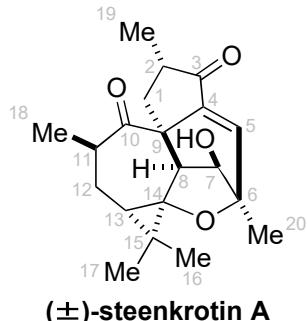
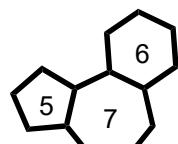
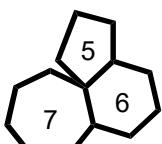


Problem Session (2) - Answer

Topic: First total synthesis of (\pm)-steenkrotin A (Ding, Hanfeng *Angew. Chem. Int. Ed.* 2015, 54, 1.)

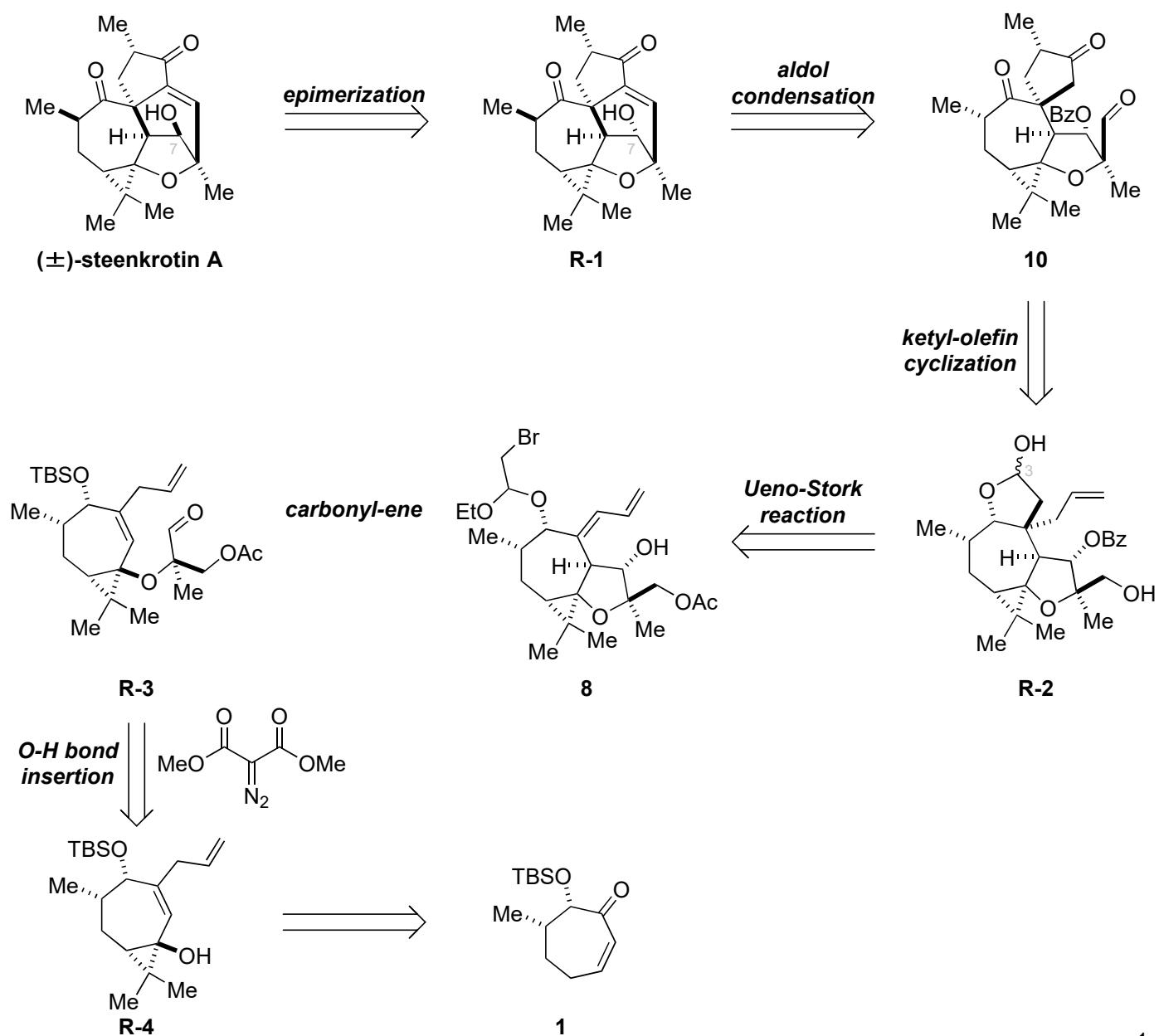


- from Croton steenkampianus Gerstner (Euphorbiaceae), tree native to central Africa and eastern parts of southern Africa.
- in 2008, isolated as a novel diterpenoid (Hussein and co-workers)
- [5,6,7] tricyclic core

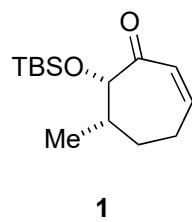


- pentacyclic framework
- eight stereogenic centers

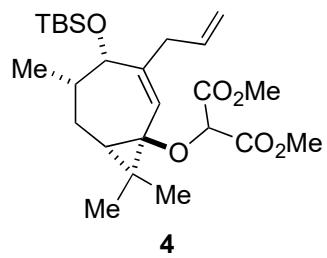
retrosynthetic analysis



Problem 1

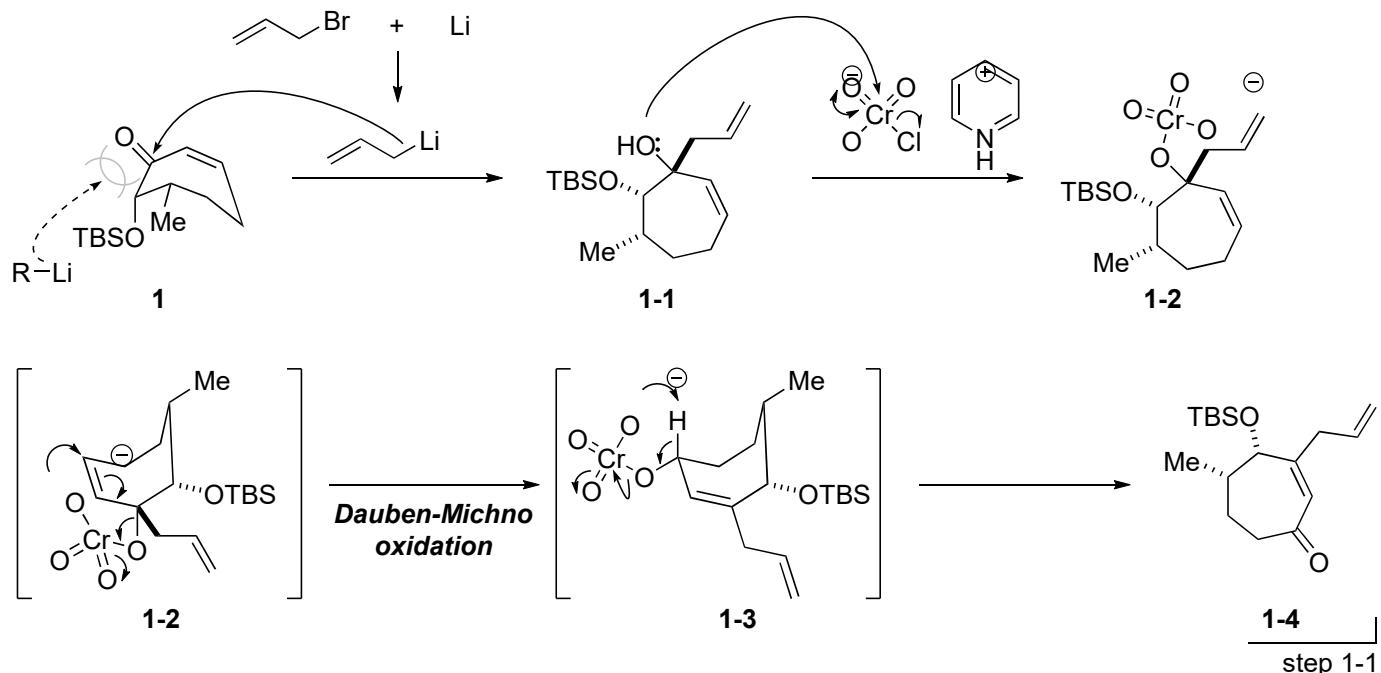


- 1) allyl bromide (1.5), Li (1.3), THF, 0 to 25 °C; PCC (2.0), SiO₂ (5.0), CH₂Cl₂, 0 to 25 °C, 72% (2 steps)
- 2) TMSOTf (1.0), Et₃N (1.5), CH₂Cl₂, -40 °C; then **2** (3.8), *n*-BuLi (3.8), Et₂O, -78 to 25 °C, 70%
- 3) [Rh₂(OAc)₄] (5 mol%), **3** (2.0), benzene, 55 °C, 73%

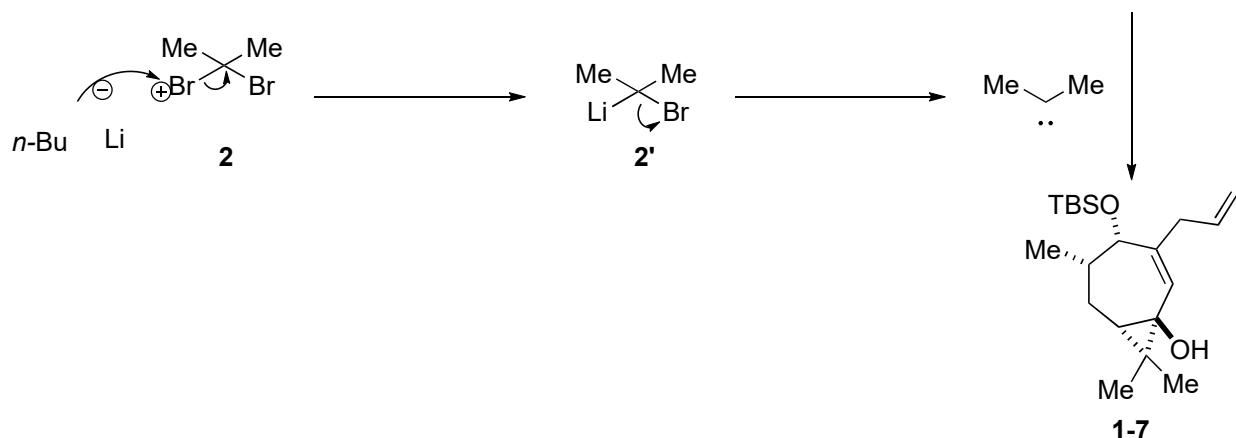
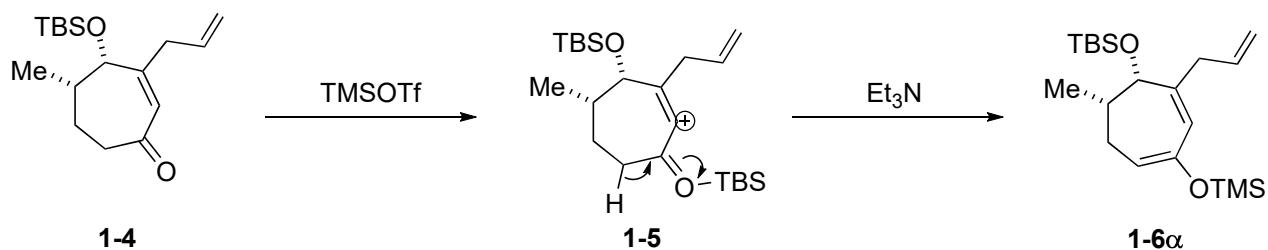


Answer:

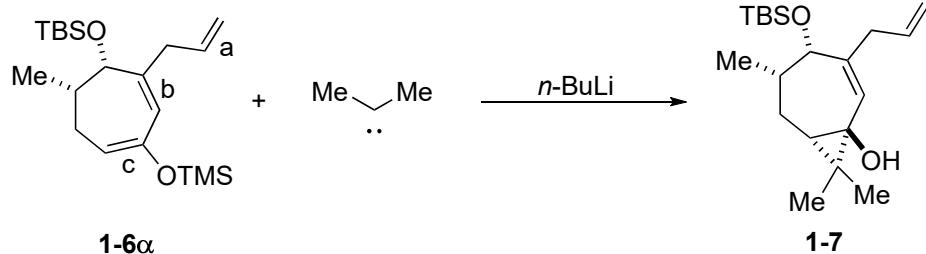
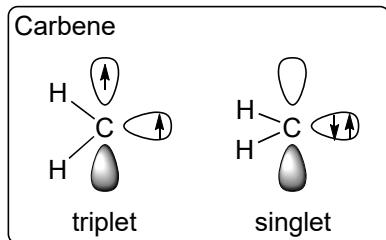
1-1. 1,2-addition of allyllithium and subsequent Dauben-Michno oxidation



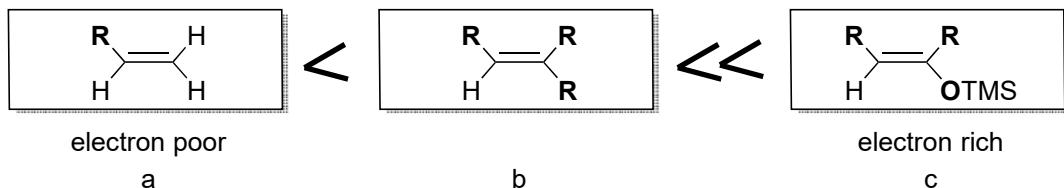
1-2. construction of cyclopropane ring



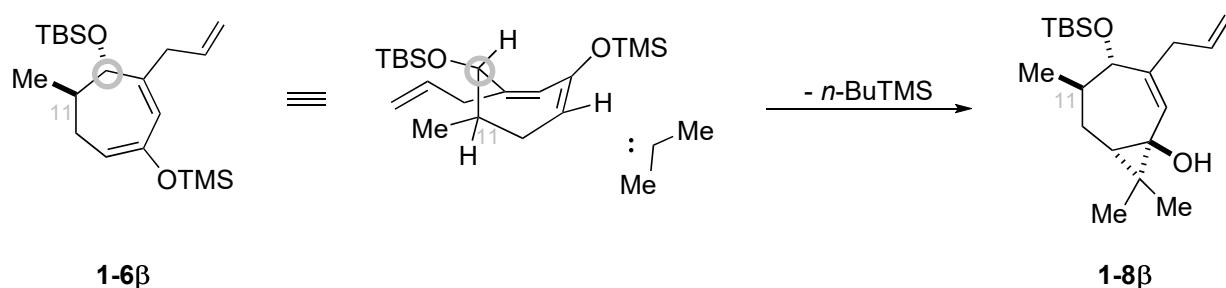
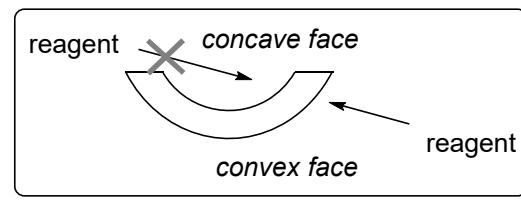
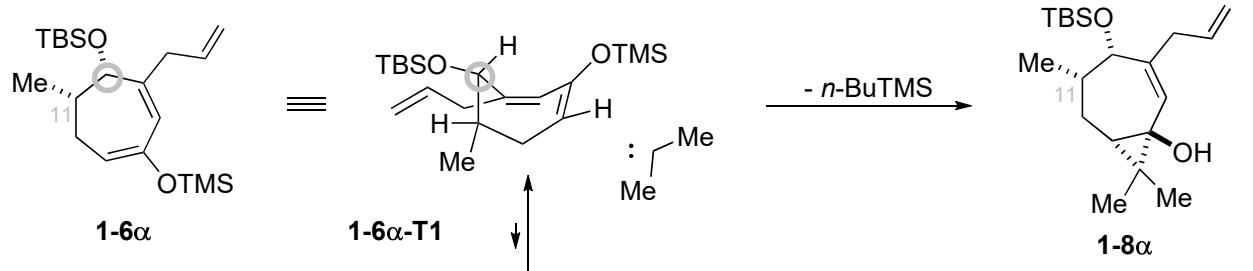
Discussion: regioselectivity and stereoselectivity on addition of dimethylcarbene



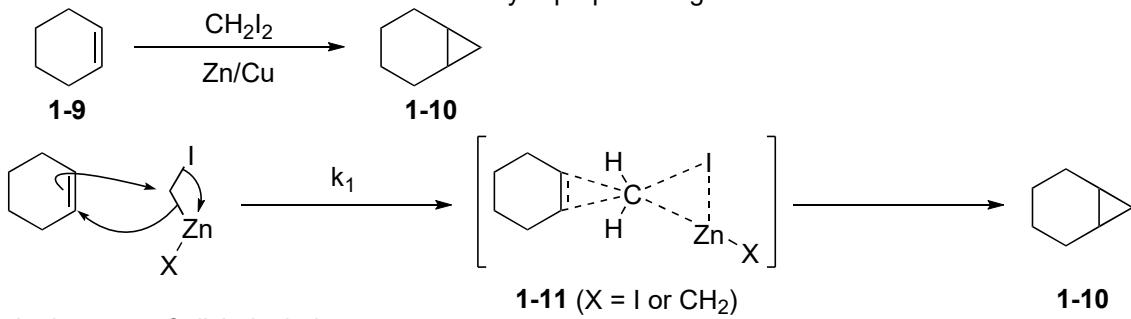
1. regioselectivity



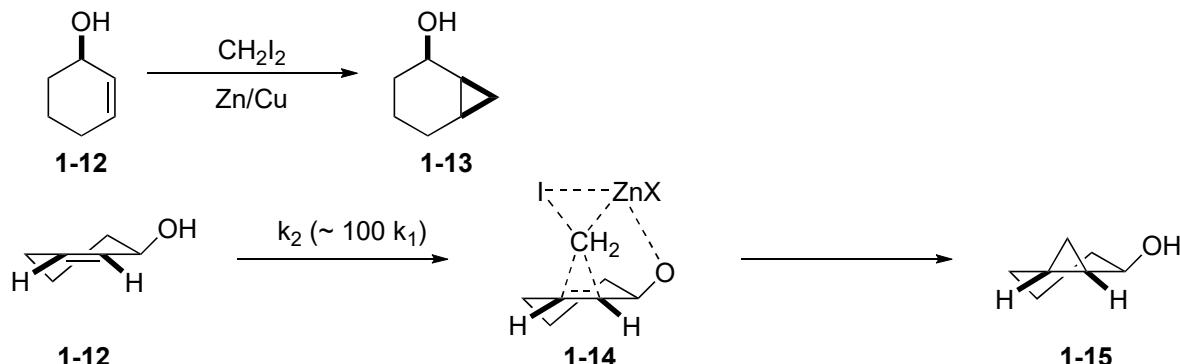
2. stereoselectivity



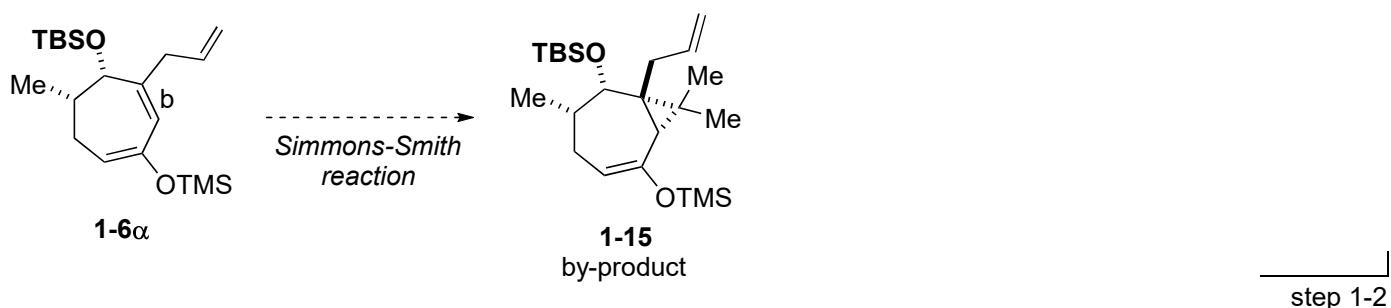
Simmons-Smith reaction: construction of cyclopropane ring



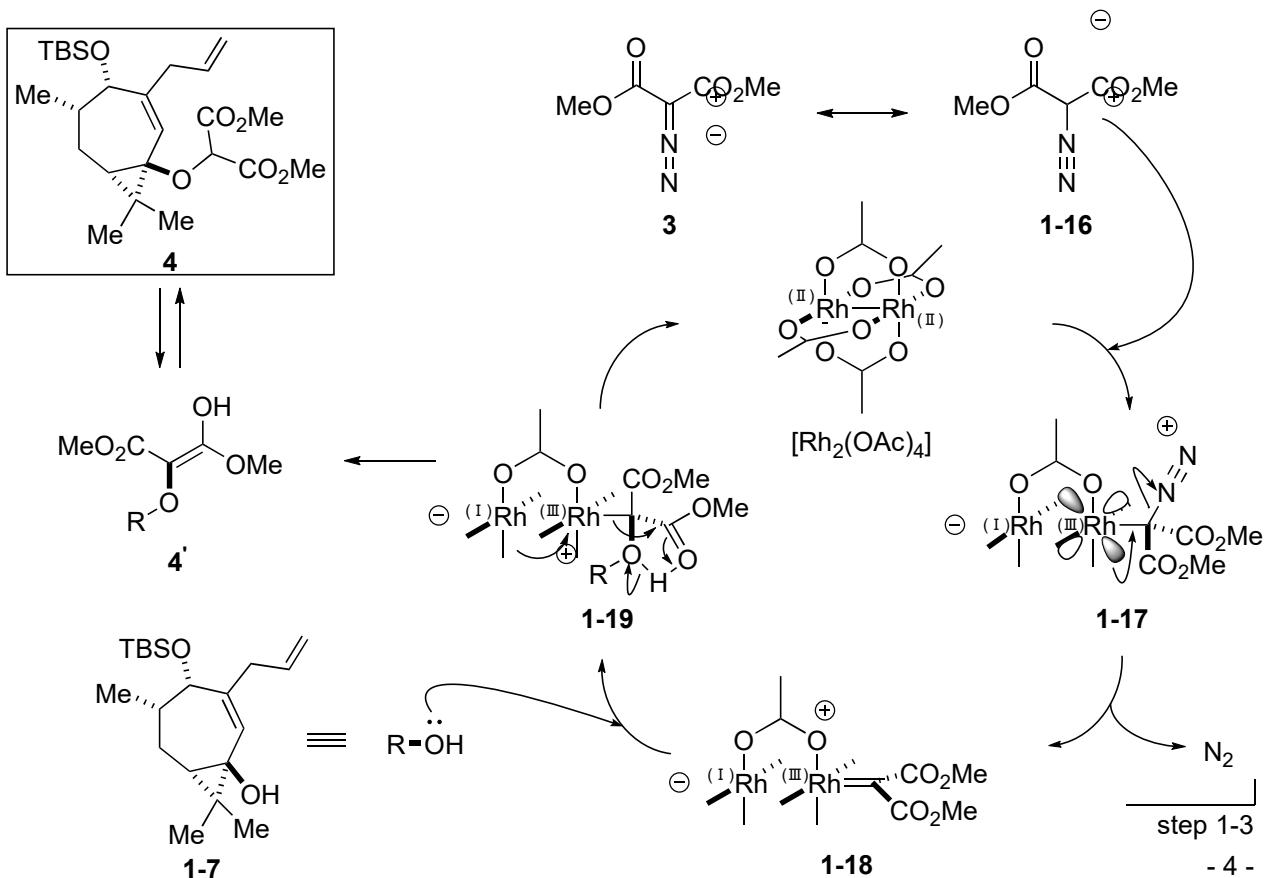
· in the case of allyl alcohol



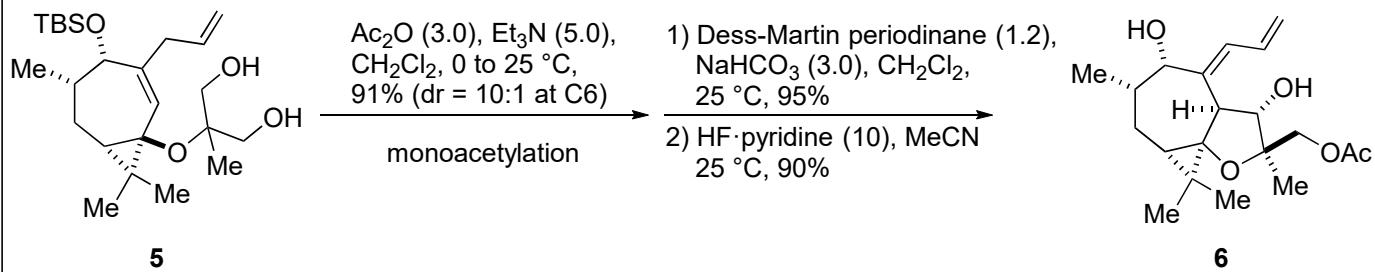
· in the case of this compound **1-6 α**



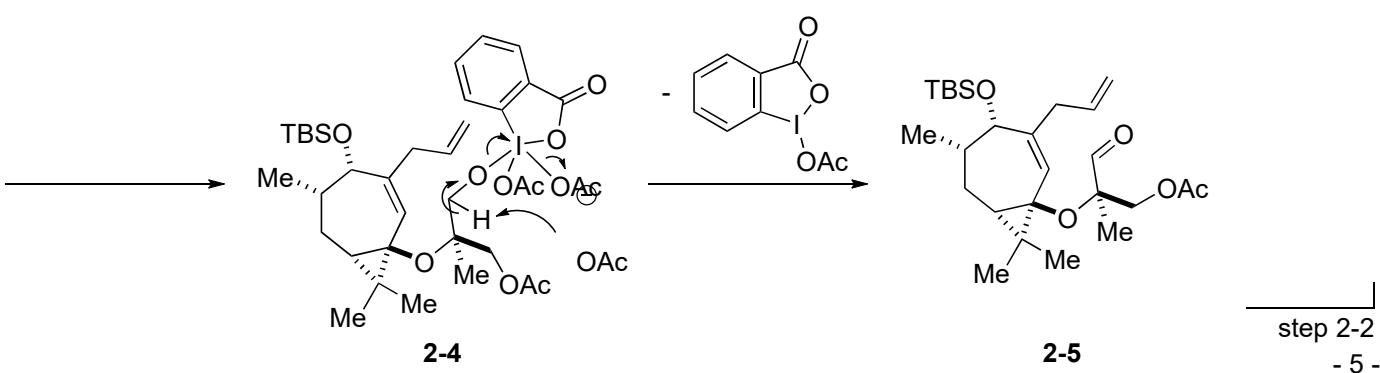
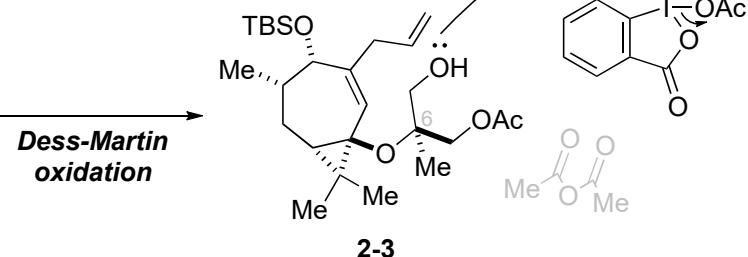
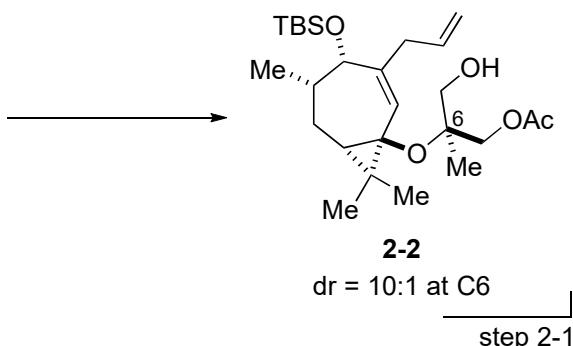
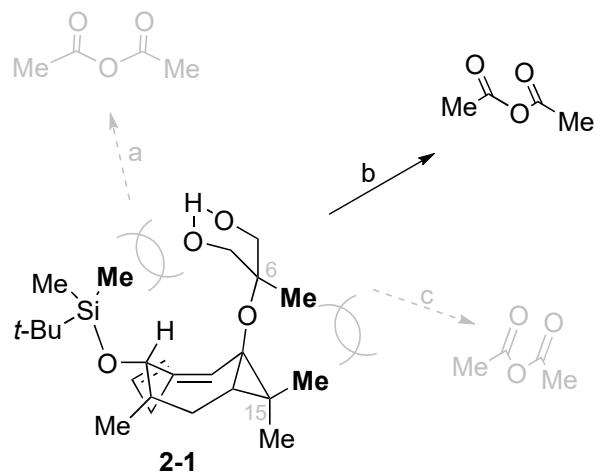
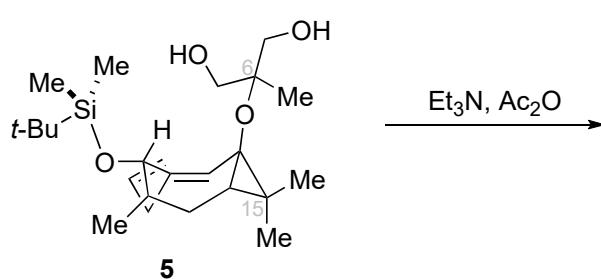
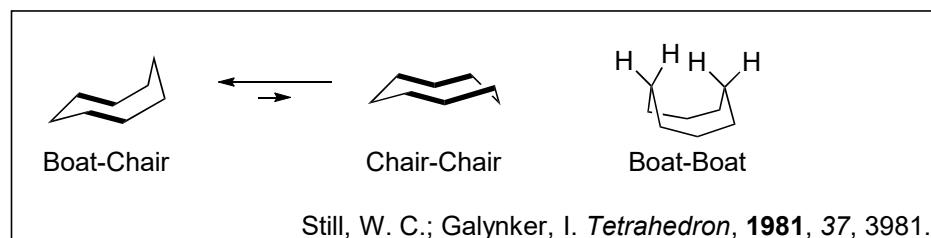
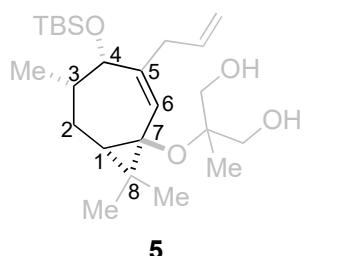
1-3. carbenoid OH insertion catalyzed by $[\text{Rh}_2(\text{OAc})_4]$



Problem 2

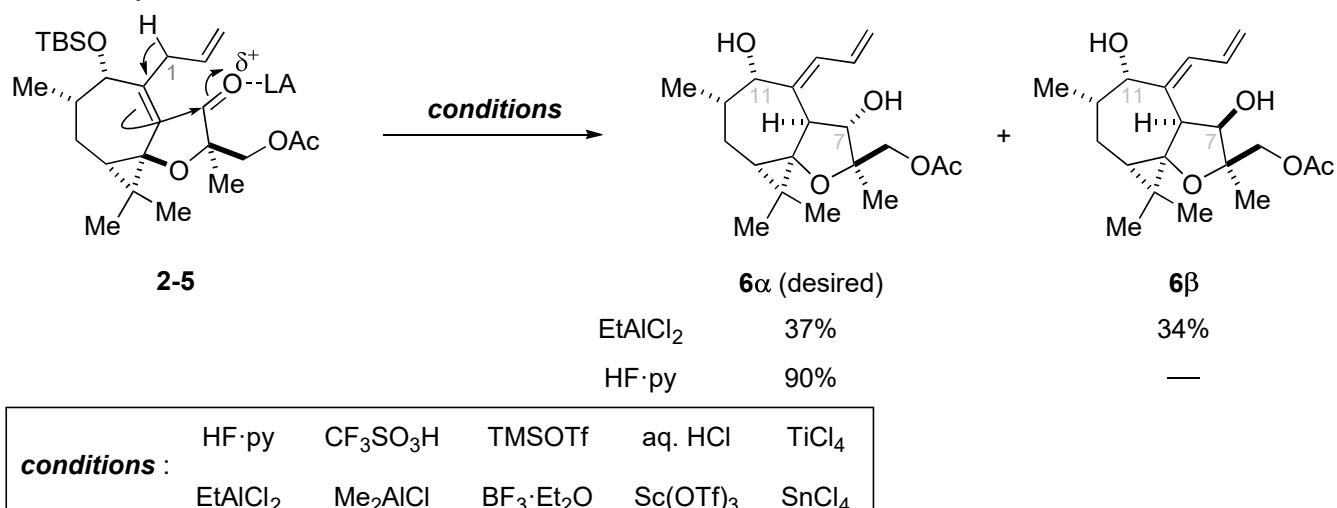


2-1. monoacetylation and Dess-Martin oxidation

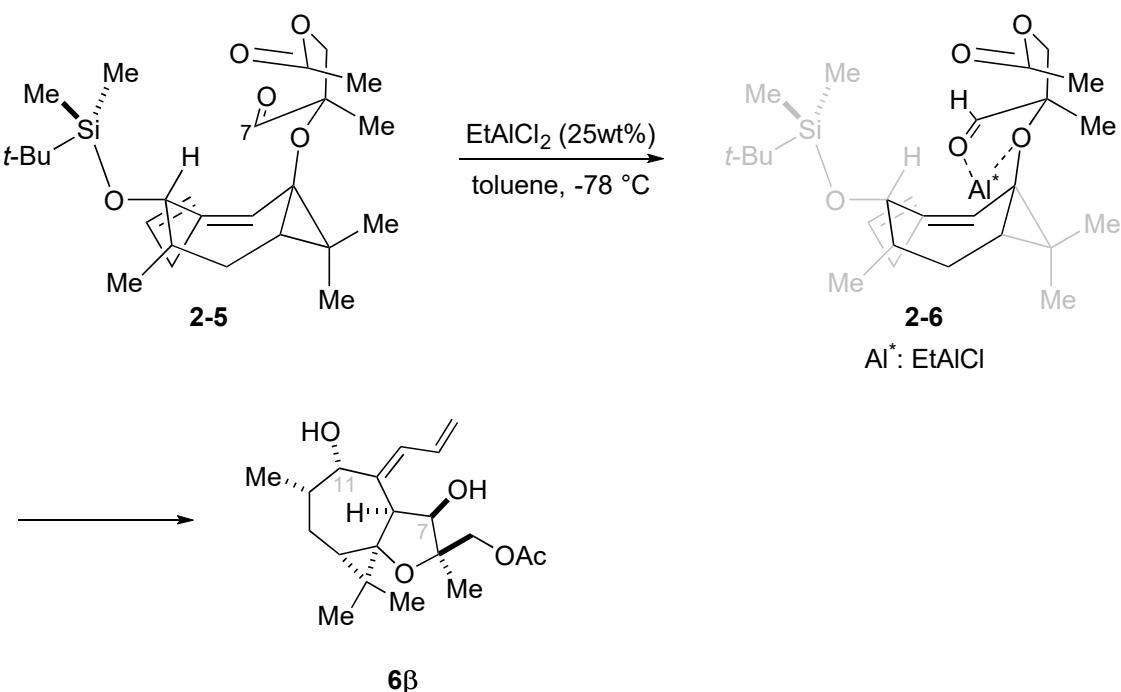


step 2-2
- 5 -

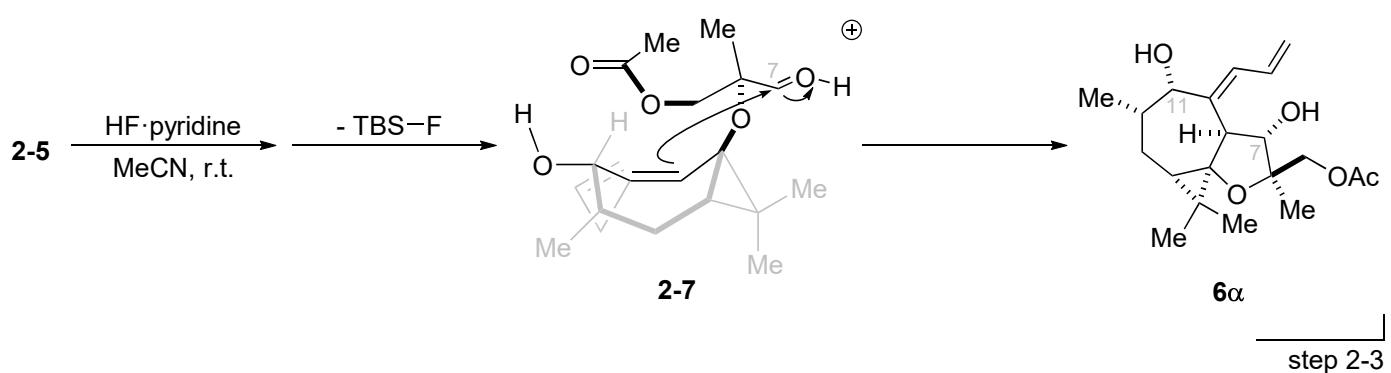
2-2. carbonyl-ene reaction



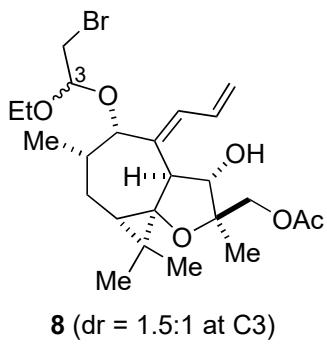
Discussion: effect of acids on carbonyl-ene reaction
production of 6β : electron density analysis



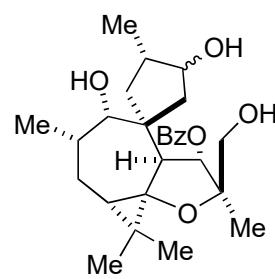
production of 6α : desilylation and hydrogen bond interaction



Problem 3

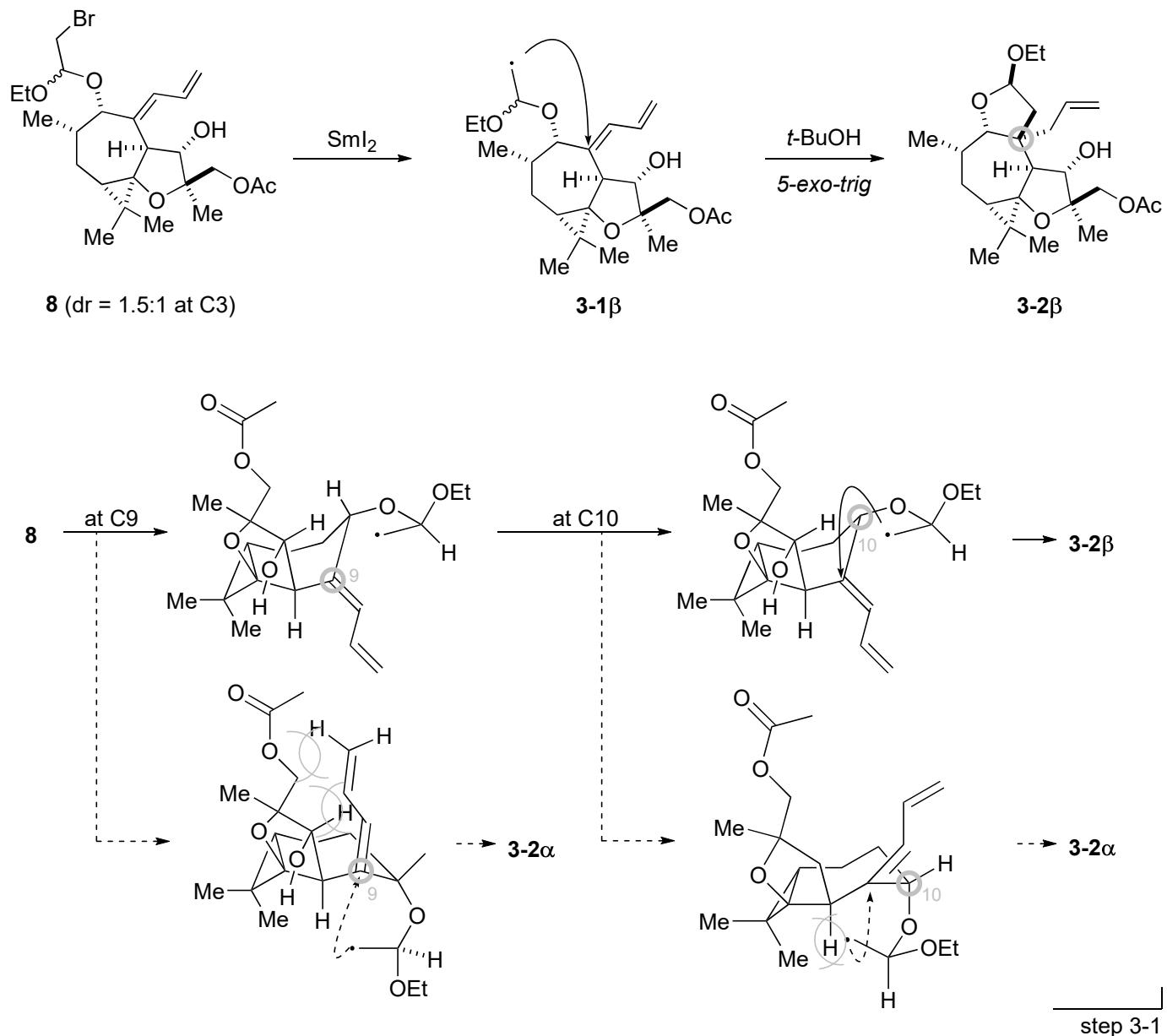


- 1) SmI_2 (2.0), HMPA (8.0), $t\text{-BuOH}$ (1.2), THF, 25 °C, 50%
- 2) Bz_2O (1.2), Et_3N (2.0), DMAP (0.2), CH_2Cl_2 , 25 °C, 95%
- 3) $p\text{-TsOH}$ (1.0), acetone/ H_2O (4:1), 60 °C, 86%, (dr = 4:1 at C3)
- 4) SmI_2 (2.0), HMPA (4.0), THF, 50 °C, 90%, (dr = 5:1 at C3)



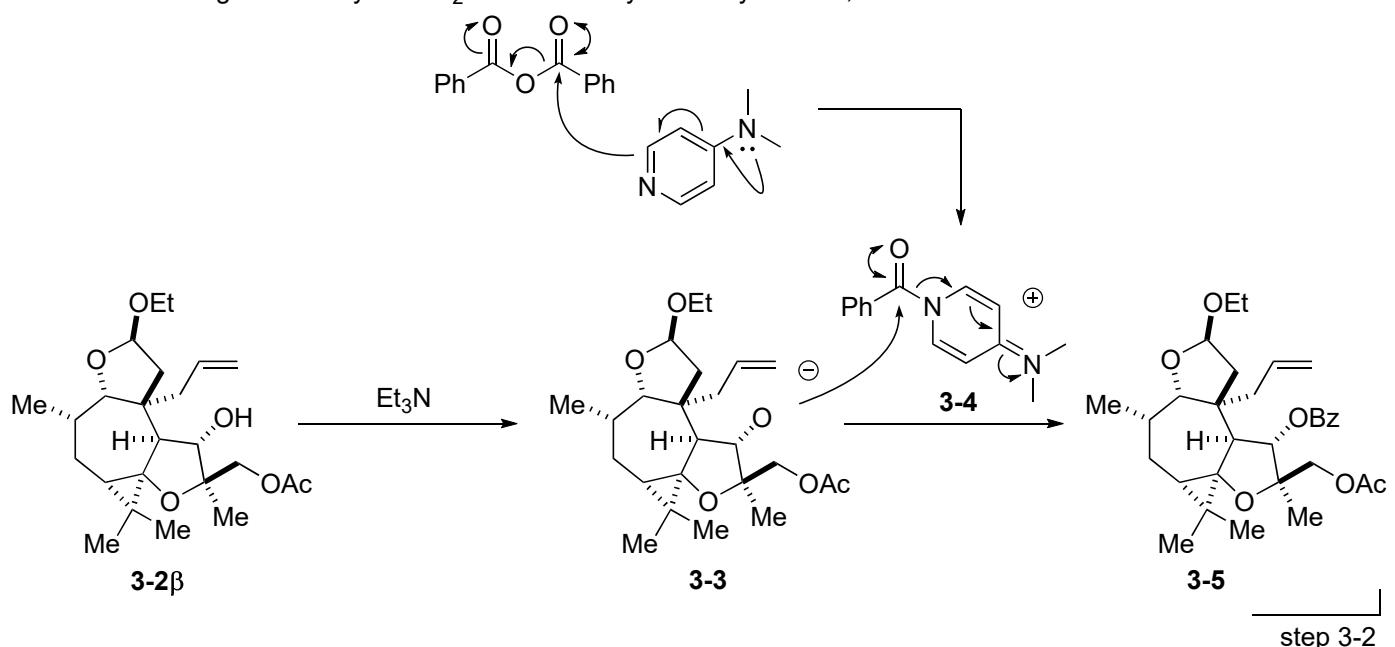
3-1. Ueno-Stork cyclizations

stereoselectivity of this reaction is concerned with C9 and C10 position

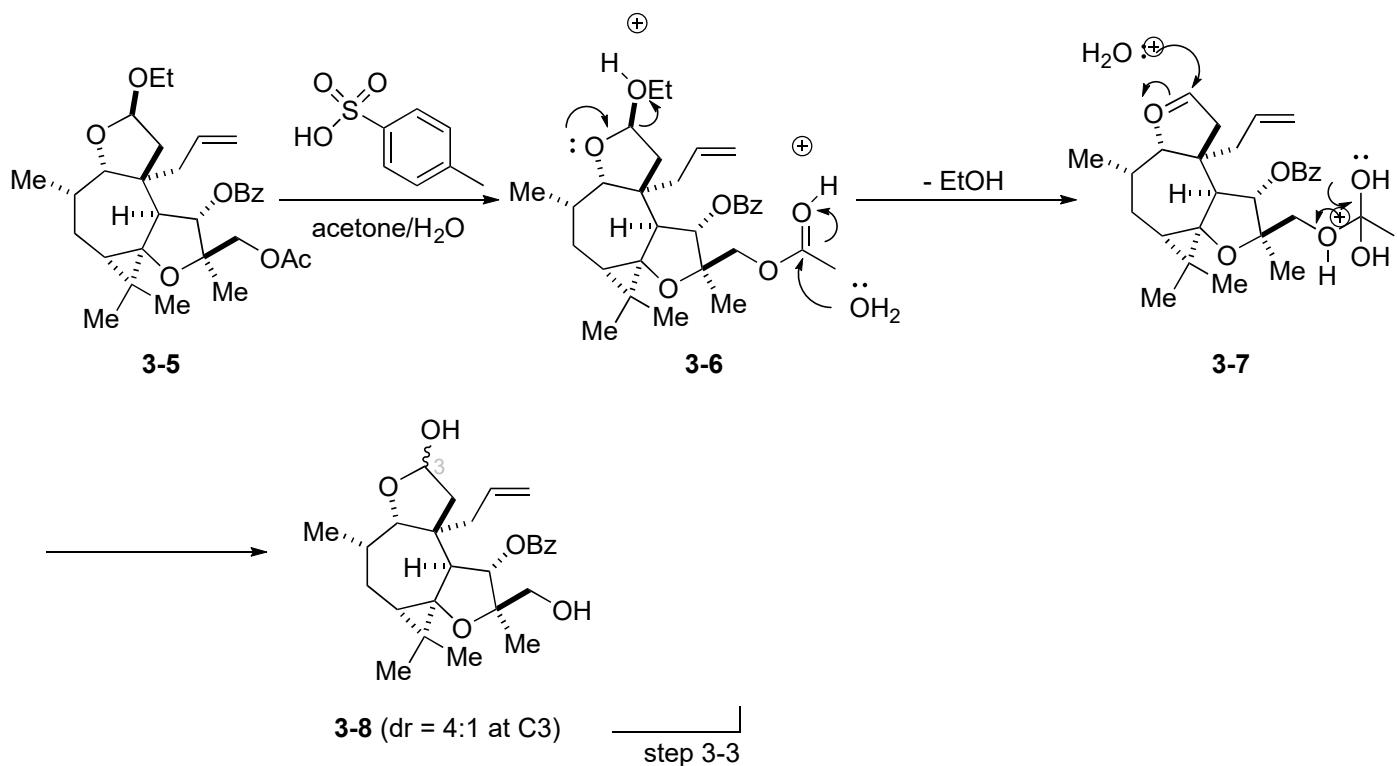


3-2. conversion of secondary alcohol to benzoate

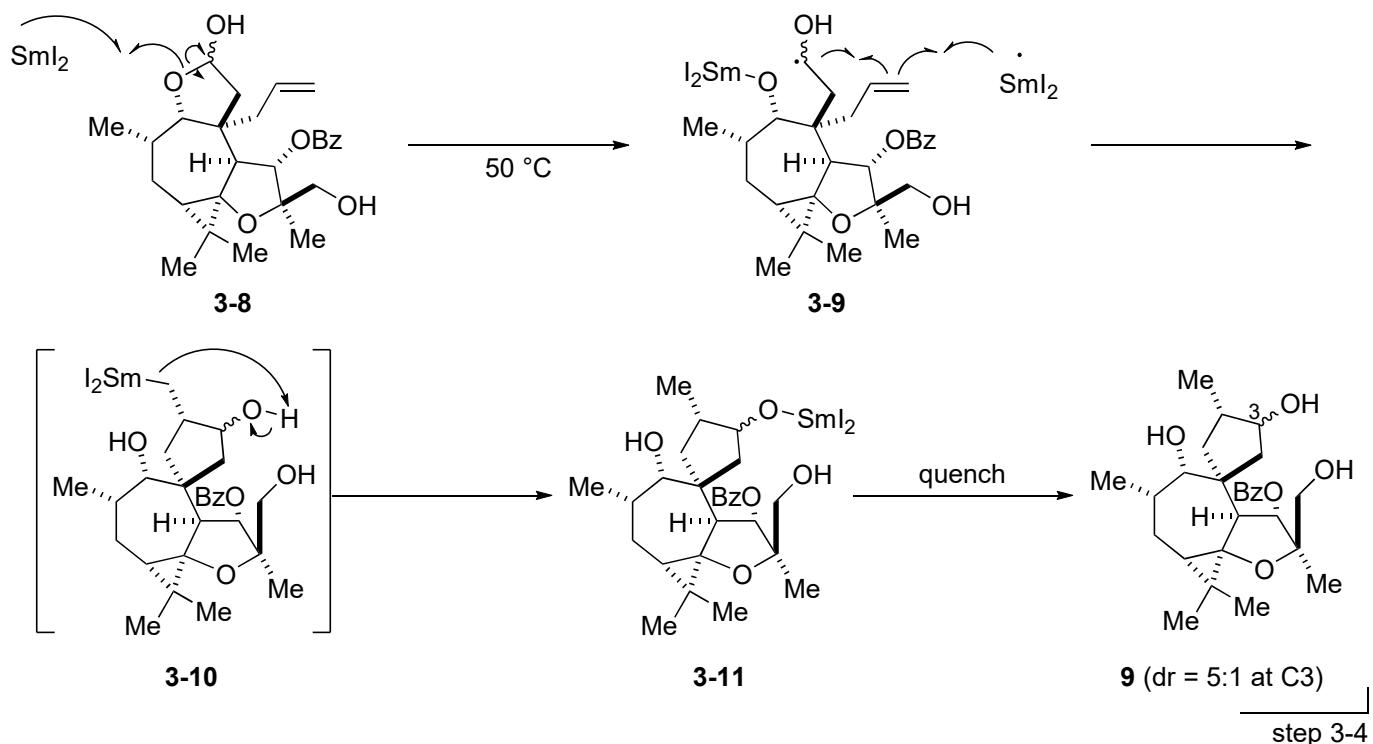
- to determine the relative stereochemistry by X-ray crystallographic analysis
- to control the regioselectivity of SmI_2 -mediated ketyl-olefin cyclization, after this reaction.



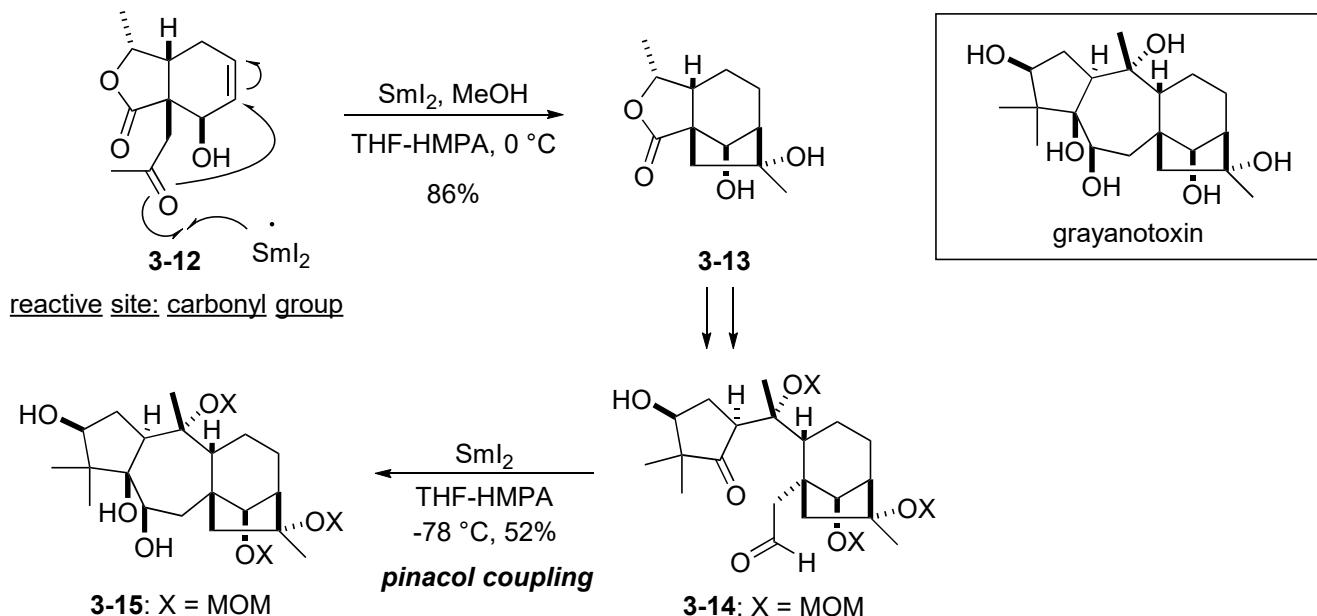
3-3. Hydrolysis of both the acetal and acetate moieties



3-4. synthesis of [5,7] spirobicycle compound through a SmI₂-mediated ketyl-olefine cyclization

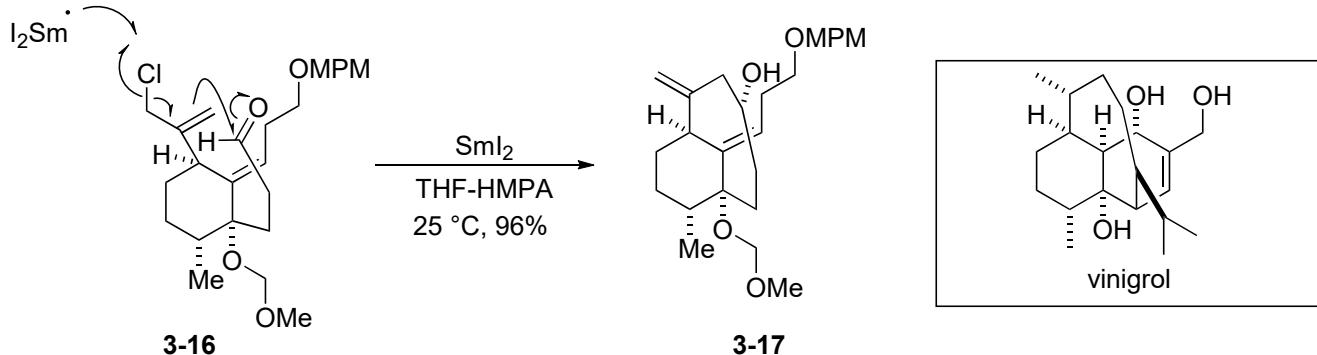


3-5: radical reaction using SmI_2
e.g.1: total synthesis of grayanotoxin



Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.

e.g.2: total synthesis of vinigrol



Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 14369.

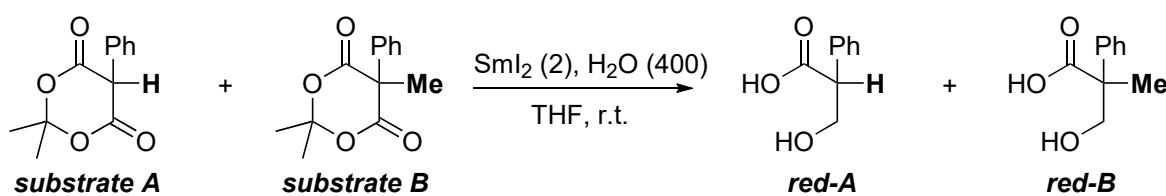
SmI_2 reacts halide, aldehyde, ketone, C-O single bond and etc....

selectivity of reactive site 1: bond dissociation energy

bond	ΔH_f^{298} (kJ/mol)
C–Br	280
C–O	749
C=O	1077

Benson, S. W. *J. Chem. Educ.*, **1965**, *42*, 502
Kerr, J. A. *Chem. Rev.*, **1966**, *66*, 465.

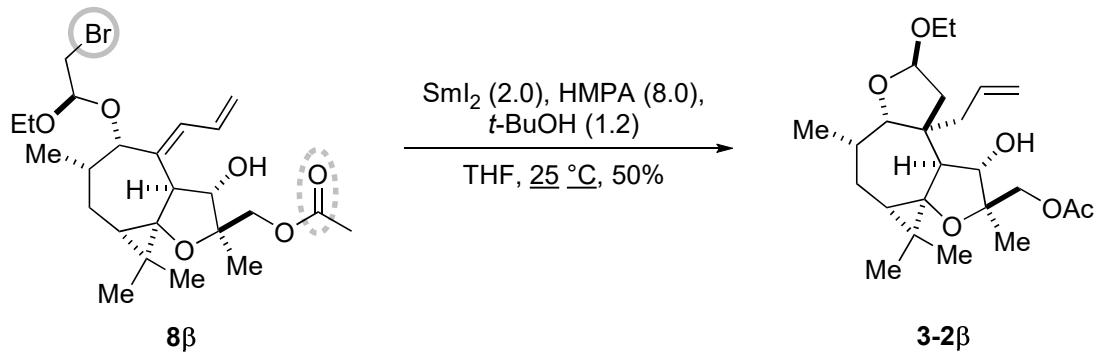
selectivity of reactive site 2: steric hindrance



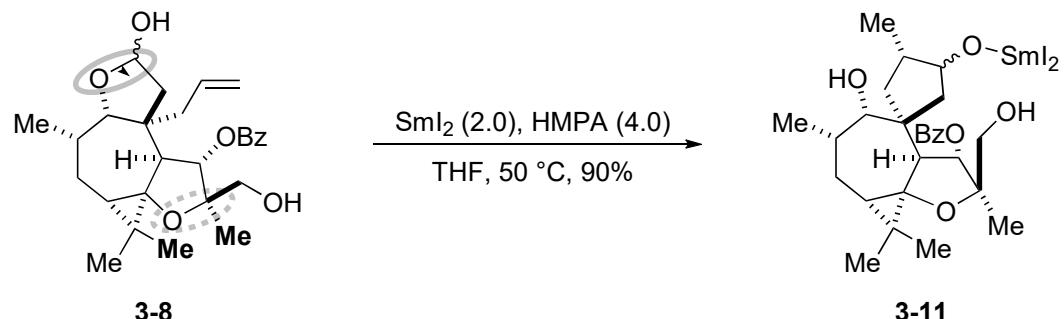
$$k_A/k_B > 20$$

Szostak, M.; Lyons, S. E.; Spain, M.; Procter, D. *J. Chem. Commun.*, **2014**, *50*, 8391.
- 10 -

first step of radical reaction: bond dissociation energy

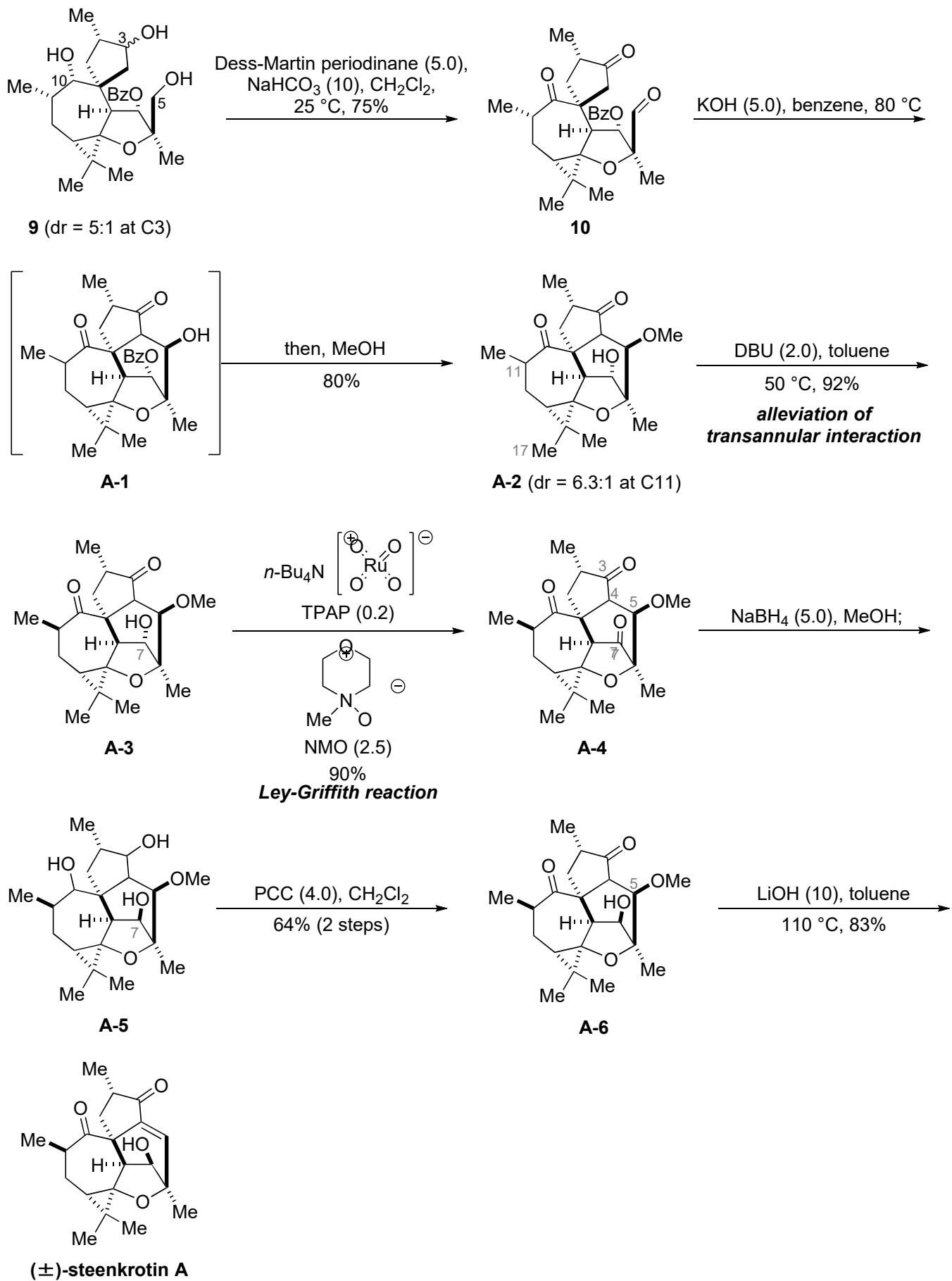


second step of radical reaction: steric hindrance (+ anomeric effect)



Appendix

5. total synthesis of (\pm)-steenkrotin A



Three dimension structure: the most stable structures calculated by Macromodel (MMFF)

