Please provide the mechanisms for the following reactions.

- 1. acryloyl chloride (1.5 eq), *i*-Pr₂NEt (3.0 eq) (-)-BTM* (20 mol%), CH₂Cl₂, 23 °C 46% (94% ee, >19:1 dr)
- 2. NBS (1.0 eq), THF, 0 °C, 85% (>19:1 dr)

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

- 3. ZnEt₂ (2.5 eq), CH₂Cl₂, 0 °C to 23 °C; CHBr₃ (2.0 eq), O₂ (1 atm), 70%
- 4. LiBr (1.4 eq), $(NH_4)_2[Ce(NO_3)_6]$ (2.0 eq) NBS (3.2 eq), MeCN/H₂O (v/v = 25/1), 100 °C
- 5. DBU (2.0 eq), CH₂Cl₂, 0 °C, 52% (2 steps)

- 6. Et₃N (5.0 eq), TESOTf (3.0 eq) CH₂Cl₂, −78 °C to 0 °C
- 7. *n*-Bu₄NF/AcOH (1/1, 5.0 eq) THF, 0 °C, 44% (2 steps)

acryloyl chloride

(-)-BTM

$$0 \stackrel{N}{\underset{\mathsf{BL}}{\bigvee}} 0$$

NBS

DBU

Problem Session (2) -Answer-

topic: Total synthesis of Rameswaralide

isolation: from soft coral Sinularia dissecta (1998¹⁾, structure determination: 2016²⁾)

bioactivity: moderate cytotoxicity, possible anti-inflammatory acitivity²⁾

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

synthesis: Romo's group (2019: synthetic study³⁾, 2022: total synthesis⁴⁾, **problem**)

rameswaralide

additional α-bromination of 1-2 didn't occur.

→ electron poorer

Discussion 1: Diels-alder/lactonization 1-1. Acylammonium intermediate⁵⁾

1-7 ■: tetra-substituted olefin → electron richer

1-2 ■: tri-subtituted olefin

favorable interaction lone pairs_O \leftrightarrow σ^*_{C-S} most favorable Ph comformation (-)-BTM 1-10-a 1-10-b ١Œ site-selective acylation using (±)-BTM, steric repulsion 1-10-c

please refer to 220827_PS_Yosuke_Nakata.

- 1 -

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

According to these mechanisms, 1-12, diastereomers of (±)-1-7, would be obtained as a racemic compound.

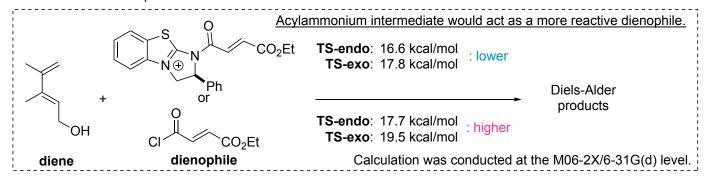
D-23 and **D-24** don't have a stereocenter, so this enantioselectivty should derive from (–)-BTM.

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

 \Rightarrow The reaction mechanism is illustrated by Diels-Alder rection \rightarrow 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 mechansims should be proper.

- 1-3. Possible reaction mechanisms: Diels-Alder reaction → lactonization
- Reactivities of dienophiles



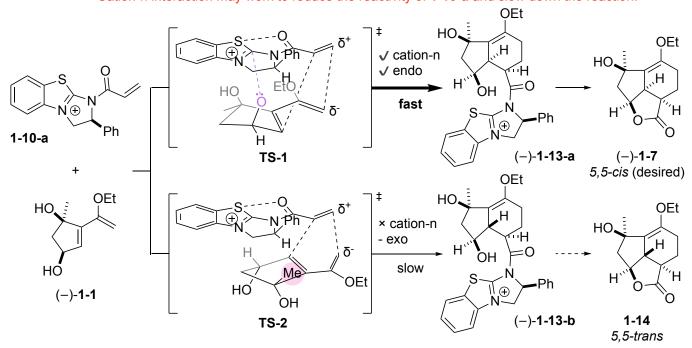
The LUMO energy would be lowered because of conjugation.

· Kinetic resolution of the Diels-Alder reaction

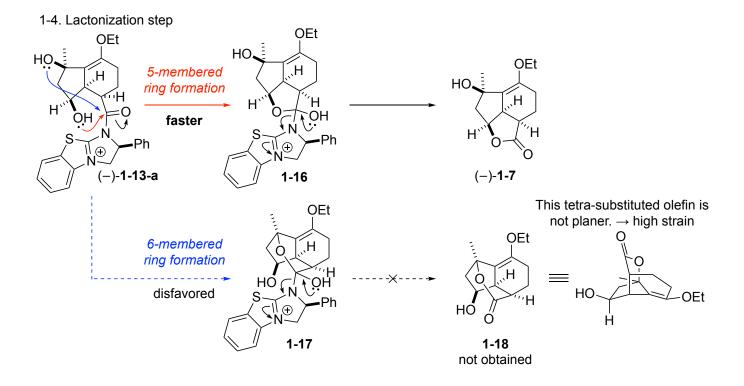
Suggestion by Prof. Inoue.

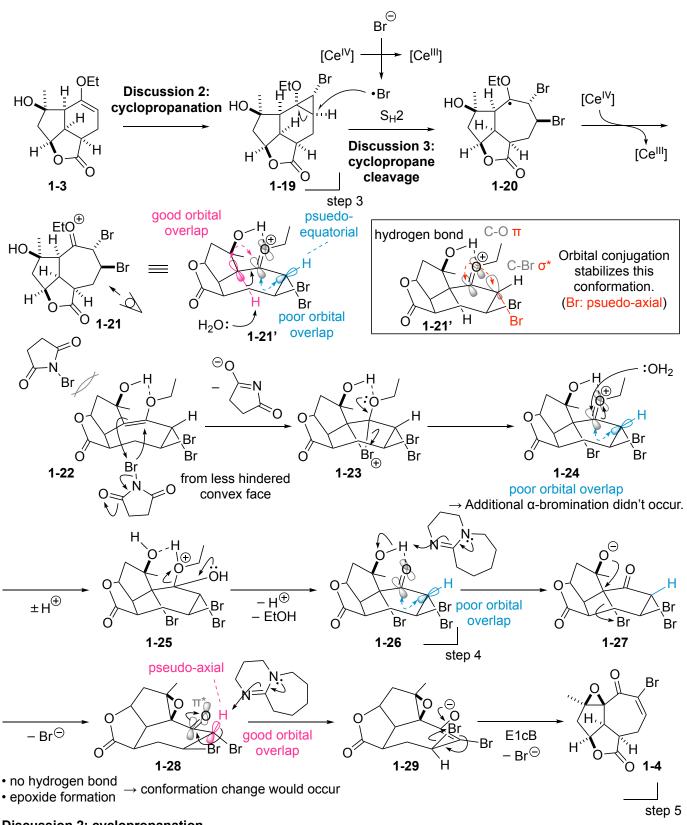
cation-n interaction → stabilize the transition state

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



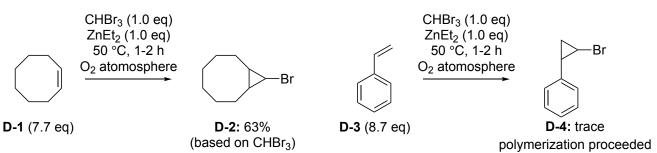
(-)-1-13-a would be the kinetic product.





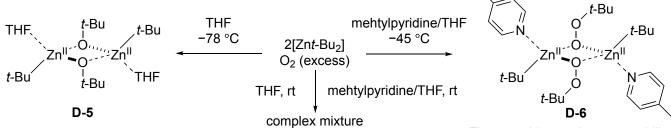
Discussion 2: cyclopropanation

2-1. CHBr₃, ZnEt₂, O₂ condition⁶⁾



→ A free radical chain mechanism for the formation of zinc carbenoid was proposed.



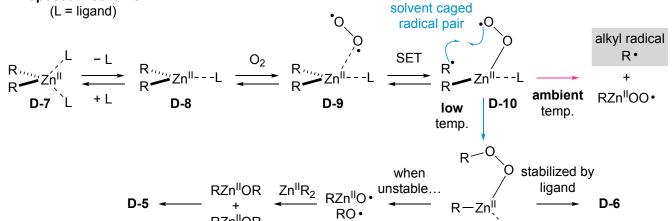


The peroxide species was stabilized by the nitrogen ligand.

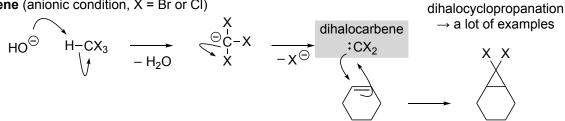
Proposed mechanism

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

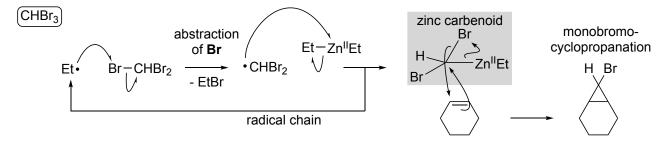
D-11

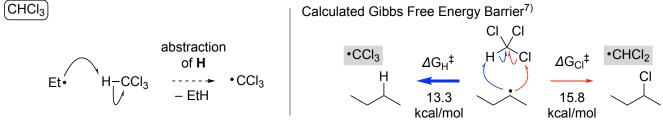


2-1-2. Reactivity of CHBr₃ (compared to CHCl₃) **dihalocarbene** (anionic condition, X = Br or Cl)



monohalocarbene (radical condition)





The generation of •CCl₃ will be favored to •CHCl₂ using alkyl radical.

→It suggests that monochloro-cyclopropanation is difficult.

$$\Delta G_H^{\ddagger} - \Delta G_{Cl}^{\ddagger} = 2.5 \text{ kcal/mol}$$

2-2. Reaction mechanism

2-3. Possible side reaction

1-36

not obtained

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

OEt

TS-6

steric repulsion between Br and lactone

high reactivity in non-coordinating solvent,
$$CH_2CI_2$$

1-33

high reactivity in non-coordinating solvent, CH_2CI_2

EtZn^{II}CHBr₂

- Et • 1-37

OEt

H

OEt

H

Br

TS-7

from less hindered convex face

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.

TES_O:

N⊝ OH S-Si Et Et Et

•Possible reasons for the low yields of these reactions.

When **D-16** was attempted to the condition of *n*-Bu₄NF/AcOH, β-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:

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- 7) Lewinski, J.; Sliwinski, W.; Dranka, M.; Justyniak, I.; Lipkowski, J. Angew. Chem. 2006, 118, 4944.