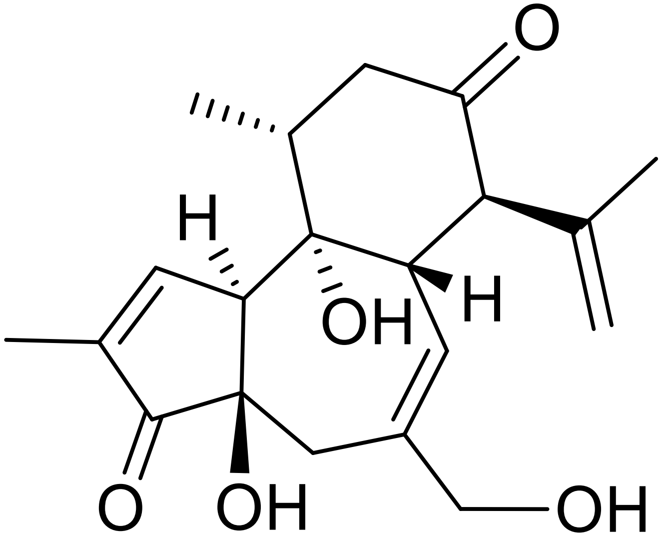
Total Synthesis of Crotophobolone

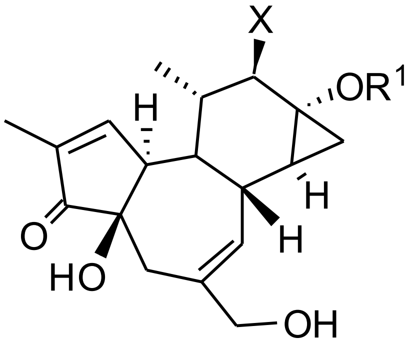


Niloofar Safaie Ashtiani
CEM 852

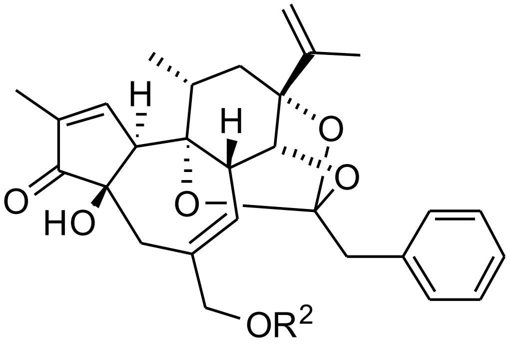
Angew. Chem. Int. Ed. **2015**, 54, 14457-14461, Inune, University of Tokyo.

Scope:

- Isolated of phorbol in 1934 and its structure determined in 1969.
- In 2010, was identified from the dried plant root of Euphorbia fischeriana Steud.
- This plant is a Chinese medicine for treatment of edema, ascites, and cancer.
- this class of molecules attracted attention because of their biological activity and architecturally complex structure.
- Only Wender has reported a total synthesis for this class of molecules

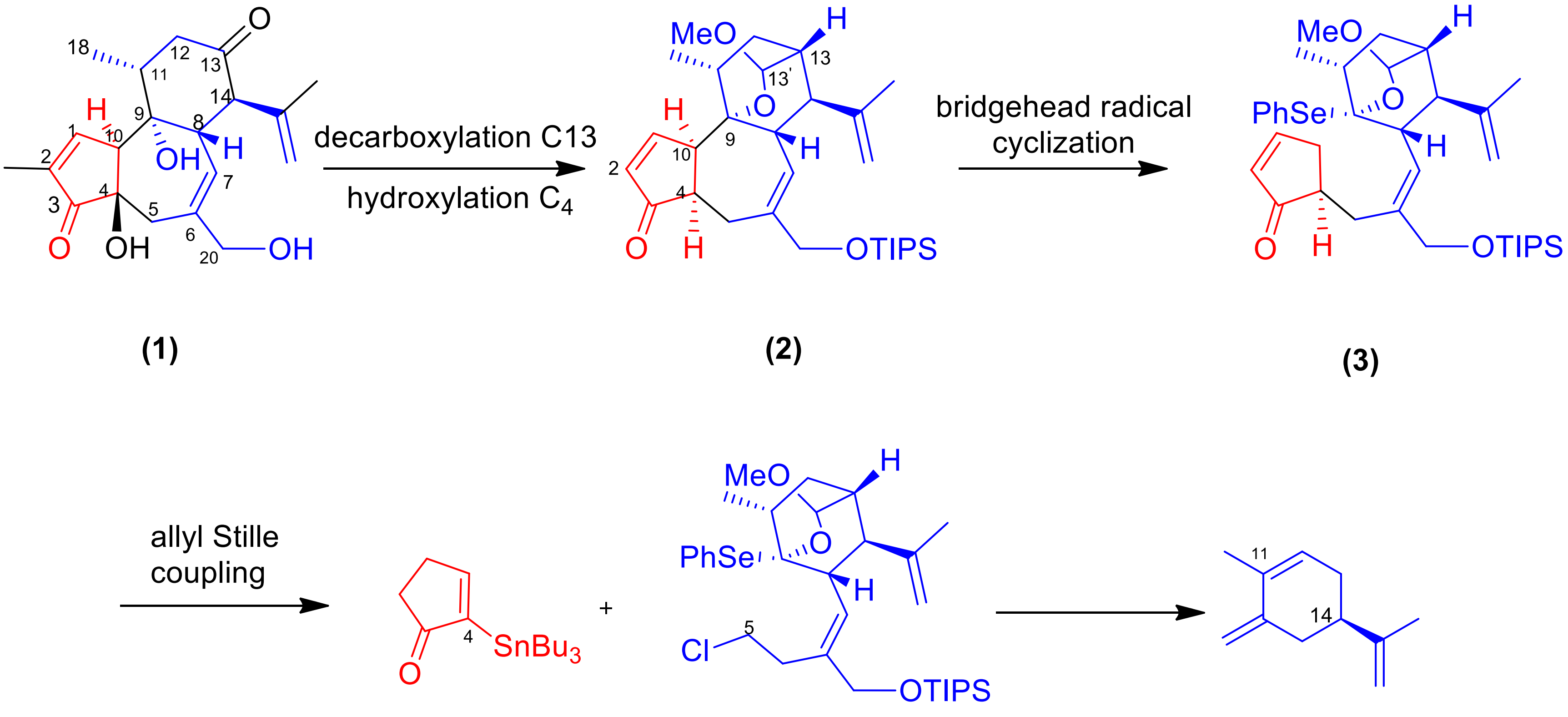


Phorbol: X = OH, R^1 = H
Prostrain: X = H, R^1 = Ac



Resiniferatoxine: R^2 = H

Approach



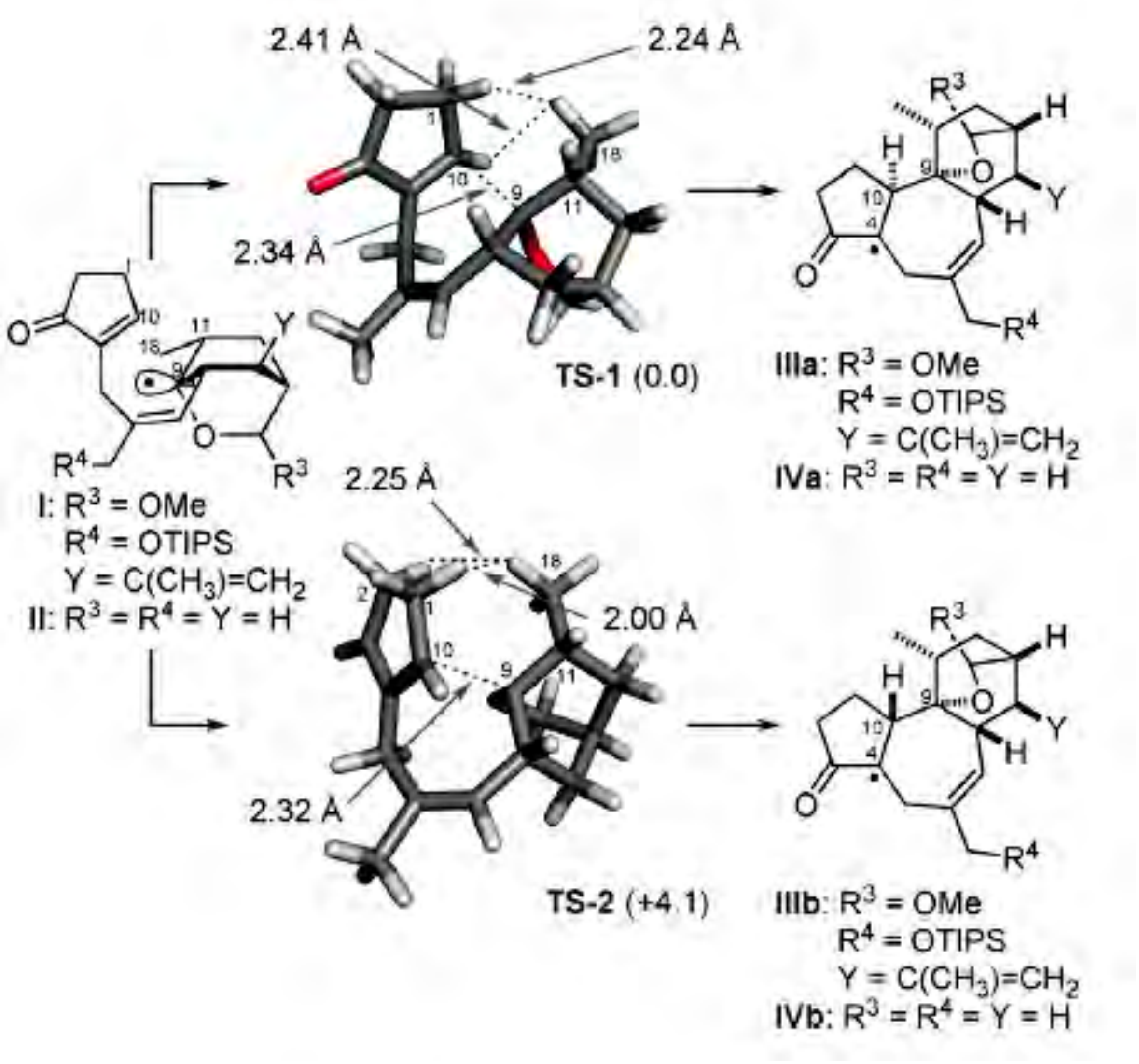
(1) (2) (3)

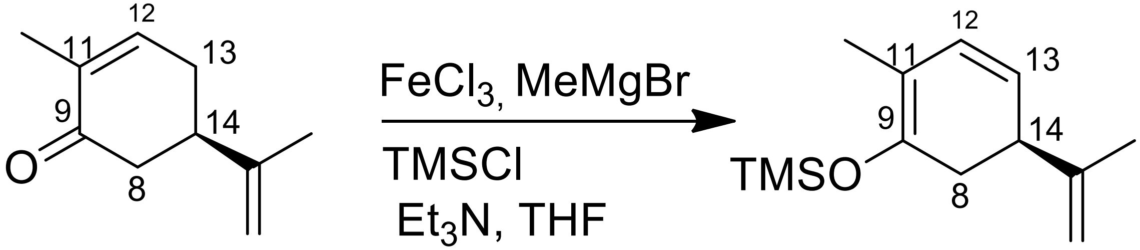
(A) (4) (R)-carvone

Challenge:

Making C9-C10 (**α-alkoxy bridgehead radical reaction**), C10 sterio center

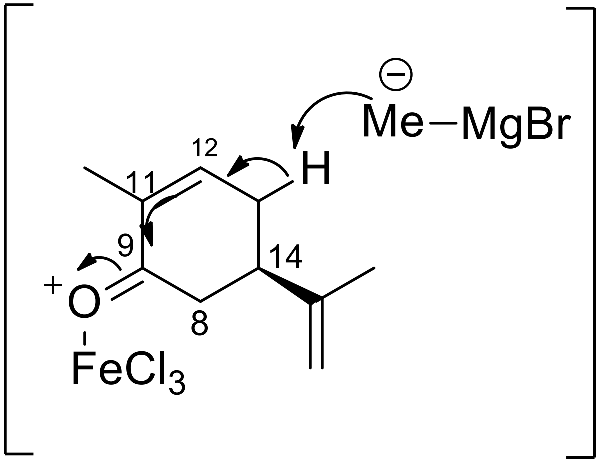
Cyclopentanone as radical acceptor and O,Se-acetal as radical donor



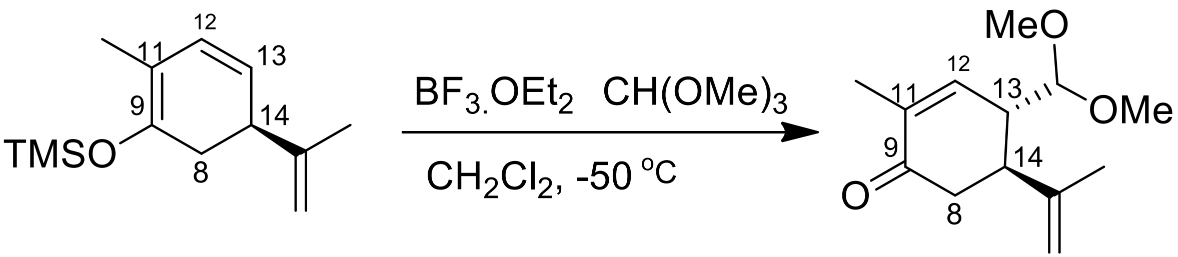

12
11
13
9
14
O
8
FeCl3, MeMgBr
TMSCl
Et3N, THF
12
11
13
9
14
TMSO
8

5

6


⊖
Me−MgBr
12
H
11
9
14
+O
8
FeCl3

Mukiyama aldol reaction



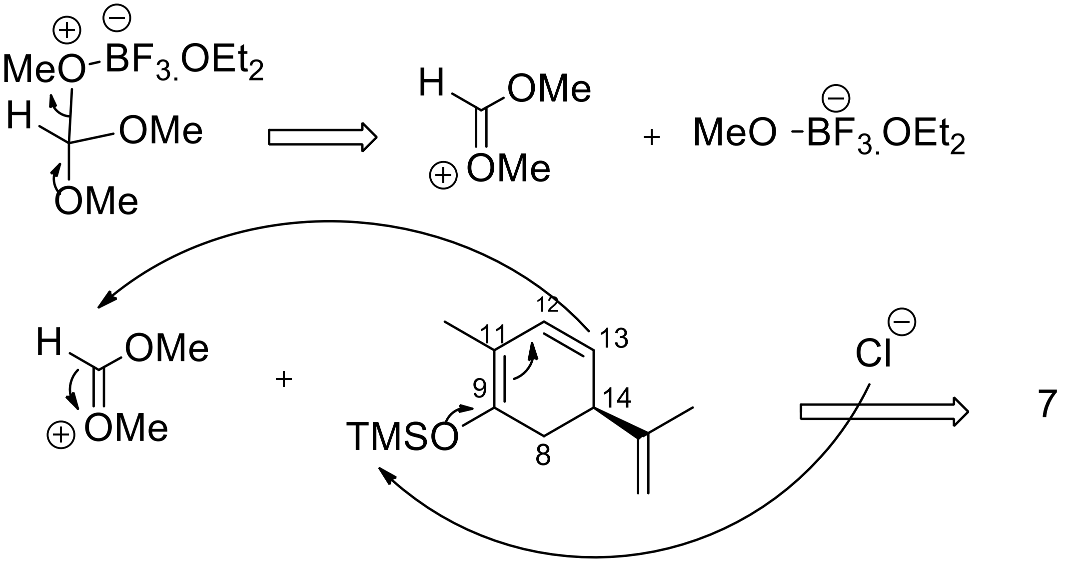
6

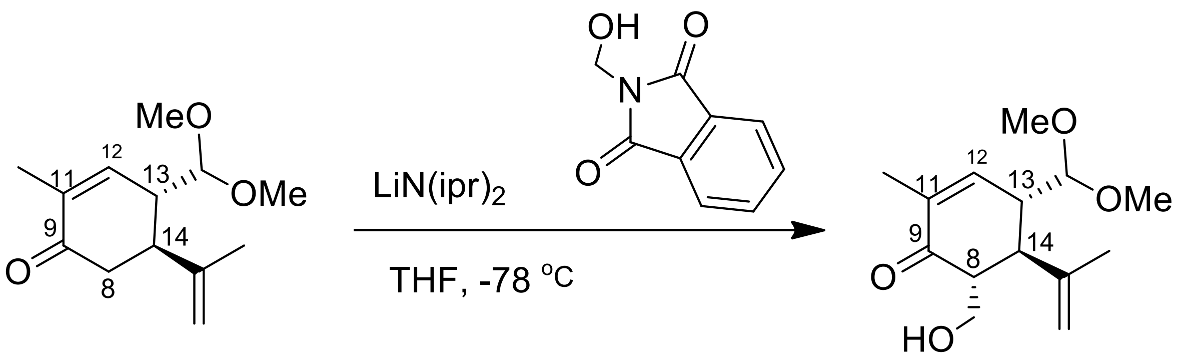
7

dr: 5:1, 2 steps

45%

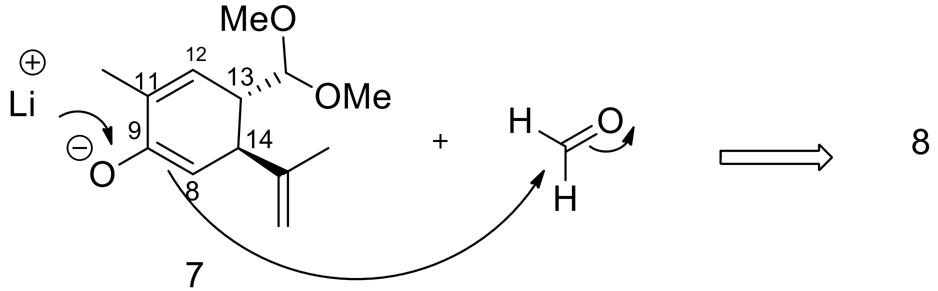
Anti to bulky isopropyl





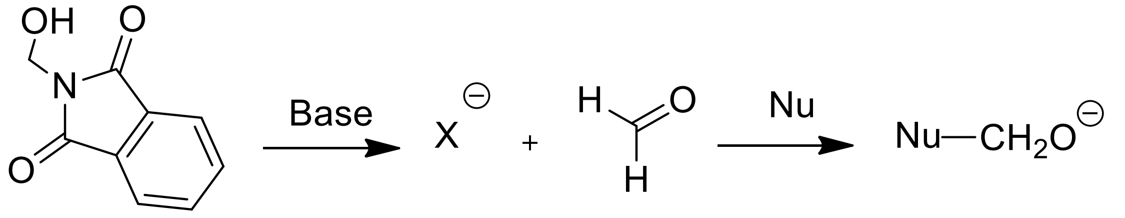
7

8

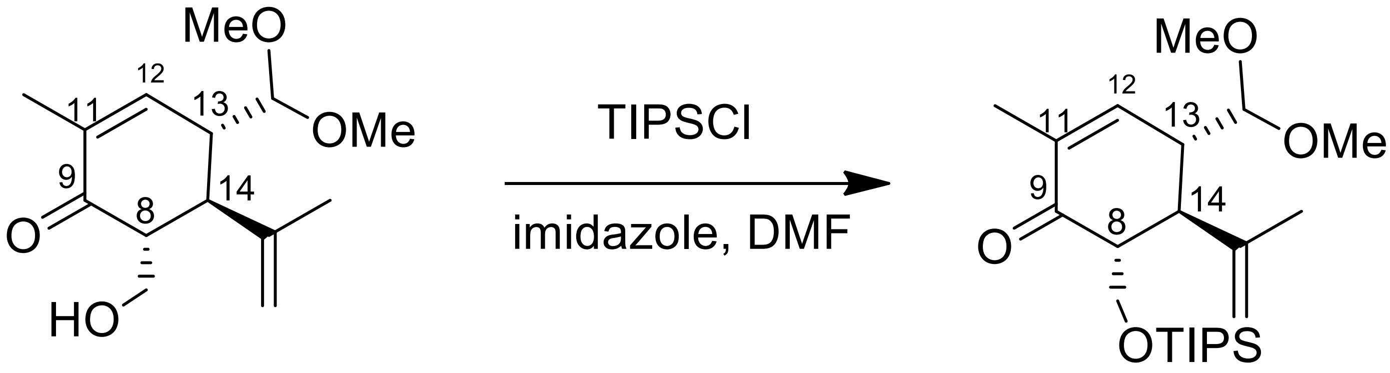


7

In-situ generation of formaldehyde

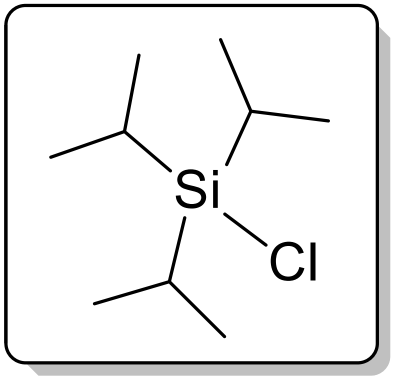


G. Deguest, L. Brishoff, C. Fruit, F. Marsais, Org. Lett. 2007, 9, 1165.

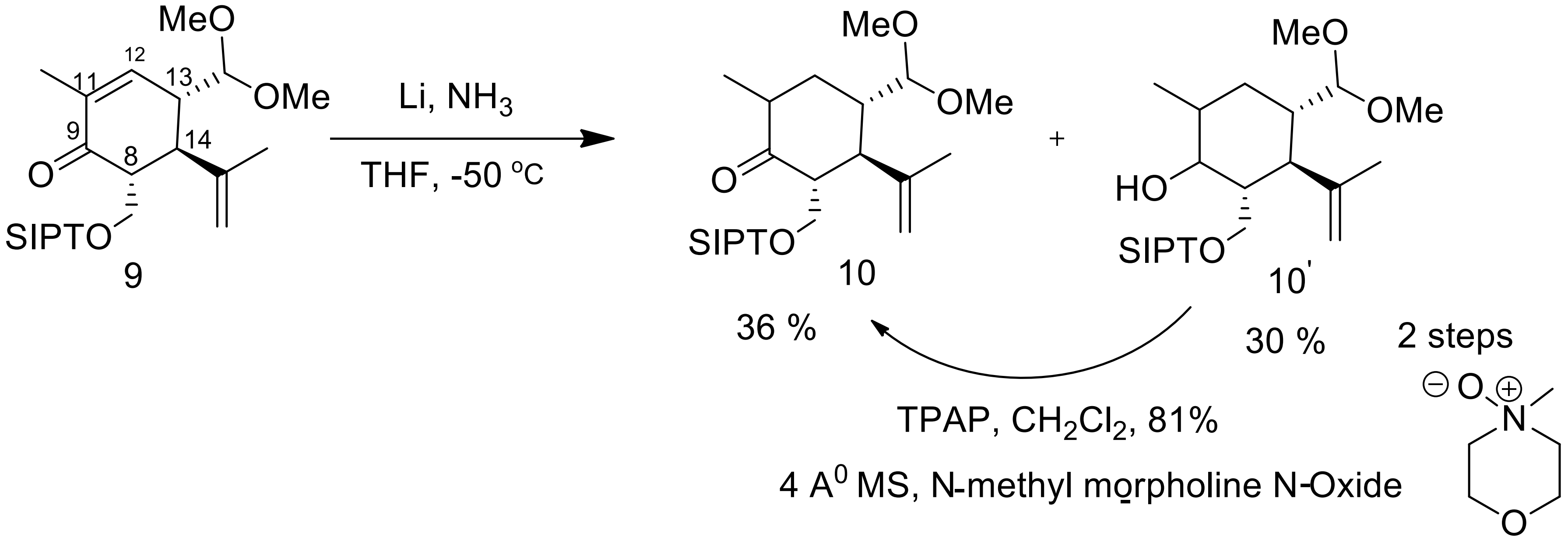

MeO
OMe
12
11
13
9
14
8
O
HO
TIPSCl
imidazole, DMF
MeO
OMe
12
11
13
9
14
8
O
OTIPS

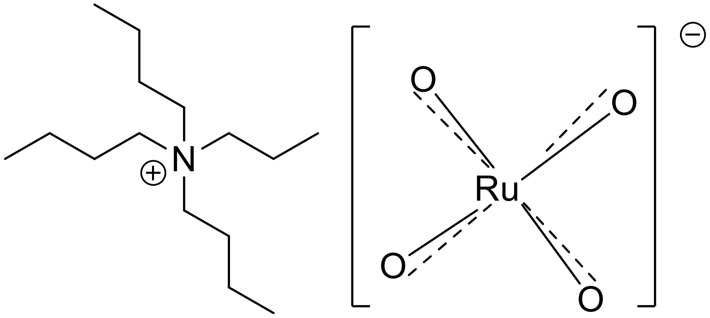
8

9

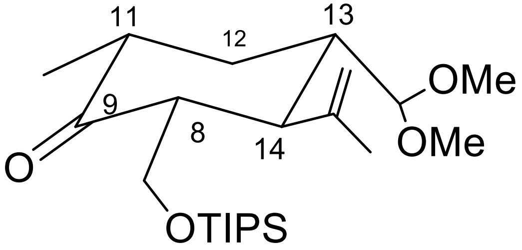

Si
Cl

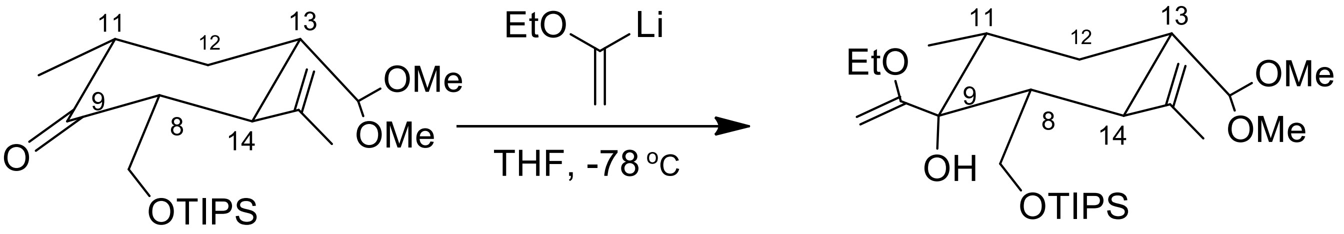
Birch reduction





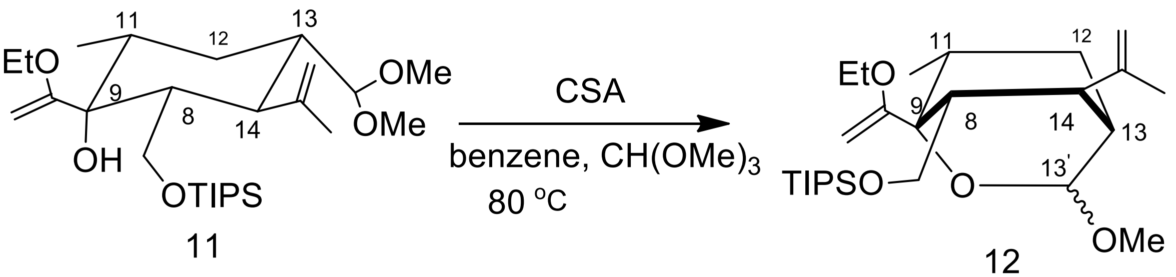
Lay-Griffith reagent



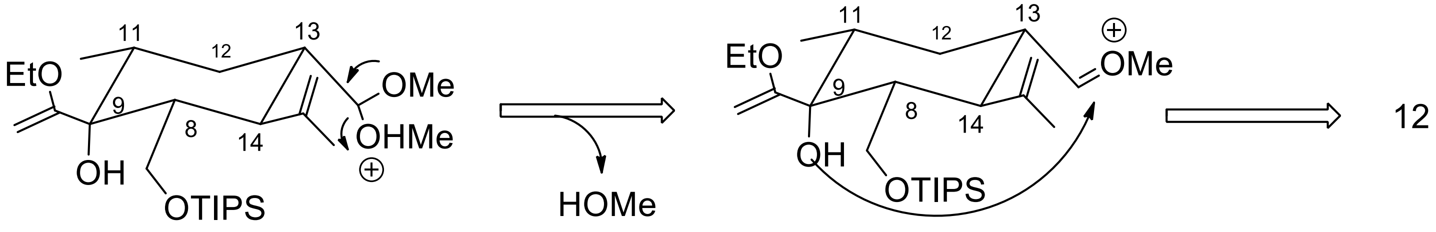

11
12
13
9
8
14
OMe
OMe
O
OTIPS
EtO
Li
THF, -78 ºC
11
12
13
EtO
9
8
14
OMe
OMe
OH
OTIPS

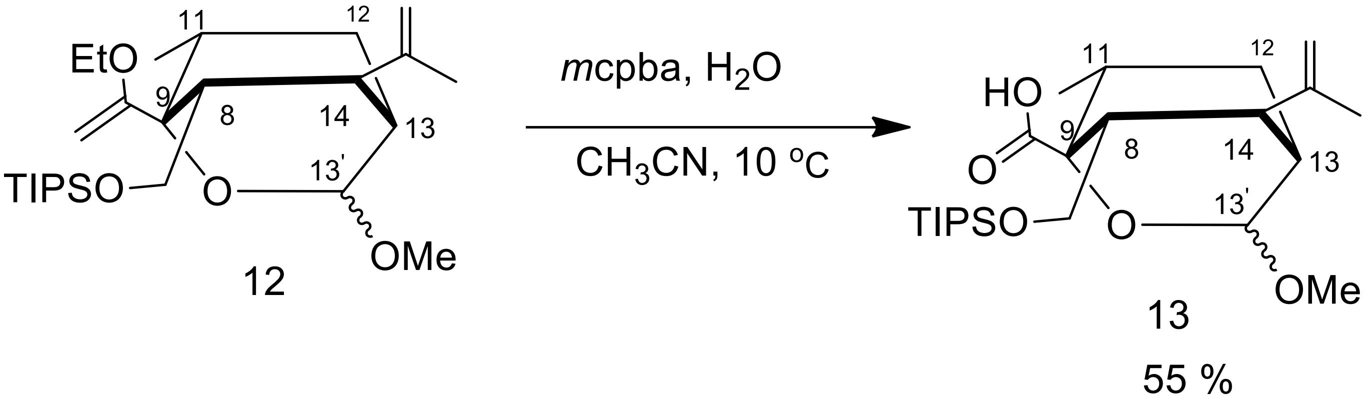
10

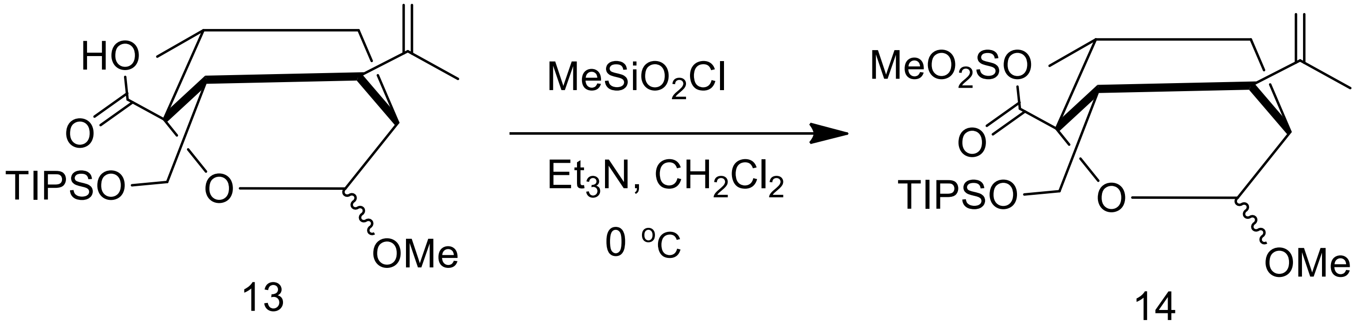
11


11
12
13
EtO
9
8
14
OMe
OMe
OH
OTIPS
11
CSA
benzene, CH(OMe)3
80 ºC
11
12
EtO
9
8
14
13
TIPSO
O
13'
OMe
12

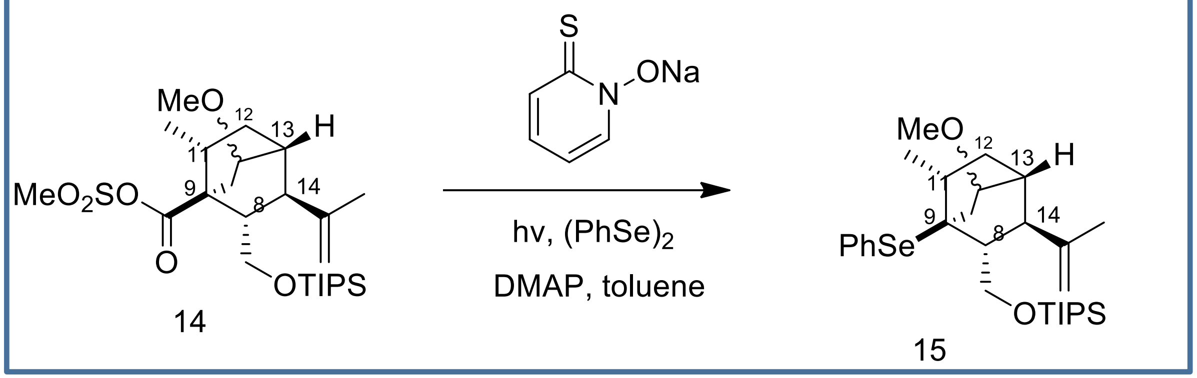
96 % dr: 1:1


11
12
13
EtO
9
8
14
OMe
OHMe
⊕
OH
OTIPS
HOMe
11
12
13
⊕
OMe
EtO
9
8
14
OH
OTIPS
12


EtO
11
12
9
8
14
13
13'
TIPSO
O
OMe
12
*m*cpba, H_2O
CH_3CN, 10 °C
HO
O
11
12
9
8
14
13
13'
TIPSO
O
OMe
13
55 %

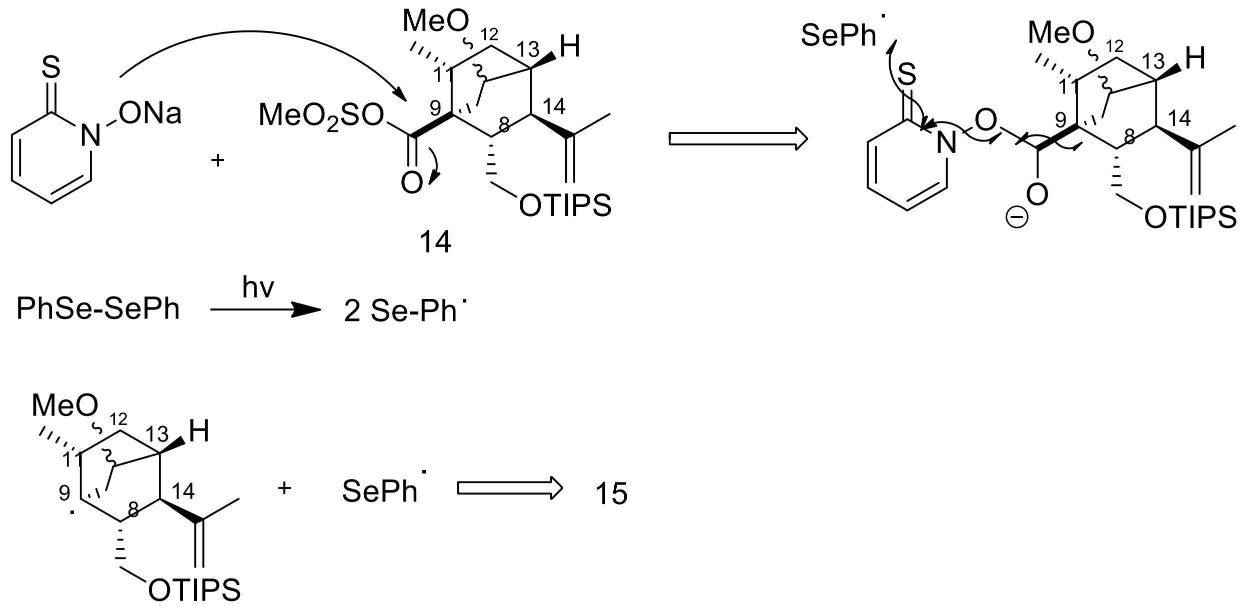

HO
O
TIPSO
O
OMe
13
$MeSiO_2Cl$
Et_3N, CH_2Cl_2
0 °C
MeO_2SO
O
TIPSO
O
OMe
14

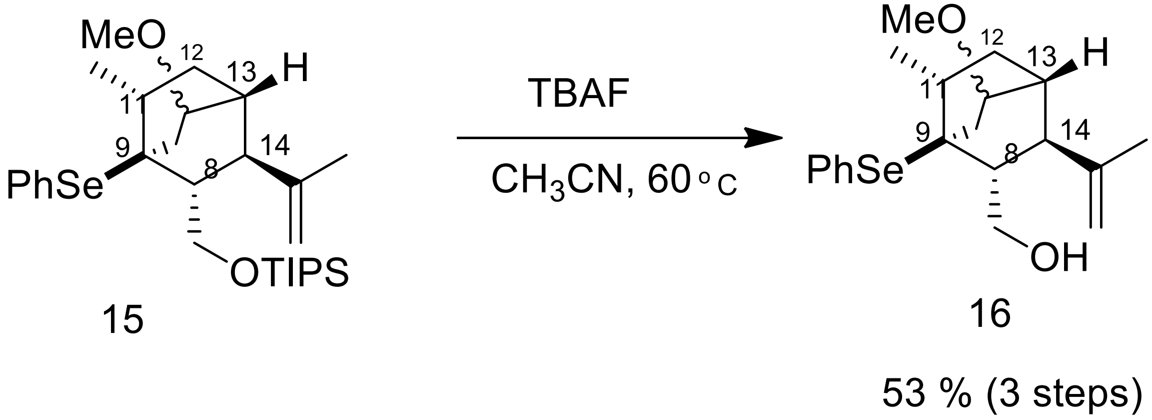
Barton decarboxylation

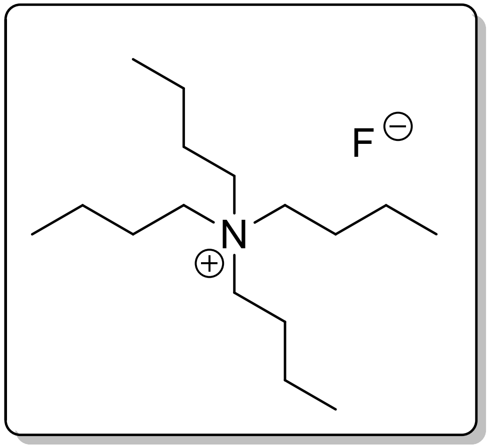


14

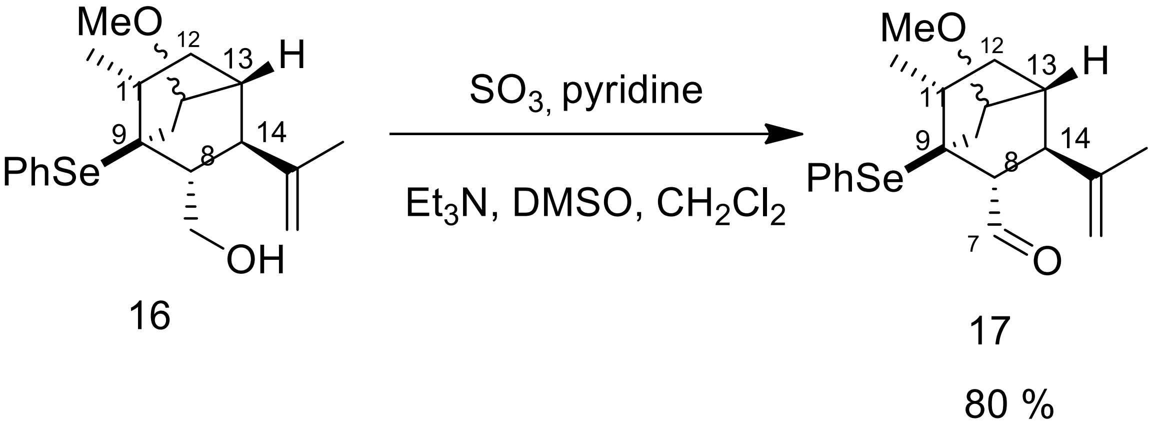
15

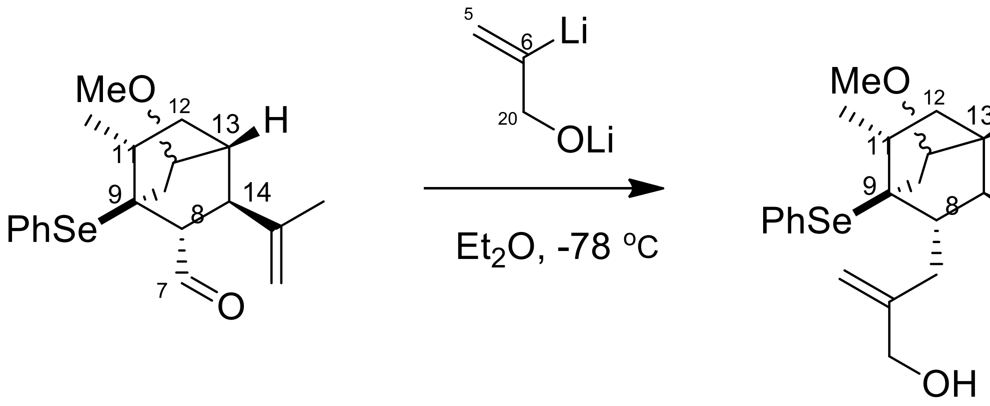






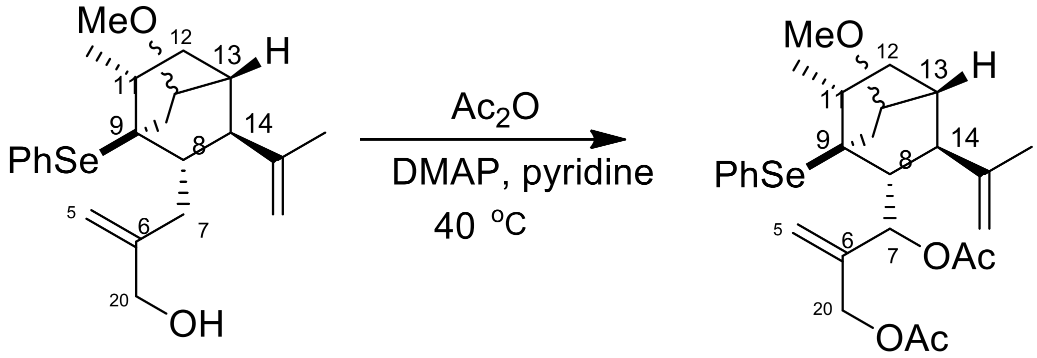
alcohol oxidation




MeO
12
13
H
11
9
14
8
PhSe
7
O
5
6
Li
20
OLi
Et$_2$O, -78 °C
MeO
12
13
H
11
9
14
8
PhSe
OH

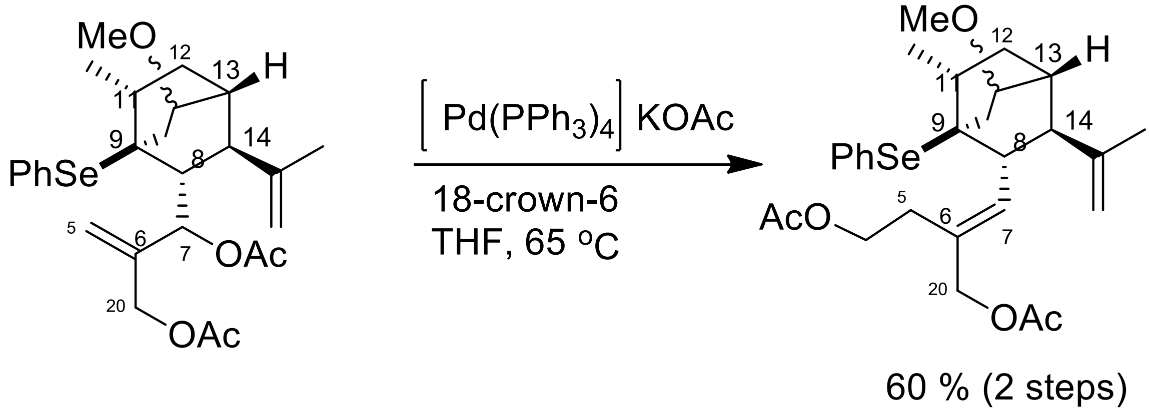
17

18


MeO
12
13
H
11
9
14
8
PhSe
5
6
7
20
OH
Ac$_2$O
DMAP, pyridine
40 °C
MeO
12
13
H
11
9
14
8
PhSe
5
6
7
OAc
20
OAc

18

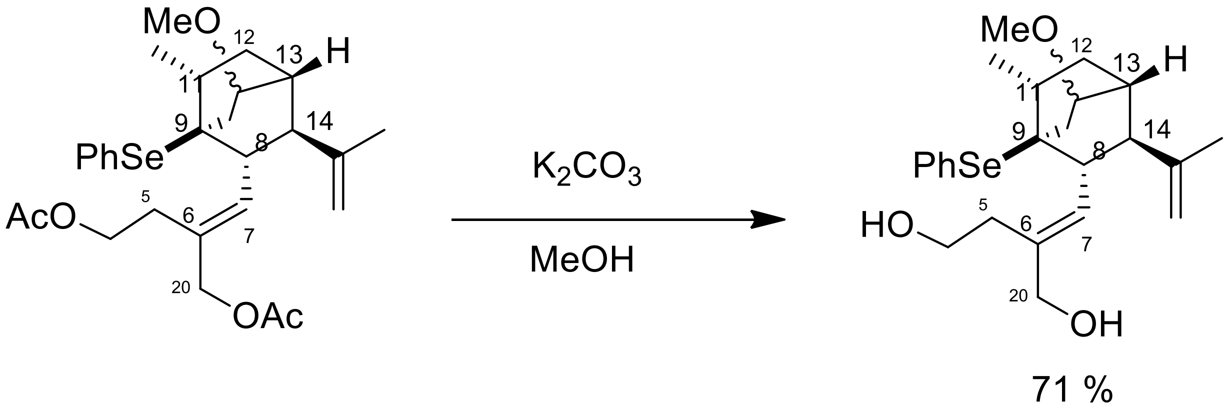
19



19

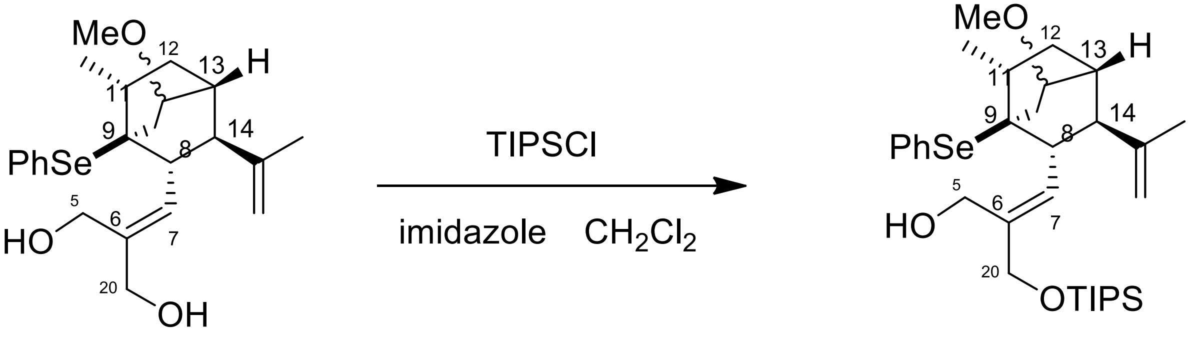
20

Catalyst isomerizes disubstituted olefin to trisubstituded olefin.



20

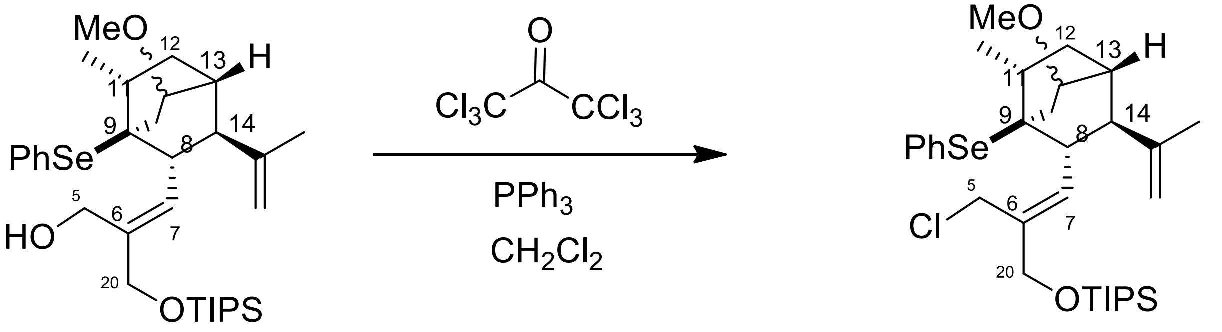
21



72 %

21

22

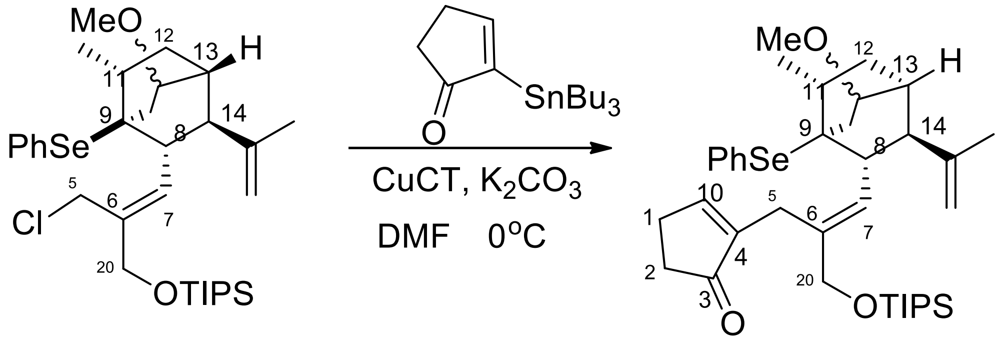


22

4

Less hindered OH will be capped by TIPSCl and the other OH will be cholorinated.

Stille coupling reaction



60 % (2 steps)

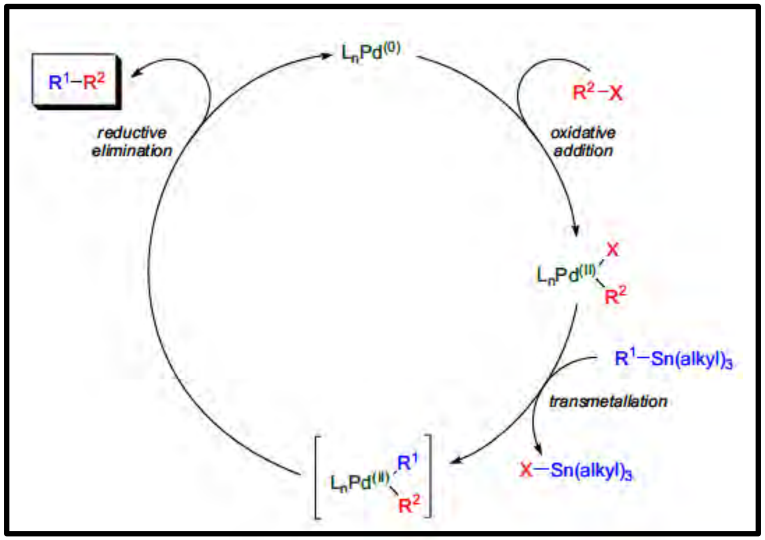
4

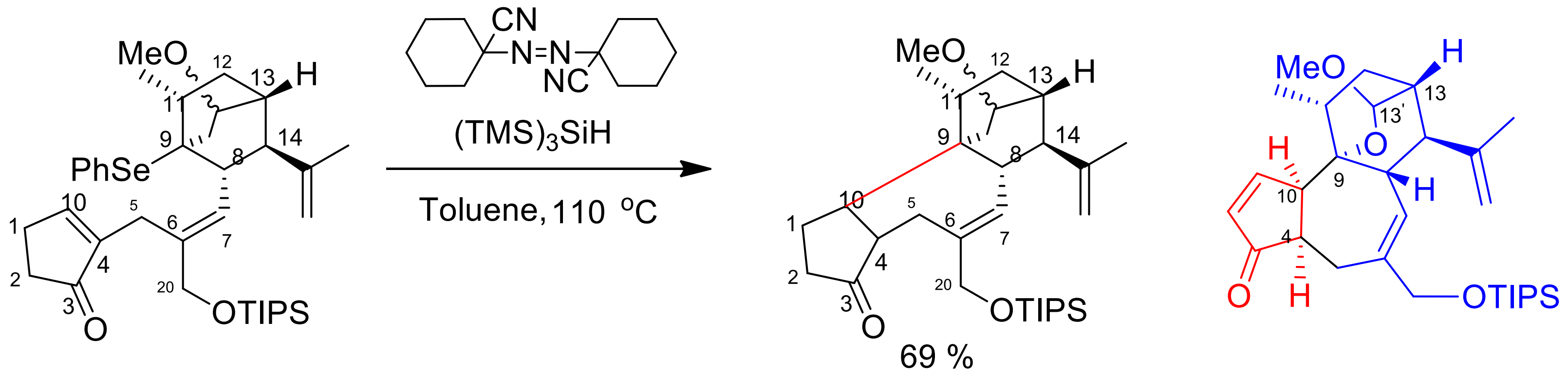
3

General scheme:

$$R^1Sn(alkyl)_3 \quad + \quad R^2X \xrightarrow{\text{Pd catalyst}} R^1{-}R^2 \quad + \quad X\text{-}Sn(alkyl)_3$$

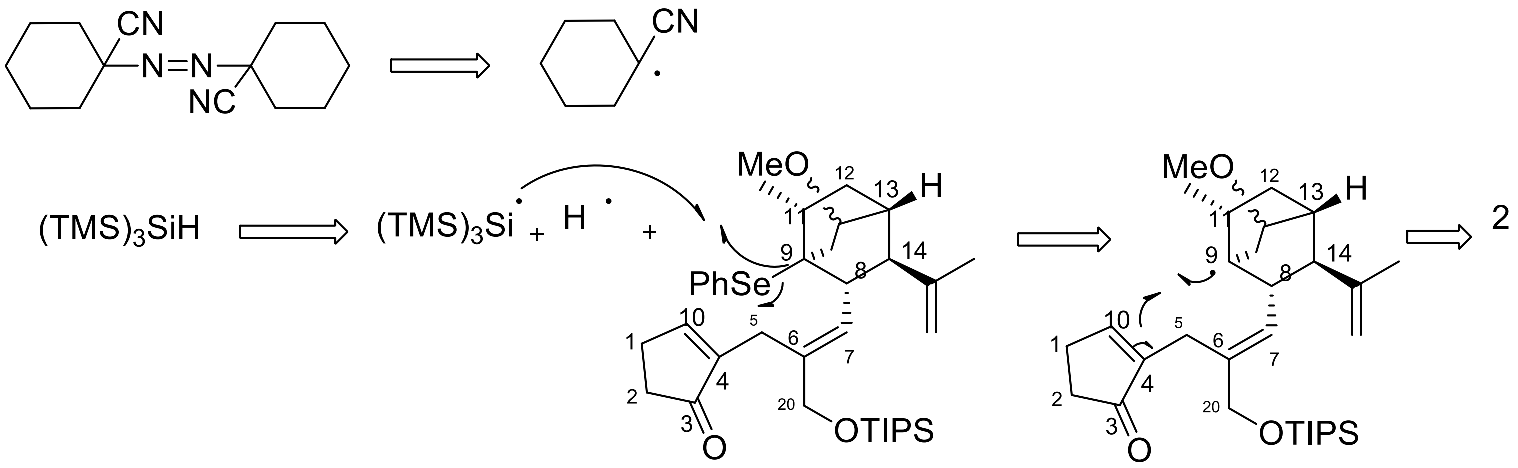
Catalytic cycle:



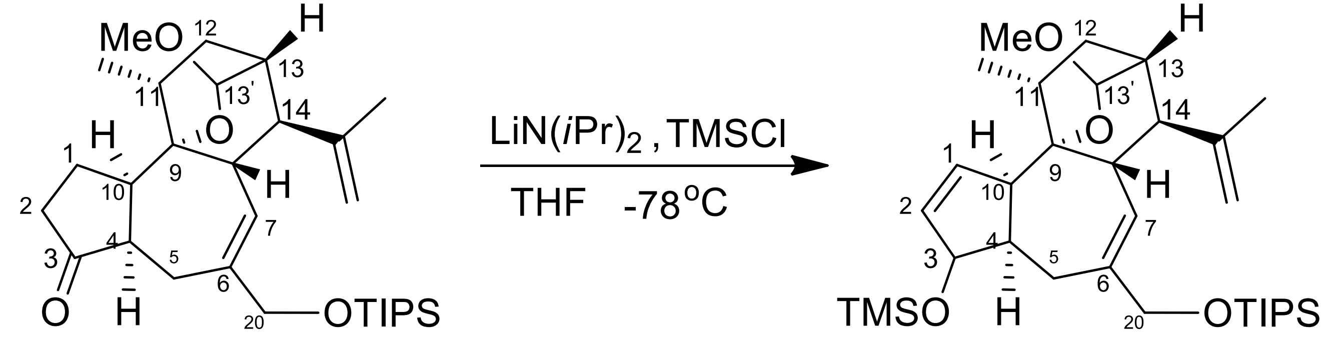

MeO
PhSe
OTIPS
CN
N=N
NC
(TMS)3SiH
Toluene, 110 °C
69 %
H
O
1
2
3
4
5
6
7
8
9
10
11
12
13
13'
14
20

3

2

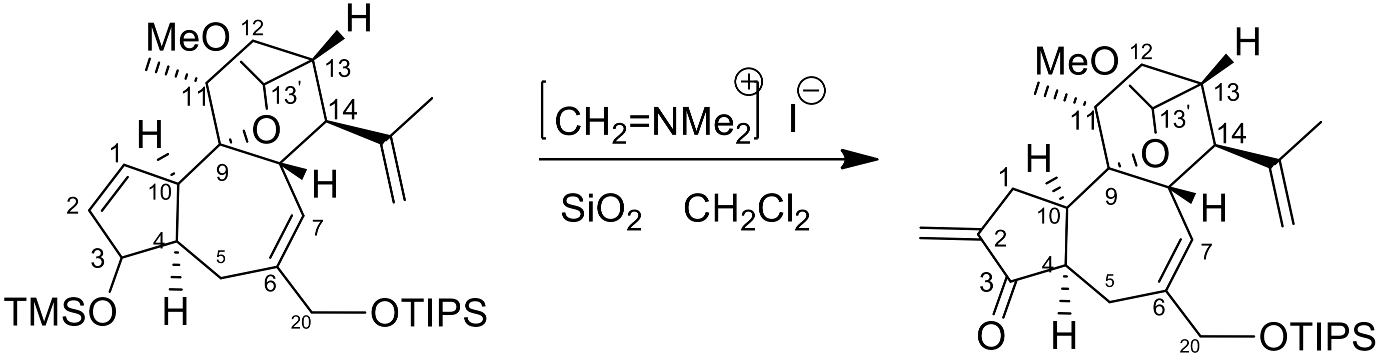

CN
N=N
NC
(TMS)3SiH
(TMS)3Si
+
H
+
MeO
PhSe
OTIPS
H
O
1
2
3
4
5
6
7
8
9
10
11
12
13
14
20
2

^{o}C



2

23



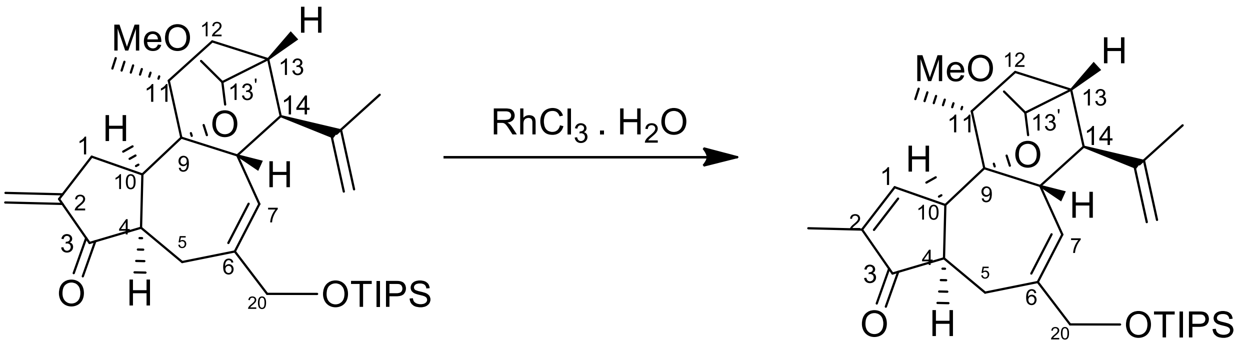
n-hexane/EtOAc
10:5

65 % (2 steps)

23

24

Eschenmoser’s reagent: enolate attack carbon

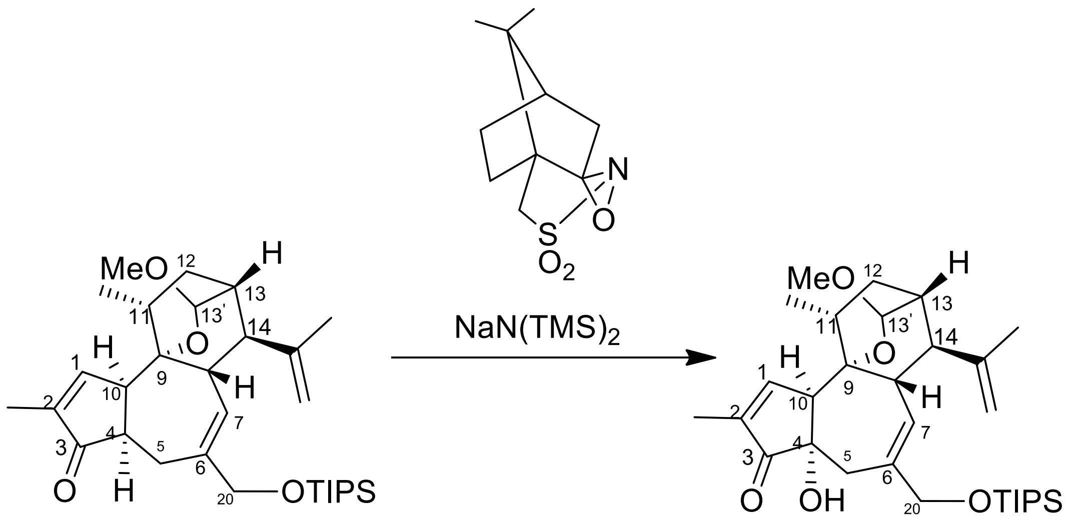


69 %

24
Exo olefin

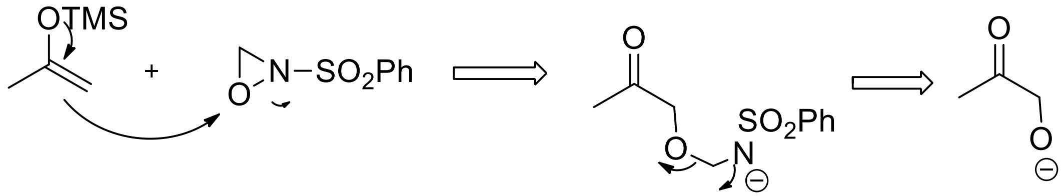
25
Endo olefin
More stable

Davis oxidation:

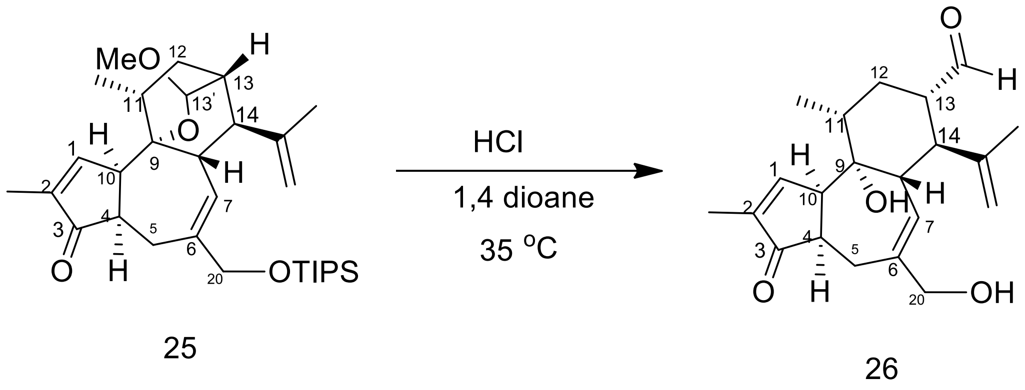


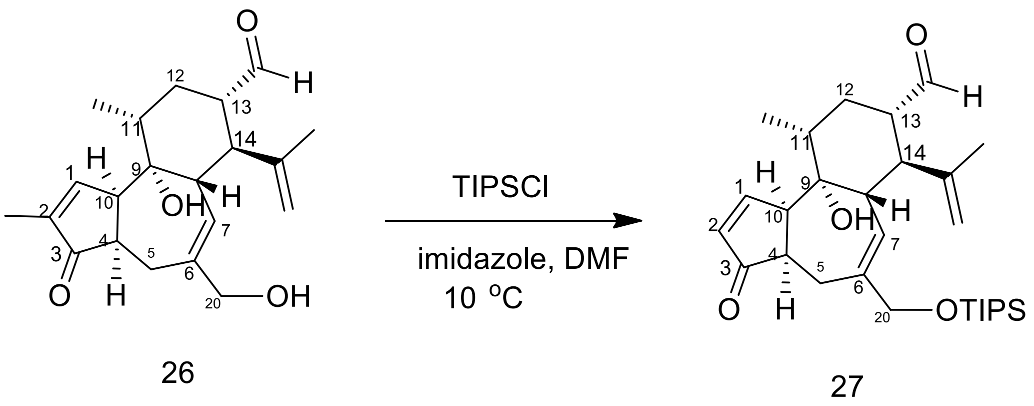
25

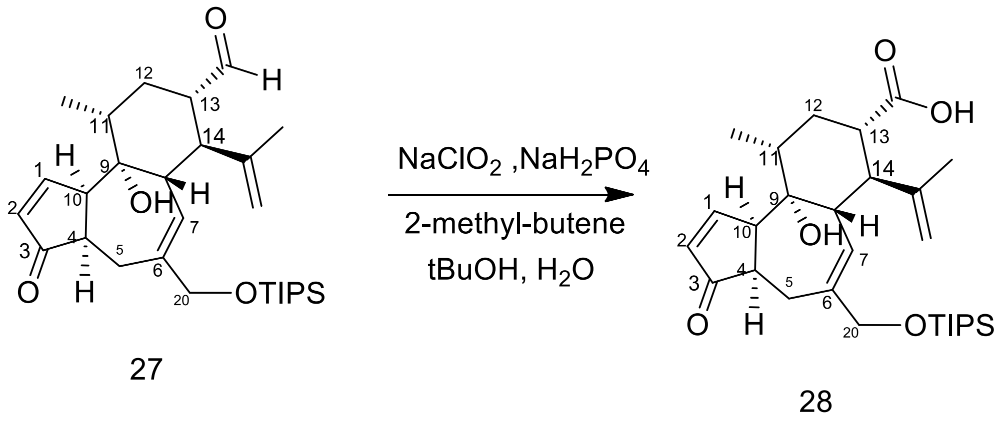
I

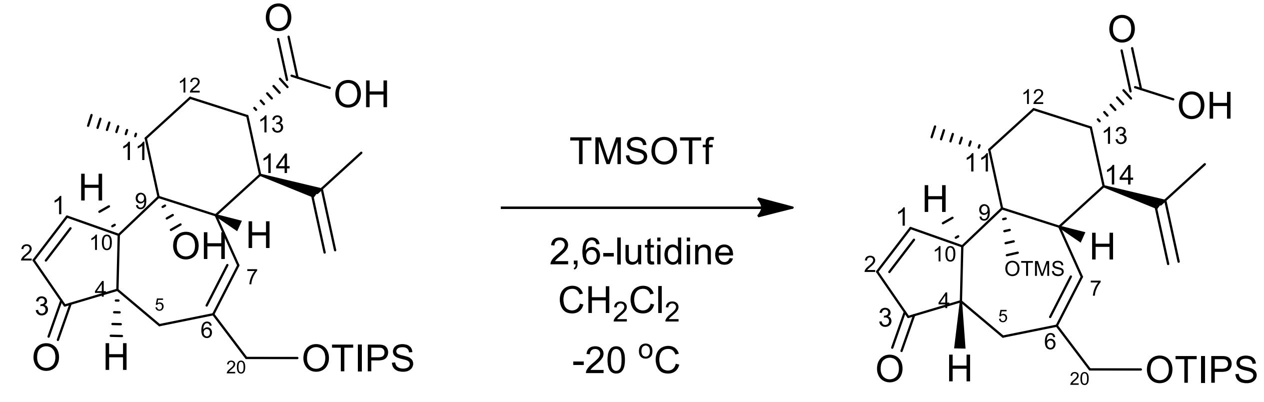


This idea did not work, because it puts OH group on back.


25
HCl
1,4 dioane
35 ^{o}C
26


26
TIPSCl
imidazole, DMF
10 ^{o}C
27

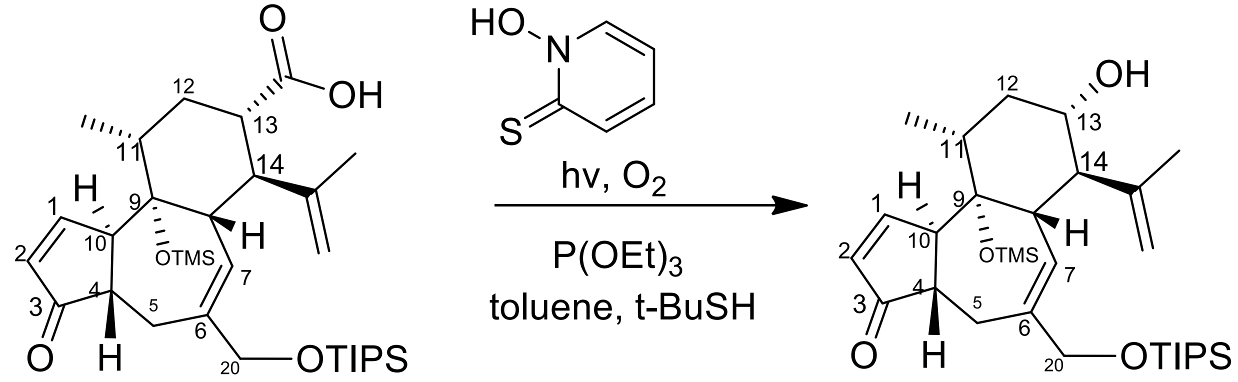

27
NaClO$_2$,NaH$_2$PO$_4$
2-methyl-butene
tBuOH, H$_2$O
28



54 % (4 steps)

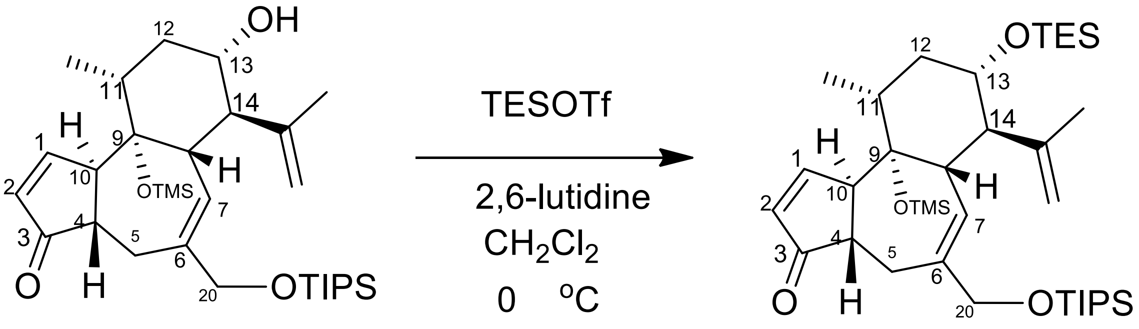
28

29



29

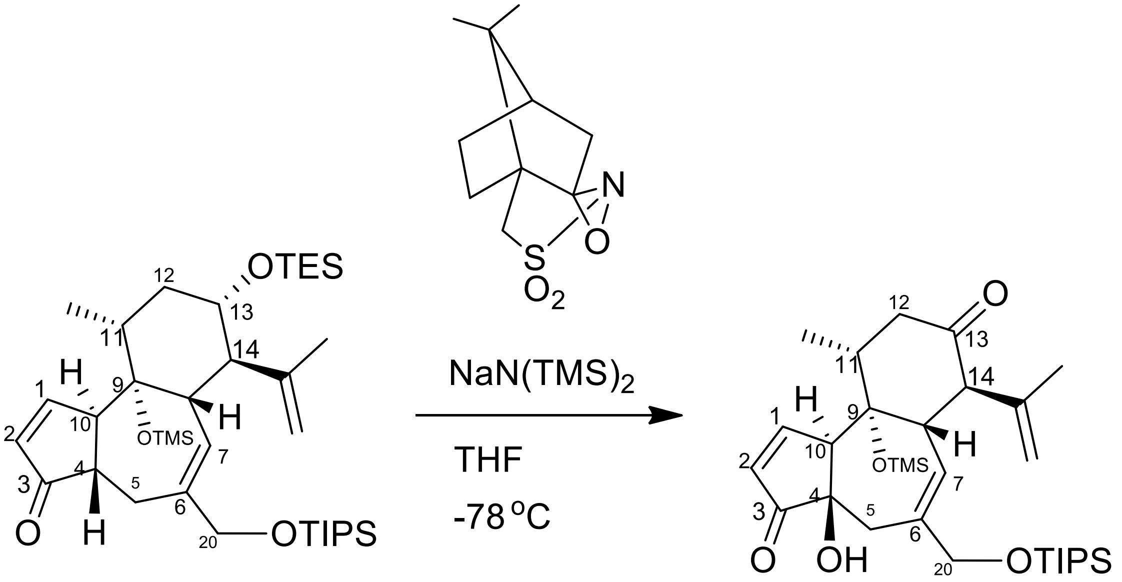
30



35 % (2 steps)

30

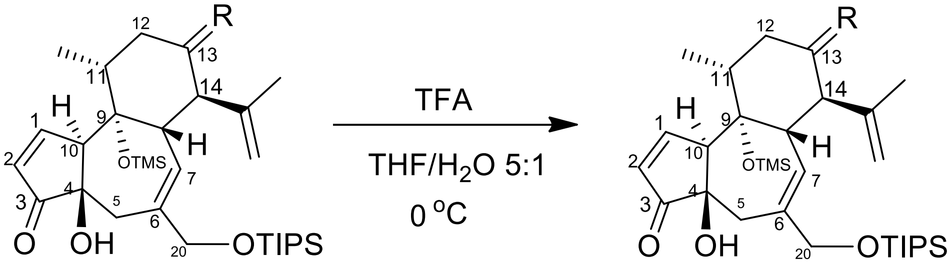
31



43 %

31

32

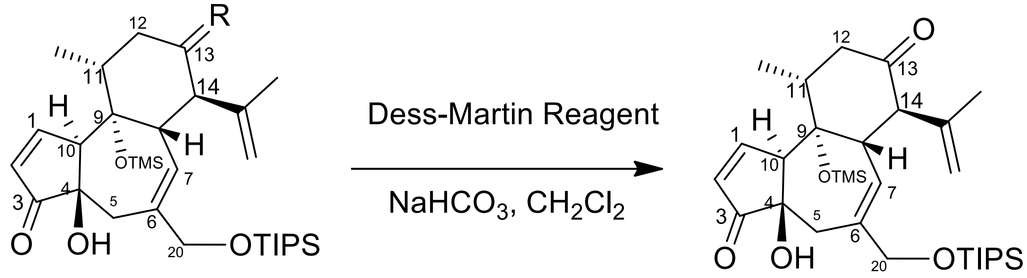


32

R: OTES, H

33

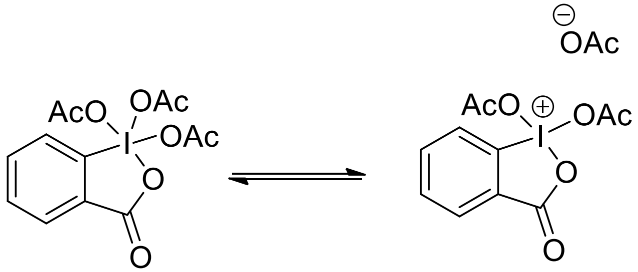
R: OH, H

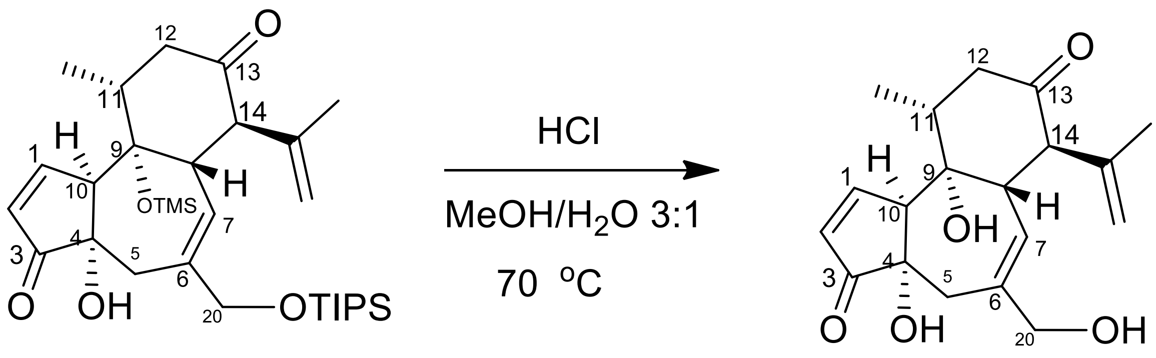


33

R: OH, H

34
80 % (2 steps)





83 %

34

1

Thank you for your attention