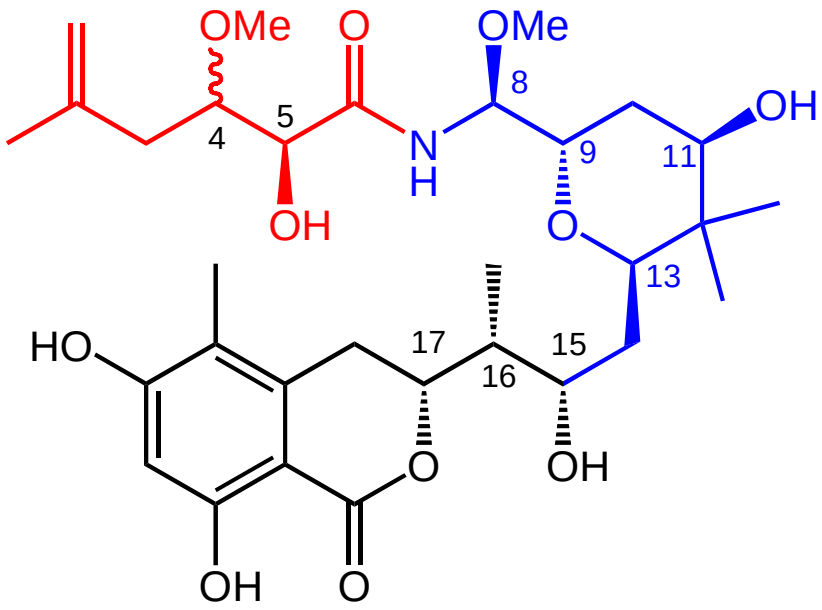
**Literature Report 2009-10-20**

周晓玉　　检查：王躲生

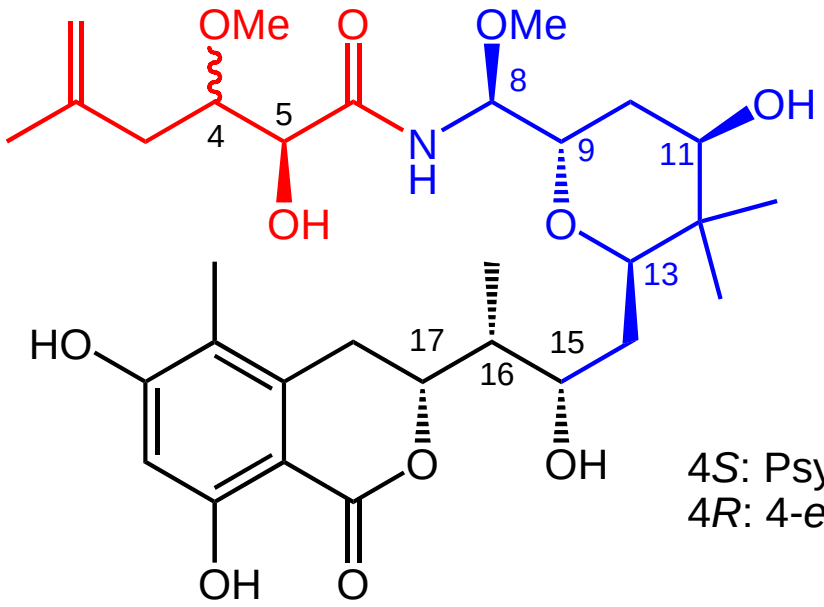
# Progress toward the Total Synthesis of Psymberin/Irciniastatin A

Konopelski, J. P. *et al J. Org. Chem.* **2009**, *74*, 5405–5410.

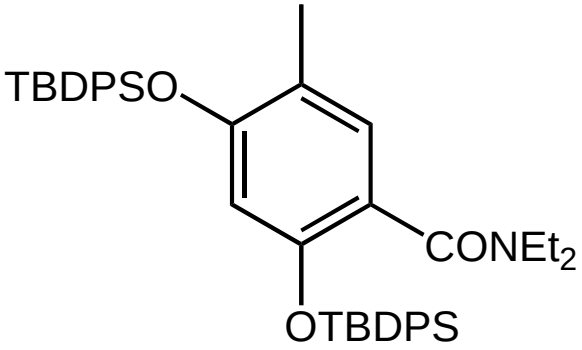



4*S*: Psymberin (**1**)
4*R*: 4-*epi*-Psymberin (**2**)

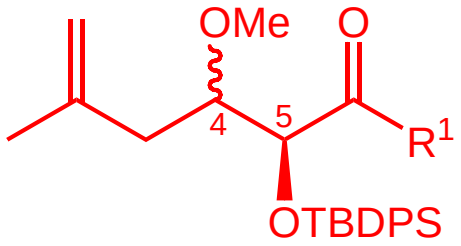
Retrosynthetic Analysis for **1** and **2**



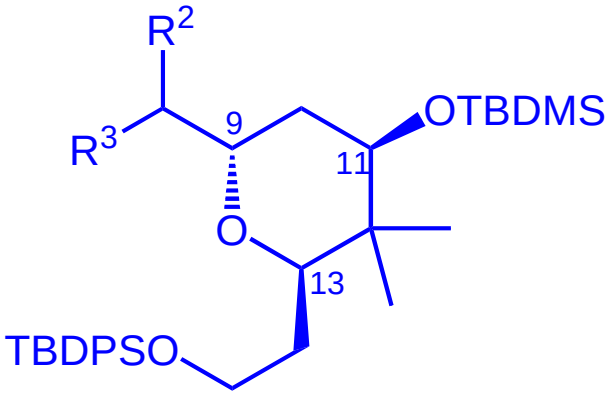

4*S*: Psymberin (**1**)
4*R*: 4-*epi*-Psymberin (**2**)



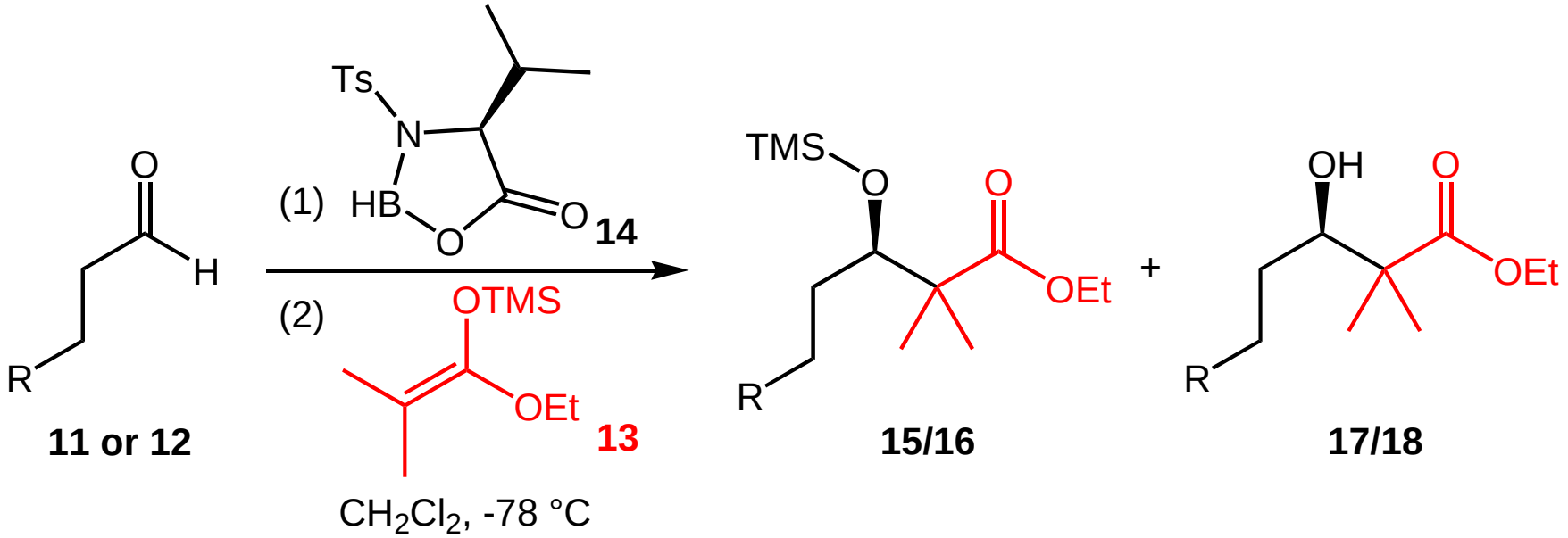

**3**

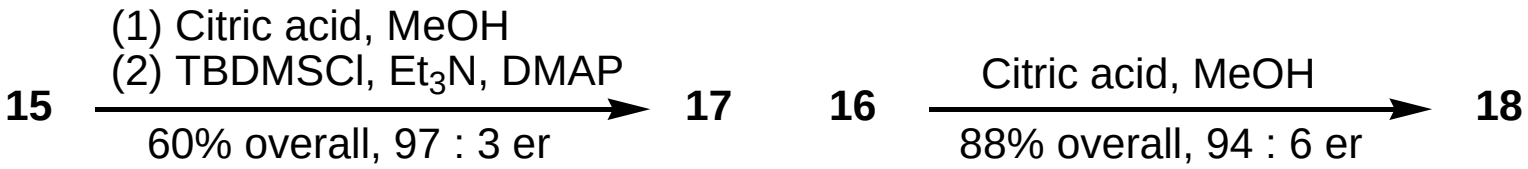



**4** 4*S*, $R^1$ = OH
**5** 4*R*, $R^1$ = $NH_2$

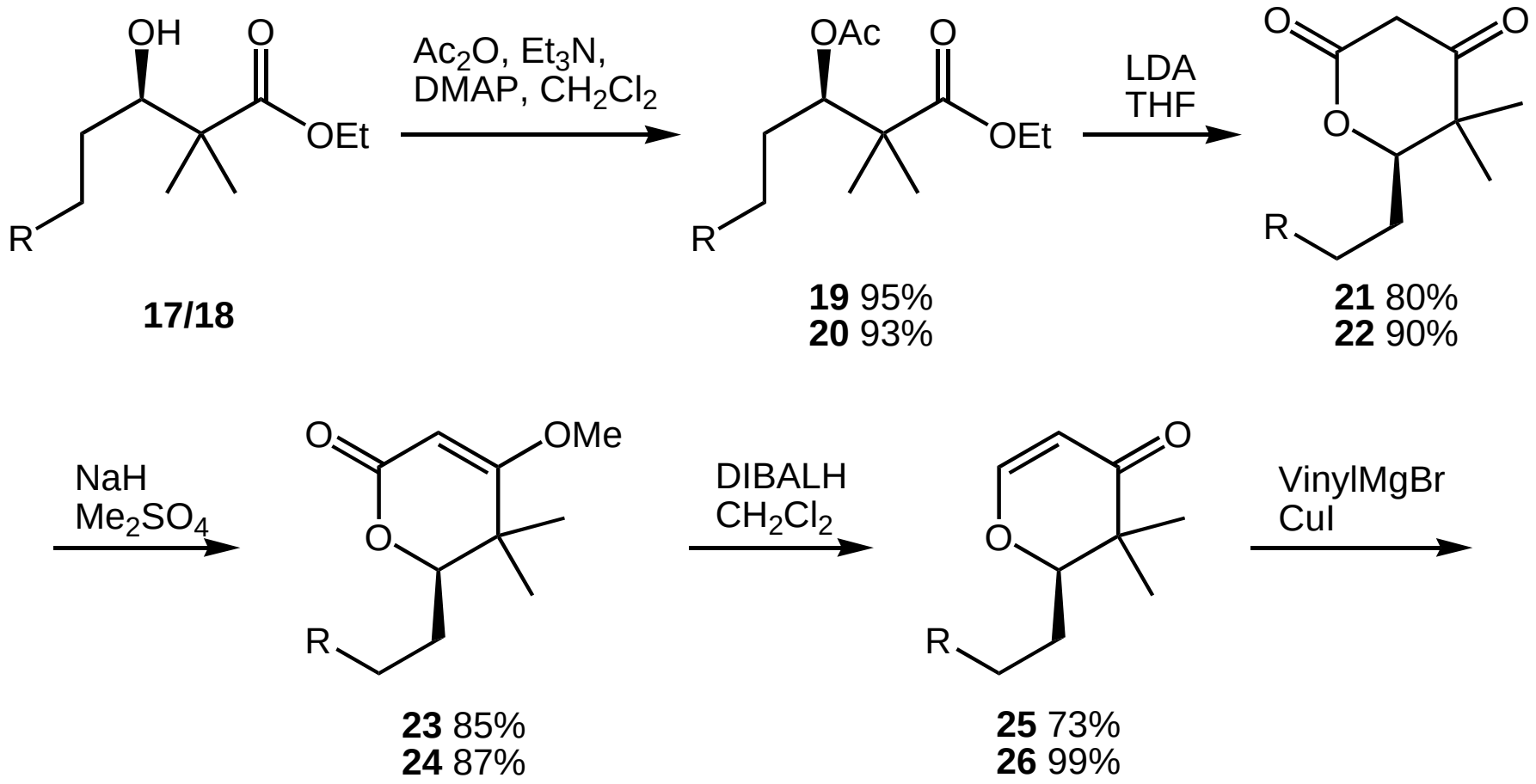



**6** $R^2$ = $R^3$ = OMe
**7** $R^2$ = $R^3$ = O




**11, 15, 17** R = $CH_2$OTBDMS
**12, 16, 18** R = OTBDPS



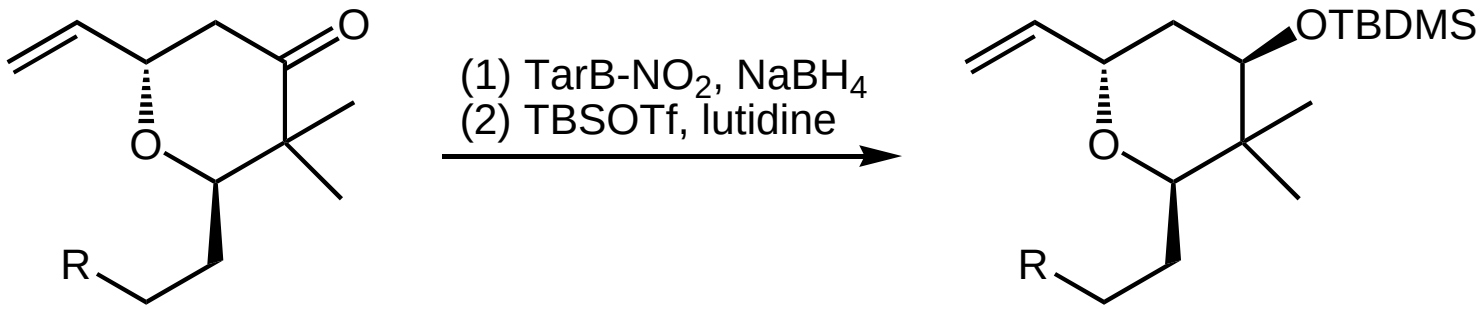

**17/18**

**19** 95%
**20** 93%

**21** 80%
**22** 90%

**23** 85%
**24** 87%

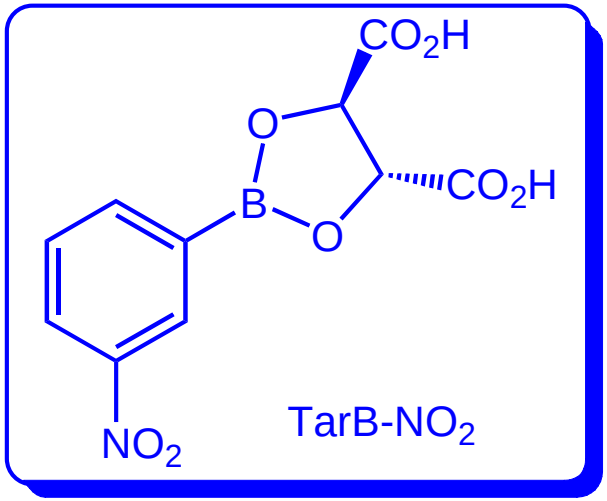
**25** 73%
**26** 99%

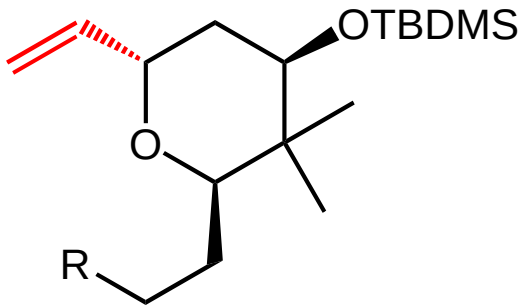



**9** 76%
**10** 93%

**27** 28%
**28** 52%

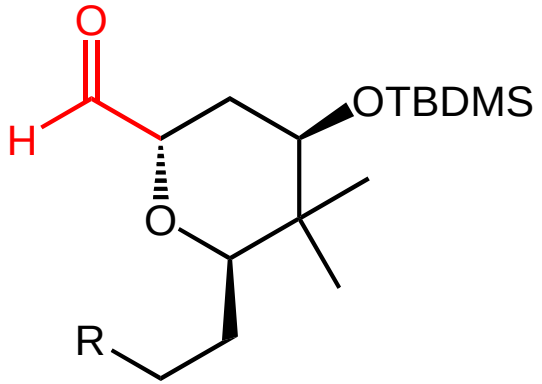
**9, 19, 21, 23, 25, 27** R = $CH_2OTBDMS$
**10, 20, 22, 24, 26, 28** R = OTBDPS



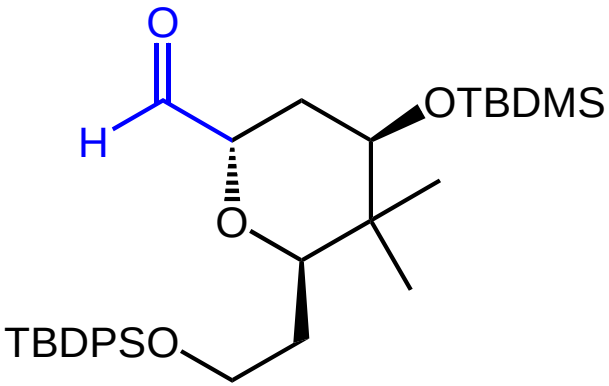



**27** R = $CH_2OTBDMS$
**28** R = OTBDPS

(1) $OsO_4$, NMO
(2) $NaIO_4$

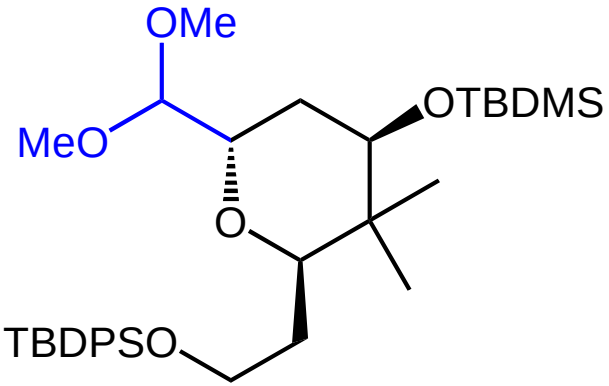



**29** R = $CH_2OTBDMS$ 50%
**7** R = OTBDPS 95%

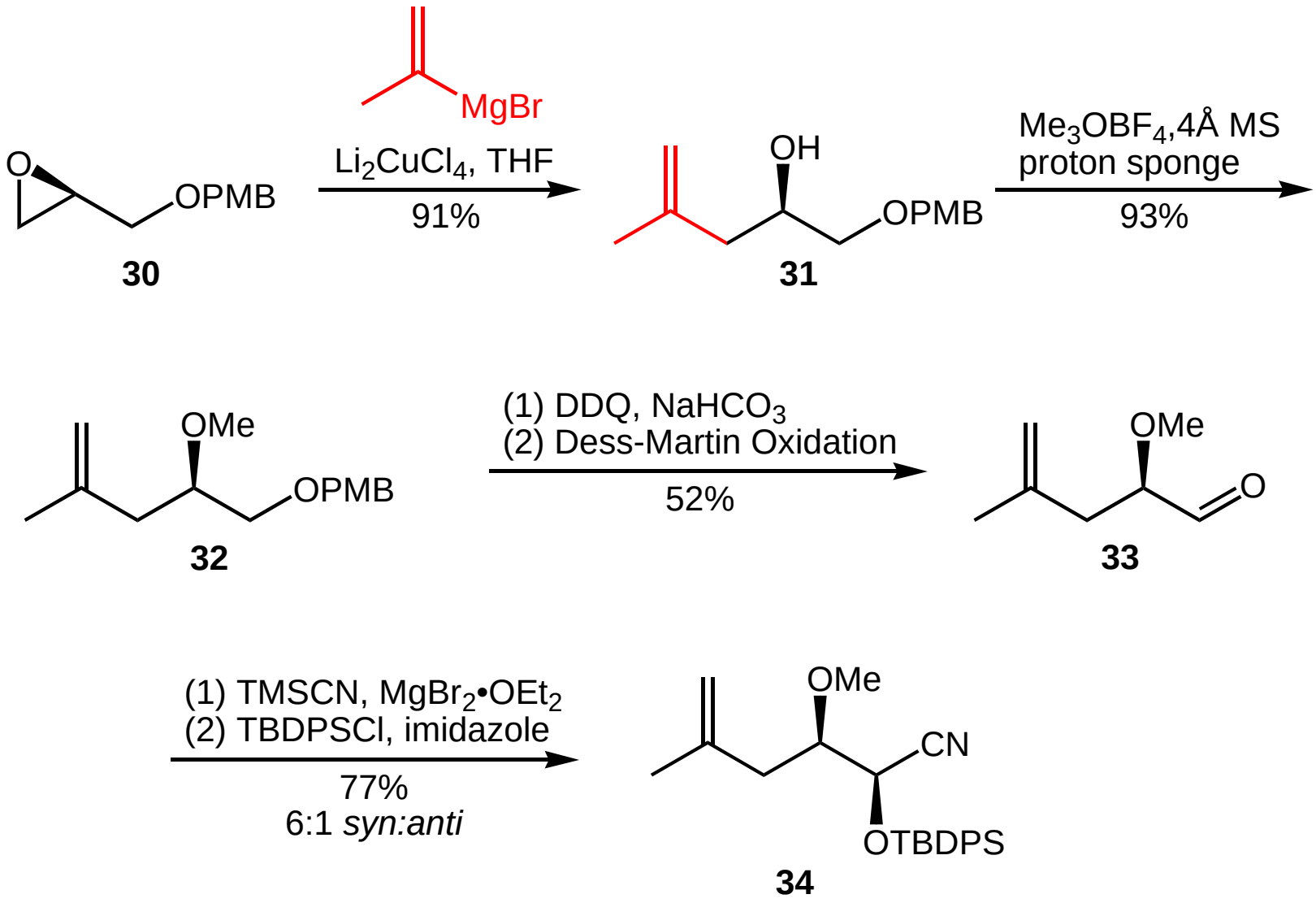


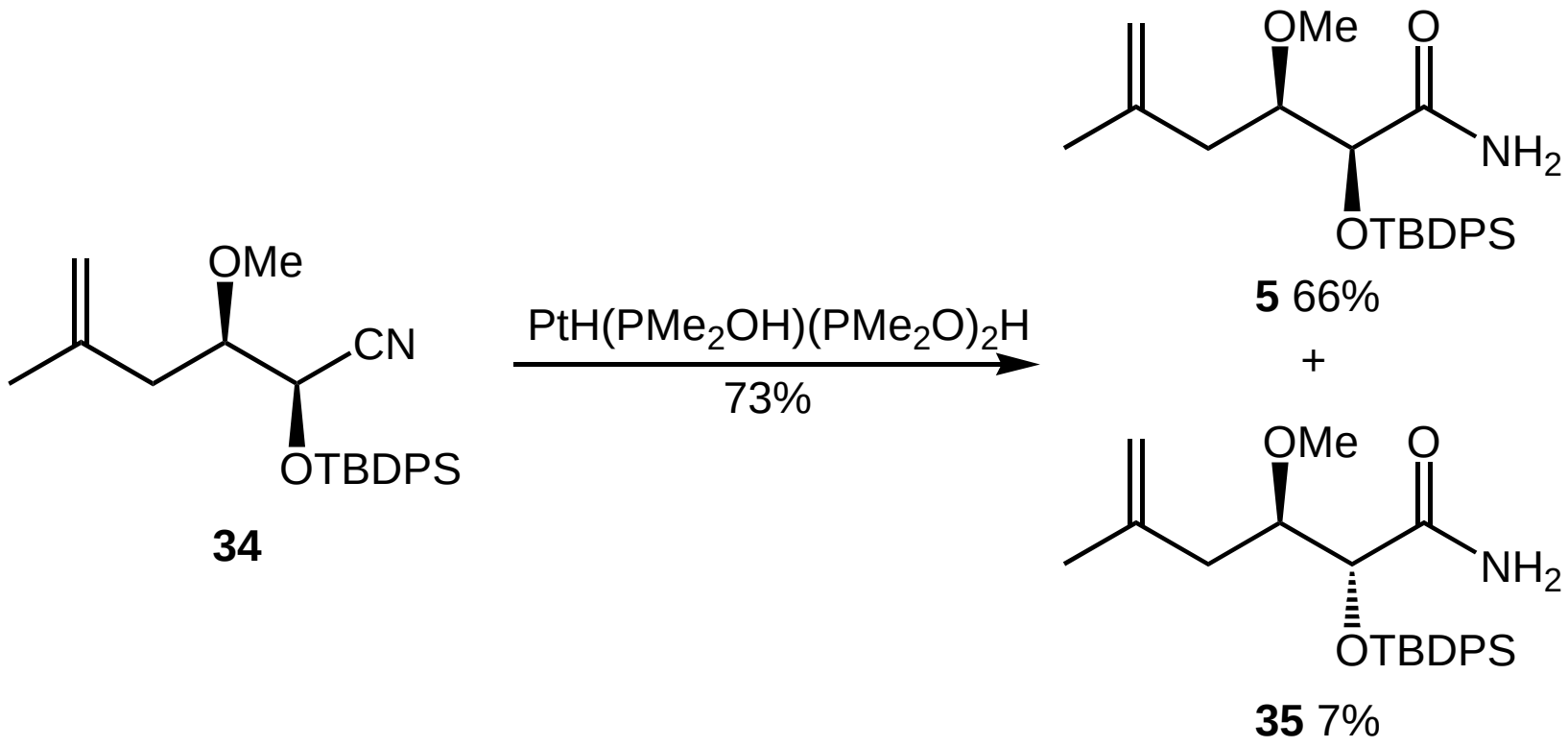

**7**

$(MeO)_3CH$, TsOH
93%




**6**

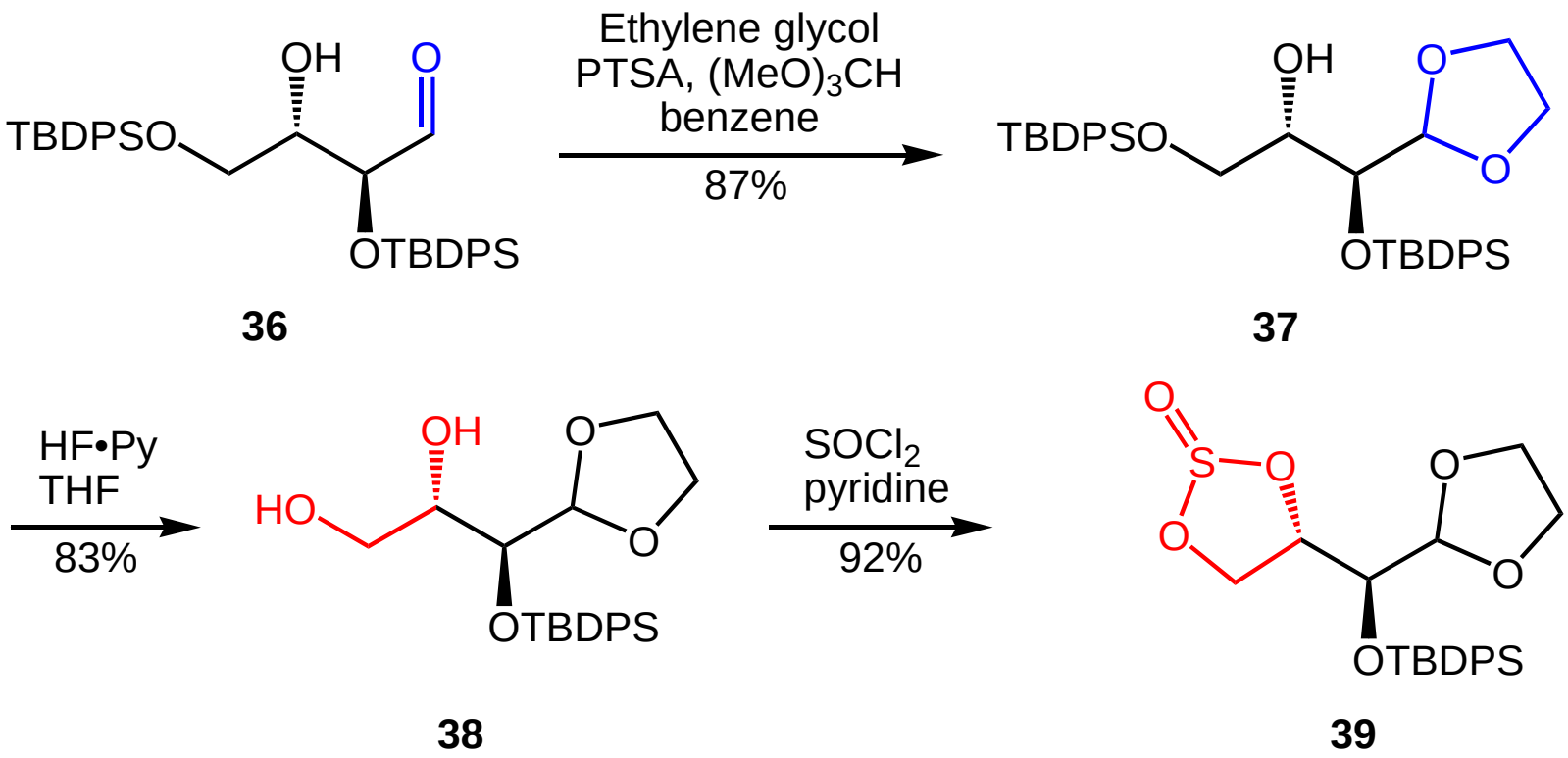

MgBr
O
OPMB
Li2CuCl4, THF
91%
OH
OPMB
Me3OBF4,4Å MS
proton sponge
93%
30
31
OMe
OPMB
(1) DDQ, NaHCO3
(2) Dess-Martin Oxidation
52%
OMe
O
32
33
(1) TMSCN, MgBr2•OEt2
(2) TBDPSCl, imidazole
77%
6:1 syn:anti
OMe
CN
OTBDPS
34


OMe
CN
OTBDPS
PtH(PMe2OH)(PMe2O)2H
73%
OMe
O
NH2
OTBDPS
+
OMe
O
NH2
OTBDPS

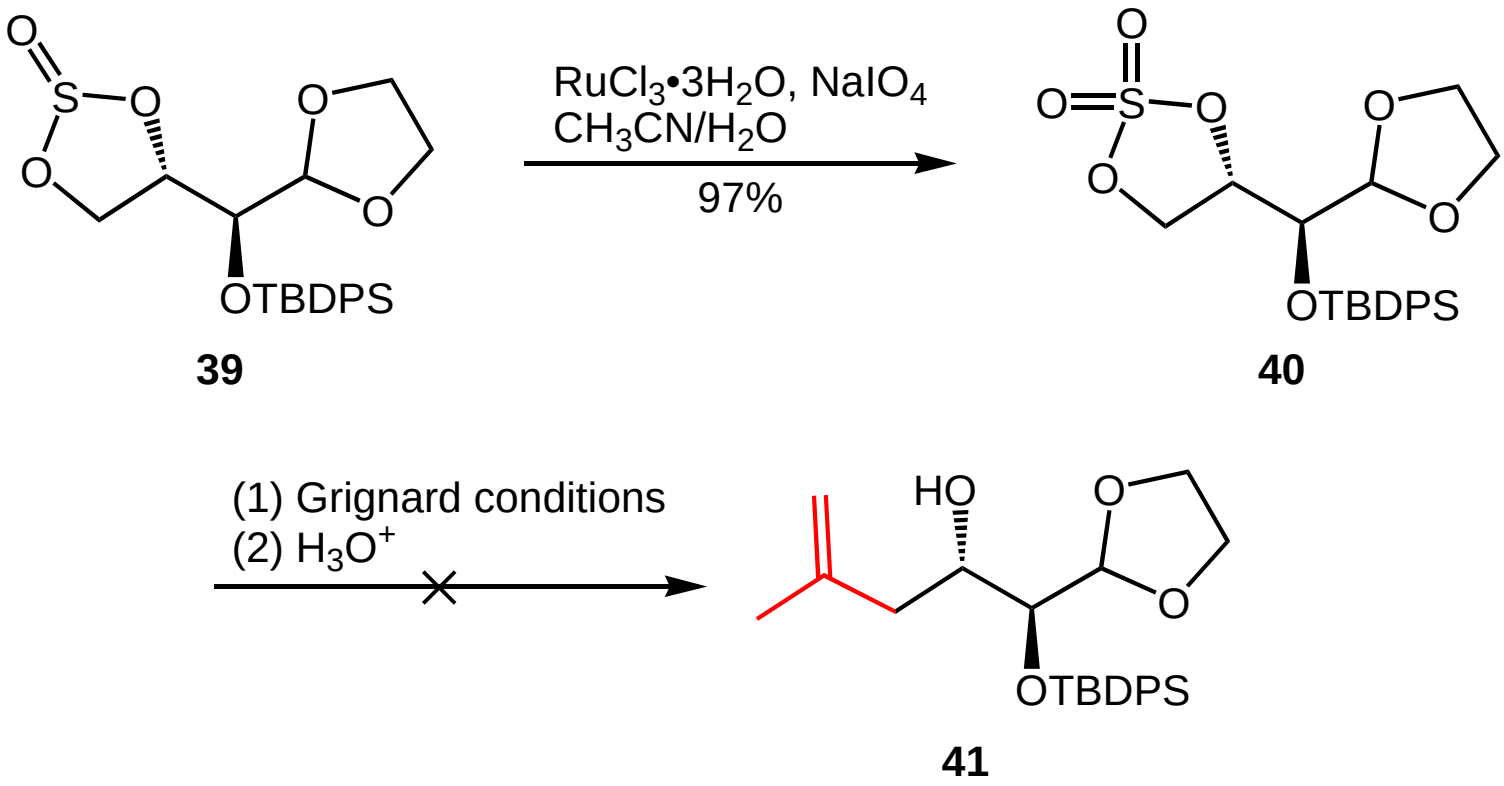
**34**

**5** 66%

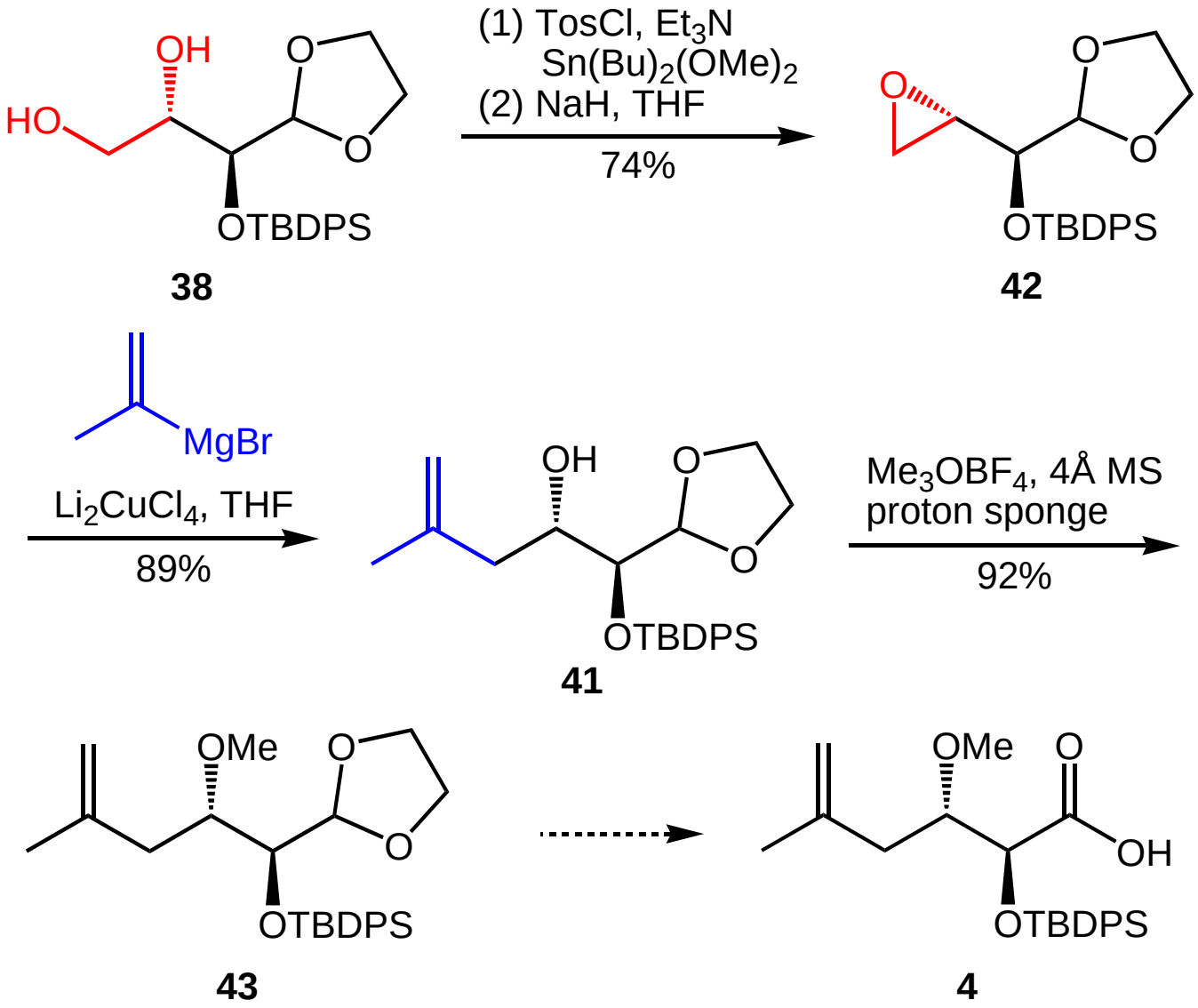
**35** 7%

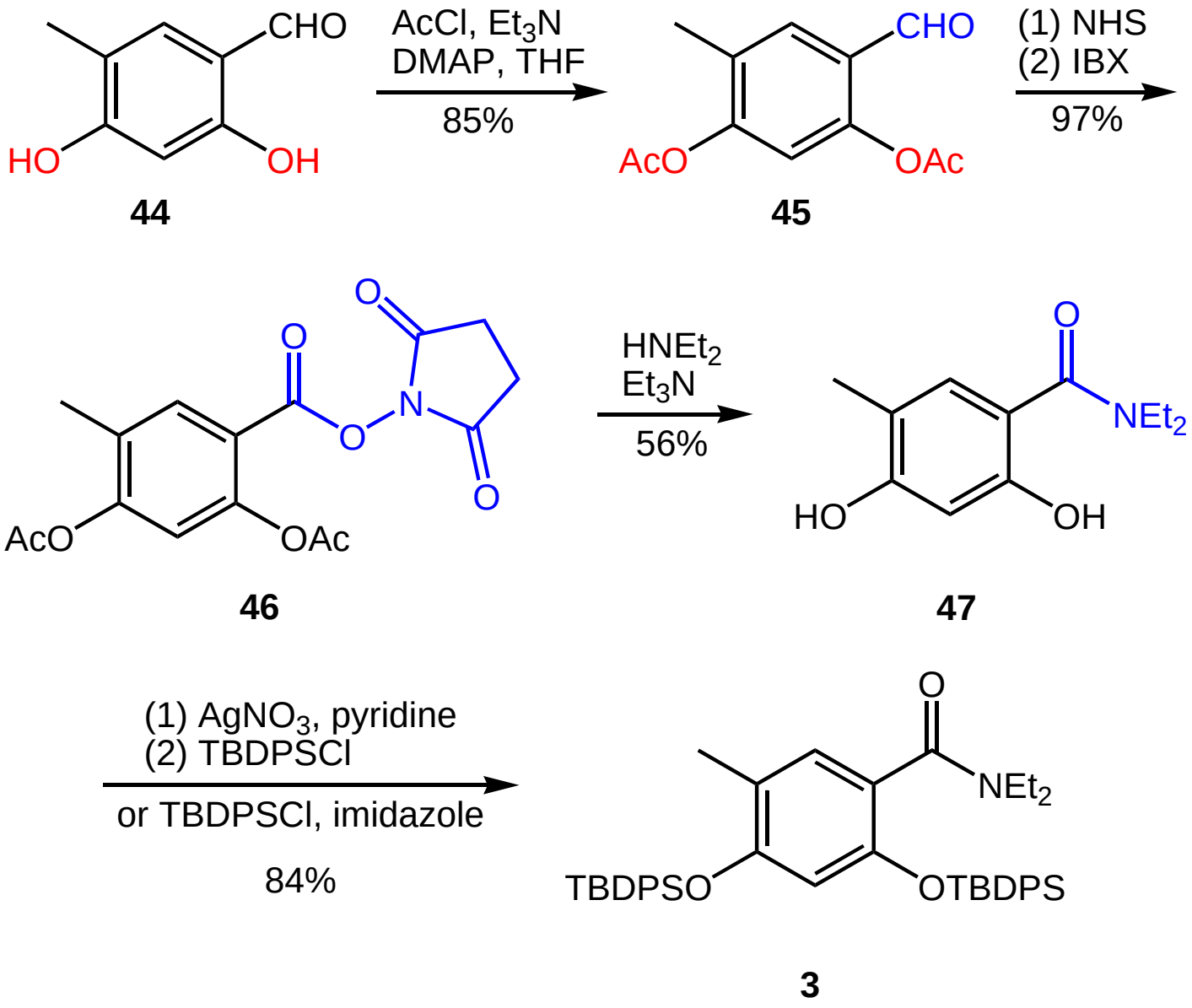

OH
O
TBDPSO
OTBDPS
Ethylene glycol
PTSA, (MeO)3CH
benzene
87%
OH
O
TBDPSO
O
OTBDPS
HF•Py
THF
83%
OH
HO
O
O
OTBDPS
SOCl2
pyridine
92%
O
S
O
O
O
O
OTBDPS

**36** **37** **38** **39**


RuCl3•3H2O, NaIO4
CH3CN/H2O
97%
OTBDPS
OTBDPS
(1) Grignard conditions
(2) H3O+
HO
OTBDPS

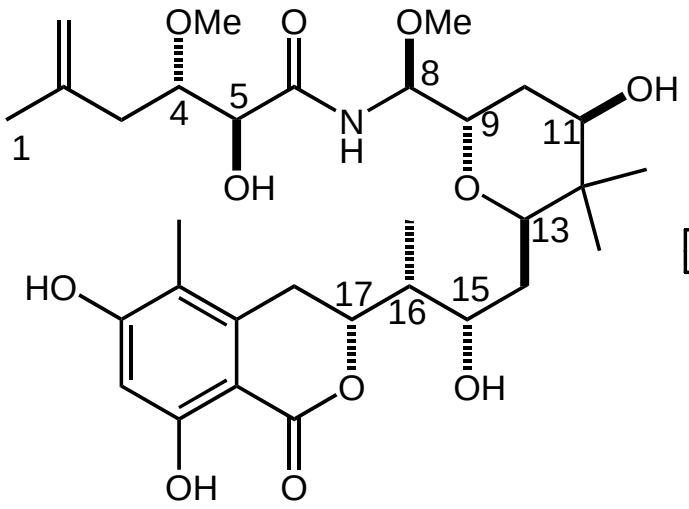
**39** **40** **41**


OH
HO
O
O
OTBDPS
38
(1) TosCl, Et3N
Sn(Bu)2(OMe)2
(2) NaH, THF
74%
O
O
O
OTBDPS
42
MgBr
Li2CuCl4, THF
89%
OH
O
O
OTBDPS
41
Me3OBF4, 4Å MS
proton sponge
92%
OMe
O
O
OTBDPS
43
OMe
O
OH
OTBDPS
4


CHO
HO
OH
AcCl, Et3N
DMAP, THF
85%
CHO
AcO
OAc
(1) NHS
(2) IBX
97%
O
O
N
O
O
AcO
OAc
HNEt2
Et3N
56%
O
NEt2
HO
OH
(1) AgNO3, pyridine
(2) TBDPSCl
or TBDPSCl, imidazole
84%
O
NEt2
TBDPSO
OTBDPS

**44** **45** **46** **47** **3**

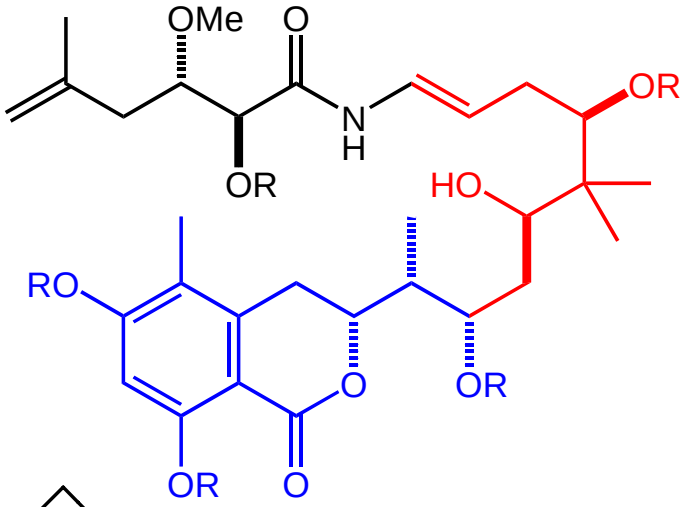
## Retrosynthetic Analysis for Psymberin 1



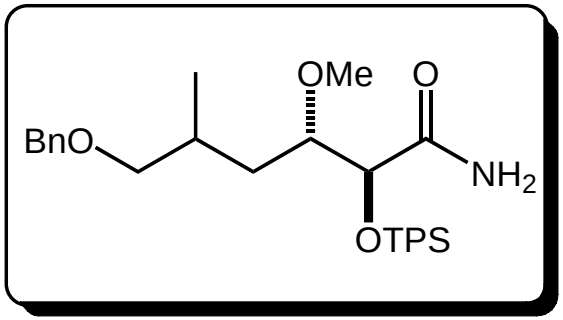

Psymberin **1**

$PhI(OAc)_2$

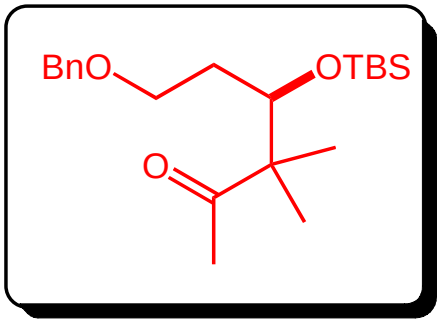
Oxidative cyclization



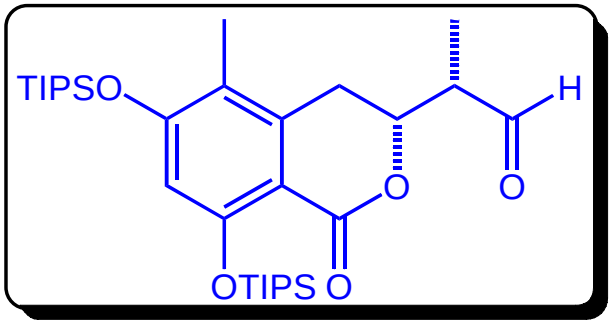

**2**




**17**

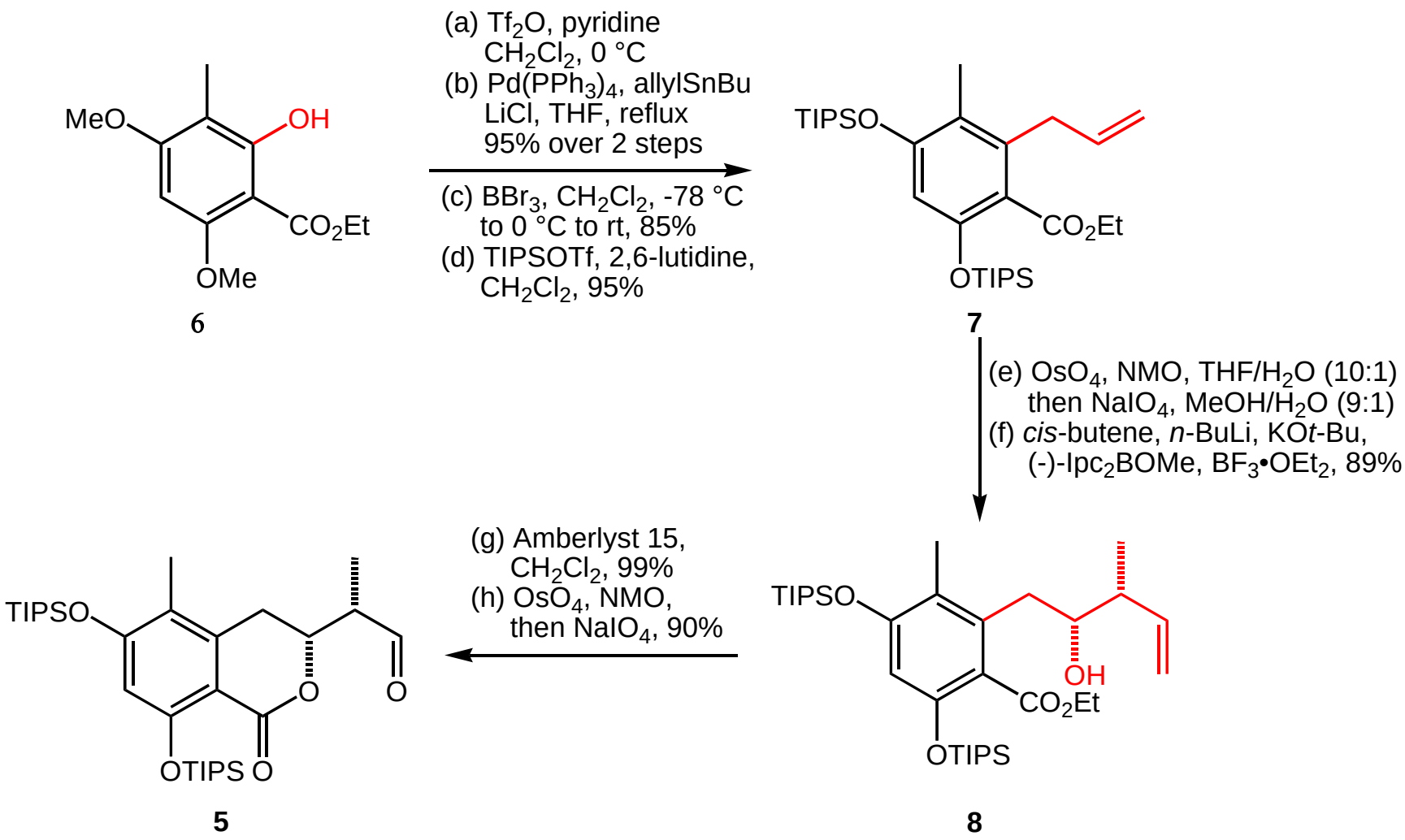


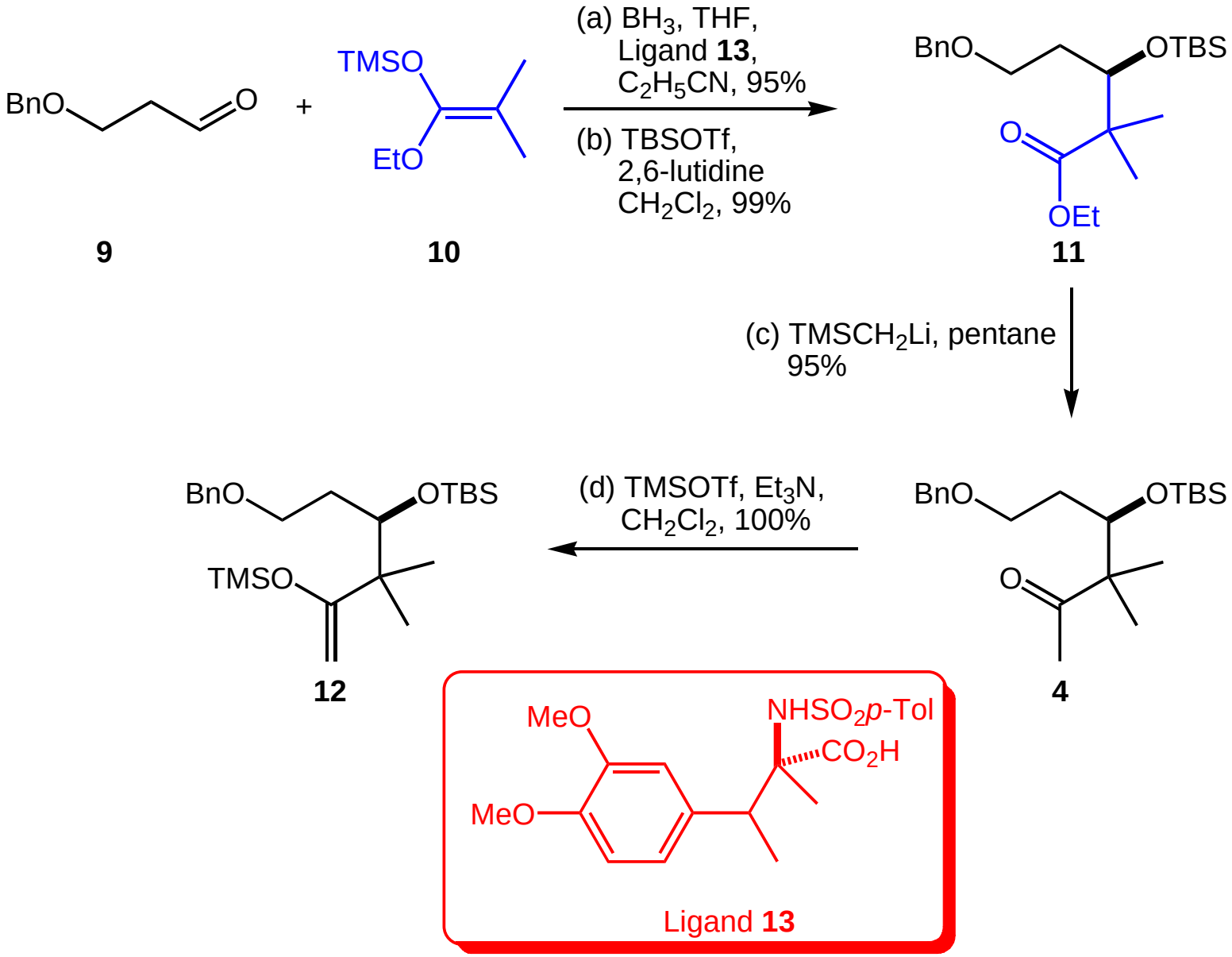

**4**

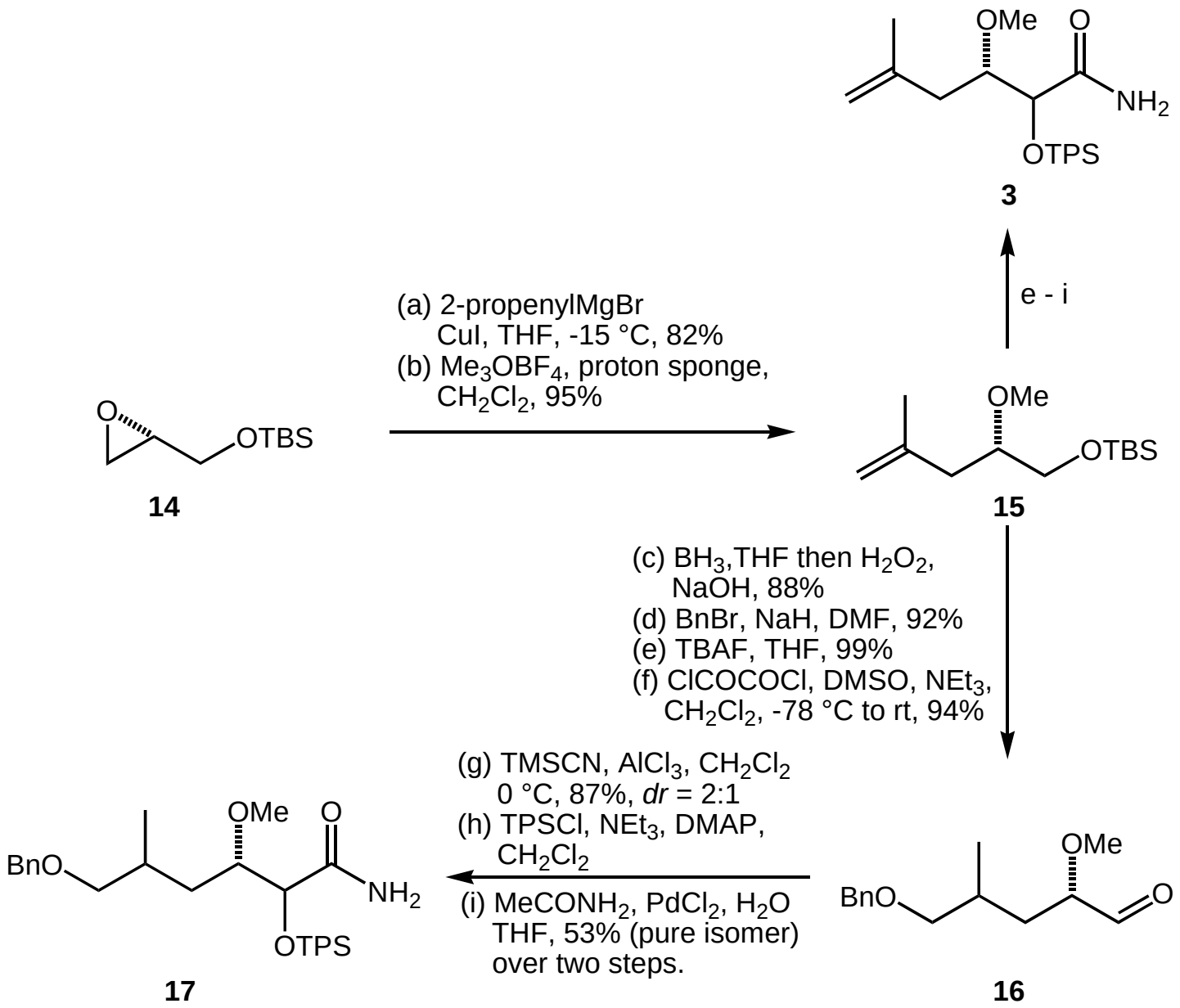


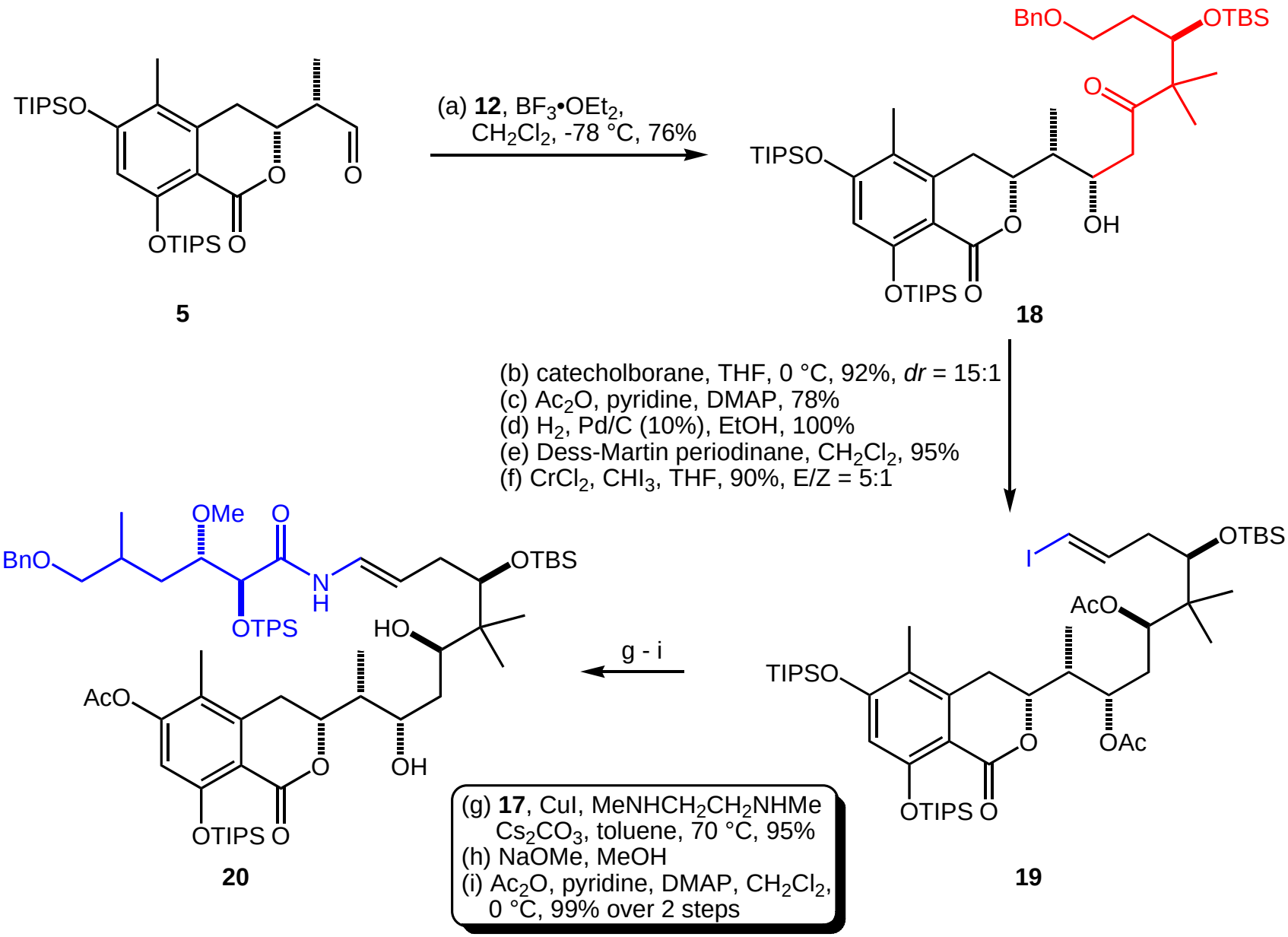

**5**

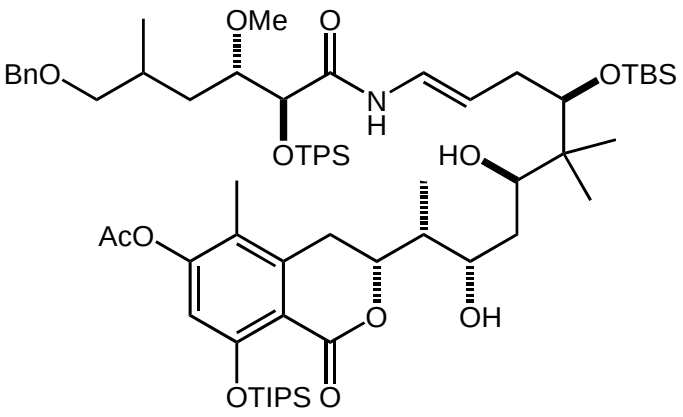
Huang, X. *Org. Lett*. **2007**, *9*, 2597-2600.


MeO
OH
CO2Et
OMe
6
(a) Tf2O, pyridine
CH2Cl2, 0 °C
(b) Pd(PPh3)4, allylSnBu
LiCl, THF, reflux
95% over 2 steps
(c) BBr3, CH2Cl2, -78 °C
to 0 °C to rt, 85%
(d) TIPSOTf, 2,6-lutidine,
CH2Cl2, 95%
TIPSO
CO2Et
OTIPS
7
(e) OsO4, NMO, THF/H2O (10:1)
then NaIO4, MeOH/H2O (9:1)
(f) cis-butene, n-BuLi, KOt-Bu,
(-)-Ipc2BOMe, BF3•OEt2, 89%
TIPSO
OH
CO2Et
OTIPS
8
(g) Amberlyst 15,
CH2Cl2, 99%
(h) OsO4, NMO,
then NaIO4, 90%
TIPSO
O
O
OTIPS
O
5


BnO
O
+
TMSO
EtO
(a) BH3, THF,
Ligand 13,
C2H5CN, 95%
(b) TBSOTf,
2,6-lutidine
CH2Cl2, 99%
BnO
OTBS
O
OEt
9
10
11
(c) TMSCH2Li, pentane
95%
BnO
OTBS
O
4
(d) TMSOTf, Et3N,
CH2Cl2, 100%
BnO
OTBS
TMSO
12
MeO
MeO
NHSO2p-Tol
CO2H
Ligand 13

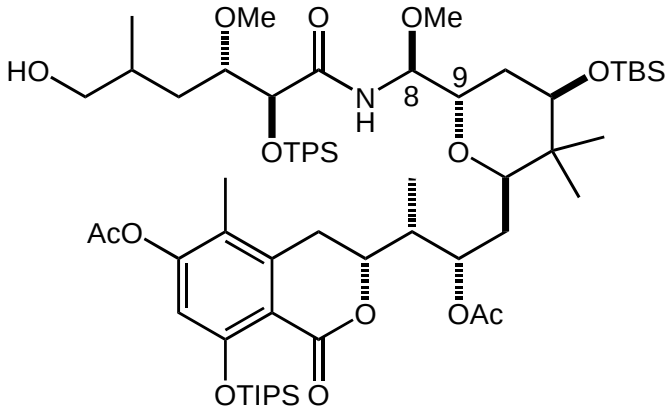

OMe
O
NH2
OTPS
3
e - i
(a) 2-propenylMgBr
CuI, THF, -15 °C, 82%
(b) Me3OBF4, proton sponge,
CH2Cl2, 95%
O
OTBS
14
OMe
OTBS
15
(c) BH3,THF then H2O2,
NaOH, 88%
(d) BnBr, NaH, DMF, 92%
(e) TBAF, THF, 99%
(f) ClCOCOCl, DMSO, NEt3,
CH2Cl2, -78 °C to rt, 94%
(g) TMSCN, AlCl3, CH2Cl2
0 °C, 87%, dr = 2:1
(h) TPSCl, NEt3, DMAP,
CH2Cl2
(i) MeCONH2, PdCl2, H2O
THF, 53% (pure isomer)
over two steps.
OMe
BnO
O
OMe
O
BnO
NH2
OTPS
17
16


TIPSO
O
O
OTIPS O
5
(a) 12, BF3•OEt2,
CH2Cl2, -78 °C, 76%
BnO
OTBS
O
TIPSO
O
OH
OTIPS O
18
(b) catecholborane, THF, 0 °C, 92%, dr = 15:1
(c) Ac2O, pyridine, DMAP, 78%
(d) H2, Pd/C (10%), EtOH, 100%
(e) Dess-Martin periodinane, CH2Cl2, 95%
(f) CrCl2, CHI3, THF, 90%, E/Z = 5:1
I
OTBS
AcO
TIPSO
O
OAc
OTIPS O
19
g - i
BnO
OMe
O
N
H
OTBS
OTPS
HO
AcO
O
OH
OTIPS O
20
(g) 17, CuI, MeNHCH2CH2NHMe
Cs2CO3, toluene, 70 °C, 95%
(h) NaOMe, MeOH
(i) Ac2O, pyridine, DMAP, CH2Cl2,
0 °C, 99% over 2 steps



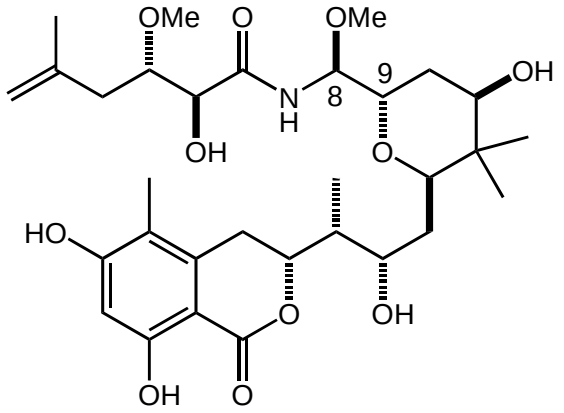

**20**

(j) $PhI(OAc)_2$, MeOH, HFIP, 72%
(k) $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$
(l) $H_2$, Pd/C, MeOH, 95% over 2 steps




**21** $C_8$, $C_9$ = *S, S*

(m) *o*-$NO_2PhSeCN$, $PBu_3$, THF
(n) $H_2O_2$, THF
(o) TBAF, THF, rt to 50 °C, 63% over 3 steps




Psymberin **1**

In late 2003, our colleagues in the research group of Professor Philip Crews isolated a highly potent cytotoxic marine natural product from “an undescribed and inconspicuous sponge, Psammocinia sp” The molecule, was later determined to be identical to iriciniastatin A, a compound isolated and reported by Pettit and coworkers from extracts of Ircinia ramose. The dual isolation of this compound from different sponges combined with the reported difficulty in isolating the compound from many sponge extracts adds evidence to the speculation that this molecule, along with structurally similar compounds, may in fact take origin from symbiotic bacteria.

Over the past 6 years, a number of publications relating to the synthesis and semisynthesis of psymberin and analogues have been developed, including De Brabander's elegant first total synthesis of **1** and **2** in 2006, which conclusively determined that psymberin is in fact the 4*S* isomer **1**. To embark on the total synthesis of this remarkably active molecule, we endeavored to develop a rapid and convergent approach to both **1** and **2** as well as libraries of stereoisomer and structural analogues. Our successful efforts to produce several key building blocks are disclosed herein.