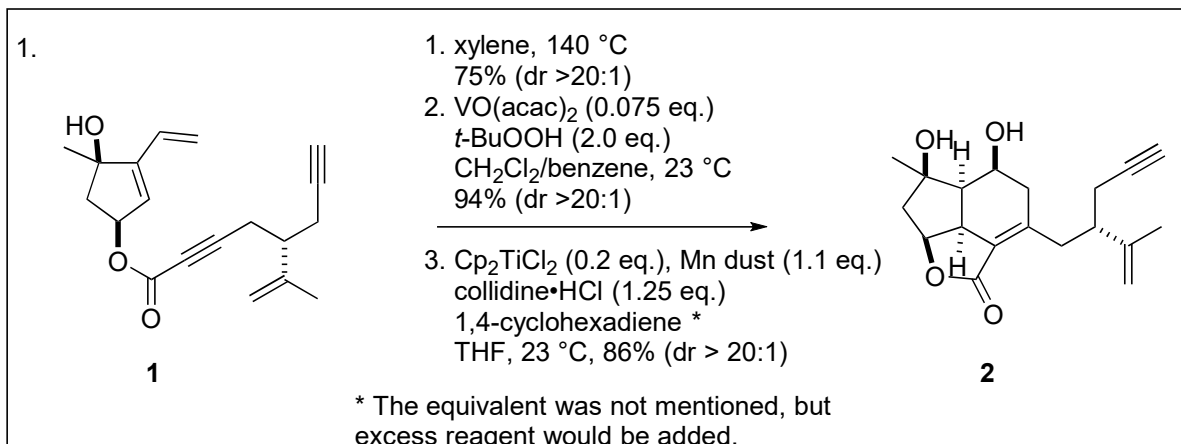


# Problem Session (4)

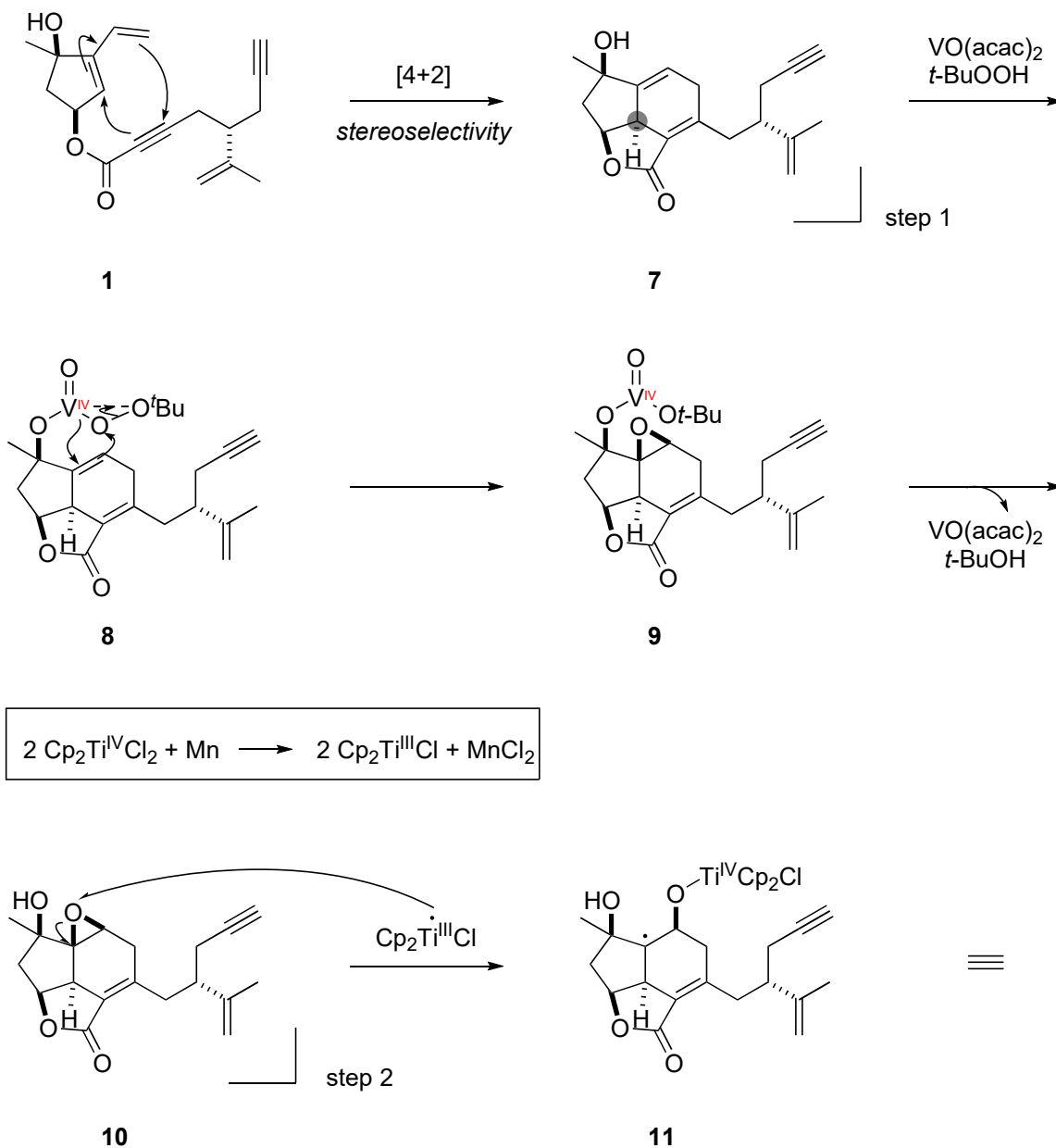
2020. 6. 6. Takahiro Watanabe

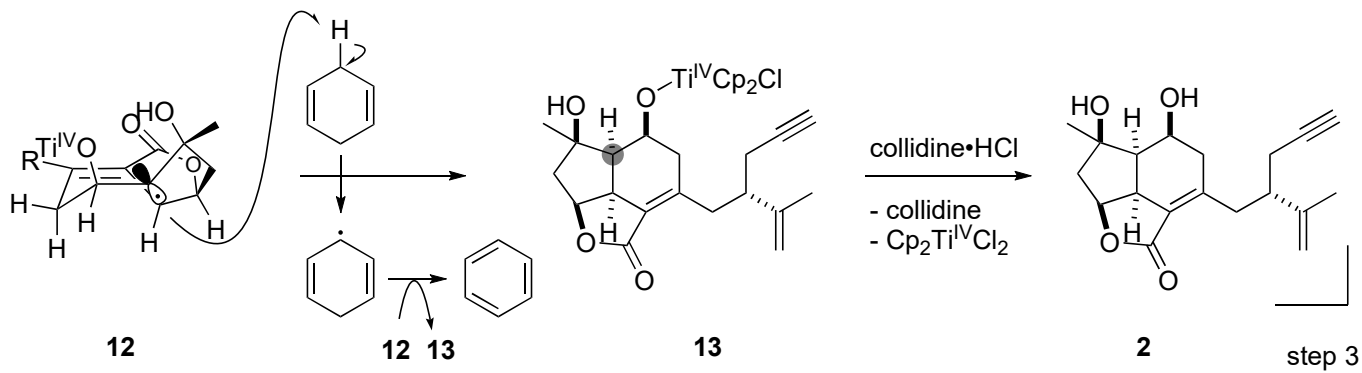
topic: total synthesis of (-)-scabrolide A

Hafeman, N. J.; Loskot, S. A.; Reimann, C. E.; Pritchett, B. P.; Virgil, S. C.; Stoltz, B. M.  
*J. Am. Chem. Soc.* **2020**, *142*, 8585.

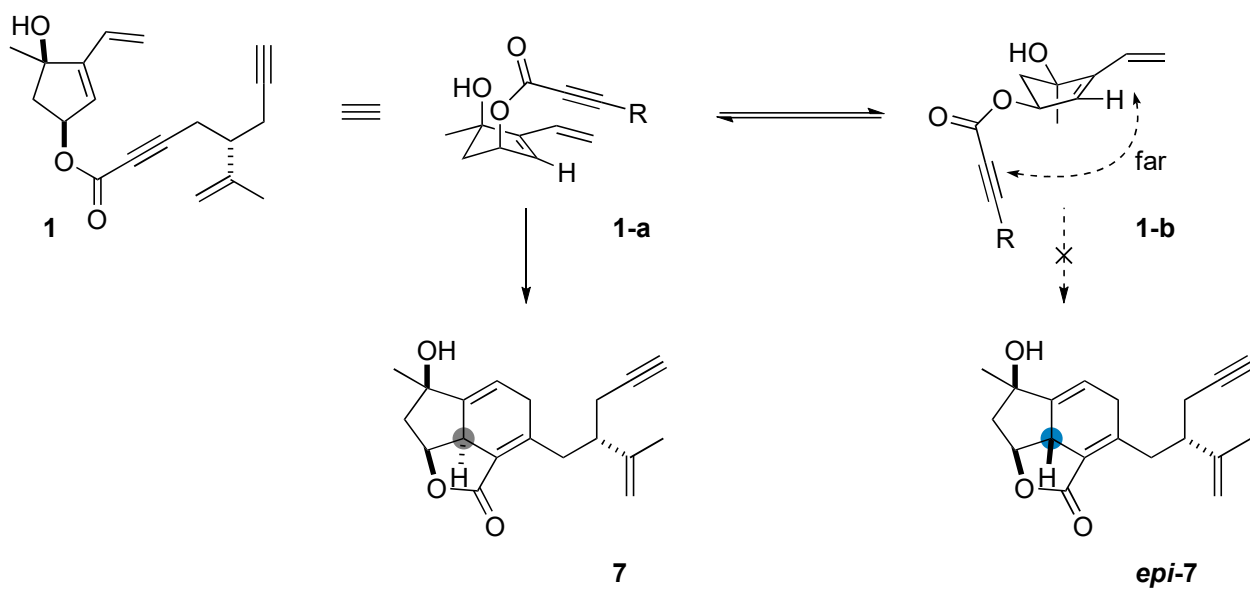


reaction mechanisms:

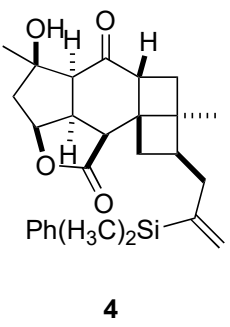
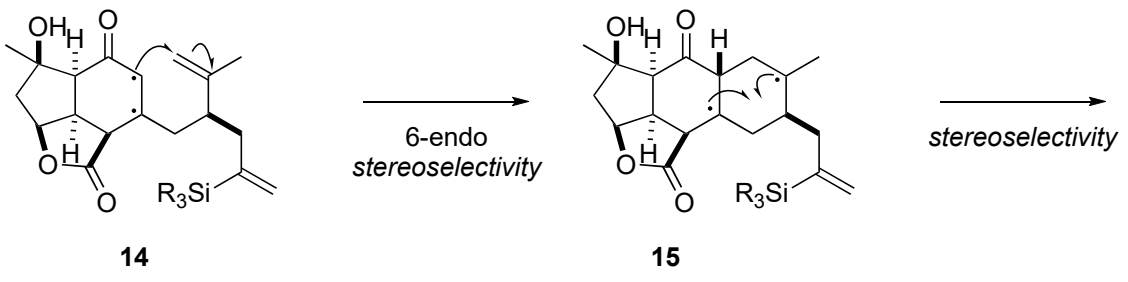
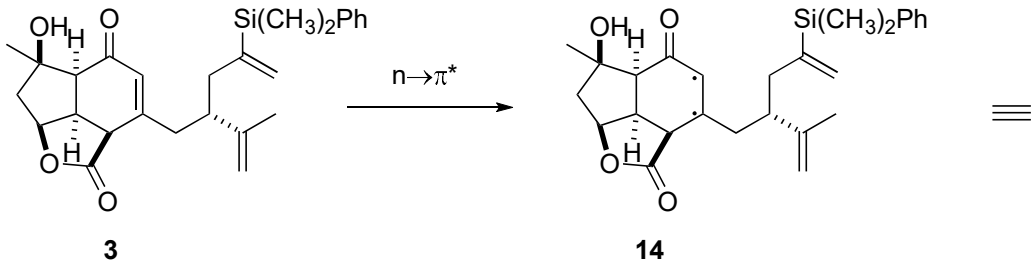
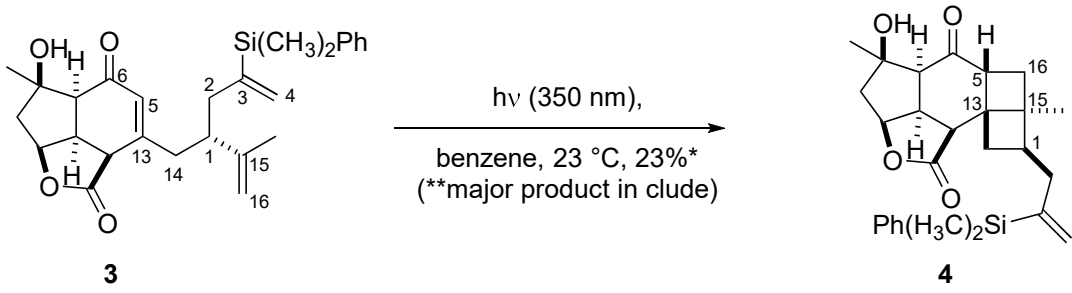




Discussion 1: stereoselectivity of Diels-Alder reaction

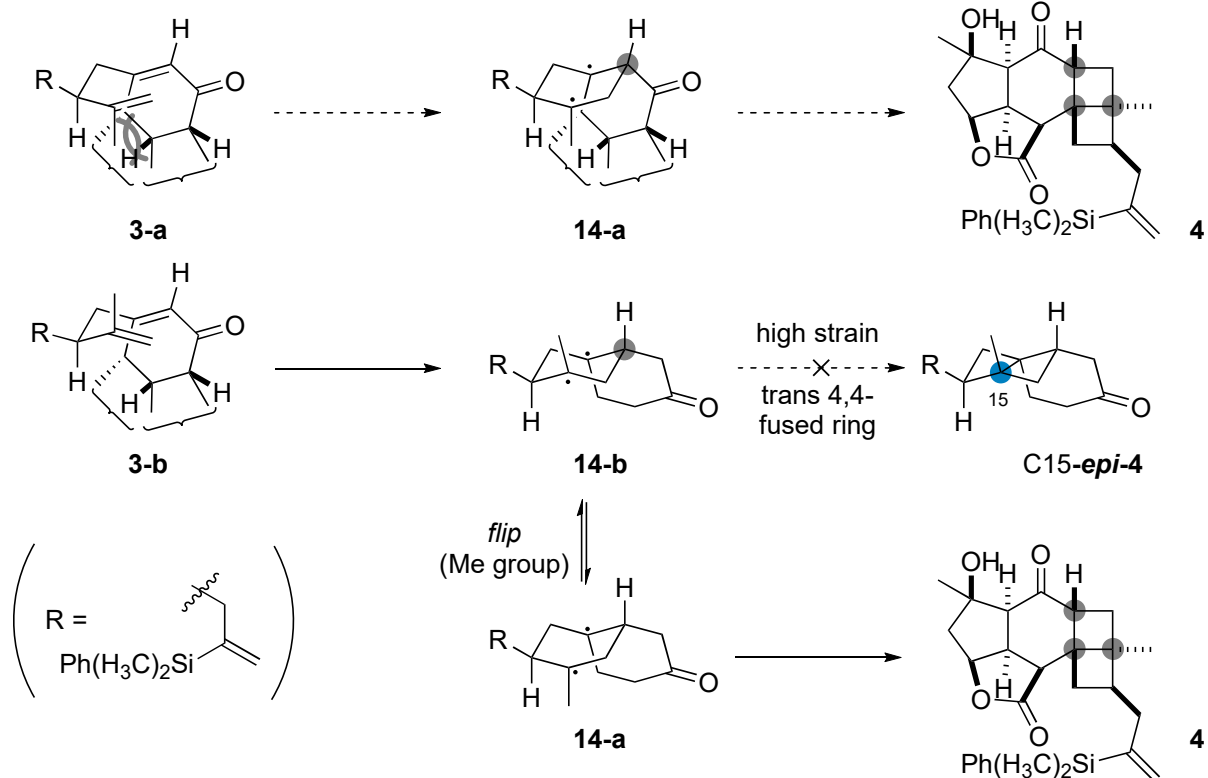


2.

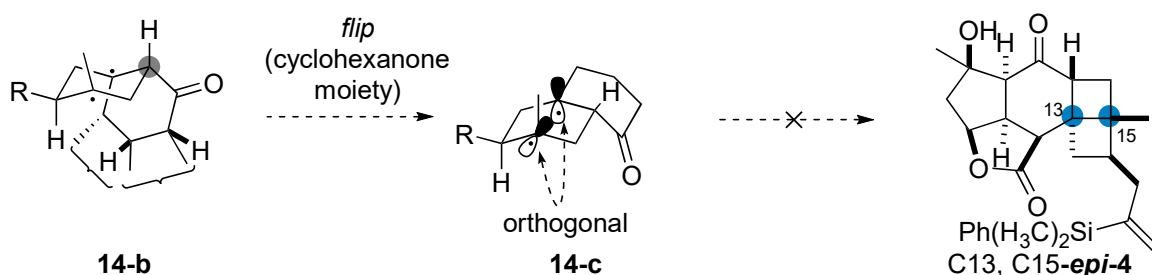


Discussion 2-1: stereoselectivity of cycloaddition  
(Substituents are omitted for clarity.)

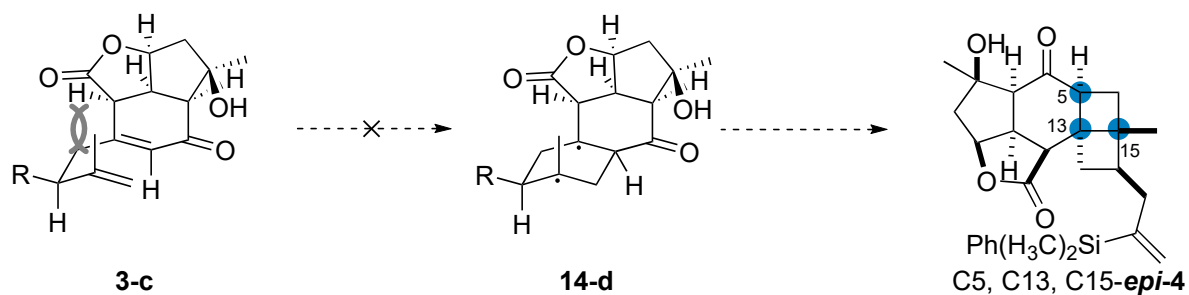
1. Path for **4**



2. Path for C13, C15-*epi*-**4**

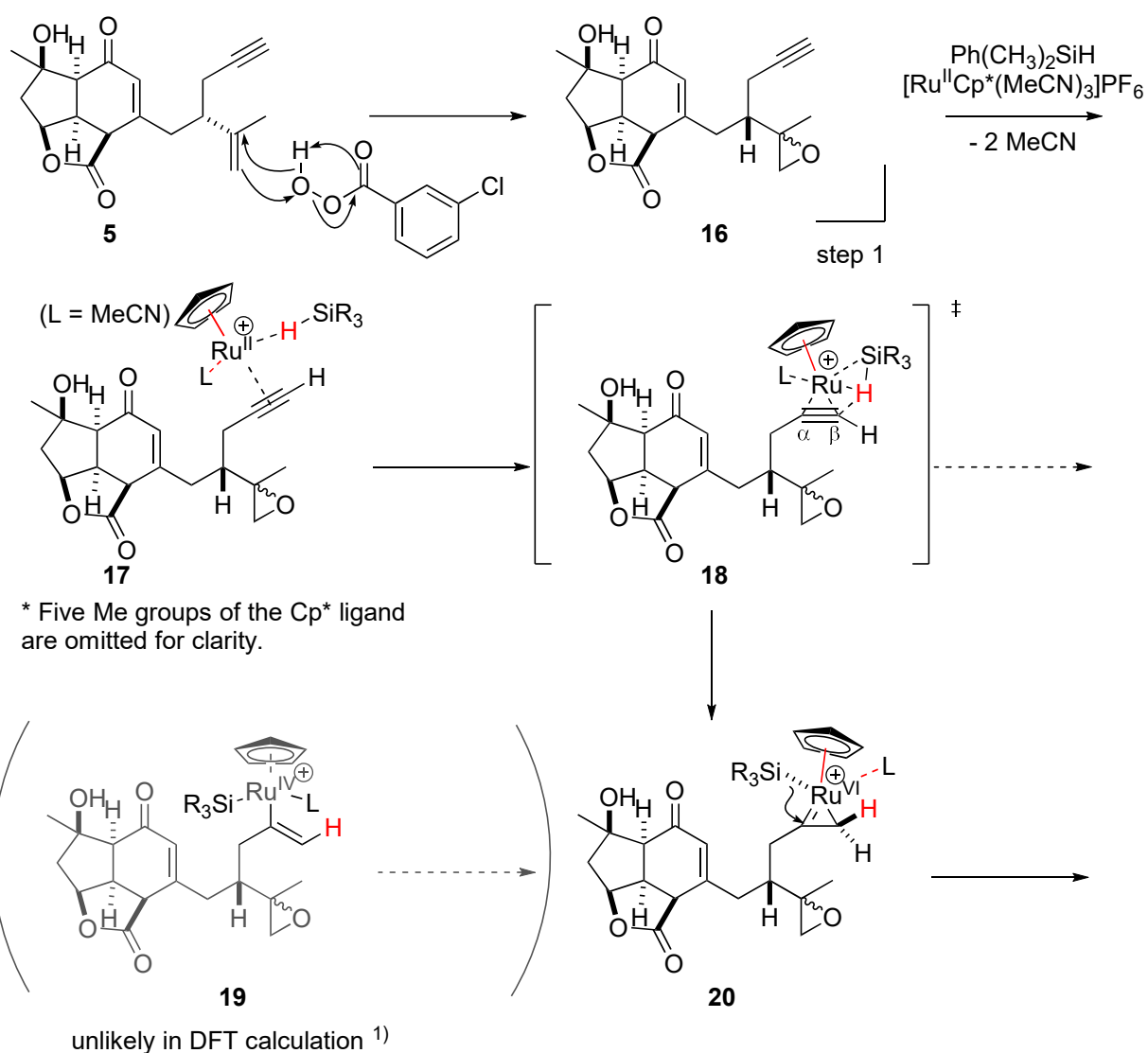
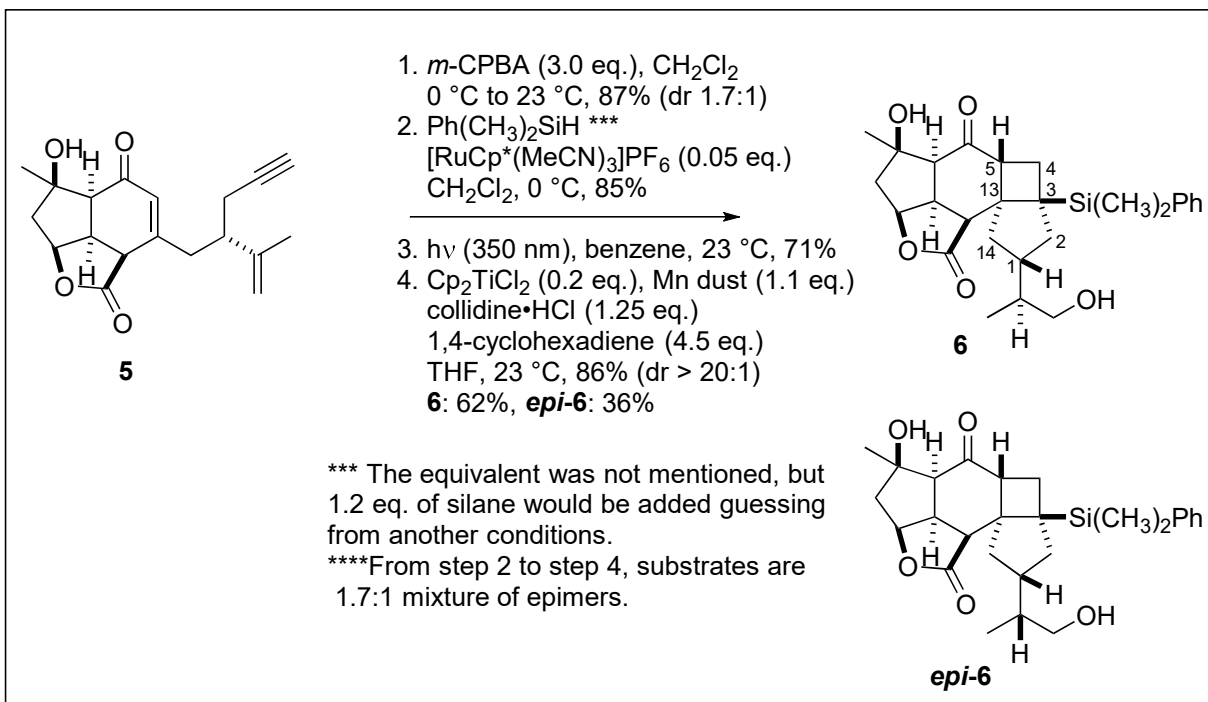


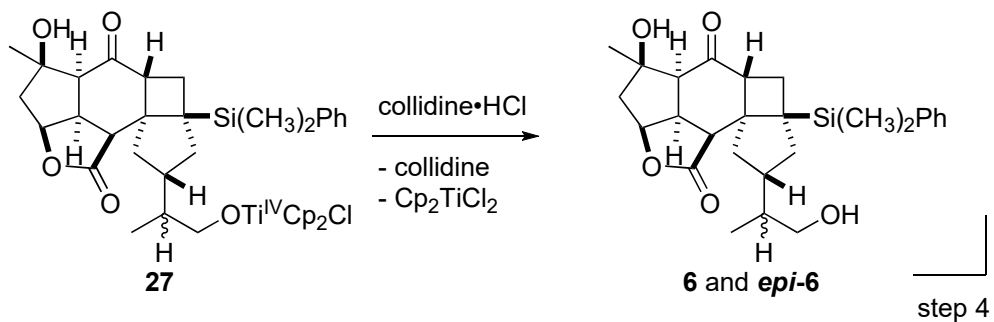
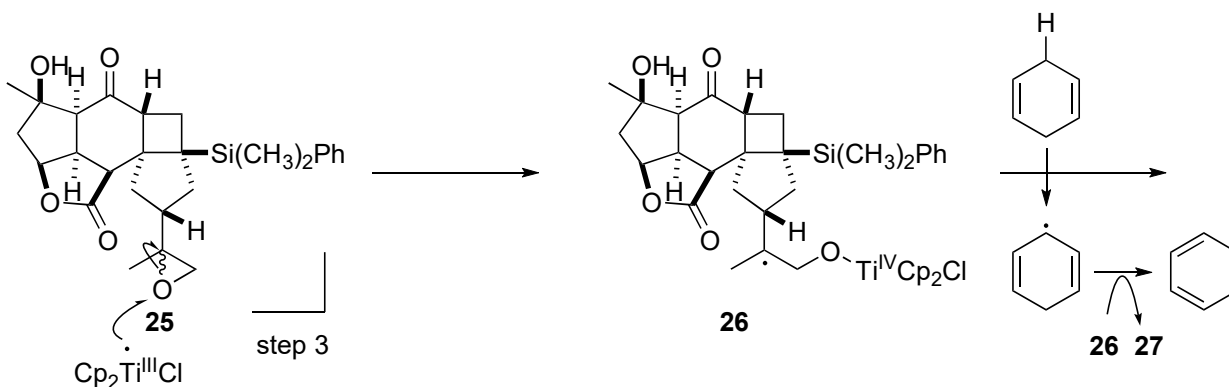
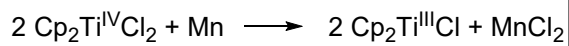
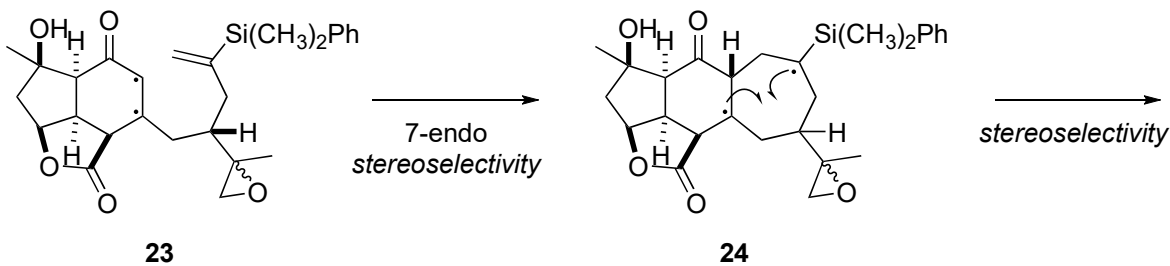
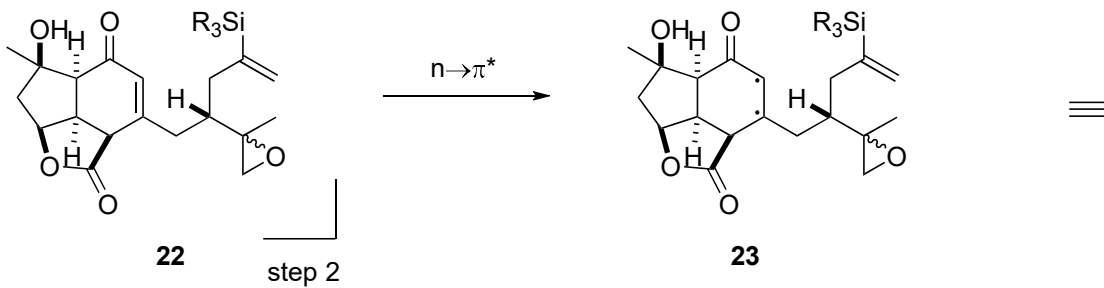
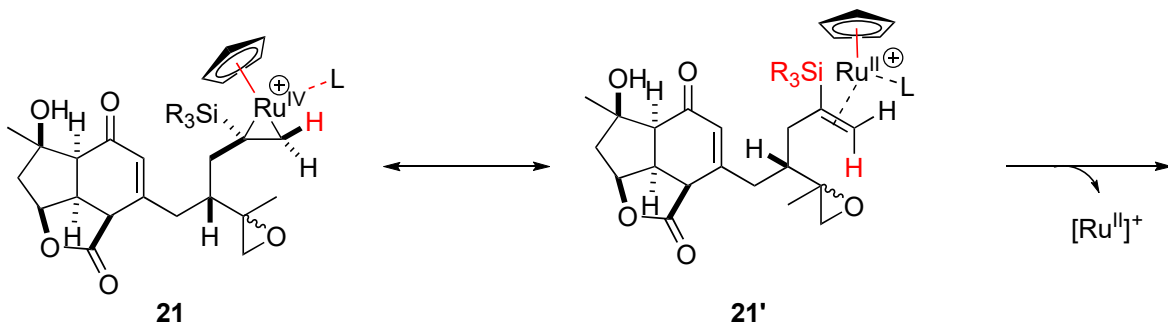
3. Path for C5, C13, C15-*epi*-**4**



Comment:

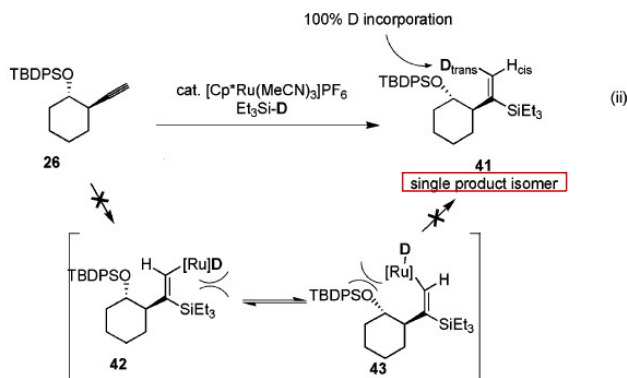
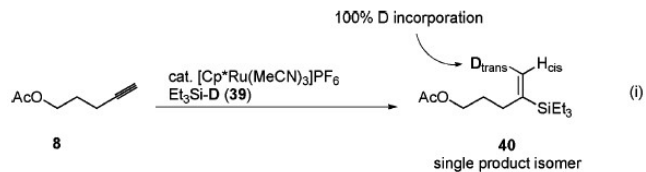
- trans-4,4-fused ring would not be formed due to high strain.
- Side chain should be positioned in the convex face of the 5,5,6-fused ring to avoid the steric repulsion with the ring, so C5 (C13 and/or C15)-*epi*-**4** would be kinetically unfavored products.





## Discussion 2-2: hydrosilylation

### 1. Deuterium experiment <sup>1)</sup>:



- Markovnikov hydrosilylation
- *anti*-addition
- cis-trans isomerization process would be unnatural.

### 2. Regiochemistry (first hydride- or silyl insertion) <sup>2)</sup>

In the case of  $[\text{RuCp}^*(\text{MeCN})_3]^+$ ,

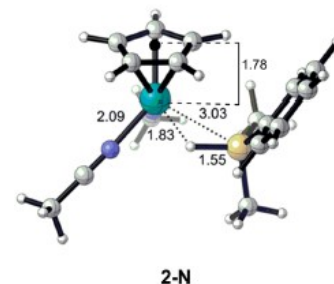
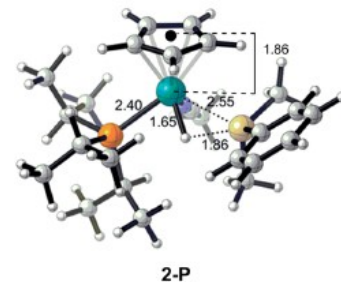
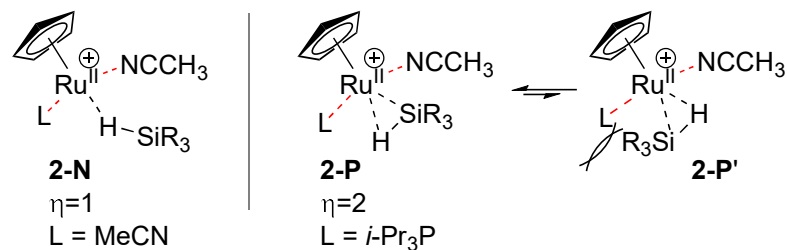
Hydride insertion occurs first (when three MeCN ligands) at less hindered carbon.

➤ Markovnikov hydrosilylation occurs.

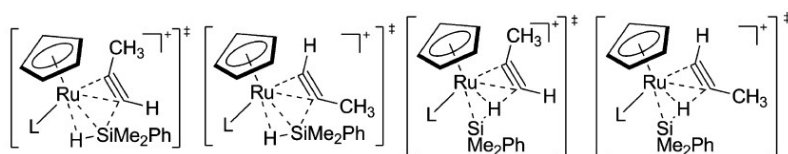
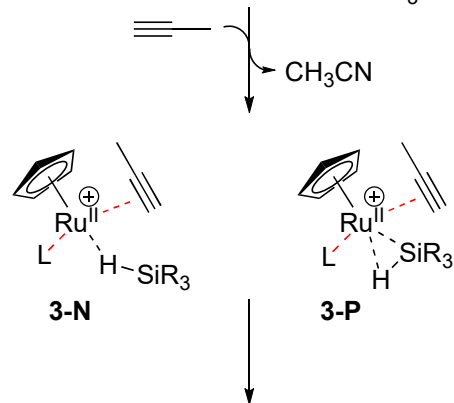
However, in the case of  $[\text{RuCp}^*(i\text{-Pr}_3\text{P})(\text{MeCN})_2]^+$ , *anti*-Markovnikov hydrosilylation occurs.

-> Coordination of silane to the ruthenium complex is different.

-> *i*-Pr<sub>3</sub>P ligand will facilitate the back-donation from the Ru center to the antibonding orbital of Si-H bond.



M06/Def2-TZVP-6-311G(d,p)

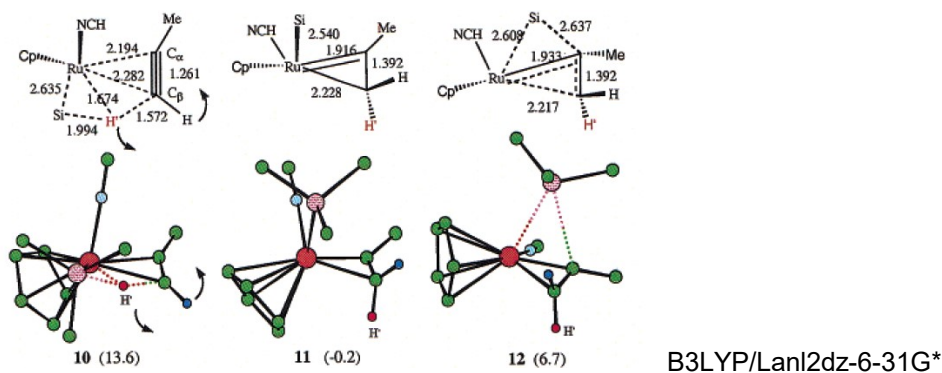


L = P'Pr<sub>3</sub>  
L = MeCN  
(kcal/mol)

L	TS4-L	TS14-L	TS24-L	TS34-L
L = P'Pr <sub>3</sub>	26.7	37.5	34.9	35.6
L = MeCN	32.0	42.7	22.1	22.9

M06/Def2-TZVP-6-311G(d,p)

### 3. Stereochemistry (*anti*-addition) <sup>1)</sup>

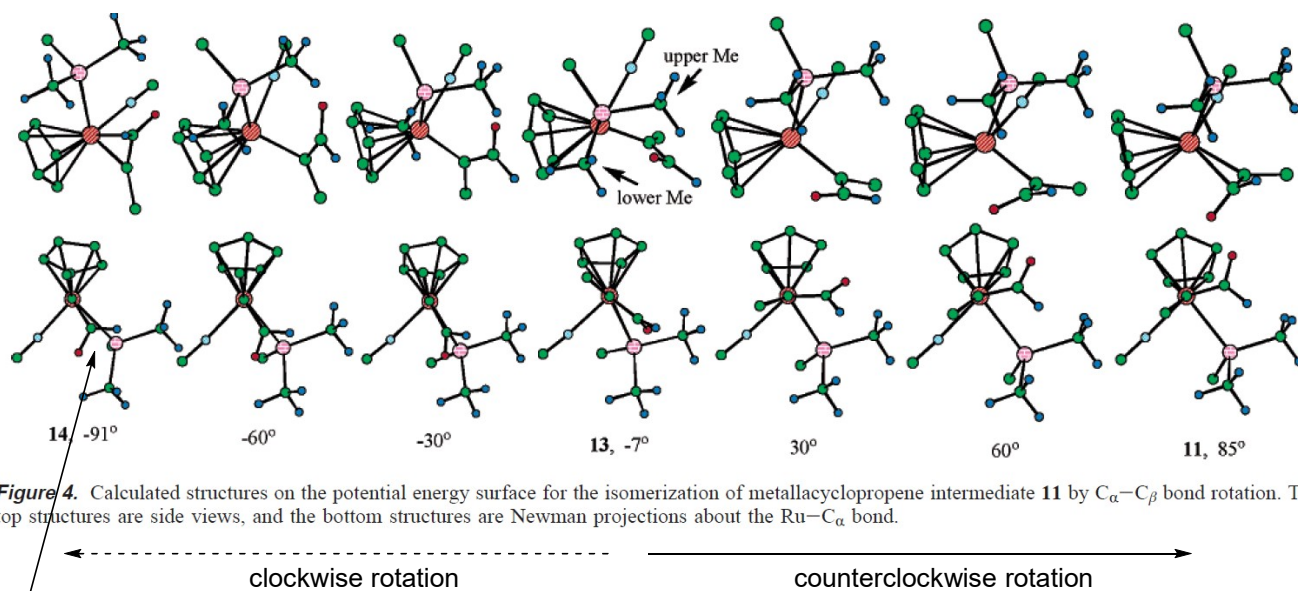


**10:** Ru, C $\alpha$ , C $\beta$  and H' are in the same plane (dihedral angle of Ru-C $\alpha$ -C $\beta$ -H' is 0°).

**11:** Counterclockwise rotation of C $\alpha$ -C $\beta$  bond

**12:** Silyl migration

Clockwise vs. counterclockwise rotation



**Figure 4.** Calculated structures on the potential energy surface for the isomerization of metallacyclopropene intermediate **11** by C $\alpha$ -C $\beta$  bond rotation. The top structures are side views, and the bottom structures are Newman projections about the Ru-C $\alpha$  bond.

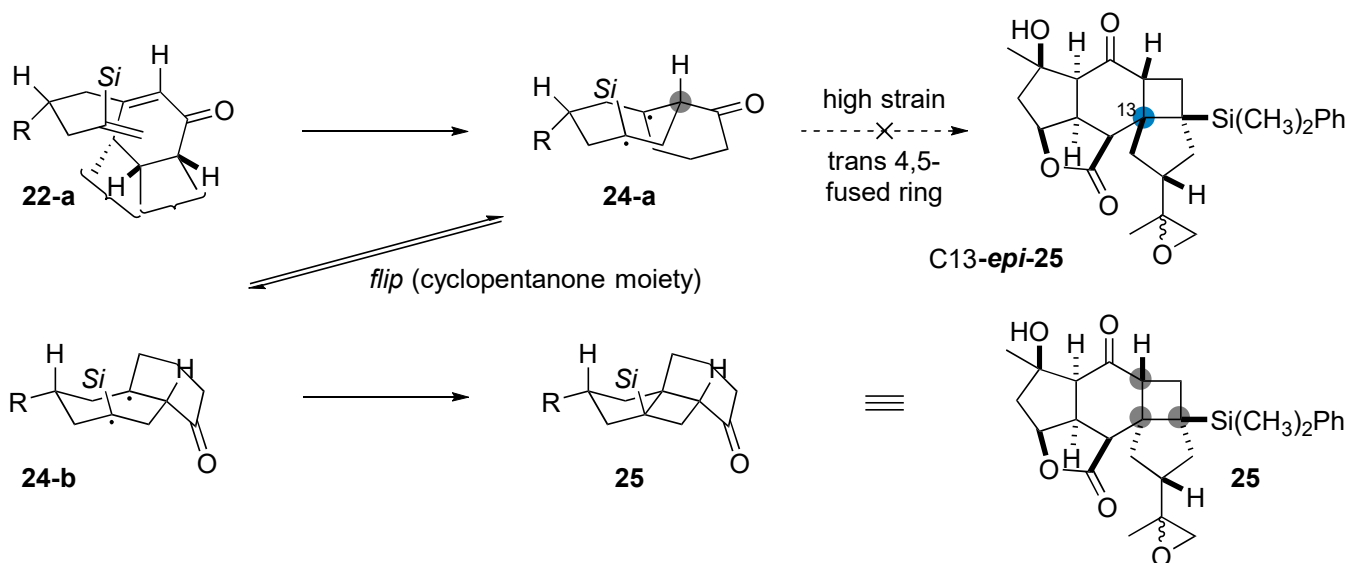
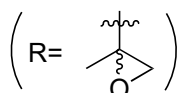
eclipsed

B3LYP/LanI2dz-6-31G\*

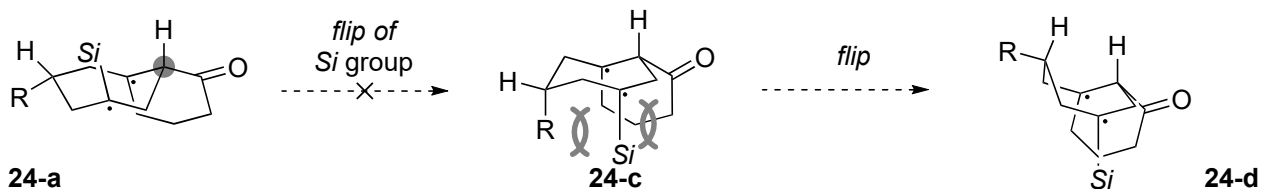


Discussion 2-3: stereoselectivity of cycloaddition  
(Substituents are omitted for clarity.)

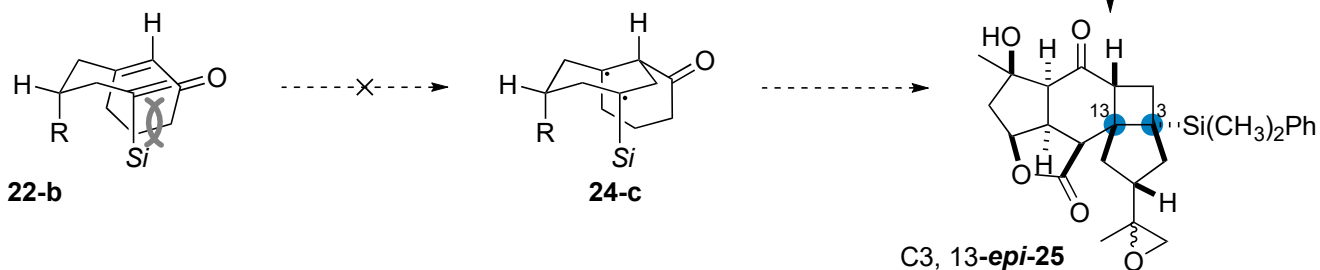
1. Path for **25**



2. Path for C3, 13-*epi*-25

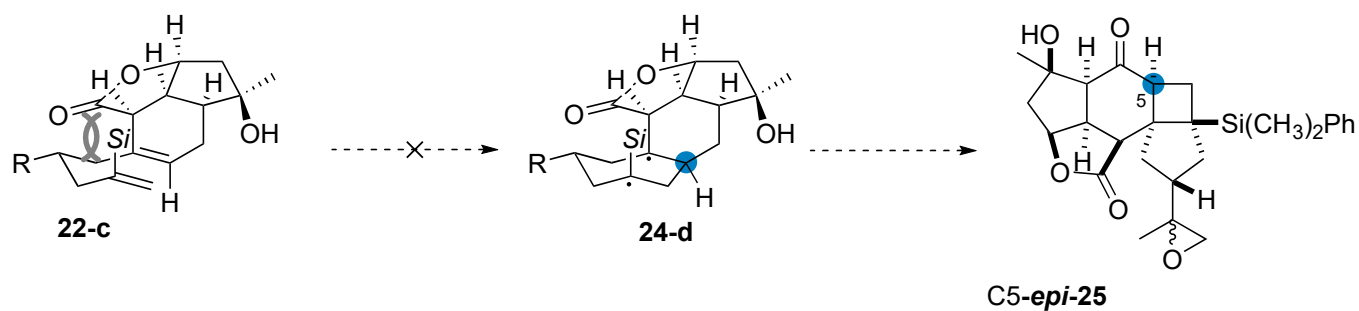


In contrast to the path for **4** in page 4, bulky silyl group would not be able to flip.



3. Path for C5 (C3 and/or C13)-*epi*-25:

The side chain should be positioned in the concave face of the 5,5,6-fused ring to generate C5-*epi*-25. Therefore, steric repulsion would be larger than above two paths.



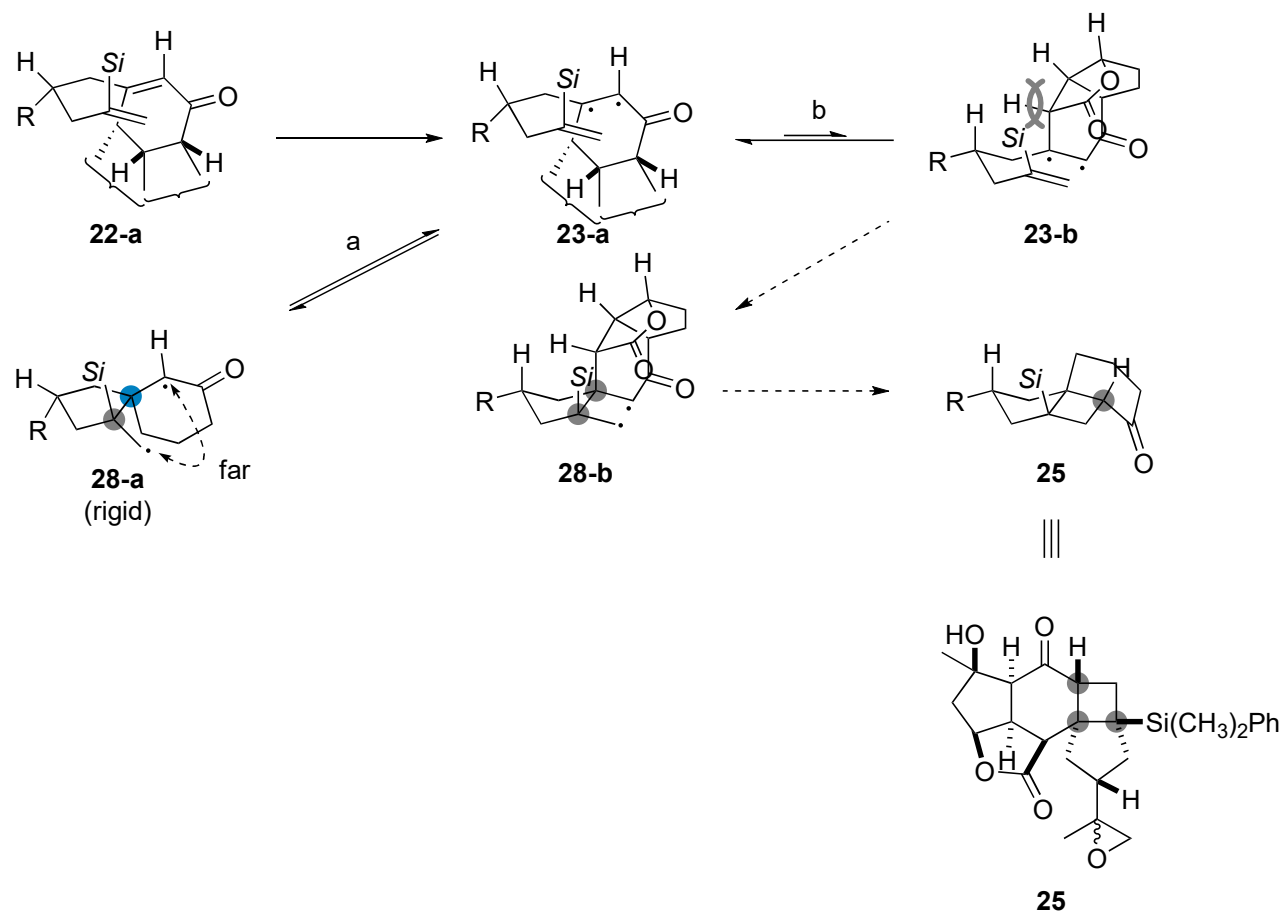
Another mechanism for **25**:

If 5-exo cyclization occurred first, the below path would be conceivable.

When the cyclization occurred from **23-a**, biradical **28-a** would be generated. However, new bond formation would not occur from **28-a** (path a).

On the other hand, path b should run to reach **25**, but repulsion between silyl group and the fused ring would arise in **23-b**.

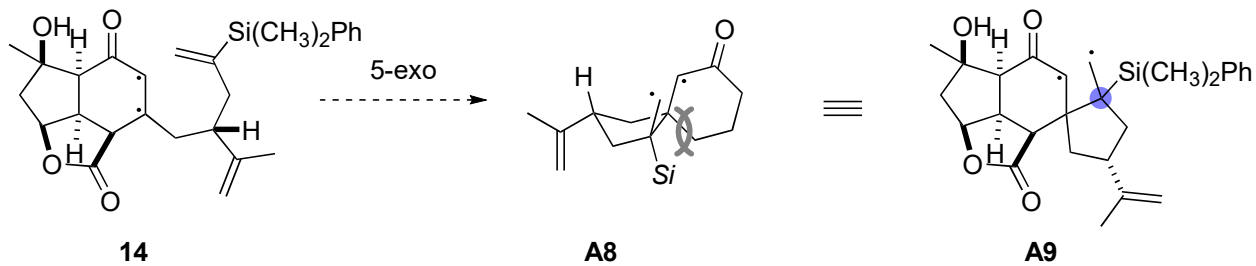
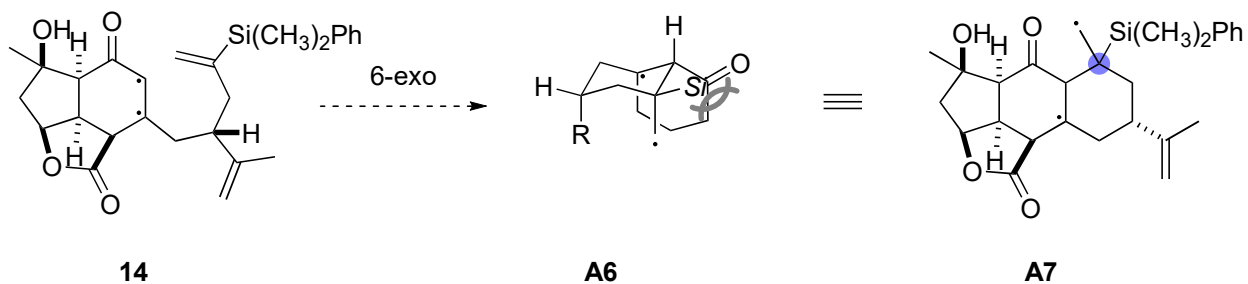
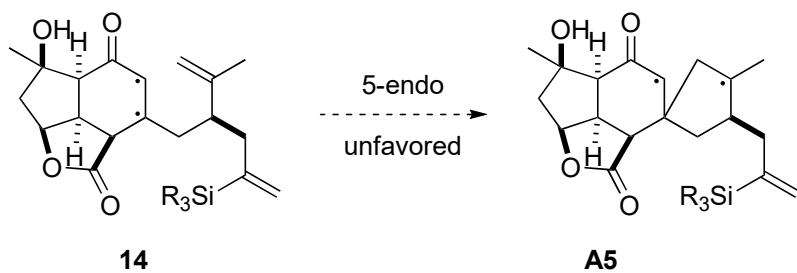
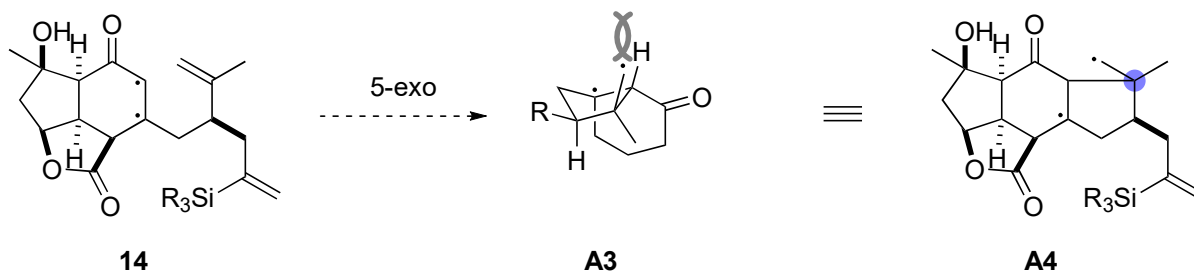
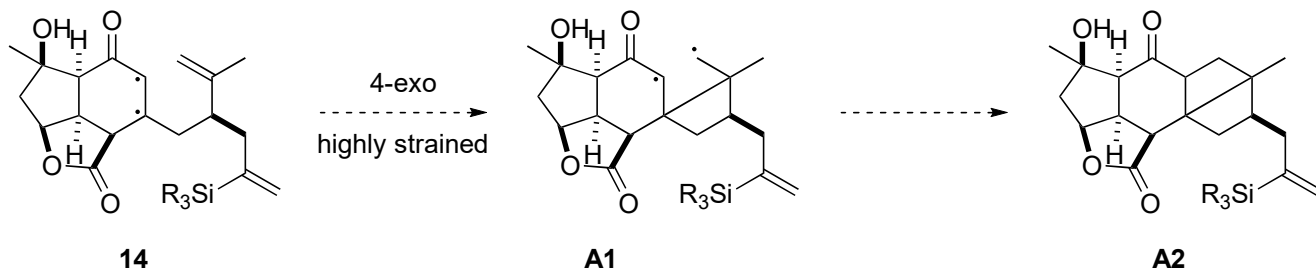
Therefore, I think the below path is less favorable than 7-endo cyclization path.



#### Reference

- 1) Chung, L. W.; Wu, Y. D.; Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 11578.
- 2) Yang, Y. F.; Chung, L. W.; Zhang, X.; Houk, K. N.; Wu, Y. D. *J. Org. Chem.* **2014**, *79*, 8856.

Additional discussion in page 4: other ring formations



- : Generation of quaternary carbons -> Energy of transition states would be higher.  
-> unfavored cyclization in this system