

Electrophilic carbonyl group reacts with nucleophiles.

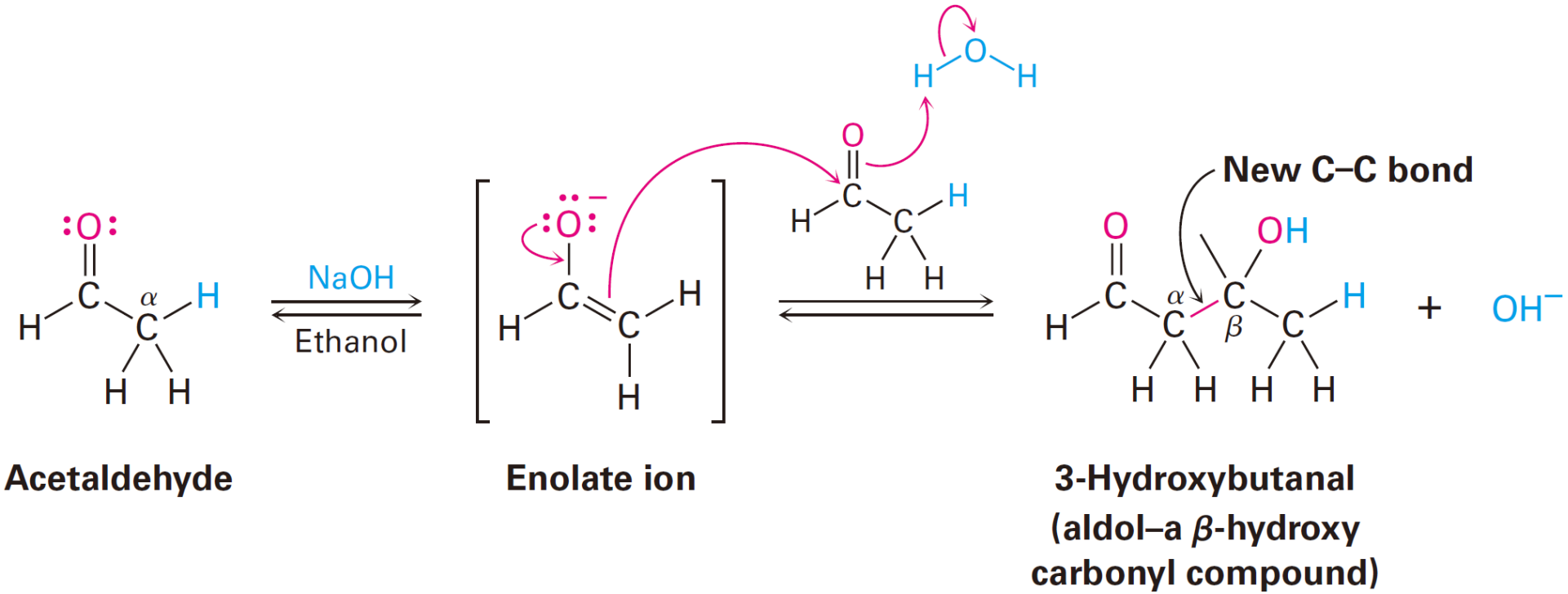
Nucleophilic enolate ion reacts with electrophiles.

23

羰基化合物的缩合反应

23.1 羟醛缩合 (Aldol condensation)

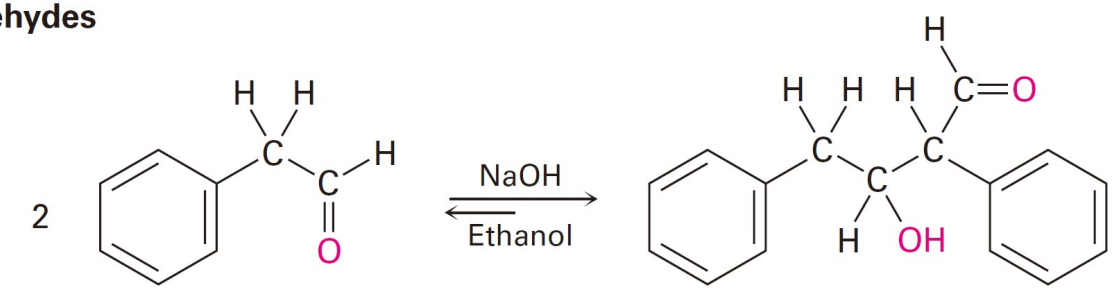
- 在碱的作用下，具有 alpha 氢的醛或者酮烯醇化，然后进攻另一分子的羰基，这样的反应叫羟醛缩合反应。



23.1 羟醛缩合 (Aldol condensation)

- 由于位阻和电性的原因，一般醛的反应活性比酮高。

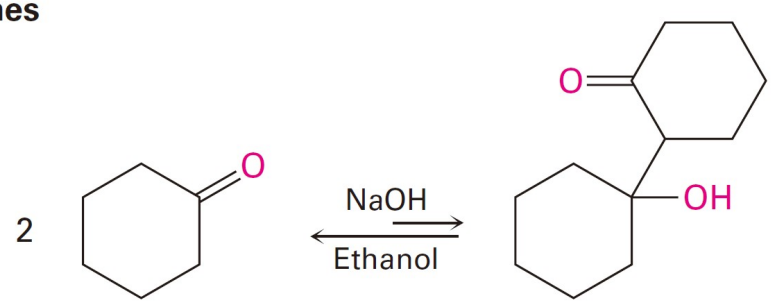
Aldehydes



Phenylacetaldehyde (10%)

(90%)

Ketones



Cyclohexanone (78%)

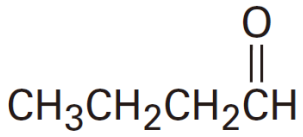
(22%)

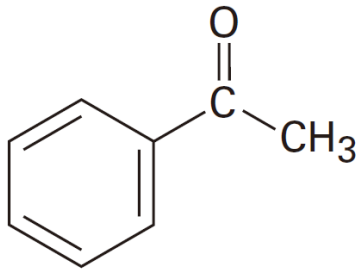
23.1 羟醛缩合 (Aldol condensation)

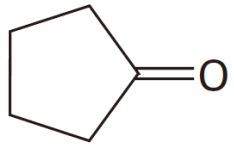
- 课堂练习

Problem 23.1

Predict the aldol reaction product of the following compounds:

(a) 

(b) 

(c) 

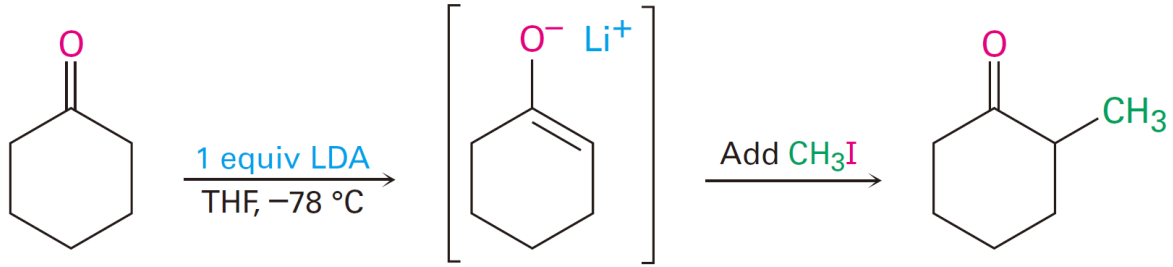
Problem 23.2

Using curved arrows to indicate the electron flow in each step, show how the base-catalyzed retro-aldol reaction of 4-hydroxy-4-methyl-2-pentanone takes place to yield 2 equivalents of acetone.

23.2 羟醛缩合与 alpha 取代反应

- Alpha 取代反应需要一当量强碱，将底物快速彻底地转化为烯醇式。这样就没有多余的底物来作为亲电试剂发生 Aldol 反应。

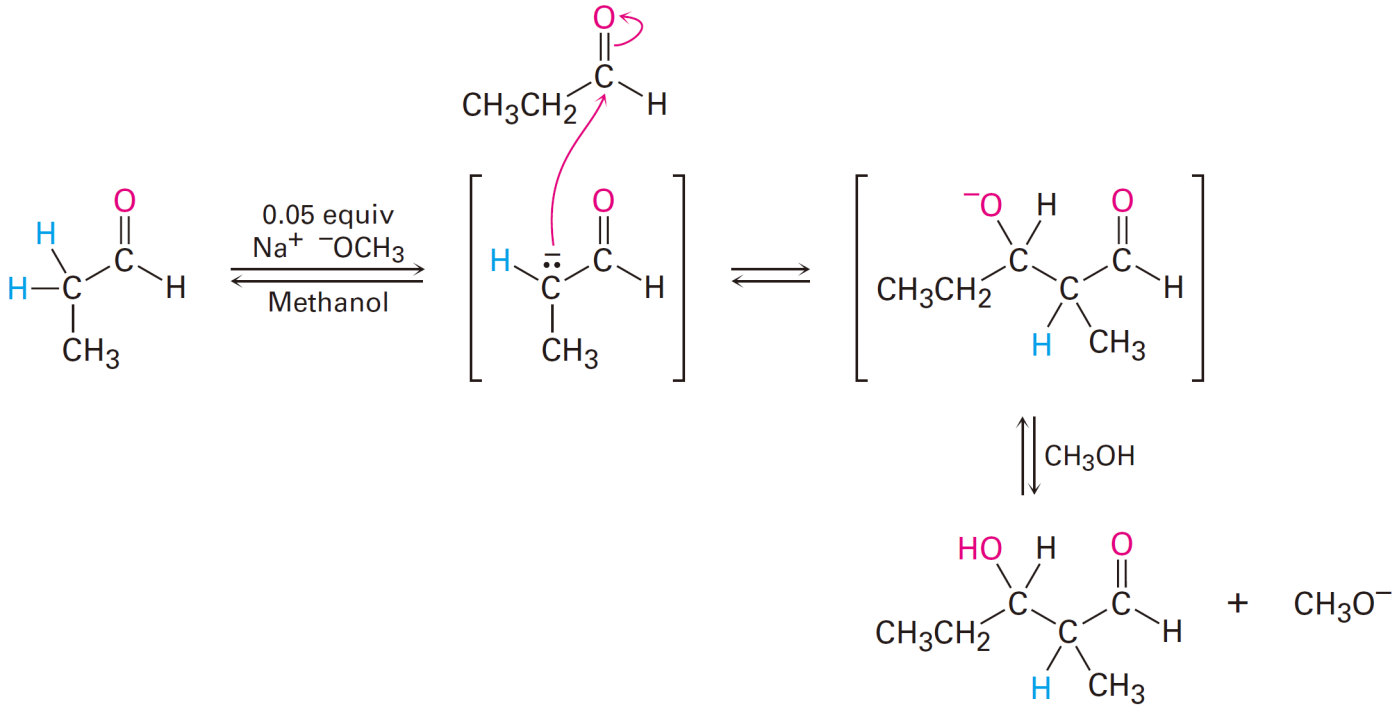
There is no simple answer to this question, but the exact experimental conditions usually have much to do with the result. Alpha-substitution reactions require a full equivalent of strong base and are normally carried out so that the carbonyl compound is rapidly and completely converted into its enolate ion at a low temperature. An electrophile is then added rapidly to ensure that the reactive enolate ion is quenched quickly. In a ketone alkylation reaction, for instance, we might use 1 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran solution at −78 °C. Rapid and complete generation of the ketone enolate ion would occur, and no unreacted ketone would be left so that no condensation reaction could take place. We would then immediately add an alkyl halide to complete the alkylation reaction.



23.2 羟醛缩合与 alpha 取代反应

- 而羟醛缩合反应需要催化量的相对较弱的碱，将一部分底物转化为烯醇式，然后进攻另一部分底物。

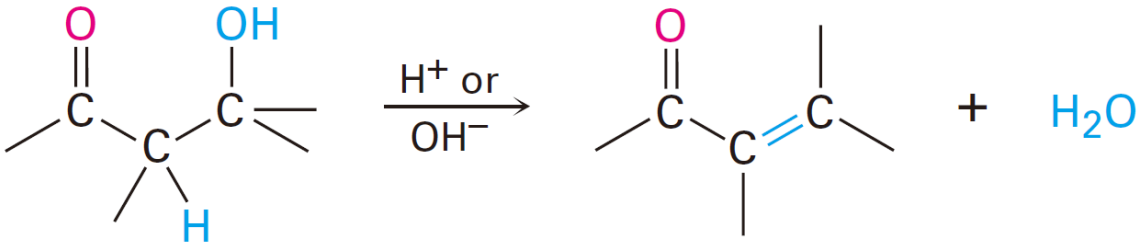
On the other hand, carbonyl condensation reactions require only a catalytic amount of a relatively weak base rather than a full equivalent so that a small amount of enolate ion is generated in the presence of unreacted carbonyl compound. Once a condensation has occurred, the basic catalyst is regenerated. To carry out an aldol reaction on propanal, for instance, we might dissolve the



23.3 Aldol 产物的失水

- Aldol 产物（beta-羟基醛或酮）很容易失水，得到 alpha,beta-不饱和醛酮化合物。

The β-hydroxy aldehydes or ketones formed in aldol reactions can be easily dehydrated to yield α,β-unsaturated products, or conjugated enones. In fact, it's this loss of water that gives the *condensation* reaction its name, because water condenses out of the reaction when the enone product forms.



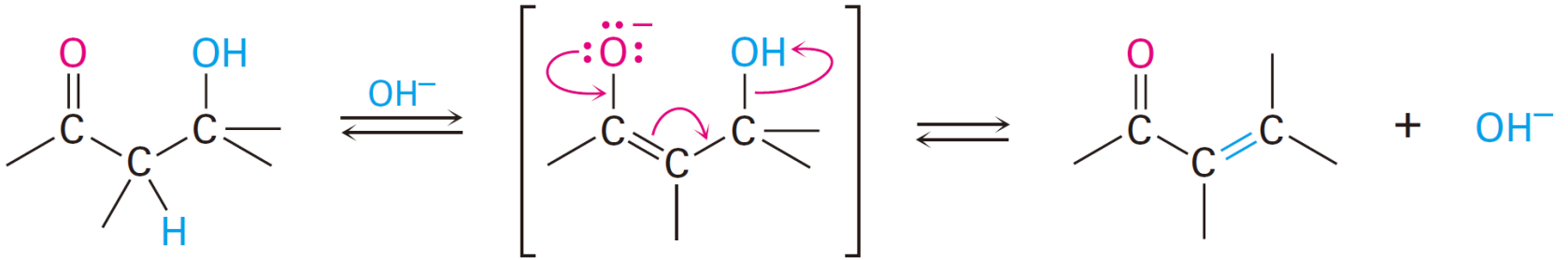
A β-hydroxy ketone or aldehyde

A conjugated enone

23.3 Aldol 产物的失水

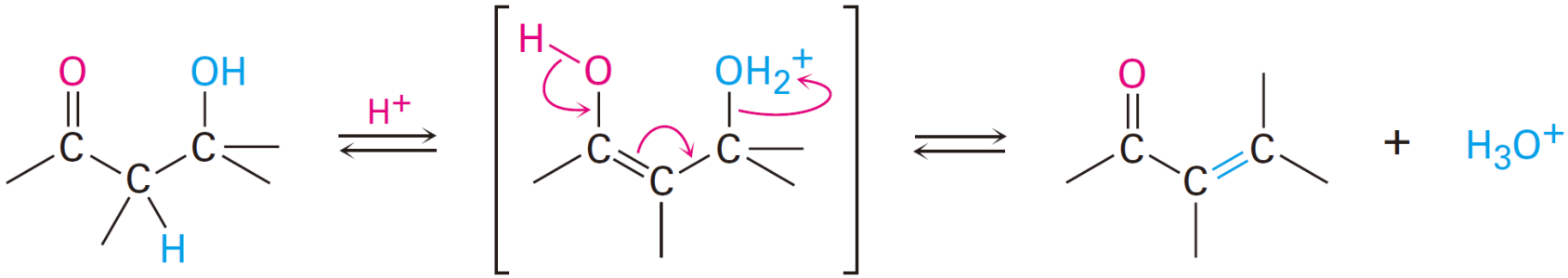
- 这一过程可以在酸性条件下进行，也可在碱性条件下进行。

Base-catalyzed



Enolate ion

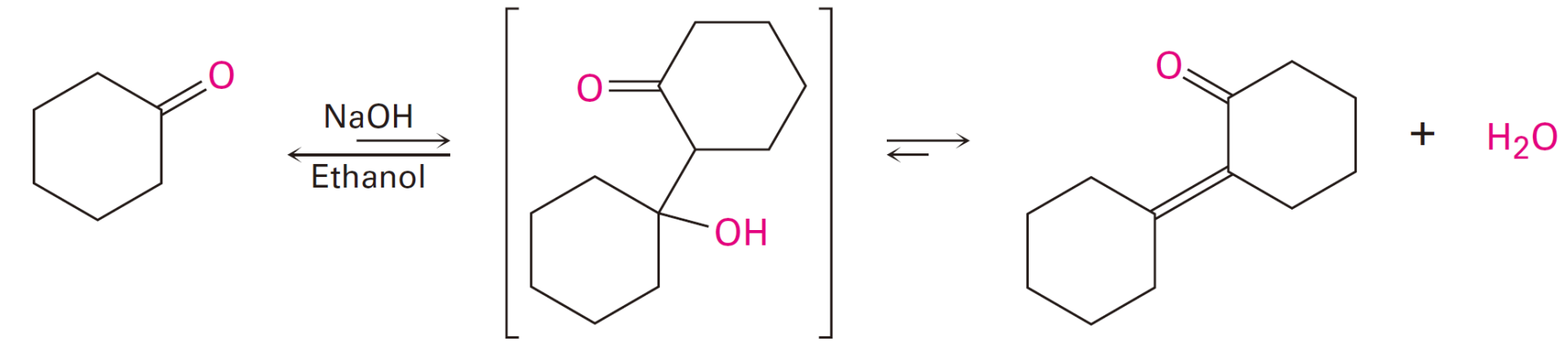
Acid-catalyzed



Enol

23.3 Aldol 产物的失水

- 有时虽然第一步羟醛缩合在平衡中不占优势，但接下来失水得到 alpha, beta- 不饱和羰基化合物容易发生，拉动平衡向右移动。



Cyclohexanone

Cyclohexylidenecyclohexanone (92%)

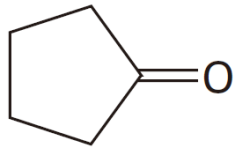
23.3 Aldol 产物的失水

- 课堂练习

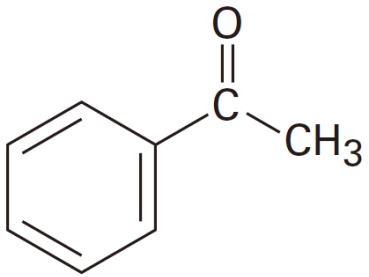
Problem 23.3

What enone product would you expect from aldol condensation of each of the following compounds?

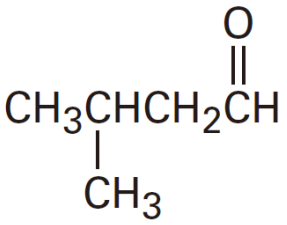
(a)



(b)



(c)

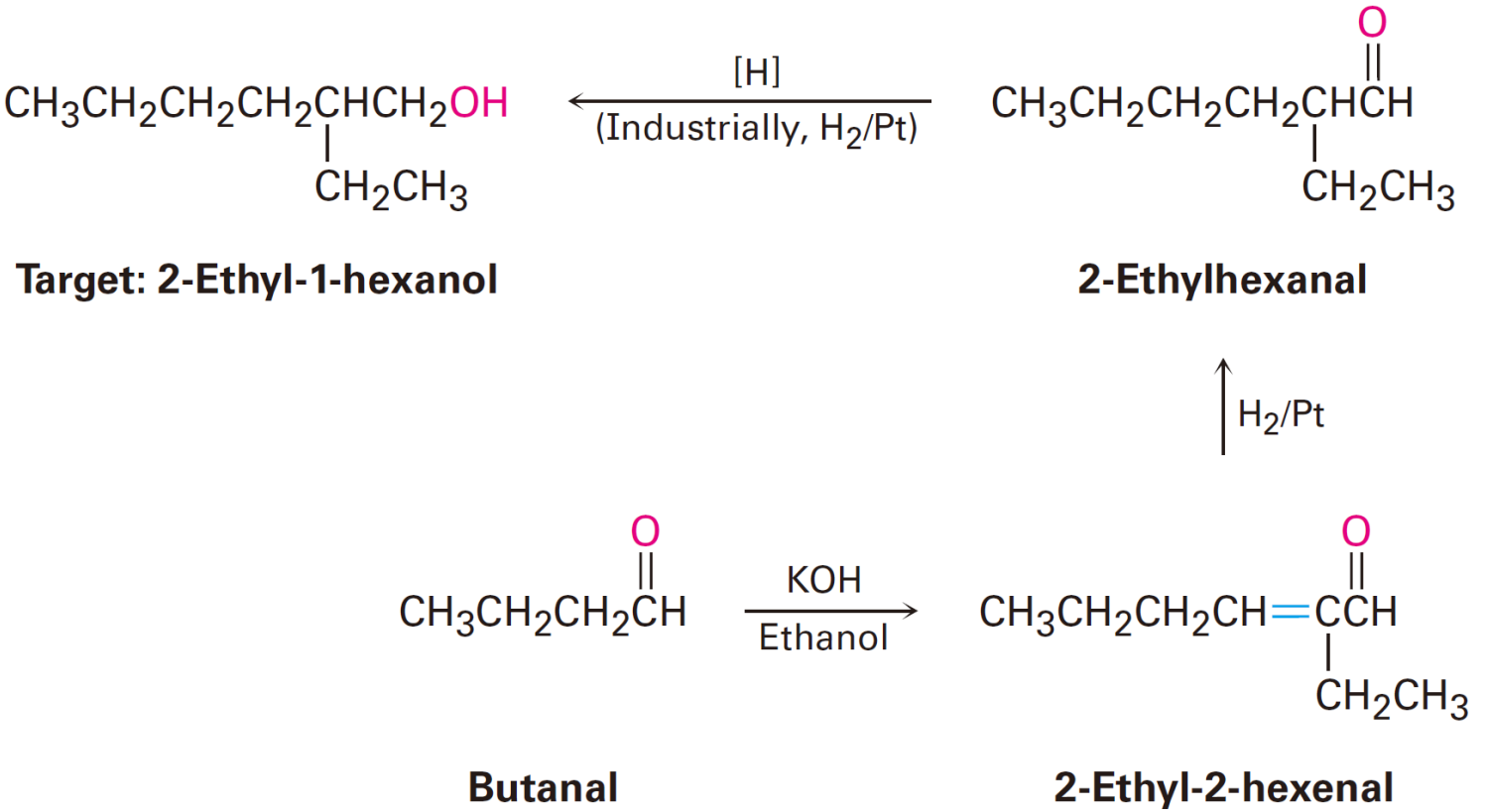


Problem 23.4

Aldol condensation of 3-methylcyclohexanone leads to a mixture of two enone products, not counting double-bond isomers. Draw them.

23.4 Aldol 反应的合成应用

- 虽然不是很直观，但确实一些化合物的工业制法是通过羟醛缩合作为主要反应来实现的。这里我们需要注意观察羰基（包括其一步转化得到的醇）的结构，如果在它的 alpha 位有取代基，那么可以考虑是否这个 C-C 键是由羟醛缩合反应得到



23.4 Aldol 反应的合成应用

- 课堂练习

Problem 23.5

Which of the following compounds are aldol condensation products? What is the aldehyde or ketone precursor of each?

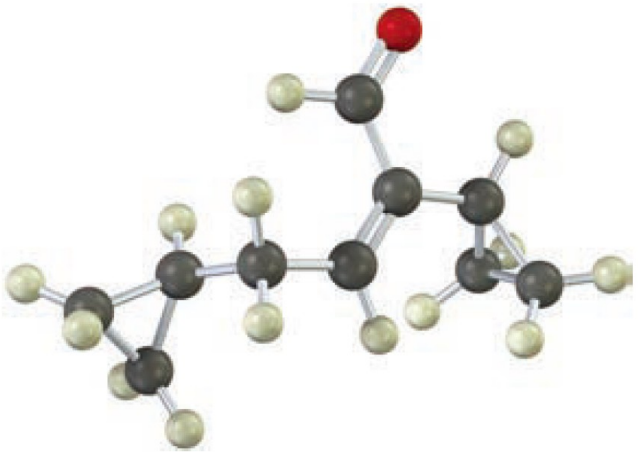
(a) 2-Hydroxy-2-methylpentanal **(b)** 5-Ethyl-4-methyl-4-hepten-3-one

Problem 23.6

1-Butanol is prepared commercially by a route that begins with an aldol reaction. Show the steps that are likely to be involved.

Problem 23.7

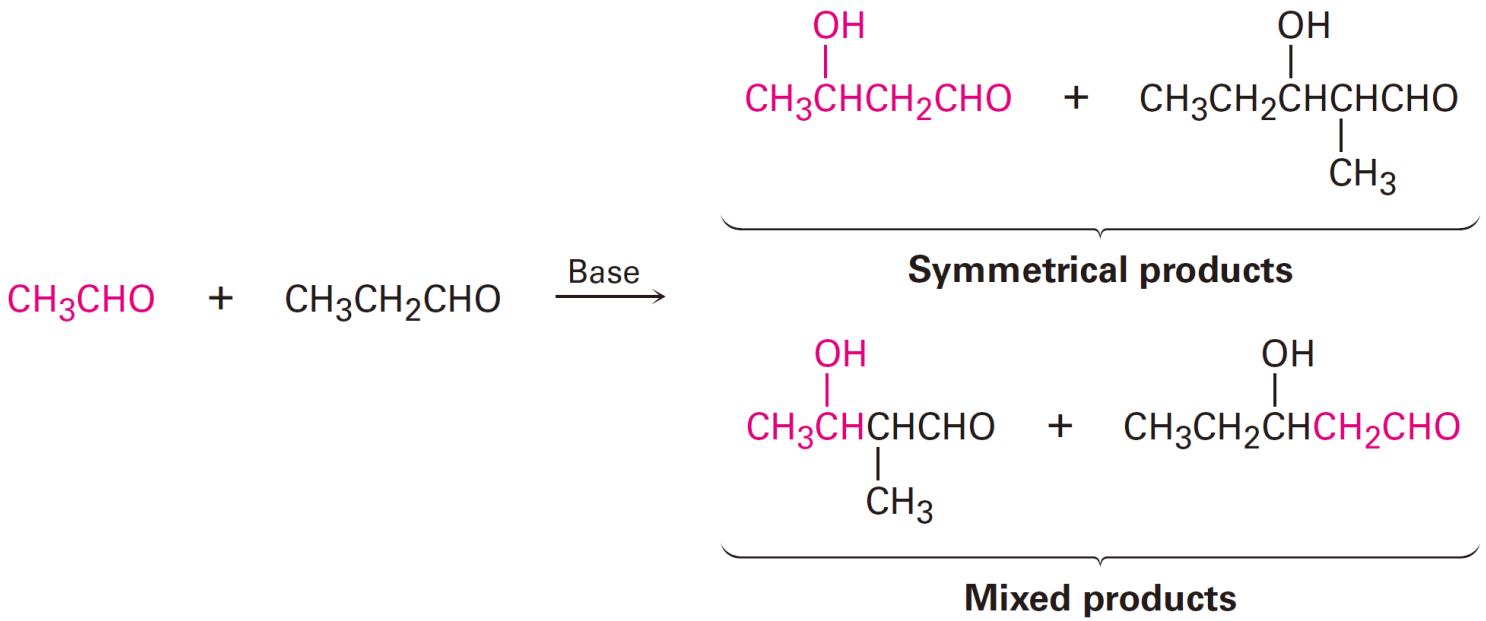
Show how you would synthesize the following compound using an aldol reaction:



23.5 混合羟醛缩合反应

- 如果两个相似的醛发生 Aldol 反应，理论上可以得到四种产物。

In general, a mixed aldol reaction between two similar aldehyde or ketone partners leads to a mixture of four possible products. For example, base treatment of a mixture of acetaldehyde and propanal gives a complex product mixture containing two "symmetrical" aldol products and two "mixed" aldol products. Clearly, such a reaction is of no practical value.



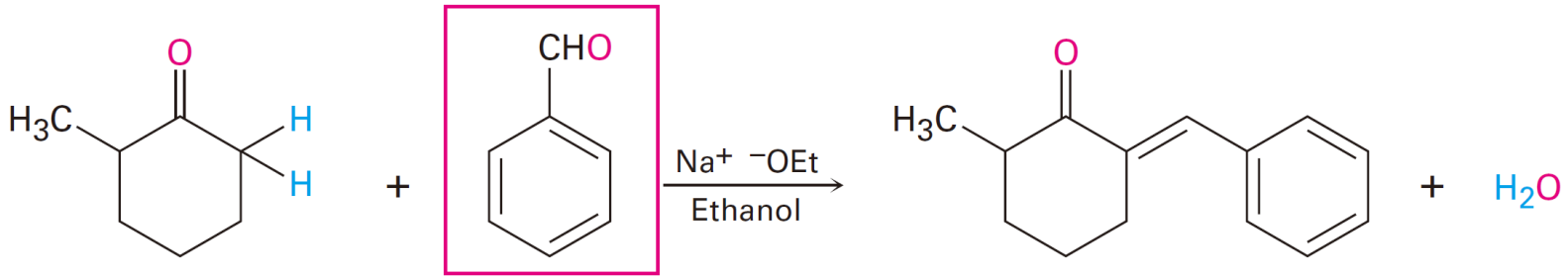
23.5 混合羟醛缩合反应

- 那如何得到单一产物呢？办法之一是使用一个没有 alpha 氢的羰基化合物，它只能作为亲电试剂被进攻 (acceptor)。

  - If one of the carbonyl partners contains no α hydrogens, and thus can't form an enolate ion to become a donor, but does contain an unhindered carbonyl group and so is a good acceptor of nucleophiles, then a mixed aldol reaction is likely to be successful. This is the case, for instance, when either benzaldehyde or formaldehyde is used as one of the carbonyl partners.

    Neither benzaldehyde nor formaldehyde can form an enolate ion to add to another partner, yet both compounds have an unhindered carbonyl group. The ketone 2-methylcyclohexanone, for instance, gives the mixed aldol product on reaction with benzaldehyde.

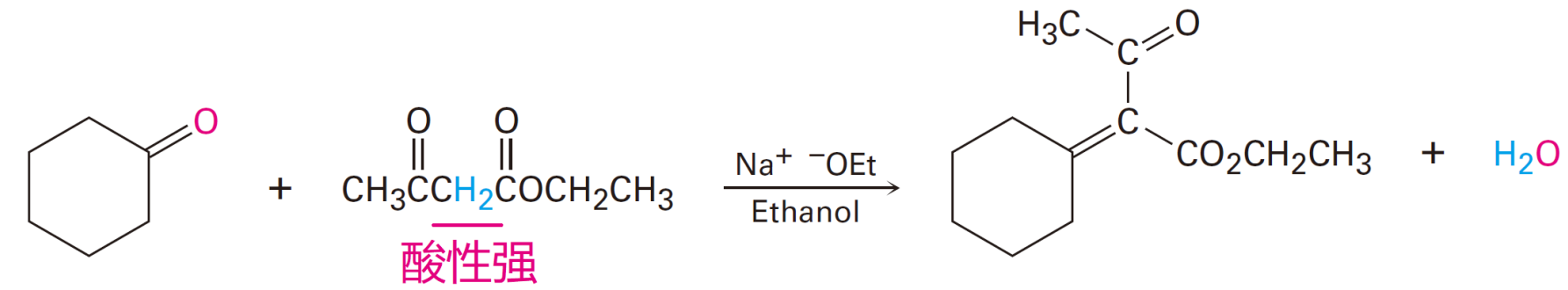
没有alpha氢



2-Methylcyclohexanone (donor) **Benzaldehyde (acceptor)** **78%**

23.5 混合羟醛缩合反应

- 另一方面，也可以利用酸性的差异，酸性强的底物首先会被转化为烯醇式，进而进攻另一个组分。
  - If one of the carbonyl partners is much more acidic than the other and so is transformed into its enolate ion in preference to the other, then a mixed aldol reaction is likely to be successful. Ethyl acetoacetate, for instance, is completely converted into its enolate ion in preference to enolate ion formation from monocarbonyl partners. Thus, aldol condensations of monoketones with ethyl acetoacetate occur preferentially to give the mixed product.



Cyclohexanone (acceptor) **Ethyl acetoacetate (donor)** **80%**

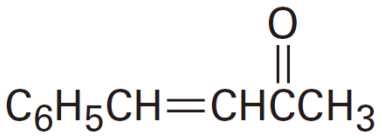
23.5 混合羟醛缩合反应

- 课堂练习

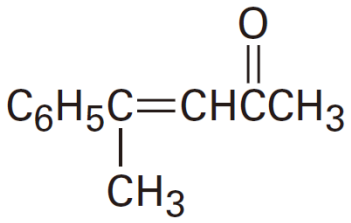
Problem 23.8

Which of the following compounds can probably be prepared by a mixed aldol reaction? Show the reactants you would use in each case.

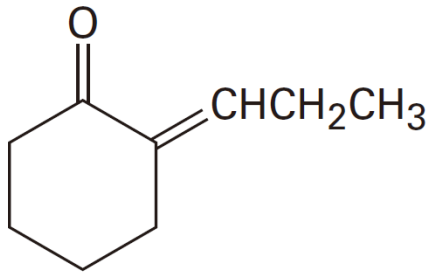
(a)



(b)

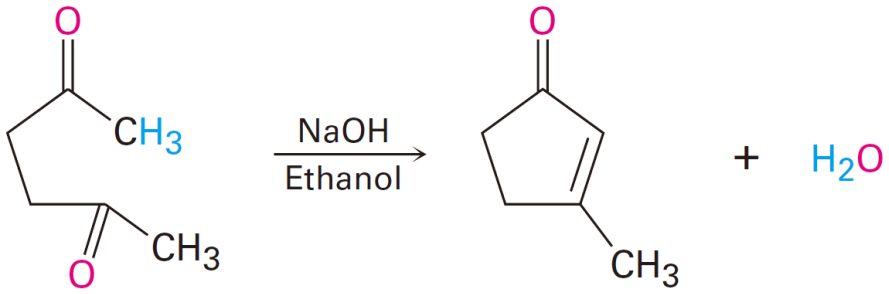


(c)

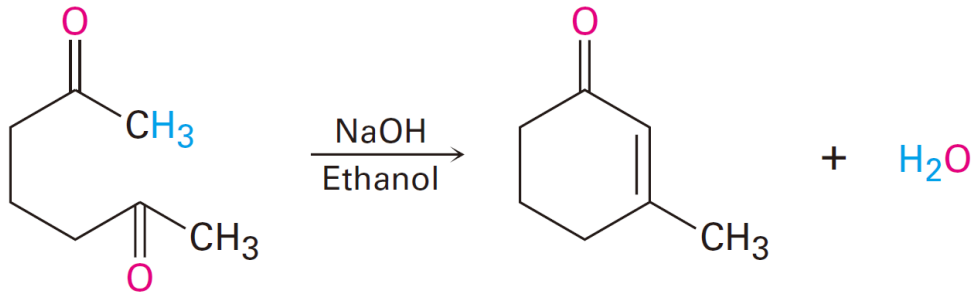


23.6 分子内的羟醛缩合反应

- 这一反应对于得到环状的 alpha, beta- 不饱和羰基化合物尤为有效。



2,5-Hexanedione (a 1,4-diketone) **3-Methyl-2-cyclopentenone**

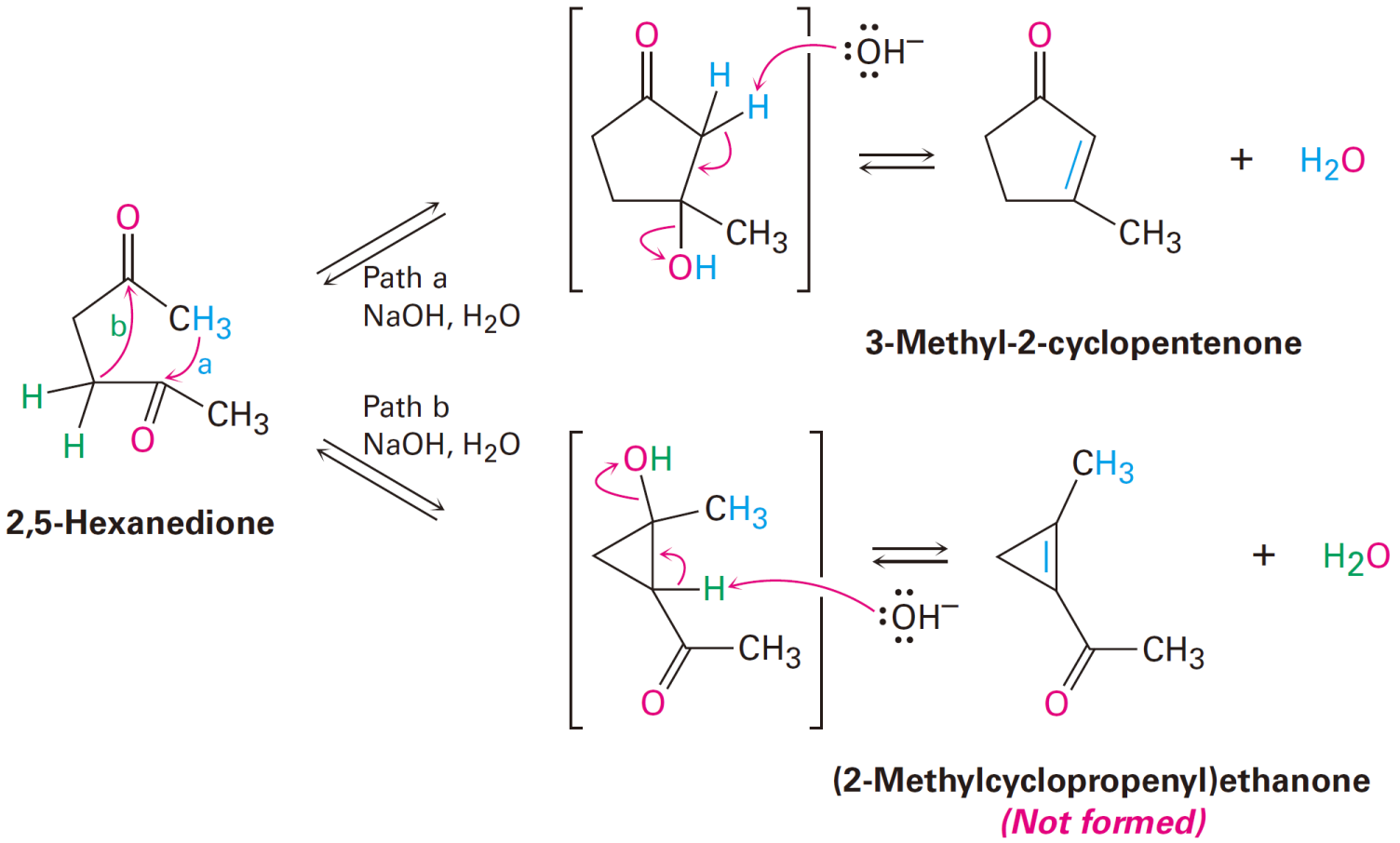


2,6-Heptanedione (a 1,5-diketone) **3-Methyl-2-cyclohexenone**

23.6 分子内的羟醛缩合反应

- 五元环张力小，容易生成。

Figure 23.3 Intramolecular aldol reaction of 2,5-hexanedione yields 3-methyl-2-cyclopentenone rather than the alternative cyclopropene.



23.6 分子内的羟醛缩合反应

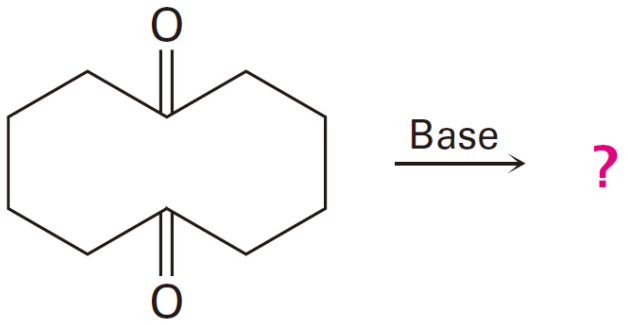
- 课堂练习

Problem 23.9

Treatment of a 1,3-diketone such as 2,4-pentanedione with base does not give an aldol condensation product. Explain.

Problem 23.10

What product would you expect to obtain from base treatment of 1,6-cyclodecanedione?

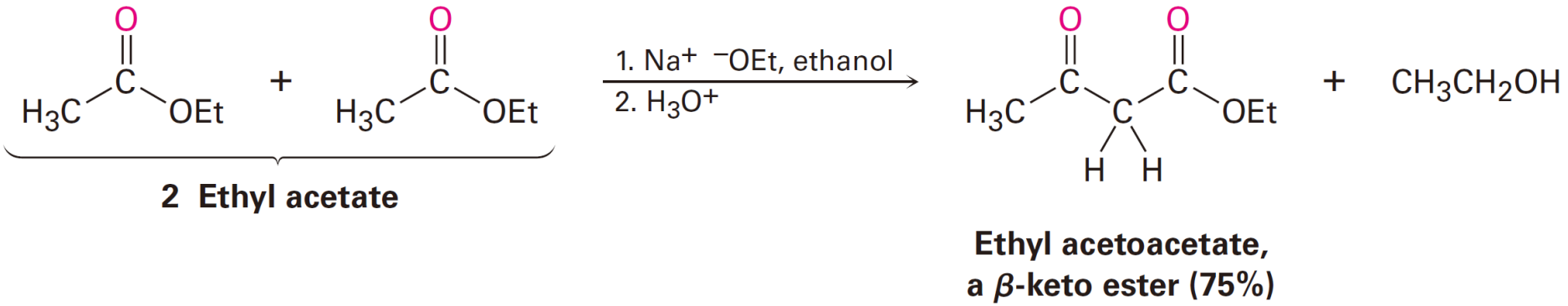


1,6-Cyclodecanedione

23.7 克莱森缩合反应

- 两个酯发生类似 Aldol 缩合的反应叫做克莱森缩合。注意观察，产物和 Aldol 缩合有何不同？

Esters, like aldehydes and ketones, are weakly acidic. When an ester with an α hydrogen is treated with 1 equivalent of a base such as sodium ethoxide, a reversible carbonyl condensation reaction occurs to yield a β-keto ester. For instance, ethyl acetate yields ethyl acetoacetate on base treatment. This reaction between two ester molecules is known as the **Claisen condensation reaction**. (We'll use ethyl esters, abbreviated "Et," for consistency, but other esters will also work.)



2 Ethyl acetate

Ethyl acetoacetate, a β-keto ester (75%)

23.7 克莱森缩合反应

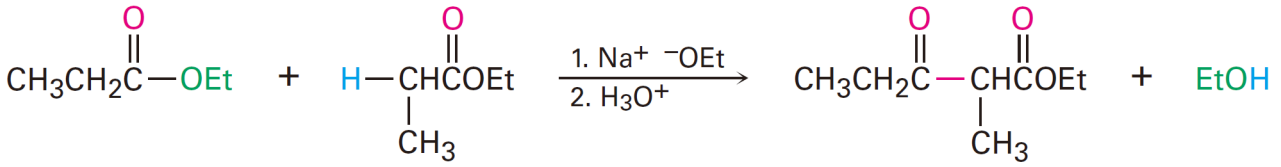
- 练习

What product would you obtain from Claisen condensation of ethyl propanoate?

Strategy

The Claisen condensation of an ester results in loss of one molecule of alcohol and formation of a product in which an acyl group of one reactant bonds to the α carbon of the second reactant. The product is a β-keto ester.

Solution



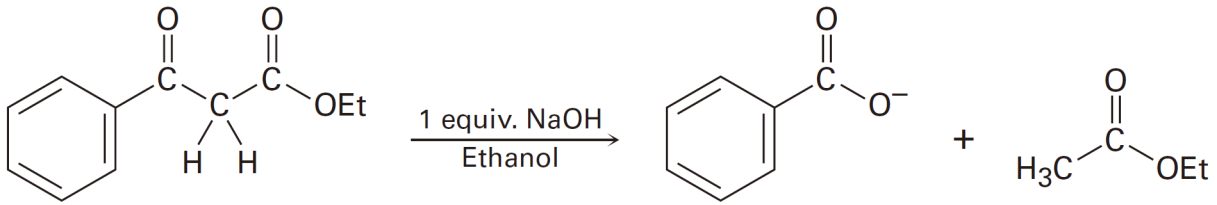
2 Ethyl propanoate **Ethyl 2-methyl-3-oxopentanoate**

Problem 23.11

Show the products you would expect to obtain by Claisen condensation of the following esters:
(a) $(CH_3)_2CHCH_2CO_2Et$ **(b)** Ethyl phenylacetate **(c)** Ethyl cyclohexylacetate

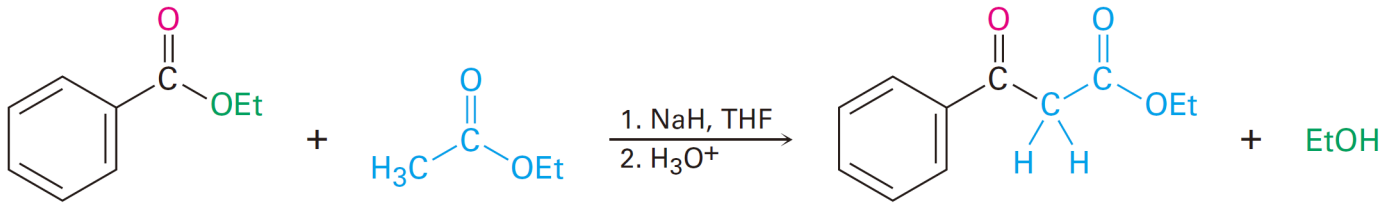
Problem 23.12

As shown in Figure 23.4, the Claisen reaction is reversible. That is, a β-keto ester can be cleaved by base into two fragments. Using curved arrows to indicate electron flow, show the mechanism by which this cleavage occurs.



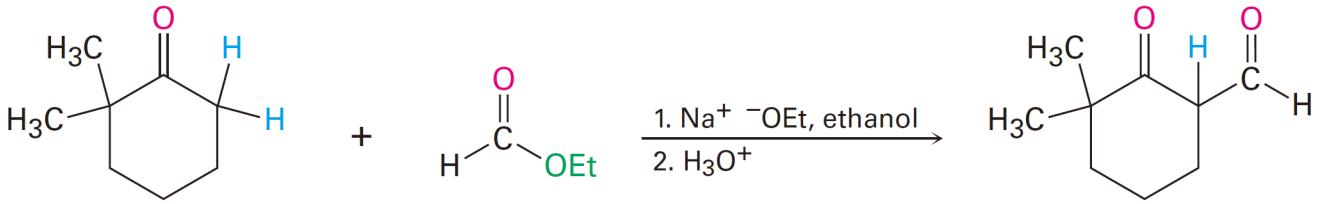
23.8 混合克莱森缩合反应

- 混合的克莱森缩合。同样，如果不想得到混合物，最好其中一个酯没有 alpha 氢，不能被烯醇化。



Ethyl benzoate (acceptor) **Ethyl acetate (donor)** **Ethyl benzoylacetate**

Mixed Claisen-like reactions can also be carried out between an ester and a ketone, resulting in the synthesis of a β-diketone. The reaction works best when the ester component has no α hydrogens and thus can't act as the nucleophilic donor. For example, ethyl formate gives high yields in mixed Claisen condensations with ketones.



2,2-Dimethylcyclohexanone (donor) **Ethyl formate (acceptor)** **A β-keto aldehyde (91%)**

23.8 混合克莱森缩合反应

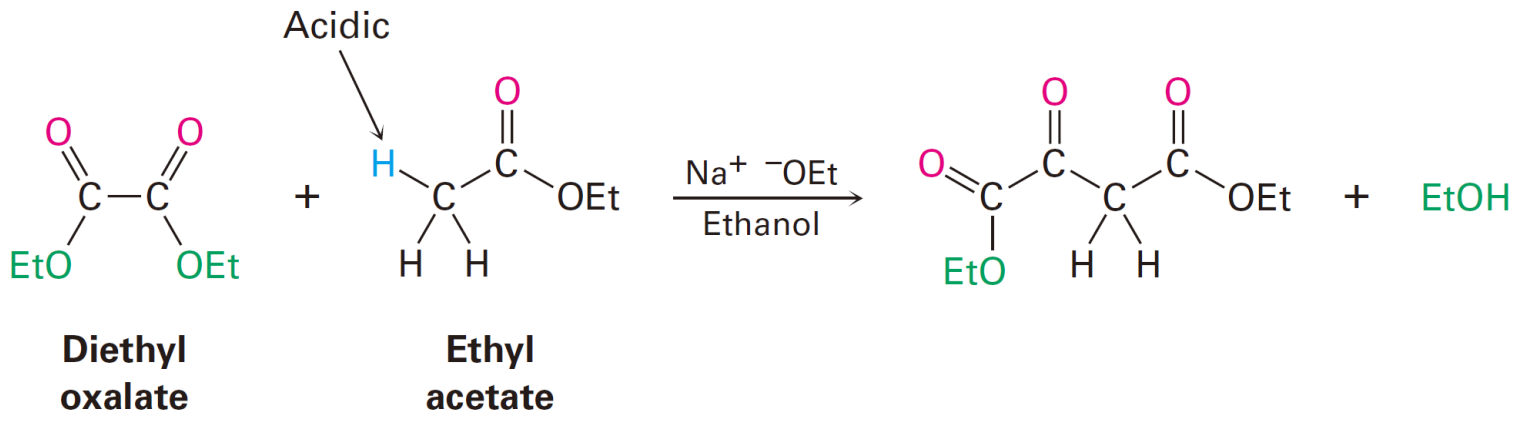
- 使用草酸酯作为亲电试剂，因为草酸酯就没有 alpha 氢。

Diethyl oxalate, $(CO_2Et)_2$, often gives high yields in mixed Claisen reactions. What product would you expect to obtain from a mixed Claisen reaction of ethyl acetate with diethyl oxalate?

Strategy

A mixed Claisen reaction is effective when only one of the two partners has an acidic α hydrogen atom. In the present case, ethyl acetate can be converted into its enolate ion, but diethyl oxalate cannot. Thus, ethyl acetate acts as the donor and diethyl oxalate as the acceptor.

Solution



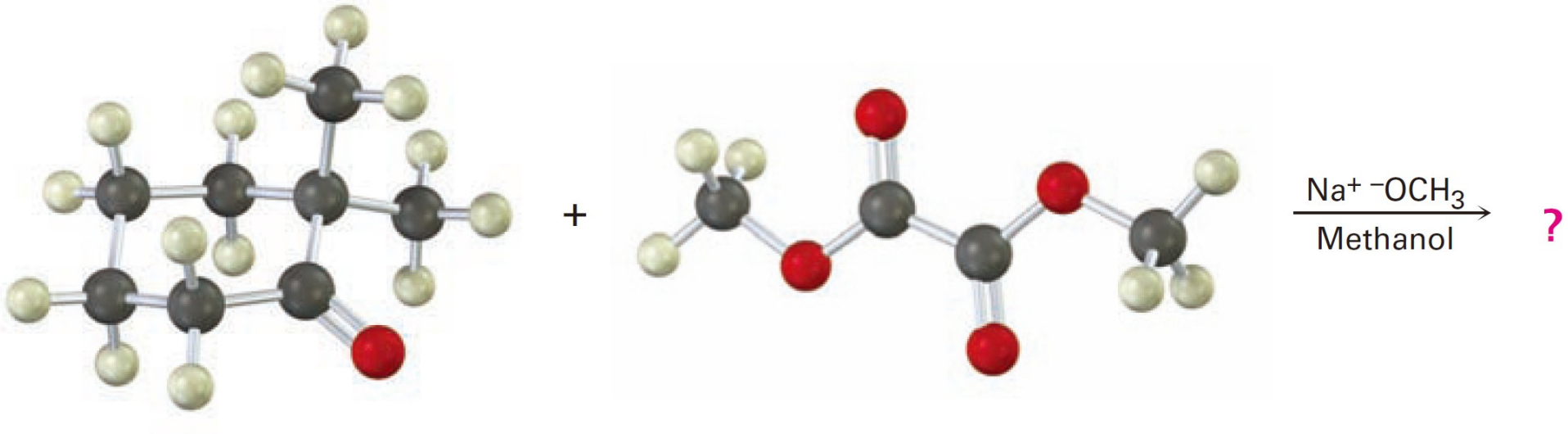
Diethyl oxalate **Ethyl acetate**

23.8 混合克莱森缩合反应

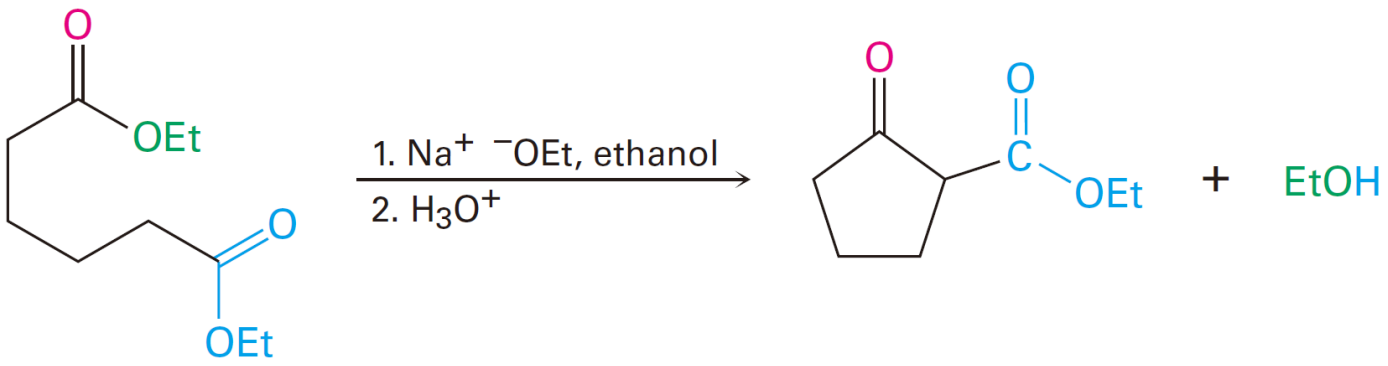
- 练习

Problem 23.13

What product would you expect from the following mixed Claisen-like reaction?

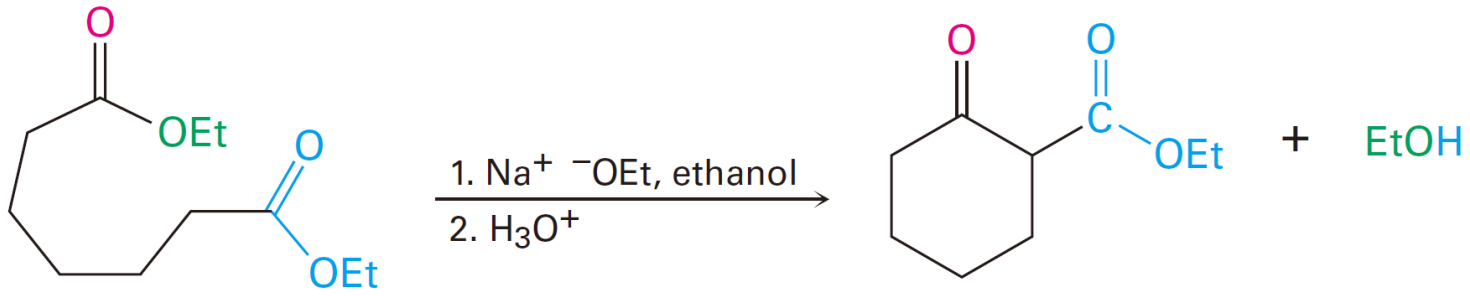


23.9 分子内克莱森缩合：狄克曼环化 (Dieckmann)



Diethyl hexanedioate
(a 1,6-diester)

Ethyl 2-oxocyclopentanecarboxylate
(82%)

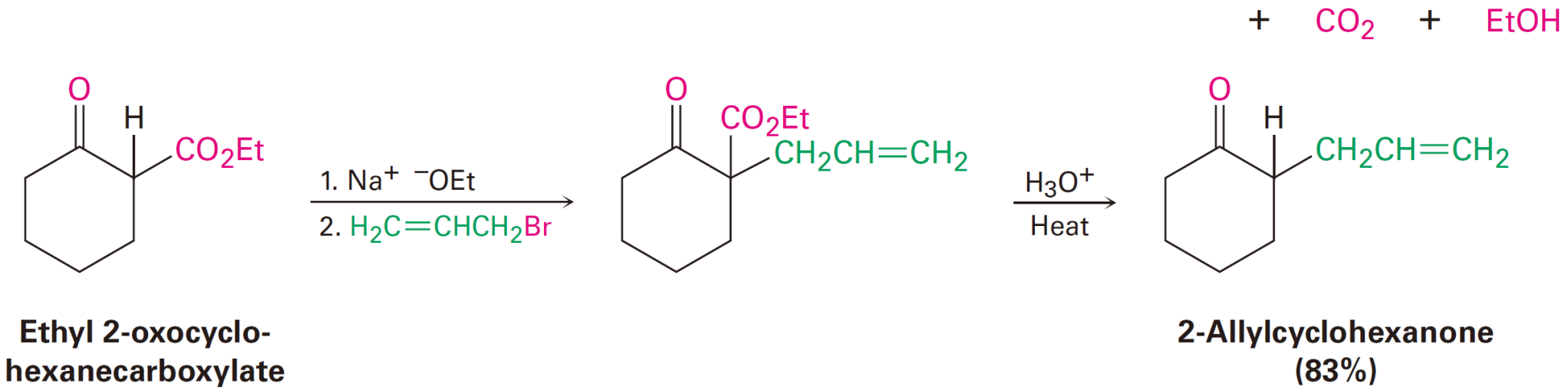


Diethyl heptanedioate
(a 1,7-diester)

Ethyl 2-oxocyclohexanecarboxylate

23.9 分子内克莱森缩合：狄克曼环化

- 合成应用



Ethyl 2-oxocyclo-hexanecarboxylate

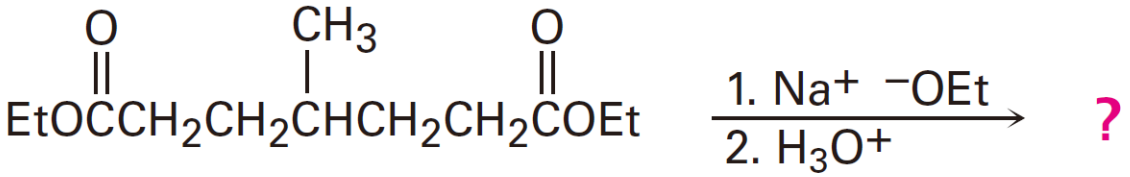
2-Allylcyclohexanone (83%)

23.9 分子内克莱森缩合：狄克曼环化

- 练习

Problem 23.14

What product would you expect from the following reaction?

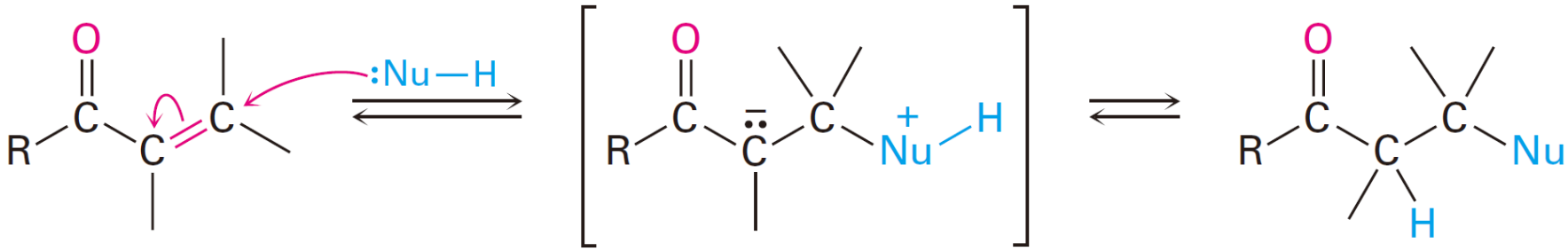


Problem 23.15

Dieckmann cyclization of diethyl 3-methylheptanedioate gives a mixture of two β-keto ester products. What are their structures, and why is a mixture formed?

23.10 迈克尔共轭加成

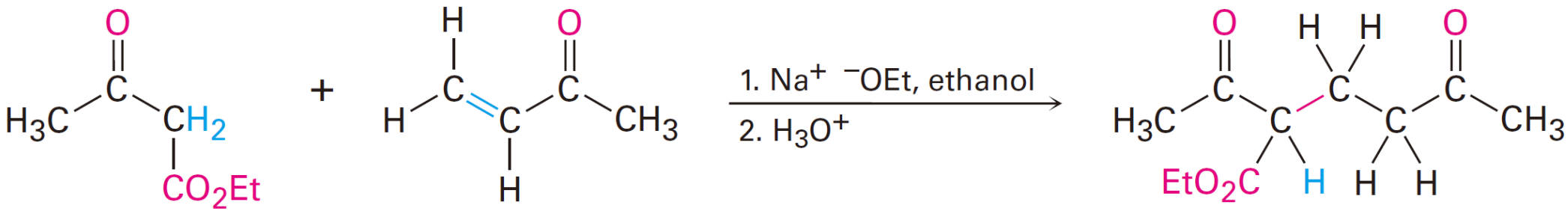
- 烯醇对 alpha, beta- 不饱和羰基化合物进行 1, 4- 加成叫迈尔克共轭加成



Conjugate addition product

Exactly the same kind of conjugate addition can occur when a nucleophilic enolate ion reacts with an α,β-unsaturated carbonyl compound—a process known as the **Michael reaction**.

23.10 迈克尔共轭加成



Ethyl acetoacetate

3-Buten-2-one

23.10 迈克尔共轭加成

- 受体是接受亲核进攻的底物，供体是亲核试剂。

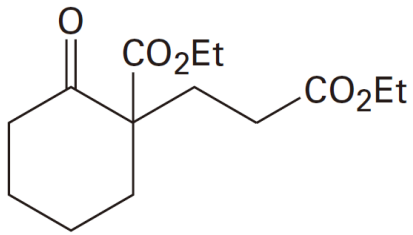
Table 23.1 Some Michael Acceptors and Michael Donors

Michael acceptors		Michael donors	
$H_2C{=}CHCH{=}O$	Propenal	$RCCH_2CR'$ (O, O)	β-Diketone
$H_2C{=}CHCCH_3$ (O)	3-Buten-2-one	$RCCH_2COEt$ (O, O)	β-Keto ester
$H_2C{=}CHCOEt$ (O)	Ethyl propenoate	$EtOCCH_2COEt$ (O, O)	Diethyl malonate
$H_2C{=}CHCNH_2$ (O)	Propenamide	$RCCH_2C{\equiv}N$ (O)	β-Keto nitrile
$H_2C{=}CHC{\equiv}N$	Propenenitrile	RCH_2NO_2	Nitro compound
$H_2C{=}CH(NO_2)$	Nitroethylene	大部分是(类)双羰化合物	

23.10 迈克尔共轭加成

- 例题

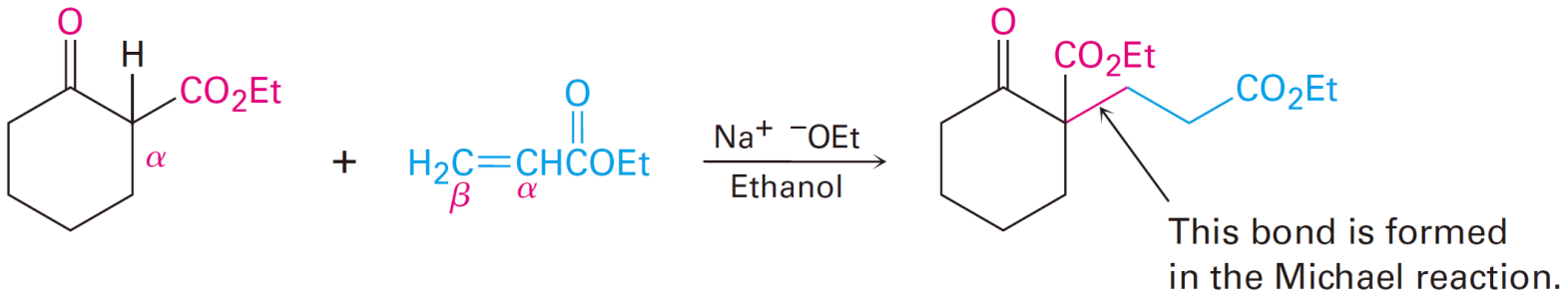
How might you obtain the following compound using a Michael reaction?



Strategy

A Michael reaction involves the conjugate addition of a stable enolate ion donor to an α,β-unsaturated carbonyl acceptor, yielding a 1,5-dicarbonyl product. Usually, the stable enolate ion is derived from a β-diketone, β-keto ester, malonic ester, or similar compound. The C—C bond made in the conjugate addition step is the one between the α carbon of the acidic donor and the β carbon of the unsaturated acceptor.

Solution



23.10 迈克尔共轭加成

- 练习

Problem 23.16

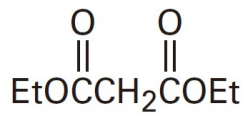
What product would you obtain from a base-catalyzed Michael reaction of 2,4-pentanedione with each of the following α,β-unsaturated acceptors?

(a) 2-Cyclohexenone **(b)** Propenenitrile **(c)** Ethyl 2-butenoate

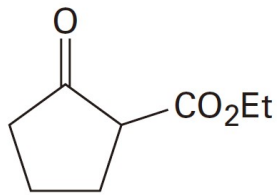
Problem 23.17

What product would you obtain from a base-catalyzed Michael reaction of 3-buten-2-one with each of the following nucleophilic donors?

(a)

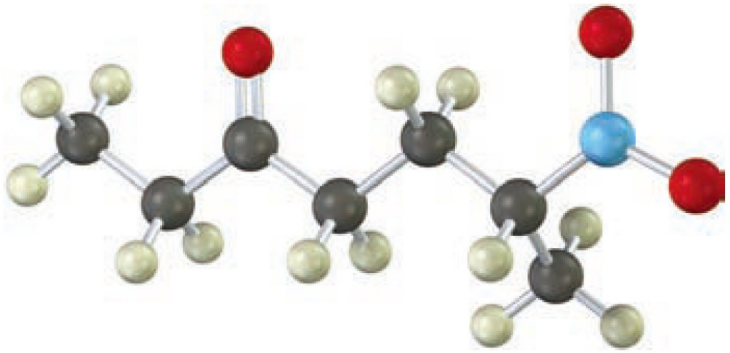


(b)



Problem 23.18

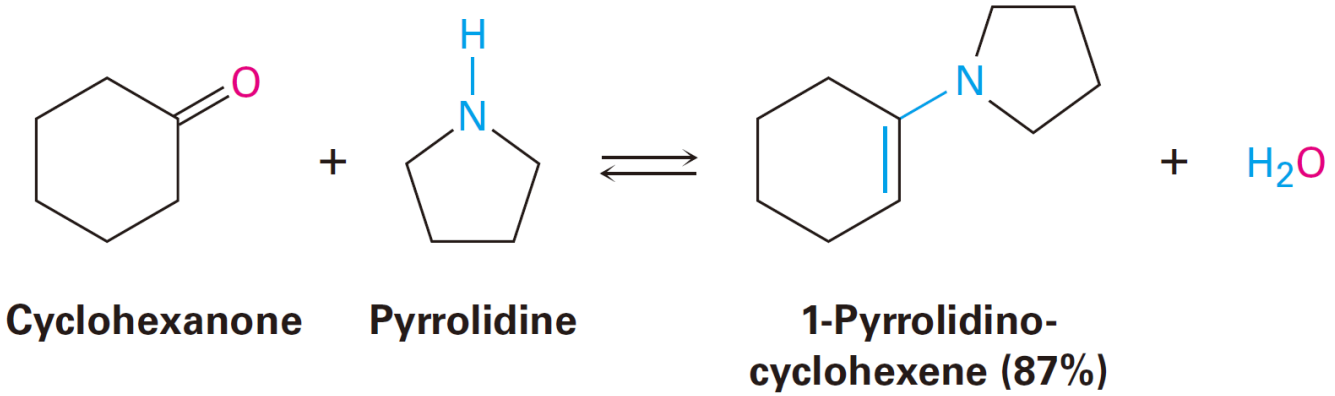
How would you prepare the following compound using a Michael reaction?



23.11 烯胺参与的缩合反应： Stork 烯胺策略

- 回顾：二级胺和醛酮反应得到烯胺。

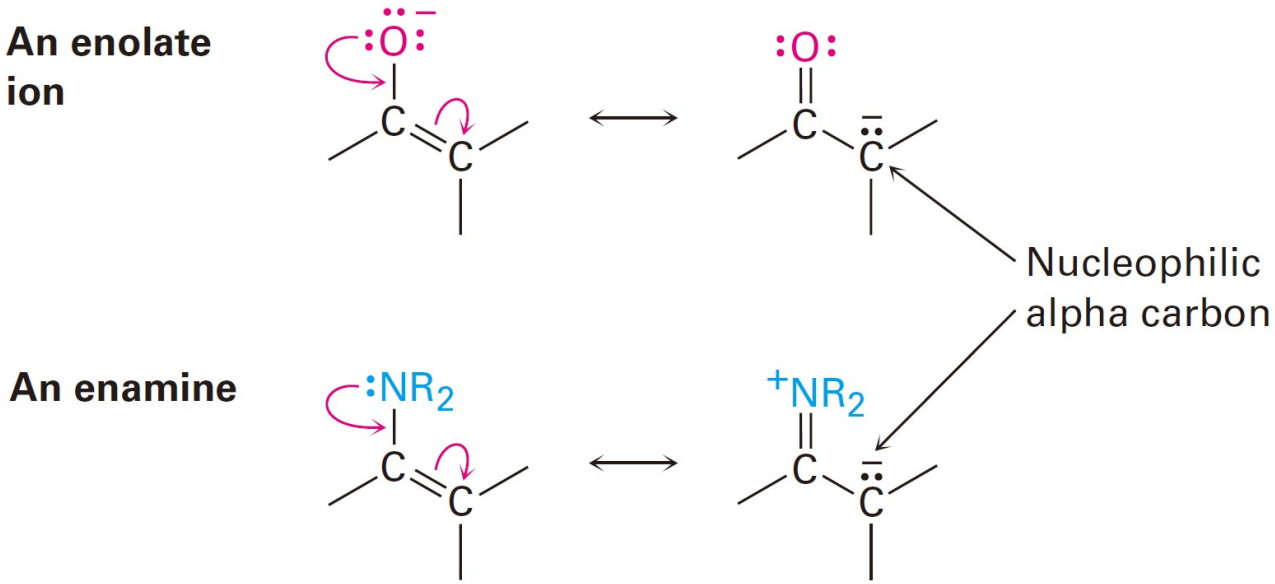
In addition to enolate ions, other kinds of carbon nucleophiles also add to α,β-unsaturated acceptors in Michael-like reactions. Among the most important and useful of such nucleophiles, particularly in biological chemistry, are *enamines*, which are readily prepared by reaction between a ketone and a secondary amine **(Section 19.8)**. For example:

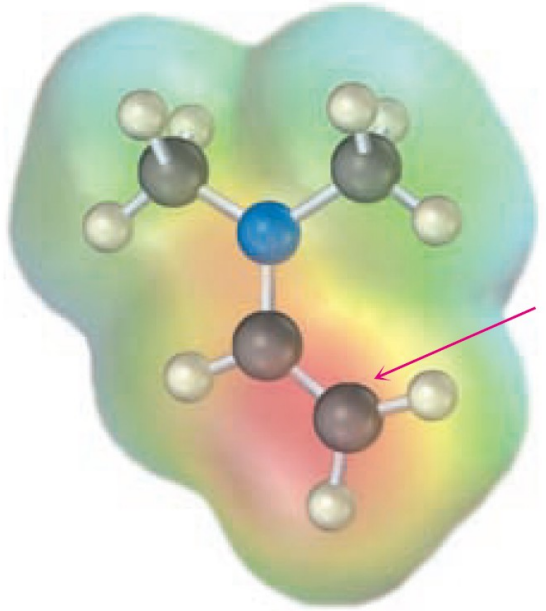


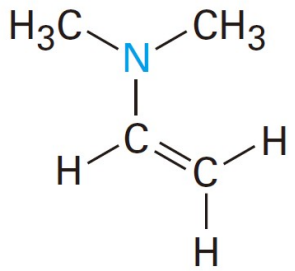
Cyclohexanone **Pyrrolidine** **1-Pyrrolidino-cyclohexene (87%)**

23.11 烯胺参与的缩合反应： Stork 烯胺策略

- 和烯醇式类似，烯胺也是在 alpha 位有碳负性质，可以作为亲核试剂。

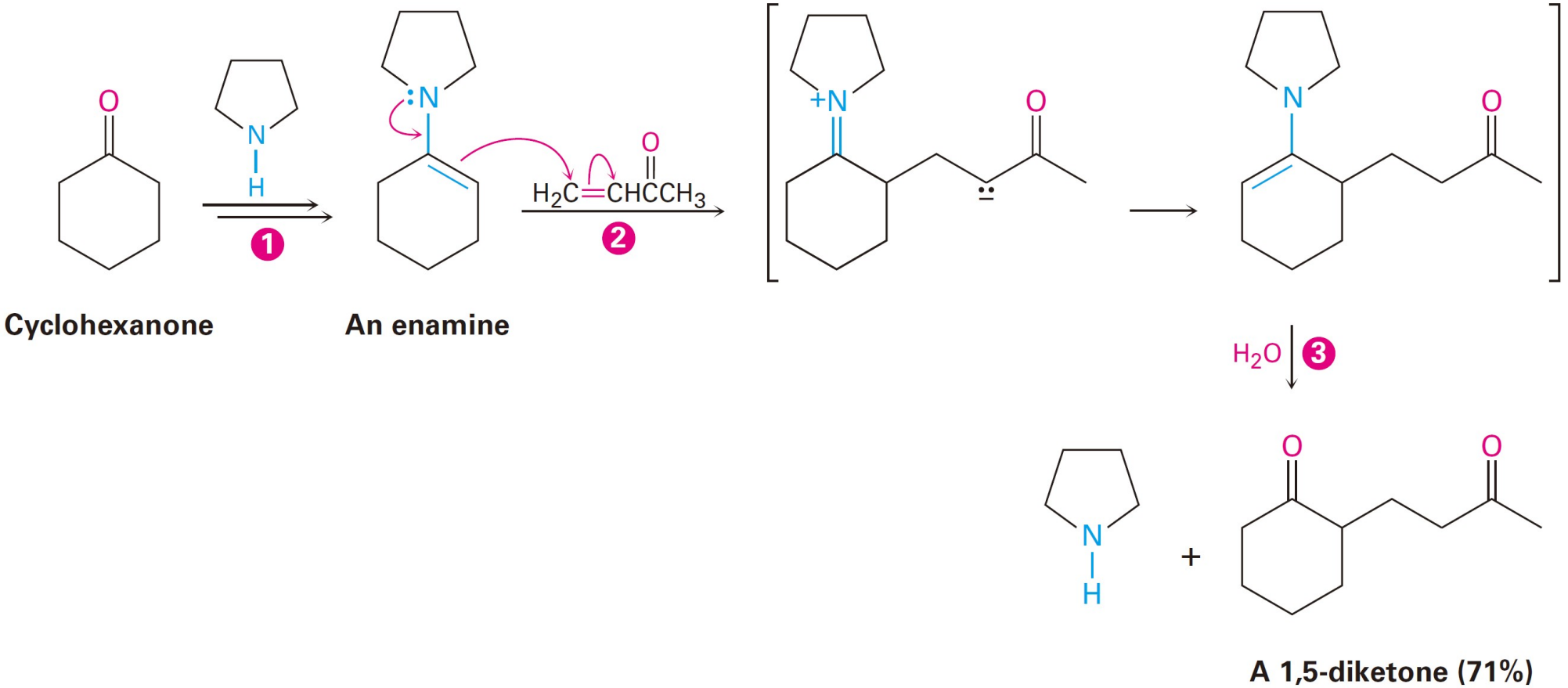






23.11 烯胺参与的缩合反应： Stork 烯胺策略

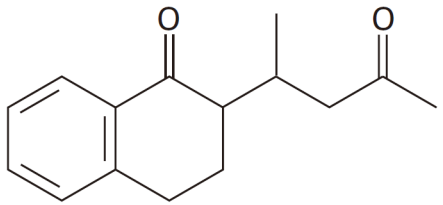
- 如下图所示，烯胺作为亲核试剂，发生迈克尔加成反应。



23.11 烯胺参与的缩合反应： Stork 烯胺策略

- 例题

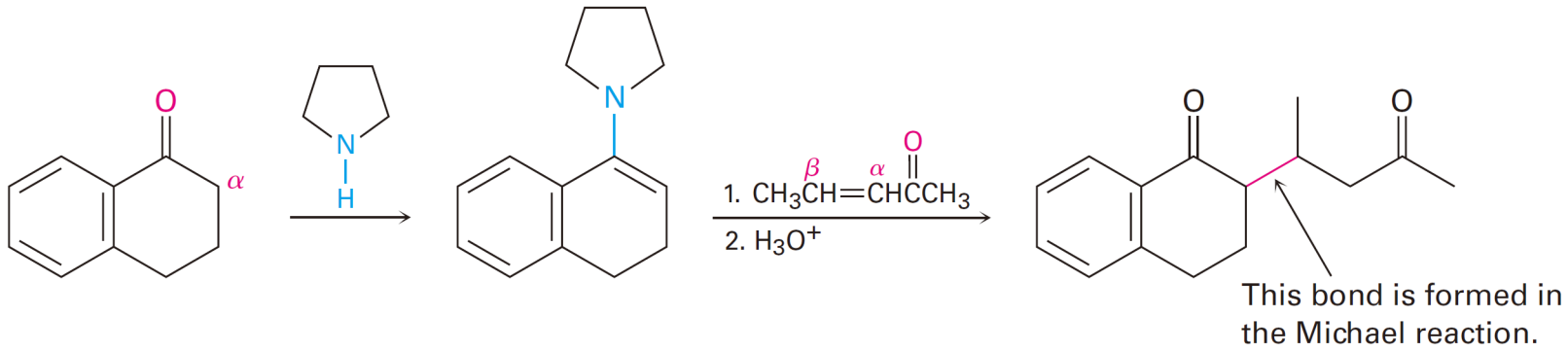
How might you use an enamine reaction to prepare the following compound?



Strategy

The overall result of an enamine reaction is the Michael addition of a ketone as donor to an α,β-unsaturated carbonyl compound as acceptor, yielding a 1,5-dicarbonyl product. The C—C bond made in the Michael addition step is the one between the α carbon of the ketone donor and the β carbon of the unsaturated acceptor.

Solution



23.11 烯胺参与的缩合反应： Stork 烯胺策略

- 练习

Problem 23.19

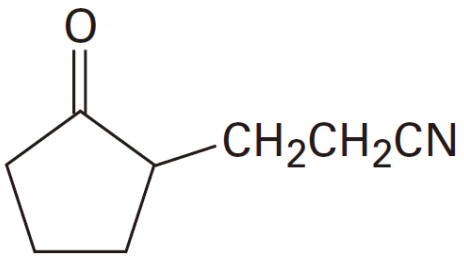
What products would result after hydrolysis from reaction of the enamine prepared from cyclopentanone and pyrrolidine with the following α,β-unsaturated acceptors?

(a) $H_2C{=}CHCO_2Et$ **(b)** $H_2C{=}CHCHO$ **(c)** $CH_3CH{=}CHCOCH_3$

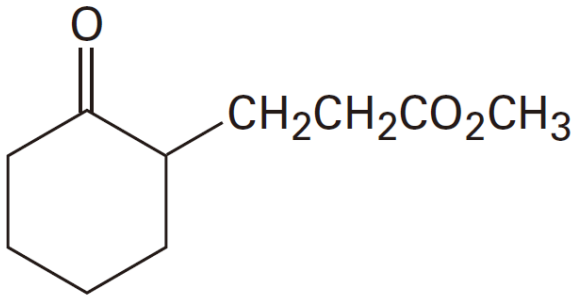
Problem 23.20

Show how you might use an enamine reaction to prepare each of the following compounds:

(a)



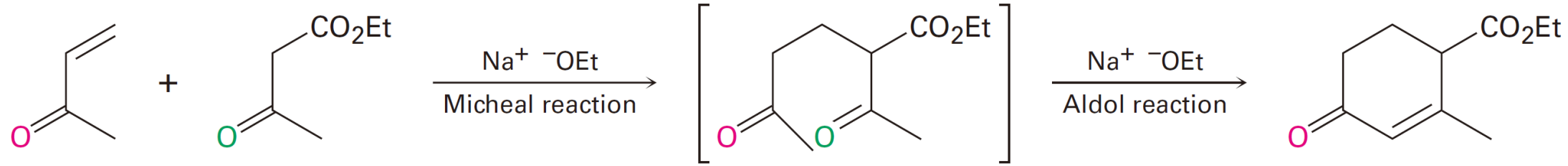
(b)



23.12 鲁滨孙环化反应

- 鲁滨孙环化反应是指结合了迈克尔加成和分子内羟醛缩合反应，得到了一个环系的过程。

The Robinson annulation is a two-step process that combines a Michael reaction with an intramolecular aldol reaction. It takes place between a nucleophilic donor, such as a β-keto ester, an enamine, or a β-diketone, and an α,β-unsaturated ketone acceptor, such as 3-buten-2-one. The product is a substituted 2-cyclohexenone.



3-Buten-2-one + **Ethyl acetoacetate** → **Michael product** → **Annulation product**

23.12 鲁滨孙环化反应

- 雌酮的合成

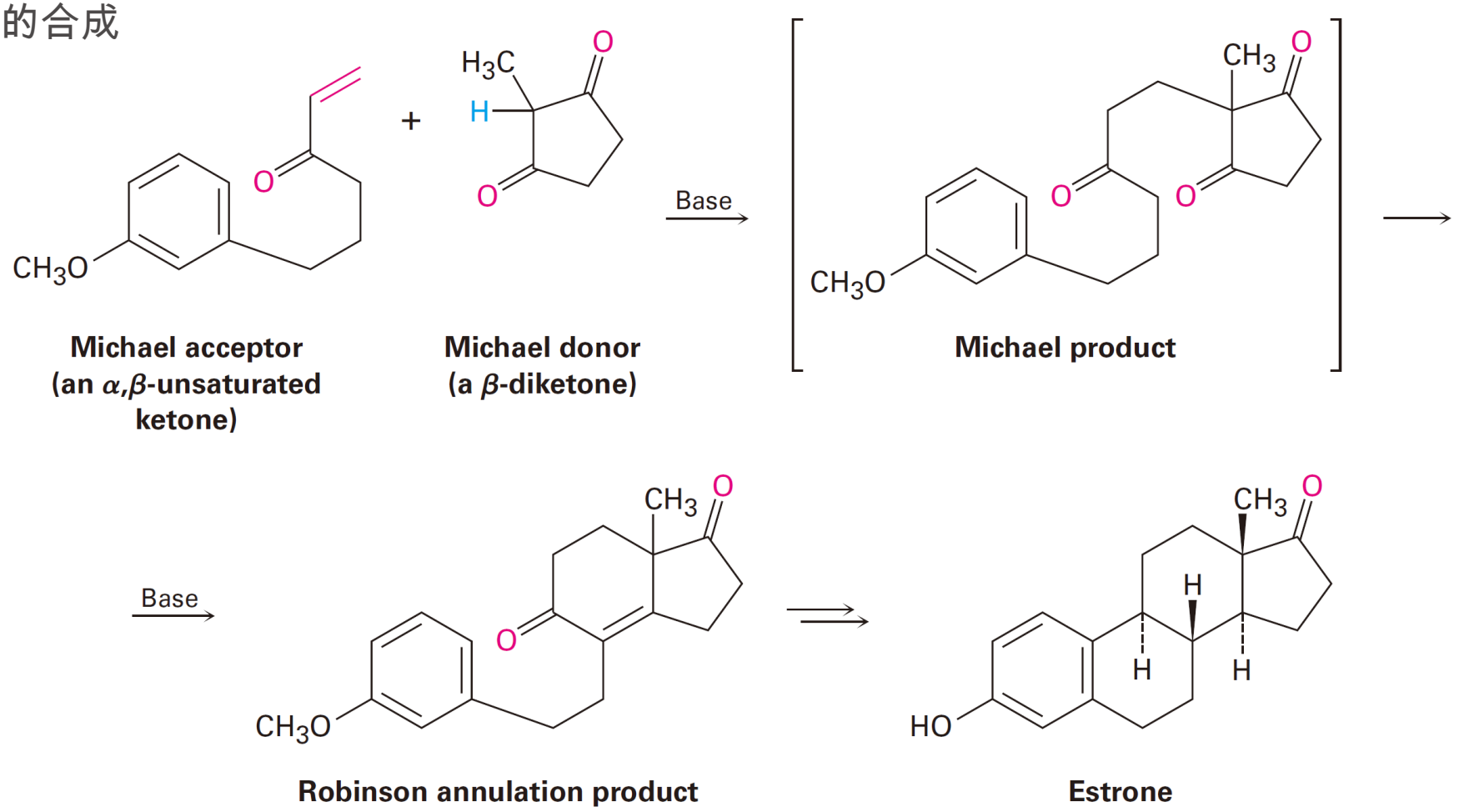


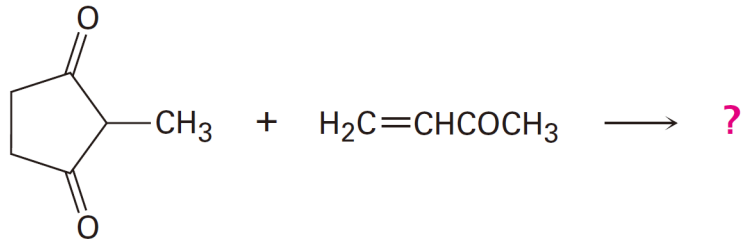
Figure 23.8 Synthesis of the steroid hormone estrone using a Robinson annulation reaction. The nucleophilic donor is a β-diketone.

23.12 鲁滨孙环化反应

- 练习

Problem 23.21

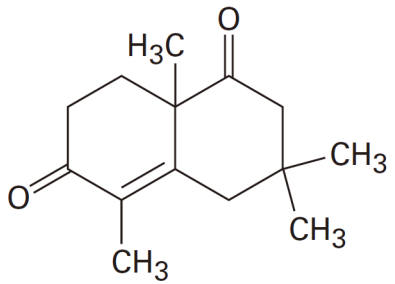
What product would you expect from a Robinson annulation reaction of 2-methyl-1,3-cyclopentanedione with 3-buten-2-one?



2-Methyl-1,3-cyclopentanedione **3-Buten-2-one**

Problem 23.22

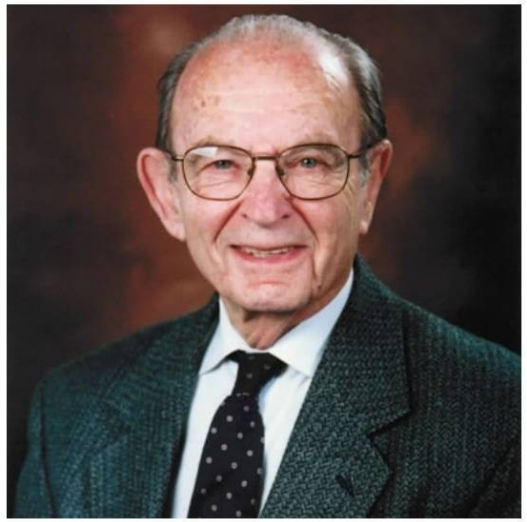
How would you prepare the following compound using a Robinson annulation reaction between a β-diketone and an α,β-unsaturated ketone? Draw the structures of both reactants and the intermediate Michael addition product.



作业

- 23.28, 23.29, 23.30, 23.35, 23.37, 23.41, 23.42, 23.43, 23.44

有机合成大师 Gilbert Stork 教授 （ 1921-2017 ）



- “我们意识到，我们缺了几毫克材料来完成多步转换反应。其他人也许会从头合成，**但我今年已经 95 岁了……**”

Organic LETTERS

Letter

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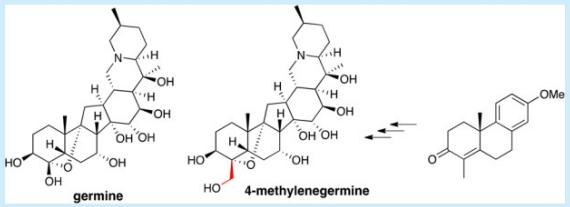
Synthetic Study toward Total Synthesis of (±)-Germine: Synthesis of (±)-4-Methylenegermine

Gilbert Stork,*,† Ayako Yamashita,† Robert M. Hanson, Ly Phan, Eifion Phillips, Daniel Dubé, Pieter H. Bos,‡ Andrew J. Clark, Maxwell Gough, Mark L. Greenlee, Yimin Jiang, Keith Jones, Masato Kitamura, John Leonard, Tongzhu Liu, Philip J. Parsons, and Aranapakam M. Venkatesan

†Department of Chemistry and ‡Chemical Probe Synthesis Facility, Department of Biological Sciences, Columbia University, New York, New York 10027, United States

Supporting Information

ABSTRACT: The total synthesis of 4-methylenegermine is described.



(22) A plan for conversion of **33a** to **1** was (with various deprotections/protections) C4-CH_2OH to C4-CO_2H, followed by Barton's conditions to change C4-CO_2H to C4-OH. Barton, D. H. R.; Gero, S. D.; Holliday, P.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron* **1998**, 54, 6751. At this point, we realized that we did not have enough material (a few milligrams) to go through the several steps for this conversion. One would have to restart the whole synthesis. But I (G.S.) am now 95 years old...

DOI: 10.1021/acs.orglett.7b02434
Org. Lett. 2017, 19, 5150−5153

https://pubs.acs.org/doi/10.1021/acs.orglett.7b02434