

Alcohols III

Reading: Wade chapter 11, sections 11-10- 11-14

Study Problems: 11-41, 11-43, 11-44, 11-48, 11-51, 11-53, 11-54. 11-56

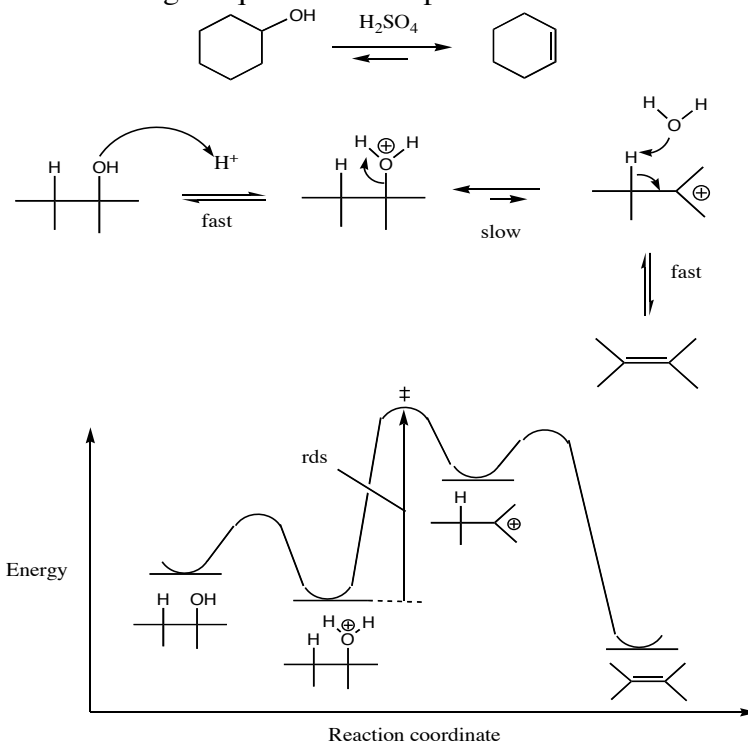
Key Concepts and Skills:

- Predict the products of the reactions of alcohols with carboxylic acids, acid chlorides, inorganic acids, sodium, potassium, and sodium hydride
- Predict the products of the reactions of alkoxide ions.
- Show how to convert an alcohol to a related compound with a different functional group.
- Predict the products of pinacol rearrangement and periodate cleavage of diols
- Use retrosynthetic analysis to propose effective single-step and multi-step syntheses of compounds using alcohols as intermediates

Lecture Topics:

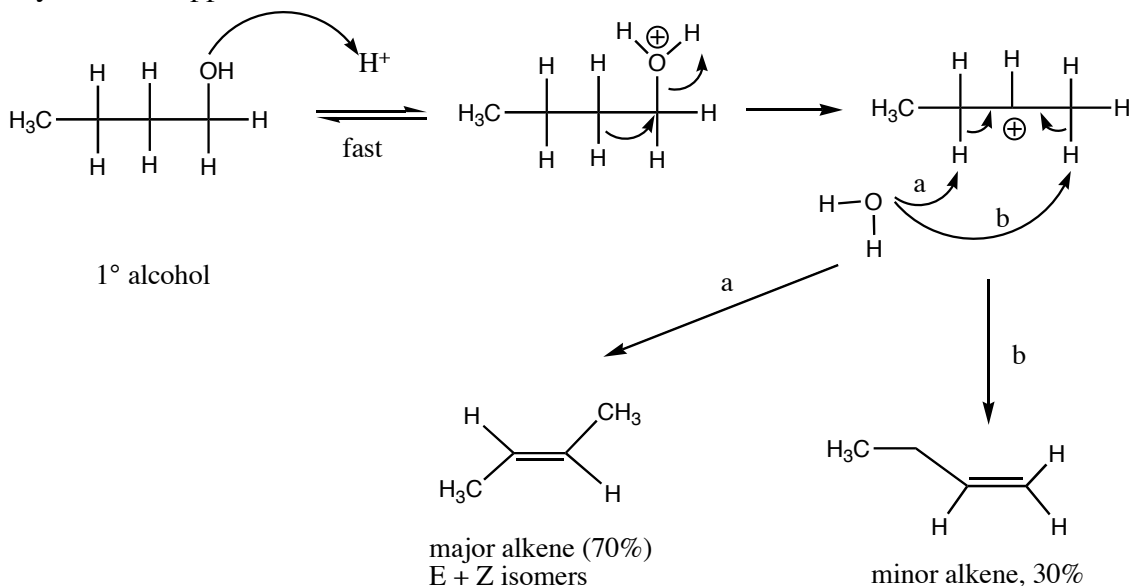
I. Dehydration of alcohols

Alkenes may be formed from the acidic dehydration of alcohols. The reaction is an equilibrium, and the alkene is favored when water is removed from the reaction mixture by using a dehydrating agent; alternatively, removal of the alkene as it forms by distillation shifts the equilibrium toward product by Le Chatelier's principle. Protonation of the alcohol is an exothermic reaction; the rate-determining step is ionization to form the carbocation (thus 3° alcohols react faster than 2° alcohols, which react faster than 1° alcohols), which then undergoes quick loss of a proton to form the alkene.

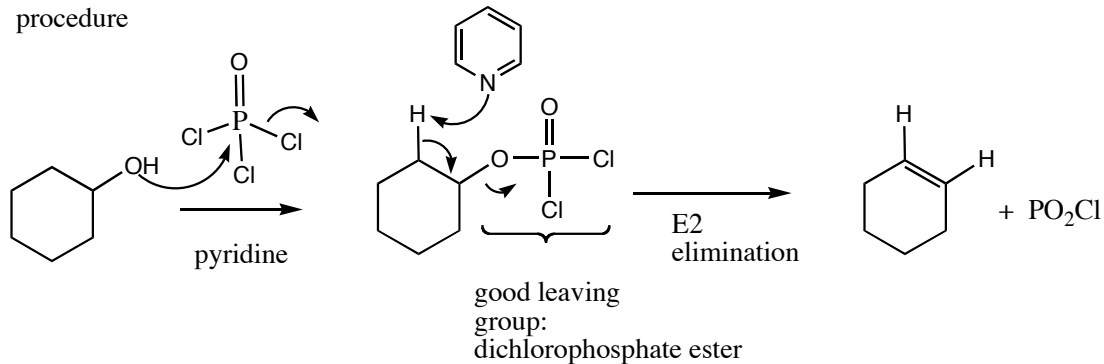


- As can be seen from the above diagram, dehydration occurs by an E2 mechanism

- Note that dehydration of alcohols may be practical for 3° and 2° alcohols but not generally for primary alcohols, which rearrange to form more stable carbocations.
- When multiple alkenes can be formed from a given carbocation intermediate, the Saytzeff rule applies:



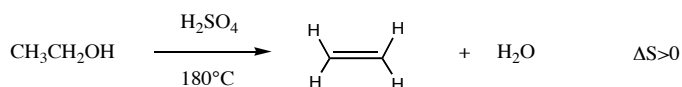
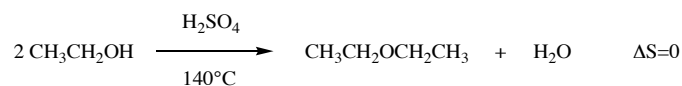
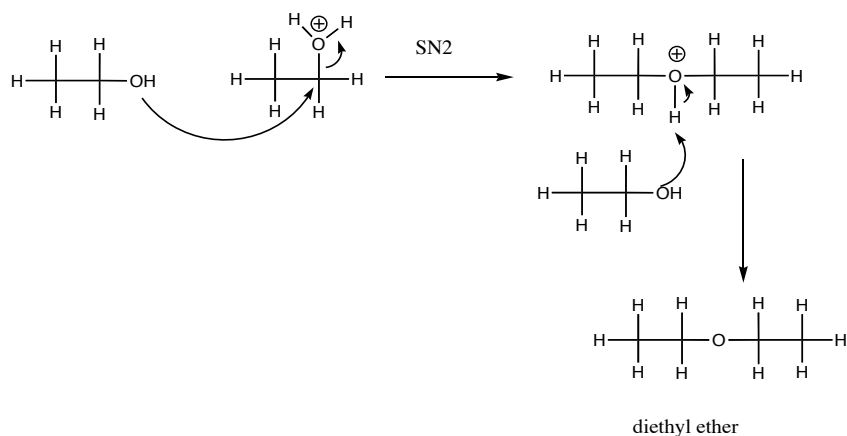
Under mildly basic conditions, an E2 elimination via POCl_3 / Pyridine is a milder dehydration procedure



A milder condition for dehydration of alcohols that avoids formation of carbocations proceeds under mildly basic conditions: POCl_3 / Pyridine. A dichlorophosphate ester intermediate is formed (a good leaving group), which undergoes E2 elimination with the mild base pyridine.

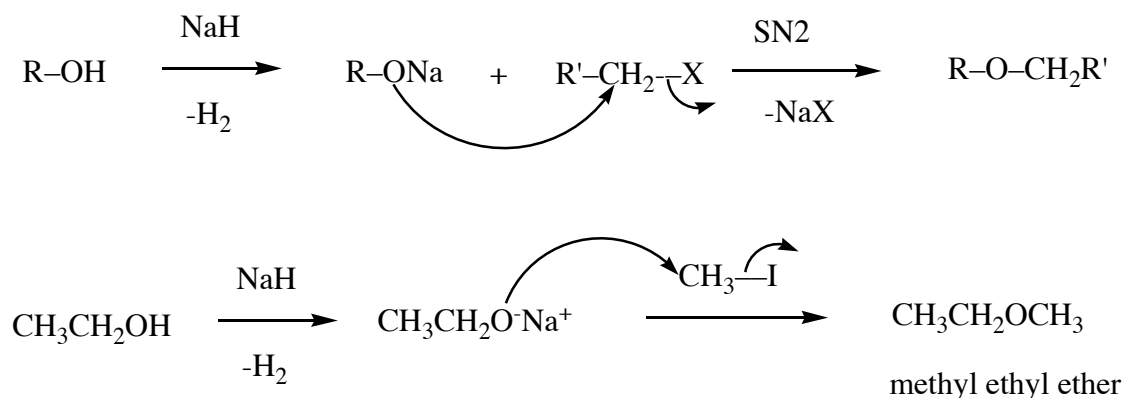
II. Synthesis of Ethers

Symmetrical ethers may be prepared from primary alcohols by $\text{S}_\text{N}2$ displacement of water. This process, which involves two molecules of alcohol and produces an ether and water, is entropically neutral ($\Delta\text{S}=0$) and is favored at lower temperatures than elimination reactions, which are entropically favored ($\Delta\text{S}>0$) since they produce 2 molecules (an alkene and water) for every molecule of alcohol reacted.



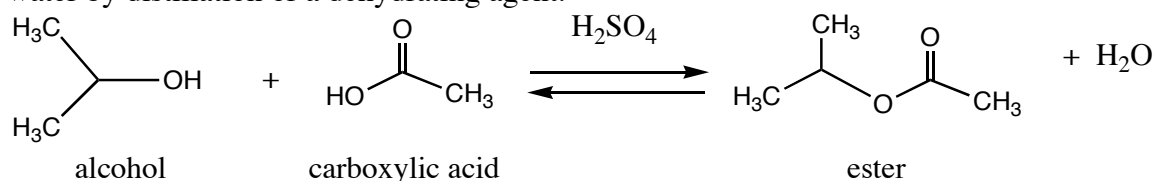
Williamson Ether Synthesis

The most practical method for ether synthesis (both symmetrical and unsymmetrical) involves deprotonation of an alcohol with sodium hydride (making a strong nucleophile) and treatment with an alkyl halide. SN2 reaction makes the desired ether.

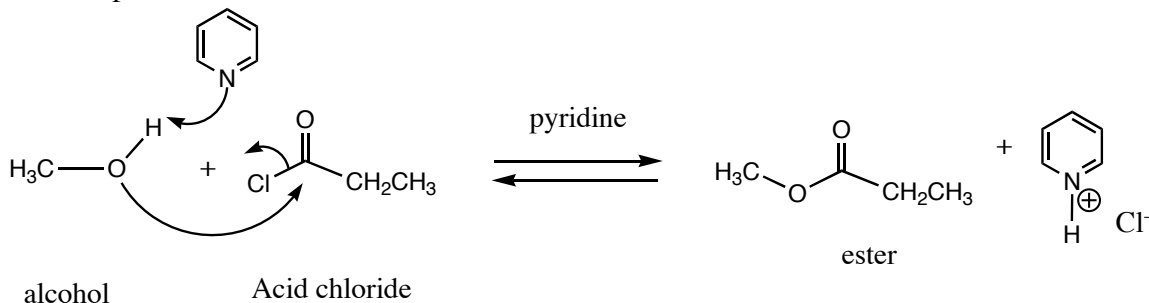


III. Esterification Reactions of Alcohols

Fischer esterification involves an acid-catalyzed dehydration of an alcohol and a carboxylic acid to form an ester. The reaction is an equilibrium, and the ester can be favored by using either an excess of the carboxylic acid or the alcohol, or by removing water by distillation or a dehydrating agent.

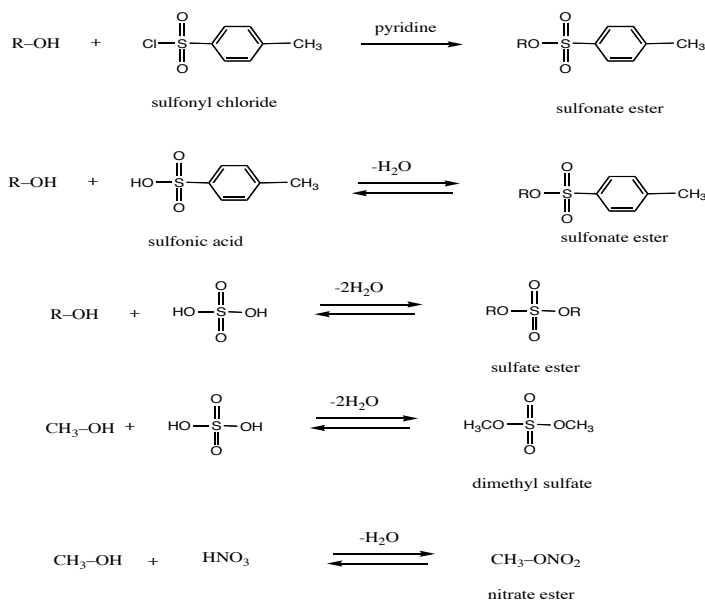


A superior method for ester formation involves reaction of the alcohol with an acid chloride, which proceeds exothermically to provide the ester and an equivalent of HCl. This procedure may be performed in the presence of pyridine as a weak base to absorb the HCl produced.



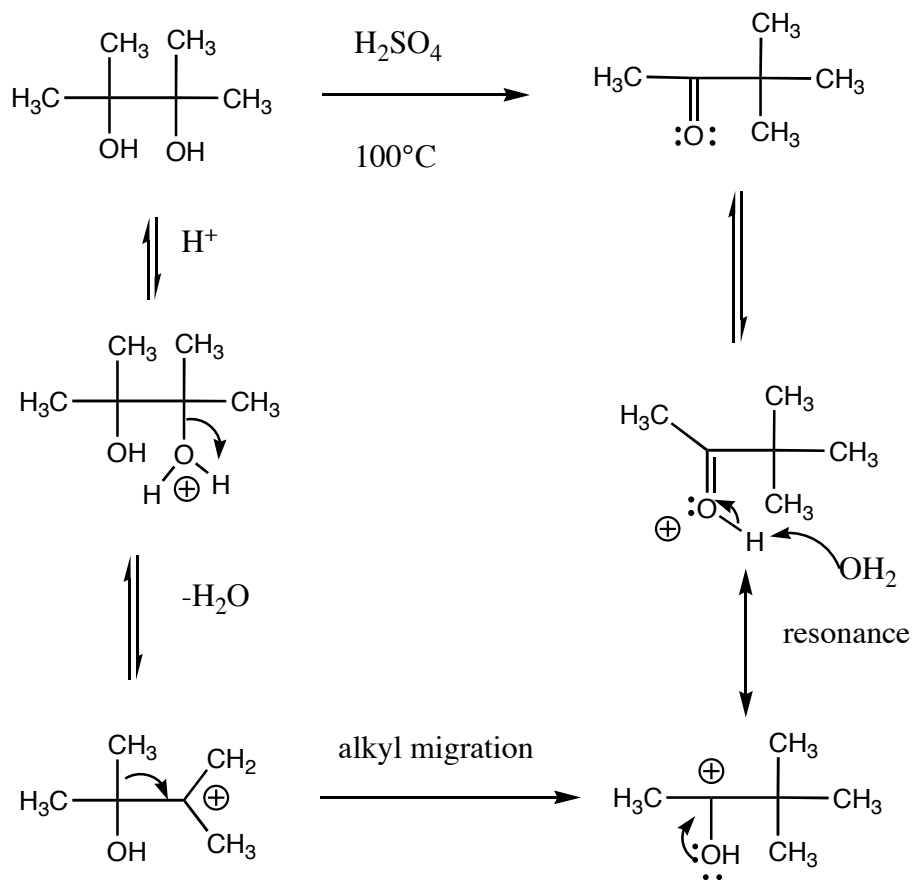
Sulfonate esters, Sulfate esters, Nitrate esters

Esters of inorganic acids are easily formed by mixing an alcohol with either a sulfonic acid, sulfuric acid, or nitric acid; dehydration occurs automatically. Note that the best method for preparation of sulfonate esters (as previously mentioned) involves reaction of the alcohol with the corresponding sulfonyl chloride

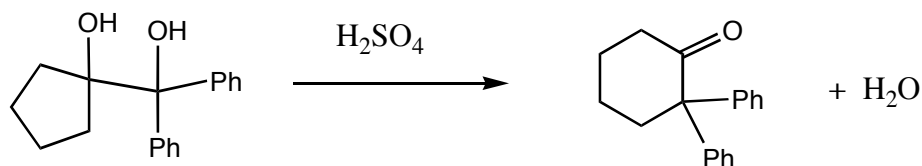


IV. Reactions of 1,2 diols

1,2 diols undergo the pinacol rearrangement under acidic conditions. This reaction usually involves alkyl group migration. Pinacol rearrangement may also be the driving force for ring expansion reactions:

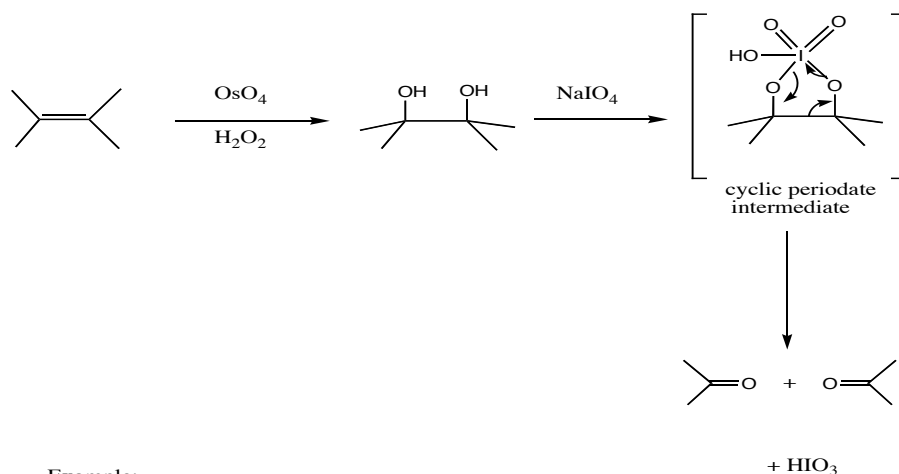


Example:

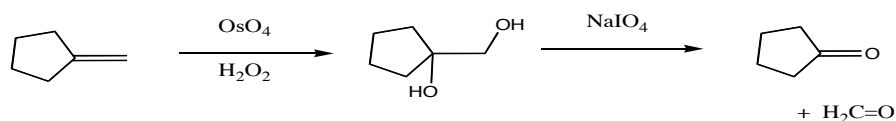


Periodate Cleavage of diols

Oxidative cleavage of 1,2 diols may be accomplished by treatment with HIO_4 or NaIO_4 . This process gives the same products as treatment of an alkene with O_3/DMS ; in fact, a milder alternative to ozone is to do the following two-step sequence on an alkene: 1. $\text{OsO}_4, \text{H}_2\text{O}_2$ 2. $\text{NaIO}_4, \text{CH}_3\text{CH}_2\text{OH}$. It is thought that periodate cleavage occurs by way of an intermediate cyclic periodate.



Example:

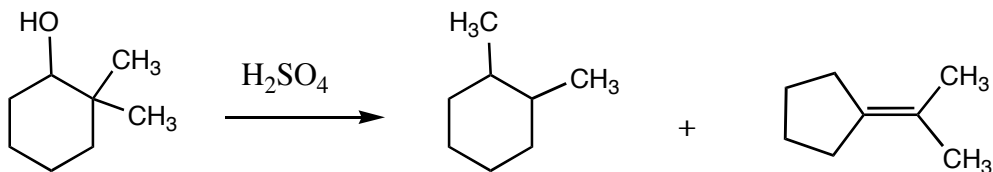


V. Retrosynthetic Analysis

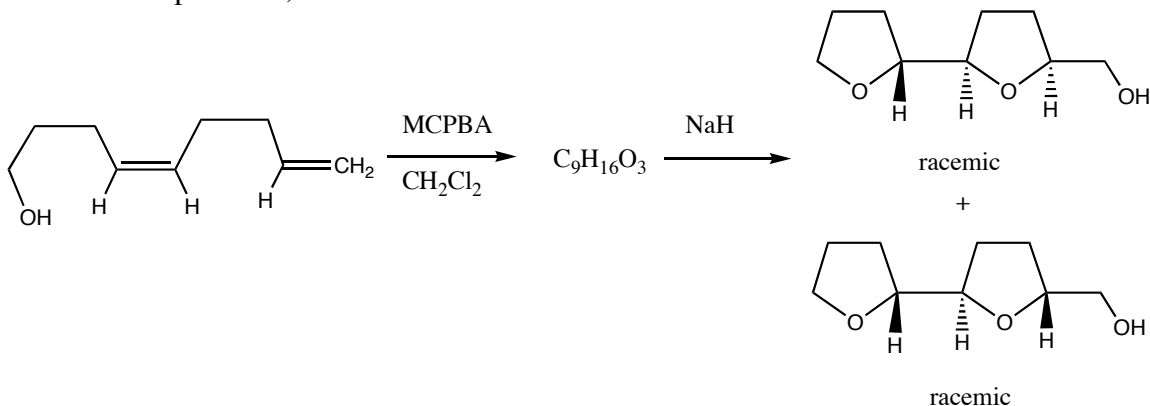
Please read pages 479-482 of your text to review the steps involved in proposing multi-step syntheses. Follow the systematic rules presented for retrosynthetic analysis of target structures, and work through as many of the problems as possible.

Additional Problems for practice:

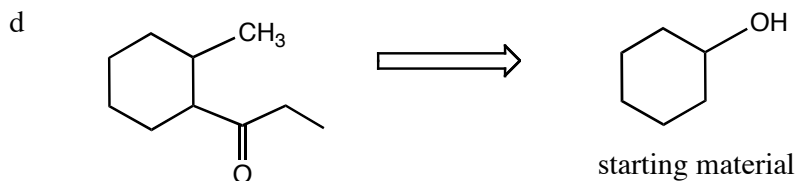
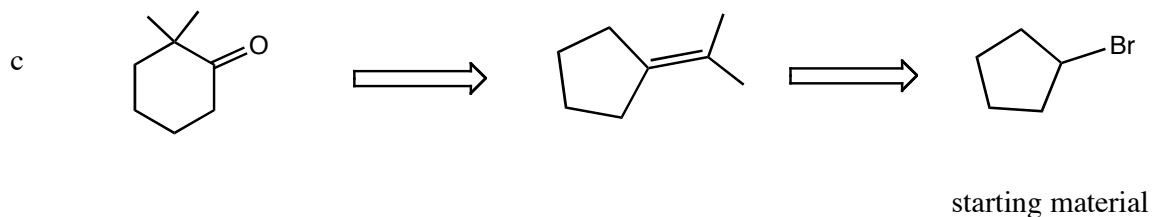
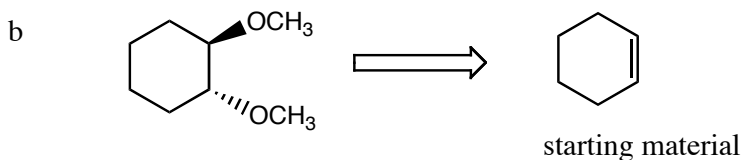
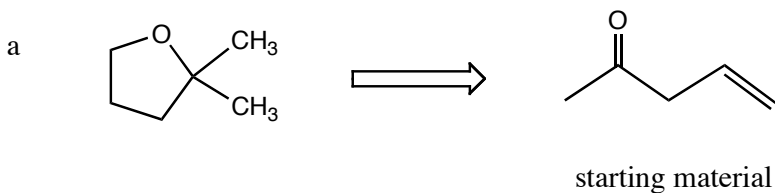
1. Acid-catalyzed dehydration of 2,2-dimethylcyclohexanol yields a mixture of 1,2-dimethylcyclohexane and isopropylidenecyclopentane. Propose a mechanism to account for the formation of both products.



2. When the following diene is treated with MCPBA in CH_2Cl_2 , an intermediate is produced with formula $\text{C}_9\text{H}_{16}\text{O}_3$. Treatment of this intermediate with sodium hydride leads to the formation of the observed products. Draw the structure of the intermediate, indicate the type of reaction which is taking place to produce the observed products, and rationalize the stereochemical outcome of the reaction.



3. Design a preparation of the following molecules from the indicated starting materials:



4. Treatment of the following diol with sulfuric acid leads to two products. Propose a mechanism which rationalizes the formation of both observed products

