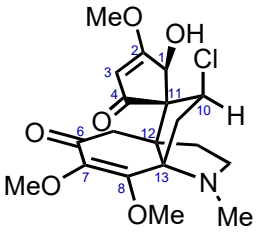
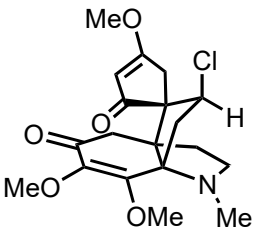
Enantioselective Synthesis of (-)-10-Hydroxyacutuminine

10.1002/anie.202117480 17.03.2022



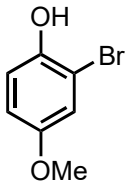
(-)-acutumine (**1**)



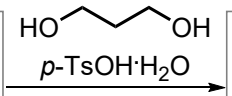
(-)-acutuminine (**3**)

C1 late-stage oxidation

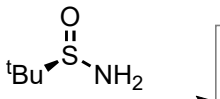
- first isolated from the Chinese moonseed plant in 1929
- structure solved by single-crystal X-ray diffraction in 1967
- selective T-cell cytotoxicity and anti-amnesic activity
- densely functionalized [4.3.3]propellane cores
- a spirofused cyclopentenone and vicinal quaternary centers



$PhI(OAc)_2$
MeOH, 0 °C
86%

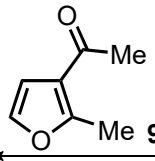


p-TsOH·H_2O
PhH, 70 °C
77%



$Ti(OEt)_4$, THF, 70 °C
67%

8

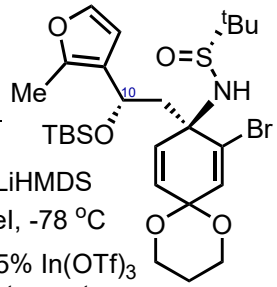


NaHMDS
THF, -78 °C
90%, >98:2 dr
>20 g scale

9

10

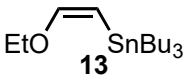
Structure?
L-Selectride, -78 °C,
then, TBSCl, imidazole
98%
single diastereomer



1) LiHMDS
MeI, -78 °C
2) 5% $In(OTf)_3$
acetone, rt
(76%, 2 steps)

11

12



5% $Pd_2(dba)_3$
20% $AsPh_3$
94%

13

14

1) I_2, acetone
2) $NaBH_4$, AcOH
3) LiOH, H_2O_2, MeOH
(53%, 3 steps)

7

Reaction Mechanism?

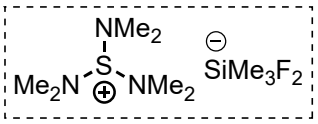
2 eq $BF_3{\cdot}Et_2O$
m-CPBA

LiOH (xs)
MeOH

$h\nu$
315-400 nm
PhH/pentane

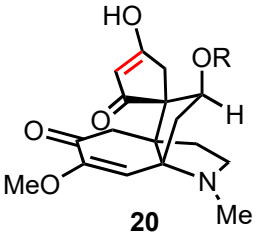
17 **16** **15**

K_2CO_3
MeOH
quantitative

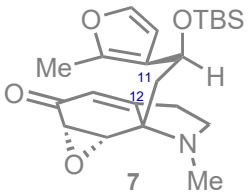


TASF (xs)
H_2O (xs)

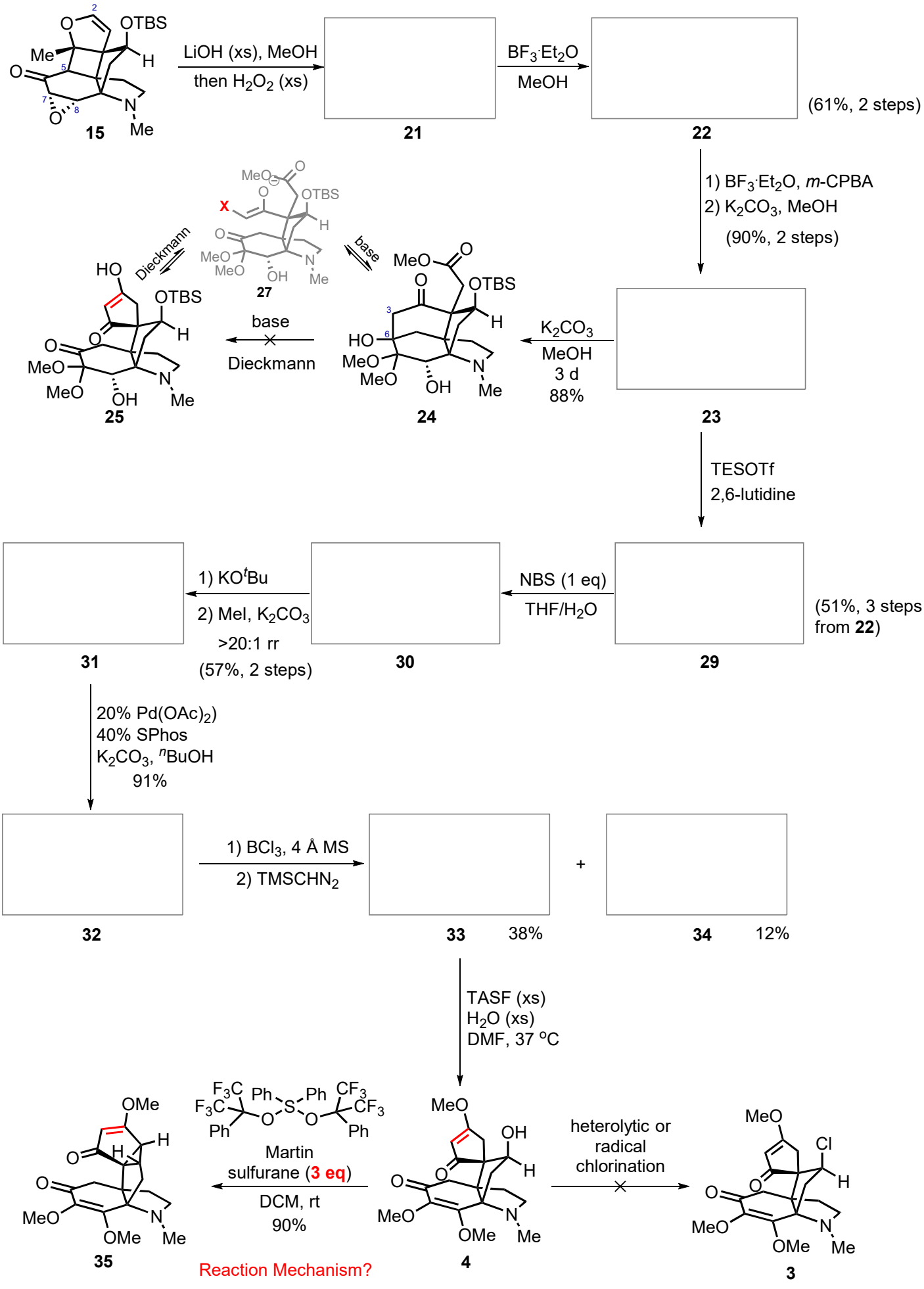
base
Dieckmann



18 **19** **20**



7


15
LiOH (xs), MeOH
then H_2O_2 (xs)
21
$BF_3{\cdot}Et_2O$
MeOH
22
(61%, 2 steps)
1) $BF_3{\cdot}Et_2O$, *m*-CPBA
2) K_2CO_3, MeOH
(90%, 2 steps)
23
K_2CO_3
MeOH
3 d
88%
24
base
Dieckmann
27
Dieckmann
base
25
TESOTf
2,6-lutidine
29
NBS (1 eq)
THF/H_2O
(51%, 3 steps
from **22**)
30
1) KO^{t}Bu
2) MeI, K_2CO_3
>20:1 rr
(57%, 2 steps)
31
20% $Pd(OAc)_2$)
40% SPhos
K_2CO_3, ^{n}BuOH
91%
32
1) BCl_3, 4 Å MS
2) $TMSCHN_2$
33
38%
+
34
12%
TASF (xs)
H_2O (xs)
DMF, 37 °C
Martin
sulfurane (**3 eq**)
DCM, rt
90%
35
4
heterolytic or
radical
chlorination
3
Reaction Mechanism?

Enantioselective Synthesis of (-)-10-Hydroxyacutuminine (Solution)

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- first isolated from the Chinese moonseed plant in 1929
- structure solved by single-crystal X-ray diffraction in 1967
- selective T-cell cytotoxicity and anti-amnesic activity
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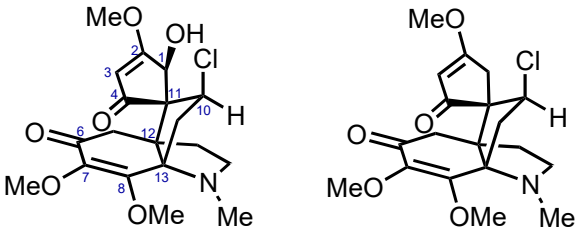
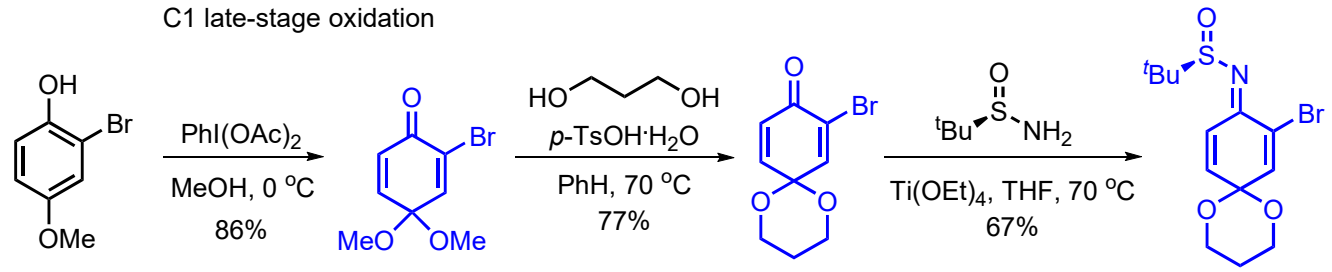
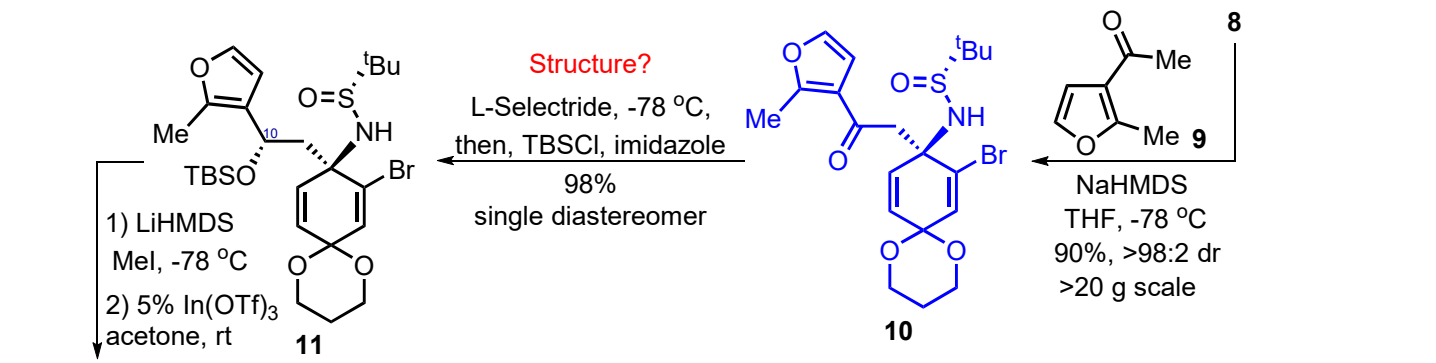
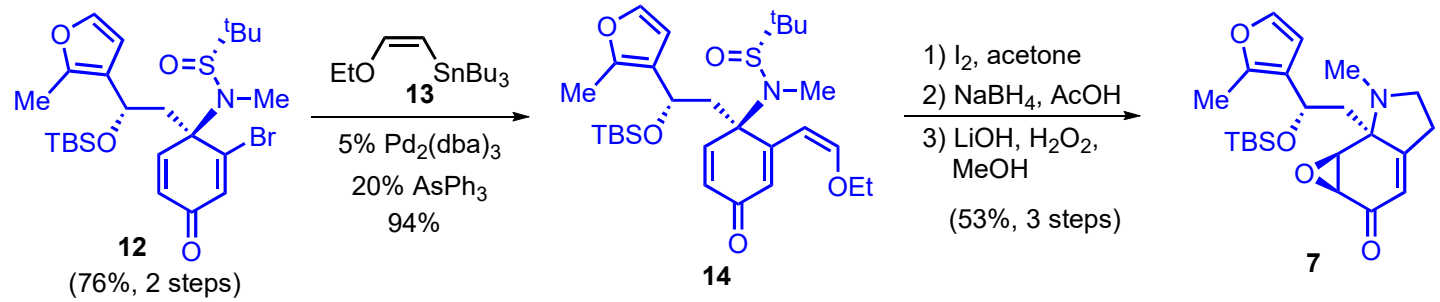
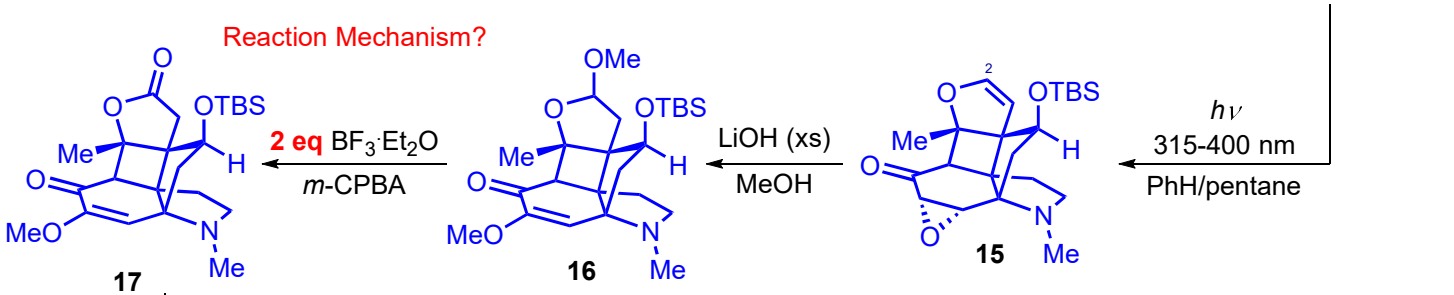
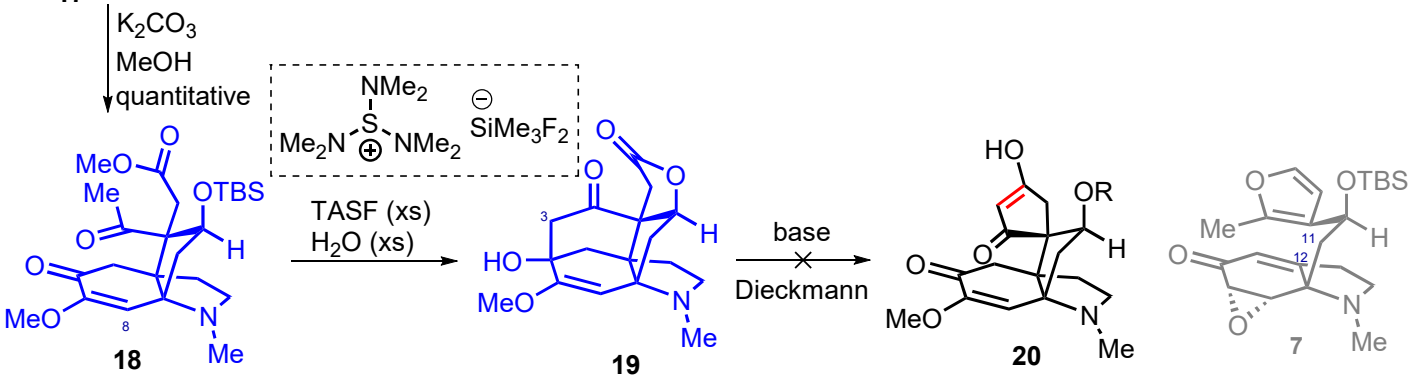


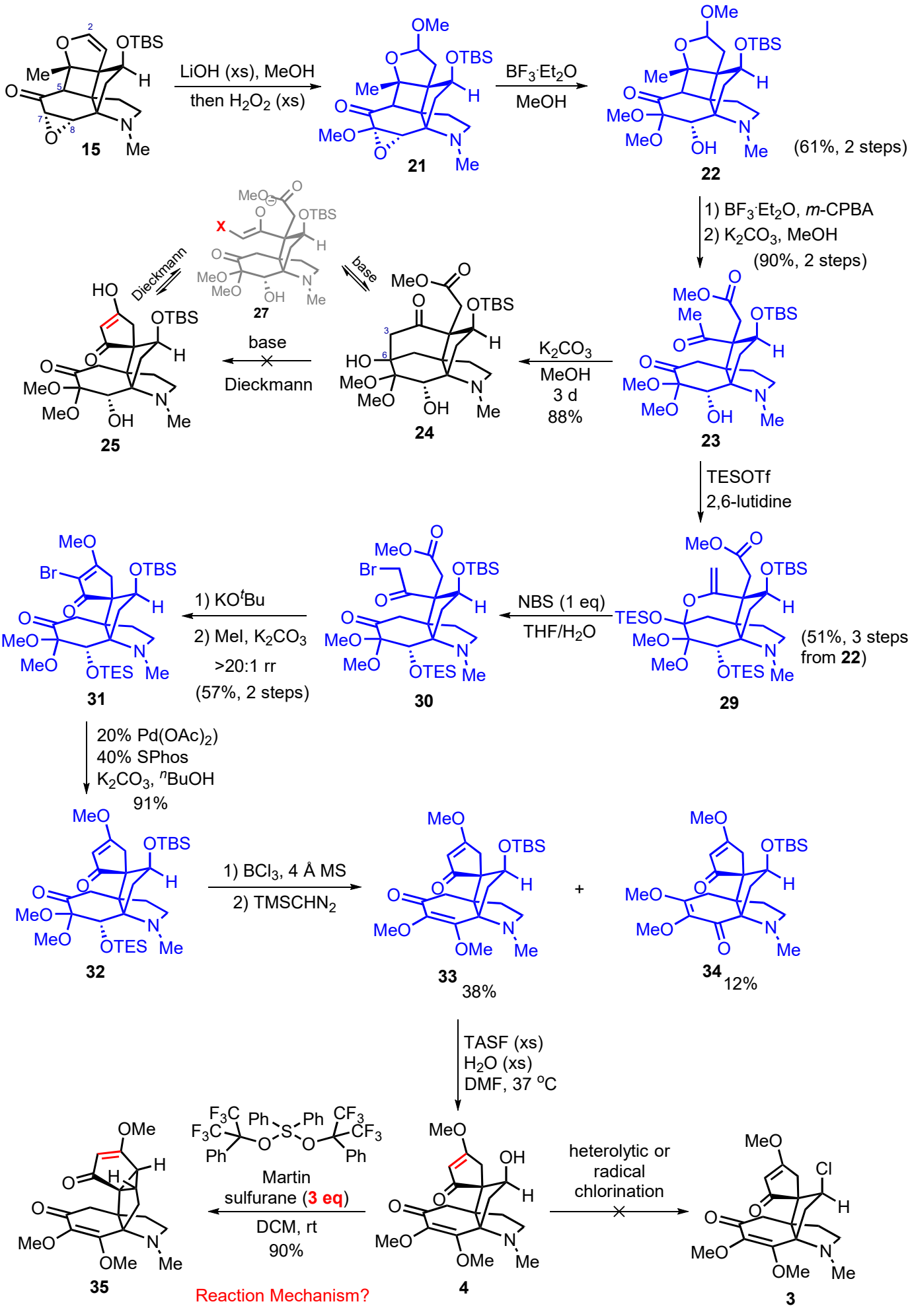




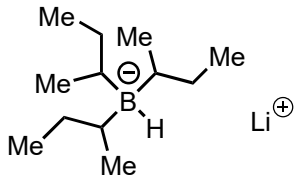







LiOH (xs), MeOH
then H2O2 (xs)
BF3·Et2O
MeOH
(61%, 2 steps)
1) BF3·Et2O, m-CPBA
2) K2CO3, MeOH
(90%, 2 steps)
K2CO3
MeOH
3 d
88%
base
Dieckmann
base
Dieckmann
TESOTf
2,6-lutidine
NBS (1 eq)
THF/H2O
(51%, 3 steps from 22)
1) KOtBu
2) MeI, K2CO3
>20:1 rr
(57%, 2 steps)
20% Pd(OAc)2)
40% SPhos
K2CO3, nBuOH
91%
1) BCl3, 4 Å MS
2) TMSCHN2
38%
12%
TASF (xs)
H2O (xs)
DMF, 37 °C
Martin
sulfurane (3 eq)
DCM, rt
90%
heterolytic or
radical
chlorination
Reaction Mechanism?

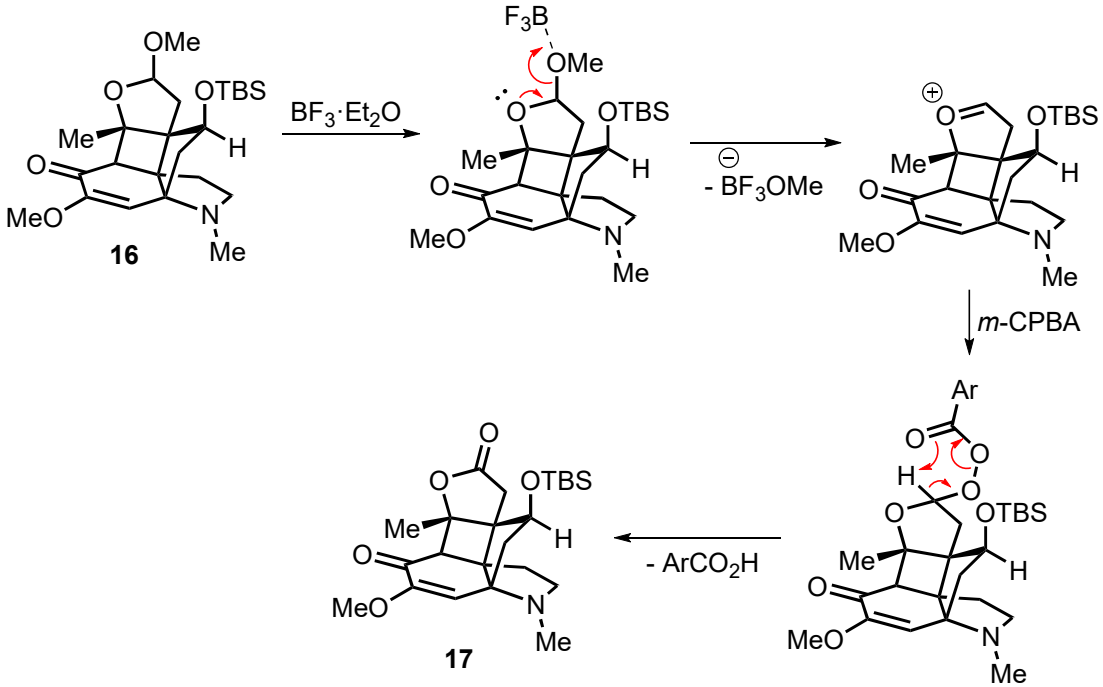
Structure of L-Selectride:



Reasons for using 2 eq $BF_3{\cdot}Et_2O$:

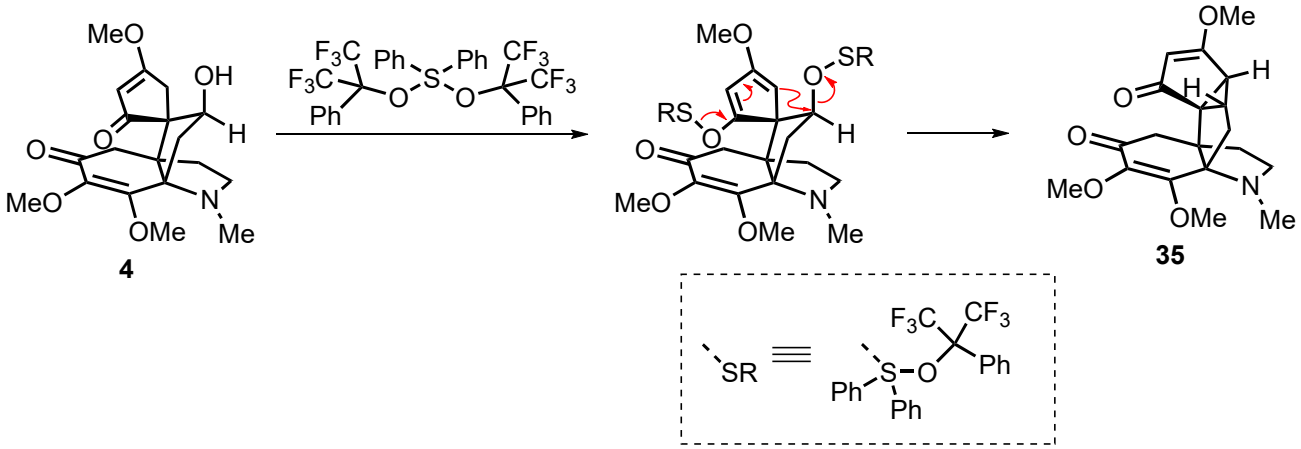
utilizing two equivalents of $BF_3{\cdot}Et_2O$ to mask the basic amine, which is otherwise rapidly oxidized by m-CPBA.

Reaction Mechanism of **16** to **17**:



Ref: P. A. Grieco, T. Oguri, Y. Yokoyama, *Tetrahedron Lett.* **1978**, *19*, 419–420.

Reaction Mechanism of **4** to **35**:



Ref: S. E. Reisman, J. M. Ready, M. M. Weiss, A. Hasuoka, M. Hirata, K. Tamaki, T. V. Ovaska, C. J. Smith, J. L. Wood, *J. Am. Chem. Soc*. **2008**, *130*, 2087–2100.