Objective 13. Apply nucleophilic addition and elimination concepts to enols and enolates reactions (aldol and Claisen condensations)

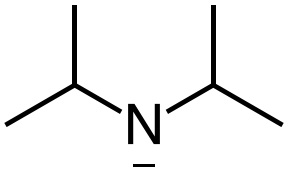
Skills: Draw structure
ID structural features and reactive sites (alpha C, beta C, LG, etc.)
ID Nu^- and E^+
use curved arrows to show bonds breaking and forming
show delocalized electrons with resonance structures.

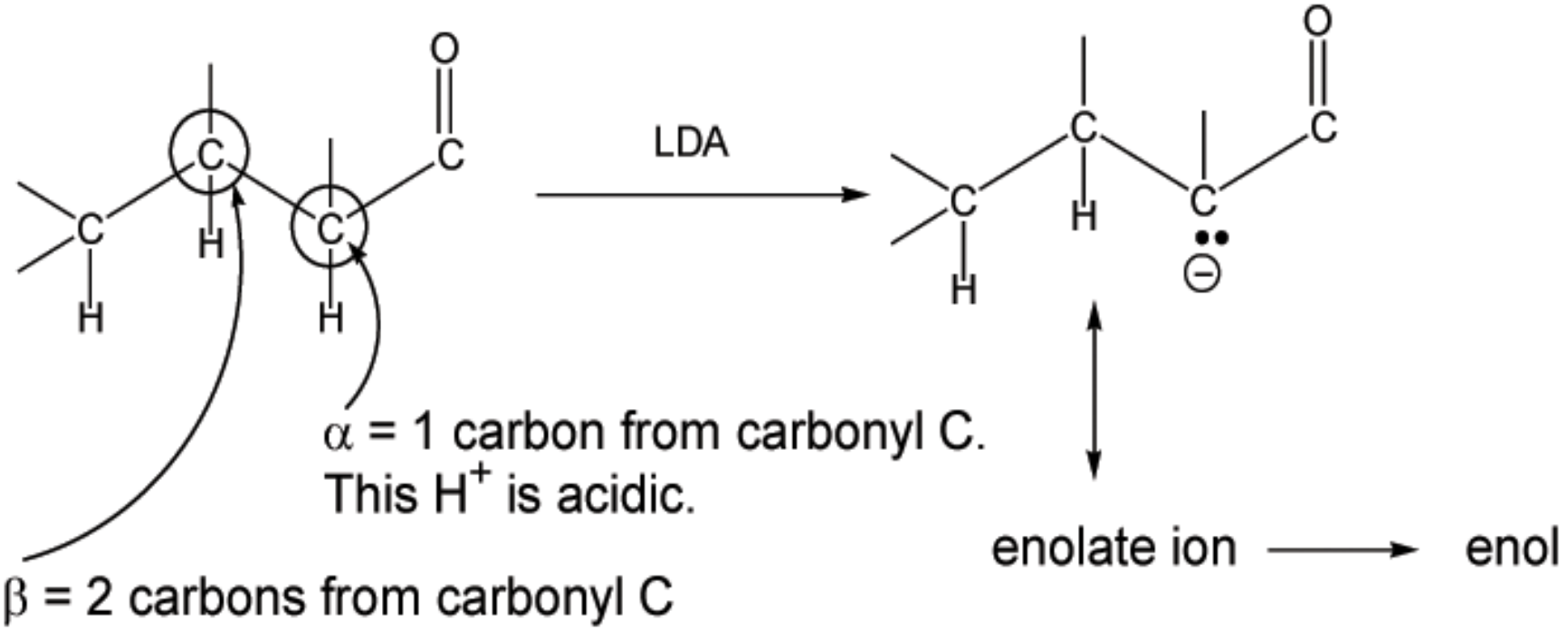
Key ideas:
new type of alpha C = C next to carbonyl C.
Enolate = Nu^- and can react like any other Nu^-.
E.g., substitution, Nu addition.

Nu:$^-$ react at Carbonyl Carbon

But a *large*, *strong* Nu:$^-$ reacts at **H bonded to α-C** = ***NEW REACTIVE SITE***.

Large, strong Nu:$^-$ = LDA (lithium diisopropyl amide)





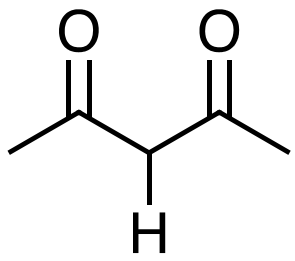
Draw the structure of the enolate ion.

What reacts with this ion?

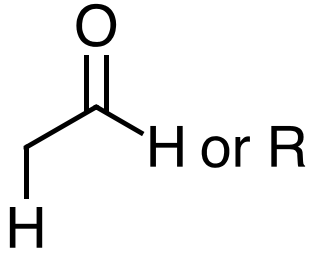
LDA is a strong base like NH_2^-. (pK_a Table: pK_a = 36 for each conjugate acid)

Table 20.1 pKa Values of Some Aldehydes, Ketones, and Esters

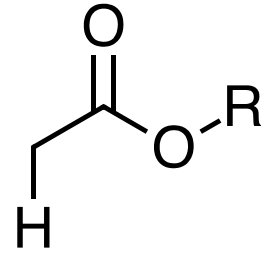
(Carey, 8th ed., p. 868)



pK_a = 9-13



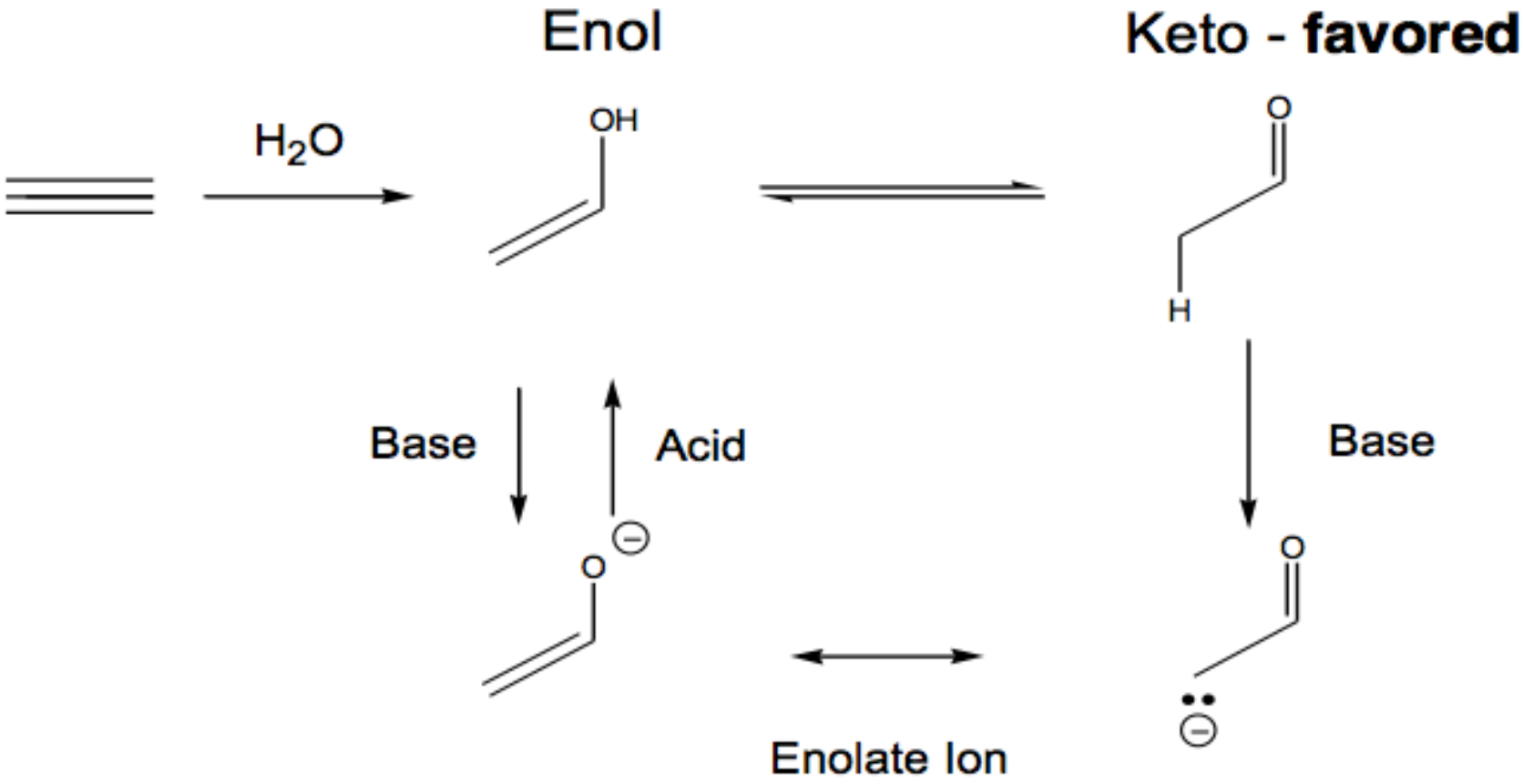
pK_a = 16-20



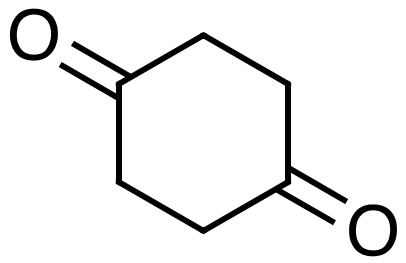
pK_a > 20

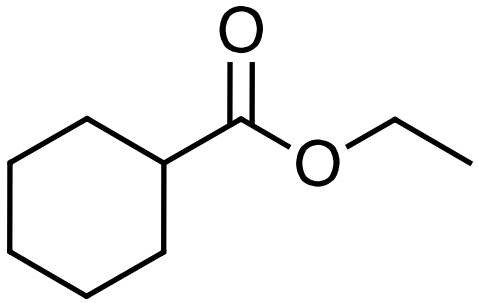
Rank the acidity from strongest to weakest.
Draw the structure of each conjugate base.
Why is the strongest acid the strongest?

We’ve seen the enolate ion before.
In keto-enol equilbrium, the KETO is favored.
So …, when you see an enol, you see <u>more</u> of the keto.



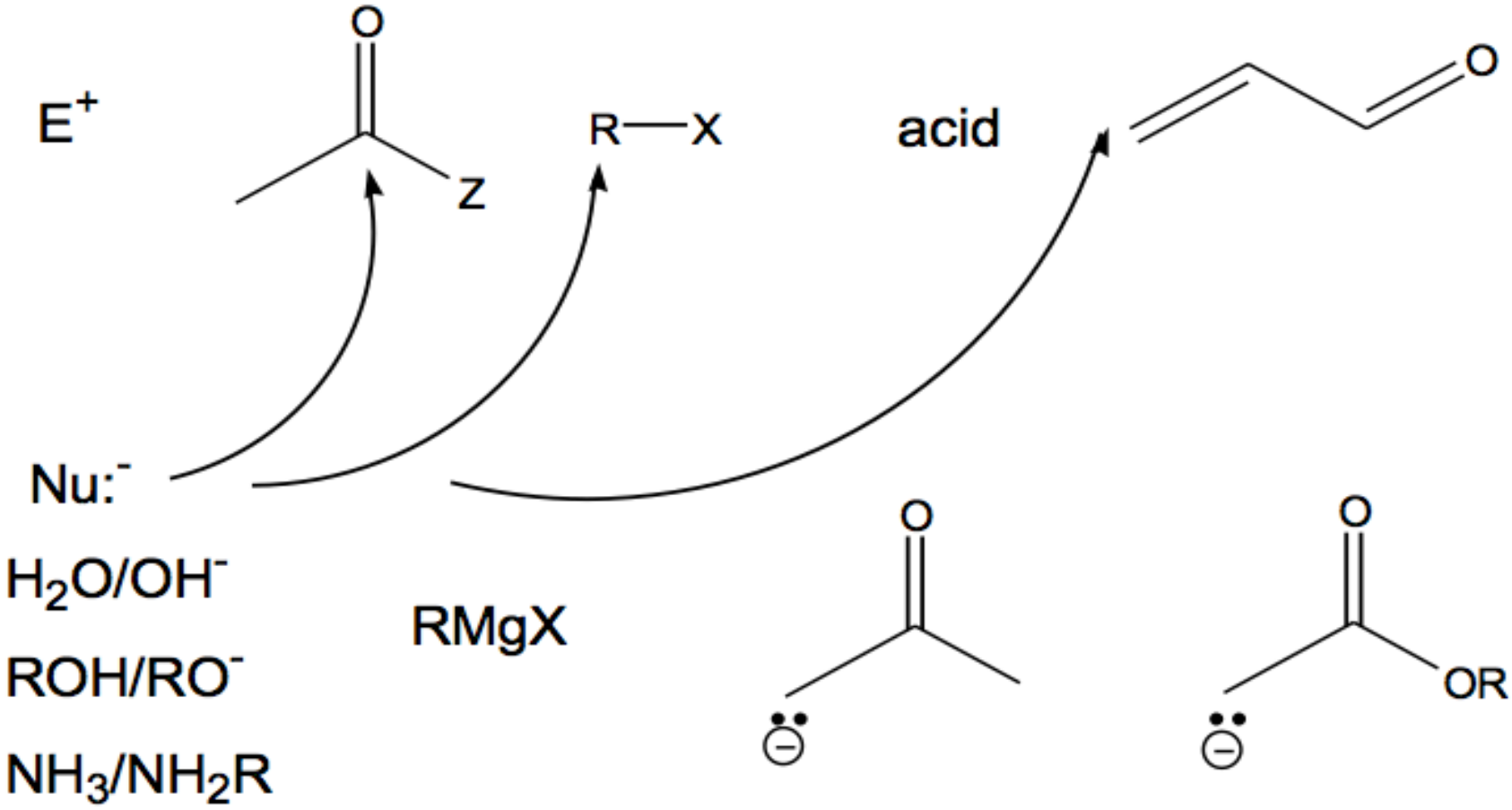
Each compound is treated with NaOEt. Use curved arrows to show how this reaction occurs. Draw the enolate or ester enolate ion that forms. Include resonance structures. Which resonance structure is the major contributor?





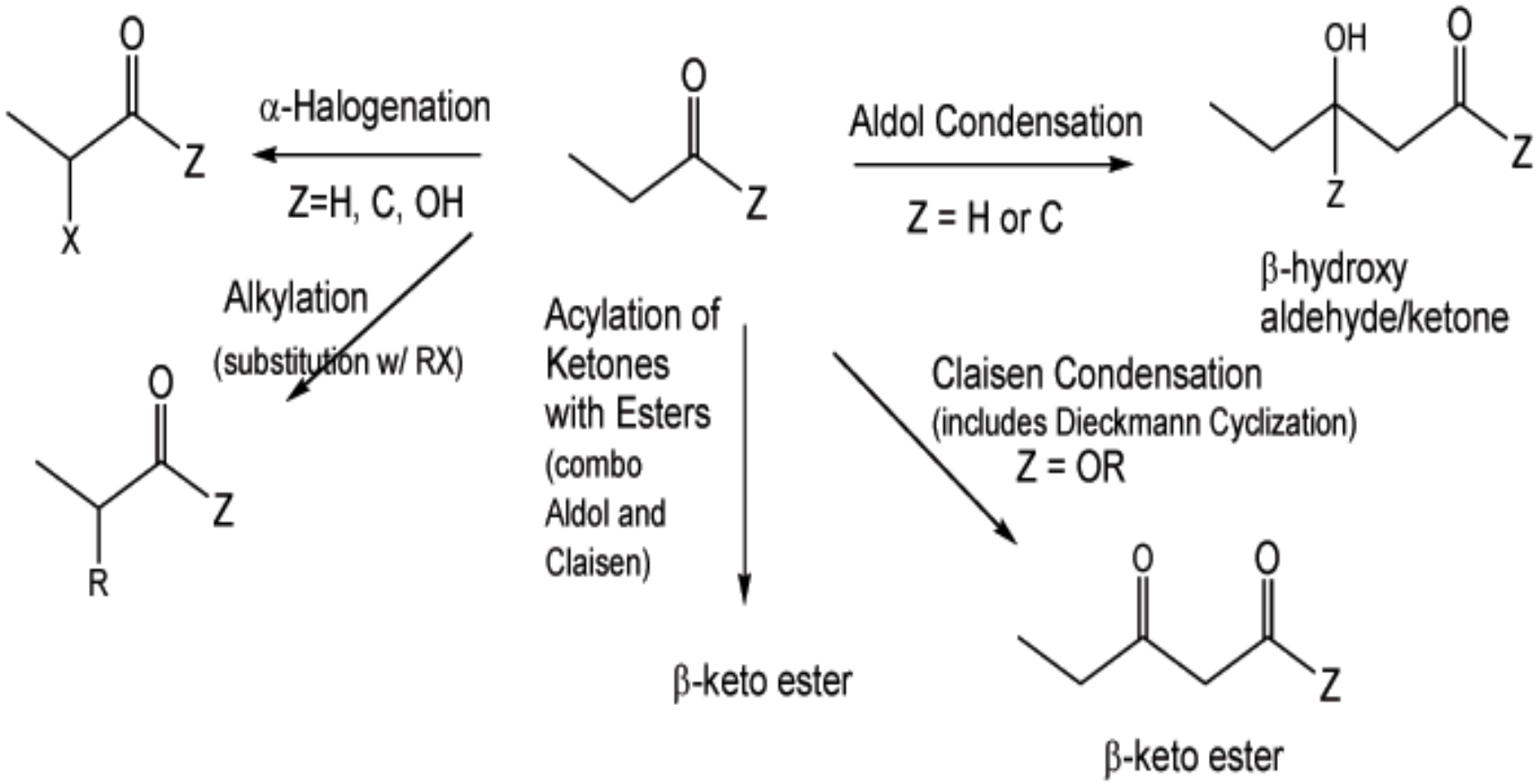
The Enolate Ion is a Nucleophile

Nucleophiles React With Electrophiles



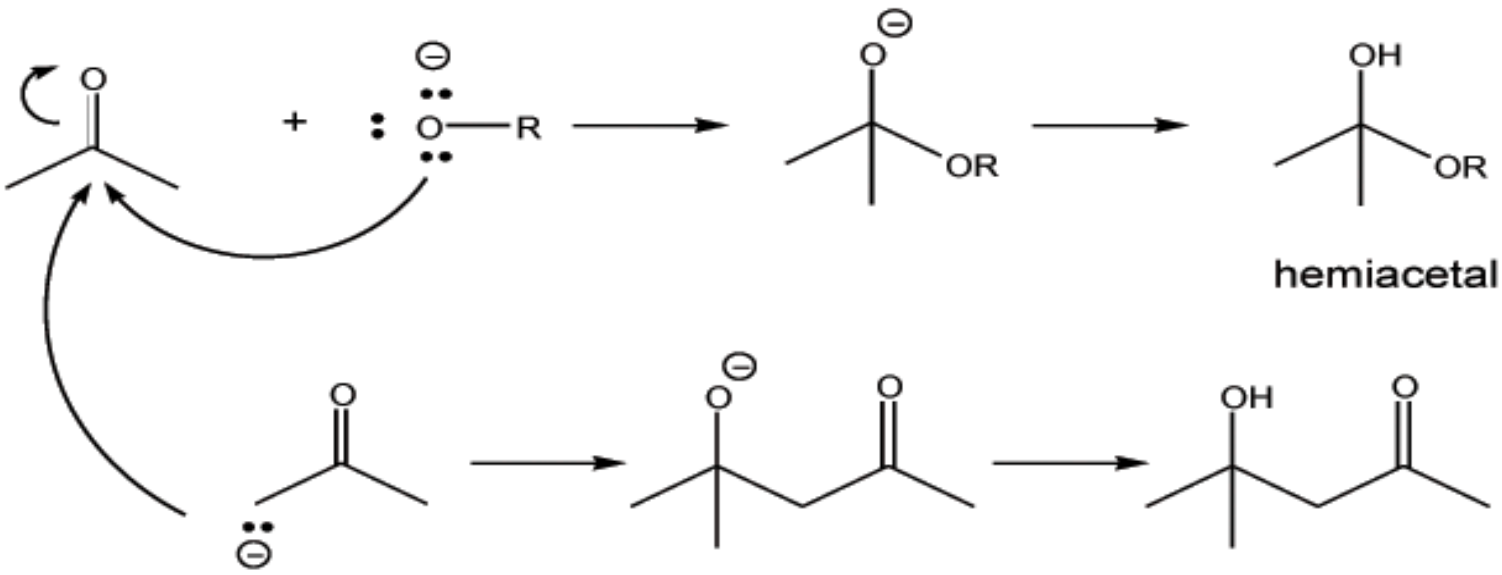
What is the *Reaction Type* at each *Reactive Site*?

The Enolate Ion is a Nucleophile



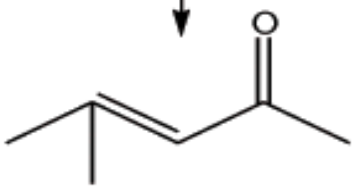
Biology: The Aldol and Claisen condensations form C-C bonds. The reverse (retro) aldol condensation breaks C-C bonds.

Aldol Condensation is the **Same** As A Nucleophilic Addition to an Aldehyde/Ketone (different Nu:$^-$)



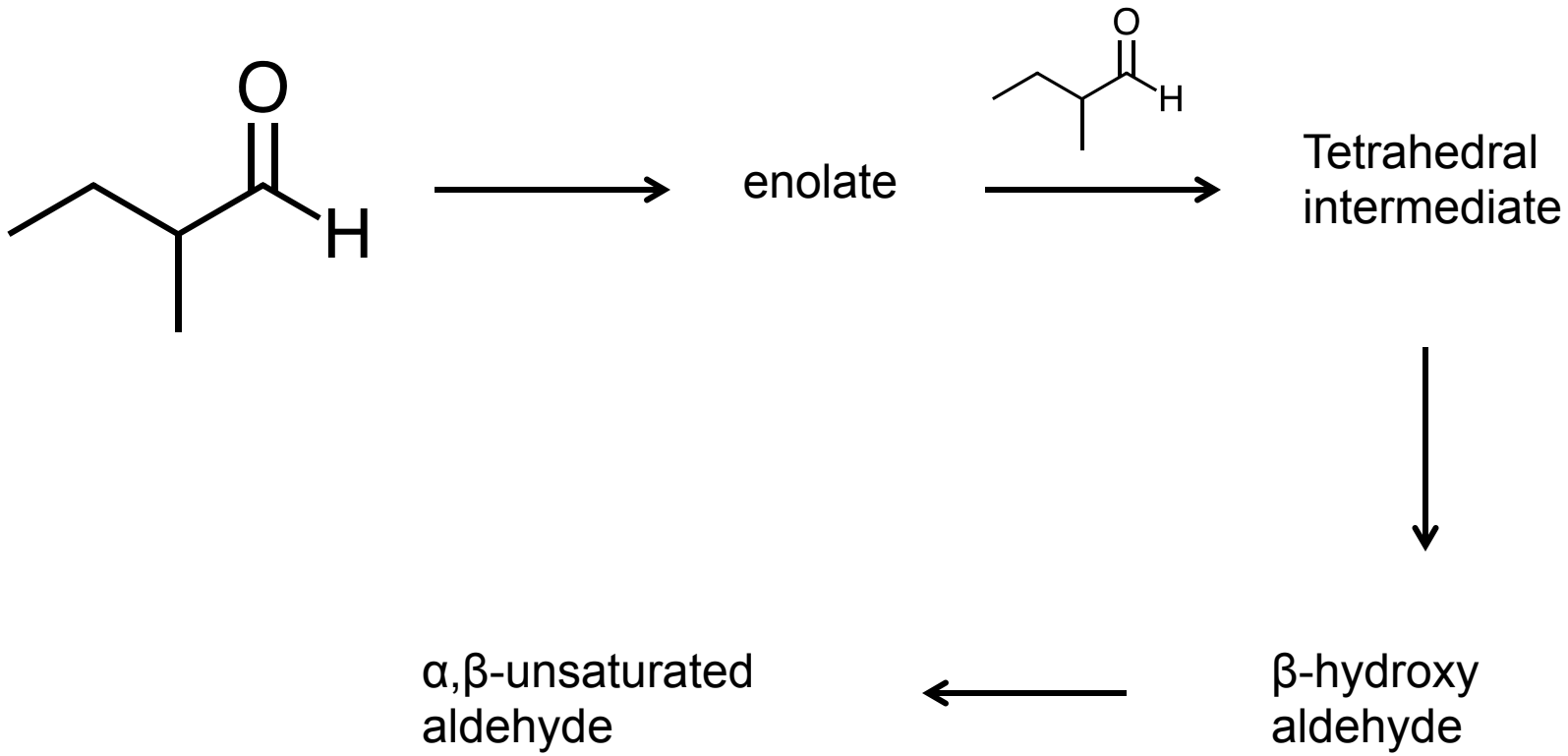
A carbon-carbon bond is formed in the **Aldol Condensation** reaction. What is the mechanism of this reaction?
How is this reaction reversed?

Reaction Type?

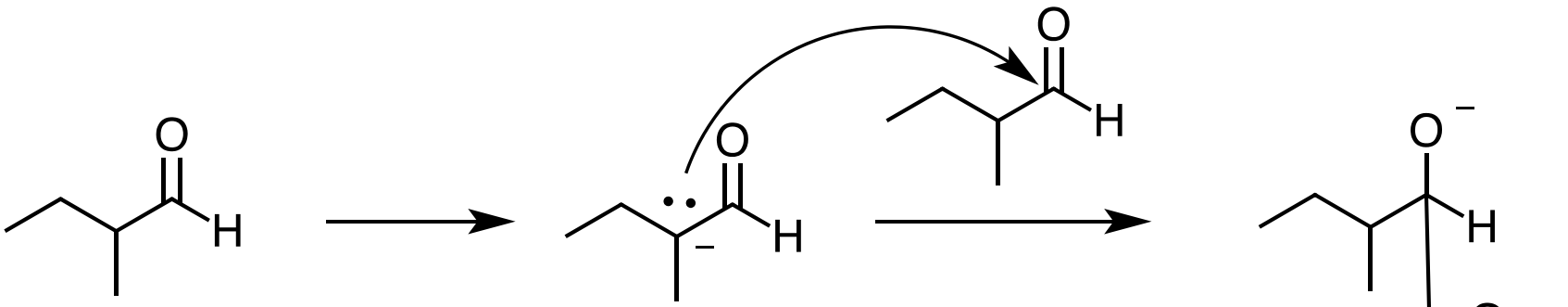


α,β-unsaturated ketone

This compound is treated with NaOH. Predict the product of the reaction:

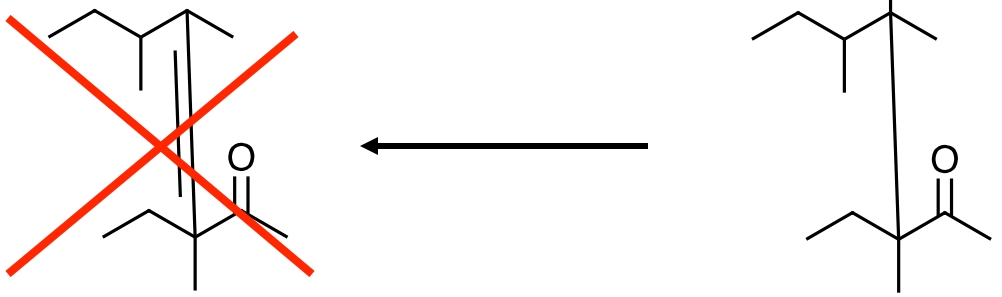


Aldol Condensation involves Nu:⁻ addition to RCHO/RCOR carbonyl C



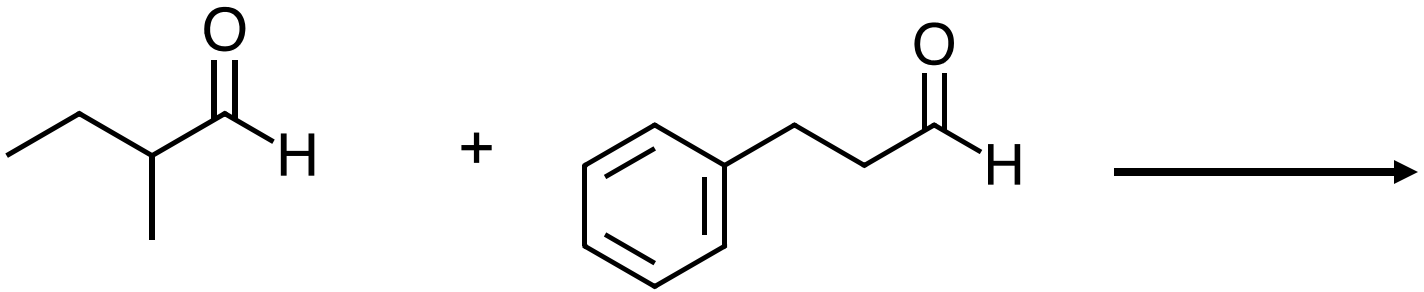
Enolate ion
Nu:⁻ reacts with carbonyl C

Which bond breaks?
Which bond forms?



Why doesn't this product form?

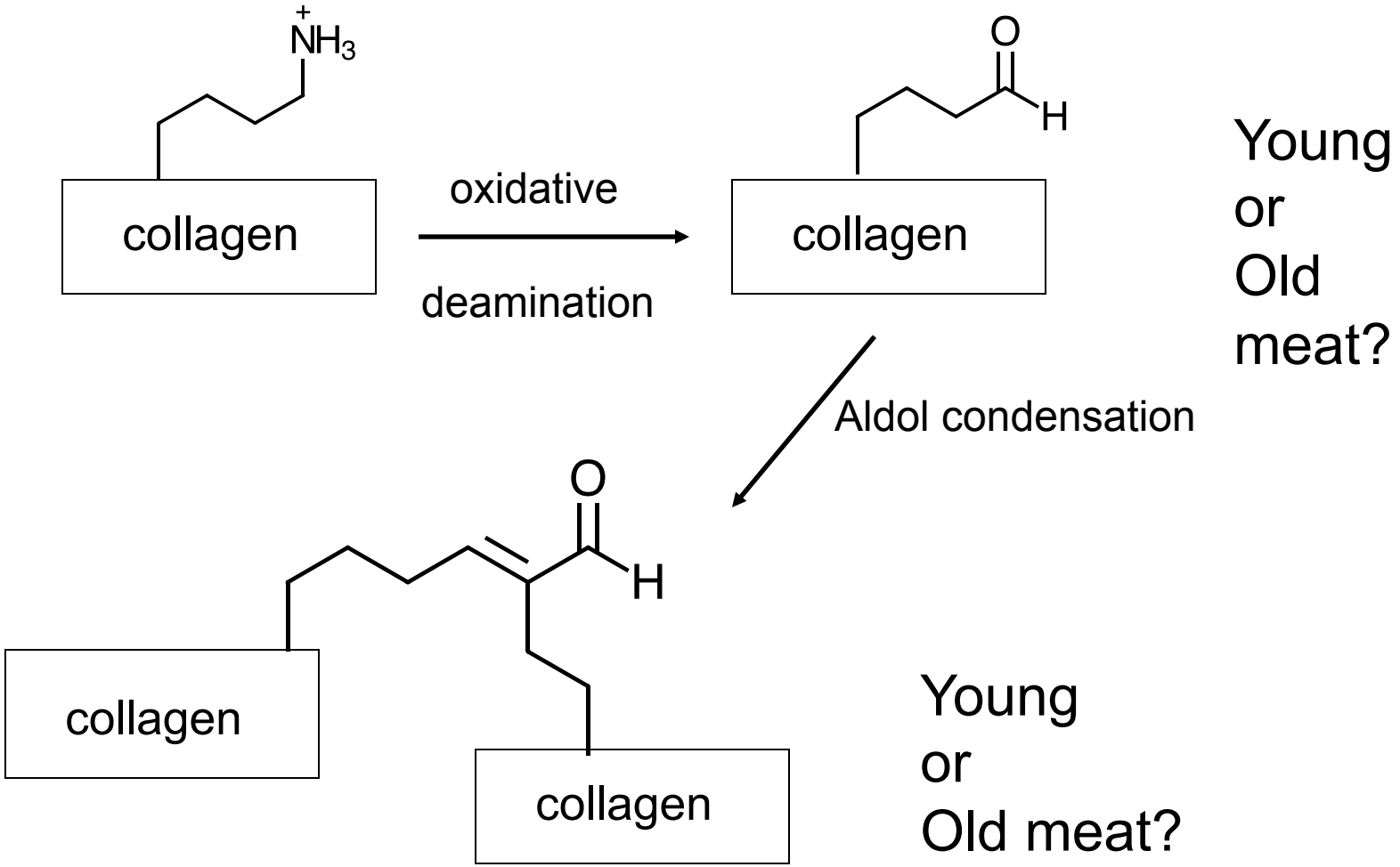
Each compound is treated with NaOH. Predict the product of the reaction. Use curved arrows to show bonds breaking and forming. Hint: more than 1 possible product.



Which bond breaks? Which bond forms?

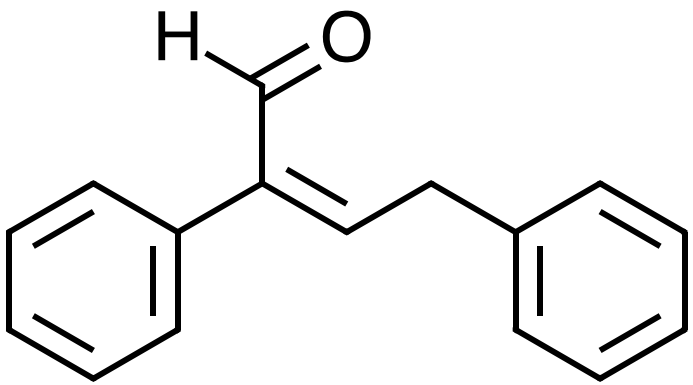
Mixed Aldol Condensation

‘Why Meat from Younger Animals is Softer” (Klein, “Organic Chemistry”, p. 1050)

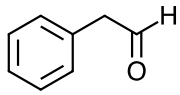


Synthesis: Identify the aldehyde or ketone to make the following compound.

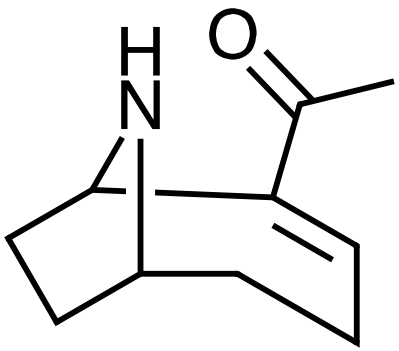
Hint: Which bond formed from the aldehyde/ketone and enolate?



Answer:



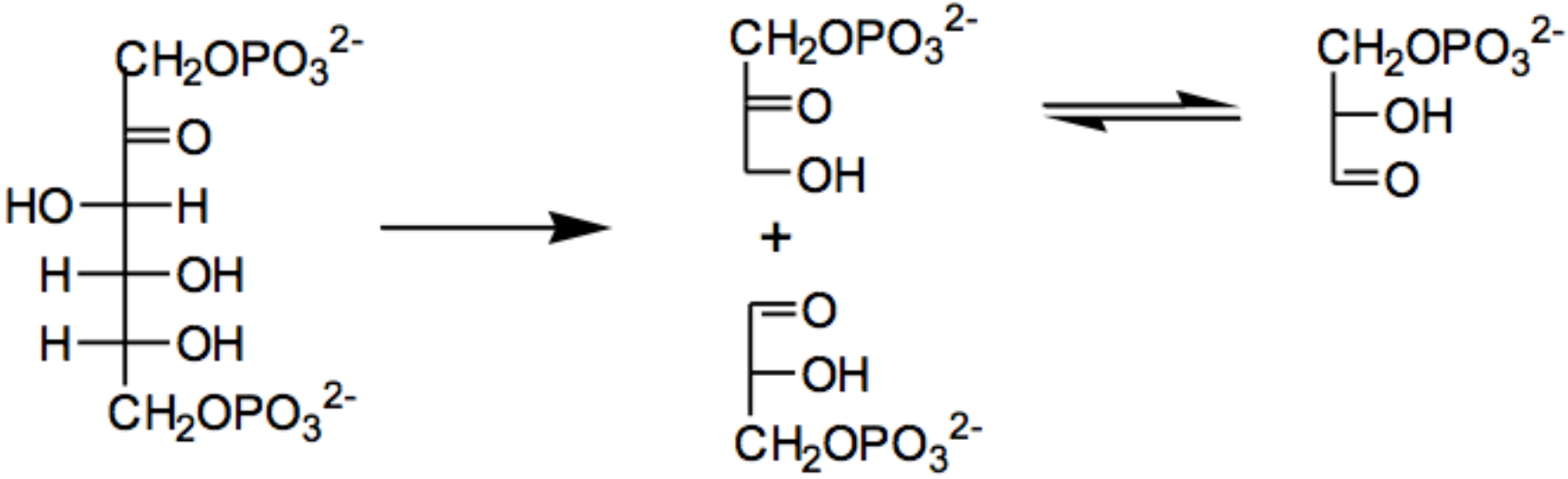
ACS Reactions (YouTube): What makes blue-green algae dangerous?



Anatoxin – a
VFDF – very fast death factor

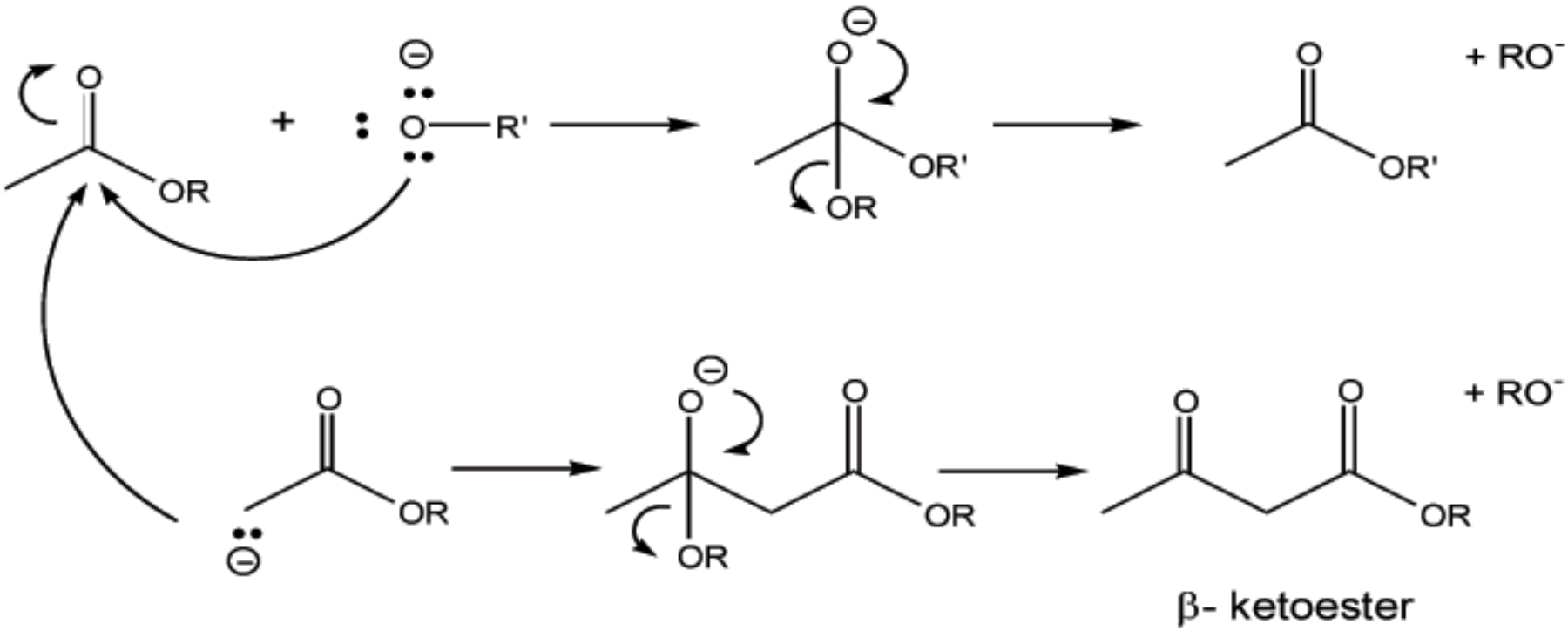
ID structural features.
Do a retro-aldol condensation. What product forms?

Glycolysis 4th step:
retro-Aldol condensation + keto-enol



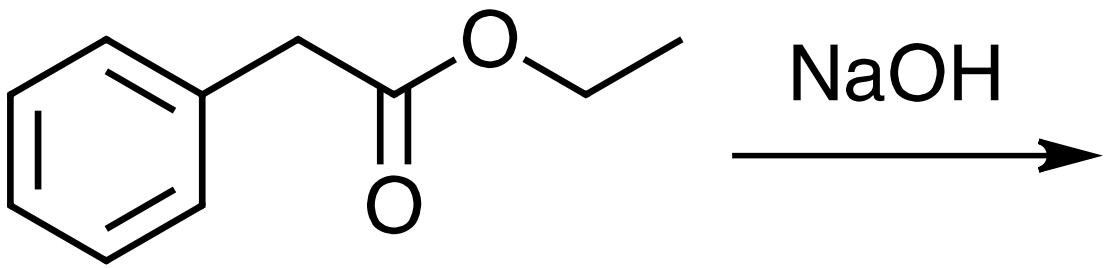
Where's the enolate?

Claisen Condensation is the **Same** As A Nucleophilic Acyl Substitution to an Ester



Identify the bond in the β-ketoester that formed from the ester. Is there a leaving group? If so, what is the LG?

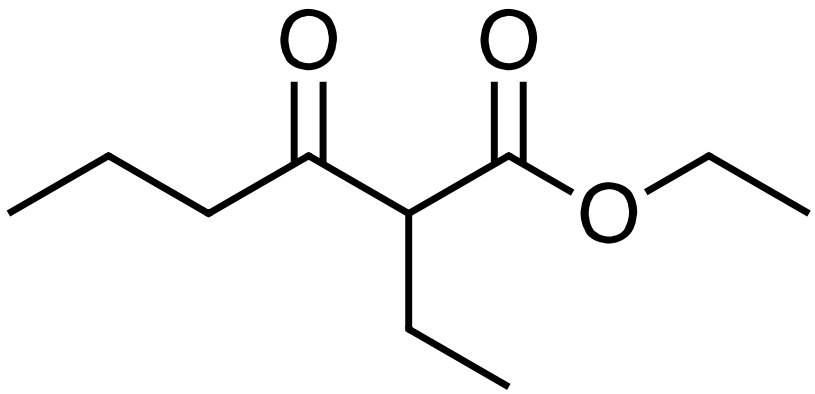
Predict the product of the Claisen condensation reaction:



Which bond breaks? Which bond forms?

Synthesis: Identify the reagents to produce the following product using a Claisen condensation.

Hint: Which bond formed from the ester and ester enolate?



Summary of Aldol and Claisen Condensations

Aldol and Claisen condensations involve ____ functional group(s).

Aldol and Claisen condensations involve a base to form an _____ ion.

The _____ ion reacts at the _____ carbon to form a _____ intermediate.

If the _____ intermediate does not have a _____ group, nucleophilic addition occurs (Aldol) to form β-hydroxy ____ or α,β-unsaturated _____.

If the _____ intermediate has a _____ group, nucleophilic acyl substitution occurs (Claisen) to form β-keto _____.