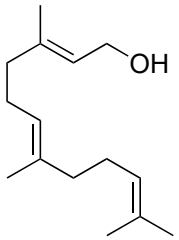
Problem Session (1)

2016/11/12 Takumi Fukuda

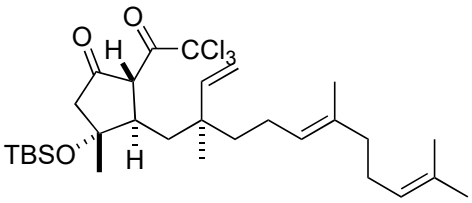
Please provide the reasonable reaction mechanisms, explain the stereoselectivities and fill in the blank.



farnesol (**1**)

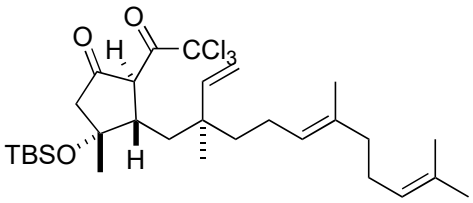
1. **A** (1.5 eq.), Et_2Zn (2.0 eq.), CH_2I_2 (4.0 eq.)
   CH_2Cl_2, 0 °C to 25 °C, 5 h (89 %)
2. I_2 (1.1 eq.), PPh_3 (1.1 eq.), imidazole (1.8 eq.),
   CH_2Cl_2, 0 °C, 1 h (75 %)
3. * *t*-BuLi (2.7 eq.), pentane/Et_2O, -78 °C, 2.5 h;
   CuI (0.53 eq.), Me_2S (2.1 eq.), -78 °C, 15 min;
   B (1.0 eq.), -78 °C to -40 °C, 4 h;
   Cl_3CCOCl (3.3 eq.), -78 °C to -40 °C, 2 h (60 %, **2**:**2'** = 3:1)

* 1.3 eq. of substrate was used.



2

+



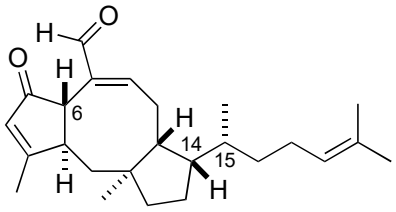
2'

2

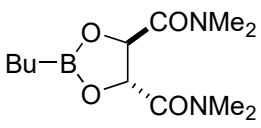
1. DIBAL-H (1.0 eq.), *n*-BuLi (1.0 eq.), Et_2O, toluene
   -78 °C to -40 °C, 2 h; AcOH (3.0 eq.);
   Ac_2O (20 eq.), pyridine (20 eq.), DMAP (0.4 eq.)
   25 °C, 1 h (80 %)
2. Et_3B (1.25 eq.), $(TMS)_3SiH$ (1.0 eq.)
   C (25 mol%), air, cyclopentane (0.009 M)
   -10 °C, 12 h (56 %, dr at C14 = 5.3:1,dr at C15 = 3.4:1)

3

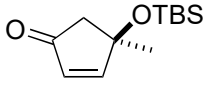
1. Me_3SI (24 eq.), *n*-BuLi (6.0 eq.)
   THF, 0 °C, 10 min (60 %)
2. Li-naphthalenide (40 eq.)
   THF, -78 °C, 20 min (77 %)
3. $(COCl)_2$ (10 eq.), DMSO (15 eq.)
   Et_3N (20 eq.)
   CH_2Cl_2, -78 °C to 0 °C, 3 h (78 %)
4. *p*-TsOH (3.0 eq.)
   CH_2Cl_2/*t*-BuOH, 40 °C, 54 h (59 %)



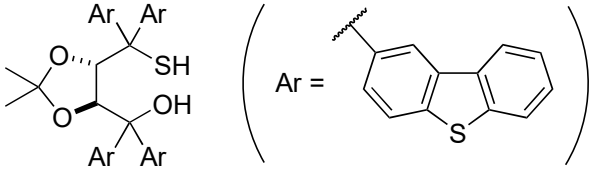
(-)-6-epi-ophiobolin N (**4**)



A



B



C

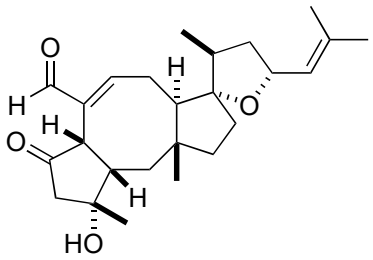
Problem Session (1) Answer

2016/11/12 Takumi Fukuda

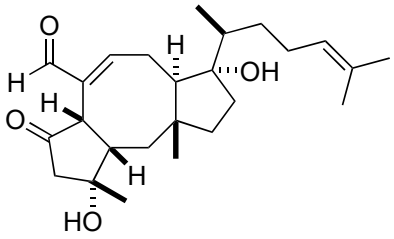
Topic: A total synthesis of (–)-6-*epi*-ophiobolin N

Brill, Z. G., Grover, H. K., Maimone, T. J. *Science* **2016**, *352*, 1078-1082.

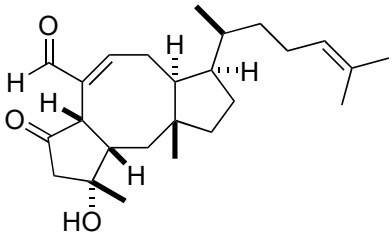
0. Introduction



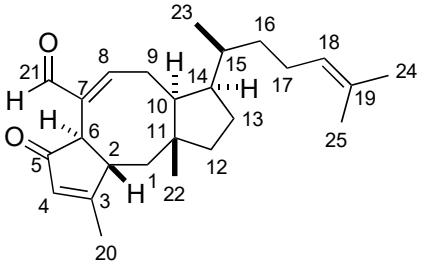
ophiobolin A (**0-1**)



ophiobolin B (**0-2**)



ophiobolin C (**0-3**)



6-*epi*-ophiobolin N (**4**)

Isolation

6-*epi*-ophiobolin N was first isolated from the extracts of the fungus, Emericella variecolor GF10, which was separated from marine sediment.

Wei, H. *et al*. *Tetrahedron* **2004**, *60*, 6015-6019.

Pharmacological activity

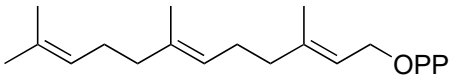
cytotoxic activity against multiple cancer cell lines.

Stractural feature

C_{25} sesterterpene
[5-8-5] tricyclicring system
6 stereocenters

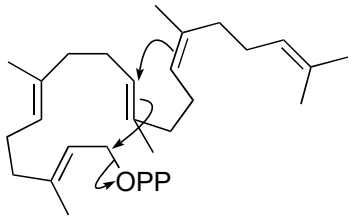
Biosynthesis

Narita, K. *et al*. *Org. Lett.* **2016**, *18*, 1980-1983.



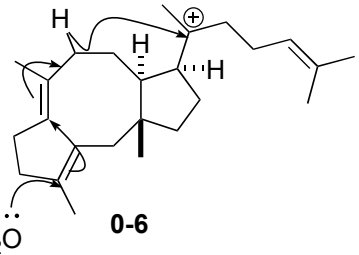
FPP (**0-4**)

(PP = diphosphate)



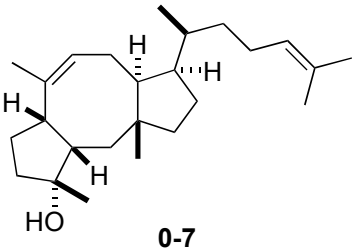
GFPP (**0-5**)

cationic
poly-cyclization

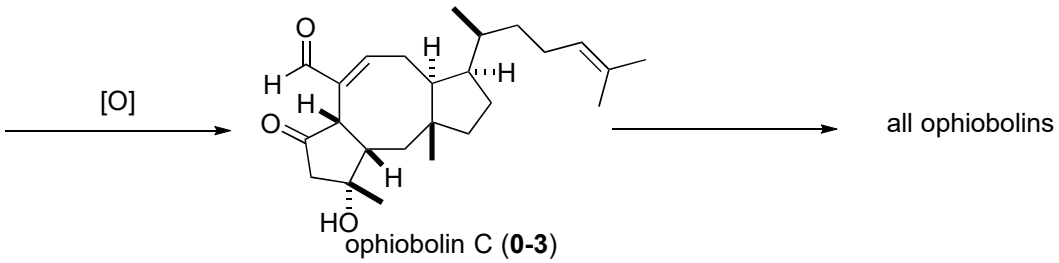


0-6

cyclization
hydride-transfer

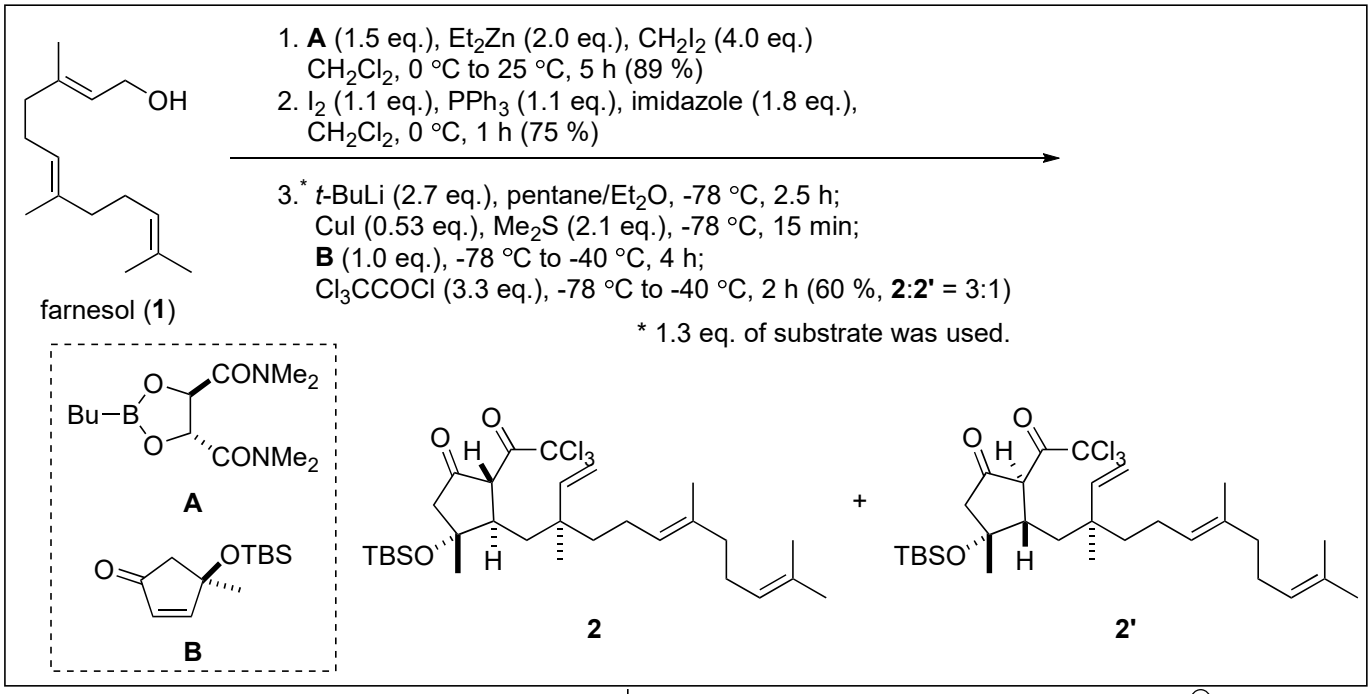


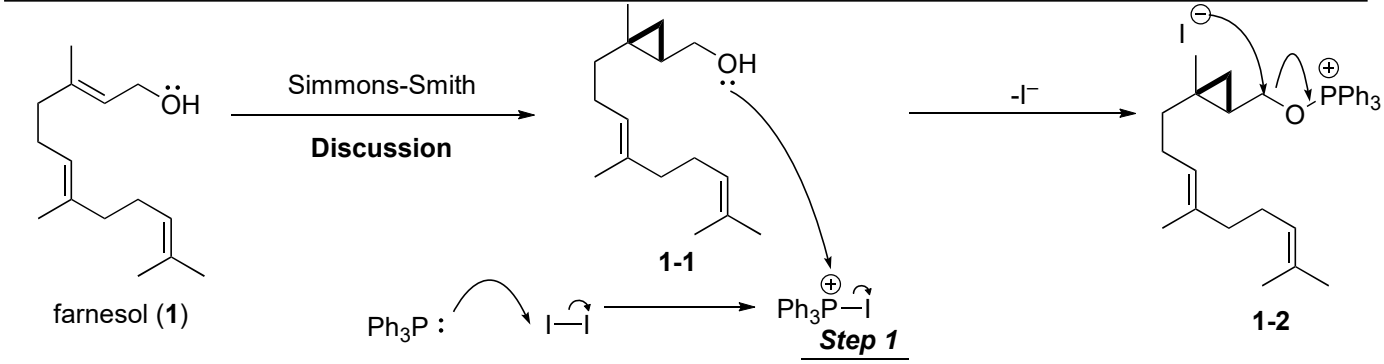
0-7

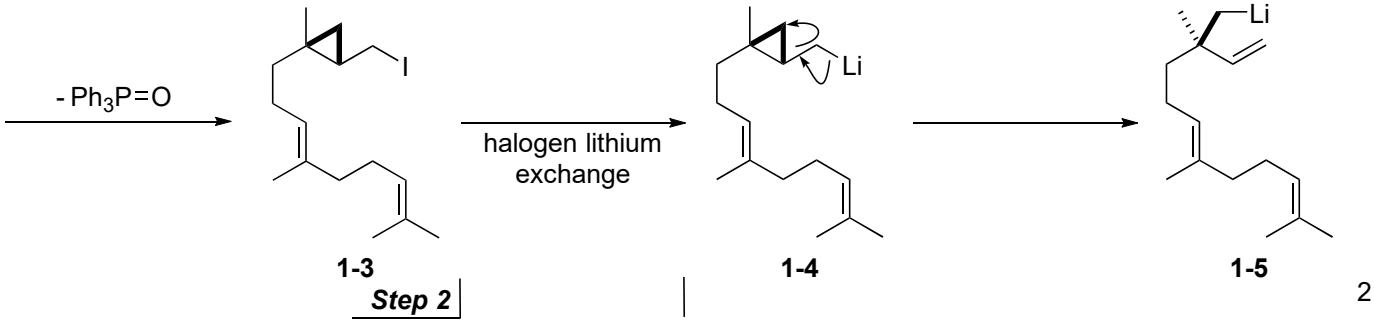


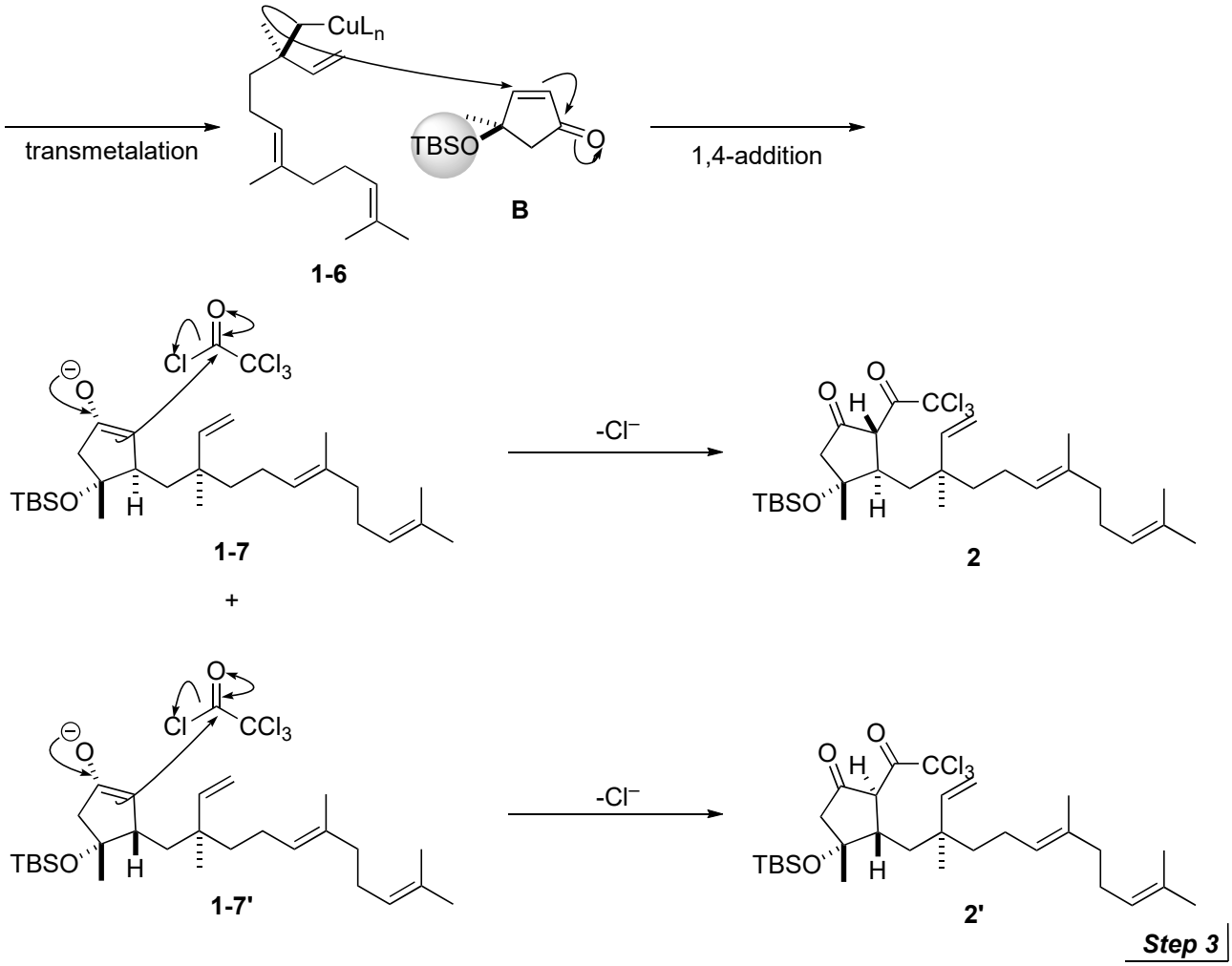
Total synthesis:
ophiobolin A: Tsuna, K., Noguchi, N. Nakada, M. *Chem. Eur. J*. **2013**, *19*, 5476-5486.
ophiobolin C: Rowley, M., Tsukamoto, M. Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735-2737.
6-*epi*-ophiobolin N: Brill, Z. G., Grover, H. K., Maimone, T. J. *Science* **2016**, *352*, 1078-1082. (Problem)

1-1. Reaction mechanism



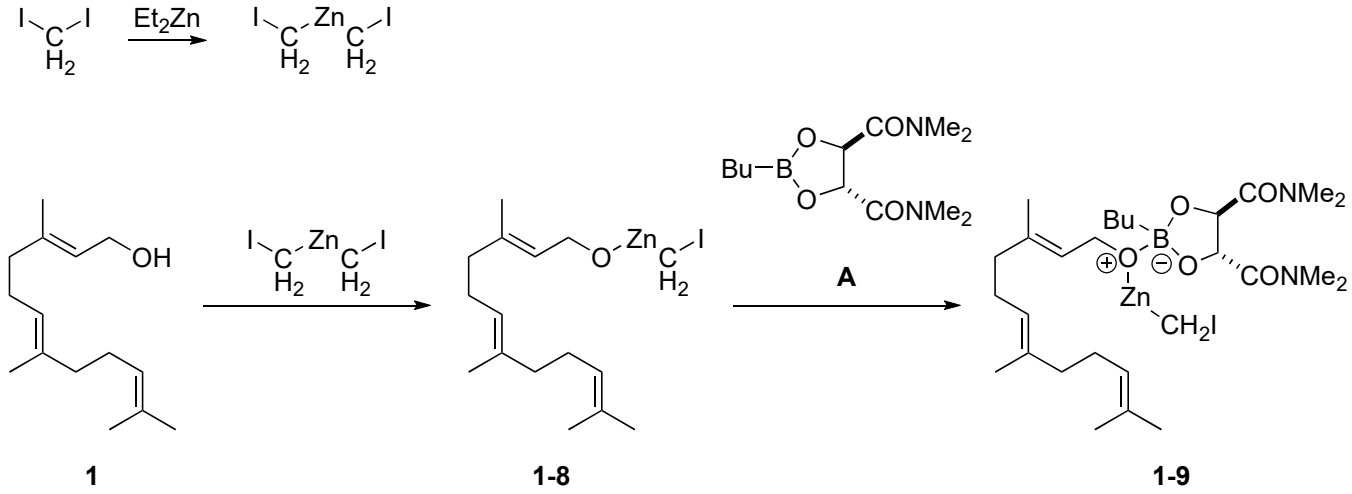


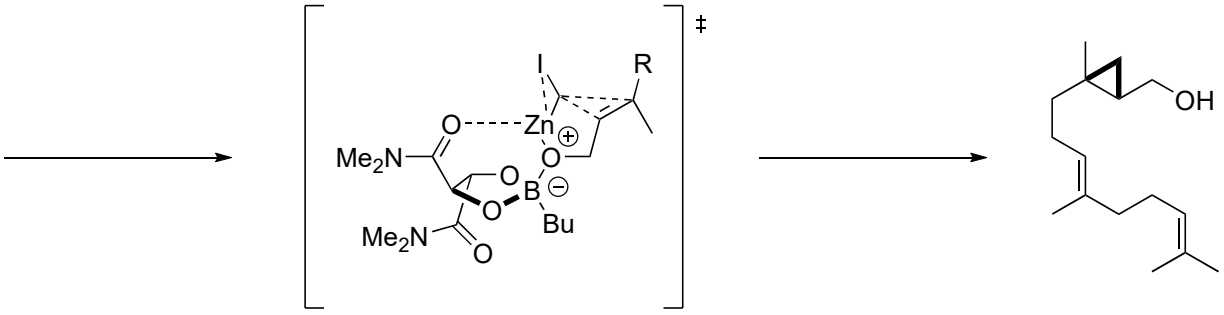




1-2. Discussion

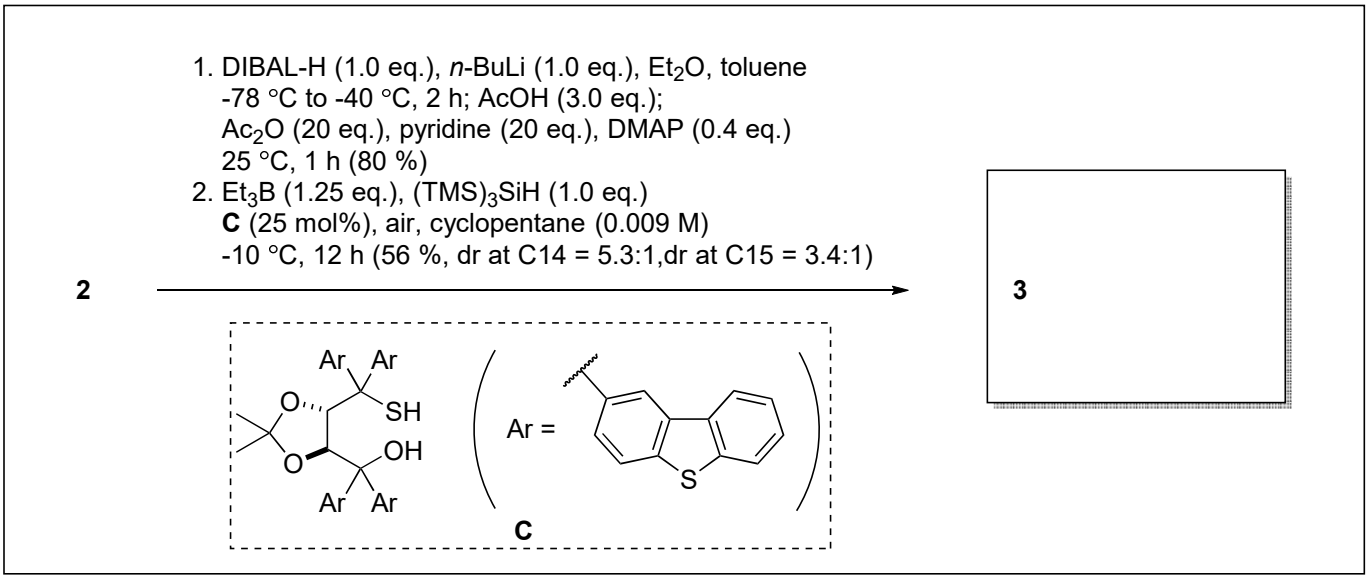
1-2-1. Simmons-Smith Reaction (Charette Asymmetric Cyclopropanation)

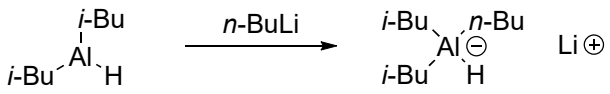


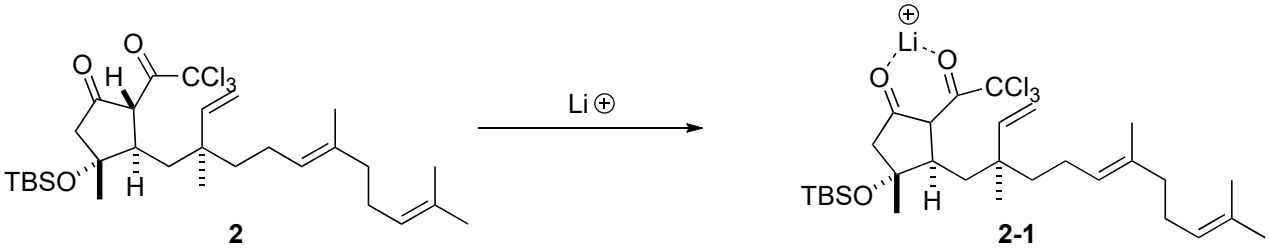


TS-1-1 **1-1**

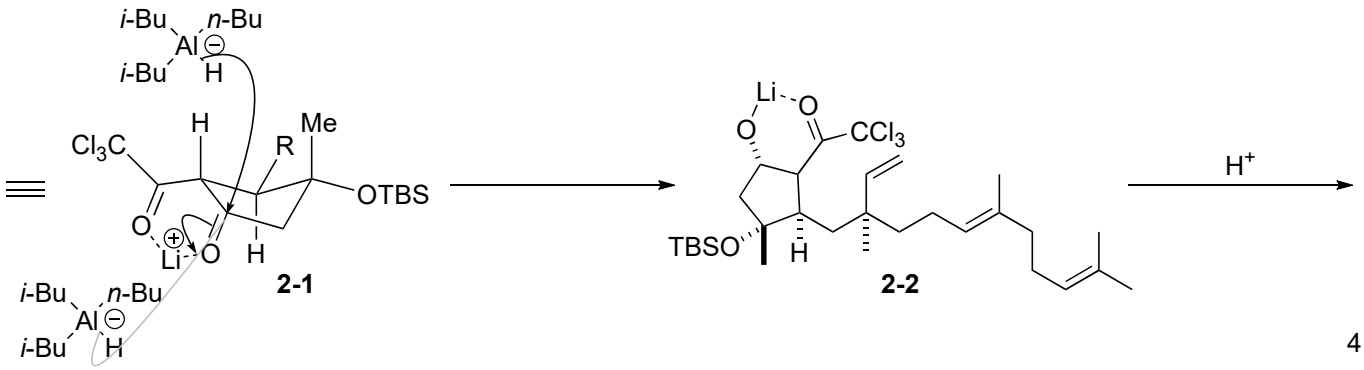
2-1. Reaction mechanism



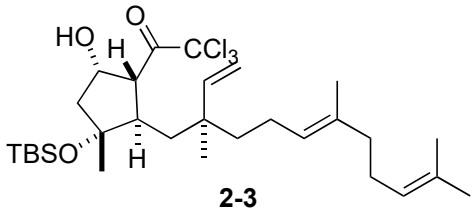




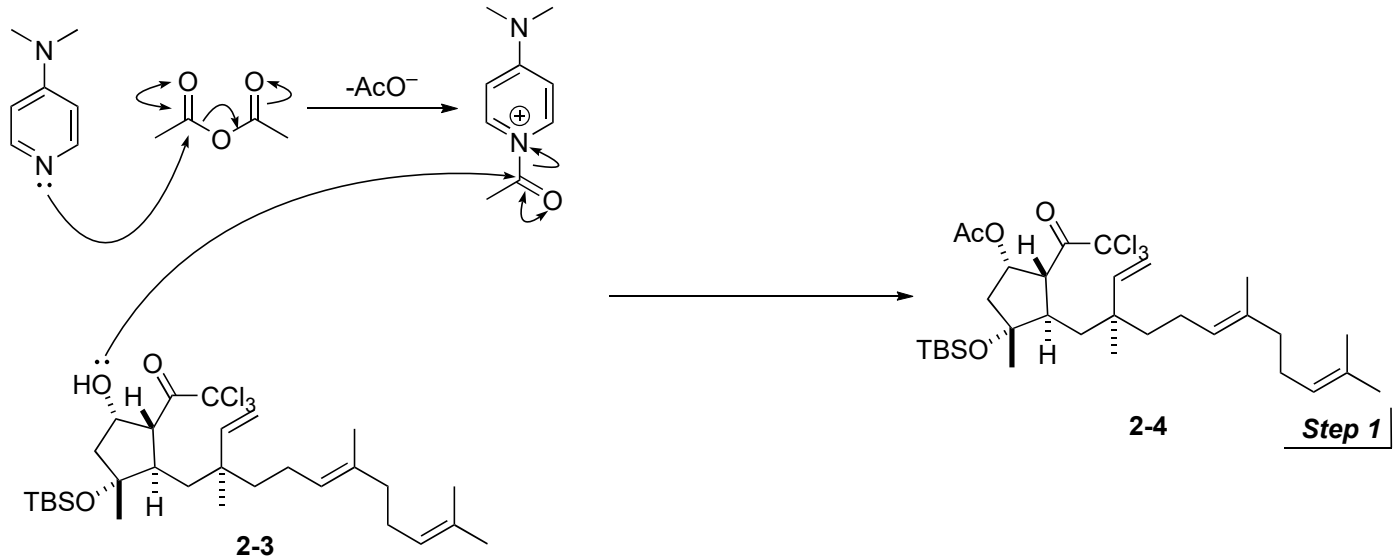
2 **2-1**



2-1 **2-2**



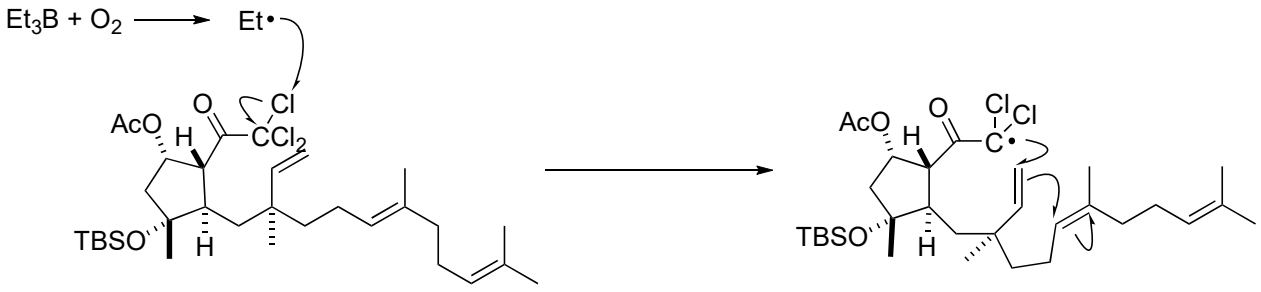
2-3



2-4

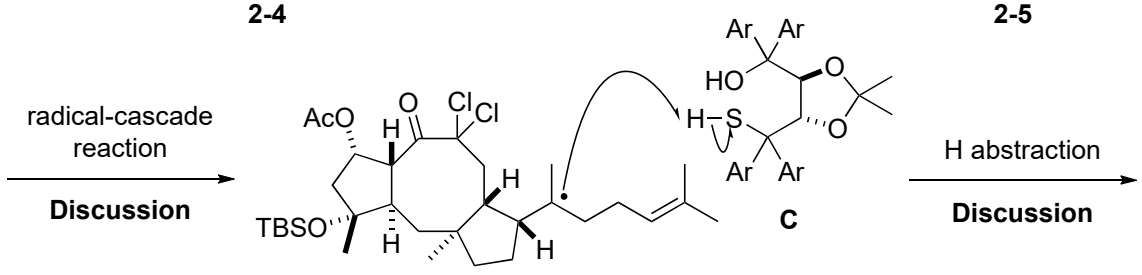
Step 1

2-3



2-4

2-5



radical-cascade reaction

Discussion

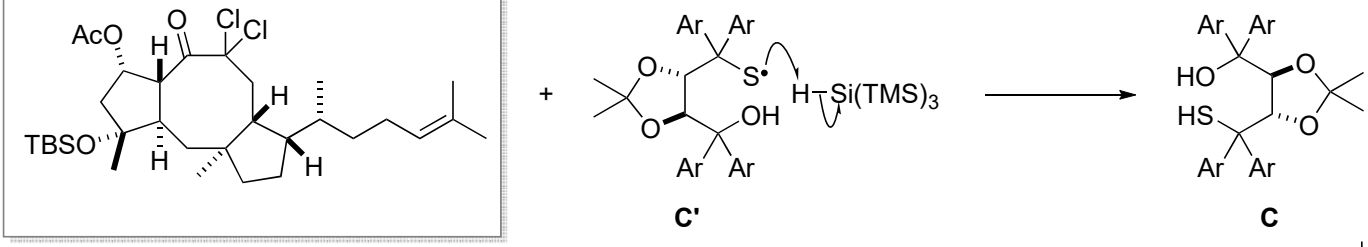
2-6

C

H abstraction

Discussion

3



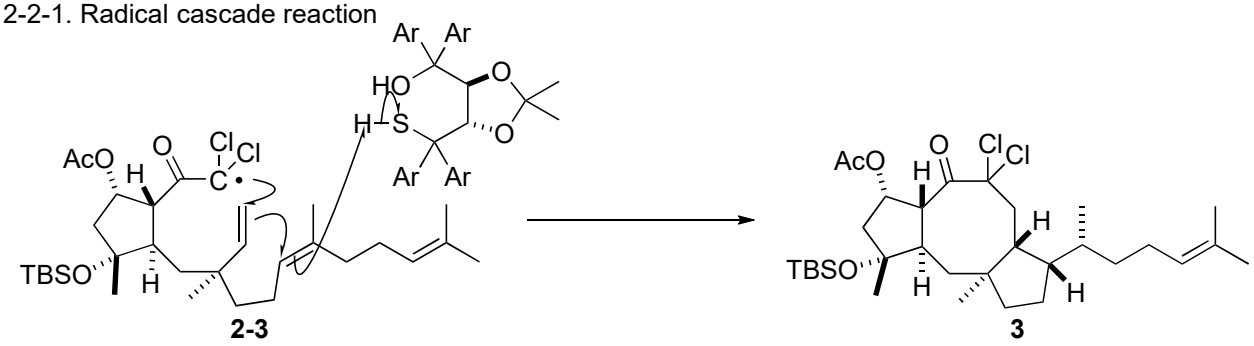
C'

C

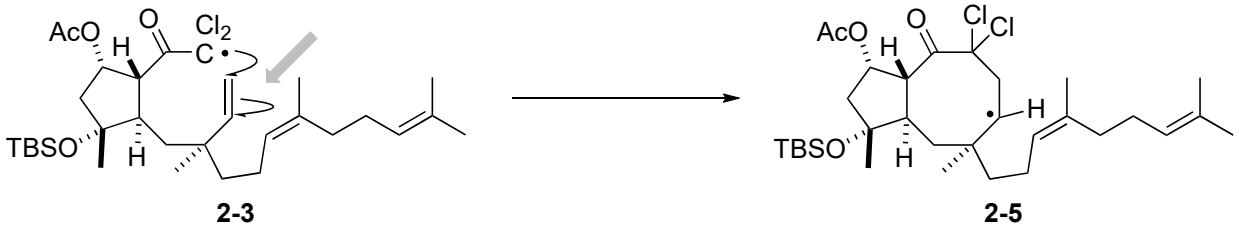
Step 2

2-2. Discussion

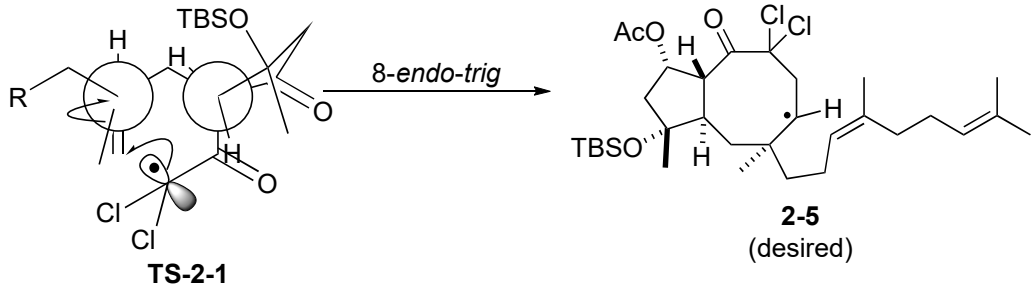
2-2-1. Radical cascade reaction



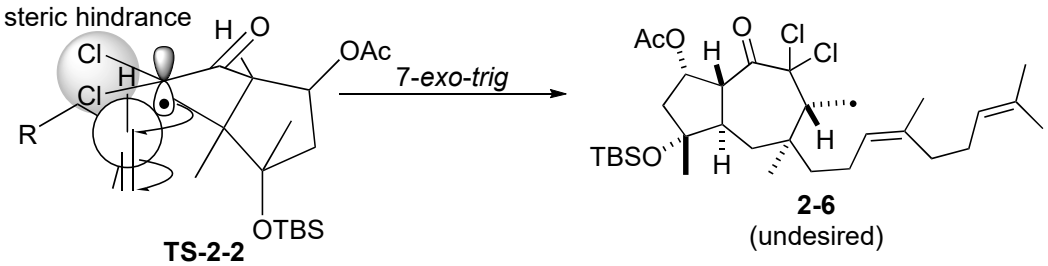
1st step: 7-*exo* or 8-*endo*



The conformation is fixed due to the 1,3-allylic strain.

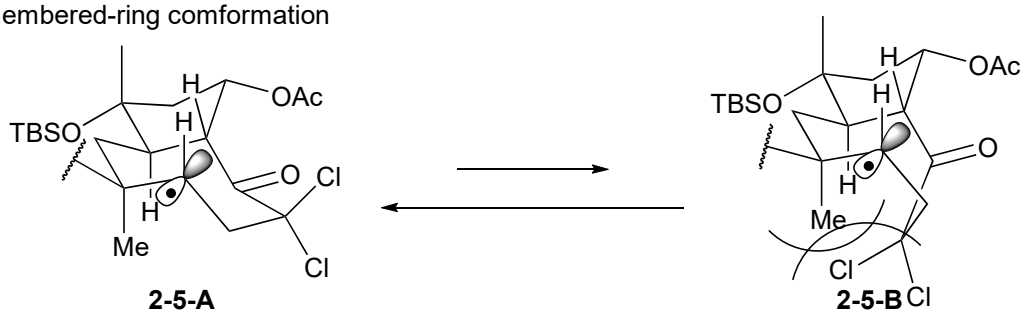


minimizing the 1,3-allylic strain.



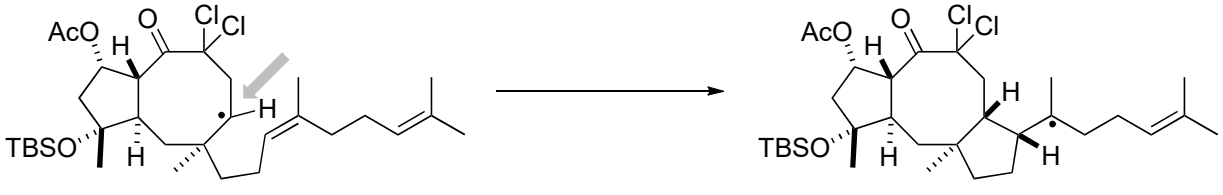
minimizing the 1,3-allylic strain.

8-membered-ring comformation

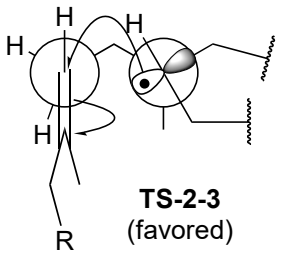


2nd step: 5-*exo* or 6-*endo* → kinetic control

The conformation is fixed due to the 1,3-allylic strain.

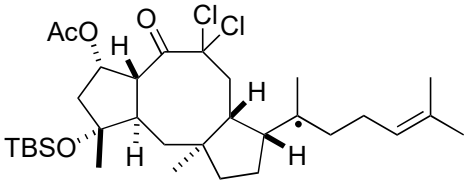


2-5 **2-7**



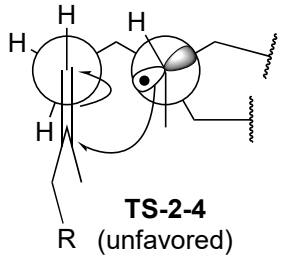
TS-2-3
(favored)

5-*exo-trig*



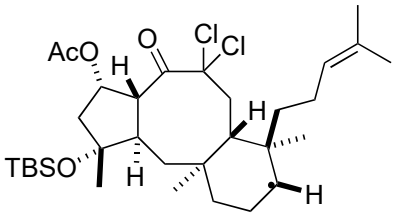
2-7 kinetically favored
(desired)

minimizing the 1,3-allylic strain.



TS-2-4
(unfavored)

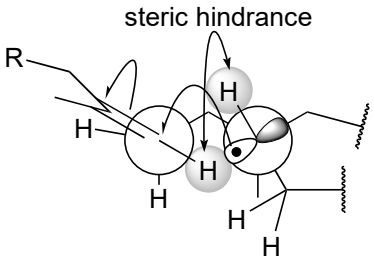
6-*endo-trig*



2-8 kinetically unfavored
(undesired)

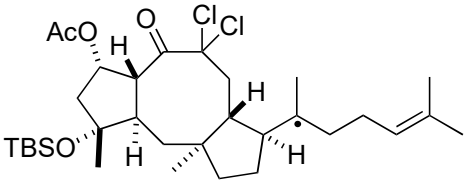
minimizing the 1,3-allylic strain.

the angle of the radical attack on the alkene is unfavored.

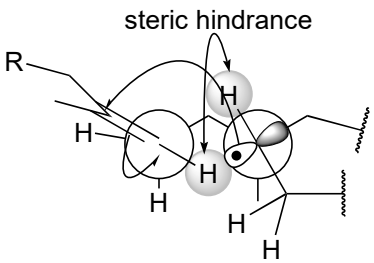


TS-2-5
(unfavored)

5-*exo-trig*

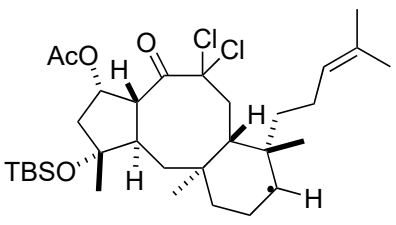


2-7' kinetically unfavored
(undesired)



TS-2-6
(unfavored)

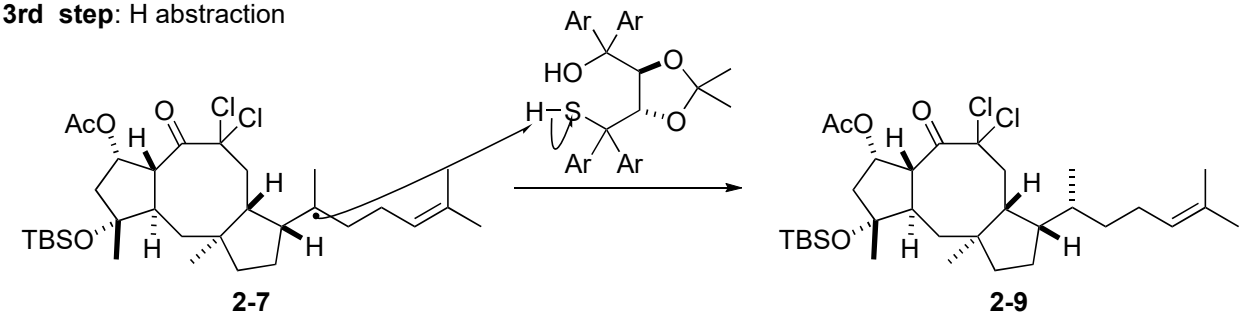
6-*endo-trig*



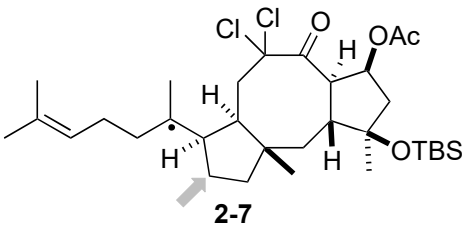
2-8' kinetically unfavored
(undesired)

The distance between the radical and one terminus of the olefinic bond is too far.

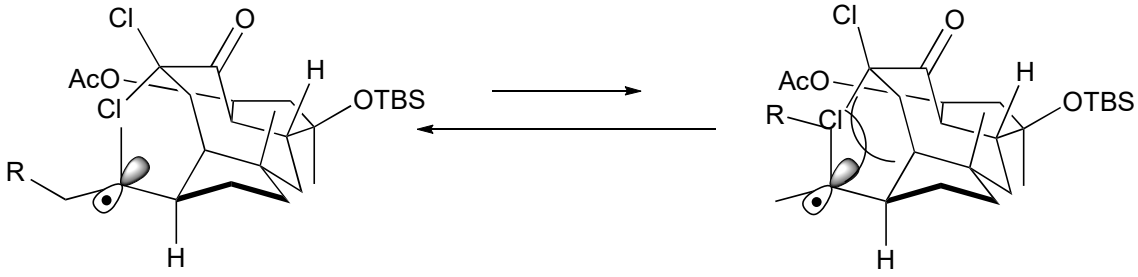
3rd step: H abstraction



2-7



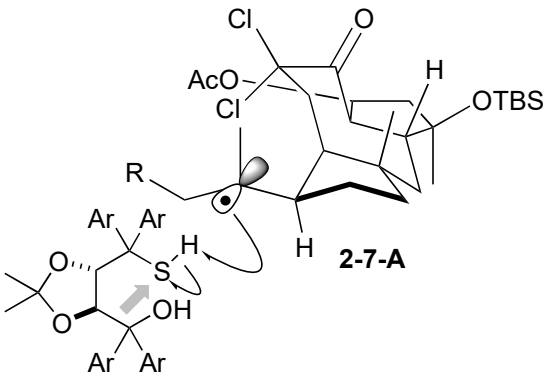
2-7



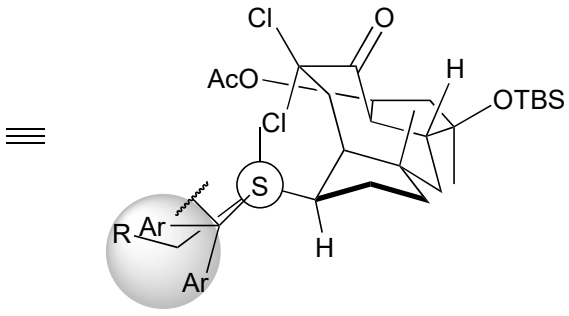
2-7-A
(more stable)

2-7-B

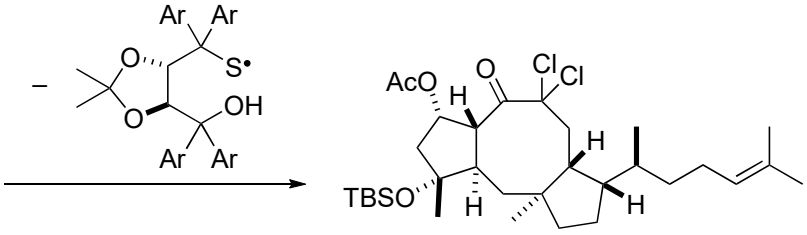
H abstraction via **2-7-A**



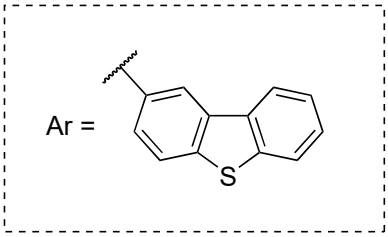
2-7-A



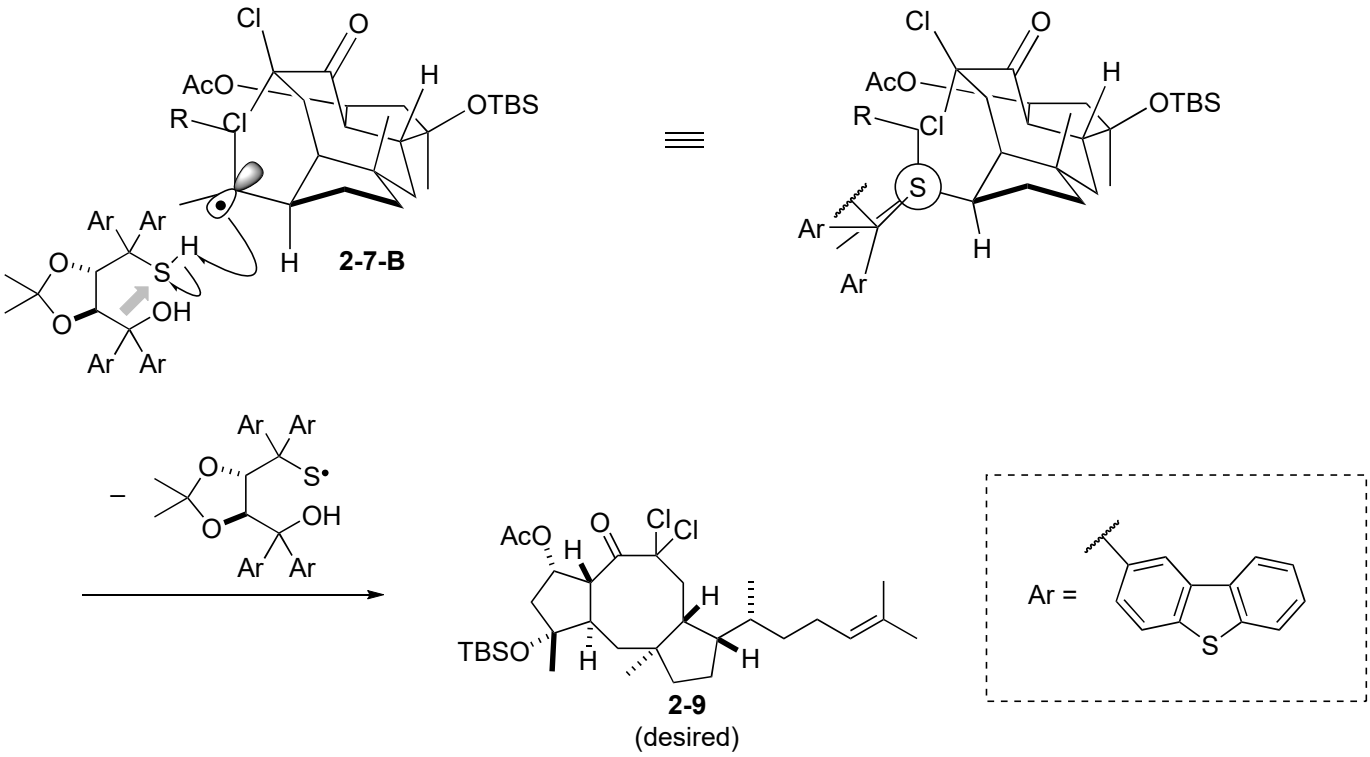
steric hindrance



2-9'
(undesired)



H abstraction via **2-7-B**



Less stable conformer reacts more quickly.

2-2-2. Polarity-reversal catalysis of H abstraction reaction Roberts, B. P. *Chem. Soc. Rev*. **1999,** 28, 25-35.

uncatalysed reaction

$$RCH_2\bullet + H{-}Si(TMS)_3 \xrightarrow[\text{slow}]{3.8 \times 10^5\ M^{-1}s^{-1}} RCH_3 + \bullet Si(TMS)_3$$

This H abstraction from a tris(trimethylsilyl)silane by an alkyl radical does not benefit from favorable polar effects in transition state, because both the silyl radical and the alkyl radical are nucleophilic.

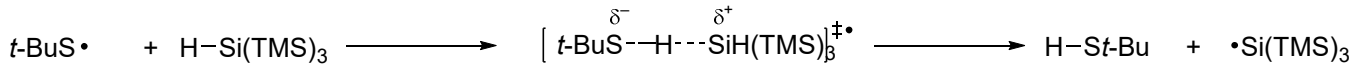
catalytic cycle

$$RCH_2\bullet + H{-}S\textit{t}\text{-}Bu \xrightarrow[\text{fast}]{8.0 \times 10^6\ M^{-1}s^{-1}} RCH_3 + \bullet S\textit{t}\text{-}Bu$$

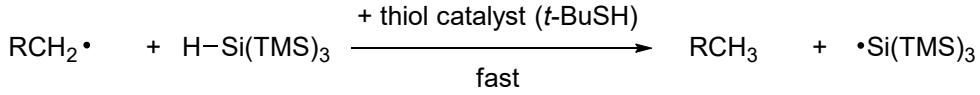
$$\textit{t}\text{-}BuS\bullet + H{-}Si(TMS)_3 \xrightarrow[\text{fast}]{} H{-}S\textit{t}\text{-}Bu + \bullet Si(TMS)_3$$

The single-step process is replaced by two H abstraction reactions both of which benefit from favorable polar effects.

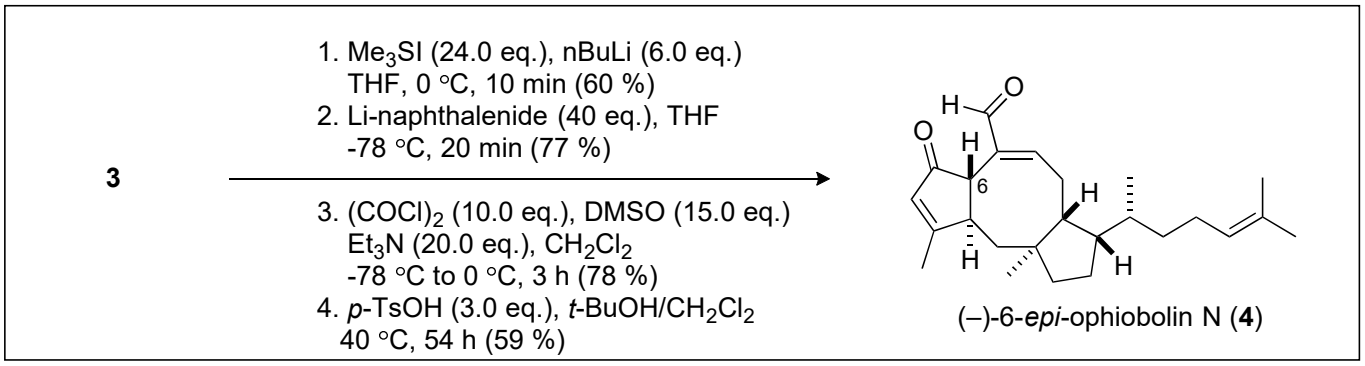
$$RCH_2\bullet + H{-}S\textit{t}\text{-}Bu \longrightarrow \left[\overset{\delta^+}{R}CH_2 \cdots H \cdots \overset{\delta^-}{S}\textit{t}\text{-}Bu \right]^{\ddagger\bullet} \longrightarrow RCH_3 + \bullet S\textit{t}\text{-}Bu$$

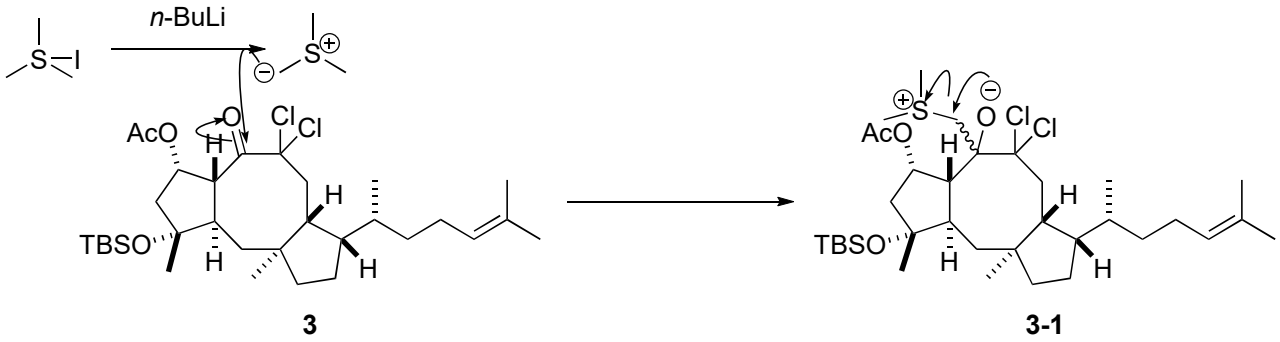


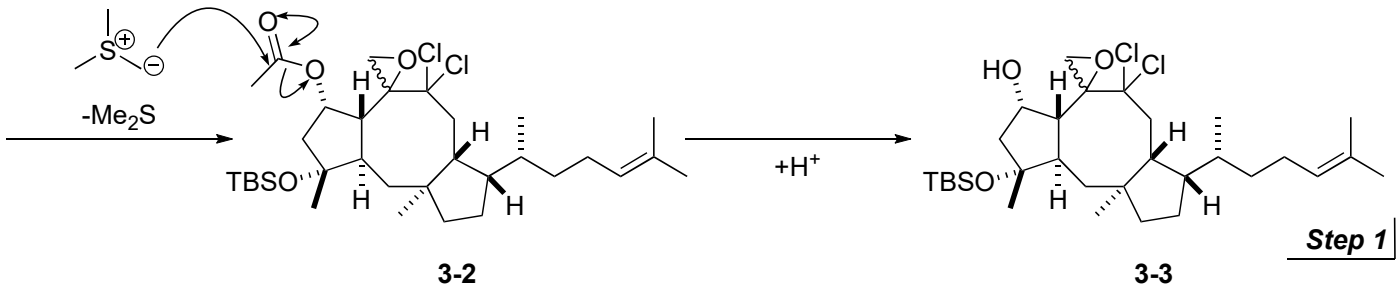
overall reaction

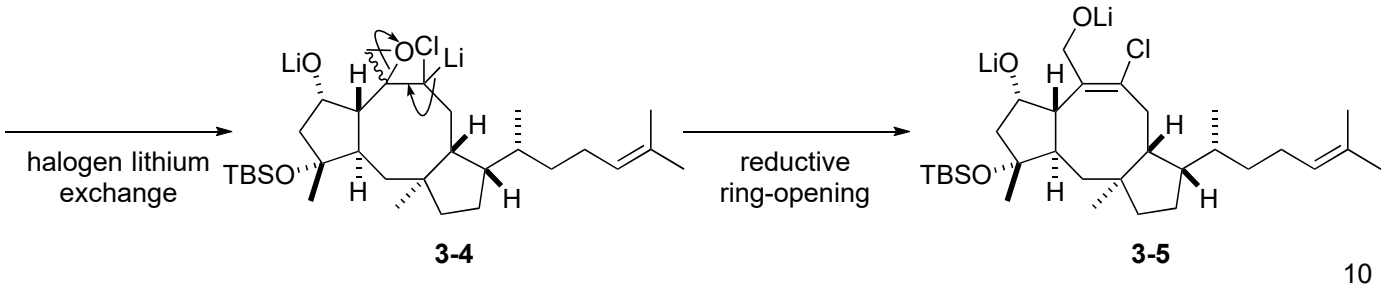


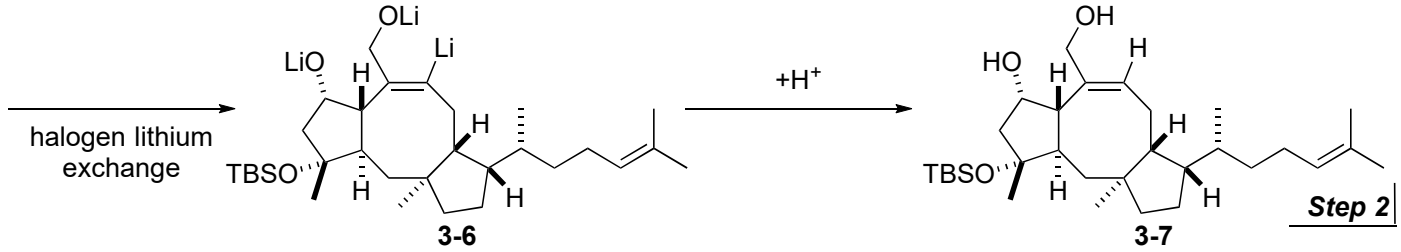
3. Reaction mechanism

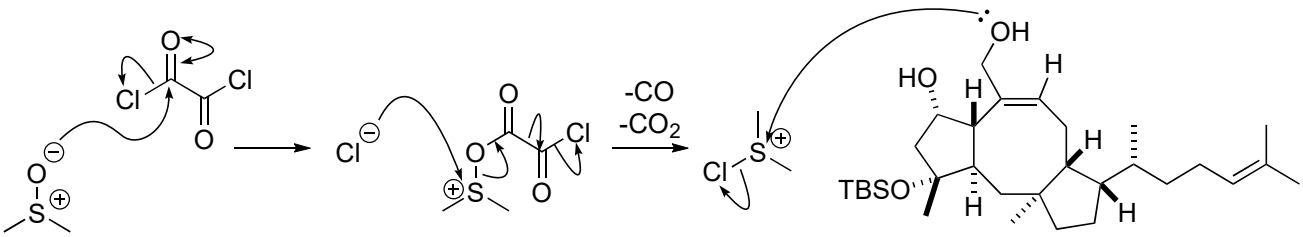


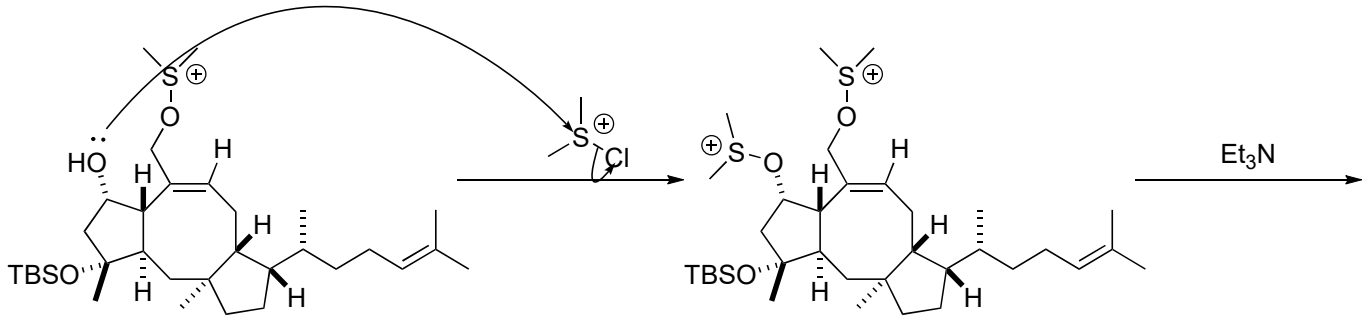


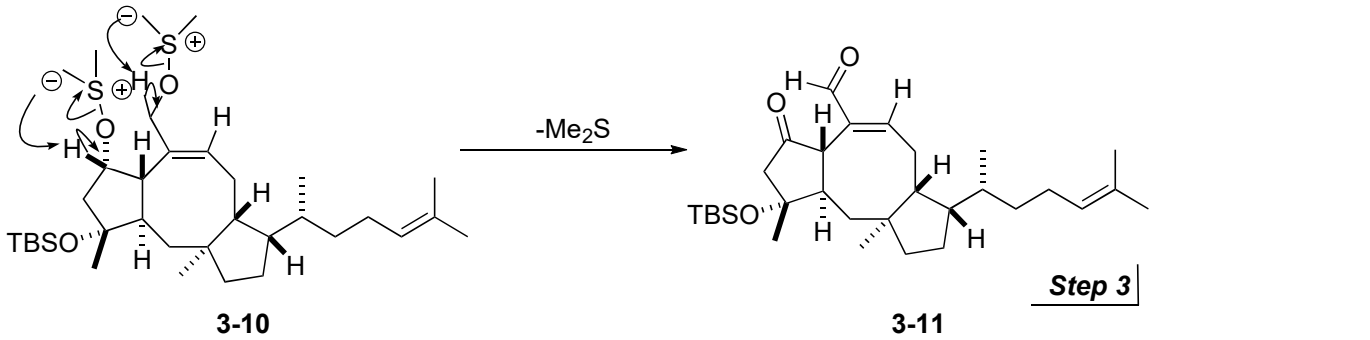


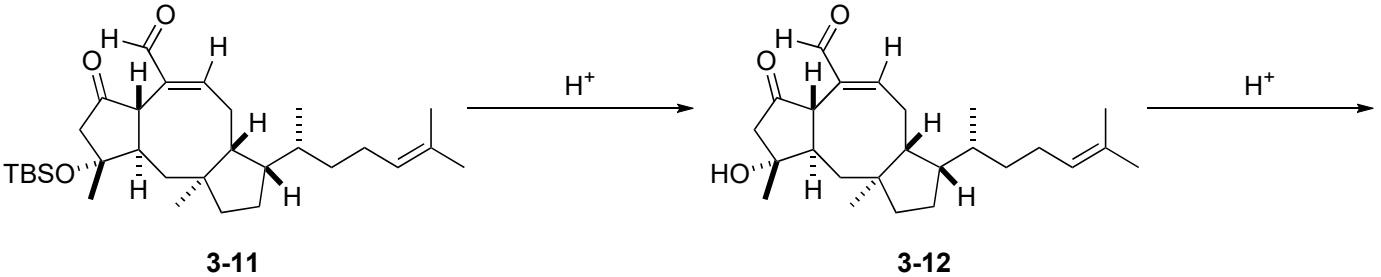


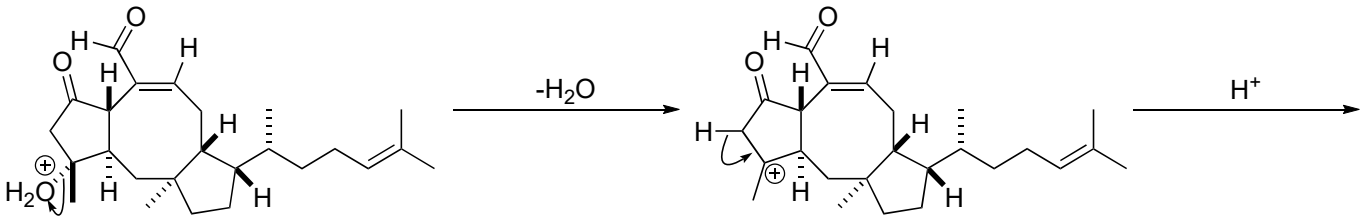

halogen lithium exchange
OLi
LiO
Li
TBSO
+H+
OH
HO
3-6
3-7
Step 2


-CO
-CO2
Cl
OH
HO
TBSO
3-7

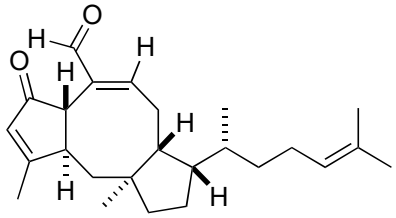

HO
TBSO
Et3N
3-8
3-9


-Me2S
TBSO
Step 3
3-10
3-11


H+
TBSO
HO
3-11
3-12



3-13 **3-14**



(–)-6-*epi*-ophiobolin N (**4**) ***Step 4***