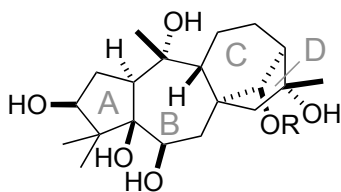


Problem Session (1) -Answer-

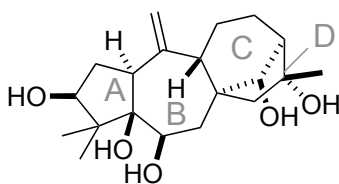
2023/10/07 Yo Matsumoto

Topic: Enantioselective Total Synthesis of Grayanane Diterpenoids and (+)-Kalmanol

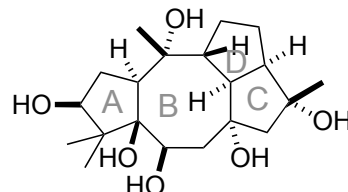
Introduction



Grayanotoxin I : R = Ac
Grayanotoxin III : R = H



Grayanotoxin II



Kalmanol

Isolation:

Grayanotoxin I, II, III : *Leucothoe grayana*²⁾

Kalmanol : *Kalmia angustifolia*³⁾

Structure feature:

5/7/6/5 or 5/8/5/5 tetracyclic carbon framework

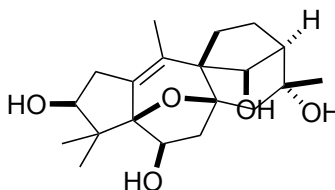
Bioactivity:

Effect on Voltage-gated sodium channels:
antinociceptive activity (Kalmanol)

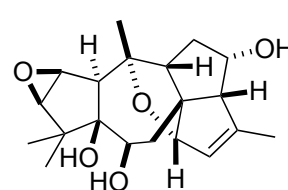
Total synthesis:

Grayanotoxin II : Matsumoto⁴⁾

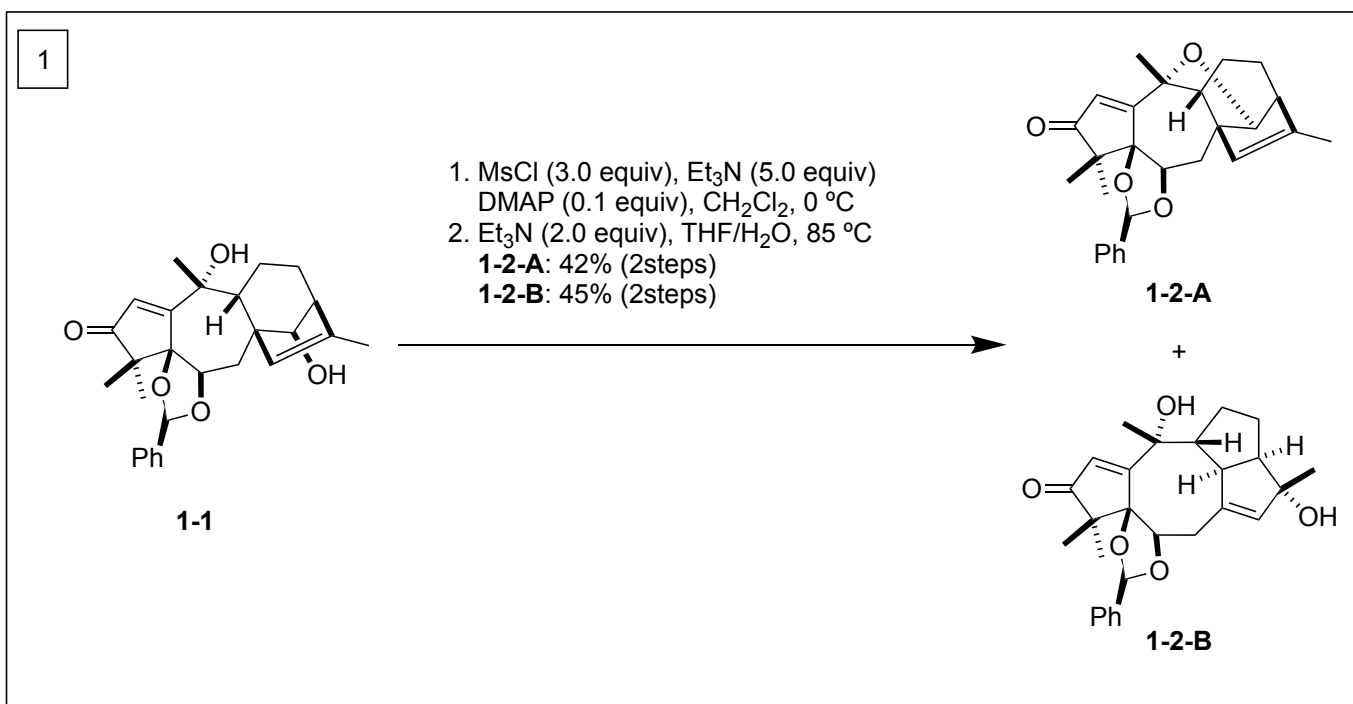
(-)-Grayanotoxin III : Shirahama⁵⁾



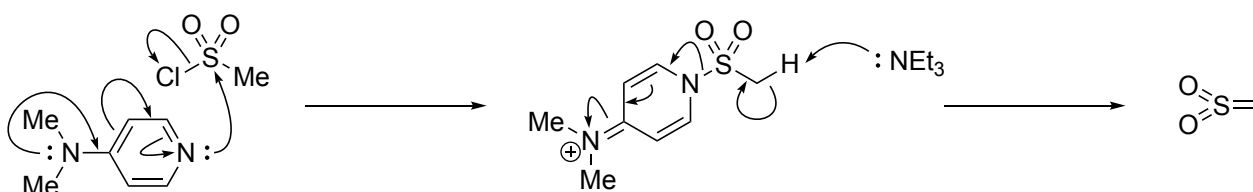
Mollanol A

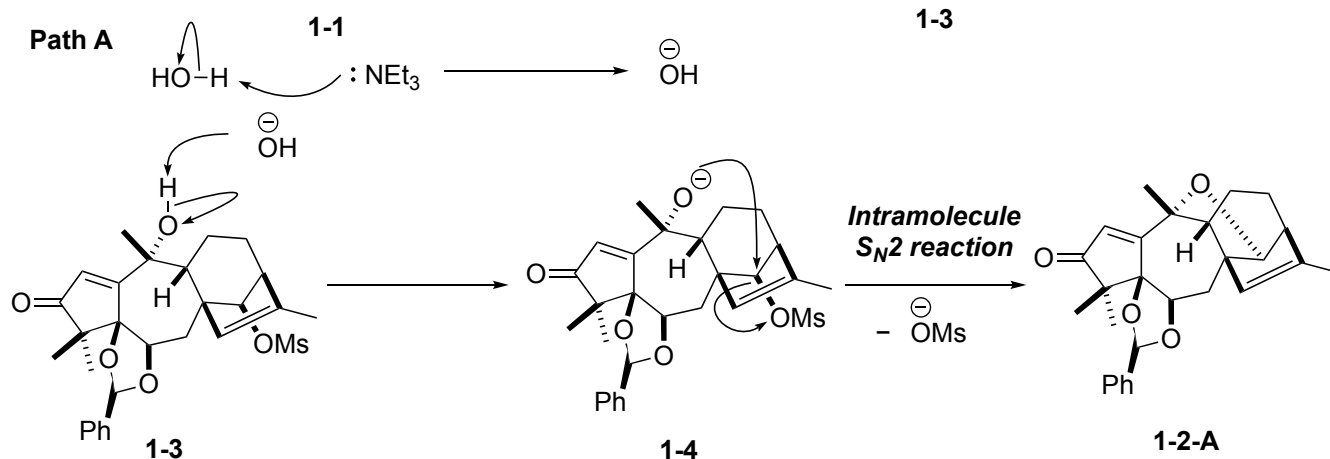
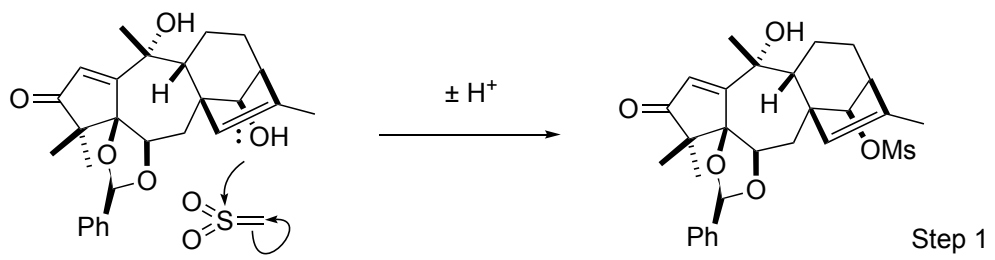


Rhodomollanol A

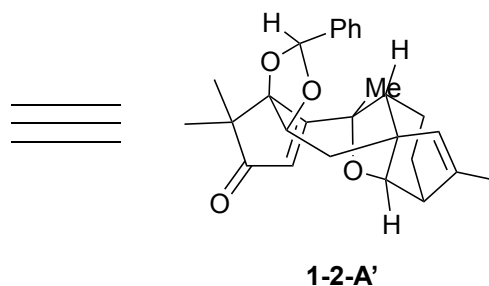


Answer:

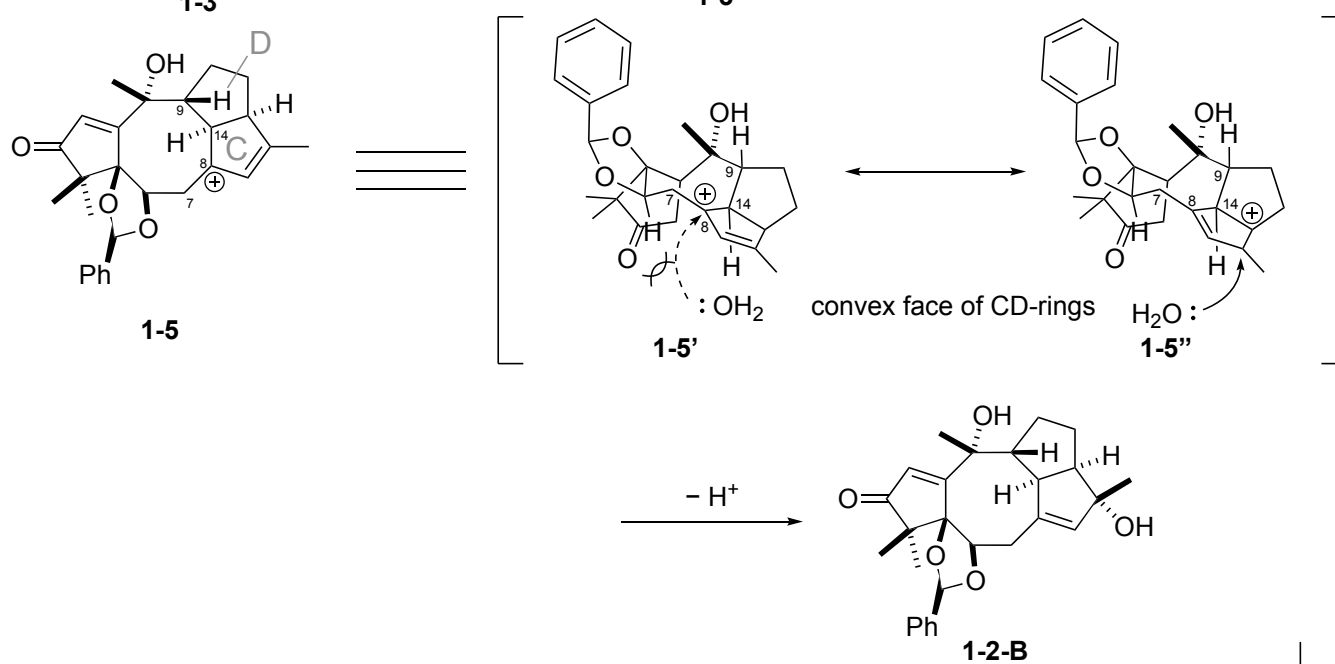
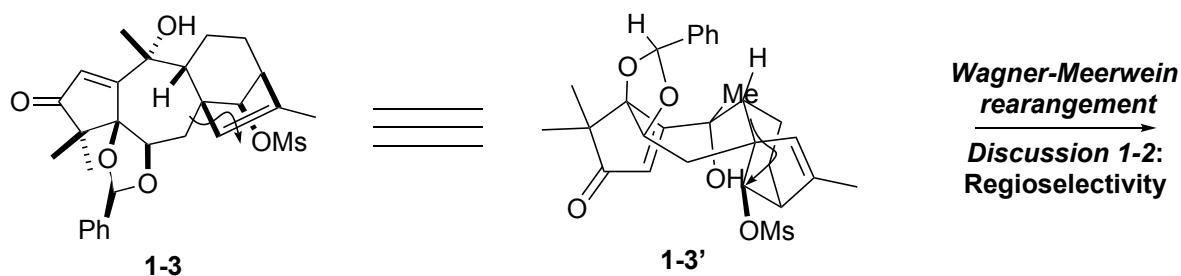




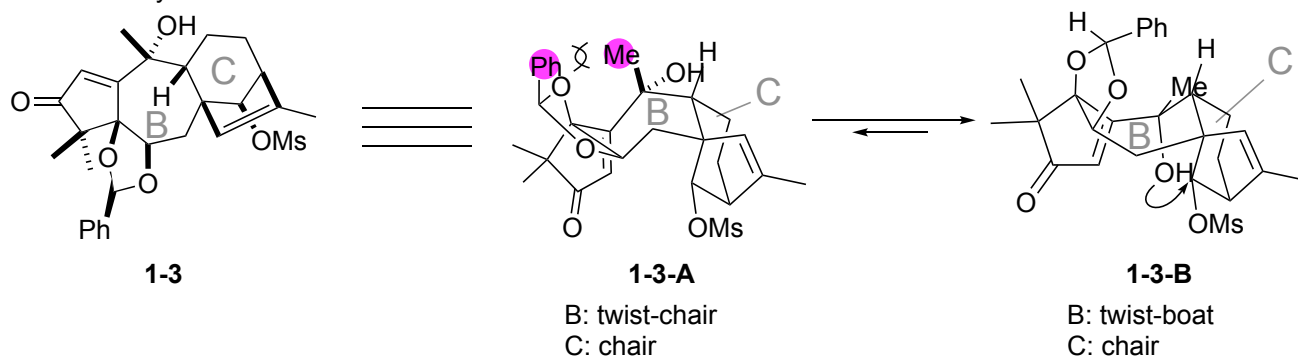
Discussion 1-1:
Selectivity of Path A and B



Path B

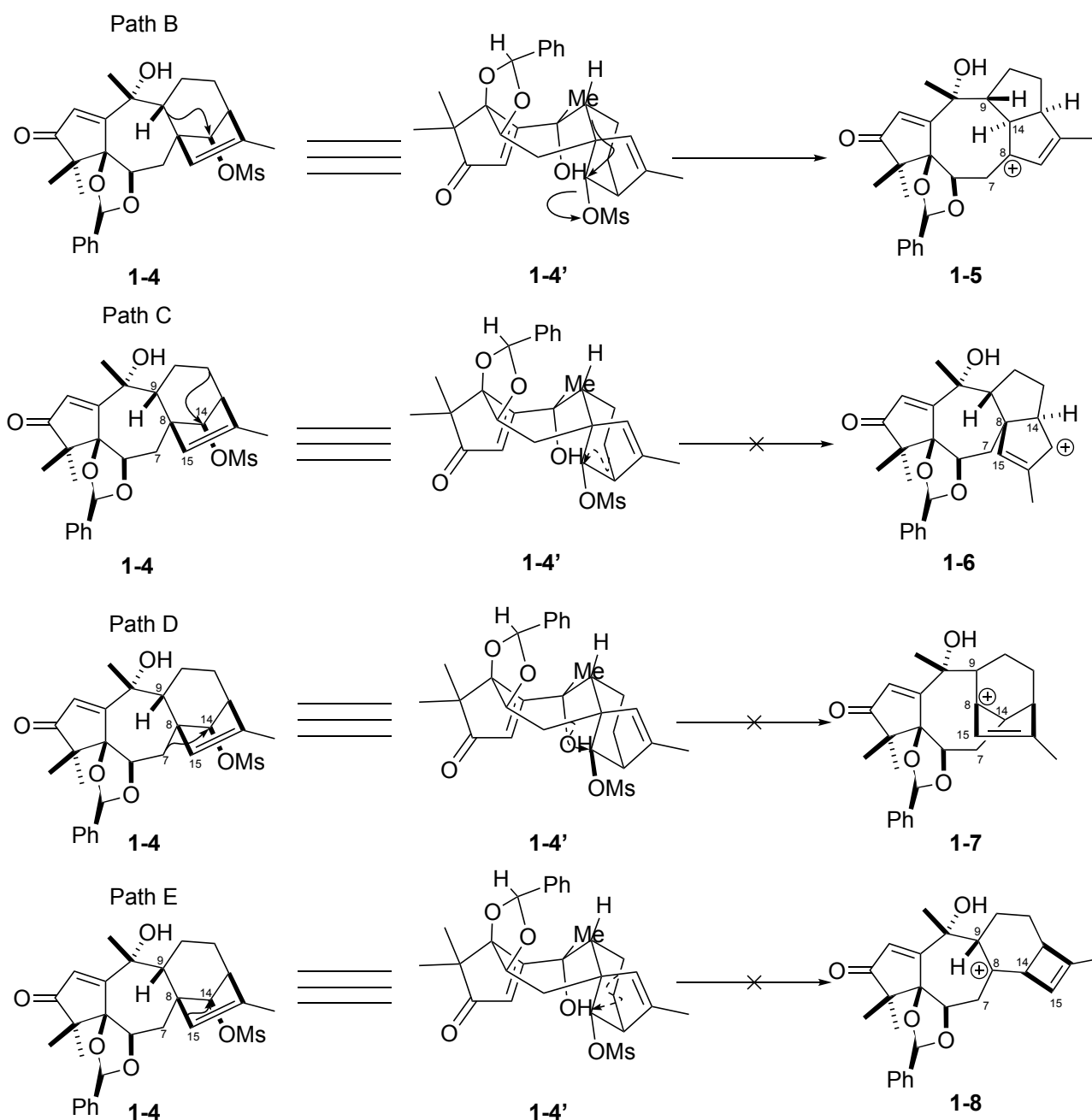


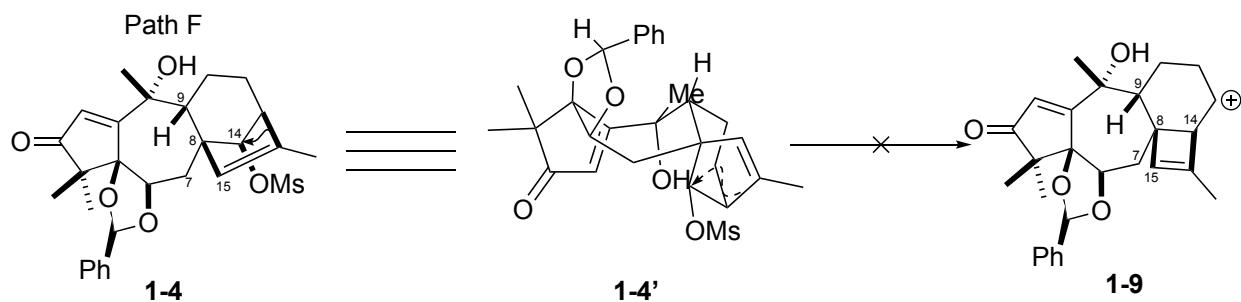
1-1. Selectivity of **1-2-A** and **1-2-B**



It is seemed that benzylideneacetal affects conformation change. Paying attention to B ring and C ring, these two conformations are proposed. **1-3-A** has diaxial interaction by phenyl and methyl. So, **1-3-B** is more stable form of this compound. In the conformation of **1-3-B**, the distance between C10-hydroxy group and C14 is small. Therefore, it is assumed that intramolecule S_N2 reaction is as fast as wagner-meerwein rearrangement in this reaction.

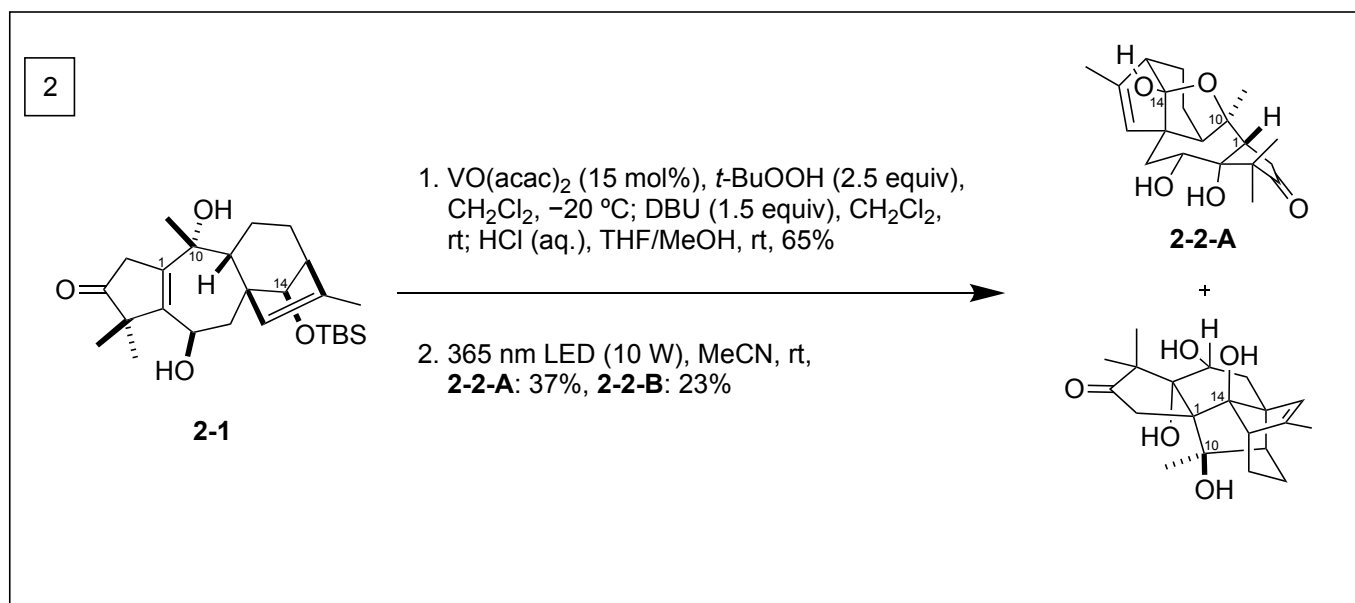
1-2. Regioselectivity





Paying attention to the direction of σ^* -orbital of C14-O bond, in the path D · E · F, these bonds don't match with that orbital. Then, only path B and C are seemed to happen. Seeing cation which is rearrangement product, **1-5** is more stable than **1-6**, which has secondary cation.

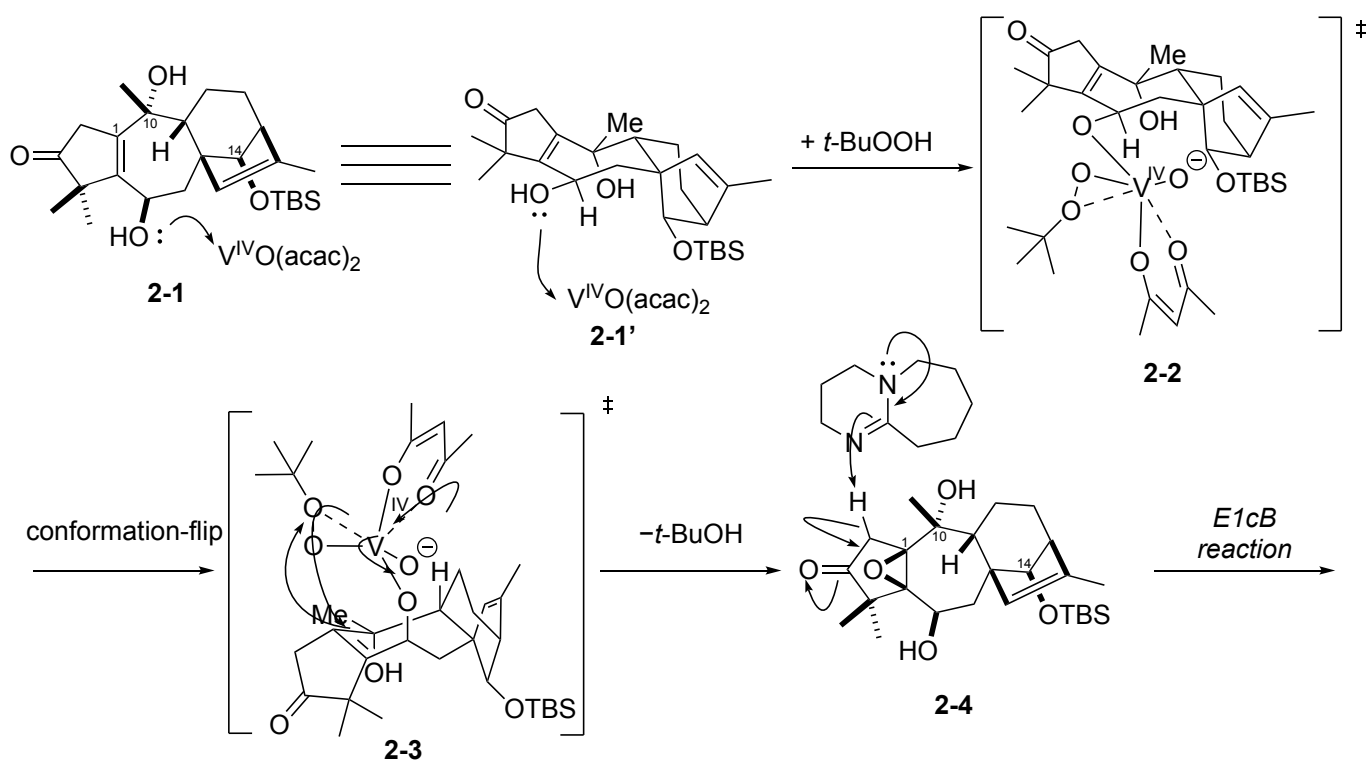
In conclusion, it says that only path B and path A (S_N2 reaction) occur.

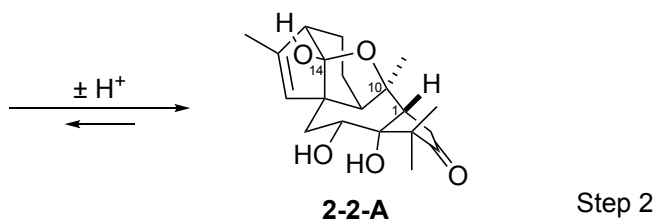
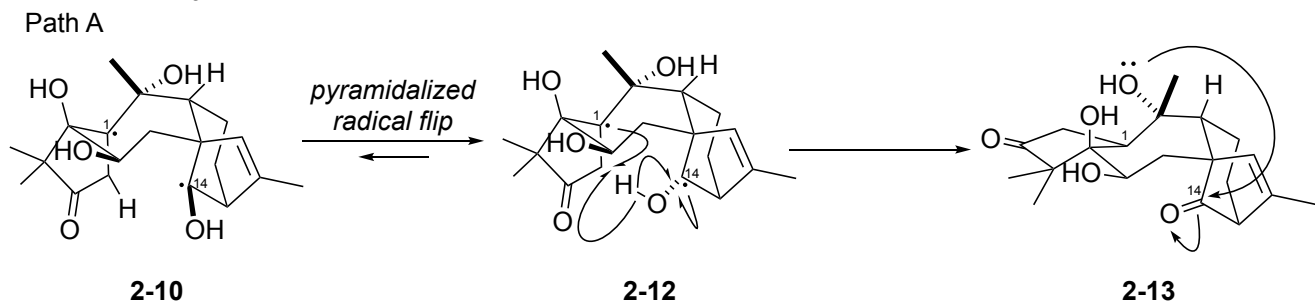
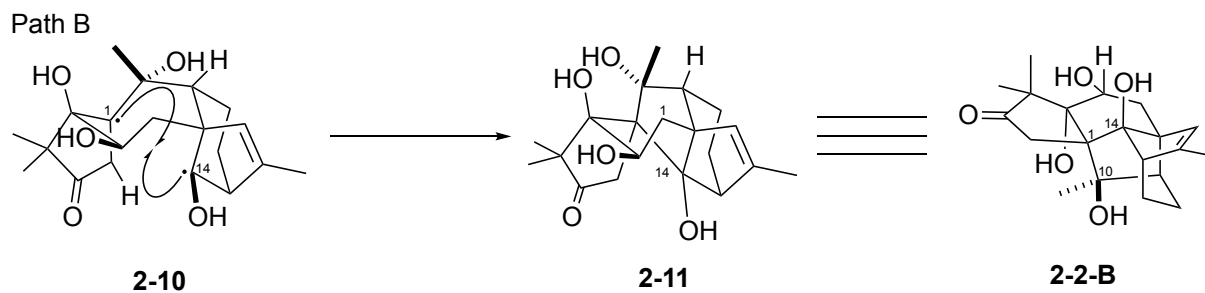
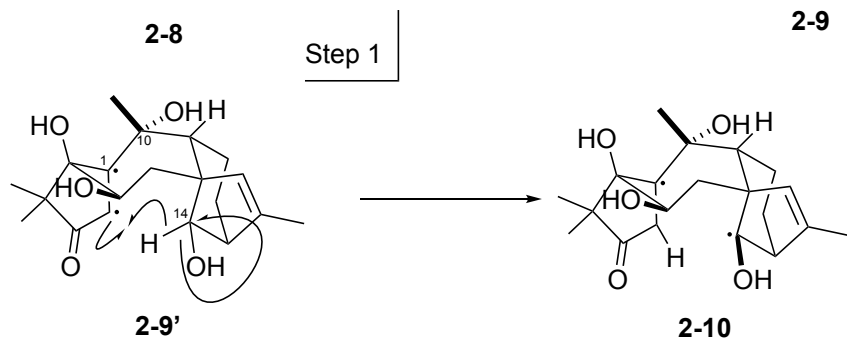
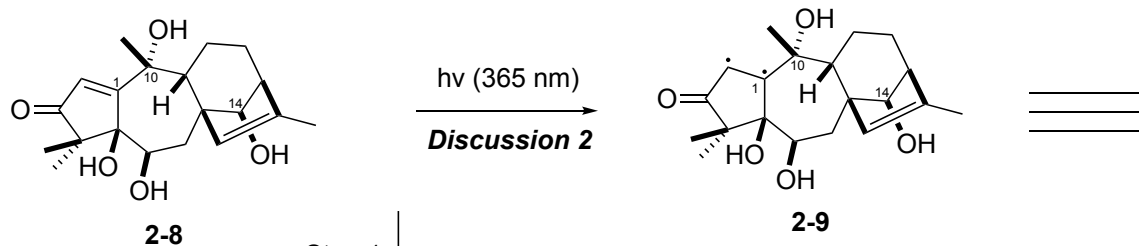
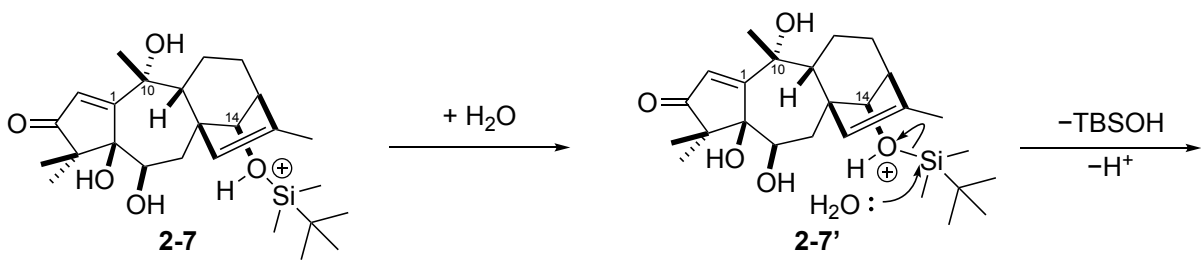
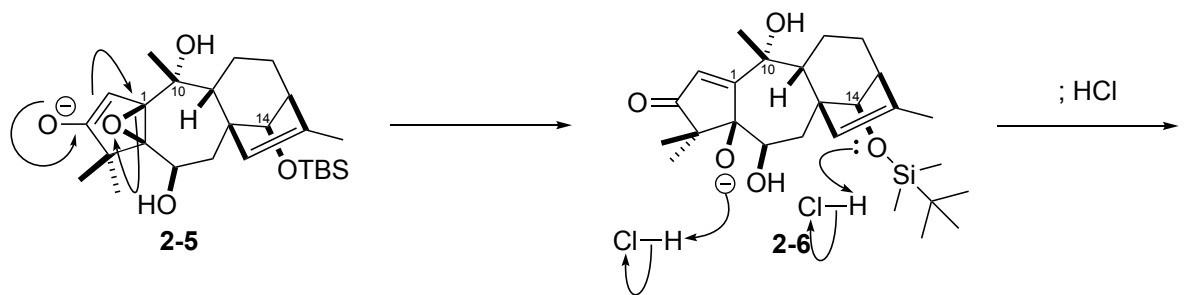


Answer:

The reaction using V(IV) is discribed.

The reaction using V(V) proceeds in the same way.⁶⁾



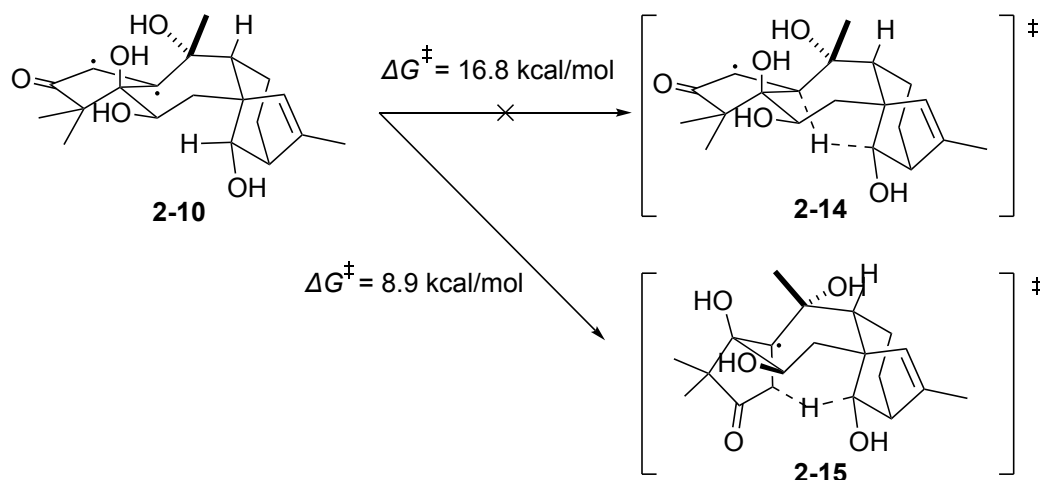


Discussion 2

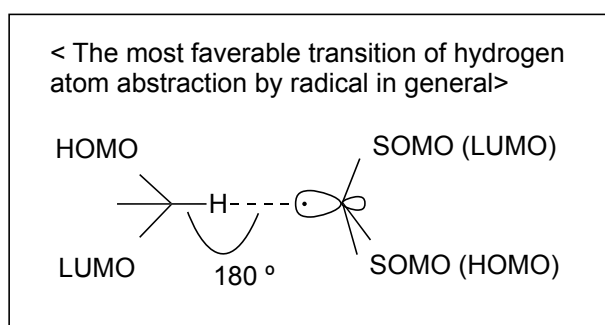
2-1. Photoreaction

2-1-1. Hydrogen atom transfer

After excitation of enones, 1,6-hydrogen atom transfer occurs. Although there is the possibility of 1,5-hydrogen atom transfer, its higher Gibbs free energy than that of 1,6-hydrogen makes it difficult to occur.



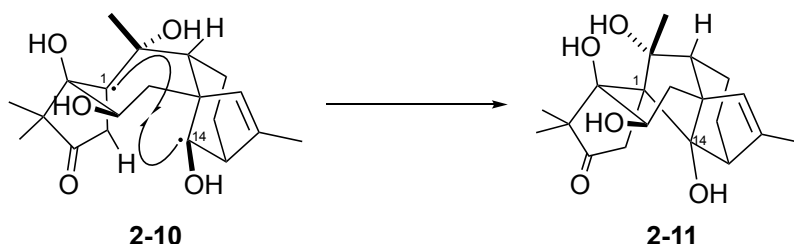
This difference of Gibbs free energy may be caused by difference of hydrogen atom abstraction by radical. Generally, in this hydrogen atom abstraction, the three points that are radical and hydrogen atom and 14-carbon atom should be in a straight line. Transition state of **2-15** is more suitable than **2-14** in that perspective. Therefore, 1,6-hydrogen atom transfer is major in this reaction.



2-1-2. Gibbs free energy level (please see the page 7)

• Path B

After 1,6-hydrogen atom transfer, via excitation of $\pi\text{-}\pi^*$ triplet state for singlet state, C1-C14 radical-radical combination occurs.



• Path A

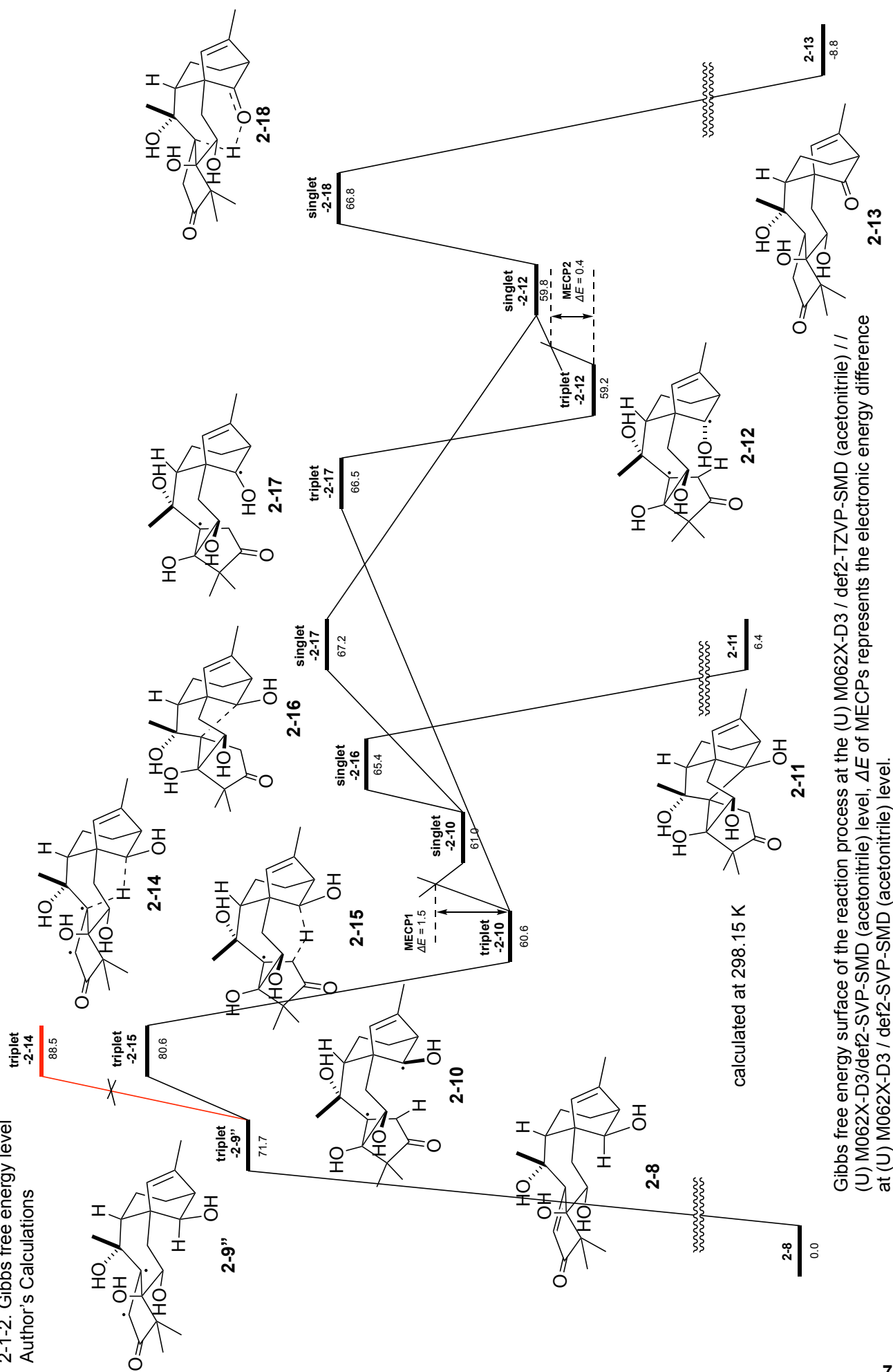
After 1,6-hydrogen atom transfer, hydrogen atom transfer happens again, between C1-radical and hydroxy group of C14. It is assumed that there are two routes before that second hydrogen atom transfer.

[1]: Transformation from $\pi\text{-}\pi^*$ triplet state to singlet state via minimum energy cross point (MECP, $\Delta E = 1.5 \text{ kcal/mol}$) \rightarrow Flipping of C14-pyramidalized radical ($\Delta G^\ddagger = 6.2 \text{ kcal/mol}$)

[2]: Flipping of C14-pyramidalized radical ($\Delta G^\ddagger = 5.9 \text{ kcal/mol}$) \rightarrow Transformation from $\pi\text{-}\pi^*$ triplet state to singlet state via MECP ($\Delta E = 0.4 \text{ kcal/mol}$)

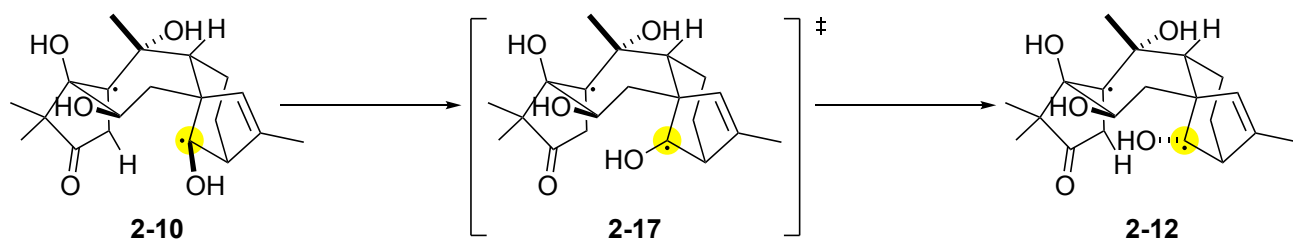
It is seemed that [2] is major because it needs less activation energy and is via triplet-**2-12** which is the most stable transition state.

2-1-2. Gibbs free energy level
Author's Calculations

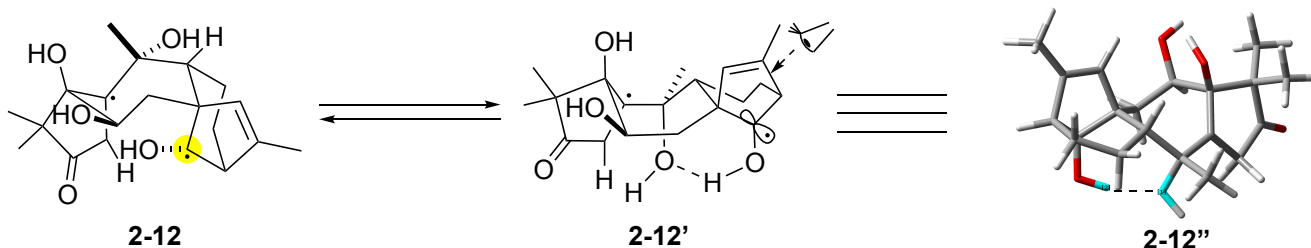


Gibbs free energy surface of the reaction process at the (U) M062X-D3 / def2-TZVP-SMD (acetonitrile) // (U) M062X-D3/def2-SVP-SMD (acetonitrile) level, ΔE of MECPs represents the electronic energy difference at (U) M062X-D3 / def2-SVP-SMD (acetonitrile) level.

C14-pyramidalized radical flipping



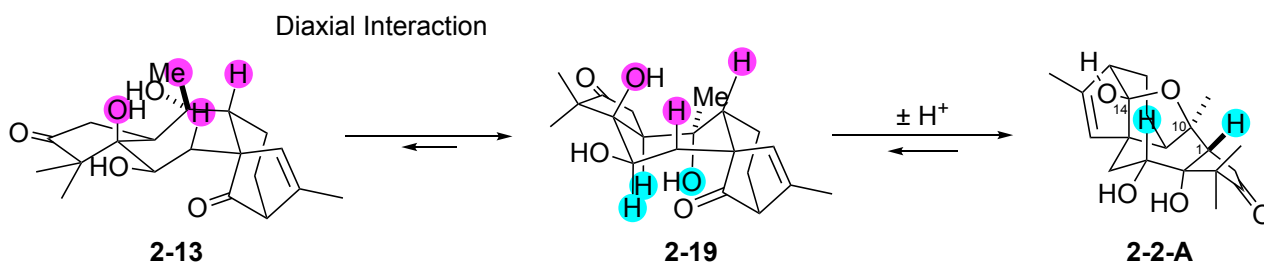
• Reasons of C14-pyramidalized radical flipping happening



hydrogen bond

2-12'' is the computing conformation. In the conformation of **2-12'**, the distance between hydrogen atom of C14-hydroxy group and oxygen atom of C10-hydroxy group is 1.81 Å. Generally, the length between hydrogen atom and acceptor atom is from 1.6 Å to 2.0 Å. Therefore, it is assumed that this hydrogen bond made **2-12** more stable than **2-10**.

2-2. Conformation change



Before substrate changes to **2-2-A** by intramolecule acetalization, the conformation of cycloheptane which has three hydroxy groups changes to less obstacle conformation. As a result, hydroxy group of C10 approaches to C14-ketone. Then, for improving diaxial interaction, structure of tetrahydrofuran is formed.

Reference

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- 2) Meguri, H.; *Yakugaku Zasshi.* **1959**, *79*, 1057.
- 3) Burke, J. W.; Dostkotch, R. W.; Ni, C.-Z.; Clardy, J.; *J. Am. Chem. Soc.* **1989**, *111*, 5831.
- 4) Gasa, S.; Hamanaka, N.; Matsunaga, S.; Okuno, T.; Takeda, N.; Matsumoto, T.; *Tetrahedron Lett.* **1976**, *17*, 553.
- 5) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H.; *J. Org. Chem.* **1994**, *59*, 5532.
- 6) Mattias, V.; Karn, L.; Pascal, V. D. V.; Michel, W.; Veronique, V. S.; *Journal of Catalysis.* **2012**, *294*, 1.