Problem Session (1) -Answer-

2025/01/11 Haruka Aritaki

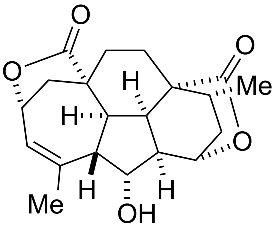
Topic: Total Synthesis of (+)-Mannolide B

0-1. Introduction

Isolation:
Cephalotaxus harringtonia

structural features:

- 5/7/5/6/6/6-Fused hexacyclic scaffold
- 2 Bridged-lactone moieties
- 10 Stereocenters: 9 contiguous
- 2 Quaternary carbon centers

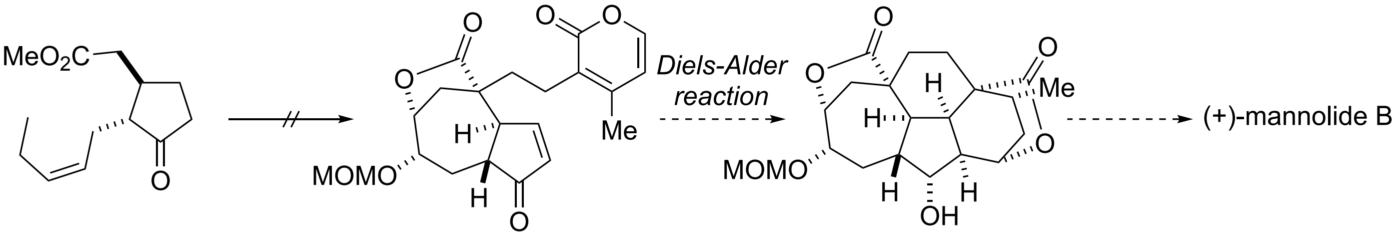


(+)-mannolide B

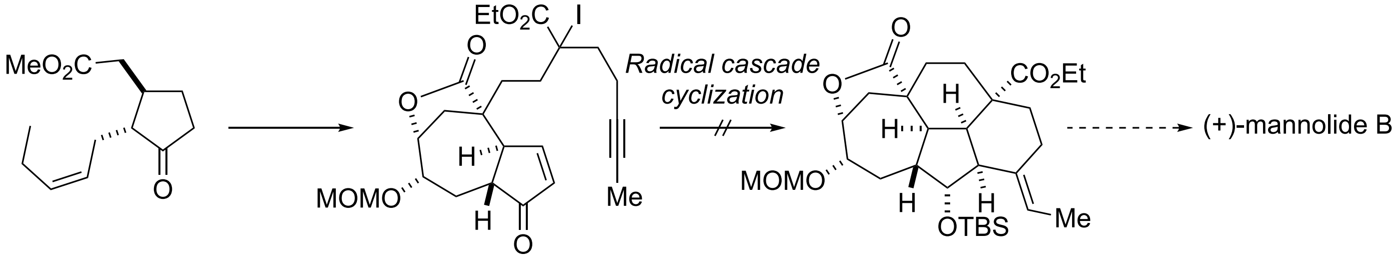
total synthesis:
Chen, P.; Chen, L.; Lin, H.; Jia, Y. *J. Am. Chem. Soc.* **2025**, *147*, 636-643.

0-2. Overview

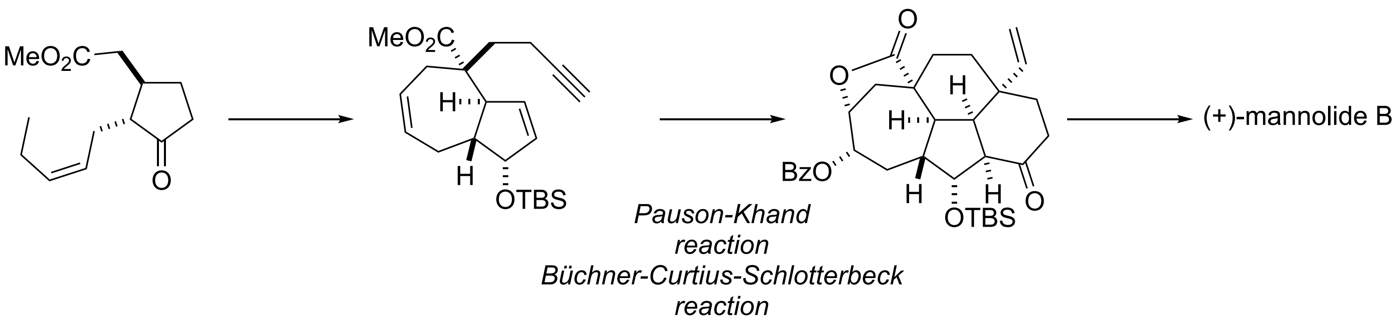
First-Generation Approach (problem 1)



Second-Generation Approach

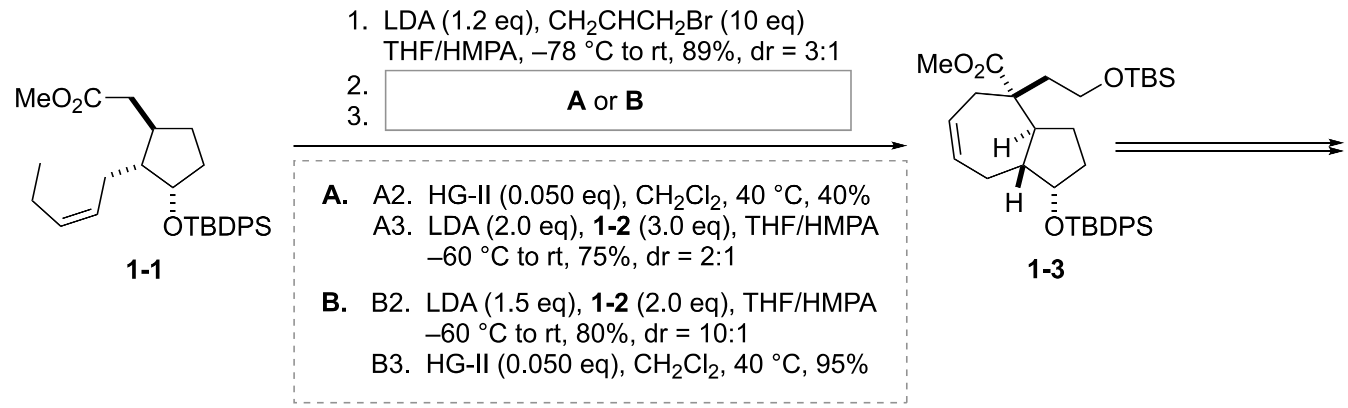


Third-Generation Approach (problem 2)



1

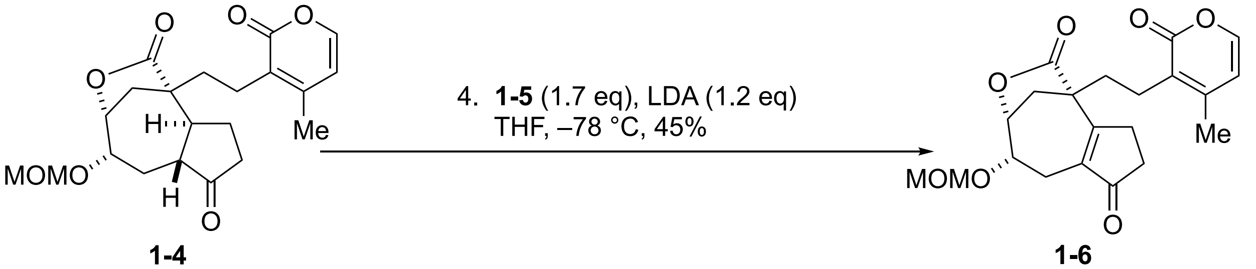
(1) Please provide the reaction mechanisms for the following reactions.
(2) Regarding Steps 2 and 3, please select the correct option from **A** or **B** within the box below.



1. LDA (1.2 eq), CH_2CHCH_2Br (10 eq) THF/HMPA, –78 °C to rt, 89%, dr = 3:1
2.
3.

A. A2. HG-II (0.050 eq), CH_2Cl_2, 40 °C, 40%
A3. LDA (2.0 eq), **1-2** (3.0 eq), THF/HMPA –60 °C to rt, 75%, dr = 2:1

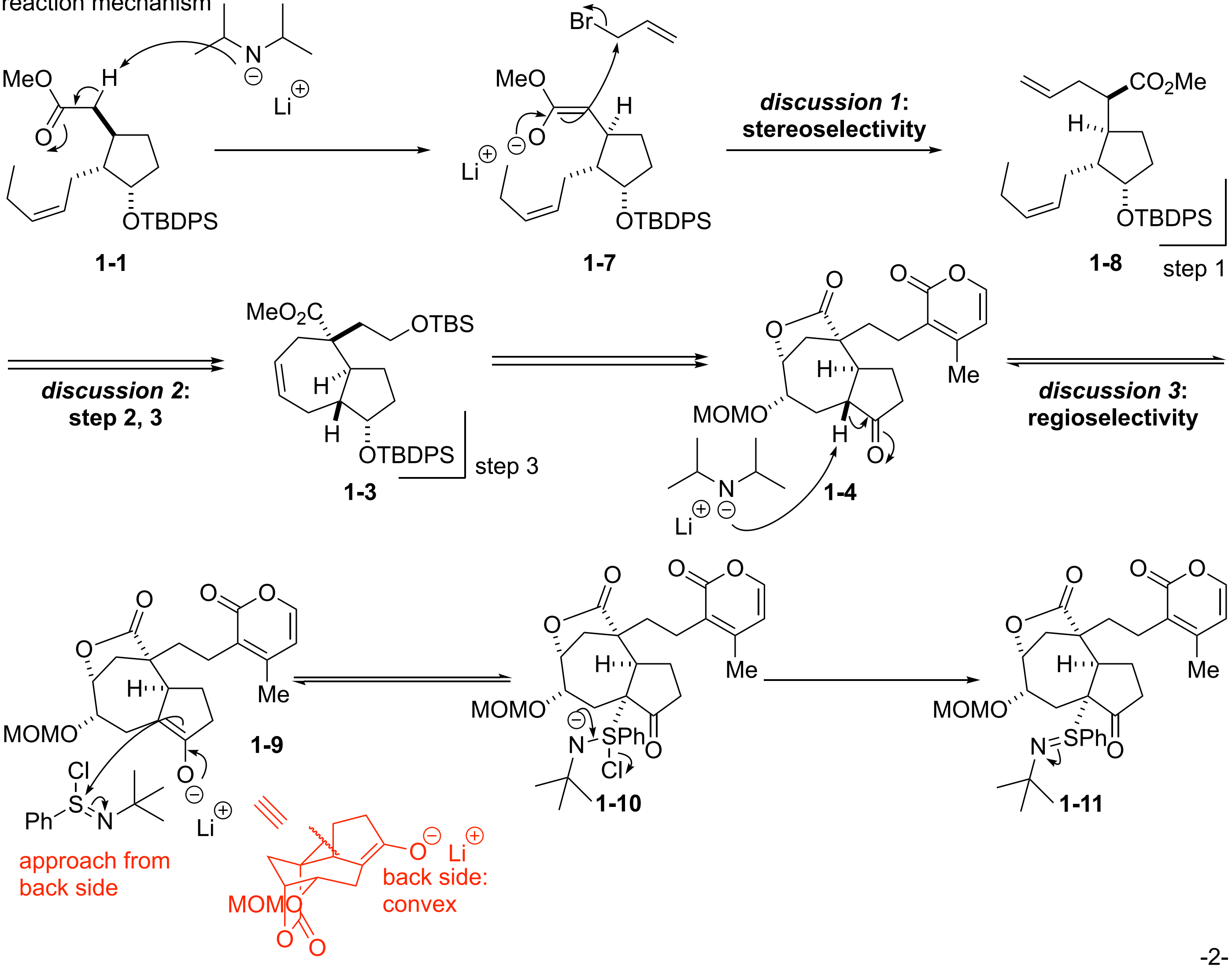
B. B2. LDA (1.5 eq), **1-2** (2.0 eq), THF/HMPA –60 °C to rt, 80%, dr = 10:1
B3. HG-II (0.050 eq), CH_2Cl_2, 40 °C, 95%

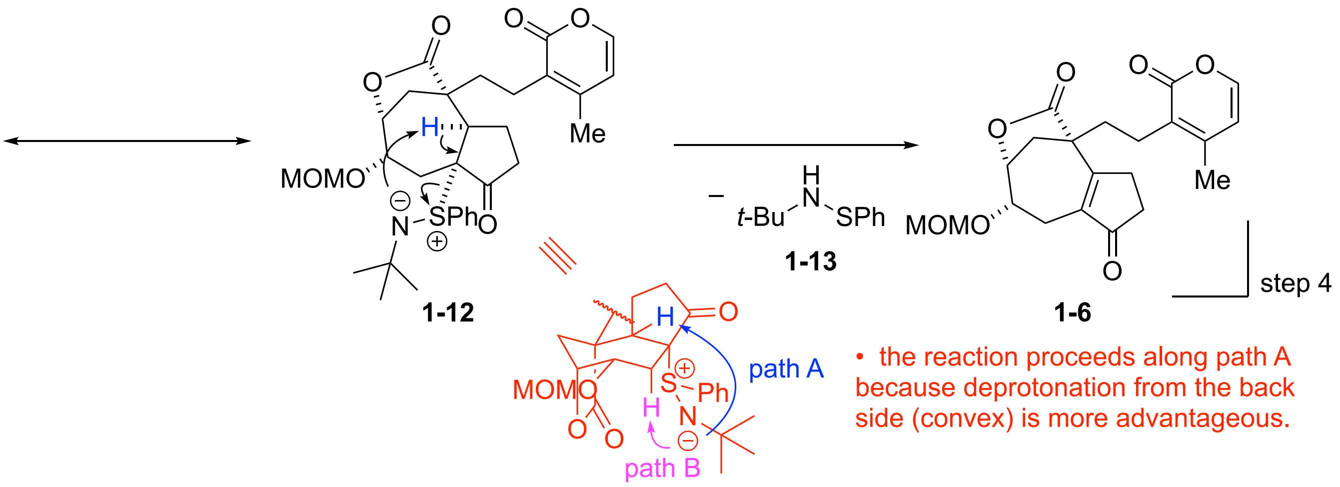


4. **1-5** (1.7 eq), LDA (1.2 eq) THF, –78 °C, 45%

Chen, P.; Chen, L.; Lin, H.; Jia, Y. *J. Am. Chem. Soc.* **2025**, *147*, 636-643.

reaction mechanism

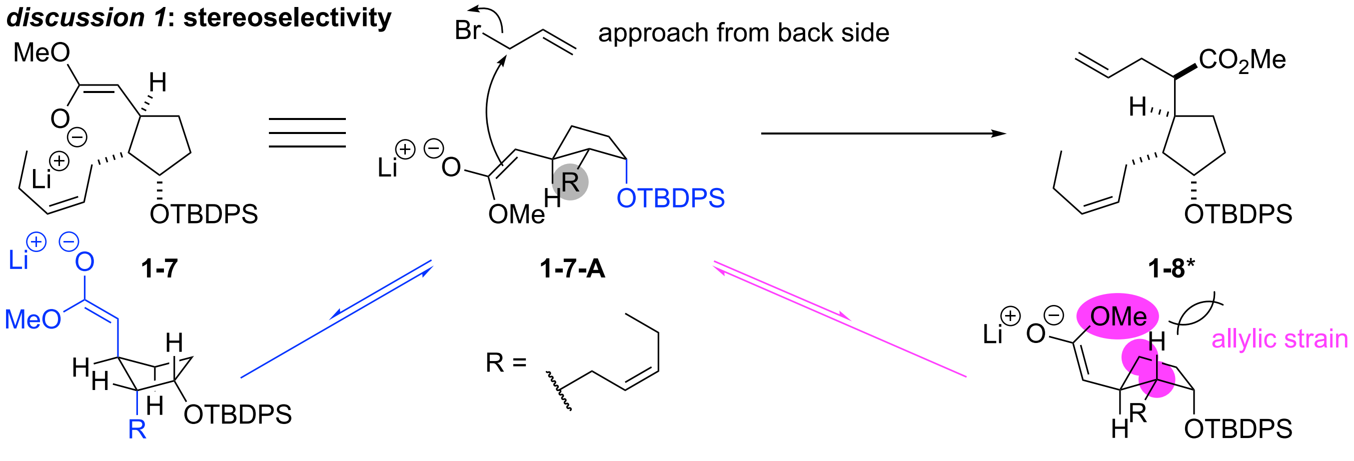




1-12 **1-13** **1-6**

- the reaction proceeds along path A because deprotonation from the back side (convex) is more advantageous.

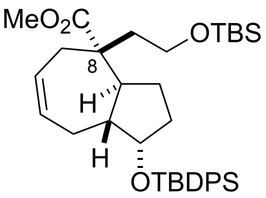
discussion 1**: stereoselectivity**



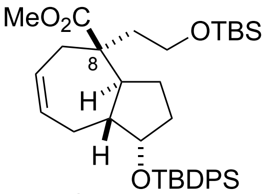
1-7 **1-7-A** **1-8*** **1-7-B** **1-7-A'**

blue: a bulky substituent in the axial position

*the authors did not comment on the stereochemistry at the C8 position



1-3



C8-*epi*-1-3

discussion 2**: step 2, 3**

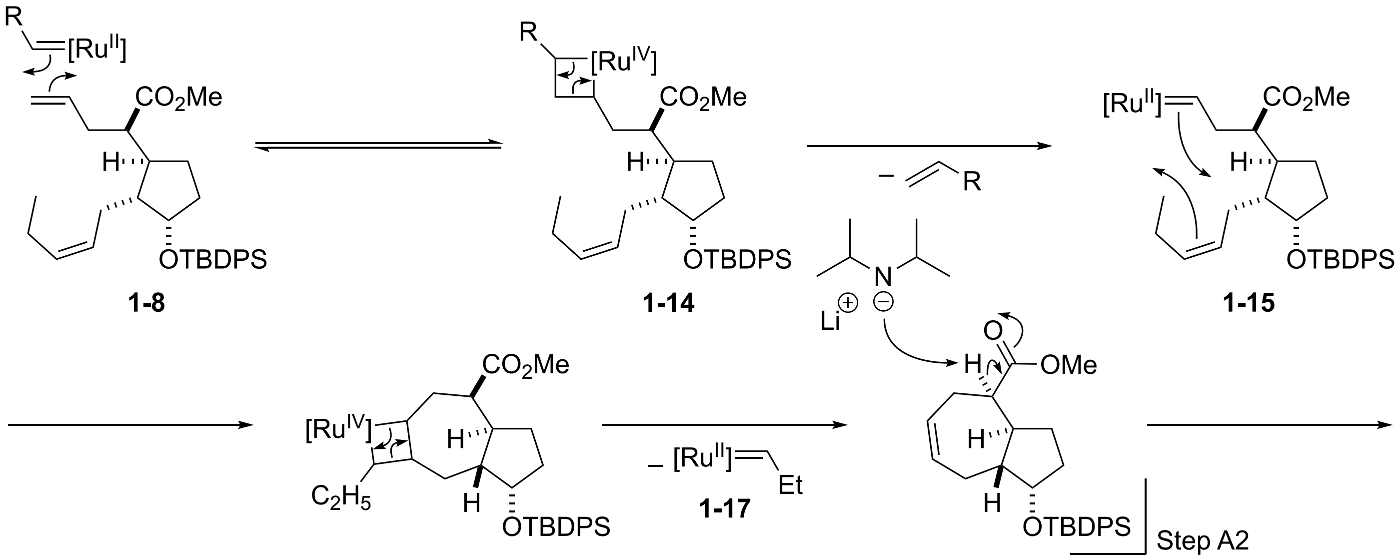
2-0. introduction

answer to question 1-(2): option B

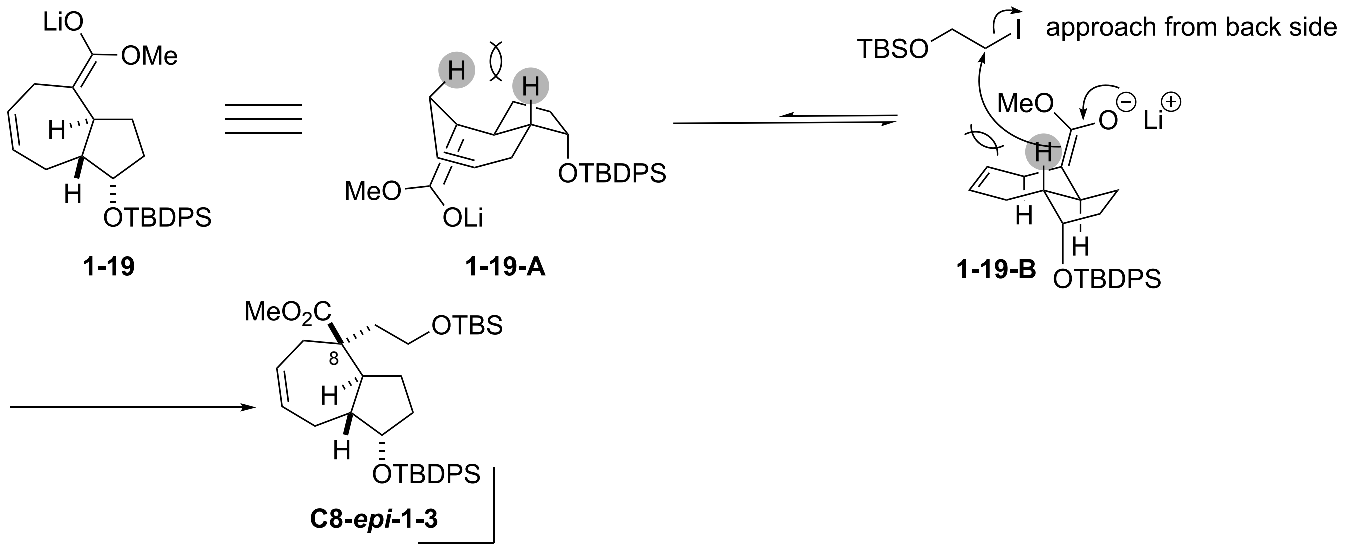
•From the two steps of option A, the main product obtained is the diastereomer **C8-*epi*-1-3**, where the stereochemistry at the C8 position of compound **1-3** is inverted. On the other hand, from the two steps of option B, compound **1-3** is predominantly obtained.

2-1. reaction mechanism and stereoselectivity

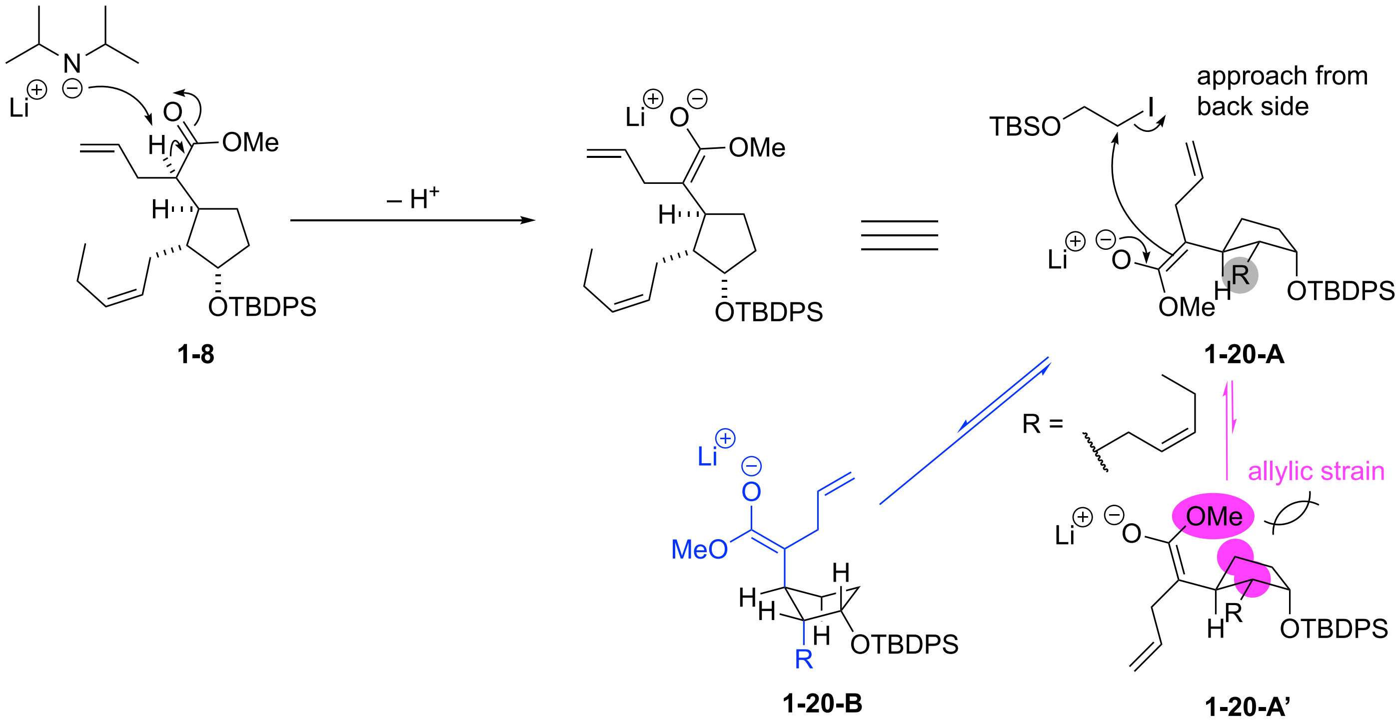
2-1-1. option A (incorrect)



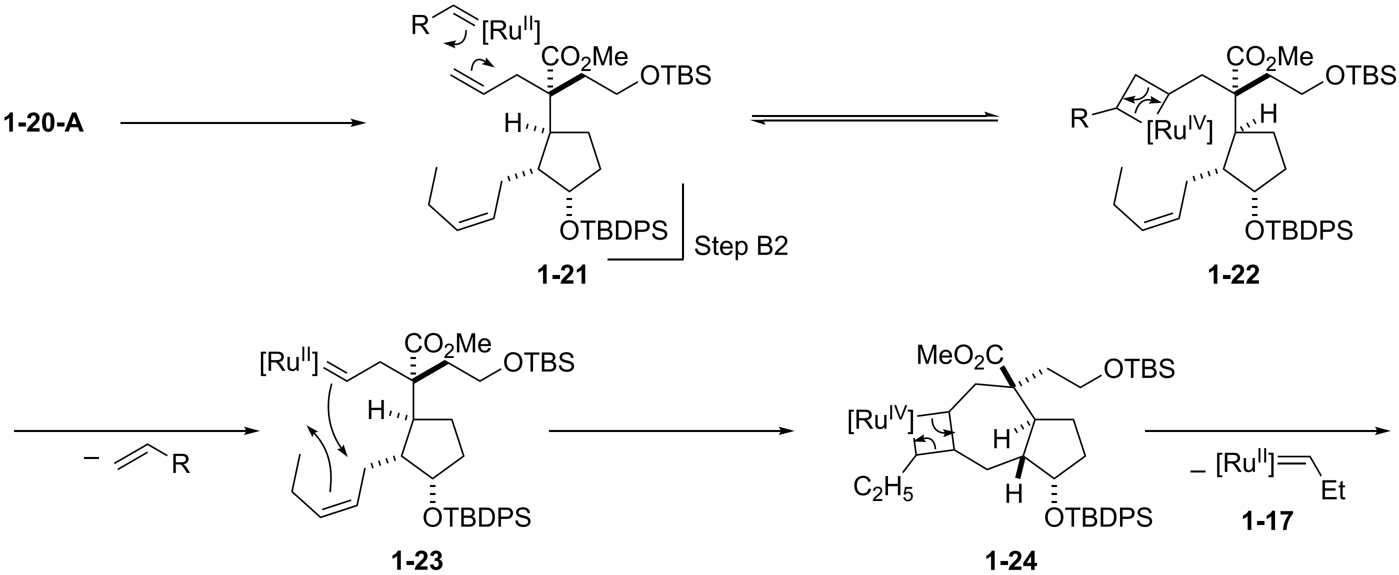
1-8 **1-14** **1-15** **1-16** **1-17** **1-18**

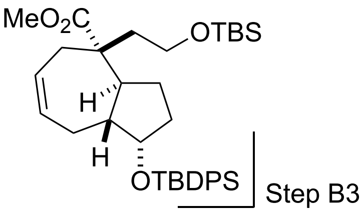


2-1-2. option B (correct)



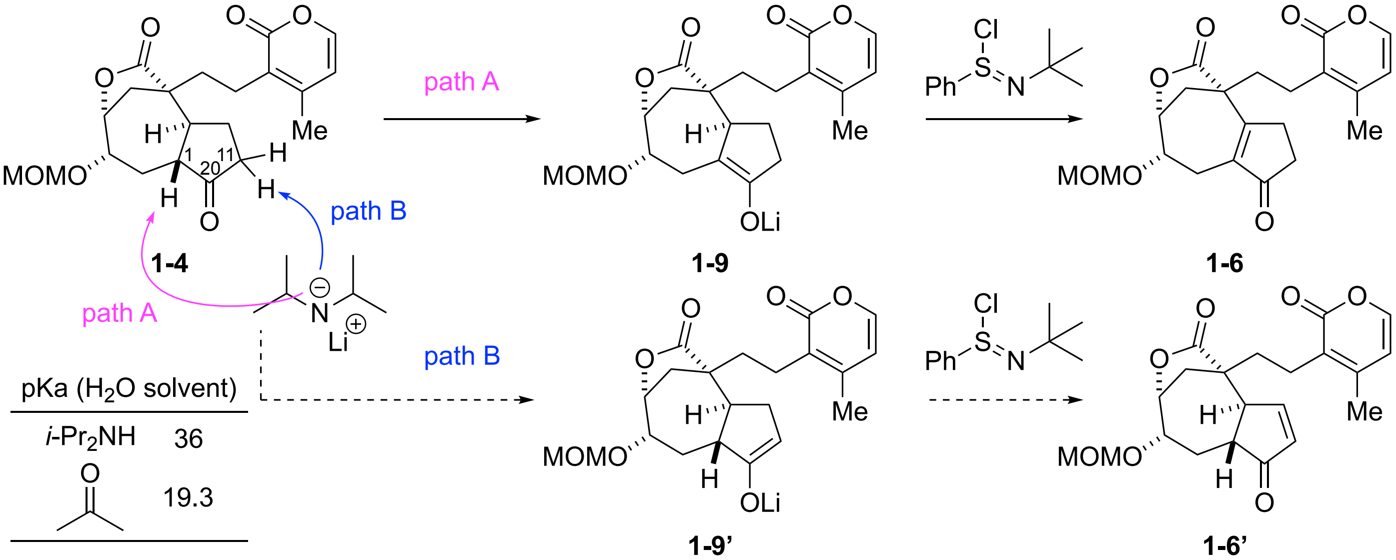
blue: a bulky substituent in the axial position





1-3

***discussion 3*: regioselectivity**

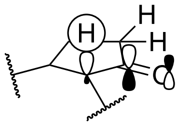


- Kinetically, it is considered more favorable for the reaction to proceed along path B, where deprotonation occurs from the site with a higher number of protons, as it is not sterically hindered. However, in this reaction, the enone **1-6'** was not obtained.

author's opinion

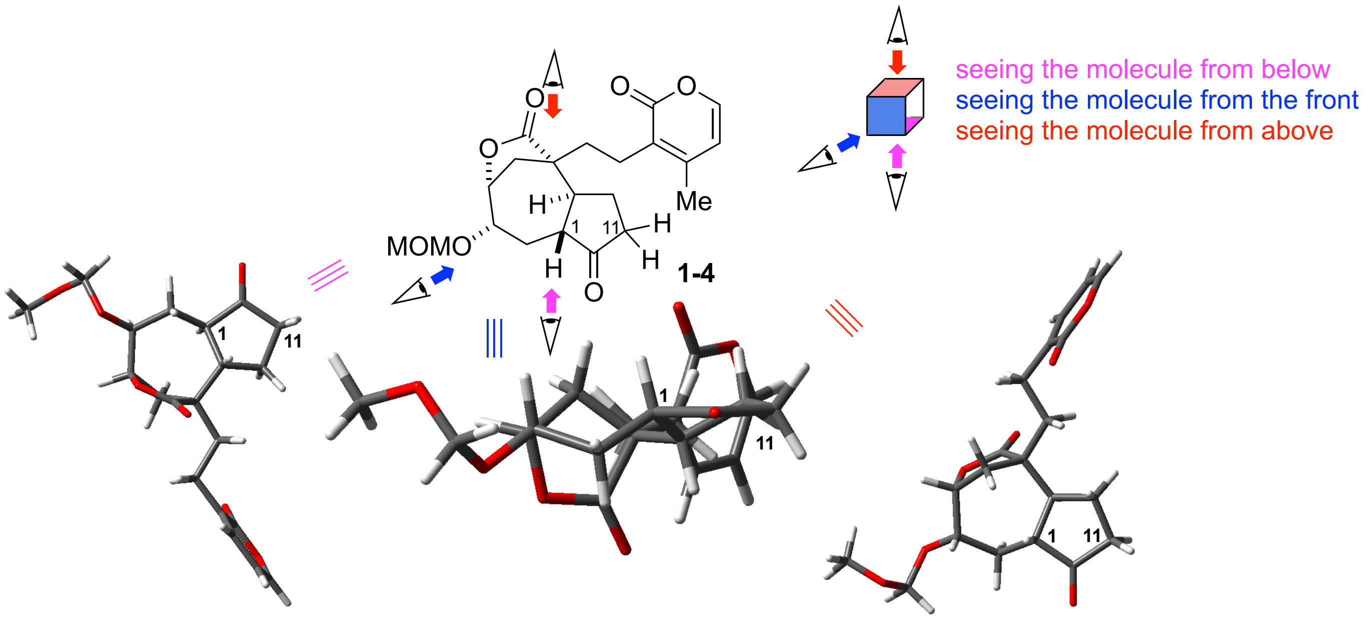
- The C-H bond at C11 is essentially perpendicular to the carbonyl group at C20, thus potentially facilitating the σ-π delocalization, so the C11 proton deprotonates more easily than the C1.

-> It is considered that the proton at the C11 position could also contribute to the electronic effects.



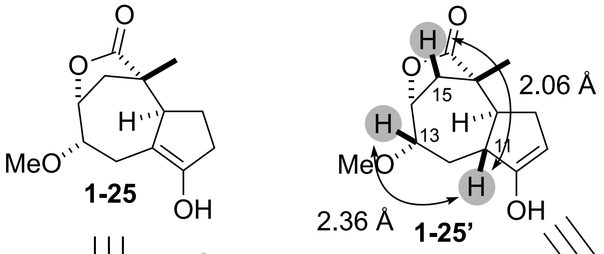
a picture that explans the author's argument -> is this picture correct?

- Referring to the most stable conformation of **1-4** calculated using the macro model, the angle between the proton on C1 and the downward proton on C11 relative to the carbonyl group appears to remain largely unchanged.

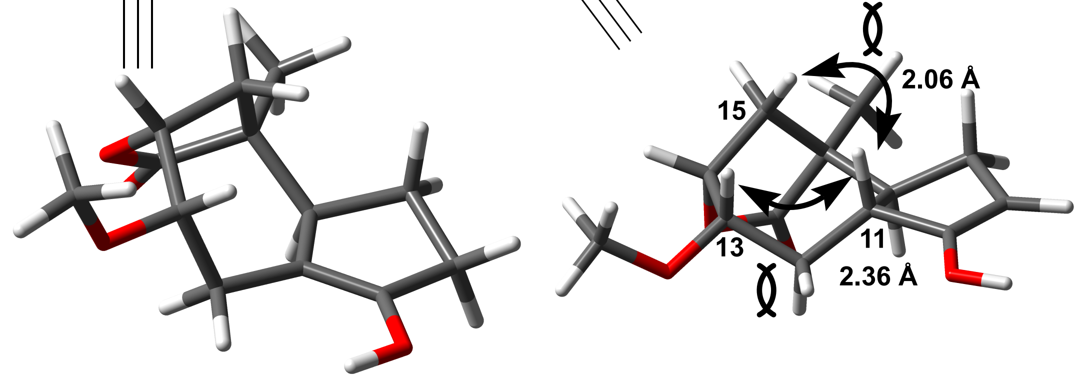


plausible explanation

The most stable conformation of a compound (**1-25 and 1-25'**) with the same skeletal features as **1-9** and **1-9'** was calculated.

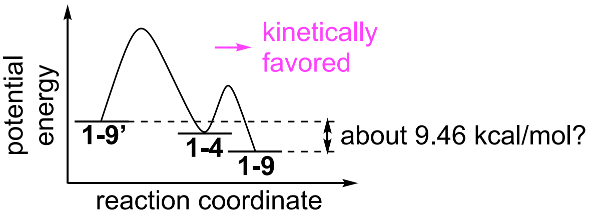


- the energy difference between **1-25** to **1-25'**: 9.46 kcal/mol
- van der waals radius of hydrogen: 120 pm = 1.20 Å
- calculated at M06-2X/6-31+G(d) level



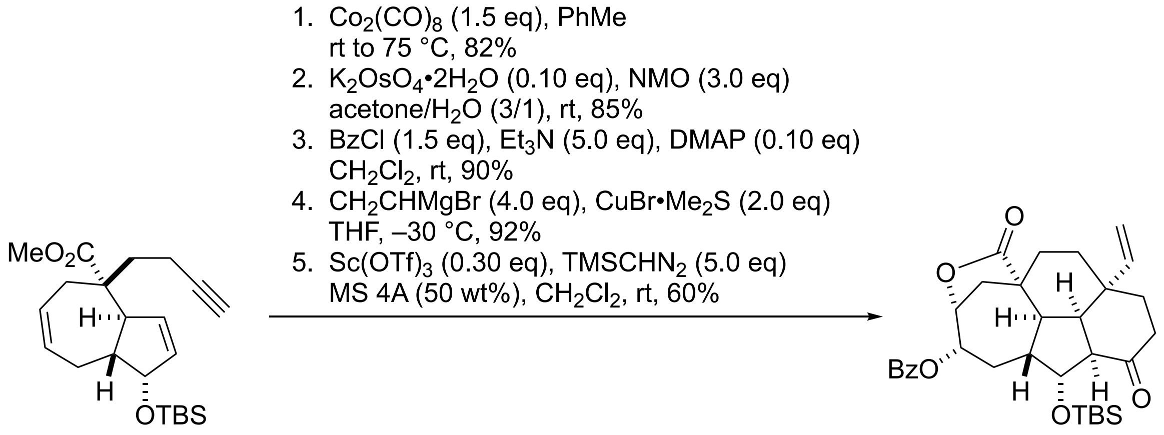
- In **1-25'**, the steric repulsion between the hydrogen atoms of C11 and C13, as well as between C11 and C15, are thought to make it 9.46 kcal/mol thermodynamically less stable than **1-25**.

- It is considered that, like **1-25'**, the structure of **1-4** is distorted due to the repulsion between hydrogen atoms on the seven-membered ring. Therefore, it is considered that the reaction progressed in a way that alleviates this distortion, leading to a more stable transition state energy, which is kinetically favorable.



2

Please provide the reaction mechanisms for the following reactions.

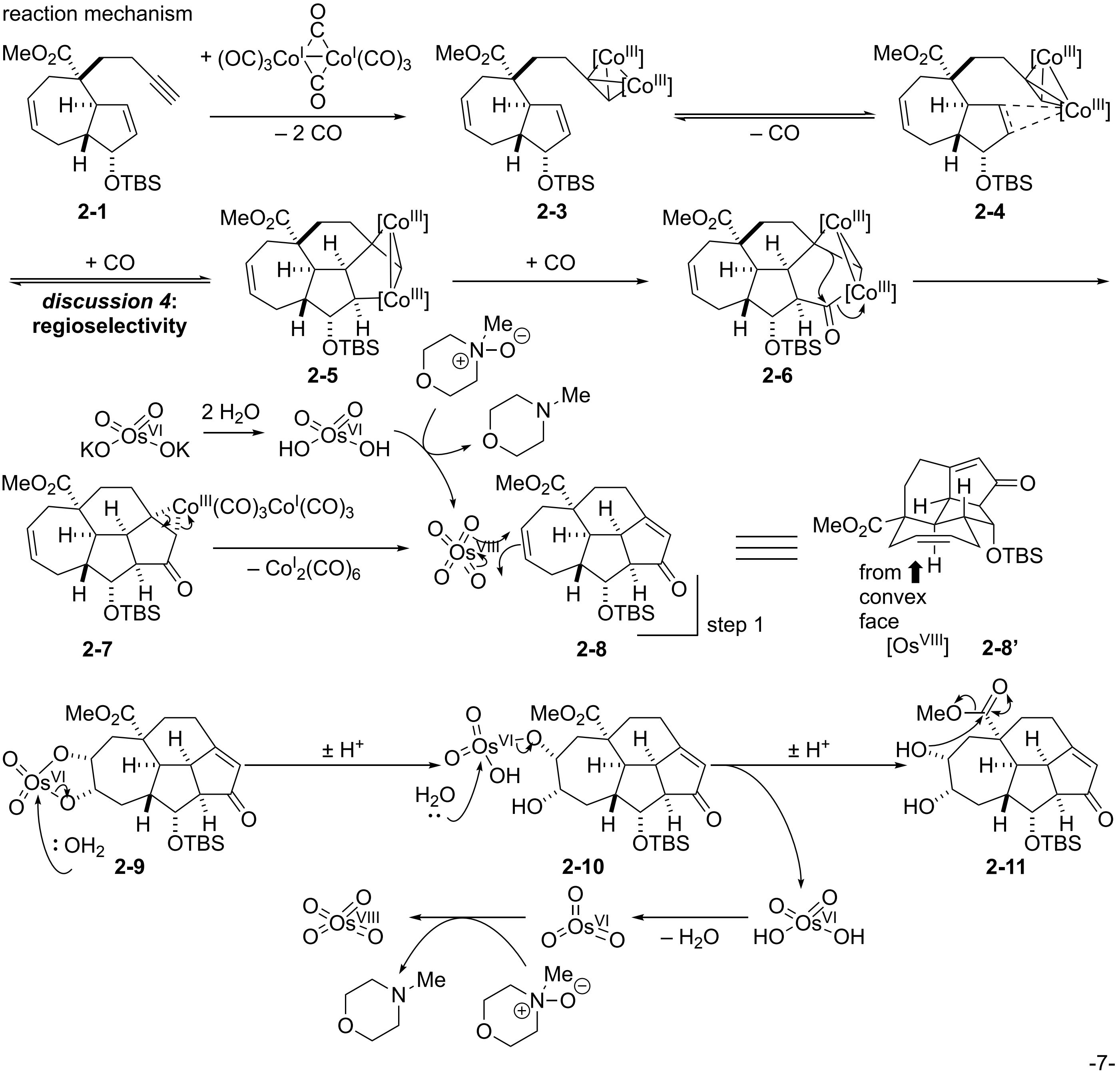


1. $Co_2(CO)_8$ (1.5 eq), PhMe
   rt to 75 °C, 82%
2. $K_2OsO_4 \cdot 2H_2O$ (0.10 eq), NMO (3.0 eq)
   acetone/H_2O (3/1), rt, 85%
3. BzCl (1.5 eq), Et_3N (5.0 eq), DMAP (0.10 eq)
   CH_2Cl_2, rt, 90%
4. $CH_2CHMgBr$ (4.0 eq), $CuBr \cdot Me_2S$ (2.0 eq)
   THF, –30 °C, 92%
5. $Sc(OTf)_3$ (0.30 eq), $TMSCHN_2$ (5.0 eq)
   MS 4A (50 wt%), CH_2Cl_2, rt, 60%

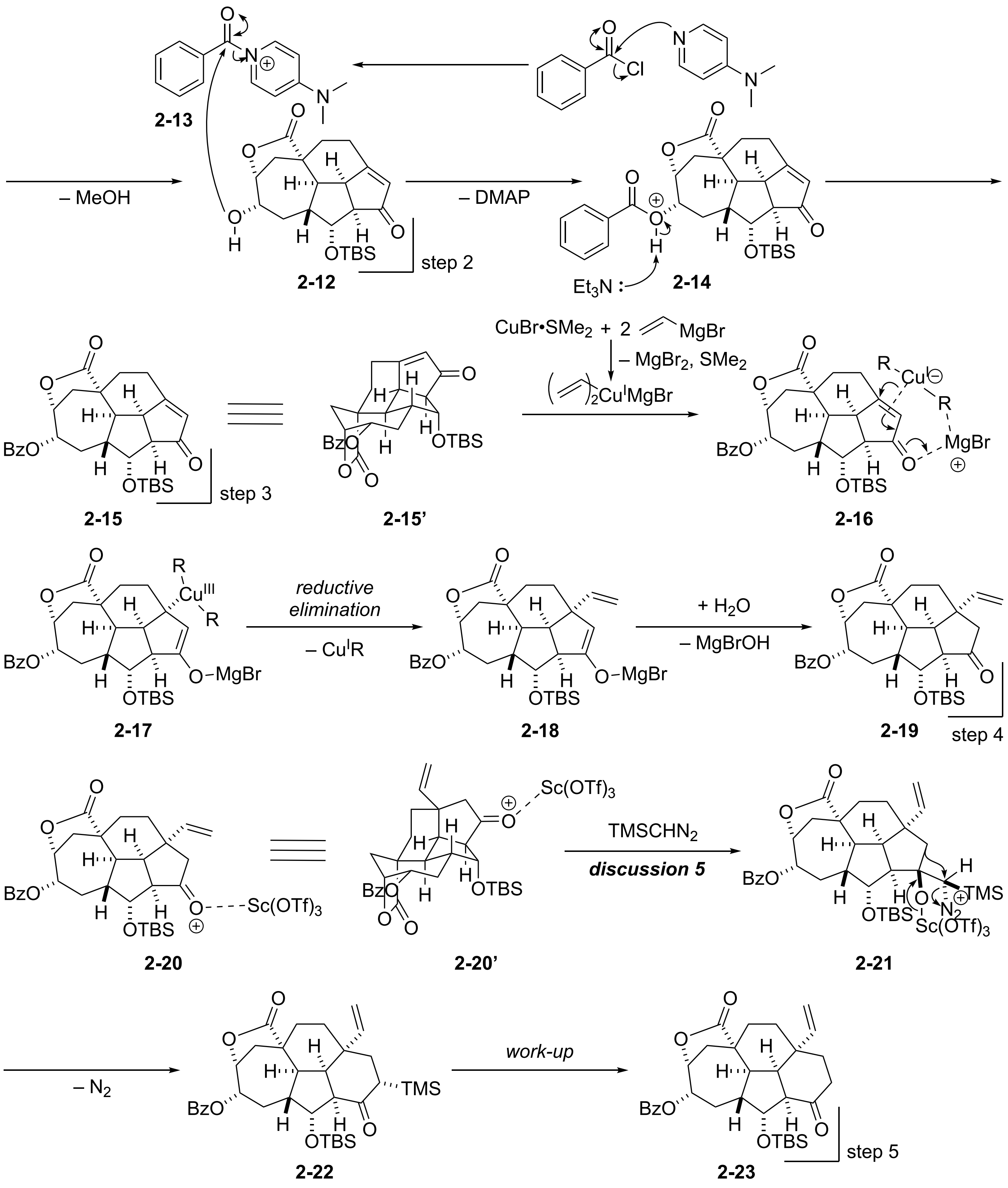
2-1 **2-2**

Chen, P.; Chen, L.; Lin, H.; Jia, Y. *J. Am. Chem. Soc.* **2025**, *147*, 636-643.

reaction mechanism

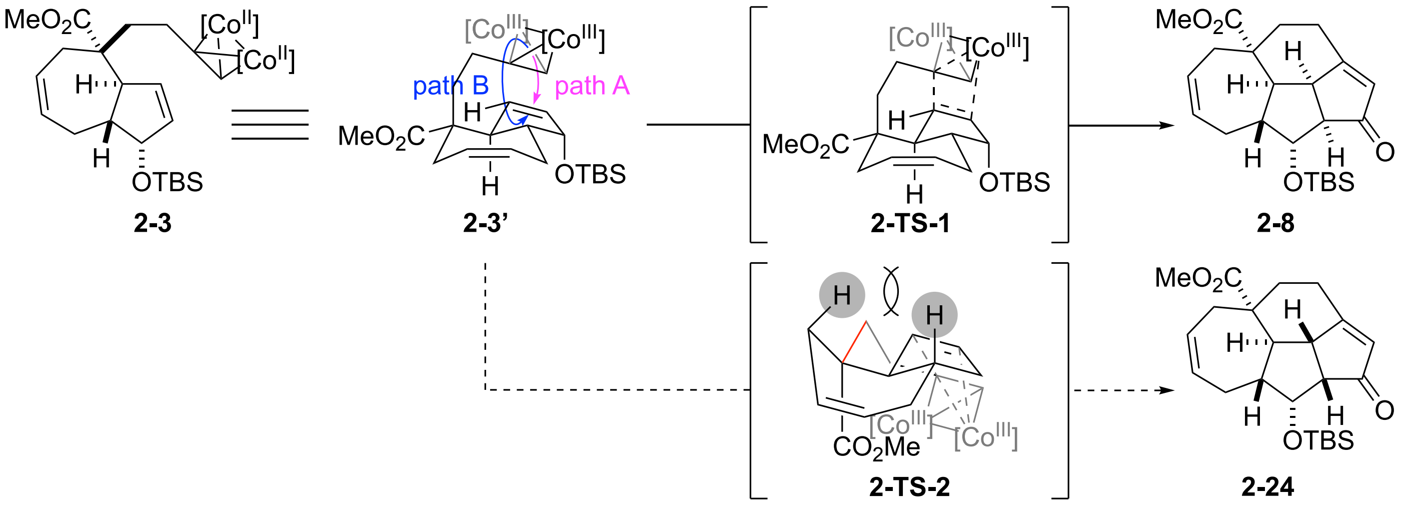


2-1 **2-3** **2-4** **2-5** **2-6** **2-7** **2-8** **2-8'** **2-9** **2-10** **2-11**



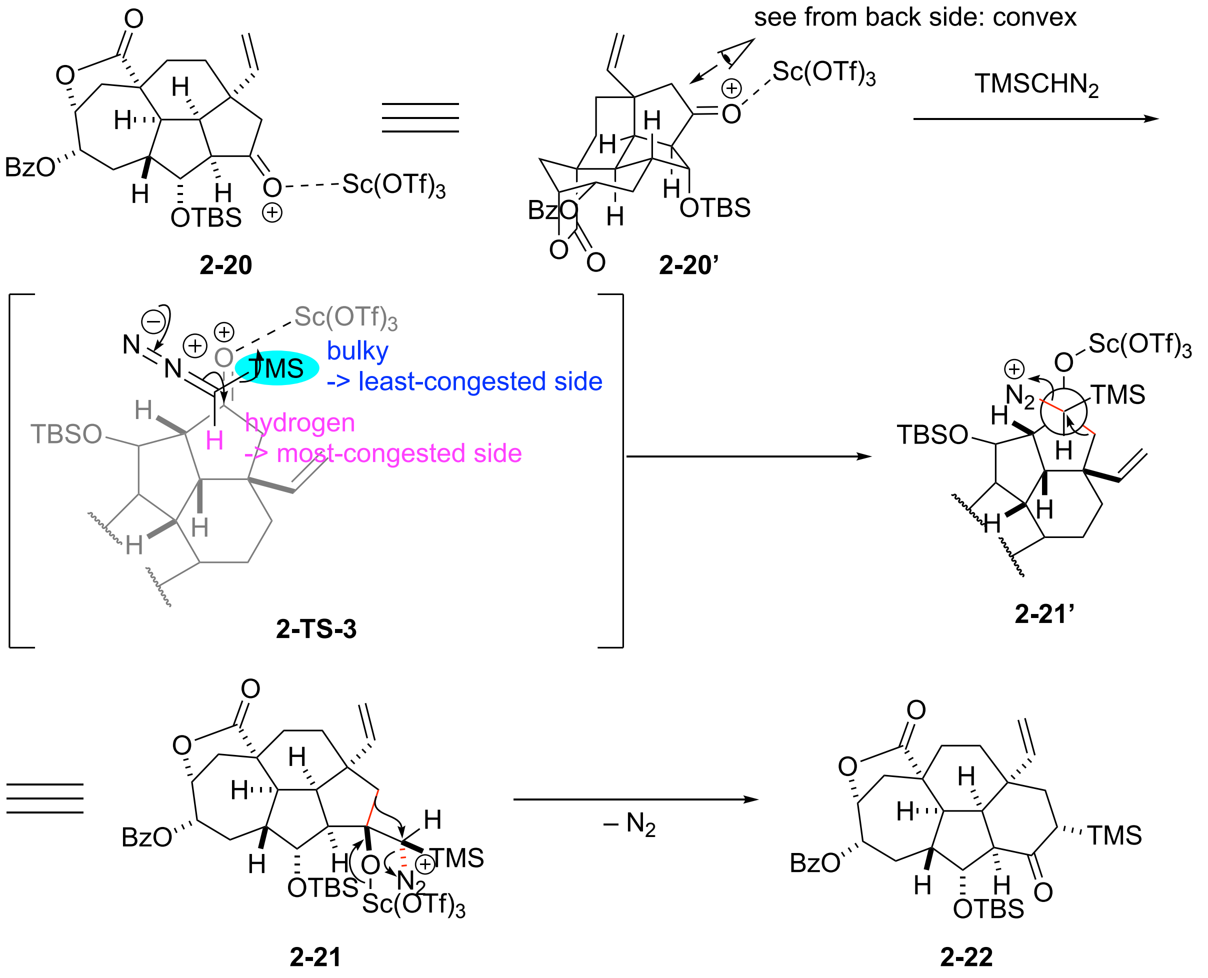
- Regarding the reaction mechanism of the addition and regioselectivity of the migration, please refer to ***discussion 5***.

discussion 4: regioselectivity



- For the cobalt complex to coordinate from below to the olefin, the carbon-carbon bond highlighted in red must point in the equatorial direction.

discussion 5: Büchner-Curtius-Schlotterbeck reaction



- The high regioselectivity of this reaction is believed to manifest during the addition step of trimethylsilyl diazomethane. During addition, trimethylsilyl diazomethane is thought to approach compound **2-20** in such a way that the bulkiest TMS group points in the direction with the most steric availability, while the hydrogen atom points in the direction with the most steric congestion.