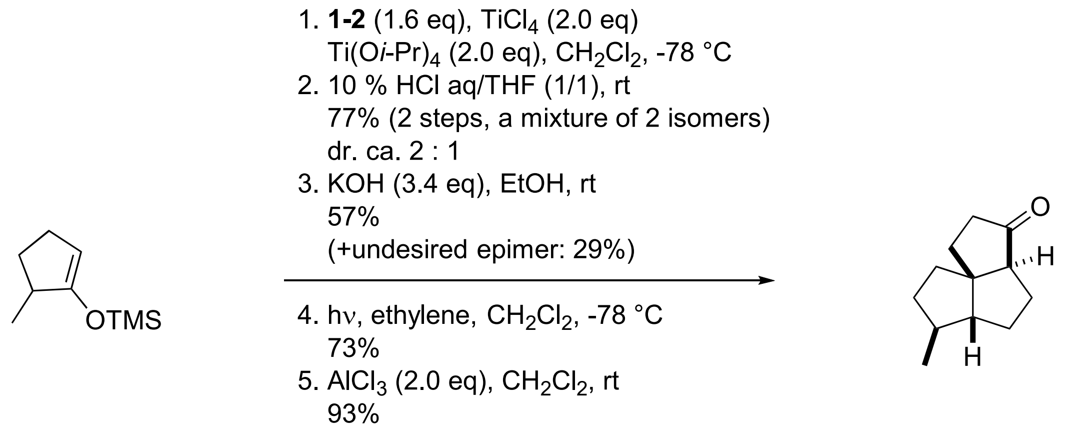
Problem Session (6)

2020/05/16 Akira Hirose

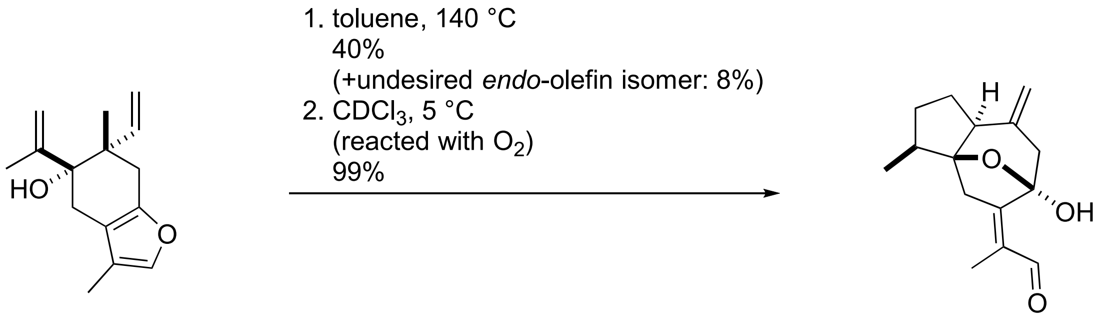
Please provide the reaction mechanisms.

1



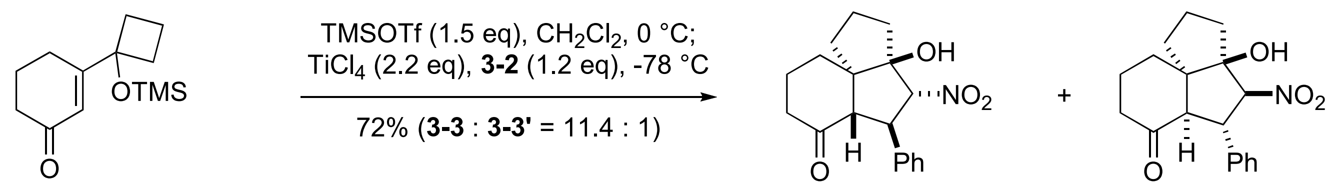
1-1 (racemic) **1-3** (racemic)

2

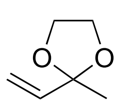


2-1 **2-2**

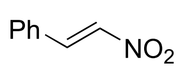
3



3-1 (racemic) **3-3** (racemic) **3-3'** (racemic)



1-2



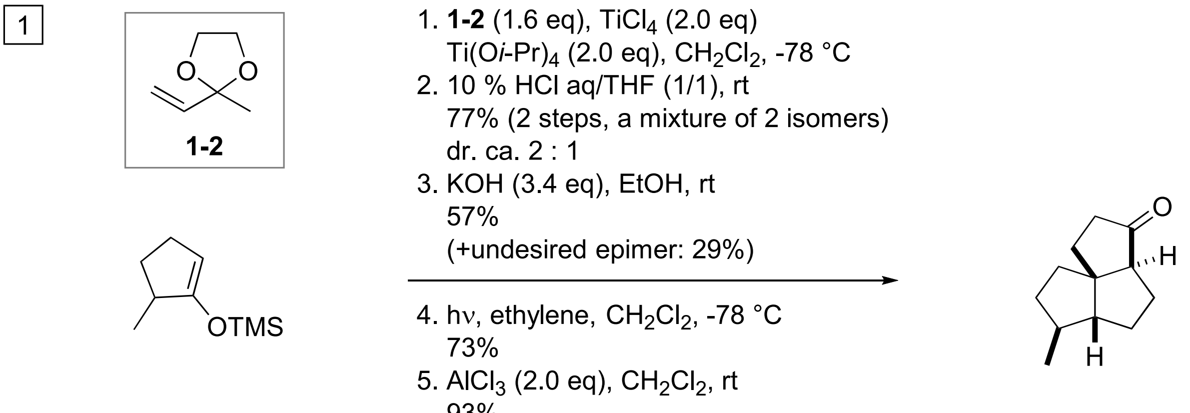
3-2

Problem Session (6)

2020/05/16 Akira Hirose

Topic: Construction fused ring systems by using ring expansion/transannular reaction

Problem 1. Construction of 5/5/5-*cis*-fused ring system

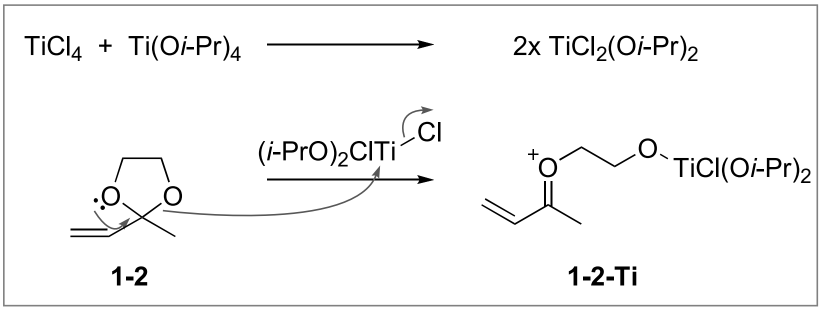


1. **1-2** (1.6 eq), $TiCl_4$ (2.0 eq), $Ti(Oi\text{-}Pr)_4$ (2.0 eq), CH_2Cl_2, -78 °C
2. 10 % HCl aq/THF (1/1), rt
   77% (2 steps, a mixture of 2 isomers)
   dr. ca. 2 : 1
3. KOH (3.4 eq), EtOH, rt
   57%
   (+undesired epimer: 29%)
4. hν, ethylene, CH_2Cl_2, -78 °C
   73%
5. $AlCl_3$ (2.0 eq), CH_2Cl_2, rt
   93%

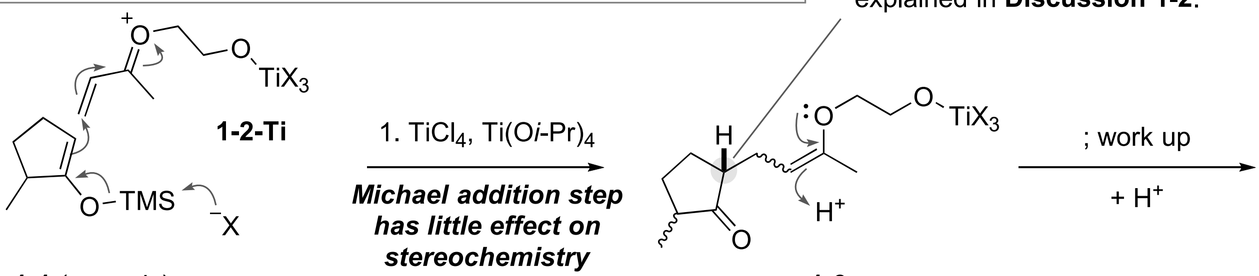
1-1 (racemic) → **1-3** (racemic)

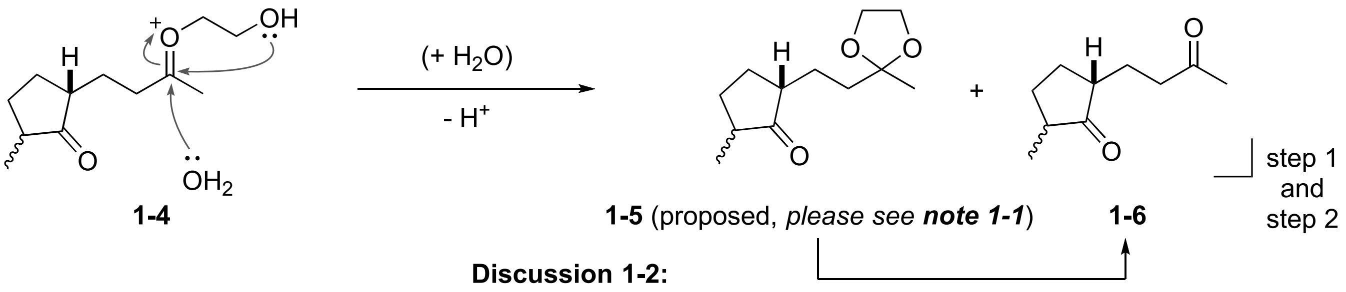
Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707.

1-1. The mechanisms of the 1st and 2nd steps: Mukaiyama-Michael reaction



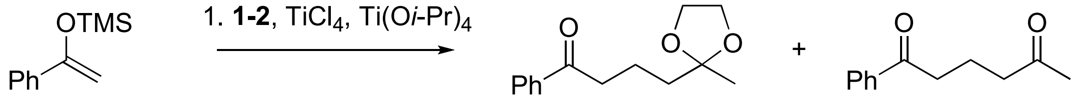
* For clarification, compounds are depicted with reference to the absolute configuration of this highlighted carbon.
** Stereochemistry of Me group will be explained in **Discussion 1-2**.





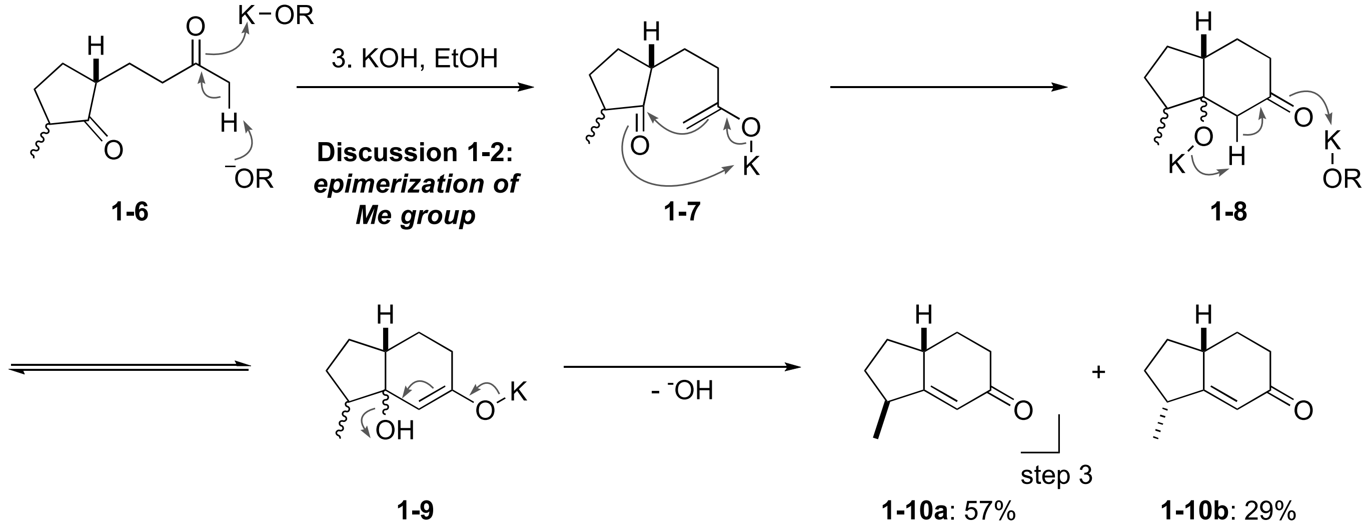
Note 1-1. ***The structure of crude mixture after the 1st step.***

· The detailed structures of obtained product after the 1ste step, so they are proposed based on the report of first Mukaiyama-Michael reaction using **1-2**.



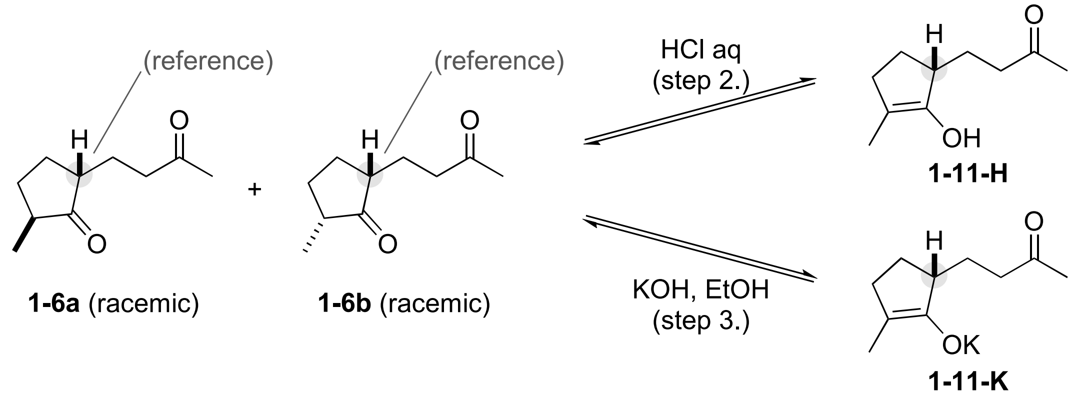
Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, *3*, 1223.

1-2. The mechanisms of the 3rd step: Robinson annulation

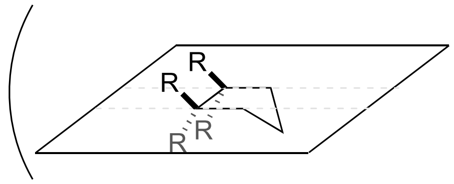


Discussion 1-2. ***Stereoselective 1-10a production***

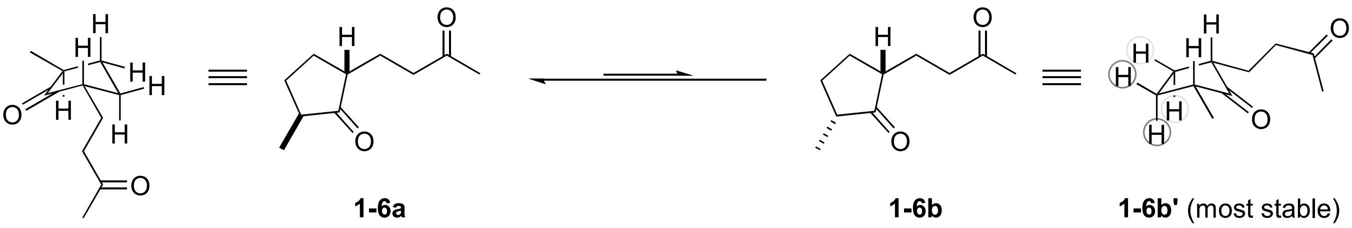
In step 2 (acidic conditions) and step 3 (basic conditions), **1-6a** and **1-6b** can epimerize via enol(ate) **1-11**.
→ Ratio of **1-6a** : **1-6b** depends on thermodynamic stability of both of them.



→ Considering the envelope conformation of cyclopentanone **1-6**s, **1-6a** would be slghtly more stable than **1-6b** due to less H-H torsional strain.



envelope conformation
· 4 carbon atoms are in the same plane.
→ posessing 1x eclipse C-C bond
· Cyclopentane in the envelope form is slightly more stable than half-chair form (3 carbons are in the same plane) by ~0.5 kcal/mol.



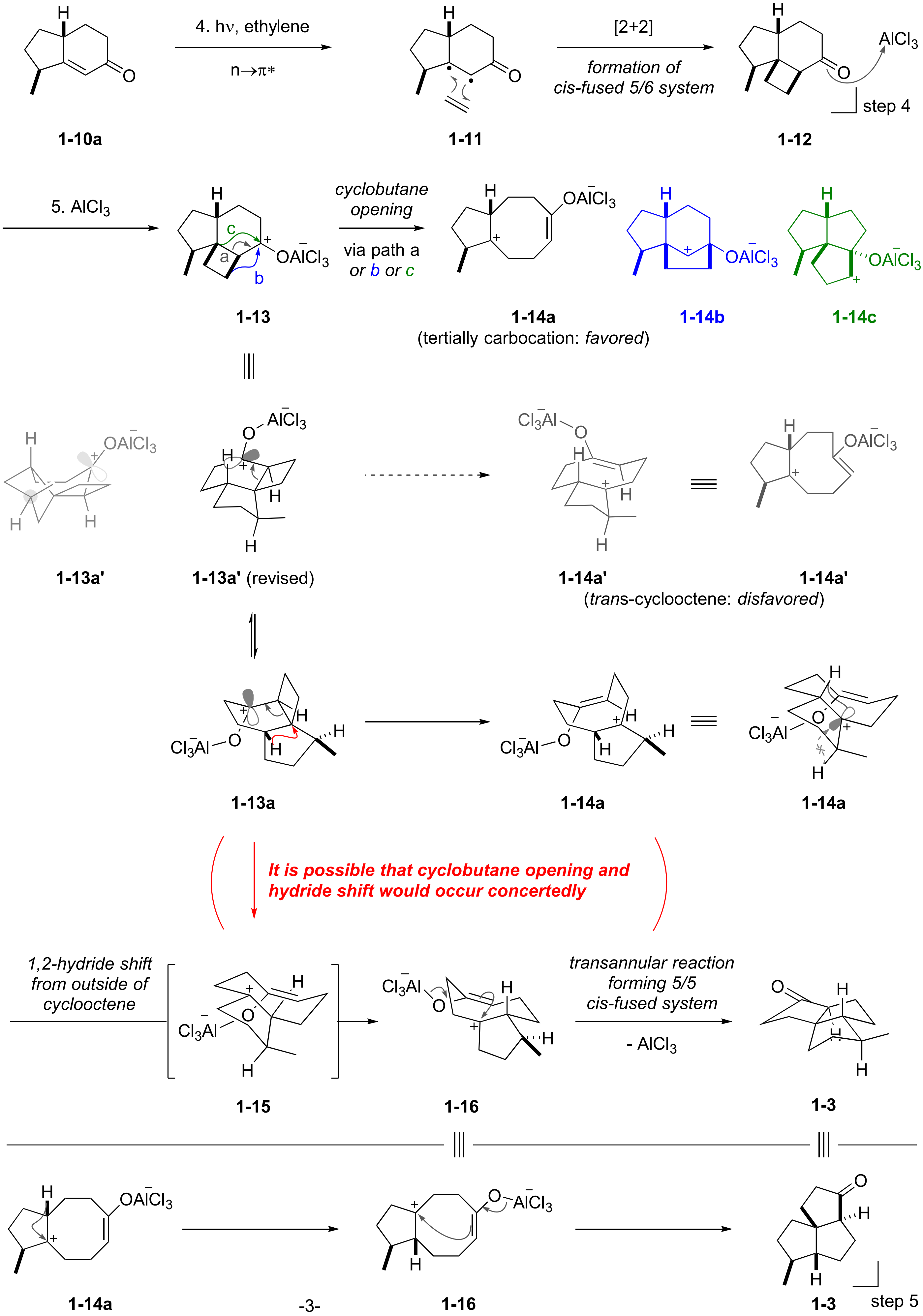
1-6a' (most stable)

· 2x 1,3-diaxial interaction

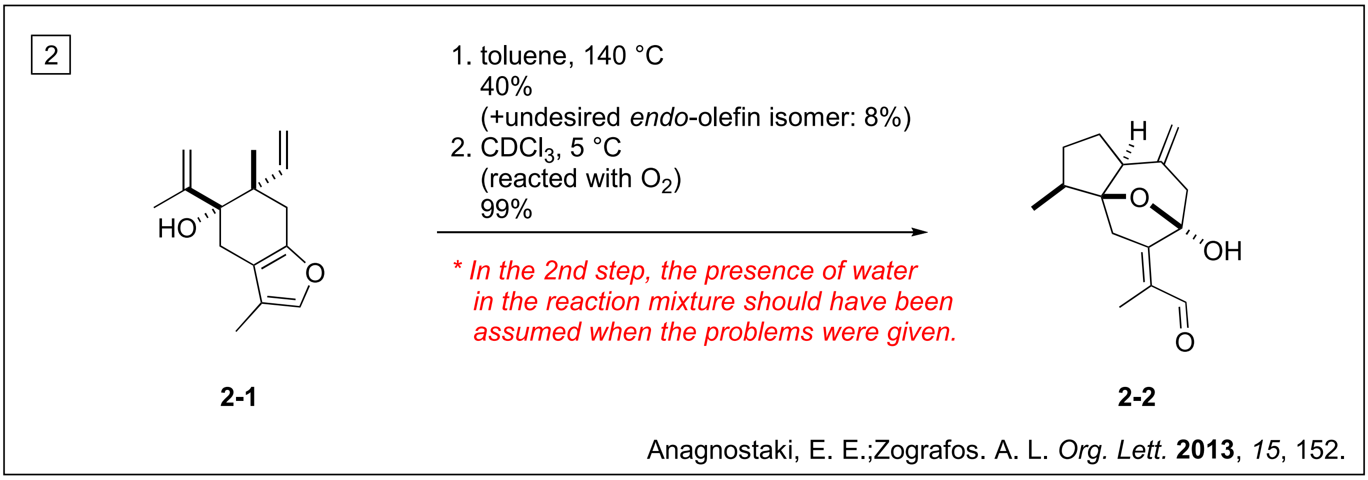
· 1x 1,3-diaxial interaction
· **2x H-H torsional strain**

→ This difference of the stability would determine the ratio of **1-6** mixture (ca. 2 : 1) and lead to stereoselectivity of Robinson annulation (**1-10a**: 57%, **1-10b**: 29%).

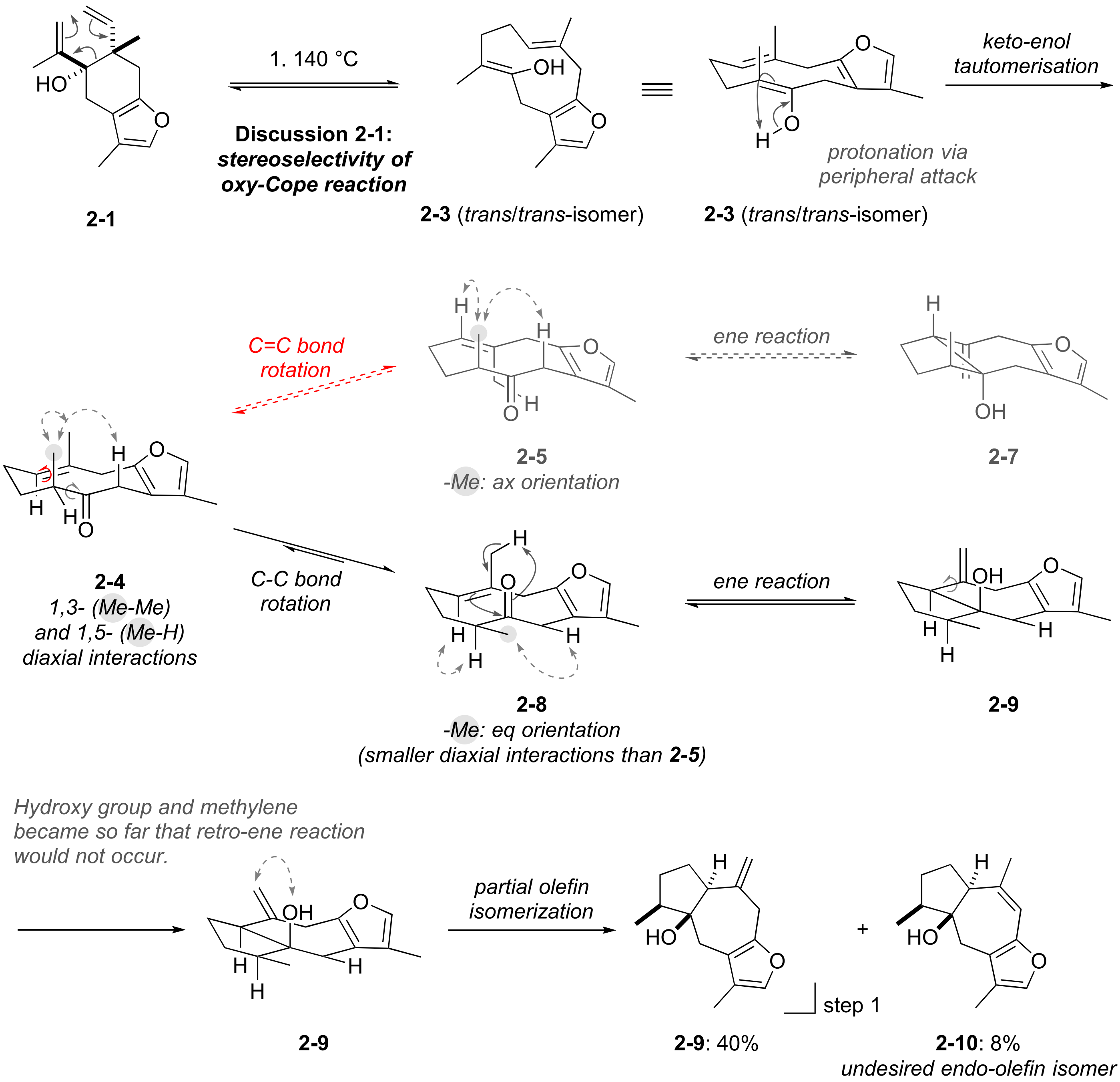
1-3. The mechanisms of the 4th and 5th steps



Problem 2. Synthesis of guaiane sesquiterpenes

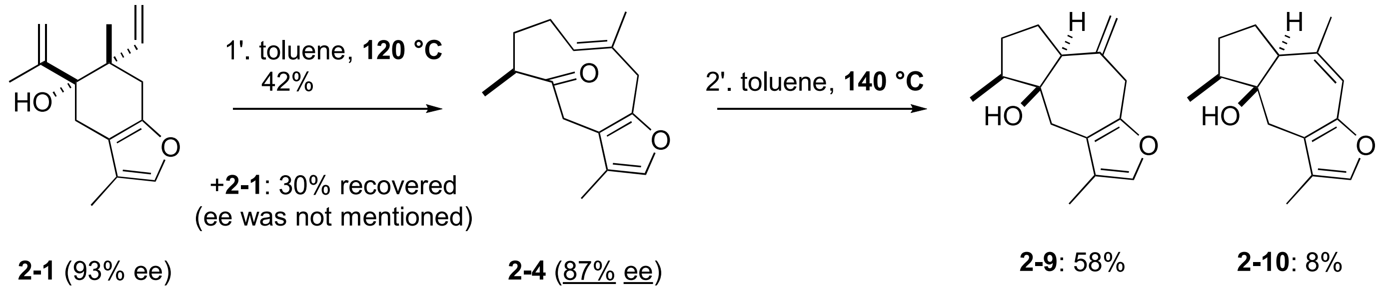


2-1. The mechanism of the 1st step: oxy-Cope/ene reaction



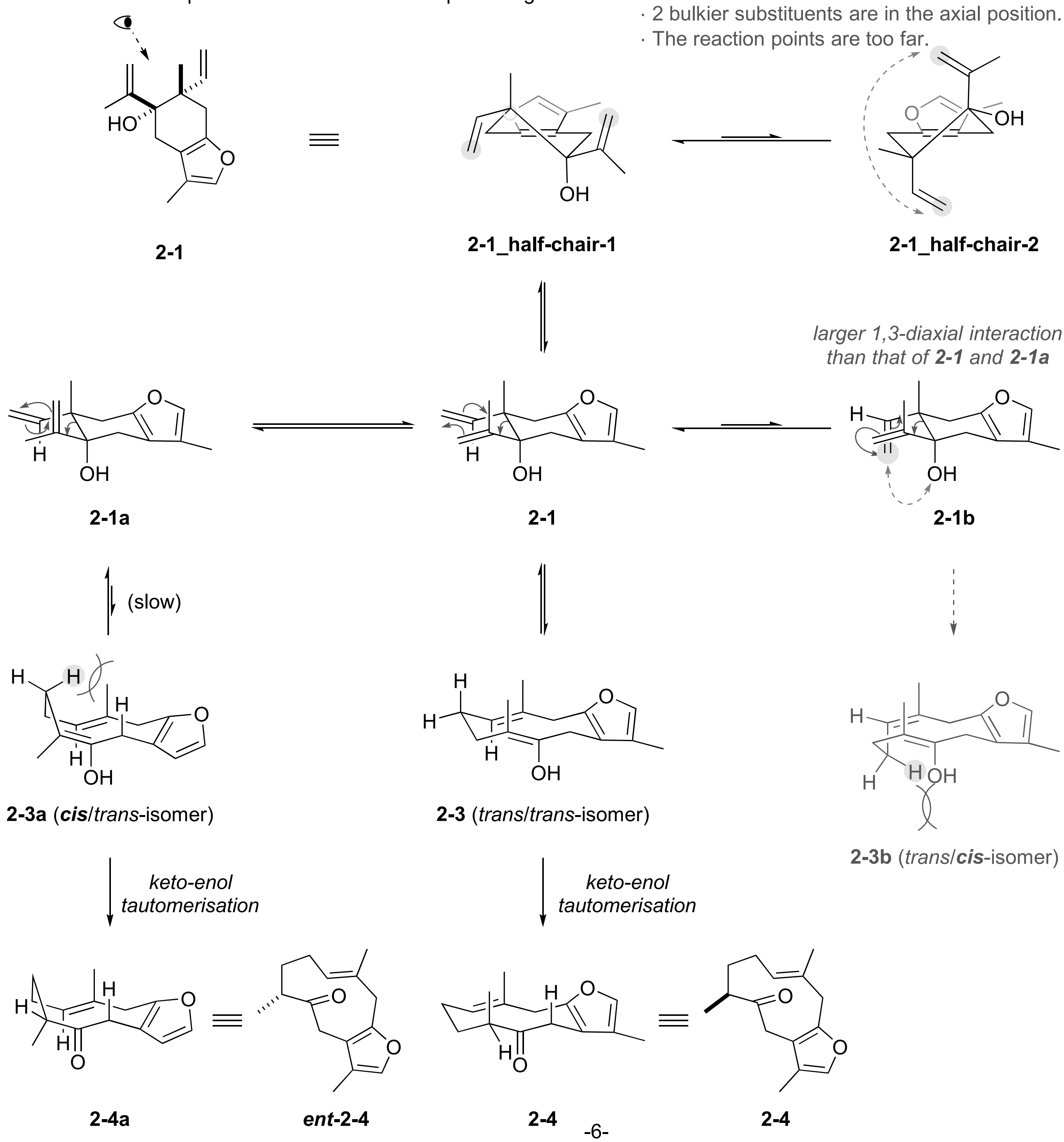
Discussion 2-1. *Stereoselectivity of Cope reaction*

2-1-1. 2 step-conversion from **2-1** to **2-9**



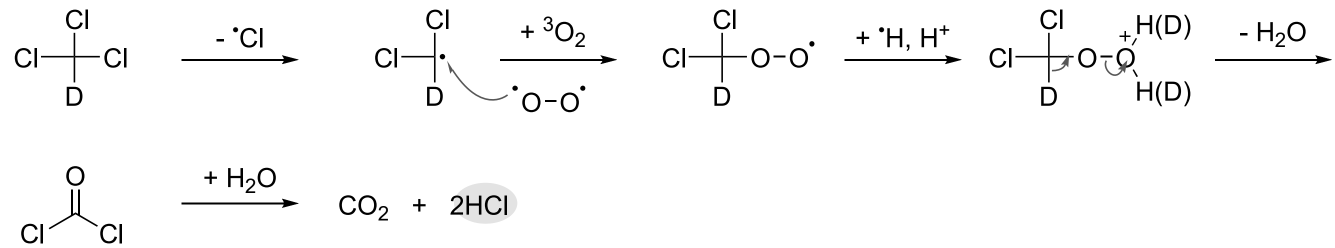
Anagnostaki, E. E.;Zografos. A. L. *Org. Lett.* **2013**, *15*, 152.

2-1-2. Plausible explanation for stereoselective producing of **2-3**



2-2. The mechanism of the 2nd step: autoxidation of furan ring (the reaction with $^3O_2$)

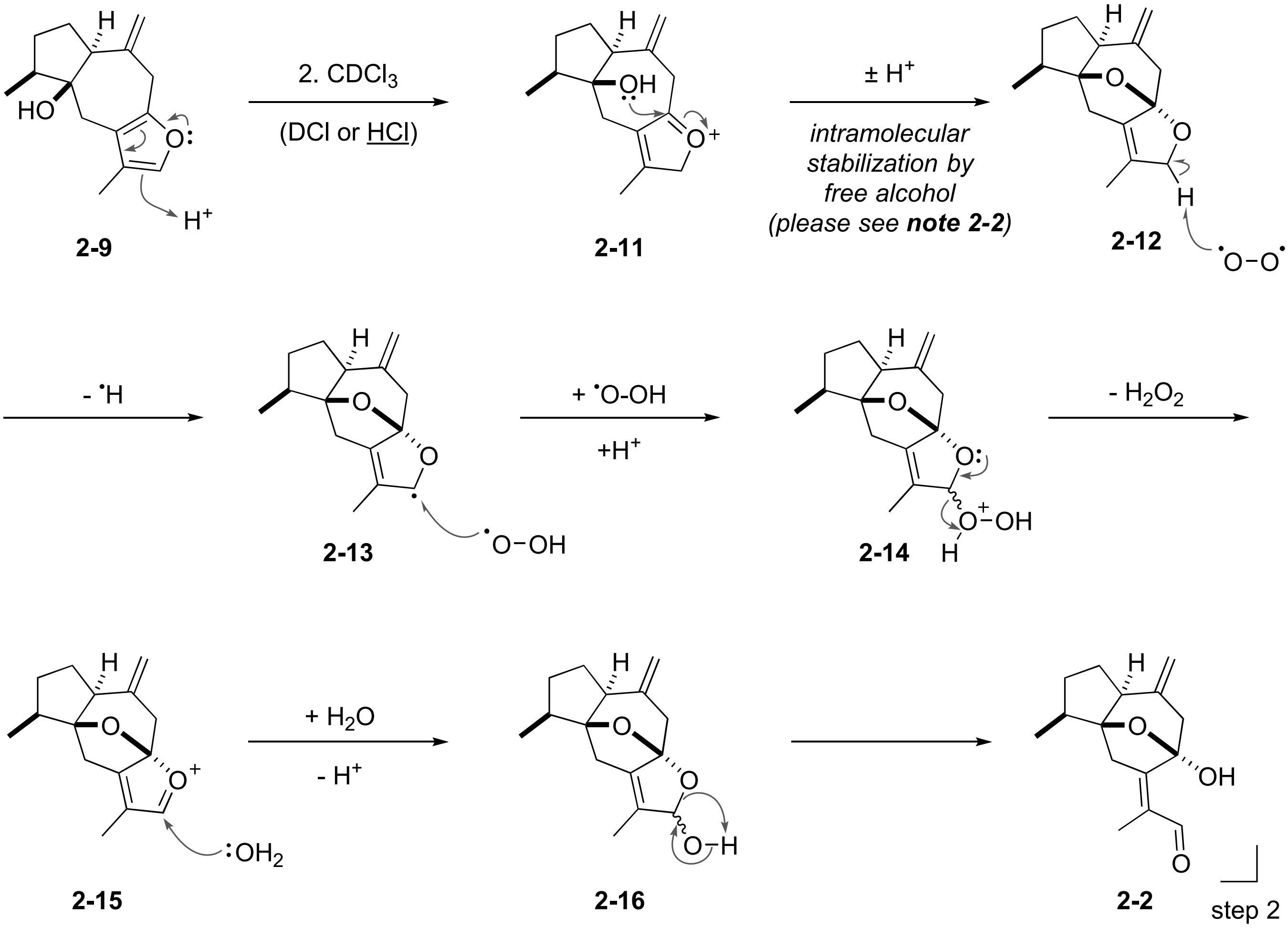
Oxidative decomposition of $CDCl_3$ to phosgene and DCl



(phosgene)

Chapman, A. T. *J. Am. Chem. Soc.* **1935**, *57*, 419.

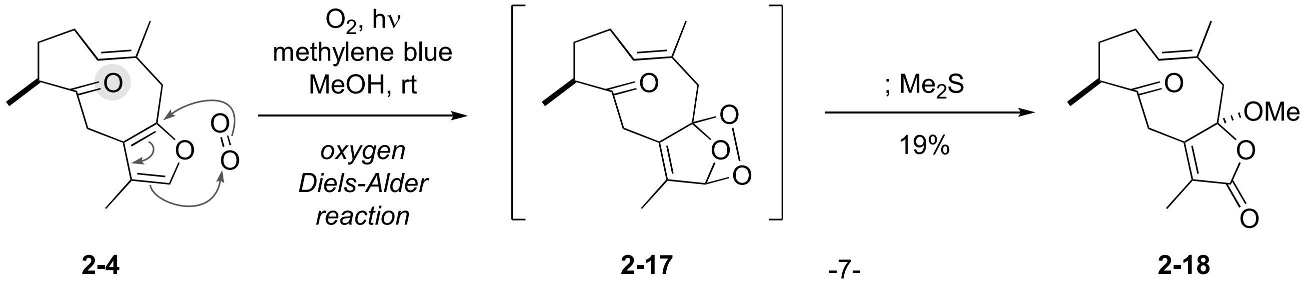
(* Although the presence of water is not definitely mentioned in the paper, it is more natural to assume that water involved the reaction mechanisms.)



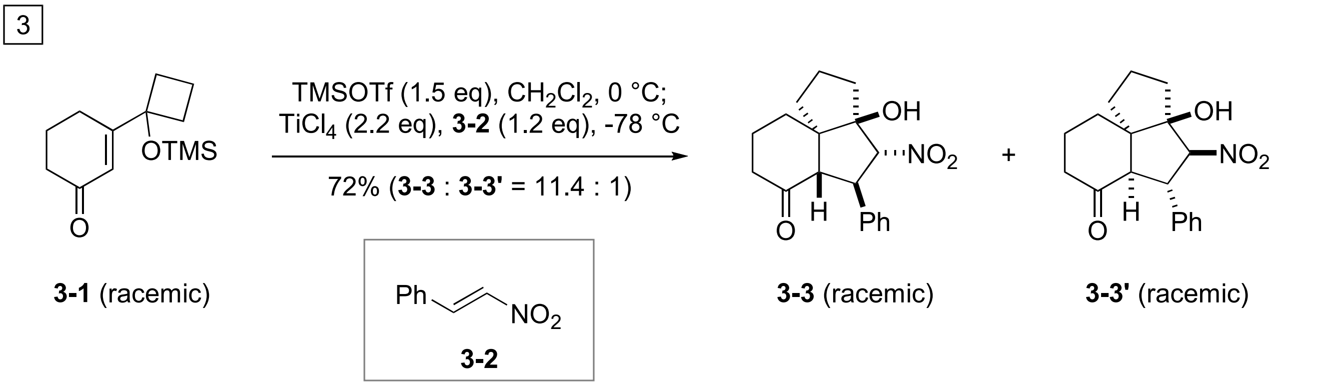
Note 2-2. ***Oxidation of the furan ring in 2-4 (the reaction with $^1O_2$)***

· Autoxidation of **2-4** (possessing ketone instead of free alcohol) did not occur.

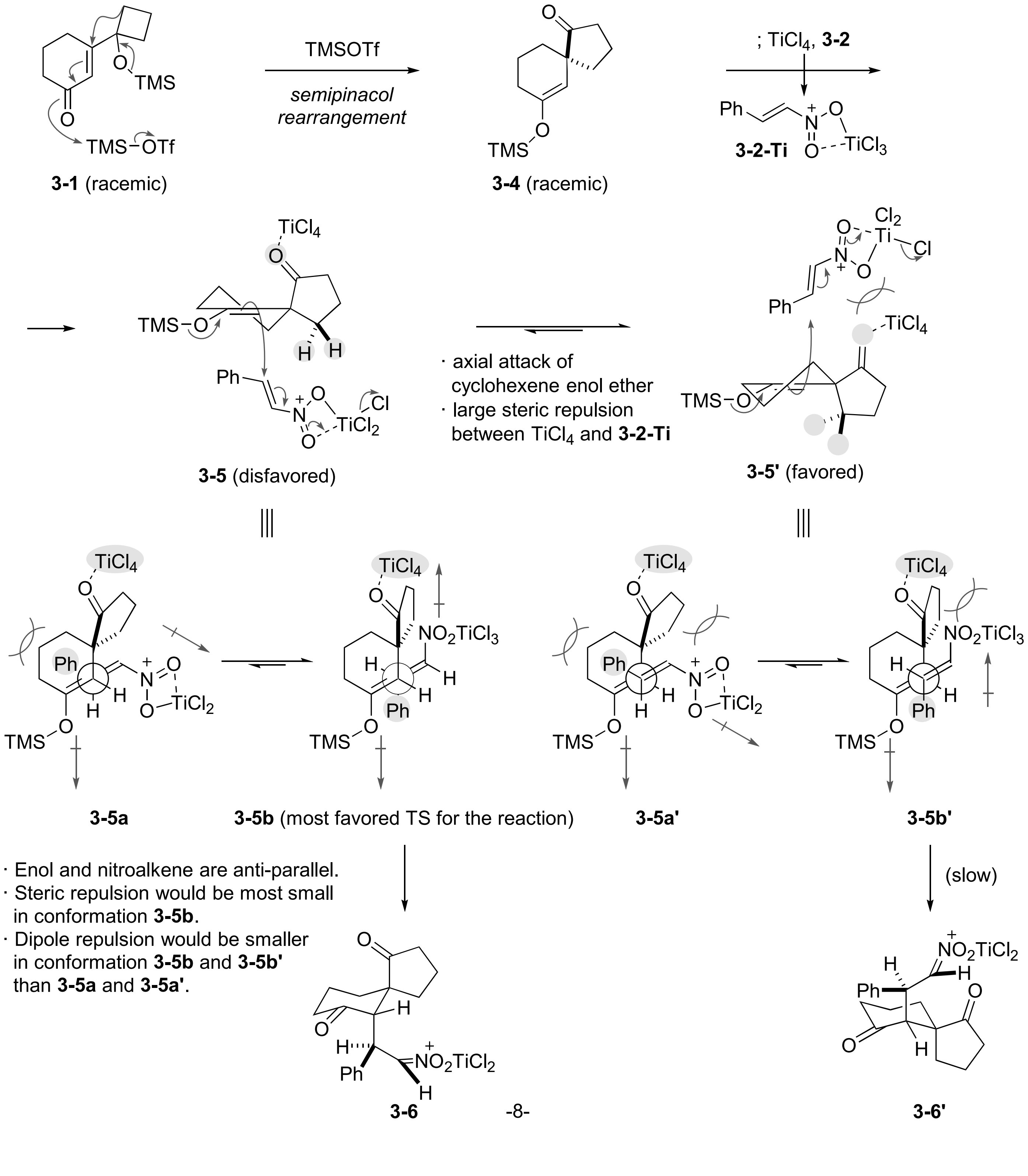
· Oxidation of furan in **2-4** required production of singlet oxygen.



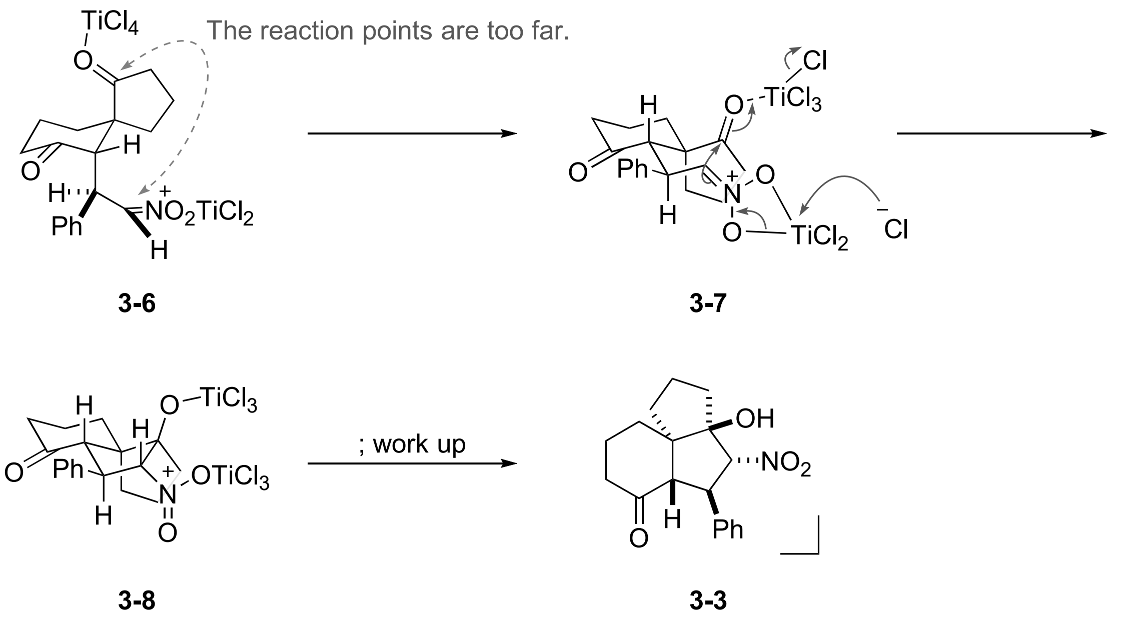
Problem 3. Construction of 6/5/5-fused ring system



Zhu, F.-P.; Guo, X.; Zhang, F.-M.; Zhang, X.-M.; Wang, H.; Tu, Y.-Q. *Org. Lett.* **2020**, *22*, 2076.



3-1. The mechanisms from **3-6** to **3-3** (a major isomer)



3-2. The mechanisms from **3-6'** to **3-3'** (a minor isomer)