Total synthesis of Highly Strained 4β-Acetoxyprobotryane-9β,15α-diol

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4β-Acetoxyprobotryane-9β,15α-diol (**6**) was isolated from a culture of *Botrytis cinerea*.

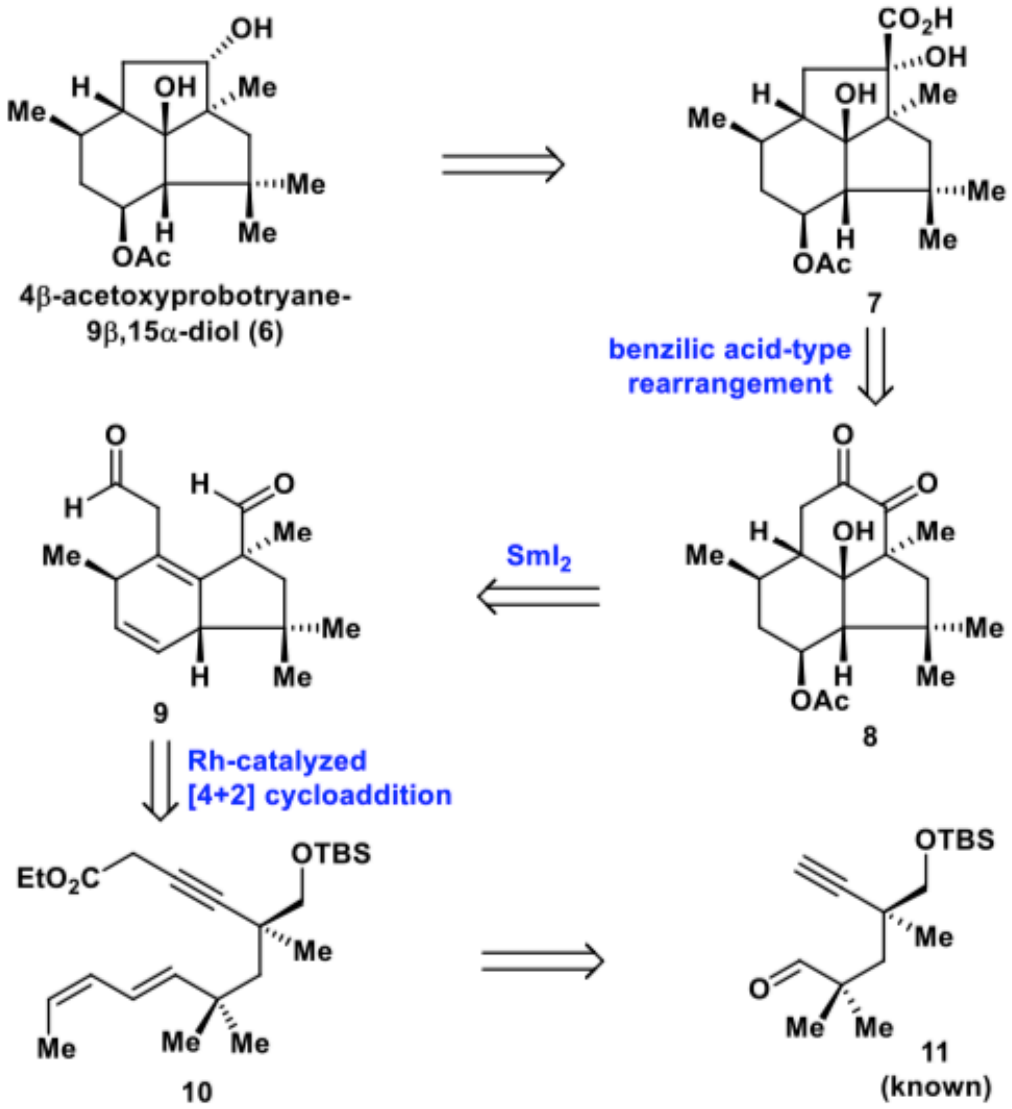
- Here is the first and asymmetric total synthesis.
- This work represents the first example of a benzilic acid type rearrangement to construct the highly strained *trans*-fused bicyclo[3.3.0] octane ring system.

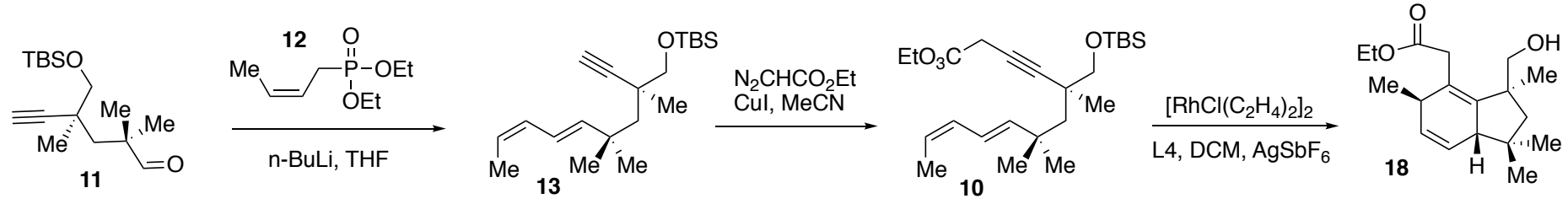
4β-acetoxyprobotryane-9β,15α-diol

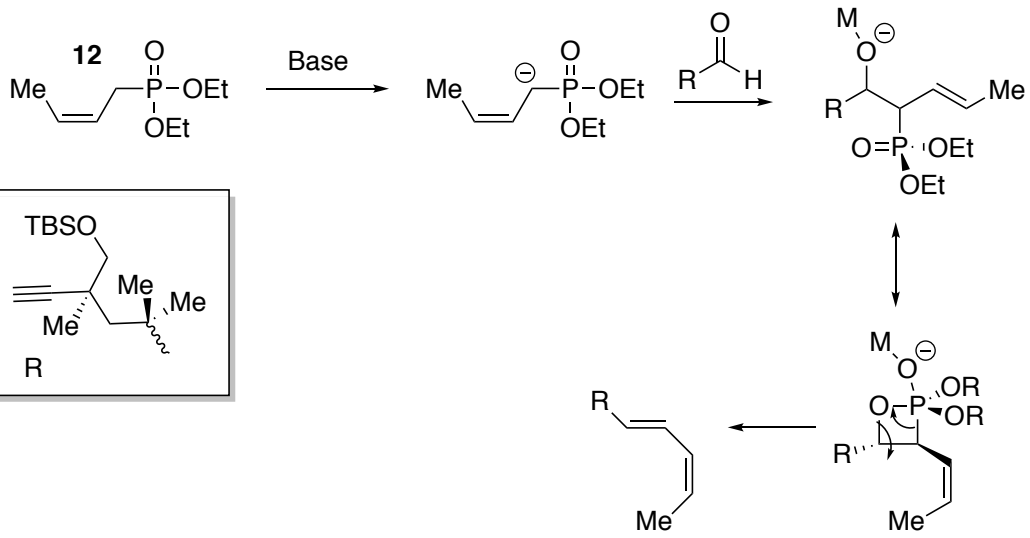
Structural features:

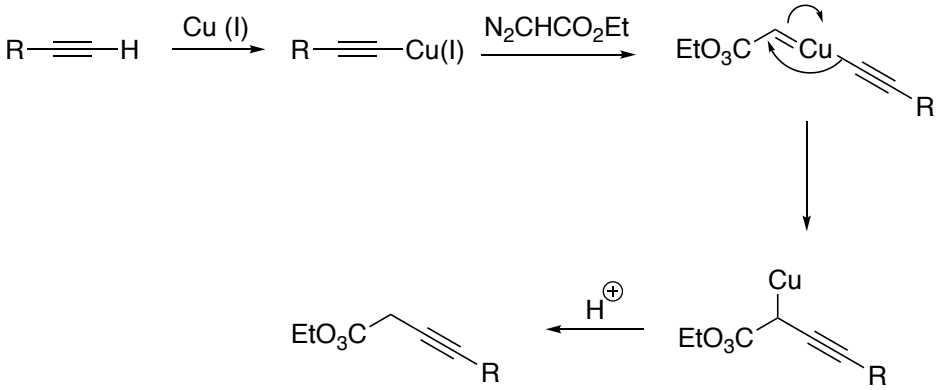
- **Strained *trans* bicyclo[3.3.0]octane**
- **7 Contiguous stereocenters:**
  two vicinal quaternary
- **This work:**
  First total synthesis

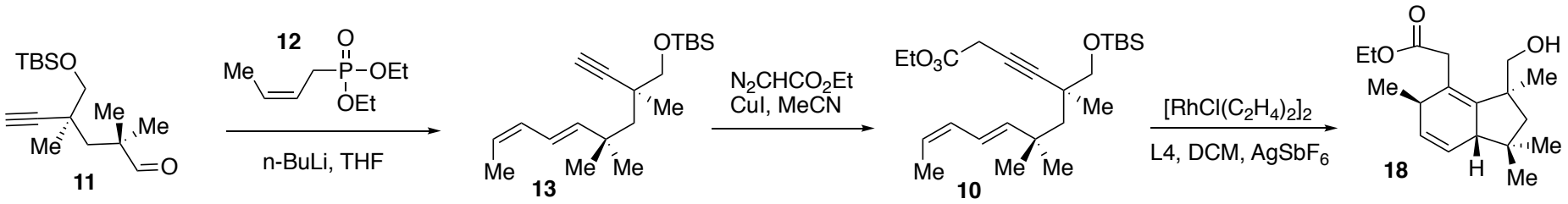
Retrosynthetic analysis



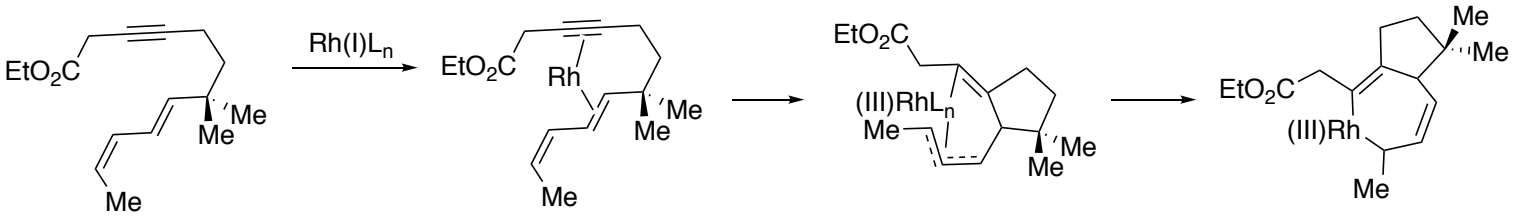

TBSO
Me
Me
Me
Me
O
11
12
O
P
OEt
OEt
Me
n-BuLi, THF
OTBS
Me
Me
Me
Me
13
N2CHCO2Et
CuI, MeCN
EtO3C
OTBS
Me
Me
Me
Me
10
[RhCl(C2H4)2]2
L4, DCM, AgSbF6
O
EtO
OH
Me
Me
Me
H
Me
18

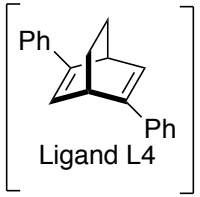

12
Me
O
P
OEt
OEt
Base
Me
O
P
OEt
OEt
R
O
H
M
O
R
Me
O=P
OEt
OEt
TBSO
Me
Me
Me
R
M
O
O
P
OR
OR
R
Me
R
Me


R
H
Cu (I)
R
Cu(I)
N2CHCO2Et
EtO3C
Cu
R
Cu
EtO3C
R
H
EtO3C
R

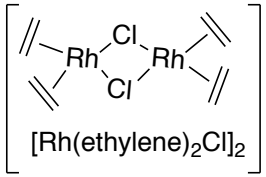


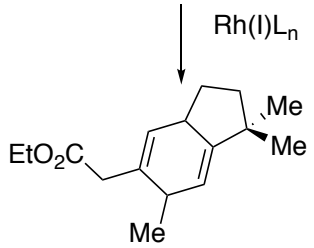
Intramolecular [4+2] cycloaddition

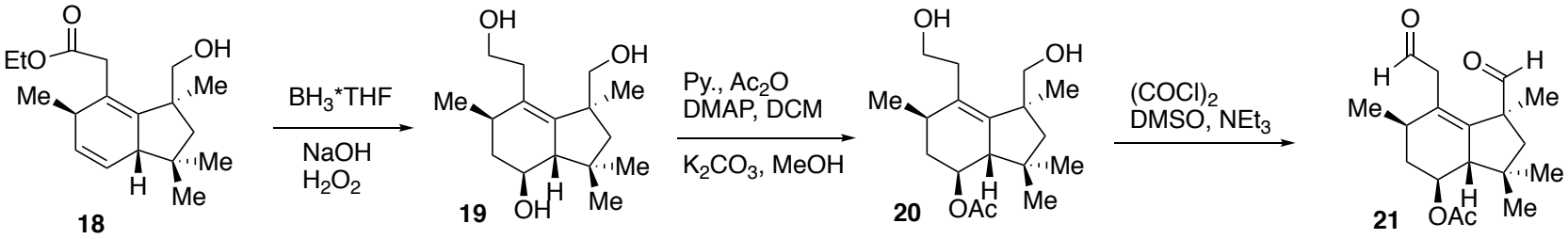


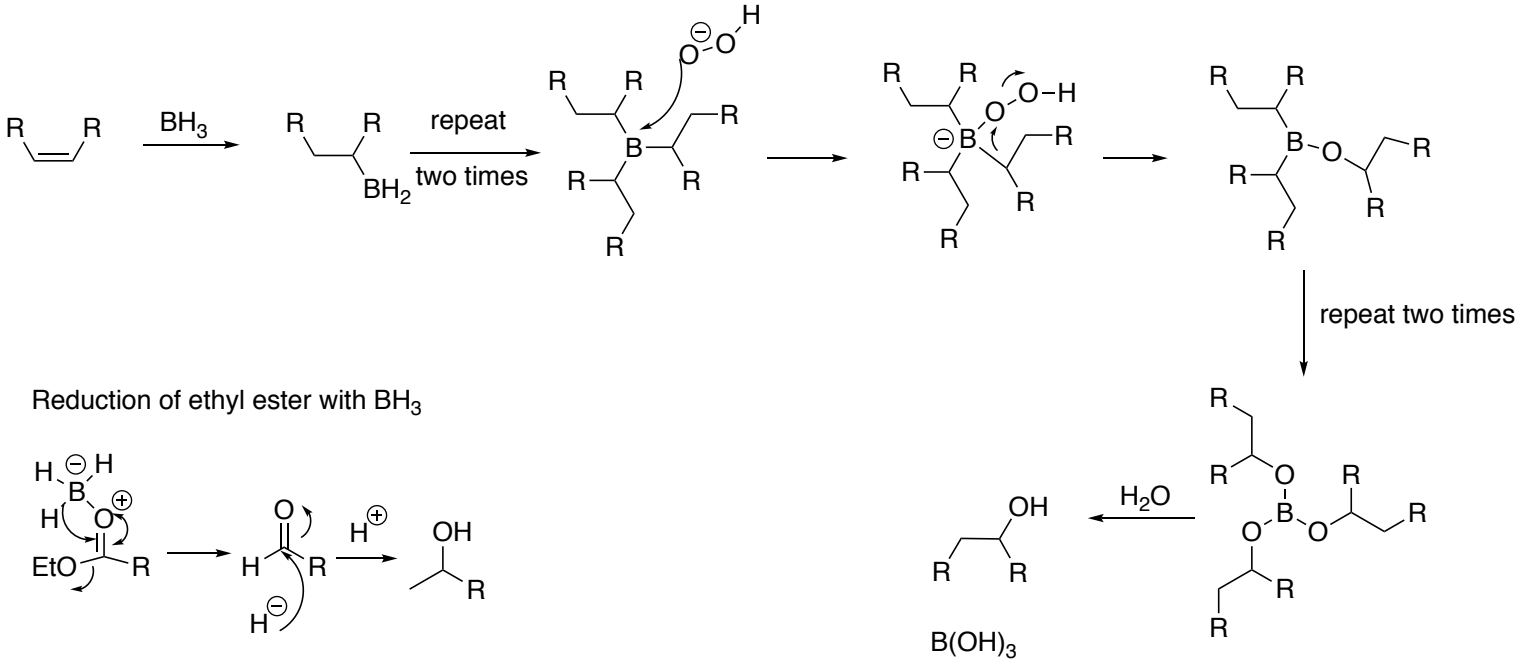


(*S,S*)-Ph-Bod (L4)

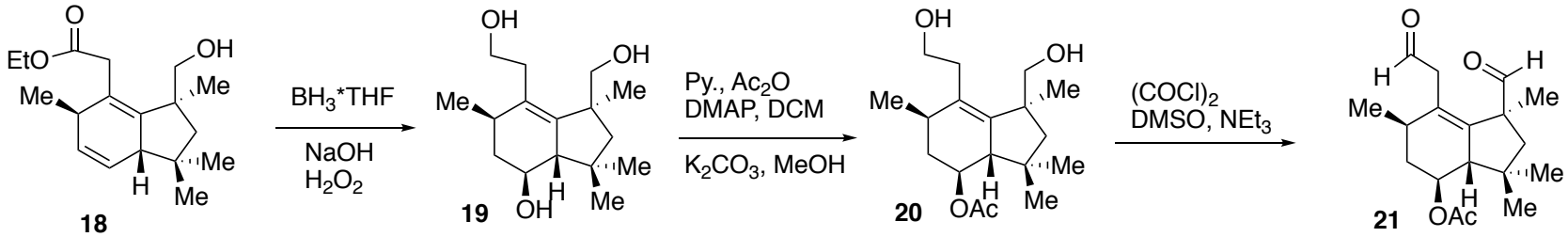




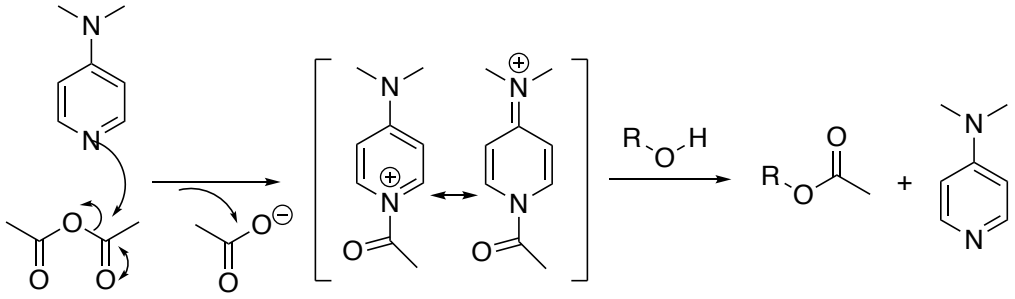


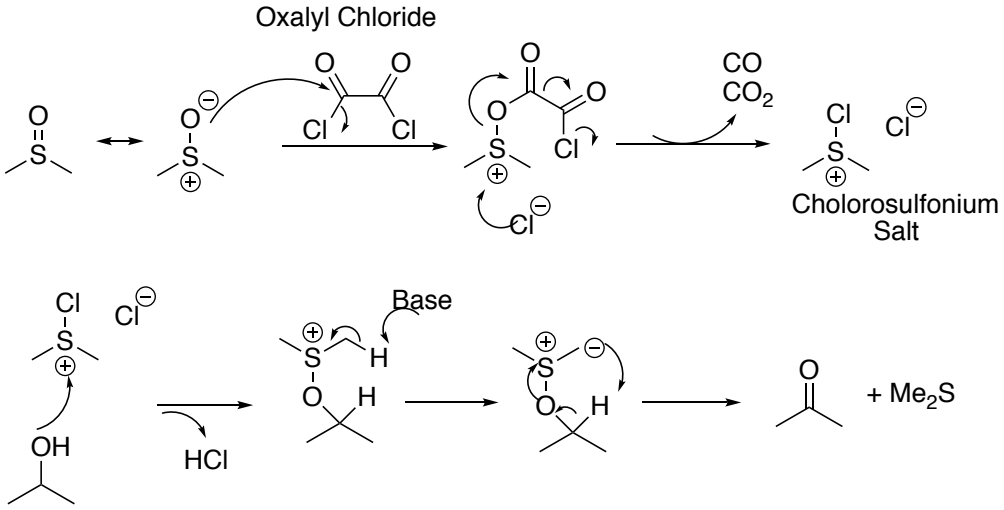


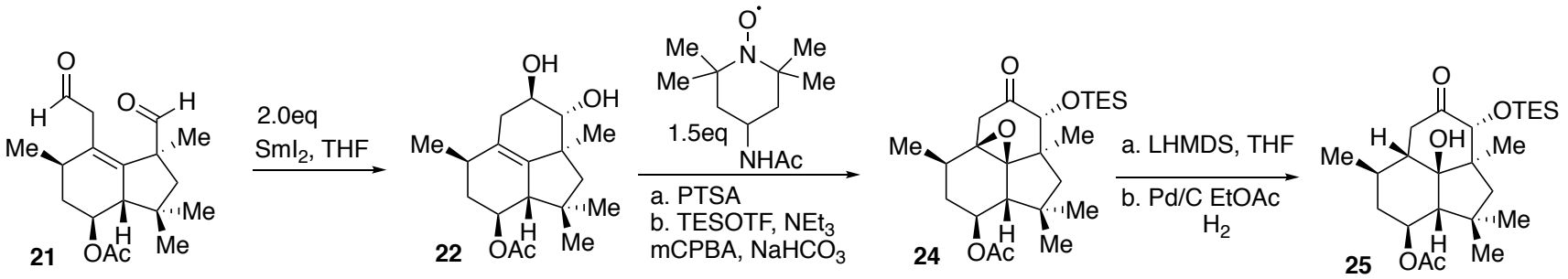
Reduction of ethyl ester with BH_3



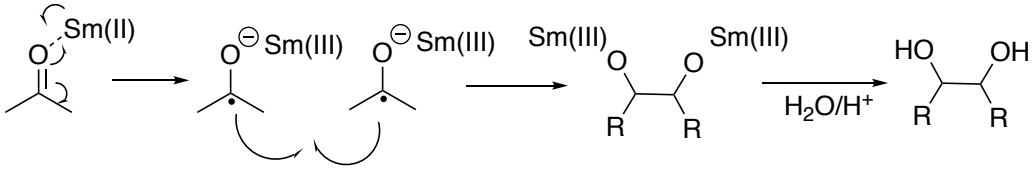
triacetylation followed by selective deacetylation in a one-pot sequence



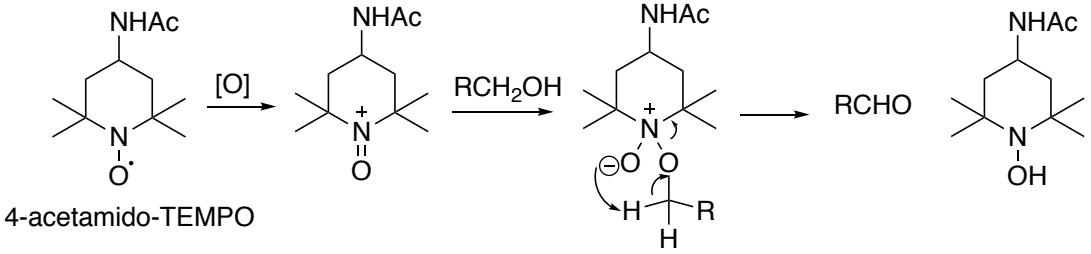


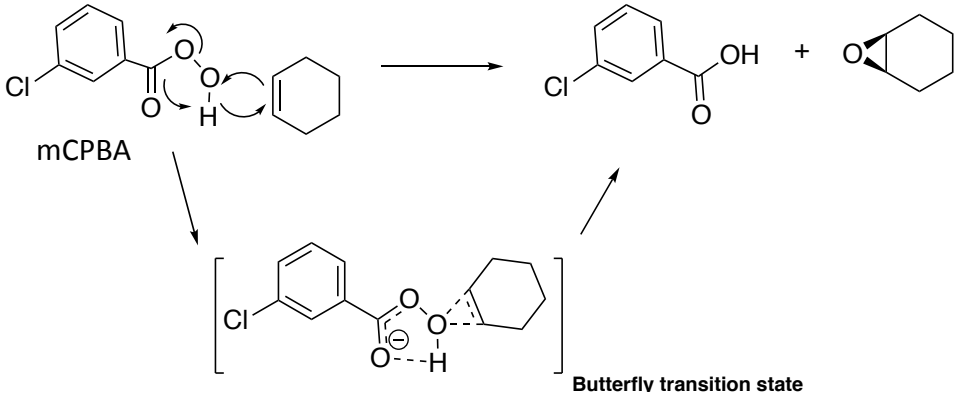


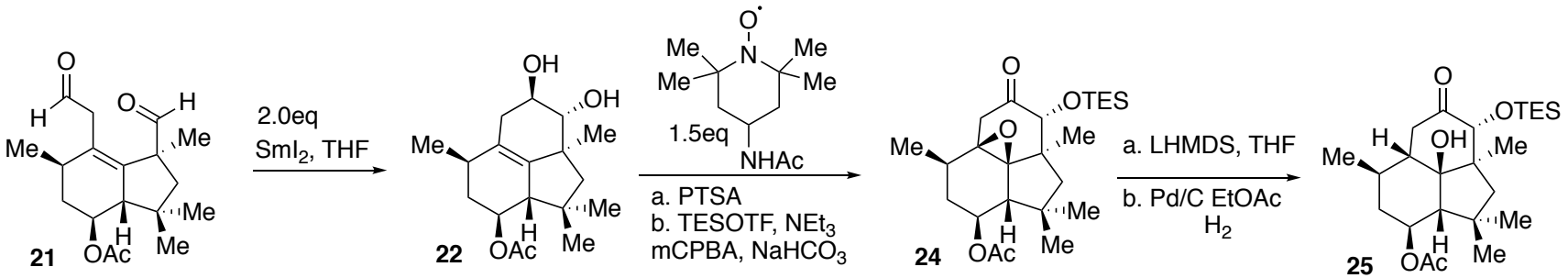
Reductive pinacol coupling

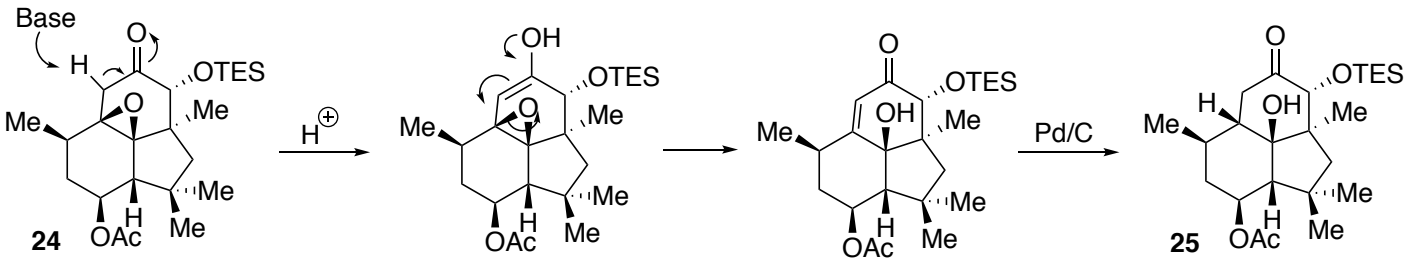


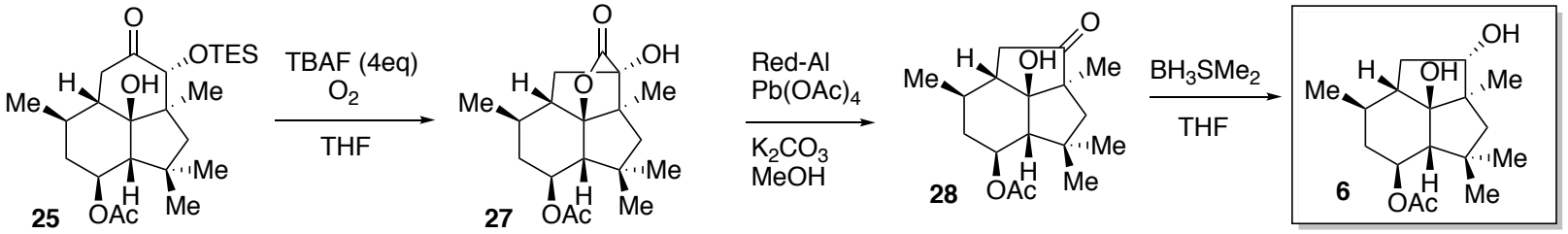
Oxidation of less hindered hydroxy group

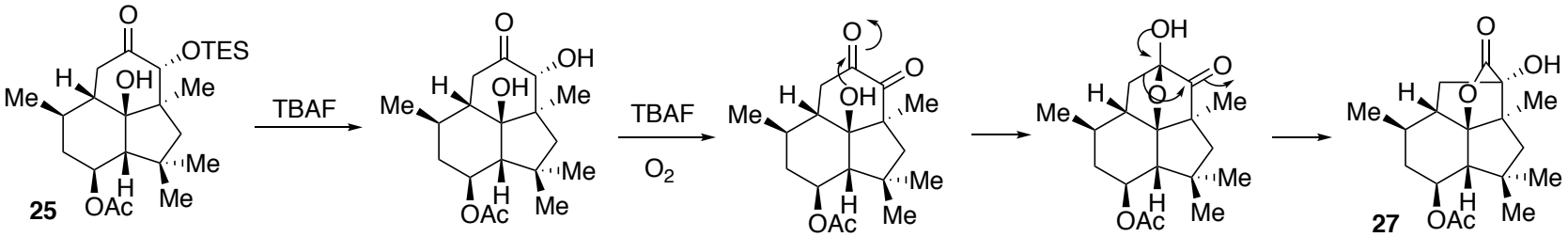




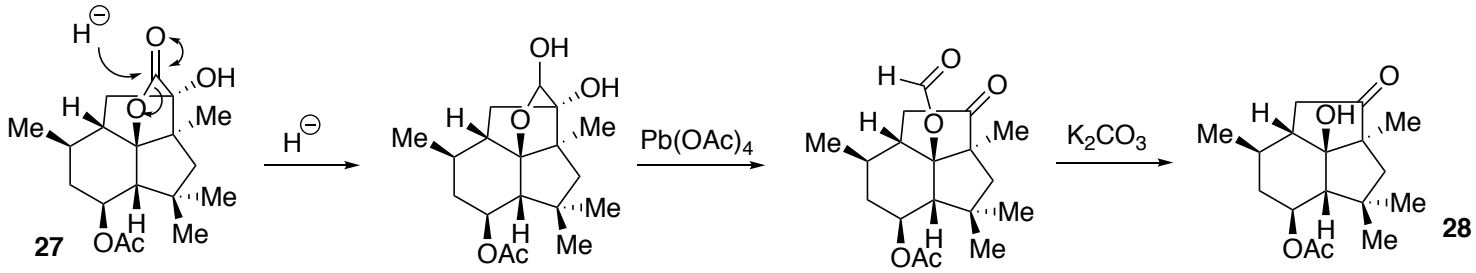

21
2.0eq
SmI2, THF
22
1.5eq
NHAc
a. PTSA
b. TESOTF, NEt3
mCPBA, NaHCO3
24
a. LHMDS, THF
b. Pd/C EtOAc
H2
25


Base
24
Pd/C
25





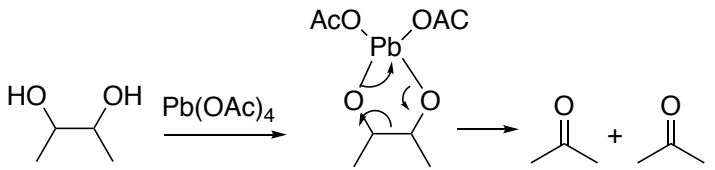
Benzillic acid-type reaarangement

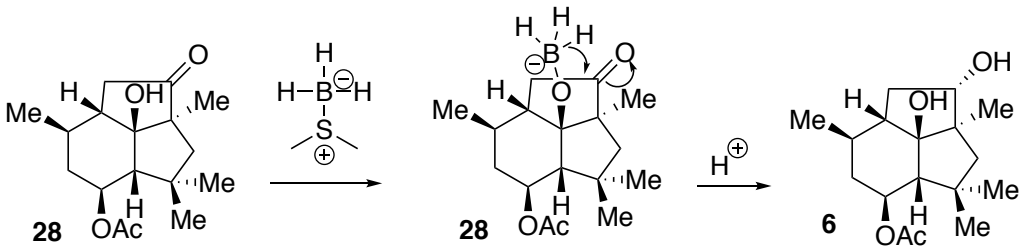


Formaion of Hemiacetal

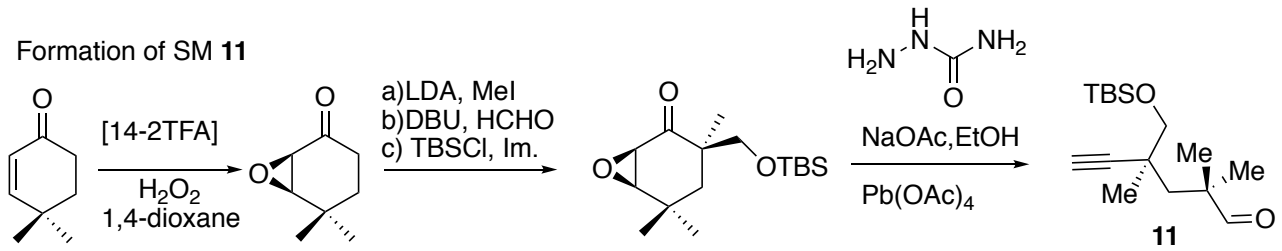
removal of fromyl group with K_2CO_3

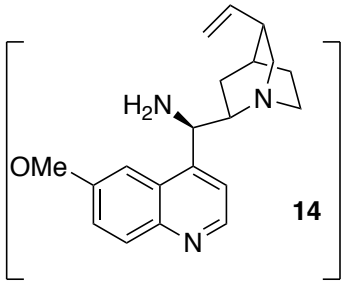
Oxidative cleavge with $Pb(OAc)_4$





Formation of SM **11**





Eschenmoser fragmentation (Synthesis of acyclic alkynals)