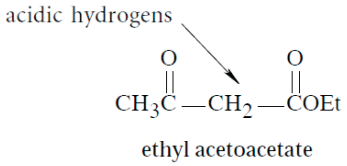
Chapter 22

The Chemistry of Enolate Ions, Enols, and α,β-Unsaturated Carbonyl Compounds

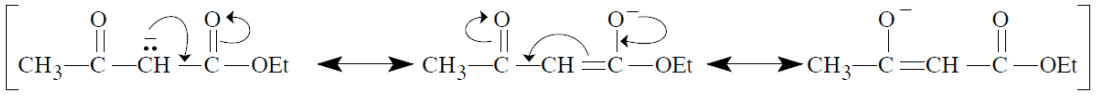
Solutions to In-Text Problems

22.1 (b) The acidic hydrogens are the α-hydrogens on the carbons between the two carbonyl groups. (—OEt = ethoxy group = —OCH_2CH_3.)

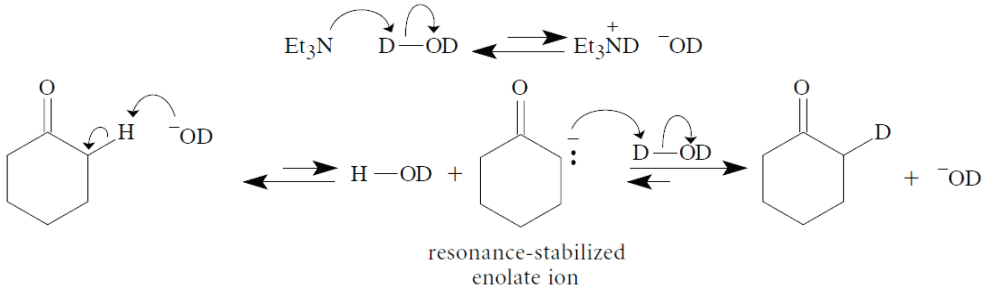


ethyl acetoacetate

The reason that these hydrogens are particularly acidic is that the conjugate-base enolate ion is stabilized by the polar effects and resonance effects of two carbonyl groups, whereas the conjugate-base enolate ion of an ordinary ester is stabilized by the corresponding effects of only one carbonyl group. The resonance structures of the conjugate-base enolate ion of ethyl acetoacetate are as follows:

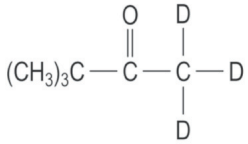


22.3 A mechanism for replacement of one hydrogen in the reaction of Eq. 22.6, text p. 1051, is shown in the following equation. (The mechanisms for replacement of the others are identical.) Only the α-hydrogens are replaced because the enolate ion is the only carbanion stable enough to be formed. The carbanion intermediates required in a similar mechanism for the replacement of the hydrogens other than the α-hydrogens are not resonance-stabilized.

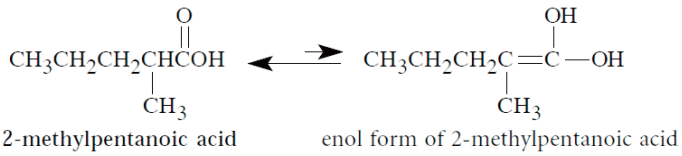


resonance-stabilized enolate ion

22.6 (b) All α-hydrogens are exchanged for deuterium. (The methyl hydrogens of the *tert*-butyl group are not α-hydrogens.)



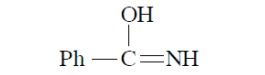
22.7 (b)



2-methylpentanoic acid enol form of 2-methylpentanoic acid

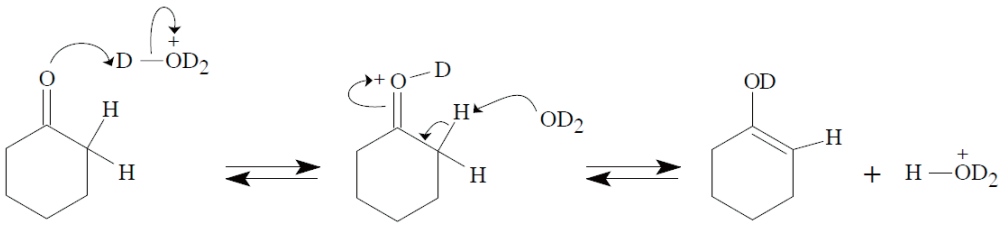
(c) Benzaldehyde, PhCH═O, has no enol forms because it has no α-hydrogens.

22.9 (b) The "enol" form of an amide that has a carbon–nitrogen double bond is called an *imidic* acid; see Eq. 21.20b, text p. 1009. Notice that this particular amide cannot enolize toward the α-carbon because it has no α-hydrogens on that carbon.

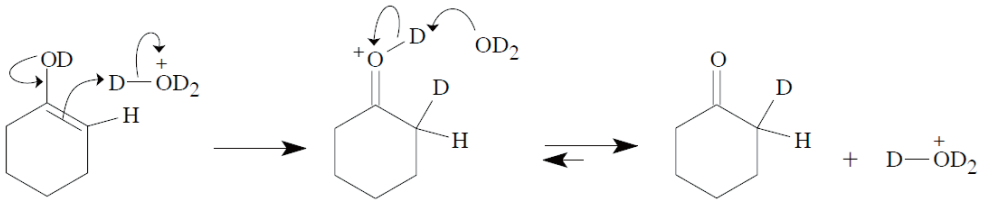


"enol" form of benzamide
(an imidic acid)

22.11 (b) The enol is formed by the mechanism shown in Eq. 22.17b on text p. 1056, except that D_3O^+ is the acid. This results in the "washout" of one α-hydrogen into the large excess of deuterated solvent.



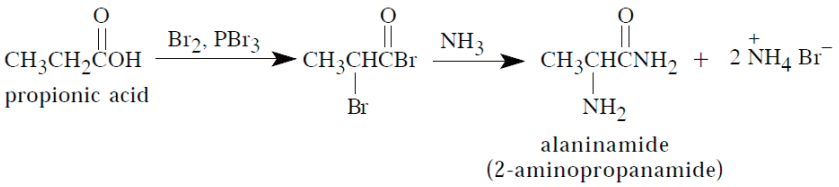
Protonation of the double bond by D_3O^+ gives a deuterium at the α-position. Replacement of one α-hydrogen by deuterium is shown; the mechanism for replacement of the other α-hydrogens is identical.



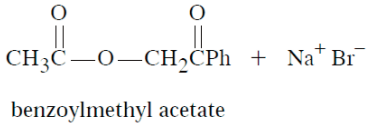
22.13 (b) Because the rate of ketone halogenation is independent of the halogen concentration, the rates of halogenation of the same ketone with two different halogens are also independent of halogen concentration and therefore independent of the identity of the halogen itself. In fact, the rate in both cases is the rate of enolization, as in part (a). The two processes are compared at the same acid concentration because the enolization process is acid-catalyzed (Eq. 22.24, text p. 1058).

22.14 In part (b), benzophenone does not halogenate because it cannot form an enolate ion (it has no α-hydrogens), and the aromatic rings are deactivated by the carbonyl group toward electrophilic halogenation.

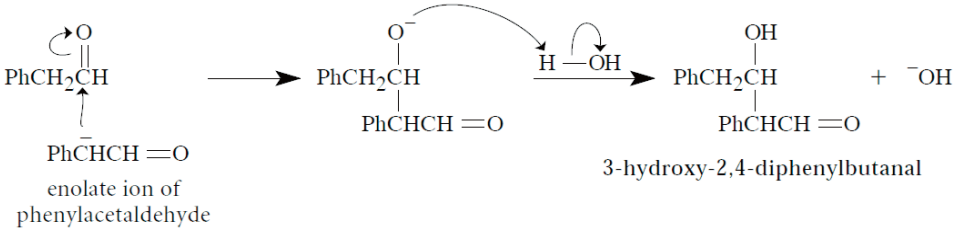
22.16 (b) The α-bromo acid bromide is formed first. Then ammonia reacts as a nucleophile with it in both an acyl substitution reaction to give the amide, and in an S_N2 reaction at the α-carbon to give the α-amino amide of the α-amino acid alanine.



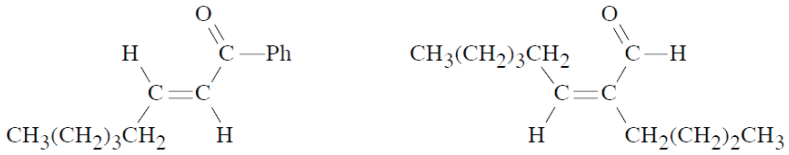
22.17 (b) The base acetate ion displaces the α-bromine to give a compound that is an example of a *phenacyl ester*.



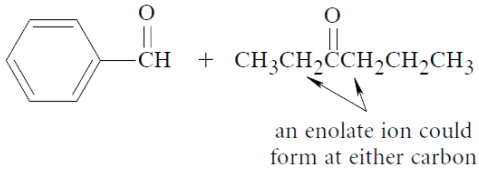
22.19 (a) The aldol addition reaction of phenylacetaldehyde:



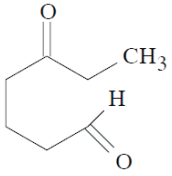
22.20 (b) As in part (a), the enolate ion of the ketone adds to the aldehyde carbonyl group to give product *A* because aldehyde carbonyl groups are more reactive than ketone carbonyl groups. It is also likely that aldol condensation of two molecules of hexanal will occur to give product *B*.



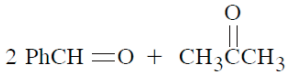
22.22 (b) The product shown would require the following starting materials. However, since the enolate ion required for the synthesis is only one of two that could form, at least two isomeric products are possible of which the desired product is only one. The desired product would therefore be formed as one component of a mixture of isomers.



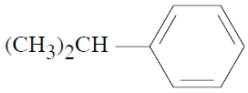
(d) This product is the result of an intramolecular reaction of a ketone enolate and an aldehyde carbonyl group; hence, its synthesis from the following starting material is reasonable.

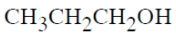


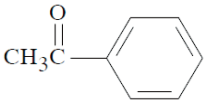
(f) This is a reaction of two equivalents of benzaldehyde with one of acetone. Because an aldehyde without α-hydrogens is involved, the reaction is a reasonable example of the Claisen–Schmidt condensation.



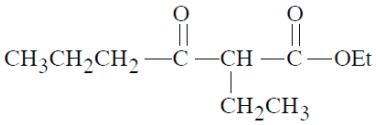
22.24 (b) (d) (f)





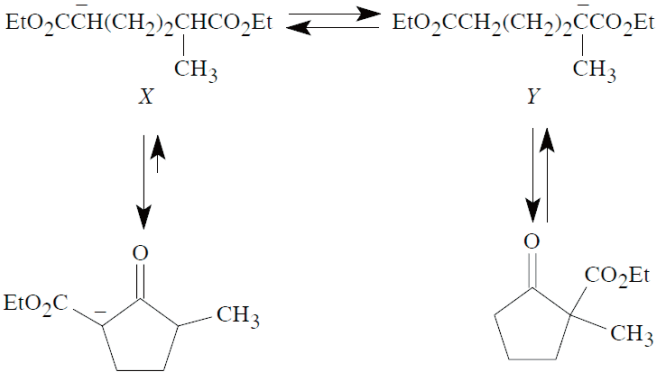


22.25 (b)



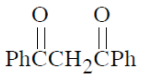
ethyl 2-ethyl-3-oxohexanoate

22.27 (b) Use reasoning similar to that used in solving part (a). Two possible enolate ions, *X* and *Y*, can form; the product derived from ion *X* is ultimately observed because only this product is formed irreversibly by ionization.



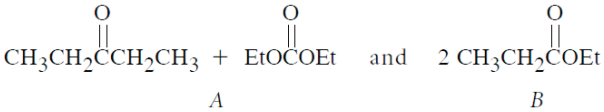
(observed product; acidification gives the keto ester)

22.28 (b)



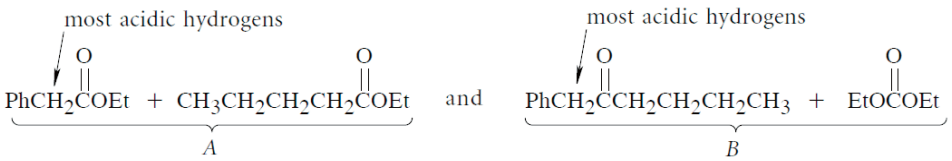
Ethanol is a by-product.

22.29 (b) The two possible sets of starting materials are as follows:



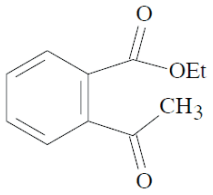
Either set would work. In set *A*, a large excess of diethyl carbonate must be used. (See Eq. 22.58, text p. 1077, and the discussion that follows.) However, set *B* would be more convenient because only one ester is required as a starting material and because we would not have to separate the product from an excess of starting material, as in set *A*.

(d) The two possible sets of starting materials are as follows:



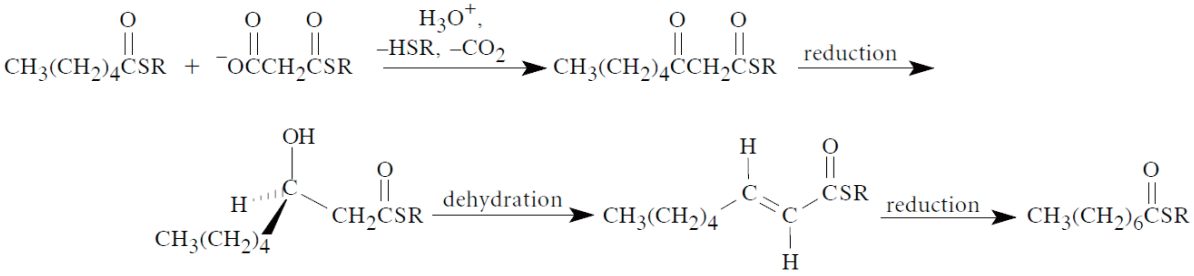
Set *A* consists of two esters with α-hydrogens; four different products are possible. Furthermore, the α-hydrogens of ethyl phenylacetate are considerably more acidic than those of ethyl valerate (why?); therefore, the major product is likely to be derived from the enolate ion formed at this position, but this is not the desired product. In set *B*, there are two sets of α-hydrogens, but the hydrogens that are α to the phenyl ring are considerably more acidic (why?). Unfortunately, the desired product is *not* derived from the enolate ion formed at this position. Hence, both sets of starting materials are unsatisfactory. In summary, the desired product cannot be made by a Claisen condensation.

22.30 (b)

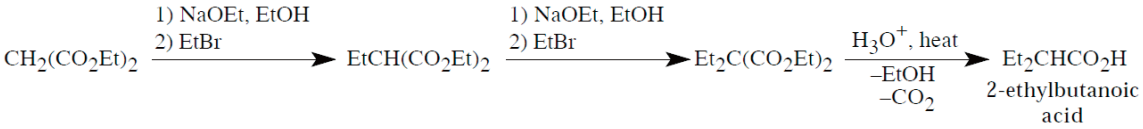


ethyl 2-acetylbenzoate

22.31 Follow the pattern in Eqs. 22.63c–d, text p. 1083.

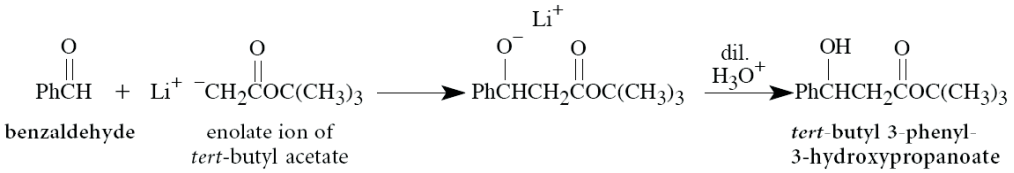


22.33 (b) 2-Ethylbutanoic acid can be prepared by a malonic ester synthesis:

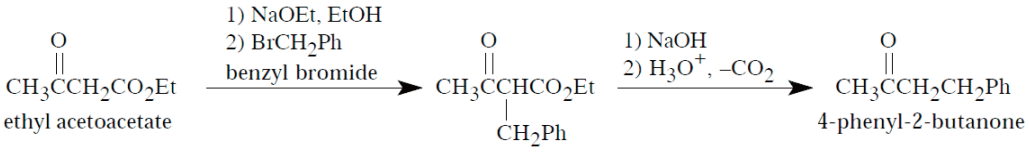


22.35 (a) Recall Sec. 18.1, text p. 823, where the four reasons for the lack of reactivity of aryl halides under S_N2 conditions is discussed. Firstly, the relatively high energy of the transition state required for the conversion of an sp^2-hybridized carbon into an *sp*-hybridized carbon (about 21 kJ mol^{-1} or 5 kcal mol^{-1}) that must occur in an S_N2 reaction at an aryl carbon. Secondly, the nucleophile, in this case the conjugate-base enolate of diethyl malonate, must approach the carbon–bromine bond in the plane of the phenyl ring, which would result in significant van der Waals repulsions (a steric effect) of both the nucleophile and the phenyl ring. Thirdly, the nucleophile must also approach the carbon–bromine bond through the plane of the phenyl ring, which is impossible. And fourthly, because the carbon at which substitution occurs would have to undergo stereochemical inversion, the reaction would necessarily yield a benzene derivative containing a twisted and highly strained double bond.

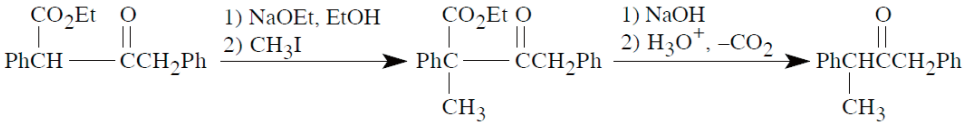
22.37 (b) By the same logic used in part (a), the β-hydroxy ester is formed.



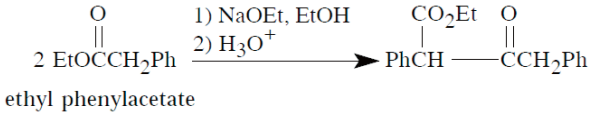
22.39 (b)



22.40 (b)



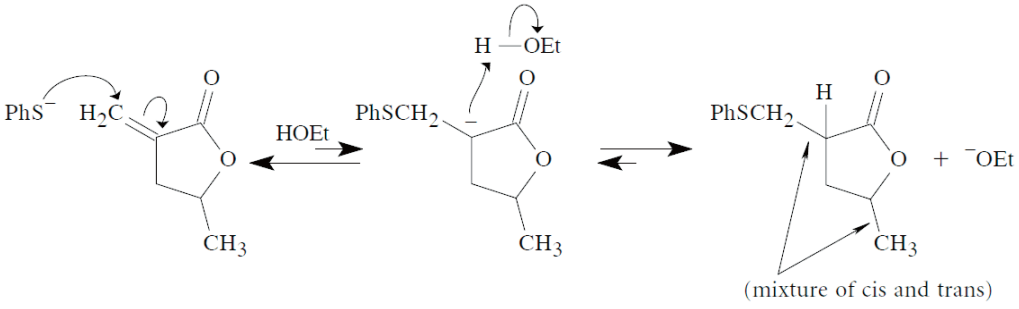
The starting β-keto ester is prepared by a Claisen condensation of ethyl phenylacetate:



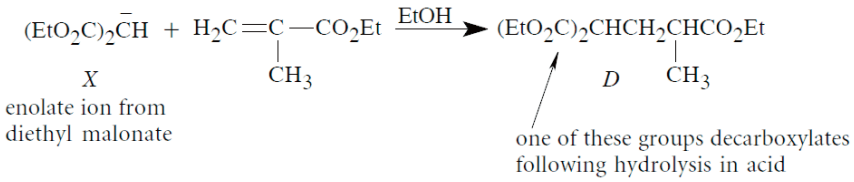
22.42 (b) (d)

In part (d), saponification occurs instead of conjugate addition because saponification is an *irreversible* nucleophilic acyl substitution reaction.

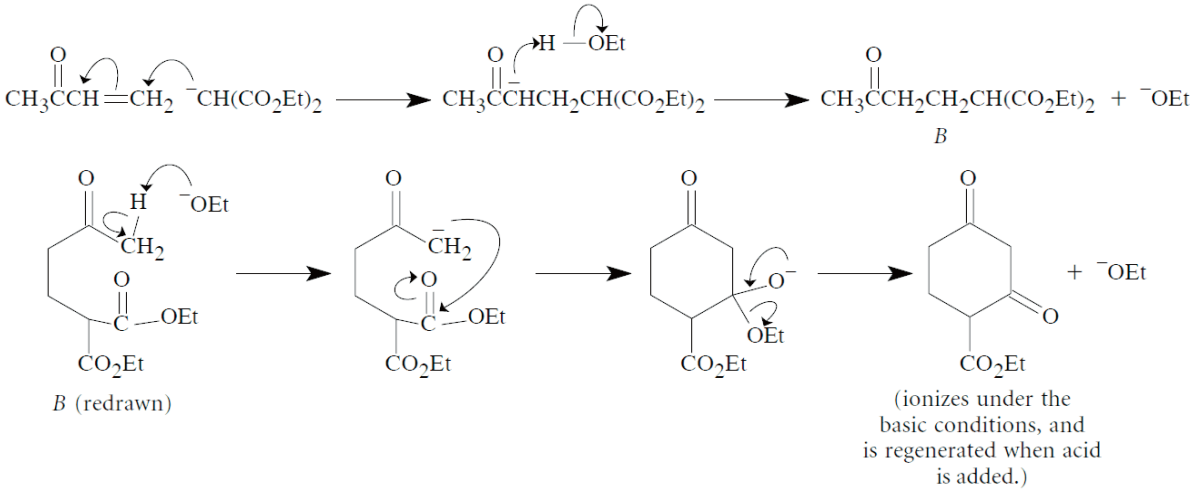
22.43 (b) This is a conjugate addition of the benzenethiolate anion to the carbon–carbon double bond. The benzenethiolate nucleophile, PhS^-, is formed by the reaction of benzenethiol, PhSH, with ^-OEt. A mixture of diastereomers is formed because the final protonation step can occur from the same face as the methyl group or from the face opposite the methyl group.

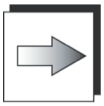


22.44 (b) The nucleophile must be a species that can be converted into a carboxymethyl (HO_2CCH_2—) group. Because the nucleophile ends up as a "substituted acetic acid," the conjugate-base enolate ion of diethyl malonate can serve as species *X*. Addition of *X* to the ester gives compound *D*. All ester groups of *D* are hydrolyzed and one of the resulting carboxy groups is decarboxylated when *D* is heated in aqueous acid.



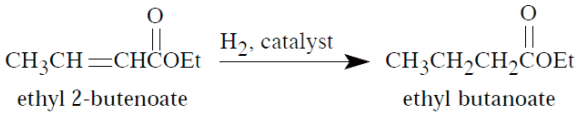
22.45 (b) A Michael addition of the diethyl malonate conjugate-base anion gives compound *B*, which undergoes an intramolecular Claisen (Dieckmann) condensation. This Dieckmann condensation, like all Claisen-type condensations, is driven to completion by ionization of the product; the un-ionized product is formed when acid is added. These final steps are not shown in the mechanism below. Note that the tertiary hydrogen of compound *B* is the most acidic hydrogen, but although the anion resulting from removal of this proton is formed in the reaction mixture, it is depleted by the reaction that gives the product.



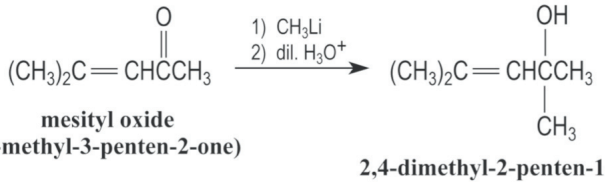


In the foregoing mechanisms many of the steps are reversible and should rigorously be shown with equilibrium arrows. However, the focus of the problem is on the mechanism of the forward reaction and not on the reversibility of the reaction. In such cases, forward arrows only are shown.

22.46 (a)

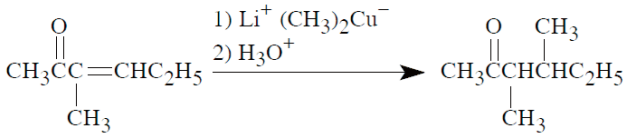


22.47 (b)



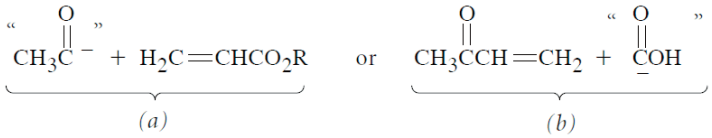
22.48 (b) Conjugate addition also occurs with α,β-unsaturated compounds in which a carbon–carbon triple bond is part of the conjugated π-electron system. The product is $(CH_3)_2C{=}CHCO_2Me$ (methyl 3-methyl-2-butenoate).

22.49 (b) An analysis similar to that used in Study Problem 22.7, text p. 1104, reveals that either a methyl group or an ethyl group can be added in the conjugate addition. (Addition of a methyl group is illustrated here.)



3-methyl-3-hexen-2-one 3,4-dimethyl-2-hexanone

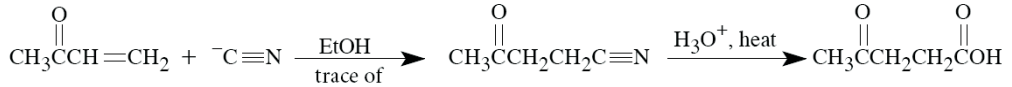
(d) An analysis similar to that in Study Problem 22.7, text p. 1104, suggests the following possibilities:



(*a*) (*b*)

A practical equivalent for the anion in (*a*) might be an acetylide anion, $^{-}$CCH. The resulting acetylene could then be hydrated to the desired ketone. Unfortunately, acetylenic cuprate reagents do not work in conjugate additions because the acetylenic ligands do not transfer from the copper. Nevertheless, if you came up with this possibility, you are analyzing the problem with considerable sophistication.

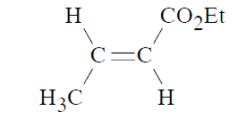
Anion (*b*) does have a simple practical equivalent: the cyanide ion:



methyl vinyl ketone (3-buten-2-one) levulinic acid (4-oxopentanoic acid)

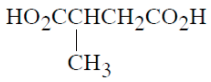
Solutions to Additional Problems

22.51 The structure of the starting material is

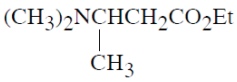


ethyl *trans*-2-butenoate

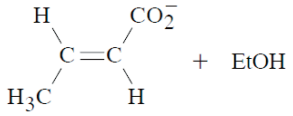
(a)



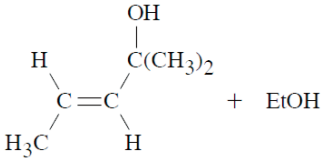
(b)



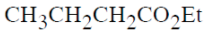
(c)



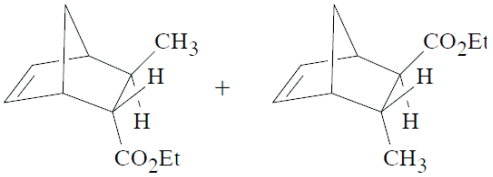
(d)



(e)



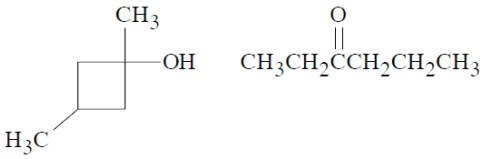
(f)



(both compounds are racemates)

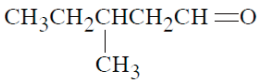
As in Problem 22.50(h), text p. 1106, the α,β-unsaturated ester in part (f) serves as a Diels–Alder dienophile.

22.52 (b)

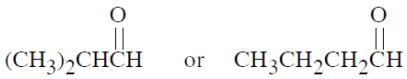


(two of several possibilities)

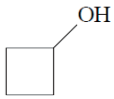
(d)



22.53 (b)

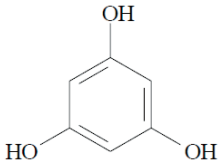


(d)



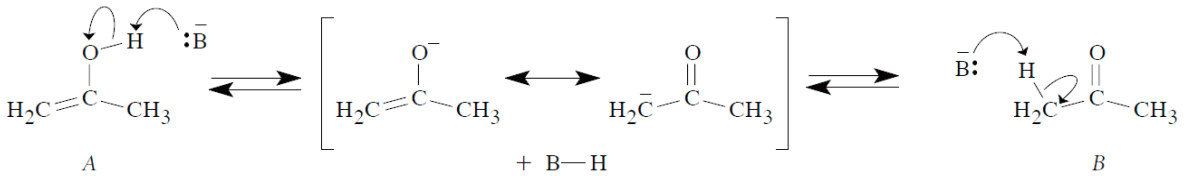
(one of several possibilities)

22.54 (b) This compound, 1,3,5-cyclohexanetrione, exists as its "triene-triol" isomer phloroglucinol because the latter is aromatic.



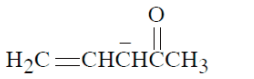
1,3,5-benzenetriol
(phloroglucinol)

22.56 (a) Removal of the O—H proton from *A* and a C—H proton from *B* gives conjugate-base anions that are resonance structures and therefore identical. ($B:^-$ = a general base.)



(b) Because the ketone is more stable than its enol, more energy must be expended for it to ionize. Consequently, the ketone is less acidic. The logic is similar to that used in the solution to Problem 22.55(b).

22.57 (b) The first compound is more acidic because the conjugate-base anion (see following structure) has the greater number of resonance structures. It is stabilized by resonance interaction with both the carbon–carbon double bond and the carbonyl group. The two possible enolate ions of the second compound lack the resonance interaction with a carbon–carbon double bond.



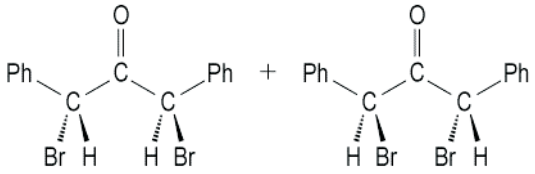
conjugate-base anion
of the most acidic compound

22.58 The order of increasing acidity (decreasing pK_a) is as follows. [Approximate pK_a values are in brackets.]

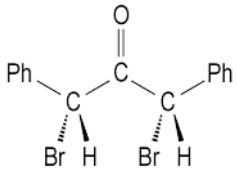
(3) [42] < (4) ≈ (5) [25] < (1)[15] < (6) [10] < (2) [4.5]

Toluene is much less acidic than phenol, and amides are much less acidic than carboxylic acids (element effect). The pK_a values of 1-alkynes and esters are very similar (about 25). The remaining rankings require knowledge of approximate pK_a values. The point of this problem is that it is very important to know the typical pK_a values of organic compounds because so much of organic reactivity is based on acid–base principles.

22.60 The dibromo derivative is a mixture of diastereomers: the (±)-diastereomer (that is, the racemate) and the meso diastereomer.

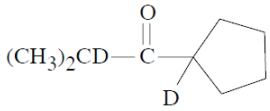


(±)-1,3-dibromo-1,3-diphenyl-2-propanone



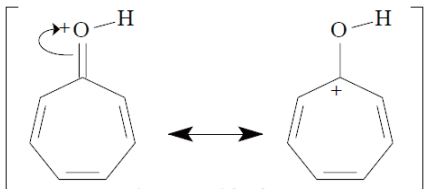
***meso*-1,3-dibromo-1,3-diphenyl-2-propanone**

22.63 (b) The two α-hydrogens are acidic enough to be replaced. These hydrogens are shown as deuteriums in the following structure.



22.64 (b) The analogous isomerization of compound *C* cannot occur because there is no α-hydrogen at the ring junction. Only the removal of an acidic hydrogen at a ring junction could lead to isomerization, and the hydrogen at the other carbon of the ring junction is not acidic enough to ionize under the conditions given.

22.67 (b) Tropone is unusually basic because its conjugate acid is an aromatic carbocation.



conjugate acid of tropone
(an aromatic α-hydroxy carbocation)

The consequences of aromaticity on the pK_a of a conjugate acid were explored in part (a), and these apply equally here.

22.70 (b) The most acidic hydrogen in either of the two carbonyl compounds is the α-hydrogen of diethyl malonate; thus, formation of the conjugate-base anion of diethyl malonate consumes the sodium ethoxide. Formation of the conjugate-base enolate ion of acetone therefore will not be a competing reaction. Ketone carbonyl groups are more reactive than ester carbonyl groups; hence, the conjugate-base anion of diethyl malonate reacts with acetone. The condensation is pulled to the right by dehydration.

22.72 (a) One full equivalent of base is required in the Claisen or Dieckmann condensation to ionize the product. Without this ionization, the condensation equilibrium is unfavorable. (See Sec. 22.5A, text pp. 1072–5.)

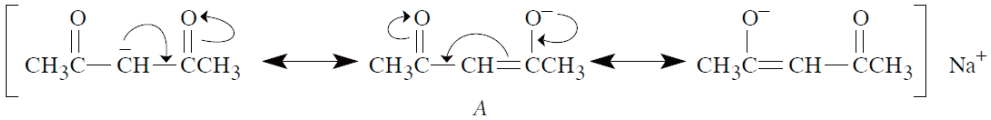
(b) Sodium phenoxide, the conjugate base of phenol, is about 10^{-5} times as basic as sodium ethoxide. Thus, sodium phenoxide is not basic enough to ionize completely the Claisen condensation product. Without such an ionization, the condensation equilibrium is unfavorable.

(c) The equilibrium for the Claisen condensation is rather unfavorable and requires the final ionization of the product to proceed to completion. Under acidic conditions, no base is available to cause this ionization. In addition, an acid-catalyzed Claisen condensation would require the enol of an ester, because enols are the α-carbon nucleophiles under acidic conditions. As shown in Eq. 22.13, p. 1054, the formation of enols from esters is *much* less favorable than the formation of enols from aldehydes or ketones. The much lower concentration of reactive intermediate would translate into a much reduced rate. In summary, both the rate of the reaction is very low, and its equilibrium constant is highly unfavorable; hence, no reaction is observed.

22.73 (b) The conjugate-base anion of diethyl malonate would be formed with sodium ethoxide, but it would not react with bromobenzene because the latter compound, an aryl halide, does not undergo S_N2 reactions. (See Sec. 18.1, text p. 823.)

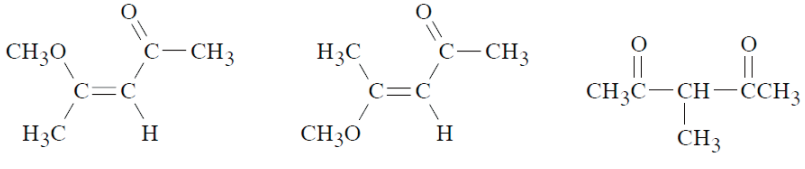
(e) This is a crossed aldol condensation in which the conjugate-base enolate ion of the ketone reacts with the aldehyde. A mixture of isomeric products will result because there are two possible conjugate-base enolate ions of the ketone that can react. Moreover, a very significant, if not predominant, competing reaction will be the aldol condensation of acetaldehyde itself.

22.74 (a) The gas is H_2 and the species *A* is the sodium salt of the conjugate-base enolate ion of 2,4-pentanedione. As the resonance structures indicate, the negative charge, and therefore the nucleophilic character, of this anion is shared by both the anionic carbon and the oxygens.



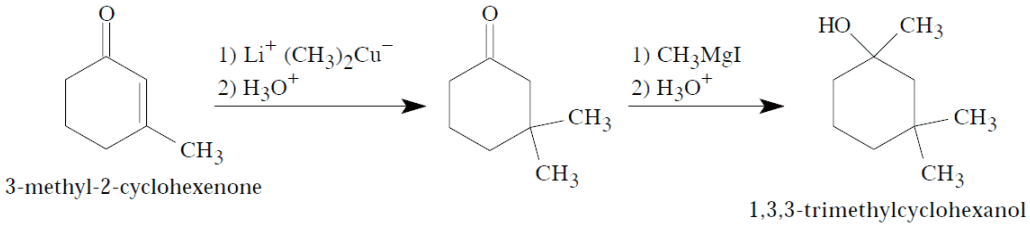
A

(b) The three species that are formed all result from reaction with a nucleophilic atom with methyl iodide in an S_N2 reaction. The products are the two stereoisomeric ethers *B* and *C* and the alkylated β-diketone *D*.



B *C* *D*

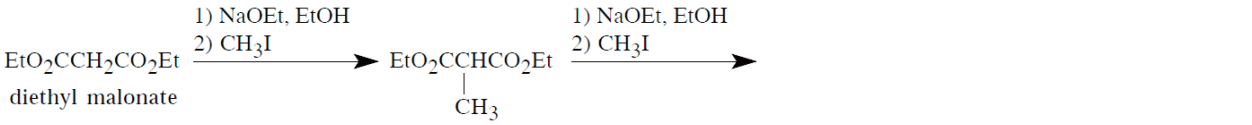
22.75 (b)



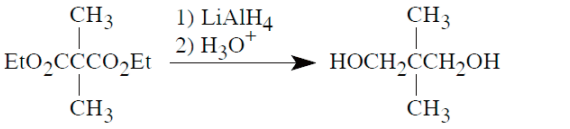
3-methyl-2-cyclohexenone

1,3,3-trimethylcyclohexanol

(d)

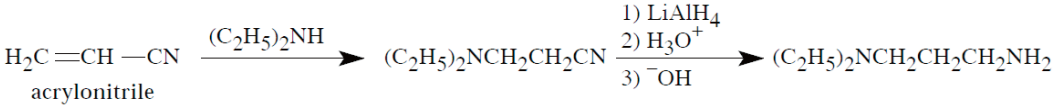


diethyl malonate



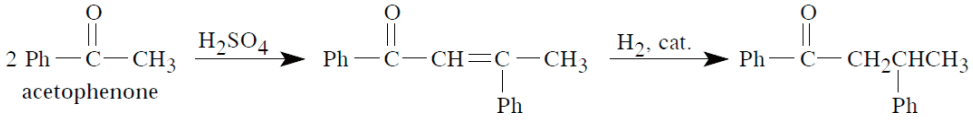
2,2-dimethyl-1,3-propanediol

(f)



acrylonitrile

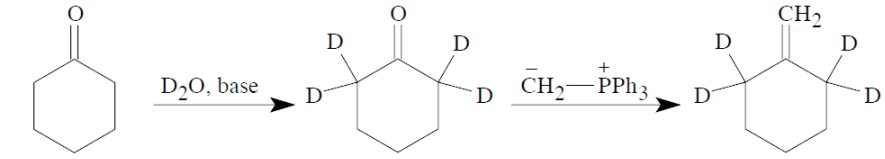
(h)



acetophenone

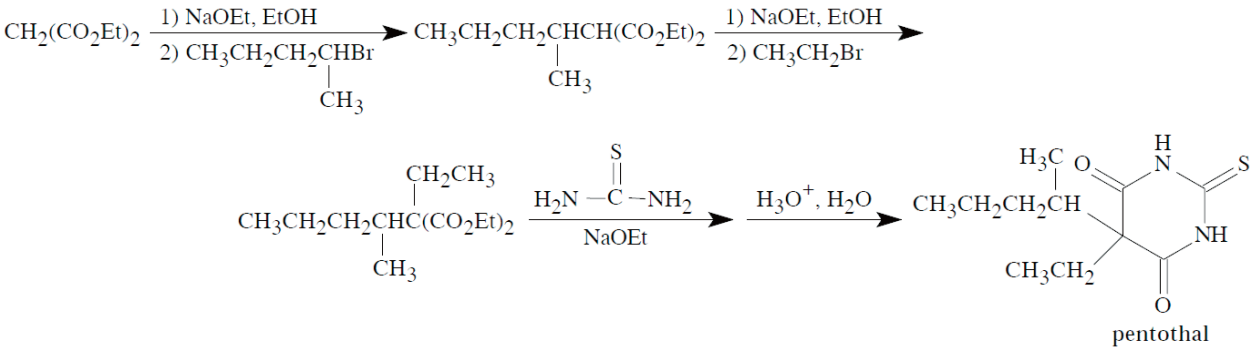
1,3-diphenyl-1-butanone

(j)



cyclohexanone

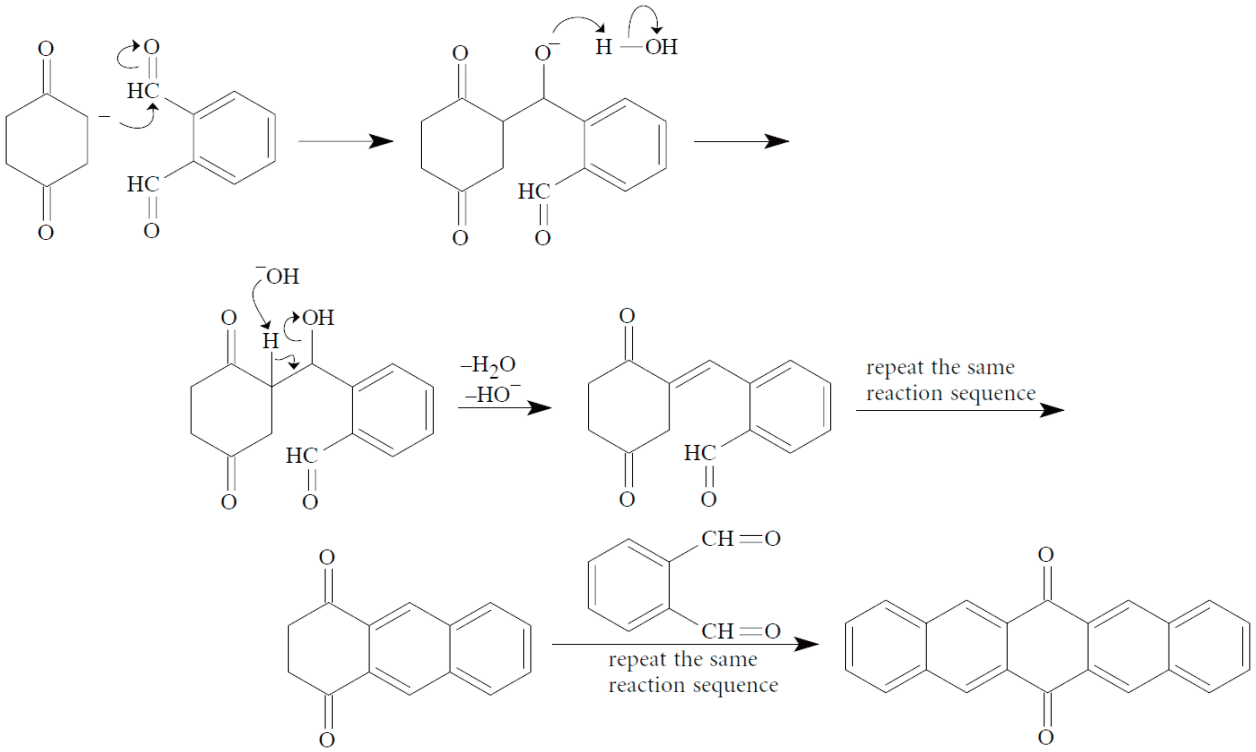
22.78 The synthesis of pentothal involves, first, preparation of the substituted malonic ester derivative, and then condensing it with thiourea, the sulfur analog of urea.



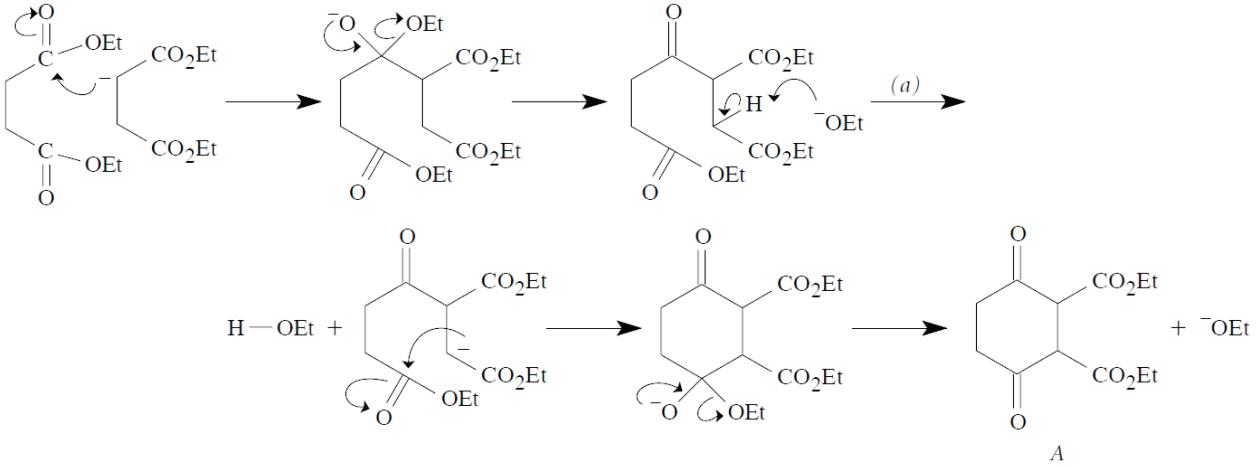
pentothal

22.80 (b) This reaction is crossed aldol condensation followed by an intramolecular crossed aldol condensation followed by the same sequence with another molecule of dialdehyde. The following mechanism begins with

the conjugate-base enolate ion of the diketone. Although the dehydration step is shown for brevity as a concerted process, it probably involves an enolate-ion intermediate. (See Eq. 22.44, text p. 1065.)

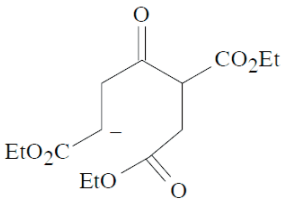


(d) This is a double Claisen condensation followed by hydrolysis and decarboxylation of the ester groups. The mechanism below begins with the conjugate-base enolate ion of the diester.

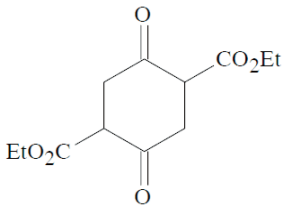


Compound *A* forms a conjugate-base enolate ion under the basic conditions but is regenerated when acid is added. Hydrolysis of the two ester groups and decarboxylation of the resulting β-keto acid groups give the product. In the step labeled *(a)*, the hydrogen that is removed is not the most acidic hydrogen in the molecule. (Which hydrogen is most acidic?) However, removal of the most acidic hydrogen does not lead to the observed product. Removal of the hydrogen shown, although occurring less frequently, leads rapidly to product.

Note also that the second condensation reaction could involve the reaction of a different enolate ion with a different ester group so that the β-keto ester shown on the right would be formed:

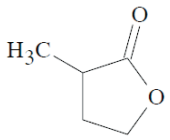


alternate enolate for second condensation

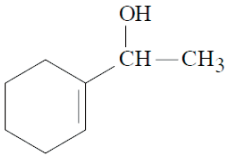


Ester hydrolysis and decarboxylation of this compound would also give the observed product.

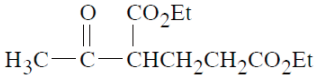
22.81 (b) The lactone, a cyclic ester, can form an enolate ion, and this ion is alkylated by methyl iodide. (The structure of γ-butyrolactone is given on text p. 988.)



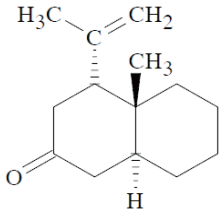
(d) Lithium aluminum hydride reduces the carbonyl group to an alcohol.



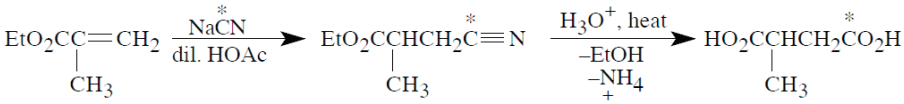
(f) This is a Michael addition in which the conjugate-base enolate ion of acetoacetic ester is the nucleophile.



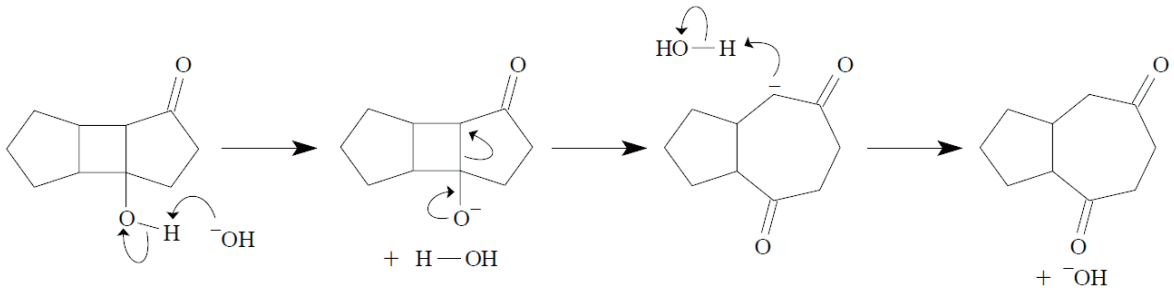
(h) This is a conjugate addition of the magnesium organocuprate reagent. Assume that the isopropenyl group (the group delivered from the organocuprate reagent) enters trans to the angular methyl group to avoid van der Waals repulsions.



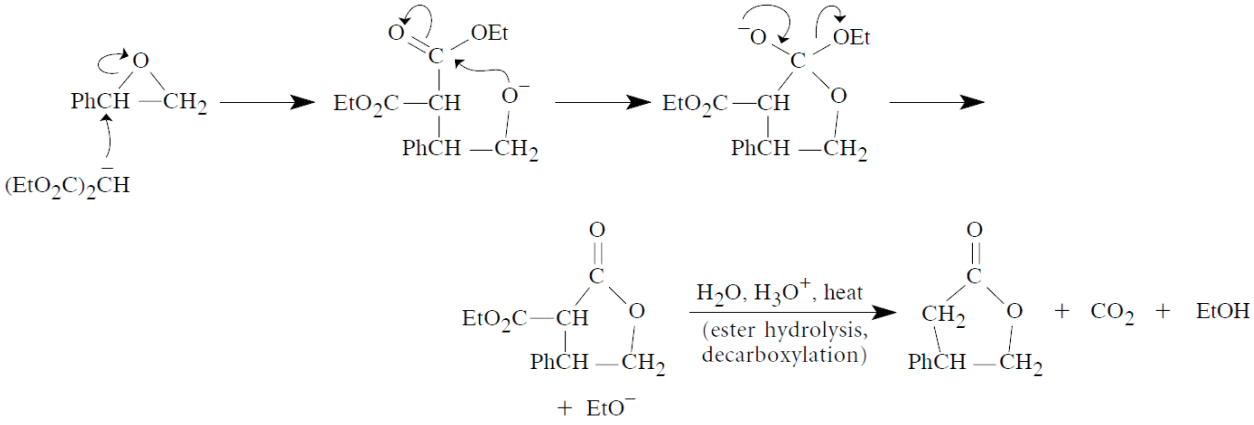
22.82 (b) Take the same approach as in part (a), but with a different ester.



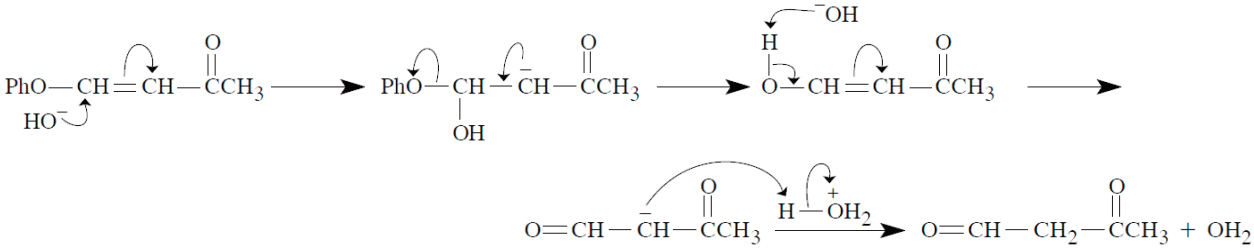
22.83 (b) The starting material is a β-hydroxy ketone. Ionization of the hydroxy group followed by the reverse of an aldol addition gives the product. The reaction is driven by relief of strain in the four-membered ring.



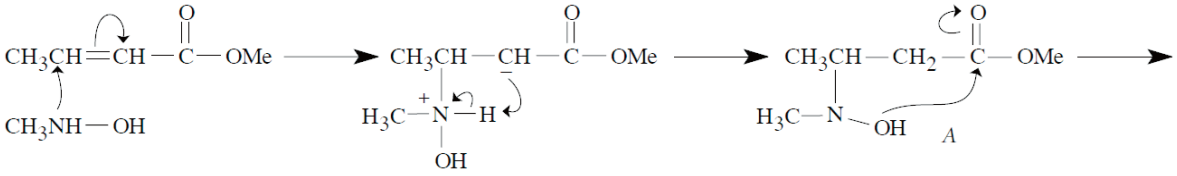
22.84 (b) The conjugate-base anion of diethyl malonate serves as the nucleophile in an epoxide-opening reaction. Normally, epoxide opening under basic conditions involves reaction with the nucleophile at the less branched carbon. In this case, however, reaction also occurs at the more branched carbon because it is benzylic and therefore activated toward nucleophilic substitution. (Only reaction at the benzylic carbon is shown below; reaction at the other carbon occurs by a similar mechanism.) The resulting alkoxide undergoes intramolecular transesterification to give a lactone; hydrolysis and decarboxylation of the remaining ester give the product. The lactone does not hydrolyze because the equilibrium favors lactone formation when five- and six-membered rings are involved; see Eqs. 21.12–21.13 on text p. 1007.

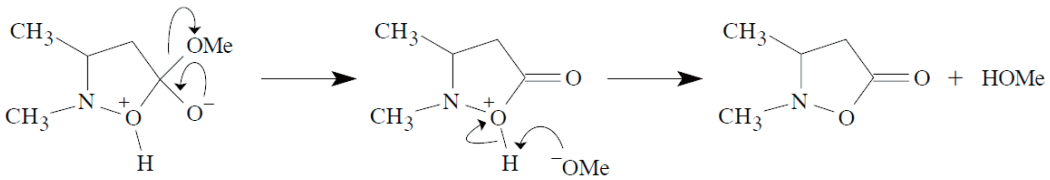


(e) This mechanism is much like that in part (d), except that basic conditions are involved in all steps but the last.

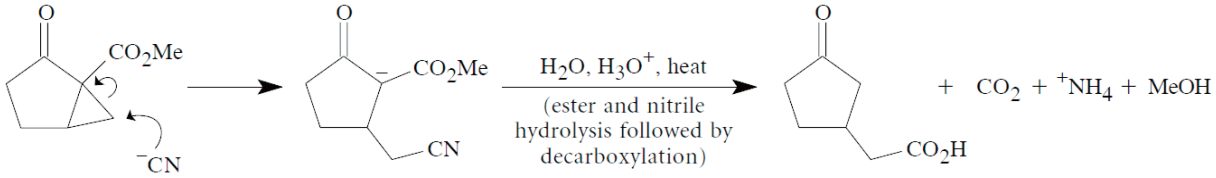


(g) Conjugate addition with the nitrogen as a nucleophile gives compound *A*, which undergoes intramolecular transesterification. Alternatively, transesterification could occur first followed by conjugate addition.





(j) This reaction is a "conjugate addition" of cyanide ion on a cyclopropane. Notice that reaction at the least branched carbon of the cyclopropane occurs and that the immediate product of ring opening is a very stable anion. Heating in acid protonates this anion, hydrolyzes the ester and nitrile groups, and decarboxylates the resulting β-keto acid.



22.85 (b) One of the two possible conjugate-base enolate ions undergoes an intramolecular nucleophilic substitution reaction to give the cyclopropane. Although the other enolate is undoubtedly also formed, its cyclization would lead to a different product. In addition, the enolate that leads to product is the more stable enolate (why?) In any case, the enolate ion shown evidently reacts more rapidly.