

Objective 15. Develop synthesis strategies for organic synthesis.

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:

Starting material --> target compound.

Count # of C's – bigger or smaller compound.

ID functional groups in starting material and target compound.

What part(s) of the starting material and target compound are the same?

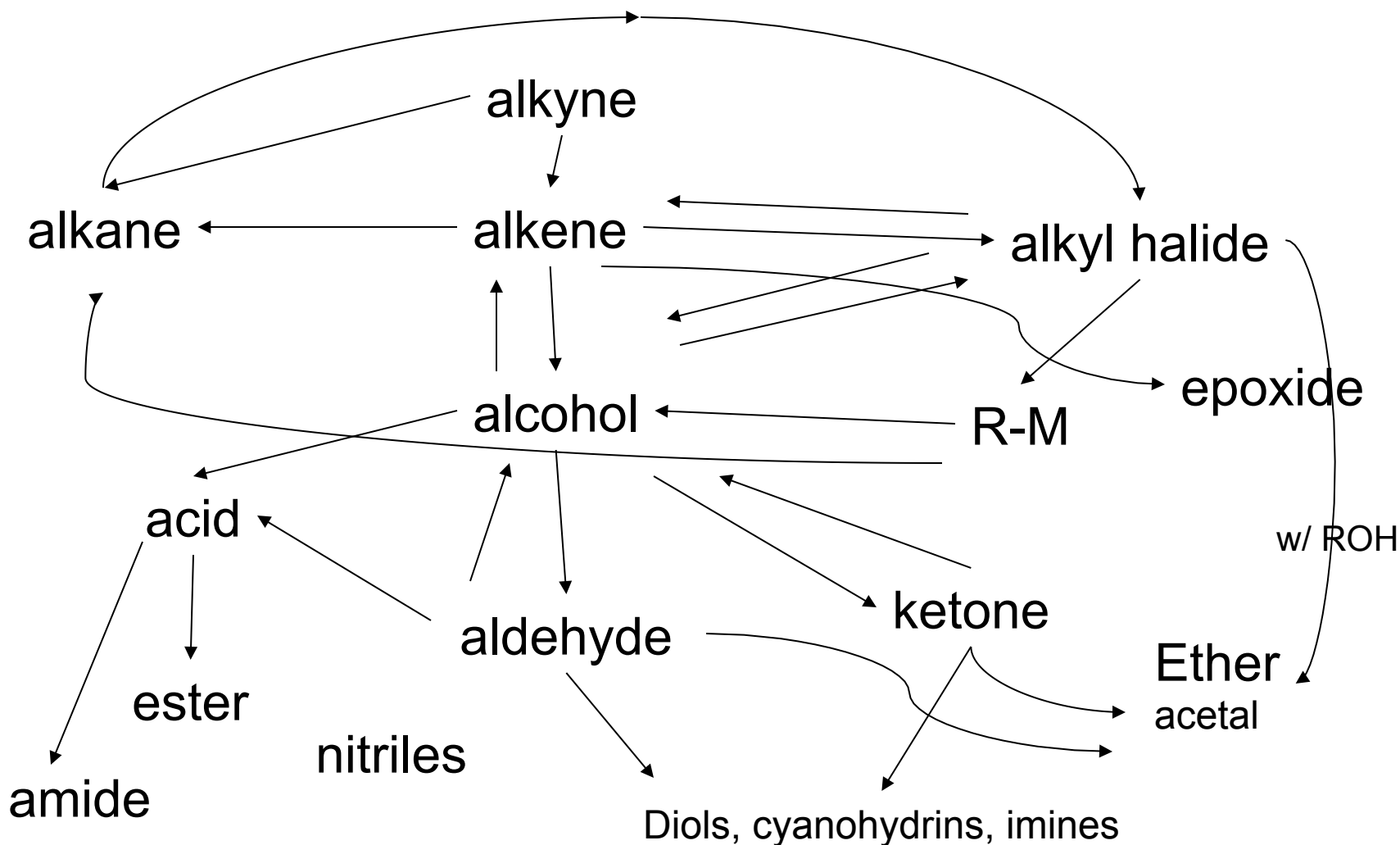
ID bonds that break/form.

Brainstorm possible reactions.

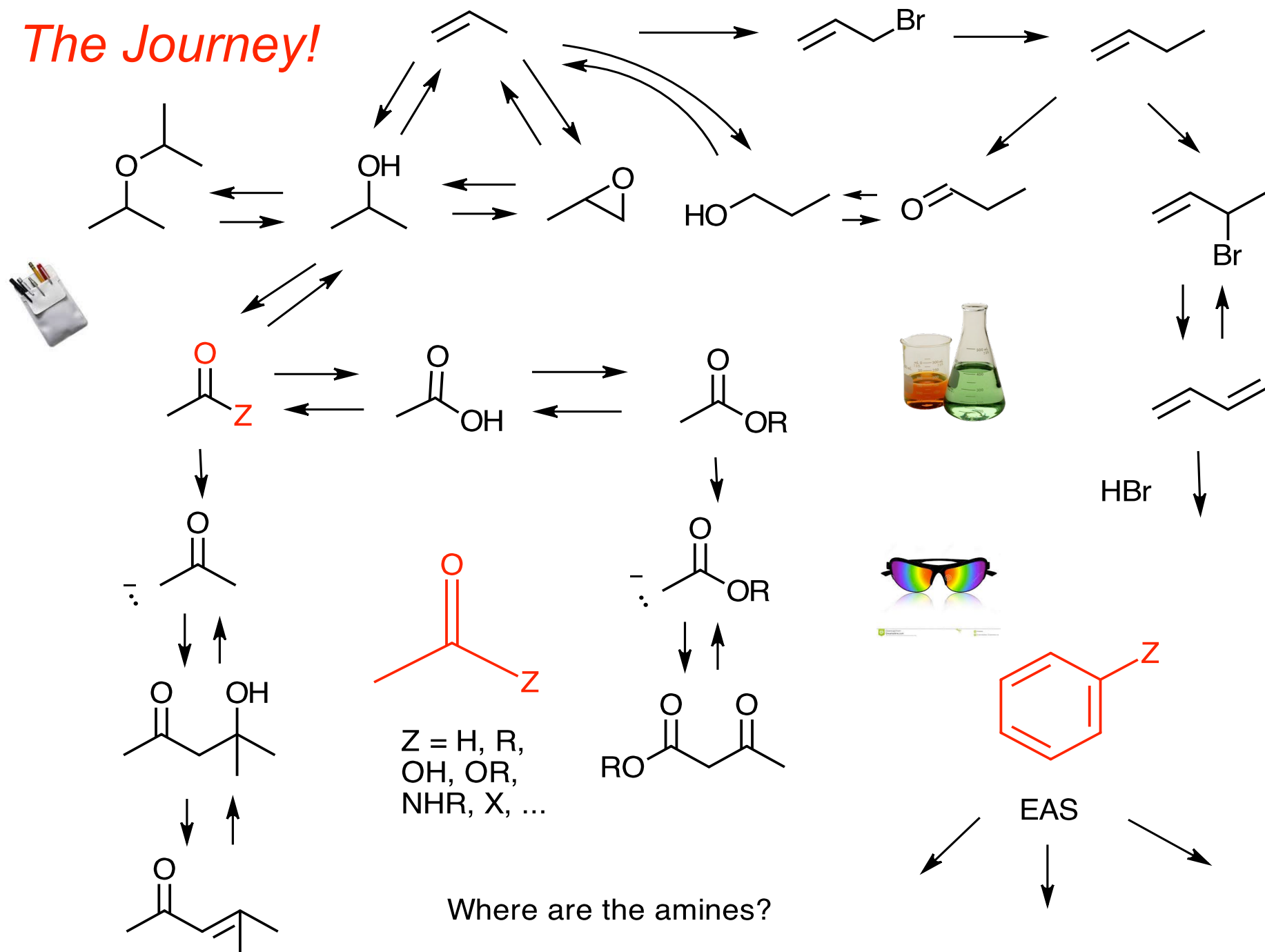
Reaction Roadmap: Which groups has an α -C? (2 types of α -C)

What are β -keto acids/esters used for?

What group makes α,β -unsaturated carbonyls?



The Journey!



ORGANIC SYNTHESIS STRATEGIES

- Convert one functional group to another
- Move a Functional Group from 1 C to adjacent C
- Make a C-C bond to make a bigger molecule
- Break a C-C bond to make a smaller molecule

How? See Structural Features → Tells you Reaction Type

Structural Features tell us:

- Which atom or bond reacts
- Reaction Type
- How to make a Compound

C=C pi bond (including conjugated diene and aromatic)

C-O, C-X, C-N compounds: α carbon, leaving group (HOH, ROH, NH_3 , X^-), H bonded to β carbon, epoxide

C=O compounds: carbonyl carbon, carbonyl oxygen, α carbon (C next to carbonyl C), β carbon

TWO structural features:

β -hydroxy aldehyde/ketone (see enolates)

α,β -unsaturated aldehyde/ketone (see enolates)

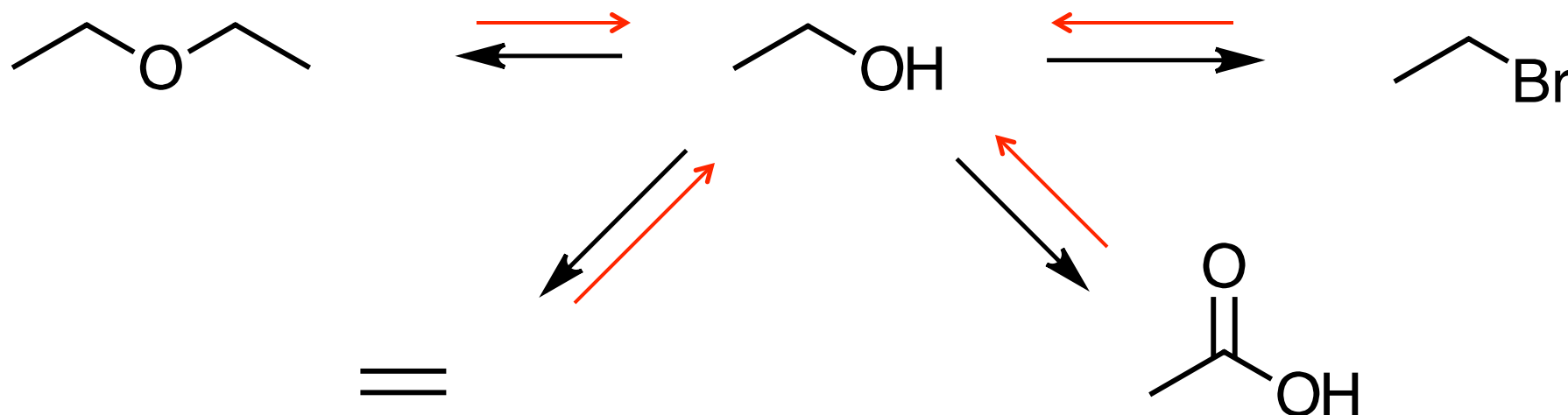
β -keto ester (see ester enolates)

| Structural Features | Reaction Type | Product |
|---|--------------------------------|-------------------------|
| Acid H (see pK table) Base (see pK table) | Acid-Base | Base Acid |
| α carbon, LG Reacts with Nu: ⁻ | Nucleophilic Substitution | ROH, RX, etc |
| Carbonyl C on Acid or Acid Derivative LG | Nucleophilic Acyl Substitution | Acid or Acid Derivative |
| Aromatic | EAS | Mono-, polysub aromatic |
| α carbon, H bonded to β carbon, LG Reacts with Nu: ⁻ | Elimination | C=C bond |
| C=C pi bond Reacts with E ⁺ | Electrophilic Addition | ROH, RX, etc. |
| Carbonyl C on RCHO, RCOR | Nucleophilic Addition | Acetal, imine, etc. |

Many Organic Reactions are *Reversible*

Example: How does ethanol react?
OR How can you make ethanol?

Ethanol Structural Features: α carbon and LG \implies **Substitution**
H bonded to β carbon and LG \implies **Elimination**
Basic O and Acidic H \implies **Acid-Base**
C-O bond \implies **Oxidation**

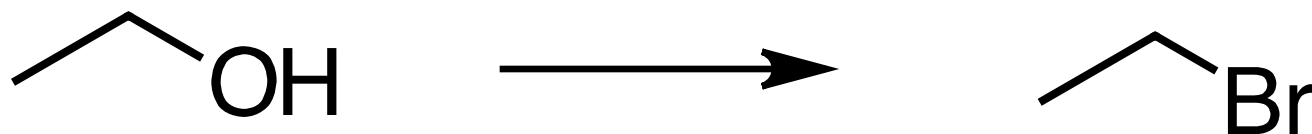


Several Ways Ethanol Reacts \rightarrow Several Ways to Make Ethanol

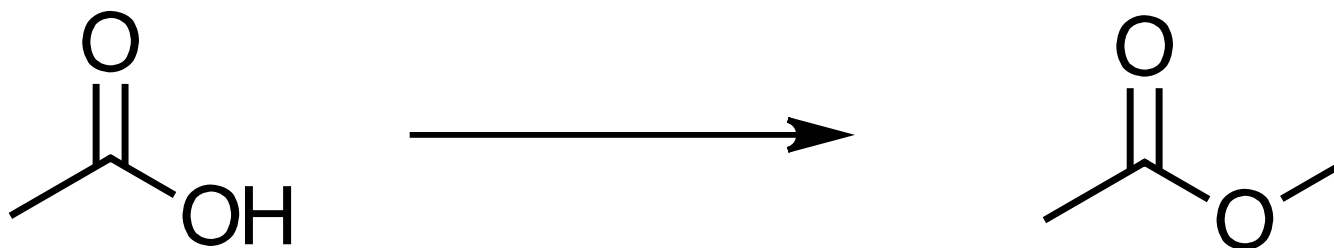
ORGANIC SYNTHESIS STRATEGIES

How? See Structural Features → Tells you Reaction Type

Convert One Functional Group To Another



Structural Features: α carbon and LG ==> Substitution

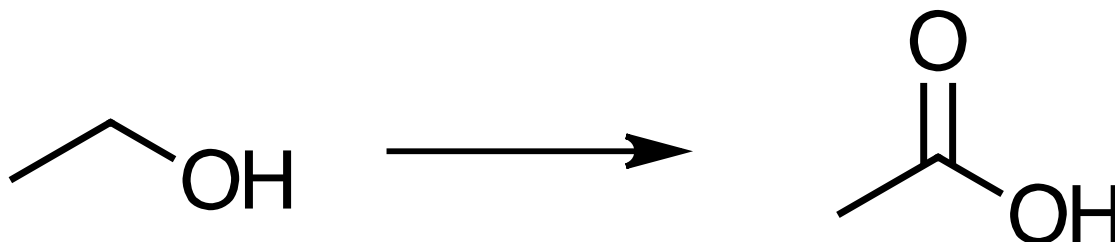


Structural Features: carbonyl C, LG ==> Substitution (acyl)

ORGANIC SYNTHESIS STRATEGIES

How? See Structural Features → Tells you Reaction Type

Convert One Functional Group To Another

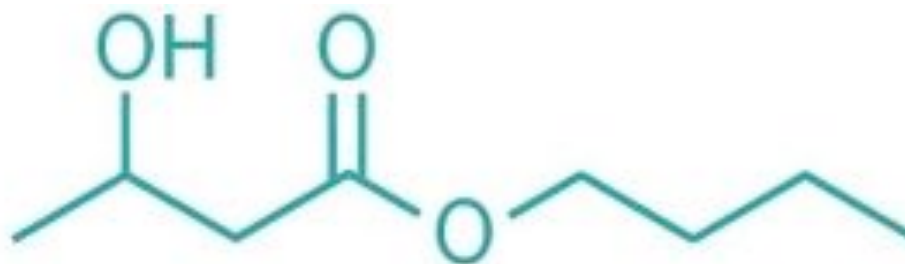


Structural Features: C-O bond to C=O, C=O ==> Oxidation

C&EN, 6/2/14, p. 24 (<http://cen.acs.org/articles/92/i23/Cleaning-Conundrum.html>)
Eastman Chemical Invents a **New Cleaning Solvent** for household and industrial cleaning products that meets the EPA standards for toxicity and VOC content.

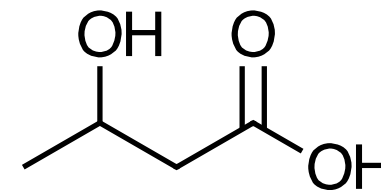
Trade Name:

Omnia



Butyl 3-hydroxybutyrate

Propose an efficient synthesis of Omnia from

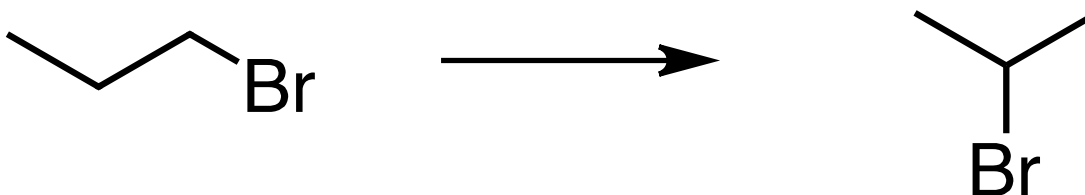


Replaces: ethylene glycol monobutyl ether (CA hazardous substance)
dipropylene glycol monomethyl ether (VOC)

ORGANIC SYNTHESIS STRATEGIES

How? See Structural Features → Tells you Reaction Type

Move a Functional Group from 1 C to adjacent C



Structural Features:

α C and LG → Sub

H on β C and LG → Elim

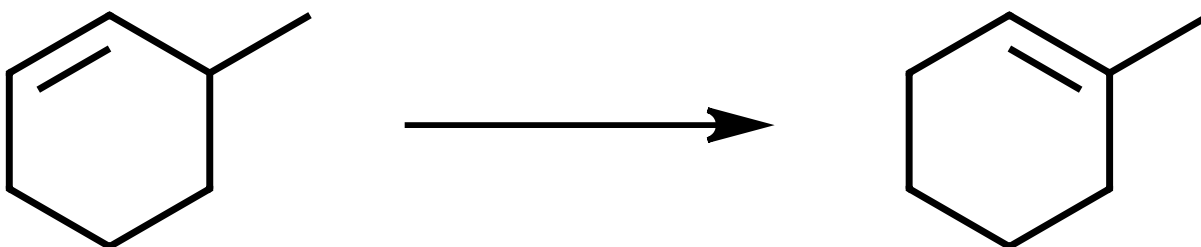
RBr → make by Sub

RBr → make by Addition

ORGANIC SYNTHESIS STRATEGIES

How? See Structural Features → Tells you Reaction Type

Move a Functional Group from 1 C to adjacent C



Structural Features:

C=C pi bond → Addition

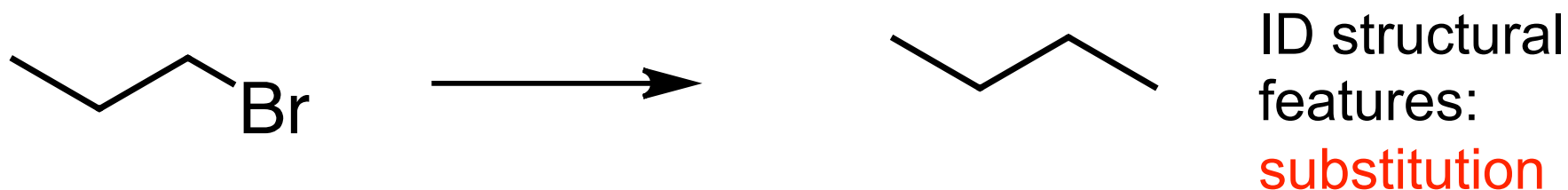
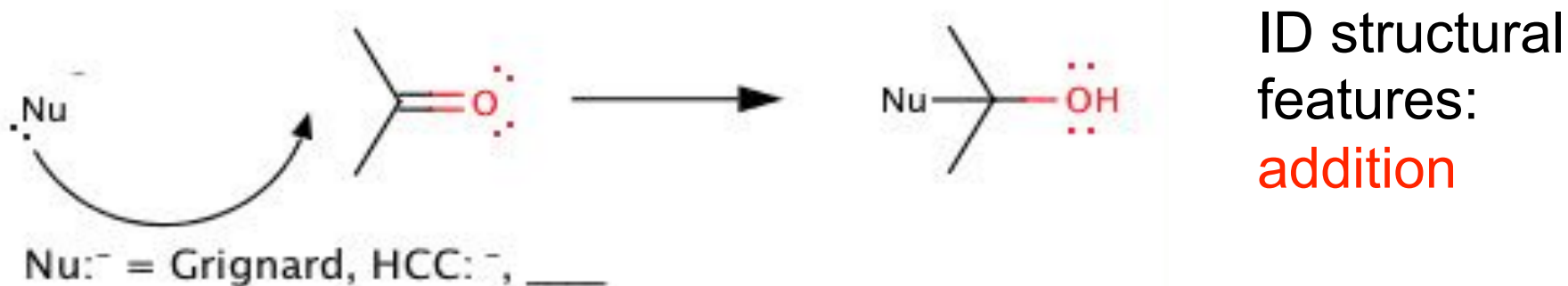
C=C pi bond → make by Elim

ORGANIC SYNTHESIS STRATEGIES

How? See Structural Features → Tells you Reaction Type

Make a C-C bond to make a bigger molecule

Use a carbon nucleophile and a carbon electrophile



Which C is electrophilic?

Which carbon nucleophile to use?

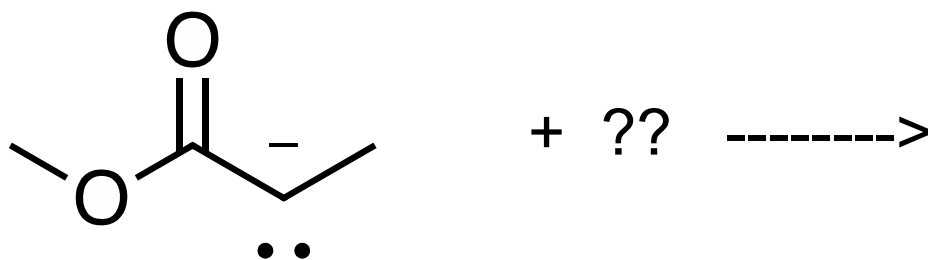
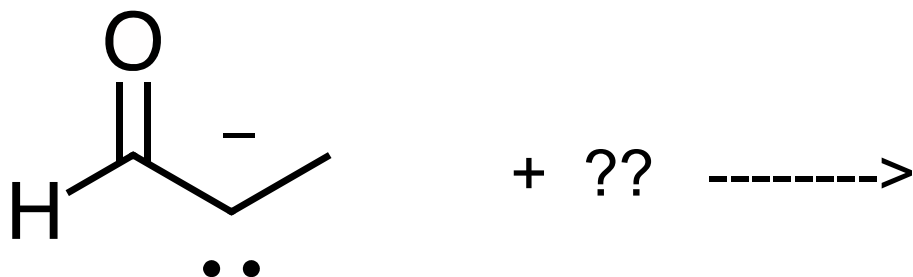
RMgX, CN⁻, acetylide ion, enolate or ester enolate

Compare C-C bond making methods:

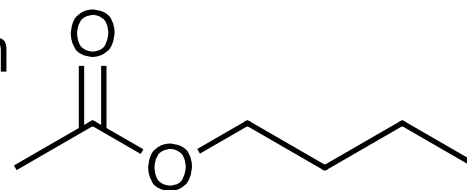
1. Grignard (to make ROH)
2. Acetylide ion (alkyne \rightarrow other functional groups)
3. CN substitution (to make nitrile \rightarrow convert to acid)
4. Enolate ion (Aldol, Claisen, RX, malonic ester, acetoacetic ester)

Note: Aldol and Claisen reactions form a C-C bond

What *else* can an enolate or ester enolate ion react with?

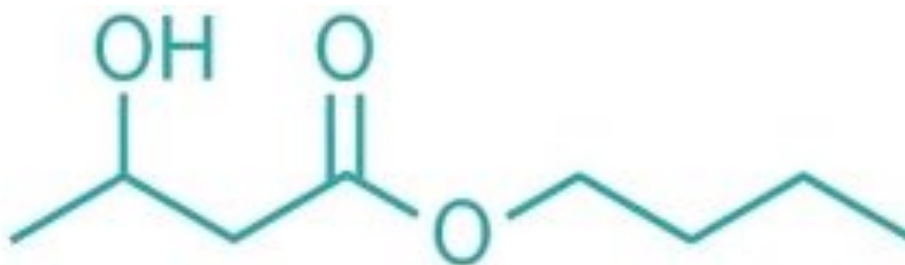


Propose an efficient synthesis of Omnia from



Trade Name:

Omnia



Butyl 3-hydroxybutyrate

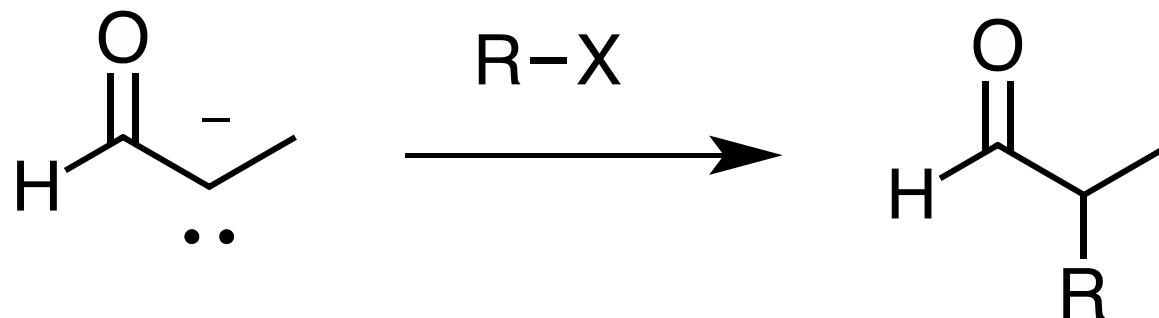
Structural Features: carbonyl C and carbonyl O (ester)

H on α C

OH on β C (β -hydroxy ester, not a β -keto ester)

O-H group: O is basic, H is acidic

Use Enolate in Nu:- substitution reaction



Problems with this method:

1. Elimination competes with substitution
2. Poor yield

Is there a Better way?

(Klein, "Organic Chemistry", p. 1063)

Objective: use malonic ester synthesis and acetoacetic ester synthesis to make a C-C bond α to carbonyl C

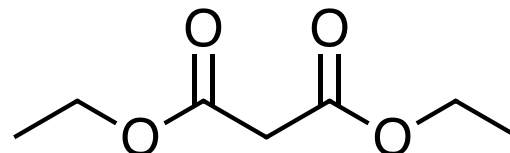
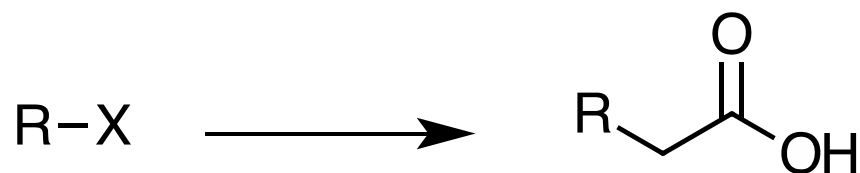
Malonic ester synthesis:

Lengthen chain by **2** carbons

Use diethyl malonate

Remove α -H to form enolate

Enolate = Nu:⁻

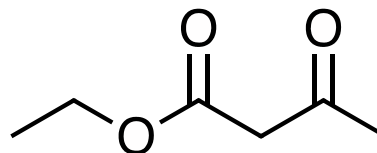
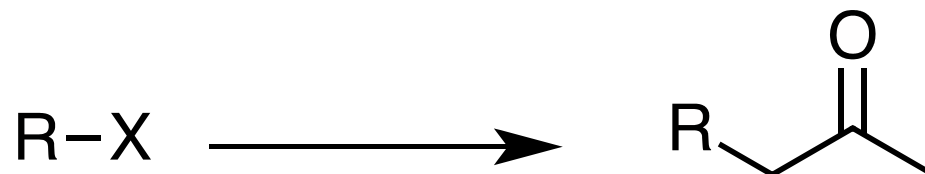


Acetoacetic ester synthesis:

Lengthen chain by **3** carbons

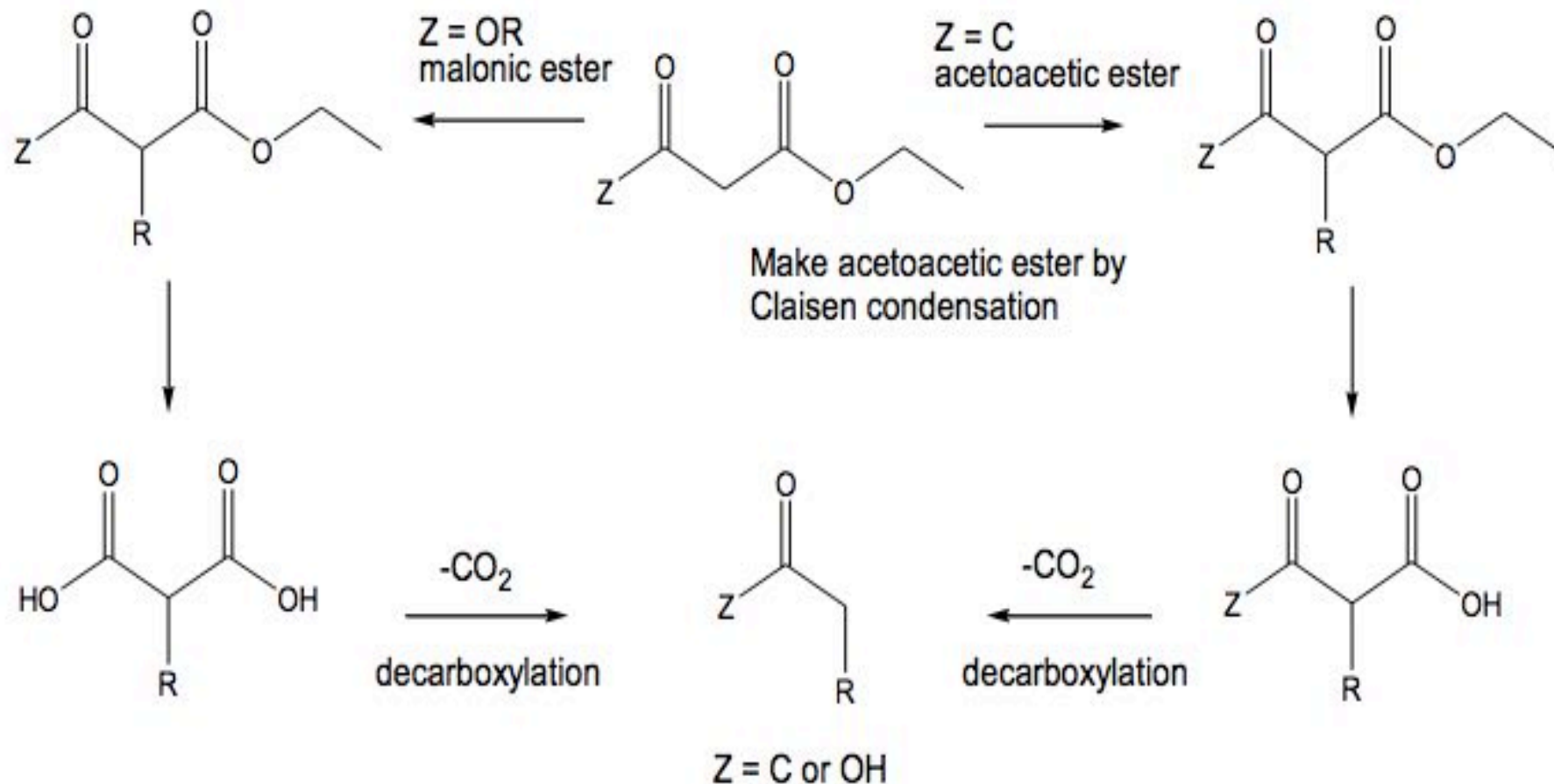
Use ethyl acetoacetate

Remove α -H to form enolate



Alkylate the α -carbon in an aldehyde/ketone: Use **Acetoacetic Ester**.

Alkylate α -carbon in an organic acid: Use **Malonic Ester**.

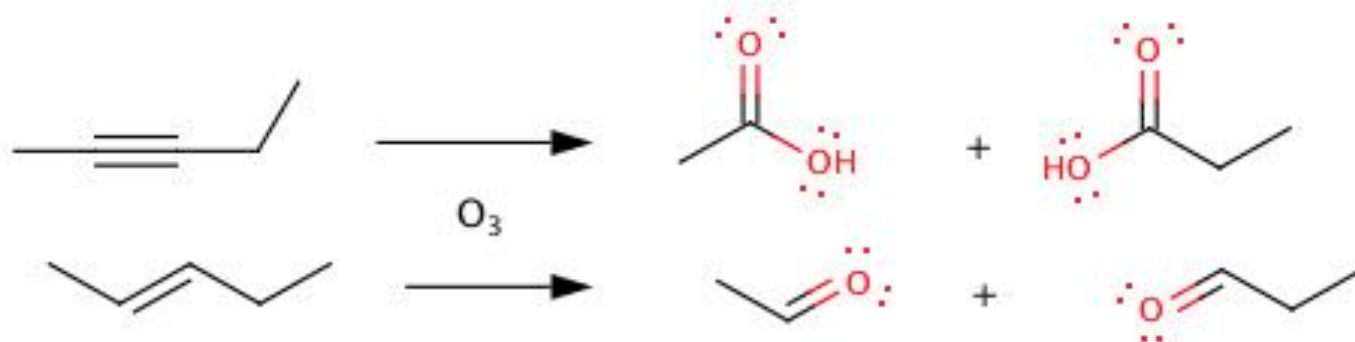


Decarboxylation Reactions Are Important in Biology

Other ORGANIC SYNTHESIS STRATEGIES

Shorten (Break C-C bond) a carbon chain:

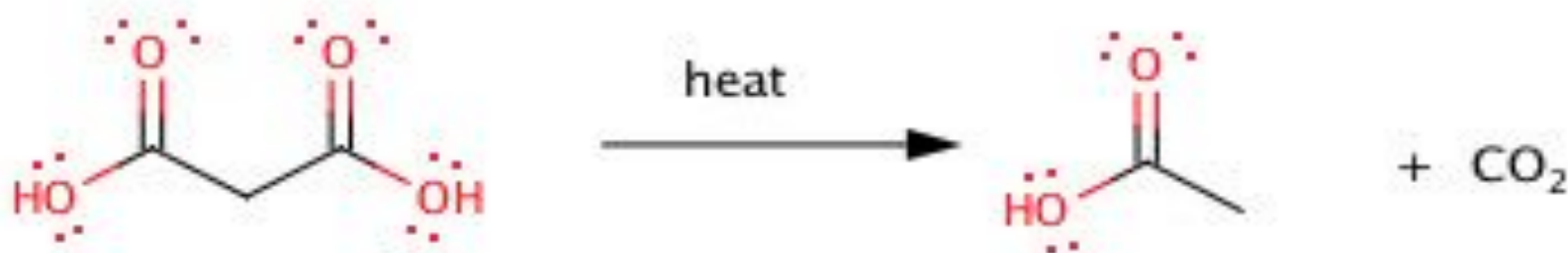
1. ozonolysis



2. Decarboxylation Reaction

Dicarboxylic acid (with 1 C between $-COOH$) -- heat --> acid + CO_2

E.g., Malonic acid (propanedioic acid) decarboxylation:



Which bond breaks?

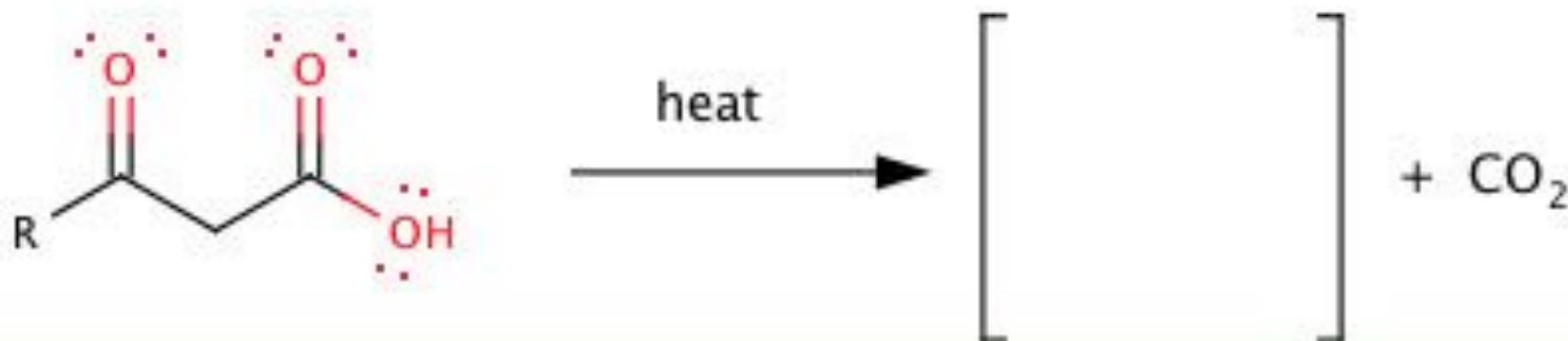
Other ORGANIC SYNTHESIS STRATEGIES

Shorten (Break C-C bond) a carbon chain:

2. Break a C-C bond by **decarboxylation of**

a. dicarboxylic acid

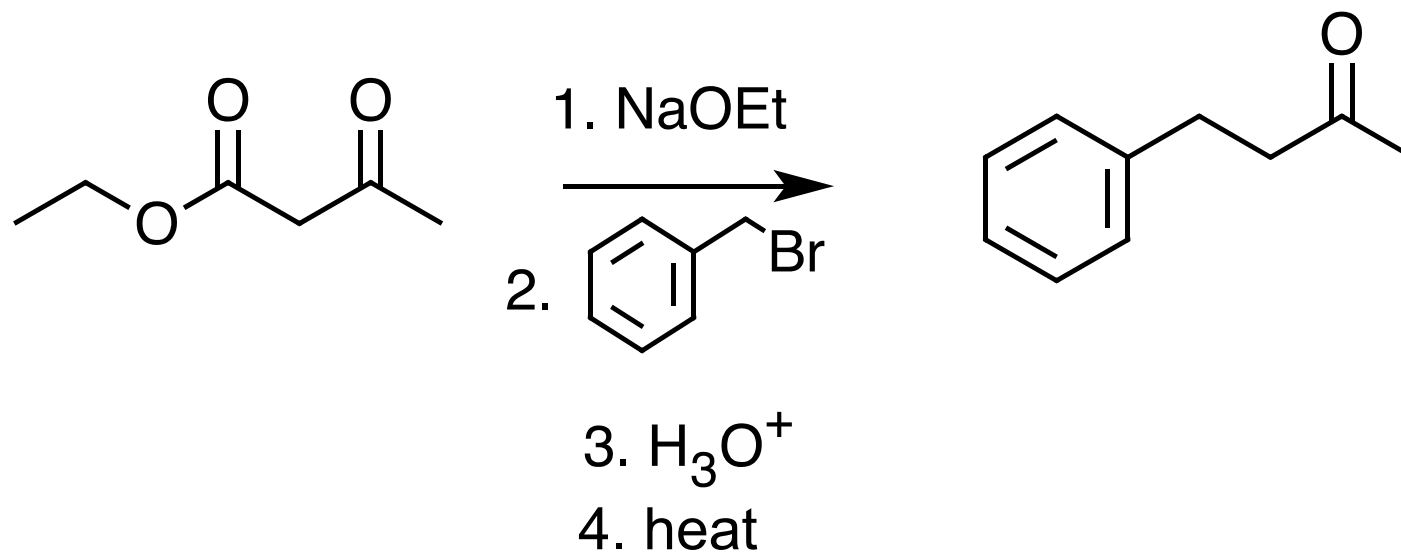
b. **β -keto acid** -- heat --> CO_2 + enol ----> ketone



1 C from -COOH is α -C
2 C from -COOH is β -C

Draw structure of product

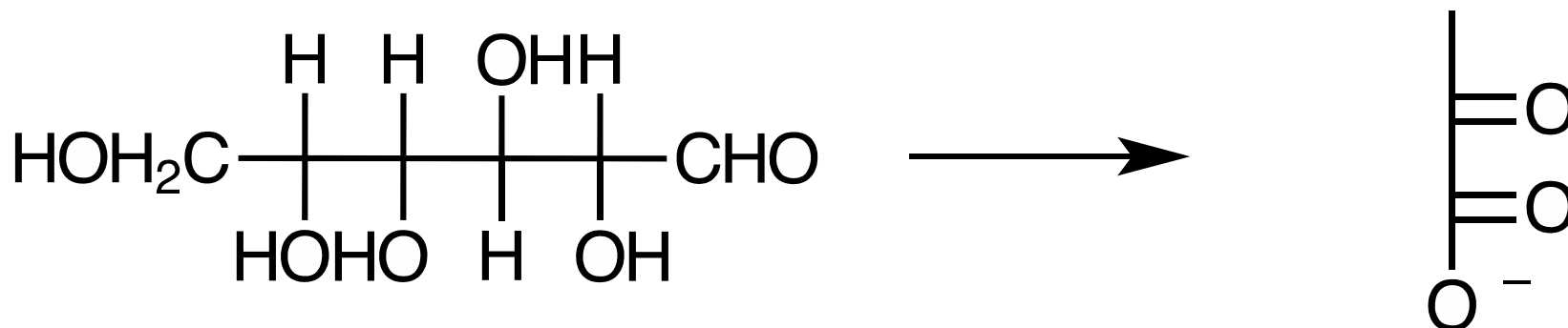
Use of Acetoacetic ester and Decarboxylation in synthesis
Draw the structure of each intermediate



Other ORGANIC SYNTHESIS STRATEGIES

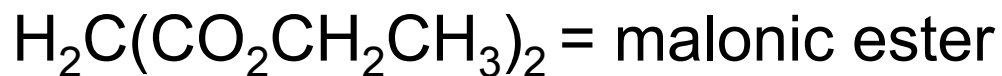
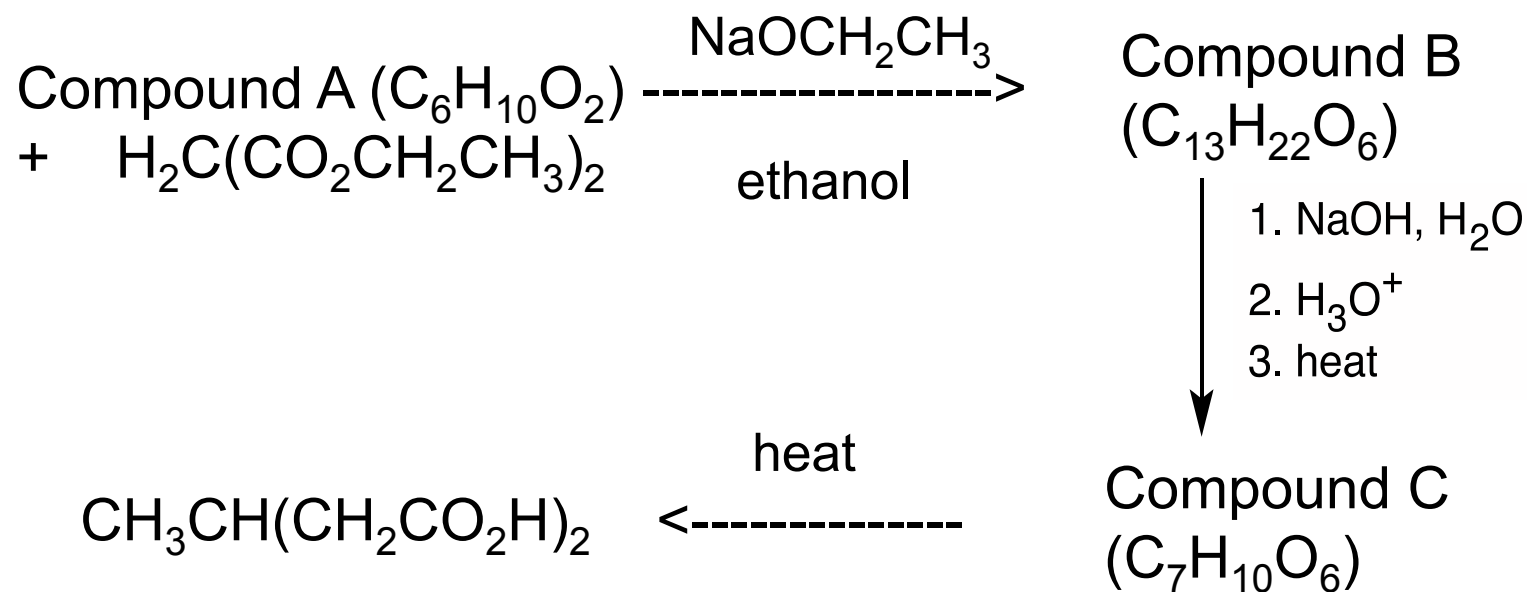
Shorten (Break C-C bond) a carbon chain:

3. **Biology**: Glucose (C_6) undergoes glycolysis to form pyruvate (C_3).
(10 steps. 4th step = reverse aldol condensation breaks C-C bond)



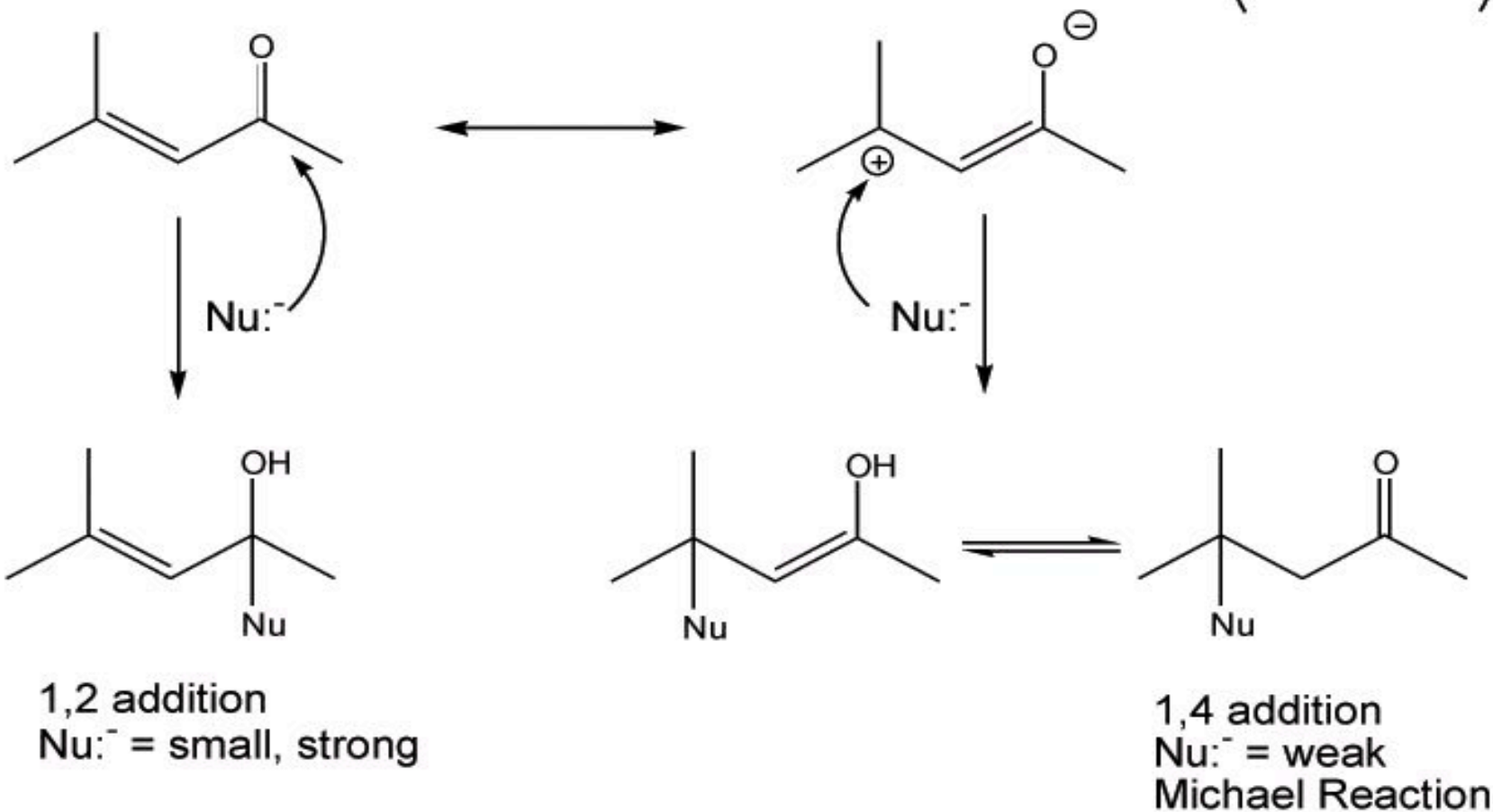
Which bond breaks?

Identify Compounds A, B, and C in the following synthetic sequence.



Conjugated dienes undergo 1,2 and 1,4 addition (Klein, Ch. 17)
 α,β -unsaturated ketones undergo 1,2 and 1,4 addition (**Michael Reaction**)

α,β -unsaturated ketone (enone) compare to conjugated dienes ()

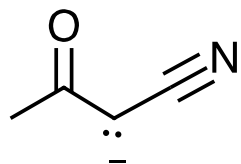
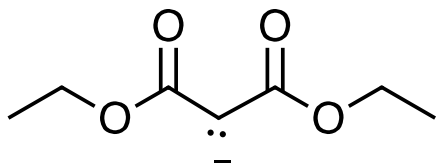
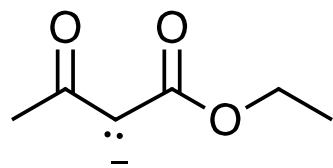
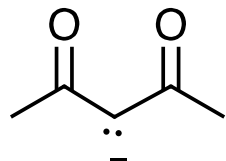


How do you make an α,β -unsaturated ketone?

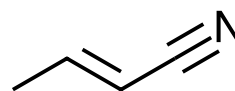
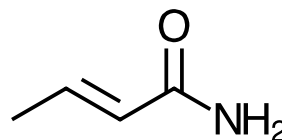
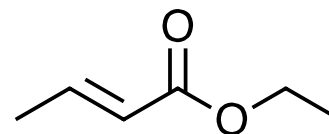
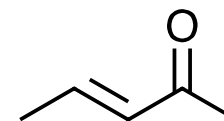
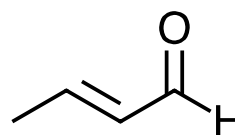
Common Michael Donors and Acceptors

(see Klein, Table 22.2, p. 1067)

Michael Donors



Michael Acceptors



R_2CuLi

($RMgX$ too strong)