

Chapter 23 – Carbonyl Condensation Reactions

Chapter Outline

I. The aldol reaction (Sections 23.1 – 23.6).

A. Characteristics of the aldol reaction (Sections 23.1 – 23.2).

1. The aldol condensation is a base-catalyzed dimerization of two aldehydes or ketones.
2. The reaction can occur between two components that have α hydrogens.
3. For simple aldehydes, the equilibrium favors the products, but for other aldehydes and ketones, the equilibrium favors the reactants.
4. One component (the nucleophilic donor) is converted to its enolate and undergoes an α -substitution reaction.
5. The other component (the electrophilic acceptor) undergoes nucleophilic addition.
6. Carbonyl condensation reactions require only a catalytic amount of base (Section 23.2).

Alpha-substitution reactions, on the other hand, use one equivalent of base.

B. Dehydration of aldol products (Section 23.3).

1. Aldol products are easily dehydrated to yield α,β -unsaturated aldehydes and ketones.
 - a. Dehydration is catalyzed by both acid and base.
 - b. Reaction conditions for dehydration are only slightly more severe than for condensation.
 - c. Often, dehydration products are isolated directly from condensation reactions.
2. Conjugated enones are more stable than nonconjugated enones.
3. Removal of the water byproduct drives the aldol equilibrium towards product formation.

C. Aldol products (Sections 23.4 – 23.5).

1. Using aldol reactions in synthesis (Section 23.4).
 - a. Obvious aldol products are:
 - i. α,β -Unsaturated aldehydes/ketones.
 - ii. β -Hydroxy aldehydes/ketones.
 - b. Often, it's possible to work backwards from a product that doesn't resemble an aldol product and recognize aldol components.
2. Mixed aldol reactions (23.5).
 - a. If two similar aldehydes/ketones react under aldol conditions, 4 products may be formed.
 - b. A single product can be formed from two different components :
 - i. If one carbonyl component has no α -hydrogens.
 - ii. If one carbonyl compound is much more acidic than the other.

D. Intramolecular aldol condensations (Section 23.6).

1. Treatment of certain dicarbonyl compounds with base can lead to cyclic products.
2. A mixture of cyclic products may result, but the more strain-free ring usually predominates.

II. The Claisen condensation (Sections 23.7 – 23.9).

A. Features of the Claisen condensation (Section 23.7).

1. Treatment of an ester with 1 equivalent of base yields a β -keto ester.
2. The reaction is reversible and has a mechanism similar to that of the aldol reaction.

3. A major difference from the aldol condensation is the expulsion of an alkoxide ion from the tetrahedral intermediate of the initial Claisen adduct.
4. Because the product is often acidic, one equivalent of base is needed; addition of base drives the reaction to completion.
5. Addition of acid yields the final product.
- B. Mixed Claisen condensations (Section 23.8).
 1. Mixed Claisen condensations of two different esters can succeed if one component has no α hydrogens.
 2. Mixed Claisen condensations between a ketone and an ester with no α hydrogens are also successful.
- C. Intramolecular Claisen condensations: the Dieckmann cyclization (Section 23.9).
 1. The Dieckmann cyclization is used to form cyclic β -keto esters.
 - a. 1,6-Diesters form 5-membered rings.
 - b. 1,7-Diesters form 6-membered rings.
 2. The mechanism is similar to the Claisen condensation mechanism.
 3. The product β -keto esters can be further alkylated.

This is a good route to 2-substituted cyclopentanones and cyclohexanones.

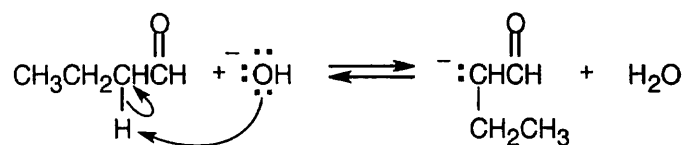
III. Other carbonyl condensation reactions (Sections 23.10 – 23.13).

- A. The Michael reaction (Section 23.10).
 1. The Michael reaction is the conjugate addition of an enolate to an α,β -unsaturated carbonyl compound.

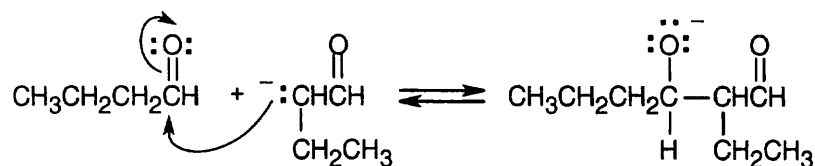
The highest-yielding reactions occur between stable enolates and unhindered α,β -unsaturated carbonyl compounds.
 2. The mechanism is a conjugate addition of a nucleophilic enolate to the β carbon of a α,β -carbonyl acceptor.
 3. Stable enolates are Michael donors, and α,β -unsaturated compounds are Michael acceptors.
- B. The Stork reaction (Section 23.11).
 1. A ketone that has been converted to an enamine can act as a Michael donor in a reaction known as the Stork reaction.
 2. The sequence of reactions in the Stork reaction:
 - a. Enamine formation from a ketone.
 - b. Michael-type addition to an α,β -unsaturated carbonyl compound.
 - c. Enamine hydrolysis back to a ketone.
 3. This sequence is equivalent to the Michael addition of a ketone to an α,β -unsaturated carbonyl compound and provides a 1,5 diketone product..
- C. The Robinson annulation reaction (Section 23.12).
 1. The Robinson annulation reaction combines a Michael reaction with an intramolecular aldol condensation to synthesize substituted ring systems.
 2. The components are a nucleophilic donor, such as a β -keto ester, and an α,β -unsaturated ketone acceptor.
 3. The intermediate 1,5-diketone undergoes an intramolecular aldol condensation to yield a cyclohexenone.
- D. Biological carbonyl condensation reactions (Section 23.13).
 1. Many biomolecules are synthesized by carbonyl condensation reactions.
 2. The enzyme aldolase catalyzes the addition of a ketone enolate to an aldehyde.
 3. Acetyl CoA is the major building block for the synthesis of biomolecules.
 - a. Acetyl CoA can act as an electrophilic acceptor by being attacked at its carbonyl group.
 - b. Acetyl CoA can act as a nucleophilic donor by loss of its acidic α hydrogen.

Solutions to Problems

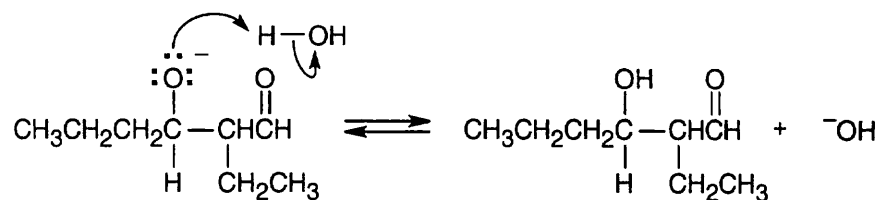
23.1 (1) Form the enolate of one molecule of the carbonyl compound.



(2) Have the enolate attack the electrophilic carbonyl of the second molecule.



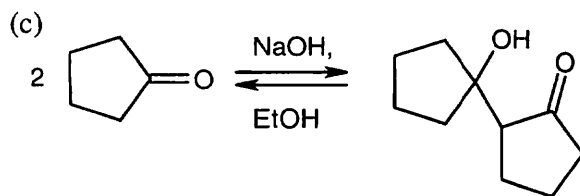
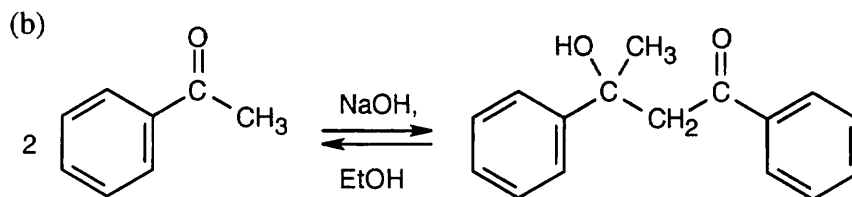
(3) Protonate the alkoxide oxygen.



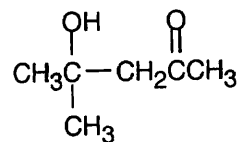
Practice writing out these steps for the other aldol condensations.

Solution:

(a) See above.

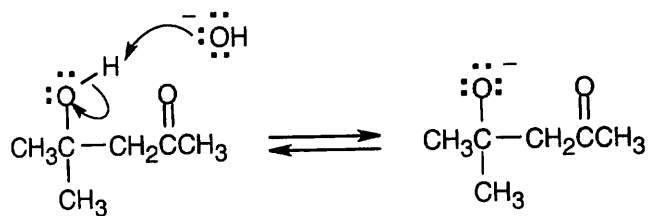


23.2

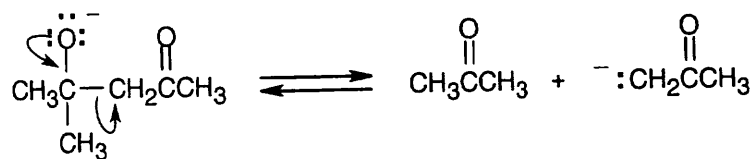
**4-Hydroxy-4-methyl-2-pentanone**

The steps for the reverse aldol are the reverse of those described in Problem 23.1.

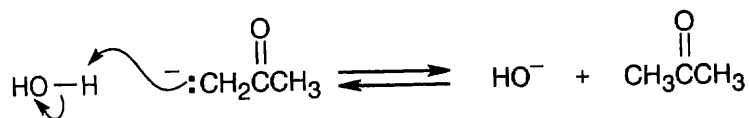
(1) Deprotonate the alcohol oxygen.



(2) Eliminate the enolate anion.

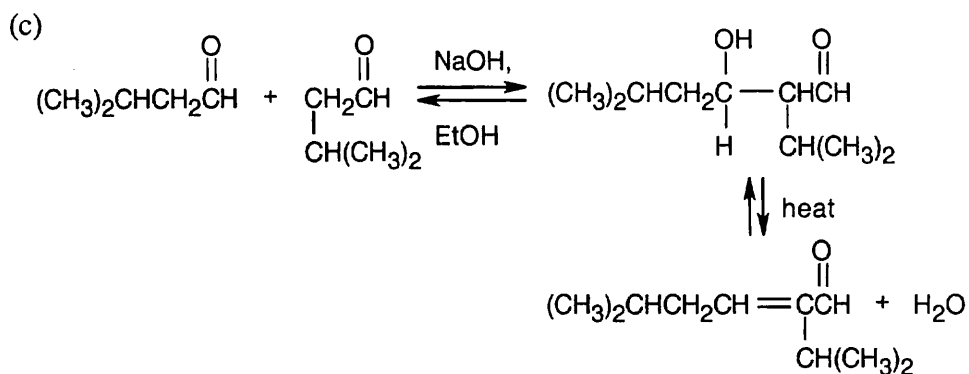
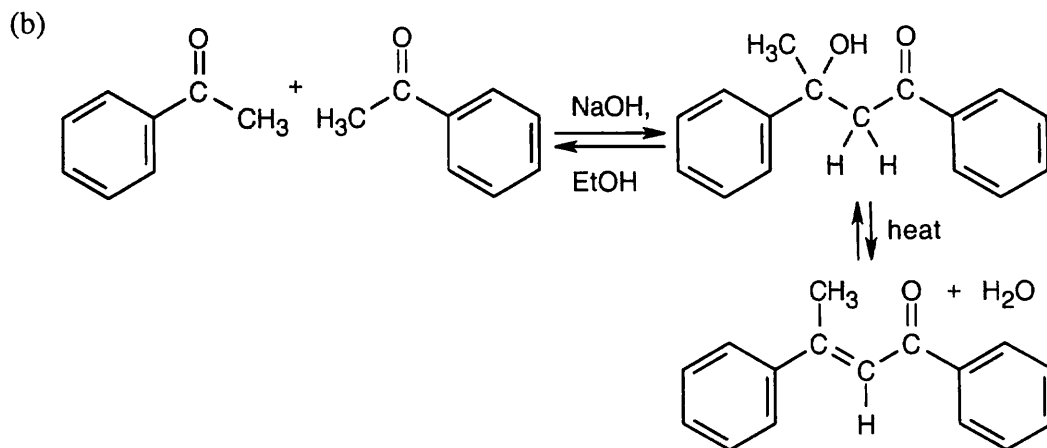
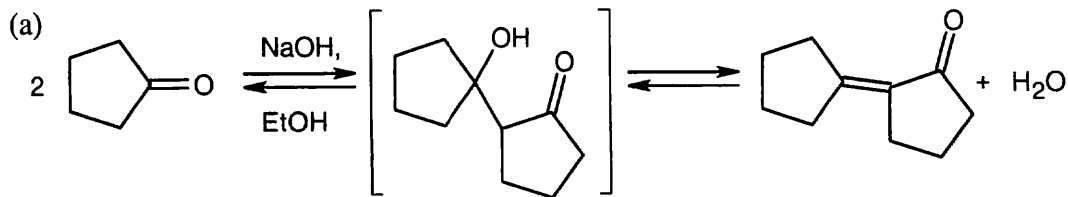


(3) Reprotonate the enolate anion.

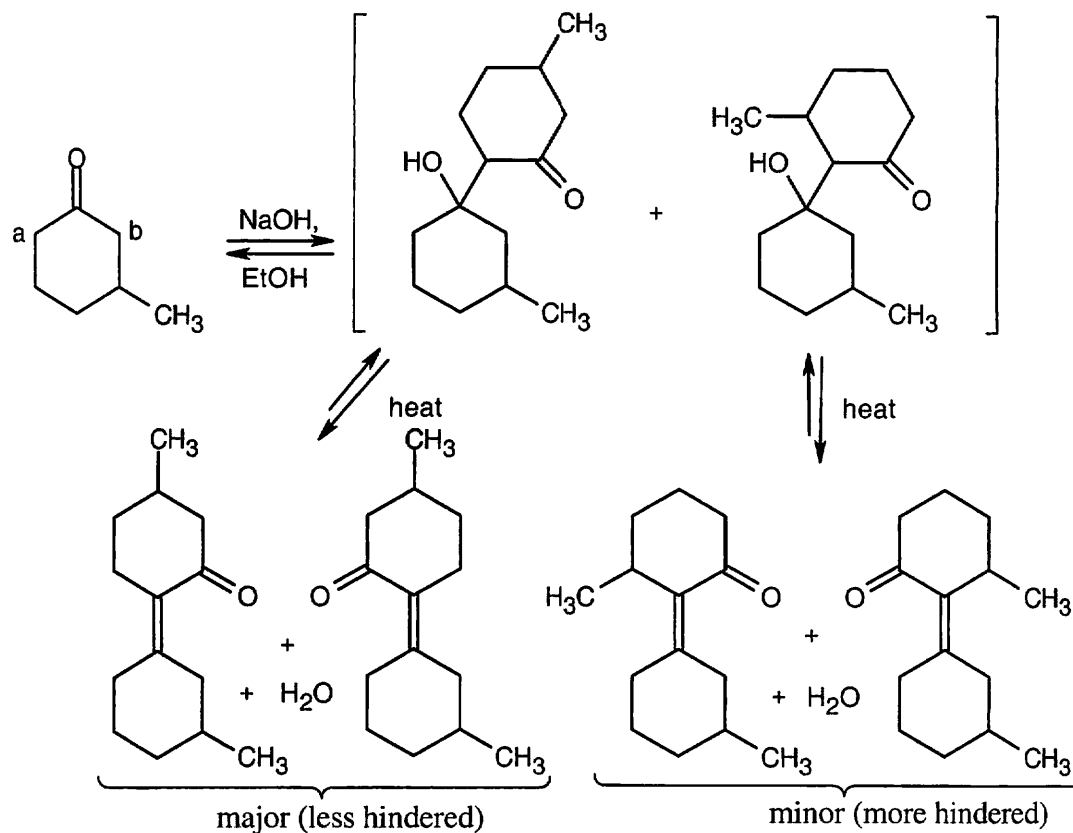


23.3 Strategy: As in Problem 23.1, align the two carbonyl compounds so that the location of the new bond is apparent. After drawing the addition product, form the conjugated enone product by dehydration. In parts (b) and (c), a mixture of *E,Z* isomers may be formed.

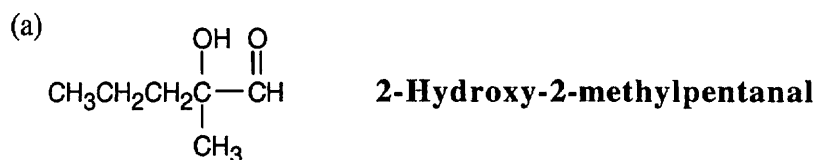
Solution:



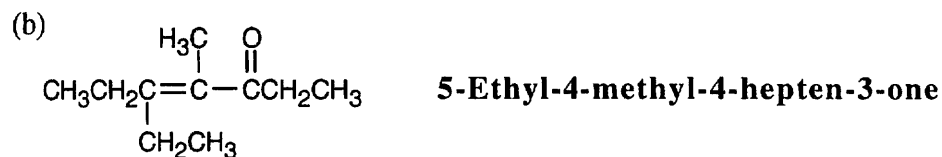
- 23.4 Including double bond isomers, 4 products can be formed. The major product is formed by reaction of the enolate formed by abstraction of a proton at position "a".



23.5

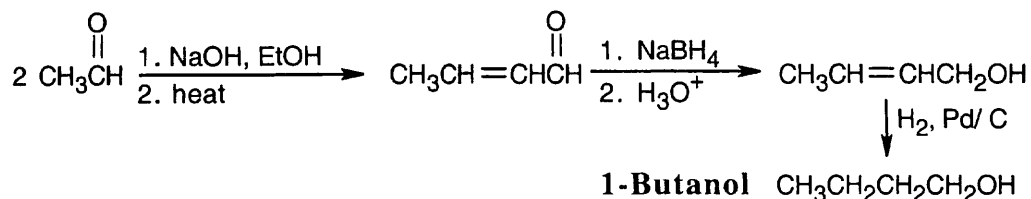


This is not an aldol product. The hydroxyl group in an aldol product must be β , not α , to the carbonyl group.

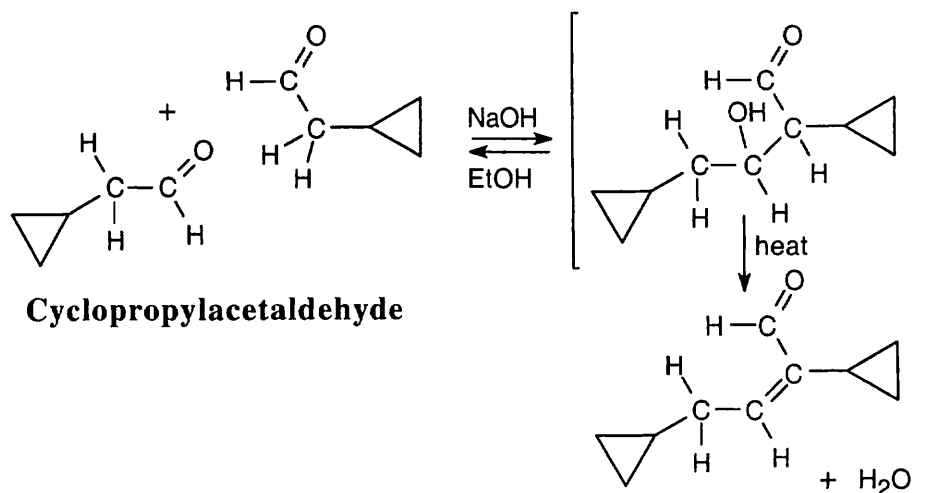


This product results from the aldol self-condensation of 3-pentanone, followed by dehydration.

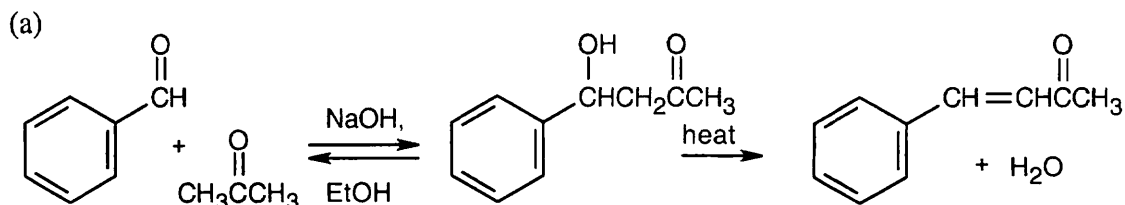
23.6



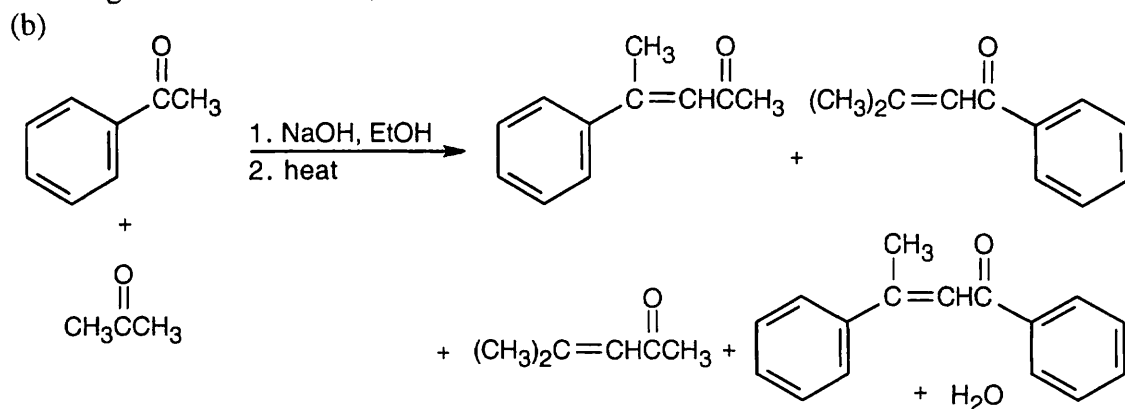
23.7



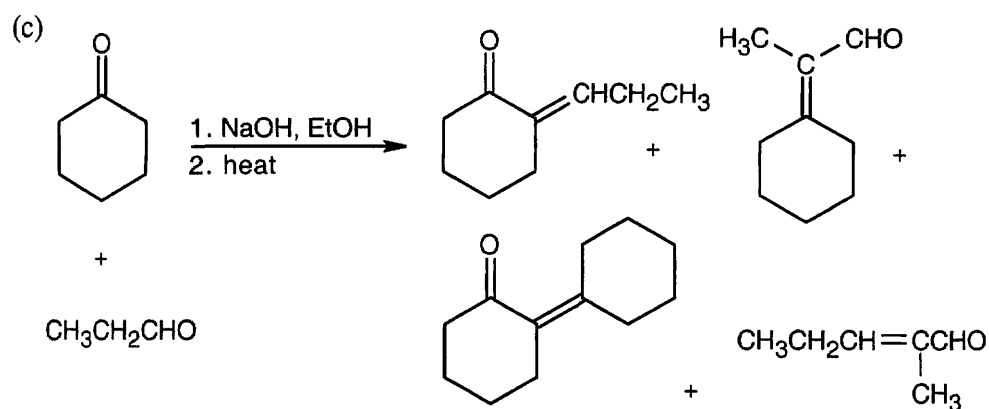
23.8

**4-Phenyl-3-buten-2-one**

This mixed aldol will succeed because one of the components, benzaldehyde, is a good acceptor of nucleophiles, yet has no α -hydrogen atoms. Although it is possible for acetone to undergo self-condensation, the mixed aldol reaction is much more favorable.

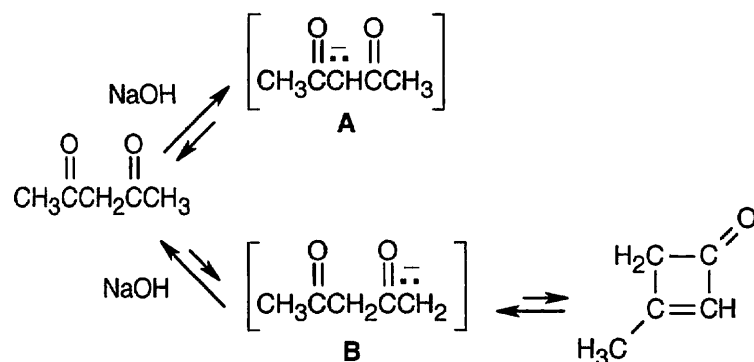


Four products result from the aldol condensation of acetone and acetophenone. The two upper compounds are mixed aldol products, and the bottom two are self-condensation products.



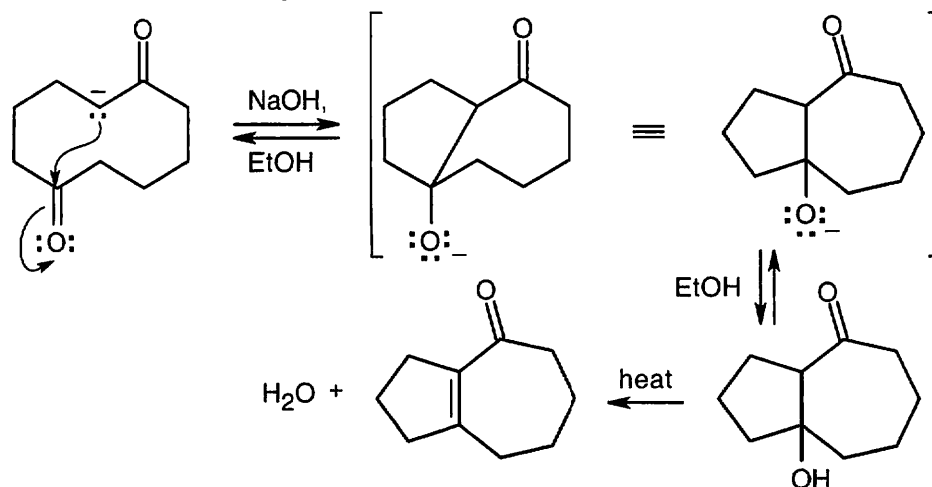
As in (b), a mixture of products is formed because both carbonyl partners contain α -hydrogen atoms. The upper two products result from mixed aldol condensations; the lower two are self-condensation products.

23.9

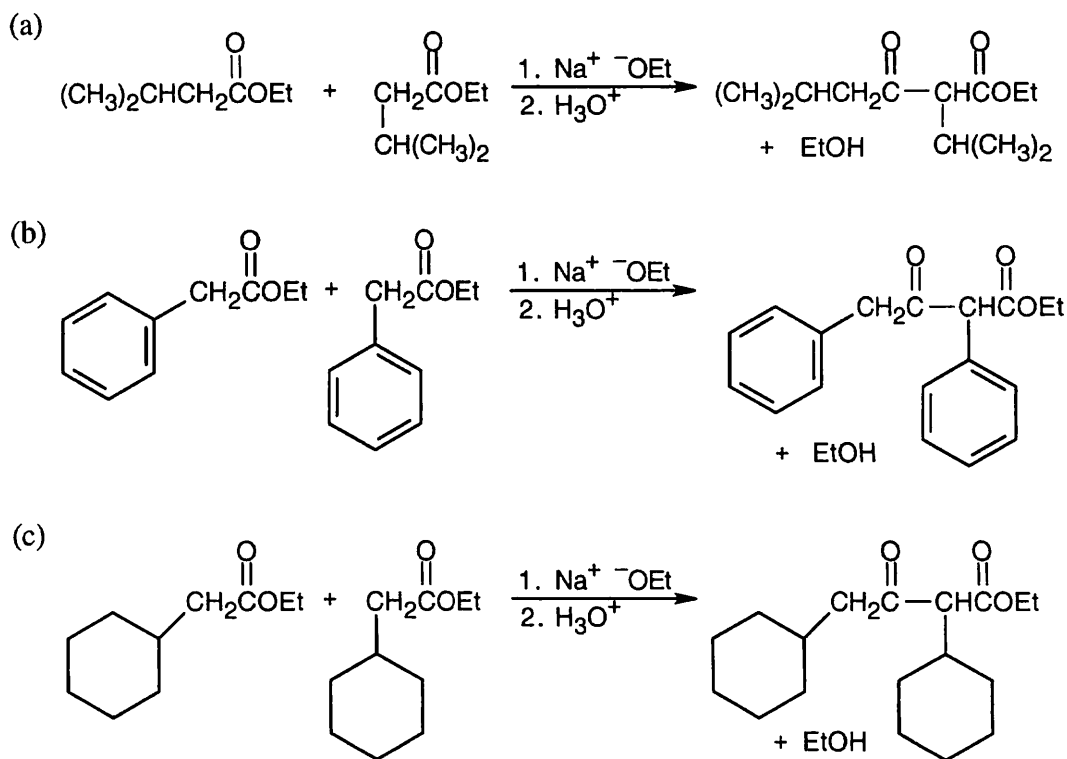


2,4-Pentanedione is in equilibrium with two enolate ions after treatment with base. Enolate A is stable and unreactive, while enolate B can undergo internal aldol condensation to form a cyclobutenone product. But, because the aldol reaction is reversible and the cyclobutenone product is highly strained, there is little of this product present when equilibrium is reached. At equilibrium, only the stable, diketone enolate ion A is present.

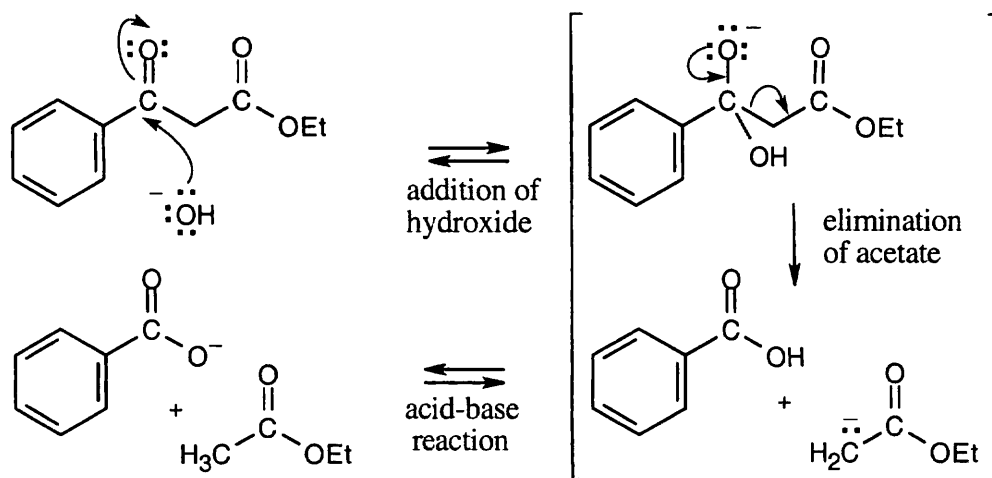
23.10 This intramolecular aldol condensation gives a product with a seven-membered ring fused to a five-membered ring.



23.11 As in the aldol condensation, writing the two Claisen components with the correct orientation makes it easier to predict the product.

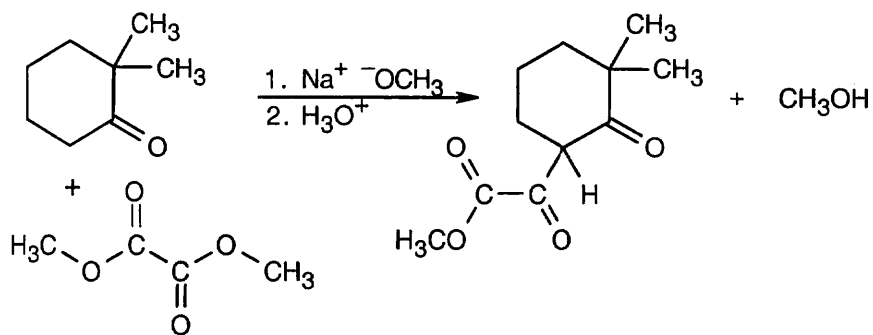


23.12

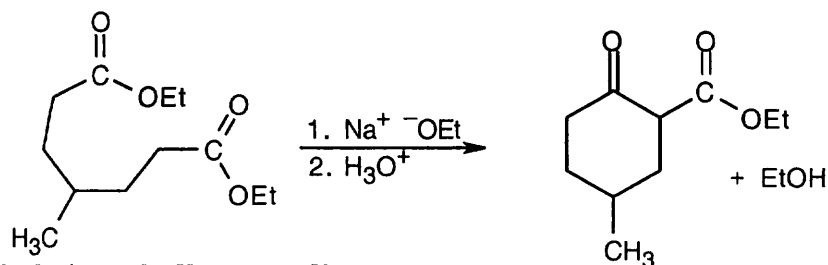


Hydroxide ion can react at two different sites of the β -keto ester. Abstraction of the acidic α -proton is more favorable but is reversible and does not lead to product. Addition of hydroxide ion to the carbonyl group, followed by irreversible elimination of ethyl acetate anion, accounts for the observed product.

23.13 As shown in Worked Example 23.4, dimethyl oxalate is a very effective reagent in mixed Claisen reactions.

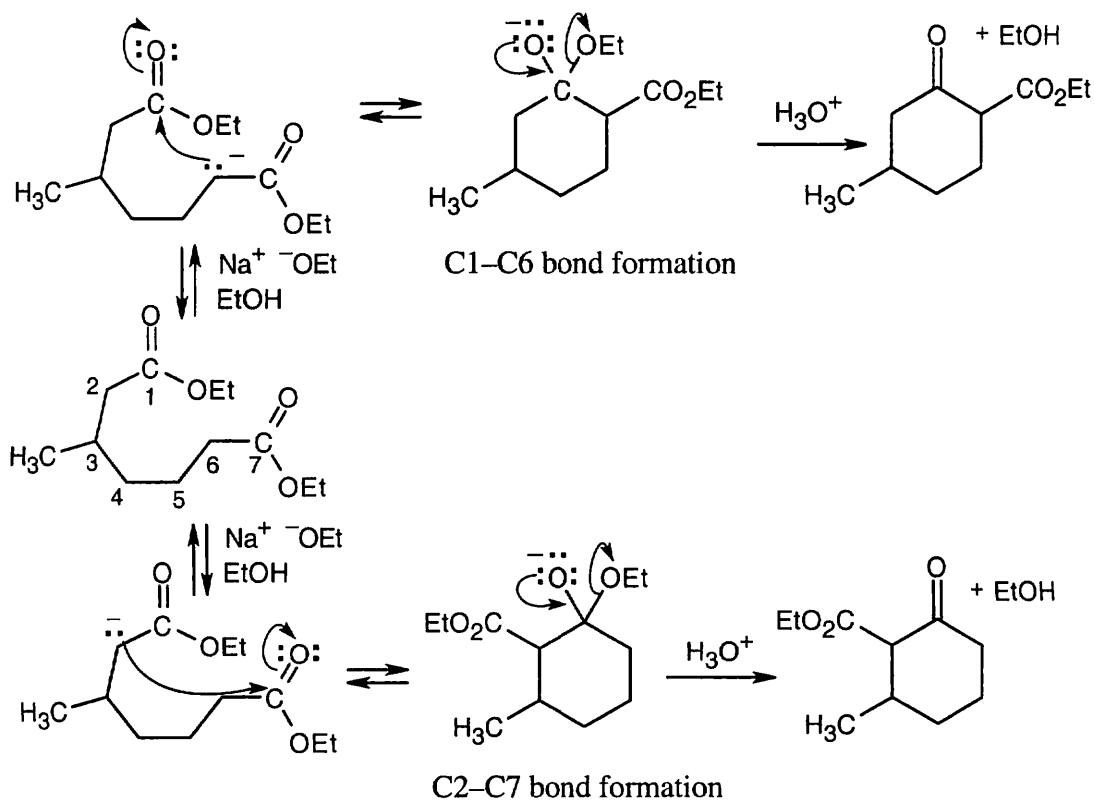


23.14



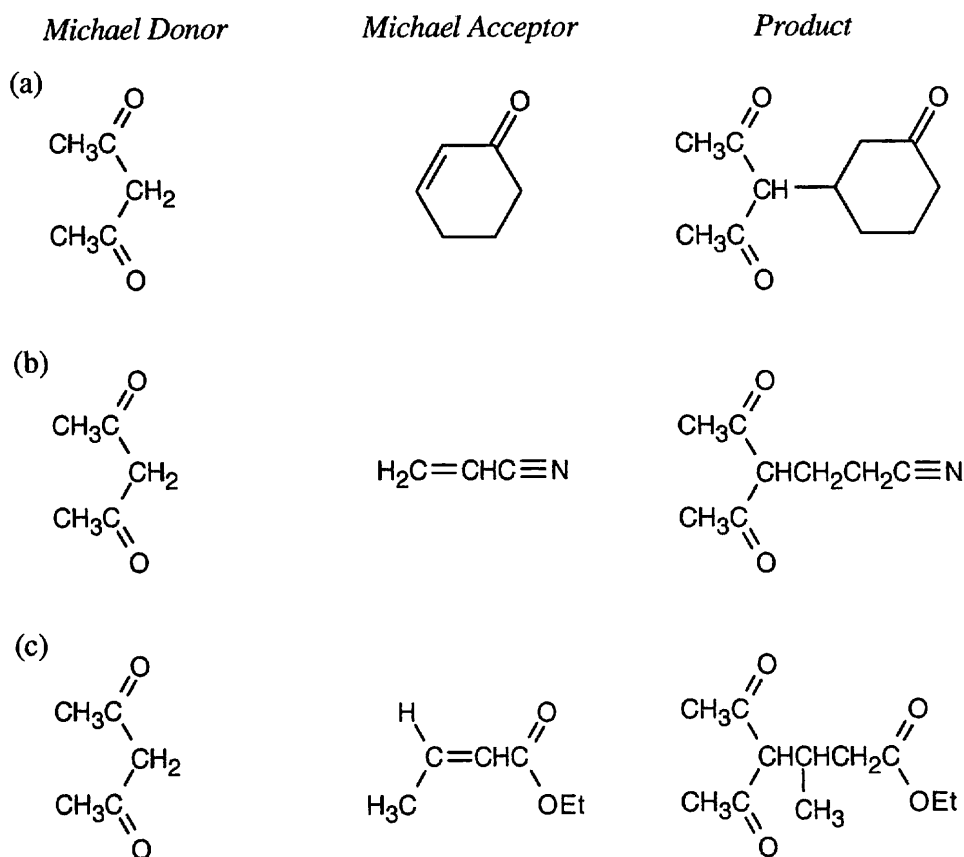
Diethyl 4-methylheptanedioate

23.15

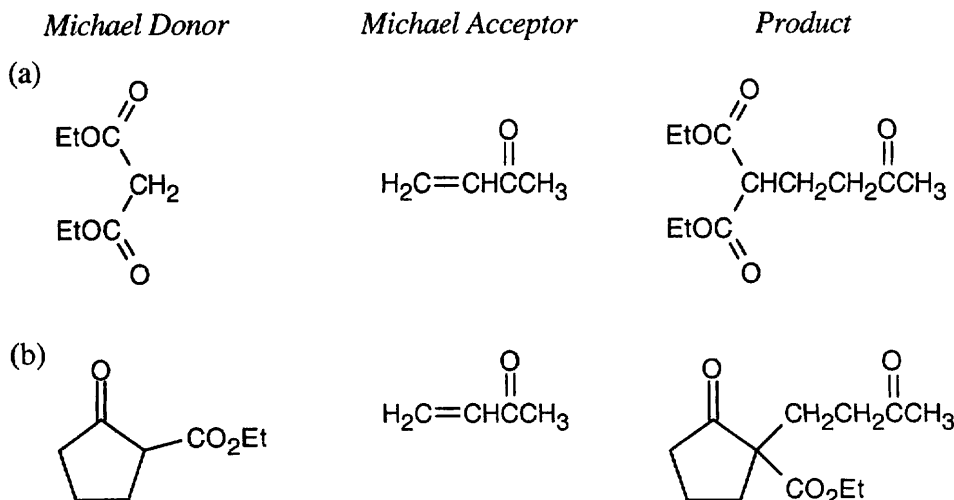


Unlike diethyl 4-methylheptanedioate shown in the previous problem, diethyl 3-methylheptanedioate is unsymmetrical. Two different enolates can form, and each can cyclize to a different product.

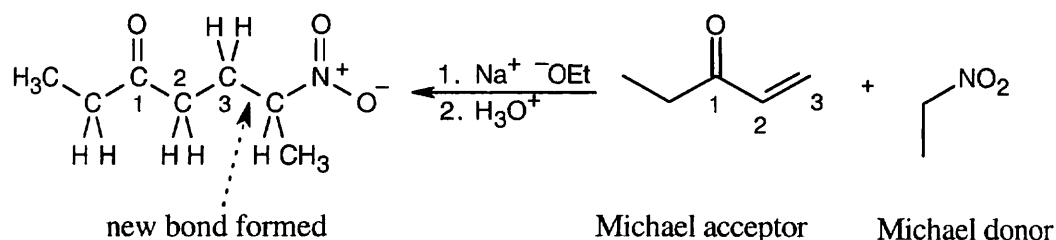
23.16 A Michael reaction takes place when a stable enolate ion (Michael donor) adds to the double bond of an α,β -unsaturated carbonyl compound (Michael acceptor). The enolate adds to the double bond of the conjugated system. Predicting Michael products is easier when the donor and acceptor are positioned so that the product is apparent.



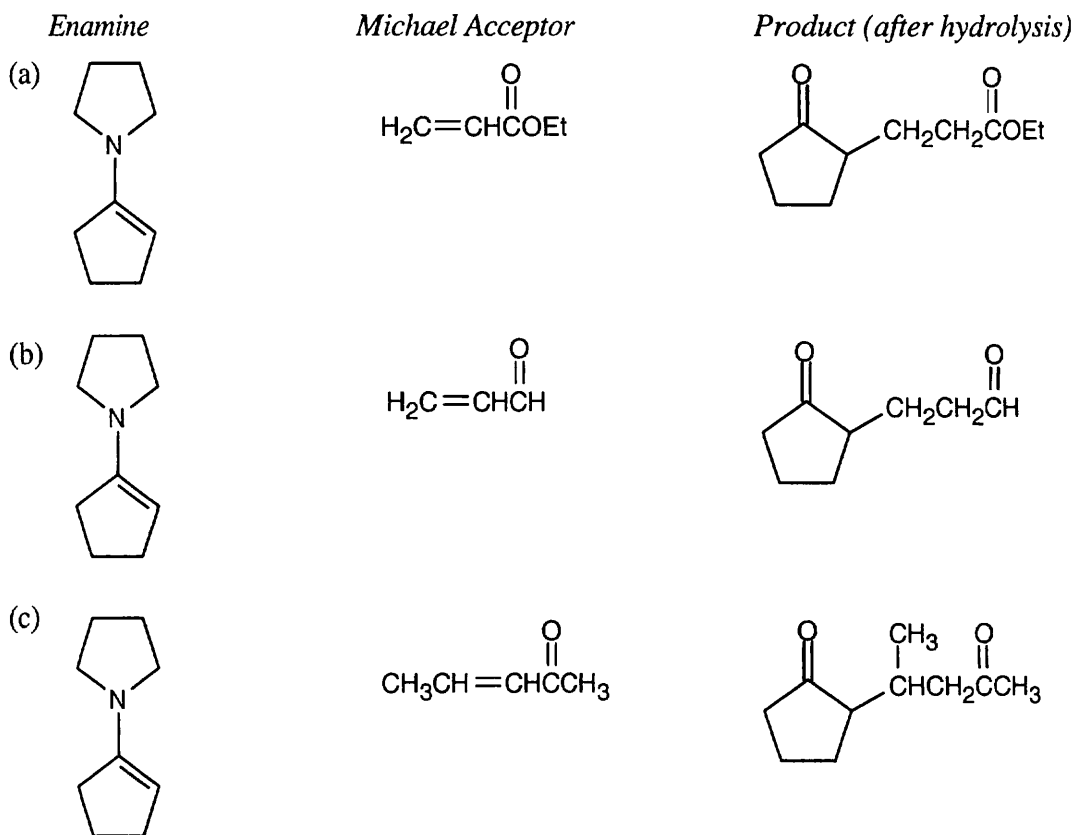
23.17



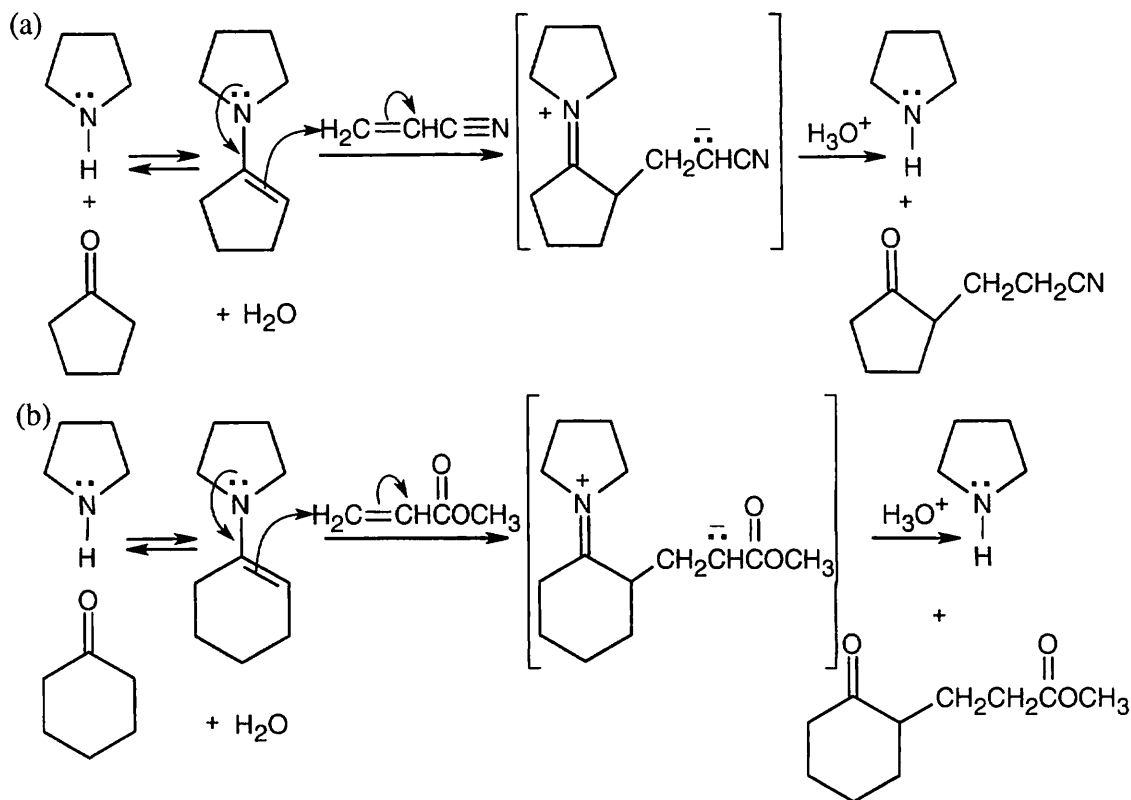
23.18 Find the carbonyl group of the Michael acceptor, and count three carbons away from the carbonyl group. The Michael donor forms the new bond to this carbon. Break this bond to identify the Michael donor and Michael acceptor.



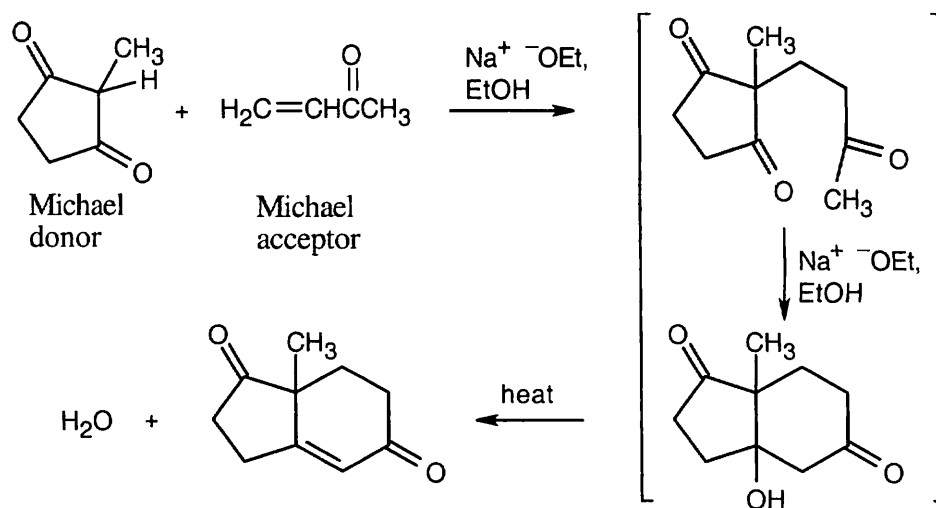
23.19 An enamine is formed from a ketone when it is necessary to synthesize a 1,5-diketone or a 1,5-dicarbonyl compound containing an aldehyde or ketone. The ketone starting material is converted to an enamine in order to increase the reactivity of the ketone and to direct the regiochemistry of addition. The process, as described in Section 23.11, is: (1) conversion of a ketone to its enamine; (2) Michael addition to an α,β -unsaturated carbonyl compound; (3) hydrolysis of the enamine to the starting ketone.



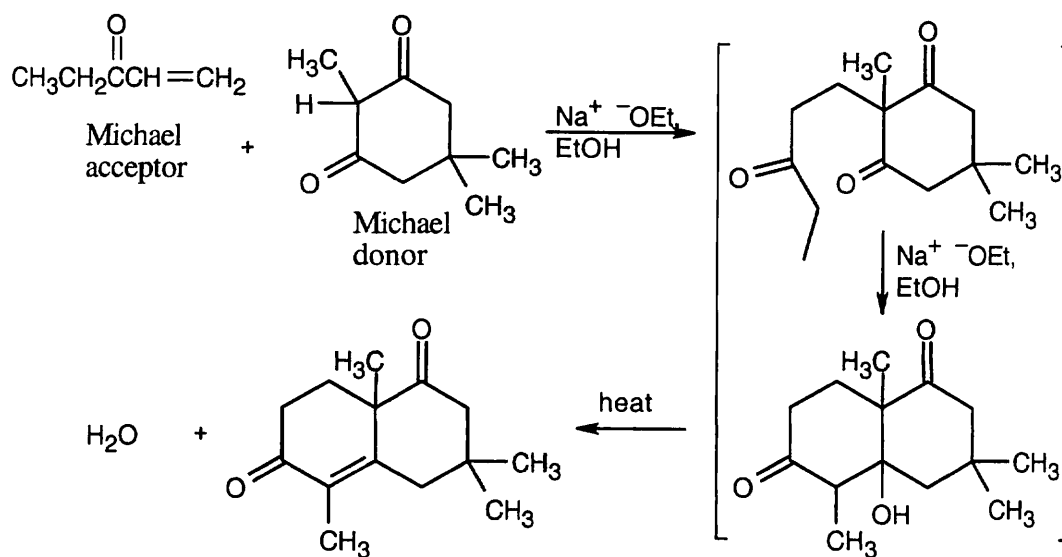
23.20 Analyze the product for the Michael acceptor and the ketone. In (a), the Michael acceptor is propenenitrile. The ketone is cyclopentanone, which is treated with pyrrolidine to form the enamine.



23.21 The Robinson annulation is a combination of two reactions covered in this chapter. First, a Michael reaction takes place between a nucleophilic donor (the diketone in this problem) and an α,β -unsaturated carbonyl compound (the enone shown). The resulting product can cyclize in an aldol reaction. The base catalyzes both reactions.



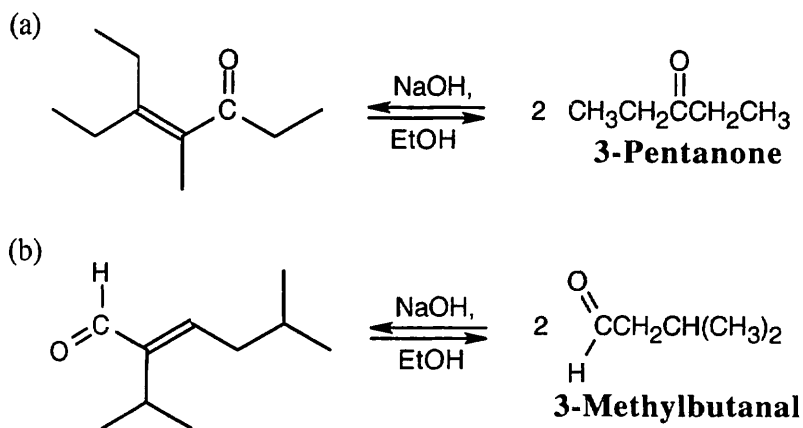
23.22



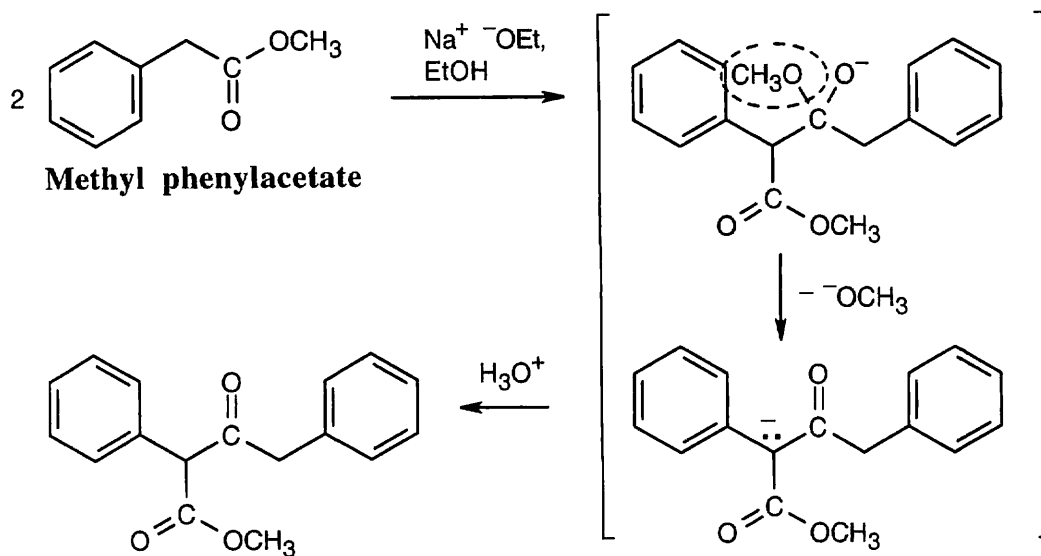
This is one of the more complicated-looking syntheses that we have seen. First, analyze the product for the two Michael components. The carbon-carbon double bond arises from dehydration of the aldol addition product, and is located where one of the two $\text{C}=\text{O}$ groups of the original diketone used to be. The Michael addition takes place at the carbon between these ketone groups. The Michael acceptor is an enone that can also enter into the aldol condensation and furnishes the methyl group attached to the double bond.

Visualizing Chemistry

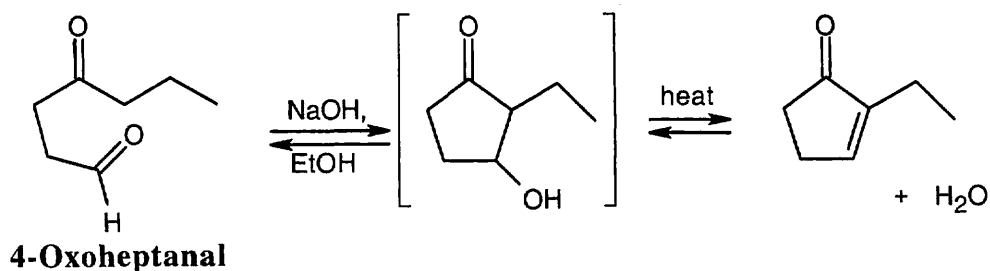
23.23



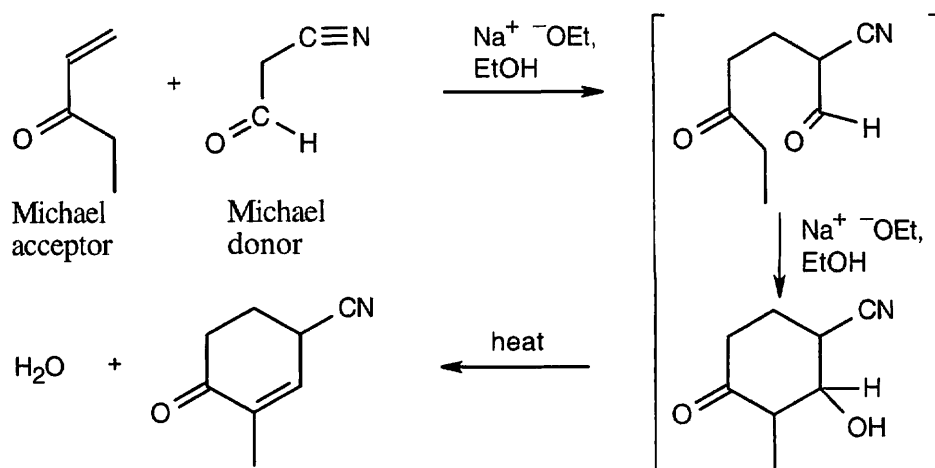
23.24 The enolate of methyl phenylacetate adds to a second molecule of methyl phenylacetate to form the Claisen intermediate that is pictured. Elimination of methoxide (circled) and acidification give the product shown.



23.25

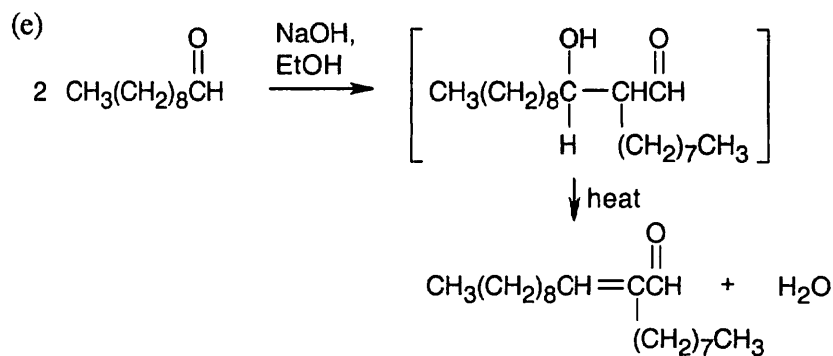
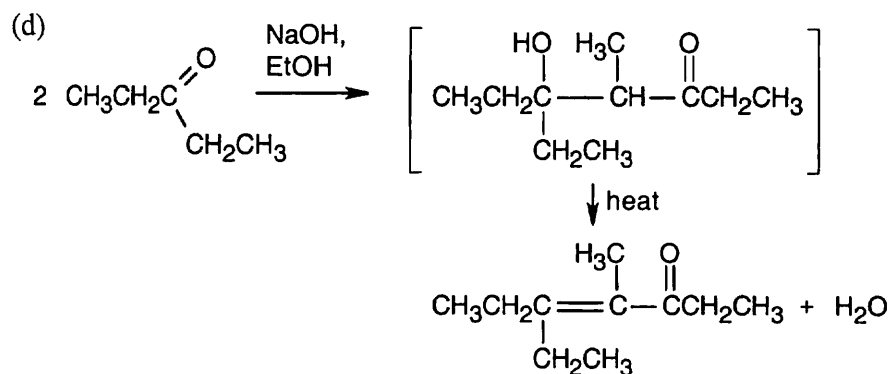
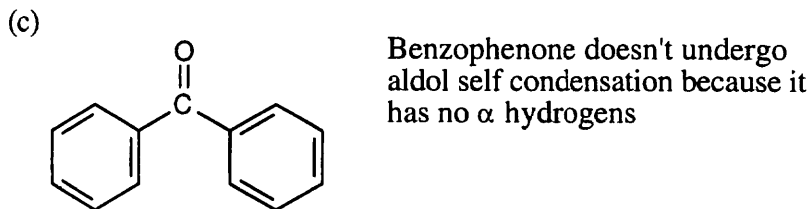
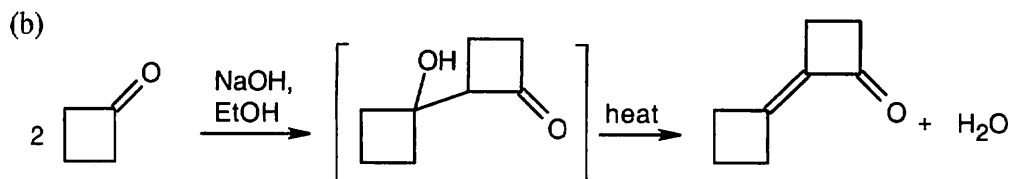


23.26 Remember that the new carbon-carbon double bond in the product connects one of the carbonyl carbons of the Michael donor with an α carbon of the Michael acceptor.



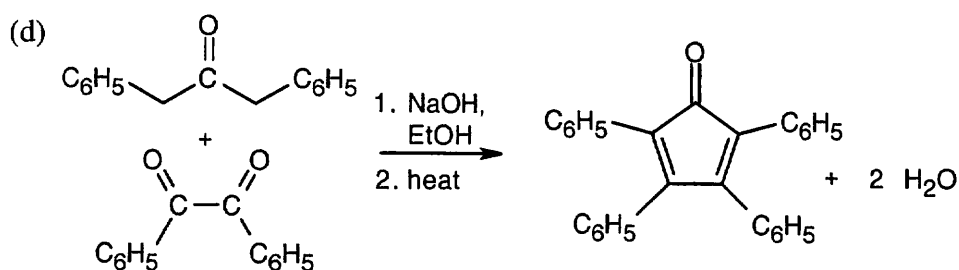
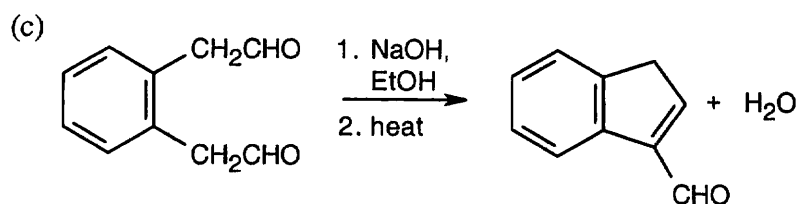
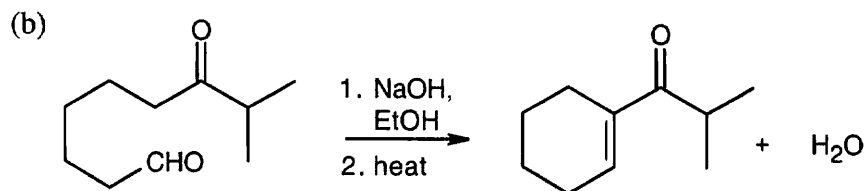
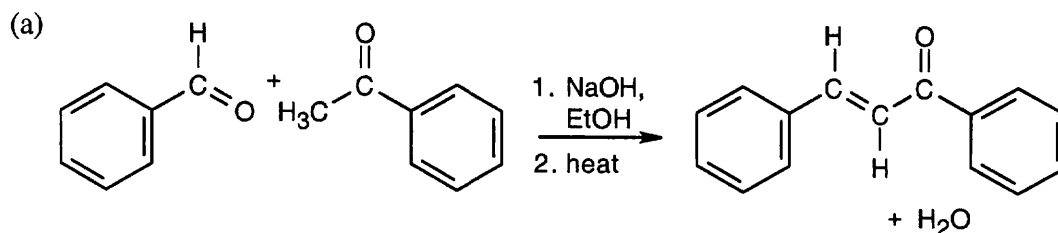
Additional Problems

23.27 (a) $(\text{CH}_3)_3\text{CCHO}$ has no α hydrogens and does not undergo aldol self-condensation.

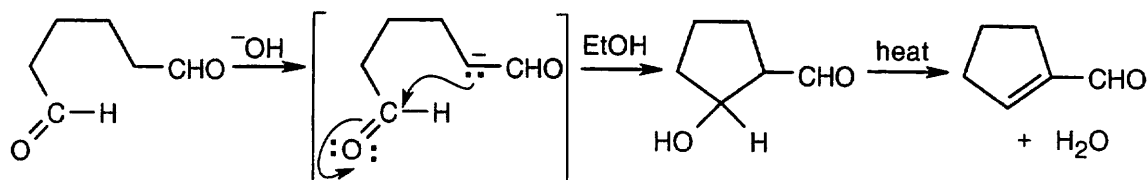


(f) $\text{C}_6\text{H}_5\text{CH}=\text{CHCHO}$ does not undergo aldol reactions because its α proton isn't acidic.

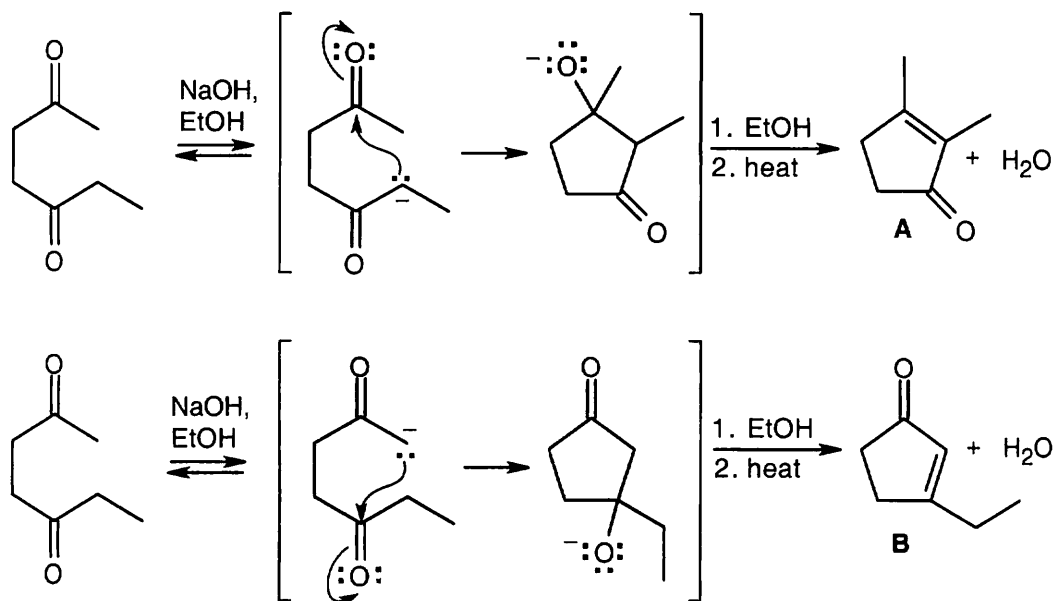
23.28 As always, analyze the product for the carbon-carbon double bond that is formed by dehydration of the initial aldol adduct. Break the bond, and add a carbonyl oxygen to the appropriate carbon to identify the carbonyl reactant(s).



23.29

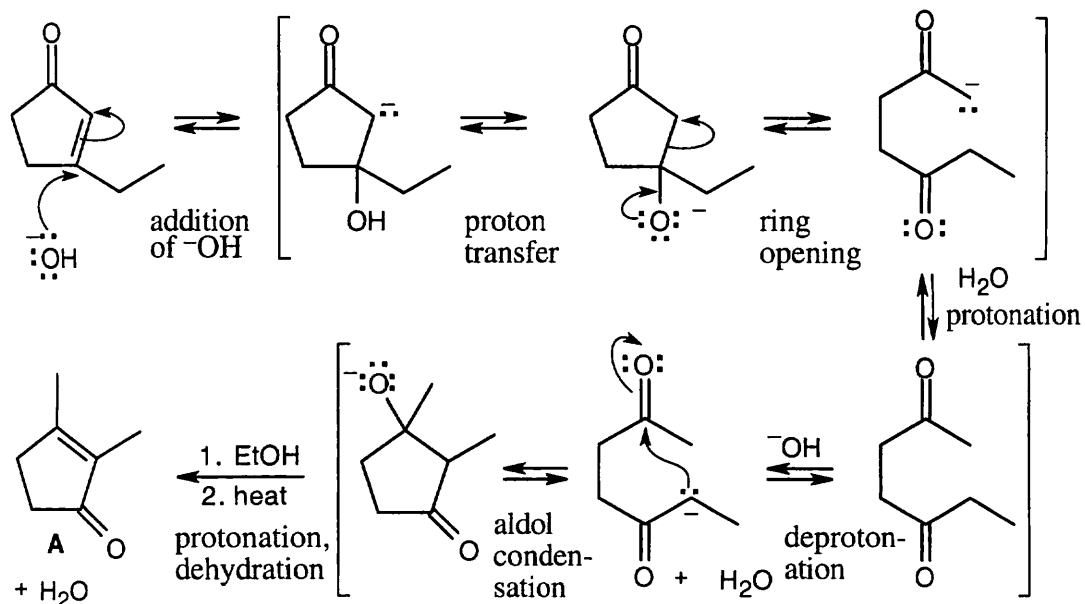


23.30



23.31 Product A, which has two singlet methyl groups and no vinylic protons in its ¹H NMR, is the major product of the intramolecular cyclization of 2,5-heptanedione.

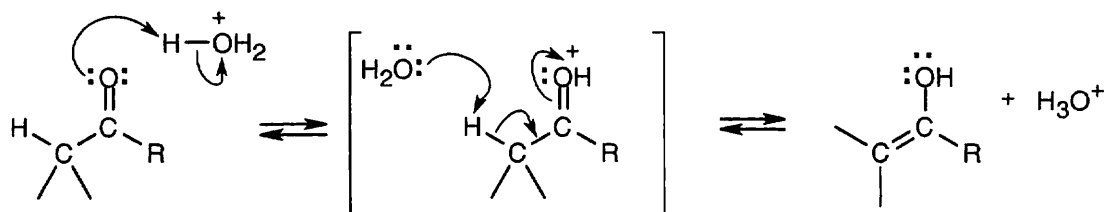
23.32



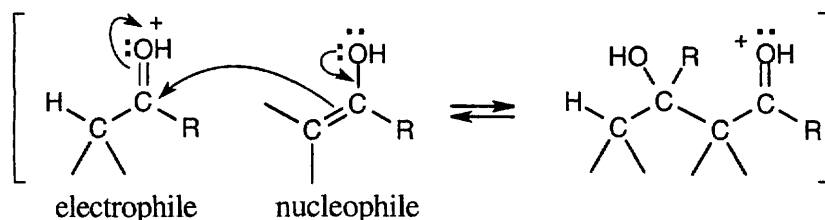
Because all steps in the aldol reaction are reversible, the more stable product is formed at equilibrium.

23.33 The reactive nucleophile in the acid-catalyzed aldol condensation is the *enol* of one of the reactants. The electrophile is a reactant with a protonated carbonyl group.

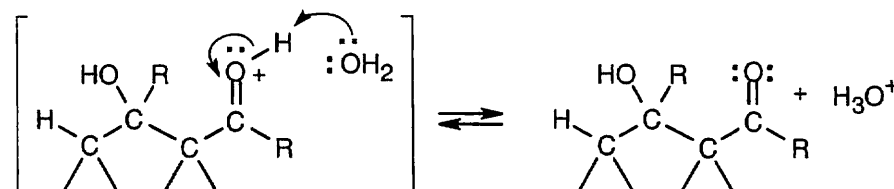
Step 1: Enol formation.



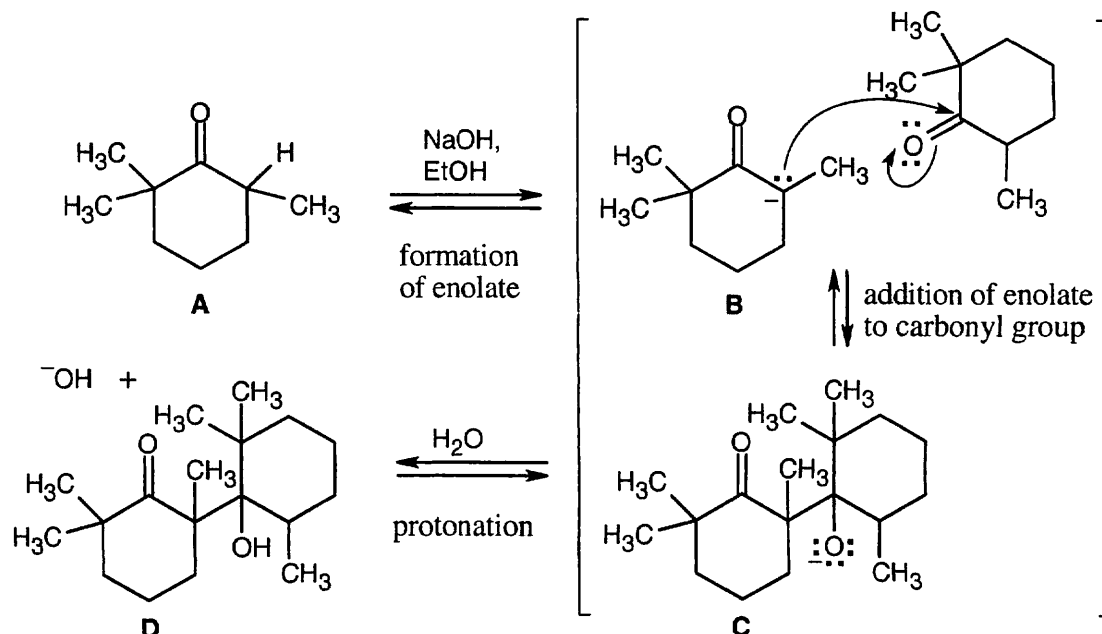
Step 2: Addition of the enol nucleophile to the protonated carbonyl compound.



Step 3: Loss of proton from the carbonyl oxygen.

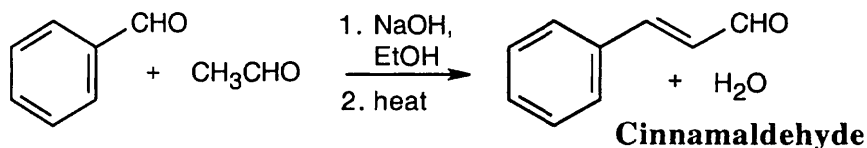


23.34



An aldol condensation involves a series of reversible equilibrium steps. In general, formation of product is favored by the dehydration of the β -hydroxy ketone to form a conjugated enone. Here, dehydration to form conjugated product can't occur. In addition, the $B \rightleftharpoons C$ equilibrium favors **B** because of steric hindrance.

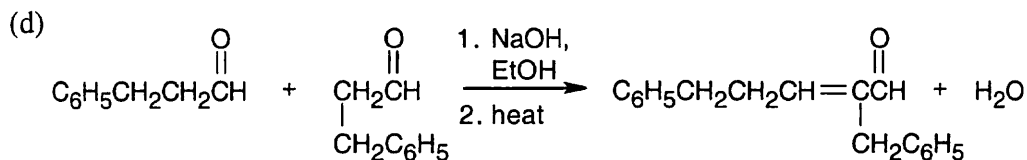
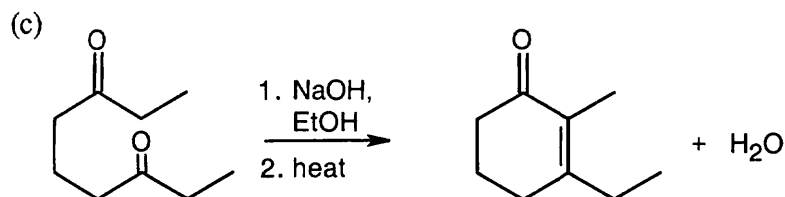
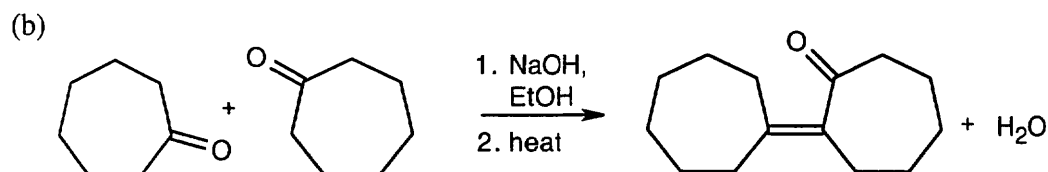
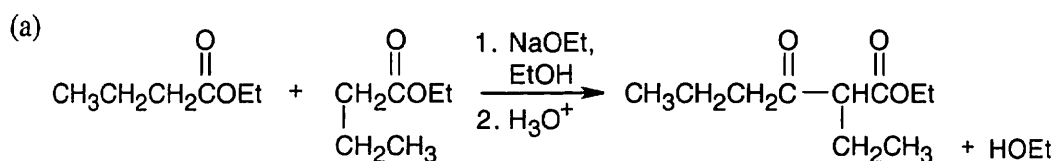
23.35



Although self-condensation of acetaldehyde can take place, the mixed aldol product predominates.

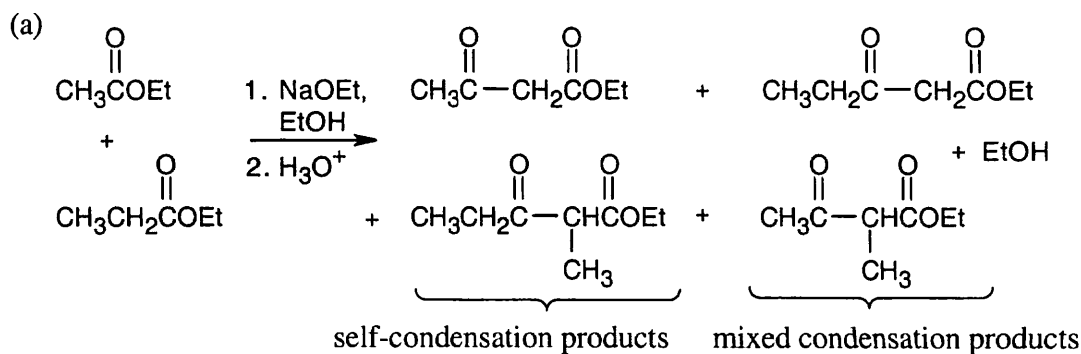
23.36 The first step of an aldol condensation is enolate formation. The ketone shown here does not enolize because double bonds at the bridgehead of small bicyclic ring systems are too strained to form. Since the bicyclic ketone does not enolize, it doesn't undergo aldol condensation.

23.37

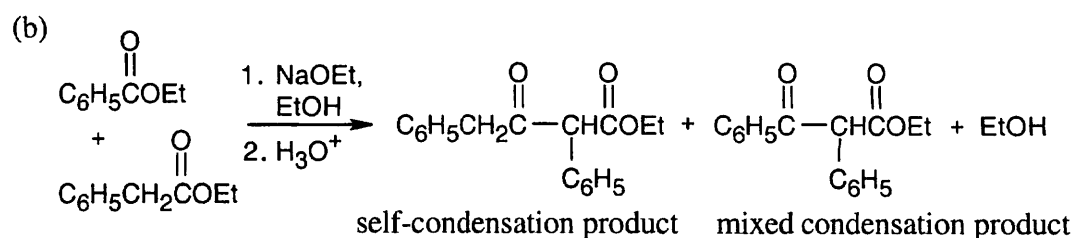


23.38 If cyclopentanone and base are mixed first, aldol self-condensation of cyclopentanone can occur before ethyl formate is added. If both carbonyl components are mixed together before adding base, the more favorable mixed Claisen condensation occurs with less competition from the aldol self-condensation reaction.

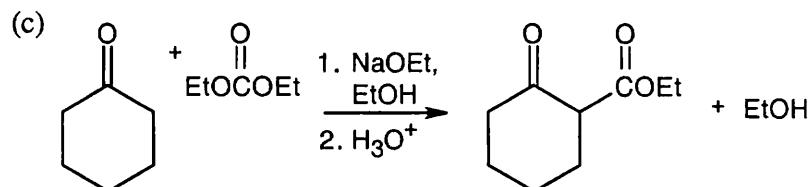
23.39



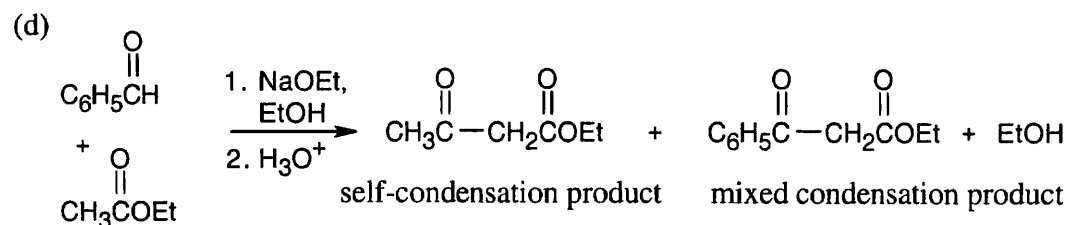
Approximately equal amounts of each product will form if the two esters are of similar reactivity.



The mixed condensation product predominates.

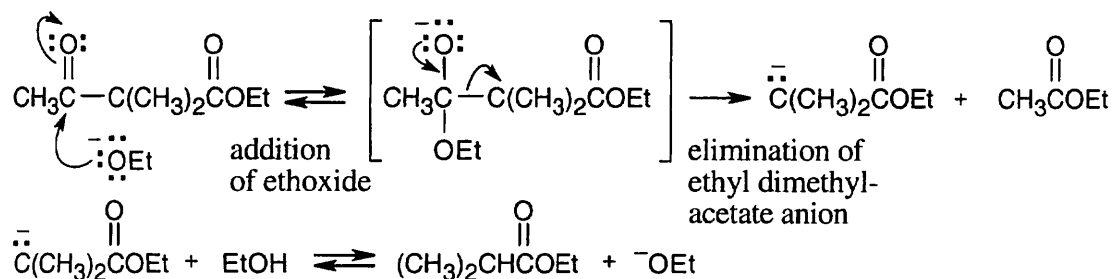


This is the only *Claisen* monocondensation product (aldol self-condensation of cyclohexanone also occurs).



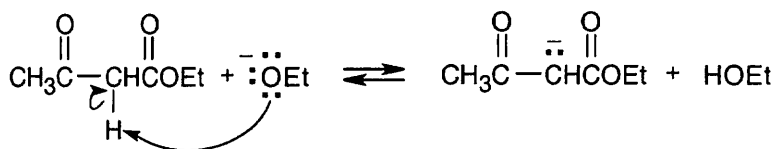
The mixed Claisen product is the major product.

23.40



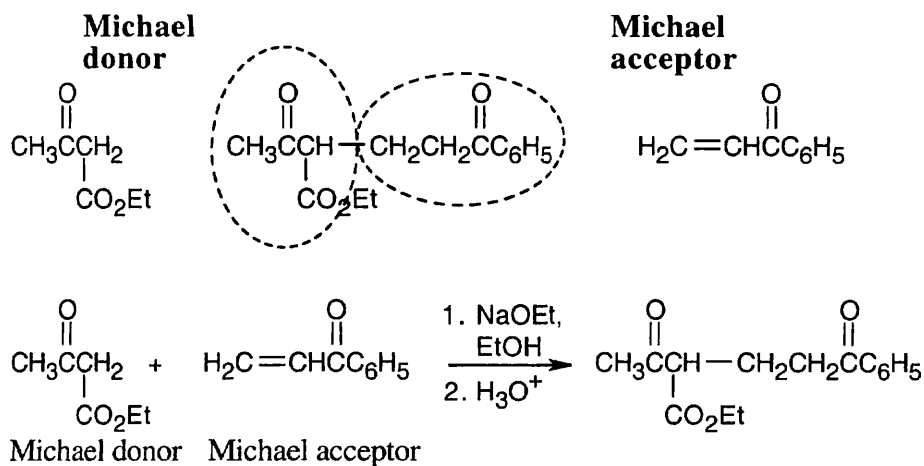
This is a reverse Claisen reaction.

- 23.41** Two different reactions are possible when ethyl acetoacetate reacts with ethoxide anion. One possibility involves attack of ethoxide ion on the carbonyl carbon, followed by elimination of the anion of ethyl acetate—a reverse Claisen reaction similar to the one illustrated in 23.40. More likely, however, is the acid–base reaction of ethoxide ion and a doubly activated α -hydrogen of ethyl acetoacetate.

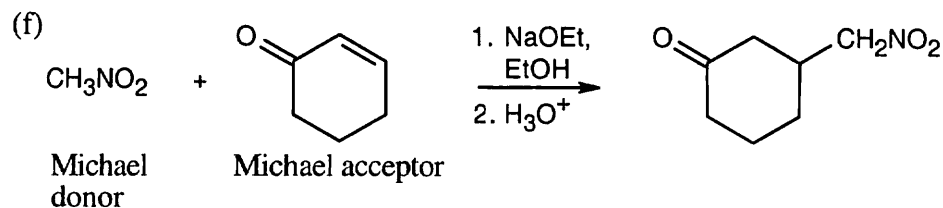
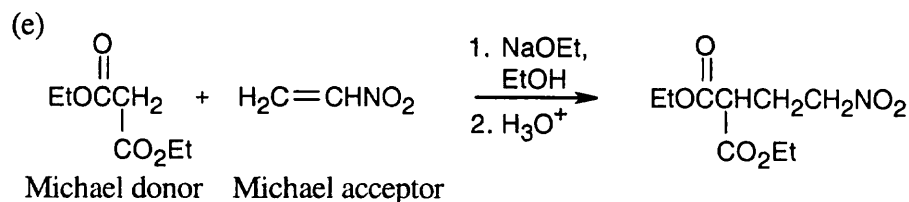
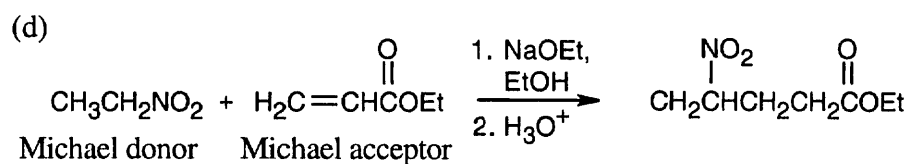
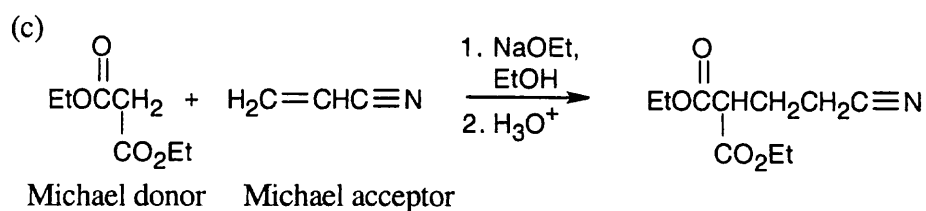
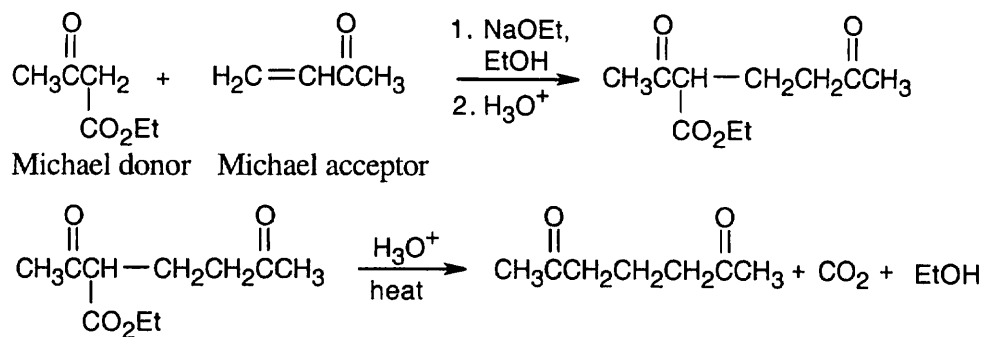


The resonance-stabilized acetoacetate anion is no longer reactive toward nucleophiles, and no further reaction occurs at room temperature. Elevated temperatures are required to make the cleavage reaction proceed. This complication doesn't occur with ethyl dimethylacetoacetate because it has no acidic hydrogens between its two carbonyl groups.

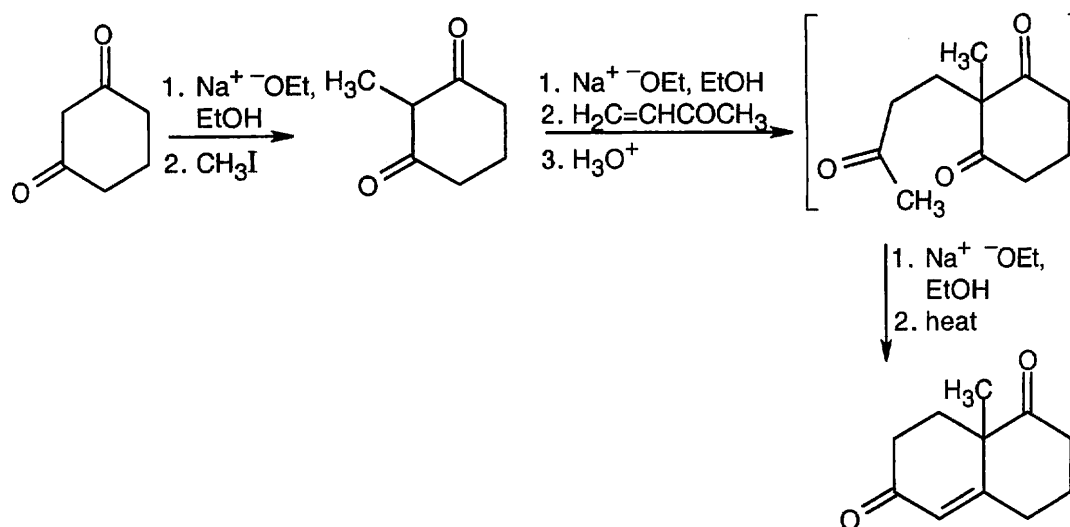
- 23.42** Michael reactions occur between stabilized enolate anions and α,β -unsaturated carbonyl compounds. Learn to locate these components in possible Michael products. Usually, it is easier to recognize the enolate nucleophile; in (a), the nucleophile is the ethyl acetoacetate anion. The rest of the compound is the Michael acceptor. Draw a double bond in conjugation with the electron-withdrawing group in this part of the molecule.



(b) When the Michael product has been decarboxylated after the addition reaction, it is more difficult to recognize the original enolate anion.



23.43

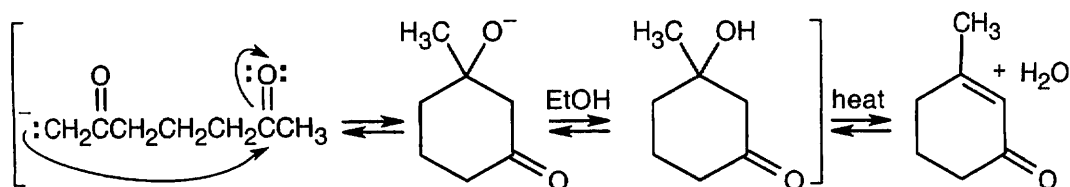


This sequence of reactions consists of an alkylation of a 1,3-diketone, followed by a Robinson annulation. The carbon-carbon double bond appears where the second carbonyl group of the diketone used to be and is the site of the ring-forming aldol reaction. A Michael reaction between the diketone and the Michael acceptor 3-buten-2-one adds the carbon atoms used to form the second ring, and an alkylation with CH_3I adds the methyl group.

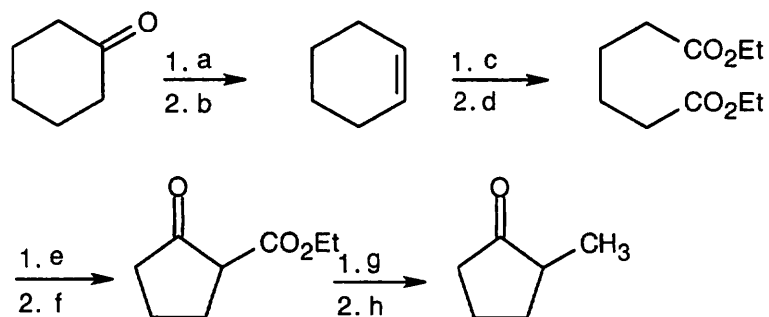
23.44 (a) Several other products are formed in addition to the one pictured. Self-condensation of acetaldehyde and acetone (less likely) can occur, and an additional mixed product is formed.

(b) There are two problems with this reaction. (1) Michael reactions occur in low yield with mono-ketones. Formation of the enamine, followed by the Michael reaction, gives a higher yield of product. (2) Addition can occur on either side of the ketone to give a mixture of products.

(c) Internal aldol condensation of 2,6-heptanedione can product a four-membered ring or a six-membered ring. The six-membered ring is more likely to form because it is less strained.

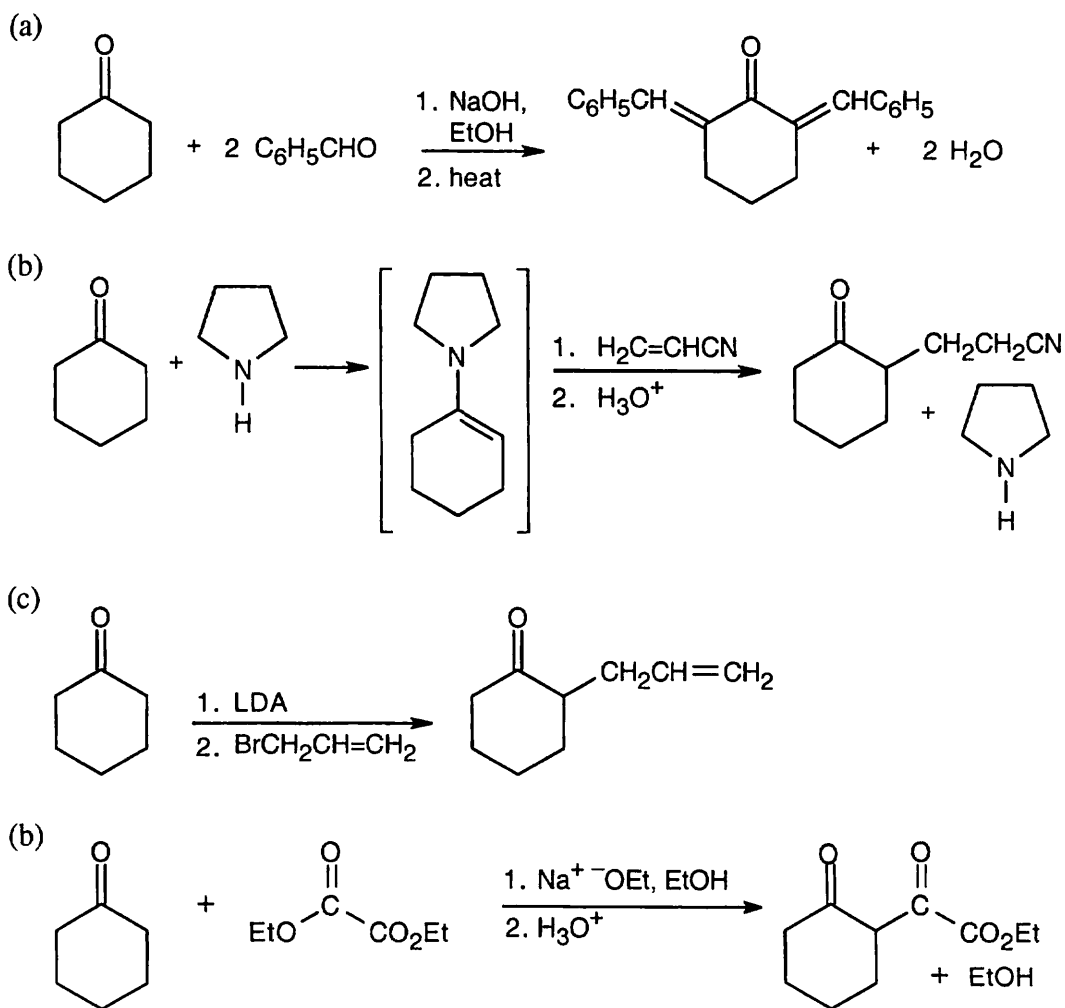


23.45

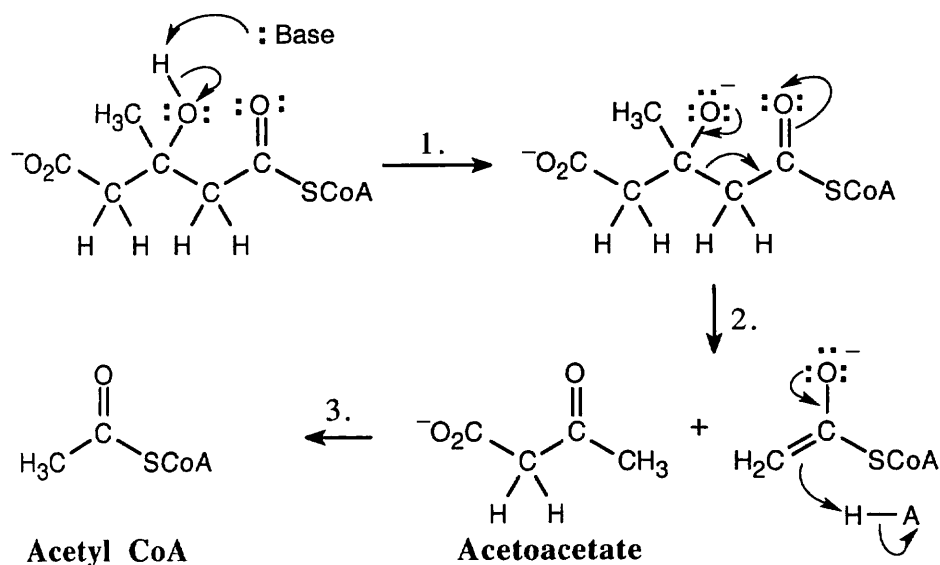


(a) LiAlH_4 , then H_3O^+ ; (b) POCl_3 , pyridine (c) KMnO_4 , H_3O^+ ; (d) $\text{CH}_3\text{CH}_2\text{OH}$, H^+ ;
 (e) $\text{Na}^+ \text{ } ^-\text{OEt}$; (f) H_3O^+ ; (g) $\text{Na}^+ \text{ } ^-\text{OEt}$, then CH_3Br ; (h) H_3O^+ , heat

23.46



23.47 This sequence is a reverse aldol reaction.

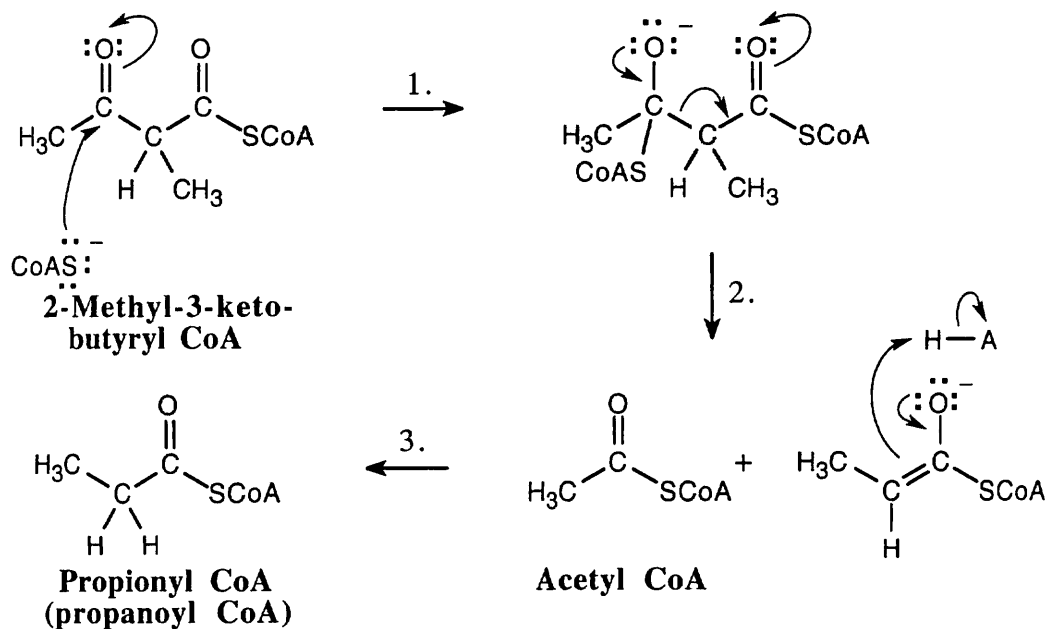


Step 1: Deprotonation by base.

Step 2: Elimination of acetyl CoA enolate.

Step 3: Protonation.

23.48 In contrast to the previous problem, this sequence is a reverse Claisen reaction. The first step (not illustrated) is the reaction of HSCoA with a base to form SCoA^- .

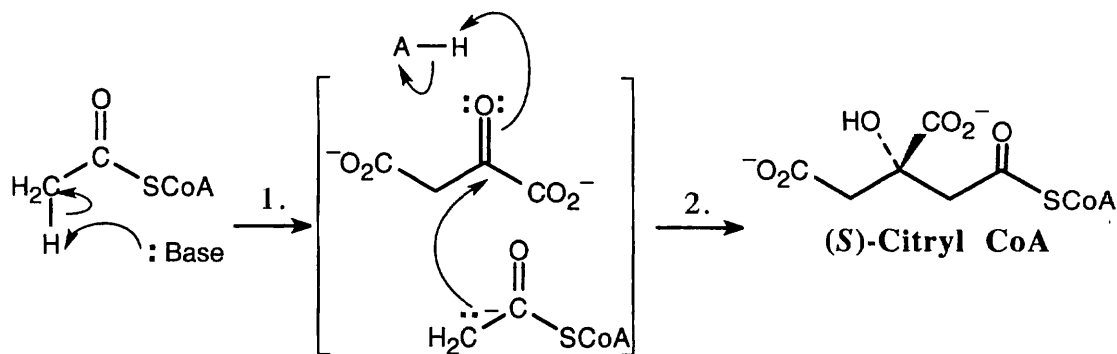


Step 1: Addition of SCoA^- to form a tetrahedral intermediate.

Step 2: Elimination of propionyl CoA anion.

Step 3: Protonation.

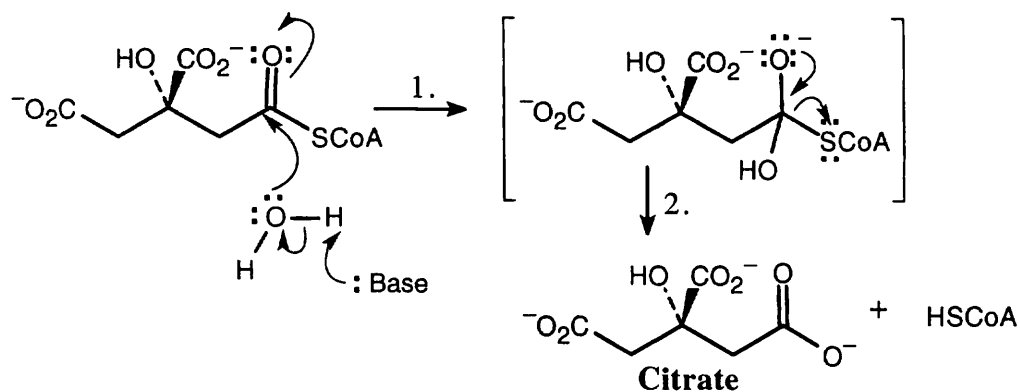
23.49 Formation of (S)-citryl CoA:



Step 1: Formation of acetyl CoA enolate.

Step 2: Aldol-like nucleophilic addition of acetyl CoA to the carbonyl group of oxaloacetate and protonation.

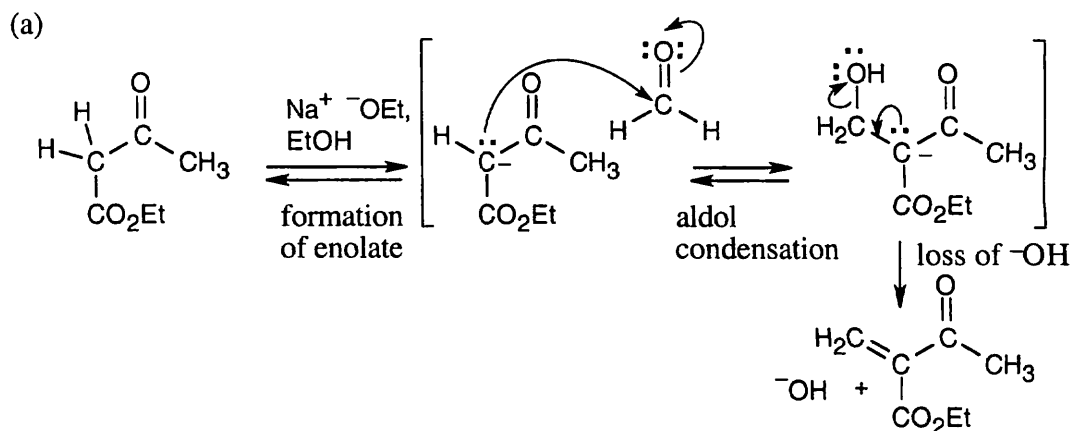
Loss of CoA to form citrate:

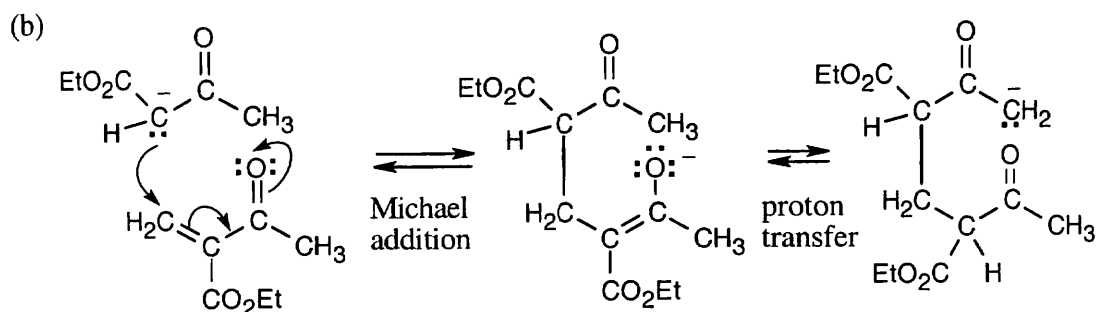


Step 1: Nucleophilic addition of hydroxyl to the carbonyl group of (S)-citryl CoA.

Step 2: Loss of SCoA^- and protonation of the leaving group.

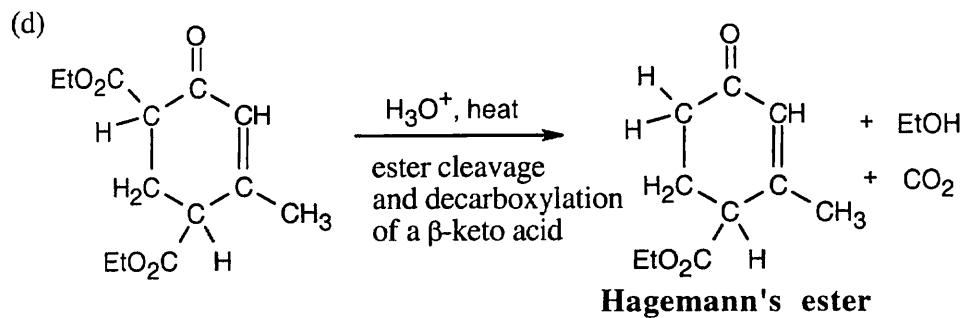
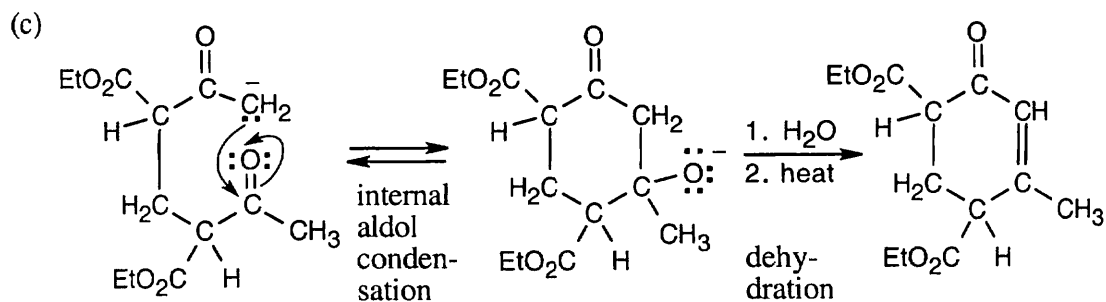
23.50



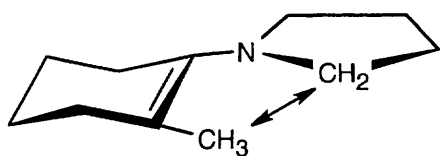


The protonated form of the above structure is the product.

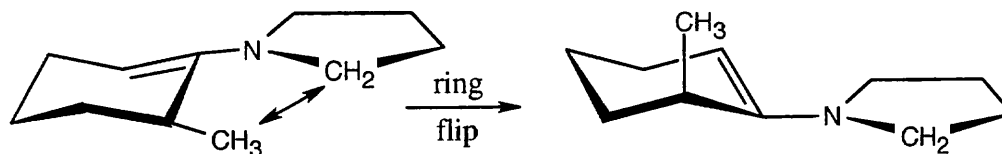
23.51



23.52

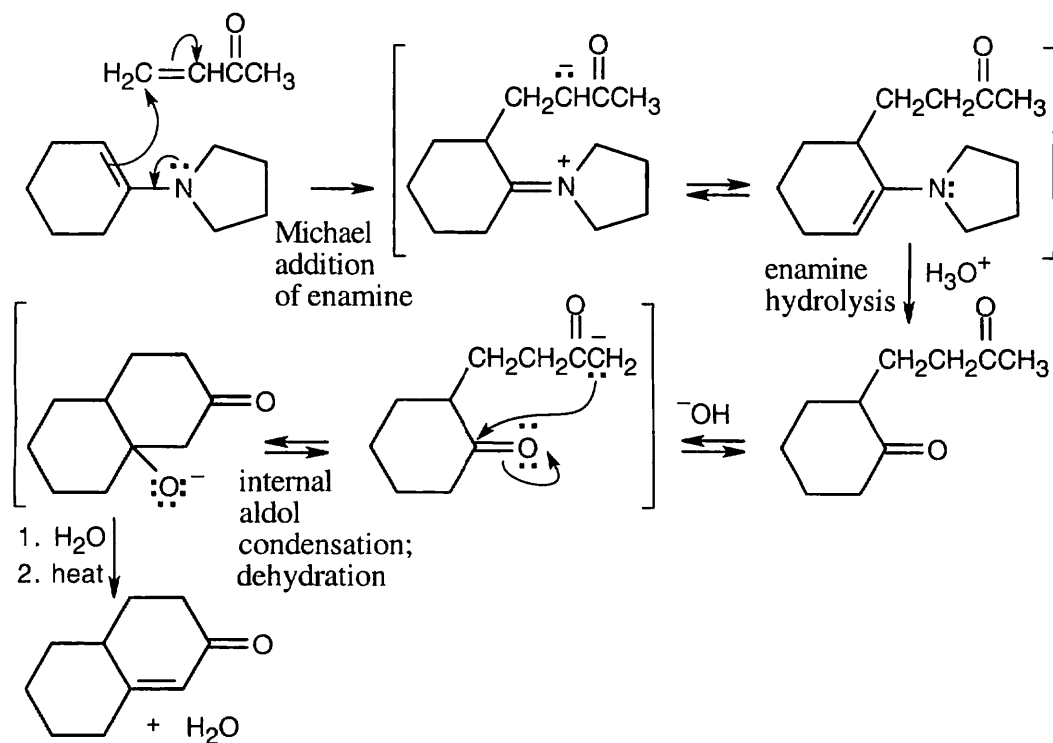


Crowding between the methyl group and the pyrrolidine ring disfavors this enamine.

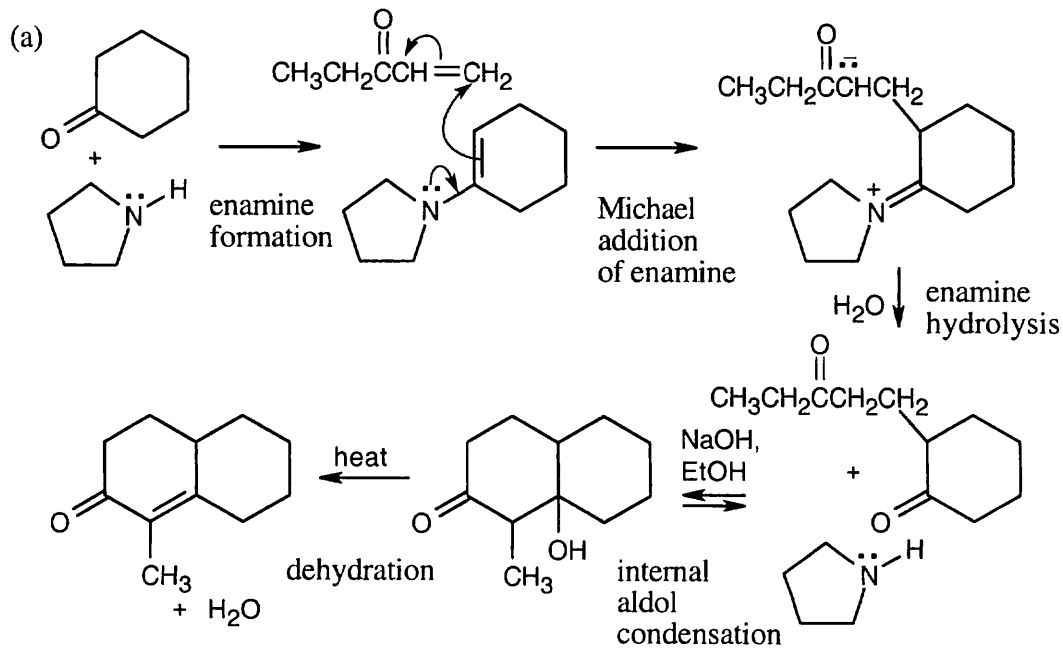


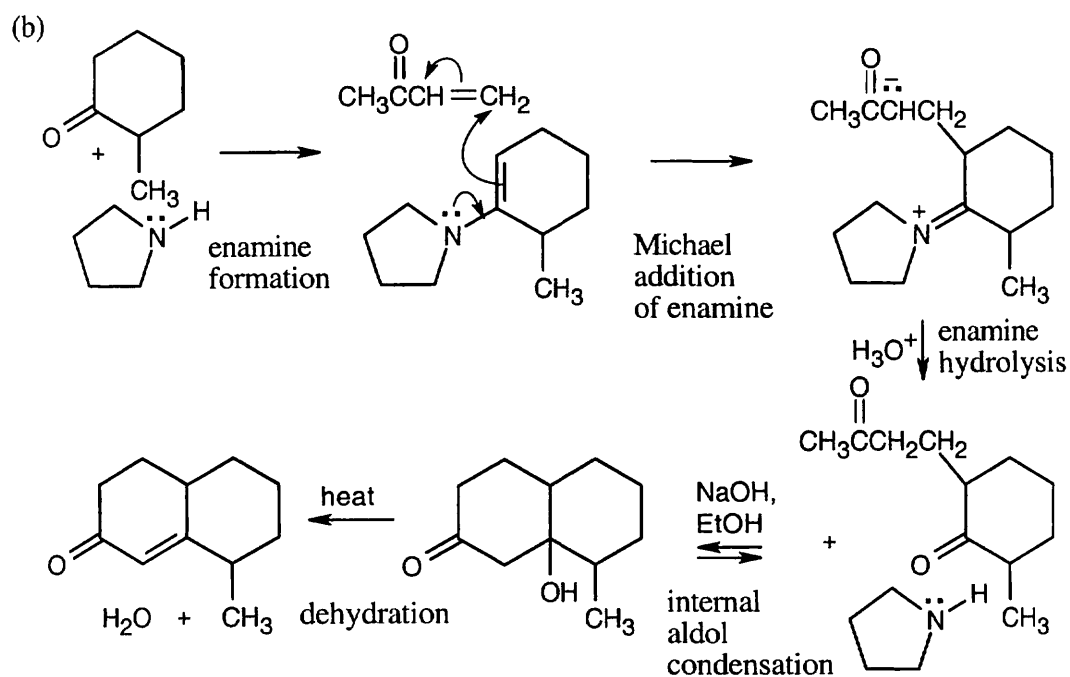
The crowding in this enamine can be relieved by a ring-flip, which puts the methyl group in an axial position. This enamine is the only one formed.

23.53

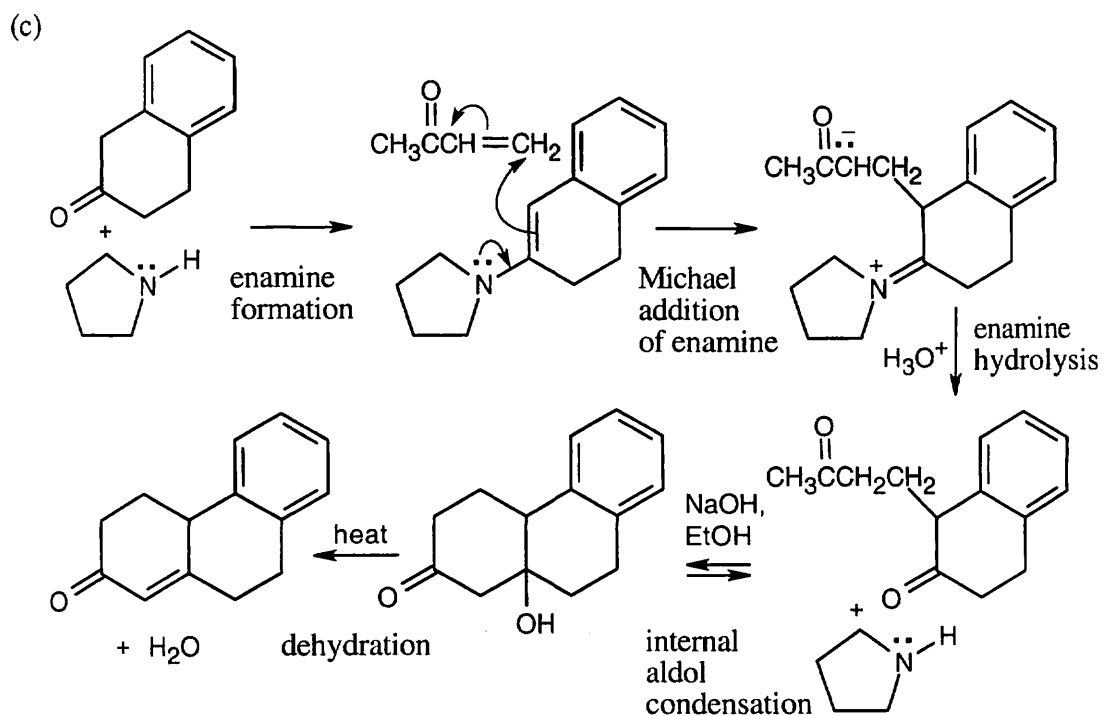


23.54



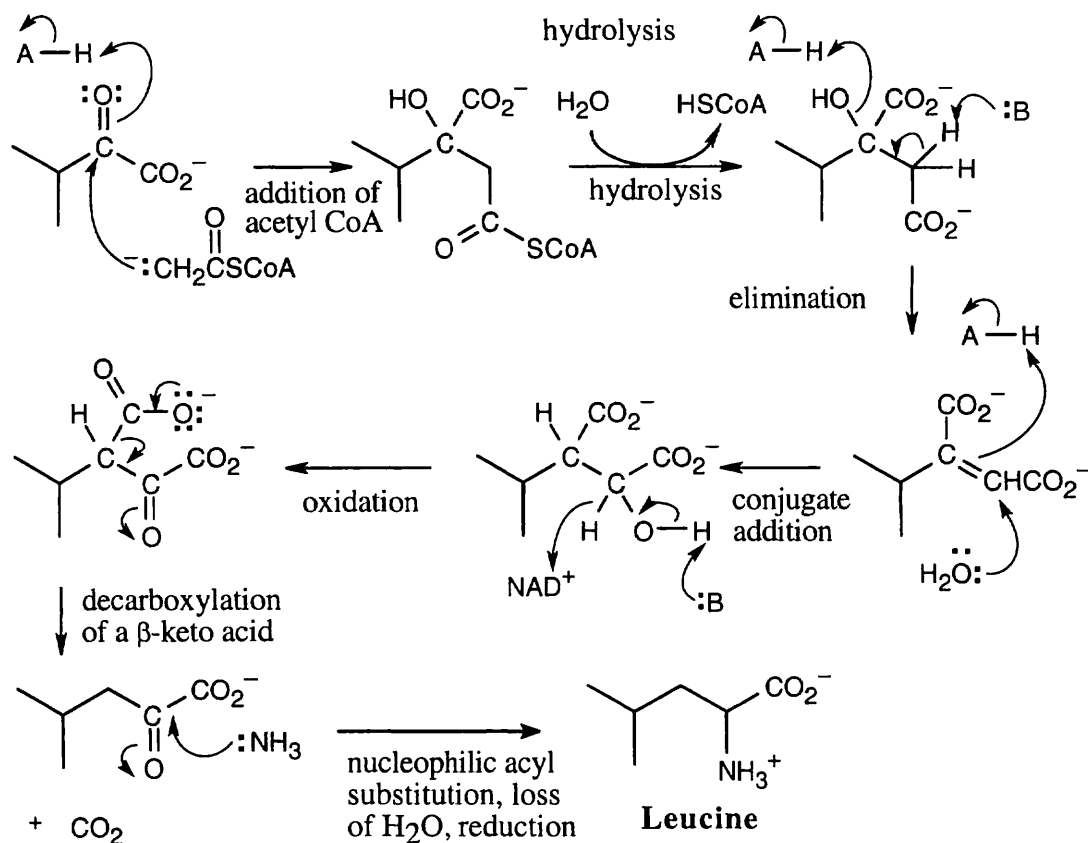


Notice that the needed enamine is formed (see Problem 23.52).

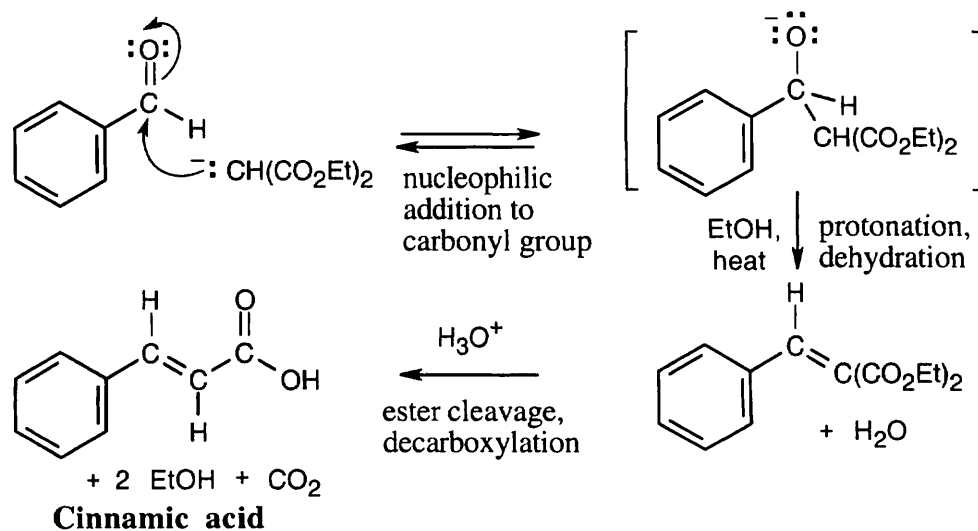
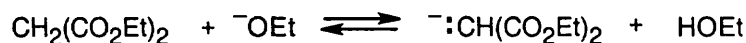


The enamine double bond is conjugated with the aromatic ring.

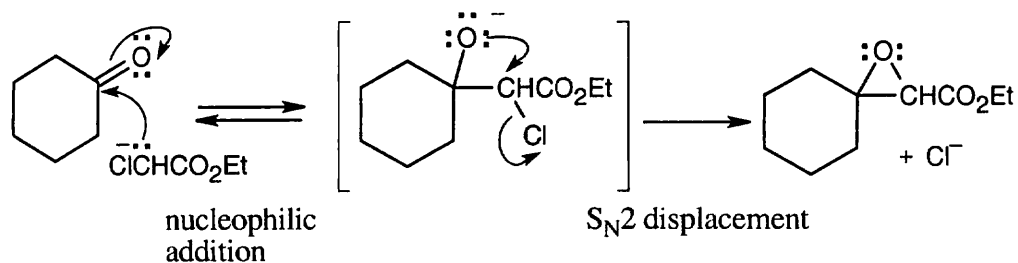
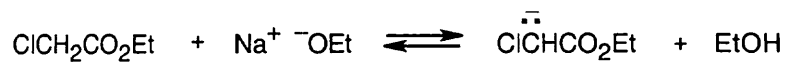
23.55



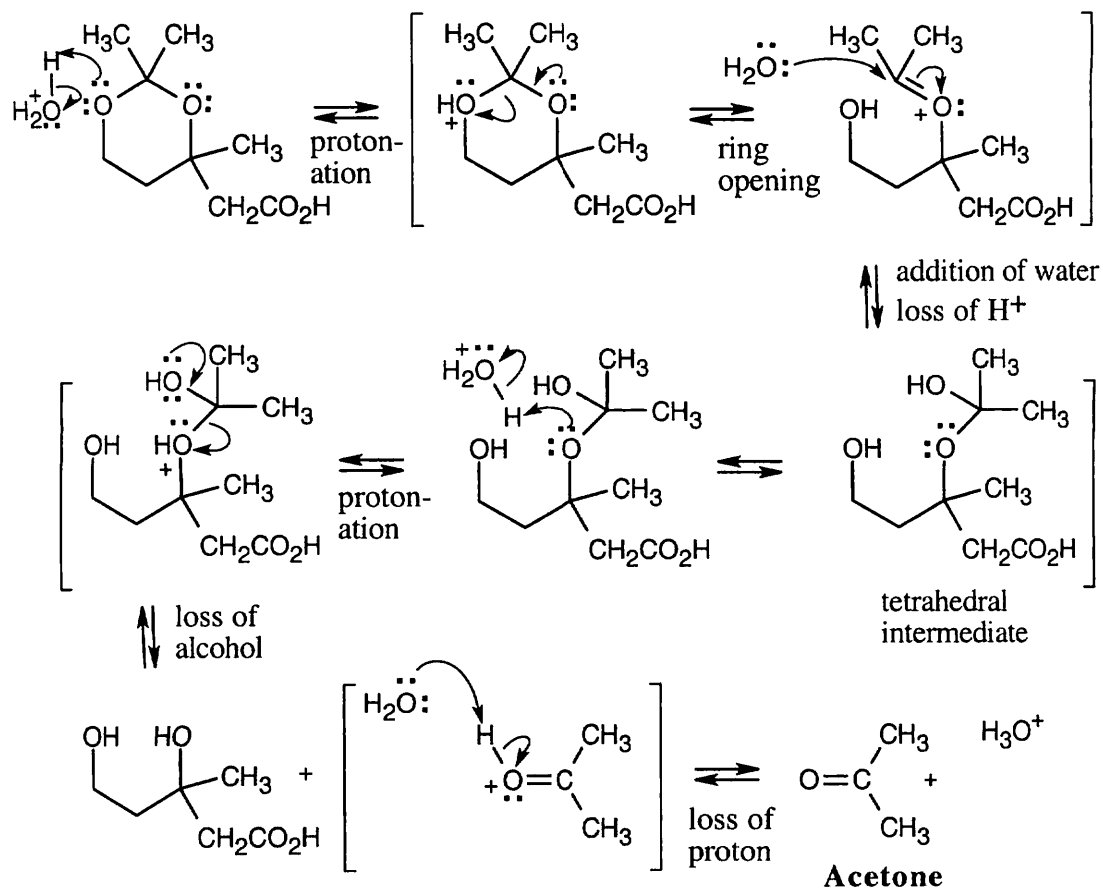
23.56 Formation of the enolate of diethyl malonate is the first step:



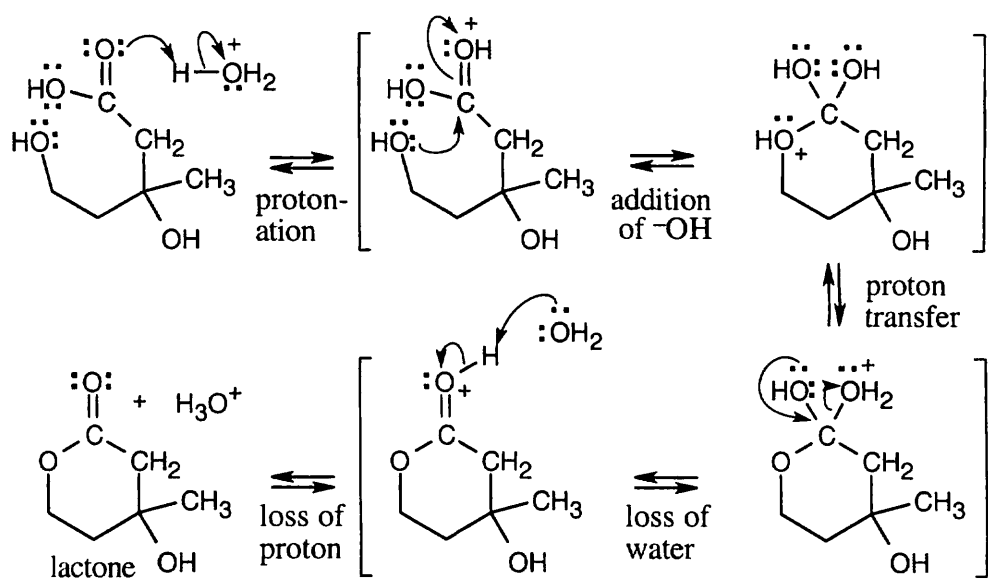
23.57



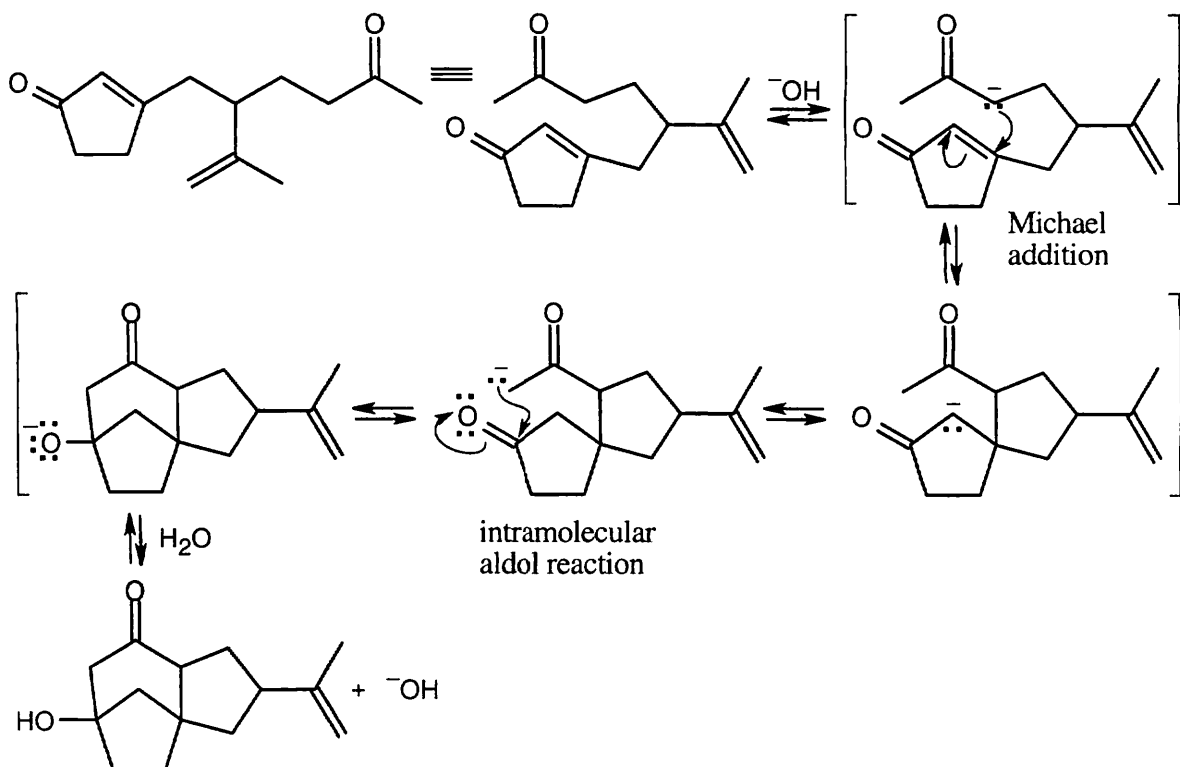
23.58 This mechanism divides into two sequences of steps. In the first part of the mechanism, an acetal is hydrolyzed to acetone and a dihydroxycarboxylic acid.



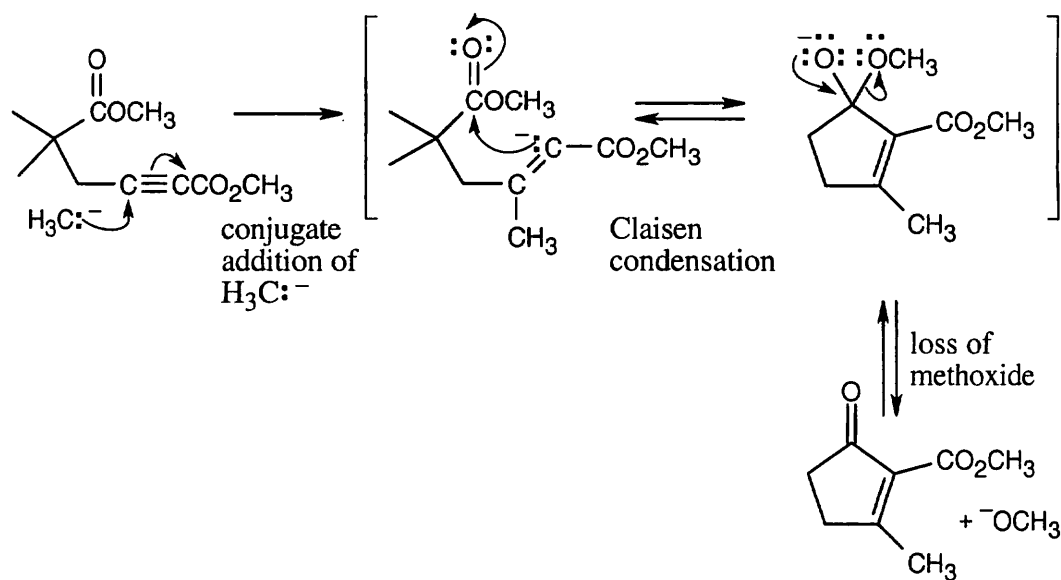
In the second set of steps, the dihydroxycarboxylic acid forms a cyclic ester (a lactone).



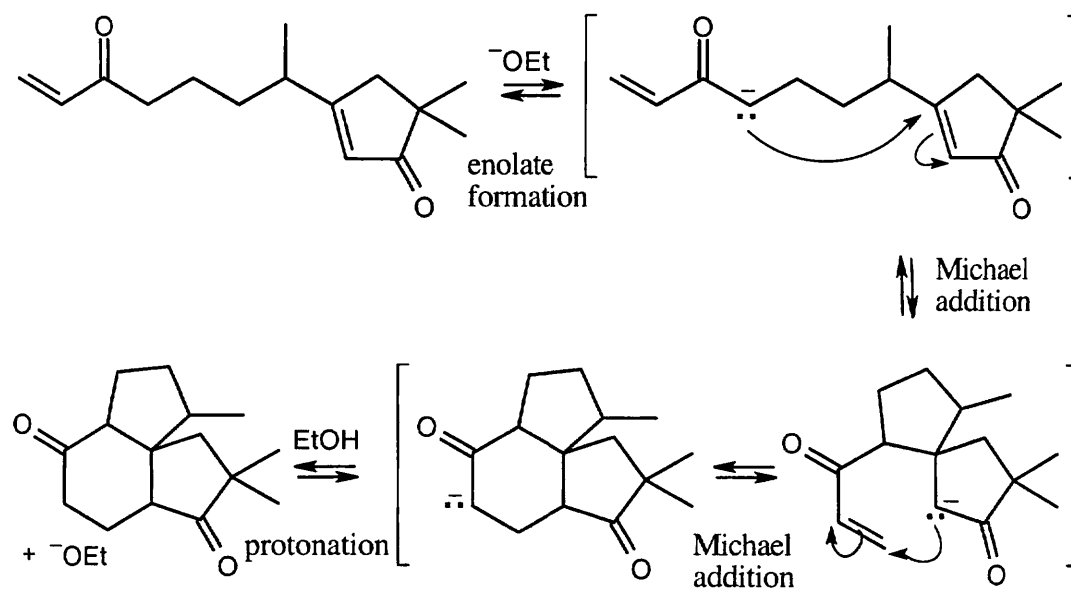
23.59 This problem becomes easier if you draw the starting material so that it resembles the product.



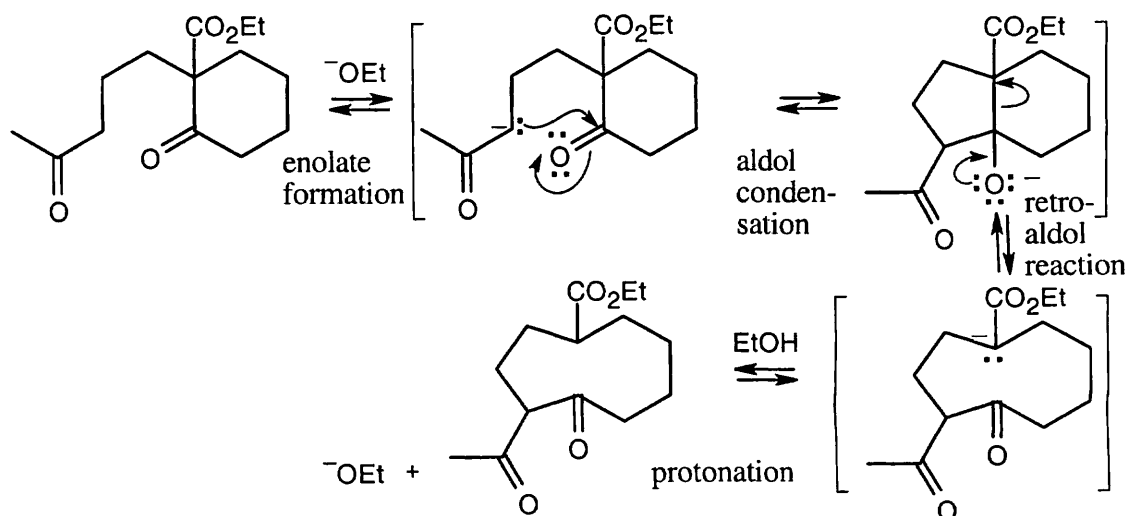
23.60



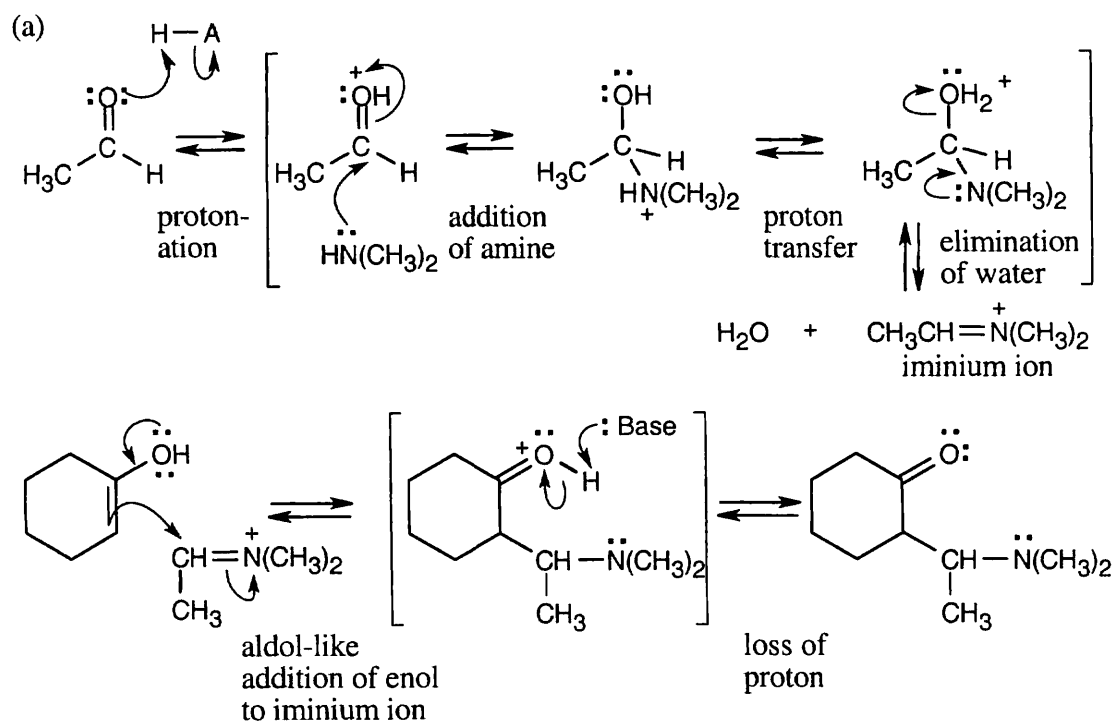
23.61



23.62



23.63



23.64 The Mannich reaction occurs between the diester, butanedial, and methylamine.

