

**Objective 3.** Apply substitution and elimination concepts to ethers and epoxides.

Skills: Draw structure

Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.)

ID Nu<sup>-</sup> and E<sup>+</sup>

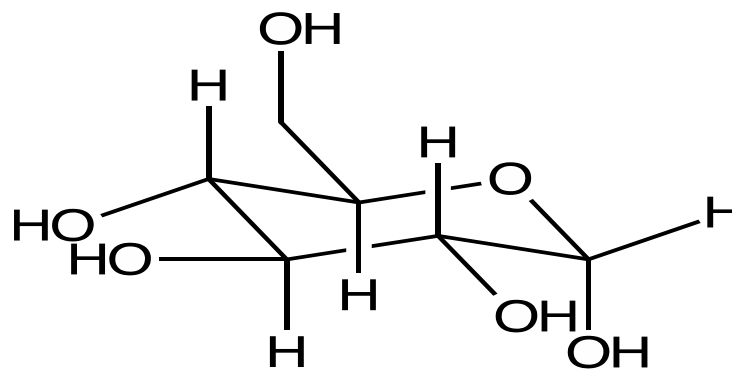
use curved arrows to show bonds breaking and forming  
show delocalized electrons with resonance structures.

Key ideas:

Compare C-O-H to C-O-C. -OH is poor LG. -OC is poor LG.  
Make into better LG by using acid.

Epoxides are reactive because of ring strain. Don't have to make into a better LG.

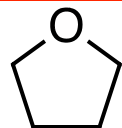
## Ethers are found in Sugars



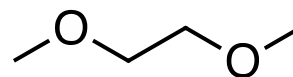
**Ethers are used as Solvents in organic reactions** (Ethers are one of the least reactive of the functional groups)



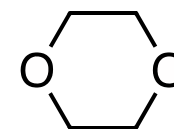
diethyl ether  
b.p. = 35°C



tetrahydrofuran (THF)  
b.p. = 66°C

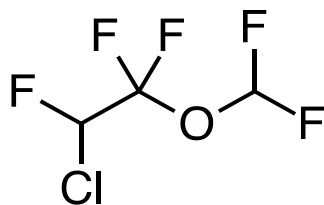


dimethoxyethane  
b.p. = 85°C

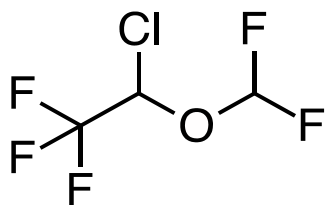


dioxane  
b.p. = 101°C

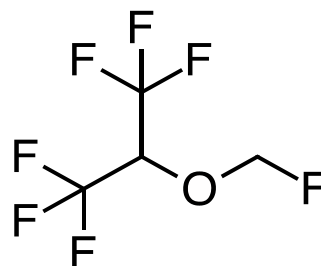
## Ethers are used as Inhalation Anesthetics



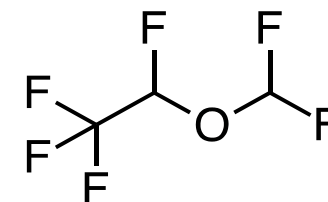
Enflurane



Isoflurane



Sevoflurane



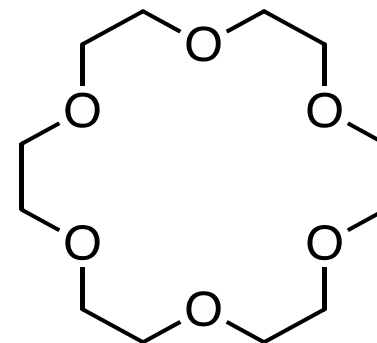
Desflurane

## Crown Ethers (cyclic polyethers)

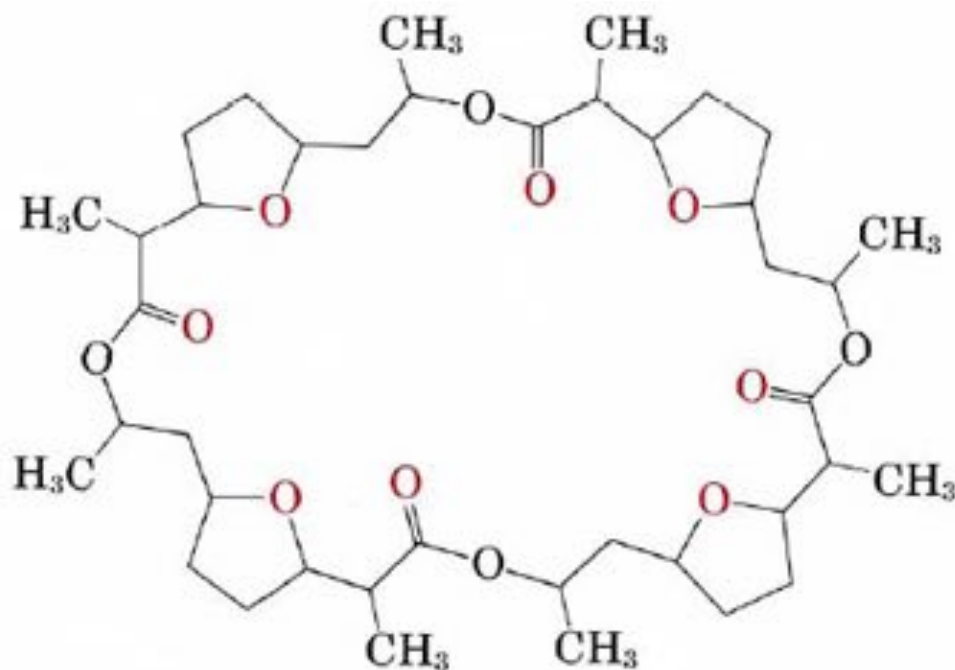
bind to metal ions.

Organic Synthesis: Solubility of metal ions in non-polar solvents

Medicine: antibiotics



crown ether  
"host-guest" chemistry  
for metal ions



Nonactin - binds to K<sup>+</sup>  
but not Na<sup>+</sup>.

Transports K<sup>+</sup> to part  
of cell where it should  
not be and breaks  
down ion gradient.  
(Klein, p. 630)

Danger!!

Storing ether solvents for a “long” time

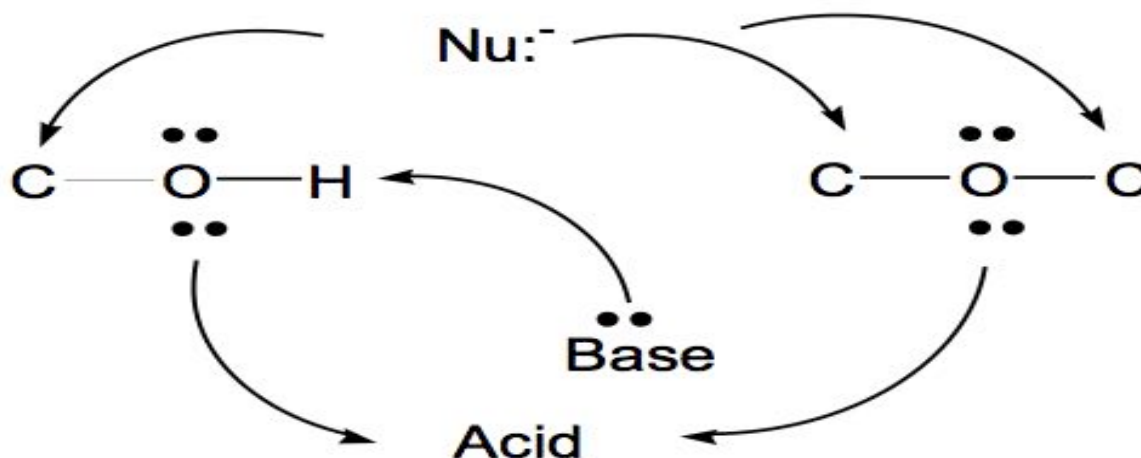
Be careful handling → possible explosion

Auto-oxidation of ethers to peroxides

Ether - O<sub>2</sub> → hydroperoxides + dialkyl peroxides  
*explosive* *explosive*

**Objective:** Determine the acid-base properties of ethers  
**Ethers are Less Reactive than Alcohols**

**C and H are Electrophilic.**  
**Lone pairs on O are Nucleophilic.**



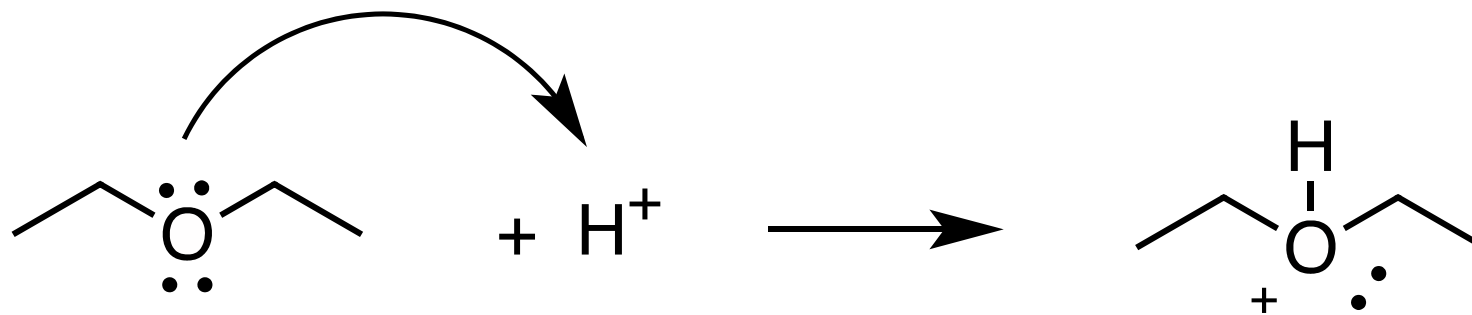
ROH behaves like an acid or base. ROR behaves like a \_\_\_\_\_.

- a. acid      b. base      c. acid or base

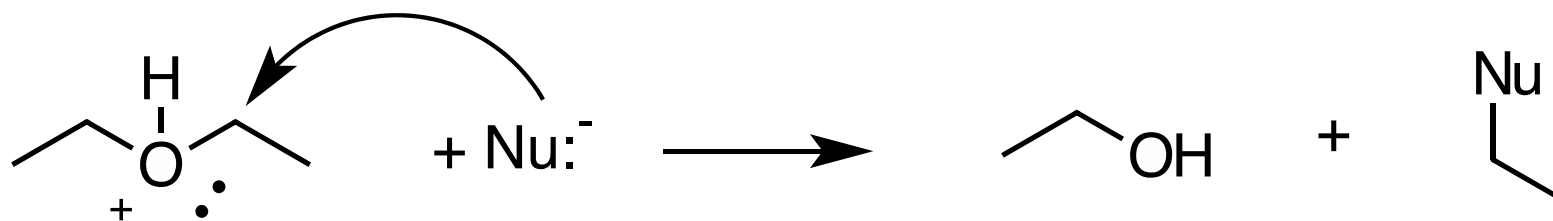
-OH is a poor LG, which can be made into a better LG. Is -OR a good LG? If not, can it be made into a better LG?

ROH undergo substitution. Does ROR undergo substitution?

An Ether can act like a Base ( $pK_a$  of  $ROHR^+ = -3$ )



$-OR$  (like  $-OH$ ) is a poor LG.  $\begin{array}{c} H \\ | \\ -O^+-R \end{array}$  (like  $-OH_2^+$ ) is a better LG.

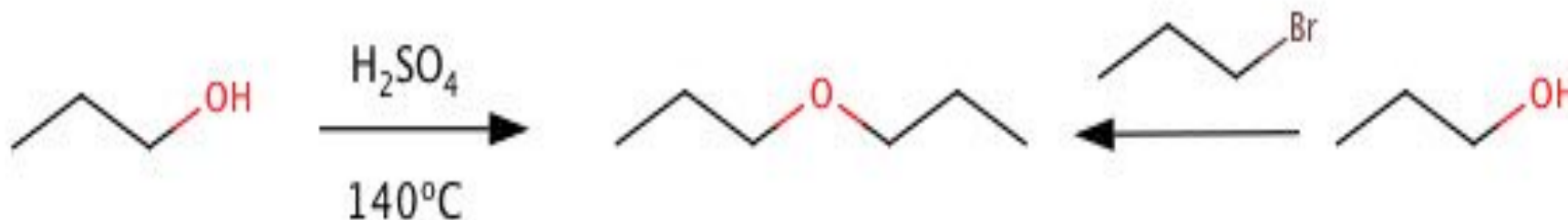


**Objective:** ID reactants to make an ether

**Ethers Are Prepared From ROH or RX** (Substitution reaction):

a. From ROH. *Ether prep from ROH is limited to 1° ROH*

b. Williamson ether synthesis:  $\text{ROH} + \text{RX} \rightarrow \text{ROR} + \text{HX}$



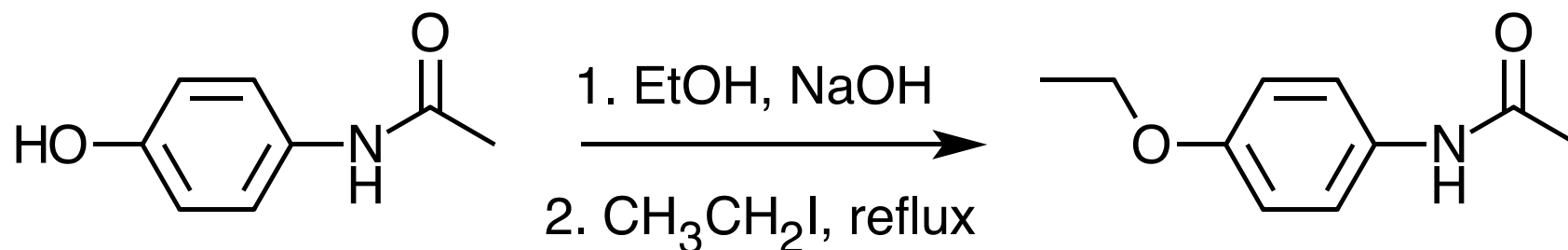
**See Practice Problem 3.**

How are these 2 reactions similar?

**Work Backwards:** which bond breaks in ROR to give the reactants?

**Objective:** ID reactants to make an ether

**Lab 2:** Acetaminophen --> Phenacetin



What is the function of EtOH and NaOH?

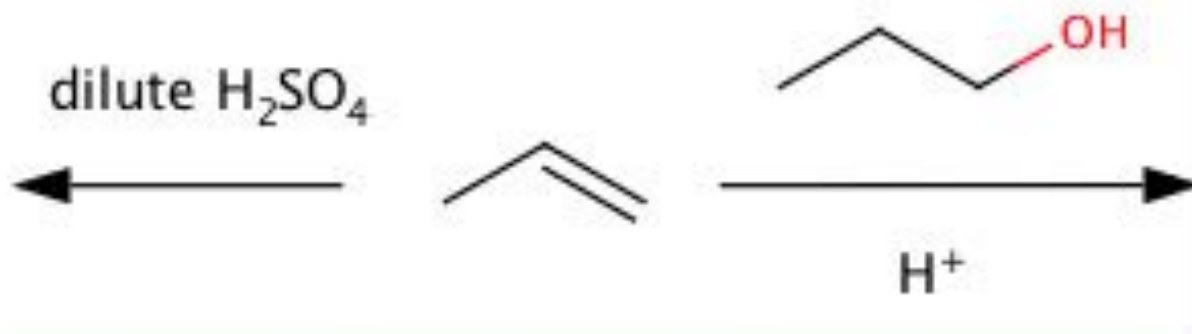
What is the function of CH<sub>3</sub>CH<sub>2</sub>I?



## Ethers can be prepared from Alkenes

Alkene addition to alcohols: similar to alkene hydration.

Draw the intermediate in each reaction. How are they related?

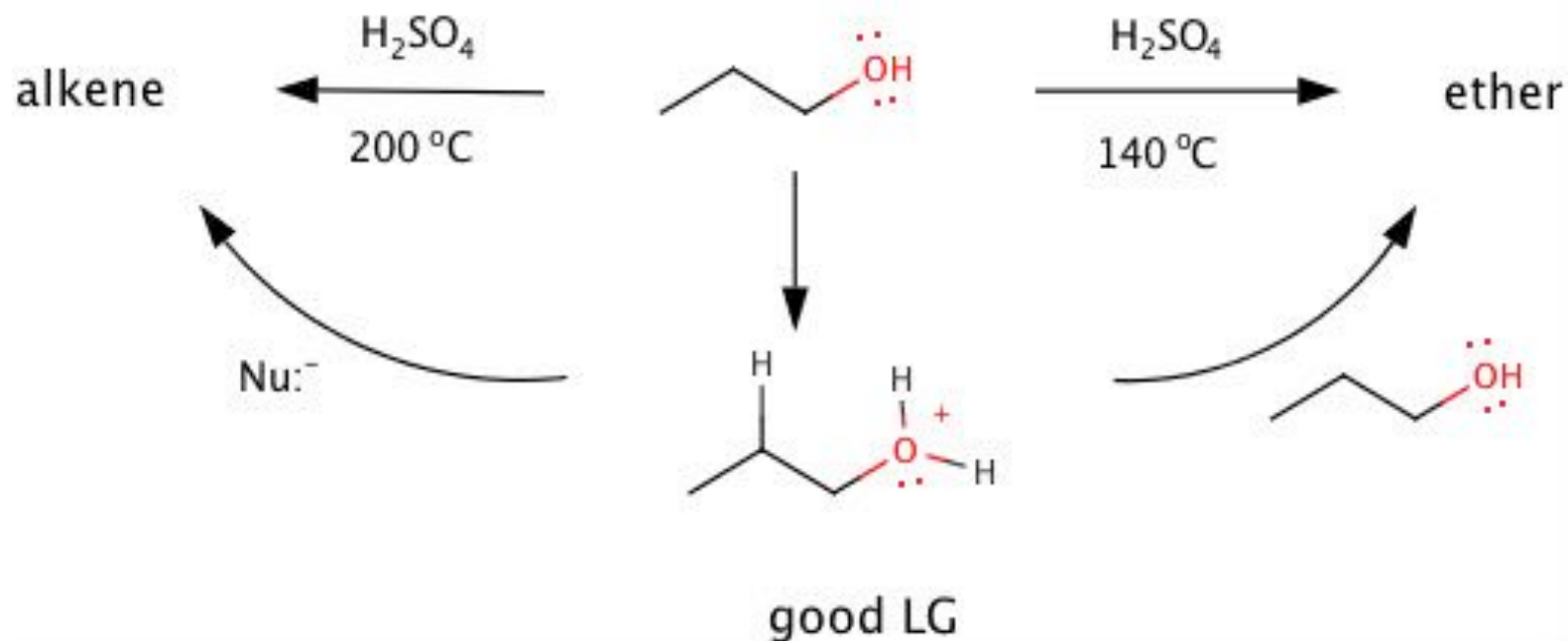


See Practice Problem 4.

How would you use this reaction to synthesize MTBE?  
(fuel additive to oxygenate fuel)

Treat a 1° ROH with  $H_2SO_4$  to make  
an Ether (low T) or Alkene (high T)

See Carey, 8th ed., p. 658.

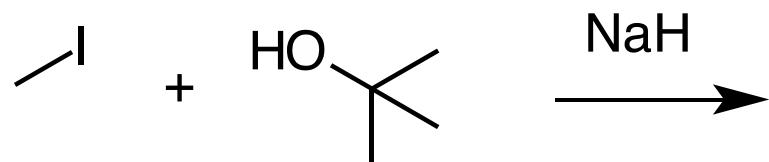
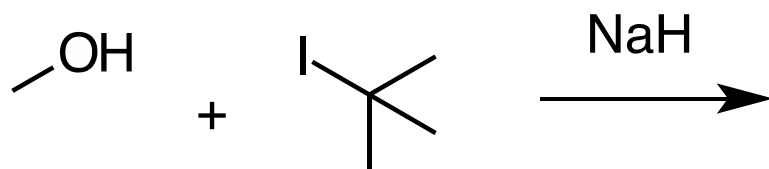


Draw the structure of the product of each reaction.

Which reaction is a substitution reaction?

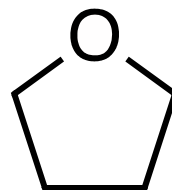
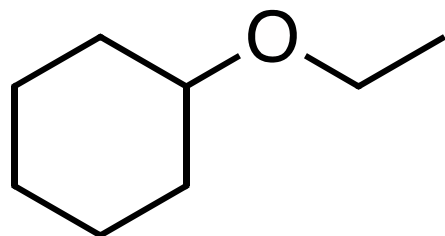
Which reaction is an elimination reaction?

**Objective:** ID reactants to make an ether  
Predict the product(s):



See Practice Problem 5a

ID the reactants to make the ether (propose a synthesis):



See Practice Problem 5b

**Objective:** Predict product of ether reactions

Ethers are one of the least reactive of the functional groups

**Ethers Reactions**

a. formation of peroxides (from solvent storage) – dangerous!

b. **Substitution:** acid-catalyzed cleavage of ethers (reverse of Williamson ether synthesis):



Describe the mechanism of this reaction.

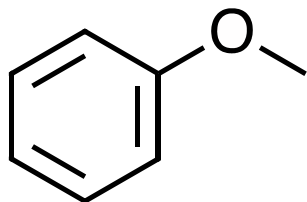
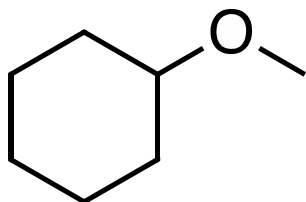


sec-butyl methyl ether

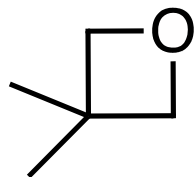
2-bromobutane (81%)

**Objective:** Predict product of ether reactions

Predict the products that are expected when each of the following compounds is heated with concentrated HBr.

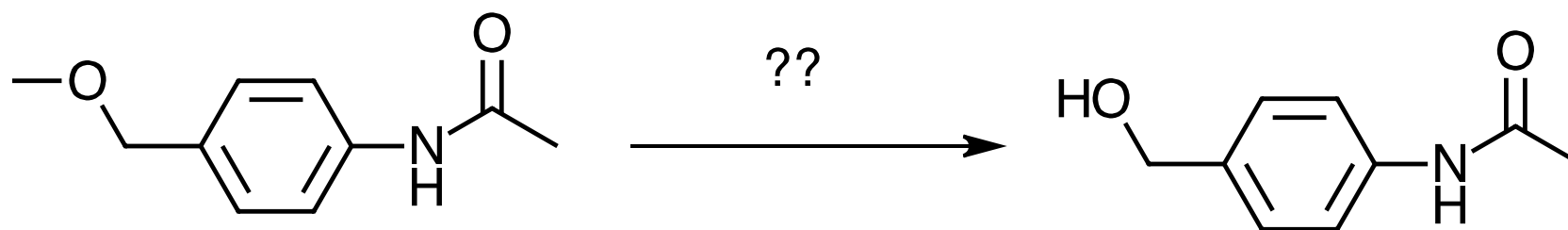


See Practice Problem 6.



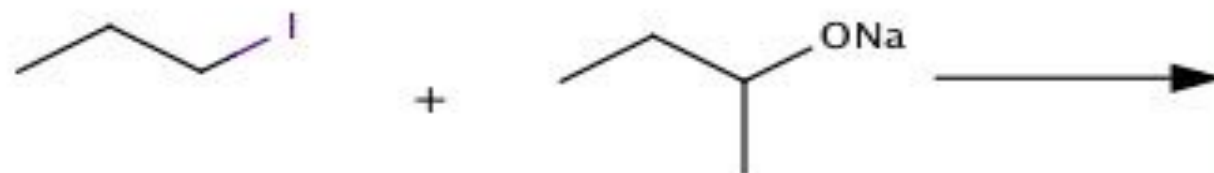
**Objective:** ID reactants to make an ether

**Lab 2:** Phenacetin --> Acetaminophen

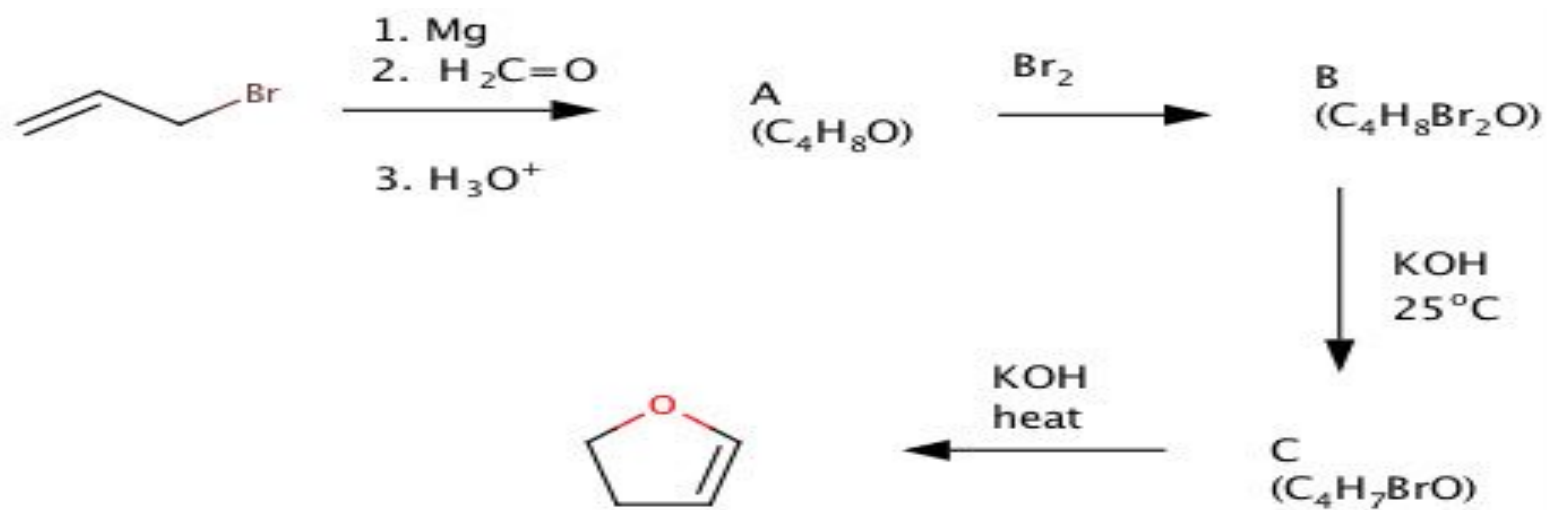


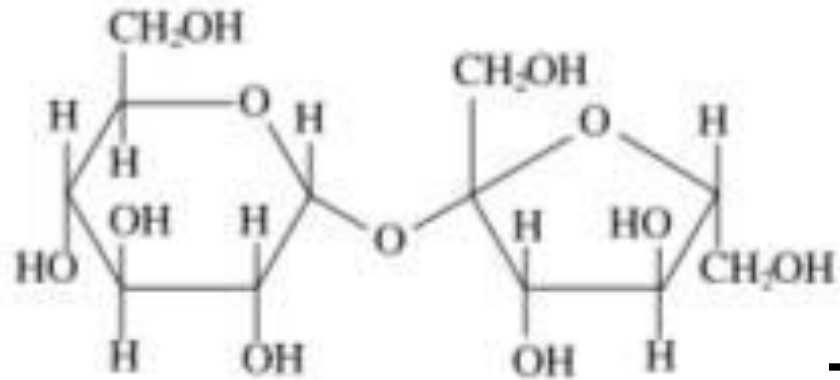
What reaction conditions will you use?

1. Predict the product of the reaction.

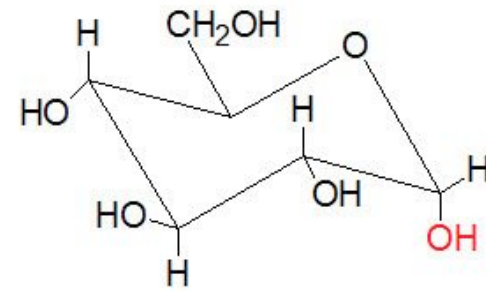


2. Determine the structure of A, B, and C.

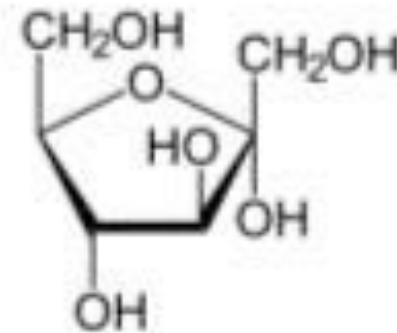




Sucrose



glucose



fructose

Show how sucrose is hydrolyzed to glucose and fructose

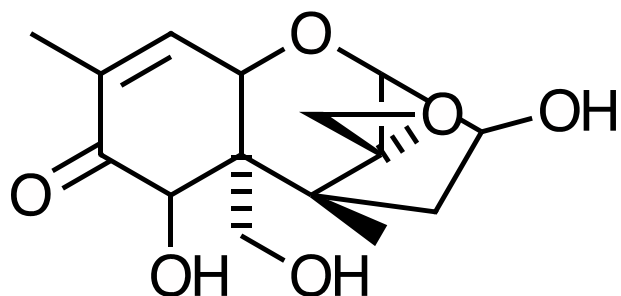
<http://themedicalbiochemistrypage.org/carbohydrates.php>  
[http://www.chempep.com/ChemPep-Generic-Term\\_Others.htm](http://www.chempep.com/ChemPep-Generic-Term_Others.htm)



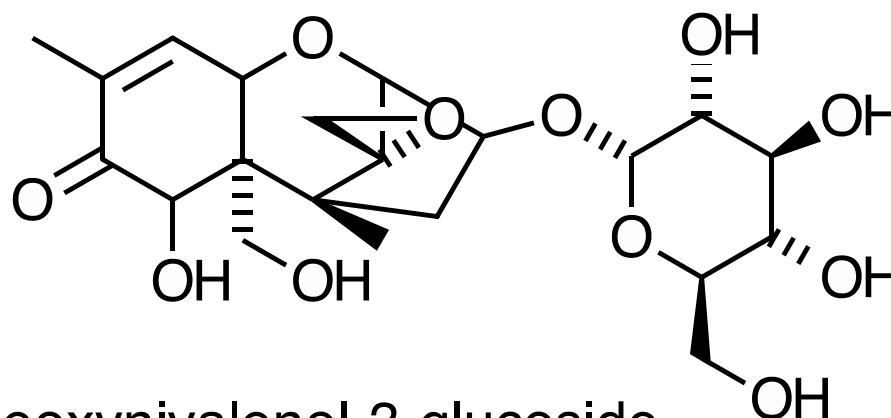
CEN, 2/11/13 “Gut Bacteria Free Hidden Toxins”, p. 9

Fungal toxins (mycotoxins) cause ailments from diarrhea to cancer.

**Plants modify these toxins to protect themselves, e.g., add a sugar or sulfate group, ==> “masked” mycotoxin derivative.** Gut bacteria converts masked derivative to toxin.



Deoxynivalenol  
mycotoxin



Deoxynivalenol-3-glucoside  
mycotoxin derivative

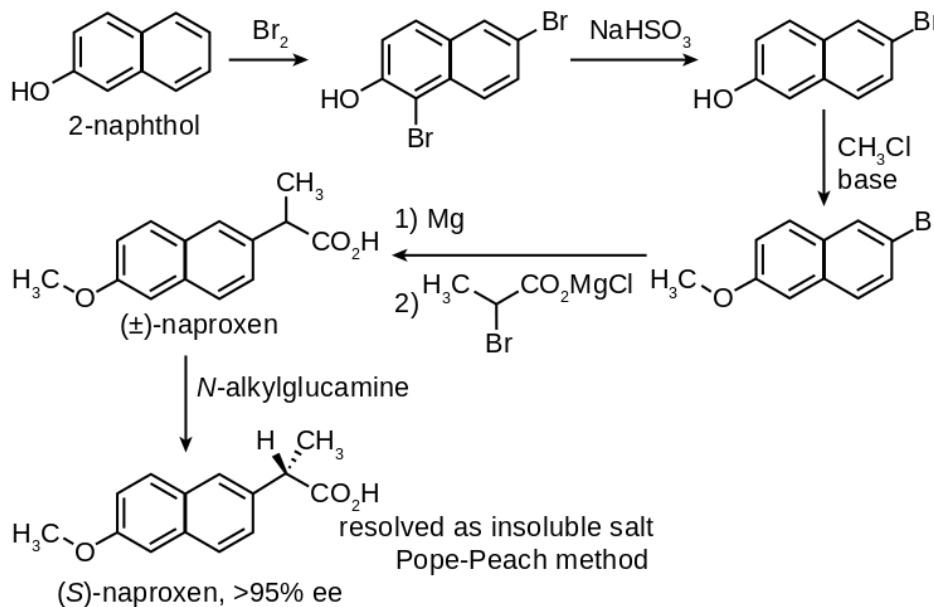
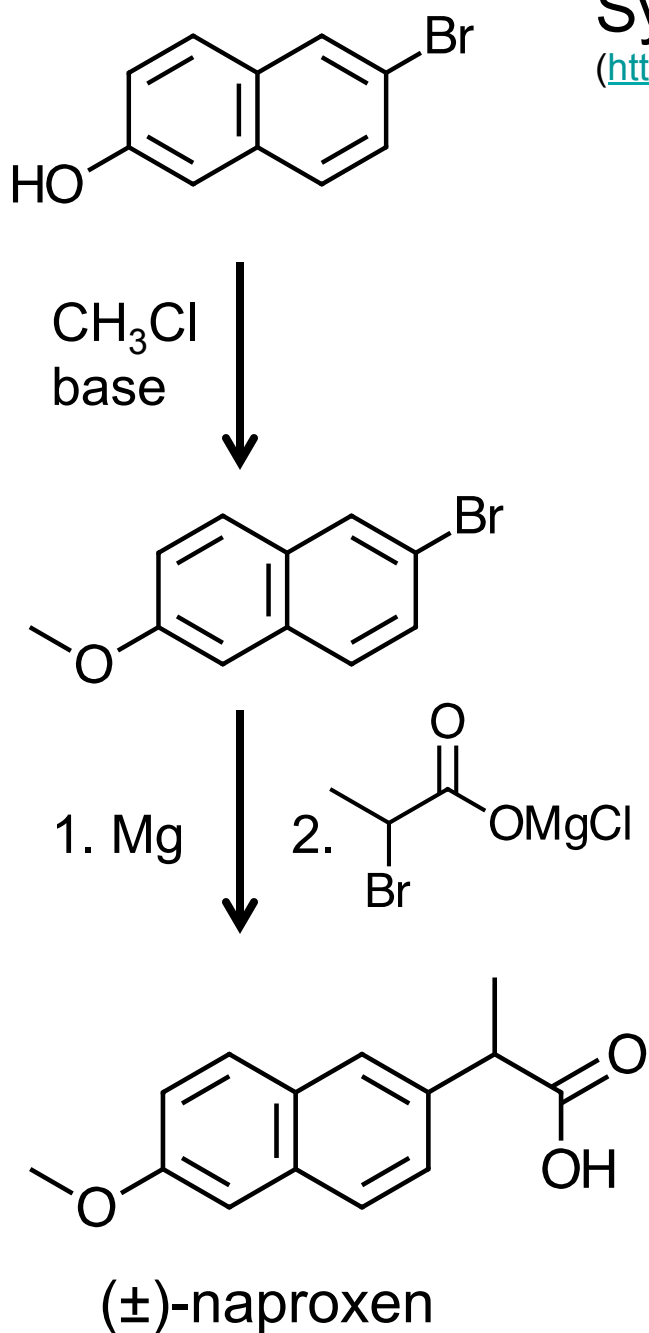
Show how Deoxynivalenol reacts with glucose to form Deoxynivalenol-3-glucoside.

Show how Deoxynivalenol-3-glucoside is converted to Deoxynivalenol.

**See Practice Problem 7.**

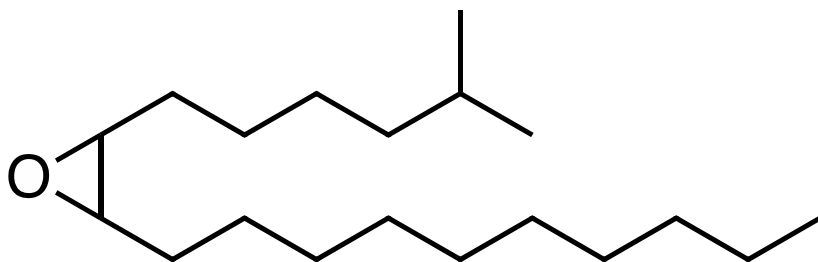
# Synthesis of Naproxen - OTC pain reliever

(<https://en.wikipedia.org/wiki/Naproxen>)

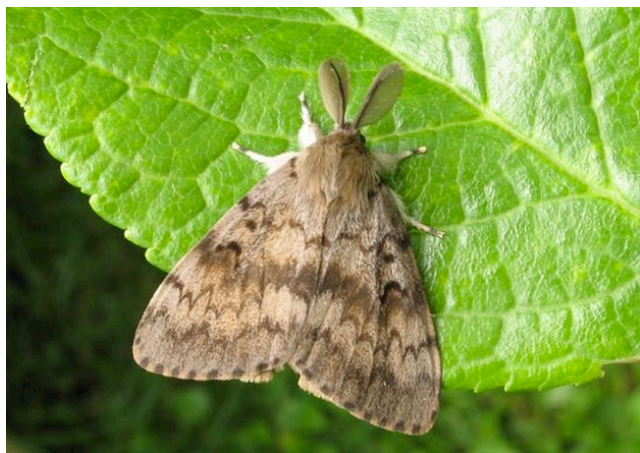


1. Use curved arrows to show how (±)-naproxen is synthesized.
2. What does “±” mean?
3. What is the mechanism type for the second step?

# Epoxides are found in Biology



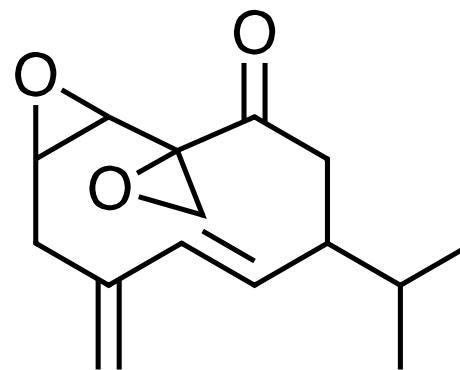
Disparlure - sex pheromone of female gypsy moth



<http://picphotos.net/gypsy-moth/>



<http://nathistoc.bio.uci.edu/orthopt/Periplaneta.htm>

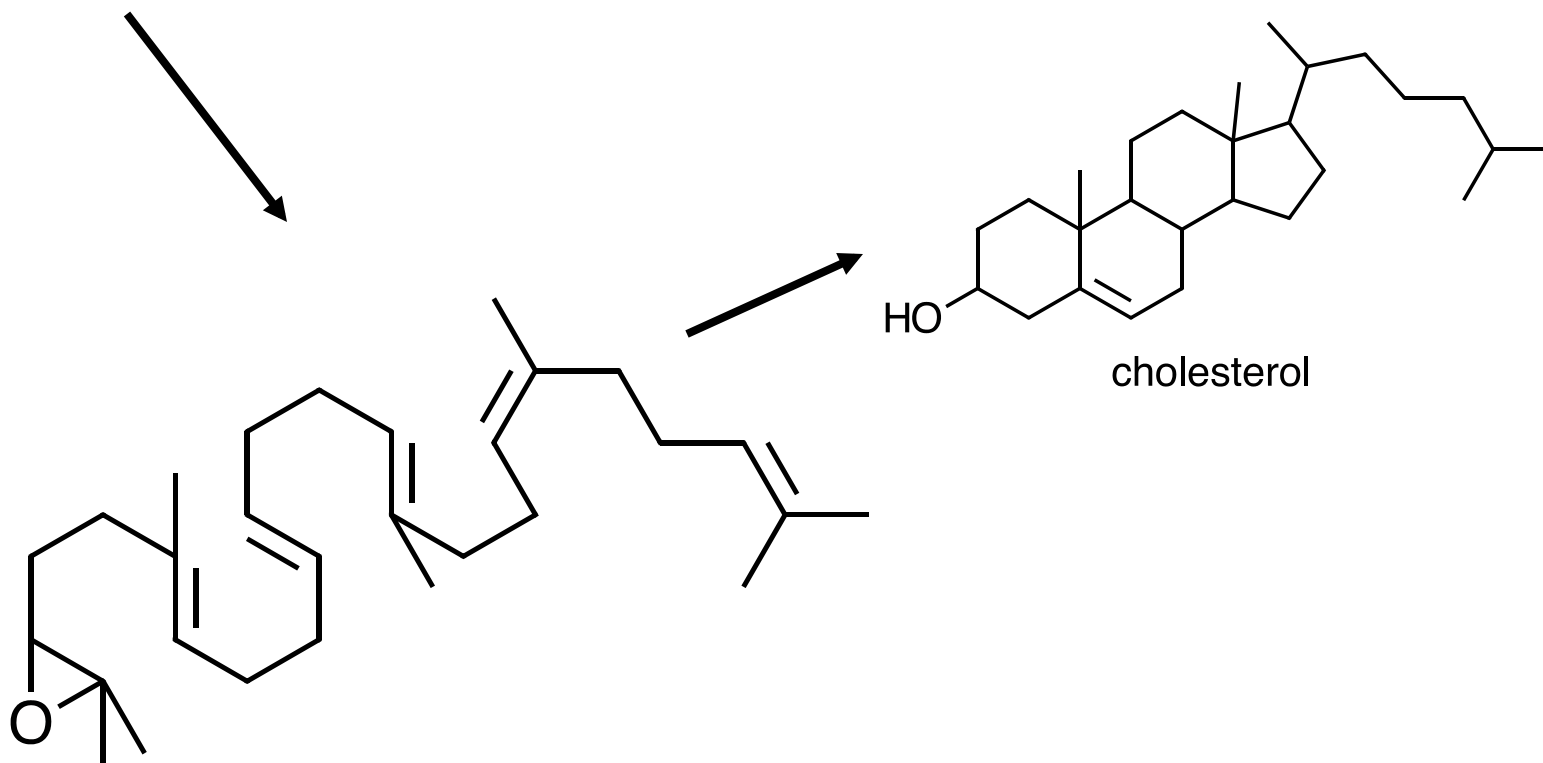
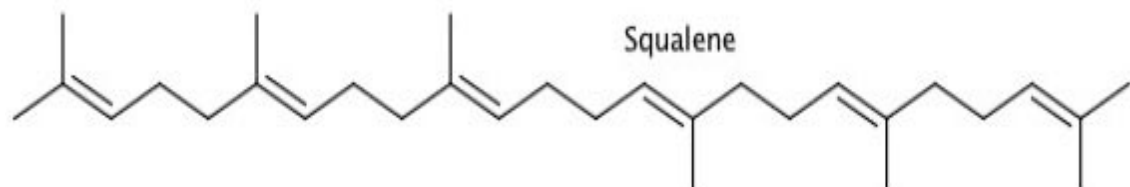


Periplanone B  
Sex pheromone of the female American cockroach

<https://diggerfortruth.wordpress.com/2013/03/21/like-the-pulsing-of-the-heart/>

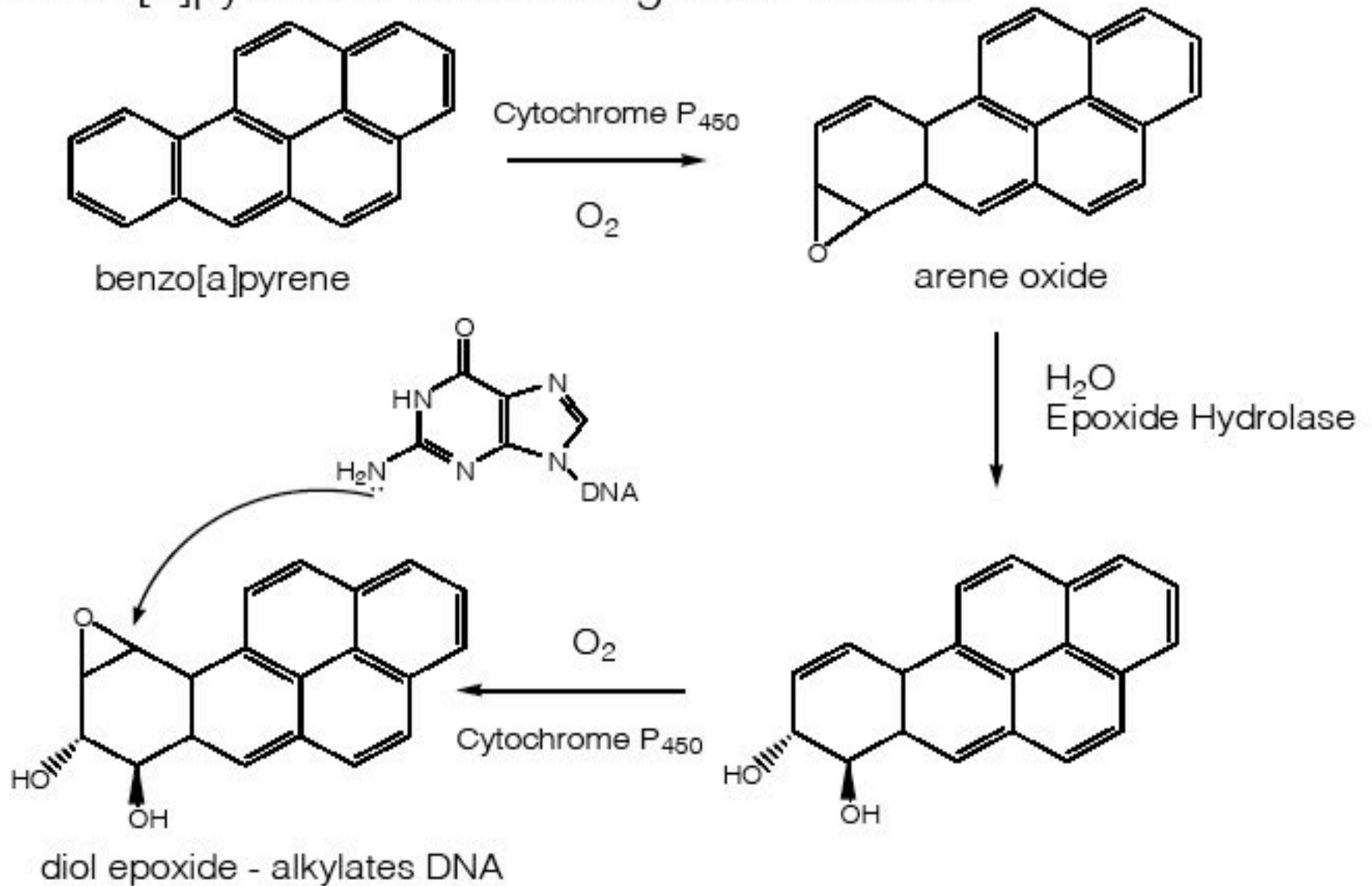
## Epoxides are found in Biology

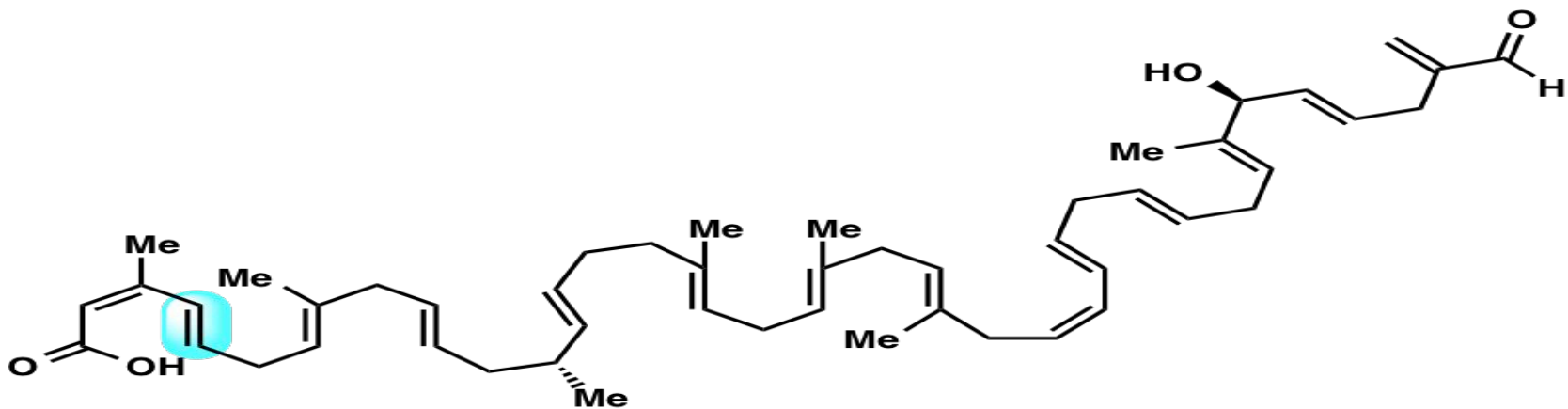
Squalene --> squalene-2,3-epoxide --> cholesterol



Squalene-2,3-epoxide

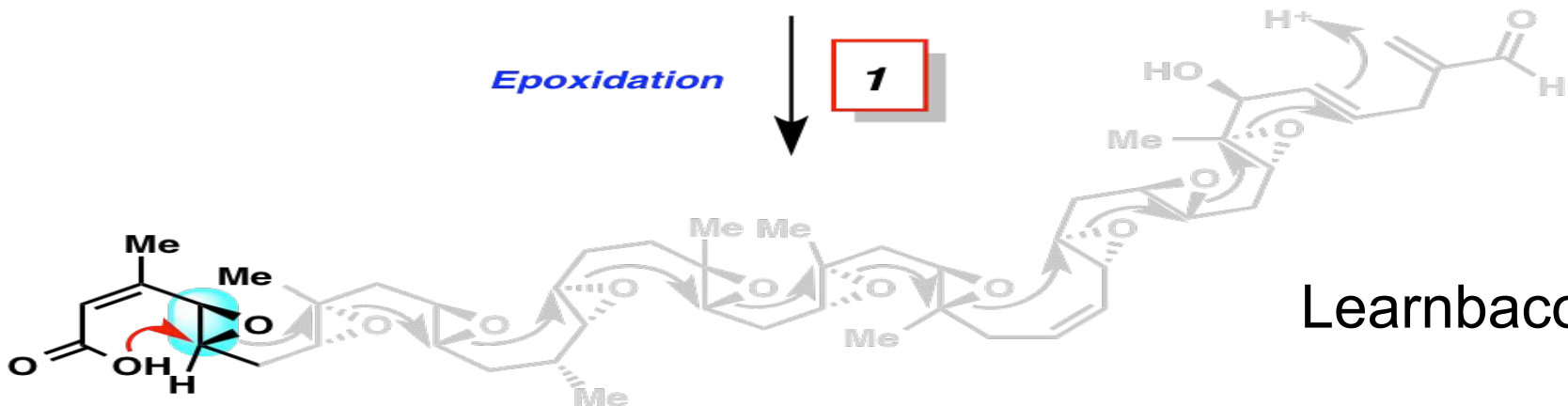
Benzo[a]pyrene is found in cigarette smoke.





*Epoxidation*

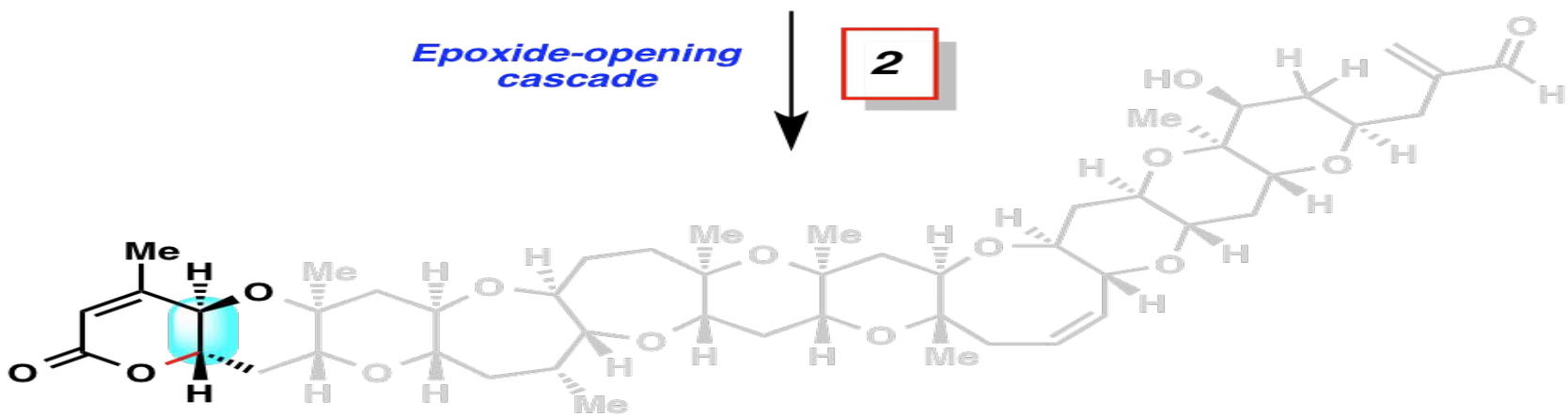
**1**



Learnbacon.com

*Epoxide-opening cascade*

**2**

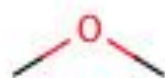


*brevetoxin B*

# Epoxides Are Much More Reactive Than Ethers

Epoxides are *much more useful* in synthesis than Ethers

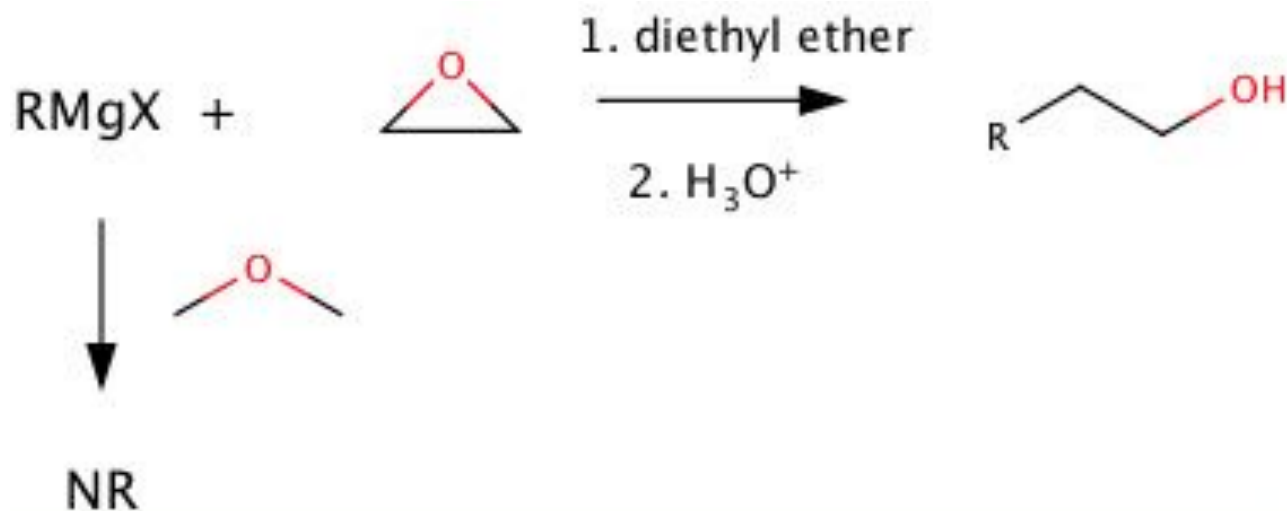
Why are epoxides more reactive than acyclic ethers?



ether



ethylene oxide  
(epoxide)



What is the reaction type?  
ID reaction features.

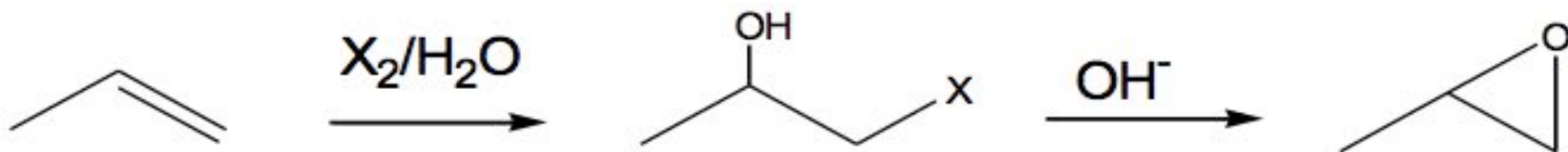
**Objective:** ID reactants to make an epoxide

**Epoxides Are Made From (i) Alkenes and (ii) Vicinal Halohydrins**

(i) alkene + peroxyacid



(ii) alkene +  $X_2/H_2O \rightarrow$  vicinal halohydrin –  $OH^- \rightarrow$  epoxide.

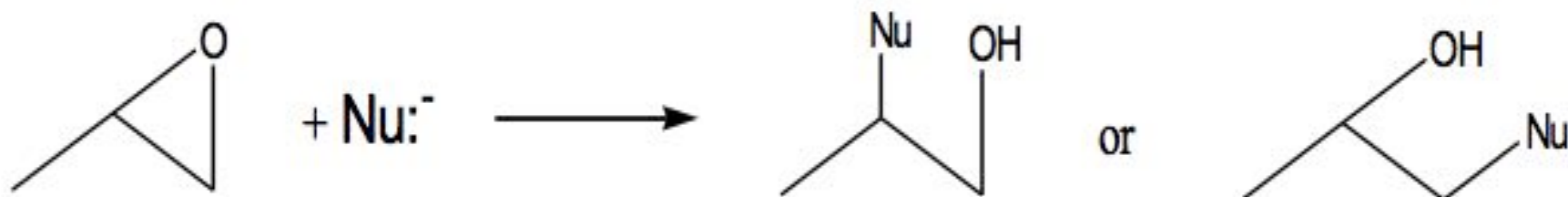


What is the reaction type? What is the reaction mechanism?

See Practice Problem 8a.



**Objective:** Predict product of Epoxide reactions  
**Epoxides React With Nu:<sup>-</sup> To Make ROH**



What is the Reaction type?

- a. Acid-base    b. Addition    c. Elimination    d. Substitution

Identify the  $\alpha$ -C and  $\beta$ -C.

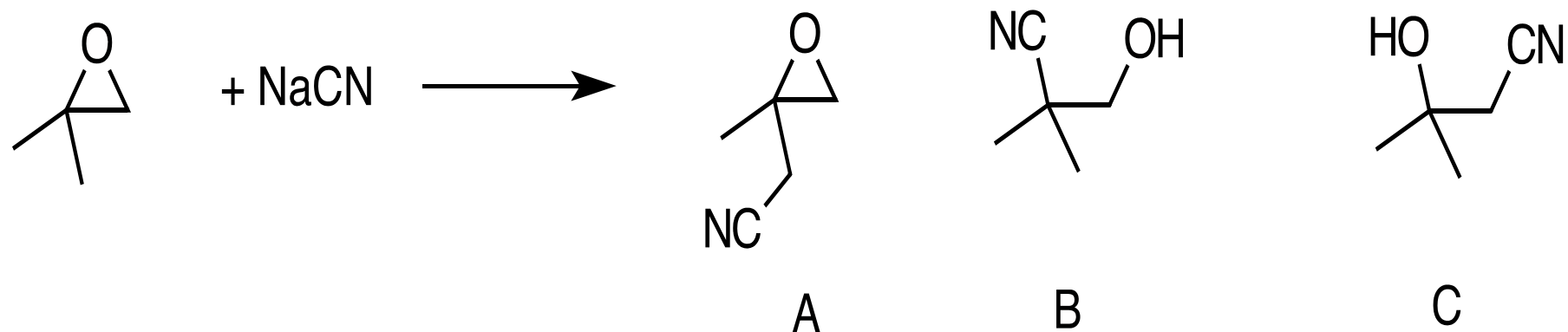
Is the  $\alpha$ -C electrophilic?

What is the leaving group?

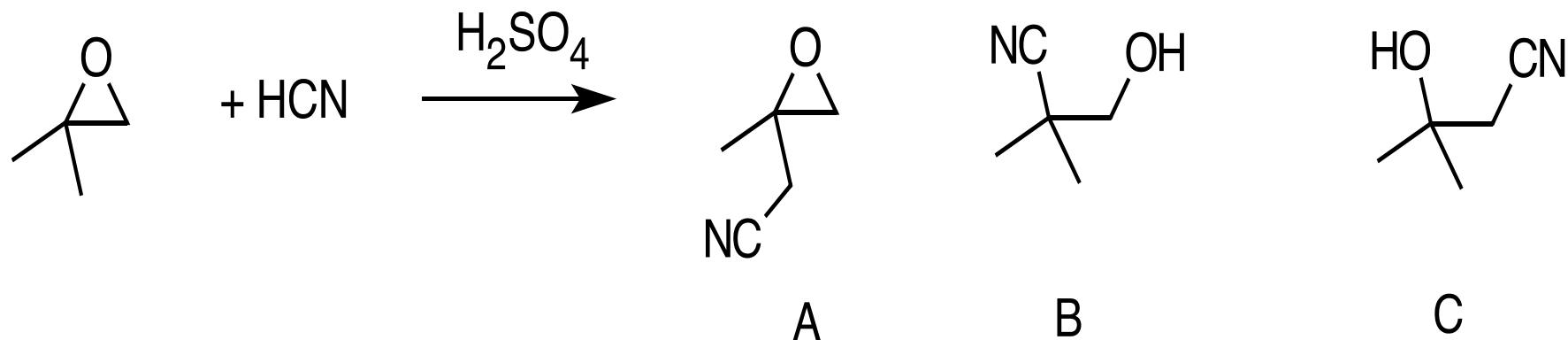
***The reaction conditions (nucleophilic or acid catalyzed) determine the position of Nu:<sup>-</sup> in epoxide ring opening reactions.***

## Access of Nu:<sup>-</sup> vs. Stability of intermediate

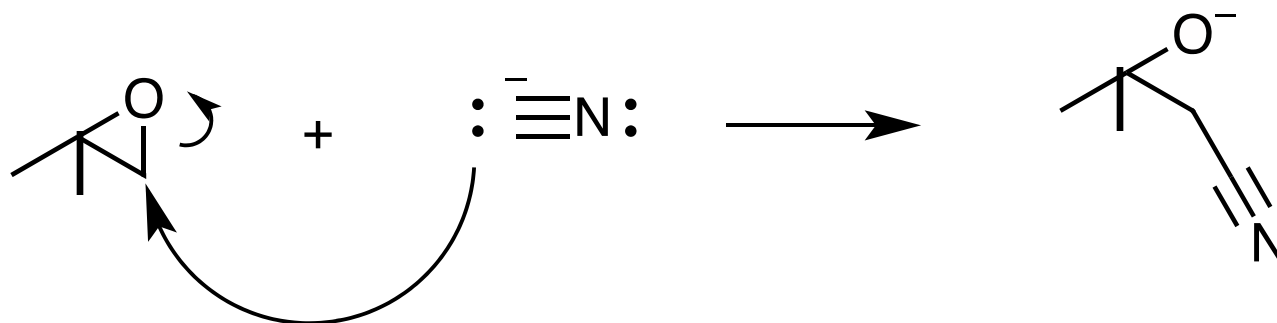
(i) **Nucleophilic**. At which C does Nu:<sup>-</sup> react?



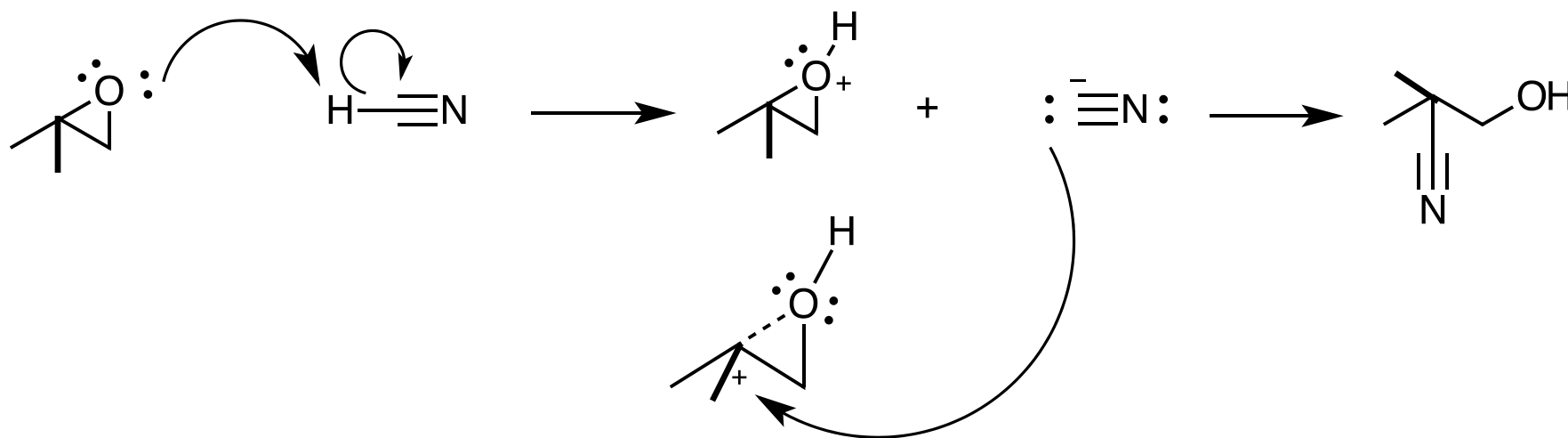
(ii) **Acid Catalyzed**. At which C does Nu:<sup>-</sup> react?



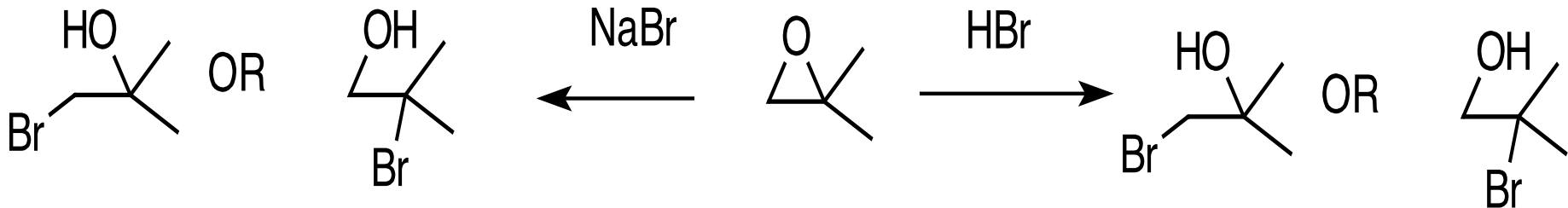
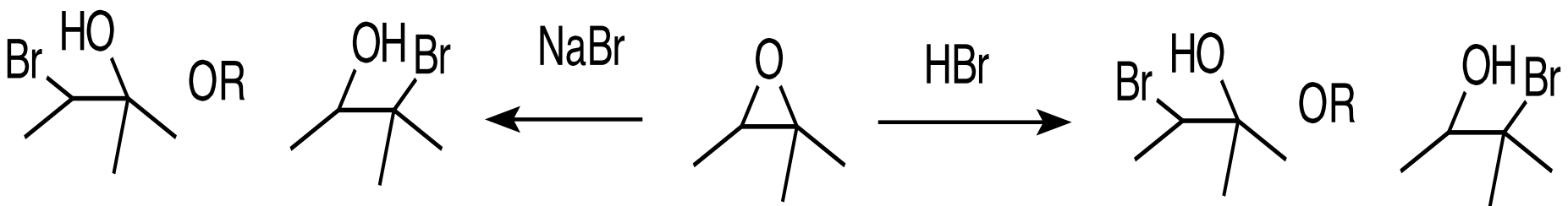
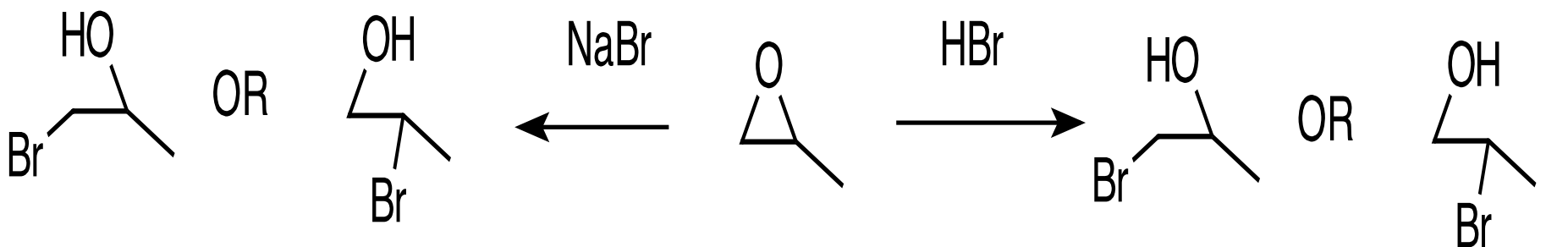
(i) **Nucleophilic**. At which C does Nu:<sup>-</sup> react?  
On **Less** substituted C (*steric effect*)



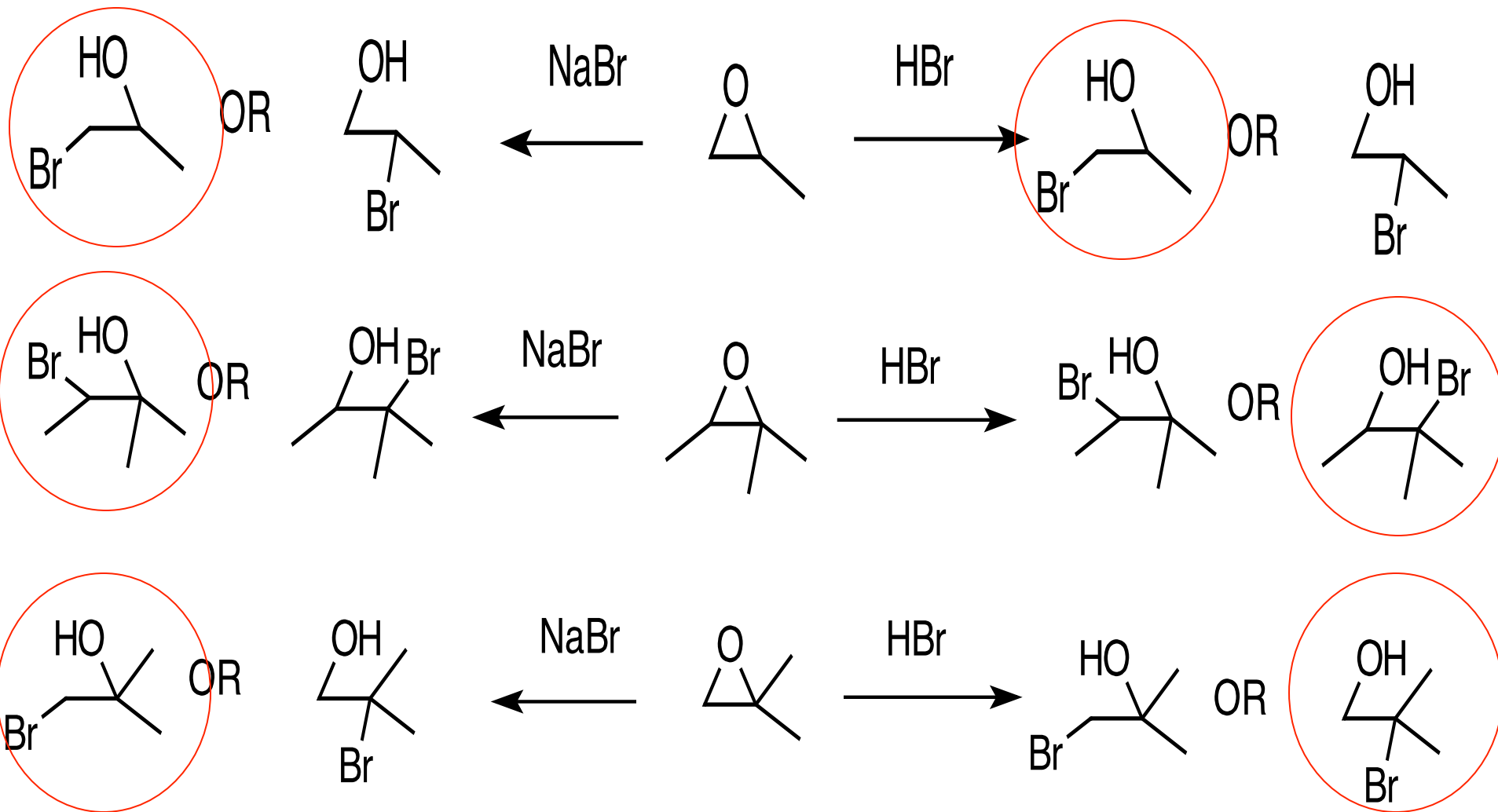
(ii) **Acid Catalyzed**. At which C does Nu:<sup>-</sup> react?  
On **More** substituted C (**for 3° only** - *electronic effect*)



Predict the Product of each Reaction:



Predict the Product of each Reaction:

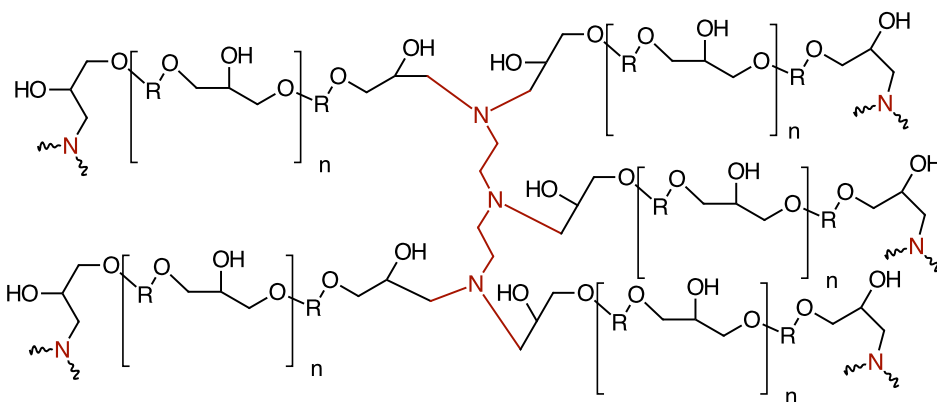
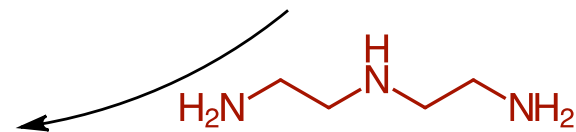
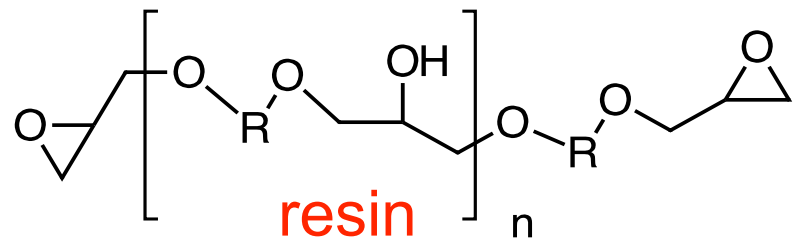
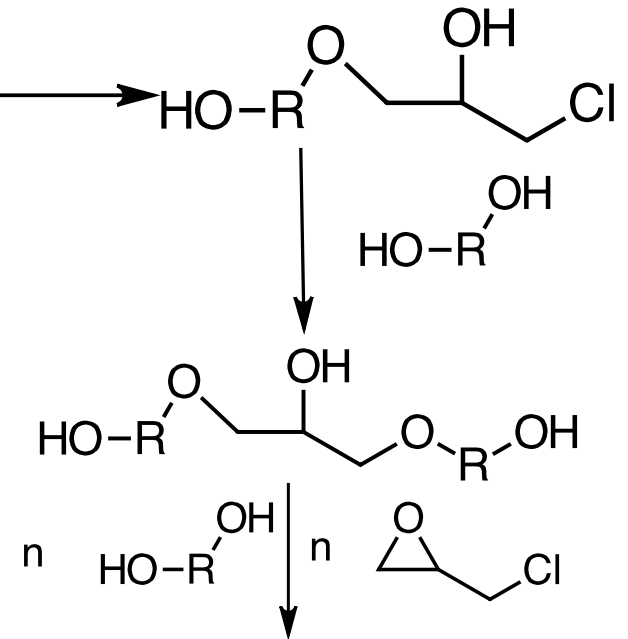
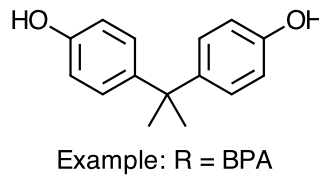
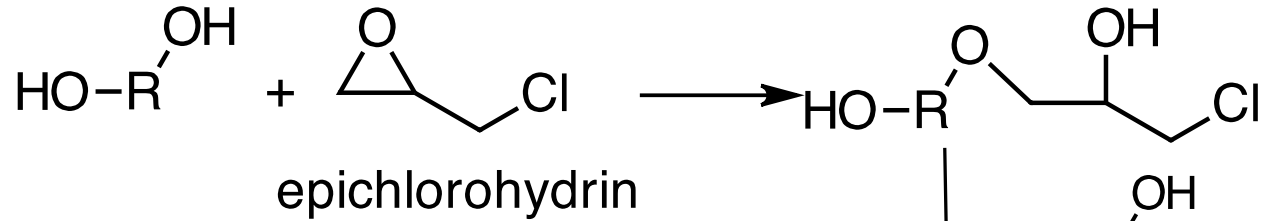


STERIC

Electronic

# Epoxy Glues are made from **Epoxides**

Mix resin with hardener (<https://en.wikipedia.org/wiki/Epoxy>)



**cured epoxy – hard from cross linking**

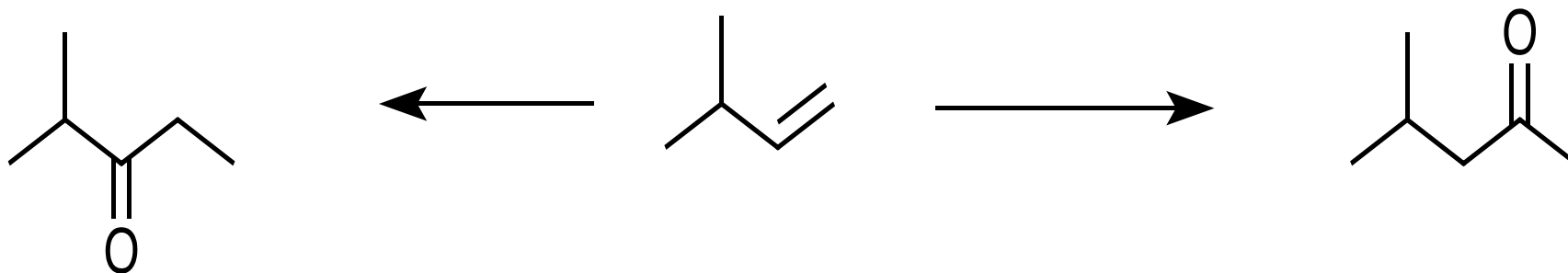
**hardener**

**Use curved arrows to show how each reaction occurs.**

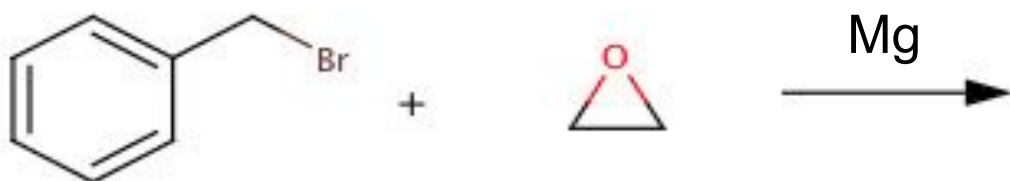
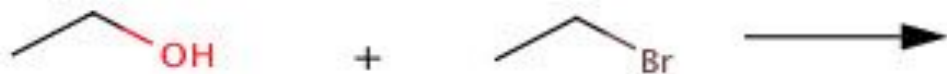
Ways to make a C-C bond:

1. Acetylide ion
2. Grignard reagent + aldehyde/ketone
3. Grignard reagent + epoxide

Which C-C bond formation method should I use?



**Objective:** Predict the product or propose a synthesis.  
See Objective 3 Practice Problem 9.





Chemical and Engineering News, 3/5/12, p. 5 “Unfavored Ring Route Revealed”  
Reaction that forms the 6-membered ether ring is ***disfavored***  
according to Baldwin’s rules of ring closure (1976).

A bacterial enzyme catalyzes the epoxide-opening cyclization.  
How is each ether ring formed?

