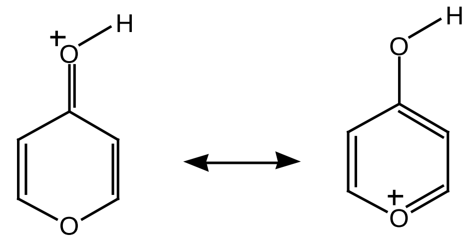
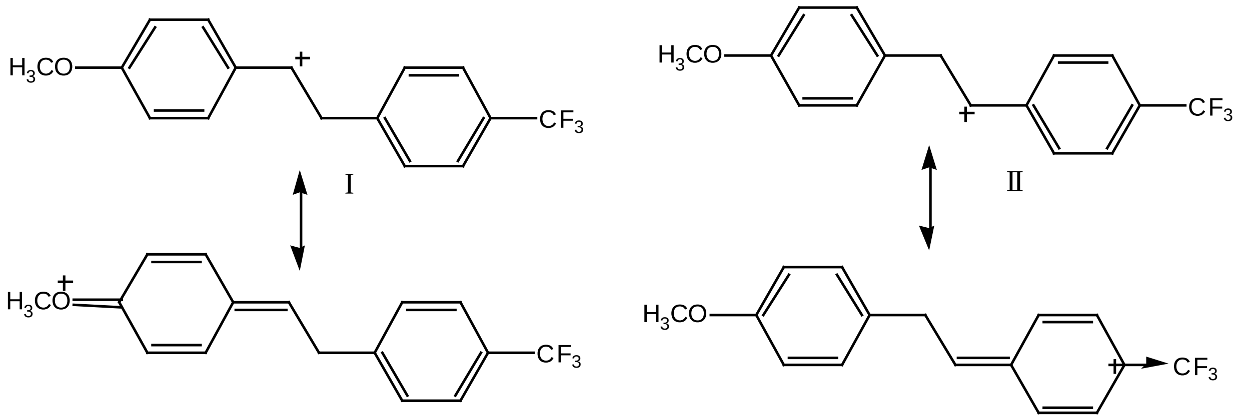
Answers to REVIEW PROBLEM SET
CH242-2002S

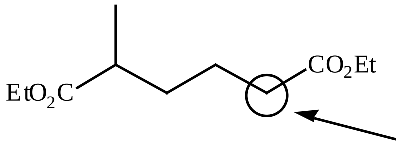
(1) (a) Protonation of γ-pyrone leads to a more stable cation that has significant contributions from aromatic structures such as the one shown below. Equivalent stabilizing features are absent in acetone which is, therefore, less basic than tha pyrone


γ-Pyrone

(b) Protonation of the starting material leads to cation I which enjoys extensive stabiliztion by interacting with the electron donating methoxy group through the ring. Cation II, however, is not favored as it involves destabilizing interaction with the electron withdrawing CF_3 group. Thus, compound A, which arises from cation I, is the observed product.



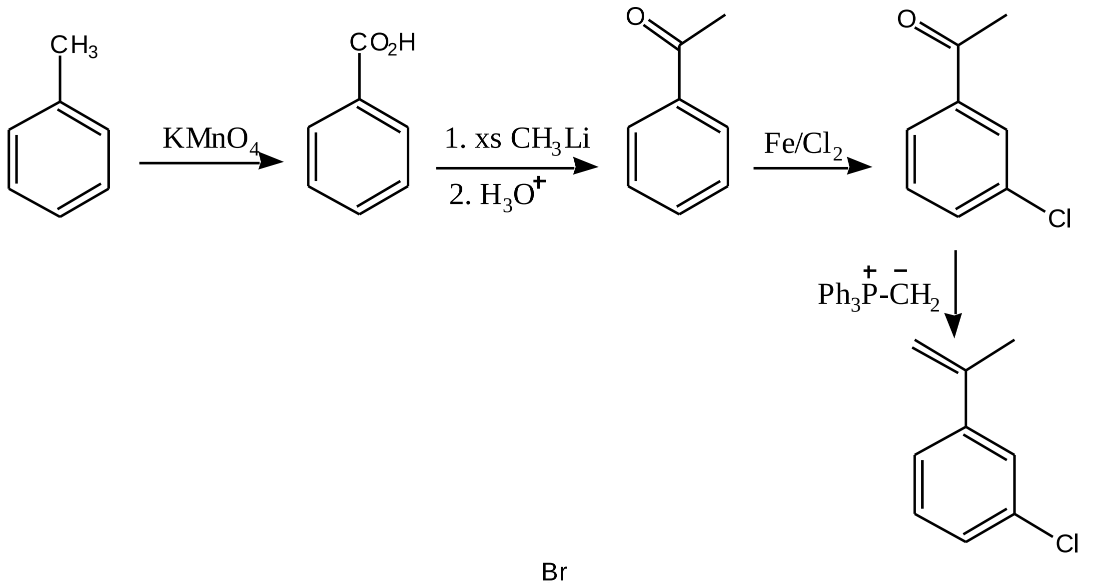
(c) This is an intramolecular Claisen aka Dieckmann reaction. As discussed in class and your text, you need at least two protons α- to the carbonyl group of the ester to drive the reaction to completion (why?). Thus, it is the anion generated at the circled position that participates in the Dieckmann condensation and eventually leads to **C**. Please push the arrows.



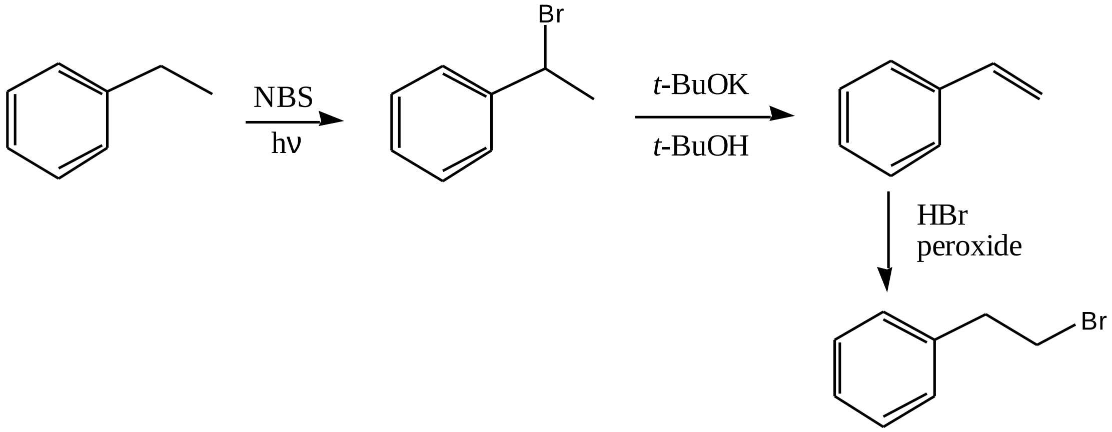
anion generated here leads to
Dieckmann reaction and gives **C**

(2)

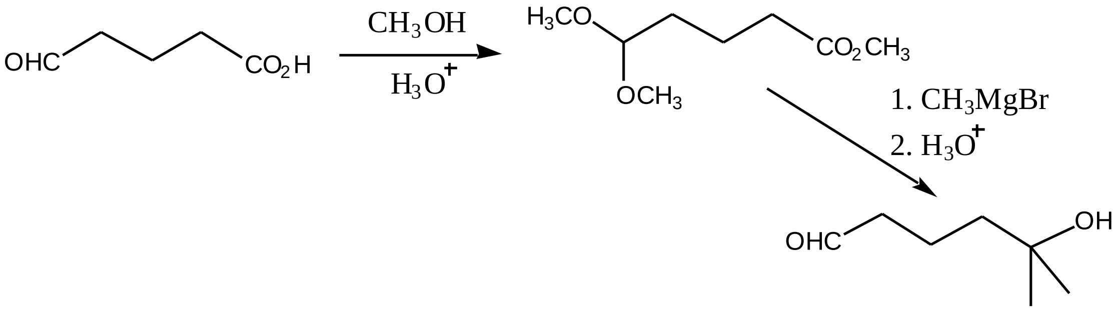
(a)



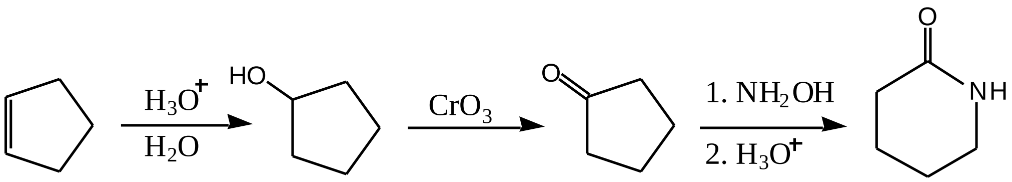
(b)



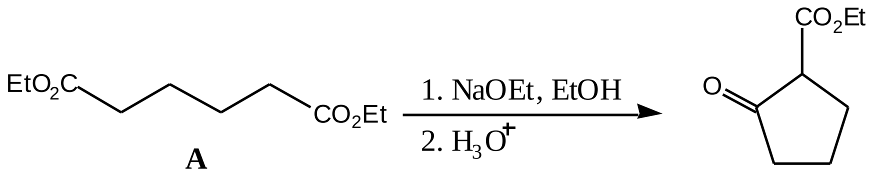
(c) The starting material and product were switched on this one. My bad.



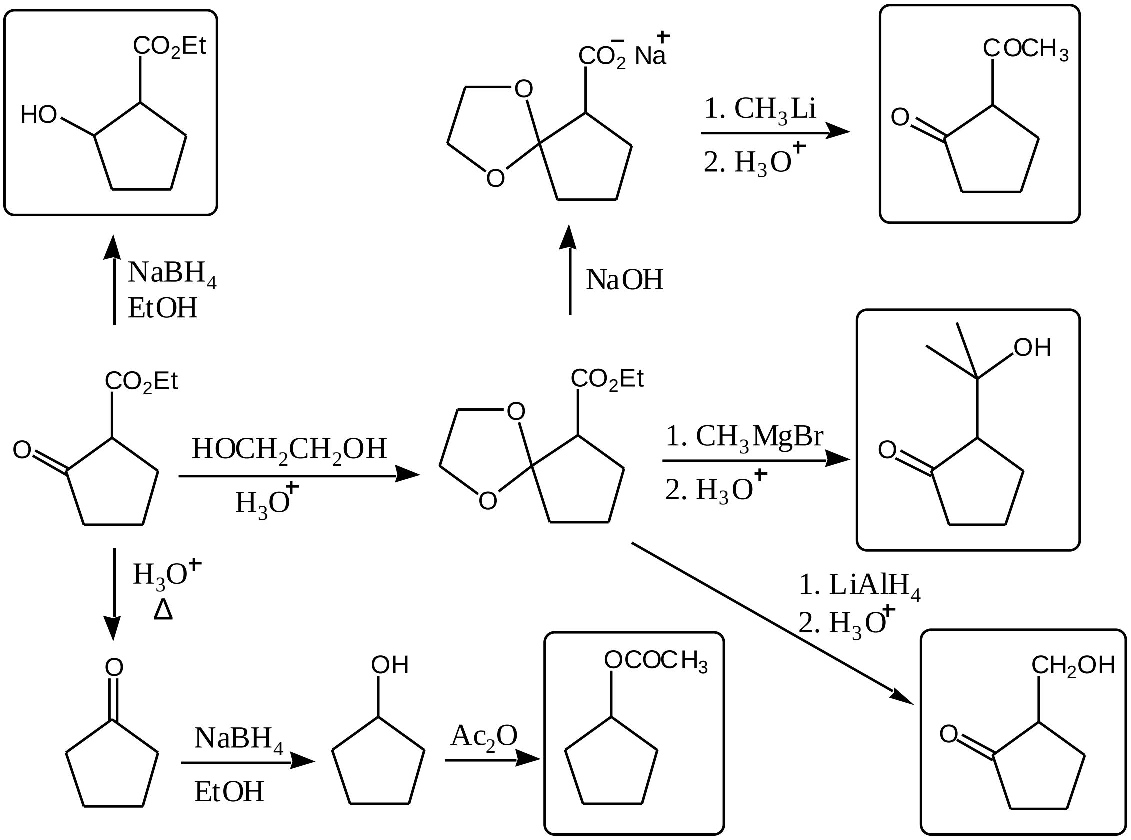
(d)



(3) (a) The product is a β-keto ester. So you should consider the possibility of a Claisen ester condensation or, in this intramolecular case, a Dieckmann reaction.

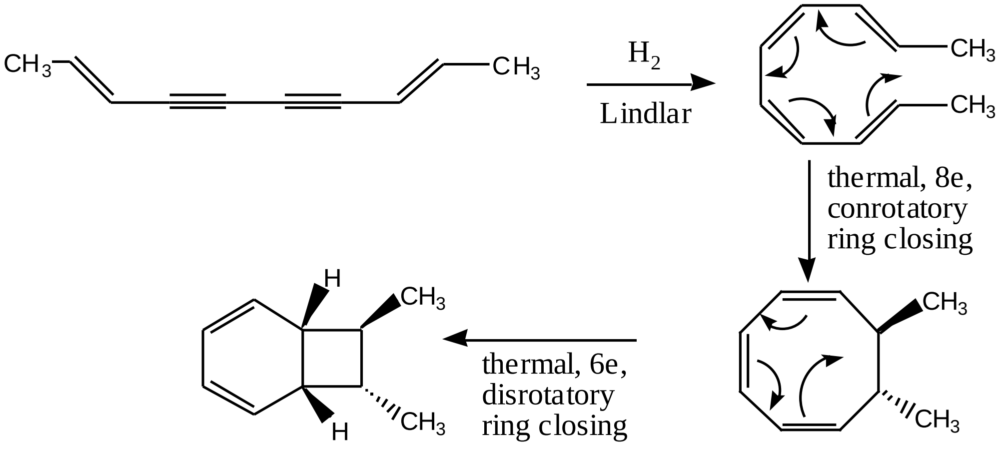


(b) Some ideas are given below. Alternative strategies are surely possible.

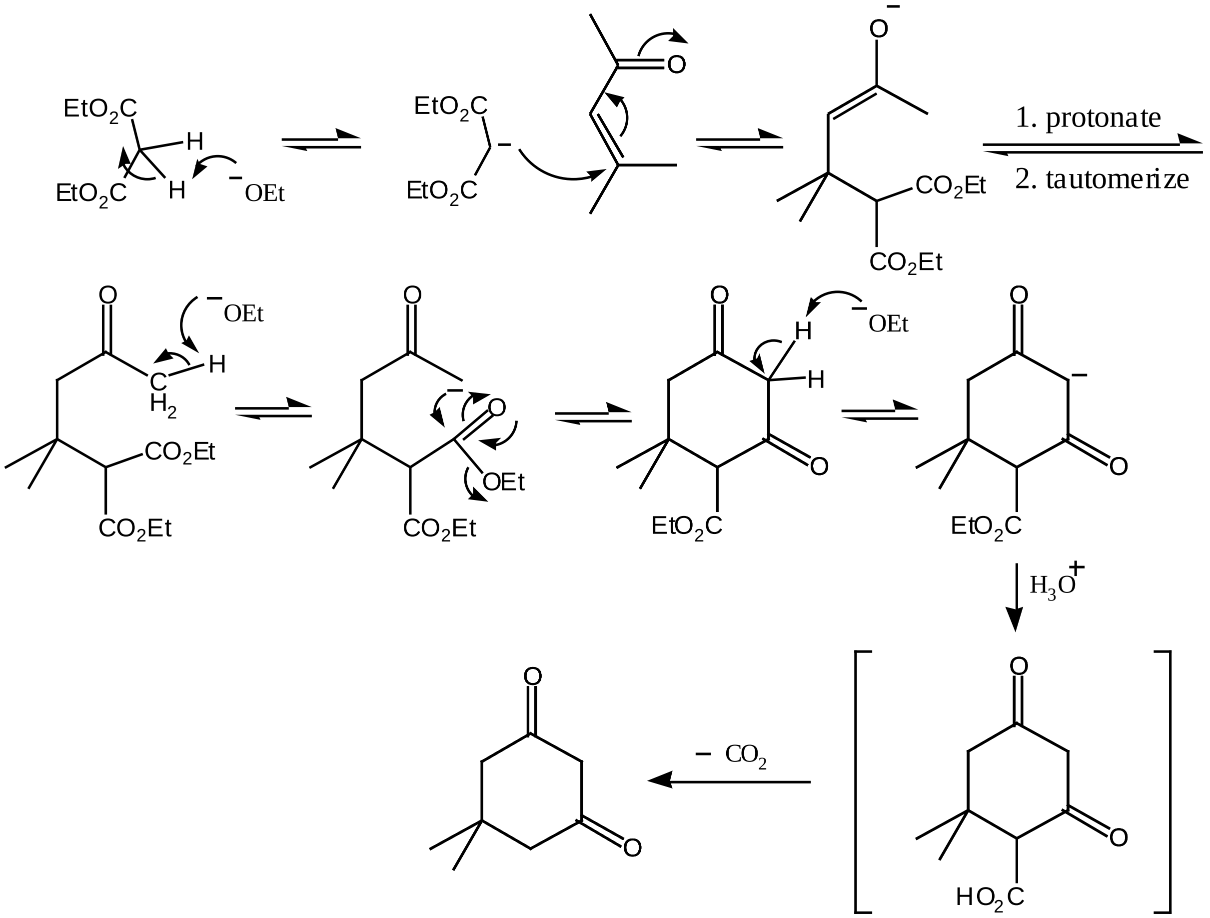


(4)

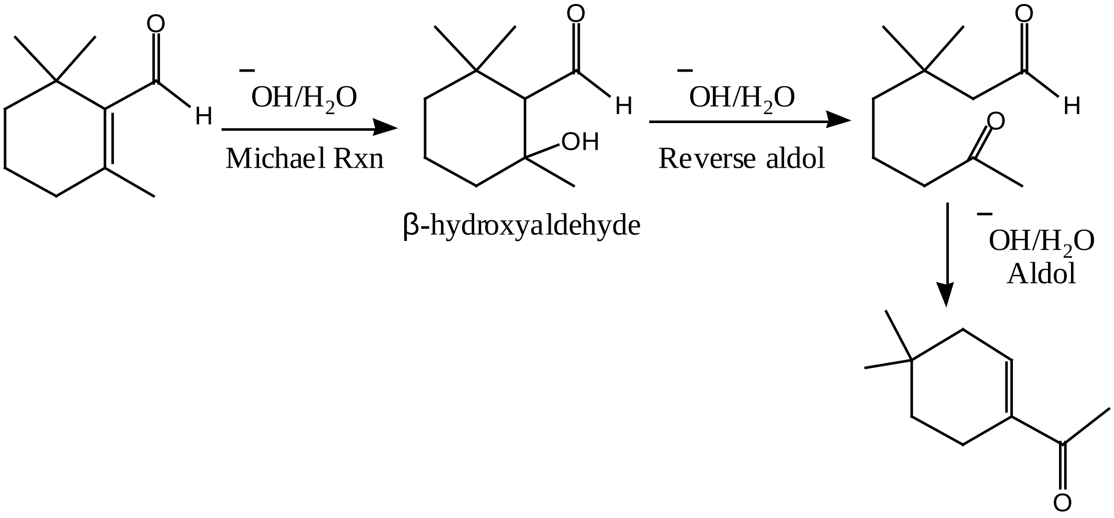
(a)



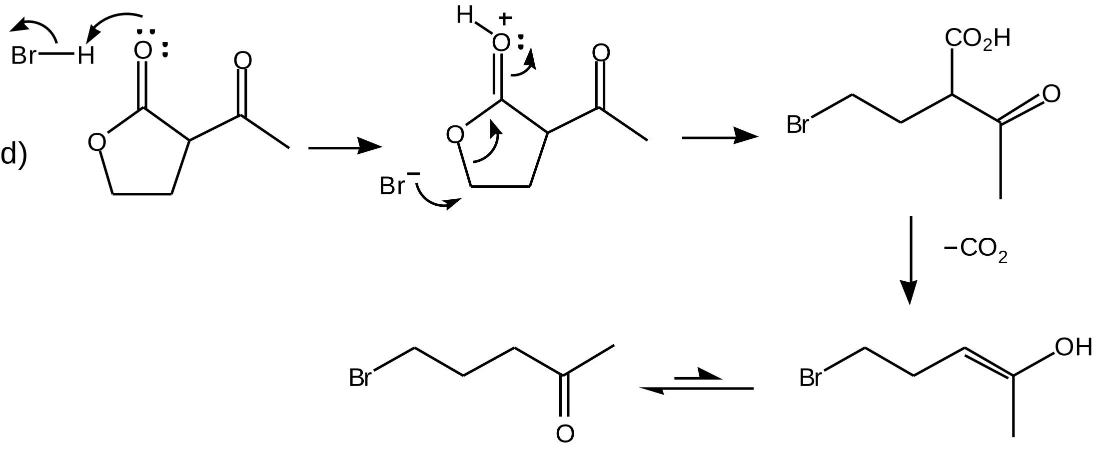
(b) You first deprotonate the malonic ester and use the resulting anion as a nucleophile to do a Michael reaction. This is followed by an intramolecular crossed Claisen condensation. Subsequent hydrolysis of the ester group releases a β-keto carboxylic acid that decarboxylates to give the product.



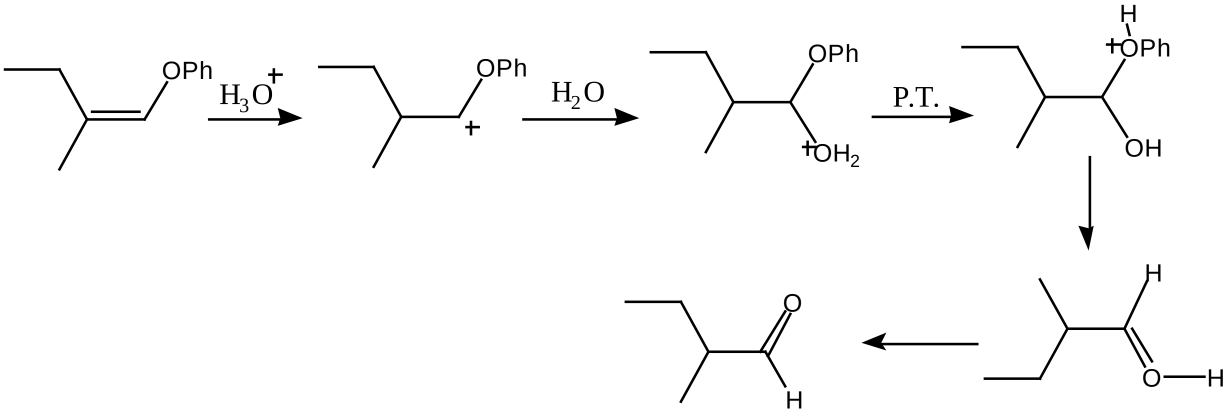
(c) In this example, I have provided only the outline. Please fill in the details by pushing arrows.



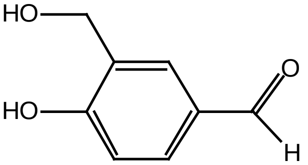
(d)



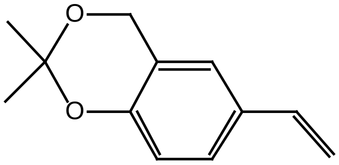
(e) Watch out. The final product is an aldehyde and the H was inadvertently left out in the problem set. Sorry. I have provided the intermediates. You supply the arrows to complete the mechanism.



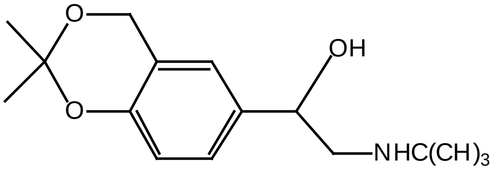
(5)



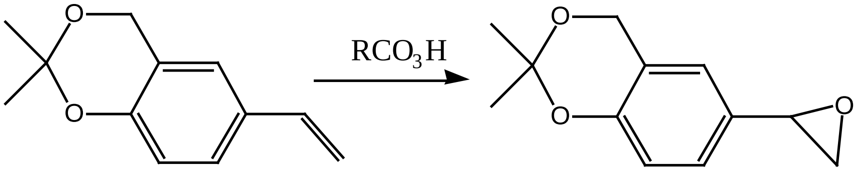
A



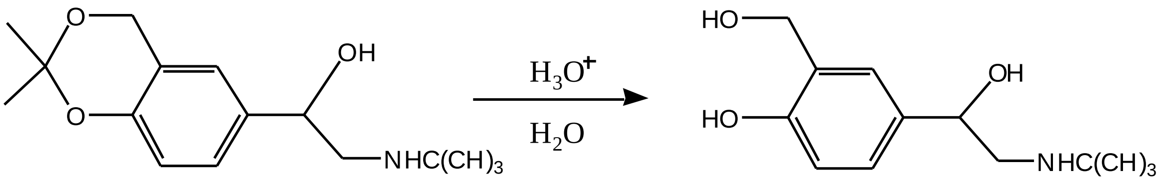
B



C

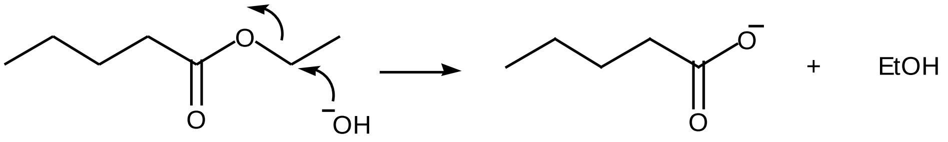


B

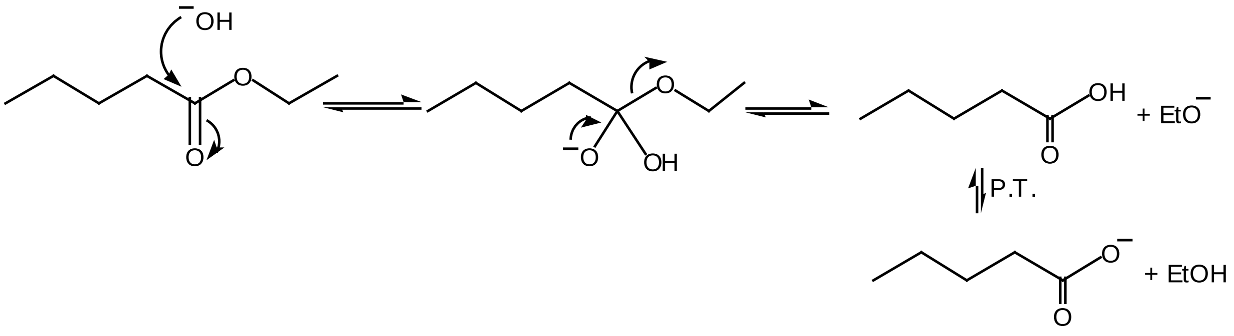


C Salbutamol

(6) Mechanism A: Direct displacement of the carboxylate leaving group by the hydroxide ion in an S_N2 type reaction.

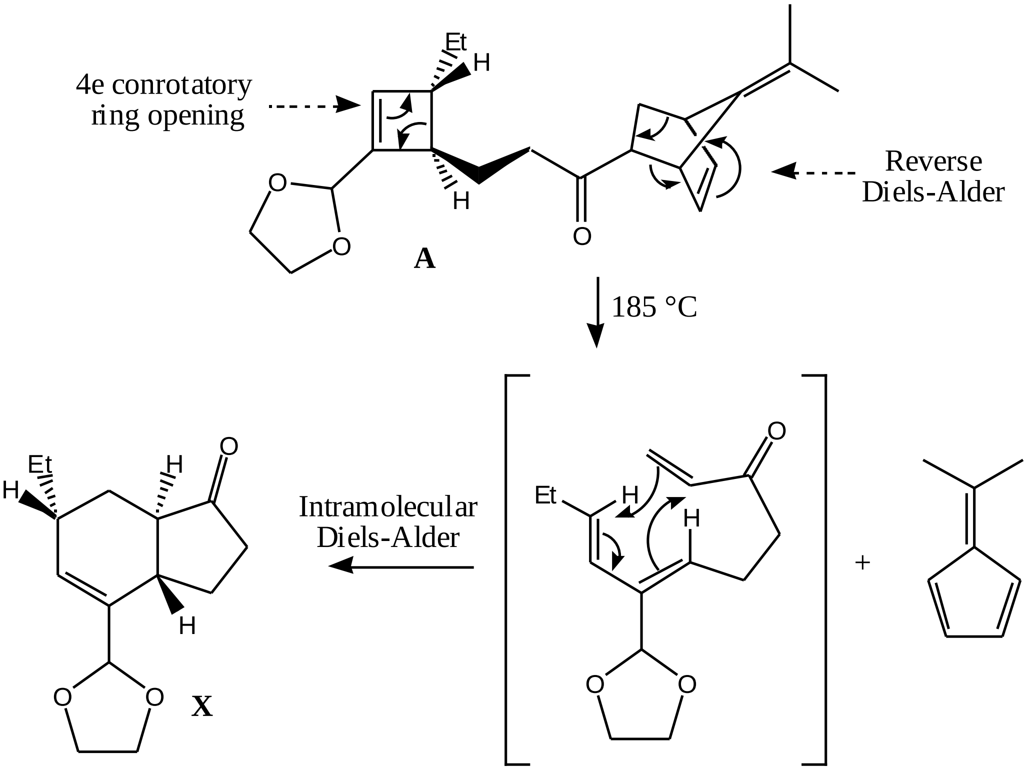


Mechanism B: This involves attack at the carbonyl carbon to produce a tetrahedral intermediate which subsequently expels the ethoxide group.

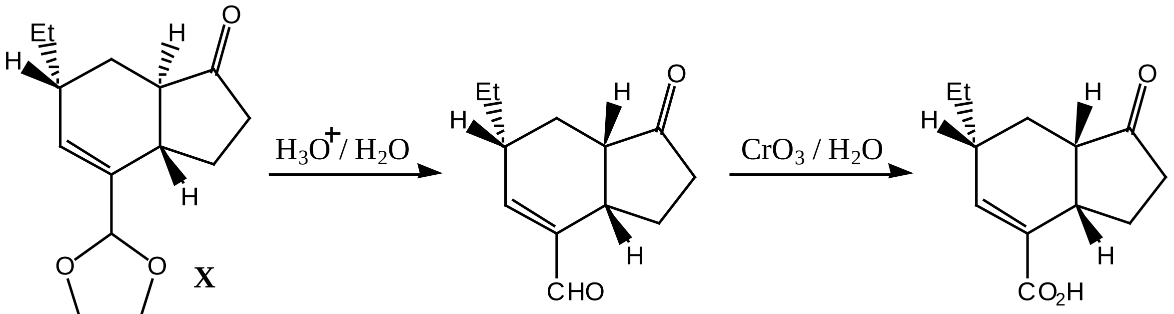


The two mechanisms may be distinguished by using ^{18}O labeled aqueous hydroxide. If mechanism A operated, the labeled oxygen should be in the product alcohol whereas mechanism B will show the label in the carboxylate ion.

(7) (a) The reaction sequence that leads from **A** to **X** consists of three pericyclic reactions. These are shown on the next page.



(b) We need to do two things to go from **X** to coronafacic acid. The stereochemistry at one of the ring junctions needs to be changed, and a carboxylic acid has to be put in place of the acetal functionality. You already know that the proton on the carbon α to the keto group is enolizable and can be exchanged in acid or base. In this case, it is of particular advantage to use acid because, under acidic conditions, the acetal protecting group can be removed in addition to changing the stereochemistry at the α position. Oxidation of the aldehyde obtained from removal of the protecting group leads to coronafacic acid.



Coronafacic acid