Montogue

Quiz CH208

Organic Chemistry

Alpha Carbon Chemistry

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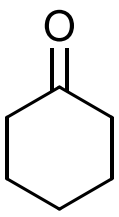
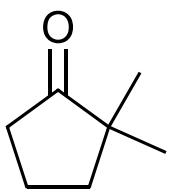
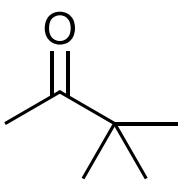
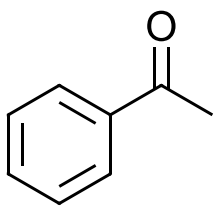
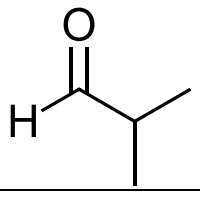
PROBLEMS

Problem 1 (Klein, 2017, w/ permission)

Draw both resonance structures of the enolate formed when each of the following ketones and aldehydes is treated with a strong base.

1.1. 	**1.2.** 
1.3. 	**1.4.** 
1.5. 	

Problem 2 (Vollhardt and Schore, 2014)

Problem 2.1: Write the structures of the aldol condensation products of

2.1.1. Pentanal

2.1.2. 3-Methylbutanal

2.1.3. Cyclopentanone

Problem 2.2: Write the structures of the aldol condensation products of

2.2.1. Acetophenone (1-phenylethanone)

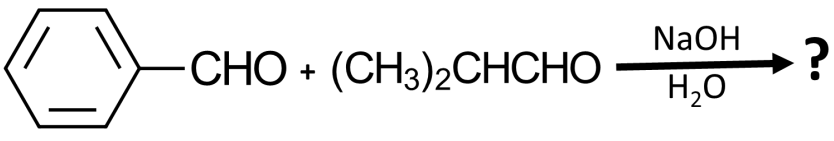
2.2.2. Acetone

2.2.3. 2,2-Dimethylcyclopentanone

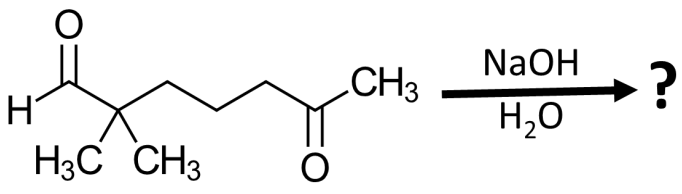
Problem 3 (Vollhardt and Schore, 2014)

Identify the products of the following reactions.

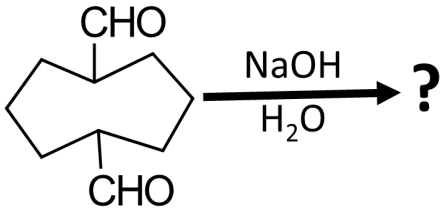
3.1.



3.2.

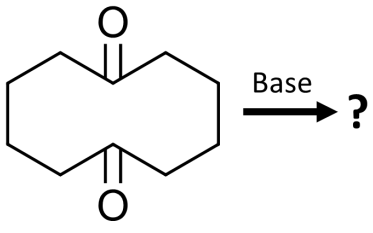


3.3.



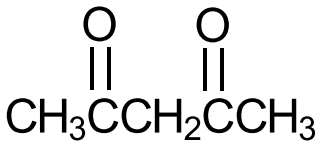
▶ **Problem 4** (McMurry, 2008, w/ permission)

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



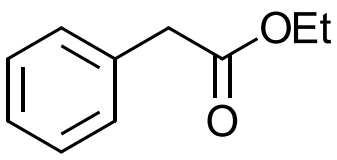
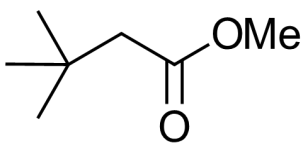
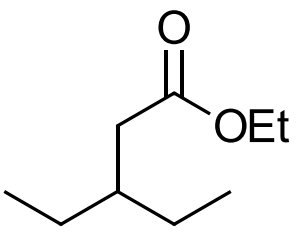
▶ **Problem 5** (McMurry, 2008, w/ permission)

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

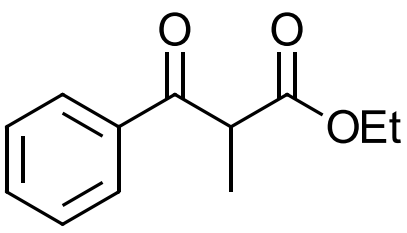
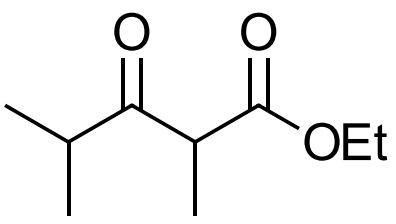
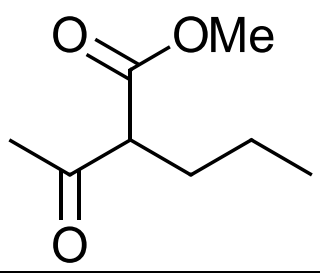
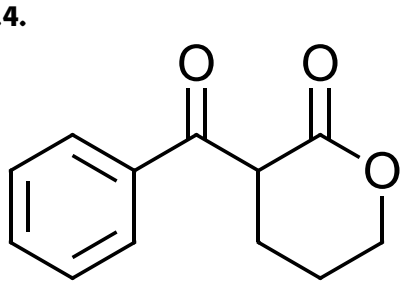


▶ **Problem 6**

Problem 6.1: Predict the major product obtained when each of the following compounds undergoes a Claisen condensation.

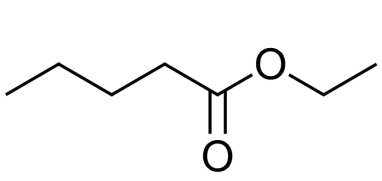
6.1.1. 	**6.1.2.** 
6.1.3. 	

Problem 6.2: Identify the reagents that you would use to produce each of the following compounds using a Claisen condensation.

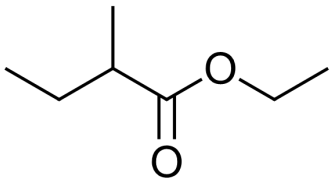
6.2.1. 	**6.2.2.** 
6.2.3. 	**6.2.4.** 

▶ Problem 7 (Carey, 2008, w/ permission)

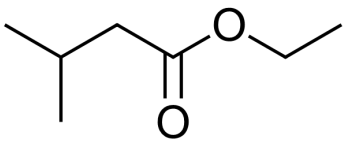
The following questions pertain to the esters shown and their behavior under conditions of Claisen condensation.



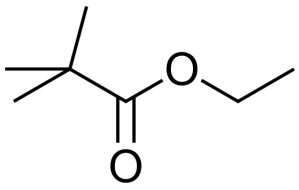
Ethyl pentanoate



Ethyl 2-methylbutanoate



Ethyl 3-methylbutanoate



Ethyl 2,2-dimethylpropanoate

7.1. Two of these esters are converted to β-keto esters in good yield on treatment with sodium ethoxide and subsequent acidification of the reaction mixture. Which two are these? Write the structure of the Claisen condensation product of each one.

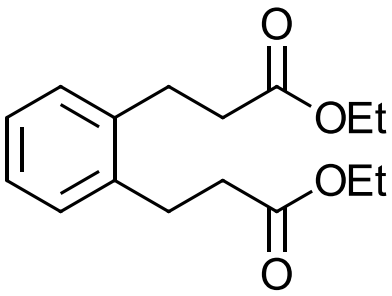
7.2. One ester is capable of being converted to a β-keto ester on treatment with sodium ethoxide, but the amount of β-keto ester that can be isolated after acidification of the reaction mixture is quite small. Which ester is this?

7.3. One ester is incapable of reaction under conditions of Claisen condensation. Which one? Why?

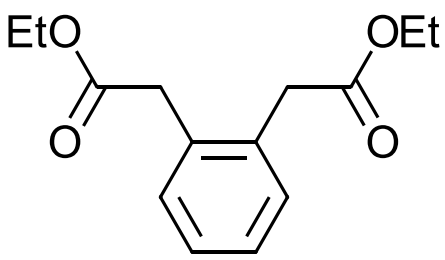
▶ Problem 8

Predict the product of Dieckmann cyclization that occurs when each of the following compounds is treated with sodium ethoxide, followed by acid workup.

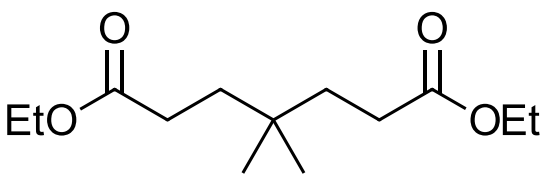
8.1.



8.2.

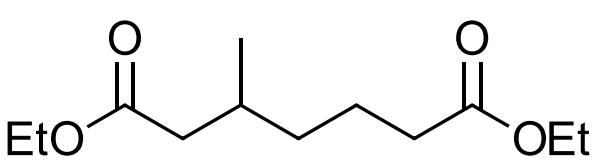


8.3.



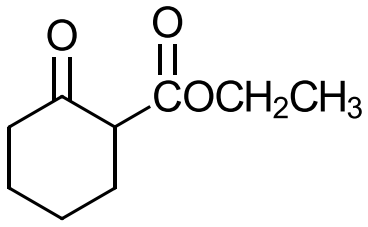
▶ Problem 9 (Klein, 2017, w/ permission)

When the following compound is treated with sodium ethoxide, followed by acid workup, two condensation products are obtained, both of which are produced via Dieckmann cyclizations. Draw both products.



▶ Problem 10 (Carey, 2008, w/ permission)

The following questions concern ethyl (2-oxocyclohexane)carboxylate.



10.1. Write a chemical equation showing how you would prepare ethyl (2-oxocyclohexane)carboxylate by a Dieckmann cyclization.

10.2. Write a chemical equation showing how you would prepare ethyl (2-oxocyclohexane)carboxylate by acylation of a ketone.

10.3. Write structural formulas for the two most stable enol forms of ethyl (2-oxocyclohexane)carboxylate.

10.4. Write the three most stable resonance contributors to the most stable enolate derived from ethyl (2-oxocyclohexane)carboxylate.

10.5. Show how you would use ethyl (2-oxocyclohexane)carboxylate to prepare 2-methylcyclohexanone.

10.6. Give the structure of the product formed on treatment of ethyl (2-oxocyclohexane)carboxylate with acrolein ($H_2C{=}CHCHO$) in ethanol in the presence of sodium ethoxide.

▶ Problem 11 (McMurry, 2008, w/ permission)

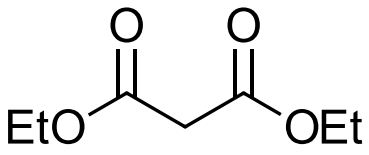
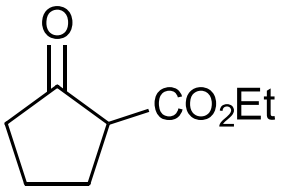
Problem 11.1: What product would you obtain from a base-catalyzed Michael reaction of 2,4-pentanedione with each of the following α,β-unsaturated acceptors?

11.1.1. 2-Cyclohexenone

11.1.2. Propenenitrile

11.1.3. Ethyl 2-butenoate

Problem 11.2: What product would you obtain from a base-catalyzed Michael reaction of 3-buten-2-one with each of the following nucleophilic donors?

11.2.1.	**11.2.2.**
	

▶ Problem 12

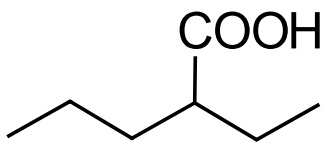
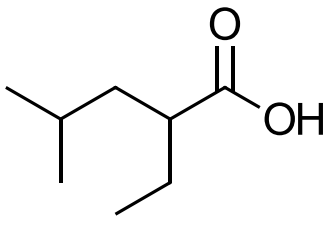
Show how the following compounds can be made using the malonic ester synthesis.

12.1. 3-Phenylpropanoic acid

12.2. 2-Methylpropanoic acid

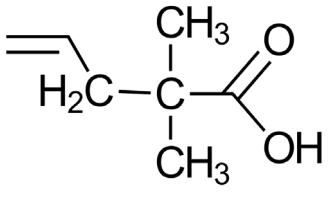
12.3. 4-Phenylbutanoic acid

12.4. Cyclopentanecarboxylic acid

12.5.	**12.6.**
	

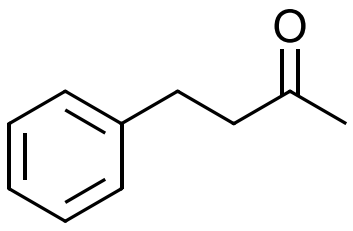
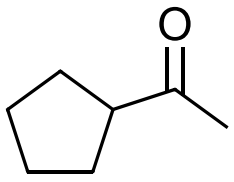
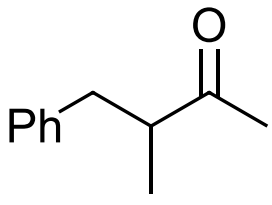
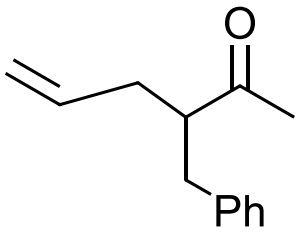
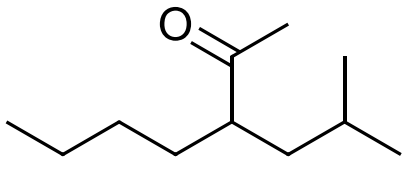
▶ Problem 13

The following compound cannot be formed by malonic ester synthesis. Why?



▶ Problem 14

Show how the following compounds can be made using the acetoacetic ester synthesis.

14.1. 	**14.2.** 
14.3. 	**14.4.** 
14.5. 	

▶ Problem 15 (Carey, 2008, w/ permission)

Give the structure of the expected organic product in the reaction of 3-phenylpropanal with each of the following.

15.1. Chlorine in acetic acid
15.2. Sodium hydroxide in ethanol, 10°C
15.3. Sodium hydroxide in ethanol, 70°C
15.4. Product of 15.3 with lithium aluminum hydride ($LiAlH_4$), then H_2O.
15.5. Product of 15.3 with sodium cyanide in acidic ethanol.

▶ Problem 16 (Carey, 2008, w/ permission)

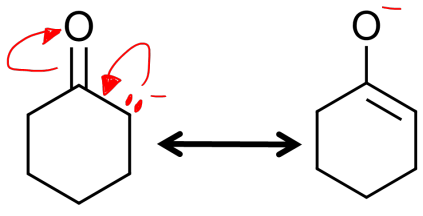
Show how each of the following compounds could be prepared from 3-pentanone. In most cases more than one synthetic transformation will be necessary.

16.1. 2-Bromo-3-pentanone
16.2. 1-Penten-3-one
16.3. 1-Penten-3-ol
16.4. 3-Hexanone
16.5. 2-Methyl-1-phenyl-1-penten-3-one

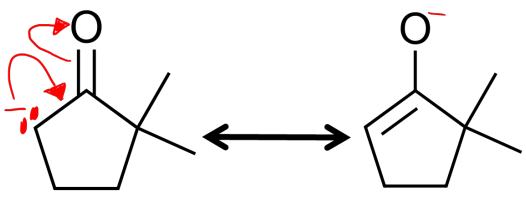
SOLUTIONS

P.1 ➡ *Solution*

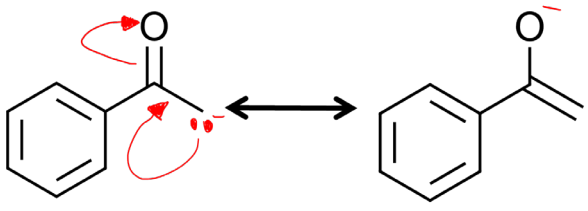
1.1: This compound has two α positions, although they are identical because the ketone is symmetrical. Deprotonation at either location will lead to the same enolate ion, which has the following resonance structures.



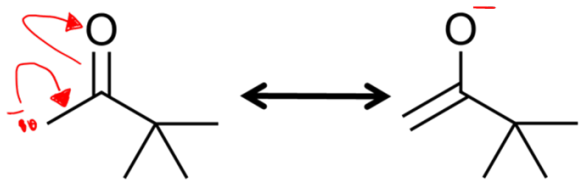
1.2: This compound has two α positions, but only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion with the following resonance structures.



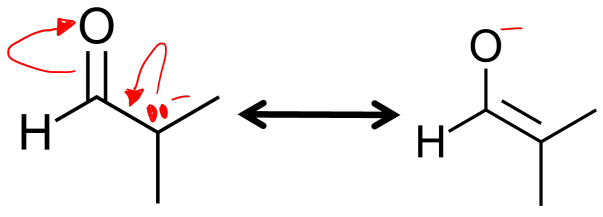
1.3: This compound has two α positions, but only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion with the following resonance structures.



1.4: This compound has two α positions, but only one of these positions bears protons. Deprotonation at that location will lead to an enolate ion with the following resonance structures.



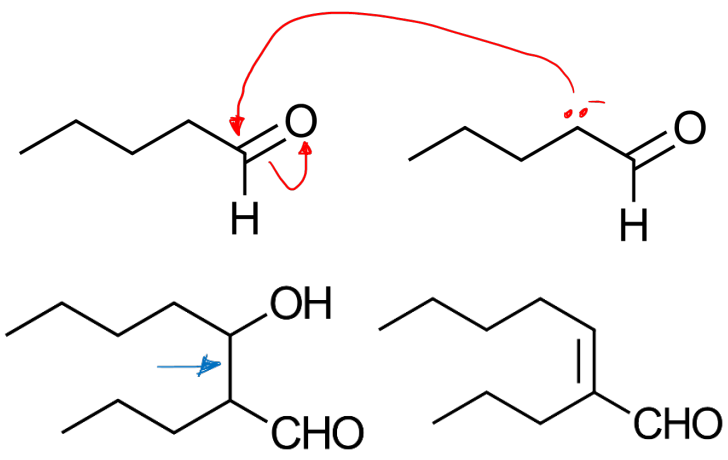
1.5: This compound is an aldehyde and therefore has only one α position. Deprotonation at that location will lead to an enolate ion with the following resonance structures.



P.2 ➡ *Solution*

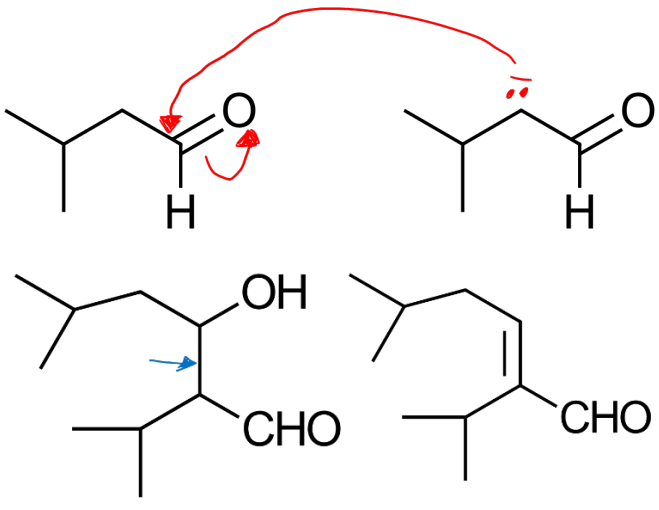
In problems 2.1.1 to 2.1.3, the direction of the nucleophilic attack is shown, and the new bond is marked with a blue arrow. Both the initial hydroxycarbonyl compound and the enone that forms upon dehydration are shown.

2.1.1:



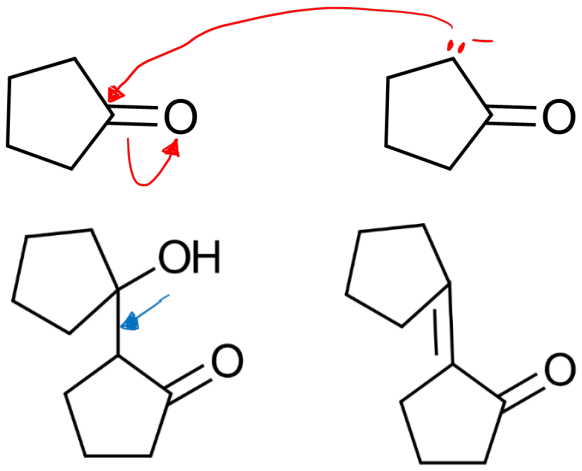
The *E* and *Z* isomers of the enone are formed.

2.1.2:



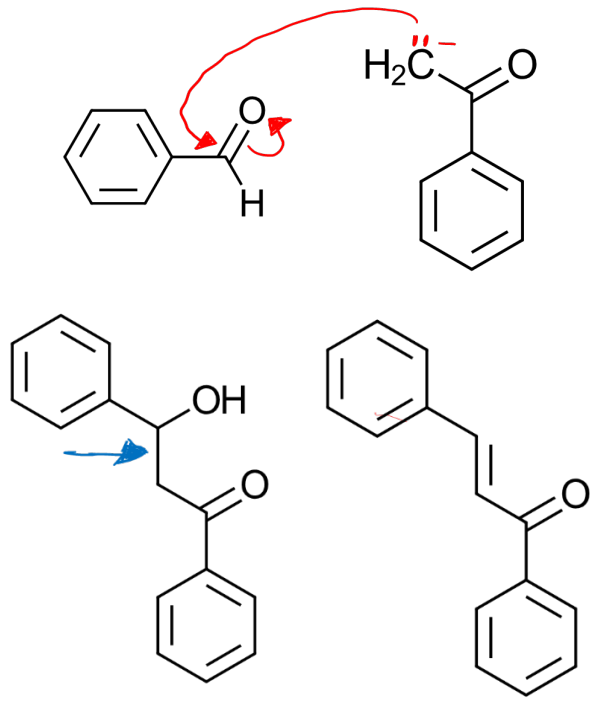
The *E* and *Z* isomers of the enone are formed.

2.1.3:



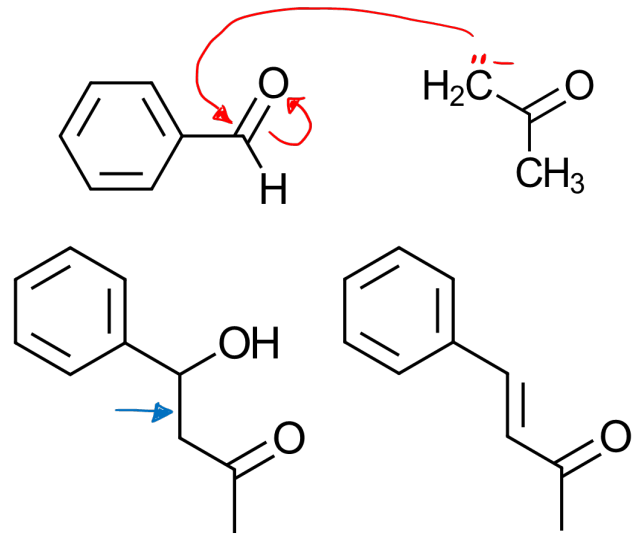
In problems 2.2.1 to 2.2.3, the direction of nucleophilic attack is shown, and the new bond is marked in the product with an arrow. Both the initial hydroxycarbonyl compound and the enone that forms upon dehydration are shown.

2.2.1:



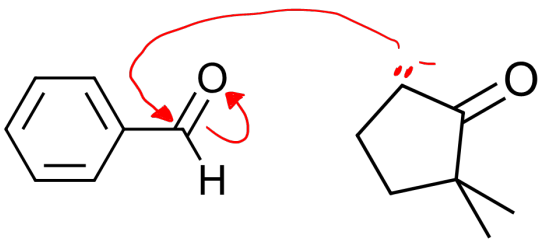
The *E* and *Z* isomers of the enone are formed.

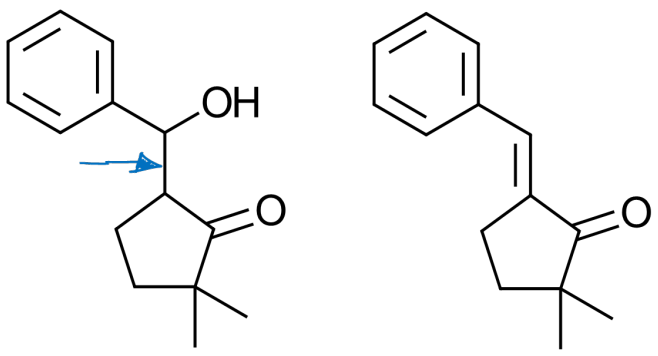
2.2.2:



The *E* and *Z* isomers of the enone are formed.

2.2.3:

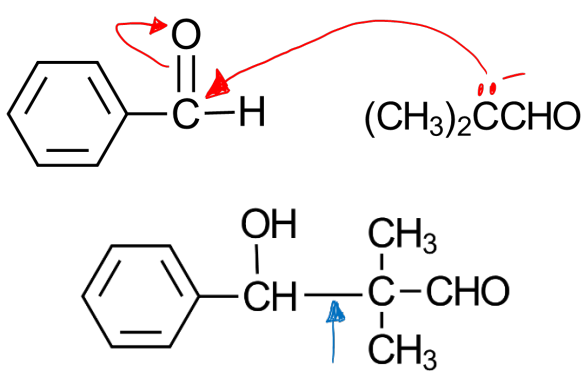




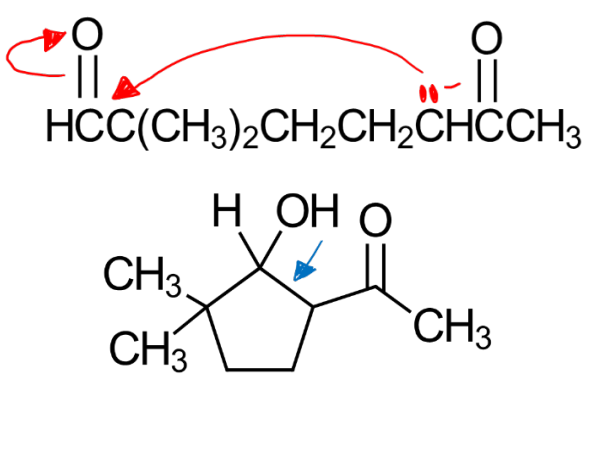
P.3 ➡ *Solution*

These problems follow the same logic as Problem 2.

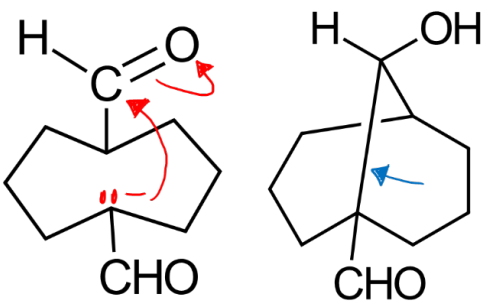
3.1:



3.2:

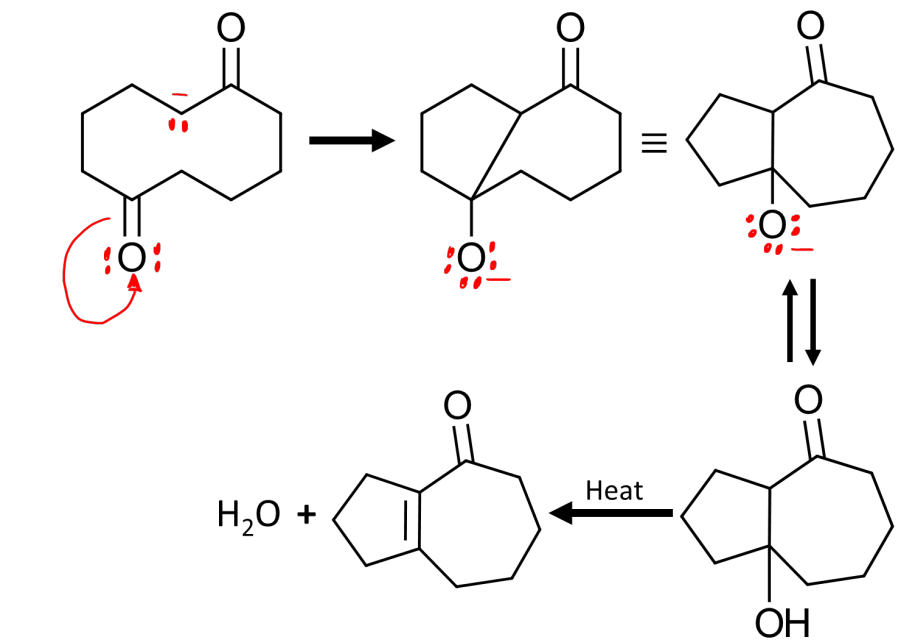


3.3:



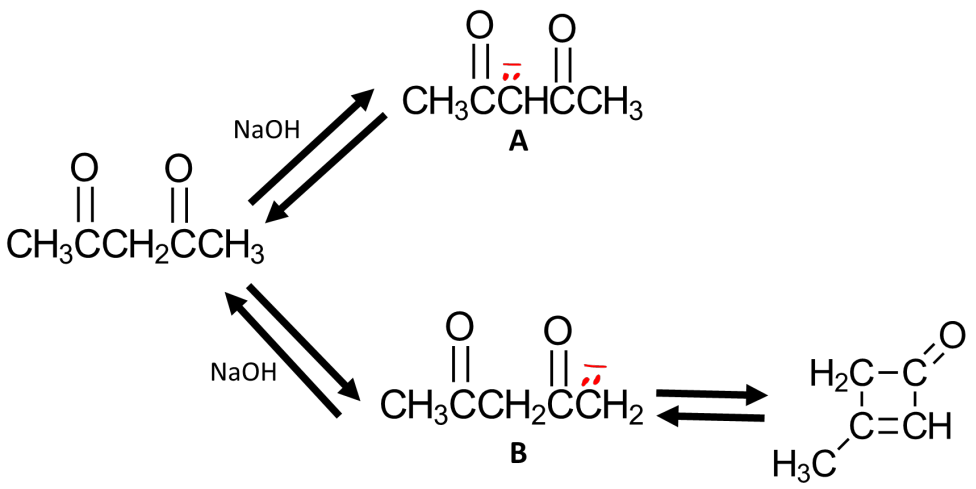
P.4 ➡ *Solution*

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



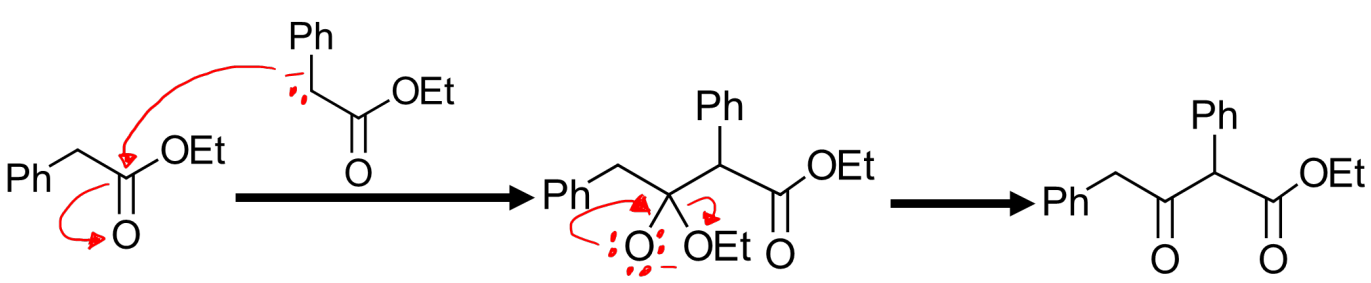
P.5 ➡ *Solution*

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

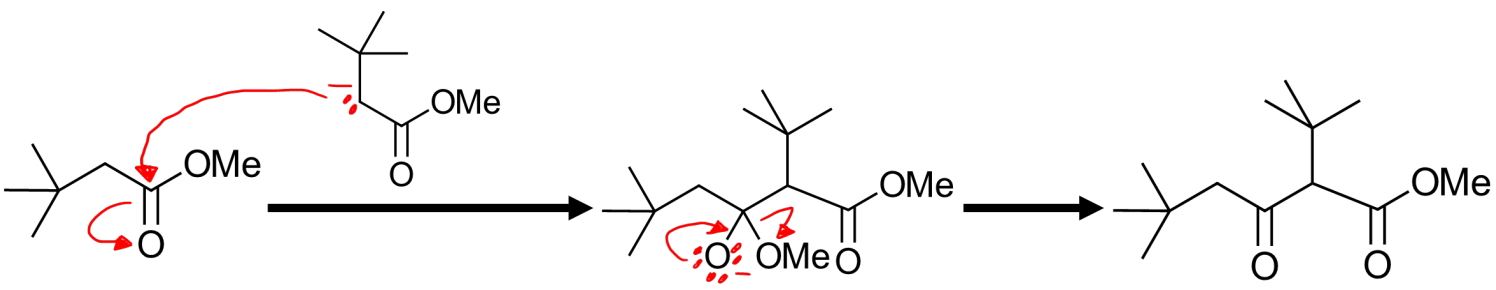


P.6 ➡ *Solution*

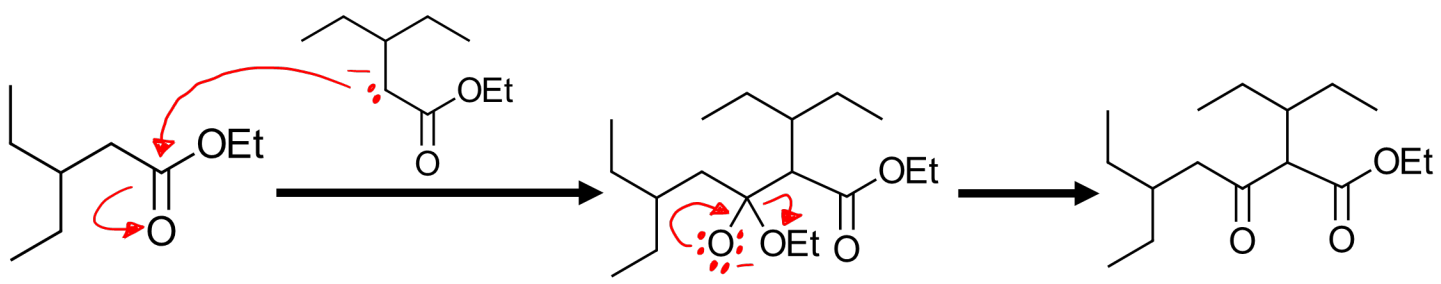
6.1.1: The α position of one molecule of the ester is deprotonated, and the resulting enolate functions as a nucleophile and attacks the carbonyl group of another molecule of the ester. As a result, a carbon-carbon bond is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, affording a β-ketoester, as shown.



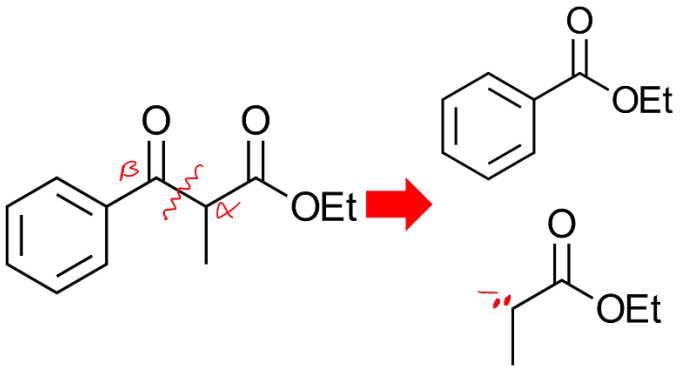
6.1.2: Claisen condensation of this molecule follows the same logic as the one in the previous problem.



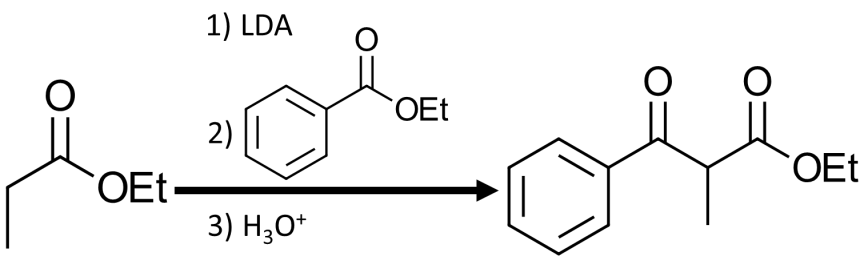
6.1.3: Claisen condensation of this molecule follows the same logic as the one in the previous problem.



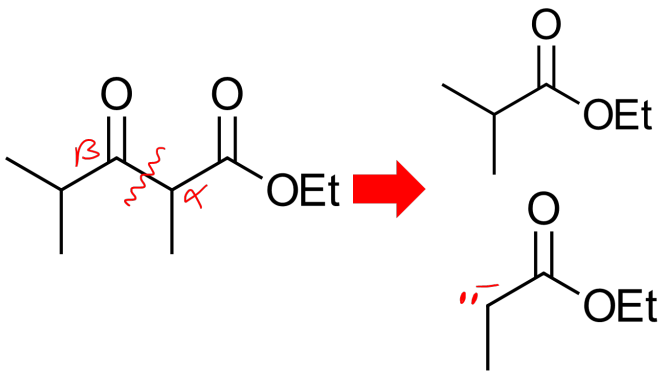
6.2.1: We first identify the α and β positions, and then apply a retrosynthetic analysis. The α position is the location between the two carbonyl groups, and the β position bears the keto group.



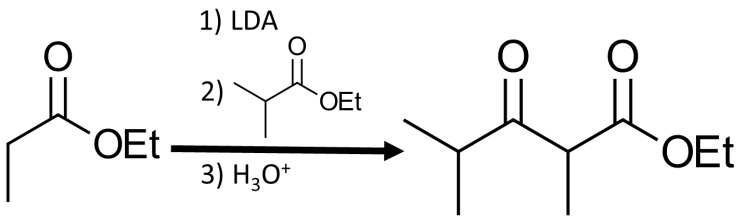
Since the two partners are different, we use a crossed Claisen condensation. Lithium diisopropylamide is the base of choice, and the final step of the process is an aqueous acid workup, as shown.



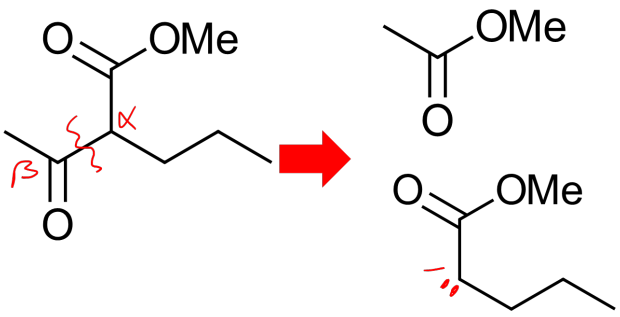
6.2.2: As was done in the previous problem, we identify the α and β carbons, noting that the α carbon is the location between the two carbonyl groups, and the β carbon bears the keto group.



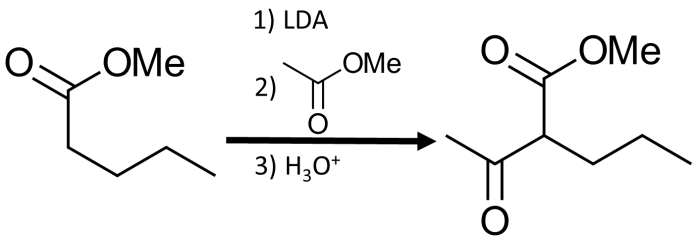
Since the two partners are different, we use a crossed Claisen condensation. As before, we treat one of the esters with LDA, then proceed to react it with the other ester. Finally, we subject the mixture to an acid workup.



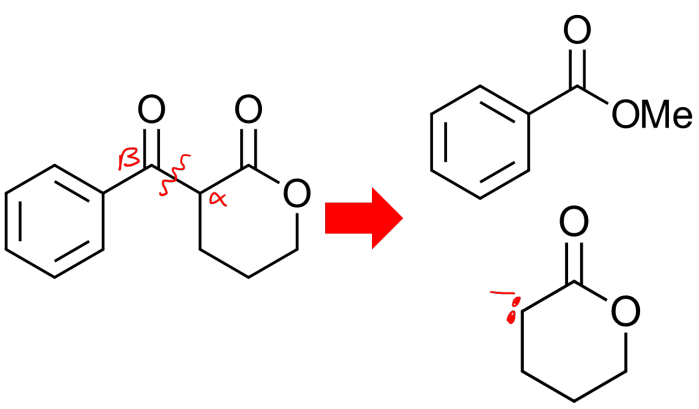
6.2.3: This problem is no different from the two previous ones; the bond that joins the α carbon to the β carbon separates the two starting esters.



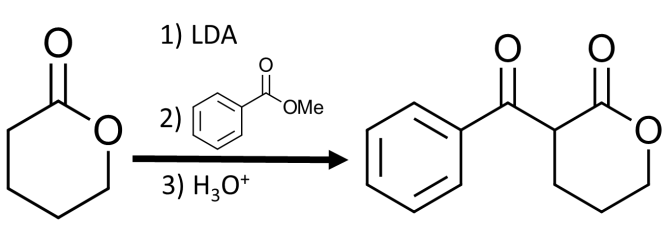
Because the two partners are different, a crossed Claisen condensation is in order. The crossed condensation can be achieved with the following sequence of reactions.



6.2.4: In this case, the ester that supplies the α carbon is cyclic in nature; aside from this, this problem is no different from the previous ones.

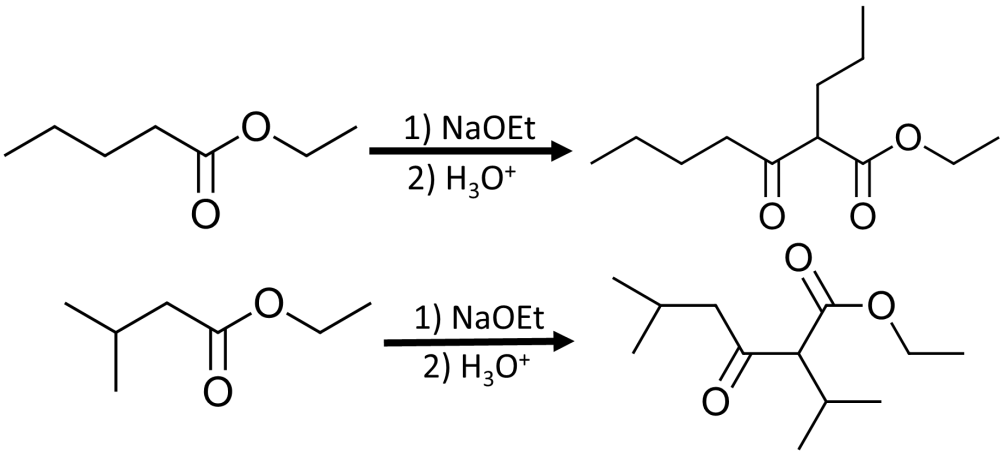


Because the two partners are different, a crossed Claisen condensation is in order. The crossed condensation can be achieved with the following sequence of reactions.

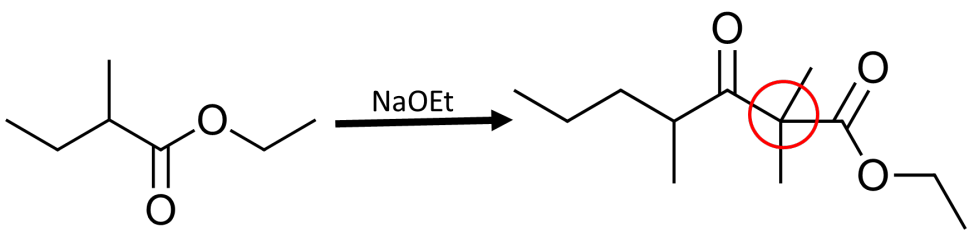


P.7 ➡ *Solution*

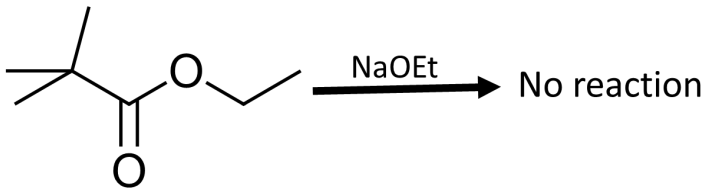
7.1: Among the esters given, ethyl pentanoate and ethyl 3-methylbutanoate undergo Claisen condensation.



7.2: The Claisen condensation product of ethyl 2-methylbutanoate cannot be deprotonated. With no protons on the α carbon, this molecule cannot form a stabilized enolate by deprotonation. As a result, the equilibrium constant for formation of the Claisen condensation product should be substantially less than 1.

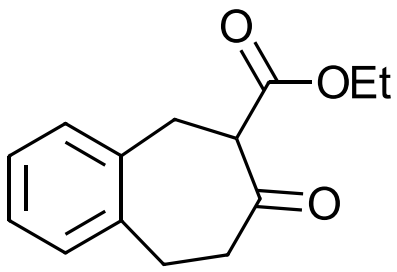


7.3: Ethyl 2,2-dimethylpropanoate has no protons on its α carbon; it cannot form the ester enolate required in the first step of Claisen condensation.



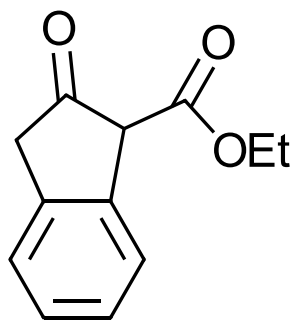
P.8 ➡ *Solution*

8.1: A Dieckmann cyclization is equivalent to an intramolecular Claisen condensation. The α position of one ester group is deprotonated, and the resulting enolate functions as a nucleophile and attacks the other carbonyl group within the same structure. As a result, a ring is formed, giving a tetrahedral intermediate. The carbonyl group is then reformed via loss of an ethoxide ion, giving the following β-ketoester.

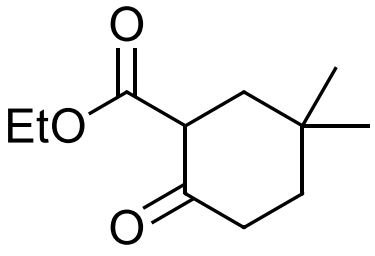


Klein notes that, under basic conditions, the β-ketoester is deprotonated to yield a doubly-stabilized enolate. An acidic workup can regenerate the β-ketoester.

8.2: The β-ketoester formed by Dieckmann cyclization of this molecule is shown below.

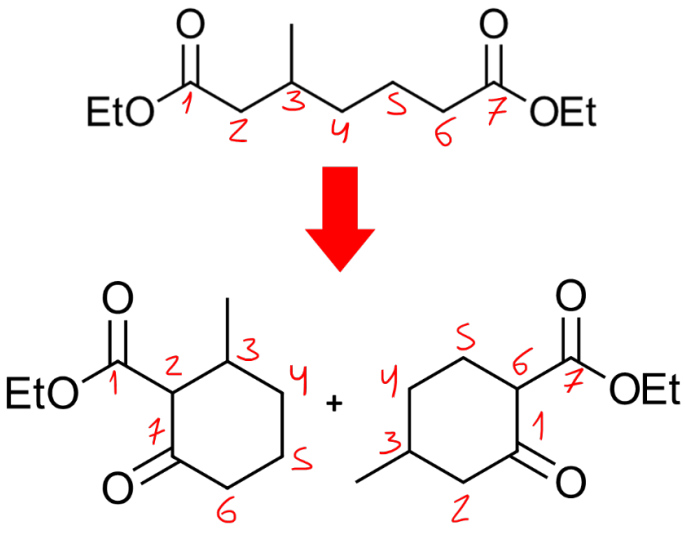


8.3: The β-ketoester formed by Dieckmann cyclization of this molecule is shown below.



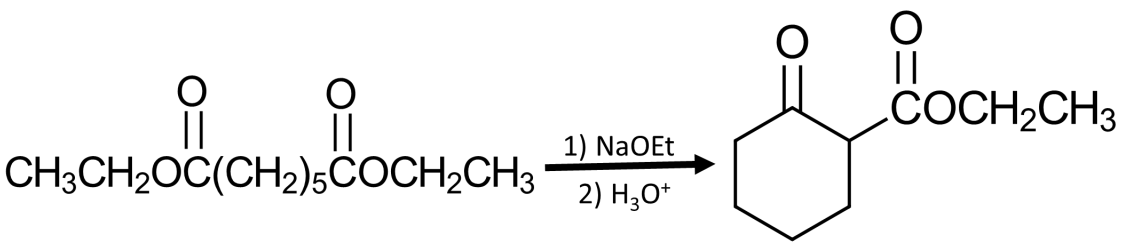
P.9 ➡ *Solution*

There are two α positions which are not identical (because of the presence of the methyl group at C3, using the carbon numbering outlined below). Therefore, either α position (C2 or C6) can be deprotonated, followed by an intramolecular attack, leading to the following two possible condensation products. That is, the cyclization process can either result in a bond between C2 and C7 or between C6 and C1, as shown.

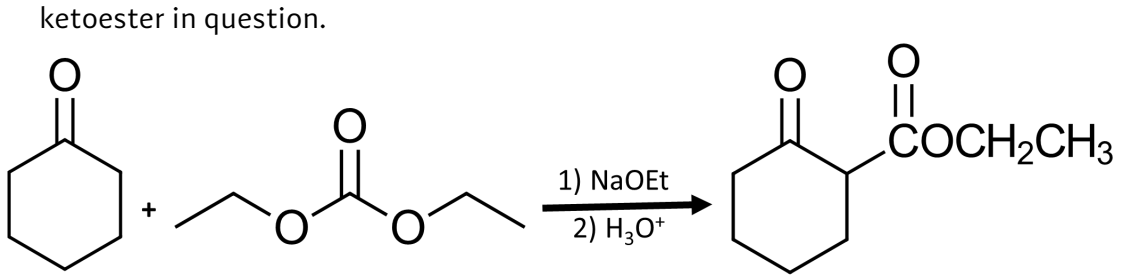


P.10 ➡ *Solution*

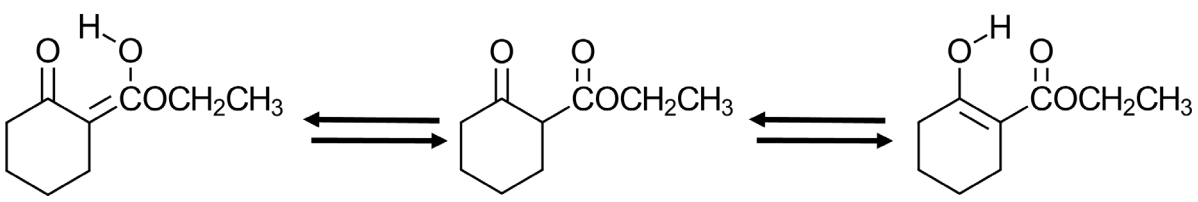
10.1: A Dieckmann cyclization is essentially an intramolecular Claisen condensation. The following diester can be used to prepare the β-ketoester in question.



10.2: Acylation of cyclohexanone with diethyl carbonate yields the β-ketoester in question.



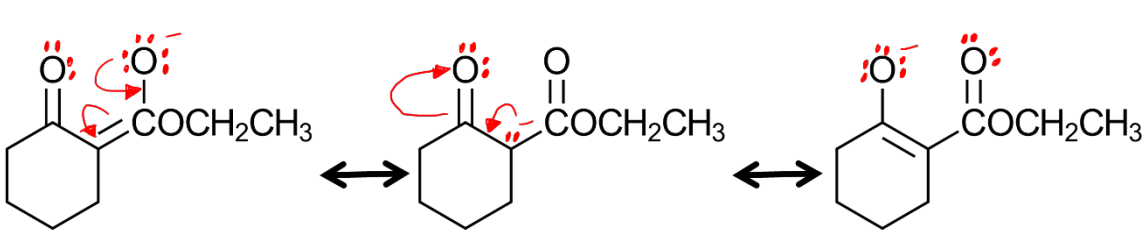
10.3: The two most stable enol forms are those that involve the proton on the carbon flanked by the two carbonyl groups.



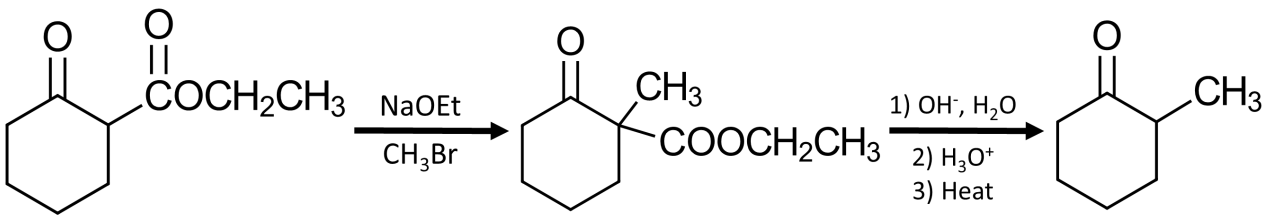
Stable enol form

Stable enol form

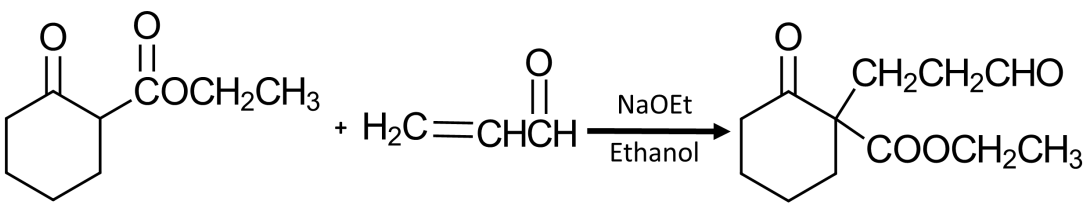
10.4: Deprotonation of the β-ketoester involves the acidic proton at the carbon flanked by the two carbonyl groups.



10.5: The methyl group is introduced by alkylation of the β-ketoester. Saponification and decarboxylation complete the synthesis.



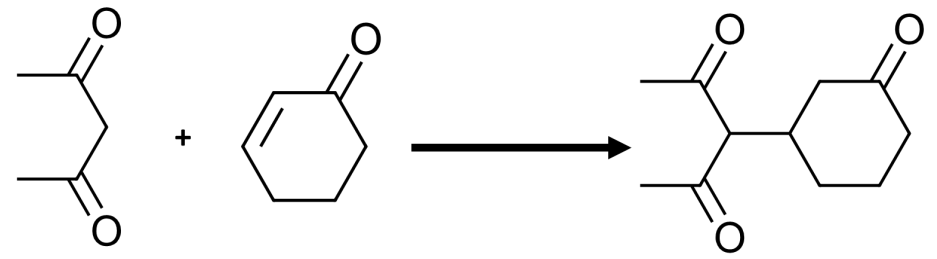
10.6: The enolate ion of the β-ketoester undergoes Michael addition to the carbon-carbon double bond of acrolein, forming the following Michael adduct. Further Michael reactions are covered in Problem 11.



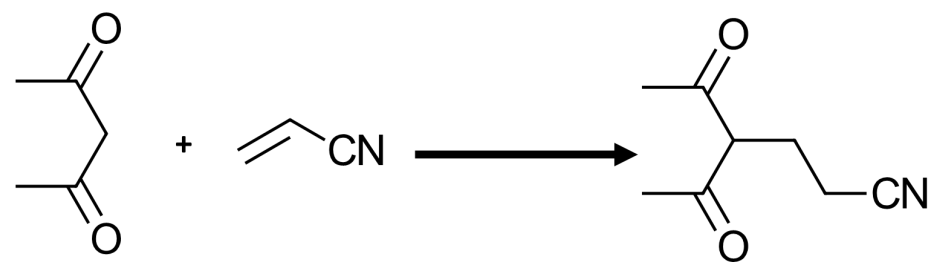
P.11 ➡ *Solution*

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

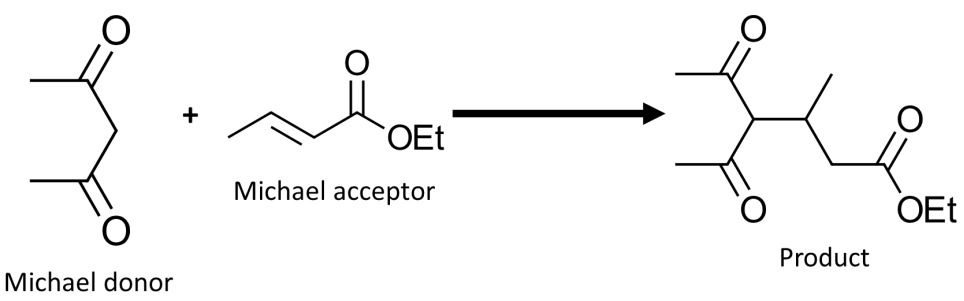
11.1.1:



11.1.2:

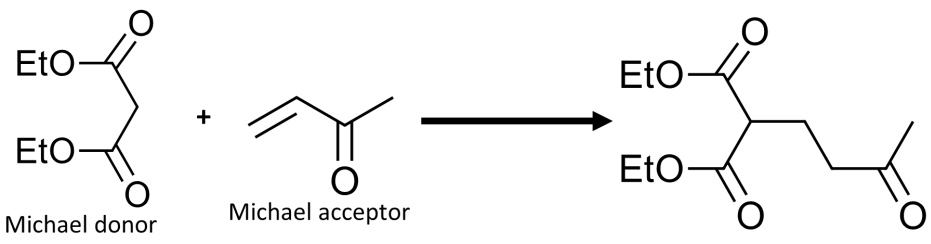


11.1.3:

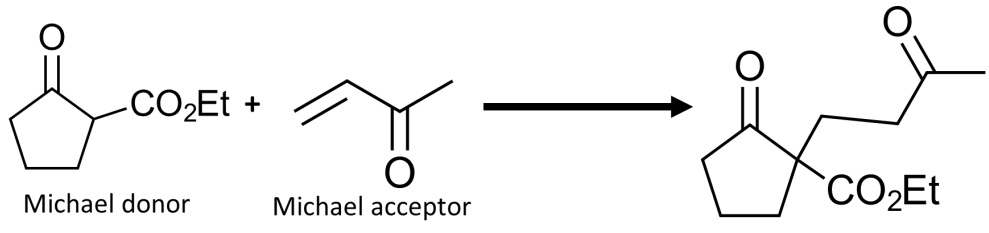


Problem 11.2 follows the same logic as Problem 11.1. In this case, the Michael acceptor, not the Michael donor, is given.

11.2.1:



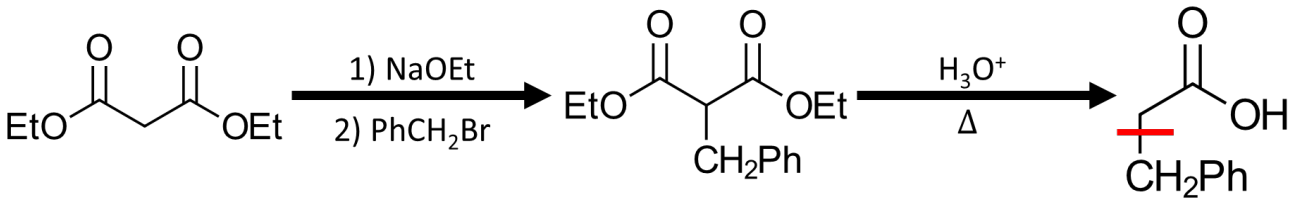
11.2.2:



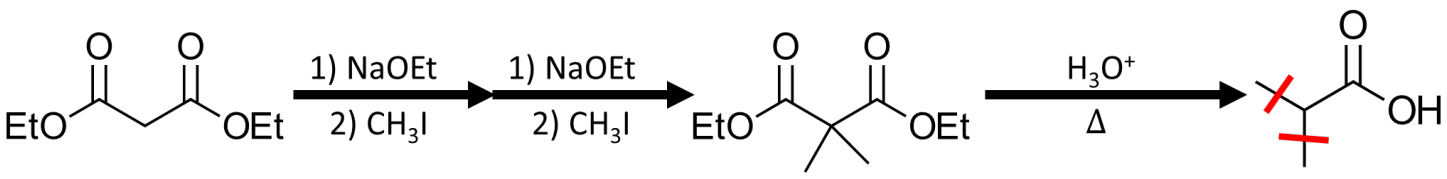
P.12 ➡ *Solution*

In the products, the red lines cross the bonds that must be made by alkylation, before hydrolysis and decarboxylation produce the substituted acetic acid. Bear in mind that carbon dioxide and ethanol are also products of each hydrolysis.

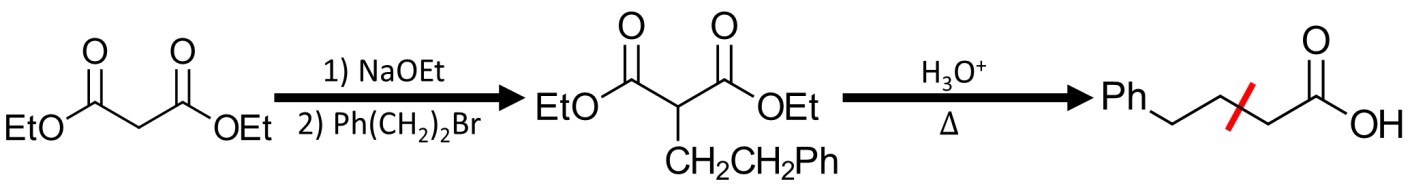
12.1:



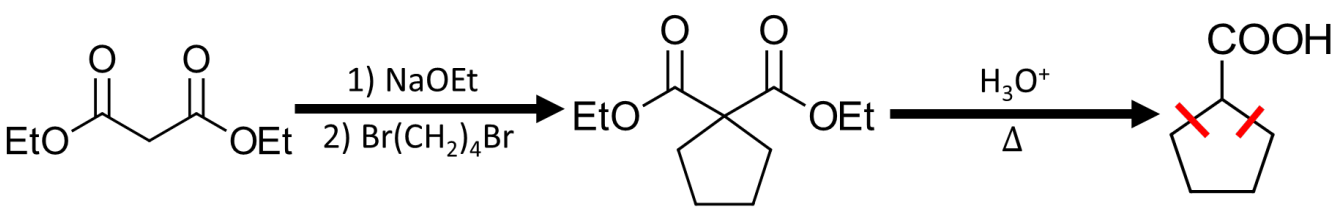
12.2:



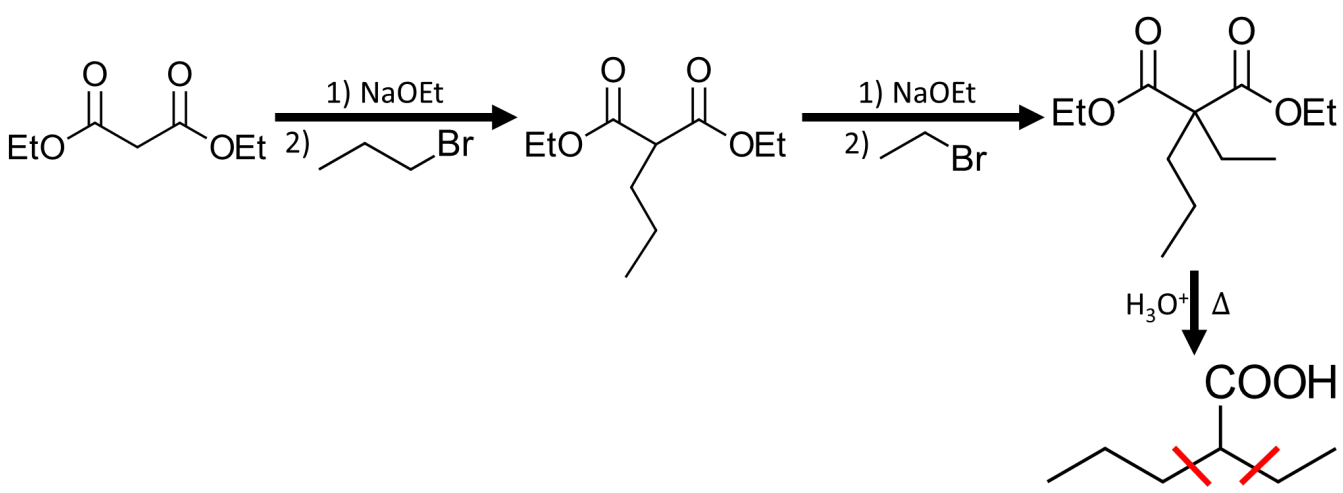
12.3:



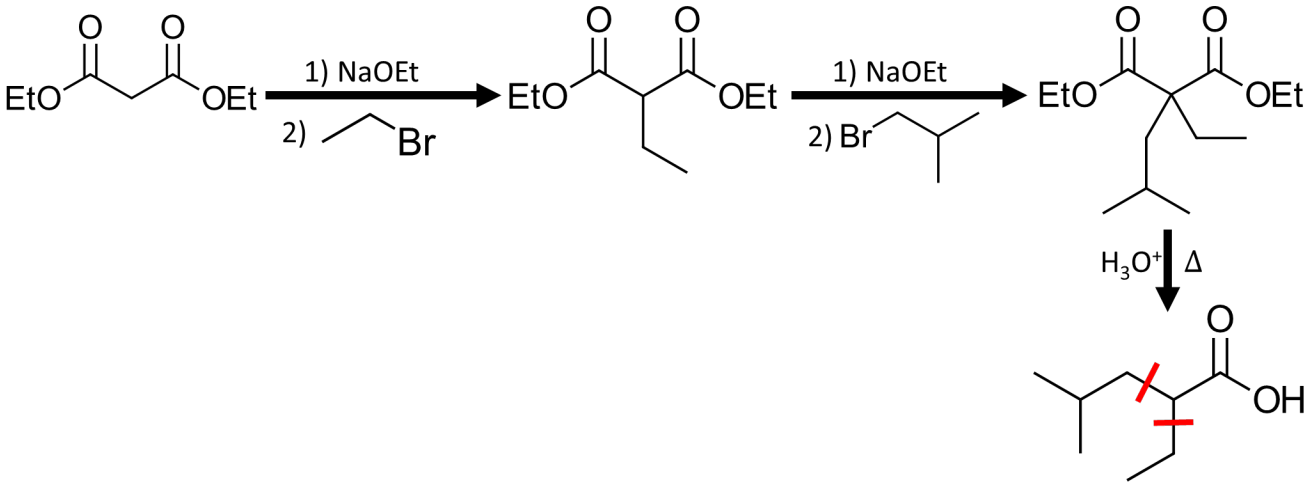
12.4:



12.5:

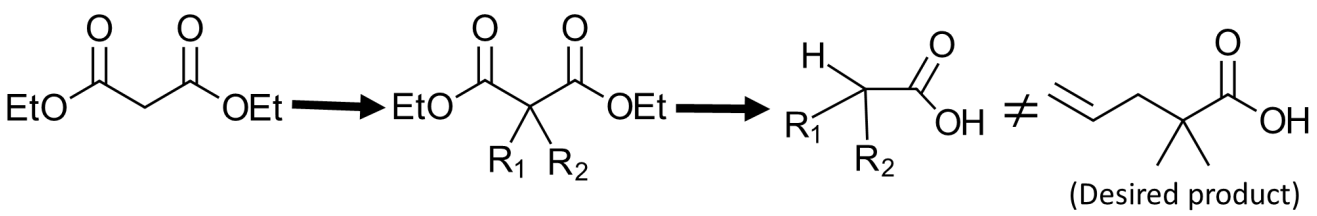


12.6:



P.13 ➡ *Solution*

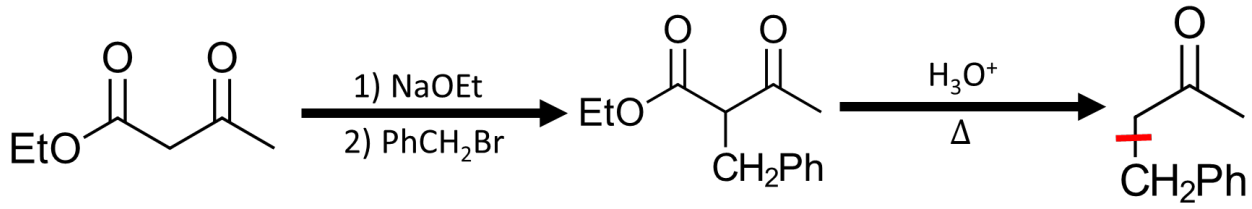
Only two substituent groups plus a hydrogen atom can appear on the alpha carbon after decarboxylation at the end of the malonic ester synthesis. The product shown has three alkyl groups, so it cannot be made by malonic ester synthesis.



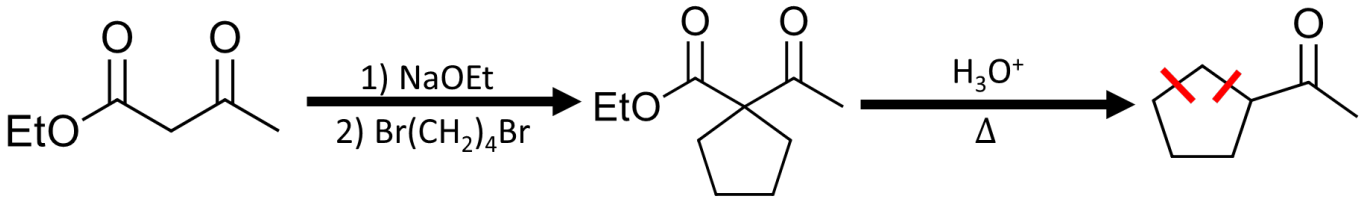
P.14 ➡ *Solution*

In the products, the red lines cross the bonds that must be made by alkylation, before hydrolysis and decarboxylation produce the substituted acetone. Bear in mind that carbon dioxide and ethanol are also products of each hydrolysis.

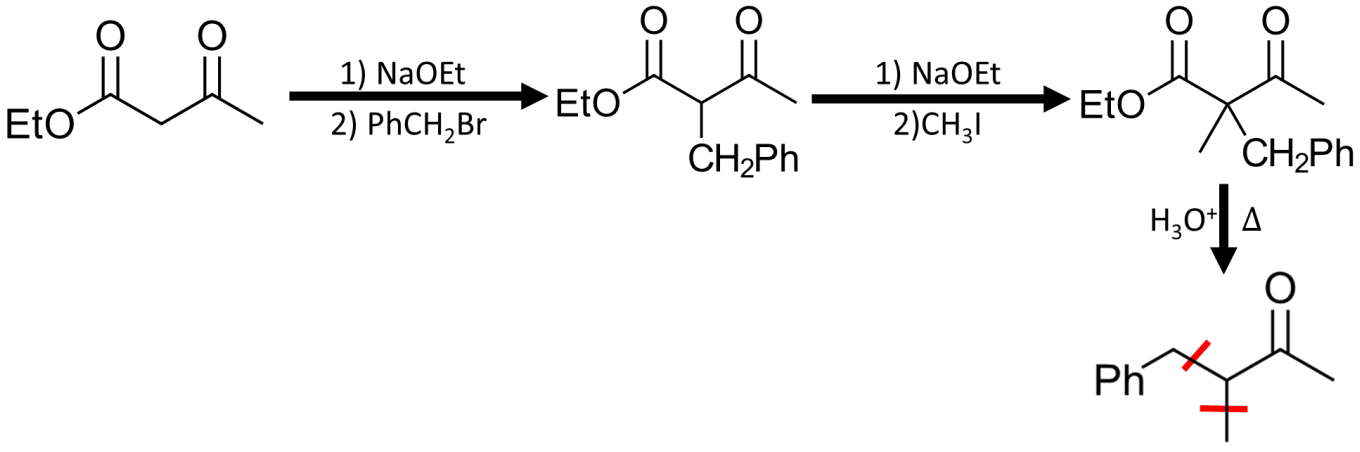
14.1:



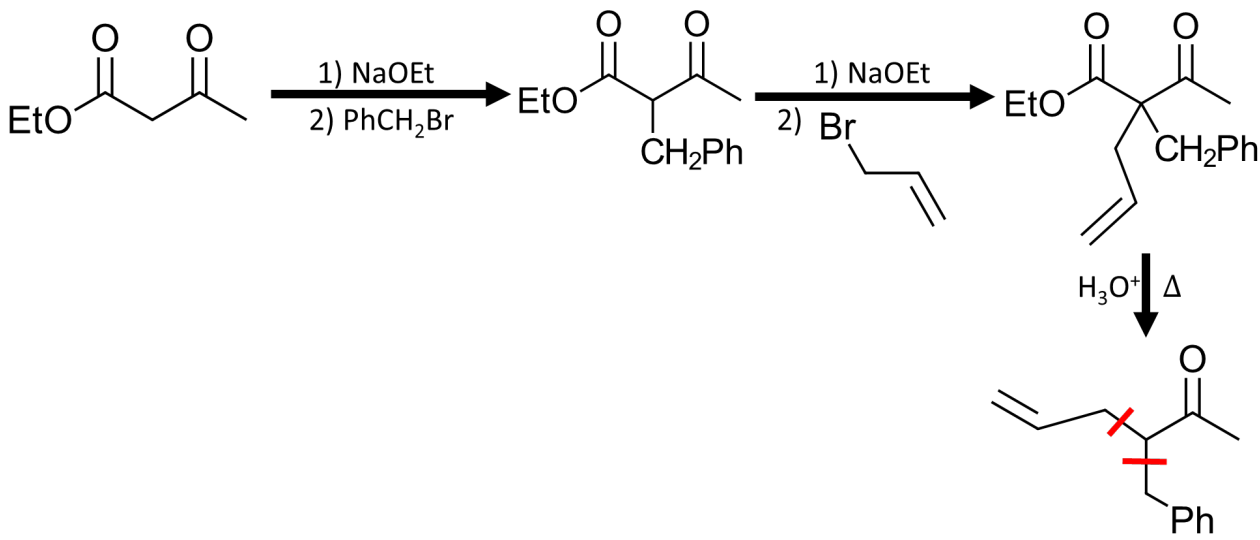
14.2:



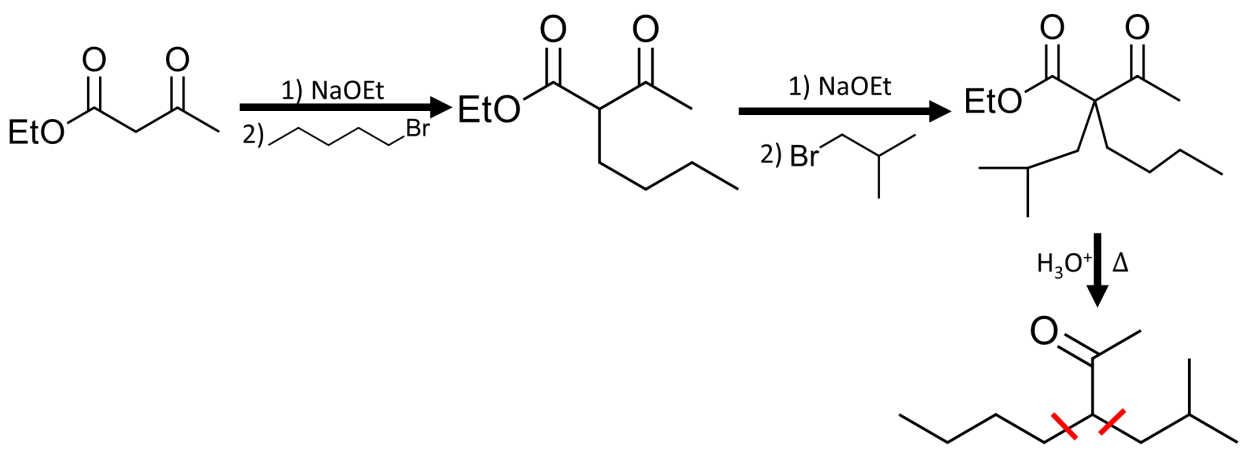
14.3:



14.4:

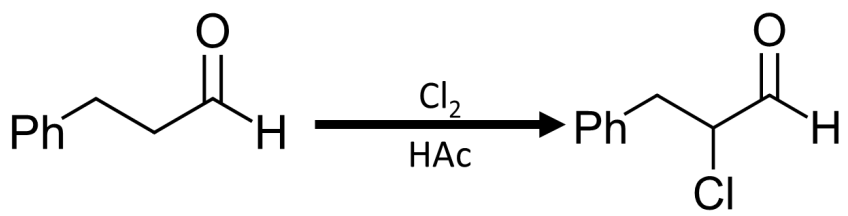


14.5:

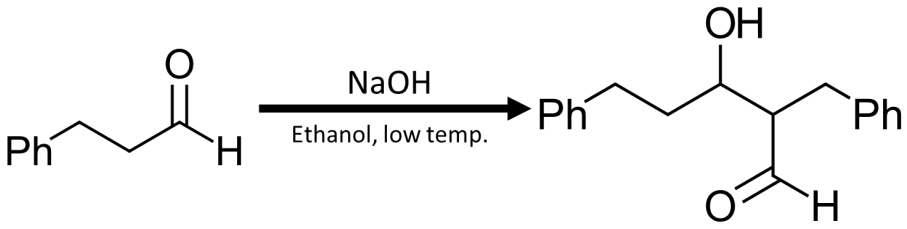


P.15 ➡ *Solution*

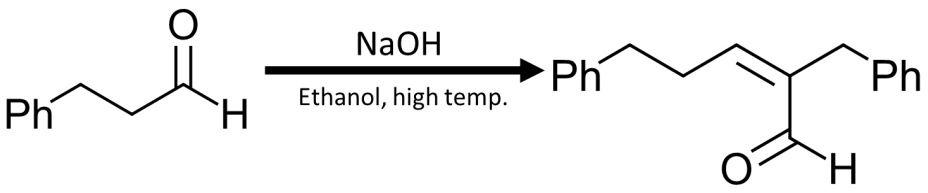
15.1: Chlorination of 3-phenylpropanal under conditions of acid catalysis occurs via the enol form and yields the α-chloro derivative.



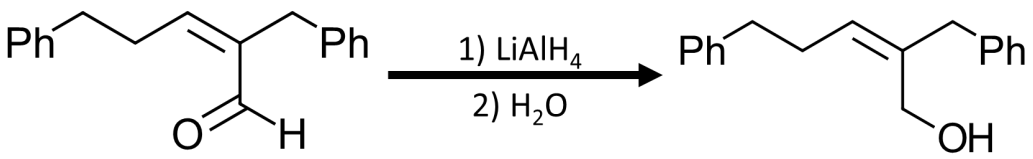
15.2: Aldehydes undergo aldol addition on treatment with base.



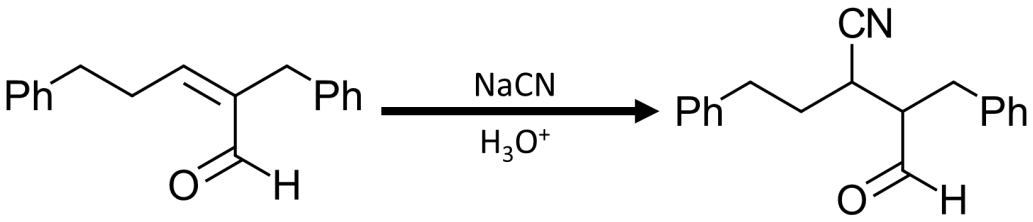
15.3: Dehydration of the aldol addition product occurs when the reaction is carried out at elevated temperature.



15.4: Lithium aluminum hydride reduces the aldehyde function to the corresponding primary alcohol.

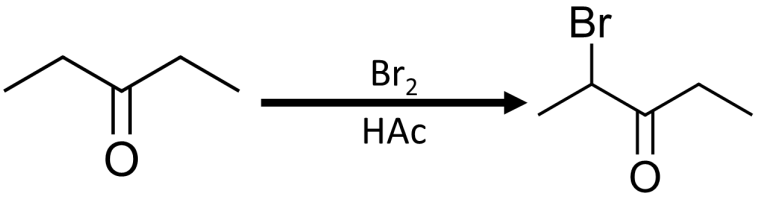


15.5: A characteristic reaction of α,β-unsaturated carbonyl compounds is their tendency to undergo conjugate addition on treatment with weakly basic nucleophiles.

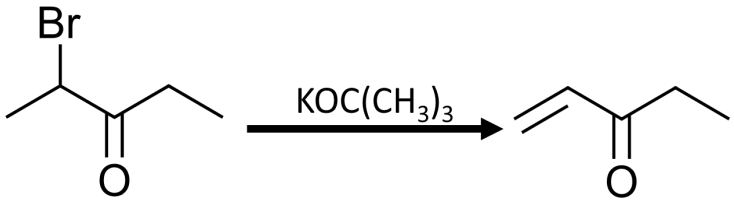


P.16 ➡ *Solution*

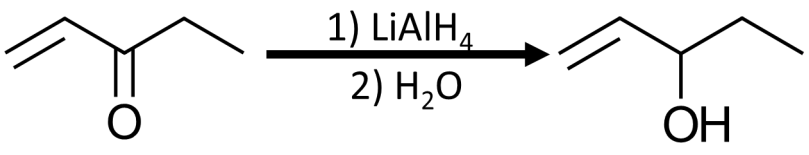
16.1: Conversion of 3-pentanone to 2-bromo-3-pentanone is best accomplished by acid-catalyzed bromination via the enol. Bromine in acetic acid is the customary reagent for this transformation.



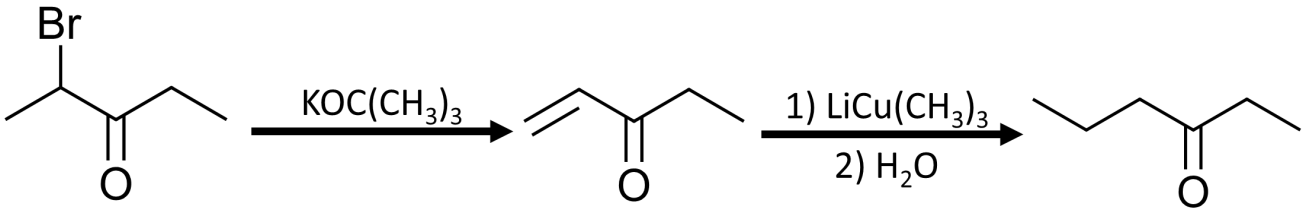
16.2: Once 2-bromo-3-pentanone has been prepared, dehydrohalogenation by base converts it to the α,β-unsaturated ketone.



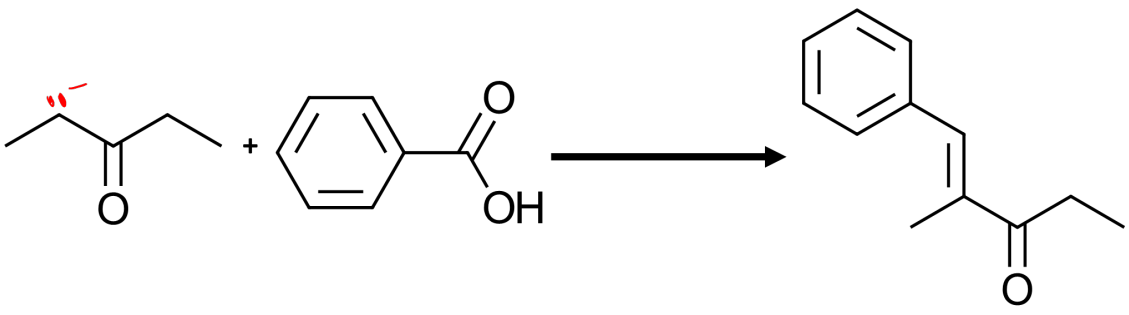
16.3: Once 1-penten-3-one has been prepared, reduction with $LiAlH_4$ followed by aqueous workup yields the desired alcohol. Catalytic hydrogenation would not be suitable for this reaction because reduction of the double bond would accompany carbonyl reduction.



16.4: Conversion of 3-pentanone to 3-hexanone requires addition of a methyl group to the β carbon. The best way to add an alkyl group to the β carbon of a ketone is via conjugate addition of a dialkylcuprate reagent to an α,β-unsaturated ketone.



16.5: The compound can be prepared as the mixed aldol condensation product of 3-pentanone and benzaldehyde.



REFERENCES

- CAREY, F. (2008). *Organic Chemistry*. 7th edition. New York: McGraw-Hill.
- KLEIN, D. (2017). *Organic Chemistry*. 3rd edition. Hoboken: John Wiley and Sons.
- MCMURRY, J. (2008). *Organic Chemistry*. 7th edition. Belmont: Thomson.
- VOLLHARDT, P. and SCHORE, N. (2014). *Organic Chemistry: Structure and Function*. 7th edition. New York: W.H. Freeman.