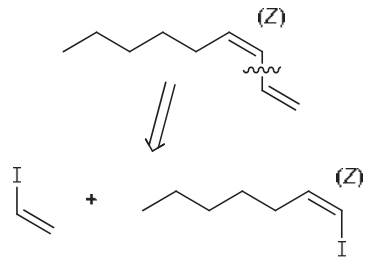
One of these organohalides must be converted into a Gilman reagent and then treated with the other organohalide. This leads to two possible synthetic routes, both of which are viable:



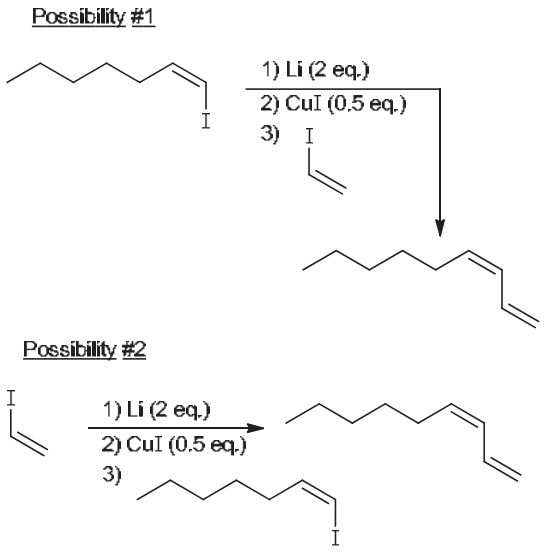
(d) First determine which bond (in the product) will be made via a coupling process:



Next, draw the two organohalides that are necessary for the coupling process. One of the organohalides has already been identified in the problem statement (vinyl iodide). The other organohalide (of our choice) must be a vinyl halide, so we draw an iodide. This latter vinyl iodide must have a *Z* configuration, because that C=C unit has the *Z* configuration in the product:

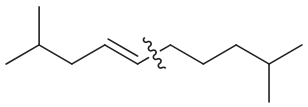


One of these organohalides must be converted into a Gilman reagent and then treated with the other organohalide. This leads to two possible synthetic routes, both of which are viable:



23.8.

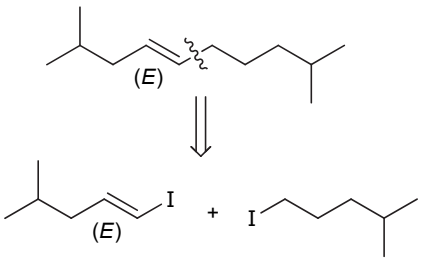
(a) First determine which bond (in the product) will be made via a coupling process. The problem statement dictates that each organohalide must have no more than 6 carbon atoms. Since the product has twelve carbon atoms, that leaves us with only one choice, indicated below with a wavy line:



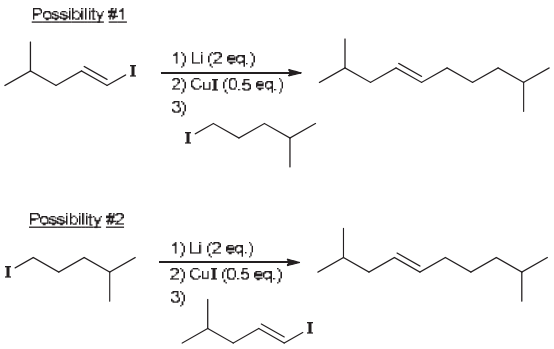
Next, draw the two organohalides that are necessary for the coupling process. In this case, we need an alkyl iodide and a vinyl iodide, as shown. Note that the vinyl

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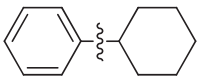
iodide must have an *E* configuration, because that C=C unit has the *E* configuration in the product:



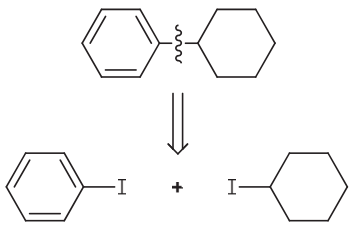
One of these organohalides must be converted into a Gilman reagent and then treated with the other organohalide. This leads to two possible synthetic routes, both of which are viable:



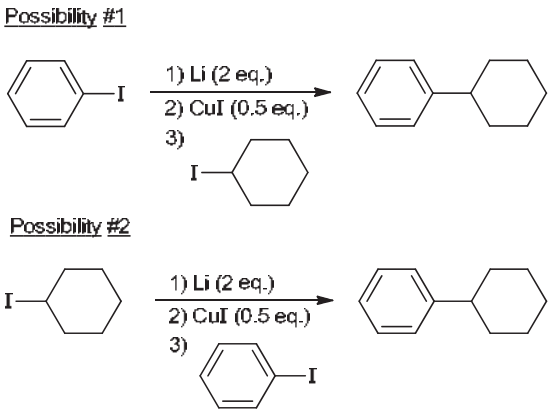
(b) First determine which bond (in the product) will be made via a coupling process. The problem statement dictates that each organohalide must have no more than 6 carbon atoms. Since the product has twelve carbon atoms, that leaves us with only one choice, indicated below with a wavy line:



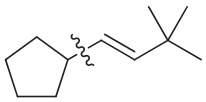
Next, draw the two organohalides that are necessary for the coupling process. In this case, we need cyclohexyl iodide and iodobenzene, as shown:



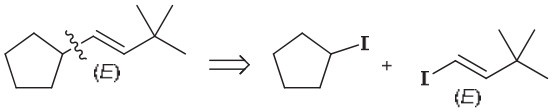
One of these organohalides must be converted into a Gilman reagent and then treated with the other organohalide. This leads to two possible synthetic routes, both of which are viable:



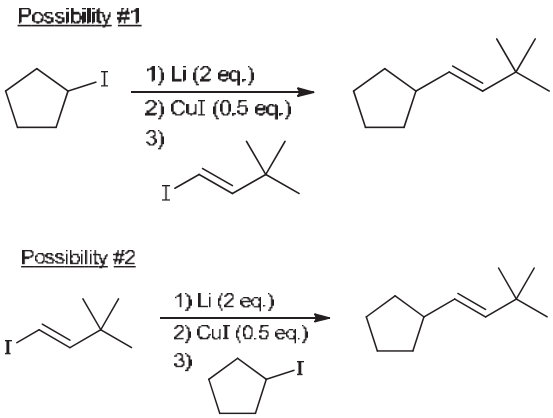
(c) First determine which bond (in the product) will be made via a coupling process. The problem statement dictates that each organohalide must have no more than 6 carbon atoms, so we select the following bond (six carbon atoms on one side and five on the other):



Next, draw the two organohalides that are necessary for the coupling process. In this case, we need cyclopentyl iodide and a vinyl iodide. Note that the vinyl iodide must have an *E* configuration, because that C=C unit has the *E* configuration in the product:



One of these organohalides must be converted into a Gilman reagent and then treated with the other organohalide. This leads to two possible synthetic routes, both of which are viable:

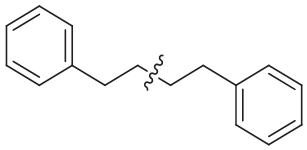


23.9.

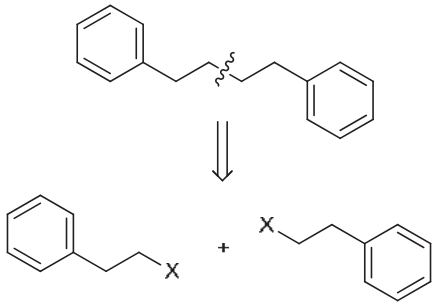
(a) First determine which bond (in the product) will be made via a coupling process. The problem statement

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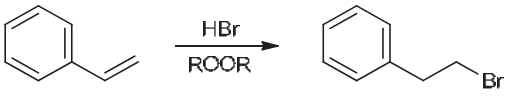
dictates that styrene (which has eight carbon atoms) must be the only source of carbon atoms. Therefore, we must create the following bond, indicated with a wavy line:



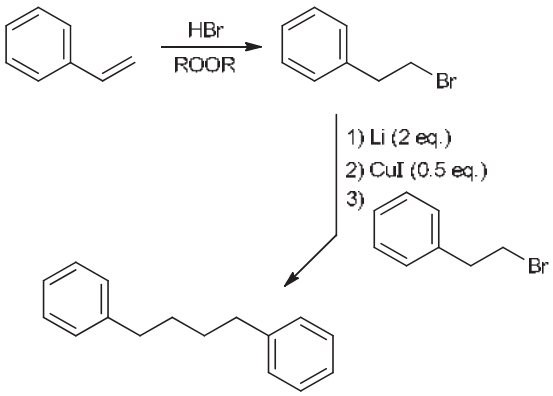
Next, draw the two organohalides that are necessary for the coupling process. In this case, we need two identical alkyl halides, as shown:



These alkyl halides can be made from styrene via the *anti*-Markovnikov addition of HBr (see Section 11.10):

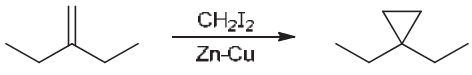


The entire synthesis is shown below:



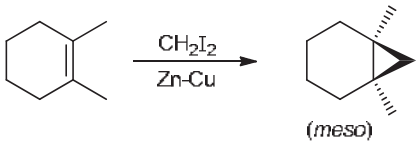
23.10.

(a) Upon treatment with CH_2I_2 and Zn-Cu, an alkene will undergo a Simmons-Smith reaction, thereby converting the C=C unit into a cyclopropane ring (with introduction of a methylene group):



In this case, the product has no chiral centers, so wedges and dashes are not drawn.

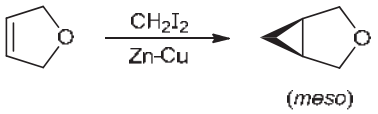
(b) Upon treatment with CH_2I_2 and Zn-Cu, an alkene will undergo a Simmons-Smith reaction, thereby converting the C=C unit into a cyclopropane ring (with introduction of a methylene group):



In this case, the product has two chiral centers, and is a *meso* compound (it does not have an enantiomer). Introduction of the methylene group can occur on either face of the π bond, giving the same *meso* compound in either case:



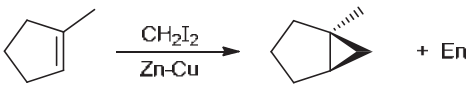
(c) Upon treatment with CH_2I_2 and Zn-Cu, an alkene will undergo a Simmons-Smith reaction, thereby converting the C=C unit into a cyclopropane ring (with introduction of a methylene group):



In this case, the product has two chiral centers, and is a *meso* compound (it does not have an enantiomer). Introduction of the methylene group can occur on either face of the π bond, giving the same *meso* compound in either case:



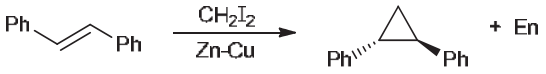
(d) Upon treatment with CH_2I_2 and Zn-Cu, an alkene will undergo a Simmons-Smith reaction, thereby converting the C=C unit into a cyclopropane ring (with introduction of a methylene group):



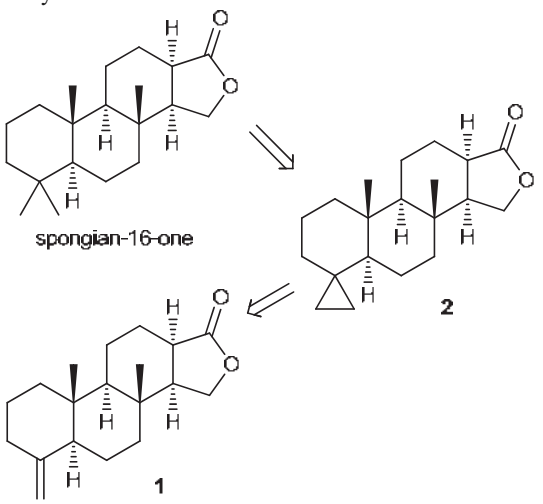
In this case, the product is not a *meso* compound. Since the methylene group can be installed on either face of the π bond, we expect a pair of enantiomers.

(e) Upon treatment with CH_2I_2 and Zn-Cu, an alkene will undergo a Simmons-Smith reaction, thereby converting the C=C unit into a cyclopropane ring (with introduction of a methylene group). In this case, the starting alkene has a *trans* configuration, which is preserved in the product. Introduction of the methylene group can occur on either face of the π bond, giving rise to a pair of enantiomers:

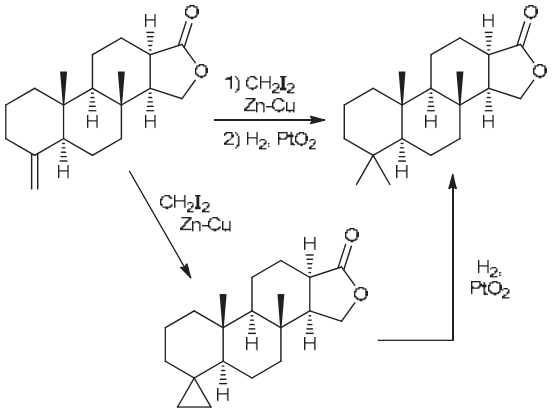
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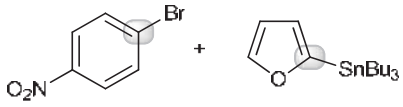
23.11.
As indicated in the problem statement, the geminal dimethyl group of spongian-16-one can be accessed via hydrogenolysis of a cyclopropane ring, and cyclopropane **2** can be prepared from compound **1** via the Simmons-Smith reaction, as shown in the following retrosynthetic analysis:



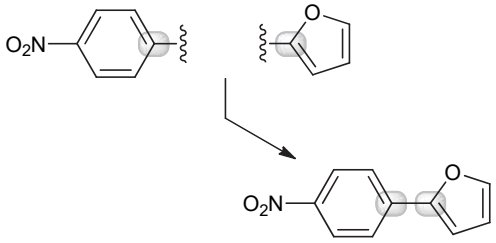
The forward reaction sequence is shown here:



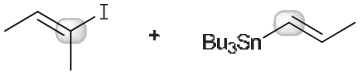
23.12.
(a) First identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide group (in the aryl bromide) will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:



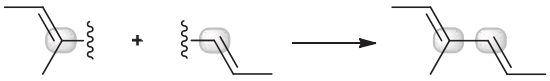
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



(b) First identify the carbon atoms that will be joined. The carbon atom connected directly to the iodide group (in the vinyl iodide) will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:

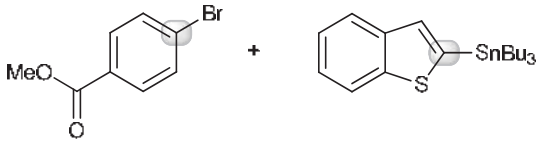


Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

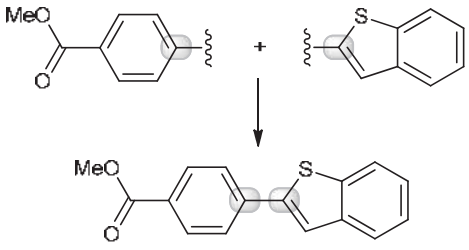


In this case, there are two C=C units (one in the organic electrophile and the other in the organostannane). So, when drawing the product, we must be careful that each of these C=C units maintains its *E* configuration.

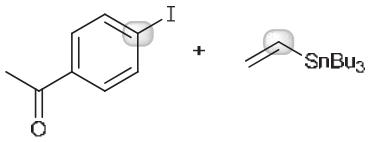
(c) First identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide group (in the aryl bromide) will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:



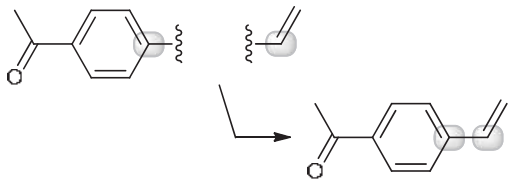
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



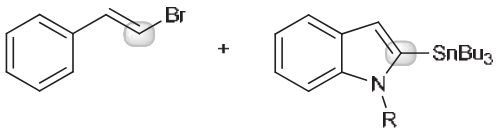
(d) First identify the carbon atoms that will be joined. The carbon atom connected directly to the iodide group (in the aryl iodide) will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:



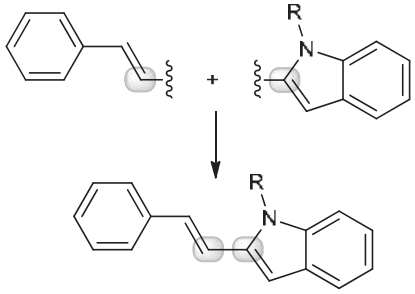
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



(e) First identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide group (in the vinyl bromide) will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:

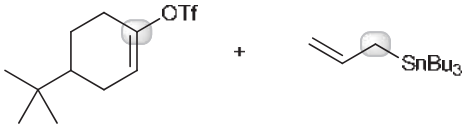


Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

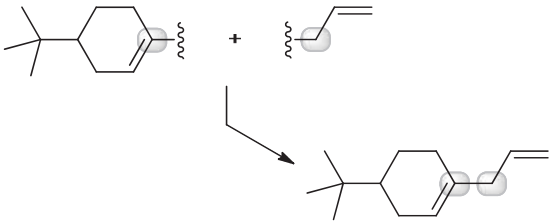


In this case, the organic electrophile has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that that this C=C unit maintains its *E* configuration.

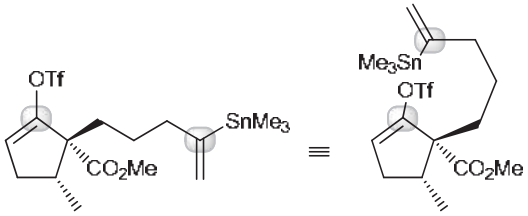
(f) First identify the carbon atoms that will be joined. The carbon atom connected directly to the triflate group (in the vinyl triflate) will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:



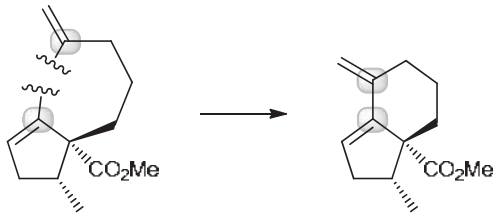
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



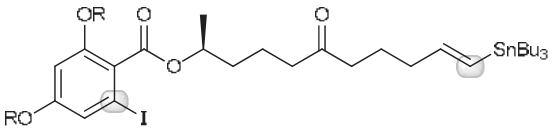
23.13. First identify the carbon atoms that will be joined. The carbon atom connected directly to the triflate group will be joined with the carbon atom connected directly to the trimethylstannane group, highlighted below. The compound is then redrawn so that the coupling partners are aligned:



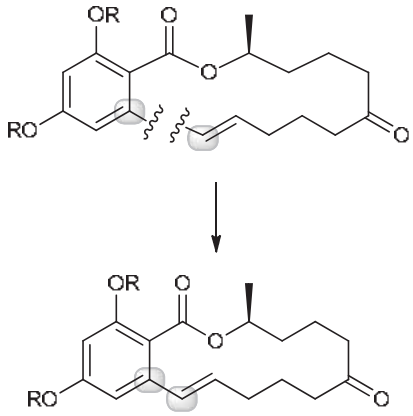
A new σ bond is then formed between the highlighted carbon atoms, giving the following diene:



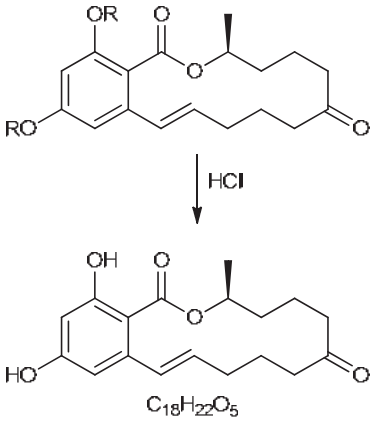
23.14. The problem statement indicates an intramolecular process, which means that both coupling partners are tethered within the same molecule. The carbon atom connected directly to the iodide group will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:



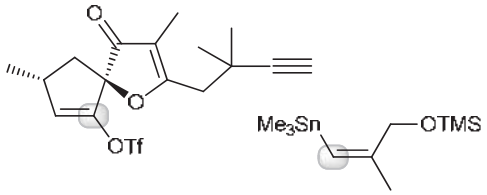
Next we align the coupling partners and draw the product of the intramolecular Stille coupling process:



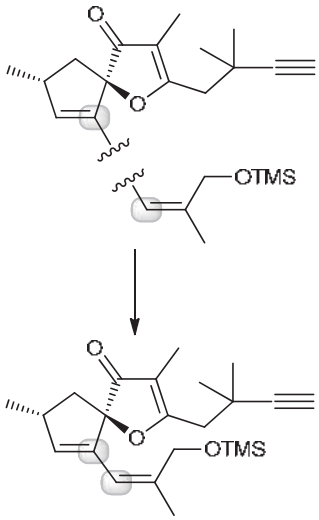
Then, in the final step of the synthesis, the coupling product is treated with HCl, converting both OR groups into OH groups, giving (*S*)-zearalenone, as shown:



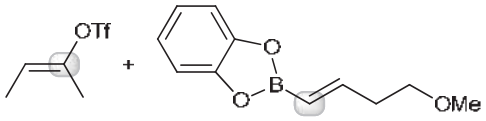
23.15. First identify the carbon atoms that will be joined. The carbon atom connected directly to the triflate group will be joined with the carbon atom connected directly to the trimethylstannane group, highlighted below:



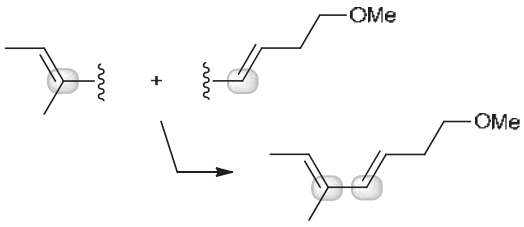
Then, redraw the coupling partners so that they are aligned to form a bond (neither of the coupling partners needs to be rotated in this case), and draw the product:



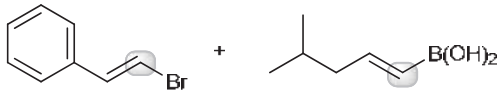
23.16.
(a) First identify the carbon atoms that will be joined. The carbon atom connected directly to the triflate group will be joined with the carbon atom connected directly to boron in the organoboron compound, highlighted here:



Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

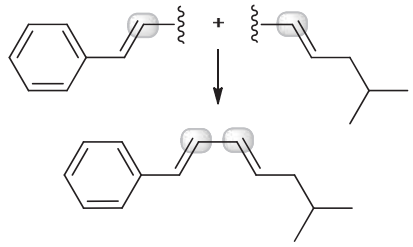


In this case, the organic electrophile has a C=C unit with the *E* configuration, and the organoboron compound has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that that each of these C=C units maintains its configuration.
(b) First identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide will be joined with the carbon atom connected directly to boron in the organoboron compound, highlighted here:



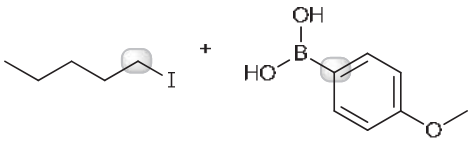
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

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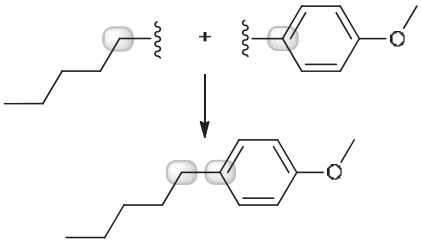


In this case, the organic electrophile has a C=C unit with the *E* configuration, and the organoboron compound has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that that each of these C=C units maintains its configuration.

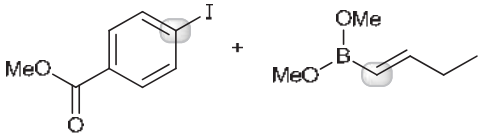
(c) First identify the carbon atoms that will be joined. The carbon atom connected directly to the iodide will be joined with the carbon atom connected directly to boron in the organoboron compound, highlighted here:



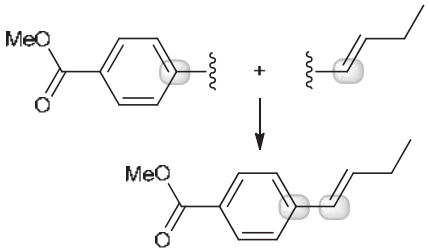
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



(d) First identify the carbon atoms that will be joined. The carbon atom connected directly to the iodide will be joined with the carbon atom connected directly to boron in the organoboron compound, highlighted here:



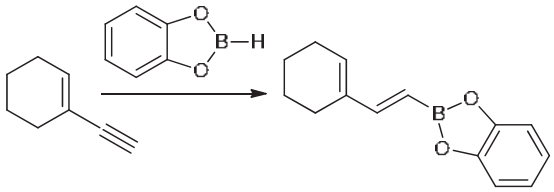
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



In this case, the organoboron compound has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that this C=C unit maintains its configuration.

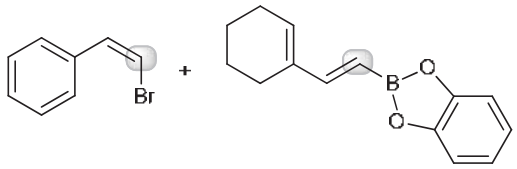
23.17.

(a) Upon treatment with catechol borane, the alkyne is converted into a vinyl boronic ester with the *E* configuration:

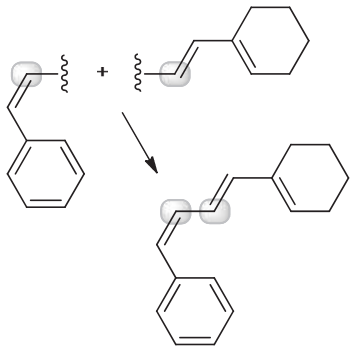


In the presence of base and catalytic $Pd(PPh_3)_4$, this vinyl boronic ester can then couple with the vinyl bromide via a Suzuki coupling reaction.

To draw the product of the Suzuki coupling reaction, first identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide will be joined with the carbon atom connected directly to boron in the organoboron compound, highlighted here:



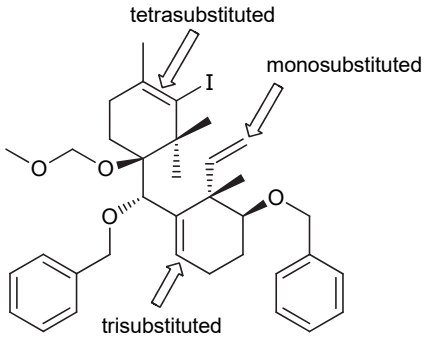
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



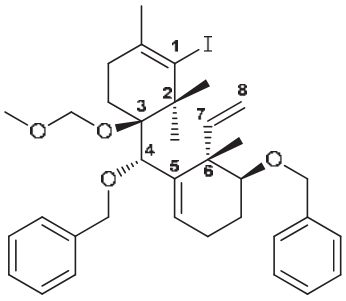
In this case, the organic electrophile has a C=C unit with the *Z* configuration, and the organoboron compound has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that that each of these C=C units maintains its configuration.

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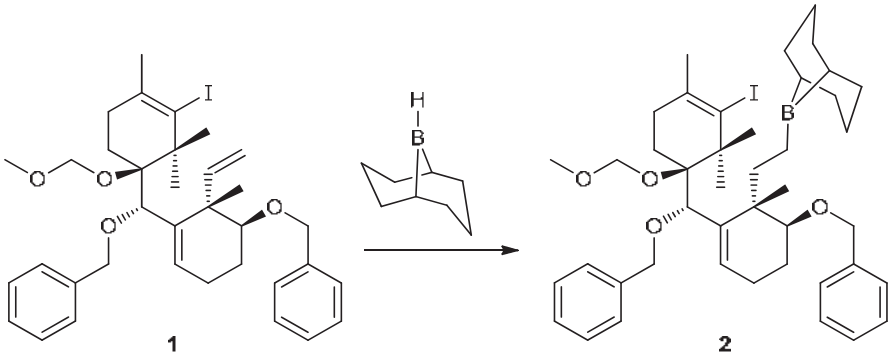
23.18. In the first step of the reaction sequence, 9-BBN adds across a π bond (hydroboration). Of the three π bonds indicated below, the one that is monosubstituted is the least sterically hindered and thus most susceptible to reaction with this bulky cyclic alkylborane.



An additional hint suggesting reaction at the monosubstituted π bond comes from the wording of the problem statement (that this sequence makes an 8-membered ring). The first reaction installs a borane group, so the second reaction is likely an intramolecular Suzuki coupling between the carbon atom bonded to the boron after step 1 (C8 below) and the carbon atom bonded to iodine (C1 below). Bond formation between these two carbon atoms would indeed make a new 8-membered ring, as indicated by the numbered atoms below.

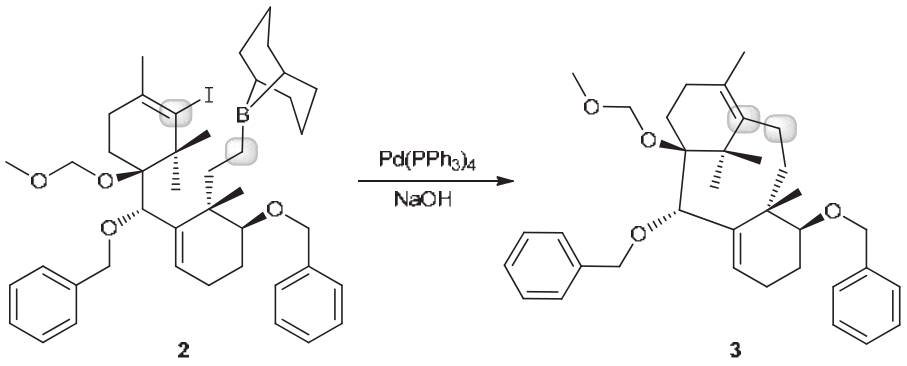


During step one of the process, 9-BBN adds across the monosubstituted π bond in an *anti*-Markovnikov addition, giving compound **2**.



Compound **2** then undergoes an intramolecular Suzuki coupling reaction upon treatment with a palladium catalyst under basic conditions, giving compound **3.** The highlighted carbon atoms are joined as result of this process:

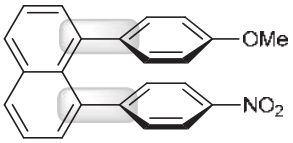
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2 3

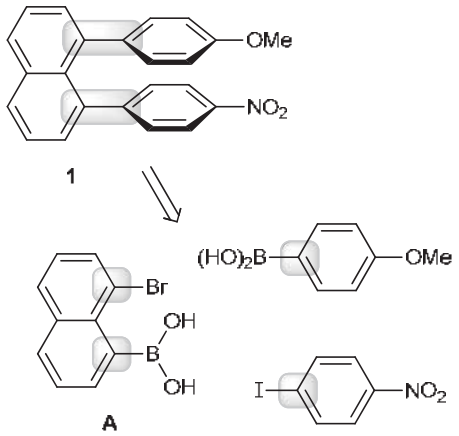
23.19.

(a) We begin by identifying the bonds in compound **1** that will be made, highlighted here:

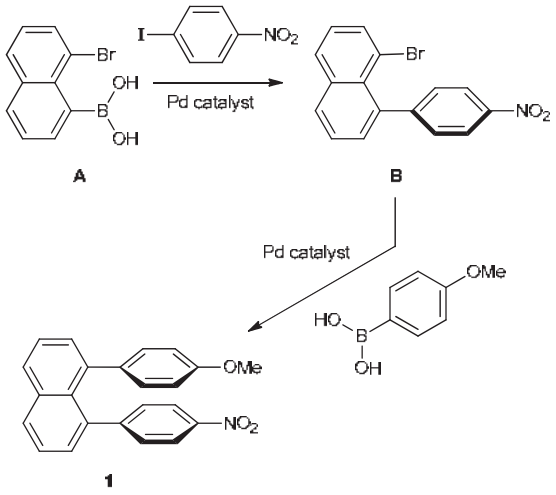


1

Compound **A** contains both an aryl bromide group and an aryl boronic acid group. So, disconnection of compound **1** at the top biaryl bond will reveal a *para*-methoxy boronic acid coupling partner, while disconnection at the bottom biaryl bond will reveal a *para*-nitro aryl iodide partner, shown below:



Now let's consider the forward reaction sequence. Compound **1** is prepared from compound **A** via two successive Suzuki cross coupling reactions:

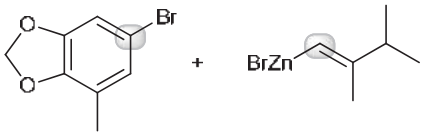


Compound **B** (shown above) is formed via the Suzuki cross coupling between compound **A** and the *para*-nitro aryl iodide.

(b) Compound **A** contains both an aryl bromide group and an aryl boronic acid group, yet it does not react with itself under these conditions. Rather, it prefers to cross couple with the *para*-nitro aryl iodide. This is likely due to the fact that aryl iodides participate much faster in Suzuki cross coupling reactions than aryl bromides.

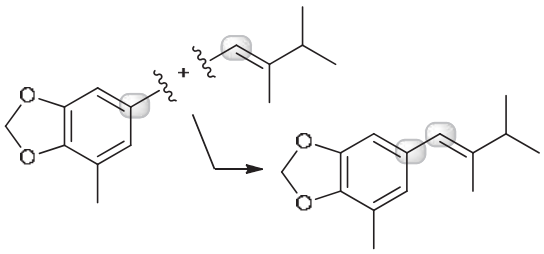
23.20.

(a) First identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide will be joined with the carbon atom connected directly to Zn in the organozinc, highlighted here:



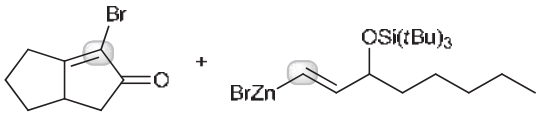
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Then, realign the coupling partners so that they are aligned to form a bond, and draw the product:

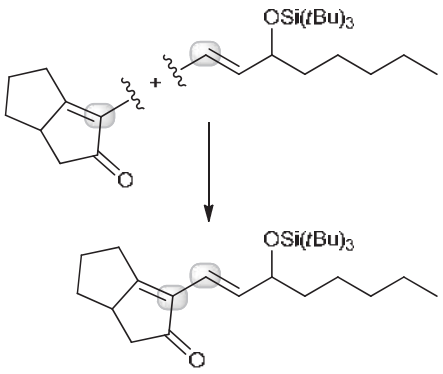


In this case, the organozinc has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that this C=C unit maintains its configuration.

(b) First identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide will be joined with the carbon atom connected directly to zinc in the organozinc, highlighted here:

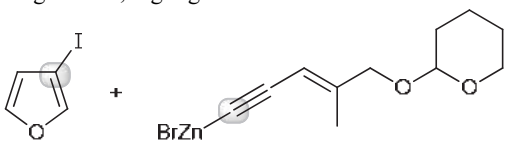


Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

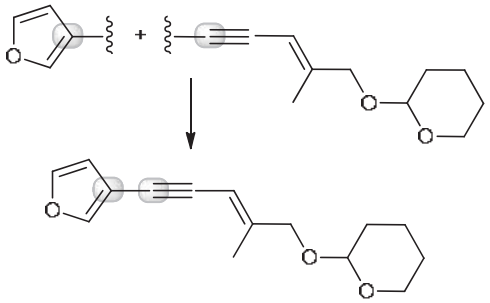


In this case, the organozinc has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that this C=C unit maintains its configuration.

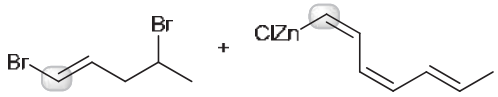
(c) First identify the carbon atoms that will be joined. The carbon atom connected directly to the iodide will be joined with the carbon atom connected directly to zinc in the organozinc, highlighted here:



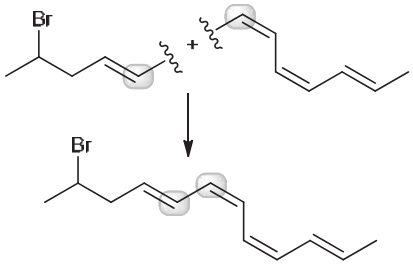
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



(d) First identify the carbon atoms that will be joined. The organic electrophile is a dibromide; and the more reactive vinyl bromide serves as the coupling partner. The sp^2 carbon atom connected directly to the bromide will be joined with the carbon atom connected directly to zinc in the organozinc, highlighted here:

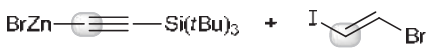


Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

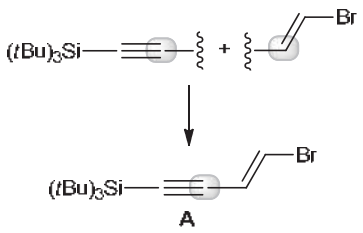


In this case, the organic electrophile has a C=C unit with the *E* configuration, and the organozinc has a C=C unit with the *Z* configuration. So, when drawing the product, we must be careful that each of these C=C units maintains its configuration. Note that each of the other two C=C units in the organozinc reagent also maintains its configuration giving the *E*,*Z*,*Z*,*E* product.

23.21. First identify the carbon atoms that will be joined in the first step. The organic electrophile is both a vinyl iodide and a vinyl bromide. The more reactive vinyl iodide serves as the coupling partner. The carbon atom connected directly to the iodide will be joined with the carbon atom connected directly to zinc in the organozinc, highlighted here:

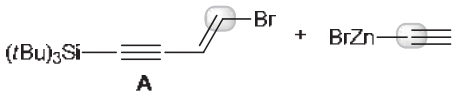


Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product (**A**):

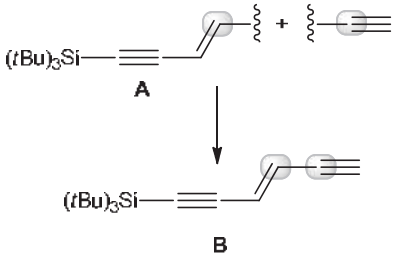


In this case, the organic electrophile has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that this C=C unit maintains its configuration.

Next identify the carbon atoms that will be joined in the second step. The carbon atom connected directly to the bromide in **A** will be joined with the carbon atom connected directly to zinc in the organozinc, highlighted here:

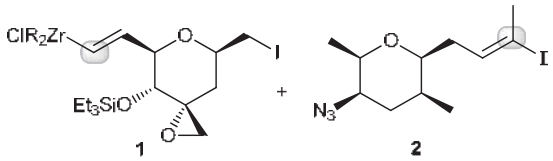


Then, redraw the coupling partners so that they are aligned to form a bond, and draw the product (**B**):

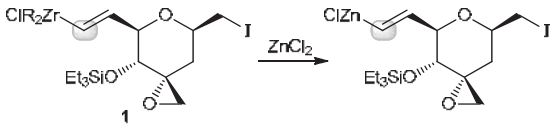


In this case, the organic electrophile has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that this C=C unit maintains its configuration.

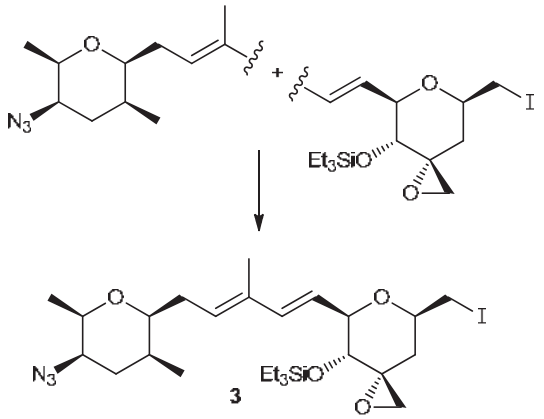
23.22. First identify the carbon atoms that will be joined. The carbon atom connected directly to the iodide (of the vinyl iodide) will be joined with the carbon atom connected directly to Zr in the organozirconium, highlighted here:



Note that $ZnCl_2$ is used in this reaction, so the active organometallic species is likely the organozinc compound resulting from a transmetallation from Zr to Zn:



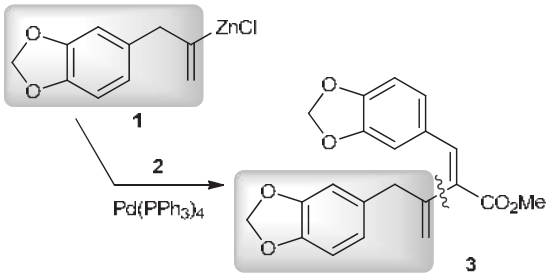
Next, realign the coupling partners so that they are aligned to form a bond, and draw the product:



In this case, the organic electrophile has a C=C unit with the *E* configuration, and the organozinc has a C=C unit with the *E* configuration. So, when drawing the product, we must be careful that each of these C=C units maintains its configuration.

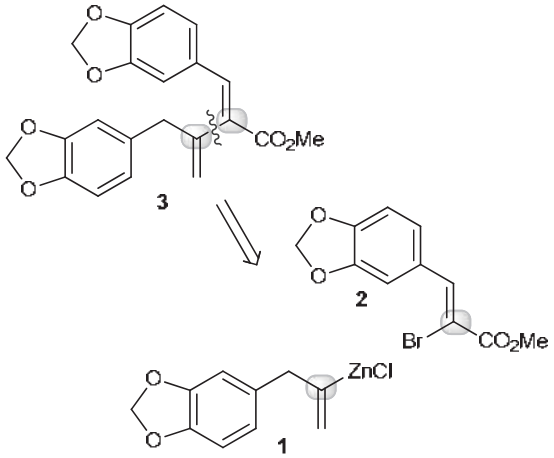
23.23.

(a) First identify the new C-C bond in compound **3** that was formed via Negishi coupling. Analysis of the structures of **1** and **3** leads to the identification of the newly formed bond in **3** as indicated here with a wavy line:



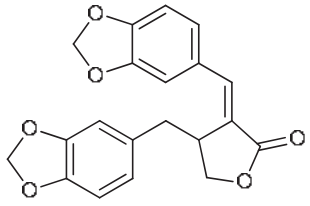
Next, identify the structure of organic electrophile **2** (a vinyl bromide) by disconnecting the C-C bond that is formed in the Negishi coupling:

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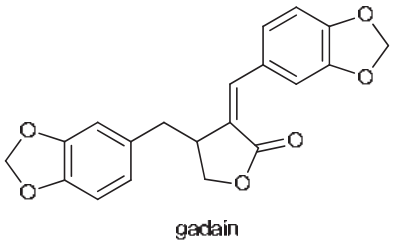


Note that at the C=C unit of **2** the arene and ester (CO_2Me) are *trans* to each other. This *trans* relationship is preserved in **3**.

(b) The question states that savinin and gadain are isomers of each other, differing only in the configuration of the C=C unit. Changing the configuration of the *E* alkene in savinin thus provides the structure of gadain, a *Z* alkene:

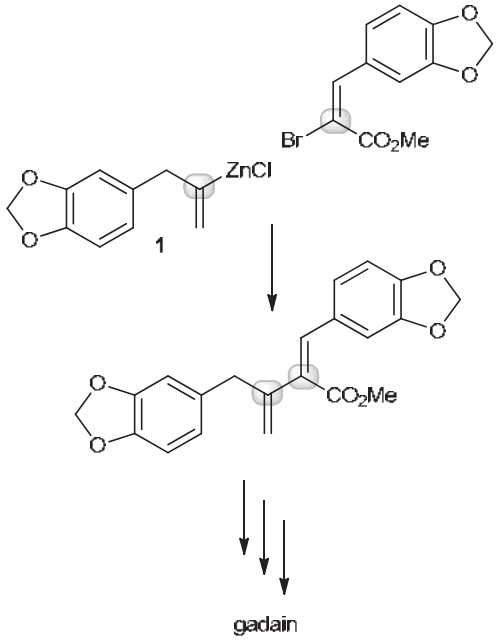


savinin



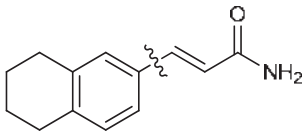
gadain

Changing the configuration of **2** gives the vinyl bromide that would be utilized to produce the intermediate that would be subsequently converted to gadain, as shown:

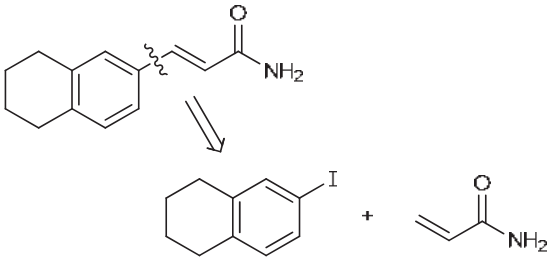


23.24.

(a) Analyze the structure of the product and determine which bond(s) can be made via a Heck reaction. Recall that a Heck reaction forms a bond between a vinyl position and either an aryl, vinyl or benzyl position. In the desired compound, there is only one bond that fits this criterion:



This bond, indicated with a wavy line, is between an aryl group and a vinyl group. To make this bond via a Heck reaction, we must start with an organohalide and an alkene. Since one of the coupling partners must be an alkene, the other partner (in this case) must be an aryl halide, as shown:

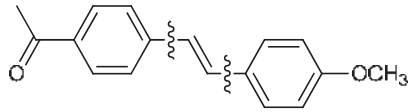


Notice that the alkene is monosubstituted, with an electron-withdrawing substituent, so we expect the reaction to be very effective.

(b) Analyze the structure of the product and determine which bond(s) can be made via a Heck reaction. Recall that a Heck reaction forms a bond between a vinyl position and either an aryl, vinyl or benzyl position. In

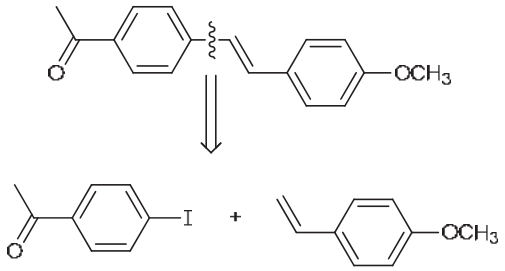
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the desired compound, there are two bonds that fit this criterion:

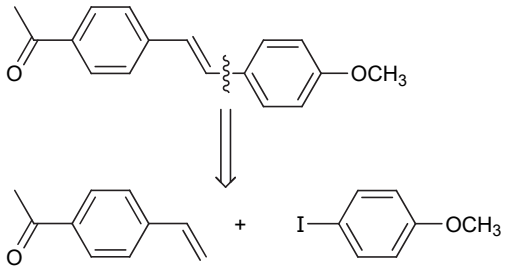


Each of these bonds, indicated with a wavy line, is between an aryl group and a vinyl group. To make either of these bonds via a Heck reaction, we must start with an organohalide and an alkene. This gives two possible synthetic routes, both of which are viable:

Possibility #1

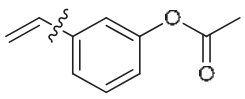


Possibility #2

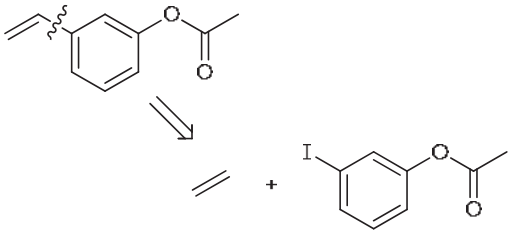


The second possibility has the added advantage that the starting monosubstituted alkene has an electron-withdrawing substituent (so we expect the reaction to be very effective).

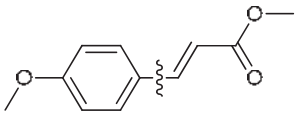
(c) Analyze the structure of the product and determine which bond(s) can be made via a Heck reaction. Recall that a Heck reaction forms a bond between a vinyl position and either an aryl, vinyl or benzyl position. In the desired compound, there is only one bond that fits this criterion:



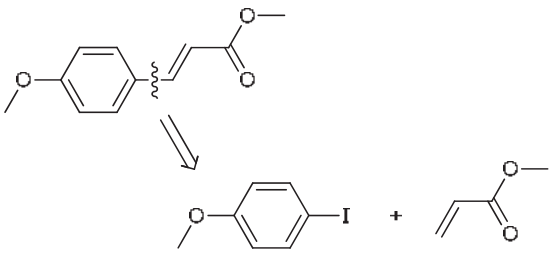
This bond, indicated with a wavy line, is between an aryl group and a vinyl group. To make this bond via a Heck reaction, we must start with an organohalide and an alkene. Since one of the coupling partners must be an alkene, the other partner (in this case) must be an aryl halide, as shown:



(d) Analyze the structure of the product and determine which bond(s) can be made via a Heck reaction. Recall that a Heck reaction forms a bond between a vinyl position and either an aryl, vinyl or benzyl position. In the desired compound, there is only one bond that fits this criterion:

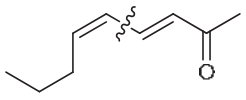


This bond, indicated with a wavy line, is between an aryl group and a vinyl group. To make this bond via a Heck reaction, we must start with an organohalide and an alkene. Since one of the coupling partners must be an alkene, the other partner (in this case) must be an aryl halide, as shown:



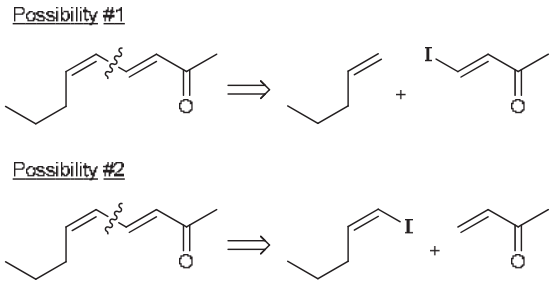
Notice that the alkene is monosubstituted, with an electron-withdrawing substituent, so we expect the reaction to be very effective.

(e) Analyze the structure of the product and determine which bond(s) can be made via a Heck reaction. Recall that a Heck reaction forms a bond between a vinyl position and either an aryl, vinyl or benzyl position. In the desired compound, there is only one bond that fits this criterion:

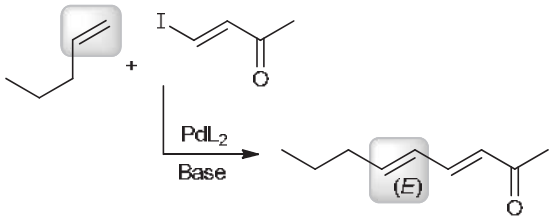


This bond, indicated with a wavy line, is between two vinyl groups. Since this bond must be made via a Heck reaction, we must consider the following two possibilities, each of which starts with an alkene and a vinyl iodide:

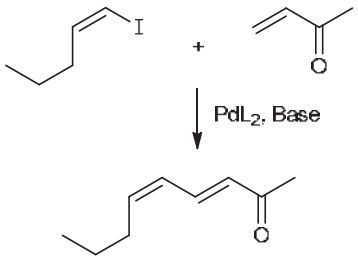
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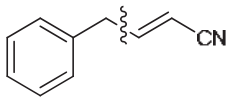
The first possibility is not viable because Heck reactions are stereoselective with respect to the starting alkene, and the *E* isomer (rather than the *Z* isomer) would be expected:



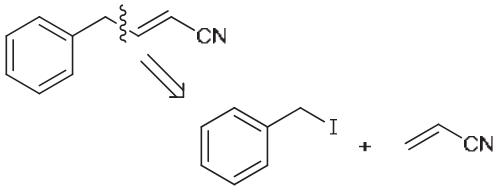
This is not the desired stereochemical outcome, so we turn our attention to the second possibility. This possibility works, and it has the added advantage that the starting alkene is monosubstituted, with an electron-withdrawing substituent (so we expect the reaction to be very effective).



(f) Analyze the structure of the product and determine which bond(s) can be made via a Heck reaction. Recall that a Heck reaction forms a bond between a vinyl position and either an aryl, vinyl or benzyl position. In the desired compound, there is only one bond that fits this criterion:

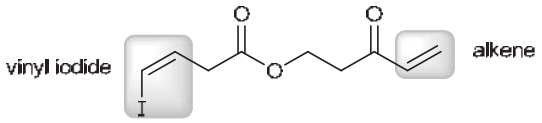


This bond, indicated with a wavy line, is between a benzyl group and a vinyl group. To make this bond via a Heck reaction, we must start with an organohalide and an alkene. Since one of the coupling partners must be an alkene, the other partner (in this case) must be a benzyl halide, as shown:

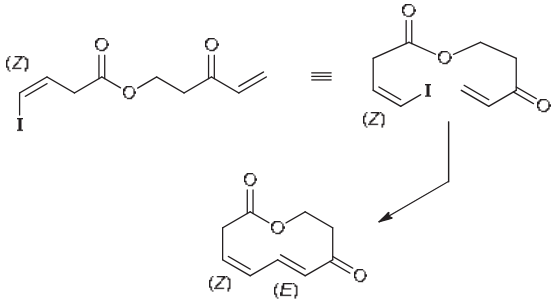


Notice that the alkene is monosubstituted, with an electron-withdrawing substituent, so we expect the reaction to be very effective.

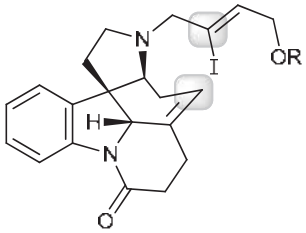
23.25. In a Heck reaction, an alkene is coupled with an organohalide. In this case, the two coupling partners are tethered together in the same compound:



Upon treatment with a base and a suitable palladium catalyst, an intramolecular Heck reaction can occur. Notice that the *Z* configuration of the vinyl iodide is preserved. The new C-C bond is formed regioselectively and stereoselectively, with the *E* configuration being formed:

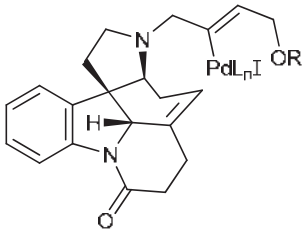


23.26. Begin by identifying the carbon atoms that will be joined. The carbon atom connected to the iodide will be joined directly to the proximal carbon of the alkene (a bond will be formed between the two highlighted positions):

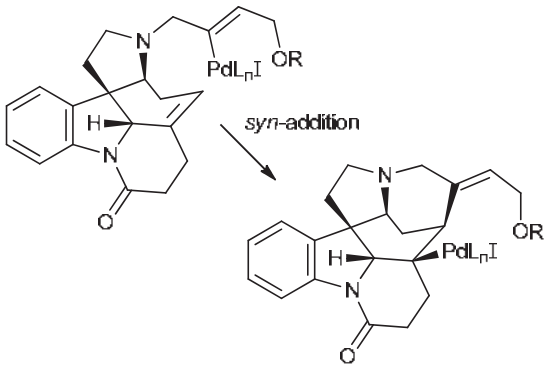


Next, consider the intermediate that forms when the palladium catalyst interacts with compound **1**.

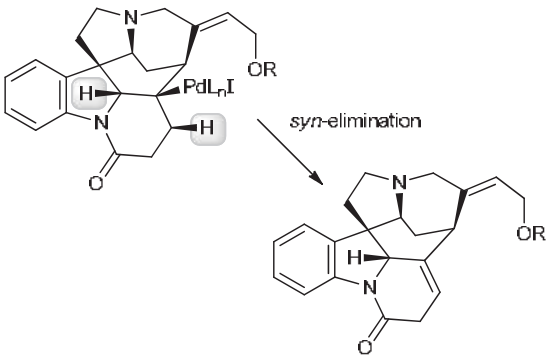
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In this case, due to the configuration about the C–N bond (the N is on a wedge, coming out of the plane of the page), we expect oxidative addition to occur above (rather than below) the plane of the boat-shaped cyclohexene ring. When *syn*-addition occurs across the alkene, the new C–C bond forms the 6-membered ring with stereochemistry as shown.

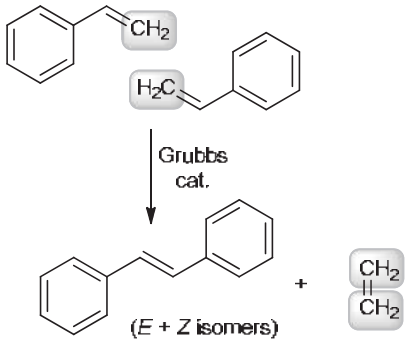


Finally, in order to regenerate the catalyst, reductive elimination must take place. The new C–Pd adduct cannot undergo a conformational change via C–C bond rotation. Therefore, the *syn*-reductive elimination will have to occur at one of two sites within the molecule with accessible *syn* hydrogen atoms *beta* to the Pd (highlighted). Due to ring strain, the alkene that forms is exocyclic to the existing boat-shaped cyclohexane ring.

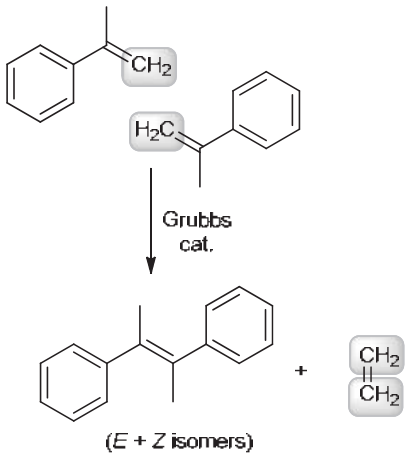


23.27.

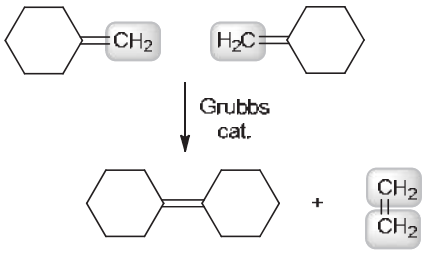
(a) The starting material is a monosubstituted alkene, which is an excellent starting material for alkene metathesis. To draw the metathesis product, we begin by drawing two molecules of the starting alkene, and we remove a methylene group from the C=C unit of each molecule (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown. Don't forget that a mixture of *E* and *Z* isomers is expected.



(b) The starting material is a 2,2-disubstituted alkene, which is an excellent starting material for alkene metathesis. To draw the metathesis product, we begin by drawing two molecules of the starting alkene, and we remove a methylene group from the C=C unit of each molecule (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown. Don't forget that a mixture of *E* and *Z* isomers is expected.

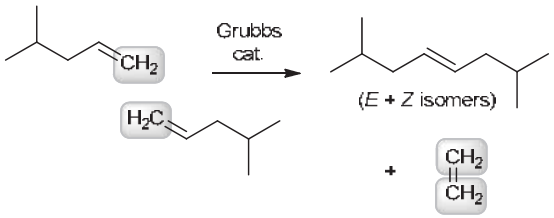


(c) The starting material is a 2,2-disubstituted alkene, which is an excellent starting material for alkene metathesis. To draw the metathesis product, we begin by drawing two molecules of the starting alkene, and we remove a methylene group from the C=C unit of each molecule (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown.

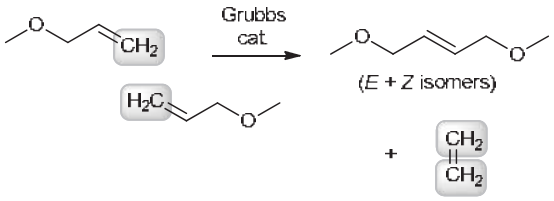


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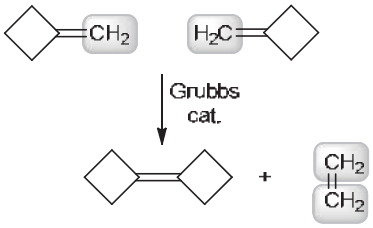
(d) The starting material is a monosubstituted alkene, which is an excellent starting material for alkene metathesis. To draw the metathesis product, we begin by drawing two molecules of the starting alkene, and we remove a methylene group from the C=C unit of each molecule (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown. Don't forget that a mixture of *E* and *Z* isomers is expected.



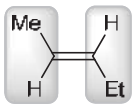
(e) The starting material is a monosubstituted alkene, which is an excellent starting material for alkene metathesis. To draw the metathesis product, we begin by drawing two molecules of the starting alkene, and we remove a methylene group from the C=C unit of each molecule (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown. Don't forget that a mixture of *E* and *Z* isomers is expected.



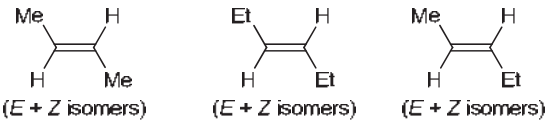
(f) The starting material is a 2,2-disubstituted alkene, which is an excellent starting material for alkene metathesis. To draw the metathesis product, we begin by drawing two molecules of the starting alkene, and we remove a methylene group from the C=C unit of each molecule (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown.



23.28. The starting alkene is *trans*-2-pentene, which is comprised of two different alkylidene fragments, highlighted here:

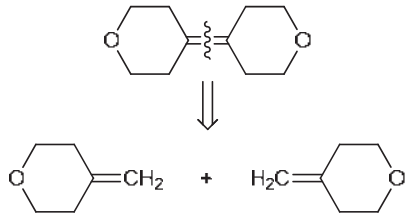


During metathesis, these alkylidene fragments are separated from each other, and then recombined in all possible permutations. In this case, there are three possible products, each of which is expected as a mixture of *E* and *Z* isomers.

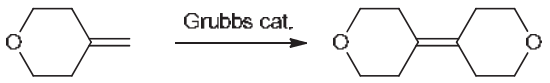


(Notice that the third product is also the starting alkene)

23.29. To draw the starting materials necessary to make the desired compound via alkene metathesis, we must separate the alkylidene fragments found in the product, and then attach a methylene group to each fragment:

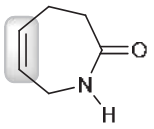


These two alkenes are identical. Therefore, the desired product can be made by treating this starting alkene with a Grubbs catalyst:

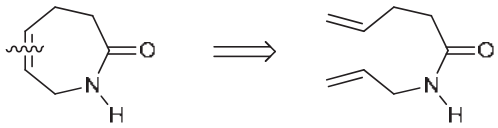


23.30.

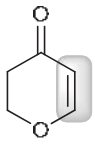
(a) First, identify any C=C unit that is incorporated into a ring. In this case, the highlighted π bond is incorporated into a seven-membered ring:



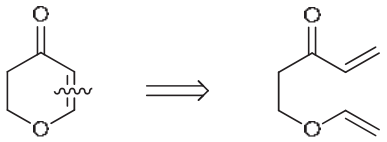
In order to draw the starting diene, we erase the highlighted C=C bond of the ring, and then connect a methylene (CH_2) group to each of the two vinyl positions, like this:



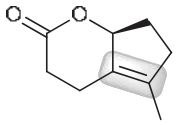
(b) First, identify any C=C unit that is incorporated into a ring. In this case, the highlighted π bond is incorporated into a six-membered ring:



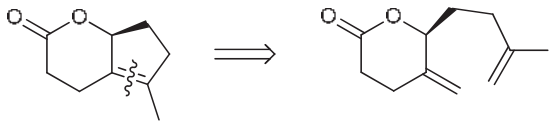
In order to draw the starting diene, we erase the highlighted C=C bond of the ring, and then connect a methylene (CH_2) group to each of the two vinyl positions, like this:



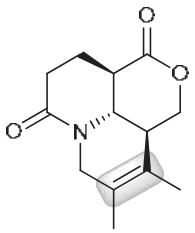
(c) First, identify any C=C unit that is incorporated into a ring. In this case, the highlighted π bond is incorporated into a five-membered ring:



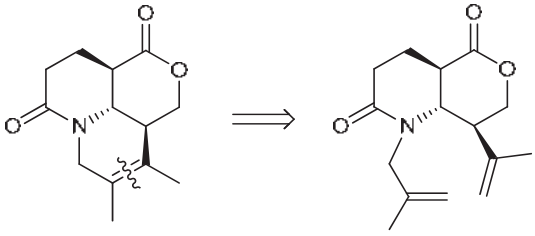
In order to draw the starting diene, we erase the highlighted C=C bond of the ring, and then connect a methylene (CH_2) group to each of the two vinyl positions, like this:



(d) First, identify any C=C unit that is incorporated into a ring. In this case, the highlighted π bond is incorporated into a six-membered ring:

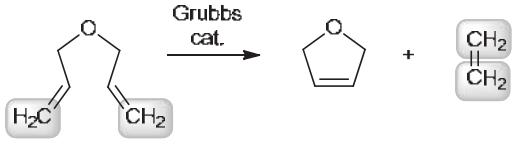


In order to draw the starting diene, we erase the highlighted C=C bond of the ring, and then connect a methylene (CH_2) group to each of the two vinyl positions, like this:

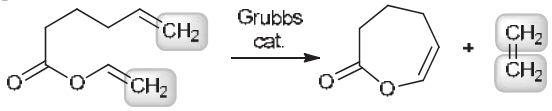


23.31.

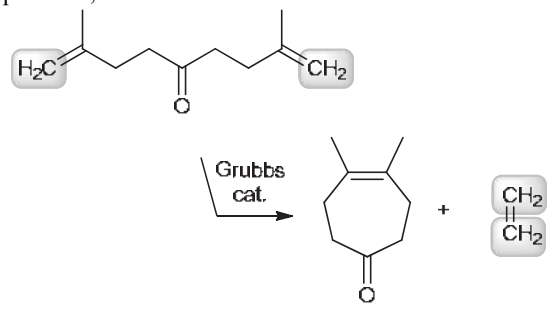
(a) The starting material is a diene, which can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown:



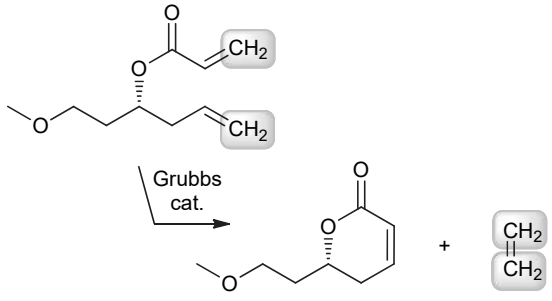
(b) The starting material is a diene, which can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown:



(c) The starting material is a diene, which can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown:

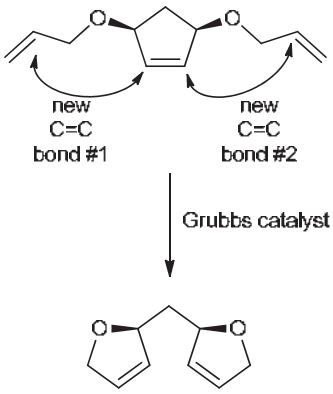


(d) The starting material is a diene, which can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, as shown:

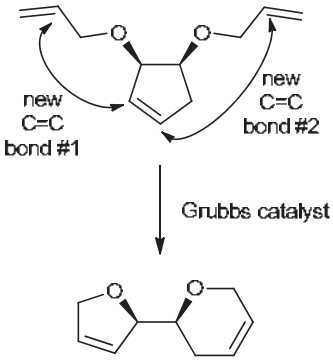


23.32.

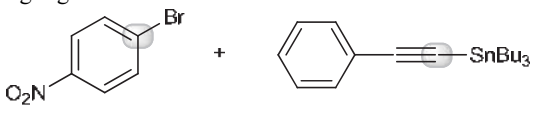
(a) As described in the problem statement, olefin metathesis of this triene results in cleavage of the cyclic C=C unit and formation of two new C=C units, giving a product with two new five-membered rings:



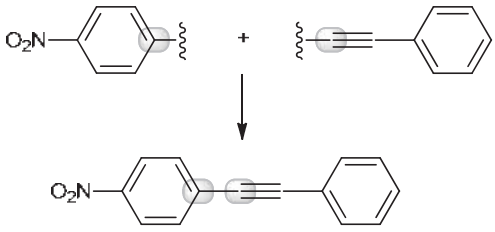
(b) As described in the problem statement, olefin metathesis of this triene results in cleavage of the cyclic C=C unit and formation of two new C=C units, giving a product with a five-membered ring and a six-membered ring:



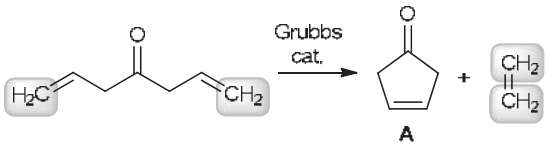
23.33. First identify the carbon atoms that will be joined. The carbon atom connected directly to the bromide (in the aryl bromide) will be joined with the carbon atom connected directly to tin (Sn) in the organostannane, highlighted here:



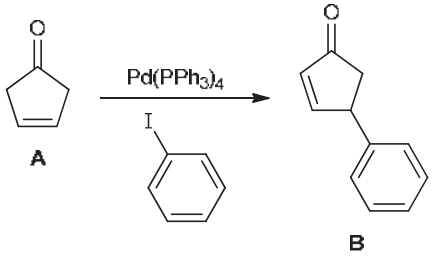
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



23.34. The starting material is a diene, which can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, giving compound **A**:

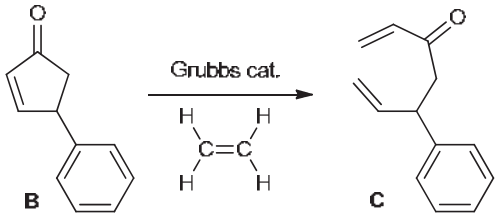


Compound **A** is an alkene, and it will undergo a Heck reaction upon treatment with an aryl halide in the presence of a suitable catalyst, to give compound **B**:

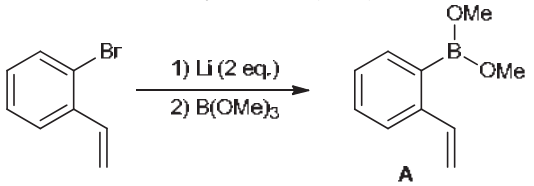


Notice the position of the π bond in compound **B**. This is the only regiochemical outcome that can accommodate *syn* elimination.

The C=C unit in compound **B** can undergo a ring-opening metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product (compound **C**), we break the C=C unit and introduce a methylene group at each vinylic position:



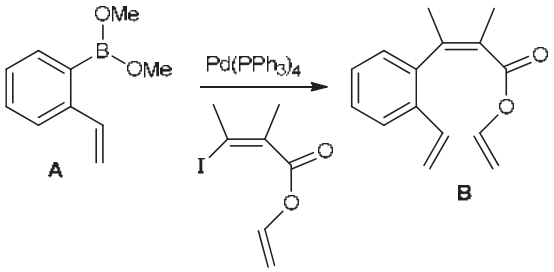
23.35. Upon treatment with two equivalents of lithium, the bromide group (in the starting material) is replaced with a lithium atom, giving an organolithium compound. This organolithium compound is then converted into the corresponding arylboronic ester (compound **A**) upon treatment with trimethylborate, $B(OMe)_3$:



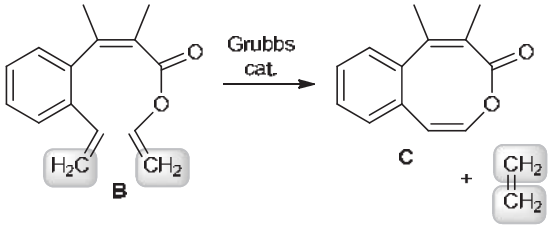
Compound **A** is an arylboronic ester, and it will undergo a Suzuki coupling reaction upon treatment with an organohalide in the presence of $Pd(PPh_3)_4$. In order to draw the coupling product (compound **B**) more easily, the organohalide has been rotated in the following drawing. Notice that the organohalide has a C=C unit

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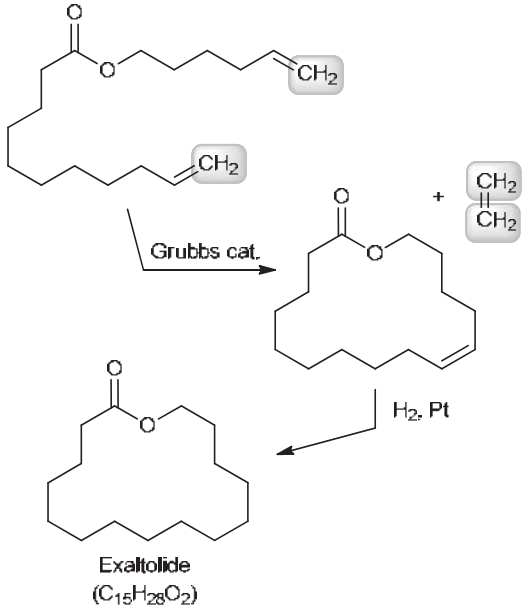
with the *Z* configuration. So, when drawing **B**, we must be careful that this C=C unit maintains its configuration.



Compound **B** has two monosubstituted C=C units that can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, giving compound **C**:

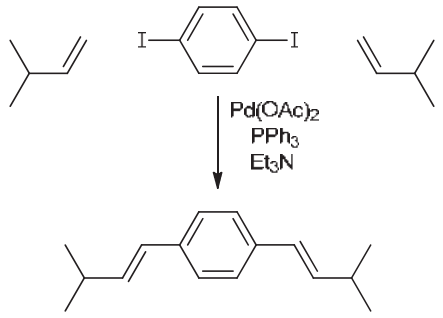


23.36. Exaltolide is a diene, which can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions. This metathesis product has a C=C unit that undergoes hydrogenation to give exaltolide, as shown below:

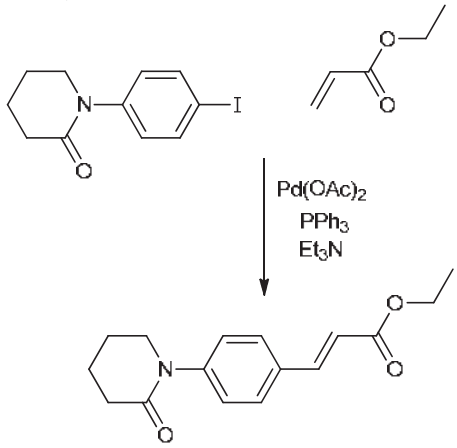


23.37.

(a) The starting materials are an aryl diiodide and two equivalents of an alkene. These compounds will serve as coupling partners in two successive Heck reactions, as shown below. The coupling partners have been rotated in order to draw the coupling product more easily. Notice that the aromatic ring is coupled to each of the C=C units regioselectively (at the less substituted position) and stereoselectively (to give an *E* alkene), as shown.

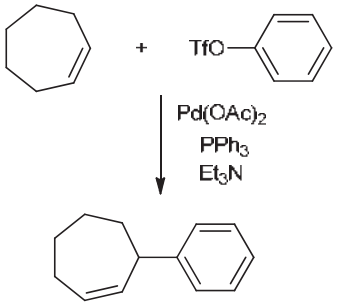


(b) The starting materials are an aryl iodide and an alkene. These compounds will serve as coupling partners in a Heck reaction, as shown below. The coupling partners have been rotated in order to draw the coupling product more easily. Notice that the aromatic ring is coupled to the C=C unit regioselectively (at the less substituted position) and stereoselectively (to give an *E* alkene), as shown.

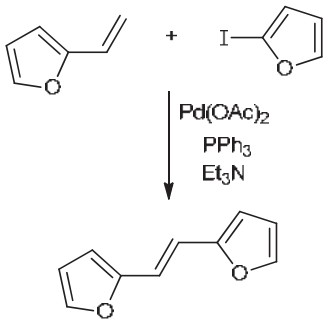


(c) The starting materials are an aryl triflate and an alkene. These compounds will serve as coupling partners in a Heck reaction, as shown. The coupling partners have been rotated in order to draw the coupling product more easily. Notice the position of the π bond in the product (this is the only regiochemical outcome that can accommodate *syn* elimination).

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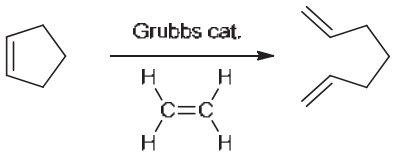


(d) The starting materials are an aryl iodide and an aryl alkene. These compounds will serve as coupling partners in a Heck reaction, as shown below. The coupling partners have been rotated in order to draw the coupling product more easily. Notice that the aryl iodide is coupled to the C=C unit regioselectively (at the less substituted position) and stereoselectively (to give an *E* alkene), as shown.

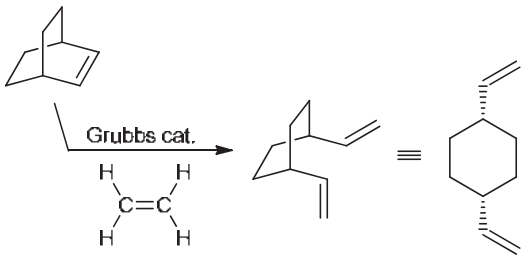


23.38.

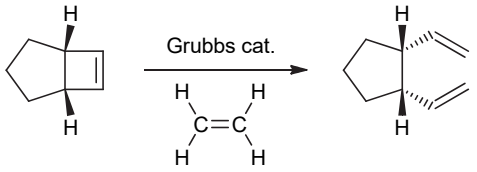
(a) The C=C unit undergoes a ring-opening metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we break the C=C unit and introduce a methylene group at each vinylic position, like this:



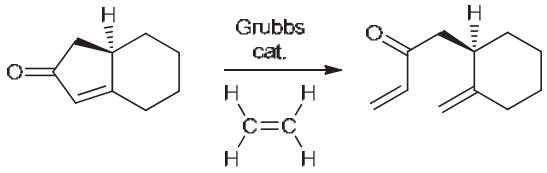
(b) The C=C unit undergoes a ring-opening metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we break the C=C unit and introduce a methylene group at each vinylic position, like this:



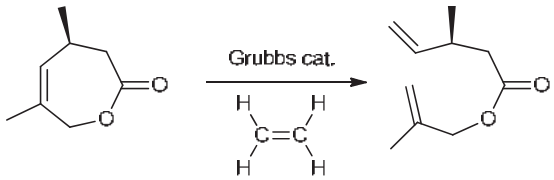
(c) The C=C unit undergoes a ring-opening metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we break the C=C unit and introduce a methylene group at each vinylic position, like this:



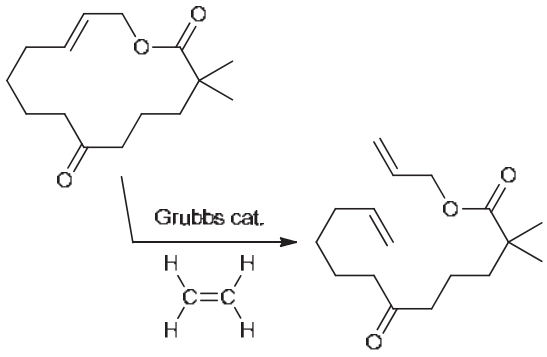
(d) The C=C unit undergoes a ring-opening metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we break the C=C unit and introduce a methylene group at each vinylic position, like this:



(e) The C=C unit undergoes a ring-opening metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we break the C=C unit and introduce a methylene group at each vinylic position, like this:



(f) The C=C unit undergoes a ring-opening metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we break the C=C unit and introduce a methylene group at each vinylic position, like this:

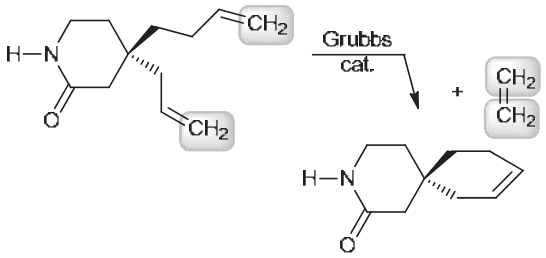


23.39.

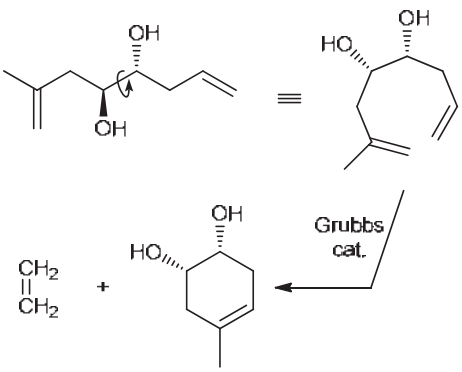
(a) The starting material has two C=C units that can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene

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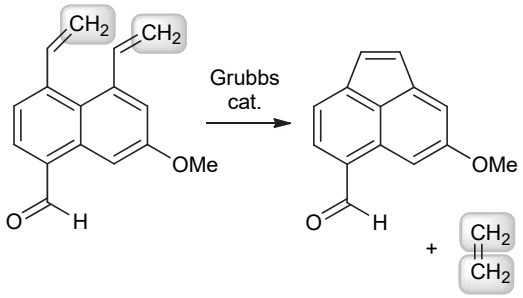
gas). We then draw a double bond between the remaining vinyl positions, giving the following product:



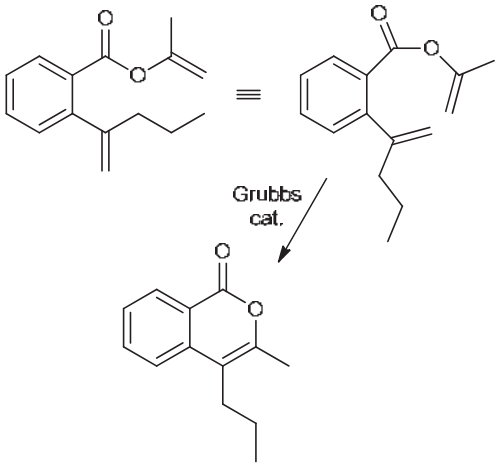
(b) The starting material has two C=C units that can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we first redraw the starting material so that the C=C units are in close proximity. Then, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, giving the following product:



(c) The starting material has two C=C units that can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, giving the following product:

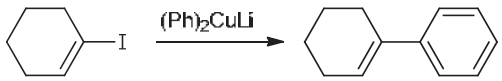


(d) The starting material has two C=C units that can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, giving the following product:

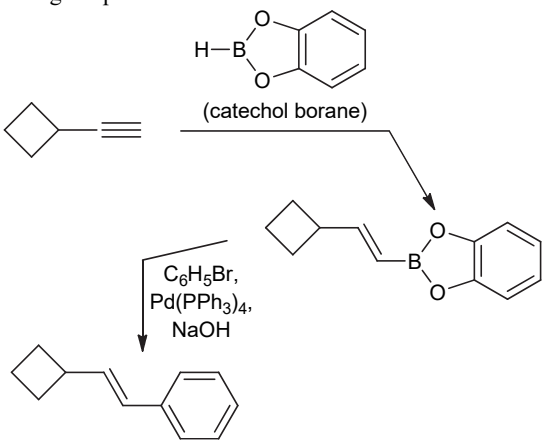


23.40.

(a) Lithium diphenyl cuprate is a Gilman reagent, and it will react with the following vinyl iodide to give a coupling product, as shown here:



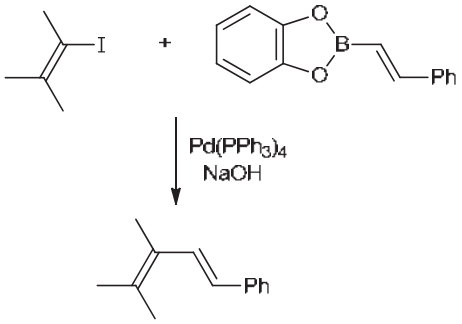
(b) Upon treatment with catechol borane, the alkyne is converted into a vinyl boronic ester with the *E* configuration. This compound then serves as a coupling partner in a Suzuki coupling reaction with bromobenzene. The carbon atom connected directly to the bromine atom will be joined with the carbon atom connected directly to boron in the organoboron compound. Notice that the *E* configuration is preserved during the process:



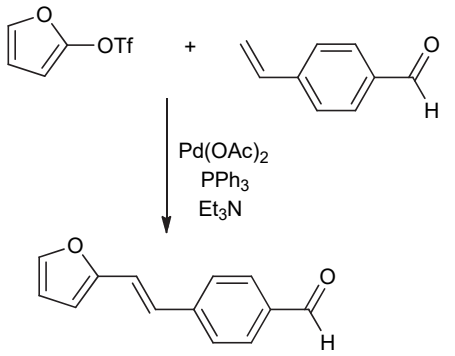
(c) The starting materials are a vinyl iodide and a vinyl boronic ester, indicating a Suzuki coupling reaction. The carbon atom connected directly to the iodide group will be joined with the carbon atom connected directly to boron in the organoboron compound, giving the product shown. The coupling partners have been rotated in order to draw the coupling product more easily. Notice that

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the configuration of the *trans* C=C unit is preserved in the process:

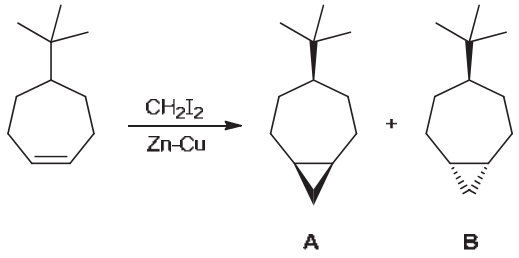


(d) The starting materials are an aryl triflate and an alkene, indicating a Heck reaction. The coupling partners have been rotated in order to draw the coupling product more easily. Notice that the aryl triflate is coupled to the C=C unit regioselectively (at the less substituted position) and stereoselectively (to give an *E* alkene), as shown:



23.41.

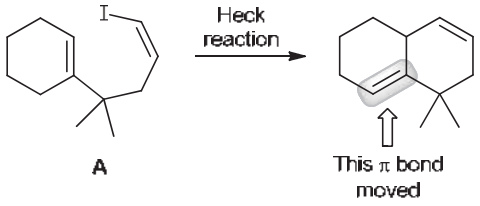
(a) In a Simmons-Smith reaction, the C=C unit is converted into a three-membered ring. This newly formed ring can be *cis* or *trans* to the *t*-butyl group, as shown:



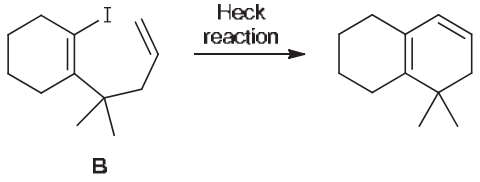
(b) Compounds **A** and **B** have the same constitution (connectivity of atoms), but they differ from each other in their configuration, so they are stereoisomers. More specifically, compounds **A** and **B** are stereoisomers that are not mirror images, so they are diastereomers.

(c) If we take steric considerations into account, we would expect that cyclopropanation will occur more readily on the face that is less sterically hindered (the face that is *trans* to the *t*-butyl group). Therefore, compound **B** is expected to predominate.

23.42. When compound **A** undergoes an intramolecular Heck reaction, the position of a π bond changes, because this is the only regiochemical outcome that can accommodate *syn* elimination:

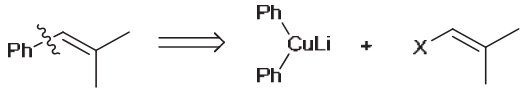


In contrast, when compound **B** undergoes an intramolecular Heck reaction, the π bonds remain in the same location:

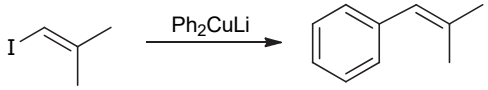


23.43.

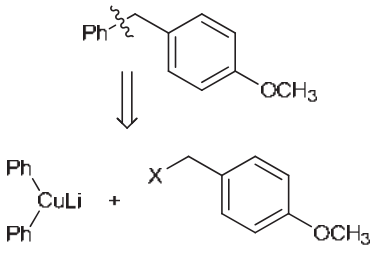
(a) The problem statement indicates that lithium diphenylcuprate must be used. This dictates which bond must be made, as well as the identity of the coupling partner (the organohalide), as shown in the following retrosynthetic scheme:



The forward synthesis is shown below, using a vinyl iodide as the organohalide. Alternatively, a vinyl triflate or vinyl bromide can be used.

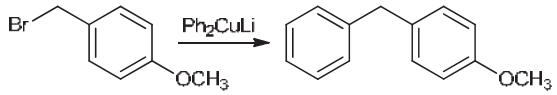


(b) The problem statement indicates that lithium diphenylcuprate must be used. This dictates which bond must be made, as well as the identity of the coupling partner (the organohalide), as shown in the following retrosynthetic scheme:

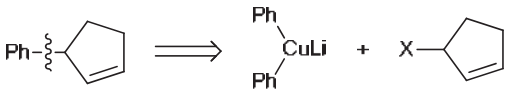


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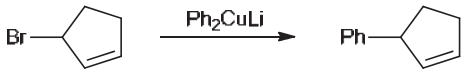
The forward synthesis is shown below, using a benzyl bromide as the organohalide. Alternatively, a benzyl iodide or benzyl triflate can be used.



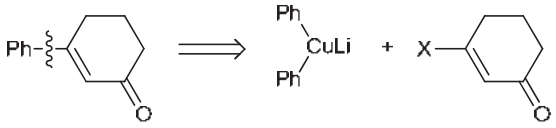
(c) The problem statement indicates that lithium diphenylcuprate must be used. This dictates which bond must be made, as well as the identity of the coupling partner (the organohalide), as shown in the following retrosynthetic scheme:



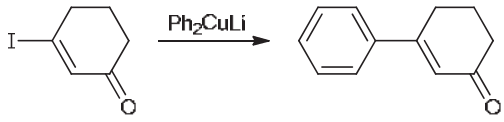
The forward synthesis is shown below, using an allyl bromide as the organohalide. Alternatively, an allyl iodide or allyl triflate can be used.



(d) The problem statement indicates that lithium diphenylcuprate must be used. This dictates which bond must be made, as well as the identity of the coupling partner (the organohalide), as shown in the following retrosynthetic scheme:

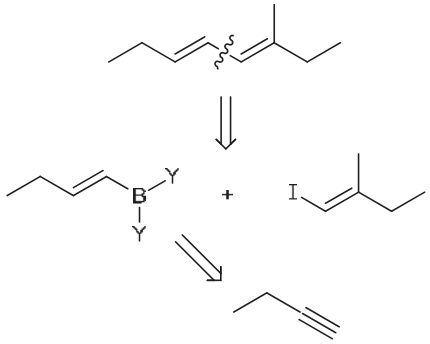


The forward synthesis is shown below, using a vinyl iodide as the organohalide. Alternatively, a vinyl triflate or vinyl bromide can be used.

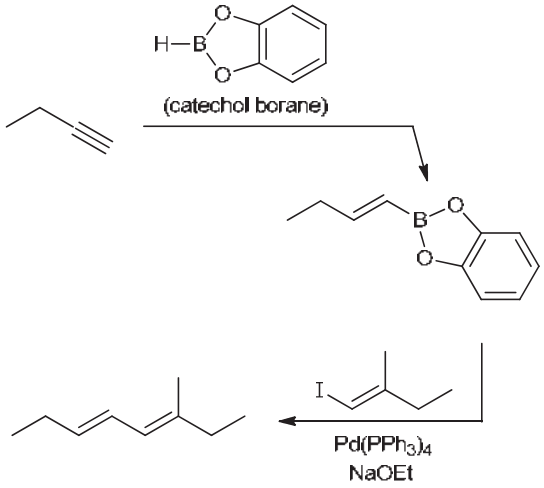


23.44.

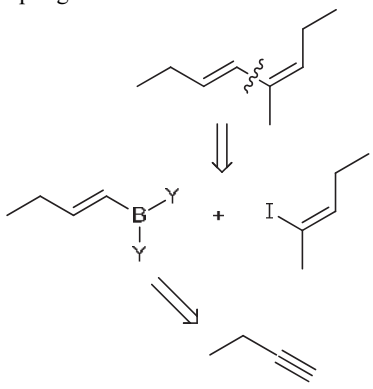
(a) The following retrosynthetic analysis shows how the desired compound can be made from 1-butyne via a Suzuki coupling reaction:



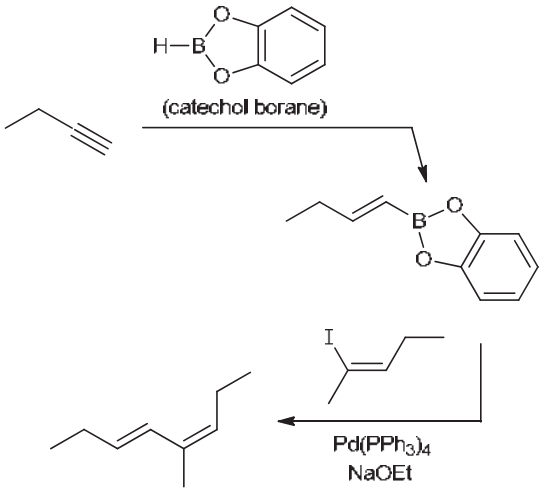
The forward scheme is shown here:



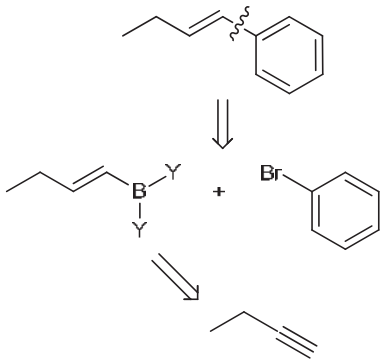
(b) The following retrosynthetic analysis shows how the desired compound can be made from 1-butyne via a Suzuki coupling reaction:



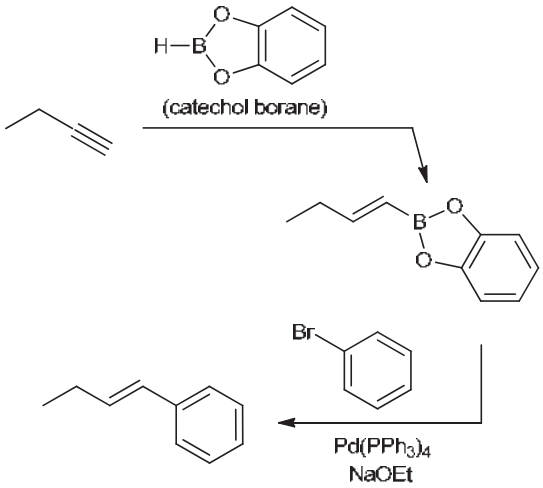
The forward scheme is shown here:



(c) The following retrosynthetic analysis shows how the desired compound can be made from 1-butyne via a Suzuki coupling reaction:

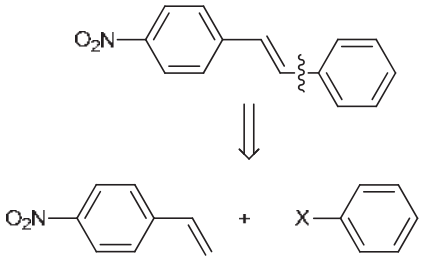


The forward scheme is shown here:

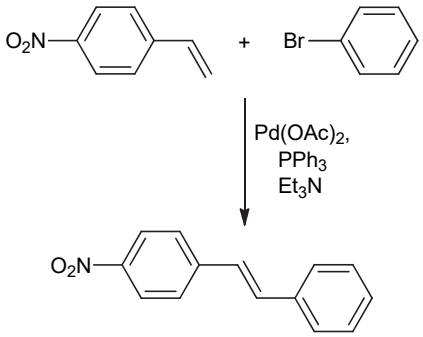


23.45.

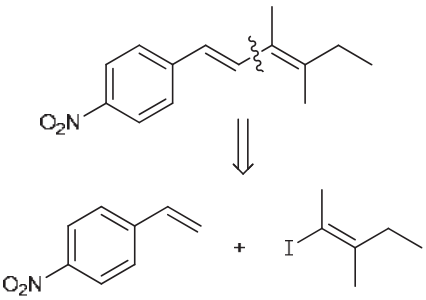
(a) As seen in the following retrosynthetic analysis, the desired product can be made from 4-nitrostyrene via a Heck reaction:



The forward synthesis is shown here, using bromobenzene as the organohalide. Alternatively, a triflate or iodide can be used. Notice that coupling occurs in a stereoselective fashion, giving the *E* isomer.

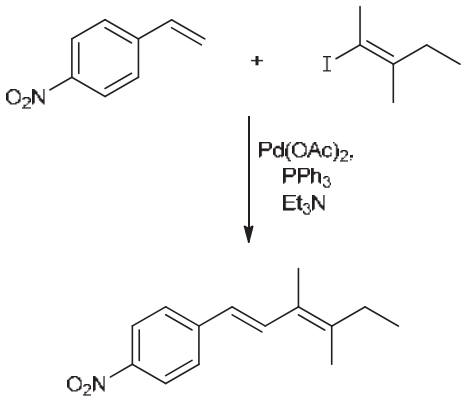


(b) As seen in the following retrosynthetic analysis, the desired product can be made from 4-nitrostyrene via a Heck reaction:

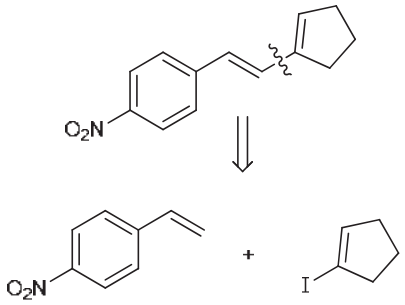


The forward synthesis is shown below, using a vinyl iodide as the organohalide. Alternatively, a triflate or bromide can be used. Notice that the configuration of the C=C unit of the vinyl iodide is preserved in the process. The other C=C unit adopts the *E* configuration, as expected.

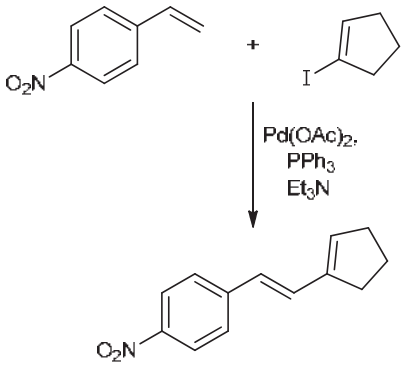
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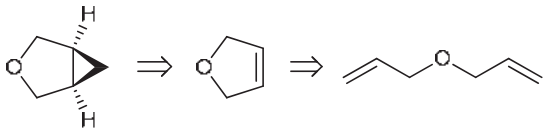
(c) As seen in the following retrosynthetic analysis, the desired product can be made from 4-nitrostyrene via a Heck reaction:



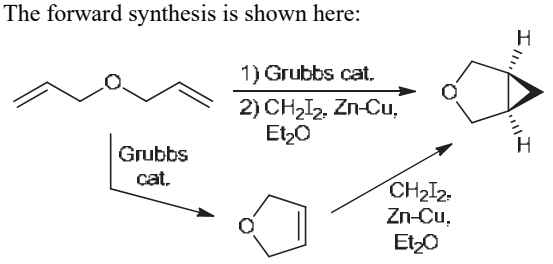
The forward synthesis is shown below, using a vinyl iodide as the organohalide. Alternatively, a triflate or bromide can be used. Notice that coupling occurs in a stereoselective fashion, giving the *E* isomer.



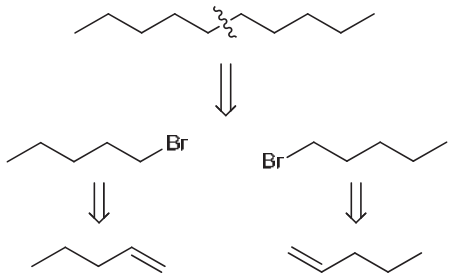
23.46. The product exhibits both a five-membered ring and a three-membered ring. The latter suggests a Simmons-Smith reaction. That is, the desired product can be made from an alkene. This alkene can be made from the starting material via ring-closing metathesis, as shown in the following retrosynthetic analysis:



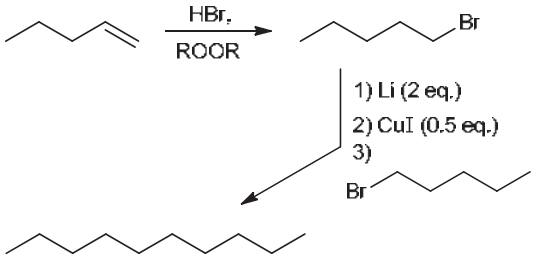
The forward synthesis is shown here:



23.47. We must first determine which bond (in the product) will be made via a coupling process. The product has ten carbon atoms, and the starting material has five carbon atoms, which means that we must form the bond between C5 and C6 via a coupling reaction. This requires that we use organohalides, as shown in the following retrosynthetic analysis:

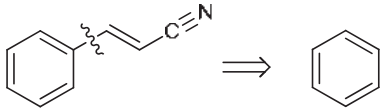


The organohalides can be made directly from the starting material via addition of HBr in the presence of peroxides. The forward synthesis is shown here:



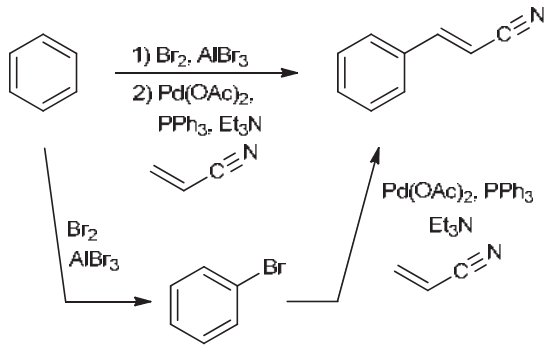
23.48.

(a) The problem statement indicates that we must start with benzene. This determines the bond (in the product) that must be made:

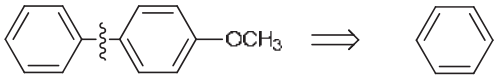


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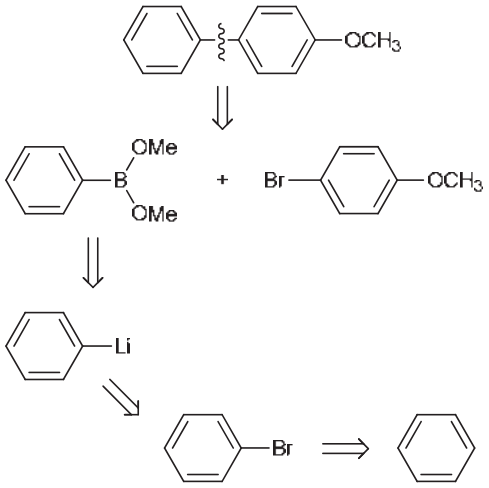
This bond can be made via a Heck reaction, as shown below. This strategy requires that we first convert benzene into bromobenzene, which can be achieved via electrophilic aromatic substitution (See Section 18.2):



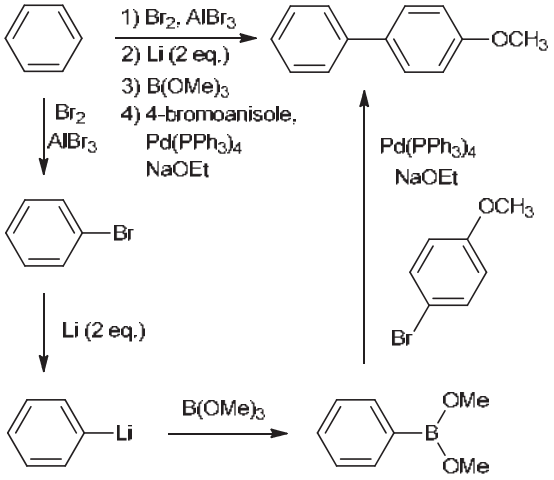
(b) The problem statement indicates that we must start with benzene. This determines the bond (in the product) that must be made:



We learned many coupling reactions in this chapter, so there are many ways to make this bond. The following retrosynthetic analysis employs a Suzuki coupling reaction:

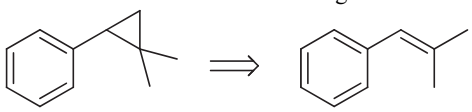


The organohalide coupling partner (4-bromoanisole) can also be made from benzene, although the problem statement indicates that we can use benzene *and any other reagents of our choice*. So, we can choose to use 4-bromoanisole and benzene as our starting materials, and we have satisfied the requirement of the problem.
The forward synthesis is shown here:

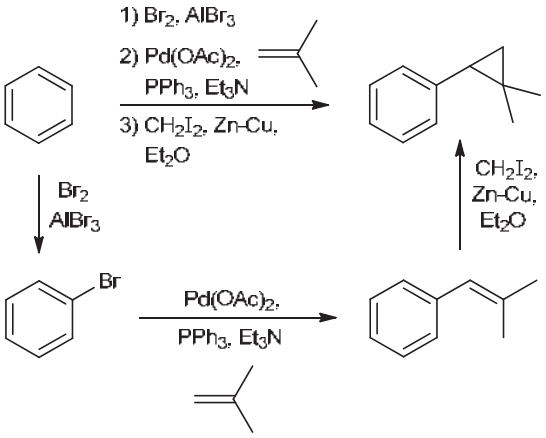


For those who are interested, 4-bromoanisole can be made using reactions that we have learned in previous chapters (chlorination of benzene to give chlorobenzene, followed by the Dow process to give phenol, followed by a Williamson ether synthesis to give methoxybenzene, followed by bromination at the *para* position).

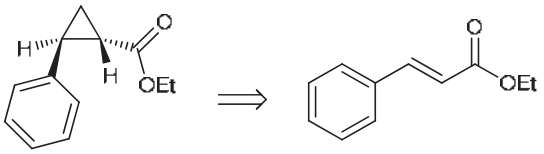
(c) The product exhibits a three-membered ring, which suggests a Simmons-Smith reaction. That is, the desired product can be made from the following alkene:



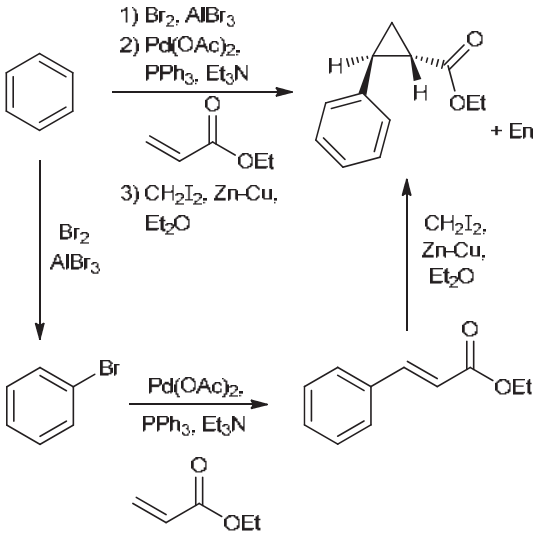
This alkene can be made from benzene through a variety of methods. The following synthesis is based on a Heck reaction, although other alternatives (such as Suzuki or Stille coupling) are perfectly viable:



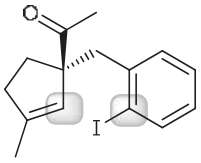
(d) The product exhibits a three-membered ring, which suggests a Simmons-Smith reaction. That is, the desired product can be made from the following *E* alkene:



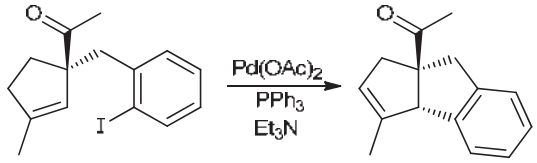
This alkene can be made from benzene through a variety of methods. The following synthesis is based on a Heck reaction, although other alternatives are perfectly viable:



23.49. The starting material is an organohalide that also exhibits a C=C unit. Upon treatment with a base and a suitable palladium catalyst, an intramolecular Heck reaction can occur, in which a bond is formed between the C=C unit and the carbon atom bearing the iodide. The coupling partners are highlighted here:



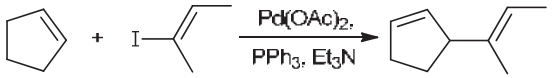
During the course of the reaction, the position of the π bond changes, because this is the only regiochemical outcome that can accommodate *syn* elimination:



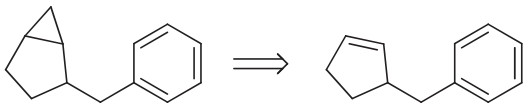
The observed diastereoselectivity can be rationalized by considering the existing chiral center (in the starting material). As a result of the configuration of this chiral center, the organohalide partner must approach the C=C unit from one particular face of the C=C bond (behind the plane of the five-membered ring). Perhaps this is best visualized through the construction of a molecular model. As a result, the newly formed chiral center has the *S* configuration (the *R* configuration is not formed).

23.50.

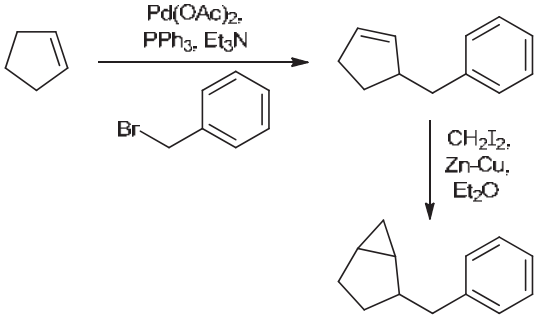
(a) The desired product can be made from cyclopentene via a Heck reaction, as shown below. Notice the position of the π bond in the product (this is the only regiochemical outcome that can accommodate *syn* elimination).



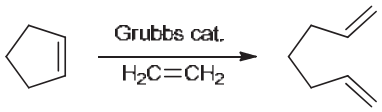
(b) The product exhibits a three-membered ring, which suggests a Simmons-Smith reaction. That is, the desired product can be made from the alkene shown here:



This alkene can be made from cyclopentene via a Heck reaction, as shown in the following synthesis:

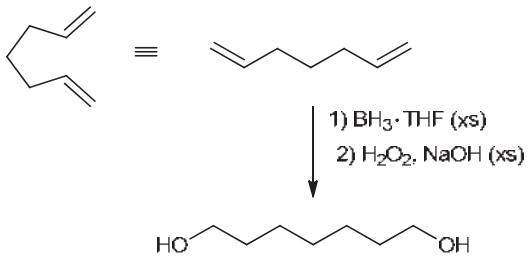


(c) The product is acyclic (no ring), but the starting material is cyclic, so our synthesis must involve breaking a C-C bond. We could perform an ozonolysis (of cyclopentene) to open the ring, but that would give us a compound with only five carbon atoms. We need a compound with seven carbon atoms, which suggests that we should open the ring with a ring-opening metathesis, thereby converting a five-membered cyclic compound into a seven-membered acyclic compound:

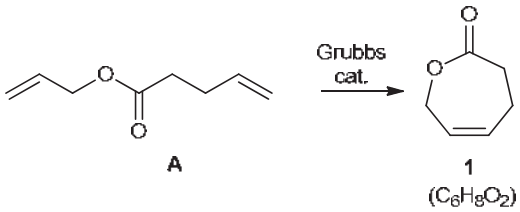


This compound can then be converted into the desired product via hydroboration/oxidation of each C=C unit.

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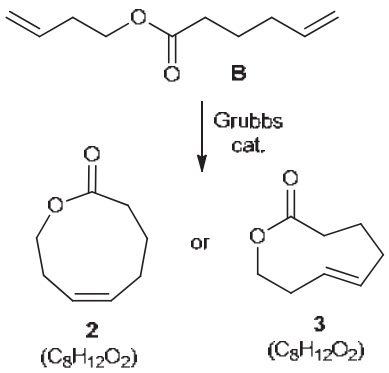


23.51. Compound **A** has two C=C units that can undergo a ring-closing metathesis upon treatment with a Grubbs catalyst. To draw the metathesis product, we remove a methylene group from each C=C unit (these methylene groups ultimately combine to give ethylene gas). We then draw a double bond between the remaining vinyl positions, giving compound **1**:



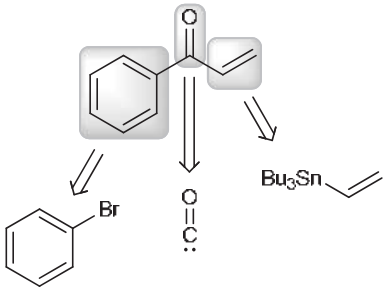
Compound **1** has a C=C unit with the *Z* configuration. The *E* configuration cannot be formed in this case, because a seven-membered ring cannot accommodate a *trans* alkene (see Bredt's rule, Section 7.7).

In contrast, compound **B** undergoes a ring-closing metathesis to give a nine-membered ring. A nine-membered ring is large enough to accommodate a *trans* alkene, so two products are possible (*cis* or *trans*):

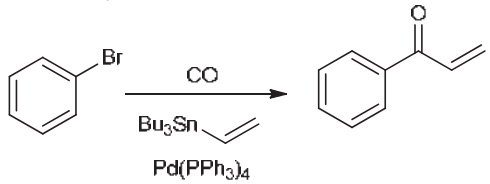


23.52.

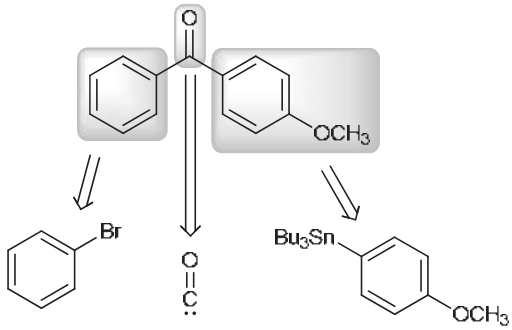
(a) Using the procedure described in the problem statement, the desired product can be assembled from bromobenzene, carbon monoxide, and an organotin coupling partner, as shown:



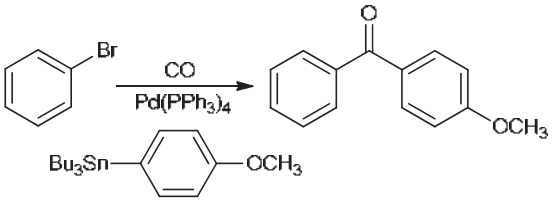
The forward synthesis is shown here:



(b) Using the procedure described in the problem statement, the desired product can be assembled from bromobenzene, carbon monoxide, and an organotin coupling partner, as shown:

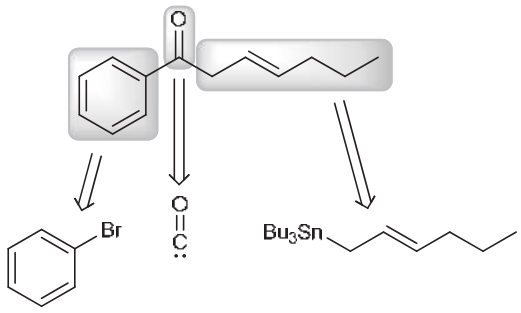


The forward synthesis is shown here:

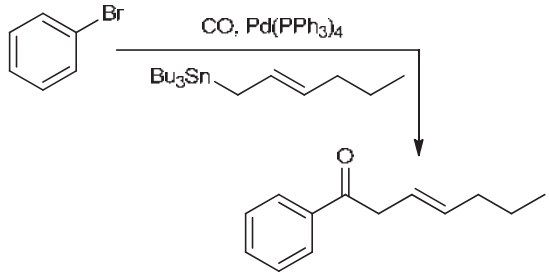


(c) Using the procedure described in the problem statement, the desired product can be assembled from bromobenzene, carbon monoxide, and an organotin coupling partner, as shown:

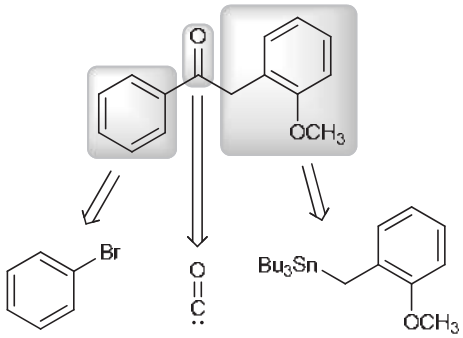
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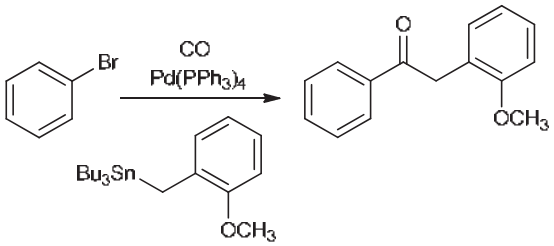
The forward synthesis is shown here:



(d) Using the procedure described in the problem statement, the desired product can be assembled from bromobenzene, carbon monoxide, and an organotin coupling partner, as shown:



The forward synthesis is shown here:

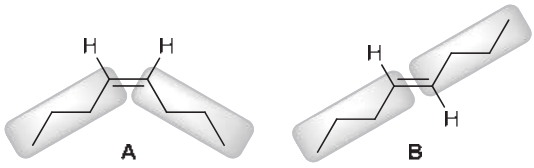


23.53.

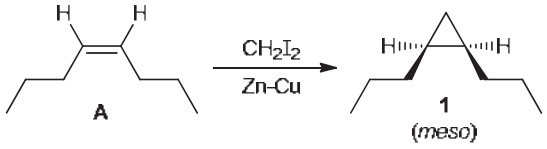
(a) The starting material (1-pentene) is comprised of two alkylidene fragments:



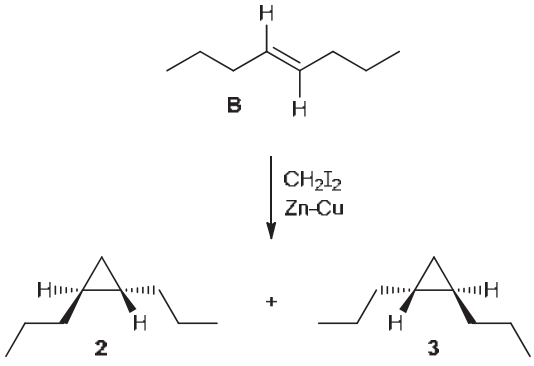
One of these fragments has four carbon atoms, and the other fragment has only one carbon atom (a methylene group). When 1-pentene is treated with a Grubbs catalyst, the methylene fragments are recombined to give ethylene gas (which evolves as a gas and is removed from the reaction vessel), while the other alkylidene fragments (with four carbon atoms) are recombined to give 4-octene. Two stereoisomers are possible (*cis* and *trans*), and both are obtained (**A** and **B**):



Compound **A** is a *cis*-disubstituted alkene, so it undergoes a Simmons-Smith reaction to give a *cis*-disubstituted cyclopropane ring (a *meso* compound):



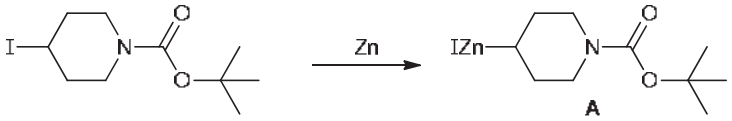
In contrast, compound **B** is a *trans*-disubstituted alkene, so it undergoes a Simmons-Smith reaction to give a *trans*-disubstituted cyclopropane ring. Two stereoisomers are possible (compounds **2** and **3**), and both are obtained:



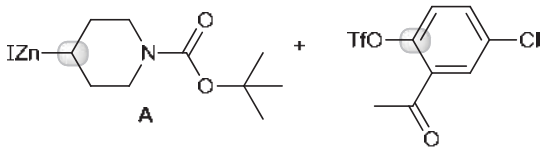
(b) Compounds **2** and **3** are nonsuperimposable mirror images of each other, so they are enantiomers.

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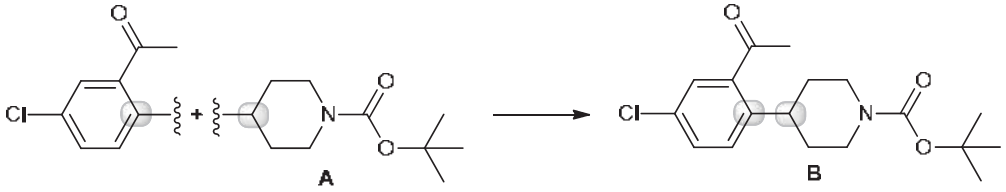
23.54. In the first step of the synthesis, Zn metal inserts into the C-I bond to produce organozinc **A**:



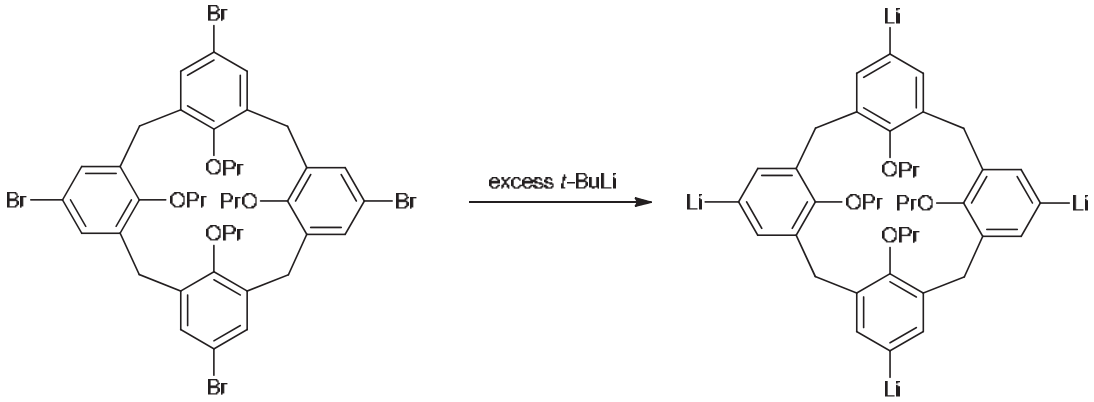
Next, identify the carbon atoms that will be joined in the Negishi coupling. The carbon atom connected directly to the triflate group (which is more reactive than the aryl chloride position) will be joined with the carbon atom connected directly to Zn in the organozinc, highlighted here:



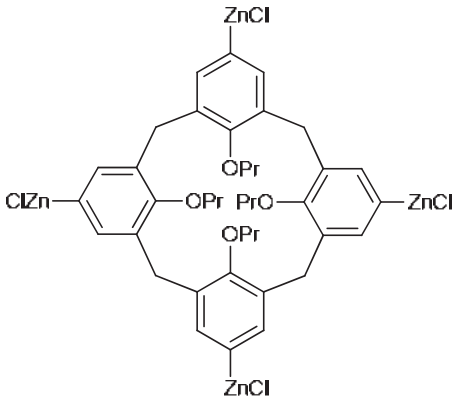
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product, **B**:



23.55. In the first step of the synthesis, excess *t*-BuLi converts each of the four aryl bromide groups to aryllithium groups:

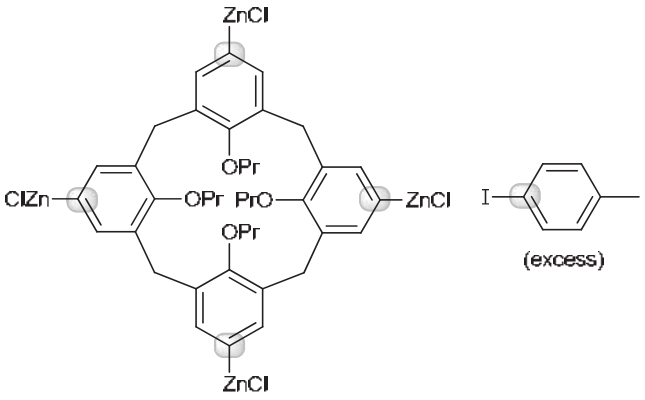


In step 2, $ZnCl_2$ converts each aryllithium group to an arylzinc, thus producing the following tetraarylzinc compound:

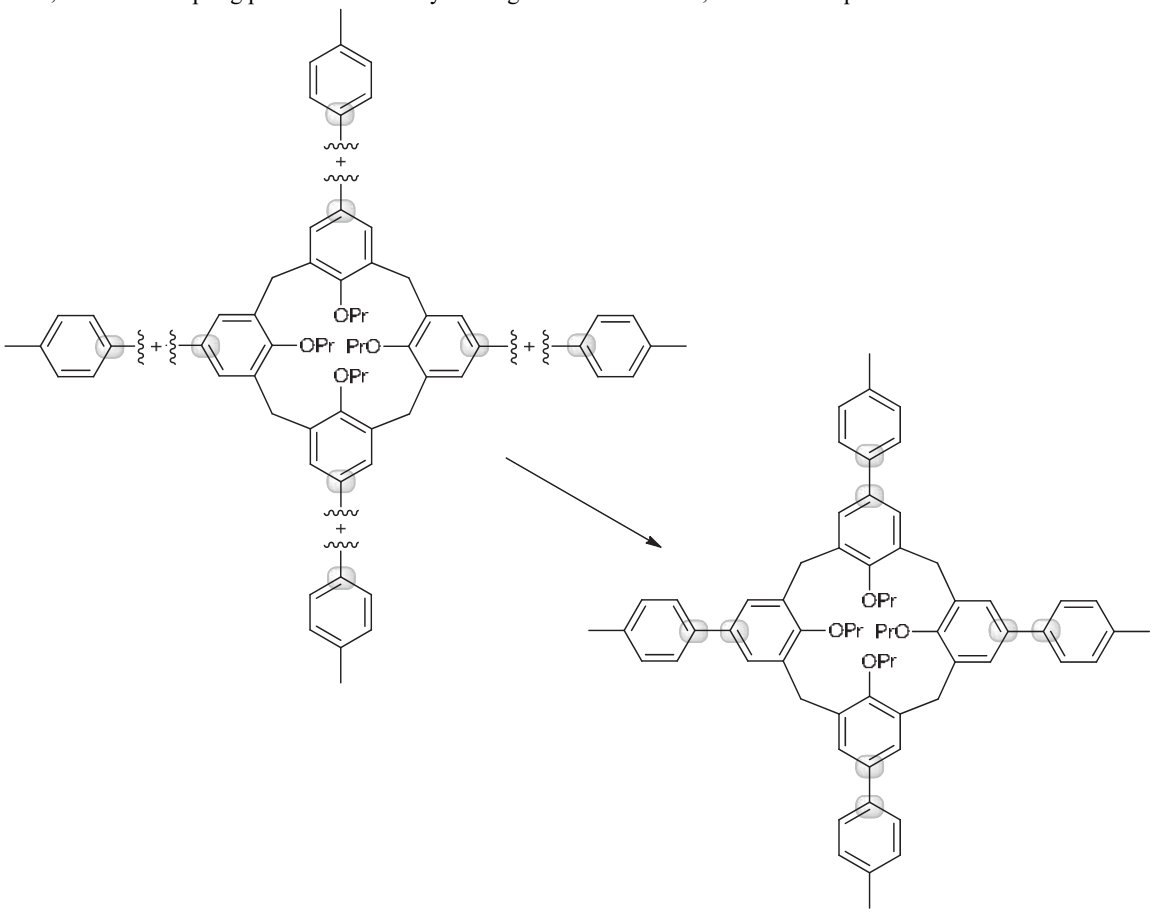


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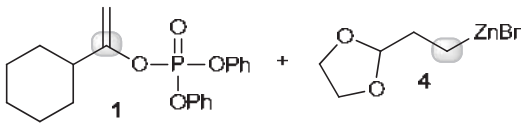
Next, identify the carbon atoms that will be joined in the Negishi coupling. The carbon atom connected directly to the iodide group will be joined with the carbon atom connected directly to Zn in the organozinc, highlighted below. In this case, four equivalents of *p*-iodotoluene will couple to the tetraiodozinc calixarene.



Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

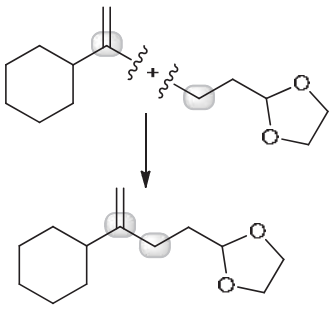


23.56.
(a) First, identify the carbon atoms that will be joined in the Negishi coupling. The vinyl carbon atom connected directly to the O in alkenyl phosphate **1** will be joined with the carbon atom connected directly to Zn in organozinc **4**, highlighted below.

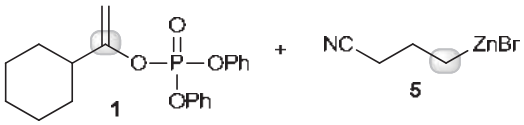


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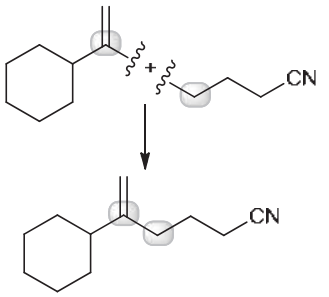
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



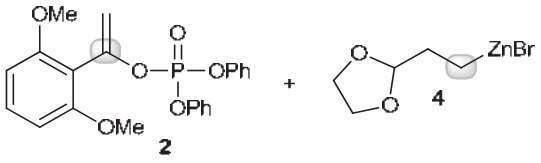
(b) First, identify the carbon atoms that will be joined in the Negishi coupling. The vinyl carbon atom connected directly to the O in alkenyl phosphate **1** will be joined with the carbon atom connected directly to Zn in organozinc **5**, highlighted below.



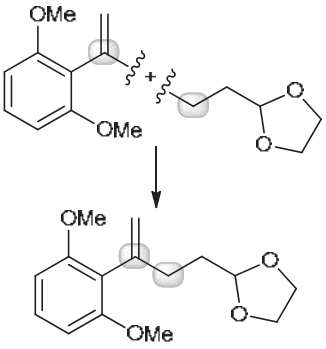
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



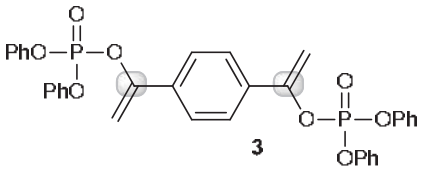
(c) First, identify the carbon atoms that will be joined in the Negishi coupling. The vinyl carbon atom connected directly to the O in alkenyl phosphate **2** will be joined with the carbon atom connected directly to Zn in organozinc **4**, highlighted below.

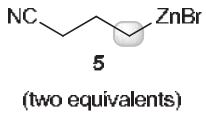


Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

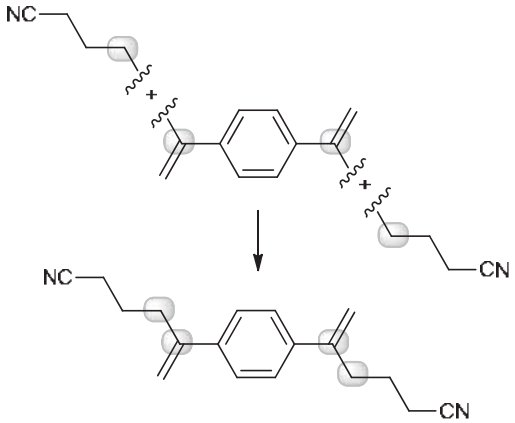


(d) First, identify the carbon atoms that will be joined in the Negishi coupling. Each of the two vinyl carbon atoms connected directly to an O in alkenyl phosphate **3** will be joined with the carbon atom connected directly to Zn in each equivalent of organozinc **5**, highlighted below.

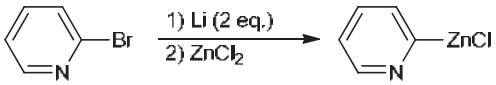




Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:

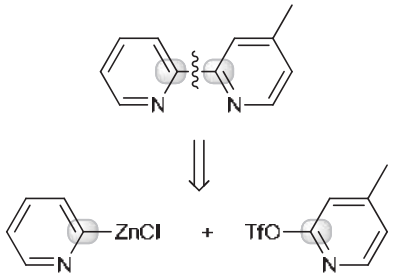


23.57. In each reaction sequence, a common synthetic intermediate is produced as a result of the first two steps: lithium-halogen exchange, followed by conversion of the resulting aryllithium to the arylzinc using $ZnCl_2$.

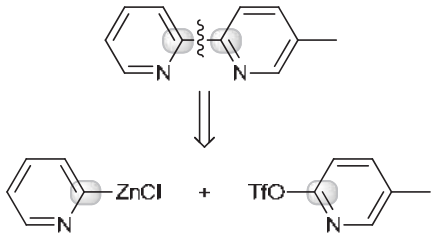


(a) Identify the C–C bond in the product that was produced in the Negishi coupling (indicated below).

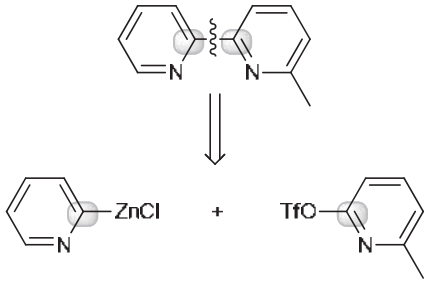
Disconnect the bond to determine the arylzinc and aryl triflate required for the reaction.



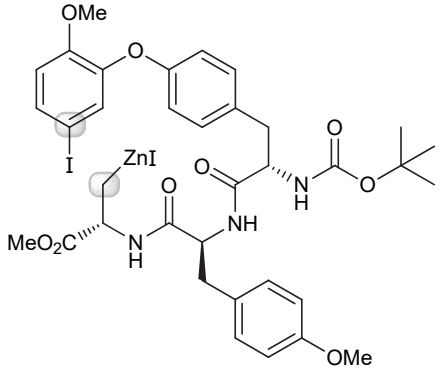
(b) Identify the C–C bond in the product that was produced in the Negishi coupling (indicated below). Disconnect the bond to determine the arylzinc and aryl triflate required for the reaction.



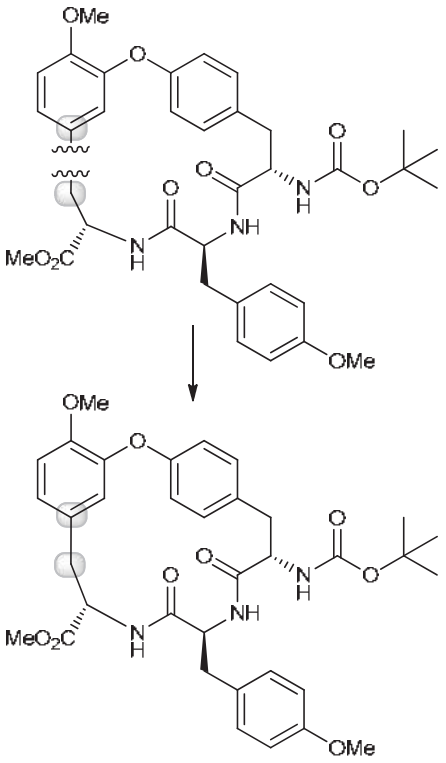
(c) Identify the C–C bond in the product that was produced in the Negishi coupling (indicated below). Disconnect the bond to determine the arylzinc and aryl triflate required for the reaction.



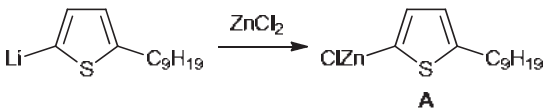
23.58. First identify the carbon atoms that will be joined. This reaction is an intramolecular Negishi coupling, in which both coupling partners are in the same molecule. The carbon atom connected directly to the iodide group will be joined with the carbon atom connected directly to Zn in the organozinc, highlighted here:



Next, realign the coupling partners so that they are aligned to form a bond, and draw the product, in which a new macrocycle (large ring) has formed:

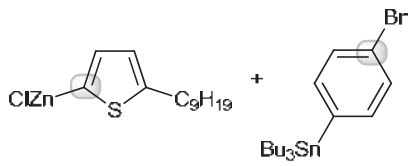


23.59. In the first step of the synthesis, $ZnCl_2$ converts the aryllithium to arylzinc **A**:

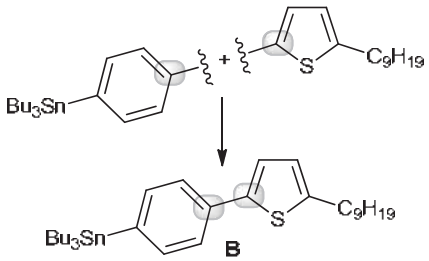


Next, identify the carbon atoms that will be joined in the Negishi coupling. The carbon atom connected directly to the bromide group will be joined with the carbon atom connected directly to Zn in the organozinc, highlighted here:

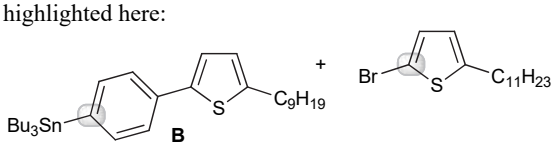
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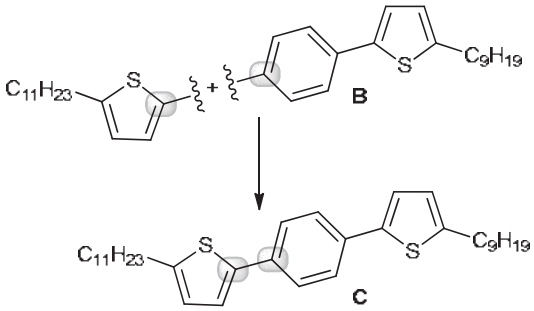
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



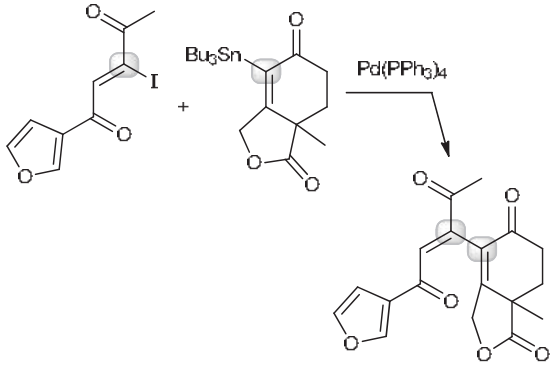
Next, identify the carbon atoms that will be joined in the Stille coupling. The carbon atom connected directly to the bromide group will be joined with the aryl carbon atom connected directly to Sn in the organostannane, highlighted here:



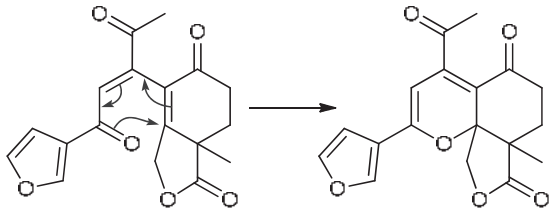
Then, rotate the coupling partners so that they are aligned to form a bond, and draw the product:



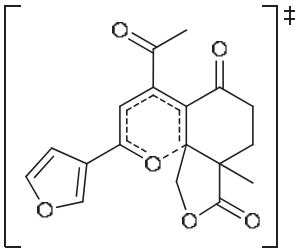
23.60. First identify the carbon atoms that will be joined. The carbon atom connected directly to the iodide group will be joined with the carbon atom connected directly to the tributylstannyl group, highlighted below:



The product of the Stille reaction subsequently undergoes an electrocyclic reaction (Section 17.9) involving the flow of 6 electrons in a cycle, as shown below:

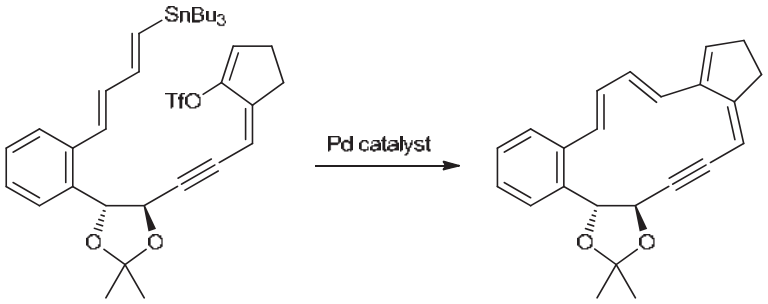


The transition state of the electrocyclic rearrangement is shown below. Three π bonds (two C=C plus one C=O) are breaking, while two π bonds (C=C) and one σ bond (C-O) are forming, resulting in the net conversion of one C=O π bond to one C-O σ bond.

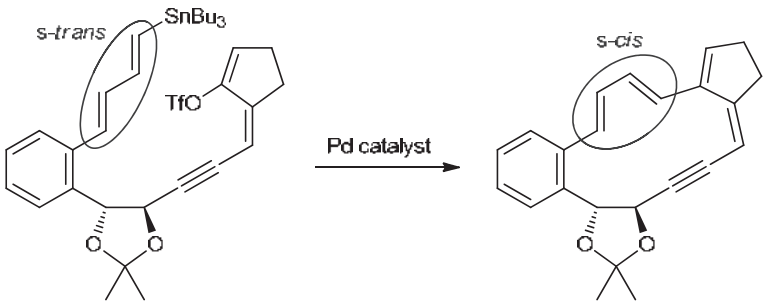


23.61. The reactant undergoes an intramolecular Stille coupling with a palladium catalyst to produce the macrocycle shown. In this reaction, the sp^2 hybridized carbon atom connected to the tin atom (in the reactant) forms a new bond to the sp^2 hybridized carbon atom connected to the triflate leaving group (in the reactant), thereby producing a new 13-membered ring.

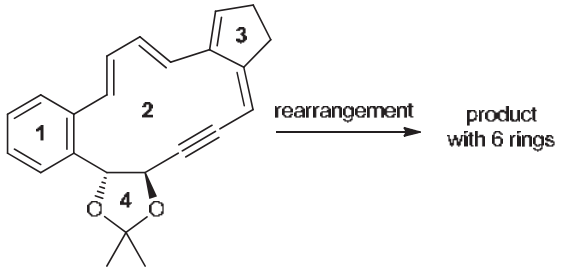
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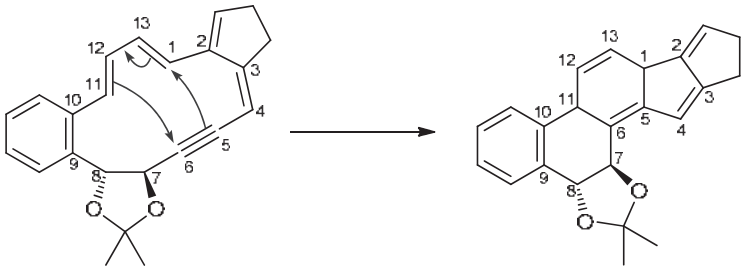
Note that the diene indicated below is primarily in the more stable s-*trans* conformation in the reactant. In the product of the Stille coupling, this diene likely adopts an s-*cis* conformation to accommodate the geometric constraints necessary for incorporation into the newly formed macrocycle.



The question indicates that this macrocycle undergoes a rearrangement to form a final product with six rings. The macrocycle product of the intramolecular Stille coupling has four rings, as indicated (numbered **1**-**4**). The rearrangement must therefore result in the formation of two new ring-forming bonds to allow for the incorporation of the two additional rings.

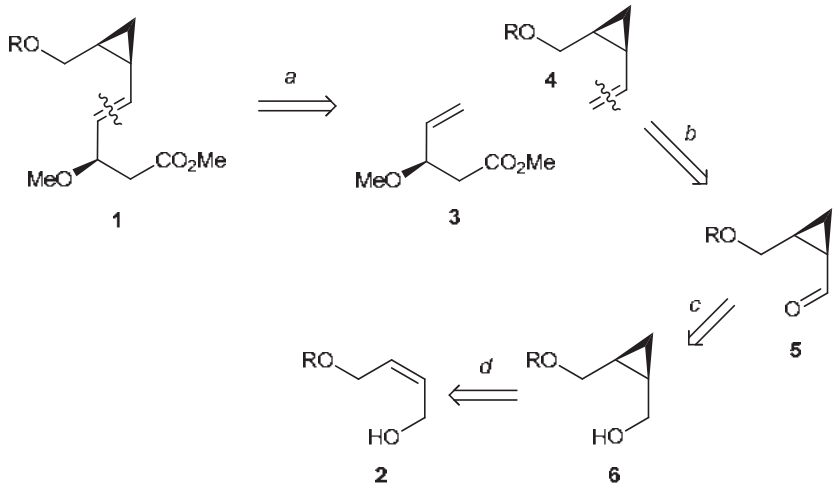


The macrocycle has an s-*cis* diene group across the macrocycle from an alkyne group. An intramolecular Diels-Alder reaction between these two entities forms two new σ bonds (C1-C5 and C6-C11 as indicated below) to produce the hexacyclic product shown.



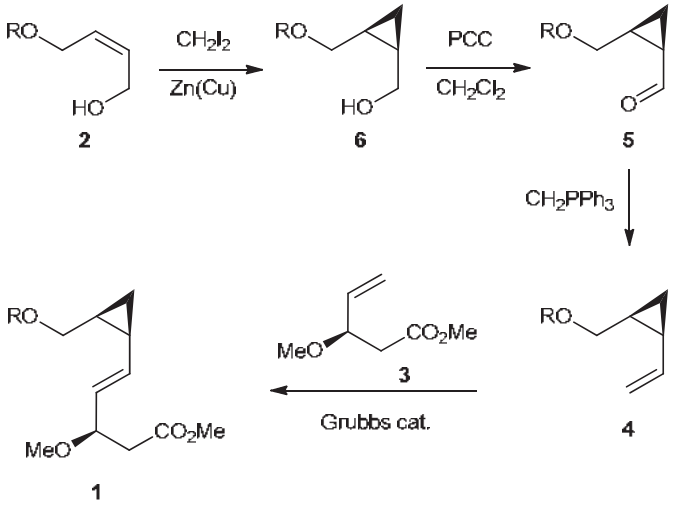
23.62. While there are certainly many acceptable solutions to this problem, we can reduce the complexity of this problem by employing two organometallic reactions we learned in this chapter. For example, compound **1** contains both a *trans* C=C bond and a cyclopropane ring. We know that cyclopropane rings can be prepared using the Simmons-Smith reaction, and *trans* C=C bonds can be accessed via cross metathesis using the Grubbs catalyst. One synthesis derives from the following retrosynthetic analysis. An explanation of each of the steps (*a*-*d*) follows.

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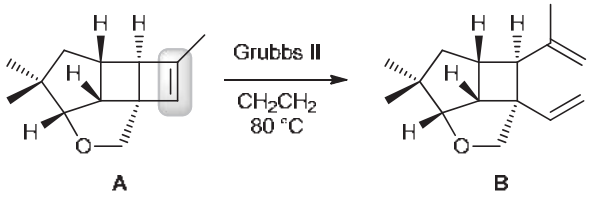


a. Compound **1** can be synthesized from the union of two terminal alkenes (**3** & **4**) using a Grubbs catalyst.
b. Alkene **4** can be made from aldehyde **5** employing the Wittig reaction.
c. Aldehyde **5** can be accessed from the corresponding alcohol (**6**), using PCC (or DMP or a Swern oxidation).
d. The cyclopropane ring can be installed via the Simmons-Smith reaction on substrate **2.**

Now let's draw the forward scheme. Alcohol **2** is treated with diiodomethane in the presence of a Zn-Cu couple to produce cyclopropane **6**. The alcohol in **6** is converted to aldehyde **5** using PCC and is subsequently treated with a phosphorus ylide to produce alkene **4**. Finally, union of alkene **4** with compound **3** using a Grubbs catalyst will produce the desired product.



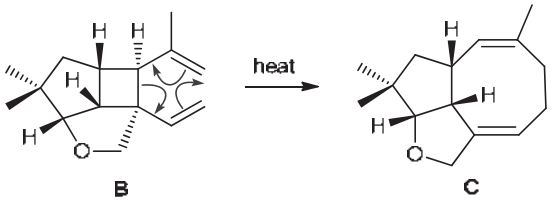
23.63.
(a) In the presence of a Grubbs catalyst and ethylene, a cycloalkene (compound **A**) is expected undergo a ring-opening metathesis. To draw the product of this process (compound **B**), we erase the C=C bond of the ring, and then connect a methylene (CH_2) group to each of the two vinyl positions, like this:



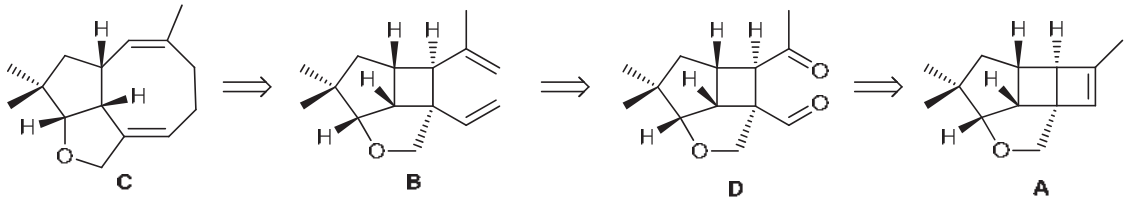
(b) The problem statement indicates that the conversion of **B** into **C** is a thermally induced rearrangement. This suggests a pericyclic reaction (Chapter 16). Notice that compound **B** has two π bonds that are separated from each

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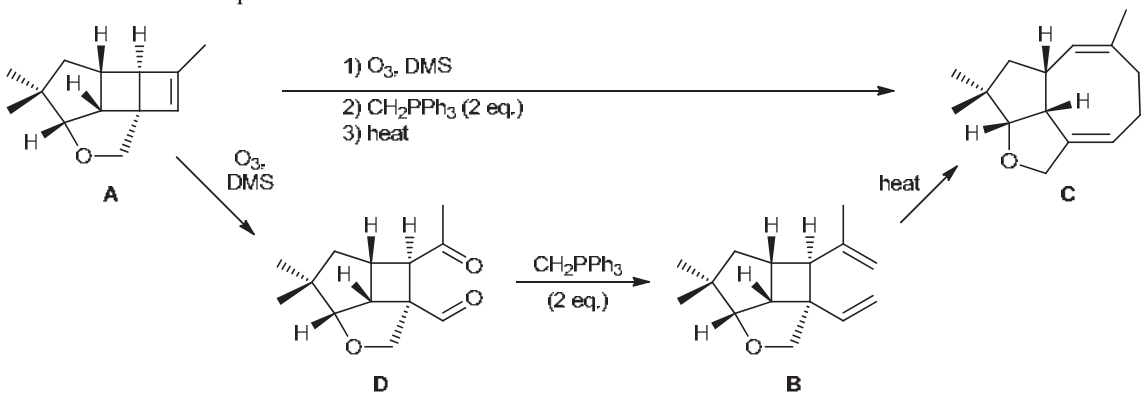
other by exactly three σ bonds. As such, in the presence of heat, this compound can undergo a [3,3] sigmatropic rearrangement (also called a Cope rearrangement) to form the 8-membered ring observed in compound **C**.



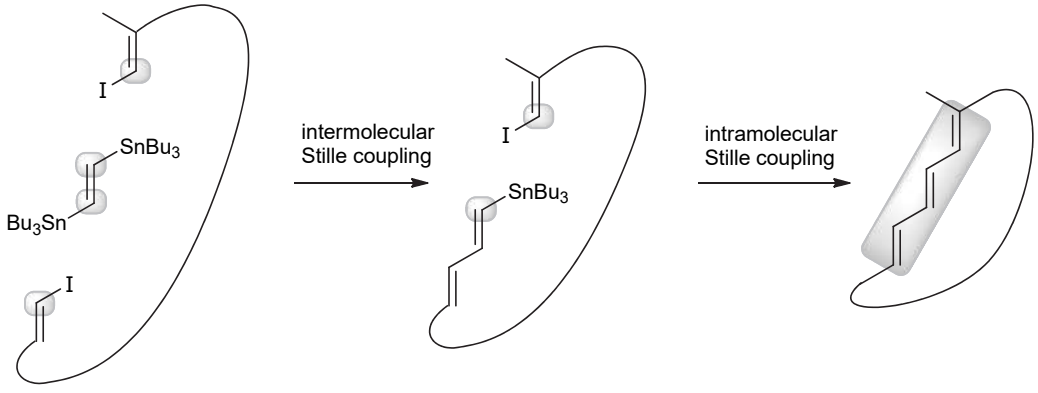
(c) There is ring strain associated with the cyclobutene ring of compound **A**, and this ring strain is alleviated when the ring is opened to give compound **B**. As a result, compound **B** is expected to be lower in energy than compound **A**, thus causing the equilibrium to favor **B** over **A**.
(d) There is ring strain associated with the cyclobutane ring of compound **B**, and this ring strain is alleviated when the ring is opened to give the eight-membered ring in compound **C**. As a result, compound **C** is expected to be lower in energy than compound **B**, thus causing the equilibrium to favor **C** over **B**.
(e) We have seen that compound **C** can be made from compound **B** via a [3,3] sigmatropic rearrangement (Cope rearrangement). Compound **B** can be prepared from compound **A** via a number of synthetic routes. The following is one possible solution. Compound **B** can be made from compound **D** via Wittig reactions, and compound **D** can be generated from **A** via ozonolysis of the C=C bond in **A**:



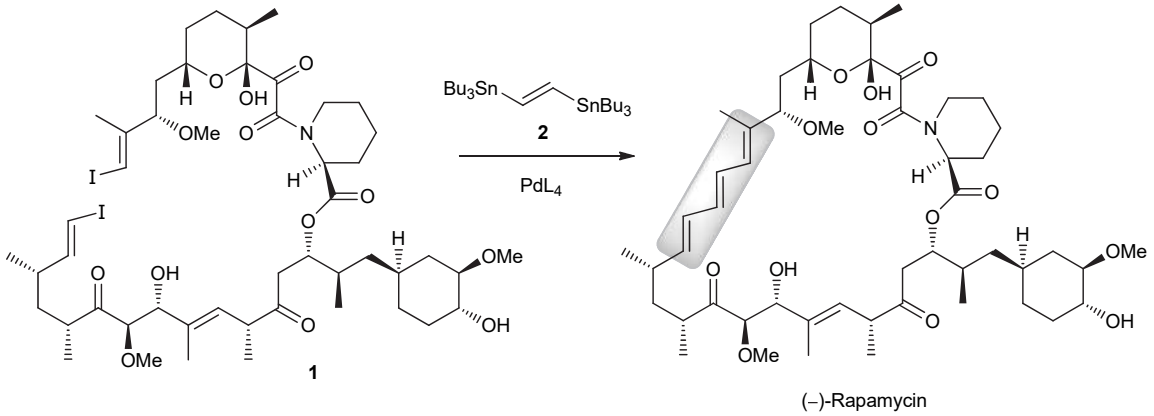
The forward reaction sequence is shown here:



23.64. Rapamycin has a large ring (it is a macrolide) which is assembled via two successive (tandem) Stille coupling reactions. The first reaction is intermolecular, and the second is intramolecular. The reactive centers are highlighted:

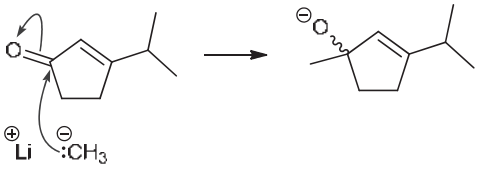


When stitched together, the large ring contains a triene group (highlighted). Notice that each of the three C=C units retains the configuration that it had in the starting materials. The rest of the structure (all of the functional groups and chiral centers) remains unaffected by these reactions conditions, so the structure of rapamycin is as follows:

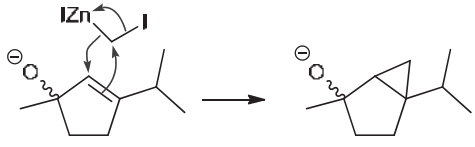


23.65.

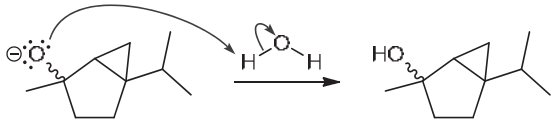
(a) In step 1, methyllithium attacks the carbonyl carbon producing a racemic allylic alkoxide (note: the wavy line indicates both possible configurations at that chiral center).



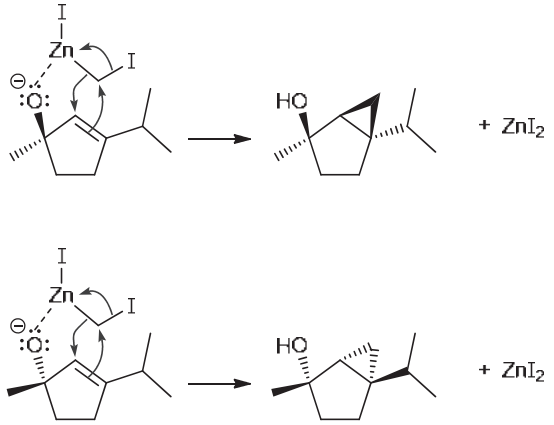
In step 2, the zinc carbenoid (formed by the reaction of the zinc-copper couple with diiodomethane) reacts in a Simmons-Smith cyclopropanation with the alkene to install the cyclopropane ring.



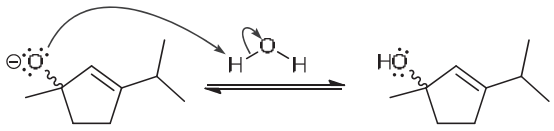
Finally, in step 3, the alkoxide ion is protonated (upon treatment with water), giving the product:



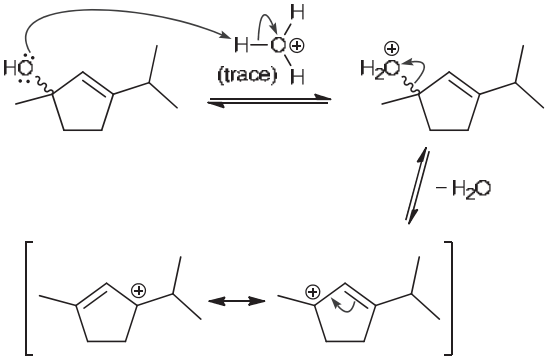
(b) In the product, the OH group and the fused cyclopropane ring are both on the same face of the cyclopentane ring (both "up" in the stereoisomer shown in the problem statement). This stereochemical outcome can be rationalized if we recognize that the anionic oxygen atom can form a Lewis acid / Lewis base complex with the zinc atom of the metal carbenoid species $IZnCH_2I$, thus directing the resulting cyclopropane to the same face of the cyclopentane ring as the oxygen atom. This is shown for each enantiomer here:



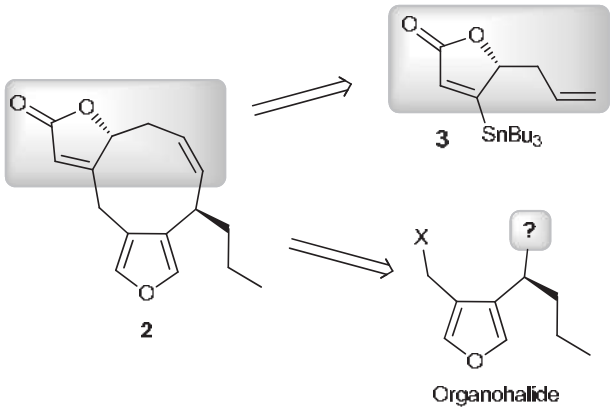
(c) If the starting material is treated with methyllithium followed by water, an allylic alcohol would be produced:



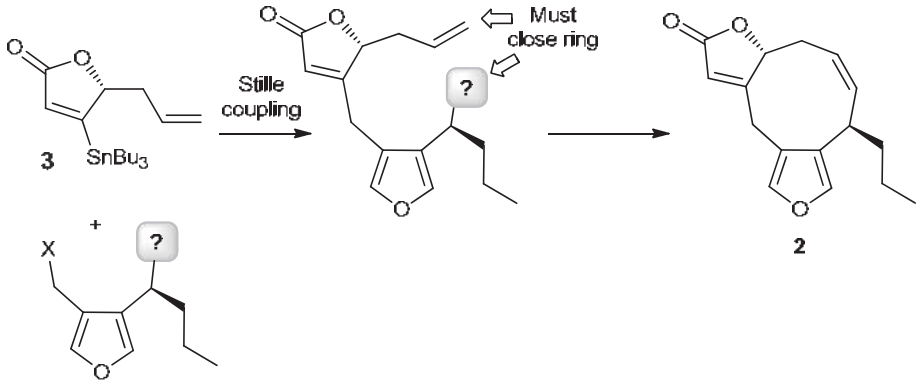
It is perhaps not surprising that this synthetic intermediate is very unstable in the presence of trace acid. Protonation of the alcohol generates an excellent leaving group (H_2O), and loss of the leaving group produces a very stable allylic carbocation (a hybrid of two tertiary carbocations) which is then susceptible to nucleophilic attack.



23.66. The starting material (compound **3**) is an organostannane, which indicates a Stille coupling reaction. To determine the structure of the starting organohalide, we analyze the structure of the product (compound **2**) and determine the part of the structure that corresponds with organostannane **3** (highlighted). The rest of compound **2** (not highlighted) must come from the organohalide, as shown:

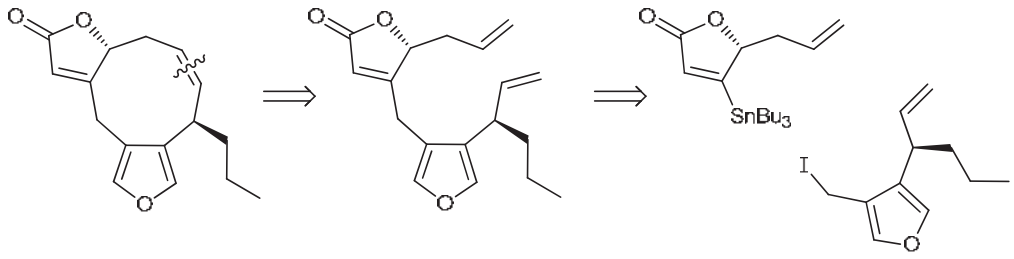


The identity of the side chain (highlighted with a question mark) must be chosen to enable the subsequent formation of the desired 9-membered ring (in compound **2**):

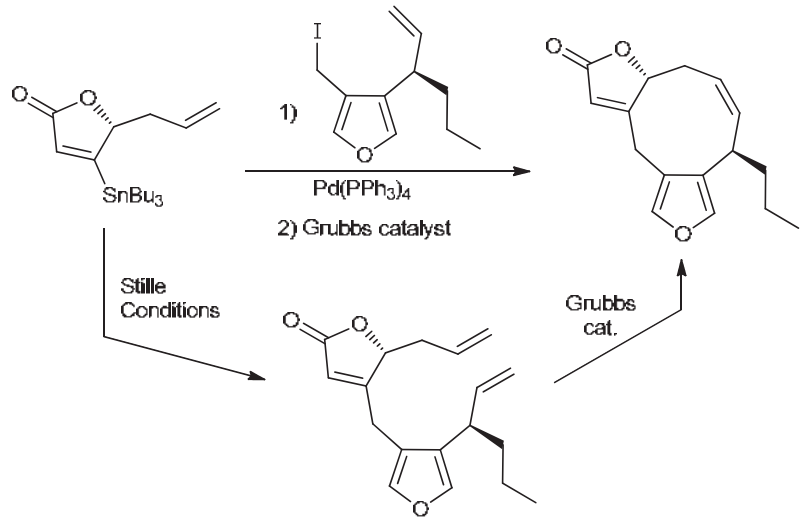


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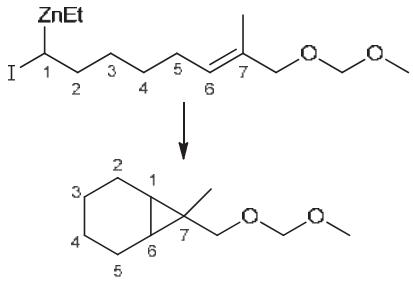
This can be achieved via a ring-closing metathesis, as shown in the following retrosynthetic analysis:



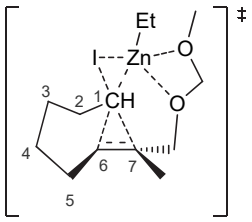
The forward process is summarized here:



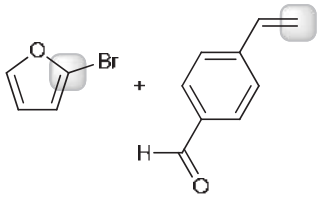
23.67. The product of the intramolecular Simmons-Smith reaction is shown below. The carbenoid carbon of the intermediate (labeled as C1 below) forms two new C-C bonds: one to each of the sp^2 hybridized carbon atoms of the C=C unit (C6 and C7), thus producing the fused bicyclic structure shown.



The observation that compound **1** successfully undergoes intramolecular Simmons-Smith reaction (while compound **2** does not) suggests that the oxygen atoms in **1** (which are absent in **2**) play a role. The zinc atom in the carbenoid intermediate is electron poor and can thus serve as a Lewis acid. The lone pairs of electrons on the oxygen atoms allow them to serve as Lewis bases. An intramolecular Lewis acid / Lewis base complex between one or both oxygen atoms and the zinc atom may align the reactive groups and facilitate the Simmons-Smith reaction. The transition state below is consistent with this explanation.

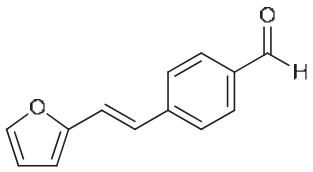


23.68. In a Heck cross-coupling reaction, an alkene is coupled with an organohalide. The following highlighted carbon atoms will be connected to each other as a result of the coupling process:



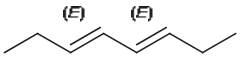
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The coupling process affords a disubstituted alkene, and we expect the *trans* isomer:

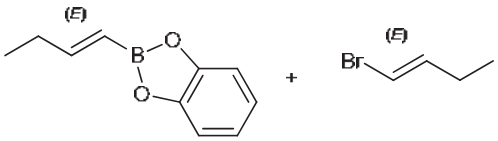


This structure corresponds with option (c).

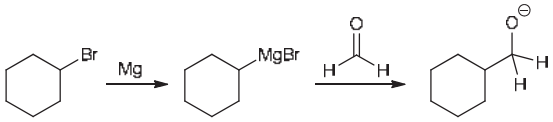
23.69. All of the options involve a vinyl bromide and a vinyl boronic ester or acid, but we must choose the coupling partners that give the desired stereochemical outcome. In the product, both C=C units have the *E* configuration:



Since the configuration of all C=C units are preserved during Suzuki coupling, we must choose reactants that have the *E* configuration, so option (d) is the correct answer:

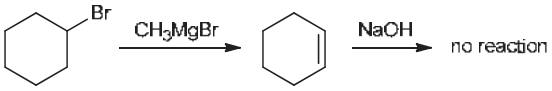


23.70. In option (a), the first step converts the alkyl bromide into a Grignard reagent, which is then expected to react with formaldehyde in the second step:

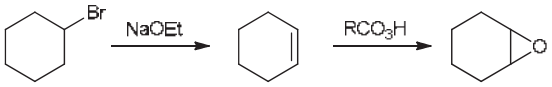


The product of this reaction sequence is NOT the desired product, so we can rule out option (a).

In option (b), the starting halide is treated with a Grignard reagent (a strong nucleophile and a strong base). Since the alkyl bromide is secondary, we would expect elimination (E2) to be favored over substitution, giving an alkene. This alkene is not expected to react with NaOH, so option (b) does not give the desired product:

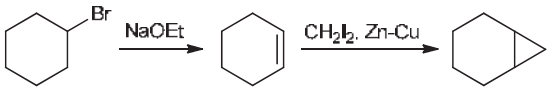


In option (c), the first step converts the secondary alkyl bromide into an alkene (because elimination is favored over substitution for secondary alkyl halides), and the alkene is then converted into an epoxide upon treatment with a peroxyacid:

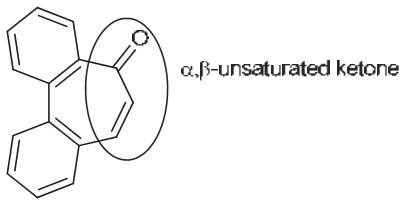


This product is similar in structure to the desired product. But we are not trying to make an epoxide. Rather, we must form a cyclopropane ring, so option (c) is not correct.

Option (d) is the correct answer. Elimination, followed by Simmons-Smith cyclopropanation, gives the desired product:



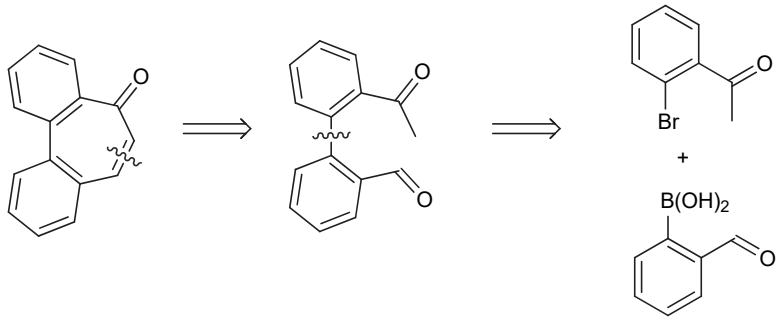
23.71. The desired product (dibenzo[*a,c*]cyclohepten-5-one) contains 15 carbon atoms, so in order to propose a synthesis from starting materials with 8 or fewer carbons, we will need to make several new C-C bonds in our synthesis. Recognition of the α,β-unsaturated ketone in the central ring suggests the possibility of utilizing an aldol condensation as part of our approach.



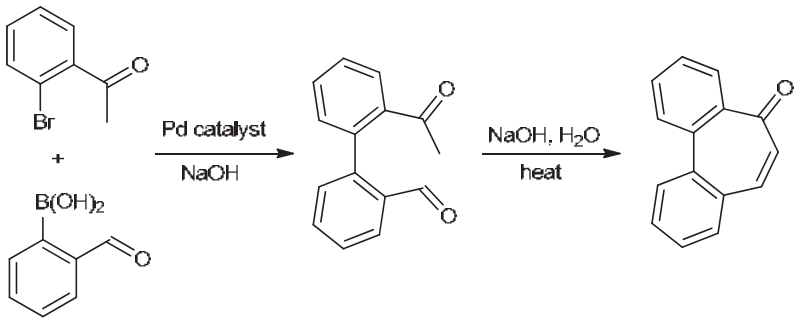
The following retrosynthesis outlines one approach to make the desired compound in two steps. The α,β-unsaturated ketone can be prepared via an intramolecular aldol condensation between the methylketone group and the aldehyde

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group on the biphenyl intermediate below. The bond between the two aromatic rings can be constructed using a Suzuki coupling reaction between the aryl bromide and the aryl boronic acid shown.

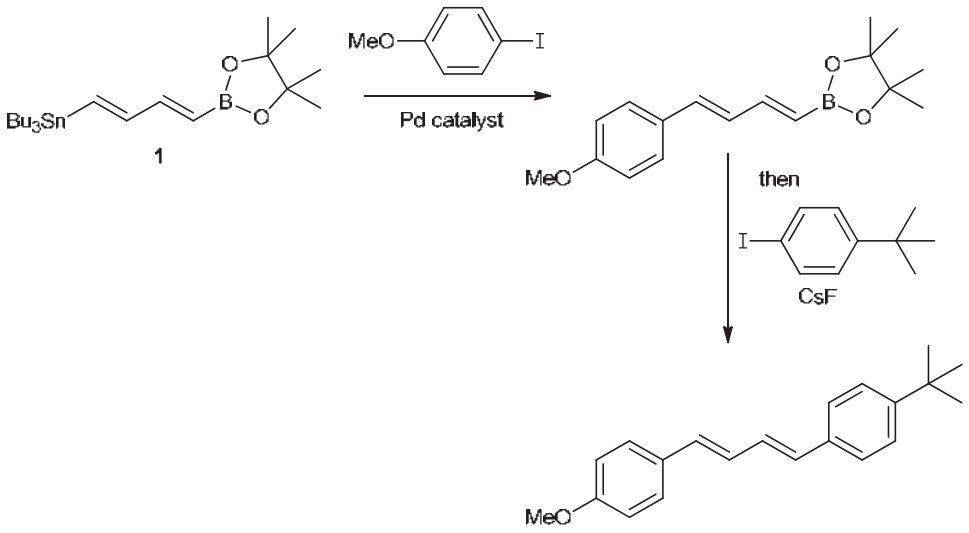


The forward synthesis is below. *o*-Bromoacetophenone and *o*-formylphenyl boronic acid are mixed together under basic conditions and treated with a palladium catalyst to give a Suzuki coupling reaction. The biphenyl keto-aldehyde intermediate is then heated under basic conditions to afford the desired aldol condensation product (via an intramolecular aldol condensation).



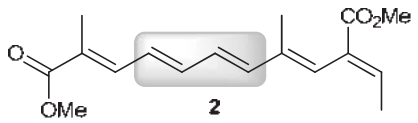
23.72.

(a) Reaction of **1** with 4-iodoanisole in the presence of a palladium catalyst affords the Stille coupling product shown. Subsequent addition of 4-*tert*-butyliodobenzene and CsF to the reaction mixture produces the final product as the result of a palladium-catalyzed Suzuki coupling between the vinyl boronic ester and the aryl iodide. Note that each of these coupling reactions proceeds with retention of configuration: the *trans*/*trans* configuration of **1** is retained in the product.



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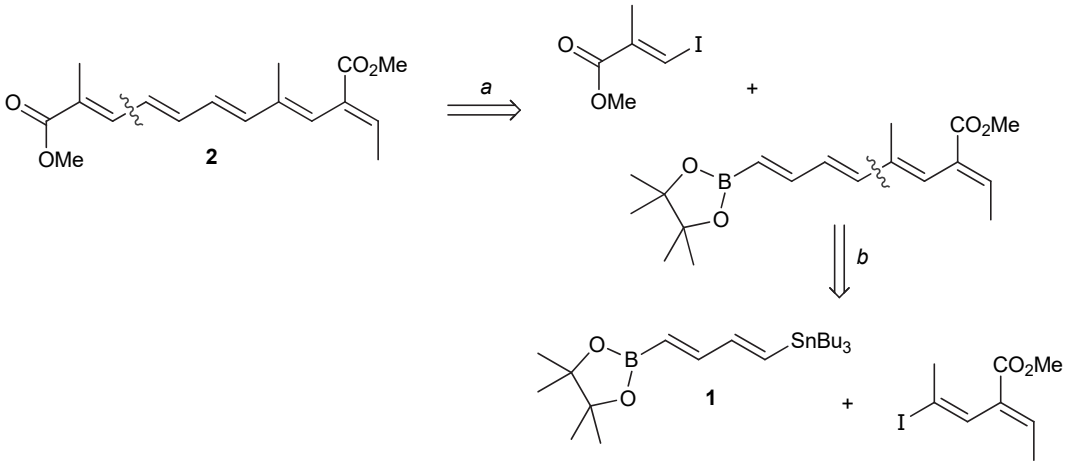
(b) An analysis of **2** reveals that it contains the *trans*/*trans* diene present in **1**, highlighted below.



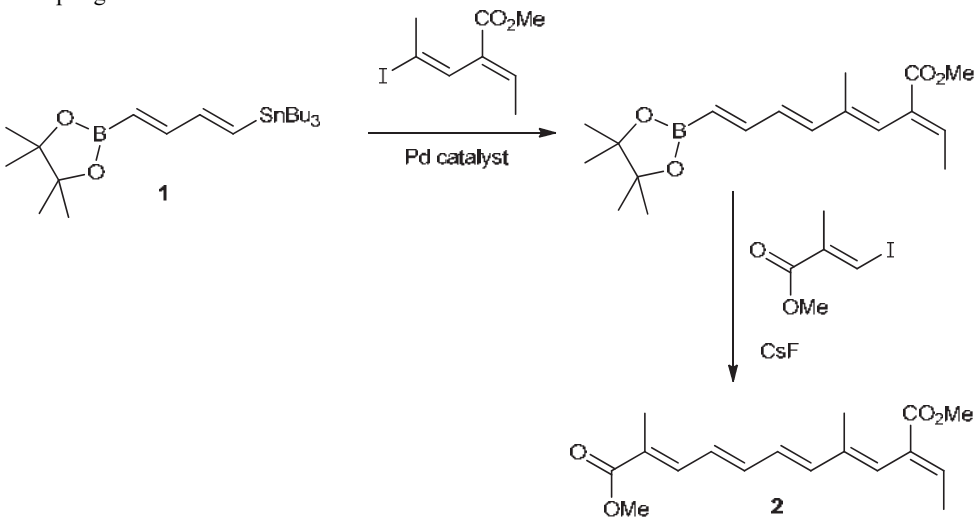
One retrosynthetic analysis of **2** is presented below.

a. Disconnection of the indicated bond in **2** suggests that it can be produced from the vinyl iodide and the vinyl boronic ester shown. Note that the configuration of the C=C unit in each coupling partner is retained in the reaction.

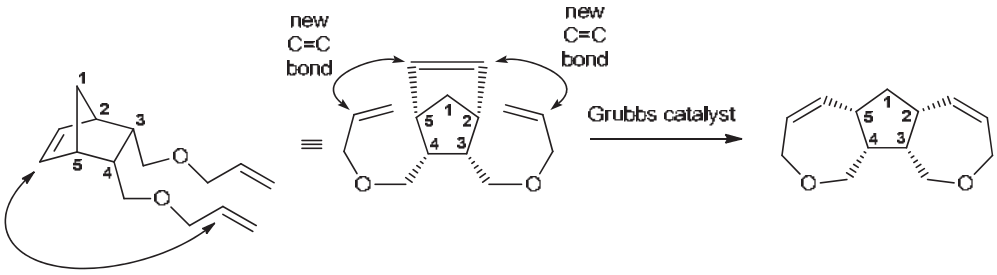
b. This tetraene intermediate can be produced via Stille coupling between **1** and the vinyl iodide shown. Again, the configuration of each coupling partner is retained in the product.



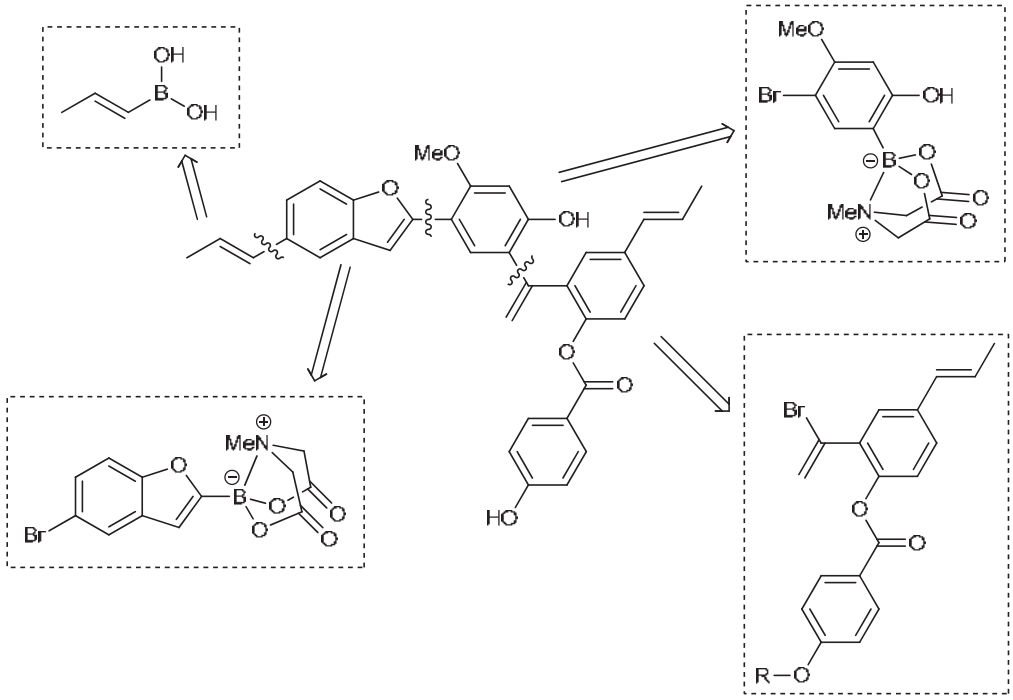
The forward scheme is presented below. Diene **1** reacts with the vinyl iodide in a palladium-catalyzed Stille reaction to afford the tetraene intermediate. Subsequent addition of the base CsF and a different vinyl iodide produces compound **2** via Suzuki coupling.



23.73. As described in the problem statement, olefin metathesis of this triene results in cleavage of the cyclic C=C unit and formation of two new C=C units, giving a product with two new seven-membered rings as part of a fused tricyclic system:

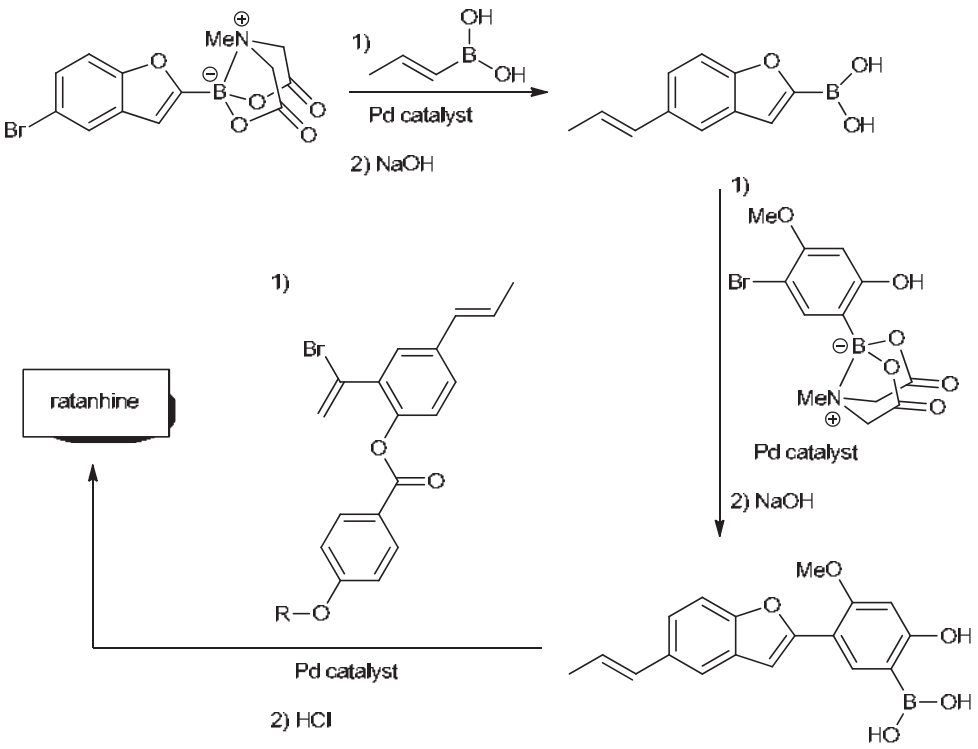


23.74. We first begin by taking inventory of the four building blocks shown. We are given a vinyl boronic acid, an aryl bromide, and two compounds which each contain both an aryl bromide and a MIDA boronate. The latter two compounds are designed to be used in iterative Suzuki coupling reactions. Next, consider the structure of ratanhine. The following illustration shows how each of the starting materials corresponds with a portion of the natural product, and the squiggly lines represent the bonds that are formed via Suzuki coupling.

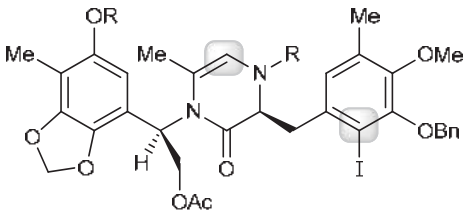


The forward reaction sequence is shown below. After the first Suzuki reaction, treatment with NaOH will reveal the boronic acid needed for the second Suzuki coupling. Likewise, after the second cross coupling, treatment with NaOH will reveal the final boronic acid. After the last Suzuki reaction, treatment with HCl cleaves the R group, giving ratanhine.

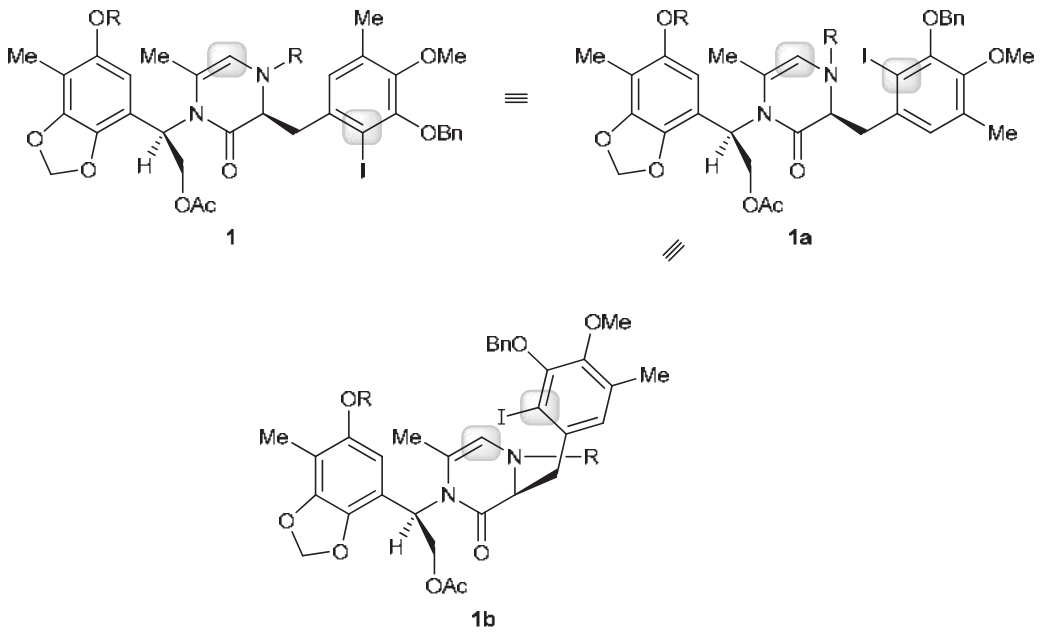
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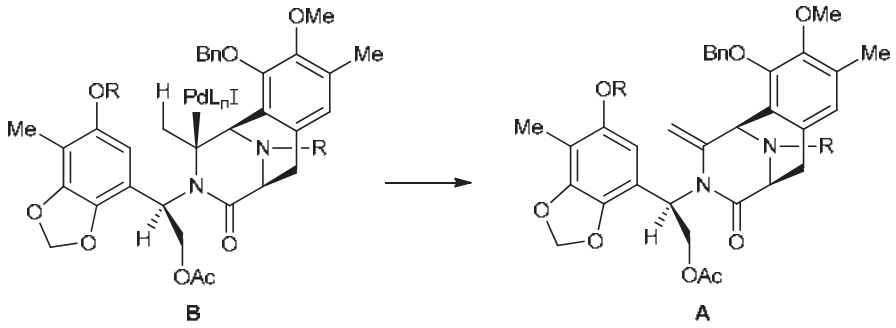
23.75. We begin by identifying the carbon atoms in compound **1** that will be joined via an intramolecular Heck reaction, highlighted here:



In order to draw the compound that is obtained when a new C–C bond is formed between these two locations, we must first redraw compound **1** so that these two centers are near each other. To do this, we first rotate the aryl group and redraw it in close proximity to the double bond. Due to the inherent stereochemistry already present in the molecule, the aryl group will be positioned above the plane of the alkene.

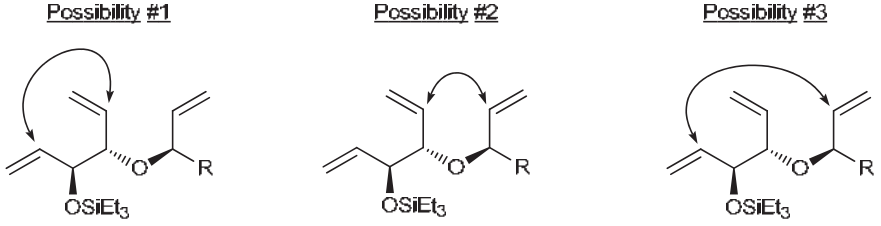


When the Pd catalyst inserts into the aryl iodide bond and then adds across the alkene in a *syn*-fashion, the new C-C bond is formed from the top face of the molecule, resulting in a *cis* junction for the newly formed 6-membered ring. The new C–Pd adduct (compound **B** below) cannot undergo a conformational change via C–C bond rotation. Therefore, the *syn*-reductive elimination can only occur at one possible site within the molecule with an accessible *syn* hydrogen atom *beta* to the Pd, resulting in compound **A**. The newly formed C=C bond is exocyclic to the 6-membered ring:

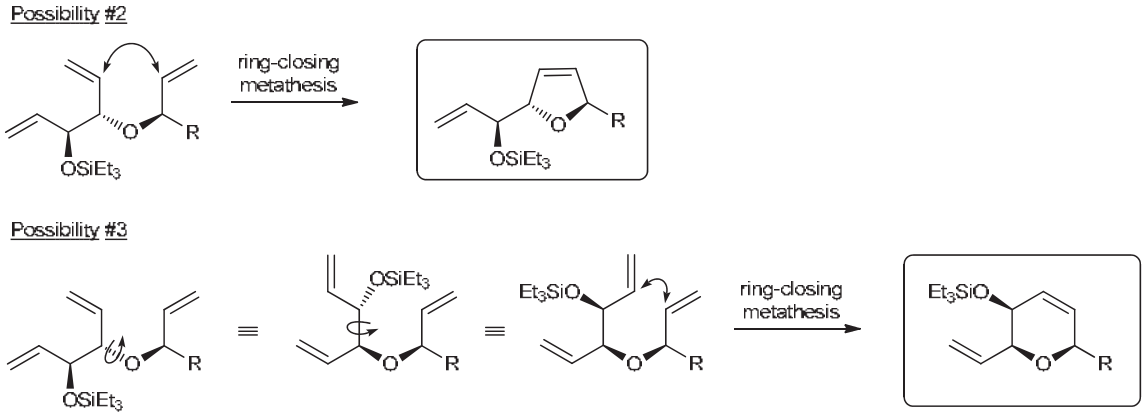


23.76.

(a) Compound **1** has three monosubstituted C=C units, giving rise to three possible ways in which ring-closing metathesis can occur:



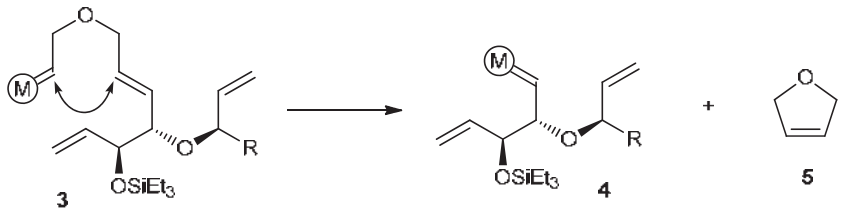
We can exclude the first possibility, because that would lead to a four-membered ring, and the problem statement indicates that a four-membered ring will not form when a five- or six-membered ring can form instead. Therefore, we consider only the latter two possibilities, which lead to a five-membered ring and a six-membered ring, respectively:



(b) When compound **2** is used instead, it reacts with the Grubbs catalyst to give intermediate **3**, which is then converted to intermediate **4**, as shown in the problem statement. Intermediate **4** will give rise to a five-membered cyclic ether. So this cyclic ether must be compound **A**.



The relay event is accompanied by the loss of compound **5** (via ring-closing metathesis) as shown:



Chapter 24
Carbohydrates

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 24. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- **Carbohydrates** are polyhydroxy _____ or ketones.
- Simple sugars are called _____ and are generally classified as **aldoses** and _____**.**
- For all **D sugars**, the chiral center farthest from the carbonyl group has the ___ configuration.
- Aldohexoses can form cyclic hemi_____ that exhibit a **pyranose** ring.
- Cyclization produces two stereoisomeric hemiacetals, called _____. The newly created chiral center is called the _____ **carbon.**
- In the **α anomer**, the hydroxyl group at the anomeric position is _____ to the CH_2OH group, while in the **β anomer**, the hydroxyl group is _____ to the CH_2OH group.
- Anomers equilibrate by a process called _____, which is catalyzed by either _____ or _____.
- Some carbohydrates, such as D-fructose, can also form five-membered rings, called _____ rings.
- Monosaccharides are converted into their ester derivatives when treated with excess _____.
- Monosaccharides are converted into their ether derivatives when treated with excess _____ and silver oxide.
- When treated with an alcohol under acid-catalyzed conditions, monosaccharides are converted into acetals, called _____. Both anomers are formed.
- Upon treatment with sodium borohydride an aldose or ketose can be reduced to yield an _____.
- When treated with a suitable oxidizing agent, an aldose can be oxidized to yield an _____.
- When treated with HNO_3 , an aldose is oxidized to give a dicarboxylic acid called an _____.
- D-Glucose and D-mannose are **epimers** and are interconverted under strongly _____ conditions.
- The **Kiliani-Fischer synthesis** can be used to lengthen the chain of an _____.
- The **Wohl degradation** can be used to shorten the chain of an _____.
- _____ are comprised of two monosaccharide units, joined together via a glycosidic linkage.
- **Polysaccharides** are polymers consisting of repeating monosaccharide units linked by _____ bonds.
- When treated with an _____ in the presence of an acid catalyst, monosaccharides are converted into their corresponding **N-glycosides**.

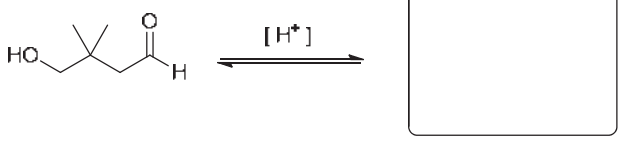
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Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 24. The answers appear in the section entitled *SkillBuilder Review*.

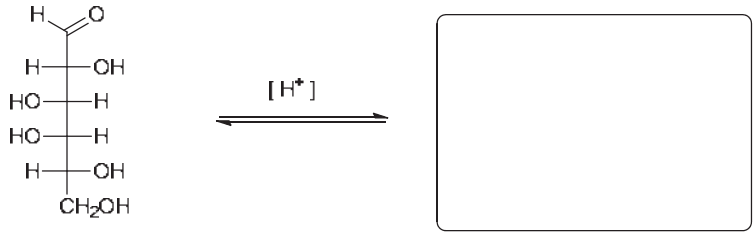
24.1 Drawing the Cyclic Hemiacetal of a Hydroxyaldehyde

DRAW THE CYCLIC HEMIACETAL THAT IS FORMED WHEN THE FOLLOWING HYDROXYALDEHYDE UNDERGOES CYCLIZATION UNDER ACIDIC CONDITIONS.



24.2: Drawing a Haworth Projection of an Aldohexose in the Pyranose Form

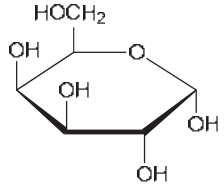
DRAW A HAWORTH PROJECTION OF α-D-GALACTOPYRANOSE.



D-GALACTOSE

24.3: Drawing the More Stable Chair Conformation of a Pyranose Ring

DRAW THE MORE STABLE CHAIR CONFORMATION OF α-D-GALACTOPYRANOSE.

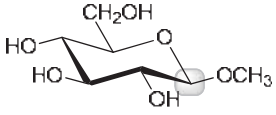


α-D-GALACTOPYRANOSE

MORE STABLE CHAIR CONFORMATION

24.4 Identifying a Reducing Sugar

STEP 1 *- IDENTIFY THE _____ POSITION.*

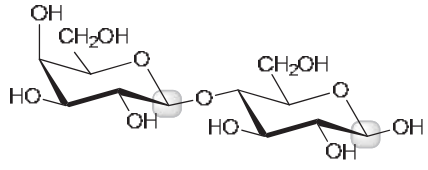


STEP 2 *- DETERMINE IF THE GROUP ATTACHED TO THE ANOMERIC POSITION IS A _____ GROUP OR _____ GROUP.*

- IF _____ GROUP, THEN THE COMPOUND IS A REDUCING SUGAR
- IF _____ GROUP, THEN THE COMPOUND IS NOT A REDUCING SUGAR.

24.5 Determining Whether a Disaccharide Is a Reducing Sugar

STEP 1 *- IDENTIFY THE _____ POSITIONS.*



STEP 2 *- DETERMINE IF THE GROUPS ATTACHED TO THE ANOMERIC POSITIONS ARE HYDROXY GROUPS OR ALKOXY GROUPS.*

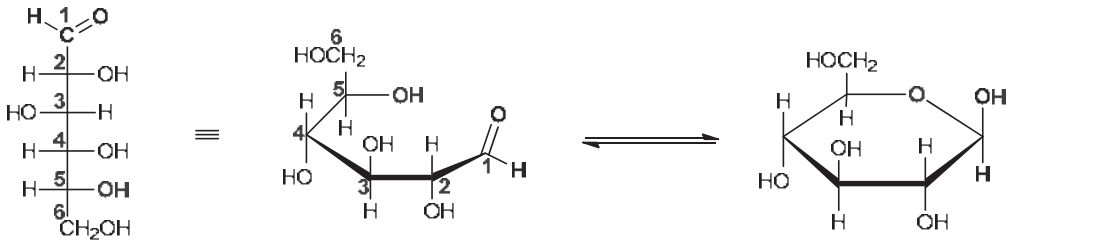
- IF ONE IS A _____ GROUP. THEN THE COMPOUND IS A REDUCING SUGAR.
- IF NEITHER ARE _____ GROUPS. THEN THE COMPOUND IS NOT A REDUCING SUGAR.

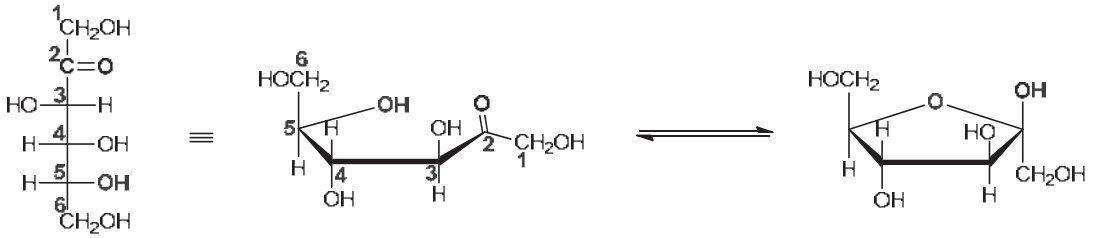
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Review of Reactions

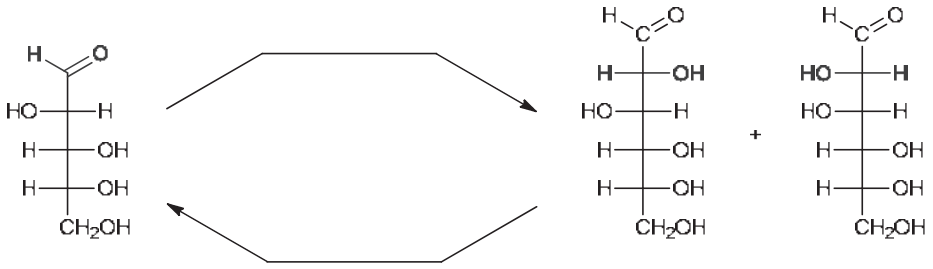
Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 24. The answers appear in the section entitled *Review of Reactions*.

Hemiacetal Formation

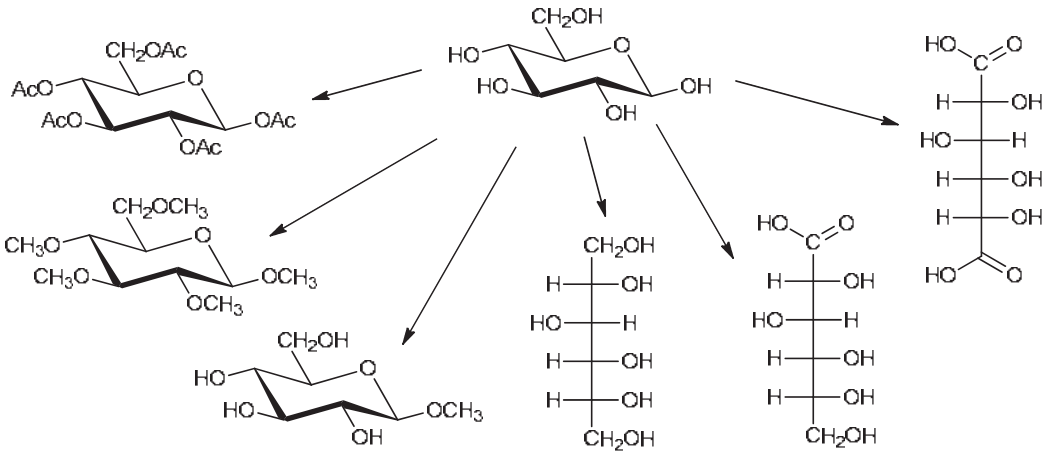




Chain Lengthening and Chain Shortening



Reactions of Monosaccharides



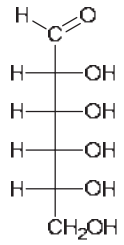
Solutions

24.1.
(a) This compound is an aldehyde and it is comprised of six carbon atoms, so it is an aldohexose.
(b) This compound is an aldehyde and it is comprised of five carbon atoms, so it is an aldopentose.
(c) This compound is a ketone and it is comprised of five carbon atoms, so it is a ketopentose.
(d) This compound is an aldehyde and it is comprised of four carbon atoms, so it is an aldotetrose.
(e) This compound is a ketone and it is comprised of six carbon atoms, so it is a ketohexose.

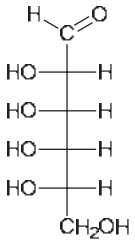
24.2. Both are hexoses so both have the molecular formula ($C_6H_{12}O_6$). Although they have the same molecular formula, they have different constitution – one is an aldehyde and the other is a ketone. Therefore, they are constitutional isomers.

24.3. All are D sugars except for (b), which is an L sugar. The configuration of each chiral center is shown here:
(a) 2*S*, 3*S*, 4*R*, 5*R*
(b) 2*R*, 3*S*, 4*S*
(c) 3*R*, 4*R*
(d) 2*S*, 3*R*
(e) 3*S*, 4*S*, 5*R*
Pay special attention to the following trend: The configuration of each chiral center is *R* when the OH group is on the right side of the Fischer projection, and the configuration is *S* when the OH group is on the left side.

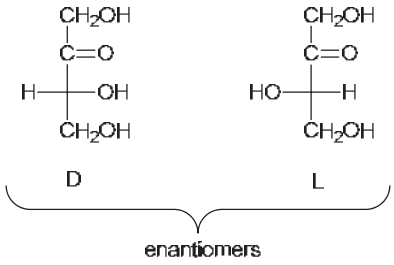
24.4.
(a) As seen in the solution to the previous problem, the *R* configuration is characterized by an OH group on the right side of the Fischer projection. D-Allose has all of the OH groups on the right side:



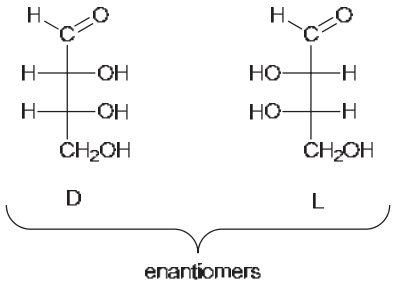
(b) L-Allose is the enantiomer of D-allose, so all of the OH groups are on the right side of the Fischer projection:

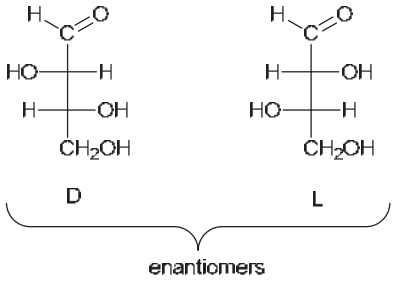


24.5. A ketotetrose has four carbon atoms and a ketone group, leaving only one chiral center, giving the following two enantiomers:

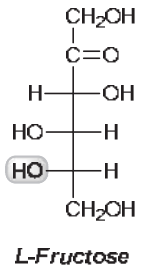


24.6. An aldotetraose has four carbon atoms and an aldehyde group. As such, there are two chiral centers, giving the following four stereoisomers:

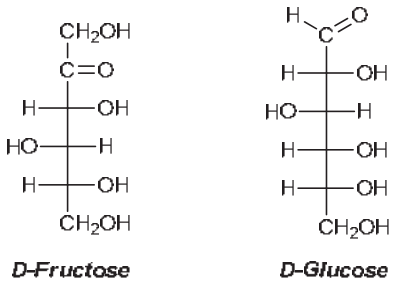




24.7. The enantiomer of D-fructose is L-fructose, in which all of the chiral centers have opposite configuration (as compared with D-fructose):

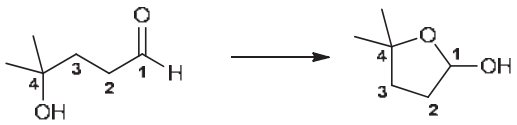


24.8. Both D-fructose and D-glucose have the molecular formula ($C_6H_{12}O_6$). However, they have different constitution – one is a ketone, and the other is an aldehyde. Therefore, they are constitutional isomers.

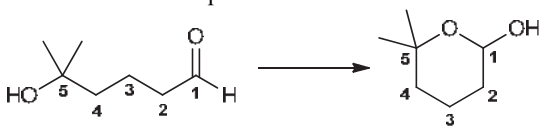


24.9.

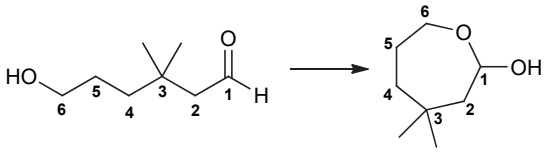
(a) We use a numbering system to determine the size of the ring that is formed. Four carbon atoms and one oxygen atom are incorporated into a five-membered ring. There are two methyl groups at C4, which must be drawn in the product:



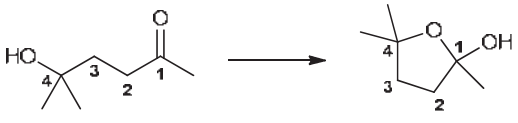
(b) We use a numbering system to determine the size of the ring that is formed. Five carbon atoms and one oxygen atom are incorporated into a six-membered ring, as shown. There are two methyl groups at C5, which must be drawn in the product:



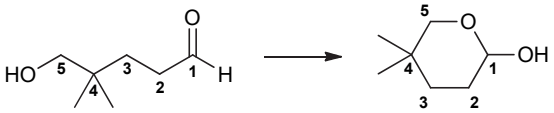
(c) We use a numbering system to determine the size of the ring that is formed. Six carbon atoms and one oxygen atom are incorporated into a seven-membered ring, as shown. There are two methyl groups at C3, which must be drawn in the product:



(d) We use a numbering system to determine the size of the ring that is formed. Four carbon atoms and one oxygen atom are incorporated into a five-membered ring, as shown. There are two methyl groups at C4 of the ring and one methyl group at C1 of the ring, which must be drawn in the product:

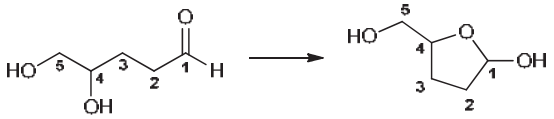


24.10. We must use a numbering system, just as we did in the previous problem. There are two methyl groups at C4, which must be drawn in the starting material:

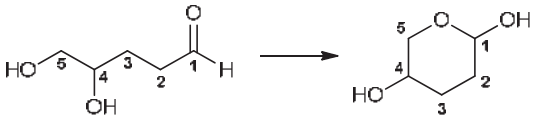


24.11.

(a) The carbonyl group can be attacked by the OH group that is connected to C4, giving a five-membered ring;



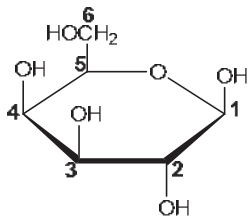
or the carbonyl group can be attacked by the OH group that is connected to C5, giving a six-membered ring:



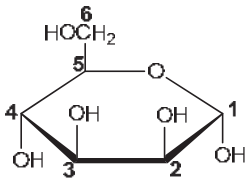
(b) The six-membered ring is expected to predominate because it has less ring strain than a five-membered ring.

24.12.

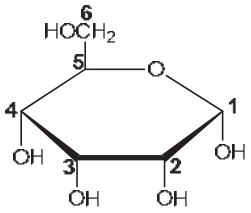
(a) We begin by drawing the skeleton of the Haworth projection. Then, we draw the CH_2OH group (at C6) pointing up. The anomeric OH group is then drawn pointing up (the β anomer). Finally, the remaining groups are drawn). All OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection (and all OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection).



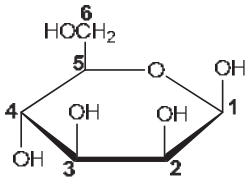
(b) We begin by drawing the skeleton of the Haworth projection. Then, we draw the CH_2OH group (at C6) pointing up. The anomeric OH group is then drawn pointing down (the α anomer). Finally, the remaining groups are drawn). All OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection (and all OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection).



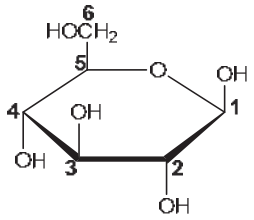
(c) We begin by drawing the skeleton of the Haworth projection. Then, we draw the CH_2OH group (at C6) pointing up. The anomeric OH group is then drawn pointing down (the α anomer). Finally, the remaining groups are drawn). All OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection (and all OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection).



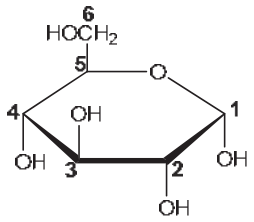
(d) We begin by drawing the skeleton of the Haworth projection. Then, we draw the CH_2OH group (at C6) pointing up. The anomeric OH group is then drawn pointing up (the β anomer). Finally, the remaining groups are drawn). All OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection (and all OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection).



(e) We begin by drawing the skeleton of the Haworth projection. Then, we draw the CH_2OH group (at C6) pointing up. The anomeric OH group is then drawn pointing up (the β anomer). Finally, the remaining groups are drawn). All OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection (and all OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection).

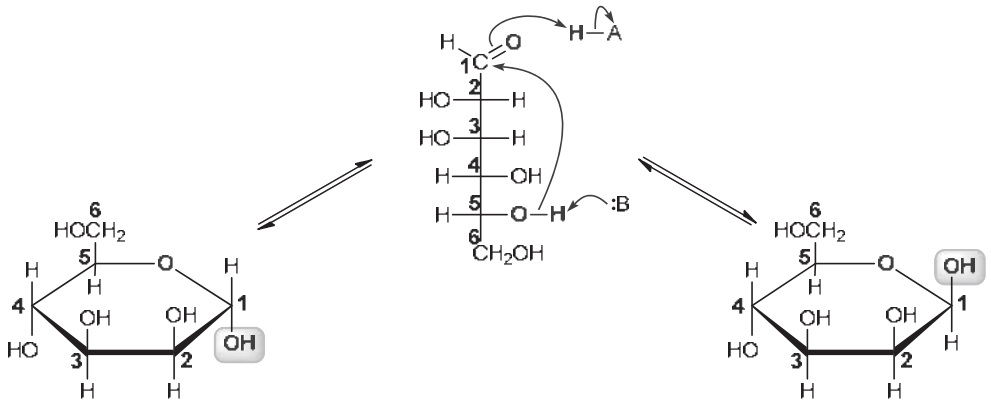


(f) We begin by drawing the skeleton of the Haworth projection. Then, we draw the CH_2OH group (at C6) pointing up. The anomeric OH group is then drawn pointing down (the α anomer). Finally, the remaining groups are drawn). All OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection (and all OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection).



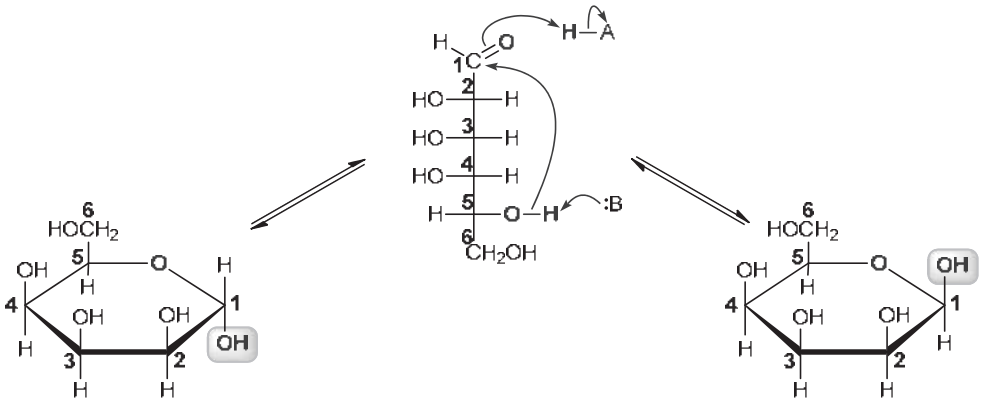
24.13. This structure represents the β anomer of the cyclic form of D-galactose and is therefore called β-D-galactopyranose.

24.14. The two pyranose forms are in equilibrium with each other, via the open-chain form, as shown:



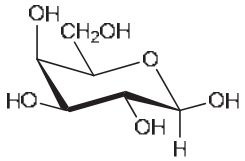
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24.15. The two pyranose forms are in equilibrium with each other, via the open-chain form, as shown:

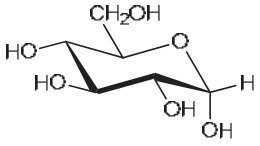


24.16.

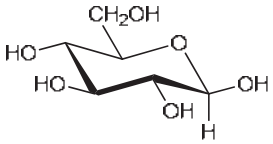
(a) The skeleton of the chair is drawn with an oxygen atom in the upper back-right corner. Each substituent is then labeled as "up" or "down" and placed on the chair accordingly. The anomeric OH group is drawn pointing up, indicating the β anomer. In this chair conformation, most of the substituents occupy equatorial positions, so this is the more stable chair conformation of β-D-galactopyranose.



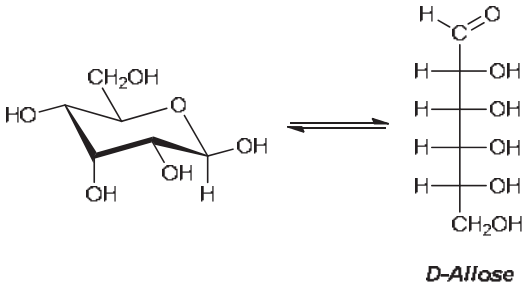
(b) The skeleton of the chair is drawn with an oxygen atom in the upper back-right corner. Each substituent is then labeled as "up" or "down" and placed on the chair accordingly. The anomeric OH group is drawn pointing down, indicating the α anomer. In this chair conformation, most of the substituents occupy equatorial positions, so this is the more stable chair conformation of α-D-glucopyranose.



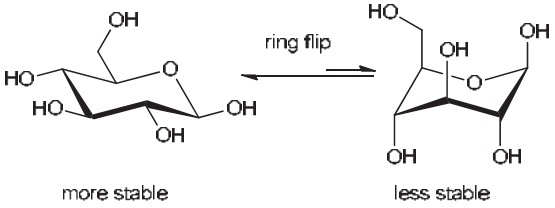
(c) The skeleton of the chair is drawn with an oxygen atom in the upper back-right corner. Each substituent is then labeled as "up" or "down" and placed on the chair accordingly. The anomeric OH group is drawn pointing up, indicating the β anomer. In this chair conformation, most of the substituents occupy equatorial positions, so this is the more stable chair conformation of β-D-glucopyranose.



24.17. The anomeric position becomes an aldehyde group in the open-chain form. The OH group at C5 (of the open-chain form) must be pointing to the right, because this is a D sugar (CH_2OH is "up" in the chair conformation). The remaining three groups (at C2, C3 and C4) are all pointing "down", so they must be on the right side of the Fischer projection of the open-chain form. This structure represents D-allose.



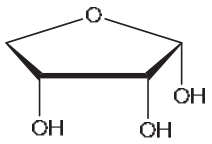
24.18. Both chair conformations of β-D-glucopyranose are shown below. The less stable conformation is the one in which all substituents occupy axial positions.



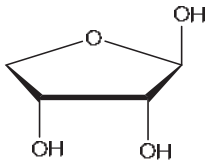
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24.19.

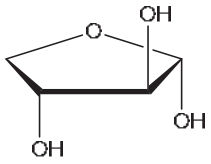
(a) The anomeric OH group is drawn pointing down (thus, the α anomer). The remaining two OH groups (at C2 and C3) are both on the right side of the Fischer projection of D-erythrose, so both OH groups are both drawn pointing down in the Haworth projection.



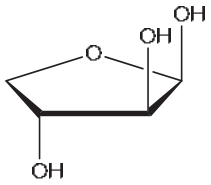
(b) The anomeric OH group is drawn pointing up (thus, the β anomer). The remaining two OH groups (at C2 and C3) are both on the right side of the Fischer projection of D-erythrose, so both OH groups are both drawn pointing down in the Haworth projection.



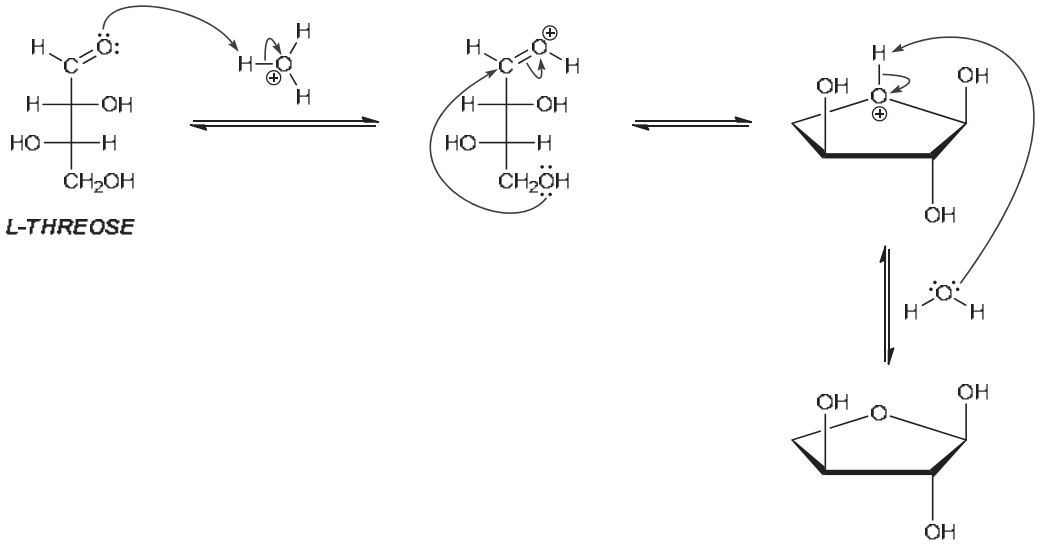
(c) The anomeric OH group is drawn pointing down (thus, the α anomer). The OH group on the left side of the Fischer projection (at C2 of D-threose) is drawn pointing up in the Haworth projection (at C2). Similarly, the OH group on the right side of the Fischer projection (at C3 of D-threose) is drawn pointing down in the Haworth projection (at C3).



(d) The anomeric OH group is drawn pointing up (thus, the β anomer). The OH group on the left side of the Fischer projection (at C2 of D-threose) is drawn pointing up in the Haworth projection (at C2). Similarly, the OH group on the right side of the Fischer projection (at C3 of D-threose) is drawn pointing down in the Haworth projection (at C3).

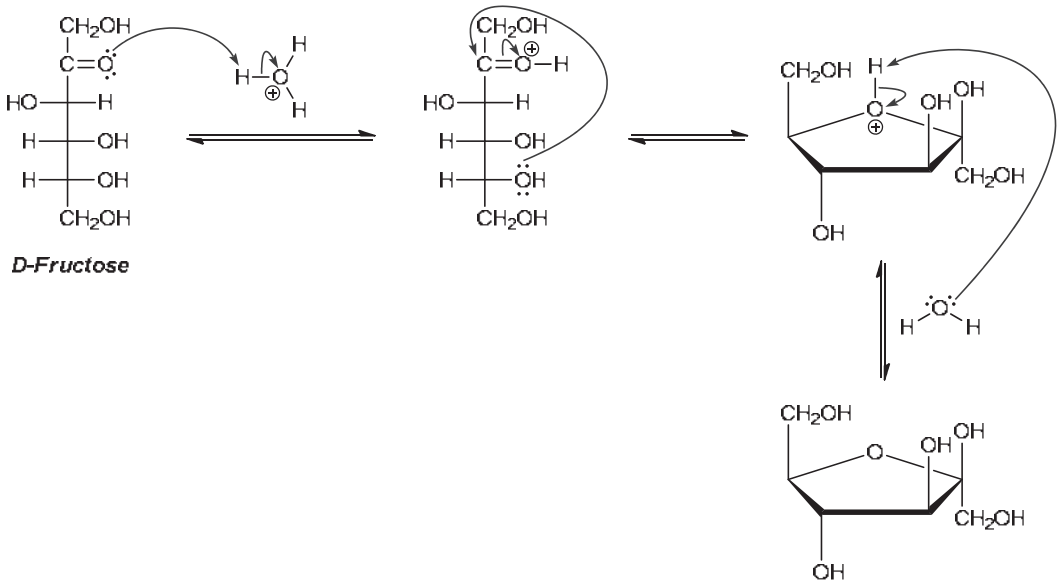


24.20. The carbonyl group is first protonated, thereby rendering it more electrophilic and more susceptible to nucleophilic attack by one of the OH groups. The OH group at C4 will attack the protonated carbonyl group to generate a furanose (five-membered) ring. Deprotonation (with water functioning as a base) gives the product, as shown.

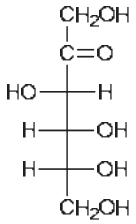


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24.21. The carbonyl group is first protonated, thereby rendering it more electrophilic and more susceptible to nucleophilic attack by one of the OH groups. The OH group at C5 will attack the protonated carbonyl group to generate a furanose (five-membered) ring. Deprotonation (with water functioning as a base) gives the product, as shown.

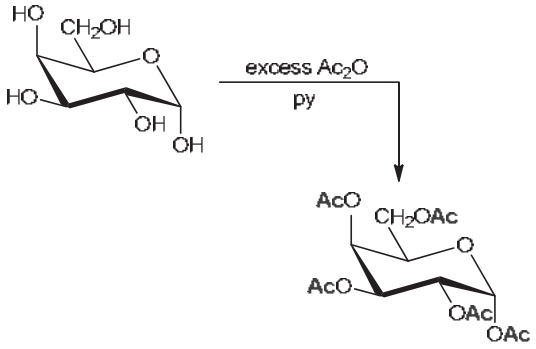


24.22. The name (α-D-fructopyranose) indicates that the open chain form is D-fructose, shown here:

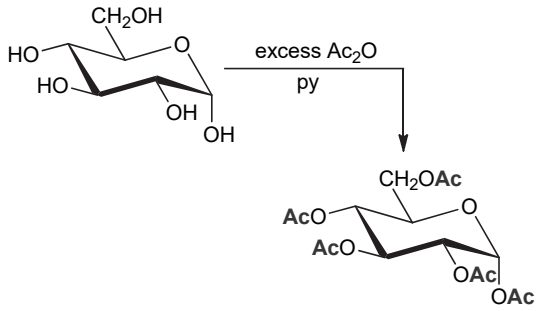


24.23.

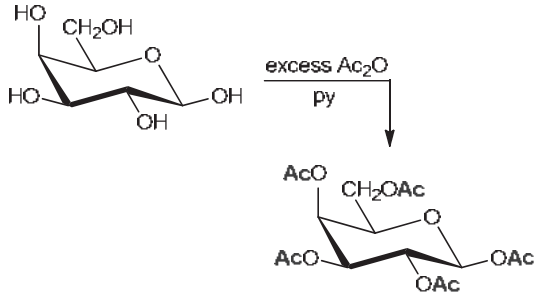
(a) Upon treatment with excess acetic anhydride and pyridine, all of the OH groups undergo acetylation, as shown:



(b) Upon treatment with excess acetic anhydride and pyridine, all of the OH groups undergo acetylation, as shown:



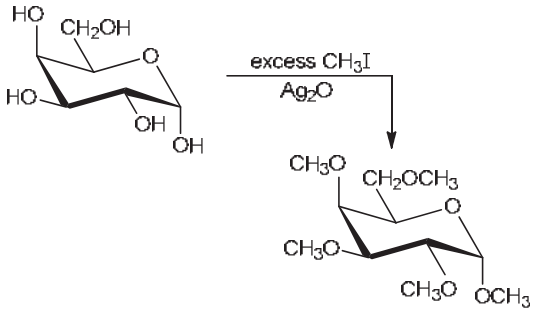
(c) Upon treatment with excess acetic anhydride and pyridine, all of the OH groups undergo acetylation, as shown:



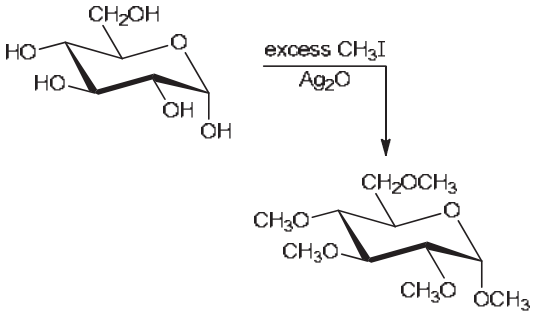
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24.24.

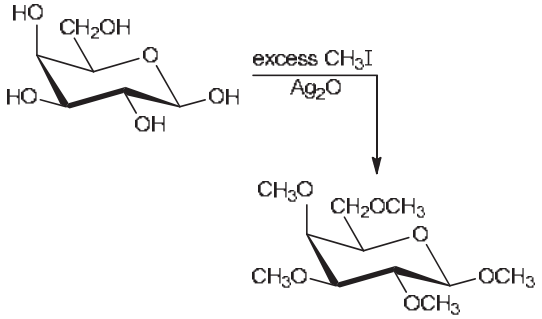
(a) Upon treatment with excess methyl iodide in the presence of silver oxide, all of the OH groups are converted into methoxy groups, as shown:



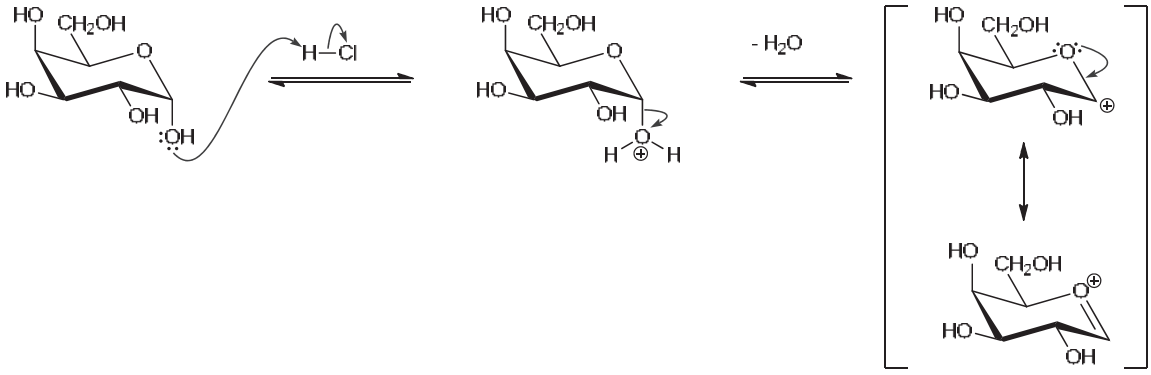
(b) Upon treatment with excess methyl iodide in the presence of silver oxide, all of the OH groups are converted into methoxy groups, as shown:



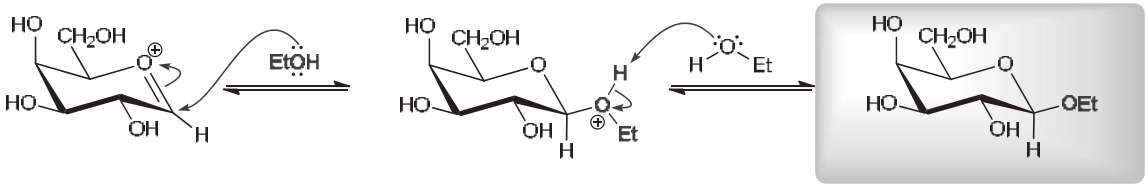
(c) Upon treatment with excess methyl iodide in the presence of silver oxide, all of the OH groups are converted into methoxy groups, as shown:



24.25. Under acidic conditions, the anomeric OH group can be protonated, giving an excellent leaving group (water). Loss of the leaving group generates a resonance-stabilized cation intermediate.

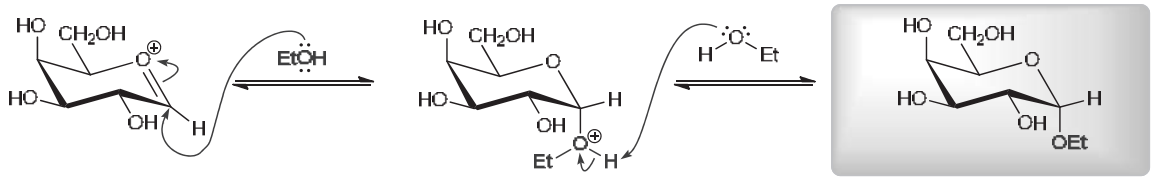


This intermediate can then be attacked by ethanol, giving an oxonium ion, which is then deprotonated to give an acetal:

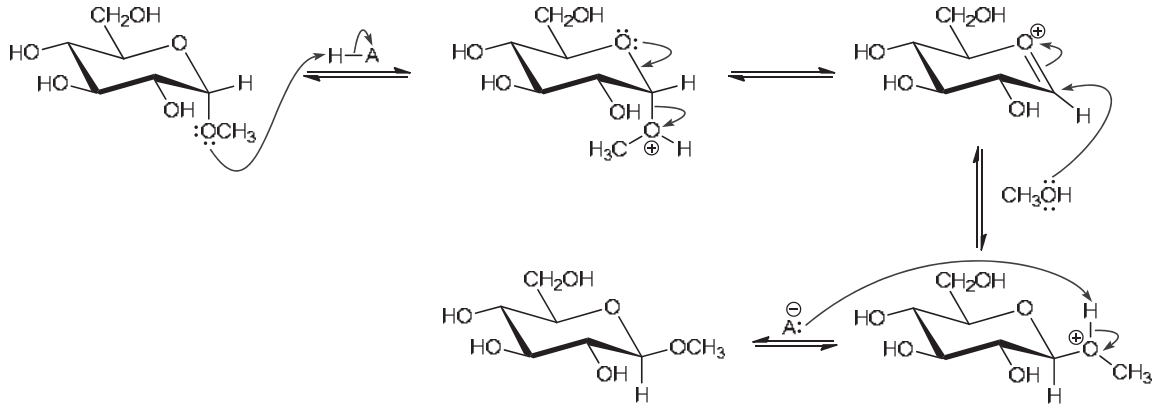


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Notice that ethanol is shown to attack from above, but it can also attack from below, giving the following acetal:

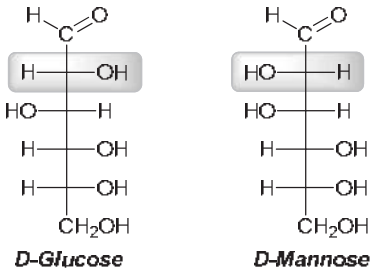


24.26. Under acidic conditions, the anomeric methoxy group can be protonated, giving an excellent leaving group (methanol). Loss of the leaving group generates a resonance-stabilized cation intermediate (resonance structures not shown) which can then be attacked by methanol. This attack can occur from either above or from below (as seen in the previous problem) giving a mixture of both anomers. In the last step of the mechanism, the oxonium ion is then deprotonated:

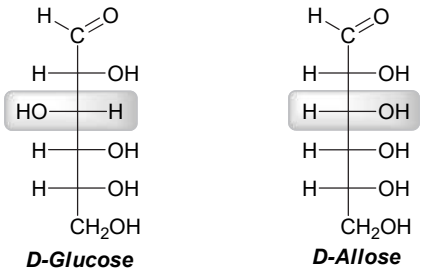


24.27.

(a) D-Mannose is epimeric with D-glucose at C2, as shown:

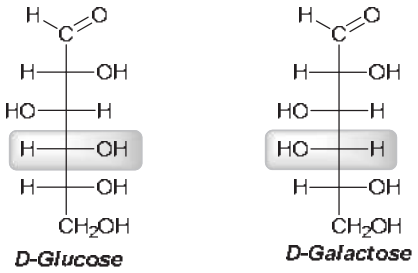


(b) D-Allose is epimeric with D-glucose at C3, as shown:

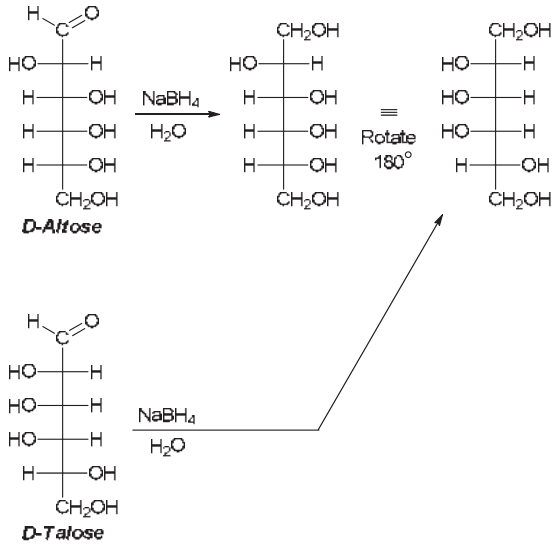


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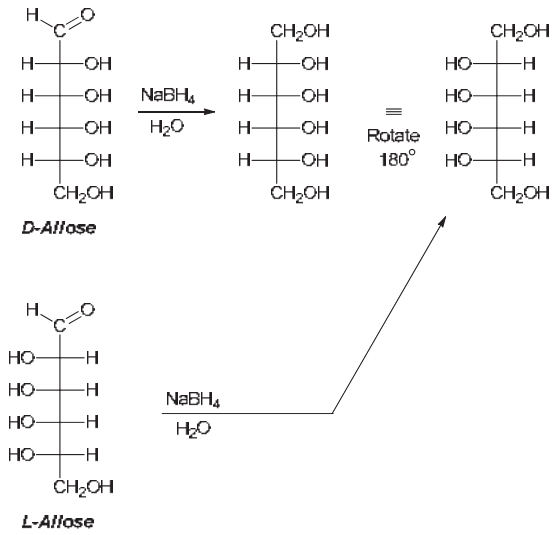
(c) D-Galactose is epimeric with D-glucose at C4, as shown:



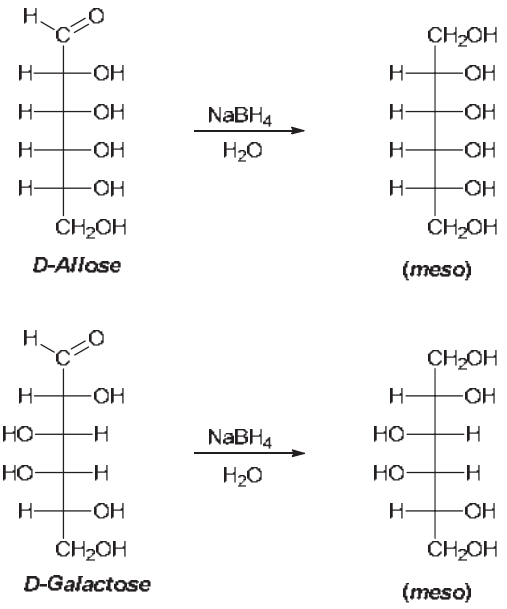
24.28. Reduction of the carbonyl group generates the same product in each case. This can be seen by rotating one of the products by 180º, as shown:



24.29. Reduction of the carbonyl group generates the same *meso* product in each case. This can be seen by rotating one of the products by 180º, as shown:



24.30. Reduction of either D-allose or D-galactose will produce a *meso* alditol. *Meso* compounds are optically inactive:



24.31.

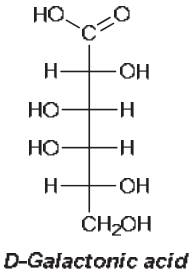
(a) The anomeric position is occupied by a methoxy group. Therefore, this compound is an acetal and is not a reducing sugar.

(b) The anomeric position is occupied by an OH group. Therefore, this compound is a reducing sugar.

(c) The anomeric position is occupied by an OH group. Therefore, this compound is a reducing sugar.

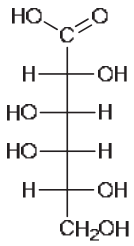
24.32.

(a) The open chain form of this compound is D-galactose, which is oxidized under these conditions to give the following aldonic acid:



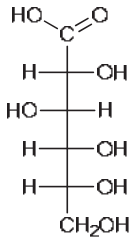
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(b) The open chain form of this compound is D-galactose, which is oxidized under these conditions to give the following aldonic acid:



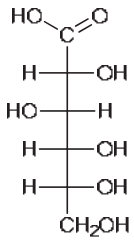
D-Galactonic acid

(c) The open chain form of this compound is D-glucose, which is oxidized under these conditions to give the following aldonic acid:



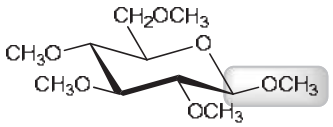
D-Gluconic acid

(d) The open chain form of this compound is D-glucose, which is oxidized under these conditions to give the following aldonic acid:



D-Gluconic acid

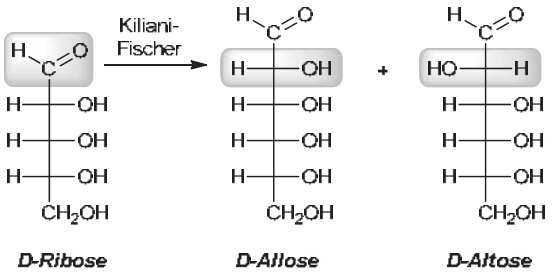
24.33. This compound will not be a reducing sugar because the anomeric position is an acetal group.



β-D-Glucopyranose pentamethyl ether

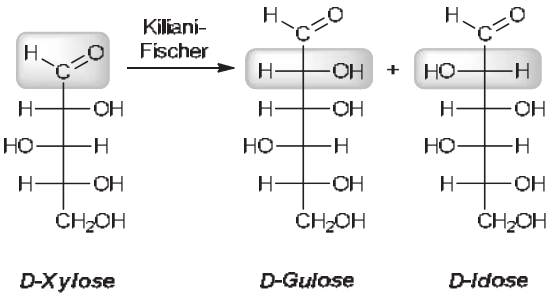
24.34.

(a) In a Kiliani-Fischer synthesis, the chain is lengthened, with C1 becoming C2 in the product. Both possible configurations of the C2 position are obtained, giving the following epimers:



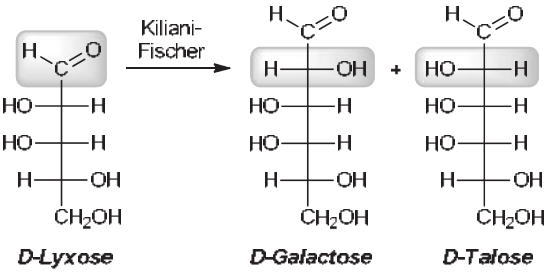
D-Ribose *D-Allose* *D-Altose*

(b) In a Kiliani-Fischer synthesis, the chain is lengthened, with C1 becoming C2 in the product. Both possible configurations of the C2 position are obtained, giving the following epimers:



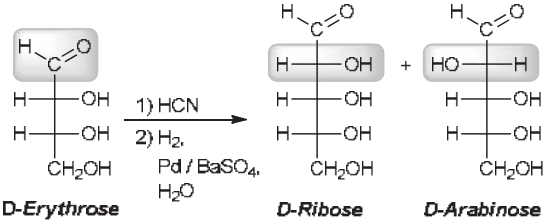
D-Xylose *D-Gulose* *D-Idose*

(c) In a Kiliani-Fischer synthesis, the chain is lengthened, with C1 becoming C2 in the product. Both possible configurations of the C2 position are obtained, giving the following epimers:



D-Lyxose *D-Galactose* *D-Talose*

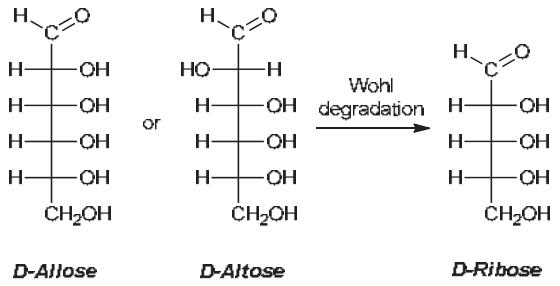
24.35. Conversion of D-erythrose (which has four carbon atoms) to D-ribose (which has five carbon atoms) requires a chain-lengthening process. This process will produce D-ribose together with its C2 epimer, D-arabinose, as shown:



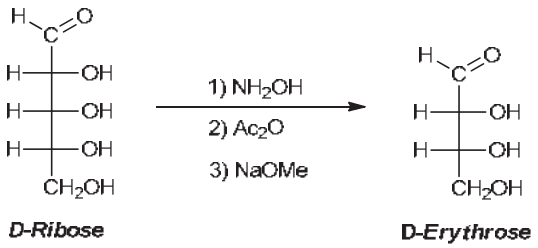
D-Erythrose *D-Ribose* *D-Arabinose*

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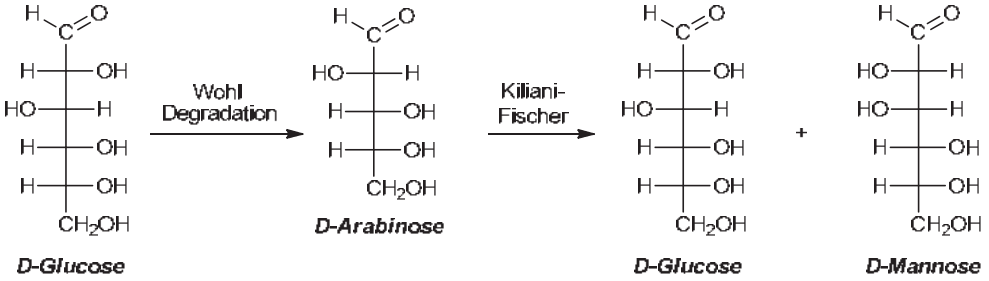
24.36. A Wohl degradation involves the removal of a carbon atom from an aldose. As shown below, D-ribose can be made from either D-allose or D-altose:



24.37. A Wohl degradation will remove a carbon atom from an aldose. This method can be used to convert D-ribose into D-erythrose, as shown:

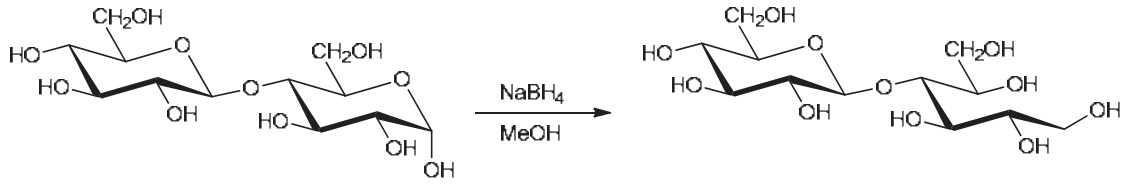


24.38. A Wohl degradation will remove a carbon atom from D-glucose. This carbon atom is then restored with a Kiliani-Fischer synthesis, giving D-glucose and its C2 epimer, D-mannose.

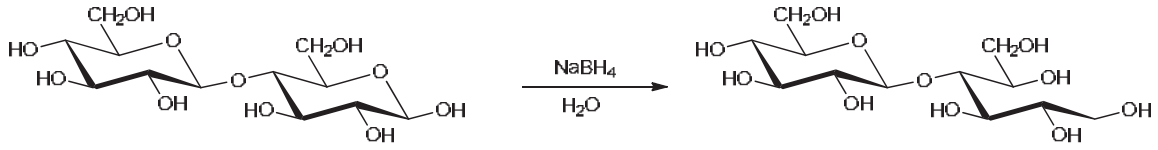


24.39.
(a) One of the anomeric positions (bottom right) bears an OH group. Therefore, this disaccharide is a reducing sugar.
(b) Both anomeric positions bear acetal groups, so this disaccharide is not a reducing sugar.
(c) Both anomeric positions bear acetal groups, so this disaccharide is not a reducing sugar.

24.40. One of the rings (bottom right) has an anomeric OH group. As such, it is in equilibrium with the open chain form, which is reduced in the presence of sodium borohydride, as shown:

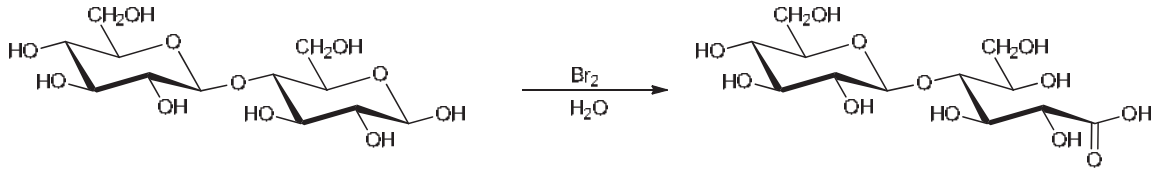


24.41.
(a) One of the rings (bottom right) has an anomeric OH group. As such, it is in equilibrium with the open chain form, which is reduced in the presence of sodium borohydride, as shown:

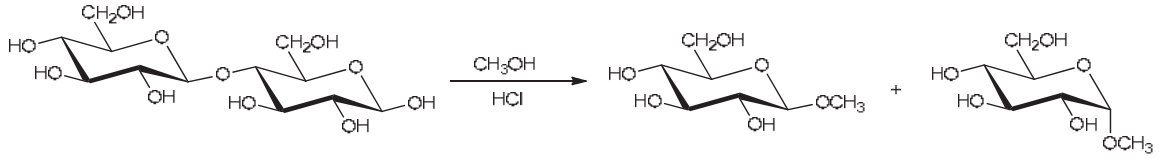


(b) One of the rings (bottom right) has an anomeric OH group, and is therefore in equilibrium with the open chain form, which is oxidized in the presence of Br_2 and H_2O (at pH = 6), as shown:

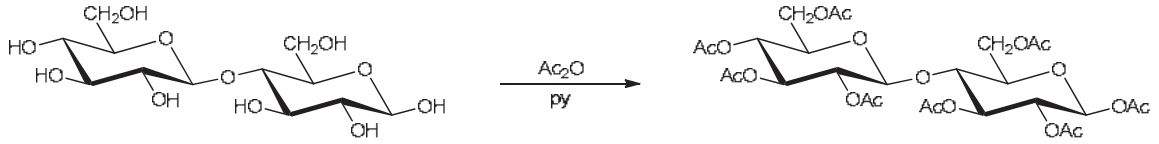
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(c) One of the rings (bottom right) has an anomeric OH group. Upon treatment with methanol in acidic conditions, this OH group undergoes methylation, giving a methoxy group, as shown:



(d) Upon treatment with excess acetic anhydride and pyridine, each of the OH groups undergoes acetylation, as shown:



24.42.
(a) The OH group connected to C3 is pointing to the right, so this is a D-sugar. The functional group at C1 is an aldehyde group, so the compound is an aldose. And finally, the compound has four carbon atoms, so it is a tetrose. In summary, this compound is a D-aldotetrose.

(b) The OH group connected to C4 is pointing to the left, so this is an L-sugar. The functional group at C1 is an aldehyde group, so the compound is an aldose. And finally, the compound has five carbon atoms, so it is a pentose. In summary, this compound is an L-aldopentose.

(c) The OH group connected to C4 is pointing to the right, so this is a D-sugar. The functional group at C1 is an aldehyde group, so the compound is an aldose. And finally, the compound has five carbon atoms, so it is a pentose. In summary, this compound is a D-aldopentose.

(d) The OH group connected to C5 is pointing to the right, so this is a D-sugar. The functional group at C1 is an aldehyde group, so the compound is an aldose. And finally, the compound has six carbon atoms, so it is a hexose. In summary, this compound is a D-aldohexose.

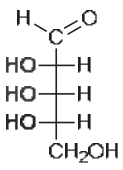
(e) The OH group connected to C4 is pointing to the right, so this is a D-sugar. The functional group at C2 is a ketone group, so the compound is a ketose. And finally, the compound has five carbon atoms, so it is a pentose. In summary, this compound is a D-ketopentose

24.43. D-Glyceraldehyde has the *R* configuration, while L-glyceraldehyde has the *S* configuration. Therefore:

(a) The chiral center has the *R* configuration. This compound is D-glyceraldehyde.
(b) The chiral center has the *S* configuration. This compound is L-glyceraldehyde.
(c) The chiral center has the *R* configuration. This compound is D-glyceraldehyde.
(d) The chiral center has the *S* configuration. This compound is L-glyceraldehyde.

24.44.
(a) This compound is D-Glucose (see Figure 24.5).
(b) This compound is D-Mannose (see Figure 24.5).
(c) This compound is D- Galactose (see Figure 24.5).
(d) This compound is L-Glucose (see Figure 24.5).

24.45.
(a) D-Ribose is epimeric with D-arabinose at C2.
(b) D-Arabinose is epimeric with D-lyxose at C2.
(c) The enantiomer of D-ribose has the opposite configuration (*S*, rather than *R*) for all three chiral centers:



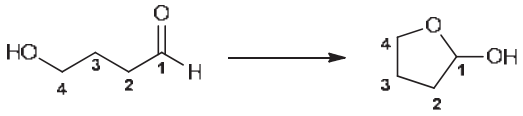
L-Ribose

(d) They are the same compound. That is, the enantiomer of D-arabinose is L-arabinose, which is also the C2 epimer of L-ribose.

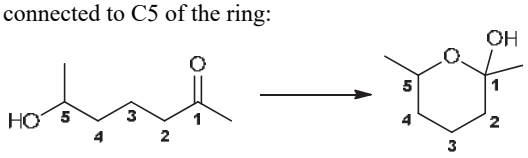
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(e) They are diastereomers because they are stereoisomers that are not mirror images.

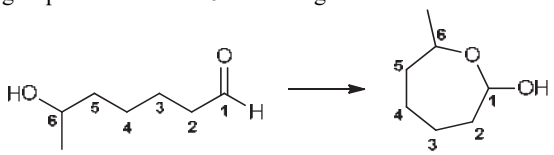
24.46.
(a) We use a numbering system to determine the size of the ring that is formed. The carbonyl group can be attacked by the OH group that is connected to C4, giving a five-membered ring:



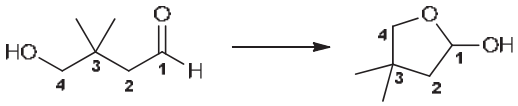
(b) We use a numbering system to determine the size of the ring that is formed. The carbonyl group can be attacked by the OH group that is connected to C5, giving a six-membered ring. Notice that there is a methyl group connected to C1 of the ring, as well as a methyl group connected to C5 of the ring:



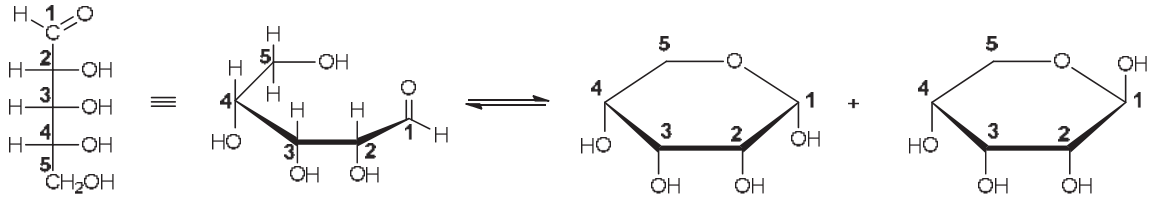
(c) We use a numbering system to determine the size of the ring that is formed. The carbonyl group can be attacked by the OH group that is connected to C6, giving a seven-membered ring. Notice that there is a methyl group connected to C6 of the ring:



24.47. We must use a numbering system, just as we did in the previous problem. There are two methyl groups at C3, which must be drawn in the starting material:

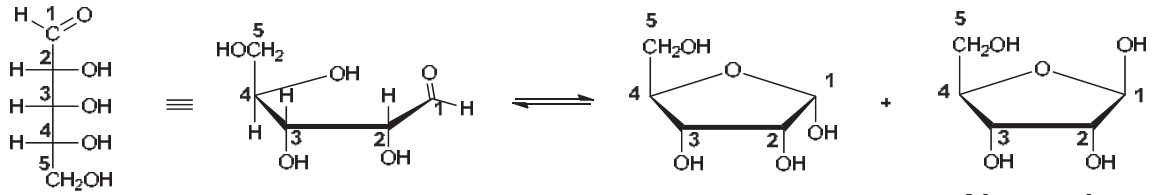


24.48.
(a) The following are the two pyranose forms (α and β anomers) of D-ribose:



D-ribose ***α pyranose ring*** ***β pyranose ring***

(b) The following are the two furanose forms (α and β anomers) of D-ribose:

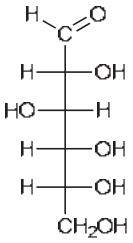


D-ribose ***α furanose ring*** ***β furanose ring***

24.49.
(a) These compounds are diastereomers that differ from each other in the configuration of only one chiral center. Therefore, they are epimers.
(b) These compounds are stereoisomers that are not mirror images of one another. Therefore, they are diastereomers.
(c) These compounds are non-superimposable mirror images of one another. Therefore, they are enantiomers.
(d) These structures are two different representations of the same compound (β-D-glucopyranose).

24.50. Upon treatment with aqueous acid, the anomeric methoxy group is replaced with an anomeric hydroxy group. The open chain form of the resulting cyclic hemiacetal is D-glucose.

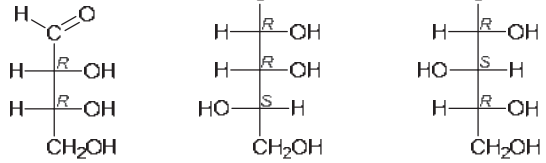
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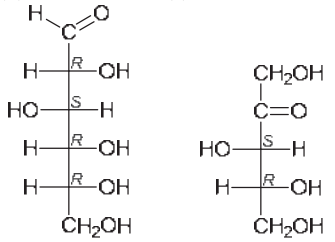
D-Glucose

24.51. To assign the configuration of each chiral center, we can use the rule of thumb that was pointed out in the solution to Problem **24.3**. Specifically, an OH on the right side of the Fischer projection indicates the *R* configuration, while an OH on the left side of the Fischer projection indicates the *S* configuration:

(a) **(b)** **(c)**

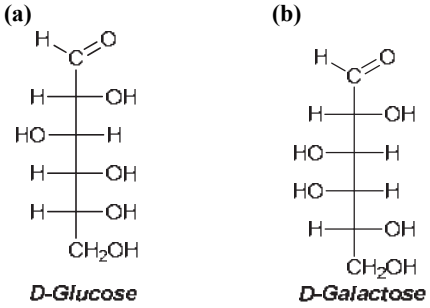


(d) **(e)**



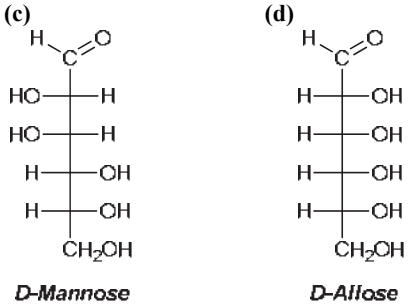
24.52. The structures below can be found in Figure 24.5:

(a) **(b)**



D-Glucose *D-Galactose*

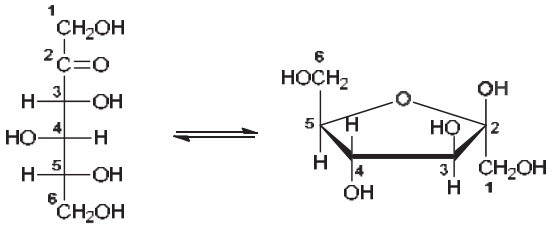
(c) **(d)**



D-Mannose *D-Allose*

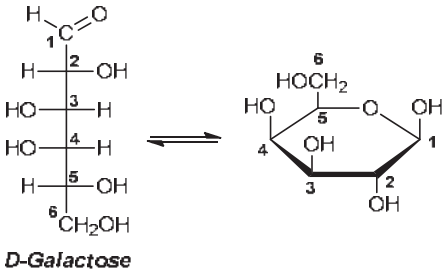
24.53.

(a) We begin by drawing the open chain form of D-fructose (see Figure 24.6). This compound is closed into a furanose form, so we draw a Haworth projection of a furanose skeleton (a five-membered ring with the oxygen atom in the back). We use a numbering system to assist us. Next, we draw the CH_2OH group (connected to C5) pointing up, because this is a D sugar. The anomeric OH group is then drawn pointing up (the β anomer). Finally, the remaining OH groups are drawn. Any OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection, while any OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection):



D-Fructose

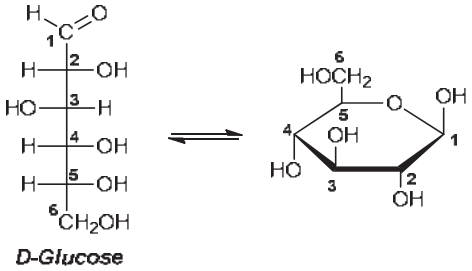
(b) We begin by considering the open chain form of D-galactose (see Figure 24.5). This compound is closed into a pyranose form, so we draw a Haworth projection of a pyranose skeleton (a six-membered ring with the oxygen atom in the back right corner). Next, we draw the CH_2OH group (connected to C5) pointing up, because this is a D sugar. The anomeric OH group is then drawn pointing up (the β anomer). Finally, the remaining OH groups are drawn. Any OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection, while any OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection):



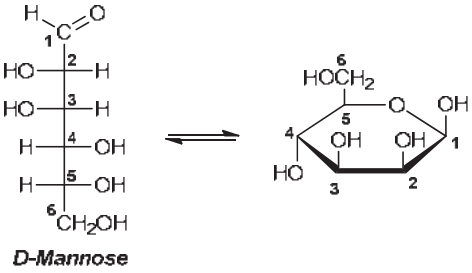
D-Galactose

(c) We begin by considering the open chain form of D-glucose (see Figure 24.5). This compound is closed into a pyranose form, so we draw a Haworth projection of a pyranose skeleton (a six-membered ring with the oxygen atom in the back right corner). Next, we draw the CH_2OH group (connected to C5) pointing up, because this is a D sugar. The anomeric OH group is then drawn pointing up (the β anomer). Finally, the remaining OH groups are drawn. Any OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection, while any OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection):

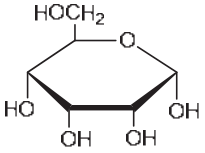
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(d) We begin by considering the open chain form of D-mannose (see Figure 24.5). This compound is closed into a pyranose form, so we draw a Haworth projection of a pyranose skeleton (a six-membered ring with the oxygen atom in the back right corner). Next, we draw the CH_2OH group (connected to C5) pointing up, because this is a D sugar. The anomeric OH group is then drawn pointing up (the β anomer). Finally, the remaining OH groups are drawn. Any OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection, while any OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection):



24.54. D-allose is the aldohexose that is epimeric with D-glucose at C3. The α-pyranose form of D-allose is shown here:



24.55.

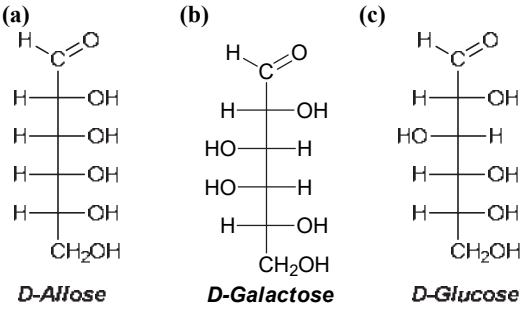
(a) This structure represents the α anomer of the pyranose form of D-allose and is therefore called α-D-allopyranose.

(b) This structure represents the β anomer of the pyranose form of D-galactose and is therefore called β-D-galactopyranose.

(c) This structure represents an acetal of the β anomer of the pyranose form of D-glucose and is called methyl β-D-glucopyranoside .

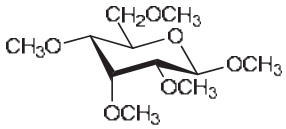
24.56. The structures of D-allose, D-galactose and D-glucose can be found in Figure 24.5.

(a) **(b)** **(c)**

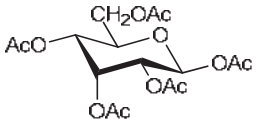


24.57.

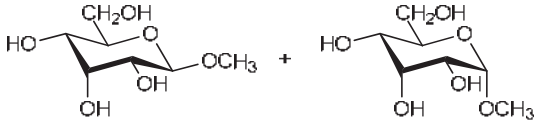
(a) When treated with excess methyl iodide and silver oxide, all of the OH groups in the β-pyranose form of D-allose are converted into methoxy groups (via methylation), giving the following compound:



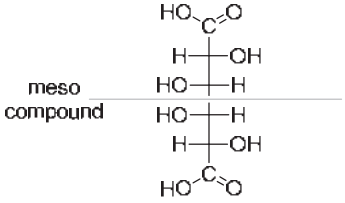
(b) When treated with excess acetic anhydride and pyridine, each of the OH groups in the β-pyranose form of D-allose will undergo acetylation to give the following compound:



(c) When treated with methanol and HCl, the anomeric OH group in the β-pyranose form of D-allose is converted into a methoxy group. Both possible anomers are formed:

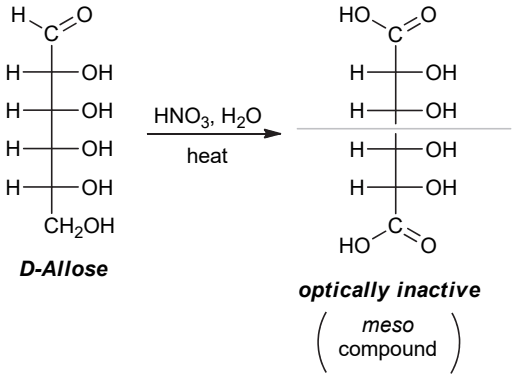


24.58. The product, shown below, is optically inactive because it is a *meso* compound:

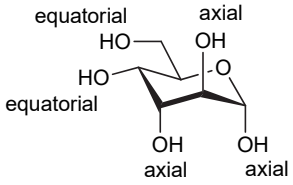


24.59. Upon treatment with nitric acid, D-allose undergoes oxidation to give an aldaric acid that is optically inactive because it is a *meso* compound:

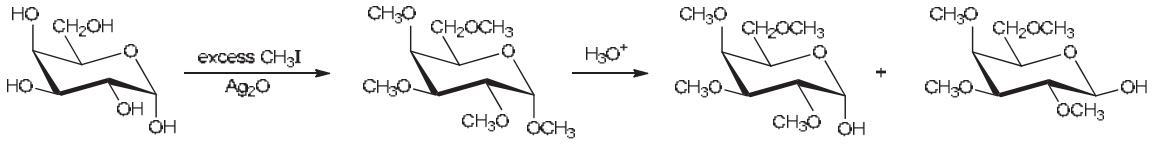
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24.60. The skeleton of the chair is drawn with an oxygen atom in the upper back-right corner. Each substituent is then labeled as "up" or "down" and placed on the chair accordingly. The anomeric OH group is drawn pointing down, indicating the α anomer. In this chair conformation, the largest substituent (CH_2OH) occupies an equatorial position, so this is the more stable chair conformation of α-D-altropyranose.

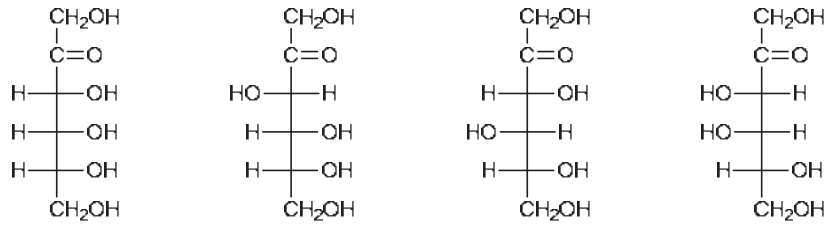


24.61. Upon treatment with excess methyl iodide in the presence of silver oxide, all of the OH groups are converted into methoxy groups, as shown. Upon treatment with aqueous acid, the acetal is hydrolyzed, giving both anomers of D-galactopyranose:

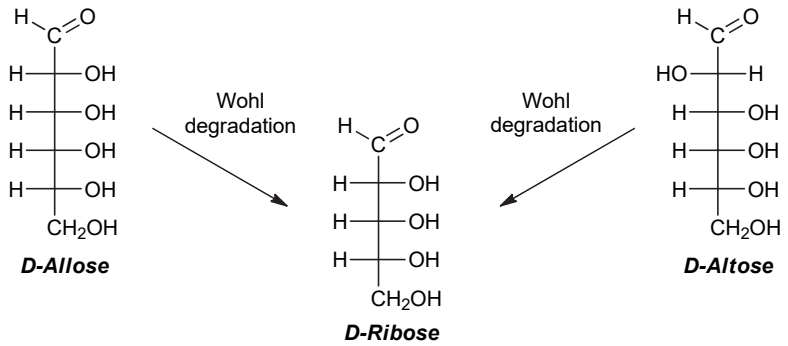


24.62.
(a) These compounds (see Figure 24.5) are stereoisomers that are not mirror images of each other, so they are diastereomers.
(b) D-Ribose and D-arabinose are C2 epimers. Therefore, removing the OH group from C2 of either compound will result in the same structure. That is, 2-deoxy-D-ribose and 2-deoxy-D-arabinose are the same compound.

24.63. 2-Ketohexoses have three chiral centers. The configuration of one of these chiral centers (at C5) is fixed because the problem statement asks only for D sugars. That leaves two other chiral centers (C3 and C4), giving rise to the following four stereoisomers:

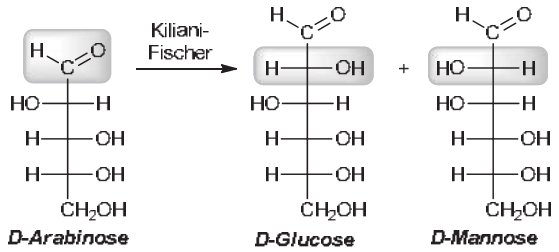


24.64. A Wohl degradation involves the removal of a carbon atom from an aldose. As shown below, D-ribose can be made from either D-allose or D-altose:

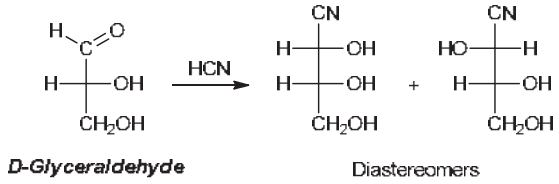


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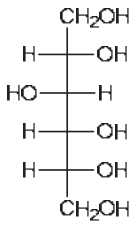
24.65. In a Kiliani-Fischer synthesis, the chain is lengthened, with C1 becoming C2 in the product. Both possible configurations of the C2 position are obtained, giving the following epimers:



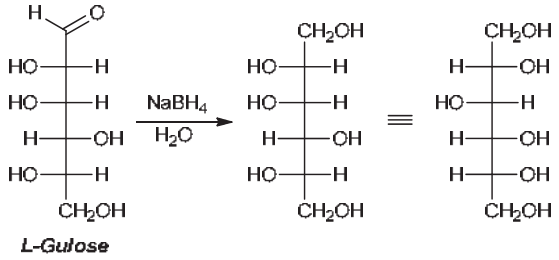
24.66. The aldehyde group is converted into a cyanohydrin. The newly installed chiral center can have either R or S configuration, giving the following diastereomers:



24.67.
(a) Upon treatment with sodium borohydride, the aldehyde group of D-glucose is reduced to an alcohol, giving the following alditol:



(b) As shown, treatment of L-gulose with sodium borohydride gives the same alditol as above (when rotated 180º).



24.68. As seen in the solution to Problem **24.30**, D-allose and D-galactose are converted into optically inactive alditols upon treatment with sodium borohydride.

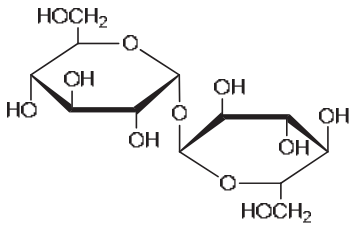
24.69.
(a) This compound will not be a reducing sugar because the anomeric position is an acetal group.
(b) This compound will be a reducing sugar because the anomeric position bears an OH group.

24.70.
(a) CH_3OH, HCl
(b) CH_3OH, HCl
(c) HNO_3, H_2O, heat
(d) excess CH_3I, Ag_2O followed by H_3O^+

24.71.
(a) The methoxy group is replaced with an OH group. Under these conditions, both anomers are formed, giving α-D-glucopyranose and β-D-glucopyranose.
(b) The ethoxy group is replaced with an OH group. Under these conditions, both anomers are formed, giving α-D-galactopyranose and β-D-galactopyranose.

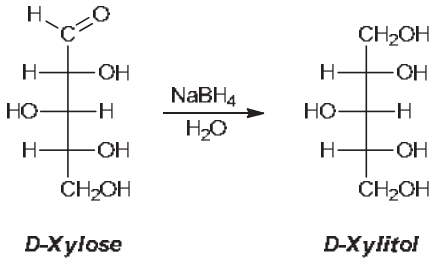
24.72.
(a) Oxidation of D-Arabinose with nitric acid gives the same aldaric acid as oxidation of D-lyxose.
(b) D-Ribose and D-xylose yield optically inactive alditols when treated with sodium borohydride.
(c) Reduction of D-xylose yields the same alditol as reduction of L-xylose.
(d) D-xylose can close into a β-pyranose form in which all substituents are equatorial.

24.73. Trehalose is a disaccharide assembled from two equivalents of the α-pyranose form of D-glucose. Trehalose is not a reducing sugar, which means that the two rings must be fused at the anomeric positions (so there is no anomeric OH group). The disaccharide is assembled from the α-pyranose form of each equivalent of D-glucose:

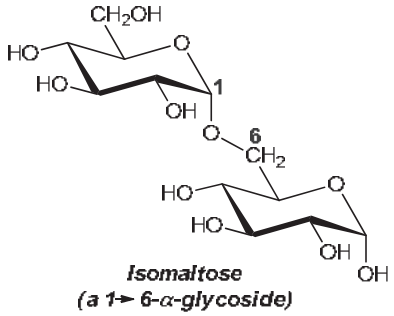


24.74. Reduction of D-xylose gives the following structure (D-xylitol):

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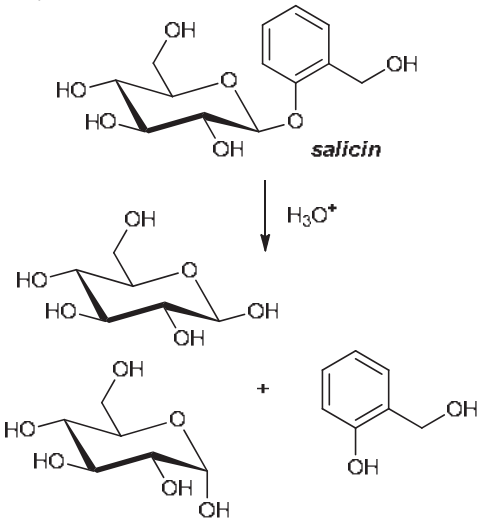
24.75. The 1→6-α-glycoside linkage of isomaltose is illustrated below:



24.76.

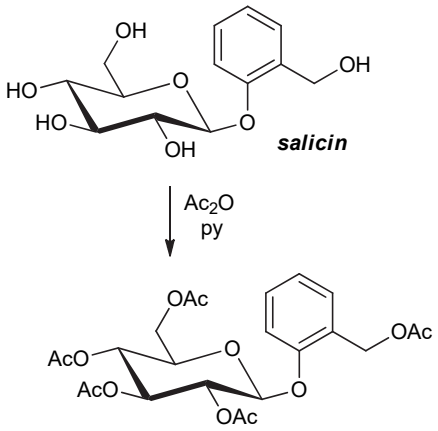
(a) No, it is not a reducing sugar because the anomeric position has an acetal group.

(b) The acetal group is hydrolyzed, giving both anomers of the cyclic hemiacetal:



(c) Salicin is a β-glycoside.

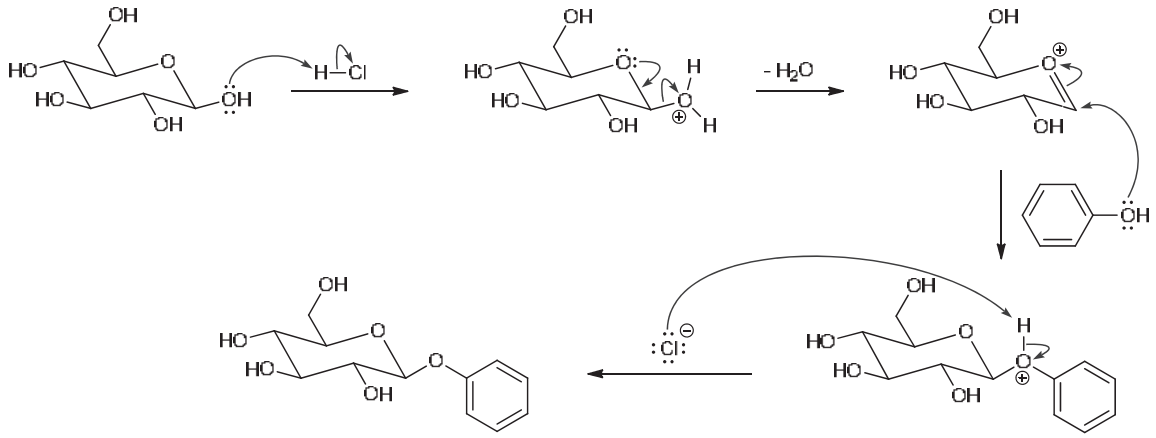
(d) Upon treatment with acetic anhydride and pyridine, all of the OH groups undergo acetylation, giving the product shown:



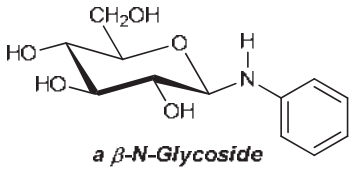
(e) No. In the absence of acid catalysis, the acetal group is not readily hydrolyzed.

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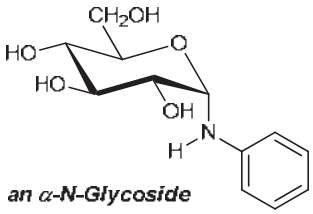
24.77. The anomeric OH group is protonated under acidic conditions, giving an excellent leaving group (water). Loss of the leaving group gives a resonance-stabilized cation (resonance structure not shown). This cation is then attacked by phenol, giving an oxonium ion that is deprotonated to give the product:



24.78. The following α and β anomers are obtained when D-glucose is treated with aniline:



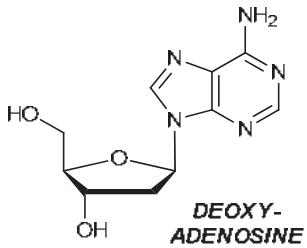
a β-N-Glycoside



an α-N-Glycoside

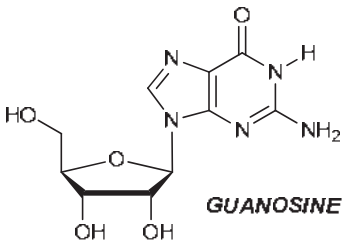
24.79.

(a) The following nucleoside is formed from 2-deoxy-D-ribose and adenine. Notice that this structure differs from adenosine (see Figure 24.13) only at the C2 position. Specifically, the C2 position in this structure does not bear an OH group (as compared with adenosine):



DEOXY-ADENOSINE

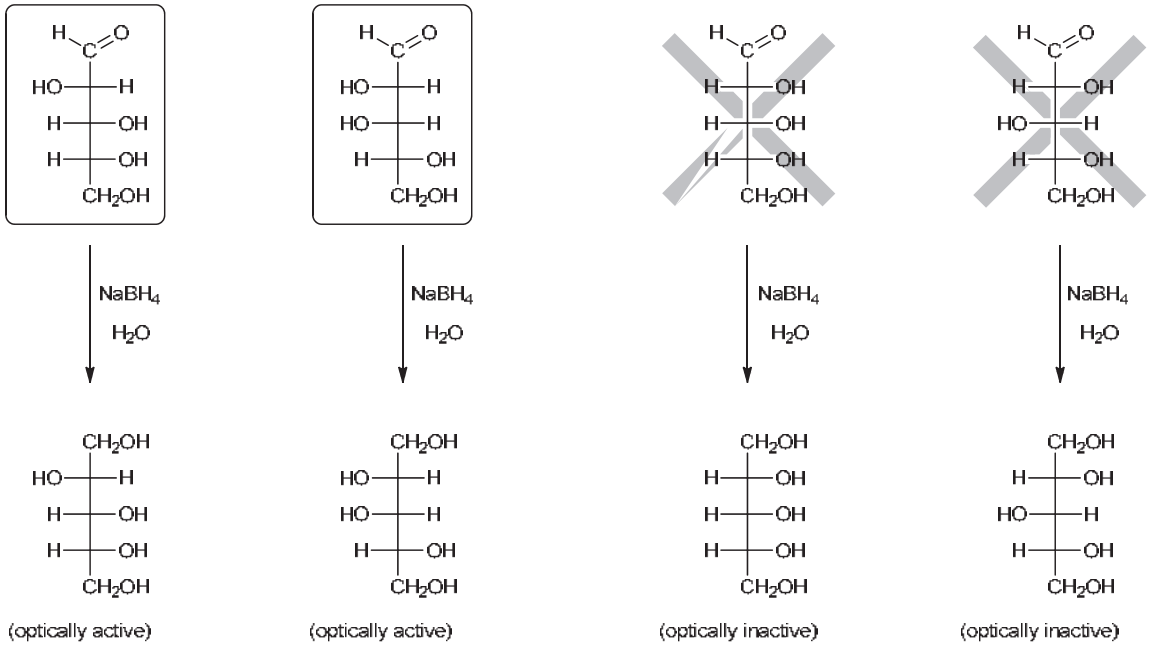
(b) The following nucleoside, called guanosine (see Figure 24.13), is formed from D-ribose and guanine:



GUANOSINE

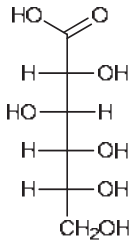
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24.80. There are only four D-aldopentoses, all which are shown below. Only the first two are reduced to give an optically active alditol, as shown. The latter two are reduced to give *meso* compounds (not optically active):

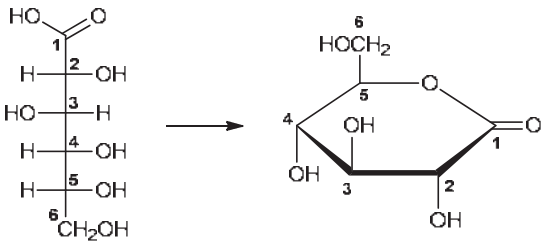


24.81.

(a) D-Gluconic acid is formed when the C1 position of D-glucose undergoes oxidation to give a carboxylic acid, shown here:



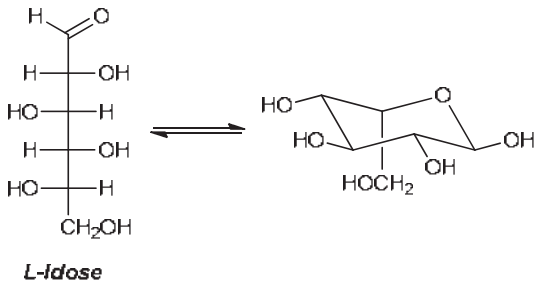
(b) A numbering system is used to help draw the product. The CH_2OH group (connected to C5) is drawn pointing up, because the starting material is a D sugar. Any OH groups on the right side of the Fischer projection will be pointing down in the Haworth projection, while any OH groups on the left side of the Fischer projection will be pointing up in the Haworth projection):



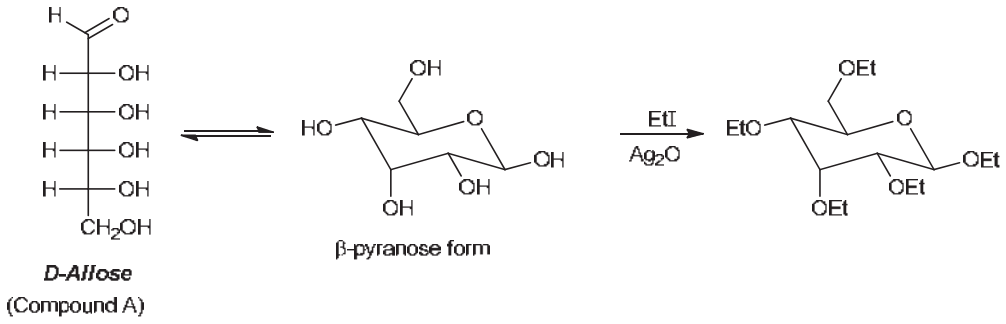
(c) Yes. The compound has chiral centers, and it is not a *meso* compound. Therefore, it will be optically active.

(d) The gluconic acid is a carboxylic acid and its IR spectrum is expected to have a broad signal between 2200 and 3600 cm^{-1}. The IR spectrum of the lactone will not have this broad signal.

24.82. In order for the CH_2OH group to occupy an equatorial position, all of the OH groups on the ring must occupy axial positions. The total energy cost associated with the steric interactions of the axial OH groups is more than the energy cost associated with one (albeit larger) CH_2OH group in an axial position. Therefore, the equilibrium will favor the form in which the CH_2OH group occupies an axial position. The structure of L-idose is shown here:

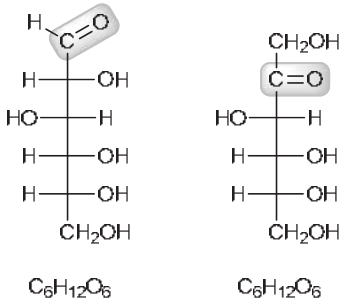


24.83. The molecular formula ($C_6H_{12}O_6$) indicates that compound **A** is a hexose (carbohydrate with six carbon atoms). Compound **A** is a reducing sugar, so it must be an aldohexose (rather than a ketohexose). Two successive Wohl degradations of compound **A** gives D-erythrose, which indicates the configurations of C4 and C5 of the aldohexose (both positions have the *R* configuration, just as in D-erythrose). Compound **A** is epimeric with glucose at C3, which indicates the *R* configuration at C3 (D-glucose has the *S* configuration at C3). Finally, C2 has the *R* configuration, giving the structure shown below (D-allose). The β-pyranose form of D-allose has also been drawn below. When treated with excess ethyl iodide in the presence of silver oxide, all of the OH groups in the β-pyranose form of compound **A** undergo alkylation, thereby converting them into ethoxy groups, as shown:



24.84. Glucose can adopt a chair conformation in which all of the substituents on the ring occupy equatorial positions. Therefore, D-glucose can achieve a lower energy conformation than any of the other D-aldohexoses.

24.85. Both of these compounds have the molecular formula $C_6H_{12}O_6$, but they have a different connectivity of atoms. The C=O bond is located at C1 in the first compound, but located at C2 in the second compound:

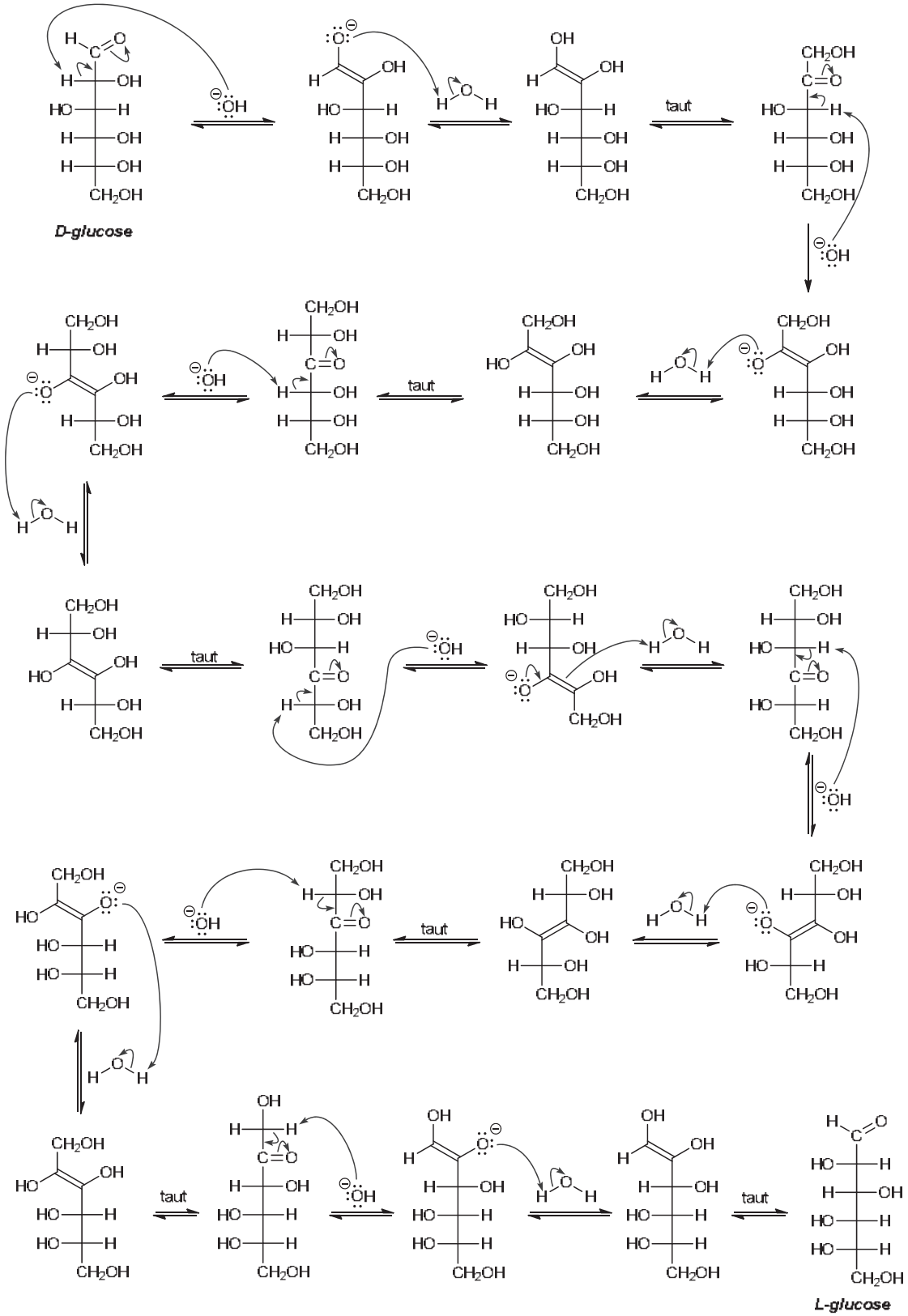


Therefore, these compounds are constitutional isomers (the first is an aldose, and the second is a ketose). Stereoisomers must have the same connectivity of atoms (differing only in configuration), so these compounds cannot be stereoisomers.

24.86. The pyranose form of glucose has a six-membered ring. The correct answer is (c).

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24.87. The following mechanism consists entirely of deprotonation and protonation steps. Notice that for each deprotonation step, hydroxide is used as the base, while water is used as the proton source for each protonation step (consistent with basic conditions):



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24.87. Compound **X** is a D-aldohexose that can adopt a β-pyranose form with only one axial substituent. Recall that D-glucose has all substituents in equatorial positions, so compound **X** must be epimeric with D-glucose either at C2 (D-mannose), C3 (D-allose), or C4 (D-galactose).

Compound **X** undergoes a Wohl degradation to produce an aldopentose, which is converted into an optically active alditol when treated with sodium borohydride. Therefore, compound **X** cannot be D-allose, because a Wohl degradation of D-allose followed by reduction produces an optically *inactive* alditol.

We conclude that compound **X** must be either D-mannose or D-galactose.

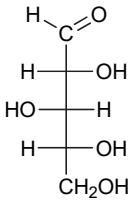
The identity of compound **X** can be determined by treating compound **X** with sodium borohohydride. Reduction of D-mannose should give an optically active alditol, while reduction of D-galactose gives an optically inactive alditol.

24.89.

(a) Compound **A** is a D-aldopentose. Therefore, there are four possible structures to consider (Figure 24.4).

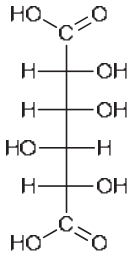
When treated with sodium borohydride, compound **A** is converted into an alditol that exhibits three signals in its ^{13}C NMR spectrum. Therefore, compound **A** must be D-ribose or D-xylose both of which are reduced to give symmetrical alditols (thus, three signals for five carbon atoms).

When compound **A** undergoes a Kiliani-Fischer synthesis, both products can be treated with nitric acid to give optically active aldaric acids. Therefore, compound **A** cannot be D-ribose, because when D-ribose undergoes a Kiliani-Fischer synthesis, one of the products is D-allose, which is oxidized to give an optically inactive aldaric acid. We conclude that the structure of compound **A** must be D-xylose.

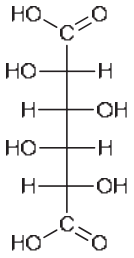


D-Xylose

(b) Compound D is expected have six signals in its ^{13}C NMR spectrum, while compound E is expected to have only three signals in its ^{13}C NMR spectrum.



Compound D



Compound E

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Chapter 25
Amino Acids, Peptides, and Proteins

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 25. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

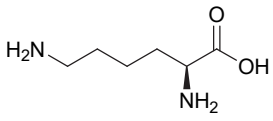
- Amino acids in which the two functional groups are separated by exactly one carbon atom are called _____ **amino acids.**
- Amino acids are coupled together by amide linkages called _____ **bonds.**
- Relatively short chains of amino acids are called _____.
- Only twenty amino acids are abundantly found in proteins, all of which are ___ **amino acids**, except for _____ which lacks a chiral center.
- Amino acids exist primarily as _____ at physiological pH
- The _____ of an amino acid is the pH at which the concentration of the zwitterionic form reaches its maximum value.
- Peptides are comprised of **amino acid** _____ joined by peptide bonds.
- Peptide bonds experience restricted rotation, giving rise to two possible conformations, called _____ and _____**.** The _____ conformation is generally more stable.
- Cysteine residues are uniquely capable of being joined to one another via _____ **bridges.**
- _____ is commonly used to form peptide bonds.
- In the **Merrifield synthesis**, a peptide chain is assembled while tethered to _____.
- The **primary structure** of a protein is the sequence of _____.
- The **secondary structure** of a protein refers to the _____ _____ of localized regions of the protein. Two particularly stable arrangements are the ___ **helix** and ____ **pleated sheet**.
- The **tertiary structure** of a protein refers to its _____.
- Under conditions of mild heating, a protein can unfold, a process called _____.
- **Quaternary structure** arises when a protein consists of two or more folded polypeptide chains, called _____, that aggregate to form one protein complex.

Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 25. The answers appear in the section entitled *SkillBuilder Review*.

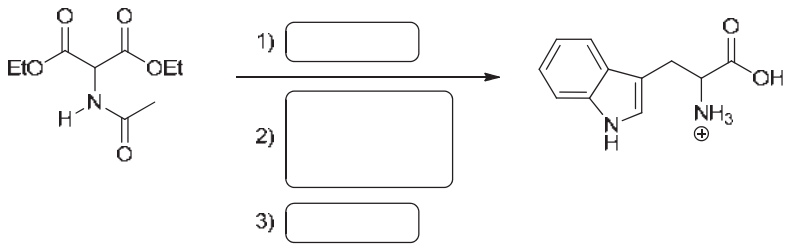
25.1 Determining the Predominant Form of an Amino Acid at a Specific pH

CONSIDER THE FOLLOWING AMINO ACID, AND DRAW THE FORM THAT PREDOMINATES AT PHYSIOLOGICAL pH.



25.2 Using the Amidomalonate Synthesis

IDENTIFY REAGENTS THAT WILL ACHIEVE THE FOLLOWING TRANSFORMATION:



25.3 Drawing a Peptide

DRAW A BOND-LINE STRUCTURE FOR THE TRIPEPTIDE Phe-Val-Trp.

25.4 Sequencing a Peptide via Enzymatic Cleavage

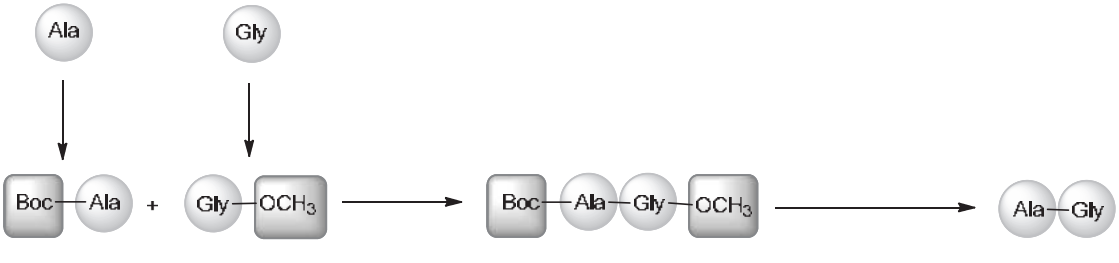
IDENTIFY THE FRAGMENTS OBTAINED FROM ENZYMATIC CLEAVAGE OF THE FOLLOWING PEPTIDE:

Ala-Phe-Lys-Pro-Met-Tyr-Gly-Arg-Ser-Trp-Leu-Hist

trypsin ***chymotrypsin***

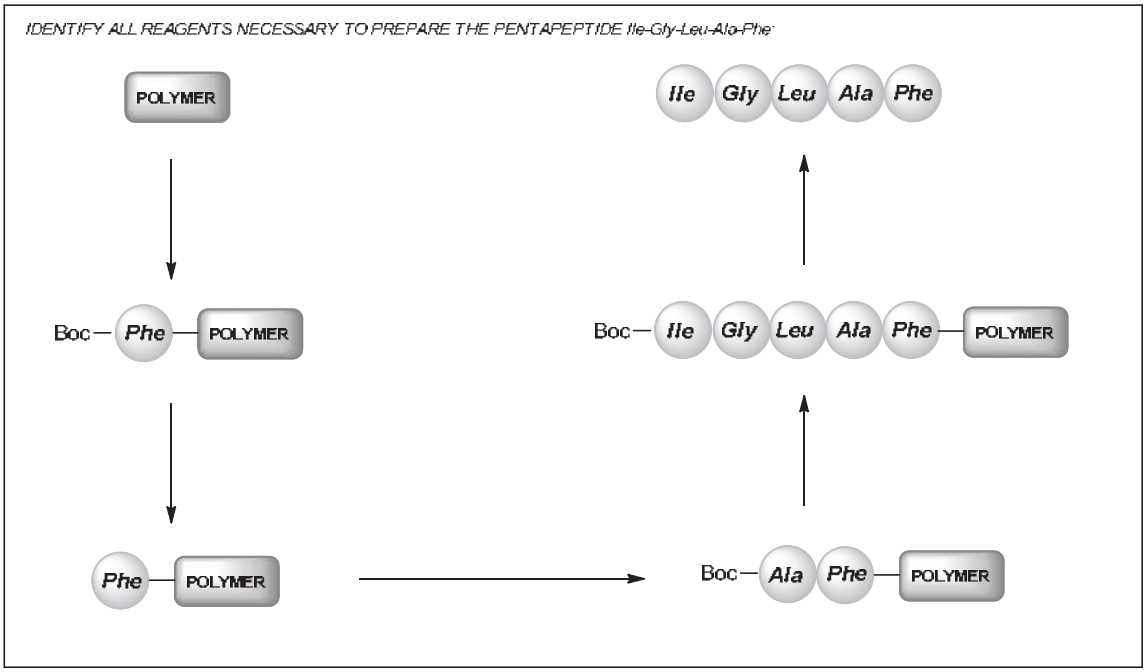
25.5 Planning the Synthesis of a Dipeptide

IDENTIFY ALL REAGENTS NECESSARY TO PREPARE THE DIPEPTIDE Ala-Gly:



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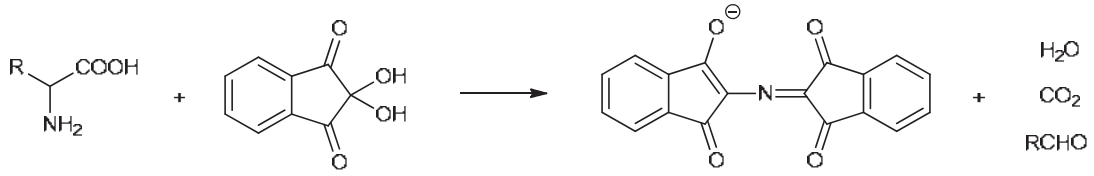
25.6 Preparing a Peptide using the Merrifield Synthesis



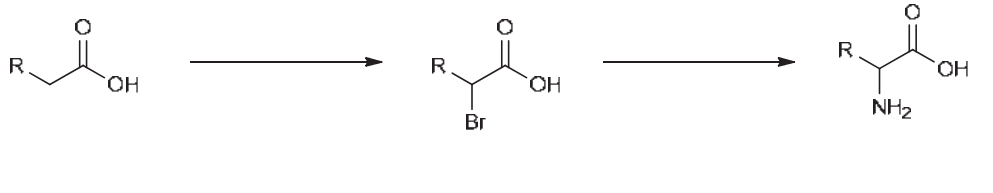
Review of Reactions

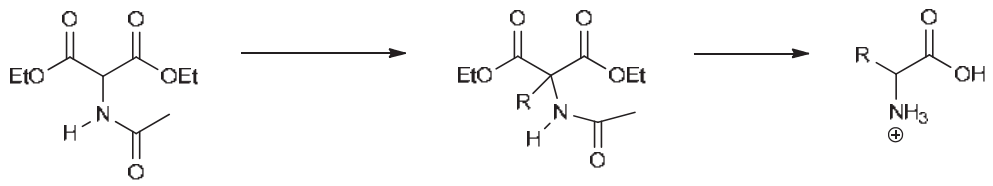
Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 25. The answers appear in the section entitled *Review of Reactions*.

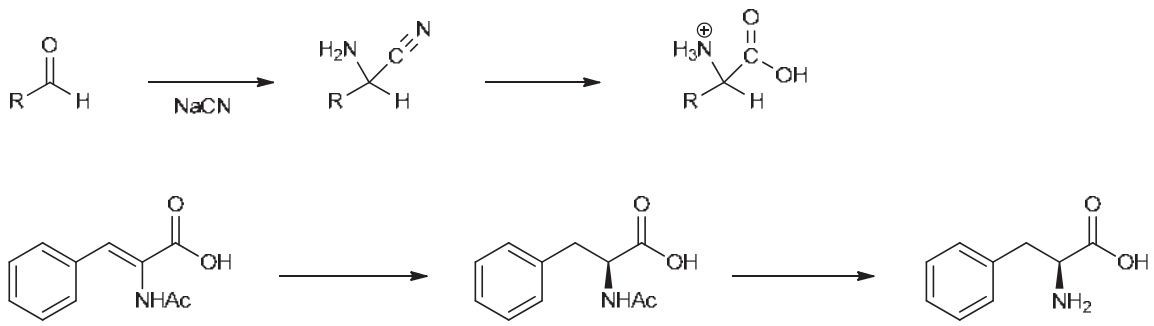
Analysis of Amino Acids



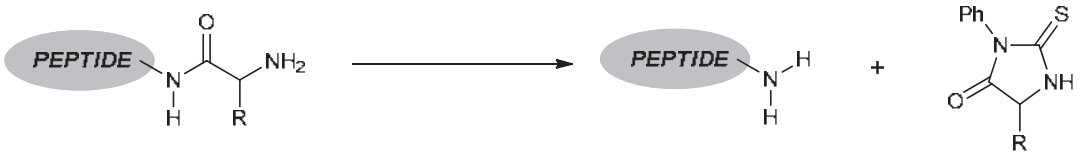
Synthesis of Amino Acids



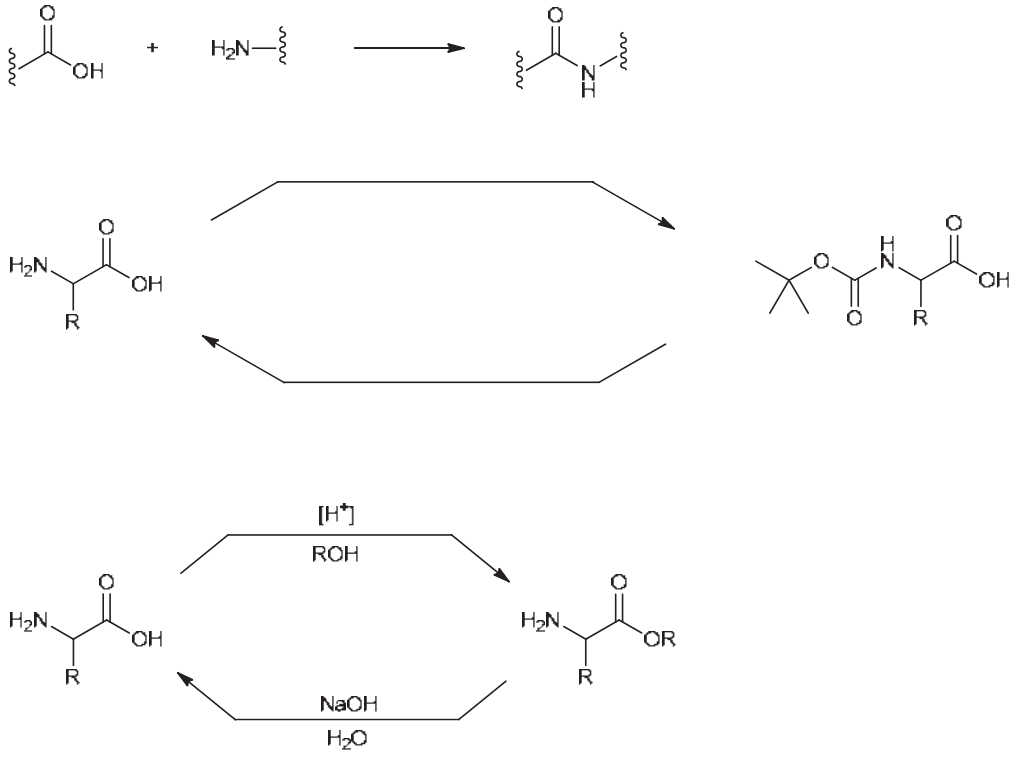




Analysis of Amino Acids



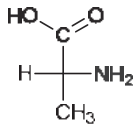
Synthesis of Peptides

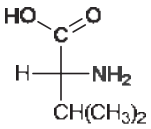


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Solutions

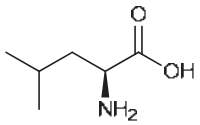
25.1. In each case, the chiral center has the *R* configuration (see SkillBuilder 5.9).


D-Alanine

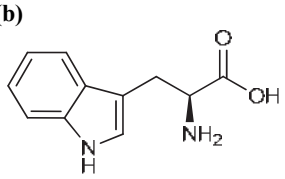

D-Valine

25.2. The structure of each of the following amino acids can be found in Table 25.1.

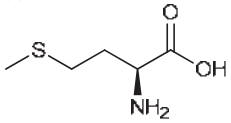
(a)



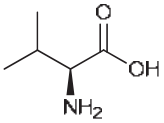
(b)



(c)



(d)



25.3.

(a) As seen in Table 25.1, the following amino acids exhibit a cyclic structure: Pro, Phe, Trp, Tyr, and His.

(b) As seen in Table 25.1, the following amino acids exhibit an aromatic side chain: Phe, Trp, Tyr, and His.

(c) As seen in Table 25.1, the following amino acids exhibit a side chain with a basic group: Arg, His, and Lys.

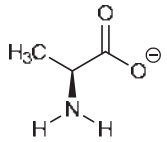
(d) As seen in Table 25.1, the following amino acids exhibit a sulfur atom: Met and Cys.

(e) As seen in Table 25.1, the following amino acids exhibit a side chain with an acidic group: Asp and Glu.

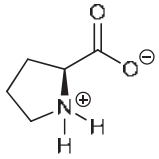
(f) As seen in Table 25.1, the following amino acids exhibit a side chain containing a proton that will likely participate in hydrogen bonding: Pro, Trp, Asn, Gln, Ser, Thr, Tyr, Cys, Asp, Glu, Arg, His, and Lys.

25.4. In each case, we first identify the pK_a of the carboxylic acid group and determine which form predominates. The protonated form (RCOOH) will predominate if pH < pK_a, while the carboxylate ion will predominate if pH > pK_a. Next, we identify the pK_a of the α-amino group and determine which form predominates. The protonated form (RNH_3^+) will predominate if pH < pK_a, while the uncharged form (RNH_2) will predominate if pH > pK_a. Finally, a similar analysis is performed for the side chain (if necessary). See Table 25.2 for pK_a values.

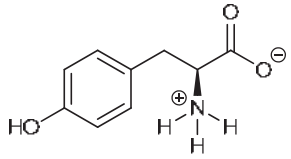
(a)



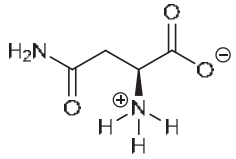
(b)



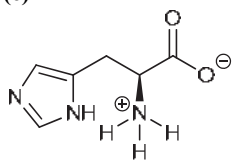
(c)



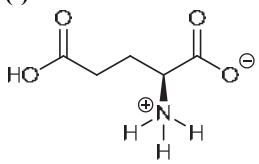
(d)



(e)



(f)



25.5. Arginine has a basic side chain, while asparagine does not. At a pH of 11, arginine exists predominantly in a form in which the side chain is protonated. Therefore, it can serve as a proton donor.

25.6. Tyrosine possesses a phenolic proton which is more readily deprotonated because deprotonation forms a resonance-stabilized phenolate ion. In contrast, deprotonation of the OH group of serine gives an alkoxide ion that is not resonance-stabilized. As a result, the OH group of tyrosine is more acidic than the OH group of serine.

25.7.

(a) Aspartic acid has two carboxylic acid groups, so the pI of aspartic acid is calculated using the pK_a values of the two carboxylic acid groups, as shown here (pK_a values can be found in Table 25.2):

$$\text{pI} = \frac{1.88 + 3.65}{2} = 2.77$$

(b) Leucine does not have an acidic side chain or a basic side chain, so the pI of leucine is calculated using the pK_a value of the carboxylic acid group and the pK_a value of the ammonium group, as shown here (pK_a values can be found in Table 25.2):

$$\text{pI} = \frac{2.36 + 9.60}{2} = 5.98$$

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(c) Lysine has two ammonium groups, so the pI of lysine is calculated using the pK_a values of the two ammonium groups, as shown here (pK_a values can be found in Table 25.2):

$$\text{pI} = \frac{8.95 + 10.93}{2} = 9.74$$

(d) Proline does not have an acidic side chain or a basic side chain, so the pI of proline is calculated using the pK_a value of the carboxylic acid group and the pK_a value of the ammonium group, as shown here (pK_a values can be found in Table 25.2):

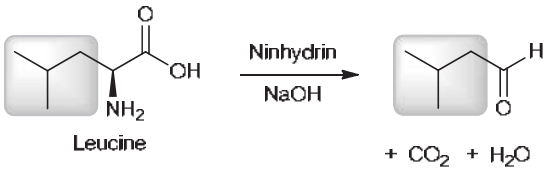
$$\text{pI} = \frac{1.99 + 10.60}{2} = 6.30$$

25.8.
(a) Aspartic acid has two carboxylic acid groups, so it is expected to have the lowest pI.
(b) Glutamic acid has two carboxylic acid groups, so it is expected to have the lowest pI.

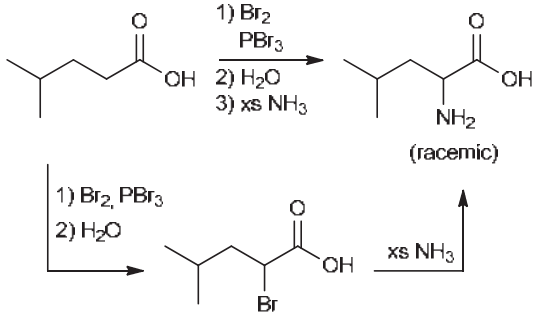
25.9. Leucine and isoleucine both exhibit the same pK_a value for the carboxylic acid group. Similarly, both leucine and isoleucine exhibit the same pK_a value for the amino group. As such, the pI value of leucine is expected to be the same as the pI value of isoleucine.

25.10. The pI of Phe = 5.48, the pI of Trp = 6.11, and the pI of Leu = 6.00. Using these values, we make the following predictions:
(a) At pH = 6.0, Phe will travel the farthest distance.
(b) At pH = 5.0, Trp will travel the farthest distance.

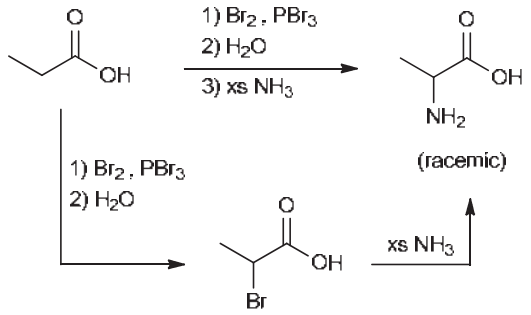
25.11. The following aldehyde is expected when L-leucine is treated with ninhydrin:



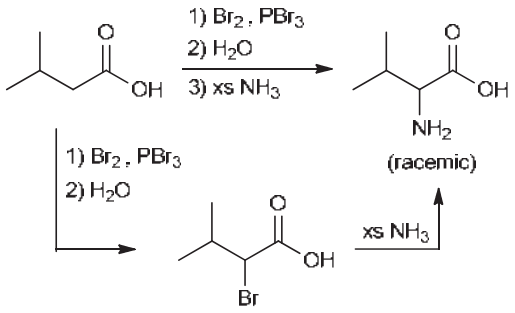
25.12.
(a) Racemic leucine can be made using a Hell-Volhard-Zelinsky reaction, as shown:



(b) Racemic alanine can be made using a Hell-Volhard-Zelinsky reaction, as shown:

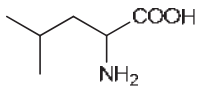


(c) Racemic valine can be made using a Hell-Volhard-Zelinsky reaction, as shown:



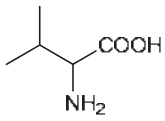
25.13. In each case, the process is a Hell-Volhard-Zelinsky reaction, which will give the following amino acids:

(a)



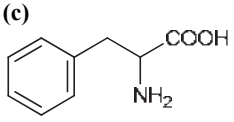
Leucine

(b)



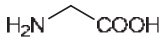
Valine

(c)



Phenylalanine

(d)



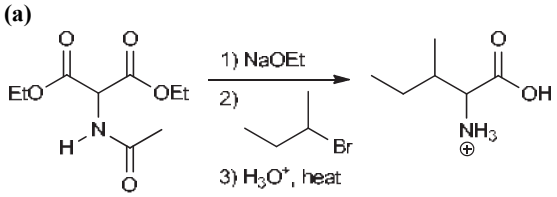
Glycine

25.14. In each case, we begin by identifying the side chain connected to the α position. Then, we identify the necessary alkyl halide and ensure that it is not tertiary (because a tertiary alkyl halide will not undergo an S_N2 reaction). An amidomalonate synthesis is performed using acetamidomalonate as the starting material, which is first treated with sodium ethoxide. The resulting conjugate base (a doubly stabilized enolate) is then treated with the alkyl halide, followed by hydrolysis with

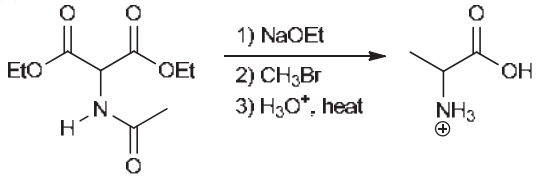
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aqueous acid and heat, to give the desired amino acid. Note that the final step employs acidic conditions, so the amino group of the resulting amino acid is protonated:

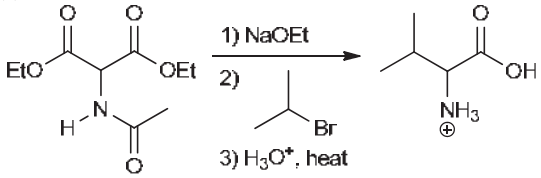
(a)



(b)

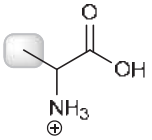


(c)

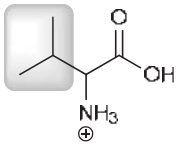


25.15.

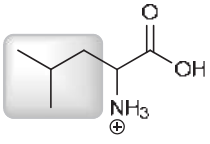
(a) Alanine is obtained when methyl chloride is used as the alkyl halide in an amidomalonate synthesis. The methyl group (from methyl chloride) is highlighted in the product:



(b) Valine is obtained when isopropyl chloride is used as the alkyl halide in an amidomalonate synthesis. The isopropyl group (from isopropyl chloride) is highlighted in the product:



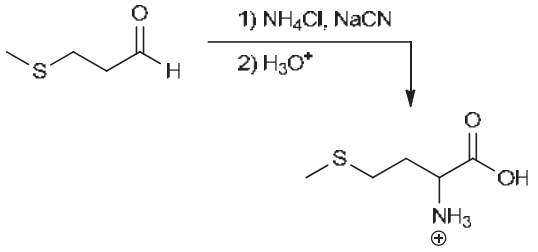
(c) Leucine is obtained when 2-methyl-1-chloropropane is used as the alkyl halide in an amidomalonate synthesis. The alkyl group (from the alkyl chloride) is highlighted in the product:



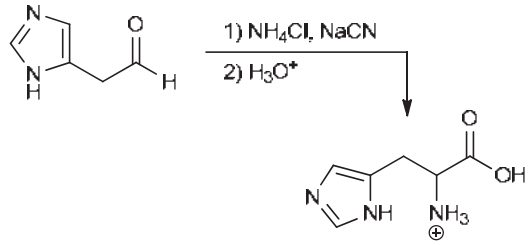
25.16. Leucine can be prepared via the amidomalonate synthesis with higher yields than isoleucine, because the former requires an S_N2 reaction with a primary alkyl halide, while the latter requires an S_N2 reaction with a secondary (more hindered) alkyl halide.

25.17.

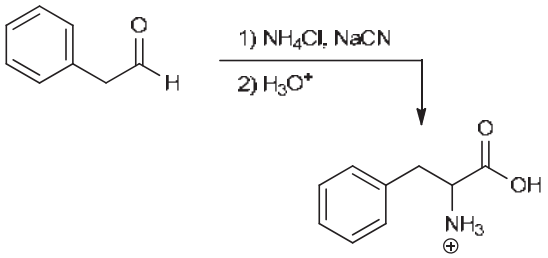
(a) Methionine can be prepared from the aldehyde below via a Strecker synthesis, as shown:



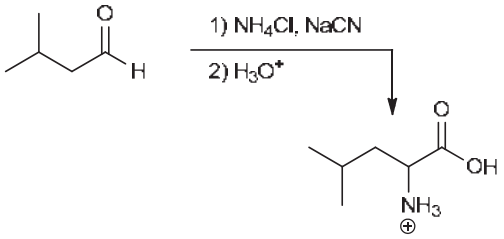
(b) Histidine can be prepared from the aldehyde below via a Strecker synthesis, as shown:



(c) Phenylalanine can be prepared from the aldehyde below via a Strecker synthesis, as shown:



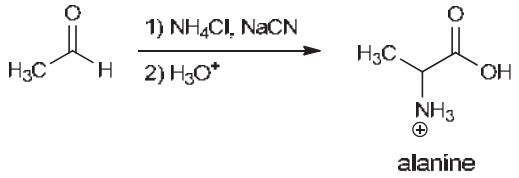
(d) Leucine can be prepared from the aldehyde below via a Strecker synthesis, as shown:



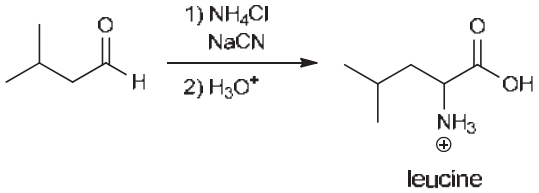
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25.18.

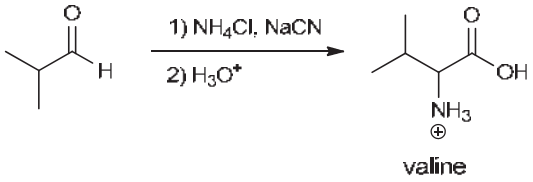
(a) Acetaldehyde is converted into a racemic mixture of alanine (via a Strecker synthesis), as shown:



(b) 3-Methylbutanal is converted into a racemic mixture of leucine (via a Strecker synthesis), as shown:

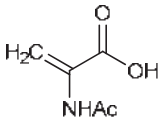


(c) 2-Methylpropanal is converted into a racemic mixture of valine (via a Strecker synthesis), as shown:

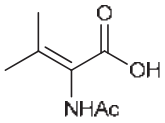


25.19.

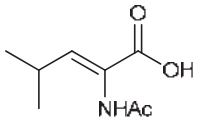
(a) L-Alanine can be prepared from the following compound via an asymmetric catalytic hydrogenation:



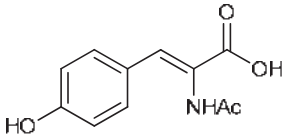
(b) L-Valine can be prepared from the compound below via an asymmetric catalytic hydrogenation:



(c) L-Leucine can be prepared from the compound below via an asymmetric catalytic hydrogenation:



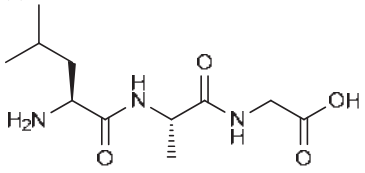
(d) L-Tyrosine can be prepared from the compound below via an asymmetric catalytic hydrogenation:



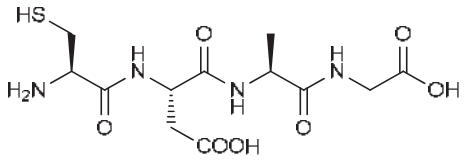
25.20. Glycine does not possess a chiral center, so the use of a chiral catalyst is unnecessary. Also, there is no alkene that would lead to glycine upon hydrogenation.

25.21. For each of the following peptides, the N terminus is drawn on the left and the C terminus on the right. Side chains at the top of the drawing are on wedges, while side chains on the bottom of the drawing are on dashes. The identity of each side chain can be found in Table 25.1.

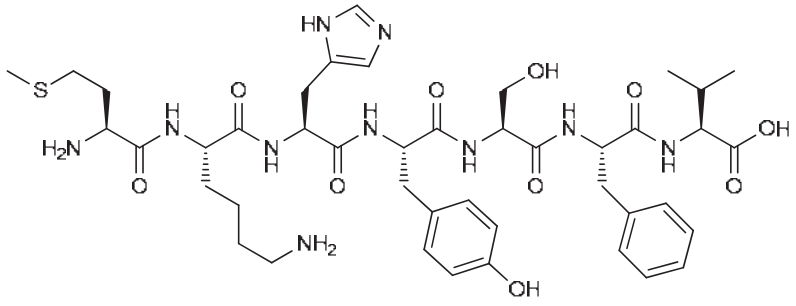
(a)



(b)



(c)



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25.22. Based on the identities of side chains (see Table 25.1), this peptide has the following sequence:

Leu-Ala-Phe-Cys-Asp

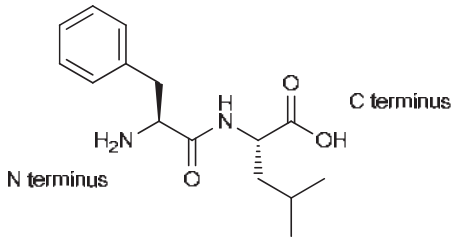
This sequence can be summarized with the following one-letter abbreviations:

L-A-F-C-D.

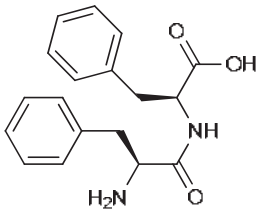
25.23. The first peptide (Cys-Tyr-Leu) is expected to have a higher molecular weight, because the amino acid residues have larger side chains (see Table 25.1).

25.24. These peptides have the same molecular formula but they differ from each other in their connectivity of atoms (or constitution). As such, they are constitutional isomers.

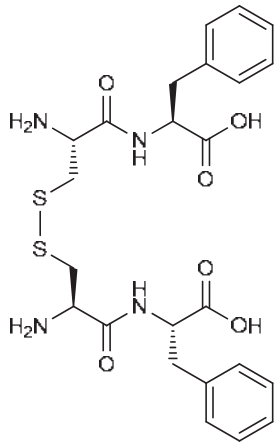
25.25. The following is the *s-trans* conformation of the dipeptide Phe-Phe. Notice that the N-terminus is on the left, while the C-terminus is on the right, as per accepted convention. Also notice that the side chain at the top of the drawing is on a wedge, while the side chain at the bottom of the drawing is on a dash (see SkillBuilder 25.3).



25.26. In the *s-cis* conformation, the phenyl groups will experience a severe steric interaction, thereby causing the *s-cis* conformation to be extremely high in energy:

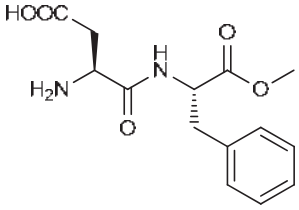


25.27. Two equivalents of the dipeptide are drawn, and they are then connected by a disulfide bridge, as shown:

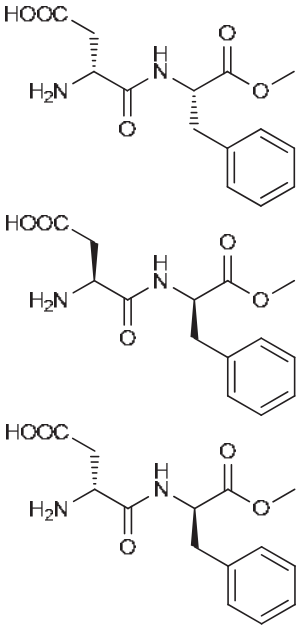


25.28.

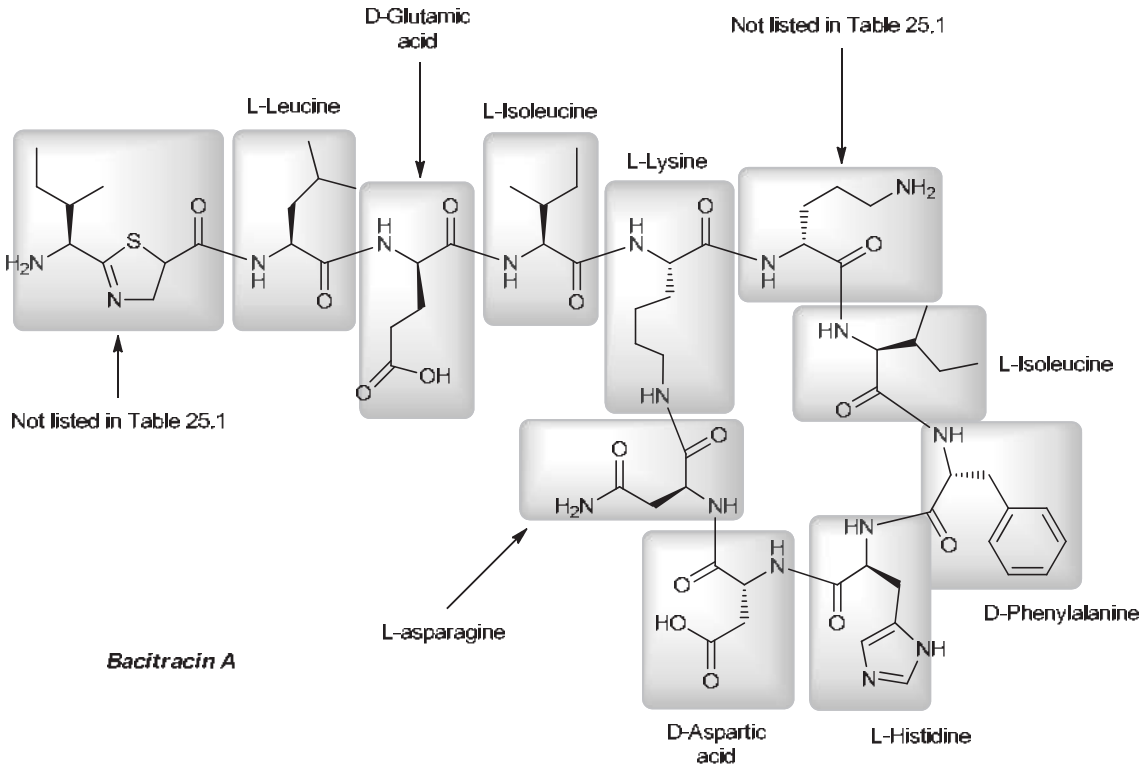
(a) The following is the structure of aspartame. Notice that the N-terminus is on the left, while the C-terminus is on the right, as per accepted convention. In this case, the C-terminus is an ester (rather than a carboxylic acid). Also notice that the side chain at the top of the drawing is on a wedge, while the side chain at the bottom of the drawing is on a dash (see SkillBuilder 25.3).



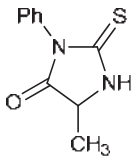
(b) The compound above has two chiral centers, giving rise to a total of four possible stereoisomers. The structure above represents one of these stereoisomers. The other three isomers are shown here:



25.29. In the following structure, each of the amino acid residues has been highlighted and labeled:



25.30. An Edman degradation will remove the amino acid residue at the N terminus, and Ala is the N terminus in Ala-Phe-Val. Therefore, alanine is removed, giving the following PTH derivative:



25.31. Only one of the trypsin fragments has a C terminus that is not arginine or lysine. This fragment, which ends with valine, must be the last fragment in the peptide sequence. The remaining three trypsin fragments can be placed in the proper order by analyzing the chymotrypsin fragments. The correct peptide sequence is:

Ala-ValMet-Phe-Val-Ala-Tyr-Lys-Pro-Val-Ile-Leu-Arg-Trp-His-Phe-Met-Cys-Arg-Gly-Pro-Phe-Ala-Val

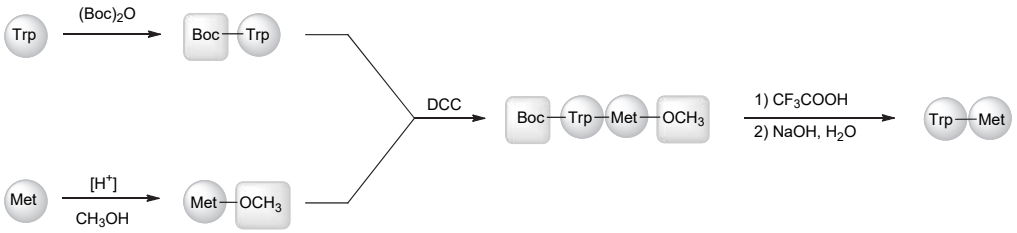
25.32. The following tetrapeptide will be cleaved by chymotrypsin to give Ala-Phe and Val-Lys:

Ala-Phe-Val-Lys

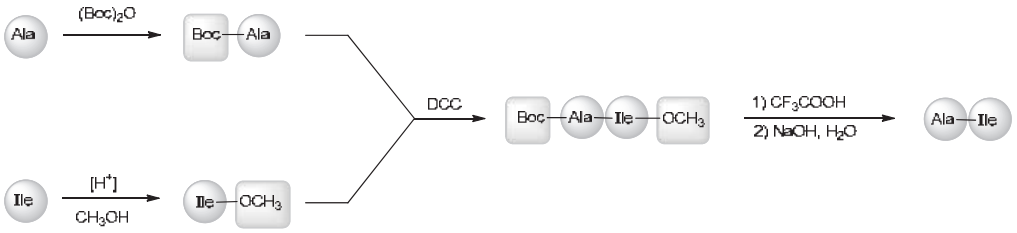
25.33. Cleavage with trypsin will produce Phe-Arg, while cleavage with chymotrypsin will produce Arg-Phe. These dipeptides are not the same. They are constitutional isomers.

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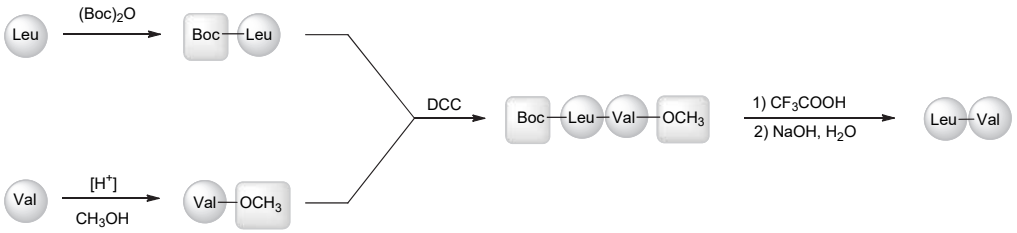
25.34.
(a) We begin by installing the appropriate protecting groups. Then, upon treatment with DCC, the protected amino acids are coupled. And finally, the protecting groups are removed, as shown:



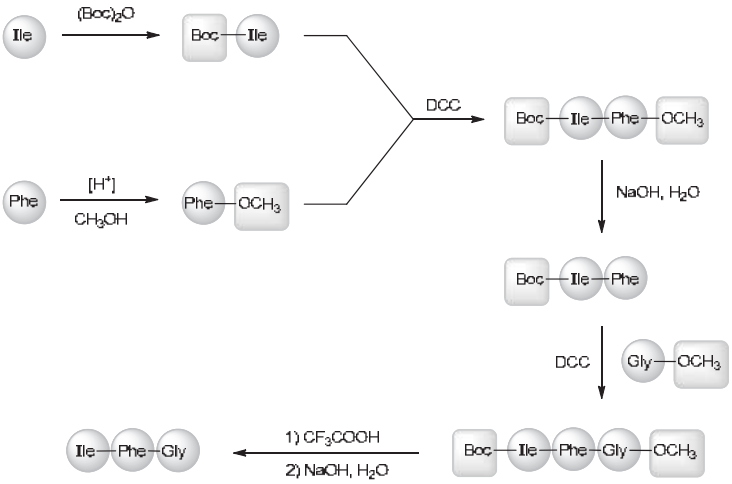
(b) We begin by installing the appropriate protecting groups. Then, upon treatment with DCC, the protected amino acids are coupled. And finally, the protecting groups are removed, as shown:



(c) We begin by installing the appropriate protecting groups. Then, upon treatment with DCC, the protected amino acids are coupled. And finally, the protecting groups are removed, as shown:

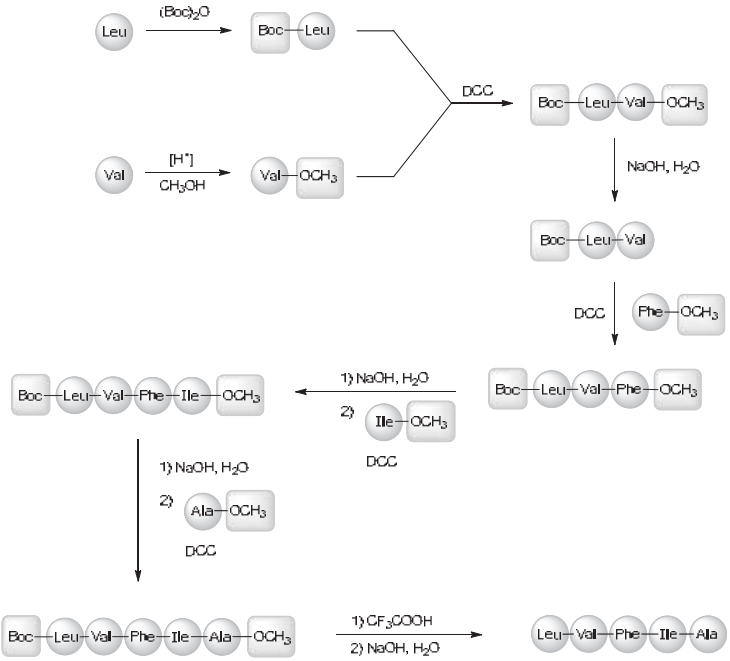


25.35. The first two amino acid residues (in the desired peptide sequence) are Ile and Phe. So we must begin with those amino acids. We first install the appropriate protecting groups. Then, upon treatment with DCC, the protected amino acids are coupled. The protecting group at the C-terminus is then removed and the resulting unprotected C-terminus is coupled with the appropriate protected amino acid (glycine, protected at the C-terminus), using DCC. And finally, the protecting groups are removed, as shown:

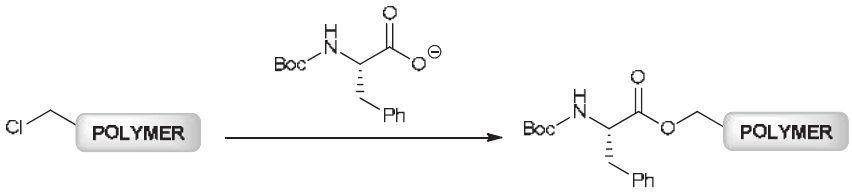


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25.36. The first two amino acid residues (in the desired peptide sequence) are Leu and Val. So we must begin with those amino acids. We first install the appropriate protecting groups. Then, upon treatment with DCC, the protected amino acids are coupled. The protecting group at the C-terminus is then removed and the resulting unprotected C-terminus is coupled with the appropriate protected amino acid, using DCC. Each additional residue is installed via deprotection of the C-terminus followed by coupling with the appropriate protected amino acid, as shown. Finally, the protecting groups are removed, giving the desired pentapeptide:

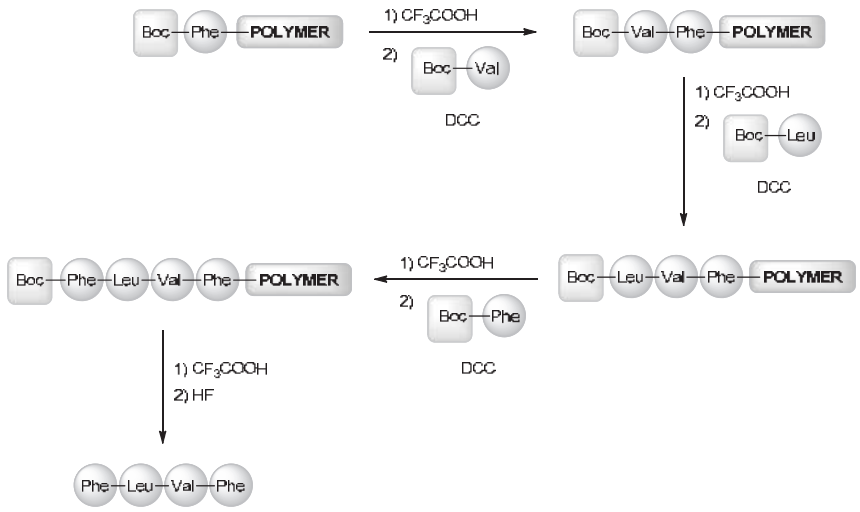


25.37.
(a) First, we attach the appropriate Boc-protected residue to the polymer:

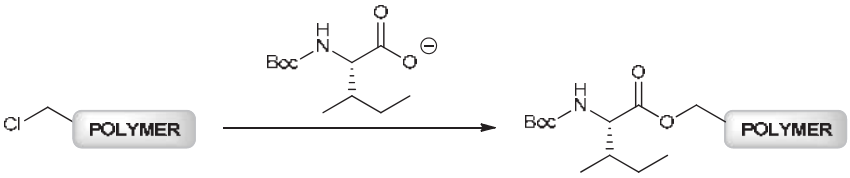


Then, the Boc protecting group is removed and a new peptide bond is formed with a Boc-protected amino acid, using DCC. This two-step process (removal of the Boc protecting group, followed by peptide bond formation) is then repeated to install each additional residue, until the desired sequence has been assembled. Finally, the Boc protecting group is removed and the desired peptide is detached from the polymer, as shown:

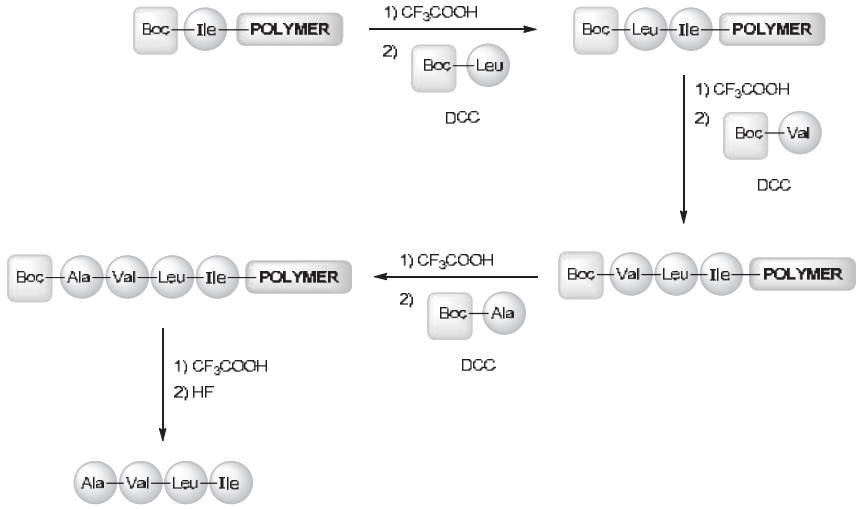
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(b) First, we attach the appropriate Boc-protected residue to the polymer:



Then, the Boc protecting group is removed and a new peptide bond is formed with a Boc-protected amino acid, using DCC. This two-step process (removal of the Boc protecting group, followed by peptide bond formation) is then repeated to install each additional residue, until the desired sequence has been assembled. Finally, the Boc protecting group is removed and the desired peptide is detached from the polymer, as shown:



25.38. First, a protected valine residue is connected to the polymer. After deprotection, a protected alanine residue is installed. Then, after deprotection again, a protected phenylalanine residue is installed. Deprotection, followed by detachment from the polymer, gives the following tripeptide:

(N terminus) Val-Ala-Phe (C terminus)

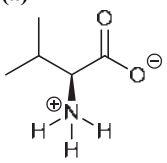
25.39. The regions that contain repeating glycine and/or alanine units are the most likely regions to form β sheets:

Trp-His-Pro-Ala-Gly-Gly-Ala-Val-His-Cyst-Asp-Ser-Arg-Arg-Ala-Gly-Ala-Phe

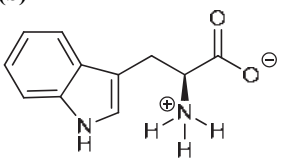
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25.40. In each case, the carboxylic acid group is drawn in its deprotonated form (as a carboxylate ion), and the amino group is drawn in its protonated form (as an ammonium ion):

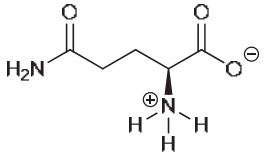
(a)



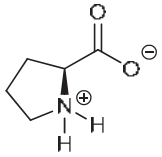
(b)



(c)



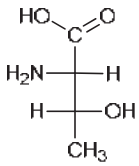
(d)



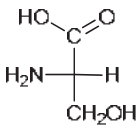
25.41. When applying the Cahn-Ingold-Prelog convention for assigning the configuration of a chiral center, the amino group generally receives the highest priority (1), followed by the carboxylic acid group (2), followed by the side chain (3), and finally the H (4). Accordingly, the *S* configuration is assigned to L amino acids. Cysteine is the one exception because the side chain has a higher priority than the carboxylic acid group. As a result, the *R* configuration is assigned.

25.42.

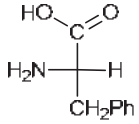
(a) L-threonine has two chiral centers (see Table 25.1). The configuration of each of these chiral centers is shown in the following Fischer projection:



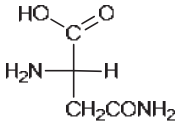
(b) L-Serine has only one chiral center (see Table 25.1). The configuration of this chiral center is shown in the following Fischer projection:



(c) L-Phenylalanine has only one chiral center (see Table 25.1). The configuration of this chiral center is shown in the following Fischer projection:



(d) L-Asparagine has only one chiral center (see Table 25.1). The configuration of this chiral center is shown in the following Fischer projection:



25.43.

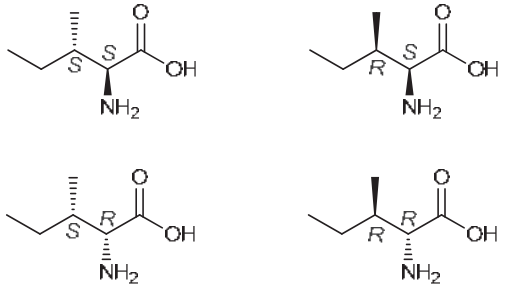
(a) Isoleucine and threonine each have two chiral centers (see Table 25.1).

(b) The Cahn-Ingold Prelog convention (SkillBuilder 5.4) gives the following configurations:

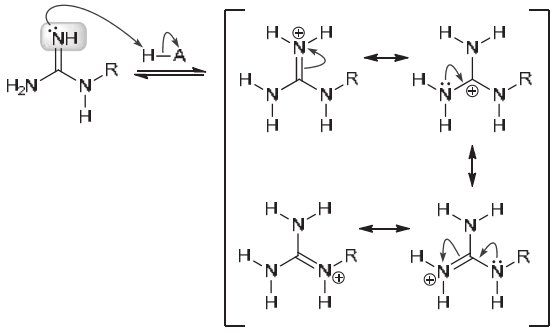
Isoleucine = 2*S*, 3*S*

Threonine = 2*S,* 3*R*

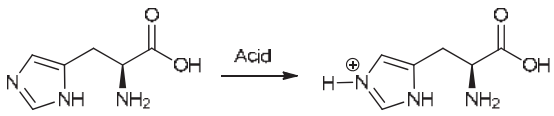
25.44. Isoleucine has two chiral centers, so we expect four possible stereoisomers, shown here. The configuration of each chiral center is shown.



25.45. Protonation of the highlighted nitrogen atom gives a conjugate acid that is highly stabilized by resonance (the positive charge is highly delocalized).



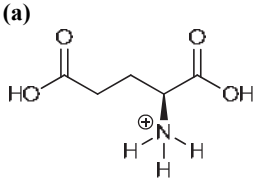
25.46. The protonated form below is aromatic. In contrast, protonation of the other nitrogen atom in the ring would result in loss of aromatic stabilization.



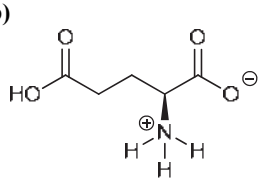
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25.47. In each case, we first identify the pK_a of the carboxylic acid group and determine which form predominates. The protonated form (RCOOH) will predominate if pH < pK_a, while the carboxylate ion will predominate if pH > pK_a. Next, we identify the pK_a of the α-amino group and determine which form predominates. The protonated form (RNH_3^+) will predominate if pH < pK_a, while the uncharged form (RNH_2) will predominate if pH > pK_a. Finally, a similar analysis is performed for the side chain (if necessary). See Table 25.2 for pK_a values.

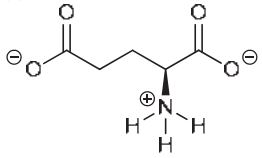
(a)



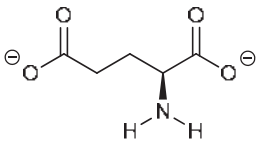
(b)



(c)

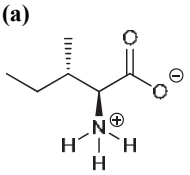


(d)

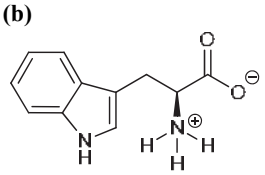


25.48. At physiological pH, each of the carboxylic acid groups is deprotonated (and will exist primarily as a carboxylate ion), while each of the amino groups is protonated (and will exist primarily as an ammonium ion):

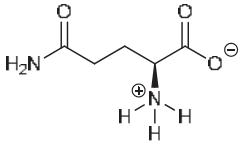
(a)



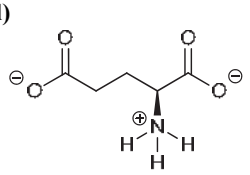
(b)



(c)



(d)



25.49.

(a) L-Alanine does not have an acidic side chain or a basic side chain, so the pI of L-alanine is calculated using the pK_a value of the carboxylic acid group and the pK_a value of the ammonium group, as shown here (pK_a values can be found in Table 25.2):

$$\text{pI} = \frac{2.34 + 9.69}{2} = 6.02$$

(b) L-Asparagine does not have an acidic side chain or a basic side chain, so the pI of L-asparagine is calculated using the pK_a value of the carboxylic acid group and the pK_a value of the ammonium group, as shown here (pK_a values can be found in Table 25.2):

$$\text{pI} = \frac{2.02 + 8.80}{2} = 5.41$$

(c) L-Histidine has a basic side chain. As such, the pI of L-histidine is calculated using the pK_a values of the two ammonium groups, as shown here (pK_a values can be found in Table 25.2):

$$\text{pI} = \frac{9.17 + 6.00}{2} = 7.58$$

(d) L-Glutamic acid has two carboxylic acid groups, so the pI of L-glutamic acid is calculated using the pK_a values of the two carboxylic acid groups, as shown here (pK_a values can be found in Table 25.2):

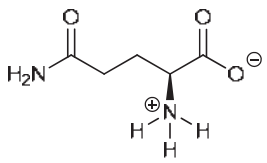
$$\text{pI} = \frac{2.19 + 4.25}{2} = 3.22$$

25.50. Lysozyme is likely to be comprised primarily of amino acid residues that contain basic side chains (arginine, histidine, and lysine), while pepsin is comprised primarily of amino acid residues that contain acidic side chains (aspartic acid and glutamic acid).

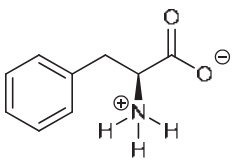
25.51. First, we must calculate the pI for each amino acid (using the procedure shown in the solution to Problem 25.49). Next, we identify the pK_a of the carboxylic acid group and determine which form predominates. The protonated form (RCOOH) will predominate if pI < pK_a, while the carboxylate ion will predominate if pI > pK_a.

Then, we identify the pK_a of the α-amino group and determine which form predominates. The protonated form (RNH_3^+) will predominate if pI < pK_a, while the uncharged form (RNH_2) will predominate if pI > pK_a. Finally, a similar analysis is performed for the side chain (if necessary). See Table 25.2 for pK_a values.

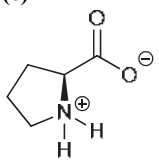
(a)



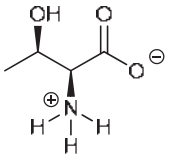
(b)



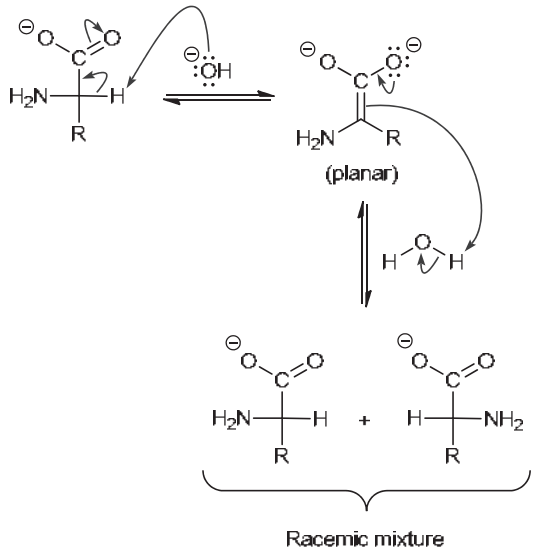
(c)



(d)



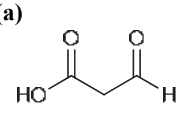
25.52. Under strongly basic conditions (NaOH), the carboxylic acid group exists as a carboxylate ion.
Under these conditions, the α position can be deprotonated, giving a dianion (resonance-stabilized). This dianion can be protonated by water (at the α position), thereby regenerating the carboxylate ion. In the process, racemization occurs at the α position because the α position is sp^2 hybridized (trigonal planar) in the dianion intermediate. Protonation of the dianion can occur on either face of the plane (with equal likelihood), giving a racemic mixture.



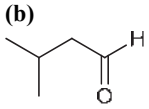
25.53. The pI of Gly = 5.97, the pI of Gln = 5.65, and the pI of Asn = 5.41. Using these values, we make the following predictions:
(a) At pH = 6.0, Asn will travel the farthest distance.
(b) At pH = 5.0, Gly will travel the farthest distance.

25.54. When treated with ninhydrin, the carboxylic acid group (connected to the α position) and the amino group (connected to the α position) are both removed, and the α position becomes an aldehyde group, giving the following products:

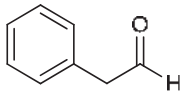
(a)



(b)



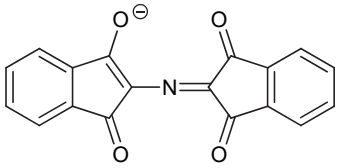
(c)



(d) Ninhydrin does not react with proline because the amino group is not primary.

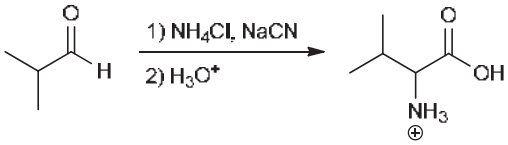
25.55.
(a) When treated with ninhydrin, each of the amino acids (except proline) is converted into an aldehyde with complete removal of the carboxylic acid group and the amino group (that are connected to the α position). Therefore, the identity of each aldehyde indicates the side chain of the corresponding amino acid from which it was made (see Table 25.1). This analysis reveals that the starting mixture must have contained methionine, valine, and glycine.

(b) The following purple product is obtained whenever ninhydrin reacts with an amino acid (except for proline).



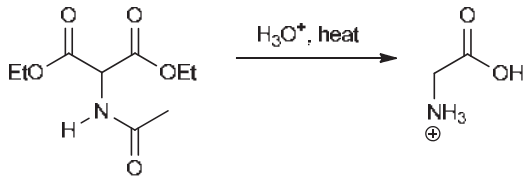
(c) The compound is highly conjugated and has a λ_{max} that is greater than 400 nm (see Section 16.12)

25.56. Valine can be made from the following aldehyde (via a Strecker synthesis), as shown:

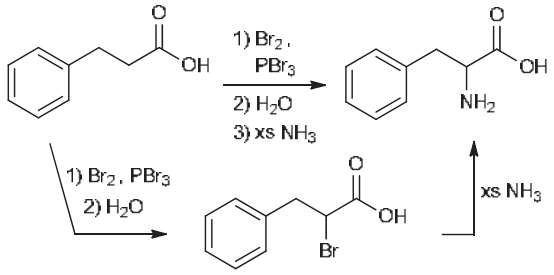


25.57. Alanine can be prepared via the amidomalonate synthesis with higher yields than valine, because the former requires an S_N2 reaction with a primary alkyl halide, while the latter requires an S_N2 reaction with a secondary (more hindered) alkyl halide.

25.58. The side chain (R) of glycine is a hydrogen atom (H). Therefore, no alkyl group needs to be installed at the α position.

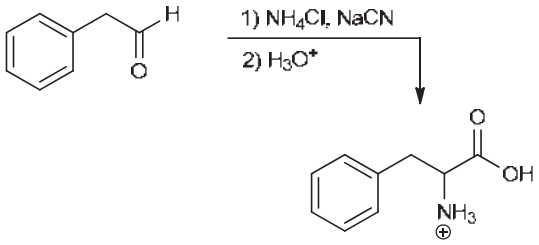


25.59.
(a) The reagents indicate a Hell-Volhard-Zelinsky reaction (thereby installing a bromine atom at the α position), followed by an S_N2 reaction (thereby replacing the bromine atom with an amino group). The product is an amino acid (phenylalanine), as shown:

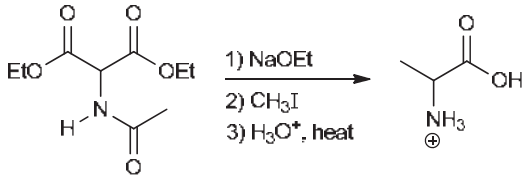


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(b) The reagents indicate a Strecker synthesis, giving an amino acid (phenylalanine), as shown:

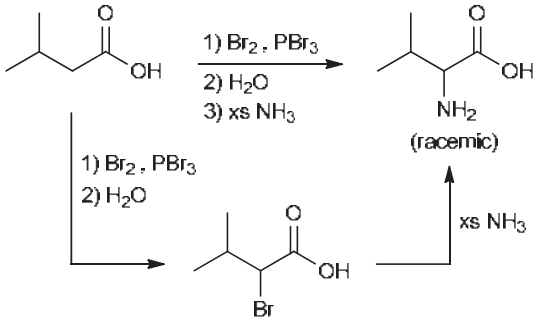


(c) The reagents indicate an amidomalonate synthesis, giving an amino acid (alanine), as shown:

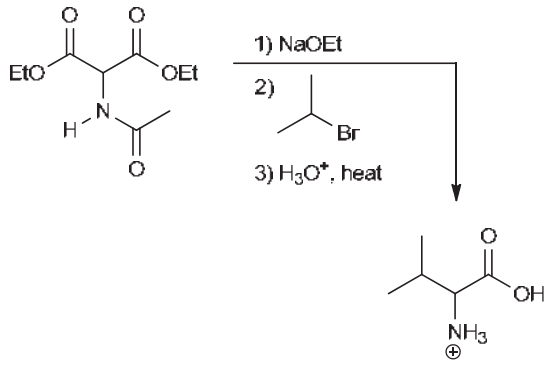


25.60.

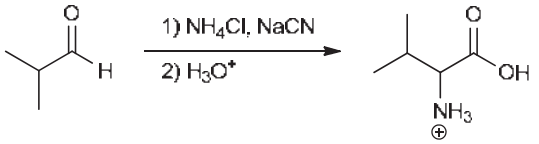
(a) Racemic valine can be made from the corresponding carboxylic acid using a Hell-Volhard-Zelinsky reaction, as shown:



(b) Racemic valine can be made from acetamidomalonate using an amidomalonate synthesis, as shown:

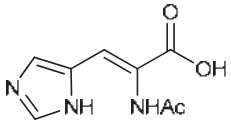


(c) Racemic valine can be made from 2-methylpropanal using a Strecker synthesis, as shown:



25.61. A pentapeptide has five amino acid residues, each of which can be any of the 20 naturally occurring amino acids. Therefore, there are $20\times20\times20\times20\times20 = 20^5 = 3{,}200{,}000$ possible pentapeptides that can be made from the naturally occurring amino acids.

25.62. L-Histidine can be prepared from the compound below via an asymmetric catalytic hydrogenation:

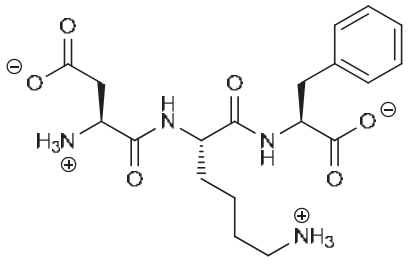


25.63. Below are the six possible sequences for a tripeptide containing L-leucine, L-methionine, and L-histidine:

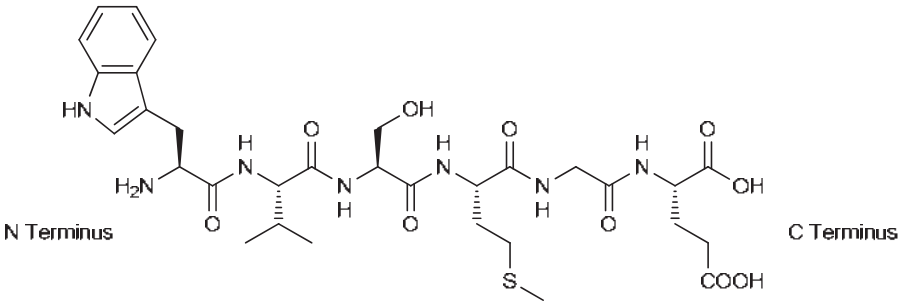
1) Leu-Met-Val
2) Leu-Val-Met
3) Met-Val-Leu,
4) Met-Leu-Val
5) Val-Met-Leu
6) Val-Leu-Met

25.64. The N terminus of this tripeptide is drawn on the left and the C terminus on the right. Side chains at the top of the drawing are on wedges, while side chains on the bottom of the drawing are on dashes. The identity of each side chain can be found in Table 25.1.

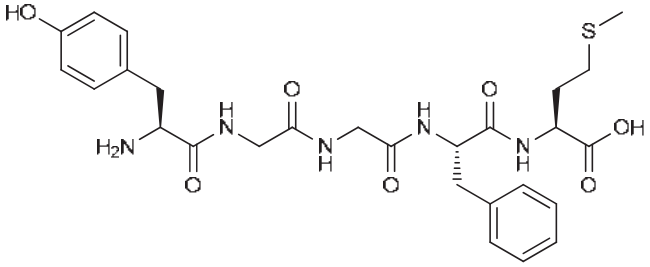
At physiological pH, the amino groups exist primarily in their protonated form (ammonium ions) while the carboxylic acid groups exist primarily in their deprotonated form (carboxylate ions):



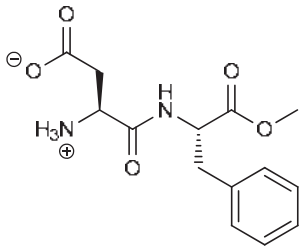
25.65. The N terminus is drawn on the left and the C terminus on the right. Side chains at the top of the drawing are on wedges, while side chains on the bottom of the drawing are on dashes. The identity of each side chain can be found in Table 25.1.



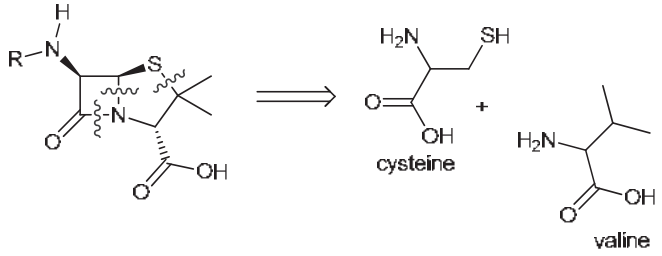
25.66. The N terminus is drawn on the left and the C terminus on the right. Side chains at the top of the drawing are on wedges, while side chains on the bottom of the drawing are on dashes. The identity of each side chain can be found in Table 25.1.



25.67. The structure of aspartame is shown in the solution to Problem 25.28. At physiological pH, the carboxylic acid group is deprotonated (and will exist primarily as a carboxylate ion), while the amino group is protonated (and will exist primarily as an ammonium ion):

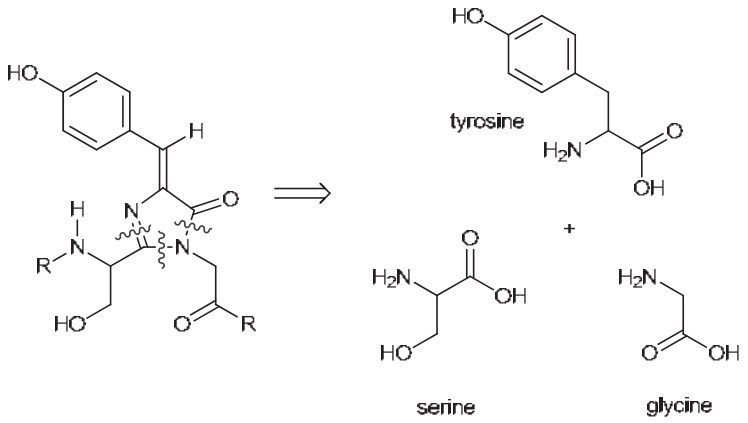


25.68. The following retrosynthetic analysis reveals the two amino acids (cysteine and valine) that are most likely utilized during the biosynthesis of penicillin antibiotics:

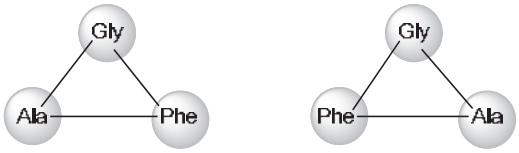


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25.69. The following retrosynthetic analysis reveals the three amino acids (tyrosine, serine, and glycine) that are necessary for biosynthesis of the fluorophore:



25.70. If a tripeptide does not react with phenyl isothiocyanate, then it must not have a free N terminus. It must be a cyclic tripeptide. Below are the two possible cyclic tripeptides:



25.71.

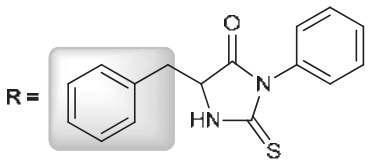
(a) Trypsin catalyzes the hydrolysis of the peptide bond at the carboxyl side of arginine, giving the following two fragments:

Arg + Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg

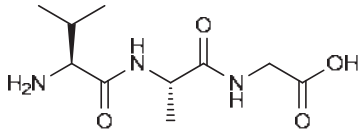
(b) Chymotrypsin catalyzes the hydrolysis of the peptide bonds at the carboxyl side of phenylalanine, giving the following three fragments:

Arg-Pro-Pro-Gly-Phe + Ser-Pro-Phe + Arg

25.72. The R group (highlighted) in the PTH derivative indicates the identity of the N-terminal residue. Since this R group is a benzylic group (–CH_2Ph), the N-terminal residue must be phenylalanine.



25.73. The first Edman degradation indicates that the N-terminal residue is valine (the R group is isopropyl). The second Edman degradation indicates that the N-terminal residue of the dipeptide is alanine. And finally, the remaining amino acid (glycine) must be at the C-terminus of the tripeptide. In summary, the tripeptide is Val-Ala-Gly, drawn here:



25.74. Only one of the trypsin fragments has a C terminus that is not arginine or lysine. This fragment (which ends with threonine), must be the last fragment in the peptide sequence. The remaining three trypsin fragments can be placed in the proper order by analyzing the chymotrypsin fragments. The correct peptide sequence is:

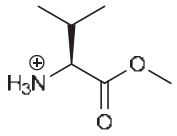
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr

There cannot be any disulfide bridges in this peptide, because it has no cysteine residues, and only cysteine residues form disulfide bridges.

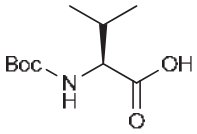
25.75. Prior to acetylation, the nitrogen atom of the amino group is sufficiently nucleophilic to attack phenyl isothiocyanate. Acetylation converts the amino group into an amide group, and the lone pair of the nitrogen atom is delocalized via resonance, rendering it much less nucleophilic.

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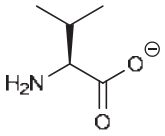
25.76.
(a) When treated with acid and methanol, the carboxylic acid group is converted into a methyl ester (via a Fischer esterification process), and the amino group is protonated, giving the following compound:



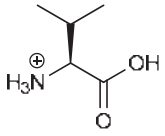
(b) When treated with di-*tert*-butyl dicarbonate, the amino group is protected with a Boc protecting group, giving the following product:



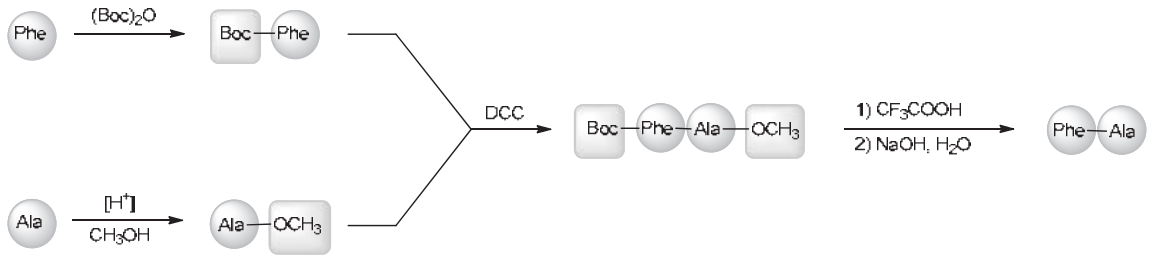
(c) Under basic conditions, the amino group is not protonated, and the carboxylic acid group is deprotonated, giving a carboxylate ion:



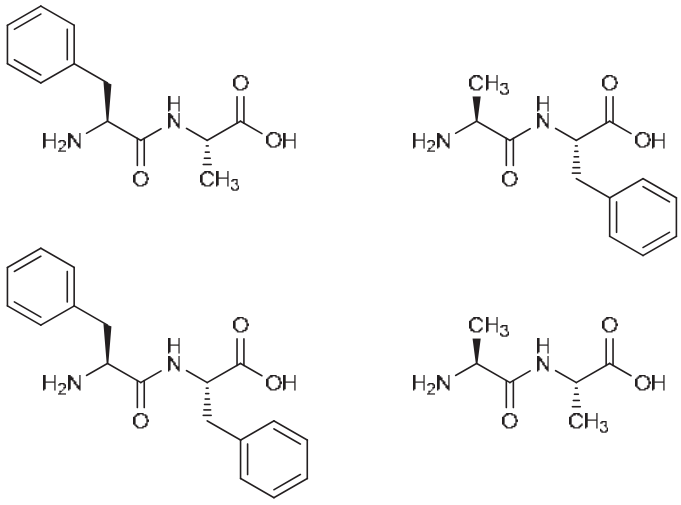
(d) Under acidic conditions, the amino group is protonated to give an ammonium ion, and the carboxylic acid group will be in its protonated form:



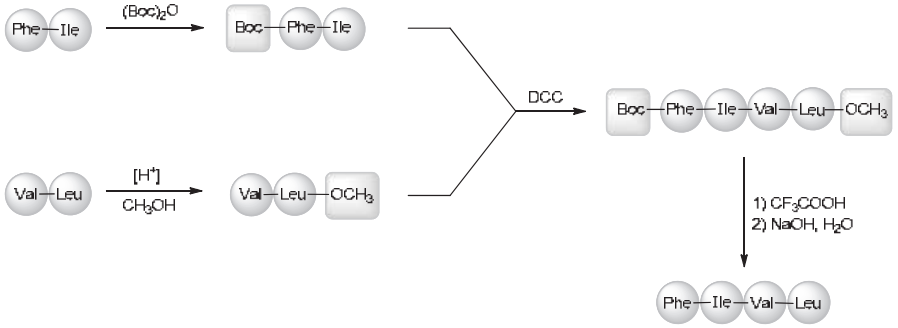
25.77. We begin by installing the appropriate protecting groups. Then, upon treatment with DCC, the protected amino acids are coupled. And finally, the protecting groups are removed, as shown:



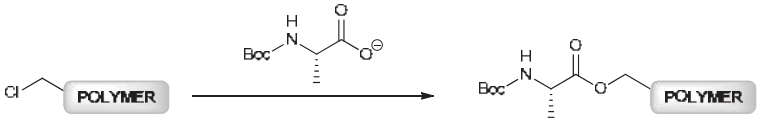
25.78. When a mixture of L-phenylalanine and L-alanine is treated with DCC, there are four possible dipeptides: 1) Phe-Ala, or 2) Ala-Phe, or 3) Phe-Phe, or 4) Ala-Ala. These four possibilities are drawn below:



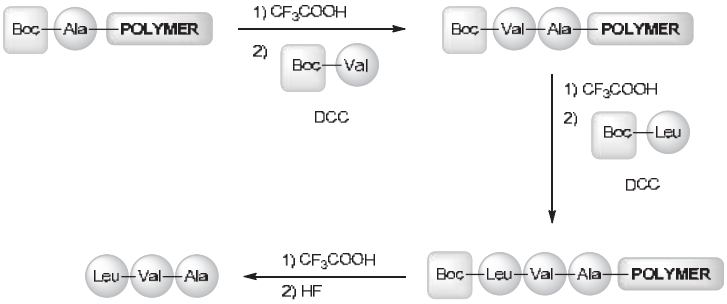
25.79. We begin by installing the appropriate protecting groups. Then, upon treatment with DCC, the protected amino acids are coupled. And finally, the protecting groups are removed, as shown:



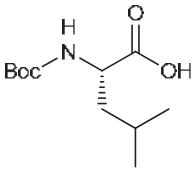
25.80. First, we attach the appropriate Boc-protected residue to the polymer:



Then, the Boc protecting group is removed and a new peptide bond is formed with a Boc-protected amino acid (valine), using DCC. This two-step process (removal of the Boc protecting group, followed by peptide bond formation) is then repeated to install the leucine residue. Finally, the Boc protecting group is removed and the desired tripeptide is detached from the polymer, as shown:



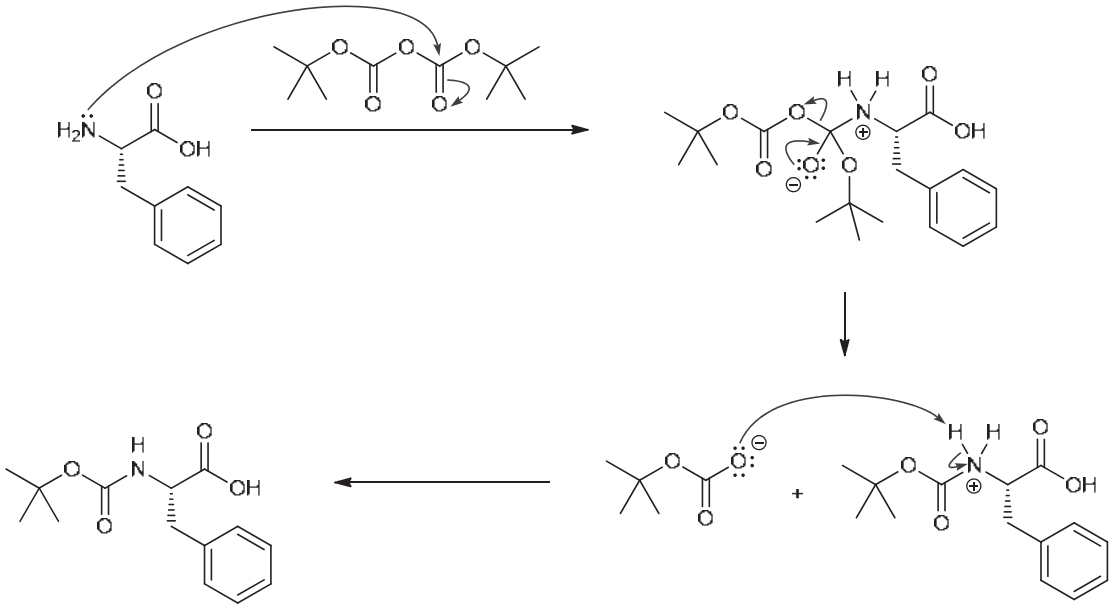
25.81. During a Merrifield synthesis, the C-terminus of the growing peptide chain remains anchored to the polymer. The C-terminus of the desired peptide (leucine enkephalin) is occupied by a leucine residue. Therefore, the following Boc-protected amino acid (leucine) must be anchored to the polymer in order to prepare leucine enkephalin via a Merrifield synthesis:



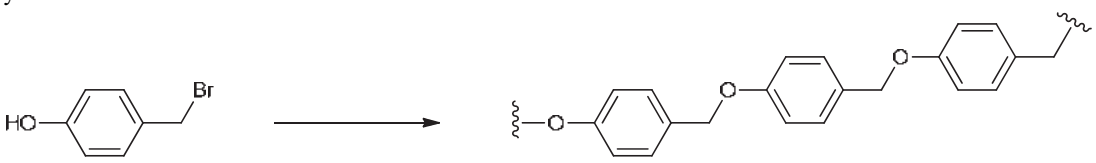
25.82. A proline residue cannot be part of an α helix, because it lacks an N-H proton and does not participate in hydrogen bonding. (The amino acid proline does indeed have an N-H group, but when incorporated into a peptide, the proline residue does not have an N-H group)

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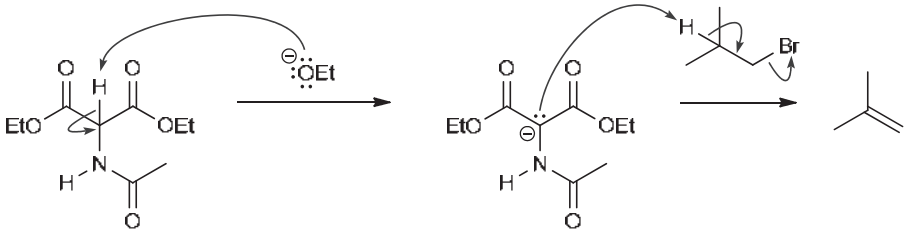
25.83. The amino group attacks one of the carbonyl groups of DCC, giving a tetrahedral intermediate. The carbonyl group is then reformed upon expulsion of a resonance-stabilized leaving group. The resulting cation is then deprotonated to give the product:



25.84. The following alkyl halide would be necessary in order to prepare tyrosine via an amidomalonate synthesis. This starting material possesses both a nucleophilic center (the OH group) as well as an electrophilic center (it is a primary benzylic bromide). As such, the molecules can react with each other via an S_N2 process, thereby forming the polymer shown:



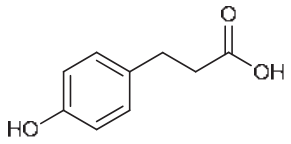
25.85. The stabilized enolate ion (formed in the first step) can function as a base, rather than a nucleophile, giving an E2 reaction:



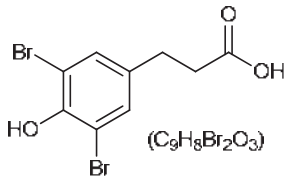
25.86. The lone pair on that nitrogen atom is highly delocalized via resonance and is participating in aromaticity. Accordingly, the lone pair is not available to function as a base.

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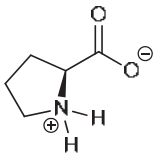
25.87.
(a) The Hell-Volhard-Zelinsky reaction will install a bromine atom at the α position of a carboxylic acid. This bromine atom can then be replaced with an amino group via an S_N2 process. As such, the following carboxylic acid is necessary in order to prepare tyrosine via a Hell-Volhard-Zelinsky reaction:



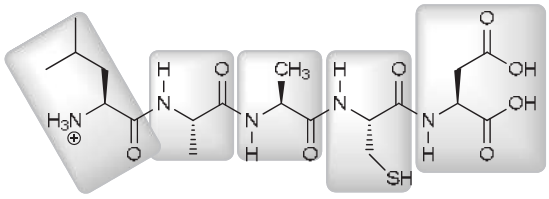
(b) The aromatic ring is highly activated toward electrophilic aromatic substitution, as a result of the presence of the OH group, which is an *ortho-para* director (as seen in Chapter 19). Therefore, the ring can undergo bromination in the two positions that are *ortho* to the OH group (the *para* position is already occupied), giving the following product:



25.88. At physiological pH, a carboxylic acid group is expected to exist predominantly as a carboxylate ion, and the amino group is expected to exist primarily as an ammonium ion. Option (d) is the correct answer.

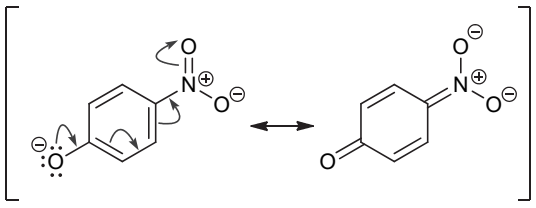


25.89. The compound is constructed from five amino acid residues, as highlighted below, and is therefore a pentapeptide:



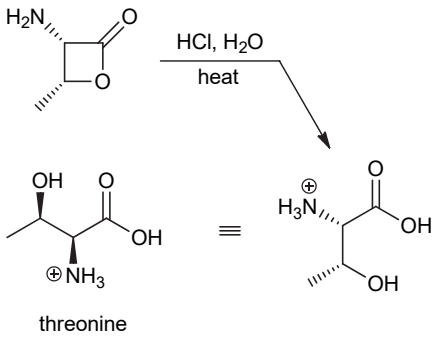
25.90. At low temperature, the barrier to rotation keeps the two methyl groups in different electronic environments (one is *cis* to the C=O bond and the other is *trans* to the C=O bond), and as a result, they give rise to separate signals. At high temperature, there is sufficient energy to overcome the energy barrier, and the protons change electronic environments on a timescale that is faster than the timescale of the NMR spectrometer. The result is an averaging effect which gives rise to only one signal.

25.91.
(a) The COOH group does not readily undergo nucleophilic acyl substitution because the OH group is not a good leaving group. By converting the COOH group into an activated ester, the compound can now undergo nucleophilic acyl substitution because it has a good leaving group.
(b) The nitro group stabilizes the leaving group via resonance. As described in Chapter 19, the nitro group serves as a reservoir for electron density:



(c) The nitro group must be in the *ortho* or *para* position in order to stabilize the negative charge via resonance (as shown above). If the nitro group is in the *meta* position, the negative charge cannot be pushed onto the nitro group.

25.92. Hydrolysis of the ester group gives threonine, as shown here:



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Chapter 26
Lipids

Review of Concepts

Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 26. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- **Lipids** are naturally occurring compounds that are extracted from cells using _____ solvents.
- **Complex lipids** readily undergo _____, while **simple lipids** do not.
- _____ are high molecular weight esters that are constructed from carboxylic acids and alcohols.
- _____ are the triesters formed from glycerol and three long-chain carboxylic acids, called **fatty acids**. The resulting triglyceride is said to contain three fatty acid _____.
- For saturated fatty acids, the melting point increases with increasing _____ _____. The presence of a _____ double bond causes a decrease in the melting point.
- Triglycerides that are solids at room temperature are called _____, while those that are liquids at room temperature are called _____.
- Triglycerides containing unsaturated fatty acid residues will undergo hydrogenation. During the hydrogenation process, some of the double bonds can isomerizes to give _____ π bonds
- In the presence of molecular oxygen, triglycerides are particularly susceptible to oxidation at the _____ position to produce hydroperoxides.
- Transesterification of triglycerides can be achieved either via _____ catalysis or _____ catalysis to produce biodiesel.
- _____ are similar in structure to triglycerides except that one of the three fatty acid residues is replaced by a phosphoester group.
- The structures of **steroids** are based on a tetracyclic ring system, involving three six-membered rings and one _____-membered ring.
- The ring fusions are all _____ in most steroids, giving steroids their rigid geometry.
- All steroids, including cholesterol, are biosynthesized from _____.
- Prostaglandins contain twenty carbon atoms and are characterized by a _____-membered ring with two side chains.
- **Terpenes** are a class of naturally occurring compounds that can be thought of as being assembled from _____ units.
- A terpene with 10 carbon atoms is called a _____, while a terpene with 20 carbon atoms is called a _____.

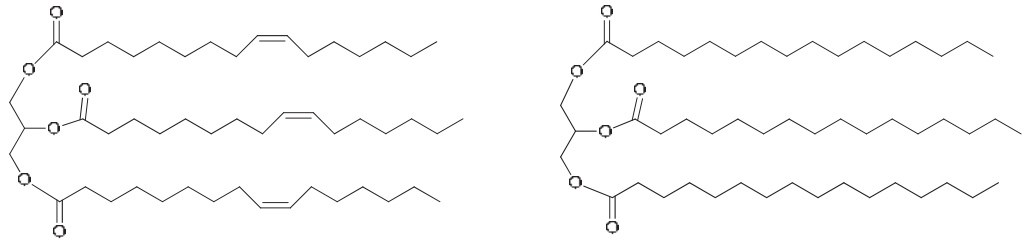
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Review of Skills

Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 26. The answers appear in the section entitled *SkillBuilder Review*.

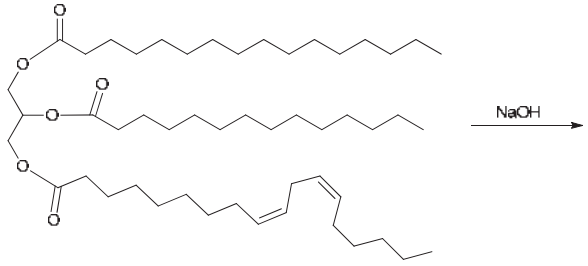
26.1 Comparing Molecular Properties of Triglycerides

CIRCLE THE TRIGLYCERIDE BELOW THAT IS EXPECTECD TO HAVE A HIGHER MELTING POINT.



26.2 Identifying the Products of Triglyceride Hydrolysis

DRAW THE PRODUCTS OBTAINED WHEN THE FOLLOWING TRIGLYCERIDE IS TREATED WITH AQUEOUS SODIUM HYDROXIDE.

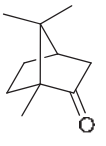


26.3 Drawing a Mechanism for Transesterification of a Triglyceride

PROTON TRANSFER	NUCLEOPHILIC ATTACK	PROTON TRANSFER	PROTON TRANSFER	LOSS OF A LEAVING GROUP	PROTON TRANSFER
A _____ _____ IS PROTONATED	THE _____ FUNCTIONS AS A NUCLEOPHILE AND ATTACKS THE PROTOANTED CARBONYL GROUP	THE RESULTING _____ INTERMEDIATE IS DEPROTOANTED, THEREBY REMOVING THE POSITIVE CHARGE	THE _____ _____ IS PROTONATED	THE _____ _____ IS REGENERATED VIA EXPULSION OF THE LEAVING GROUP	DEPROTONATION YIELDS THE PRODUCT

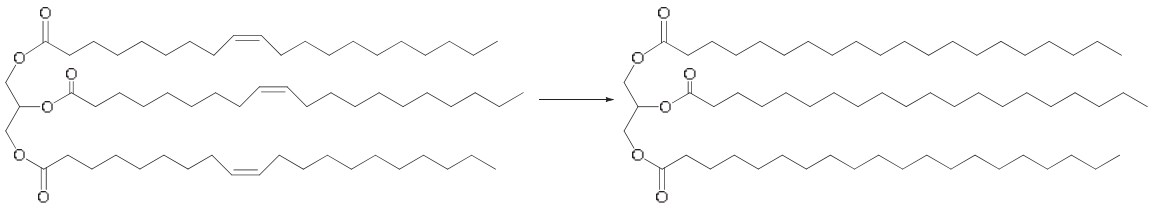
26.4 Identifying Isoprene Units in a Terpene

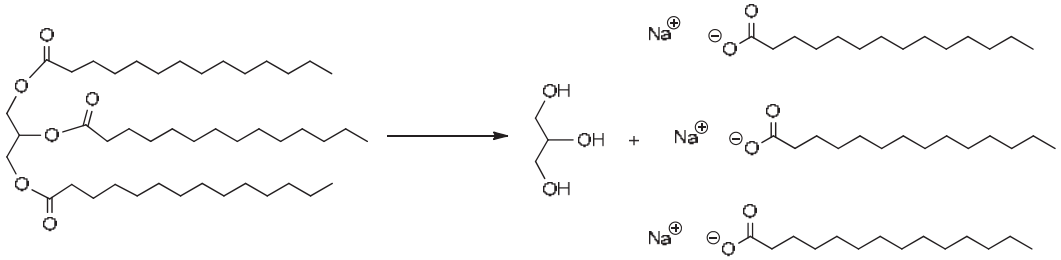
IDENTIFY THE ISOPRENE UNITS IN THE FOLLOWING TERPENE

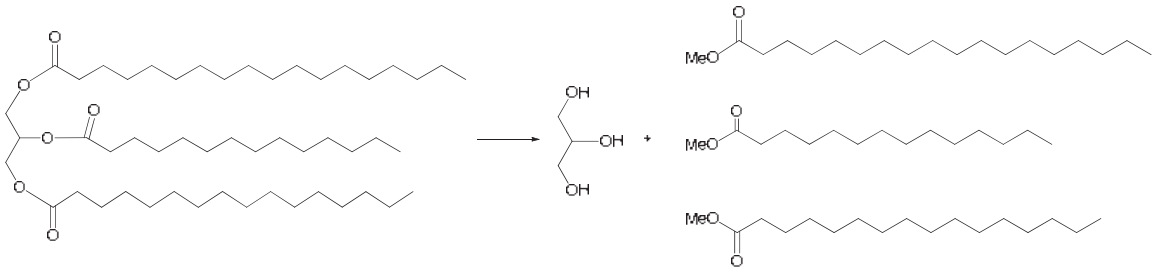


Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 26. The answers appear in the section entitled *Review of Reactions*.





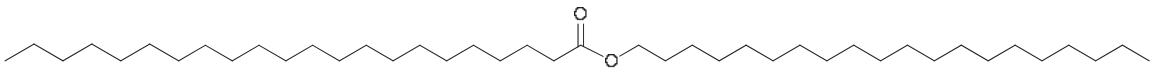


Solutions

26.1 Hydrolysis of triacontyl hexadecanoate gives a carboxylic acid with sixteen carbon atoms and an alcohol with thirty carbon atoms, as shown:



26.2. The products of hydrolysis suggest the following ester:



26.3.
(a) Trimyristin is expected to have a higher melting point because the fatty acid residues in trimyristin have more carbon atoms than the fatty acid residues of trilaurin.

(b) Triarachidin is expected to have a higher melting point because the fatty acid residues in triarachidin have more carbon atoms and less unsaturation than the fatty acid residues of trilinolein.

(c) Triolein is expected to have a higher melting point because the fatty acid residues in triolein have less unsaturation than the fatty acid residues of trilinolein.

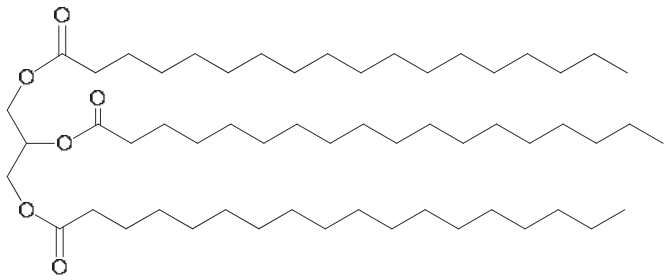
(d) Tristearin is expected to have a higher melting point because the fatty acid residues in tristearin have more carbon atoms than the fatty acid residues of trimyristin.

26.4. Of the three triglycerides, tristearin is expected to have the highest melting point because the fatty acid residues in tristearin have more carbon atoms and less unsaturation than the fatty acid residues of tripalmitolein or tripalmitin. Tripalmitolein is expected to have the lowest melting point because the fatty acid residues in tripalmitolein have fewer carbon atoms and more unsaturation than the fatty acid residues of tristearin or tripalmitin.

26.5. The fatty acid residues in triarachidin have more carbon atoms than the fatty acid residues in tristearin. Therefore, triarachadin is expected to have a higher melting point. It should be a solid at room temperature, and should therefore be classified as a fat, rather than an oil. Therefore, triglycerides made from lauric acid will also have a low melting point.

26.6.
(a) All three fatty acid residues are saturated, with either 16 or 18 carbon atoms, so the triglyceride is expected to have a high melting point. It should be a solid at room temperature, so it is a fat.
(b) All three fatty acid residues are unsaturated, so the triglyceride is expected to have a low melting point. It should be a liquid at room temperature, so it is an oil.

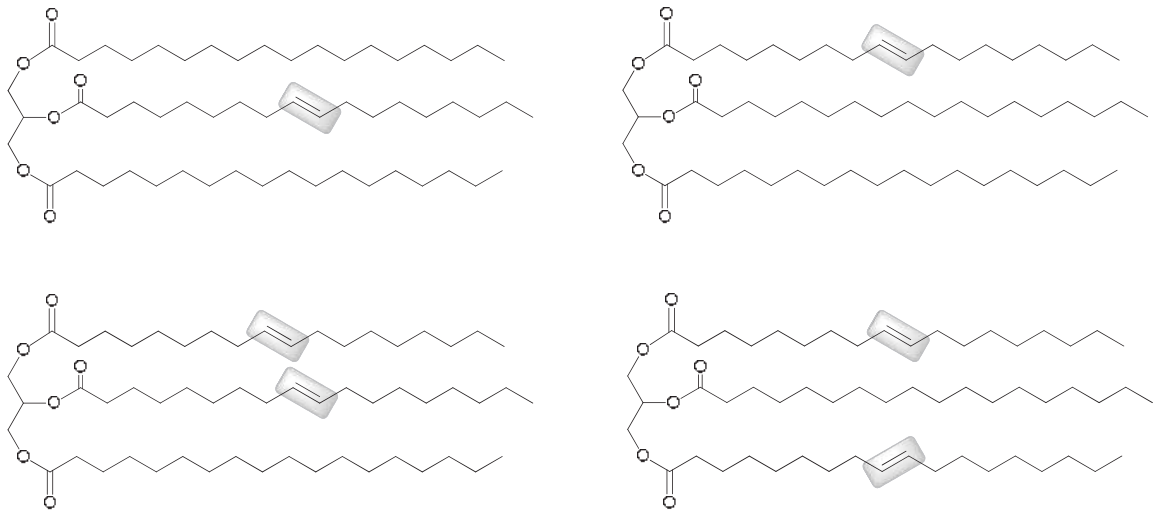
26.7.
(a) The C=C bond in each oleic acid residue undergoes hydrogenation, giving the following saturated triglyceride:



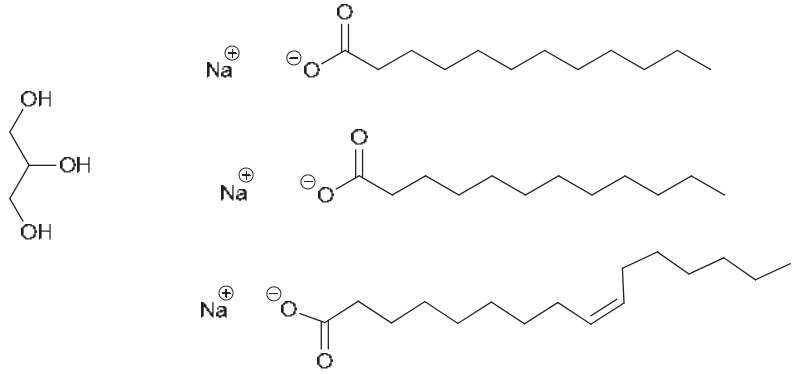
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(b) The triglyceride obtained from hydrogenation (shown above) has three stearic acid residues, so it is called tristearin.
(c) Tristearin is expected to have a higher melting point because the fatty acid residues in tristearin are saturated, while the fatty acid residues of triolein are unsaturated.
(d) Upon treatment with aqueous base, each of the ester groups will undergo hydrolysis, giving three equivalents of stearic acid.

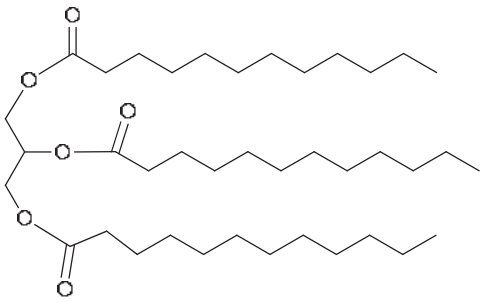
26.8. There are three fatty acid residues. Partial hydrogenation indicates that either one or two of these residues has a double bond (in the *trans* configuration). There are two isomers that exhibit one C=C bond, and there are two isomers that exhibit two C=C bonds, as shown here:



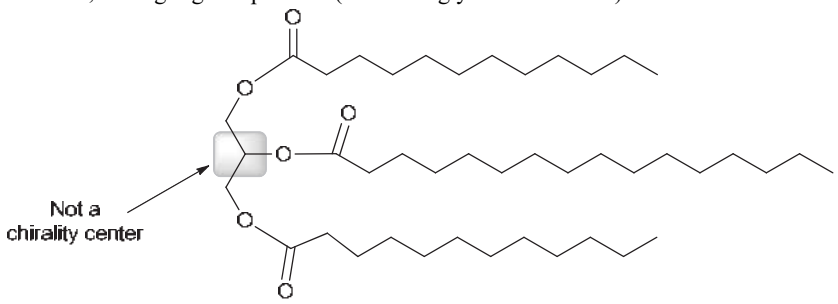
26.9. When a triglyceride is treated with aqueous base, each of the ester groups is hydrolyzed, giving glycerol and three carboxylate ions, as shown:



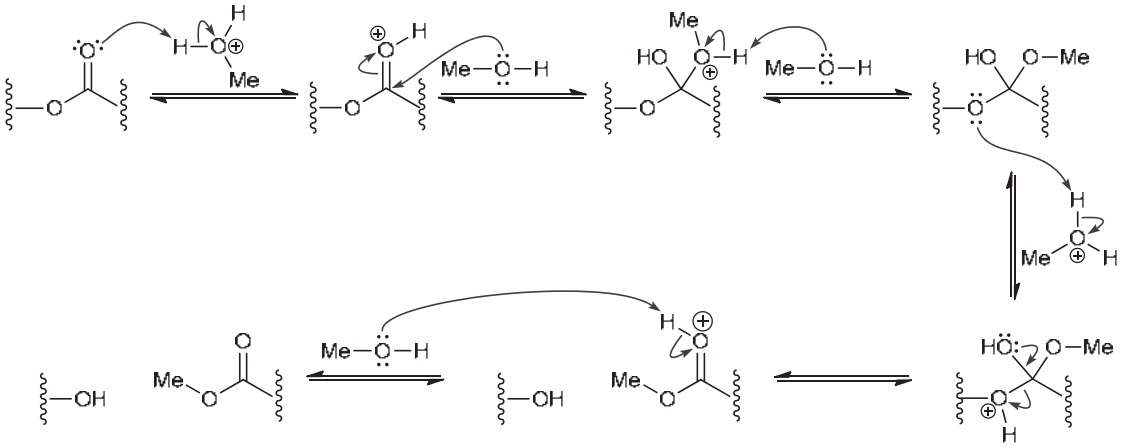
26.10. The products of hydrolysis indicate that the starting triglyceride has three lauric acid residues, as shown:



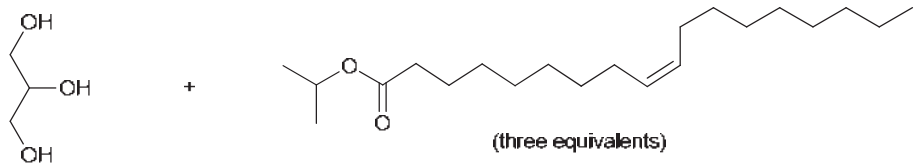
26.11. The products of hydrolysis indicate that the starting triglyceride has two lauric acid residues and one palmitic acid residue. In order to be achiral, the palmitic acid residue must be connected to C2 of the glycerol backbone, as shown below. Otherwise, the highlighted position (C2 of the glycerol backbone) would be a chiral center:



26.12. Each of the three ester groups undergoes transesterification via the following mechanism. The carbonyl group is protonated and the resulting resonance-stabilized cation is then attacked by methanol, giving a tetrahedral intermediate (an oxonium ion). Deprotonation, followed by protonation, gives another oxonium ion, which then loses a leaving group, thereby regenerating the carbonyl group. Deprotonation then gives the products (glycerol and three equivalents of the ester):

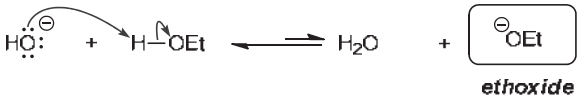


26.13. When triolein undergoes transesterification with isopropyl alcohol, the glycerol backbone is released, along with three equivalents of the isopropyl ester shown:



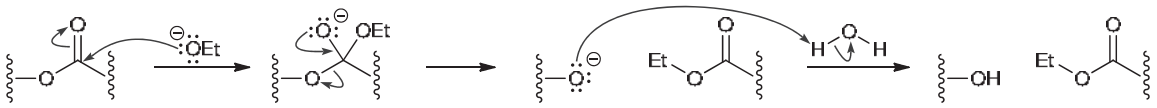
26.14.

(a) Hydroxide functions as a catalyst by establishing an equilibrium in which some ethoxide ions are present.



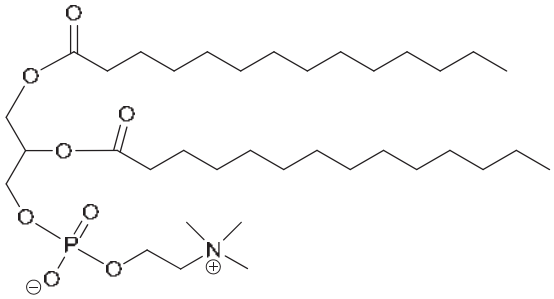
Then, each ester group undergoes transesterification via the following mechanism. The carbonyl group is attacked by ethoxide, giving a tetrahedral intermediate (an alkoxide ion). The carbonyl group is then reformed via expulsion of an alkoxide leaving group, which is then protonated by water, giving glycerol and three equivalents of an ethyl ester, as shown.

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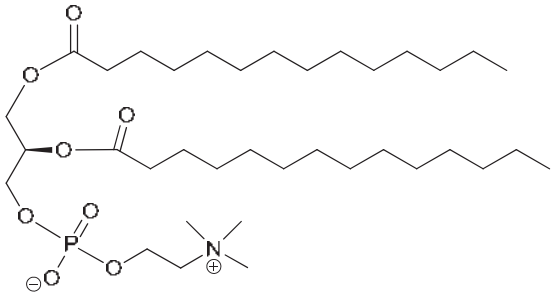


(b) Hydroxide can function as a nucleophile and attack each ester group directly, giving hydrolysis rather than transesterification.

26.15.
(a) The following lecithin has two myristic acid residues:

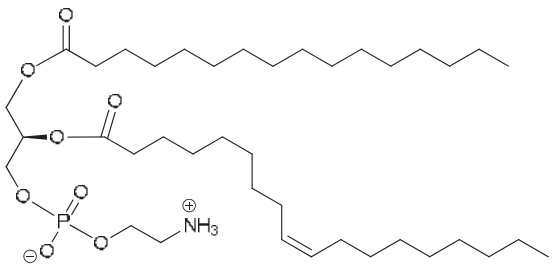


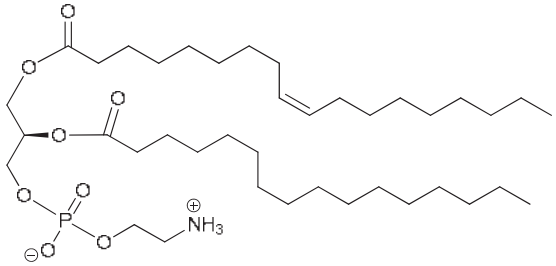
(b) The C2 position (of a lecithin) will be a chiral center and will generally have the *R* configuration, as shown:



(c) No. The C2 position would no longer be a chiral center, because it would be connected to two identical groups.

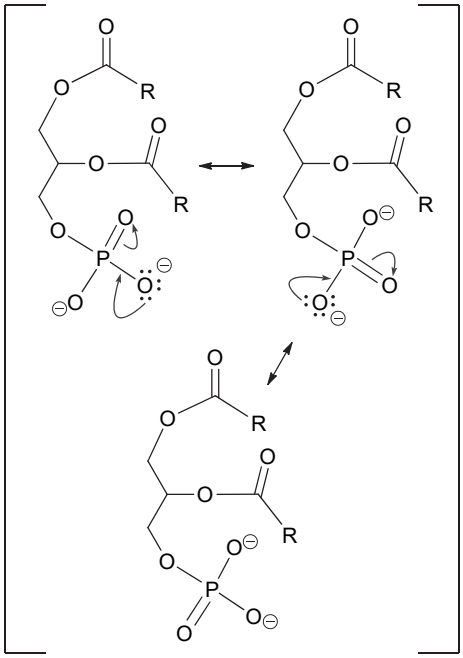
26.16.
(a) Each of the following two cephalins has one palmitic acid residue and one oleic acid residue. In each case, the C2 position is a chiral center with the *R* configuration.





(b) Yes. The C2 position would still be connected to four different groups so it would still be a chiral center.

26.17. The phosphate group has three resonance structures, as shown:



26.18. Octanol has a longer hydrophobic tail than hexanol and is therefore more efficient at crossing the nonpolar environment of the cell membrane.

26.19. No. Glycerol has three OH groups (hydrophilic) and no hydrophobic tail. It cannot cross the nonpolar environment of the cell membrane.

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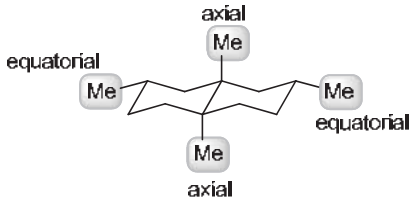
26.20. A ring-flip is not possible for *trans*-decalin because one of the rings would have to achieve a geometry that resembles a six-membered ring with a *trans*-alkene, which is not possible.



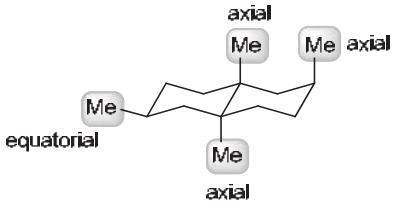
The ring fusions of cholesterol all resemble the ring fusion in *trans*-decalin, so none of the rings in cholesterol are free to undergo ring-flipping.

26.21.

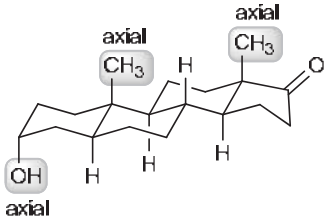
(a) The two rings are fused together in a *trans*-decalin system. The position of each substituent is labeled:



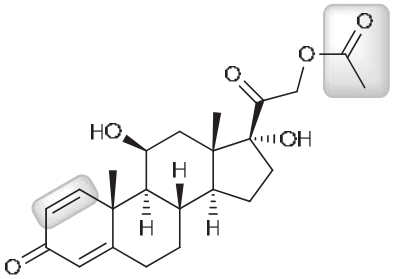
(b) The two rings are fused together in a *trans*-decalin system. The position of each substituent is labeled:



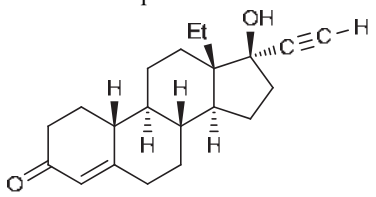
(c) Each set of neighboring rings are fused together, much like in a *trans*-decalin system. The position of each substituent is labeled:



26.22. The structure of prednisolone acetate is shown below. As described in the problem statement, this structure is different from the structure of cortisol in two ways, highlighted below:

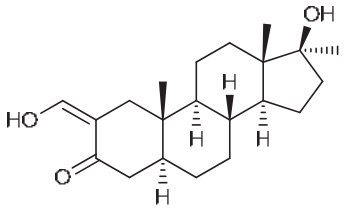


26.23. One of these compounds is extremely similar in structure to norethindrone (an oral contraceptive), except that the methyl group of norethindrone has been replaced with an ethyl group. This structure is likely norgestrel, because the problem statement indicates that nogestrel is used as an oral contraceptive.



norgestrel

Oxymetholone is an anabolic steroid and it is similar in structure to nandrolone (a synthetic androgen analogue):



oxymetholone

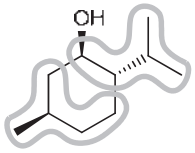
26.24.

(a) This prostaglandin has the PGE substitution pattern, and there is only one π bond in the side chains, so this compound is PGE_1 .

(b) This prostaglandin has the PGF substitution pattern, and there is only one π bond in the side chains. For a PGF substitution pattern, an additional descriptor is added to the name to indicate the configuration of the OH groups. A *cis* diol is designated as α, so this compound is $PGF_{1\alpha}$.

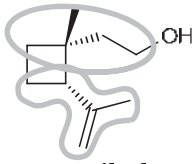
26.25.

(a) This terpene has ten carbon atoms and is therefore comprised of two isoprene units, shown here:



menthol

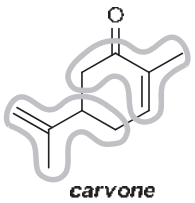
(b) This terpene has ten carbon atoms and is therefore comprised of two isoprene units, shown here:



grandisol

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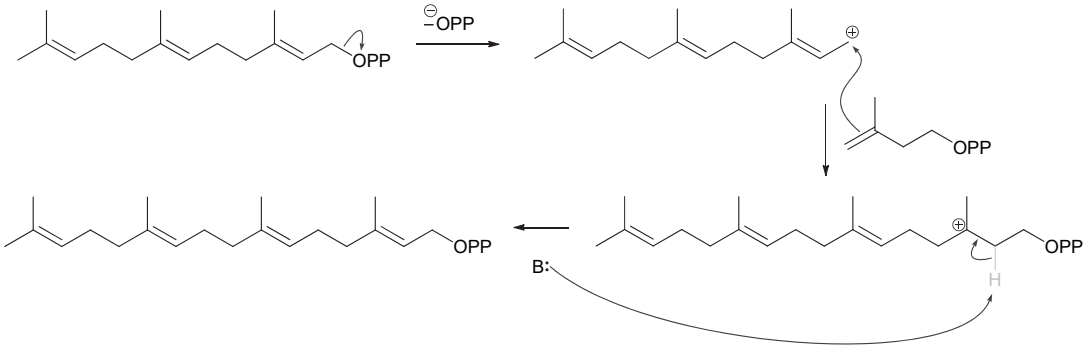
(c) This terpene has ten carbon atoms and is therefore comprised of two isoprene units, shown here:



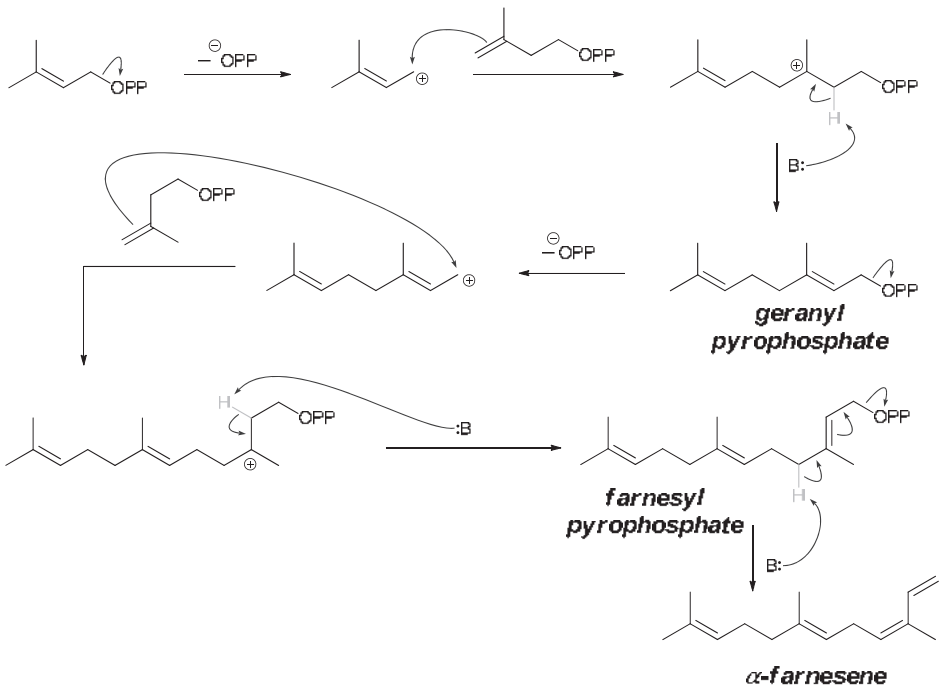
carvone

26.26.
(a) Yes, this compound has 10 carbon atoms and is comprised of two isoprene units.
(b) No, this compound is not a terpene, because it has 11 carbon atoms. In order to be a terpene, the number of carbon atoms must be divisible by 5.
(c) No, this compound is not a terpene, because it has 11 carbon atoms. In order to be a terpene, the number of carbon atoms must be divisible by 5.
(d) This compound has 10 carbon atoms, but the branching pattern cannot be achieved by joining two isoprene units, so this compound is not a terpene.

26.27. The pyrophosphate leaving group is expelled to give a resonance-stabilized (allylic) carbocation. The π bond of isopentyl phosphate then functions as a nucleophile and attacks the carbocation. Finally, a basic amino acid residue of the enzyme removes a proton to give the product:



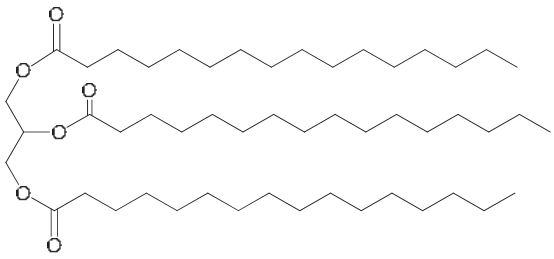
26.28. The pyrophosphate leaving group is expelled to give a resonance-stabilized (allylic) carbocation. The π bond of isopentyl phosphate then functions as a nucleophile and attacks the carbocation. A basic amino acid residue of the enzyme then removes a proton to give geranyl pyrophosphate. The previous three steps are then repeated to give farnesyl pyrophosphate, followed by an elimination process to give α-farnesene, as shown:



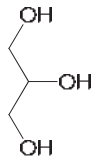
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26.29.
(a) As seen in Section 26.6, stanozolol is a steroid.
(b) As seen in Section 26.8, lycopene is a terpene.
(c) As seen in Section 26.3, tristearin is a triglyceride.
(d) As seen in Section 26.5, lecithins are phospholipids.
(e) As seen in Section 26.7, PGF_2 is a prostaglandin.
(f) As seen in Section 26.2, pentadecyl octadecanoate is a wax.

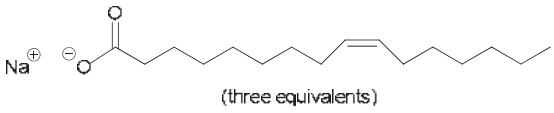
26.30.
(a) When treated with excess molecular hydrogen and a metal catalyst (Ni), the C=C bond in each palmitoleic acid residue undergoes hydrogenation, giving the following saturated triglyceride:



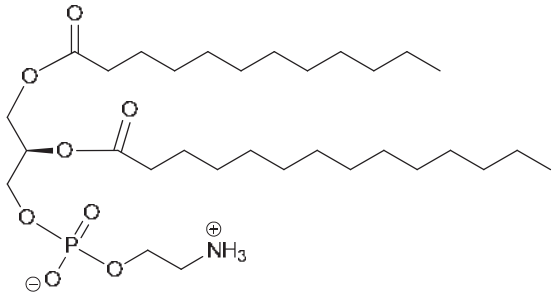
(b) When a triglyceride is treated with aqueous base, each of the ester groups is hydrolyzed, thereby releasing glycerol:

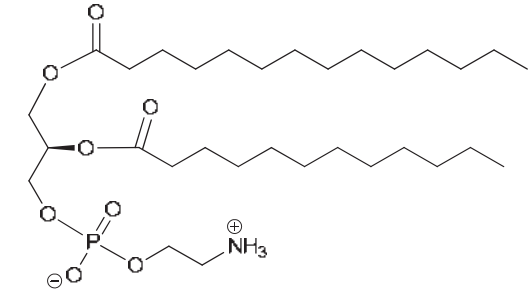


and three carboxylate ions, as shown:

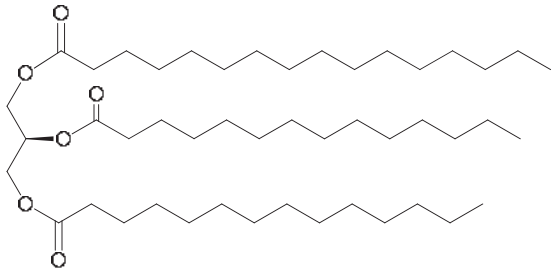


26.31. Each of the following two cephalins has one lauric acid residue and one myristic acid residue. In each case, the C2 position is a chiral center with the *R* configuration. Both compounds are chiral:



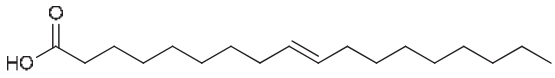


26.32. The fatty acid residues in this triglyceride are saturated, and will not react with molecular hydrogen.



26.33.
(a) This compound is an amino acid. It is not a lipid.
(b) This compound has a large hydrophobic tail and is therefore a lipid.
(c) Lycopene is terpene, which is a type of lipid.
(d) Trimyristin is a triglyceride, which is a type of lipid.
(e) Palmitic acid has a large hydrophobic tail and is therefore a lipid.
(f) D-Glucose is a carbohydrate. It is not a lipid.
(g) Testosterone is a steroid, which is a type of lipid.
(h) D-Mannose is a carbohydrate. It is not a lipid.

26.34. *trans*-Oleic acid has 18 carbon atoms and a *trans* π bond between C9 and C10, as shown:



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26.35. The fatty acid residues of tristearin are saturated and are therefore less susceptible to auto-oxidation than the unsaturated fatty acid residues in triolein.

26.36. A monoglyceride exhibits two OH groups (of the glycerol backbone) and is therefore expected to be the most water-soluble of the three compounds. A triglyceride has no OH groups (all three positions of the glycerol backbone are occupied), so a triglyceride will be the least water-soluble.

26.37. Water would not be appropriate because it is a polar solvent, and terpenes are nonpolar compounds. Hexane is a nonpolar solvent and would be suitable.

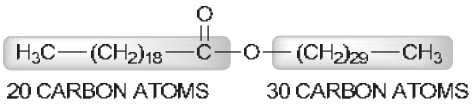
26.38.
(a) As seen in Table 26.1, palmitic acid is a saturated fatty acid.
(b) As seen in Table 26.1, myristic acid is a saturated fatty acid.
(c) As seen in Table 26.1, oleic acid is an unsaturated fatty acid.
(d) As seen in Table 26.1, lauric acid is a saturated fatty acid.
(e) As seen in Table 26.1, linoleic acid is an unsaturated fatty acid.
(f) As seen in Table 26.1, arachidonic acid is an unsaturated fatty acid.

26.39. As seen in Table 26.1, arachidonic acid has four carbon-carbon double bonds.

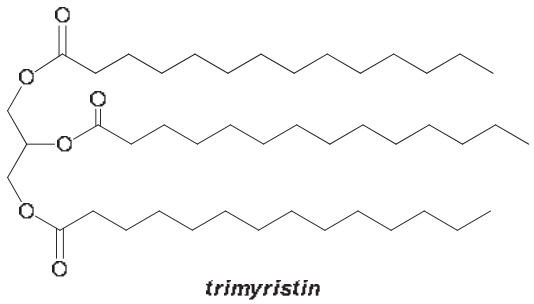
26.40.
(a) No. It is an oil.
(b) No. The fatty acid residues in triolein are unsaturated, so triolein is reactive towards molecular hydrogen in the presence of Ni.
(c) Yes. It undergoes hydrolysis to produce unsaturated fatty acids.
(d) Yes. It is a complex lipid because it undergoes hydrolysis.
(e) No. It is not an ester with a high molecular weight. It is not a wax.
(f) No. It does not have a phosphate group.

26.41.
(a) Yes. It is a fat.
(b) Yes. The fatty acid residues in tristearin are saturated, so tristearin is not reactive towards molecular hydrogen in the presence of Ni.
(c) No. It undergoes hydrolysis to produce fatty acids that are saturated.
(d) Yes. It is a complex lipid because it undergoes hydrolysis.
(e) No. It is not an ester with a high molecular weight. It is not a wax.
(f) No. It does not have a phosphate group.

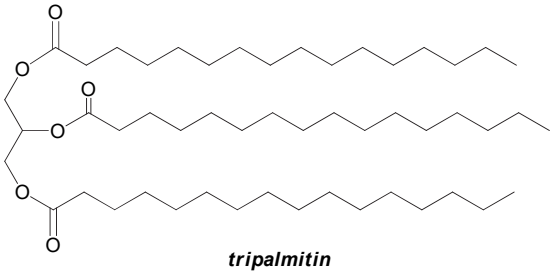
26.42. The products of hydrolysis suggest the following ester:



26.43. Trimyristin is expected to have a lower melting point than tripalmitin because the former is comprised of fatty acid residues with fewer carbon atoms (14 instead of 16).



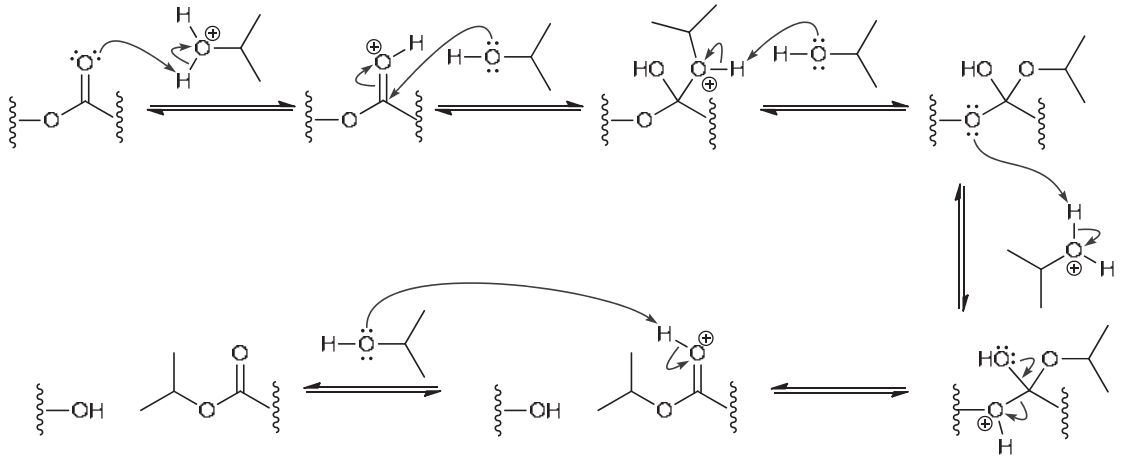
trimyristin



tripalmitin

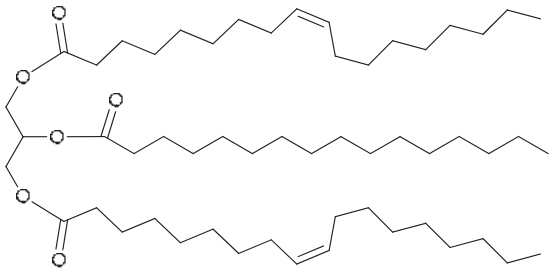
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26.44. Each of the three ester groups undergoes transesterification via the following mechanism. The carbonyl group is protonated and the resulting resonance-stabilized cation is then attacked by isopropanol, giving a tetrahedral intermediate (an oxonium ion). Deprotonation, followed by protonation, gives another oxonium ion, which then loses a leaving group, thereby regenerating the carbonyl group. Deprotonation then gives the products (glycerol and three equivalents of the isopropyl ester):



26.45. See the solution to Problem 26.14.

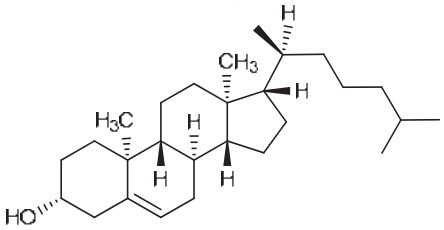
26.46. In order to be achiral, the palmitic acid residue must be connected to C2 of the glycerol backbone (shown below). Otherwise, C2 would be a chiral center. This way, C2 is connected to two identical groups, so it is not a chiral center.



26.47. In order for the triglyceride to be achiral, the palmitic acid residue cannot be connected to C2 of the glycerol backbone (as explained in the previous problem).

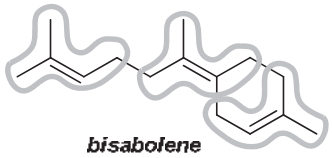


26.48. The carbon skeleton of cholesterol is redrawn, but all wedges are replaced with dashes, and all dashes are replaced with wedges, giving the following structure (the enantiomer of cholesterol):



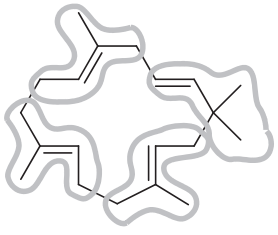
26.49.

(a) This terpene has fifteen carbon atoms and is therefore comprised of three isoprene units, shown here:



bisabolene

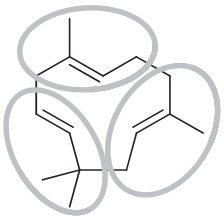
(b) This terpene has twenty carbon atoms and is therefore comprised of four isoprene units, shown here:



flexibilene

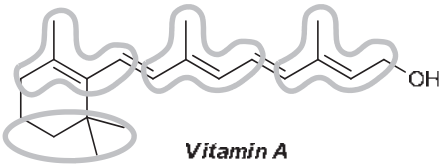
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(c) This terpene has fifteen carbon atoms and is therefore comprised of three isoprene units, shown here:



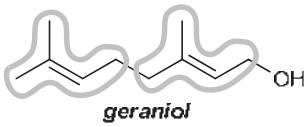
humulene

(d) This terpene has twenty carbon atoms and is therefore comprised of four isoprene units, shown here:



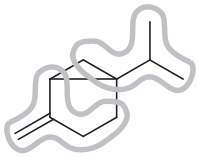
Vitamin A

(e) This terpene has ten carbon atoms and is therefore comprised of two isoprene units, shown here:



geraniol

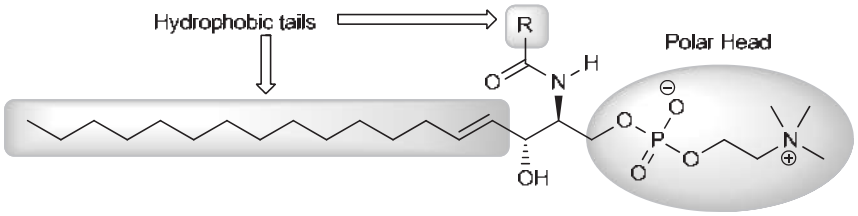
(f) This terpene has ten carbon atoms and is therefore comprised of two isoprene units, shown here:



sabinene

26.50.

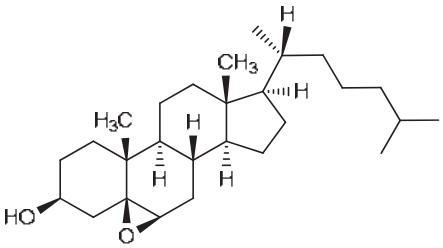
(a) The polar head and the two hydrophobic tails are labeled in the following structure:



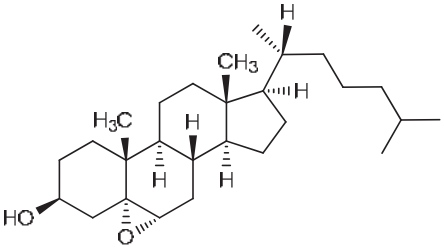
(b) Yes, they have one polar head and two hydrophobic tails. See Figure 26.6.

26.51.

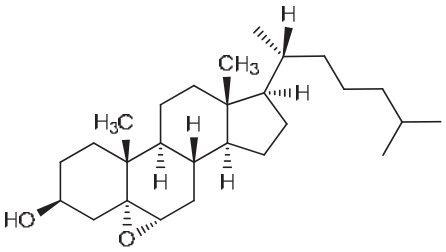
(a) The epoxide can be formed on the top face of the π bond, as shown:



or the epoxide can be formed on the bottom face of the π bond, as shown:



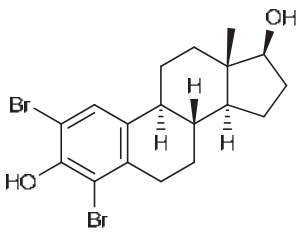
(b) The methyl group (C19) provides steric hindrance that blocks one side of the π bond, and only the following epoxide is obtained:



26.52.

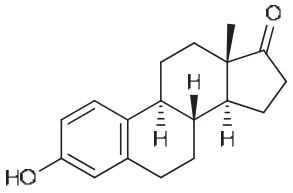
(a) Estradiol has an aromatic ring that bears an OH group. As such, the ring is strongly activated toward electrophilic aromatic substitution. Upon treatment with excess Br_2, bromination occurs at the two positions that are *ortho* to the OH group, which is an *ortho-para* director.

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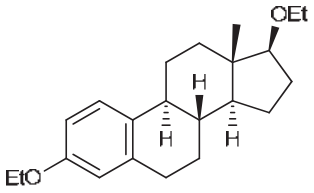


The *para* position is already occupied so bromination does not occur at that location.

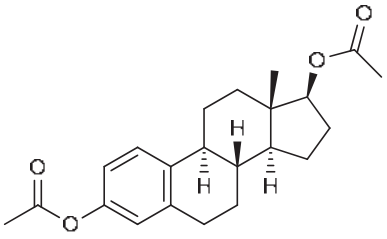
(b) Upon treatment with PCC, the secondary alcohol is oxidized to give the following ketone:



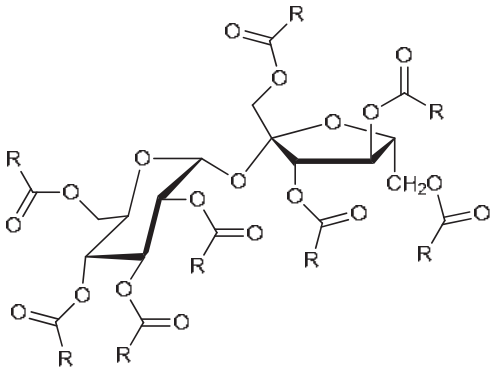
(c) Upon treatment with a strong base, followed by excess ethyl iodide, each of the OH group undergoes alkylation, thereby converting the OH groups into ethoxy groups, as shown:



(d) Upon treatment with excess acetyl chloride in the presence of pyridine, each of the OH group undergoes acetylation, giving the following product:



26.53. Every one of the OH groups in sucrose (see Section 24.7) is converted into an ester group, where R is used to represent the hydrophobic tail of each lauric acid residue. This compound is not superimposable on its mirror image, so it is chiral (much like sucrose).



26.54.

(a) This transformation requires reduction (hydrogenation) of the C=C bond in oleic acid, which can be achieved upon treatment with H_2 in the presence of Ni.

(b) This transformation requires reduction (hydrogenation) of the C=C bond in oleic acid, as well as conversion of the OH group to an ethoxy group. This can be achieved upon treatment with H_2 and Ni, followed by NaOH, followed by EtI.

(c) This transformation requires reduction (hydrogenation) of the C=C bond in oleic acid, as well as reduction of the carboxylic acid group to give a primary alcohol. This can be achieved upon treatment with H_2 and Ni, followed by $LiAlH_4$, followed by water work-up.

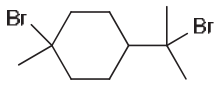
(d) Ozonolysis (O_3, followed by DMS) followed by oxidation with $Na_2Cr_2O_7$ and H_2SO_4 will generate the desired dicarboxylic acid.

(e) This transformation requires reduction (hydrogenation) of the C=C bond in oleic acid, as well as installation of a bromine atom at the α position. This can be achieved upon treatment with H_2 and Ni, followed by PBr_3 and Br_2, followed by H_2O.

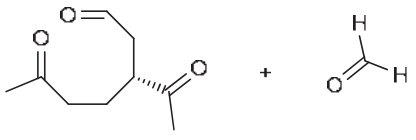
26.55.

(a) Limonene is comprised of 10 carbon atoms and is therefore a monoterpene.

(b) The compound does not have any chiral centers and is, therefore, achiral:

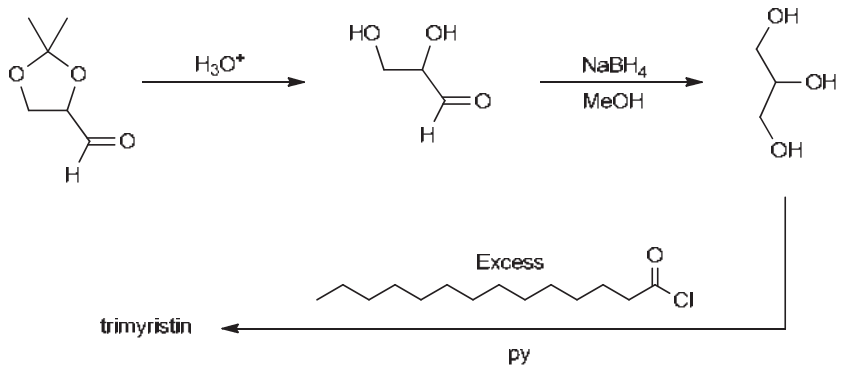


(c) Ozonolysis of limonene causes cleavage of each C=C bond, giving a tricarbonyl compound and formaldehyde, as shown:



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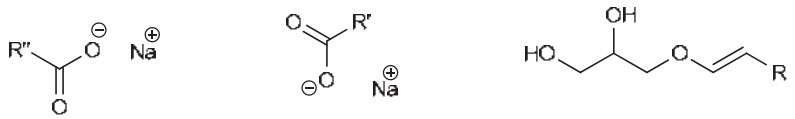
26.56. The starting material is a cyclic acetal. Upon treatment with aqueous acid, the acetal is opened to give a dihydroxyaldehyde. Reduction of the aldehyde group gives glycerol, which is then converted into the desired triglyceride upon treatment with an excess of the acyl halide in the presence of pyridine:



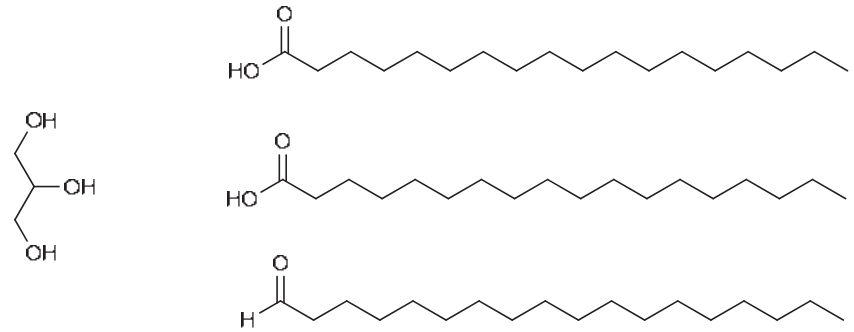
26.57.

(a) Fats and oils have a glycerol backbone connected to three fatty acid residues. This compound also has a glycerol backbone, but it is only connected to two fatty acid residues. The third group (left) is not a fatty acid residue.

(b) Each of the ester groups is hydrolyzed upon treatment with aqueous base, giving the following products:



(c) In aqueous acid, the two ester groups undergo hydrolysis, just as we saw in basic conditions. Under these conditions, the ether also undergoes acidic cleavage, thereby freeing glycerol and an enol. Upon its formation, the enol rapidly tautomerizes to give an aldehyde. In summary, we expect the following products:



Chapter 27
Synthetic Polymers

Review of Concepts

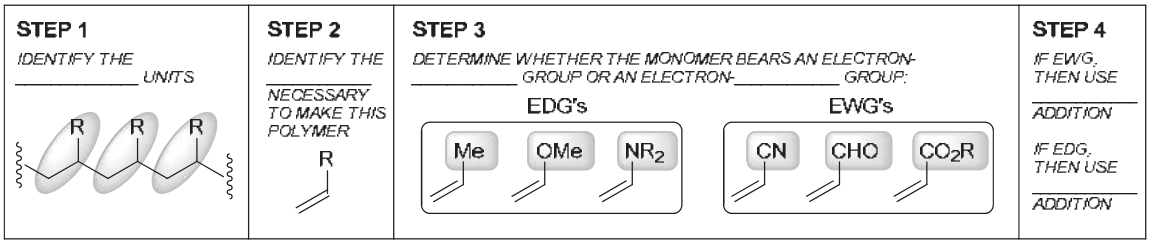
Fill in the blanks below. To verify that your answers are correct, look in your textbook at the end of Chapter 27. Each of the sentences below appears verbatim in the section entitled *Review of Concepts and Vocabulary*.

- Polymers are comprised of repeating units that are constructed by joining _____ together.
- A _____ is a polymer made up of a single type of monomer. Polymers made from two or more different types of monomers are called _____.
- In a _____ **copolymer**, different homopolymer subunits are connected together in one chain. In a _____ **copolymer**, sections of one homopolymer have been grafted onto a chain of another homopolymer.
- Monomers can join together to form **addition polymers** by cationic, anionic, or _____ addition.
- Most derivatives of ethylene will undergo _____ polymerization under suitable conditions.
- Cationic addition is only efficient with derivatives of ethylene that contain an electron-_____ group.
- Anionic addition is only efficient with derivatives of ethylene that contain an electron-_____ group.
- Polymers generated via condensation reactions are called _____ **polymers**.
- _____**-growth polymers** are formed under conditions in which each monomer is added to the growing chain one at a time. The monomers do not react directly with each other. ,
- _____**-growth polymers** are formed under conditions in which the individual monomers react with each other to form _____, which are then joined together to form polymers.
- **Crossed-linked polymers** contain _____ bridges or branches that connect neighboring chains.
- **Thermoplastics** are polymers that are _____ at room temperature but _____ when heated. They are often prepared in the presence _____ to prevent the polymer from being brittle.
- _____ are polymers that return to their original shape after being stretched.
- _____ **polymers** can be broken down by enzymes produced by microorganisms in the soil.

Review of Skills

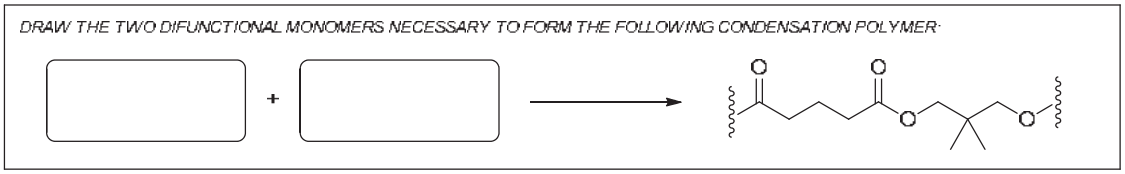
Fill in the blanks and empty boxes below. To verify that your answers are correct, look in your textbook at the end of Chapter 27. The answers appear in the section entitled *SkillBuilder Review*.

27.1 Determining Which Polymerization Technique is More Efficient



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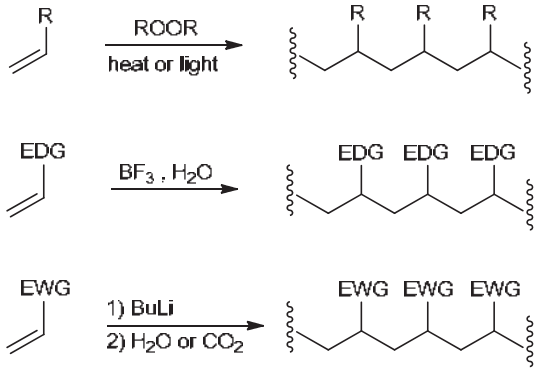
27.2 Identifying the Monomers Required to Produce a Desired Condensation Polymer



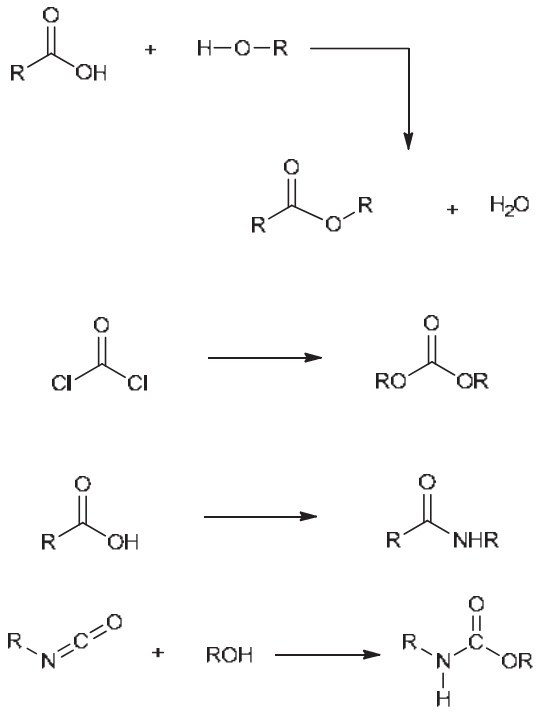
Review of Reactions

Identify the reagents necessary to achieve each of the following transformations. To verify that your answers are correct, look in your textbook at the end of Chapter 27. The answers appear in the section entitled *Review of Reactions*.

Reactions for Formation of Chain-Growth Polymers



Reactions for Formation of Step-Growth Polymers

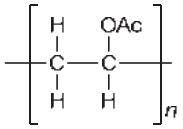


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Solutions

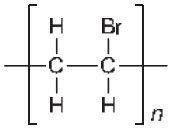
27.1.

(a) Polymerization of vinyl acetate gives poly(vinyl acetate):



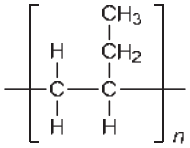
poly(vinyl acetate)

(b) Polymerization of vinyl bromide gives poly(vinyl bromide):



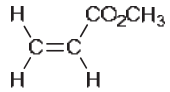
poly(vinyl bromide)

(c) Polymerization of α-butylene gives poly-α-butylene:



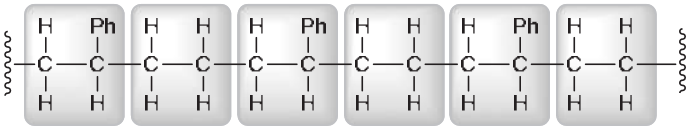
poly-α-butylene

27.2. Poly(methyl acrylate) can be made from methyl acrylate, shown here:

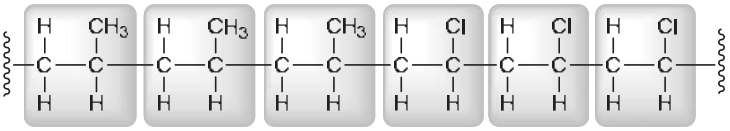


methyl acrylate

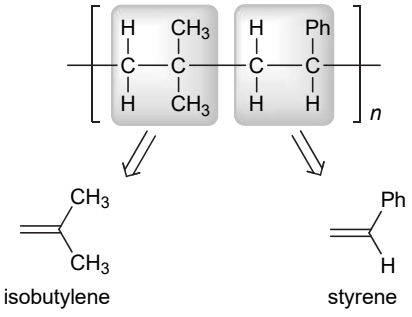
27.3. The following structure represents an alternating copolymer constructed from styrene and ethylene. The styrene and ethylene units are highlighted:



27.4. The following structure represents a block copolymer constructed from propylene and vinyl chloride. The propylene and vinyl chloride units are highlighted:



27.5. This copolymer can be made from isobutylene and styrene, as shown:



27.6. In each case, we identify the nature of the vinylic group, which determines the conditions to use. Anionic conditions are used if the vinylic group is electron-withdrawing, while cationic conditions are used for an an electron-donating group:

(a) A cyano group is an electron-withdrawing substituent (see Table 18.1 and associated discussion), so preparation of this compound would be best achieved via anionic addition.

(b) A methoxy group is an electron-donating substituent (see Table 18.1 and associated discussion), so preparation of this compound would be best achieved via cationic addition.

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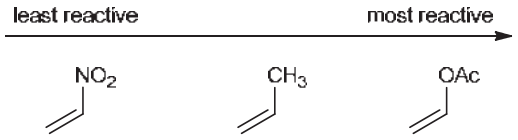
(c) Methyl groups are electron-donating substituents (see Table 18.1 and associated discussion), so preparation of this compound would be best achieved via cationic addition.

(d) An acetate group is an electron-donating substituent (see Table 18.1 and associated discussion), so preparation of this compound would be best achieved via cationic addition.

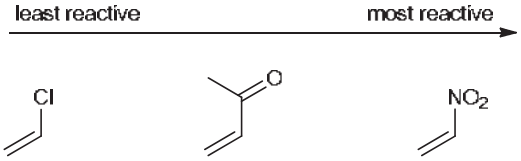
(e) A nitro group is an electron-withdrawing substituent (see Table 18.1 and associated discussion), so preparation of this compound would be best achieved via anionic addition.

(f) A trichloromethyl group is an electron-withdrawing substituent (see Table 18.1 and associated discussion), so preparation of this compound would be best achieved via anionic addition.

27.7. An acetate group is more powerfully electron donating (via resonance) than a methyl group (via hyperconjugation), so vinyl acetate is expected be the most reactive toward cationic polymerization. A nitro group is electron withdrawing, so nitroethylene is expected to be the least reactive toward cationic polymerization.

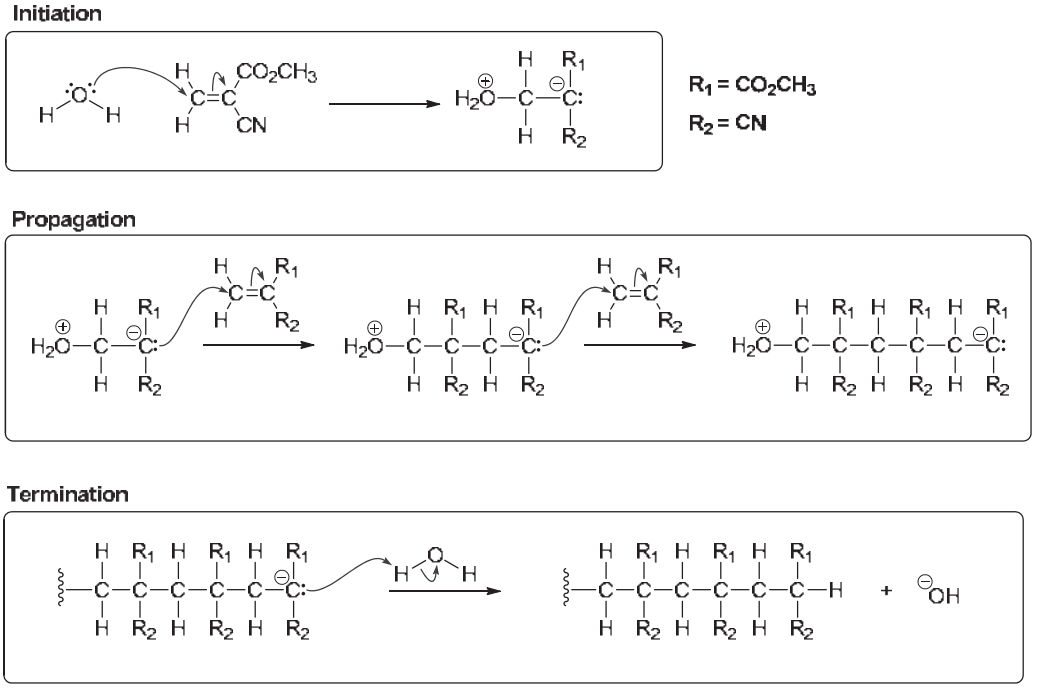


27.8. A nitro group is a very powerful electron withdrawing group (see Table 18.1 and associated discussion), so nitroethylene is expected to be the most reactive toward anionic polymerization. A chlorine atom is only weakly electron-withdrawing, as compared with a nitro group or a carbonyl group (see Table 18.1 and associated discussion), so vinyl chloride is expected to be the least reactive toward anionic polymerization.



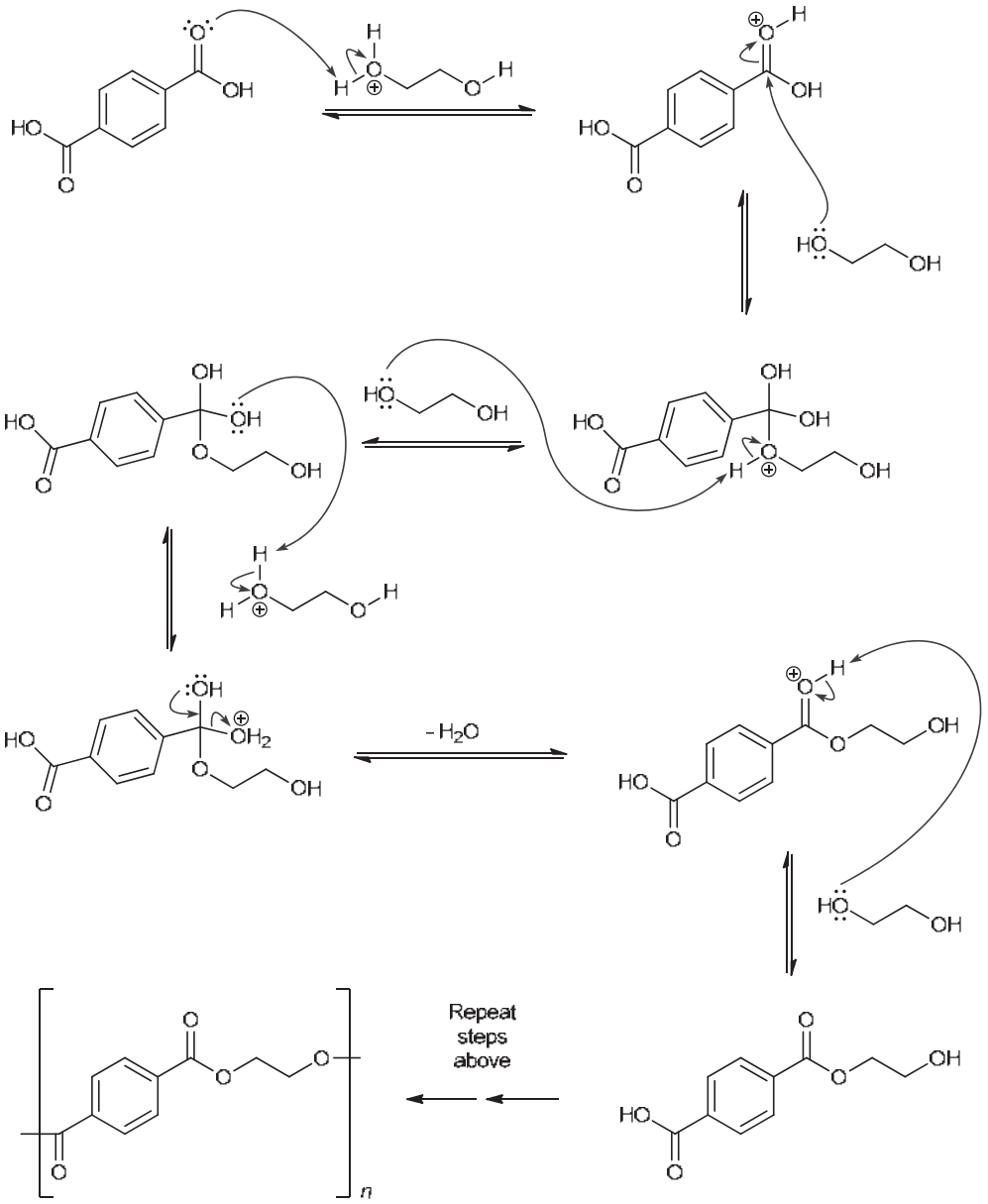
27.9. A benzylic anion, cation or radical will be stabilized by resonance.

27.10. In the initiation step, water attacks one molecule of the monomer, giving a carbanion. This carbanion then attacks another molecule of the monomer in a propagation step. This propagation step repeats itself, thereby growing the polymer chain. A termination step can occur if the carbanion is protonated by water, as shown:

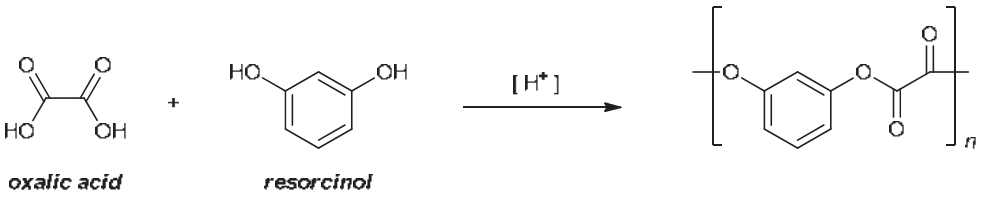


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27.11. Protonation of one of the carbonyl groups renders it even more electrophilic, and it is then attacked by ethylene glycol to give a tetrahedral intermediate (an oxonium ion). Two successive proton transfer steps convert the oxonium ion into another oxonium ion, which can lose water to regenerate the C=O bond. Deprotonation generates an ester. This ester has a carbonyl group on the left side, and an OH group on the right side. As a result, this compound can serve as a monomer for polymerization, (via a repetition of the steps described above).



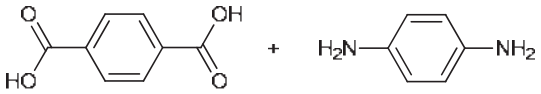
27.12. Oxalic acid bears two carboxylic acid groups, while resorcinol bears two OH groups. These two compounds can polymerize via successive Fischer esterification reactions, giving the following polymer:



oxalic acid ***resorcinol***

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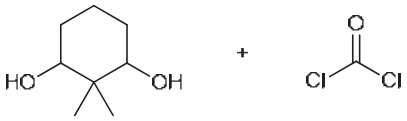
27.13. Each of the amide groups can be made via the reaction between a carboxylic acid group and an amino group. Therefore, Kevlar can be made from the following dicarboxylic acid and the following diamine:



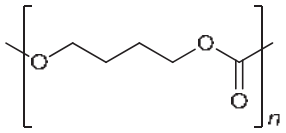
27.14.
(a) Each of the ester groups can be made from the reaction between a carboxylic acid group and an alcohol (via a Fischer esterification reaction). Therefore, the desired polymer can be made from the following diol and the following dicarboxylic acid:



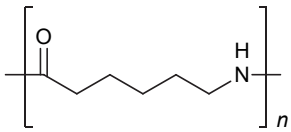
(b) Each carbonate group can be made from the reaction between phosgene and two alcohols. Therefore, the desired polymer can be made from the following diol and phosgene:



27.15. Each of the OH groups in 1,4-butanediol can attack phosgene, giving the following polymer:



27.16.
(a) ε-Aminocaproic acid has both a carboxylic acid group and an amino group (which can react with each, in an intermolecular fashion, to give an amide linkage). As such, this compound will polymerize to from the following polymer:



(b) Nylon 6 exhibits a smaller repeating unit than Nylon 6,6.

27.17.
(a) Each monomer has two growth points, so we expect that polymerization will generate a step-growth polymer.

(b) When these monomers react are used to form a copolymer, the growing polymer chain has only one growth point, so we expect that polymerization will generate a chain-growth polymer.

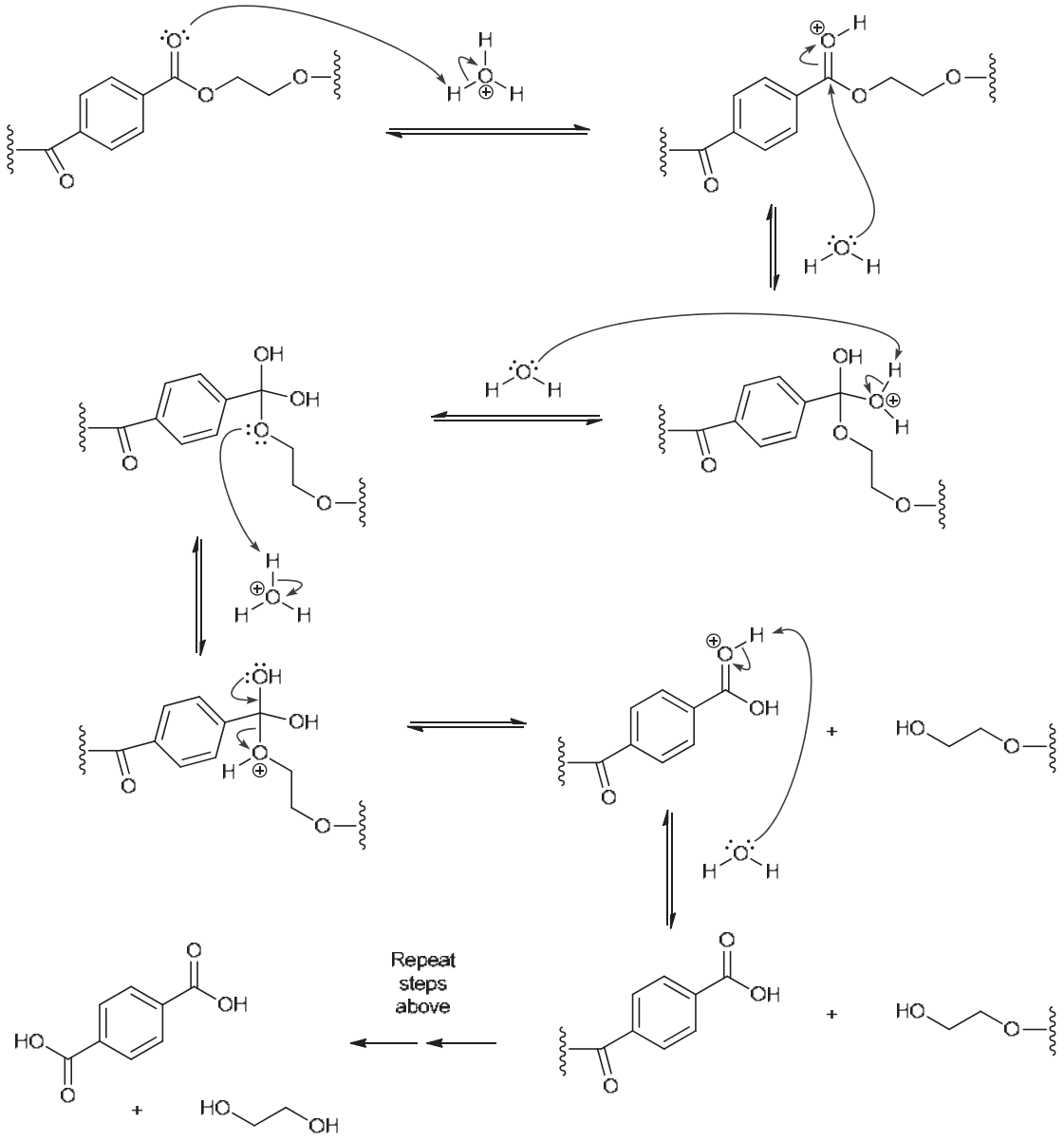
27.18. This polymer exhibits repeating carbonate groups, so it can be made from phosgene and the appropriate diol. Since the diol has two growth points (and since the growing oligomers also have two growth points), this polymer can be classified as a step-growth polymer.

27.19. Polyisobutylene does not have any chiral centers.

27.20. LDPE is used to make Ziploc bags (a flexible product, like trash bags) and HDPE is used to make folding tables (an inflexible product, like Tupperware).

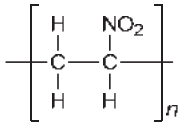
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27.21. Protonation of the ester renders it even more electrophilic, and it is then attacked by water to give a tetrahedral intermediate (an oxonium ion). Two successive proton transfer steps convert the oxonium ion into another oxonium ion, which can lose a leaving group to regenerate the C=O bond. Deprotonation generates a carboxylic acid (and an alcohol). These steps are then repeated to give terephthalic acid and ethylene glycol, as shown:



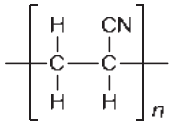
27.22.

(a) Polymerization of nitroethylene gives polynitroethylene:



polynitroethylene

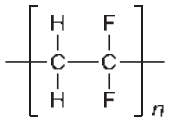
(b) Polymerization of acrylonitrile gives polyacrylonitrile:



polyacrylonitrile

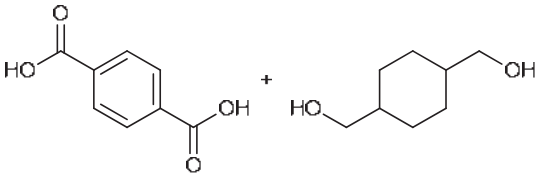
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(c) Polymerization of vinylidene fluoride gives poly(vinylidene fluoride):



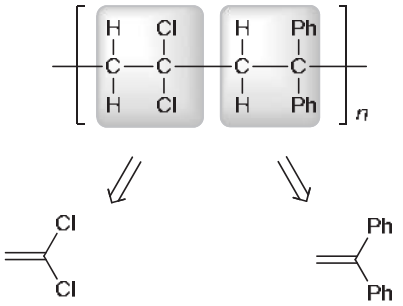
poly(vinylidene fluoride)

27.23.
(a) Each of the ester groups can be made from the reaction between a carboxylic acid group and an alcohol (via a Fischer esterification reaction). Therefore, the desired polymer can be made from the following dicarboxylic acid and the following diol:

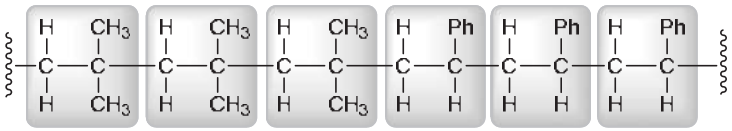


(b) A Fischer esterification requires acidic conditions.

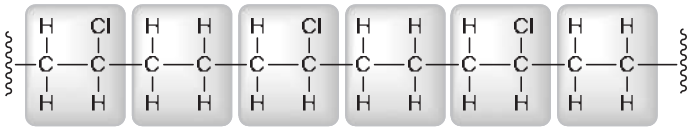
27.24. This copolymer can be made from the following monomers:



27.25. The following structure represents a block copolymer constructed from isobutylene and styrene. The isobutylene and styrene units are highlighted:



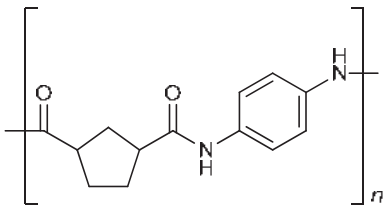
27.26. The following structure represents an alternating copolymer constructed from vinyl chloride and ethylene. The vinyl chloride and ethylene units are highlighted:



27.27. An acetate group is an electron-donating substituent (via resonance), while the other two groups (CN and Cl) are electron-withdrawing substituents. Therefore, vinyl acetate is expected be the most reactive toward cationic polymerization.

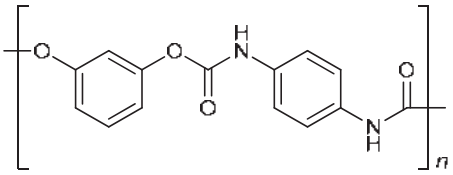
27.28. A cyano group is an electron-withdrawing substituent (via resonance), while the other two groups (acetate and methyl) are both electron-donating substituents. Therefore, the compound bearing the cyano group is expected be the most reactive toward anionic polymerization.

27.29. All three polymers are step-growth polymers, because in each case, the growing oligomers have two growth points.
(a) The starting materials are a diacid and a diamine, which can be linked together via amide groups, giving the following polymer:

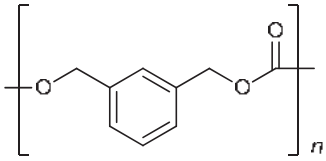


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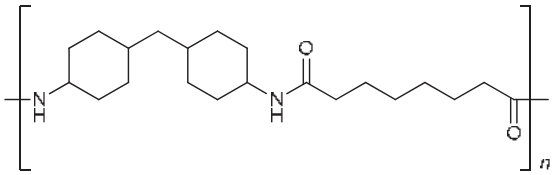
(b) The starting materials are a diol and a diisocyanate, which can be linked together as carbamate groups, giving the following polyurethane:



(c) The starting materials are a diol and phosgene, which will react with each other to give carbonate groups, and thus the following polycarbonate:

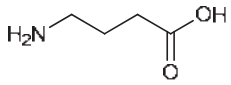


27.30.
(a) The starting materials are a diacid and a diamine, which can be linked together via amide groups, giving the following polymer:

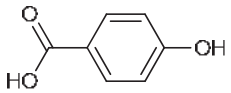


(b) Quiana is a polyamide.
(c) Quiana is a step-growth polymer, because each of the growing oligomers has two growth points.
(d) Quiana is a condensation polymer because it is made via a condensation process (between carboxylic acid and amino groups).

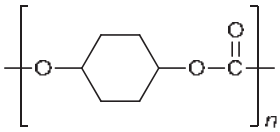
27.31.
(a) Each of the amide groups can be made from the reaction between a carboxylic acid and an amino group. Therefore, this polymer can be made from the following monomer, which bears both the amino group and the carboxylic acid group:



(b) Each of the ester groups can be made from the reaction between a carboxylic acid and an alcohol. Therefore, this polymer can be made from the following monomer, which bears both a hydroxyl group and a carboxylic acid group:



27.32. The starting materials are a diol and phosgene, which will react with each other to give carbonate groups, and thus the following polycarbonate:



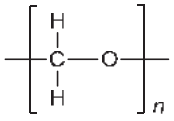
27.33.
(a) Each monomer has two growth points, so we expect that polymerization will generate a step-growth polymer.

(b) When these monomers react are used to form a copolymer, the growing polymer chain has only one growth point, so we expect that polymerization will generate a chain-growth polymer.

27.34. Nitro groups are among the most powerful electron-withdrawing groups, and a nitro group stabilizes a negative charge on an adjacent carbon atom, thereby facilitating anionic polymerization.

27.35. Shower curtains are made from PVC, which is a thermoplastic polymer. To prevent the polymer from being brittle, the polymer is prepared in the presence of plasticizers which become trapped between the polymer chains where they function as lubricants. Over time, the plasticizers evaporate, and the polymer becomes brittle.

27.36.
(a) Polyformaldehyde is a polymer that is assembled from repeating formaldehyde (CH_2O) units, as shown:



polyformaldehyde

(b) Polyformaldehyde has repeating ether groups, so it is a polyether.
(c) The growing polymer chain has only one growth point, so polyformaldehyde is classified as a chain-growth polymer.
(d) Polyformaldehyde is an addition polymer, because it is formed via successive addition reactions (involving the π bond in each molecule of formaldehyde).

27.37. It bears an electron-withdrawing group (CN) that can stabilize a negative charge via resonance, but it also bears an electron-donating group (OMe) that can stabilize a positive charge via resonance.

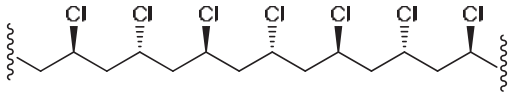
27.38. The nitro group serves as a reservoir of electron density that stabilizes a negative charge via resonance (see Chapter 18).

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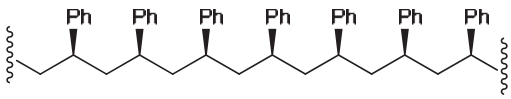
27.39. The methoxy group is an electron donating group that stabilizes a positive charge via resonance (see Chapter 18).

27.40. A methoxy group can only donate electron density via resonance if it is located in an *ortho* or *para* position. It cannot stabilize the developing carbocation if it is located in a *meta* position (see Chapter 18).

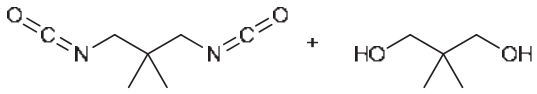
27.41.
(a) In a syndiotactic polymer, the chiral centers exhibit alternating configuration, as shown:



(b) In an isotactic polymer, the chiral centers all exhibit the same configuration, as shown:

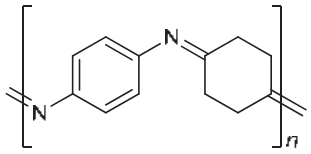


27.42.
(a) The desired polymer is a polyurethane, which can be prepared from the following diisocyanate and the following diol:



(b) Each monomer has two growth points, so we expect that polymerization will generate a step-growth polymer.
(c) Polyurethanes are classified as addition polymers (see end of Section 27.5), because they are formed via successive addition reactions.

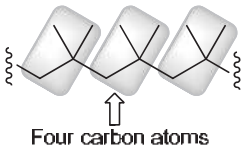
27.43. A ketone will react with a primary amine (under acid-catalyzed conditions) to give an imine (see Section 19.6). The starting materials are a dione and a diamine, so we expect formation of the following polyimine:



27.44. Vinyl alcohol is an enol, which is not stable. If it is prepared, it undergoes rapid tautomerization to give an aldehyde, which will not produce the desired product upon polymerization.

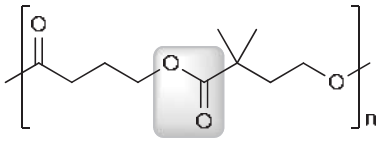
27.45. The ester groups undergo hydrolysis in basic conditions, which breaks down the polymer into monomers.

27.46. The repeating units are comprised of four carbon atoms:

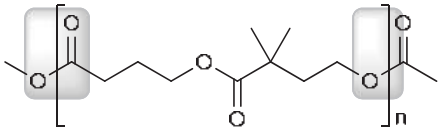


Therefore, the required monomer must also have four carbon atoms. So we can rule out options (a) and (c). The remaining two options, (b) and (d), have the same carbon skeleton, but only option (b) has a functional group (a π bond). This π bond is necessary for the polymerization process to occur under acid catalyzed conditions (see Mechanism 27.2).

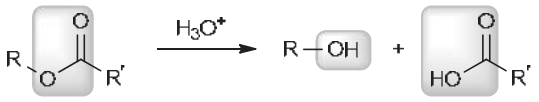
27.47. There are two ester groups that are hydrolyzed. One ester group can be seen in the center of the structure:



And the other ester group is located at the connection between the repeating units:

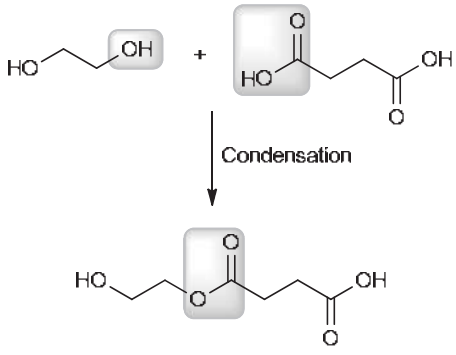


Each ester group is hydrolyzed to give a carboxylic acid and an alcohol:



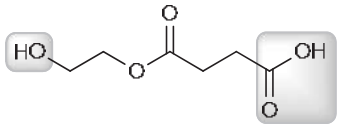
Therefore, option (b) is the correct answer, because the structures have the correct functional groups. In all of the other options, one or both of the carboxylic acid groups have been replaced by an aldehydic group.

27.48. An alcohol will react with a carboxylic acid to give an ester:

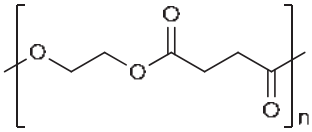


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This initial condensation product still has one OH group and one carboxylic acid group (highlighted),



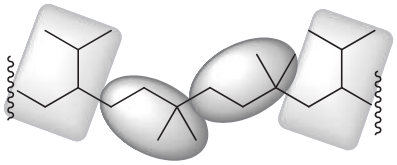
so it can undergo further condensation to give the following polymer:



Therefore, the correct answer is (b).

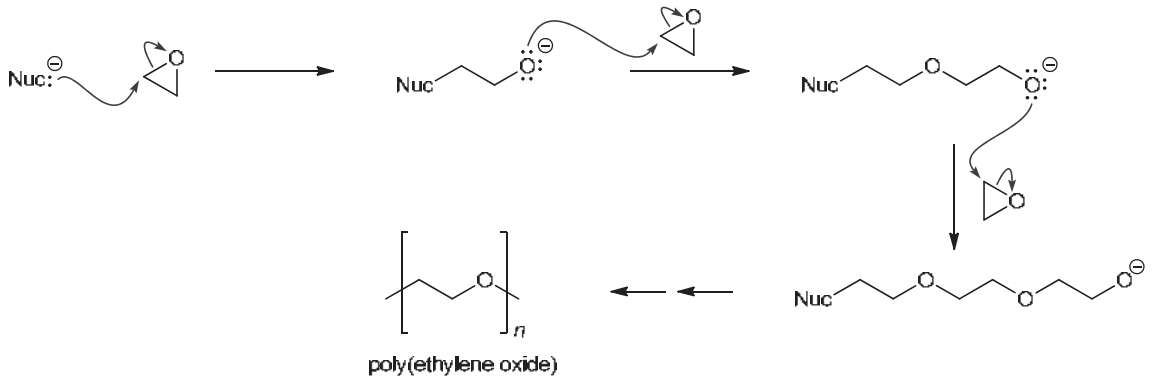
27.49.
(a) The carbocation that is initially formed is a secondary carbocation, and it can undergo a carbocation rearrangement to give a more stable, tertiary carbocation. In some cases, the secondary carbocation will be added to the growing polymer chain before it has a chance to rearrange. In other cases, the secondary carbocation will rearrange first and then be added to the growing polymer chain. The result is the incorporation of two different repeating units in the growing polymer chain.

(b) The following structure represents a segment of the random copolymer described in the solution to part (a). The repeating units are highlighted:



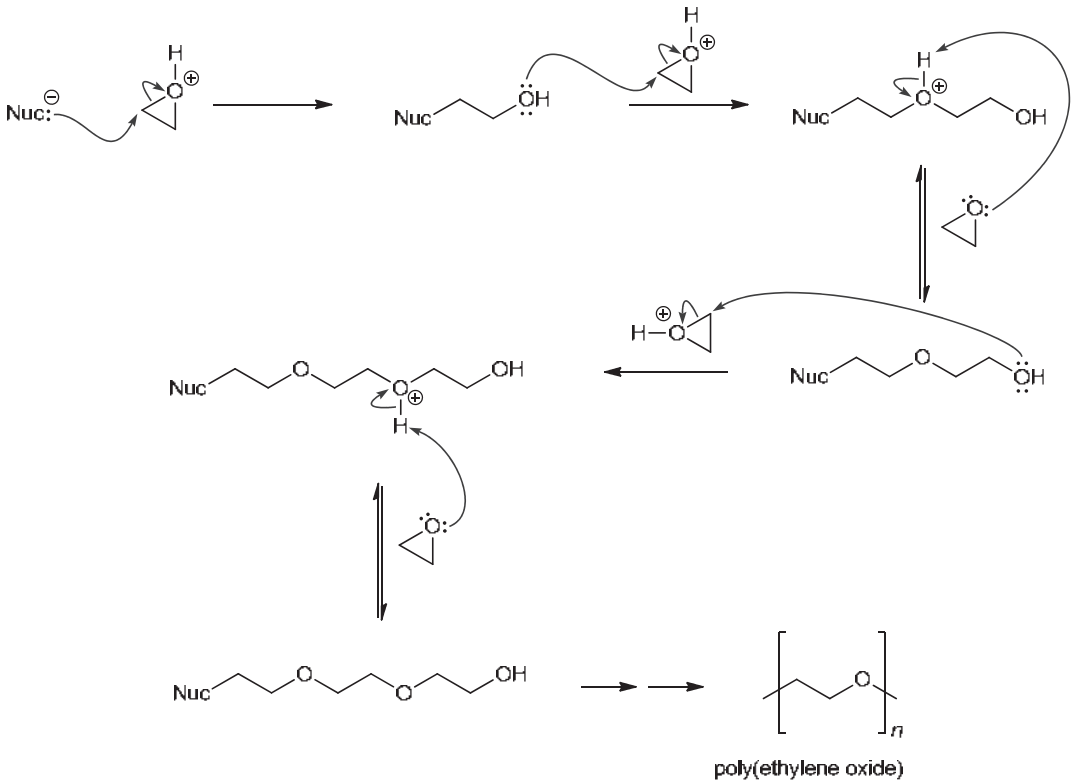
(c) Yes, because a secondary carbocation is formed when 3,3-dimethyl-1-butene is protonated, and a methyl shift can occur that converts the secondary carbocation into a tertiary carbocation.

27.50.
(a) As described in the problem statement, the epoxide ring is opened with a strong nucleophile to form an alkoxide ion, which then functions as a nucleophile and attacks another molecule of ethylene oxide. This process repeats itself, thereby forming poly(ethylene oxide), as shown:



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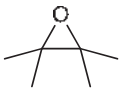
(b) Under acidic conditions, an epoxide can be protonated. A nucleophile can then attack the protonated epoxide, thereby opening the ring, and forming an alcohol. An alcohol is a weak nucleophile and it can then attack another protonated epoxide, once again opening the ring. The resulting oxonium ion is then deprotonated. If the base for this step is a molecule of the epoxide, the resulting protonated epoxide can then serve as the electrophile for the next step. This process can repeat itself, thereby forming poly(ethylene oxide), as shown:



(c) The desired polymer is similar in structure to poly(ethylene oxide), but there is a *gem*-dimethyl group present in the repeating unit. This polymer can be made if the starting epoxide also bears a *gem*-dimethyl group:



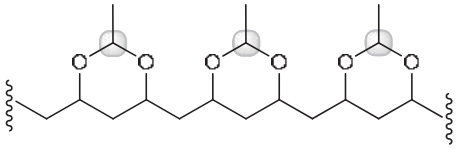
(d) Preparation of this polymer would require the following epoxide:



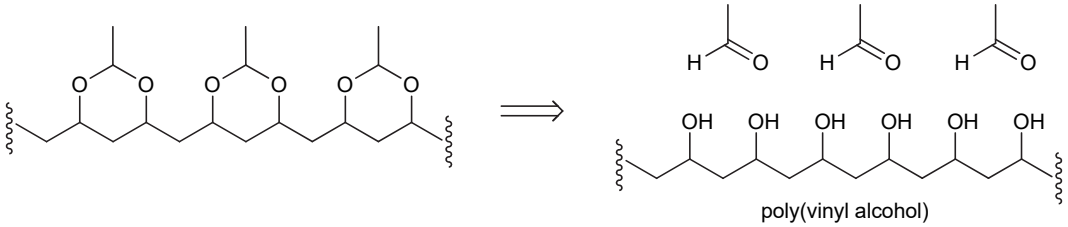
Acidic conditions will be required, because the epoxide is too sterically hindered to be attacked under basic conditions (see Section 13.10).

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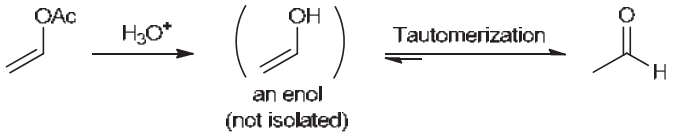
27.51. Each of the highlighted positions represents an acetal group (see Section 20.5):



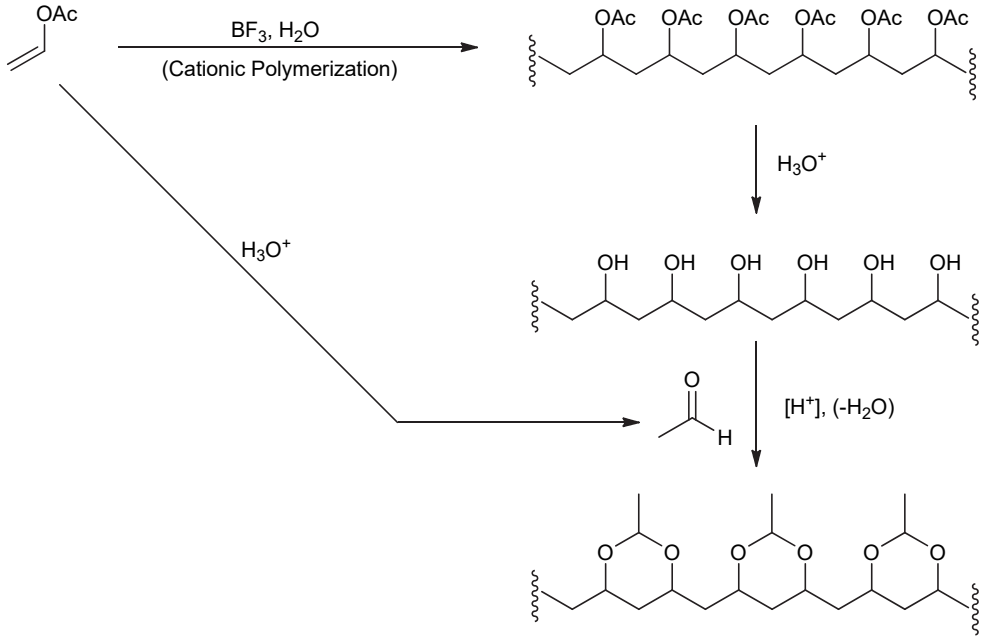
Therefore, this polymer can be made via acetal formation, from poly(vinyl alcohol) and acetaldehyde:



Poly(vinyl alcohol) can be made from vinyl acetate in just two steps (as seen in Problem 27.44). Acetaldehyde can also be made from vinyl acetate (upon treatment with aqueous acid). Under these conditions, the acetate group is hydrolyzed, giving an enol, which tautomerizes to give acetaldehyde:



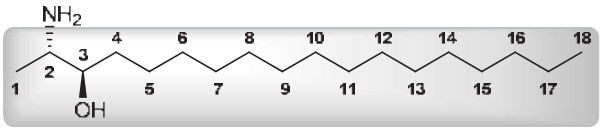
The forward scheme is shown here. Polymerization of vinyl acetate gives poly(vinyl acetate), which can be treated with aqueous acid to give poly(vinyl alcohol), as seen in Problem 27.44. This polymer can then be treated with acetaldehyde (formed by treating vinyl acetate with aqueous acid) to give the desired polymer:



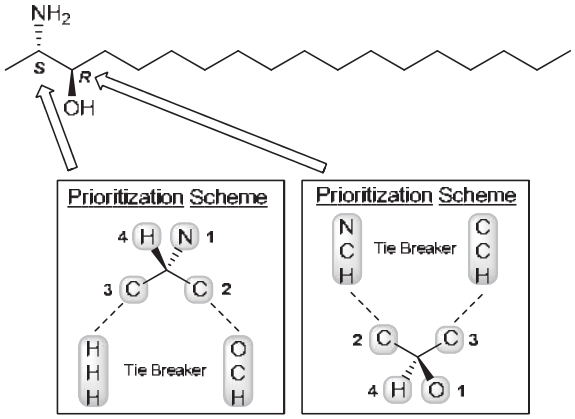
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APPENDIX
Nomenclature of Polyfunctional Compounds

A.1. This compound is a primary amine because there is only one alkyl group attached to the nitrogen, but it also has a hydroxyl group. Because alcohol functionalities have a higher suffix priority than amine groups, the compound will be named as an alcohol, and the amine will be named as a substituent (an amino group). Referencing Table 4.1, we can infer that an 18-carbon chain is called an octadecane, so this alcohol is an octadecanol. Numbering from left to right gives the alcohol and the amine the lowest possible numbers.



The name so far is 2-amino-3-octadecanol (or 2-aminooctadecan-3-ol using the new IUPAC rules). Lastly, the configuration of each chiral center must be specified.



The full IUPAC name is thus (2*S*,3*R*)-2-amino-3-octadecanol.

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