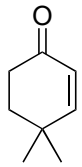
Problem Session (1) -Answer-

2022.1.22. Jaejoong Han

Topic: Total synthesis of (+)-Jungermatrobrunin A

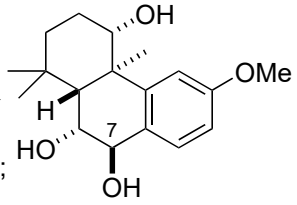
1.



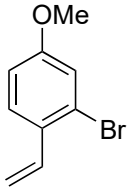
1-1

1. **1-2** (1.9 eq), Cp_2ZrHCl (1.8 eq), **A** (0.1 eq), TMSCl (3.2 eq), CH_2Cl_2, 0 ºC, 3 d, 69%, 94% ee (recrystallized)
2. **B** (3 mol%), *t*-BuONa (1.1 eq), THF, 63 ºC, 6 h
3. *t*-BuONa (1.0 eq), MeI (3.1 eq), MeCN, 25 ºC, 2h, 64% (2 steps)
4. Jones reagent (7.5 eq)*, acetone, 25 ºC, 11 h, 56%
5. $CeCl_3•7H_2O$ (3.0 eq), MeOH, 40 ºC, 10 h; $NaBH_4$ (4.4 eq), 0 ºC, 2 h; 10% aq. NH_4Cl; $NaBH_4$ (11 eq), 25 ºC, 52%

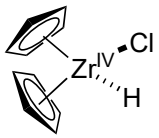
* Calculated based on reagent information from Aldrich.



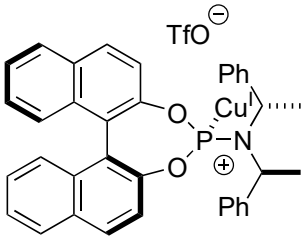
(-)-1-3
(5.1:1 d.r. at C7)



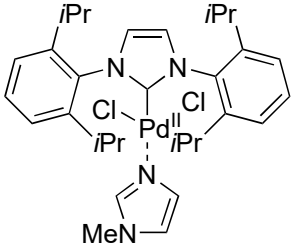
1-2



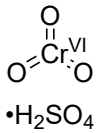
Cp_2ZrHCl



A



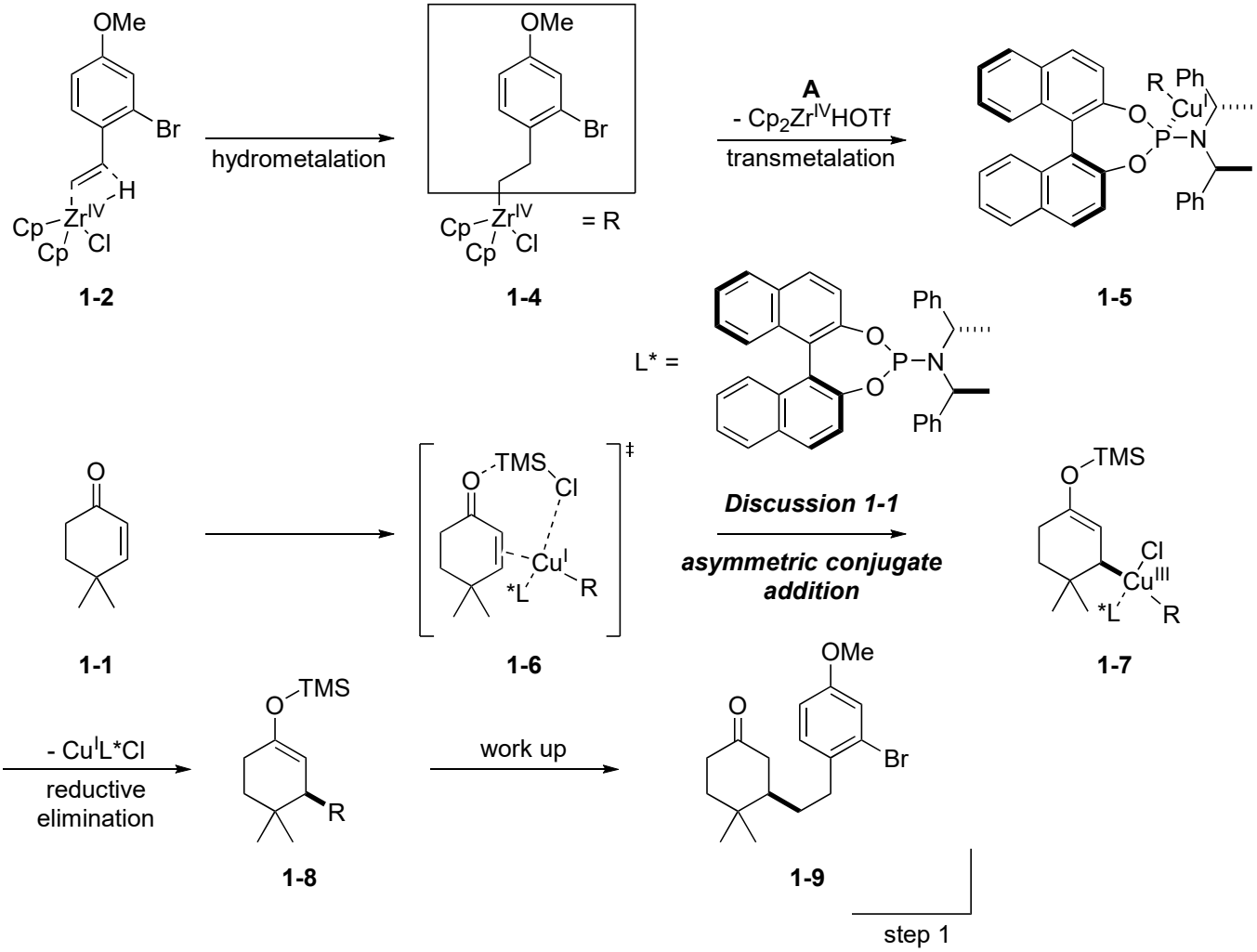
B



Jones reagent

J. Wu.; Y. Kadonaga.; B. Hong.; J. Wang.; X. Lei. *Angew.Chem. Int. Ed*. **2019**, *58*, 10879-10883.

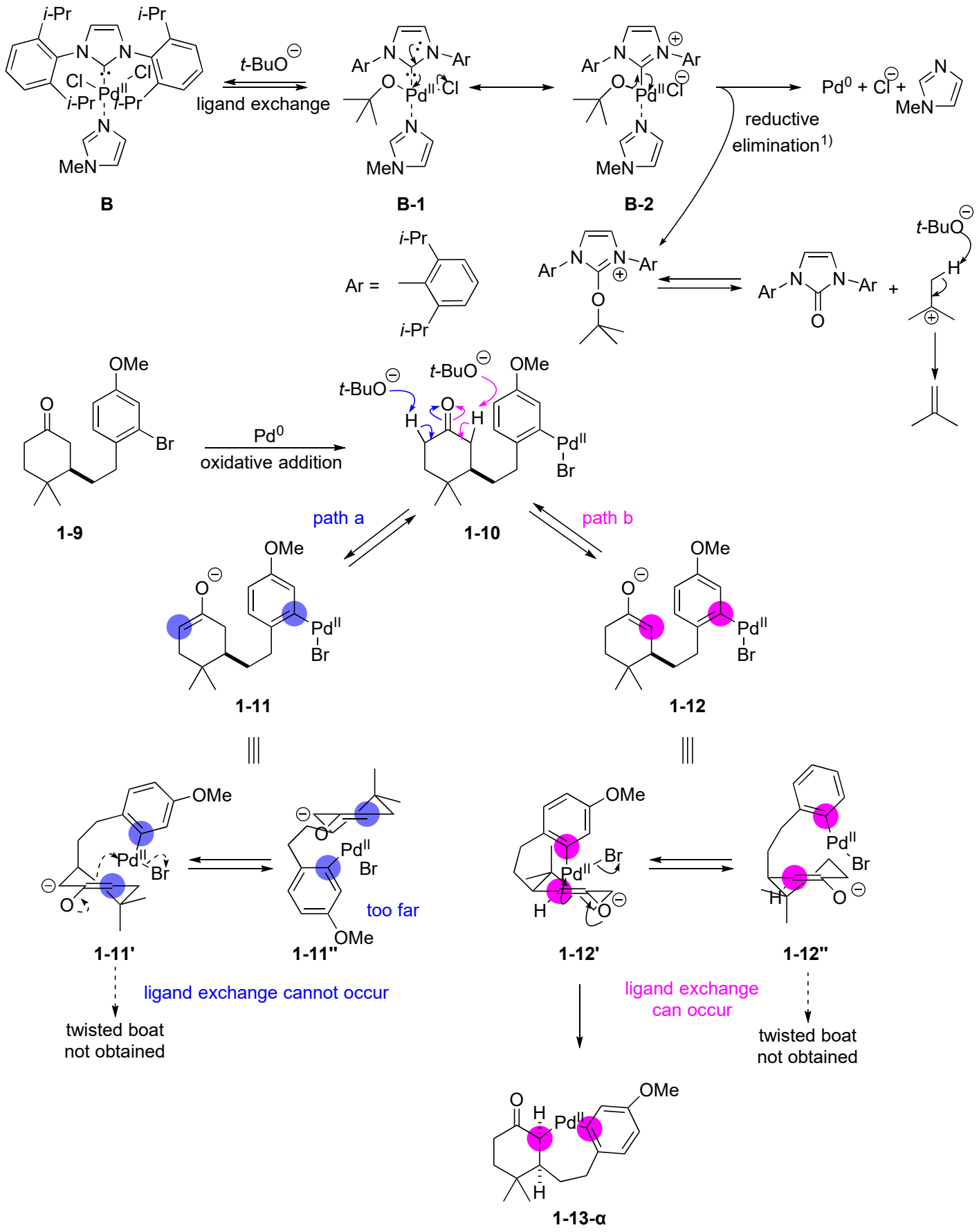
Answer

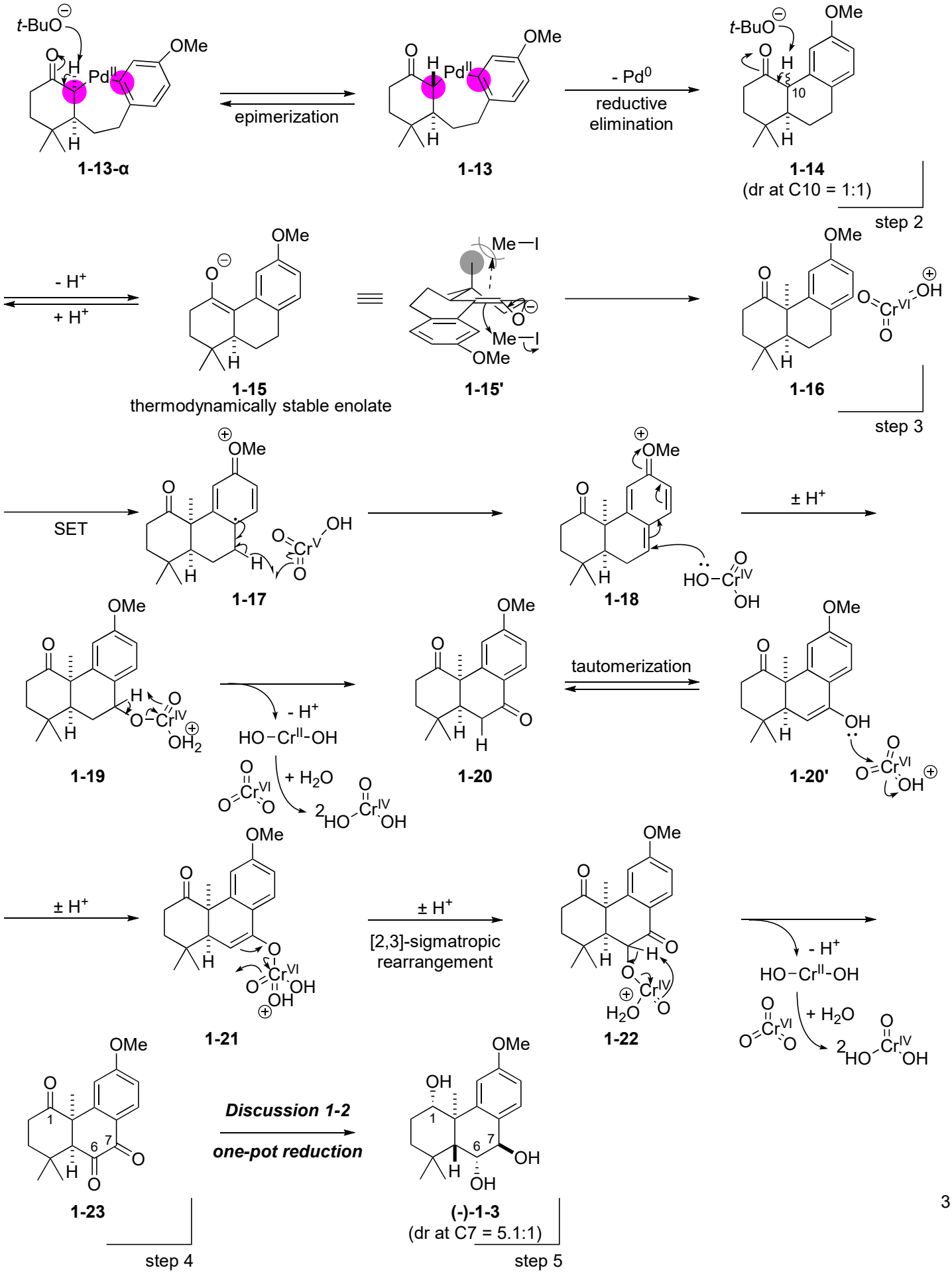


1-2 **1-4** **1-5**

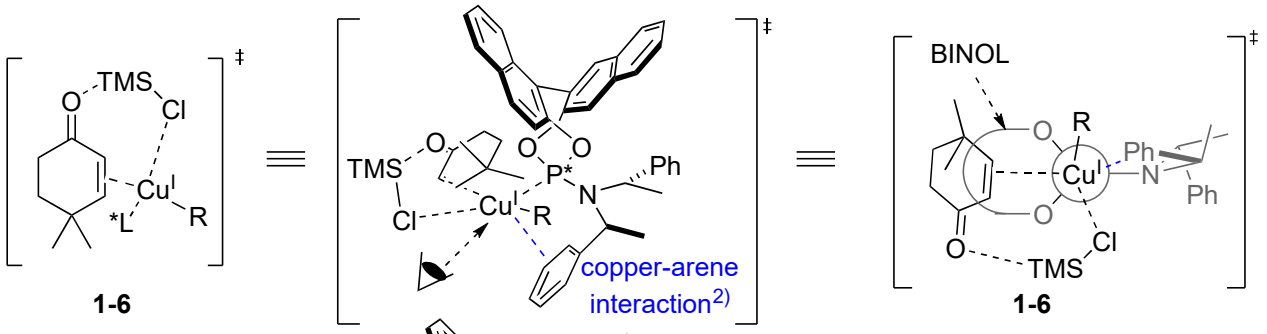
1-1 **1-6** **1-7**

1-8 **1-9**

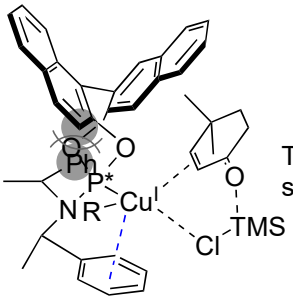

B
B-1
B-2
ligand exchange
reductive elimination[1)]
Ar =
1-9
oxidative addition
1-10
path a
path b
1-11
1-12
too far
1-11'
1-11"
1-12'
1-12"
ligand exchange cannot occur
ligand exchange can occur
twisted boat not obtained
twisted boat not obtained
1-13-α


t-BuO
OMe
Pd^II
epimerization
- Pd^0
reductive elimination
10
1-13-α
1-13
1-14
(dr at C10 = 1:1)
step 2
- H+
+ H+
Me—I
1-15
thermodynamically stable enolate
1-15'
1-16
step 3
SET
Cr^V
Cr^VI
1-17
1-18
± H+
HO–Cr^IV–OH
1-19
- H+
HO–Cr^II–OH
+ H2O
2 HO–Cr^IV–OH
1-20
tautomerization
1-20'
± H+
1-21
[2,3]-sigmatropic rearrangement
1-22
- H+
HO–Cr^II–OH
+ H2O
2 HO–Cr^IV–OH
1-23
Discussion 1-2
one-pot reduction
(-)-1-3
(dr at C7 = 5.1:1)
step 4
step 5

Discussion 1-1: asymmetric conjugate addition

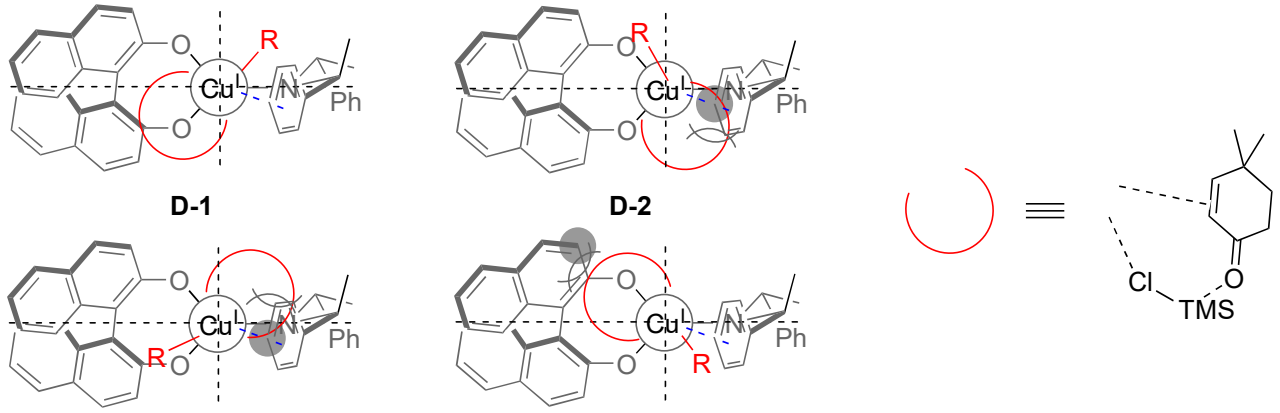


1-6 **1-6**



This conformation is not appropriate due to large steric repulsion between phenyl and binaphthol group.

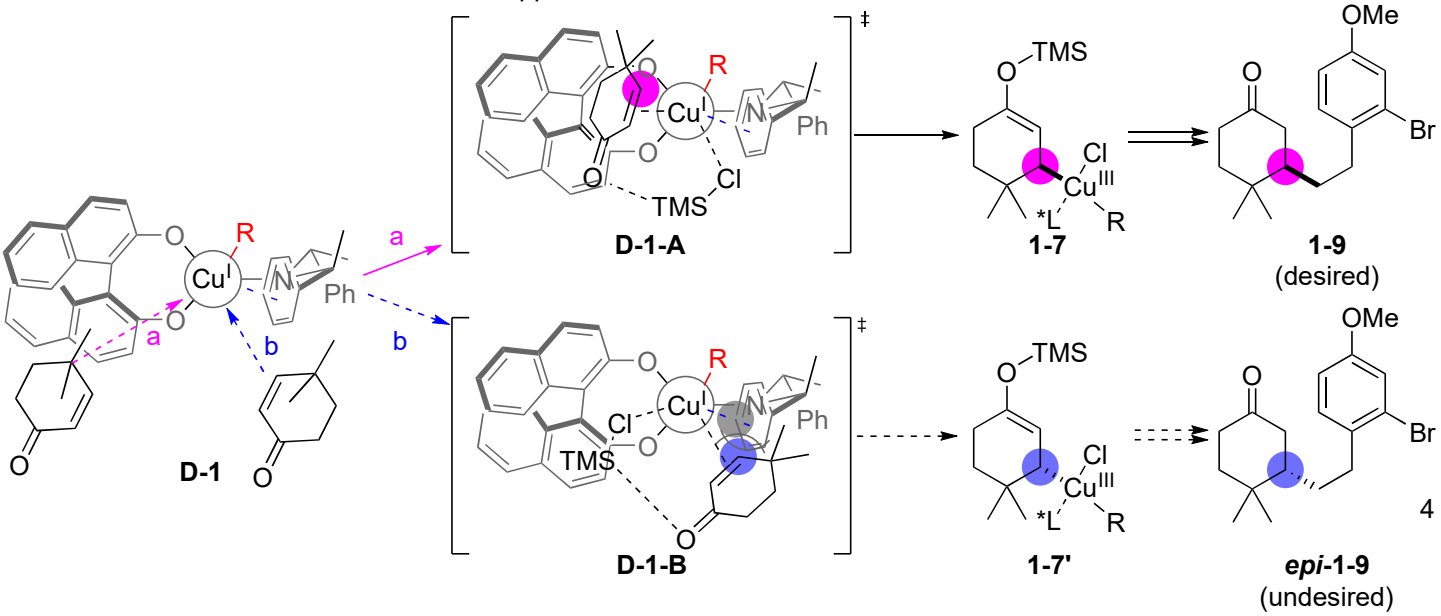
In transition state, Cu^{I} is center of tetrahedral coordination. Cu^{I} coordinates with chiral phosphoramidite, R^1, enone and Cl. Taking coordination field into account, **D-1** is favorable, while others are unfavorable due to steric repulsion .



D-1 **D-2**

D-3 **D-4**

Enone approaches from opposite side of phosphoramidite, and ketone faces the other way from R^1. This is because of formation of coordinate bond between copper, TMSCl and enone in TS.



D-1 **D-1-A** **1-7** **1-9** (desired)

D-1-B **1-7'** ***epi*-1-9** (undesired)

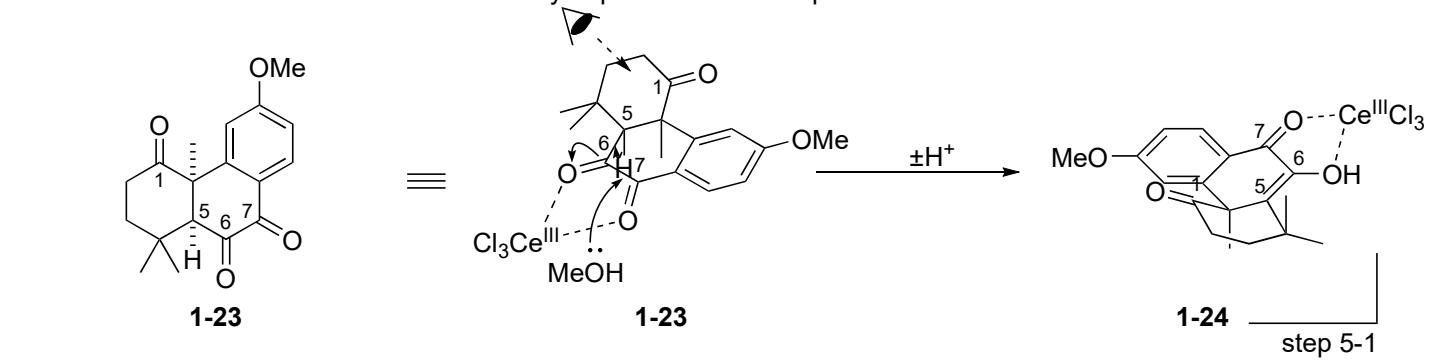
Discussion 1-2: one-pot reduction

The procedure is as follows:

1. $CeCl_3 \cdot 7H_2O$ (3.0 eq), MeOH, 40 ºC, 10 h 2. $NaBH_4$ (4.4 eq), 0 ºC, 2 h 3. 10% aq. NH_4Cl 4. $NaBH_4$ (11 eq), 25 ºC

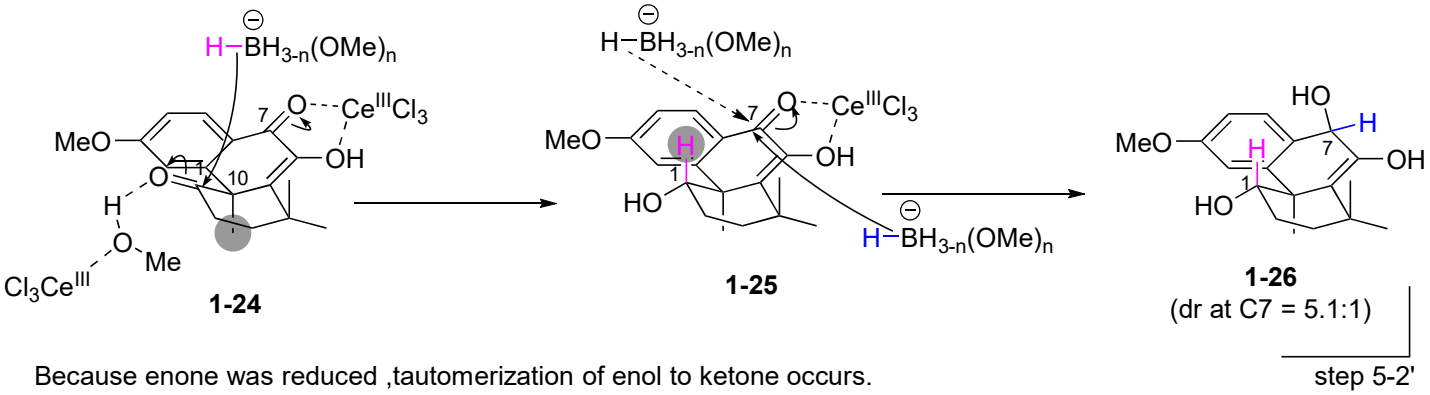
1. Addition of $CeCl_3 \cdot 7H_2O$

Isomerization of diketone to enone occurs by deprotonation at C5 position.

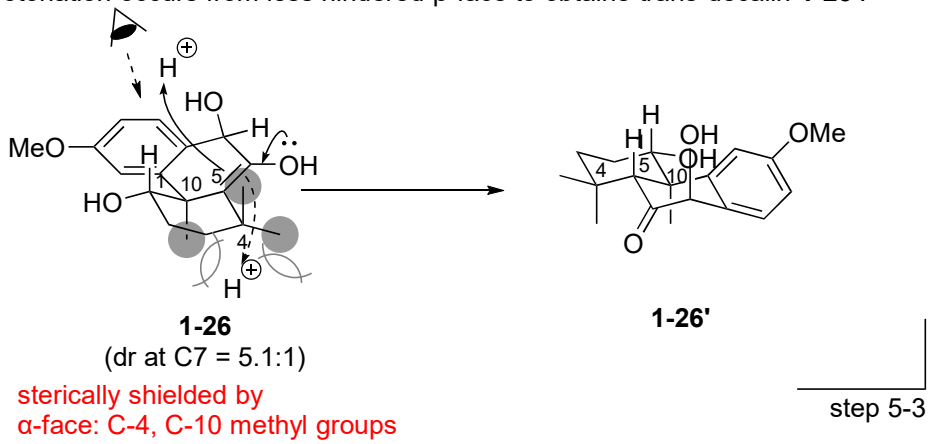


2. Addition of $NaBH_4$

Under Luche conditions, reduction of C-1 and C-7 ketone occurs. Reduction of C-1 ketone occurs from β-face because of large steric repulsion of C-10 methyl group. Due to C-1 H of 1-24, reduction of C-7 occurs from α-face.



Because enone was reduced ,tautomerization of enol to ketone occurs.
Protonation occurs from less hindered β-face to obtaine trans-decalin **1-25'**.



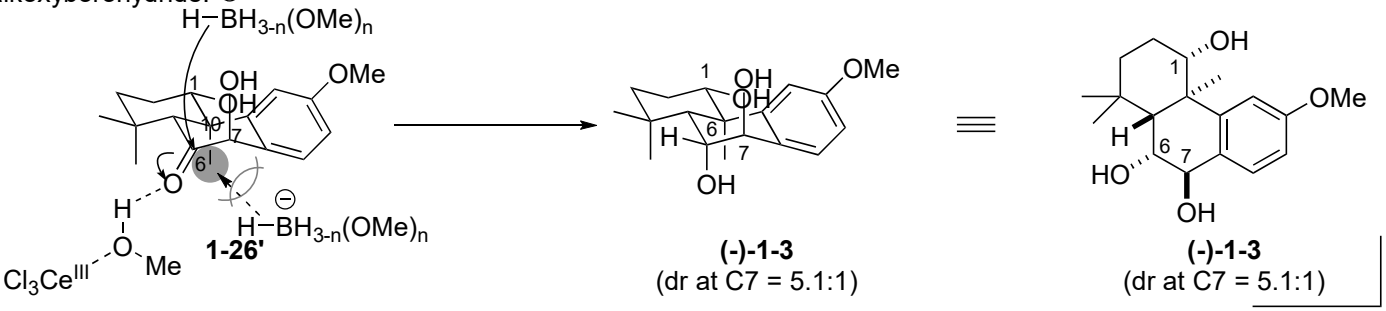
sterically shielded by
α-face: C-4, C-10 methyl groups
β-face: C-4 methyl group

4. Addition of $NaBH_4$

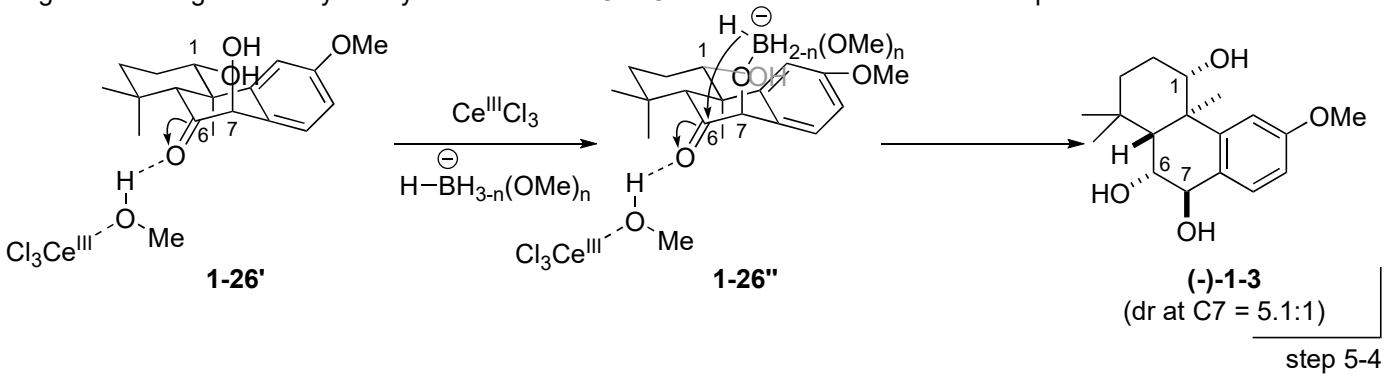
Reduction of C-6 ketone occurs.

The stereoselectivity of reduction of C-6 ketone can be explained either way.

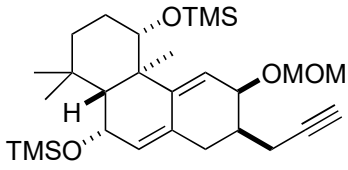
1. Steric repulsion between C-10 methyl group and alkoxyborohydride is larger than that of C7 OH group and alkoxyborohydride.



2. Ligand exchange of alkoxyborohydride occurs at C-7 OH. Then reduction occurs from β-face.



2.



2-1

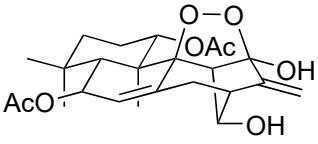
1. AIBN (0.55 eq), *n*-Bu_3SnH*, *t*-BuOH/toluene (2/1), 100 ºC, 2.5 h;
   PPTS (3.3 eq), CH_2Cl_2, 25 ºC, 13 h;
   DABCO (11 eq), OsO_4 (0.16 eq), $NaIO_4$ (22 eq) 1,4-dioxane/H_2O (2/3), 50 ºC, 6 h, 48%
2. Ac_2O (20 eq), $Sc(OTf)_3$ (0.19 eq), MeCN, 0 ºC, 0.5 h; Ac_2O/$Me_2NCH_2NMe_2$/DMF (1/1/1), 100 ºC, 16 h; 1 N aq. NaOH/MeOH (1/1), 10 min, 67%

* The amount of *n*-Bu_3SnH was not mentioned.

2-2
($C_{24}H_{36}O_6$)

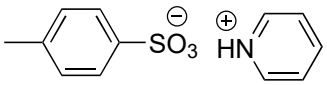
3. 24 W white LED, Rose bengal, O_2, MeCN/pyridine (40/1), 25 ºC, 36 h, 57%

4. *hv* (365 nm), MeOH, 25 ºC, 3.5 h, 14% (72% brsm)

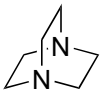


2-3
((+)-Jungermatrobrunin A)

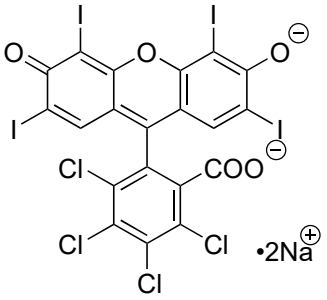
2-4



PPTS



DABCO



Rose bengal

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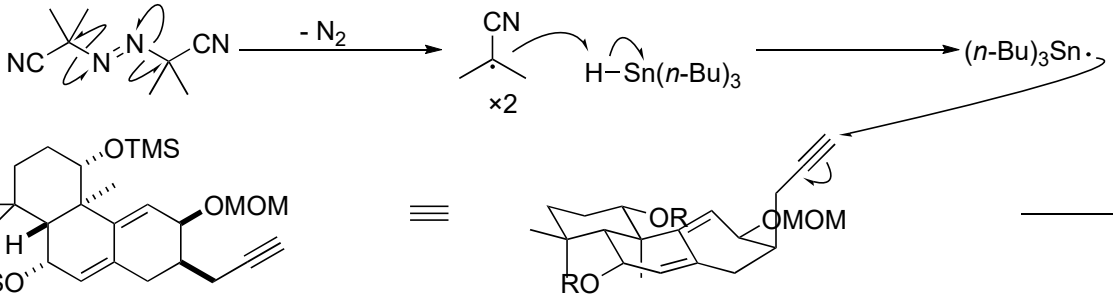
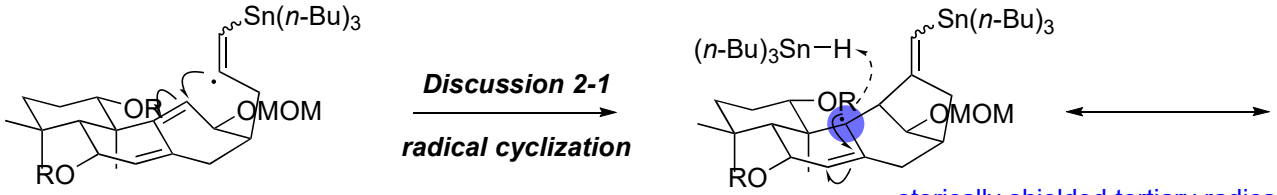
Answer



2-1

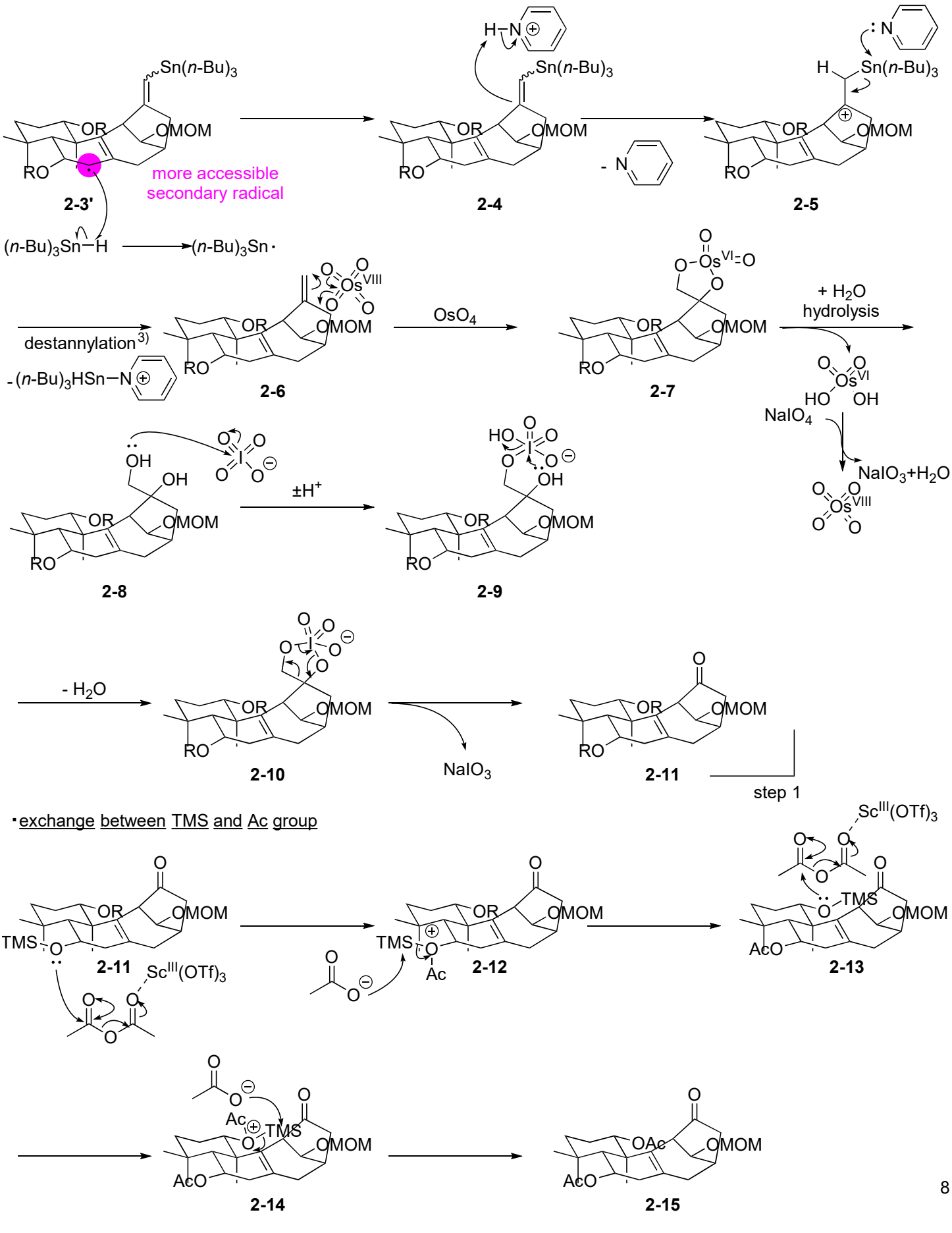
2-1
R = TMS



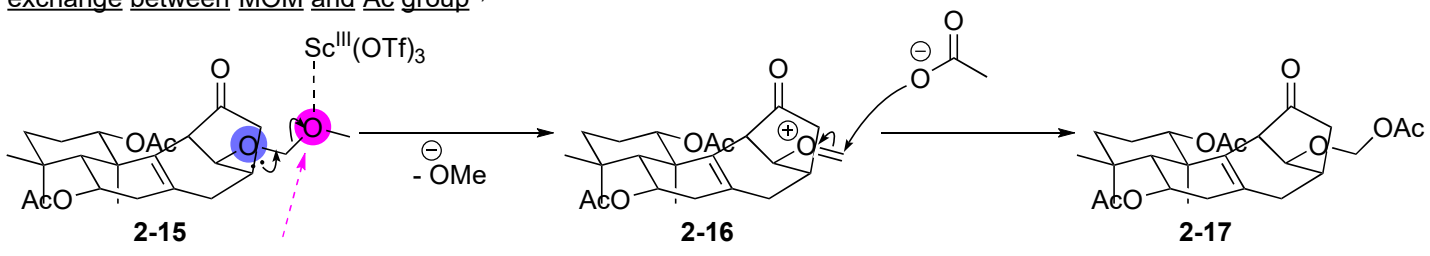
2-2

2-3

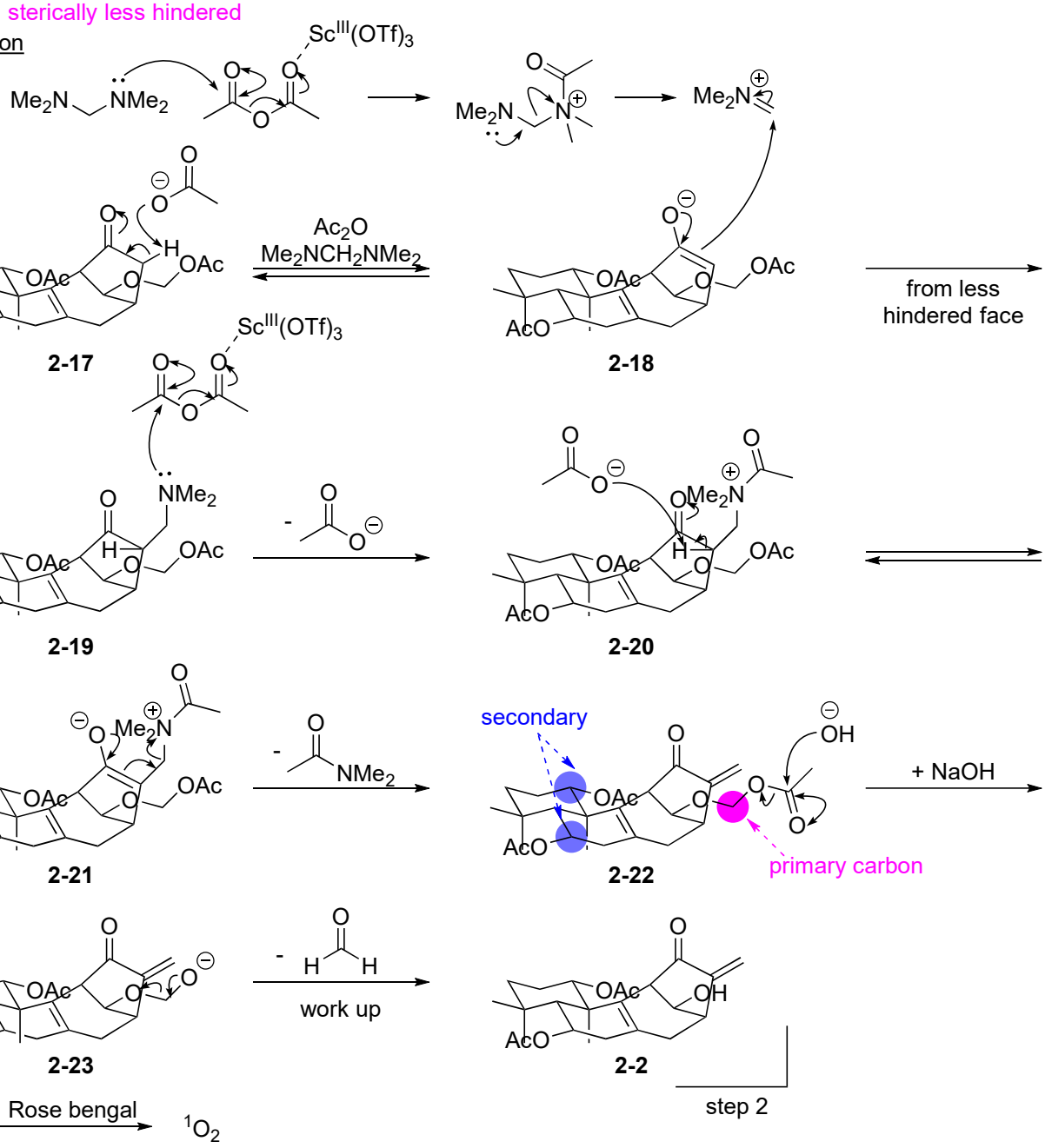
sterically shielded tertiary radical


more accessible
secondary radical
2-3'
2-4
2-5
destannylation 3)
2-6
OsO4
2-7
+ H2O
hydrolysis
NaIO4
NaIO3+H2O
±H+
2-8
2-9
- H2O
2-10
NaIO3
2-11
step 1
exchange between TMS and Ac group
Sc(III)(OTf)3
2-12
2-13
2-14
2-15

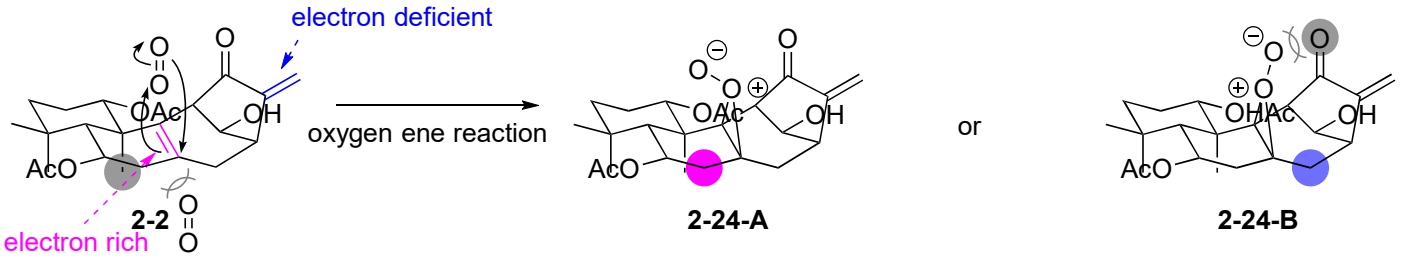
- exchange between MOM and Ac group[4)]

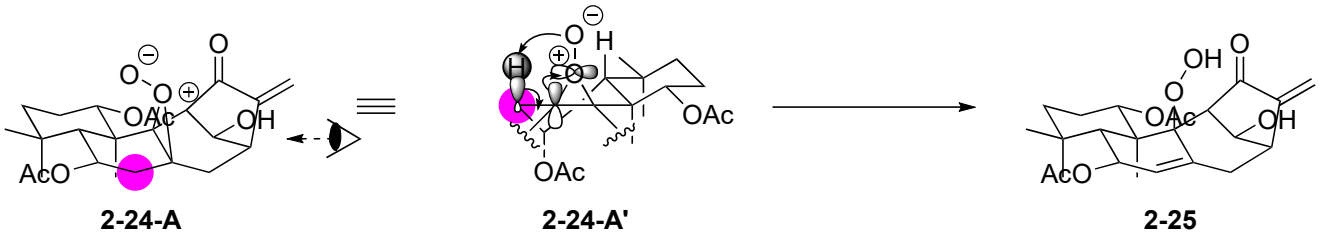


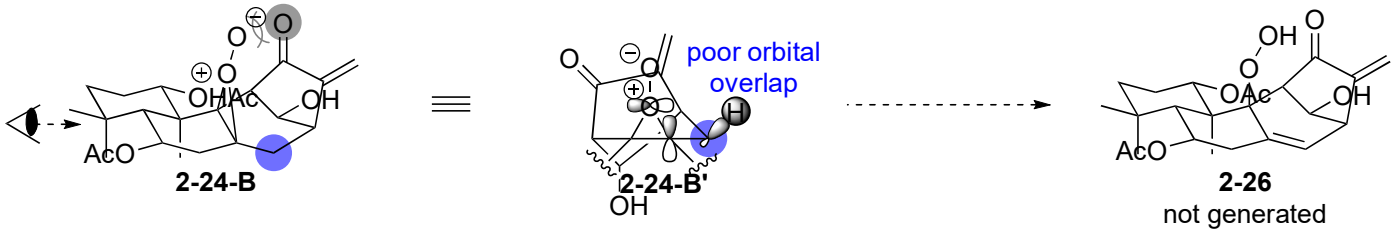
- α-methylation

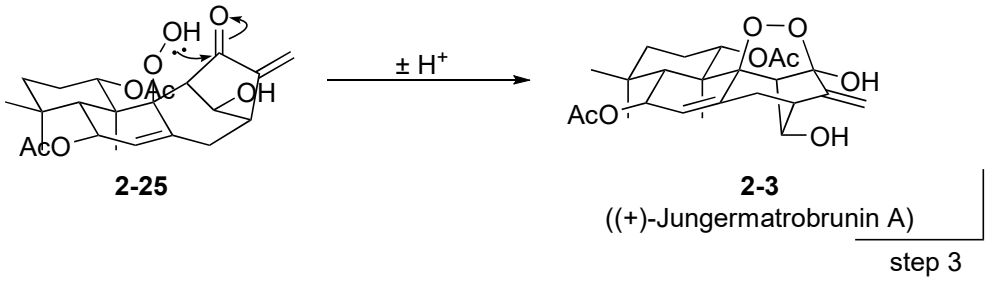


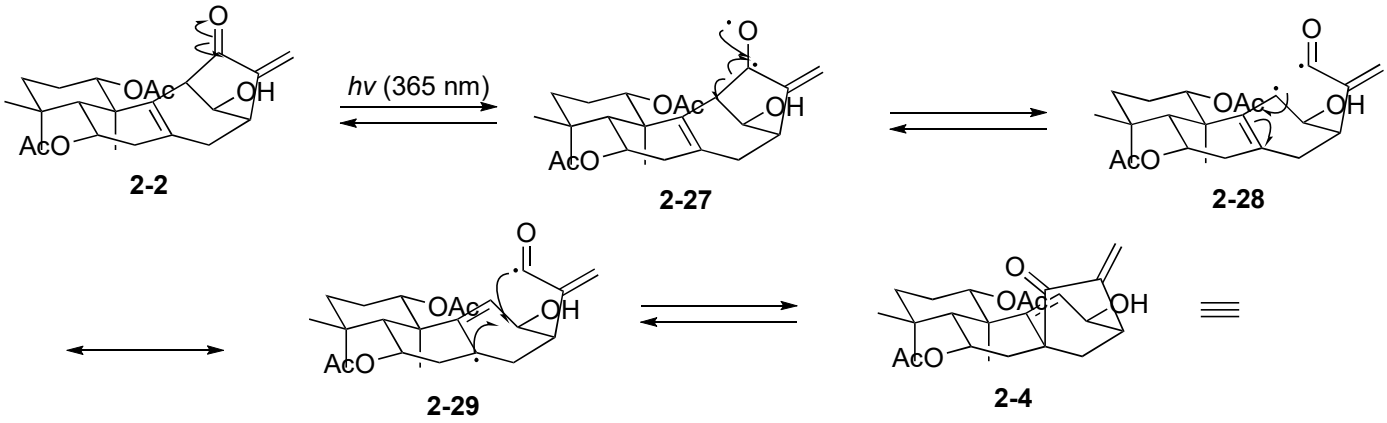
$^3O_2$ —*hv*, Rose bengal→ $^1O_2$

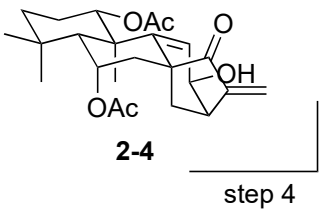



2-24-A
2-24-A'
2-25

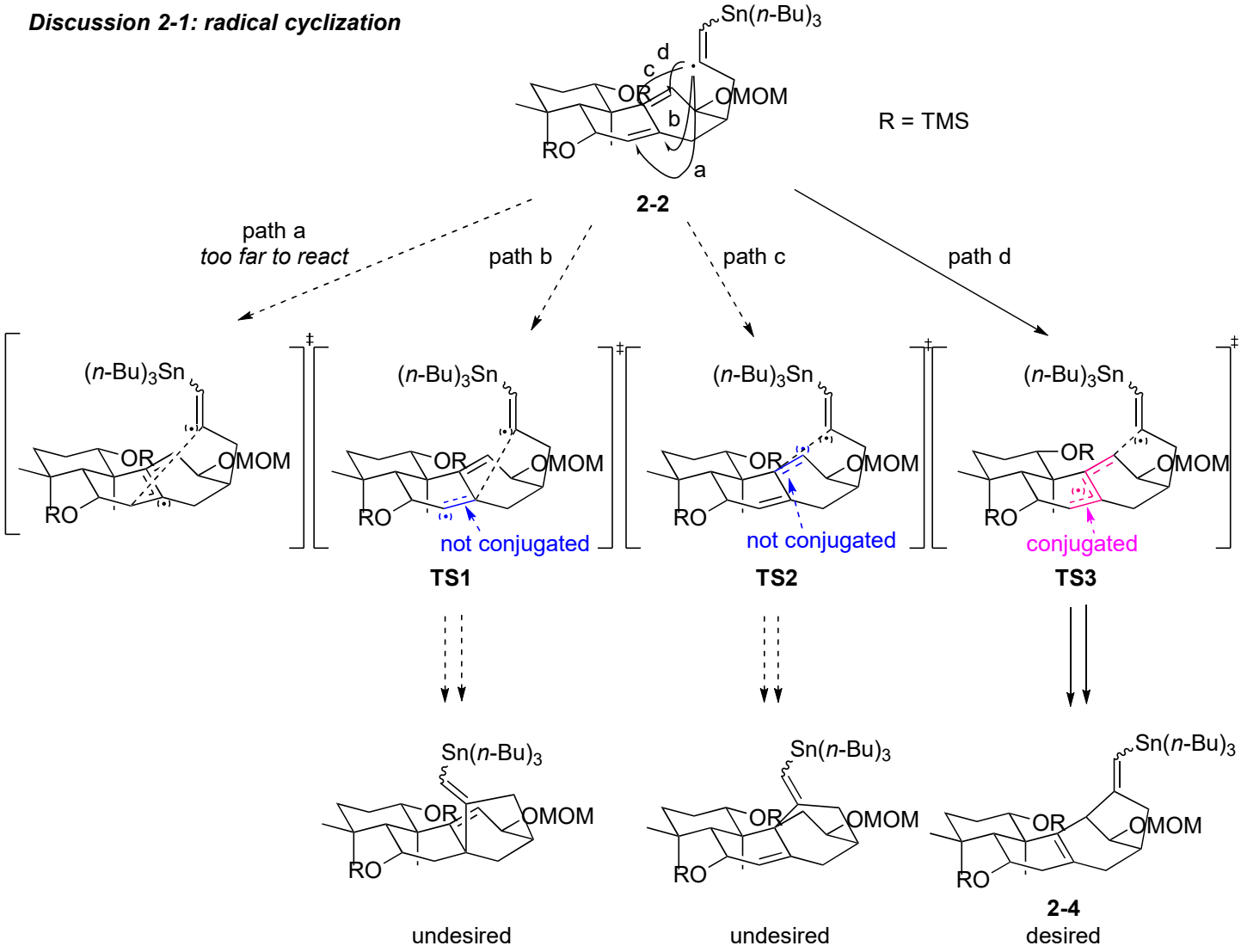

poor orbital
overlap
2-24-B
2-24-B'
2-26
not generated


± H+
2-25
2-3
((+)-Jungermatrobrunin A)
step 3


hv (365 nm)
2-2
2-27
2-28
2-29
2-4


2-4
step 4

Discussion 2-1: radical cyclization



reaction point

path a: too far to react (6-membered ring would be formed)

path b: close enough to react fast (5-membered ring would be formed)

path c: close enough to react, though farther than pathb and path d (6-membered ring would be formed)

path d: close enough to react fast (5-membered ring is formed)

stabilization in TS

In **TS1-3**, secondary radical is partially generated. In **TS1** and **TS2** the partial secondary radical is localized, while in **TS3**, partial radical is delocalized to adjacent olefin. Thus, **TS3** is more stabilized than **TS1** and **TS2**[6].

In total, path d is kinetically most favorable.

Reference

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