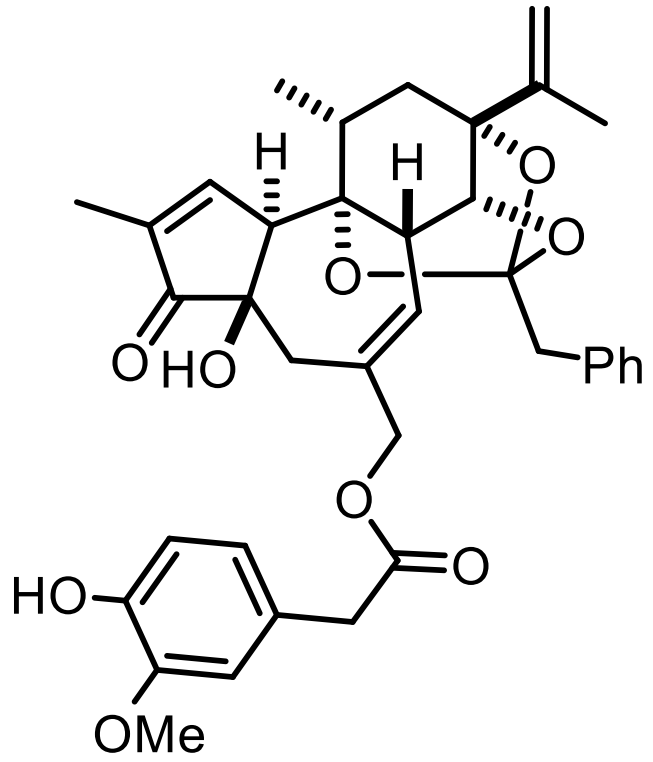
Total Synthesis of Resiniferatoxin



resiniferatoxin

Satoshi Hashimoto et al., *J. Am. Chem. Soc.* **2017**, *139*, 16420-16429
Yuto Hikone et al., *Org. Lett.* **2022**, *24*, 929-933

Hongpeng Lin
2025.12.11

Introduction of Prof. Masayuki Inoue

1989-1993 The University of Tokyo, B.S. in Chemistry,
1993-1998 The University of Tokyo, Ph.D. in Organic Chemistry,
Research advisor: Professor Kazuo Tachibana
1998-2000 Sloan-Kettering Institute for Cancer Research, Postdoctoral Fellow,
Research advisor: Professor Samuel J. Danishefsky

Department of Chemistry, Graduate School of Science, Tohoku University
2000 Assistant Professor (Laboratory of Professor Masahiro Hirama)
2003 Lecturer
2004 Associate Professor

Department of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, the University of Tokyo
2007 Professor

Introduction of Resiniferatoxin

Euphorbia resinifera

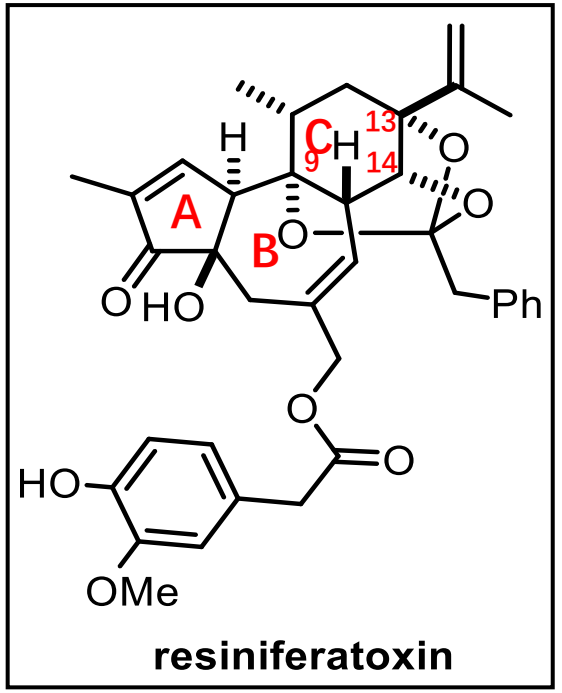
Isolation： from the latex of ***Euphorbia resinifera*** by Hecker et al. in 1975.

Synthesis：

1997, Wender, 44 steps
2017, Masayuki Inoue, 41 steps
2021, Masayuki Inoue, 20 steps, unified
2022, Masayuki Inoue, 27 steps, formal
2022, Maimone , 15 steps
2025, Tuoping Luo, 20 steps, (+)-resiniferatoxin

Structure：

a trans-fused 5/7/6-tricyclic structure (ABC-ring)
a C9,13,14-orthoester motif
a C13-isopropenyl group on the C-ring



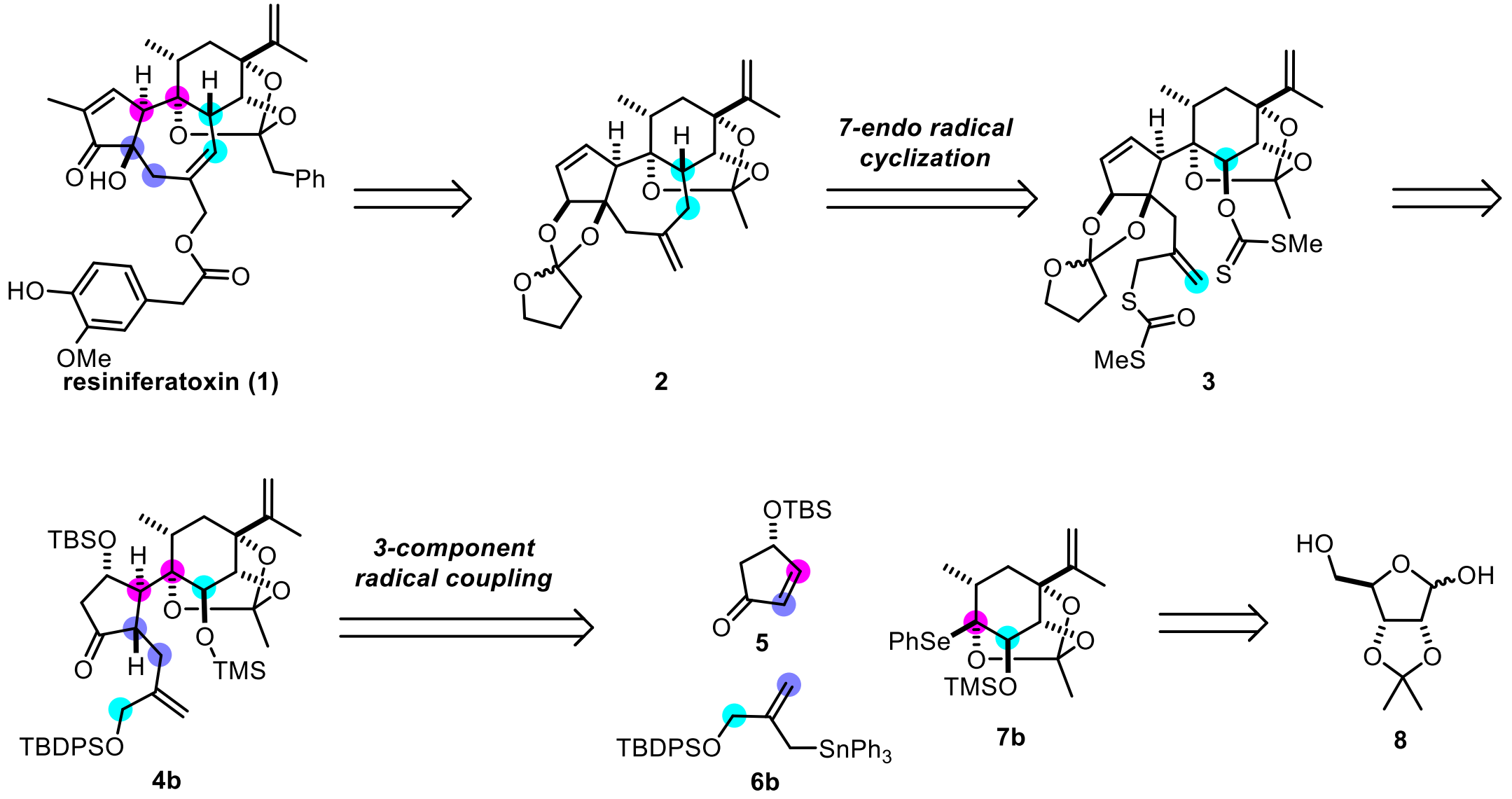
resiniferatoxin

Activity：

potently activating TRPV1
(Which is expected to act as an analgesic agent for pain induced by chronic inflammation, neuropathy, and cancer.)

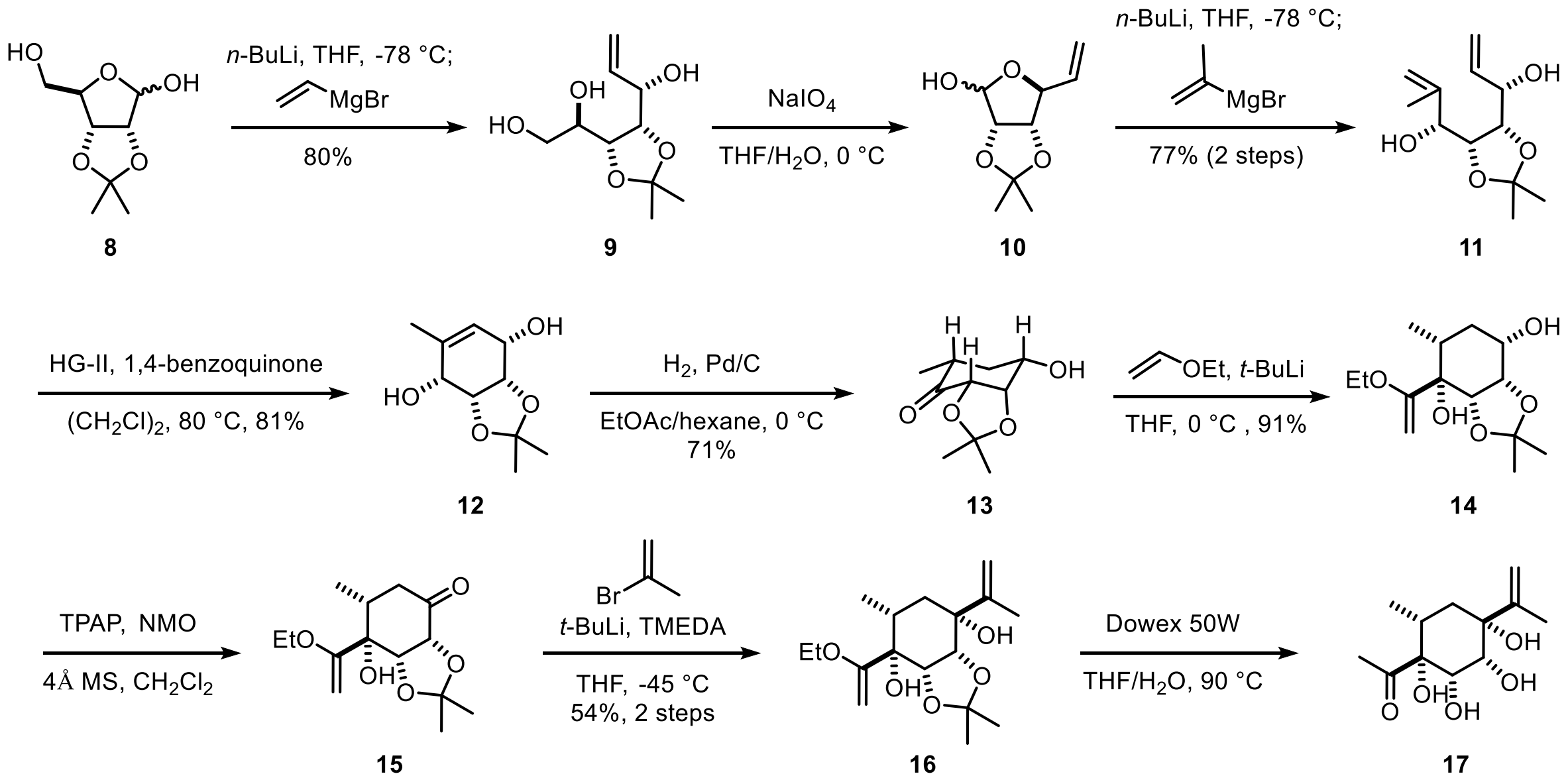
Hergenhahn, M. et al., *Tetrahedron Lett.* **1975**, *16*, 1595-1598
Paul A. Wender et al., *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977
Satoshi Hashimoto et al., *J. Am. Chem. Soc.* **2017**, *139*, 16420-16429
Akira Hirose et al., *J. Am. Chem. Soc.* **2021**, *143*, 12387-12396
Yuto Hikone et al., *Org. Lett.* **2022**, *24*, 929-933
Vasil H. Vasilev et al., *J. Am. Chem. Soc.* **2022**, *144*, 16332-16337
Hang Yu et al., *J. Am. Chem. Soc.* **2025**, *147*, 42164−42169

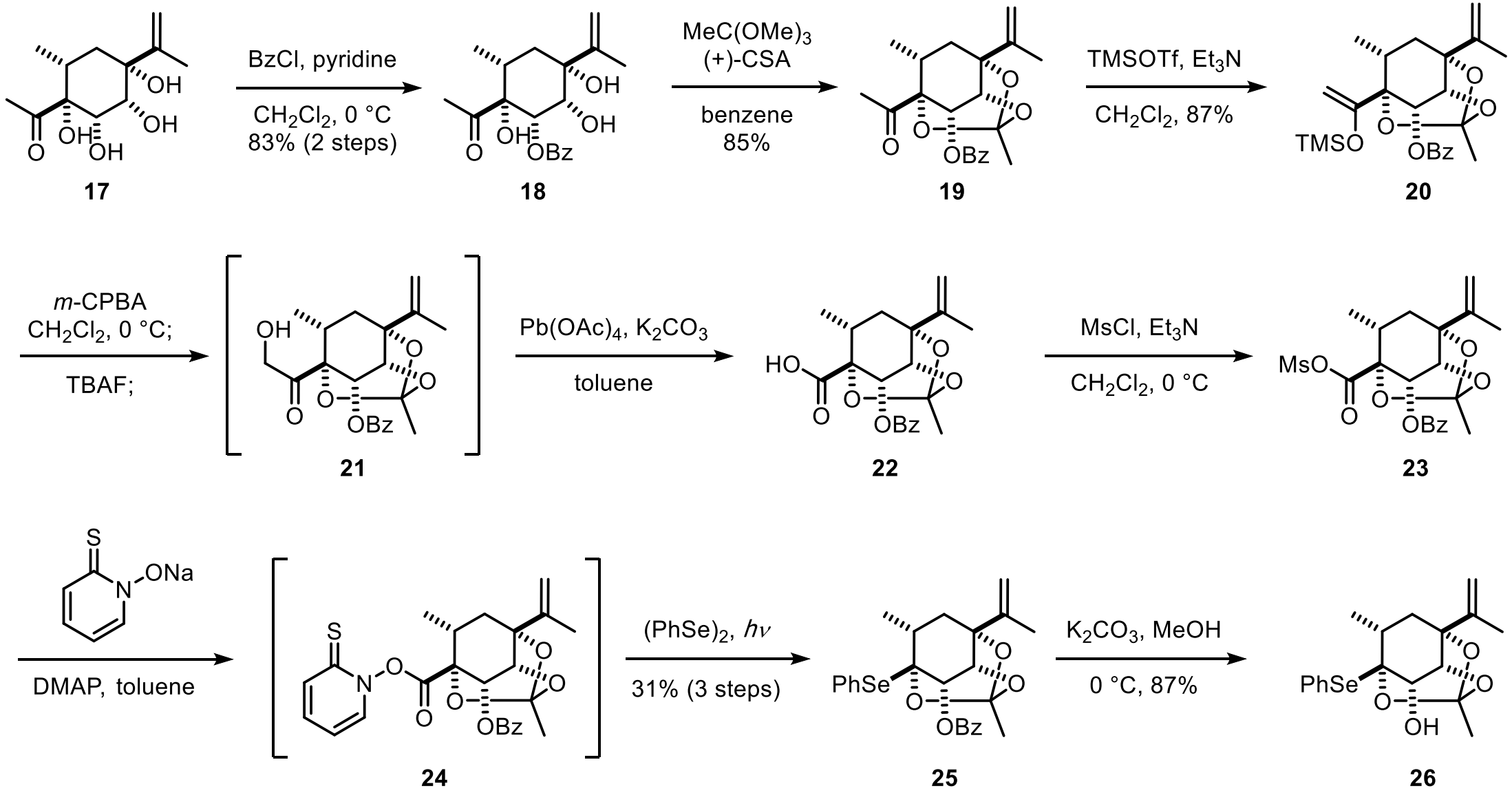
Retrosynthetic Analysis (Route 1)

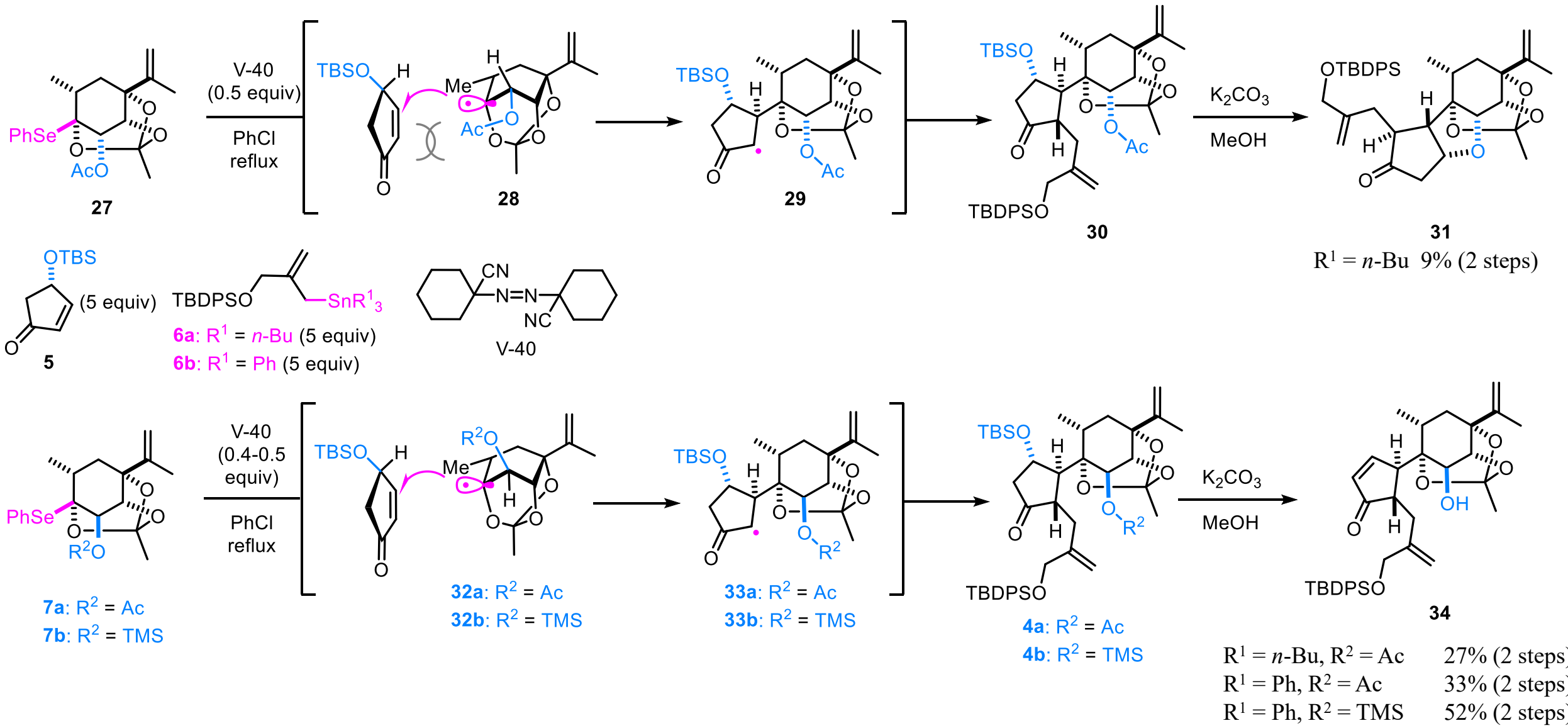


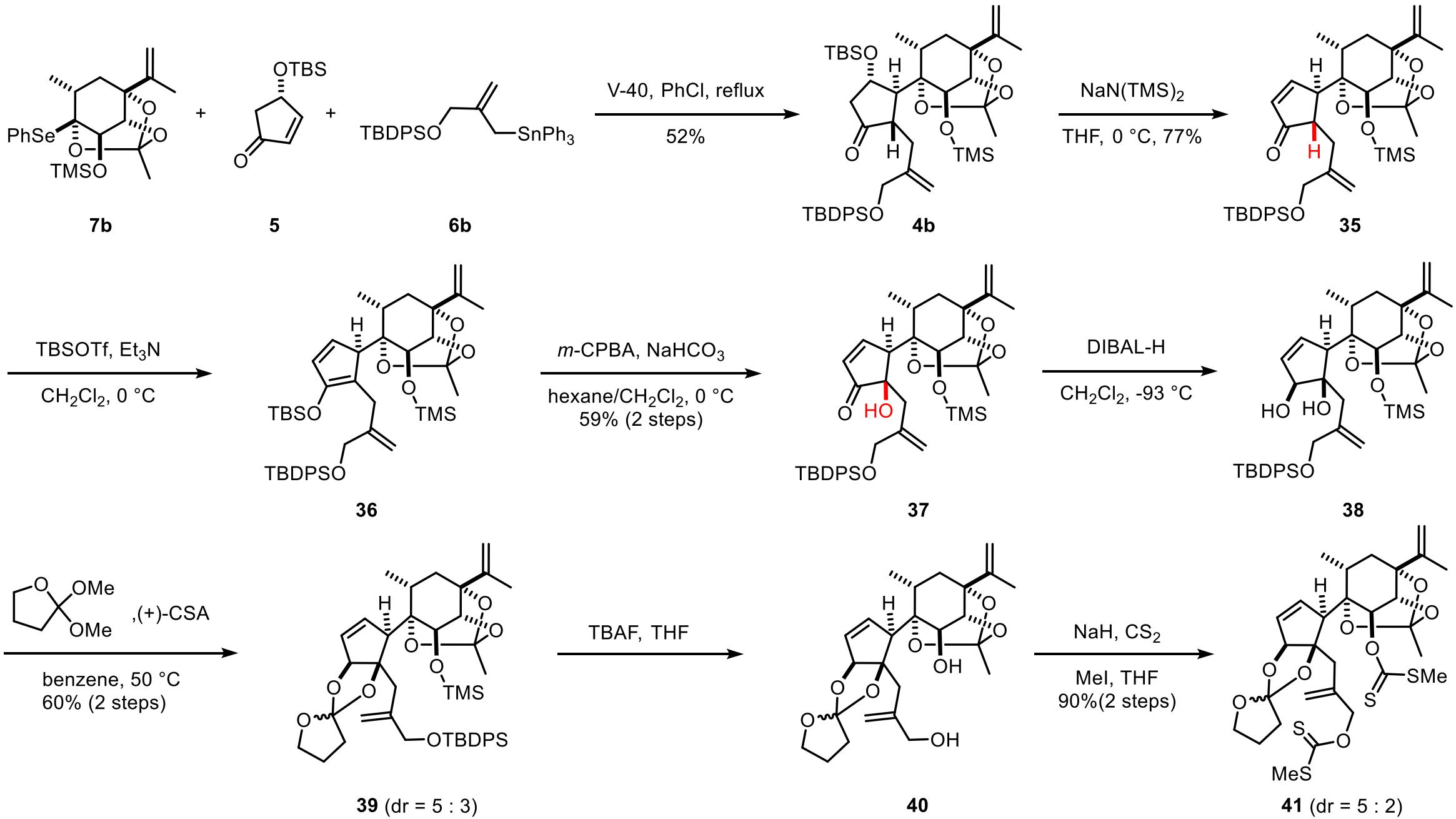
Satoshi Hashimoto et al., *J. Am. Chem. Soc.* **2017**, *139*, 16420-16429

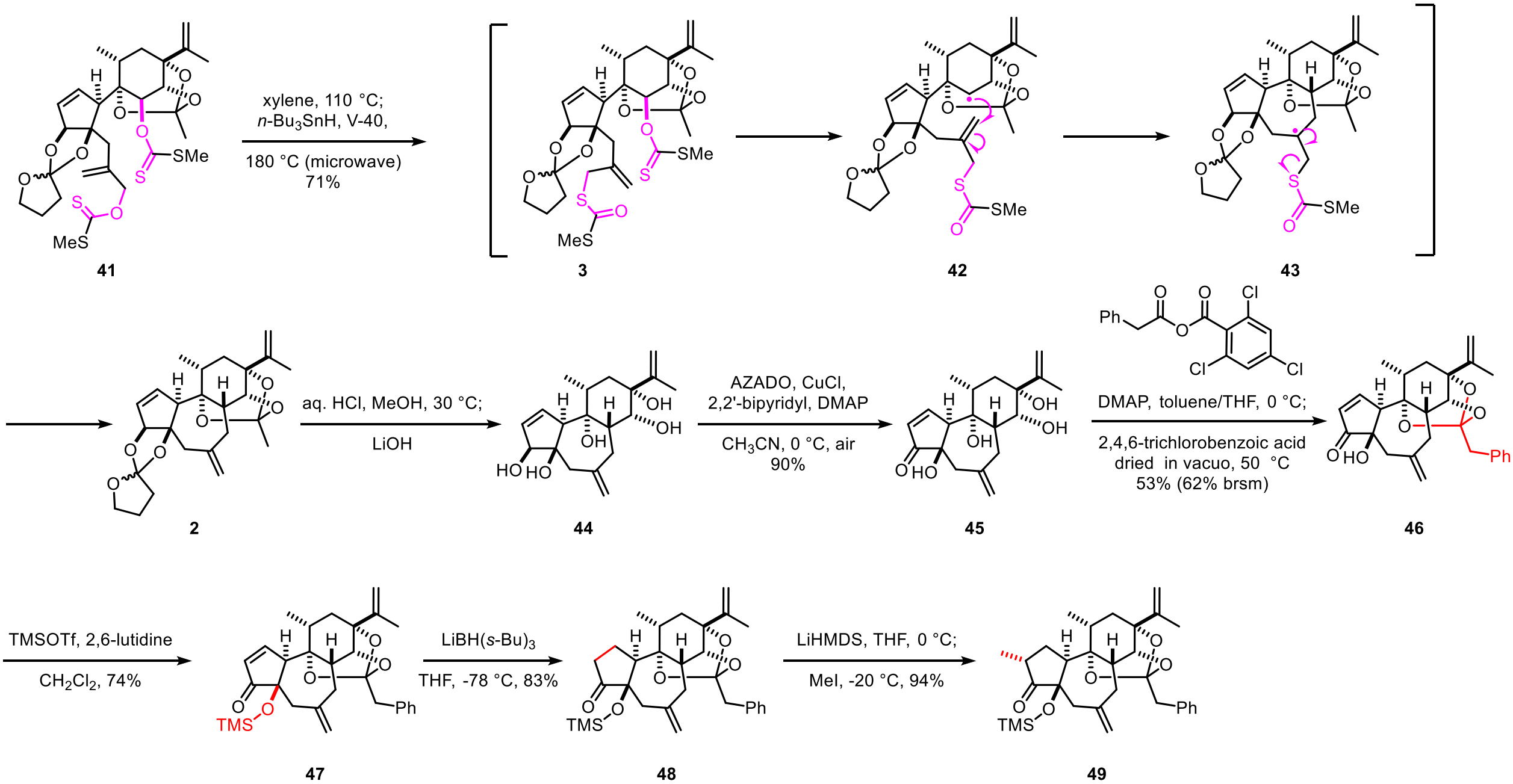
Total Synthesis of Resiniferatoxin (Route 1)



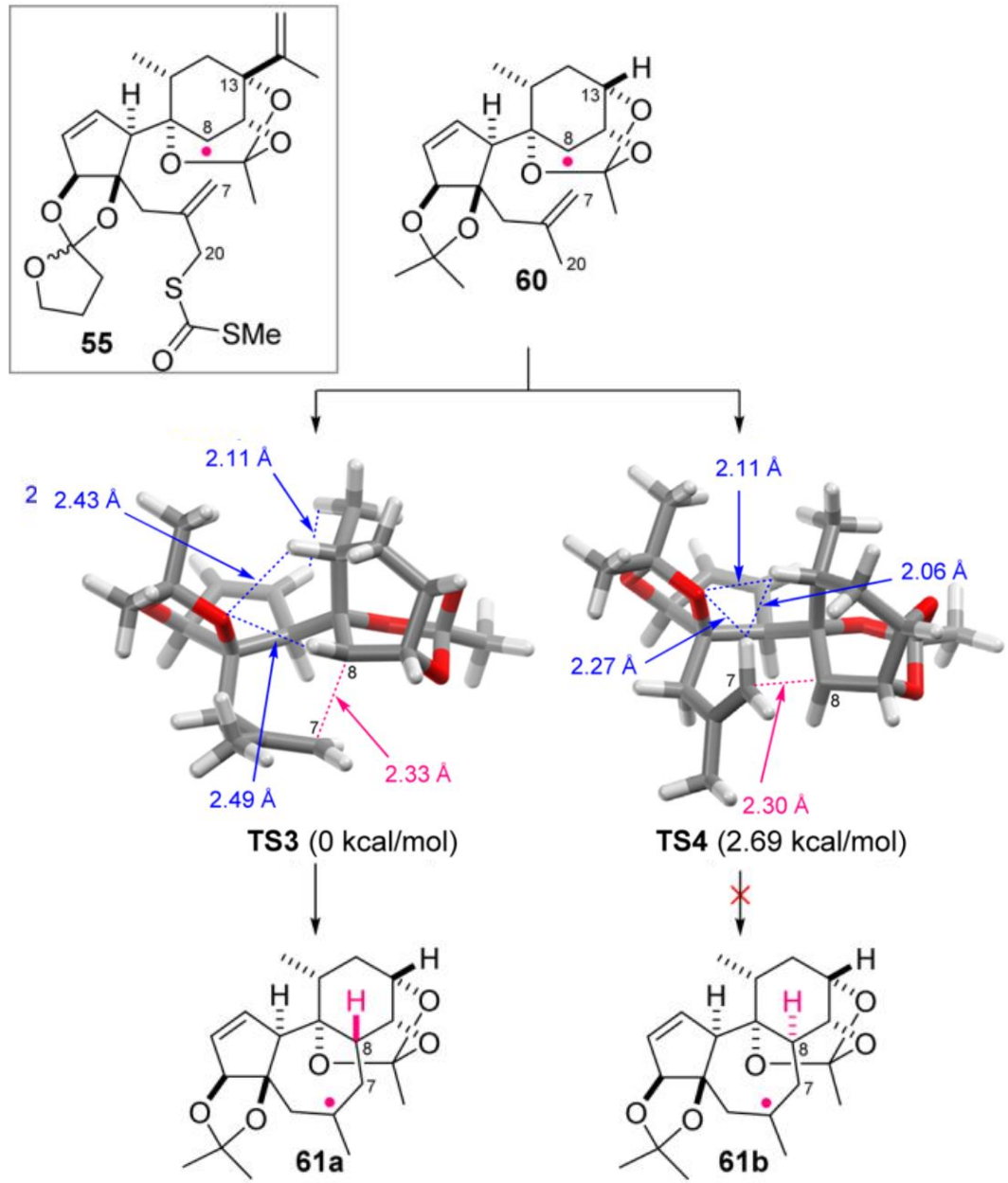

BzCl, pyridine
CH2Cl2, 0 °C
83% (2 steps)
MeC(OMe)3
(+)-CSA
benzene
85%
TMSOTf, Et3N
CH2Cl2, 87%
m-CPBA
CH2Cl2, 0 °C;
TBAF;
Pb(OAc)4, K2CO3
toluene
MsCl, Et3N
CH2Cl2, 0 °C
DMAP, toluene
(PhSe)2, hν
31% (3 steps)
K2CO3, MeOH
0 °C, 87%
17
18
19
20
21
22
23
24
25
26

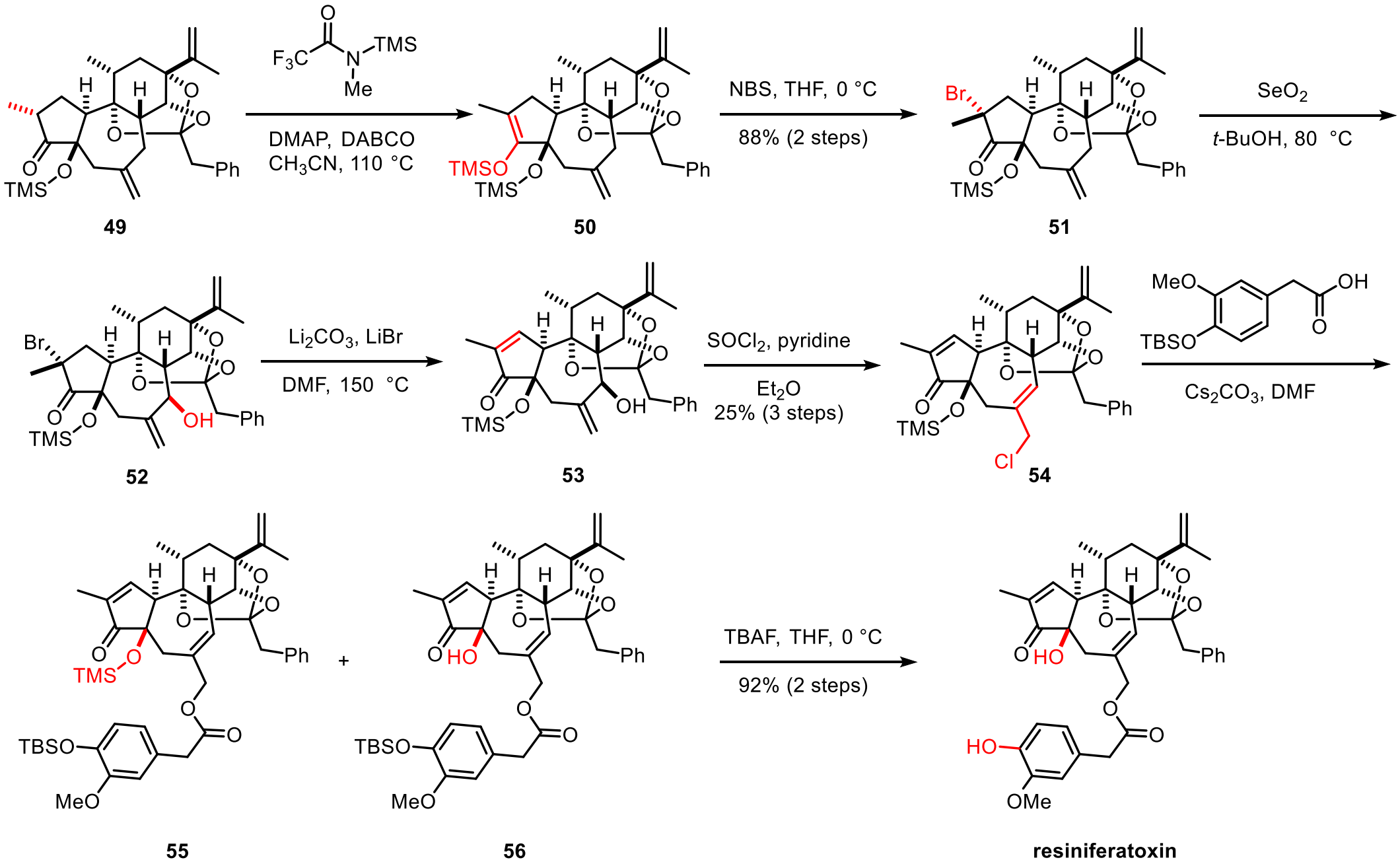

V-40
(0.5 equiv)
PhCl
reflux
27
28
29
30
31
K2CO3
MeOH
OTBS
(5 equiv)
5
TBDPSO
SnR1 3
6a: R1 = n-Bu (5 equiv)
6b: R1 = Ph (5 equiv)
CN
N=N
NC
V-40
R1 = n-Bu 9% (2 steps)
V-40
(0.4-0.5
equiv)
PhCl
reflux
7a: R2 = Ac
7b: R2 = TMS
32a: R2 = Ac
32b: R2 = TMS
33a: R2 = Ac
33b: R2 = TMS
4a: R2 = Ac
4b: R2 = TMS
34
R1 = n-Bu, R2 = Ac 27% (2 steps)
R1 = Ph, R2 = Ac 33% (2 steps)
R1 = Ph, R2 = TMS 52% (2 steps)


PhSe
O
O
TMSO
7b
+
OTBS
O
5
+
TBDPSO
SnPh3
6b
V-40, PhCl, reflux
52%
TBSO
H
O
O
O
TMS
O
H
TBDPSO
4b
NaN(TMS)2
THF, 0 °C, 77%
H
O
O
O
TMS
O
H
TBDPSO
35
TBSOTf, Et3N
CH2Cl2, 0 °C
H
O
O
O
TBSO
TMS
TBDPSO
36
m-CPBA, NaHCO3
hexane/CH2Cl2, 0 °C
59% (2 steps)
H
O
O
O
O
HO
TMS
TBDPSO
37
DIBAL-H
CH2Cl2, -93 °C
H
O
O
O
HO
HO
TMS
TBDPSO
38
OMe
OMe
,(+)-CSA
benzene, 50 °C
60% (2 steps)
H
O
O
O
O
O
TMS
OTBDPS
39 (dr = 5 : 3)
TBAF, THF
H
O
O
O
OH
O
OH
40
NaH, CS2
MeI, THF
90%(2 steps)
H
O
O
O
O
O
SMe
S
S
O
MeS
41 (dr = 5 : 2)

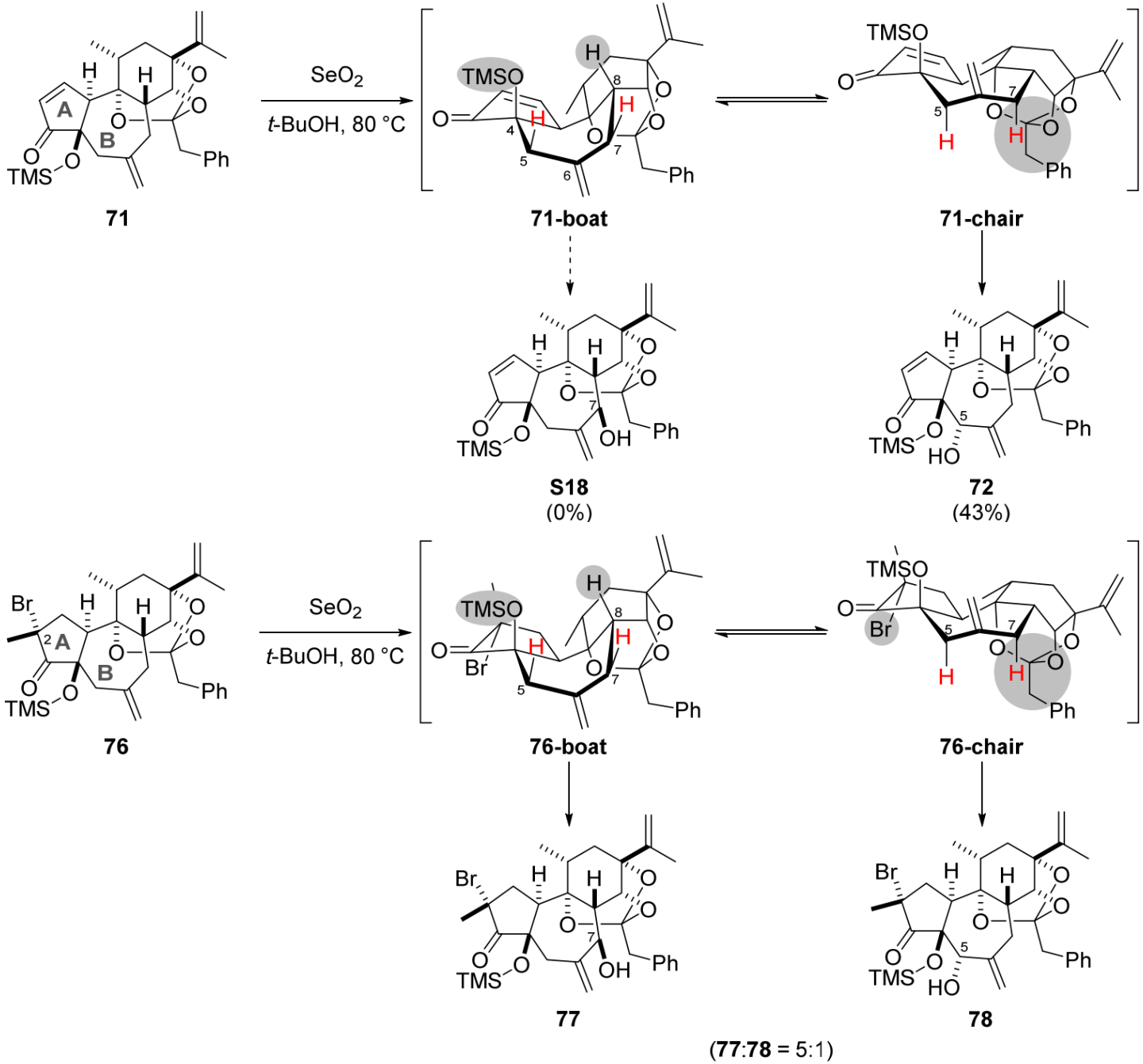

xylene, 110 °C;
n-Bu3SnH, V-40,
180 °C (microwave)
71%
41
3
42
43
aq. HCl, MeOH, 30 °C;
LiOH
2
44
AZADO, CuCl,
2,2'-bipyridyl, DMAP
CH3CN, 0 °C, air
90%
45
DMAP, toluene/THF, 0 °C;
2,4,6-trichlorobenzoic acid
dried in vacuo, 50 °C
53% (62% brsm)
46
TMSOTf, 2,6-lutidine
CH2Cl2, 74%
47
LiBH(s-Bu)3
THF, -78 °C, 83%
48
LiHMDS, THF, 0 °C;
MeI, -20 °C, 94%
49

Scheme 7. Rationale of the C8-Stereoselectivity[a]

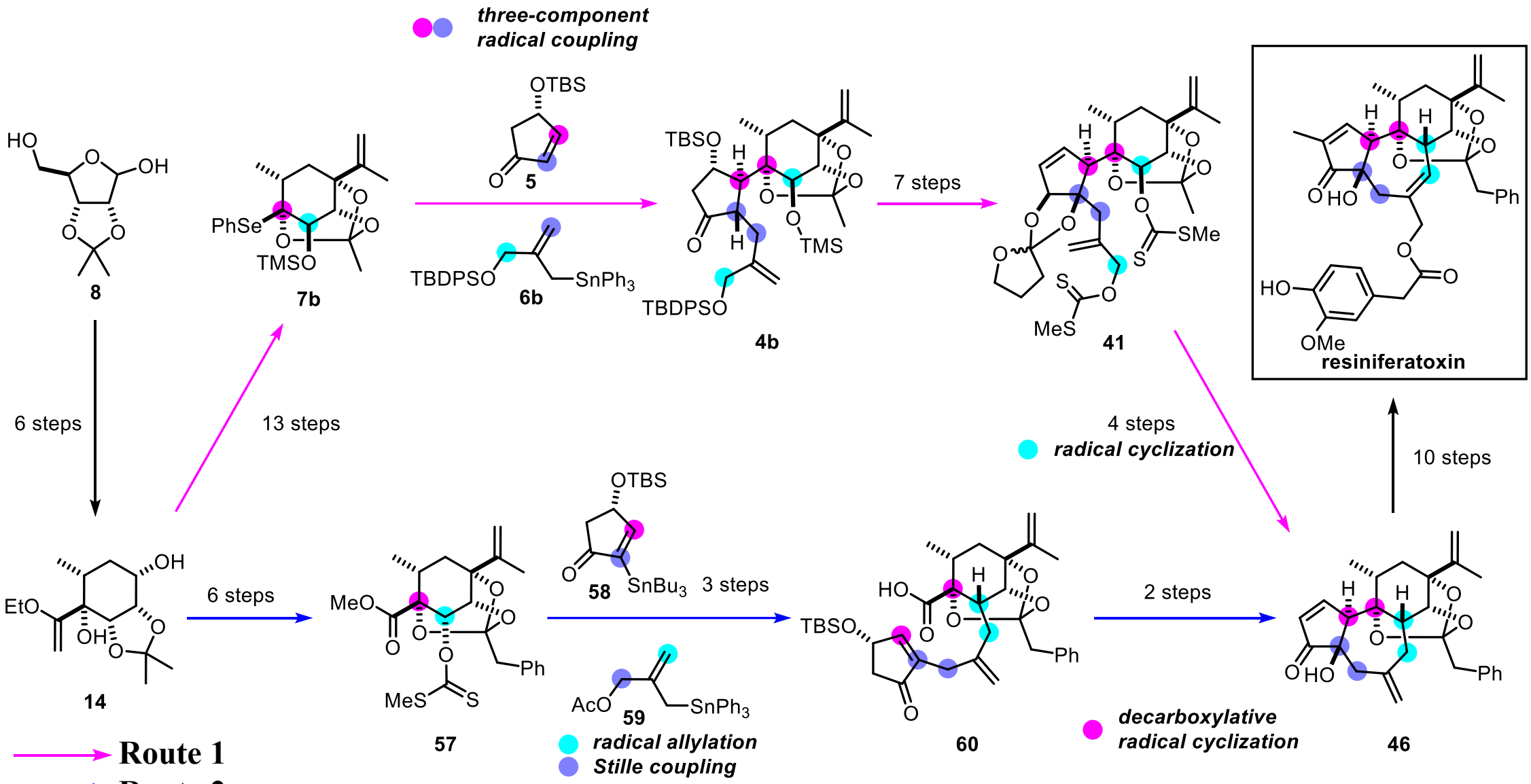



F3C
N
TMS
Me
DMAP, DABCO
CH3CN, 110 °C
NBS, THF, 0 °C
88% (2 steps)
SeO2
t-BuOH, 80 °C
Li2CO3, LiBr
DMF, 150 °C
SOCl2, pyridine
Et2O
25% (3 steps)
Cs2CO3, DMF
TBAF, THF, 0 °C
92% (2 steps)
TMS
TMSO
Br
OH
Cl
HO
TBSO
MeO
OMe
Ph
49
50
51
52
53
54
55
56
resiniferatoxin

Scheme S1. Rationale of the C5/7-site-selectivity.

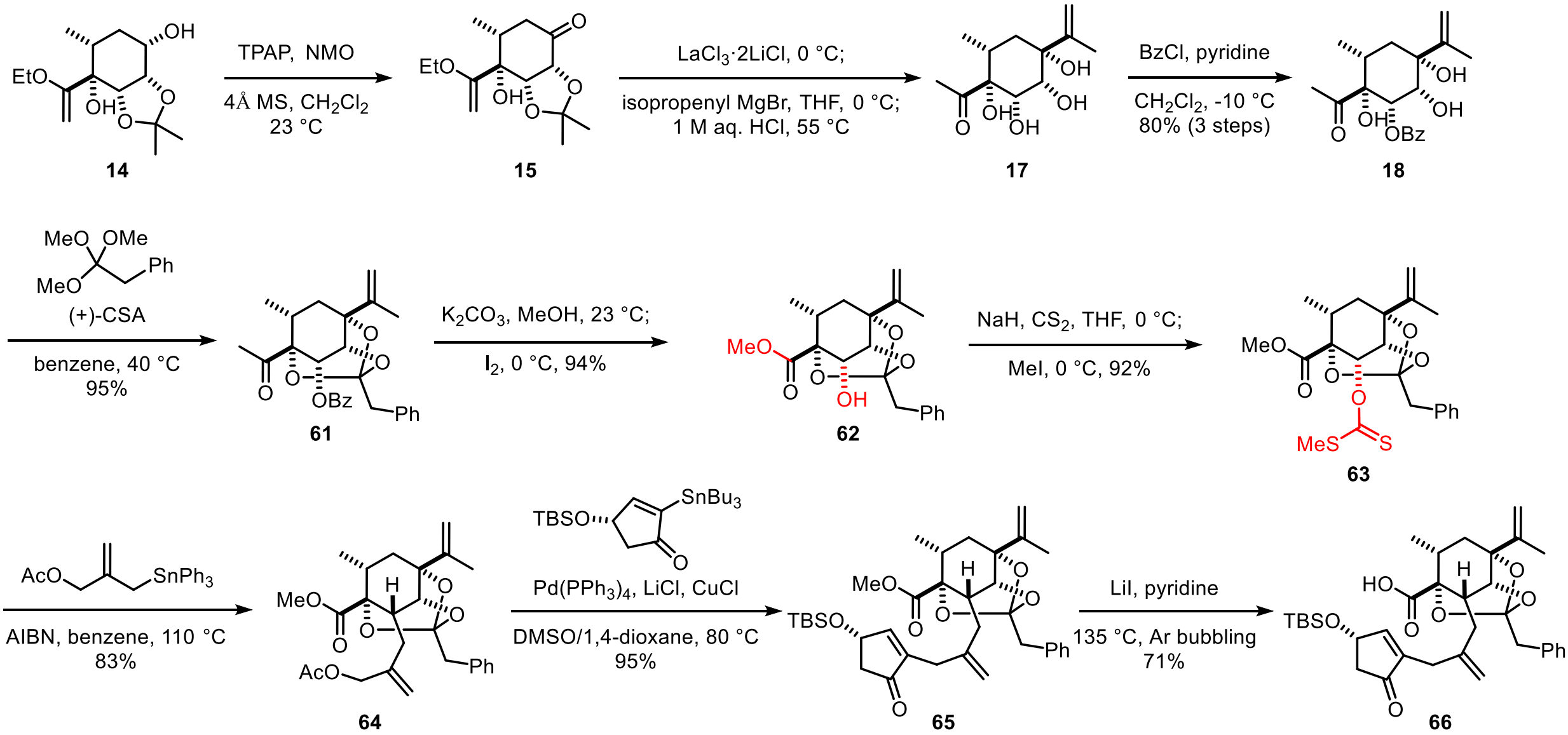


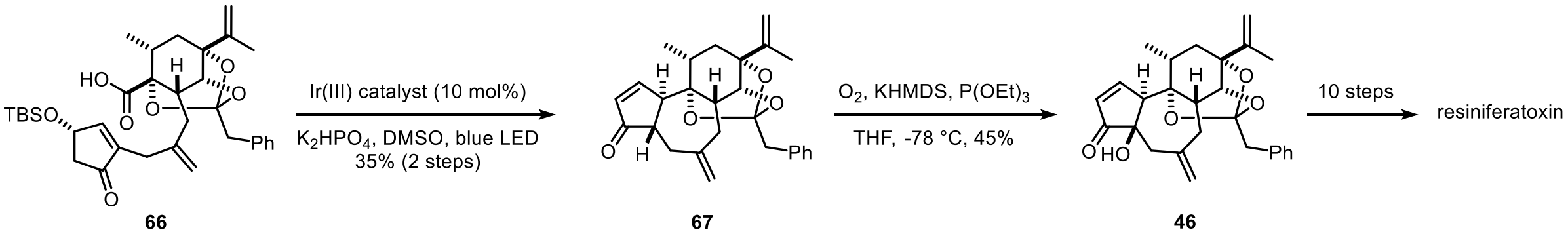
Comparison Between Route 1 and Route 2



Yuto Hikone et al., *Org. Lett.* **2022**, *24*, 929-933

Total Synthesis of Resiniferatoxin (Route 2)




HO
TBSO
H
O
O
O
O
Ph
Ir(III) catalyst (10 mol%)
K_2HPO_4, DMSO, blue LED
35% (2 steps)
H
H
O
O
O
H
Ph
O_2, KHMDS, $P(OEt)_3$
THF, -78 °C, 45%
H
H
O
O
O
HO
Ph
10 steps
resiniferatoxin

66 **67** **46**

Mechanism

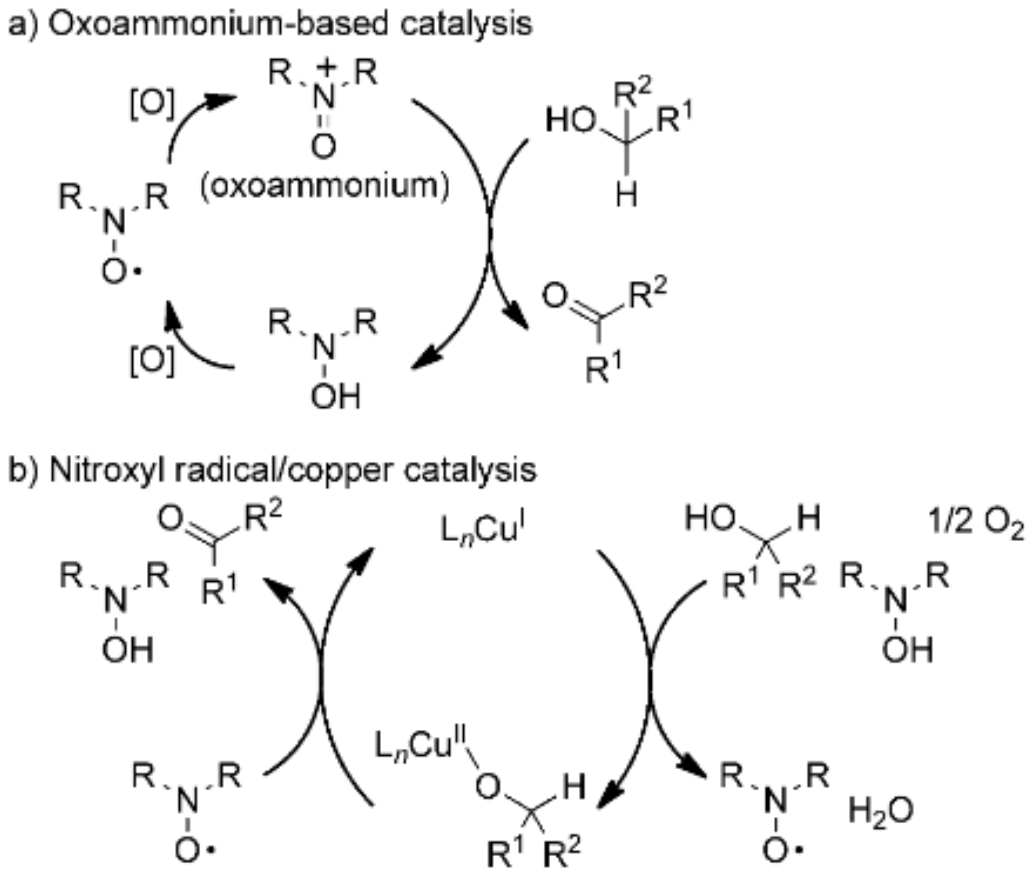
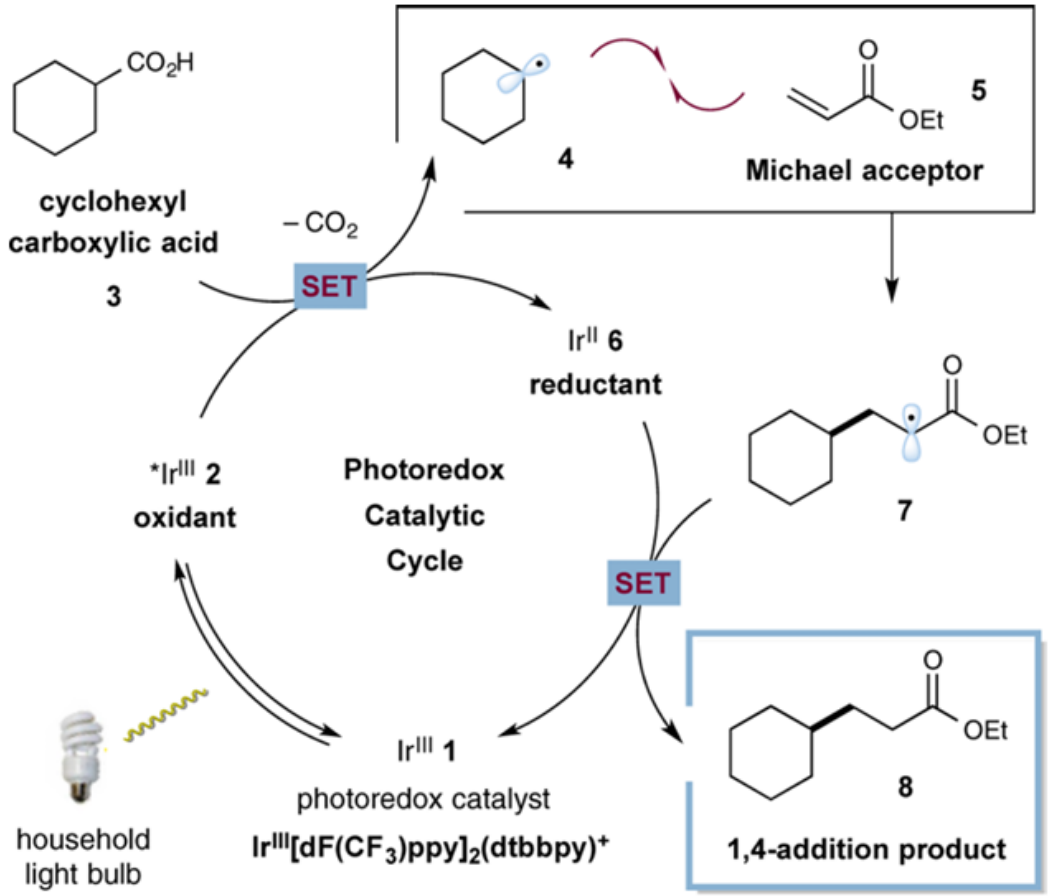


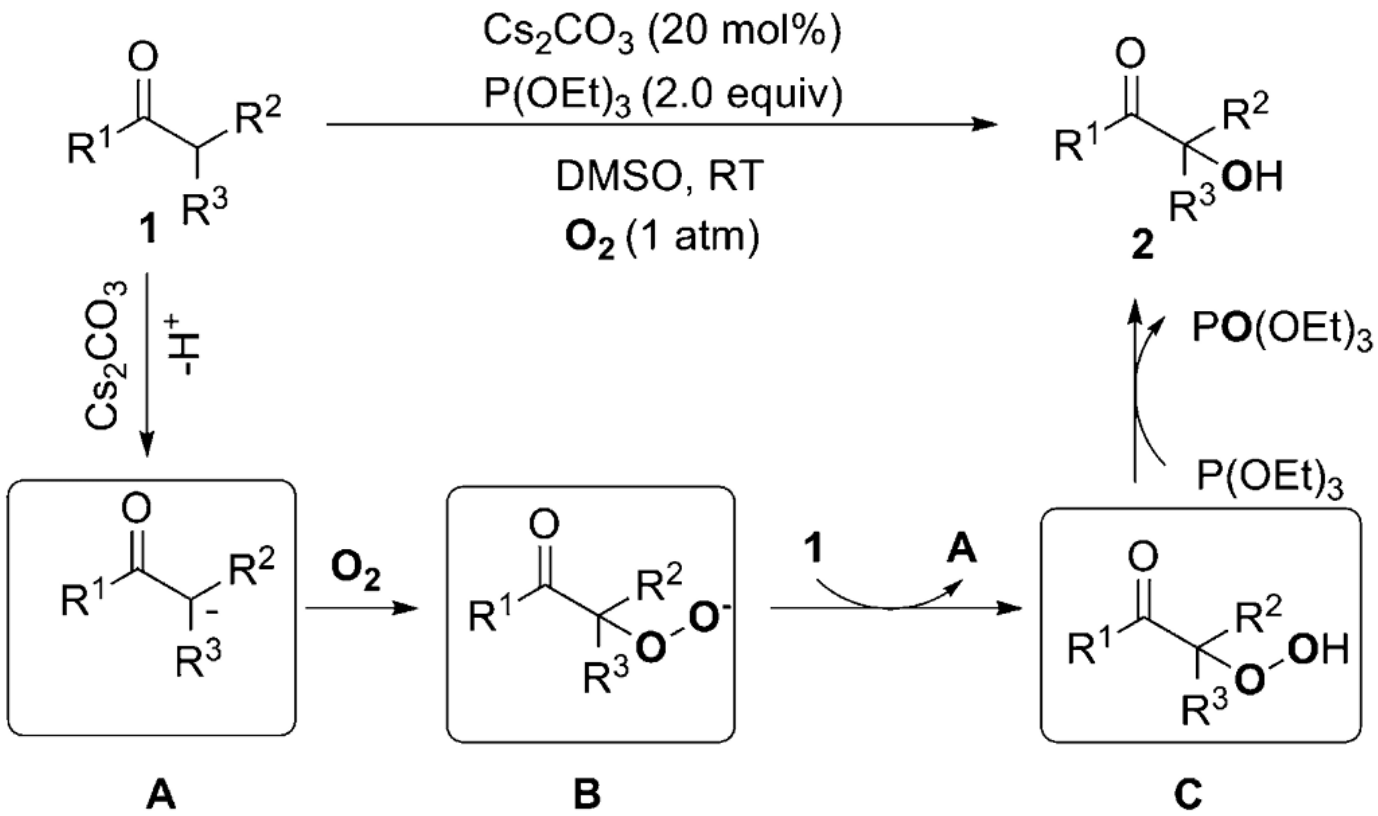
Figure 1. Simplified reaction mechanisms of nitroxyl-radical-catalyzed alcohol oxidation.

Yusuke Sasano et al., *Angew. Chem. Int. Ed.* **2014**, *53*, 3236 –3240

Scheme 1. Proposed Mechanism for Decarboxylative Alkylation



Lingling Chu et al., *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889



Yu-Feng Liang and Ning Jiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 548 –552