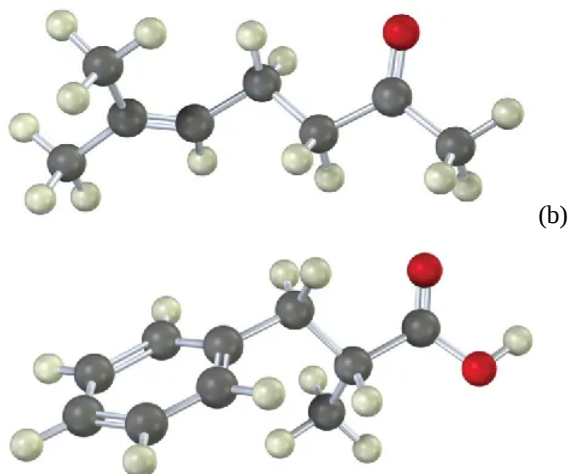


## 8.9: Additional Problems

22 • Additional Problems 22 • Additional Problems

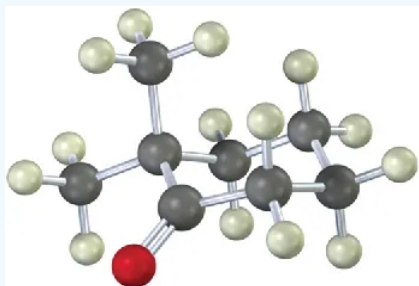
### Visualizing Chemistry

Show the steps in preparing each of the following substances using either a malonic ester synthesis or an acetoacetic ester synthesis: (a)

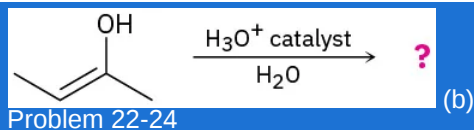
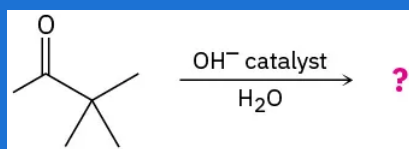


Unlike most  $\beta$ -diketones, the following  $\beta$ -diketone has no detectable enol content and is about as acidic as acetone.

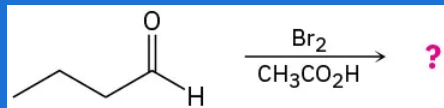
For a given  $\alpha$ -hydrogen atom to be acidic, the C-H bond must be perpendicular to the plane of the adjacent carbonyl group. Identify the most acidic hydrogen atom in the following  $\beta$ -diketone.



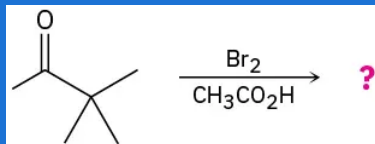
### Mechanism Problems



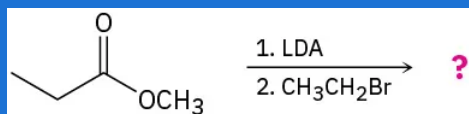
Problem 22-21 Predict the product(s) and show the mechanism for each of the following reactions: (a)



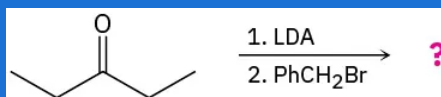
(b)



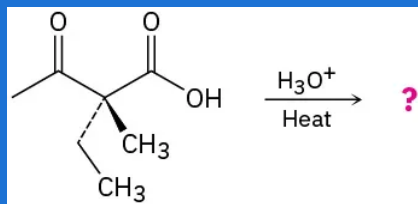
Problem 22-22 Predict the product(s) and show the mechanism for each of the following reactions: (a)



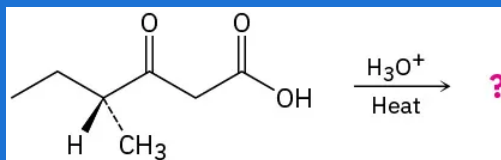
(b)



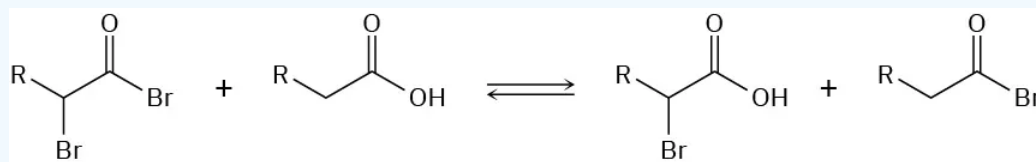
Problem 22-23 The following two optically active  $\beta$ -keto acids were decarboxylated under the conditions typically used for the acetoacetic ester synthesis. Will the ketone products be optically active? Explain. (a)



(b)

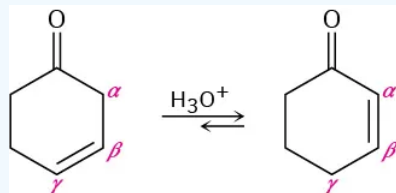


In the Hell-Volhard-Zelinskii reaction, only a catalytic amount of  $\text{PBr}_3$  is necessary because of the following equilibrium. Propose a mechanism for formation of the equilibrium.

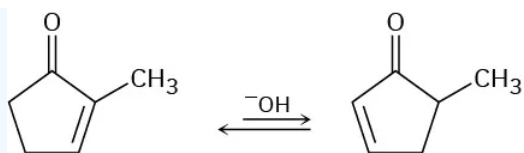


When a ketone is treated with a halogen under acidic conditions, the  $\alpha$ -monohalogenated product can be obtained in high yield. Under basic conditions however it is difficult to isolate the monohalogenated product. Explain.

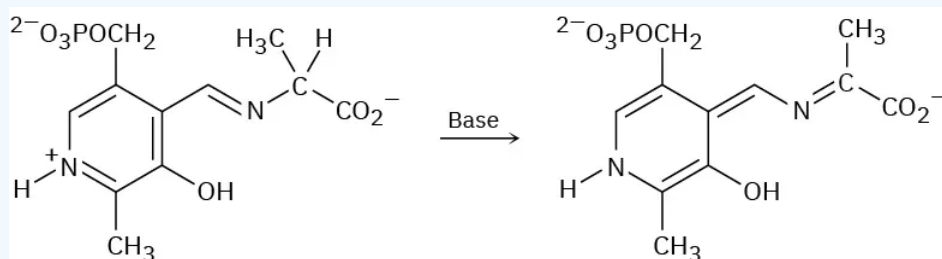
Nonconjugated  $\beta,\gamma$ -unsaturated ketones, such as 3-cyclohexenone, are in an acid-catalyzed equilibrium with their conjugated  $\alpha,\beta$ -unsaturated isomers. Propose a mechanism for the isomerization.



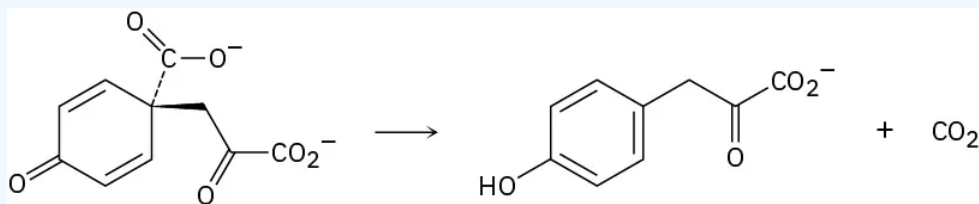
2-substituted 2-cyclopentenones can be interconverted with 5-substituted 2-cyclopentenones under basic conditions. Propose a mechanism for this isomerization.



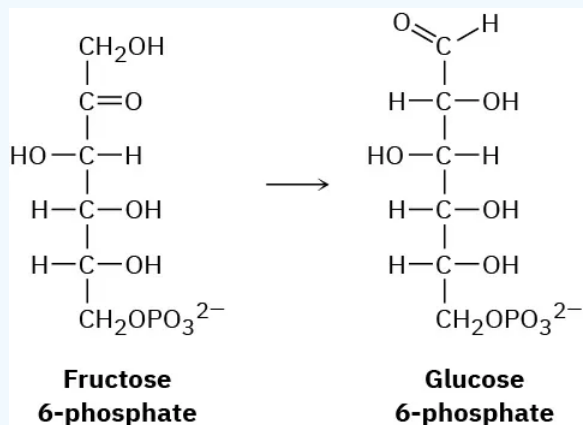
Using curved arrows, propose a mechanism for the following reaction, one of the steps in the metabolism of the amino acid alanine.



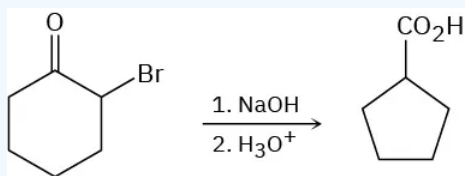
Using curved arrows, propose a mechanism for the following reaction, one of the steps in the biosynthesis of the amino acid tyrosine.



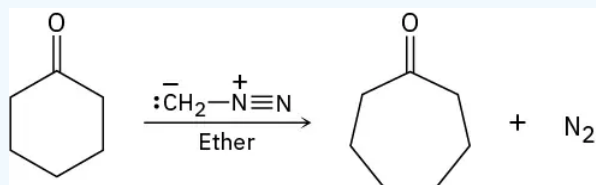
One of the later steps in glucose biosynthesis is the isomerization of fructose 6-phosphate to glucose 6-phosphate. Propose a mechanism, using acid or base catalysis as needed.



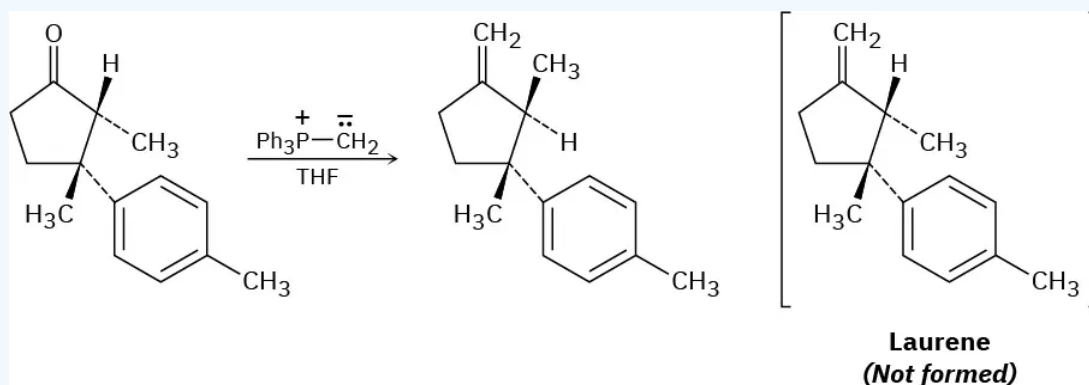
The *Favorskii reaction* involves treatment of an  $\alpha$ -bromo ketone with base to yield a ring-contracted product. For example, reaction of 2-bromocyclohexanone with aqueous  $\text{NaOH}$  yields cyclopentanecarboxylic acid. Propose a mechanism.



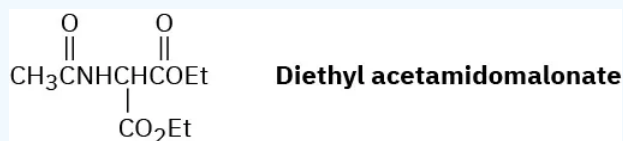
Treatment of a cyclic ketone with diazomethane is a method for accomplishing a ring-expansion reaction. For example, treatment of cyclohexanone with diazomethane yields cycloheptanone. Propose a mechanism.



The final step in an attempted synthesis of laurene, a hydrocarbon isolated from the marine alga *Laurencia glandulifera*, involved the Wittig reaction shown. The product obtained, however, was not laurene but an isomer. Propose a mechanism to account for the unexpected results.

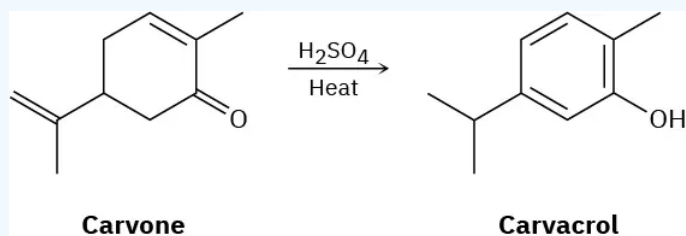


Amino acids can be prepared by reaction of alkyl halides with diethyl acetamidomalonate, followed by heating the initial alkylation product with aqueous HCl. Show how you would prepare alanine,  $\text{CH}_3\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ , one of the twenty amino acids found in proteins, and propose a mechanism for acid-catalyzed conversion of the initial alkylation product to the amino acid.

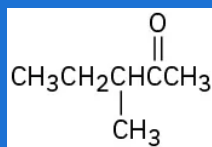


Amino acids can also be prepared by a two-step sequence that involves Hell–Volhard–Zelinskii reaction of a carboxylic acid followed by treatment with ammonia. Show how you would prepare leucine,  $(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ , and identify the mechanism of the second step.

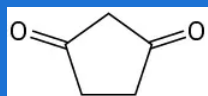
Heating carvone with aqueous sulfuric acid converts it into carvacrol. Propose a mechanism for the isomerization.



## Acidity of Carbonyl Compounds

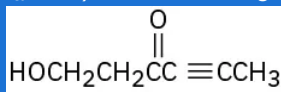


(b)

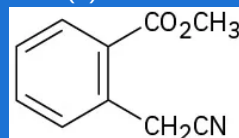


(c)

$K_a < 25$  in the following molecules: (a)

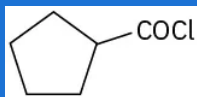


(d)

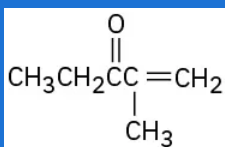


(e)

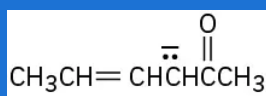
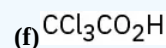
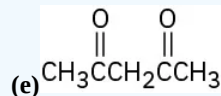
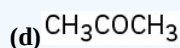
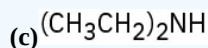
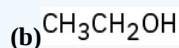
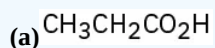
Problem  
22-38



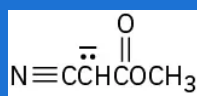
(f)



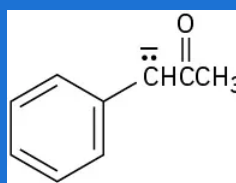
Rank the following compounds in order of increasing acidity:



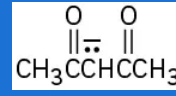
(c)



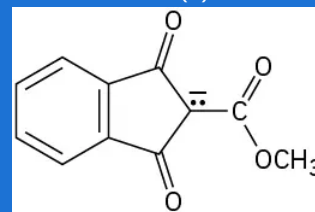
(d)



(e)

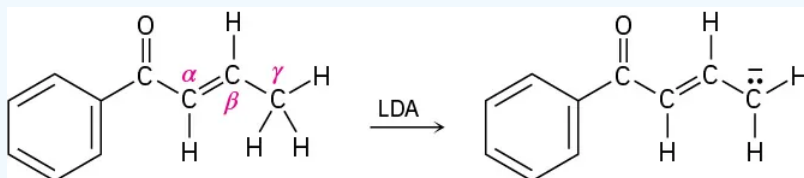


(b)

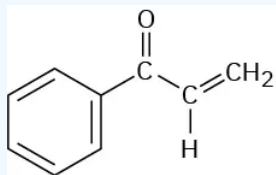


Problem  
22-40

Base treatment of the following  $\alpha,\beta$ -unsaturated carbonyl compound yields an anion by removal of  $\text{H}^+$  from the  $\gamma$  carbon. Why are hydrogens on the  $\gamma$  carbon atom acidic?

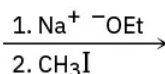


Treatment of 1-phenyl-2-propenone with a strong base such as LDA does not yield an anion, even though it contains a hydrogen on the carbon atom next to the carbonyl group. Explain.

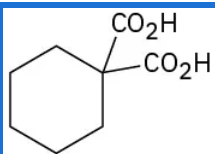


**1-Phenyl-2-propenone**

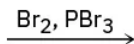
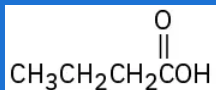
### $\alpha$ -Substitution Reactions



(c) ?



(b) ?

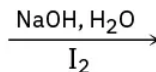
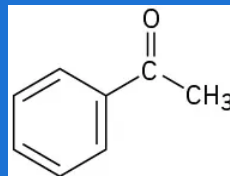


?



?

(d)



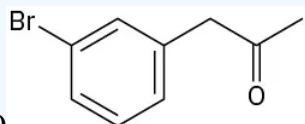
?

Problem 22-43

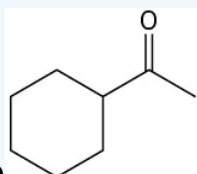
Which, if any, of the following compounds can be prepared by a malonic ester synthesis? Show the alkyl halide you would use in each case.

- (a) Ethyl pentanoate (b) Ethyl 3-methylbutanoate (c) Ethyl 2-methylbutanoate  
(d) Ethyl 2,2-dimethylpropanoate

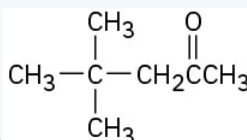
Which, if any, of the following compounds can be prepared by an acetoacetic ester synthesis? Explain.



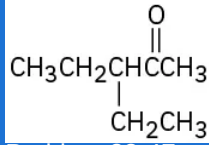
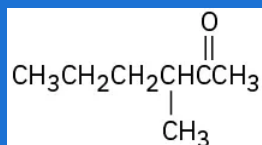
(a)



(b)



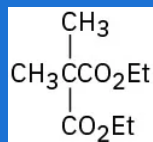
(c)



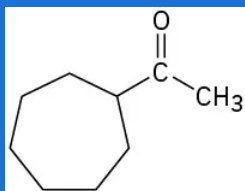
(b)

Problem 22-47

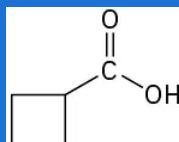
Problem 22-46 How would you prepare the following compounds using either an acetoacetic ester synthesis or a malonic ester synthesis? (a)



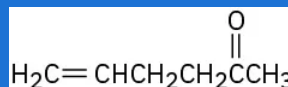
(b)



(c)



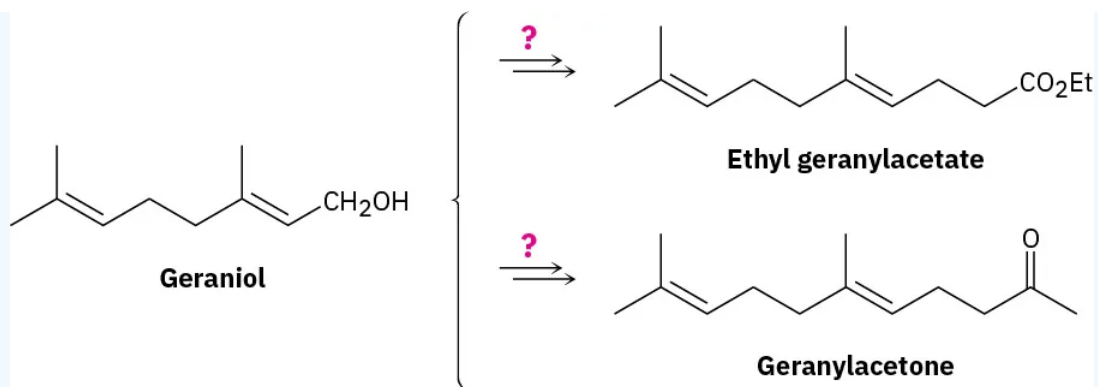
(d)



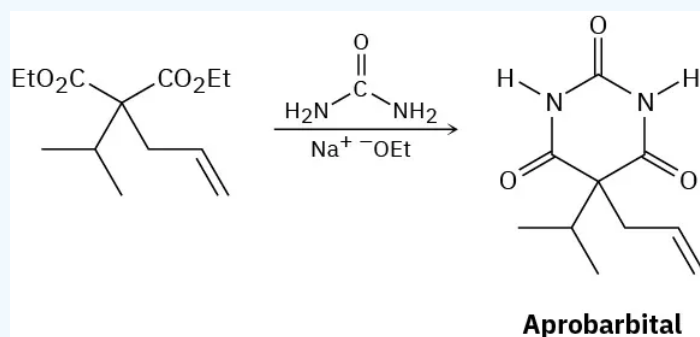
Which of the following substances would undergo the haloform reaction?

- (a)  $\text{CH}_3\text{COCH}_3$  (b) Acetophenone (c)  $\text{CH}_3\text{CH}_2\text{CHO}$  (d)  $\text{CH}_3\text{CO}_2\text{H}$  (e)  $\text{CH}_3\text{C}\equiv\text{N}$

How might you convert geraniol into either ethyl geranylacetate or geranylacetone?



Aprobarbital, a barbiturate once used in treating insomnia, is synthesized in three steps from diethyl malonate. Show how you would synthesize the necessary dialkylated intermediate, and then propose a mechanism for the reaction of this intermediate with urea to give aprobarbital.



### General Problems

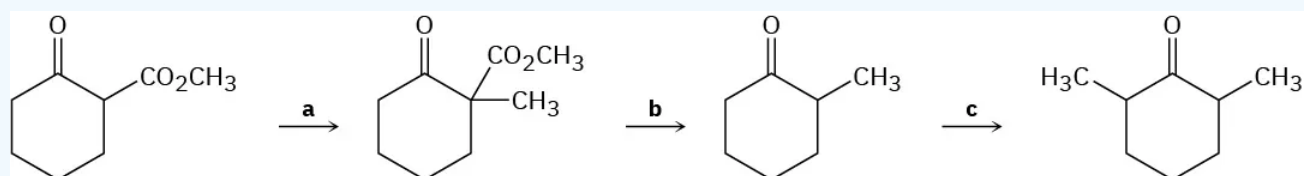
One way to determine the number of acidic hydrogens in a molecule is to treat the compound with NaOD in D<sub>2</sub>O, isolate the product, and determine its molecular weight by mass spectrometry. For example, if cyclohexanone is treated with NaOD in D<sub>2</sub>O, the product has MW = 102. Explain how this method works.

When optically active (*R*)-2-methylcyclohexanone is treated with either aqueous base or acid, racemization occurs. Explain.

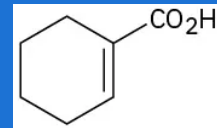
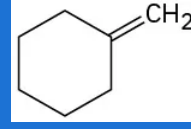
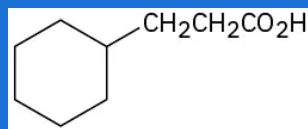
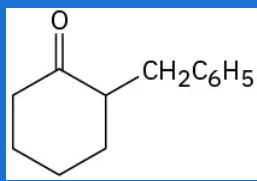
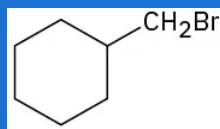
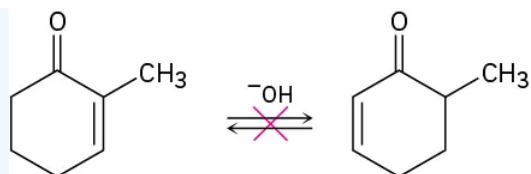
Would you expect optically active (*S*)-3-methylcyclohexanone to be racemized on acid or base treatment in the same way as 2-methylcyclohexanone (Problem 22-51)? Explain.

When an optically active carboxylic acid such as (*R*)-2-phenylpropanoic acid is brominated under Hell–Volhard–Zelinskii conditions, is the product optically active or racemic? Explain.

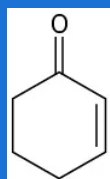
Fill in the reagents **a–c** that are missing from the following scheme:



Although 2-substituted 2-cyclopentenones are in a base-catalyzed equilibrium with their 5-substituted 2-cyclopentenone isomers, the analogous isomerization is not observed for 2-substituted 2-cyclohexenones. Explain.

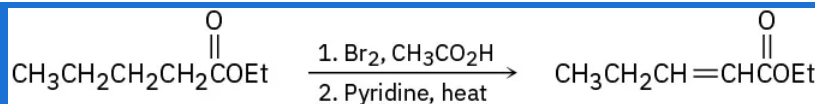


Problem



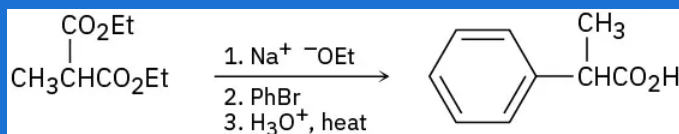
m 22-57

The two isomers *cis*- and *trans*-4-*tert*-butyl-2-methylcyclohexanone are interconverted by base treatment. Which isomer do you think is more stable, and why?

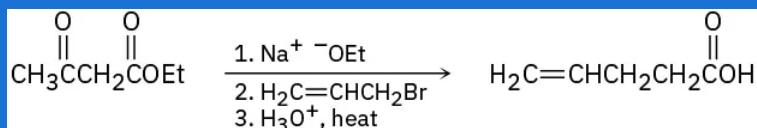


(b)

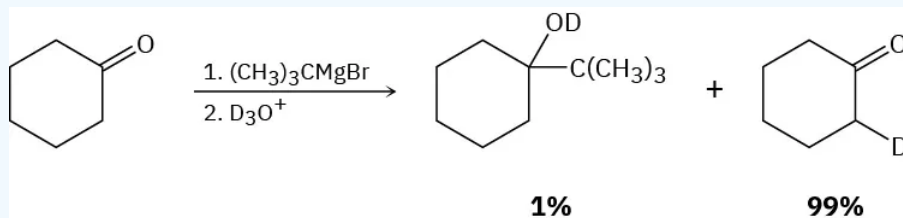
Problem 22-59



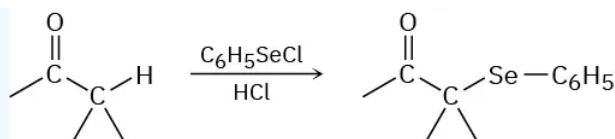
(c)



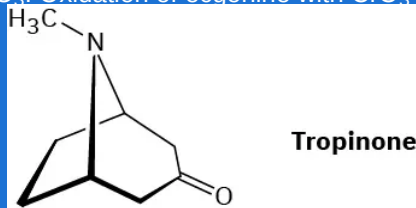
Attempted Grignard reaction of cyclohexanone with *tert*-butylmagnesium bromide yields only about 1% of the expected addition product along with 99% unreacted cyclohexanone. If  $\text{D}_3\text{O}^+$  is added to the reaction mixture after a suitable period, however, the “unreacted” cyclohexanone is found to have one deuterium atom incorporated into it. Explain.



Ketones react slowly with benzeneselenenyl chloride in the presence of HCl to yield  $\alpha$ -phenylseleno ketones. Propose a mechanism for this acid-catalyzed  $\alpha$ -substitution reaction.



South American Incas chewed the leaves of the coca bush, *Erythroxylon coca*, to combat fatigue. Chemical studies of *Erythroxylon coca* by Friedrich Wöhler in 1862 resulted in the discovery of *cocaine*,  $\text{C}_{17}\text{H}_{21}\text{NO}_4$ , as the active component. Basic hydrolysis of cocaine leads to methanol, benzoic acid, and another compound called *ecgonine*,  $\text{C}_9\text{H}_{15}\text{NO}_3$ . Oxidation of ecgonine with  $\text{CrO}_3$  yields a keto acid that readily loses  $\text{CO}_2$  on



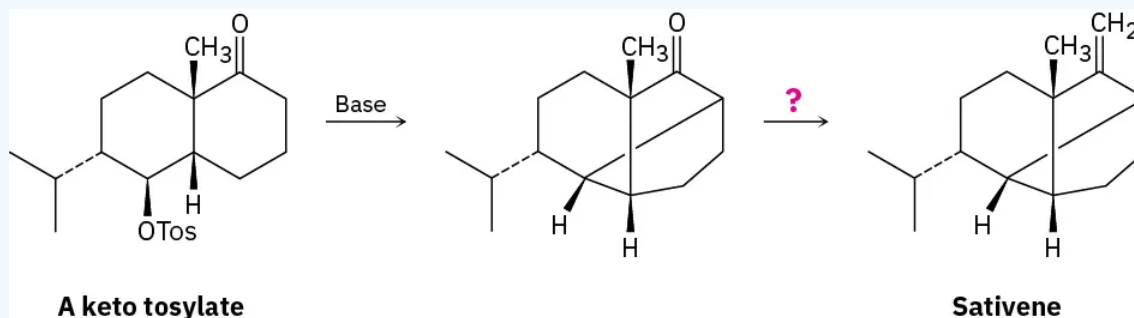
heating, giving tropinone.

(a)

What is a likely structure for the keto acid?

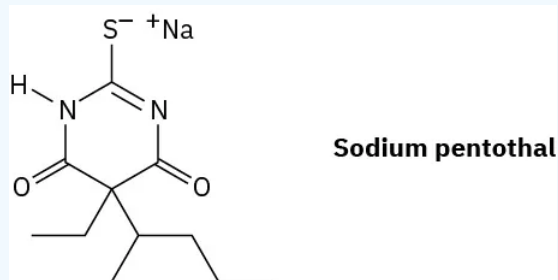
(b) What is a likely structure for ecgonine, neglecting stereochemistry? (c) What is a likely structure for cocaine, neglecting stereochemistry?

The key step in a reported laboratory synthesis of sativene, a hydrocarbon isolated from the mold *Helminthosporium sativum*, involves the following base treatment of a keto tosylate. What kind of reaction is occurring? How would you complete the synthesis?



Sodium pentothal is a short-acting barbiturate derivative used as a general anesthetic and known in popular culture as a truth serum. It is synthesized like other barbiturates (see the *Chemistry Matters* at the end of this chapter), using thiourea,  $(\text{H}_2\text{N})_2\text{C}$

Unexpected text node: 'S, in place of urea. How would you synthesize sodium pentothal?'



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