3.20: Solutions to Selected Problems, Part B

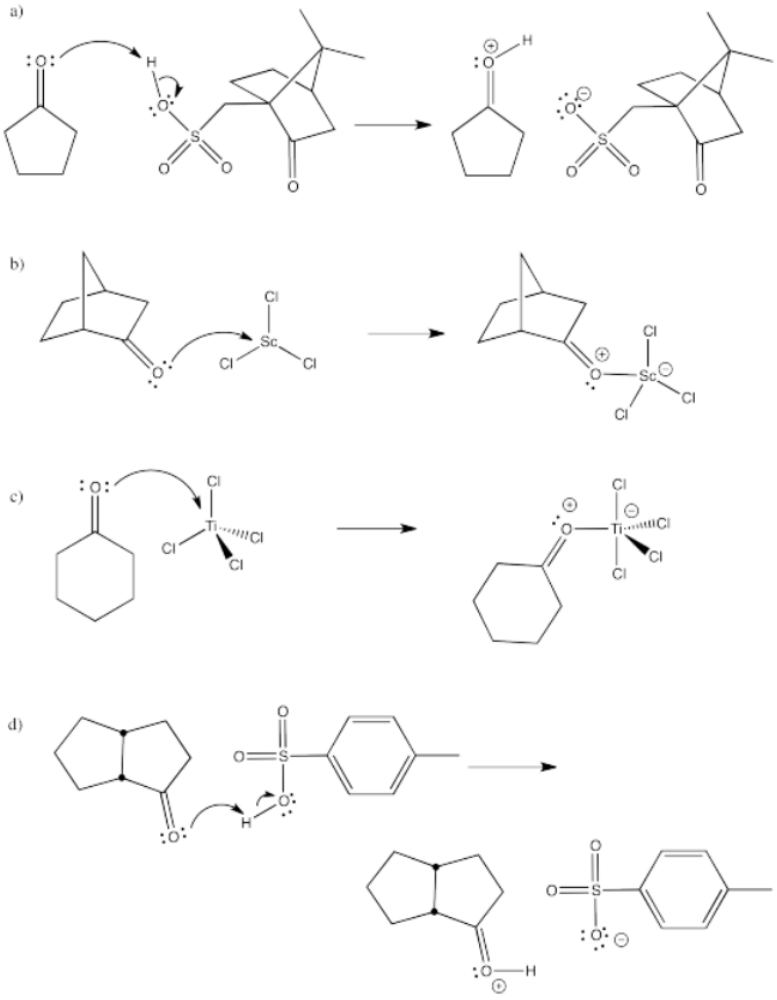
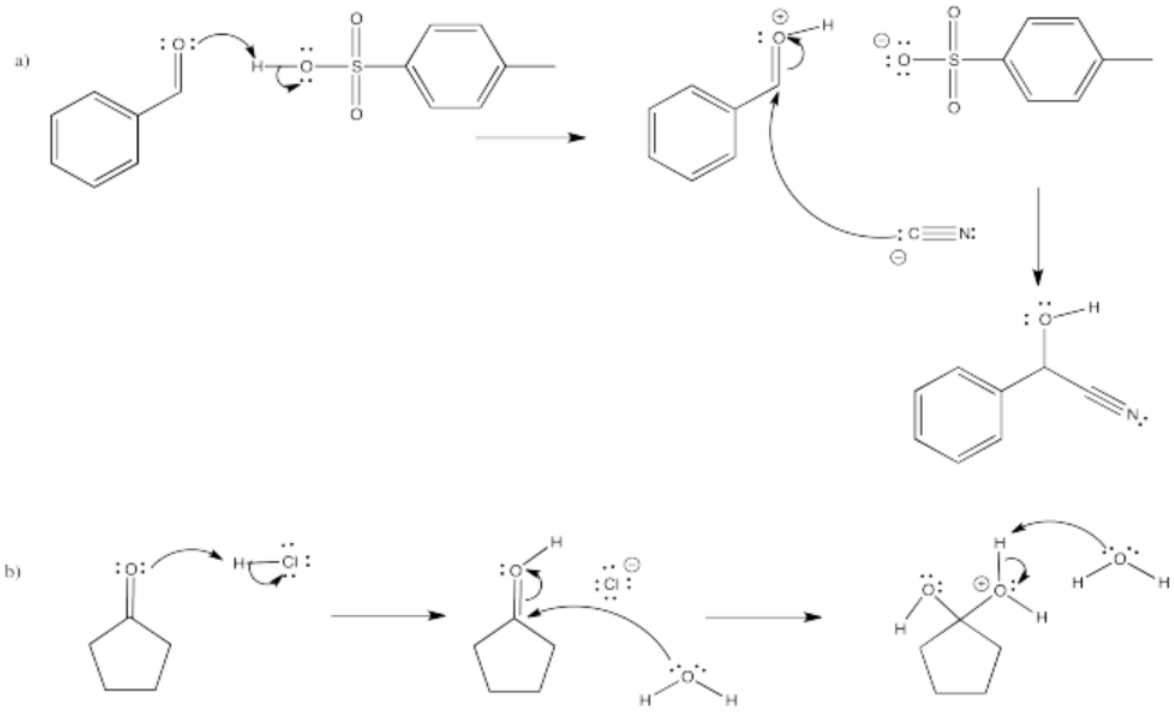
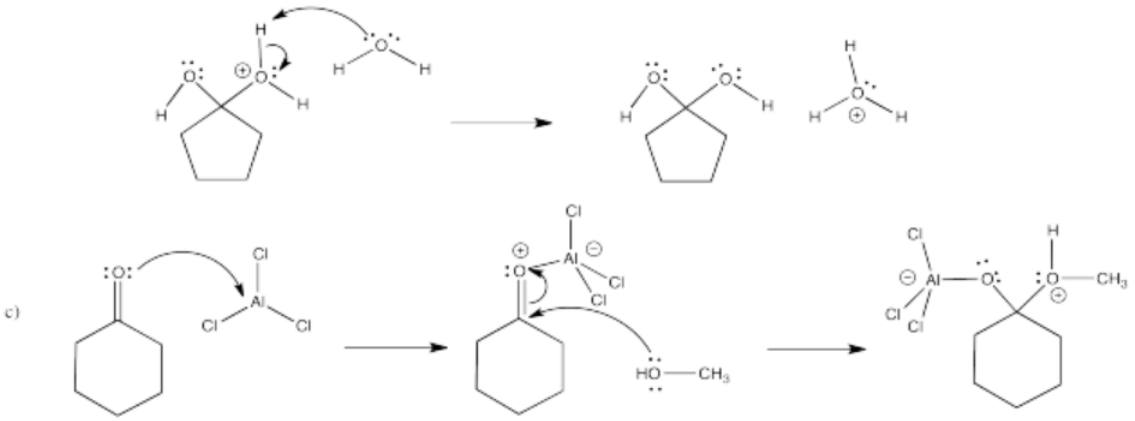


Figure 3.20.1:

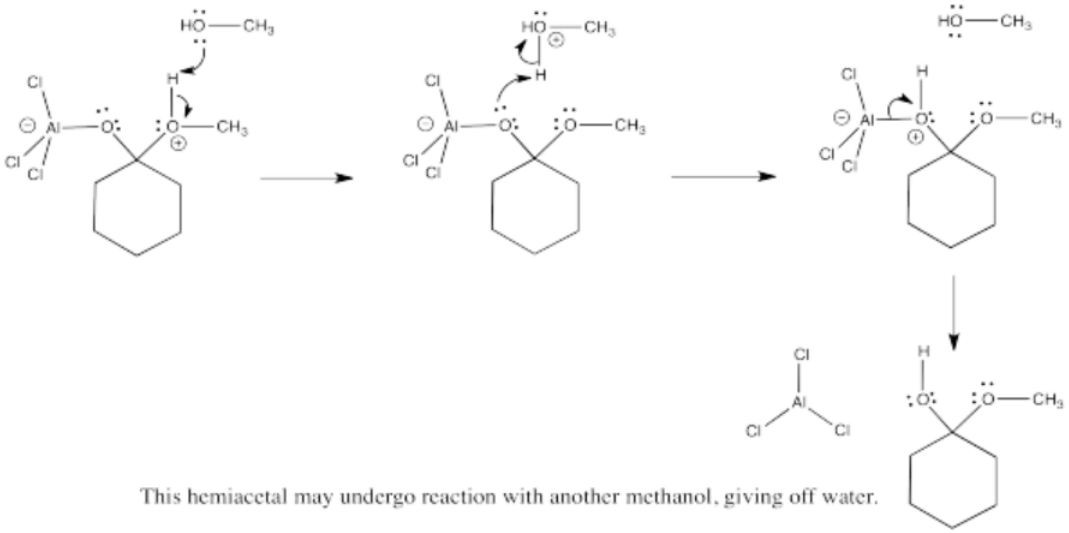


Nucleophilic donation would probably be followed by a proton transfer step (below)

Figure 3.20.2:

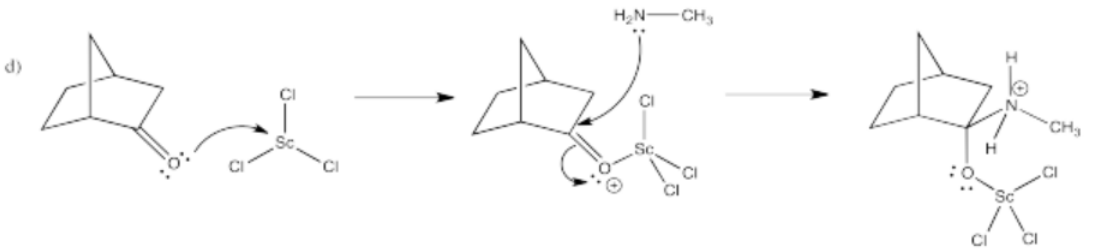


Nucleophilic donation would probably be followed by a series of other steps (below)



This hemiacetal may undergo reaction with another methanol, giving off water.

Figure 3.20.3:



Nucleophilic donation would probably be followed by a series of other steps (below)

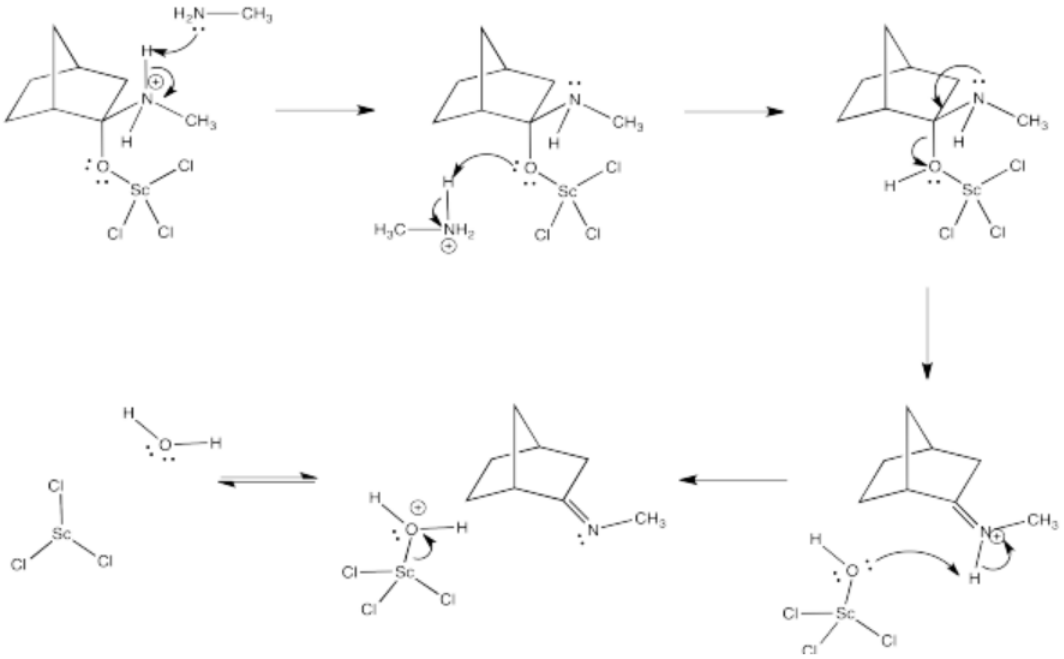


Figure 3.20.4:

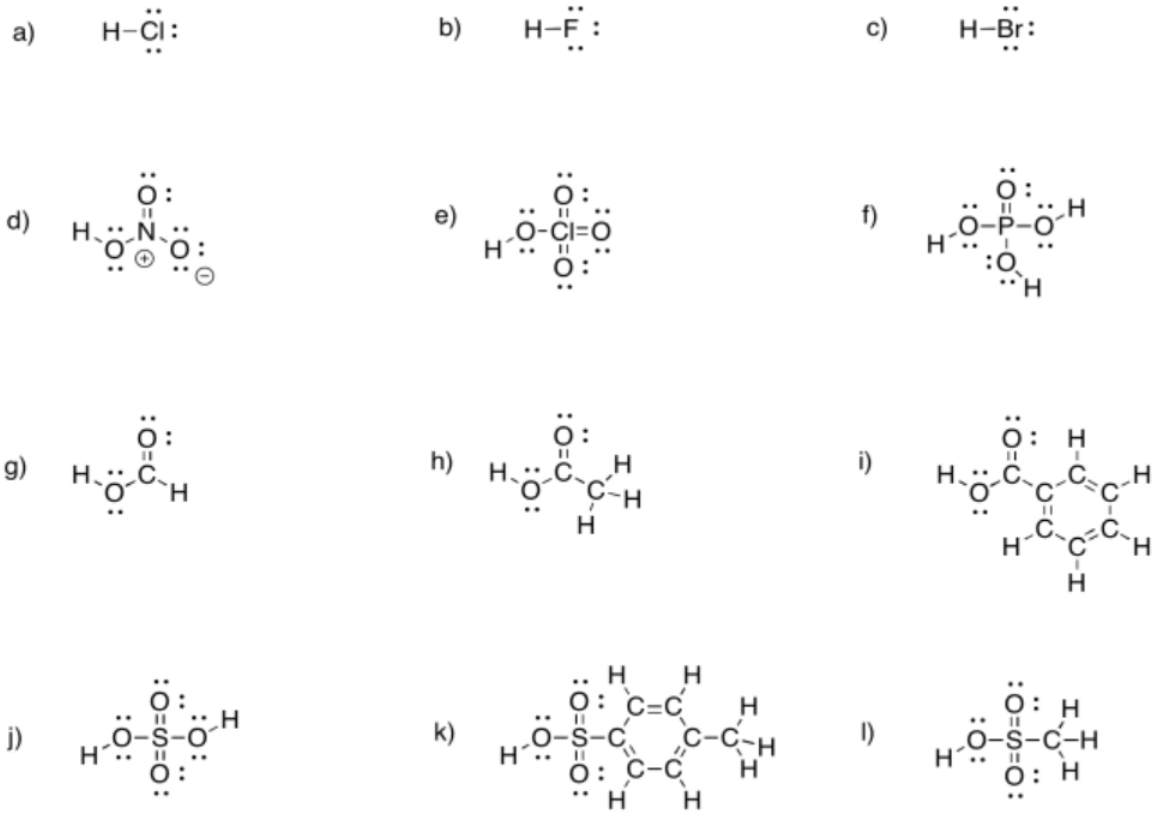


Figure 3.20.5:

Part a.

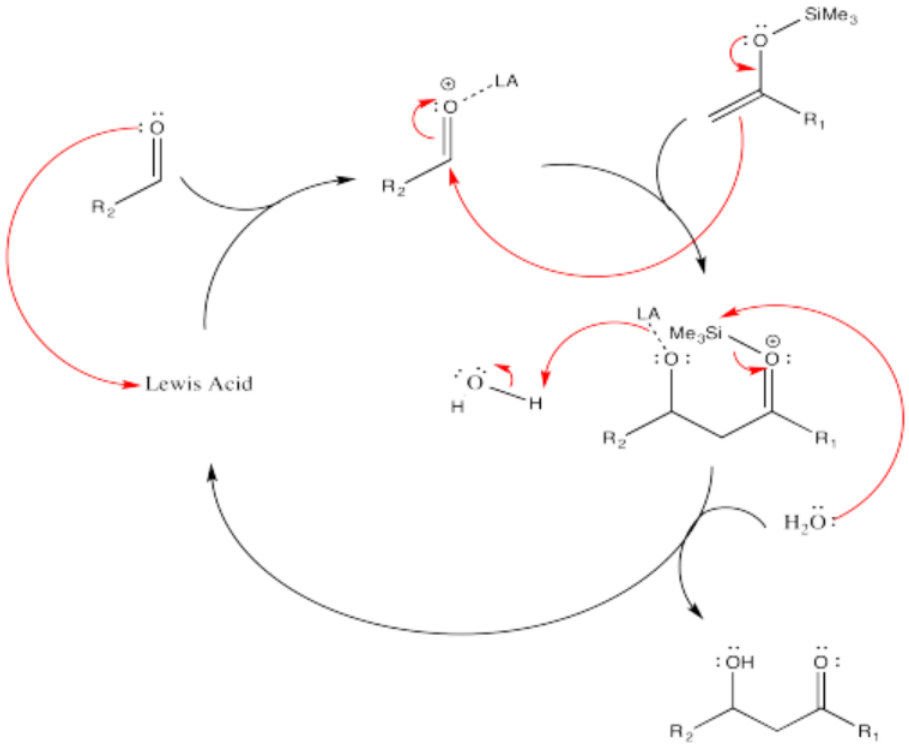
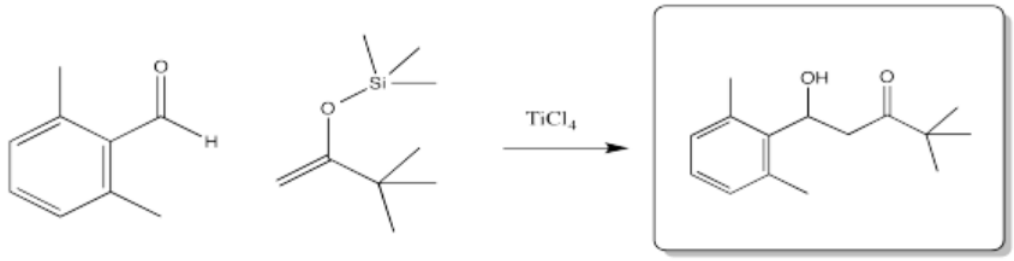


Figure 3.20.6:

Part b.



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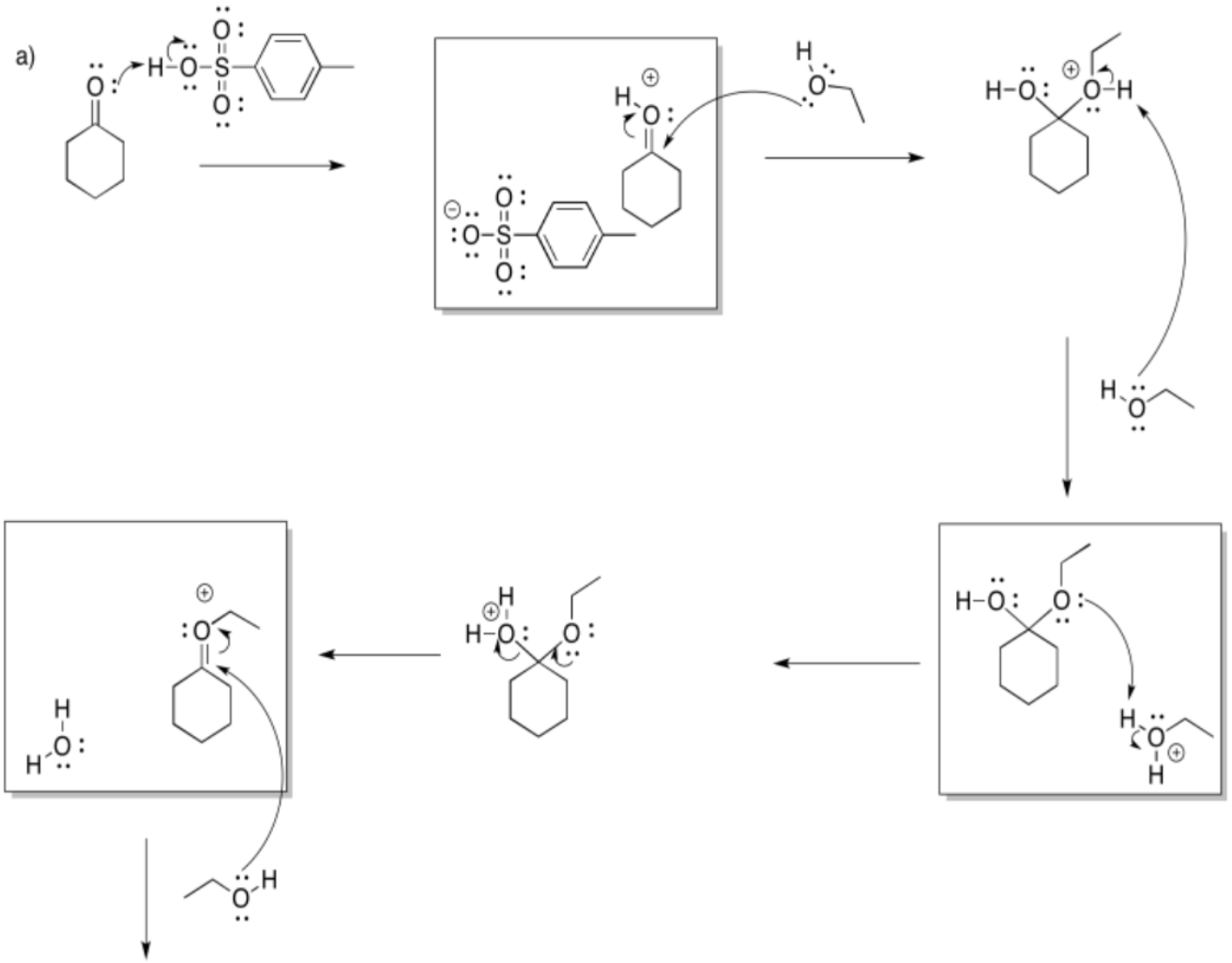

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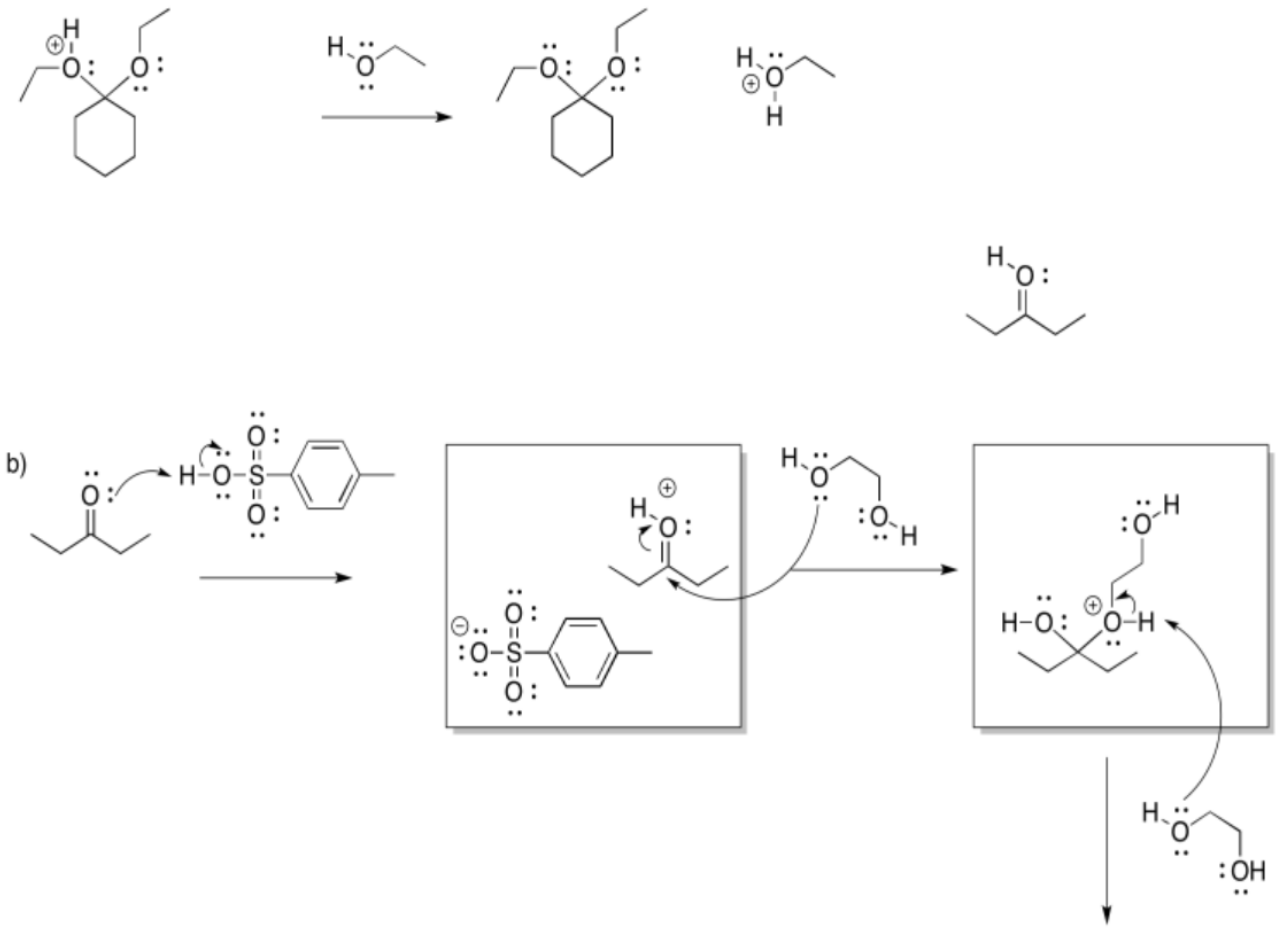

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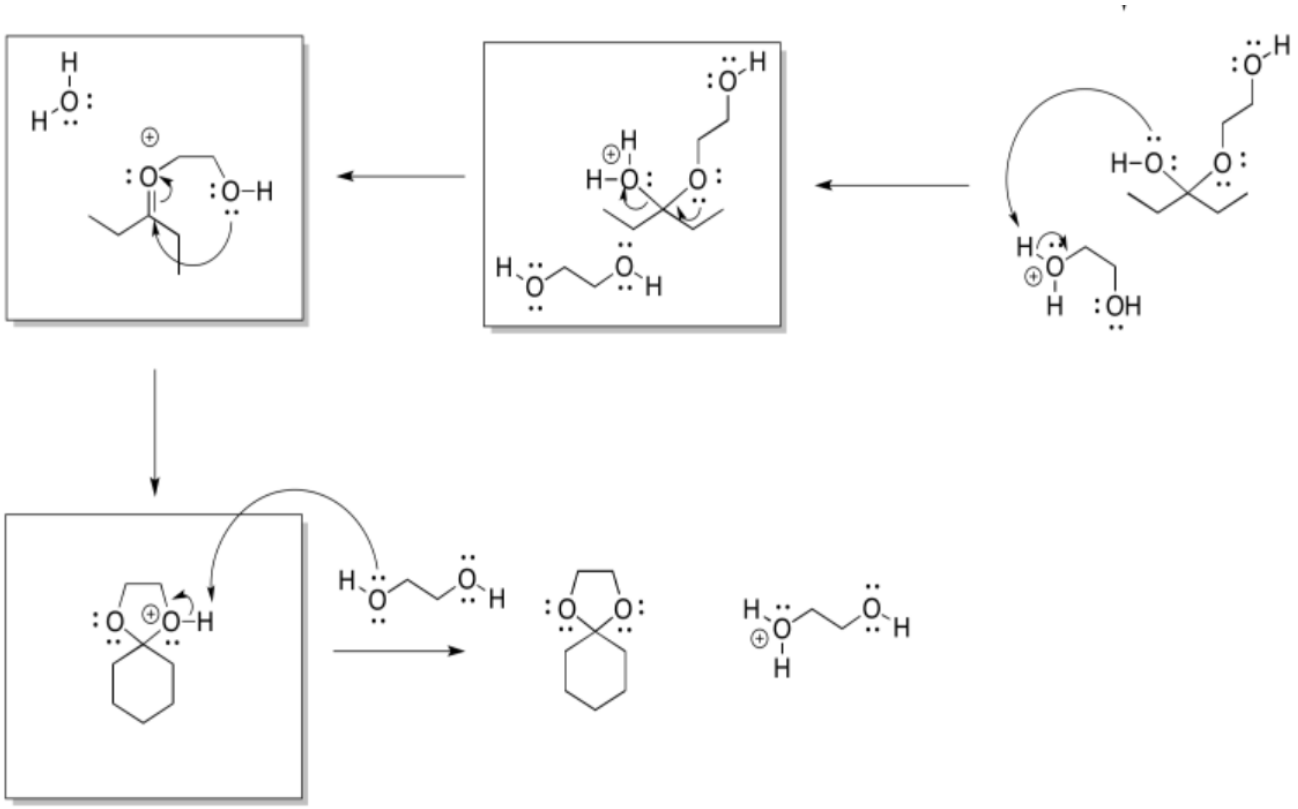
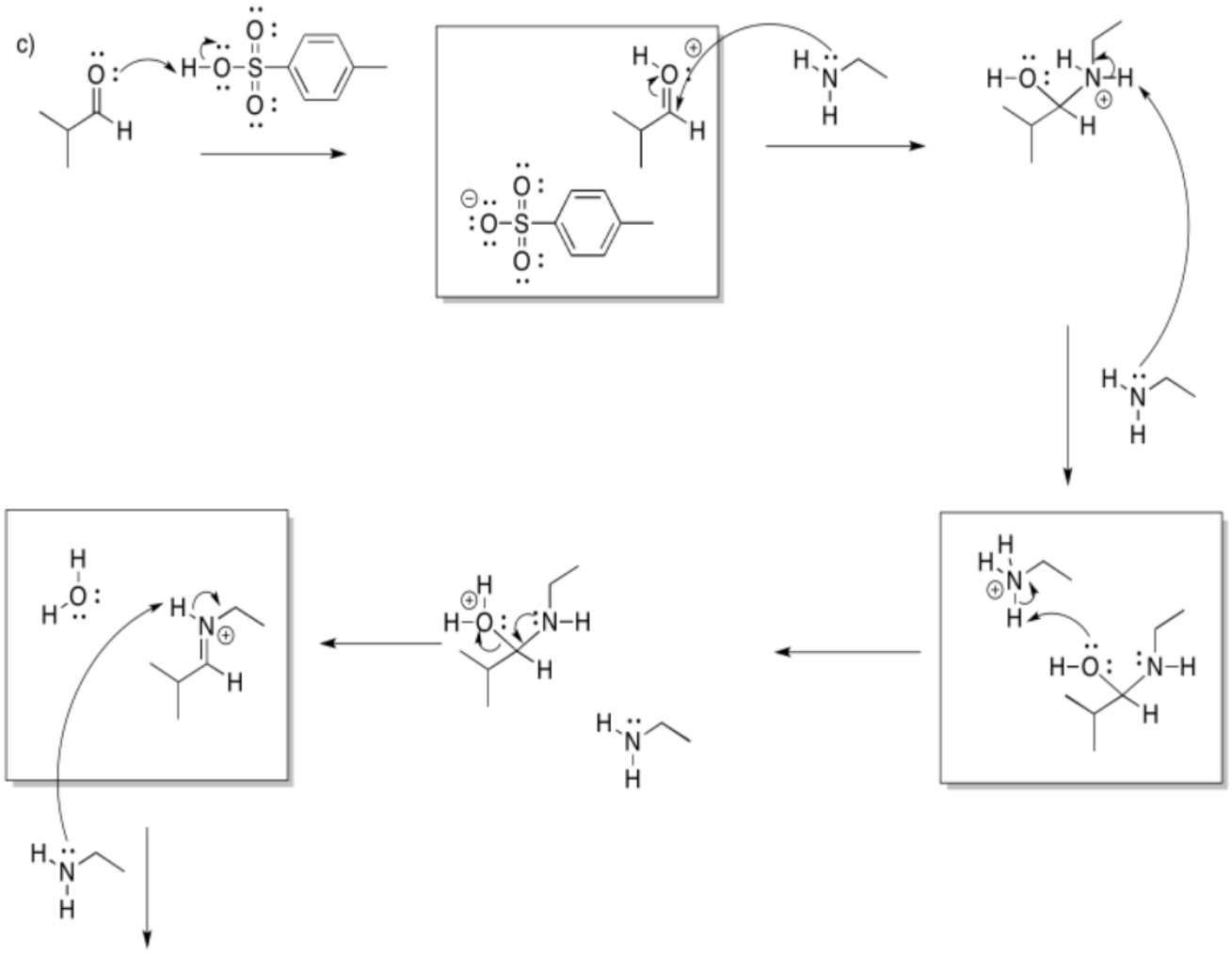


Figure 3.20.10:



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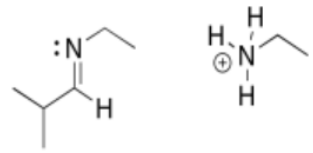

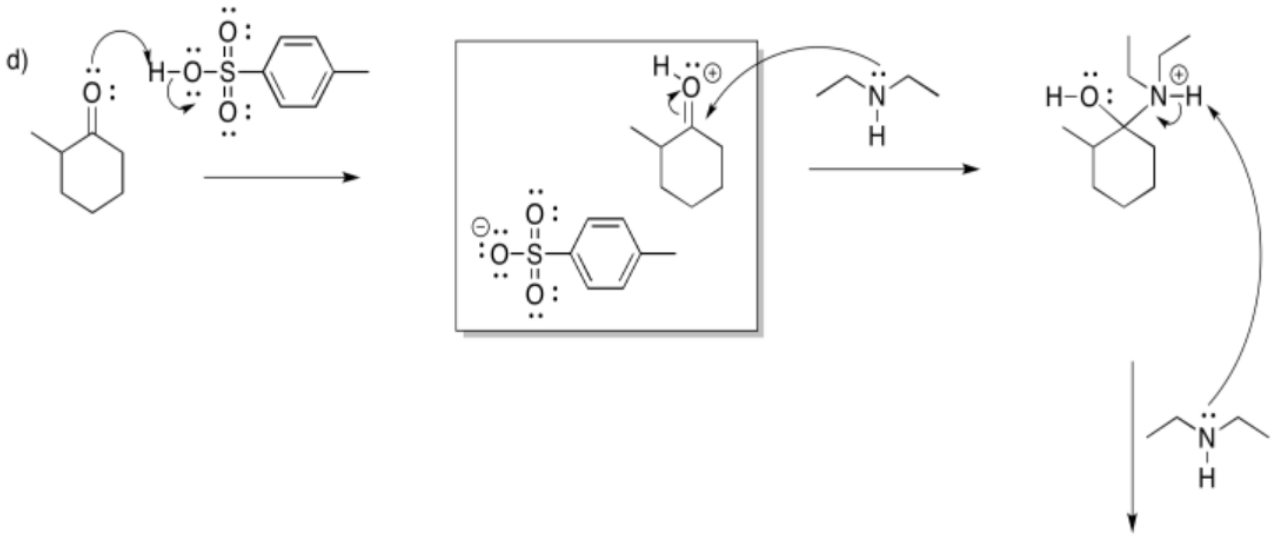

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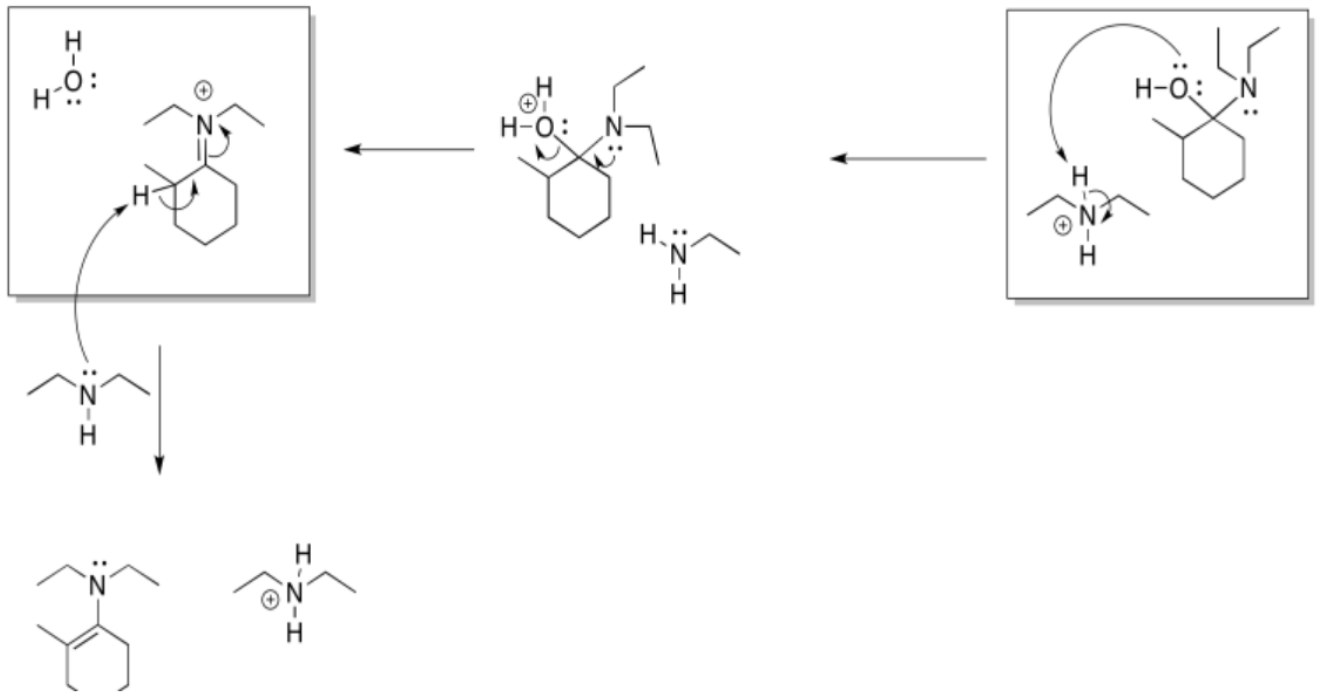

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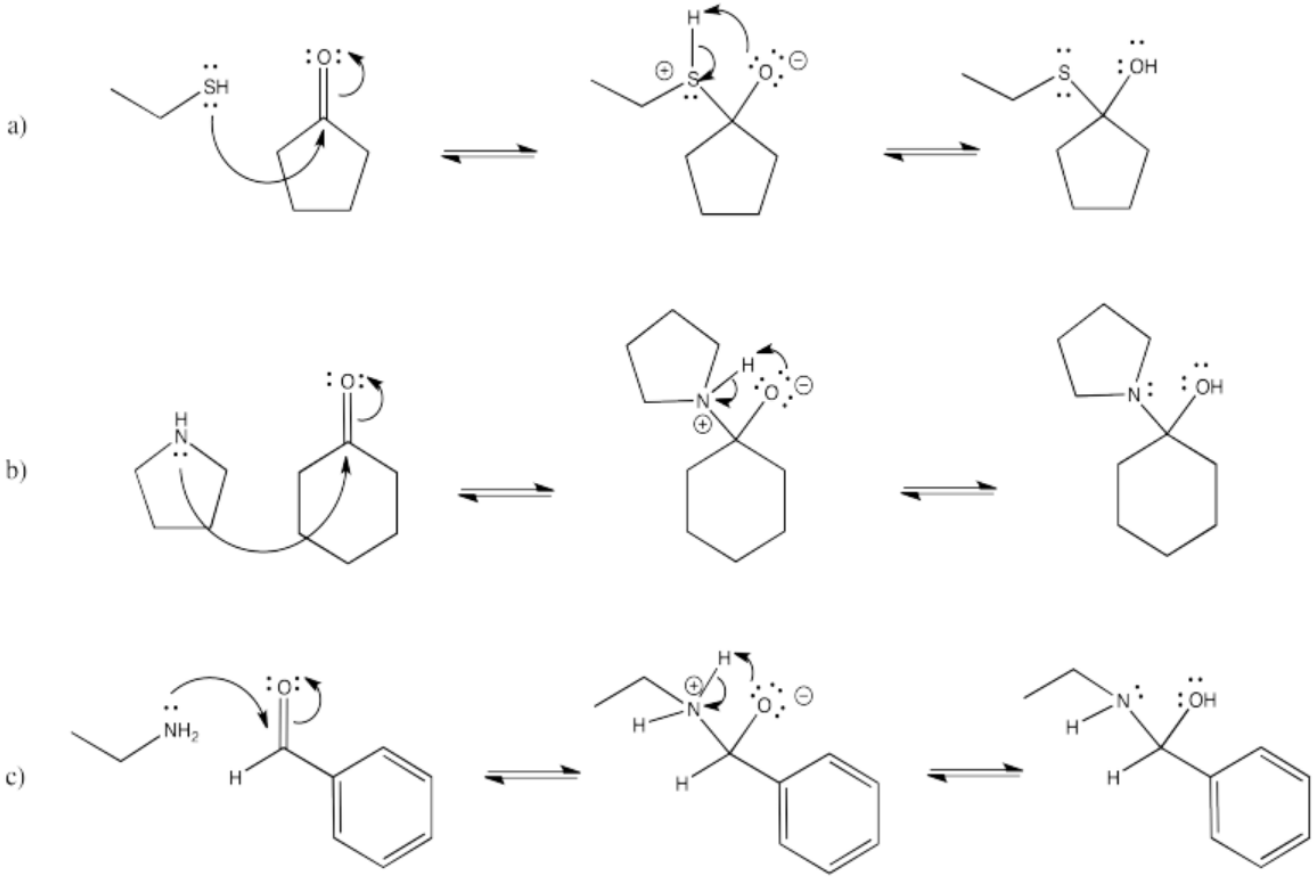

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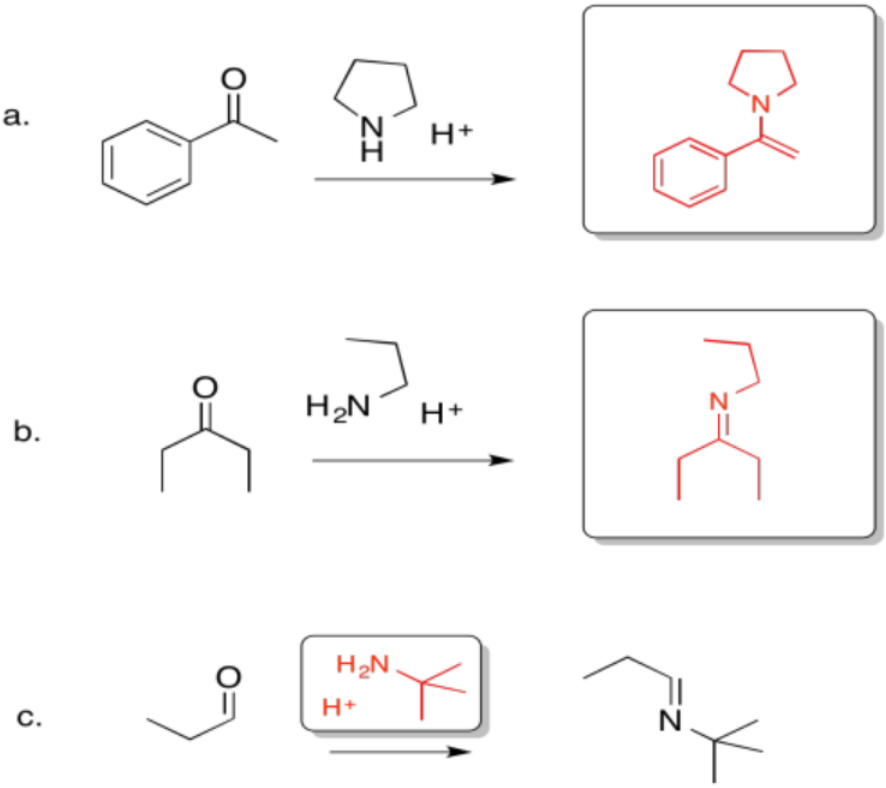

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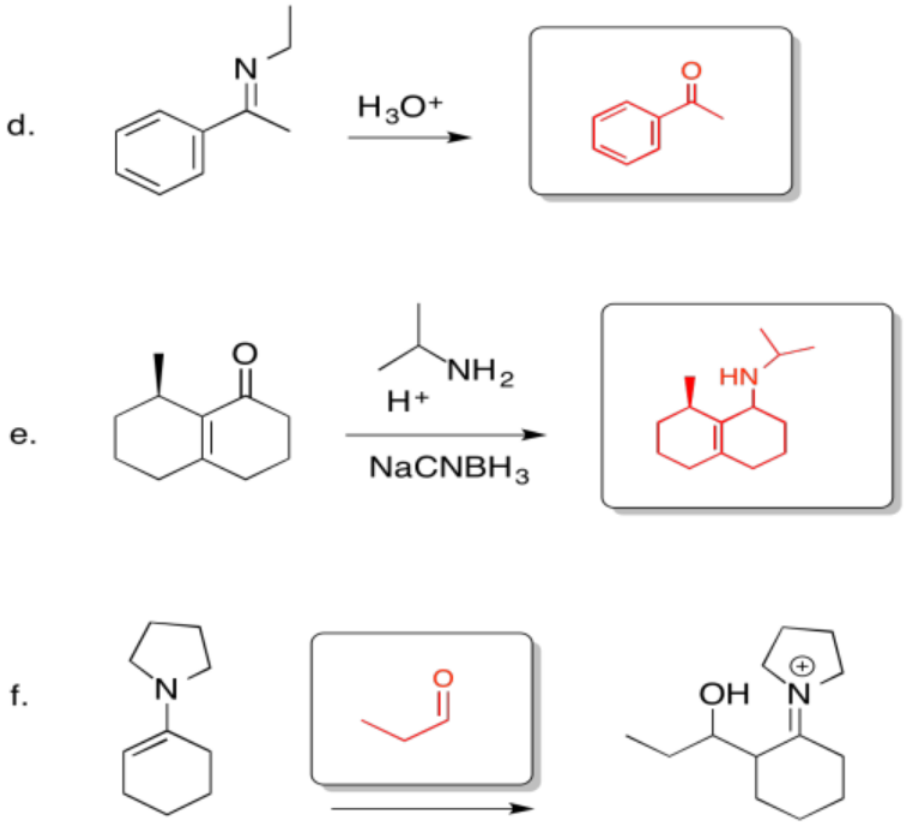

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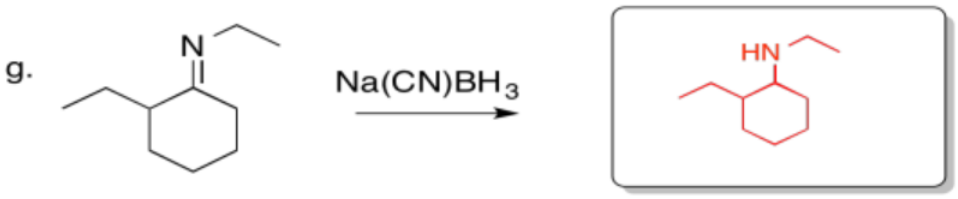

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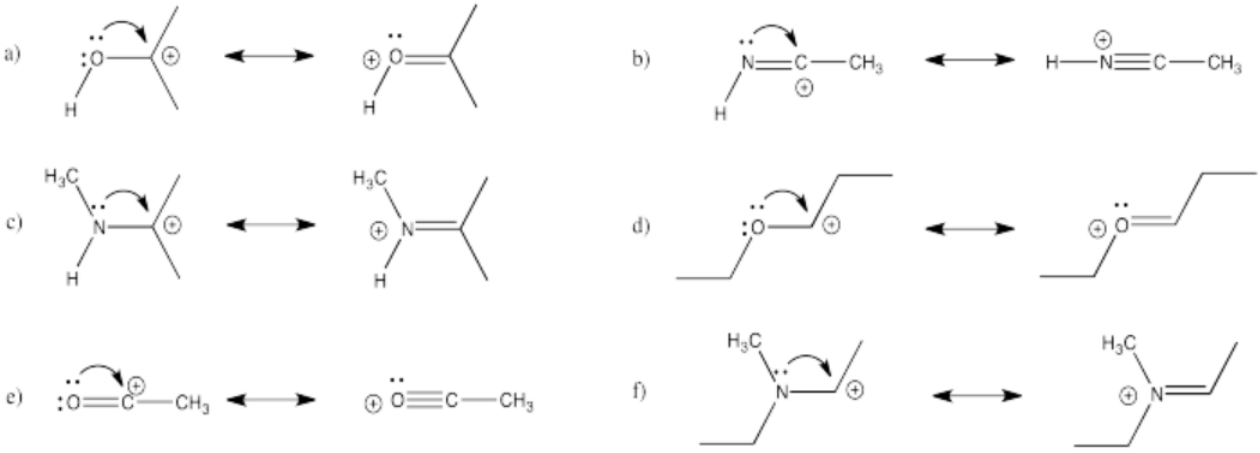
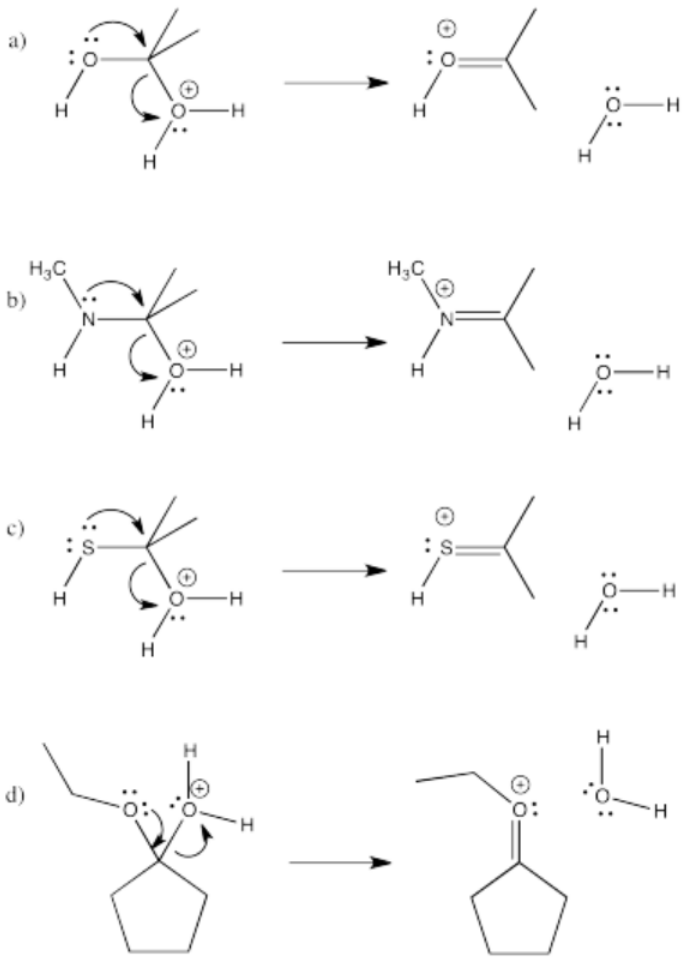


Figure 3.20.18:



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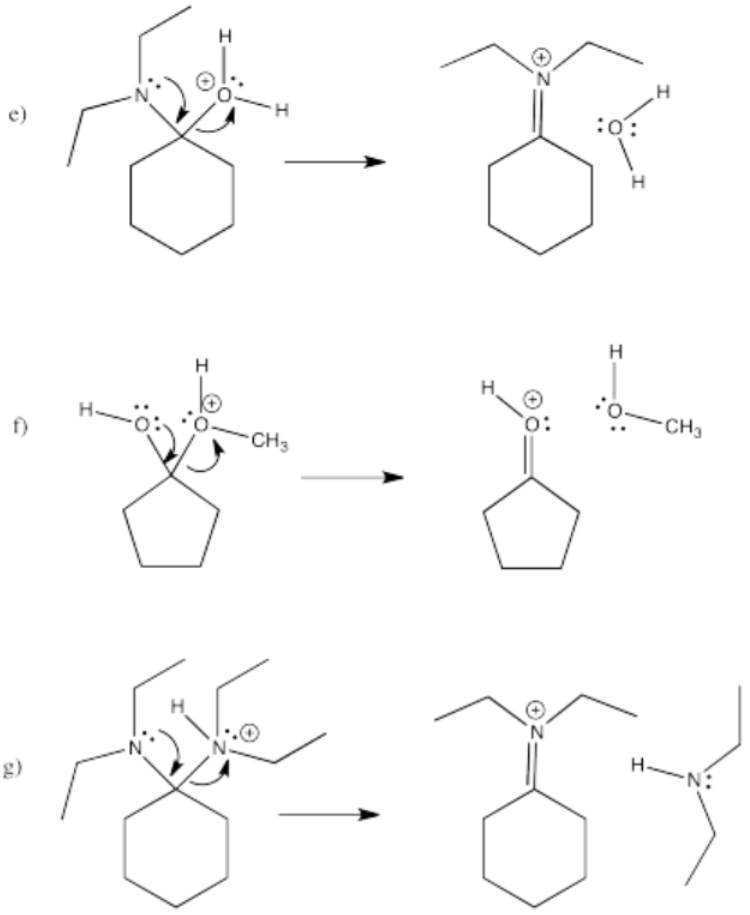
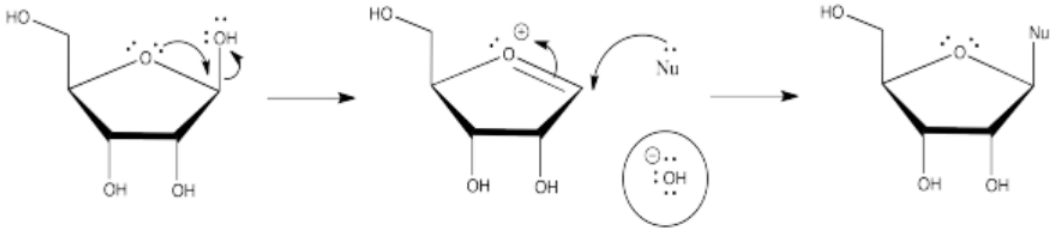
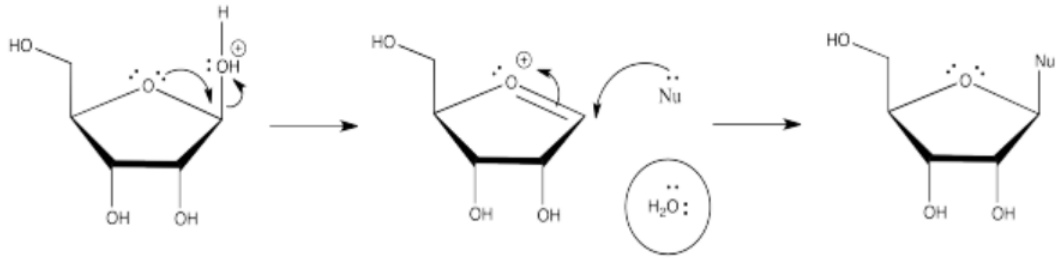


Figure 3.20.20:



The leaving group in the above reaction is a reactive hydroxide ion, but if the oxygen is protonated, the leaving group is a stable water molecule.



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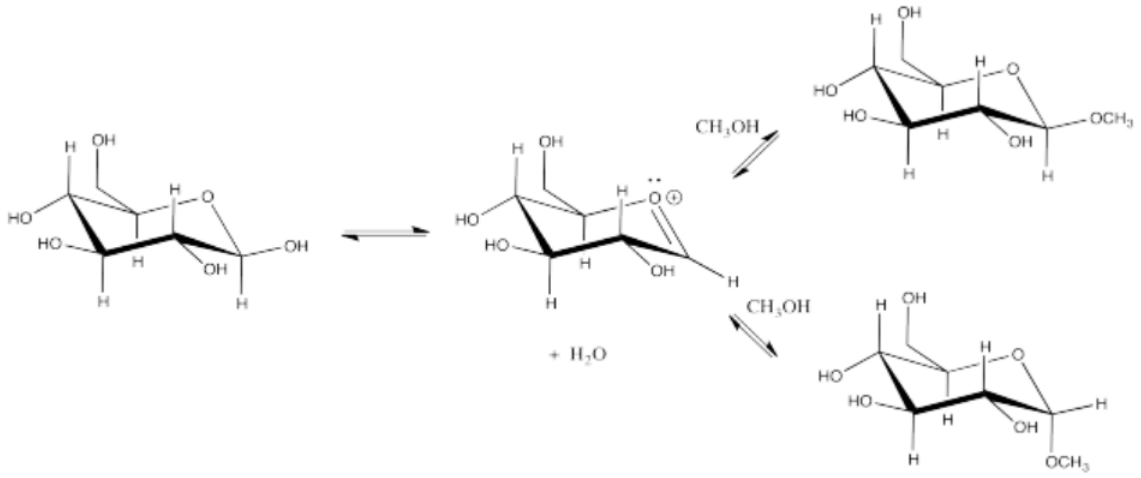

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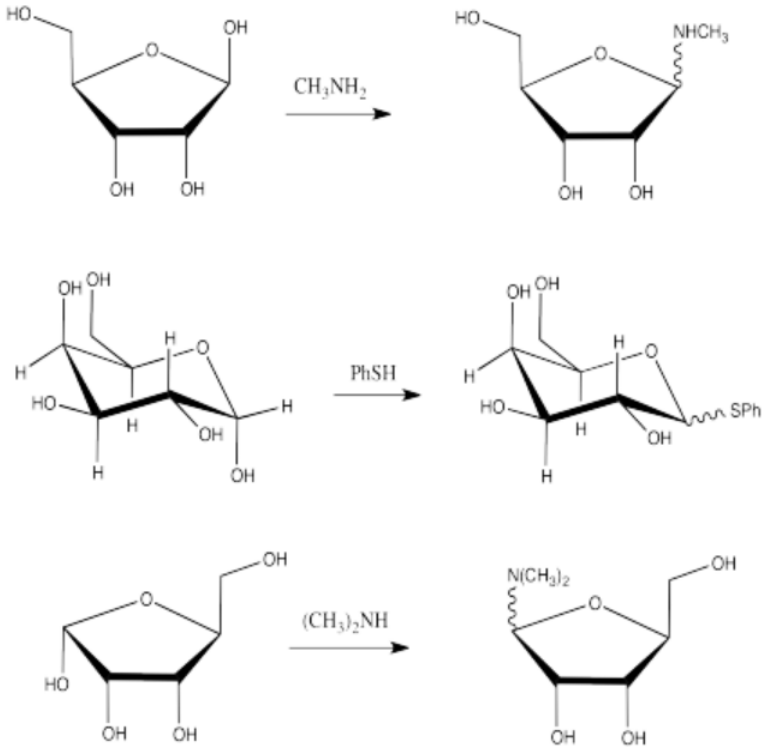
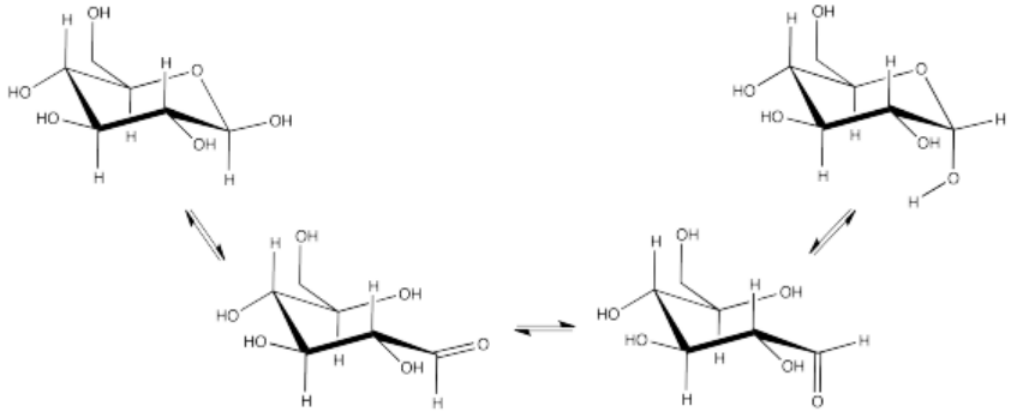


Figure 3.20.23:



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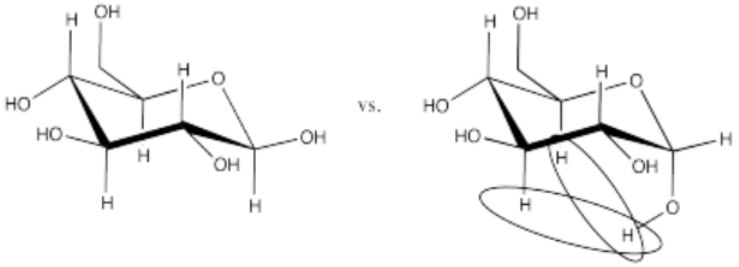

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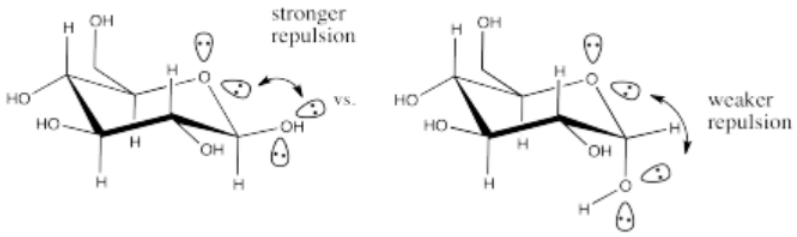

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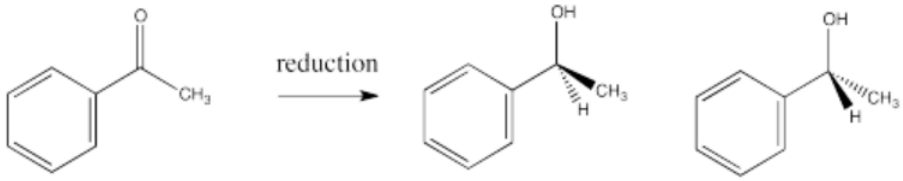
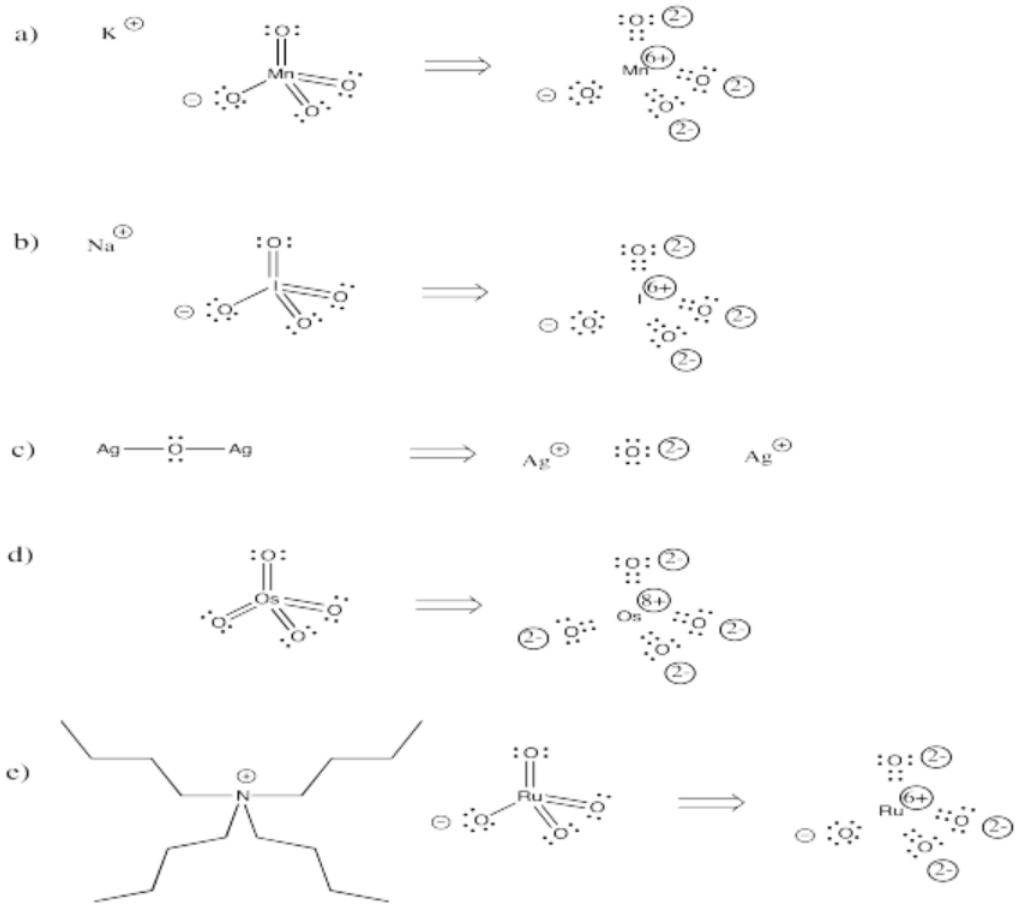


Figure 3.20.27:

Figure 3.20.28:



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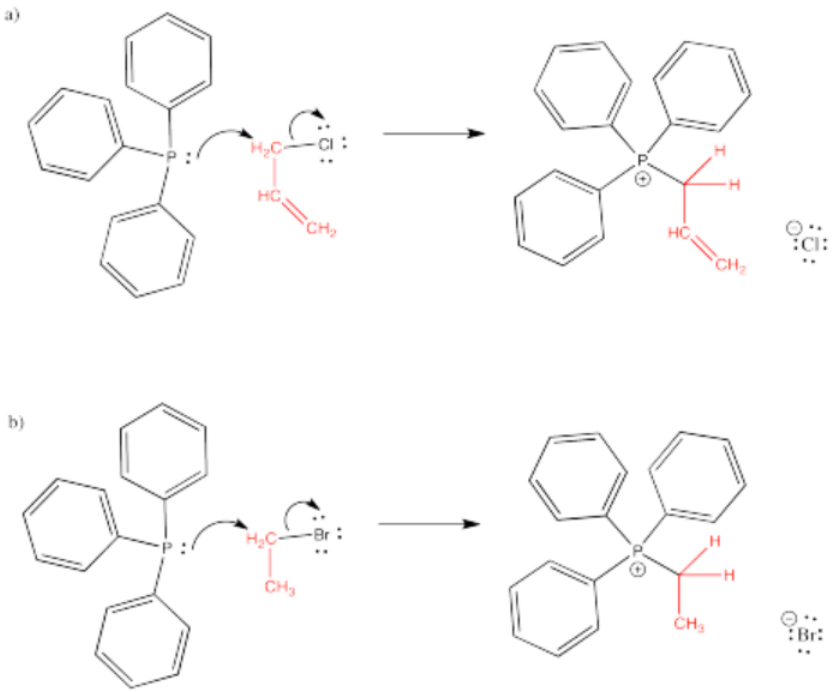

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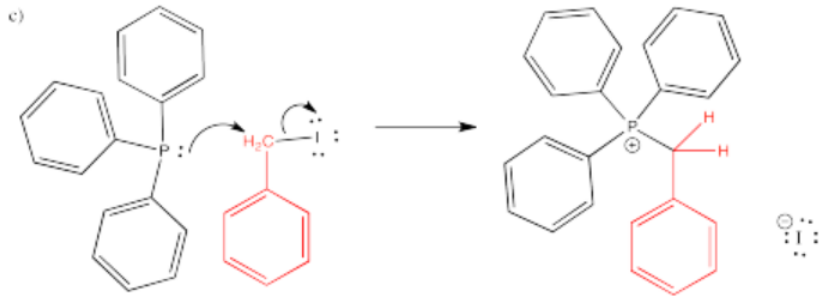

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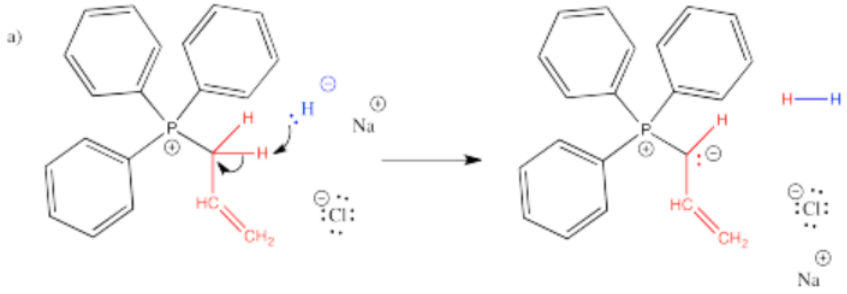


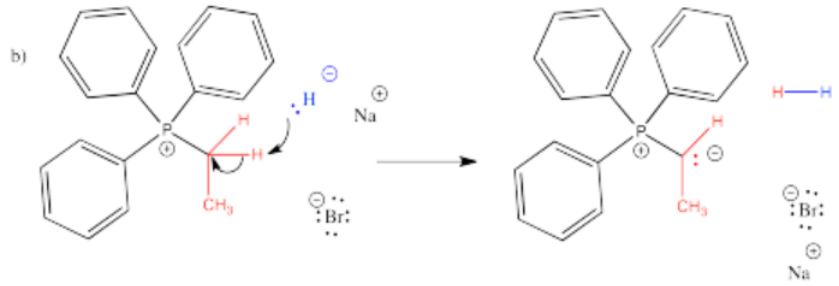


Figure 3.20.32:

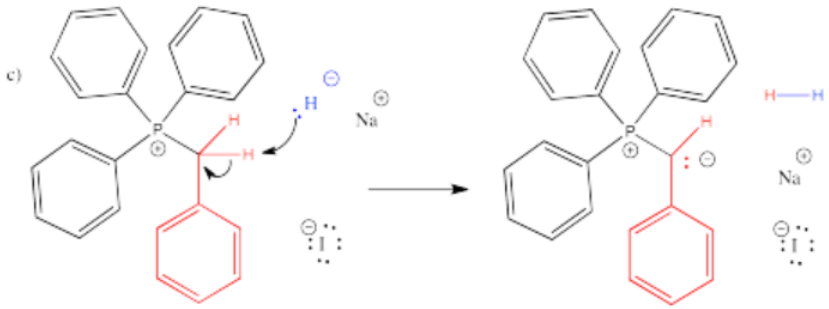
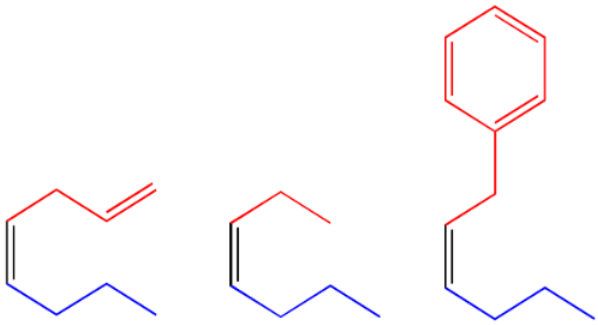


Figure 3.20.33:

a)



b)

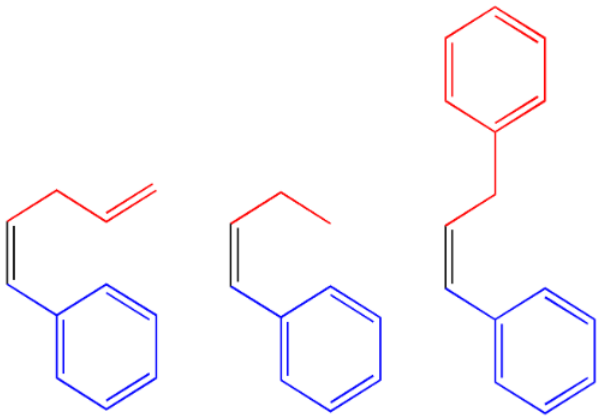


Figure 3.20.34:

c)

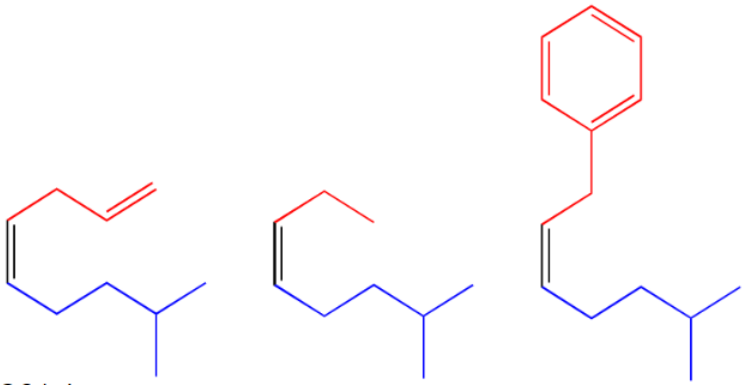


Figure 3.20.35:

One of the keys in this problem is recognizing that in some steps, two different reactions are involved. For example, in the first box, there is an addition of a diol to a carbonyl followed by an ylide addition.

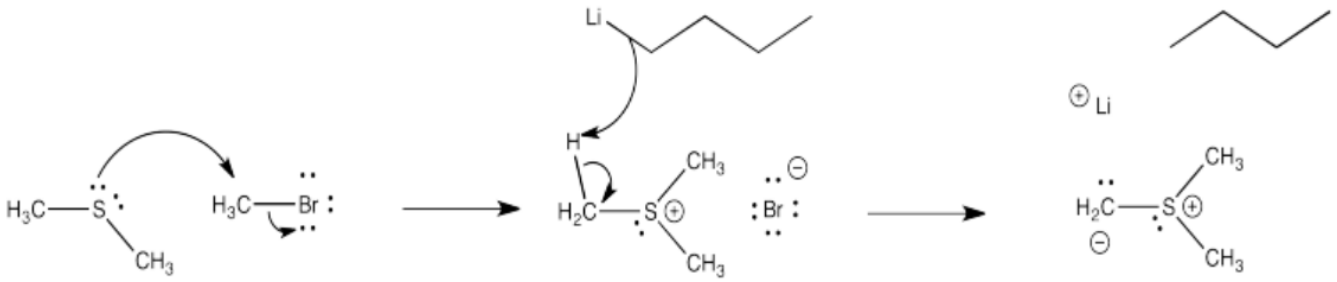
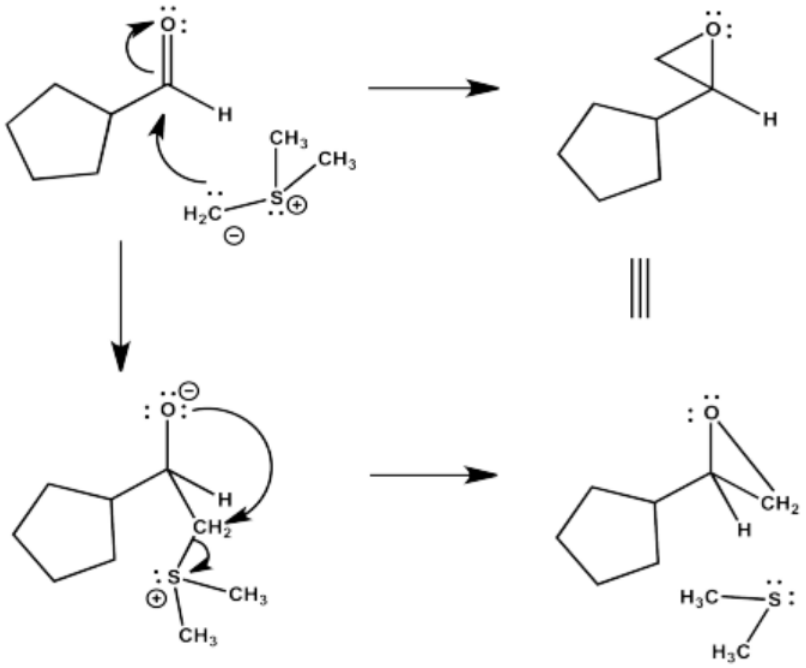


Figure 3.20.36:



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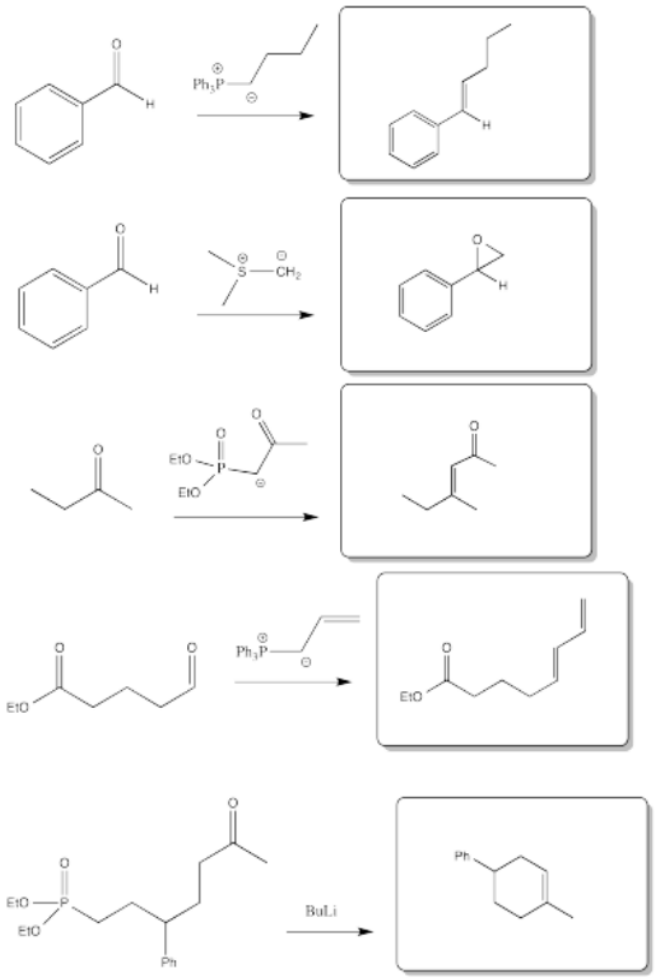
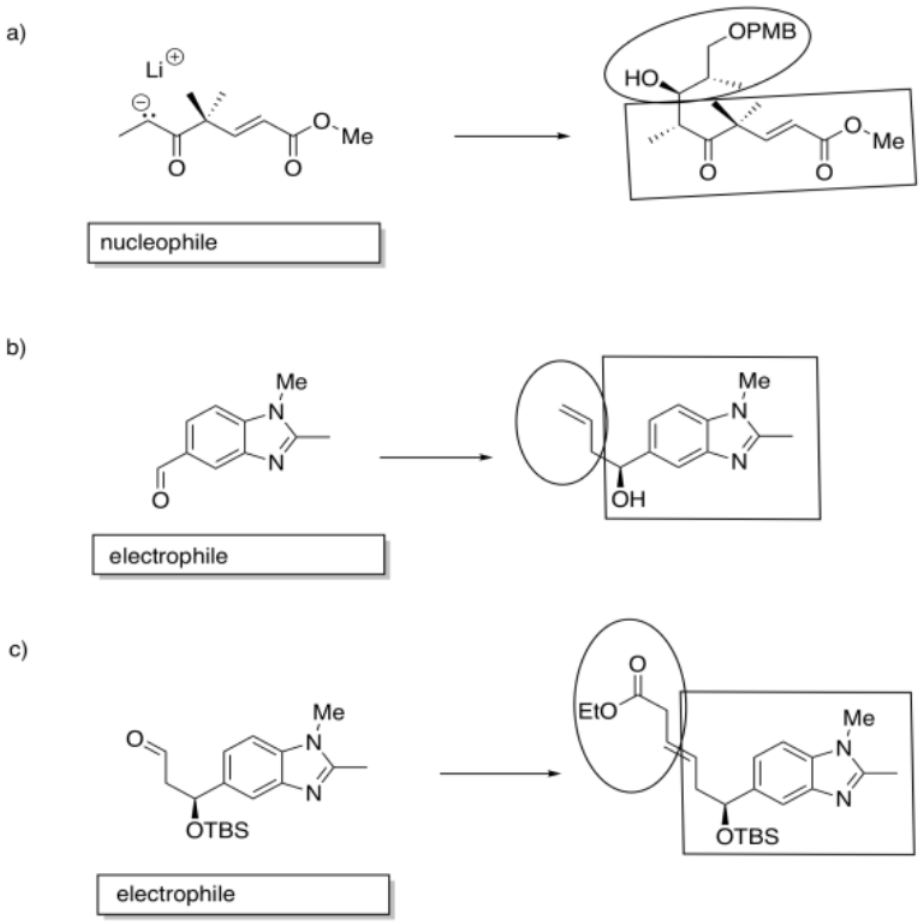


Figure 3.20.38:



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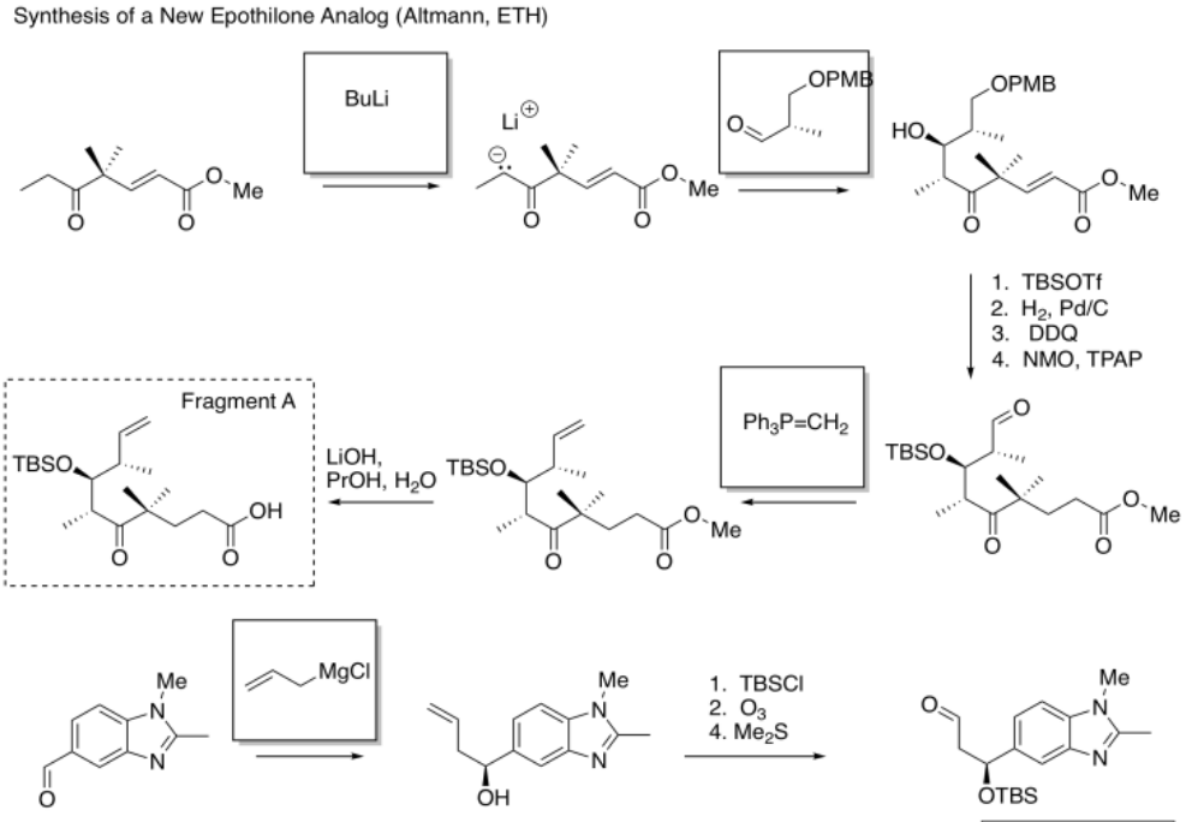

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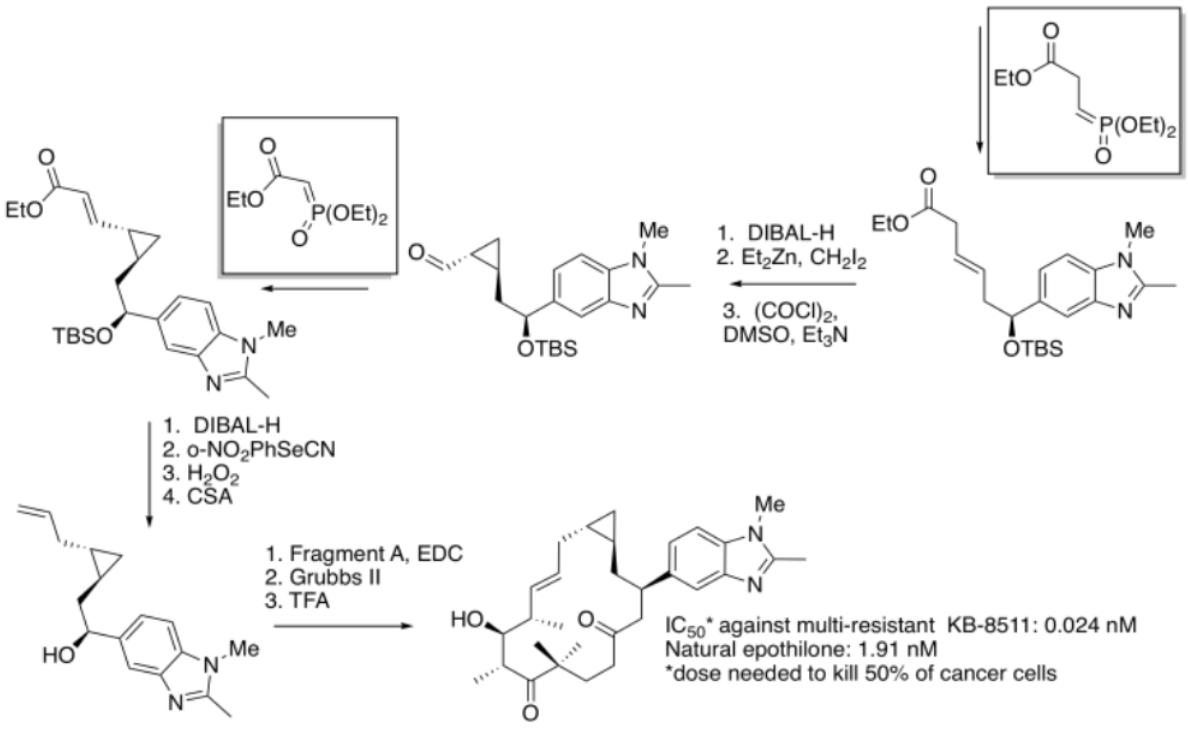


Figure 3.20.41:

a)

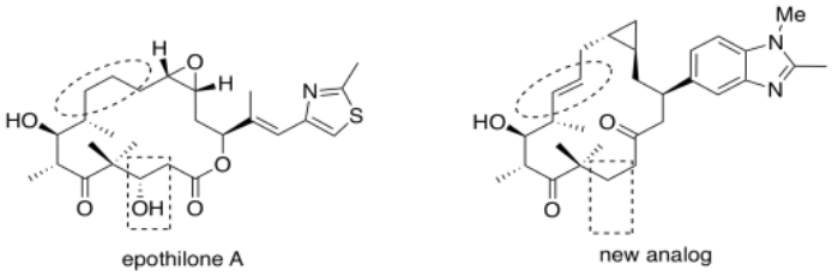


Figure 3.20.42:

b) The circled part changed from a single bond to a doube bond. The boxed part changed from an alcohol to unadorned hydrocarbon chain.

c) Hydrogen bonding is the most obvious.

d) However, the analog works better without this group; this particular alcohol group is probably not an important part of the pharmacophore. It is probably not needed in order to bind to the target.

e) In epothilone A, as drawn, the dihedral angle appears to be 0 degrees.

f) In the new analog, the dihedral angle is 180 degrees.

g) Based on the superior activity of the analog, the active conformation of the ring is probably more like the one on the right than the one on the left. The circled bond probably adopts a dihedral angle closer to 180 degrees, with the rest of the ring twisting into a shape more like the one shown on the right, in order to bind to the target.

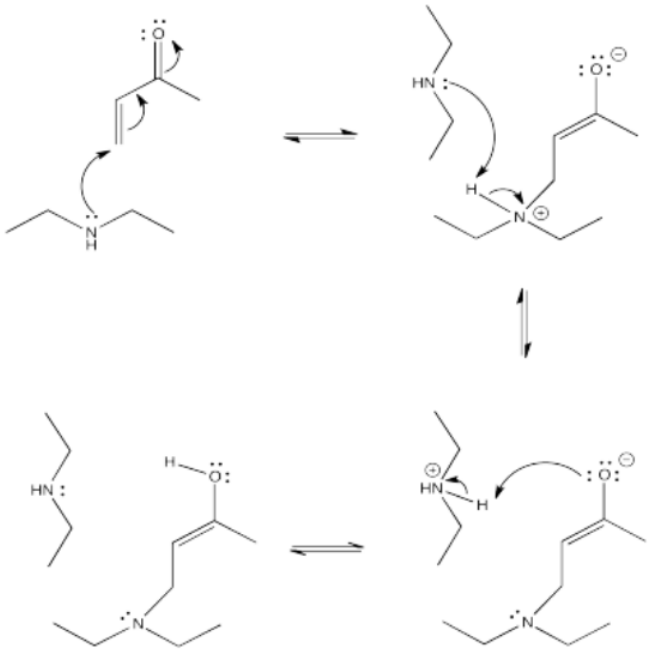


Figure 3.20.43:

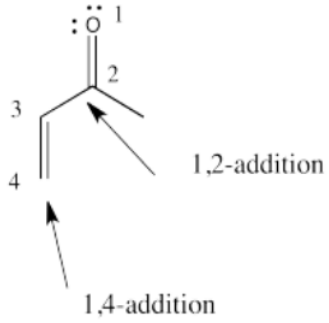
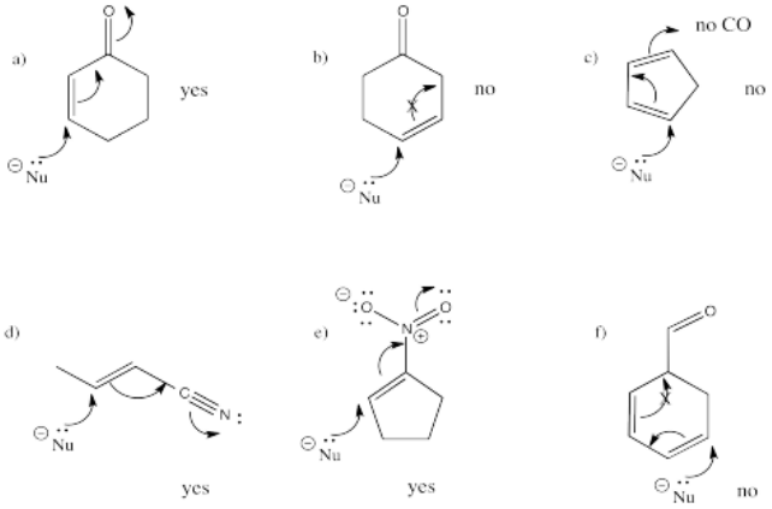


Figure 3.20.44:



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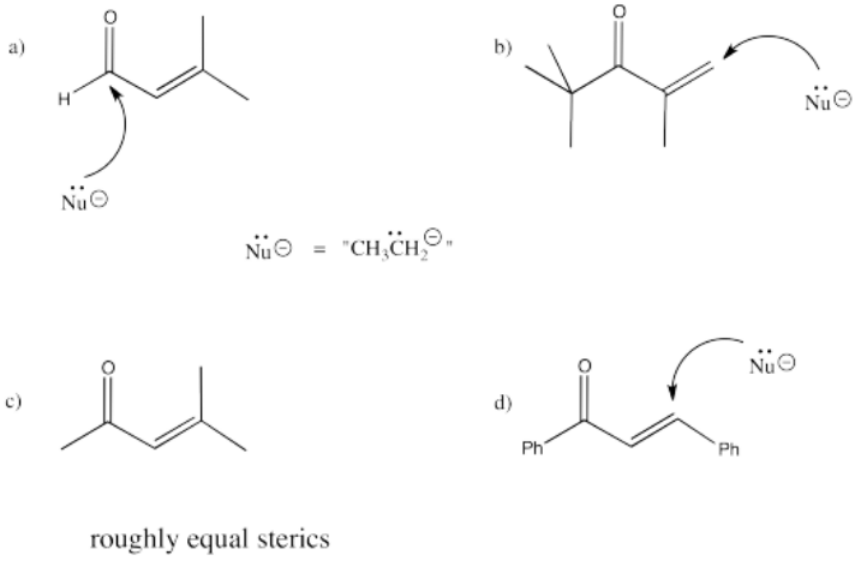
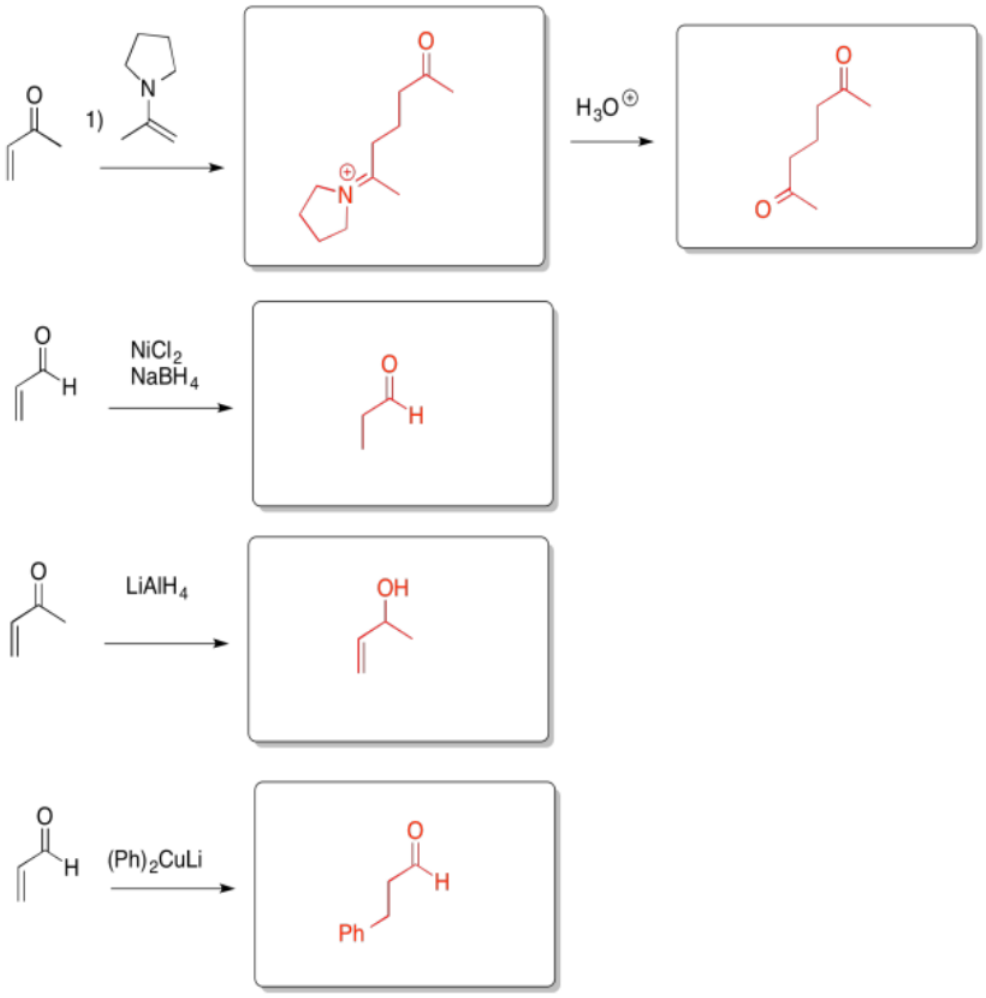


Figure 3.20.46:



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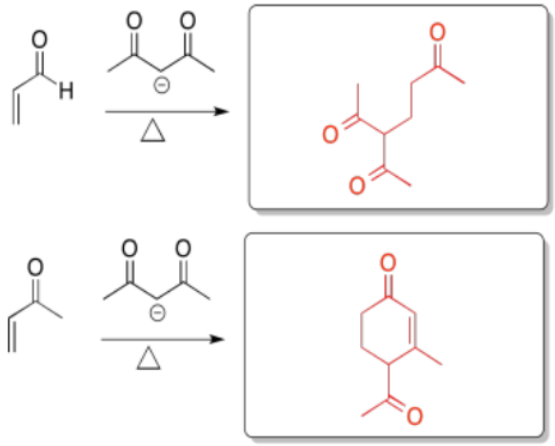

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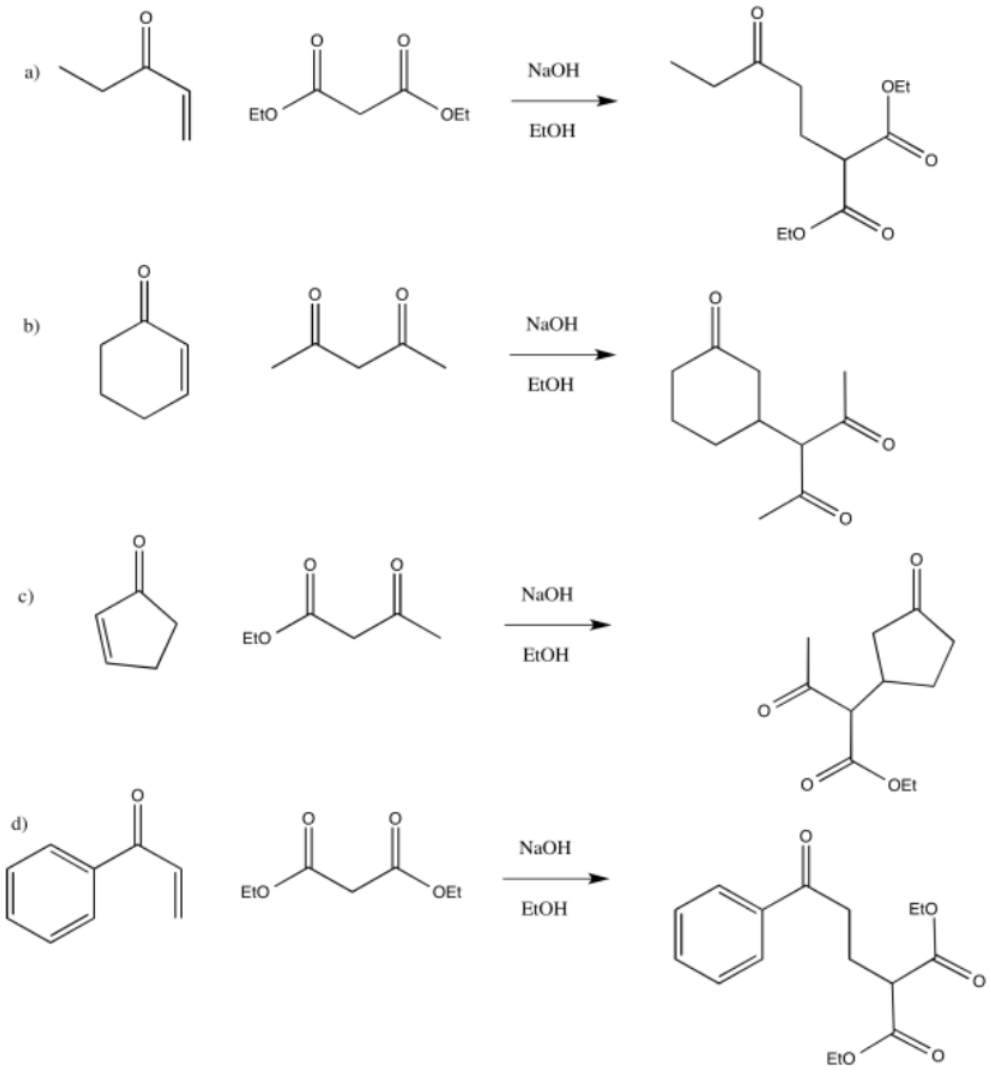
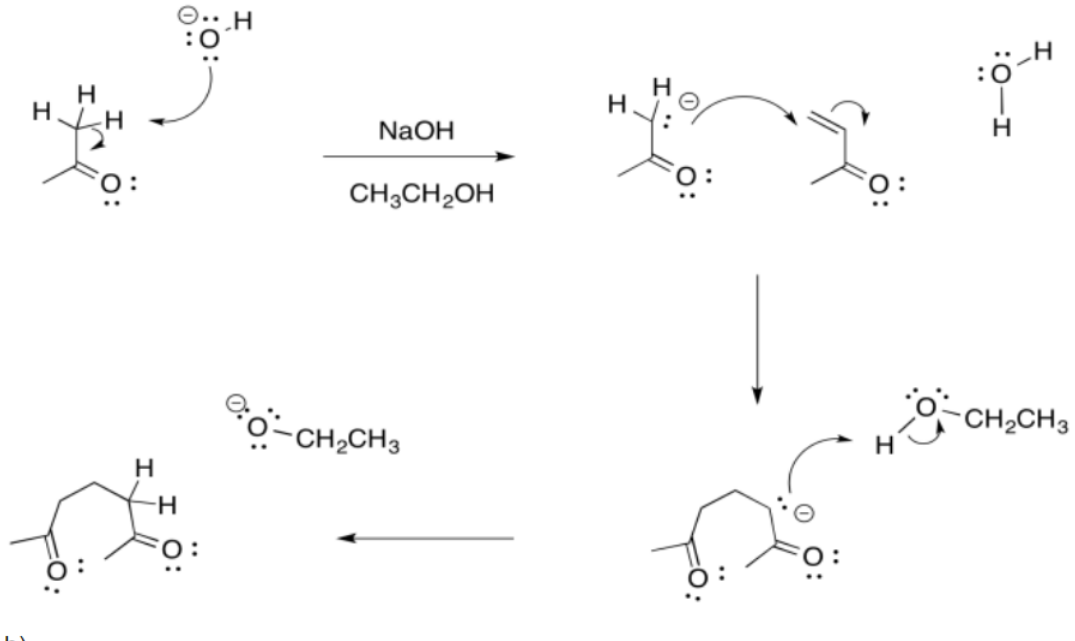


Figure 3.20.49:

a)



b)

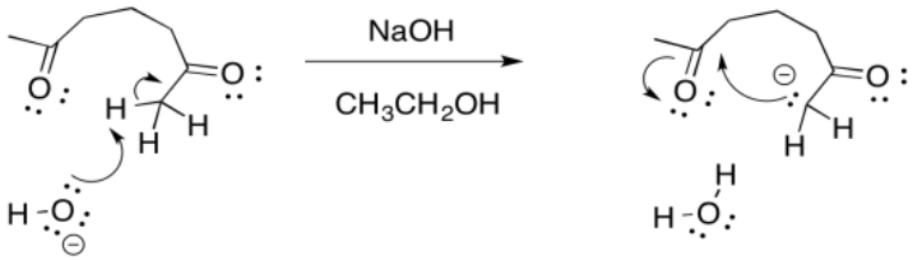
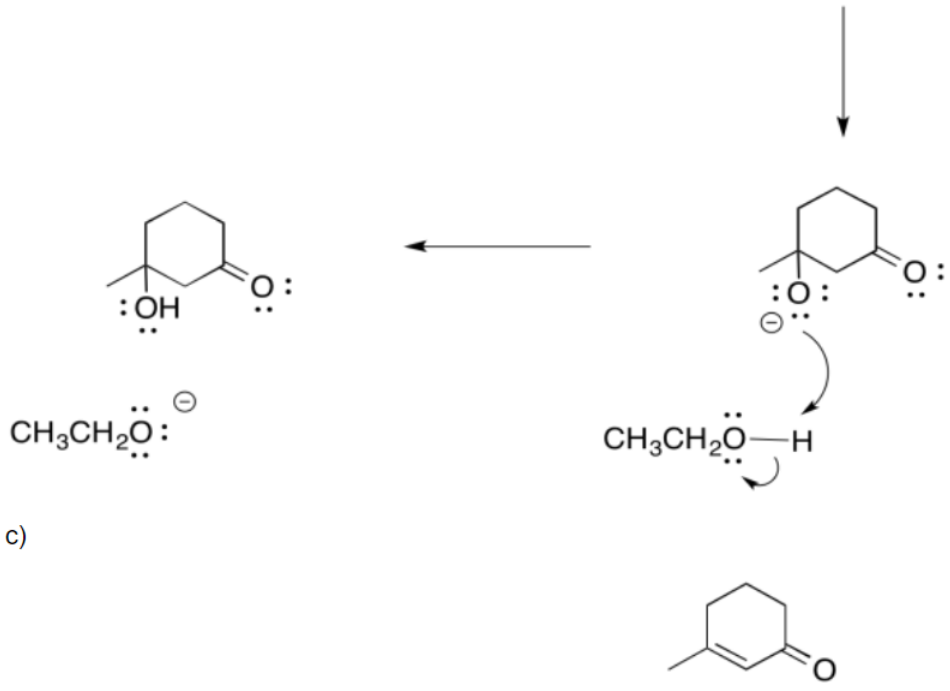
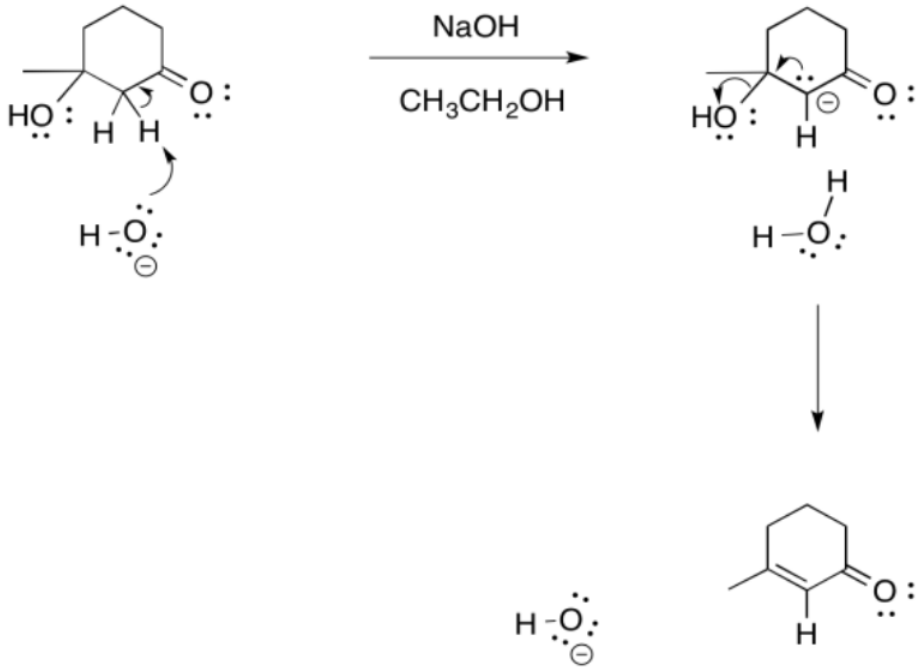


Figure 3.20.50:



c)

Figure 3.20.51:



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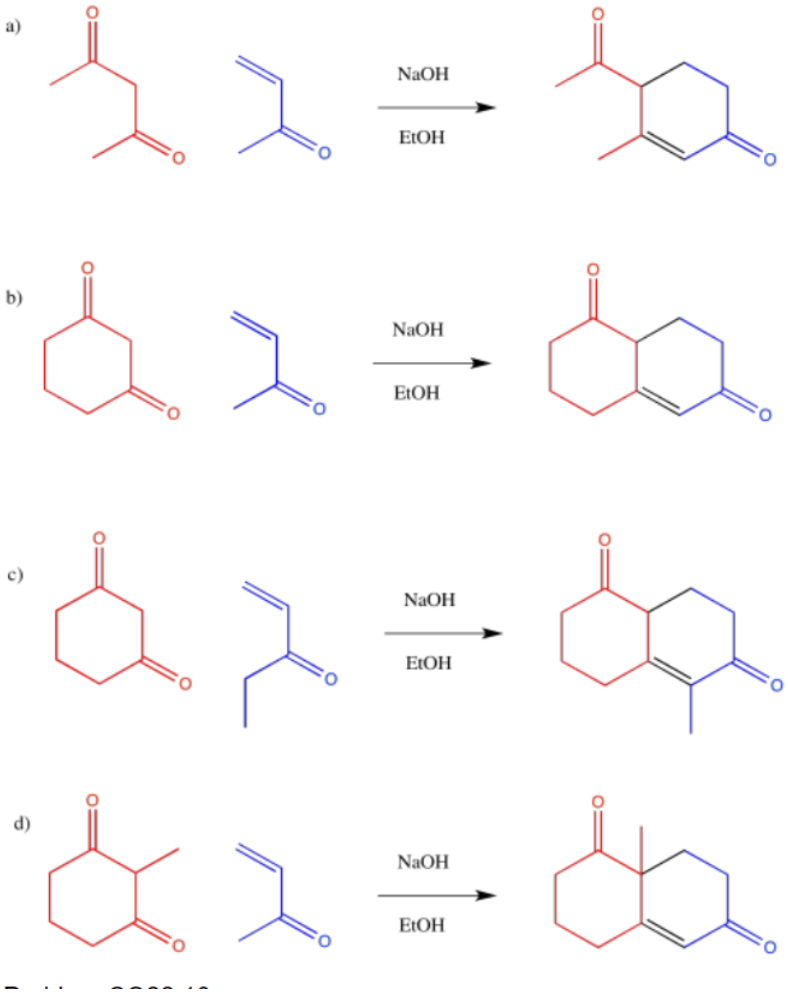


Figure 3.20.53:

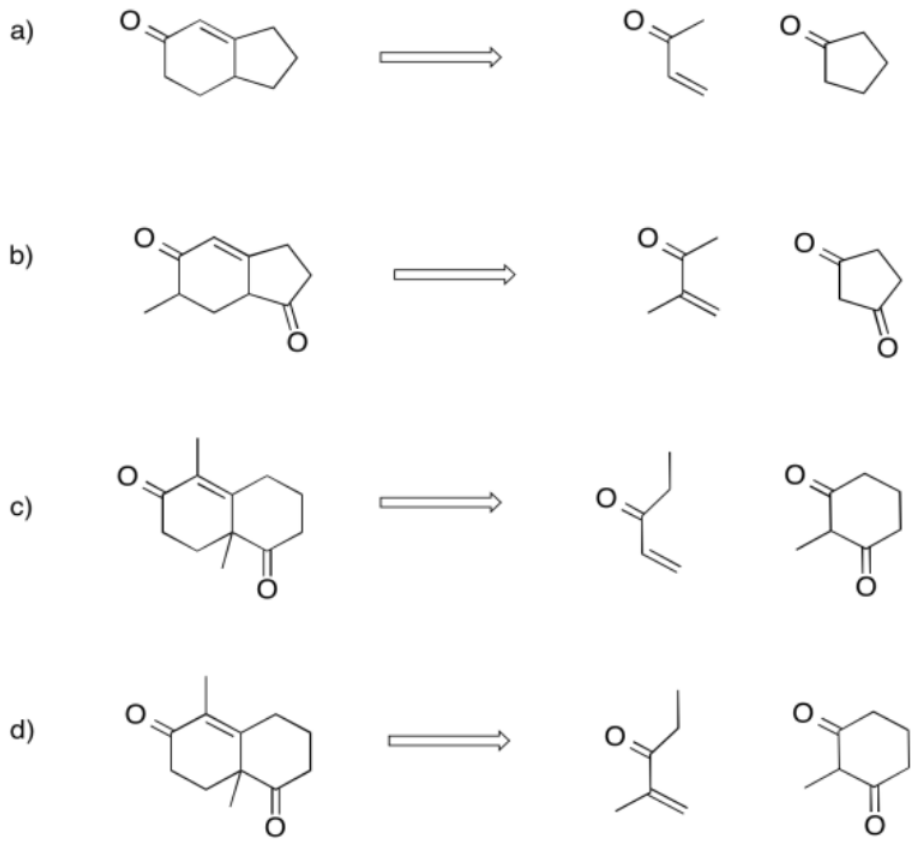
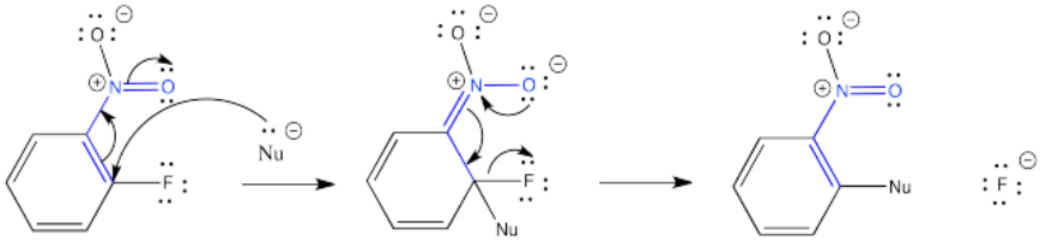


Figure 3.20.54:

Figure 3.20.55:



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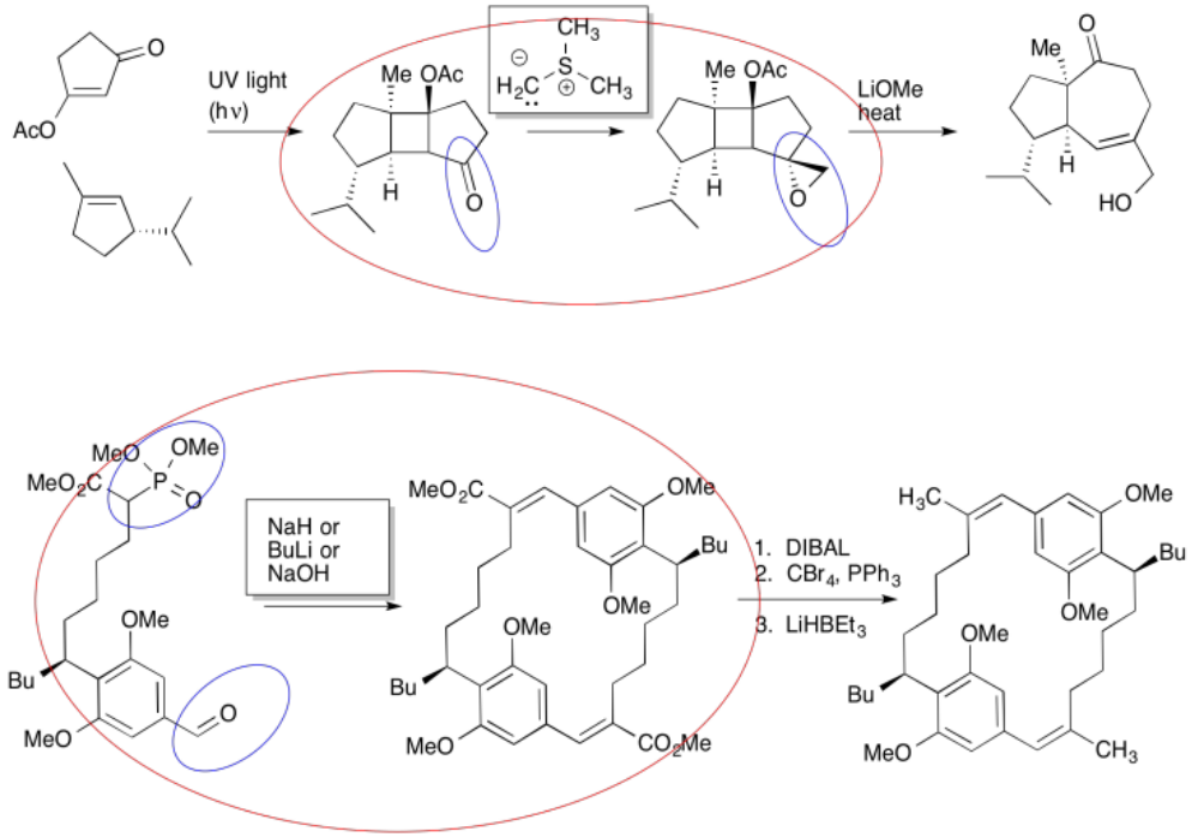

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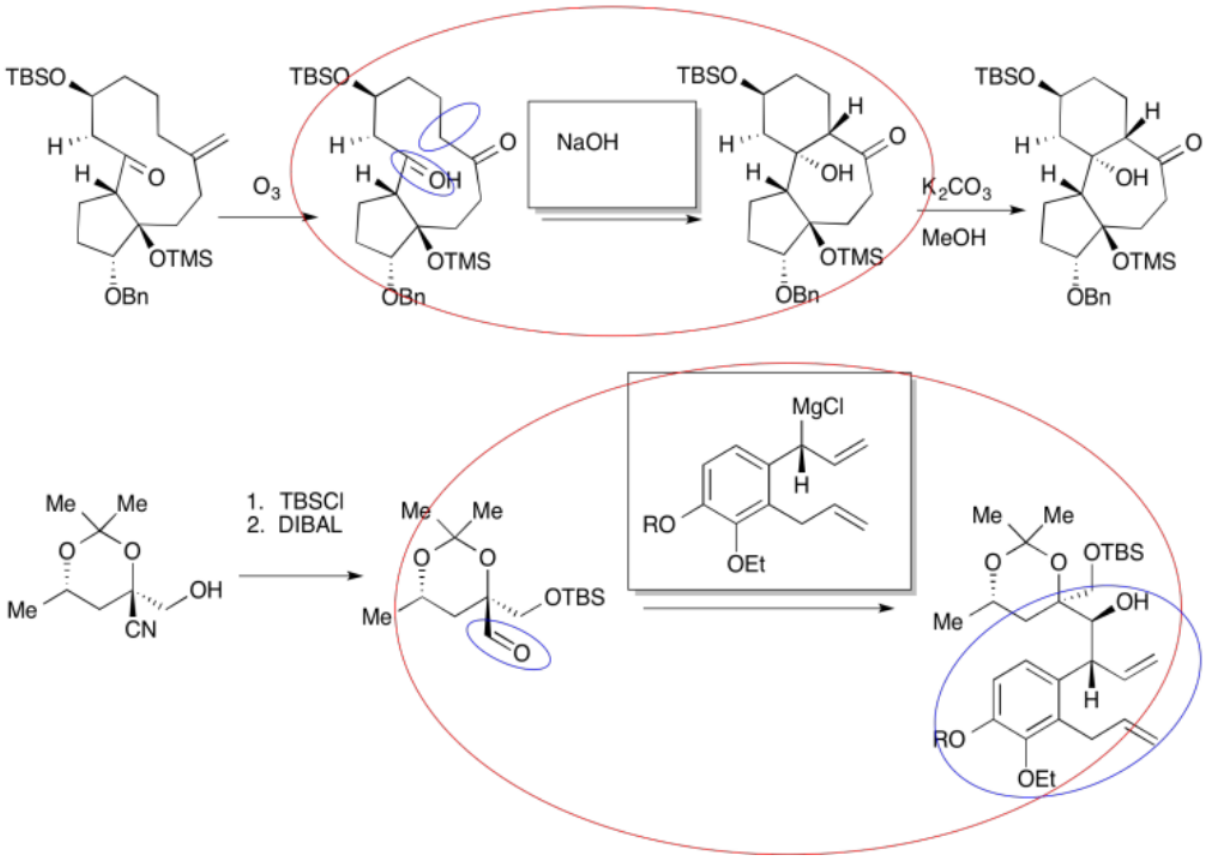
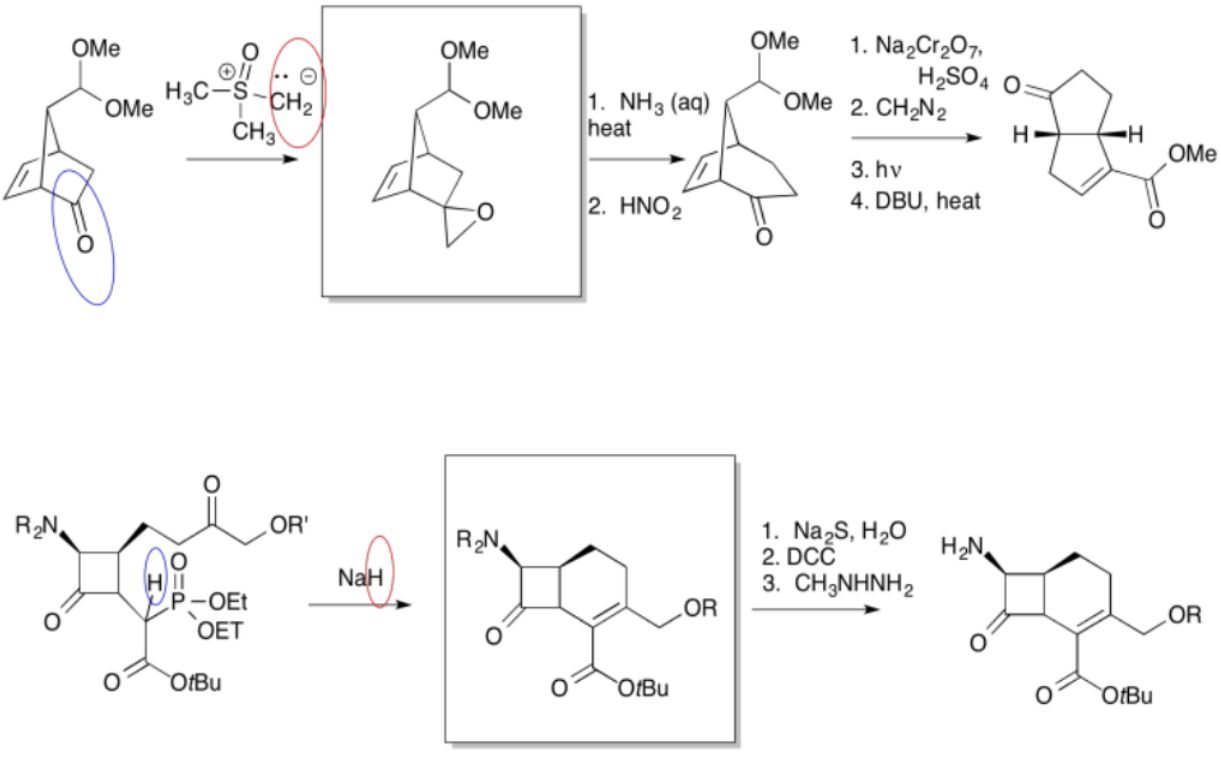


Figure 3.20.58:



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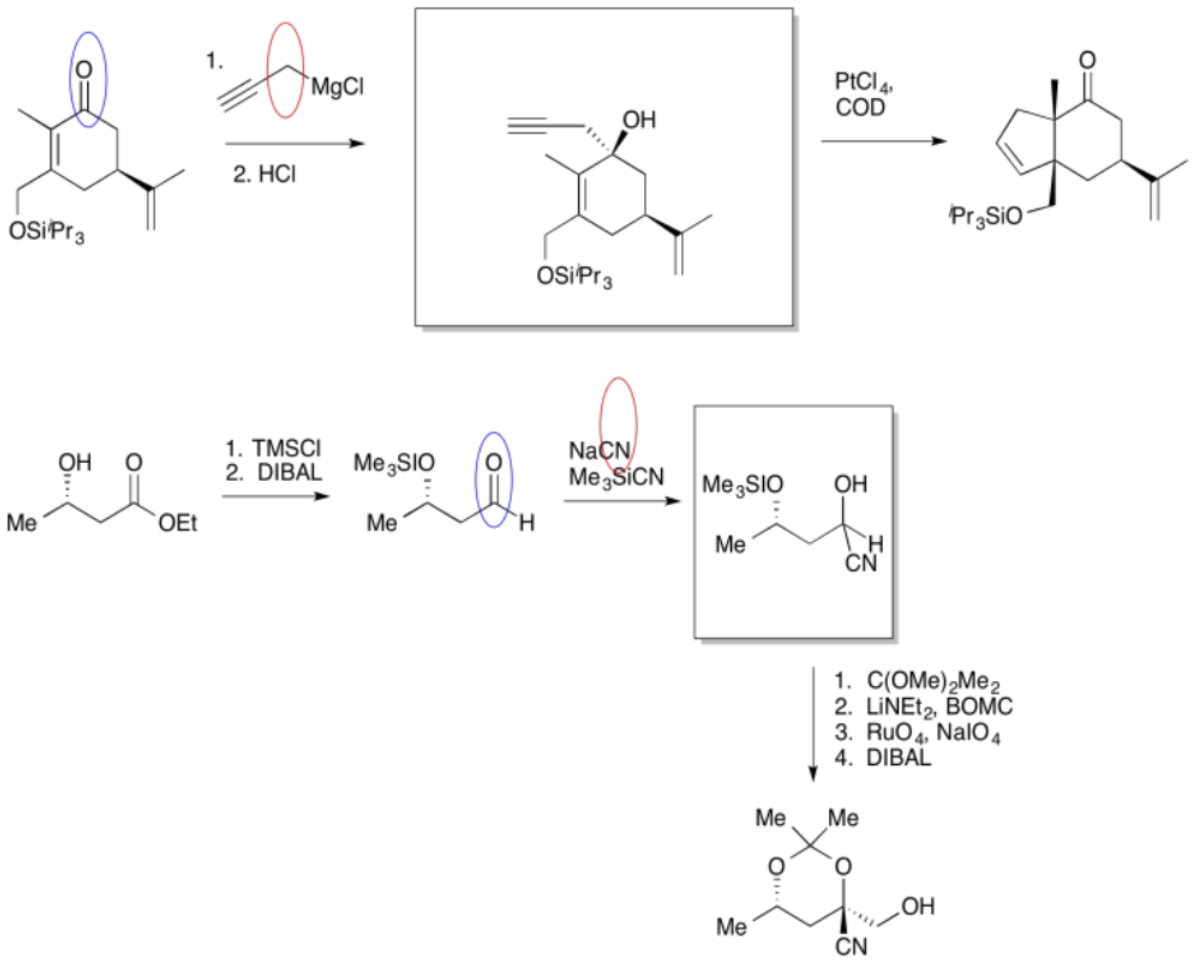

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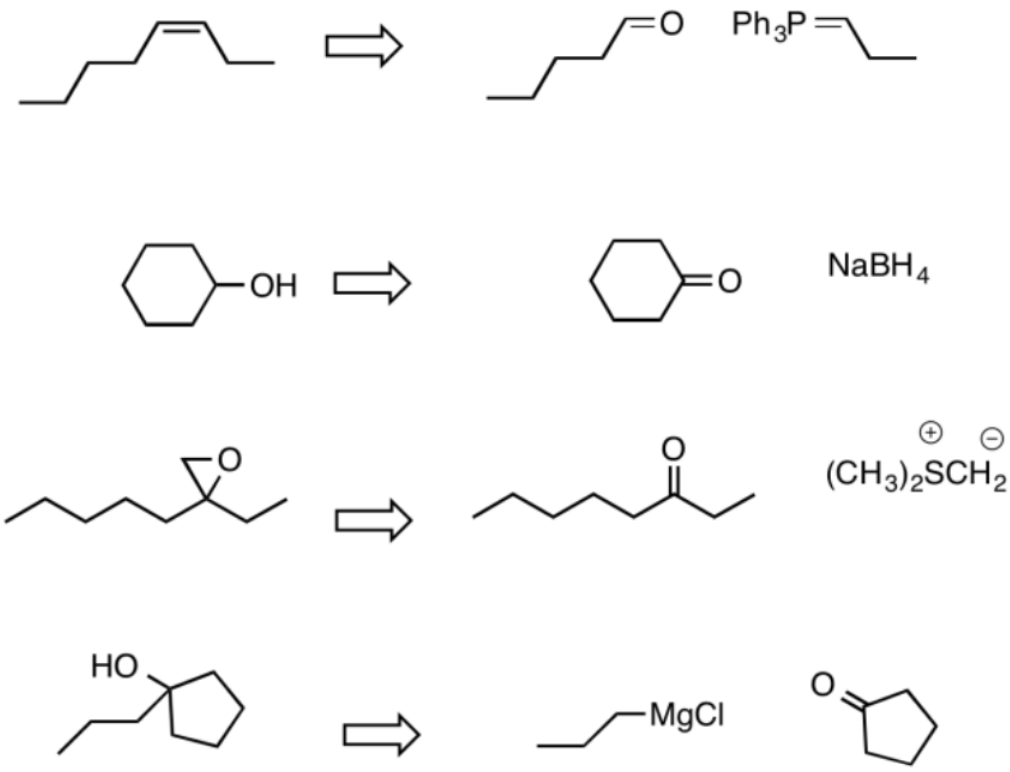


Figure 3.20.61:

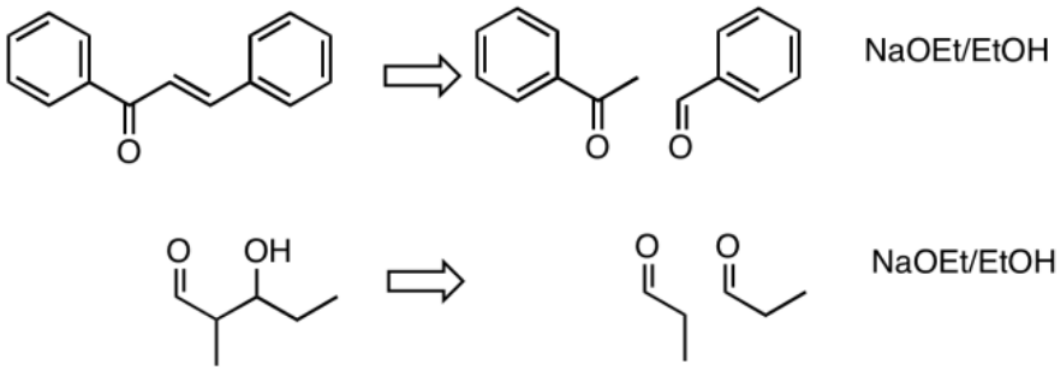
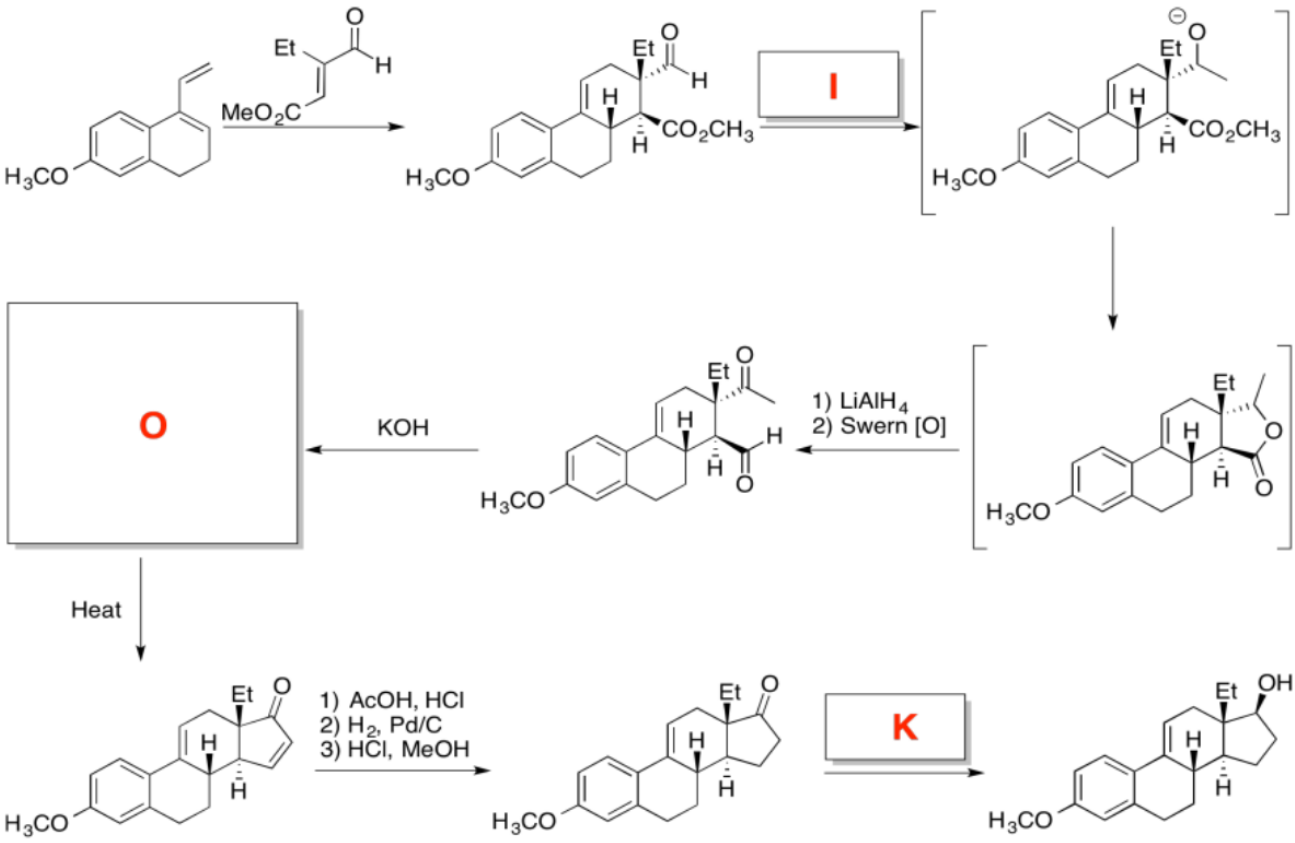


Figure 3.20.62:



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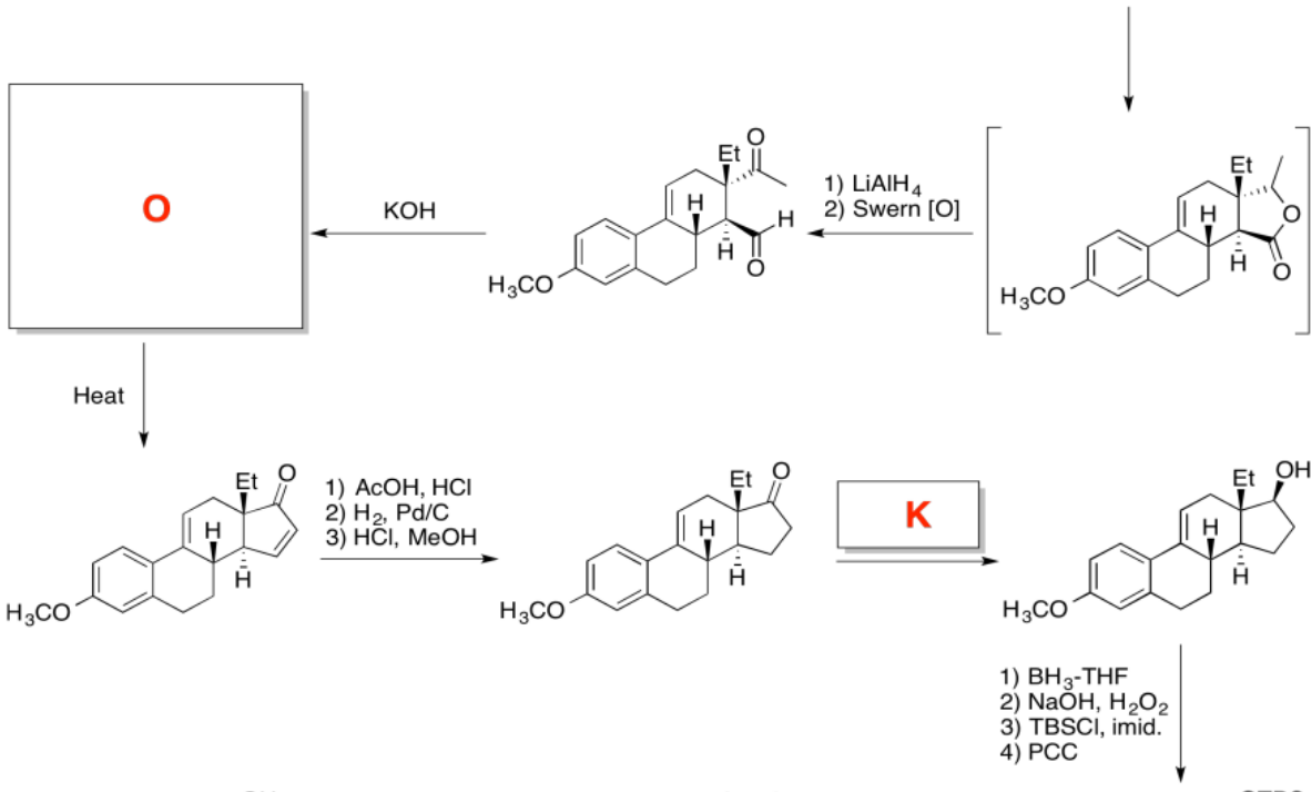

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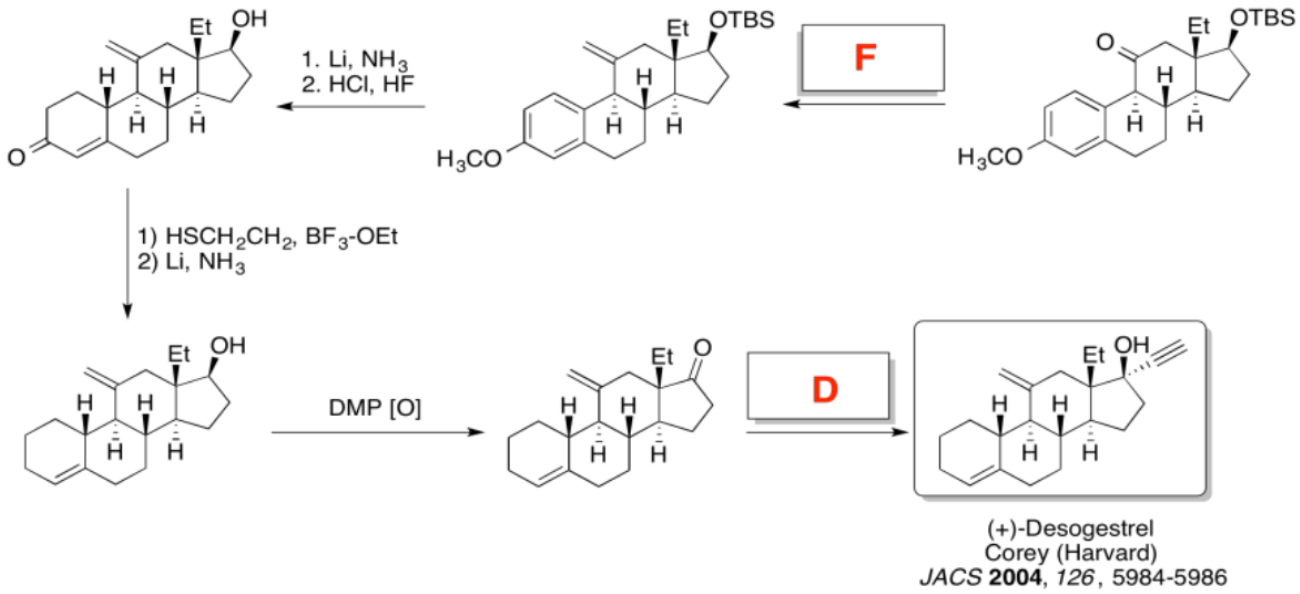


Figure 3.20.65:

Synthesis of tulearin A, Janine Cossy, ESPCI ParisTech, 2009
Isolated from a Madagascar marine sponge; potent activity against leukemia cell lines.

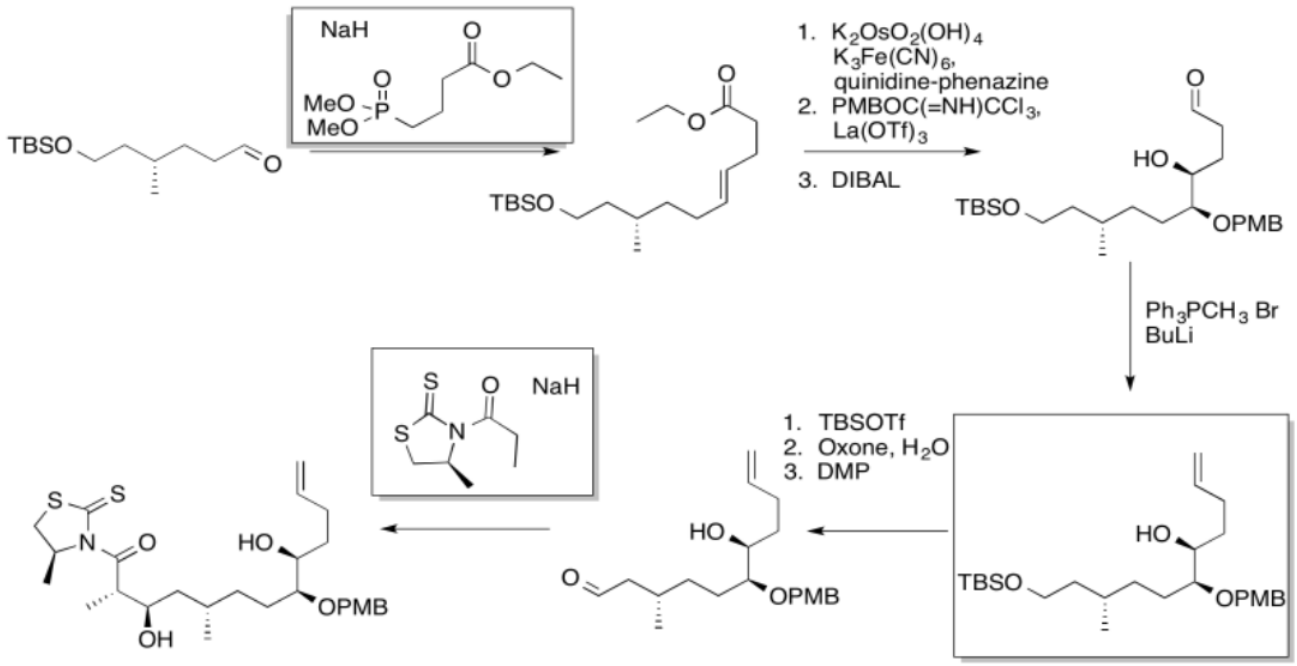


Figure 3.20.66:

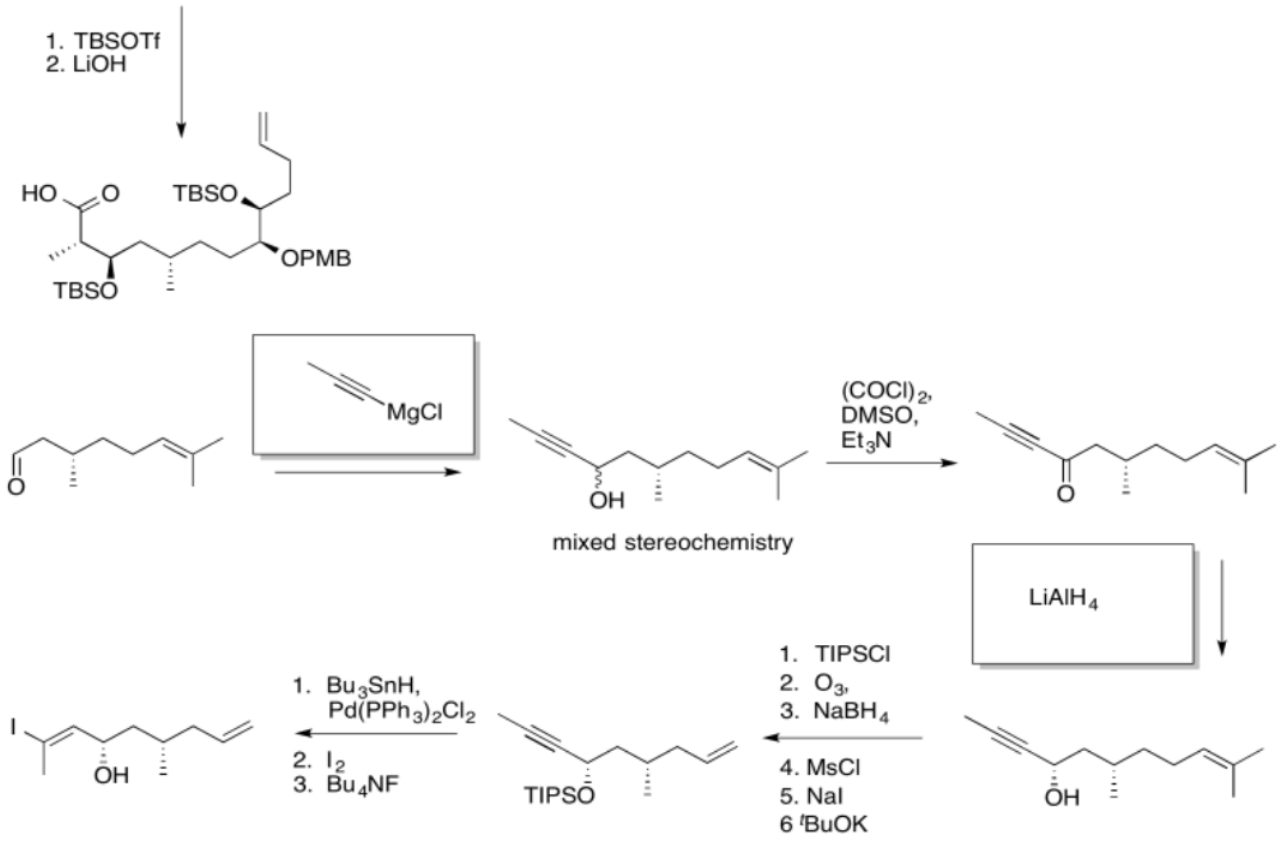


Figure 3.20.67:

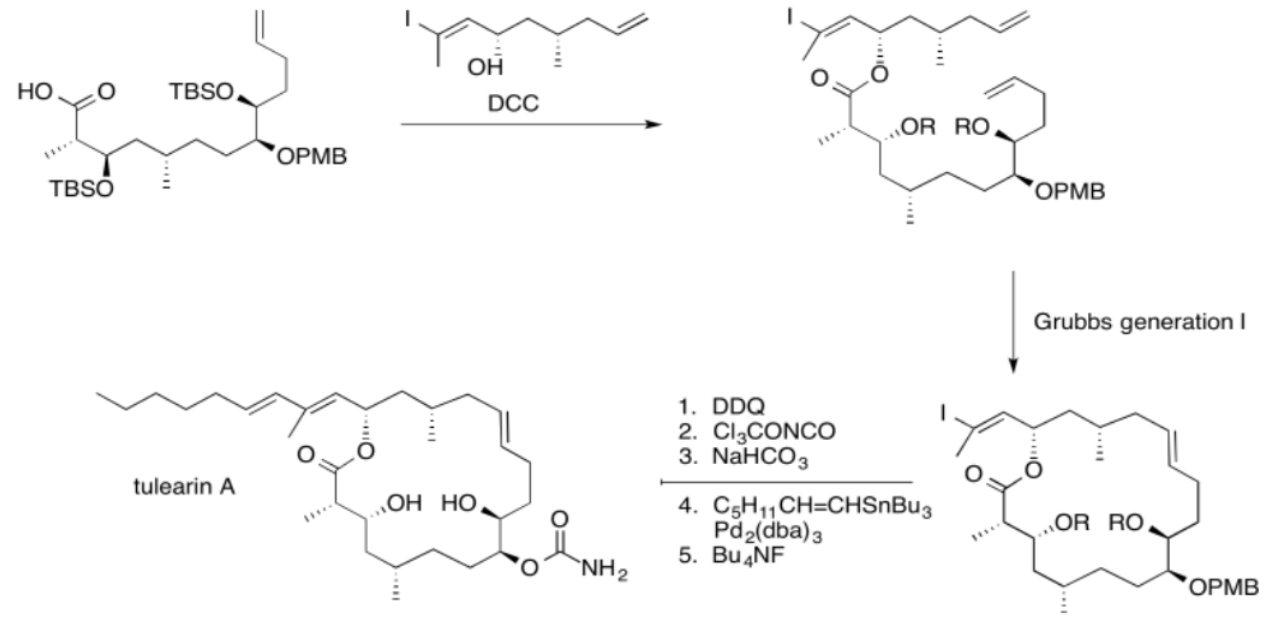


Figure 3.20.68:

Partial Synthesis of Brevenal, Crimmins, UNC Chapel Hill, 2010.
Isolated from marine dinoflagellates off Florida coast. Competitively displaces red tide neurotoxin, dihydrobrevetoxin-B, from voltage-sensitive sodium channels.

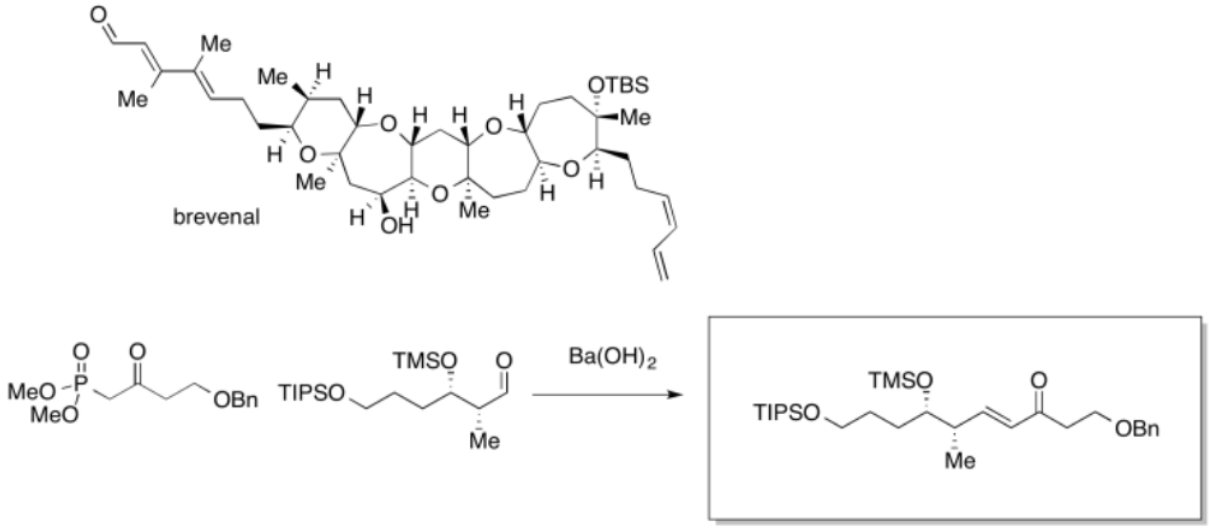


Figure 3.20.69:

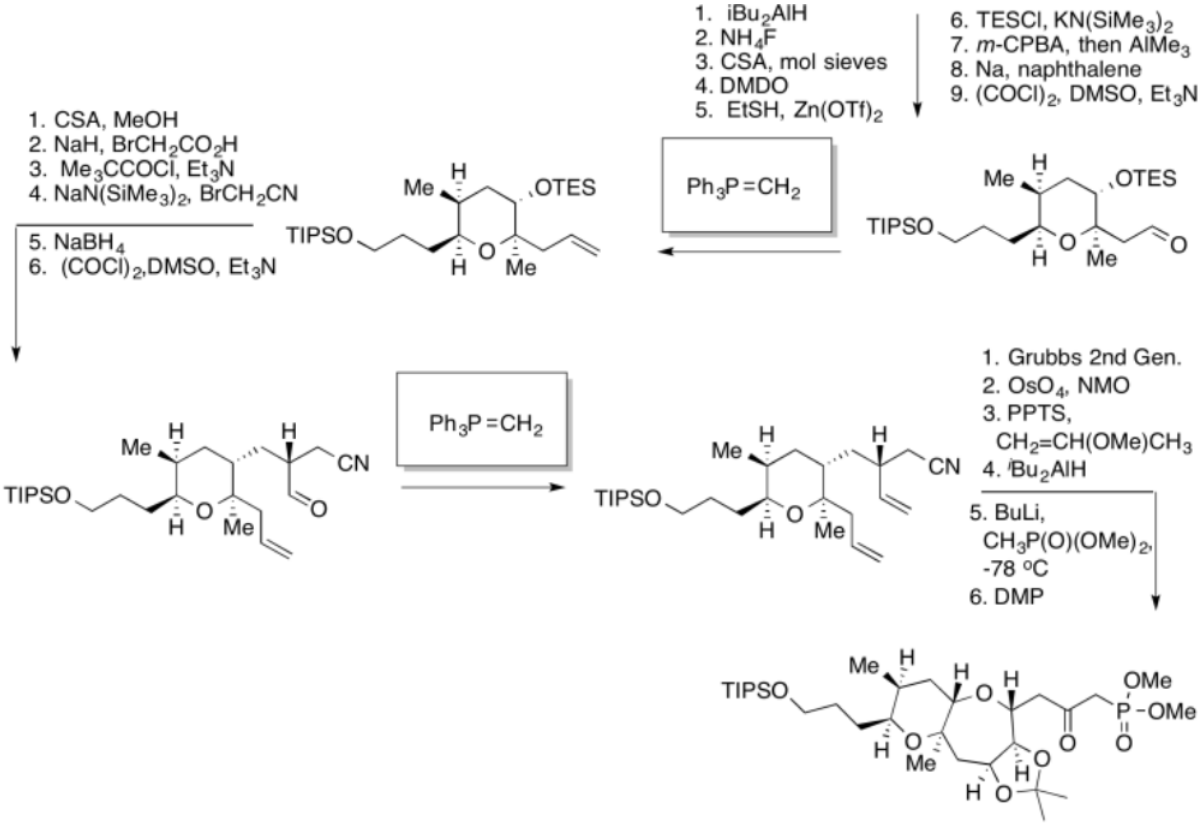


Figure 3.20.70:

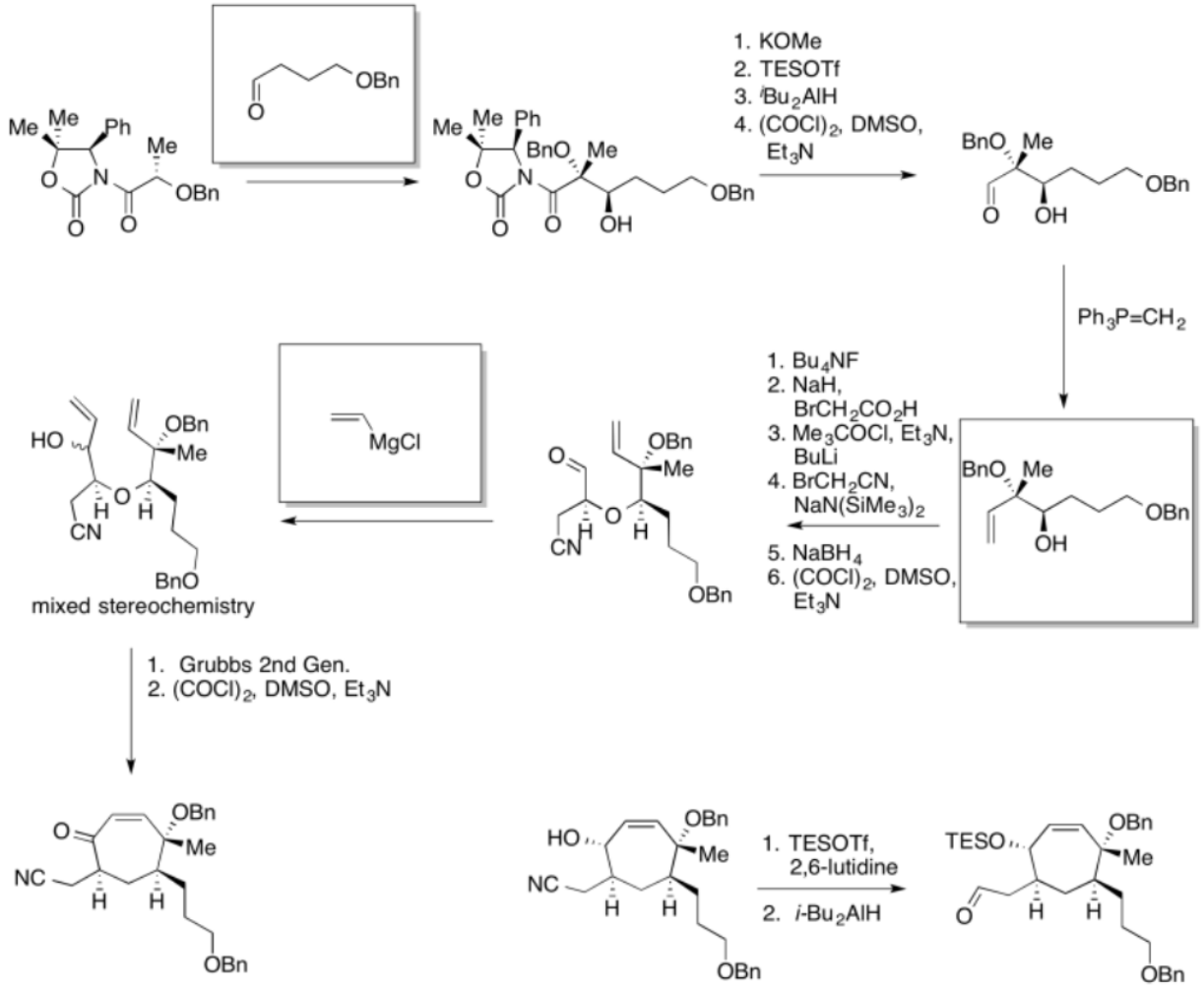


Figure 3.20.71:

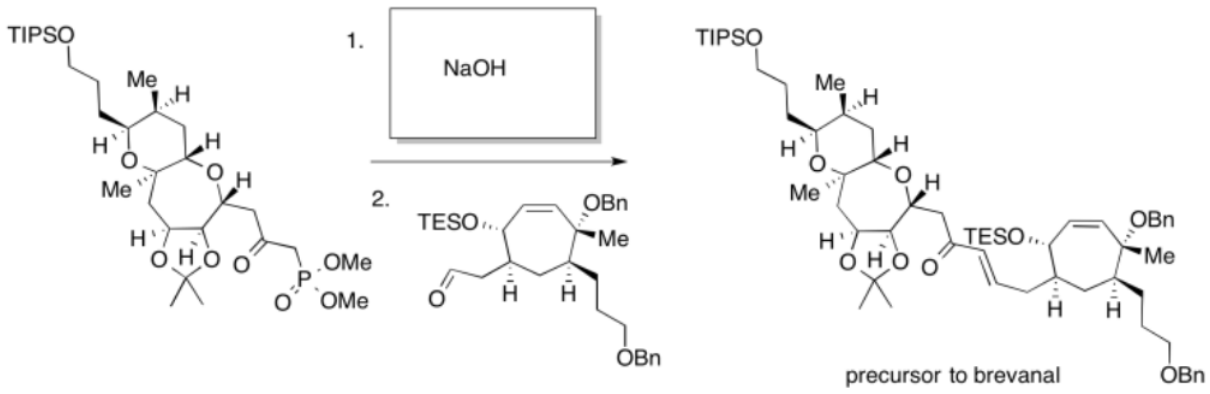


Figure 3.20.72:

Synthesize the following stating from acetone.

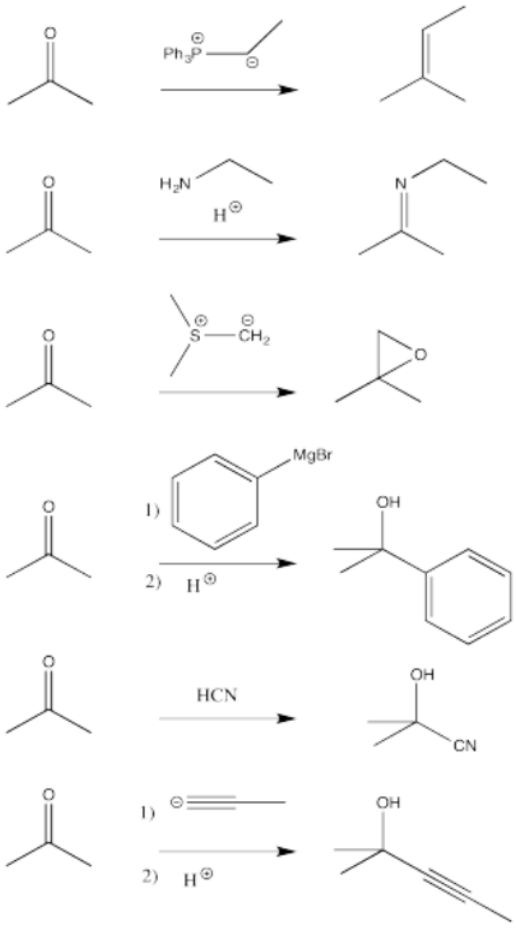


Figure 3.20.73:

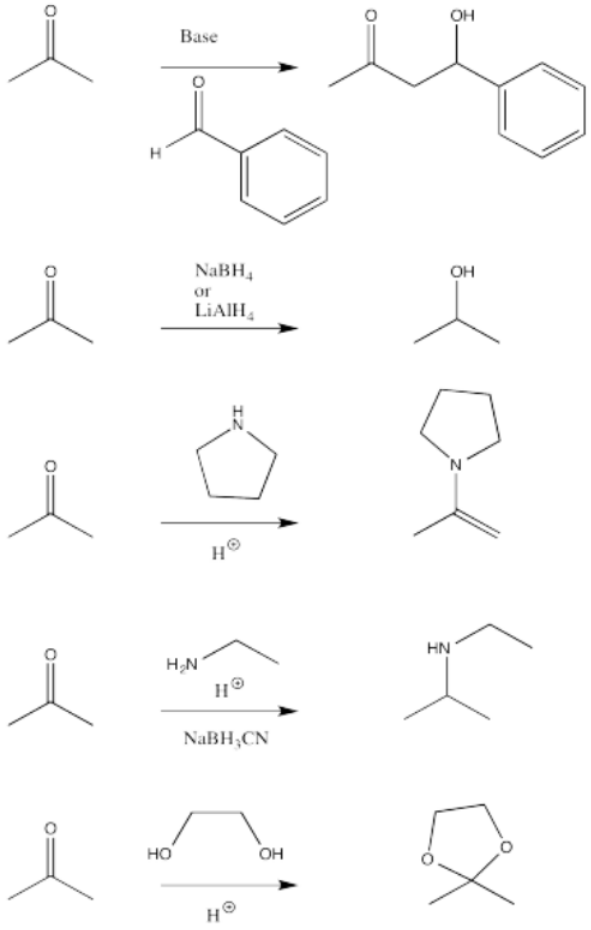


Figure 3.20.74:

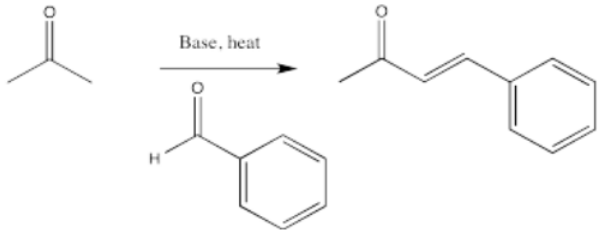


Figure 3.20.75:

Researchers are investigating cyclohexenone derivatives as potential inhibitors for esterases. Below is a scheme for the synthesis of several of these derivatives. Fill in the boxes with the appropriate intermediates or reagents.

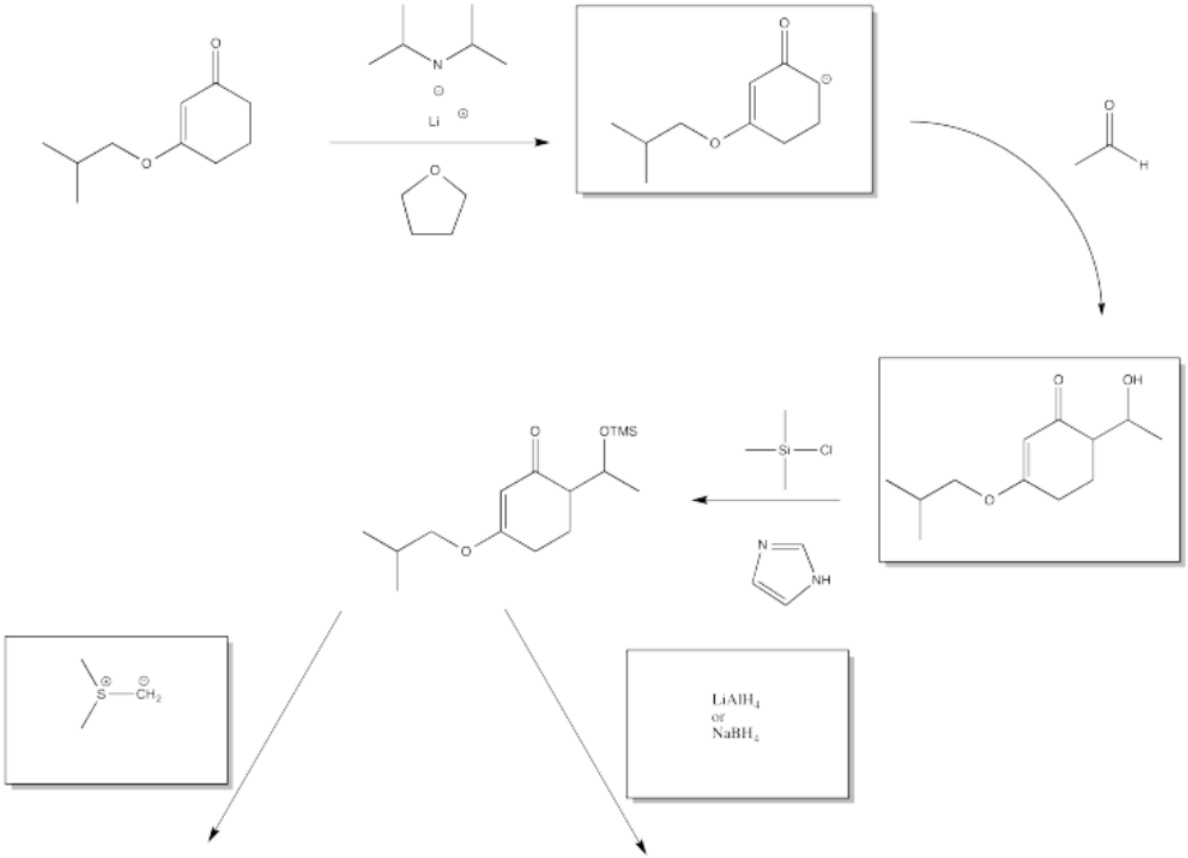
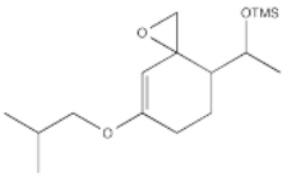
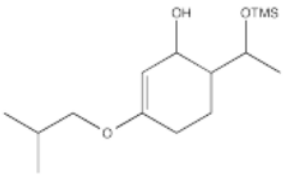


Figure 3.20.76:





Below is another derivative that they made. Provide a mechanism (make sure to draw arrows) for the following reaction:

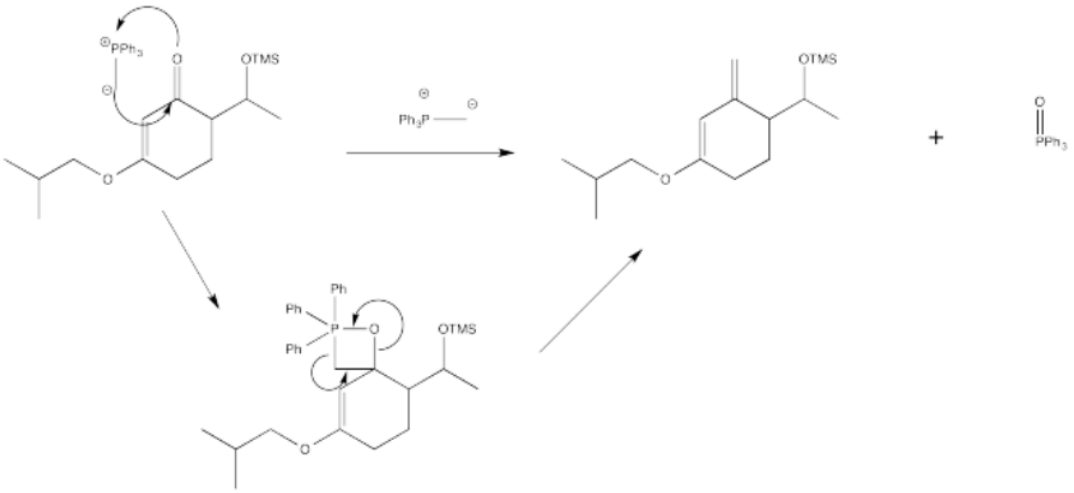


Figure 3.20.77:

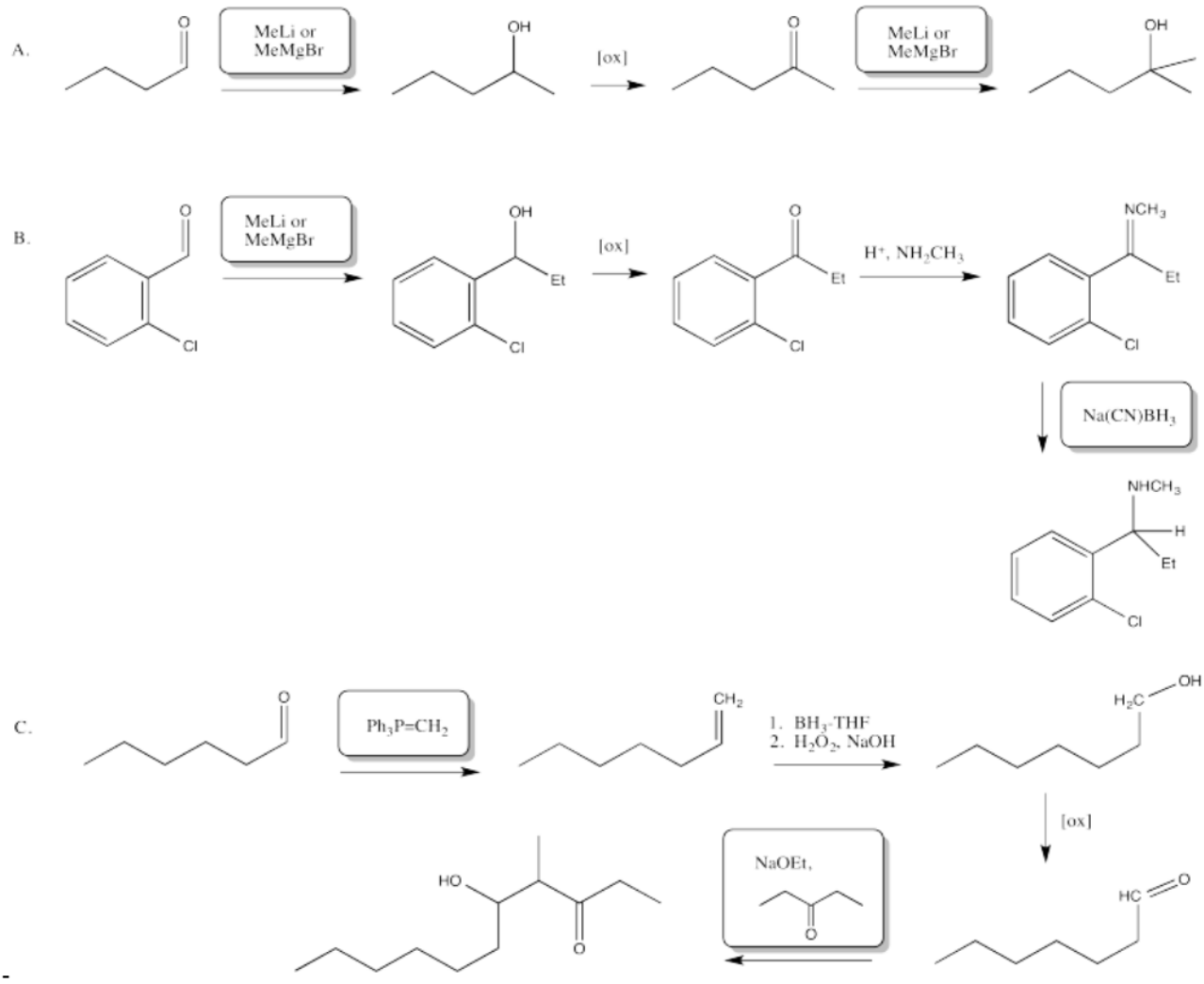


Figure 3.20.78:

Weber, Dehn, Schlager, Dieter, and Kirschning, *Org. Lett.*, **2014**, 16(2), 568-571.

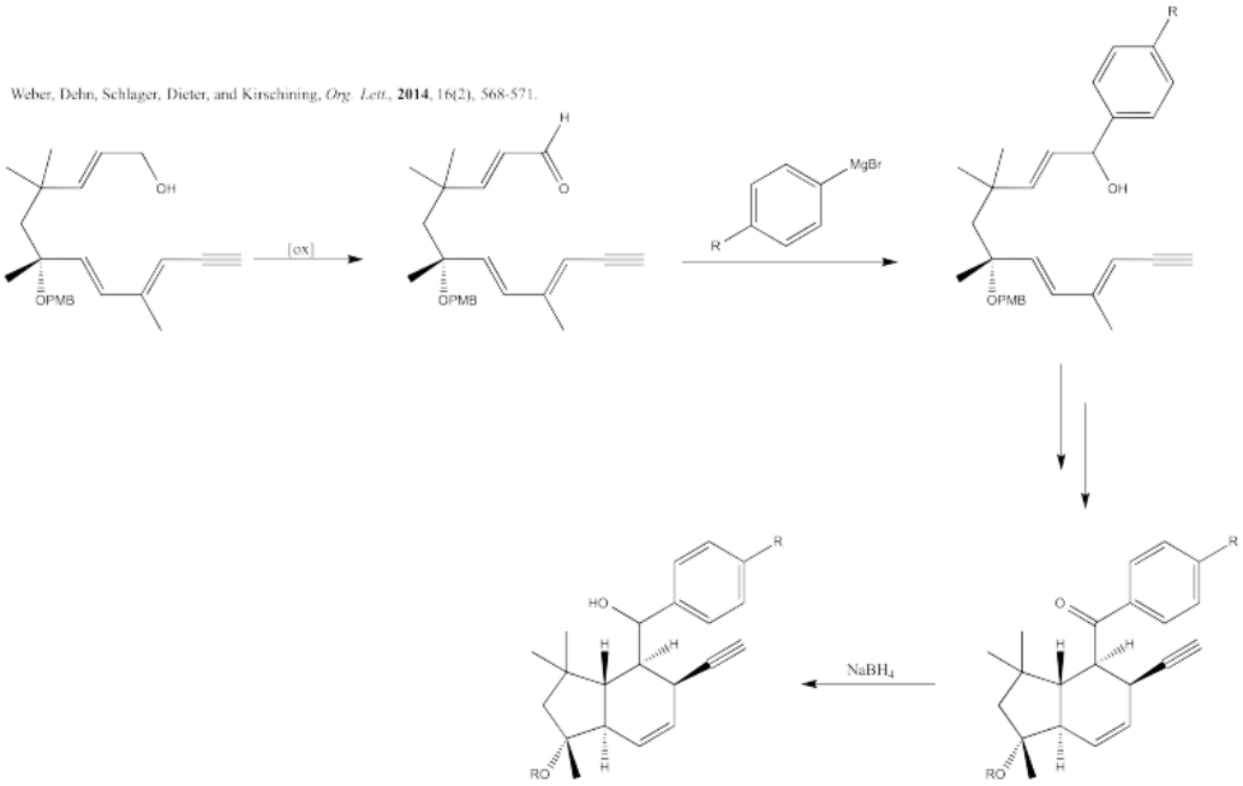


Figure 3.20.79:

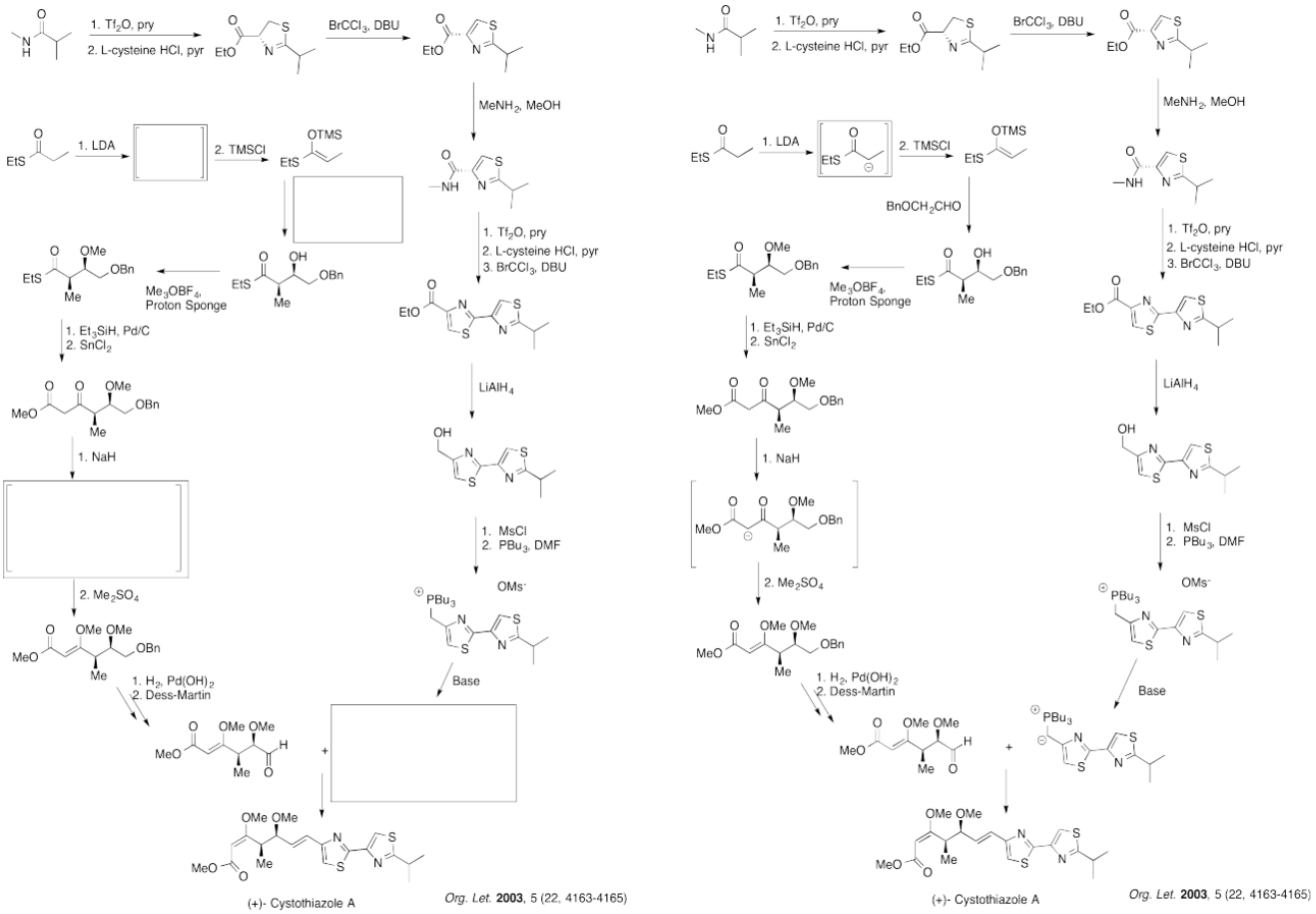


Figure 3.20.80:

20,21 didehydroacutiphycin

Smith, Chen, Nelsom, Reichert, Salvatore, *J. Am. Chem. Soc.* **1997**, *119*, 10935.

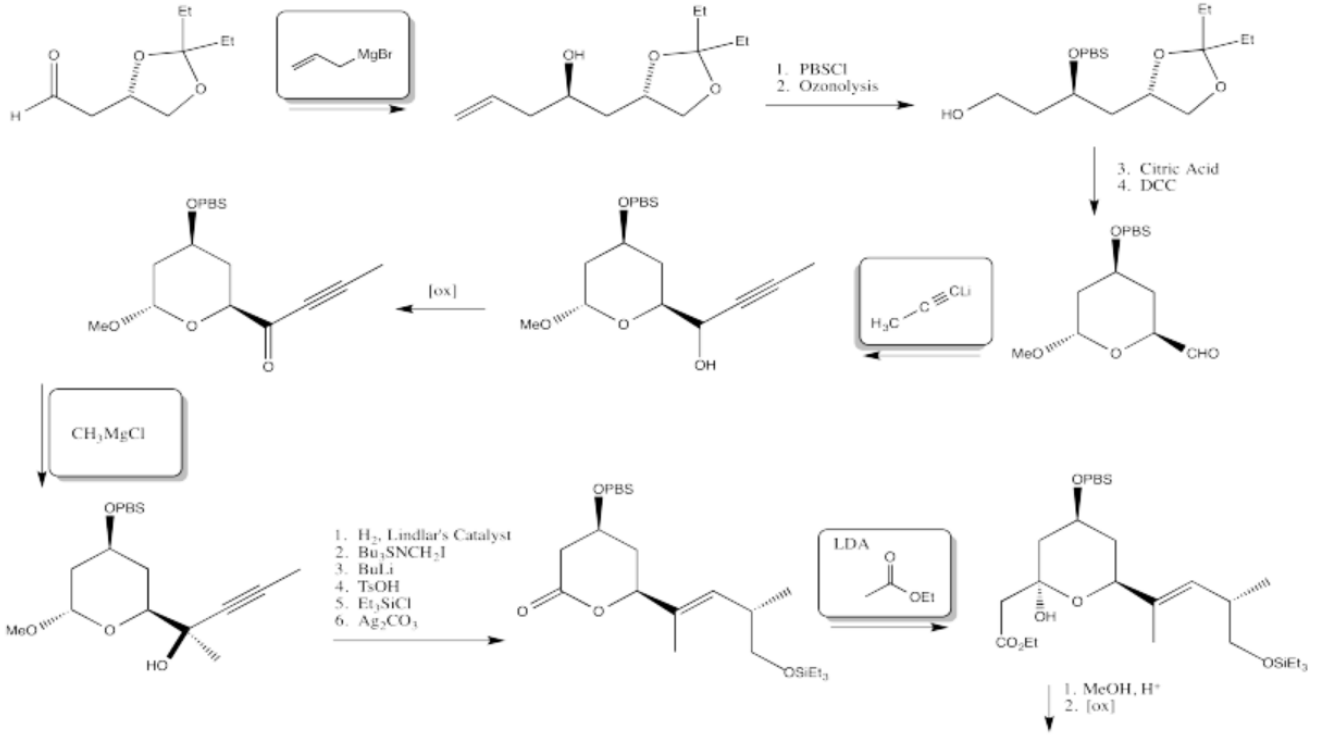


Figure 3.20.81:

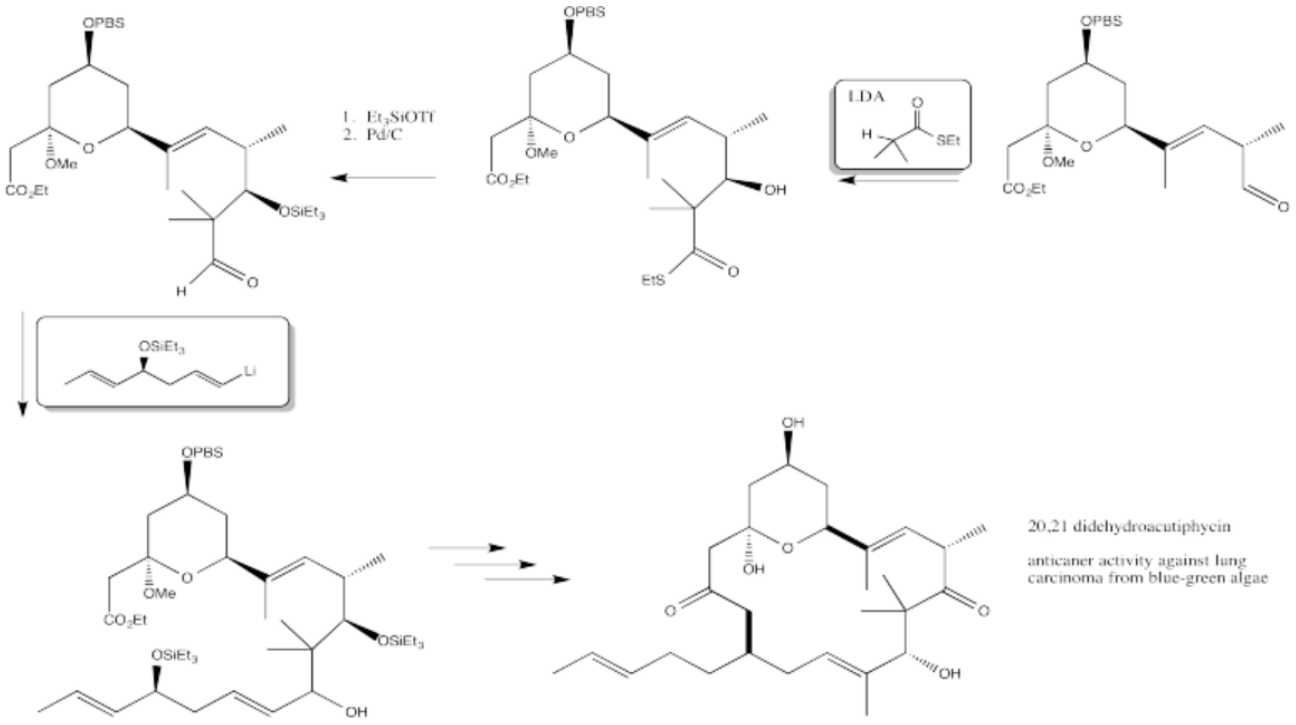


Figure 3.20.82:

Bourbonene

White and Gupta, *J. Am. Chem. Soc.* **1966**, *88*, 5364-5365.

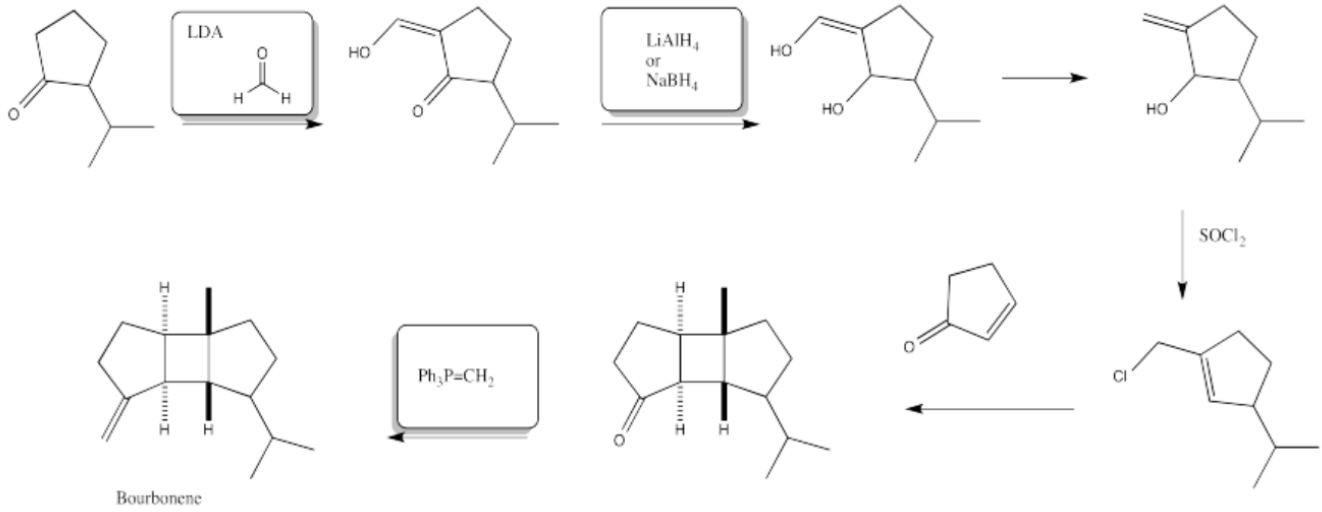


Figure 3.20.83:

Problem CO26.8.

Onocerin

Stork, et. al., *J. Am. Chem. Soc.*, **1963**, *85*, 3419-3425.

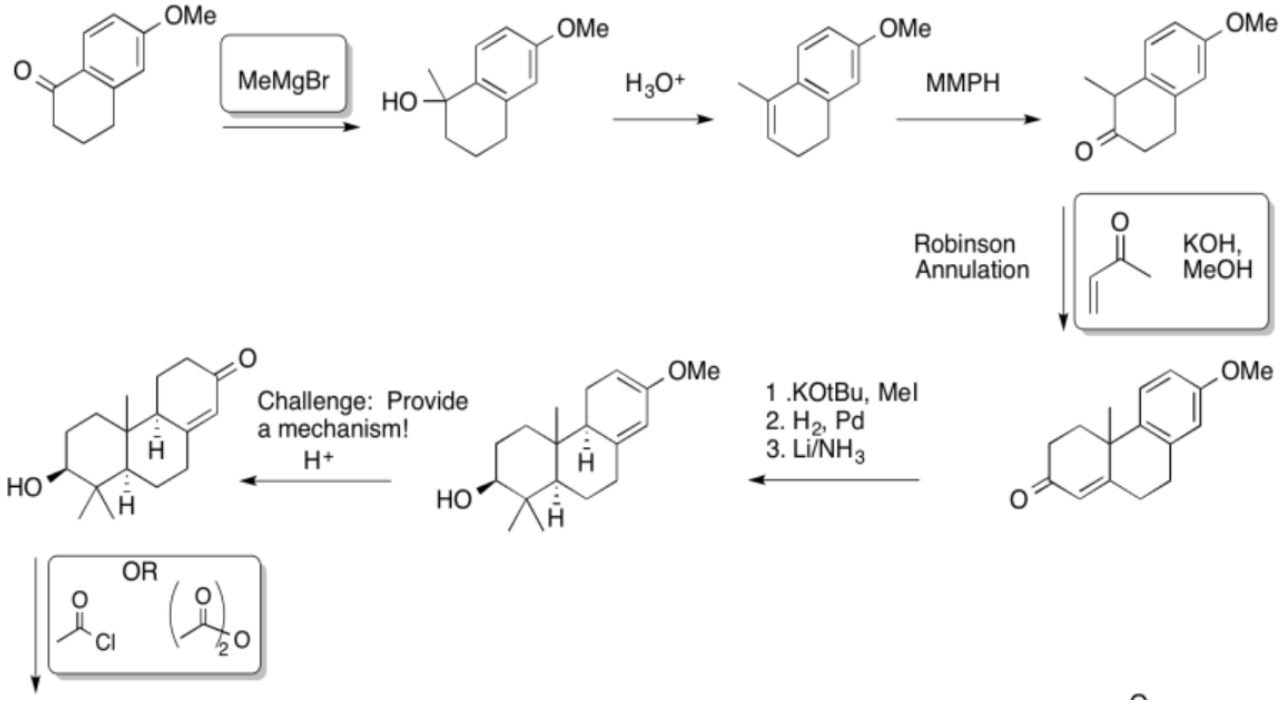


Figure 3.20.84:

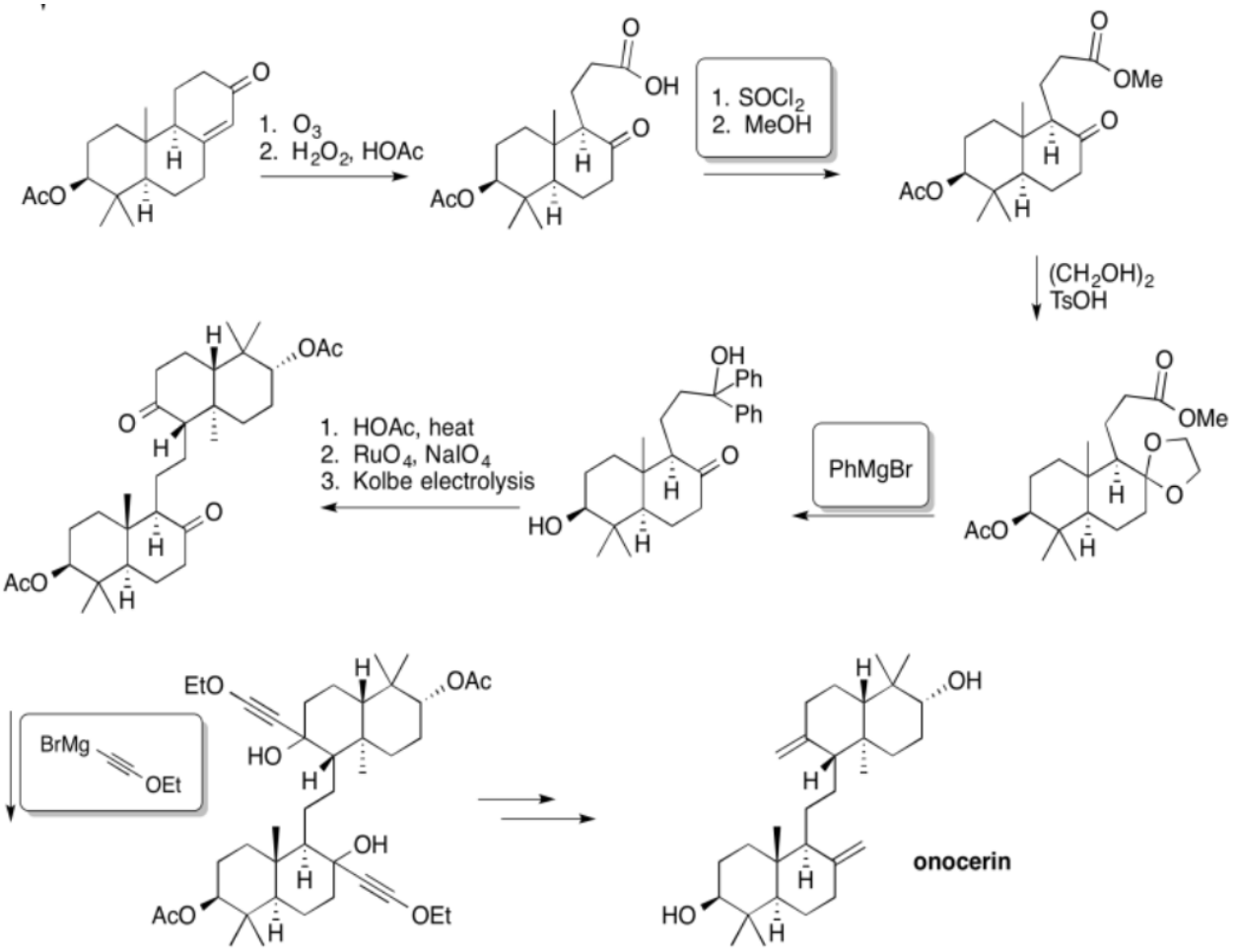


Figure 3.20.85:

Taber and Saleh, *J. Am. Chem. Soc.*, **1980**, *102*, 5085-5088.

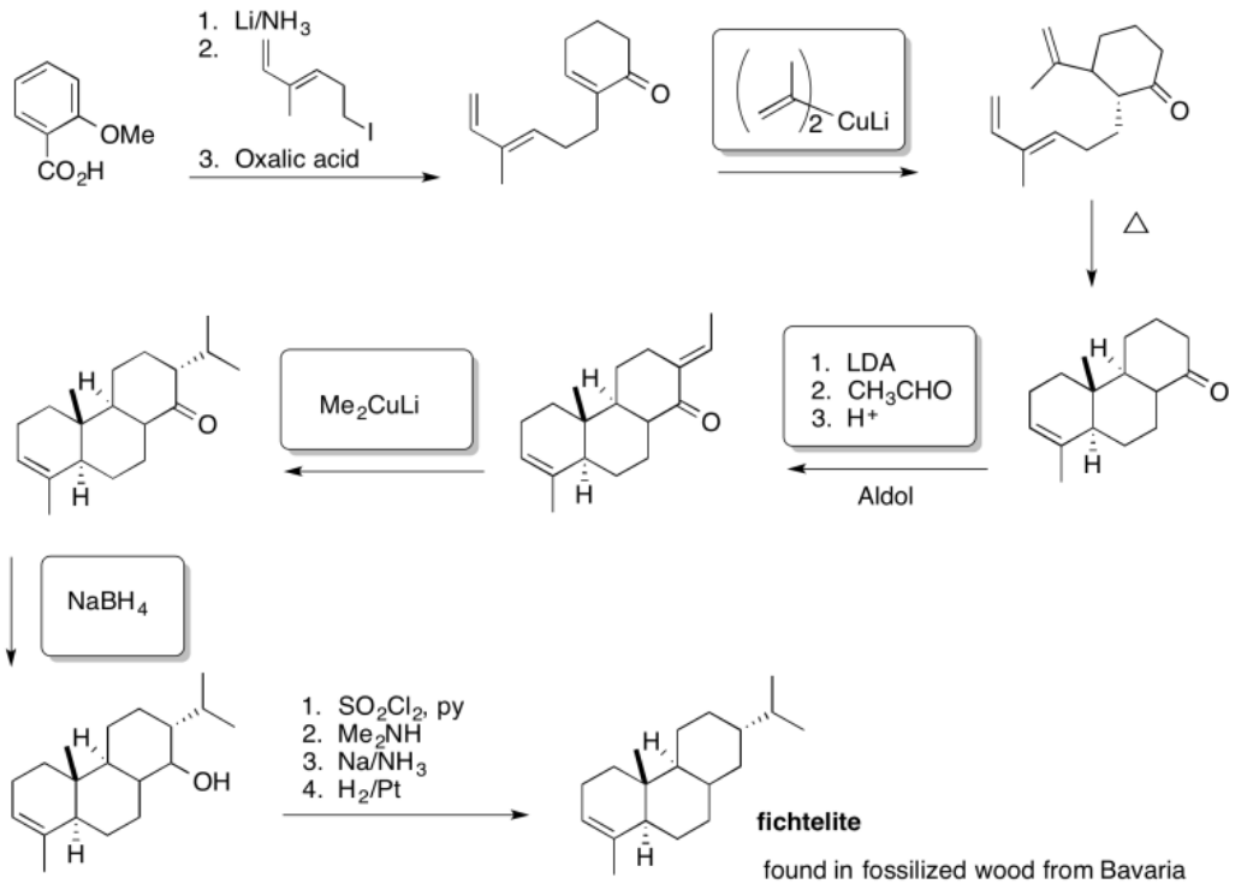


Figure 3.20.86:
