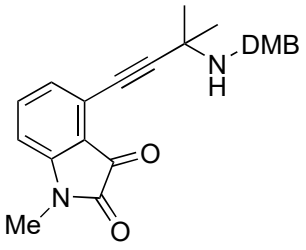
Problem Session 1

2018. 1. 11. Akira Tomiyama

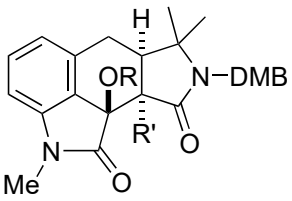
Please fill in the blank and provide each reaction mechanisms.

1



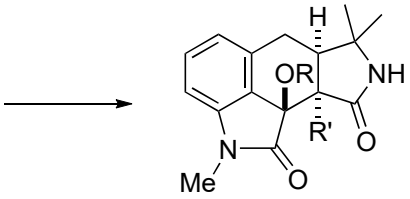
1-1

1. **1-A**, *i*-Pr_2NEt (excess), DCM, -78 °C; then **1-1**, DCM, -78 °C, 57%
2. H_2, Raney Ni, MeOH; DMP, DCM, 69%
3. TMSOTf, Et_3N, DCM, 0 to 35 °C; $TiCl_4$, DCM, -78 °C to rt, 78%



1-2

R = TMS
R' = CO_2Me



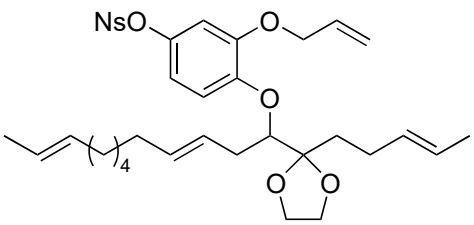
1-3
($C_{21}H_{28}N_2O_5Si$)

4. MeOTf, DCM, 76%
5. **1-B**, MeCN, 50 °C, 89%
6. Oxone, MeCN/H_2O, 0 °C, 67%
7. PIFA, DCM, rt; TFA/H_2O (3/1), 55 °C, 26%

1-4

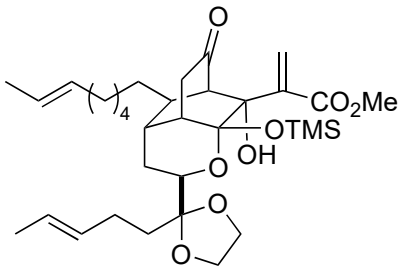
($C_{21}H_{22}N_2O_8$)

2



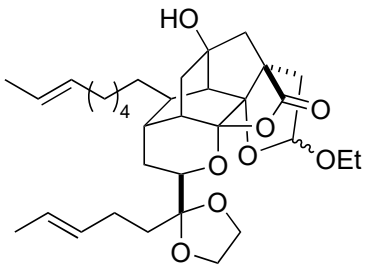
2-1

1. $Pd(PPh_3)_4$, $NaBH_4$, EtOH, rt
2. $Pb(OAc)_4$, DCE, reflux; Silica gel, DCM, rt, 56% (2 steps, 1:3 dr)
3. TMSCl, Et_3N, DCM, rt, 86%
4. **2-A**, LDA, Et_2O, -40 °C, 54%
5. PhSH, Cs_2CO_3, MeCN, rt
6. *m*-CPBA, Al_2O_3, DCM, 0 °C to rt, 60% (2 steps)



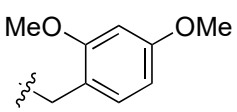
2-2

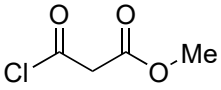
7. TBAF, AcOH, THF, 0 °C to rt, 81%
8. **2-B**, *N*,*N*-dimethylaniline, DCM, rt
9. SmI_2, THF, rt, 60% (2 steps)



2-3

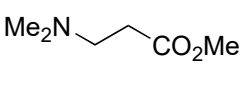
DMB =



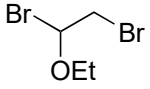


1-A

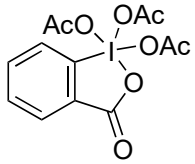
1-B



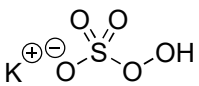
2-A



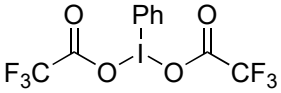
2-B



DMP



Oxone



PIFA

Problem Session 1 - Answer -

2018. 1. 11. Akira Tomiyama

Topic: Total syntheses by John L. Wood

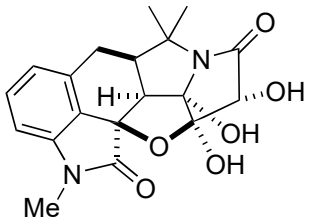
Prof. John Louis Wood

1980-1985: B.A., Chemistry, University of Colorado
1985-1991: Ph.D., Organic Chemistry, University of Pennsylvania
(Prof. Amos B. Smith III)
1991-1993: American Cancer Society Postdoctoral Fellow, Harvard University
1993-1997: Assistant Professor of Chemistry, Yale University
1997-1998: Associate Professor of Chemistry (non tenured), Yale University
1998-2006: Professor of Chemistry, Yale University
2006-2013: A. I. Meyers Professor of Chemistry, Colorado State University
2013-Present: Robert A. Welch Distinguished Professor and Cancer Prevention Research Institute Scholar, Baylor University

1 Total synthesis of (±)-aspergilline A

isolaton:
from the fungus *Aspergillus versicolor*
Zhou, M.; Miao, M.-M.; Du, G.; Li, X.-N.; Shang, S.-Z.; Zhao, W.; Liu, Z.-H.; Yang, G.-Y.; Che, C.-T.; Hu, Q.-F.; Gao, X.-M. *Org. Lett.* **2014**, *16*, 5016.

structural feature:
- caged hexacyclic (6/5/6/5/5/5) heterocyclic ring system
- six contiguous stereocenters
- heavily substituted tetramic acid

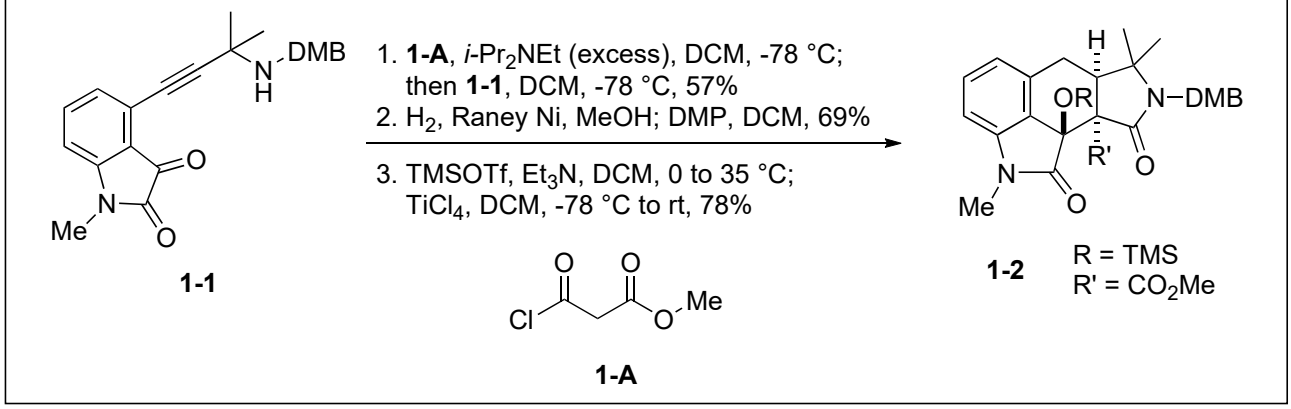


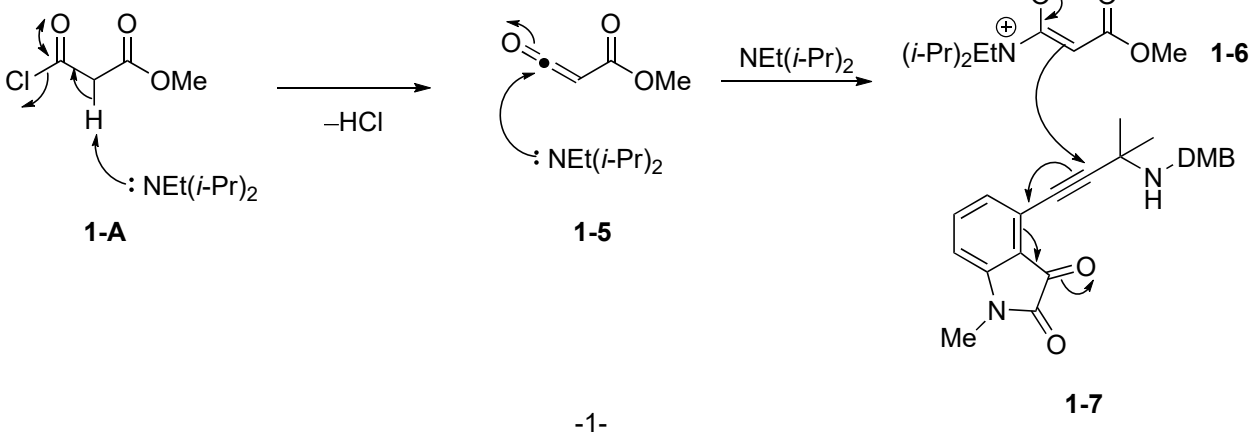
Aspergilline A

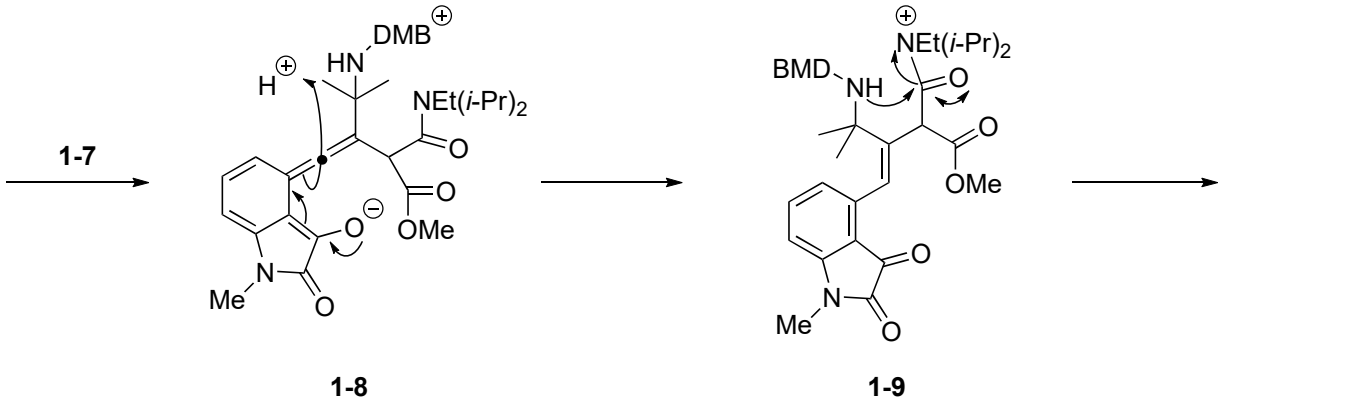
bioactivity:
- against tobacco mosaic virus
- against several human cancer cell lines

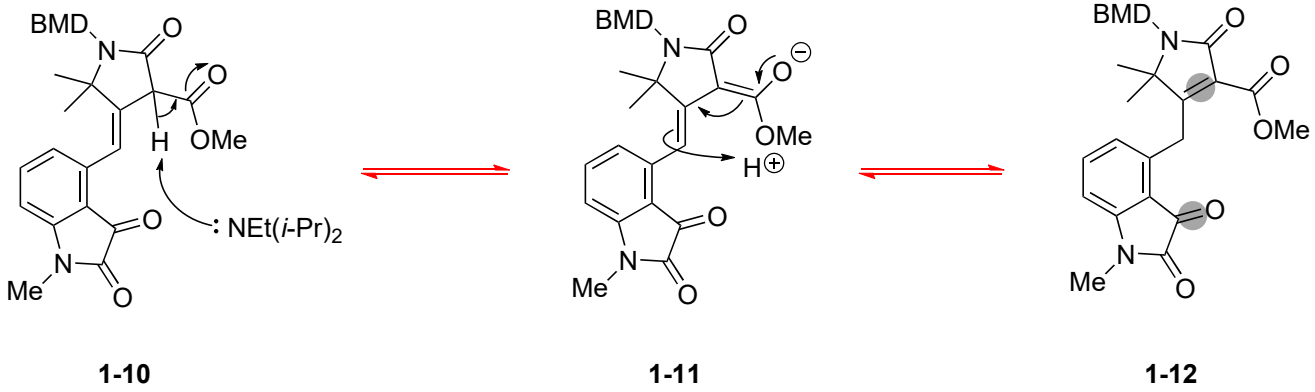
Gao, X.-M. et al. *Org. Lett.* **2014**, *16*, 5016.

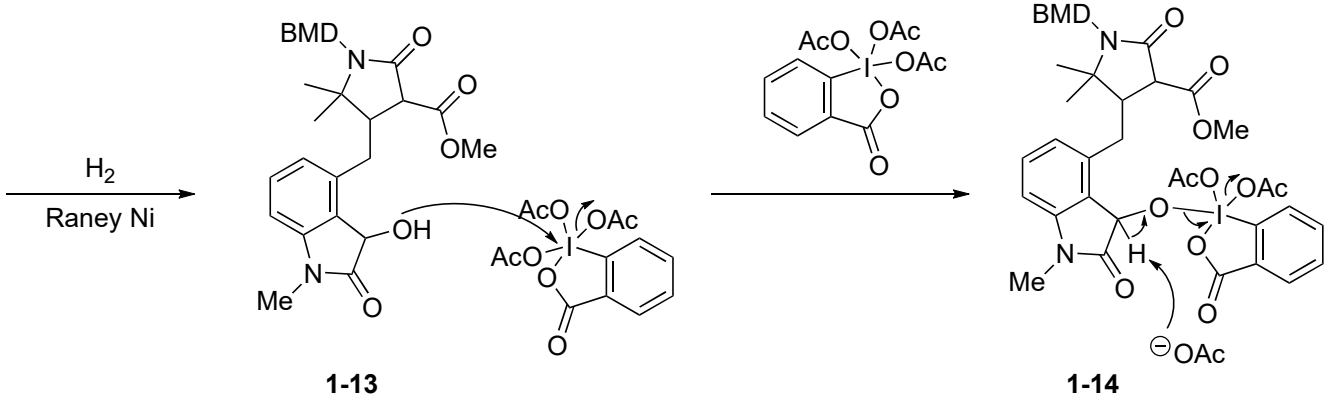
total synthesis:
Nakhla, M. C.; Wood, J. L. *J. Am. Chem. Soc.* **2017**, *139*, 18504 (**problem 1**)

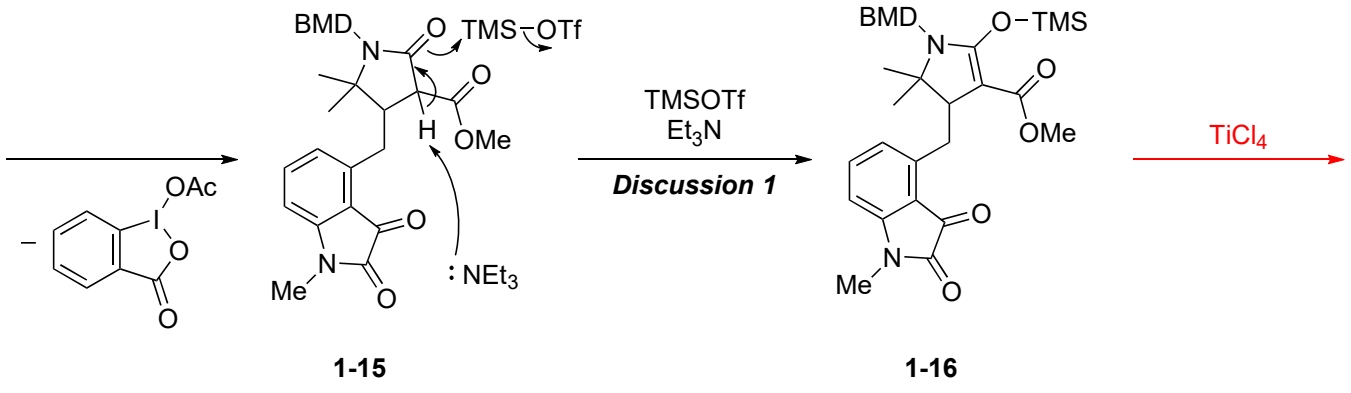


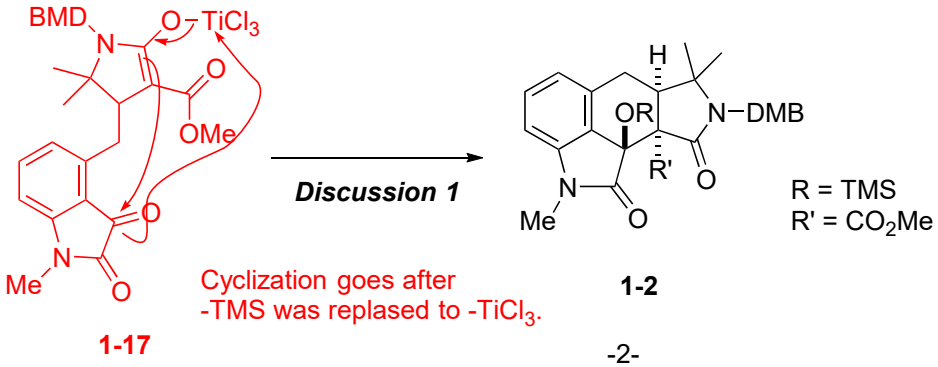



1-7
DMB
HN
H
NEt(i-Pr)2
O
OMe
N
Me
1-8
BMD
NH
NEt(i-Pr)2
1-9

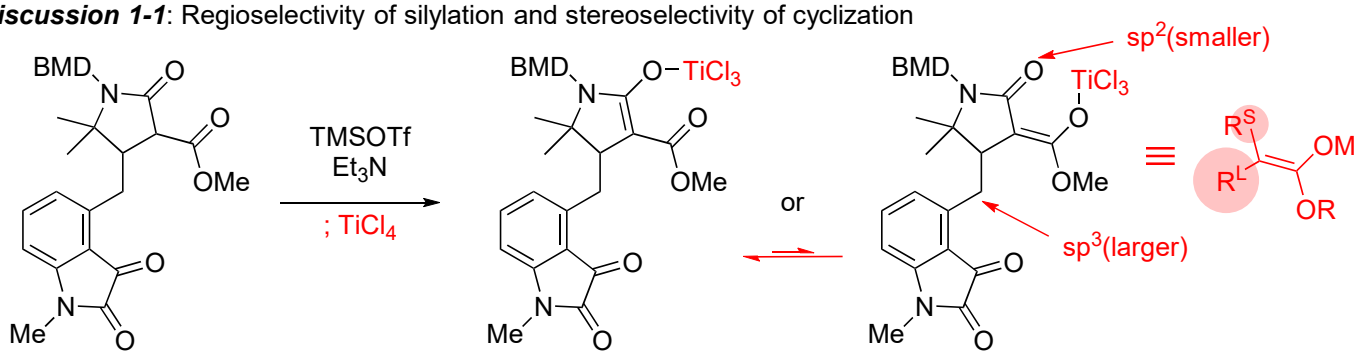

BMD
H
OMe
: NEt(i-Pr)2
1-10
1-11
1-12


H2
Raney Ni
OH
AcO
OAc
I
1-13
1-14


TMS–OTf
TMSOTf
Et3N
Discussion 1
TiCl4
: NEt3
1-15
1-16

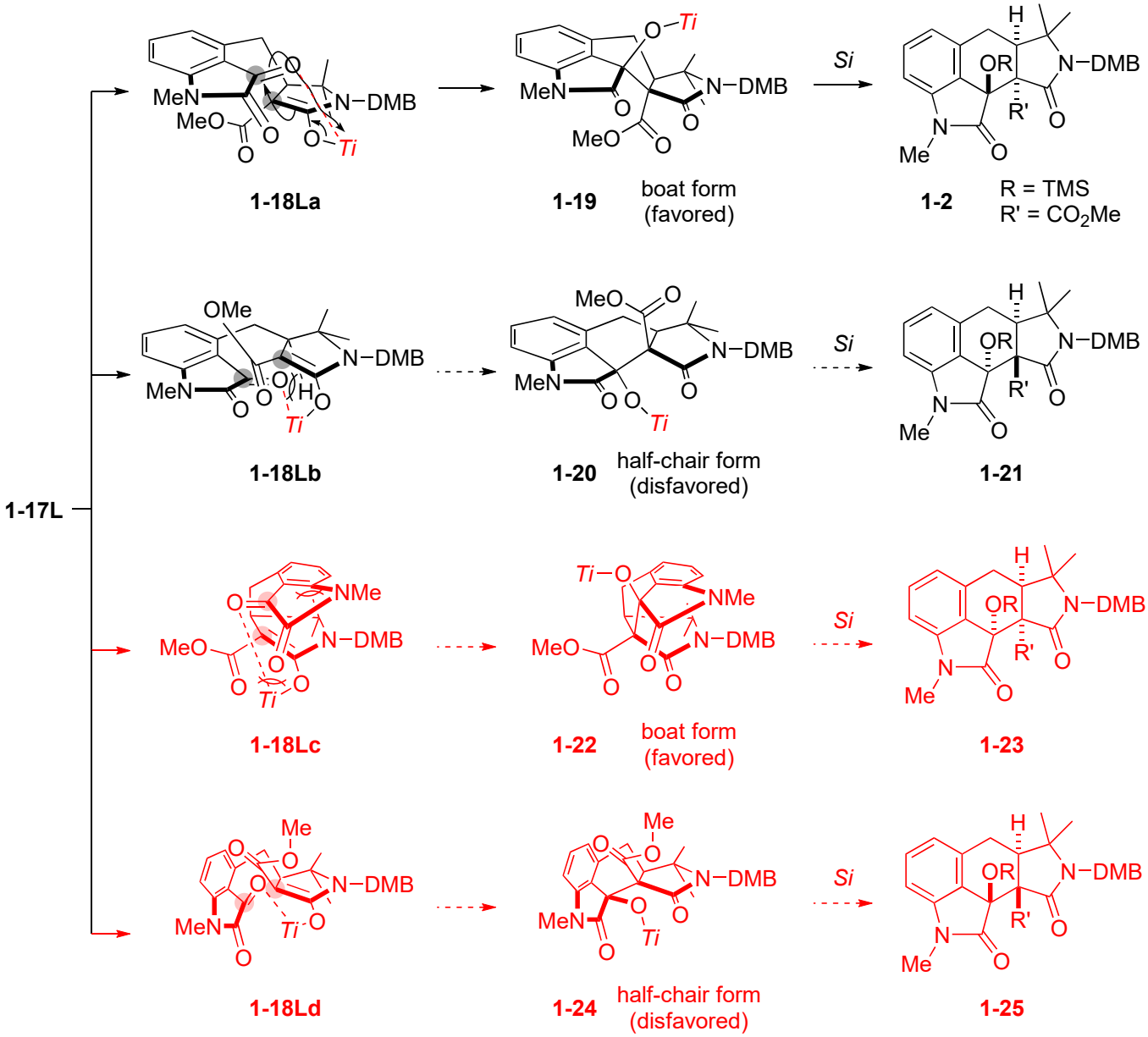

BMD
O–TiCl3
OMe
Discussion 1
OR
R'
N–DMB
R = TMS
R' = CO2Me
Cyclization goes after
-TMS was replased to -TiCl3.
1-17
1-2

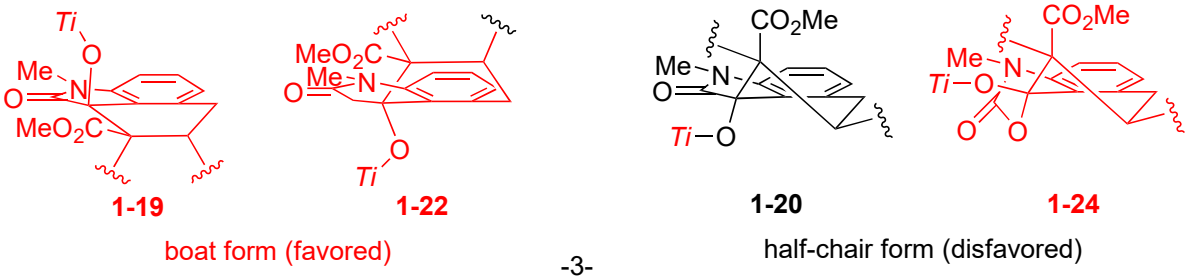
Discussion 1-1: Regioselectivity of silylation and stereoselectivity of cyclization

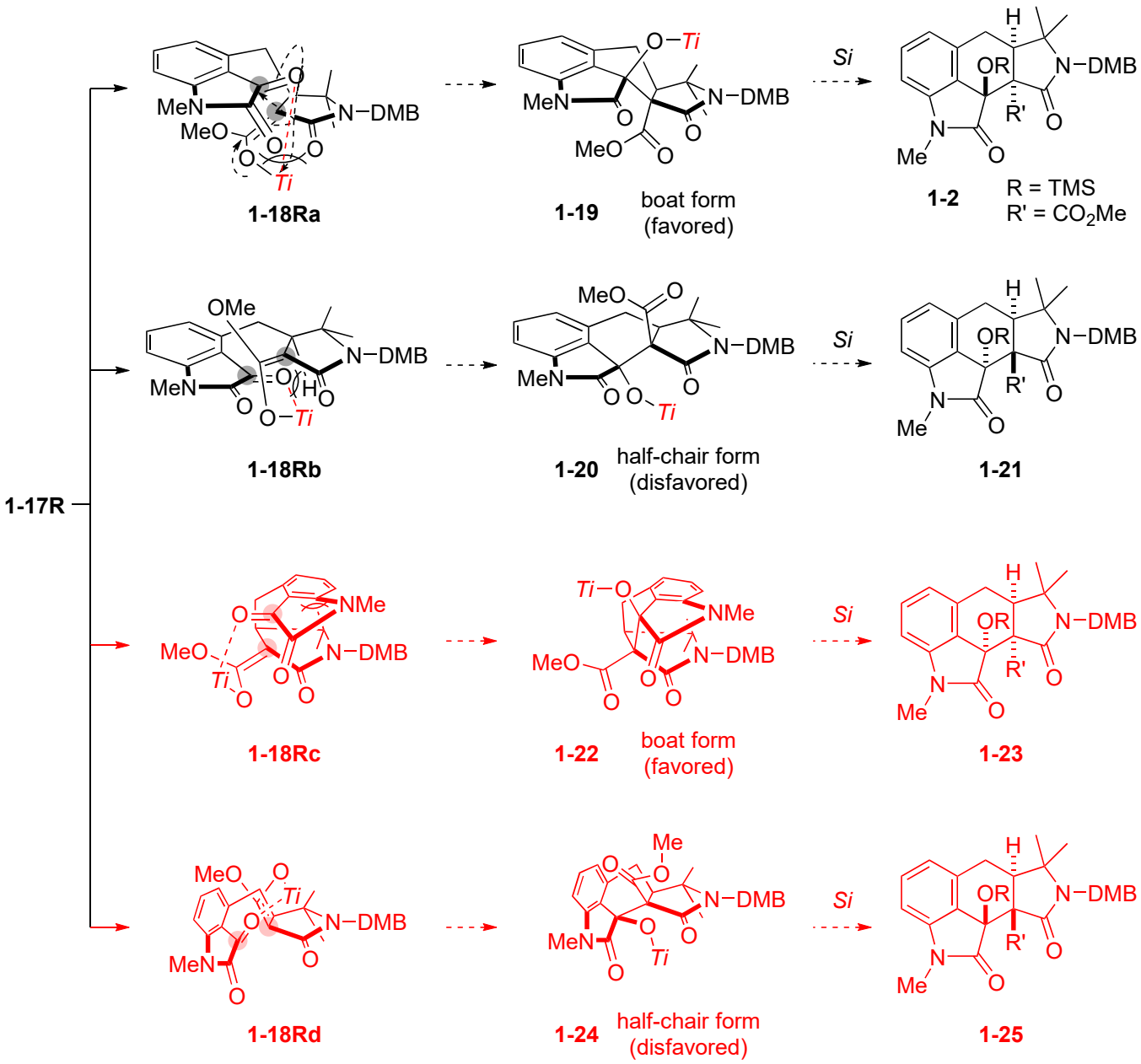


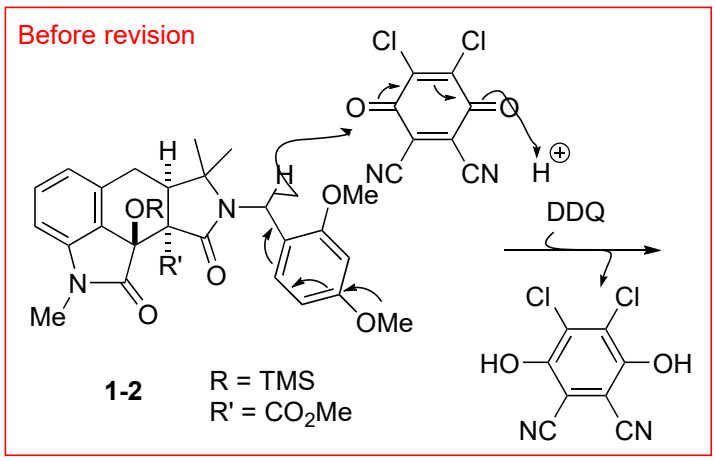
1-15 **1-17L** major **1-17R** (*trans*-enolate) minor

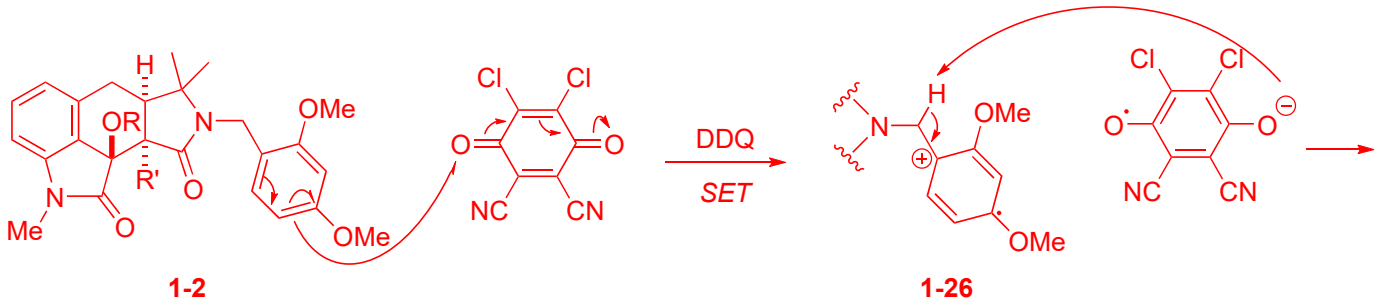
(∵ Lewis basicity of amide-O is higher than that of ester-O.)



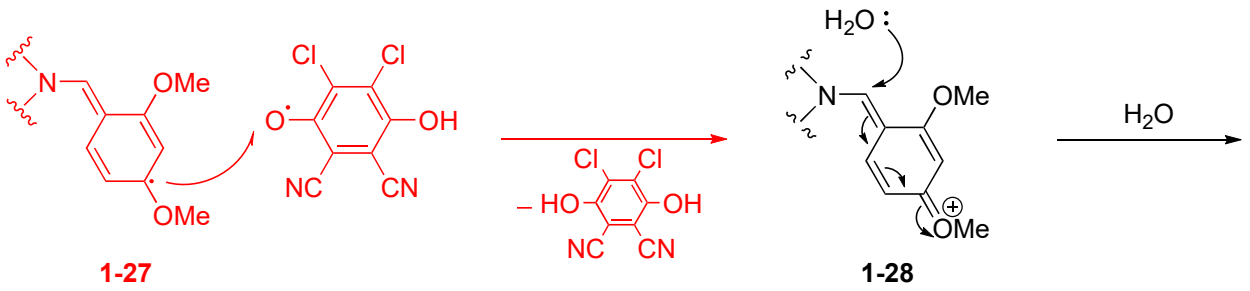



1-17R
1-18Ra
1-19
boat form
(favored)
1-2
R = TMS
R' = CO2Me
1-18Rb
1-20
half-chair form
(disfavored)
1-21
1-18Rc
1-22
boat form
(favored)
1-23
1-18Rd
1-24
half-chair form
(disfavored)
1-25
Si

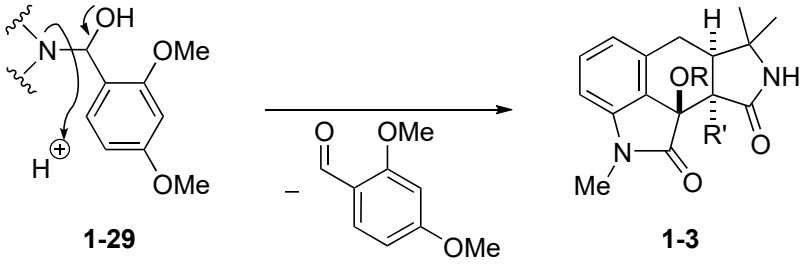

Before revision
1-2
R = TMS
R' = CO2Me
DDQ
1-28



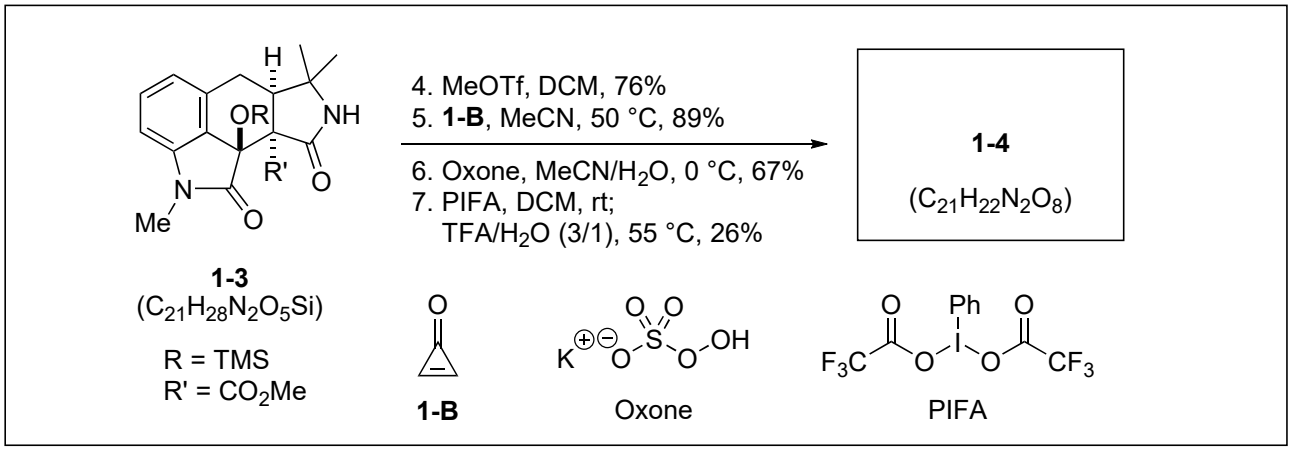
1-2 **1-26**

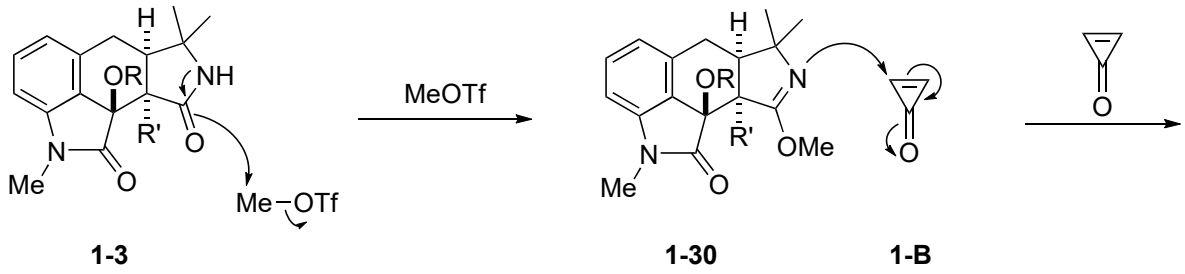


1-27 **1-28**

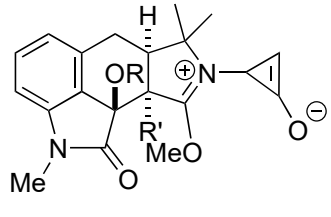


1-29 **1-3**



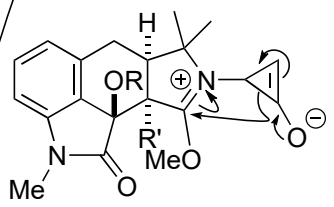


1-3 **1-30** **1-B**

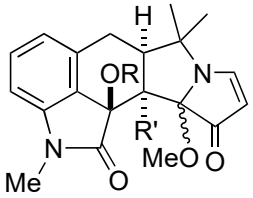


1-31

Possible reaction mechanisms

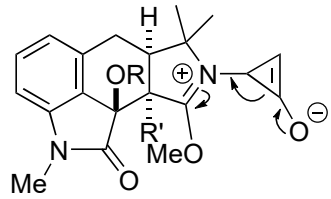


1-30a

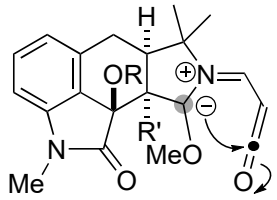


1-35 (u:d = 3:2)

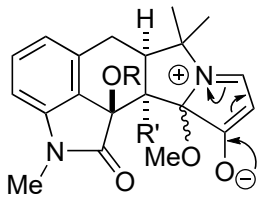
Hemming, K. et al.
Tetrahedron Lett. **2008**, *49*, 6316.



1-30b



1-32

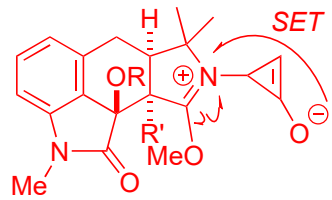


1-33

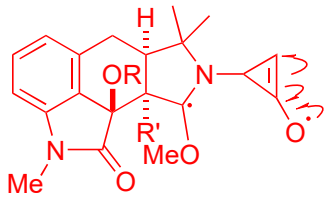
~~negative charge on electron-rich carbon~~

No problem
(∵ Inductive effect of -OMe can stabilize the carbanion.)

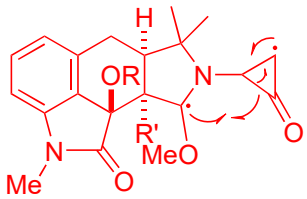
1-35



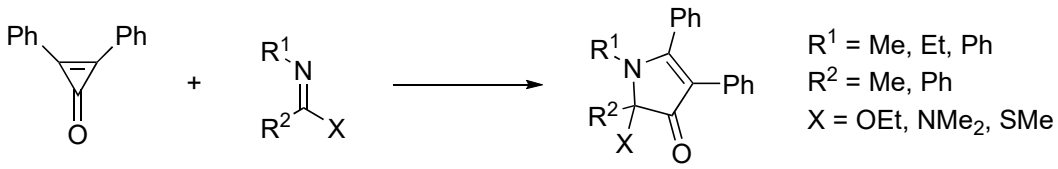
1-30c



1-34

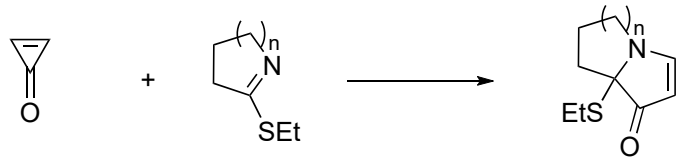


1-35



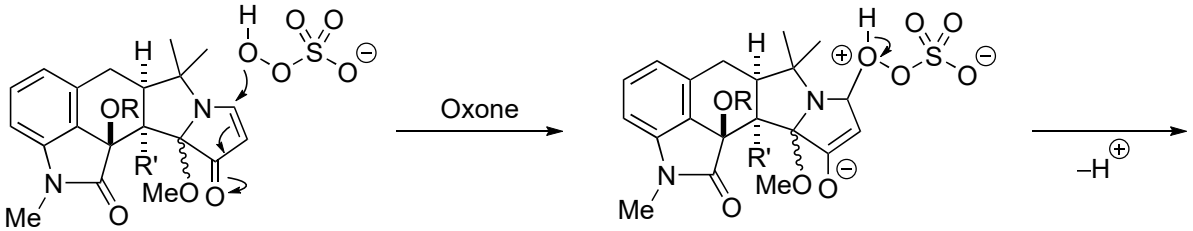
R^1 = Me, Et, Ph
R^2 = Me, Ph
X = OEt, NMe_2, SMe

Matsumoto, K. et al. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3849.

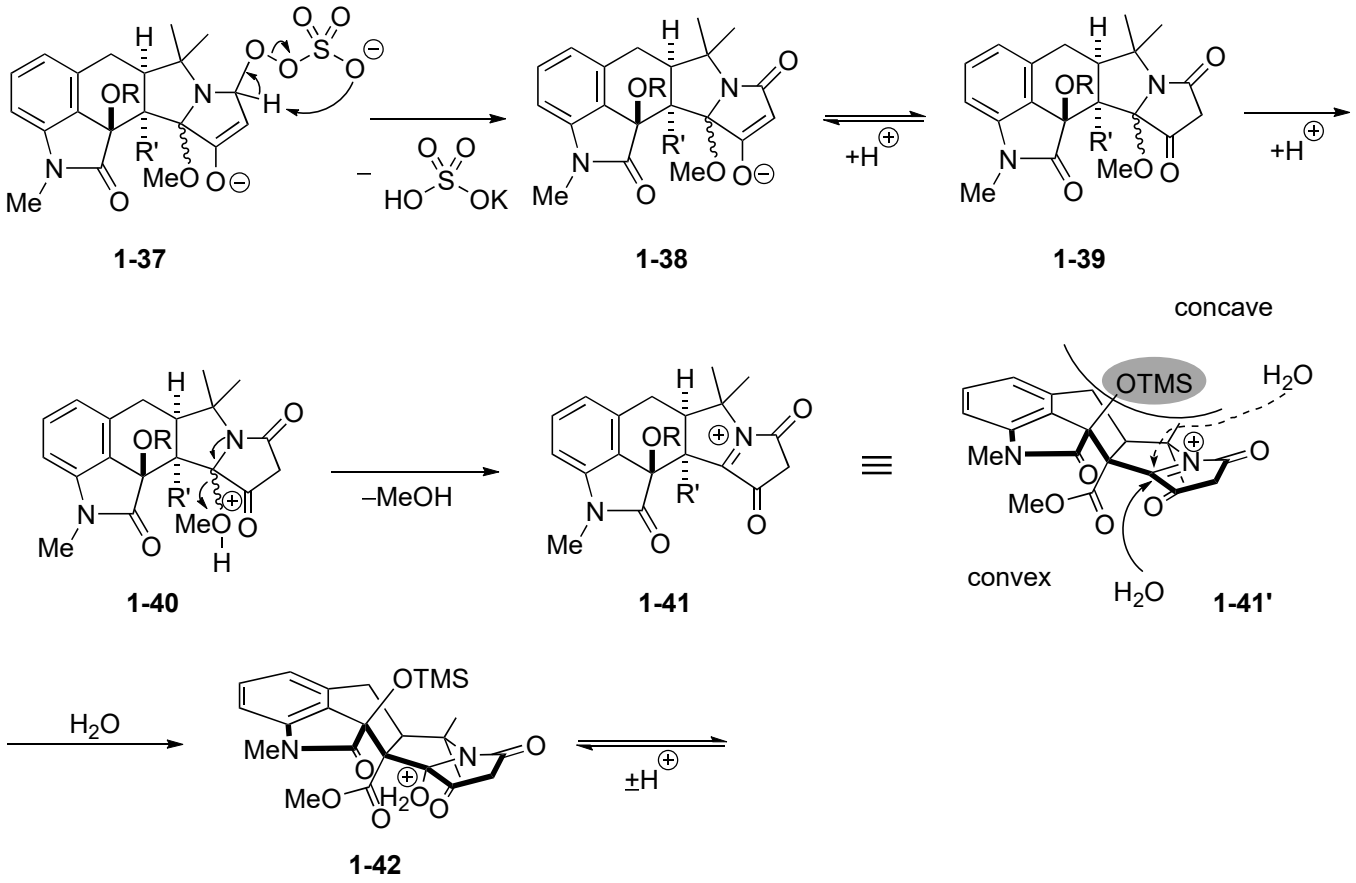


n = 1, 2, 3

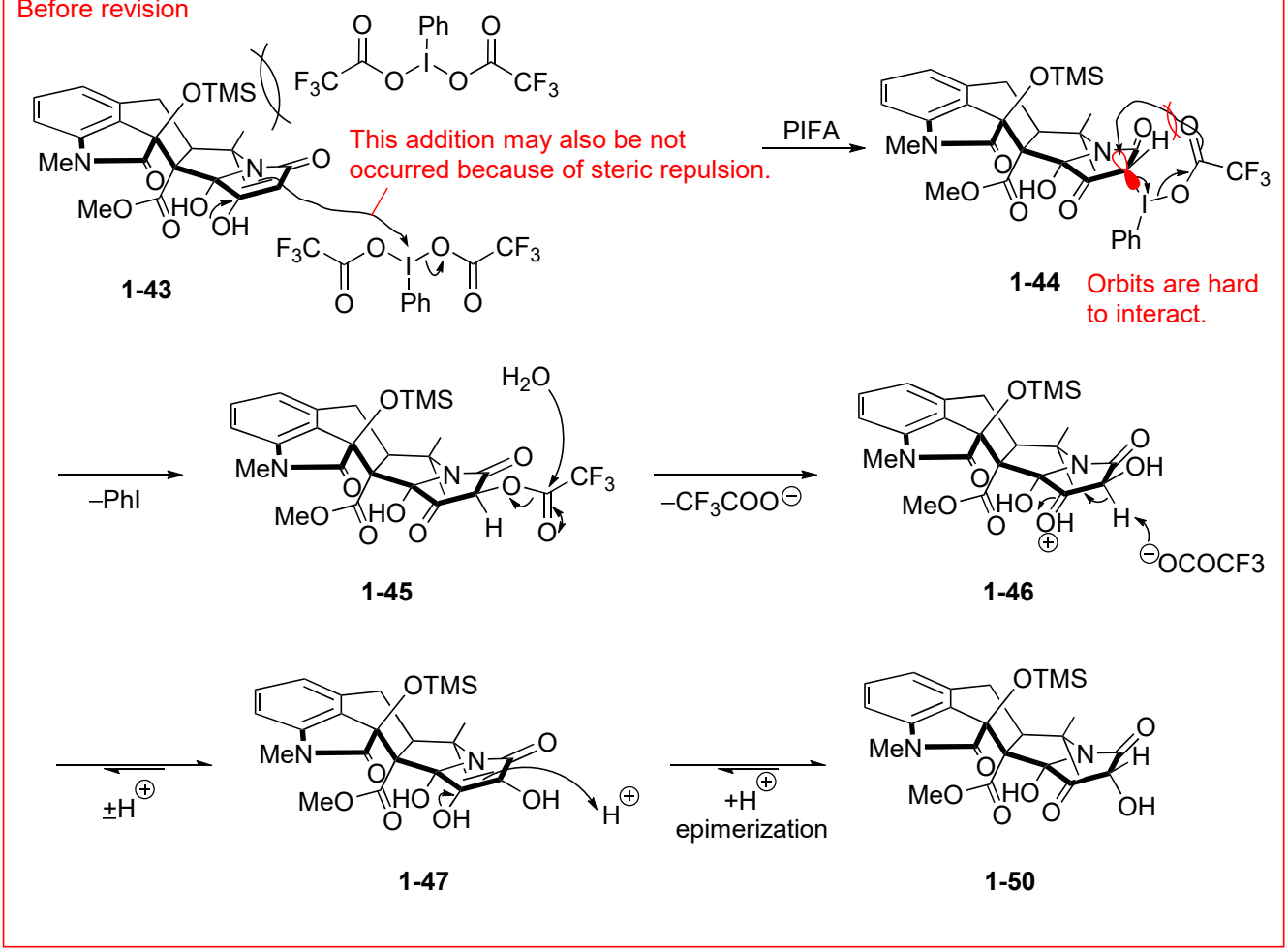
Hemming, K. et al. *Tetrahedron Lett.* **2008**, *49*, 6316.

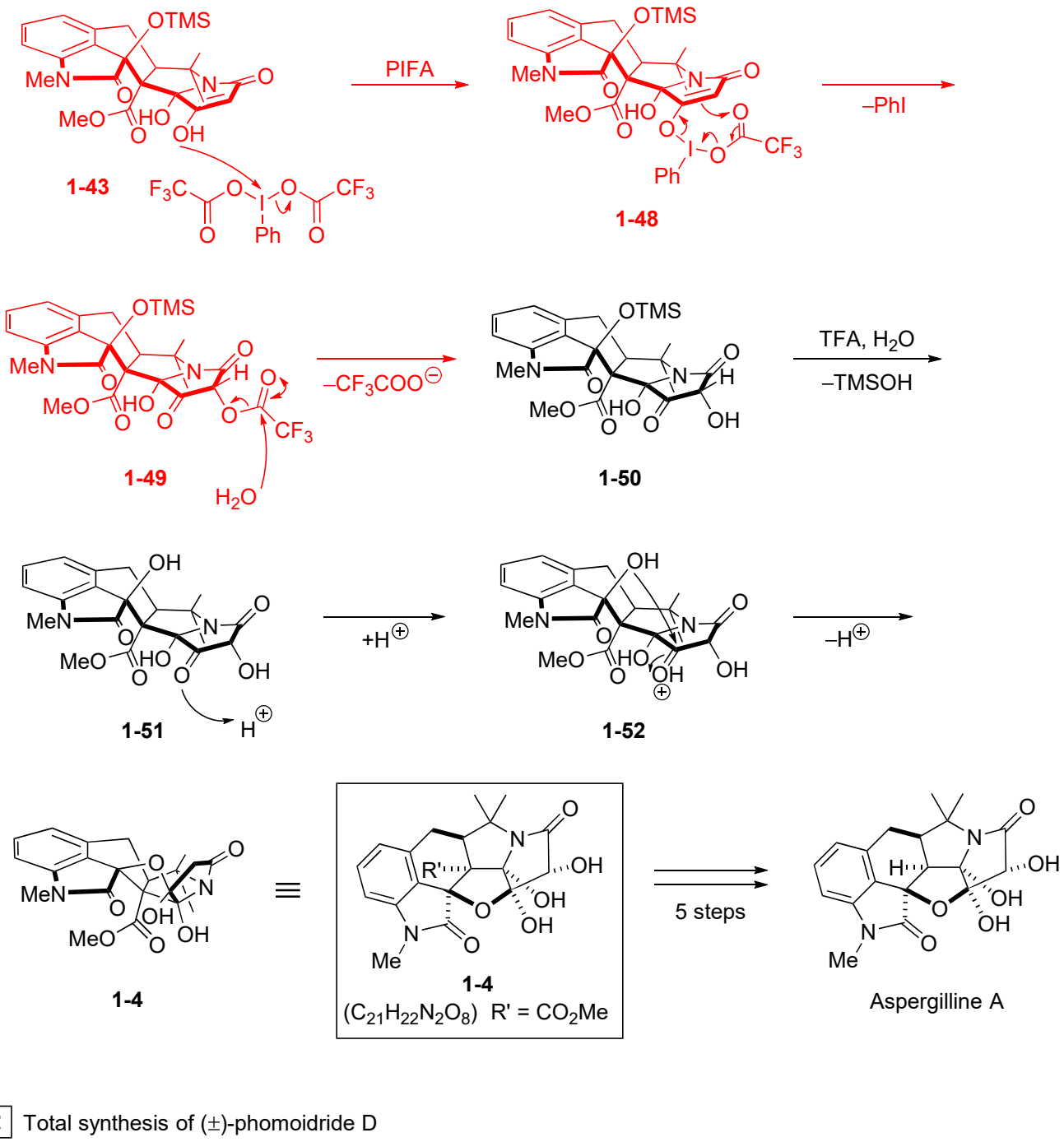


1-35 **1-36**



Before revision



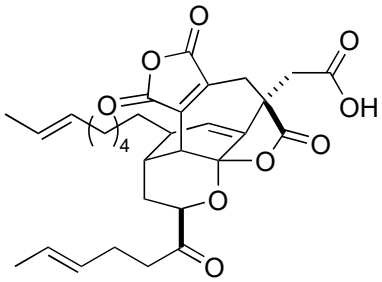


2 Total synthesis of (±)-phomoidride D

isolaton:
from a nonsporulating fungus ATCC 74256
Spencer, P.; Agnelli, F.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 1443.

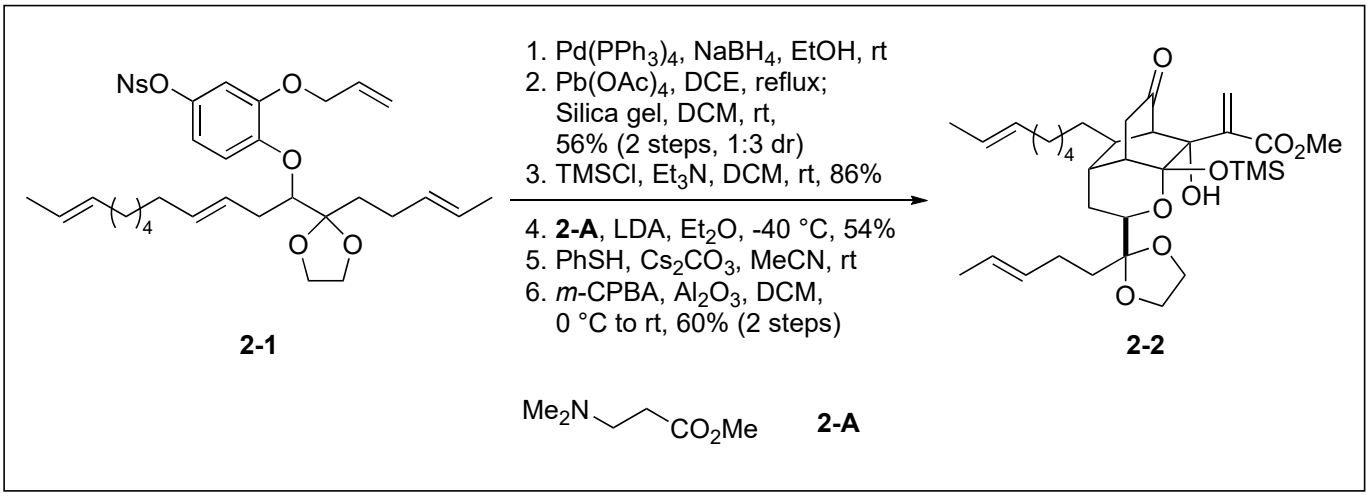
structural feature:
- [4.3.1] bicyclo system containing a bridgehead double bond
- four contiguous stereocenters
- maleic anhydride moiety

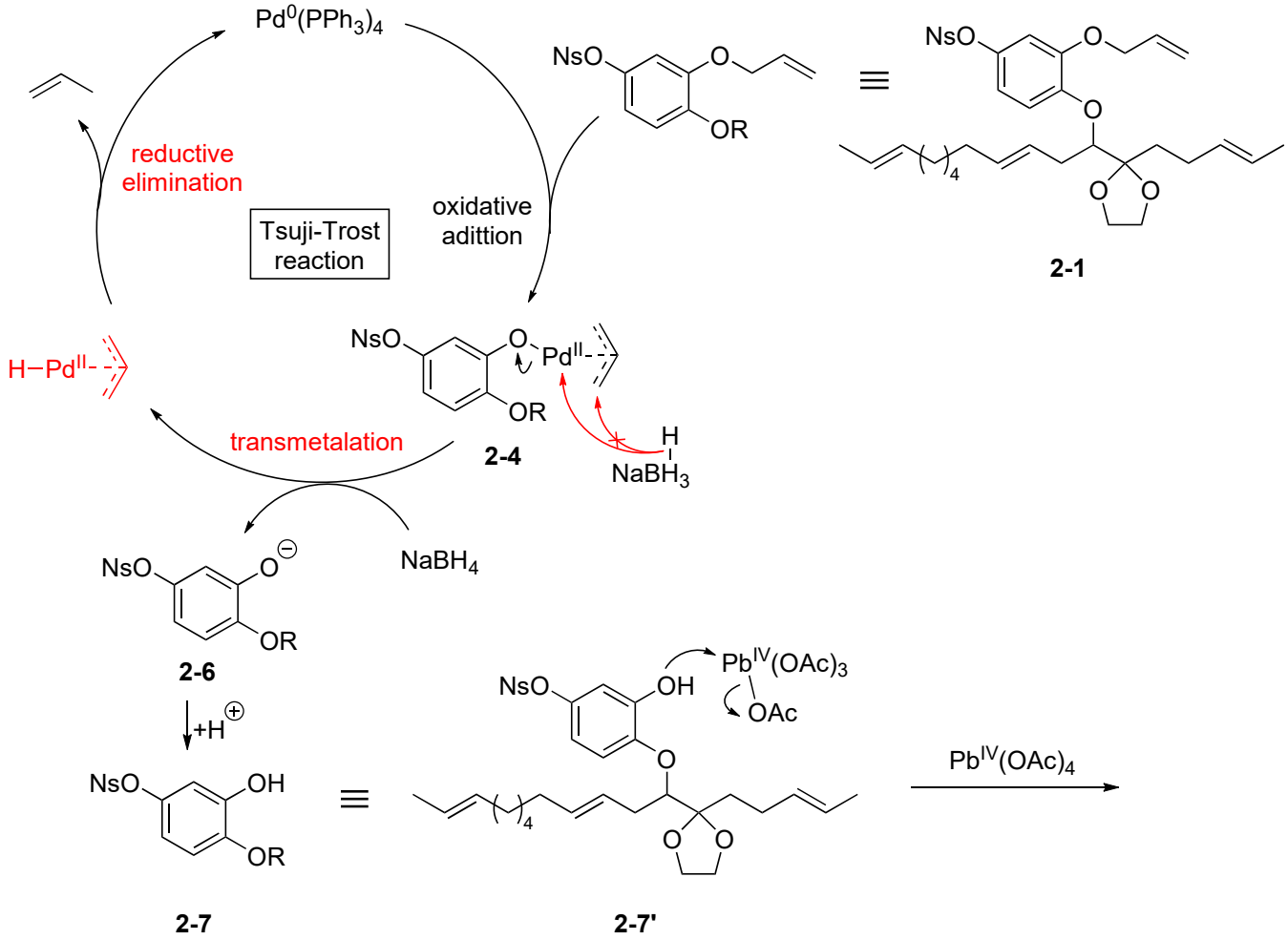
bioactivity:
not reported



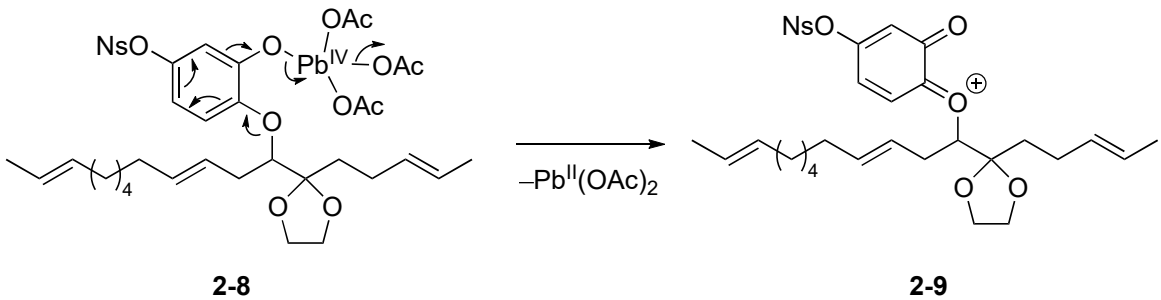
Phomoidride D

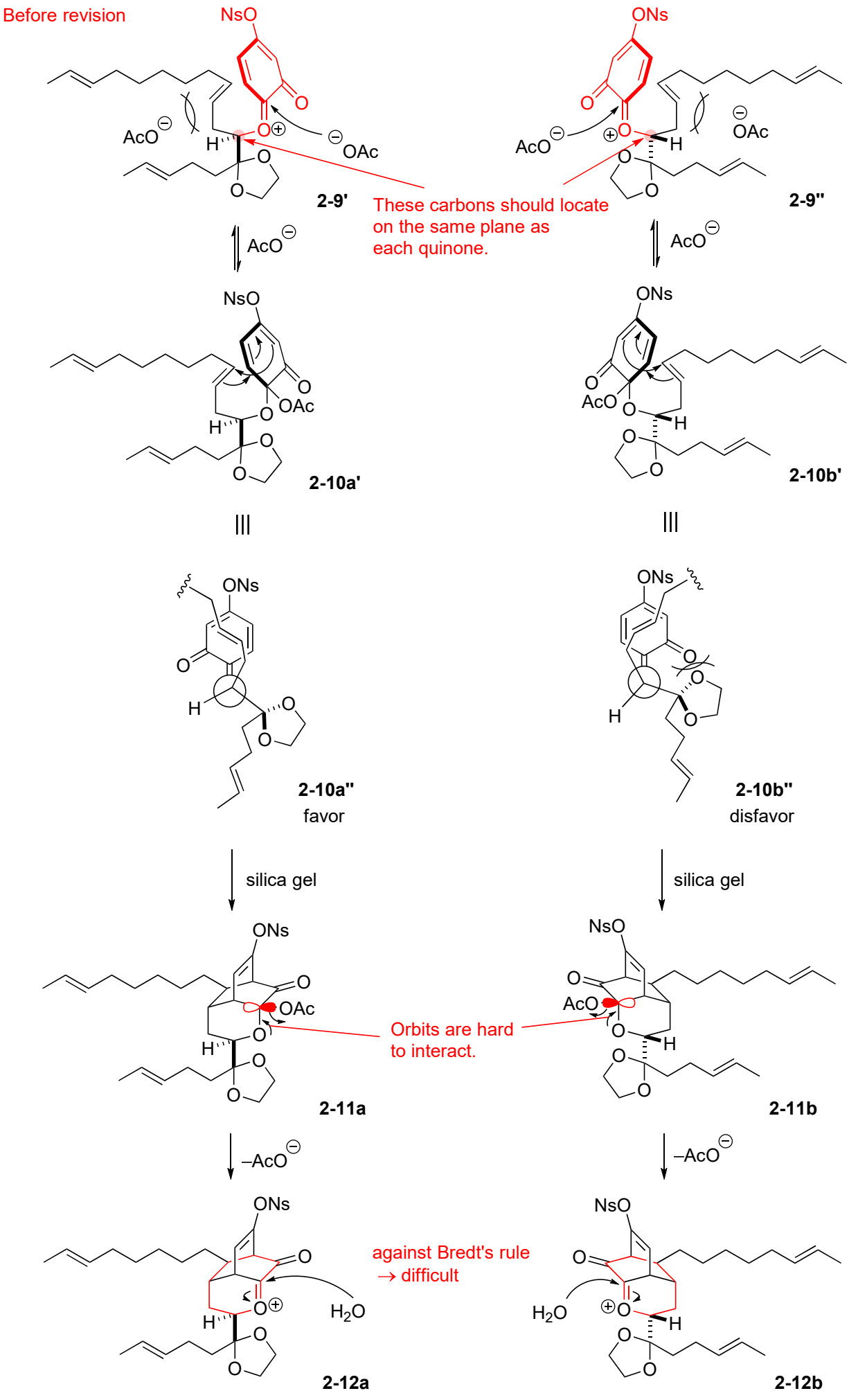
total synthesis:
Leung, J. C.; Bedermann, A. A.; Njardarson, J. T.; Spiegel, D. A.; Murphy, G. K.; Hama, N.; Twenter, B. M.; Dong, P.; Shirahata, T.; McDonald, I. M.; Inoue, M.; Taniguchi, N.; McMahon, T. C.; Schneider, C. M.; Tao, N.; Stoltz, B. M.; Wood, J. *Angew. Chem.* doi: 10.1002/ange.201712369 (**problem 2**)

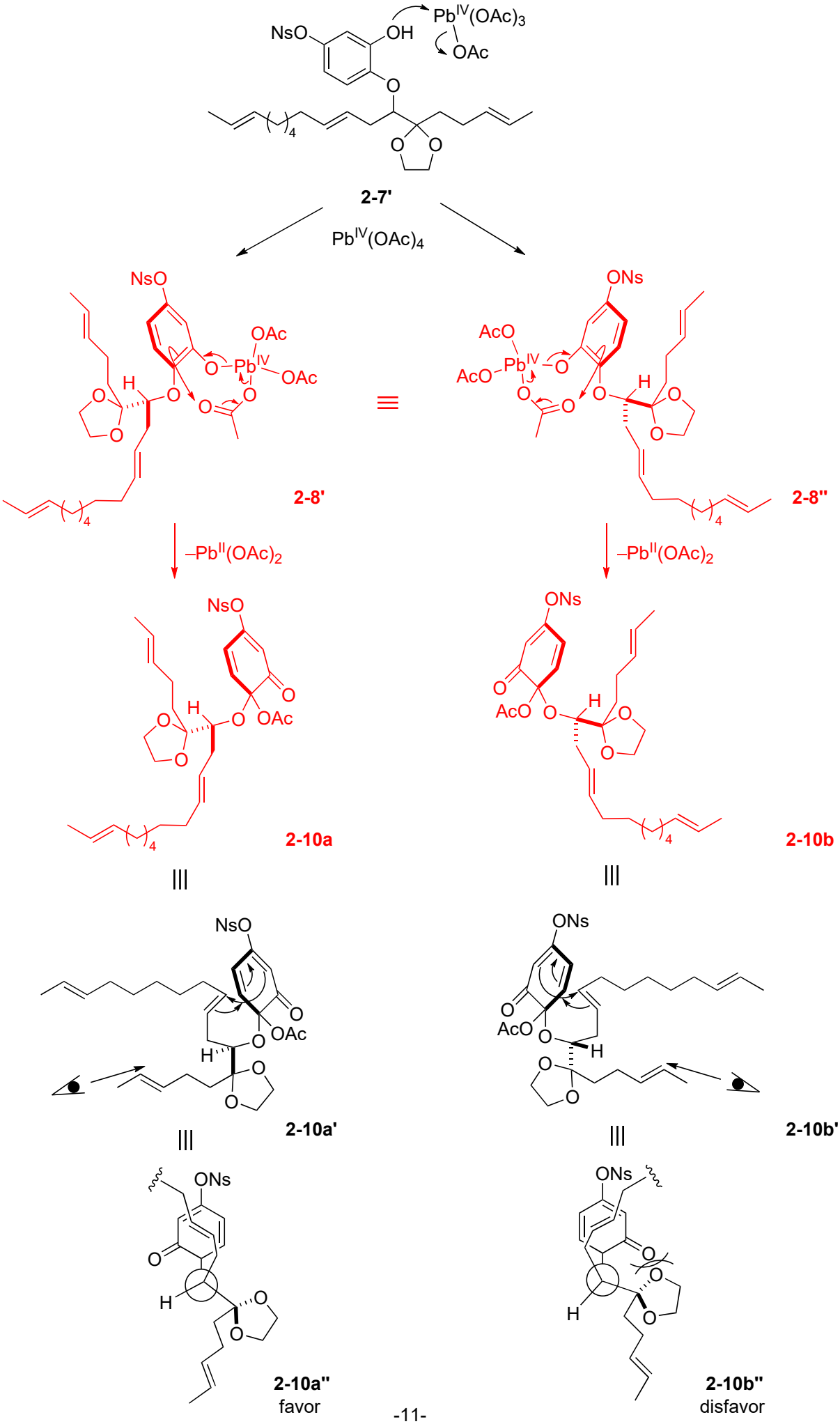


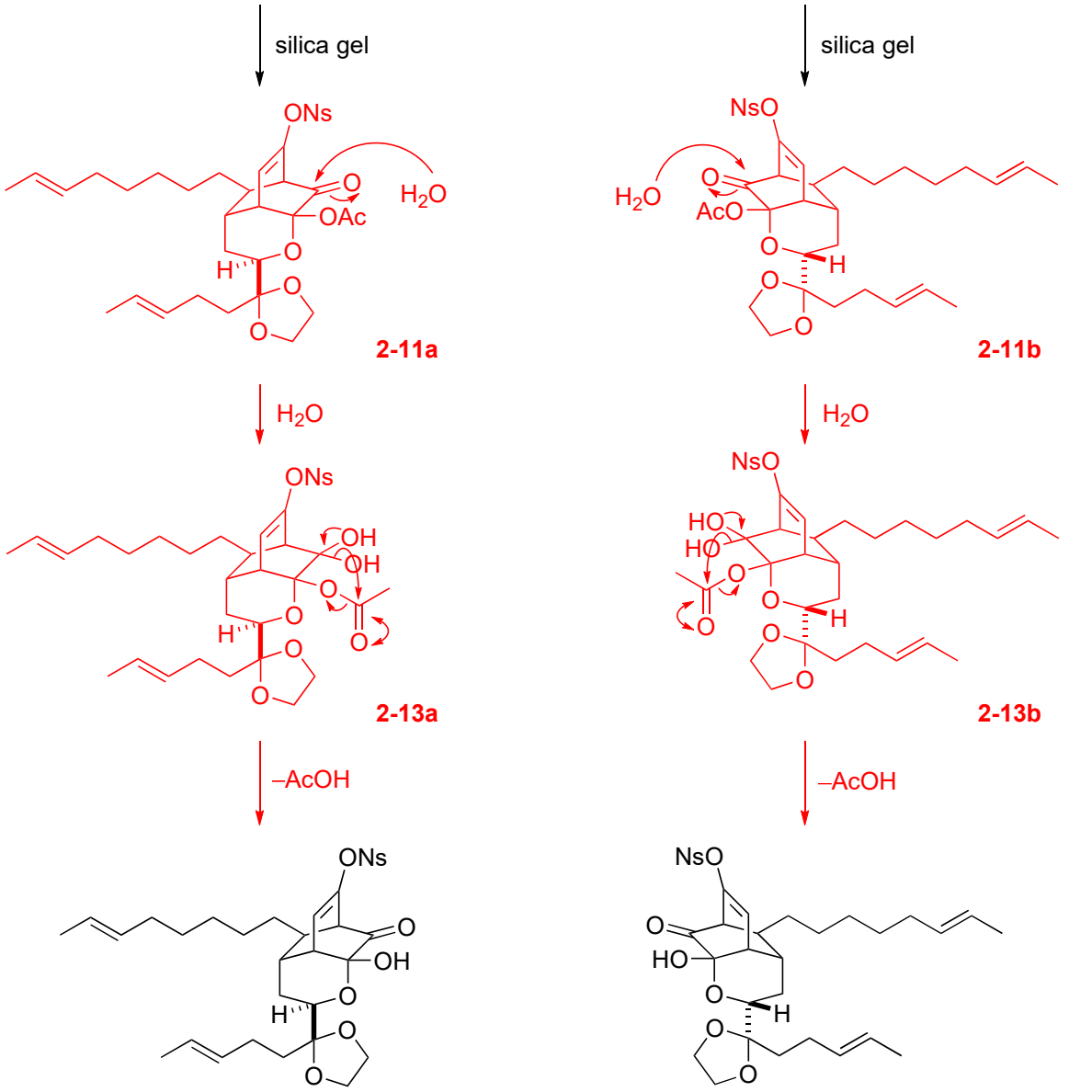


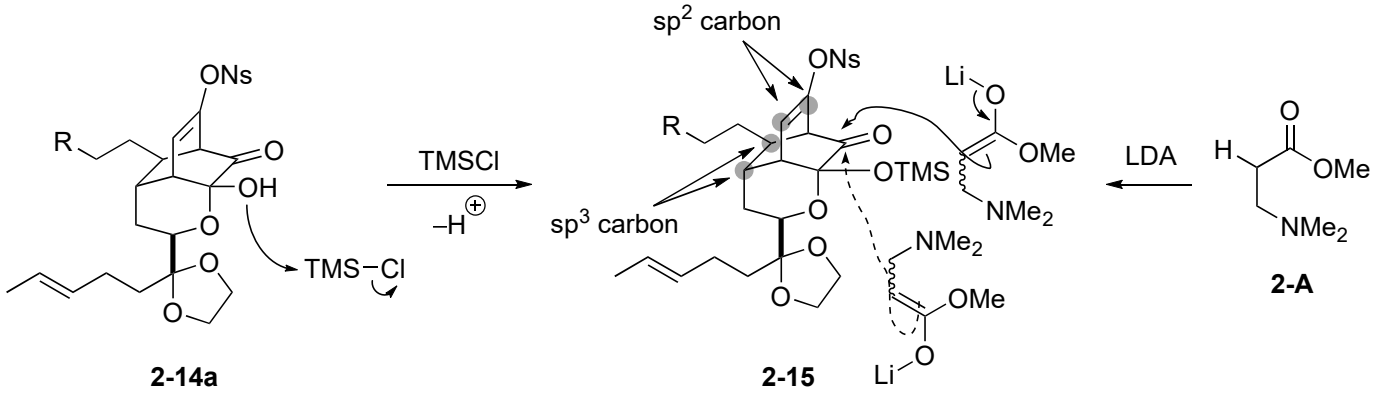
Before revision

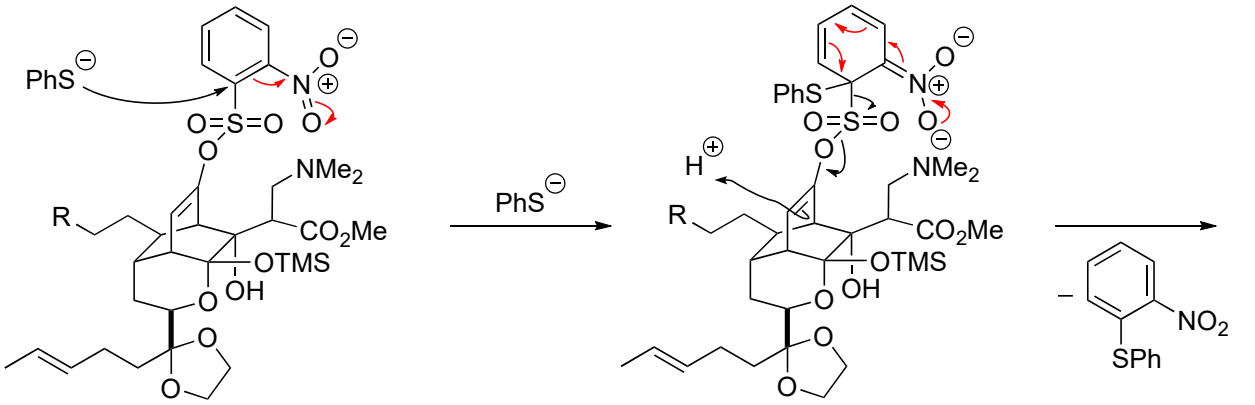



Before revision
NsO
AcO
OAc
2-9'
These carbons should locate on the same plane as each quinone.
ONs
2-9"
AcO
NsO
OAc
2-10a'
ONs
AcO
2-10b'
ONs
2-10a"
favor
ONs
2-10b"
disfavor
silica gel
silica gel
ONs
OAc
2-11a
Orbits are hard to interact.
NsO
AcO
2-11b
–AcO
–AcO
ONs
H2O
2-12a
against Bredt's rule
→ difficult
NsO
H2O
2-12b

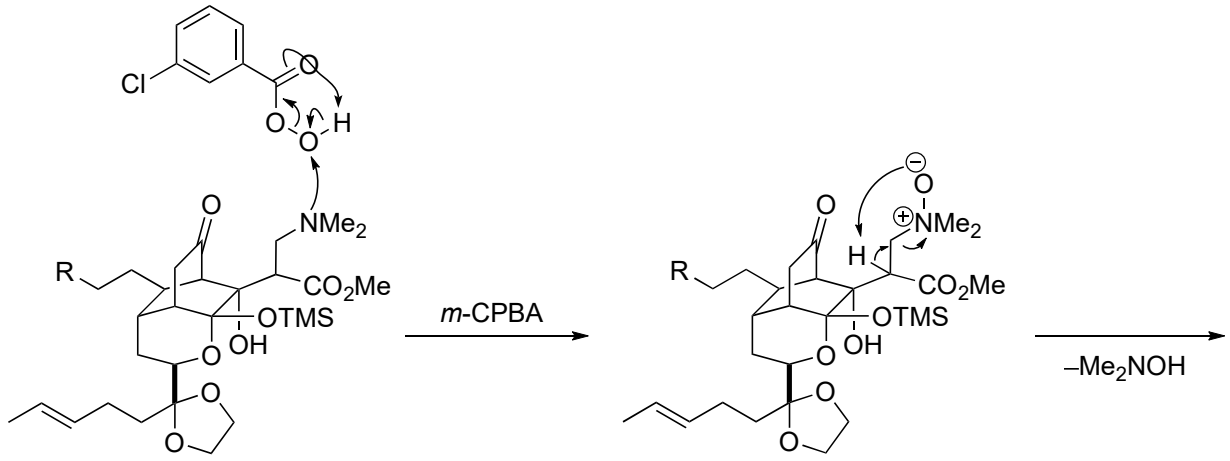

NsO
OH
Pb^IV(OAc)3
OAc
O
4
O
O
2-7'
Pb^IV(OAc)4
NsO
OAc
Pb^IV
OAc
O
O
O
H
O
O
O
4
2-8'
≡
ONs
AcO
Pb^IV
AcO
O
O
O
H
O
O
4
2-8''
–Pb^II(OAc)2
–Pb^II(OAc)2
NsO
O
H
O
OAc
O
O
4
2-10a
ONs
O
AcO
O
H
O
O
4
2-10b
|||
|||
NsO
O
OAc
O
H
O
O
2-10a'
ONs
O
AcO
O
H
O
O
2-10b'
|||
|||
ONs
O
H
O
O
2-10a''
favor
ONs
O
O
H
O
2-10b''
disfavor


silica gel
silica gel
ONs
NsO
H2O
H2O
OAc
AcO
2-11a
2-11b
H2O
H2O
ONs
NsO
OH
HO
2-13a
2-13b
–AcOH
–AcOH
ONs
NsO
OH
HO
2-14a
major product
(dr = 3:1)
2-14b
minor product

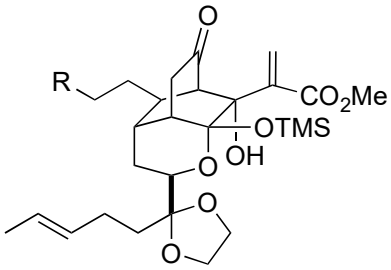

sp2 carbon
ONs
R
TMSCl
–H⊕
TMS–Cl
sp3 carbon
Li
OMe
OTMS
NMe2
LDA
2-14a
2-15
2-A



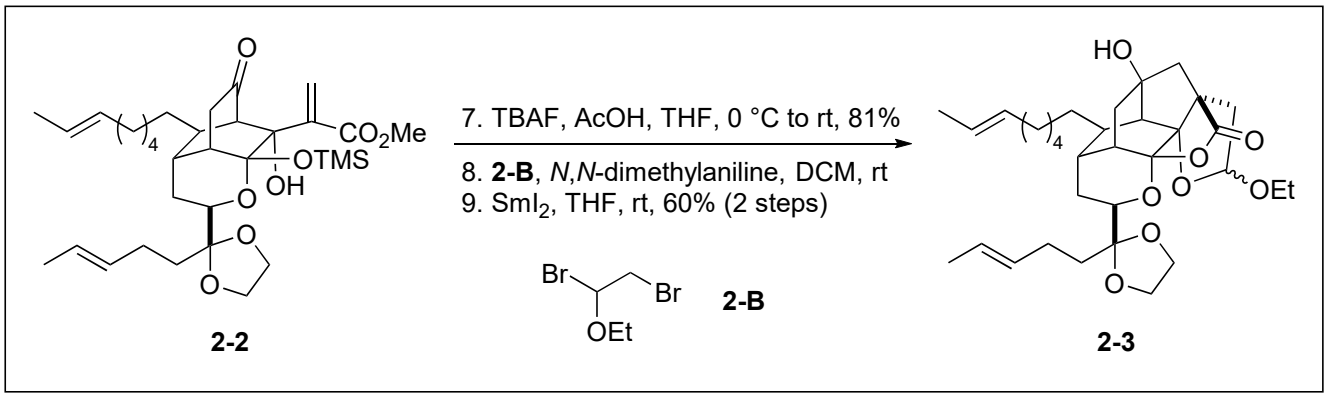
2-16 **2-17**



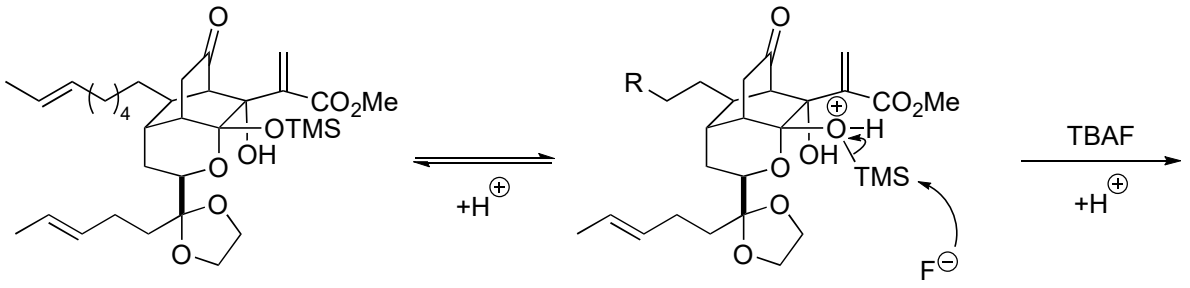
2-18 **2-19**



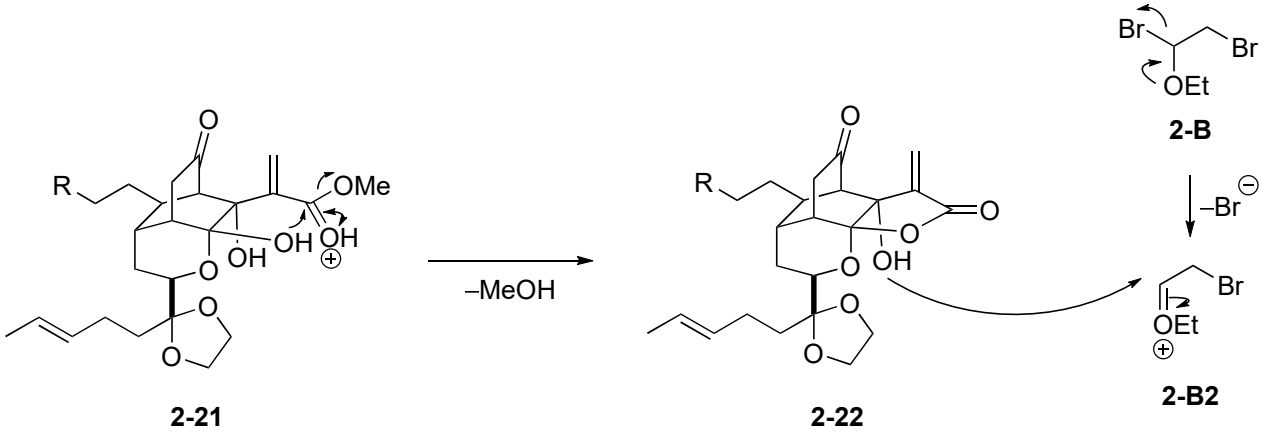
2-2



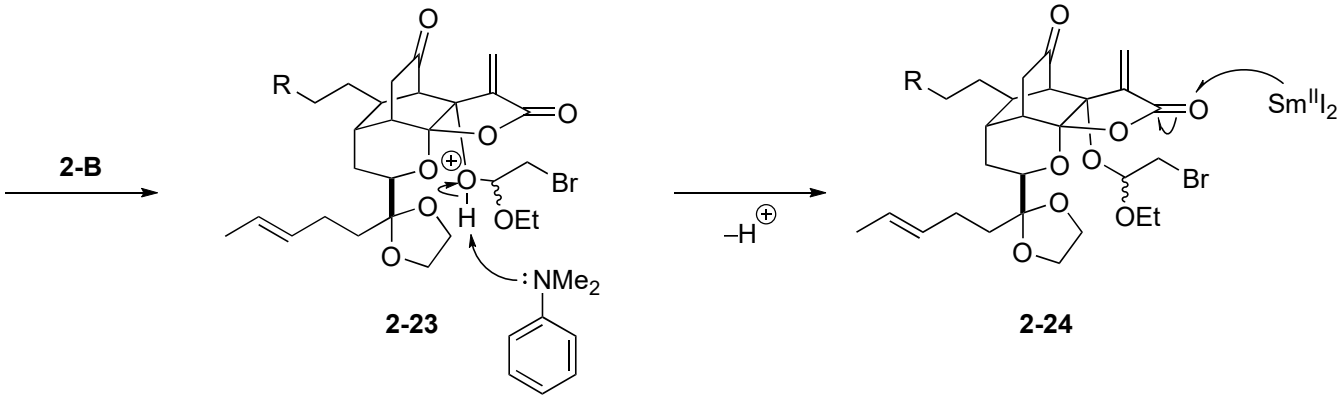
2-2 **2-B** **2-3**



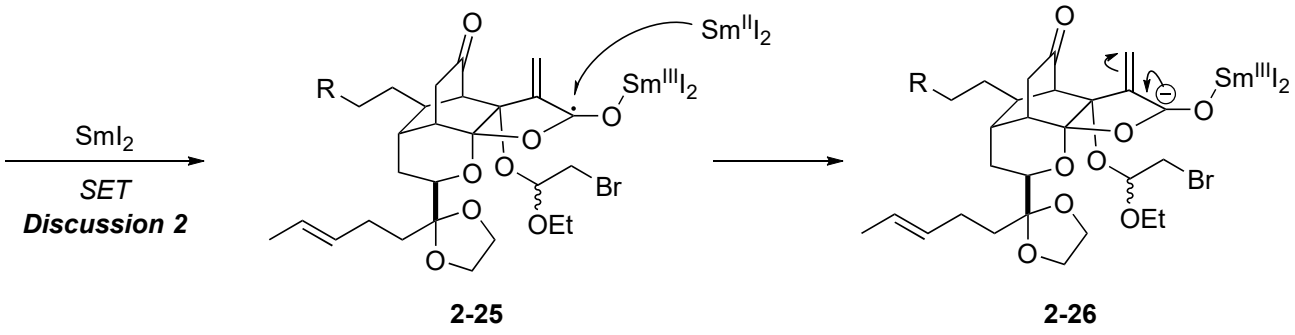
2-2 **2-20**



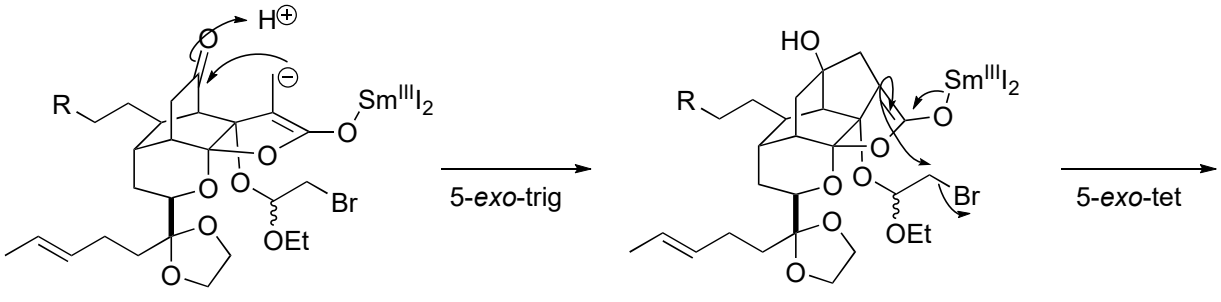
2-21 **2-22**



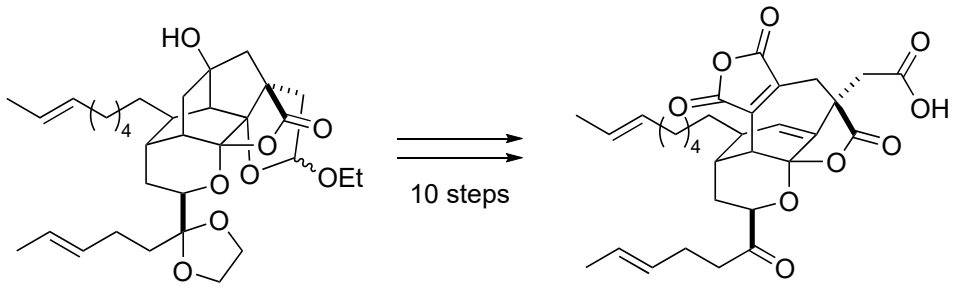
2-23 **2-24**



2-25 **2-26**

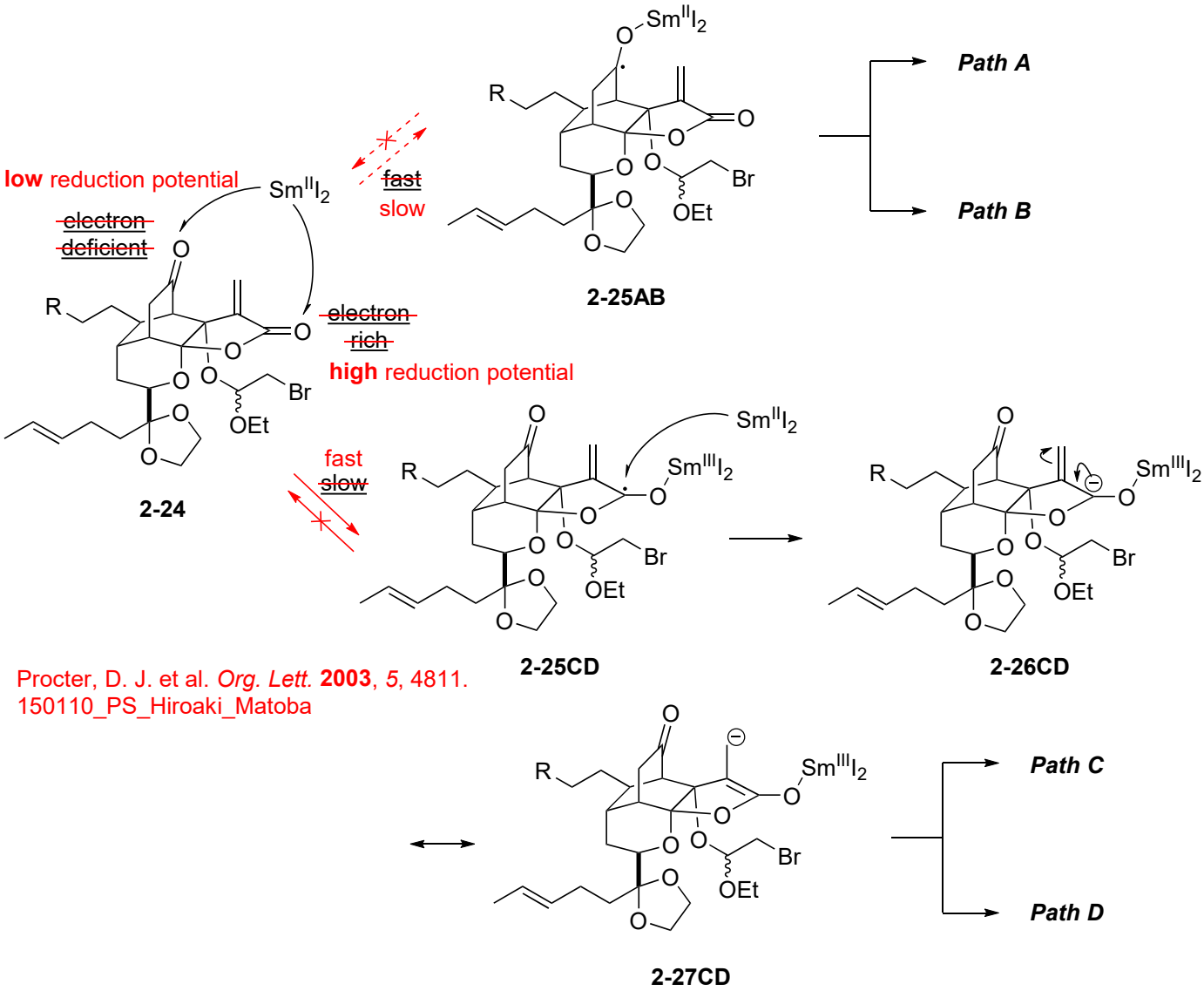


2-27 **2-28**

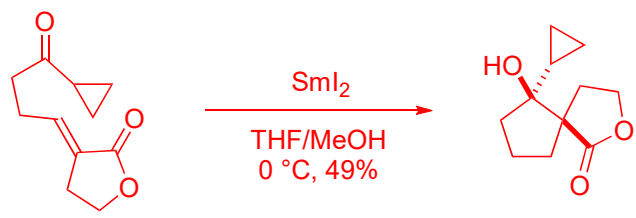


2-3 Phomoidride D

Discussion 2: Radical cascade cyclization promoted by single electron transfer



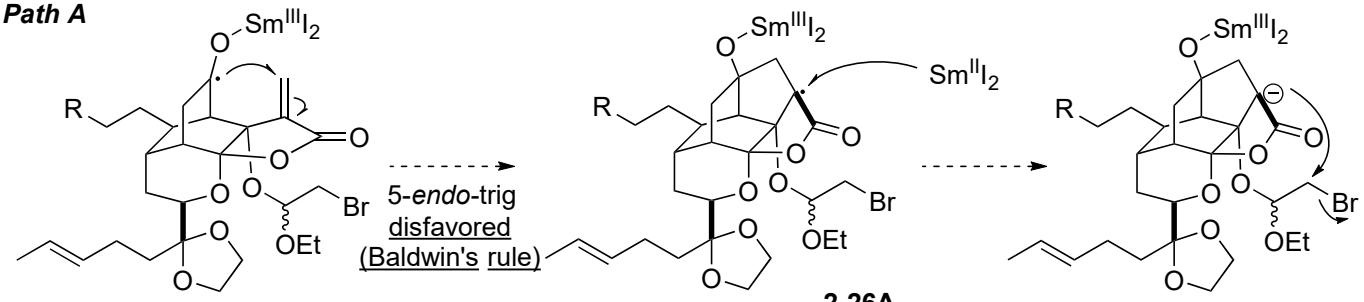
Procter, D. J. et al. *Org. Lett.* **2003**, *5*, 4811.
150110_PS_Hiroaki_Matoba



Cyclopropane ring was not opened.
→ Unsaturated lactone was reducted.

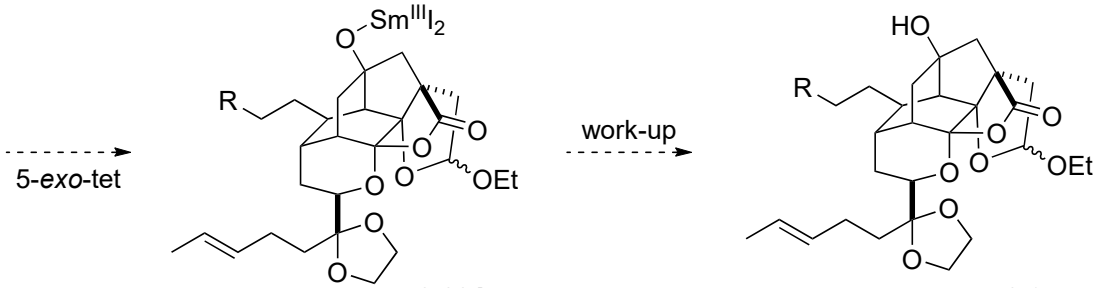
Procter, D. J. et al. *Org. Lett.* **2003**, *5*, 4811.

Path A



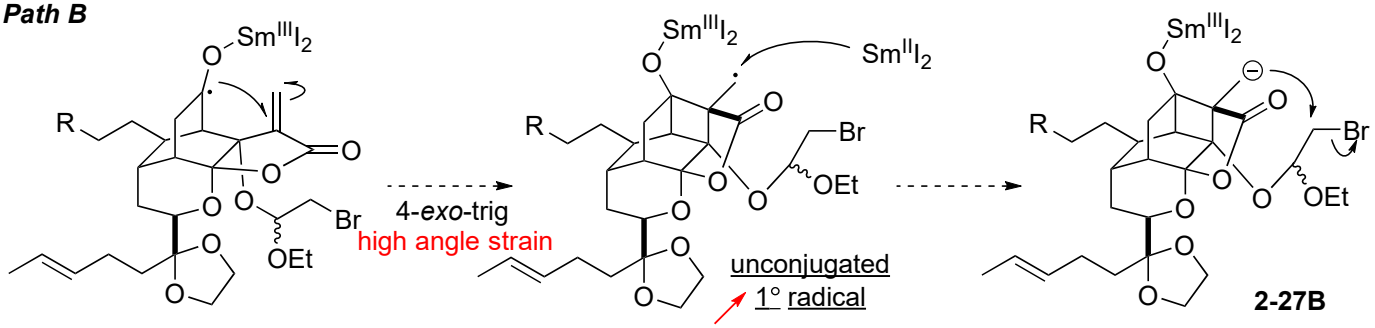
2-25AB **2-26A** **2-27A**

But 5-*endo*-trig often precedes 4-*exo*-trig.
Gimisis, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 10765.



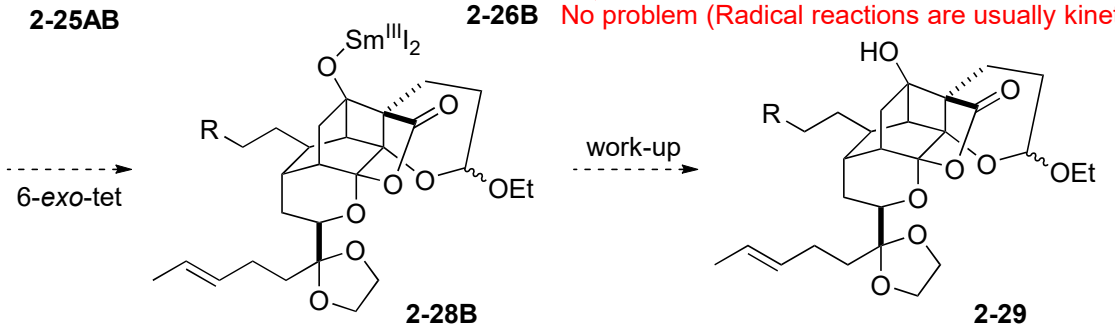
2-28A **2-3**

Path B



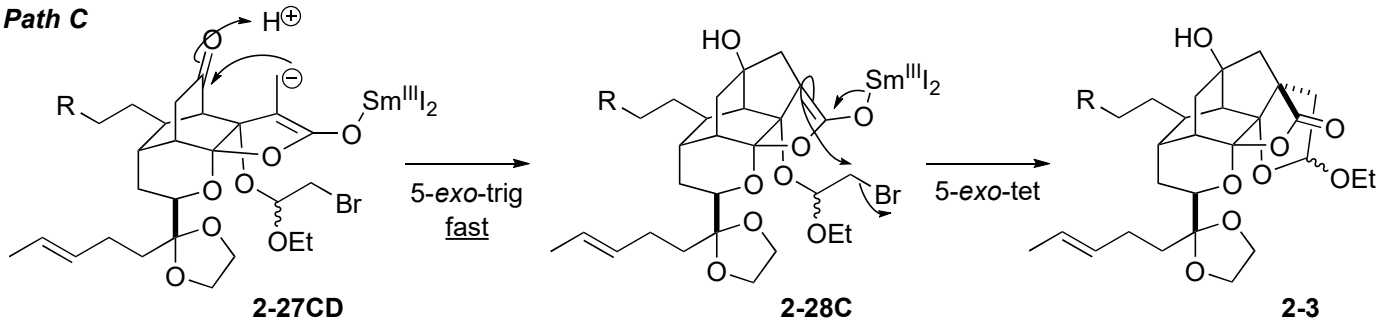
2-25AB **2-26B** **2-27B**

No problem (Radical reactions are usually kinetic control.)



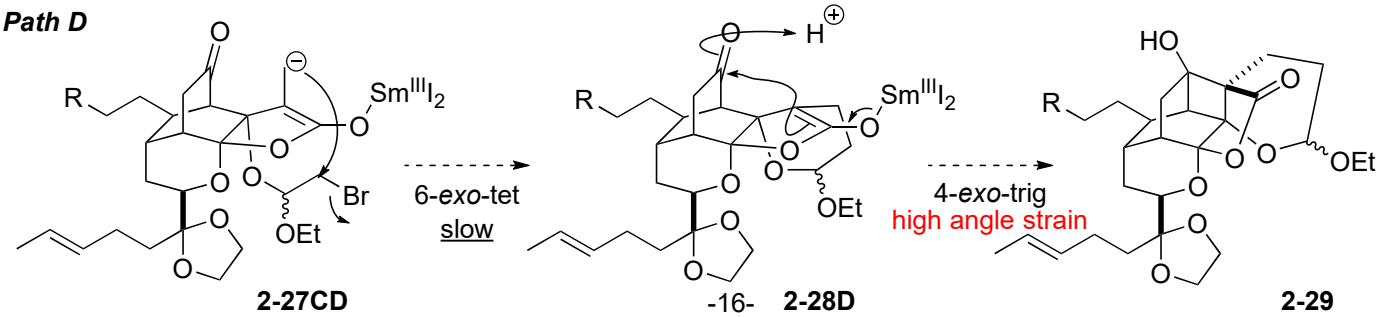
2-28B **2-29**

Path C



2-27CD **2-28C** **2-3**

Path D



2-27CD **2-28D** **2-29**