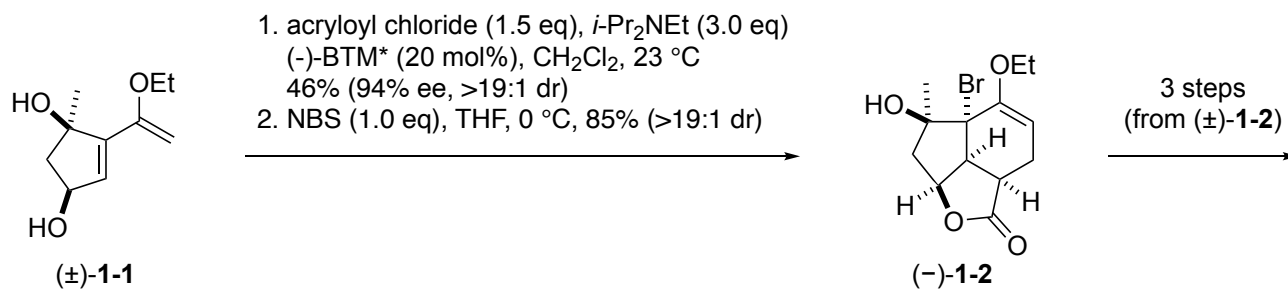


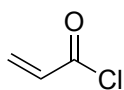
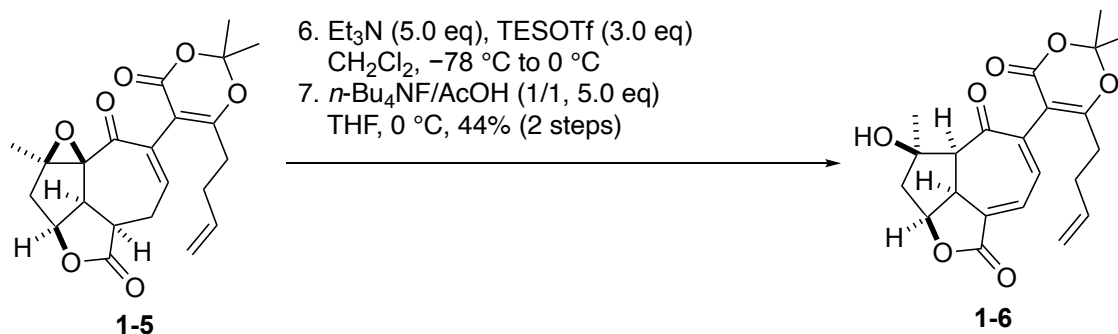
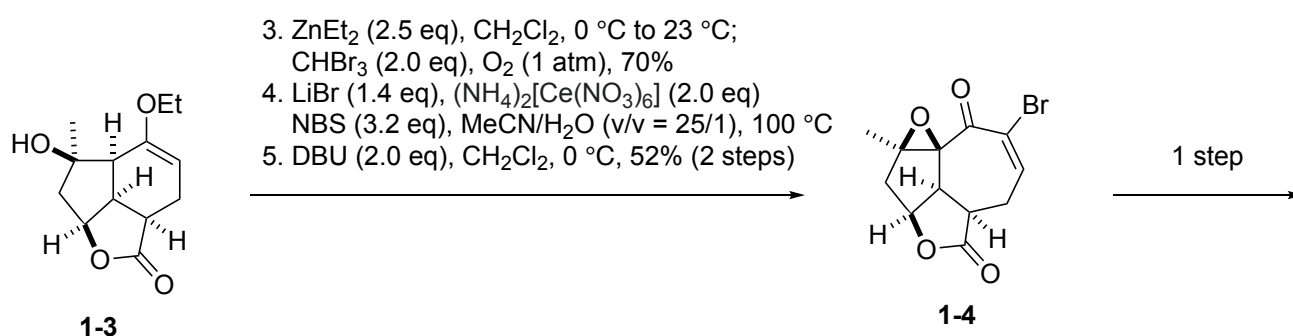
## Problem Session (2)

2023.12.2 Shintaro Fukaya

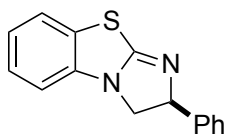
Please provide the mechanisms for the following reactions.



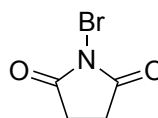
\* For scale up, (±)-BTM (50 mol%) was used to synthesize (±)-1-2.  
 All the following reactions were performed with racemic compounds.



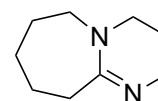
acryloyl chloride



(-)-BTM



NBS

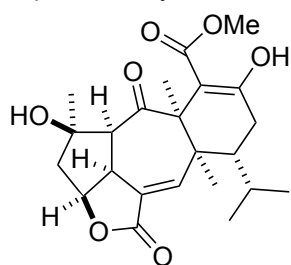


DBU

## Problem Session (2) -Answer-

2023.12.2 Shintaro Fukaya

topic: Total synthesis of Rameswaralide



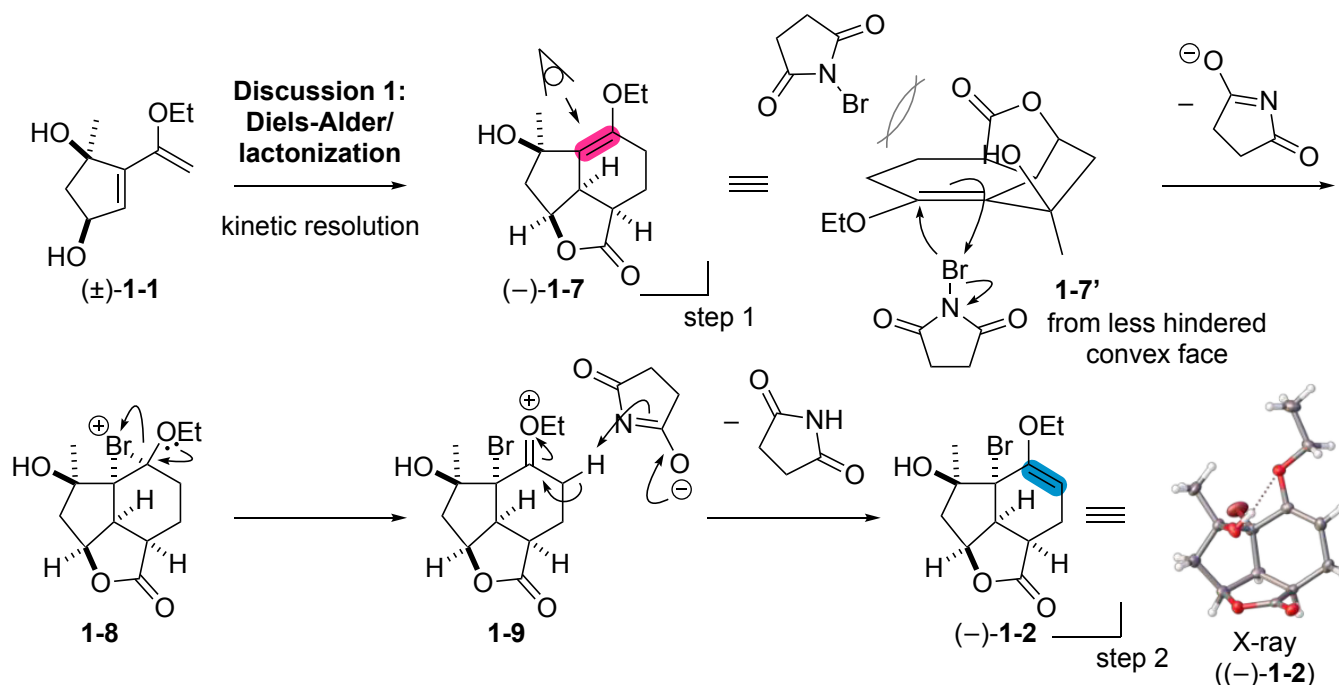
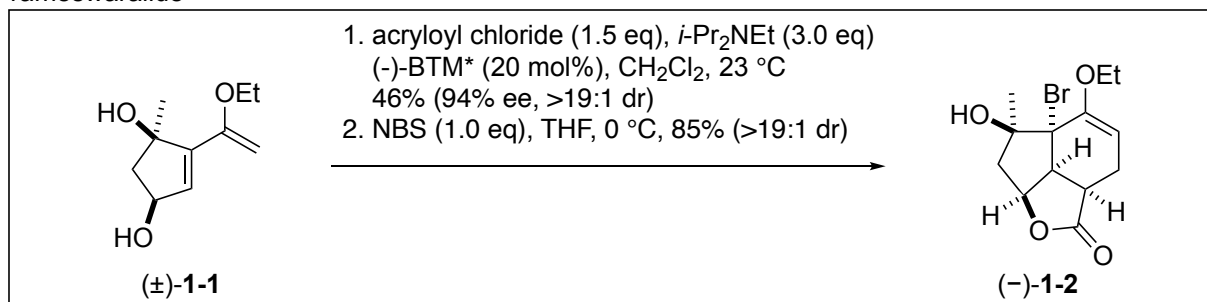
rameswaralide

isolation: from soft coral *Sinularia dissecta* (1998<sup>1</sup>), structure determination: 2016<sup>2</sup>)

bioactivity: moderate cytotoxicity, possible anti-inflammatory activity<sup>2</sup>)

structure: [5,5,7,6] all cis-fused ring system, 7 stereocenters

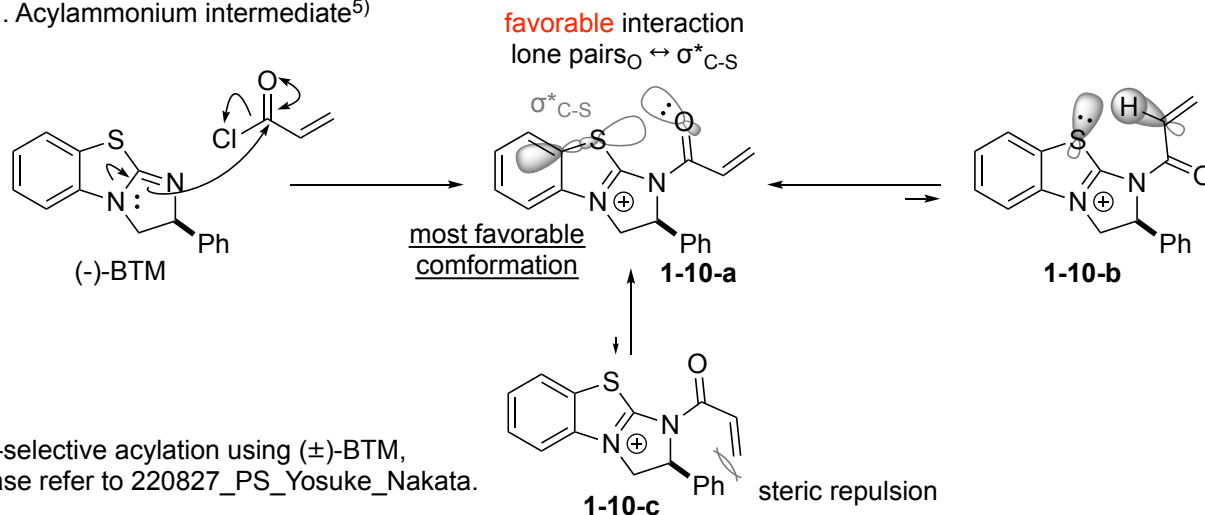
synthesis: Romo's group (2019: synthetic study<sup>3</sup>), 2022: total synthesis<sup>4</sup>), **problem**)



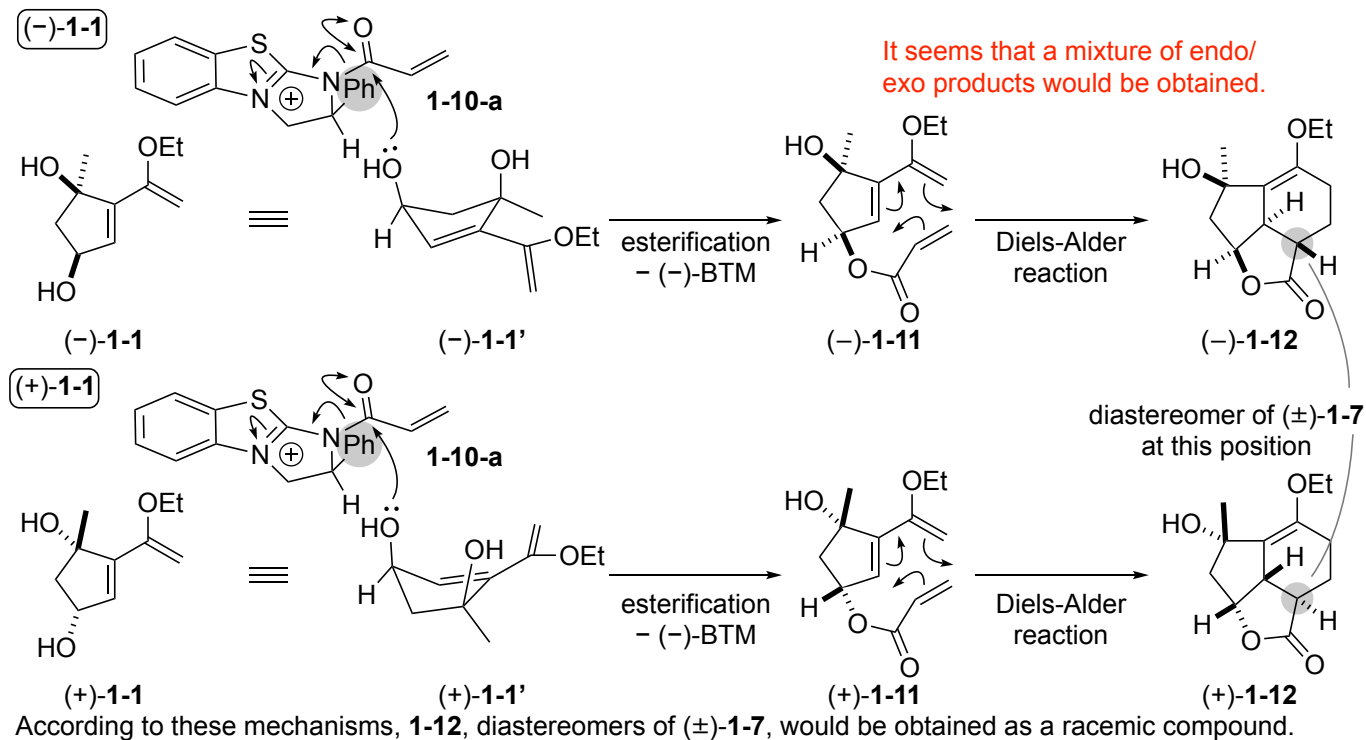
1-7 ■: tetra-substituted olefin → electron richer  
 1-2 ■: tri-substituted olefin → electron poorer ⇒ NBS (1.0 eq) reacted with 1-7 prior to 1-2, and additional α-bromination of 1-2 didn't occur.

### Discussion 1: Diels-alder/lactonization

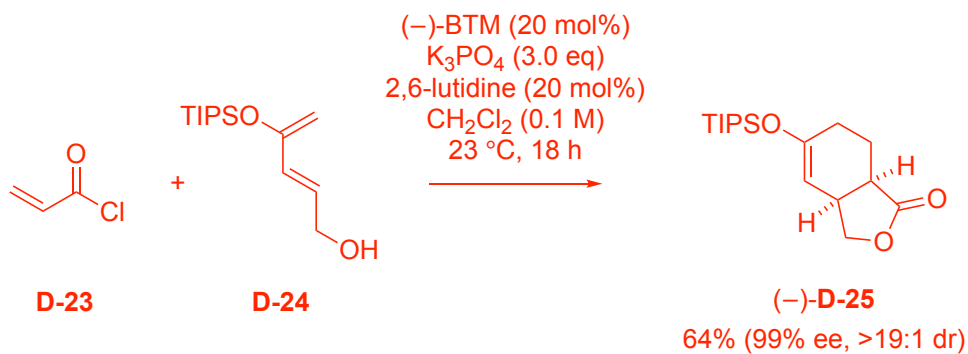
1-1. Acylammonium intermediate<sup>5</sup>)



1-2. Possible reaction mechanisms: esterification → Diels-Alder reaction

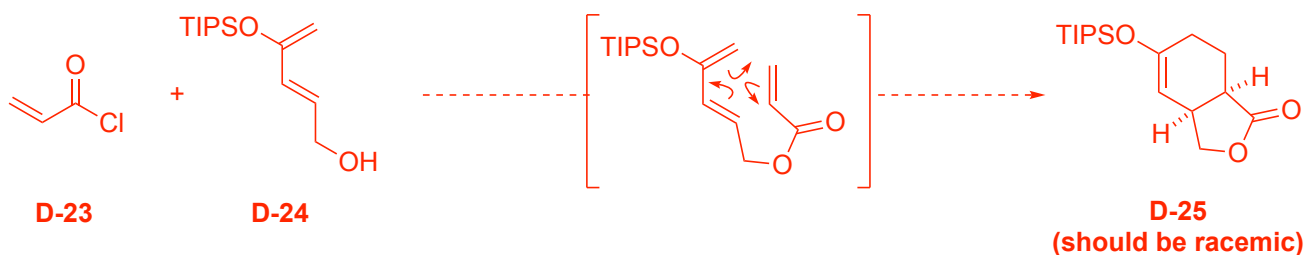


5)



**D-23** and **D-24** don't have a stereocenter, so this enantioselectivity should derive from (-)-BTM.

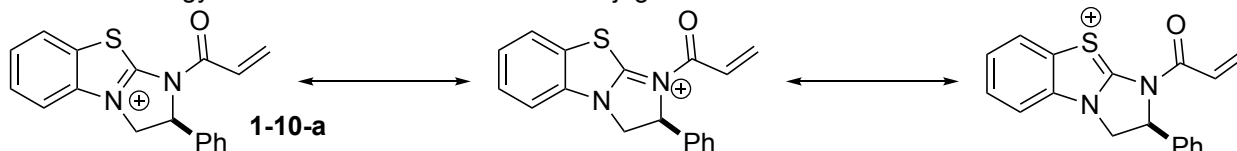
• If esterification proceeds in the first step, **D-25** would be obtained as a racemic compound.



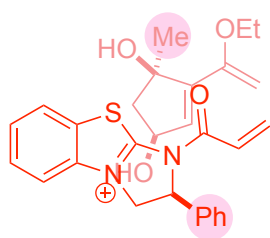
⇒ The reaction mechanism is illustrated by Diels-Alder reaction → lactonization.

**D-25** is generated through Diels-Alder reaction followed by lactonization from **D-23** and **primary alcohol D-24**. In the case of **1-1**, which has secondary and tertiary alcohols (less reactive than primary alcohol), the same reaction mechanisms should be proper.

- Reactivities of dienophiles



**Suggestion by Prof. Inoue.**

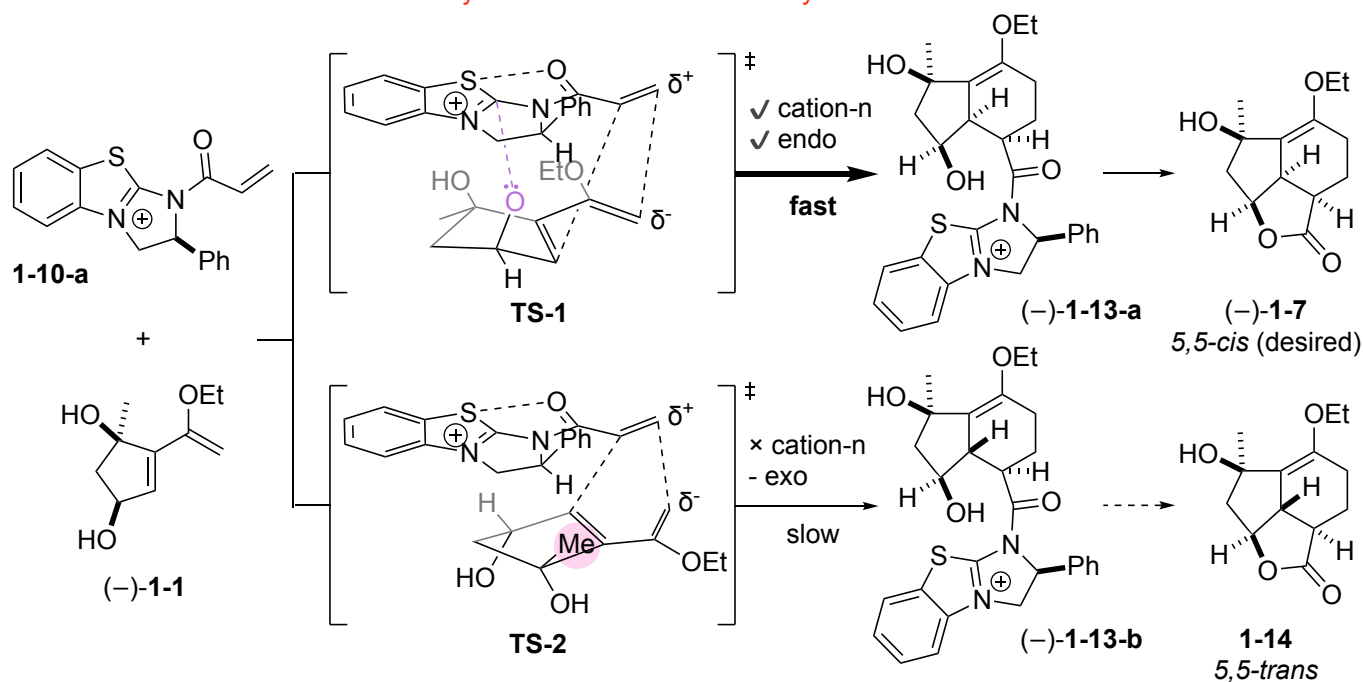


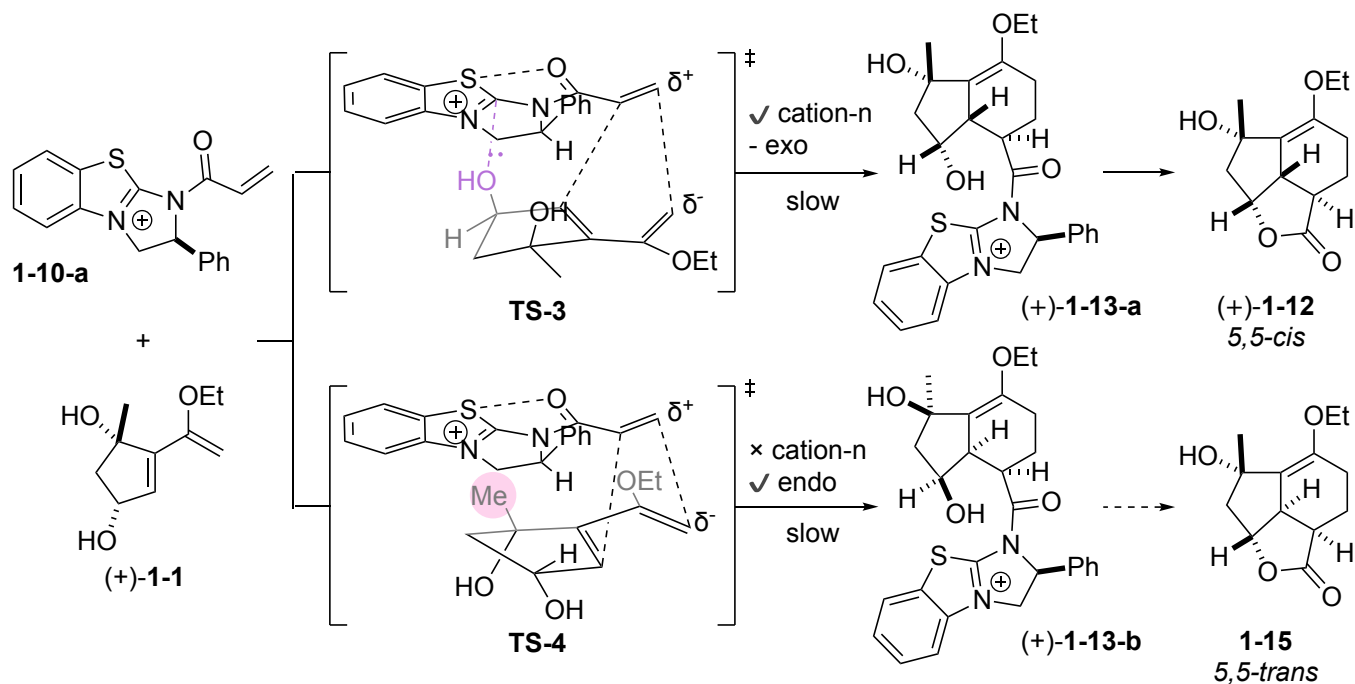
These compounds approach each other to avoid steric repulsion with highlighted Me and Ph groups, giving the desired (–)-**1-13-a**.



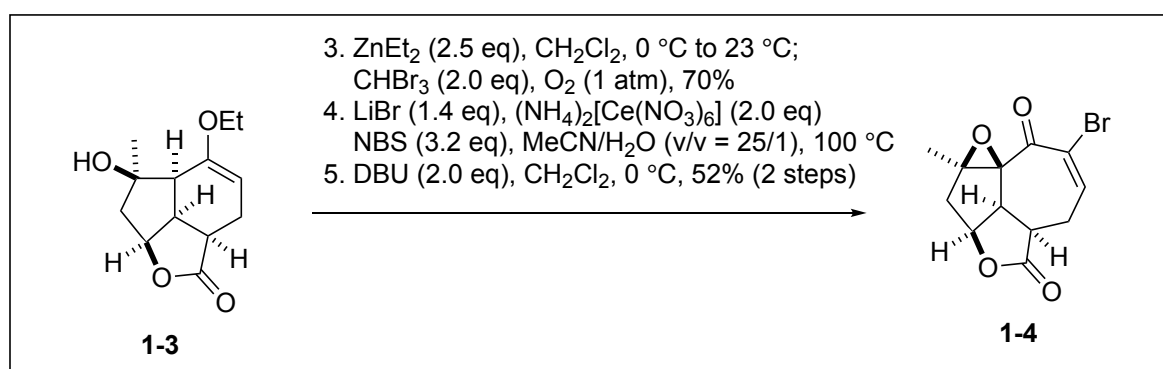
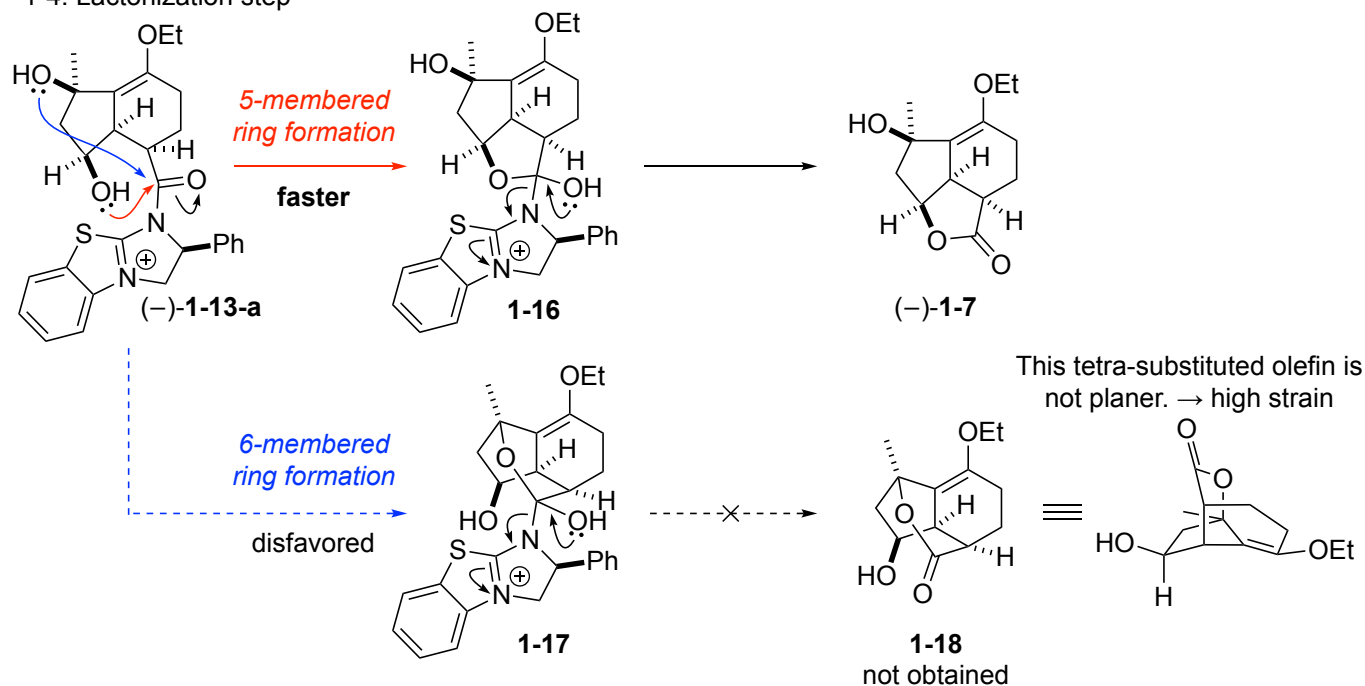
cation- $\pi$  interaction  $\rightarrow$  stabilize the transition state

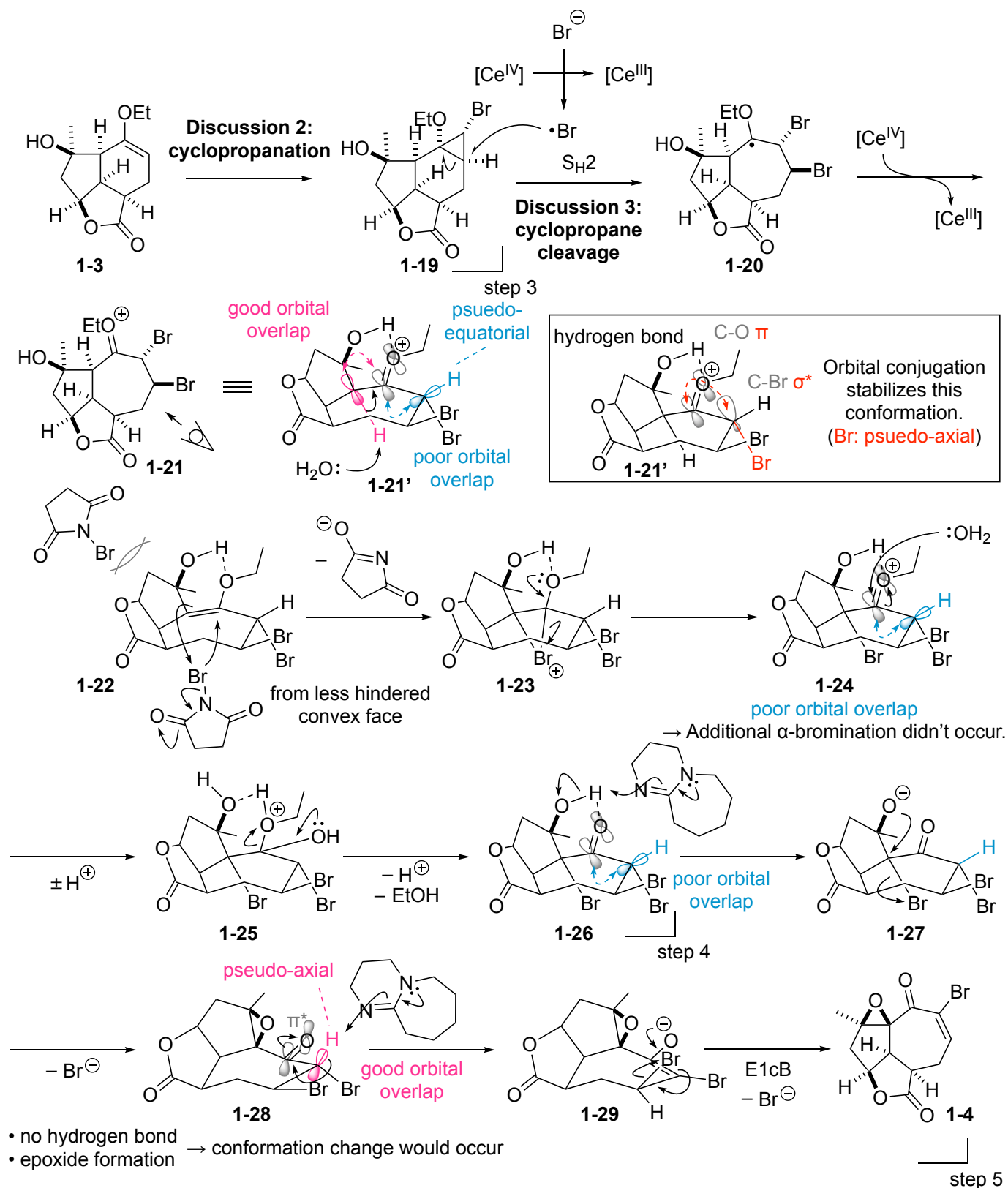
Cation-n interaction may work to reduce the reactivity of **1-10-a** and slow down the reaction.



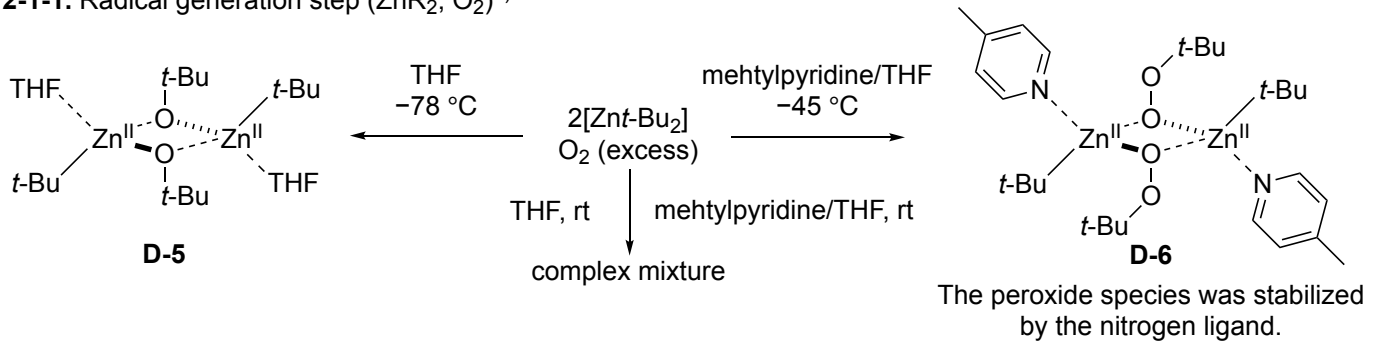


#### 1-4. Lactonization step



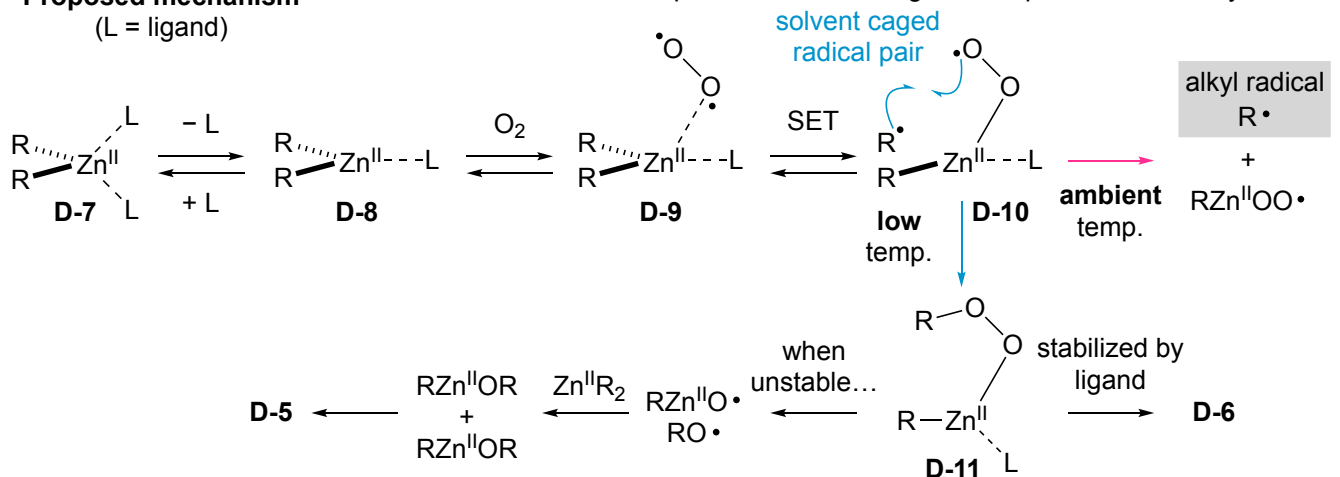


### 2-1-1. Radical generation step ( $\text{ZnR}_2, \text{O}_2$ )<sup>7)</sup>



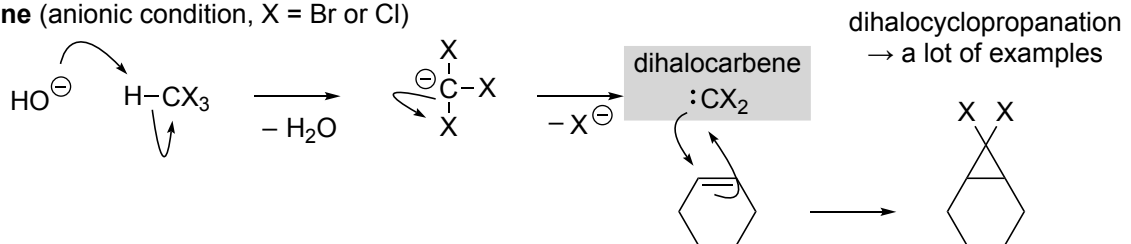
#### Proposed mechanism (L = ligand)

At ambient temperature, solvent cage decomposes to form alkyl radicals.

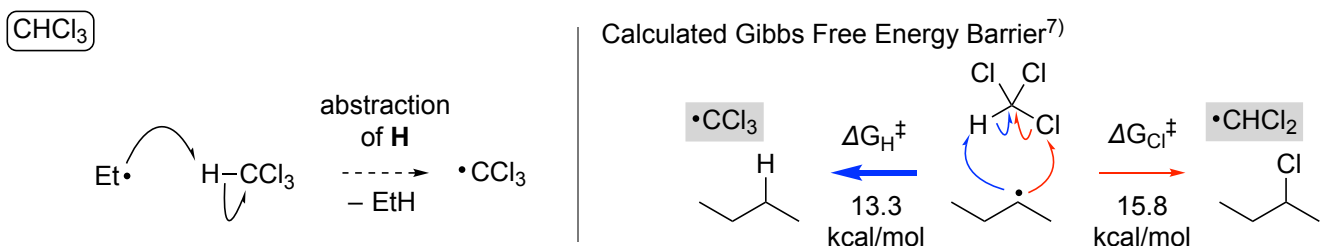
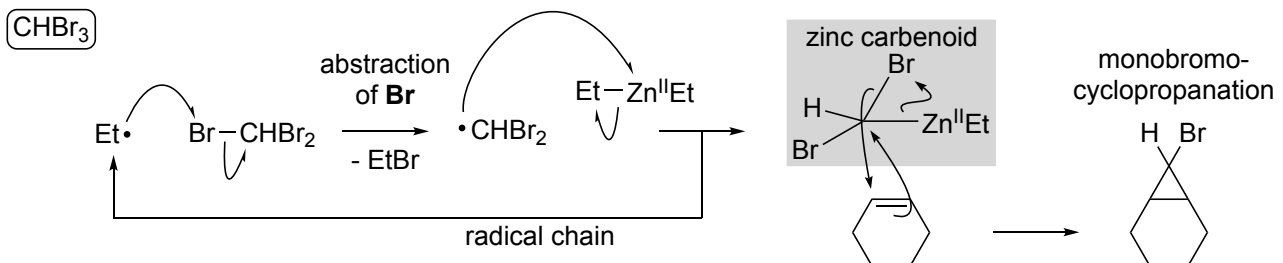
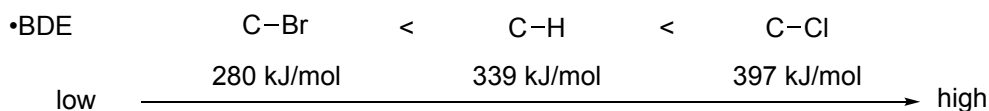


### 2-1-2. Reactivity of $\text{CHBr}_3$ (compared to $\text{CHCl}_3$ )

**dihalocarbene** (anionic condition, X = Br or Cl)

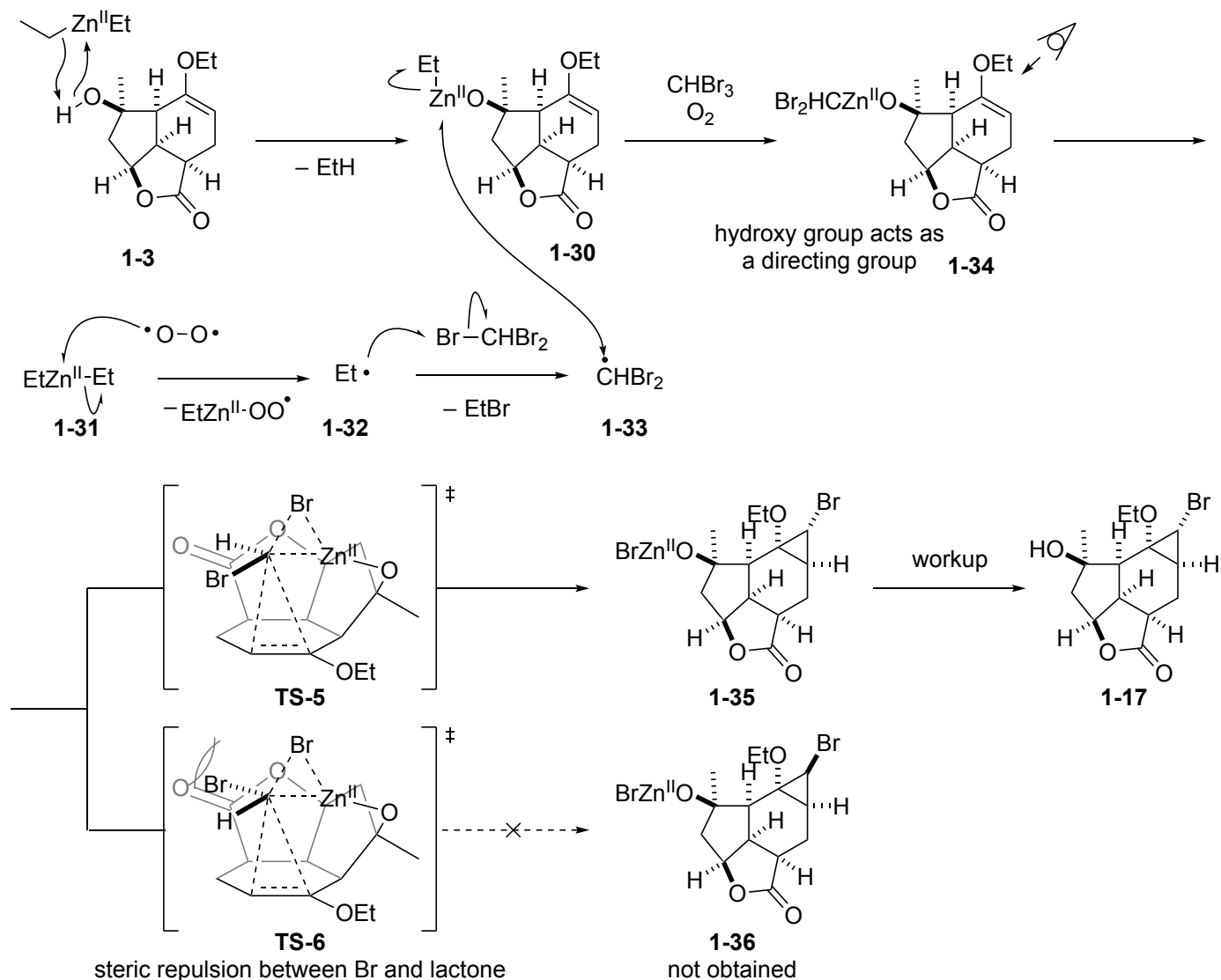


**monohalocarbene** (radical condition)

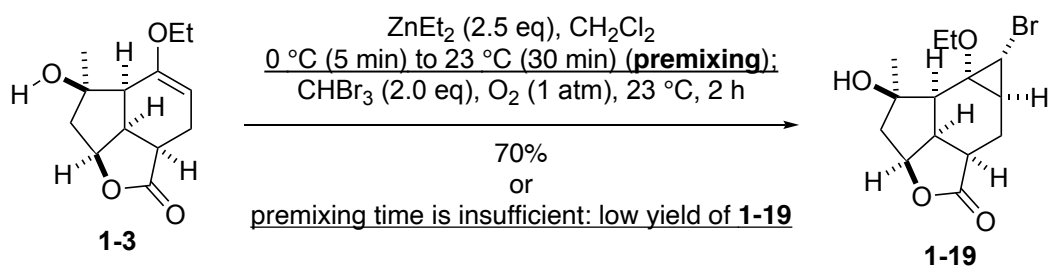


The generation of  $\bullet\text{CCl}_3$  will be favored to  $\bullet\text{CHCl}_2$  using alkyl radical.  
→ It suggests that monochloro-cyclopropanation is difficult.

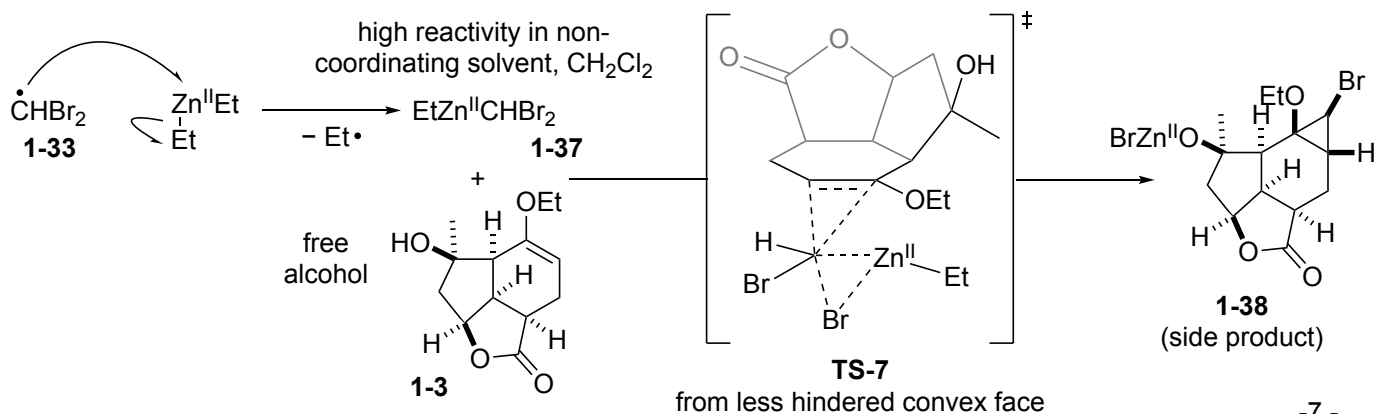
## 2-2. Reaction mechanism



## 2-3. Possible side reaction



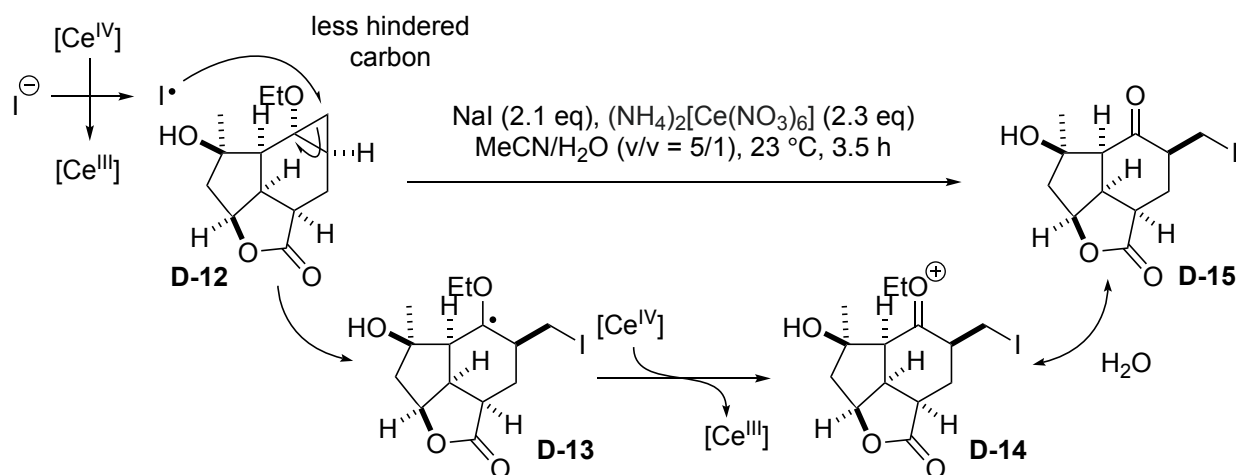
From the above result, zinc alkoxide formation is important for reaction. Free *tert*-alcohol **1-3** would react with the zinc carbenoid as follows.





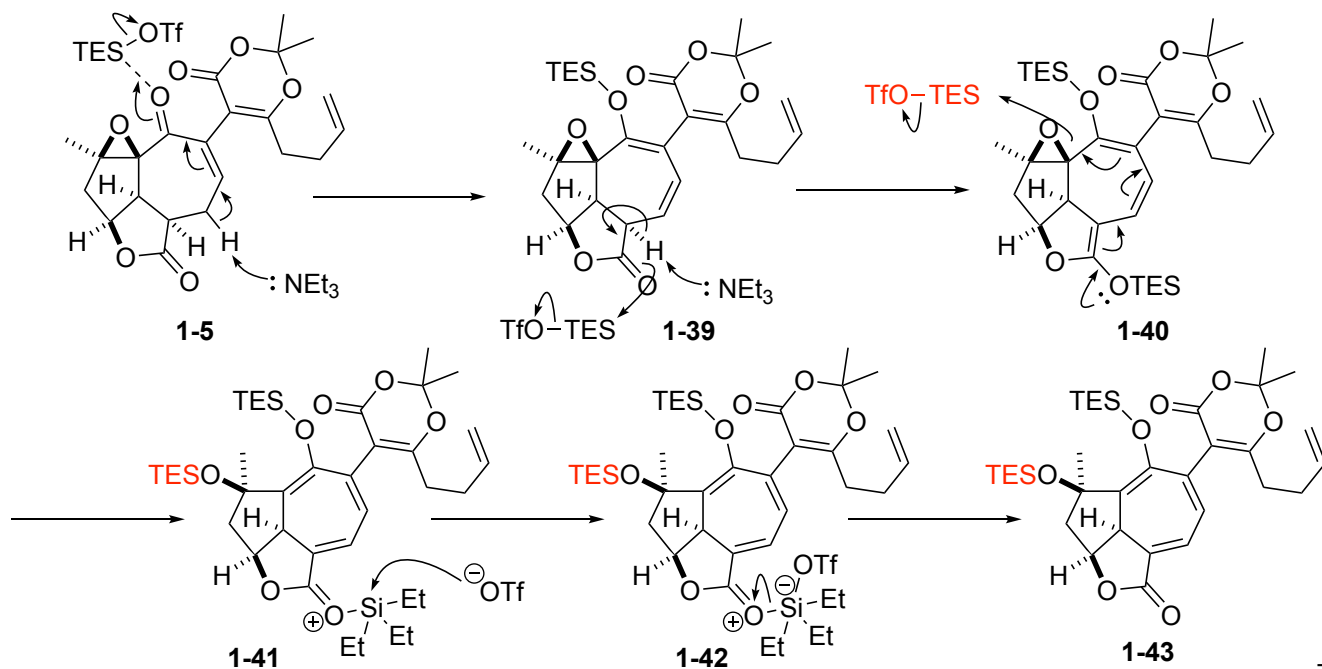
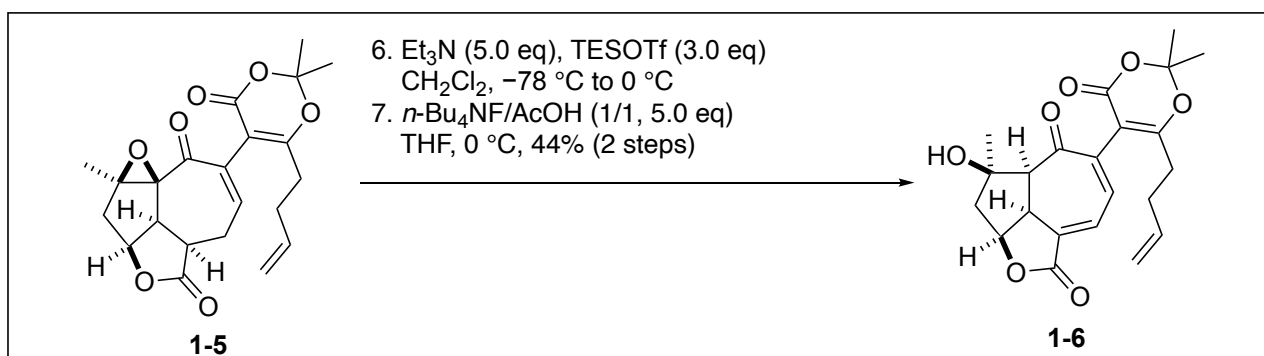
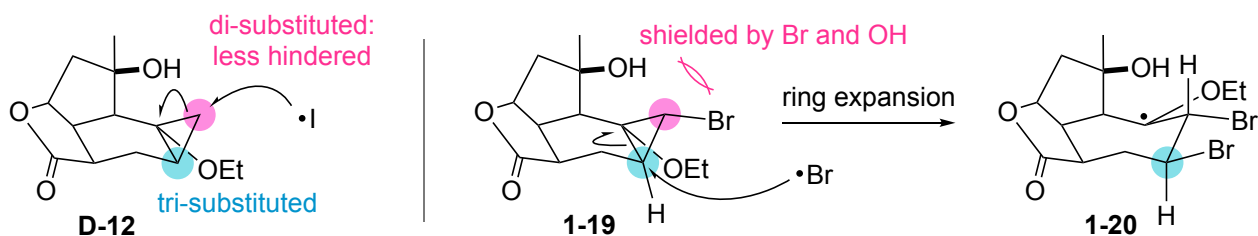
### Discussion 3: cyclopropane cleavage

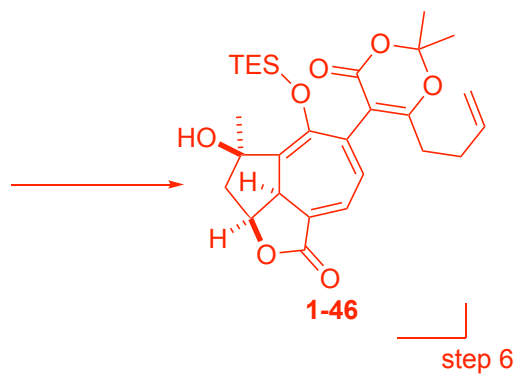
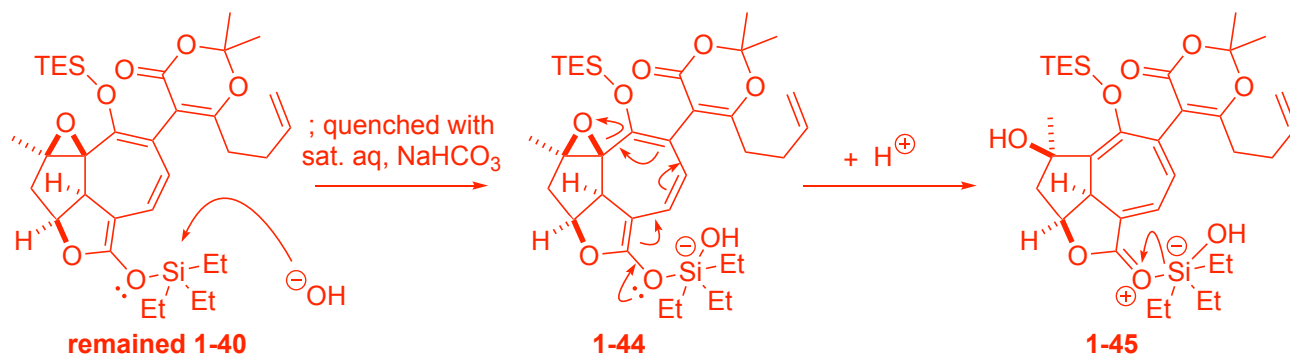
Previous result:



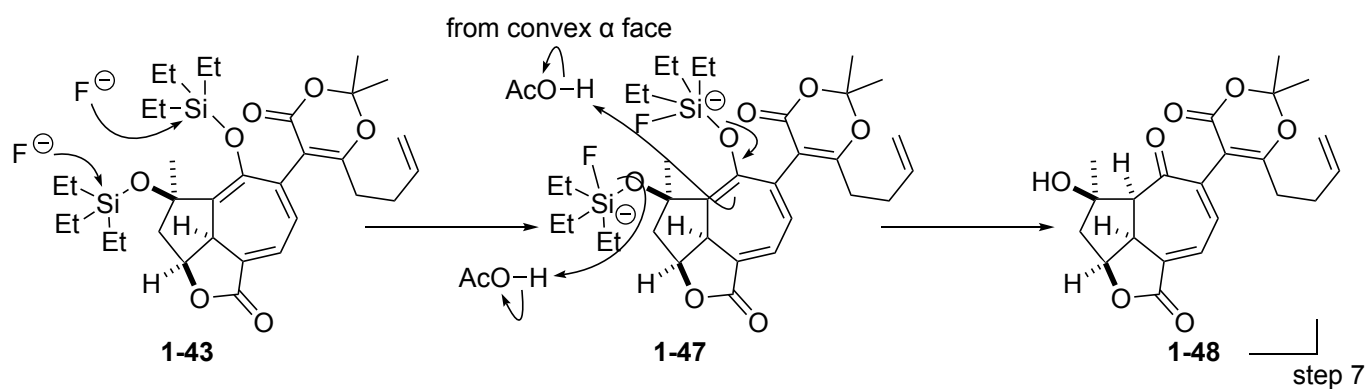
When the cyclopropane ring was not halogenated, ring expansion didn't occur.

→ Introduction of Br changed the steric environment, and then desired ring expansion proceeded.



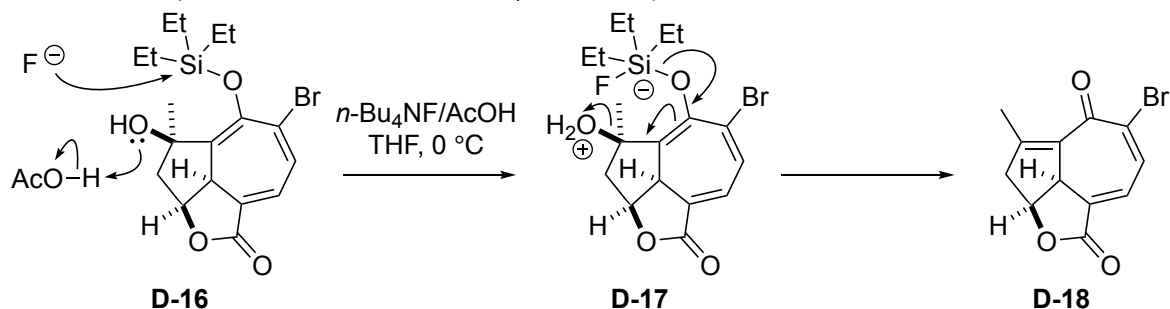


1-43 and 1-46 were obtained as a mixture.  
 It seems that 1-40 was not fully converted to 1-43 in the reaction, and remained 1-40 was hydrolyzed by quenching.

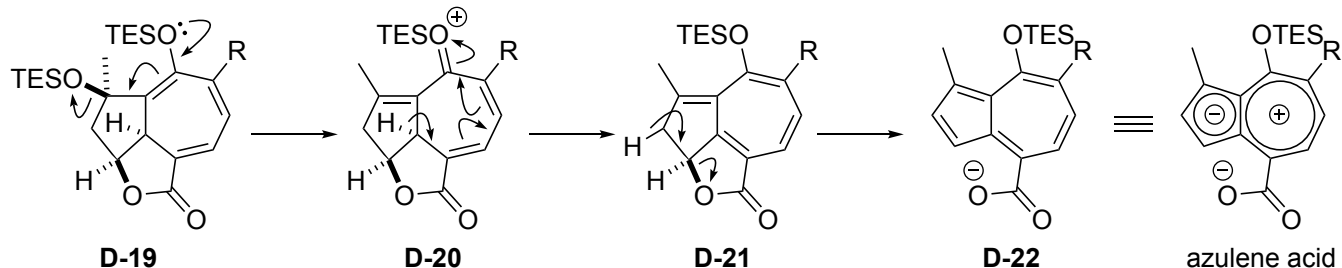


•Possible reasons for the low yields of these reactions.

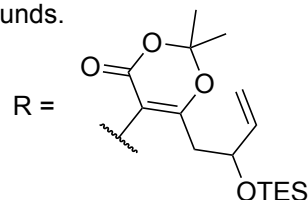
When **D-16** was attempted to the condition of  $n\text{-Bu}_4\text{NF}/\text{AcOH}$ ,  $\beta$ -elimination was occurred.



When **D-19** was purified by silica gel (basic-treated), the compound turned blue, suggesting azulene acid formation.



It appears that **1-43** and **1-44** are readily decomposed to form highly conjugated compounds.



#### References:

- 1) Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y.; Reddy, M. V. R.; Faulkner, D. J. *Tetrahedron Lett.* **1998**, 39, 8217.
- 2) Chitturi, B. R.; Tatipamula, V. B.; Dokuburra, C. B.; Mangamuri, U. K.; Tuniki, V. R.; Kalivendi, S. V.; Bunce, R. A.; Yenamandra, V. *Tetrahedron* **2016**, 72, 1933.
- 3) Truax, N. J.; Ayinde, S.; Van, K.; Liu, J. O.; Romo, D. *Org. Lett.* **2019**, 21, 7394.
- 4) Truax, N. J.; Ayinde, S.; Liu, J. O.; Romo, D. *J. Am. Chem. Soc.* **2022**, 144, 18575.
- 5) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2014**, 136, 4492.
- 6) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1975**, 46, 892.
- 7) Lewinski, J.; Sliwinski, W.; Dranka, M.; Justyniak, I.; Lipkowski, J. *Angew. Chem.* **2006**, 118, 4944.