



Alpha Carbon Chemistry: Enols and Enolates

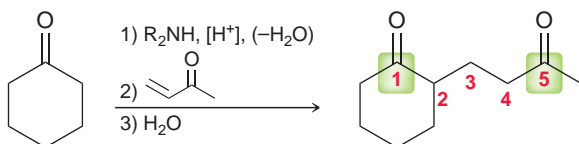
Klein, D. (2012). Alpha Carbon Chemistry. Enols and Enolates. En *Organic Chemistry*. (pp. 1082-1088). USA: Wiley.

22.8 DETERMINING WHICH ADDITION OR CONDENSATION REACTION TO USE

For compounds with two functional groups, the relative positioning of the groups, as well as their oxidation states, will dictate which addition or condensation reaction to use.

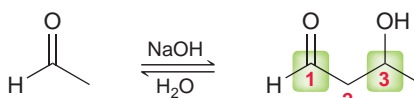
1,5-DIFUNCTIONALIZED COMPOUNDS

Stork enamine synthesis

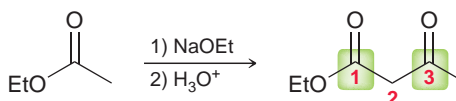


1,3-DIFUNCTIONALIZED COMPOUNDS

Aldol addition



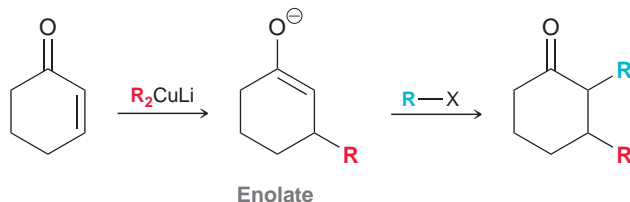
Claisen condensation



→ Try Problems 22.51–22.53, 22.87d

22.9 ALKYLATING THE α AND β POSITIONS

A strategy for installing two neighboring alkyl groups at the α and β positions.

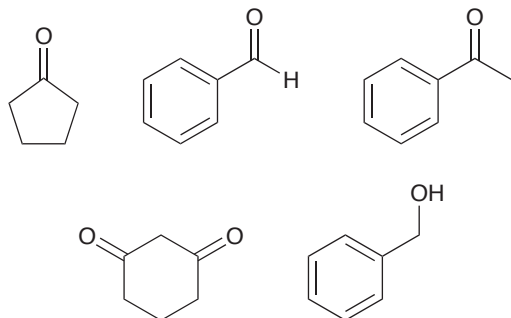


→ Try Problems 22.54–22.56, 22.82, 22.89

PRACTICE PROBLEMS

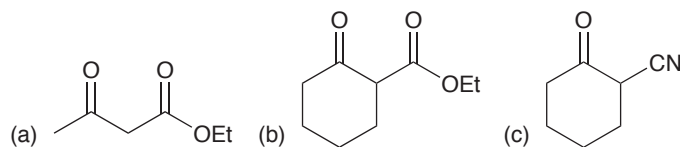
Note: Most of the Problems are available within **WILEY PLUS** *WileyPLUS*, an online teaching and learning solution.

22.57 Identify which of the following compounds are expected to have $pK_a < 20$. For each compound with $pK_a < 20$, identify the most acidic proton in the compound.



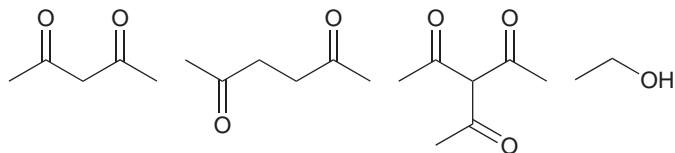
22.58 One of the compounds from the previous problem has $pK_a < 10$. Identify that compound, and explain why it is so much more acidic than all of the other compounds.

22.59 Draw resonance structures for the conjugate base that is produced when each of the following compounds is treated with sodium ethoxide.

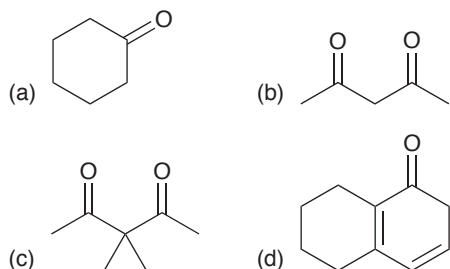




22.60 Rank the following compounds in terms of increasing acidity.

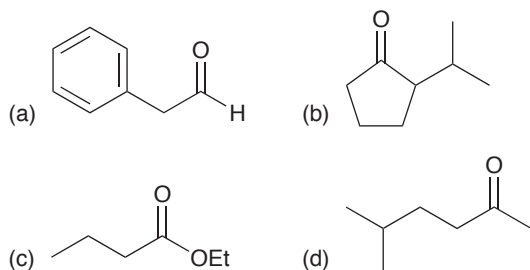


22.61 Draw the enol of each of the following compounds, and identify whether the enol exhibits a significant presence at equilibrium. Explain.



22.62 Ethyl acetoacetate has three enol isomers. Draw all three.

22.63 Draw the enolate that is formed when each of the following compounds is treated with LDA.



22.64 When 2-hepten-4-one is treated with LDA, a proton is removed from one of the gamma (γ) positions. Identify which γ position is deprotonated, and explain why the γ proton is the most acidic proton in the compound.

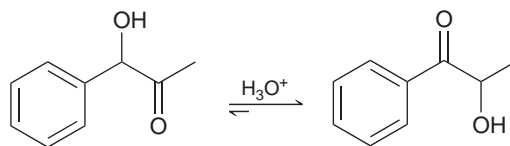
22.65 When optically active (*S*)-2-methylcyclopentanone is treated with aqueous base, the compound loses its optical activity. Explain this observation, and draw a mechanism that shows how racemization occurs.

22.66 The racemization process described in the previous problem also occurs in acidic conditions. Draw a mechanism for the racemization process in aqueous acid.

22.67 Draw all four β -hydroxyaldehydes that are formed when a mixture of acetaldehyde and pentanal is treated with aqueous sodium hydroxide.

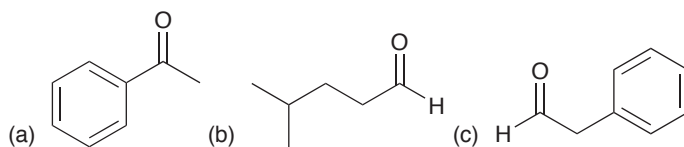
22.68 Identify all of the different β -hydroxyaldehydes that are formed when a mixture of benzaldehyde and hexanal is treated with aqueous sodium hydroxide.

22.69 Propose a mechanism for the following isomerization, and explain the driving force behind this reaction. In other words, explain why the equilibrium favors the product.



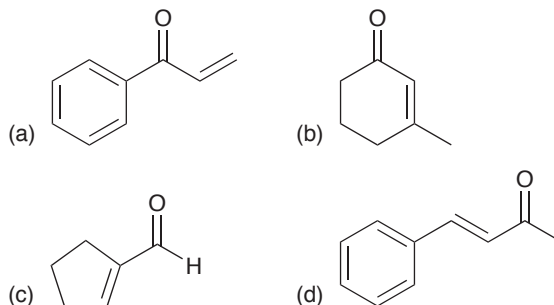
22.70 The isomerization in the previous problem can also occur in basic conditions. Draw a mechanism for the transformation in the presence of catalytic hydroxide.

22.71 Draw the product obtained when each of the following compounds is heated in the presence of a base to give an aldol condensation.

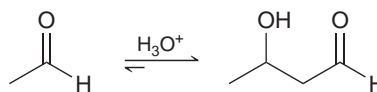


22.72 Trimethylacetaldehyde does not undergo an aldol reaction when treated with base. Explain why not.

22.73 Identify the reagents necessary to make each of the following compounds with an aldol condensation.



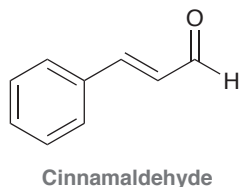
22.74 When acetaldehyde is treated with aqueous acid, an aldol reaction can occur. In other words, aldol reactions can also occur in acidic conditions, although the intermediate is different than the intermediate involved in the base-catalyzed reaction. Draw a mechanism for the acid-catalyzed process.



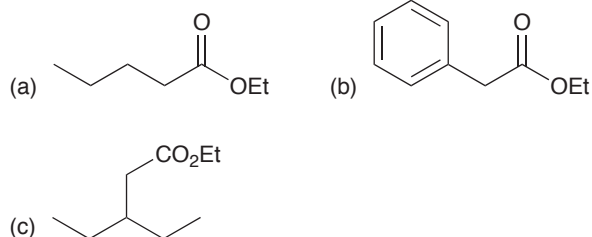
22.75 Diethyl malonate (the starting material for the malonic ester synthesis) reacts with bromine in acid-catalyzed conditions to form a product with molecular formula $C_7H_{11}BrO_4$.

- Draw the structure of the product.
- Draw a mechanism of formation for the product.
- Would you expect this product to be more or less acidic than diethyl malonate?

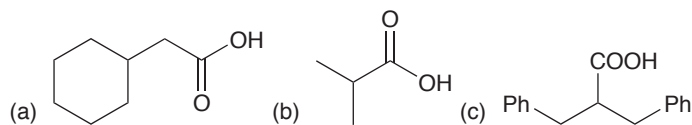
22.76 Cinnamaldehyde is one of the primary constituents of cinnamon oil and contributes significantly to the odor of cinnamon. Starting with benzaldehyde and using any other necessary reagents, show how you might prepare cinnamaldehyde.



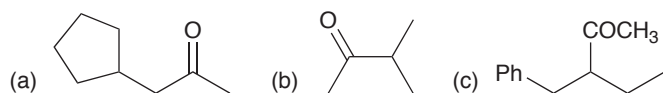
22.77 Draw the condensation product that is expected when each of the following esters is treated with sodium ethoxide followed by acid workup.



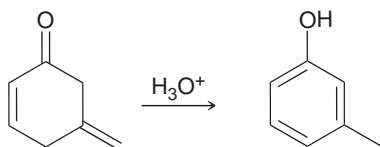
22.78 Starting with diethyl malonate, and using any other reagents of your choice, show how you would prepare each of the following compounds.



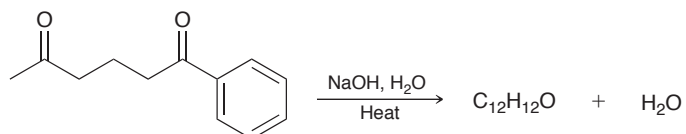
22.79 Starting with ethyl acetoacetate, and using any other reagents of your choice, show how you would prepare each of the following compounds.



22.80 Propose a mechanism for the following transformation.

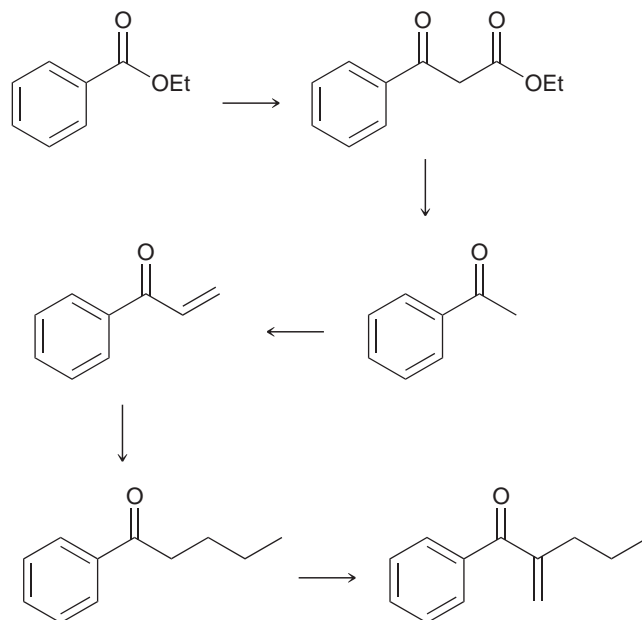


22.81 Draw the condensation product obtained when the following compound is heated in the presence of aqueous sodium hydroxide.



22.82 Identify the reagents you would use to convert 3-pentanone into 3-hexanone.

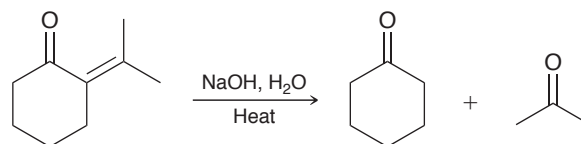
22.83 Identify the reagents necessary to achieve each of the following transformations.



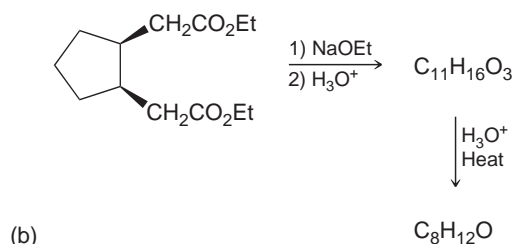
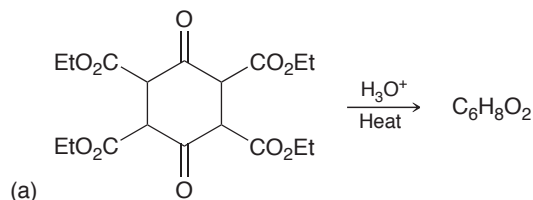
22.84 Draw the structure of the product that is obtained when acetophenone is treated with each of following reagents:

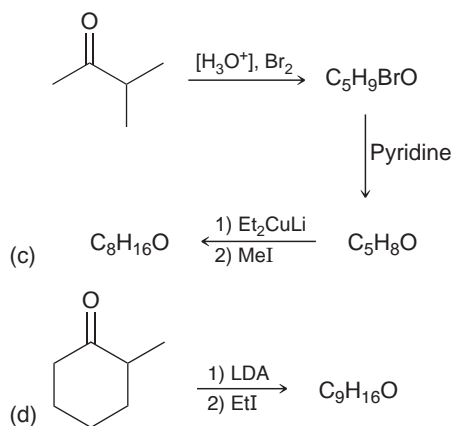
- (a) Sodium hydroxide and excess iodine followed by H_3O^+
 (b) Bromine in acetic acid
 (c) Aqueous sodium hydroxide at elevated temperature

22.85 Draw a reasonable mechanism for the following transformation.

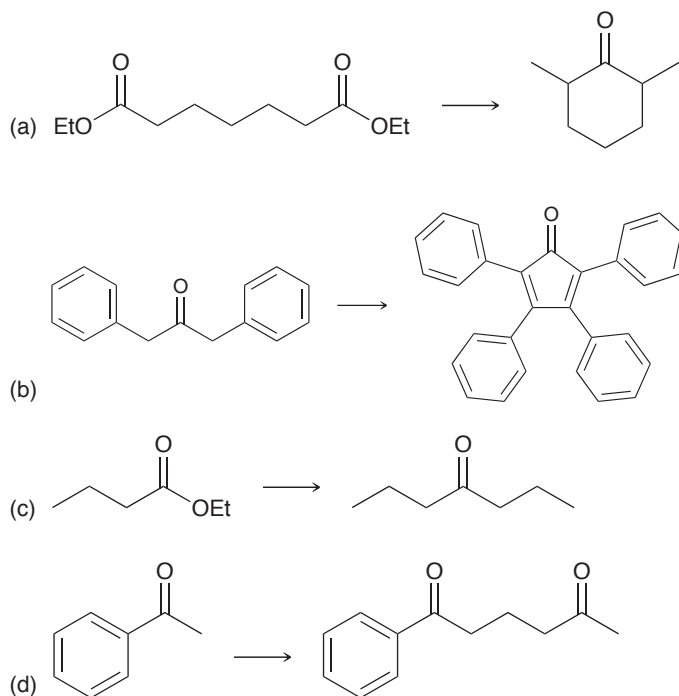


22.86 Predict the major product for each of the following transformations.

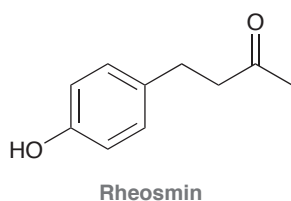




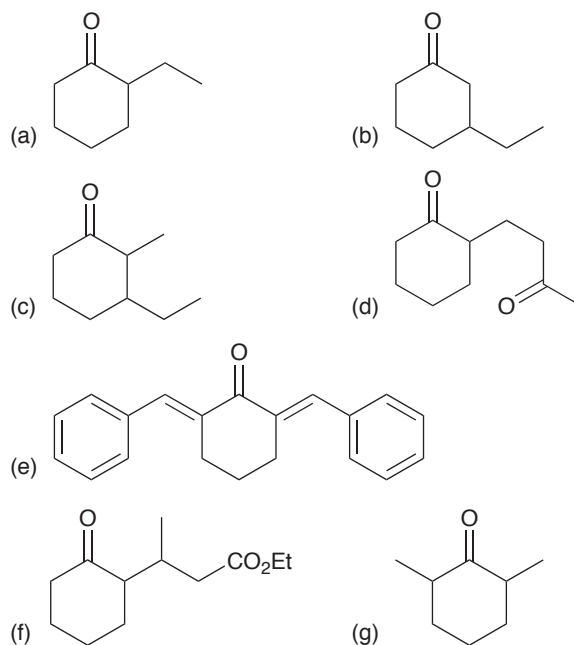
22.87 Propose an efficient synthesis for each of the following transformations.



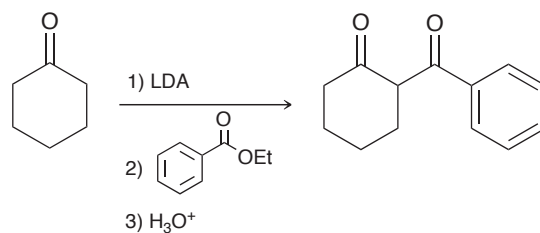
22.88 The product of an aldol condensation is an α,β -unsaturated ketone which is capable of undergoing hydrogenation to yield a saturated ketone. Using this technique, identify the reagents that you would need in order to prepare rheosmin via a crossed aldol reaction. Rheosmin is isolated from raspberries and is often used in perfume formulations for its pleasant odor. **HINT:** The presence of a phenolic proton will be problematic during an aldol reaction. (Can you explain why?) Consider using a protecting group (Section 13.7).



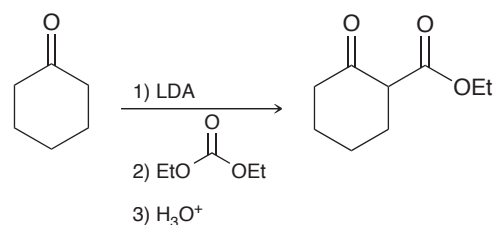
22.89 Identify the reagents you would use to convert cyclohexanone into each of the following compounds.



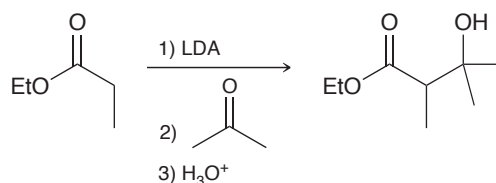
22.90 The enolate of a ketone can be treated with an ester to give a diketone. Draw a mechanism for this Claisen-like reaction, and explain why an acid source is required after the reaction is complete.



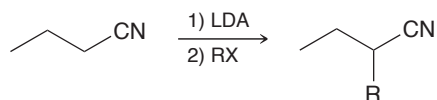
22.91 Beta-keto esters can be prepared by treating the enolate of a ketone with diethyl carbonate. Draw a plausible mechanism for this reaction.



22.92 The enolate of an ester can be treated with a ketone to give a β -hydroxy ester. Draw a mechanism for this aldol-like reaction.

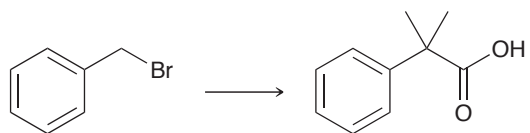


22.93 Nitriles undergo alkylation at the α position much like ketones undergo alkylation at the α position.

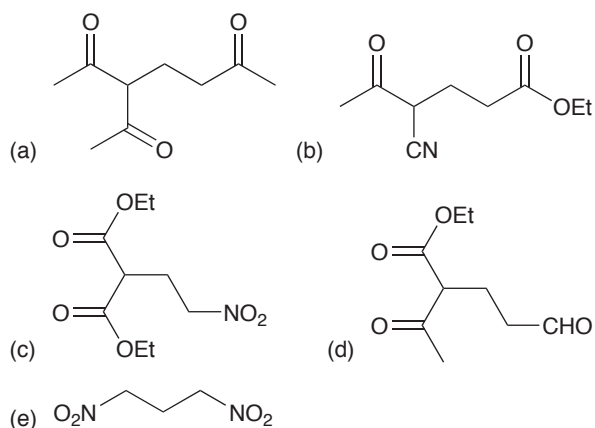


The α position of the nitrile is first deprotonated to give a resonance-stabilized anion (like an enolate), which then functions as a nucleophile to attack the alkyl halide.

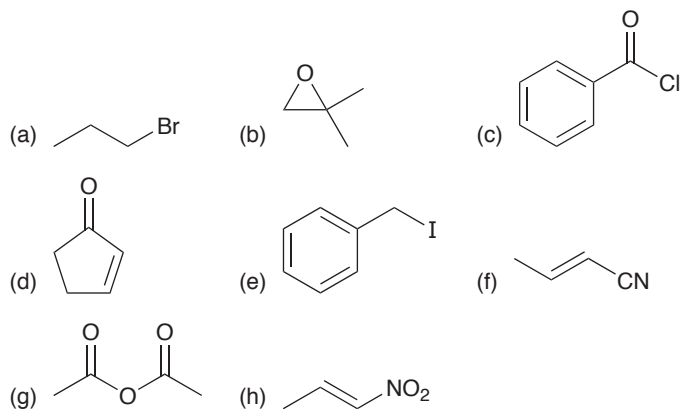
- (a) Draw the mechanism for this process.
 (b) Using this process, show the reagents you would use to achieve the following transformation:



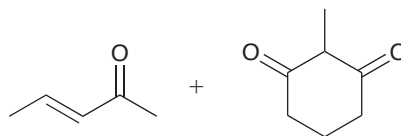
22.94 Identify the Michael donor and Michael acceptor that could be used to prepare each of the following compounds via a Michael addition.



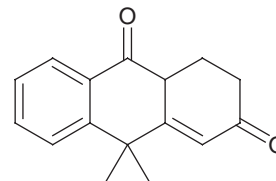
22.95 The conjugate base of diethyl malonate can serve as a nucleophile to attack a wide range of electrophiles. Identify the product that is formed when the conjugate base of diethyl malonate reacts with each of the following electrophiles followed by acid workup.



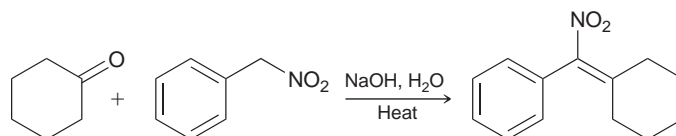
22.96 Draw the product of the Robinson annulation reaction that occurs when the following compounds are treated with aqueous sodium hydroxide.



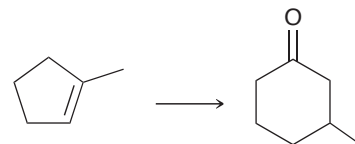
22.97 Identify what reagents you would use to make the following compound with a Robinson annulation reaction.



22.98 Draw a plausible mechanism for the following transformation.



22.99 Propose an efficient synthesis for the following transformation.

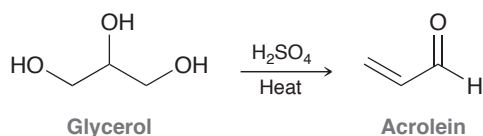




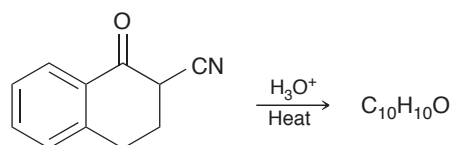
INTEGRATED PROBLEMS

22.100 For a pair of keto-enol tautomers, explain how IR spectroscopy might be used to identify whether the equilibrium favors the ketone or the enol.

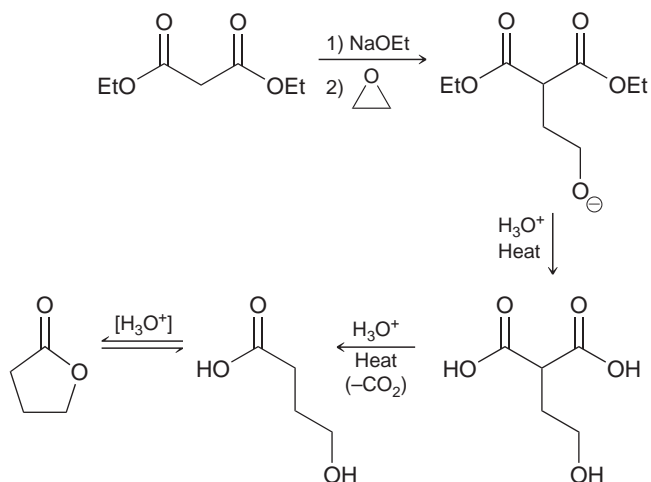
22.101 Acrolein is an α,β -unsaturated aldehyde that is used in the production of a variety of polymers. Acrolein can be prepared by treating glycerol with an acid catalyst. Propose a plausible mechanism for this transformation.



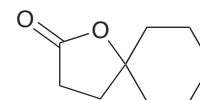
22.102 Draw the structure of the product with molecular formula C₁₀H₁₀O that is obtained when the compound below is heated with aqueous acid.



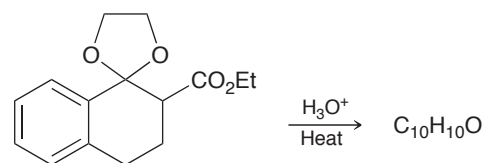
22.103 Lactones can be prepared from diethyl malonate and epoxides. Diethyl malonate is treated with a base, followed by an epoxide, followed by heating in aqueous acid:



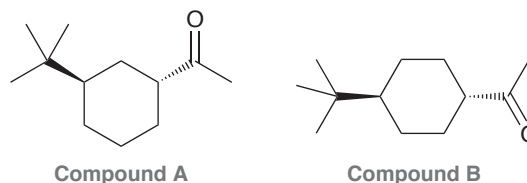
Using this process, identify what reagents you would need to prepare the following compound:



22.104 Predict the major product of the following transformation.

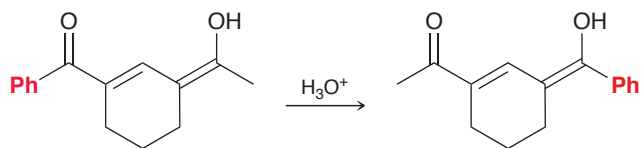


22.105 Consider the structures of the constitutional isomers, Compound **A** and Compound **B** (below). When treated with aqueous acid, Compound **A** undergoes isomerization to give a *cis* stereoisomer. In contrast, Compound **B** does not undergo isomerization when treated with the same conditions. That is, Compound **B** remains in the *trans* configuration. Explain the difference in reactivity between Compound **A** and Compound **B**.

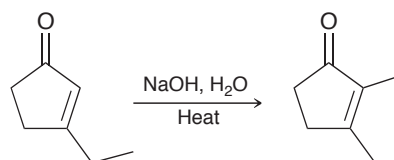


CHALLENGE PROBLEMS

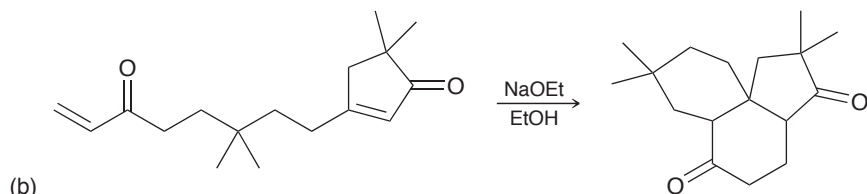
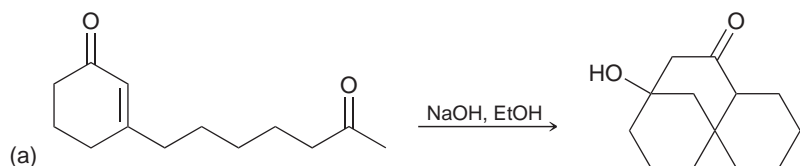
22.106 Propose a plausible mechanism for the following transformation.



22.107 Propose a plausible mechanism for the following transformation.



22.108 This chapter covered many C—C bond-forming reactions, including aldol reactions, Claisen condensations, and Michael addition reactions. Two or more of these reactions are often performed sequentially, providing a great deal of versatility and complexity in the type of structures that can be prepared. Propose a plausible mechanism for each of the following transformations.



22.109 The following transformation cannot be accomplished by direct alkylation of an enolate. Explain why not, and then devise an alternate synthesis for this transformation.

