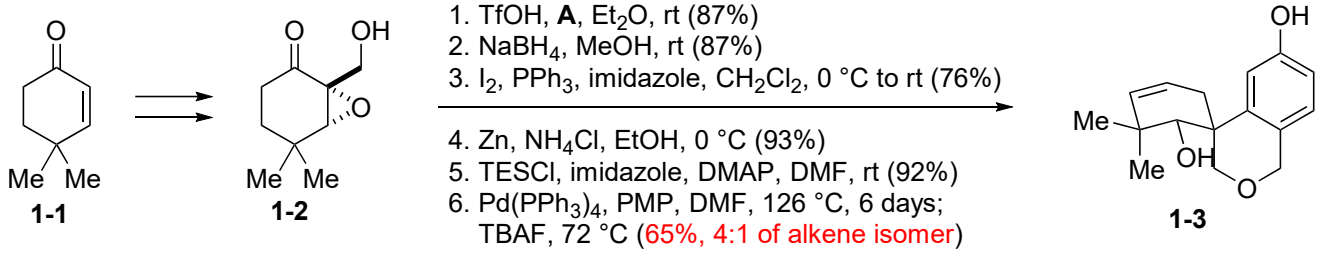
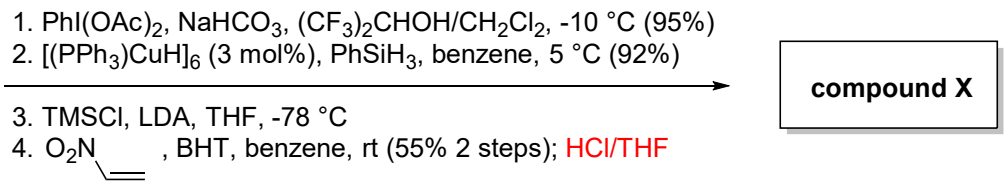
Problem Session (1) - Problem

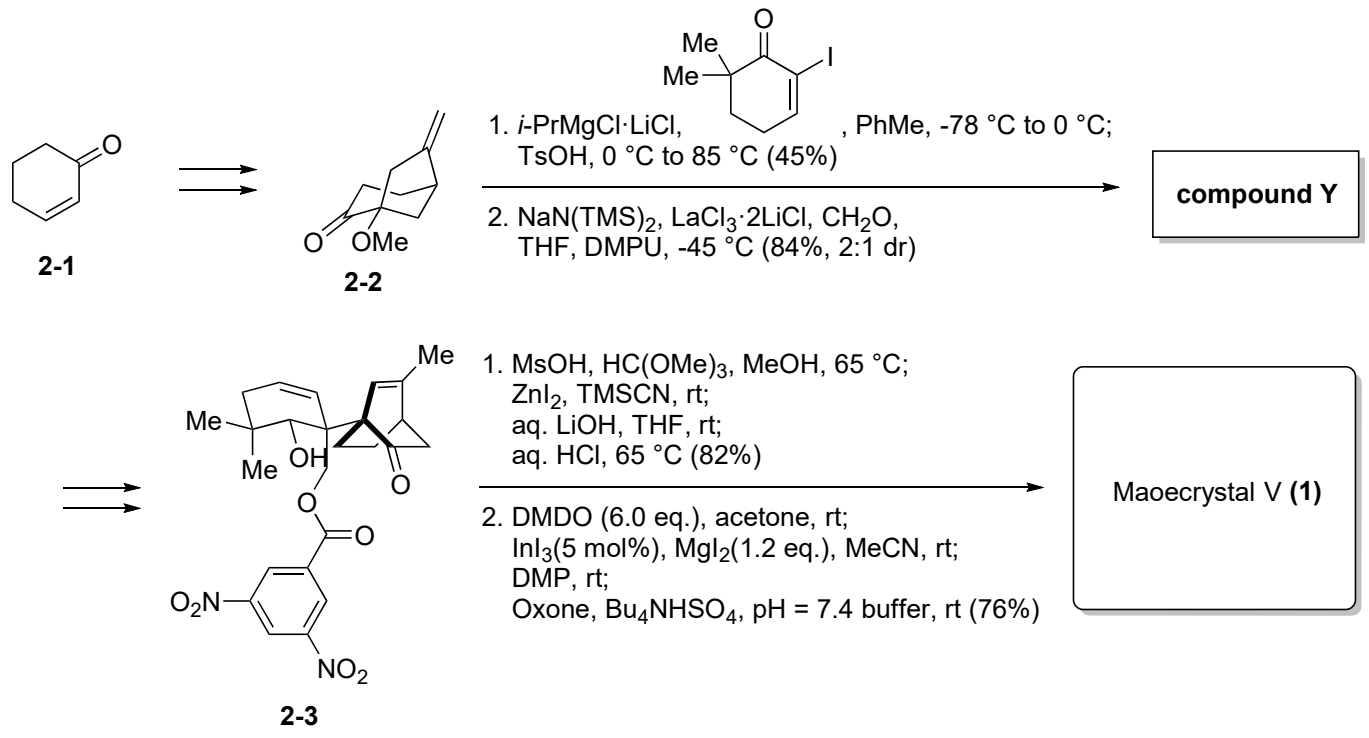
2016.10.8 Yusuke Imamura

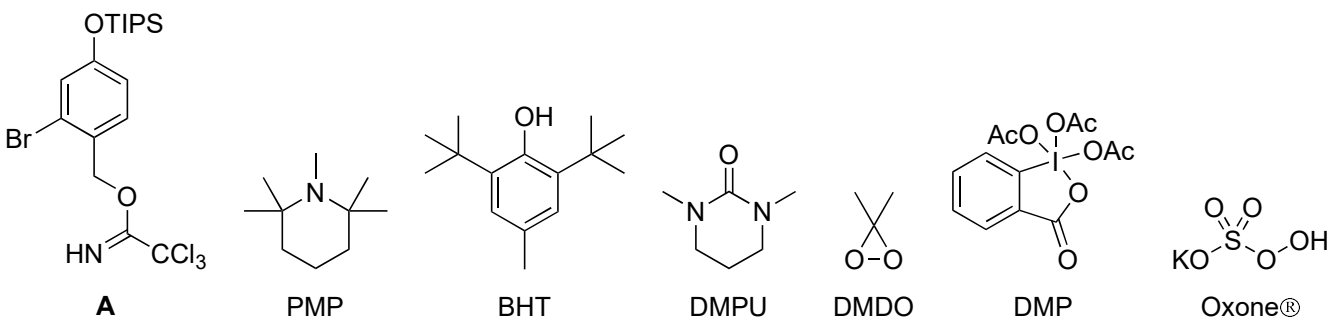
1. Please fill in the blank and explain the reaction mechanisms.





2. Please fill in the blanks and explain the reaction mechanisms.



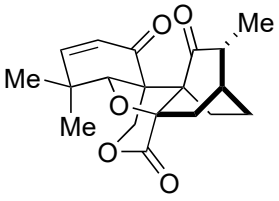


Problem Session (1) - Answer

2016.10.8 Yusuke Imamura

Isolation

isolated from *Isodon eriocalyx* (Sun. H.-D. *et. al. Org. Lett.* **2004**, *6*, 4327-4330)



Maoecrystal V **(1)**

Biological Activity

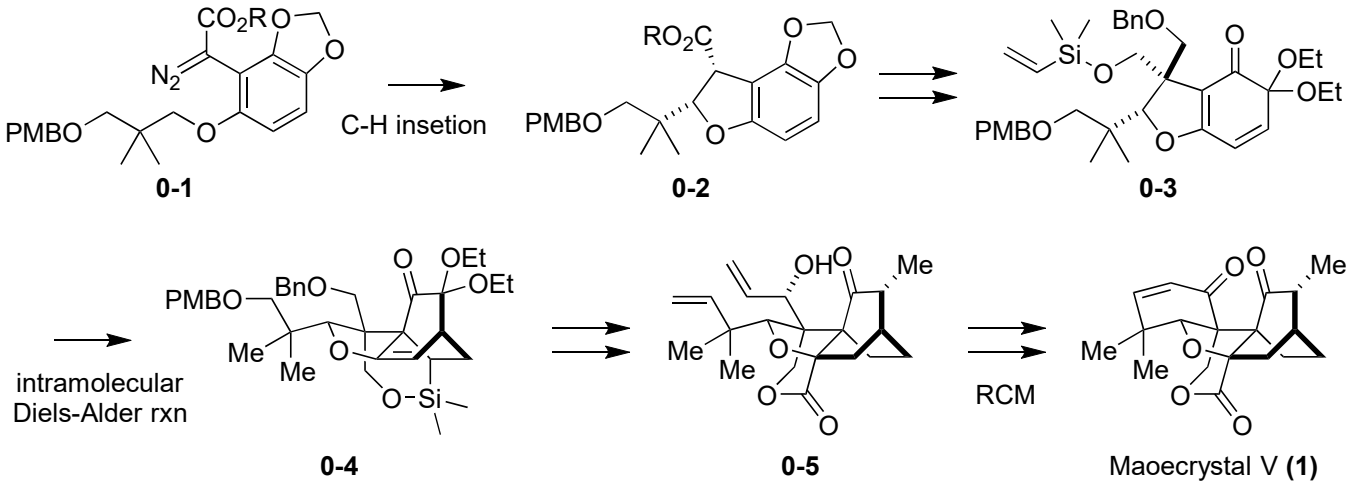
Maoecrystal V was thought to have cytotoxicity against HeLa cell,
but it is now found to have no acticity against cancer cell (including HeLa).

Structural Feature

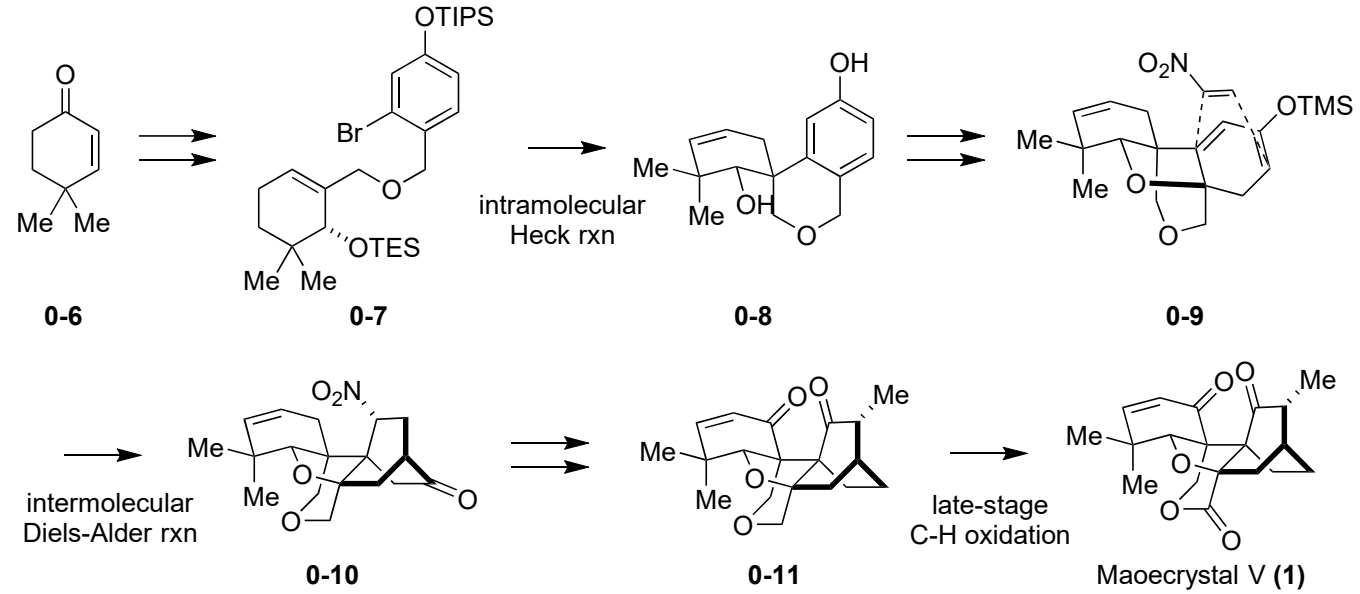
C_{19} diterpenoid with a 6,7-seco-6-nor15(8->9)-abeo-5,8-epoxy-*ent*-kaurane skelton
intricate blend of bicyclo[2,2,2]octan, δ-valerolactone, and cyclohexene subunits with a strained central oxolane ring
6 stereogenic centers including 2 adjacent quaternary center

Total Synthesis

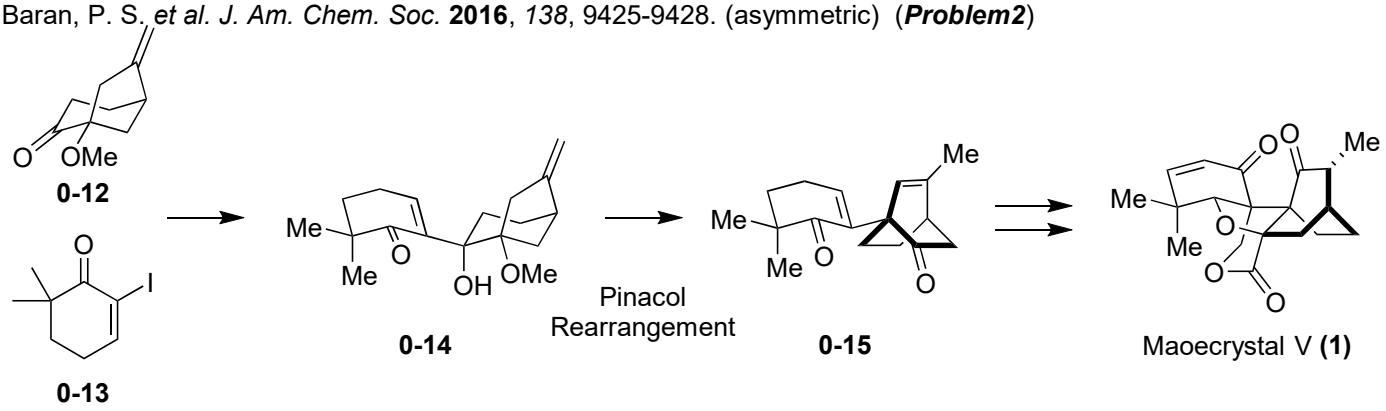
Danishefsky, S. J. *et. al. J. Am. Chem. Soc.* **2012**, *134*, 18860-18867. (racemic)
Yang, Z. *et. al. J. Am. Chem. Soc.* **2010**, *132*, 16745-16746. (racemic)
Yang, Z. *et. al. Chem. Asian J.* **2015**, *10*, 1874-1880. (asymmetric)
For the detail of synthetic study of Maoecrystal V until 2013, see also
-130105_LS_Tomoya_YAMASHITA_Total_Synthesis_of_Maoecrystal_V.pdf
Zakarian, A. *et. al. J. Am. Chem. Soc.* **2013**, *135*, 14552-14555. (racemic)
Zakarian, A. *et. al. J. Am. Chem. Soc.* **2014**, *136*, 17738-17749. (asymmetric)

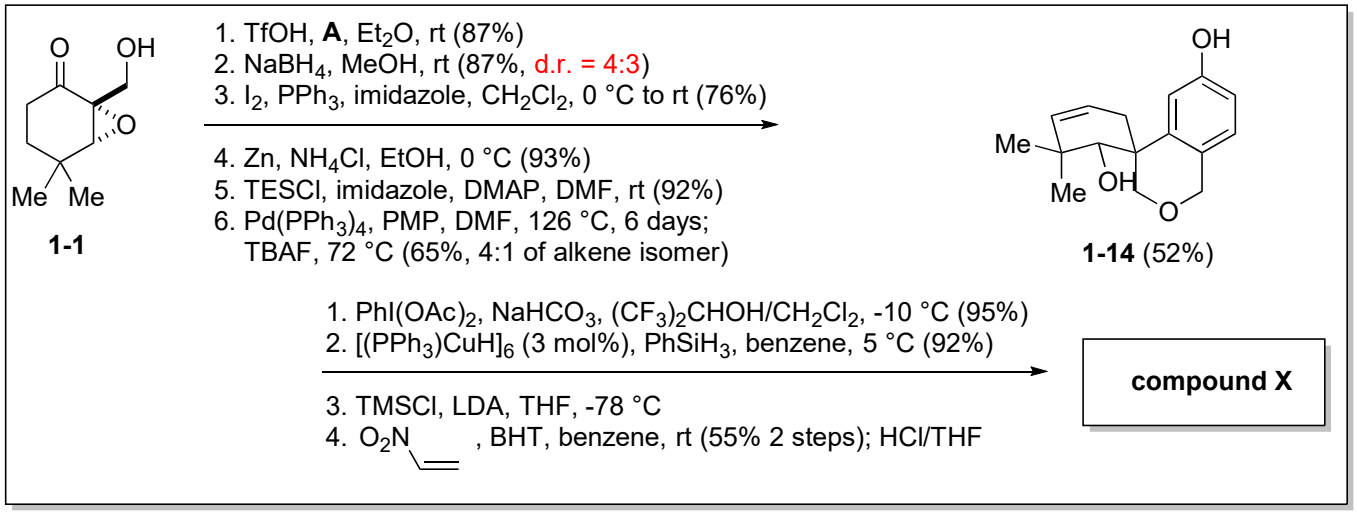


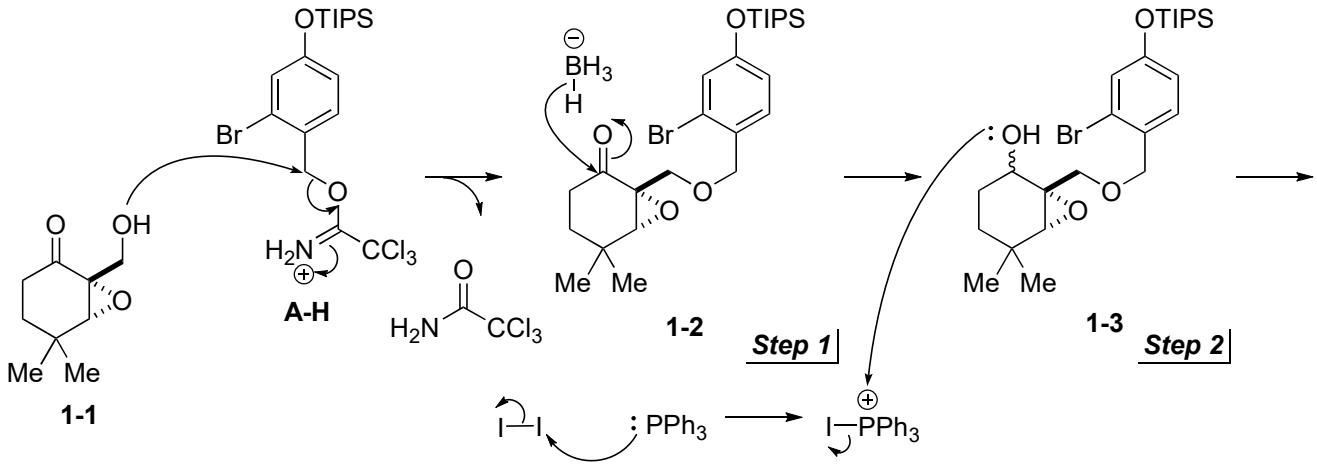
Thomson, R. J. *et. al. J. Am. Chem. Soc.* **2014**, *136*, 17750-17756. (asymmetric) (***Problem1***)

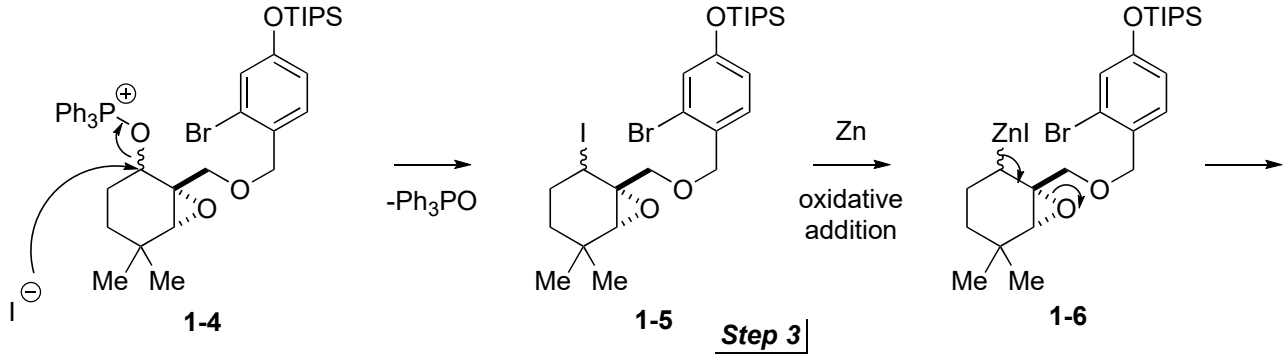


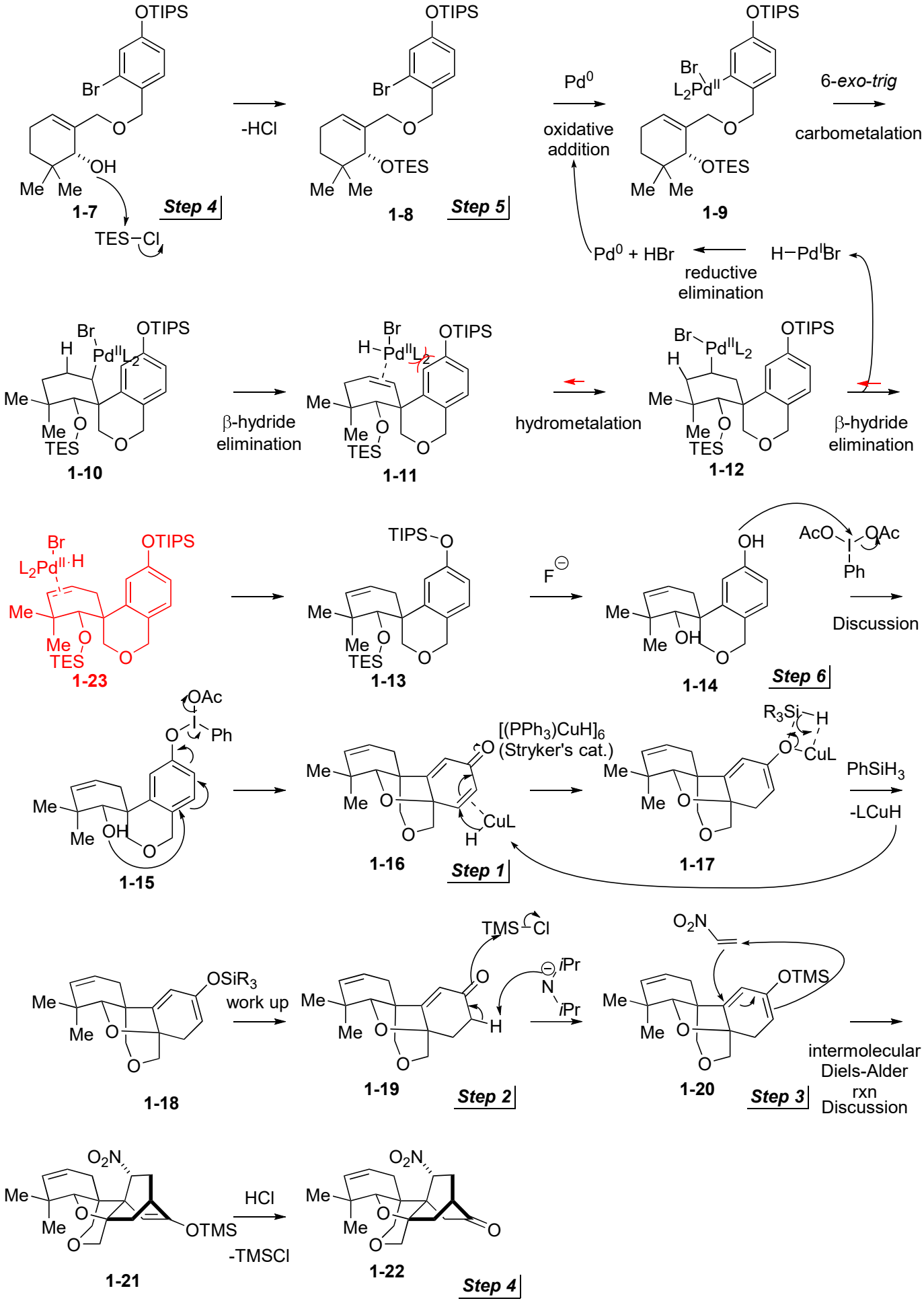
Baran, P. S. *et al. J. Am. Chem. Soc.* **2016**, *138*, 9425-9428. (asymmetric) (***Problem2***)





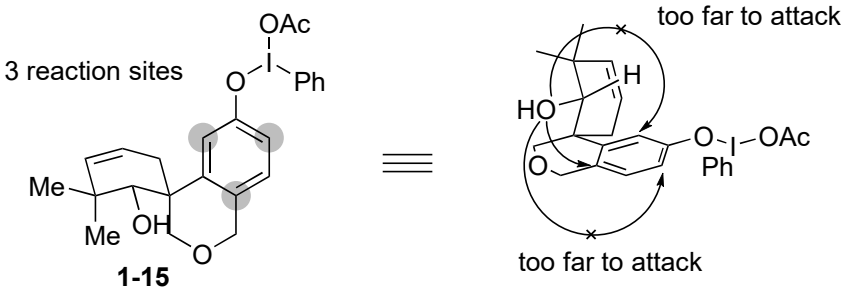





OTIPS
Br
OH
Me Me
1-7
Step 4
TES–Cl
-HCl
OTIPS
Br
OTES
Me Me
1-8
Step 5
Pd0
oxidative addition
OTIPS
Br
L2PdII
OTES
Me Me
1-9
6-exo-trig
carbometalation
Pd0 + HBr
reductive elimination
H–PdIBr
Br
OTIPS
H
PdIIL2
Me
Me O
TES
O
1-10
β-hydride elimination
1-11
hydrometalation
1-12
β-hydride elimination
Br
L2PdII·H
OTIPS
Me
Me O
TES
O
1-23
TIPS–O
F⊖
OH
AcO
OAc
Ph
Discussion
1-13
1-14
Step 6
OAc
O
Ph
Me
Me OH
O
1-15
[(PPh3)CuH]6
(Stryker's cat.)
O
CuL
H
1-16
Step 1
R3Si
H
O
CuL
1-17
PhSiH3
-LCuH
OSiR3
work up
1-18
TMS–Cl
O
iPr
N
iPr
H
1-19
Step 2
O2N
OTMS
1-20
Step 3
intermolecular Diels-Alder rxn Discussion
HCl
OTMS
-TMSCl
1-21
1-22
Step 4

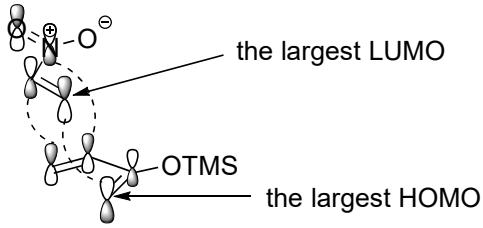
Discussion

1. Dearomatization



2. Diels-Alder reaction

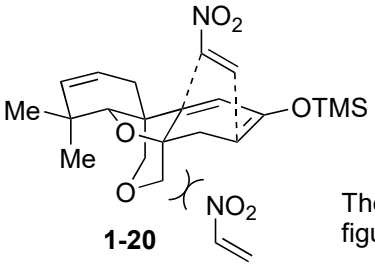
regioselectivity and *exo/endo* selectivity



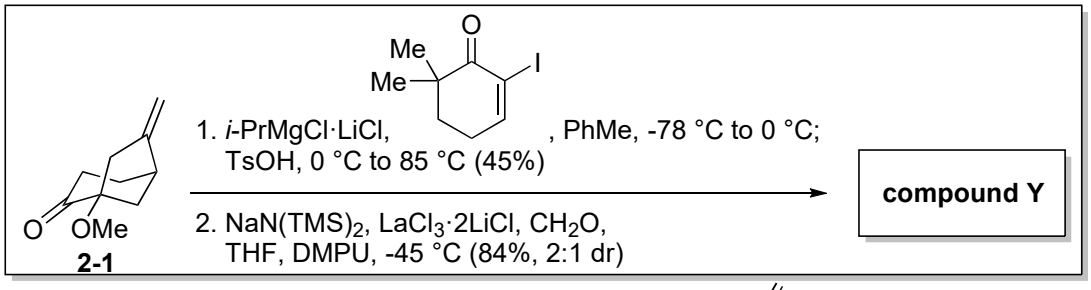
For both orbital and steric reasons, regioselectivity is determined.

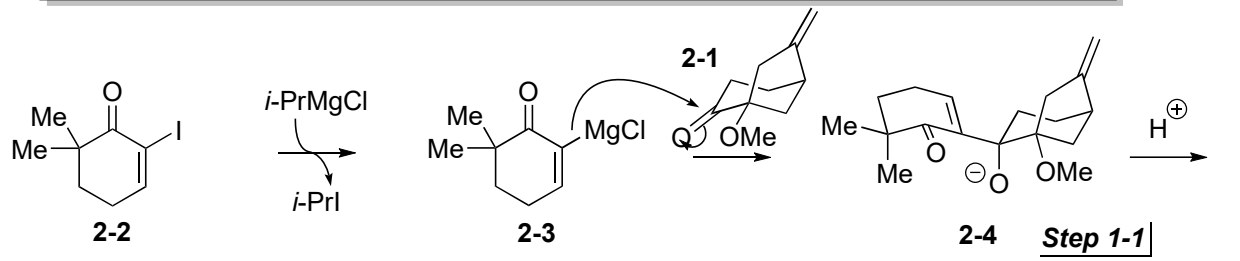
Orbital interaction favors *endo* compound.

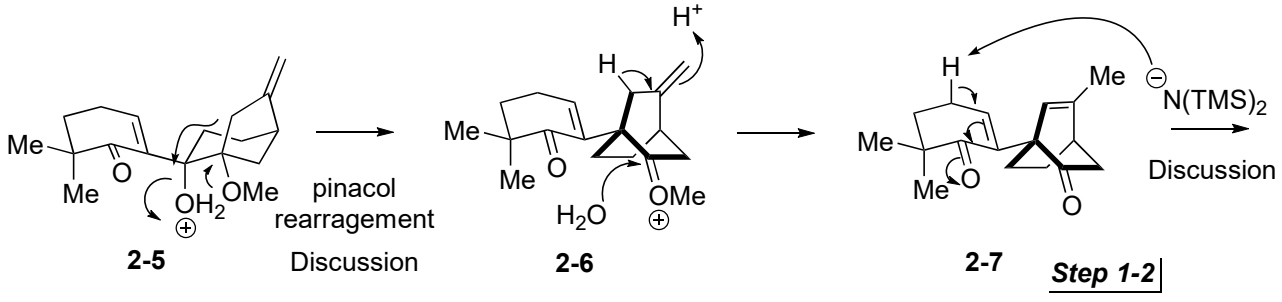
faceselectivity

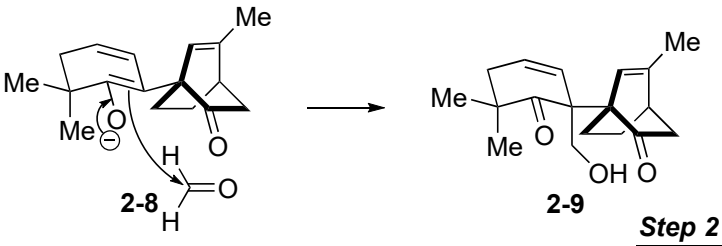


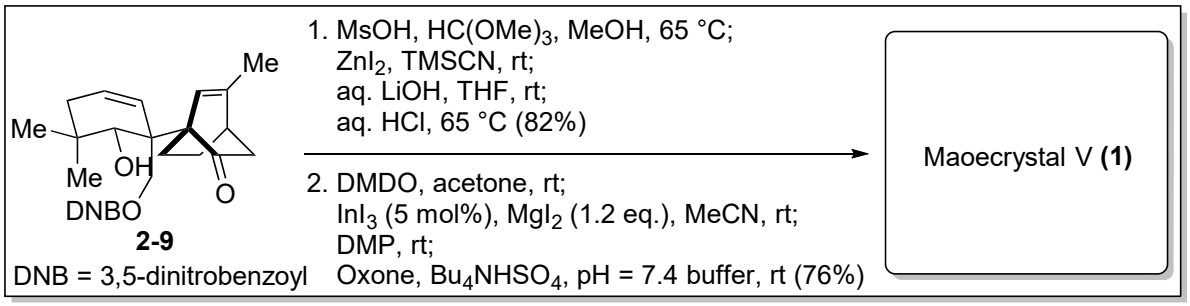
The comformation of the dienophile is highly fixed, and under side in the left figure is masked by THP ring.

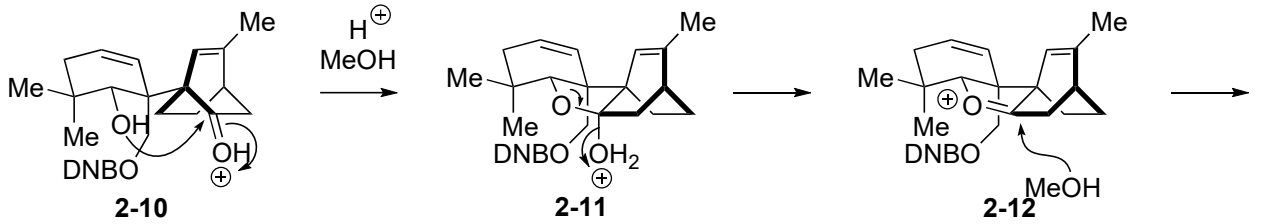

1. i-PrMgCl·LiCl, , PhMe, -78 °C to 0 °C;
TsOH, 0 °C to 85 °C (45%)
2. NaN(TMS)2, LaCl3·2LiCl, CH2O,
THF, DMPU, -45 °C (84%, 2:1 dr)
compound Y
2-1

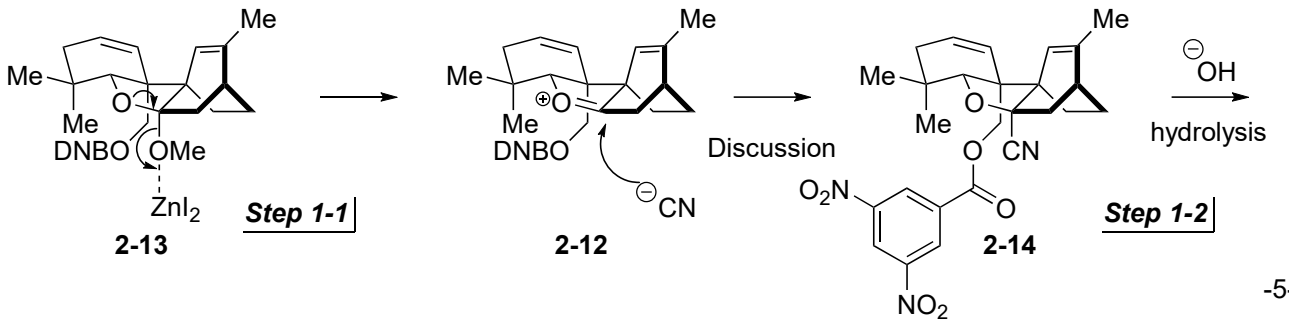

2-1
i-PrMgCl
i-PrI
2-2
2-3
2-4
Step 1-1

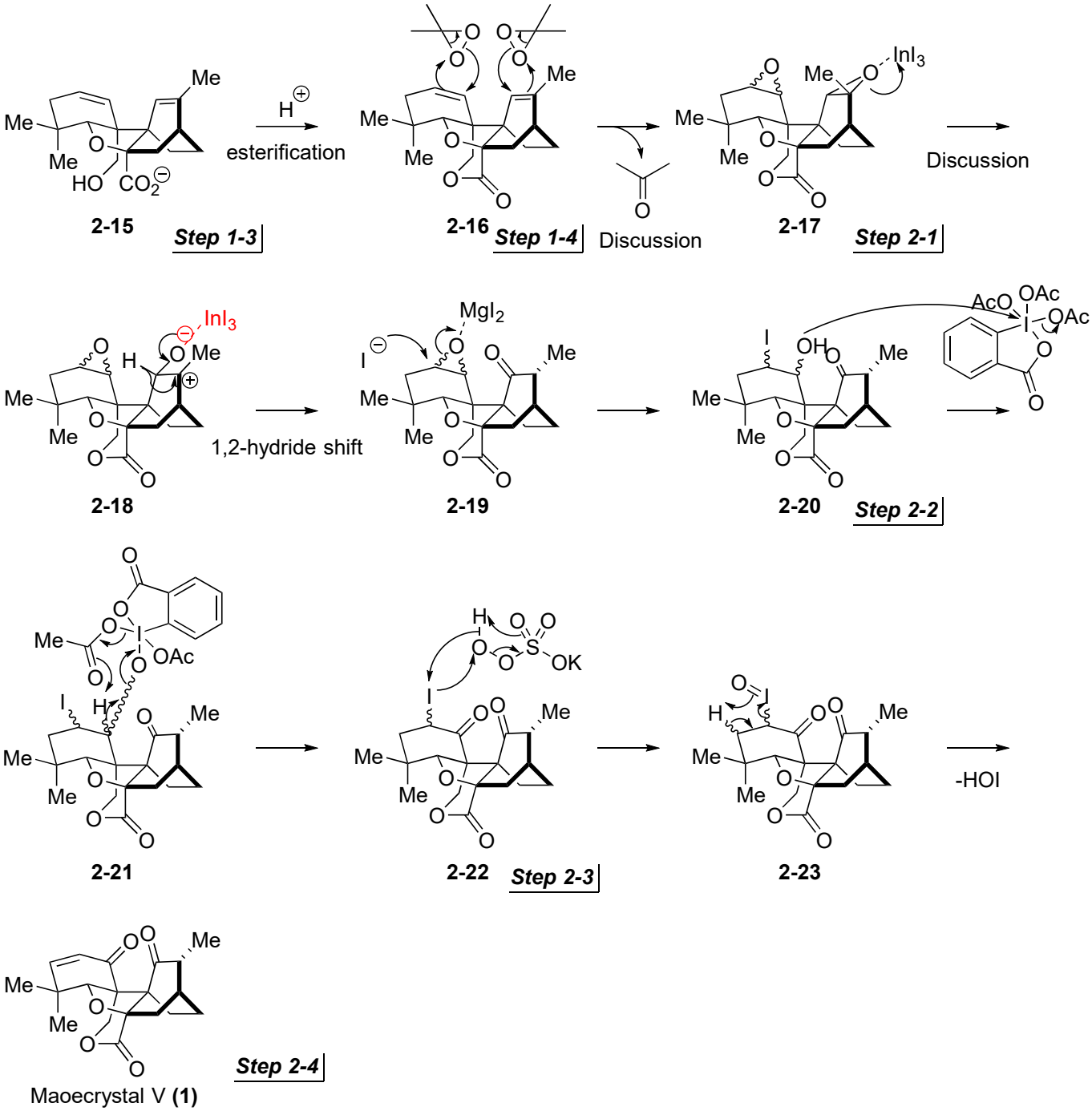

pinacol
rearragement
Discussion
2-5
2-6
2-7
Step 1-2
N(TMS)2
Discussion


2-8
2-9
Step 2


1. MsOH, HC(OMe)3, MeOH, 65 °C;
ZnI2, TMSCN, rt;
aq. LiOH, THF, rt;
aq. HCl, 65 °C (82%)
2. DMDO, acetone, rt;
InI3 (5 mol%), MgI2 (1.2 eq.), MeCN, rt;
DMP, rt;
Oxone, Bu4NHSO4, pH = 7.4 buffer, rt (76%)
Maoecrystal V (1)
2-9
DNB = 3,5-dinitrobenzoyl

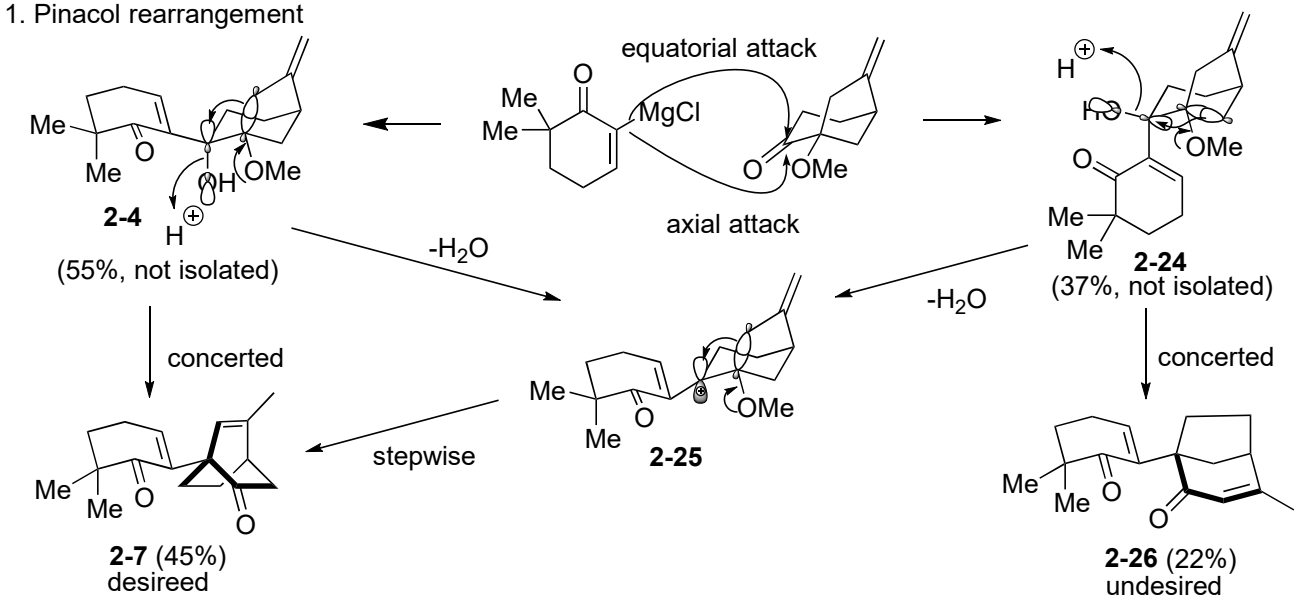

MeOH
2-10
2-11
2-12


2-13
Step 1-1
2-12
Discussion
2-14
Step 1-2
hydrolysis

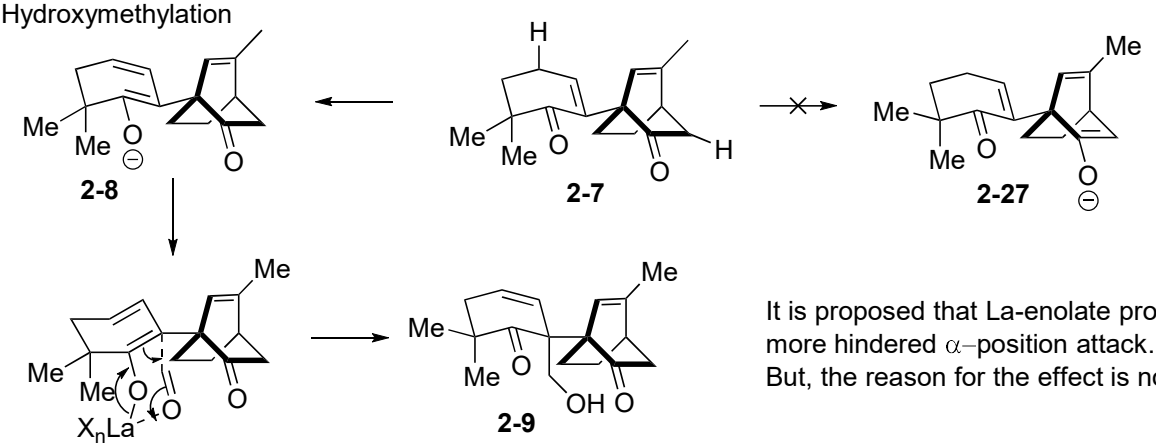


Discussion

1. Pinacol rearrangement

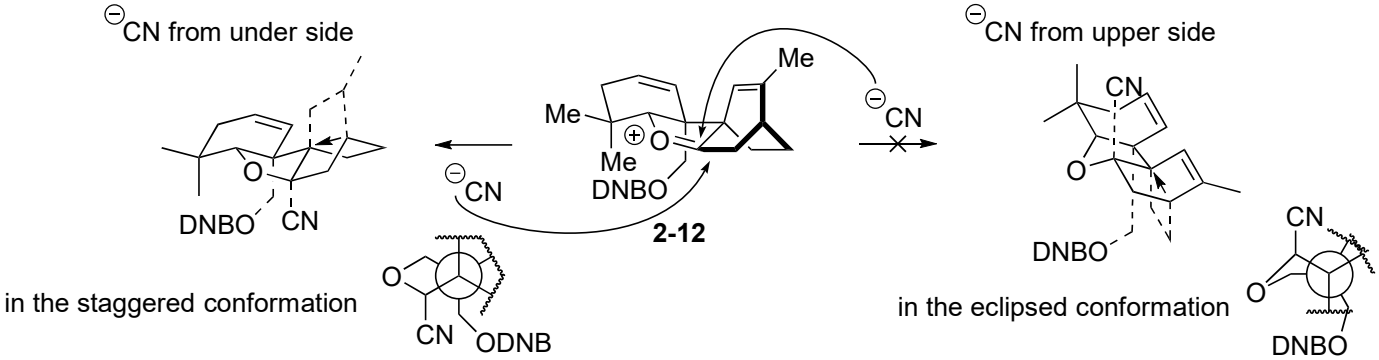


2. Hydroxymethylation

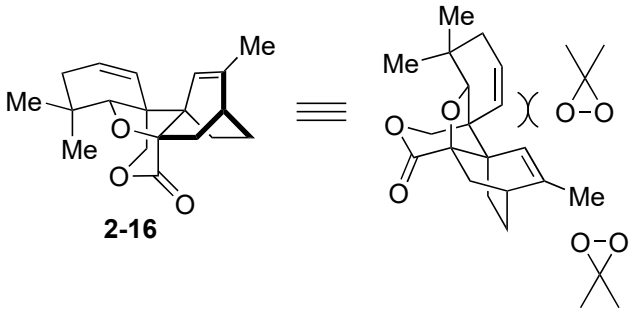


It is proposed that La-enolate promotes more hindered α–position attack.
But, the reason for the effect is not known.

3. Cyanation

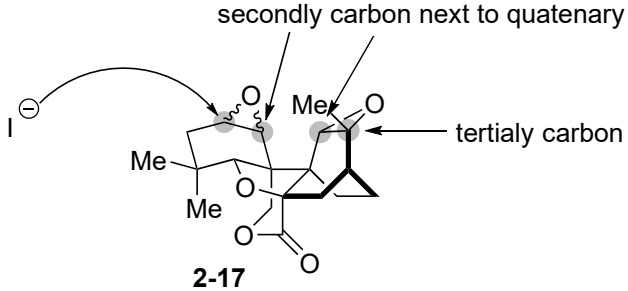


4. Epoxidation



upper side is masked by axial oxigen and cyclohexene.

5. Iodination
4 position for iodide to attack



Iodide can't atack to epoxide in bicyclooctane, so opening of epoxide proceed.