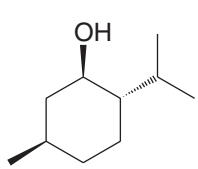
CHAPTER

11

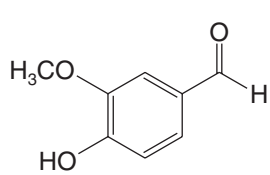
Alcohols and Ethers

SYNTHESIS AND REACTIONS

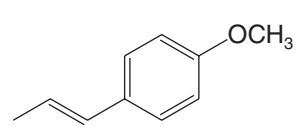
Have you ever walked into a bakery and caught a whiff of vanilla or peppermint emanating from a cake or pastry? Maybe you like to snack on licorice. These smells and flavors, as well as many others that you encounter in daily life, arise from naturally occurring molecules that contain either an alcohol or an ether functional group. Hundreds of such molecules are known, and in addition to their use as flavorings, some have other kinds of commercial roles, for example, as antifreezes or pharmaceuticals. An understanding of the physical properties and reactivity of these compounds will enable you to see how they can be used to create new materials with different and even more valuable characteristics.



(–)-Menthol
(from peppermint)



Vanillin
(from vanilla beans)



Anethole
(from fennel)

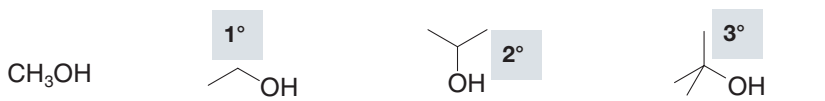
IN THIS CHAPTER WE WILL CONSIDER:

- the structures, properties, and nomenclature of common alcohols and ethers
- key molecules that contain such groups
- the reactivity of alcohols, ethers, and a special group of ethers known as epoxides

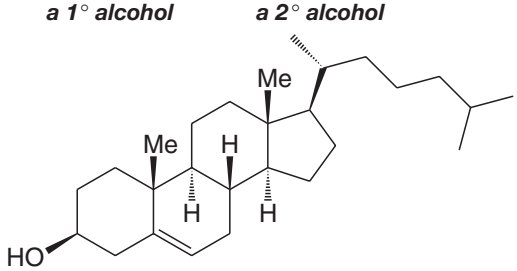
[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will see how the reactivity of epoxides can not only make highly complex molecules containing dozens of rings from acyclic precursors in a single step, but also help detoxify cancer-causing compounds from grilled meat, cigarettes, and peanuts.

11.1 STRUCTURE AND NOMENCLATURE

Alcohols have a hydroxyl (—OH) group bonded to a *saturated* carbon atom. The alcohol carbon atom may be part of a simple alkyl group, as in some of the following examples, or it may be part of a more complex molecule, such as cholesterol. Alcohols are also classified as 1°, 2°, or 3°, depending on the number of carbons bonded to the alcohol carbon.

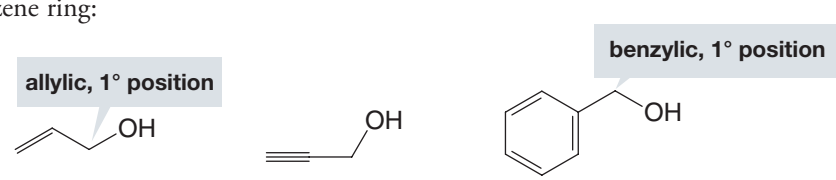


Methanol (methyl alcohol) | **Ethanol (ethyl alcohol), *a 1° alcohol*** | **2-Propanol (isopropyl alcohol), *a 2° alcohol*** | **2-Methyl-2-propanol (*tert*-butyl alcohol), *a 3° alcohol***



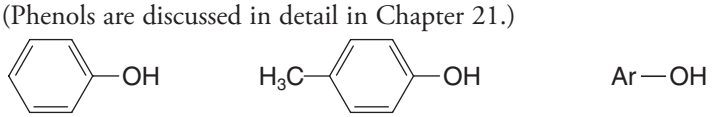
Cholesterol

The alcohol carbon atom may also be a saturated carbon atom adjacent to an alkenyl or alkynyl group, or the carbon atom may be a saturated carbon atom that is attached to a benzene ring:



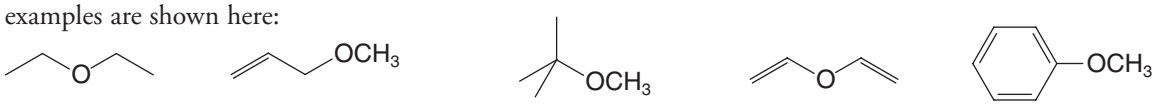
2-Propenol (or prop-2-en-1-ol, or allyl alcohol), *an allylic alcohol* | **2-Propynol (or prop-2-yn-1-ol, or propargyl alcohol)** | **Benzyl alcohol (*a benzylic alcohol*)**

Compounds that have a hydroxyl group attached *directly* to a benzene ring are called **phenols**. (Phenols are discussed in detail in Chapter 21.)



Phenol | ***p*-Methylphenol, *a substituted phenol*** | **General formula for a phenol**

Ethers differ from alcohols in that the oxygen atom of an ether is bonded to two carbon atoms. The hydrocarbon groups may be alkyl, alkenyl, vinyl, alkynyl, or aryl. Several examples are shown here:



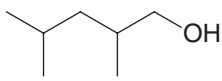
Diethyl ether | **Allyl methyl ether** | ***tert*-Butyl methyl ether** | **Divinyl ether** | **Methyl phenyl ether**

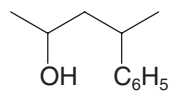
11.1A Nomenclature of Alcohols

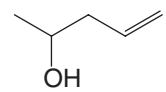
We studied the IUPAC system of nomenclature for alcohols in Sections 2.6 and 4.3F. As a review consider the following problem.

SOLVED PROBLEM 11.1

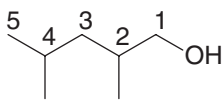
Give IUPAC substitutive names for the following alcohols:

(a) 

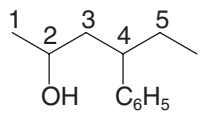
(b) 

(c) 

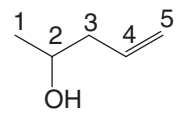
ANSWER: The longest chain ***to which the hydroxyl group is attached*** gives us the ***base name***. The ending is **-ol**. We then number ***the longest chain from the end that gives the carbon bearing the hydroxyl group the lower number***. Thus, the names, in both of the accepted IUPAC formats, are

(a) 

2,4-Dimethyl-1-pentanol
(or 2,4-dimethylpentan-1-ol)

(b) 

4-Phenyl-2-pentanol
(or 4-phenylpentan-2-ol)

(c) 

4-Penten-2-ol
(or pent-4-en-2-ol)

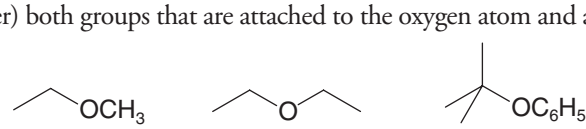
- The hydroxyl group has precedence over double bonds and triple bonds in deciding which functional group to name as the suffix [see example (c) above].

In common functional class nomenclature (Section 2.6) alcohols are called **alkyl alcohols** such as methyl alcohol, ethyl alcohol, and so on.

PRACTICE PROBLEM 11.1 What is wrong with the use of such names as "isopropanol" and "*tert*-butanol"?

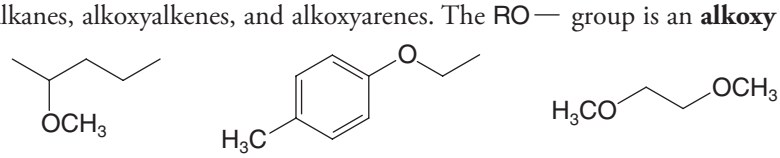
11.1B Nomenclature of Ethers

Simple ethers are frequently given common functional class names. One simply lists (in alphabetical order) both groups that are attached to the oxygen atom and adds the word *ether*:



Ethyl methyl ether **Diethyl ether** ***tert*-Butyl phenyl ether**

IUPAC substitutive names should be used for complicated ethers, however, and for compounds with more than one ether linkage. In this IUPAC style, ethers are named as alkoxyalkanes, alkoxyalkenes, and alkoxyarenes. The RO— group is an **alkoxy** group.



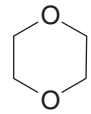
2-Methoxypentane **1-Ethoxy-4-methylbenzene** **1,2-Dimethoxyethane (DME)**

Cyclic ethers can be named in several ways. One simple way is to use **replacement nomenclature**, in which we relate the cyclic ether to the corresponding hydrocarbon ring system and use the prefix **oxa**- to indicate that an oxygen atom replaces a CH_2 group. In another system, a cyclic three-membered ether is named **oxirane** and a four-membered ether is called **oxetane.** Several simple cyclic ethers also have common names; in the examples below, these common names are given in parentheses. Tetrahydrofuran (THF) and 1,4-dioxane are useful solvents:

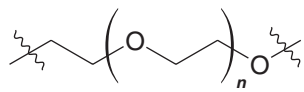
Oxacyclopropane or oxirane (ethylene oxide)

Oxacyclobutane or oxetane

Oxacyclopentane (tetrahydrofuran or THF)



1,4-Dioxacyclohexane (1,4-dioxane)



Polyethylene oxide (PEO) (a water-soluble polymer made from ethylene oxide)

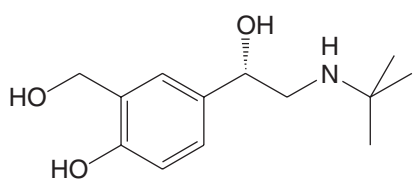
Blend/Image Source

Polyethylene oxide is used in some skin creams.

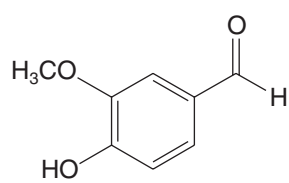
Ethylene oxide is the starting material for polyethylene oxide (PEO, also called polyethylene glycol, PEG). Polyethylene oxide has many practical uses, including covalent attachment to therapeutic proteins such as interferon, a use that has been found to increase the circulatory lifetime of the drug. PEO is also used in some skin creams, and as a laxative prior to digestive tract procedures.

SOLVED PROBLEM 11.2

Albuterol (used in some commonly prescribed respiratory medications) and vanillin (from vanilla beans) each contain several functional groups. Name the functional groups in albuterol and vanillin and, if appropriate for a given group, classify them as primary (1°), secondary (2°), or tertiary (3°).



Albuterol (an asthma medication)



Vanillin (from vanilla beans)

Photo by Lisa Gee for John Wiley & Sons, Inc

Albuterol is used in some respiratory medications.

STRATEGY AND ANSWER: Albuterol has the following functional groups: 1° alcohol, 2° alcohol, phenol, and 2° amine. Vanillin has aldehyde, ether, and phenol functional groups. See Chapter 2 for a review of how to classify alcohol and amine functional groups as 1°, 2°, or 3°.

PRACTICE PROBLEM 11.2

Give bond-line formulas and appropriate names for all of the alcohols and ethers with the formulas **(a)** C_3H_8O and **(b)** $C_4H_{10}O$.

11.2 PHYSICAL PROPERTIES OF ALCOHOLS AND ETHERS

The physical properties of a number of alcohols and ethers are given in Tables 11.1 and 11.2.

- Ethers have boiling points that are roughly comparable with those of hydrocarbons of the same molecular weight (MW).

For example, the boiling point of diethyl ether (MW = 74) is 34.6 °C; that of pentane (MW = 72) is 36 °C.

- Alcohols have much higher boiling points than comparable ethers or hydrocarbons.

The boiling point of butyl alcohol (MW = 74) is 117.7 °C. We learned the reason for this behavior in Section 2.13C.

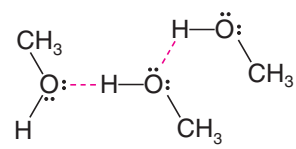
TABLE 11.1 PHYSICAL PROPERTIES OF SOME COMMON ALCOHOLS

Name	Formula	mp (°C)	bp (°C) (1 atm)	Water Solubility (g/100 mL H_2O)
	Monohydroxy Alcohols			
Methanol	CH_3OH	−97	64.7	∞
Ethanol	CH_3CH_2OH	−117	78.3	∞
Propyl alcohol	$CH_3CH_2CH_2OH$	−126	97.2	∞
Isopropyl alcohol	$CH_3CH(OH)CH_3$	−88	82.3	∞
Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	−90	117.7	8.3
Isobutyl alcohol	$CH_3CH(CH_3)CH_2OH$	−108	108.0	10.0
sec-Butyl alcohol	$CH_3CH_2CH(OH)CH_3$	−114	99.5	26.0
tert-Butyl alcohol	$(CH_3)_3COH$	25	82.5	∞
	Diols and Triols			
Ethylene glycol	CH_2OHCH_2OH	−12.6	197	∞
Propylene glycol	$CH_3CHOHCH_2OH$	−59	187	∞
Trimethylene glycol	$CH_2OHCH_2CH_2OH$	−30	215	∞
Glycerol	$CH_2OHCHOHCH_2OH$	18	290	∞

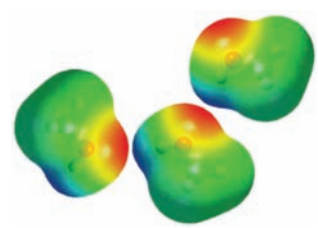
Photo courtesy of AMSOIL, INC.

Propylene glycol (1,2-propanediol) is used as an environmentally friendly engine coolant because it is biodegradable, has a high boiling point, and is miscible with water.

- Alcohol molecules can associate with each other through **hydrogen bonding**, whereas those of ethers and hydrocarbons cannot.

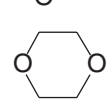


Hydrogen bonding between molecules of methanol



Ethers, however, *are* able to form hydrogen bonds with compounds such as water. Ethers, therefore, have solubilities in water that are similar to those of alcohols of the same molecular weight and that are very different from those of hydrocarbons.

TABLE 11.2 PHYSICAL PROPERTIES OF SOME COMMON ETHERS

Name	Formula	mp (°C)	bp (°C) (1 atm)
Dimethyl ether	CH_3OCH_3	−138	−24.9
Ethyl methyl ether	$CH_3OCH_2CH_3$		10.8
Diethyl ether	$CH_3CH_2OCH_2CH_3$	−116	34.6
1,2-Dimethoxyethane (DME)	$CH_3OCH_2CH_2OCH_3$	−68	83
Oxirane		−112	12
Tetrahydrofuran (THF)		−108	65.4
1,4-Dioxane		11	101

Diethyl ether and 1-butanol, for example, have the same solubility in water, approximately 8 g per 100 mL at room temperature. Pentane, by contrast, is virtually insoluble in water.

Methanol, ethanol, both propyl alcohols, and *tert*-butyl alcohol are completely miscible with water (Table 11.1). The solubility of alcohols in water gradually decreases as the hydrocarbon portion of the molecule lengthens; long-chain alcohols are more "alkane-like" and are, therefore, less like water.

SOLVED PROBLEM 11.3

1,2-Propanediol (propylene glycol) and 1,3-propanediol (trimethylene glycol) have higher boiling points than any of the butyl alcohols (see Table 11.1), even though they all have roughly the same molecular weight. Propose an explanation.

STRATEGY AND ANSWER: The presence of two hydroxyl groups in each of the diols allows their molecules to form more hydrogen bonds than the butyl alcohols. Greater hydrogen-bond formation means that the molecules of 1,2-propanediol and 1,3-propanediol are more highly associated and, consequently, their boiling points are higher.

11.3 IMPORTANT ALCOHOLS AND ETHERS

11.3A Methanol

At one time, most methanol was produced by the destructive distillation of wood (i.e., heating wood to a high temperature in the absence of air). It was because of this method of preparation that methanol came to be called "wood alcohol." Today, most methanol is prepared by the catalytic hydrogenation of carbon monoxide. This reaction takes place under high pressure and at a temperature of 300–400 °C:

$$CO + 2\,H_2 \xrightarrow[200\text{–}300\ \text{atm}\ \ ZnO\text{–}Cr_2O_3]{300\text{–}400\ ^\circ C} CH_3OH$$

Methanol is highly toxic. Ingestion of even small quantities of methanol can cause blindness; large quantities cause death. Methanol poisoning can also occur by inhalation of the vapors or by prolonged exposure to the skin.

11.3B Ethanol

Ethanol can be made by the fermentation of sugars, and it is the alcohol of all alcoholic beverages. The synthesis of ethanol in the form of wine by the fermentation of the sugars of fruit juices was among our first accomplishments in the field of organic synthesis. Sugars from a wide variety of sources can be used in the preparation of alcoholic beverages. Often, these sugars are from grains, and it is this derivation that accounts for ethanol having the synonym "grain alcohol."

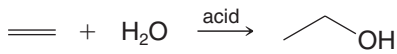
Fermentation is usually carried out by adding yeast to a mixture of sugars and water. Yeast contains enzymes that promote a long series of reactions that ultimately convert a simple sugar ($C_6H_{12}O_6$) to ethanol and carbon dioxide:

$$C_6H_{12}O_6 \xrightarrow{\text{yeast}} 2\,CH_3CH_2OH + 2\,CO_2$$

(~95% yield)

Fermentation alone does not produce beverages with an ethanol content greater than 12–15% because the enzymes of the yeast are deactivated at higher concentrations. To produce beverages of higher alcohol content, the aqueous solution must be distilled.

Ethanol is an important industrial chemical. Most ethanol for industrial purposes is produced by the acid-catalyzed hydration of ethene:



About 5% of the world's ethanol supply is produced this way.

Photo Disc, Inc./Getty Images, Inc.

Vineyard grapes for use in fermentation.

THE CHEMISTRY OF... Ethanol as a Biofuel

Ethanol is said to be a renewable energy source because it can be made by fermentation of grains and other agricultural sources such as switchgrass and sugarcane. The crops themselves grow, of course, by converting light energy from the sun to chemical energy through photosynthesis. Once obtained, the ethanol can be combined with gasoline in varying proportions and used in internal combustion engines. During the year 2007, the United States led the world in ethanol production with 6.5 billion U.S. gallons, followed closely by Brazil with 5 billion gallons.

When used as a replacement for gasoline, ethanol has a lower energy content, by about 34% per unit volume. This, and other factors, such as costs in energy required to produce the agricultural feedstock, especially corn, have created doubts about the wisdom of an ethanol-based program as a renewable energy source. Production of ethanol from corn is 5 to 6 times less efficient than producing it from sugarcane, and it also diverts production of a food crop into an energy source. World food shortages may be a result.

Media Bakery

Ethanol is a *hypnotic* (sleep producer). It depresses activity in the upper brain even though it gives the illusion of being a stimulant. Ethanol is also toxic, but it is much less toxic than methanol. In rats the lethal dose of ethanol is 13.7 g kg^{-1} of body weight.

11.3C Ethylene and Propylene Glycols

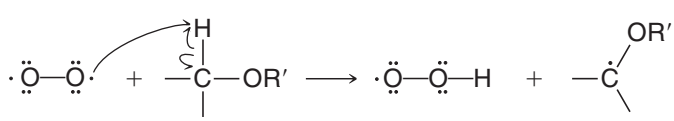
Ethylene glycol ($HOCH_2CH_2OH$) has a low molecular weight, a high boiling point, and is miscible with water (Table 11.1). These properties made ethylene glycol a good automobile antifreeze. Unfortunately, however, ethylene glycol is toxic. Propylene glycol (1,2-propanediol) is now widely used as a low-toxicity, environmentally friendly alternative to ethylene glycol.

11.3D Diethyl Ether

Diethyl ether is a very low boiling, highly flammable liquid. Care should always be taken when diethyl ether is used in the laboratory, because open flames or sparks from light switches can cause explosive combustion of mixtures of diethyl ether and air.

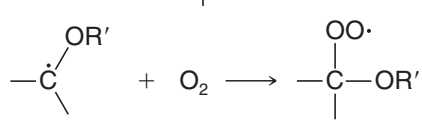
Most ethers react slowly with oxygen by a radical process called **autoxidation** (see Section 10.12D) to form hydroperoxides and peroxides:

Step 1

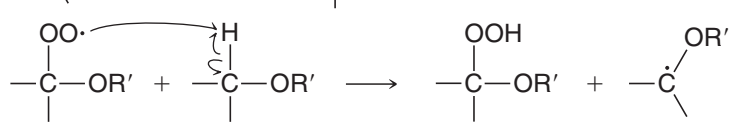


Hydrogen abstraction adjacent to the ether oxygen occurs readily.

Step 2



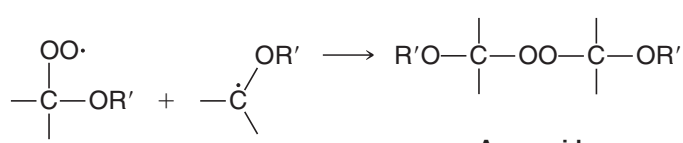
Step 3a



A hydroperoxide

or

Step 3b

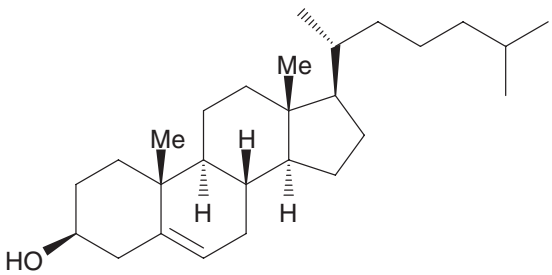


A peroxide

Hydroperoxides and peroxides can be explosive.

THE CHEMISTRY OF... Cholesterol and Heart Disease

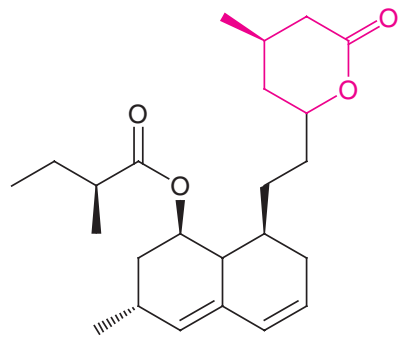
Cholesterol (below, see also Section 23.4B) is an alcohol that is a precursor of steroid hormones and a vital constituent of cell membranes. It is essential to life. On the other hand, deposition of cholesterol in arteries is a cause of heart disease and atherosclerosis, two leading causes of death in humans. For an organism to remain healthy, there has to be a delicate balance between the biosynthesis of cholesterol and its utilization, so that arterial deposition is kept at a minimum.



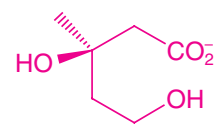
Cholesterol

For some individuals with high blood levels of cholesterol, the remedy is as simple as following a diet low in cholesterol and fat. For those who suffer from elevated blood cholesterol levels for genetic reasons, other means of cholesterol reduction are required. One remedy involves taking a drug called a *statin*, a drug designed to interfere with the biosynthesis of cholesterol.

In the body, the biosynthesis of cholesterol takes place through a series of steps, one of which is catalyzed by the enzyme *HMG-CoA reductase* and which uses mevalonate ion as a substrate. The statin interferes with this step and thereby reduces blood cholesterol levels.



Lovastatin



Mevalonate ion

Lovastatin, a compound isolated from the fungus *Apergillus terreus*, was the first statin to be marketed. Now many others are in use.

Lovastatin, because a part of its structure resembles mevalonate ion, can apparently bind at the active site of HMGA-CoA-reductase and act as a competitive inhibitor of this enzyme and thereby reduce cholesterol biosynthesis.

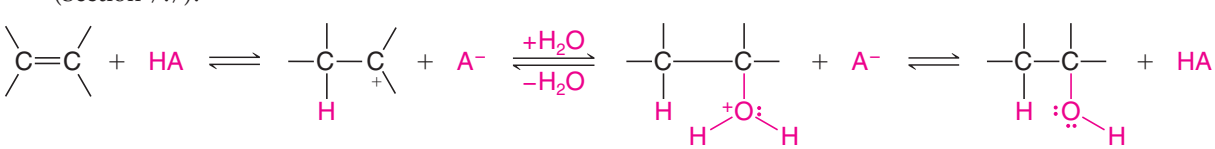
These hydroperoxides and peroxides, which often accumulate in ethers that have been stored for months or longer in contact with air (the air in the top of the bottle is enough), are dangerously explosive. They often detonate without warning when ether solutions are distilled to near dryness. Since ethers are used frequently in extractions, one should take care to test for and decompose any peroxides present in the ether before a distillation is carried out. (Consult a laboratory manual for instructions.)

Diethyl ether was at one time used as a surgical anesthetic. The most popular modern anesthetic is halothane ($CF_3CHBrCl$). Unlike diethyl ether, halothane is not flammable. (See "The Chemistry of... Ethers as General Anesthetics," Section 2.7, for more information.)

11.4 SYNTHESIS OF ALCOHOLS FROM ALKENES

We have already studied the acid-catalyzed **hydration** of alkenes, **oxymercuration**–demercuration, and **hydroboration**–oxidation as methods for the synthesis of alcohols from alkenes (see Sections 8.4, 8.5, and 8.6, respectively). Below, we briefly summarize these methods.

1. **Acid-Catalyzed Hydration of Alkenes** Alkenes add water in the presence of an acid catalyst to yield alcohols (Section 8.5). The addition takes place with **Markovnikov regioselectivity**. The reaction is reversible, and the mechanism for the acid-catalyzed hydration of an alkene is simply the reverse of that for the dehydration of an alcohol (Section 7.7).



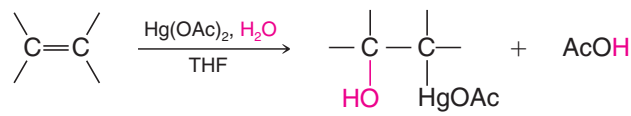
Alkene **Alcohol**

Acid-catalyzed hydration of alkenes has limited synthetic utility, however, because the carbocation intermediate may rearrange if a more stable or isoenergetic carbocation is possible by hydride or alkanide migration. Thus, a mixture of isomeric alcohol products may result.

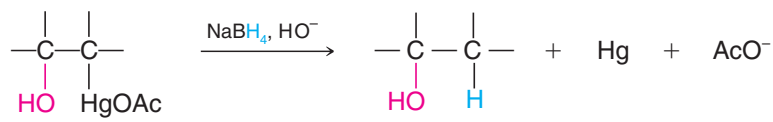
2. **Oxymercuration–Demercuration** Alkenes react with mercuric acetate in a mixture of water and tetrahydrofuran (THF) to produce (hydroxyalkyl)mercury compounds. These can be reduced to alcohols with sodium borohydride and water (Section 8.5).

Mercury compounds are hazardous. Before you carry out a reaction involving mercury or its compounds, you should familiarize yourself with current procedures for its use and disposal.

Oxymercuration



Demercuration



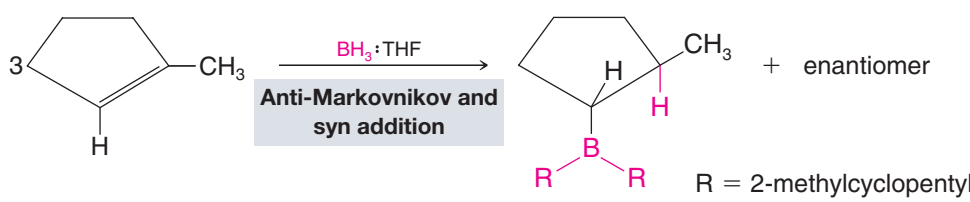
In the oxymercuration step, water and mercuric acetate add to the double bond; in the demercuration step, sodium borohydride reduces the acetoxymercury group and replaces it with hydrogen. The net addition of H— and —OH takes place with **Markovnikov regioselectivity** and **generally takes place without the complication of rearrangements**, as sometimes occurs with acid-catalyzed hydration of alkenes. The overall alkene hydration is not stereoselective because even though the oxymercuration step occurs with anti addition, the demercuration step is not stereoselective (radicals are thought to be involved), and hence a mixture of syn and anti products results.

Helpful Hint

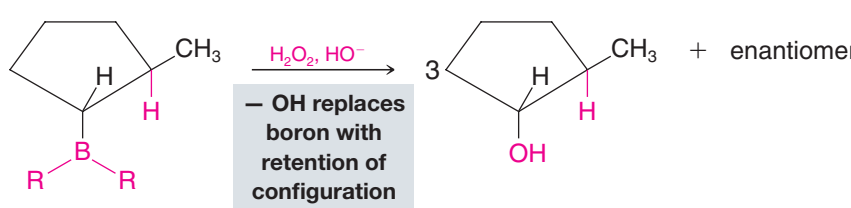
Oxymercuration–demercuration and hydroboration–oxidation have complementary regioselectivity.

3. **Hydroboration–Oxidation** An alkene reacts with BH_3:THF or diborane to produce an alkylborane. Oxidation and hydrolysis of the alkylborane with hydrogen peroxide and base yield an alcohol (Section 8.6).

Hydroboration



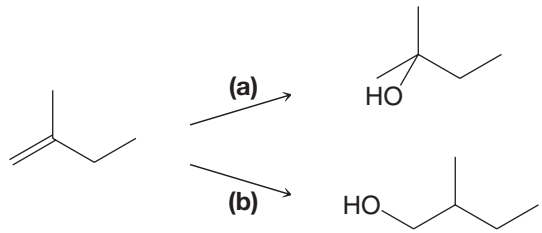
Oxidation



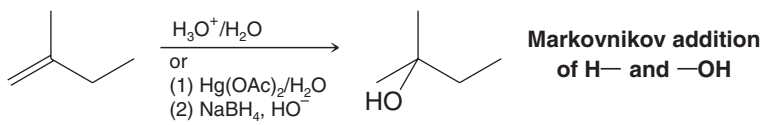
In the first step, boron and hydrogen undergo syn addition to the alkene; in the second step, treatment with hydrogen peroxide and base replaces the boron with —OH with retention of configuration. The net addition of —H and —OH occurs with **anti-Markovnikov regioselectivity** and **syn stereoselectivity.** Hydroboration–oxidation, therefore, serves as a useful regiochemical complement to oxymercuration–demercuration.

SOLVED PROBLEM 11.4

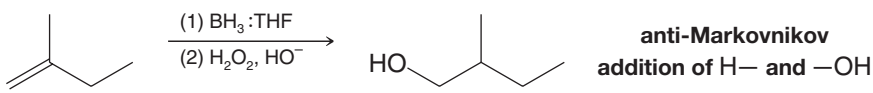
What conditions would you use for each reaction?



STRATEGY AND ANSWER: We recognize that synthesis by path (a) would require a Markovnikov addition of water to the alkene. So, we could use either acid-catalyzed hydration or oxymercuration–demercuration.

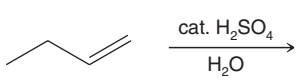


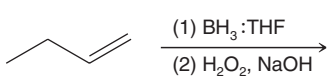
Synthesis by path (b) requires an anti-Markovnikov addition, so we would choose hydroboration–oxidation.

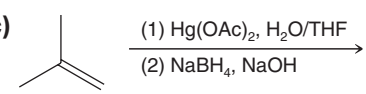


PRACTICE PROBLEM 11.3

Predict the major products of the following reactions:

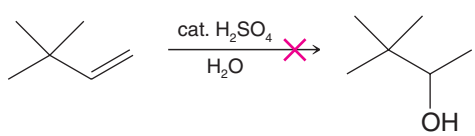
(a) 

(b) 

(c) 

PRACTICE PROBLEM 11.4

The following reaction does not produce the product shown.



(a) Predict the major product from the conditions shown above, and write a detailed mechanism for its formation.

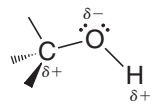
(b) What reaction conditions would you use to successfully synthesize the product shown above (3,3-dimethyl-2-butanol).

11.5 REACTIONS OF ALCOHOLS

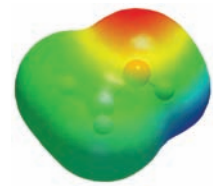
The reactions of alcohols have mainly to do with the following:

- The oxygen atom of the hydroxyl group is nucleophilic and weakly basic.
- The hydrogen atom of the hydroxyl group is weakly acidic.
- The hydroxyl group can be converted to a leaving group so as to allow substitution or elimination reactions.

Our understanding of the reactions of alcohols will be aided by an initial examination of the electron distribution in the alcohol functional group and of how this distribution affects its reactivity. The oxygen atom of an alcohol polarizes both the C—O bond and the O—H bond of an alcohol:



The C—O and O—H bonds of an alcohol are polarized

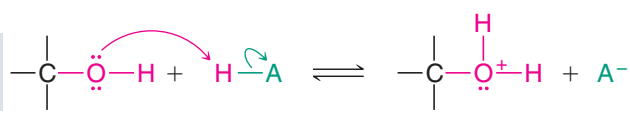


An electrostatic potential map for methanol shows partial negative charge at the oxygen and partial positive charge at the hydroxyl proton.

Polarization of the O—H bond makes the hydrogen partially positive and explains why alcohols are weak acids (Section 11.6). Polarization of the C—O bond makes the carbon atom partially positive, and if it were not for the fact that HO^- is a strong base and, therefore, a very poor leaving group, this carbon would be susceptible to nucleophilic attack.

The electron pairs on the oxygen atom make it both ***basic*** and ***nucleophilic***. In the presence of strong acids, alcohols act as bases and accept protons in the following way:

Protonation of an alcohol

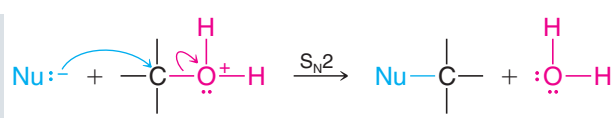


- Protonation of the alcohol converts a poor leaving group (HO^-) into a good one (H_2O).

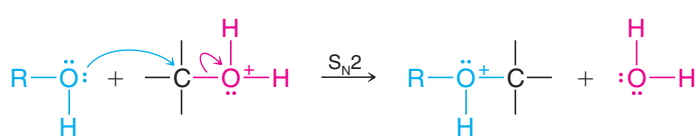
Protonation also makes the carbon atom even more positive (because $-\overset{+}{O}H_2$ is more electron withdrawing than —OH) and, therefore, even more susceptible to nucleophilic attack.

- Once the alcohol is protonated substitution reactions become possible (S_N2 or S_N1, depending on the class of alcohol, Section 11.8).

The protonated hydroxyl group is a good leaving group (H_2O)



Because alcohols are nucleophiles, they, too, can react with protonated alcohols. This, as we shall see in Section 11.11A, is an important step in one synthesis of ethers:



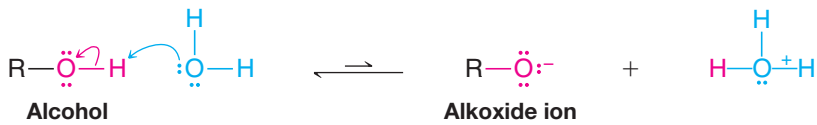
At a high enough temperature and in the absence of a good nucleophile, protonated alcohols are capable of undergoing E1 or E2 reactions. This is what happens in alcohol dehydrations (Section 7.7).

Alcohols also react with PBr_3 and $SOCl_2$ to yield alkyl bromides and alkyl chlorides. These reactions, as we shall see in Section 11.9, are initiated by the alcohol using its unshared electron pairs to act as a nucleophile.

11.6 ALCOHOLS AS ACIDS

- Alcohols have acidities similar to that of water.

Methanol is a slightly stronger acid than water ($pK_a = 15.7$) but most alcohols are somewhat weaker acids. Values of pK_a for several alcohols are listed in Table 11.3.



Alcohol **Alkoxide ion**

(If R is bulky, there is less stabilization of the alkoxide by solvation and greater destabilization due to inductive effects. Consequently, the equilibrium lies even further toward the alcohol.)

TABLE 11.3 pK_a VALUES FOR SOME WEAK ACIDS

Acid	pK_a
CH_3OH	15.5
H_2O	15.74
CH_3CH_2OH	15.9
$(CH_3)_3COH$	18.0

- Sterically hindered alcohols such as *tert*-butyl alcohol are less acidic, and hence their conjugate bases more basic, than unhindered alcohols such as ethanol or methanol.

One reason for this difference in acidity has to do with the effect of solvation. With an unhindered alcohol, water molecules can easily surround, solvate, and hence stabilize the alkoxide anion that would form by loss of the alcohol proton to a base. As a consequence of this stabilization, formation of the alcohol's conjugate base is easier, and therefore its acidity is increased. If the R group of the alcohol is bulky, solvation of the alkoxide anion is hindered. Stabilization of the conjugate base is not as effective, and consequently the hindered alcohol is a weaker acid. Another reason that hindered alcohols are less acidic has to do with the inductive electron-donating effect of alkyl groups. The alkyl groups of a hindered alcohol donate electron density, making formation of an alkoxide anion more difficult than with a less hindered alcohol.

Helpful Hint

Remember: Any factor that stabilizes the conjugate base of an acid increases its acidity.

- All alcohols are much stronger acids than terminal alkynes, and they are very much stronger acids than hydrogen, ammonia, and alkanes (see Table 3.1).

Relative Acidity

Water and alcohols are the strongest acids in this series.

$$H_2O > ROH > RC{\equiv}CH > H_2 > NH_3 > RH$$

Sodium and potassium alkoxides can be prepared by treating alcohols with sodium or potassium metal or with the metal hydride (Section 6.15B). Because most alcohols are weaker acids than water, most alkoxide ions are stronger bases than the hydroxide ion.

- Conjugate bases of compounds with higher pK_a values than an alcohol will deprotonate an alcohol.

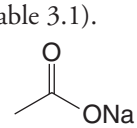
Relative Basicity

$$R^- > H_2N^- > H^- > RC{\equiv}C^- > RO^- > HO^-$$

Hydroxide is the weakest base in this series.

PRACTICE PROBLEM 11.5

Write equations for the acid–base reactions that would occur (if any) if ethanol were added to solutions of each of the following compounds. In each reaction, label the stronger acid, the stronger base, and so forth (consult Table 3.1).

(a) $NaNH_2$ **(b)** H—C≡C:$^-$ Na^+ **(c)**  **(d)** NaOH

Sodium and potassium alkoxides are often used as bases in organic syntheses (Section 6.15B). We use alkoxides, such as ethoxide and *tert*-butoxide, when we carry out reactions that require stronger bases than hydroxide ion but do not require exceptionally powerful bases, such as the amide ion or the anion of an alkane. We also use alkoxide ions when, for reasons of solubility, we need to carry out a reaction in an alcohol solvent rather than in water.

11.7 CONVERSION OF ALCOHOLS INTO ALKYL HALIDES

In this and several following sections we will be concerned with reactions that involve substitution of the alcohol hydroxyl group.

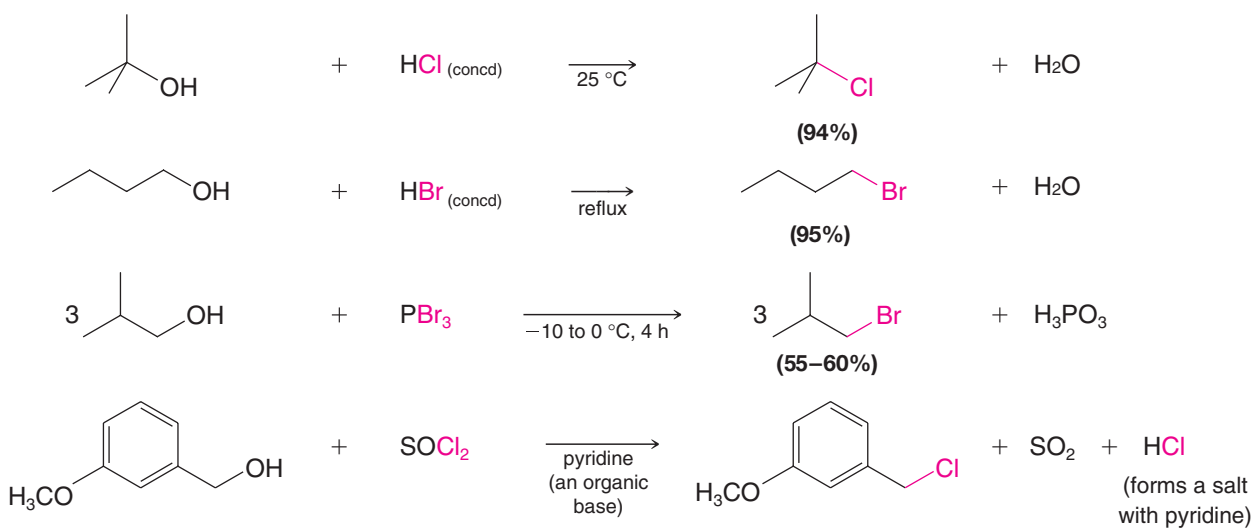
- A hydroxyl group is such a poor leaving group (it would depart as hydroxide) that a common theme of these reactions will be conversion of the hydroxyl to a group that can depart as a weak base.

These processes begin by reaction of the alcohol oxygen as a base or nucleophile, after which the modified oxygen group undergoes substitution. First, we shall consider reactions that convert alcohols to alkyl halides.

The most commonly used reagents for conversion of alcohols to alkyl halides are the following:

- Hydrogen halides (HCl, HBr, HI)
- Phosphorus tribromide (PBr_3)
- Thionyl chloride ($SOCl_2$)

Examples of the use of these reagents are the following. All of these reactions result in cleavage of the C—O bond of the alcohol. In each case, the hydroxyl group is first converted to a suitable leaving group. We will see how this is accomplished when we study each type of reaction.



11.8 ALKYL HALIDES FROM THE REACTION OF ALCOHOLS WITH HYDROGEN HALIDES

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:

$$R{-}OH + HX \longrightarrow R{-}X + H_2O$$

- The order of reactivity of alcohols is $3° > 2° > 1° <$ methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

The reaction is *acid catalyzed*. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:

$$ROH + NaX \xrightarrow{H_2SO_4} RX + NaHSO_4 + H_2O$$

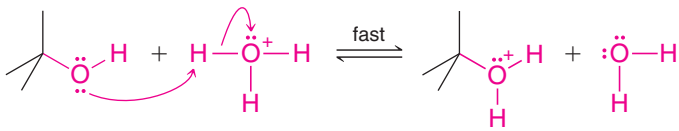
11.8A Mechanisms of the Reactions of Alcohols with HX

- Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation—a mechanism that we first saw in Section 3.13 and that you should now recognize *as an S_N1 reaction with the protonated alcohol acting as the substrate*.

We again illustrate this mechanism with the reaction of *tert*-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-).

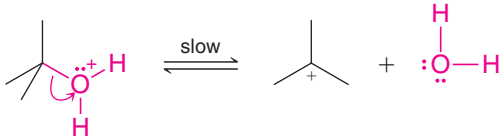
The first two steps in this S_N1 substitution mechanism are the same as in the mechanism for the dehydration of an alcohol (Section 7.7).

Step 1



The alcohol accepts a proton.

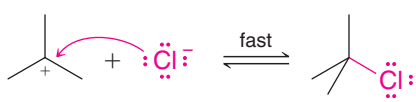
Step 2



The protonated hydroxyl group departs as a leaving group to form a carbocation and water.

In step 3 the mechanisms for the dehydration of an alcohol and the formation of an alkyl halide differ. In dehydration reactions the carbocation loses a proton in an E1 reaction to form an alkene. In the formation of an alkyl halide, the carbocation reacts with a nucleophile (a halide ion) in an S_N1 reaction.

Step 3



A halide anion reacts with the carbocation.

How can we account for S_N1 substitution in this case versus elimination in others?

When we dehydrate alcohols, we usually carry out the reaction in concentrated sulfuric acid and at high temperature. The hydrogen sulfate (HSO_4^-) present after protonation of the alcohol is a weak nucleophile, and at high temperature the highly reactive carbocation forms a more stable species by losing a proton and becoming an alkene. Furthermore, the alkene is usually volatile and distills from the reaction mixture as it is formed, thus drawing the equilibrium toward alkene formation. The net result is *an E1 reaction*.

In the reverse reaction, that is, the hydration of an alkene (Section 8.5), the carbocation *does* react with a nucleophile. It reacts with water. Alkene hydrations are carried out in dilute sulfuric acid, where the water concentration is high. In some instances, too, carbocations may react with HSO_4^- ions or with sulfuric acid, itself. When they do, they form alkyl hydrogen sulfates ($R—OSO_2OH$).

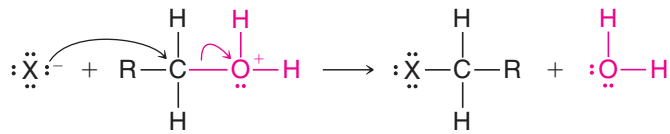
When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and *in the presence of halide ions*, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an S_N1 reaction.

These two reactions, dehydration and the formation of an alkyl halide, also furnish another example of the competition between nucleophilic substitution and elimination (see Section 6.18). Very often, in conversions of alcohols to alkyl halides, we find that the reaction is accompanied by the formation of some alkene (i.e., by elimination). The free energies of activation for these two reactions of carbocations are not very different from one another. Thus, not all of the carbocations become stable products by reacting with nucleophiles; some lose a β proton to form an alkene.

Primary Alcohols Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations.

- Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism.

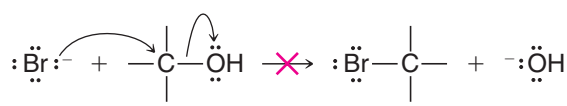
In these reactions the function of the acid is to produce *a protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:



(Protonated 1° alcohol or methanol) (A good leaving group)

Acid Is Required Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves.

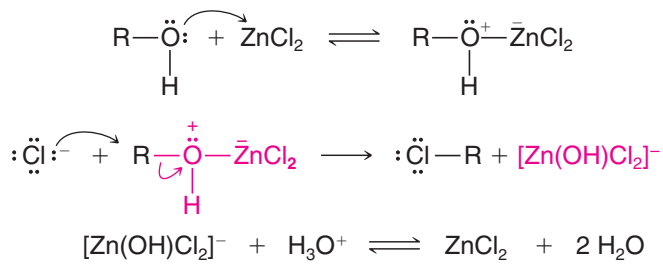
- Reactions like the following do not occur because the leaving group would have to be a strongly basic hydroxide ion:



We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

- Acid protonates the alcohol hydroxyl group, making it a good leaving group.

Because the chloride ion is a weaker nucleophile than bromide or iodide ions, hydrogen chloride does not react with primary or secondary alcohols unless zinc chloride or some similar Lewis acid is added to the reaction mixture as well. Zinc chloride, a good Lewis acid, forms a complex with the alcohol through association with an unshared pair of electrons on the oxygen atom. This enhances the hydroxyl group's leaving potential sufficiently that chloride can displace it.



- As we might expect, many reactions of alcohols with hydrogen halides, particularly those in which carbocations are formed, *are accompanied by rearrangements*.

How do we know that rearrangements can occur when secondary alcohols are treated with a hydrogen halide? Results like that in Solved Problem 11.5 indicate this to be the case.

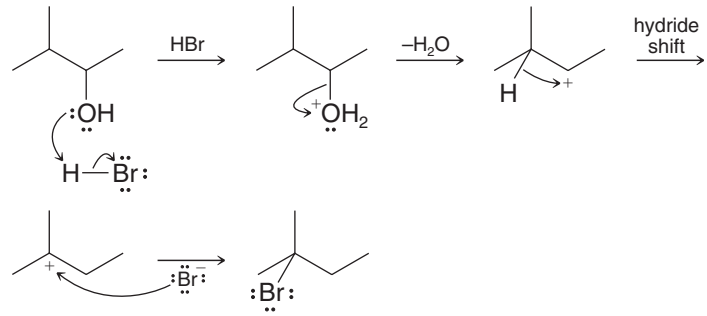
Helpful Hint

The reverse reaction, that is, the reaction of an alkyl halide with hydroxide ion, does occur and is a method for the synthesis of alcohols. We saw this reaction in Chapter 6.

SOLVED PROBLEM 11.5

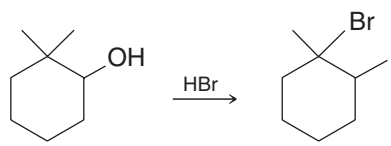
Treating 3-methyl-2-butanol (see the following reaction) yields 2-bromo-2-methylbutane as the sole product. Propose a mechanism that explains the course of the reaction.

STRATEGY AND ANSWER: The reaction must involve a rearrangement by a hydride shift from the initially formed carbocation.



PRACTICE PROBLEM 11.6

Write a detailed mechanism for the following reaction.



PRACTICE PROBLEM 11.7

(a) What factor explains the observation that tertiary alcohols react with HX faster than secondary alcohols? **(b)** What factor explains the observation that methanol reacts with HX faster than a primary alcohol?

Since rearrangements can occur when some alcohols are treated with hydrogen halides, how can we successfully convert a secondary alcohol to an alkyl halide without rearrangement? The answer to this question comes in the next section, where we discuss the use of reagents such as thionyl chloride ($SOCl_2$) and phosphorus tribromide (PBr_3).

11.9 ALKYL HALIDES FROM THE REACTION OF ALCOHOLS WITH PBr_3 OR $SOCl_2$

Primary and secondary alcohols react with phosphorus tribromide to yield alkyl bromides.

$$3\ R\text{—}OH\ +\ PBr_3 \longrightarrow 3\ R\text{—}Br\ +\ H_3PO_3$$

(1° or 2°)

Helpful Hint

PBr_3: A reagent for synthesizing 1° and 2° alkyl bromides.

- The reaction of an alcohol with PBr_3 does not involve the formation of a carbocation and *usually occurs without rearrangement* of the carbon skeleton (especially if the temperature is kept below 0 °C).
- Phosphorus tribromide is often preferred as a reagent for the transformation of an alcohol to the corresponding alkyl bromide.

The mechanism for the reaction involves sequential replacement of the bromine atom in PBr_3 by three molecules of the alcohol to form a trialkylphosphite, $P(OR)_3$, and three molecules of HBr.

$$ROH\ +\ PBr_3 \longrightarrow P(OR)_3\ +\ 3\ HBr$$

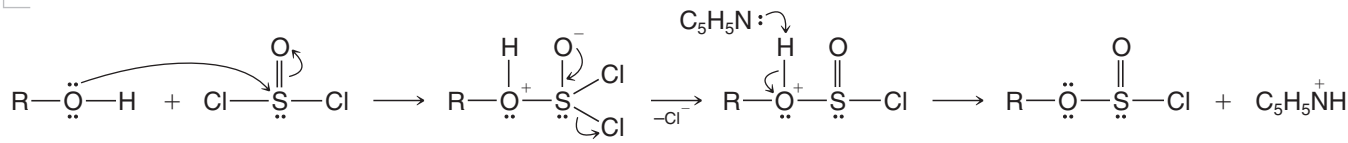
The trialkylphosphite goes on to react with three molecules of HBr to form three molecules of the alkyl bromide and a molecule of phosphonic acid.

$$P(OR)_3\ +\ 3\ HBr \longrightarrow 3\ RBr\ +\ H_3PO_3$$

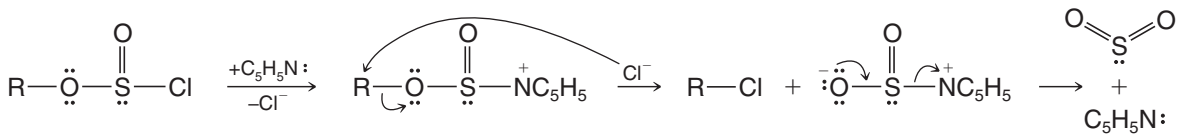
Helpful Hint

$SOCl_2$: A reagent for synthesizing 1° and 2° alkyl chlorides.

Thionyl chloride ($SOCl_2$) converts primary and secondary alcohols to alkyl chlorides. Pyridine (C_5H_5N) is often included to promote the reaction. The alcohol substrate attacks thionyl chloride as shown below, releasing a chloride anion and losing its proton to a molecule of pyridine. The result is an alkylchlorosulfite.



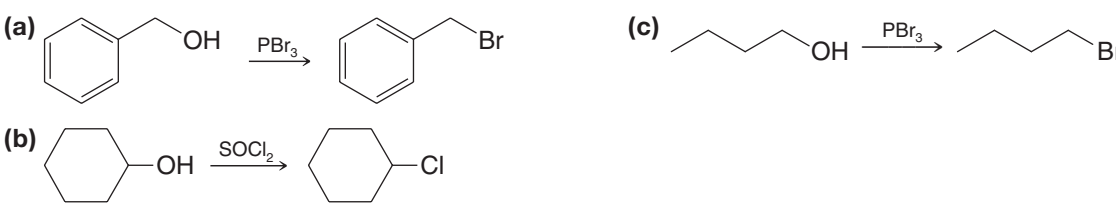
The alkylchlorosulfite intermediate then reacts rapidly with another molecule of pyridine, in the same fashion as the original alcohol, to give a pyridinium alkylsulfite intermediate, with release of the second chloride anion. A chloride anion then attacks the substrate carbon, displacing the sulfite leaving group, which in turn decomposes to release gaseous SO_2 and pyridine. (In the absence of pyridine the reaction occurs with retention of configuration. See Problem 11.55.)



SOLVED PROBLEM 11.6

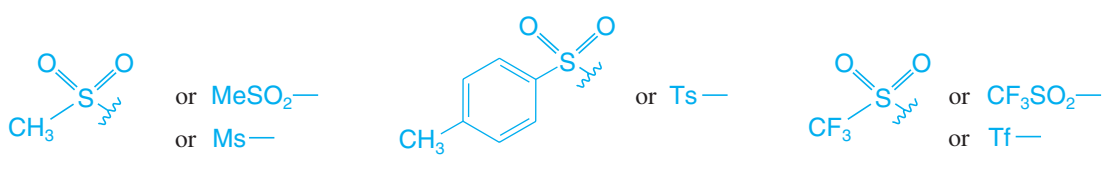
Starting with alcohols, outline a synthesis of each of the following: **(a)** benzyl bromide, **(b)** cyclohexyl chloride, and **(c)** butyl bromide.

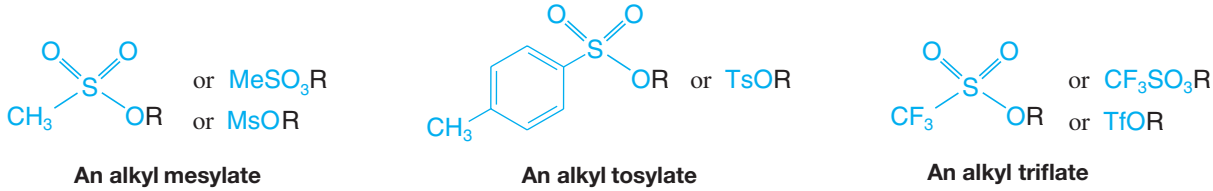
POSSIBLE ANSWERS:



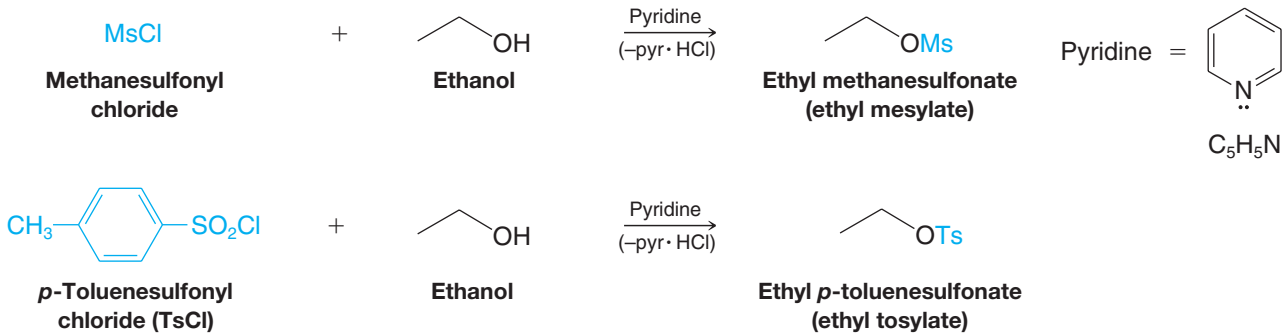
11.10 TOSYLATES, MESYLATES, AND TRIFLATES: LEAVING GROUP DERIVATIVES OF ALCOHOLS

The hydroxyl group of an alcohol can be converted to a good leaving group by conversion to a **sulfonate ester** derivative. The most common sulfonate esters used for this purpose are methanesulfonate esters ("**mesylates**"), *p*-toluenesulfonate esters ("**tosylates**"), and trifluoromethanesulfonates ("**triflates**").





The desired sulfonate ester is usually prepared by reaction of the alcohol in pyridine with the appropriate sulfonyl chloride, that is, methanesulfonyl chloride (mesyl chloride) for a mesylate, *p*-toluenesulfonyl chloride (tosyl chloride) for a tosylate, or trifluoromethanesulfonyl chloride [or trifluoromethanesulfonic anhydride (triflic anhydride)] for a triflate. Pyridine (C_5H_5N, pyr) serves as the solvent and to neutralize the HCl formed. Ethanol, for example, reacts with methanesulfonyl chloride to form ethyl methanesulfonate and with *p*-toluenesulfonyl chloride to form ethyl *p*-toluenesulfonate:

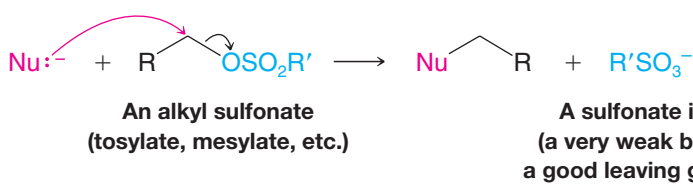


Helpful Hint

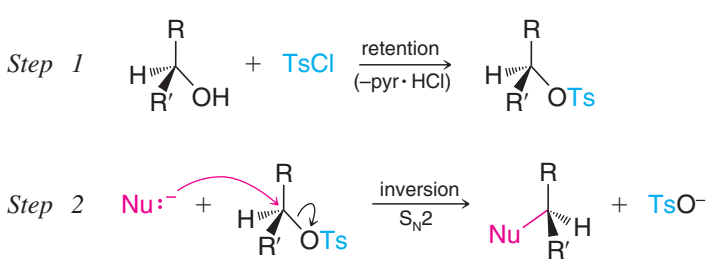
A method for making an alcohol hydroxyl group into a leaving group.

It is important to note that formation of the sulfonate ester does not affect the stereochemistry of the alcohol carbon, because the C—O bond is not involved in this step. Thus, if the alcohol carbon is a chirality center, no change in configuration occurs on making the sulfonate ester—the reaction proceeds with **retention of configuration.** On reaction of the sulfonate ester with a nucleophile, the usual parameters of nucleophilic substitution reactions become involved.

Substrates for Nucleophilic Substitution Mesylates, tosylates, and triflates, because they are good leaving groups, are frequently used as substrates for nucleophilic substitution reactions. They are good leaving groups because the sulfonate anions they become when they depart are very weak bases. The triflate anion is the weakest base in this series, and is thus the best leaving group among them.

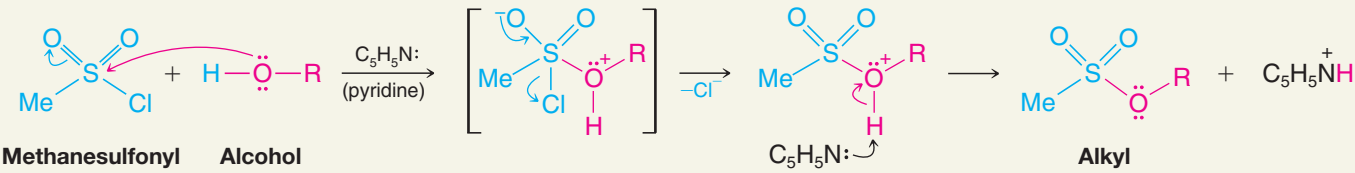


- To carry out a nucleophilic substitution on an alcohol, we first convert the alcohol to an alkyl sulfonate and then, in a second reaction, allow it to react with a nucleophile.
- If the mechanism is S_N2, as shown in the second reaction of the following example, **inversion of configuration** takes place at the carbon that originally bore the alcohol hydroxyl group:



The fact that the C—O bond of the alcohol does not break during formation of the sulfonate ester is accounted for by the following mechanism. Methanesulfonyl chloride is used in the example.

A MECHANISM FOR THE REACTION — Conversion of an Alcohol into a Mesylate (an Alkyl Methanesulfonate)



Methanesulfonyl chloride **Alcohol**

The alcohol oxygen attacks the sulfur atom of the sulfonyl chloride.

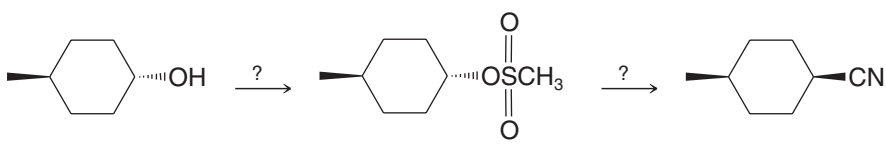
The intermediate loses a chloride ion.

Loss of a proton leads to the product.

Alkyl methanesulfonate

SOLVED PROBLEM 11.7

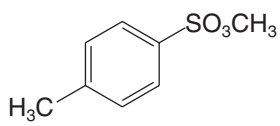
Supply the missing reagents.



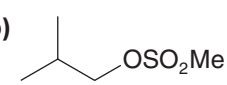
STRATEGY AND ANSWER: The overall transformation over two steps involves replacing an alcohol hydroxyl group by a cyano group with inversion of configuration. To accomplish this, we need to convert the alcohol hydroxyl to a good leaving group in the first step, which we do by making it a methanesulfonate ester (a mesylate) using methanesulfonyl chloride in pyridine. The second step is an S_N2 substitution of the methanesulfonate (mesyl) group, which we do using potassium or sodium cyanide in a polar aprotic solvent such as dimethylformamide (DMF).

PRACTICE PROBLEM 11.8 Show how you would prepare the following compounds from the appropriate sulfonyl chlorides.

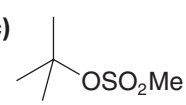
(a)



(b)

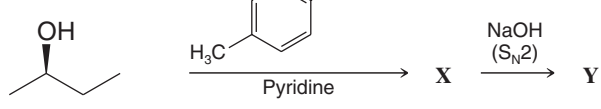


(c)



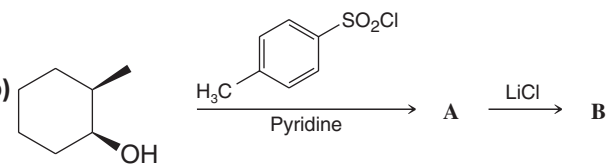
PRACTICE PROBLEM 11.9 Write structures for products **X, Y, A**, and **B**, showing stereochemistry.

(a)



(*R*)-2-Butanol

(b)



PRACTICE PROBLEM 11.10 Suggest an experiment using an isotopically labeled alcohol that would prove that the formation of an alkyl sulfonate does not cause cleavage at the C—O bond of the alcohol.

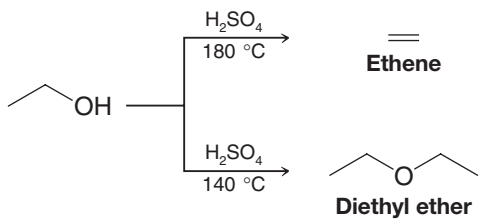
11.11 SYNTHESIS OF ETHERS

11.11A Ethers by Intermolecular Dehydration of Alcohols

Two alcohol molecules can form an ether by loss of water through an acid-catalyzed substitution reaction.

$$R{-}OH + HO{-}R \xrightarrow[-H_2O]{HA} R{-}O{-}R$$

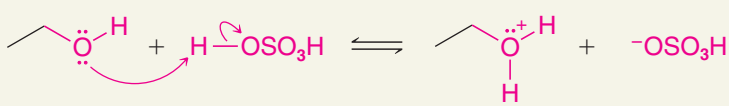
This reaction competes with the formation of alkenes by acid-catalyzed alcohol dehydration (Sections 7.7 and 7.8). Intermolecular dehydration of alcohols usually takes place at lower temperature than dehydration to an alkene, and dehydration to the ether can be aided by distilling the ether as it is formed. For example, diethyl ether is made commercially by dehydration of ethanol. Diethyl ether is the predominant product at 140 °C; ethene is the predominant product at 180 °C.



The formation of the ether occurs by an S_N2 mechanism with one molecule of the alcohol acting as the nucleophile and another protonated molecule of the alcohol acting as the substrate (see Section 11.5).

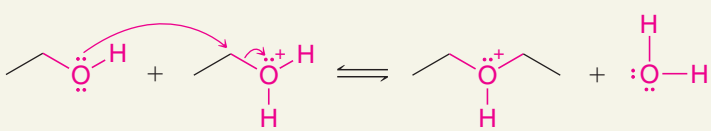
A MECHANISM FOR THE REACTION — Intermolecular Dehydration of Alcohols to Form an Ether

Step 1



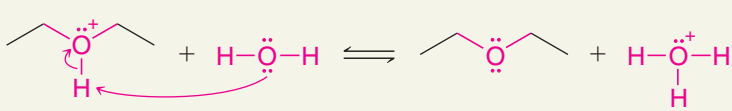
This is an acid–base reaction in which the alcohol accepts a proton from the sulfuric acid.

Step 2



Another molecule of the alcohol acts as a nucleophile and attacks the protonated alcohol in an S_N2 reaction.

Step 3

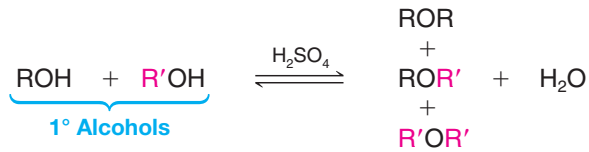


Another acid–base reaction converts the protonated ether to an ether by transferring a proton to a molecule of water (or to another molecule of the alcohol).

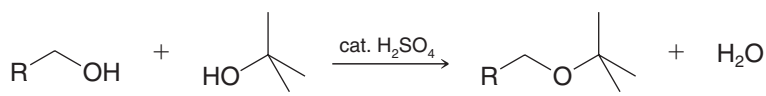
Complications of Intermolecular Dehydration The method of synthesizing ethers by intermolecular dehydration has some important limitations.

- Attempts to synthesize ethers by intermolecular dehydration of secondary alcohols are usually unsuccessful because alkenes form too easily.
- Attempts to make ethers with tertiary alkyl groups lead predominantly to alkenes.

- Intermolecular dehydration is not useful for the preparation of unsymmetrical ethers from primary alcohols because the reaction leads to a mixture of products:



PRACTICE PROBLEM 11.11 An exception to what we have just said has to do with syntheses of unsymmetrical ethers in which one alkyl group is a *tert*-butyl group and the other group is primary. For example, this synthesis can be accomplished by adding *tert*-butyl alcohol to a mixture of the primary alcohol and H_2SO_4 at room temperature.



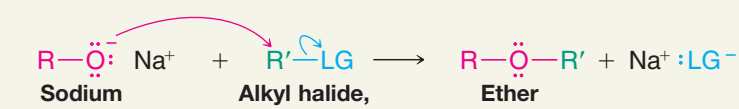
Give a likely mechanism for this reaction and explain why it is successful.

11.11B The Williamson Ether Synthesis

An important route to unsymmetrical ethers is a nucleophilic substitution reaction known as the **Williamson ether synthesis**.

- The Williamson ether synthesis consists of an S_N2 reaction of a sodium alkoxide with an alkyl halide, alkyl sulfonate, or alkyl sulfate.

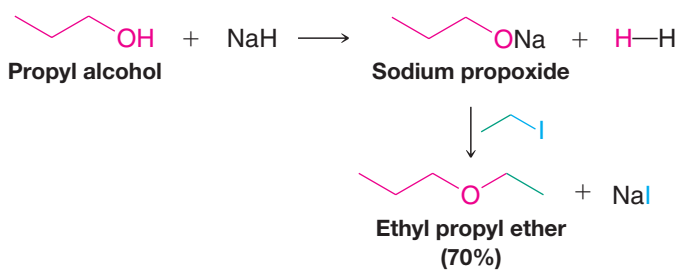
A MECHANISM FOR THE REACTION — The Williamson Ether Synthesis



The alkoxide ion reacts with the substrate in an S_N2 reaction, with the resulting formation of an ether. The substrate must be unhindered and bear a good leaving group. Typical substrates are 1° or 2° alkyl halides, alkyl sulfonates, and dialkyl sulfates:

—LG = —Br:, —I:, —OSO_2R'', or —OSO_2OR''

The following reaction is a specific example of the Williamson ether synthesis. The sodium alkoxide can be prepared by allowing an alcohol to react with NaH:



The usual limitations of S_N2 reactions apply here.

- Best results are obtained when the alkyl halide, sulfonate, or sulfate is primary (or methyl). **If the substrate is tertiary, elimination is the exclusive result.** Substitution is also favored over elimination at lower temperatures.

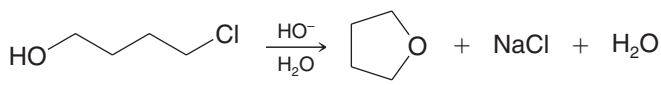
Helpful Hint
Conditions that favor a Williamson ether synthesis.

PRACTICE PROBLEM 11.12

(a) Outline two methods for preparing isopropyl methyl ether by a Williamson ether synthesis.
(b) One method gives a much better yield of the ether than the other. Explain which is the better method and why.

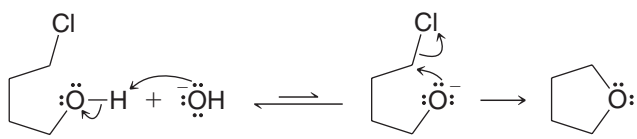
SOLVED PROBLEM 11.8

The cyclic ether tetrahydrofuran (THF) can be synthesized by treating 4-chloro-1-butanol with aqueous sodium hydroxide (see below). Propose a mechanism for this reaction.



Tetrahydrofuran

STRATEGY AND ANSWER: Removal of a proton from the hydroxyl group of 4-chloro-1-butanol gives an alkoxide ion that can then react with itself in an intramolecular S_N2 reaction to form a ring.

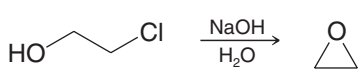


Even though treatment of the alcohol with hydroxide does not favor a large equilibrium concentration of the alkoxide, the alkoxide anions that are present react rapidly by the intramolecular S_N2 reaction. As alkoxide anions are consumed by the substitution reaction, their equilibrium concentration is replenished by deprotonation of additional alcohol molecules, and the reaction is drawn to completion.

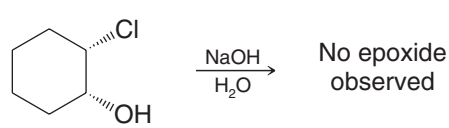
PRACTICE PROBLEM 11.13

Epoxides can be synthesized by treating halohydrins with aqueous base. Propose a mechanism for reactions **(a)** and **(b)**, and explain why no epoxide formation is observed in **(c)**.

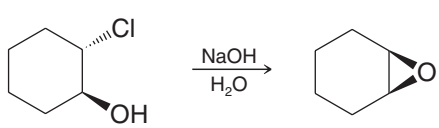
(a)



(c)

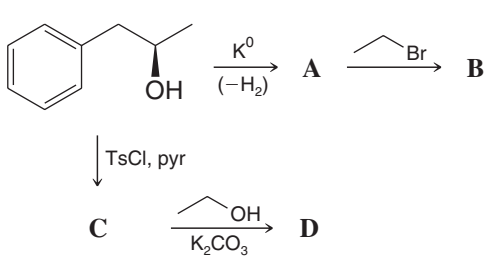


(b)



PRACTICE PROBLEM 11.14

Write structures for products **A, B, C**, and **D**, showing stereochemistry. (*Hint:* **B** and **D** are stereoisomers.)

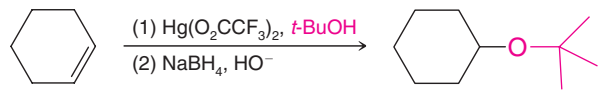


11.11C Synthesis of Ethers by Alkoxymercuration–Demercuration

Alkoxymercuration–demercuration is another method for synthesizing ethers.

- The reaction of an alkene with an alcohol in the presence of a mercury salt such as mercuric acetate or trifluoroacetate leads to an alkoxymercury intermediate, which on reaction with sodium borohydride yields an ether.

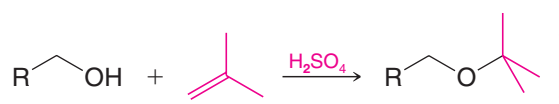
When the alcohol reactant is also the solvent, the method is called solvomercuration–demercuration. This method directly parallels hydration by oxymercuration–demercuration (Section 8.5):



(98% Yield)

11.11D *tert*-Butyl Ethers by Alkylation of Alcohols: Protecting Groups

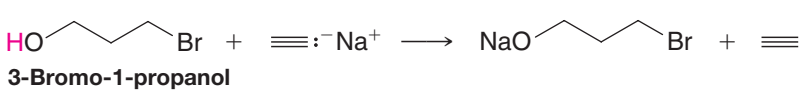
Primary alcohols can be converted to *tert*-butyl ethers by dissolving them in a strong acid such as sulfuric acid and then adding isobutylene to the mixture. (This procedure minimizes dimerization and polymerization of the isobutylene.)



***tert*-Butyl protecting group**

- A *tert*-butyl ether can be used to "protect" the hydroxyl group of a primary alcohol while another reaction is carried out on some other part of the molecule.
- A *tert*-butyl **protecting group** can be removed easily by treating the ether with dilute aqueous acid.

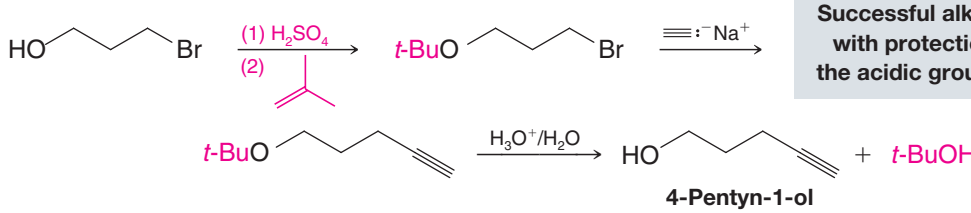
Suppose, for example, we wanted to prepare 4-pentyn-1-ol from 3-bromo-1-propanol and sodium acetylide. If we allow them to react directly, the strongly basic sodium acetylide will react first with the hydroxyl group, making the alkylation unsuccessful:



3-Bromo-1-propanol

Unsuccessful alkylation due to competing acid–base reaction.

However, if we protect the —OH group first, the synthesis becomes feasible:

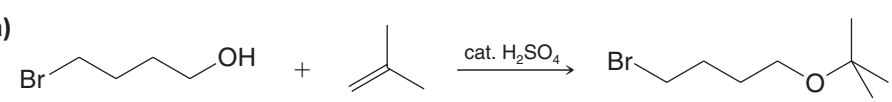


4-Pentyn-1-ol

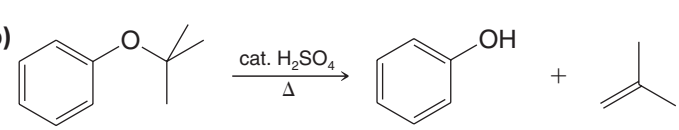
Successful alkylation with protection of the acidic group first.

PRACTICE PROBLEM 11.15 Propose mechanisms for the following reactions.

(a)



(b)

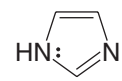


11.11E Silyl Ether Protecting Groups

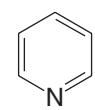
- A hydroxyl group can be protected from acid–base reactions by converting it to a **silyl ether** group.

One of the most common silyl ether **protecting groups** is the *tert*-butyldimethylsilyl ether group [*tert*-butyl $(Me)_2Si—O—R$, or TBS—O—R], although triethylsilyl, triisopropylsilyl, *tert*-butyldiphenylsilyl, and others can be used. The *tert*-butyldimethylsilyl ether is stable over a pH range of roughly 4–12. A TBS group can be added by allowing the alcohol to react with *tert*-butyldimethylsilyl chloride in the presence of an aromatic amine (a base) such as imidazole or pyridine:

***tert*-Butylchlorodimethylsilane (TBSCl)** **(R—O—TBS)**

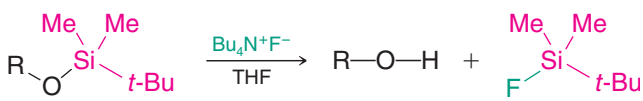


Imidazole



Pyridine

- The TBS group can be removed by treatment with fluoride ion (tetrabutylammonium fluoride or aqueous HF is frequently used). These conditions tend not to affect other functional groups, which is why TBS ethers are such good protecting groups.

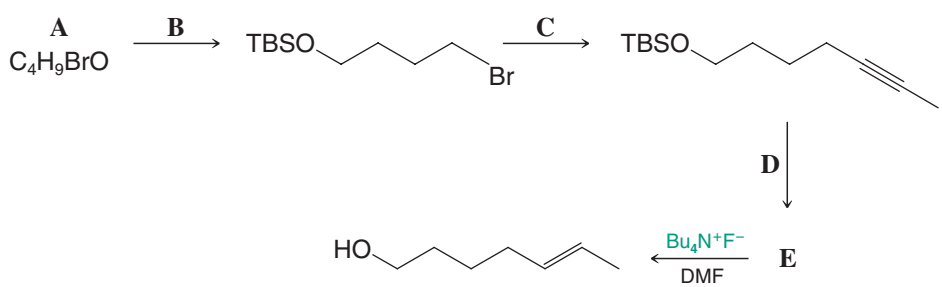


(R—O—TBS)

Converting an alcohol to a silyl ether also makes it much more volatile. This increased volatility makes the alcohol (as a silyl ether) much more amenable to analysis by gas chromatography. Trimethylsilyl ethers are often used for this purpose. The trimethylsilyl ether group is too labile to use as a protecting group in most reactions, however.

SOLVED PROBLEM 11.9

Supply the missing reagents and intermediates **A–E**.



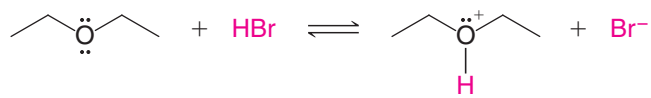
STRATEGY AND ANSWER: We start by noticing several things: a TBS (*tert*-butyldimethylsilyl) protecting group is involved, the carbon chain increases from four carbons in **A** to seven in the final product, and an alkyne is reduced to a trans alkene. **A** does not contain any silicon atoms, whereas the product after the reaction under conditions **B** does. Therefore, **A** must be an alcohol that is protected as a TBS ether by conditions specified as **B. A** is therefore 4-bromo-1-butanol, and conditions **B** are TBSCl (*tert*-butyldimethylsilyl chloride) with imidazole in DMF. Conditions **C** involve loss of the bromine and chain extension by three carbons with incorporation of an alkyne. Thus, the reaction conditions for **C** must involve sodium propynide, which would come from deprotonation of propyne using an appropriate base, such as $NaNH_2$ or CH_3MgBr. The conditions leading from **E** to the final product are those for removal of a TBS group, and not those for converting an alkyne to a trans alkene; thus, **E** must still contain the TBS ether but already contain the trans alkene. Conditions **D**, therefore, must be (1) Li, Et_2NH, (2) NH_4Cl, which are those required for converting the alkyne to a trans alkene. **E**, therefore, must be the TBS ether of 5-heptyn-1-ol (which can also be named 1-*tert*-butyldimethylsiloxy-5-heptynol).

11.12 REACTIONS OF ETHERS

Dialkyl ethers react with very few reagents other than acids. The only reactive sites that molecules of a dialkyl ether present to another reactive substance are the C—H bonds of the alkyl groups and the —Ö— group of the ether linkage. Ethers resist attack by nucleophiles (why?) and by bases. This lack of reactivity coupled with the ability of ethers to solvate cations (by donating an electron pair from their oxygen atom) makes ethers especially useful as solvents for many reactions.

Ethers are like alkanes in that they undergo halogenation reactions (Chapter 10), but these reactions are of little synthetic importance. They also undergo slow autoxidation to form explosive peroxides (see Section 11.3D).

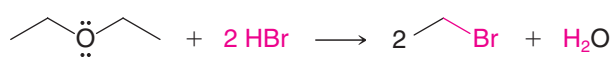
The oxygen of the ether linkage makes ethers weakly basic. Ethers can react with proton donors to form **oxonium salts**:



An oxonium salt

11.12A Cleavage of Ethers

Heating dialkyl ethers with very strong acids (HI, HBr, and H_2SO_4) causes them to undergo reactions in which the carbon–oxygen bond breaks. Diethyl ether, for example, reacts with hot concentrated hydrobromic acid to give two molecular equivalents of bromoethane:

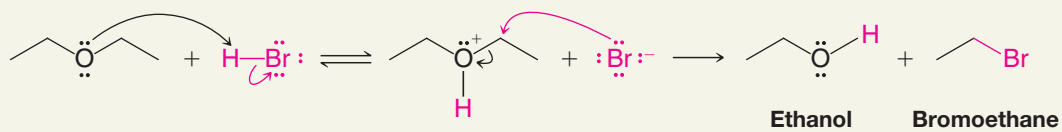


Cleavage of an ether

The mechanism for this reaction begins with formation of an oxonium cation. Then, an S_N2 reaction with a bromide ion acting as the nucleophile produces ethanol and bromoethane. Excess HBr reacts with the ethanol produced to form the second molar equivalent of bromoethane.

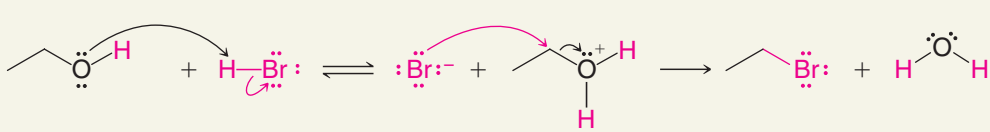
A MECHANISM FOR THE REACTION — Ether Cleavage by Strong Acids

Step 1



Ethanol **Bromoethane**

Step 2 **In step 2 the ethanol (just formed) reacts with HBr (present in excess) to form a second molar equivalent of bromoethane**

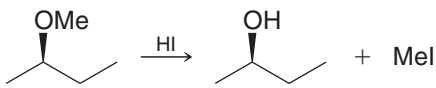


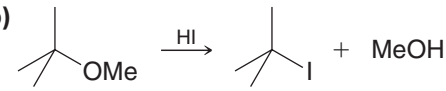
PRACTICE PROBLEM 11.16

When an ether is treated with *cold* concentrated HI, cleavage occurs as follows:

$$R{-}O{-}R + HI \longrightarrow ROH + RI$$

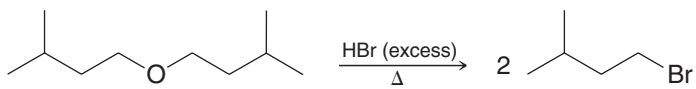
When mixed ethers are used, the alcohol and alkyl iodide that form depend on the nature of the alkyl groups. Use mechanisms to explain the following observations:

(a) 

(b) 

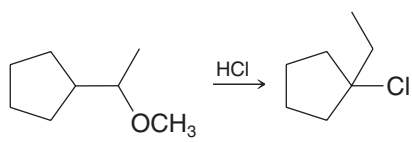
PRACTICE PROBLEM 11.17

Write a detailed mechanism for the following reaction.



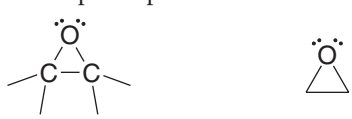
PRACTICE PROBLEM 11.18

Provide a mechanism for the following reaction.



11.13 EPOXIDES

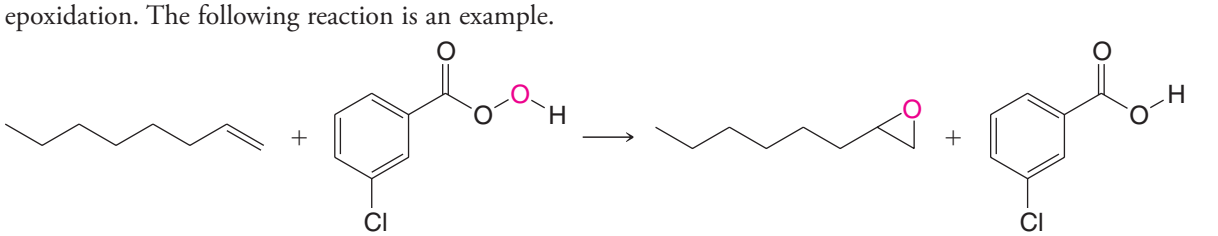
Epoxides are cyclic ethers with three-membered rings. In IUPAC nomenclature epoxides are called **oxiranes**. The simplest epoxide has the common name ethylene oxide:



An epoxide **IUPAC name: oxirane**
Common name: ethylene oxide

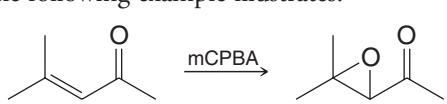
11.13A Synthesis of Epoxides: Epoxidation

Epoxides can be synthesized by the reaction of an alkene with an organic **peroxy acid** (RCO_3H—sometimes called simply a **peracid**), a process that is called **epoxidation**. *meta*-Chloroperoxybenzoic acid (mCPBA) is one peroxy acid reagent commonly used for epoxidation. The following reaction is an example.



1-Octene **mCPBA** **(81%)** ***meta*-Chlorobenzoic acid**

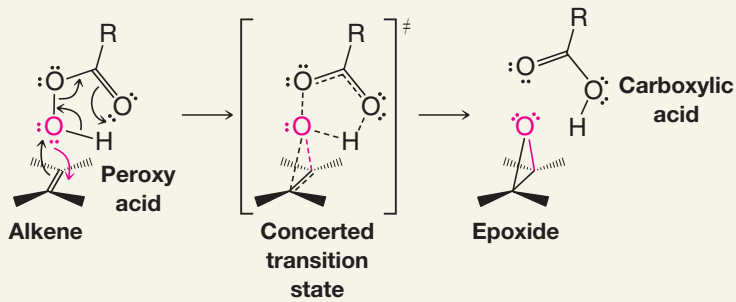
meta-Chlorobenzoic acid is a by-product of the reaction. Often it is not written in the chemical equation, as the following example illustrates.



(77%)

As the first example illustrates, the peroxy acid transfers an oxygen atom to the alkene. The following mechanism has been proposed.

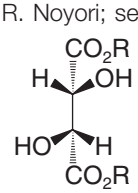
A MECHANISM FOR THE REACTION — Alkene Epoxidation



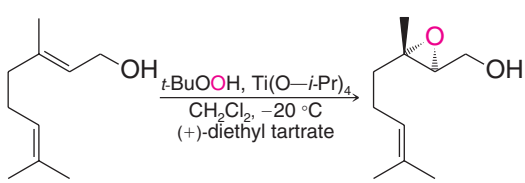
The peroxy acid transfers an oxygen atom to the alkene in a cyclic, single-step mechanism. The result is the syn addition of the oxygen to the alkene, with the formation of an epoxide and a carboxylic acid.

THE CHEMISTRY OF... The Sharpless Asymmetric Epoxidation

In 1980, K. B. Sharpless (then at the Massachusetts Institute of Technology, presently at The Scripps Research Institute) and co-workers reported a method that has since become one of the most valuable tools for chiral synthesis. The Sharpless asymmetric epoxidation is a method for converting allylic alcohols (Section 11.1) to chiral epoxy alcohols with very high enantioselectivity (i.e., with preference for one enantiomer rather than formation of a racemic mixture). In recognition of this and other work in asymmetric oxidation methods (see Section 8.16A), Sharpless received half of the 2001 Nobel Prize in Chemistry (the other half was awarded to W. S. Knowles and R. Noyori; see Section 7.14). The Sharpless asymmetric epoxidation involves treating the allylic alcohol with *tert*-butyl hydroperoxide, titanium(IV) tetraisopropoxide [$Ti(O—i\text{-}Pr)_4$], and a specific stereoisomer of a tartrate ester. (The tartrate stereoisomer that is chosen depends on the specific enantiomer of the epoxide desired). The following is an example:



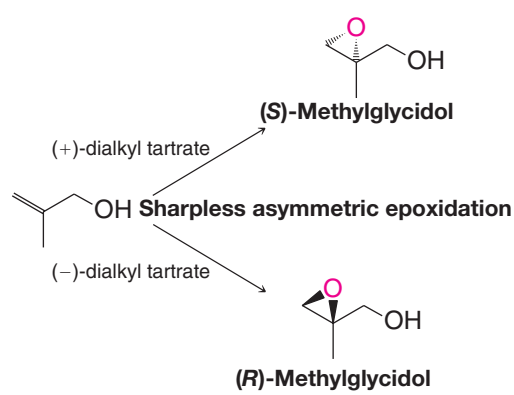
A (+)-dialkyl tartrate ester

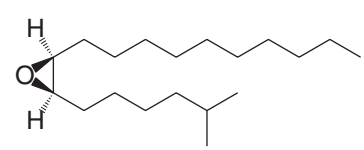


Geraniol — **77% yield (95% enantiomeric excess)**

© Universal Images Group/SuperStock

The oxygen that is transferred to the allylic alcohol to form the epoxide is derived from *tert*-butyl hydroperoxide. The enantioselectivity of the reaction results from a titanium complex among the reagents that includes the enantiomerically pure tartrate ester as one of the ligands. The choice of whether to use the (+)- or (–)-tartrate ester for stereochemical control depends on which enantiomer of the epoxide is desired. [The (+)- and (–)-tartrates are either diethyl or diisopropyl esters.] The stereochemical preferences of the reaction have been well studied, such that it is possible to prepare either enantiomer of a chiral epoxide in high enantiomeric excess, simply by choosing the appropriate (+)- or (–)-tartrate stereoisomer as the chiral ligand:

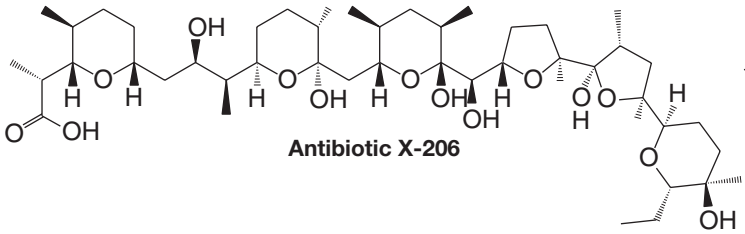




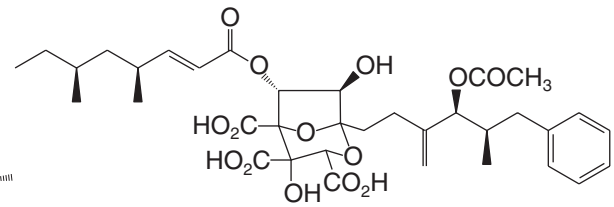
(7*R*,8*S*)-Disparlure

Compounds of this general structure are extremely useful and versatile synthons because combined in one molecule are an epoxide functional group (a highly reactive electrophilic site), an alcohol functional group (a potentially nucleophilic site), and at least one chirality center that is present in high enantiomeric purity. The synthetic utility of chiral epoxy alcohol synthons produced by the Sharpless asymmetric epoxidation has been demonstrated over and over in enantioselective syntheses of many important compounds. Some examples include the synthesis

of the polyether antibiotic X-206 by E. J. Corey (Harvard), the J. T. Baker commercial synthesis of the gypsy moth pheromone (7*R*,8*S*)-disparlure, and synthesis by K. C. Nicolaou (University of California San Diego and Scripps Research Institute) of zaragozic acid A (which is also called squalestatin S1 and has been shown to lower serum cholesterol levels in test animals by inhibition of squalene biosynthesis; see "The Chemistry of… Cholesterol Biosynthesis," online in *WileyPLUS* after Chapter 8).



Antibiotic X-206

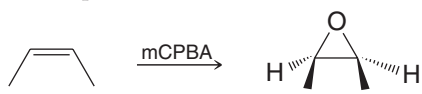


Zaragozic acid A (squalestatin S1)

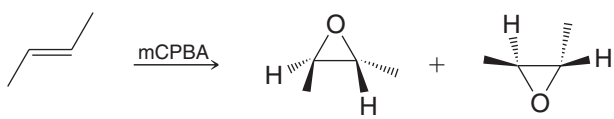
11.13B Stereochemistry of Epoxidation

- The reaction of alkenes with peroxy acids is, of necessity, a **syn** addition, and it is **stereospecific**. Furthermore, the oxygen atom can add to either face of the alkene.

For example, *trans*-2-butene yields racemic *trans*-2,3-dimethyloxirane, because addition of oxygen to each face of the alkene generates an enantiomer. *cis*-2-Butene, on the other hand, yields only *cis*-2,3-dimethyloxirane, no matter which face of the alkene accepts the oxygen atom, due to the plane of symmetry in both the reactant and the product. If additional chirality centers are present in a substrate, then diastereomers would result.



***cis*-2-Butene** ***cis*-2,3-Dimethyloxirane (a meso compound)**



***trans*-2-Butene** **Enantiomeric *trans*-2,3-dimethyloxiranes**

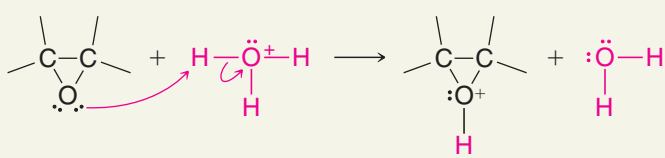
In Special Topic D (Section D.3, in *WileyPLUS*) we present a method for synthesizing epoxides from aldehydes and ketones.

11.14 REACTIONS OF EPOXIDES

- The highly strained three-membered ring of epoxides makes them much more reactive toward nucleophilic substitution than other ethers.

Acid catalysis assists epoxide ring opening by providing a better leaving group (an alcohol) at the carbon atom undergoing nucleophilic attack. This catalysis is especially important if the nucleophile is a weak nucleophile such as water or an alcohol. An example is the acid-catalyzed hydrolysis of an epoxide.

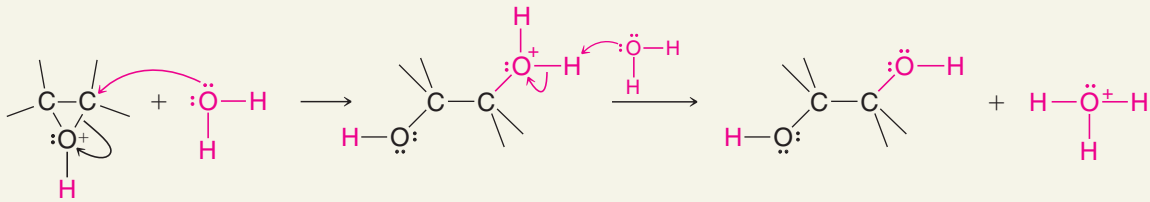
A MECHANISM FOR THE REACTION — Acid-Catalyzed Ring Opening of an Epoxide



Epoxide **Protonated epoxide**

The acid reacts with the epoxide to produce a protonated epoxide.

(mechanism continues on the next page)

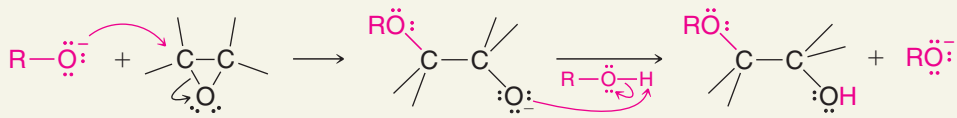


Protonated epoxide | Weak nucleophile | Protonated 1,2-diol | 1,2-Diol

The protonated epoxide reacts with the weak nucleophile (water) to form a protonated 1,2-diol, which then transfers a proton to a molecule of water to form the 1,2-diol and a hydronium ion.

Epoxides can also undergo base-catalyzed ring opening. Such reactions do not occur with other ethers, but they are possible with epoxides (because of ring strain), provided that the attacking nucleophile is also a strong base such as an alkoxide ion or hydroxide ion.

A MECHANISM FOR THE REACTION — Base-Catalyzed Ring Opening of an Epoxide



Strong nucleophile | Epoxide | An alkoxide ion

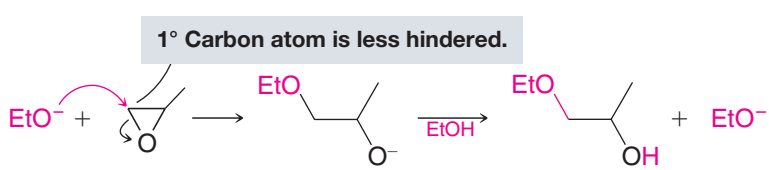
A strong nucleophile such as an alkoxide ion or a hydroxide ion is able to open the strained epoxide ring in a direct S_N2 reaction.

Helpful Hint

Regioselectivity in the opening of epoxides.

- **Base-catalyzed ring opening** of an unsymmetrical epoxide occurs primarily by attack of the nucleophile ***at the less substituted carbon atom***.

For example, methyloxirane reacts with an alkoxide ion mainly at its primary carbon atom:

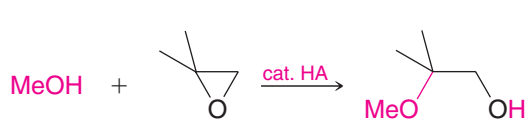


Methyloxirane | 1-Ethoxy-2-propanol

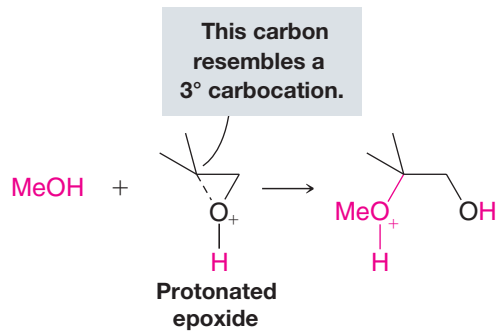
This is just what we should expect: the reaction is, after all, an S_N2 reaction, and, as we learned earlier (Section 6.13A), primary substrates react more rapidly in S_N2 reactions because they are less sterically hindered.

- **Acid-catalyzed ring opening** of an unsymmetrical epoxide occurs primarily by attack of the nucleophile ***at the more substituted carbon atom***.

For example,



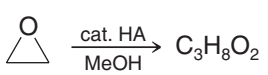
The reason: bonding in the protonated epoxide (see the following reaction) is unsymmetrical, with the more highly substituted carbon atom bearing a considerable positive charge; the reaction is S_N1 like. The nucleophile, therefore, attacks this carbon atom even though it is more highly substituted:



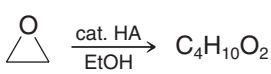
The more highly substituted carbon atom bears a greater positive charge because it resembles a more stable tertiary carbocation. [Notice how this reaction (and its explanation) resembles that given for halohydrin formation from unsymmetrical alkenes in Section 8.14 and attack on mercurinium ions.]

PRACTICE PROBLEM 11.19

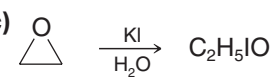
Propose structures for each of the following products derived from oxirane (ethylene oxide):

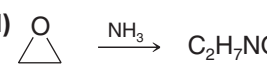
(a) 

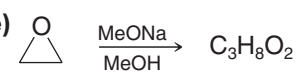
Methyl Cellosolve

(b) 

Ethyl Cellosolve

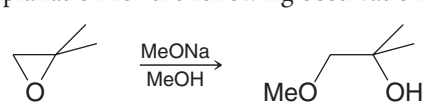
(c) 

(d) 

(e) 

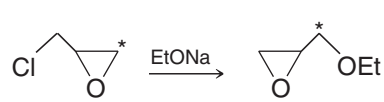
PRACTICE PROBLEM 11.20

Provide a mechanistic explanation for the following observation.



PRACTICE PROBLEM 11.21

When sodium ethoxide reacts with 1-(chloromethyl)oxirane (also called epichlorohydrin), labeled with ^{14}C as shown by the asterisk in **I**, the major product is **II**. Provide a mechanistic explanation for this result.



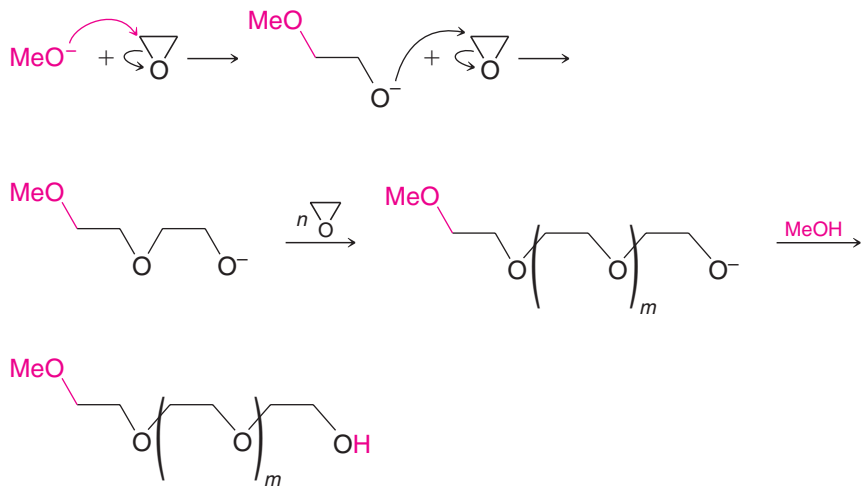
I

1-(Chloromethyl)oxirane (epichlorohydrin)

II

11.14A Polyethers from Epoxides

Treating ethylene oxide with sodium methoxide (in the presence of a small amount of methanol) can result in the formation of a **polyether**:



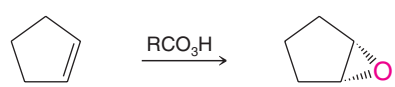
Poly(ethylene glycol)
(a polyether)

This is an example of **anionic polymerization** (Section 10.11). The polymer chains continue to grow until methanol protonates the alkoxide group at the end of the chain. The average length of the growing chains and, therefore, the average molecular weight of the polymer can be controlled by the amount of methanol present. The physical properties of the polymer depend on its average molecular weight.

Polyethers have high water solubilities because of their ability to form multiple hydrogen bonds to water molecules. Marketed commercially as **carbowaxes**, these polymers have a variety of uses, ranging from use in gas chromatography columns to applications in cosmetics.

11.15 ANTI 1,2-DIHYDROXYLATION OF ALKENES VIA EPOXIDES

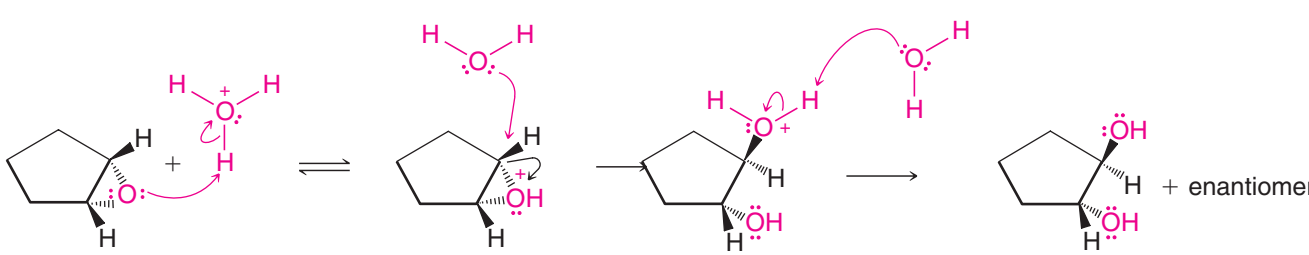
Epoxidation of cyclopentene with a peroxycarboxylic acid produces 1,2-epoxycyclopentane:



Cyclopentene **1,2-Epoxycyclopentane**

Helpful Hint
A synthetic method for anti 1,2-dihydroxylation.

Acid-catalyzed hydrolysis of 1,2-epoxycyclopentane, shown below, yields a trans diol, *trans*-1,2-cyclopentanediol. Water acting as a nucleophile attacks the protonated epoxide from the side opposite the epoxide group. The carbon atom being attacked undergoes an inversion of configuration. We show here only one carbon atom being attacked. Attack at the other carbon atom of this symmetrical system is equally likely and produces the enantiomeric form of *trans*-1,2-cyclopentanediol:



***trans*-1,2-Cyclopentanediol**

Epoxidation followed by acid-catalyzed hydrolysis gives us, therefore, a method for **anti 1,2-dihydroxylation** of a double bond (as opposed to syn 1,2-dihydroxylation, Section 8.16). The stereochemistry of this technique parallels closely the stereochemistry of the bromination of cyclopentene given earlier (Section 8.13).

PRACTICE PROBLEM 11.22

Outline a mechanism similar to the one just given that shows how the enantiomeric form of *trans*-1,2-cyclopentanediol is produced.

SOLVED PROBLEM 11.10

In Section 11.13B we showed the epoxidation of *cis*-2-butene to yield *cis*-2,3-dimethyloxirane and epoxidation of *trans*-2-butene to yield *trans*-2,3-dimethyloxirane. Now consider acid-catalyzed hydrolysis of these two epoxides and show what product or products would result from each. Are these reactions stereospecific?

ANSWER: (a) The meso compound, *cis*-2,3-dimethyloxirane (Fig. 11.1), yields on hydrolysis (2*R*,3*R*)-2,3-butanediol and (2*S*,3*S*)-2,3-butanediol. These products are enantiomers. Since the attack by water at either carbon [path **(a)** or path **(b)** in Fig. 11.1] occurs at the same rate, the product is obtained in a racemic form.

When either of the *trans*-2,3-dimethyloxirane enantiomers undergoes acid-catalyzed hydrolysis, the only product that is obtained is the meso compound, (2*R*,3*S*)-2,3-butanediol. The hydrolysis of one enantiomer is shown in Fig. 11.2. (You might construct a similar diagram showing the hydrolysis of the other enantiomer to convince yourself that it, too, yields the same product.)

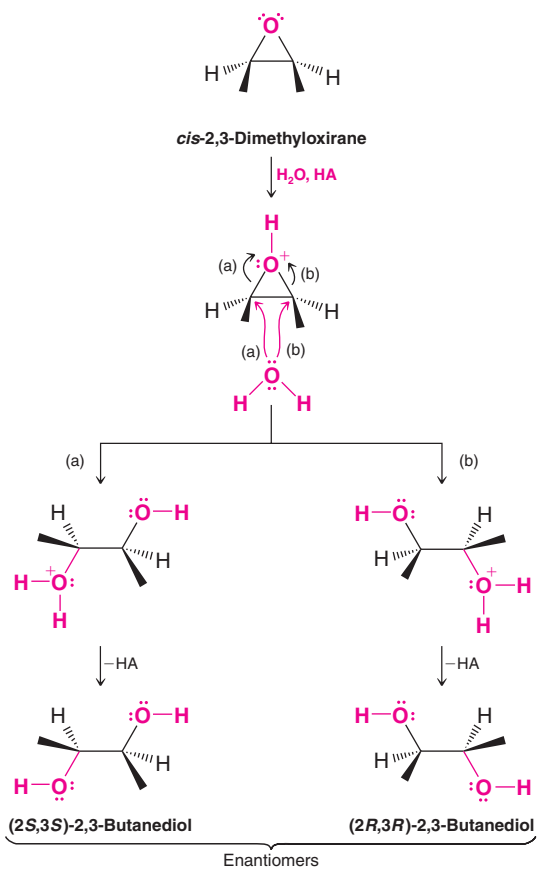


FIGURE 11.1 Acid-catalyzed hydrolysis of *cis*-2,3-dimethyloxirane yields (2*S*,3*S*)-2,3-butanediol by path (a) and (2*R*,3*R*)-2,3-butanediol by path (b). (Use models to convince yourself.)

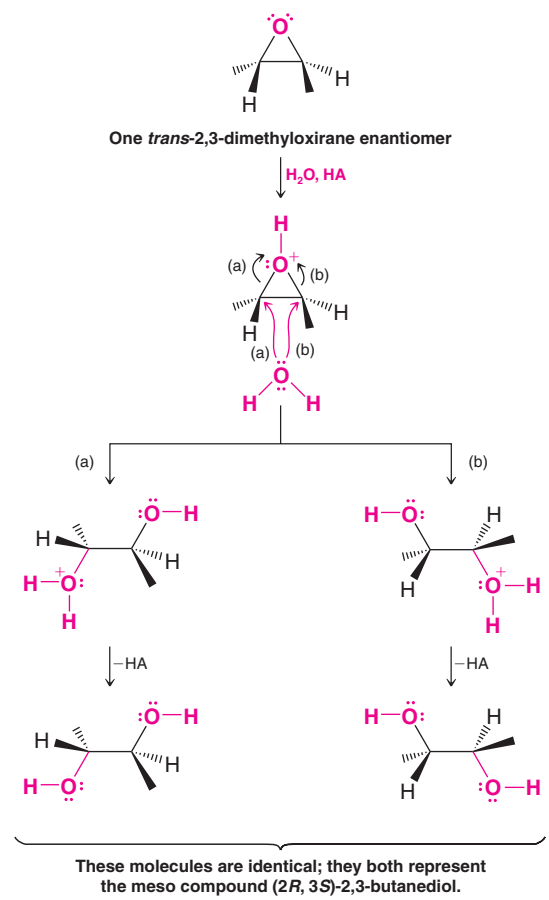


FIGURE 11.2 The acid-catalyzed hydrolysis of one *trans*-2,3-dimethyloxirane enantiomer produces the meso compound, (2*R*,3*S*)-2,3-butanediol, by path (a) or by path (b). Hydrolysis of the other enantiomer (or the racemic modification) would yield the same product. (You should use models to convince yourself that the two structures given for the products do represent the same compound.)

(continues on next page)

(b) Since both steps in this method for the conversion of an alkene to a 1,2-diol (glycol) are stereospecific (i.e., both the epoxidation step and the acid-catalyzed hydrolysis), the net result is a stereospecific anti 1,2-dihydroxylation of the double bond (Fig. 11.3).

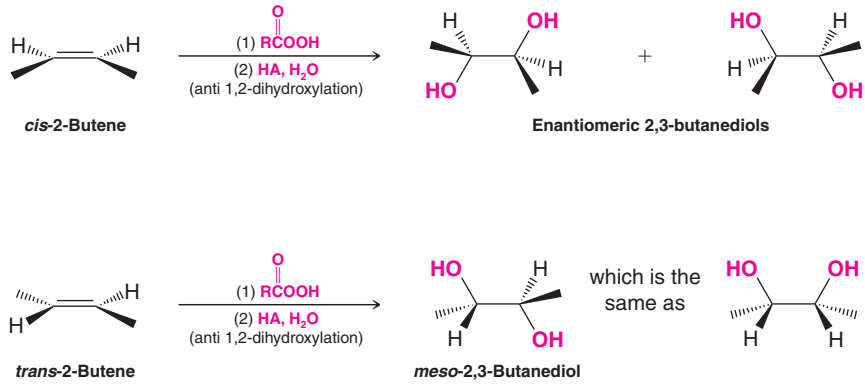
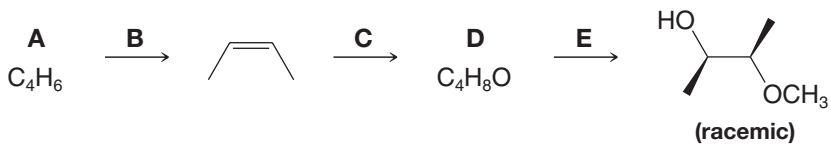


FIGURE 11.3 The overall result of epoxidation followed by acid-catalyzed hydrolysis is a stereospecific anti 1,2-dihydroxylation of the double bond. *cis*-2-Butene yields the enantiomeric 2,3-butanediols; *trans*-2-butene yields the meso compound.

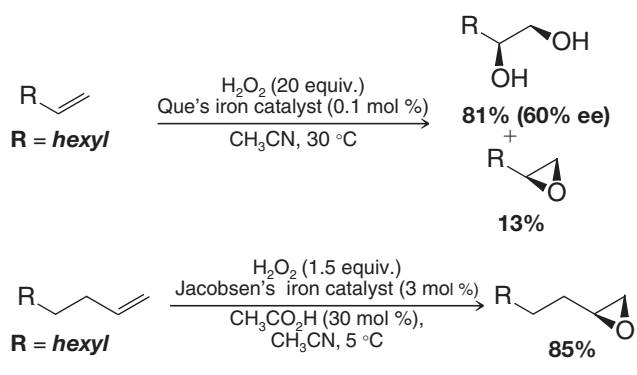
PRACTICE PROBLEM 11.23 Supply the missing reagents and intermediates **A–E**.

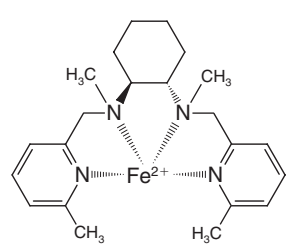


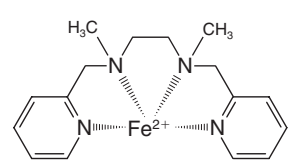
THE CHEMISTRY OF... Environmentally Friendly Alkene Oxidation Methods

The effort to develop synthetic methods that are environmentally friendly is a very active area of chemistry research. The push to devise "green chemistry" procedures includes not only replacing the use of potentially hazardous or toxic reagents with ones that are more friendly to the environment but also developing catalytic procedures that use smaller quantities of potentially harmful reagents when other alternatives are not available. The catalytic syn 1,2-dihydroxylation methods that we described in Section 8.16 (including the Sharpless asymmetric dihydroxylation procedure) are environmentally friendly modifications of the original procedures because they require only a small amount of OsO_4 or other heavy metal oxidant.

Nature has provided hints for ways to carry out environmentally sound oxidations as well. The enzyme methane monooxygenase (MMO) uses iron to catalyze hydrogen peroxide oxidation of small hydrocarbons, yielding alcohols or epoxides, and this example has inspired development of new laboratory methods for alkene oxidation. A 1,2-dihydroxylation procedure developed by L. Que (University of Minnesota) yields a mixture of 1,2-diols and epoxides by action of an iron catalyst and hydrogen peroxide on an alkene. (The ratio of diol to epoxide formed depends on the reaction conditions, and in the case of dihydroxylation, the procedure shows some enantioselectivity.) Another green reaction is the epoxidation method developed by E. Jacobsen (Harvard University). Jacobsen's procedure uses hydrogen peroxide and a similar iron catalyst to epoxidize alkenes (without the complication of diol formation). Que's and Jacobsen's methods are environmentally friendly because their procedures employ catalysts containing a nontoxic metal, and an inexpensive, relatively safe oxidizing reagent is used that is converted to water in the course of the reaction.



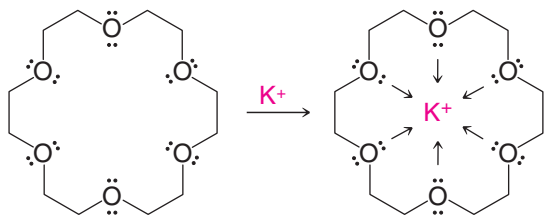




The quest for more methods in green chemistry, with benign reagents and by-products, catalytic cycles, and high yields, will no doubt drive further research by present and future chemists. In coming chapters we shall see more examples of green chemistry in use or under development.

11.16 CROWN ETHERS

Crown ethers are compounds having structures like that of 18-crown-6, below. 18-Crown-6 is a cyclic oligomer of ethylene glycol. Crown ethers are named as *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. A key property of crown ethers is that they are able to bind cations, as shown below for 18-crown-6 and a potassium ion.

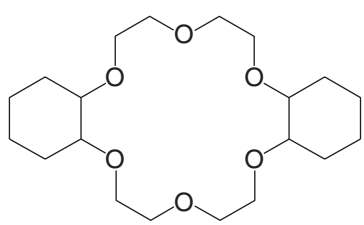


18-Crown-6

Crown ethers render many salts soluble in nonpolar solvents. For this reason they are called **phase transfer catalysts**. When a crown ether coordinates with a metal cation it masks the ion with a hydrocarbon-like exterior. 18-Crown-6 coordinates very effectively with potassium ions because the cavity size is correct and because the six oxygen atoms are ideally situated to donate their electron pairs to the central ion in a Lewis acid–base complex.

- The relationship between a crown ether and the ion it binds is called a **host–guest relationship**.

Salts such as KF, KCN, and potassium acetate can be transferred into aprotic solvents using catalytic amounts of 18-crown-6. Use of a crown ether with a nonpolar solvent can be very favorable for an S_N2 reaction because the nucleophile (such as F^-, CN^-, or acetate from the compounds just listed) is unencumbered by solvent in an aprotic solvent, while at the same time the cation is prevented by the crown ether from associating with the nucleophile. Dicyclohexano-18-crown-6 is another example of a phase transfer catalyst. It is even more soluble in nonpolar solvents than 18-crown-6 due to its additional hydrocarbon groups. Phase transfer catalysts can also be used for reactions such as oxidations. (There are phase transfer catalysts that are not crown ethers, as well.)



Dicyclohexano-18-crown-6

The development of crown ethers and other molecules "with structure specific interactions of high selectivity" led to awarding of the 1987 Nobel Prize in Chemistry to Charles J. Pedersen (DuPont Company, deceased), Donald J. Cram (University of California, Los Angeles, deceased), and Jean-Marie Lehn (Louis Pasteur University, Strasbourg, France). Their contributions to our understanding of what is now called "molecular recognition" have implications for how enzymes recognize their substrates, how hormones cause their effects, how antibodies recognize antigens, how neurotransmitters propagate their signals, and many other aspects of biochemistry.

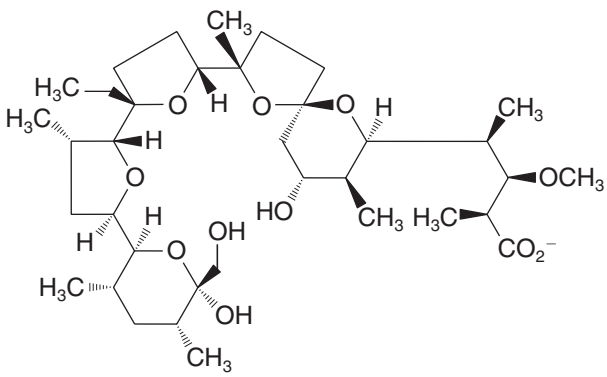
The 1987 Nobel Prize in Chemistry was awarded to Pedersen, Cram, and Lehn for their work relating to crown ethers.

Write structures for **(a)** 15-crown-5 and **(b)** 12-crown-4.

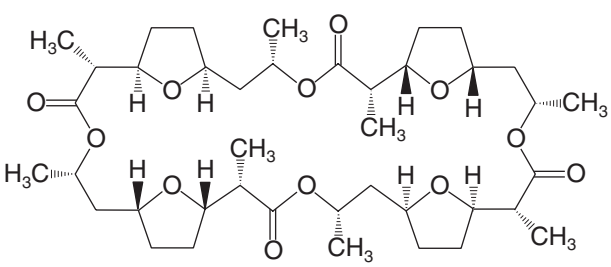
PRACTICE PROBLEM 11.24

THE CHEMISTRY OF... Transport Antibiotics and Crown Ethers

There are several antibiotics called ionophores. Some notable examples are monensin, nonactin, gramicidin, and valinomycin. The structures of monensin and nonactin are shown below. Ionophore antibiotics like monensin and nonactin coordinate with metal cations in a manner similar to crown ethers. Their mode of action has to do with disrupting the natural gradient of ions on each side of the cell membrane.



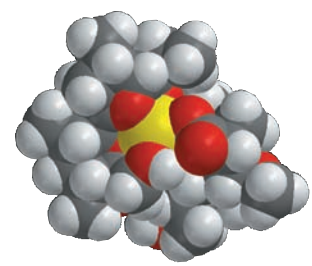
Monensin



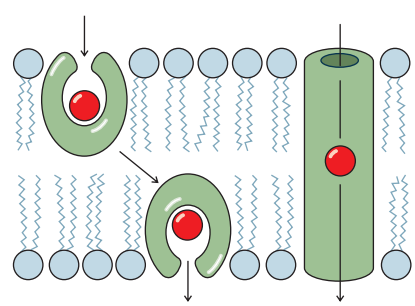
Nonactin

The cell membrane, in its interior, is like a hydrocarbon because it consists in this region primarily of the hydrocarbon portions of lipids (Chapter 23). Normally, cells must maintain a gradient between the concentrations of sodium and potassium ions inside and outside the cell membrane. Potassium ions are "pumped" in, and sodium ions are pumped out. This gradient is essential to the functions of nerves, transport of nutrients into the cell, and maintenance of proper cell volume. The biochemical transport of sodium and potassium ions through the cell membrane is slow, and requires an expenditure of energy by the cell. (The 1997 Nobel Prize in Chemistry was awarded in part for work regarding sodium and potassium cell membrane transport.*)

Monensin is called a carrier ionophore because it binds with sodium ions and carries them across the cell membrane. Gramicidin and valinomycin are channel-forming antibiotics because they open pores that extend through the membrane. The ion-trapping ability of monensin results principally from its many ether functional groups, and as such, it is an example of a polyether antibiotic. Its oxygen atoms bind with sodium ions by Lewis acid–base interactions, forming the octahedral complex shown here in the molecular model. The complex is a hydrophobic "host" for the cation that allows it to be carried as a "guest" of monensin from one side of the cell membrane to the other. The transport process destroys the critical sodium concentration gradient needed for cell function. Nonactin is another ionophore that upsets the concentration gradient by binding strongly to potassium ions, allowing the membrane to be permeable to potassium ions, also destroying the essential concentration gradient.



The ionophore antibiotic monensin complexed with a sodium cation.



Carrier (left) and channel-forming modes of transport ionophores. (Reprinted with permission of John Wiley & Sons, Inc. from Voet, D. and Voet, J. G. *Biochemistry*, Second Edition. Copyright 1995 Voet, D., and Voet, J. G.)

*Discovery and characterization of the actual molecular pump that establishes the sodium and potassium concentration gradient (Na^+, K^+ -ATPase) earned Jens Skou (Aarhus University, Denmark) half of the 1997 Nobel Prize in Chemistry. The other half went to Paul D. Boyer (UCLA) and John E. Walker (Cambridge) for elucidating the enzymatic mechanism of ATP synthesis.

11.17 SUMMARY OF REACTIONS OF ALKENES, ALCOHOLS, AND ETHERS

Helpful Hint
Some tools for synthesis.

We have studied reactions in this chapter and in Chapter 8 that can be extremely useful in designing syntheses. Most of these reactions involving alcohols and ethers are summarized in the Summary Review Tools at the end of the chapter.

- We can use alcohols to make alkyl halides, sulfonate esters, ethers, and alkenes.
- We can oxidize alkenes to make epoxides, diols, aldehydes, ketones, and carboxylic acids (depending on the specific alkene and conditions).
- We can use alkenes to make alkanes, alcohols, and alkyl halides.
- If we have a terminal alkyne, such as could be made from an appropriate vicinal dihalide, we can use the alkynide anion derived from it to form carbon–carbon bonds by nucleophilic substitution.

All together, we have a repertoire of reactions that can be used to directly or indirectly interconvert almost all of the functional groups we have studied so far. In Section 11.17A we summarize some reactions of alkenes.

11.17A HOW TO Use Alkenes in Synthesis

- Alkenes are an entry point to virtually all of the other functional groups that we have studied.

For this reason, and because many of the reactions afford us some degree of control over the regiochemical and/or stereochemical form of the products, alkenes are versatile intermediates for synthesis.

- We have two methods to **hydrate a double bond in a Markovnikov orientation**: (1) *oxymercuration–demercuration* (Section 8.5), and (2) *acid-catalyzed hydration* (Section 8.4).

Of these methods oxymercuration–demercuration is the most useful in the laboratory because it is easy to carry out and *is not accompanied by rearrangements*.

- We can **hydrate a double bond in an anti-Markovnikov orientation** by *hydroboration–oxidation* (Section 8.6). With hydroboration–oxidation we can also achieve a *syn addition of the* H— *and* —OH *groups*.

Remember, too, **the boron group of an organoborane can be replaced by hydrogen, deuterium, or tritium** (Section 8.11), and that hydroboration, itself, involves a *syn addition of* H— *and* —B—.

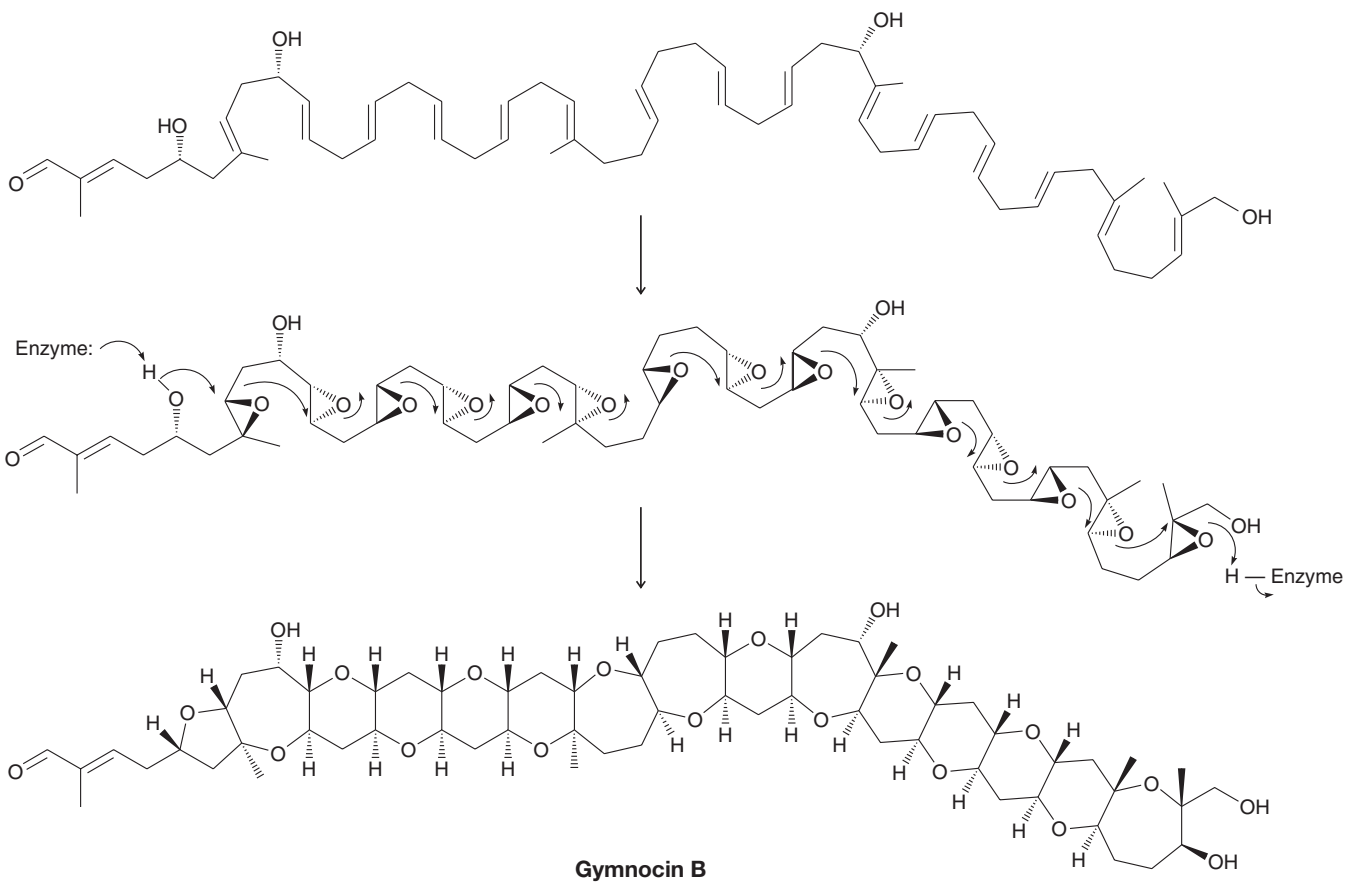
- We can **add** HX **to a double bond in a Markovnikov sense** (Section 8.2) using HF, HCl, HBr, or HI.
- We can **add** HBr **in an anti-Markovnikov orientation** (Section 10.9), by treating an alkene with HBr *and a peroxide*. (The other hydrogen halides do not undergo anti-Markovnikov addition when peroxides are present.)
- We can **add bromine or chlorine to a double bond** (Section 8.12) and the addition is an *anti addition* (Section 8.13).
- We can also **add** X— **and** —OH to a double bond (i.e., synthesize a halohydrin) by carrying out a bromination or chlorination in water (Section 8.14). This addition, too, is an *anti addition*.
- We can carry out a **syn 1,2-dihydroxylation of a double bond** using either $KMnO_4$ in cold, dilute, and basic solution or OsO_4 followed by $NaHSO_3$ (Section 8.16). Of these two methods, the latter is preferable because of the tendency of $KMnO_4$ to overoxidize the alkene and cause cleavage at the double bond.
- We can carry out **anti 1,2-dihydroxylation of a double bond** by converting the alkene to an *epoxide* and then carrying out an acid-catalyzed hydrolysis (Section 11.15).

Equations for most of these reactions are given in the Synthetic Connections reviews for Chapters 7 and 8 and this chapter.

WHY Do These Topics Matter?]

IMPORTANT, BUT HIDDEN, EPOXIDES

Because of the strain and reactivity of epoxides, it is quite rare to isolate a compound from nature that actually contains an epoxide ring. That does not mean that this functional group does not serve diverse purposes. In fact, there are many instances where epoxides appear to play a critical role in the formation of new bonds within complex natural products. For example, if a long chain of alkenes such as that shown below could be epoxidized at every double bond in a stereocontrolled way (likely using enzymes), then subsequent activation of the terminal epoxide with a proton could potentially initiate a cascade, or domino-like, set of cyclizations leading to many new ring systems with complete stereocontrol. This process is shown here specifically for gymnocin B, one member of a large class of marine-based natural products known as cyclic polyethers. These compounds are potent neurotoxins.



Gymnocin B

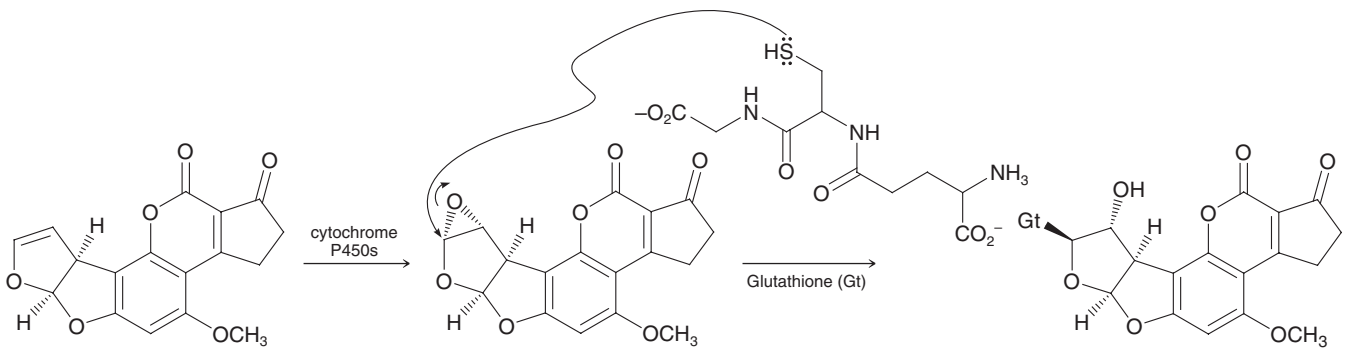
Above structure from Vilotijevic, I.; Jamison, T.F.: Epoxide-Opening Cascades Promoted by Water. SCIENCE 317:1189 (2007). Reprinted with permission from AAAS.

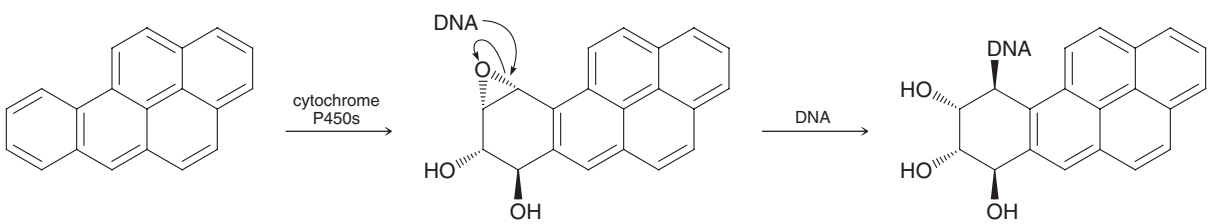
Epoxides also play a critical role in eliminating some dangerous molecules we might ingest, a role that again is hidden if we only look at starting materials and products. We will consider two compounds. The first is aflatoxin B_1, a compound that can contaminate peanuts and some cereal grains depending on the soil conditions where the crop was grown. The second is benzo[a]pyrene, a substance found in cigarette smoke and grilled meat (it is a component of the char marks). Aflatoxin B_1 is a carcinogen and benzo[a]pyrene can intercalate with DNA and prevent gene transcription (a topic we will discuss in more detail in Chapter 25).

Michael Patrick O'Neill/Photo Researchers, Inc.

Image Source

The body's system to eliminate these toxic chemicals begins by oxidizing their carbon frameworks using enzymes known as cytochrome P450s; these enzymes are found in the liver and intestines. For both aflatoxin B_1 and benzo[a]pyrene, at least one of their double bonds can be converted into an epoxide, as shown below. The next step is for a highly polar nucleophile, such as glutathione, to add to that reactive ring system and make the resulting molecule water soluble so it can be excreted quickly. However, these reactions are risky because other nucleophiles can attack as well. For example, nucleotide bases within DNA can also react with these epoxides. If that happens, as shown for the epoxidized form of benzo[a]pyrene, cancer can result. Thus, the epoxide in these instances is a two-edged sword—it serves as a way to remove a potentially toxic molecule while also creating a species that is sometimes even more dangerous and reactive than the original material. As a challenge question with this closing essay, why do you think the two nucleophile additions shown below occur only at the indicated positions?





To learn more about these topics, see:

1. Vilotijevic, I.; Jamison, T. F. "Epoxide–Opening Cascades Promoted by Water" in *Science* **2007**, *317*, 1189 and references therein.
2. Nakanishi, K. "The Chemistry of Brevetoxins: A Review" in *Toxicon* **1985**, *23*, 473–479.

SUMMARY AND REVIEW TOOLS

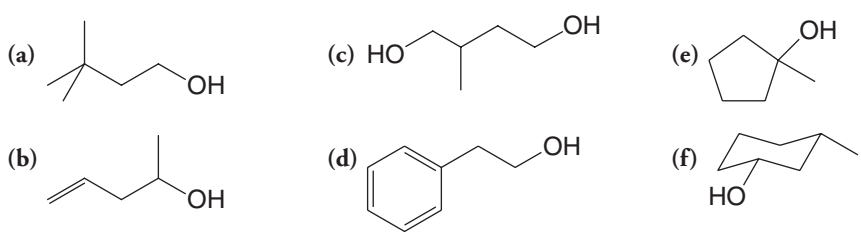
In addition to Section 11.17, which summarizes many of the reactions of alkenes, alcohols, and ethers, the study aids for this chapter also include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com) and a Synthetic Connections chart.

PROBLEMS

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

NOMENCLATURE

11.25 Give an IUPAC substitutive name for each of the following alcohols:

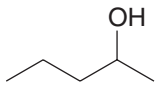


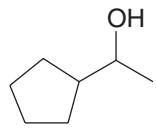
11.26 Write structural formulas for each of the following:

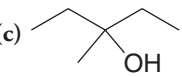
(a) (*Z*)-But-2-en-1-ol
(b) (*R*)-Butane-1,2,4-triol
(c) (1*R*,2*R*)-Cyclopentane-1,2-diol
(d) 1-Ethylcyclobutanol
(e) 2-Chlorohex-3-yn-1-ol
(f) Tetrahydrofuran
(g) 2-Ethoxypentane
(h) Ethyl phenyl ether
(i) Diisopropyl ether
(j) 2-Ethoxyethanol

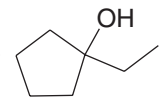
REACTIONS AND SYNTHESIS

11.27 Provide the alkene needed to synthesize each of the following by oxymercuration–demercuration.

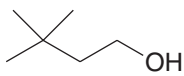
(a) 

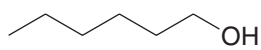
(b) 

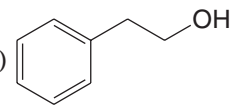
(c) 

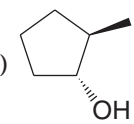
(d) 

11.28 Provide the alkene needed to synthesize each of the following by hydroboration–oxidation.

(a) 

(b) 

(c) 

(d) 

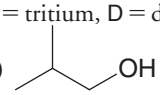
11.29 Starting with each of the following, outline a practical synthesis of 1-butanol:

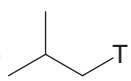
(a) 1-Butene **(b)** 1-Chlorobutane **(c)** 2-Chlorobutane **(d)** 1-Butyne

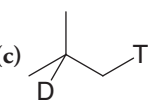
11.30 Show how you might prepare 2-bromobutane from

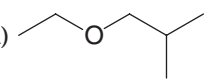
(a) 2-Butanol **(b)** 1-Butanol **(c)** 1-Butene **(d)** 1-Butyne

11.31 Starting with 2-methylpropene (isobutylene) and using any other needed reagents, outline a synthesis of each of the following (T = tritium, D = deuterium):

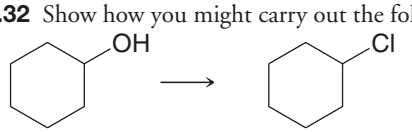
(a) 

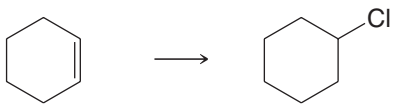
(b) 

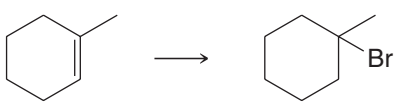
(c) 

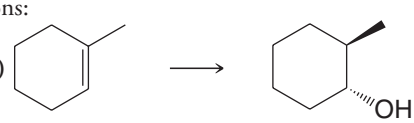
(d) 

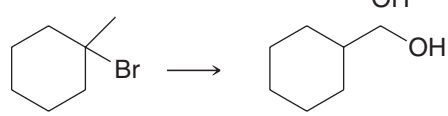
11.32 Show how you might carry out the following transformations:

(a) 

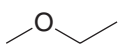
(b) 

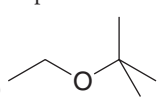
(c) 

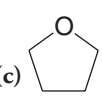
(d) 

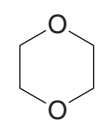
(e) 

11.33 What compounds would you expect to be formed when each of the following ethers is refluxed with excess concentrated hydrobromic acid?

(a) 

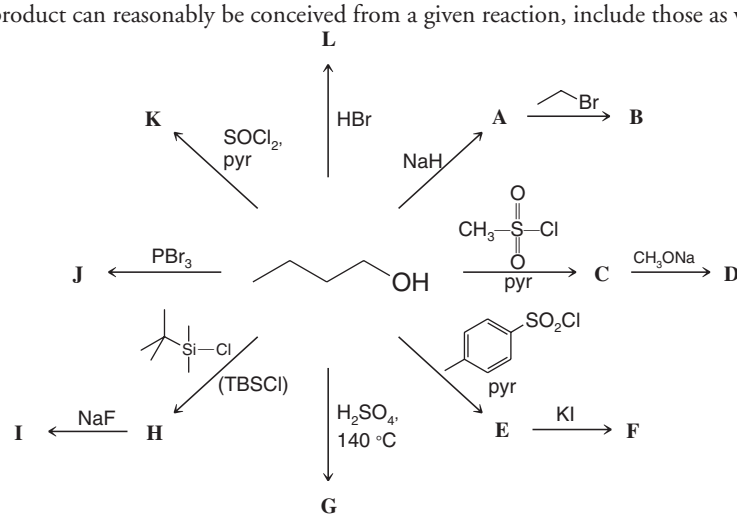
(b) 

(c) 

(THF)
(d) 

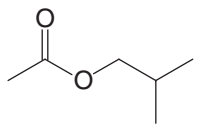
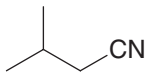
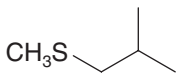
(1,4-dioxane)

11.34 Considering **A–L** to represent the major products formed in each of the following reactions, provide a structure for each of **A** through **L**. If more than one product can reasonably be conceived from a given reaction, include those as well.



11.35 Write structures for the products that would be formed under the conditions in Problem 11.34 if cyclopentanol had been used as the starting material. If more than one product can reasonably be conceived from a given reaction, include those as well.

11.36 Starting with isobutane, show how each of the following could be synthesized. (You need not repeat the synthesis of a compound prepared in an earlier part of this problem.)

(a) *tert*-Butyl bromide
(b) 2-Methylpropene
(c) Isobutyl bromide
(d) Isobutyl iodide
(e) Isobutyl alcohol (two ways)
(f) *tert*-Butyl bromide
(g) Isobutyl methyl ether
(h) 
(i) 
(j) 
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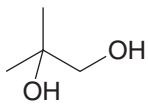
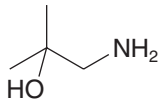
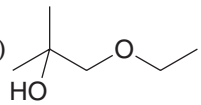
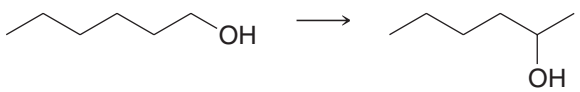
(l) 
(m) 
(n) 

11.37 Outlined below is a synthesis of the gypsy moth sex attractant disparlure (a pheromone). Give the structure of disparlure and intermediates **A–D**.

$$HC{\equiv}CNa \xrightarrow[\text{liq. } NH_3]{\text{1-bromo-5-methylhexane}} \mathbf{A}\ (C_9H_{16}) \xrightarrow[\text{liq. } NH_3]{NaNH_2} \mathbf{B}\ (C_9H_{15}Na)$$

$$\xrightarrow{\text{1-bromodecane}} \mathbf{C}\ (C_{19}H_{36}) \xrightarrow[Ni_2B(P\text{-}2)]{H_2} \mathbf{D}\ (C_{19}H_{38}) \xrightarrow{\text{mCPBA}} \textbf{Disparlure}\ (C_{19}H_{38}O)$$

11.38 Provide the reagents necessary for the following syntheses. More than one step may be required.

(a) 
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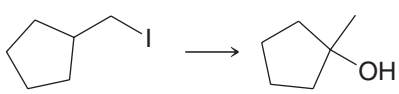
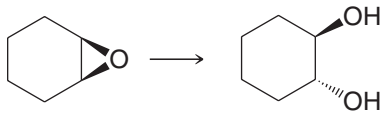
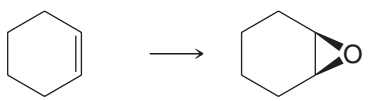
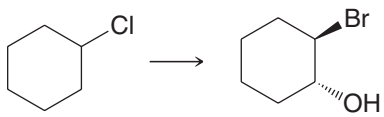
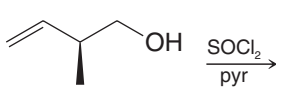
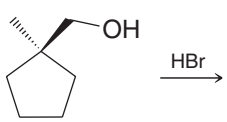
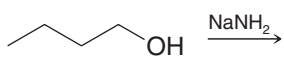
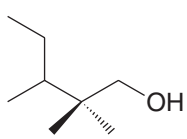
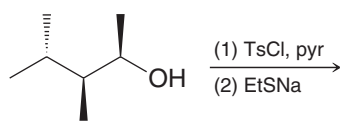
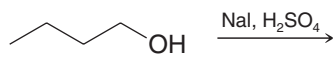
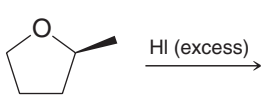
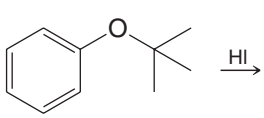
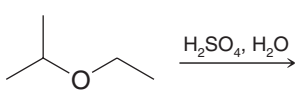
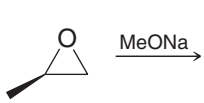
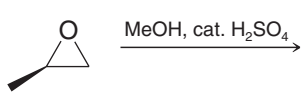
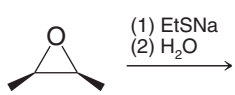
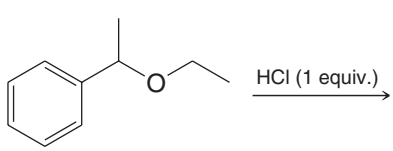
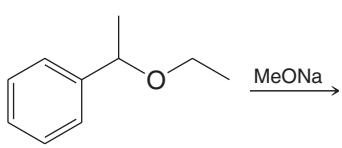
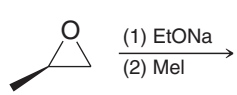
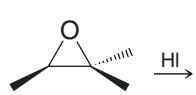
(c) 
(d) 
(e) 
(f) 

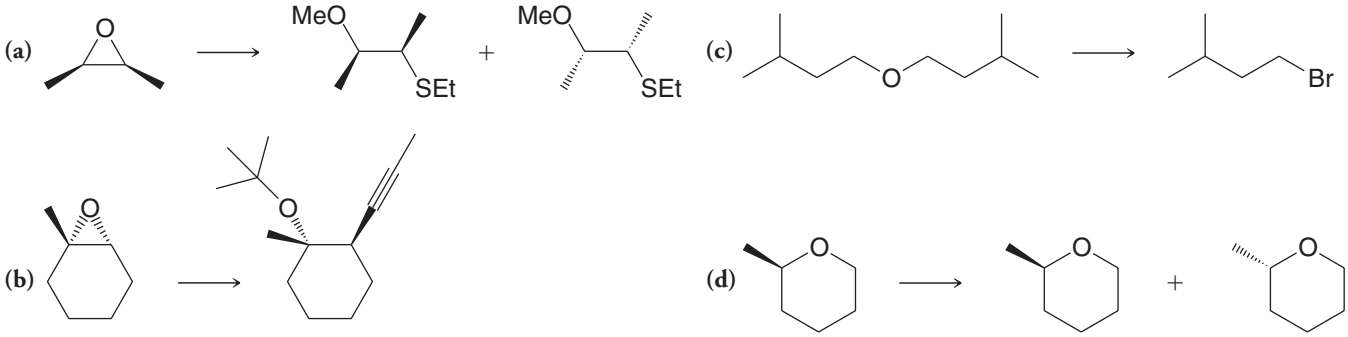
11.39 Predict the major product from each of the following reactions.

(a) 
(b) 
(c) 
(d) 
(e) 
(f) 

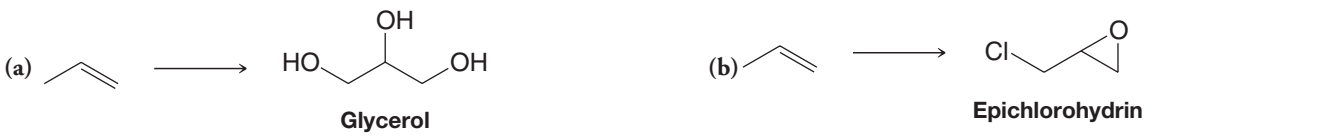
11.40 Predict the products from each of the following reactions.

(a) 
(b) 
(c) 
(d) 
(e) 
(f) 
(g) 
(h) 
(i) 
(j) 

11.41 Provide the reagents necessary to accomplish the following syntheses.

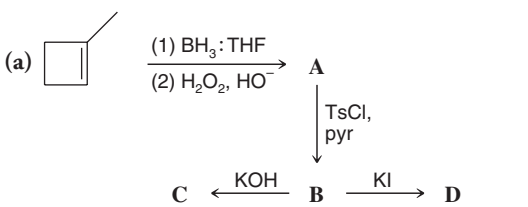


11.42 Provide reagents that would accomplish the follwing syntheses.

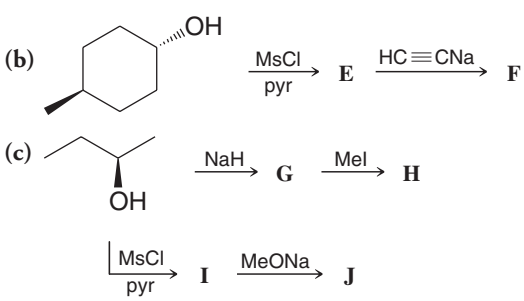


Glycerol **Epichlorohydrin**

11.43 Write structures for compounds **A–J** showing stereochemistry where appropriate.



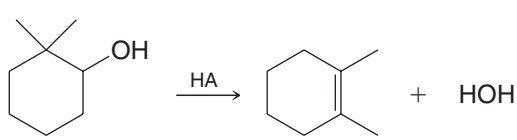
What is the stereochemical relationship between **A** and **C**?



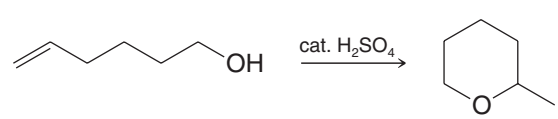
What is the stereochemical relationship between **H** and **J**?

MECHANISMS

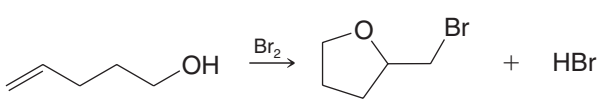
11.44 Write a mechanism that accounts for the following reaction:



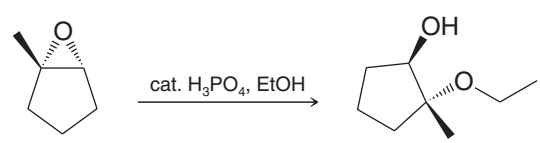
11.45 Propose a reasonable mechanism for the following reaction.



11.46 Propose a reasonable mechanism for the following reaction.

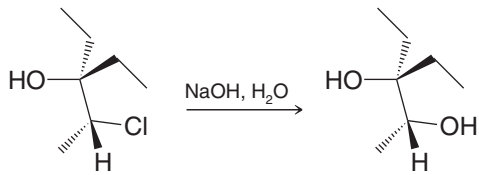


11.47 Propose a reasonable mechanism for the following reaction.

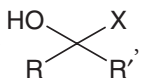


11.48 Vicinal halo alcohols (halohydrins) can be synthesized by treating epoxides with HX. (**a**) Show how you would use this method to synthesize 2-chlorocyclopentanol from cyclopentene. (**b**) Would you expect the product to be *cis*-2-chlorocyclopentanol or *trans*-2-chlorocyclopentanol; that is, would you expect a net syn addition or a net anti addition of —Cl and —OH? Explain.

11.49 Base-catalyzed hydrolysis of the 1,2-chlorohydrin **1** is found to give a chiral glycol **2** with retention of configuration. Propose a reasonable mechanism that would account for this transformation. Include all formal charges and arrows showing the movement of electrons.

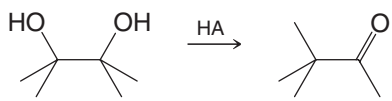


1 **2**

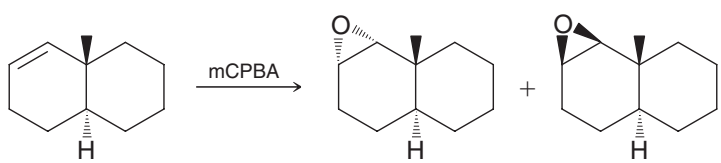
11.50 Compounds of the type 

, called α-haloalcohols, are unstable and cannot be isolated. Propose a mechanistic explanation for why this is so.

11.51 While simple alcohols yield alkenes on reaction with dehydrating acids, diols form carbonyl compounds. Rationalize mechanistically the outcome of the following reaction:



11.52 When the bicyclic alkene **I**, a *trans*-decalin derivative, reacts with a peroxy acid, **II** is the major product. What factor favors the formation of **II** in preference to **III**? (You may find it helpful to build a handheld molecular model.)

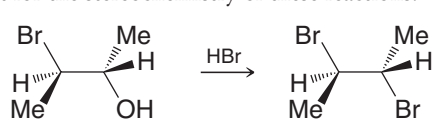


I **II (major)** **III (minor)**

11.53 Use Newman projection formulas for ethylene glycol (1,2-ethanediol) and butane to explain why the gauche conformer of ethylene glycol is expected to contribute more to its ensemble of conformers than would the gauche conformer of butane to its respective set of conformers.

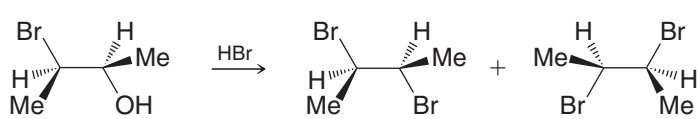
CHALLENGE PROBLEMS

11.54 When the 3-bromo-2-butanol with the stereochemical structure **A** is treated with concentrated HBr, it yields *meso*-2,3-dibromobutane; a similar reaction of the 3-bromo-2-butanol **B** yields (±)-2,3-dibromobutane. This classic experiment performed in 1939 by S. Winstein and H. J. Lucas was the starting point for a series of investigations of what are called *neighboring group effects*. Propose mechanisms that will account for the stereochemistry of these reactions.



A **2,3-Dibromobutane (meso)**

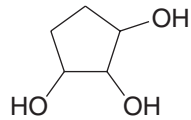
versus



B **2,3-Dibromobutane (racemic)**

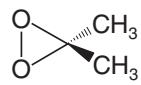
11.55 Reaction of an alcohol with thionyl chloride in the presence of a tertiary amine (e.g., pyridine) affords replacement of the OH group by Cl *with inversion of configuration* (Section 11.9). However, if the amine is omitted, the result is usually replacement with retention of configuration. The same chlorosulfite intermediate is involved in both cases. Suggest a mechanism by which this intermediate can give the chlorinated product without inversion.

11.56 Draw all of the stereoisomers that are possible for 1,2,3-cyclopentanetriol. Label their chirality centers and say which are enantiomers and which are diastereomers.



(*Hint*: Some of the isomers contain a "pseudoasymmetric center," one that has two possible configurations, each affording a different stereoisomer, each of which is identical to its mirror image. Such stereoisomers can only be distinguished by the order of attachment of ***R*** versus ***S*** groups at the pseudoasymmetric center. Of these the ***R*** group is given higher priority than the ***S***, and this permits assignment of configuration as ***r*** or ***s***, lowercase letters being used to designate the pseudoasymmetry.)

11.57 Dimethyldioxirane (DMDO), whose structure is shown below, is another reagent commonly used for alkene epoxidation. Write a mechanism for the epoxidation of (*Z*)-2-butene by DMDO, including a possible transition state structure. What is the by-product of a DMDO epoxidation?



Dimethyldioxirane (DMDO)

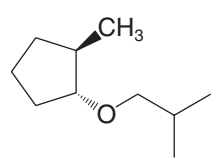
11.58 Two configurations can actually be envisioned for the transition state in the DMDO epoxidation of (*Z*)-2-butene, based on analogy with geometric possibilities fitting within the general outline for the transition state in a peroxycarboxylic acid epoxidation of (*Z*)-2-butene. Draw these geometries for the DMDO epoxidation of (*Z*)-2-butene. Then, open the molecular models on the book's website for these two possible transition state geometries in the DMDO epoxidation of (*Z*)-2-butene and speculate as to which transition state would be lower in energy.

LEARNING GROUP PROBLEMS

1. Devise two syntheses for *meso*-2,3-butanediol starting with acetylene (ethyne) and methane. Your two pathways should take different approaches during the course of the reactions for controlling the origin of the stereochemistry required in the product.

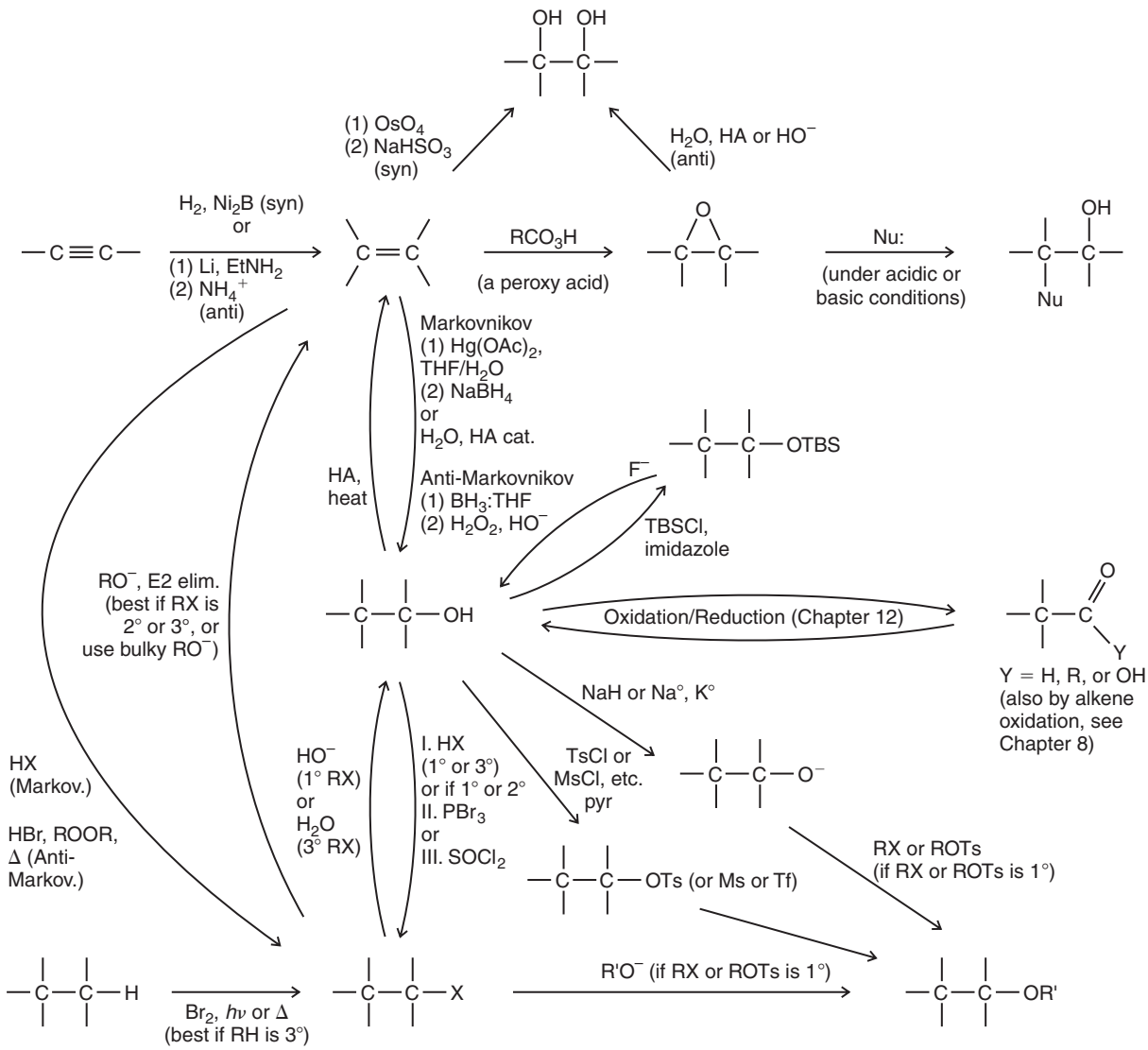
2. **(a)** Write as many chemically reasonable syntheses as you can think of for ethyl 2-methylpropyl ether (ethyl isobutyl ether). Be sure that at some point in one or more of your syntheses you utilize the following reagents (not all in the same synthesis, however): PBr_3, $SOCl_2$, *p*-toluenesulfonyl chloride (tosyl chloride), NaH, ethanol, 2-methyl-1-propanol (isobutyl alcohol), concentrated H_2SO_4, $Hg(OAc)_2$, ethene (ethylene).
(b) Evaluate the relative merits of your syntheses on the basis of selectivity and efficiency. (Decide which ones could be argued to be the "best" syntheses and which might be "poorer" syntheses.)

3. Synthesize the compound shown below from methylcyclopentane and 2-methylpropane using those compounds as the source of the carbon atoms and any other reagents necessary. Synthetic tools you might need include Markovnikov or anti-Markovnikov hydration, Markovnikov or anti-Markovnikov hydrobromination, radical halogenation, elimination, and nucleophilic substitution reactions.



SUMMARY AND REVIEW TOOLS

Some Synthetic Connections of Alkenes, Alkynes, Alcohols, Alkyl Halides, and Ethers



- Alkynes to alkenes
- Alkenes and alcohols
- Alcohols and alkyl halides
- Alkenes and alkyl halides
- Alcohols and ethers
- Alkenes, epoxides, and 1,2-diols
- Alkanes to alkyl halides
- Alcohol silyl protecting group
- Alcohols to carbonyl compounds