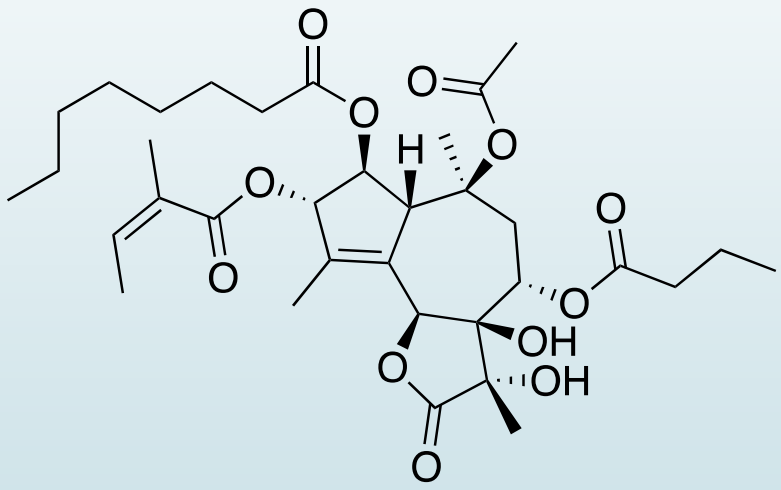
Total Synthesis of Thapsigargin

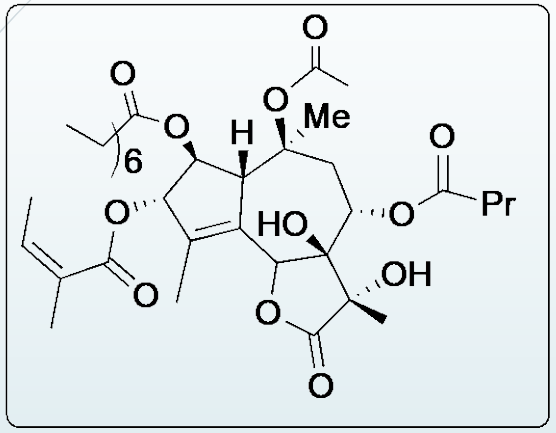
Aria Vahdani



Thapsigargin

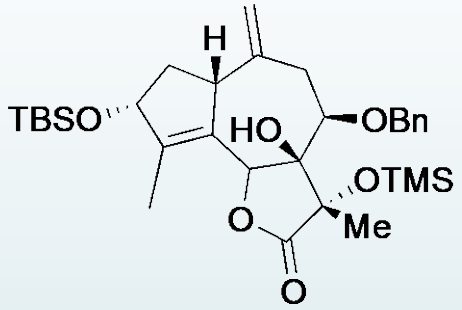
Thapsia Gargancia

Retrosynthesis



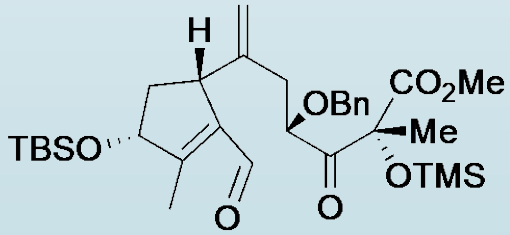
Thapsigargin

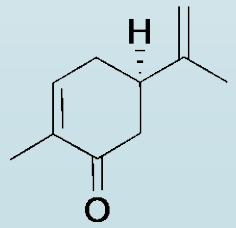
FGI



5 Steps

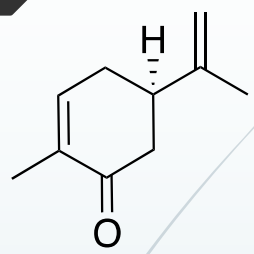
Pinacol





(R)(-)Carvone

Regioselective allylic chlorination



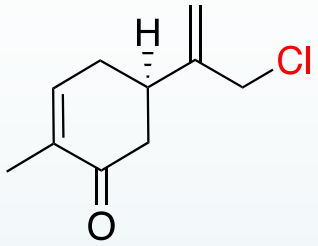
(*R*)-(-)-Carvone

^{t}BuOCl (1.2 equiv),

SiO_2 (20.14 eqiuv)

pentane, rt 12 h

no yield provided

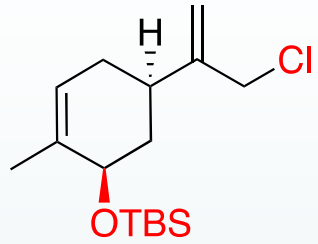


Dibal-H (1.11 equiv)

TBSCl (3.02 equiv)

Imidazole (3.02 equiv)

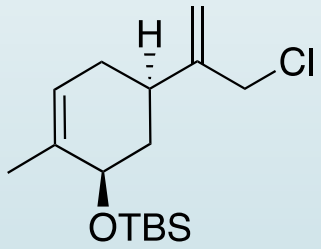
DCM, -78°C—> rt 12h



88% (over two steps)

dr ≥ 19:1

Tsuji-Trost Alkylation

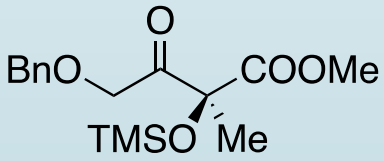


$Pd_2(dba)_3 \cdot CHCl_3$ (1 mol %)

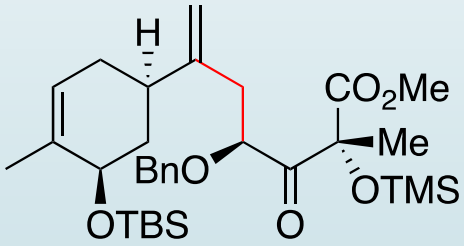
(S)-BINAP (4 mol %)

LiCl (2.4 equiv)

LiHMDS (1.01 equiv)



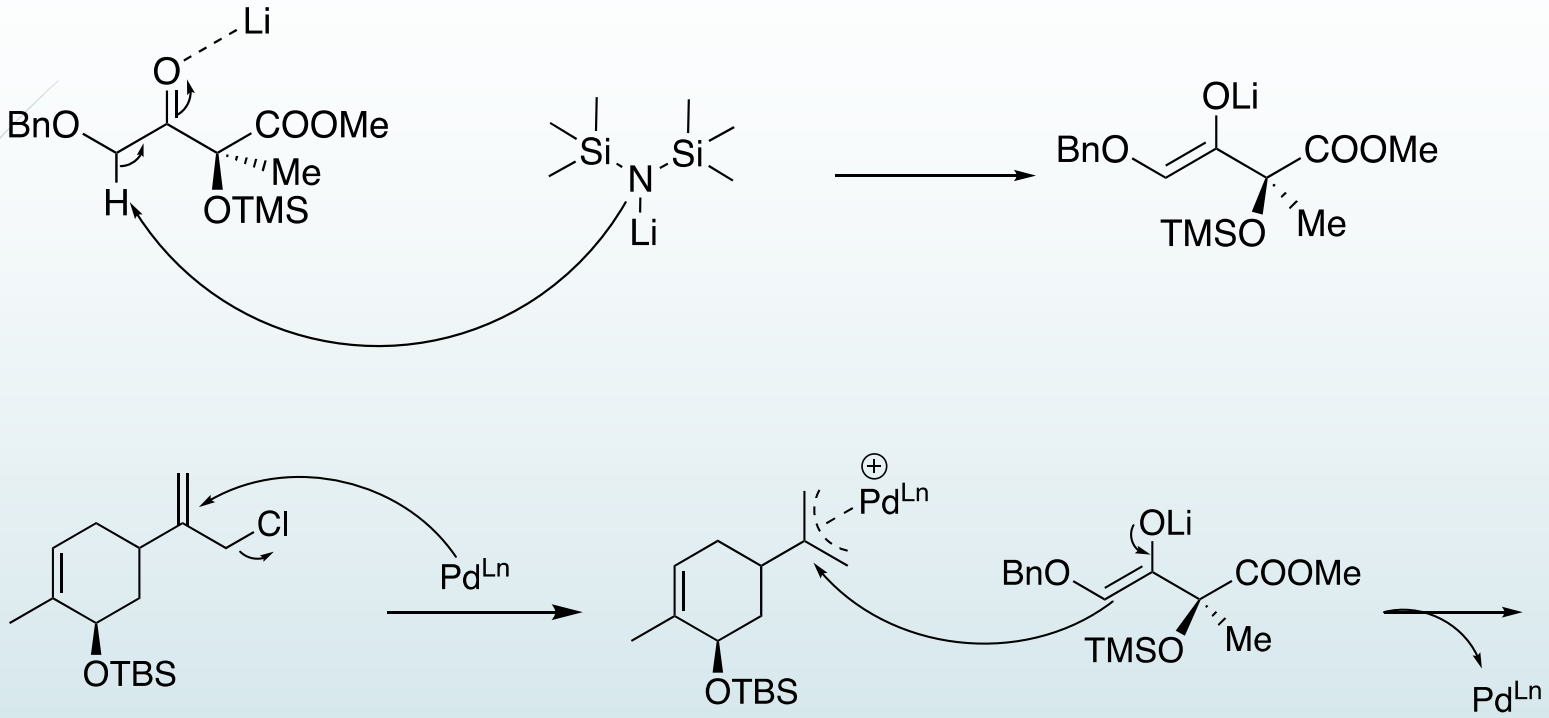
THF, 0°C

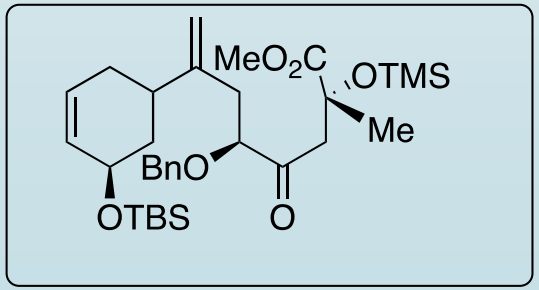


93%

dr = 8:1

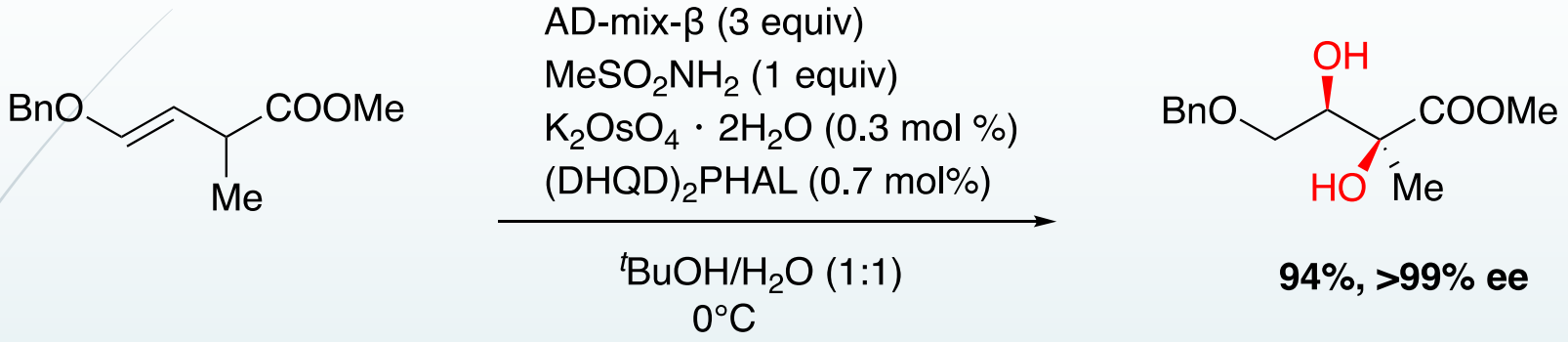
Tsuji-Trost Alkylation





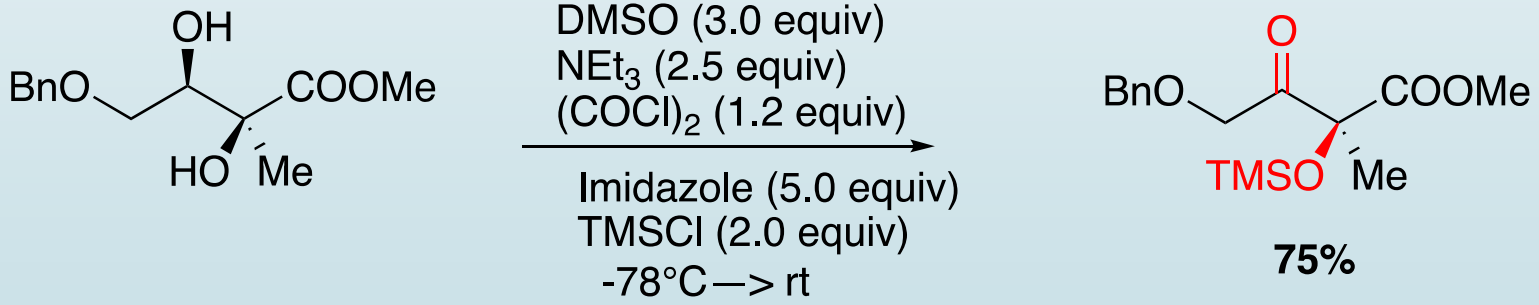
Generation of the ketone used in palladium cycle

Sharpless dihydroxylation

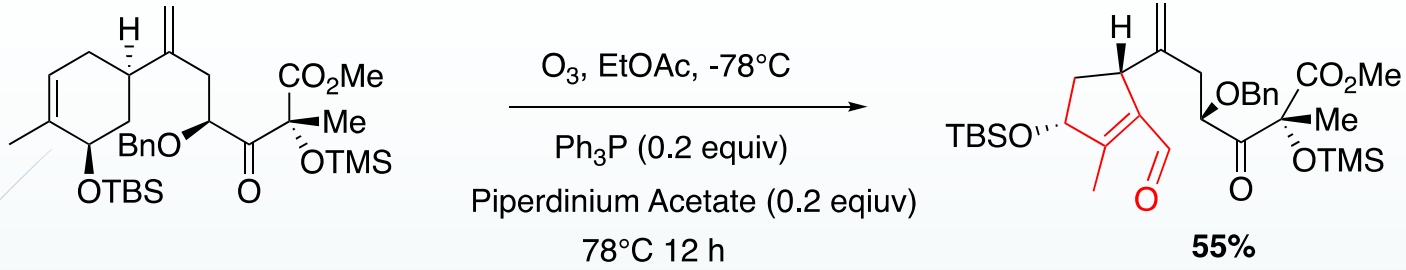


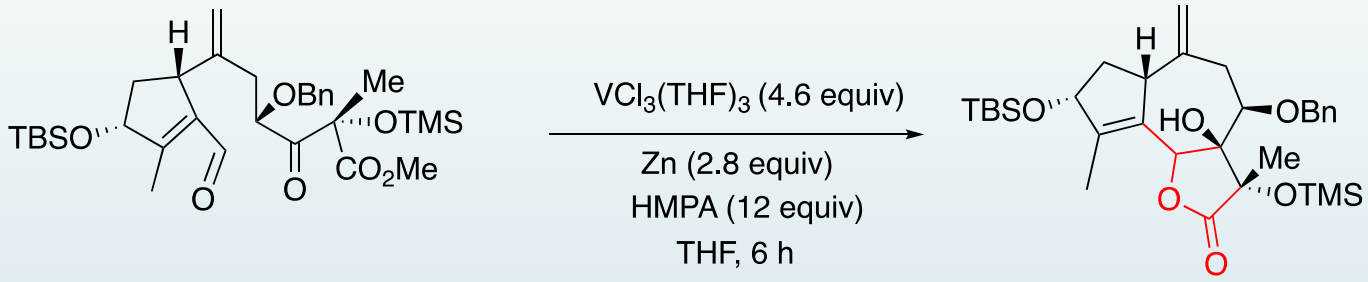
94%, >99% ee

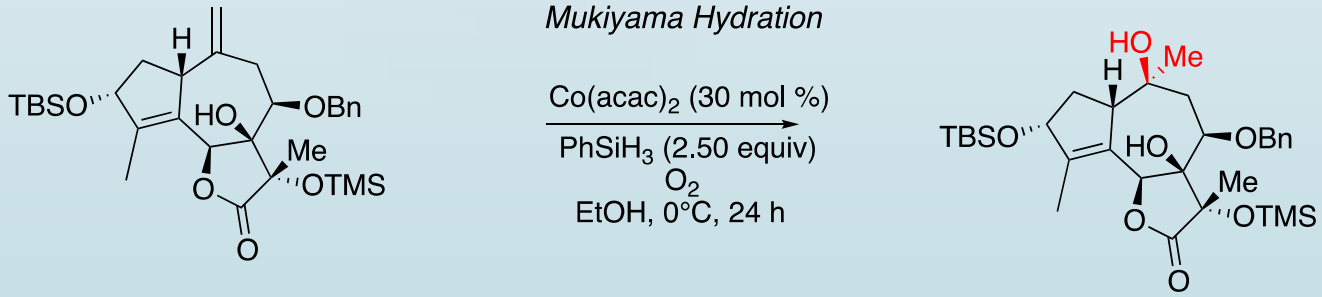
Swern-Oxidation followed by TBS protection



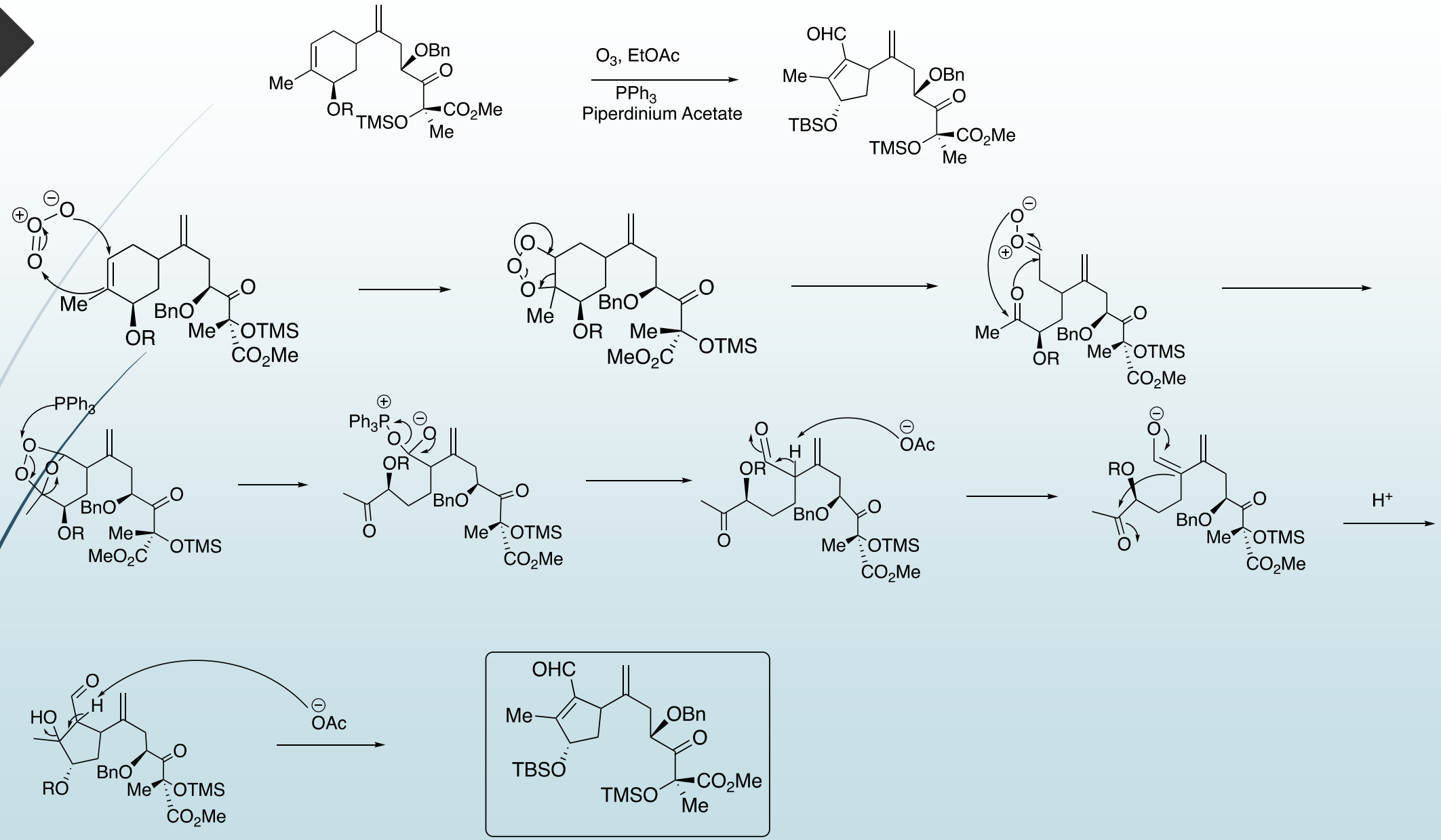
75%


H
CO2Me
Me
BnO
OTMS
OTBS
O
O3, EtOAc, -78°C
Ph3P (0.2 equiv)
Piperdinium Acetate (0.2 eqiuv)
78°C 12 h
H
OBn
CO2Me
TBSO
Me
OTMS
O
O
55%

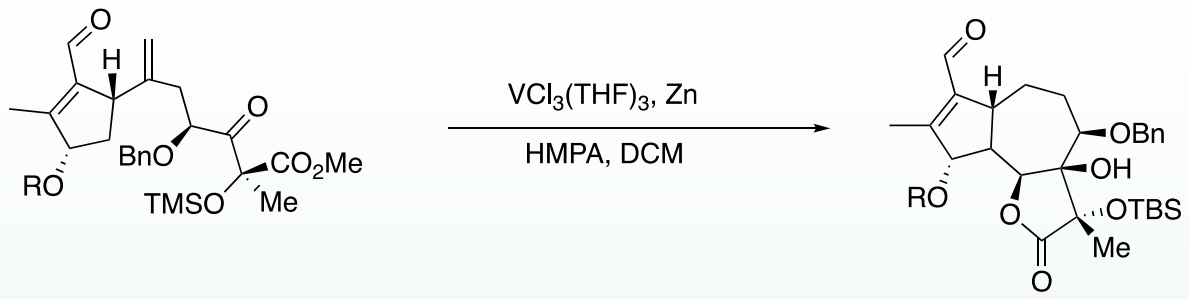

H
OBn
Me
TBSO
OTMS
CO2Me
O
O
VCl3(THF)3 (4.6 equiv)
Zn (2.8 equiv)
HMPA (12 equiv)
THF, 6 h
H
TBSO
HO
OBn
Me
O
OTMS
O
60%
dr ≥ 19:1


H
TBSO
HO
OBn
Me
O
OTMS
O
Mukiyama Hydration
Co(acac)2 (30 mol %)
PhSiH3 (2.50 equiv)
O2
EtOH, 0°C, 24 h
HO
Me
H
TBSO
HO
OBn
Me
O
OTMS
O
79%
dr ≥ 19:1

Selective Ozonolysis followed by in situ intramolecular aldol

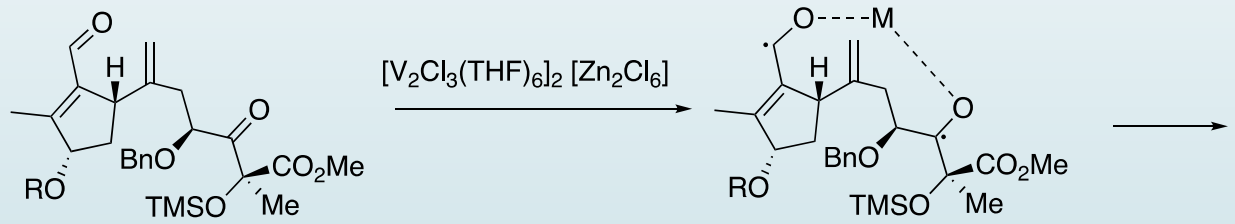


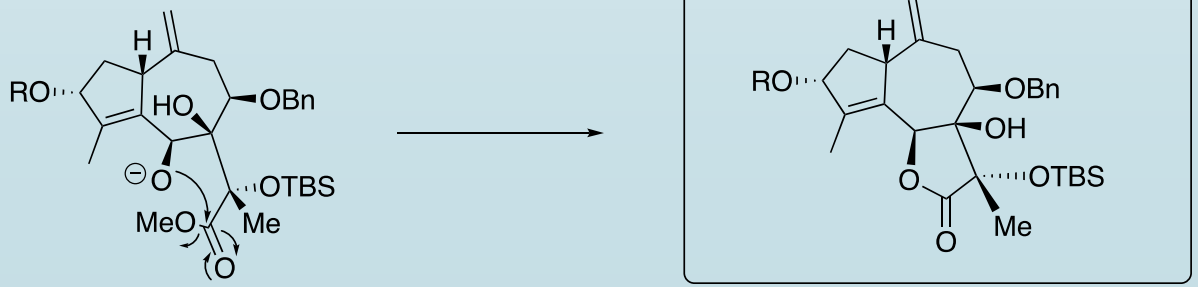
Vanadium Based Intramolecular Pinacol Coupling



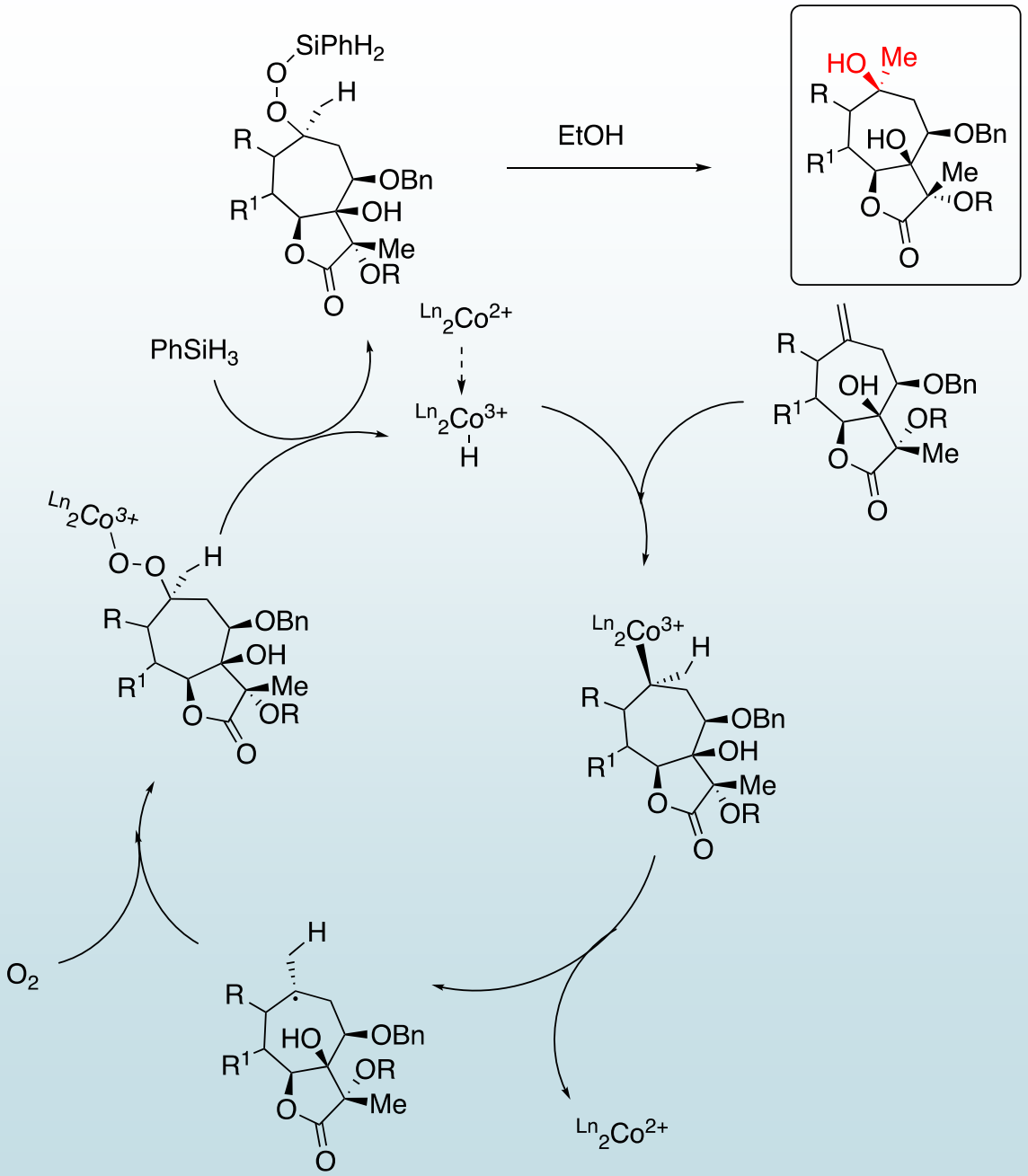
$VCl_3(THF)_3 + Zn \xrightarrow{HMPA} [V_2Cl_3(THF)_6]_2\,[Zn_2Cl_6]$

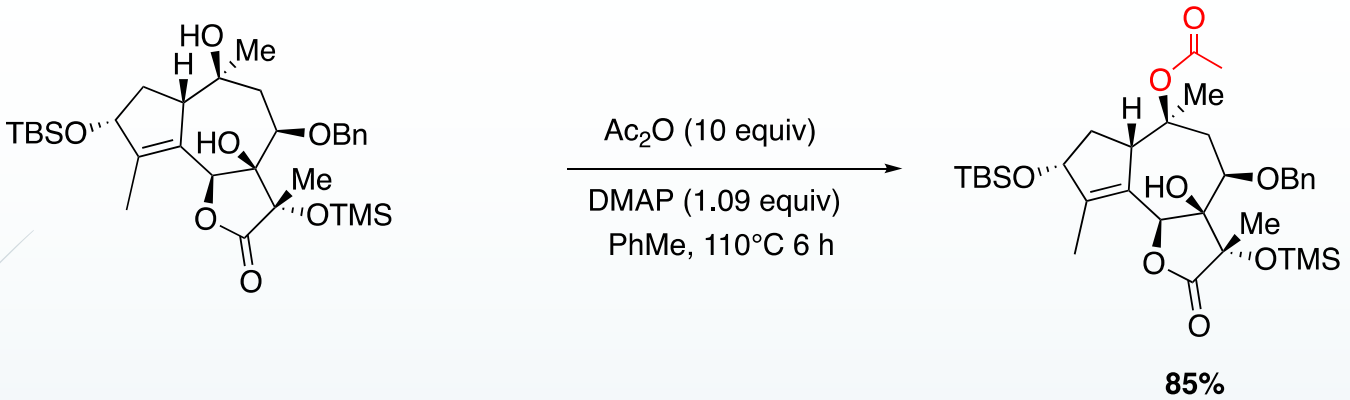
in situ dimerization

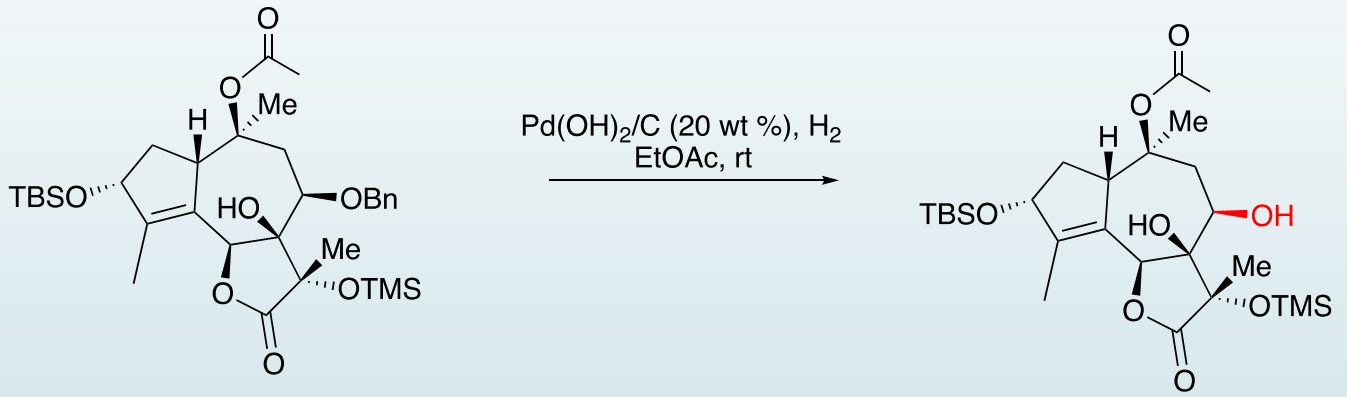


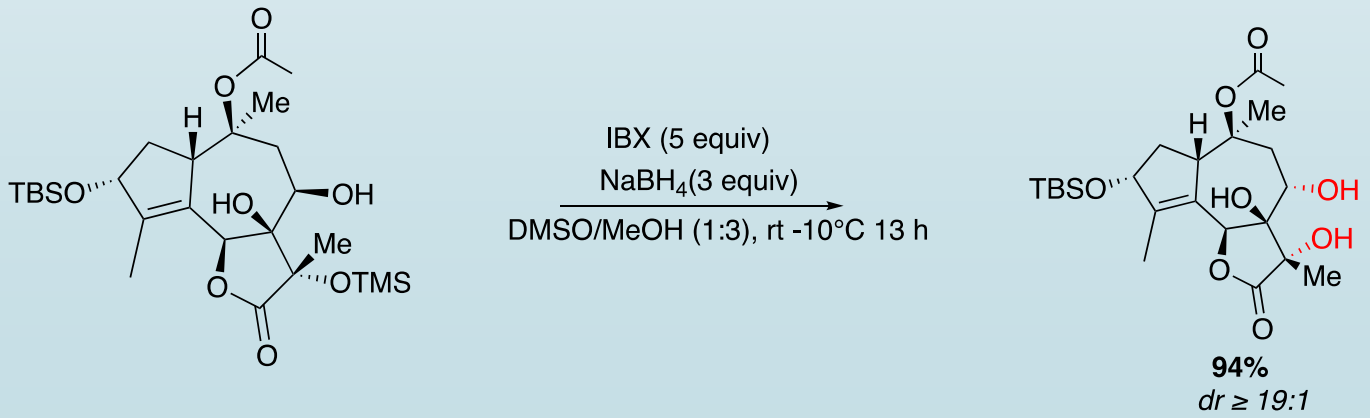


Mukiyama Hydration

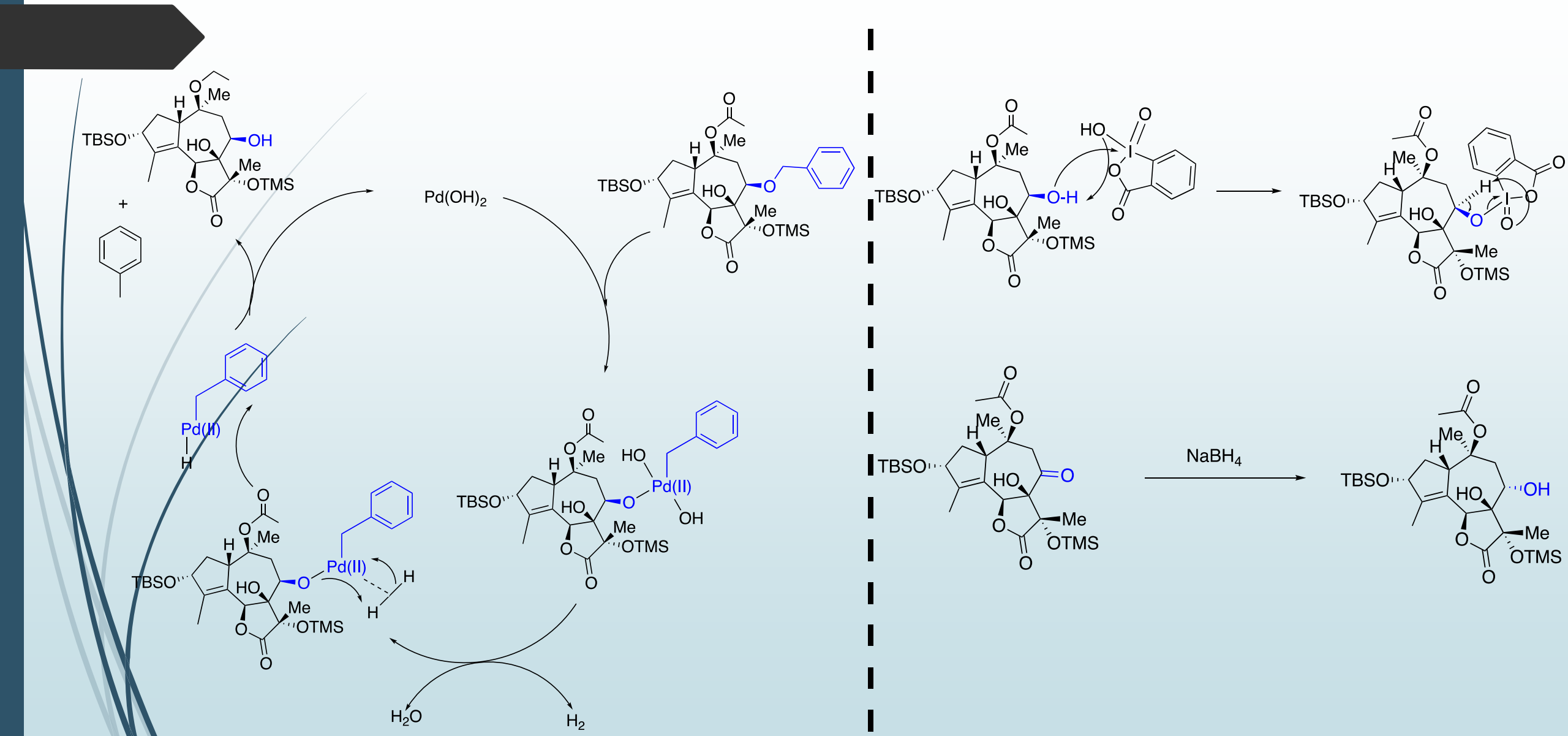


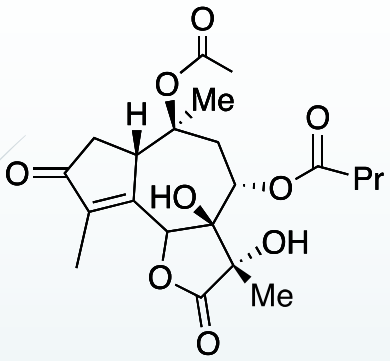

HO
Me
H
TBSO
OBn
HO
Me
O
OTMS
O
Ac2O (10 equiv)
DMAP (1.09 equiv)
PhMe, 110°C 6 h
O
O
Me
H
TBSO
OBn
HO
Me
O
OTMS
O
85%


O
O
Me
H
TBSO
OBn
HO
Me
O
OTMS
O
Pd(OH)2/C (20 wt %), H2
EtOAc, rt
O
O
Me
H
TBSO
OH
HO
Me
O
OTMS
O


O
O
Me
H
TBSO
OH
HO
Me
O
OTMS
O
IBX (5 equiv)
NaBH4(3 equiv)
DMSO/MeOH (1:3), rt -10°C 13 h
O
O
Me
H
TBSO
OH
HO
OH
Me
O
O
94%
dr ≥ 19:1

Pd Hydrogenation followed by oxidation & reduction

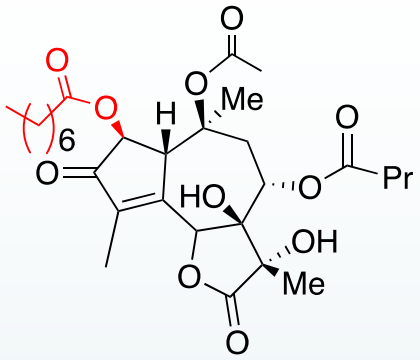




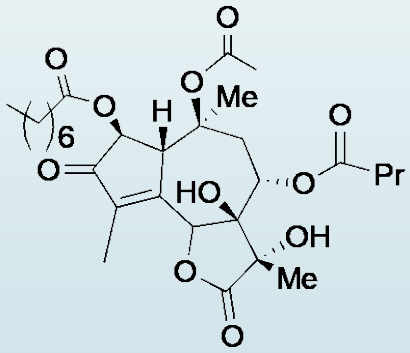
$Mn(OAc)_3 \cdot 2H_2O$ (6 equiv)

Octanoic acid: Benzene (1:5)

rt, 4 h



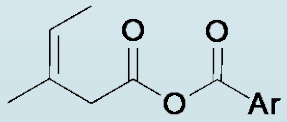
61%

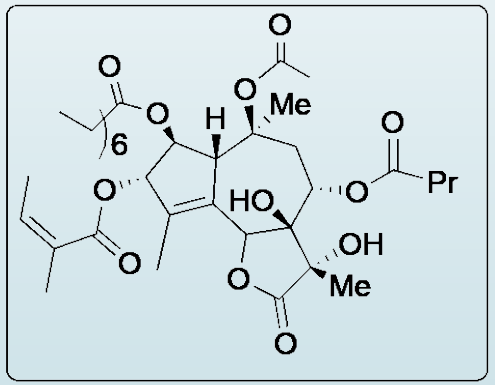


1.) $Zn(BH4)_2$ (11.1 equiv)

Et_2O, -20℃

2.) $NaHCO_3$ (2 equiv)



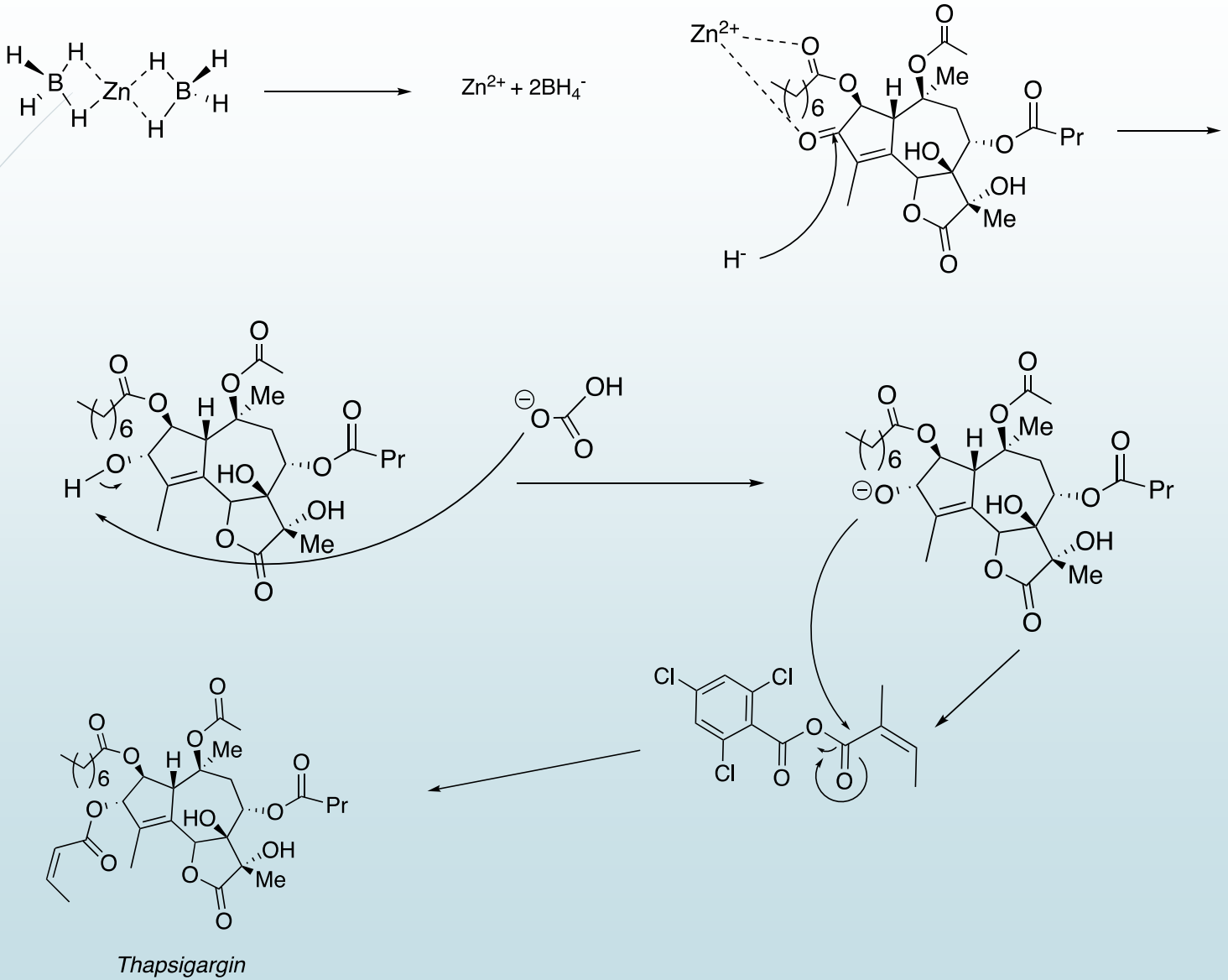


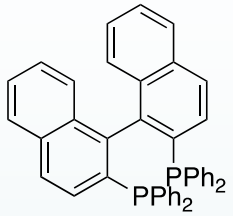
Thapsigargin

64%

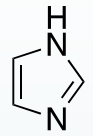
12 total steps & 5.8% linear yield

Diasteroselective Zinc Reduction followed by Angeloylation of C-3 Alcohol

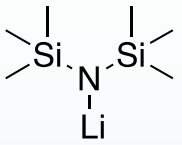




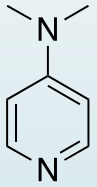
S-BINAP



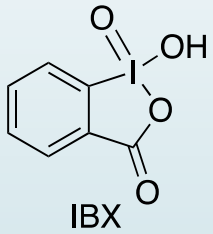
Imidazole



LiHMDS



DMAP



IBX