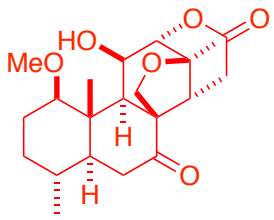
Problem Session (2)

2015/11/20 Daiki Kamakura

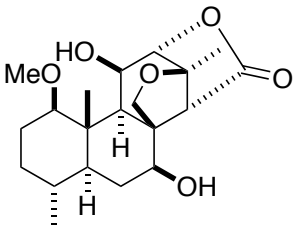
1) Please provide the reaction mechanisms.
2) Please fill in the blanks **2-1**, **2-3** and **2-5**.

1



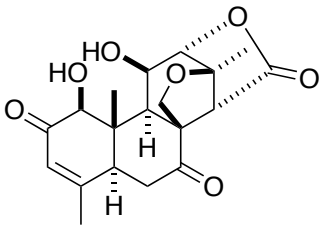
1-1

1) $NaBH_4$, MeOH, THF, 95%
2) $Cu(OAc)_2 \cdot H_2O$, (1.0 eq.), pyridine
DIPEA, MeOH, O_2, 44%



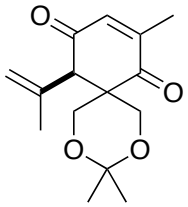
1-2

12 steps



(±)-Samaderine B (**1-3**)

2

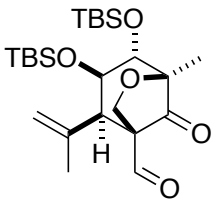


2-0
($C_{15}H_{20}O_4$)

1) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH
2) TBSOTf, Et_3N, CH_2Cl_2, 87% (2 steps)
3) TBHP, NaOH aq., MeOH
4) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH
5) TFA, CH_2Cl_2; 2,2-dimethoxypropane
PTSA, 73% (3 steps)

2-1
($C_{21}H_{38}O_5Si$)

3 steps

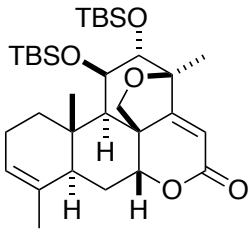


2-2
($C_{24}C_{44}O_5Si_2$)

1) **A**, Et_2O, 78%
2) NaH, 4-methylbenzo[15]crown-5, THF
3) Ac_2O, Et_3N, DMAP, CH_2Cl_2 83% (2 steps)
4) toluene, 180 °C, 92% (dr = 2 : 1)

2-3
($C_{32}H_{56}O_6Si_2$)

5 steps

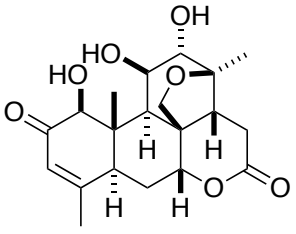


2-4
($C_{32}H_{54}O_5Si_2$)

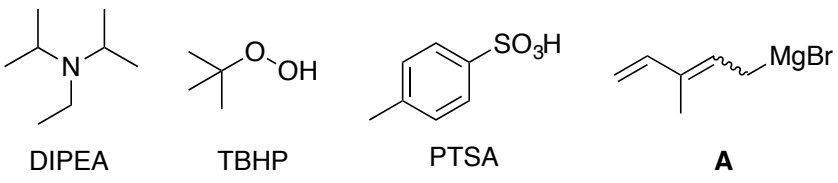
1) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH
; conc. HCl, MeOH, 78%
2) $Mn(OAc)_3 \cdot 2H_2O$ (10 mol%),
TBHP (5.0 eq.), MS3A, EtOAc, rt, 72%
3) $Mn(OAc)_3 \cdot 2H_2O$ (1.0 eq.), benzene
reflux, 78%

2-5
($C_{35}H_{60}O_8Si_2$)

5 steps



(–)-Samaderine Y (**2-6**)



Problem Session (2)-Answer

2015.11.20 Daiki Kamakura

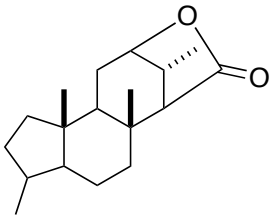
Topic: Total synthesis of Samaderine

0-1: Introduction to Quassinoids

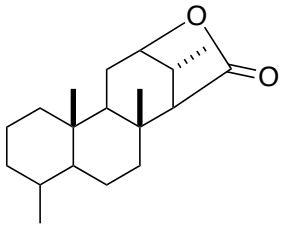
quassinoids: the bitter principle derived from the *Simaroubaceae* family
over 150 isolated

structural features: tetra- or pentacyclic framework
highly oxygenated terpenoid
five main skeltone

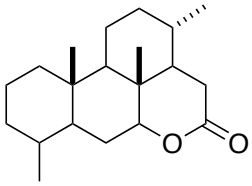
Total synthesis: more than 15 reports



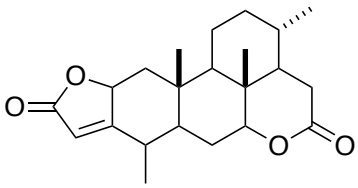
C_{18}



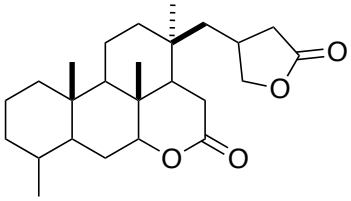
C_{19}



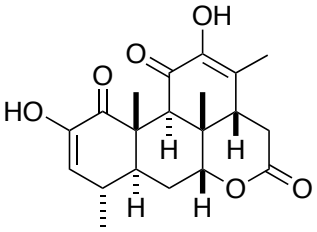
C_{20}



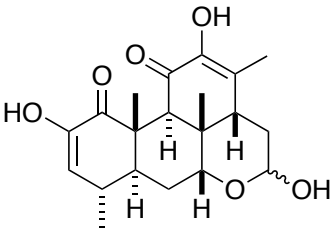
C_{22}



C_{25}



Quassin (**0-1**)



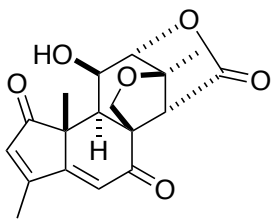
Neoquassin (**0-2**)

0-2: Introduction to Samaderine

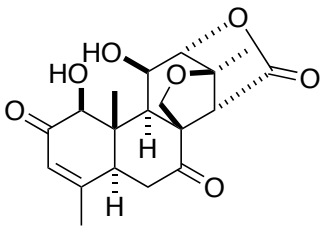
Samaderines: subclass of quassinoids
isolated from *Samadera indica*
eight samaderines have been identified

structural features: containing a lactone and a tetrahydrofuran ring

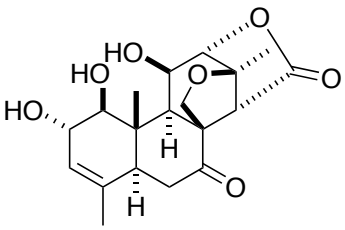
Total synthesis: two reports
Samaderine B (**1-3**): Grieco, P. A.; Pineiro, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606. (**Q.1**)
Samaderine Y (**2-6**): Shing, T. K. M.; Yeung, Y. *Angew. Chem. Int. Ed.* **2005**, *117*, 8195. (**Q.2**)



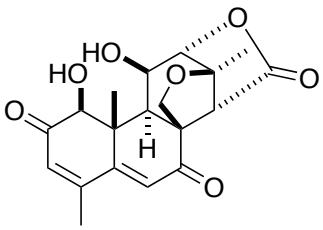
Samaderine A (**0-3**)



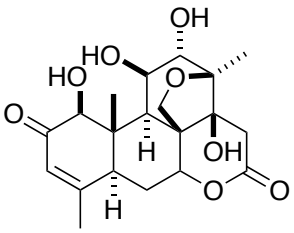
Samaderine B (**1-3**)



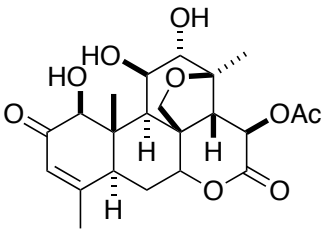
Samaderine C (**0-4**)



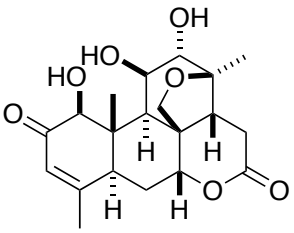
Samaderine D (**0-5**)



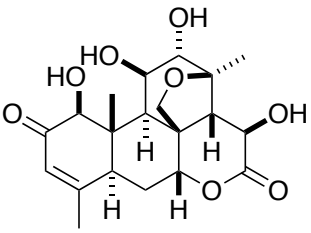
Samaderine E (**0-6**)



Samaderine X (**0-7**)



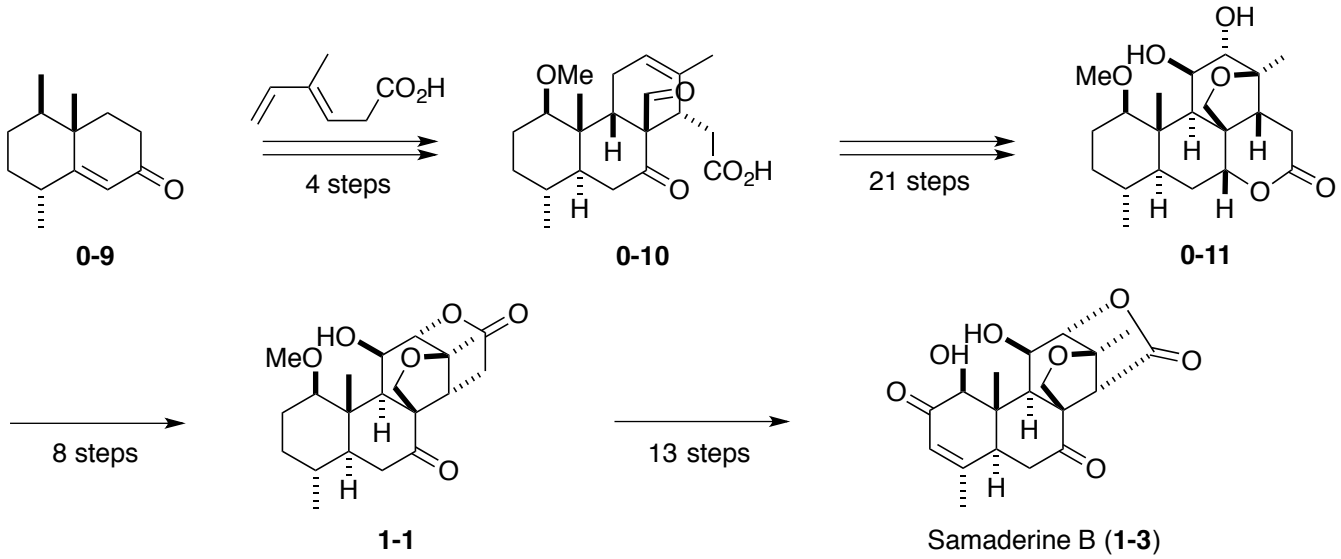
Samaderine Y (**2-6**)



Samaderine Z (**0-8**)

Biosynthesis of quassinoids are not clear yet.

0-3: Grieco's Total Synthesis of Samaderine B

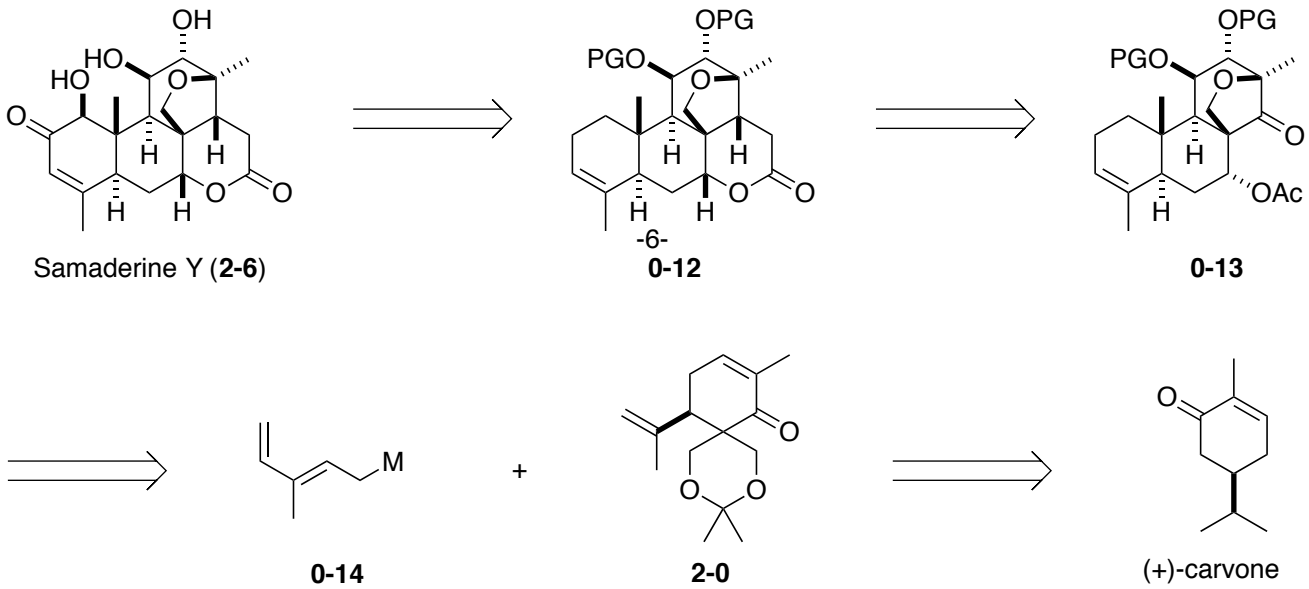


0-9 **0-10** **0-11**

1-1

Samaderine B (**1-3**)

0-4: Shing's retrosynthetic analysis of Samaderine Y



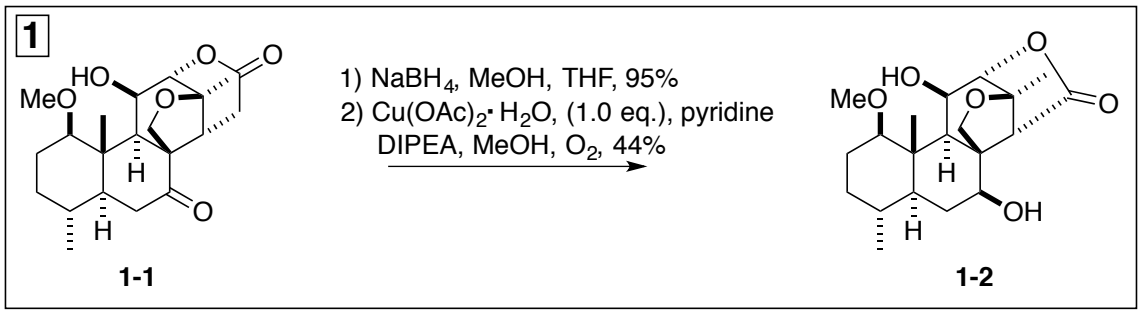
Samaderine Y (**2-6**)

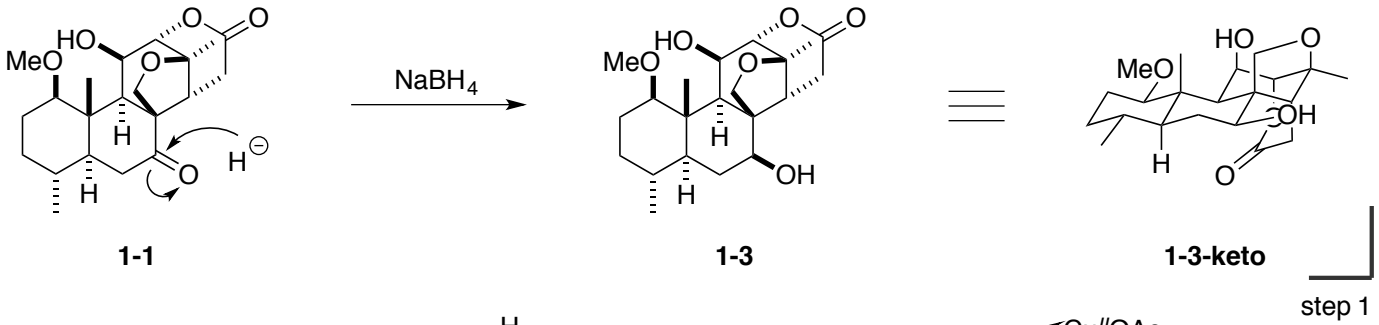
-6-

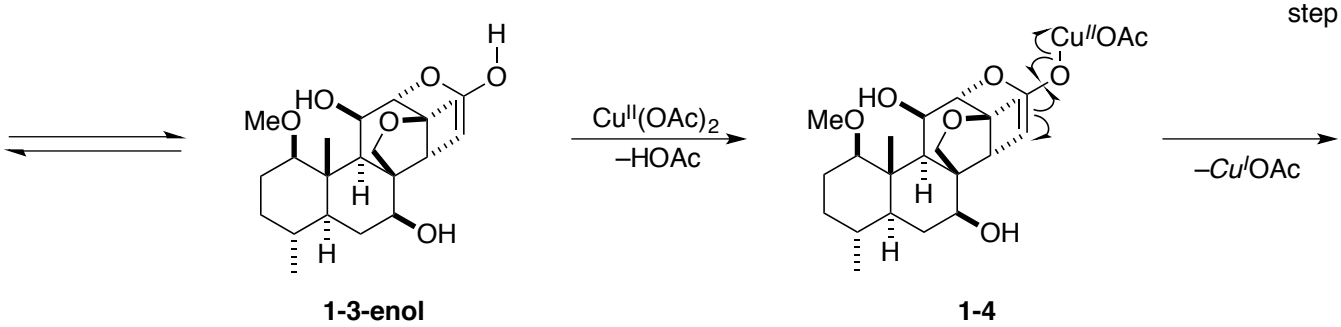
0-12 **0-13**

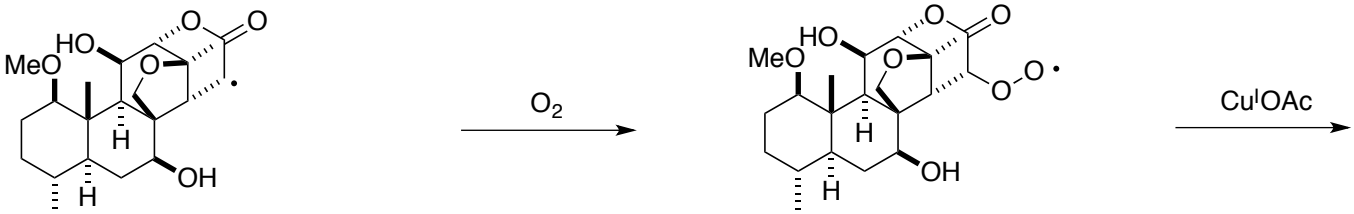
0-14 **2-0**

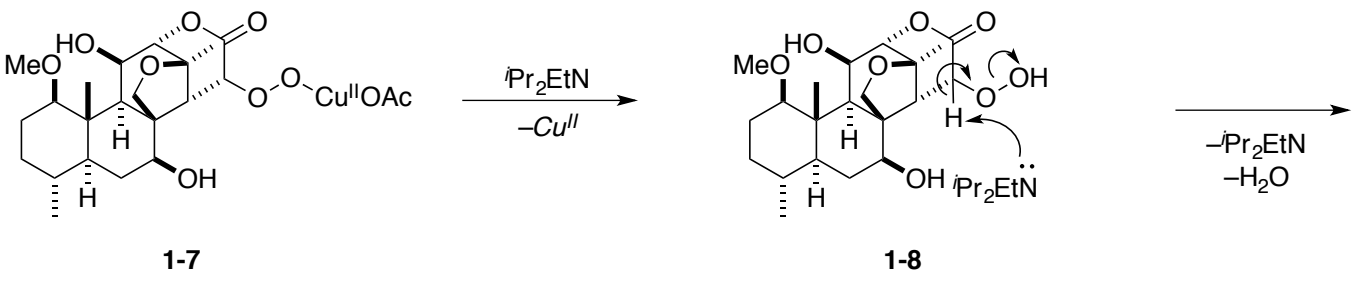
(+)-carvone

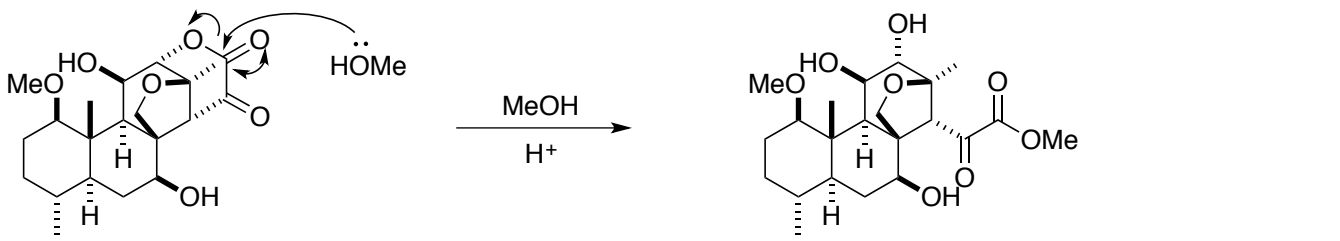

1
1) NaBH4, MeOH, THF, 95%
2) Cu(OAc)2· H2O, (1.0 eq.), pyridine
DIPEA, MeOH, O2, 44%
1-1
1-2

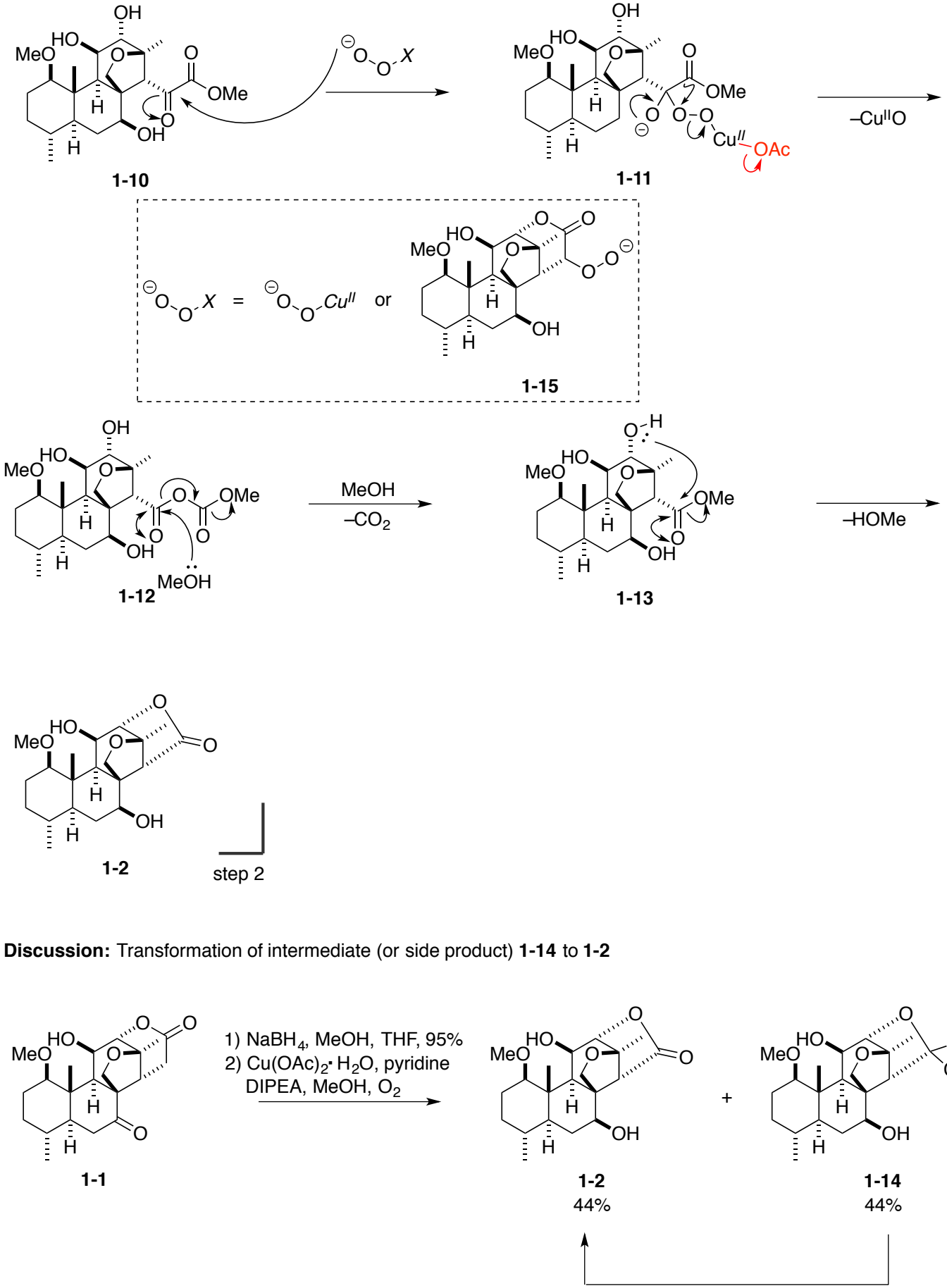

NaBH4
1-1
1-3
1-3-keto
step 1


Cu^II(OAc)2
–HOAc
Cu^IIOAc
–Cu^IOAc
1-3-enol
1-4


O2
Cu^IOAc
1-5
1-6

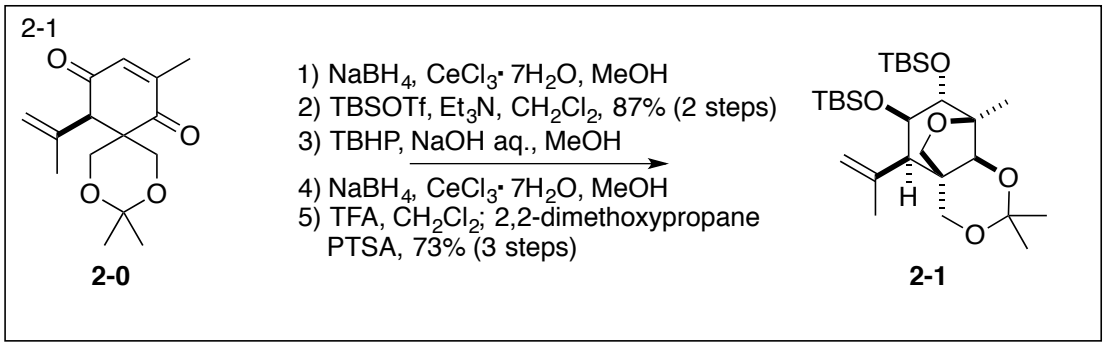

iPr2EtN
–Cu^II
–iPr2EtN
–H2O
Cu^IIOAc
1-7
1-8

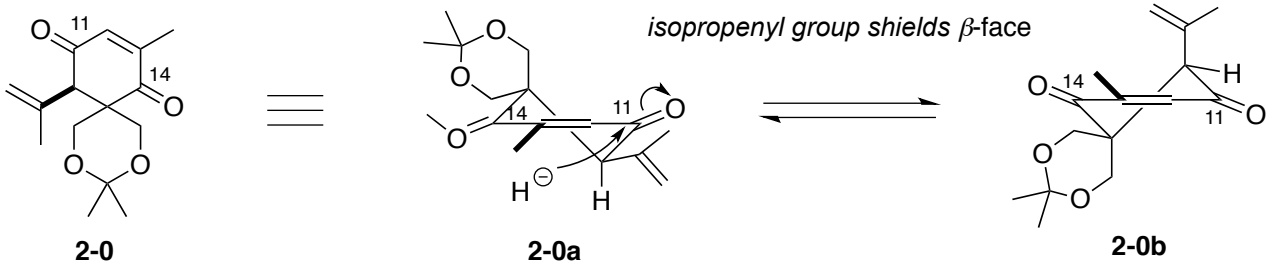

HOMe
MeOH
H+
OMe
1-9
1-10

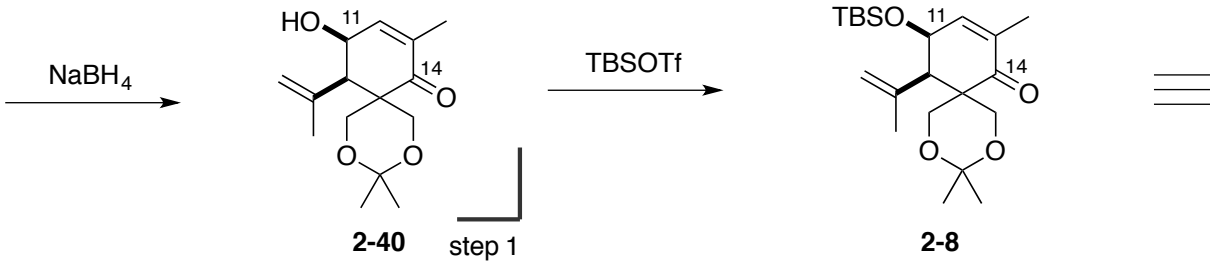


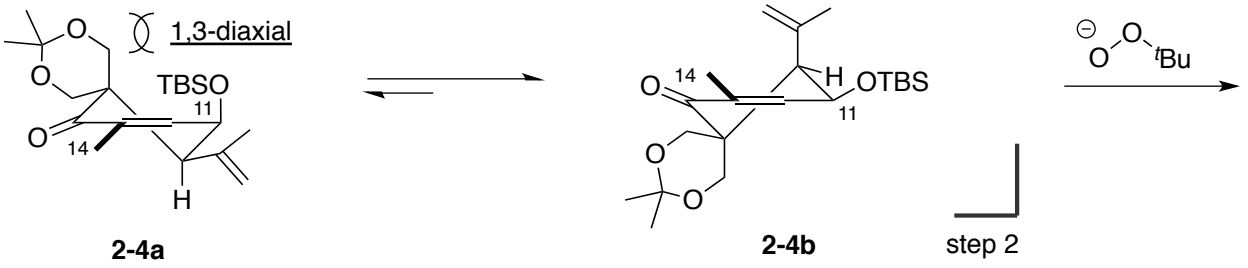
Discussion: Transformation of intermediate (or side product) **1-14** to **1-2**

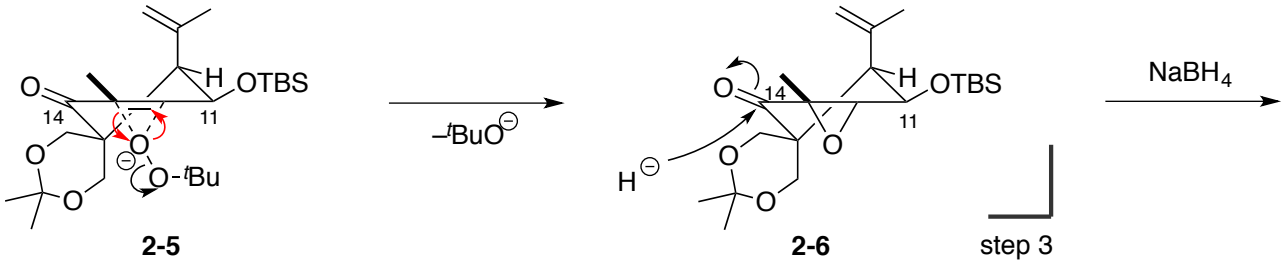
Baeyer-Villiger oxidation could convert **1-14** to **1-2**

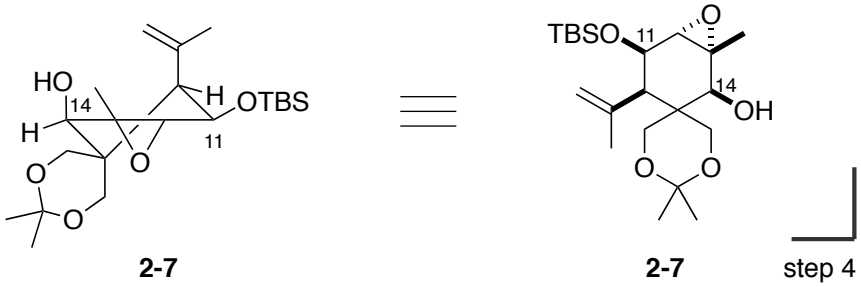

2-1
1) NaBH4, CeCl3· 7H2O, MeOH
2) TBSOTf, Et3N, CH2Cl2, 87% (2 steps)
3) TBHP, NaOH aq., MeOH
4) NaBH4, CeCl3· 7H2O, MeOH
5) TFA, CH2Cl2; 2,2-dimethoxypropane
PTSA, 73% (3 steps)
TBSO
2-0
2-1

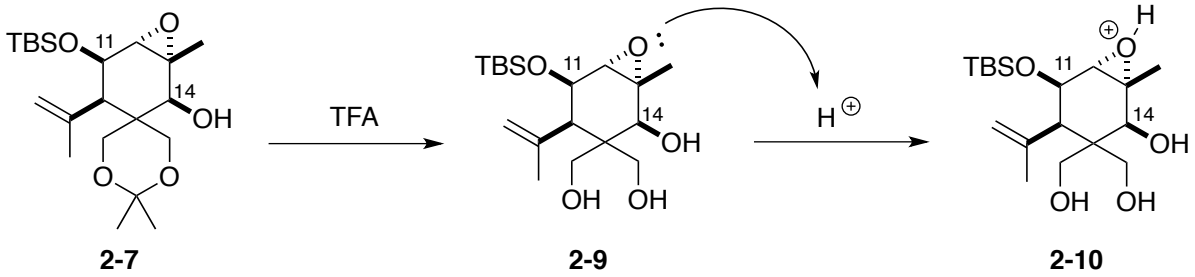

isopropenyl group shields β-face
2-0
2-0a
2-0b

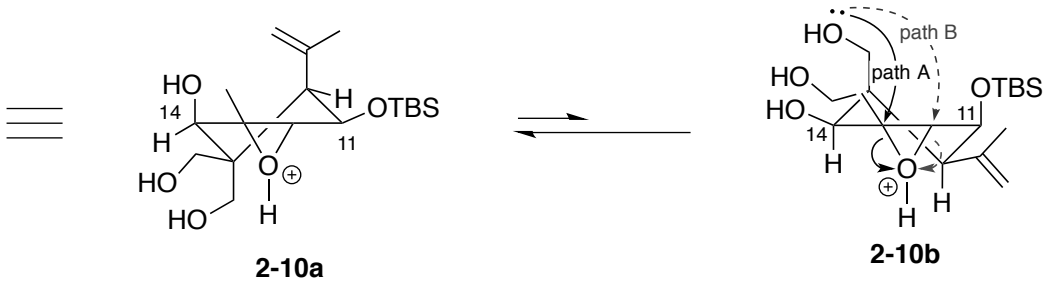

NaBH4
TBSOTf
2-40
step 1
2-8

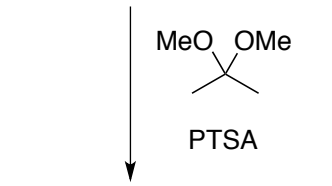

1,3-diaxial
2-4a
2-4b
step 2

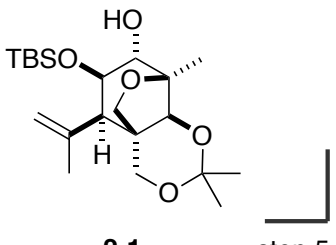

–tBuO
2-5
2-6
step 3
NaBH4


2-7
2-7
step 4

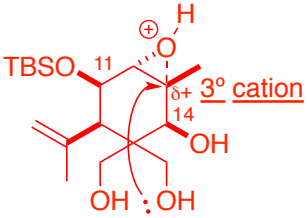




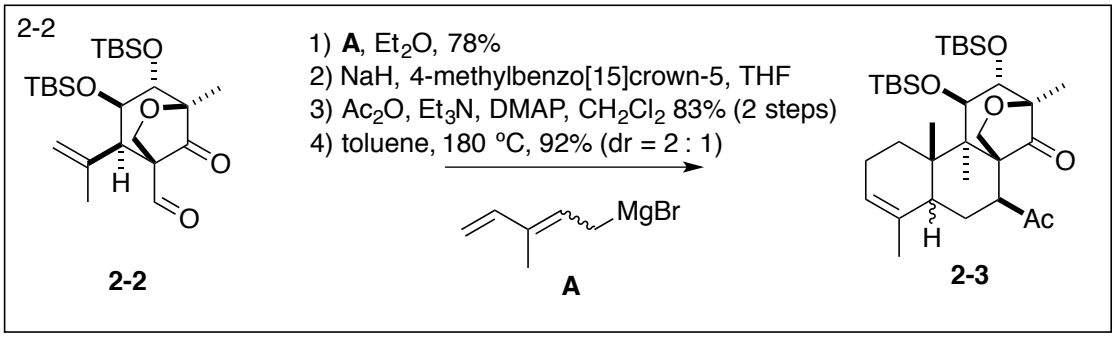


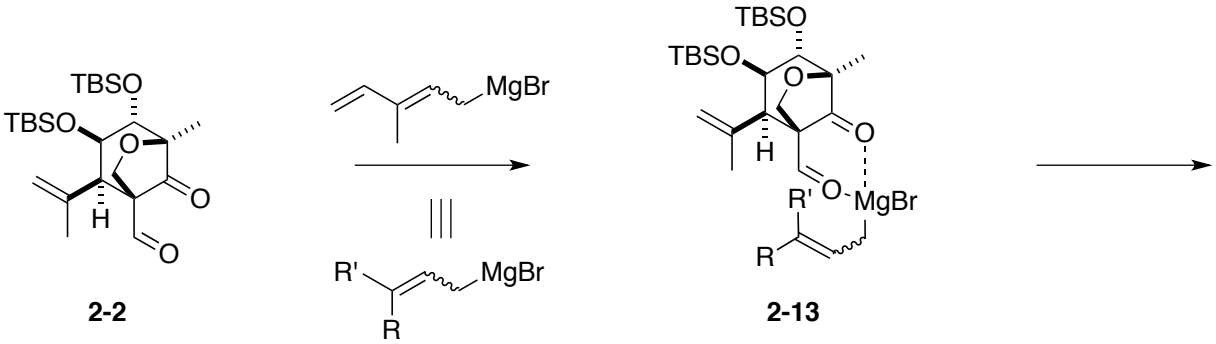


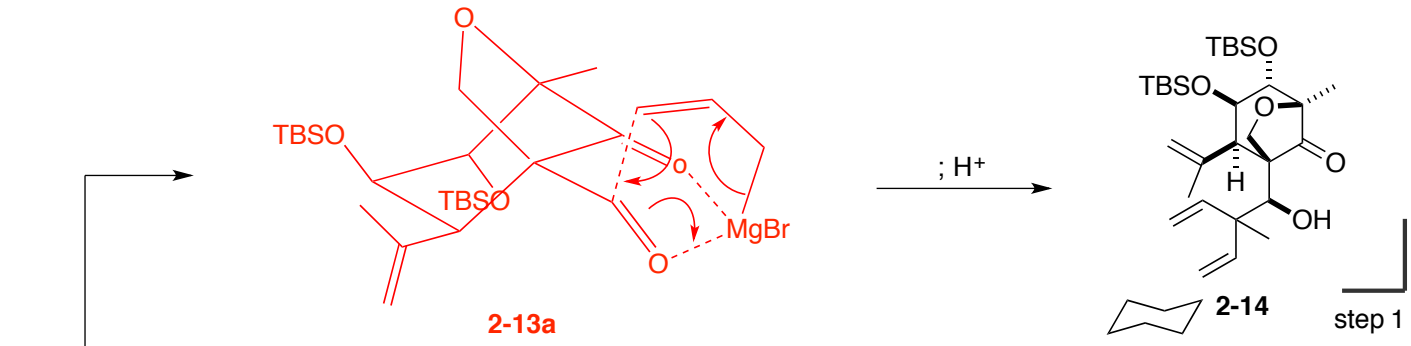
another explanation: more stable carbocation would formed

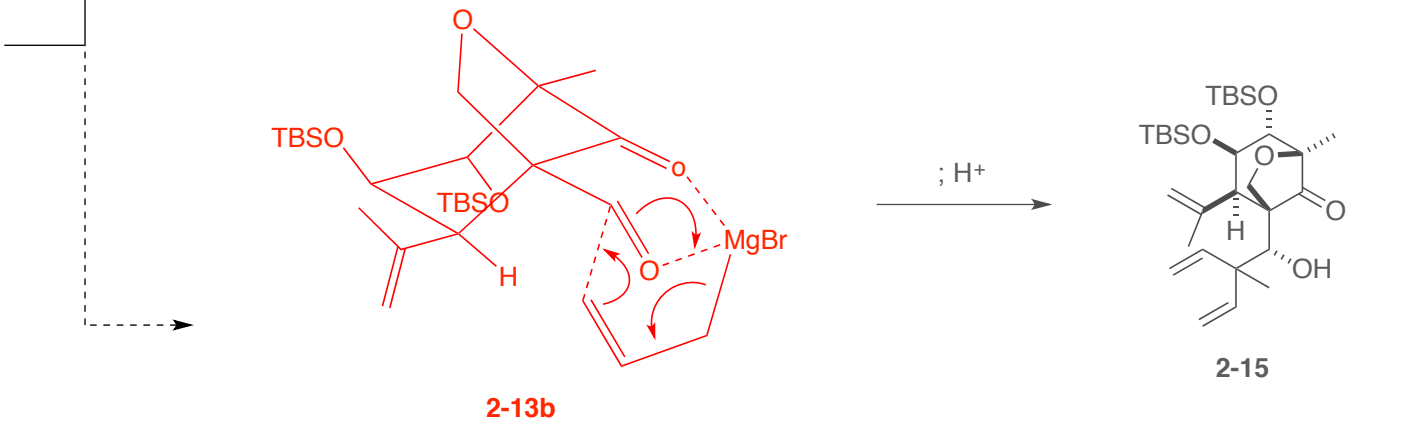


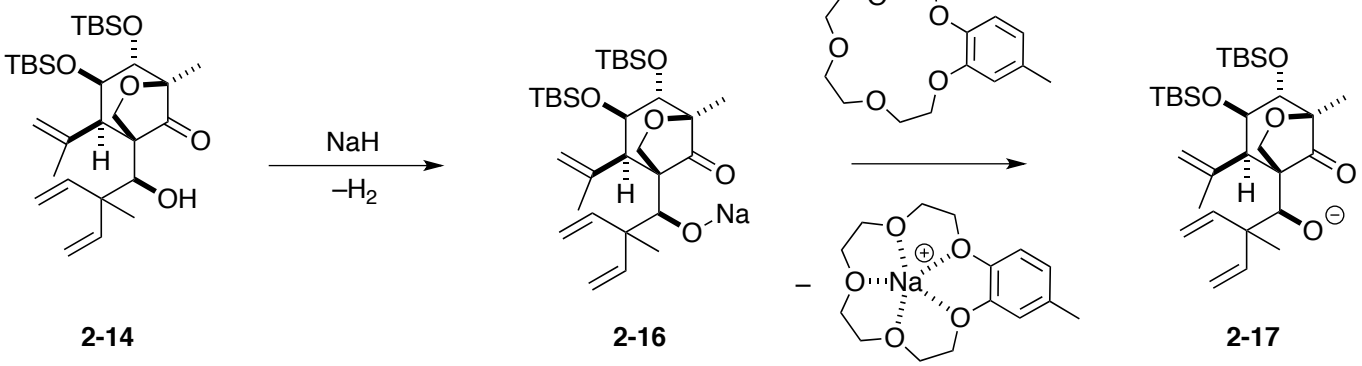
2-11

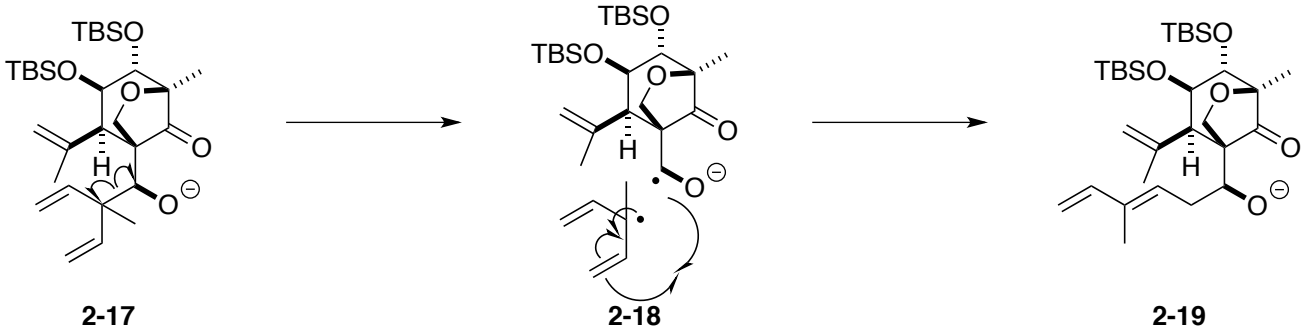

2-2
TBSO
TBSO
O
H
O
O
1) A, Et2O, 78%
2) NaH, 4-methylbenzo[15]crown-5, THF
3) Ac2O, Et3N, DMAP, CH2Cl2 83% (2 steps)
4) toluene, 180 °C, 92% (dr = 2 : 1)
MgBr
A
TBSO
TBSO
O
O
Ac
H
2-3


TBSO
TBSO
O
H
O
O
2-2
MgBr
R'
MgBr
R
TBSO
TBSO
O
H
O
R'
O
MgBr
R
2-13

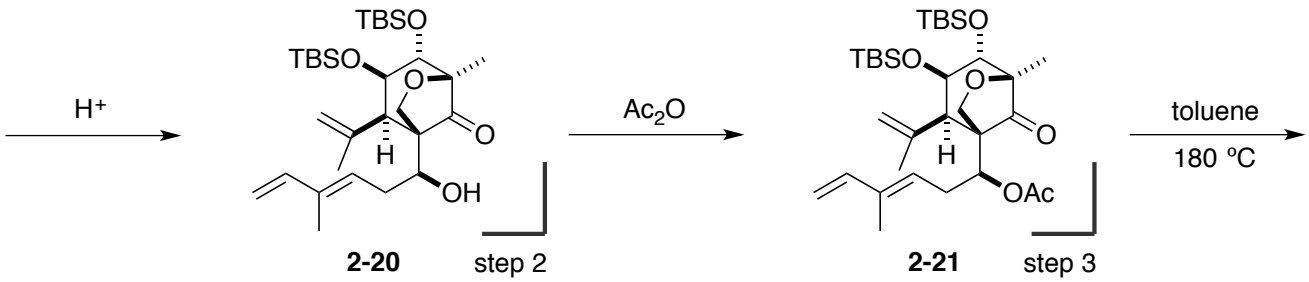

O
TBSO
TBSO
O
MgBr
O
2-13a
; H+
TBSO
TBSO
O
H
OH
2-14
step 1


O
TBSO
TBSO
H
O
MgBr
O
2-13b
; H+
TBSO
TBSO
O
H
OH
2-15

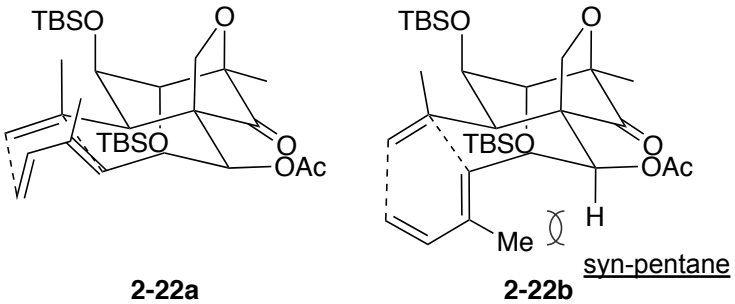

TBSO
TBSO
O
H
OH
2-14
NaH
–H2
TBSO
TBSO
O
H
O
Na
2-16
O
O
O
O
O
O
O
Na
O
O
–
TBSO
TBSO
O
H
O
O
2-17



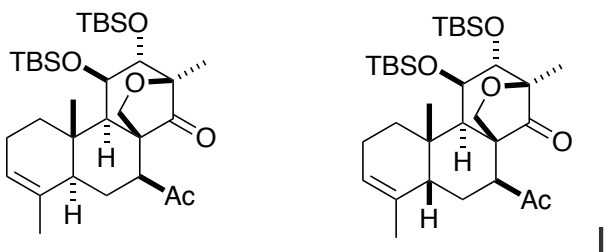
2-17 **2-18** **2-19**



2-20 step 2 **2-21** step 3



2-22a **2-22b** syn-pentane



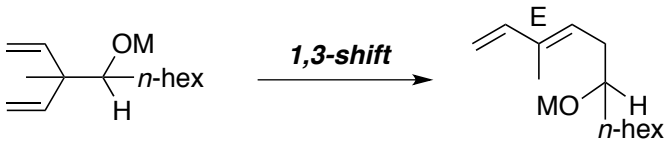
2-3-*trans* **2-3-*cis***

2-3-*trans* : **2-3-*cis***
= 2 : 1

step 2

Discussion: Alkoxide-accelerated 1,3-shift

1: Solvent and cation effects

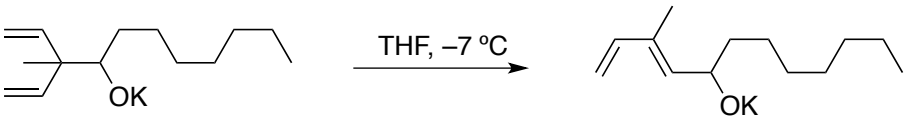


2-25 **2-26**

M	solvent	temp./°C	harf-life
Li	THF	65	4 h
Na	THF	65	2 h
Na	HMPA	0	30 min
K	THF	0	10 min
K	Et_2O	0	40 min

$\Longrightarrow$ naked alkoxide accelerated this reaction

2: Effects of crown ether

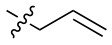


2-27 **2-28**

harf-life: 40 min (without 18-crown-6)
5 min (18-crown-6 was used)

Wilson, S. R.; Mao, D. T. Jernberg, K. M. Ezmirly, S. T. *Tetrahedron Lett*, **1977**, *30*, 2559.

3: Calculated bond dissociation energies of alkoxides

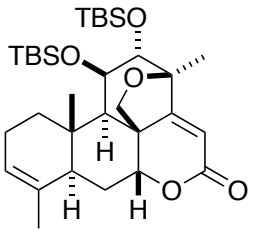
R	HOH_2C-R	$^{\ominus}OCH_2$-R
H	93	76
Me	83	68
	71	58

$\Longrightarrow$ carbon-carbon bond homolysis would occur

Calculated bond dissociation energy (kcal/mol)

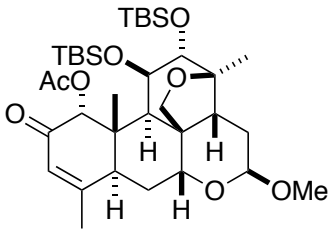
Evans, D. A.; Baillargeon, D. J. *Tetrahedron Lett*, **1978**, 36, 3319.

2-3

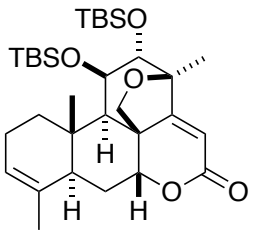


2-4
($C_{32}H_{54}O_5Si_2$)

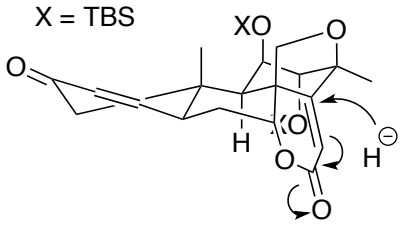
1) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH ; conc. HCl, MeOH, 78%
2) $Mn(OAc)_3 \cdot 2H_2O$ (10 mol%), TBHP (5.0 eq.), MS3A, EtOAc, rt, 72%
3) $Mn(OAc)_3 \cdot 2H_2O$ (1.0 eq.), benzene reflux, 78%



2-5

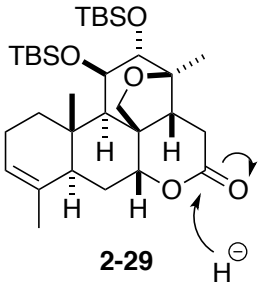


2-4



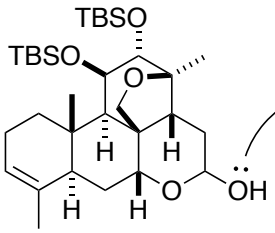
2-4

$NaBH_4$, $NiCl_2$; H^+



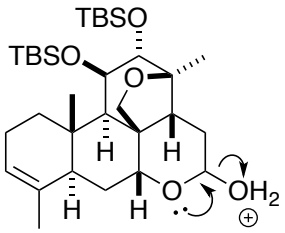
2-29

$NaBH_4$

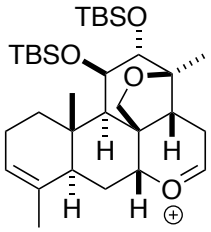


2-30

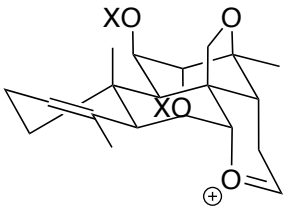
H^+



2-31

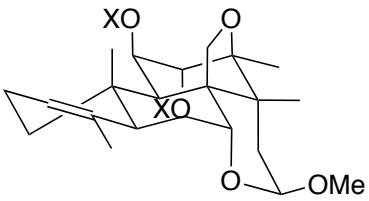


2-32

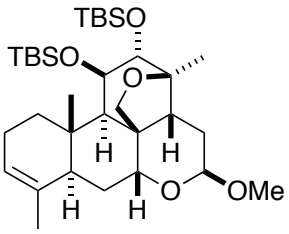


2-32

MeOH
$-H^+$

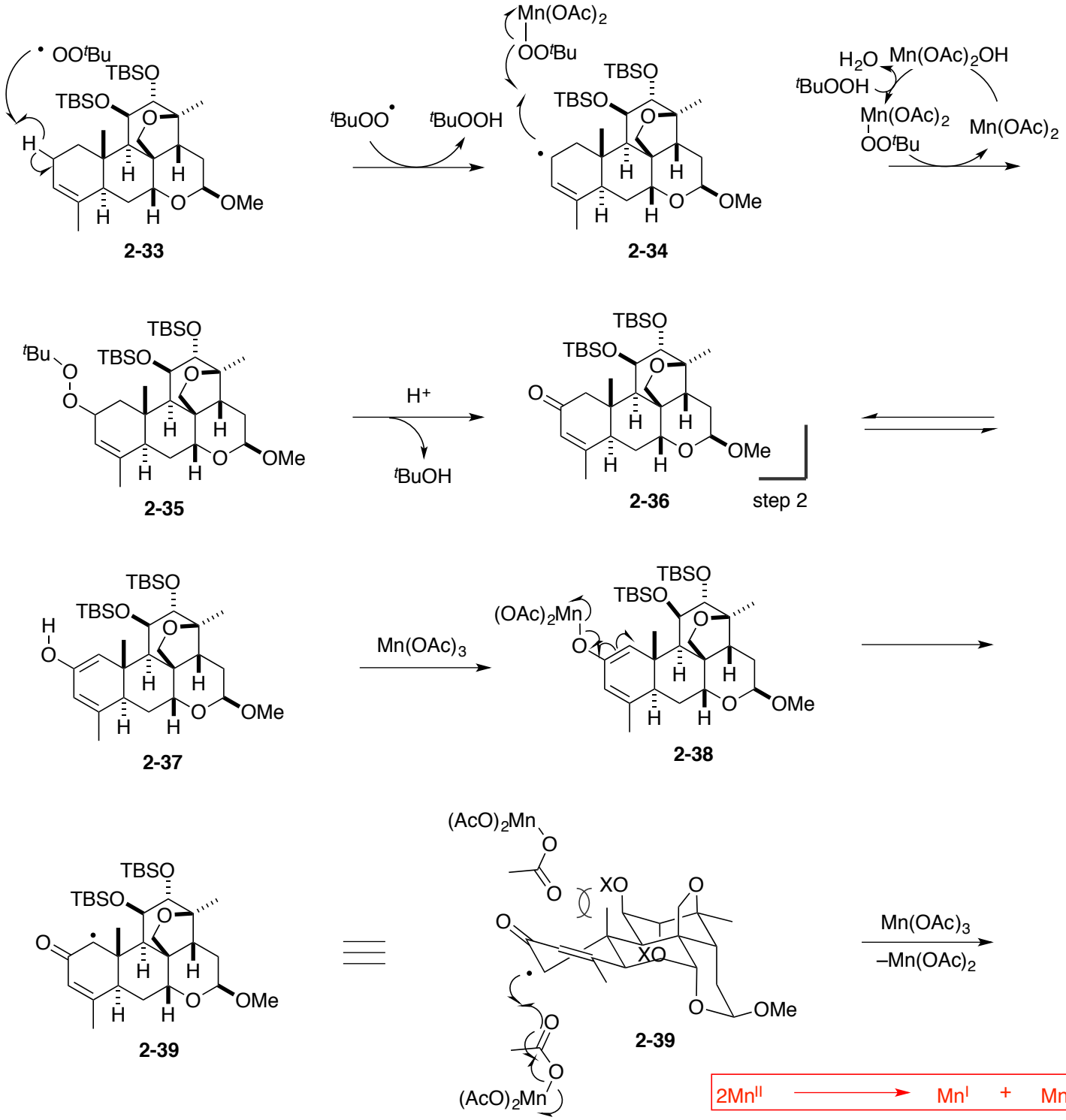


2-33a
(anomeric effect stabilize this conformer)



2-33

step 1


OO^{t}Bu
TBSO
TBSO
H
O
OMe
2-33
^{t}BuOO
^{t}BuOOH
Mn(OAc)$_2$
OO^{t}Bu
2-34
H$_2$O
Mn(OAc)$_2$OH
^{t}BuOOH
Mn(OAc)$_2$
OO^{t}Bu
Mn(OAc)$_2$
^{t}Bu
2-35
H$^+$
^{t}BuOH
2-36
step 2
2-37
Mn(OAc)$_3$
(OAc)$_2$Mn
2-38
2-39
(AcO)$_2$Mn
XO
Mn(OAc)$_3$
–Mn(OAc)$_2$
2-39
2Mn^{II}
Mn^I
+
Mn^{III}
AcO
2-5
2-5