

Problem Session (3) -Answer

2024.1.27 Kyohei Oga

Topic: Total synthesis of artatrovirenel A

Lavernhe, R.; Domke, P.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2023**, *145*, 24408.

(doi: org/10.1021/jacs.3c09683)

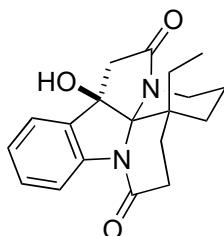
0. Introduction

0-1. Prof. Jieping Zhu

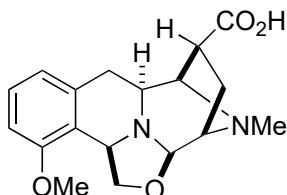


Education

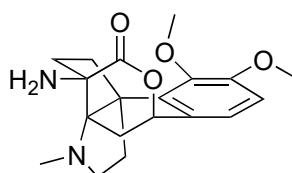
- 1984, B.S., Hangzhou Normal University
- 1987, M.S., Lanzhou University (Prof. Li)
- 1991, Ph.D., University Paris XI (Prof. Husson and Prof. Quirion)
- 1992, Postdoct., Texas A&M University (Prof. D. H. R. Barton)
- 2000, "Charge de Recherche", ICSN
- 2010, Director of Research, ICSN
- present, Professor, Swiss Federal Institute of Technology in Lausanne (EPFL)



(-)Scholarisine G
140116_LS_Yuki_Matsui

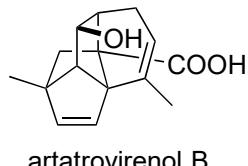
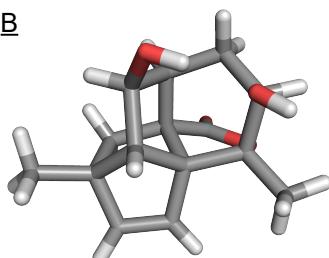


quinocarcin
J. Am. Chem. Soc. **2008**, *130*, 7148.



stephadiamine
J. Am. Chem. Soc. **2023**, *145*, 5001.

0-2. Artatrovirenel A and B



Isolation

Artemisia plants (isolated yield; 6.0 mg/60 kg, air-dried plants)

Structural feature

5/5/6/5/5-pentacyclic system, 8-contiguous stereocenters

Biological activity

cytotoxicity against human hepatoma cell lines
(HepG2, SMMC-7721 and Huh7)

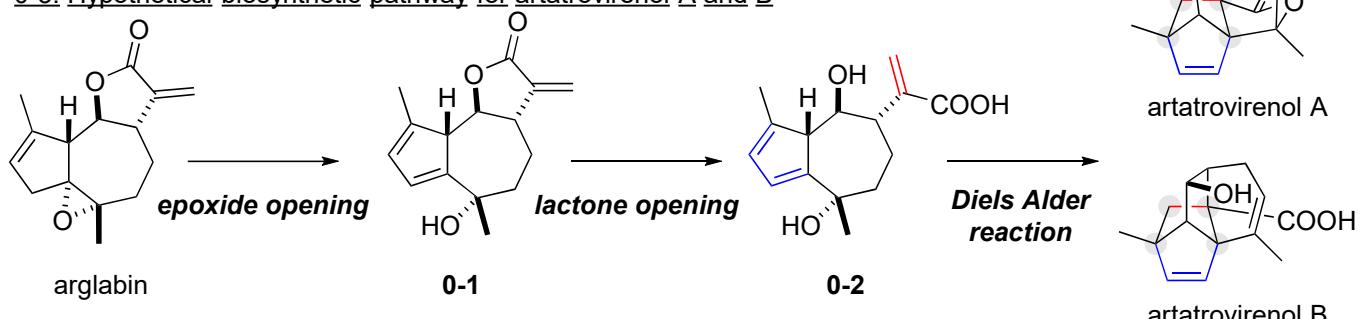


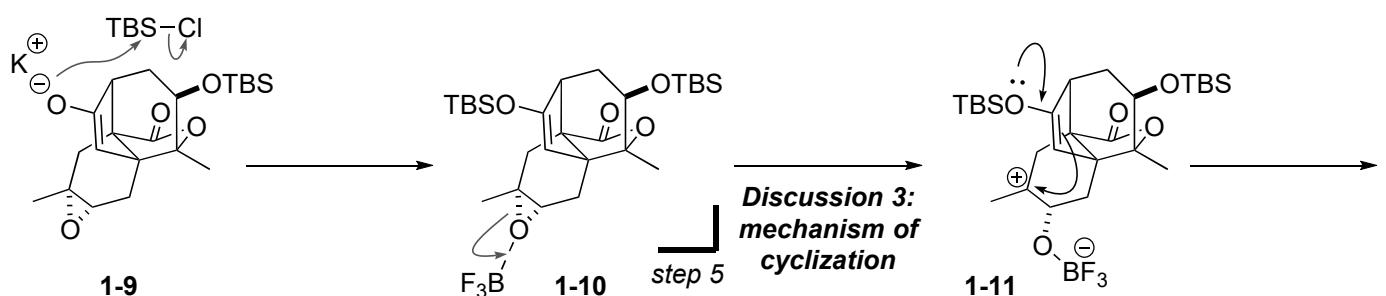
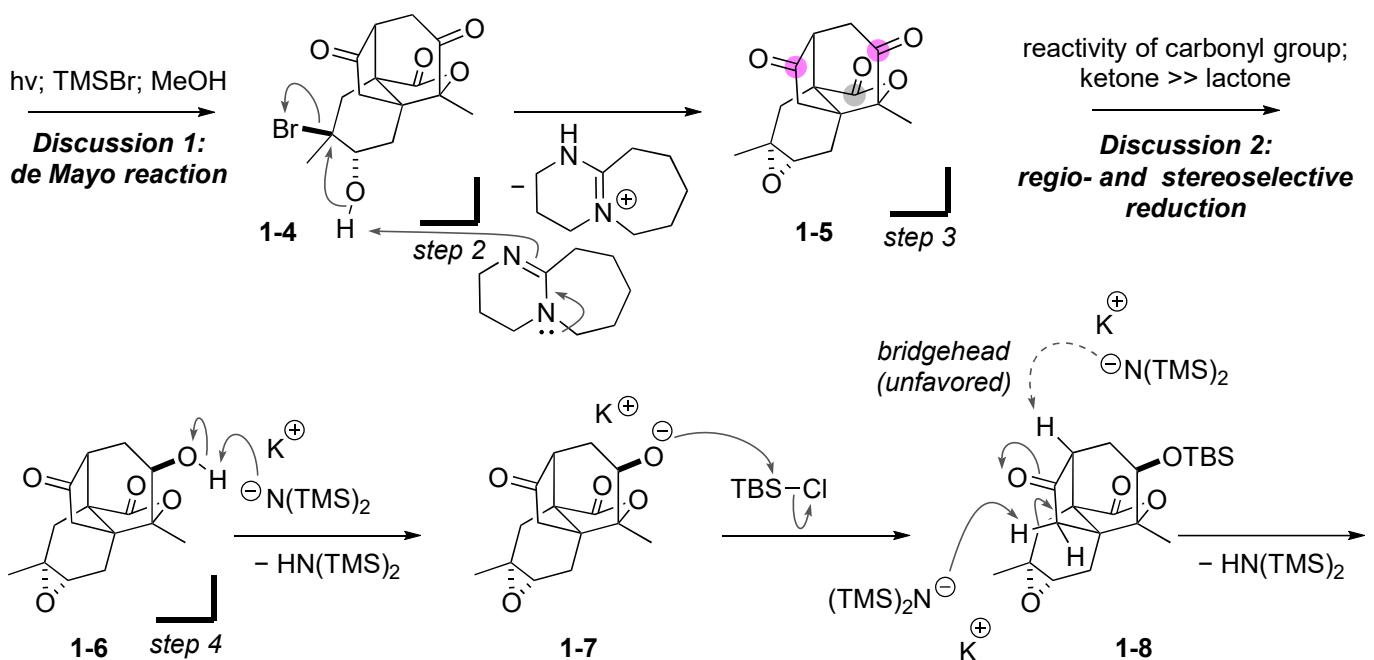
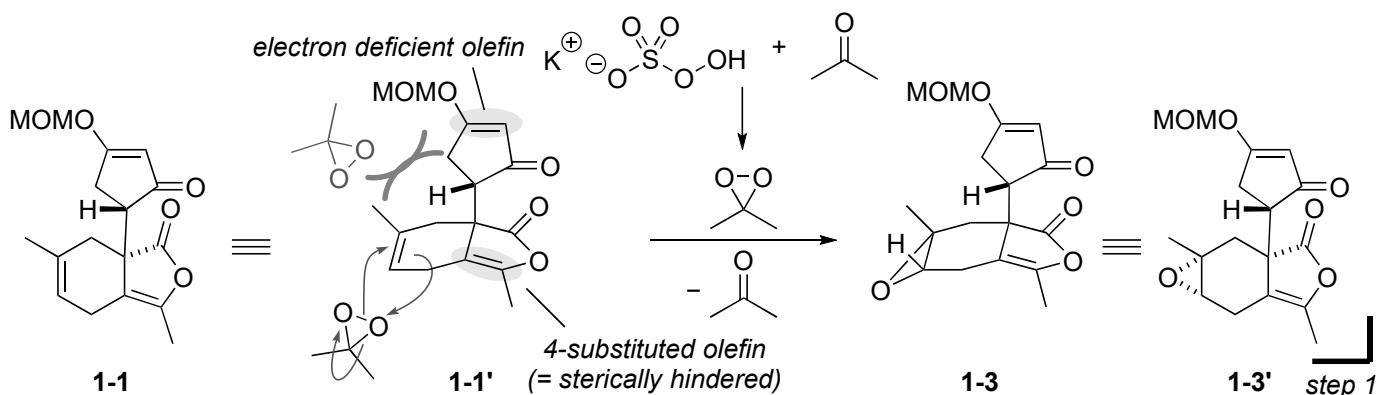
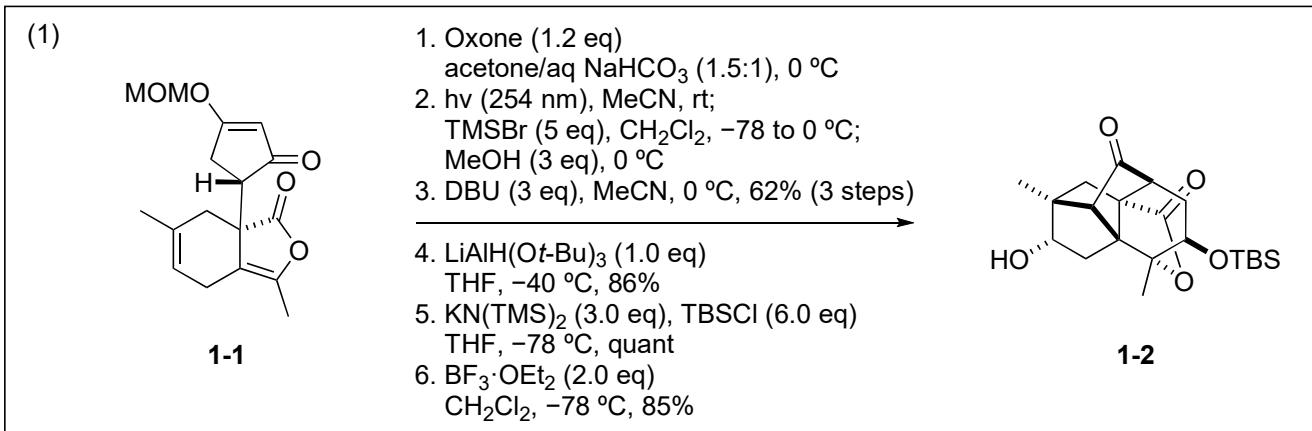
Artemisia Plants

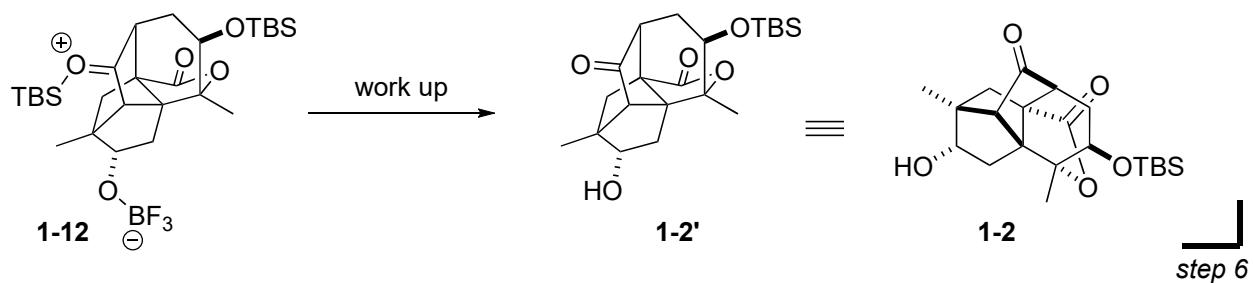
Total synthesis

not reported

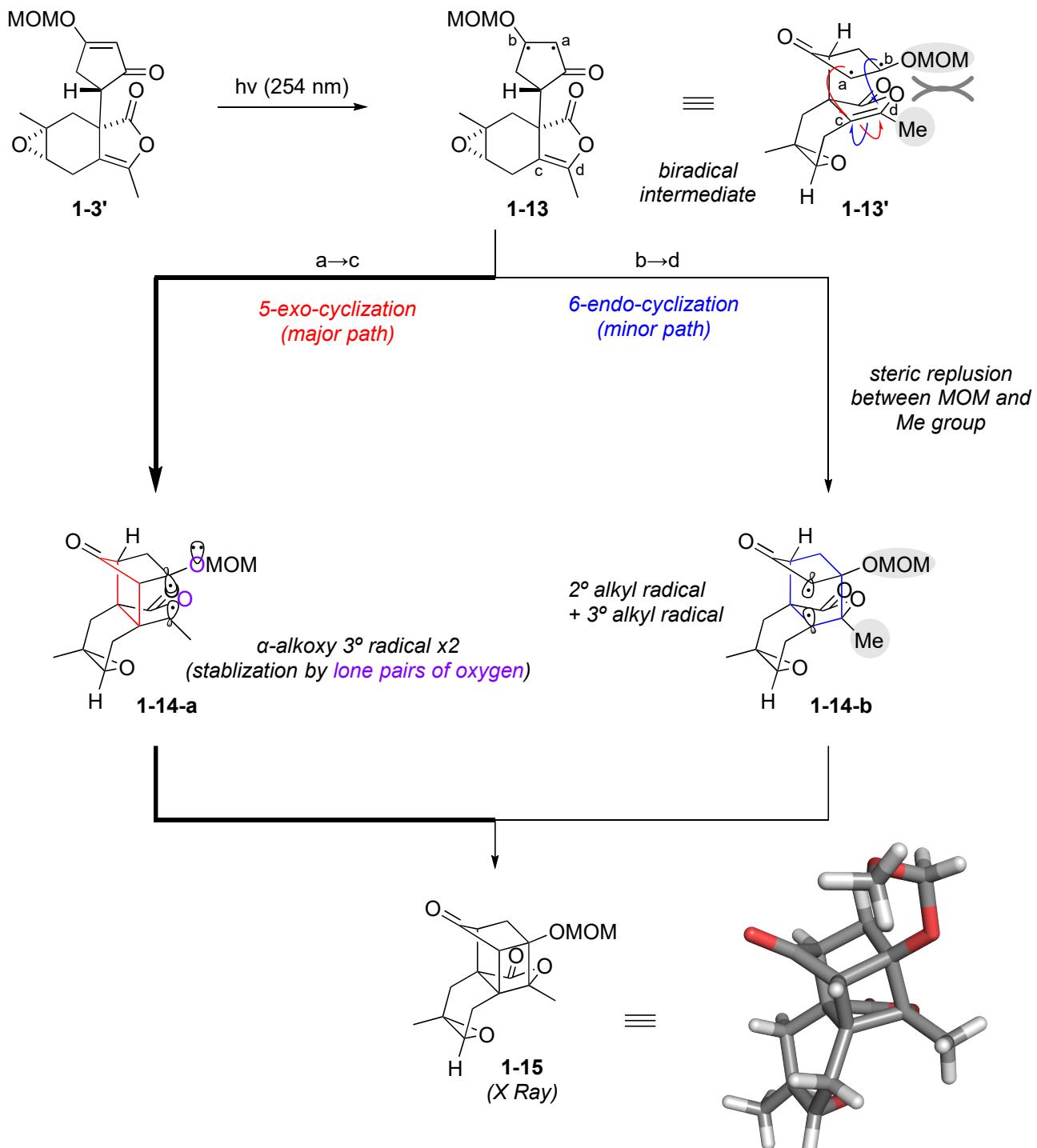
0-3. Hypothetical biosynthetic pathway for artatrovirenel A and B





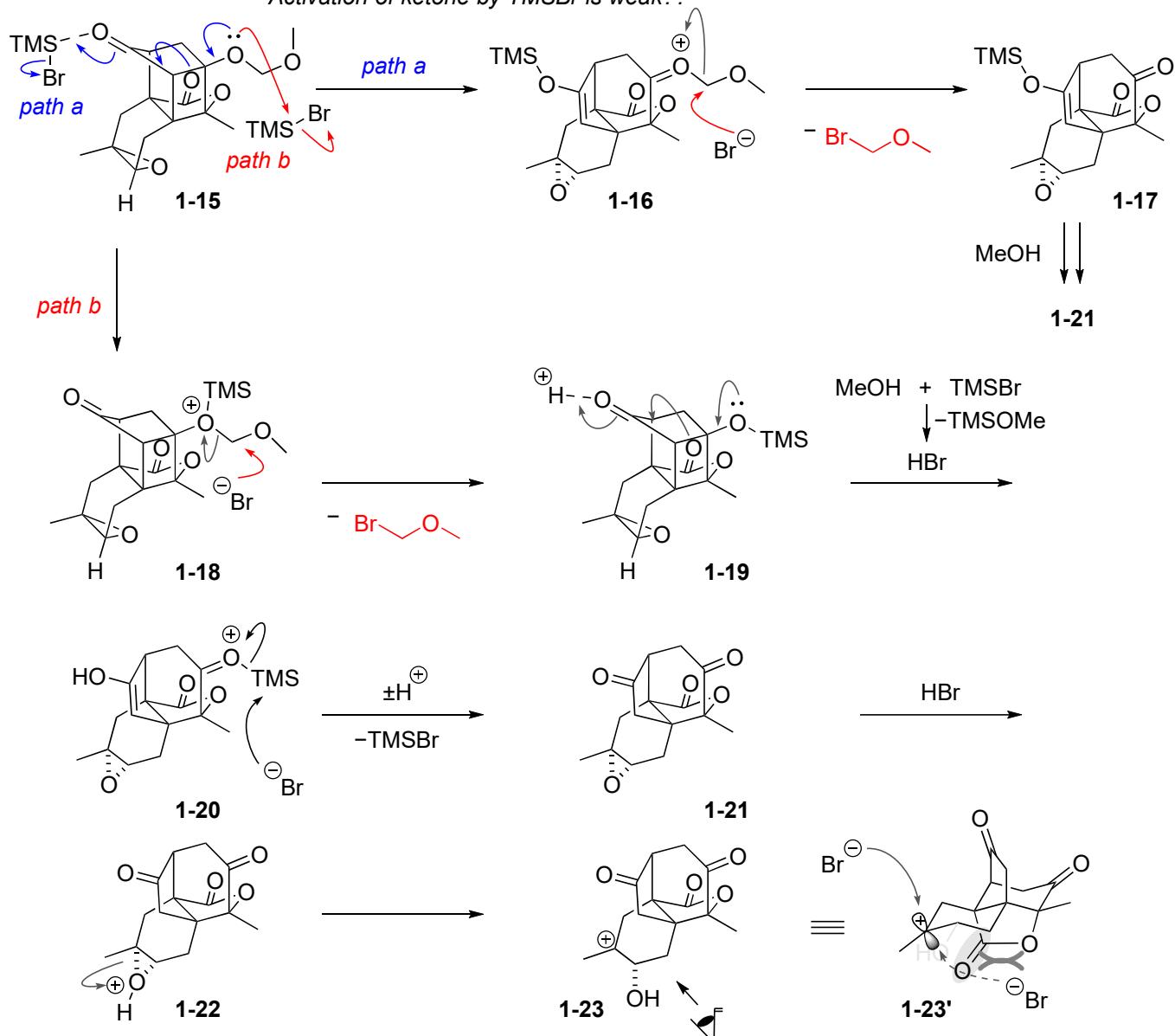


Discussion 1: de Mayo reaction ^{ref. 1}
1. mechanism of [2+2] cyclization

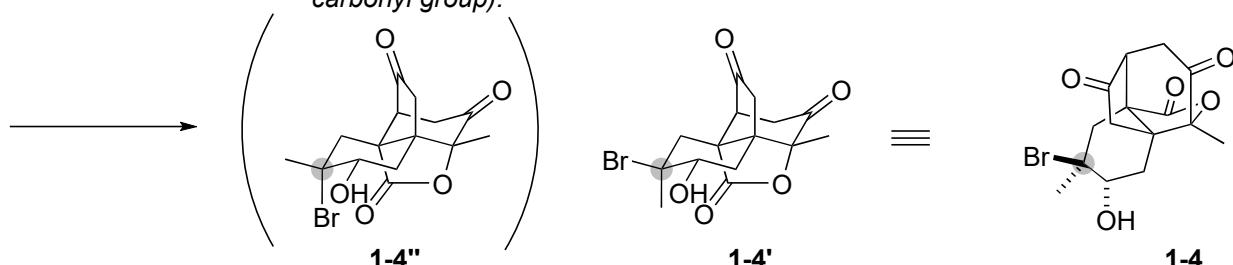


2. retro aldol reaction ^{ref. 2}

Activation of ketone by TMSBr is weak??

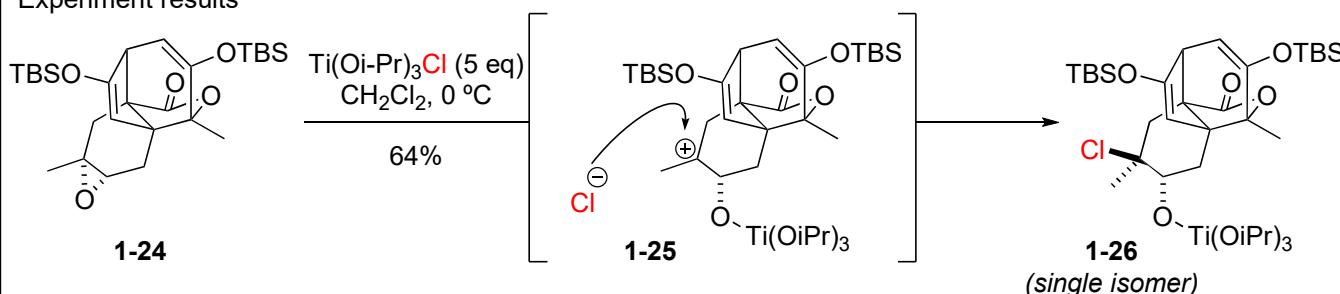


Equatorial attack is more favorable than axial attack due to steric repulsion (highlighted carbonyl group).

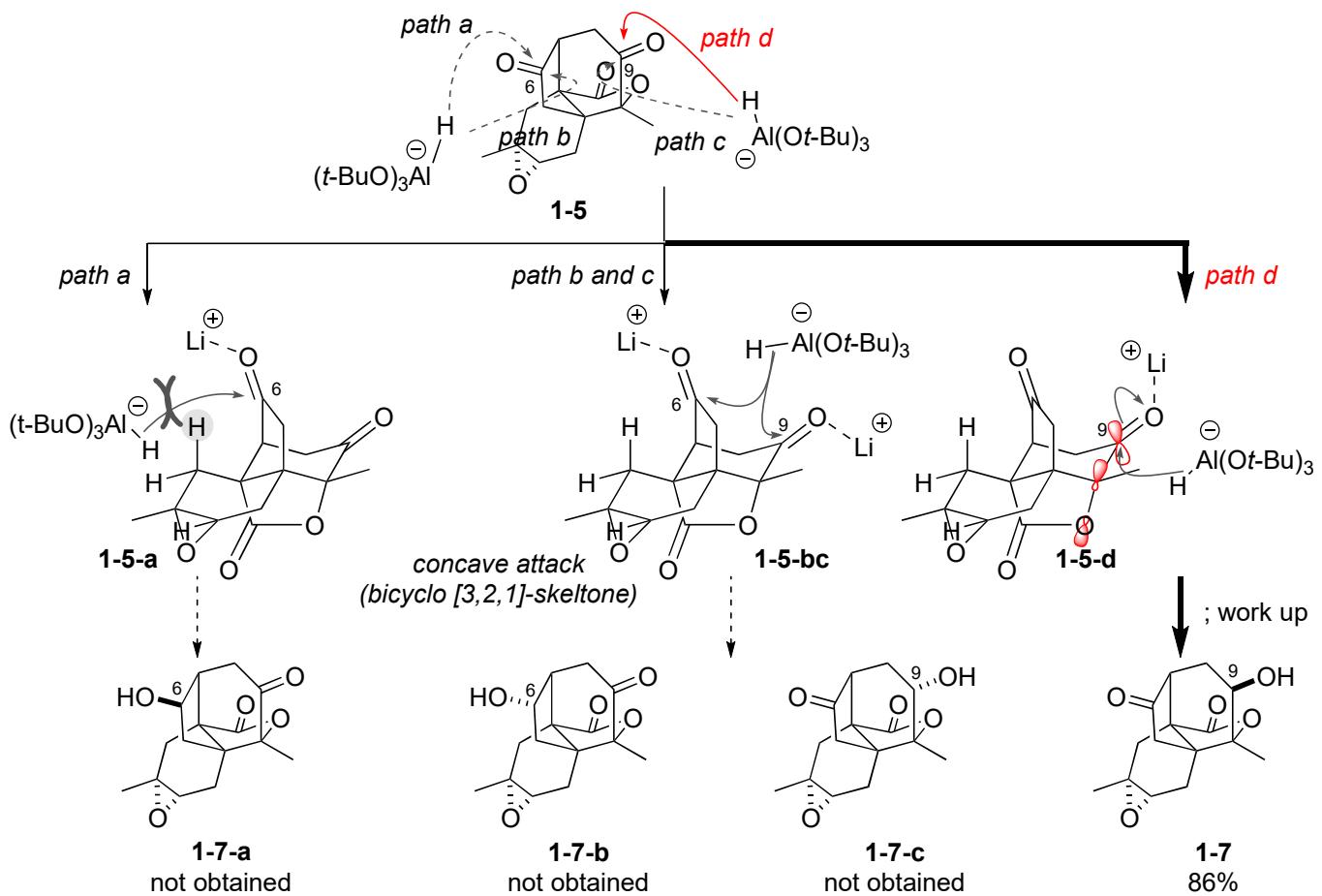


Although the stereochemistry was not determined by the authors, the experimental results below suggest that it might be 1-4' (my proposal).

Experiment results

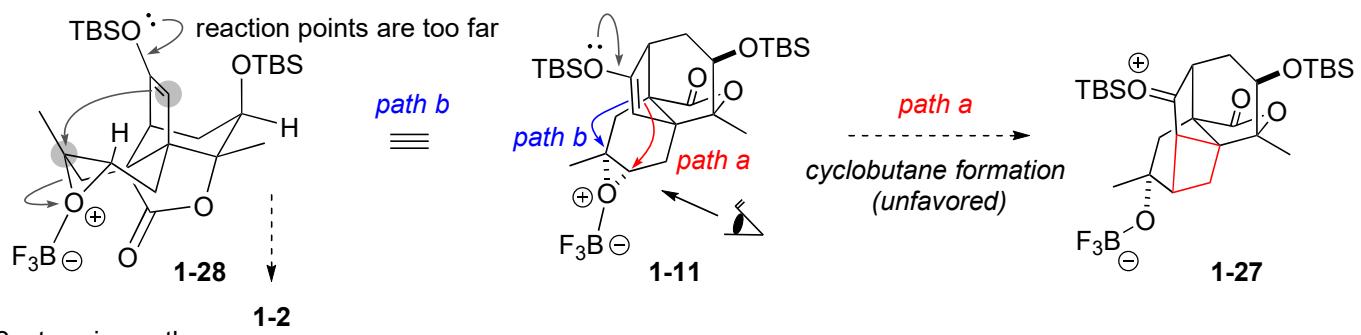


Discussion 2: regio- and stereoselective reduction of ketone

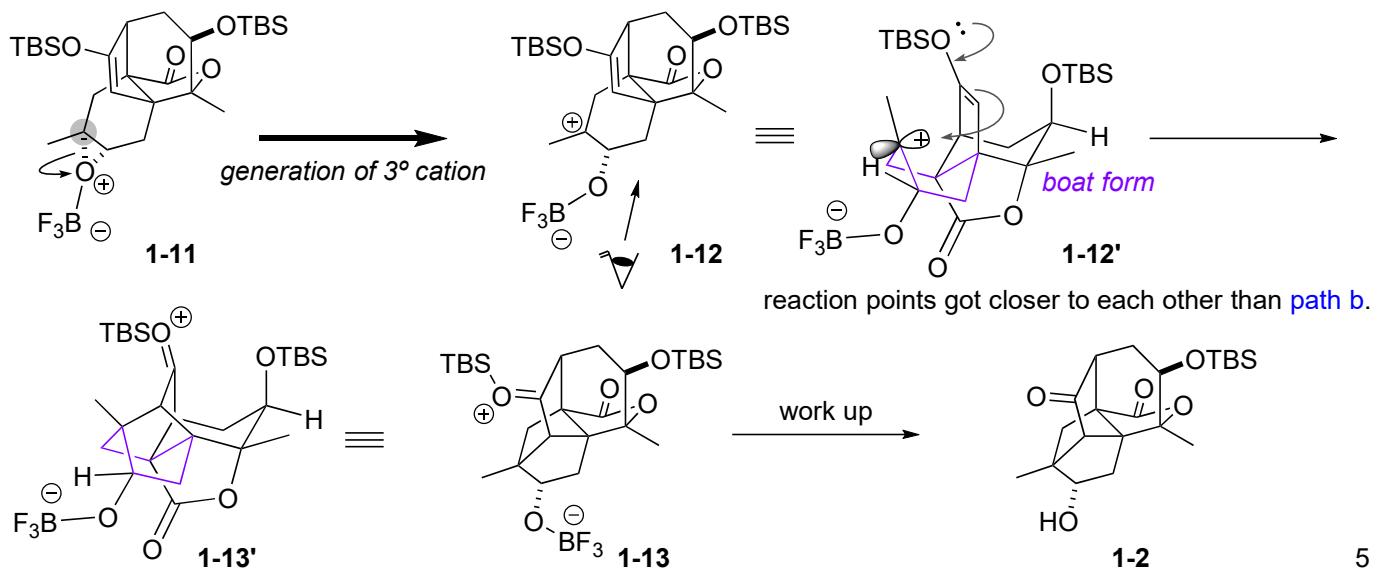


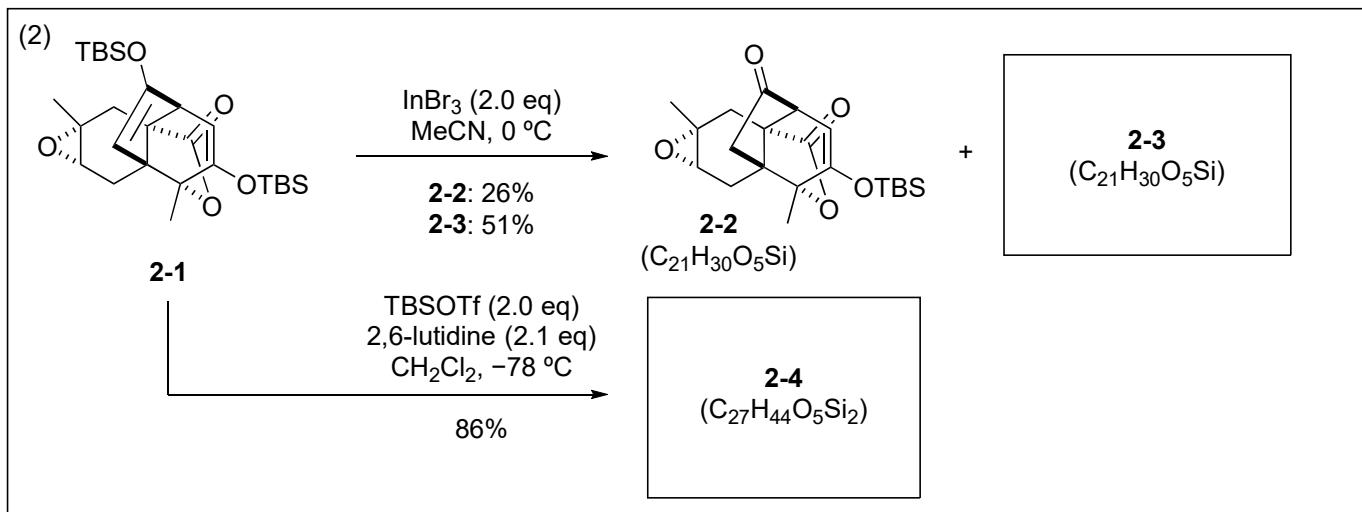
Discussion 3: cyclization

1. concerted pathway

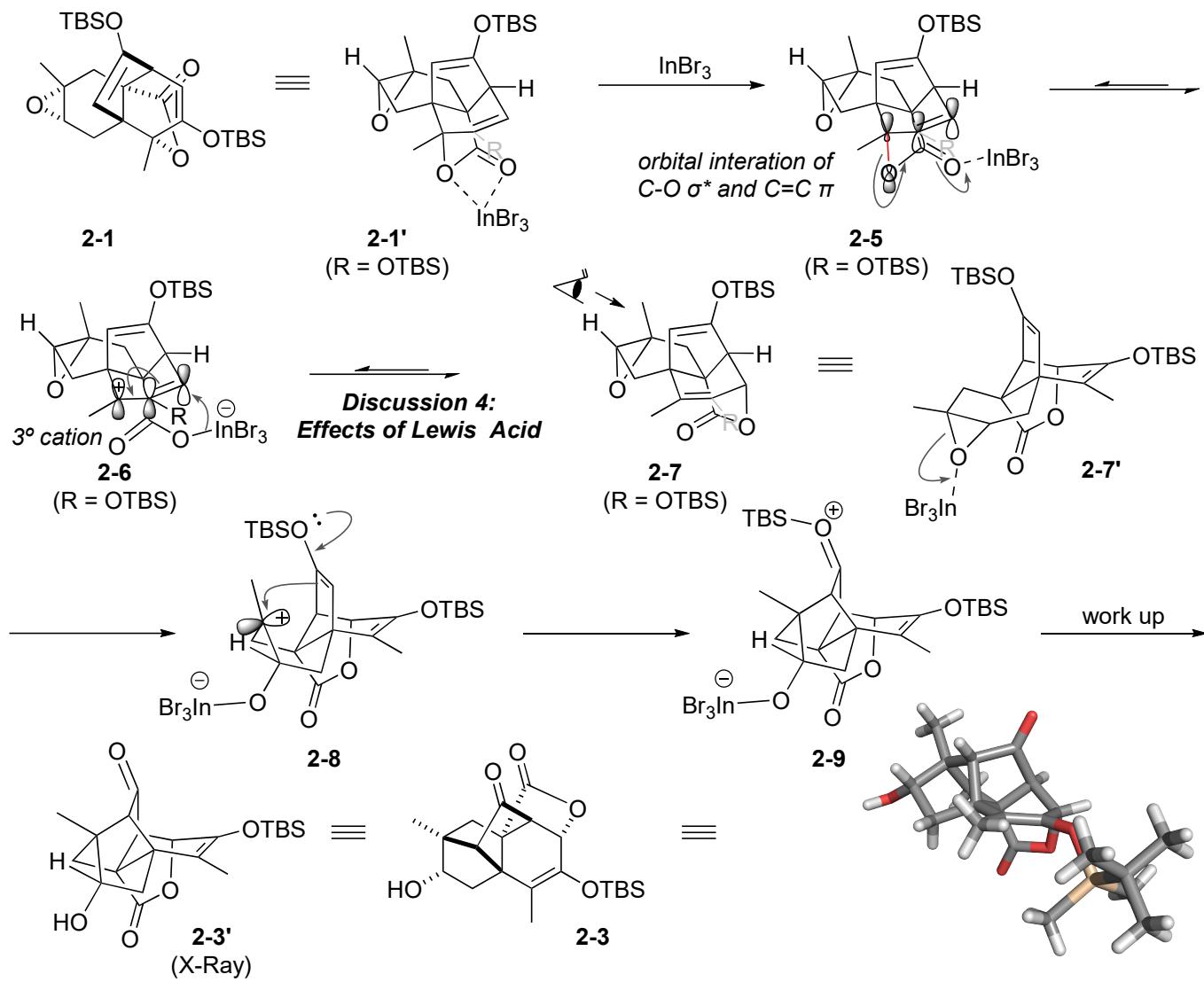


2. stepwise pathway

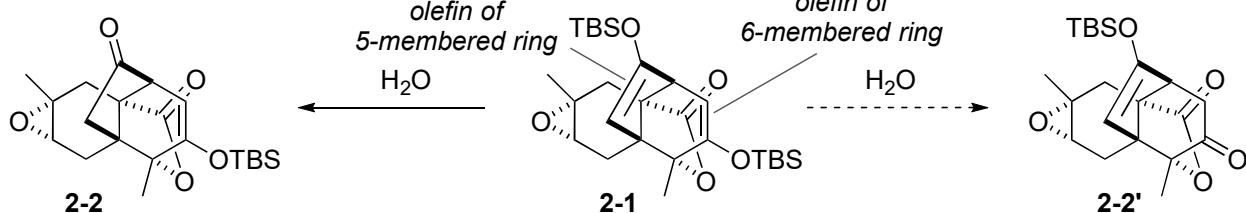




reaction mechanism (2-3)

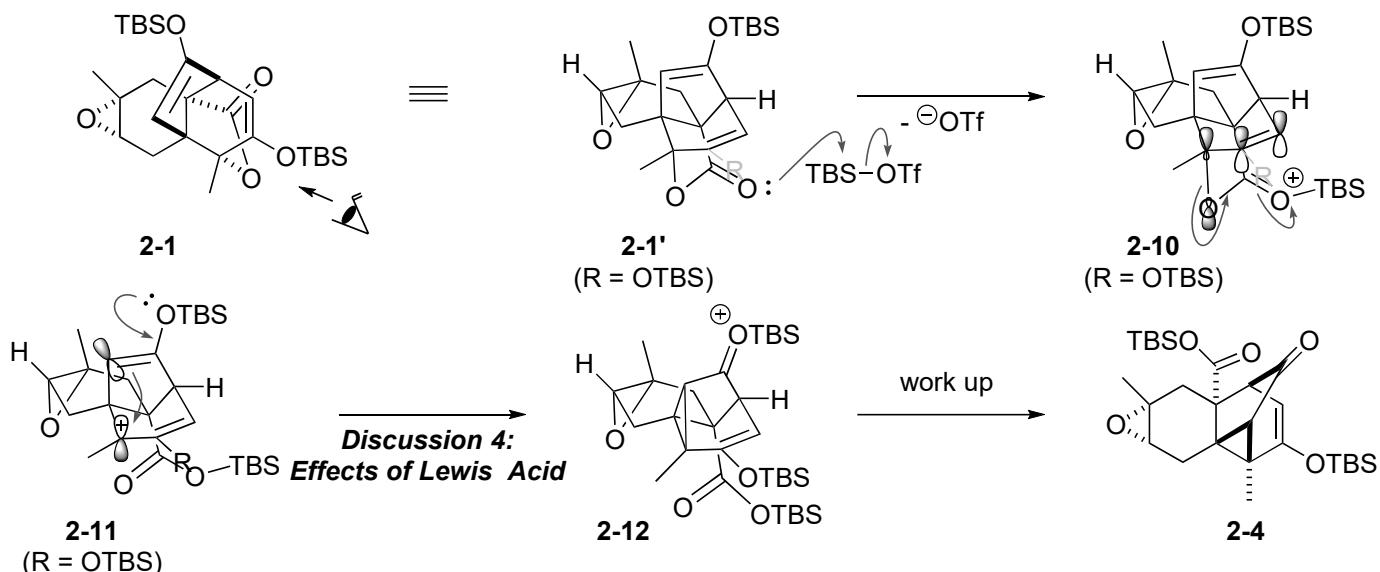


reaction mechanism (2-2)



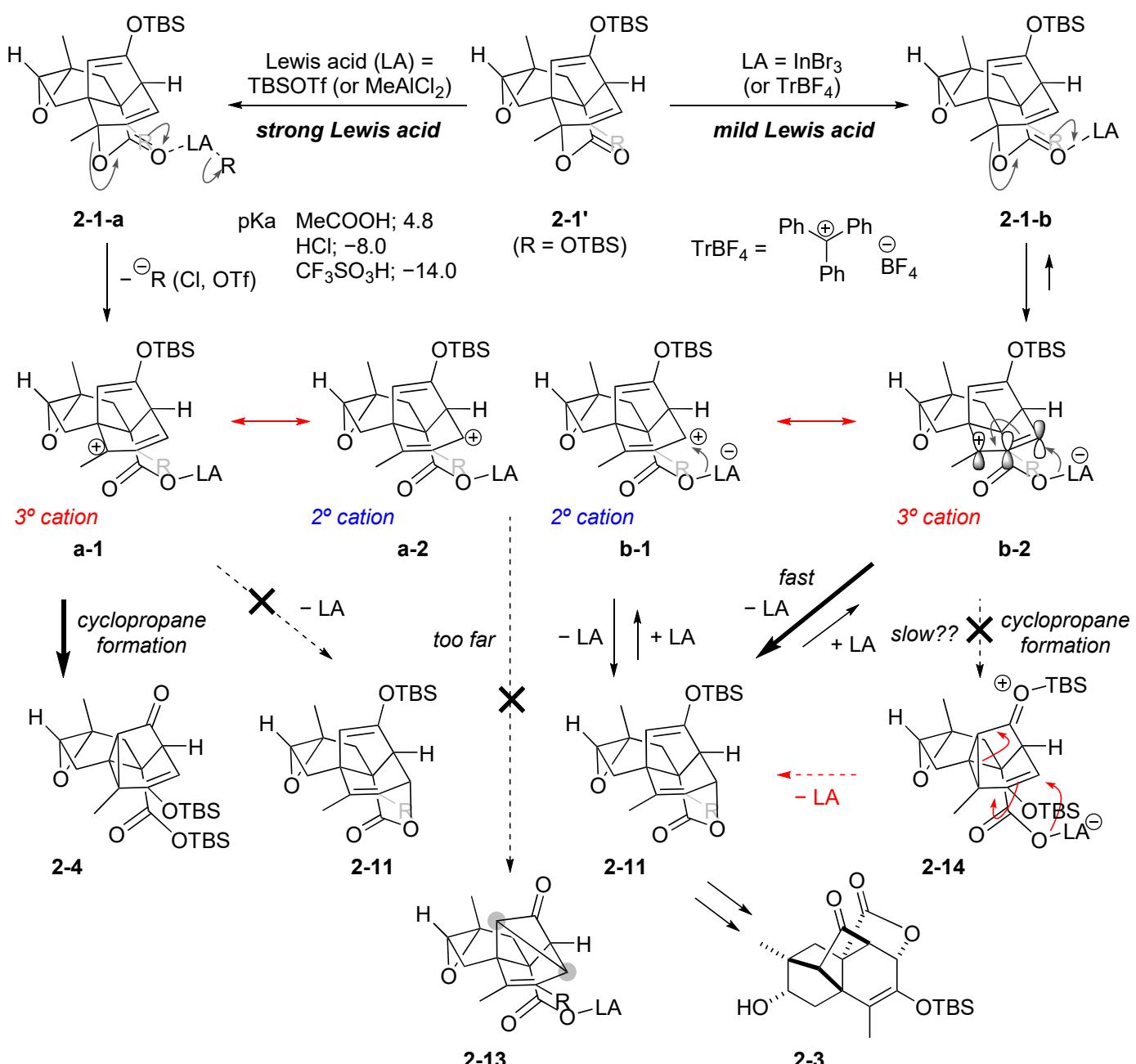
The olefin of 5-membered ring is more strained due to bond angles and hydrolyzed faster than the 6-membered ring olefin.

reaction mechanism (2-4)

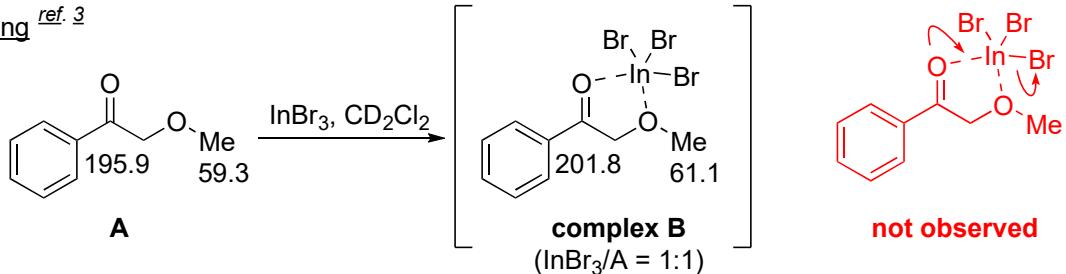


Discussion 4: Effects of Lewis Acid

1. Equilibrium reaction with Lewis acid

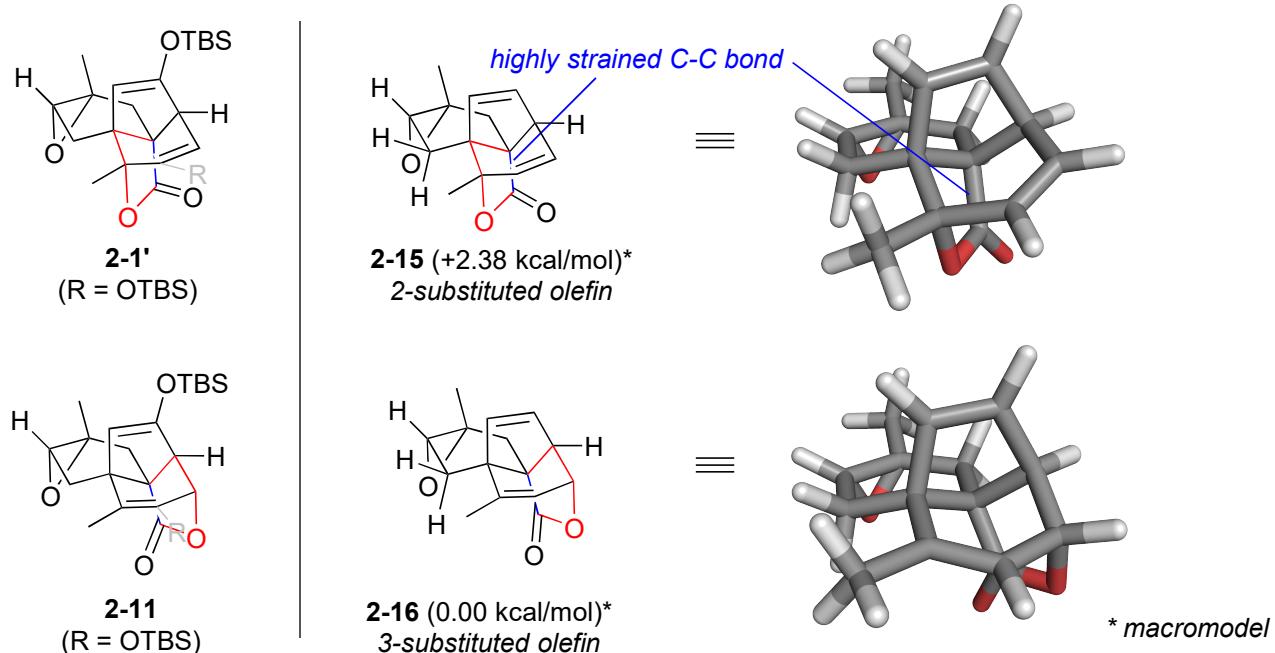


2. Chelating ref. 3



The chemical shift variation of the signals of the carbonyl and methoxy carbon atoms indicate that indium bromide is involved in a two-side-binding interaction with heterosubstituted ketone.

3. Thermodynamic stability

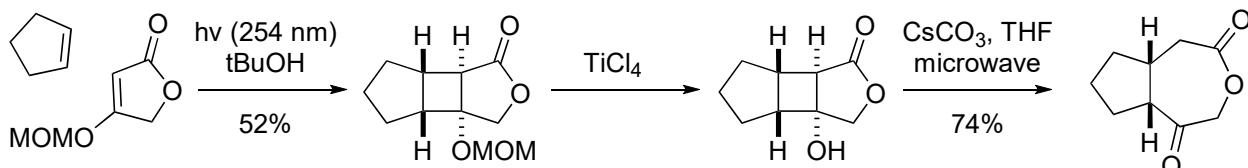


•stability of 6-membered olefin: 3-substituted olefin (**2-16**) > 2-substituted olefin (**2-15**)

•Focusing on the 5-membered ring lactone, the blue C-C bond is distorted in **2-15** compared to **2-16**.

Reference

- 1.a) Challand, B. D.; Hikino, H.; Kornis, G.; Lange, G.; Mayo, P. D. *J. Org. Chem.* **1968**, *34*, 794.
- b) Hoffman, N. *Chem. Rev.* **2008**, *108*, 1052.
- c) Salaverri, N.; Aleman, J.; Marzo, L. *Adv. Synth. Catal.* **2023**, *365*, 1.
2. Kemmler, M.; Herdtweck, E.; Bach, T. *J. Org. Chem.* **2004**, *4582*.



3. Bandini, M.; Cozzi, P. G.; Garelli, A.; Melchirre, P.; Ronchi, A. U. *Eur. J. Org. Chem.* **2002**, *3243*.