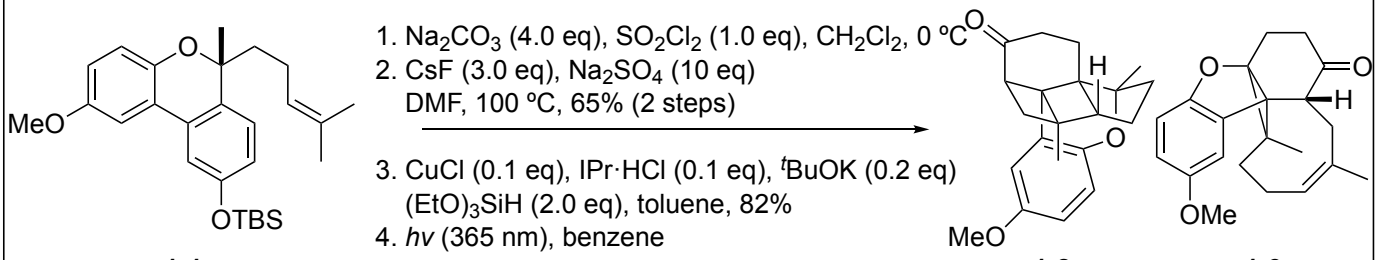
Problem Session (1) -Answer-

2025/01/16 Kaede Ono

Topic: Total synthesis of Cochlearol B

Problem 1: Total synthesis of Cochlearol B by Zhao group.

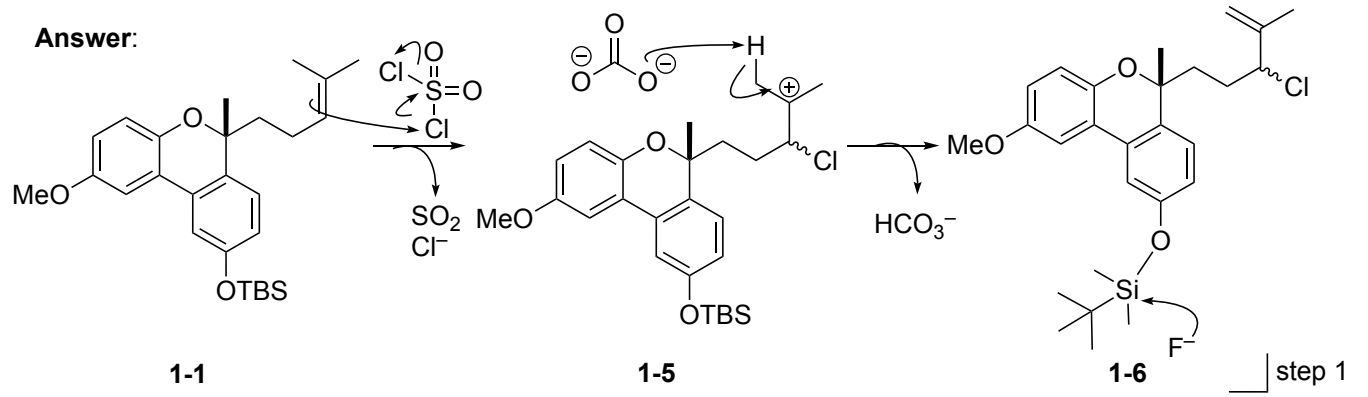
1 Please provide the reaction mechanisms. In step4, the reaction intermediate **1-4** was also obtained and it has 9-membered ring. Please determine the structure of **1-4**.



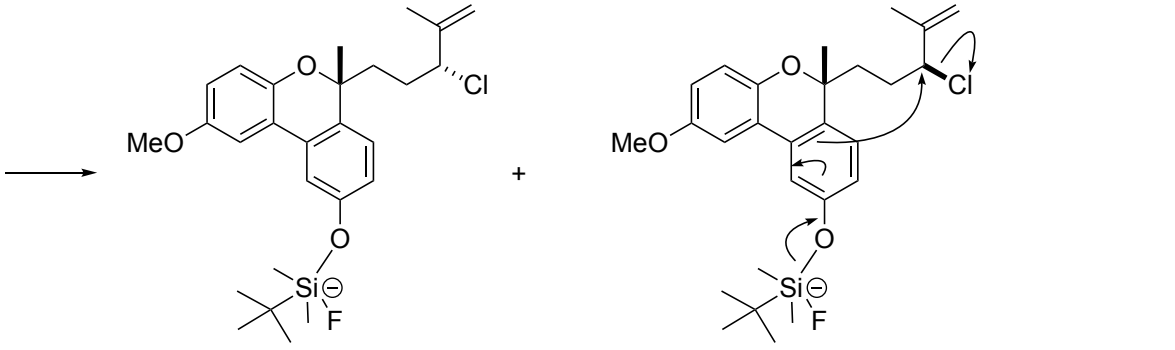
1-1 **1-2** **1-3**

Zhou, Q.; Ma, X.; Qiao, J.; He, W.; Jiang, M.; Shao, H.; Zhao, Y. *Chem. Eur. J.* **2024**, *30*, e202400084.

Answer:

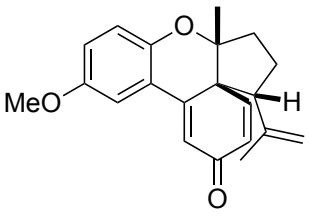


1-1 **1-5** **1-6**

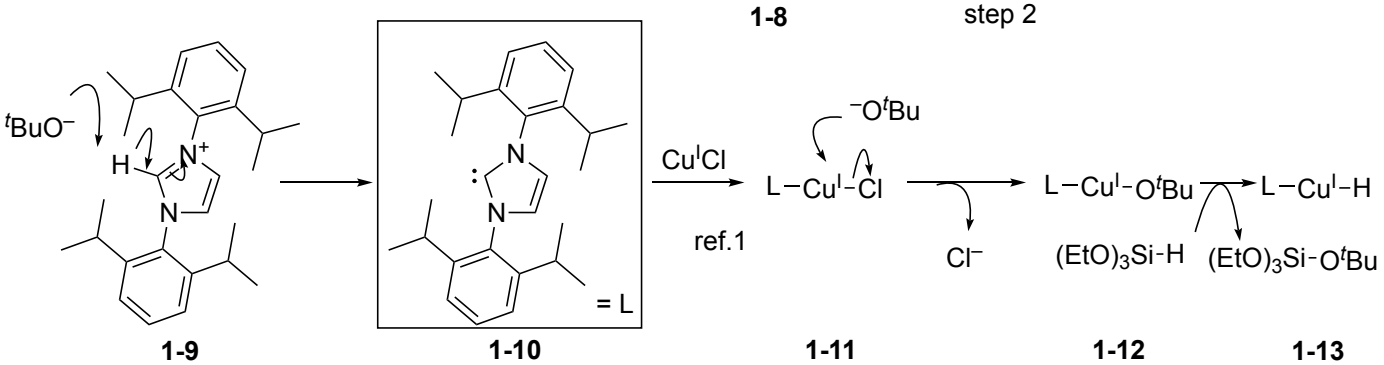


1-7a **1-7b**

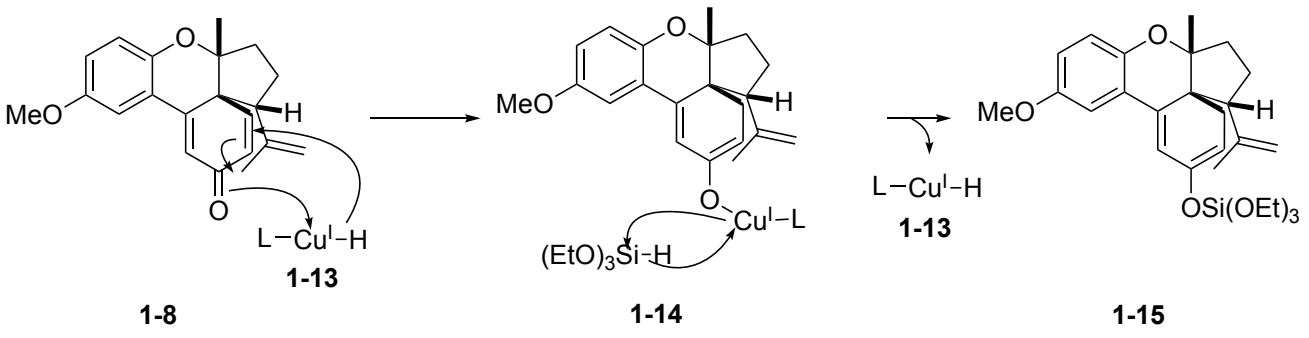
discussion 1: *stereoselective cyclization*

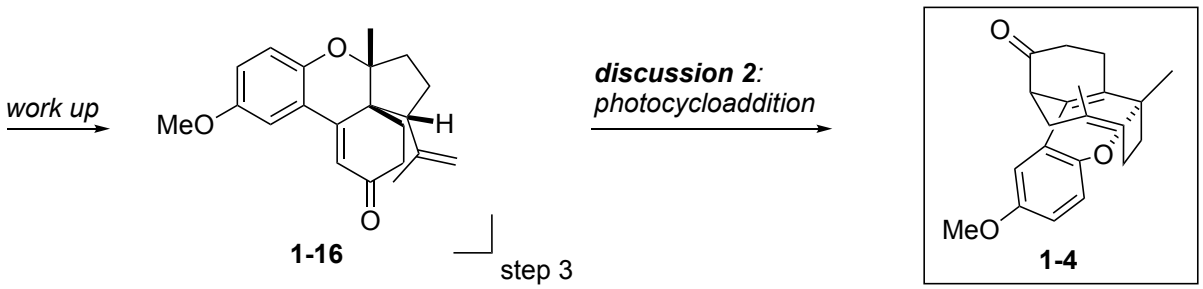


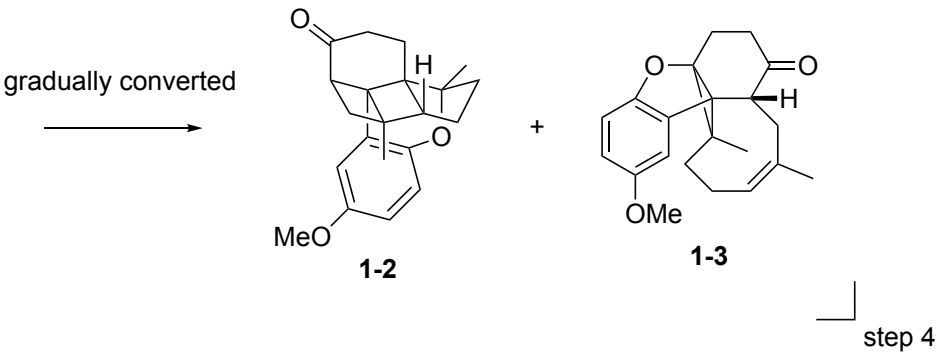
1-8



1-9 **1-10** **1-11** **1-12** **1-13**

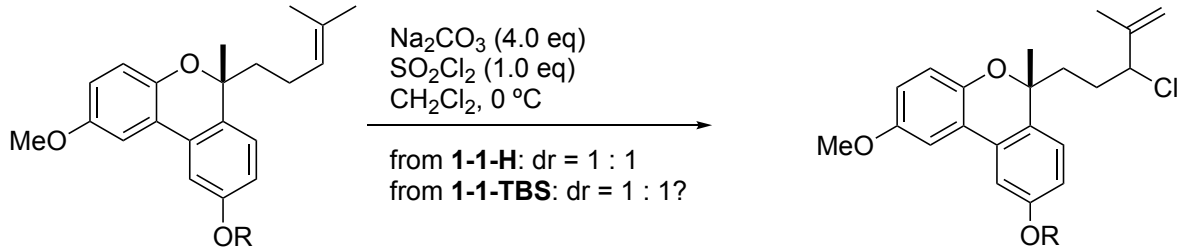






Discussion 1*:* stereoselective cyclization

1-1. The different results of the reactions from two similar compounds.[ref.2]

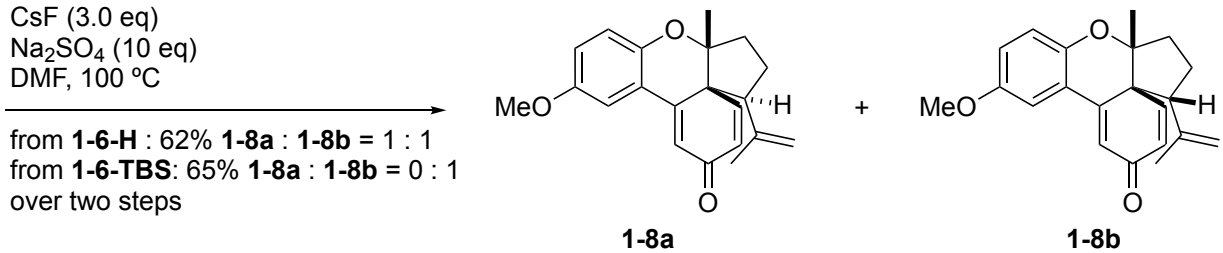


1-1-H: R = H

1-1-TBS: R= TBS

1-6-H: R = H

1-6-TBS: R= TBS

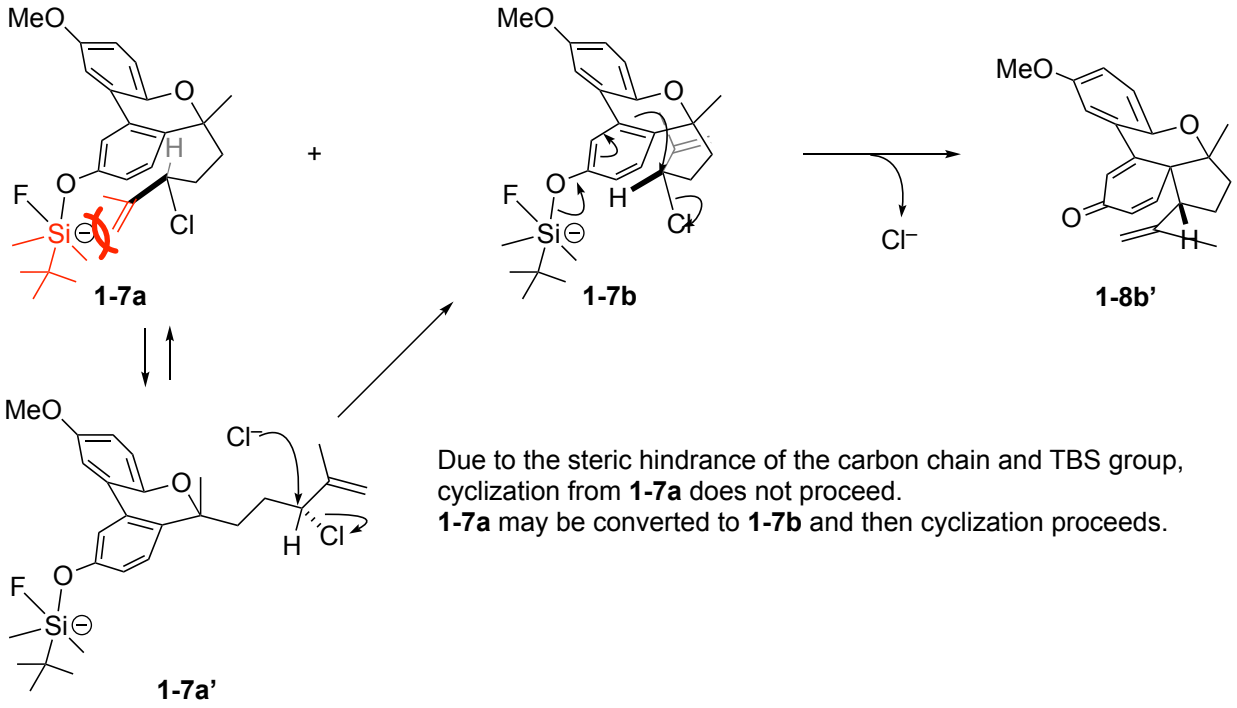


1-8a

1-8b

The results show that TBS group affects on the stereoselectivity.

1-2. reaction mechanism

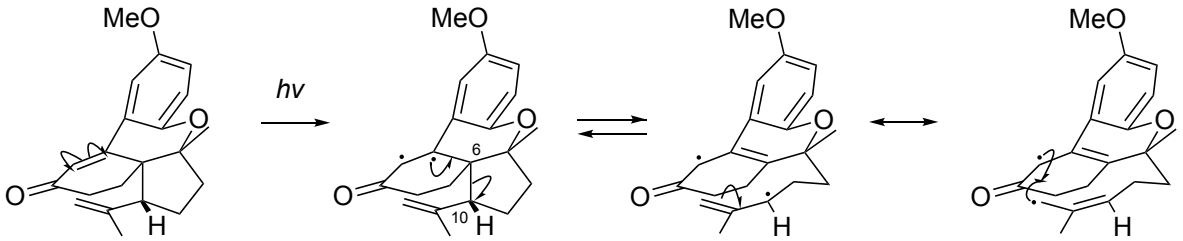


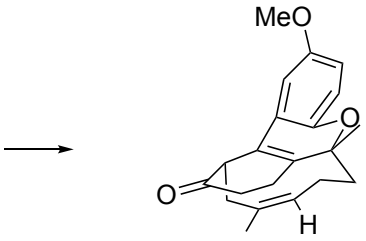
Due to the steric hindrance of the carbon chain and TBS group, cyclization from **1-7a** does not proceed.
1-7a may be converted to **1-7b** and then cyclization proceeds.

Discussion 2: Photocycloaddition

2-1. Reaction mechanisms from **1-16** to **1-4**

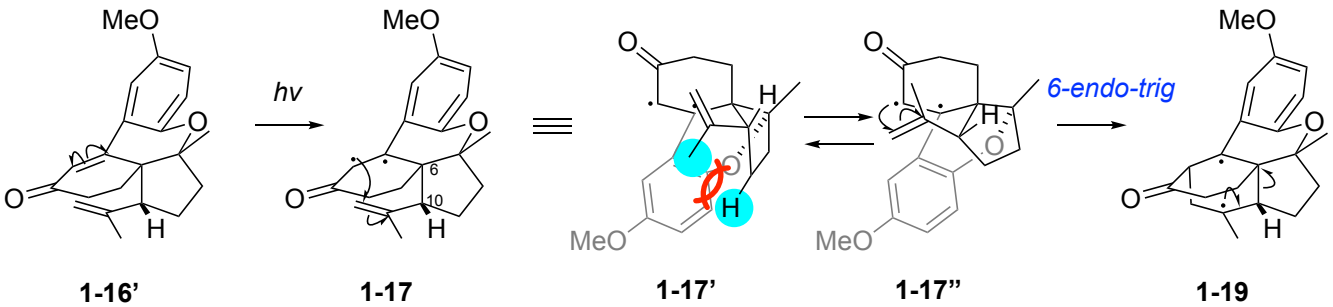
2-1-1. Author's proposed mechanism



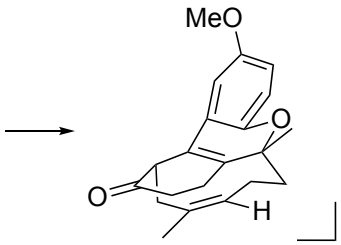


· The reaction starts with the stable benzyl radical of **1-17**.
· The ring strain of 5-membered ring of **1-17** may not be large, so I think C6-C10 bond cleavage does not occur.

2-1-2. my opinion

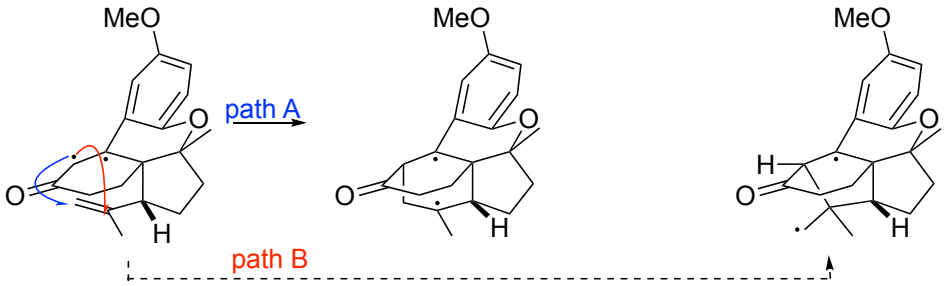


*stereochemistry will be discussed later



1-4'

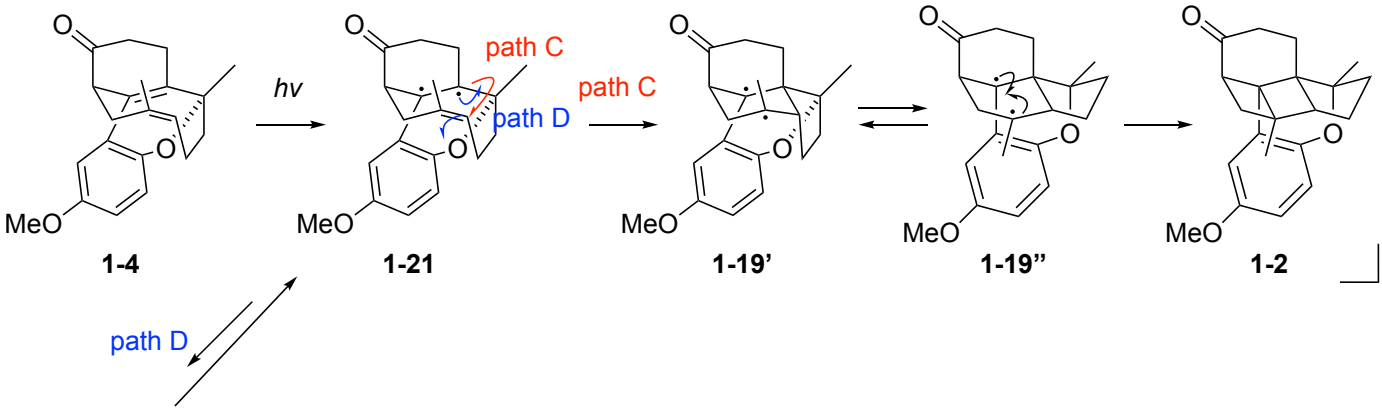
· The reaction starts from the α-keto radical of **1-17** (relatively unstable).
· C6-C10 bond cleavage easily occurs to form **1-4'**.



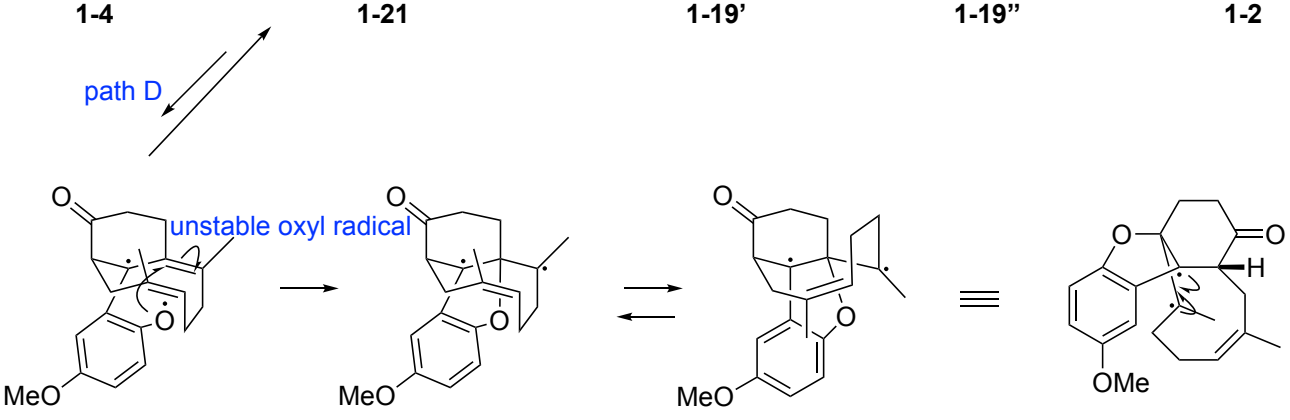
1-17 **1-19** **1-20**

	path A	path B
steric-hinderance :	small (exo-side of olefin)	large (endo-side of olefin)
cyclization type :	disfavored (6-endo-trig)	favored (5-exo-trig)
stability :	high (benzyl and tertiary)	low (benzyl and primary)

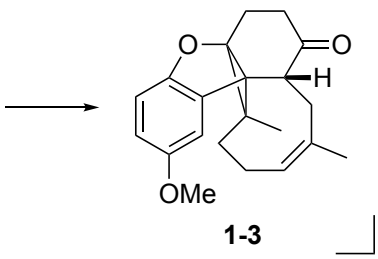
2-2. Reaction mechanism from **1-4** to **1-2** and **1-3**



1-4 **1-21** **1-19'** **1-19"** **1-2**



1-22 **1-23** **1-23'** **1-23"**



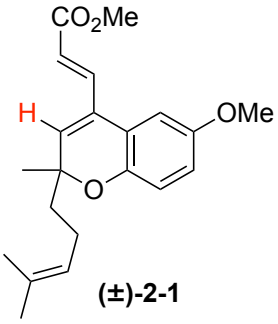
1-3

The author suggests that **1-4** is rapidly generated. With prolonged reaction time, **1-4** gradually disappeared, converting into **1-2** and **1-3**. Cleavage of olefin of **1-4** is less for excitation than cleavage of α,β unsaturated bonds of **1-16** .
The reaction from **1-4** is therefore slow, and 9-membered ring **1-4** may be an intermediate.

In path D, unstable oxyl radical is formed and ring cleavage occurs. So, path D may be less favourable than path C and the yield of **1-3** is lower than **1-2**.

Problem 2: Total synthesis of Cochlearol B by Schindler group.

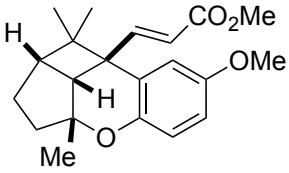
2 Please provide the reaction mechanisms and explain the differences between the two reactions.



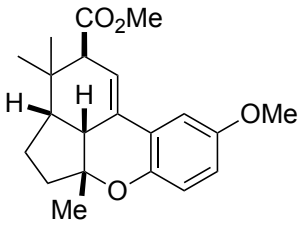
(±)-2-1

$Ir^{III}[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.01 eq)
blue LEDs (427 nm), MeCN

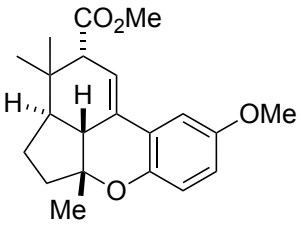
(±)-2-2 : 29%,
(±)-2-3 + **(±)-2-4** : 32% (3 : 1)



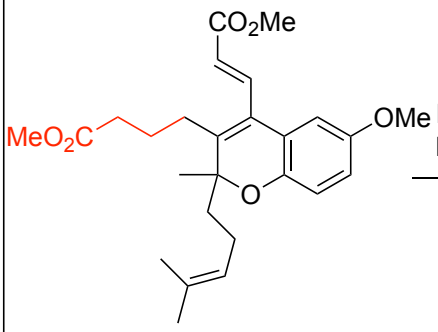
(±)-2-2



(±)-2-3

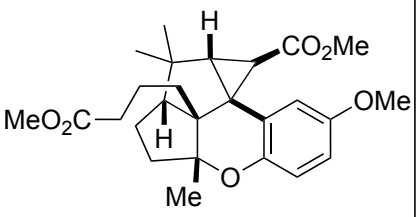


(±)-2-4



(±)-2-5

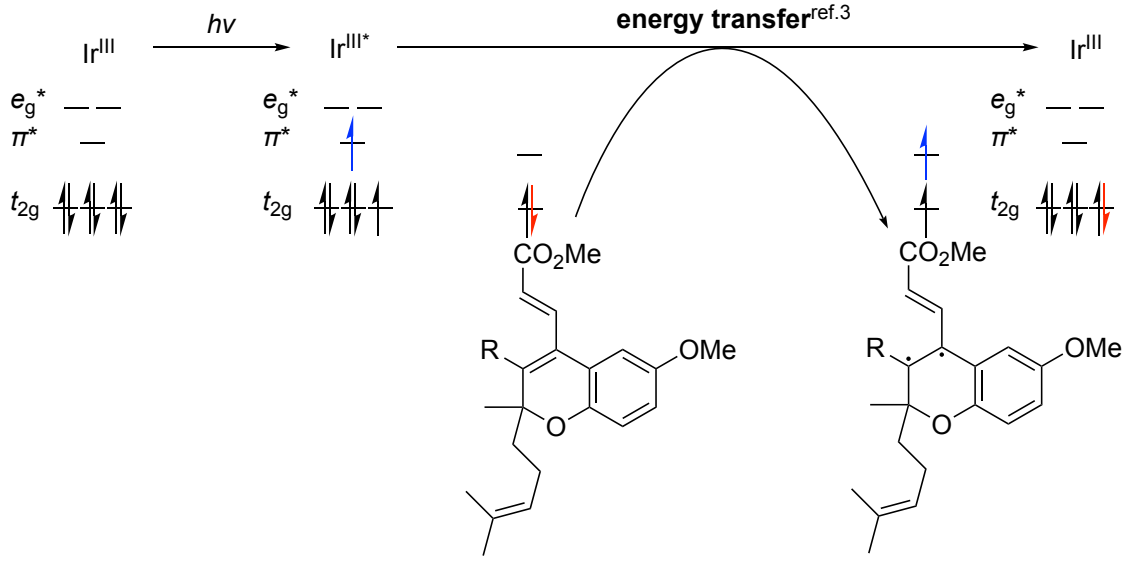
$Ir^{III}[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.01 eq)
blue LEDs (427 nm), MeCN, 85%



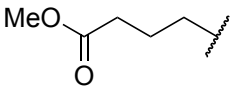
(±)-2-6

Richardson, A.; Vogel, T.; Traficante, F.; Glover, K.; Schindler, C. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201213.

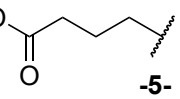
Answer:



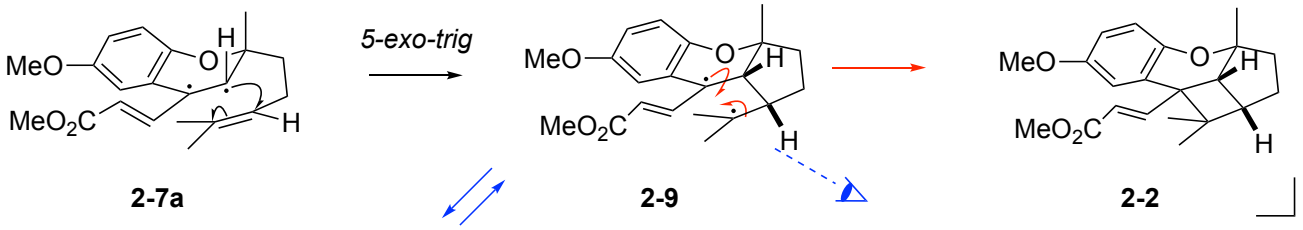
2-1: R = H

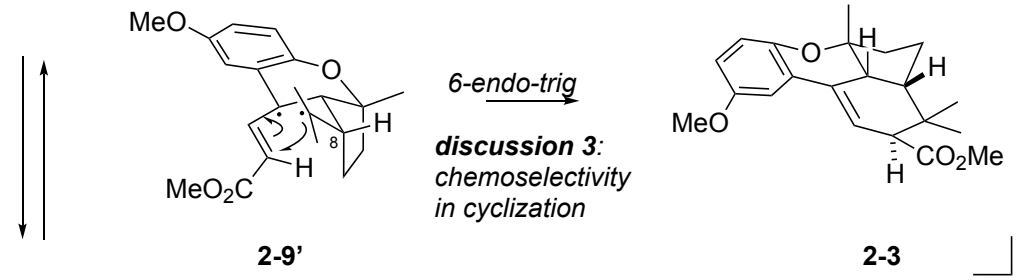
2-5: R= 

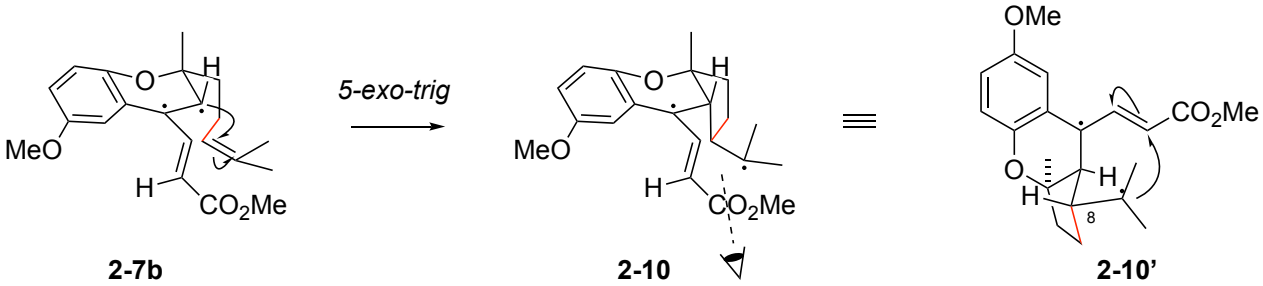
2-7: R = H

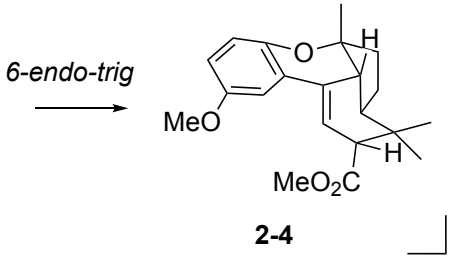
2-8: R= 

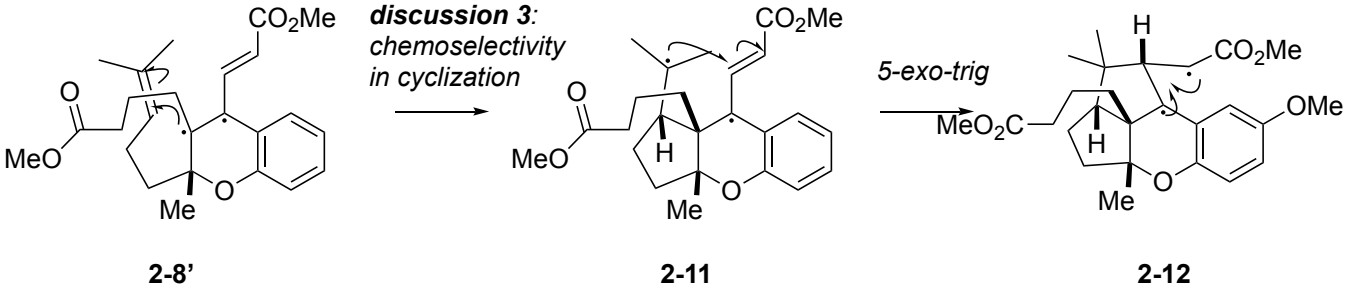
Biradical **2-7** and **2-8** stabilized at benzyl radical.

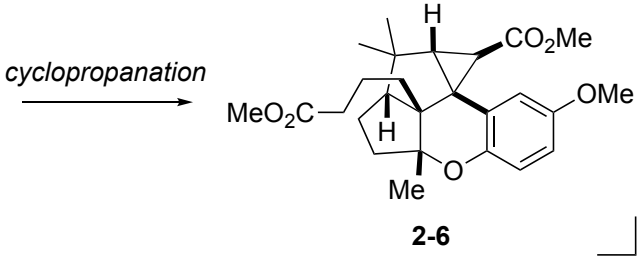








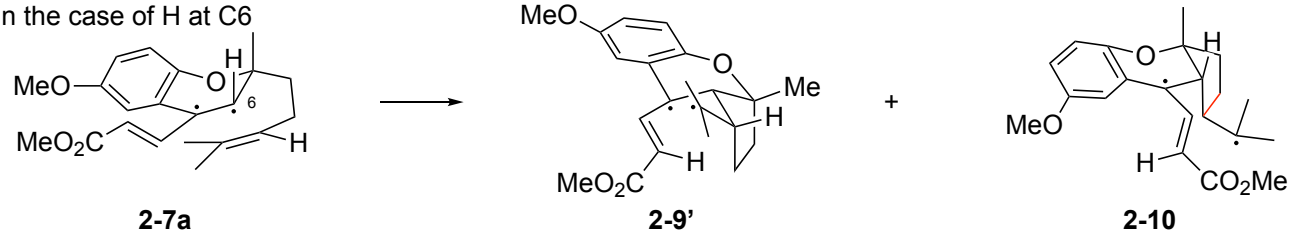




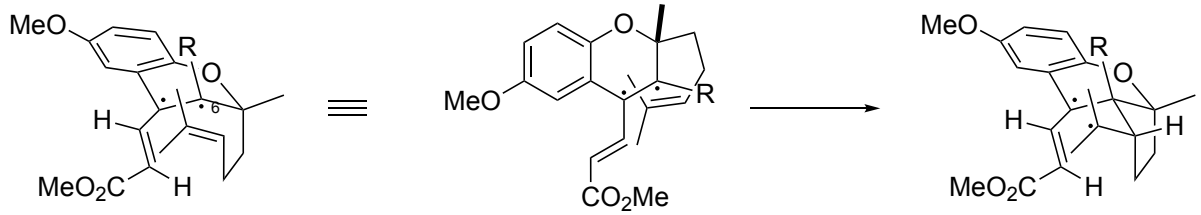
Discussion 3: Chemoselectivity of cyclization

3-1. stereoselectivity of 5-membered ring formation

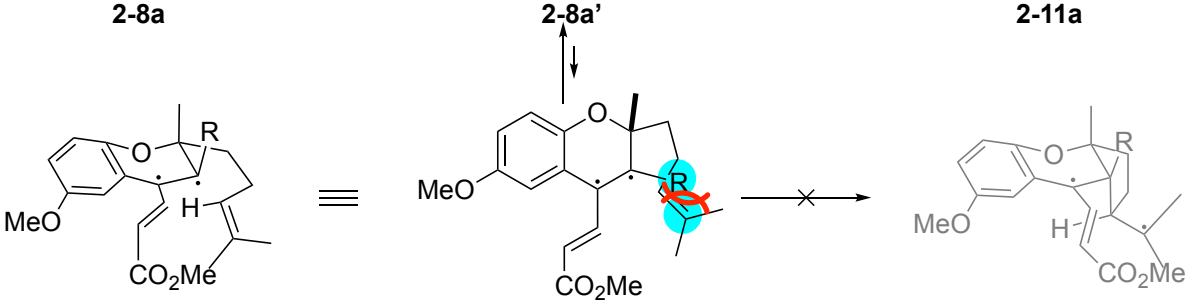
In the case of H at C6



In the case of R at C6



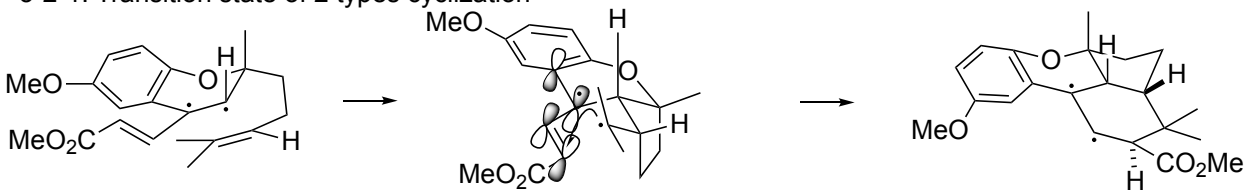
2-8a **2-8a'** **2-11a**



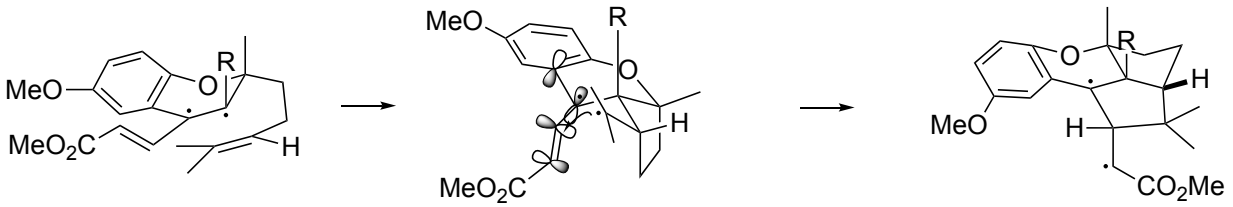
2-8b **2-8b'** **2-11b**

3-2. *5-exo-trig* vs *6-endo-trig*

3-2-1. Transition state of 2 types cyclization



2-7 **2-9'** **2-13**

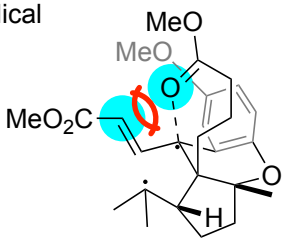


2-8 **2-11a** **2-12'**

From **2-9'**, cyclization may proceed with the radical and the double bond which is conjugated with aromatic ring.
From **2-11a**, cyclization proceeds with a loss of conjugation.
Substitution might play a role in decoujugation. (shown in 3-2-2)

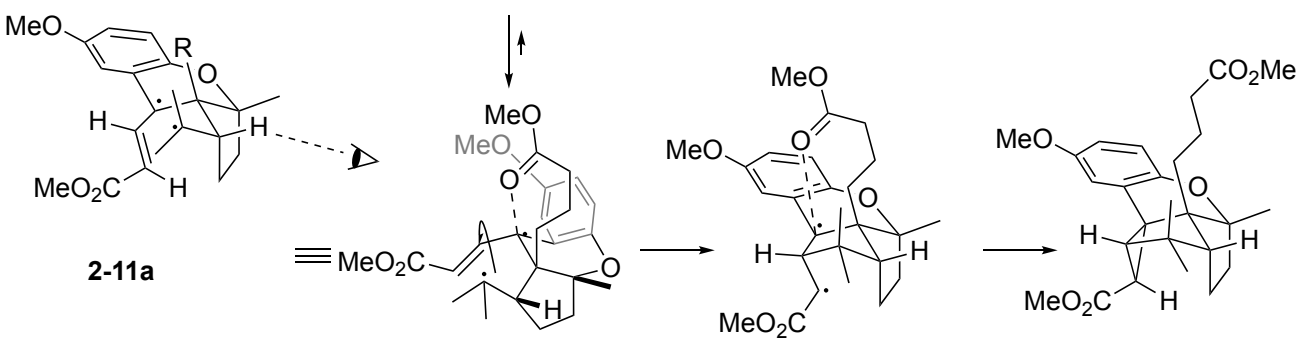
3-2-2. Electronic and steric effects of substitution

3-2-2-1. Donate electrons to radical



2-11a-1

There is no documentary evidence of this type of electron donation. The radical at the ketone γ-position is electron-rich and is unlikely to intaract with oxygen atom.



2-11a **2-11a-2** **2-12"** **2-6**

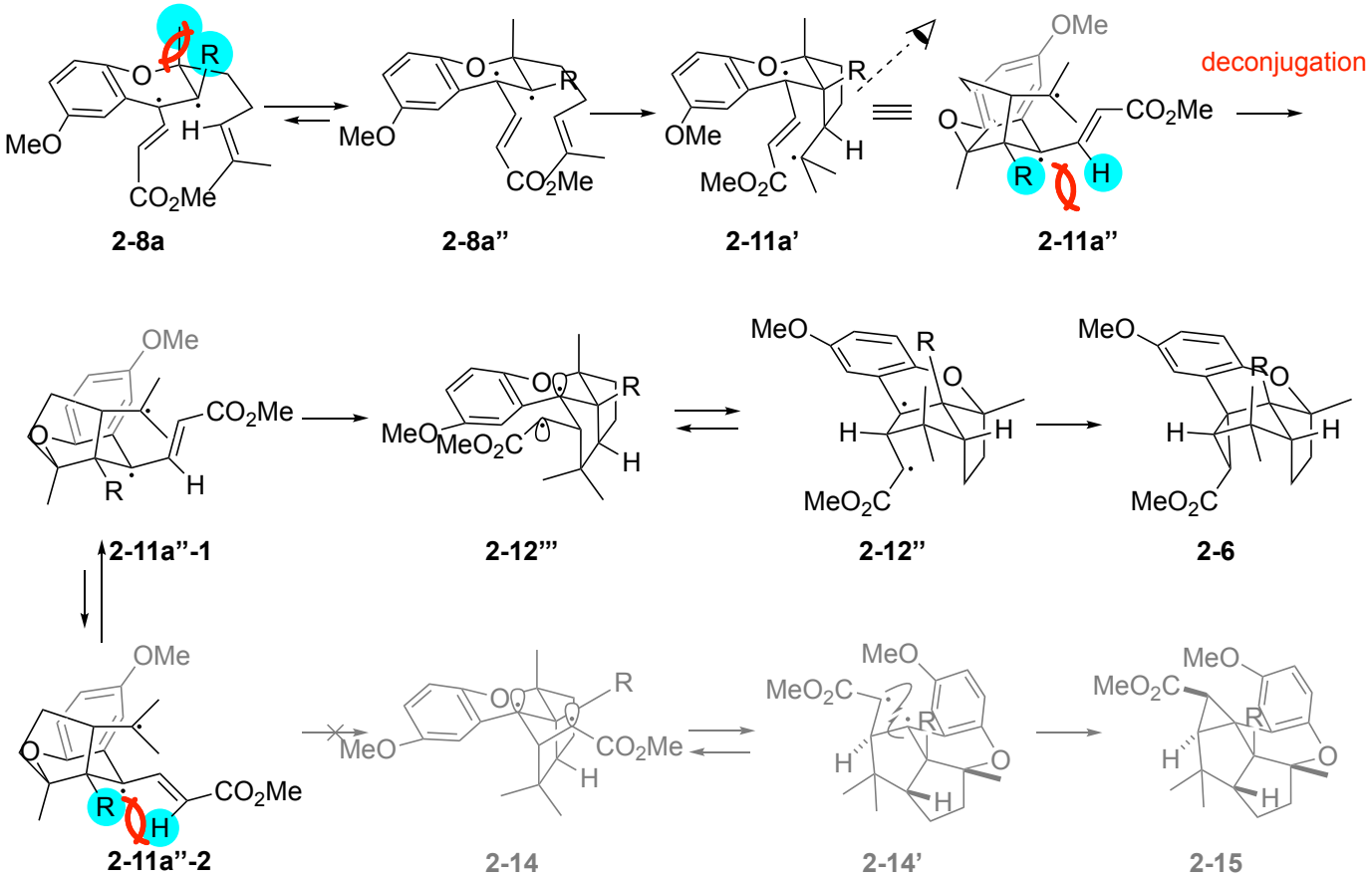
Electronic and steric effect

· Oxygen atom may donate electron to the benzyl radical. The radical turns to sp^3 state from sp^2 state. The conformation of six-membered ring fixed to boat.

· The carbonyl α- and γ- positions become electron-rich and β-position is electron deficient. Therefore, the reactivity of β-position against nucleophilic radical is relatively increase.

· Steric hinderance shown in **2-11a-1** results in the formation of a single diastereomer.

3-2-2-2. Change the conformation of the six-membered ring from boat to chair.



Only steric effect

· The steric hindrance between R and Me results in the formation of the six-membered ring change to chair. The steric hindrance indicated in **1-11a”** is generated, which causes deconjugation between the enone and aromatic ring.

· Steric hinderance shown in **2-11a”-2** result in the formation of a single diastereomer.

References:

1) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 14.
2) Shao, H.; Gao, X.; Wang, Z.; Gao, Z.; Zhao, Y. *Angew. Chem. Int. Ed*. **2020**, *59*, 7419.
3) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190.