Organic Chemistry III

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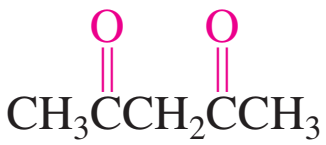
23. Ester Enolates and the Claisen Condensation

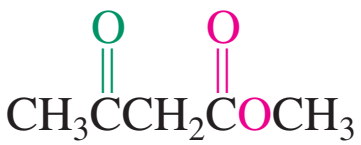
The aldol condensation is a powerful method for converting aldehydes and ketones into **β**-hydroxycarbonyl compounds.

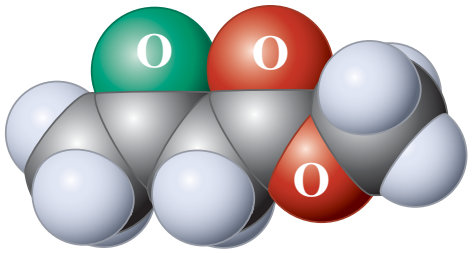
In **Claisen condensation**, attack of an ester enolate on a carbonyl group generates a new carbon–carbon bond, 1,3-dicarbonyl compounds, more commonly known as **β**-dicarbonyl compounds.

Examples of *β*-Dicarbonyl Compounds

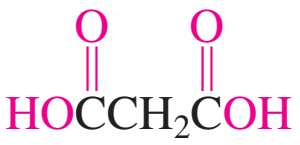


2,4-Pentanedione
(Acetylacetone)
(A *β*-diketone)





Methyl 3-oxobutanoate (Methyl acetoacetate)
(A *β*-ketoester)



Propanedioic acid
(Malonic acid)
(A *β*-dicarboxylic acid)

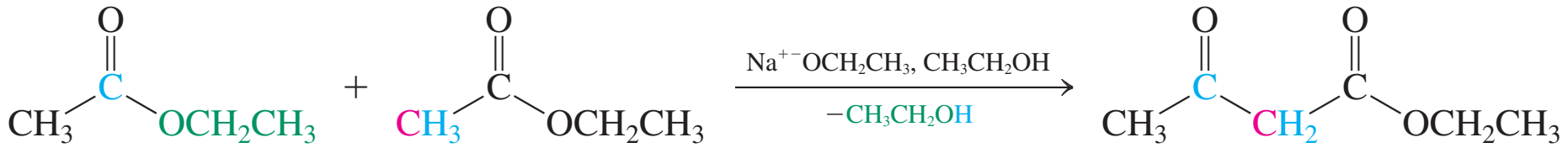
23-1 β-Dicarbonyl compounds: Claisen condensations

Ester enolates undergo addition–elimination reactions with ester functions, furnishing **β**-ketoesters. These transformations, known as Claisen condensations, are the ester analogs of the aldol reaction.

Claisen condensations form **β**-dicarbonyl compounds

Ethyl acetate reacts with a stoichiometric amount of sodium ethoxide to give ethyl 3-oxobutanoate (ethyl acetoacetate).

Claisen Condensation of Ethyl Acetate



Ethyl acetate

Ethyl 3-oxobutanoate (Ethyl acetoacetate)

Unlike the aldol condensation, in which two molecules are joined with elimination of water, the Claisen condensation proceeds by expelling a molecule of alcohol.

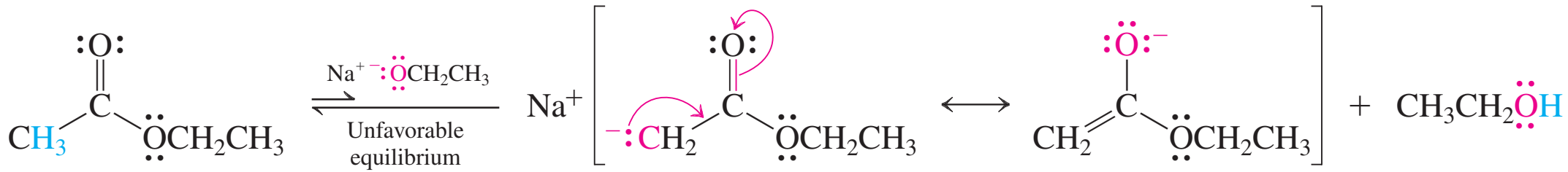
It is also not catalytic: its mechanism requires the presence of a little over a full equivalent of base in order for the starting materials to proceed to product.

Keys to success: The Claisen condensation works because hydrogens flanked by two carbonyl groups are acidic

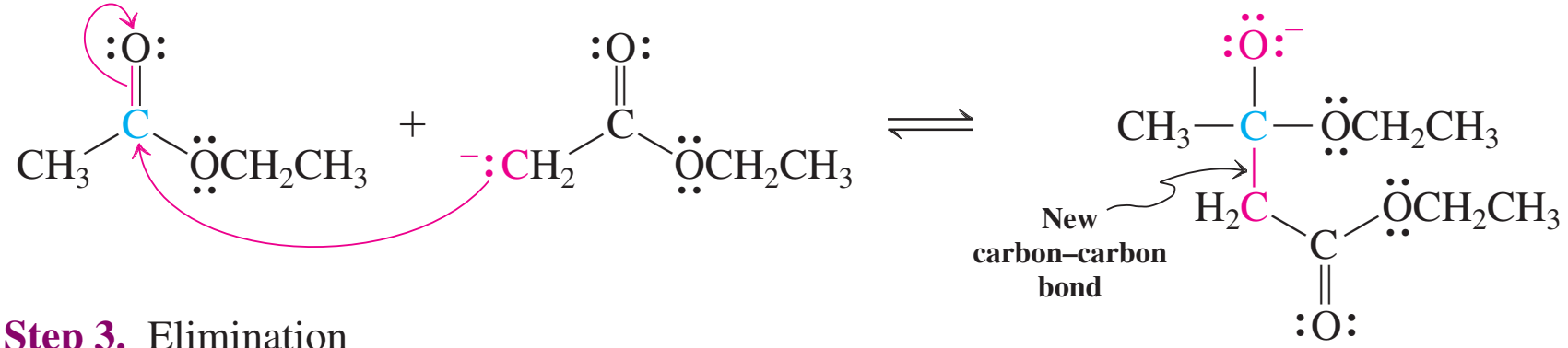
The mechanism of the Claisen condensation begins with deprotonation of the ester by ethoxide to form the ester enolate ion (step 1). This step is unfavorable because of the large difference in acidity between the ***α***-hydrogens of the ester (pK_a ≈ 25) and ethanol (pK_a = 15.9).

The small equilibrium concentration of enolate thus formed adds to the carbonyl group of another ester molecule (step 2); loss of ethoxide completes an addition–elimination sequence, giving ethyl 3-oxobutanoate (a 3- or **β**-ketoester) (step 3).

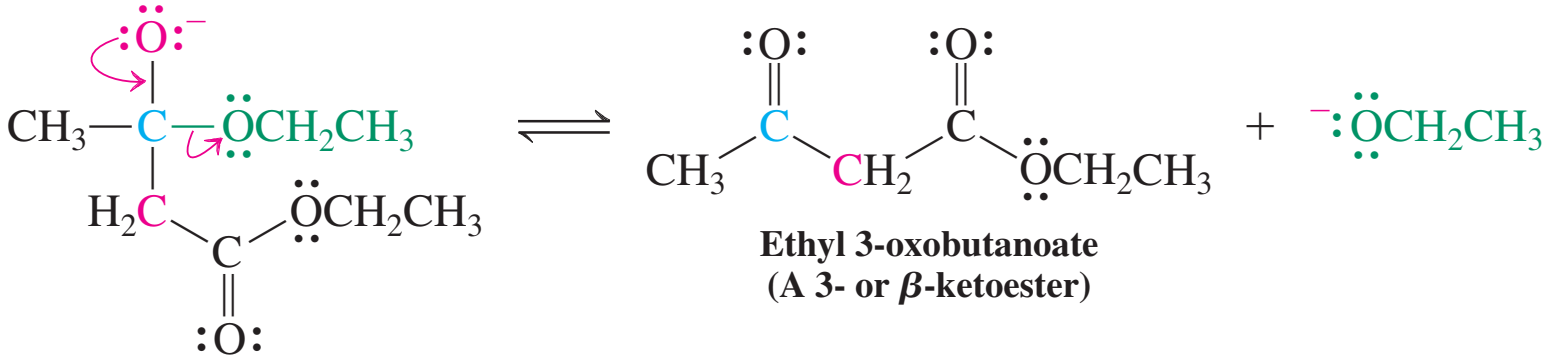
Step 1. Ester enolate formation



Step 2. Nucleophilic addition



Step 3. Elimination

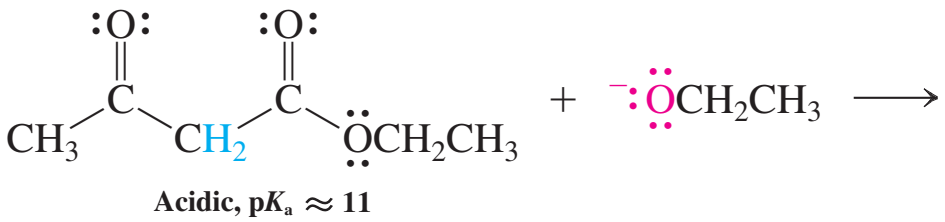


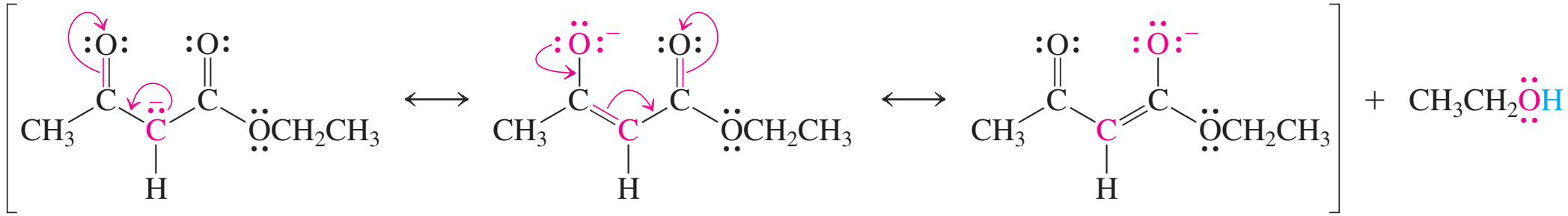
Ethyl 3-oxobutanoate
(A 3- or *β*-ketoester)

Because this step depletes the mixture of the ethoxide necessary for step 1, the need for (a little more than) a stoichiometric equivalent of ethoxide base now becomes clear: It is to assure that enough base will be present to deprotonate all of the intermediate 3-ketoester, in this way pushing the overall equilibrium forward to the deprotonated ketoester.

With the equilibrium driven forward to the deprotonated condensation product, all that remains is to restore a proton to its central carbon by work-up with aqueous acid (step 5), thus completing the process.

Step 4. Deprotonation of ketoester drives equilibrium





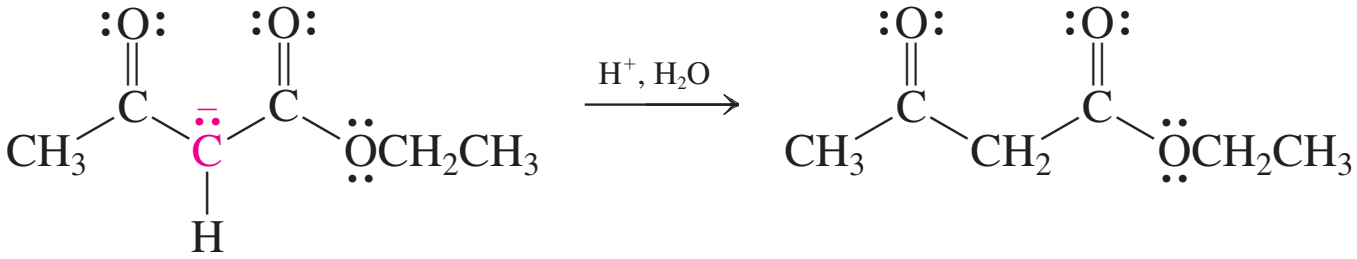
Le Chatelier's principle again: Step 4 depletes the ketoester from the reaction mixture, and steps 1 through 3 shift to replenish it.

At this stage, however, the sequence is endothermic. Because each step is reversible, the overall equilibrium lies strongly on the side of the initial starting materials. It is the hydrogens at the center of the 3-ketoester that are the key to driving these equilibria forward.

These hydrogens are unusually acidic, with a pK_a ≈ 11, less than that of ethanol. The reason is the presence of the two adjacent, inductively electron-withdrawing carbonyl groups and the extensive delocalization of the negative charge of the anion resulting upon deprotonation.

Thus, every molecule of 3-ketoester that forms in step 3 is acidic enough to react immediately with the coproduct ethoxide in step 4.

Step 5. Protonation upon acidic aqueous work-up



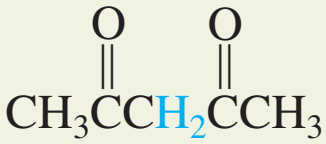
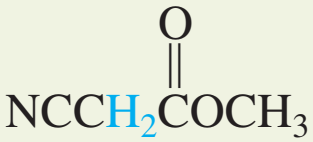
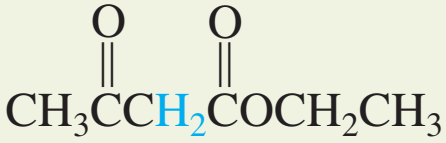
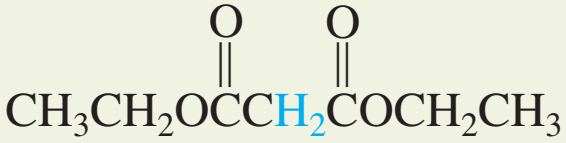
You will have noted that the conditions of the Claisen condensation, ester plus alkoxide in alcohol, are identical to those used in base-catalyzed transesterifications. Why, then, did we not see condensation products in such ester exchanges?

The answer is that transesterification is much faster than the Claisen process (step 1). Indeed, in order to avoid product mixtures, the latter always employs alkoxides that are identical to that in the ester function, in this way relegating transesterification to a nonproductive background transformation.

The unusual acidity of the hydrogens in ethyl 3-oxobutanoate is general for all **β**-dicarbonyl compounds and extends to other groups that are electron withdrawing by induction and resonance.

The corresponding enolates and related carbanions are relatively nonbasic and, are useful nucleophiles in organic synthesis.

Table 23-1 pK_a Values for β-Dicarbonyl and Related Compounds

Name	Structure	pK_a
2,4-Pentanedione (Acetylacetone)		9
Methyl 2-cyanoacetate		9
Ethyl 3-oxobutanoate (Ethyl acetoacetate)		11
Propanedinitrile (Malonodinitrile)		13
Diethyl propanedioate (Diethyl malonate)		13

More acidic

Retro-Claisen condensation: β-Ketoesters lacking central hydrogens are cleaved by alkoxide

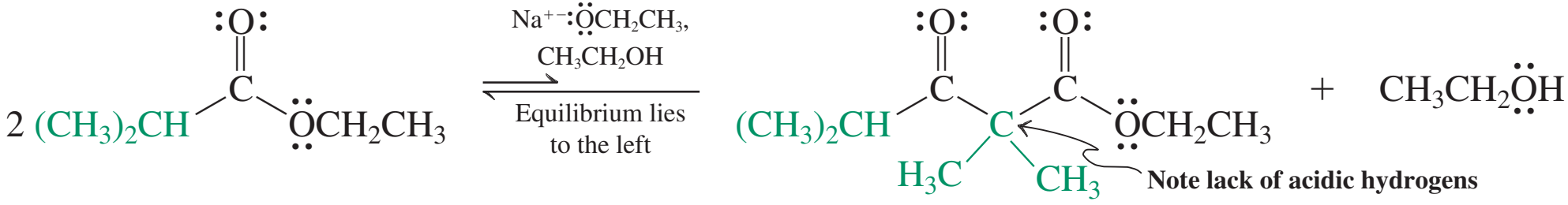
Attempted Claisen condensation using an ester with only one ***α***-hydrogen fails. As the reaction below shows, the product would be a 2,2-disubstituted 3-ketoester.

Lacking a central hydrogen that may be removed by base to shift the overall equilibrium to product (step 4), the trial is doomed by the unfavorable thermodynamics of steps 1–3.

It leads to a reversible "dead end," and no Claisen condensation product is observed.

Although 2,2-disubstituted **β**-ketoesters cannot be formed directly using the Claisen condensation, they can be synthesized in another way (Section 23-2).

Failure of a Claisen Condensation—A Mechanistic "Dead End"



Ethyl 2-methylpropanoate

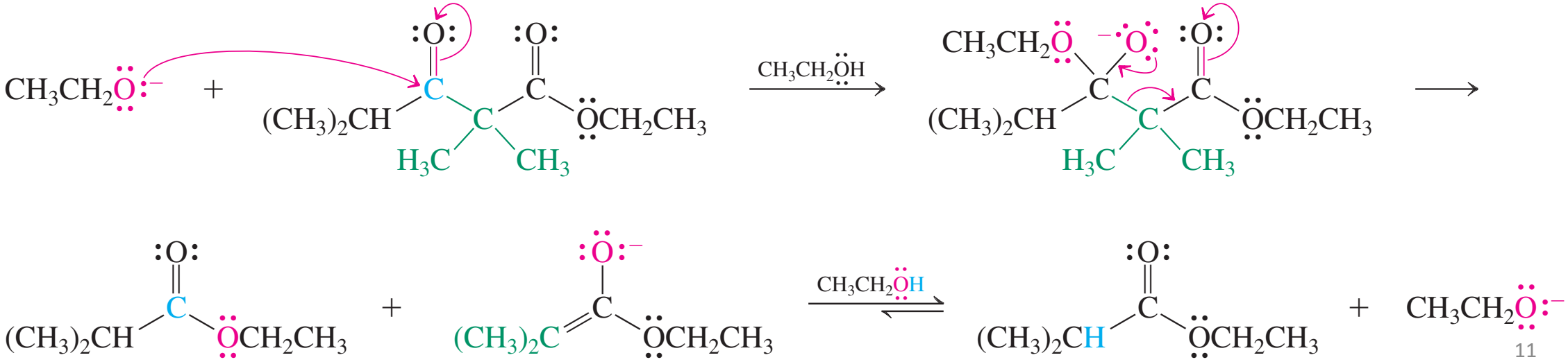
Ethyl 2,2,4-trimethyl-3-oxopentanoate
(Not observed)

What happens if such a ketoester is treated with alkoxide base?

Complete reversal of the Claisen condensation ensues, giving two molecules of simple ester through a mechanism that is the exact reverse of the forward reaction. Having no central hydrogen for the base to remove, addition of alkoxide to the ketone carbonyl group occurs instead.

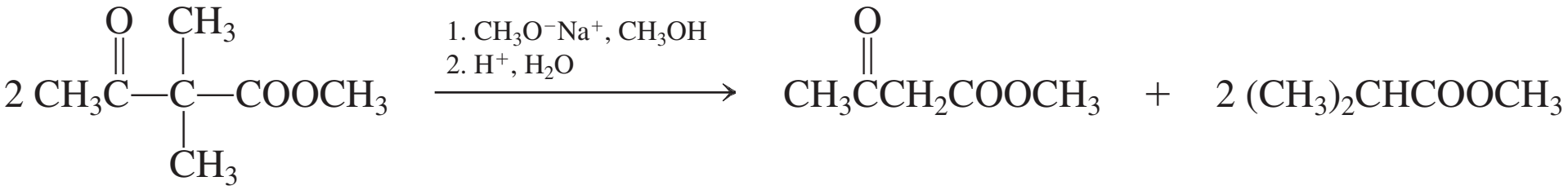
The resulting tetrahedral intermediate fragments to release the enolate ion of the original ester. This process, called **retro-Claisen condensation,** confirms the thermodynamic basis for the failure of the Claisen condensation "dead end".

Reversal of a Claisen Condensation (Retro-Claisen Condensation)



Exercise 23-2

Explain the following observation.



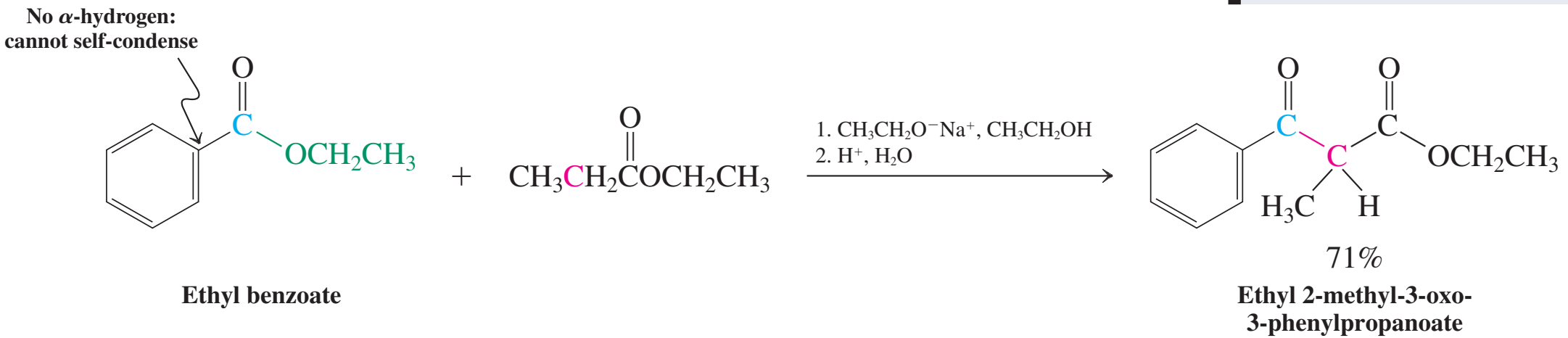
Claisen condensations can have two different esters as reactants

Mixed Claisen condensations start with two different esters. Like crossed aldol condensations, they are typically unselective and furnish product mixtures.

However, a selective mixed condensation is possible when one of the reacting partners has no ***α***-hydrogens, as in ethyl benzoate.

A Selective Mixed Claisen Condensation

propanoate, the benzoate ester is used in excess.



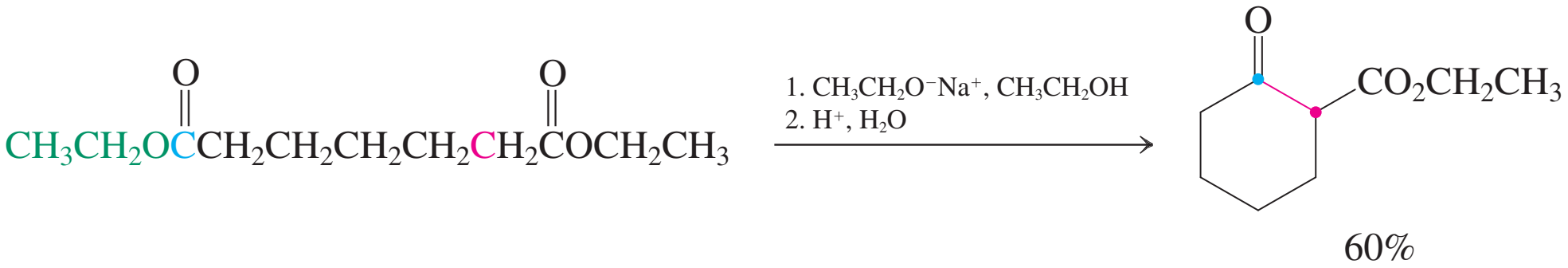
Ethyl benzoate

Ethyl 2-methyl-3-oxo-3-phenylpropanoate

Intramolecular Claisen condensations result in cyclic compounds

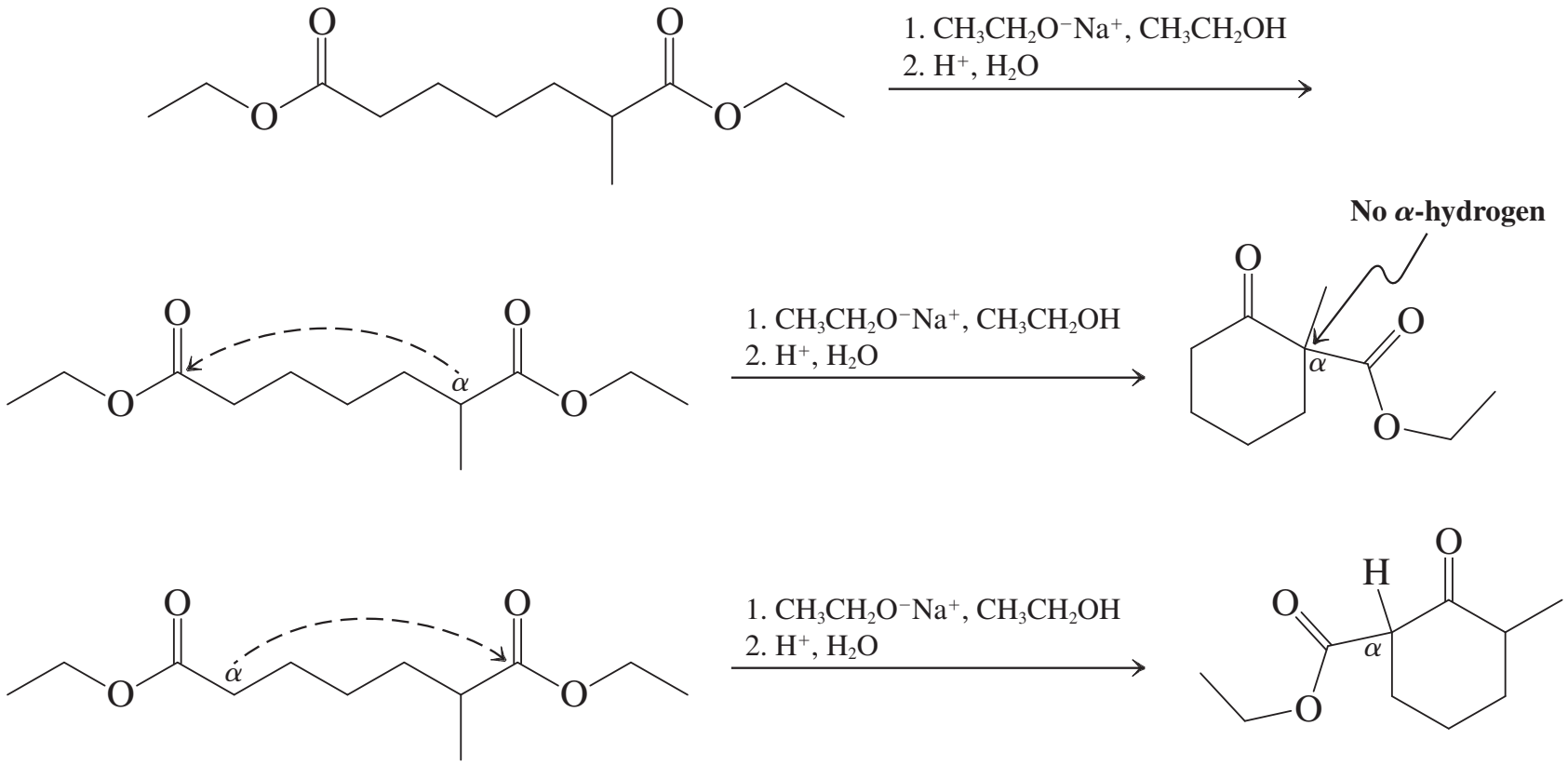
The intramolecular version of the Claisen reaction, called the **Dieckmann condensation**, produces cyclic 3-ketoesters.

As expected, it works best for the formation of five- and six-membered rings.



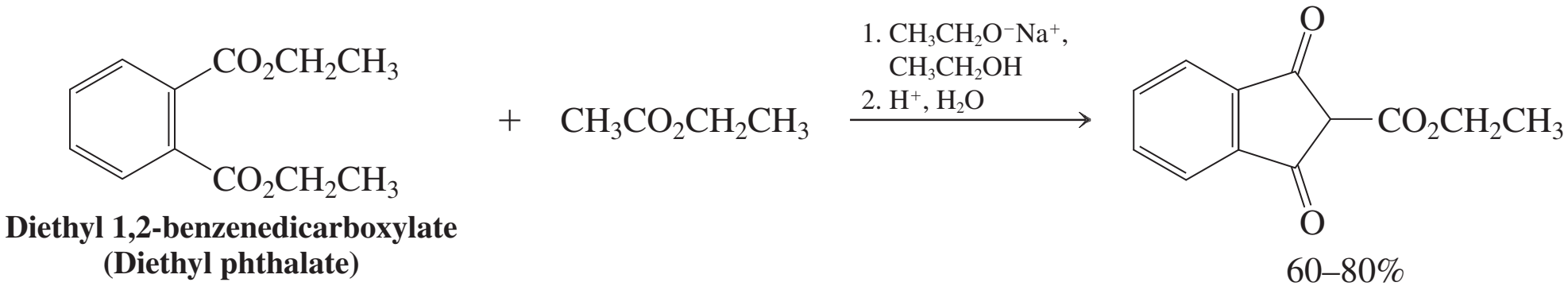
Solved Exercise 23-5

Two cyclic products are possible from the Dieckmann (intramolecular Claisen) condensation shown below, but only one of them actually forms. Describe and explain briefly the outcome of this reaction.



Exercise 23-6

Formulate a mechanism for the following reaction.



Diethyl 1,2-benzenedicarboxylate (Diethyl phthalate)

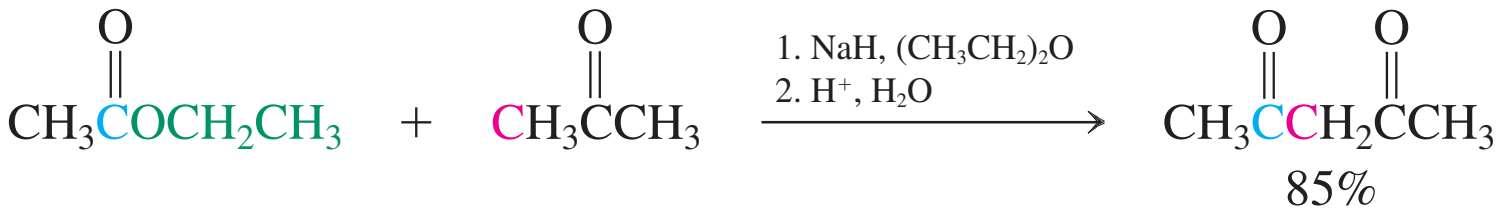
60–80%

Ketones undergo **mixed Claisen reactions**

Ketones can participate in the Claisen condensation. Because they are more acidic than esters, they are deprotonated before the ester has a chance to undergo self-condensation.

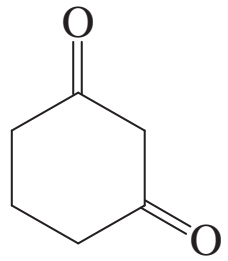
The products (after acidic work-up) may be **β**-diketones, **β**-ketoaldehydes, or other **β**-dicarbonyl compounds.

The reaction can be carried out with a variety of ketones and esters both inter- and intramolecularly.



Exercise 23-7

1,3-Cyclohexanedione can be prepared by an intramolecular mixed Claisen condensation between the ketone carbonyl and ester functions of a single molecule. What is the structure of this substrate molecule?



1,3-Cyclohexanedione

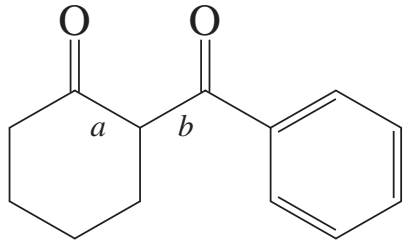
Retrosynthetic analysis clarifies the synthetic utility of the Claisen condensation

Three facts are available to help us: (1) Claisen condensations always form 1,3-dicarbonyl compounds; (2) one of the reaction partners in a Claisen condensation must be an ester, whose alkoxide group is lost in the course of the condensation; and (3) the other reaction partner (the source of the nucleophilic enolate) must contain at least two acidic hydrogens on an ***α***-carbon.

In addition, if a mixed condensation is being considered, one reaction partner should be incapable of self-condensation (e.g., it should lack ***α***-hydrogens).

If we are given the structure of a target molecule and wish to determine whether (and, if so, how) it can be made by a Claisen condensation, we must analyze it retrosynthetically with the preceding points in mind.

It is a 1,3-dicarbonyl compound, meeting the first requirement.

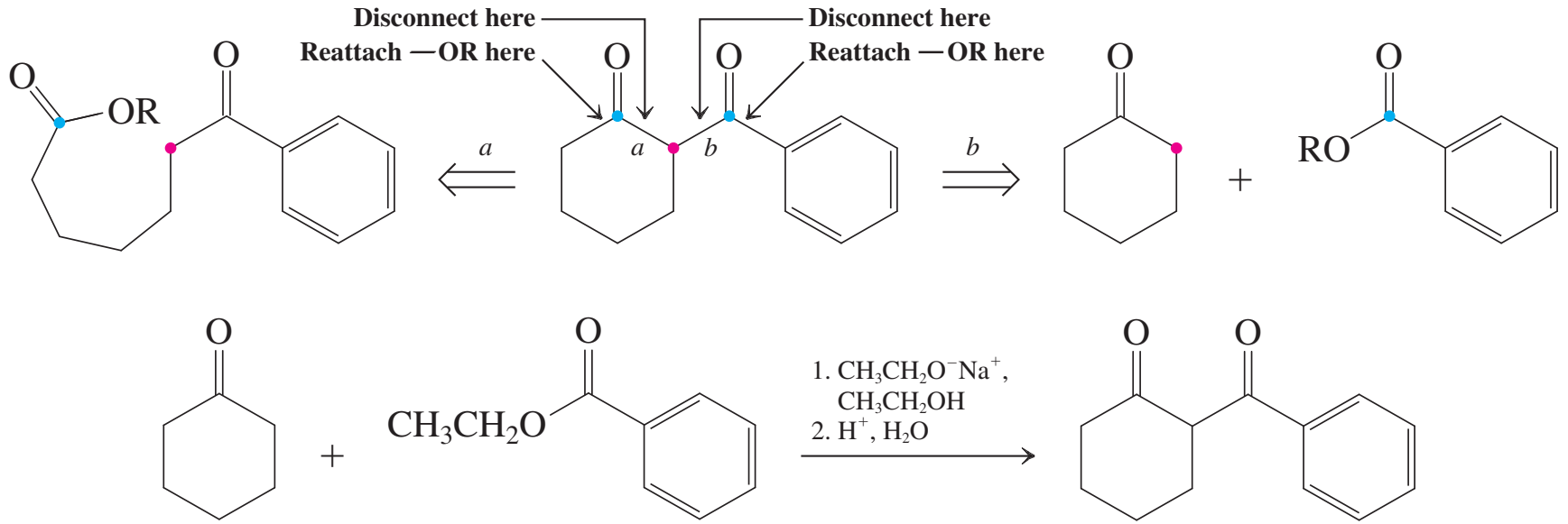


2-Benzoylcyclohexanone

What bond forms in a Claisen condensation? The new bond in the product always connects one of the carbonyl groups of the 1,3-dicarbonyl moiety to the carbon atom *between* them.

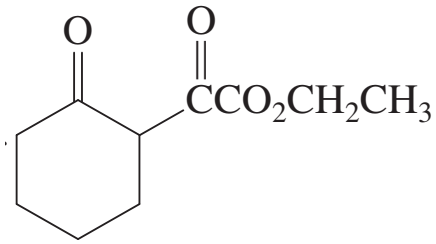
The target molecule contains two such bonds, labeled ***a*** and ***b***. The carbonyl group at which the new carbon–carbon bond forms starts out as part of an ester function.

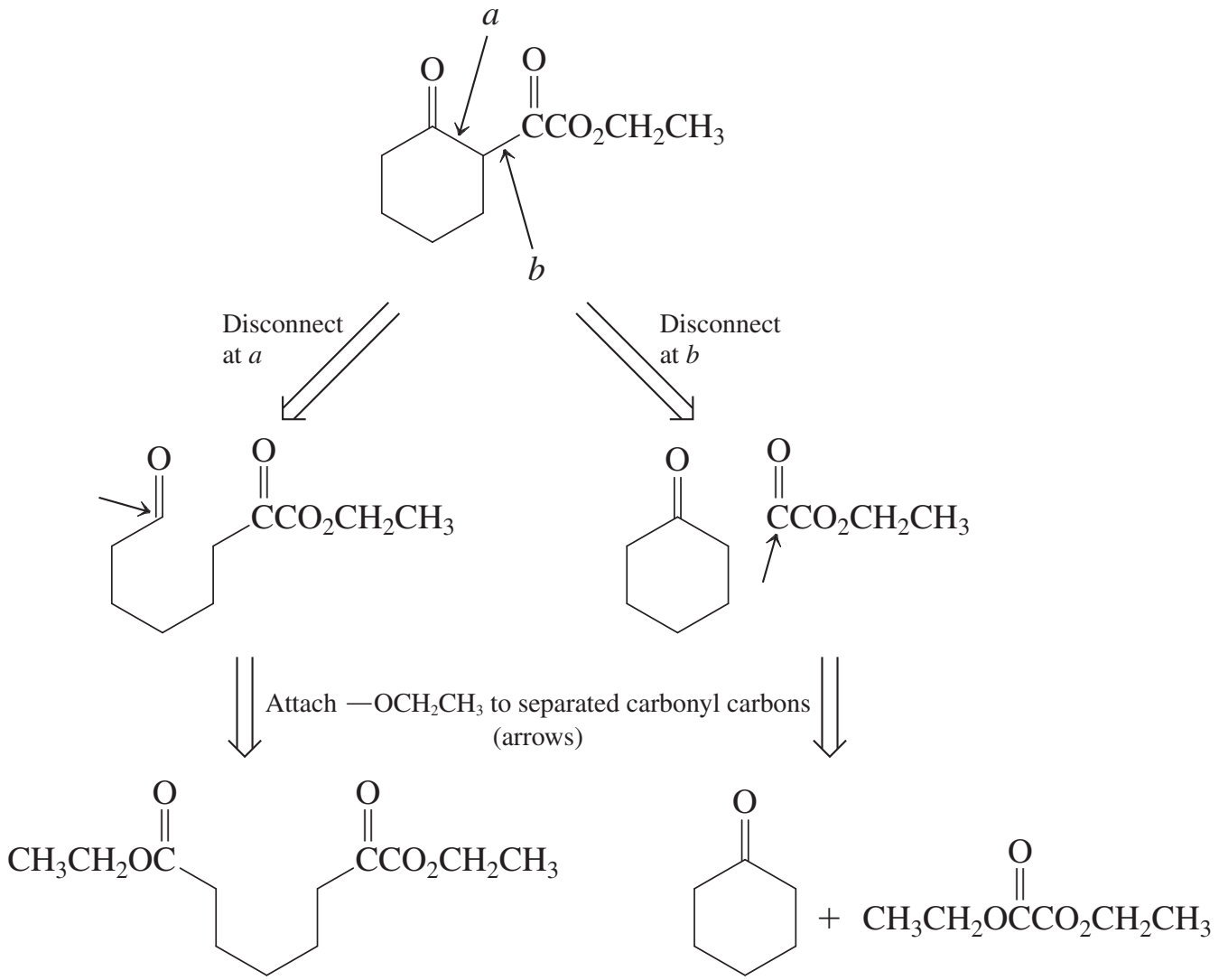
Disconnection of bond **a** reveals a ketoester, which undergoes intramolecular Claisen condensation in the forward direction, whereas disconnection of bond **b** gives cyclohexanone and a benzoic ester. Both condensations are quite feasible; however, the second is preferable because it constructs the target from two smaller pieces:



Solved Exercise 23-8

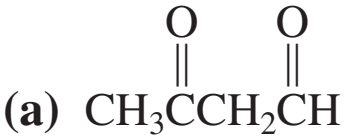
Show a synthesis of using a Claisen or a Dieckmann condensation.

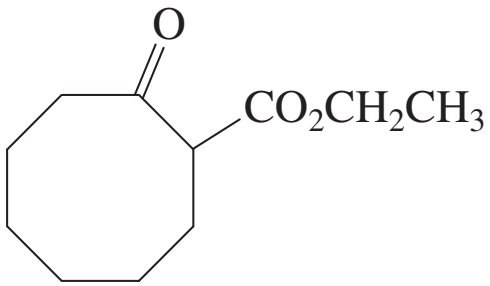




Exercise 23-9

Suggest syntheses of the following molecules by Claisen or Dieckmann condensations.

(a) 

(b) 

(c)