CHAPTER

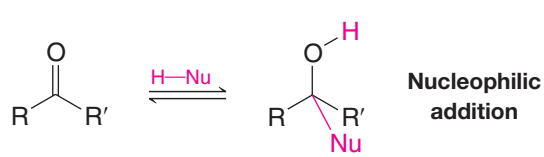
18

Reactions at the α Carbon of Carbonyl Compounds

ENOLS AND ENOLATES

When we exercise vigorously, our bodies rely heavily on the metabolic process of glycolysis to derive energy from glucose. Glycolysis splits glucose into two three-carbon molecules. Only one of these three-carbon molecules (glyceraldehyde-3-phosphate, GAP) is directly capable of going further in the glycolytic pathway. The other three-carbon molecule (dihydroxyacetone-3-phosphate, DHAP) is not wasted, however. It is converted to a second molecule of GAP, via a type of intermediate that is key to our studies in this chapter—an enol (so named because the intermediate is an alkene alcohol). We shall learn about enols and enolates, their conjugate bases, in this chapter.

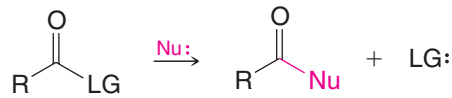
In Chapter 16, we saw how aldehydes and ketones can undergo nucleophilic addition at their carbonyl groups. For example:



Nucleophilic addition

PHOTO CREDIT: © Adam Burn/fStop/Age Fotostock America, Inc.

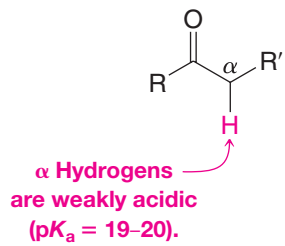
In Chapter 17 we saw how substitution could occur at a carbonyl group if a suitable leaving group is present. This type of reaction is called acyl substitution. For example:



(Proton transfer steps are involved in some nucleophilic addition and acyl substitution reactions, as detailed in Chapters 16 and 17.)

IN THIS CHAPTER WE WILL CONSIDER:

- Reactions that derive from the weak acidity of hydrogen atoms on carbon atoms adjacent to α carbonyl group. These hydrogen atoms are called the **α hydrogens**, and the carbon to which they are attached is called the **α carbon**.



- The processes by which enols and enolates can be formed
- The concept of kinetic and thermodynamic deprotonations to generate different enolates from the same starting material
- Alkylations, acylations, and other electrophile additions to enols and enolates
- A special version of the same chemistry using the nitrogen analog of an enol—that is, an enamine

[WHY DO THESE TOPICS MATTER?] At the end of this chapter, we will show how the chemistry of enamines affords the ability to execute highly complex bond formations pertinent to the synthesis of complex, bioactive molecules, and how this chemistry has even been used to produce several tons of a highly valuable medicine.

18.1 THE ACIDITY OF THE α HYDROGENS OF CARBONYL COMPOUNDS: ENOLATE ANIONS

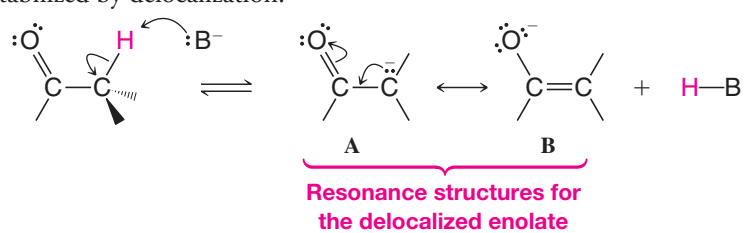
When we say that the α hydrogens of carbonyl compounds are acidic, *we mean that they are unusually acidic for hydrogen atoms attached to carbon*.

- The pK_a values for the α hydrogens of most simple aldehydes or ketones are of the order of 19–20.

This means that they are more acidic than hydrogen atoms of ethyne, $pK_a = 25$, and are far more acidic than the hydrogens of ethene ($pK_a = 44$) or of ethane ($pK_a = 50$).

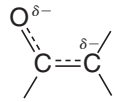
The reasons for the unusual acidity of the α hydrogens of carbonyl compounds are straightforward.

- The carbonyl group is strongly electron withdrawing, and when a carbonyl compound loses an α proton, the anion that is produced, called an **enolate**, is stabilized by delocalization.



Two resonance structures, **A** and **B**, can be written for the enolate. In structure **A** the negative charge is on carbon, and in structure **B** the negative charge is on oxygen. Both

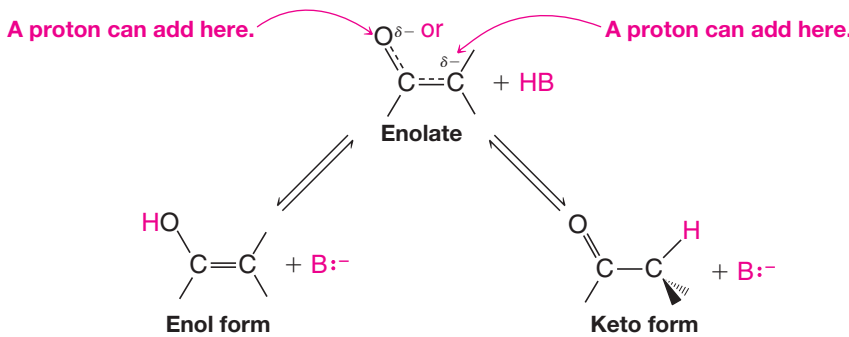
structures contribute to the hybrid. Although structure **A** is favored by the strength of its carbon–oxygen π bond relative to the weaker carbon–carbon π bond of **B**, structure **B** makes a greater contribution to the hybrid because oxygen, being highly electronegative, is better able to accommodate the negative charge. We can depict the enolate hybrid in the following way:



Hybrid resonance structure for an enolate

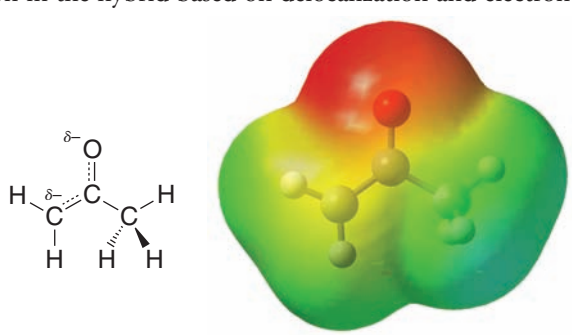
When this resonance-stabilized enolate accepts a proton, it can do so in either of two ways: It can accept the proton at carbon to form the original carbonyl compound in what is called the **keto form** or it may accept the proton at oxygen to form an **enol** (alk**en**e alcoh**ol**).

- The enolate is the conjugate base of both the enol and keto forms.



- Both of these reactions are reversible.

A calculated electrostatic potential map for the enolate of acetone is shown below. The map indicates approximately the outermost extent of electron density (the van der Waals surface) of the acetone enolate. Red color near the oxygen is consistent with oxygen being better able to stabilize the excess negative charge of the anion. Yellow at the carbon where the α hydrogen was removed indicates that some of the excess negative charge is localized there as well. These implications are parallel with the conclusions above about charge distribution in the hybrid based on delocalization and electronegativity effects.



Acetone enolate

18.2 KETO AND ENOL TAUTOMERS

The keto and enol forms of carbonyl compounds are constitutional isomers, but of a special type. Because they are easily interconverted by proton transfers in the presence of an acid or base, chemists use a special term to describe this type of constitutional isomerism.

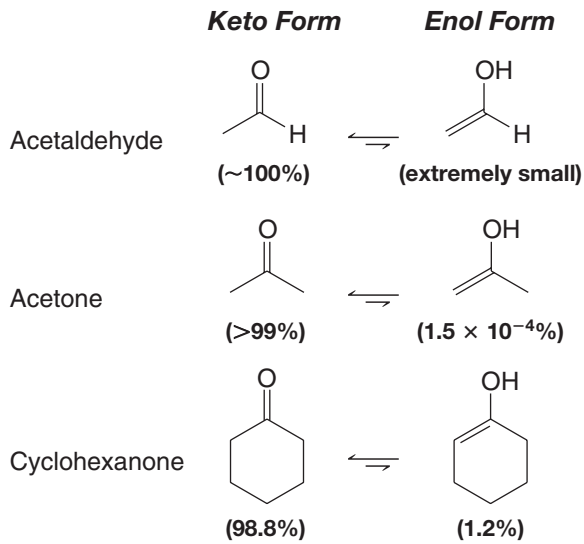
- Interconvertible **keto and enol forms** are called **tautomers**, and their interconversion is called **tautomerization**.

Under most circumstances, we encounter keto–enol tautomers in a state of equilibrium. (The surfaces of ordinary laboratory glassware are able to catalyze the interconversion and establish the equilibrium.) For simple monocarbonyl compounds such as acetone and

acetaldehyde, the amount of the enol form present at equilibrium is *very small*. In acetone it is much less than 1%; in acetaldehyde the enol concentration is too small to be detected. The greater stability of the following keto forms of monocarbonyl compounds can be related to the greater strength of the carbon–oxygen π bond compared to the carbon–carbon π bond (~364 versus ~ 250 kJ mol^{-1}):

Helpful Hint

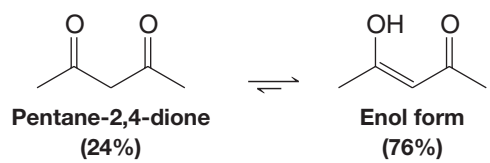
Keto–enol tautomers are not resonance structures. They are constitutional isomers in equilibrium (generally favoring the keto form).



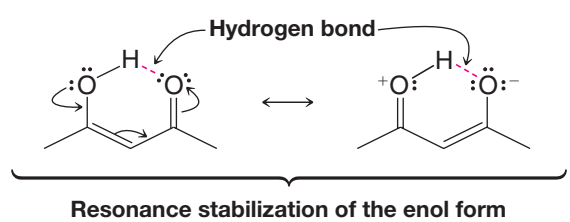
In compounds whose molecules have two carbonyl groups separated by one carbon atom (called β-dicarbonyl compounds), the amount of enol present at equilibrium is far higher. For example, pentane-2,4-dione exists in the enol form to an extent of 76%:

Helpful Hint

See "The Chemistry of... TIM (Triose Phosphate Isomerase) Recycles Carbon via an Enol" in *WileyPLUS* for more information relating to this chapter's opener about an important energy-yielding biochemical process.



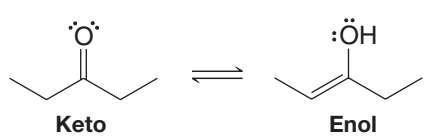
- The greater stability of the enol form of β-dicarbonyl compounds can be attributed to resonance stabilization of the conjugated double bonds and (in a cyclic form) through hydrogen bonding.



SOLVED PROBLEM 18.1

Write bond-line structures for the keto and enol forms of 3-pentanone.

ANSWER:



PRACTICE PROBLEM 18.1

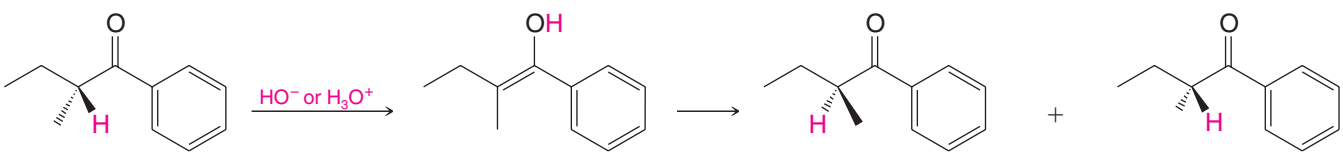
For all practical purposes, the compound cyclohexa-2,4-dien-1-one exists totally in its enol form. Write the structure of cyclohexa-2,4-dien-1-one and of its enol form. What special factor accounts for the stability of the enol form?

18.3 REACTIONS VIA ENOLS AND ENOLATES

18.3A Racemization

When a solution of (*R*)-(+)-2-methyl-1-phenylbutan-1-one (see the following reaction) in aqueous ethanol is treated with either acids or bases, the solution gradually loses its optical activity. After a time, isolation of the ketone shows that it has been completely racemized. The (+) form of the ketone has been converted to an equimolar mixture of its enantiomers through its enol form.

Racemization via an enol

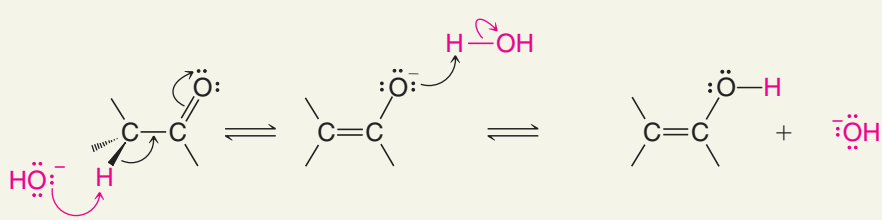


(*R*)-(+)-2-Methyl-1-phenylbutan-1-one | Enol (achiral) | (±)-2-Methyl-1-phenylbutan-1-one (racemic form)

- Racemization at an α carbon takes place in the presence of acids or bases because the keto form slowly but reversibly changes to its enol *and the enol is achiral*. When the **enol** reverts to the **keto form**, it can produce equal amounts of the two enantiomers.

A base catalyzes the formation of an enol through the intermediate formation of an **enolate** anion.

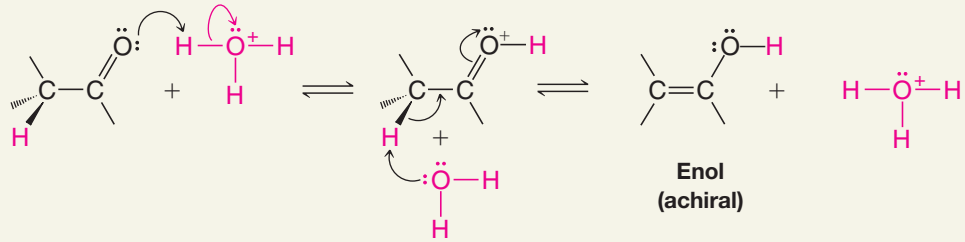
A MECHANISM FOR THE REACTION — Base-Catalyzed Enolization



Enolate (achiral) | Enol (achiral)

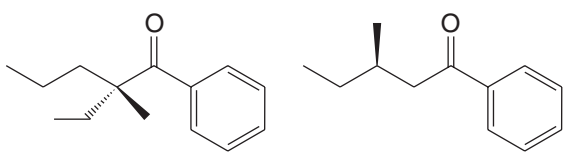
An acid can catalyze enolization in the following way.

A MECHANISM FOR THE REACTION — Acid-Catalyzed Enolization



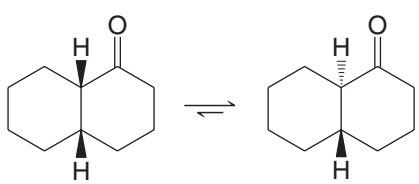
In acyclic ketones, the enol or enolate formed can be (*E*) or (*Z*). Protonation on one face of the (*E*) isomer and protonation on the same face of the (*Z*) isomer produces enantiomers.

PRACTICE PROBLEM 18.2 Would optically active ketones such as the following undergo acid- or base-catalyzed racemization? Explain your answer.



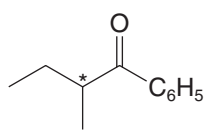
- Diastereomers that differ in configuration at only one of several chirality centers are sometimes called **epimers**.

Keto–enol tautomerization can sometimes be used to convert a less stable epimer to a more stable one. This equilibration process is an example of **epimerization**. An example is the epimerization of *cis*-decalone to *trans*-decalone:

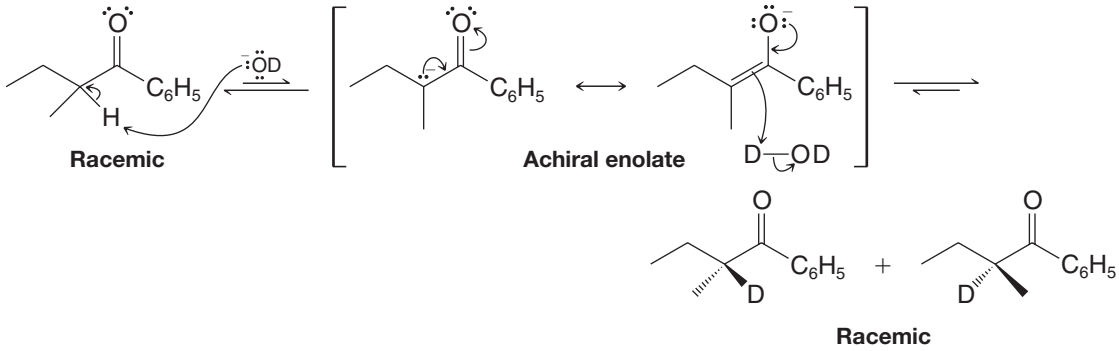


SOLVED PROBLEM 18.2

Treating racemic 2-methyl-1-phenylbutan-1-one with NaOD in the presence of D_2O produces a deuterium-labeled compound as a racemic form. Write a mechanism that explains this result.



STRATEGY AND ANSWER: Either enantiomer of the ketone can transfer an α proton to the ^-OD ion to form an achiral enolate that can accept a deuteron to form a racemic mixture of the deuterium-labeled product.

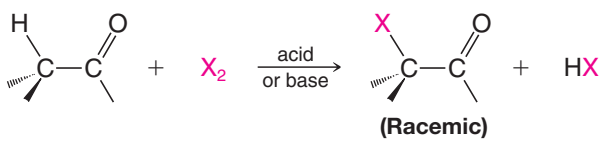


PRACTICE PROBLEM 18.3

Write a mechanism using sodium ethoxide in ethanol for the epimerization of *cis*-decalone to *trans*-decalone. Draw chair conformational structures that show why *trans*-decalone is more stable than *cis*-decalone. You may find it helpful to also examine handheld molecular models of *cis*- and *trans*-decalone.

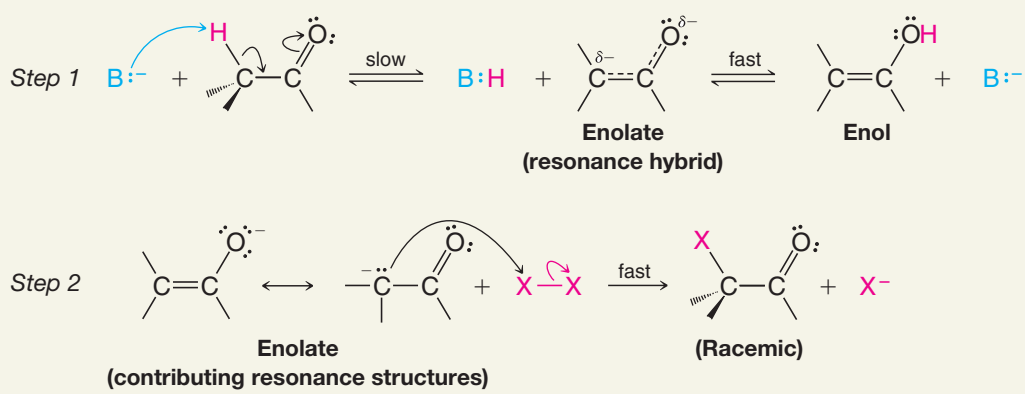
18.3B Halogenation at the α Carbon

- Carbonyl compounds bearing an α hydrogen can undergo halogen substitution at the α carbon in the presence of acid or base.



Base-Promoted Halogenation In the presence of bases, halogenation takes place through the slow formation of an enolate anion or an enol followed by a rapid reaction of the enolate or enol with halogen.

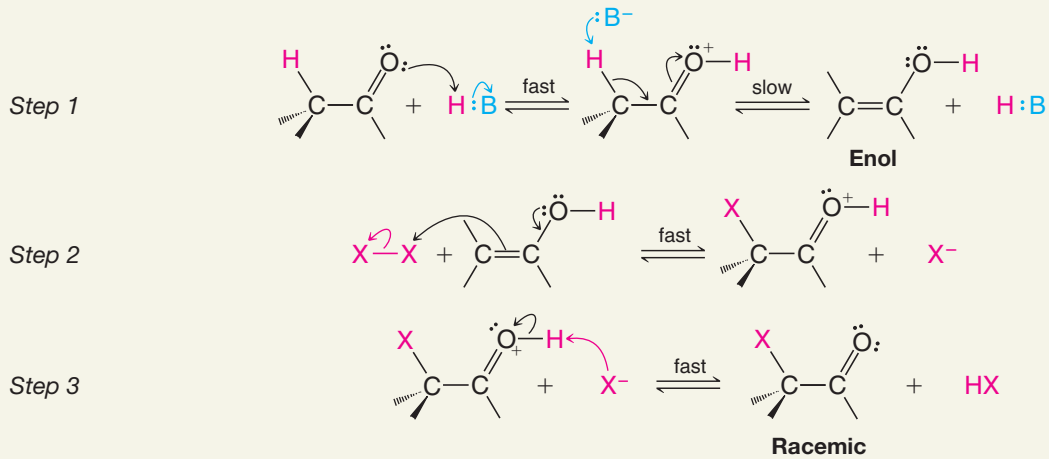
A MECHANISM FOR THE REACTION — Base-Promoted Halogenation of Aldehydes and Ketones



As we shall see in Section 18.3C, multiple halogenations can occur.

Acid-Catalyzed Halogenation In the presence of acids, halogenation takes place through the slow formation of an enol followed by rapid reaction of the enol with the halogen.

A MECHANISM FOR THE REACTION — Acid-Catalyzed Halogenation of Aldehydes and Ketones



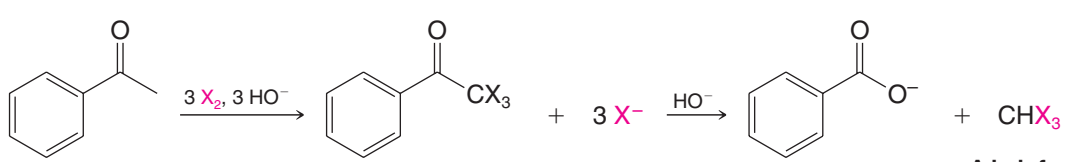
Part of the evidence that supports these mechanisms comes from studies of reaction kinetics. Both base-promoted and acid-catalyzed halogenations of ketones *show initial rates that are independent of the halogen concentration*. The mechanisms that we have written are in accord with this observation: in both instances the slow step of the mechanism occurs before the intervention of the halogen. (The initial rates are also independent of the nature of the halogen; see Practice Problem 18.5.)

PRACTICE PROBLEM 18.4 Why do we say that the halogenation of ketones in a base is "base promoted" rather than "base catalyzed"?

PRACTICE PROBLEM 18.5 Additional evidence for the halogenation mechanisms that we just presented comes from the following facts: **(a)** Optically active 2-methyl-1-phenylbutan-1-one undergoes acid-catalyzed racemization at a rate exactly equivalent to the rate at which it undergoes acid-catalyzed halogenation. **(b)** 2-Methyl-1-phenylbutan-1-one undergoes acid-catalyzed iodination at the same rate that it undergoes acid-catalyzed bromination. **(c)** 2-Methyl-1-phenylbutan-1-one undergoes base-catalyzed hydrogen–deuterium exchange at the same rate that it undergoes base-promoted halogenation. Explain how each of these observations supports the mechanisms that we have presented.

18.3C The Haloform Reaction

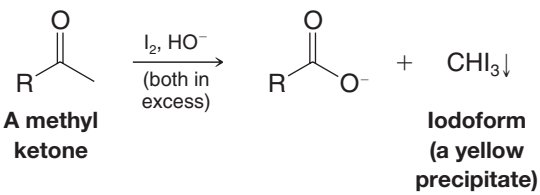
When methyl ketones react with halogens in the presence of excess base, multiple halogenations always occur at the carbon of the methyl group. Multiple halogenations occur because introduction of the first halogen (owing to its electronegativity) makes the remaining α hydrogens on the methyl carbon more acidic. The resulting CX_3 group bonded to the carbonyl can be a leaving group, however. Thus, when hydroxide is the base, an acyl substitution reaction follows, leading to a carboxylate salt and a haloform (CHX_3, e.g., chloroform, bromoform, or iodoform). The following is an example.



A haloform (X = Cl, Br, I)

The haloform reaction is one of the rare instances in which a carbanion acts as a leaving group. This occurs because the trihalomethyl anion is unusually stable; its negative charge is dispersed by the three electronegative halogen atoms (when X = Cl, the conjugate acid, $CHCl_3$, has $pK_a = 13.6$). In the last step, a proton transfer takes place between the carboxylic acid and the trihalomethyl anion.

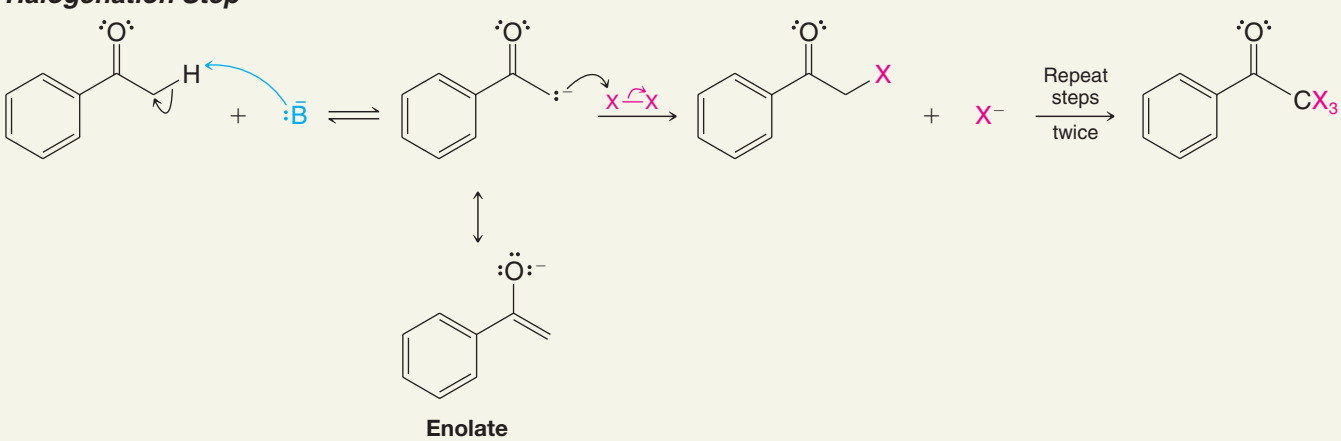
The **haloform reaction** is synthetically useful as a means of converting methyl ketones to carboxylic acids. When the haloform reaction is used in synthesis, chlorine and bromine are most commonly used as the halogen component. Chloroform ($CHCl_3$) and bromoform ($CHBr_3$) are both liquids that are immiscible with water and are easily separated from the aqueous solution containing the carboxylate anion. When iodine is the halogen component, the bright yellow solid iodoform (CHI_3) results. This version is the basis of the iodoform classification test for methyl ketones and methyl secondary alcohols (which are oxidized to methyl ketones first under the reaction conditions):



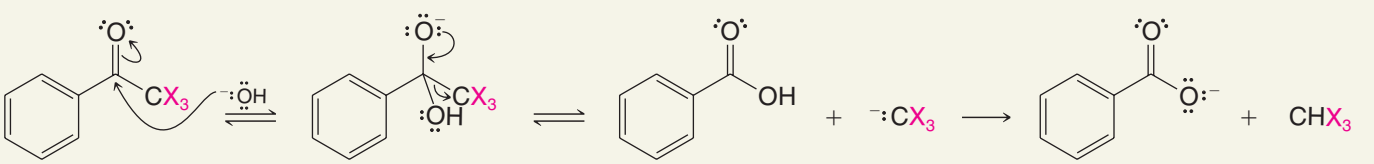
A methyl ketone — **Iodoform (a yellow precipitate)**

A MECHANISM FOR THE REACTION — The Haloform Reaction

Halogenation Step



Acyl Substitution Step



Carboxylate anion — **A haloform**

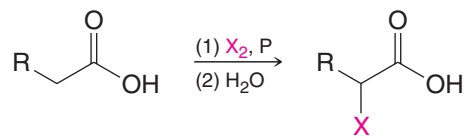
THE CHEMISTRY OF... Chloroform in Drinking Water

When water is chlorinated to purify it for public consumption, chloroform is produced from organic impurities in the water via the haloform reaction. (Many of these organic impurities are naturally occurring, such as humic substances.) The presence of chloroform in public water is of concern for water treatment plants and environmental officers, because chloroform is carcinogenic. Thus, the technology that solves one problem creates another. It is worth recalling, however, that before chlorination of water was introduced, thousands of people died in epidemics of diseases such as cholera and dysentery.

18.3D α-Halo Carboxylic Acids: The Hell–Volhard–Zelinski Reaction

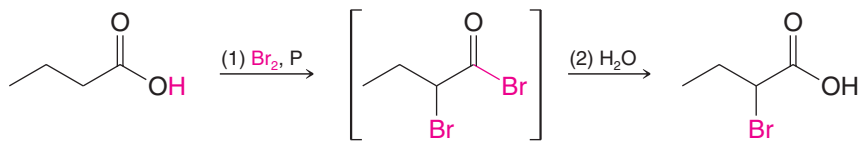
Carboxylic acids bearing **α hydrogen** atoms react with bromine or chlorine in the presence of phosphorus (or a phosphorus halide) to give α-halo carboxylic acids through a reaction known as the Hell–Volhard–Zelinski (or HVZ) reaction.

General Reaction



α-Halo acid

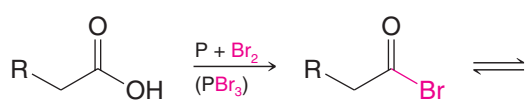
Specific Example



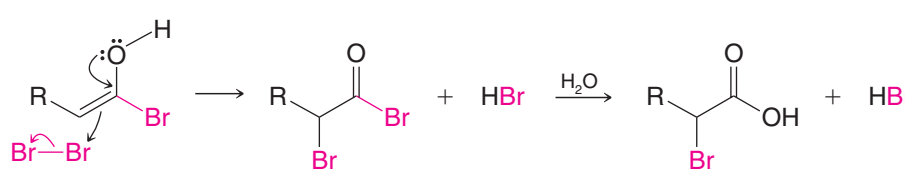
Butanoic acid **2-Bromobutanoic acid (77%)**

If more than one molar equivalent of bromine or chlorine is used in the reaction, the products obtained are α,α-dihalo acids or α,α,α-trihalo acids.

Important steps in the reaction are formation of an acyl halide and the enol derived from the acyl halide. The acyl halide is key because carboxylic acids do not form enols readily since the carboxylic acid proton is removed before the α hydrogen. Acyl halides lack the carboxylic acid hydrogen.

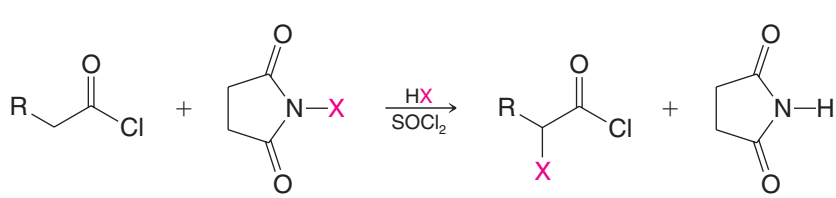


Acyl bromide



Enol form

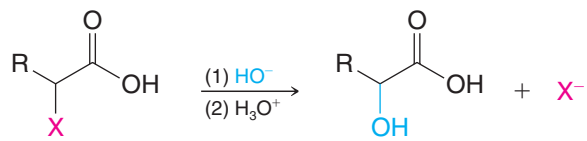
An alternative method for α-halogenation has been developed by D. N. Harpp (McGill University). Acyl chlorides, formed *in situ* by the reaction of the carboxylic acid with $SOCl_2$, are treated with the appropriate *N*-halosuccinimide and a trace of HX to produce α-chloro and α-bromo acyl chlorides.



α-Iodo acyl chlorides can be obtained by using molecular iodine in a similar reaction.

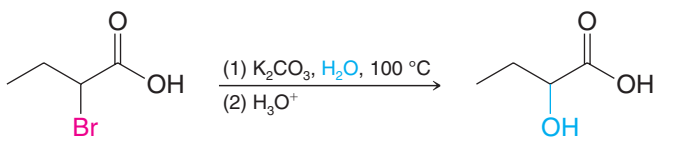
α-Halo acids are important synthetic intermediates because they are capable of reacting with a variety of nucleophiles:

Conversion to α-Hydroxy Acids



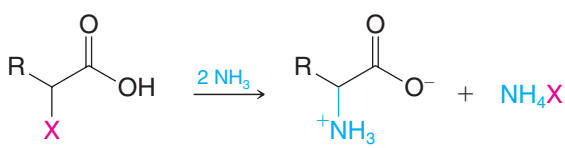
α-Halo acid **α-Hydroxy acid**

Specific Example



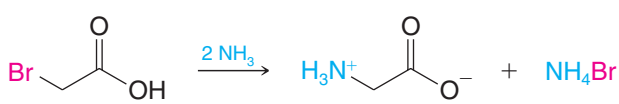
2-Hydroxybutanoic acid
(69%)

Conversion to α-Amino Acids



α-Halo acid **α-Amino acid**

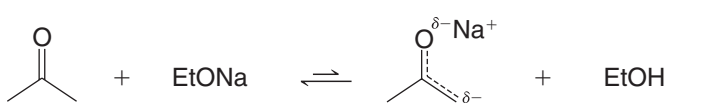
Specific Example



Aminoacetic acid
(glycine)
(60–64%)

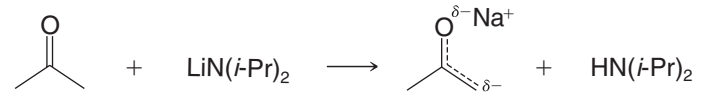
18.4 LITHIUM ENOLATES

The position of the equilibrium by which an **enolate** forms depends on the strength of the base used. If the base employed is a weaker base than the enolate, then the equilibrium lies to the left. This is the case, for example, when a ketone is treated with sodium ethoxide in ethanol.



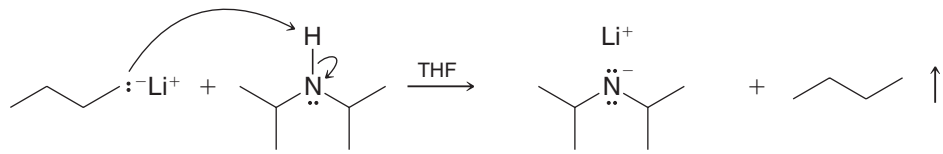
Weaker acid (pK_a = 19) **Weaker base** **Stronger base** **Stronger acid** (pK_a = 16)

On the other hand, if a very strong base is employed, the equilibrium lies far to the right. One very useful strong base for converting carbonyl compounds to enolates is **lithium diisopropylamide (LDA)** or $LiN(i\text{-}Pr)_2$:



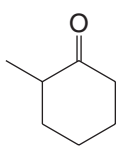
Ketone (stronger acid) (pK_a = 19) | **LDA (stronger base)** | **Enolate (weaker base)** | **Diisopropylamine (weaker acid) (pK_a = 38)**

- Lithium diisopropylamide (LDA) can be prepared by dissolving diisopropylamine in a solvent such as diethyl ether or THF and treating it with an alkyllithium:



Butyllithium (BuLi) | **Diisopropylamine (pK_a = 38)** | **Lithium diisopropylamide [LDA or LiN(*i*-Pr)$_2$]** | **Butane (pK_a = 50)**

18.4A Regioselective Formation of Enolates



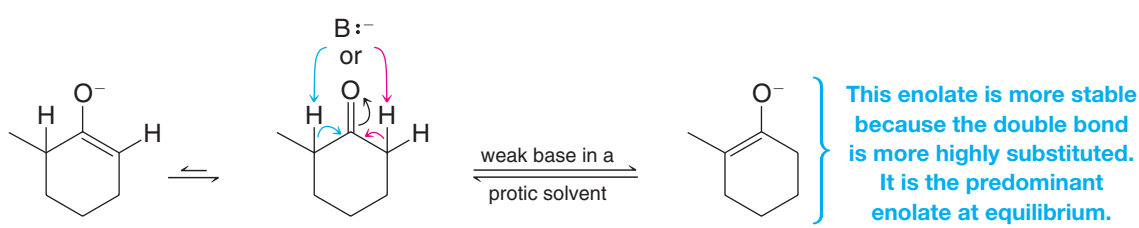
2-Methylcyclohexanone

An unsymmetrical ketone such as 2-methylcyclohexanone can form two possible enolates, arising by removal of an α hydrogen from one side or the other of the carbonyl group. Which enolate predominates in the reaction depends on whether the enolate is formed under conditions that favor an acid–base equilibrium.

- The **thermodynamic enolate** is that which is most stable among the possible enolates. Enolate stability is evaluated in the same way as for alkenes, meaning that the more highly substituted enolate is the more stable one.
- The **thermodynamic enolate** predominates under conditions of **thermodynamic control** where a deprotonation–protonation equilibrium allows interconversion among the possible enolates, such that eventually the more stable enolate exists in higher concentration. This is the case when the pK_a of the conjugate acid of the base is similar to the pK_a of the α hydrogen of the carbonyl compound. Use of hydroxide or an alkoxide in a protic solvent favors formation of the thermodynamic enolate.
- The **kinetic enolate** is that which is formed fastest. It is usually formed by removal of the least sterically hindered α hydrogen.
- The **kinetic enolate** predominates under conditions of **kinetic control** that do not favor equilibrium among the possible enolates. Use of a very strong and sterically hindered base in an aprotic solvent, such as LDA in tetrahydrofuran (THF) or dimethoxyethane (DME) favors formation of the kinetic enolate.

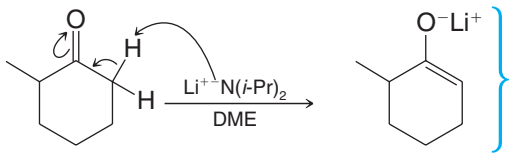
Conditions favoring formation of the thermodynamic and kinetic enolates from 2-methylcyclohexanone are illustrated below.

Formation of a Thermodynamic Enolate



Kinetic (less stable) enolate | **2-Methylcyclohexanone** | **Thermodynamic (more stable) enolate**

Formation of a Kinetic Enolate

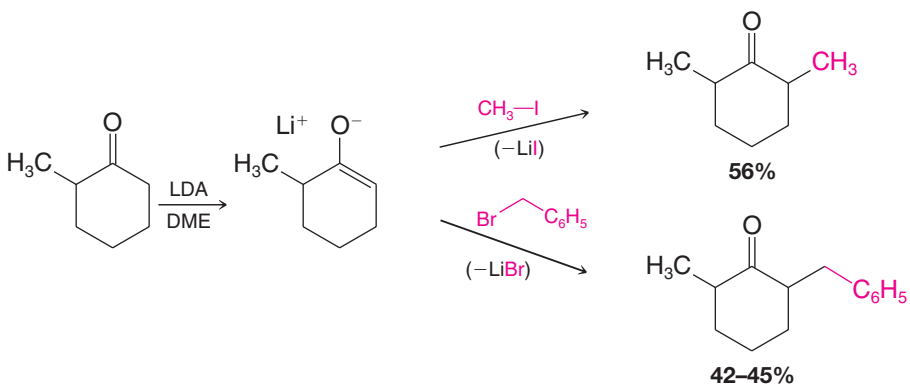


Kinetic enolate

This enolate is formed faster because the hindered strong base removes the less hindered proton faster.

18.4B Direct Alkylation of Ketones via Lithium Enolates

The formation of lithium enolates using lithium diisopropylamide furnishes a useful way of alkylating ketones in a regioselective way. For example, the lithium enolate formed from 2-methylcyclohexanone can be methylated or benzylated at the less hindered α carbon by allowing it to react with LDA followed by methyl iodide or benzyl bromide, respectively:



Helpful Hint

Alkylation of lithium enolates is a useful method for synthesis.

Alkylation reactions like these have an important limitation, however, because the reactions are S_N2 reactions, and also because enolates are strong bases.

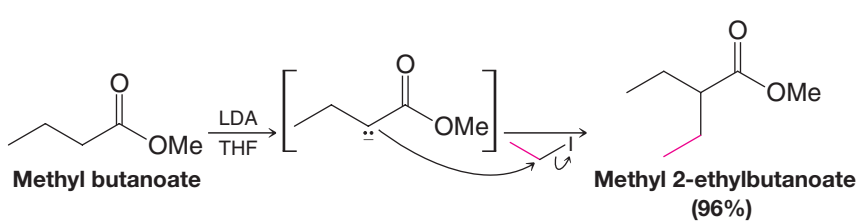
- Successful alkylations occur only when primary alkyl, primary benzylic, and primary allylic halides are used. With secondary and tertiary halides, elimination becomes the main course of the reaction.

Helpful Hint

Proper choice of the alkylating agent is key to successful lithium enolate alkylation.

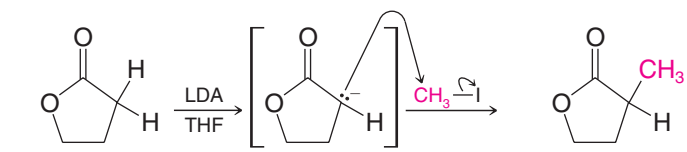
18.4C Direct Alkylation of Esters

Examples of the **direct alkylation** of esters are shown below. In the second example the ester is a lactone (Section 17.7C):



Methyl butanoate

Methyl 2-ethylbutanoate (96%)

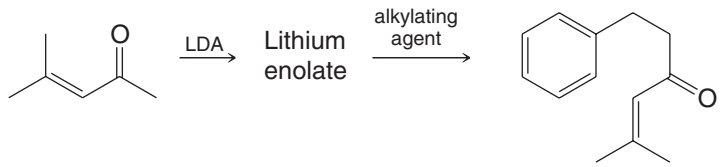


Butyrolactone

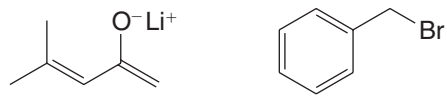
2-Methylbutyrolactone (88%)

SOLVED PROBLEM 18.3

The following synthesis illustrates the **alkylation** of a ketone via a lithium enolate. Give the structures of the enolate and the alkylating agent.

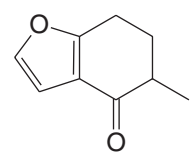


ANSWER:

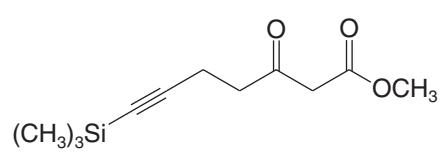


Lithium enolate **Alkylating agent**

PRACTICE PROBLEM 18.6 **(a)** Write a reaction involving a lithium enolate for introduction of the methyl group in the following compound (an intermediate in a synthesis by E. J. Corey of cafestol, an anti-inflammatory agent found in coffee beans):

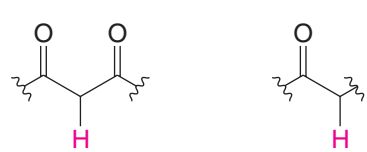


(b) Dienolates can be formed from β-keto esters using two equivalents of LDA. The dienolate can then be alkylated selectively at the more basic of the two enolate carbons. Write a reaction for synthesis of the following compound using a dienolate and the appropriate alkyl halide:



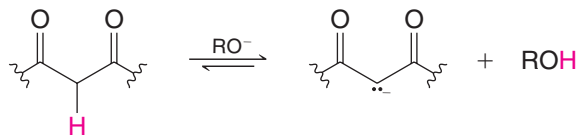
18.5 ENOLATES OF β-DICARBONYL COMPOUNDS

- Hydrogen atoms that are between two carbonyl groups, as in a **β-dicarbonyl compound**, have pK_a values in the range of 9–11. Such α-hydrogen atoms are much more acidic than α hydrogens adjacent to only one carbonyl group, which have pK_a values of 18–20.

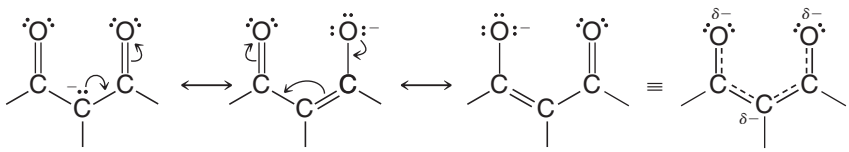


pK_a 9–11 **pK_a 18–20**

- A much weaker base than LDA, such as an alkoxide, can be used to form an enolate from a β-dicarbonyl compound.

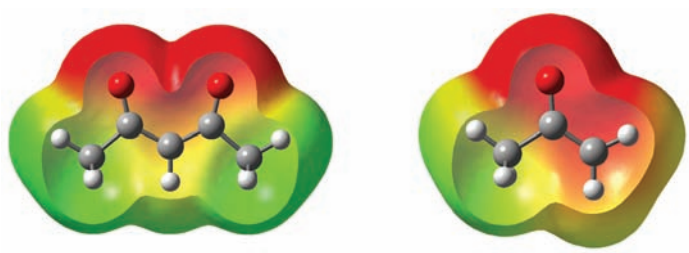


We can account for the greater acidity of β-dicarbonyl systems, as compared to single carbonyl systems, by delocalization of the negative charge to two oxygen atoms instead of one. We can represent this delocalization by drawing contributing resonance structures for a β-dicarbonyl enolate and its resonance hybrid:



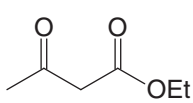
Contributing resonance structures **Resonance hybrid**

We can visualize the enhanced charge delocalization of a β-dicarbonyl enolate by examining maps of electrostatic potential for enolates derived from pentane-2,4-dione and acetone. Here we see that the negative charge of the enolate from pentane-2,4-dione is associated substantially with the two oxygen atoms, as compared with the enolate from acetone, where significant negative charge in the enolate remains at the α-carbon atom:

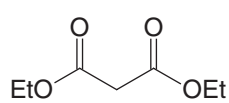


Pentane-2,4-dione enolate **Acetone enolate**

Two specific β-dicarbonyl compounds have had broad use in organic synthesis. These are acetoacetic ester (ethyl acetoacetate, ethyl 3-oxobutanoate), which can be used to make substituted acetone derivatives, and diethyl malonate (diethyl 1,3-propanedicarboxylic acid), which can be used to make substituted acetic acid derivatives. We shall consider syntheses involving ethyl acetoacetate and diethyl malonate in the upcoming sections of this chapter.



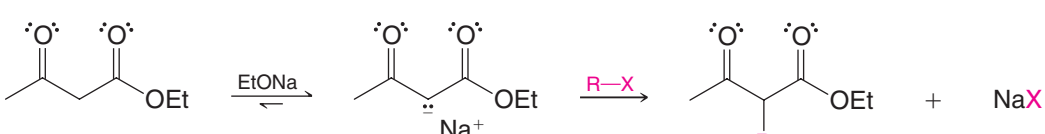
Acetoacetic ester (ethyl acetoacetate; ethyl 3-oxobutanoate)



Diethyl malonate (diethyl 1,3-propanedicarboxylic acid)

18.6 SYNTHESIS OF METHYL KETONES: THE ACETOACETIC ESTER SYNTHESIS

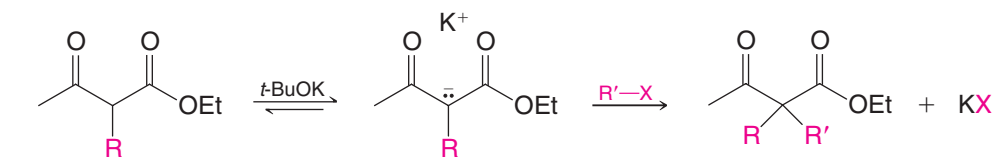
Acetoacetic ester, because it is a β-dicarbonyl compound, can easily be converted to an enolate using sodium ethoxide. We can then alkylate the resulting enolate (called sodioacetoacetic ester) with an alkyl halide. This process is called an **acetoacetic ester synthesis**.



Acetoacetic ester **Sodioacetoacetic ester** **Monoalkylacetoacetic ester**

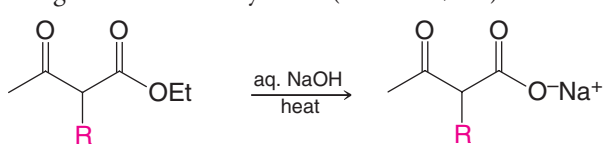
- Since the alkylation in the reaction above is an S_N2 reaction, the best yields are obtained from the use of primary alkyl halides (including primary allylic and benzylic halides) or methyl halides. Secondary halides give lower yields, and tertiary halides give only elimination.

Dialkylation The monoalkylacetoacetic ester shown above still has one appreciably acidic hydrogen, and, if we desire, we can carry out a second alkylation. Because a monoalkylacetoacetic ester is somewhat less acidic than acetoacetic ester itself due to the electron-donating effect of the added alkyl group, it is usually helpful to use a stronger base than ethoxide ion for the second alkylation. Use of potassium *tert*-butoxide is common because it is a stronger base than sodium ethoxide. Potassium *tert*-butoxide, because of its steric bulk, is also not likely to cause transesterification.

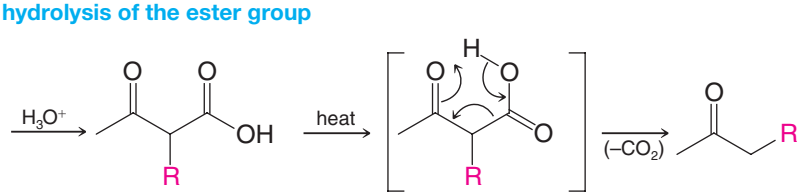


Monoalkylacetoacetic ester **Dialkylacetoacetic ester**

Substituted Methyl Ketones To synthesize a monosubstituted methyl ketone (monosubstituted acetone), we carry out only one alkylation. Then we hydrolyze the monoalkylacetoacetic ester using aqueous sodium or potassium hydroxide. Subsequent acidification of the mixture gives an alkyl-acetoacetic acid, and heating this β-keto acid to 100 °C brings about decarboxylation (Section 17.10):

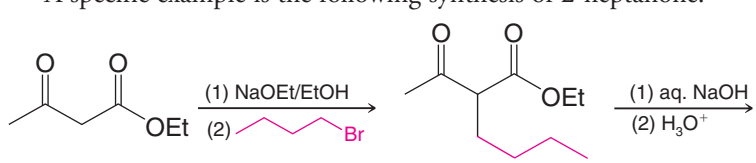


Basic hydrolysis of the ester group

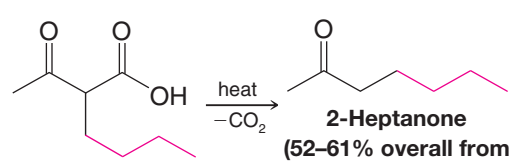


Acidification **Decarboxylation of the β-keto acid**

A specific example is the following synthesis of 2-heptanone:

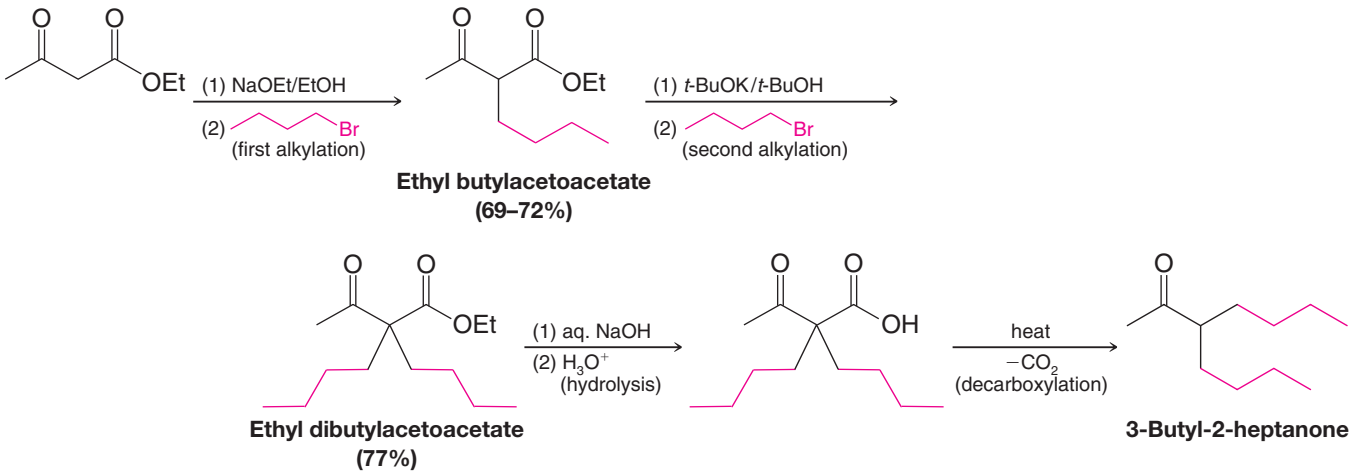


Ethyl acetoacetate (acetoacetic ester) **Ethyl butylacetoacetate (69–72%)**



2-Heptanone (52–61% overall from ethyl acetoacetate)

If our goal is the preparation of a disubstituted acetone, we carry out two successive alkylations, we hydrolyze the dialkylacetoacetic ester that is produced, and then we decarboxylate the dialkylacetoacetic acid. An example of this procedure is the synthesis of 3-butyl-2-heptanone.



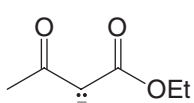
Although both alkylations in the example just given were carried out with the same alkyl halide, we could have used different alkyl halides if our synthesis had required it.

- As we have seen, ethyl acetoacetate is a useful reagent for the preparation of substituted acetones (methyl ketones) of the types shown below.

A monosubstituted acetone **A disubstituted acetone**

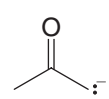
- Ethyl acetoacetate therefore serves as the synthetic equivalent of the enolate from acetone shown below.

A **synthetic equivalent** is a reagent whose structure, when incorporated into a product, gives the appearance of having come from one type of precursor when as a reactant it actually had a different structural origin. Although it is possible to form the enolate of acetone, use of ethyl acetoacetate as a synthetic equivalent is often more convenient because its α hydrogens are so much more acidic ($pK_a = 9–11$) than those of acetone itself ($pK_a = 19–20$). If we had wanted to use the acetone enolate directly, we would have had to use a much stronger base and other special conditions (e.g., a lithium enolate, Section 18.4).



Ethyl acetoacetate ion

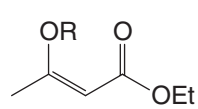
is the synthetic equivalent of



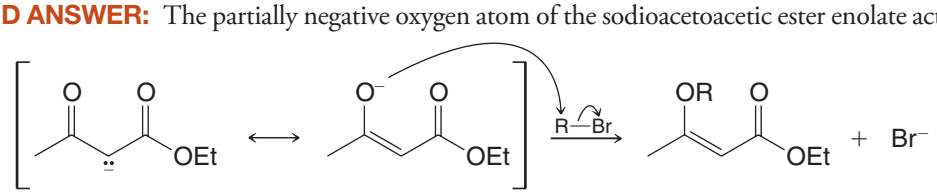
Acetone enolate

SOLVED PROBLEM 18.4

Explain how compounds with the following general structure are formed as occasional side products of sodioacetoacetic ester alkylations.



STRATEGY AND ANSWER: The partially negative oxygen atom of the sodioacetoacetic ester enolate acts as a nucleophile.

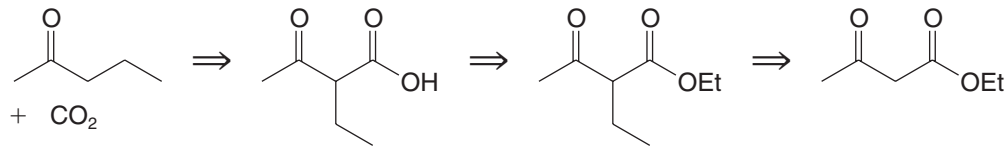


SOLVED PROBLEM 18.5

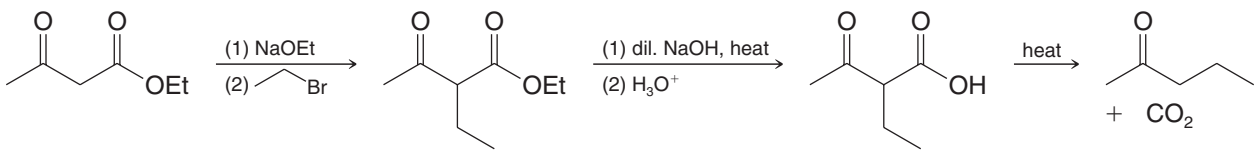
Show a retrosynthetic analysis and a synthetic pathway for the preparation of 2-pentanone from ethyl acetoacetate (acetoacetic ester).

STRATEGY AND ANSWER:

Retrosynthetic Analysis



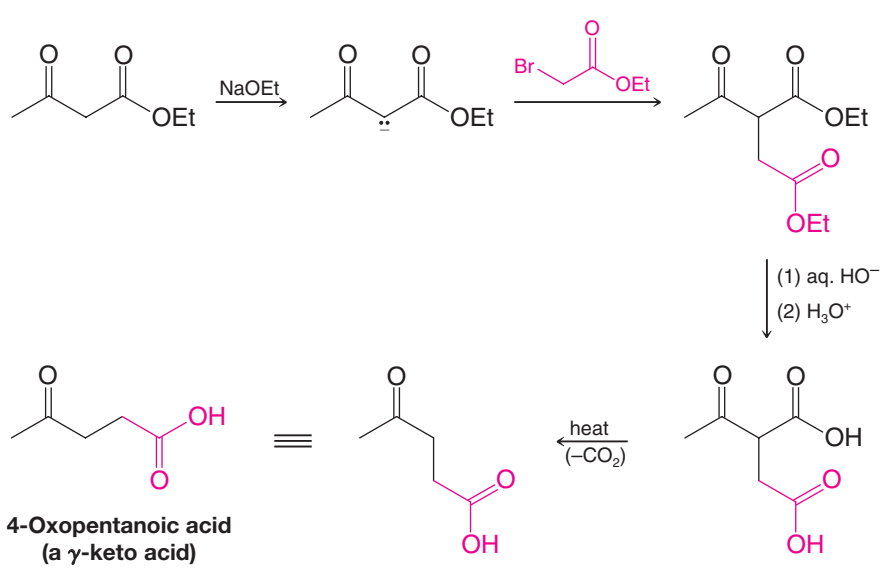
Synthesis



PRACTICE PROBLEM 18.7 Show how you would use the acetoacetic ester synthesis to prepare **(a)** 3-propyl-2-hexanone and **(b)** 4-phenyl-2-butanone.

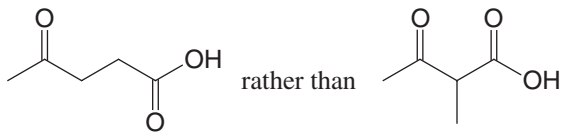
PRACTICE PROBLEM 18.8 The acetoacetic ester synthesis generally gives best yields when primary halides are used in the alkylation step. Secondary halides give low yields, and tertiary halides give practically no alkylation product at all. **(a)** Explain. **(b)** What products would you expect from the reaction of sodioacetoacetic ester and *tert*-butyl bromide? **(c)** Bromobenzene cannot be used as an arylating agent in an acetoacetic ester synthesis in the manner we have just described. Why not?

The acetoacetic ester synthesis can also be carried out using halo esters and halo ketones. The use of an α-halo ester provides a convenient synthesis of γ-keto acids:



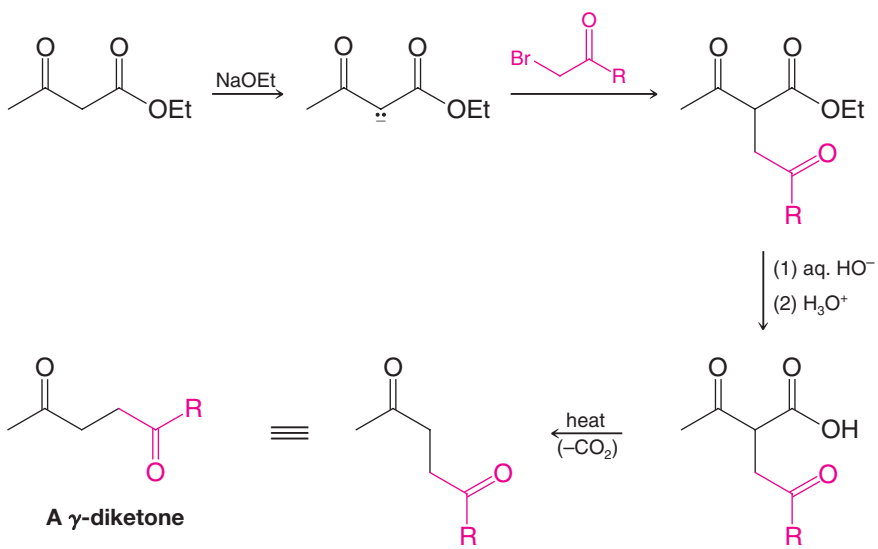
PRACTICE PROBLEM 18.9

In the synthesis of the keto acid just given, the dicarboxylic acid decarboxylates in a specific way; it gives



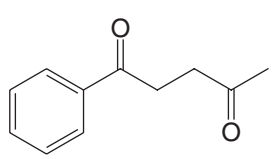
Explain.

The use of an α-halo ketone in an acetoacetic ester synthesis provides a general method for preparing γ-diketones:



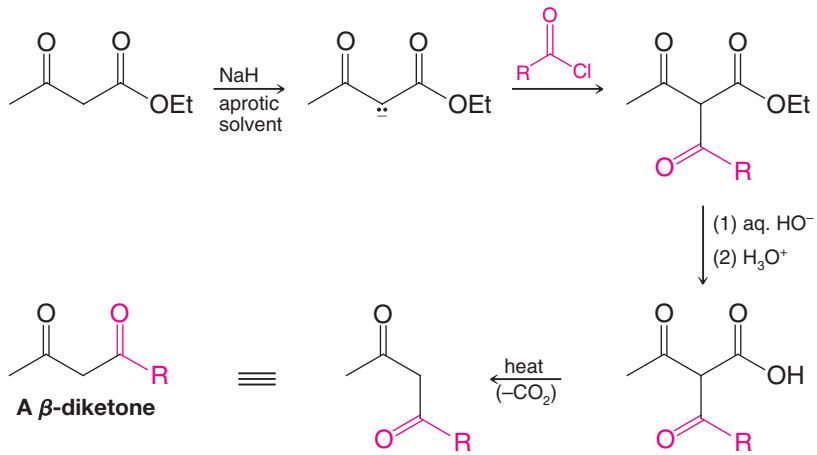
PRACTICE PROBLEM 18.10

How would you use the acetoacetic ester synthesis to prepare the following?

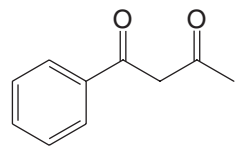


18.6A Acylation

Anions obtained from acetoacetic esters undergo acylation when they are treated with acyl chlorides or acid anhydrides. Because both of these acylating agents react with alcohols, acylation reactions cannot be carried out in ethanol and must be carried out in aprotic solvents such as DMF or DMSO (Section 6.13C). (If the reaction were to be carried out in ethanol, using sodium ethoxide, for example, then the acyl chloride would be rapidly converted to an ethyl ester and the ethoxide ion would be neutralized.) Sodium hydride can be used to generate the enolate ion in an aprotic solvent:

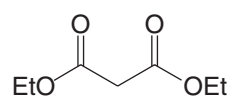


PRACTICE PROBLEM 18.11 How would you use the acetoacetic ester synthesis to prepare the following?



18.7 SYNTHESIS OF SUBSTITUTED ACETIC ACIDS: THE MALONIC ESTER SYNTHESIS

A useful counterpart of the acetoacetic ester synthesis—one that allows the synthesis of *mono-* and *disubstituted acetic acids*—is called the **malonic ester synthesis**. The starting compound is the diester of a β-dicarboxylic acid, called a malonic ester. The most commonly used malonic ester is diethyl malonate.

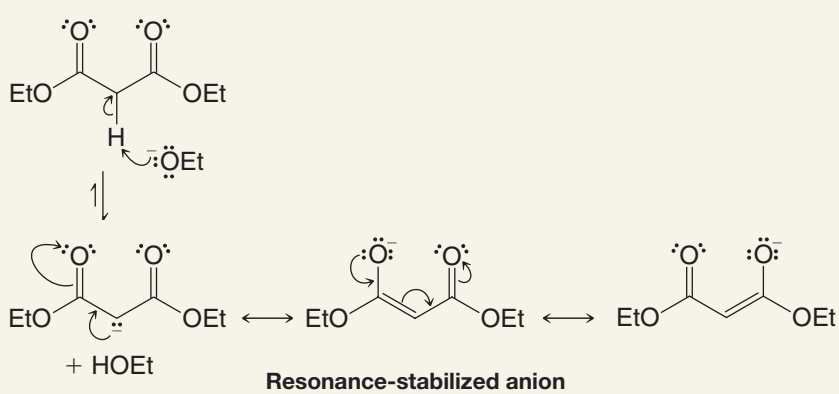


Diethyl malonate (a β-dicarboxylic acid ester)

We shall see by examining the following mechanism that the malonic ester synthesis resembles the acetoacetic ester synthesis in several respects.

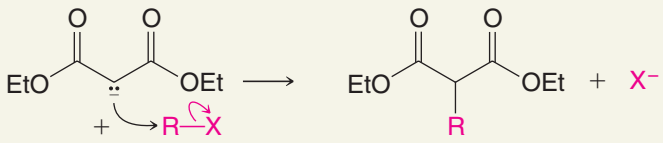
A MECHANISM FOR THE REACTION — The Malonic Ester Synthesis of Substituted Acetic Acids

Step 1 Diethyl malonate, the starting compound, forms a relatively stable enolate:



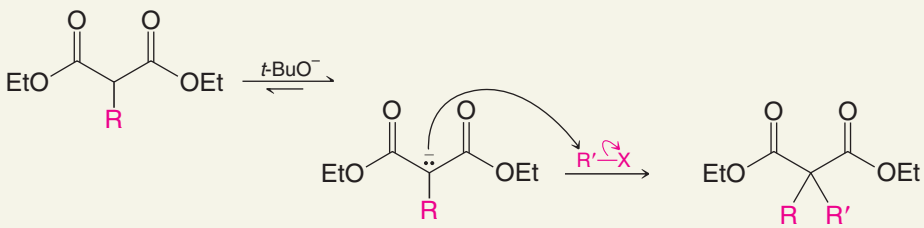
Resonance-stabilized anion

Step 2 *This enolate can be alkylated in an S_N2 reaction,*



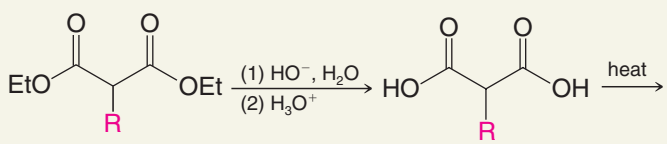
Enolate **Monoalkylmalonic ester**

and the product can be alkylated again if our synthesis requires it:

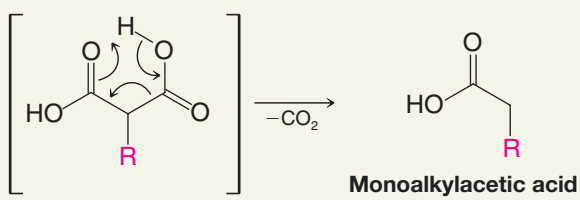


Dialkylmalonic ester

Step 3 *The mono- or dialkylmalonic ester can then be hydrolyzed to a mono- or dialkylmalonic acid, and substituted malonic acids decarboxylate readily. Decarboxylation gives a mono- or disubstituted acetic acid:*

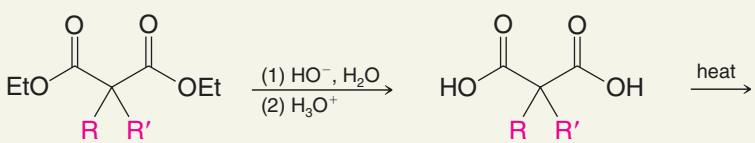


Monoalkylmalonic ester

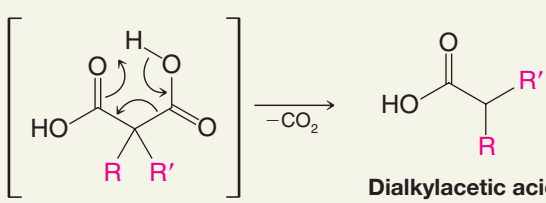


Monoalkylacetic acid

or after dialkylation,



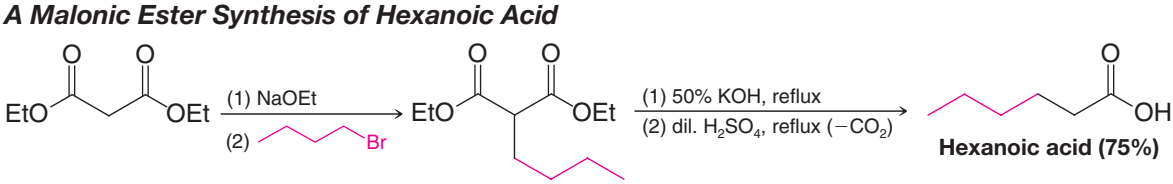
Dialkylmalonic ester



Dialkylacetic acid

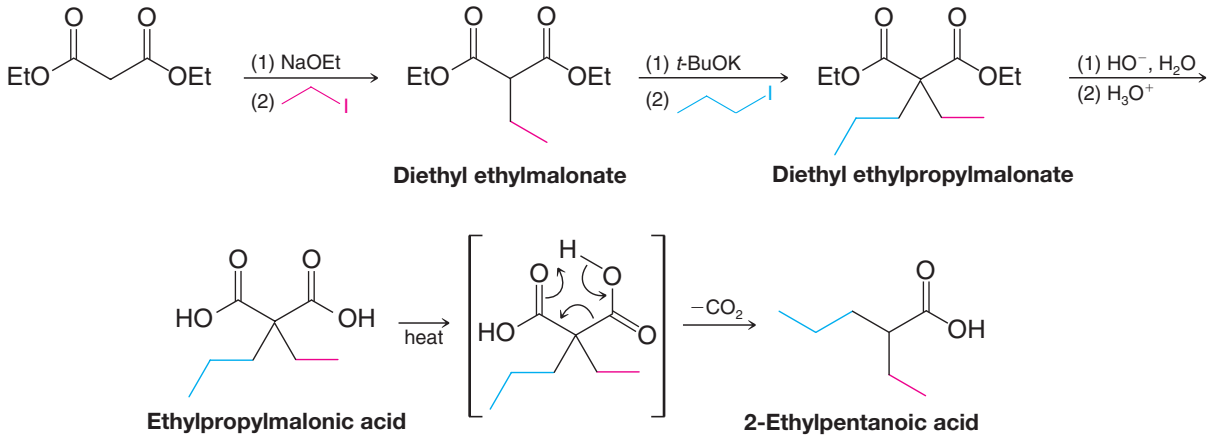
Two specific examples of the malonic ester synthesis are the syntheses of hexanoic acid and 2-ethylpentanoic acid that follow.

A Malonic Ester Synthesis of Hexanoic Acid



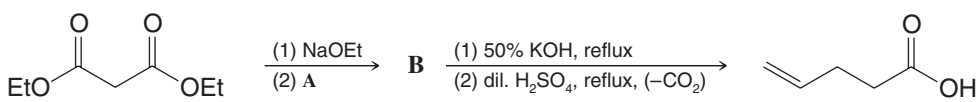
Diethyl butylmalonate (80–90%) **Hexanoic acid (75%)**

A Malonic Ester Synthesis of 2-Ethylpentanoic Acid

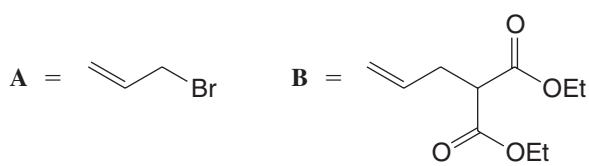


SOLVED PROBLEM 18.6

Provide structures for compounds **A** and **B** in the following synthesis.

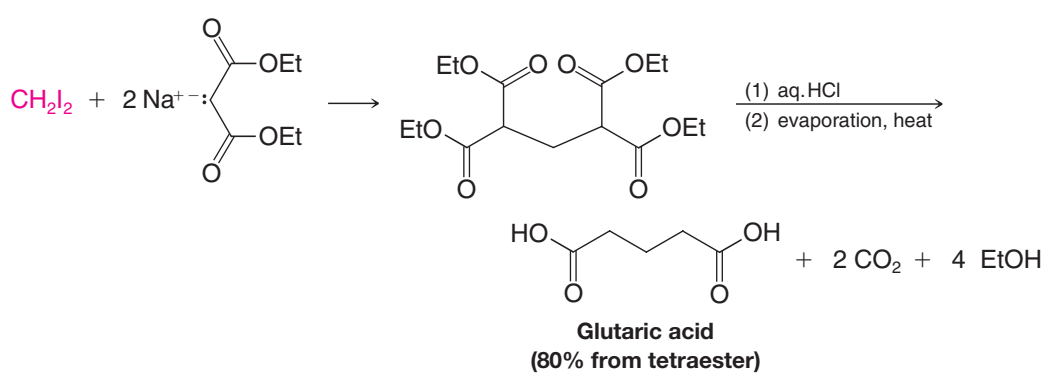


ANSWER:

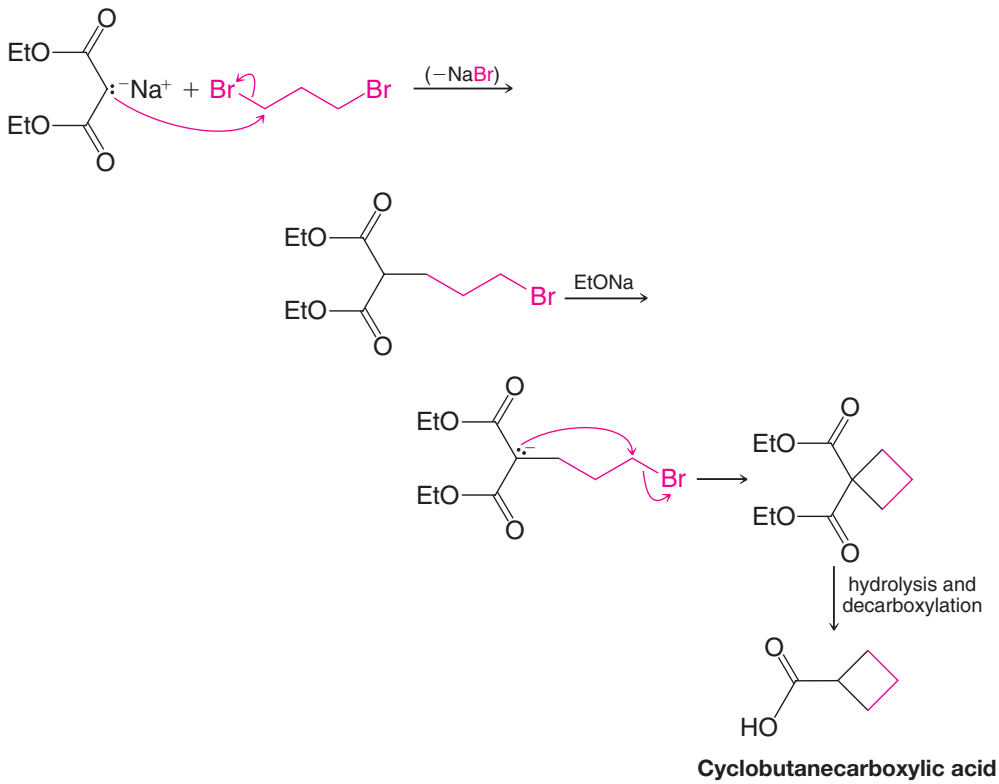


PRACTICE PROBLEM 18.12 Outline all steps in a malonic ester synthesis of each of the following: **(a)** pentanoic acid, **(b)** 2-methylpentanoic acid, and **(c)** 4-methylpentanoic acid.

Two variations of the malonic ester synthesis make use of dihaloalkanes. In the first of these, two molar equivalents of sodiomalonic ester are allowed to react with a dihaloalkane. Two consecutive alkylations occur, giving a tetraester; hydrolysis and decarboxylation of the tetraester yield a dicarboxylic acid. An example is the synthesis of glutaric acid:

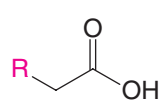


In a second variation, one molar equivalent of sodiomalonic ester is allowed to react with one molar equivalent of a dihaloalkane. This reaction gives a haloalkylmalonic ester, which, when treated with sodium ethoxide, undergoes an internal alkylation reaction. This method has been used to prepare three-, four-, five-, and six-membered rings. An example is the synthesis of cyclobutanecarboxylic acid:

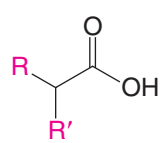


Cyclobutanecarboxylic acid

- As we have seen, the malonic ester synthesis is a useful method for preparing mono- and dialkylacetic acids:



A monoalkylacetic acid

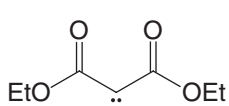


A dialkylacetic acid

Helpful Hint

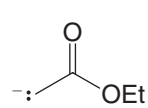
The malonic ester synthesis is a tool for synthesizing substituted acetic acids.

- Thus, the malonic ester synthesis provides us with a synthetic equivalent of an ester enolate of acetic acid or acetic acid dianion.

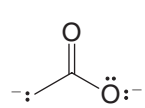


Diethyl malonate anion

is the synthetic equivalent of



and

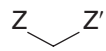


Direct formation of such anions is possible (Section 18.4), but it is often more convenient to use diethyl malonate as a synthetic equivalent because its α hydrogens are more easily removed.

In Special Topic E (in *WileyPLUS*) we shall see biosynthetic equivalents of these anions.

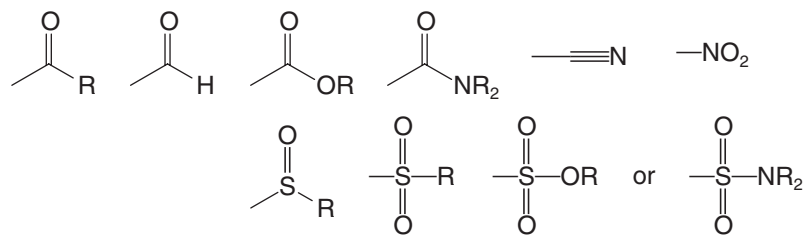
18.8 FURTHER REACTIONS OF ACTIVE HYDROGEN COMPOUNDS

Because of the acidity of their methylene hydrogens malonic esters, acetoacetic esters, and similar compounds are often called **active hydrogen compounds** or active methylene compounds. Generally speaking, active hydrogen compounds have two electron-withdrawing groups attached to the same carbon atom:



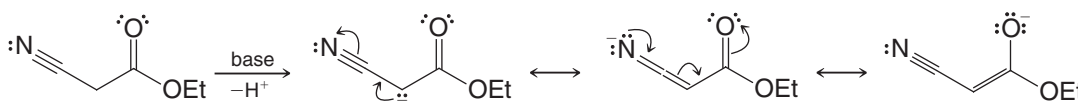
Active hydrogen compound
(Z and Z′ are electron-withdrawing groups.)

The electron-withdrawing groups can be a variety of substituents, including



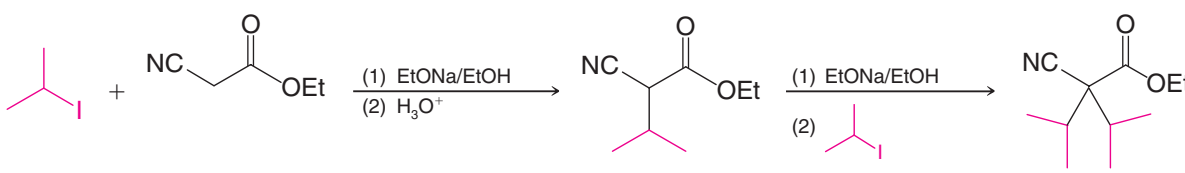
The range of pK_a values for such active methylene compounds is 3–13.

Ethyl cyanoacetate, for example, reacts with a base to yield a resonance-stabilized anion:



Ethyl cyanoacetate **Resonance structures for ethyl cyanoacetate anion**

Ethyl cyanoacetate anions also undergo alkylations. They can be dialkylated with isopropyl iodide, for example:

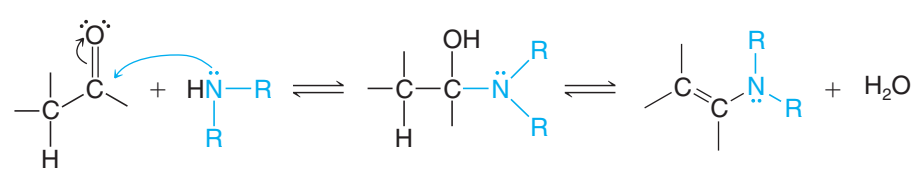


63% **95%**

PRACTICE PROBLEM 18.13 The antiepileptic drug valproic acid is 2-propylpentanoic acid (administered as the sodium salt). One commercial synthesis of valproic acid begins with ethyl cyanoacetate. The penultimate step of this synthesis involves a decarboxylation, and the last step involves hydrolysis of a nitrile. Outline this synthesis.

18.9 SYNTHESIS OF ENAMINES: STORK ENAMINE REACTIONS

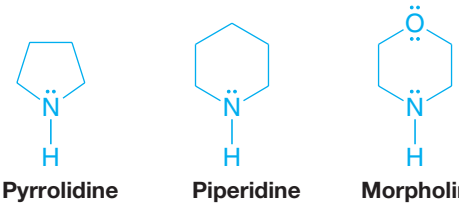
Aldehydes and ketones react with secondary amines to form compounds called **enamines**. The general reaction for enamine formation can be written as follows:



Aldehyde or ketone **2° Amine** **Enamine**

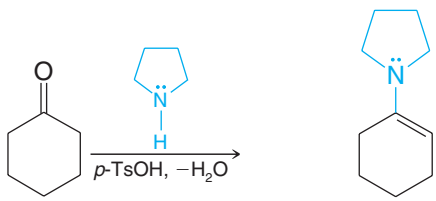
See Section 16.8C for the mechanism of enamine formation.

Since enamine formation requires the loss of a molecule of water, enamine preparations are usually carried out in a way that allows water to be removed as an azeotrope or by a drying agent. This removal of water drives the reversible reaction to completion. Enamine formation is also catalyzed by the presence of a trace of an acid. The secondary amines most commonly used to prepare enamines are cyclic amines such as pyrrolidine, piperidine, and morpholine:



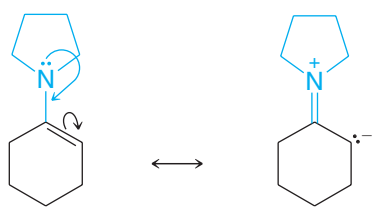
Pyrrolidine **Piperidine** **Morpholine**

Cyclohexanone, for example, reacts with pyrrolidine in the following way:



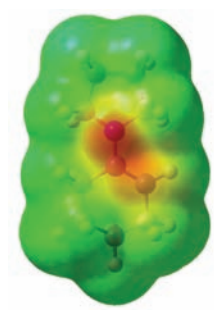
***N*-(1-Cyclohexenyl)pyrrolidine (an enamine)**

Enamines are good nucleophiles. Examination of the resonance structures that follow show that we should expect enamines to have both a nucleophilic nitrogen and a *nucleophilic carbon*. A map of electrostatic potential highlights the nucleophilic region of an enamine.



Contribution to the hybrid made by this structure confers nucleophilicity on nitrogen.

Contribution to the hybrid made by this structure confers nucleophilicity on carbon and decreases the nucleophilicity of nitrogen.



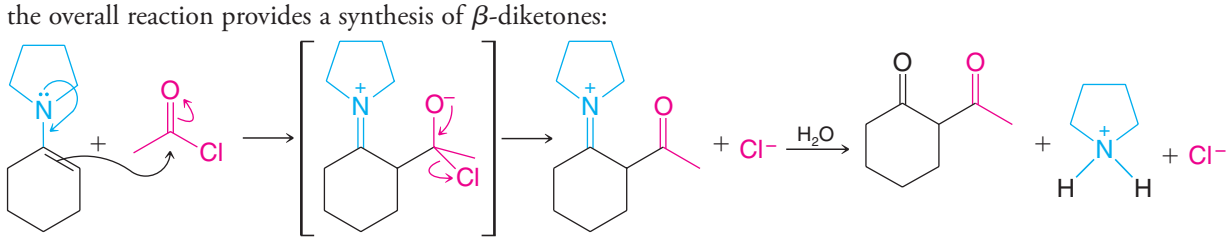
A map of electrostatic potential for *N*-(1-cyclohexenyl)pyrrolidine shows the distribution of negative charge and the nucleophilic region of an enamine.

The nucleophilicity of the carbon of enamines makes them particularly useful reagents in organic synthesis because they can be **acylated, alkylated,** and used in **Michael additions** (see Section 19.7A). Enamines can be used as synthetic equivalents of aldehyde or ketone enolates because the alkene carbon of an enamine reacts the same way as does the α carbon of an aldehyde or ketone enolate and, after hydrolysis, the products are the same. Development of these techniques originated with the work of Gilbert Stork of Columbia University, and in his honor they have come to be known as **Stork enamine reactions**.

Helpful Hint

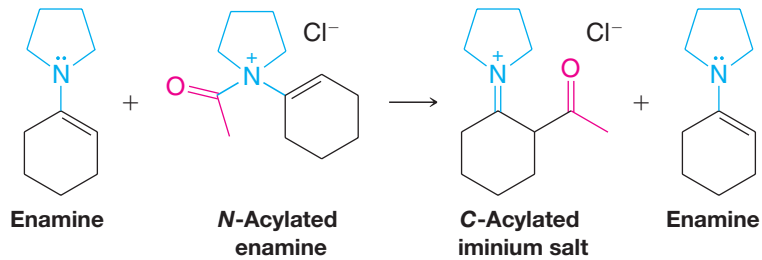
Enamines are the synthetic equivalents of aldehyde and ketone enolates.

When an enamine reacts with an acyl halide or an acid anhydride, the product is the *C*-acylated compound. The iminium ion that forms hydrolyzes when water is added, and the overall reaction provides a synthesis of β-diketones:



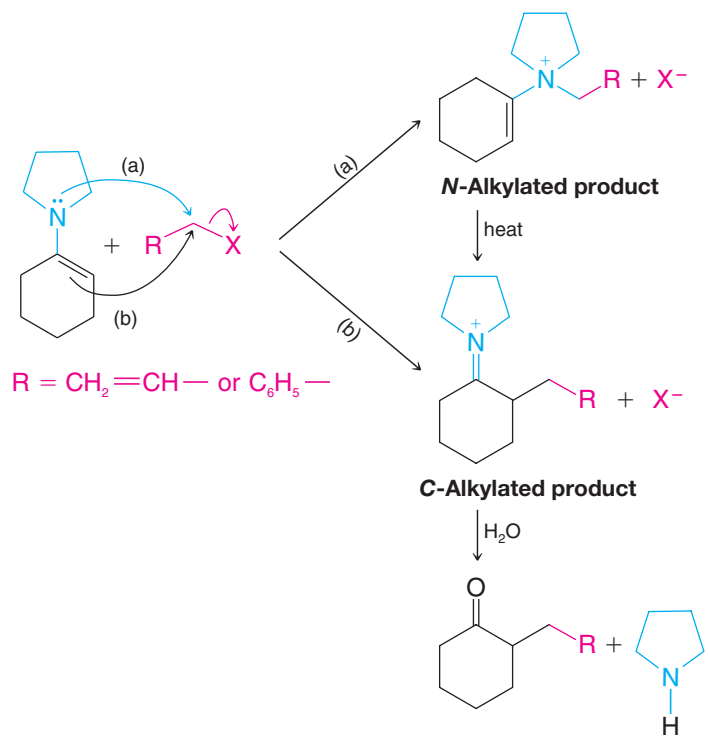
Iminium salt **2-Acetylcyclohexanone (a β-diketone)**

Although *N*-acylation may occur in this synthesis, the *N*-acyl product is unstable and can act as an acylating agent itself:

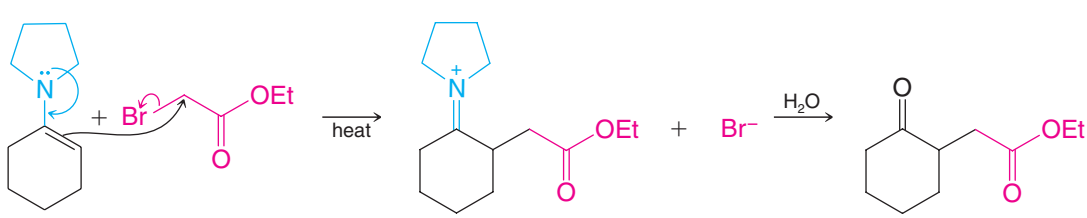


As a consequence, the yields of *C*-acylated products are generally high.

Enamines can be alkylated as well as acylated. Although alkylation may lead to the formation of a considerable amount of *N*-alkylated product, heating the *N*-alkylated product often converts it to a *C*-alkyl compound. This rearrangement is particularly favored when the alkyl halide is an allylic halide, benzylic halide, or α-haloacetic ester:



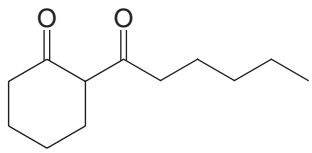
Enamine alkylations are S_N2 reactions; therefore, when we choose our alkylating agents, we are usually restricted to the use of methyl, primary, allylic, and benzylic halides. α-Halo esters can also be used as the alkylating agents, and this reaction provides a convenient synthesis of β-keto esters:

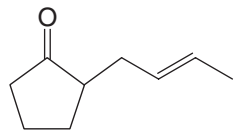


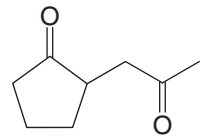
A γ-keto ester (75%)

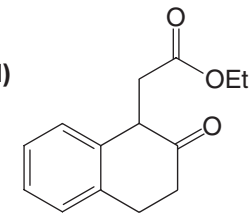
PRACTICE PROBLEM 18.14

Show how you could employ enamines in syntheses of the following compounds:

(a) 

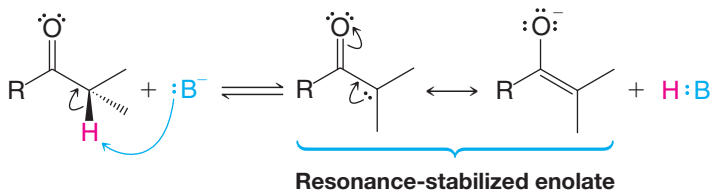
(b) 

(c) 

(d) 

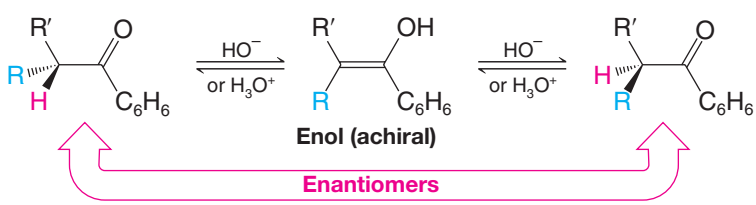
18.10 SUMMARY OF ENOLATE CHEMISTRY

1. ***Formation of an Enolate*** **(Section 18.1)**



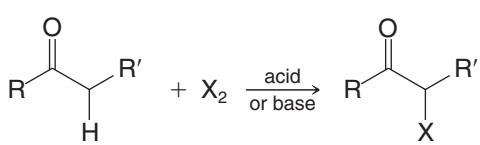
:B = :ÖH, :ÖR, or :N(*i*-Pr)$_2$ (Section 18.4)

2. ***Racemization*** **(Section 18.3A)**

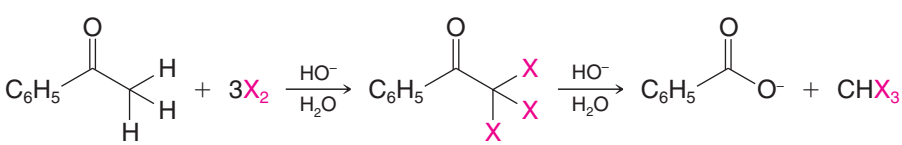


3. ***Halogenation of Aldehydes and Ketones*** **(Sections 18.3B and 18.3C)**

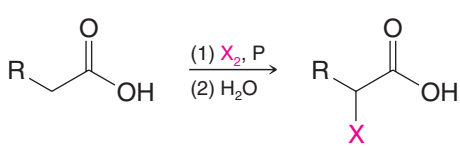
General Reaction



Specific Example—Haloform Reaction

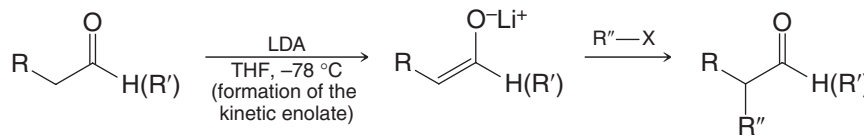


4. ***Halogenation of Carboxylic Acids: The HVZ Reaction*** **(Section 18.3D)**

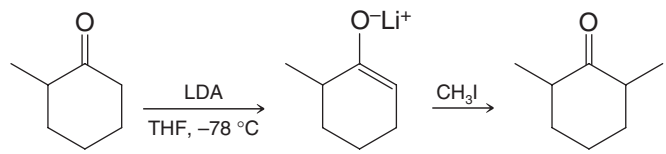


5. *Direct Alkylation via Lithium Enolates* (Section 18.4)

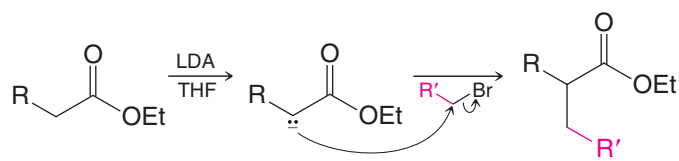
General Reaction



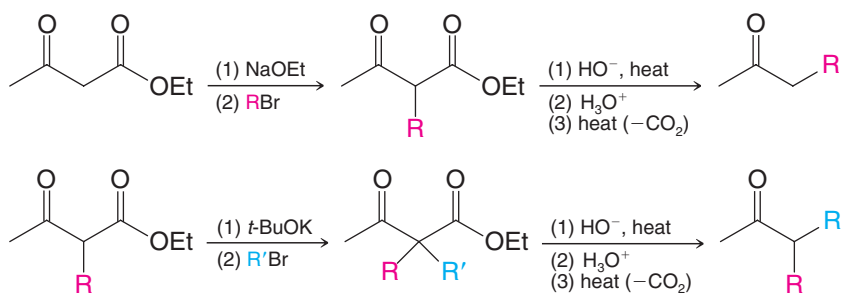
Specific Example



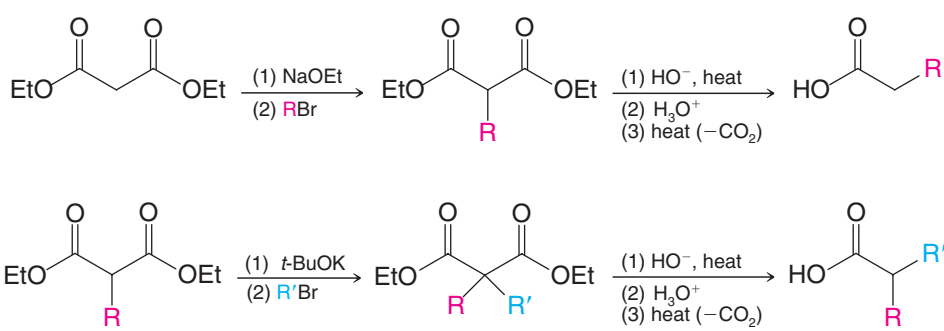
6. *Direct Alkylation of Esters* (Section 18.4C)



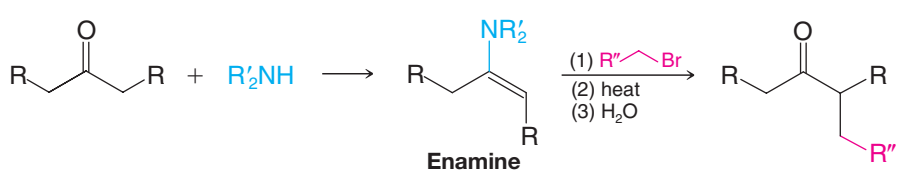
7. *Acetoacetic Ester Synthesis* (Section 18.6)



8. *Malonic Ester Synthesis* (Section 18.7)



9. *Stork Enamine Reaction* (Section 18.9)



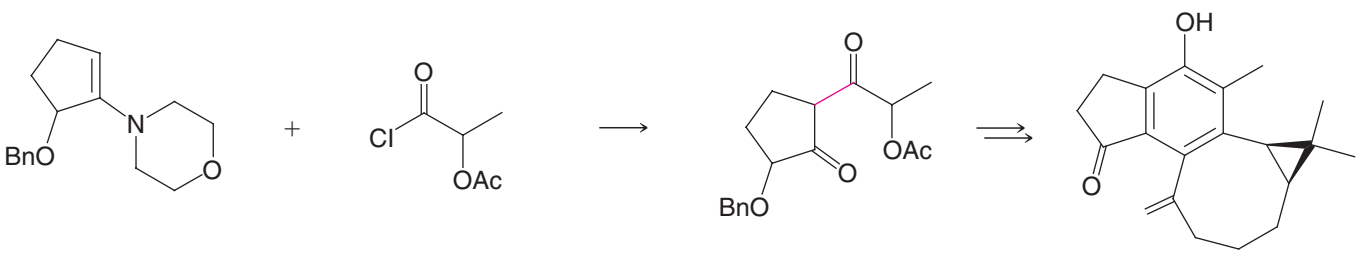
Enamine

[WHY Do These Topics Matter?

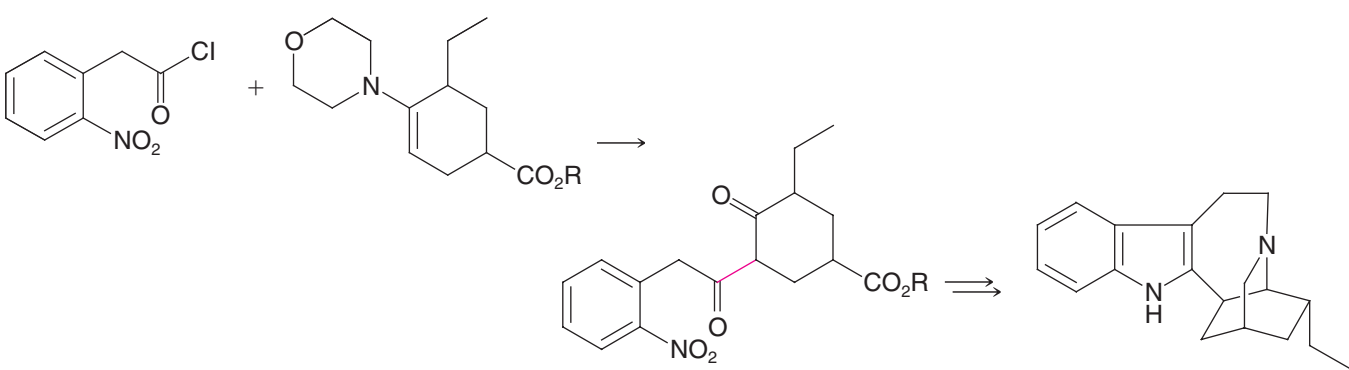
USING ENAMINE CHEMISTRY TO MAKE COMPLEXITY

The reactions that you have learned in this chapter are not just of academic interest; they are critical tools that make possible the syntheses of powerful pharmaceuticals and bioactive molecules, some even on ton scale! These reactions are significant because they constitute highly powerful methods for forming C—C bonds. Of the reactions you have seen thus far, though, perhaps the most versatile is the Stork enamine reaction. This general transformation was inspired by trying to copy mechanisms that nature uses for forming such C—C bonds. Since its initial discovery over half a century ago, the Stork enamine reaction has found countless applications. Here, we will mention four.

The first two reactions shown below highlight the merger of acid chlorides with enamines to make new C—C bonds (shown in red) along the lines presented in Section 18.9. One reason this transformation is of such importance is that so many functional groups can be contained within the reactants. As a result, the products possess most of the handles needed to form the final targets. Shown here are syntheses of jatrapholone A, which has antitumor properties, and epiibogamine, an alkaloid known to have value in fighting chemical addictions and cancer.

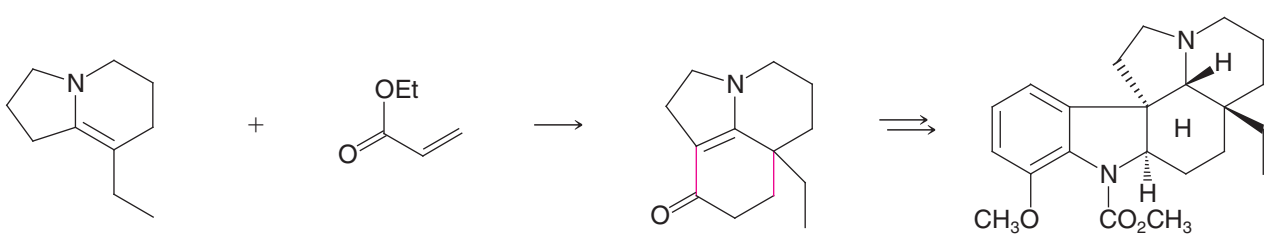


Jatrapholone A



Epiibogamine

Enamine chemistry can also leave the nitrogen atom of the original enamine in the final product. Although understanding the specific examples shown below requires knowledge of some of the reactions found in the next chapter, we provide them now in the hope that they will build further appreciation for the power of the enamine functional group and its bond-forming coupling reactions. In the first case, it afforded a rapid synthesis of aspidospermine, a molecule with diuretic and respiratory stimulant activity; in the second, it provided a ton-scale synthesis of a novel drug candidate from AstraZeneca that has been evaluated in clinical trials to treat urinary incontinence.



Aspidospermine

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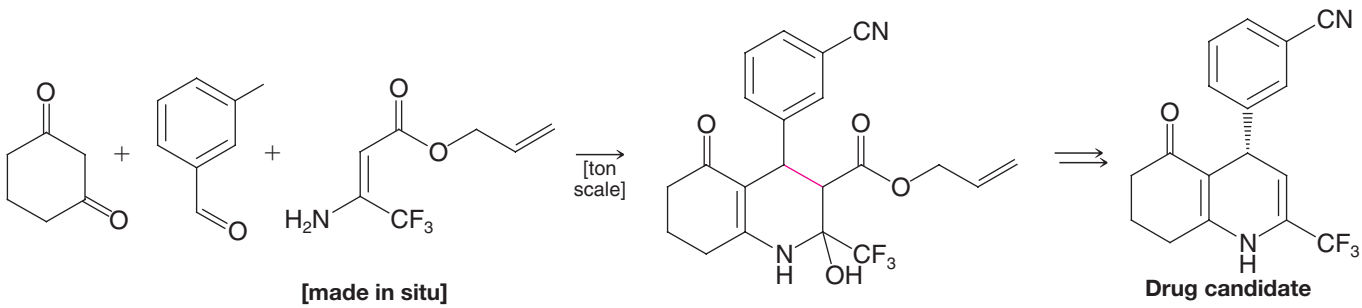


To learn more about these topics, see:

1. Kürti, L.: Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier: London **2005**, pp. 444–445.
2. Kuehne, M. E. "Application of enamines to syntheses of natural products and related compounds" in *Synthesis* **1970**, 510–537.
3. Hopes, P. A.; Parker, A. J.; Patel, I. "Development and optimization of an unsymmetrical Hantzsch reaction for plant-scale manufacture" in *Org. Proc. Res. Dev*. **2006**, *10*, 808–813.
4. Smith, III, A. B.; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. "Total Synthesis of (+) Jatropholones A and B: Exploitation of the High-pressure Technique." *J. Am. Chem. Soc.* **1986**, *108*, 3040-3048.

SUMMARY AND REVIEW TOOLS

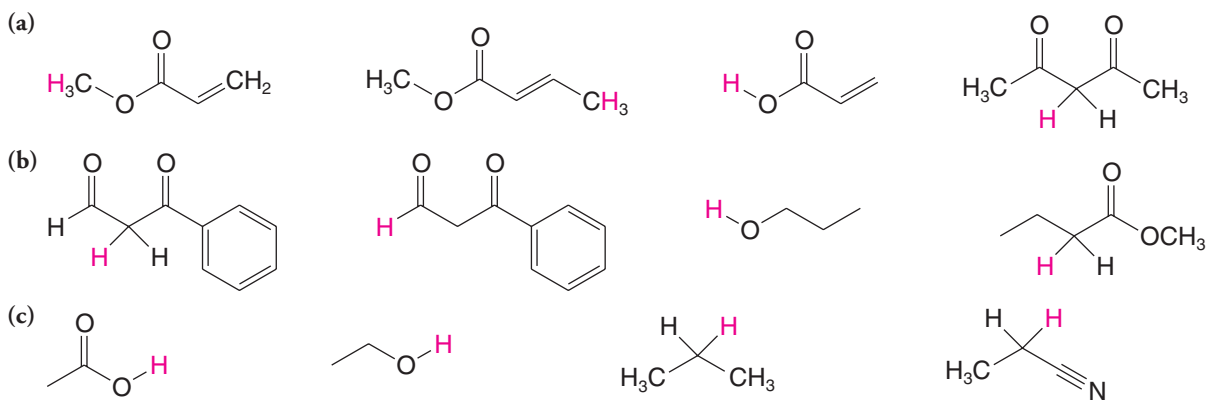
The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com), the list of reaction types in Section 18.10, and the Summary of Mechanisms scheme for enolates and α-substitution.

PROBLEMS

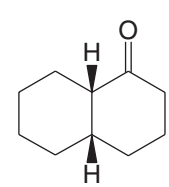
Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

ENOLATES, ENOLS, AND CARBONYL α-CARBON REACTIVITY

18.15 Rank the following in order of increasing acidity for the indicated hydrogen atoms (bold) (1 = least acidic; 4 = most acidic).



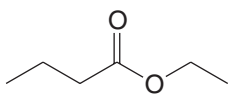
18.16 Treating a solution of *cis*-1-decalone with base causes an isomerization to take place. When the system reaches equilibrium, the solution is found to contain about 95% *trans*-1-decalone and about 5% *cis*-1-decalone. Explain this isomerization.

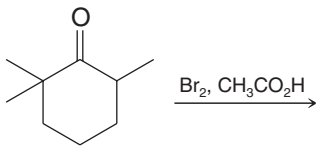

***cis*-1-Decalone**

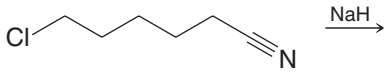
18.17 Explain the variation in enol content that is observed for solutions of acetylacetone (pentane-2,4-dione) in the several solvents indicated:

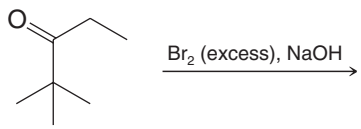
Solvent	% Enol
H_2O	15
CH_3CN	58
C_6H_{14}	92
Gas phase	92

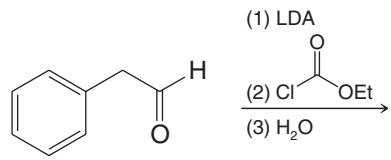
18.18 Provide a structural formula for the product from each of the following reactions.

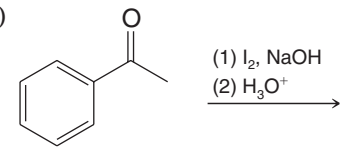
(a) 

(b) 

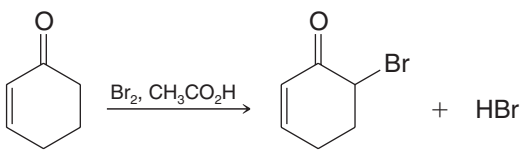
(c) 

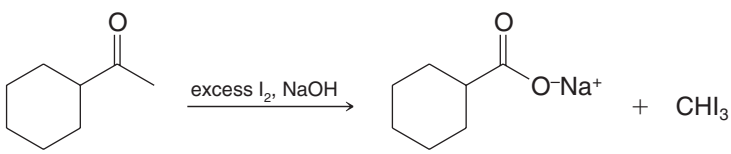
(d) 

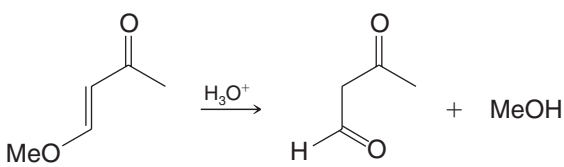
(e) 

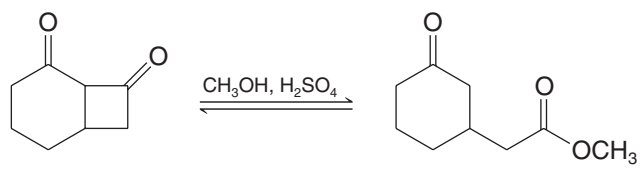
(f) 

18.19 Write a stepwise mechanism for each of the following reactions.

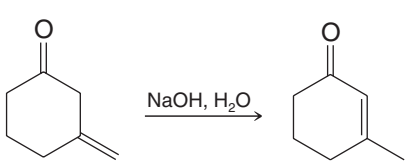
(a) 

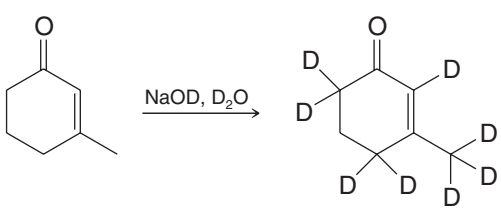
(b) 

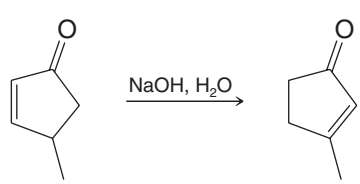
(c) 

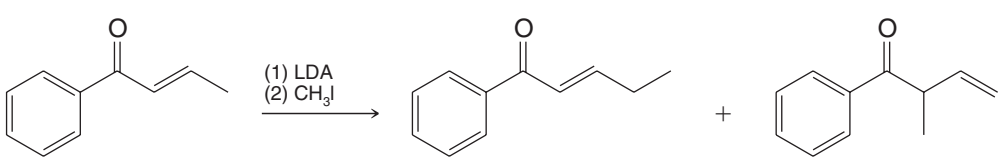
(d) 

18.20 Write a stepwise mechanism for each of the following reactions.

(a) 

(b) 

(c) 

(d) 

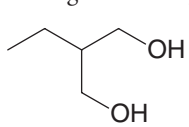
ACETOACETIC ESTER AND MALONIC ESTER SYNTHESES

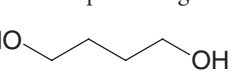
18.21 Outline syntheses of each of the following from acetoacetic ester and any other required reagents:

(a) *tert*-Butyl methyl ketone
(b) 2-Hexanone
(c) 2,5-Hexanedione
(d) 4-Hydroxypentanoic acid
(e) 2-Ethyl-1,3-butanediol
(f) 1-Phenyl-1,3-butanediol

18.22 Outline syntheses of each of the following from diethyl malonate and any other required reagents:

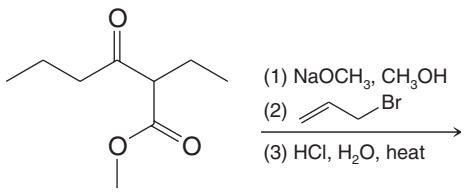
(a) 2-Methylbutanoic acid
(b) 4-Methyl-1-pentanol

(c) 

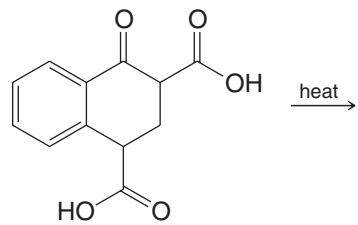
(d) 

18.23 Provide a structural formula for the product from each of the following reactions.

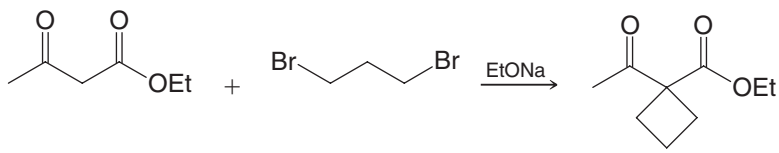
(a)



(b)



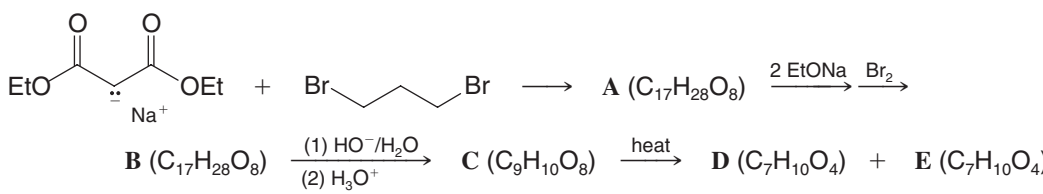
18.24 The synthesis of cyclobutanecarboxylic acid given in Section 18.7 was first carried out by William Perkin, Jr., in 1883, and it represented one of the first syntheses of an organic compound with a ring smaller than six carbon atoms. (There was a general feeling at the time that such compounds would be too unstable to exist.) Earlier in 1883, Perkin reported what he mistakenly believed to be a cyclobutane derivative obtained from the reaction of acetoacetic ester and 1,3-dibromopropane. The reaction that Perkin had expected to take place was the following:



The molecular formula for his product agreed with the formulation given in the preceding reaction, and alkaline hydrolysis and acidification gave a nicely crystalline acid (also having the expected molecular formula). The acid, however, was quite stable to heat and resisted decarboxylation. Perkin later found that both the ester and the acid contained six-membered rings (five carbon atoms and one oxygen atom). Recall the charge distribution in the enolate ion obtained from acetoacetic ester and propose structures for Perkin's ester and acid.

18.25 **(a)** In 1884 Perkin achieved a successful synthesis of cyclopropanecarboxylic acid from sodiomalonic ester and 1,2-dibromoethane. Outline the reactions involved in this synthesis.

(b) In 1885 Perkin synthesized five-membered carbocyclic compounds **D** and **E** in the following way:

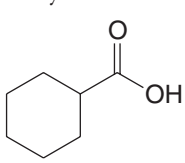


where **D** and **E** are diastereomers; **D** can be resolved into enantiomeric forms while **E** cannot. What are the structures of **A**–**E**?

(c) Ten years later Perkin was able to synthesize 1,4-dibromobutane; he later used this compound and diethyl malonate to prepare cyclopentanecarboxylic acid. Show the reactions involved.

18.26 Synthesize each of the following compounds from diethyl malonate or ethyl acetoacetate and any other organic and inorganic reagents.

(a)



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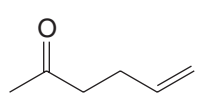
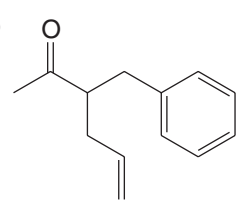
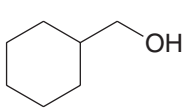


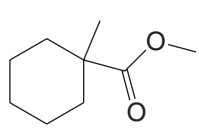
(e)



(b)



(d)



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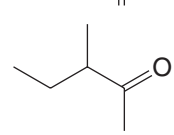
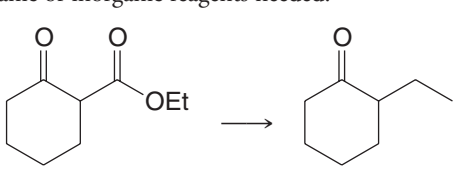


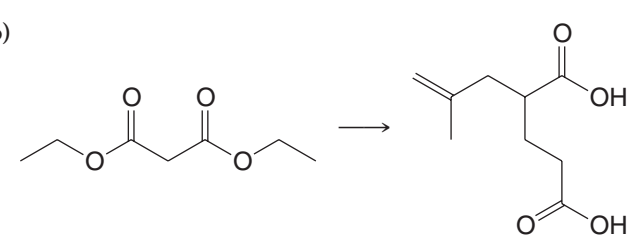
GENERAL PROBLEMS

18.27 Outline a reaction sequence for synthesis of each of the following compounds from the indicated starting material and any other organic or inorganic reagents needed.

(a)



(b)



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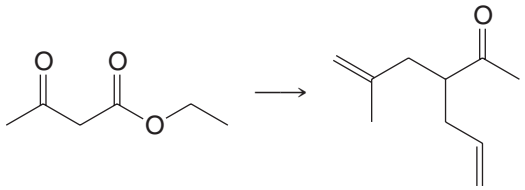

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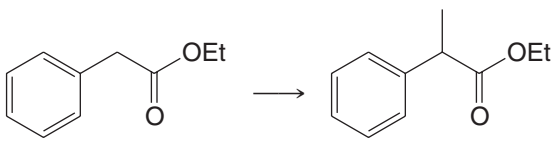

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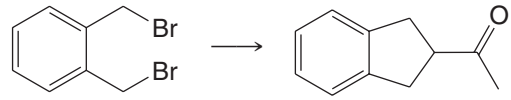

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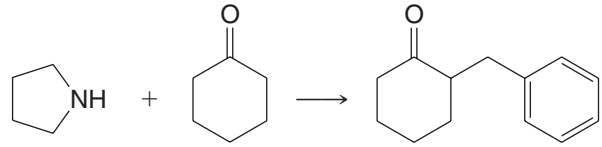
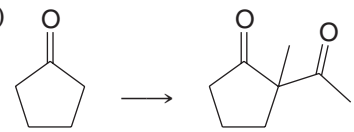
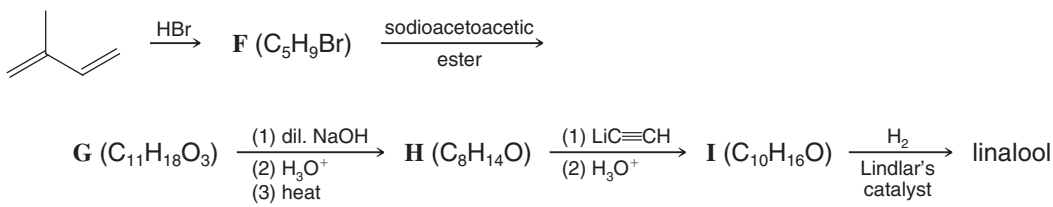


(g)

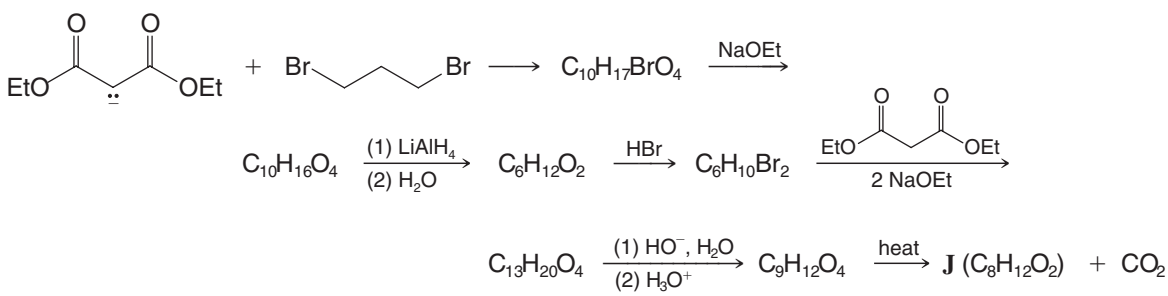


18.28 Linalool, a fragrant compound that can be isolated from a variety of plants, is 3,7-dimethyl-1,6-octadien-3-ol. Linalool is used in making perfumes, and it can be synthesized in the following way:

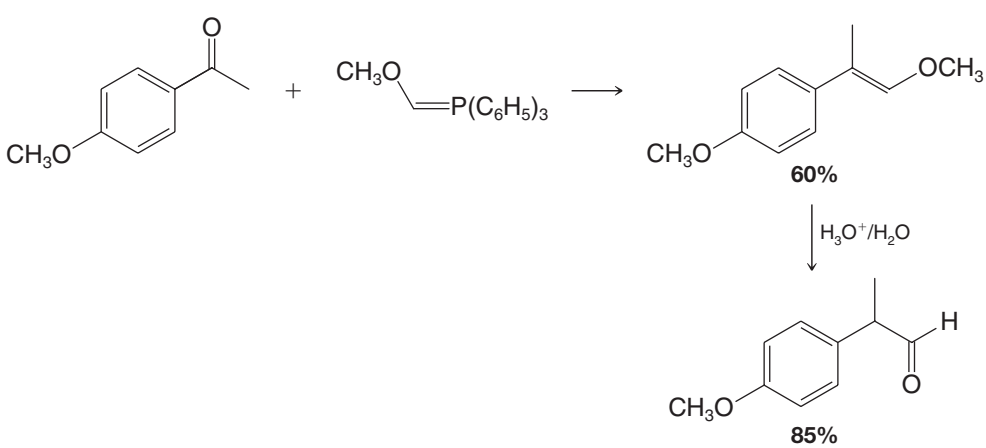


Outline the reactions involved. (*Hint*: Compound **F** is the more stable isomer capable of being produced in the first step.)

18.29 Compound **J**, a compound with two four-membered rings, has been synthesized by the following route. Outline the steps that are involved.

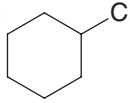


18.30 The Wittig reaction (Section 16.10) can be used in the synthesis of aldehydes, for example,

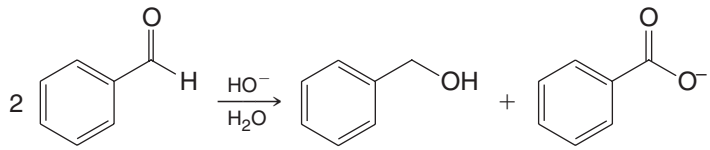


(a) How would you prepare $CH_3OCH{=}P(C_6H_5)_3$?

(b) Show with a mechanism how the second reaction produces an aldehyde.

(c) How would you use this method to prepare  from cyclohexanone?

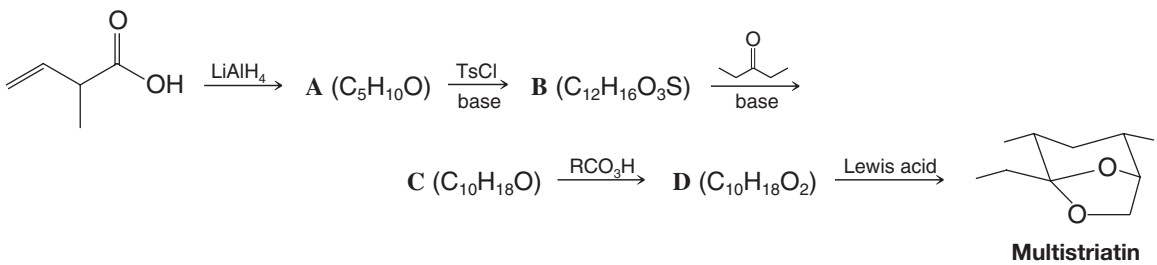
18.31 Aldehydes that have no α hydrogen undergo an intermolecular oxidation–reduction called the **Cannizzaro reaction** when they are treated with concentrated base. An example is the following reaction of benzaldehyde:



(a) When the reaction is carried out in D_2O, the benzyl alcohol that is isolated contains no deuterium bound to carbon. It is $C_6H_5CH_2OD$. What does this suggest about the mechanism for the reaction?

(b) When $(CH_3)_2CHCHO$ and $Ba(OH)_2/H_2O$ are heated in a sealed tube, the reaction produces only $(CH_3)_2CHCH_2OH$ and $[(CH_3)_2CHCO_2]_2Ba$. Provide an explanation for the formation of these products.

18.32 Shown below is a synthesis of the elm bark beetle pheromone, multistriatin (see Problem 16.44). Give structures for compounds **A, B, C**, and **D**.



Multistriatin

SPECTROSCOPY

18.33 **(a)** A compound **U** ($C_9H_{10}O$) gives a negative iodoform test. The IR spectrum of **U** shows a strong absorption peak at 1690 cm^{-1}. The ^1H NMR spectrum of **U** gives the following:

Triplet	δ 1.2 (3H)
Quartet	δ 3.0 (2H)
Multiplet	δ 7.7 (5H)

What is the structure of **U**?

(b) A compound **V** is an isomer of **U**. Compound **V** gives a positive iodoform test; its IR spectrum shows a strong peak at 1705 cm^{-1}. The ^1H NMR spectrum of **V** gives the following:

Singlet	δ 2.0 (3H)
Singlet	δ 3.5 (2H)
Multiplet	δ 7.1 (5H)

What is the structure of **V**?

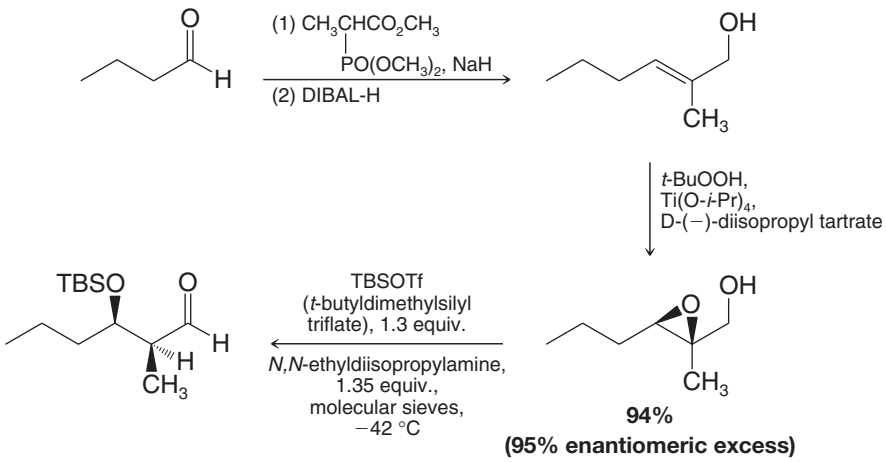
18.34 Compound **A** has the molecular formula $C_6H_{12}O_3$ and shows a strong IR absorption peak at 1710 cm^{-1}. When treated with iodine in aqueous sodium hydroxide, **A** gives a yellow precipitate. When **A** is treated with Tollens' reagent (a test for an aldehyde or a group that can be hydrolyzed to an aldehyde), no reaction occurs; however, if **A** is treated first with water containing a drop of sulfuric acid and then with Tollens' reagent, a silver mirror (positive Tollens' test) forms in the test tube. Compound **A** shows the following ^1H NMR spectrum:

Singlet	δ 2.1
Doublet	δ 2.6
Singlet	δ 3.2 (6H)
Triplet	δ 4.7

Write a structure for **A**.

CHALLENGE PROBLEM

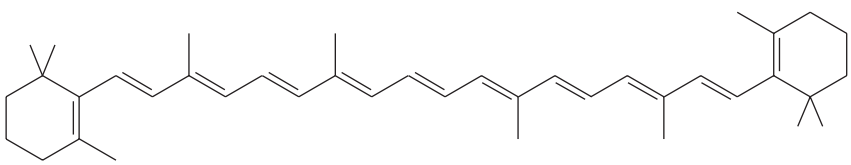
18.35 The following is an example of a reaction sequence developed by Derin C. D'Amico and Michael E. Jung (UCLA) that results in enantiospecific formation of two new chirality centers and a carbon–carbon bond. The sequence includes a Horner–Wadsworth–Emmons reaction (Section 16.10B), a Sharpless asymmetric epoxidation (Section 11.13), and a novel rearrangement that ultimately leads to the product. Propose a mechanism for rearrangement of the epoxy alcohol under the conditions shown to form the aldol product. [*Hint*: The rearrangement can also be accomplished by preparing a trialkylsilyl ether from the epoxy alcohol in a separate reaction first and then treating the resulting silyl ether with a Lewis acid catalyst (e.g., BF_3).]



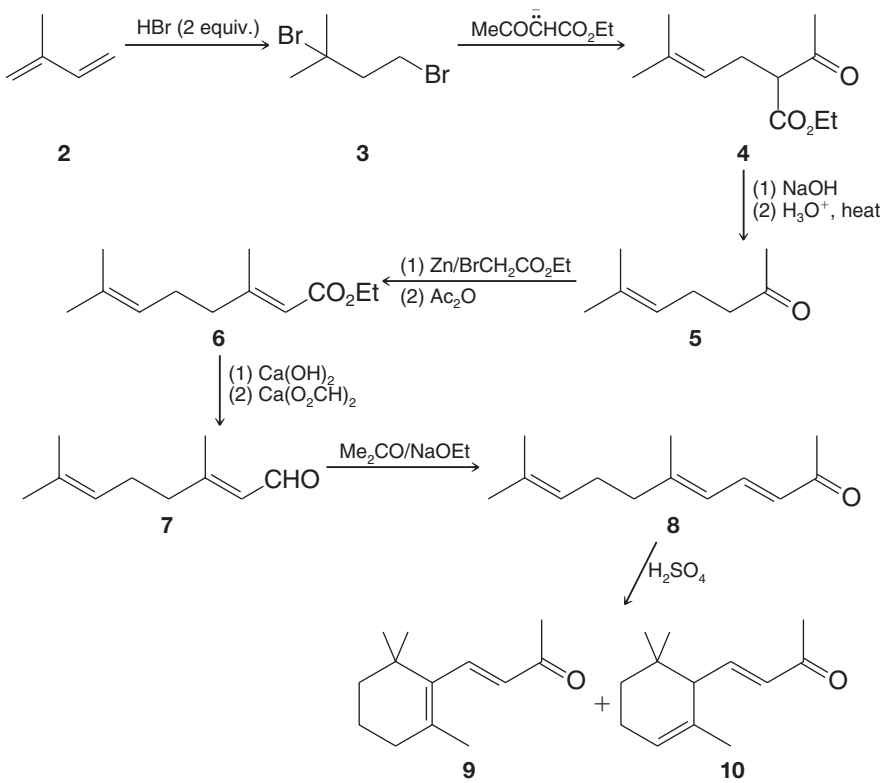
LEARNING GROUP PROBLEMS

β-CAROTENE, DEHYDROABEITIC ACID

1. β-Carotene is a highly conjugated hydrocarbon with an orange-red color. Its biosynthesis occurs via the isoprene pathway (Special Topic E in *WileyPLUS*), and it is found in, among other sources, pumpkins. One of the chemical syntheses of β-carotene was accomplished near the turn of the twentieth century by W. Ipatiew (*Ber.* **1901**, *34*, 594–596). The first few steps of this synthesis involve chemistry that should be familiar to you. Write mechanisms for all of the reactions from compounds **2** to **5**, and from **8** to **9** and **10**.



β-Carotene

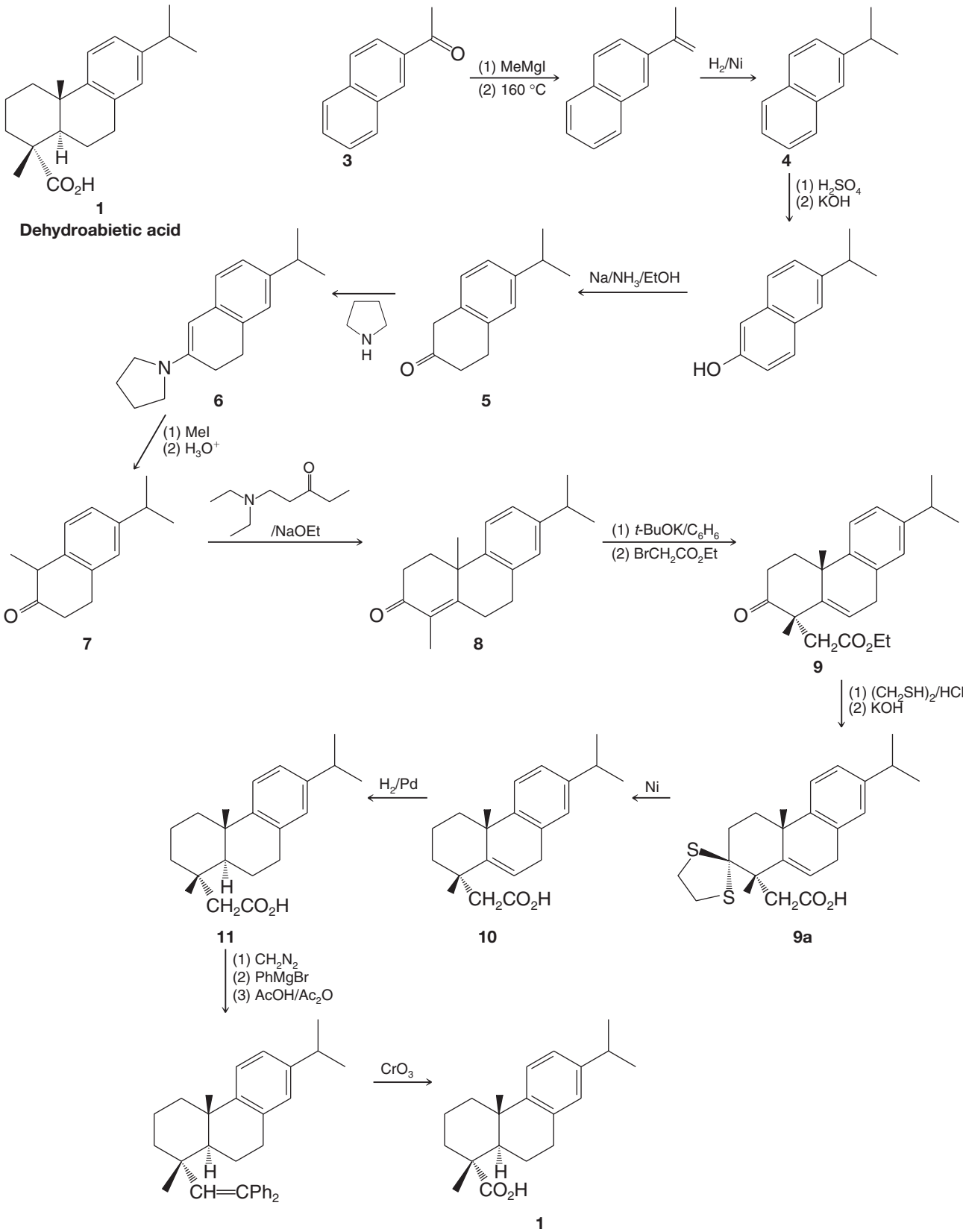


2 **3** **4** **5** **6** **7** **8** **9** **10**

2. Dehydroabietic acid is a natural product isolated from *Pinus palustris*. It is structurally related to abietic acid, which comes from rosin. The synthesis of dehydroabietic acid (*J. Am. Chem. Soc*. **1962**, *84*, 284–292) was accomplished by Gilbert Stork. In the course of this synthesis, Stork discovered his famous enamine reaction.

(a) Write detailed mechanisms for the reactions from **5** to **7** below.

(b) Write detailed mechanisms for all of the reactions from **8** to **9a** in Stork's synthesis of dehydroabietic acid. Note that **9a** contains a dithioacetal, which forms similarly to acetals you have already studied (Chapter 16).

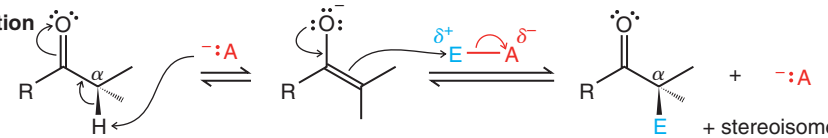


(Structures from Fleming, I., *Selected Organic Synthesis*, p. 76. Copyright John Wiley & Sons, Limited. Reproduced with permission.)

SUMMARY OF MECHANISMS

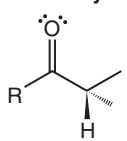
Enolates: α-Substitution

General Reaction

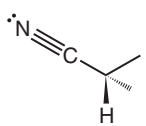


+ stereoisomer (if α carbon is, and/or if E contains, a stereogenic center)

Some groups that increase α-hydrogen acidity



Carbonyl



Nitrile
(cyano group)

(and in general, other groups that can stabilize an α-carbanion)

Typical bases (⁻:A) and solvents for enolate formation

I. HO^- in H_2O or ROH; or RO^- in ROH;
Useful for reactions involving thermodynamically favored enolates and equilibrium product control

II. LDA (lithium diisopropylamide) in THF or DME;
useful, in general, for forming enolates in aprotic solvents (especially kinetically favored enolates and direct alkylation)

Possible electrophiles (E–A)

H—A

Deprotonation–protonation
(may lead to racemization or epimerization)

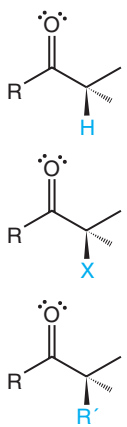
:X—X:

Halogenation

R′—X:

Alkylation

Product(s)



Substitution of enolate α hydrogen by H, X, or R

PLUS See Special Topic C in *WileyPLUS*