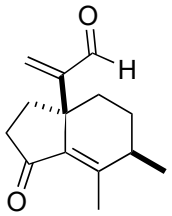
Problem session (3)

2018.7.7 Yuri Takada

Please fill in blanks and provide the mechanism of the following reactions.

1.



1-1

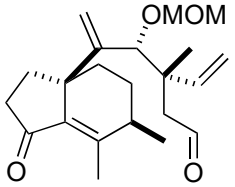
1. **1-2**, (*R*)-3,3'-Br_2-BINOL (20 mol%)
t-BuOH, 3Å MS, PhMe, 0 °C, 80%

1-3a $C_{39}H_{44}O_3$ + **1-3b** $C_{39}H_{44}O_3$

1-3a : 1-3b = 1.2 : 1 (diastereomer)

1-3a

1. MOMCl, *i*Pr_2NEt, CH_2Cl_2, rt
2. HCO_2H, Et_2O, 70%, 2 steps
3. $[Cu(MeCN)_4]OTf$ (5 mol%), 4-OMebpy (5 mol%), ABNO (1 mol%), *N*-methylimidazole (1 mol%), MeCN, rt; open to the atmosphere, 92%

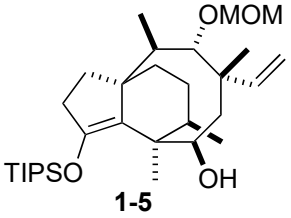


1-4a

1-3b the same conditions above → **1-4b**

1-4a

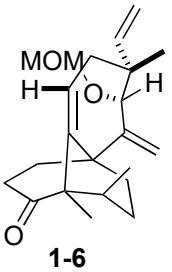
1. SmI_2 (3 eq.), H_2O (6 eq.), THF, 0 °C; TMSCl, (5 eq.), 93%, d.r. = 23:1
2. LiHMDS, TIPSOTf, THF, -78 to 0 °C, 76%
3. $Mn(dpm)_3$ (13 mol%), $PhSiH_3$, TBHP, *i*PrOH, rt, 55%
4. Li/NH_3, EtOH, -78 °C, 61%, d.r. = 14:1



1-5

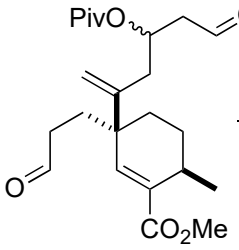
1-4b

1. SmI_2 (3 eq.), H_2O (6 eq.), THF, 0 °C; TMSCl, (5 eq.), 20%



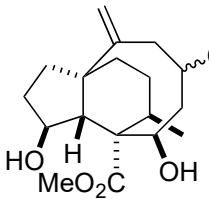
1-6

2.



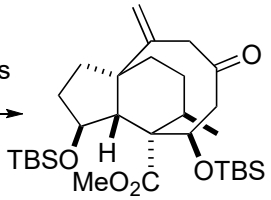
2-1

1. SmI_2 (2.5 eq.), THF/*t*BuOH, 0 °C, 88%



2-2

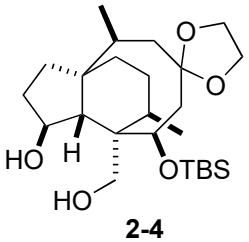
3 steps →



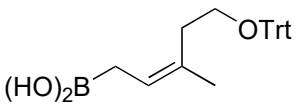
2-3

2-3

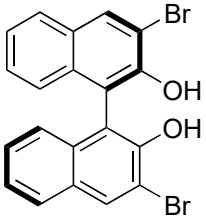
1. H_2, 10% Pd/C, EtOH, rt, 93%, d.r. = 3:1
2. 1,2-ethanediol, $HC(OCH_3)_3$, Amberlyst 15 (5 eq.), PhMe, MeCN, rt, 96%
3. SmI_2 (20 eq.), pyrrolidine (60 eq.), H_2O (60 eq.), THF, rt, 95%



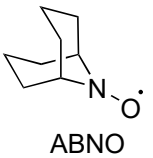
2-4



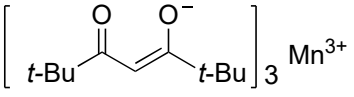
1-2



(*R*)-3,3'-Br_2-BINOL



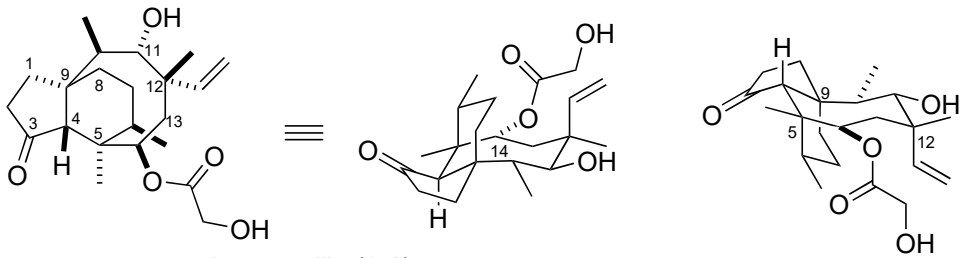
ABNO



$Mn(dpm)_3$

Problem session (3)-Answer

2018.7.7 Yuri Takada

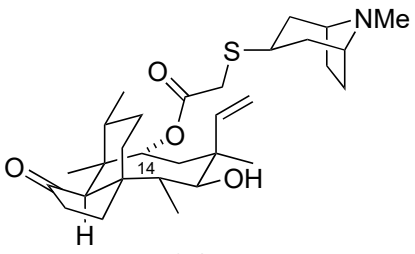


pleuromutilin (**0-1**)

Introduction

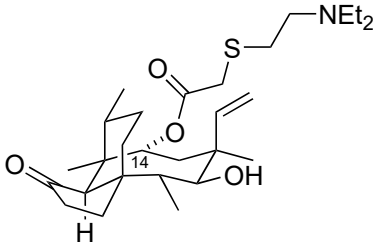
<Isolation> from edible mushroom *Pleurotus mutilus* (*Clitopilus scyphoides*)
(Kavanagh, F.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 570.)

<Bioactivity> antibacterial activity (Gram-positive) by binding to the ribosome



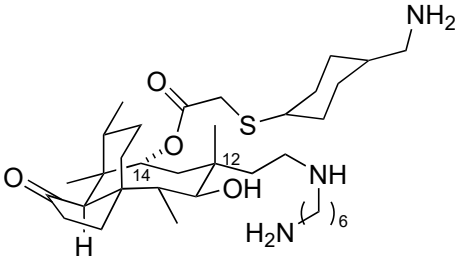
0-2

retapamulin
(ALTABAX®, GlaxoSmithKline)
antibiotics for human
(WO 2015/110481 A1)



0-3

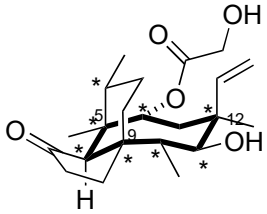
tiamulin
(Denegard®, Novartis Animal Health)
antibiotics for pigs and poultry



0-4

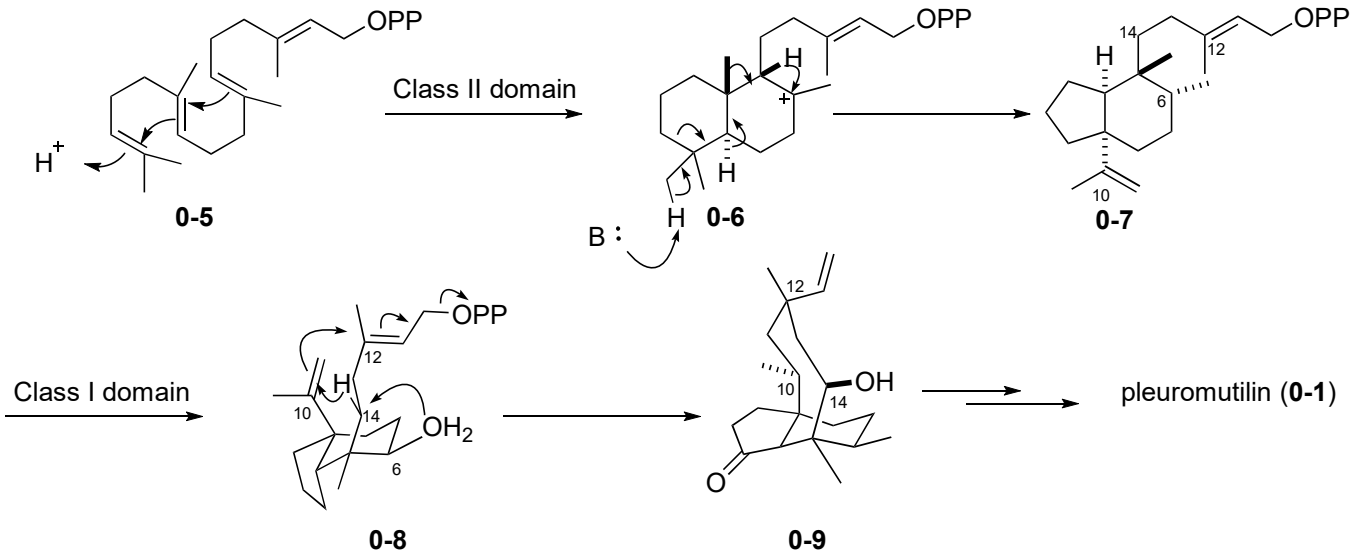
12-*epi* derivative
⋮
active against
Gram negative bacteria

<Structural features>



structural features
- tricyclo skeleton
- 8-membered ring
- 8 stereogenic centers*
- three quaternary carbons (C5, 9, 12)

<proposed biosynthetic pathway>



0-5 **0-6** **0-7** **0-8** **0-9**

<Total synthesis>

racemic total synthesis

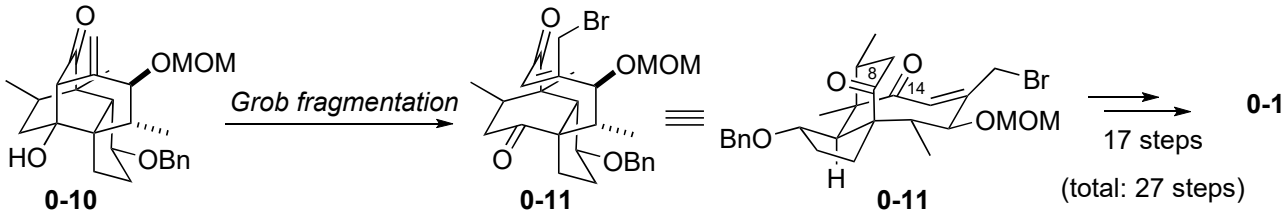
- Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767.
- Boeckman, R. K. Jr.; Springer, D. M.; Alessi, T. R. *J. Am. Chem. Soc*. **1989**, *111*, 8284.)

(130622_PS_Taro_ASABA)

enantiomeric total synthesis

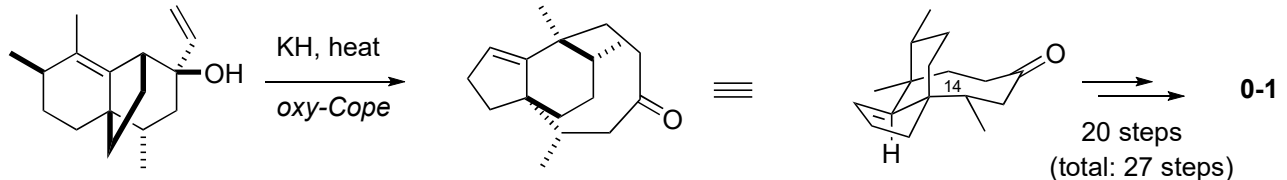
- Fazakerley, N. J.; helm, M. D.; Procter, D. J. *Chem. Eur. J.* **2013**, *19*, 6718. (*problem 2*)
- Murphy, S. K.; Zeng, M.; Herzon, S. B. *Science,* **2017**, *356*, 956. (170617_LS_Hiroaki_Matoba)
- Farney, E. P.; Feng, S. S.; Schäfers, F.; Reisman, S. E. *J. Am. Chem. Soc.*, **2018,** *140*, 1267. (*problem 1*)

Gibbons (1982)



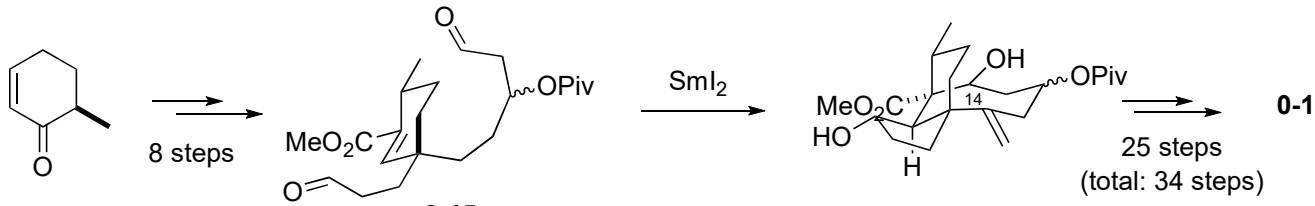
0-10 **0-11** **0-11**

Boeckman (1989)



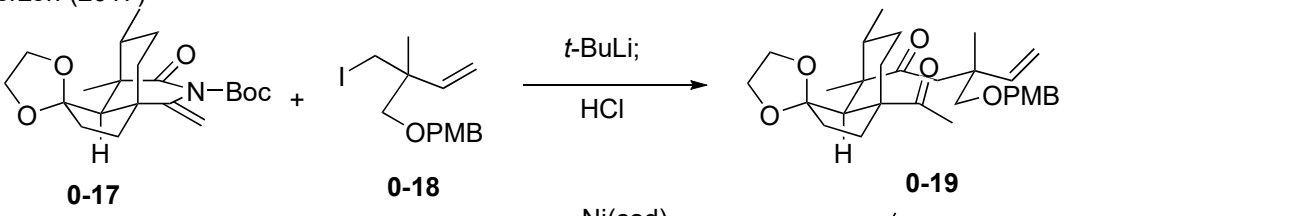
0-12 **0-13** **0-13**

Procter (2013), *problem 1*



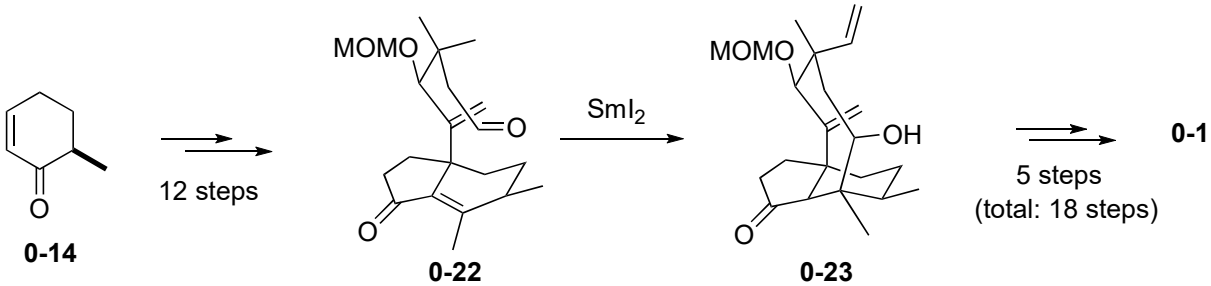
0-14 **0-15** **0-16**

Herzon (2017)



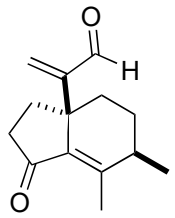
0-17 **0-18** **0-19** **0-20** **0-21**

Reisman (2018), *problem 2*



0-14 **0-22** **0-23**

1.



1-1

1. **1-2**, (*R*)-3,3'-Br_2-BINOL (20 mol%)
t-BuOH, 3Å MS, PhMe, 0 °C, 80%

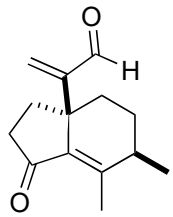
1-3a $C_{39}H_{44}O_3$ + **1-3b** $C_{39}H_{44}O_3$

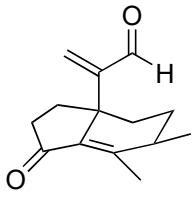
1-3a : 1-3b = 1.2 : 1 (diastereomer)

1. MOMCl, *i*Pr_2NEt, CH_2Cl_2, rt
2. HCO_2H, Et_2O, 70%, 2 steps
3. $[Cu(MeCN)_4]OTf$ (5 mol%), 4-OMebpy (5 mol%), ABNO (1 mol%), *N*-methylimidazole (1 mol%), MeCN, rt; open to the atmosphere, 92%

1-3a → **1-4a**

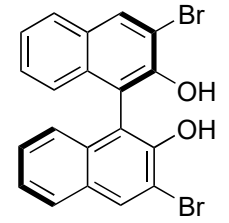
1-3b → (the same conditions above) **1-4b**

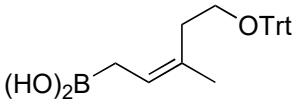


1-1 ≡ 

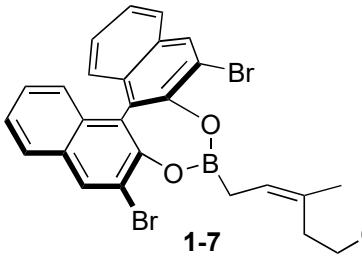
1-1

1-7

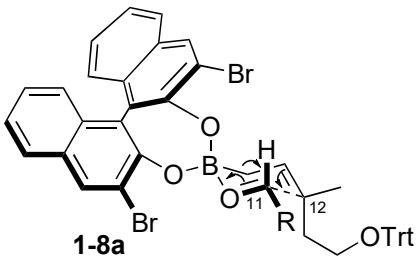


(*R*)-3,3'-Br_2-BINOL + 

1-2

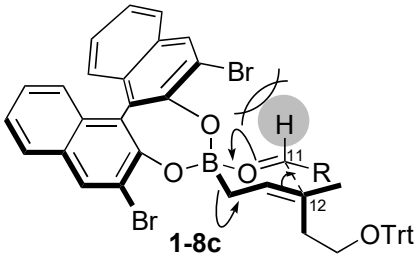


1-7



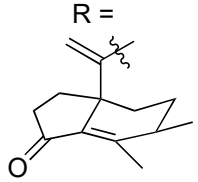
1-8a

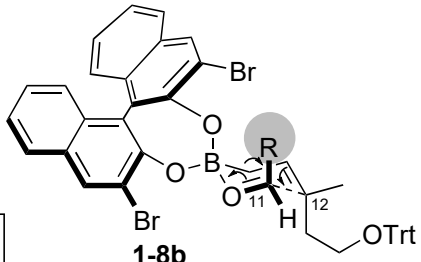
favored



1-8c

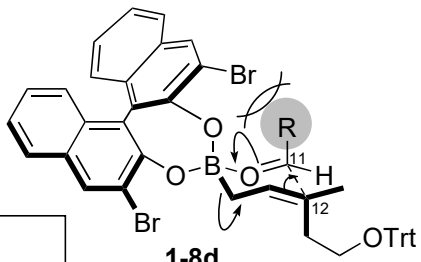
disfavored

R = 



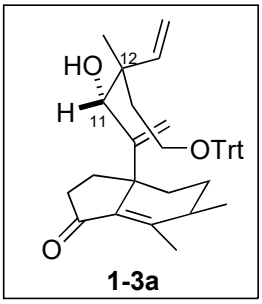
1-8b

not form



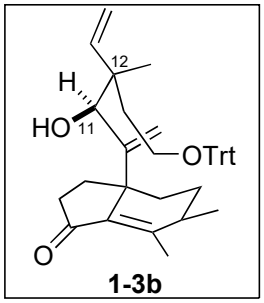
1-8d

not form

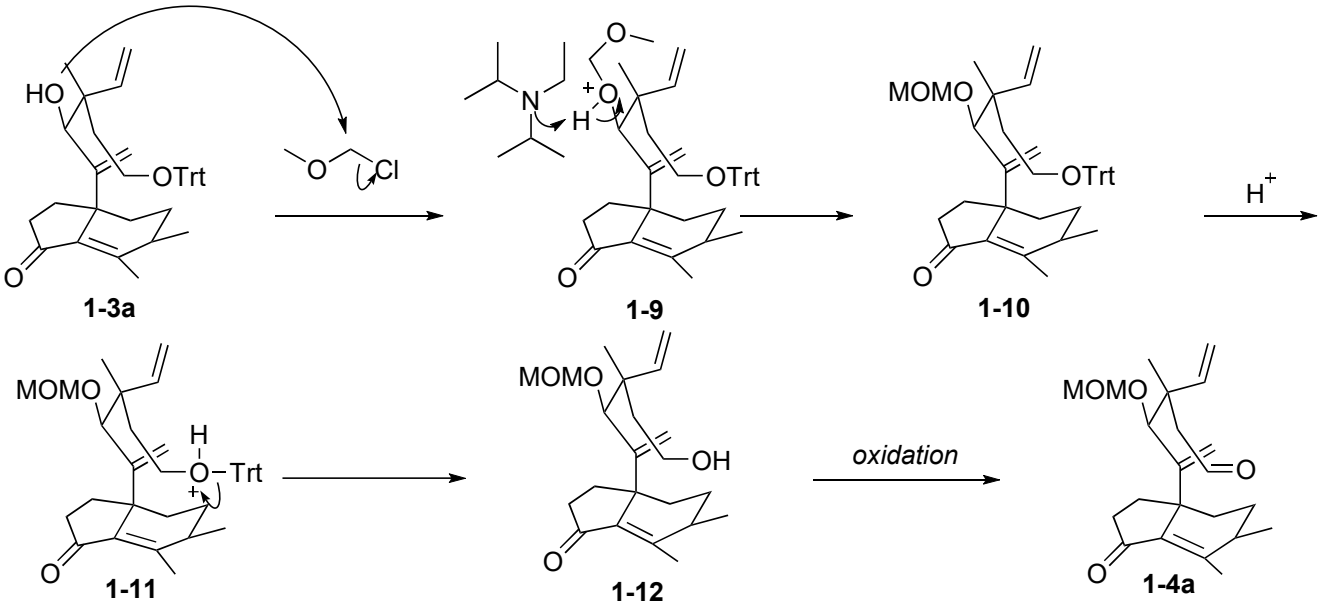


1-3a

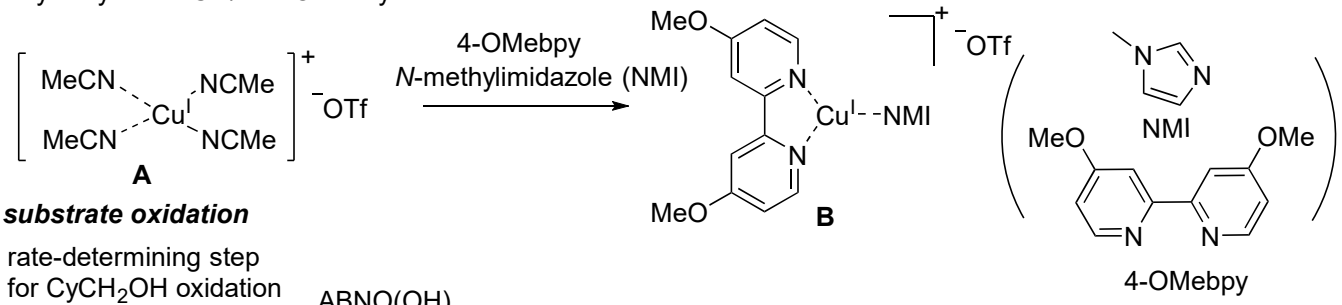
1-3a : 1-3b = 1.2 : 1



1-3b (11, 12-bis-*epi* **1-3a**)

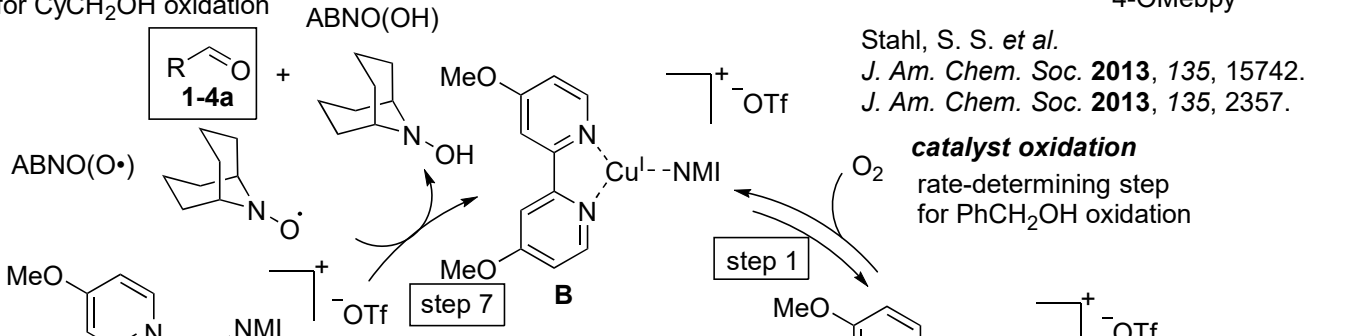


catalytic cycle for Cu^{I}/ABNO-catalyzed aerobic alcohol oxidation



substrate oxidation

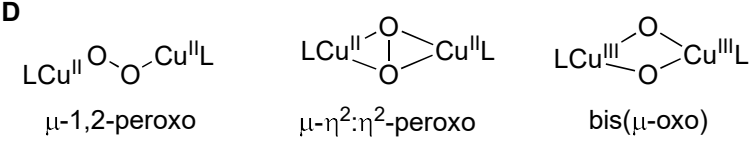
rate-determining step
for $CyCH_2OH$ oxidation



Stahl, S. S. *et al.*
J. Am. Chem. Soc. **2013**, *135*, 15742.
J. Am. Chem. Soc. **2013**, *135*, 2357.

catalyst oxidation

D



μ-1,2-peroxo μ-η²:η²-peroxo bis(μ-oxo)

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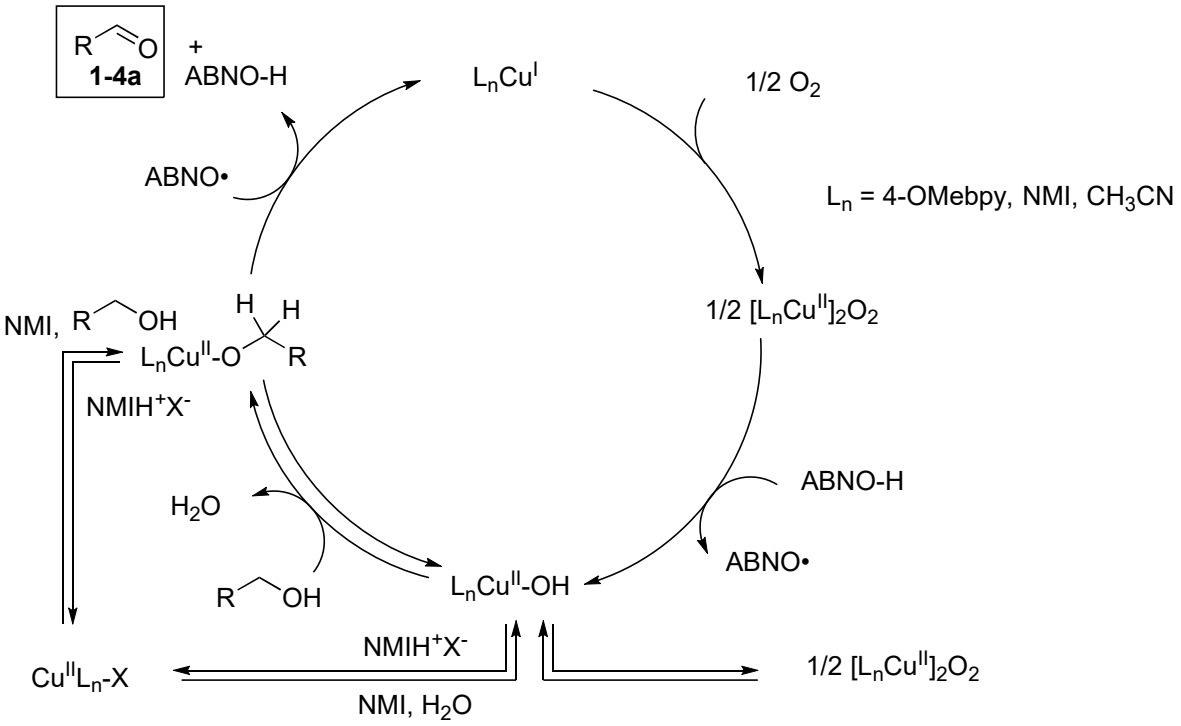
catalytic cycle 2 for Cu^{I}/ABNO-catalyzed aerobic alcohol oxidation

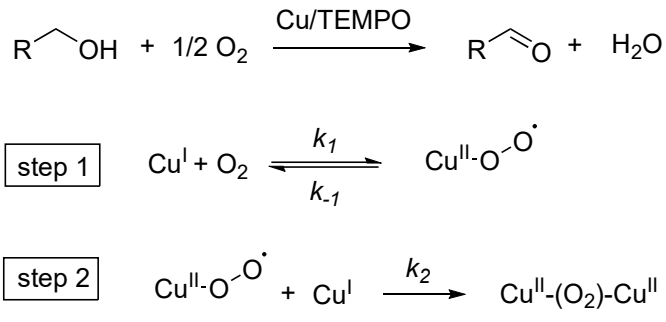


$$\text{rate} = \frac{k_1 k_2 [\text{Cu}]^2_{\text{tot}} [\text{O}_2]}{k_{-1} + k_2 [\text{Cu}]_{\text{tot}}}$$

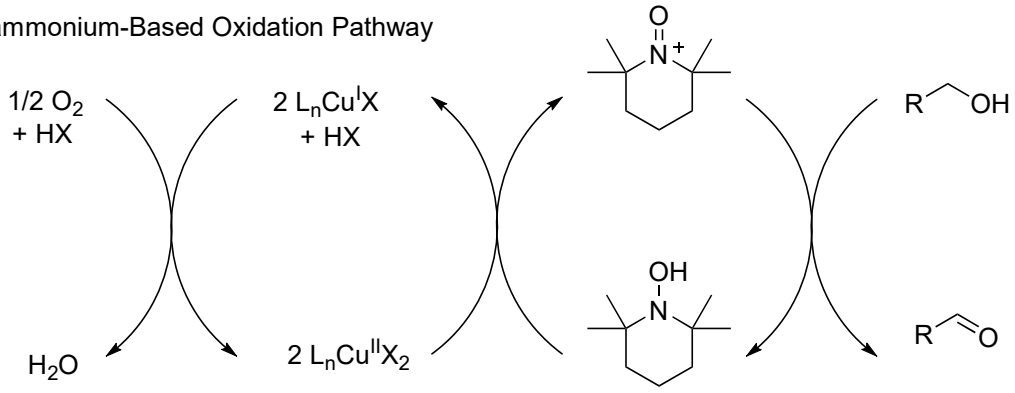
$$\frac{[\text{Cu}]_{\text{tot}}}{\text{rate}} = \frac{k_{-1}}{k_1 k_2 [\text{Cu}]_{\text{tot}} [\text{O}_2]} + \frac{1}{k_1 [\text{O}_2]}$$

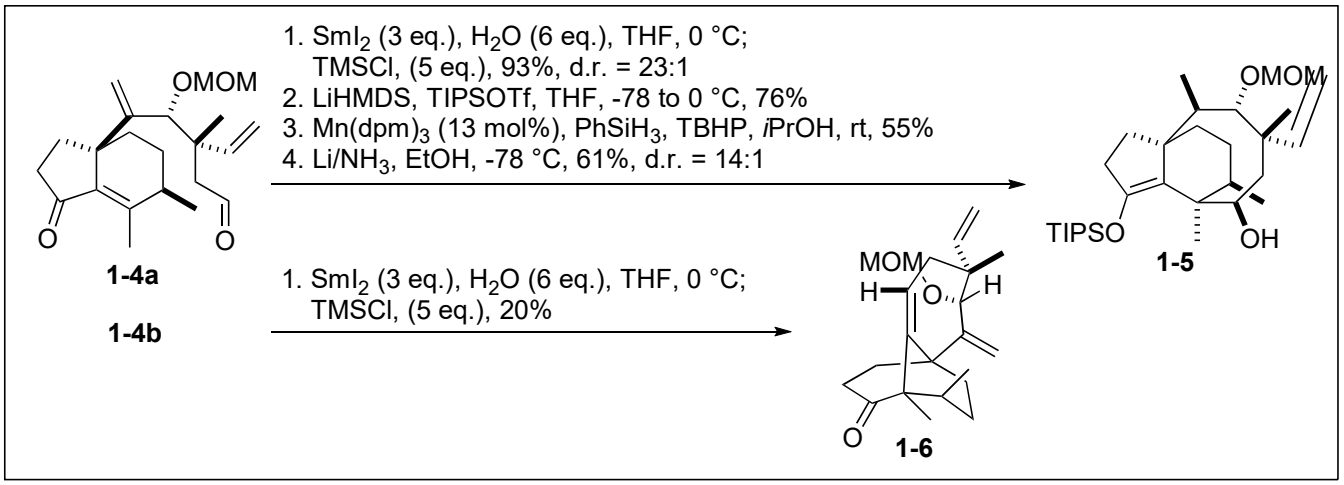
$k_1 = 4.2\ M^{-1}s^{-1}$

$k_{-1}/k_2 = 3.8 \times 10^{-3}\ M^{-1}$



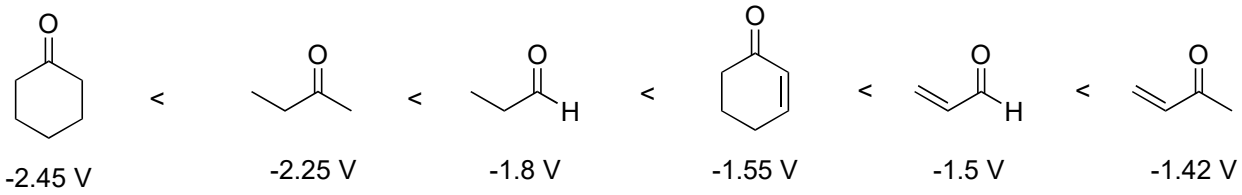
Oxoammonium-Based Oxidation Pathway





selectivity of reduction

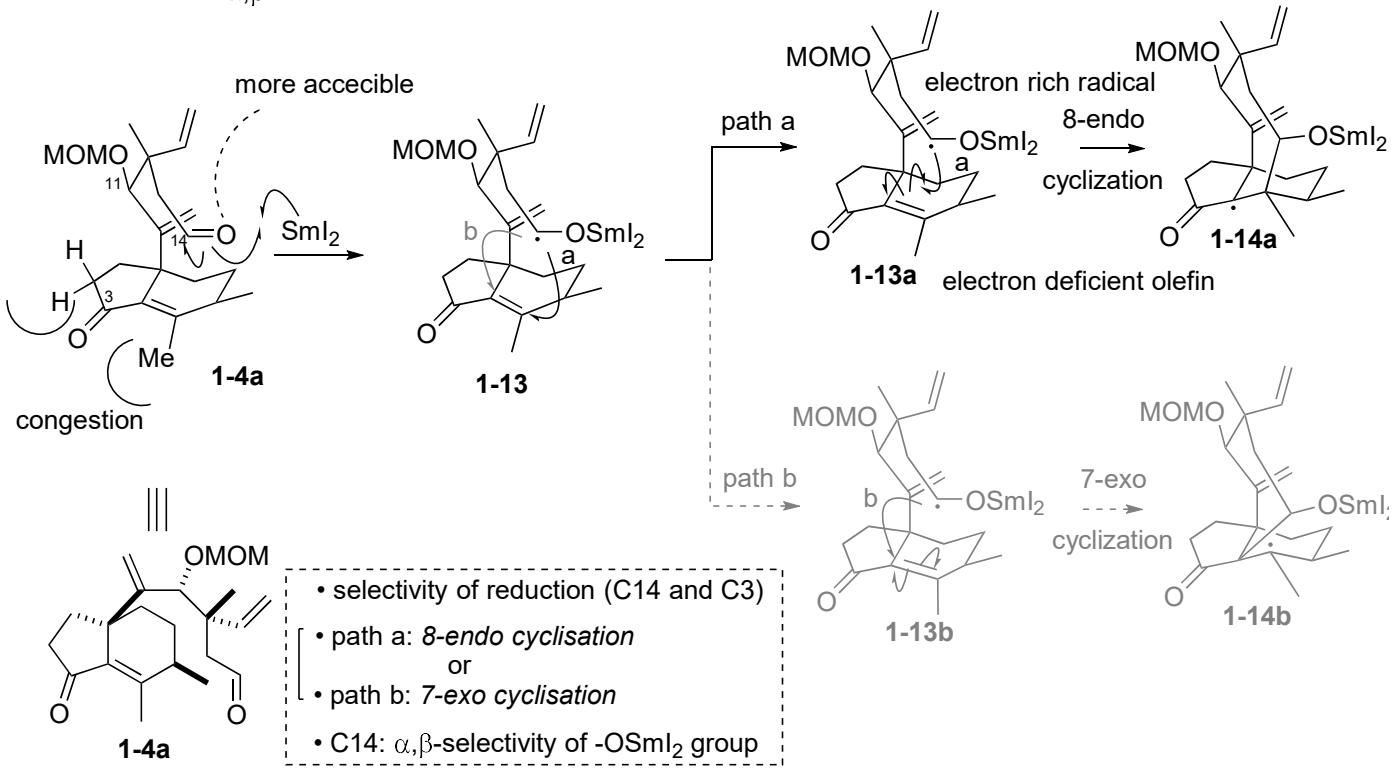
reduction potential of carbonyl groups (vs. SCE)

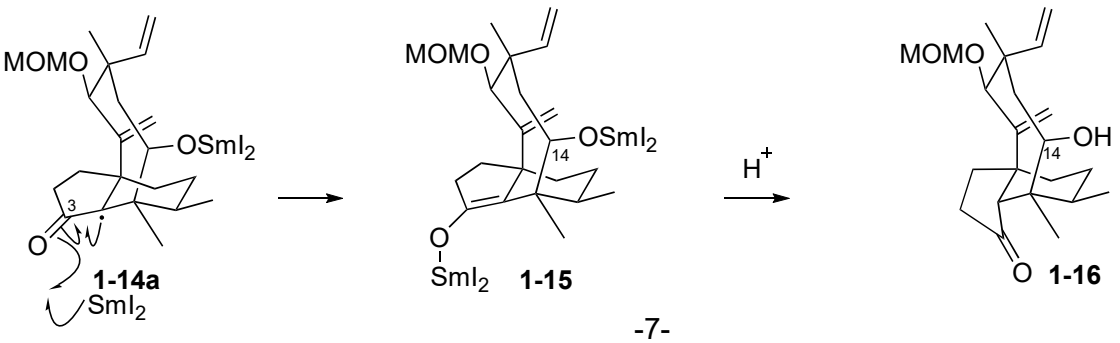


-2.45 V < -2.25 V < -1.8 V < -1.55 V < -1.5 V < -1.42 V

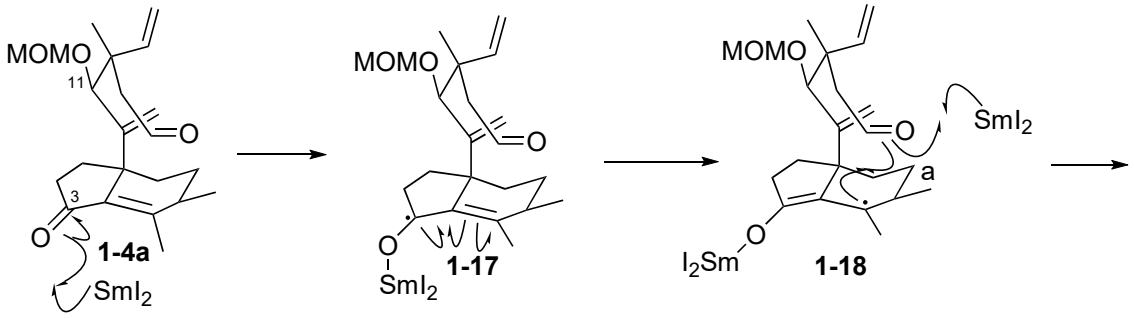
Reduction of aldehyde is easier than ketone

Reduction of α,β-unsaturated katone is easier than ketone

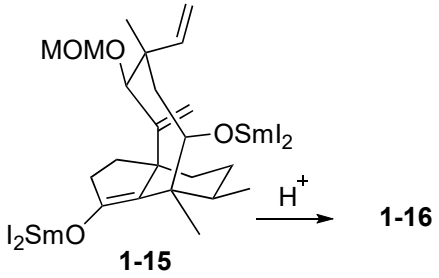




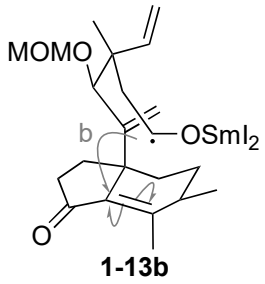
(case: reduction from C3 -> C14)



8-membered ring formation

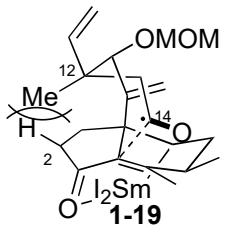


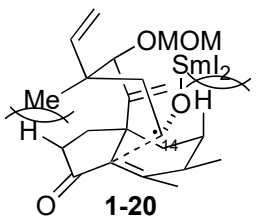
pattern 1: 7-membered ring formation



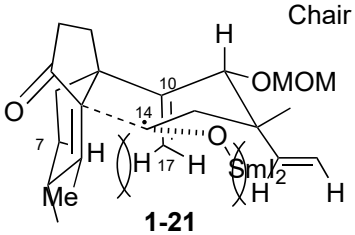
2

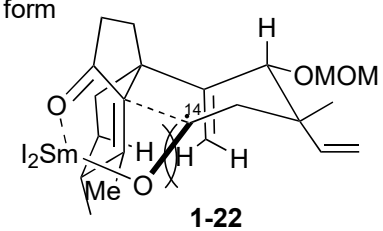
Boat form





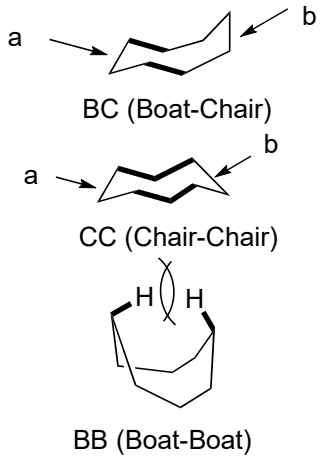
Chair form

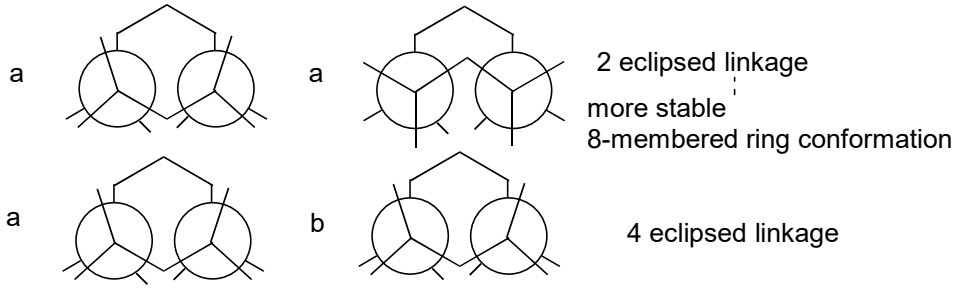


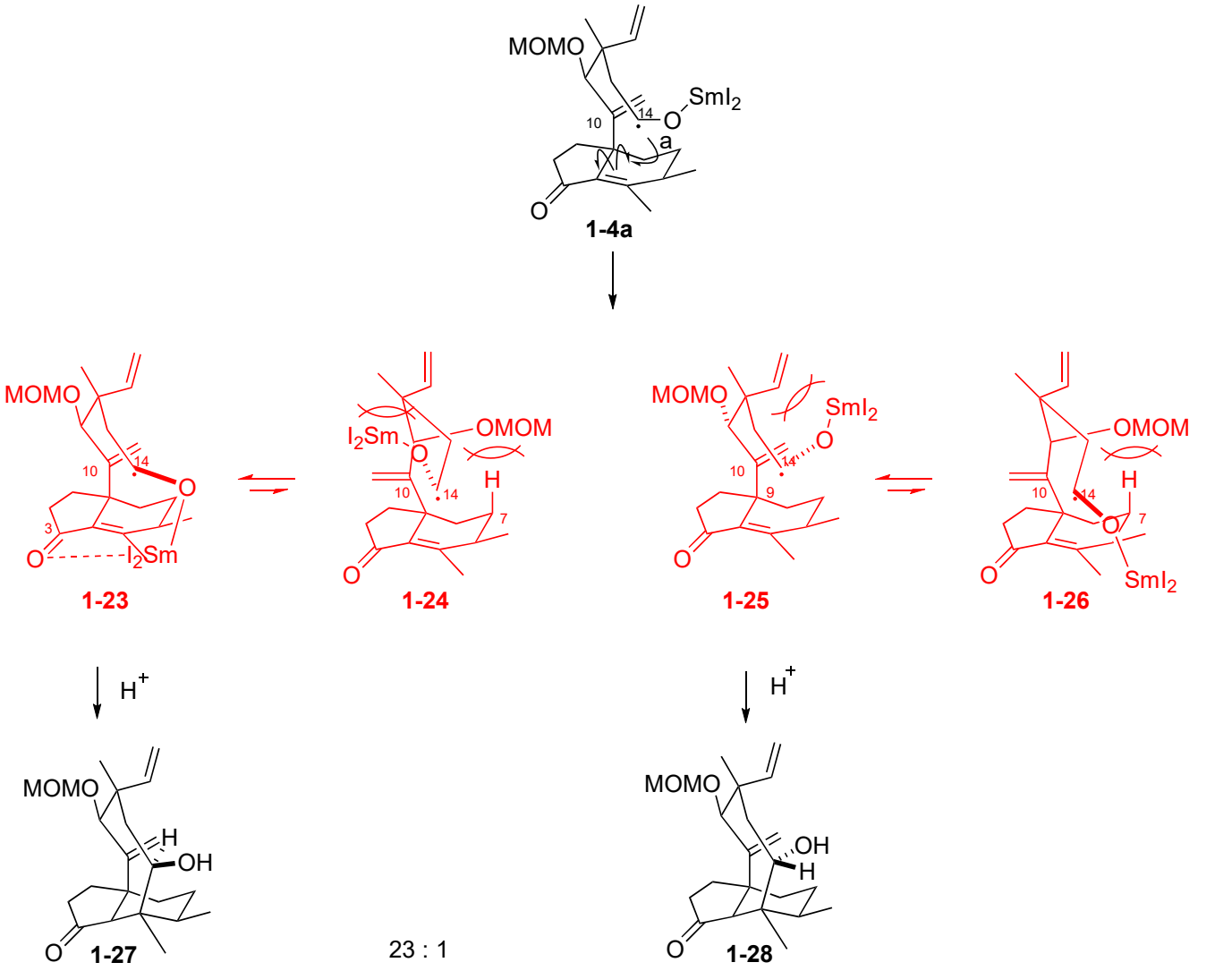


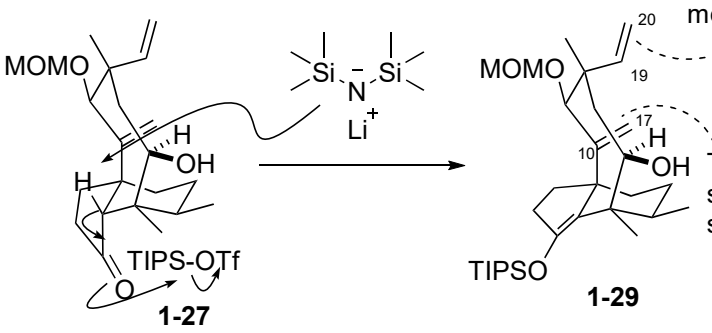
pattern 2: 8-membered ring formation (path a)

8-membered ring formation





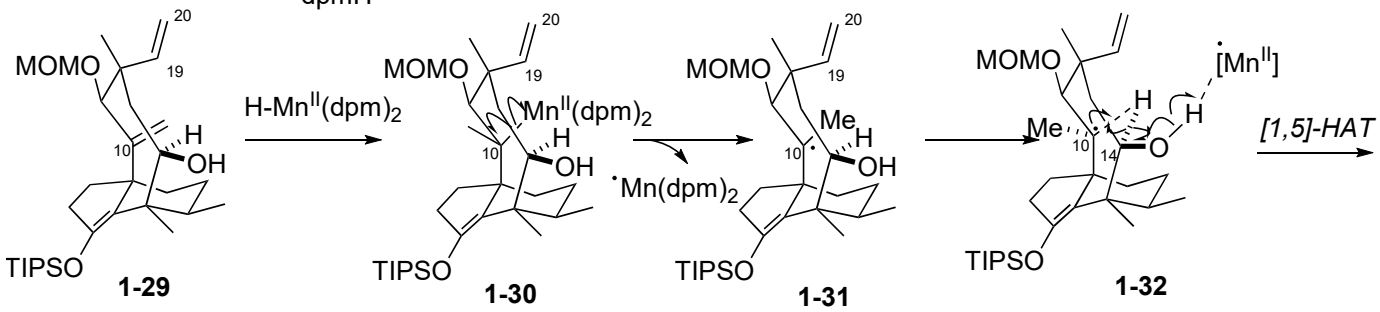




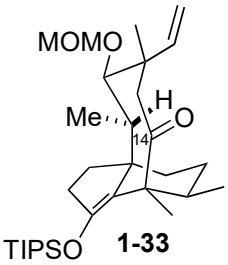
1-27 **1-29**

The chemoselective reduction of the more substituted alkene likely reflects increased transition state stabilization of the developing tertiary radical.

$Mn^{III}(dpm)_3$, $PhSiH_3$ $\xrightarrow[\text{-dpmH}]{}$ H-$Mn^{II}(dpm)_2$



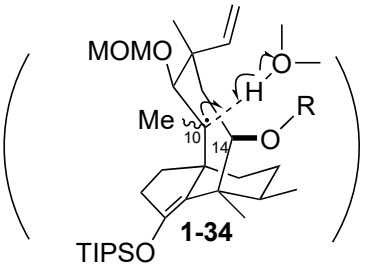
1-29 **1-30** **1-31** **1-32**



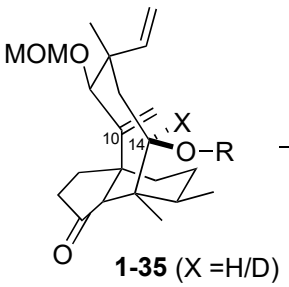
1-33

single diastereomer

C14 alcohol is protected perform poorly under the HAT conditions suggests that cleavage of the O-H bond to form the C14 ketone serves as a driving force for this transformation.

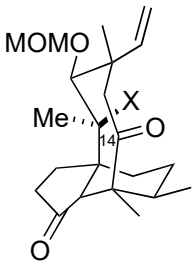


1-34



1-35 (X =H/D)

$Mn(dpm)_3$, $PhSiH_3$
TBHP, i*Pr*OH, rt

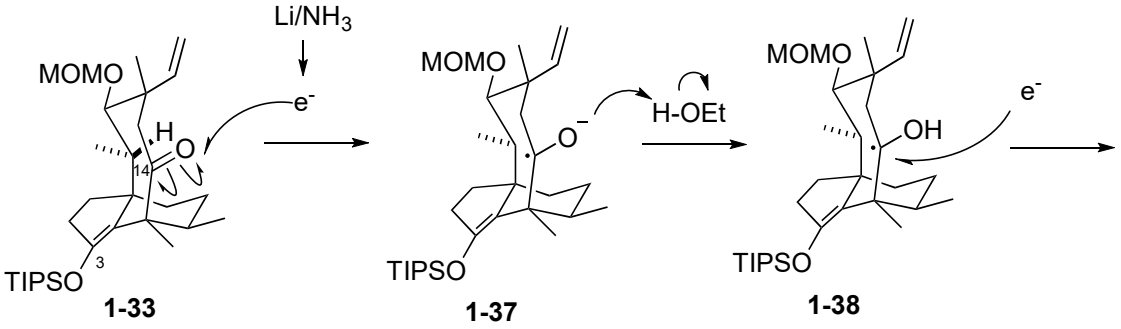


1-36 (X =H/D)

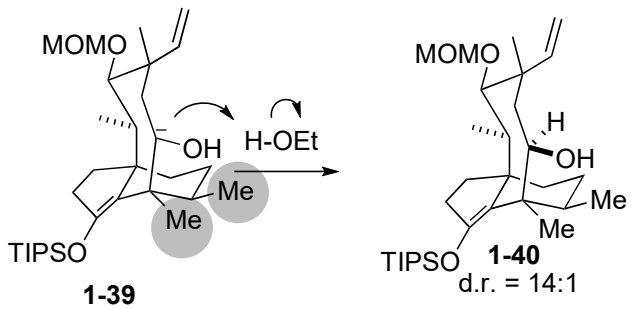
R = H

X = H, 56%
X = D, 47%
>98% D transfer

R = protecting group
X = H, 6-10% conversion
C10 stereocenter: mixture of diastereomer

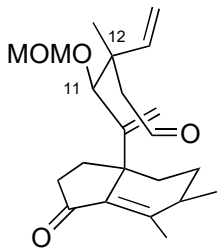


1-33 **1-37** **1-38**



1-39 **1-40**

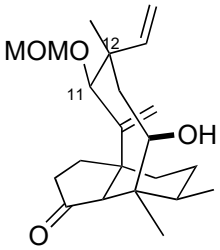
d.r. = 14:1



1-4a

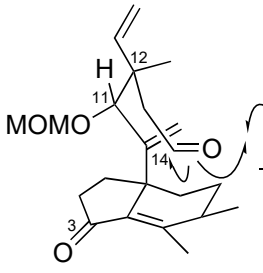
12-epi-**1-4a**

SmI_2 (3 eq.), H_2O (6 eq.), THF, 0 °C;
TMSCl, (5 eq.)



1-16 (77%, d.r. = 17 : 1)

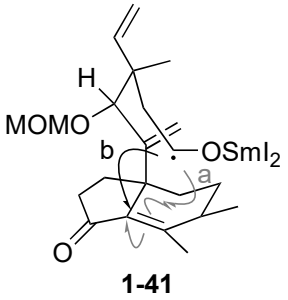
12-epi-**1-16** (88%, d.r. = 23 : 1)



1-4b

(11, 12-bis-*epi* **1-4a**)

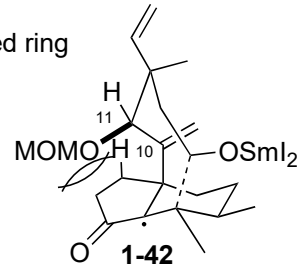
SmI_2



1-41

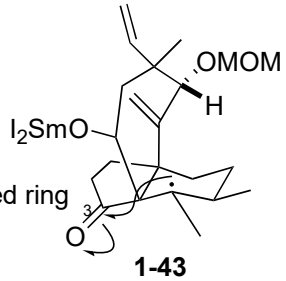
8-membered ring formation

path a



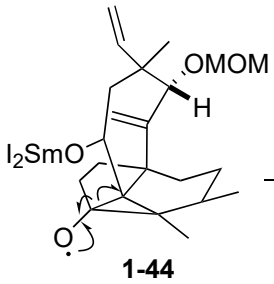
1-42

path b

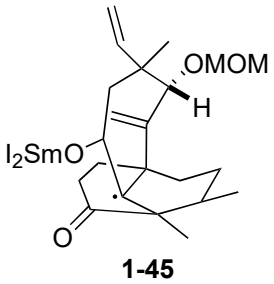


1-43

7-membered ring formation

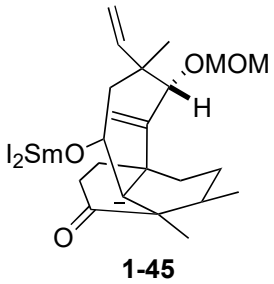


1-44

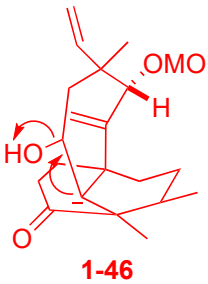


1-45

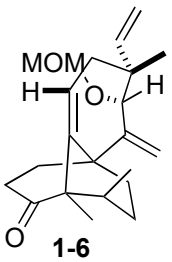
SmI_2



1-45

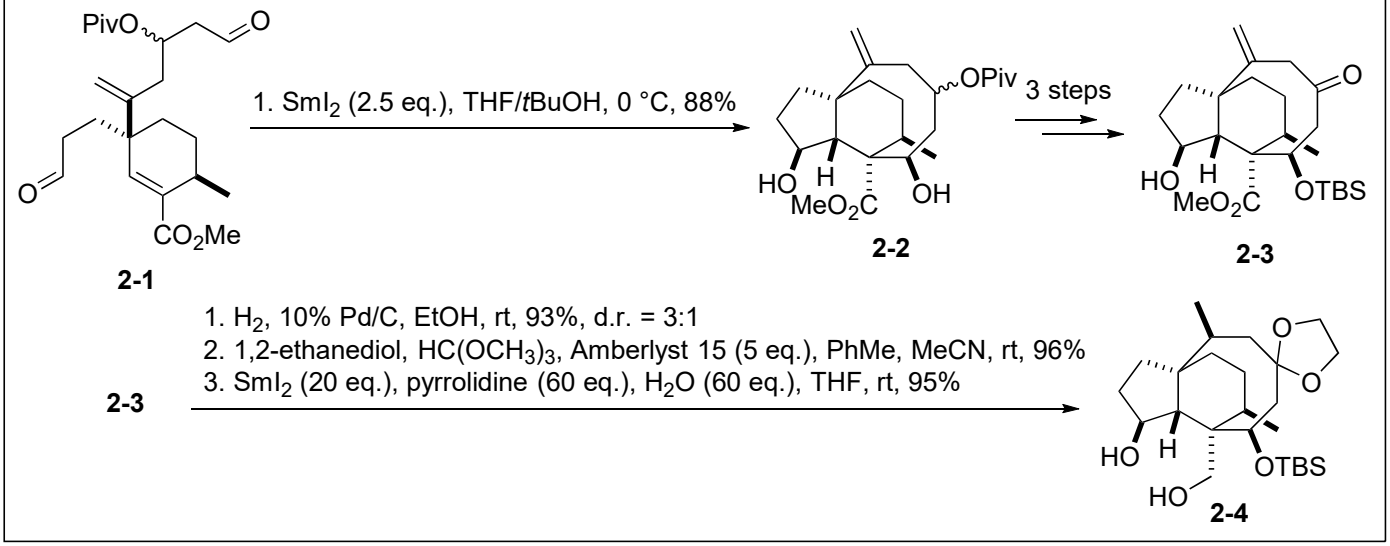


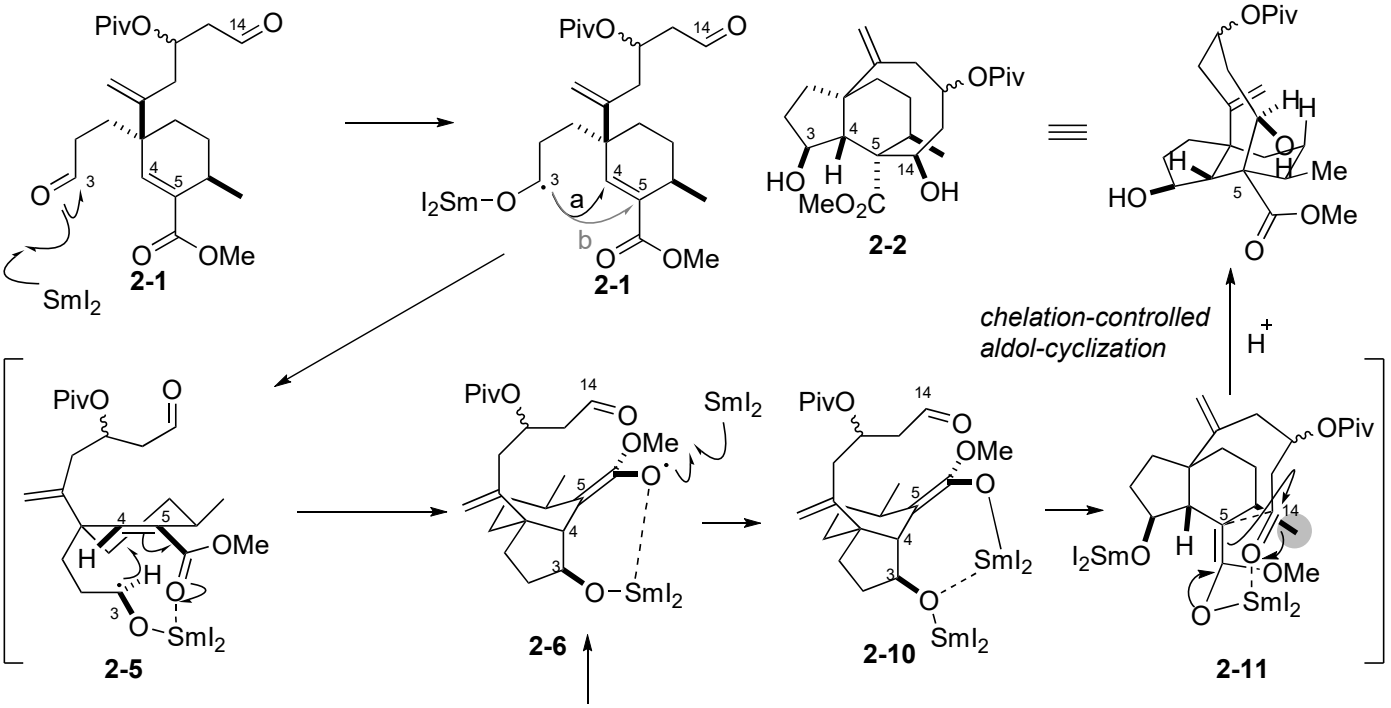
1-46

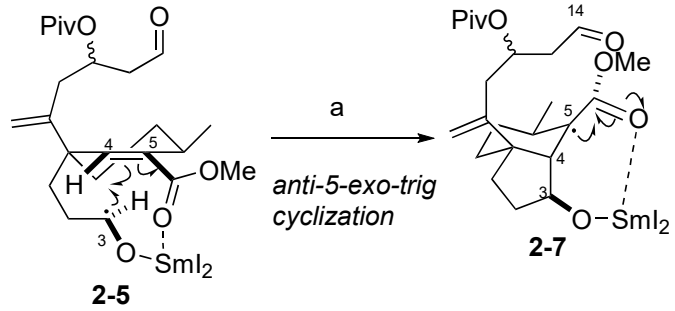


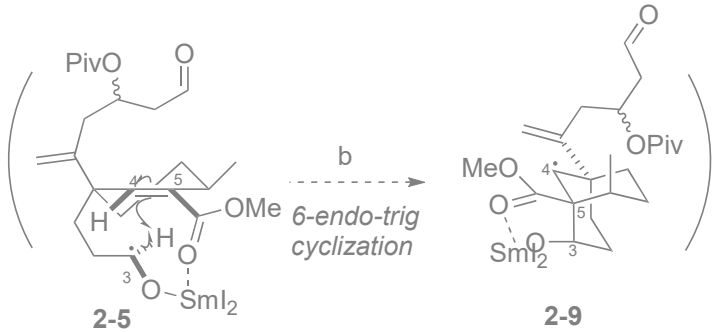
1-6

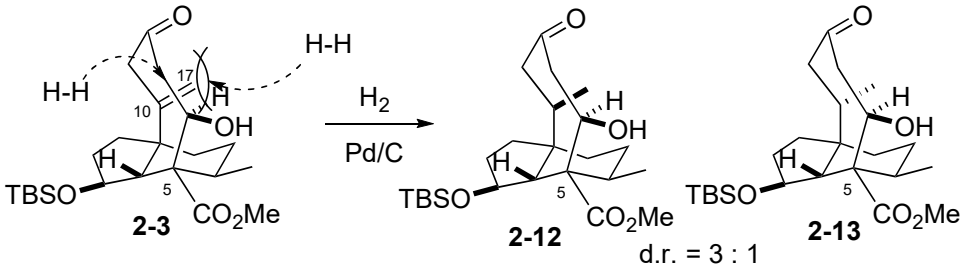
2.

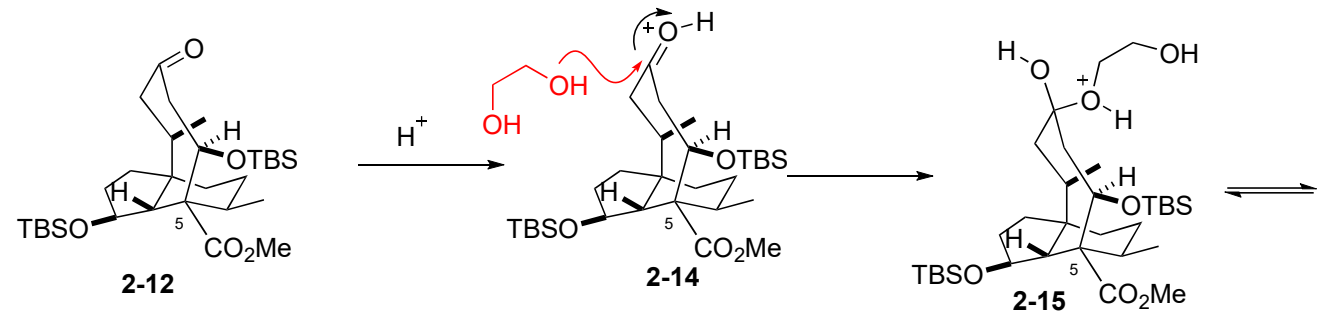

PivO
O
O
CO2Me
1. SmI2 (2.5 eq.), THF/tBuOH, 0 °C, 88%
OPiv
HO
H
MeO2C
OH
3 steps
OTBS
2-1
2-2
2-3
1. H2, 10% Pd/C, EtOH, rt, 93%, d.r. = 3:1
2. 1,2-ethanediol, HC(OCH3)3, Amberlyst 15 (5 eq.), PhMe, MeCN, rt, 96%
3. SmI2 (20 eq.), pyrrolidine (60 eq.), H2O (60 eq.), THF, rt, 95%
2-3
HO
H
OTBS
HO
2-4

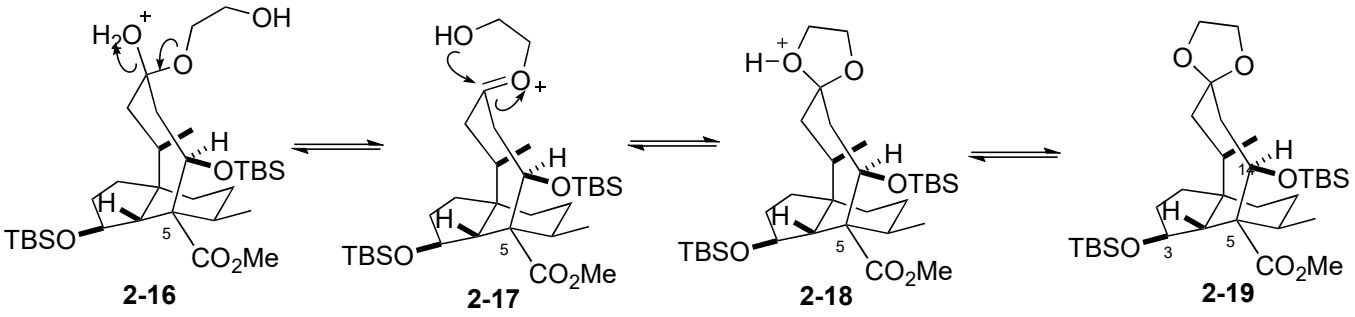

PivO
14
O
3
4
5
OMe
SmI2
2-1
I2Sm−O
a
b
OPiv
HO
H
MeO2C
OH
2-2
Me
OMe
chelation-controlled
aldol-cyclization
H+
2-5
2-6
2-10
2-11
I2SmO
Sml2

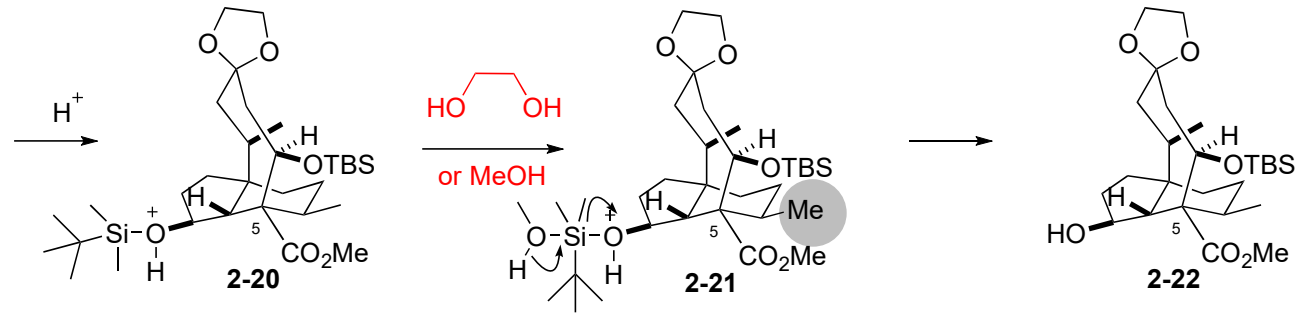

PivO
O
OMe
a
anti-5-exo-trig
cyclization
2-5
2-7
Sml2

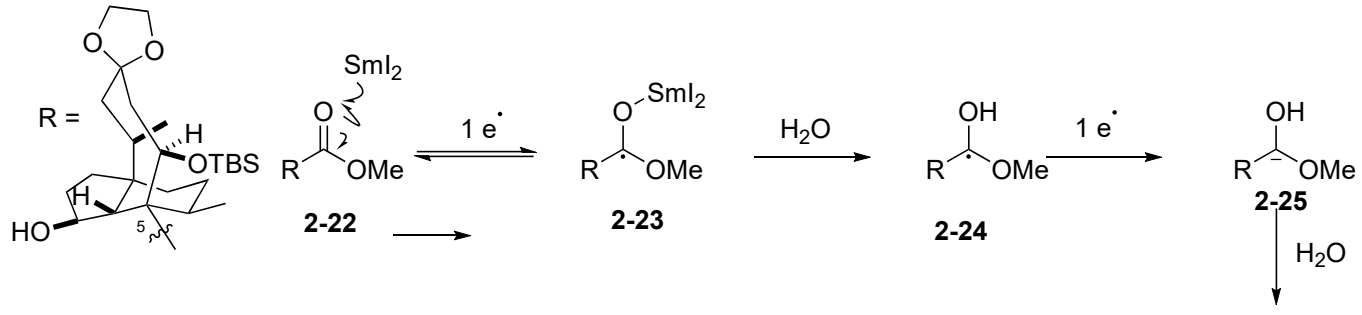

PivO
O
OMe
b
6-endo-trig
cyclization
2-5
2-9
OPiv
MeO
Sml2

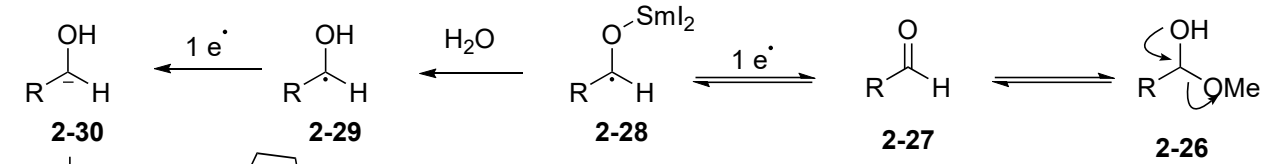

H-H
H-H
17
10
H
OH
H
TBSO
5
CO2Me
2-3
H2
Pd/C
2-12
2-13
d.r. = 3 : 1


H
OTBS
TBSO
5
CO2Me
2-12
H+
OH
2-14
2-15


H2O+
OH
HO
H
OTBS
TBSO
5
CO2Me
2-16
2-17
2-18
2-19


H+
Si
O
H
OTBS
5
CO2Me
2-20
HO
OH
or MeOH
Me
2-21
2-22

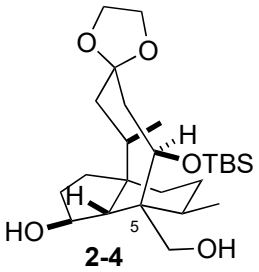

R =
HO
OTBS
5
2-22
SmI2
1 e
2-23
H2O
OH
OMe
2-24
2-25


H2O
2-26
2-27
2-28
2-29
2-30
2-4
OTBS
OH

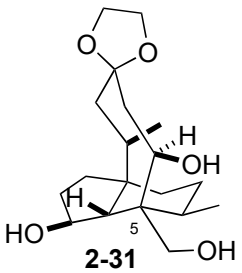
effect of base

Table 1

Reductant	**2-4** (%)	**2-31** (%)	**2-22** (%)
$LiAlH_4$	21	43	23
$SmI_2/Et_3N/H_2O$	92		
SmI_2/pyrrolidine/H_2O	95		
SmI_2/HMPA/H_2O	<5		



2-4

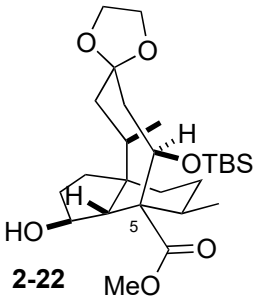


2-31

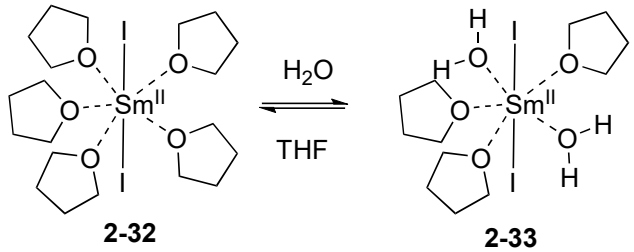
The addition of the base improved the reduction rate.

Table 2

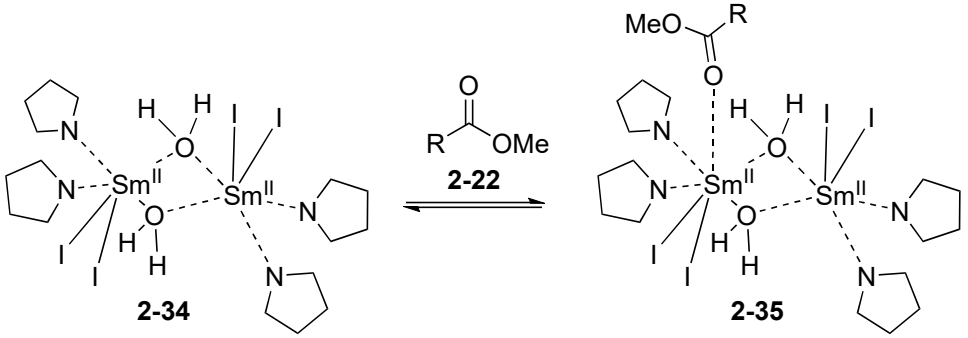
Reductant	Standard Potential, V (versus SCE)
SmI_2 (THF)	-0.98
SmI_2-HMPA (THF)	-1.75
$SmI_2/Et_3N/H_2O$ (THF)	-2.8



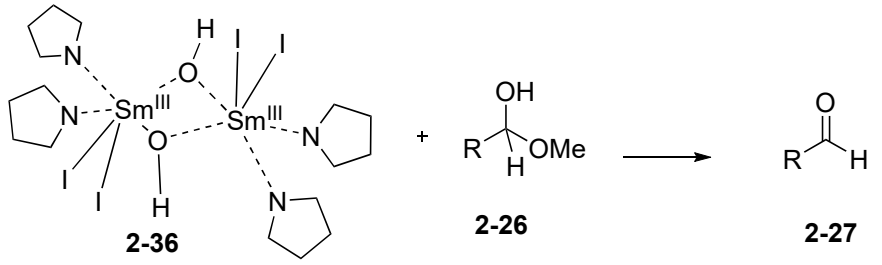
2-22



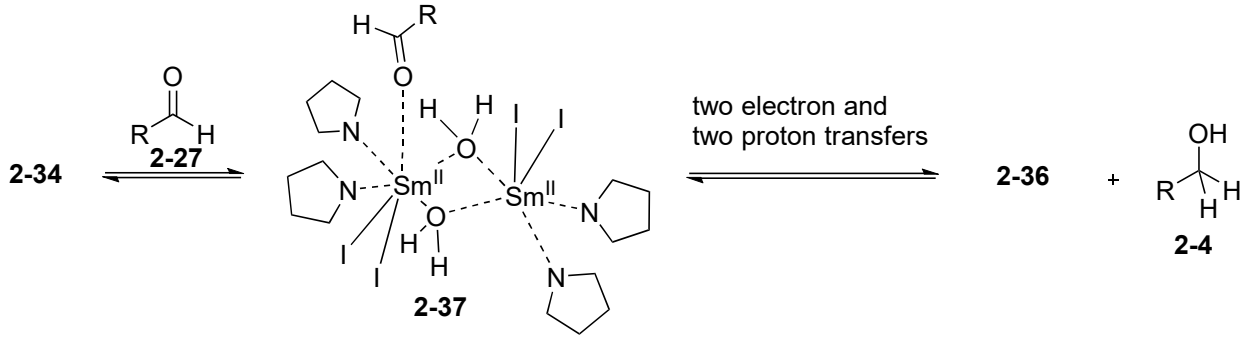
2-32 **2-33**



2-34 **2-22** **2-35**



2-36 **2-26** **2-27**



2-37 **2-4**