Retro-Synthetic Analysis of Condensation Products

If the product:

Then:

1. \(\beta\)-hydroxy-carbonyl (or enone)?
   - **Aldol reaction**
     - a) Are the fragments identical?
       - Then Aldol works well
     - b) Do both fragments have enolizable Hs?
       - If only one enolate can form, Aldol works well
     - c) Can you make one fragment more acidic?
       - Start with \(\beta\)-dicarbonyl
     - d) Is the product cyclic with internal C=C?
       - Intramolecular, start with dicarbonyl
     - e) Is the product \(\alpha,\beta\)-unsaturated carboxylic acid?
       - Start with dialkylmalonate

2. 1,3-dicarbonyl compound?
   - **Claisen reaction**
     - a) Are the fragments identical?
       - Then Claisen works well
     - b) Do both fragments have enolizable Hs?
       - If only one enolate can form, Claisen works well
     - c) Can you make one fragment more acidic?
       - Start with \(\beta\)-dialkyl malonate
     - d) Is the product cyclic?
       - Intramolecular, start with diester
     - e) Is the product \(\beta\)-keto acid?
       - Saponify ester
     - f) Is the product a ketone or aldehyde?
       - Start with dialkyl carbonate

3. 1,5 dicarbonyl compound?
   - **Michael reaction**
     - a) Is nucleophilic fragment acidic?
       - Then Michael works well
     - b) Is nucleophilic fragment not acidic?
       - Start with \(\beta\)-keto-ester or enamine
     - c) Is product 1,5 dicarbonyl & cyclic?
       - Robinson annulation

1. Aldol Reactions

Fragment skeleton between the \(\alpha\) and \(\beta\) carbons, e.g.

And then convert the hydroxy to a carbonyl and add H to other fragment:

... or if product is enone fragment between \(\alpha\) and \(\beta\) positions and insert O and 2 Hs:
There are still several questions to consider.

1a) Does the retro-synthetic analysis give two fragments that are identical?

Yes, the fragments are identical. Aldol is easy to do in high yield. For example:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\alpha & \quad \alpha
\end{align*}
\]
\[
\text{O} \quad \text{O}
\]
\[
\beta & \quad \beta
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\alpha & \quad \alpha
\end{align*}
\]
\[
\text{O} \quad \text{O}
\]
\[
\beta & \quad \beta
\]

In the forward direction it looks like this:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\alpha & \quad \alpha
\end{align*}
\]
\[
\text{O} \quad \text{O}
\]
\[
\beta & \quad \beta
\]

No, the fragments are not identical. Go to 1b.

1b) How many of the fragment have no enolizable \( \alpha \) Hs?

Only one fragment has enolizable \( \alpha \) Hs. This crossed Aldol should go in high yield.

The only enolate that can be made is from the acetone. The benzaldehyde is the more reactive carbonyl, so this reaction goes in high yield. In the forward direction it looks like this:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\alpha & \quad \alpha
\end{align*}
\]
\[
\text{O} \quad \text{O}
\]
\[
\beta & \quad \beta
\]

1c) Both fragments have enolizable \( \alpha \) Hs – make one fragment more acidic.

This cross-Aldol is potential trouble because so many products could form.

One possible work-around for this troublesome Aldol is to make one fragment more acidic by adding carbonyl. For example, ethyl acetoacetate is more acidic than acetone.

\[
\begin{align*}
\text{pK}_a & = 19 \\
\text{pK}_a & = 11
\end{align*}
\]
So start with the β-ketoester and make its enolate selectively:

This doesn’t look quite like the correct product, but you can easily saponify and decarboxylate:

Thus the extra carbonyl added at the very start of the synthesis to acidify the acetone will be removed in the end.

1d) Is the product cyclic with internal C=C?

If so, then the reaction is intramolecular. This only works with 5- and 6-membered rings.

In the forward direction it looks like this:

1e) Is the product an α,β-unsaturated carboxylic acid?

The problem here is that you can’t make the enolate of a carboxylic acid. If you try to you will deprotonate at the (more acidic) oxygen rather than the (less acid) carbon.

The work-around is to start with dialkyl malonate rather than carboxylic acid. In the forward direction it looks like this:
This doesn’t look like product, but the esters can be saponified to carboxylic acids and the β-diacid can be decarboxylated.

2. **Claisen Reaction**

Fragment between α and β carbons of ester, then insert –OR:

![Claisen Reaction Diagram](image_url)

There are still several questions to consider.

2a) *Does the retro-synthetic analysis give two fragments that are identical?*

*Yes, the fragments are identical.* The Claisen is easy to do in high yield. For example:

![Claisen Reaction Diagram](image_url)

In the forward direction it looks like this:

![Claisen Reaction Diagram](image_url)

*No, the fragments are not identical. Go to 1b.*

2b) *How many of the fragment have no enolizable α Hs?*

*Only one fragment has enolizable α Hs.*

![Claisen Reaction Diagram](image_url)

This particular cross Claisen should go in good yields. In the forward direct we have:
Both fragments contain enolizable H’s.

This is potential trouble. In the forward direction there are too many possible products.

2c) If both fragments have enolizable H’s, make one component more acidic:

The second component is not only many orders of magnitude more acidic, is completely (100%) deprotonated by "OEt, thus there is only one nucleophile and one electrophile present. In the forward direction we have:

Note that this is not the product you set out to make . . . but it is close. Saponification of the esters to carboxylic acids, followed by decarboxylation will yield the desired β-keto ester.

Finally, as a reminder, don’t go willy-nilly removing CO₂ from carboxylic acids. It is a special reaction limited to carboxylic acids with a second carbonyl at the β-position.

Let return to our original problem, which we solved by cleaving between the α,β position:
Although this method worked there is an alternative retro-synthesis that is much simpler. It is much easier to alkylate in the last step:

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\beta & \quad \alpha \\
\rightarrow & \\
\text{EtO} & \quad \text{EtO} \\
\beta & \quad \alpha \\
\rightarrow & \\
\text{EtO} & \quad \text{EtO} \\
\alpha & \quad \beta \\
\end{align*}
\]

H\textsubscript{3}C−Br

In fact this is the acetoacetic ester synthesis. In the forward direction it looks like this:

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\alpha & \quad \beta \\
\rightarrow & \\
\text{EtO} & \quad \text{EtO} \\
\alpha & \quad \beta \\
\rightarrow & \\
\text{EtO} & \quad \text{EtO} \\
\alpha & \quad \beta \\
\end{align*}
\]

2d) Is the product cyclic?

If cyclic then an intramolecular Claisen (Dieckmann) was used.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\alpha & \quad \beta \\
\rightarrow & \\
\text{MeO} & \quad \text{MeO} \\
\alpha & \quad \beta \\
= & \\
\text{MeO} & \quad \text{MeO} \\
\alpha & \quad \beta \\
\end{align*}
\]

2e) Is the product a β-keto carboxylic acid (or related cmpd)?

Claisen products are most easy recognized as β-keto esters. However since esters are easily saponified to acids, β-keto acids and any members of the carboxylic acid family are potential Claisen products.

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\alpha & \quad \beta \\
\rightarrow & \\
\text{EtO} & \quad \text{EtO} \\
\alpha & \quad \beta \\
\rightarrow & \\
\text{EtO} & \quad \text{EtO} \\
\alpha & \quad \beta \\
\end{align*}
\]

In the forward direction it looks like this:
2f) Is the product a (mono) ketone?

This is the most difficult case to analyze since there is no 1,3 – dicarbonyl that is so characteristic of Claisen products. The trick is to judiciously place (create) a second carbonyl at a β position.

This can be decarboxylated to give a monoketone. Remember Claisen (and Aldol) chemistry does not work on carboxylic acids (why?), so be sure to work with esters.

This β-keto ester in turn is derived from alkylation of acetoacetic ester. In fact this is the acetoacetic ester synthesis: