CHAPTER

19

Condensation and Conjugate Addition Reactions of Carbonyl Compounds

MORE CHEMISTRY OF ENOLATES

We have already learned how new C—C bonds can be generated at the carbon adjacent to certain carbonyl functional groups through enolate chemistry using various electrophiles, such as alkyl halides and halogens. However, we have not yet considered what might be an even more valuable group of electrophiles—the carbonyl-containing molecules themselves. As we shall see, such electrophiles allow for two additional types of C—C bond-forming reactions: condensation reactions and conjugate additions. Both of these processes are extremely useful in synthesizing complex molecules, and they have important biological significance. Indeed, these types of processes relate to the cancer-fighting properties of 5-fluorouracil, a compound that masquerades as the natural metabolite uracil and blocks the biosynthesis of a compound needed for DNA replication.

IN THIS CHAPTER WE WILL CONSIDER:

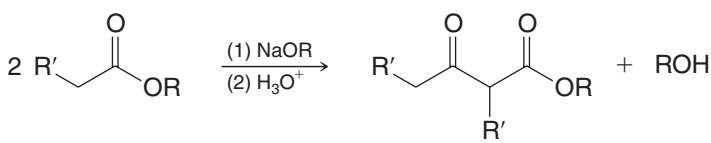
- Additional chemistry of enolates with carbonyl-containing molecules as electrophiles in both condensation and conjugate addition processes
- Reactions using these concepts that allow for the synthesis of varied rings
- A special version of such reactions involving nitrogen that creates some unique carbonyl-containing amines

[WHY DO THESE TOPICS MATTER?] In "The Chemistry of… A Suicide Enzyme Substrate," we shall see how 5-fluorouracil works. Then, at the end of this chapter, we will show how the combination of several of these reactions in series, each setting up the next step like dominos falling in a row, can enable the one-pot preparation of a highly important alkaloid known as tropinone. Tropinone contains the core of several useful pharmaceuticals.

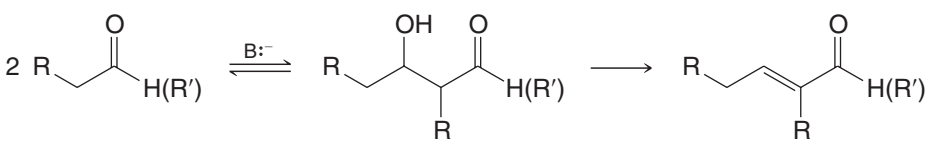
19.1 INTRODUCTION

In carbonyl **condensation reactions** the enolate or enol of one carbonyl compound reacts with the carbonyl group of another to join the two reactants. As part of the process, a new molecule that is derived from them "condenses" (forms). Often this molecule is that of an alcohol or water. The main types of condensation reactions we shall study are the **Claisen condensation** and the **aldol condensation**. Aldol condensations are preceded mechanistically by aldol additions, which we shall also study. The name **aldol** derives from the fact that **ald**ehyde and alcoh**ol** functional groups are present in the products of many aldol reactions.

An Example of a Claisen Condensation



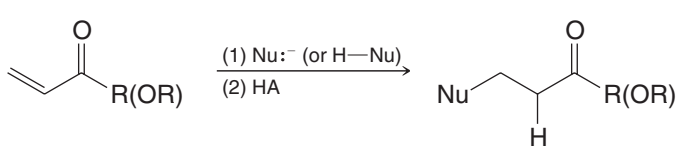
An Example of an Aldol Addition and Condensation



Aldol addition product **Aldol condensation product**

Conjugate addition reactions involve a nucleophile, which is often an enolate, adding to the β position of an α,β-unsaturated carbonyl compound. One of the most common conjugate addition reactions is the Michael addition. As we shall see, the aldol condensation provides a way to synthesize α,β-unsaturated carbonyl compounds that we can then use for subsequent conjugate addition reactions.

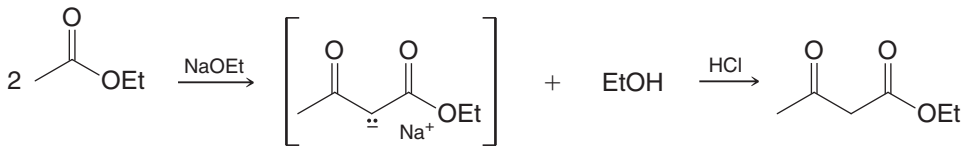
An Example of Conjugate Addition



19.2 THE CLAISEN CONDENSATION: A SYNTHESIS OF β-KETO ESTERS

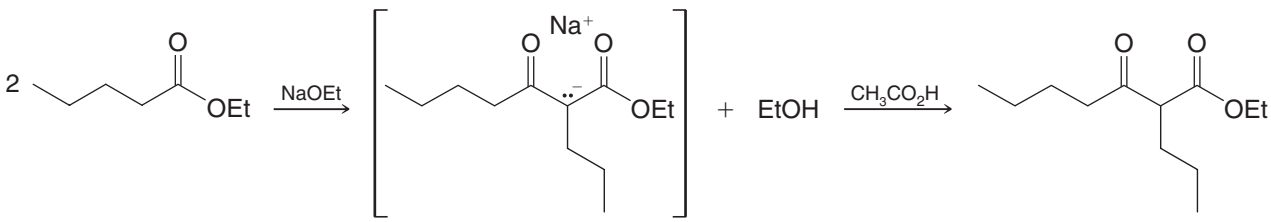
The Claisen condensation is a carbon–carbon bond-forming reaction that is useful for synthesizing β-keto esters. In Chapter 18 we saw how β-keto esters are useful in synthesis. In a Claisen condensation, the enolate of one ester molecule adds to the carbonyl group of another, resulting in an acyl substitution reaction that forms a β-keto ester and an alcohol molecule. The alcohol molecule that is formed derives from the alkoxyl group of the ester.

A classic example is the Claisen condensation by which ethyl acetoacetate (acetoacetic ester) can be synthesized.



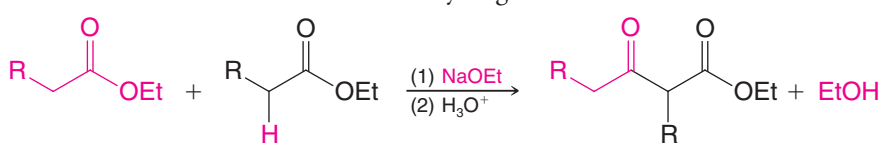
Sodioacetoacetic ester | **(removed by distillation)** | **Ethyl acetoacetate (acetoacetic ester) (76%)**

Another example is the Claisen condensation of two molecules of ethyl pentanoate, leading to ethyl 3-oxo-2-propylheptanoate.



Ethyl pentanoate | **Ethyl 3-oxo-2-propylheptanoate (77%)**

If we look closely at these examples, we can see that, overall, both reactions involve a condensation in which one ester loses an α hydrogen and the other loses an ethoxide ion:

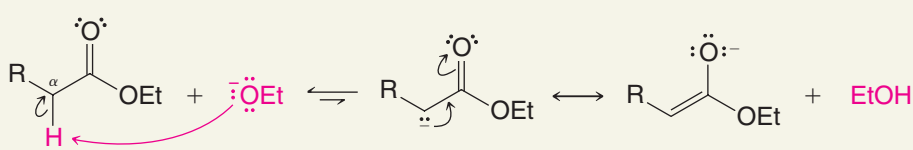


(R may also be H) | **A β-keto ester**

We can understand how this happens if we examine the reaction mechanism in detail. In doing so, we shall see that the Claisen condensation mechanism is a classic example of acyl substitution (nucleophilic addition–elimination at a carbonyl group).

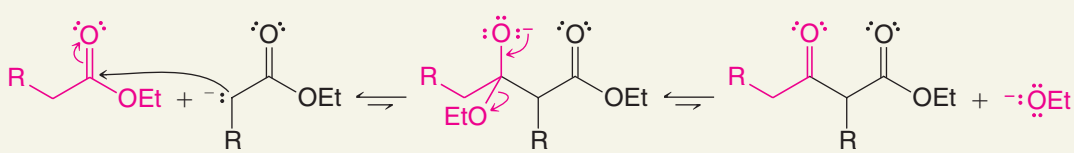
A MECHANISM FOR THE REACTION — The Claisen Condensation

Step 1



An alkoxide base removes an α proton from the ester, generating a nucleophilic enolate ion. (The alkoxide base used to form the enolate should have the same alkyl group as the ester, e.g., ethoxide for an ethyl ester; otherwise transesterification may occur.) Although the α protons of an ester are not as acidic as those of aldehydes and ketones, the resulting enolate is stabilized by resonance in a similar way.

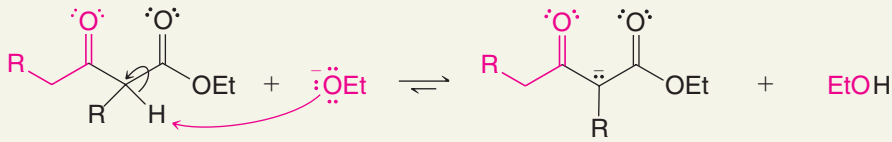
Step 2



Nucleophilic addition | **Tetrahedral intermediate and elimination**

The enolate attacks the carbonyl carbon of another ester molecule, forming a tetrahedral intermediate. The tetrahedral intermediate expels an alkoxide ion, resulting in substitution of the alkoxide by the group derived from the enolate. The net result is nucleophilic addition–elimination at the ester carbonyl group. *The overall equilibrium for the process is unfavorable thus far, however*, but it is drawn toward the final product by removal of the acidic α hydrogen from the new β-dicarbonyl system.

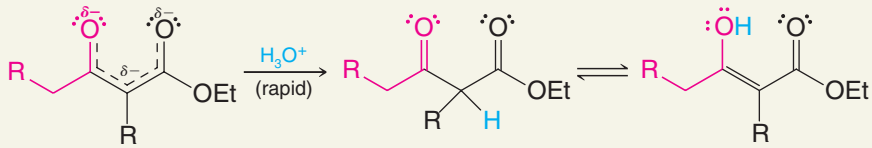
Step 3



β-Keto ester (pK_a ~9; stronger acid) **Ethoxide ion (stronger base)** **β-Keto ester anion (weaker base)** **Ethanol (pK_a 16; weaker acid)**

An alkoxide ion removes an α proton from the newly formed condensation product, resulting in a resonance stabilized β-keto ester ion. This step is highly favorable and draws the overall equilibrium toward product formation. The alcohol by-product (ethanol in this case) can be distilled from the reaction mixture as it forms, thereby further drawing the equilibrium toward the desired product.

Step 4



Keto form **Enol form**

Addition of acid quenches the reaction by neutralizing the base and protonating the Claisen condensation product. The β-keto ester product exists as an equilibrium mixture of its keto and enol tautomers.

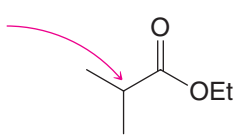
- When planning a reaction with an ester and an alkoxide ion it is important to use an alkoxide that has the same alkyl group as the alkoxyl group of the ester.

The alkoxyl group of the ester and the alkoxide must be the same so as to avoid transesterification (which occurs with alkoxides by the same mechanism as base-promoted ester hydrolysis; Section 17.7B). Ethyl esters and methyl esters, as it turns out, are the most common ester reactants in these types of syntheses. Therefore, we use sodium ethoxide when ethyl esters are involved and sodium methoxide when methyl esters are involved. There are some occasions when we shall choose to use other bases, but we shall discuss these later.

- Esters that have only one α hydrogen do not undergo the usual Claisen condensation.

An example of an ester that does not react in a normal Claisen condensation, because it has only one α hydrogen, is ethyl 2-methylpropanoate:

The α carbon has only one hydrogen.



This ester does not undergo a Claisen condensation.

Ethyl 2-methylpropanoate

- Inspection of the mechanism just given will make clear why this is so: an ester with only one α hydrogen will not have an acidic hydrogen when step 3 is reached, and step 3 provides the favorable equilibrium that ensures the success of the reaction.

In Section 19.2B we shall see how esters with only one α hydrogen can be converted to a β-keto ester by a method that uses a strong base.

PRACTICE PROBLEM 19.1

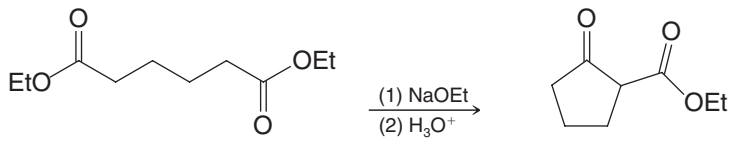
(a) Write a mechanism for all steps of the Claisen condensation that take place when ethyl propanoate reacts with ethoxide ion. **(b)** What products form when the reaction mixture is acidified?

PRACTICE PROBLEM 19.2

Since the products obtained from Claisen condensations are β-keto esters, subsequent hydrolysis and decarboxylation of these products give a general method for the synthesis of ketones. Show how you would employ this technique in a synthesis of 4-heptanone.

19.2A Intramolecular Claisen Condensations: The Dieckmann Condensation

An intramolecular Claisen condensation is called a **Dieckmann condensation**. For example, when diethyl hexanedioate is heated with sodium ethoxide, subsequent acidification of the reaction mixture gives ethyl 2-oxocyclopentanecarboxylate:

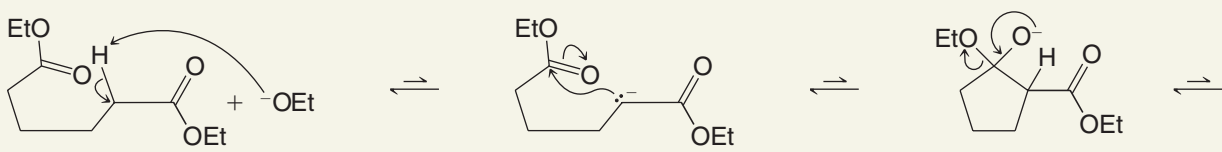


Diethyl hexanedioate (diethyl adipate) → **Ethyl 2-oxocyclopentanecarboxylate (74–81%)**

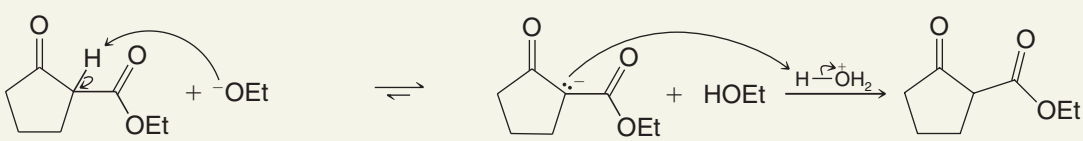
- In general, the Dieckmann condensation is useful only for the preparation of five- and six-membered rings.

Rings smaller than five are disfavored due to angle strain. Rings larger than seven are entropically less favorable due to the greater number of conformations available to a longer chain precursor, in which case intermolecular condensation begins to compete strongly.

A MECHANISM FOR THE REACTION — The Dieckmann Condensation



Ethoxide ion removes an α hydrogen. → **The enolate ion attacks the carbonyl group at the other end of the chain.** → **An ethoxide ion is expelled.**



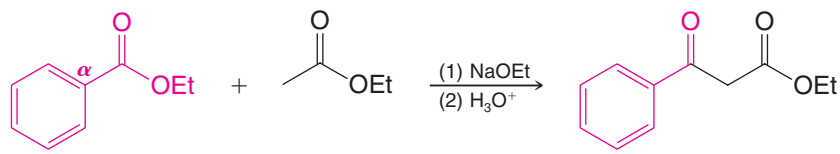
The ethoxide ion removes the acidic hydrogen located between two carbonyl groups. This favorable equilibrium drives the reaction. → **Addition of aqueous acid rapidly protonates the anion, giving the final product.**

PRACTICE PROBLEM 19.3 **(a)** What product would you expect from a Dieckmann condensation of diethyl heptanedioate? **(b)** Can you account for the fact that diethyl pentanedioate (diethyl glutarate) does not undergo a Dieckmann condensation?

19.2B Crossed Claisen Condensations

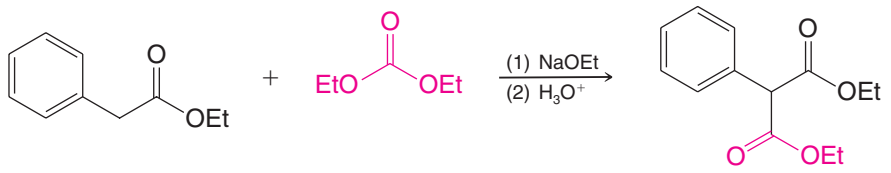
- Crossed Claisen condensations are possible **when one ester component has no α hydrogens** and, therefore, is unable to form an enolate ion and undergo self-condensation.

Ethyl benzoate, for example, condenses with ethyl acetate to give ethyl benzoylacetate:



Ethyl benzoate (no α hydrogen) → **Ethyl benzoylacetate (60%)**

Ethyl phenylacetate condenses with diethyl carbonate to give diethyl phenylmalonate:



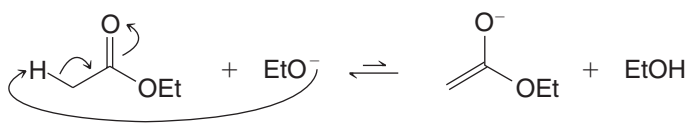
Ethyl phenylacetate | **Diethyl carbonate (no α carbon)** | **Diethyl phenylmalonate (65%)**

SOLVED PROBLEM 19.1

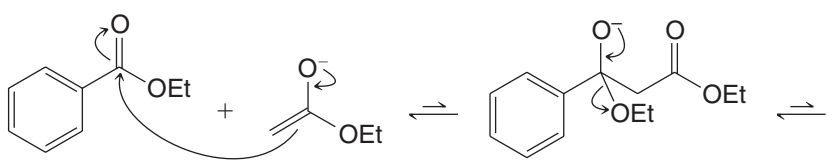
Write a mechanism for all of the steps in the Claisen condensation above between ethyl benzoate and ethyl acetate.

ANSWER: Ethyl benzoate contains no α hydrogens, so we begin by removing an α hydrogen from ethyl acetate to form an enolate.

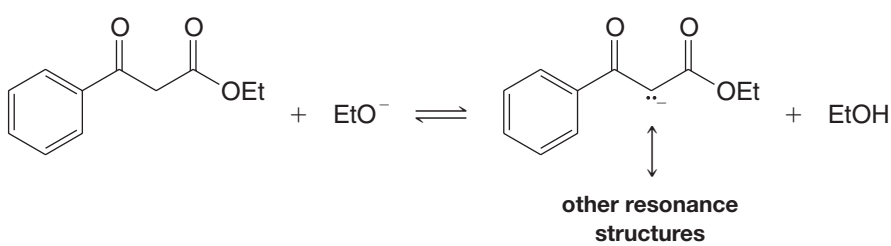
Step 1



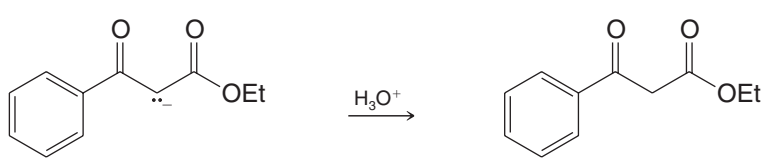
Step 2



Step 3



Step 4



PRACTICE PROBLEM 19.4

Write mechanisms that account for the products that are formed in the crossed Claisen condensation illustrated earlier between ethyl phenylacetate and diethyl carbonate.

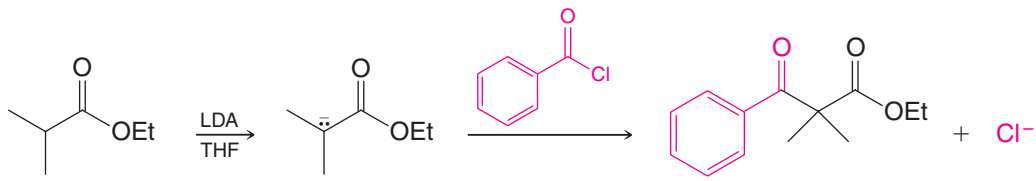
PRACTICE PROBLEM 19.5

What products would you expect to obtain from each of the following crossed Claisen condensations?

(a) Ethyl propanoate + diethyl oxalate $\xrightarrow[(2)\ H_3O^+]{(1)\ NaOEt}$

(b) Ethyl acetate + ethyl formate $\xrightarrow[(2)\ H_3O^+]{(1)\ NaOEt}$

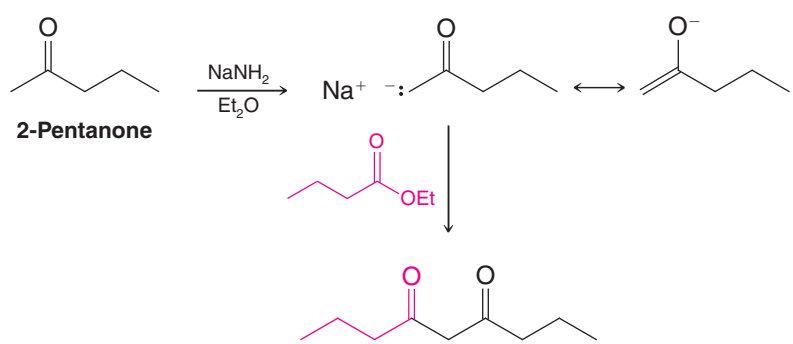
As we learned earlier in this section, esters that have only one α hydrogen cannot be converted to β-keto esters by sodium ethoxide. However, they can be converted to β-keto esters by reactions that use very strong bases such as lithium diisopropylamide (LDA) (Section 18.4). The strong base converts the ester to its enolate ion in nearly quantitative yield. This allows us to *acylate* the enolate ion by treating it with an acyl chloride or an ester. An example of this technique using LDA is shown here:



Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate

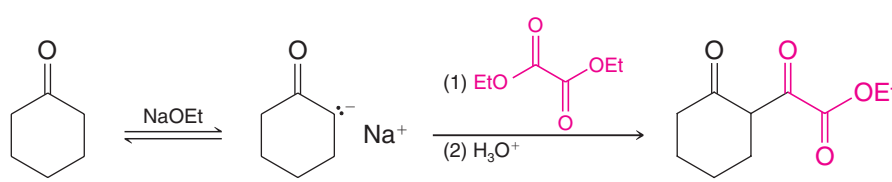
19.3 β-DICARBONYL COMPOUNDS BY ACYLATION OF KETONE ENOLATES

Enolate ions derived from ketones also react with esters in nucleophilic substitution reactions that resemble Claisen condensations. In the following first example, although two anions are possible from the reaction of the ketone with sodium amide, the major product is derived from the primary carbanion. This is because (a) the primary α hydrogens are slightly more acidic than the secondary α hydrogens and (b) in the presence of the strong base ($NaNH_2$) in an aprotic solvent (Et_2O), the kinetic enolate is formed (see Section 18.4). LDA could be used similarly as the base.



2-Pentanone

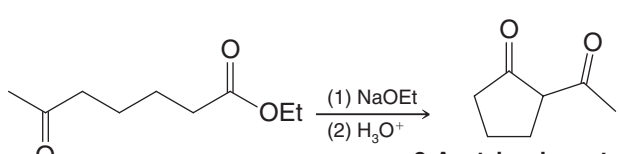
4,6-Nonanedione (76%)



67%

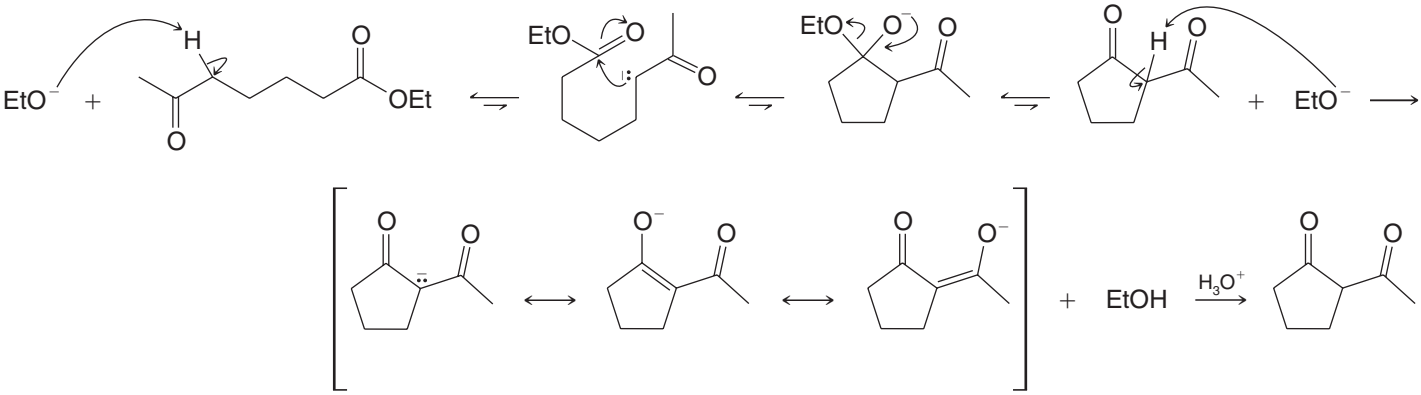
SOLVED PROBLEM 19.2

Keto esters are capable of undergoing cyclization reactions similar to the Dieckmann condensation. Write a mechanism for the following reaction.



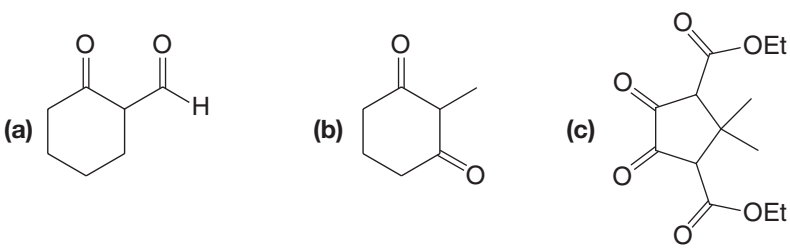
2-Acetylcyclopentanone

ANSWER:



PRACTICE PROBLEM 19.6

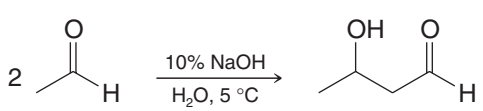
Show how you might synthesize each of the following compounds using, as your starting materials, esters, ketones, acyl halides, and so on:



19.4 ALDOL REACTIONS: ADDITION OF ENOLATES AND ENOLS TO ALDEHYDES AND KETONES

- Aldol additions and aldol condensations together represent an important class of carbon–carbon bond-forming reaction.

An **aldol reaction** begins with addition of an enolate or enol to the carbonyl group of an aldehyde or ketone, leading to a β-hydroxy aldehyde or ketone as the initial product. A simple example is shown below, whereby two molecules of acetaldehyde (ethanal) react to form 3-hydroxybutanal. 3-Hydroxybutanal is an "**aldol**" because it contains both an **ald**ehyde and an alcoh**ol** functional group. Reactions of this general type are known as **aldol additions**.



3-Hydroxybutanal (50%)

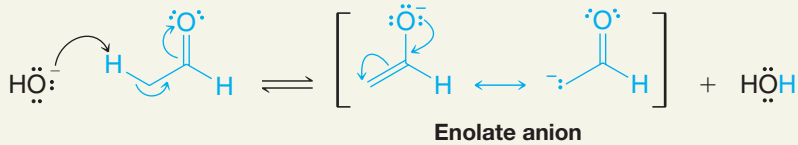
As we shall see, the initial aldol addition product often dehydrates to form an α,β-unsaturated aldehyde or ketone. When this is the result, the overall reaction is an **aldol condensation**. First let us consider the mechanism of an aldol addition.

19.4A Aldol Addition Reactions

An aldol addition is an equilibrium reaction when it is conducted in a protic solvent with a base such as hydroxide or an alkoxide. The mechanism for an aldol addition involving an aldehyde is shown on the next page.

A MECHANISM FOR THE REACTION — The Aldol Addition

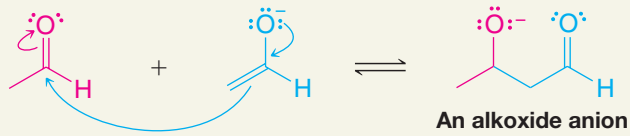
Step 1 *Enolate formation*



Enolate anion

In this step the base (a hydroxide ion) removes a proton from the α carbon of one molecule of acetaldehyde to give a resonance-stabilized enolate.

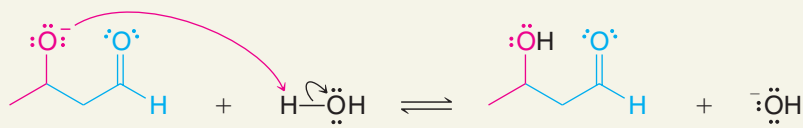
Step 2 *Addition of the enolate*



An alkoxide anion

The enolate then acts as a nucleophile and attacks the carbonyl carbon of a second molecule of acetaldehyde, producing an alkoxide anion.

Step 3 *Protonation of the alkoxide*



Stronger base **The aldol product** **Weaker base**

The alkoxide anion now removes a proton from a molecule of water to form the aldol product.

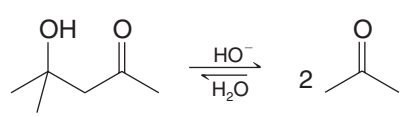
With ketones, the addition step leading to the aldol is unfavorable due to steric hindrance, and the equilibrium favors the aldol precursors rather than the addition product (Section 19.4B). However, as we shall see in Section 19.4C, dehydration of the aldol addition product can draw the equilibrium toward completion, whether the reactant is an aldehyde or a ketone. Enolate additions to both aldehydes and ketones are also feasible when a stronger base (such as LDA) is used in an aprotic solvent (Section 19.5B).

19.4B The Retro-Aldol Reaction

Helpful Hint

See "The Chemistry of… A Retro-Aldol Reaction in Glycolysis: Dividing Assets to Double the ATP Yield", page 870, for an important biochemical application that increases the energy yield from glucose.

Because the steps in an aldol addition mechanism are readily reversible, a **retro-aldol reaction** can occur that converts a β-hydroxy aldehyde or ketone back to the precursors of an aldol addition. For example, when 4-hydroxy-4-methyl-2-pentanone is heated with hydroxide in water, the final equilibrium mixture consists primarily of acetone, the retro-aldol product.

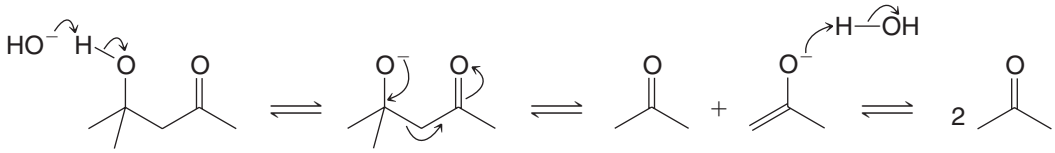


This result is not surprising, because we know that the equilibrium for an aldol addition (the reverse of the reaction above) is not favorable when the enolate adds to a ketone. But, as mentioned earlier, dehydration of an aldol addition product can draw the equilibrium forward. We shall discuss the dehydration of aldols next (Section 19.4C).

SOLVED PROBLEM 19.3

The carbon–carbon bond cleavage step in a retro-aldol reaction involves, under basic conditions, a leaving group that is an enolate, or under acidic conditions, an enol. Write a mechanism for the retro-aldol reaction of 4-hydroxy-4-methyl-2-pentanone under basic conditions (shown above).

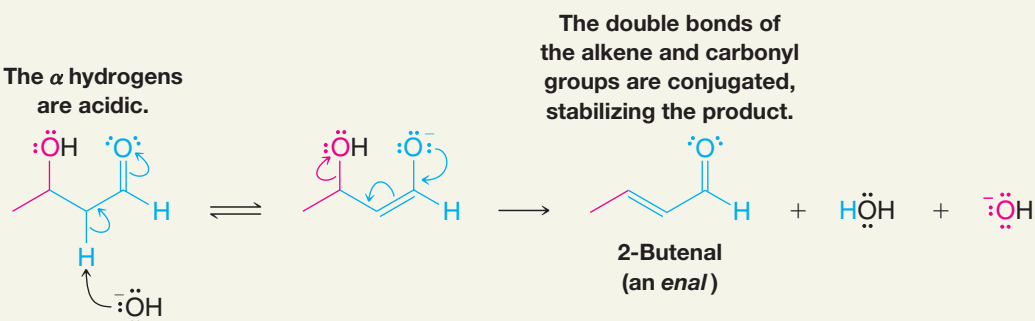
STRATEGY AND ANSWER: Base removes the proton from the β-hydroxyl group, setting the stage for reversal of the aldol addition. As the alkoxide reverts to the carbonyl group, a carbon–carbon bond breaks with expulsion of the enolate as a leaving group. This liberates one of the original carbonyl molecules. Protonation of the enolate forms the other.



19.4C Aldol Condensation Reactions: Dehydration of the Aldol Addition Product

Dehydration of an aldol addition product leads to a conjugated α,β-unsaturated carbonyl system. The overall process is called an **aldol condensation**, and the product can be called an enal (alk*ene* *al*dehyde) or enone (alk*ene* ket*one*), depending on the carbonyl group in the product. The stability of the conjugated enal or enone system means that the dehydration equilibrium is essentially irreversible. For example, the aldol addition reaction that leads to 3-hydroxybutanal, shown in Section 19.4, dehydrates on heating to form 2-butenal. A mechanism for the dehydration is shown here.

A MECHANISM FOR THE REACTION — Dehydration of the Aldol Addition Product



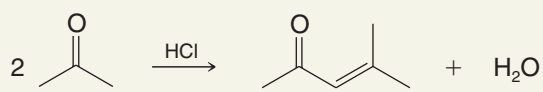
Even though hydroxide is a leaving group in this reaction, the fact that each dehydrated molecule forms irreversibly, due to the stability from conjugation, draws the reaction forward.

19.4D Acid-Catalyzed Aldol Condensations

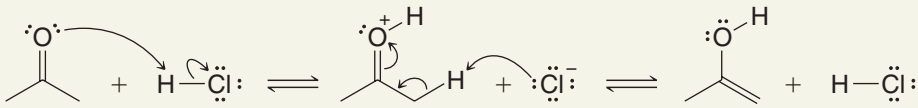
Aldol reactions can occur under acid catalysis, in which case the reaction generally leads to the α,β-unsaturated product by direct dehydration of the β-hydroxy aldol intermediate. This is one way by which ketones can successfully be utilized in an aldol reaction. The following is an example, in which acetone forms its aldol condensation product, 4-methylpent-3-en-2-one, on treatment with hydrogen chloride.

A MECHANISM FOR THE REACTION — The Acid-Catalyzed Aldol Reaction

Reaction

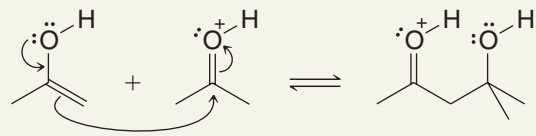


Mechanism

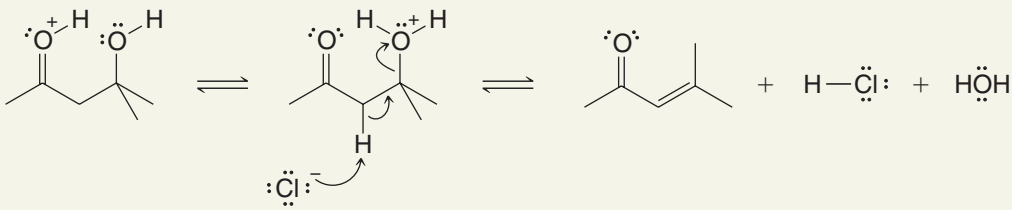


The mechanism begins with the acid-catalyzed formation of the enol.

(mechanism continues on the next page)



Then the enol adds to the protonated carbonyl group of another molecule of acetone.



Finally, proton transfers and dehydration lead to the product.

Acid catalysis can promote further reactions after the aldol condensation. An example is given in Practice Problem 19.8. Generally, it is more common in synthesis for an aldol reaction to be conducted under basic rather than acidic conditions.

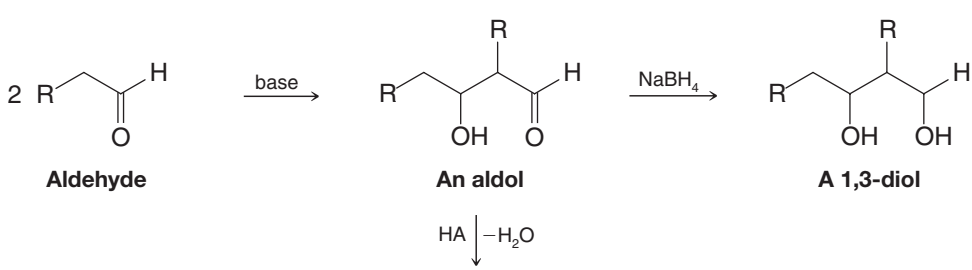
PRACTICE PROBLEM 19.7 The acid-catalyzed aldol condensation of acetone (just shown) also produces some 2,6-dimethylhepta-2,5-dien-4-one. Give a mechanism that explains the formation of this product.

PRACTICE PROBLEM 19.8 Heating acetone with sulfuric acid leads to the formation of mesitylene (1,3,5-trimethylbenzene). Propose a mechanism for this reaction.

19.4E Synthetic Applications of Aldol Reactions

As we are beginning to see, aldol additions and aldol condensations are important methods for carbon–carbon bond formation. They also result in β-hydroxy and α,β-unsaturated carbonyl compounds that are themselves useful for further synthetic transformations. Some representative reactions are shown below.

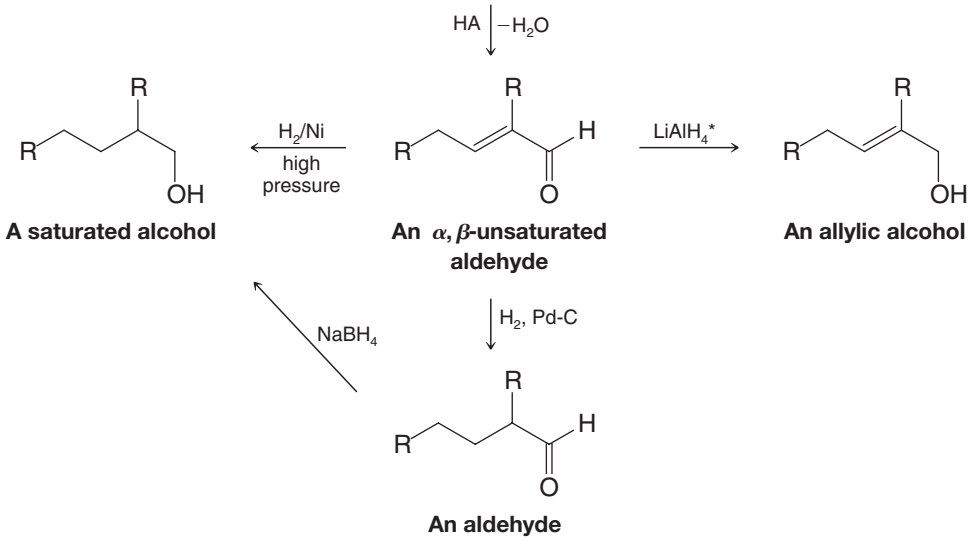
The Aldol Reaction in Synthesis



Aldehyde **An aldol** **A 1,3-diol**

Helpful Hint

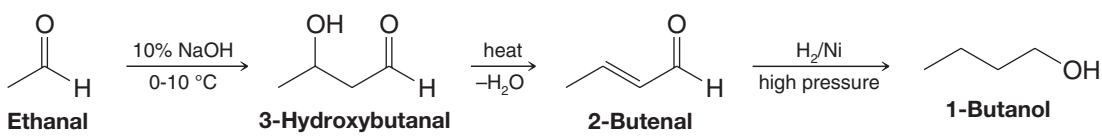
The aldol reaction: a tool for synthesis. See also the Synthetic Connections review at the end of the chapter.



SOLVED PROBLEM 19.4

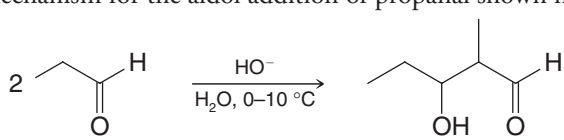
One industrial process for the synthesis of 1-butanol begins with ethanal. Show how this synthesis might be carried out.

STRATEGY AND ANSWER: Ethanal can be converted to an aldol via an aldol addition. Then, dehydration would produce 2-butenal, which can be hydrogenated to furnish 1-butanol.



PRACTICE PROBLEM 19.9

(a) Provide a mechanism for the aldol addition of propanal shown here.



(b) How can you account for the fact that the product of the aldol addition is 3-hydroxy-2-methylpentanal and not 4-hydroxyhexanal?

(c) What products would be formed if the reaction mixture were heated?

PRACTICE PROBLEM 19.10

Show how each of the following products could be synthesized from butanal:

(a) 2-Ethyl-3-hydroxyhexanal
(b) 2-Ethylhex-2-en-1-ol
(c) 2-Ethylhexan-1-ol
(d) 2-Ethylhexane-1,3-diol (the insect repellent "6–12")

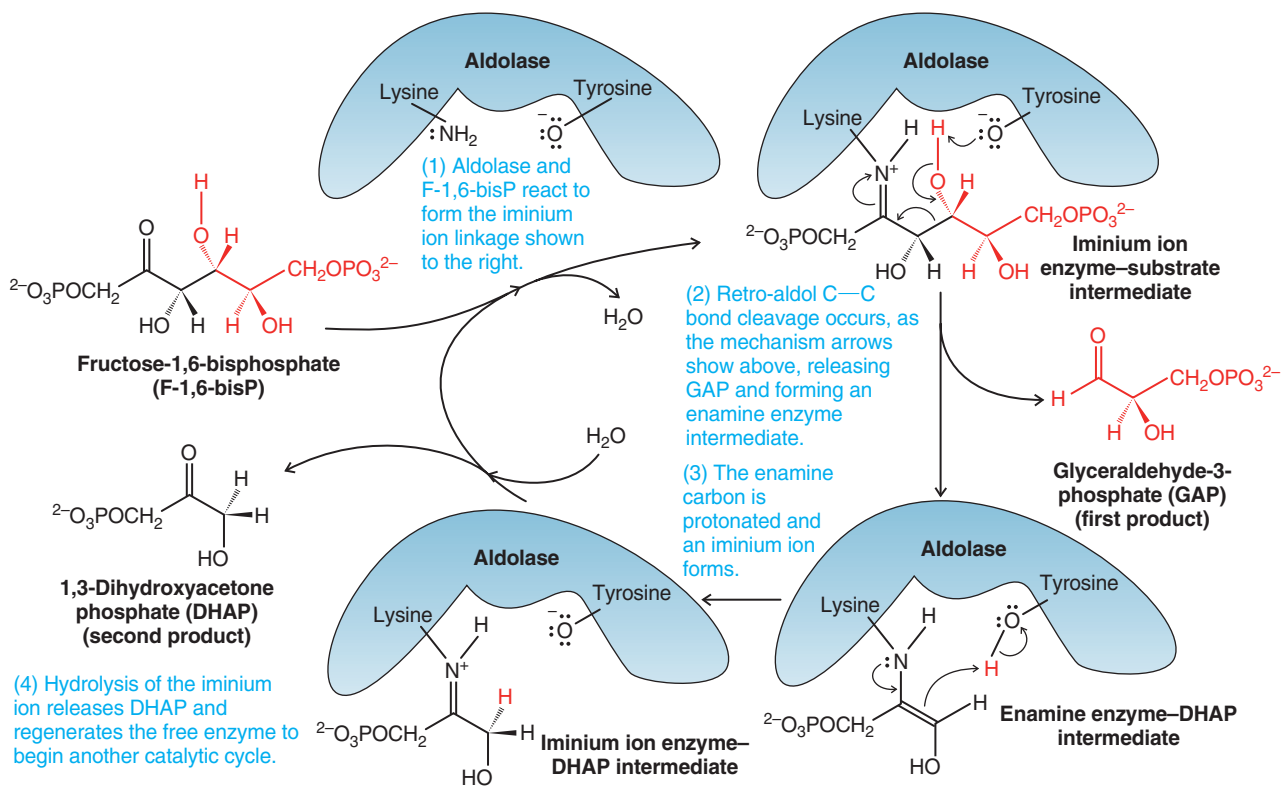
Thus far we have only considered examples of aldol reactions where the reactant forms a product by dimerization. In the coming sections we shall discuss the use of aldol reactions to more generally prepare β-hydroxy and α,β-unsaturated carbonyl compounds. We shall then study reactions called conjugate addition reactions (Section 19.7), by which we can further build on the α,β-unsaturated carbonyl systems that result from aldol condensations.

*$LiAlH_4$ reduces the carbonyl group of α,β-unsaturated aldehydes and ketones cleanly. $NaBH_4$ often reduces the carbon–carbon double bond as well.

THE CHEMISTRY OF... A Retro-Aldol Reaction in Glycolysis—Dividing Assets to Double the ATP Yield

Glycolysis is a fundamental pathway for production of ATP in living systems. The pathway begins with glucose and ends with two molecules of pyruvate and a net yield of two ATP molecules. Aldolase, an enzyme in glycolysis, plays a key role by dividing the six-carbon compound fructose-1,6-bisphosphate (derived from glucose) into two compounds that each have three carbons, glyceraldehyde-3-phosphate (GAP) and 1,3-dihydroxyacetone phosphate (DHAP). This process is essential because it provides two three-carbon units for the final stage of glycolysis, wherein the net yield of two ATP molecules per glucose is realized. (Two ATP molecules are consumed to form fructose-1,6-bisphosphate, and only two are generated per pyruvate. Thus, two passages through the second stage of glycolysis are necessary to obtain a net yield of two ATP molecules per glucose.)

The cleavage reaction catalyzed by aldolase is a net retro-aldol reaction. Details of the mechanism are shown here, beginning at the left with fructose-1,6-bisphosphate.

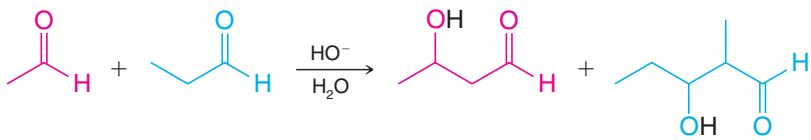


Two key intermediates in the aldolase mechanism involve functional groups that we have studied (Chapter 16)—an imine (protonated in the form of an iminium cation) and an enamine. In the mechanism of aldolase, an iminium cation acts as a sink for electron density during C—C bond cleavage (step 2), much like a carbonyl group does in a typical retro-aldol reaction. In this step the iminium cation is converted to an enamine, corresponding to the enolate or enol that is formed when a carbonyl group accepts electron density during C—C bond cleavage in an ordinary retro-aldol reaction. The enamine intermediate is then a source of an electron pair used to bond with a proton taken from the tyrosine hydroxyl at the aldolase active site (step 3). Finally, the resulting iminium group undergoes hydrolysis (step 4), freeing aldolase for another catalytic cycle and releasing DHAP, the second product of the retro-aldol reaction. Then, by a process catalyzed by the enzyme TIM (triose phosphate isomerase), DHAP undergoes isomerization to GAP for processing to pyruvate and synthesis of two more ATP molecules.

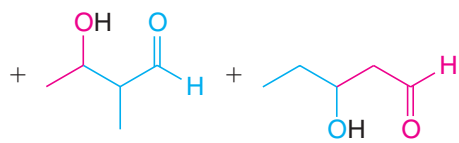
As we have seen with aldolase, imine and enamine functional groups have widespread roles in biological chemistry. Yet the functions of imines and enamines in biology are just as we would predict based on their native chemical reactivity.

19.5 CROSSED ALDOL CONDENSATIONS

An **aldol reaction** that starts with two different carbonyl compounds is called a **crossed aldol reaction**. Unless specific conditions are involved, a crossed aldol reaction can lead to a mixture of products from various pairings of the carbonyl reactants, as the following example illustrates with ethanal and propanal:



Ethanal **Propanal** **3-Hydroxybutanal (from two molecules of ethanal)** **3-Hydroxy-2-methylpentanal (from two molecules of propanal)**



3-Hydroxy-2-methylbutanal **3-Hydroxypentanal**
(from one molecule of ethanal and one molecule of propanal)

We shall therefore consider crossed aldol condensations by two general approaches that allow control over the distribution of products. The first approach hinges on structural factors of the carbonyl reactants and the role that favorable or unfavorable aldol addition equilibria play in determining the product distribution. In this approach relatively weak bases such as hydroxide or an alkoxide are used in a protic solvent such as water or an alcohol. The second approach, called a directed aldol reaction, involves use of a strong base such as LDA in an aprotic solvent. With a strong base, one reactant can be converted essentially completely to its enolate, which can then be allowed to react with the other carbonyl reactant.

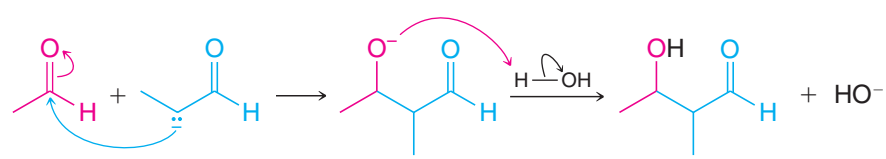
SOLVED PROBLEM 19.5

Show how each of the four products shown at the beginning of this section is formed in the crossed aldol addition between ethanal and propanal.

ANSWER: In the basic aqueous solution, four organic entities will initially be present: molecules of ethanal, molecules of propanal, enolate anions derived from ethanal, and enolate anions derived from propanal.

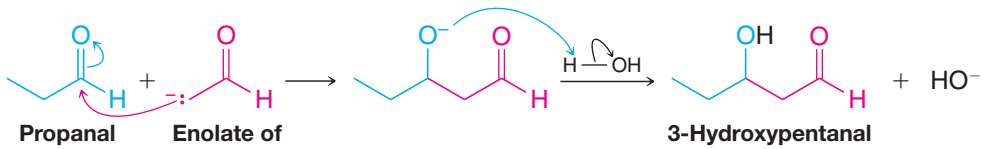
We have already seen (Section 19.4) how a molecule of ethanal can react with its enolate to form 3-hydroxybutanal (aldol). We have also seen (Practice Problem 19.9) how propanal can react with its enolate anion to form 3-hydroxy-2-methylpentanal. The other two products are formed as follows.

3-Hydroxy-2-methylbutanal results when the enolate of propanal reacts with ethanal.



Ethanal **Enolate of propanal** **3-Hydroxy-2-methylbutanal**

And finally, 3-hydroxypentanal results when the enolate of ethanal reacts with propanal.

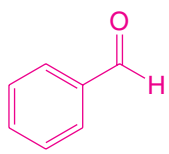
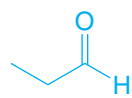
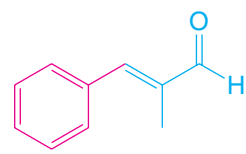
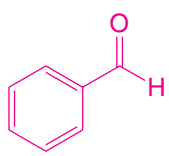
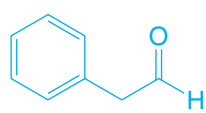
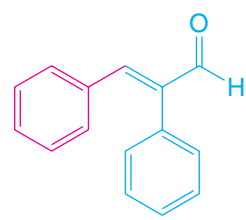
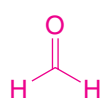
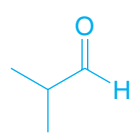
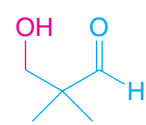


Propanal **Enolate of ethanal** **3-Hydroxypentanal**

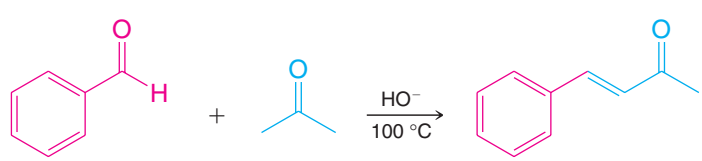
19.5A Crossed Aldol Condensations Using Weak Bases

Crossed aldol reactions are possible with weak bases such as hydroxide or an alkoxide when one carbonyl reactant does not have an α hydrogen. A reactant without α hydrogens cannot self-condense because it cannot form an enolate. We avoid self-condensation of the other reactant, that which has an α hydrogen, by adding it slowly to a solution of the first reactant and the base. Under these conditions the concentration of the reactant with an α hydrogen is always low, and it is present mostly in its enolate form. The main reaction that takes place is between this enolate and the carbonyl compound that has no α hydrogens. The reactions shown in Table 19.1 illustrate results from this approach.

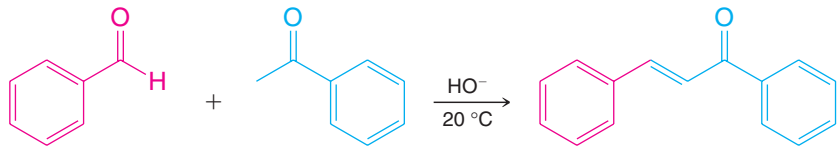
TABLE 19.1 CROSSED ALDOL REACTIONS

The reactant with no α hydrogen is placed in base	The reactant with an α hydrogen Is added slowly	Product
 **Benzaldehyde**	+  **Propanal**	HO^-, 10 °C  **2-Methyl-3-phenyl-2-propenal (α-methylcinnamaldehyde) (68%)**
 **Benzaldehyde**	+  **Phenylacetaldehyde**	HO^-, 20 °C  **2,3-Diphenyl-2-propenal**
 **Formaldehyde**	+  **2-Methylpropanal**	dilute Na_2CO_3, 40 °C  **3-Hydroxy-2,2-dimethylpropanal (>64%)**

The crossed aldol examples shown in Table 19.1 involve aldehydes as both reactants. A ketone can be used as one reactant, however, because ketones do not self-condense appreciably due to steric hindrance in the aldol addition stage. The following are examples of crossed aldol condensations where one reactant is a ketone. Reactions such as these are sometimes called Claisen–Schmidt condensations. Schmidt discovered and Claisen developed this type of aldol reaction in the late 1800s.



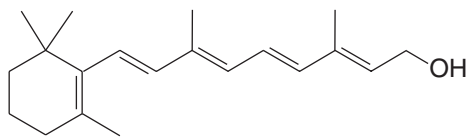
4-Phenylbut-3-en-2-one (benzalacetone) (70%)



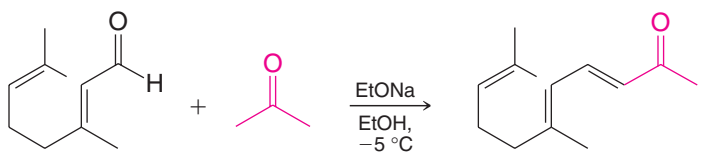
1,3-Diphenylprop-2-en-1-one
(benzalacetophenone)
(85%)

In these reactions, dehydration occurs readily because the double bond that forms is conjugated both with the carbonyl group and with the benzene ring. In general, dehydration of the aldol is especially favorable when it leads to extended conjugation.

As a further example, an important step in a commercial synthesis of vitamin A makes use of a crossed aldol condensation between geranial and acetone:



Vitamin A



Geranial **Pseudoionone**
(49%)

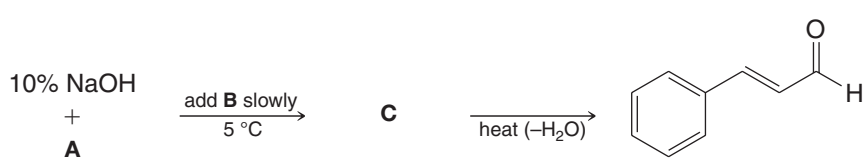
Geranial is a naturally occurring aldehyde that can be obtained from lemongrass oil. Its α hydrogen is *vinylic* and, therefore, not appreciably acidic. Notice, in this reaction, too, dehydration occurs readily because dehydration extends the conjugated system.

Helpful Hint

See "The Chemistry of... Antibody-catalyzed Aldol Condensations" in *WileyPLUS* for a method that uses the selectivity of antibodies to catalyze aldol reactions.

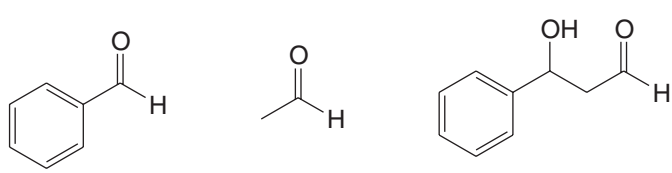
SOLVED PROBLEM 19.6

Outlined below is a practical crossed aldol reaction that can be used for the synthesis of cinnamaldehyde (the essence of cinnamon, used in cooking). Provide the missing ingredients for this recipe.



CInnamaldehyde

STRATEGY AND ANSWER: Compound **A** is benzaldehyde, **B** is ethanal (acetaldehyde), and the intermediate **C** is shown below.



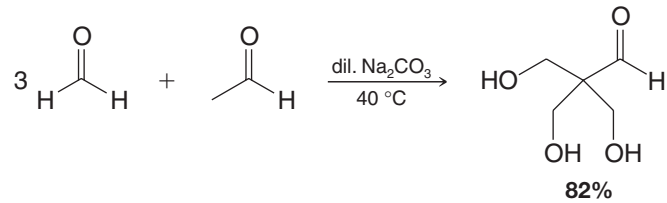
A **B** **C**

PRACTICE PROBLEM 19.11

Outlined below is a synthesis of a compound used in perfumes, called lily aldehyde. Provide all of the missing structures.

p-tert-Butylbenzyl alcohol $\xrightarrow[CH_2Cl_2]{PCC}$ $C_{11}H_{14}O$ $\xrightarrow[HO^-]{propanal}$ $C_{14}H_{18}O$ $\xrightarrow[CH_2Cl_2]{H_2,\ Pd\text{-}C}$ lily aldehyde ($C_{14}H_{20}O$)

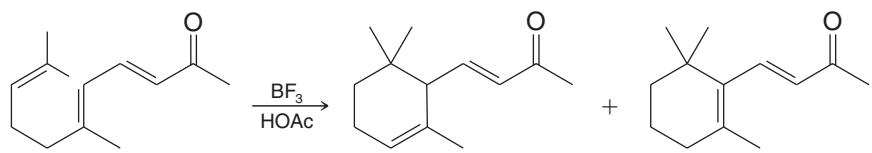
PRACTICE PROBLEM 19.12 When excess formaldehyde in basic solution is treated with ethanal, the following reaction takes place:



82%

Write a mechanism that accounts for the formation of the product.

PRACTICE PROBLEM 19.13 When pseudoionone is treated with BF_3 in acetic acid, ring closure takes place and α- and β-ionone are produced. This is the next step in the vitamin A synthesis.



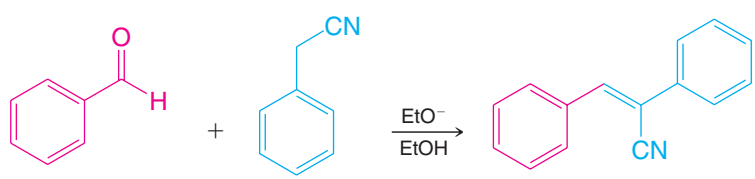
Pseudoionone **α-Ionone** **β-Ionone**

(a) Write mechanisms that explain the formation of α- and β-ionone.

(b) β-Ionone is the major product. How can you explain this?

(c) Which ionone would you expect to absorb at longer wavelengths in the UV–visible region? Why?

Nitriles with α hydrogens are also weakly acidic ($pK_a \cong 25$) and consequently these nitriles undergo condensations of the aldol type. An example is the condensation of benzaldehyde with phenylacetonitrile:



PRACTICE PROBLEM 19.14 **(a)** Write resonance structures for the anion of acetonitrile that account for its being much more acidic than ethane. **(b)** Give a step-by-step mechanism for the condensation of benzaldehyde with acetonitrile.

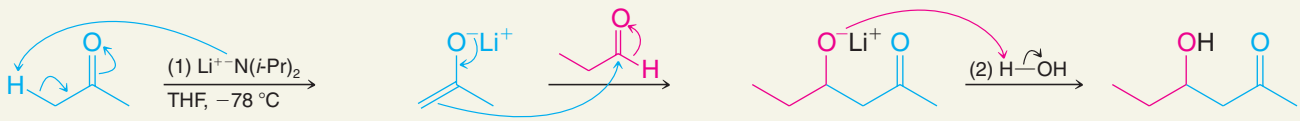
19.5B Crossed Aldol Condensations Using Strong Bases: Lithium Enolates and Directed Aldol Reactions

Helpful Hint

Lithium enolates are useful for crossed aldol syntheses.

One of the most effective and versatile ways to bring about a crossed aldol reaction is to use a lithium enolate obtained from a ketone as one component and an aldehyde or ketone as the other. An example of this approach, called a **directed aldol reaction**, is shown by the following mechanism.

A MECHANISM FOR THE REACTION — A Directed Aldol Synthesis Using a Lithium Enolate



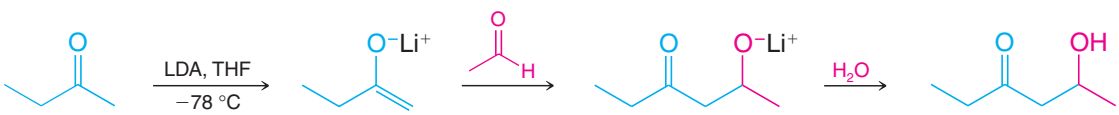
The ketone is added to $LiN(i\text{-}Pr)_2$ (LDA), a strong base, which removes an α hydrogen from the ketone to produce an enolate.

The aldehyde is added and the enolate reacts with the aldehyde at its carbonyl carbon.

An acid–base reaction occurs when water is added at the end, protonating the lithium alkoxide.

Regioselectivity can be achieved when unsymmetrical ketones are used in directed aldol reactions by generating the kinetic enolate using lithium diisopropylamide (LDA). This ensures production of the enolate in which the proton has been removed from the less substituted α carbon. The following is an example:

An Aldol Reaction via the Kinetic Enolate (Using LDA)

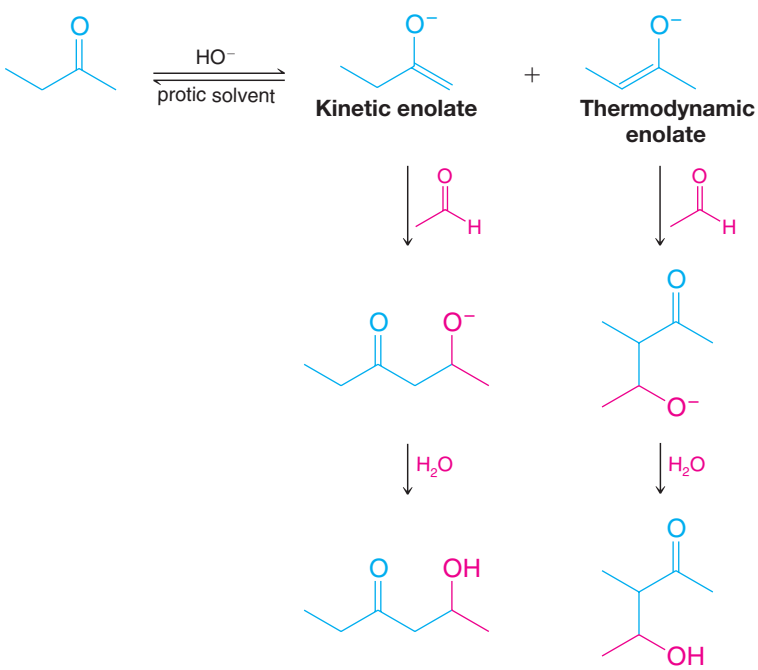


75%

A single crossed aldol product results.

If this aldol reaction had been carried out in the classic way (Section 19.5A) using hydroxide ion as the base, then at least two products would have been formed in significant amounts. Both the kinetic and thermodynamic enolates would have been formed from the ketone, and each of these would have added to the carbonyl carbon of the aldehyde:

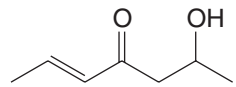
An Aldol Reaction That Produces a Mixture via Both Kinetic and Thermodynamic Enolates (Using a Weaker Base under Protic Conditions)



A mixture of crossed aldol products results.

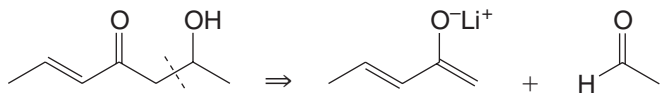
SOLVED PROBLEM 19.7

Outline a directed aldol synthesis of the following compound.

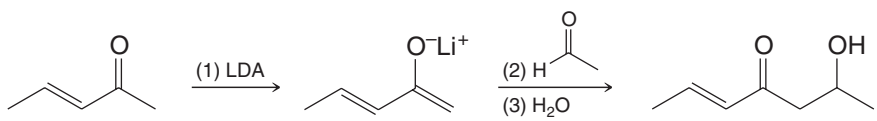


STRATEGY AND ANSWER:

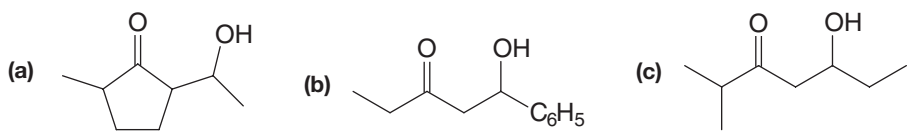
Retrosynthetic Analysis



Synthesis

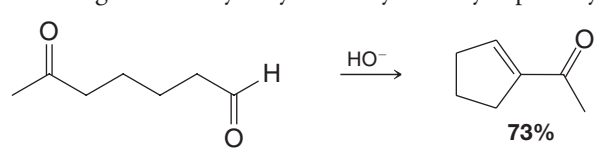


PRACTICE PROBLEM 19.15 Starting with ketones and aldehydes of your choice, outline a directed aldol synthesis of each of the following using lithium enolates:



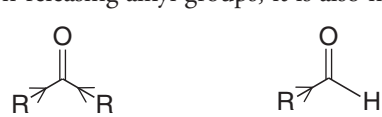
19.6 CYCLIZATIONS VIA ALDOL CONDENSATIONS

The aldol condensation also offers a convenient way to synthesize molecules with five- and six-membered rings (and sometimes even larger rings). This can be done by an intramolecular aldol condensation using a dialdehyde, a keto aldehyde, or a diketone as the substrate. For example, the following keto aldehyde cyclizes to yield 1-cyclopentenyl methyl ketone:



This reaction almost certainly involves the formation of at least three different enolates. However, it is the enolate from the ketone side of the molecule that adds to the aldehyde group leading to the product.

The reason the aldehyde group undergoes addition preferentially may arise from the greater reactivity of aldehydes toward nucleophilic addition generally. The carbonyl carbon atom of a ketone is less positive (and therefore less reactive toward a nucleophile) because it bears two electron-releasing alkyl groups; it is also more sterically hindered.



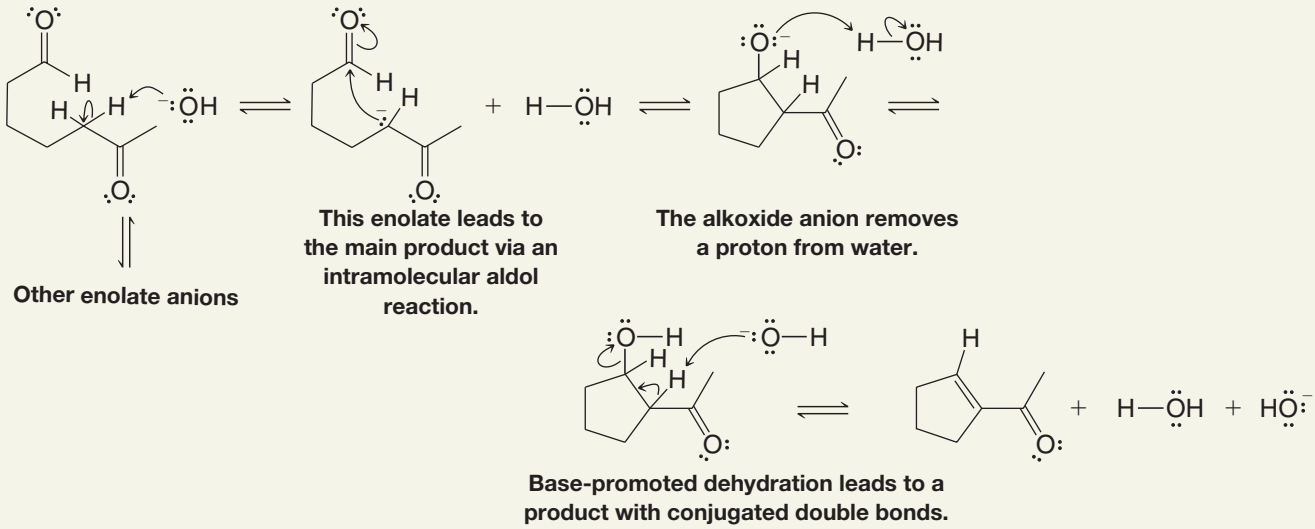
Ketones are less electrophilic than aldehydes, and hence less reactive with nucleophiles, because ketones have two electron-releasing alkyl groups and more steric hindrance.

Helpful Hint

Selectivity in aldol cyclizations is influenced by carbonyl type and ring size.

In reactions of this type, five-membered rings form far more readily than seven-membered rings, and six-membered rings are more favorable than four- or eight-membered rings, when possible.

A MECHANISM FOR THE REACTION — The Aldol Cyclization

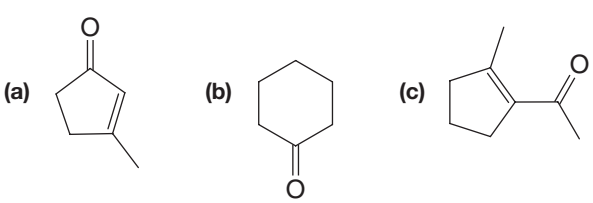


PRACTICE PROBLEM 19.16

Assuming that dehydration occurs, write the structures of the two other products that might have resulted from the aldol cyclization just given. (One of these products will have a five-membered ring and the other will have a seven-membered ring.)

PRACTICE PROBLEM 19.17

What starting compound would you use in an aldol cyclization to prepare each of the following?



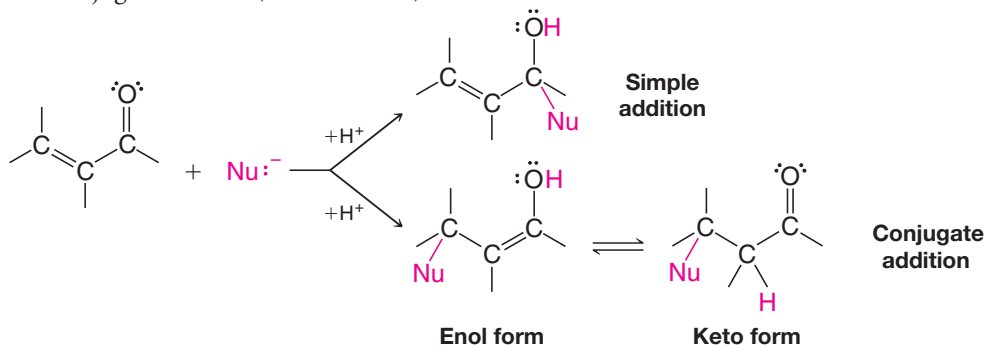
PRACTICE PROBLEM 19.18

What experimental conditions would favor the cyclization process in an intramolecular aldol reaction over intermolecular condensation?

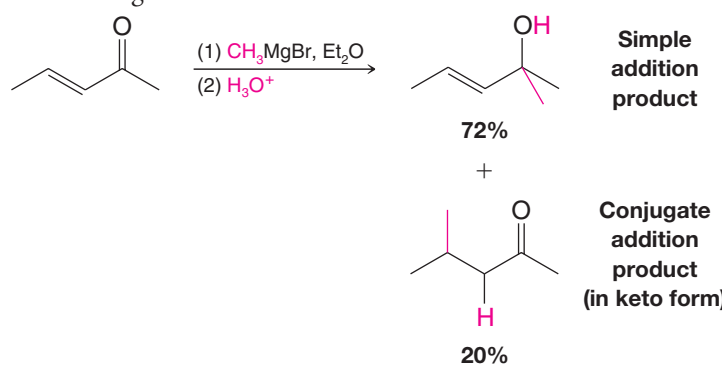
19.7 ADDITIONS TO α,β-UNSATURATED ALDEHYDES AND KETONES

When α,β-unsaturated aldehydes and ketones react with nucleophilic reagents, they may do so in two ways. They may react by a **simple addition,** that is, one in which the nucleophile adds across the double bond of the carbonyl group, or they may react by a

conjugate addition. These two processes resemble the 1,2- and the 1,4-addition reactions of conjugated dienes (Section 13.10):

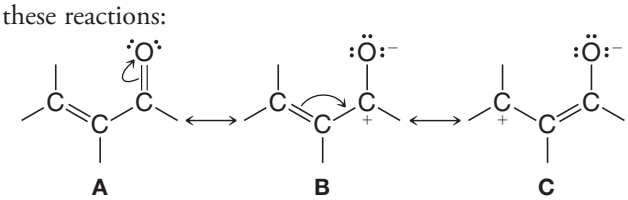


In many instances both modes of addition occur in the same mixture. As an example, let us consider the Grignard reaction shown here:

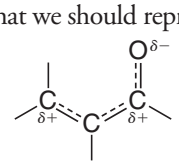


In this example we see that simple addition is favored, and this is generally the case with strong nucleophiles. Conjugate addition is favored when weaker nucleophiles are employed.

If we examine the resonance structures that contribute to the overall hybrid for an α,β-unsaturated aldehyde or ketone (see structures **A**–**C**), we shall be in a better position to understand these reactions:

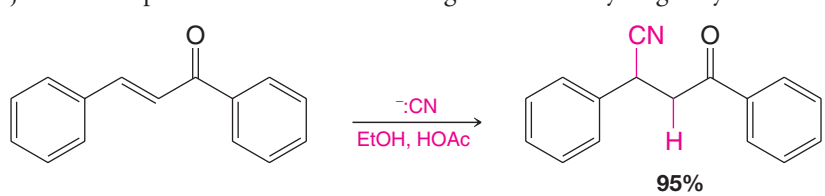


Although structures **B** and **C** involve separated charges, they make a significant contribution to the hybrid because, in each, the negative charge is carried by electronegative oxygen. Structures **B** and **C** also indicate that *both the carbonyl carbon and the β carbon should bear a partial positive charge*. They indicate that we should represent the hybrid in the following way:



This structure tells us that we should expect a nucleophilic reagent to attack either the carbonyl carbon or the β carbon.

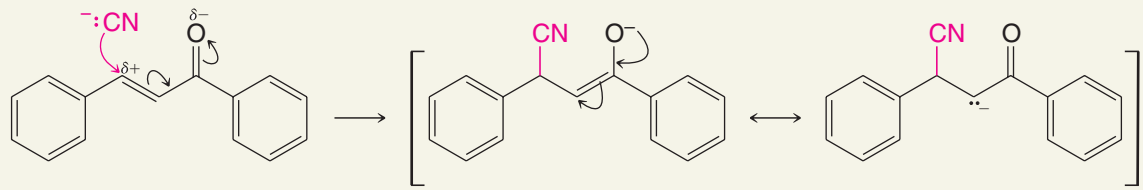
Almost every nucleophilic reagent that adds at the carbonyl carbon of a simple aldehyde or ketone is capable of adding at the β carbon of an α,β-unsaturated carbonyl compound. In many instances when weaker nucleophiles are used, conjugate addition is the major reaction path. Consider the following addition of hydrogen cyanide:



Helpful Hint

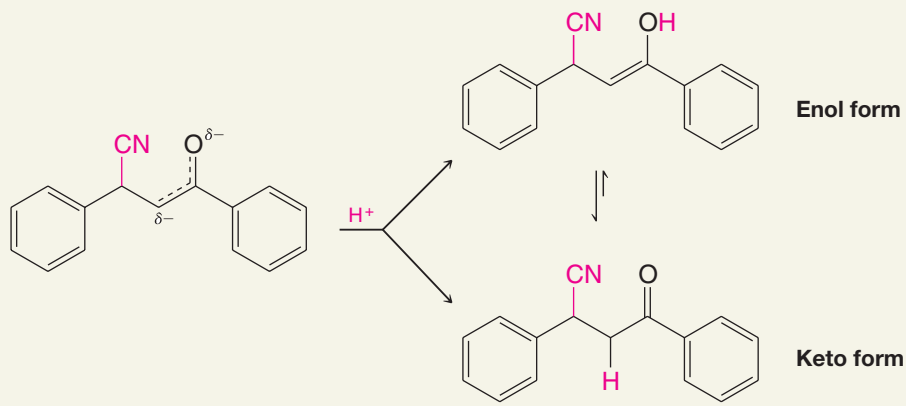
Note the influence of nucleophile strength on conjugate versus simple addition.

A MECHANISM FOR THE REACTION — The Conjugate Addition of HCN

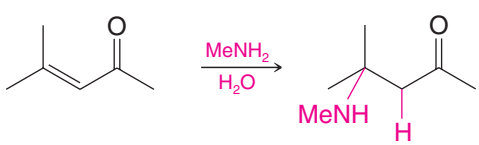


Enolate intermediate

Cyanide attacks at the partially positive β carbon. Then, the enolate intermediate accepts a proton in either of two ways:

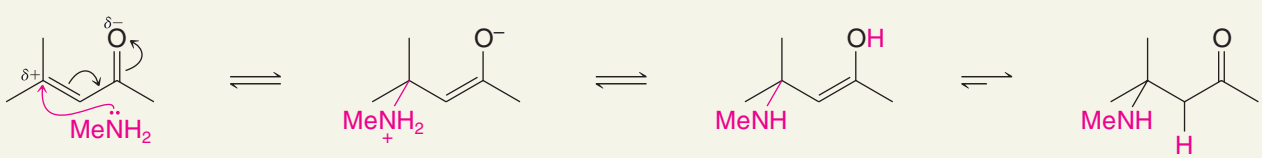


Another example of this type of addition is the following:



75%

A MECHANISM FOR THE REACTION — The Conjugate Addition of an Amine



The nucleophile attacks the partially positive β carbon.

In two separate steps, a proton is lost from the nitrogen atom and a proton is gained at the oxygen.

Enol form

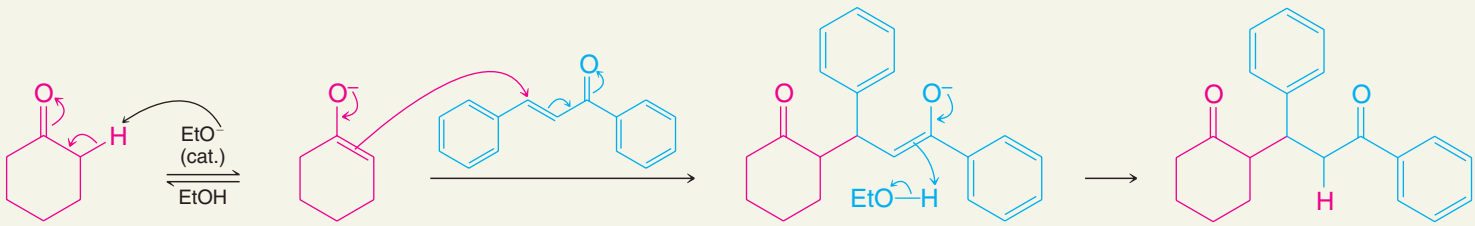
Keto form

We shall see examples of biochemically relevant conjugate additions in "The Chemistry of…Conjugate Additions to Activate Drugs" (see Section 19.7B) and in "The Chemistry of…A Suicide Enzyme Substrate" (Section 19.8).

19.7A Conjugate Additions of Enolates: Michael Additions

Conjugate additions of enolates to α,β-unsaturated carbonyl compounds are known generally as **Michael additions** (after their discovery, in 1887, by Arthur Michael, of Tufts University and later of Harvard University). The following mechanism box provides an example of a Michael addition.

A MECHANISM FOR THE REACTION — The Michael Addition

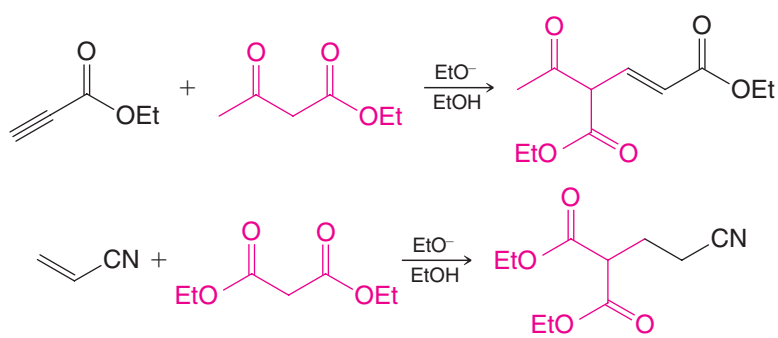


A base removes an α proton to form an enolate from one carbonyl reactant.

This enolate adds to the β carbon of the α,β-unstaturated carbonyl compound, forming a new carbon–carbon bond between them. As this bond is formed, electron density in the α,β-unsaturated compound shifts to its carbonyl oxygen, leading to a new enolate.

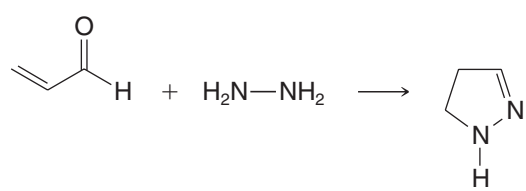
Protonation of the resulting enolate leads to the final Michael addition product.

Michael additions take place with a variety of other reagents; these include acetylenic esters and α,β-unsaturated nitriles:



PRACTICE PROBLEM 19.19 What product would you expect to obtain from the base-catalyzed Michael reaction of **(a)** 1,3-diphenylprop-2-en-1-one (Section 19.5A) and acetophenone and **(b)** 1,3-diphenylprop-2-en-1-one and cyclopentadiene? Show all steps in each mechanism.

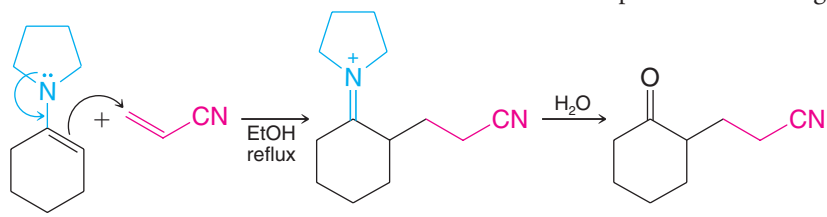
PRACTICE PROBLEM 19.20 When acrolein (propenal) reacts with hydrazine, the product is a dihydropyrazole:



Acrolein **Hydrazine** **A dihydropyrazole**

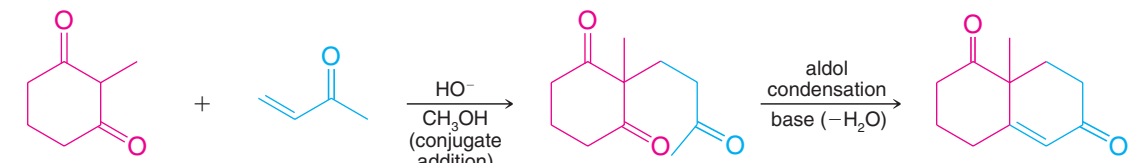
Suggest a mechanism that explains this reaction.

Enamines can also be used in Michael additions. An example is the following:



19.7B The Robinson Annulation

A Michael addition followed by a simple aldol condensation may be used to build one ring onto another. This procedure is known as the *Robinson annulation* (ring-forming) reaction, after the English chemist, Sir Robert Robinson, who won the Nobel Prize in Chemistry in 1947 for his research on naturally occurring compounds:



2-Methylcyclohexane-1,3-dione + **Methyl vinyl ketone** → **65%**

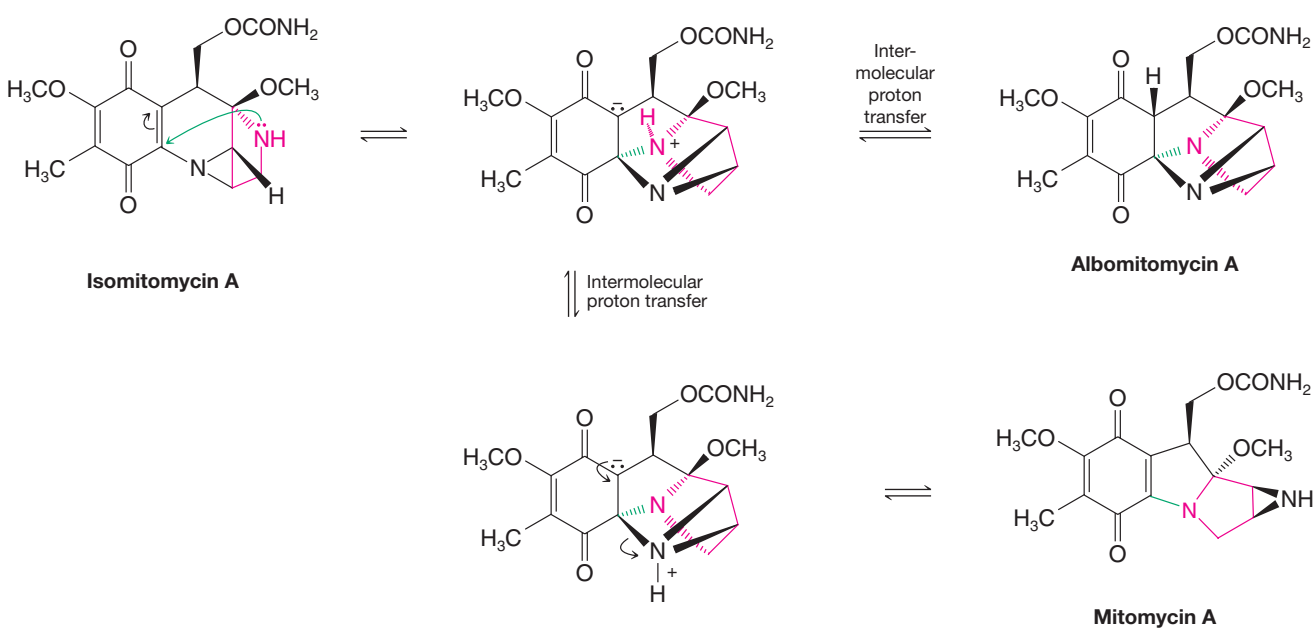
PRACTICE PROBLEM 19.21

(a) Propose step-by-step mechanisms for both transformations of the Robinson annulation sequence just shown. **(b)** Would you expect 2-methylcyclohexane-1,3-dione to be more or less acidic than cyclohexanone? Explain your answer.

THE CHEMISTRY OF... Conjugate Additions to Activate Drugs

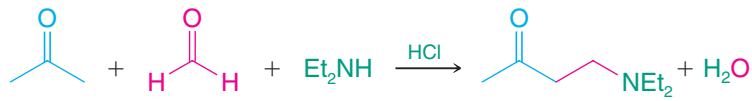
At the end of Chapter 10, we considered the special reactivity of an antitumor antibiotic known as calicheamycin γ_1^I. There, we focused on how a chemical reaction transformed a stable enediyne into one capable of undergoing a Bergman cycloaromatization. Now that we have covered conjugate additions in Section 19.7, you can understand the reaction that started the process. It turns out that there are many situations where a conjugate, or Michael, addition can set a critical process in motion. Here we briefly present the story of the mitomycins, molecules from nature known to possess antitumor properties.

If any one of the three natural products denoted below (isomitomycin A, albomitomycin A, or mitomycin A) is simply dissolved in an alcohol solvent like methanol, it will rearrange into an equilibrium mixture that contains the other two materials; the favored compound is mitomycin A. The process for that equilibration is a series of Michael reactions and retro-Michael reactions as shown. All are potent compounds, but it is their ability to rearrange through such chemistry that is equally remarkable!



19.8 THE MANNICH REACTION

Compounds capable of forming an enol react with imines from formaldehyde and a primary or secondary amine to yield β-aminoalkyl carbonyl compounds called Mannich bases. The following reaction of acetone, formaldehyde, and diethylamine is an example:

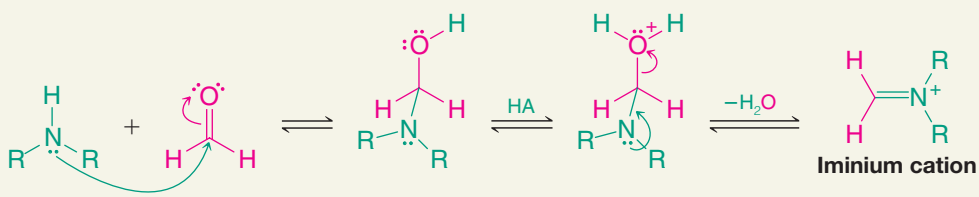


A Mannich base

The **Mannich reaction** apparently proceeds through a variety of mechanisms depending on the reactants and the conditions that are employed. The mechanism below appears to operate in neutral or acidic media. Note the aspects in common with imine formation and with reactions of enols and carbonyl groups.

A MECHANISM FOR THE REACTION — The Mannich Reaction

Step 1

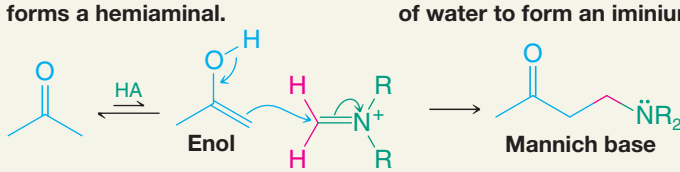


Iminium cation

Reaction of the secondary amine with the aldehyde forms a hemiaminal.

The hemiaminal loses a molecule of water to form an iminium cation.

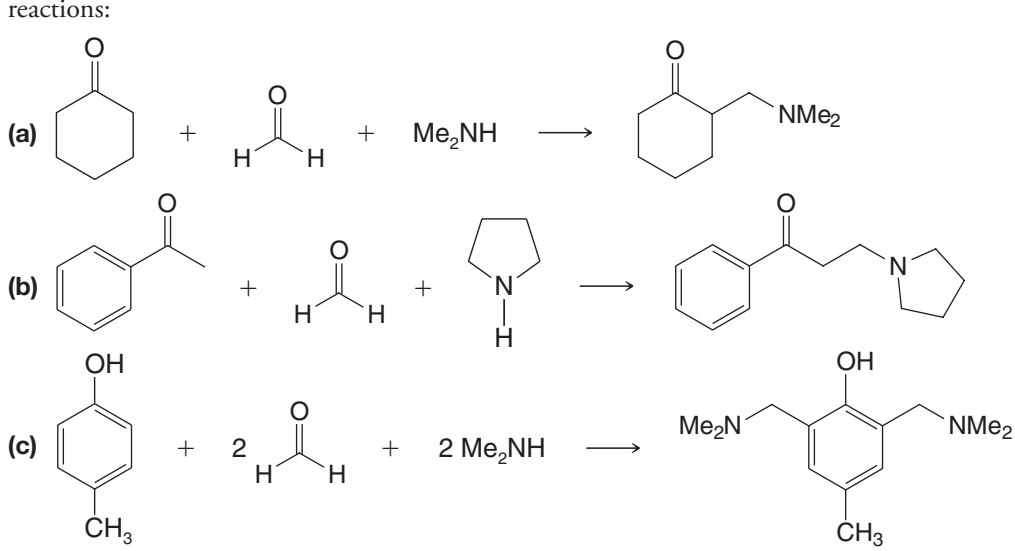
Step 2



Enol **Iminium cation** **Mannich base**

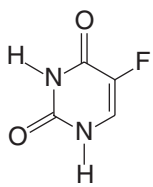
The enol form of the active hydrogen compound reacts with the iminium cation to form a β-aminocarbonyl compound (a Mannich base).

PRACTICE PROBLEM 19.22 Outline reasonable mechanisms that account for the products of the following Mannich reactions:

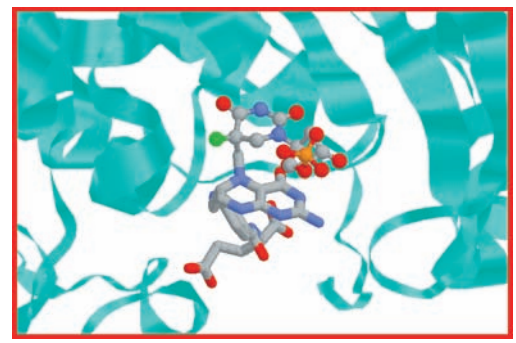


THE CHEMISTRY OF... A Suicide Enzyme Substrate

5-Fluorouracil is a chemical imposter for uracil and a potent clinical anticancer drug. This effect arises because 5-fluorouracil irreversibly destroys the ability of thymidylate synthase (an enzyme) to catalyze a key transformation needed for DNA synthesis. 5-Fluorouracil acts as a mechanism-based inhibitor (or suicide substrate) because it engages thymidylate synthase as though it were the normal substrate but then leads to self-destruction of the enzyme's activity by its own mechanistic pathway. The initial deception is possible because the fluorine atom in the inhibitor occupies roughly the same amount of space as the hydrogen atom does in the natural substrate. Disruption of the enzyme's mechanism occurs because a fluorine atom cannot be removed by a base in the way that is possible for a hydrogen atom to be removed.



5-Fluorouracil



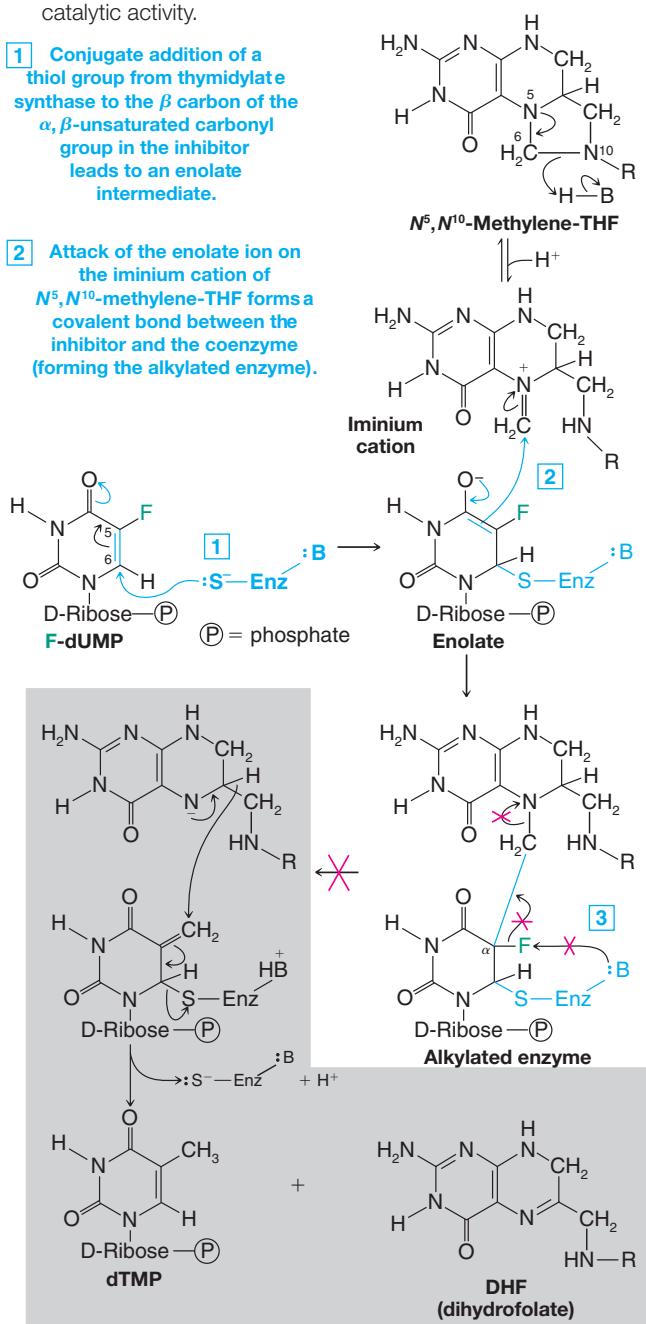
5-Fluorodeoxyuracil monophosphate covalently bound to tetrahydrofolate in thymidylate synthase, blocking the enzyme's catalytic activity.

The mechanism of thymidylate synthase in both its normal mode and when it is about to be blocked by the inhibitor involves attack of an enolate ion on an iminium cation. This process is closely analogous to the Mannich reaction discussed in Section 19.8. The enolate ion in this attack arises by conjugate addition of a thiol group from thymidylate synthase to the α,β-unsaturated carbonyl group of the substrate. This process is analogous to the way an enolate intermediate occurs in a Michael addition. The iminium ion that is attacked in this process derives from the coenzyme N^5,N^{10}-methylenetetrahydrofolate (N^5,N^{10}-methylene-THF). Attack by the enolate in this step forms the bond that covalently links the substrate to the enzyme. It is this bond that cannot be broken when the fluorinated inhibitor is used. The mechanism of inhibition is shown at right.

1 Conjugate addition of a thiol group from thymidylate synthase to the β carbon of the α,β-unsaturated carbonyl group in the inhibitor leads to an enolate intermediate.

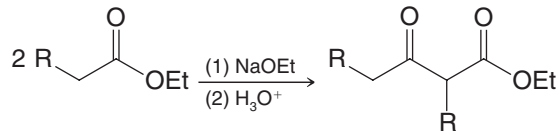
2 Attack of the enolate ion on the iminium cation of N^5,N^{10}-methylene-THF forms a covalent bond between the inhibitor and the coenzyme (forming the alkylated enzyme).

3 The next step in the normal mechanism would be an elimination reaction involving loss of a proton at the carbon α to the substrate's carbonyl group, releasing the tetrahydrofolate coenzyme as a leaving group. In the case of the fluorinated inhibitor, this step is not possible because a fluorine atom takes the place of the hydrogen atom needed for removal in the elimination. The enzyme cannot undergo the elimination reaction necessary to free it from the tetrahydrofolate coenzyme. These blocked steps are marked by cross-outs. Neither can the subsequent hydride transfer occur from the coenzyme to the substrate, which would complete formation of the methyl group and allow release of the product from the enzyme thiol group. These blocked steps are shown in the shaded area. The enzyme's activity is destroyed because it is irreversibly bonded to the inhibitor.

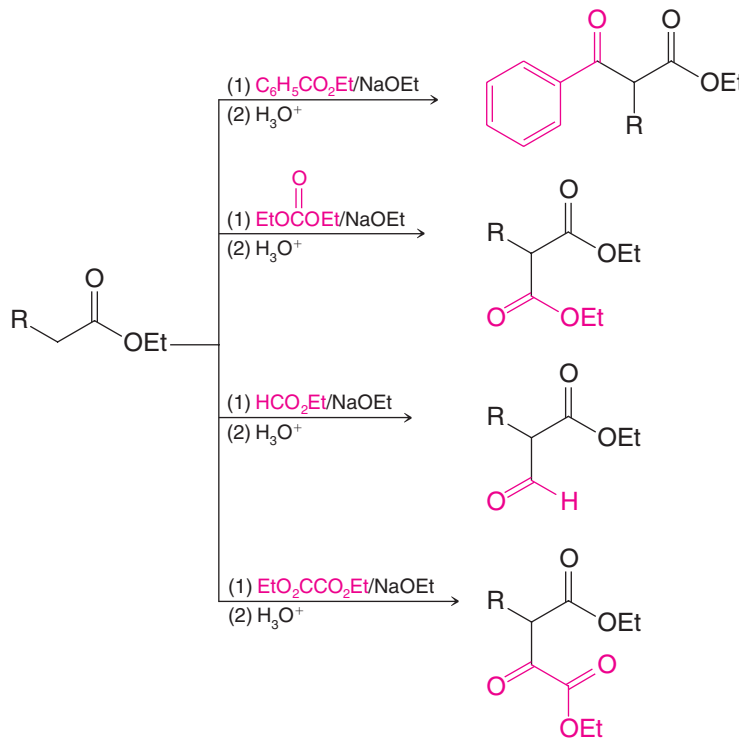


19.9 SUMMARY OF IMPORTANT REACTIONS

1. Claisen Condensation (Section 19.2):

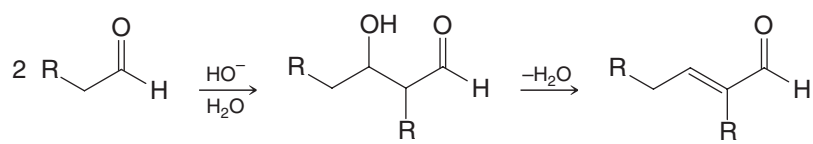


2. Crossed Claisen Condensation (Section 19.2B):

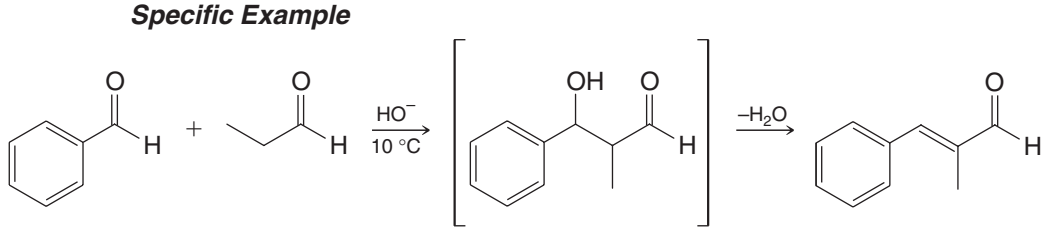


3. Aldol Reaction (Section 19.4)

General Reaction

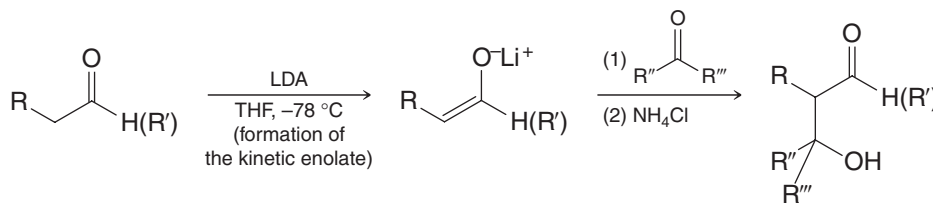


Specific Example

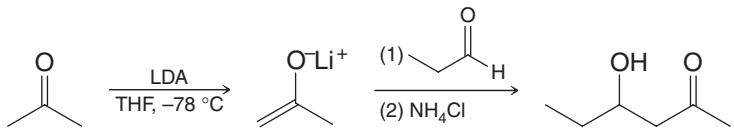


4. Directed Aldol Reactions via Lithium Enolates (Section 19.5B)

General Reaction

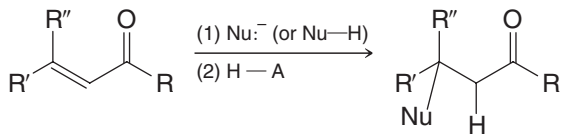


Specific Example



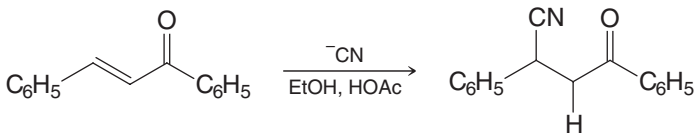
5. Conjugate Addition (Section 19.7)

General Example

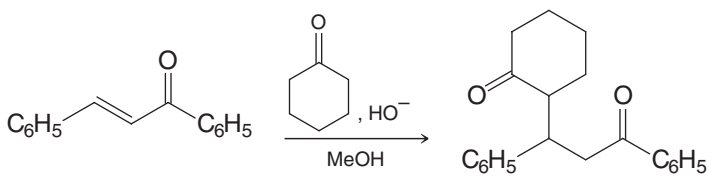


Nu:⁻ = ⁻CN ; an enolate (Michael addition); R‴MgBr
Nu—H = 1° or 2° amines; an enamine

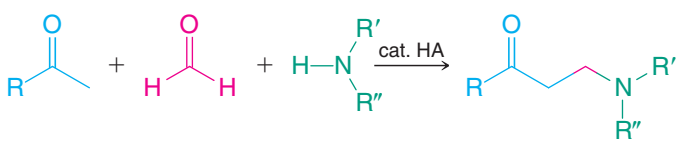
Specific Example



Specific Example (Michael Addition)



6. Mannich Reaction (Section 19.8):



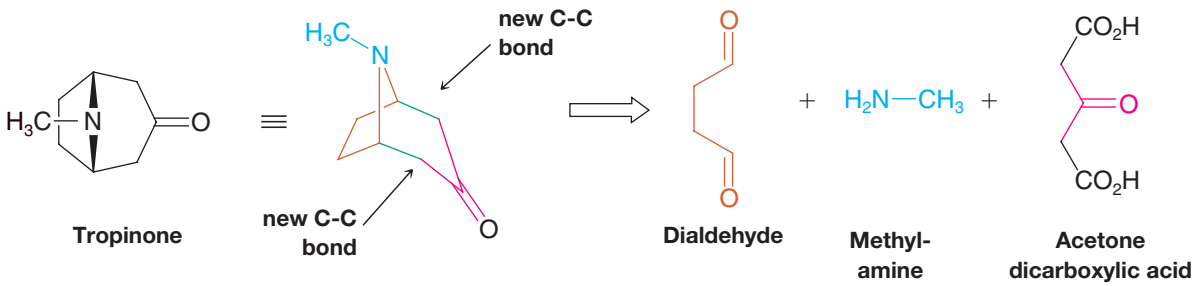
[WHY Do These Topics Matter?

PUTTING MULTIPLE REACTIONS TOGETHER IN ONE POT

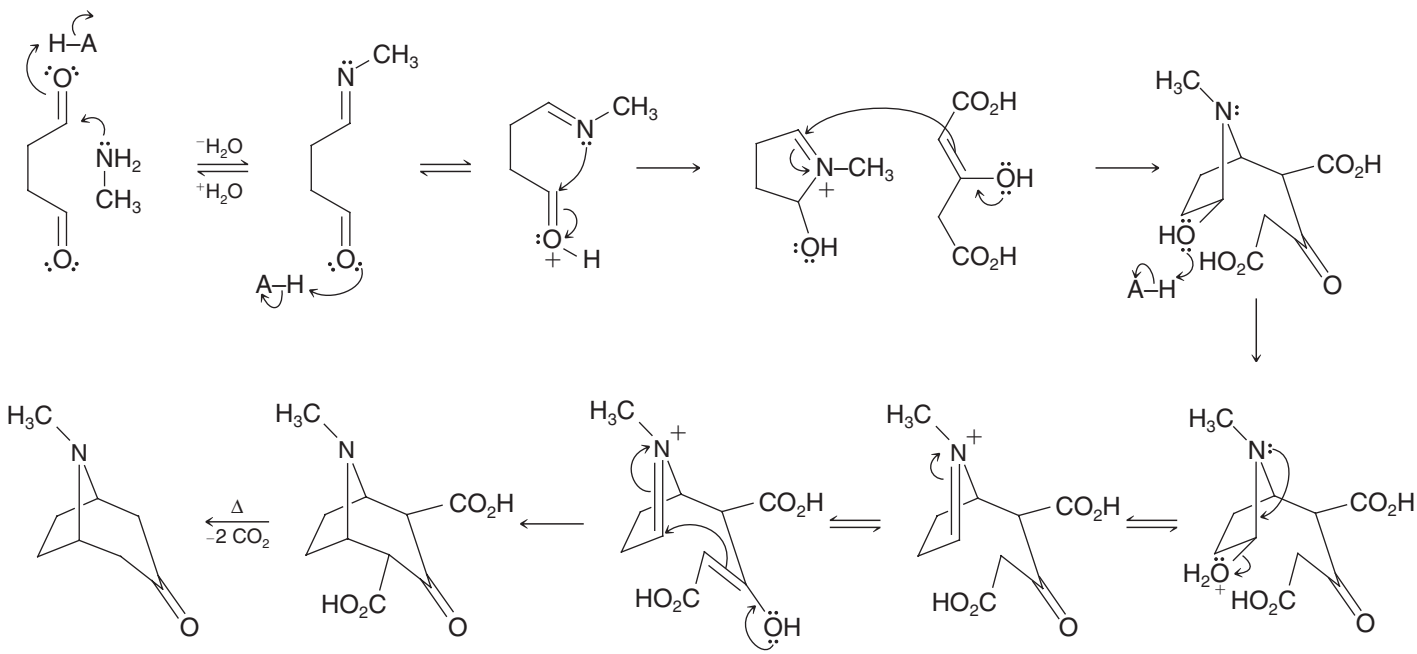
Over the course of the past several chapters, you have had the chance to learn about several powerful tools in C—C bond construction using carbonyls and their derivatives as both nucleophiles and electrophiles. While these reactions are clearly powerful in their own right, when they are combined in series, they can deliver incredibly complex molecules all at once. Such processes are known as cascade, or domino, sequences in that each step sets the stage for the next event, all in the same reaction flask. Here we illustrate what is perhaps the earliest example of this concept as accomplished by Sir Robert Robinson (a future chemistry Nobel Laureate) during the middle of World War I (1917). His target was a natural product known as tropinone. This compound constitutes the core of a number of other bioactive substances, including cocaine and atropine. At that point in the war, atropine was desperately needed by soldiers at the front to combat poisoning from organophosphate nerve agents.

How could this complex bicyclic compound be synthesized efficiently? Using the positioning of the nitrogen atom relative to the ketone, Robinson believed that the entire molecule could potentially arise from a dialdehyde, methylamine, and acetone dicarboxylic acid in a single, one-pot transformation, as color-coded below. The key reactions in the actual union would be a series of carefully orchestrated iminium ion formations and Mannich reactions to make the new C—C bonds (colored in green), followed by carboxylic acid decarboxylations to complete the target.

(continues on next page)



As shown below, that idea actually worked! Only the critical intermediates are shown below, but as a check of what you have learned so far you should be able to write the mechanisms for all the intervening steps. Key is that after the five-membered nitrogen-containing ring is formed, the first new C—C bond is generated through an intermolecular Mannich reaction. Because the reaction conditions are acidic, it is an enol tautomer that serves as the key nucleophile in this event; the two carboxylic acids attached to the acetone core of this piece aid in the ease of that tautomerization. Following acid-induced expulsion of the alcohol within the resultant aminal, a new iminium ion is generated. Once formed, an intramolecular Mannich reaction can then form the second C—C bond needed to complete the entire core of the target. Finally, the two carboxylic acids positioned strategically in a 1,3-fashion relative to the central ketone undergo decarboxylation upon heating to deliver tropinone. Pretty amazing what these reactions in series can accomplish!



To learn more about these topics, see:

1. Nicolaou, K. C.; Montagnon, T. *Molecules that Changed the World.* Wiley-VCH: Weinheim, **2008**, p. 366.

2. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P.S. "The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century" in *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122.

SUMMARY AND REVIEW TOOLS

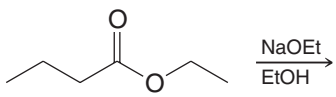
The study aids for this chapter include key terms and concepts (which are highlighted in bold, blue text within the chapter and defined in the Glossary (at the back of the book) and have hyperlinked definitions in the accompanying *WileyPLUS* course (www.wileyplus.com), the list of reaction types in Section 19.9, and the Summary of Mechanisms scheme for Enolate Reactions with Carbonyl Electrophiles and Synthetic Connections Involving Enolates.

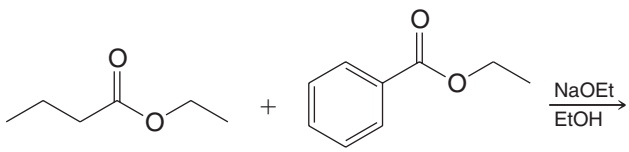
PROBLEMS

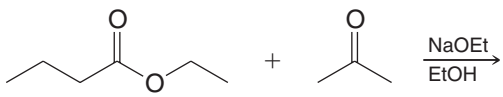
Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

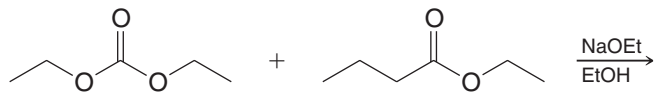
CLAISEN CONDENSATION REACTIONS

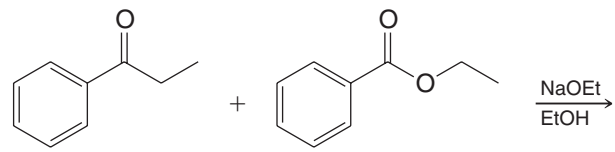
19.23 Write a structural formula for the product from each of the following reactions.

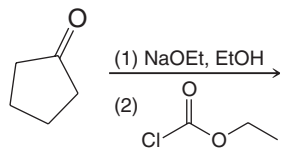
(a) 

(b) 

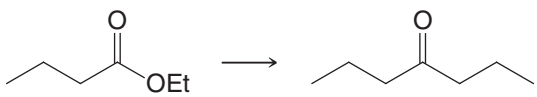
(c) 

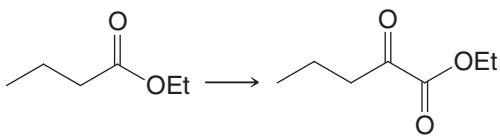
(d) 

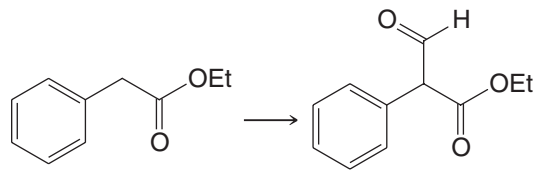
(e) 

(f) 

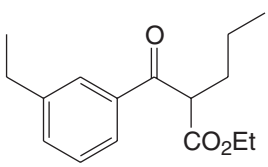
19.24 Show all steps in the following syntheses. You may use any other needed reagents but you should begin with the compound given.

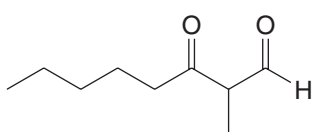
(a) 

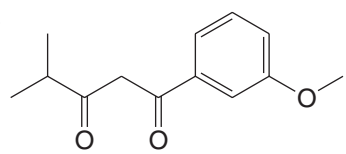
(b) 

(c) 

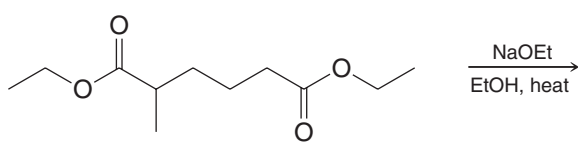
19.25 Provide the starting materials needed to synthesize each compound by acylation of an enolate.

(a) 

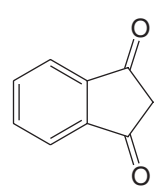
(b) 

(c) 

19.26 Write structural formulas for both of the possible products from the following Dieckmann condensation, and predict which one would likely predominate.

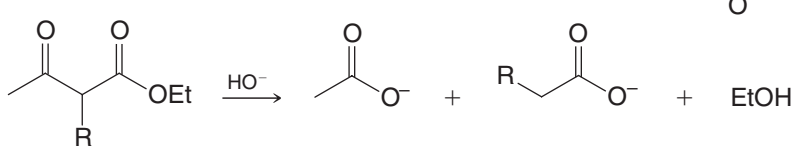


19.27 When a Dieckmann condensation is attempted with diethyl succinate, the product obtained has the molecular formula $C_{12}H_{16}O_6$. What is the structure of this compound?



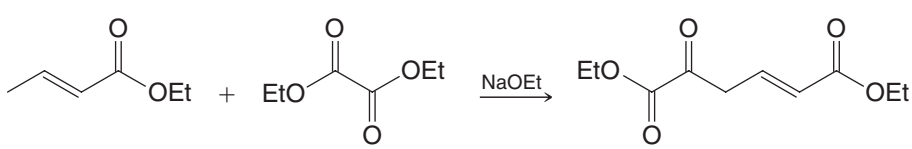
19.28 Show how this diketone could be prepared by a condensation reaction:

19.29 In contrast to the reaction with dilute alkali (Section 18.6), when concentrated solutions of NaOH are used, acetoacetic esters undergo cleavage as shown below.



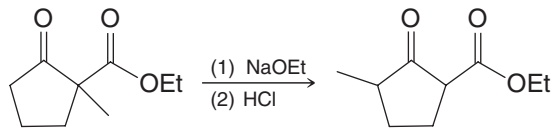
Provide a mechanistic explanation for this outcome.

19.30 Write a detailed mechanism for the following reaction.

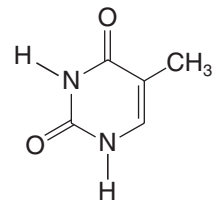


Ethyl crotonate **Diethyl oxalate**

19.31 In the presence of sodium ethoxide the following transformation occurs. Explain.



19.32 Thymine is one of the heterocyclic bases found in DNA. Starting with ethyl propanoate and using any other needed reagents, show how you might synthesize thymine.

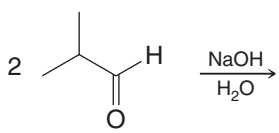


Thymine

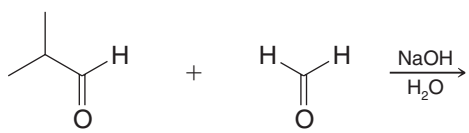
ALDOL REACTIONS

19.33 Predict the products from each of the following aldol reactions.

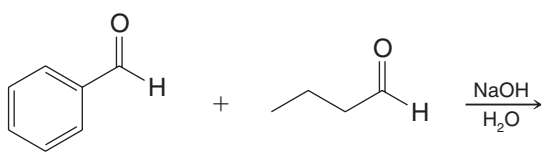
(a)



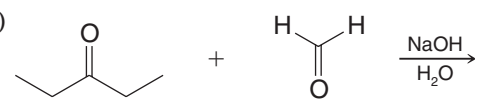
(b)



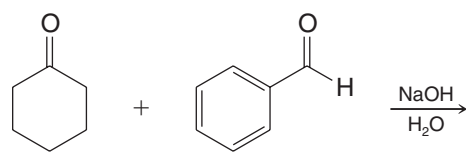
(c)



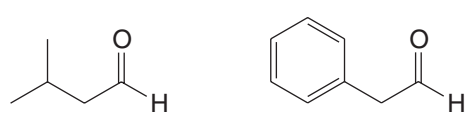
(d)



(e)

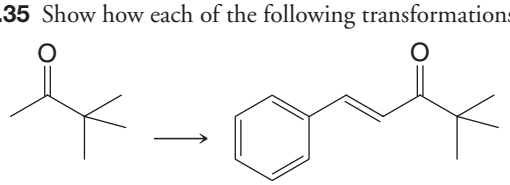


19.34 What four β-hydroxy aldehydes would be formed by a crossed aldol reaction between the following compounds?



19.35 Show how each of the following transformations could be accomplished. You may use any other required reagents.

(a)



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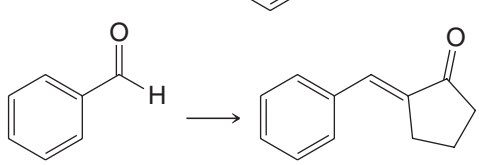

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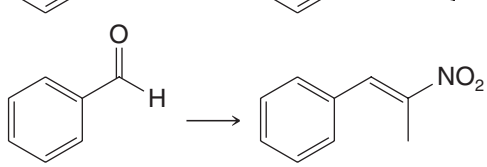

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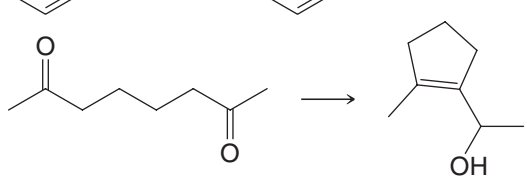

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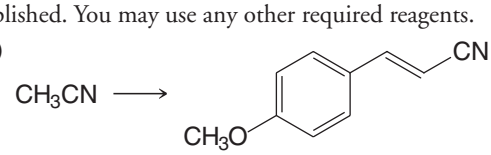
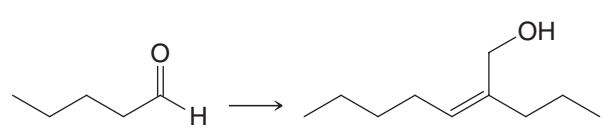
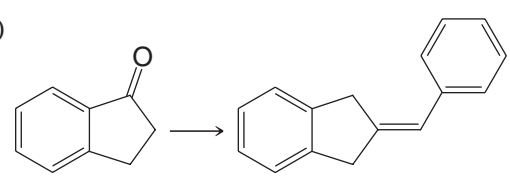


(f)

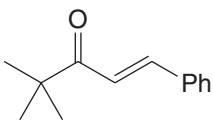


(g)

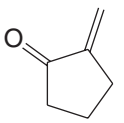


19.36 What starting materials are needed to synthesize each of the following compounds using an aldol reaction?

(a)



(b)



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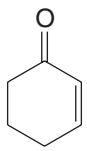
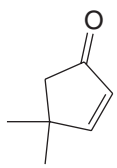
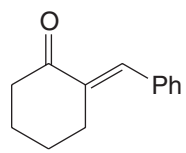


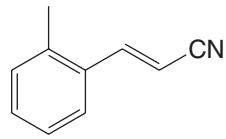
(d)



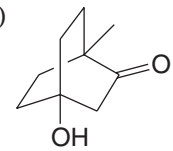
(e)



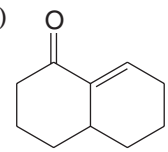
(f)



(g)

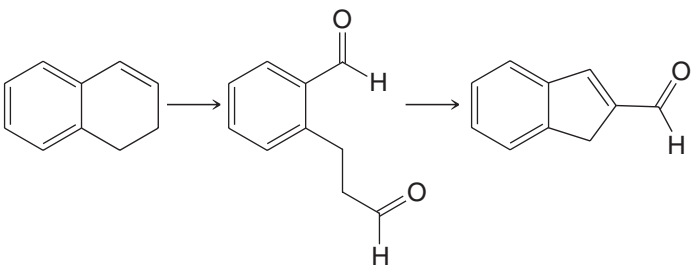


(h)

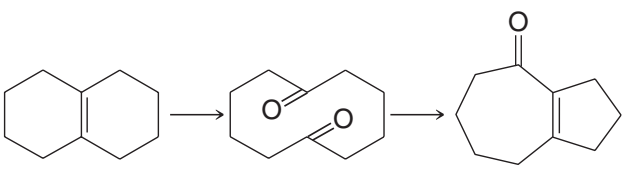


19.37 What reagents would you use to bring about each step of the following syntheses?

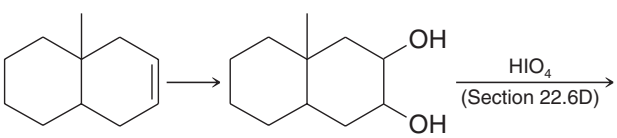
(a)

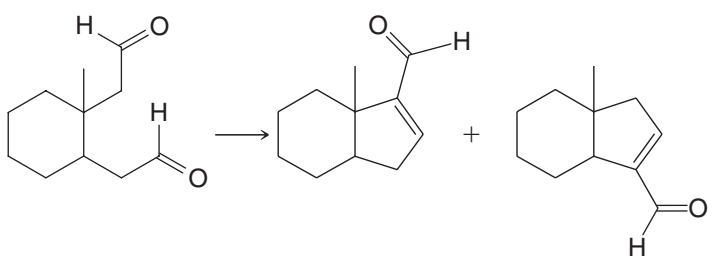


(b)

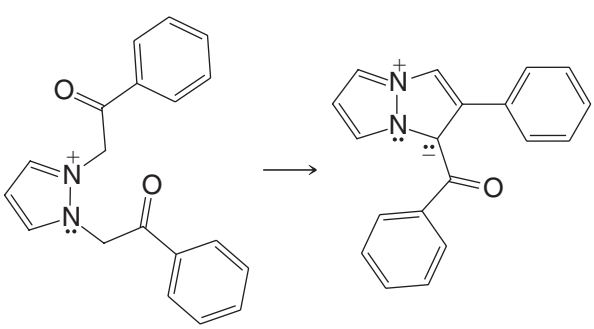


(c)

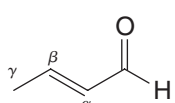




(d)



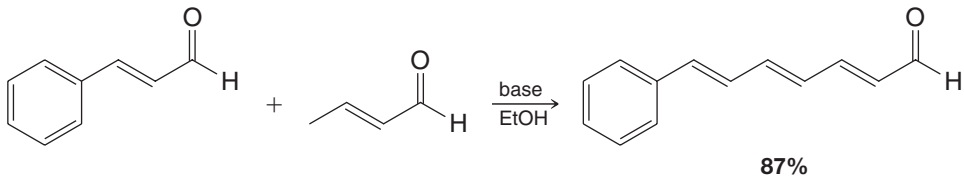
19.38 The hydrogen atoms of the γ carbon of crotonaldehyde are appreciably acidic ($pK_a \cong 20$).



Crotonaldehyde

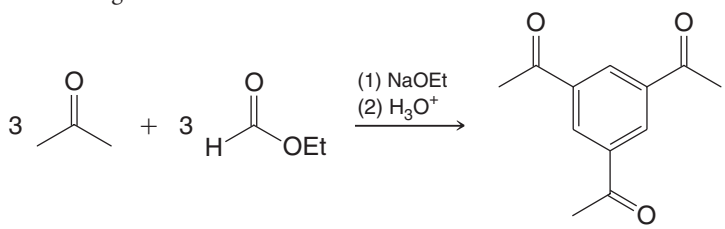
(a) Write resonance structures that will explain this fact.

(b) Write a mechanism that accounts for the following reaction:



87%

19.39 Provide a mechanism for the following reaction.

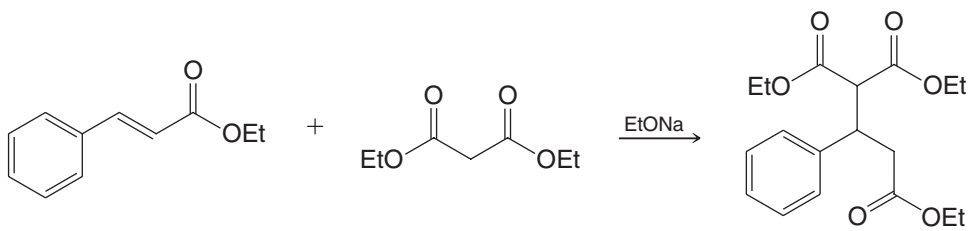


19.40 When the aldol reaction of acetaldehyde is carried out in D_2O, no deuterium is found in the methyl group of unreacted aldehyde. However, in the aldol reaction of acetone, deuterium is incorporated in the methyl group of the unreacted acetone. Explain this difference in behavior.

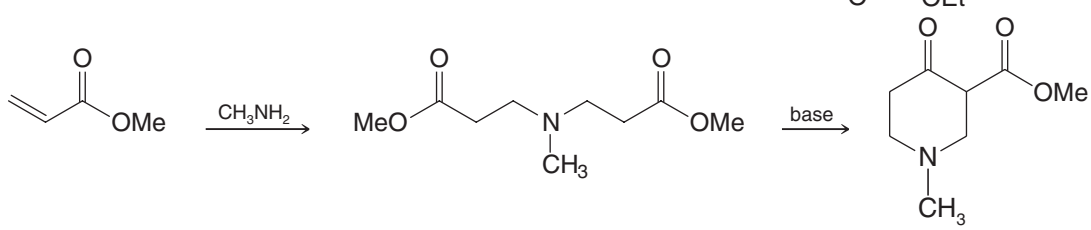
CONJUGATE ADDITION REACTIONS

19.41 Write mechanisms that account for the products of the following reactions:

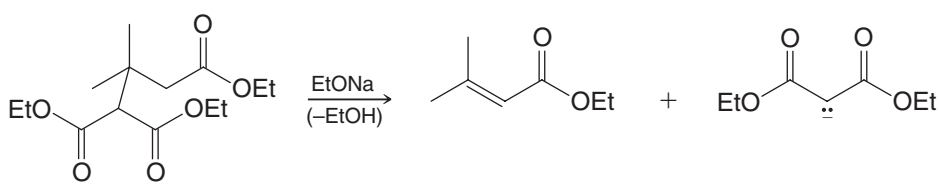
(a)



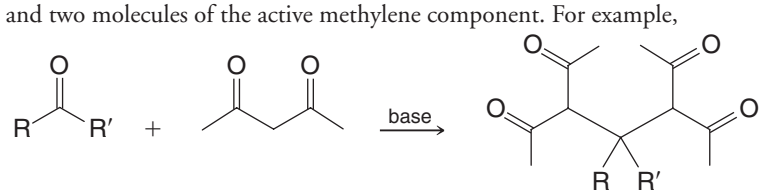
(b)



(c)

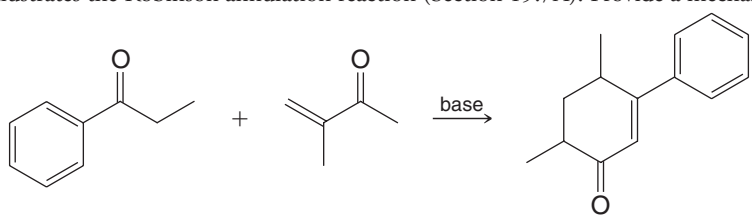


19.42 Condensations in which the active hydrogen compound is a β-keto ester or a β-diketone often yield products that result from one molecule of aldehyde or ketone and two molecules of the active methylene component. For example,



Suggest a reasonable mechanism that accounts for the formation of these products.

19.43 The following reaction illustrates the Robinson annulation reaction (Section 19.7A). Provide a mechanism.



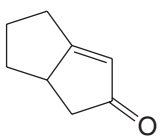
19.44 What is the structure of the *cyclic* compound that forms after the Michael addition of **1** to **2** in the presence of sodium ethoxide?

1 **2**

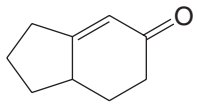
GENERAL PROBLEMS

19.45 Synthesize each compound starting from cyclopentanone.

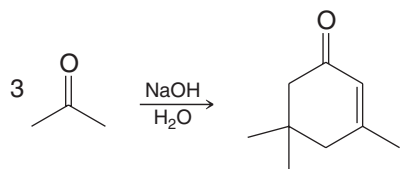
(a)



(b)

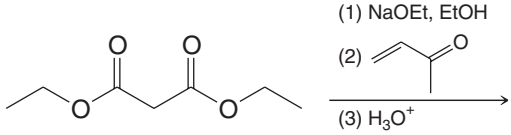


19.46 Provide a mechanism for the following reaction.

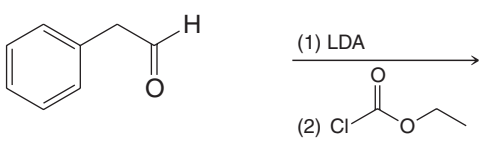


19.47 Predict the products of the following reactions.

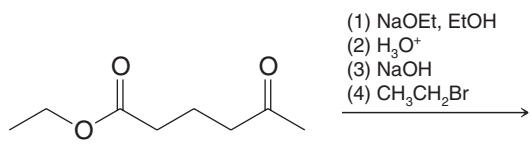
(a)



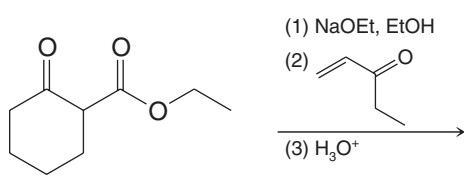
(b)



(c)

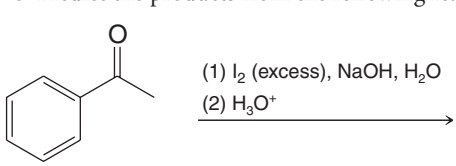


(d)

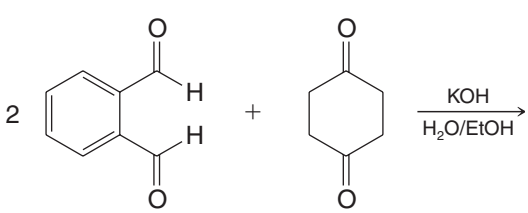


19.48 Predict the products from the following reactions.

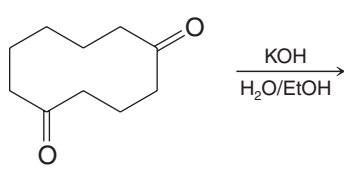
(a)



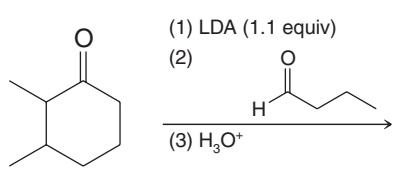
(b)



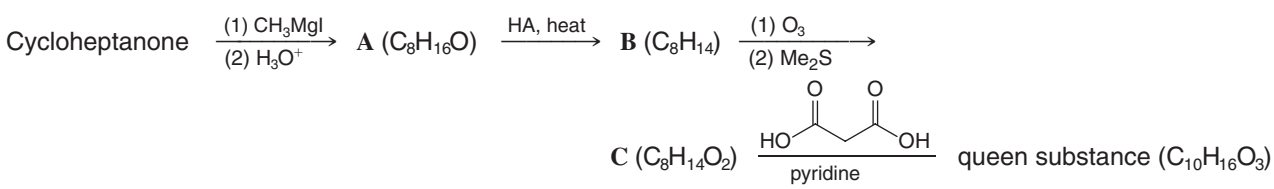
(c)



(d)



19.49 The mandibular glands of queen bees secrete a fluid that contains a remarkable compound known as "queen substance." When even an exceedingly small amount of the queen substance is transferred to worker bees, it inhibits the development of their ovaries and prevents the workers from bearing new queens. Queen substance, a monocarboxylic acid with the molecular formula $C_{10}H_{16}O_3$, has been synthesized by the following route:

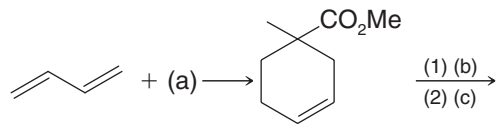


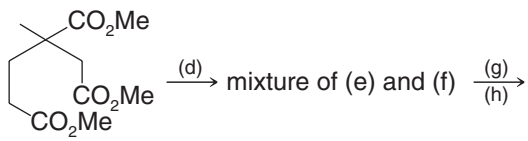
On catalytic hydrogenation, queen substance yields compound **D**, which, on treatment with iodine in sodium hydroxide and subsequent acidification, yields a dicarboxylic acid **E**; that is,

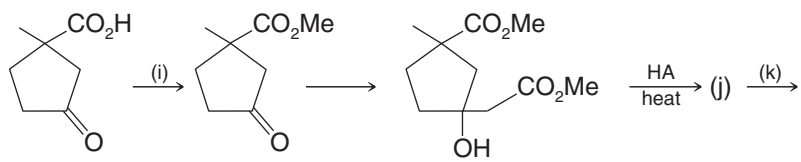
$$\text{Queen substance} \xrightarrow[\text{Pd}]{H_2} \mathbf{D}\ (C_{10}H_{18}O_3) \xrightarrow[(2)\ H_3O^+]{(1)\ I_2 \text{ in aq. NaOH}} \mathbf{E}\ (C_9H_{16}O_4)$$

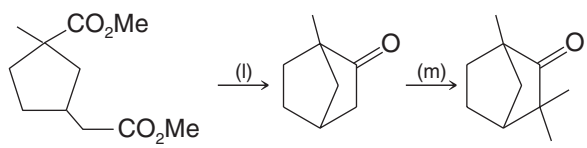
Provide structures for the queen substance and compounds **A–E**.

19.50 (+)-Fenchone is a terpenoid that can be isolated from fennel oil. (±)-Fenchone has been synthesized through the following route. Supply the missing intermediates and reagents.



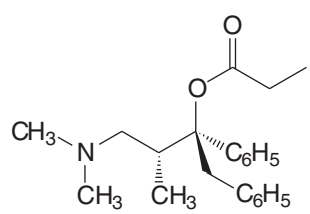




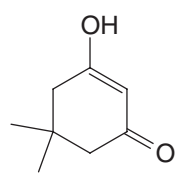


(±)-Fenchone

19.51 Outline a racemic synthesis of Darvon (below), an analgesic compound whose use has been discontinued, starting with ethyl phenyl ketone.



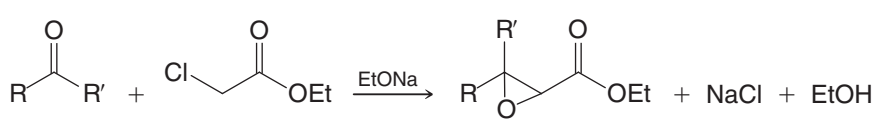
19.52 Show how dimedone can be synthesized from malonic ester and 4-methyl-3-penten-2-one (mesityl oxide) under basic conditions.



Dimedone

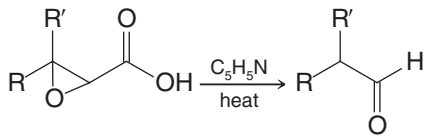
19.53 Write the mechanistic steps in the cyclization of ethyl phenylacetoacetate (ethyl 3-oxo-4-phenylbutanoate) in concentrated sulfuric acid to form naphthoresorcinol (1,3-naphthalenediol).

19.54 When an aldehyde or a ketone is condensed with ethyl α-chloroacetate in the presence of sodium ethoxide, the product is an α,β-epoxy ester called a *glycidic ester*. The synthesis is called the Darzens condensation.

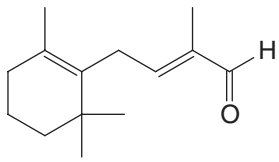


A glycidic ester

(a) Outline a reasonable mechanism for the Darzens condensation. **(b)** Hydrolysis of the epoxy ester leads to an epoxy acid that, on heating with pyridine, furnishes an aldehyde. What is happening here?



(c) Starting with β-ionone (Practice Problem 19.13), show how you might synthesize the following aldehyde. (This aldehyde is an intermediate in an industrial synthesis of vitamin A.)



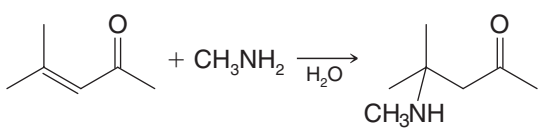
19.55 The *Perkin condensation* is an aldol-type condensation in which an aromatic aldehyde (ArCHO) reacts with a carboxylic acid anhydride, $(RCH_2CO)_2O$, to give an α,β-unsaturated acid ($ArCH{=}CRCO_2H$). The catalyst that is usually employed is the potassium salt of the carboxylic acid (RCH_2CO_2K). **(a)** Outline the Perkin condensation that takes place when benzaldehyde reacts with propanoic anhydride in the presence of potassium propanoate. **(b)** How would you use a Perkin condensation to prepare *p*-chlorocinnamic acid, $p\text{-}ClC_6H_4CH{=}CHCO_2H$?

SPECTROSCOPY

19.56

(a) Infrared spectroscopy provides an easy method for deciding whether the product obtained from the addition of a Grignard reagent to an α,β-unsaturated ketone is the simple addition product or the conjugate addition product. Explain. (What peak or peaks would you look for?)

(b) How might you follow the rate of the following reaction using UV spectroscopy?



19.57 Allowing acetone to react with 2 molar equivalents of benzaldehyde in the presence of KOH in ethanol leads to the formation of compound **X**. The ^{13}C NMR spectrum of **X** is given in Fig. 19.1. Propose a structure for compound **X**.

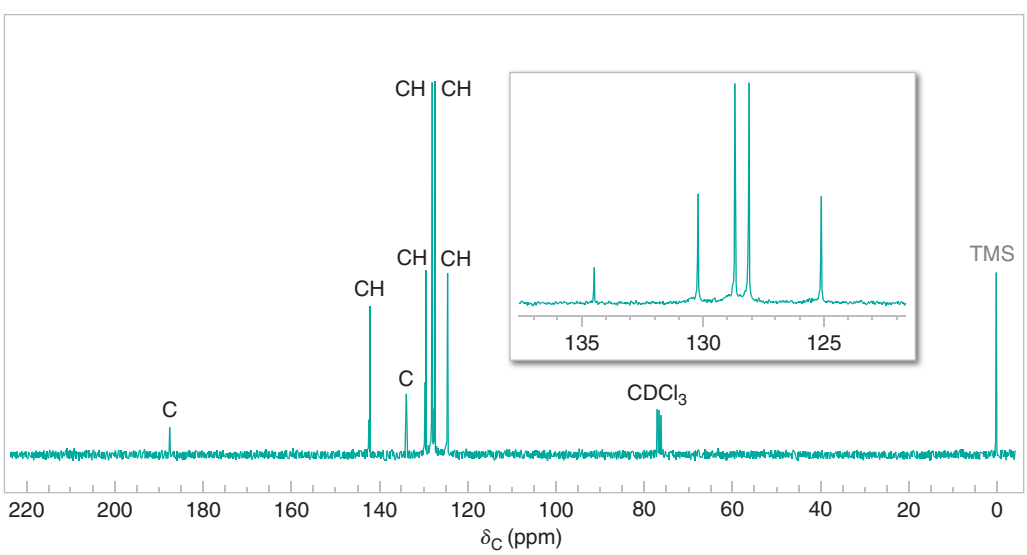
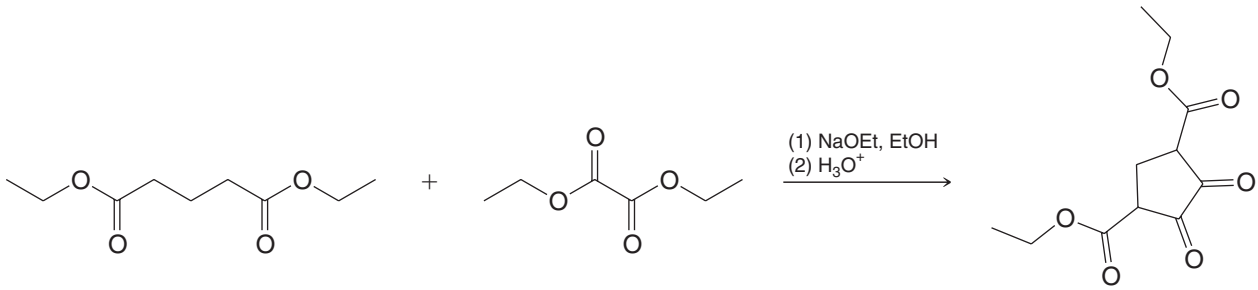


FIGURE 19.1 The broadband proton-decoupled ^{13}C NMR spectrum of compound X, Problem 19.57. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

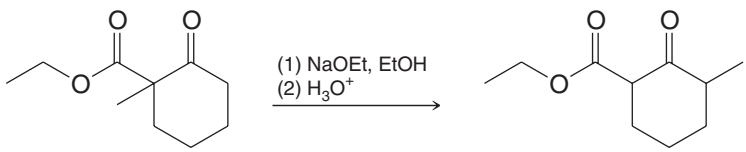
CHALLENGE PROBLEMS

19.58 Provide a mechanism for each of the following reactions.

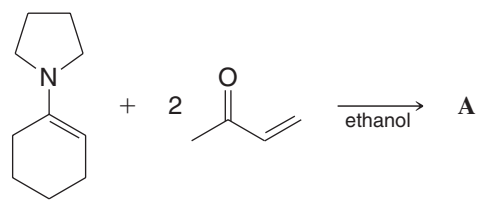
(a)



(b)



19.59 **(a)** Deduce the structure of product **A**, which is highly symmetrical:



The following are selected spectral data for **A**:

MS (*m/z*): 220 ($M^{+\cdot}$)

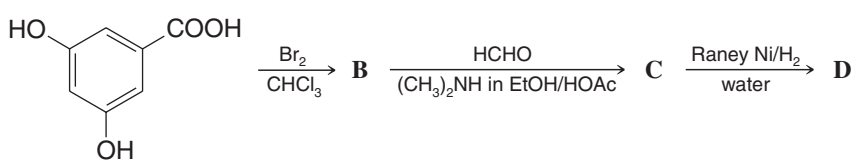
IR (cm^{-1}): 2930, 2860, 1715

^{1}H **NMR** (δ): 1.25 (m), 1.29 (m), 1.76 (m), 1.77 (m), 2.14 (s), and 2.22 (t); (area ratios 2:1:2:1:2:2, respectively)

^{13}C **NMR** (δ): 23 (CH_2), 26 (CH_2), 27 (CH_2), 29 (C), 39 (CH), 41 (CH_2), 46 (CH_2), 208 (C)

(b) Write a mechanism that explains the formation of **A**.

19.60 Write the structures of the three products involved in this reaction sequence:



Spectral data for **B**:

MS (*m/z*): 314, 312, 310 (relative abundance 1:2:1)

^{1}H **NMR** (δ): only 6.80 (s) after treatment with D_2O

Data for **C**:

MS (*m/z*): 371, 369, 367 (relative abundance 1:2:1)

^{1}H **NMR** (δ): 2.48 (s) and 4.99 (s) in area ratio 3:1; broad singlets at 5.5 and 11 disappeared after treatment with D_2O.

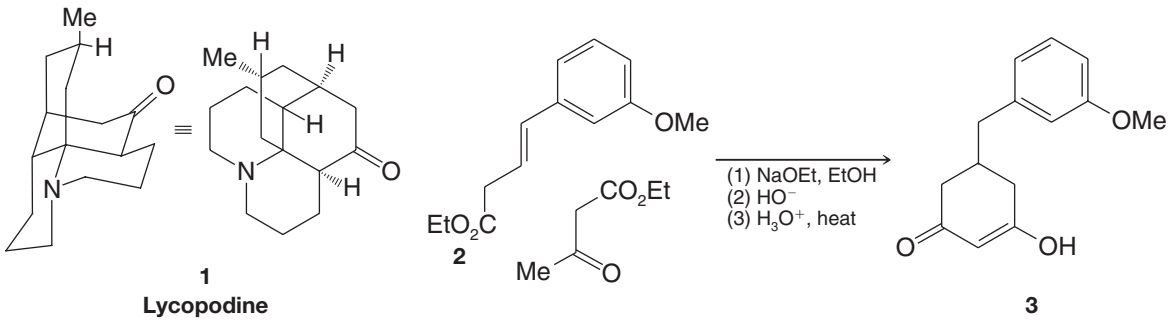
Data for **D**:

MS (*m/z*): 369 ($M^{+\cdot} - CH_3$) [when studied as its tris(trimethylsilyl) derivative]

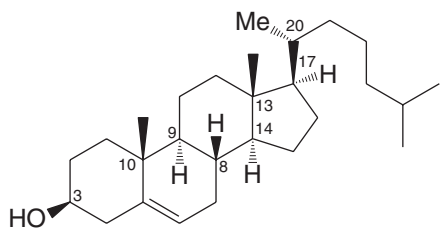
^{1}H **NMR** (δ): 2.16 (s) and 7.18 (s) in area ratio 3:2; broad singlets at 5.4 and 11 disappeared after treatment with D_2O.

LEARNING GROUP PROBLEMS

1. Lycopodine is a naturally occurring amine. As such, it belongs to the family of natural products called alkaloids. Its synthesis (*J. Am. Chem. Soc.* **1968**, *90*, 1647–1648) was accomplished by one of the great synthetic organic chemists of our time, Gilbert Stork (Columbia University). Write a detailed mechanism for all the steps that occur when **2** reacts with ethyl acetoacetate in the presence of ethoxide ion. Note that a necessary part of the mechanism will be a base-catalyzed isomerization (via a conjugated enolate) of the alkene in **2** to form the corresponding α,β-unsaturated ester.



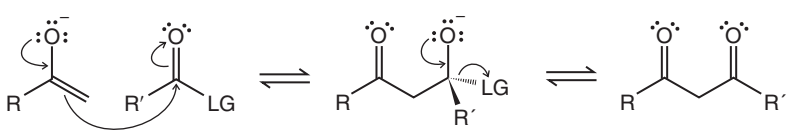
2. Steroids are an extremely important class of natural and pharmaceutical compounds. Synthetic efforts directed toward steroids have been underway for many years and continue to be an area of important research. The synthesis of cholesterol by R. B. Woodward (Harvard University, recipient of the Nobel Prize in Chemistry for 1965) and co-workers represents a paramount accomplishment in steroid synthesis, and it is rich with examples of carbonyl chemistry and other reactions we have studied. Selected reactions from Woodward's cholesterol synthesis and the questions for this Learning Group Problem are shown in the *WileyPLUS* materials for this chapter. Access those materials online to complete this problem.



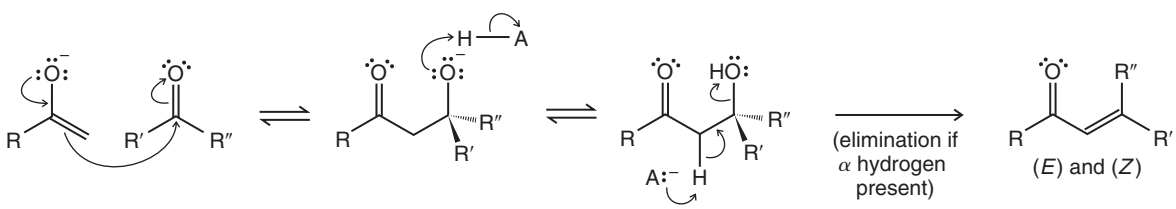
Cholesterol

SUMMARY OF MECHANISMS

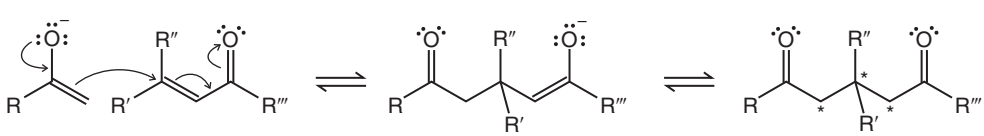
Enolate Reactions with Carbonyl Electrophiles



Acyl substitution (addition–elimination), e.g., Claisen condensation when LG = OR



Aldol reactions (addition and condensation)



Michael (conjugate) addition

SYNTHETIC CONNECTIONS

Some Synthetic Connections Involving Enolates

- Enolate formation
- Keto–enol tautomerism
- Halogenation
- Alkylation
- Acylation

Enolates provide many ways to functionalize the α-carbon of a carbonyl compound. Most importantly, enolates provide ways to form new carbon–carbon bonds. Some of these synthetic connections are shown here. Previously studied reactions of carbonyl, alcohol, and alkene functional groups (e.g., reduction, oxidation, addition, substitution) lead to or from some of these pathways.

- Claisen condensation
- Aldol reactions
- Addition of Grignard and RLi
- Michael addition
- Conjugate addition of HCN
- Conjugate addition of amines