

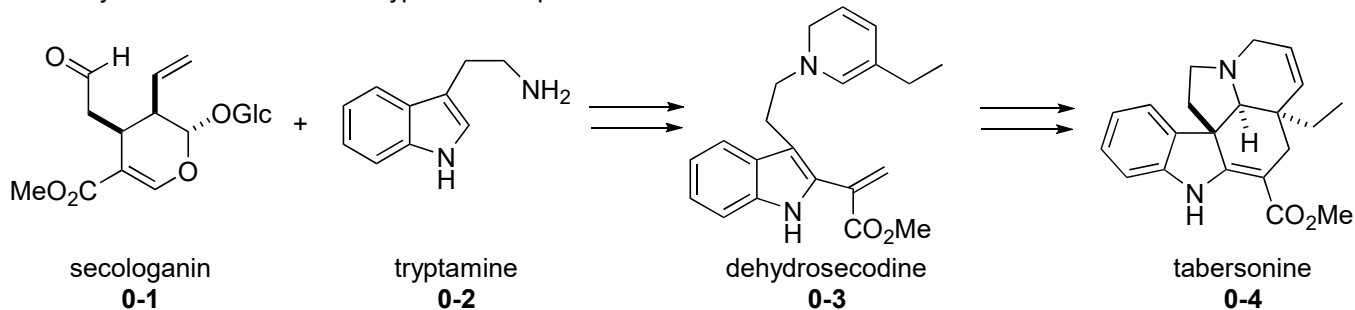
Problem Session (1) -Answer-

2016.10.24. Tsukasa Shimakawa

Topic: tabersonine type monoterpene indole alkaloid

0. Introduction

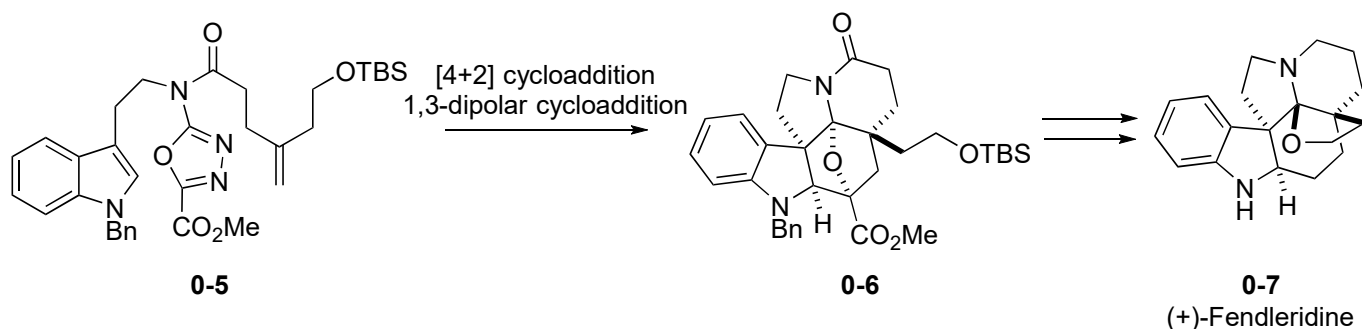
0-1. Biosynthesis of tabersonine type monoterpene indole alkaloid



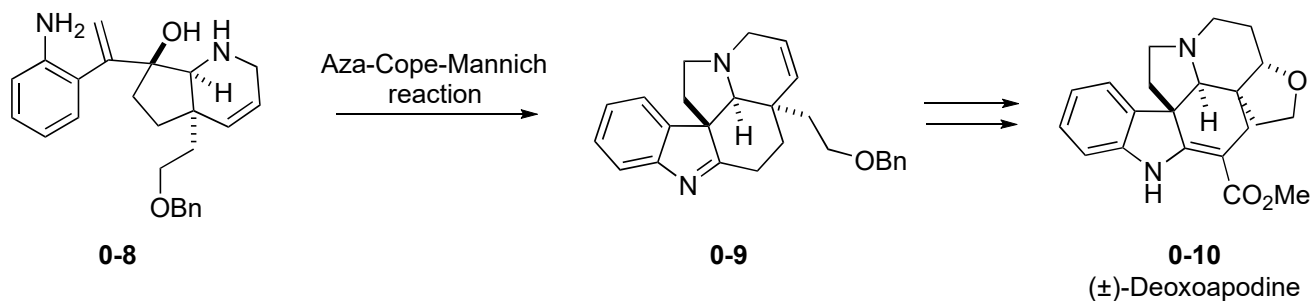
Connor, S. E. and Maresh, J. J. *Nat. Prod. Rep.* **2006**, 23, 532.

0-2. Synthetic study of tabersonine type skeleton

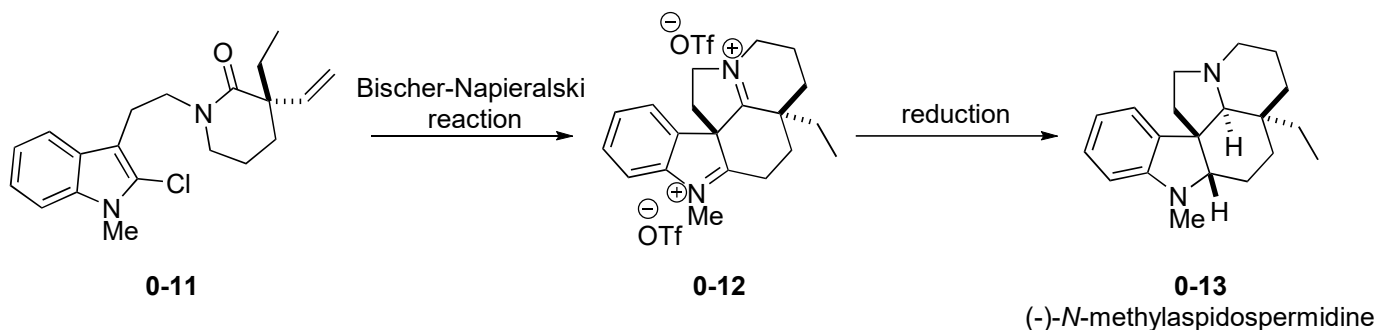
0-2-1. Cascade pericyclic reaction (Boger, D. L *et al.*, *J. Am. Chem. Soc.* **2010**, 132, 3009.)



0-2-2. Aza-Cope-Mannich reaction (Overman, L. E *et al.*, *J. Am. Chem. Soc.* **1991**, 113, 2598.)

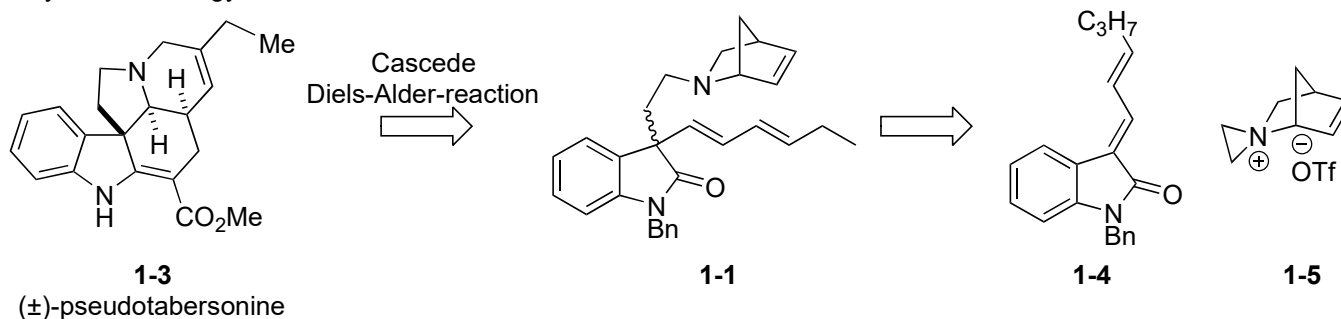


0-2-3. Double cyclization strategy (Movassaghi, M *et al.*, *Angew. Chem. Int. Ed.* **2012**, 124, 4650.)



1. Total synthesis of (±)-pseudotabersonine

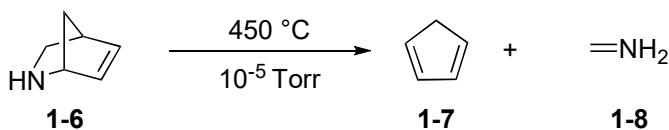
1-1. Synthetic strategy



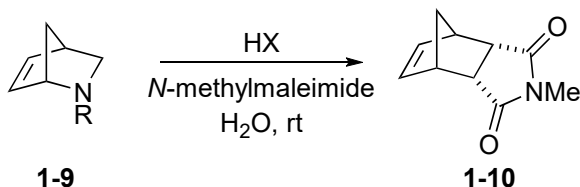
1-2. Introduction of azanorbornene

Norbornene is resistant to thermolysis, requiring temperatures in excess 250 °C^a).

Retro-Diels-Alder reaction of azanorbornene have commonly conducted at temperatures in the range of 450-600 °C^b).



However, acid catalyzed Retro-Diels-Alder reaction of azanorbornene undergoes at room temperature^c).

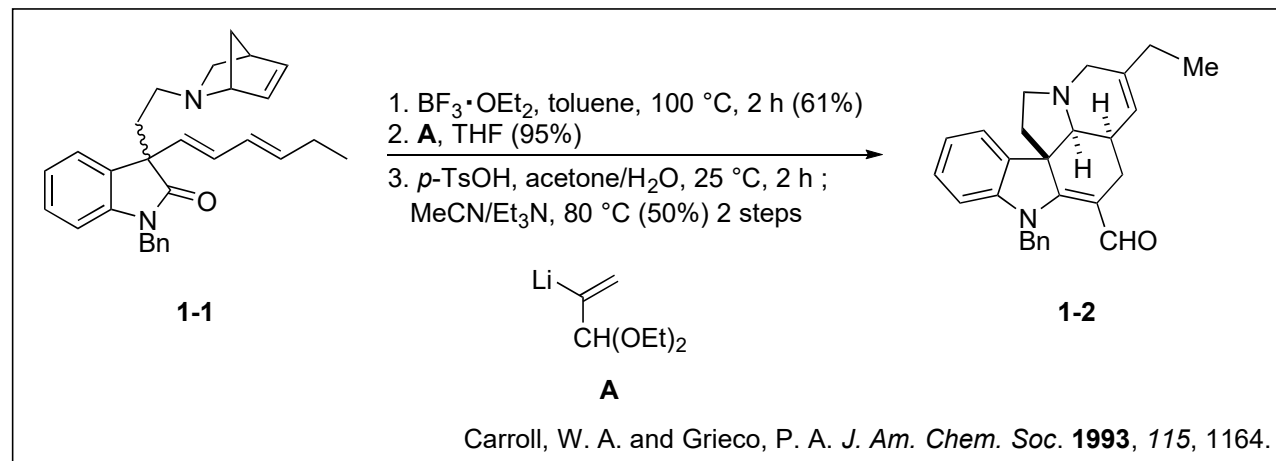


^a) Walsh, R.; Wells, J. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 52.

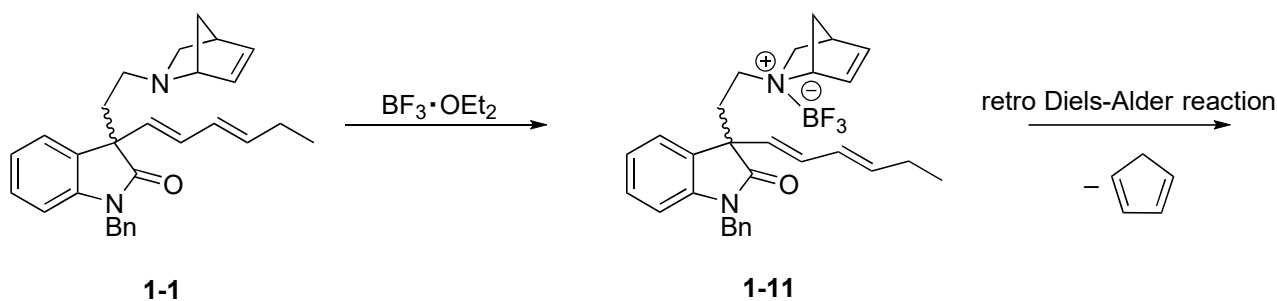
^b) Braillon, B *et al.*, *Nouv. J. Chim.* **1982**, 6, 121.

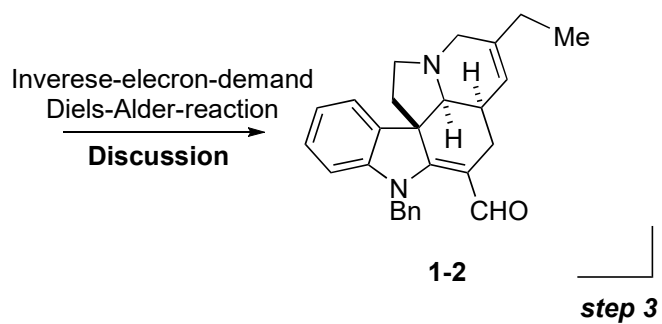
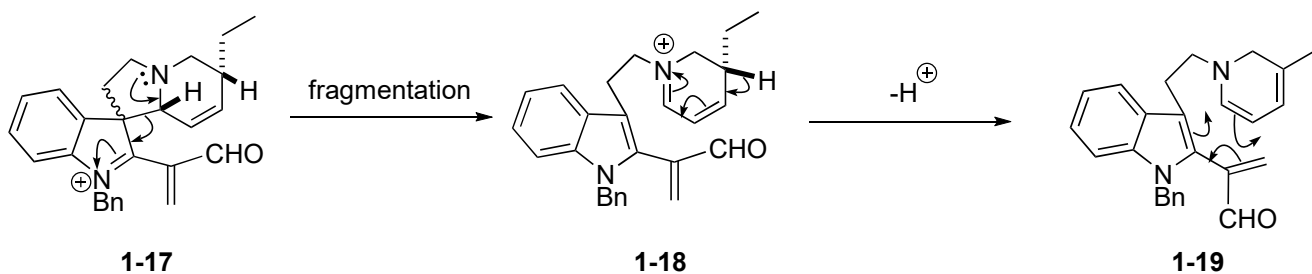
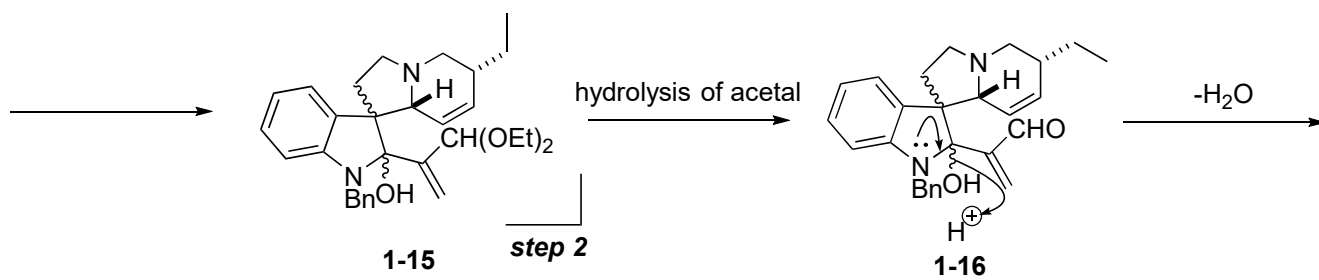
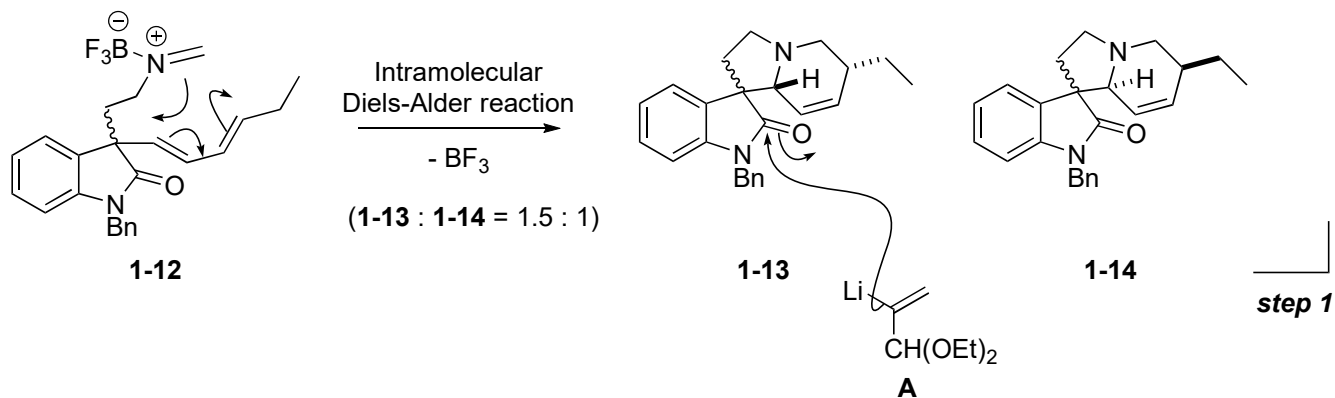
^c) Grieco, P. A *et al.*, *J. Am. Chem. Soc.* **1987**, 109, 5859.

1-3. Reaction mechanism



Key Point: Cascade Diels-Alder reaction

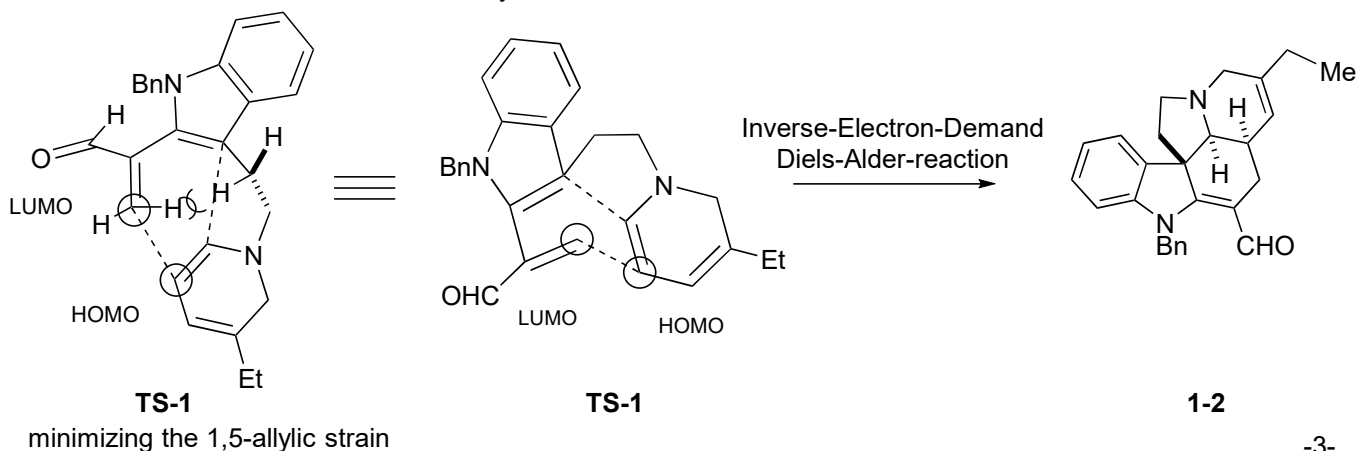




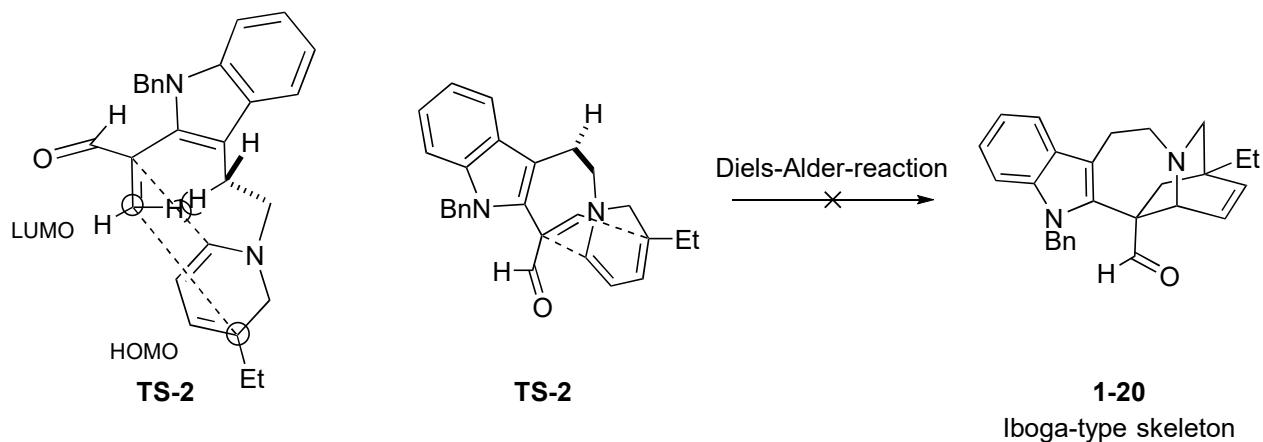
1-3. Discussion

1-3-1. Diastereoselectivity of Intramolecular Diels-Alder reaction

The conformation is fixed due to the 1,5-allylic strain.

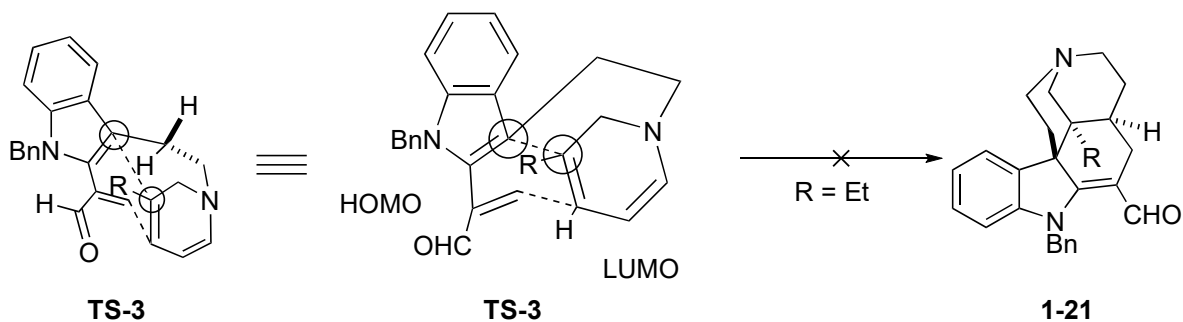


Another type of intramolecular Diels-Alder-reaction



minimizing the 1,5-allylic strain

This type of cycloaddition would be occurred. However, **1-20** contains seven-membered-ring, so, retro Diels-Alder reaction would be fast, and thermodynamically favored is only obtained.

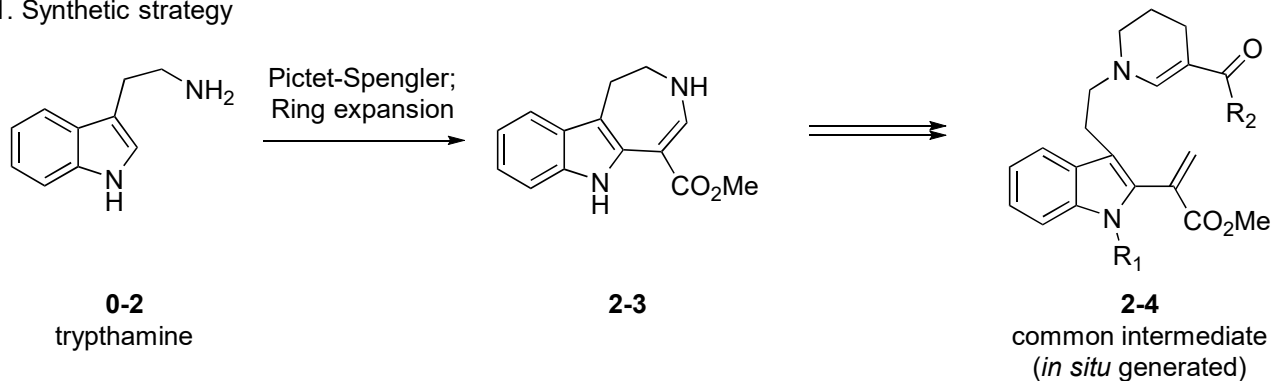


minimizing the 1,5-allylic strain

From the view of orbital coefficients of HOMO and LUMO, this format of cycloaddition is unfavored.

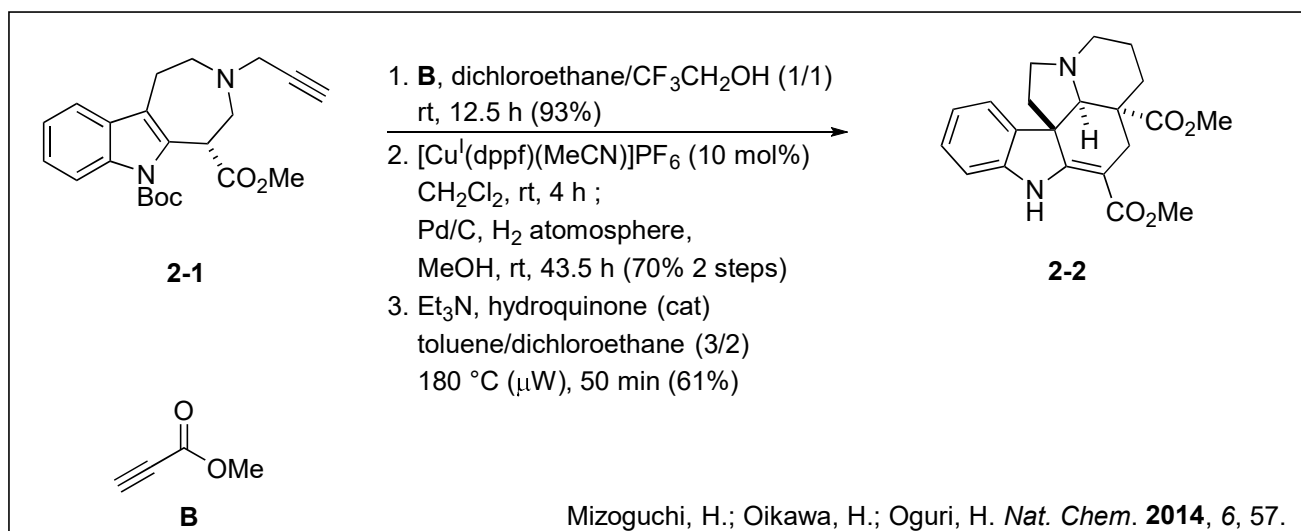
2. Unified synthesis of monoterpene indole alkaloid skeleton

2-1. Synthetic strategy

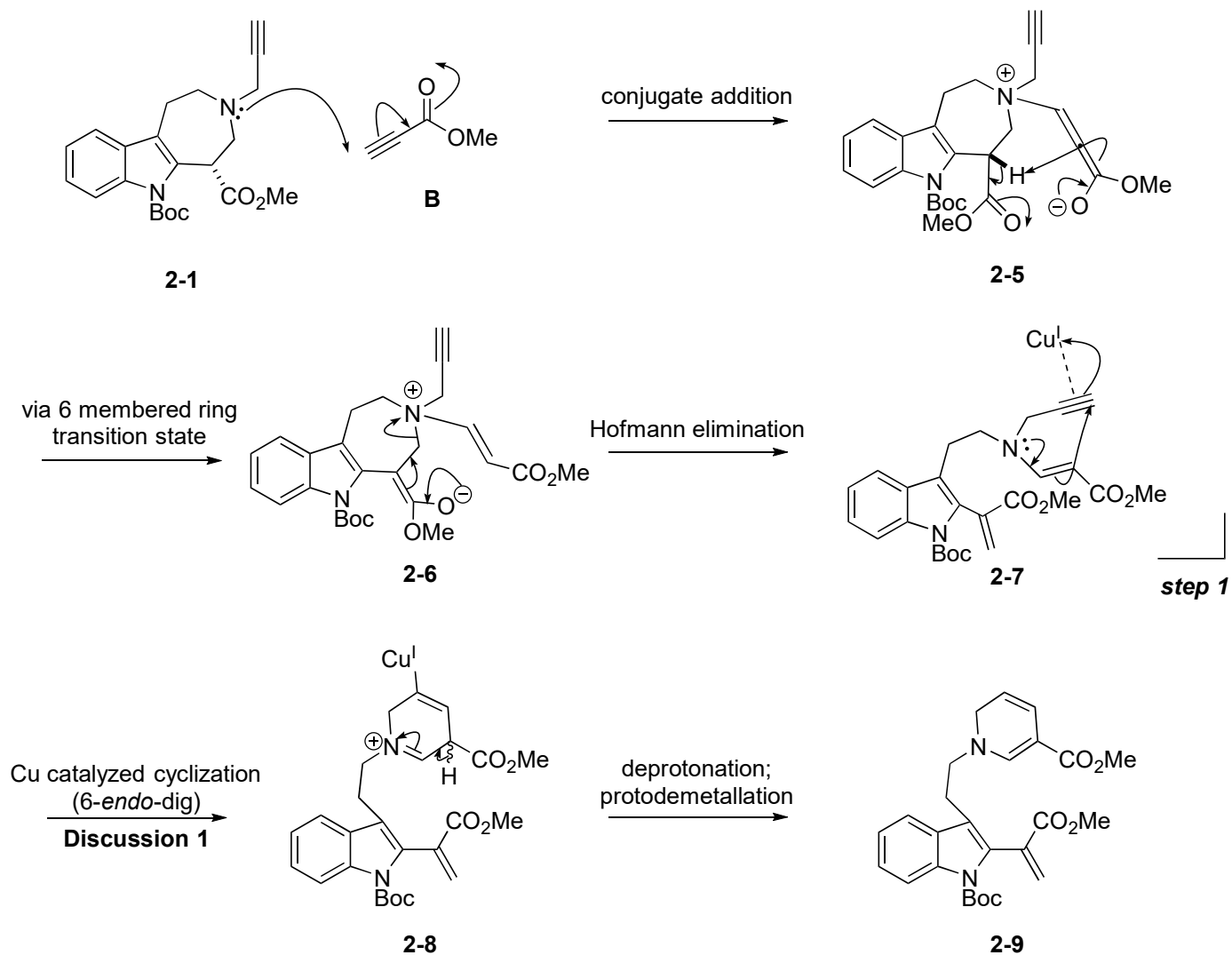


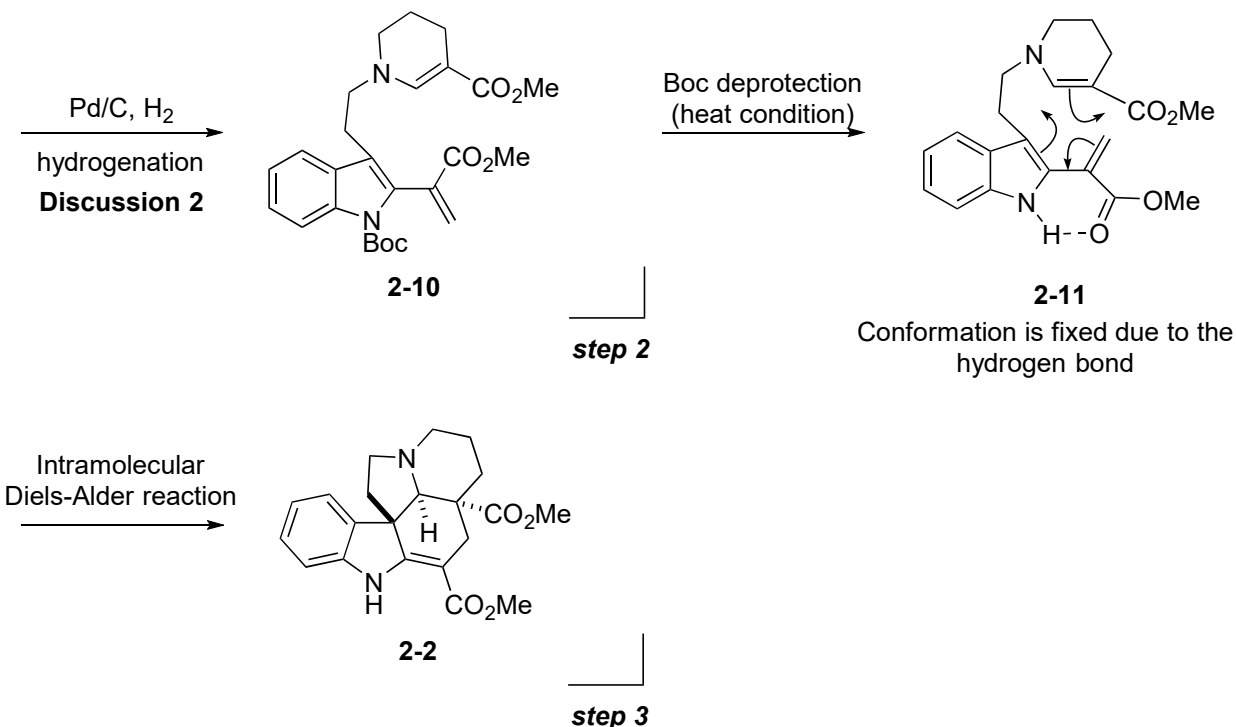
⇒ various type monoterpene indole alkaloid
(Iboga type, Aspidosperma type, Andranginine type, Ngouniensine type)

2-2. Reaction mechanism



Key Points: Hofmann elimination. Cu catalyzed DHP ring formation. Intramolecular Diels-Alder reaction.





2-3. Discussion

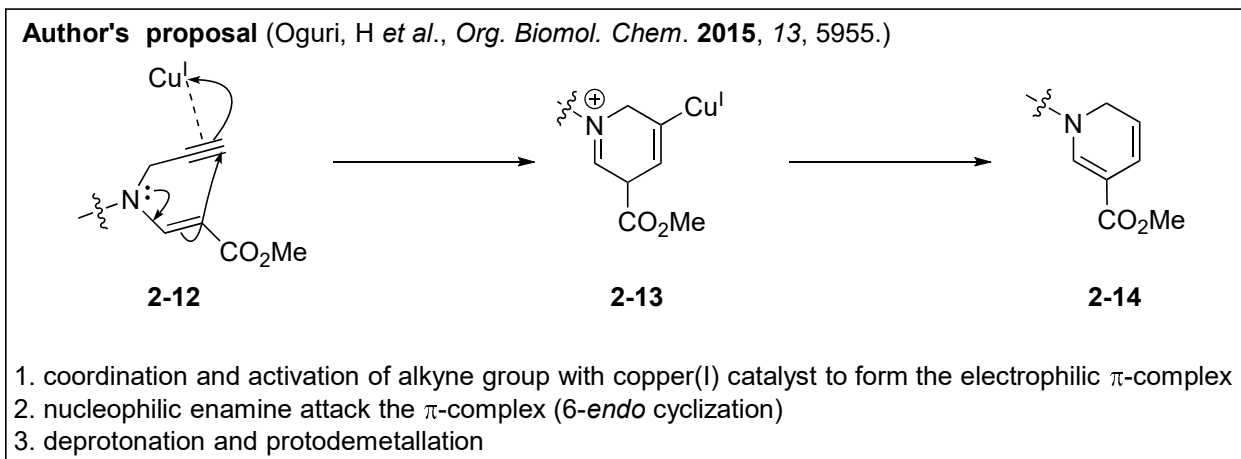
2-3-1. Cu(I) catalyzed DHP ring formation (5-*exo*-dig vs 6-*endo*-dig)

Other examples of Metal catalyzed cyclization of *N*-propargyl enamine derivatives

Kim, H. and Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 6336. (Rh catalyzed)

Filisti, E *et al.*, *Org. Lett.* **2008**, *10*, 2629. (Cu catalyzed)

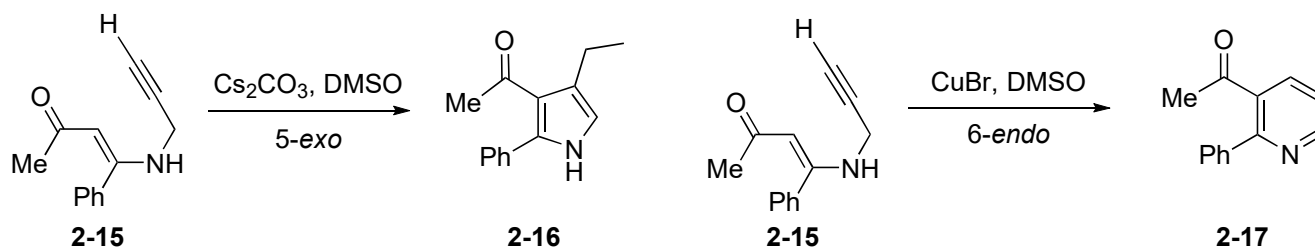
Bonaccorso, H. G *et al.*, *Tetrahedron Lett.* **2013**, *54*, 847. (Ag catalyzed)



Following to this reaction mechanism, 5-*exo* cyclization would be possible.

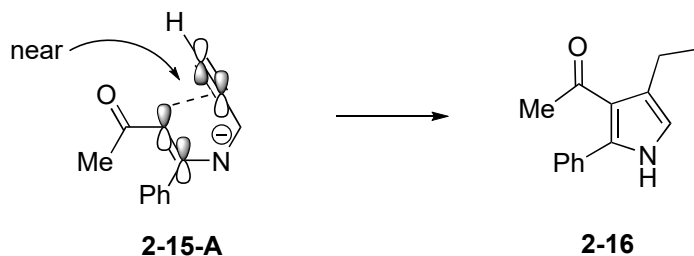
Format of cyclization is different whether used catalyst is base or transition metal.

(Filisti, E *et al.*, *Org. Lett.* **2008**, *10*, 2629.)



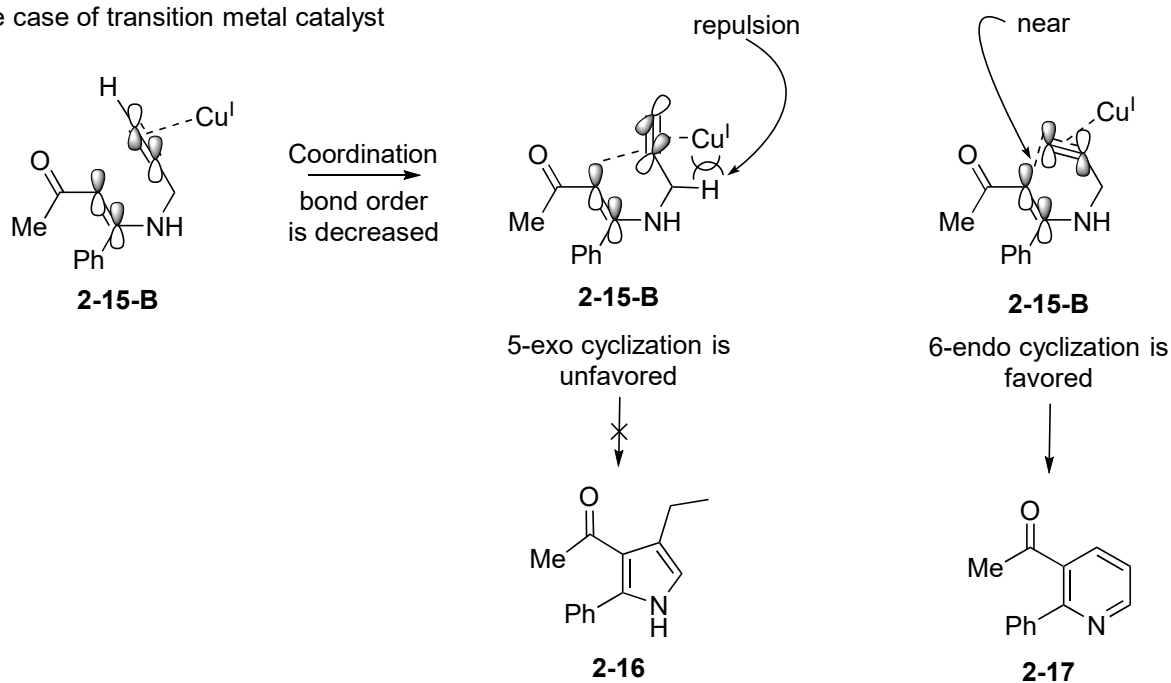
Coordination of the C-C triple bond to the transition metal would decrease its bond order. Therefore, the form of cyclization would be changed.

· the case of base catalyst



5-exo cyclization is favored

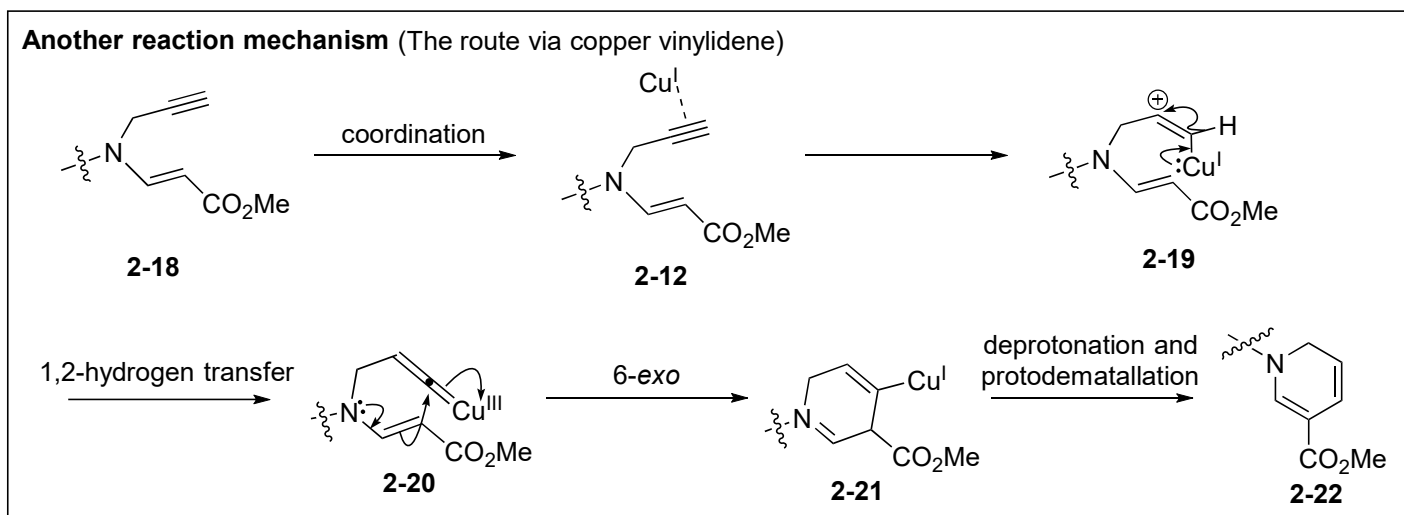
· the case of transition metal catalyst



From the calculational experiment*, in the case of π -alkyne complex, the angle of $C\equiv C-R$ is about 160 degrees. In other words, the angle is about 20 degrees shifted. Therefore, the form of cyclization would be changed.

* Morokuma, K et al., *J. Am. Chem. Soc.* **1994**, *116*, 8105.

Valerga, P et al., *J. Am. Chem. Soc.* **2003**, *125*, 3311.

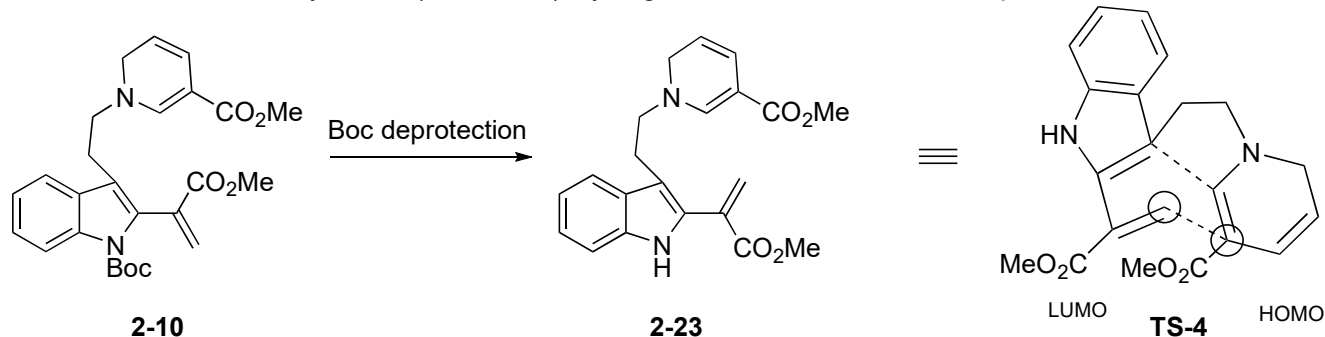


From the calculation experiment*, in the case of Ru(II) complex, vinylidene form is more stable than π -alkyne form. In addition, 1,2-hydrogen migration is occurred when acetylene π -coordination form converts to vinylidene form. If the reaction proceeds via copper vinylidene, the possible format would be only 6-exo cyclization.

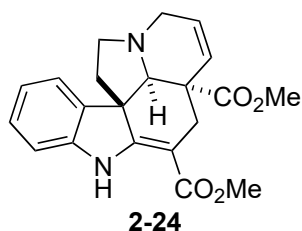
*Morokuma, K et al., *J. Am. Chem. Soc.* **1994**, *116*, 8105.

2-3-2. The reason hydrogenation is needed

Referred to the Grieco's synthesis (**Problem 1**), hydrogenation would be useless step.

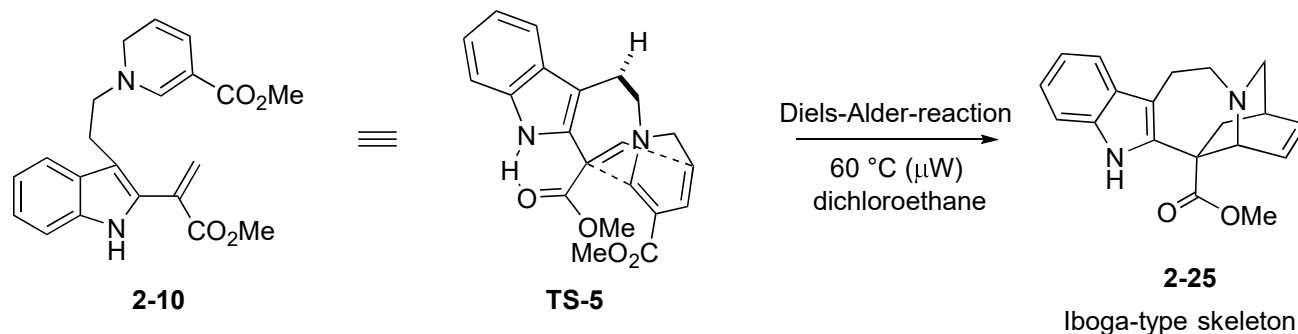


Inverse electron demand
Diels-Alder reaction



The energy level of HOMO is decreased because of the electronwithdrawing group.

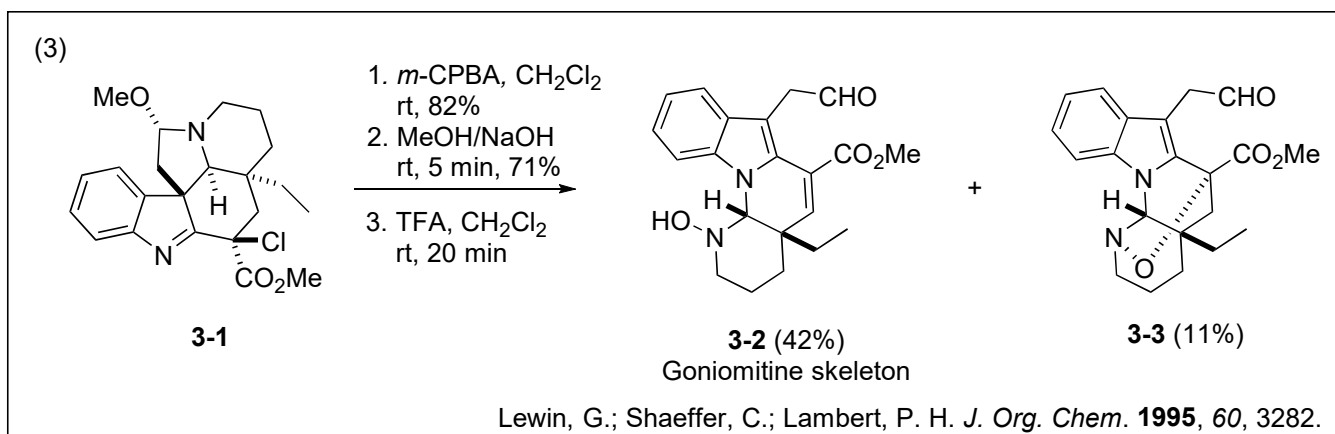
Under the condition of Intramolecular Diels-Alder reaction, **2-24** is not obtained. However, Iboga-type skeleton product **2-25** is obtained.



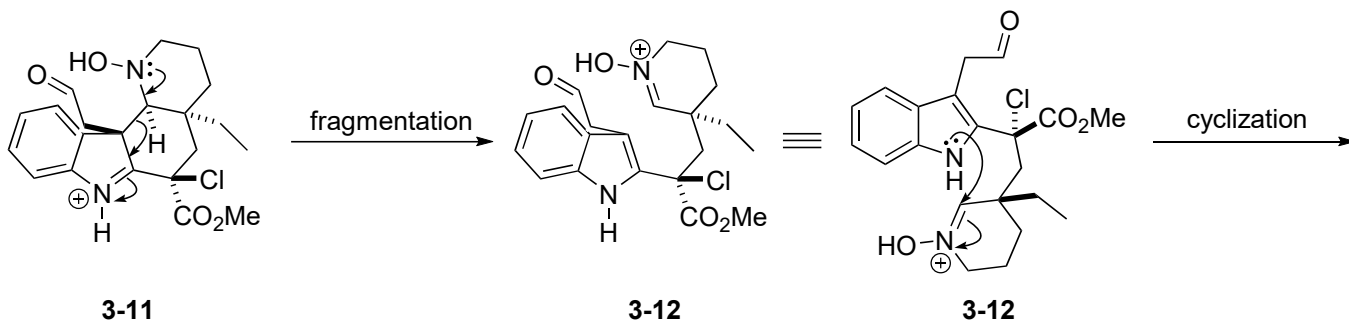
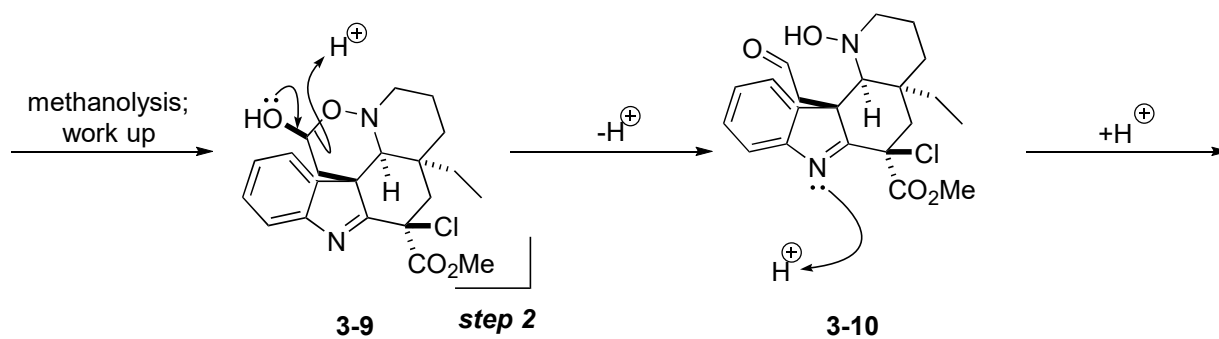
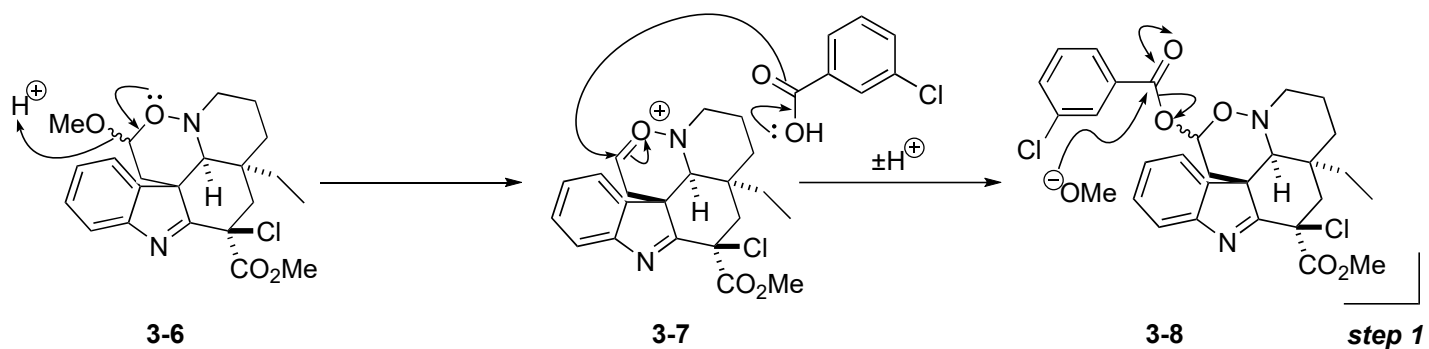
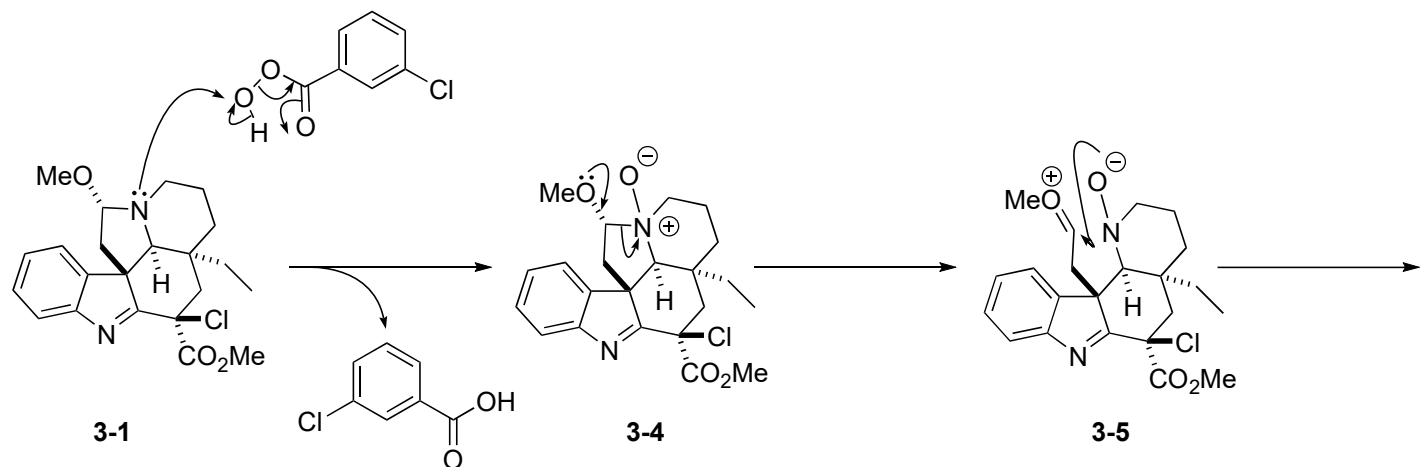
Due to the hydrogen bond, the energy level of LUMO is decreased. Therefore, this type of cycloaddition is favored.

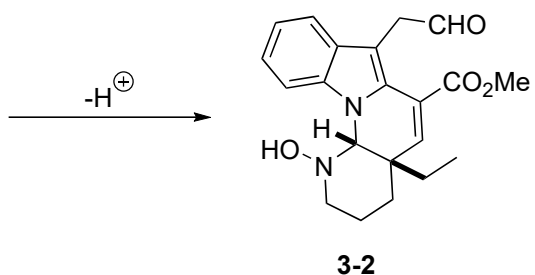
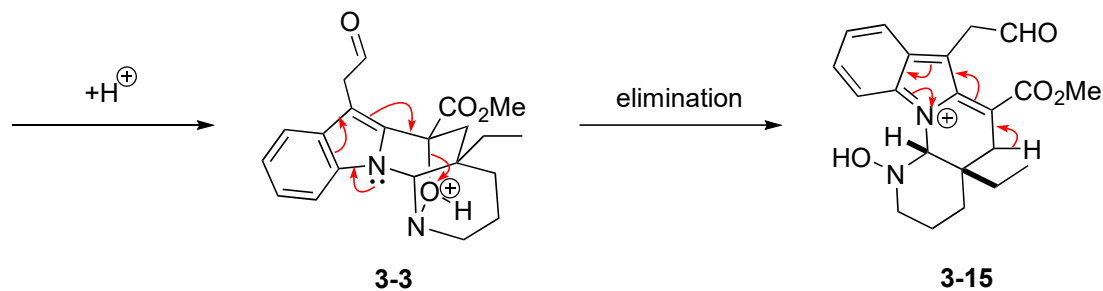
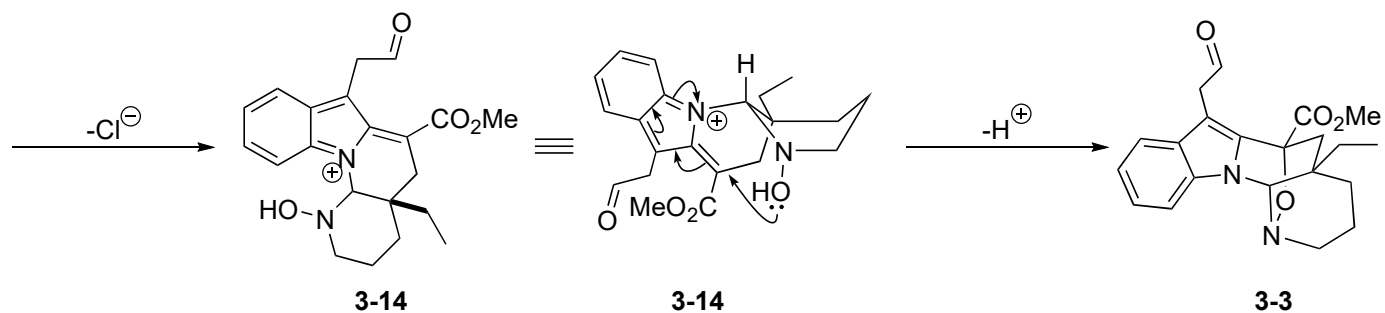
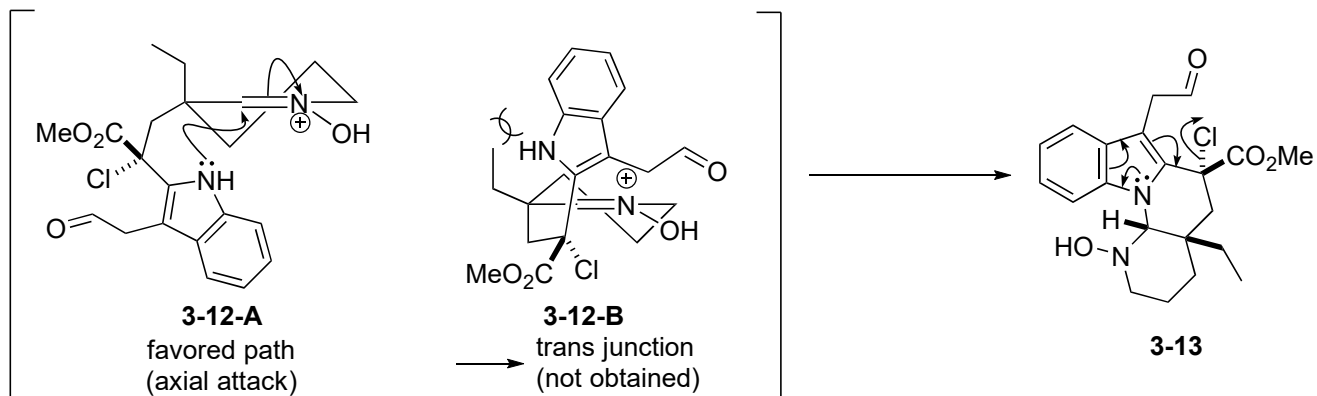
3. Conversion of the skeleton from tabersonine type to Goniomitine type

3-1. Reaction mechanism



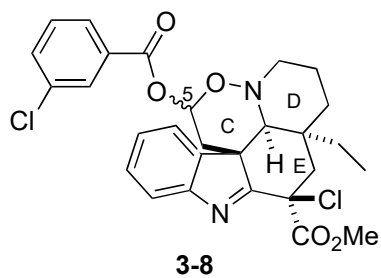
Key Point : *m*-CPBA mediated ring expansion





4-2. Discussion

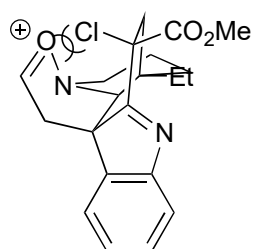
4-2-1. Stereochemistry of C5



Stereochemistry of C5 $\alpha : \beta = 3 : 1$ or $1 : 3$

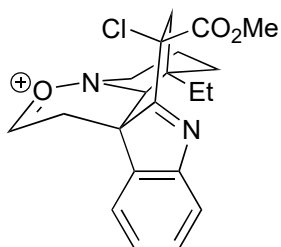
C,E ring: Boat conformation
 D ring: Chair conformation

C, D ring: cis junction



3-7

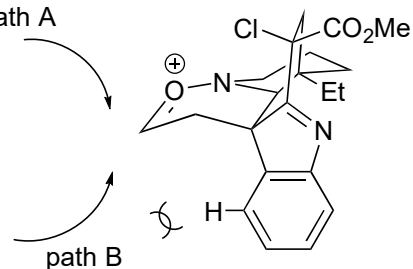
C, D ring: trans junction



3-7

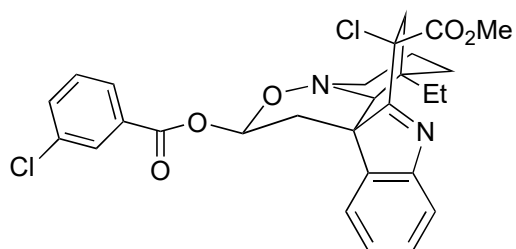
trans junction form is more stable than cis junction form.

path A



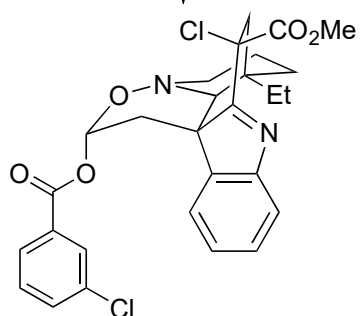
3-7

path A



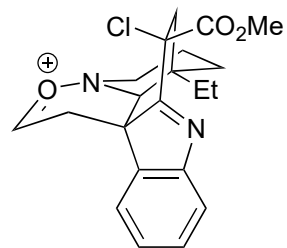
3-17

kinetically and thermodynamically favored



3-16

H⁺



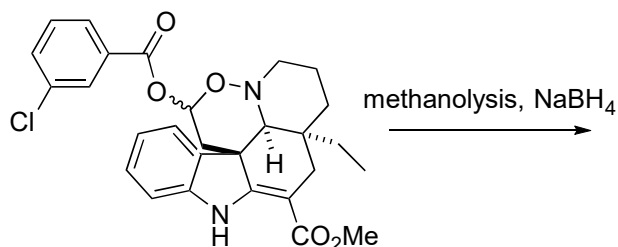
3-7

thermodynamically unfavored due to the 1,3-diaxial interaction

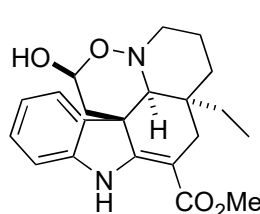
4-2-2. Stereochemistry of C5 after methanolysis

From the paper, stereochemistry of C5 after methanolysis is only β .

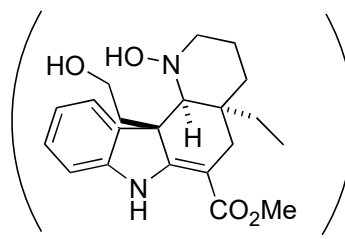
Methanolysis of analog **3-18** in the presence of NaBH₄, **3-19** is only obtained



3-18



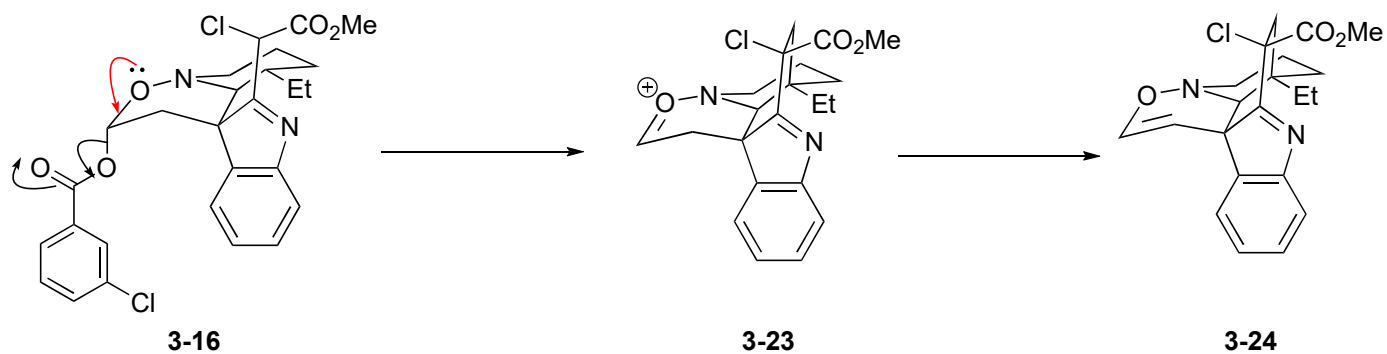
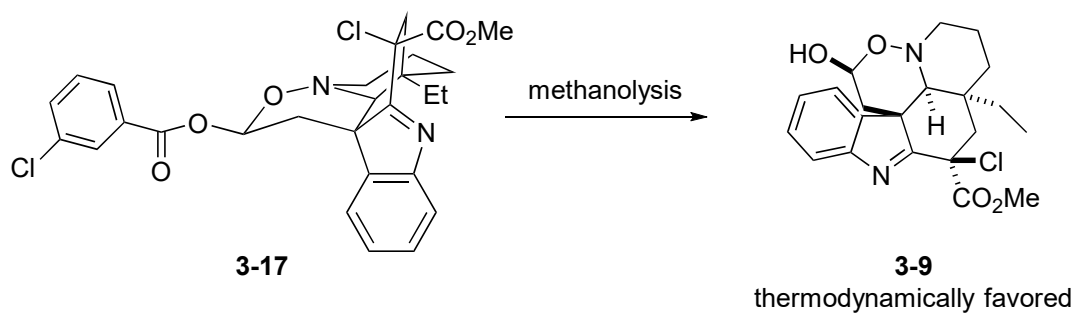
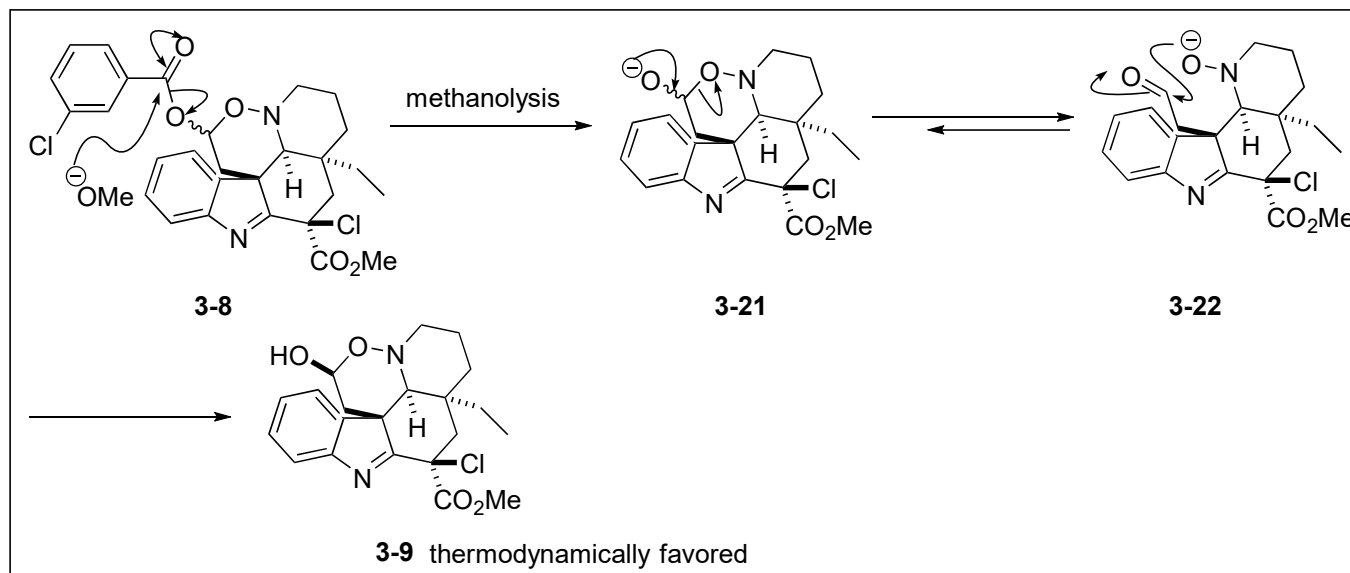
3-19



not obtained

3-20

From the model experiment in page 11, the reaction mechanism below is denied.



Under the condition of methanolysis, α would be converted to enol ether.

Because of the 1,3-diaxial interaction, approaching the methoxide ion to the hydrogen would be faster than methanolysis.