Organic Chemistry, *Fourth Edition*

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Chapter 24
Lecture Outline

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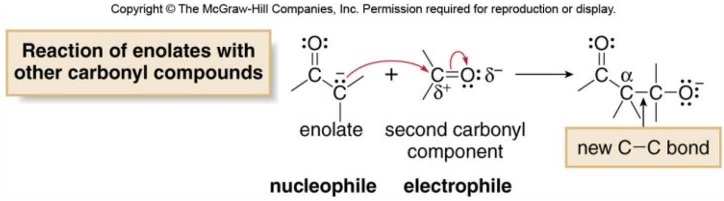
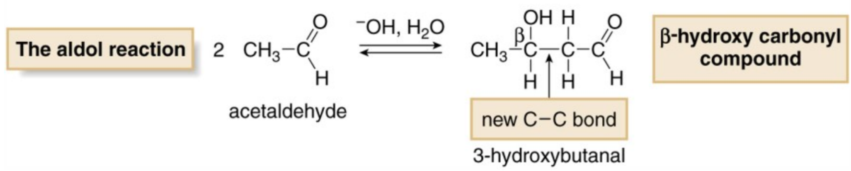
Condensation Reactions Between Two Carbonyl Compounds

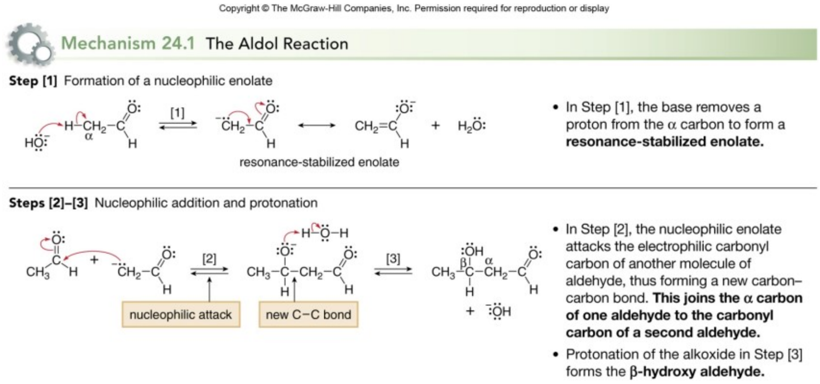
- **Enolates and enols can react with other carbonyl compounds to form a new carbon–carbon bond.**
- **In these reactions, one carbonyl component serves as the nucleophile and one serves as the electrophile.**
- **In each case, a new bond is formed at the α carbon of one reactant to the carbonyl group of the other.**
- **The presence or absence of a leaving group on the electrophilic carbonyl carbon determines the structure of the product.**



The Aldol Reaction

- In the **aldol reaction**, two molecules of an aldehyde or ketone react with each other in the presence of a base to form a β-hydroxy carbonyl compound.





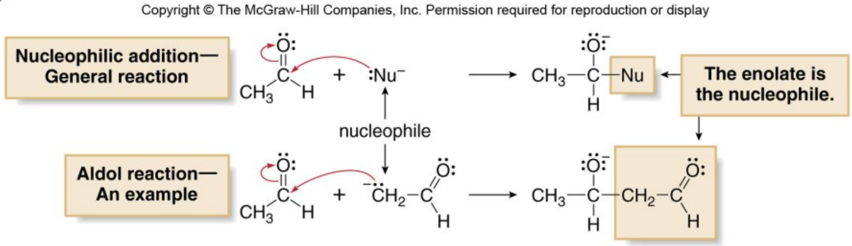
Aldol Reaction

- The aldol reaction has a reversible equilibrium, so the position of the equilibrium depends on the base and the carbonyl compound.
- $^{-}$OH is the base typically used in an aldol reaction.
- Although with $^{-}$OH only a small amount of enolate is formed, this is appropriate because the starting aldehyde is needed to react with the enolate in the second step of the reaction.
- Aldol reactions can be carried out with either aldehydes or ketones.
- With aldehydes, the equilibrium usually favors products, but with ketones the equilibrium favors the starting materials.
- However, there are ways of driving the equilibrium toward products.

Nucleophilic Addition of Enolates

- The characteristic reaction of aldehydes and ketones is **nucleophilic addition**.
- An aldol reaction is a nucleophilic addition in which an enolate is the nucleophile.

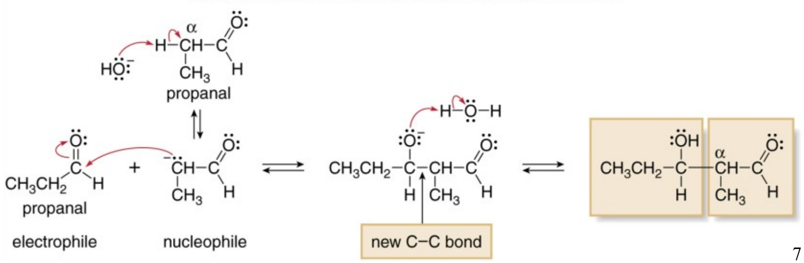
Figure 24.1



- Aldehydes and ketones react by nucleophilic addition. In an aldol reaction, an enolate is the nucleophile that adds to the carbonyl group.

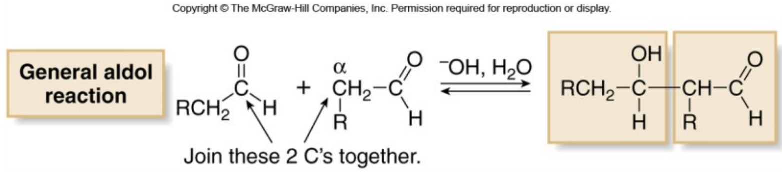
Aldol Reaction with Propanal

- A second example of an aldol reaction is shown with propanal as the starting material.
- The two molecules of the aldehyde that participate in the aldol reaction react in opposite ways.
  - One molecule becomes an enolate—an electron-rich *nucleophile*.
  - One molecule serves as the *electrophile* because its carbonyl is electron deficient.



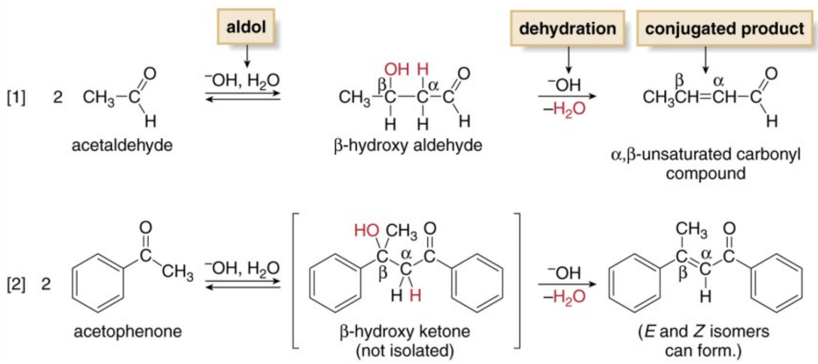
Joining Carbons to Form Aldol Products

- The α carbon of one carbonyl component becomes bonded to the carbonyl carbon of the other component.



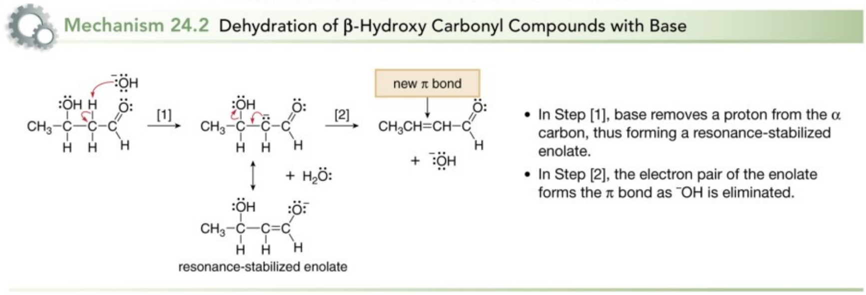
Dehydration of the Aldol Product

- **Under basic reaction conditions, the initial aldol product is often not isolated.**
- **Instead, it loses the elements of H_2O from the α and β carbons to form an α,β-unsaturated carbonyl compound.**



Condensation Reactions

- **An aldol reaction is often called an aldol condensation because the β-hydroxy carbonyl compound that is initially formed loses H_2O by dehydration.**
- **A condensation reaction is one in which a small molecule, in this case, H_2O, is eliminated during the reaction.**
- **It may or may not be possible to isolate the β-hydroxy carbonyl compound under the conditions of the aldol reaction.**
- **When the α,β-unsaturated carbonyl compound is further conjugated with a carbon–carbon double bond or a benzene ring (as is the case in reaction of acetophenone), elimination of H_2O is spontaneous and the β-hydroxy carbonyl compound cannot be isolated.**



E1cB Mechanism

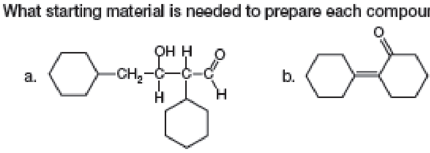
- The elimination reaction that results in the dehydration proceeds via an E1cB mechanism.
- E1cB stands for Elimination, unimolecular, conjugate base.
- The E1cB mechanism differs from the E1 and E2 mechanisms.
  - Like the E1 elimination, E1cB requires two steps.
  - Unlike E1 though, the intermediate in E1cB is a carbanion, not a carbocation.
- Regular alcohols dehydrate only in the presence of acid, not base, because hydroxide is a poor leaving group.
- However, when the hydroxy group is β to a carbonyl, loss of H and OH from the α and β carbons forms a conjugated double bond, and the stability of the conjugated system makes up for having such a poor leaving group.
- Dehydration of the initial β-hydroxy carbonyl compound drives the equilibrium of an aldol reaction to the right, thus favoring product formation.

Retrosynthetic Analysis of Aldol Products

- **To utilize the aldol reaction in synthesis, you must be able to determine which aldehyde or ketone is needed to prepare a particular β-hydroxy carbonyl compound or α,β-unsaturated carbonyl compound—that is, you must be able to work backwards in the retrosynthetic direction.**

How To Synthesize a Compound Using the Aldol Reaction

Example What starting material is needed to prepare each compound by an aldol reaction?



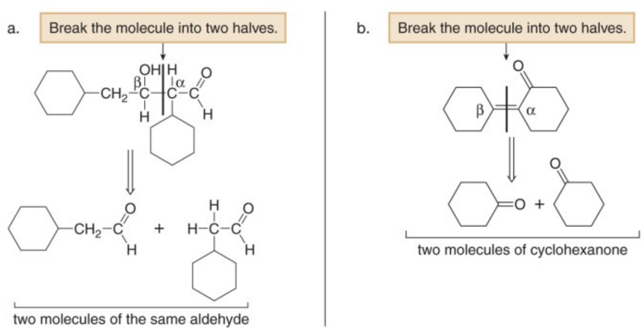
Step [1] Locate the α and β carbons of the carbonyl group.

- When a carbonyl group has two different α carbons, choose the side that contains the OH group (in a β-hydroxy carbonyl compound) or is part of the C=C (in an α,β-unsaturated carbonyl compound).

Retrosynthetic Analysis of Aldol Products

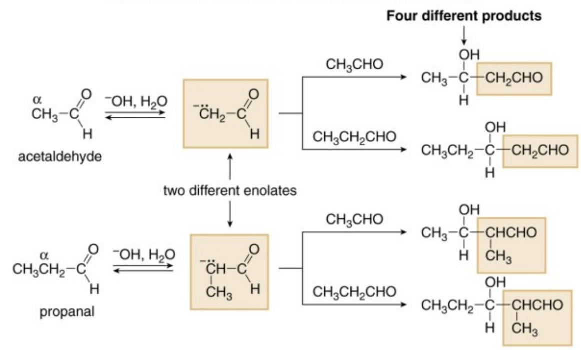
Step [2] Break the molecule into two components between the α and β carbons.

- The α carbon and all remaining atoms bonded to it belong to one carbonyl component. The β carbon and all remaining atoms bonded to it belong to the other carbonyl component. Both components are identical in all aldols we have thus far examined.



Crossed Aldol Reactions

- Sometimes it is possible to carry out an aldol reaction between two different carbonyl compounds.
- Such reactions are called crossed or mixed aldol reactions.

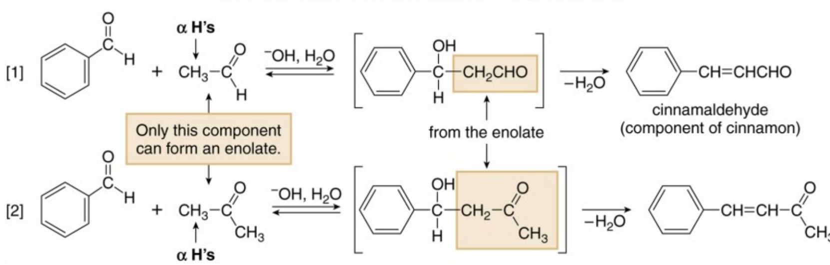


- Conclusion: When two different aldehydes have α hydrogens, a crossed aldol reaction is *not* synthetically useful.

Use of Crossed Aldol Reactions

Crossed aldols are synthetically useful in two different situations:

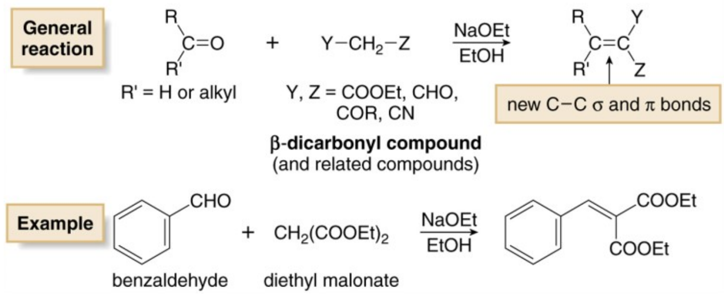
[1] When only one carbonyl component has α hydrogens—such cases often lead to the formation of only one product.



Use of Crossed Aldol Reactions

[2] When one carbonyl component has especially acidic α hydrogens, these hydrogens are more readily removed than the other α H atoms.

- **As a result, the β-dicarbonyl compound always becomes the enolate component of the aldol reaction.**

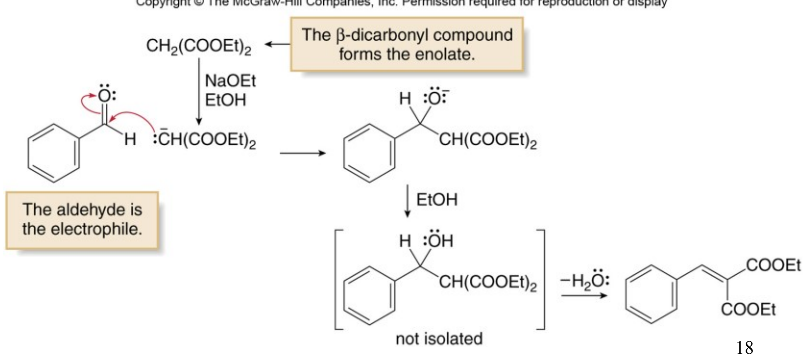


17

Example of Crossed Aldol Reactions

- **In this type of crossed aldol reaction, the initial β-hydroxy compound always loses water to form the highly conjugated product.**

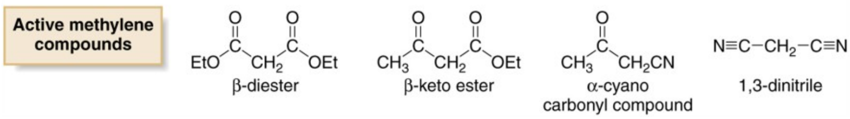
Figure 24.2
Crossed aldol reaction between benzaldehyde and diethyl malonate



18

Active Methylene Compounds

- β-Dicarbonyl compounds are sometimes called active methylene compounds because they are more reactive towards base than other carbonyl compounds.
- 1,3-Dinitriles and α-cyano carbonyl compounds are also active methylene compounds.

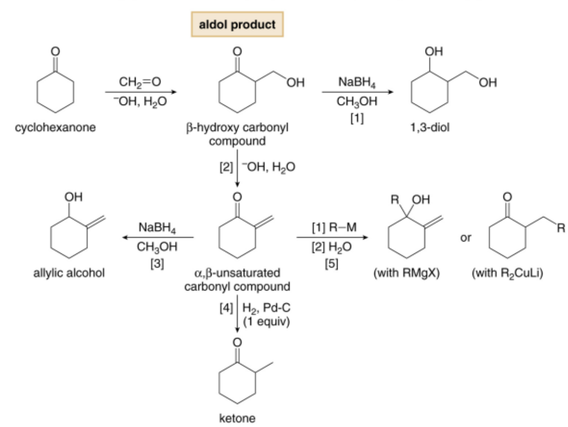


19

Useful Transformations of Aldol Products

- The aldol reaction is synthetically useful because it forms new carbon–carbon bonds, generating products with two functional groups.
- β-Hydroxy carbonyl compounds formed in aldol reactions are readily transformed into a variety of other compounds.

Figure 24.3
Conversion of a β-hydroxy carbonyl compound into other compounds



20

Directed Aldol Reactions

- A **directed aldol reaction** is one that clearly defines which carbonyl compound becomes the nucleophilic enolate and which reacts at the electrophilic carbonyl carbon:

[1] The enolate of one carbonyl component is prepared with LDA.

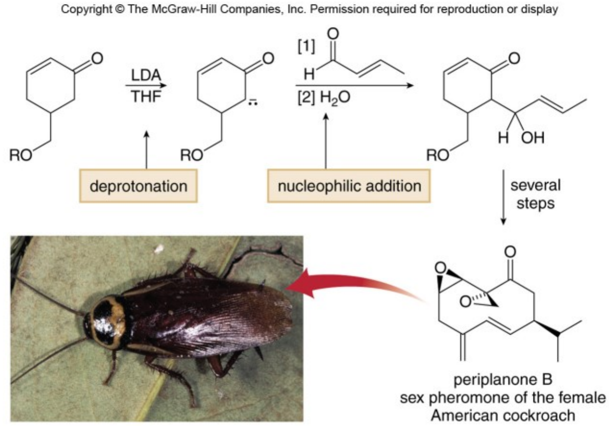
[2] The second carbonyl compound (the electrophile) is added to this enolate.

- **Both carbonyl components can have α hydrogens because only one enolate is prepared with LDA.**
- **When an unsymmetrical ketone is used, LDA selectively forms the less substituted kinetic enolate.**

Directed Aldol Reactions

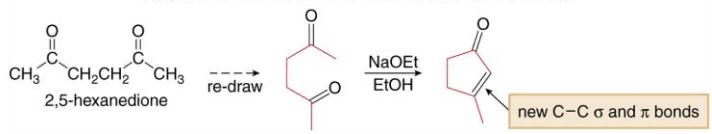
- **Periplanone B is an extremely active compound produced in small amounts by the American cockroach.**
- **Its structure was determined using 200 μg isolated from more than 75,000 female cockroaches.**

Figure 24.4
A directed aldol reaction in the synthesis of periplanone B

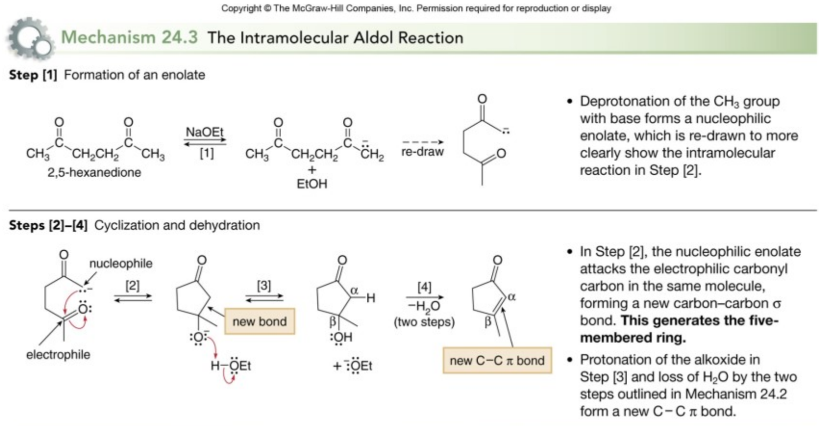


Intramolecular Aldol Reactions

- Aldol reactions with dicarbonyl compounds can be used to make five- and six-membered rings.
- The enolate formed from one carbonyl group is the nucleophile, and the carbonyl carbon of the other is the electrophile.
- For example, treatment of 2,5-hexadienone with base forms a five-membered ring.

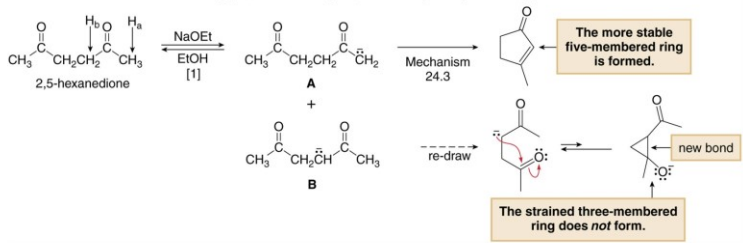


- 2,5-Hexanedione is called a 1,4-dicarbonyl compound to emphasize the relative positions of its carbonyl groups.
- 1,4-Dicarbonyl compounds are starting materials for synthesizing five-membered rings.



Use of Crossed Aldol Reactions

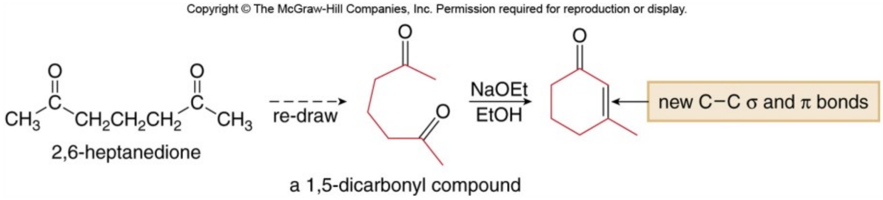
- When 2,5-hexanedione is treated with base in Step [1], two different enolates are possible—enolates A and B, formed by removal of H_a and H_b, respectively.
- Although enolate A goes on to form the five-membered ring, intramolecular cyclization using enolate B would lead to a strained three-membered ring.



- Because the three-membered ring is much higher in energy than the enolate starting material, equilibrium greatly favors the starting materials and the three-membered ring does not form.

Intramolecular Aldol Reactions

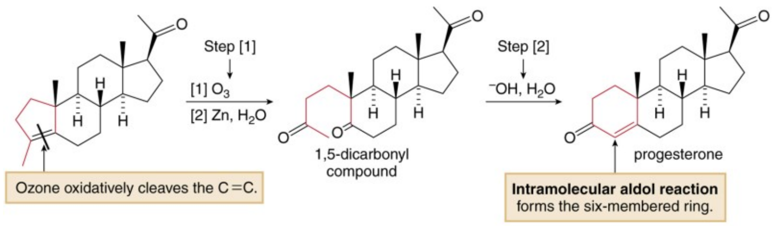
- In a similar fashion, six-membered rings can be formed from the intramolecular aldol reaction of 1,5-dicarbonyl compounds.



Synthesis of Progesterone Using Intramolecular Aldol Reactions

- **The synthesis of the female sex hormone progesterone involves an intramolecular aldol reaction.**

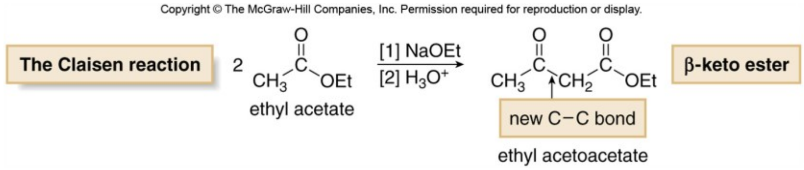
Figure 24.5



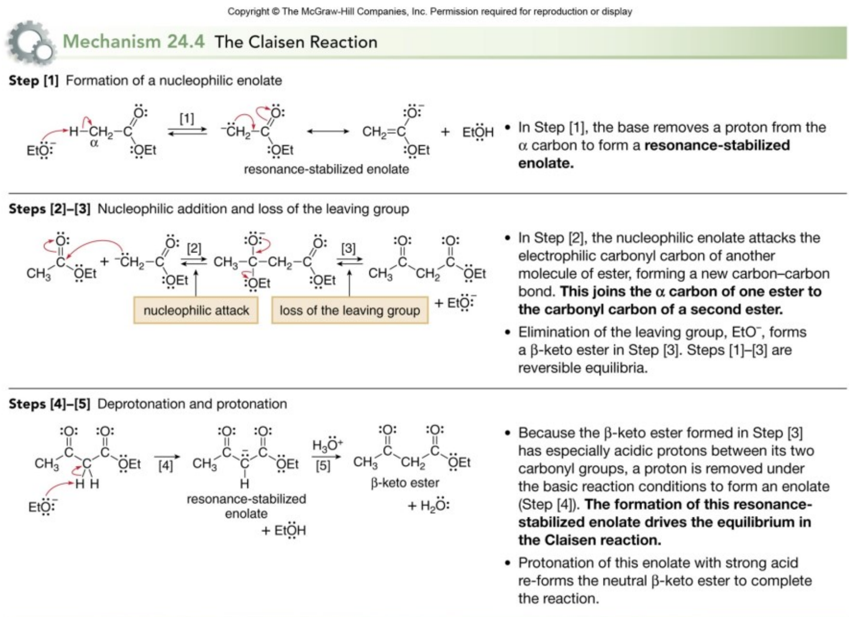
- **Step [1]:** Oxidative cleavage of the alkene with O_3, followed by Zn, H_2O (Section 12.10), gives the 1,5-dicarbonyl compound.
- **Step [2]:** Intramolecular aldol reaction of the 1,5-dicarbonyl compound with dilute ^-OH in H_2O solution forms progesterone.
- **This two-step reaction sequence converts a five-membered ring into a six-membered ring.** Reactions that synthesize larger rings from smaller ones are called **ring expansion reactions.**

The Claisen Reactions

- **In the Claisen reaction, two molecules of an ester react with each other in the presence of an alkoxide base to form a β-keto ester.**
- **Unlike the aldol reaction which is base-catalyzed, a full equivalent of base is needed to deprotonate the β-keto ester formed in Step [3] of the Claisen reaction.**



- **Since esters have a leaving group on the carbonyl carbon, loss of the leaving group occurs to form the product of substitution, not addition.**

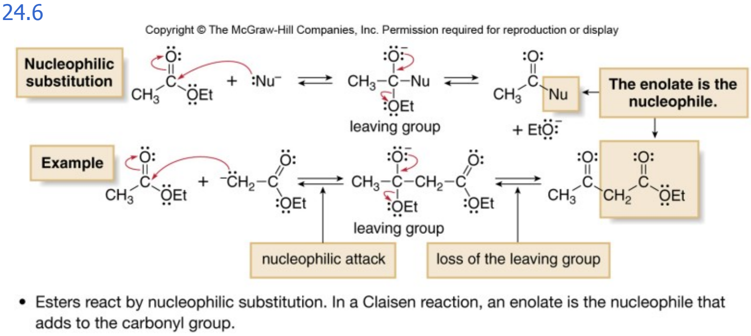


29

Claisen Reaction—Example of Nucleophilic Substitution

- **The characteristic reaction of esters is nucleophilic substitution.**
- **A Claisen reaction is a nucleophilic substitution in which an enolate is the nucleophile.**

Figure 24.6

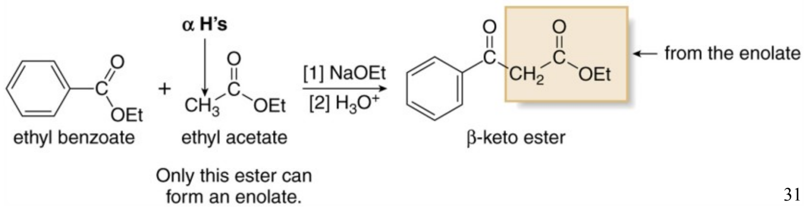


30

Crossed Claisen Reaction

- **Like the aldol reaction, it is sometimes possible to carry out a Claisen reaction with two different carbonyl components as starting materials.**
- **A Claisen reaction between two different carbonyl compounds is called a crossed Claisen reaction.**
- **A crossed Claisen is synthetically useful in two different instances:**

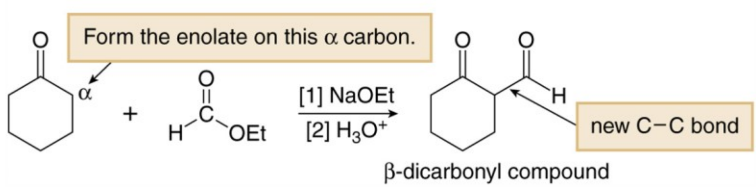
[1] Between two different esters when only one has α hydrogens, one product is usually formed.



Crossed Claisen Reaction

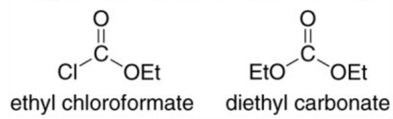
[2] Between a ketone and an ester—the enolate is always formed from the ketone component, and the reaction works best when the ester has no α hydrogens.

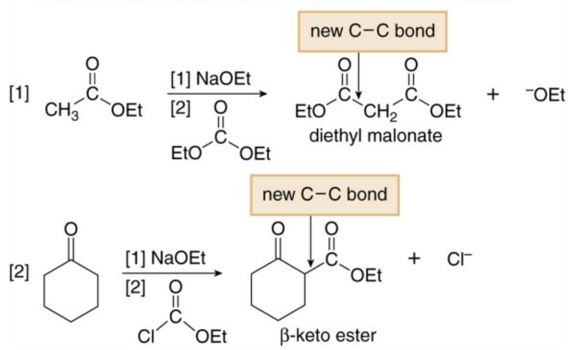
- **The product of this crossed Claisen reaction is a β-dicarbonyl compound, not a β-keto ester.**



Forming β-Dicarbonyl Compounds

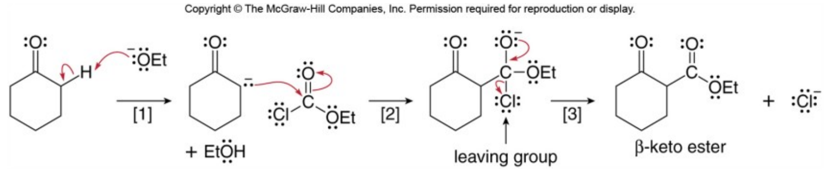
- β-Dicarbonyl compounds are also prepared by reacting an enolate with ethyl chloroformate or diethyl carbonate.





Preparing β-Keto Esters

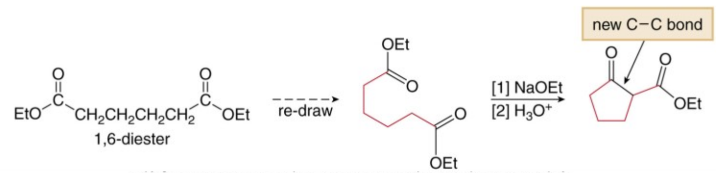
- Reaction [2] is noteworthy because it provides easy access to **β-keto esters**, which are useful starting materials in the acetoacetic ester synthesis.
- In this reaction, Cl^- is eliminated rather than ^-OEt in Step [3] because Cl^- is a better leaving group, as shown in the following steps.



The Dieckmann Reaction

- An intramolecular Claisen reaction is called a **Dieckmann reaction**.
- Two types of diesters give good yields of cyclic products.

- 1,6-Diesters yield five-membered rings by the Dieckmann reaction.



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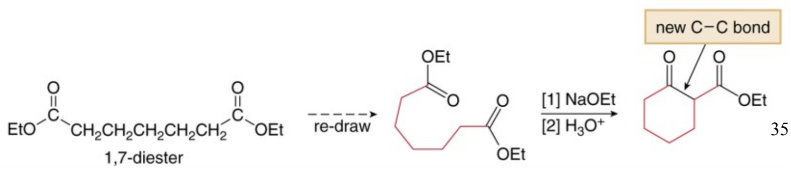
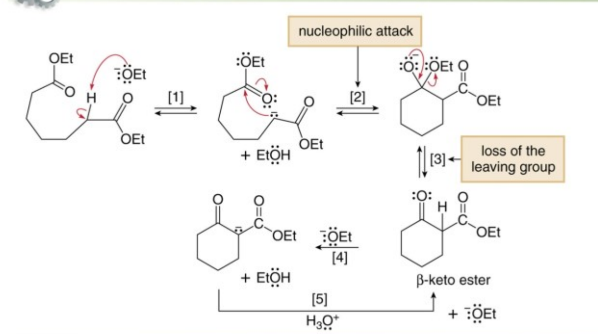


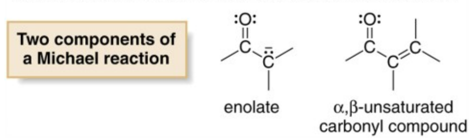
Mechanism 24.5 The Dieckmann Reaction



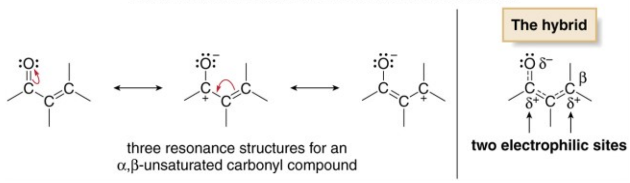
- In Step [1], the base removes a proton to form an enolate, which attacks the carbonyl group of the second ester in Step [2], thus forming a new carbon–carbon bond.
- In Step [3], elimination of $^-$OEt forms the β-keto ester.
- To complete the reaction, the proton between the two carbonyl groups is removed with base, and then protonation of the enolate re-forms the β-keto ester (Steps [4] and [5]).

The Michael Reaction

- The **Michael reaction** involves two carbonyl components—the enolate of one carbonyl compound and an α,β-unsaturated carbonyl compound.



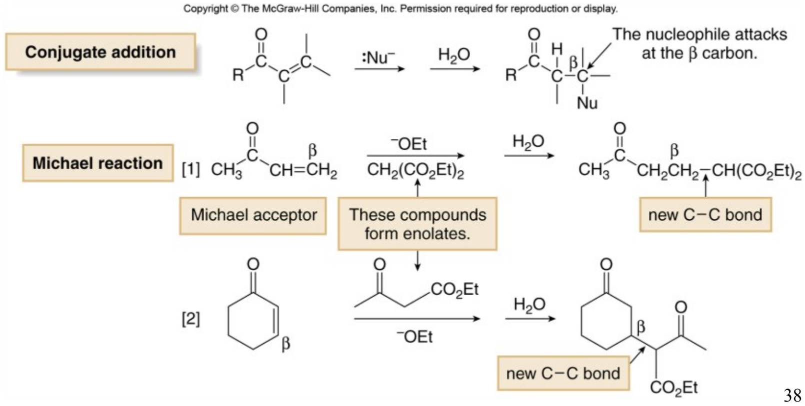
- Recall that α,β-unsaturated carbonyl compounds are resonance stabilized and have two electrophilic sites—the carbonyl carbon and the β carbon.

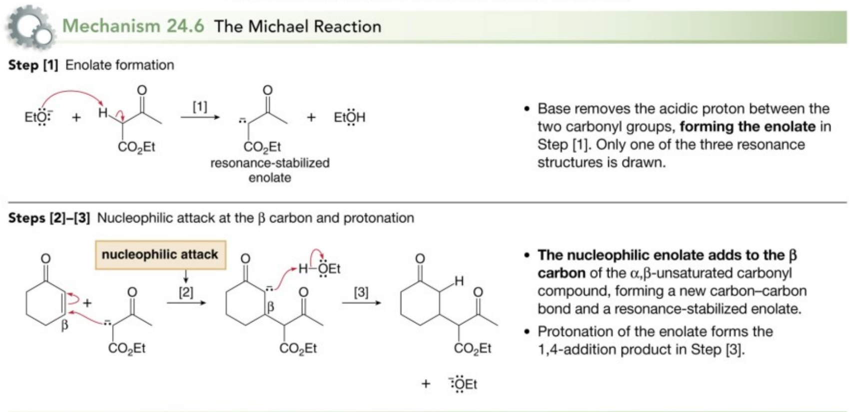


Michael Acceptors

- The Michael reaction involves the conjugate addition (1,4-addition) of a resonance-stabilized enolate to the β carbon of an α,β-unsaturated carbonyl system.

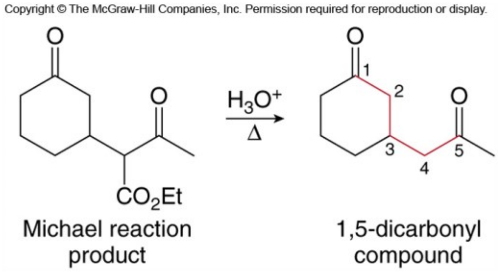
- The α,β-unsaturated carbonyl component is often called a **Michael acceptor**.





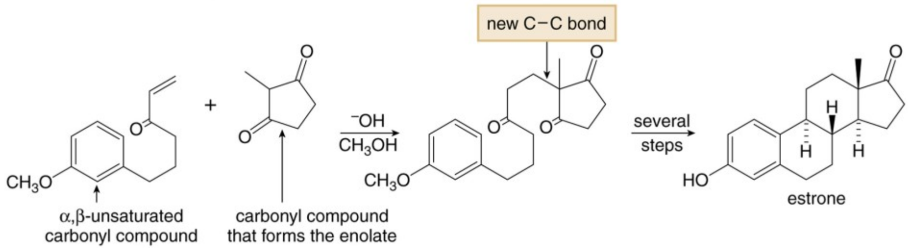
Michael Reaction Products

- When the product of a Michael reaction is also a β-keto ester, it can be hydrolyzed and decarboxylated by heating in aqueous acid.
- This forms a 1,5-dicarbonyl compound.
- 1,5-dicarbonyl compounds are starting materials for intramolecular aldol reactions.



Using the Michael Reaction

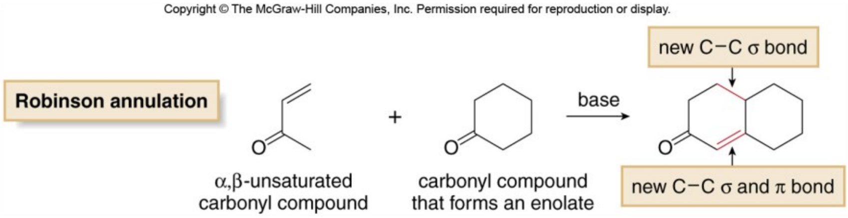
Figure 24.7
Using a Michael reaction in the synthesis of the steroid estrone



41

The Robinson Annulation

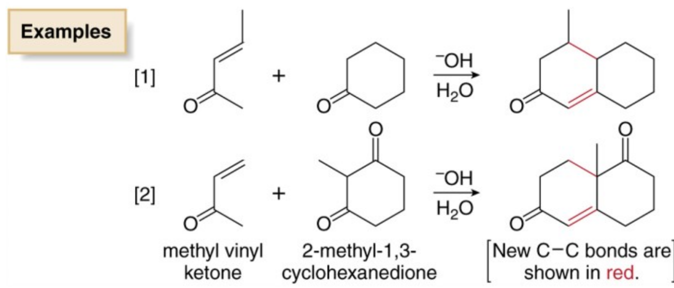
- The **Robinson annulation** is a ring-forming reaction that combines a Michael reaction with an intramolecular aldol reaction.
- The starting materials for a Robinson annulation are an α,β-unsaturated carbonyl compound and an enolate.

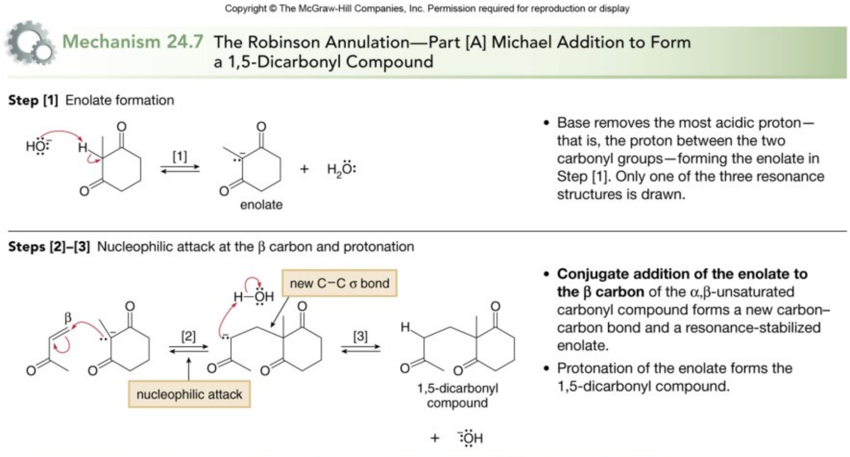


42

The Robinson Annulation

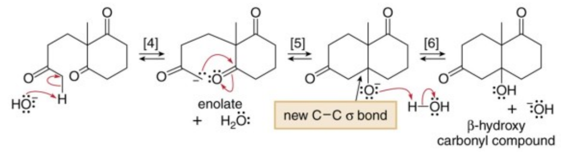
- **The Robinson annulation forms a six-membered ring and three new C–C bonds—two σ bonds and one π bond.**
- **The product contains an α,β-unsaturated ketone in a cyclohexane ring—that is, a 2-cyclohexenone.**
- **To generate the enolate component of the Robinson annulation, ^{-}OH in H_2O or ^{-}OEt in EtOH are typically used.**





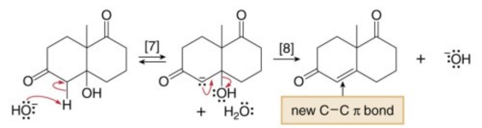
Mechanism 24.8 The Robinson Annulation—Part [B] Intramolecular Aldol Reaction to Form a 2-Cyclohexenone

Steps [4]–[6] Intramolecular aldol reaction to form a β-hydroxy ketone



- The **intramolecular aldol reaction** consists of three steps: [4] **enolate formation,** [5] **nucleophilic attack,** and [6] **protonation.** This forms another carbon–carbon σ bond and a β-hydroxy carbonyl compound (compare Section 24.4).

Steps [7]–[8] Dehydration to form the α,β-unsaturated ketone



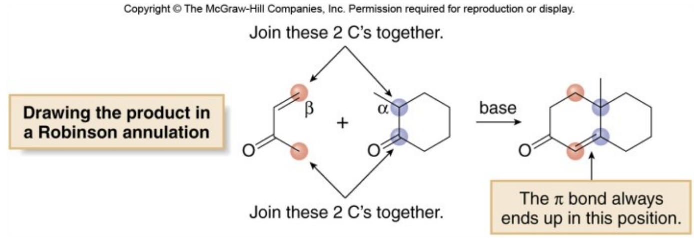
- Dehydration consists of two steps: **deprotonation** and **loss of ⁻OH** (Section 24.1B). This reaction forms the new π bond in the α,β-unsaturated ketone.

Drawing Products of Robinson Annulation

- **To draw the product of Robinson annulation without writing out the entire mechanism each time:**

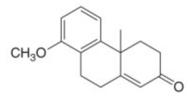
[1] Place the α carbon of the carbonyl compound that becomes the enolate next to the β carbon of the α,β-unsaturated carbonyl compound.

[2] Join the appropriate carbons together as shown. If you follow this method of drawing the starting materials, the double bond in the product always ends up in the same position of the six-membered ring.



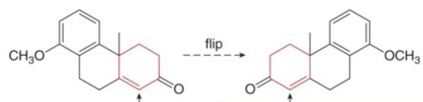
How To Synthesize a Compound Using the Robinson Annulation

Example What starting materials are needed to synthesize the following compound using a Robinson annulation?



Step [1] **Locate the 2-cyclohexenone ring and re-draw the target molecule if necessary.**

- To most easily determine the starting materials, always arrange the α,β-unsaturated carbonyl system in the same location. The target compound may have to be flipped or rotated, and you must be careful not to move any bonds to the wrong location during this process.



Synthesize this ring.

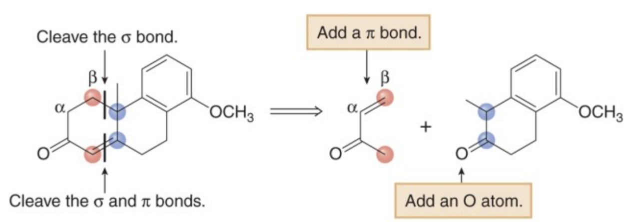
Arrange the C=O and C=C in the same positions as in previous examples of the Robinson annulation.

47

Synthesis Using the Robinson Annulation

Step [2] **Break the 2-cyclohexenone ring into two components.**

- Break the C = C. One half becomes the carbonyl group of the enolate component.
- Break the bond between the β carbon and the carbon to which it is bonded.



two components needed for the Robinson annulation

48