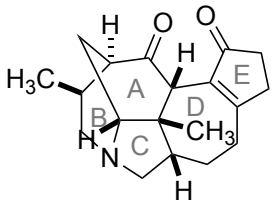
Problem session (1) Answer

2025/02/15 Kosuke Morita

Topic: Total synthesis of Himalensin A

Introduction

1) Himalensine A and *Daphniphyllum* alkaloids



Himalensine A

Daphniphyllum alkaloids
- isolated from *Daphniphyllum (Yuzuriha)* genus
- classified into over 20 subtypes
- biological activities: anticancer, anti-HIV, antioxidation

Himalensine A
- classified into Calyciphylline A-type
- structual features
  - pentacyclic fused-ring system
  - six strereogenic centers

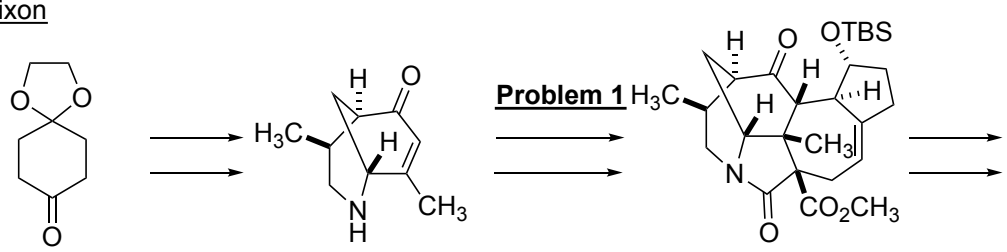
Subtypes of *Daphniphyllum* alkaloids

subtypes	Former seminars
Calyciphylline A-type (including Himalensine A) ***today's topic***	221001_LS_Shuji_Toyama 240210_LS_Sota_Mochizuki 140510_PS_Shun_Yoshioka 171216_PS_Kotaro_Tokumoto 230520_PS_Hisahiro_Morozumi
Daphmanidin A-type	111224_PS_Shoko_Matsutaka
Yuzurine-type	221119_PS_Junhao_Fu
Daphnicyclidin-type	240629_PS_Mizuki_Sawada
Others	111117_PS_Hiroaki_Itoh 150314_PS_Kosuke_Minagawa

2) Total synthesis of Himalensine A

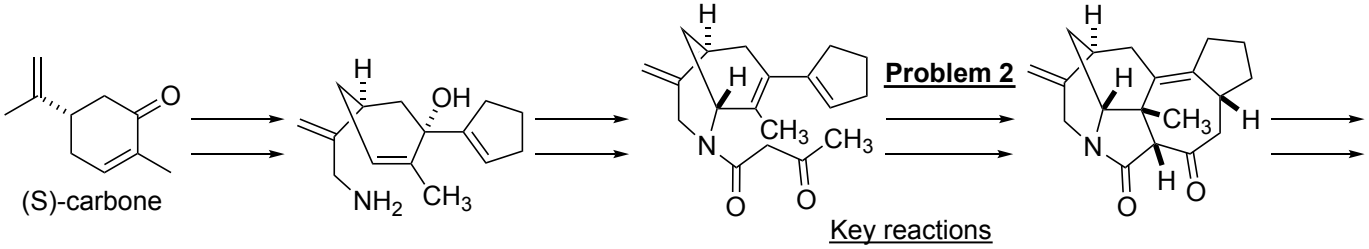
Dixon (2023) (today's topic), Qiu (2021) (today's topic), Gao (2019), Xu (2019)

Dixon



Key reactions
- Claisen rearrangement
- ring-closing metathesis

Qiu



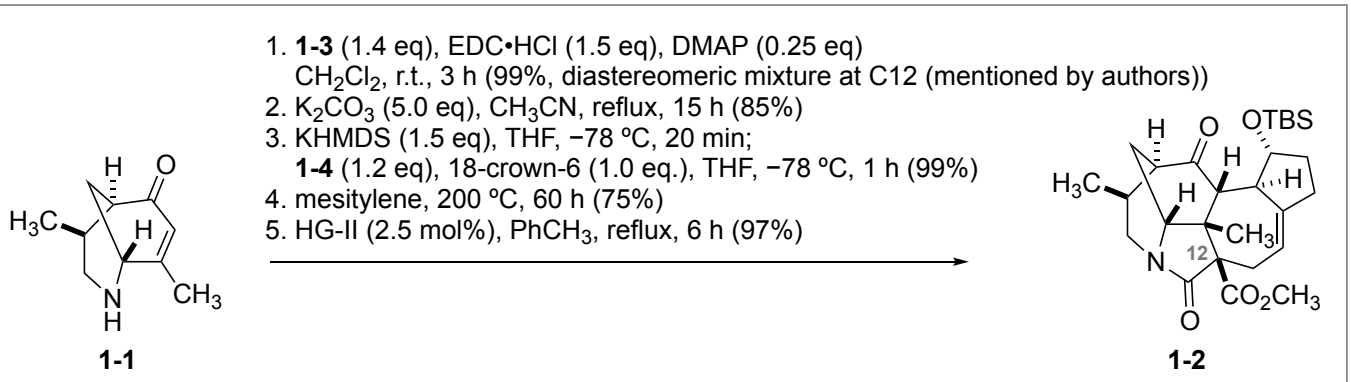
Key reactions
- cyclopropanation
- Claisen rearrangement

Gao: Zhong, J.; Chen, K.; Qiu, Y.; He, H.; Gao, S. *Org. Lett*. **2019**, *21*, 3741.

Xu: Chen, Y.; Hu, J.; Guo, L-D.; Zhong, W.; Ning, C.; Xu, J. *Angew. Chem., Int. Ed.* **2019**, *58*, 7390.

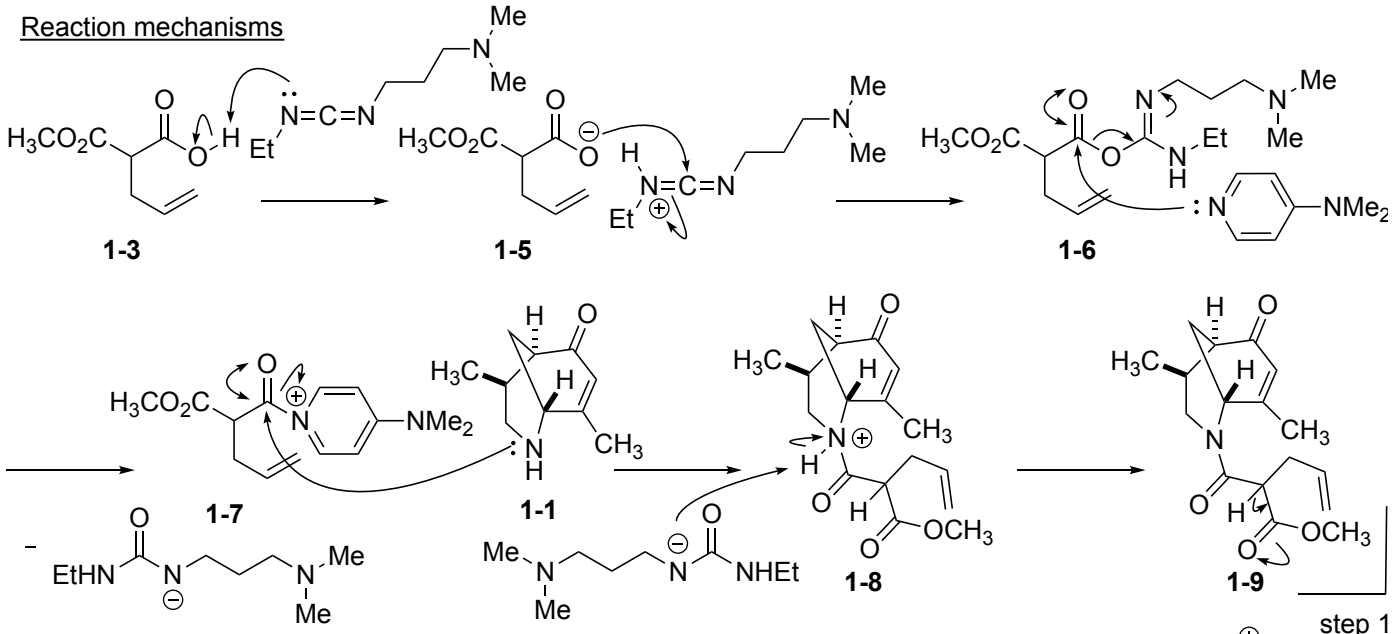
Answer

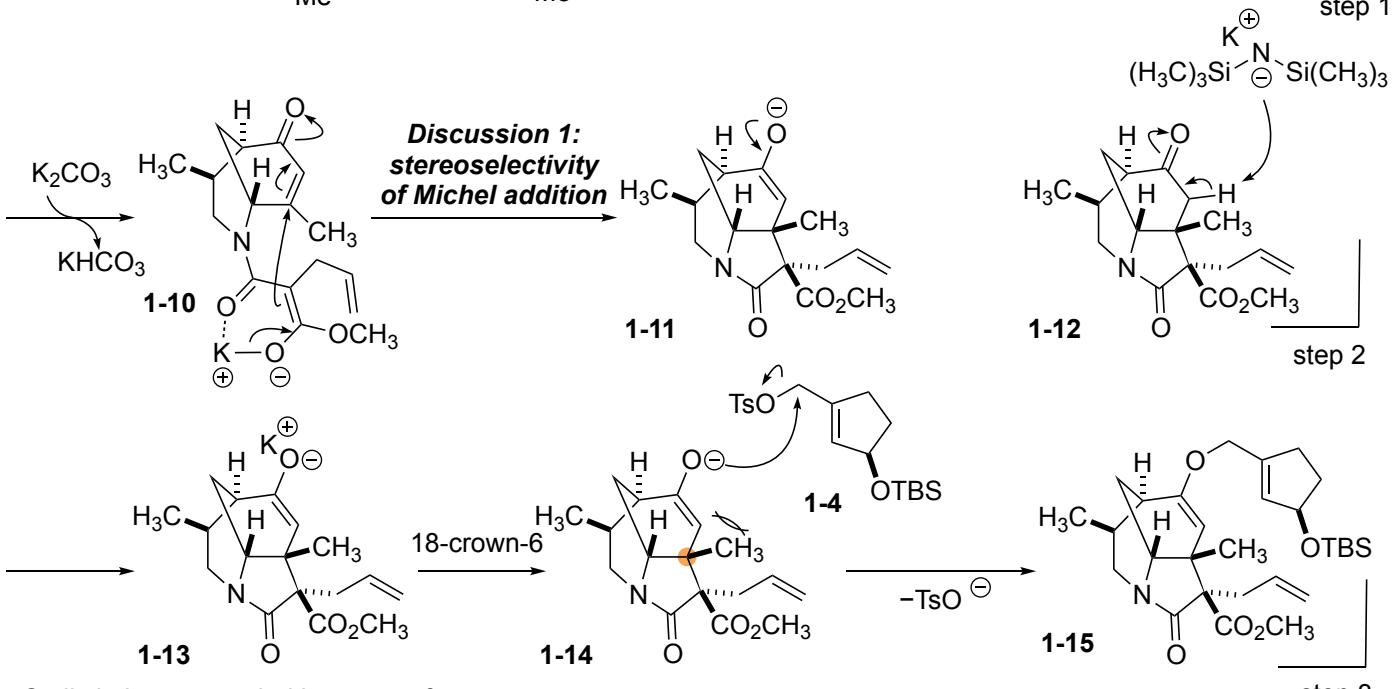
Problem1



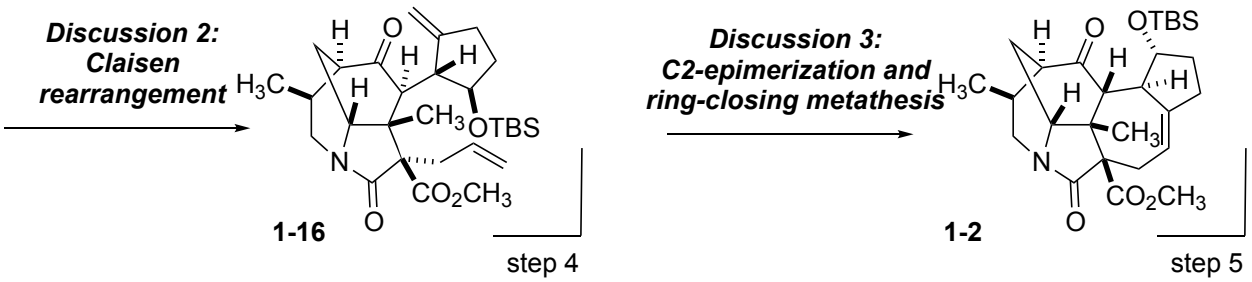
Kučera, R.; Ellis, S. R.; Yamazaki, K.; Cooke, J. H.; Chekshin, N.; Christensen, K. E.; Hamlin, T. A.; Dixon, D. J. *J. Am. Chem. Soc.* **2023**, *145*, 5422.

Reaction mechanisms

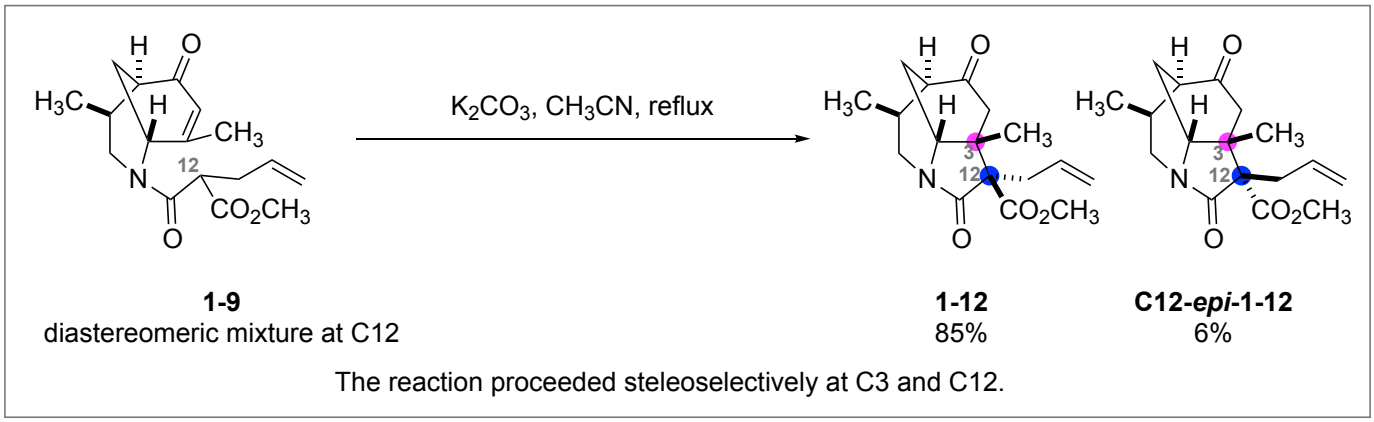




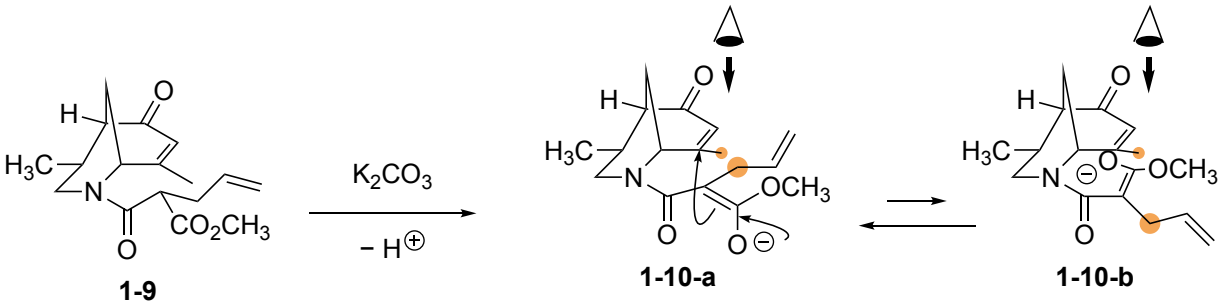
O-alkylation proceeded because of:
- hardness of the electrophile by polarized C-O bond
- steric hinderance of 4° carbon (C3)



Discussion 1: steleoselectivity of Michael addition

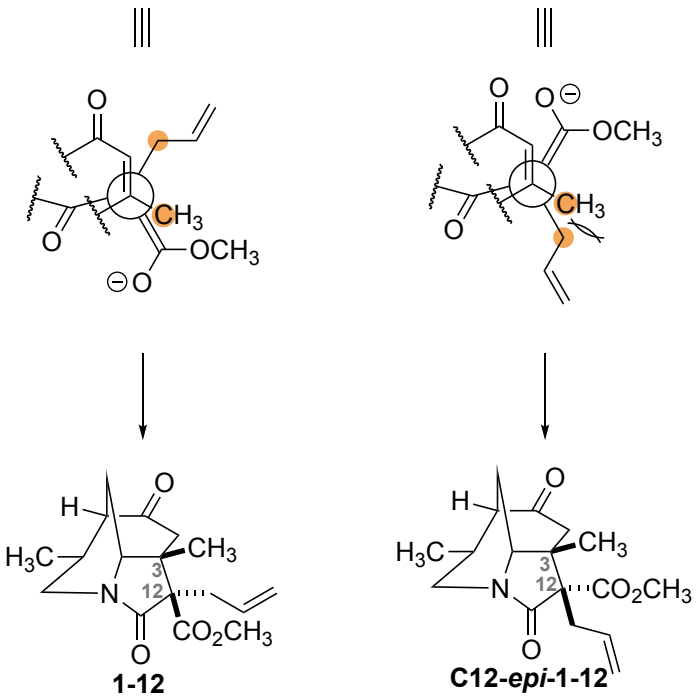


the mechanism of stereoselectivity (my proposal)

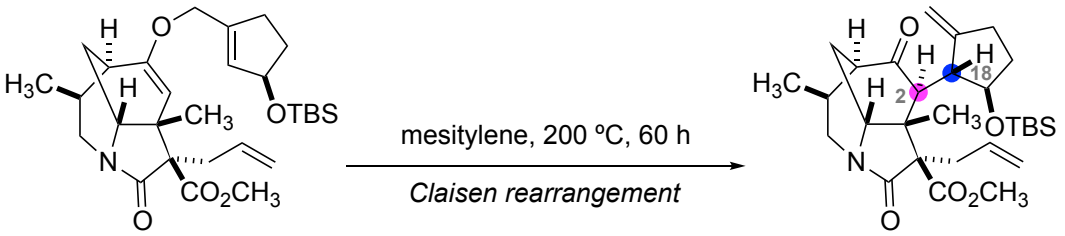


- Considering the steric repulsion of eclipced sp^3 carbons, **1-10-b** is destabilized compared **1-10-a**.

- The enolate approaches the enone from its bottom face because of the rigid bicyclic skeleton.



Discussion 2: Claisen rearrangement

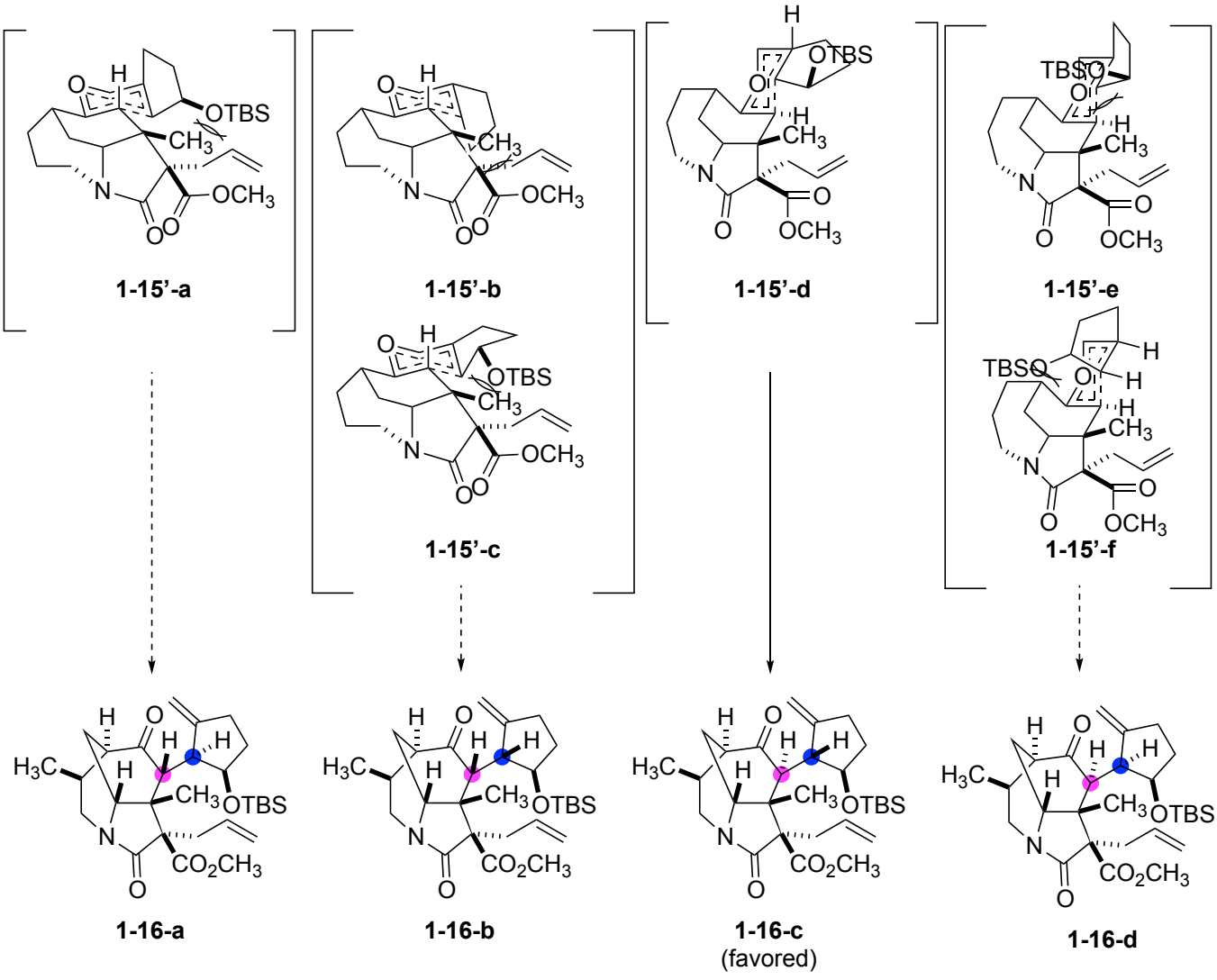


1-15 **1-16**

The reaction was proceeded stereoselectively at C2 and C18.

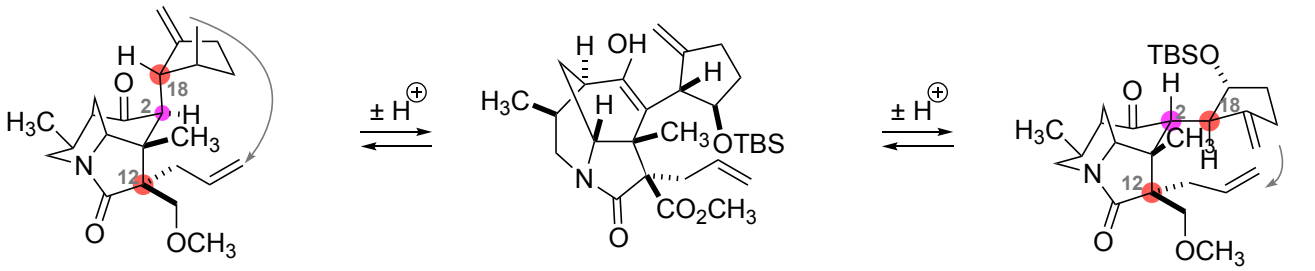
the mechanism of stereoselectivity (my proposal)

It is proposed that the stereoselectivity was kinetically controlled.



the mechanism of epimerization

It is proposed that 7-membered ring formation by ring-closing metathesis does not proceed from the product of former reaction, **1-16** due to the *anti-* and *pseudo-axial-* configurations of C12 and C18 against the 6-membered ring. - **1-16** undergoes epimerization at C2 via enol **1-17** and then ring-closing metathesis proceeds.



1-16
(1-16-a)

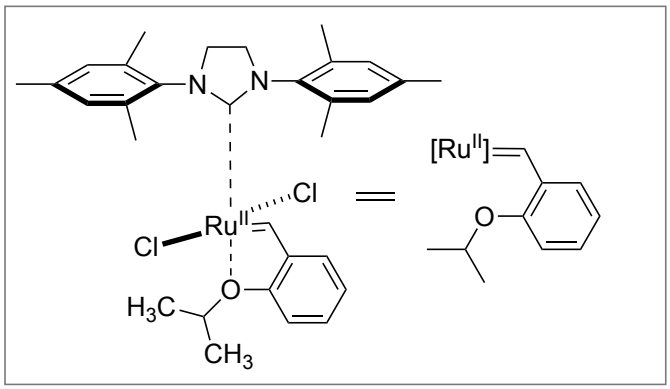
olefins are too far
for ring-closing metathesis

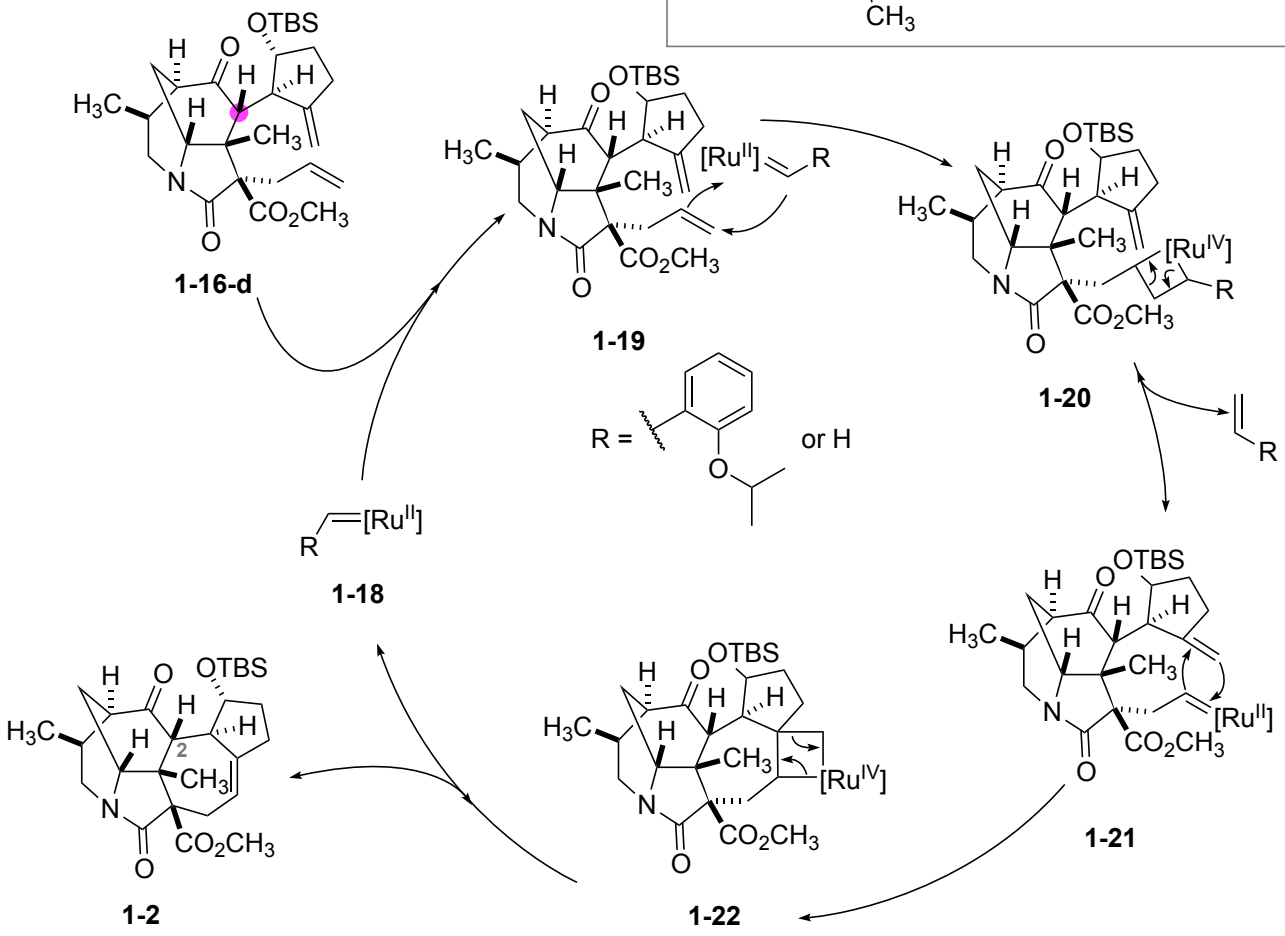
1-17

1-16-d

close enough
for ring formation

the mechanism of ring-closing metathesis





1-16-d

1-19

1-20

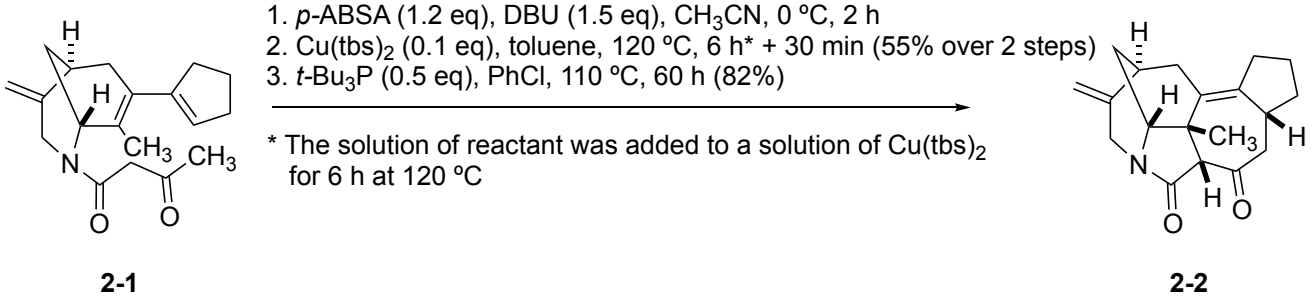
1-21

1-22

1-2

1-18

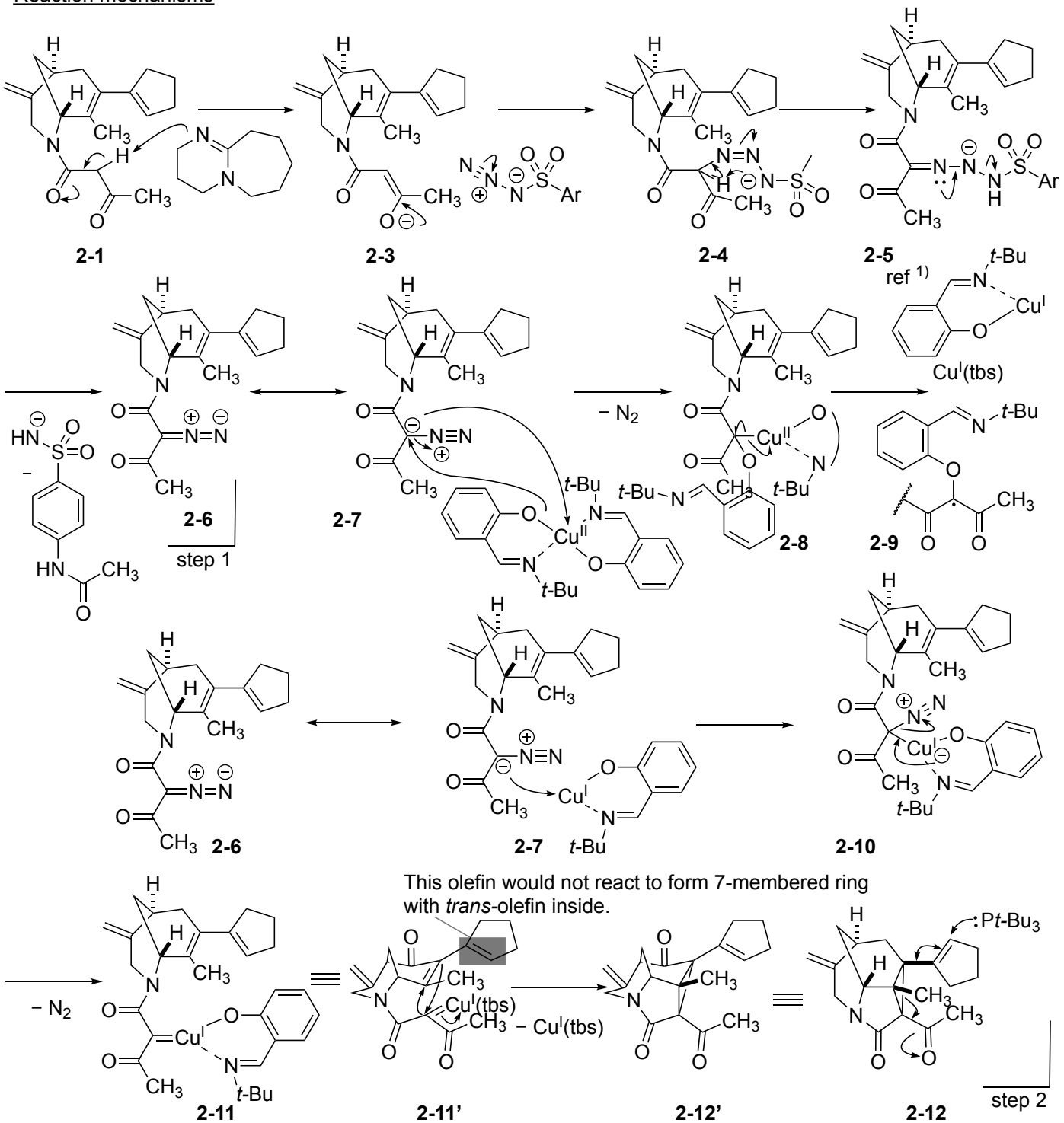
Problem2



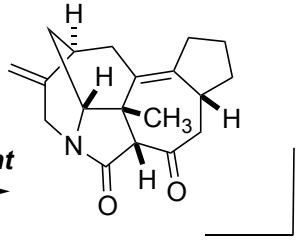
2-1 **2-2**

Wang, B.; Xu, B.; Xun, W.; Guo, Y.; Zhang, J.; Qiu, F. G. *Angew. Chem. Int. Ed*. **2021**, *60*, 9439.

Reaction mechanisms



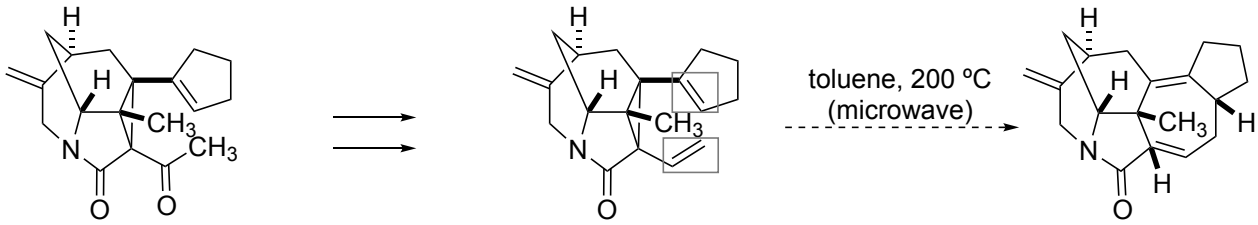
Discussion 4:
S_N2' reaction + Claisen rearrangement



2-2 step 3

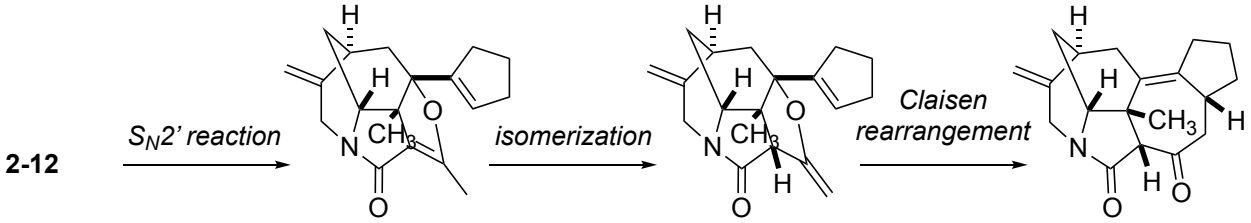
Discussion 4: S_N2' reaction + Claisen rearrangement
(my proposal for detailed reaction mechanism and stereoselectivity)

experimental results:
Rearrangement of divinylcyclopropane **2-11** was unsuccessful.



2-12 **2-13** **2-14**
(not obtained)

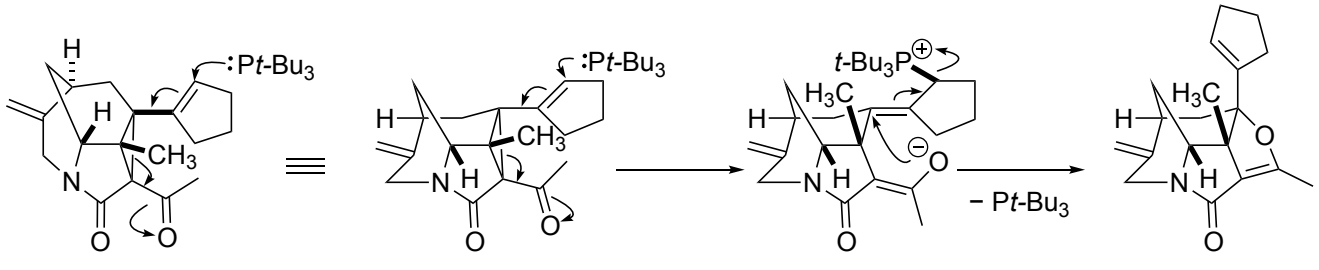
The authors utilized phosphine-catalyzed rearrangement of cyclopropane reported by Xu[2)],
which was successful to give 7-membered ring-formed **2-2**.



2-15 **2-16** **2-2**: 82%

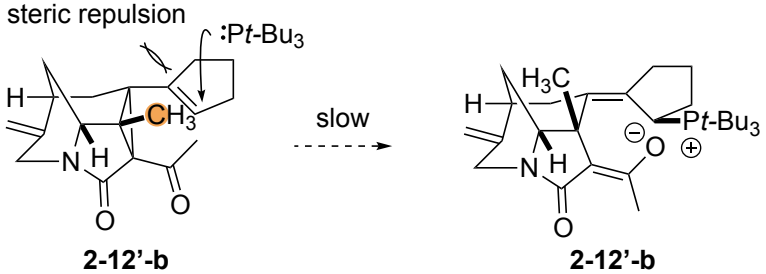
It is proposed that the conformation of two olefins of **2-12** were too free to react.
- To fix the conformation of olefin by cyclization, the formation of seven-membered ring would be proceeded.

1) intramolecular S_N2' reaction driving force: release of strain of cyclopropane/cancellation of zwitterinonic state



2-12 **2-12'-a** **2-17'-a** **2-15**

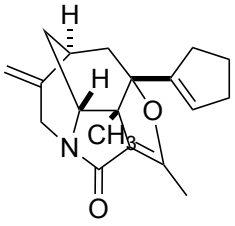
steric repulsion



2-12'-b **2-12'-b**

2) strain release by olefin isomerization driving force: release the distortion of bond angle

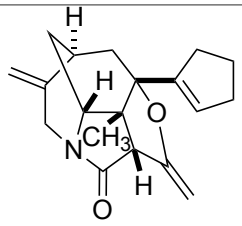
actual bond angle of cyclopentane: 108°
ideal bond angle of:
- sp^2 carbon: 120°
- sp^3 carbon: 109.5°



2-15

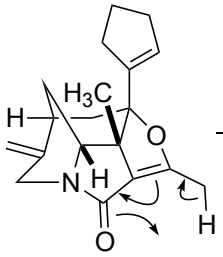
sp^2 carbon in ring

C ring : 2
D' ring : 2

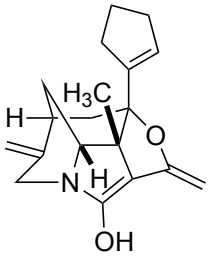


2-16

C ring : 1
D' ring : 1

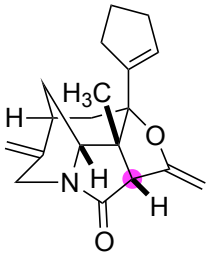


2-15'



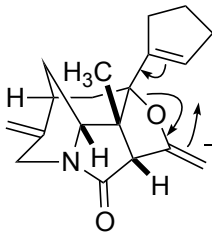
2-18

tautormerization
protonation from convex face

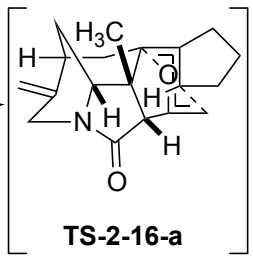


2-16

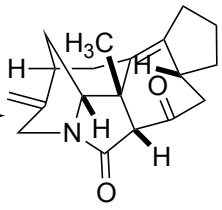
3) Claisen rearrangement driving force: transformation of the enol ether to ketone



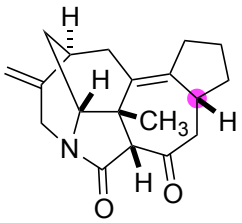
2-16'



TS-2-16-a

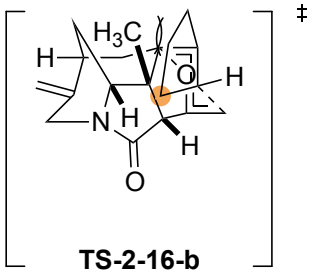


2-2'

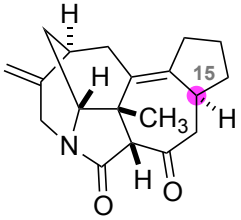


2-2
(favored)

TS-2-14-b was hard to generate because of steric hindrance.



TS-2-16-b



C15-*epi*-2-2
(unfavored)

References

1) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.
2) J, Wu.; Y, Tang.; W, Wei.; Y, Wu.; Y, Li.; J, Zhang.; Y, Zheng.; S, Xu. *Angew. Chem. Int. Ed.* **2018**, *57*, 6284.