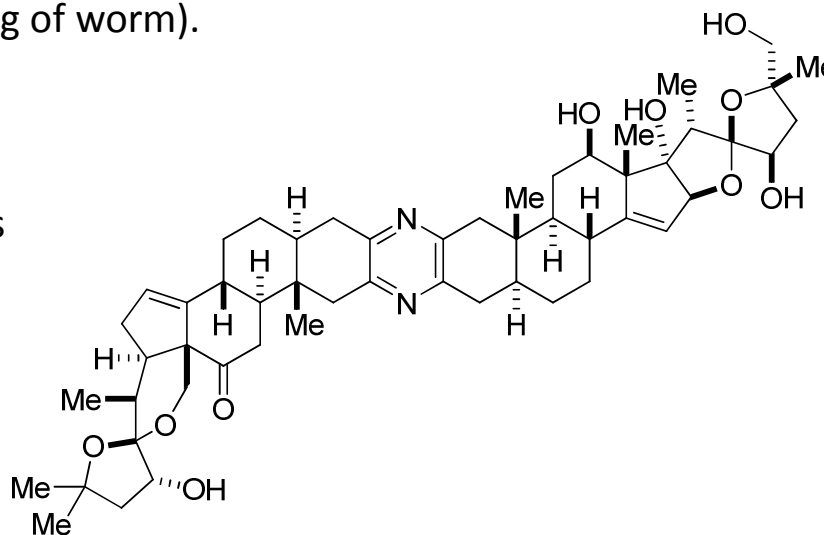


# Total Synthesis of Cephalostatin 1

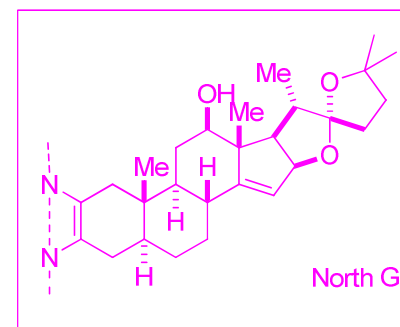
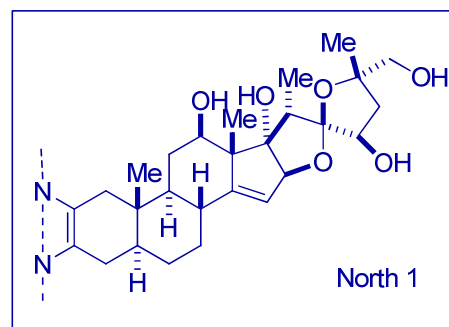
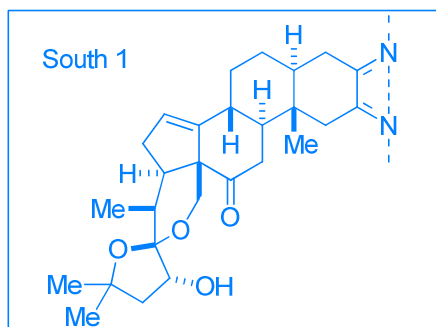
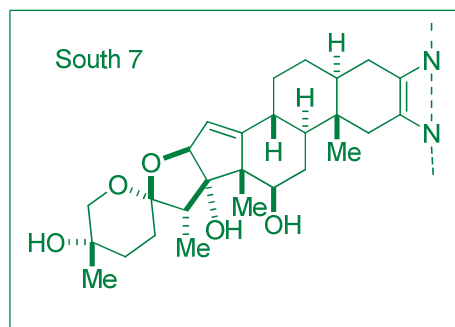
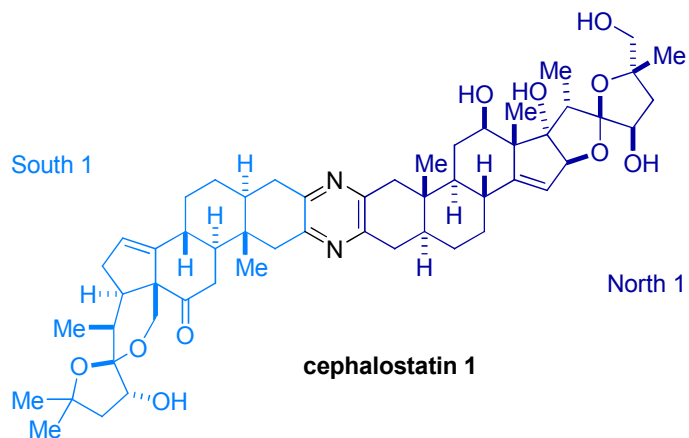
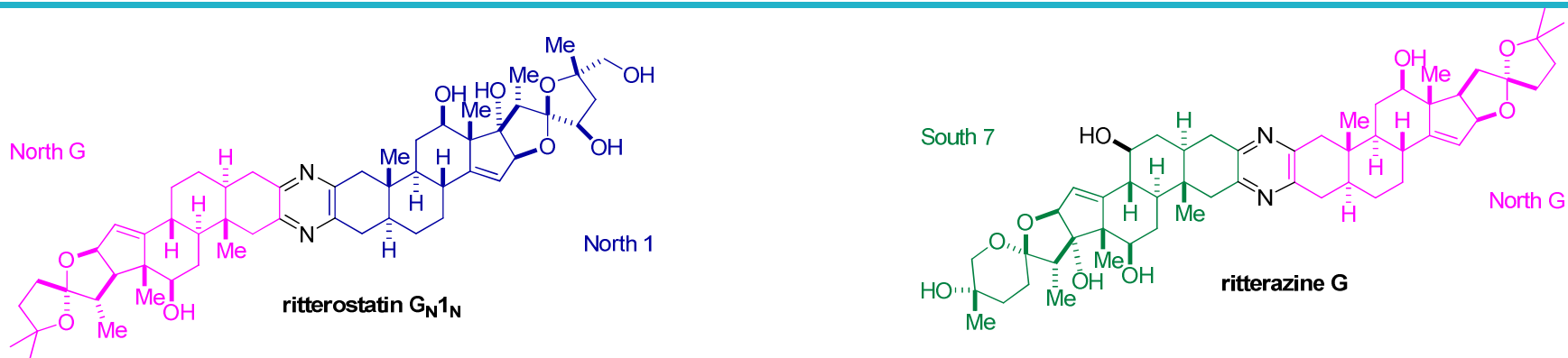
Lizzie O'Bryan  
Literature Group Meeting  
February 12, 2010

# Background

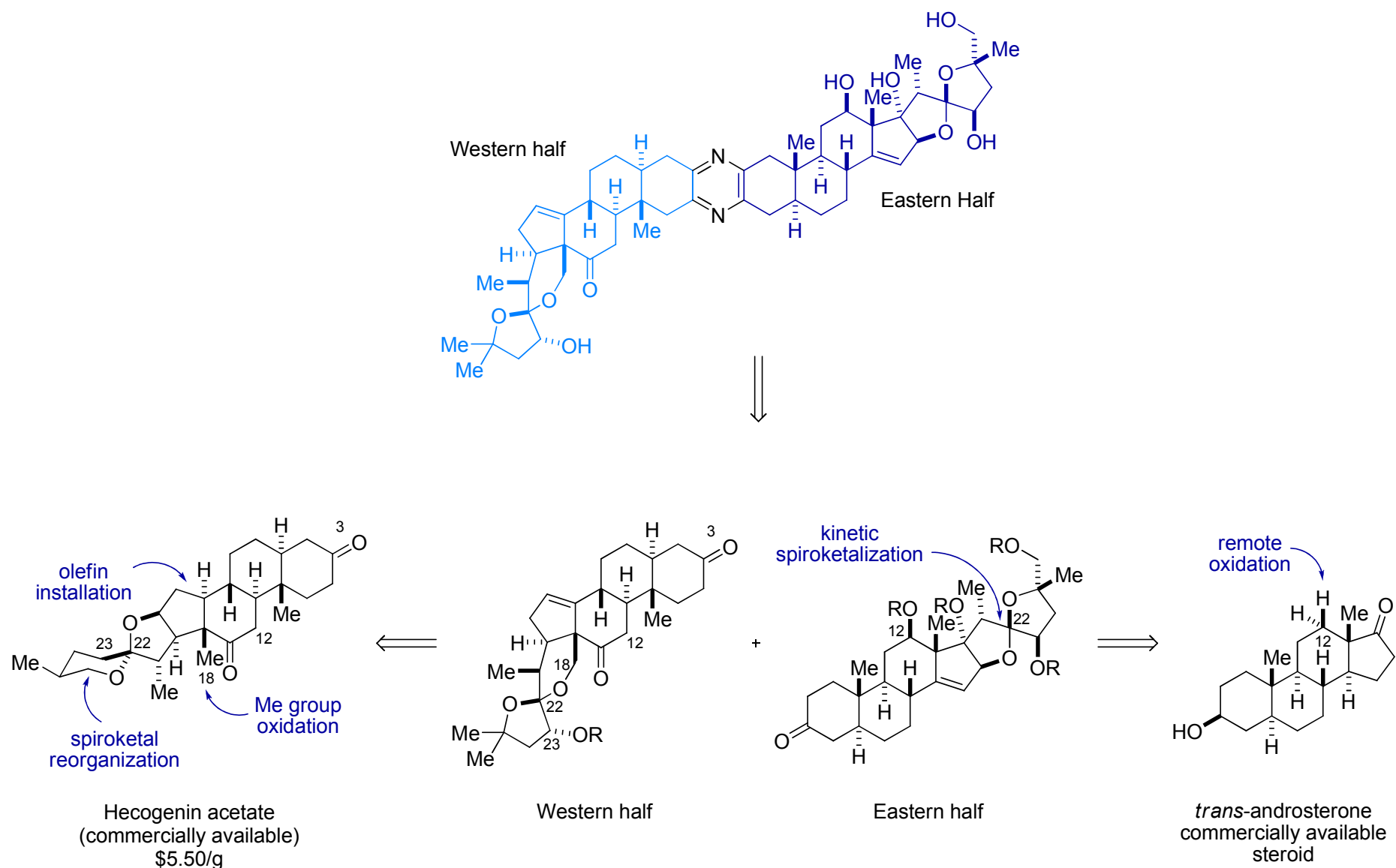
- Cephalostatin 1 was isolated in 1988 from the marine tube worm *Cephalodiscus gilchristi* in the Indian Ocean by Pettit
- Over 40 trisdecacyclic pyrazines have been isolated so far from cephalostatin and ritterazine family of natural products
- Made up of two C<sub>27</sub> steroids which are substituted isomers of hecogenin
- Cephalostatin 1 has very potent (subnanomolar activity) anticancer agent against several human cancer cell lines.
- Clinical trials of cephalostatin 1 have stalled because of severe difficulties in harvesting in the white shark infested waters off East Africa (0.1 g from 450 kg of worm).
- Related ritterazines also have potent cytotoxicity, interest in preparing derivatives and hybrids composed of ritterazine and cephalostatin subunits
- Two total syntheses:
  - Fuchs (*JACS*, **1995**, *117*, 10157)
  - Shair (*JACS*, **2010**, *132*, 275)



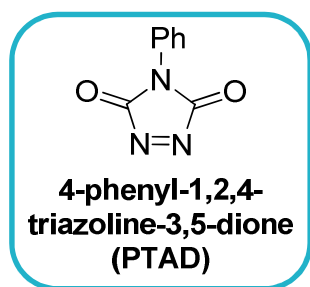
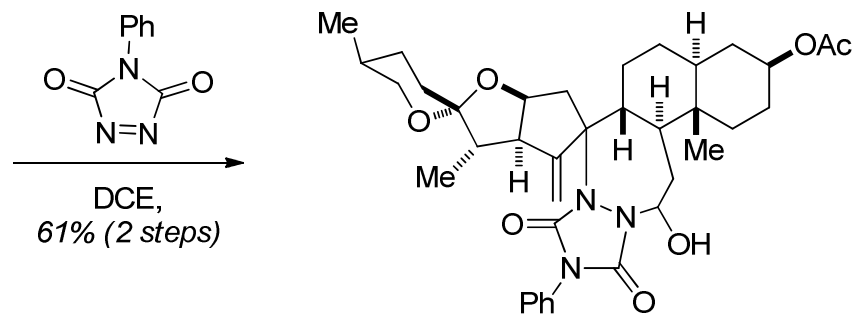
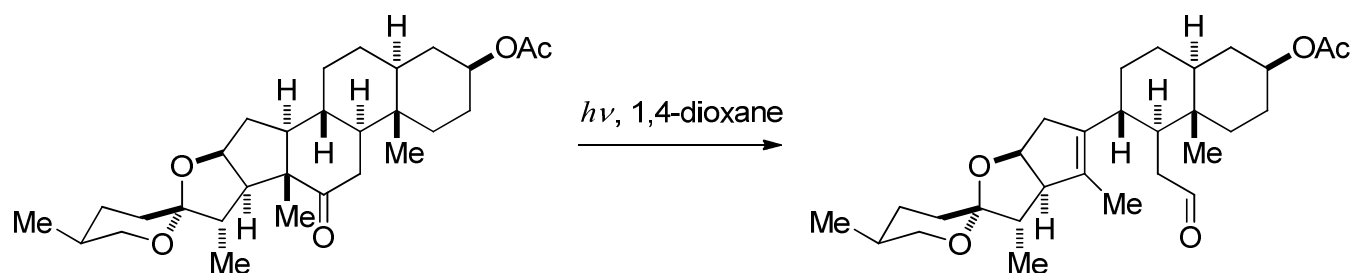
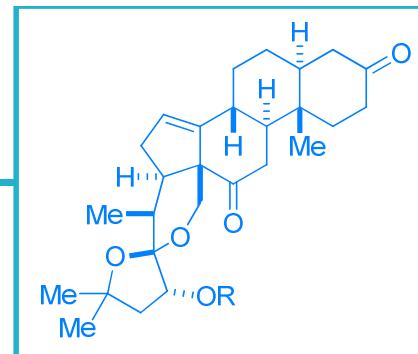
# Related Natural Products



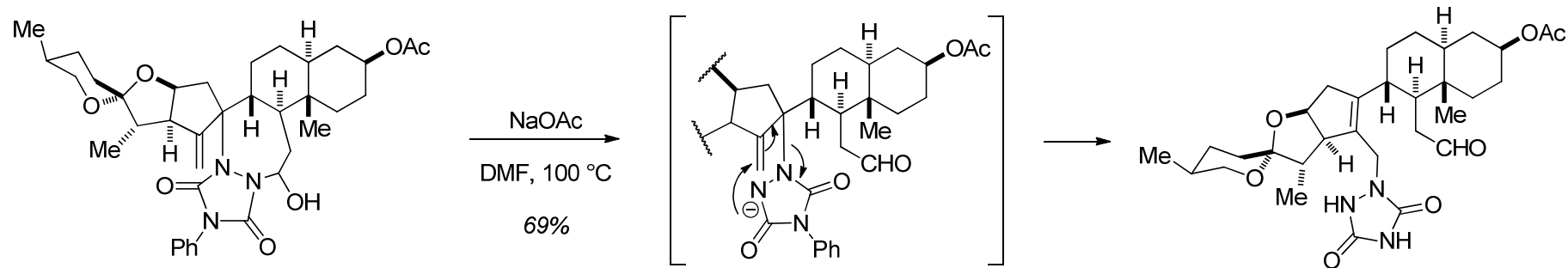
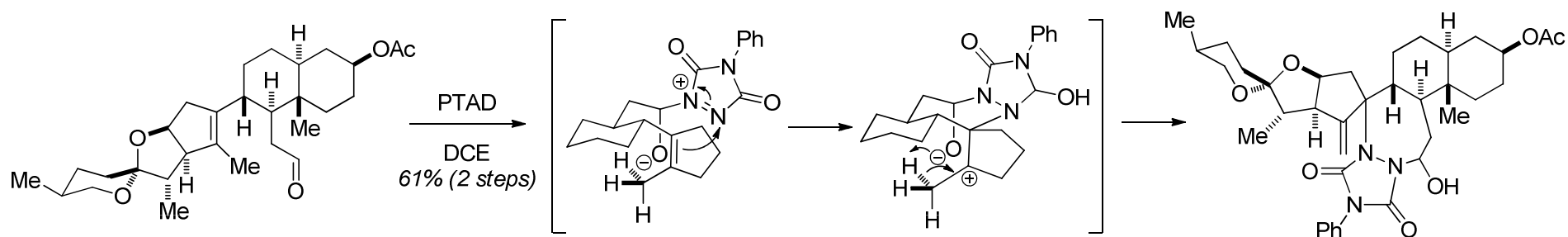
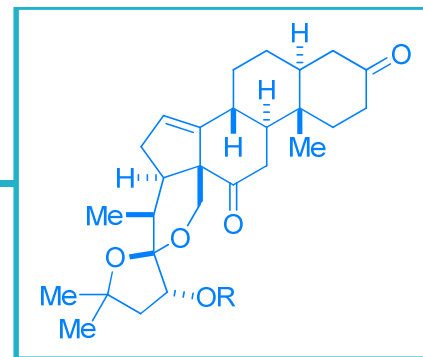
# Retrosynthetic Analysis- Shair



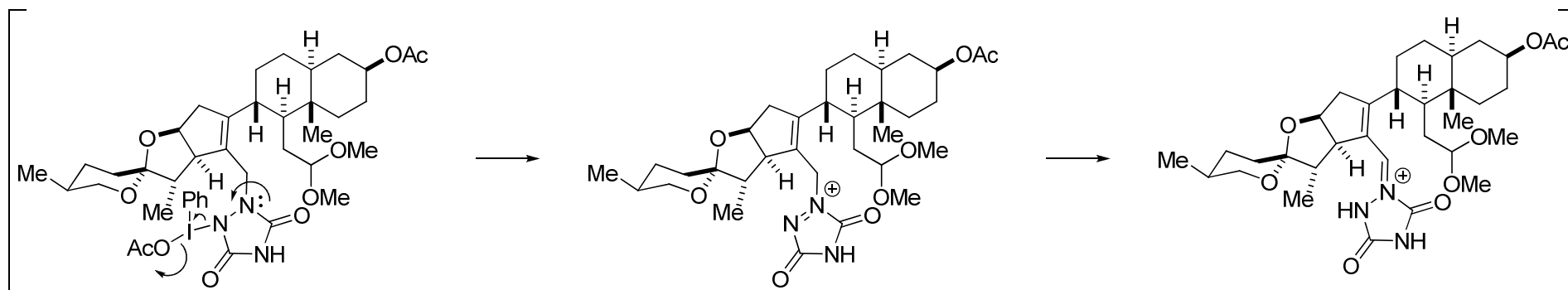
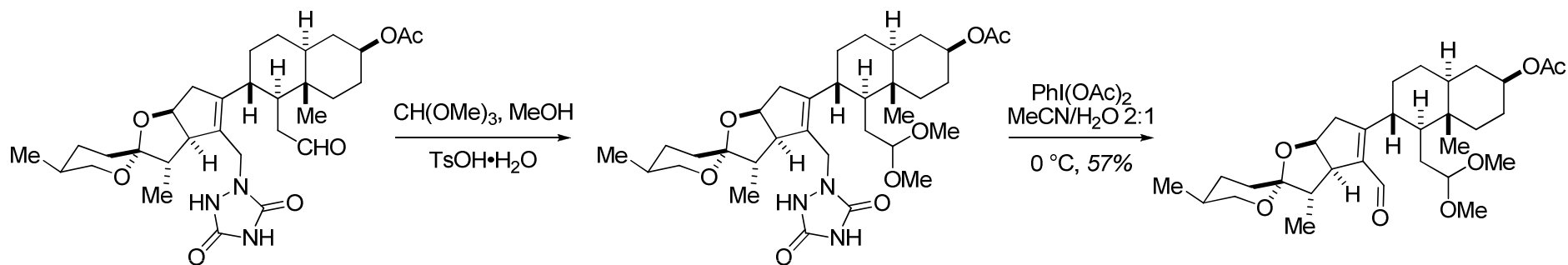
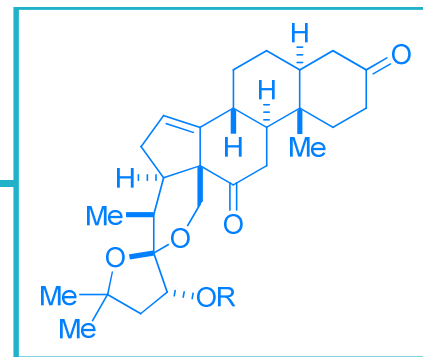
# Synthesis of the Western Half



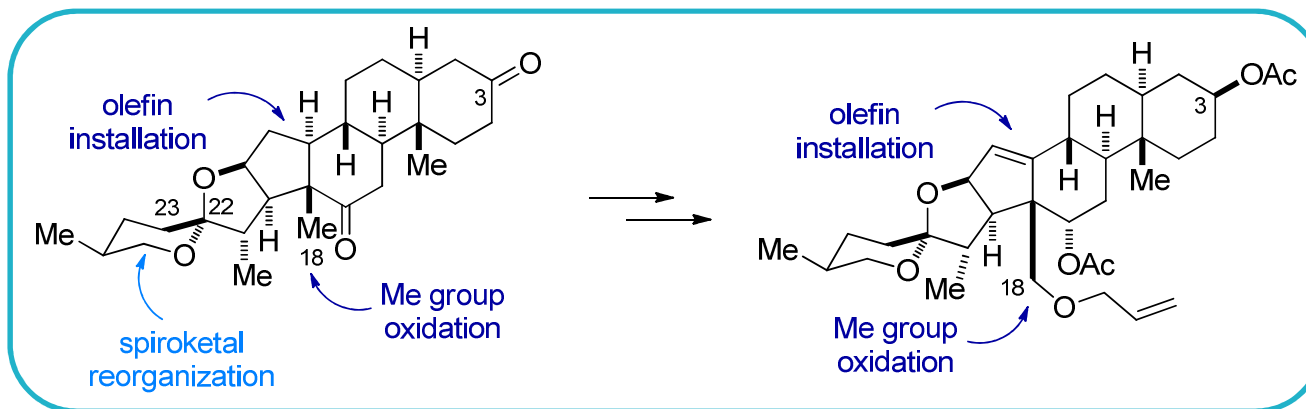
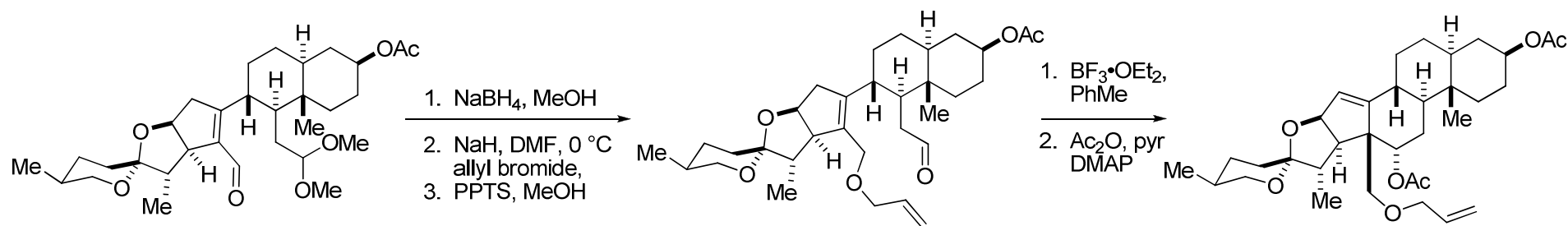
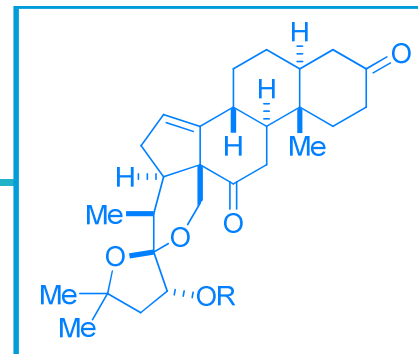
# Western Half (continued)



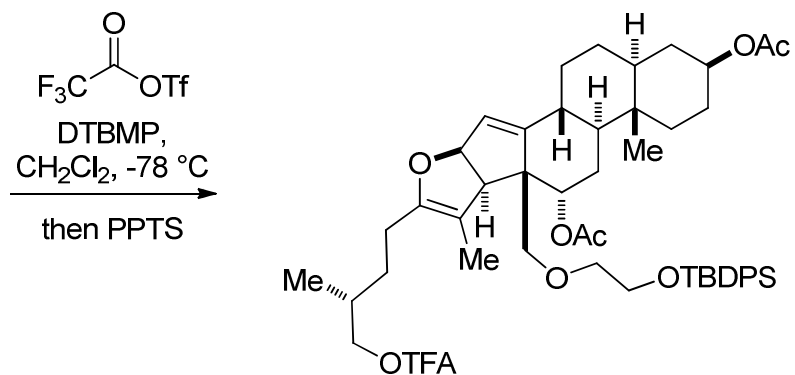
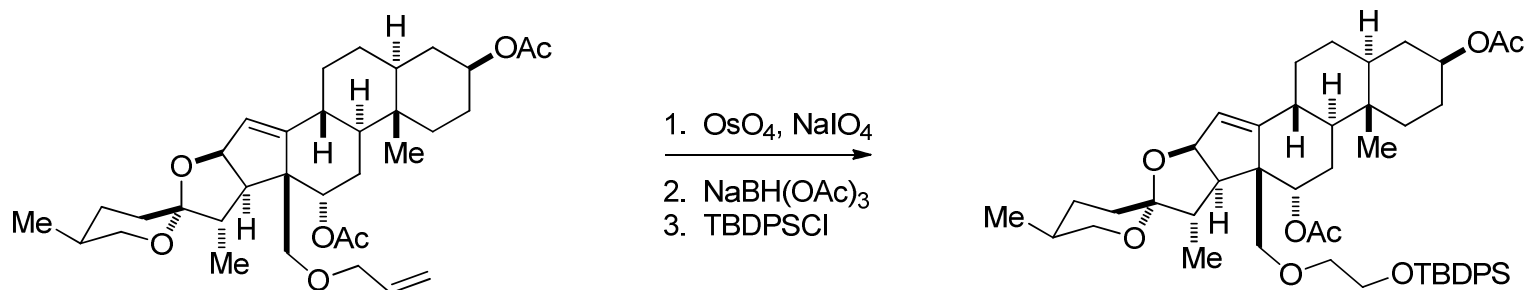
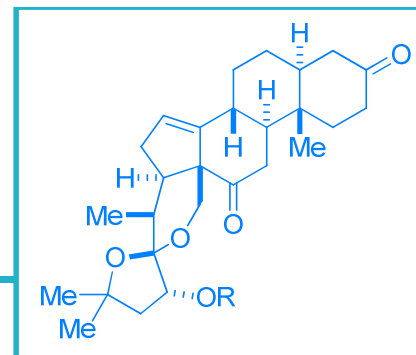
# Western Half (continued)



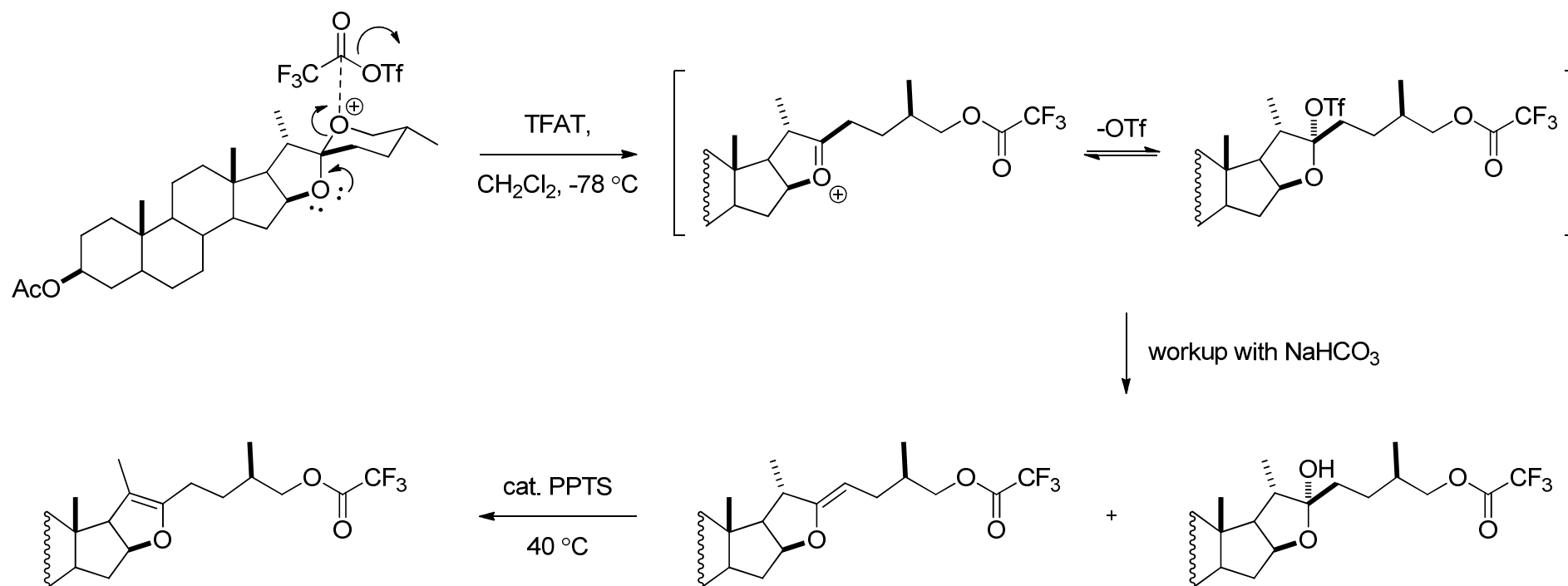
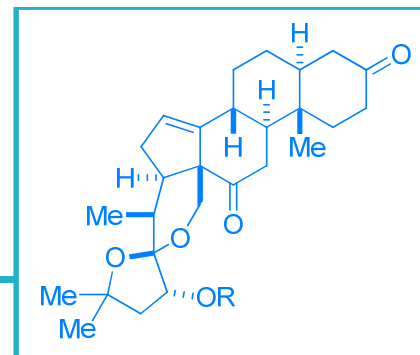
# Western Half (continued)



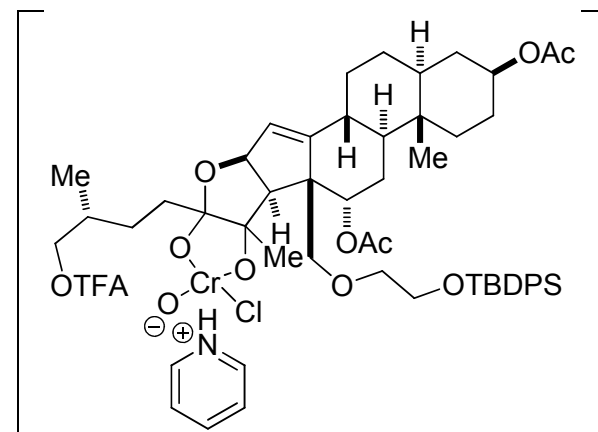
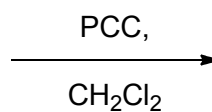
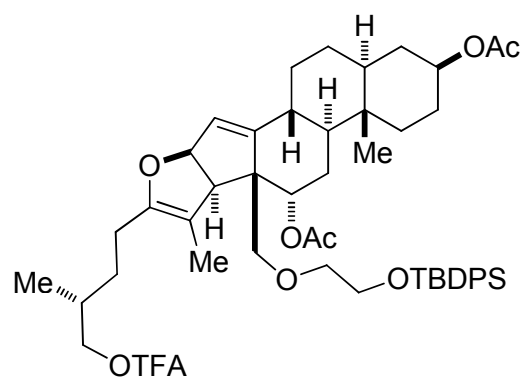
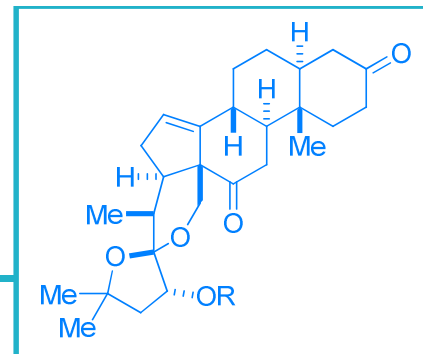
# Synthesis of the Western Half-Spiroketal Rearrangement



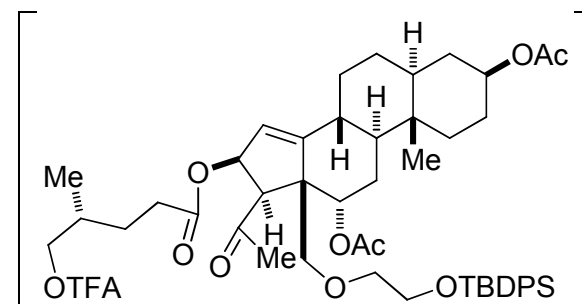
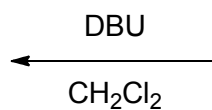
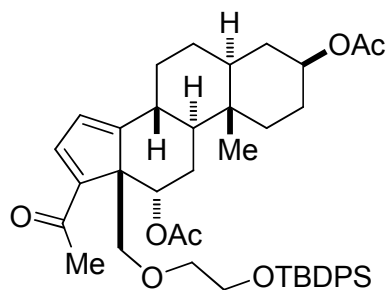
# Synthesis of the Western Half-Spiroketal Rearrangement



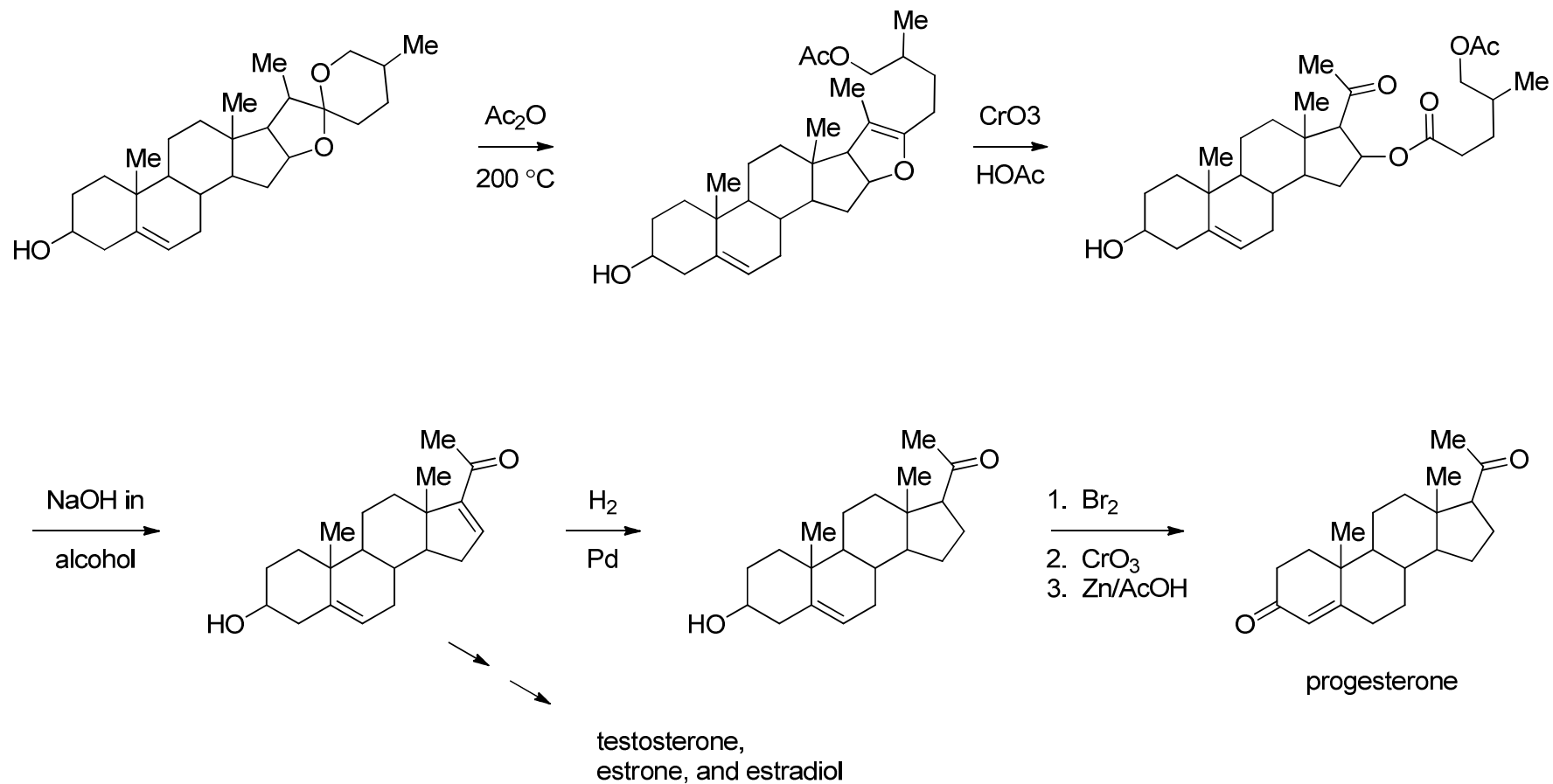
# Synthesis of the Western Half-Spiroketal Rearrangement



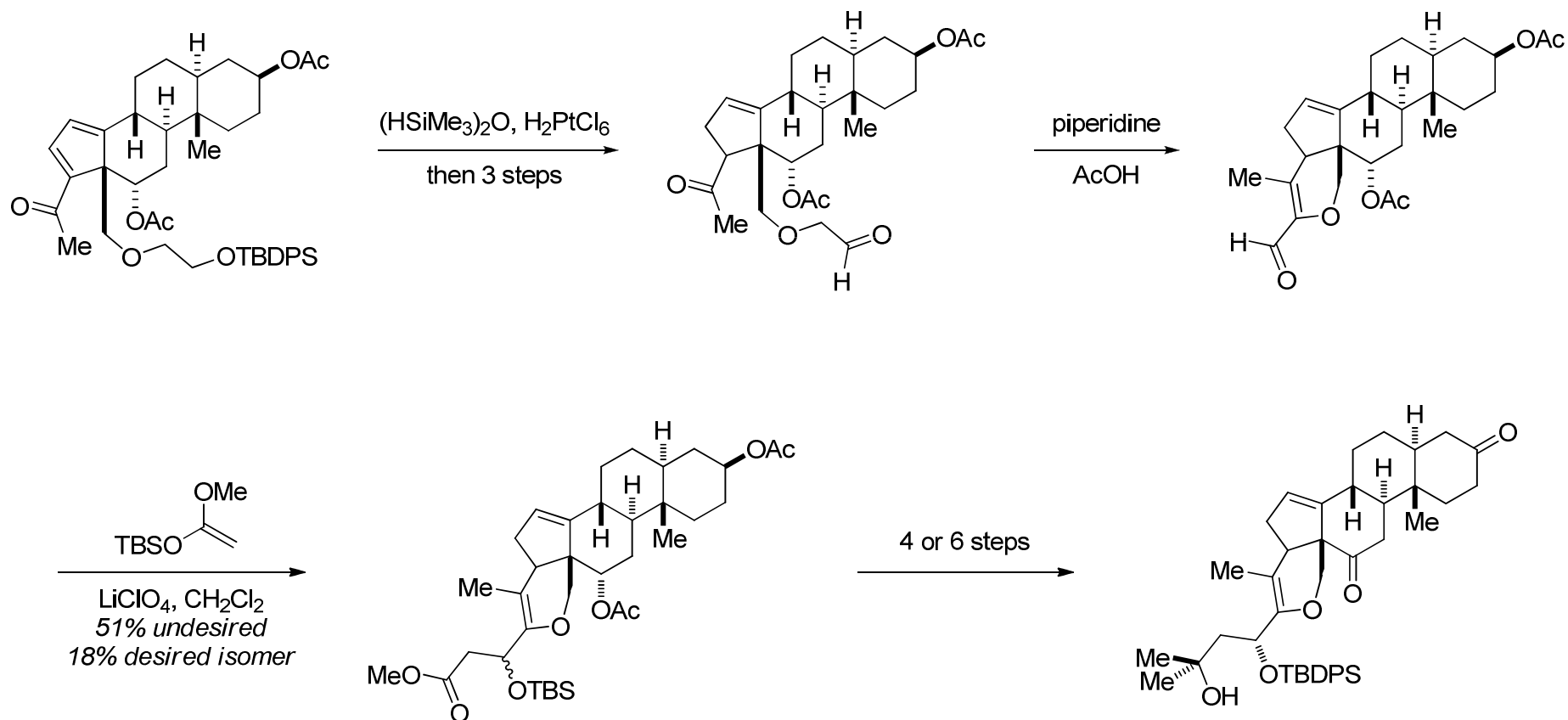
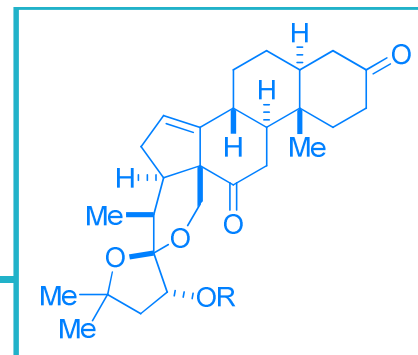
oxidative  
cleavage



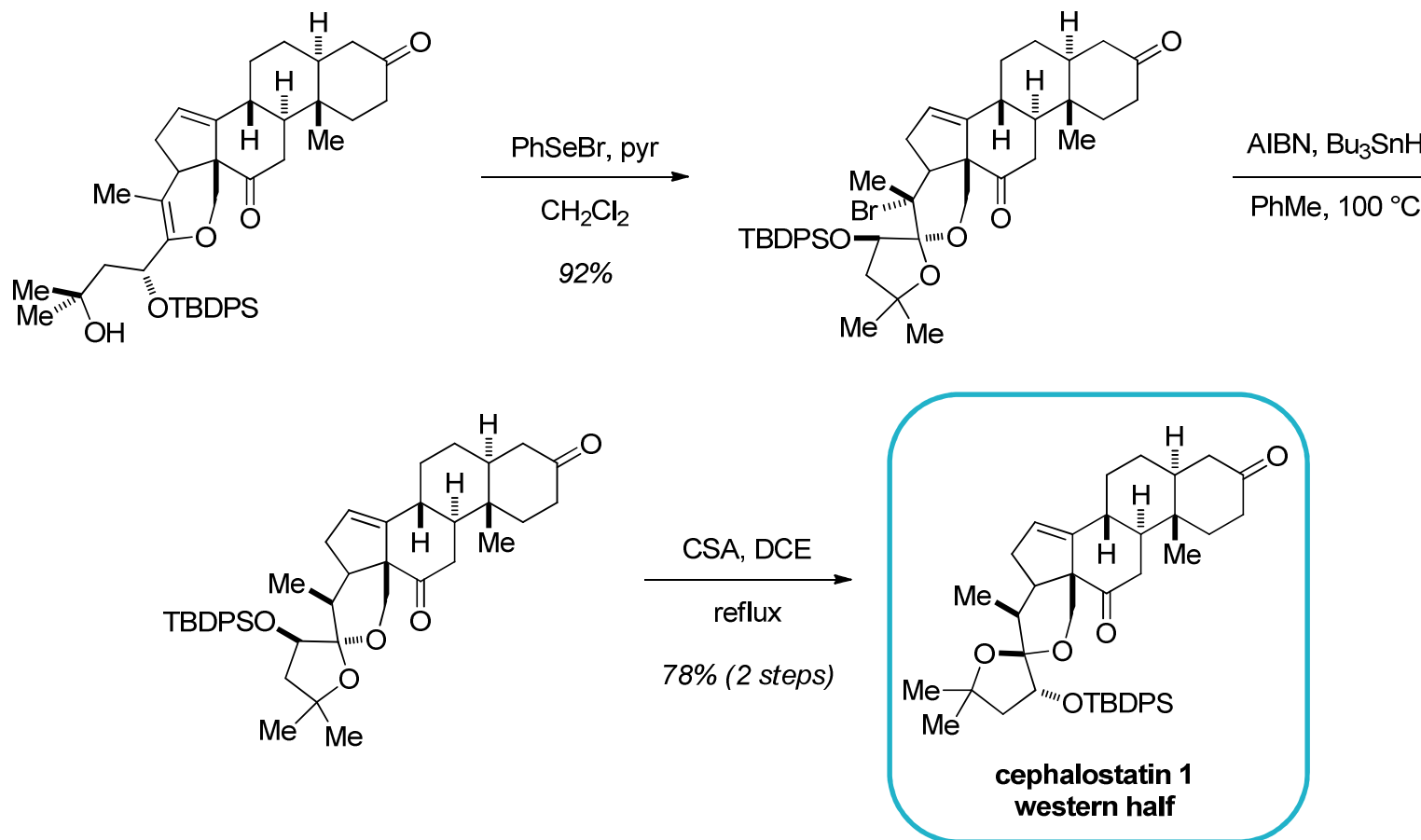
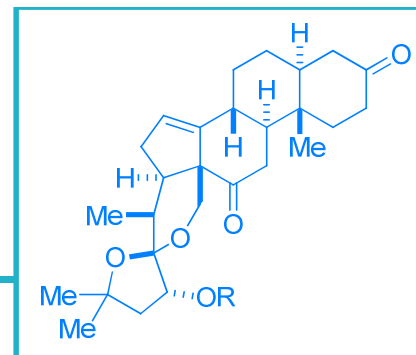
# The Marker Degradation



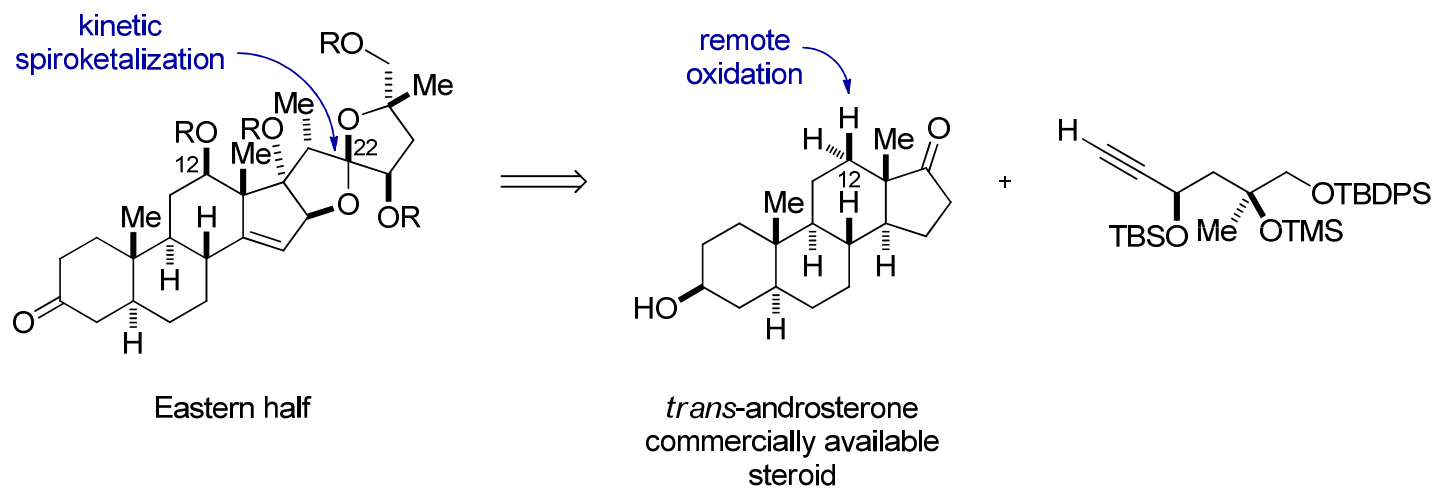
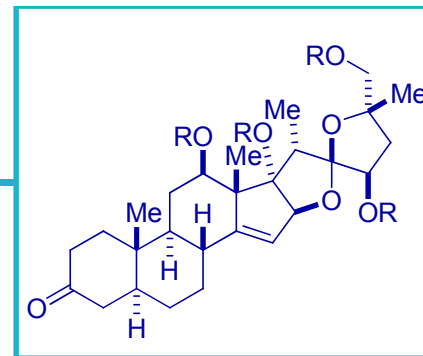
# Synthesis of the Western Half-Spiroketal Rearrangement



# Synthesis of the Western Half-Spiroketal Rearrangement



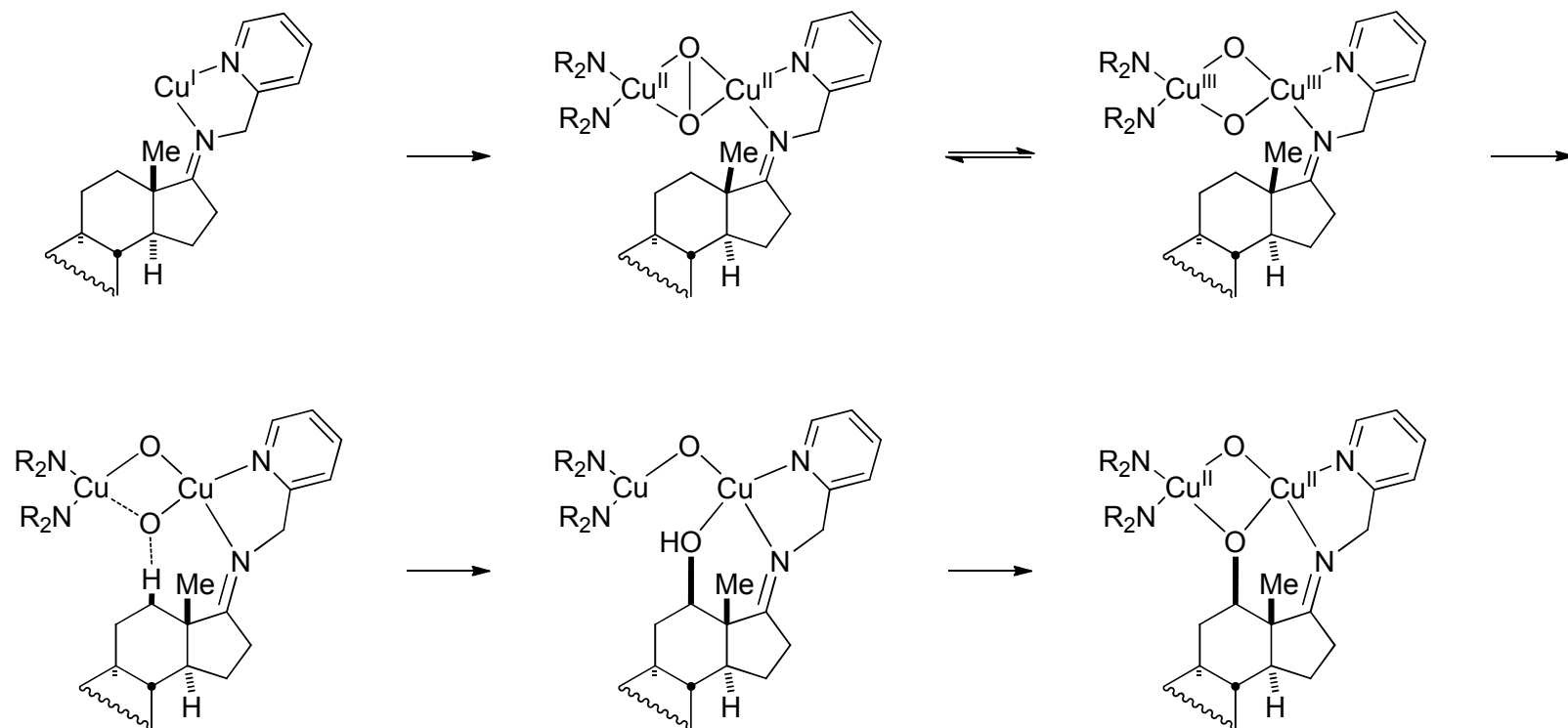
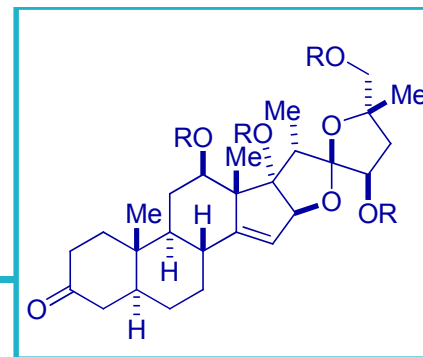
# Synthesis of the Eastern Half



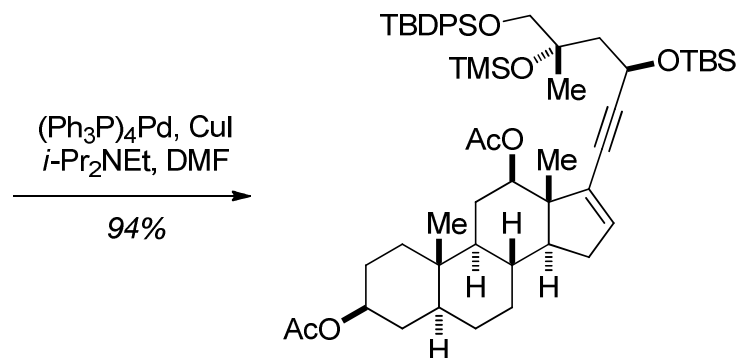
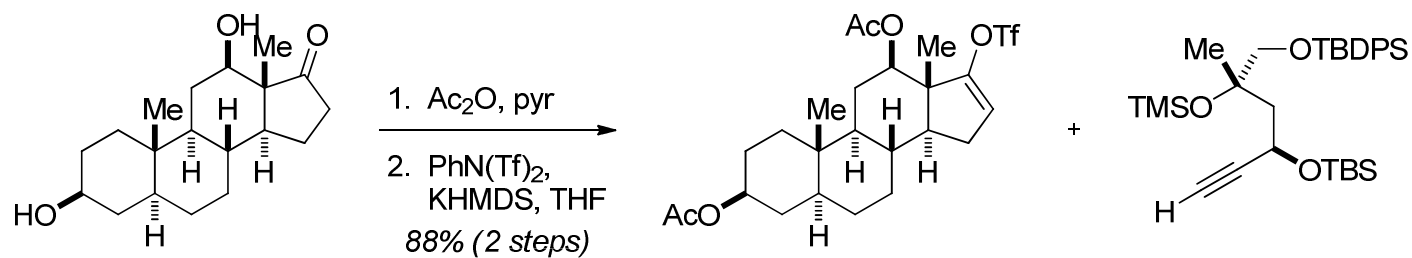
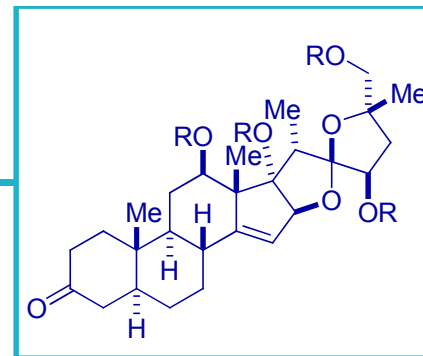




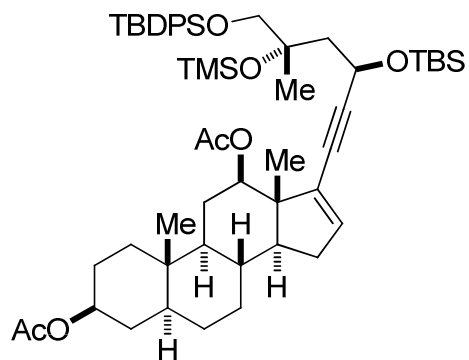
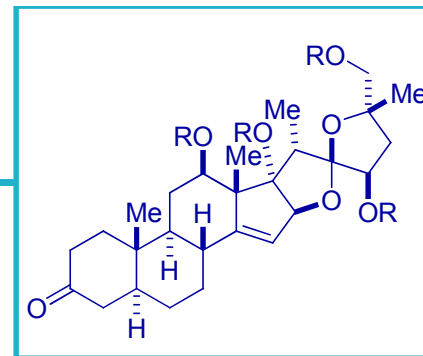
# Mechanism for Hydroxylation of Unactivated C-H Bond



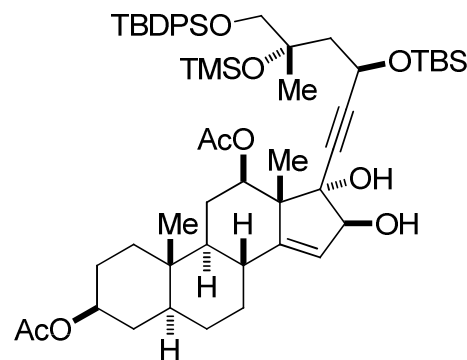
# Eastern Half (continued)



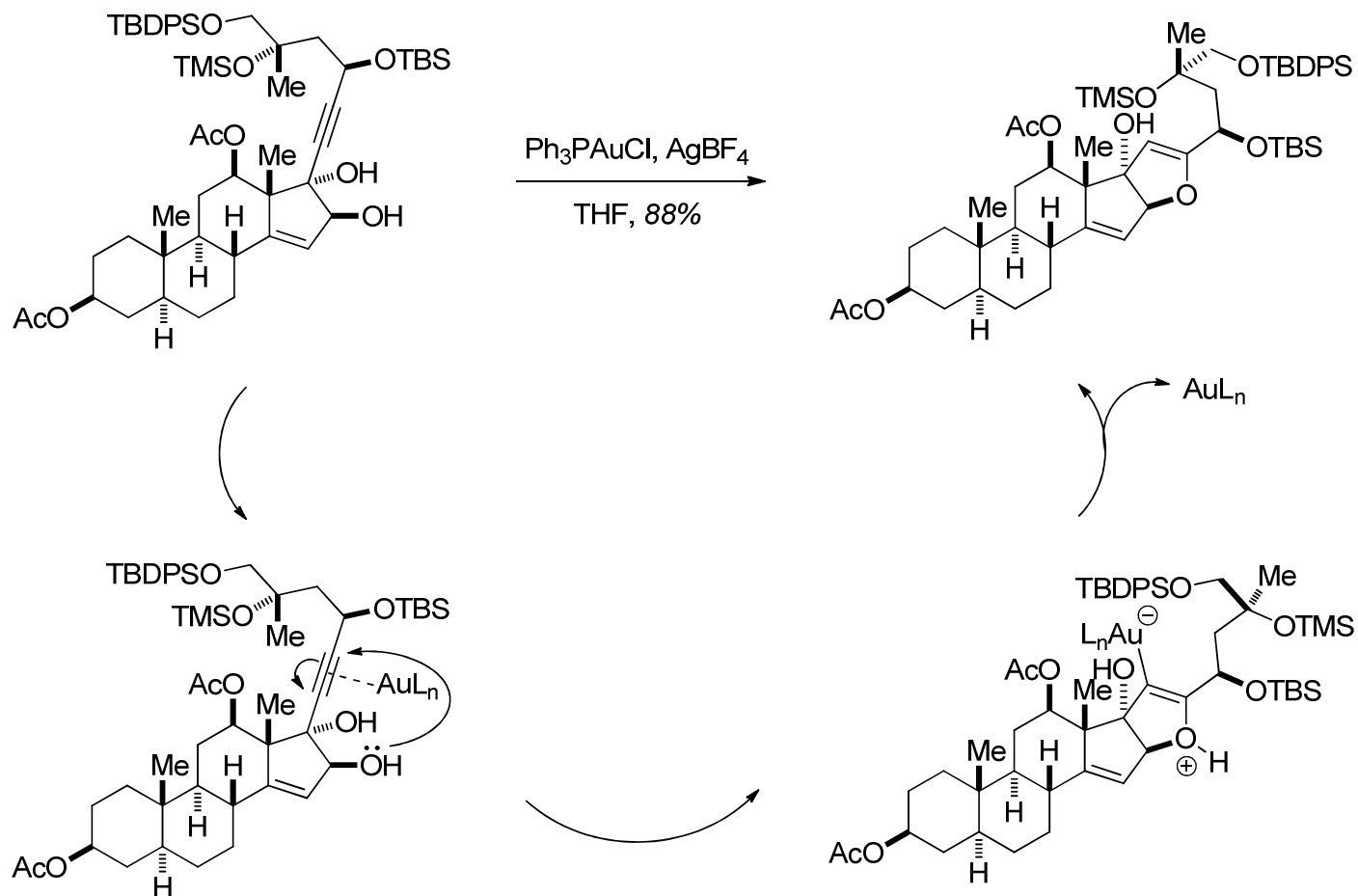
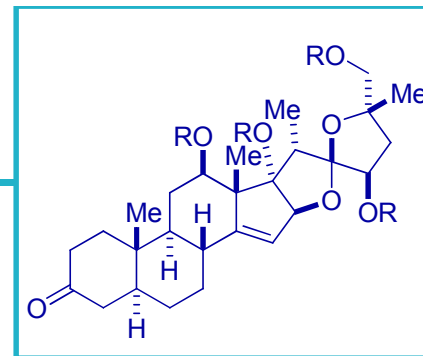
# Eastern Half (continued)



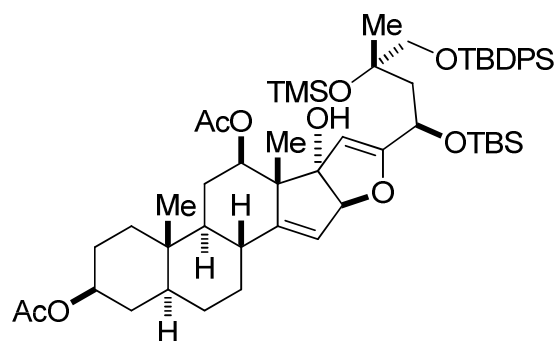
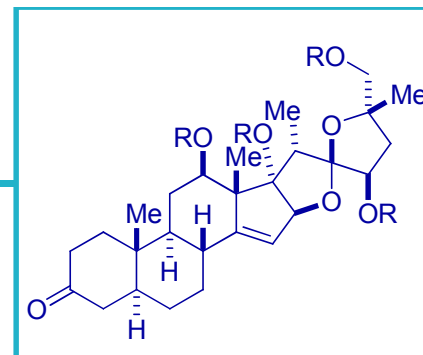
1. Sharpless dihydroxylation
  2.  $(\text{PhSeO})_2\text{O}$ ,  $\text{K}_2\text{CO}_3$   
PhMe, 110 °C
  3.  $\text{NaBH}(\text{OAc})_3$
- 34% (3 steps)



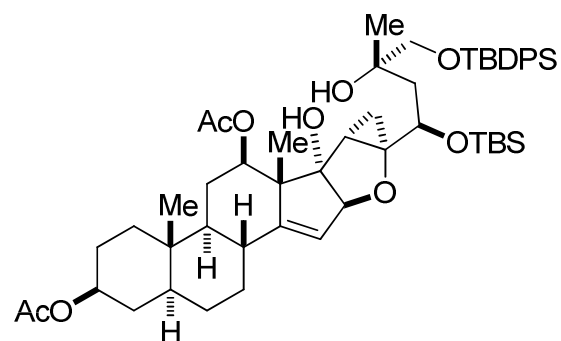
# Eastern Half (continued)



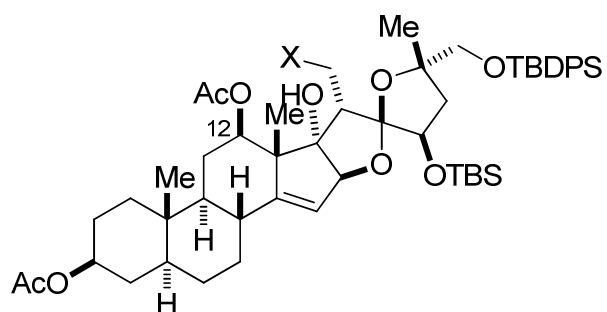
# Eastern Half (continued)



1.  $\text{CH}_2\text{I}_2$ ,  $\text{Et}_2\text{Zn}$   
PhMe,  $0^\circ\text{C}$
2. PPTS,  $\text{CH}_2\text{Cl}_2$   
MeOH

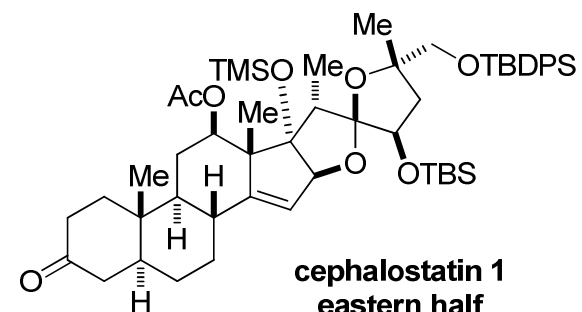


Zeise's dimer:  
 $[\{\eta^2\text{-C}_2\text{H}_4\}\text{PtCl}_2]_2$   
 100%, 13:1 *undesired*  
 or  
 NBS, THF,  $-10^\circ\text{C}$   
 5:1 *desired*

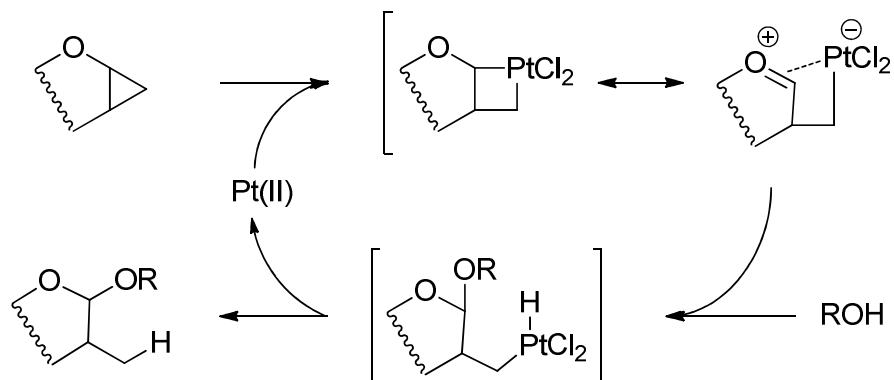
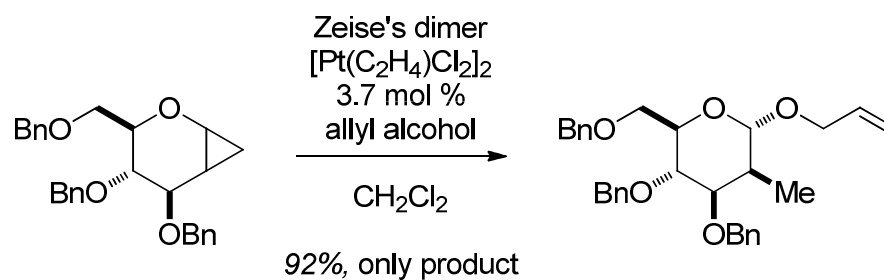
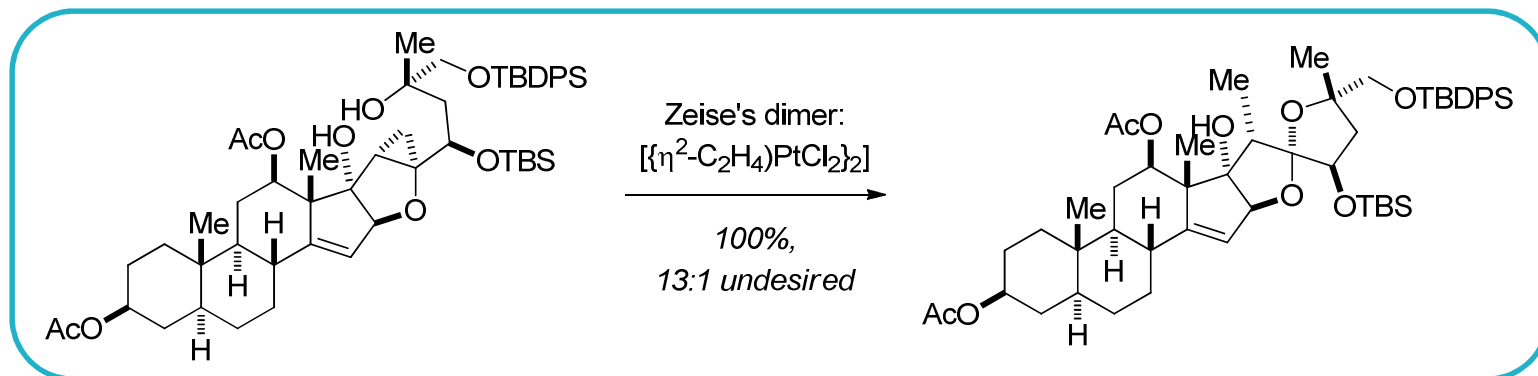


1. AIBN,  $\text{Bu}_3\text{SnH}$   
PhMe,  $110^\circ\text{C}$
2. TMSOTf, pyr (neat)
3.  $\text{KHCO}_3$ , MeOH,  $65^\circ\text{C}$
4.  $\text{HCrO}_4$ ,  $\text{Et}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$

X = H for Zeise's dimer  
 X = Br with NBS



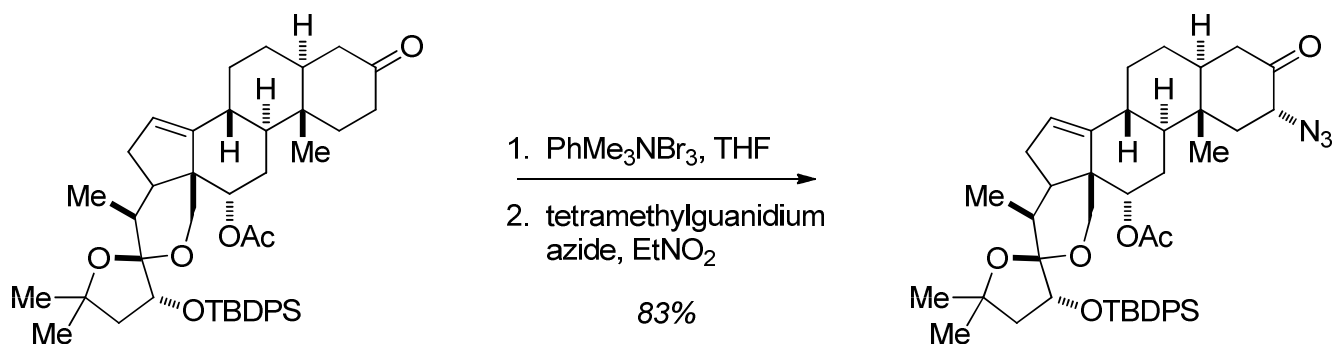
# Zeise's Dimer



*JACS*, **2010**, *132*, 275.; *JACS*, **1998**, *120*, 12137.

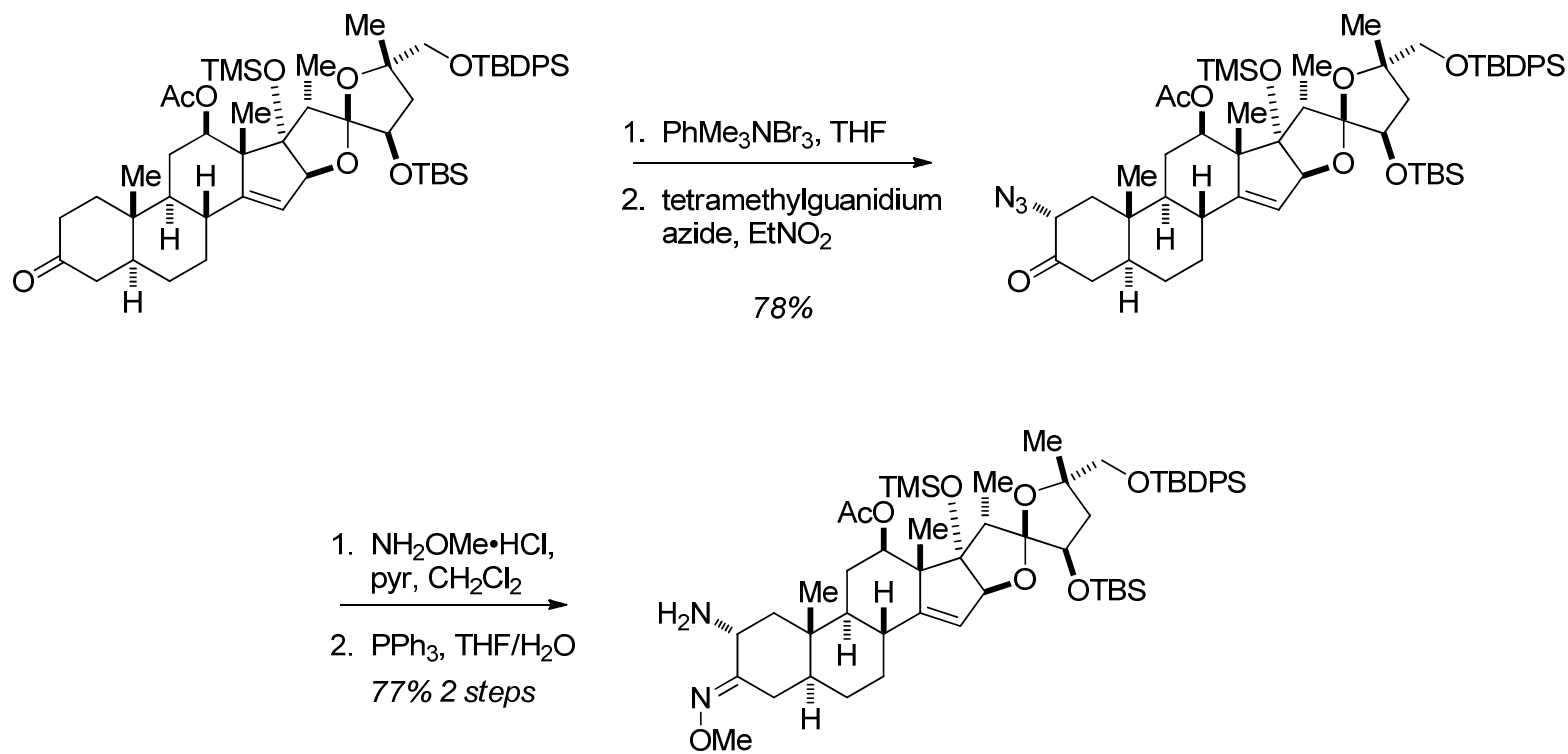
# Endgame-Preparing to Couple Fragments

Western Half:

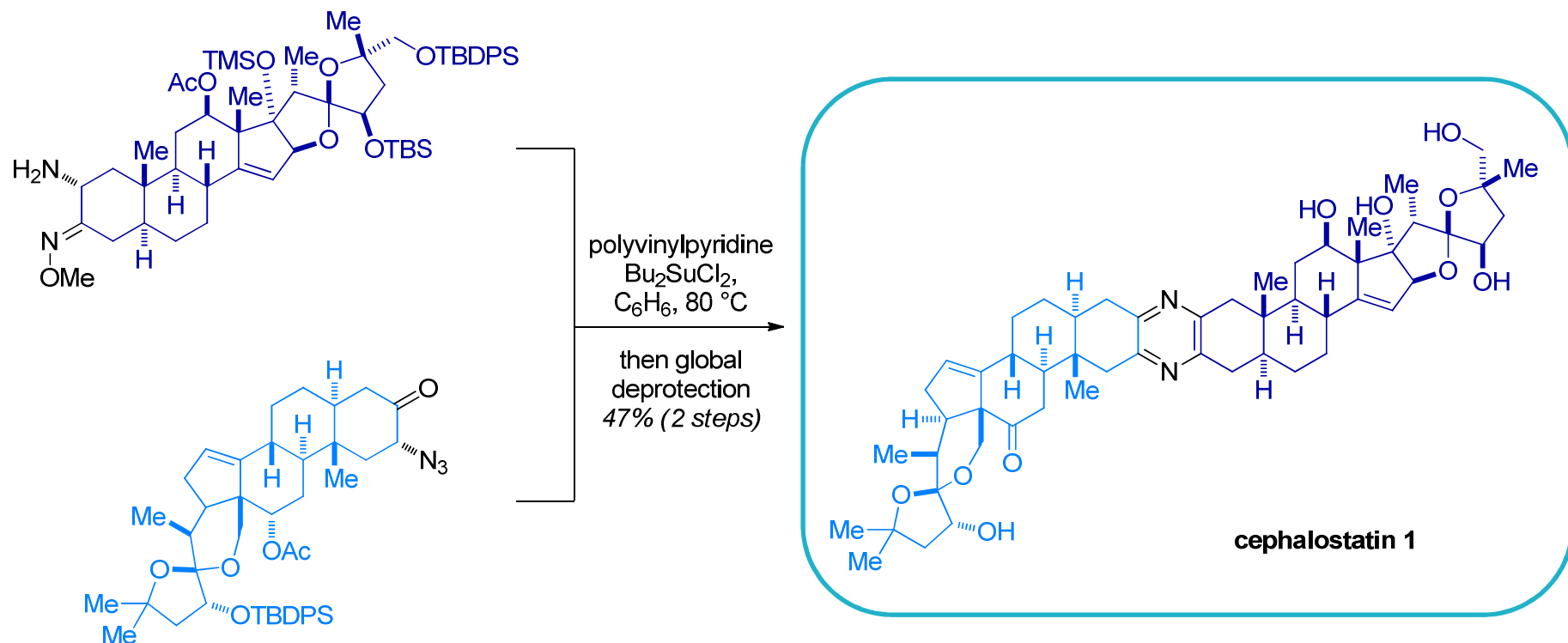


# Endgame-Preparing to Couple Fragments

Eastern Half:



# Endgame-Coupling the Fragments



# Mechanism for Formation of Unsymmetrical Pyrazines

