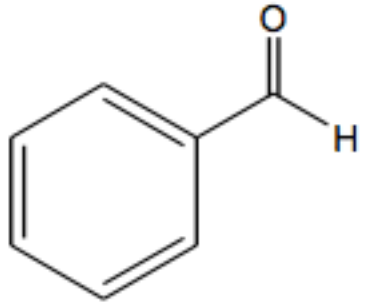
Objective 9. Understand nucleophilic addition reactions of O and C nucleophiles to C=O compounds.

Skills: Draw structure
ID structural features and reactive sites (alpha C, beta C, LG, etc.)
ID Nu^- and E^+
use curved arrows to show bonds breaking and forming
show delocalized electrons with resonance structures.

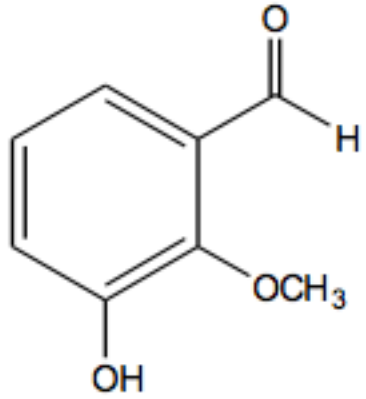
Key ideas: acetals are common in biology
C=O bond has pi bond but bond is polarized. See resonance.
Carbonyl C = E^+.
Reacts with Nu^- to form tetrahedral intermediate.

Oxygen Nu^-: OH^-, H_2O, RO^-, ROH
Carbon Nu^-: RMgX, CN^-

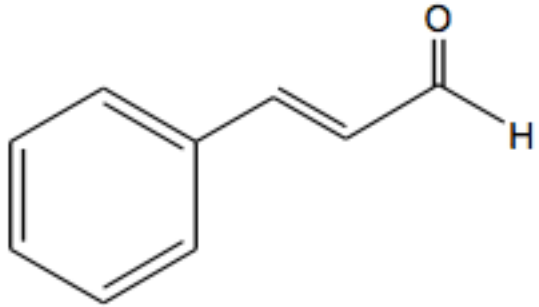
Aldehydes and Ketones Have Distinctive Smells and Odors and Flavors



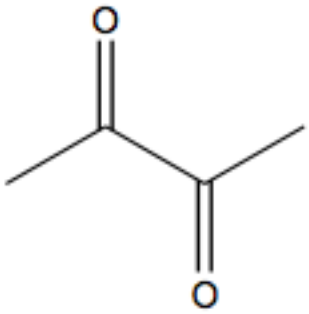
Benzaldehyde
almonds



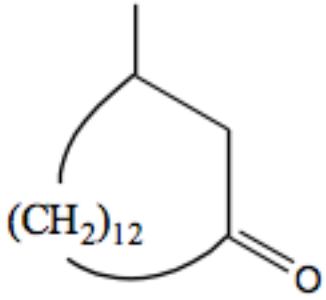
Vanillan
vanilla



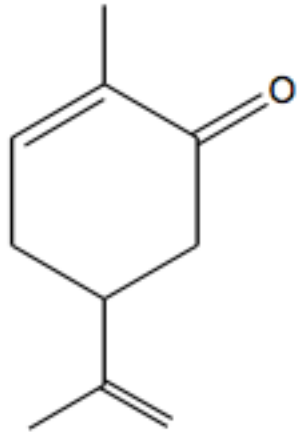
Cinnemaldehyde
cinnamon



Butanedione
butter flavor

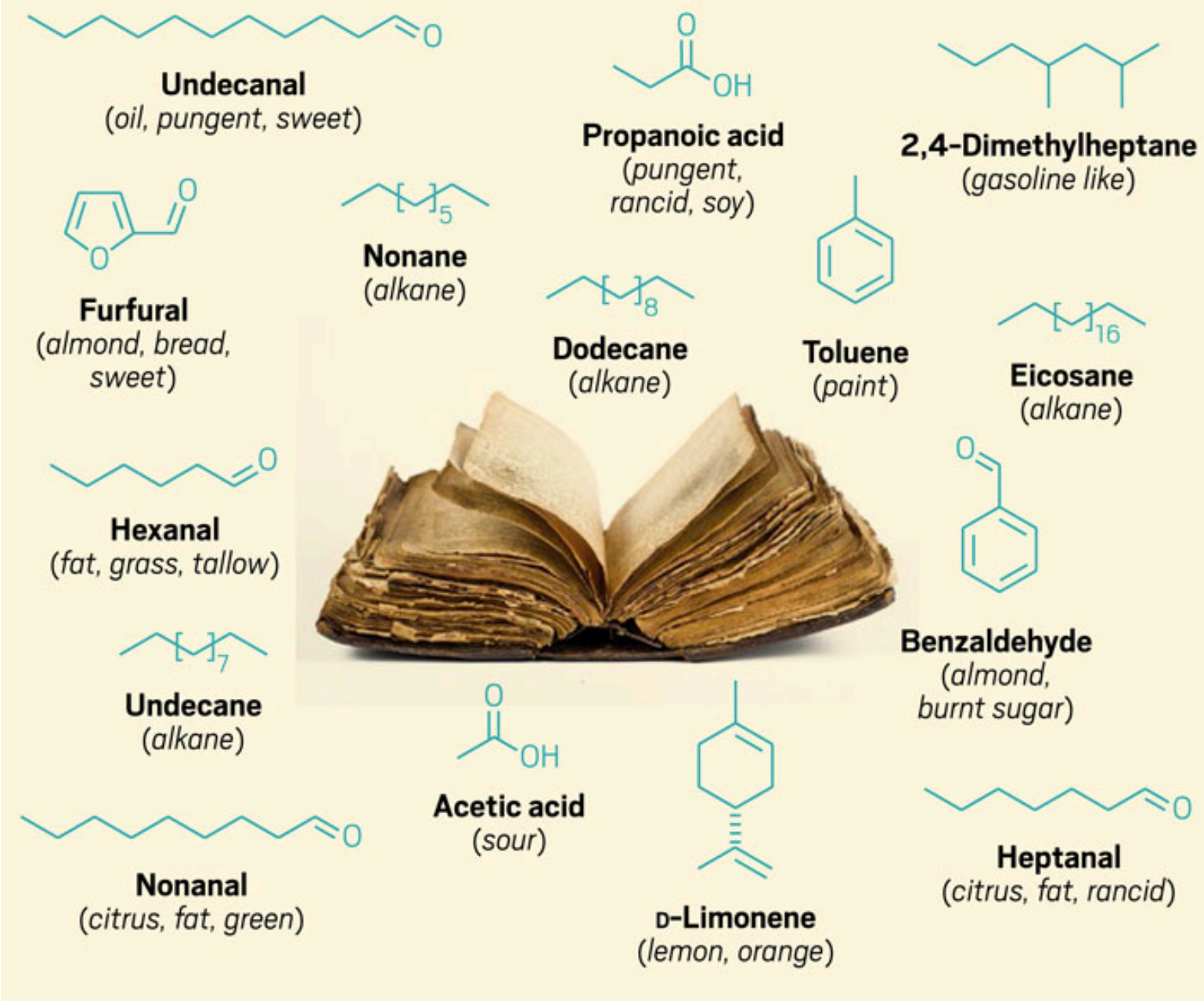


Muscone
musk



Carvone
spearmint

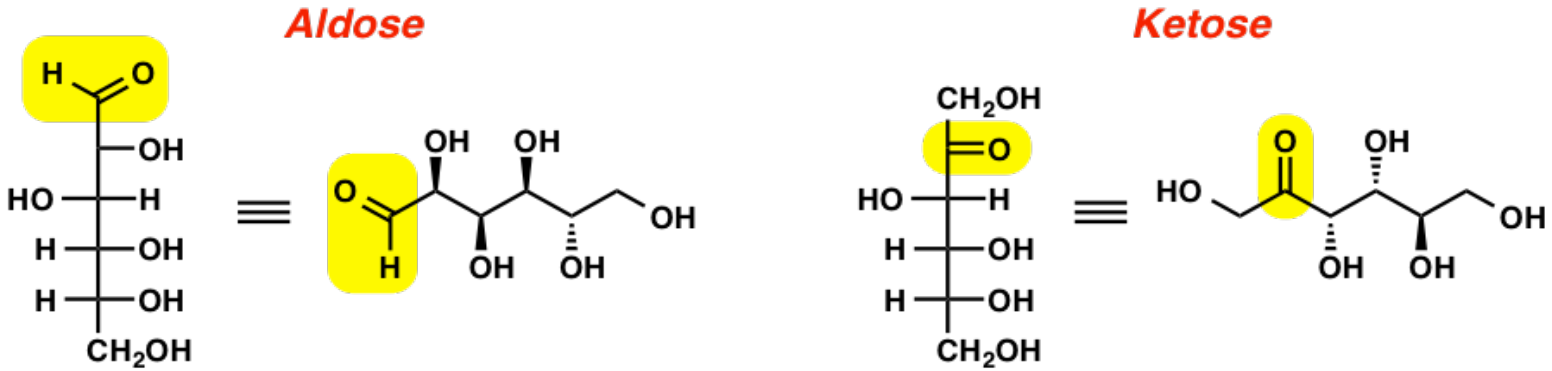
Like the Smell of Old Books? https://cen.acs.org/articles/95/i47/science-help-us-smell-past.html



IDENTIFY THE ALDEHYDES

Aldehydes and Ketones are found in Carbohydrates

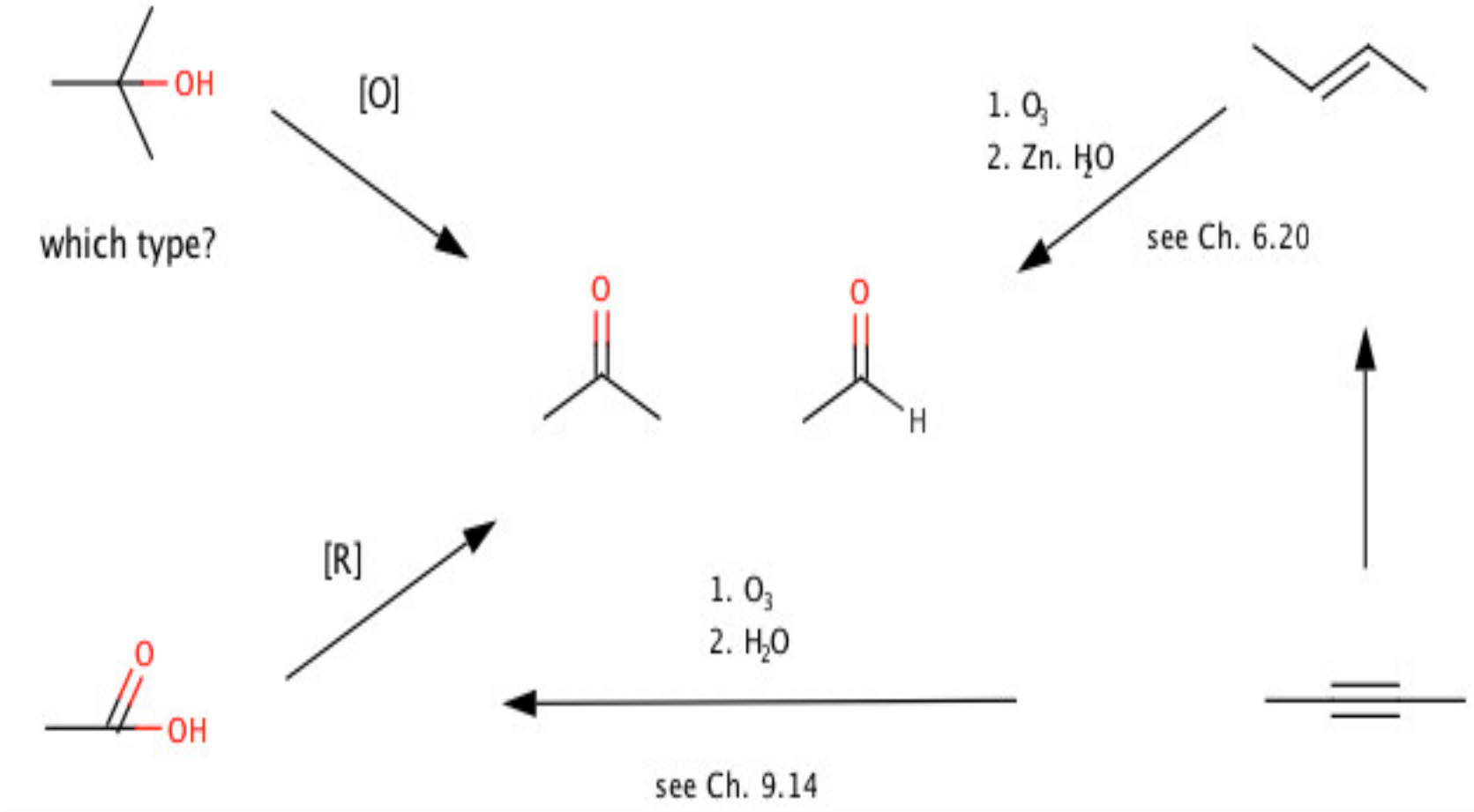
LearnBacon.com



energy source in most organisms

high fructose corn syrup

Preparation: Aldehydes and Ketones are Made from Various Functional Groups
ID the functional group(s) to Make RCOR/RCHO



Organic CONCEPTS:

Reactants: ID structural feature(s).

ID each structural feature as a $Nu:^-$ or E^+.

Name a $Nu:^-$ or E^+ that reacts with each structural feature.

Products: What structural feature is FORMED from the REACTANT structural feature?

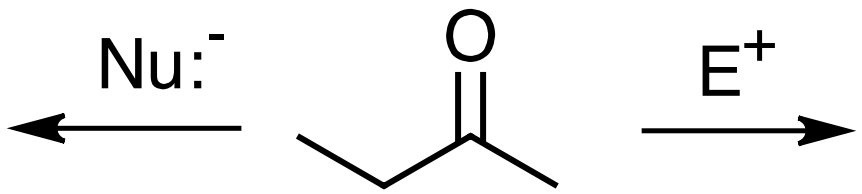
E.g., Electrophilic addition: C=C bond ---> ??

Nucleophilic addition: C=O bond ---> ??

(What happens at the C?)

<u>OChem Objectives</u>:

(1) given reactants and reaction conditions ==> predict products. Determine all possible products. Use curved arrows to show bonds breaking and forming.

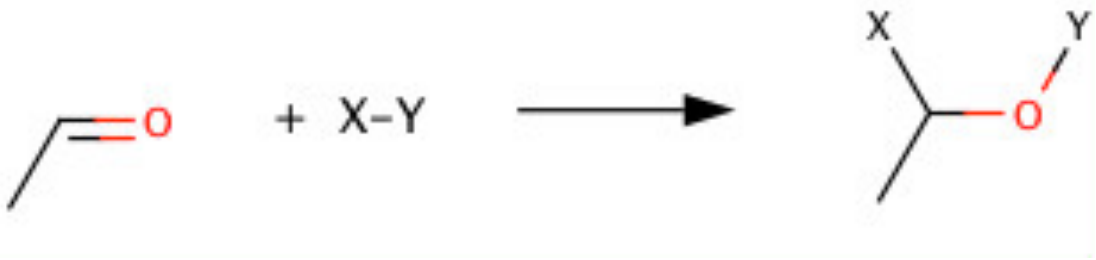


Compare Electrophilic Addition to Nucleophilic Addition

C=C undergoes ***Addition*** reactions (Electrophilic Addition)

C=O undergoes ***Addition*** reactions (Nucleophilic Addition)

Y = E^+



Y = H

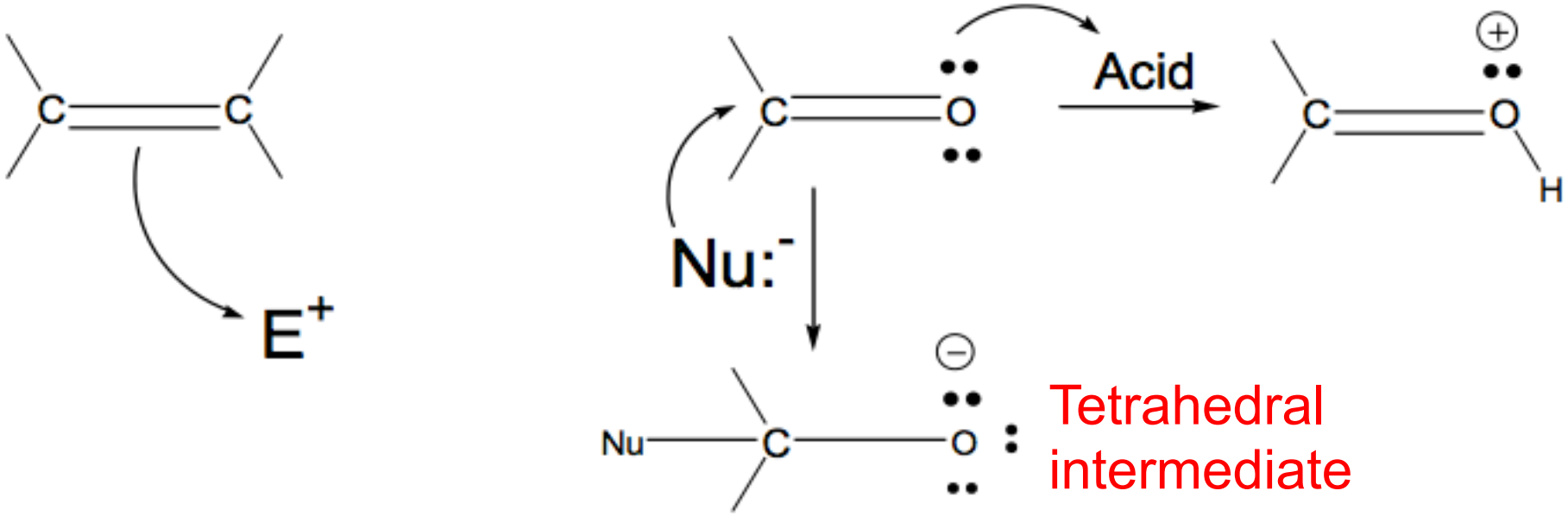
Each Mechanism is ***Different***:

Alkene is $Nu:^-$ and reacts with E^+ first

The C in C=O is E^+ and reacts with $Nu:^-$ first

The C=O Bond (Carbonyl Group) Reacts With Nucleophiles Or Acids

Pi bonds and lone pairs on O are Nucleophiles.
The C bonded to O is an Electrophile.



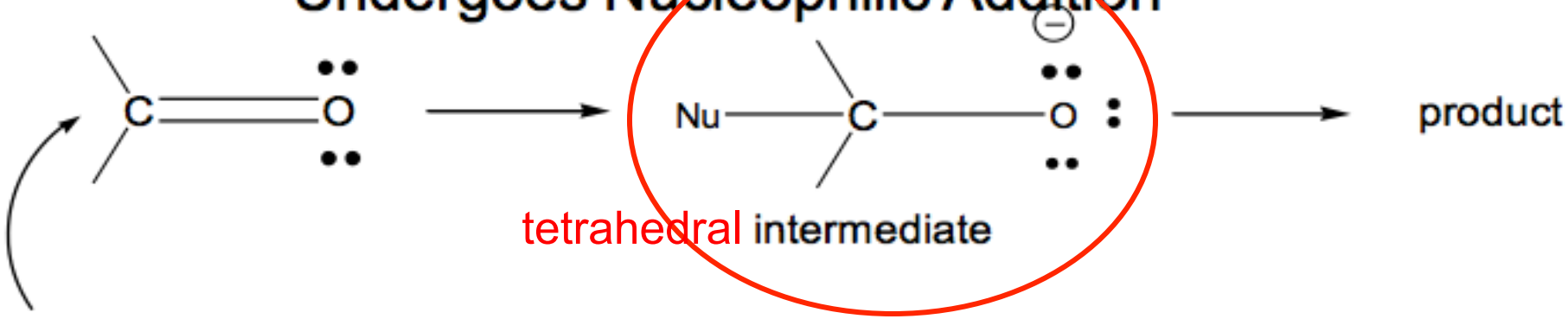
How does an organic compound react with another organic compound? Compare C=C bond to C=O bond.

(i) At which atom(s) will a reaction occur?

(ii) Does the atom behave like a _____ or _____?

(iii) Would you expect reactivity to be the same or different?

The C=O Bond (Polarized Multiple Bond) Undergoes Nucleophilic Addition



$Nu:^-$ =

a. H_2O (acid or base catalyzed) --> gem diol
b. ROH --> acetal
c. HCN --> cyanohydrin
d. RNH_2 --> imine
e. R_2NH --> eneamine
f. hydride --> alcohol
g. Grignard: RMgX --> ROH
h. Wittig reaction (ylide) --> alkene (skip)

How are these reactions similar?

See mechanisms: http://treefrog.fullerton.edu/chem/orm.html

Practice Problems: Carey, 8th ed., Ch. 17.26

C Nucleophile = Grignard Reagent

form C-C bond to make a big molecule from a smaller molecule.

Grignard reagent: R-X + Mg → RMgX

Is RMgX a Nu:$^-$ or E$^+$??

Then, RMgX + _____ → ??

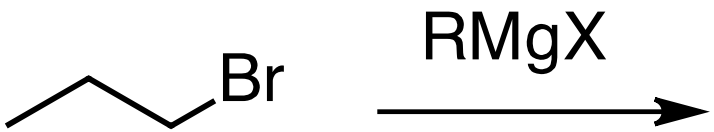
One Big Problem: ***WATER*** reacts with RMgX.
Use curved arrows to show how water reacts with RMgX.
What's the problem with water?

Name 2 other substances that react with RMgX.
Use curved arrows to show how each substance reacts with RMgX.

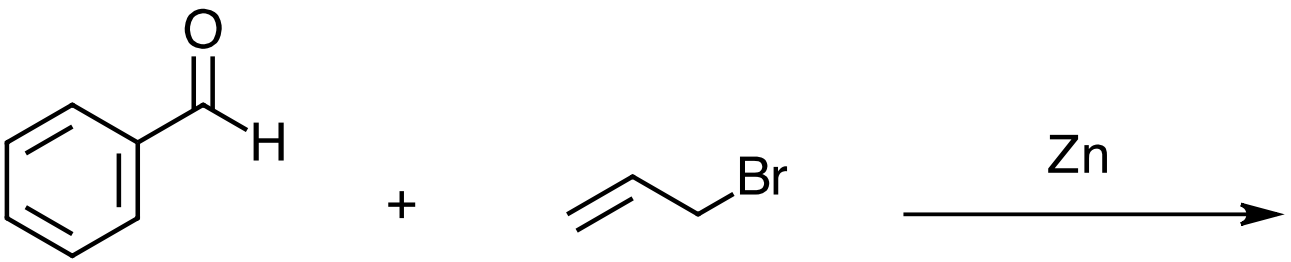
C Nucleophile = Grignard Reagent

form C-C bond to make a big molecule from a smaller molecule.

Name 2 other substances that react with RMgX.
Use curved arrows to show how each substance reacts with RMgX.



Lab 6. Grignard-like reaction

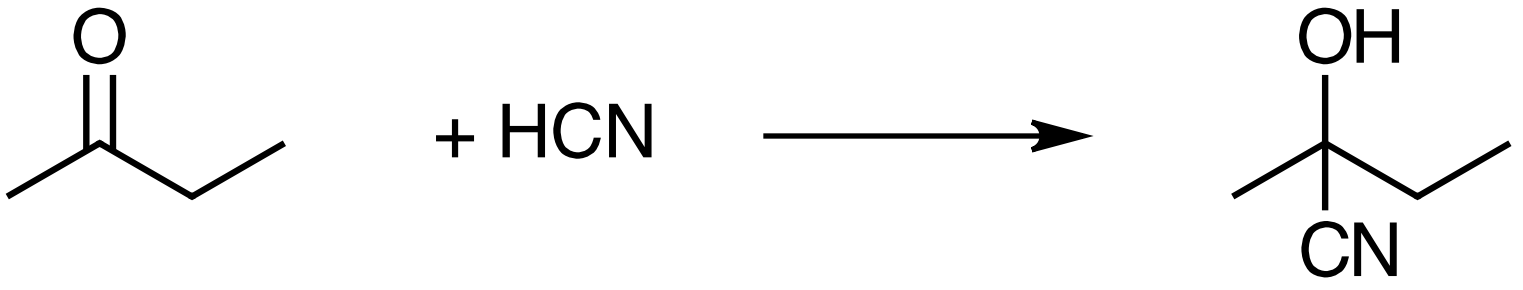


Advantage of this reaction over Grignard: can do in water.

Compare RMgX to RZnX. Which is the better $Nu:^-$?

C Nucleophile = CN^-

Cyanohydrins are found in natural products.

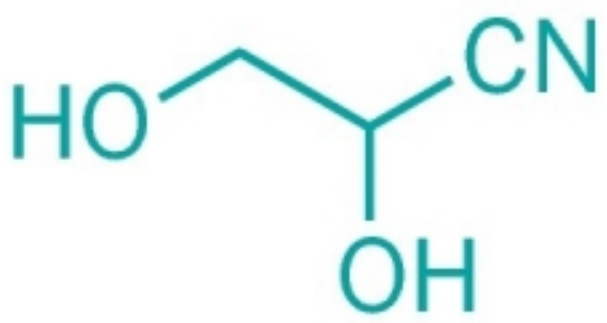


cyanohydrin

Acid conditions are need for this reaction. Explain why. (Draw resonance structure of $R_2C{=}O^+H$)

Use curved arrows to show how the cyanohydrin is formed.

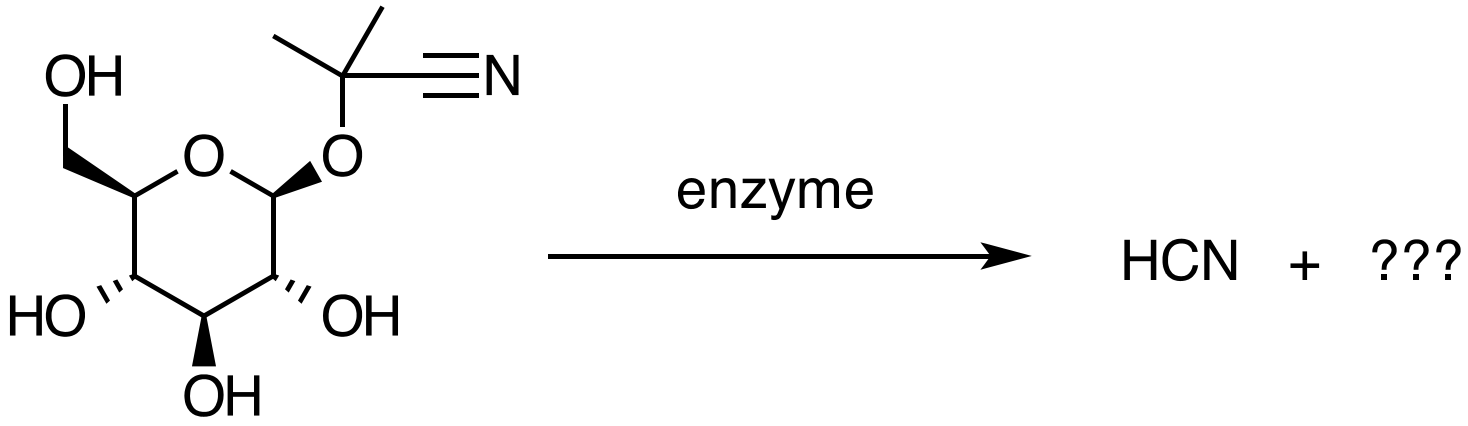
A cyanohydrin (from smoke from burning vegetation) may stimulate seed germination ==> re-grow forest after fire
http://cen.acs.org/articles/89/i26/Smoke-awakens-seeds-cyanohydrins.html



Glyceronitrile

ID reactants (what functional groups) and conditions to make glyceronitrile.
Which carbon came from the carbonyl carbon?

Cassava roots are used to make tapioca … but don't eat them raw ==> cook them!

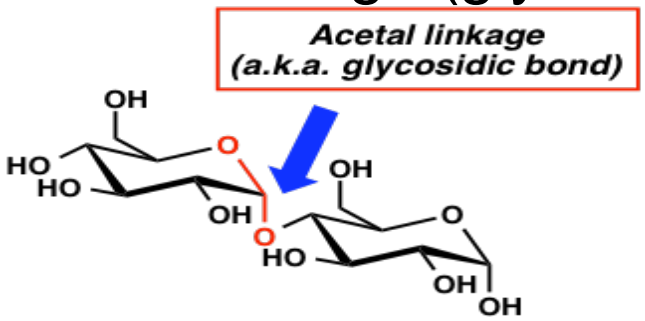


Linamarin
cyanogenic glucoside

http://www.pbs.org/wgbh/nova/body/can-i-eat-that.html
http://en.wikipedia.org/wiki/Cassava
http://en.wikipedia.org/wiki/Linamarin

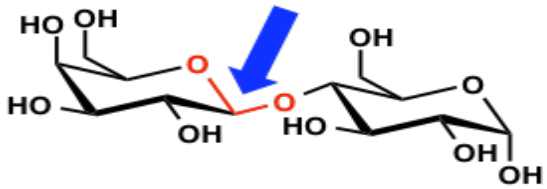
HEMIACETALS and ACETALS:

Cyclic monosaccharides form polysaccharides – connected by ACETAL linkage (glycosidic bond). LearnBacon.com



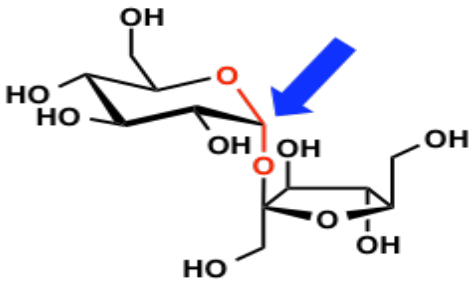
Maltose (glucose + glucose)

beer, cereal, and pasta



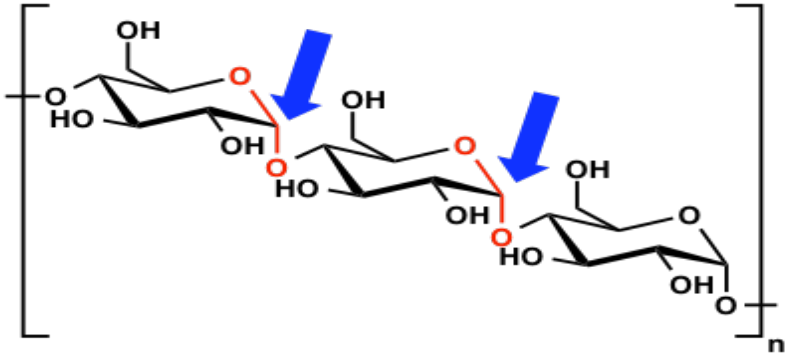
Lactose (galactose + glucose)

milk, cheese, and yogurt



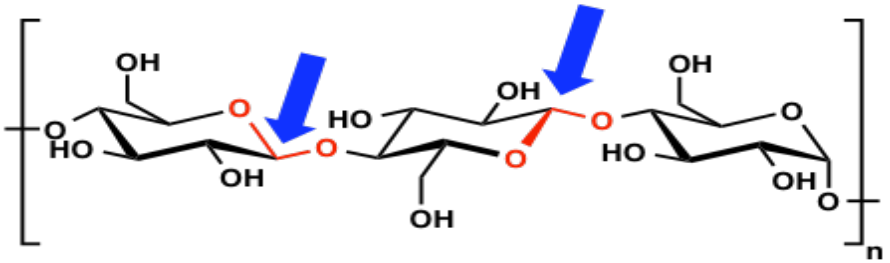
Sucrose (glucose + fructose)

table sugar and cane sugar



Starch (glucose polymer)

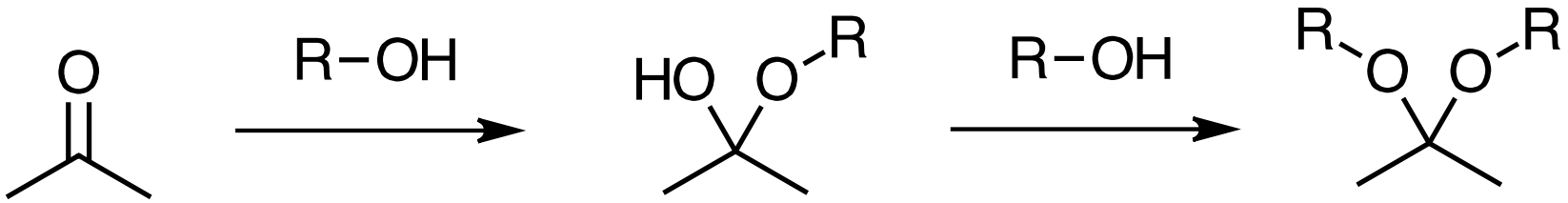
potatoes, wheat, corn and rice



Cellulose (glucose polymer)

cell wall of plants and algae

O Nucleophile - Hemiacetal and Acetal Formation:



hemiacetal

acetal

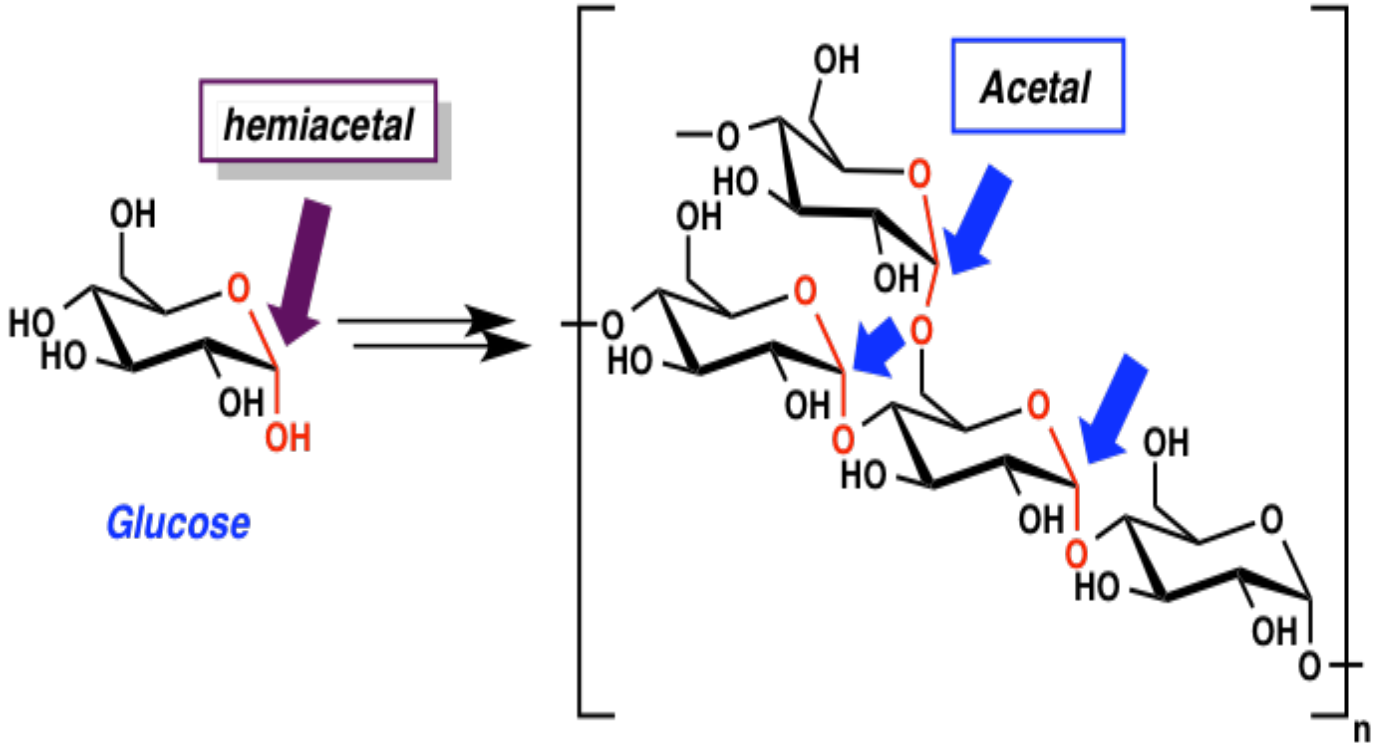
See Practice Problems:
Is ROH a strong enough $Nu:^-$ to react at carbonyl C?
If not, how can you make the carbonyl C a better E^+?

Use curved arrows to show how hemiacetal and acetal are formed.
Hint: a tetrahedral intermediate forms.

O Nucleophile - Hemiacetal and Acetal Formation:

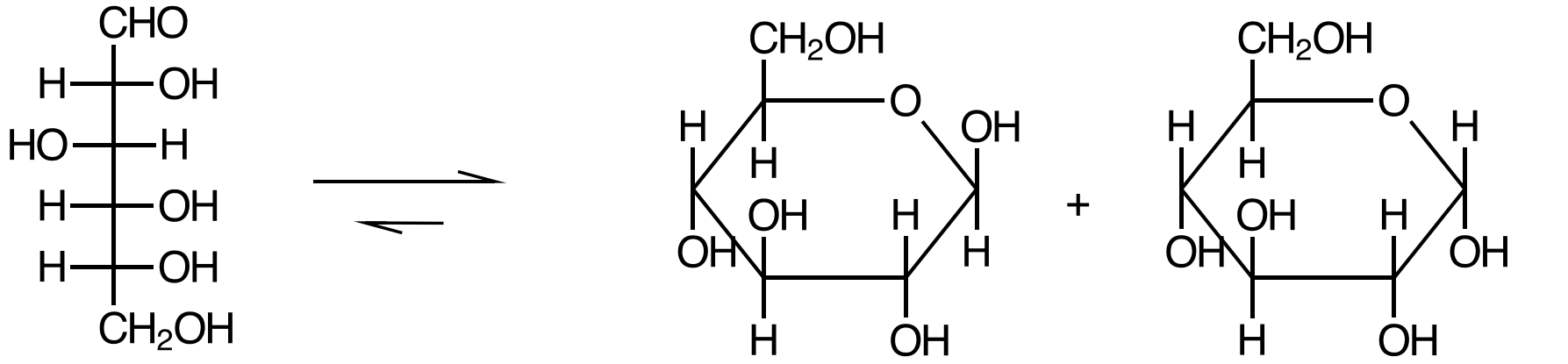
Diabetes – insulin is a peptide hormone that regulates blood glucose levels and signals the uptake of glucose from our blood into our cells.

Glucose can be converted to polysaccharides called glycogens (energy storage molecules) using consecutive ACETAL formation reactions. LearnBacon.com



Foods that increase glycogen levels

Biology: Carbohydrates form rings with *hemiacetal* group.
D-glucose exists as an open chain (trace) or closed ring (most).

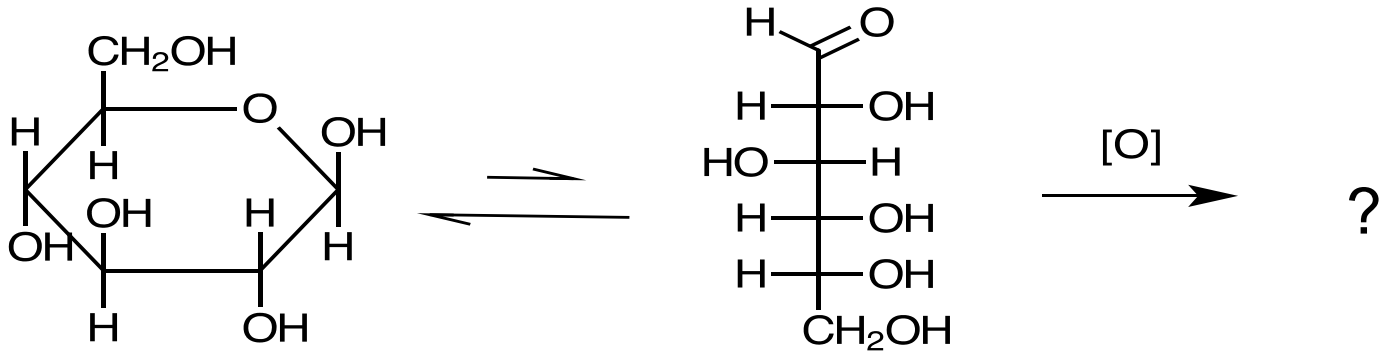


D-glucose β-D-glucopyranose α-D-glucopyranose

1. Show how the chain form of glucose is converted to the ring (pyranose ring = 6 membered ring with 5 carbons and 1 oxygen).
2. Are the rings enantiomers or diastereomers?
3. Which ring is more stable? Give reasons.
4. Which carbon is the *anomeric* carbon?

Reducing Sugars reduce Oxidizing Agents

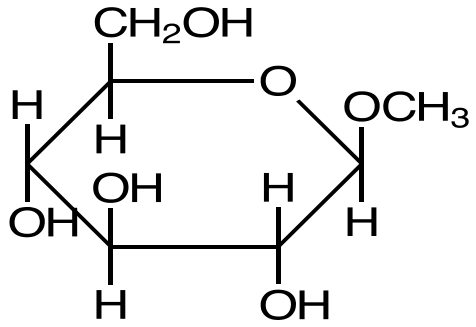
Tollens' reagent (Ag^+ in NH_3 (aq)), Fehlings' reagent (Cu^{2+} in sodium tartrate), Benedict's reagent (Cu^{2+} in sodium citrate) are used to test for Reducing Sugars



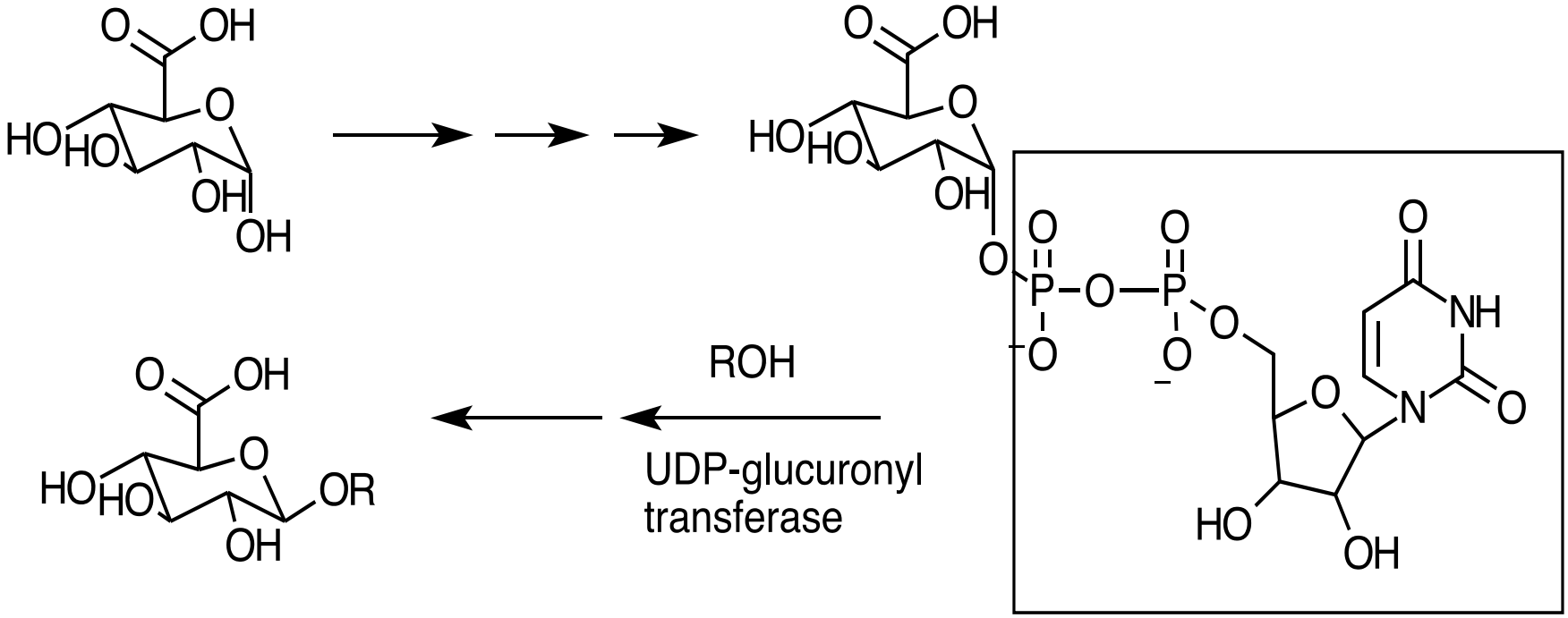
Reducing Sugars contain ***aldehyde*** or ***ketone*** group in ***chain.***

Or ***hemiacetal*** group in ***ring.***

Acetal group in ring (**glycosides**) do **not** reduce oxidizing agents.



A common drug metabolic pathway is *glucuronidation*.
Drug contains -OH group and forms *glycoside* (metabolite).
Insufficient Glycoside Formation may cause disease (Crigler-Najjar syndrome , Gilbert's syndrome, gray baby syndrome).



UDP
(uridine-5'-diphospho-a-D-glucuronic acid)

Which substance is the glycoside?
What is the reaction type?
Why use UDP?

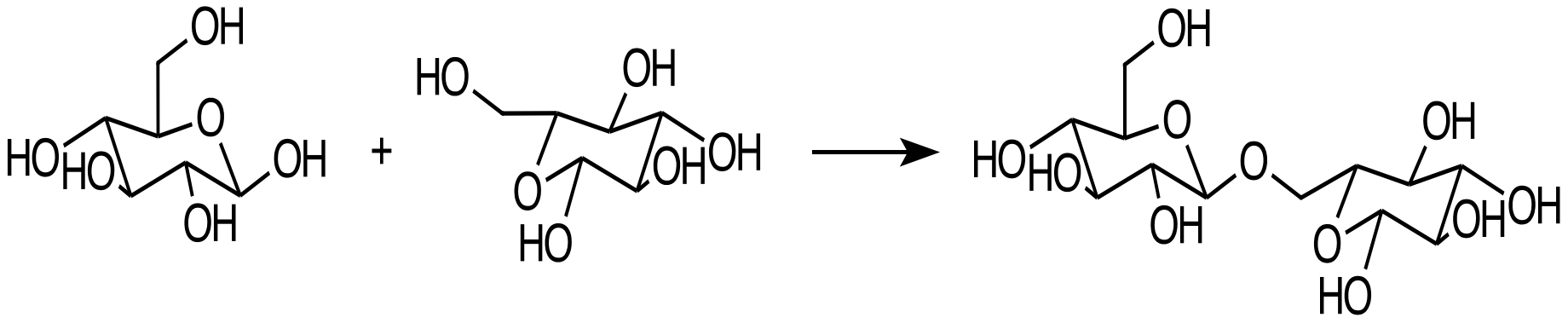
Reference: D. Klein, "Organic Chemistry", 2012, p. 595, 1156.

ROH --> ROR

Glucose + ROH --> Glycoside (cyclic acetal)

Glucose (-OH) + Glucose (-OH) --> Oligo- and Polysaccharides

Glycosidic bond = R-O-R



D-glucose D-glucose Gentibiose
found in saffron

<u>Synthetic strategy</u>:

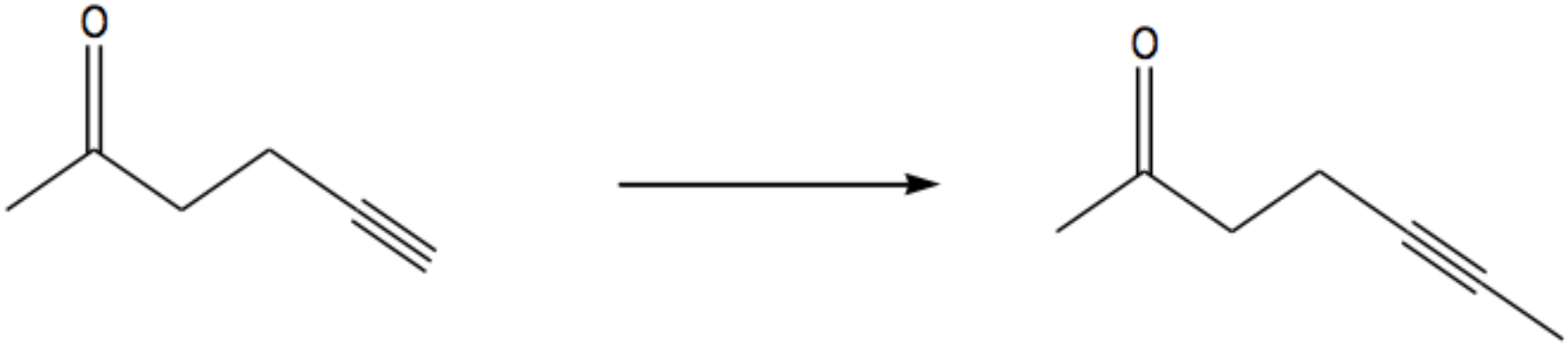
What is the reaction type?

How to react at desired -OH?

Is a better LG needed?

Acetals are Unreactive Ethers and are used as Protecting Groups

How would you accomplish the following synthesis? **(work backwards)**



ID functional group(s).	C=O	alkyne
How does each group react?	$Nu:^-$ addn	E^+ addn, acid-base

Compare reactant (starting material) to product (target compound).

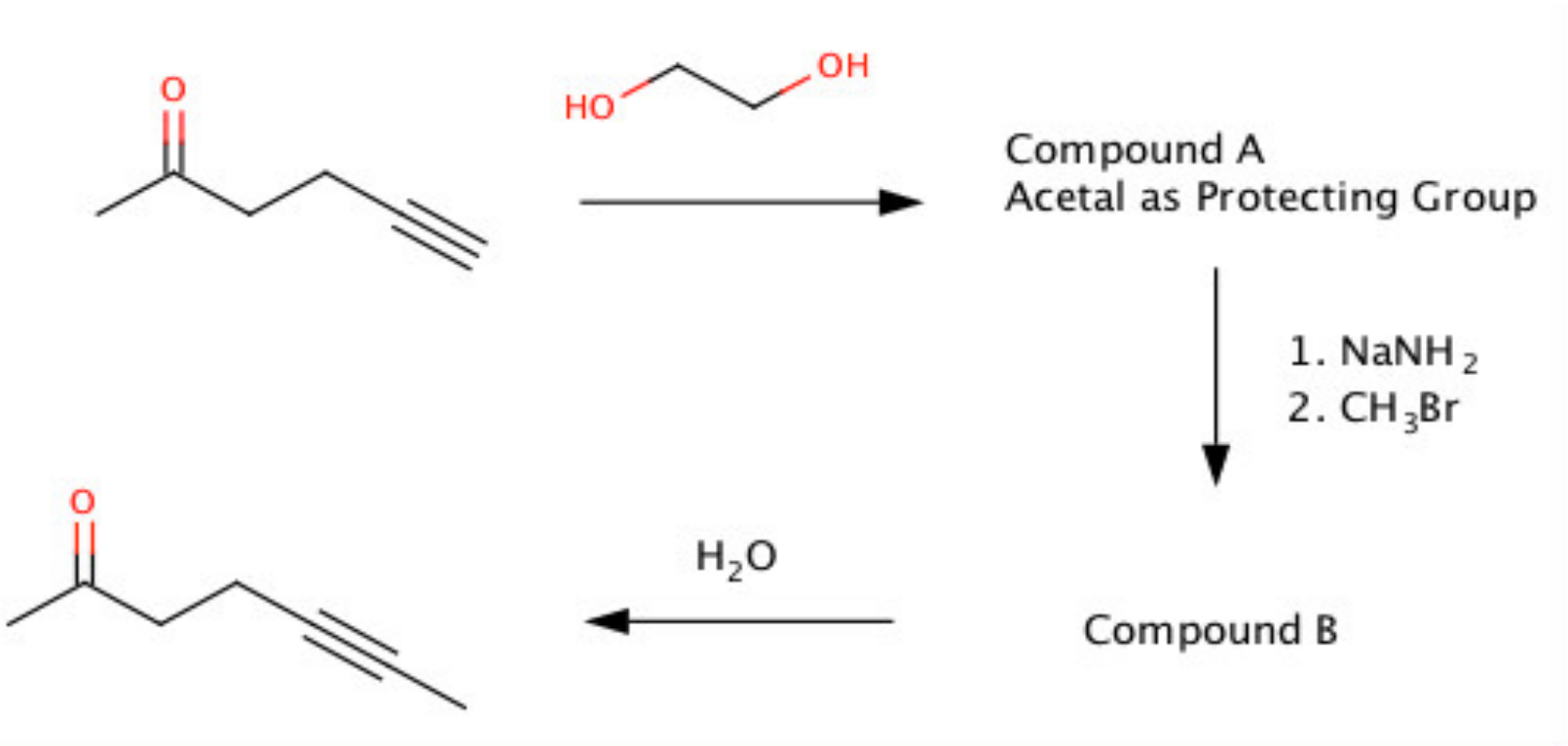
How are they the same? Same functional groups.

Different? Add 1 C to alkyne.

How to add 1C to alkyne? Use acetylide ion with strong base.

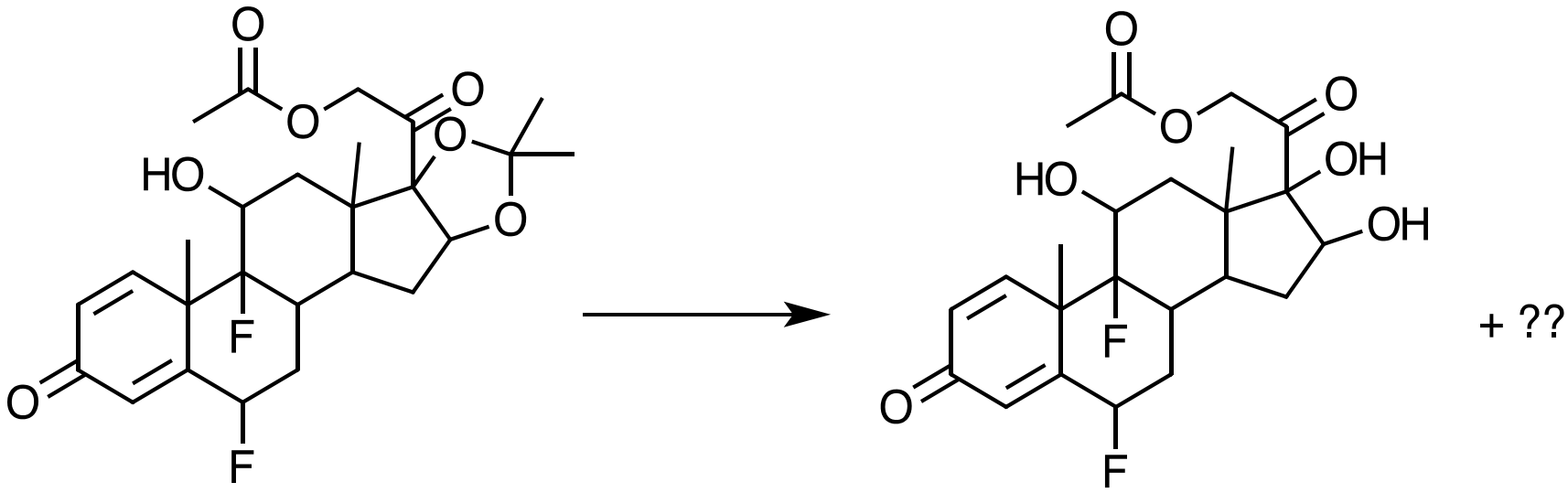
But strong base reacts with _____.

Acetals are Unreactive Ethers and are used as Protecting Groups



Fluocinonide treats skin conditions, e.g., eczema
And is a Prodrug
And is an Acetal

Klein, "Organic Chemistry," p. 930 (1st ed.), p. 946 (2nd ed.)



Fluocinonide
Prodrug

Active Drug

Where is the acetal?
What conditions convert
the prodrug to active drug?

What is the other product?