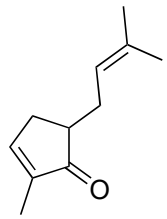
Problem Session (1)

2022.12.24. Shuji Toyama

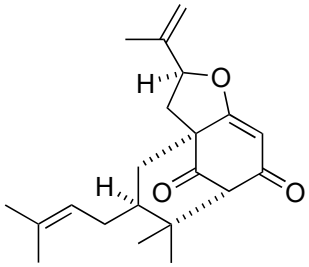
Topic: Construction of bicyclo[3.3.1]nonane skeleton
Please explain the reaction mechanism.

1.



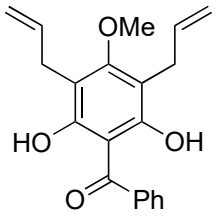
1-1

1. **1-2** (2.4 eq.), THF, rt, 98%
2. KH (3 eq.), 18-Crown-6 (3 eq.), THF, rt
   ; $MgBr_2$ (5 eq.), 50 °C; MeI (5 eq.), 50 °C
3. LiTMP (1.2 eq.), THF/Et_2O (1:1), −78 to 0 °C
   ; **1-3** (1.2 eq.), −40 °C, 29% (2 steps)
4. $Pd(OAc)_2$ (15 mol%), $Cu(OAc)_2$ (1.1 eq.)
   DMSO/TMSOH (7:3), rt, 95%
5. KOH (100 eq.), MeOH; $PhI(OAc)_2$ (2.7 eq.), −10-0 °C, 75%



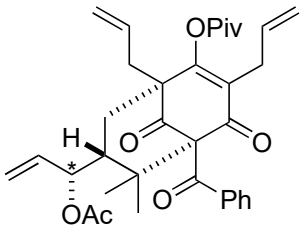
1-4

2.



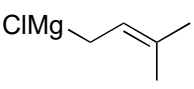
2-1

1. $LiN(TMS)_2$ (2 eq.), **2-2** (3 eq.), THF, 0 °C to rt, 92%
2. conc. HCl aq. (6 eq.), THF, 0 °C to rt, 75%
3. $CeCl_3$ (2.5 eq.), **2-3** (2.5 eq.), THF, −70 to −30 °C
4. Piv_2O (2.2 eq.), pyridine (11 eq.), DMAP (3 mol%), 0 °C to rt
5. Ac_2O (2 eq.), Et_3N (2.5 eq.), DMAP (3 mol%)
   CH_2Cl_2, 0 °C, 45% (3 steps)

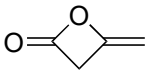


2-4
single diastereomer

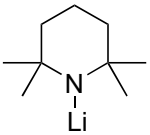
* proposed stereochemistry



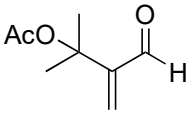
1-2



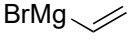
1-3



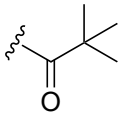
LiTMP



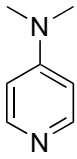
2-2



2-3



Piv



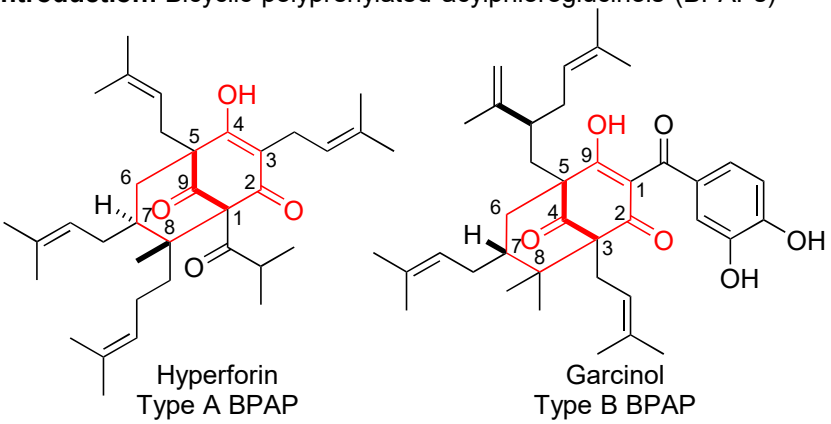
DMAP

Problem Session (1) -Answer-

2022.12.24. Shuji Toyama

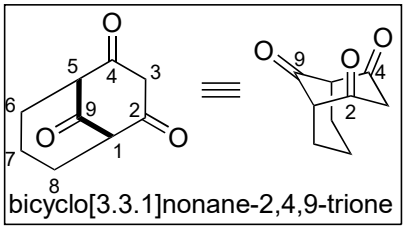
Topic: Construction of bicyclo[3.3.1]nonane skeleton

Introduction: Bicyclic polyprenylated acylphloroglucinols (BPAPs)



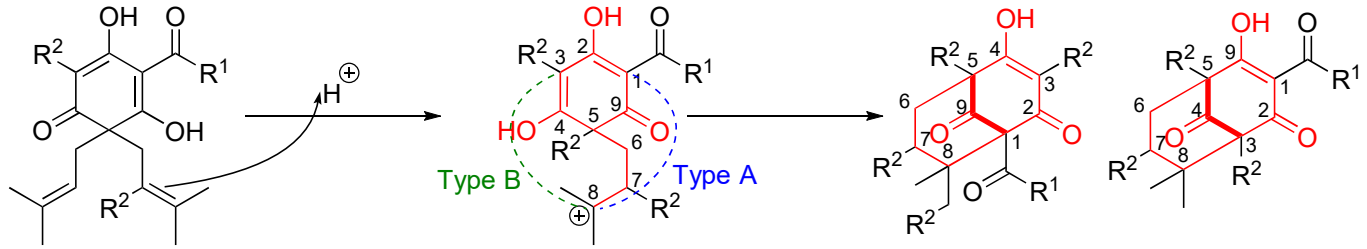
Hyperforin
Type A BPAP

Garcinol
Type B BPAP



bicyclo[3.3.1]nonane-2,4,9-trione

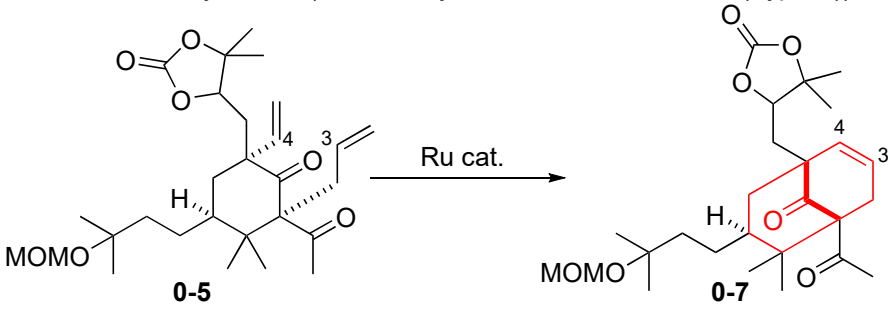
Biosynthesis



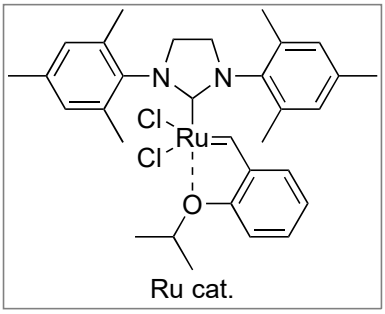
0-1 R^1 = *i*-Pr, *s*-Bu, or Ph; R^2 = prenyl, geranyl, Me, etc. **0-2** **0-3** Type A **0-4** Type B

Yang, X. W.; Li, M. M.; Liu, X.; Ferreira, D.; Ding, Y.; Zhang, J. J.; Liao, Y.; Qin, H. B.; Xu, G. *J. Nat. Prod.* **2015**, *78*, 885.

Shibasaki's synthesis (first total synthesis of Garsubellin A (Type A))



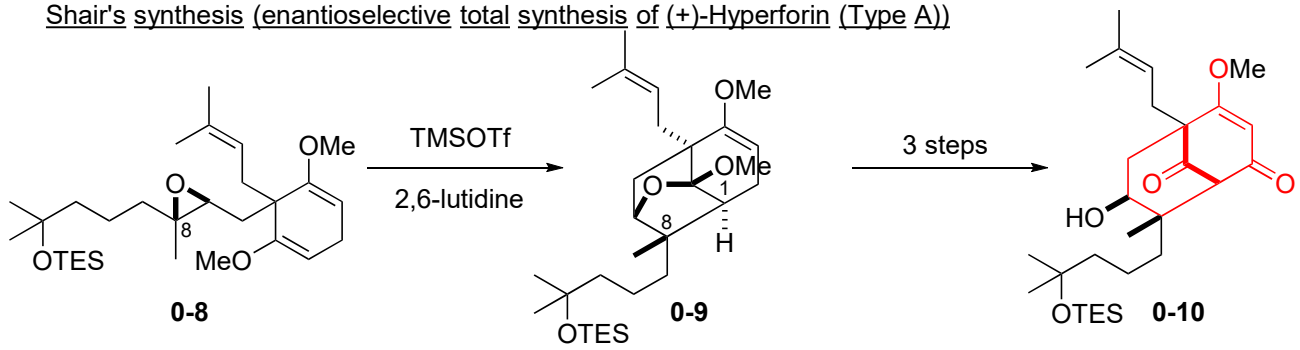
0-5 **0-7**



By Ring-closing metathesis, C3 and C4 were connected.

Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200.

Shair's synthesis (enantioselective total synthesis of (+)-Hyperforin (Type A))



0-8 **0-9** **0-10**

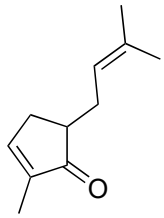
Nucleophilic attack from methyl enol ether to epoxide activated by TMSOTf connected C1 and C8. Following acetal hydrolysis gave bicyclo[3.3.1]nonane skeleton.

Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.

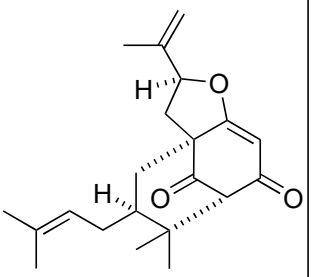
140111_PS_Yusuke_Sesoko.

1.

1. **1-2** (2.4 eq.), THF, rt, 98%
2. KH (3 eq.), 18-Crown-6 (3 eq.), THF, rt
   ; $MgBr_2$ (5 eq.), 50 °C; MeI (5 eq.), 50 °C
3. LiTMP (1.2 eq.), THF/Et_2O (1:1), −78 to 0 °C
   ; **1-3** (1.2 eq.), −40 °C, 29% (2 steps)
4. $Pd(OAc)_2$ (15 mol%), $Cu(OAc)_2$ (1.1 eq.)
   DMSO/TMSOH (7:3), rt, 95%
5. KOH (100 eq.), MeOH; $PhI(OAc)_2$ (2.7 eq.), −10-0 °C, 75%

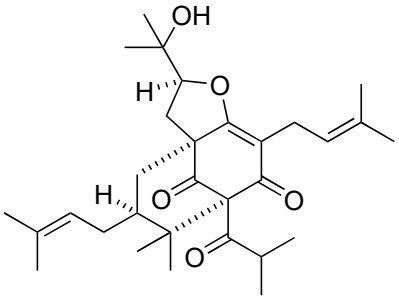


1-1

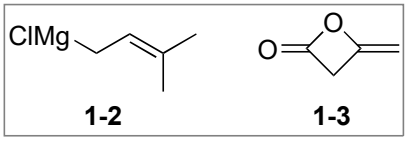


1-4

4 steps

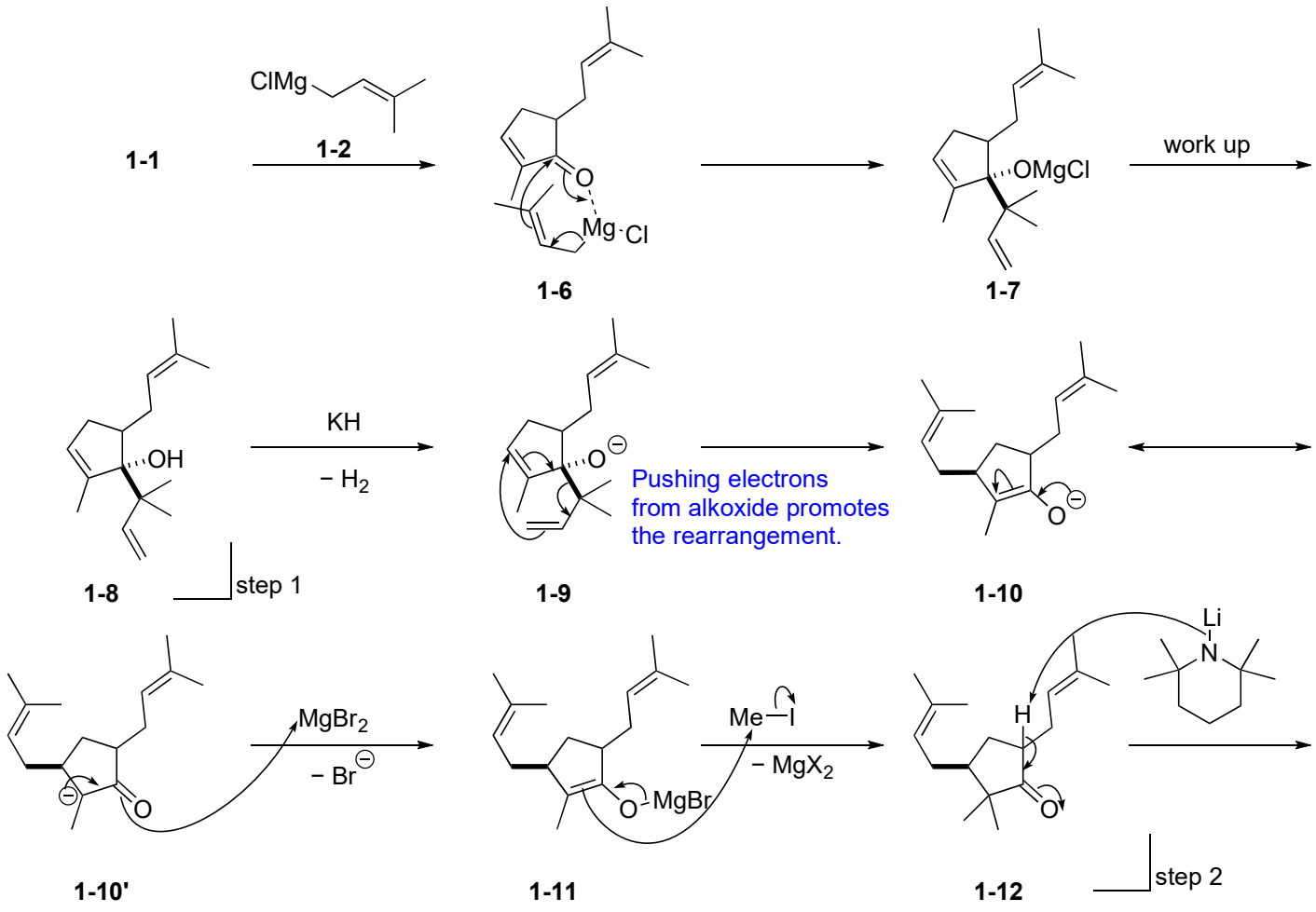


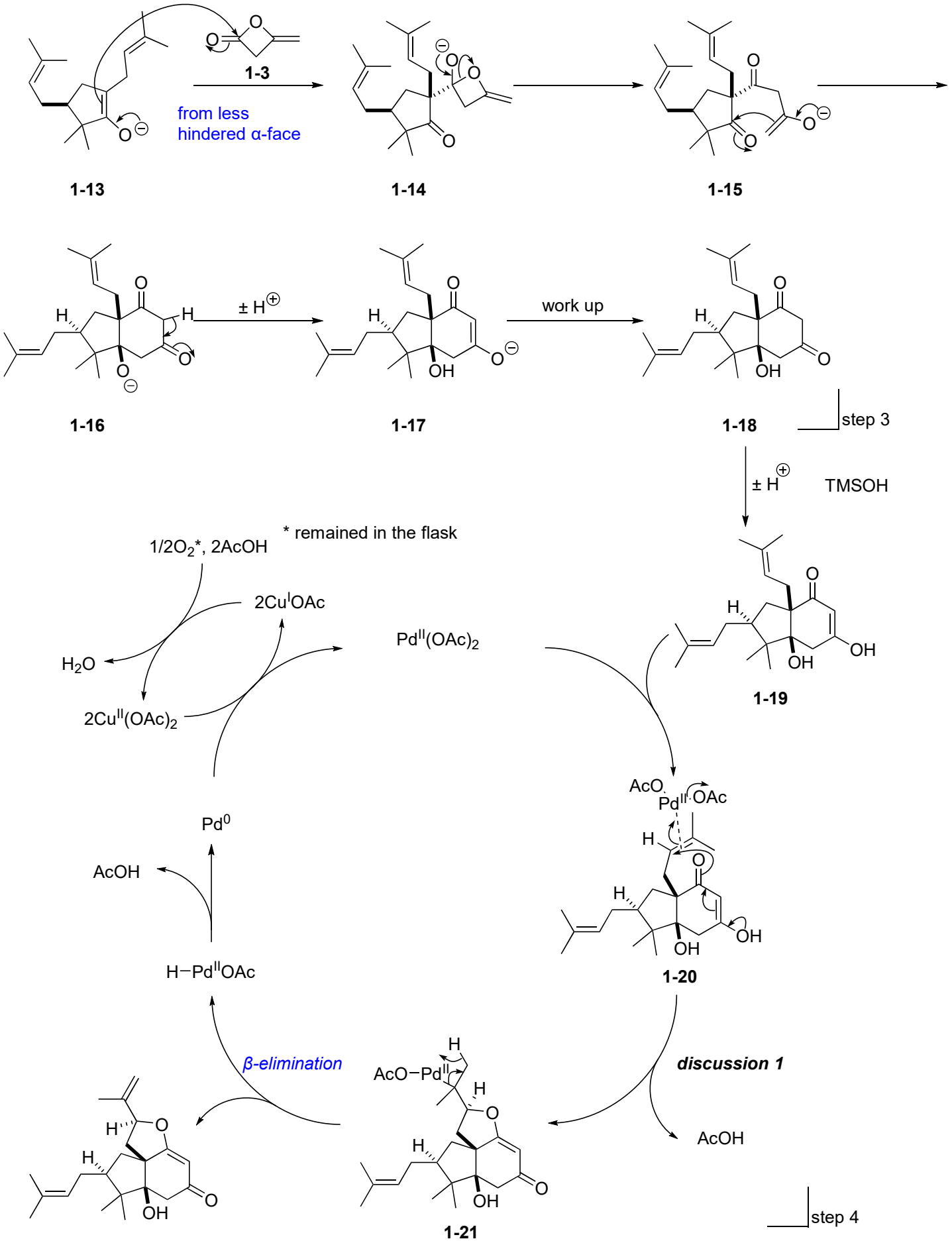
Garsubellin A (**1-5**)

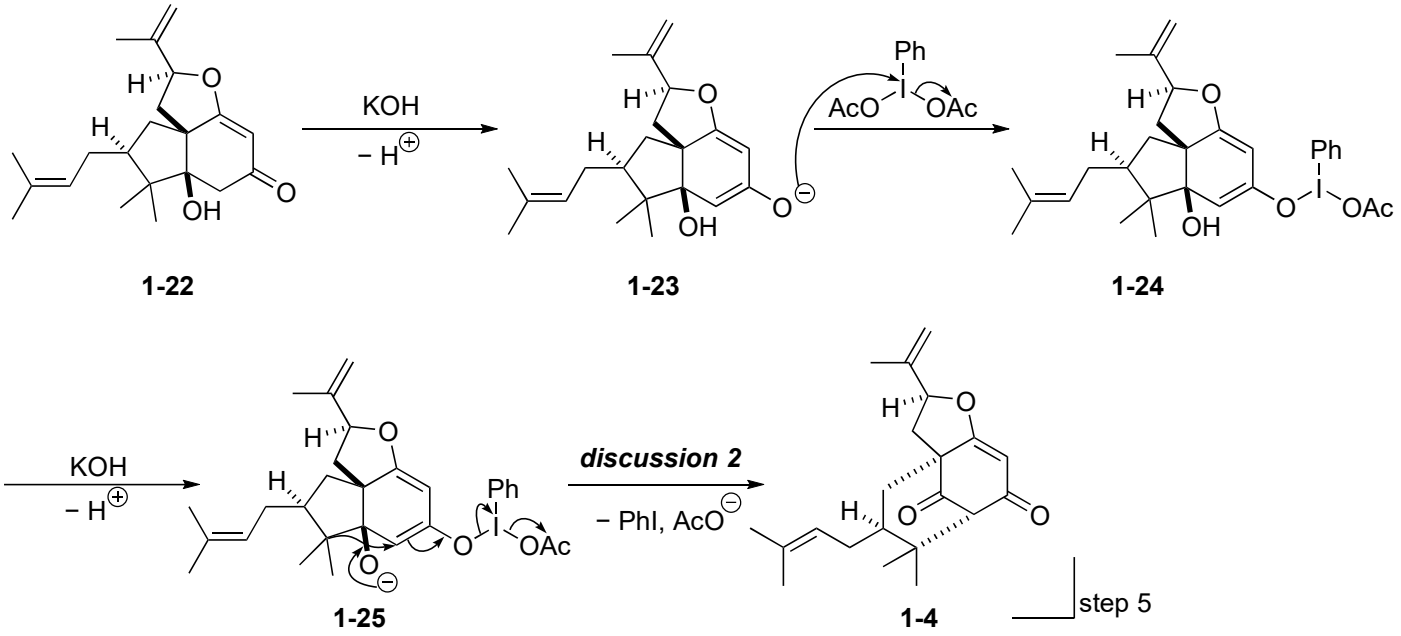


1-2 **1-3**

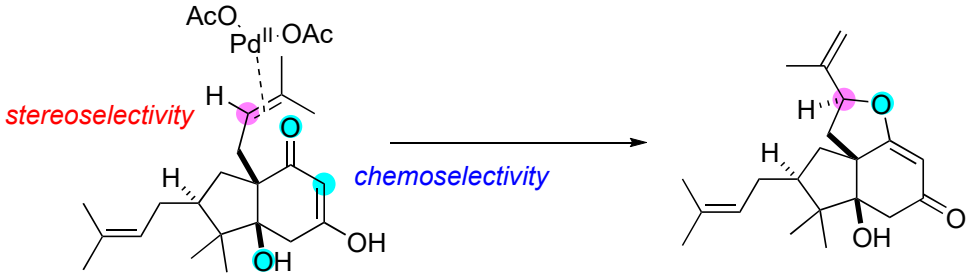
Shen, X.; Ting, C. P.; Xu, G.; Maimone, T. J. *Nat. Commun.* **2020**, *11*, 508.



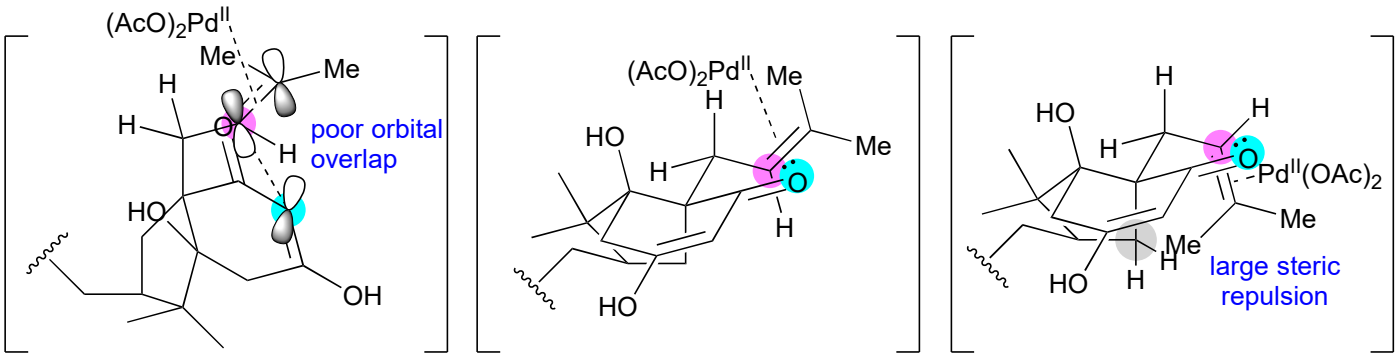

1-3
from less
hindered α-face
1-13
1-14
1-15
1-16
± H⊕
1-17
work up
1-18
step 3
± H⊕
TMSOH
1-19
* remained in the flask
1/2O2*, 2AcOH
2CuIOAc
H2O
2CuII(OAc)2
PdII(OAc)2
Pd0
AcOH
H−PdIIOAc
AcO
PdII·OAc
1-20
discussion 1
AcOH
β-elimination
AcO−PdII
1-21
1-22
step 4


KOH
− H⊕
Ph
AcO
OAc
OH
1-22
1-23
1-24
KOH
− H⊕
discussion 2
− PhI, AcO⊖
1-25
1-4
step 5

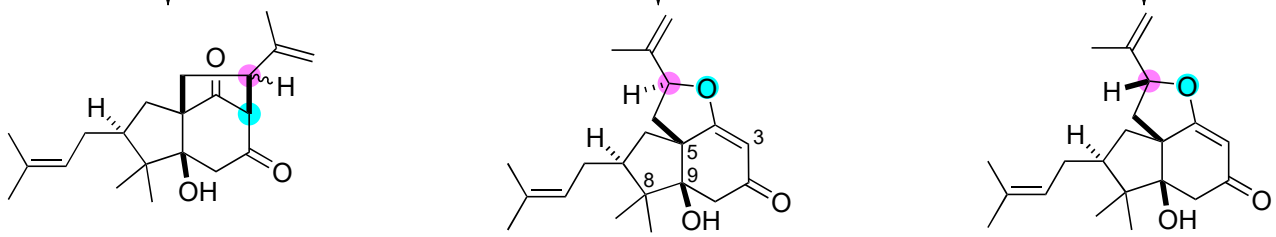
Discussion 1: Palladium catalized oxidative cyclization



1-20 Tertiary alcohol is less nucleophilic. **1-22**



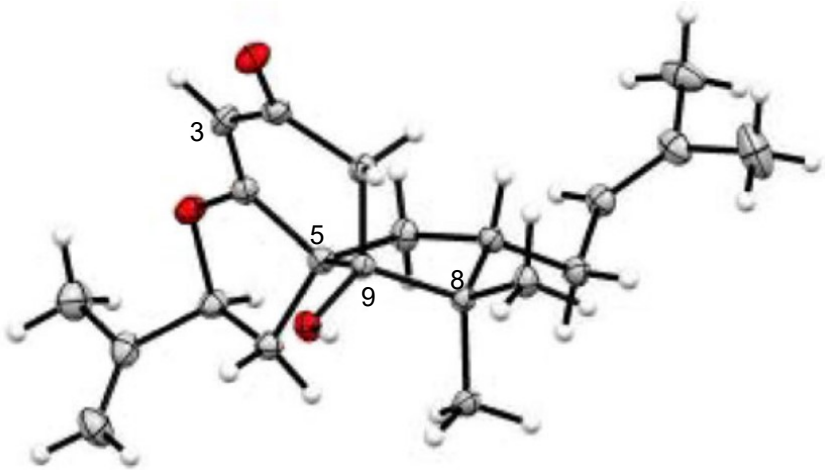
TS1-1 **TS1-2** **TS1-3**



1-26
not obtained

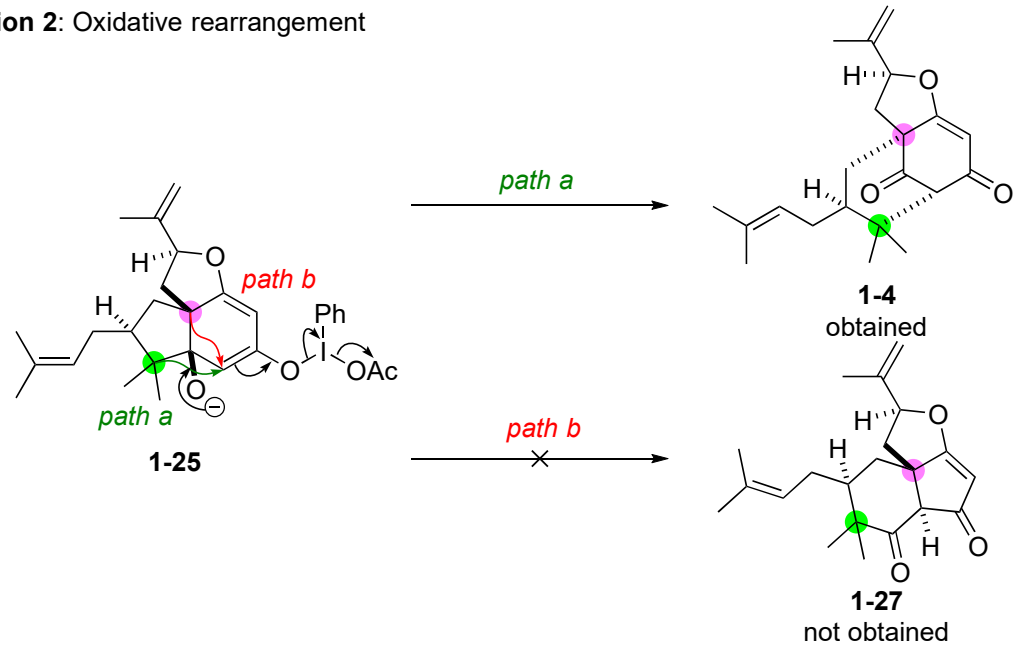
1-22
obtained

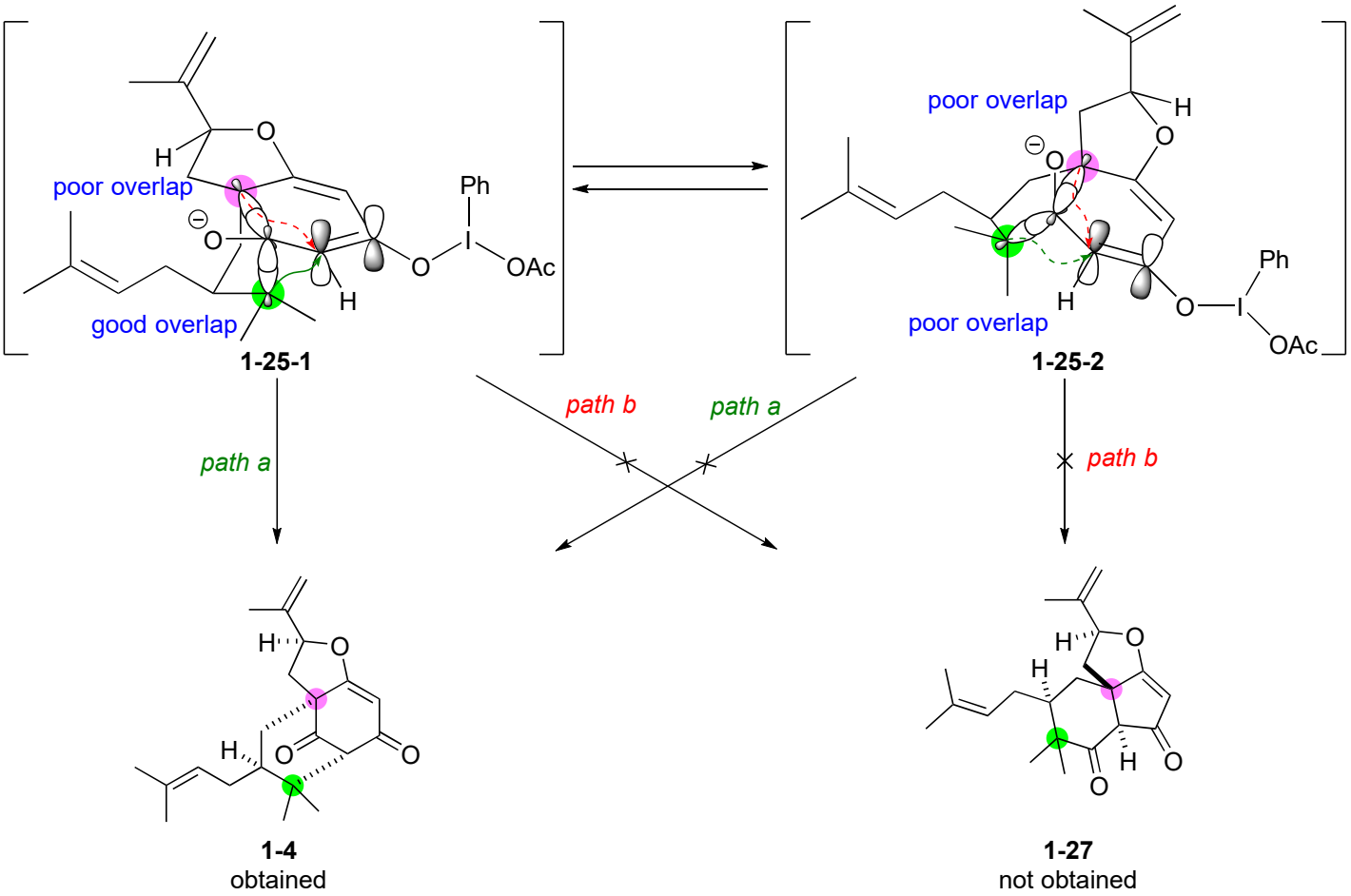
***epi*-1-22**
not obtained



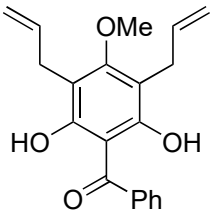
X-ray structure of **1-22**

Discussion 2: Oxidative rearrangement



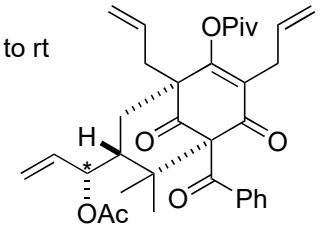


2.



2-1

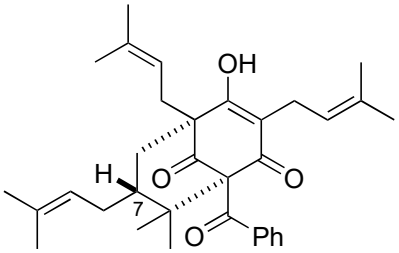
1. $LiN(TMS)_2$ (2 eq.), **2-2** (3 eq.), THF, 0 °C to rt, 92%
2. conc. HCl aq. (6 eq.), THF, 0 °C to rt, 75%
3. $CeCl_3$ (2.5 eq.), **2-3** (2.5 eq.), THF, −70 to −30 °C
4. Piv_2O (2.2 eq.), pyridine (11 eq.), DMAP (3 mol%), 0 °C to rt
5. Ac_2O (2 eq.), Et_3N (2.5 eq.), DMAP (3 mol%)
   CH_2Cl_2, 0 °C, 45% (3 steps)



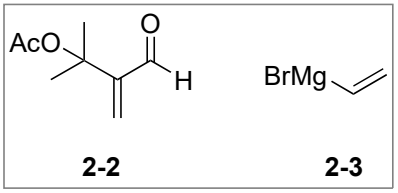
2-4
single diastereomer

* proposed stereochemistry

3 steps

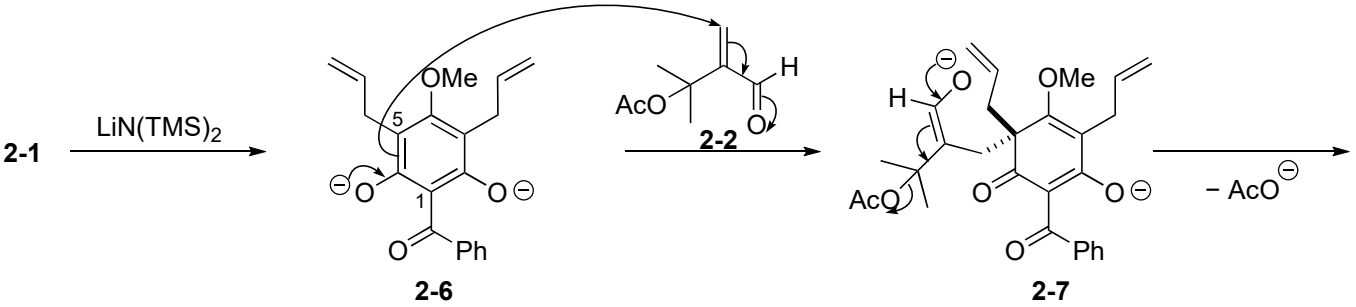


7-*epi*-Nemorosone (**2-5**)

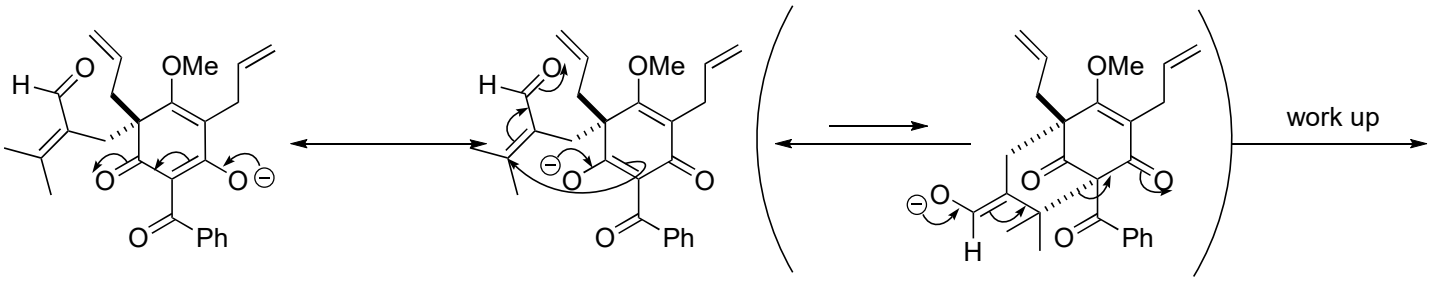


2-2 **2-3**

Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc*. **2010**, *132*, 14212.
Zhang, Q.; Porco, J. A., Jr. *Org. Lett*. **2012**, *14*, 1796.



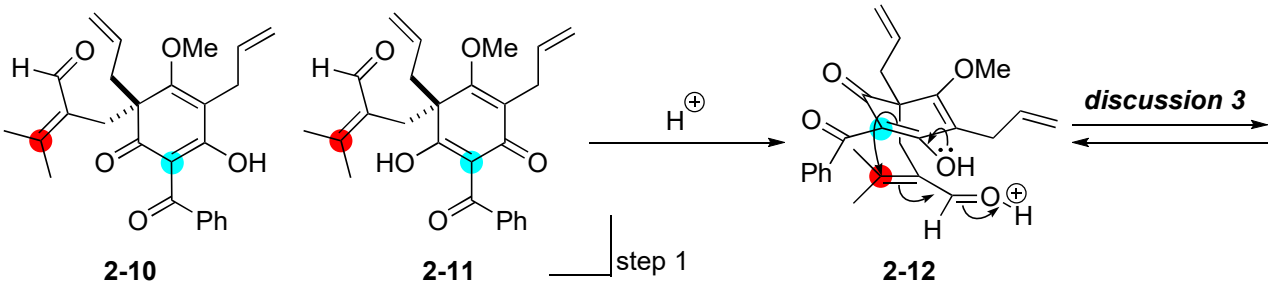
2-6 **2-7**



2-8-a **2-8-b** **2-9**

Conjugated enolate **2-8** is more stable than **2-9**.

work up

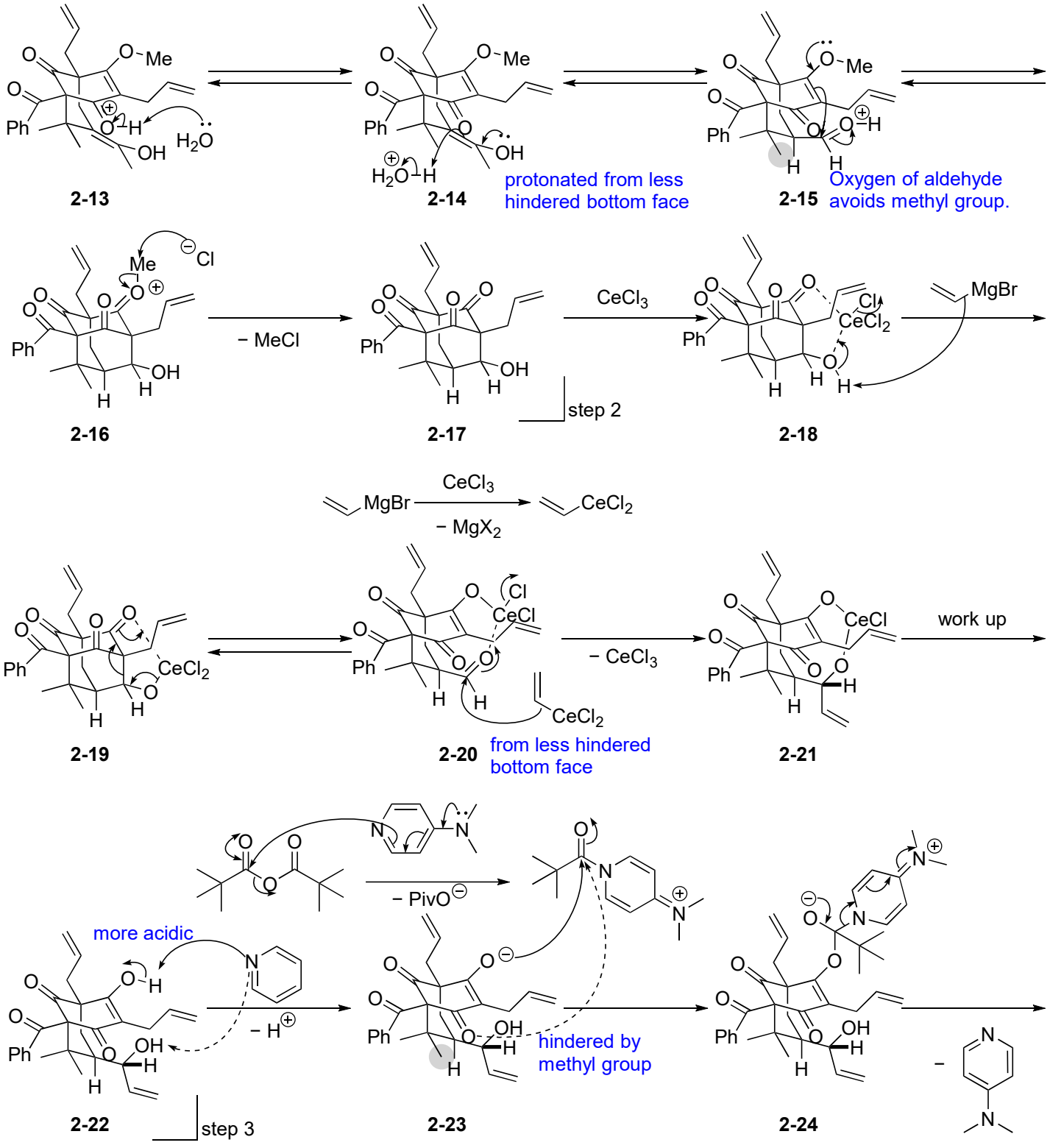


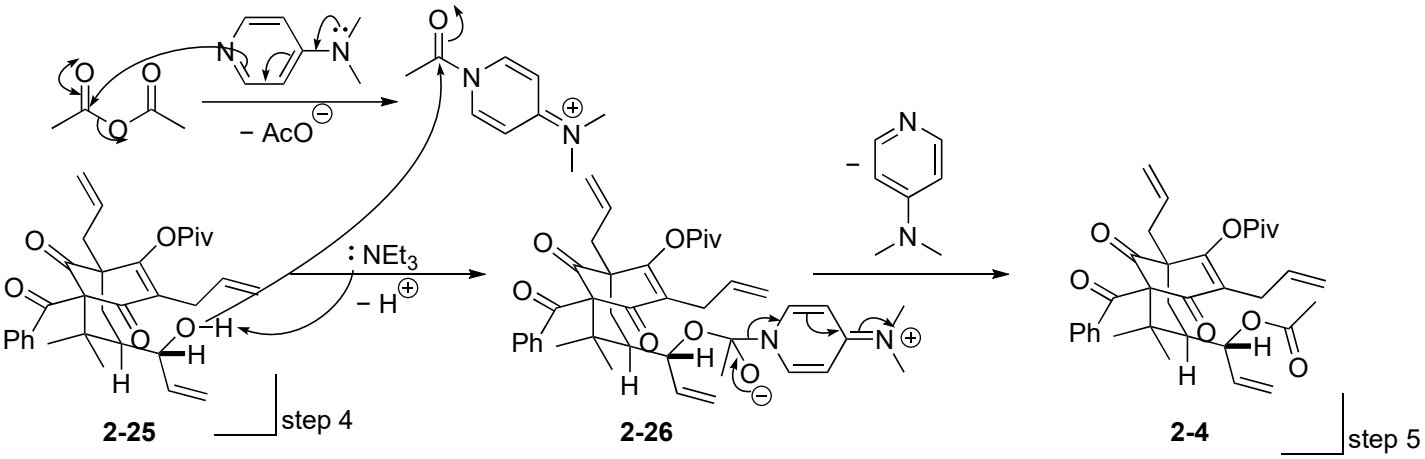
2-10 **2-11** **2-12**

step 1

discussion 3

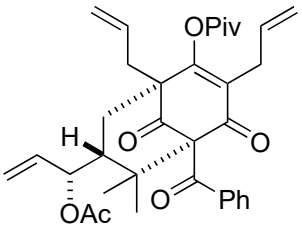
1.6:1 tautomeric mixture
(the major tautomer is not determined.)


2-13
2-14
protonated from less hindered bottom face
2-15
Oxygen of aldehyde avoids methyl group.
− MeCl
2-16
2-17
step 2
CeCl3
2-18
MgBr
CeCl3
− MgX2
CeCl2
2-19
2-20
from less hindered bottom face
− CeCl3
2-21
work up
more acidic
− PivO
− H
2-22
step 3
2-23
hindered by methyl group
2-24



2-25 **2-26** **2-4**

≡

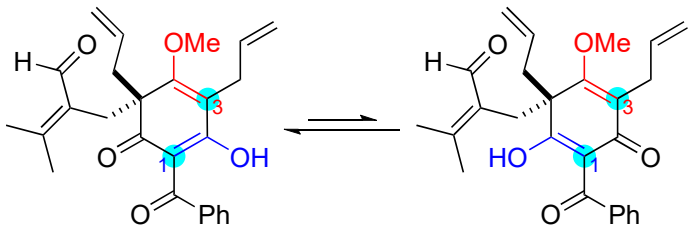


2-4

Discussion 3: Sequential cyclization

3-1. Comparison of C1 and C3

There are two possible nucleophilic carbon, C1 and C3.

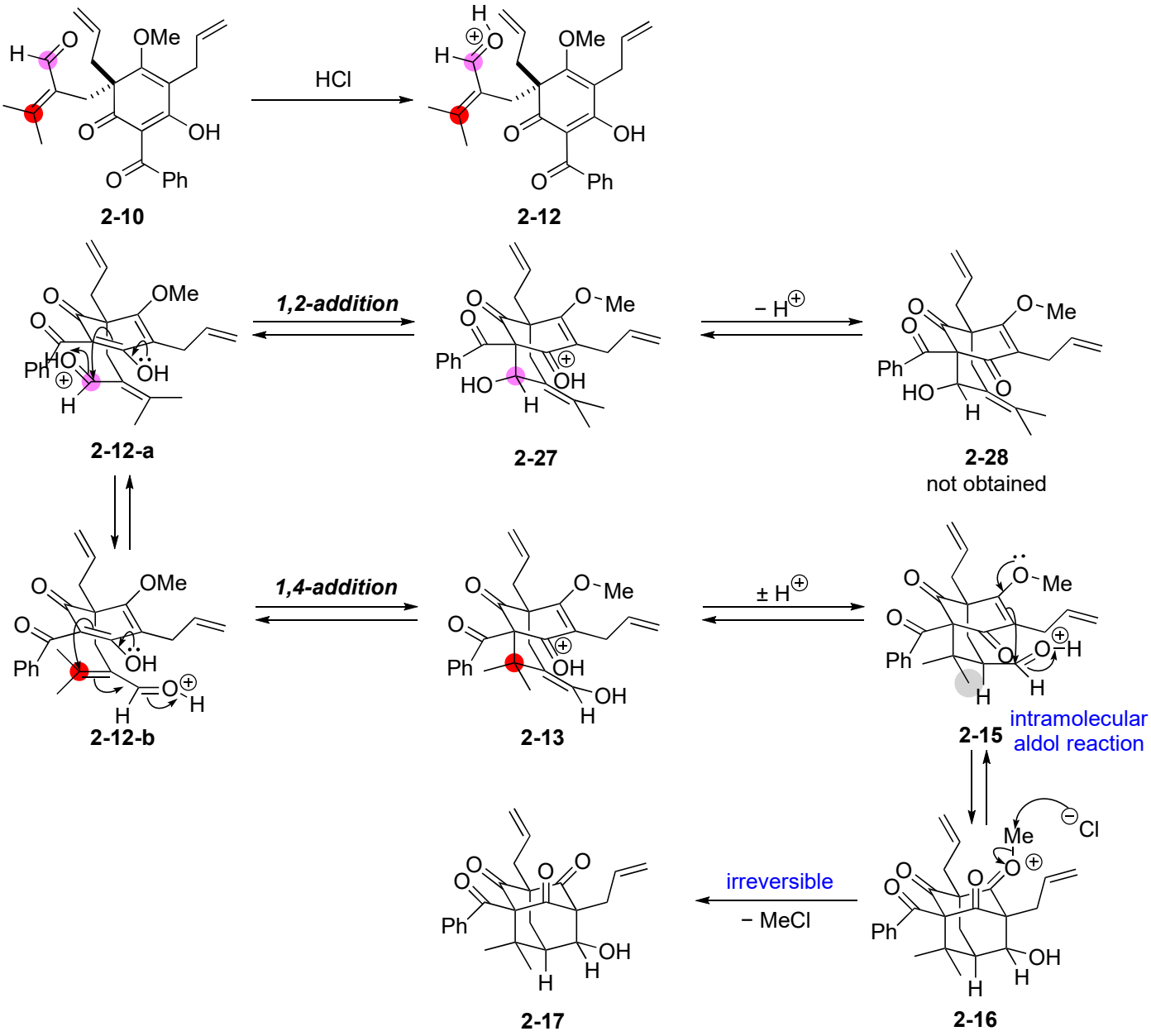


2-10 **2-11**

C3 is less nucleophilic than C1 because of the inductive effect of methyl group on oxygen. So the reaction may occur at C1 position first.

3-2. Comparison of 1,2-addition and 1,4-addition

Both 1,2-addition and 1,4-addition may be possible.



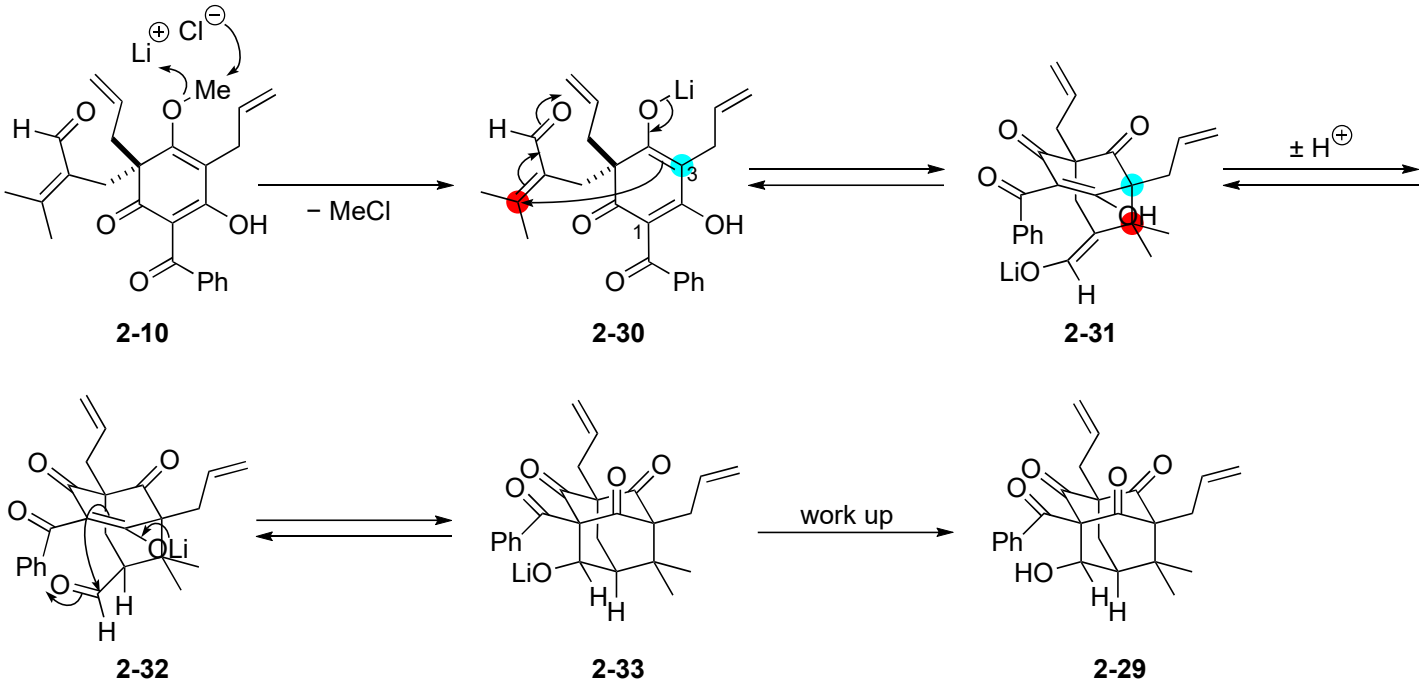
2-10 **2-12** **2-12-a** **2-27** **2-28** not obtained **2-12-b** **2-13** **2-15** **2-16** **2-17**

Most of the reactions are reversible. As soon as **2-16** is generated, irreversible demethylation gives **2-17**.

3-3. The order of demethylation

Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 14212.

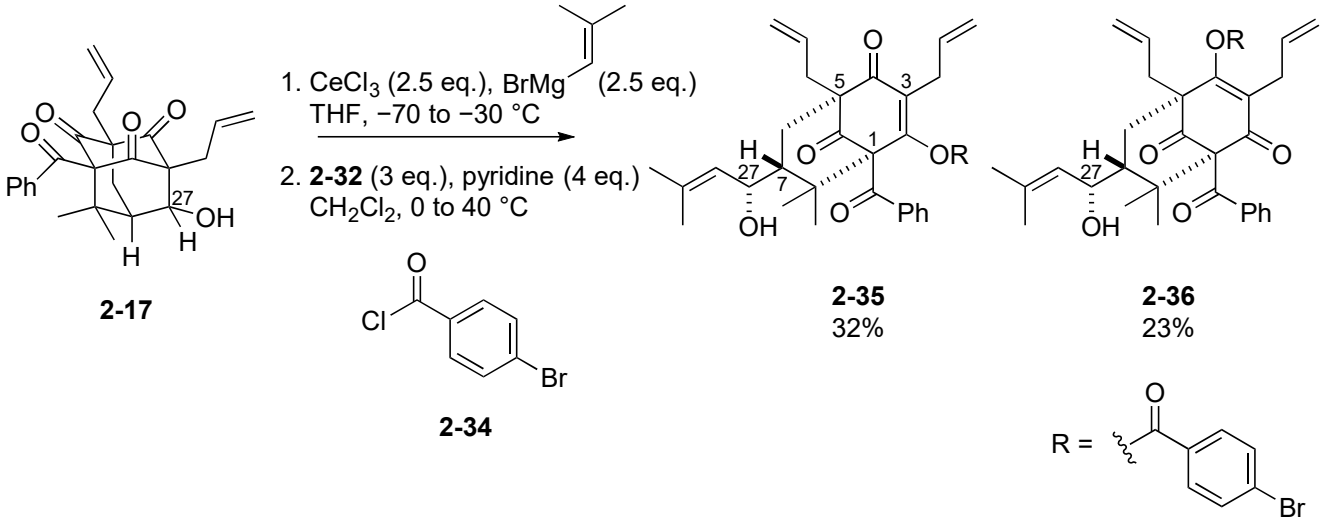
By using LiCl, **2-29** was generated, which has different carbon skeleton from **2-17**.
Demethylation of **2-10** by LiCl would give **2-29** instead of **2-17** as follows.



Demethylation would induce nucleophilic attack from C3, so the order seems to be important.

Appendix:

Determination of C27-stereochemistry

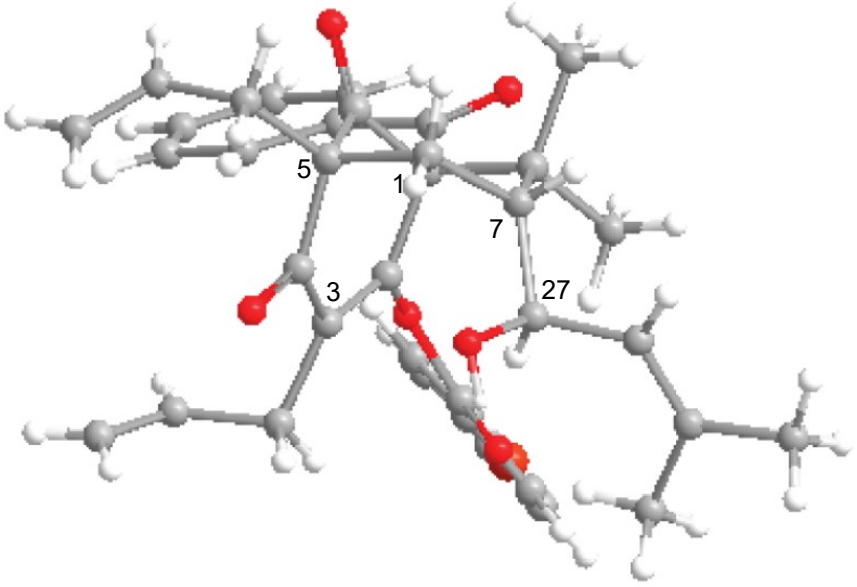


2-17

2-34

2-35
32%

2-36
23%



X-ray structure of **2-35**

According to this result, C27-stereochemistry of **2-4** was proposed.