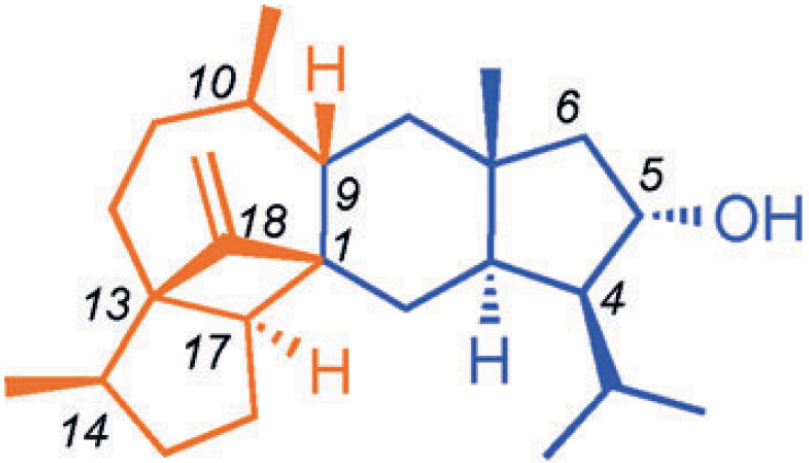
Total synthesis of Astellatol

Zhao, N .; Yin, S.; Xu, J. "Total Synthesis Astellatol" Angew. Chem. Int. Ed. **2018,** *ASAP*.



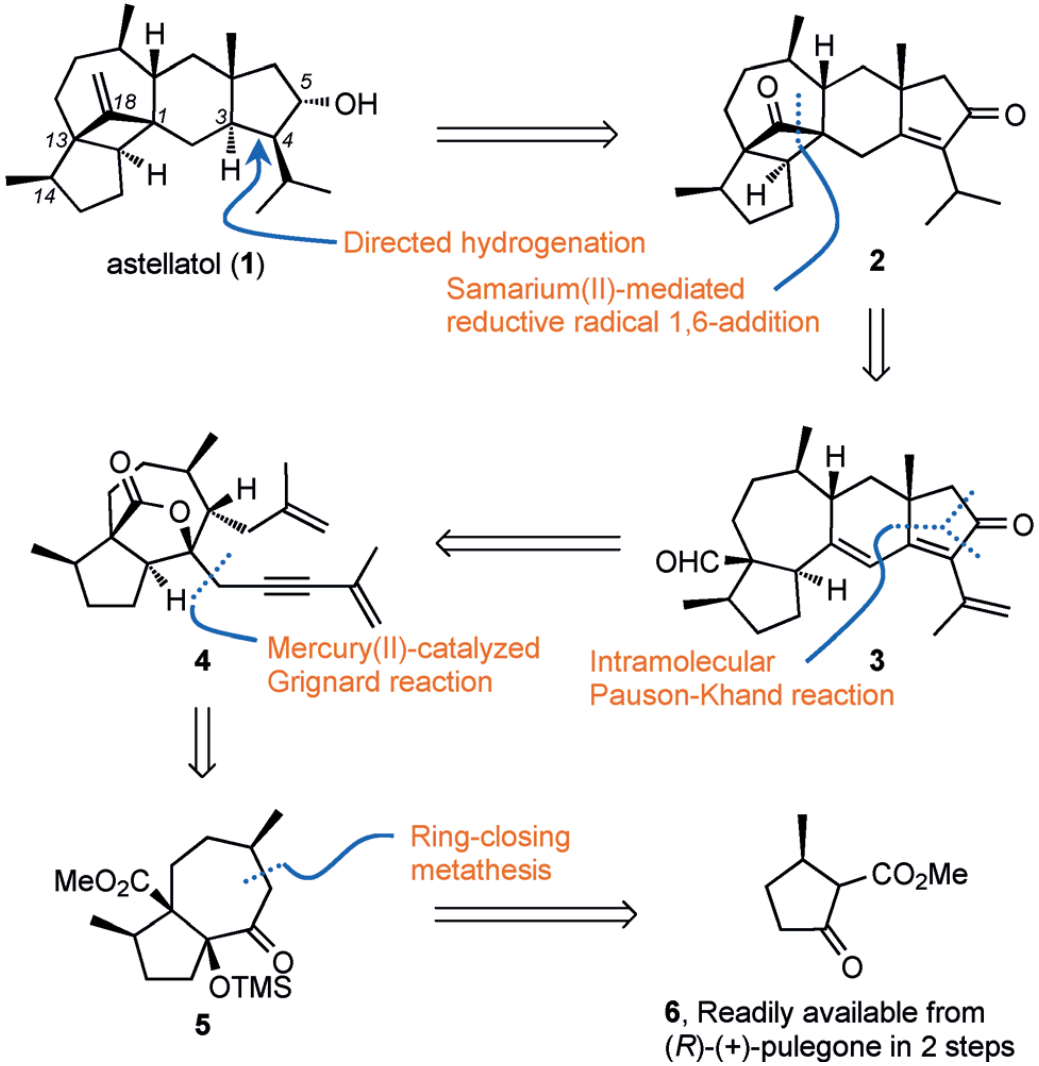
astellatol (**1**)

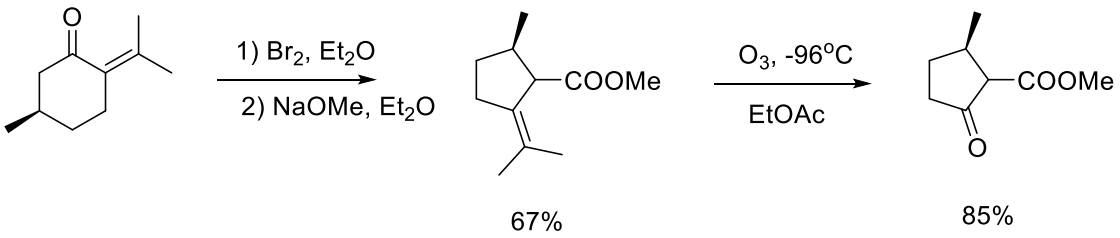
Astellatol was isolated from *Aspergillus stellatus and* structurally determined in 1989.

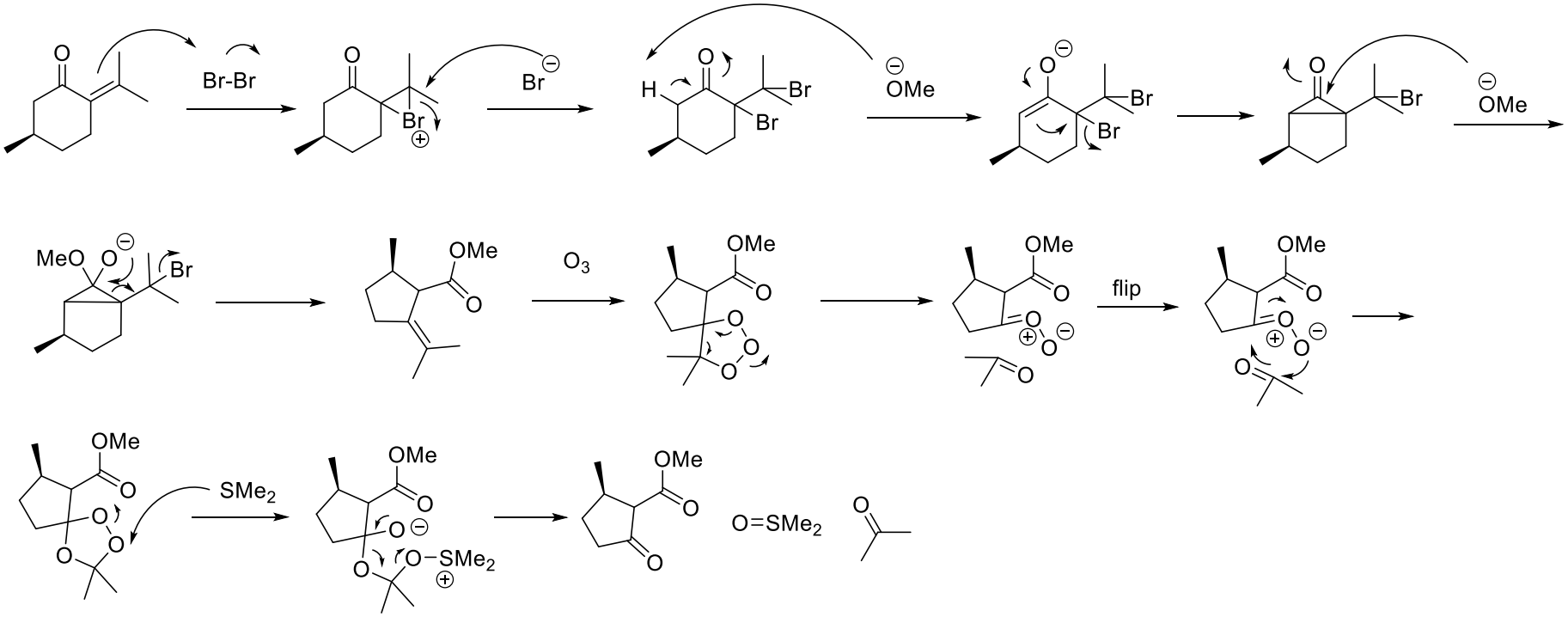
This rare sesterterpenoid was a nearly 30 years old unanswered synthetic puzzle.

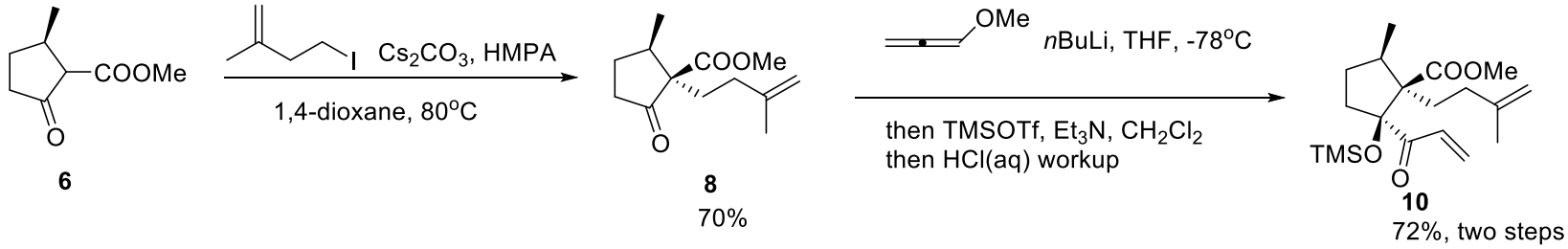
- Its rare pentacyclic skeleton contains a unique bicyclo[4.1.1] octane, ten stereocenters, a cyclobutane containing two quaternary centers.
- The synthesis of astellatol showcases a rapid, scalable strategy to access diverse complex isopropyl trans-hydrindane sesterterpenoids.

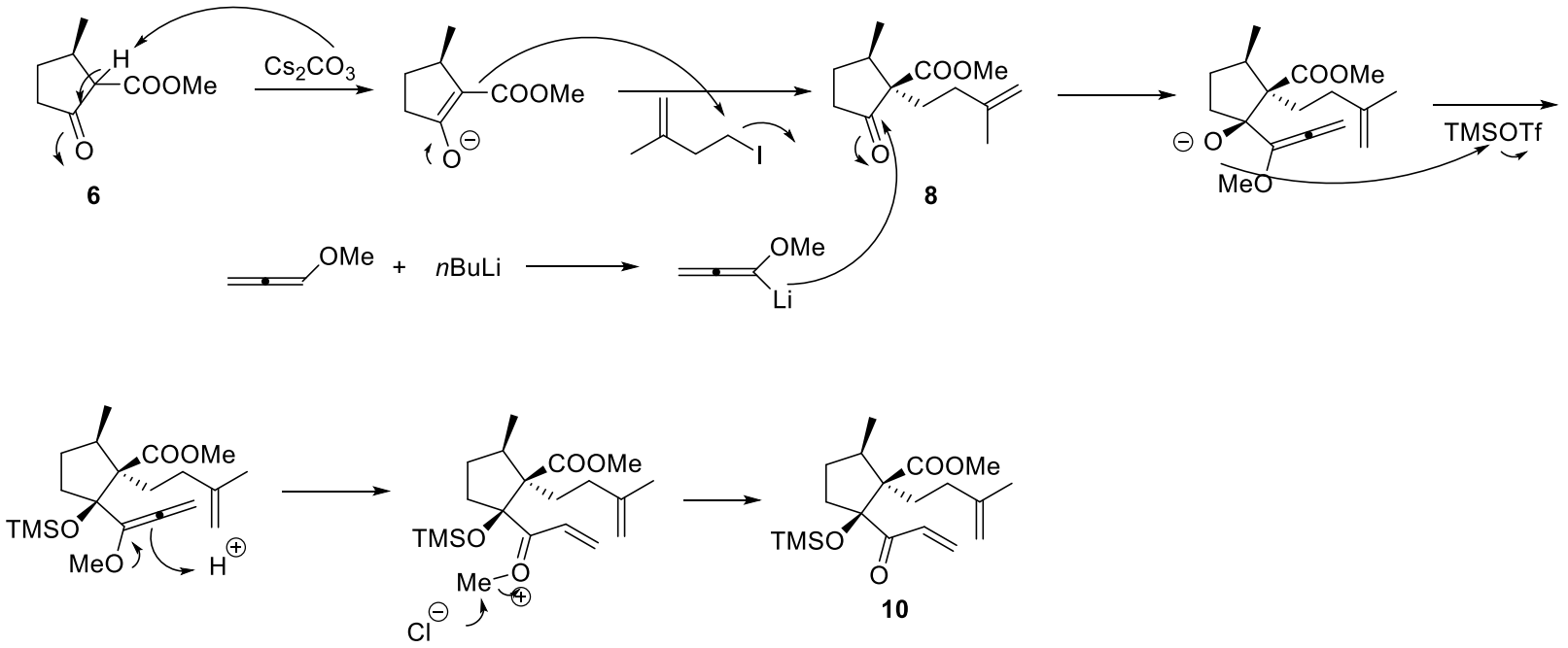
Retrosynthetic analysis

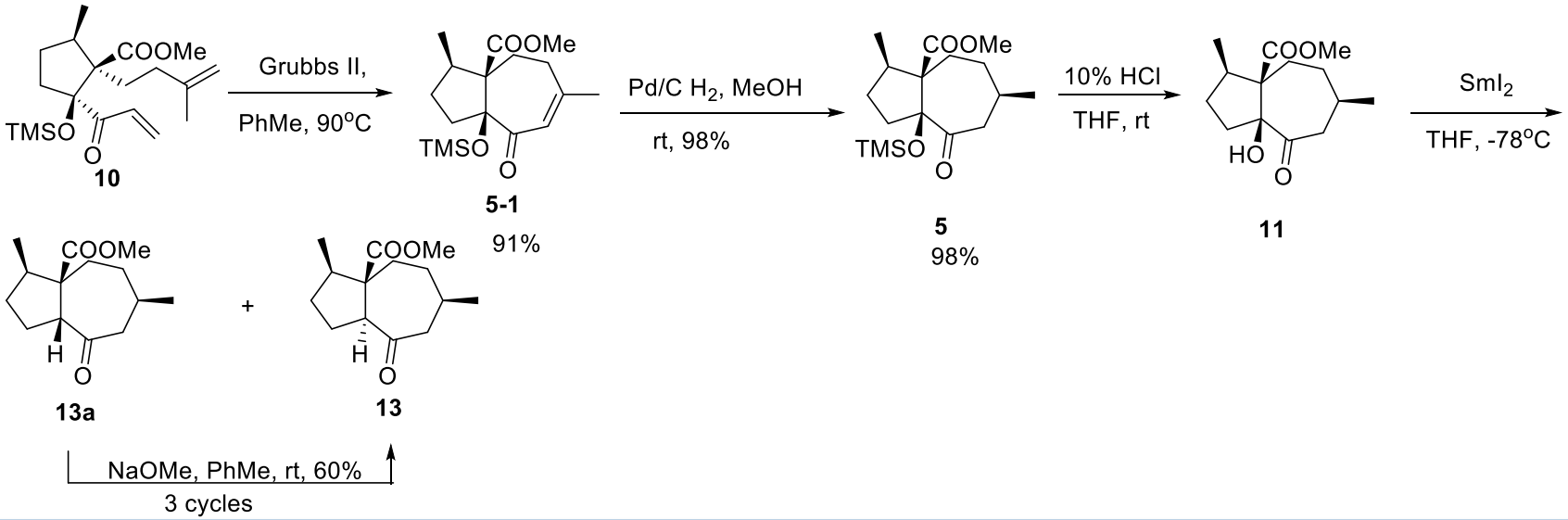


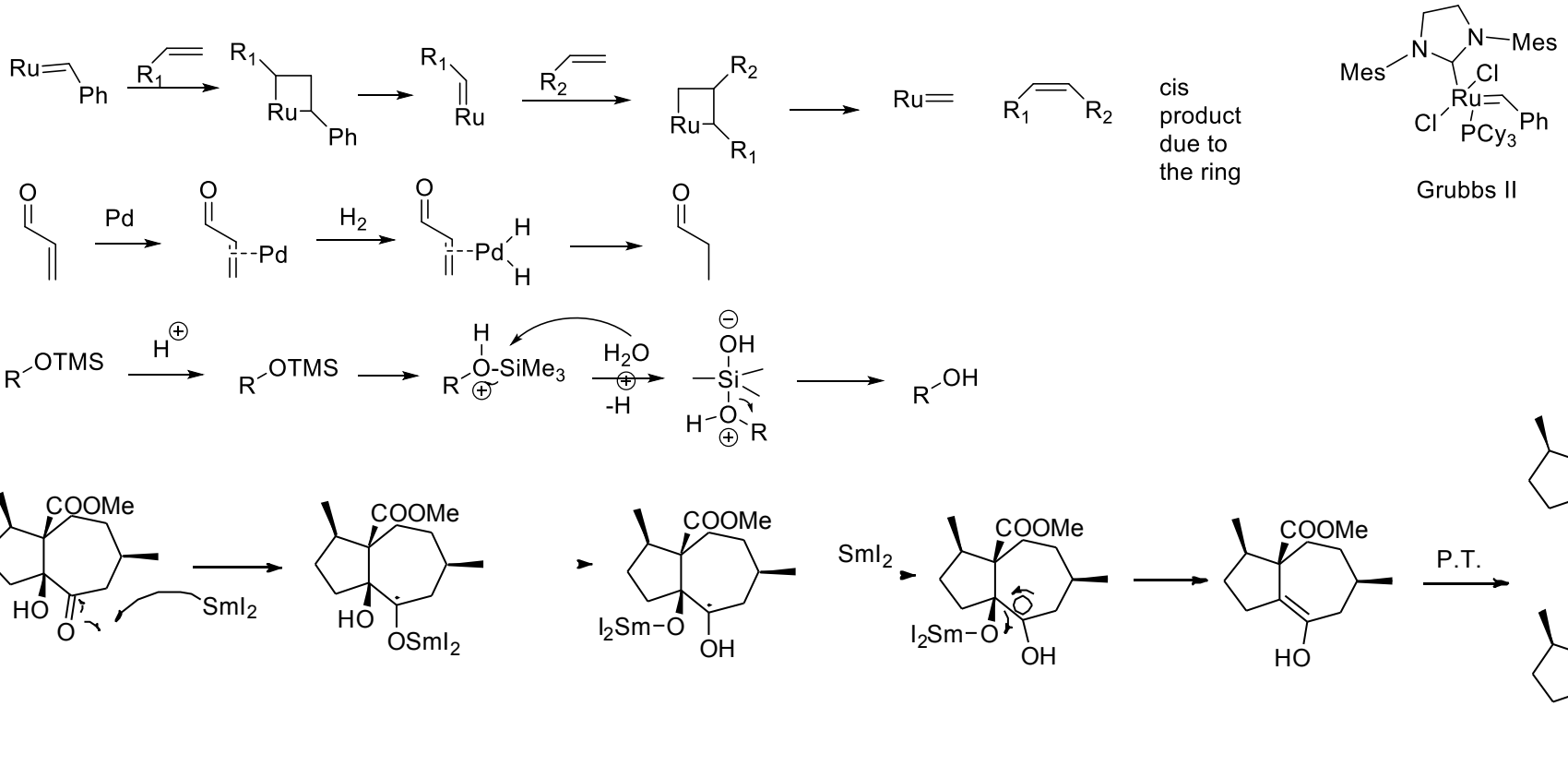

1) Br2, Et2O
2) NaOMe, Et2O
COOMe
O3, -96°C
EtOAc
COOMe
67%
85%

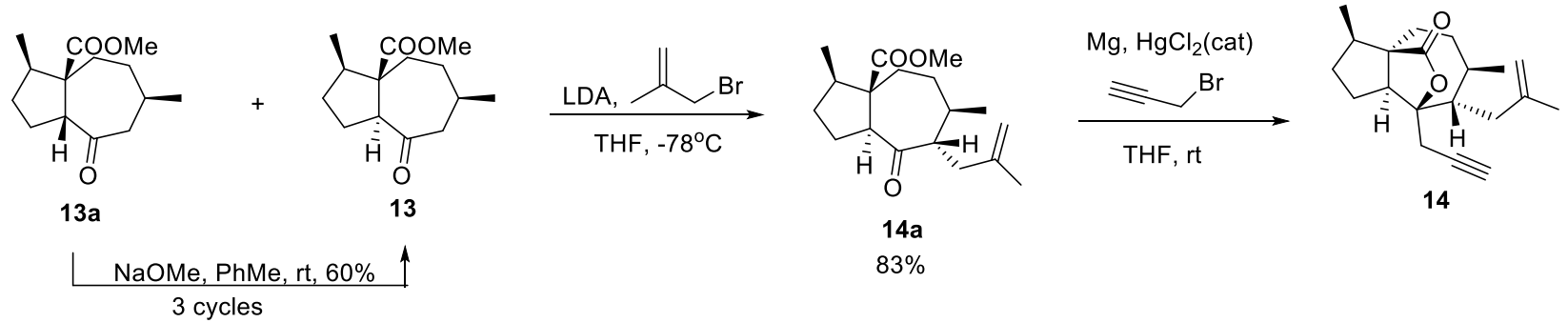

Br-Br
Br
OMe
MeO
Br
OMe
O3
flip
SMe2
O=SMe2

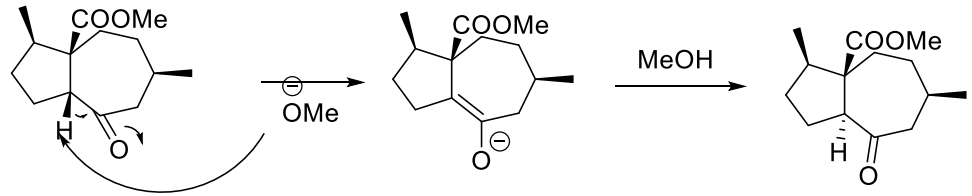

COOMe
O
6
I
Cs2CO3, HMPA
1,4-dioxane, 80°C
COOMe
O
8
70%
OMe
nBuLi, THF, -78°C
then TMSOTf, Et3N, CH2Cl2
then HCl(aq) workup
COOMe
TMSO
O
10
72%, two steps

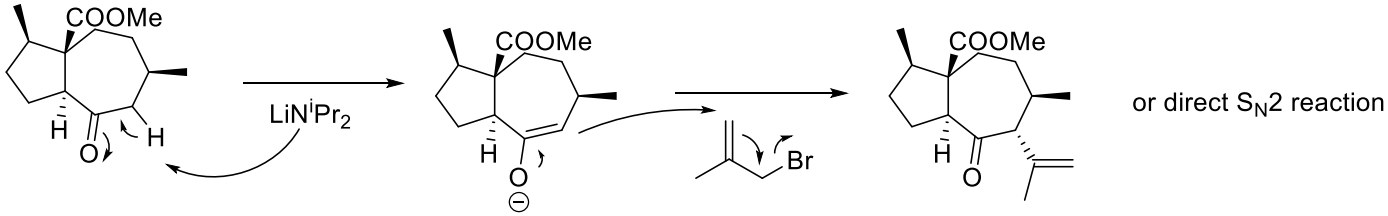

H
COOMe
O
6
Cs2CO3
COOMe
O
I
COOMe
O
8
COOMe
O
MeO
TMSOTf
OMe
+
nBuLi
OMe
Li
COOMe
TMSO
MeO
H
COOMe
TMSO
Me
O
Cl
COOMe
TMSO
O
10


COOMe
TMSO
O
10
Grubbs II,
PhMe, 90°C
5-1
91%
Pd/C H2, MeOH
rt, 98%
5
98%
10% HCl
THF, rt
HO
11
SmI2
THF, -78°C
13a
+
13
NaOMe, PhMe, rt, 60%
3 cycles

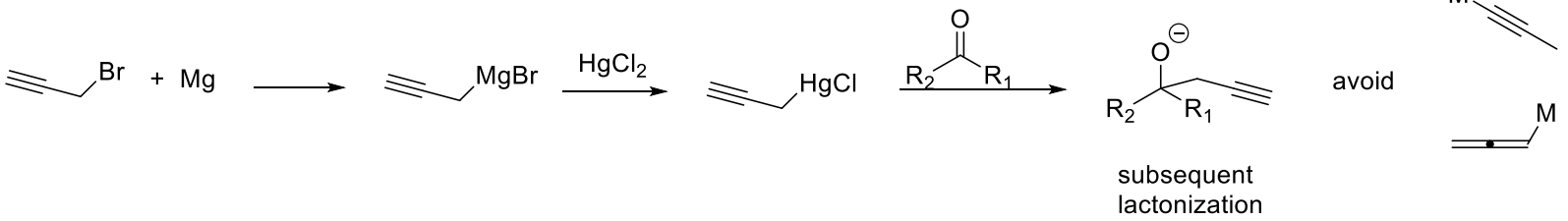

Ru
Ph
R1
R2
cis
product
due to
the ring
Mes
N
Cl
PCy3
Grubbs II
Pd
H2
OTMS
H2O
-H
OH
Si
SmI2
P.T.
I2Sm-O

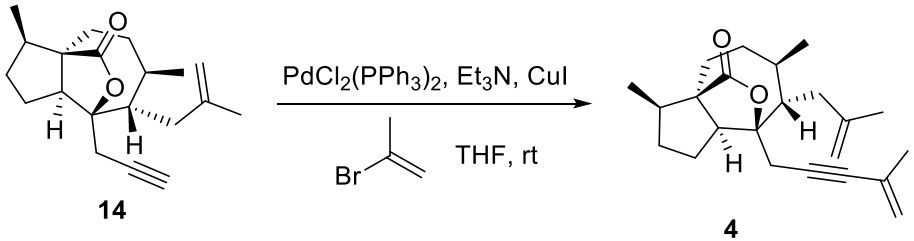


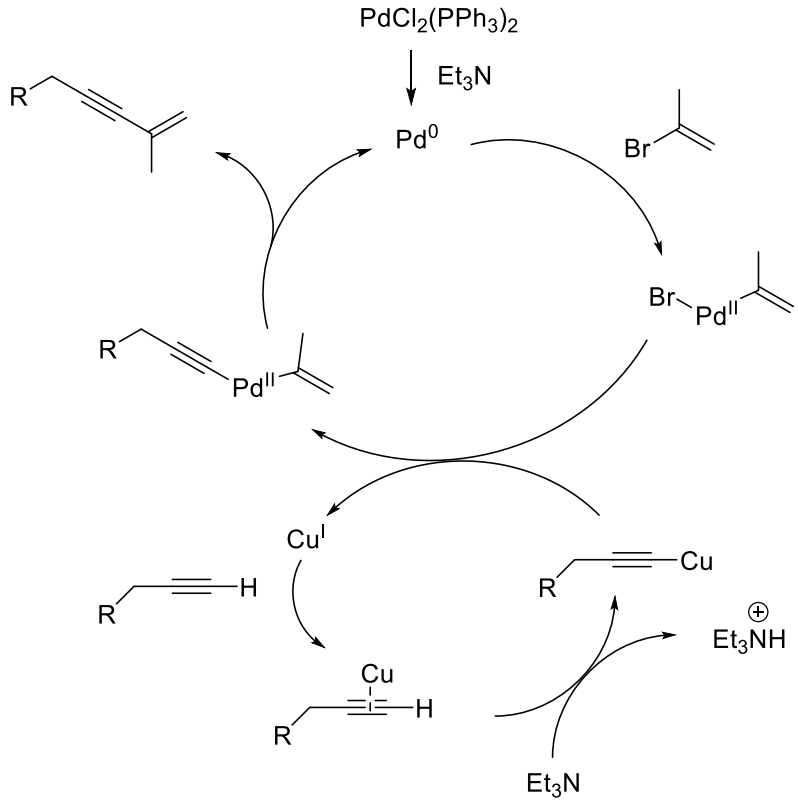


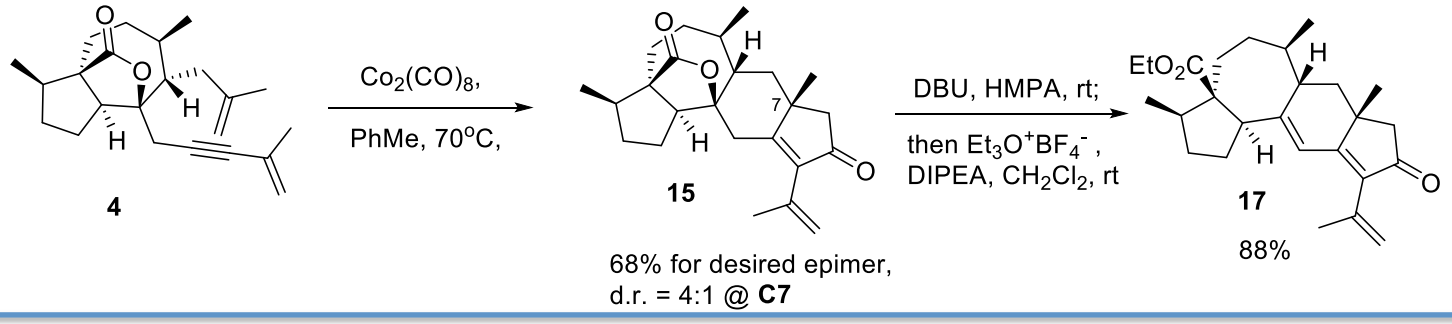


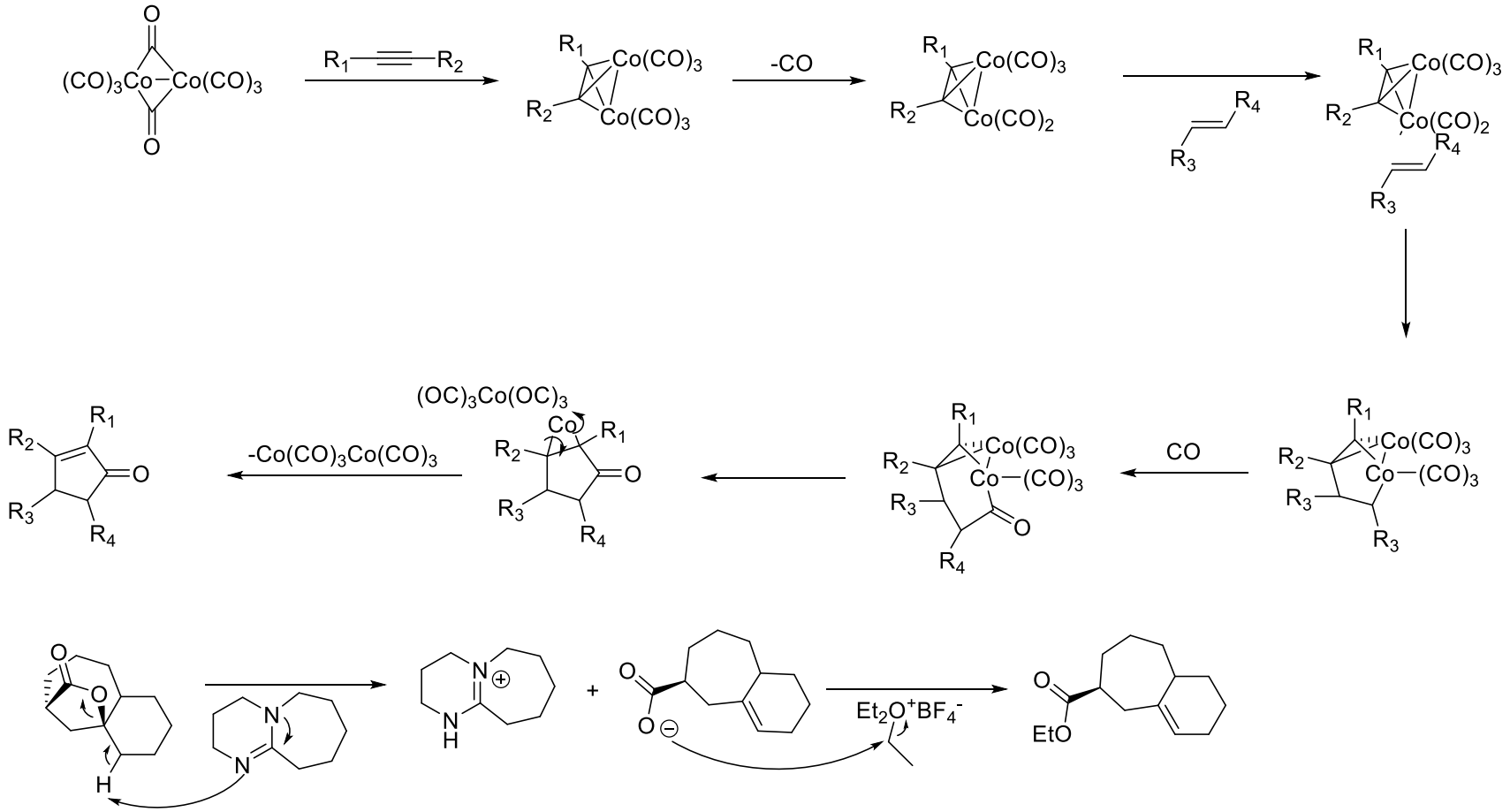
or direct S_N2 reaction

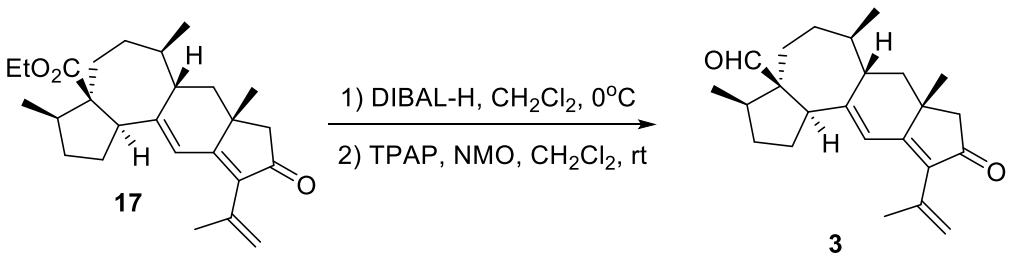


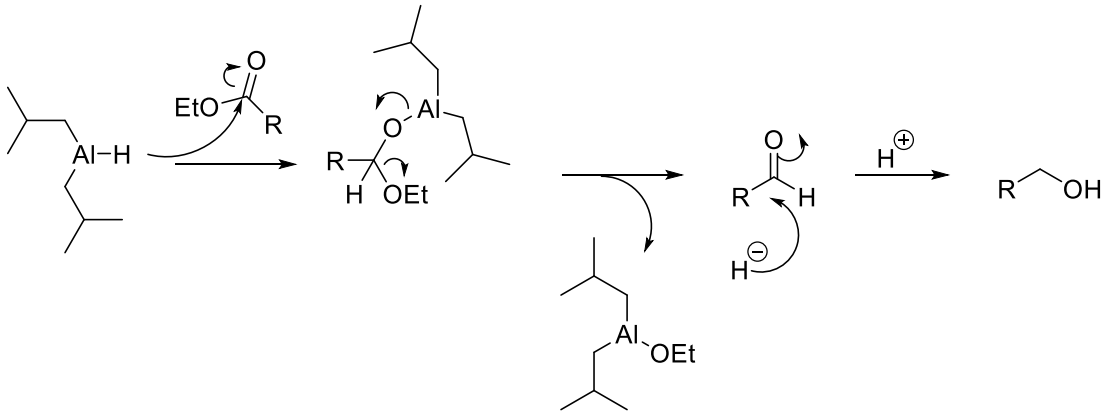

PdCl2(PPh3)2, Et3N, CuI
THF, rt
Br
14
4
67%, two steps

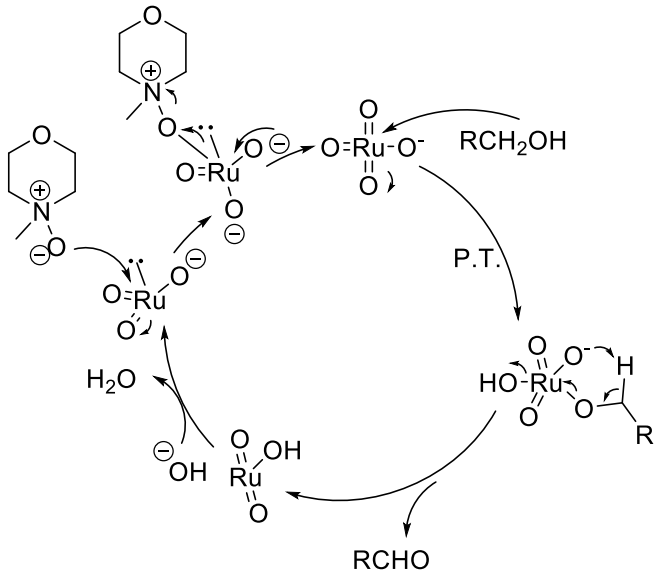

PdCl2(PPh3)2
Et3N
Pd0
Br
R
Br
PdII
R
PdII
CuI
R
H
R
Cu
Et3NH
Cu
R
H
Et3N

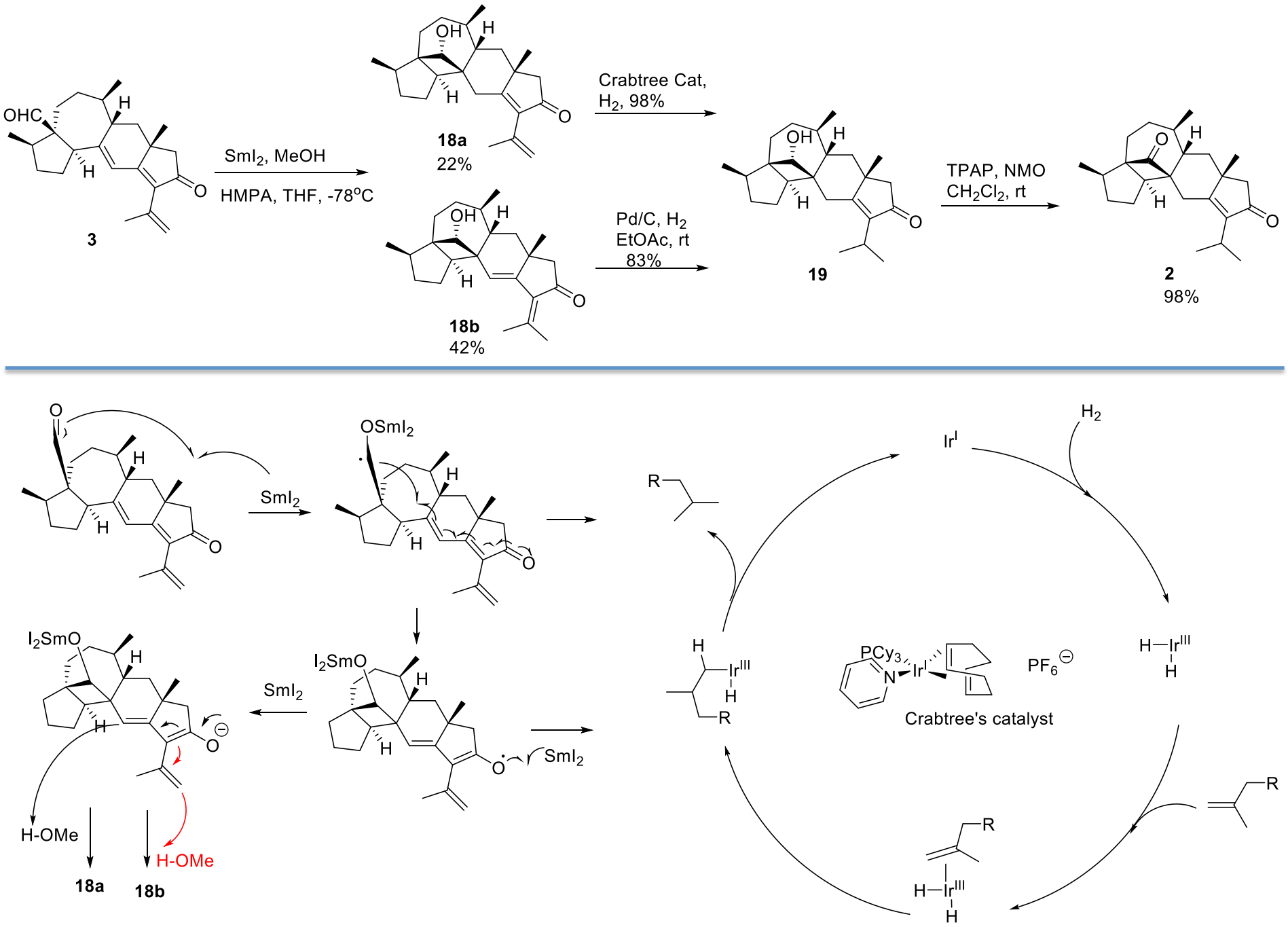

4
$Co_2(CO)_8$,
PhMe, 70°C,
15
68% for desired epimer,
d.r. = 4:1 @ **C7**
DBU, HMPA, rt;
then $Et_3O^+BF_4^-$,
DIPEA, CH_2Cl_2, rt
17
88%

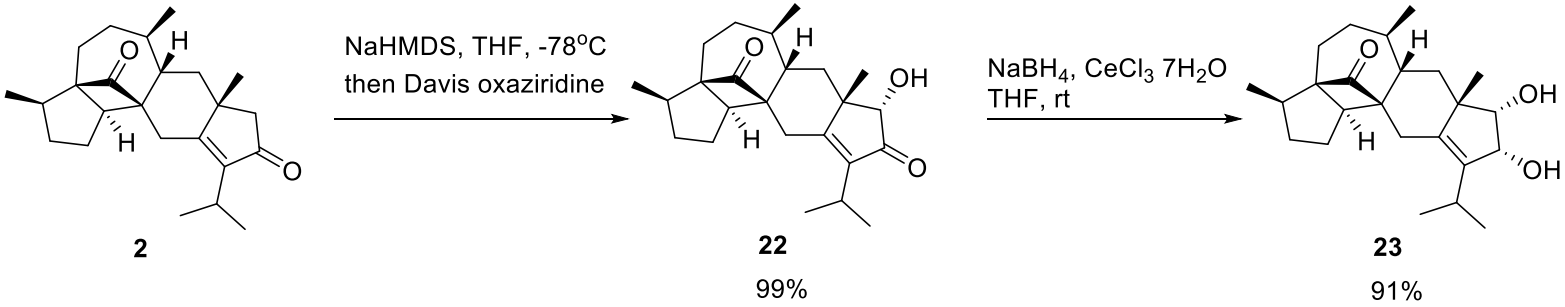

$(CO)_3Co-Co(CO)_3$
$R_1-\equiv-R_2$
$Co(CO)_3$
$Co(CO)_2$
-CO
CO
$(OC)_3Co(OC)_3$
$-Co(CO)_3Co(CO)_3$
$Et_2O^+BF_4^-$
EtO


EtO2C
H
H
O
17
1) DIBAL-H, CH2Cl2, 0°C
2) TPAP, NMO, CH2Cl2, rt
OHC
H
H
O
3
74%, two steps

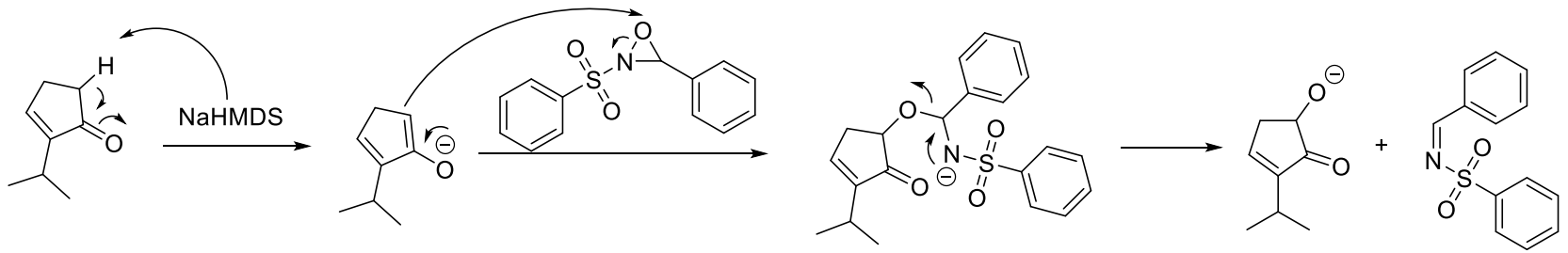

Al−H
EtO
O
R
Al
O
R
H
OEt
Al
OEt
R
O
H
H
H
R
OH

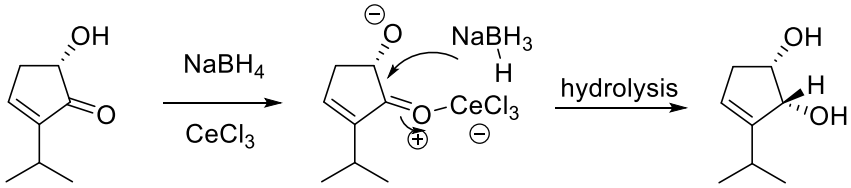

N
O
O=Ru
O
O=Ru-O-
O
RCH2OH
P.T.
HO-Ru
H
R
H2O
OH
OH
Ru
O
RCHO

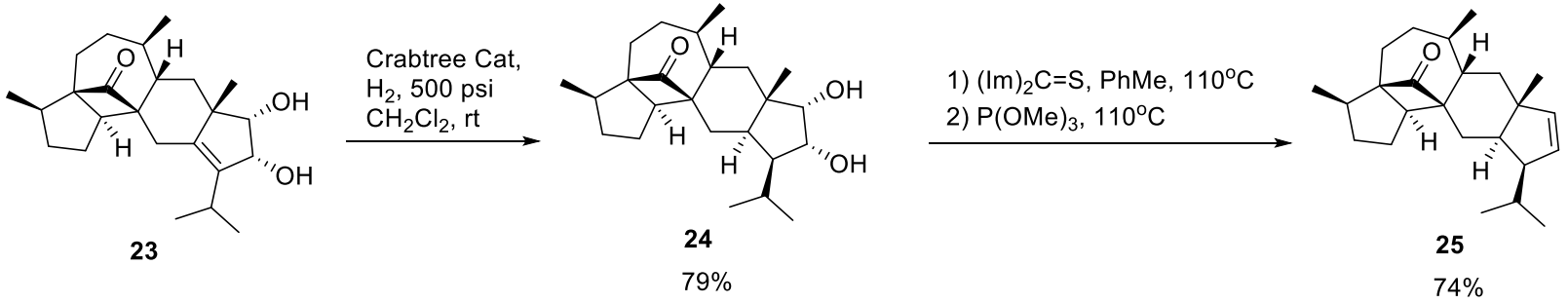

OHC
H
H
O
3
SmI2, MeOH
HMPA, THF, -78°C
OH
H
H
O
18a
22%
OH
H
H
O
18b
42%
Crabtree Cat,
H2, 98%
Pd/C, H2
EtOAc, rt
83%
OH
H
H
O
19
TPAP, NMO
CH2Cl2, rt
O
H
H
O
2
98%
O
H
H
O
SmI2
OSmI2
H
H
O
I2SmO
H
H
O
SmI2
I2SmO
H
H
O
SmI2
H
H
O
H-OMe
18a
H-OMe
18b
R
H
IrIII
H
R
IrI
H2
PCy3
N
IrI
PF6
Crabtree's catalyst
H—IrIII
H
R
H—IrIII
H
R


NaHMDS, THF, -78°C
then Davis oxaziridine
NaBH4, CeCl3 7H2O
THF, rt

2 **22** 99% **23** 91%


NaHMDS


NaBH4
CeCl3
NaBH3
H
CeCl3
hydrolysis


Crabtree Cat,
H_2, 500 psi
CH_2Cl_2, rt
1) $(Im)_2C=S$, PhMe, 110°C
2) $P(OMe)_3$, 110°C

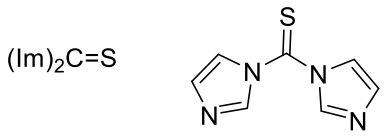
23

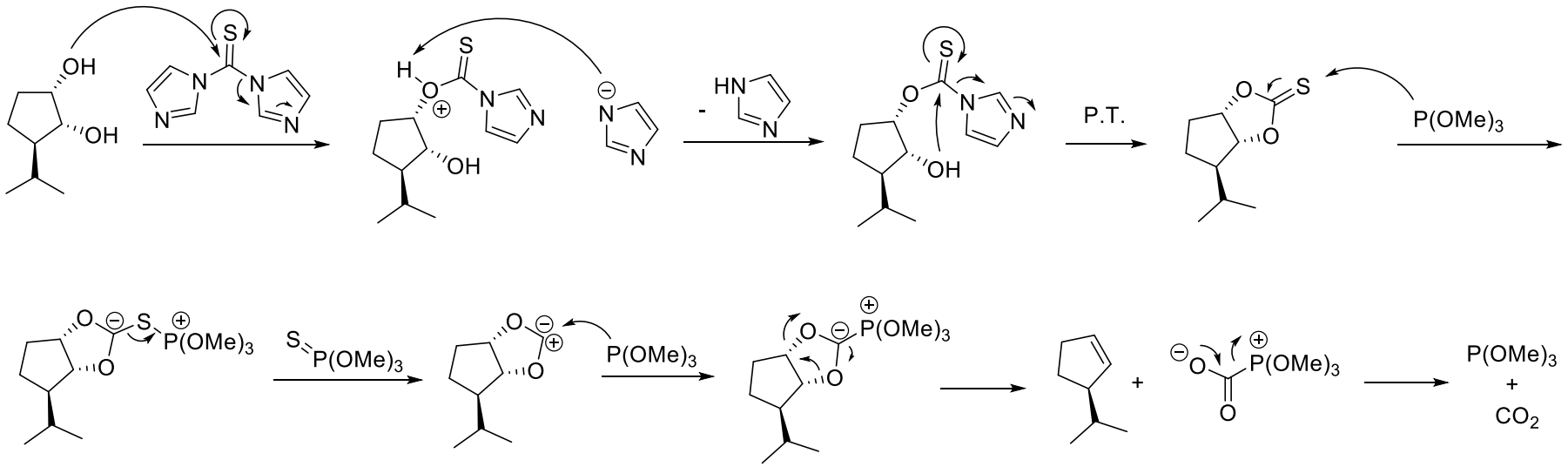
24

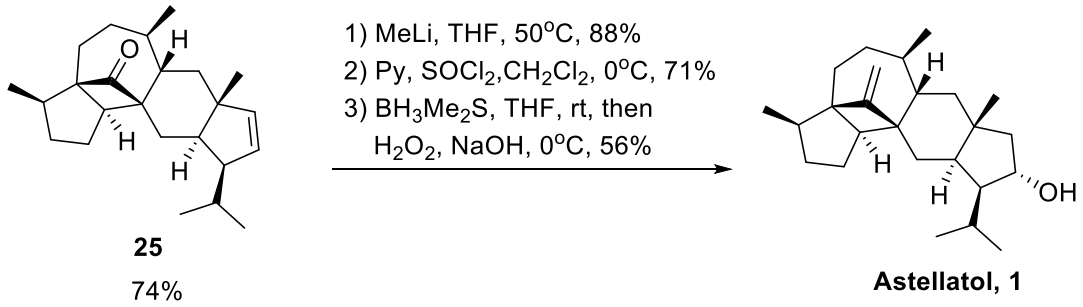
79%

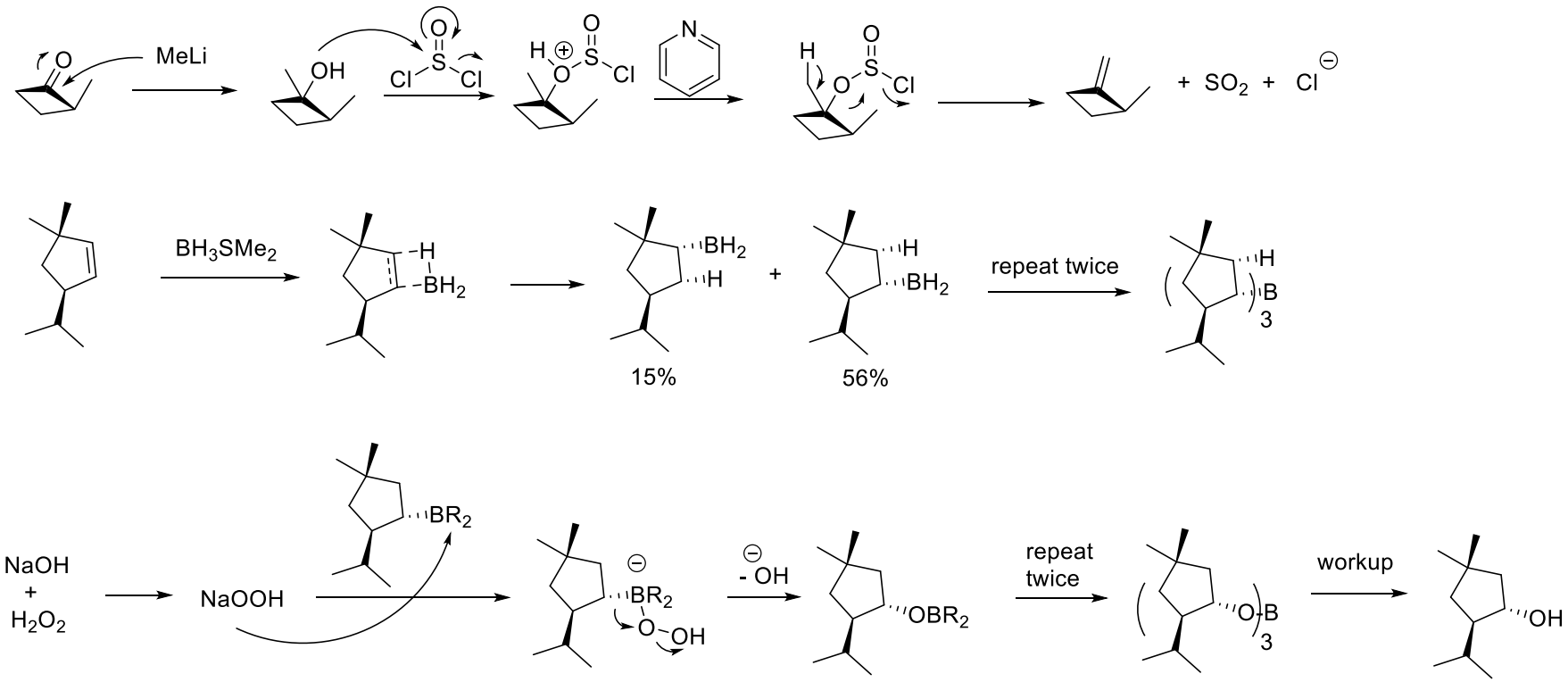
25

74%


$(Im)_2C=S$


P.T.
$P(OMe)_3$
$P(OMe)_3$
$P(OMe)_3$
$P(OMe)_3$
$P(OMe)_3$
CO_2


1) MeLi, THF, 50°C, 88%
2) Py, SOCl2,CH2Cl2, 0°C, 71%
3) BH3Me2S, THF, rt, then
H2O2, NaOH, 0°C, 56%
25
74%
Astellatol, 1


MeLi
+ SO2 + Cl
BH3SMe2
15%
56%
repeat twice
NaOH
+
H2O2
NaOOH
- OH
repeat
twice
workup