9-1 In order to convert methanol into a significant quantity of methoxide ion, we need a base that is stronger than is methoxide ion. Conversely, this will require a base whose conjugate acid is weaker than is methanol. From Table 2-2 we see that the pKa of methanol is 15.5 whereas that for HCN is 9.2. HCN is a stronger acid than is methanol and thus cyanide ion is too weak a base for the deprotonation of methanol.

9-2 Through protonation, the poor leaving group —OH is converted to a good leaving group —OH$_2$.
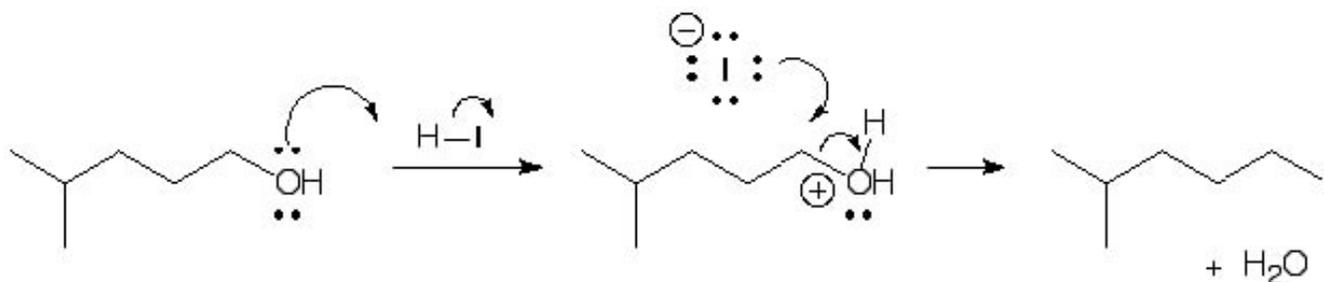

9-3 Here we have a tertiary alcohol treated with strong acid, either HCl or sulfuric. As in exercise 9-2, thepoor leaving group —OH is converted to a good leaving group —OH$_2$. Because of the substitution of the carbon, in this case reaction follows a first order pathway and water is lost to form a tertiary carbocation. The difference between HCl and sulfuric acid is that the conjugate base of the former is a good nucleophilewhereas that of the latter, the bisulfate anion, is not. As a result, substitution occurs with HCl whereaselimination to form alkenes is the dominant pathway with sulfuric acid. Of the two possible alkenes, one istrisubstituted and the other is disubstituted. The more stable trisubstituted alkene dominates.

**9-4** This exercise is worked out on page 339 as "Working with Concepts".

9-5 The key here is that in both cases we have reactions of secondary alcohols with strong acid. Under these conditions, the secondary alcohols will form carbocations that can undergo rearrangement to form tertiary carbocations. The products obtained are those from nucleophilic addition to these tertiary carbocations.

(a)

(b)
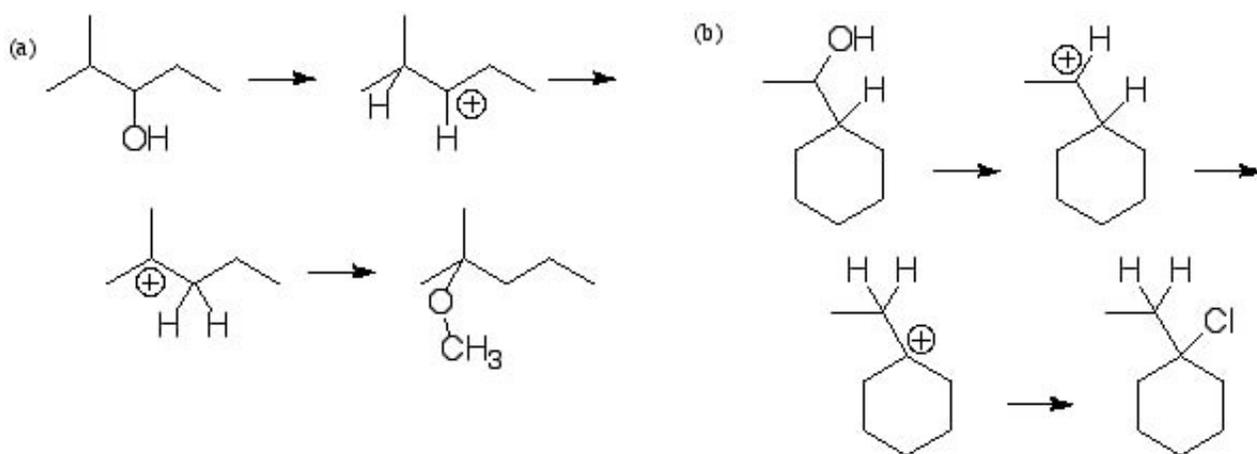
**9-6** Here we have an example of a hydride shift.
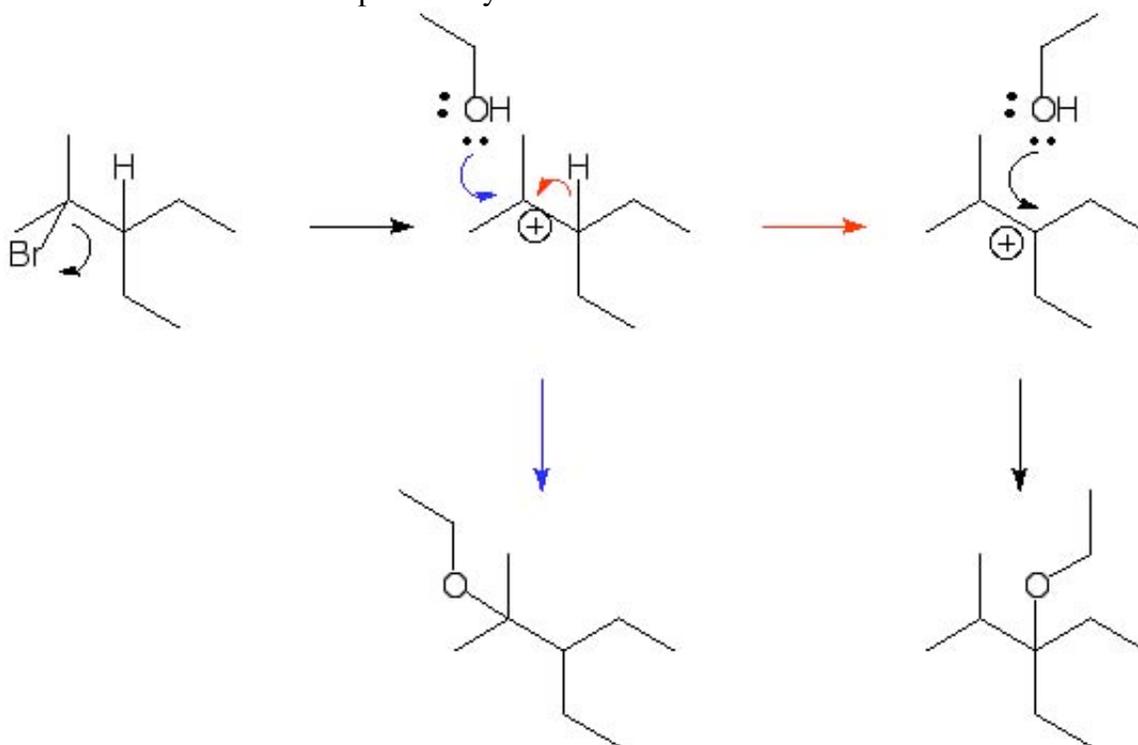
Loss of chloride ion from 2-chloro-4-methylpentane will result in a secondary carbocation. In this case, migration of *any* group from an adjacent carbon does not lead to a carbon cation. Migration of a hydride from the adjacent CH2 group leads to a different secondary carbocation and now migration of another hydride (this time from C-4) produces a tertiary carbocation. This is a good example of the driving force inherent in the formation of tertiary carbocations.
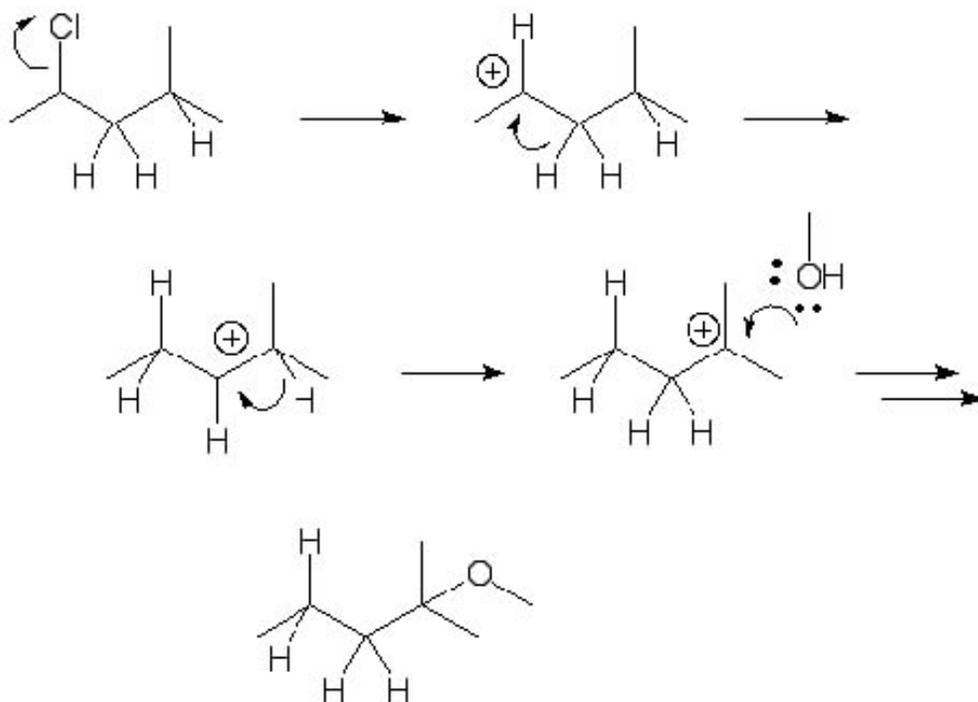
9-7 As with exercise 9-6, we have examples of hydride shifts. Protonation and loss of water from 2-methyl2-pentanol produces a tertiary carbocation. Under the conditions of elevated temperature with only poor nucleophiles present, loss of a proton from an adjacent carbon atom forming an alkene is the dominant pathway taken by the cation. As expected, the dominant alkene is the trisubstituted alkene rather than the disubstituted alkene that would form from loss of a proton from one of the methyl groups. Starting with 4methyl-2-pentanol, the initially formed cation is secondary which can undergo two successive hydride shifts to form the very same carbocation as generated from 2-methyl-2-pentanol.

For the conversion of 4-methylcyclohexanol to 1-methylcyclohexene, we can propose a pathway very similar to that detailed above, except now we need three hydride shifts before we arrive at a tertiary carbocation.

While the authors of this text explain these results with hydride shifts, there is an alternatively, more widely held explanation. Instead of hydride shifts, which tend to be rather slow, a proton is lost from the cation to form an alkene. Under the strongly acidic conditions necessary for protonation of an alcohol, the alkeneitself can be protonated. Being unsymmetrical, protonation can lead either to the same cation or a new one, exactly the same cation that would result from hydride transfer.
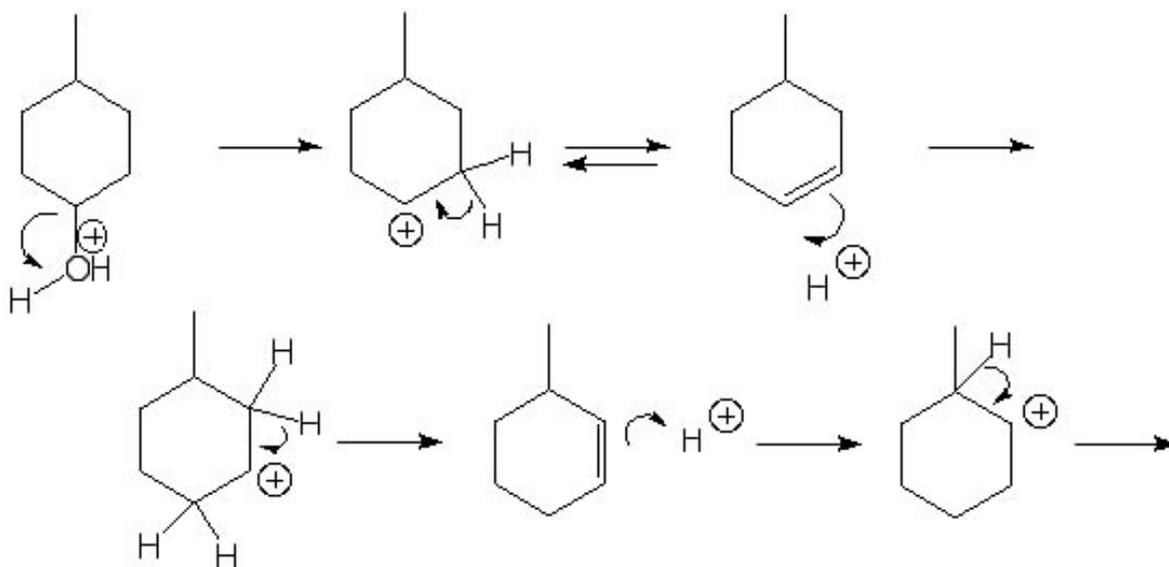
9-8 This exercise is worked out on page 342 as "Working with Concepts".

9-9 As the temperature of a reaction is increased, the amounts of entropically favored products increases. Treatment of an alcohol with HBr can lead to both subsititution and elimination. In both cases, water isformed as a by-product. However, in substitution, the HBr is consumed whereas in elimination it is a catalyst. Thus, in substitution, the number of molecules stays the same whereas in elimination, there is an increase in the number of molecules and thus, elimination is entropically favored.
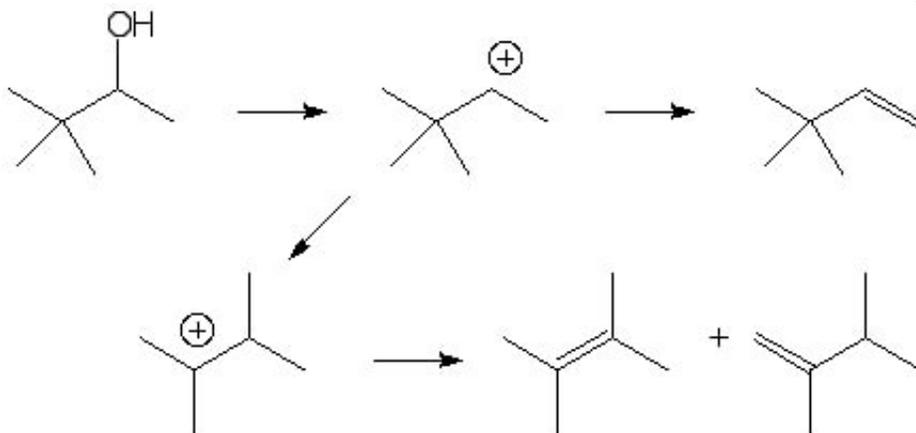
9-10 The key to this two-step sequence is inversion of configuration. The first step converts the alcohol to a leaving group by replacement of the H with a sulfonate group without disruption of the C—O bond. In the second step, the sulfonate group is replaced by second order substitution with inversion of configuration.

9-11 Do not be concerned if your reagents do not match those provide in the book's answer to this exercise. There is a range of possibilities for reagents that convert alcohols into alkyl halides. For alkyl chlorides, the most straightforward reagent is HCl (ZnCl2 is added for primary alcohols to provide practical rates). Often,

formation of an alkyl iodide is accomplished by iodide displacement of another leaving group, often a halogen. Here, the trick of using KI in acetone provides a halide that is soluble but the result of displacement of a chlorine or bromine in the form of KCl or KBr is not soluble and thus precipitation of these salts from solution provides a driving force for the reaction.

9-12 A Williamson ether synthesis involves the formation of the second of the two C—O bonds present in an ether by the reaction of an alkoxide with an alkyl halide. If both alkyl groups are the same in the ether (asymmetrical ether), then there is only one way possible. Conversely, if the ether is unsymmetrical, then there are two different C—O bonds that could be formed in the ether synthesis. It is almost always the case that higher yields will be obtained when the alkyl halide is the least substituted possible.

    (a) There is little to recommend one over the other of the two possible syntheses, as in both cases, the alkylhalide will be primary.

    (b) Here we have a choice between a methyl alkyl halide and a secondary alkyl halide. The methyl halide is preferred.

    (c) Primary versus secondary alkyl halide here---the former wins.

    (d) Strictly speaking, Williamson didn't know about sulfonate esters as leaving groups---he was fixated on alkyl halides so a correct answer to the question as worded would require the reaction of an alkoxide with an alkyl halide. As all of the carbons attached to oxygen in the target diether are primary, either could be used as the alkyl halide.

9-13 What is not shown on this page is the position of corresponding non-cyclic reactions in the rate ordering. The proper position is shown below:

$k_3 \geq k_5 > k_6 > k_4 >$ non-cyclic $> k_7 > k_8$.

Thus, when there is the possibility of an intramolecular reaction to form a ring of size 3-6, the rate of ring formation will be greater than *inter*molecular reactions.

9-14 This exercise is worked out on page 355 as "Working with Concepts".

9-15 Both the bromine and the oxygen must be axial for formation of the epoxide. For diastereomer B, all three substituents are either equatorial or axial. Placing all three axial puts a t-butyl group axial, a no-no.

9-16 See the mechanisms provide on page A-15 of the textbook. This exercise nicely illustrates the different pathways followed by tertiary and primary groups during substitution. Only second order reactions occur at primary centers and when there are both primary and tertiary centers present, formation of the cation intermediate from the latter will be faster that second order substitution at the former.

9-17 The problem has set forth that we are to start with both a haloalkane and an alcohol so it is unclear why this exercise is in a section devoted to the formation of ethers from alcohols in the presence of strong acid.

   (a) Because this is an unsymmetrical, secondary/tertiary ether, the use of second order substitution willprovide poor results. At the best, we would be using a secondary alkyl halide reacting with the anion of atertiary alcohol, a combination that will lead predominantly to elimination. Thus, solvolysis is called forwhere we pick the alkyl bromide to be tertiary to facilitate the formation of the cation. Note that it would bebest to include a mild base such as sodium carbonate to absorb the HBr that would be otherwise released.
   (b) Use of methyl bromide and the appropriate alkoxide can only lead to substitution by a second order reaction and is the best method for formation of this ether.

9-18 The mechanism provided on page A-14 of the textbook is correct and thus will not be reproduced here. Note that because the replacement of oxygen with iodine occurs on primary carbons, the substitutions aresecond order, with protonation of oxygen providing a good leaving group.

9-19 The mechanism provided on page A-14 of the textbook is correct and thus will not be reproduced here.Note that because the replacement of oxygen with iodine occurs on primarly carbons, the substitutions ar esecond order, with protonation of oxygen providing a good leaving group. This exercise is redundant with9-16--- exactly the same chemistry occurs.

9-20 (a) We know that we can replace a halogen of an alkyl halide with a proton (or deuterium) by reaction of the alkyl halide with magnesium and then with a proton source. In this exercise, we are faced with the challenge that in addition to the halogen, there is a second functional group present an alcohol. No functional group that is a proton source can be present at the same time as a Grignard reagent because of proton transfer. Now the smart student might say, "well, isn't that exactly what we want to happen in the end?" So in theory, one could covert the alcohol present to an —OD group by shaking with D_2O and then form the Grignard reagent with Mg which would immediately react with the —OD group, replacing the metal with a deuterium. So much for theory. In practice, the resulting —OMgBr precipitates from solution and covers the magnesium preventing it from further reaction. So what is required is to "hide" the acidic OHgroup by protecting it. We learned in this section that tertiary ethers can be used as protecting groups foralcohols as they are easily formed and removed under acidic conditions.
(b) We might have thought that an excess of methyl Grignard reagent would work here, with one equivalent being consumed by reaction with the alcohol and a second equivalent reacting as desired with the aldehyde. But here again, the salt formed from the Grignard and the alcohol is not soluble in the ether solvents used for

Grignard reactions.

9-21 This exercise is worked out on page 361 as "Working with Concepts".

9-22 Reduction of an epoxide (an oxacyclopropane) results in cleavage of one of the two carbon-carbon bonds and the formation of an alcohol. So we can derive a possible epoxide from the product alcohol by removing a proton from a carbon atom adjacent to that bearing the OH group and attaching the oxygen to that carbon. Our target is unsymmetrical so there are two possible epoxides:
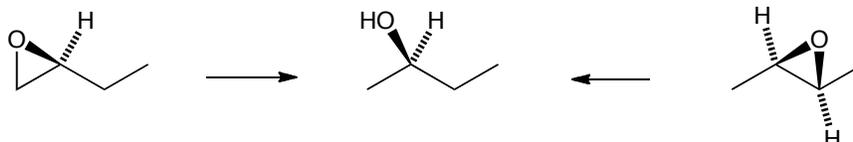

We know that LiAlH$_4$ reacts preferentially with the less substituted carbon of an unsymmetrical epoxide. However, if we start with the symmetrical epoxide, then *R*-2-butanol can be the only possible product from reduction.

9-23 In order to find an efficient synthetic route, it is important to note if a carbon—carbon bond forming reaction is called for and, if so, what restrictions on the number of carbons that can be present in starting materials. In this exercise, we are to make an alcohol with six carbons from any ultimate precursors containing no more than four carbons each. We thus try to find a C—C bond in the product that, if broken, results in two fragments each of which contains no more than four carbons. There are two unique bonds of this type, a and b:
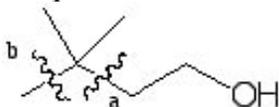
However, we have only a very limit set of carbon—carbon bond forming reactions and none result in the formation of a bond that is in the position "b" relative to an OH group. On the other hand, "a" is the type of bond formed by the reaction of an alcohol with an epoxide.
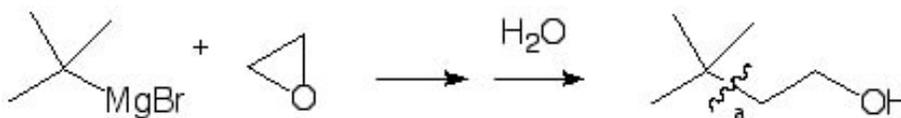

9-24 The key to this exercise lies in understanding that under acidic conditions, ring opening of an epoxide occurs by attack at the more substituted carbon whereas with strong nucleophiles under basic conditions, the opposite regiochemistry is observed with the nucleophile reacting with the less substituted carbon of the epoxide. This typical regiochemistry of addition can become muddied with Grignard reagents because the magnesium present is a good Lewis acid. Even here, the order of addition

of the two reactants plays a roleas adding the epoxide slowly to the Grignard reagents ensures that the reaction occurs with the maximum amount of Lewis acid present. See:

9-25 The reaction of simple nucleophiles such as hydroxide ion and hydrogen sulfide anion with epoxides results in products which, under the reaction conditions, can be deprotonated and then react with the epoxide. In this fashion, hydroxide ion can be reacted with a large excess of ethylene oxide (oxacyclopropane) to produce a polymer known as polyethylene glycol. In this exercise, this normal limitation is used to advantage in the reaction of hydrogen sulfide anion with two more equivalents of ethylene oxide. The resulting diol can be easily converted to mustard gas.
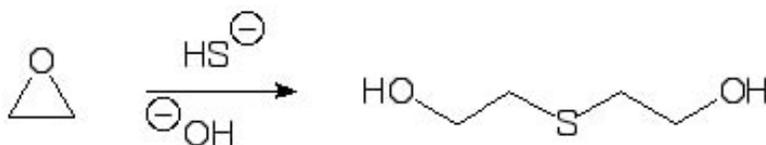
Virtually any reagent that typically converts alcohols to alkyl chlorides can be use to replace the OH groups with Cl. The presence of the sulfur greatly facilitates this substitution by first formation of a cyclicsulfonium ion. Indeed, this ion is readily formed as is the active form of mustard gas that reacts with various amino groups in cells causing devistating destruction. See: