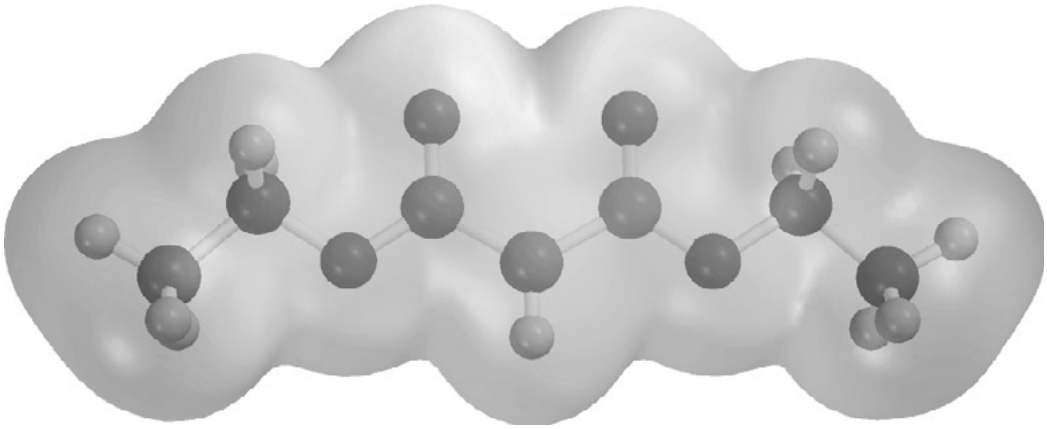
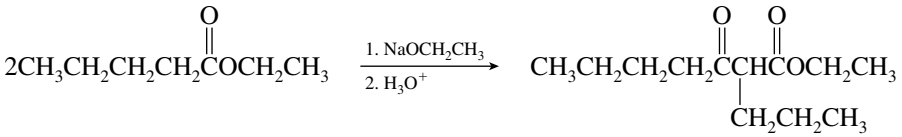


CHAPTER 21

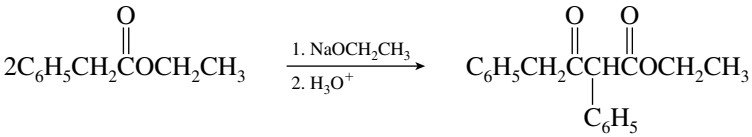
ESTER ENOLATES

SOLUTIONS TO TEXT PROBLEMS

21.1 Ethyl benzoate cannot undergo the Claisen condensation, because it has no protons on its α-carbon atom and so cannot form an enolate. Ethyl pentanoate and ethyl phenylacetate can undergo the Claisen condensation.

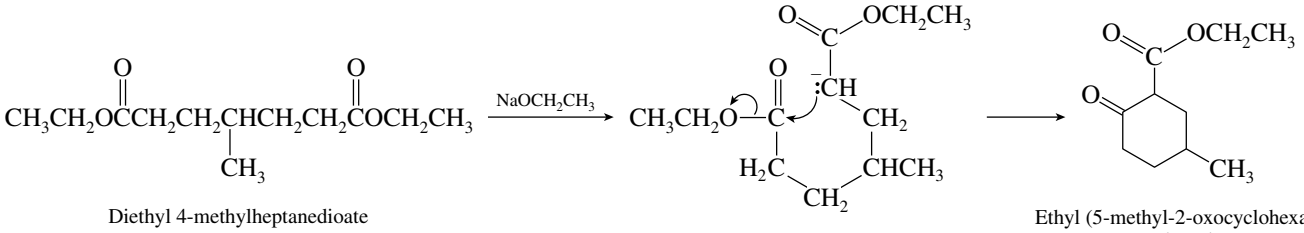


Ethyl pentanoate — Ethyl 3-oxo-2-propylheptanoate



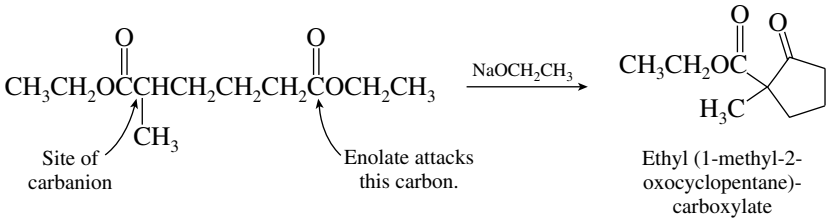
Ethyl phenylacetate — Ethyl 3-oxo-2,4-diphenylbutanoate

21.2 (*b*) The enolate formed by proton abstraction from the α-carbon atom of diethyl 4-methylheptanedioate cyclizes to form a six-membered β-keto ester.

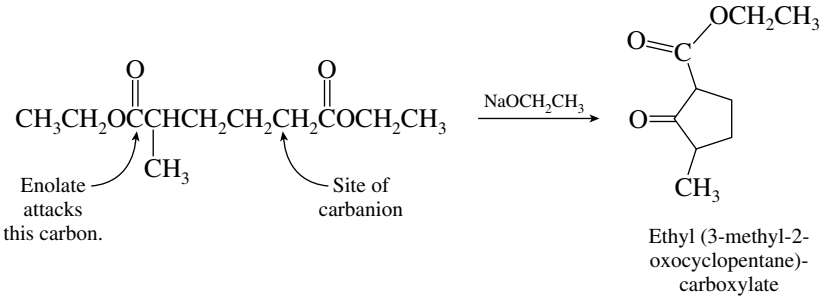


Diethyl 4-methylheptanedioate — Ethyl (5-methyl-2-oxocyclohexane)-carboxylate

(*c*) The two α carbons of this diester are not equivalent. Cyclization by attack of the enolate at C-2 gives

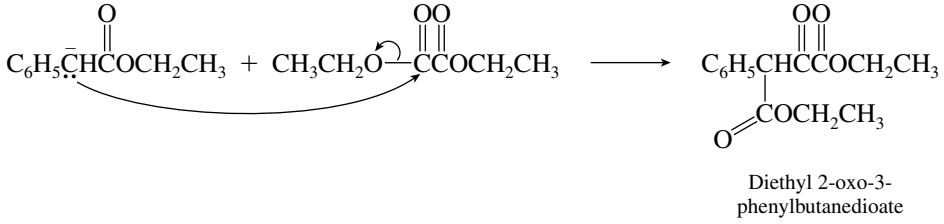


This β-keto ester cannot form a stable enolate by deprotonation. It is present in only small amounts at equilibrium. The major product is formed by way of the other enolate.

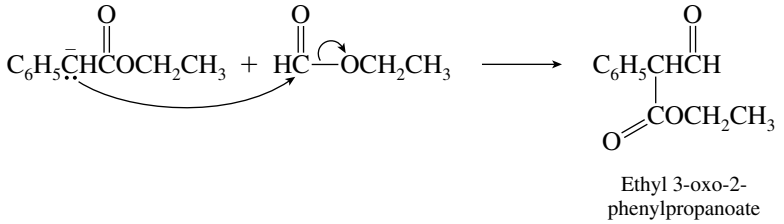


This β-keto ester is converted to a stable enolate on deprotonation, causing the equilibrium to shift in its favor.

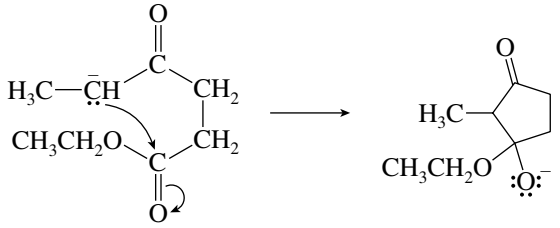
21.3 (*b*) Both carbonyl groups of diethyl oxalate are equivalent. The enolate of ethyl phenylacetate attacks one of them.

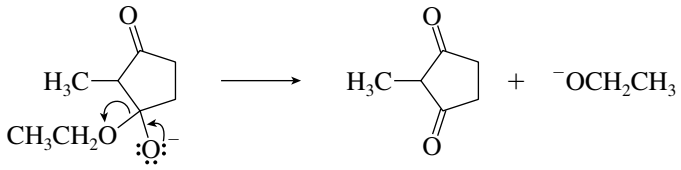


(*c*) The enolate of ethyl phenylacetate attacks the carbonyl group of ethyl formate.



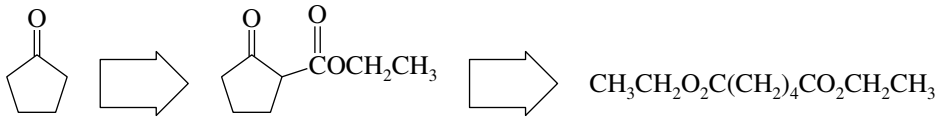
21.4 In order for a five-membered ring to be formed, C-5 must be the carbanionic site that attacks the ester carbonyl.



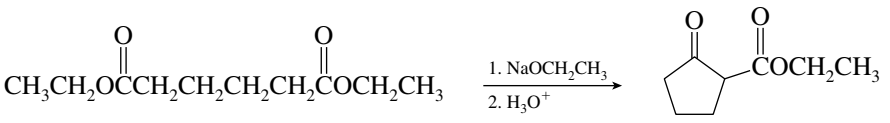


2-Methyl-1,3-cyclopentanedione

21.5 The desired ketone, cyclopentanone, is derived from the corresponding β-keto ester. This key intermediate is obtained from a Dieckmann cyclization of the starting material, diethyl hexanedioate.



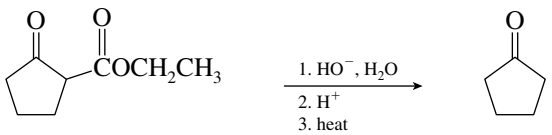
First treat the diester with sodium ethoxide to effect the Dieckmann cyclization.



Diethyl hexanedioate

Ethyl (2-oxocyclopentane)-carboxylate

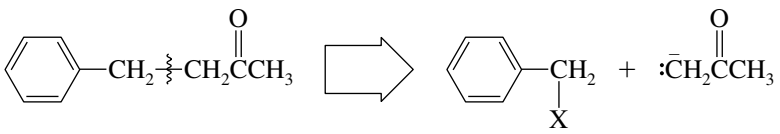
Next convert the β-keto ester to the desired product by saponification and decarboxylation.



Ethyl (2-oxocyclopentane)-carboxylate

Cyclopentanone

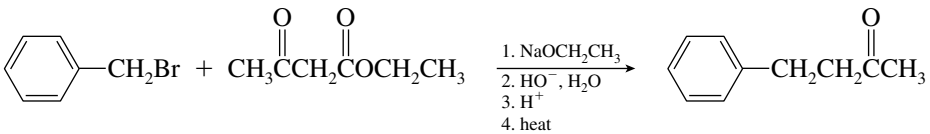
21.6 (*b*) Write a structural formula for the desired product; then disconnect a bond to the α-carbon atom.



Required alkyl halide

Derived from ethyl acetoacetate

Therefore

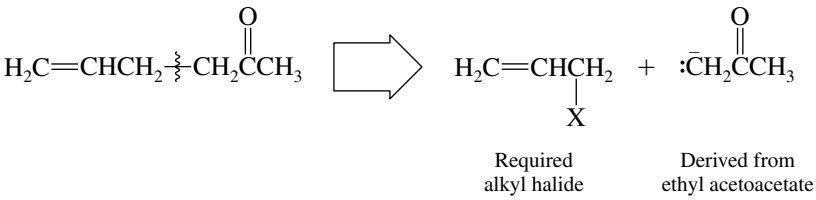


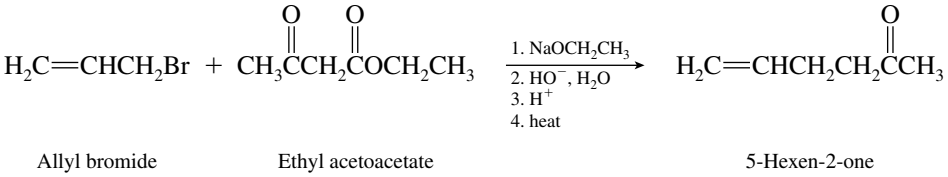
Benzyl bromide

Ethyl acetoacetate

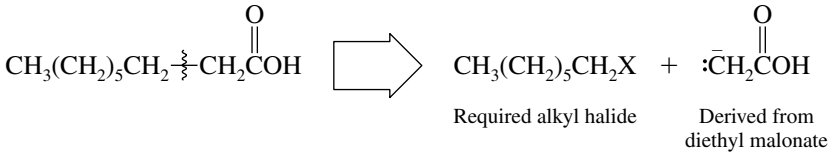
4-Phenyl-2-butanone

(*c*) The disconnection approach to retrosynthetic analysis reveals that the preparation of 5-hexen-2-one by the acetoacetic ester synthesis requires an allylic halide.

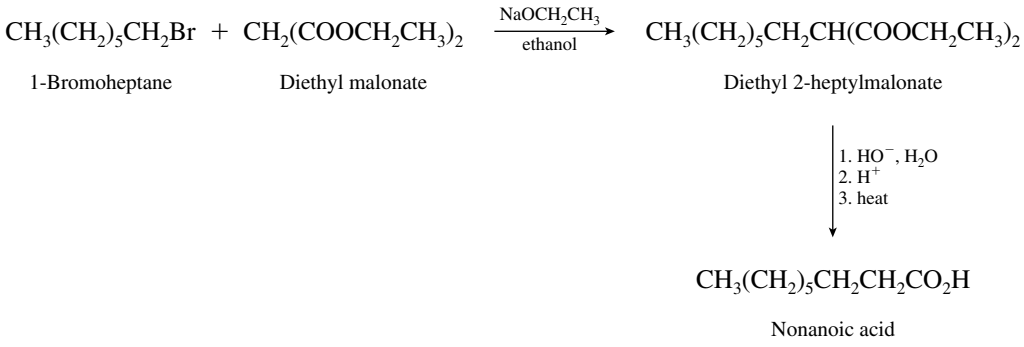




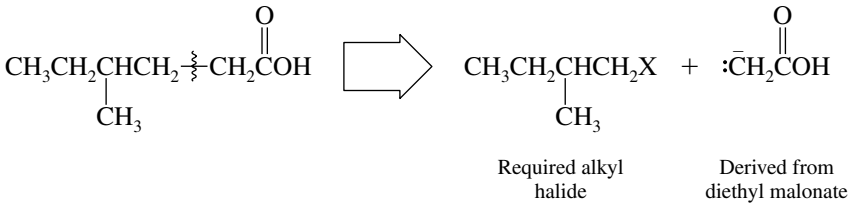
21.7 (*b*) Nonanoic acid has a $CH_3(CH_2)_5CH_2$— unit attached to the CH_2COH synthon.



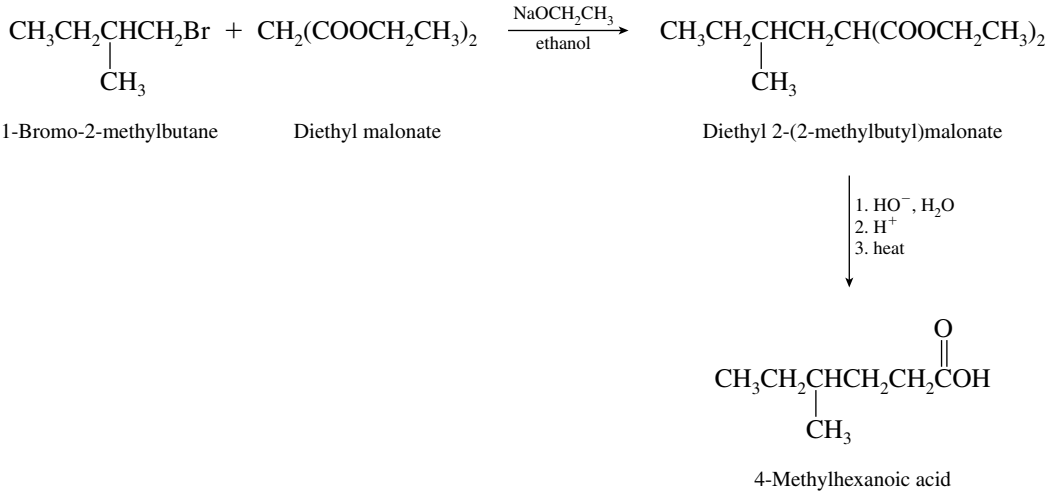
Therefore the anion of diethyl malonate is alkylated with a 1-haloheptane.



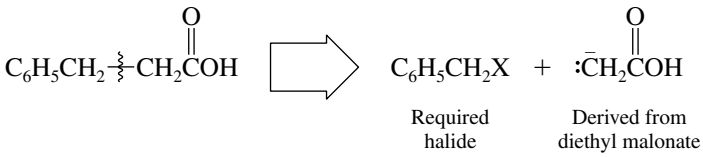
(*c*) Disconnection of the target molecule adjacent to the α carbon reveals the alkyl halide needed to react with the enolate derived from diethyl malonate.



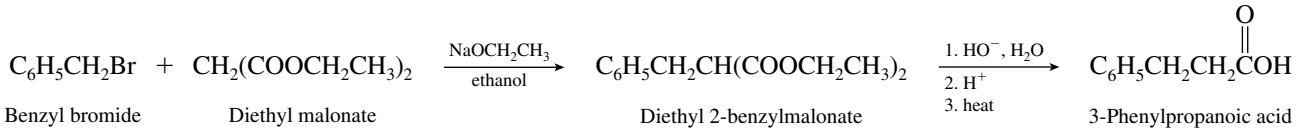
The necessary alkyl halide in this synthesis is 1-bromo-2-methylbutane.



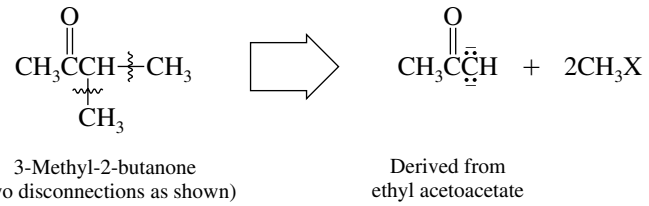
(*d*) Once again disconnection reveals the necessary halide, which is treated with diethyl malonate.



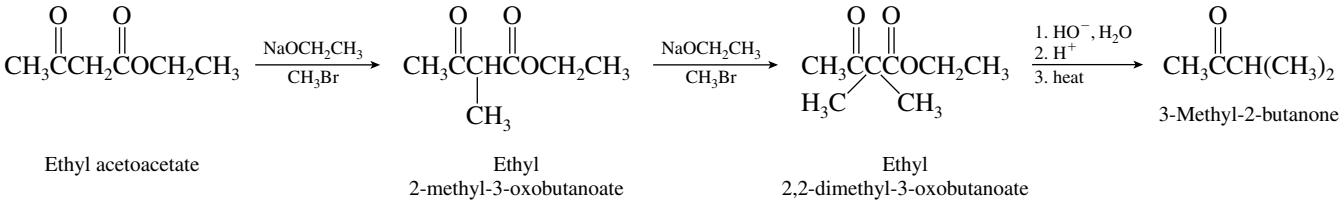
Alkylation of diethyl malonate with benzyl bromide is the first step in the preparation of 3-phenylpropanoic acid.



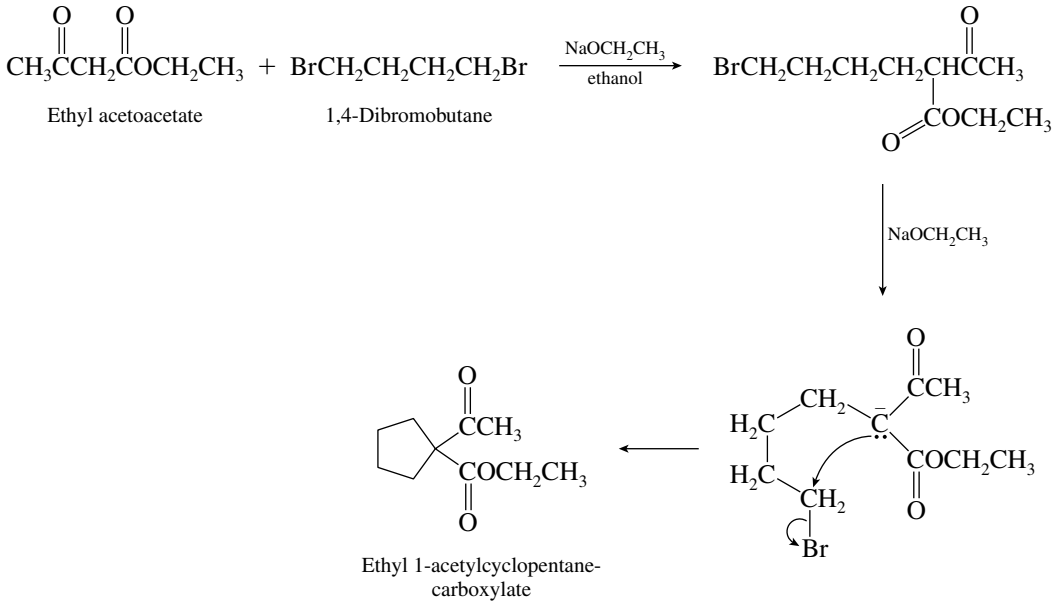
21.8 Retrosynthetic analysis of the formation of 3-methyl-2-butanone is carried out in the same way as for other ketones.



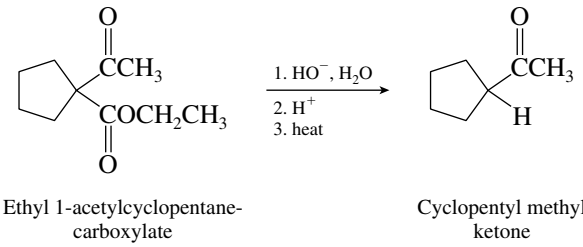
The two alkylation steps are carried out sequentially.



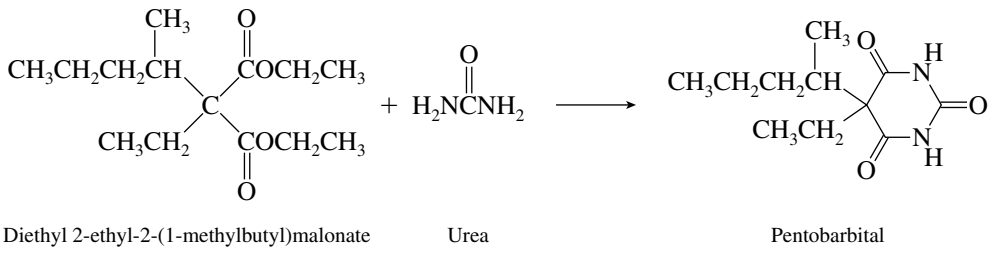
21.9 Alkylation of ethyl acetoacetate with 1,4-dibromobutane gives a product that can cyclize to a five-membered ring.



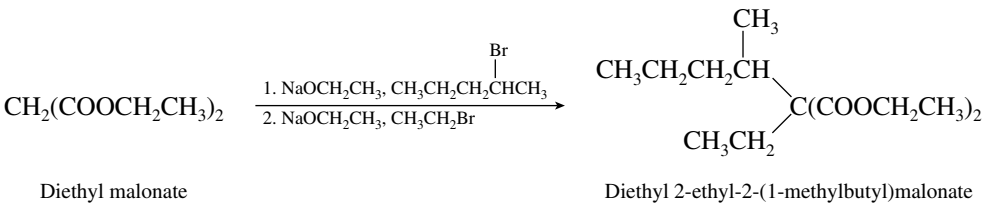
Saponification followed by decarboxylation gives cyclopentyl methyl ketone.



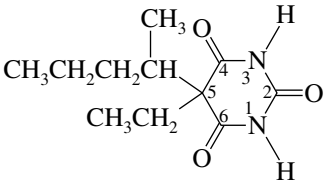
21.10 The last step in the synthesis of pentobarbital is the reaction of the appropriately substituted derivative of diethyl malonate with urea.



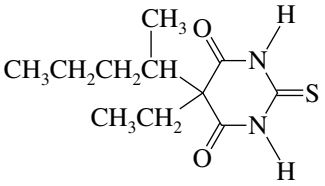
The dialkyl derivative of diethyl malonate is made in the usual way. It does not matter whether the ethyl group or the 1-methylbutyl group is introduced first.



21.11 The carbonyl oxygen at C-2 of pentobarbital is replaced by sulfur in Pentothal (thiopental).

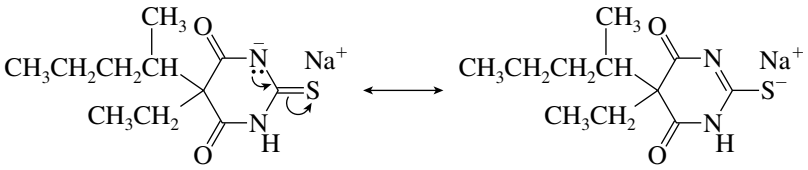


Pentobarbital; prepared from urea, $(H_2N)_2C{=}O$



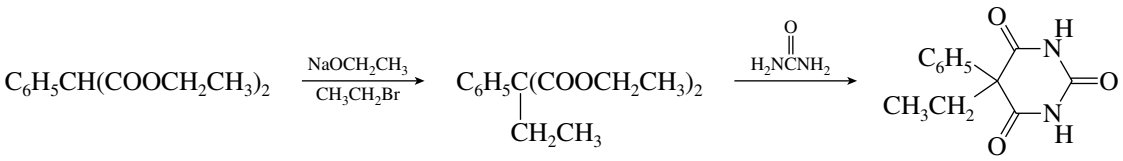
Pentothal; prepared from thiourea, $(H_2N)_2C{=}S$

The sodium salt of Pentothal is formed by removal of a proton from one of the N—H groups by sodium hydroxide.



Pentothal sodium

21.12 The synthesis of phenobarbital requires diethyl 2-phenylmalonate as the starting material.

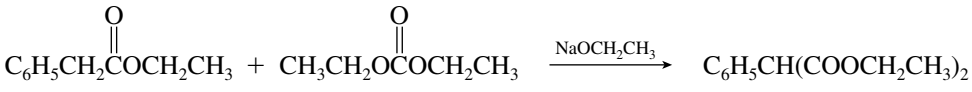


Diethyl 2-phenylmalonate

Diethyl 2-ethyl-2-phenylmalonate

Phenobarbital

Diethyl 2-phenylmalonate is prepared by a mixed Claisen condensation between ethyl phenylacetate and diethyl carbonate.

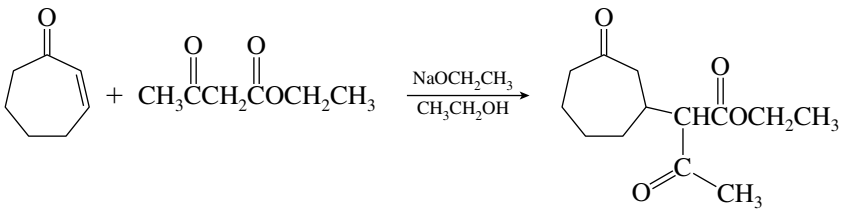


Ethyl phenylacetate

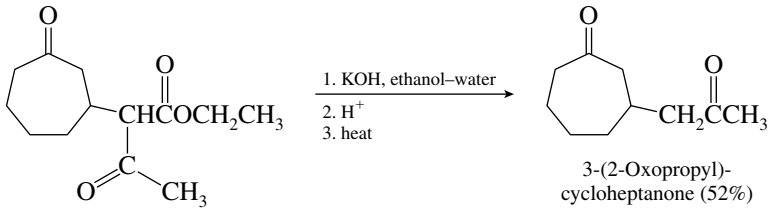
Diethyl carbonate

Diethyl 2-phenylmalonate

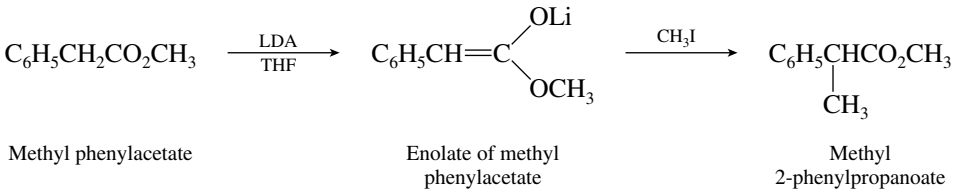
21.13 Like diethyl malonate, ethyl acetoacetate undergoes Michael addition to an α, β-unsaturated ketone.



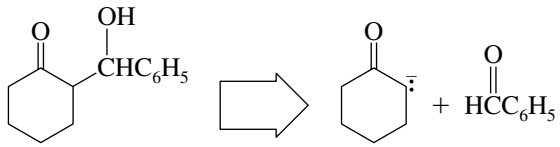
Basic ester hydrolysis followed by acidification and decarboxylation gives the diketone 3-(2-oxopropyl)cycloheptanone as the major product of the reaction sequence.



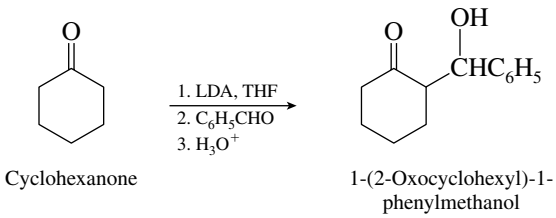
21.14 (*b*) The α-carbon atom of the ester bears a phenyl substituent and a methyl group. Only the methyl group can be attached to the α carbon by nucleophilic substitution. Therefore generate the enolate of methyl phenylacetate with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and then alkylate with methyl iodide.



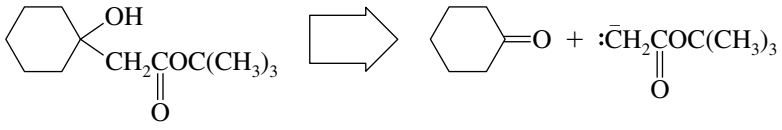
(*c*) The desired product corresponds to an aldol addition product.



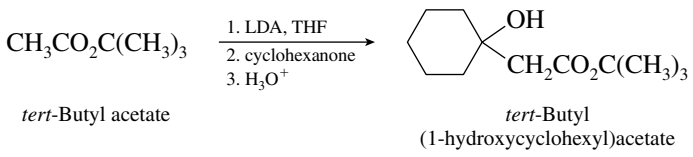
Therefore convert cyclohexanone to its enolate and then treat with benzaldehyde.



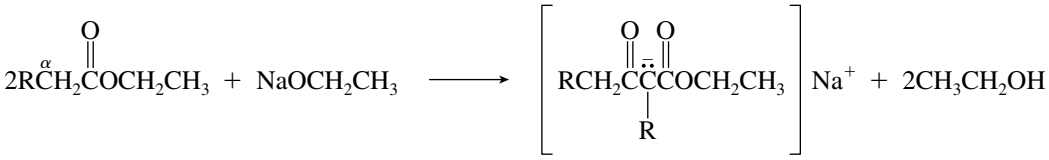
(*d*) This product corresponds to the addition of the enolate of *tert*-butyl acetate to cyclohexanone.



Generate the enolate of *tert*-butyl acetate with lithium diisopropylamide; then add cyclohexanone.

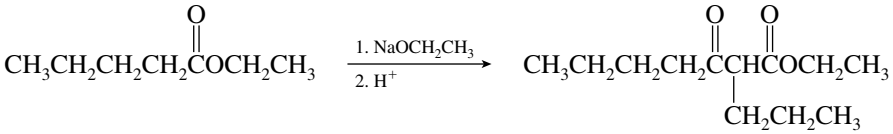


21.15 To undergo a Claisen condensation, an ester must have at least two protons on the α carbon:

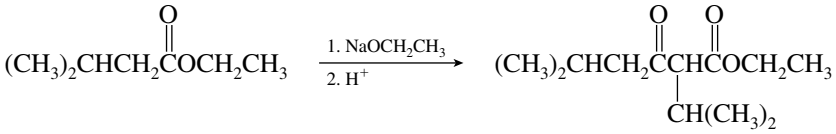


The equilibrium constant for condensation is unfavorable unless the β-keto ester can be deprotonated to form a stable anion.

(*a*) Among the esters given, ethyl pentanoate and ethyl 3-methylbutanoate undergo the Claisen condensation

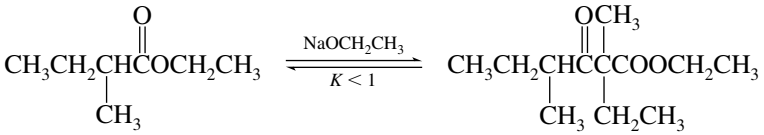


Ethyl pentanoate — Ethyl 3-oxo-2-propylheptanoate



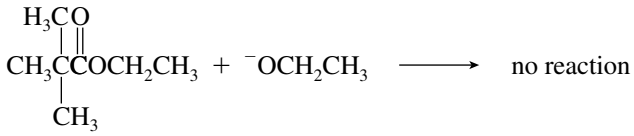
Ethyl 3-methylbutanoate — Ethyl 2-isopropyl-5-methyl-3-oxohexanoate

(*b*) The Claisen condensation product of ethyl 2-methylbutanoate cannot be deprotonated; the equilibrium constant for its formation is less than 1.



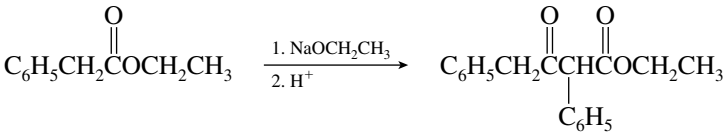
Ethyl 2-methylbutanoate — No protons on α-carbon atom; cannot form stabilized enolate by deprotonation

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



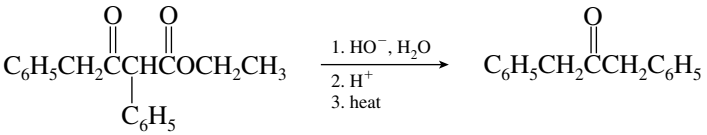
Ethyl 2,2-dimethylpropanoate

21.16 (*a*) The Claisen condensation of ethyl phenylacetate is given by the equation



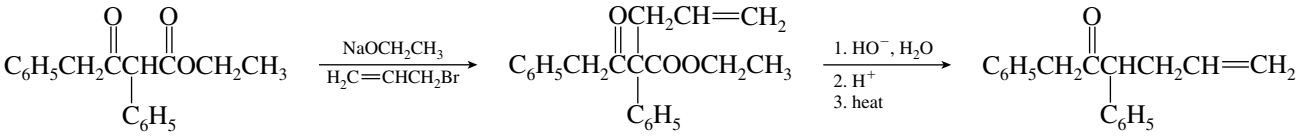
Ethyl phenylacetate — Ethyl 3-oxo-2,4-diphenylbutanoate

(*b*) Saponification and decarboxylation of this β-keto ester gives dibenzyl ketone.



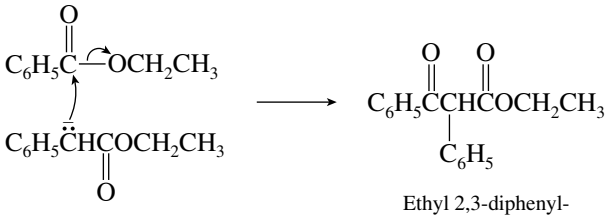
Ethyl 3-oxo-2,4-diphenylbutanoate — Dibenzyl ketone

(*c*) This process illustrates the alkylation of a β-keto ester with subsequent saponification and decarboxylation.



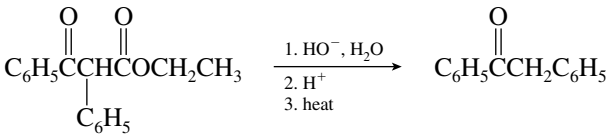
Ethyl 3-oxo-2,4-diphenylbutanoate — 1,3-Diphenyl-5-hexen-2-one

(*d*) The enolate ion of ethyl phenylacetate attacks the carbonyl carbon of ethyl benzoate.



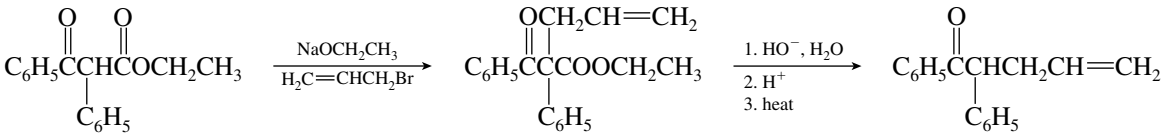
Ethyl 2,3-diphenyl-3-oxopropanoate

(*e*) Saponification and decarboxylation yield benzyl phenyl ketone.



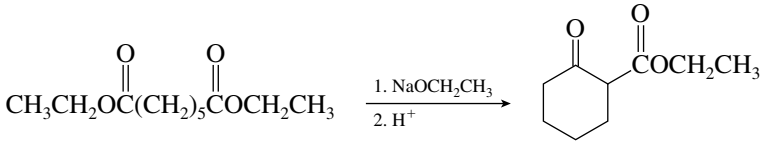
Ethyl 3-Oxo-2,3-diphenylpropanoate — Benzyl phenyl ketone

(*f*) This sequence is analogous to that of part (*c*).



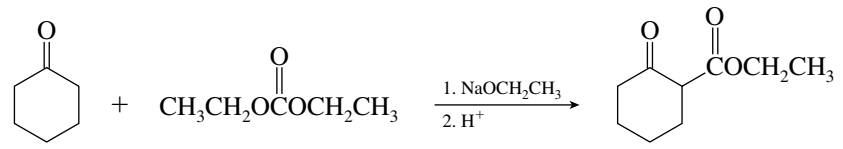
1,2-Diphenyl-4-penten-1-one

21.17 (*a*) The Dieckmann reaction is the intramolecular version of the Claisen condensation. It employs a diester as starting material.



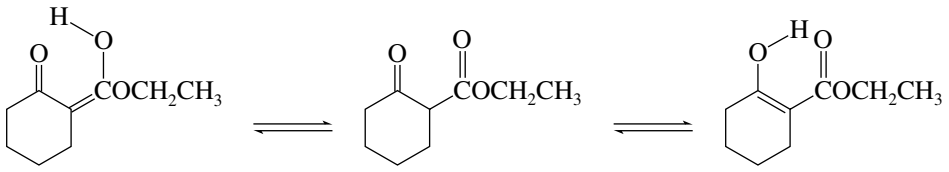
Diethyl heptanedioate — Ethyl (2-oxocyclohexane)-carboxylate

(*b*) Acylation of cyclohexanone with diethyl carbonate yields the same β-keto ester formed in part (*a*).

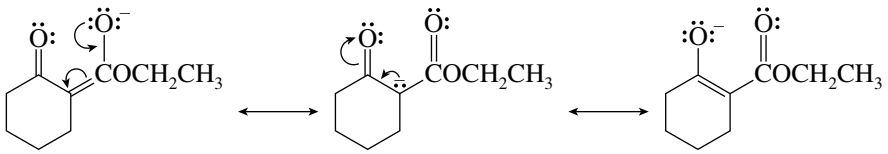


Cyclohexanone — Diethyl carbonate — Ethyl (2-oxocyclohexane)-carboxylate

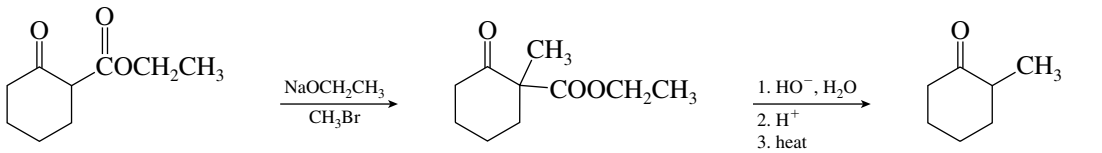
(*c*) The two most stable enol forms are those that involve the proton on the carbon flanked by the two carbonyl groups.



(*d*) Deprotonation of the β-keto ester involves the acidic proton at the carbon flanked by the two carbonyl groups

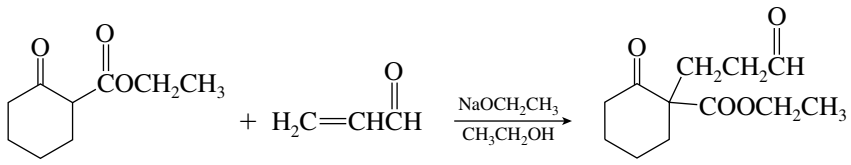


(*e*) The methyl group is introduced by alkylation of the β-keto ester. Saponification and decarboxylation complete the synthesis.



Ethyl (2-oxocyclohexane)-carboxylate — Ethyl (1-methyl-2-oxocyclohexane)-carboxylate — 2-Methylcyclohexanone

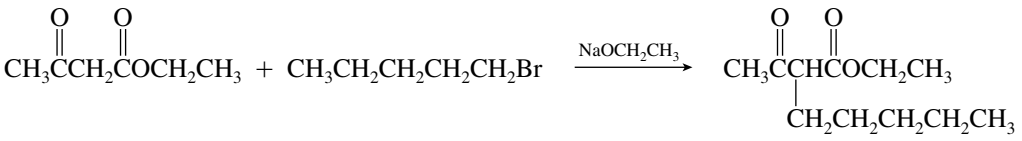
(*f*) The enolate ion of the β-keto ester [see part (*d*)] undergoes Michael addition to the carbon–carbon double bond of acrolein.



Ethyl (2-oxocyclohexane)-carboxylate — Acrolein — Michael adduct

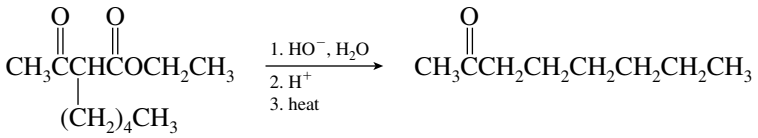
This reaction has been reported in the chemical literature and proceeds in 65–75% yield.

21.18 (*a*) Ethyl acetoacetate is converted to its enolate ion with sodium ethoxide; this anion then acts as a nucleophile toward 1-bromopentane.



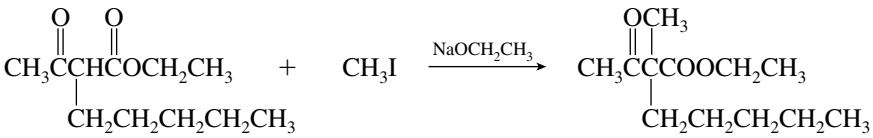
Ethyl acetoacetate — 1-Bromopentane — Ethyl 2-acetylheptanoate

(*b*) Saponification and decarboxylation of the product in part (*a*) yields 2-octanone.



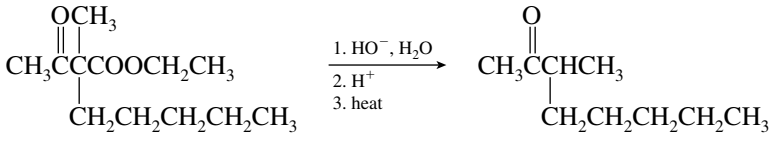
Ethyl 2-acetylheptanoate — 2-Octanone

(*c*) The product derived from the reaction in part (*a*) can be alkylated again:



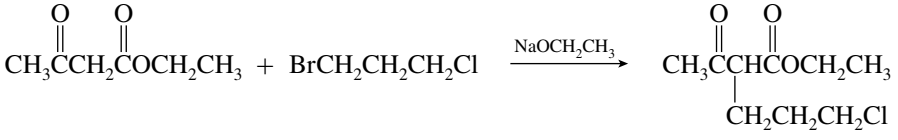
Ethyl 2-acetylheptanoate — Ethyl 2-acetyl-2-methylheptanoate

(*d*) The dialkylated derivative of acetoacetic ester formed in part (*c*) can be converted to a ketone by saponification and decarboxylation.



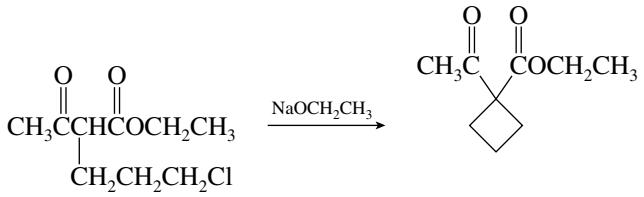
Ethyl 2-acetyl-2-methylheptanoate — 3-Methyl-2-octanone

(*e*) The anion of ethyl acetoacetate acts as a nucleophile toward 1-bromo-3-chloropropane. Bromide is a better leaving group than chloride and is displaced preferentially.



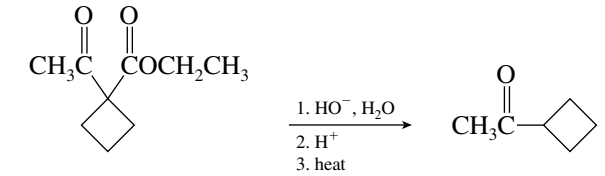
Ethyl acetoacetate — 1-Bromo-3-chloropropane — Ethyl 2-acetyl-5-chloropentanoate

(*f*) Treatment of the product of part (*e*) with sodium ethoxide gives an enolate ion that cyclizes by intramolecular nucleophilic substitution of chloride.



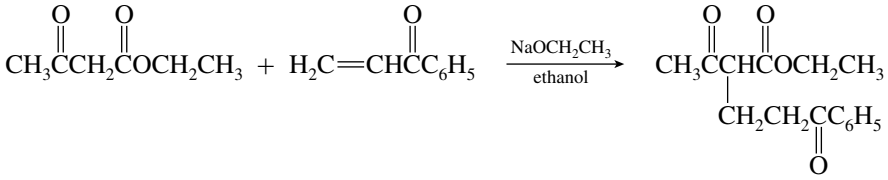
Ethyl 2-acetyl-5-chloropentanoate — Ethyl 1-acetylcyclobutanecarboxylate

(*g*) Cyclobutyl methyl ketone is formed by saponification and decarboxylation of the product in part (*f*).



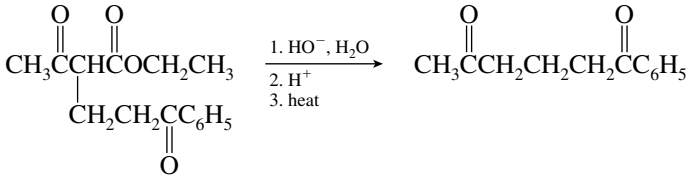
Ethyl 1-acetylcyclobutanecarboxylate — Cyclobutyl methyl ketone

(*h*) Ethyl acetoacetate undergoes Michael addition to phenyl vinyl ketone in the presence of base.



Ethyl acetoacetate — Phenyl vinyl ketone — Ethyl 2-acetyl-5-oxo-5-phenylpentanoate

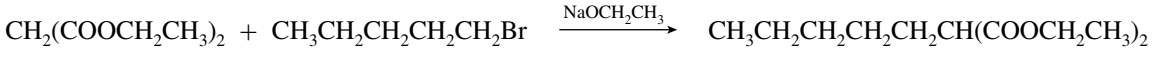
(*i*) A diketone results from saponification and decarboxylation of the Michael adduct.



Ethyl 2-acetyl-5-oxo-5-phenylpentanoate — 1-Phenyl-1,5-hexanedione

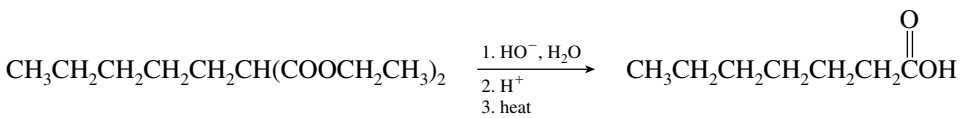
21.19 Diethyl malonate reacts with the reagents given in the preceding problem in a manner analogous to that of ethyl acetoacetate.

(*a*)



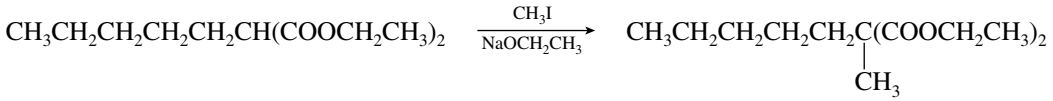
Diethyl malonate — 1-Bromopentane — Diethyl 1,1-hexanedicarboxylate (diethyl pentylmalonate)

(*b*)



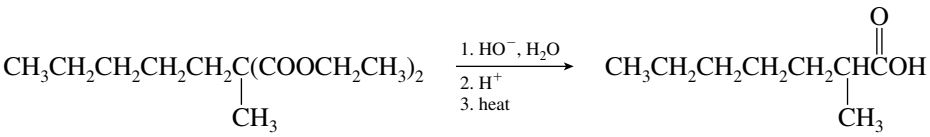
Diethyl 1,1-hexanedicarboxylate — Heptanoic acid

(*c*)



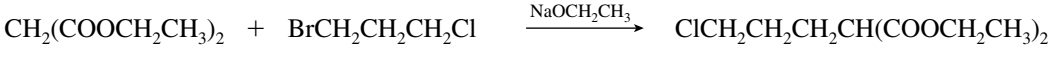
Diethyl 1,1-hexanedicarboxylate — Diethyl 2,2-heptanedicarboxylate

(*d*)



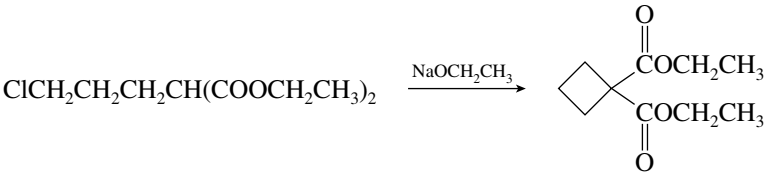
Diethyl 2,2-heptanedicarboxylate — 2-Methylheptanoic acid

(*e*)



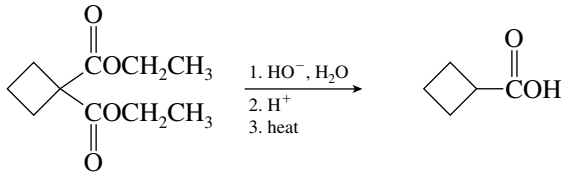
Diethyl malonate — 1-Bromo-3-chloropropane — Diethyl 4-chloro-1,1-butanedicarboxylate

(*f*)



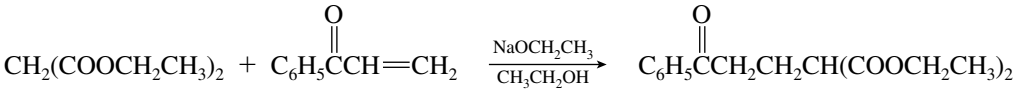
Diethyl 4-chloro-1,1-butanedicarboxylate — Diethyl cyclobutane-1,1-dicarboxylate

(*g*)



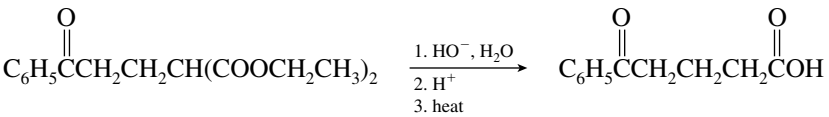
Diethyl cyclobutane-1,1-dicarboxylate — Cyclobutanecarboxylic acid

(*h*)



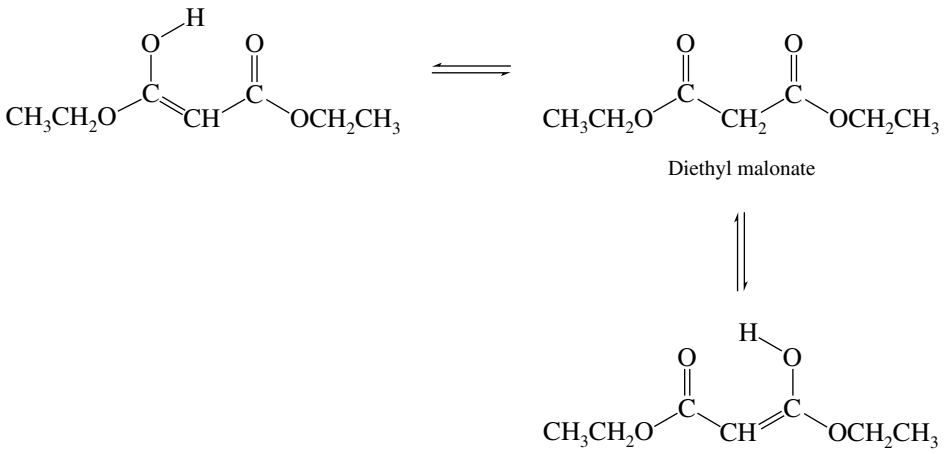
Diethyl malonate — Phenyl vinyl ketone — Diethyl 4-oxo-4-phenylbutane-1,1-dicarboxylate

(*i*)

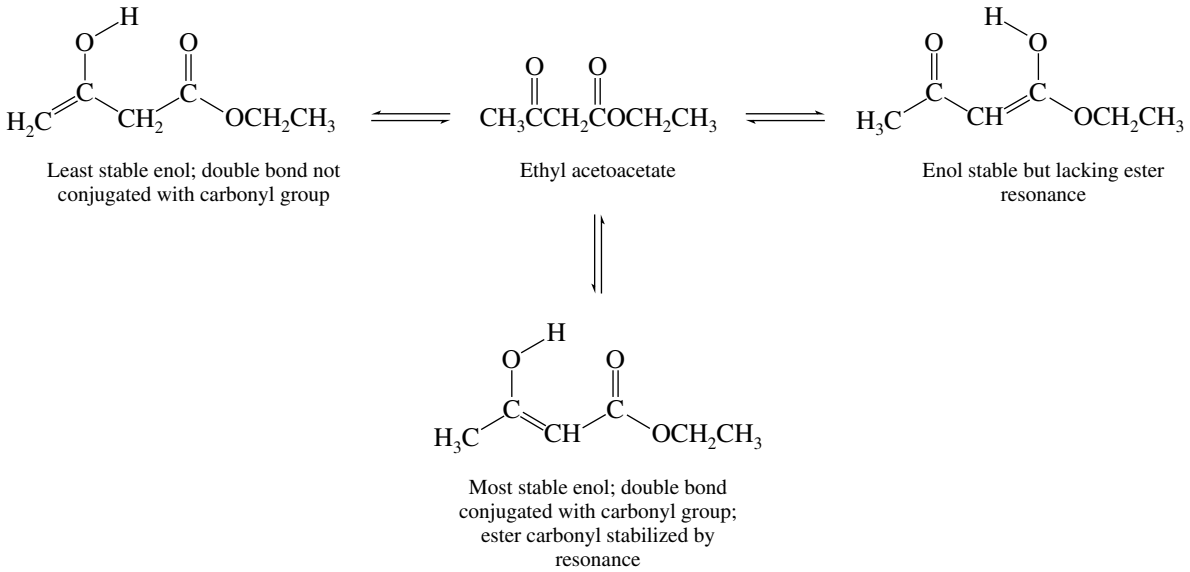


Diethyl 4-oxo-4-phenylbutane-1,1-dicarboxylate — 5-Oxo-5-phenylpentanoic acid

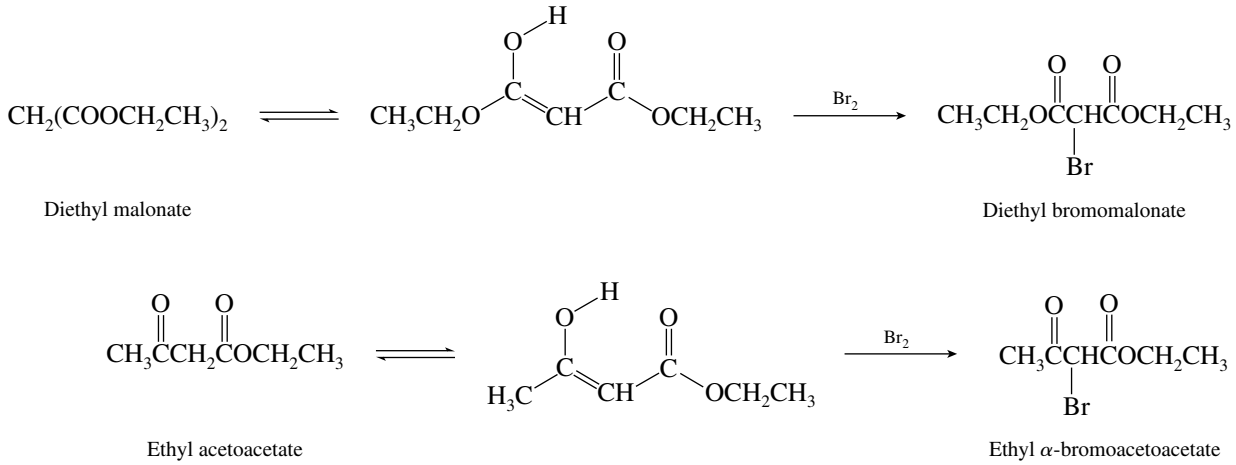
21.20 (*a*) Both carbonyl groups of diethyl malonate are equivalent, and so enolization can occur in either direction.



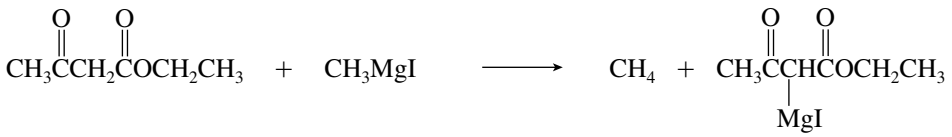
(*b*) Ethyl acetoacetate can give three constitutionally isomeric enols:



(*c*) Bromine reacts with diethyl malonate and ethyl acetoacetate by way of the corresponding enols:

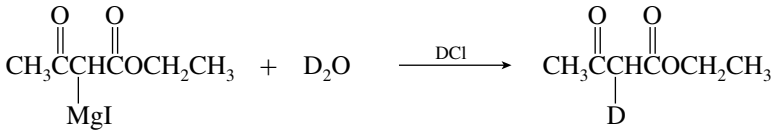


21.21 (*a*) Recall that Grignard reagents are destroyed by reaction with proton donors. Ethyl acetoacetate is a stronger acid than water; it transfers a proton to a Grignard reagent.



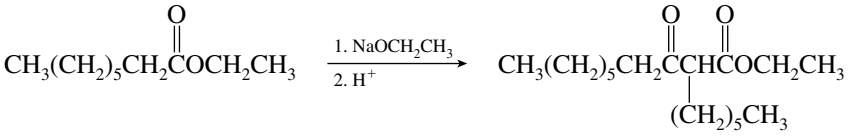
Ethyl acetoacetate — Methylmagnesium iodide — Methane — Iodomagnesium salt of ethyl acetoacetate

(*b*) Adding D_2O and DCl to the reaction mixture leads to D^+ transfer to the α-carbon atom of ethyl acetoacetate.



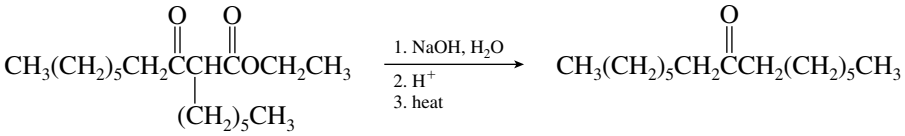
Iodomagnesium salt of ethyl acetoacetate — Deuterium oxide — Ethyl α-deuterioacetoacetate

21.22 (*a*) Ethyl octanoate undergoes a Claisen condensation to form a β-keto ester on being treated with sodium ethoxide.



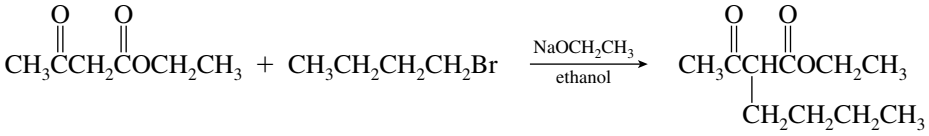
Ethyl octanoate — Ethyl 2-hexyl-3-oxodecanoate

(*b*) Saponification and decarboxylation of the β-keto ester yields a ketone.



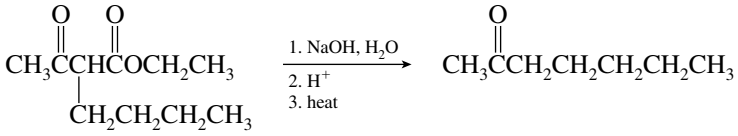
Ethyl 2-hexyl-3-oxodecanoate — 8-Pentadecanone

(*c*) On treatment with base, ethyl acetoacetate is converted to its enolate, which reacts as a nucleophile toward 1-bromobutane.



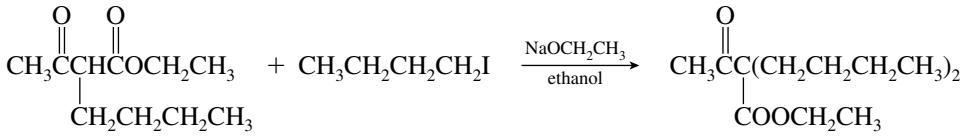
Ethyl acetoacetate — 1-Bromobutane — Ethyl 2-acetylhexanoate

(*d*) Alkylation of ethyl acetoacetate, followed by saponification and decarboxylation, gives a ketone. The two steps constitute the acetoacetic ester synthesis.



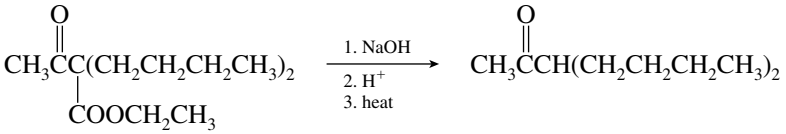
Ethyl 2-acetylhexanoate — 2-Heptanone

(*e*) An alkylated derivative of ethyl acetoacetate is capable of being alkylated a second time.



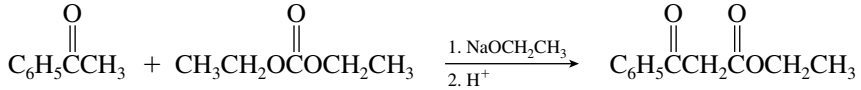
Ethyl 2-acetylhexanoate — 1-Iodobutane — Ethyl 2-acetyl-2-butylhexanoate

(*f*) The dialkylated derivative of acetoacetic ester formed in part (*e*) is converted to a ketone by saponification and decarboxylation.



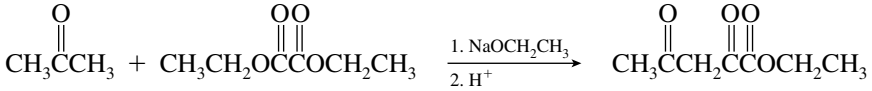
Ethyl 2-acetyl-2-butylhexanoate — 3-Butyl-2-heptanone

(*g*) The enolate of acetophenone attacks the carbonyl group of diethyl carbonate.



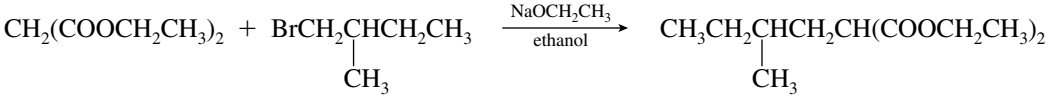
Acetophenone — Diethyl carbonate — 3-Oxo-3-phenylpropanoate

(*h*) Diethyl oxalate acts as an acylating agent toward the enolate of acetone.



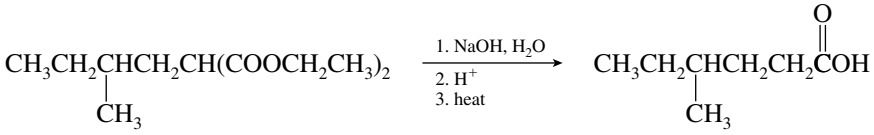
Acetone — Diethyl oxalate — Ethyl 2,4-dioxopentanoate

(*i*) The first stage of the malonic ester synthesis is the alkylation of diethyl malonate with an alkyl halide.



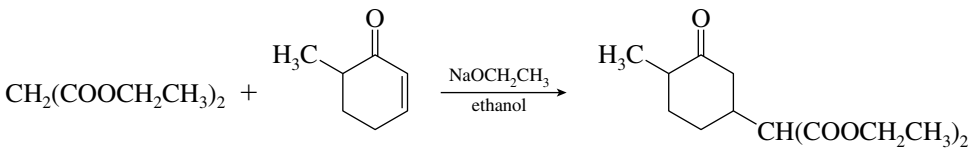
Diethyl malonate — 1-Bromo-2-methylbutane — Diethyl 3-methylpentane-1,1-dicarboxylate

(*j*) Alkylation of diethyl malonate is followed by saponification and decarboxylation to give a carboxylic acid.



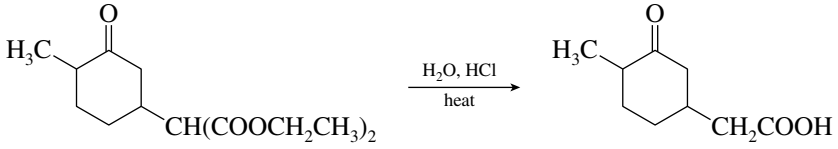
Diethyl 3-methylpentane-1,1-dicarboxylate — 4-Methylhexanoic acid (57% yield from 1-bromo-2-methylbutane)

(*k*) The anion of diethyl malonate undergoes Michael addition to 6-methyl-2-cyclohexenone.



Diethyl malonate — 6-Methyl-2-cyclohexenone — Diethyl 2-(4-methyl-3-oxocyclohexyl)malonate (isolated yield, 50%)

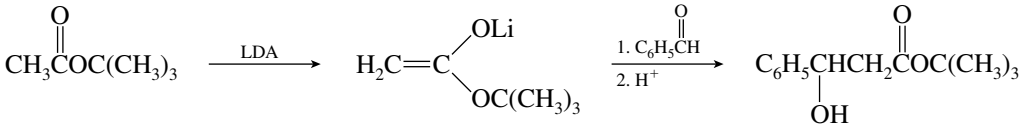
(*l*) Acid hydrolysis converts the diester in part (*k*) to a malonic acid derivative, which then undergoes decarboxylation.



Diethyl 2-(4-methyl-3-oxocyclohexyl)malonate

(4-Methyl-3-oxocyclohexyl)acetic acid (isolated yield, 80%)

(*m*) Lithium diisopropylamide (LDA) is used to convert esters quantitatively to their enolate ions. In this reaction the enolate of *tert*-butyl acetate adds to benzaldehyde.

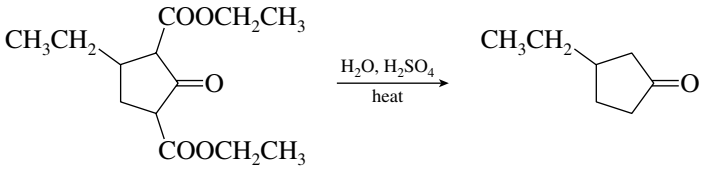


tert-Butyl acetate

Lithium enolate of *tert*-butyl acetate

tert-Butyl 3-hydroxy-3-phenylpropanoate

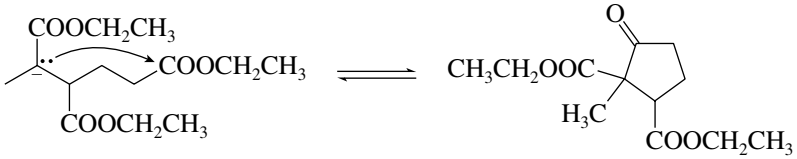
21.23 (*a*) Both ester functions in this molecule are β to a ketone carbonyl. Hydrolysis is followed by decarboxylation.



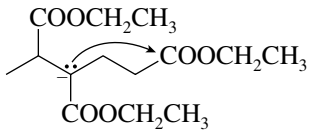
Diethyl 3-ethylcyclopentanone-2,5-dicarboxylate

3-Ethylcyclopentanone ($C_7H_{12}O$)

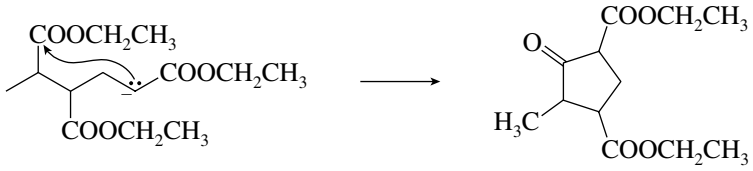
(*b*) Examine each carbon that is α to an ester function to see if it can lead to a five-, six-, or seven-membered cyclic β-keto ester by a Dieckmann cyclization.



Cyclization to a five-membered ring possible, but β-keto ester cannot be deprotonated to give a stable anion.

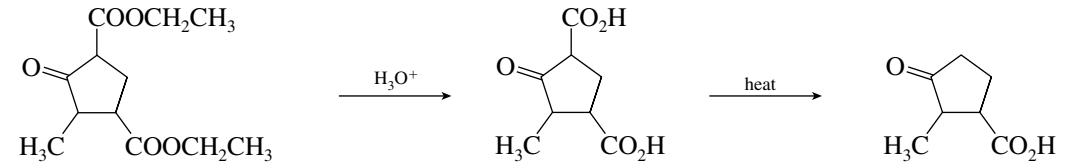


Cyclization not likely; resulting ring is four-membered and highly strained.



Cyclization gives a five-membered ring; β-keto ester deprotonated under reaction conditions; this is the observed product ($C_{12}H_{18}O_5$).

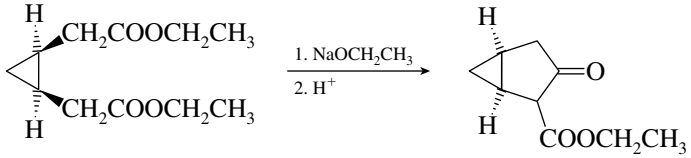
(*c*) Both ester function undergo hydrolysis in acid, but decarboxylation occurs only at the carboxyl group that is β to the ketone carbonyl.



Diethyl 2-methylcyclopentanone-3,5-dicarboxylate

2-Methylcyclopentanone-3-carboxylic acid ($C_7H_{10}O_3$)

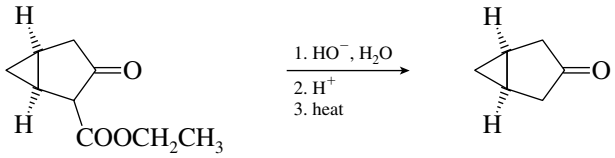
(*d*) A Dieckmann cyclization occurs, giving a five-membered ring fused to the original three-membered ring.



Diethyl *cis*-1,2-cyclopropanediacetate

Ethyl bicyclo[3.1.0]-hexan-3-one-2-carboxylate ($C_9H_{12}O_3$, 79%)

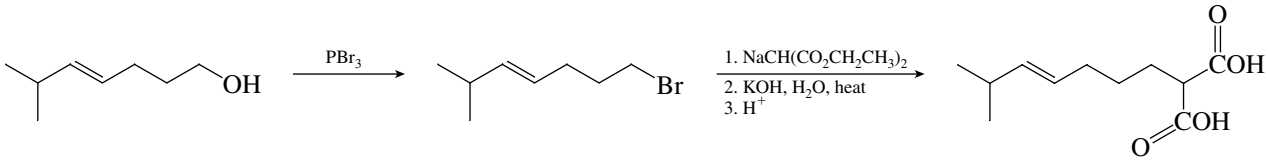
(*e*) Saponification and decarboxylation convert the β-keto ester to a ketone.



Ethyl bicyclo[3.1.0]hexan-3-one-2-carboxylate

Bicyclo[3.1.0]hexan-3-one (C_6H_8O, 43%)

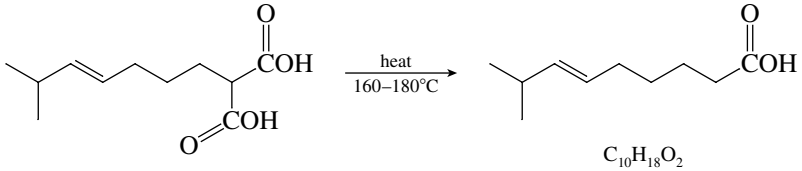
21.24 The heart of the preparation of capsaicin is a malonic ester synthesis. The first step is bromination of the primary alcohol by phosphorous tribromide. The resulting primary alkyl bromide is used to alkylate the sodium salt of diethyl malonate. A substituted malonic acid derivative is obtained following basic hydrolysis of the ester groups.



$C_8H_{15}Br$

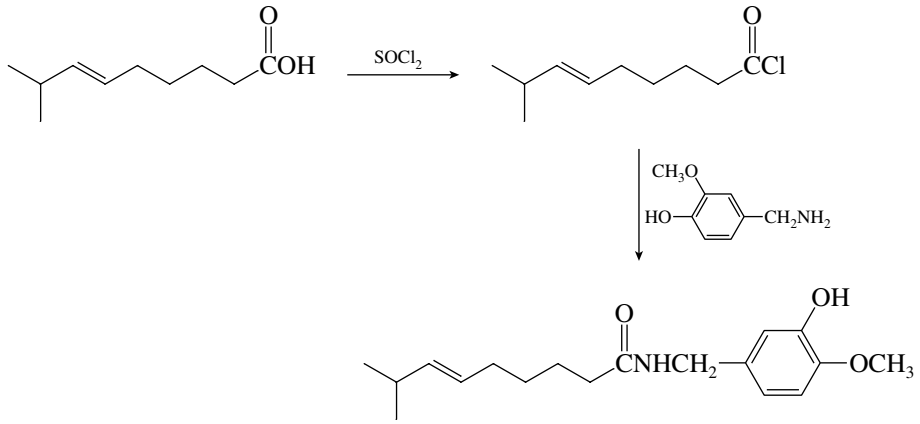
$C_{11}H_{18}O_4$

Malonic acid derivatives undergo decarboxylation on heating.



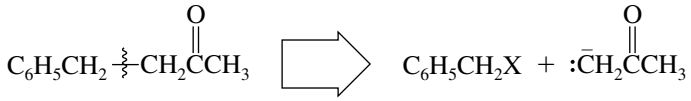
$C_{10}H_{18}O_2$

Formation of the amide completes the synthesis of capsaicin.

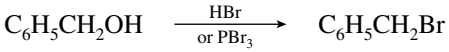


Capsaicin ($C_{18}H_{27}NO_3$)

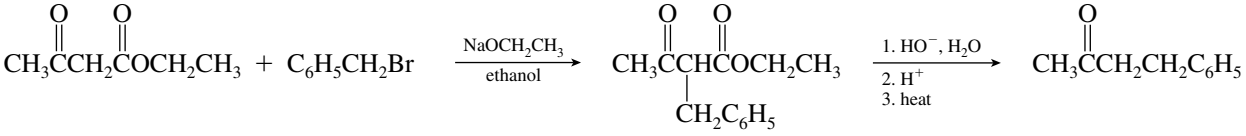
21.25 (*a*) First write out the structure of 4-phenyl-2-butanone and identify the synthon that is derived from ethyl acetoacetate.



Therefore carry out the acetoacetic ester synthesis using a benzyl halide as the alkylating agent.

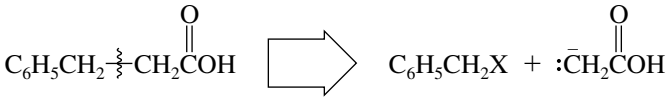


Benzyl alcohol — Benzyl bromide

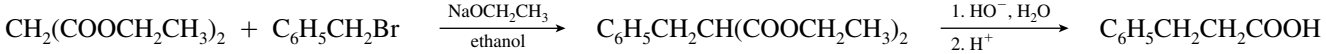


Ethyl acetoacetate — Benzyl bromide — Ethyl 2-benzyl-3-oxobutanoate — 4-Phenyl-2-butanone

(*b*) Identify the synthon in 3-phenylpropanoic acid that is derived from malonic ester by disconnecting the molecule at its α-carbon atom.

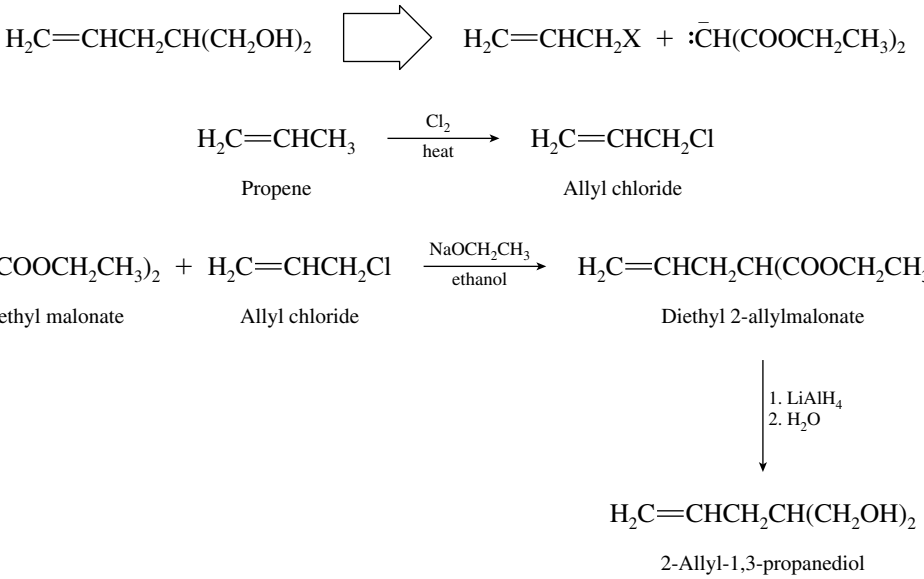


Here, as in part (*a*), a benzyl halide is the required alkylating agent.

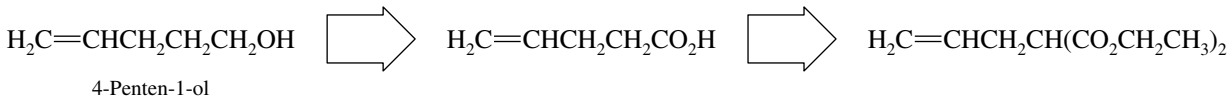


Diethyl malonate — Benzyl bromide — Diethyl benzylmalonate — 3-Phenylpropanoic acid

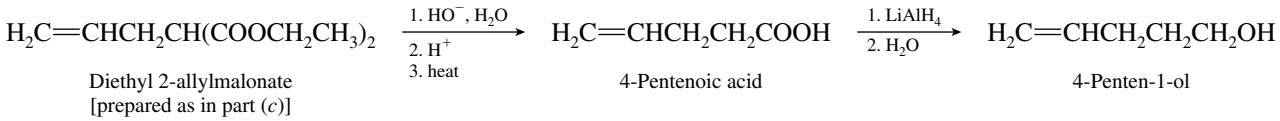
(*c*) In this synthesis the desired 1,3-diol function can be derived by reduction of a malonic ester derivative. First propene must be converted to an allyl halide for use as an alkylating agent.



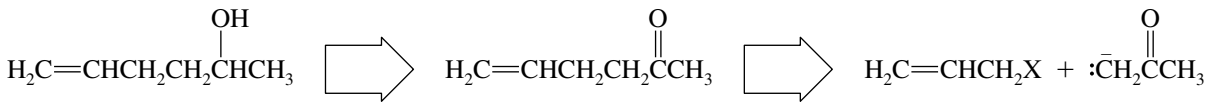
(*d*) The desired primary alcohol may be prepared by reduction of the corresponding carboxylic acid, which in turn is available from the malonic ester synthesis using allyl chloride, including saponification and decarboxylation of the diester [prepared in part (*c*)].



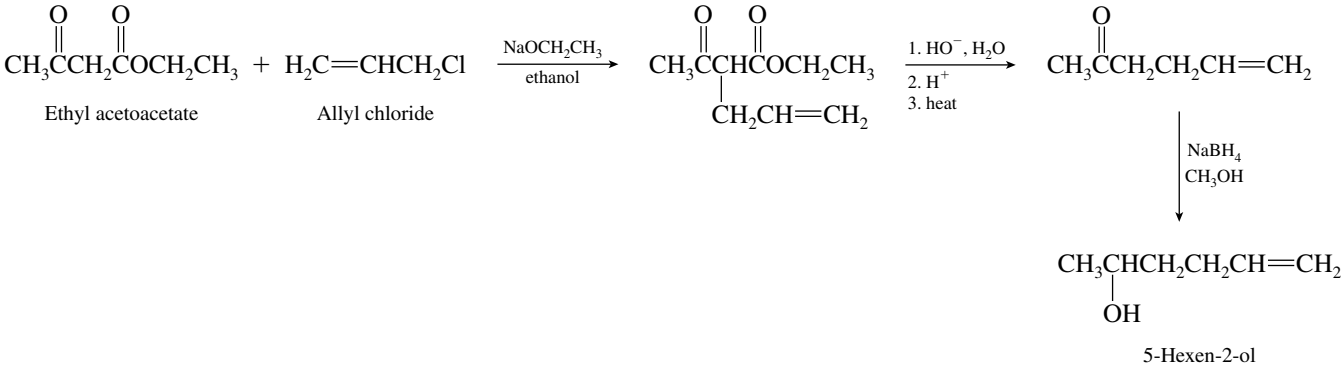
The correct sequence of reactions is



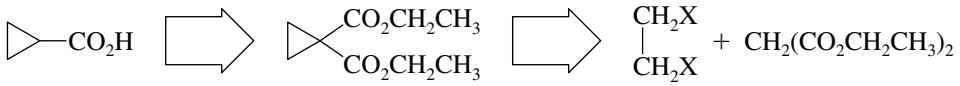
(*e*) The desired product is an alcohol. It can be prepared by reduction of a ketone, which in turn can be prepared by the acetoacetic ester synthesis.



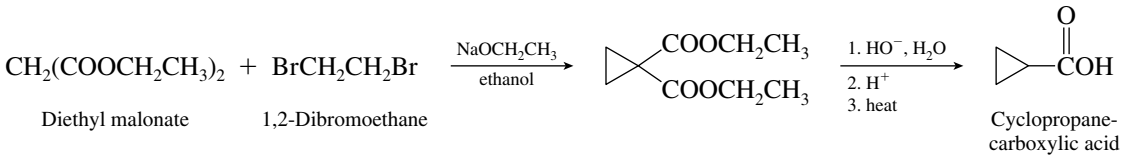
Therefore



(*f*) Cyclopropanecarboxylic acid may be prepared by a malonic ester synthesis, as retrosynthetic analysis shows.

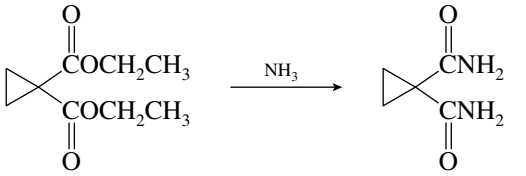


The desired reaction sequence is



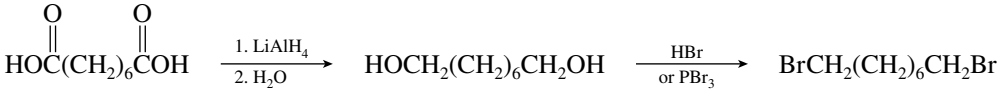
Diethyl malonate — 1,2-Dibromoethane — Cyclopropanecarboxylic acid

(*g*) Treatment of the diester formed in part (*f*) with ammonia gives a diamide.

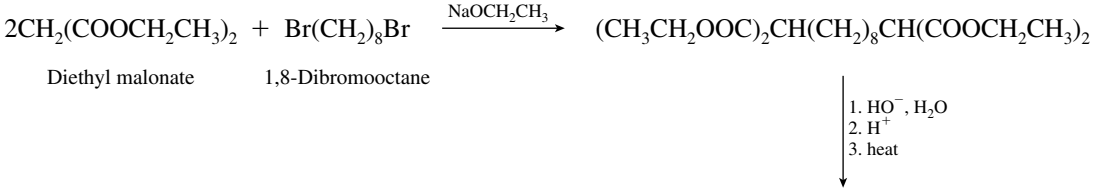


Diethyl cyclopropane-1,1-dicarboxylate [prepared as in part (*f*)] — Cyclopropane-1,1-dicarboxamide

(*h*) We need to extend the carbon chain of the starting material by *four* carbons. One way to accomplish this is by way of a malonic ester synthesis at each end of the chain.

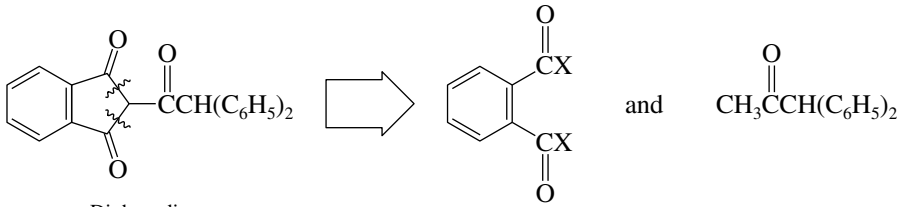


Octanedioic acid — 1,8-Dibromooctane



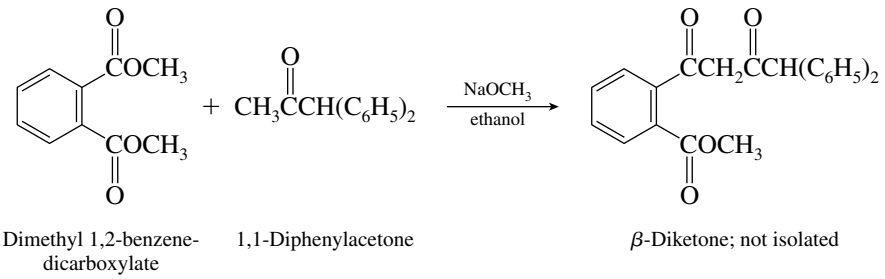
Diethyl malonate — 1,8-Dibromooctane — Dodecanedioic acid

21.26 The problem states that diphenadione is prepared from 1,1-diphenylacetone and dimethyl 1,2-benzenedicarboxylate. Therefore, disconnect the molecule in a way that reveals the two reactants.

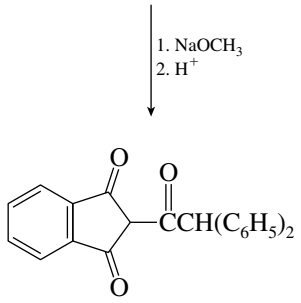


Diphenadione

Thus all that is required is to treat dimethyl 1,2-benzenedicarboxylate and 1,1-diphenylacetone with base. Two successive acylations of a ketone enolate occur; the first is intermolecular, the second intramolecular.

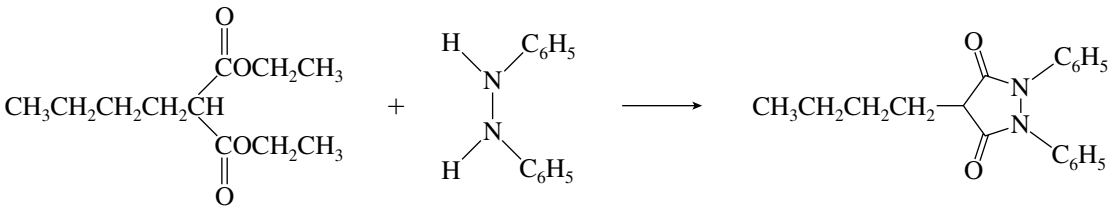


Dimethyl 1,2-benzene-dicarboxylate | 1,1-Diphenylacetone | β-Diketone; not isolated



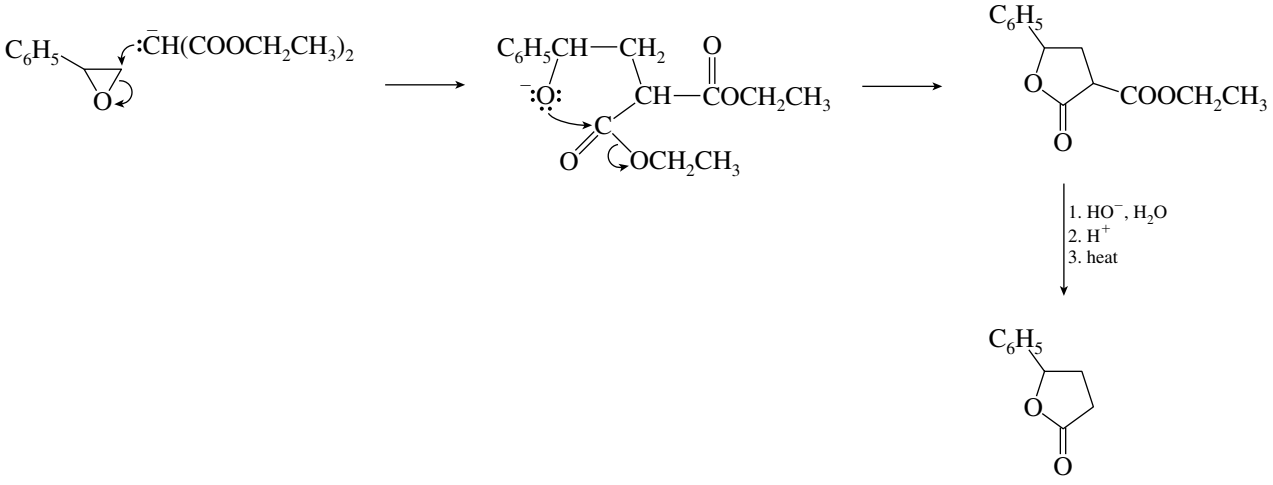
Diphenadione

21.27 Esters react with amines to give amides. Each nitrogen of 1,2-diphenylhydrazine reacts with a separate ester function of diethyl 2-butylmalonate.



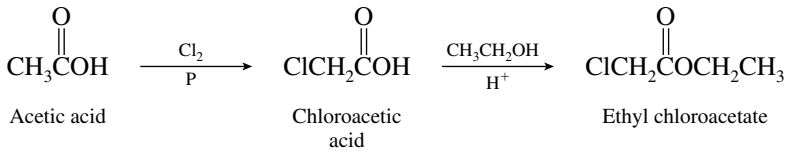
Diethyl 2-butylmalonate | 1,2-Diphenylhydrazine | Phenylbutazone ($C_{19}H_{20}N_2O_2$)

21.28 Styrene oxide will be attacked by the anion of diethyl malonate at its less hindered ring position.



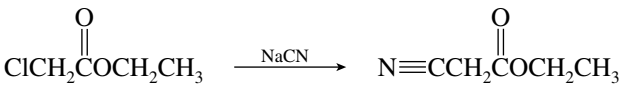
The product is 4-phenylbutanolide. It has been prepared in 72% yield by this procedure.

21.29 The first task is to convert acetic acid to ethyl chloroacetate.



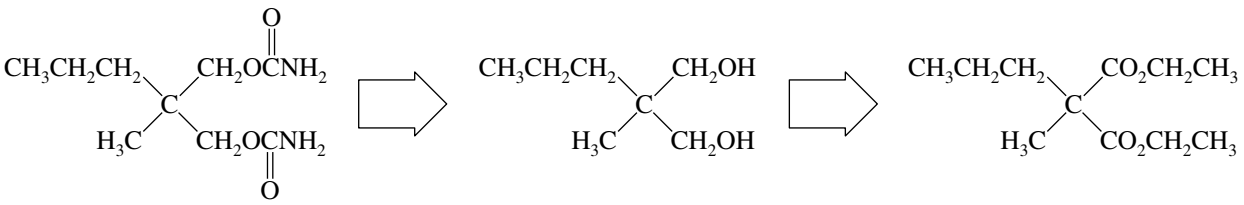
Acetic acid — Chloroacetic acid — Ethyl chloroacetate

Chlorination must precede esterification, because the Hell–Volhard–Zelinsky reaction requires a carboxylic acid, not an ester, as the starting material. The remaining step is a nucleophilic substitution reaction.

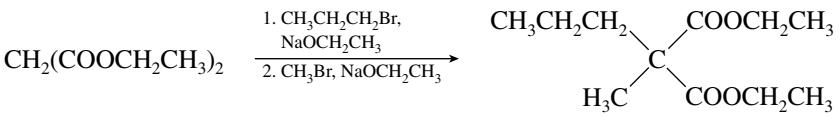


Ethyl chloroacetate — Ethyl cyanoacetate

21.30 From the hint given in the problem, it can be seen that synthesis of 2-methyl-2-propyl-1,3-propanediol is required. This diol is obtained by a sequence involving dialkylation of diethyl malonate.

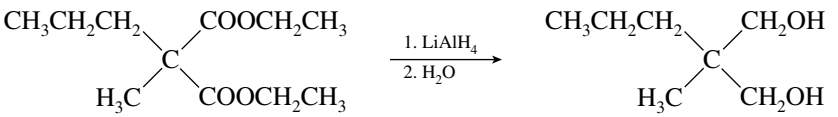


Begin the synthesis by dialkylation of diethyl malonate.



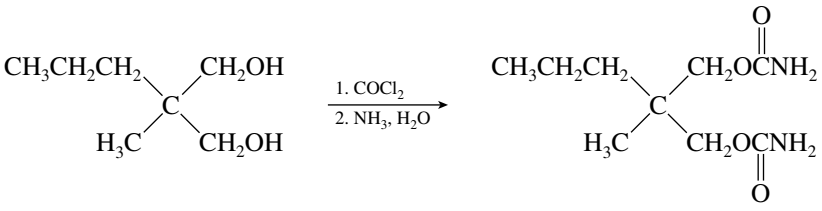
Diethyl malonate — Diethyl 2-methyl-2-propylmalonate

Convert the ester functions to primary alcohols by reduction.



Diethyl 2-methyl-2-propylmalonate — 2-Methyl-2-propyl-1,3-propanediol

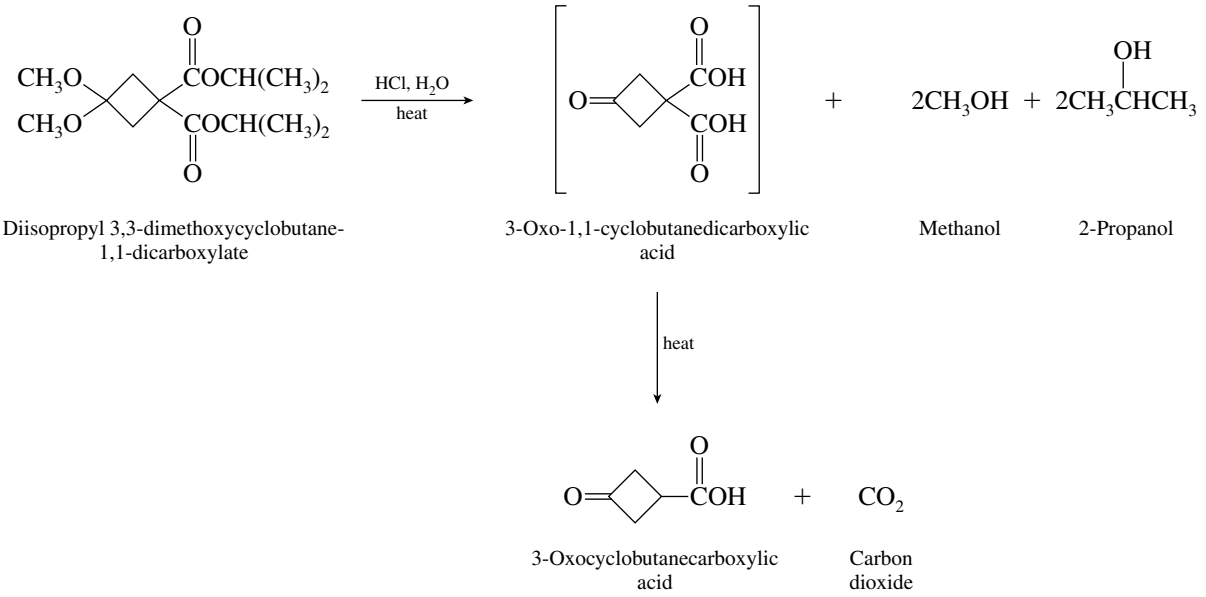
Conversion of the primary alcohol groups to carbamate esters completes the synthesis.



2-Methyl-2-propyl-1,3-propanediol — Meprobamate

21.31 The compound given in the problem contains three functionalities that can undergo acid-catalyzed hydrolysis: an acetal and two equivalent ester groups. Hydrolysis yields 3-oxo-1,1-cyclobutanedicarboxylic acid and 2 moles each of methanol and 2-propanol. The hydrolysis product is a malonic

acid derivative that decarboxylates on heating. The final product of the reaction is 3-oxocyclobutanecarboxylic acid ($C_5H_6O_3$).



Diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate

3-Oxo-1,1-cyclobutanedicarboxylic acid

Methanol

2-Propanol

3-Oxocyclobutanecarboxylic acid

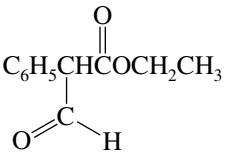
Carbon dioxide

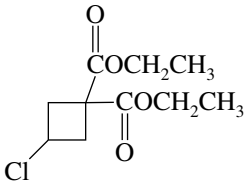
SELF-TEST

PART A

A-1. Give the structure of the reactant, reagent, or product omitted from each of the following:

(*a*) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3}$?

(*b*) $\overset{O}{\overset{\|}{H}}COCH_2CH_3 + ? \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3}$ 

(*c*)  $\xrightarrow[2.\ H_3O^+\ 3.\ heat]{1.\ HO^-,\ H_2O}$? (two isomeric products; $C_5H_7ClO_2$)

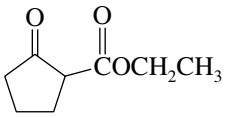
(*d*) $(CH_3CH_2OOC)_2CH_2 + H_2C{=}CH\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[ethanol]{NaOCH_2CH_3}$?

(*e*) $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[2.\ C_6H_5CH_2Br]{1.\ NaOCH_2CH_3}$?

(*f*) Product of part (*e*) $\xrightarrow{?}$ $C_6H_5CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

(*g*) $CH_3\overset{O}{\overset{\|}{C}}CHCH_2CO_2H$ (with CO_2H on the CH) $\xrightarrow{\text{heat}}$ CO_2 + ?

A-2. Provide the correct structures of compounds A through E in the following reaction sequences:

(*a*) A $\xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3}$  $\xrightarrow[2.\ CH_3CH_2I]{1.\ NaOCH_2CH_3}$ B $\xrightarrow[2.\ H_3O^+\ 3.\ \text{heat}]{1.\ HO^-,\ H_2O}$ C

(*b*) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$ $\xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3}$ D $\xrightarrow[2.\ H_3O^+\ 3.\ \text{heat}]{1.\ HO^-,\ H_2O}$ E + CO_2

A-3. Give a series of steps that will enable preparation of each of the following compounds from the starting material(s) given and any other necessary reagents:

(*a*) $CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OH$ from ethyl acetoacetate

(*b*) $C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$ from $C_6H_5\overset{O}{\overset{\|}{C}}CH_3$ and diethyl carbonate

A-4. Write a stepwise mechanism for the reaction of ethyl propanoate with sodium ethoxide in ethanol.

A-5. Ethyl 2-methylpropanoate does not undergo a Claisen condensation, whereas ethyl 3-methylbutanoate does. Provide a mechanistic explanation for this observation.

PART B

B-1. Which of the following compounds is the strongest acid?

(*a*) $HCO_2CH_2CH_3$

(*b*) $CH_3CH_2O_2CCH_2CO_2CH_2CH_3$

(*c*) $CH_3CH_2O_2CCH_2CH_2CO_2CH_2CH_3$

(*d*) $CH_3CO_2CH_2CH_3$

B-2. Which of the following will yield a ketone and carbon dioxide following saponification, acidification, and heating?

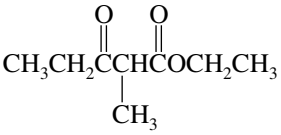
(*a*) $CH_3CH_2CHCH_2\overset{O}{\overset{\|}{C}}CH_3$ (with $\overset{O}{\overset{\|}{C}}OCH_2CH_3$ on the CH)

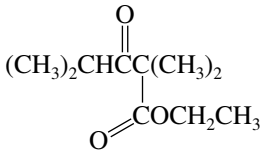
(*b*) $CH_3CH_2CH\overset{O}{\overset{\|}{C}}OCH_2CH_3$ (with $\overset{O}{\overset{\|}{C}}OCH_2CH_3$ on the CH)

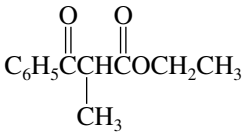
(*c*) $CH_3CH_2CH\overset{O}{\overset{\|}{C}}CH_3$ (with $\overset{O}{\overset{\|}{C}}CH_2CH_3$ on the CH)

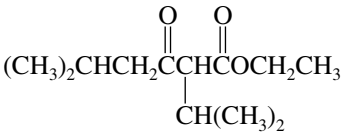
(*d*) $CH_3CH_2CH\overset{O}{\overset{\|}{C}}CH_3$ (with $\overset{O}{\overset{\|}{C}}OCH_2CH_3$ on the CH)

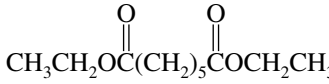
B-3. Which of the following keto esters is *not* likely to have been prepared by a Claisen condensation?

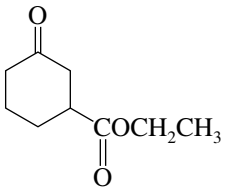
(*a*) 

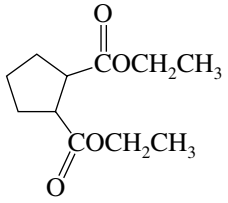
(*c*) 

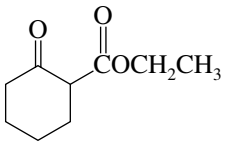
(*b*) 

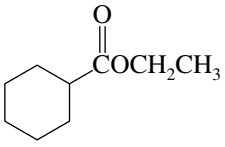
(*d*) 

B-4. Dieckmann cyclization of  will yield

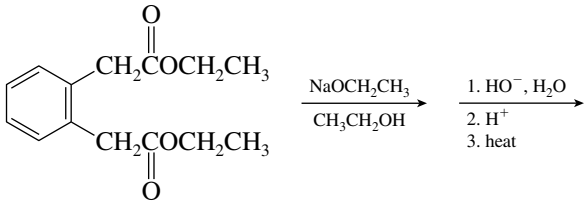
(*a*) 

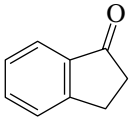
(*c*) 

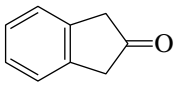
(*b*) 

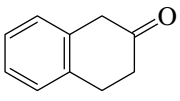
(*d*) 

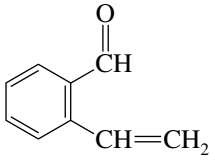
B-5. What is the final product of this sequence?



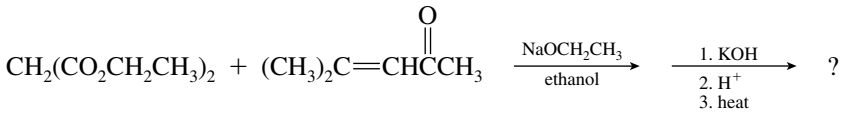
(*a*) 

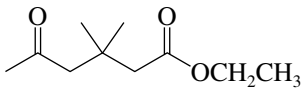
(*c*) 

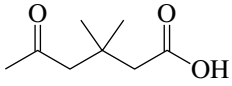
(*b*) 

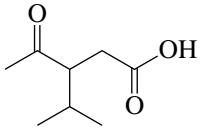
(*d*) 

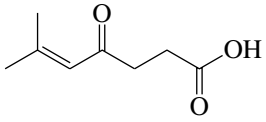
B-6. What is the final product of the following sequence of reactions?



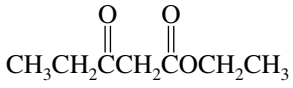
(*a*) 

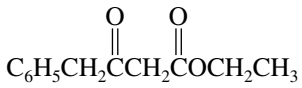
(*c*) 

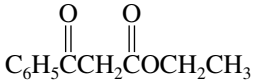
(*b*) 

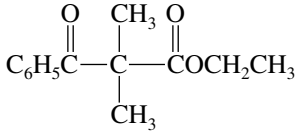
(*d*) 

B-7. Which of the following would be a suitable candidate for preparation by a mixed Claisen condensation?

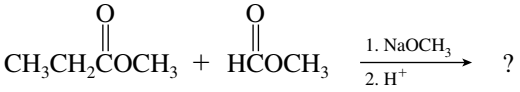
(*a*) 

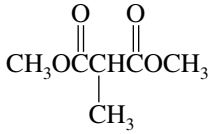
(*c*) 

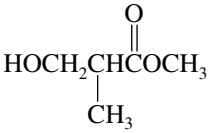
(*b*) 

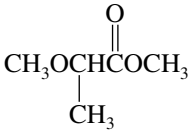
(*d*) 

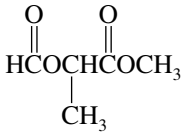
B-8. What is the major product of the following reaction?



(*a*) 

(*c*) 

(*e*) 

(*b*) 

(*d*)