

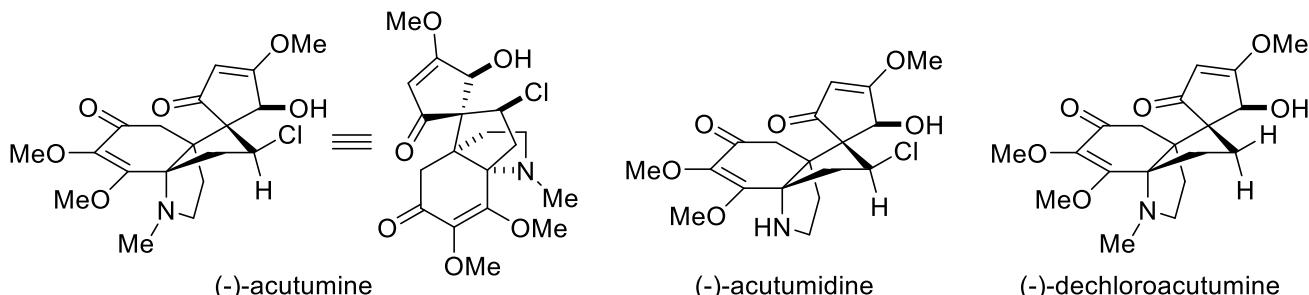
Problem session (1) Answer

2015. 10. 16. Kotaro Tokumoto

Topic: A total synthesis of (-)-Acutumine by Herzog's group

King, S. M.; Calandra, N. A.; Herzog, S. B. *Angew. Chem. Int. Ed.* **2013**, 52, 3642.

Introduction: About acutumine



◆ Isolation:

First obtained from the roots of *Sinomenium acutum* Rehd et Wils (Japanese name: Oh-tsuzurafuji) in 1929

Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, 4, 220.

◆ Pharmacological activity:

- i) Selective T-cell cytotoxicity

Yu, B.-W. *et al.*, *Phytochemistry* **2002**, 61, 439.

- ii) Antiamnesic properties

Qin, G.-W. *et al.*, P. PCT. Int. Appl. WO 20040000815, 2003.

◆ Structure:

The structure was determined in 1971.

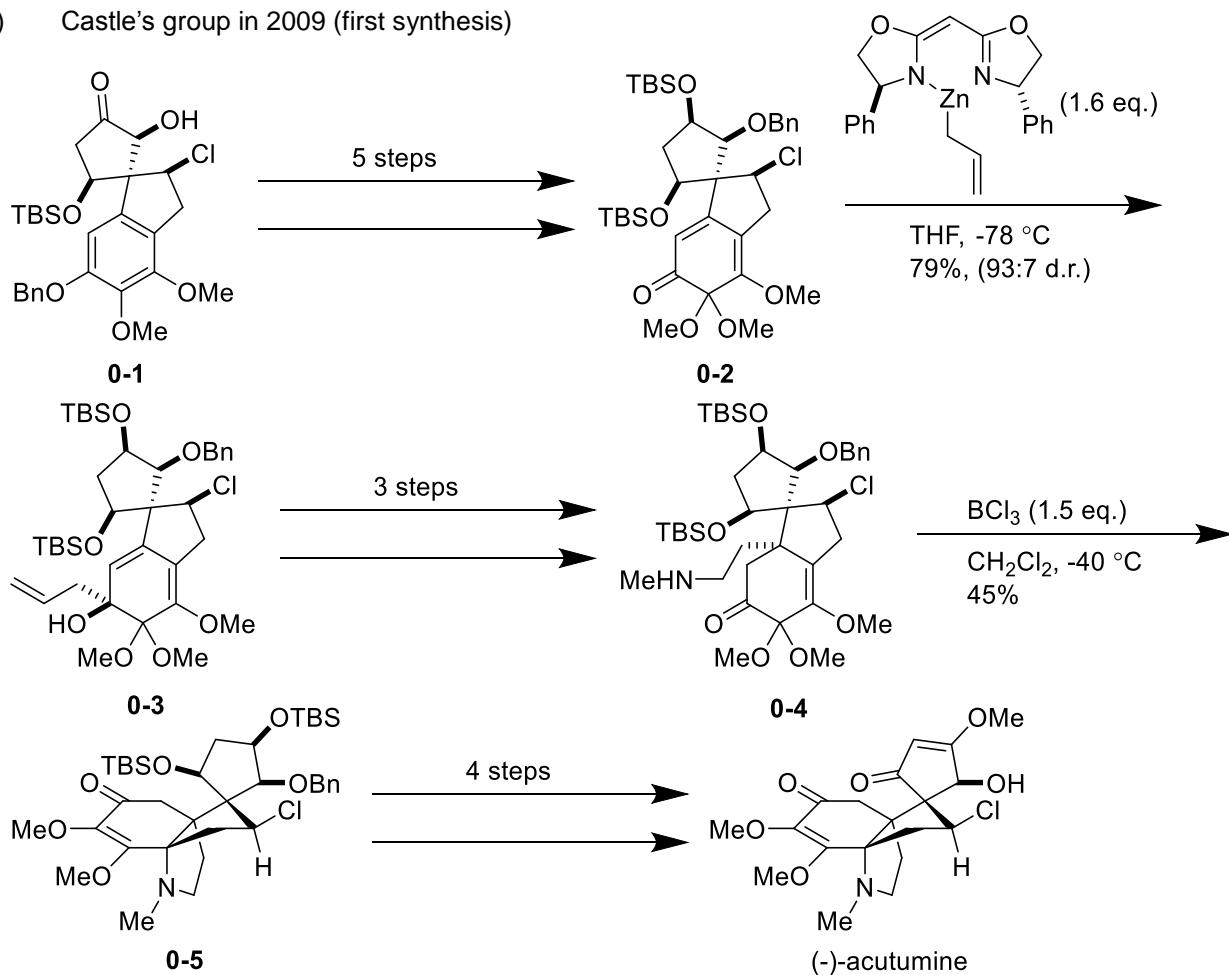
Tomita, M. *et al.*, *Chem. Pharm. Bull.* **1971**, 19, 770.

Structural features:

- i) A [4.3.3]propellane-type system
- ii) A spirocycle
- iii) A neopentyllic secondary chloride

◆ Total synthesis:

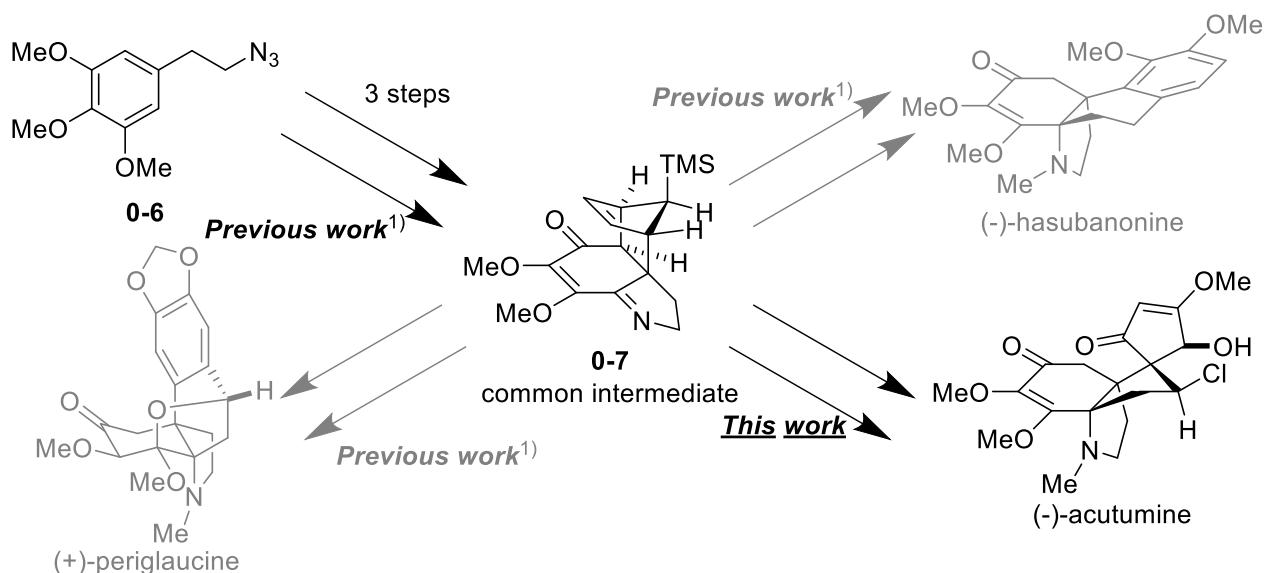
- i) Castle's group in 2009 (first synthesis)



Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc.* **2009**, 131, 6674.

(For more details, please see Amaoka-san's LS on 2010/01/06.)

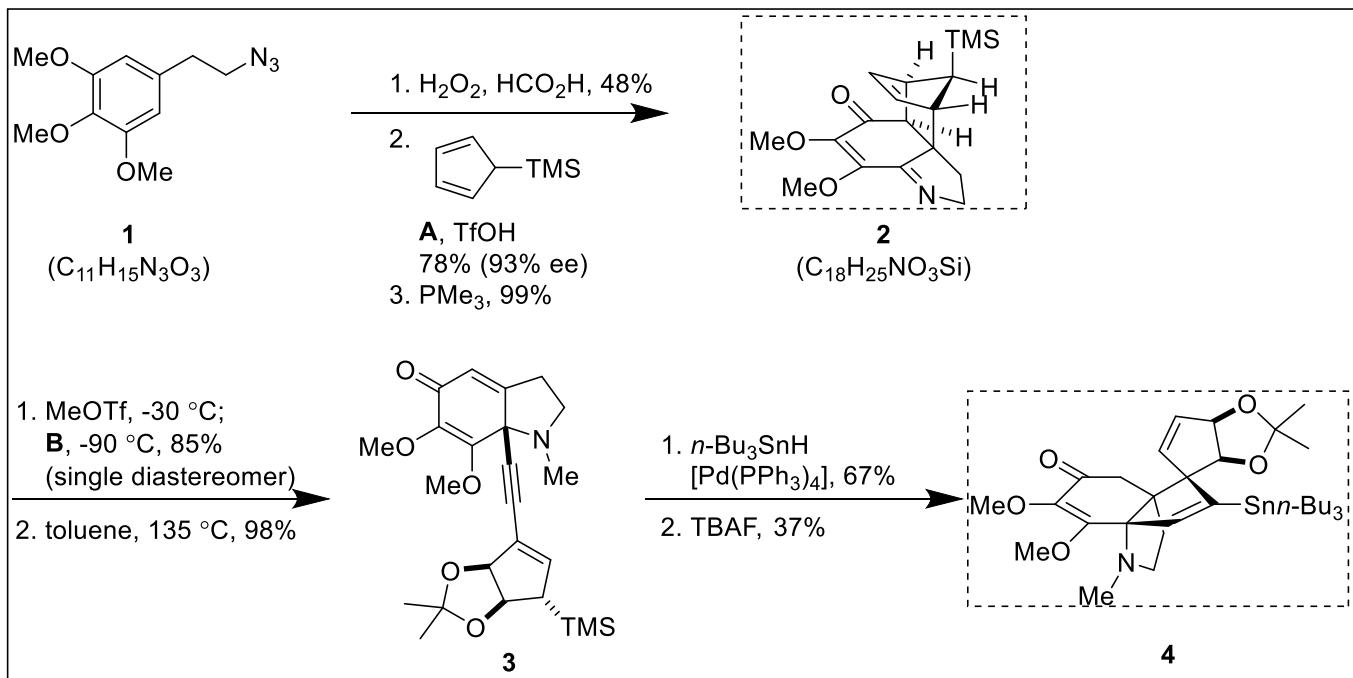
- ii) Herson's group in 2013 (this problem)



1) Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chemie* **2011**, 123, 9025.

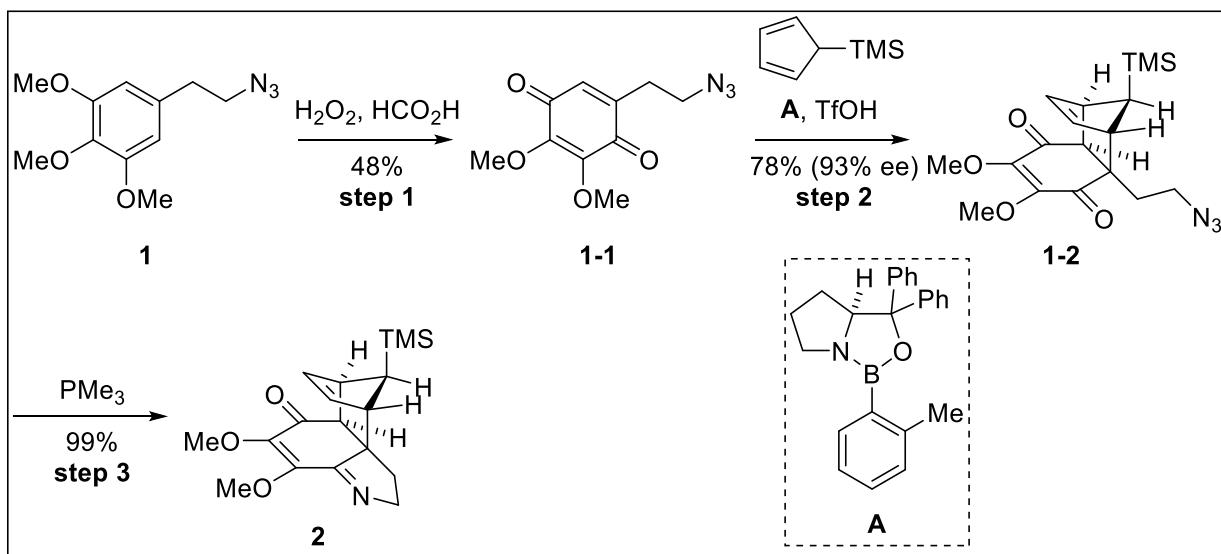
Answer:

Q1.



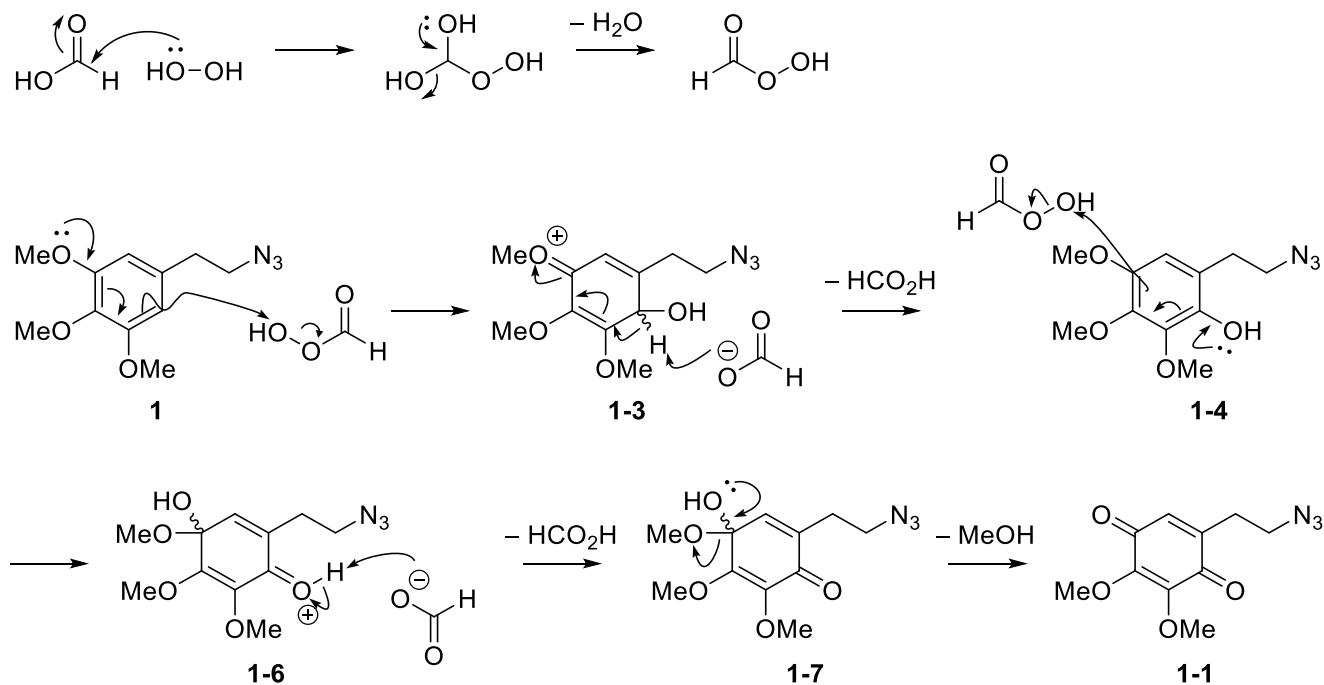
Q2.

◆ 1 to 2

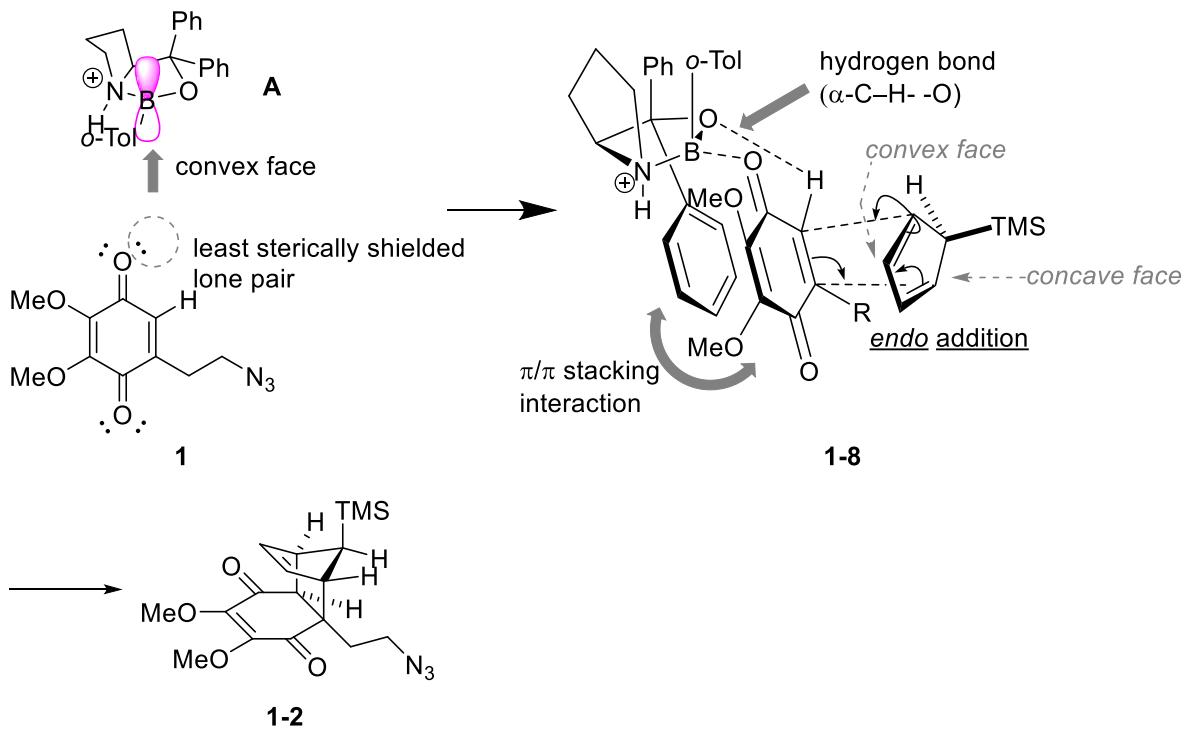


Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chemie* **2011**, 123, 9025.

step 1: Generation of performic acid and oxidation of 1 to form quinone 1-2



step 2: regio- and stereoselective Diels-Alder reaction catalyzed by the chiral oxazaborolidinium cation A



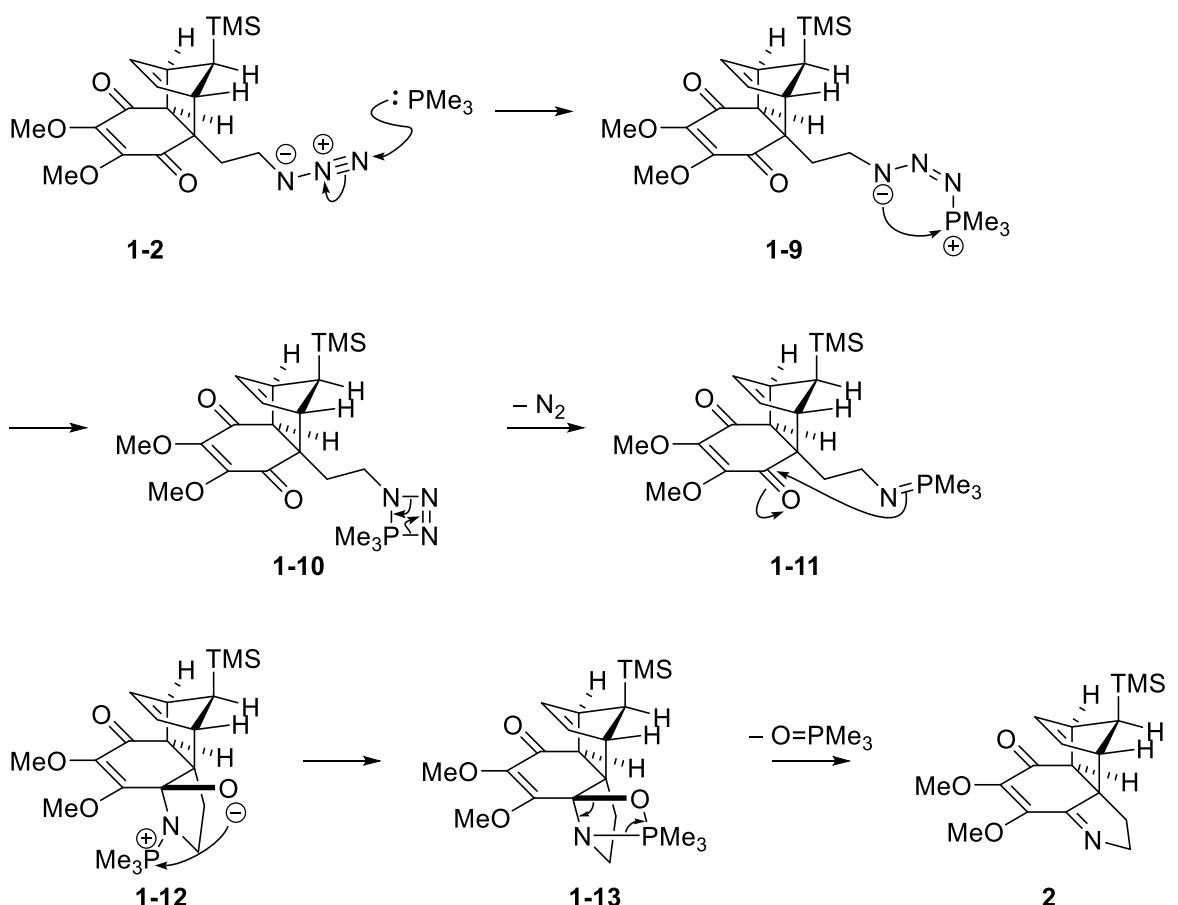
For details about Diels-Alder reaction catalyzed by chiral oxazaborolidinium cation:

Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, 124, 3808.

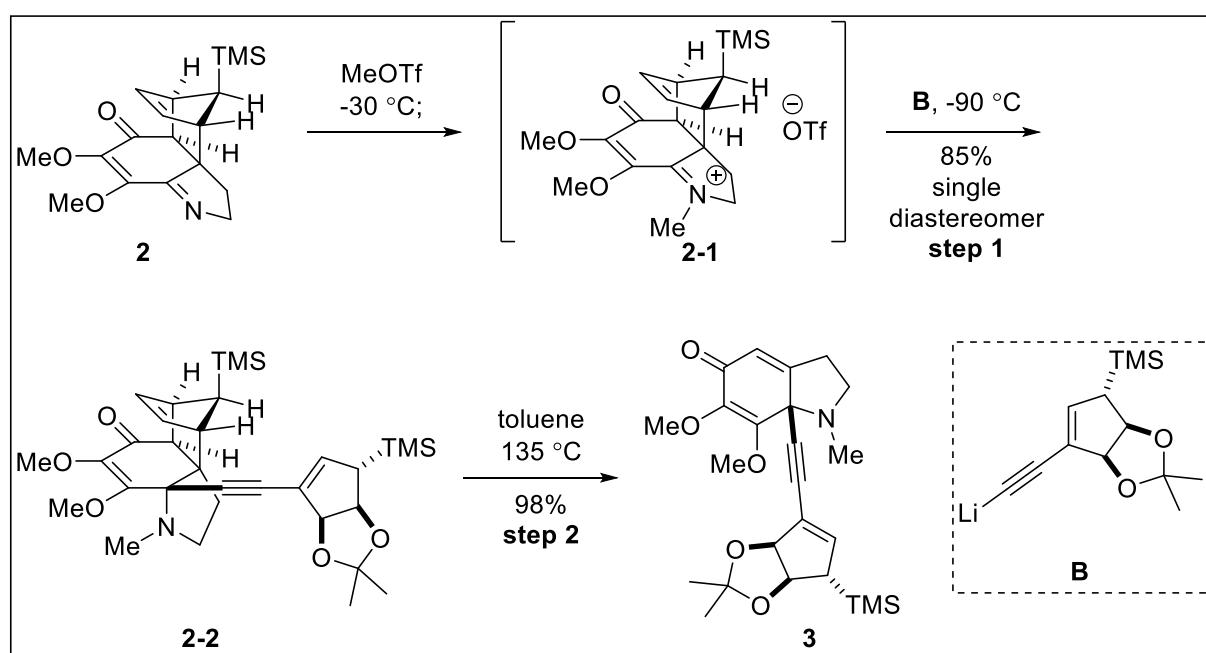
Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, 124, 9992.

Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, 126, 4800.

step 3: Staudinger reduction to form imine **2**

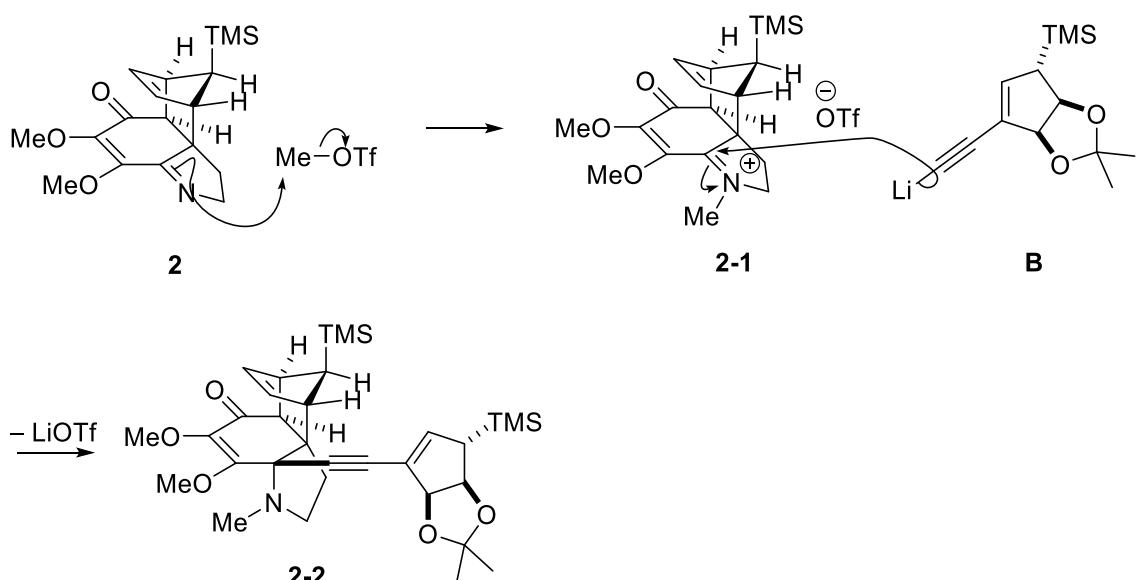


◆ **2 to 3**

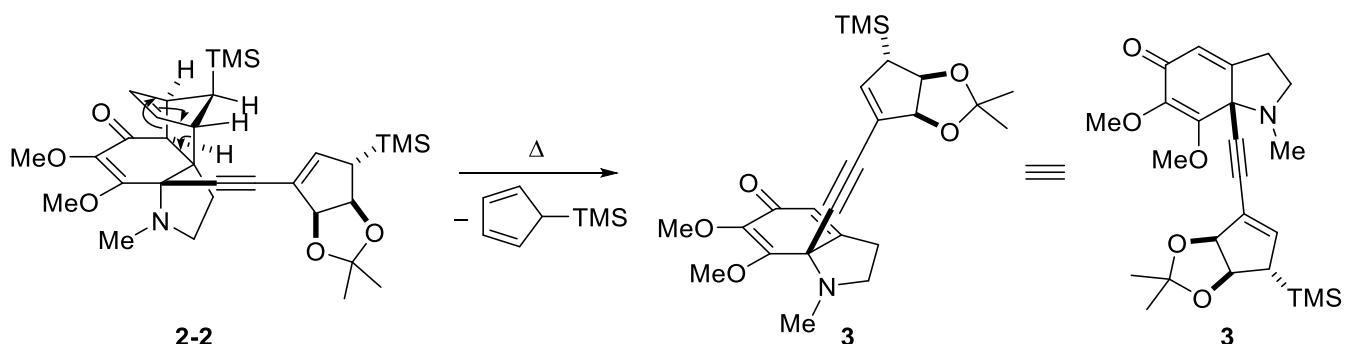


King, S. M.; Calandra, N. A.; Herzon, S. B. *Angew. Chem. Int. Ed.* **2013**, 52, 3642.

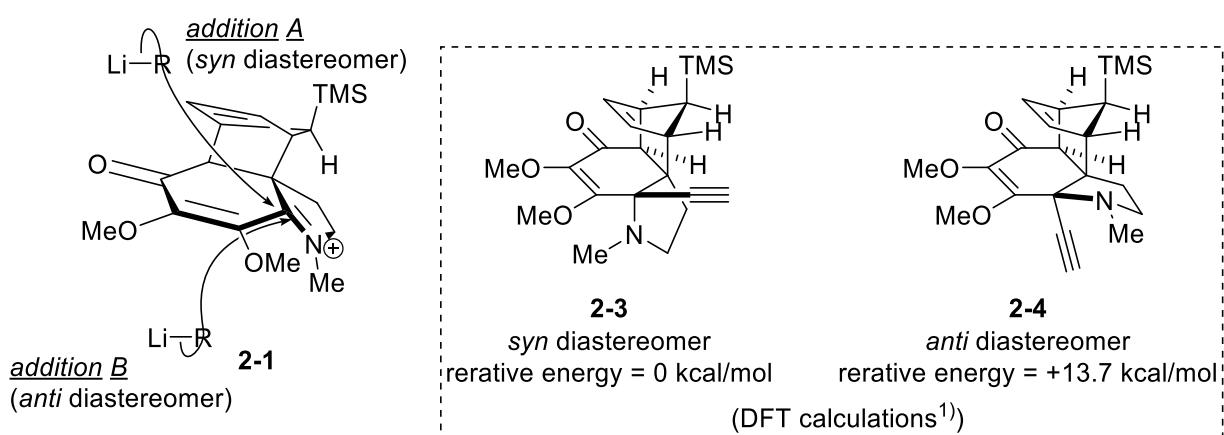
step 1: *N*-methylation followed by addition of the lithium acetylide **B**



step 2: retro-Diels-Alder reaction



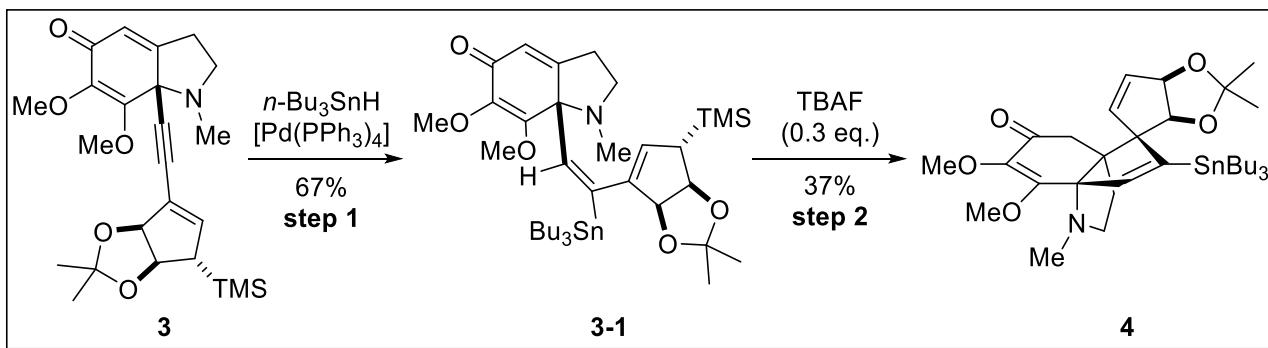
Discussion: stereoselectivity of addition of **B**



- Steric hindrance of methoxy group and *N*-Methyl group prevents the addition B.
- Strain associated with the *anti* addition to form the *anti*-6,5 ring in **2-4** seems unfavored.

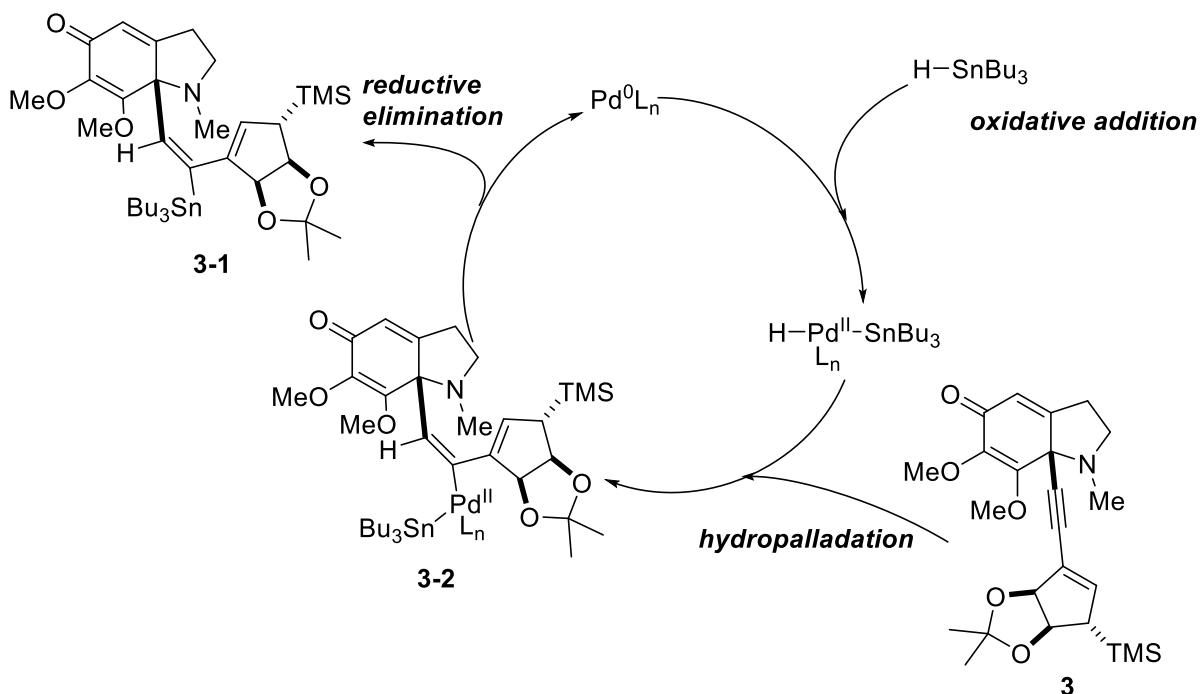
1) King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, 136, 6884.

◆ 3 to 4

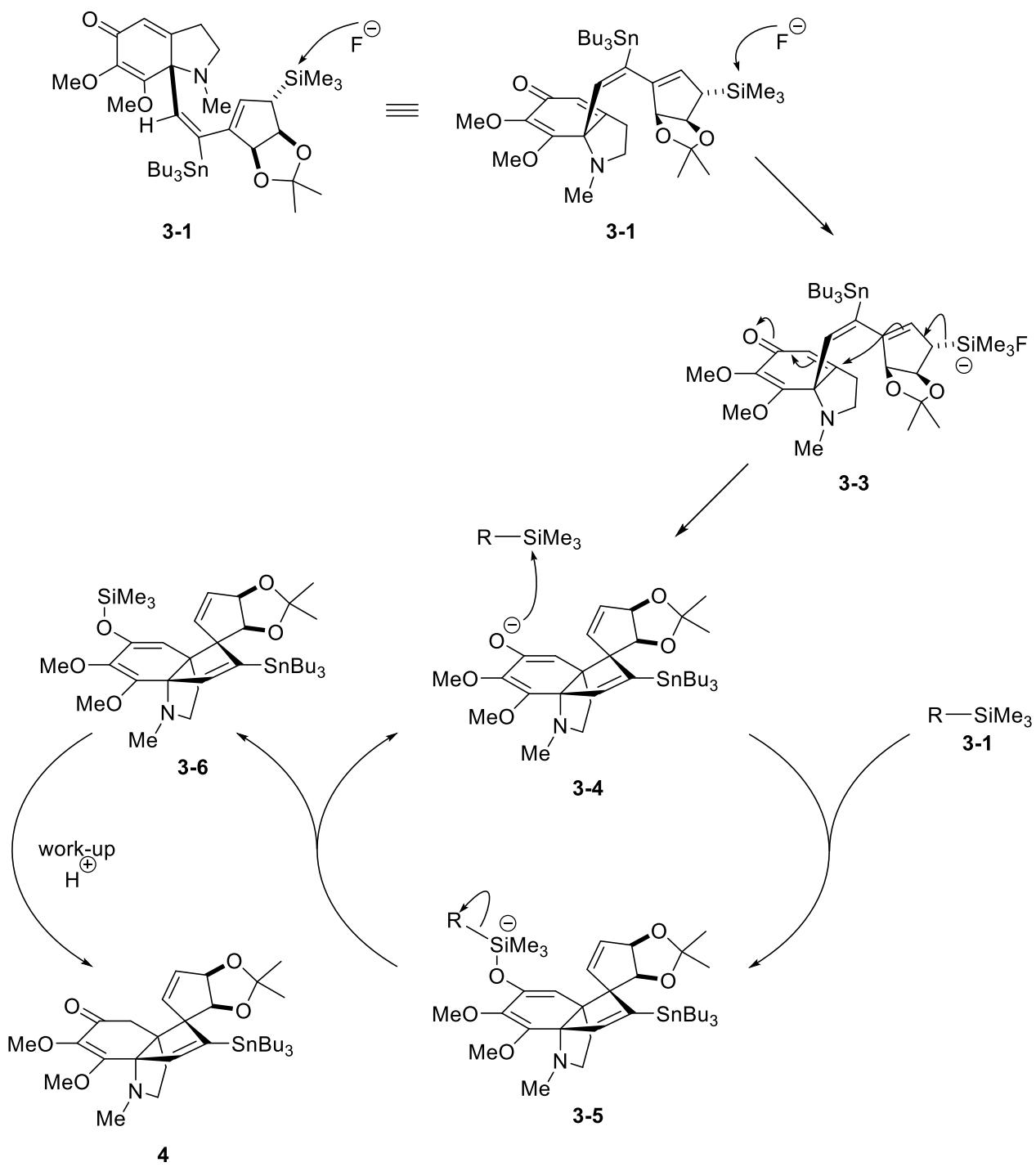


King, S. M.; Calandra, N. A.; Herzon, S. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 3642.

step 1: Pd-catalyzed regioselective hydrostannylation



step 2: Autocatalytic Hosomi-Sakurai allylation triggered by TBAF

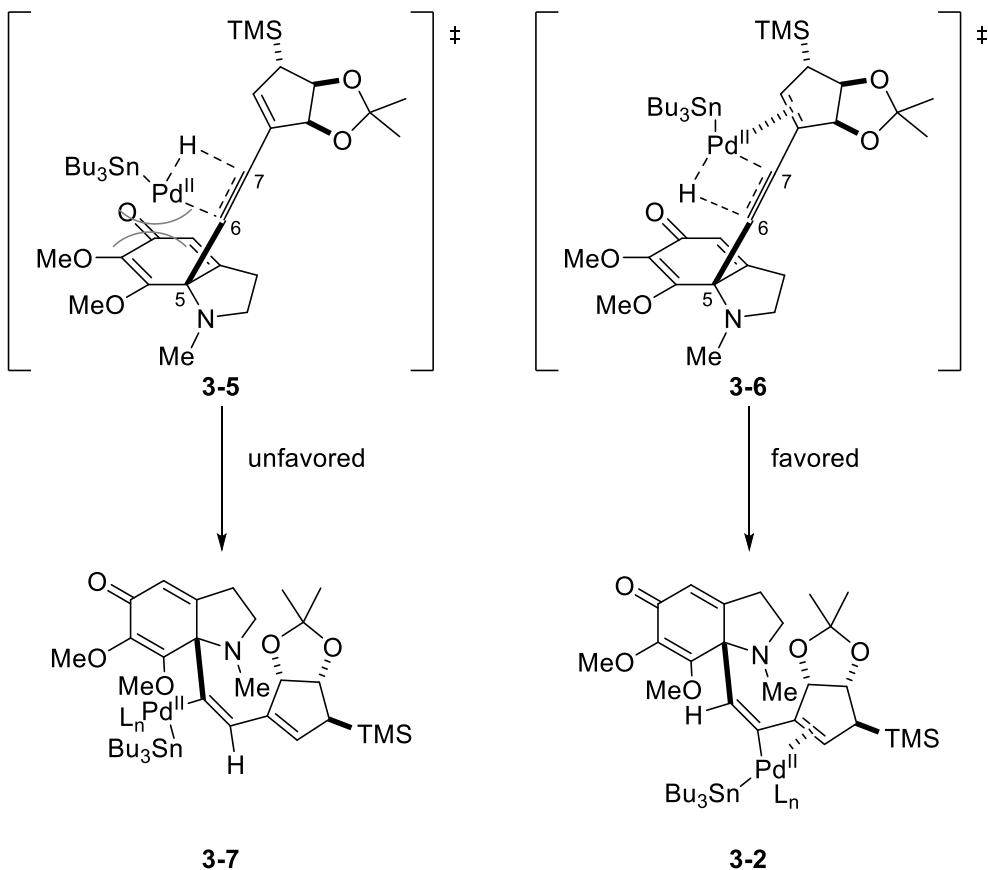


For details about autocatalytic Hosomi-Sakurai allylation:

Wang, D.-K. et al. *J. Org. Chem.* **1999**, *64*, 4233.

Discussion1: regioselectivity of hydrostannylation

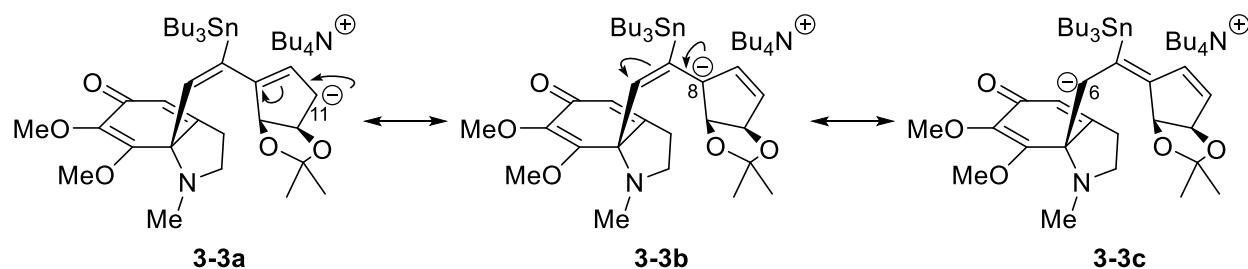
- i) steric congestion from the full substituted C-5 carbon inhibits formation of Pd-C bond at C-6.
- ii) Pd atom can interact with olefin to form π complex if Pd-C bond is formed at C-7.



Discussion2: selectivity of Hosomi-Sakurai allylation (3-3 to 4)

- i) possible nucleophilic carbons

C-6, C-8 and C11



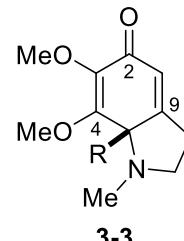
For simplicity, silyl group is omitted.

- ii) possible electrophilic carbons

1,2-addition: C-2

1,4-addition: C-4 and C-9

C-4 carbon seems less electrophilic due to electron-donating methoxy groups.



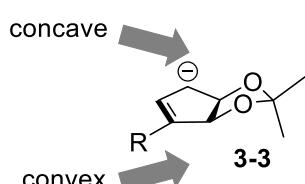
- iii) type of ring closure

		electrophilic carbon		
nucleophilic carbon		C-2	C-4	C-9
	C-6	5-exo-trig	3-exo-trig	3-exo-trig
	C-8	7-exo-trig	5-exo-trig	5-exo-trig
	C-11	9-exo-trig	7-exo-trig	7-exo-trig

3 emphasized closures seem fast.

- iv) face selectivity of cyclopentene ring

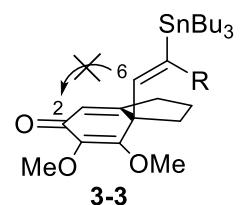
When C-8 or C-11 carbon attacks electrophilic carbon, it seems that attack from convex face is favored.



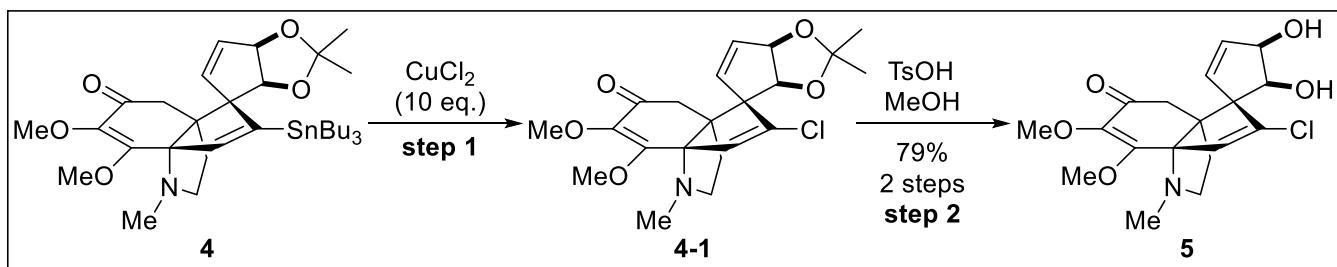
- v) structural demands

- C-6 to C-2

It seems very difficult for C-6 to proximate to C-2 due to the high planarity of dienone.



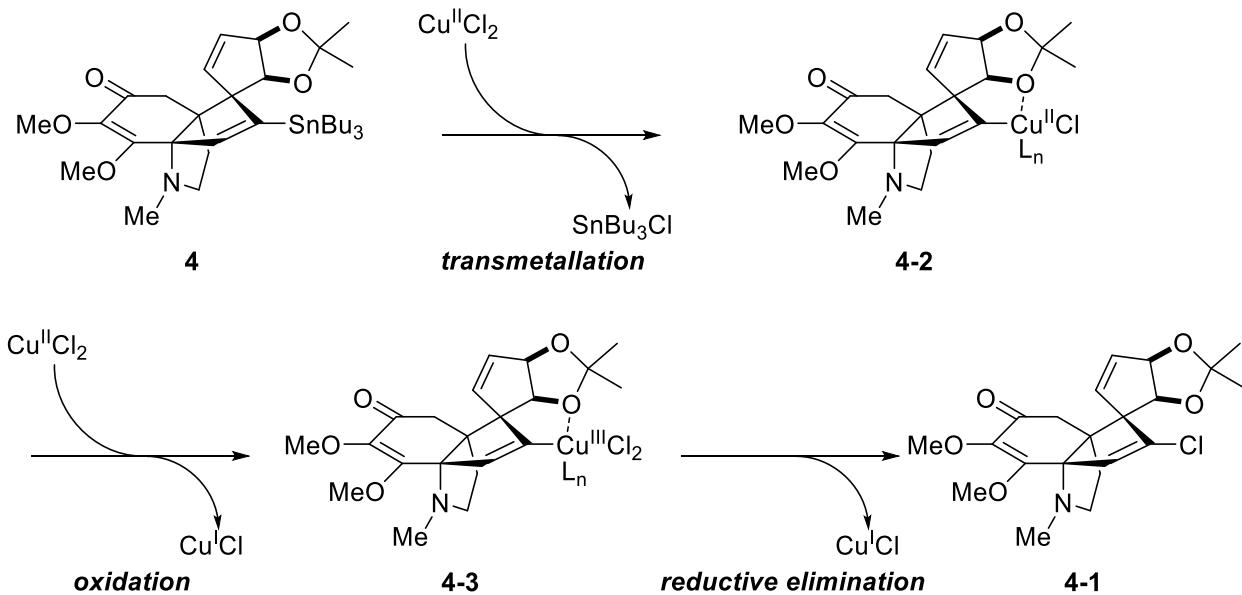
◆ 4 to 5



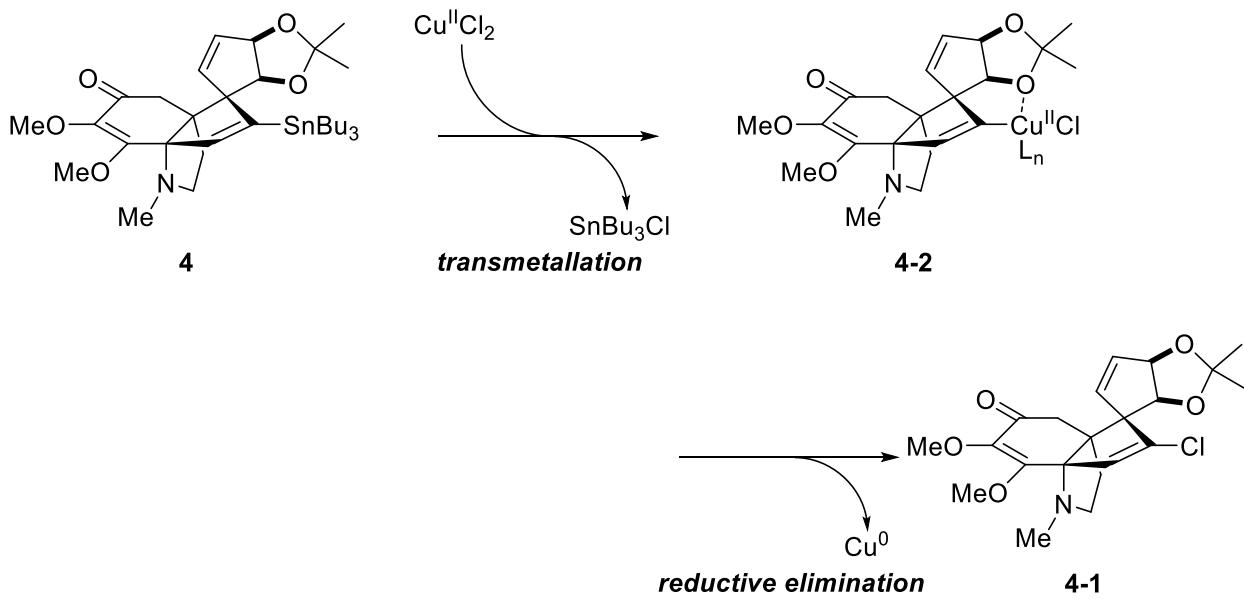
King, S. M.; Calandra, N. A.; Herzon, S. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 3642.

step 1: Copper-mediated chlorodestannylation

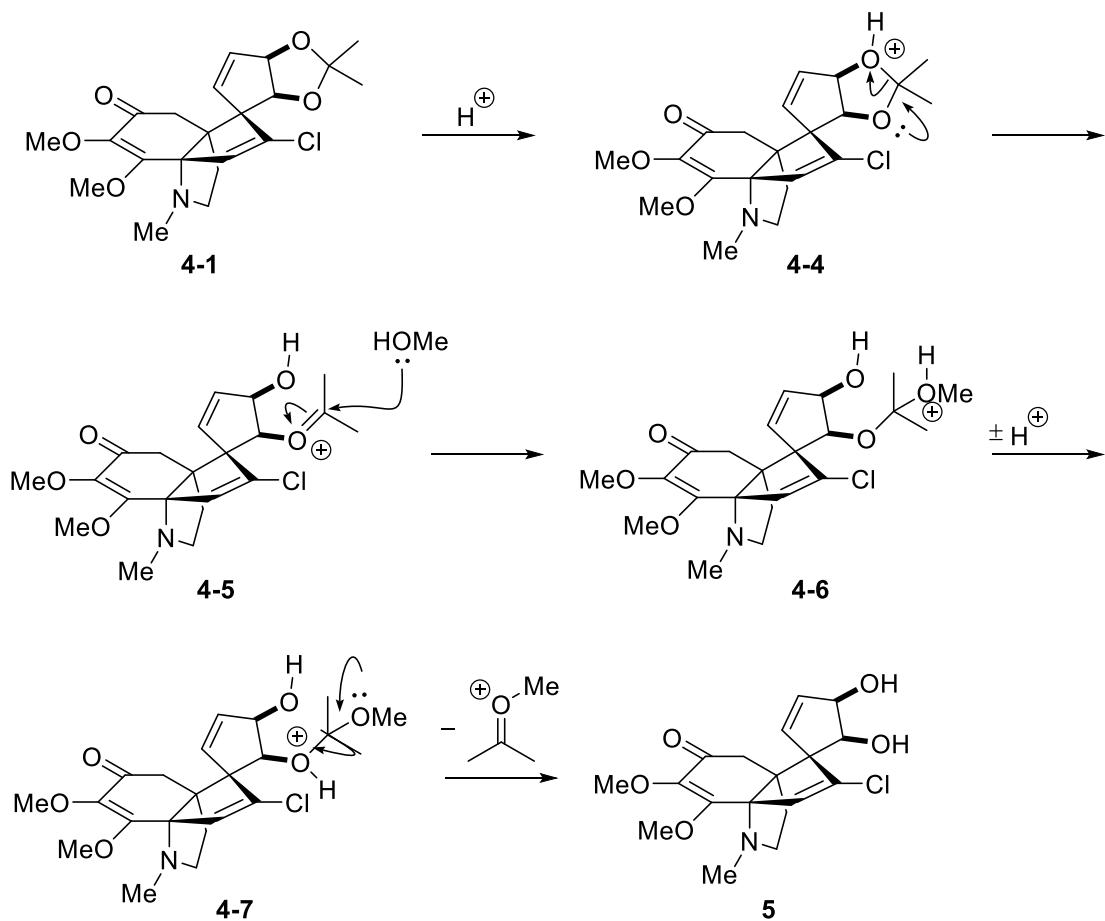
proposed mechanism 1:



proposed mechanism 2:

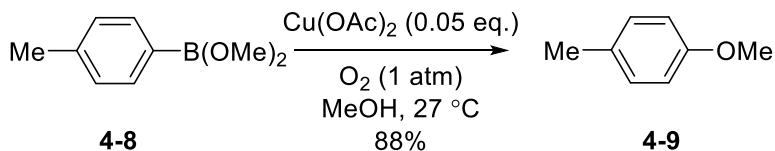


step 2: removal of acetonide



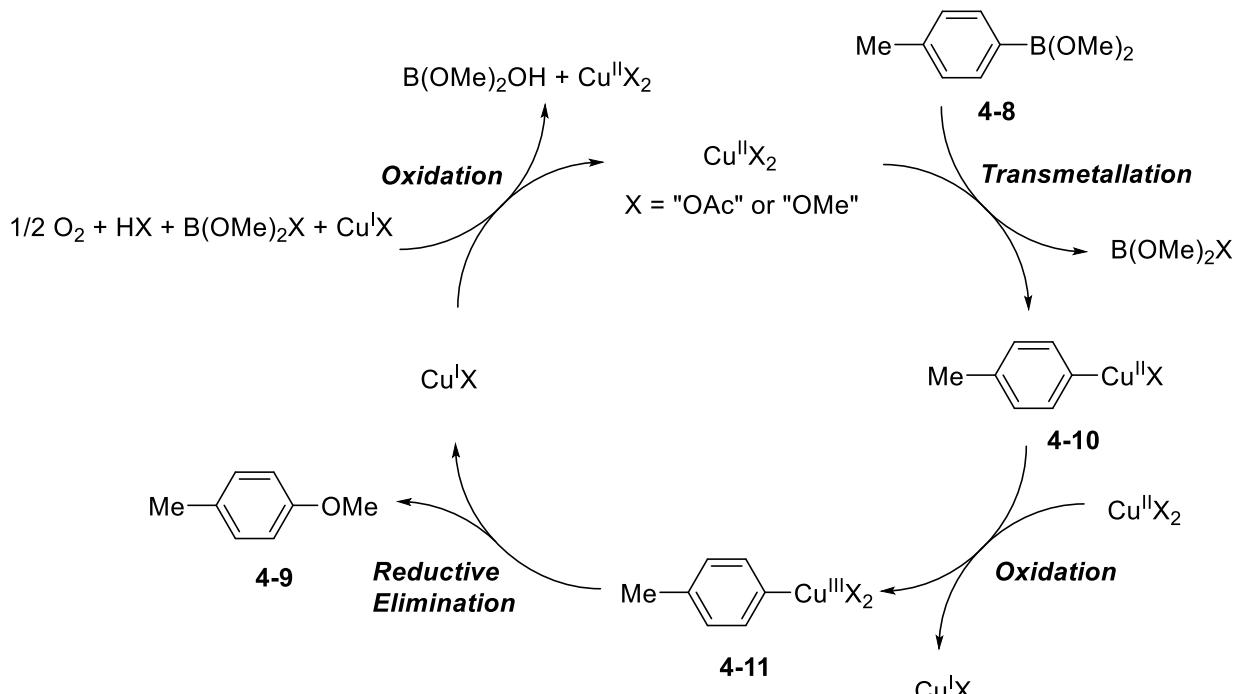
Discussion: Mechanism of the copper mediated chlorodestannylation

Similar reaction: Chan-Evans-Lam coupling reaction



King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, 131, 5044.

■ Proposed mechanism (mechanistic study was conducted)

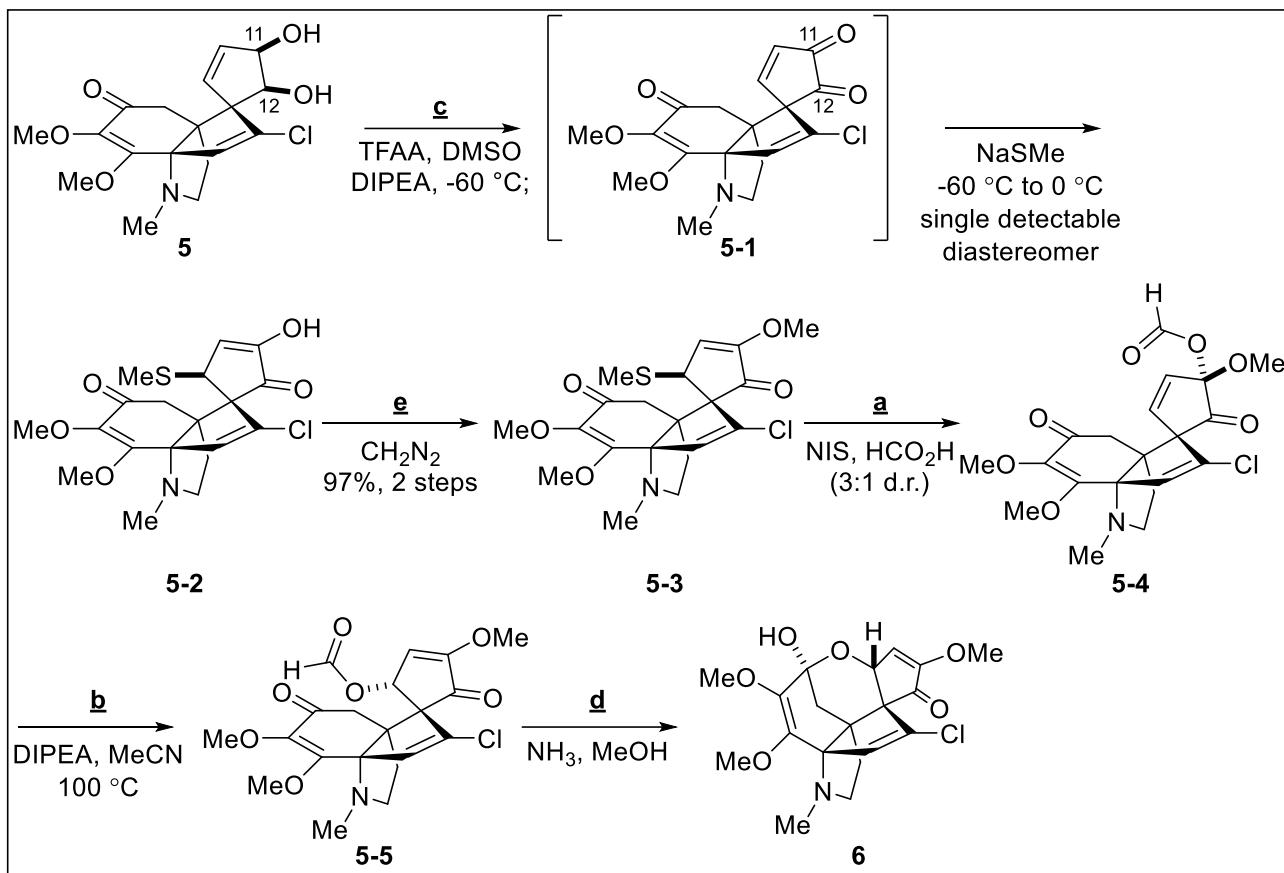


For more details, please see:

King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, 131, 5044.

King, A. E. *et al. Organometallics* **2012**, 31, 7948.

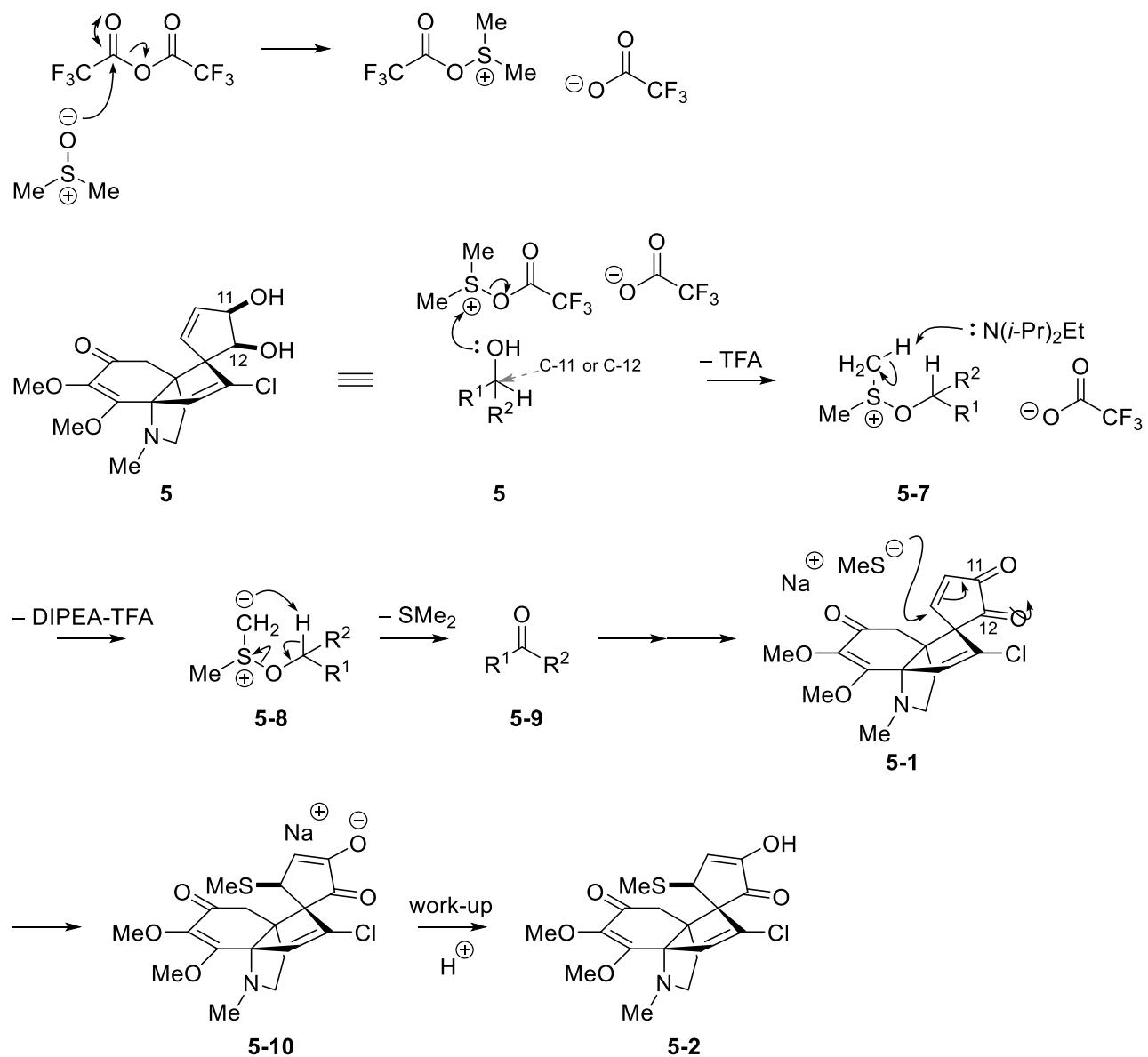
Q3.



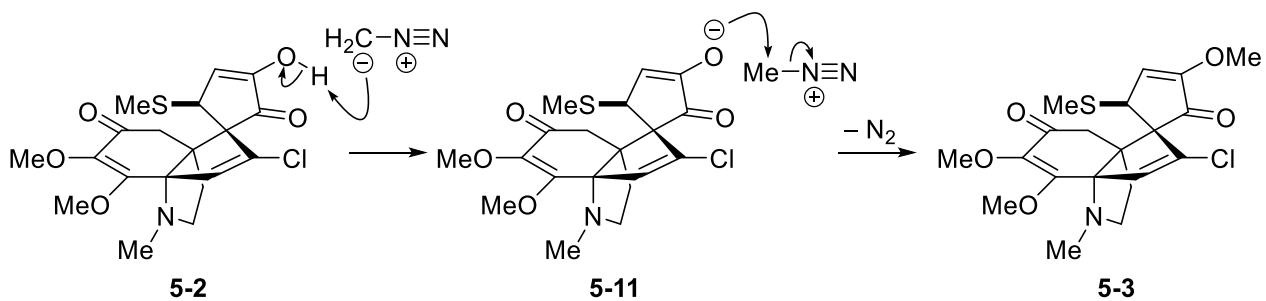
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◆ reaction mechanisms

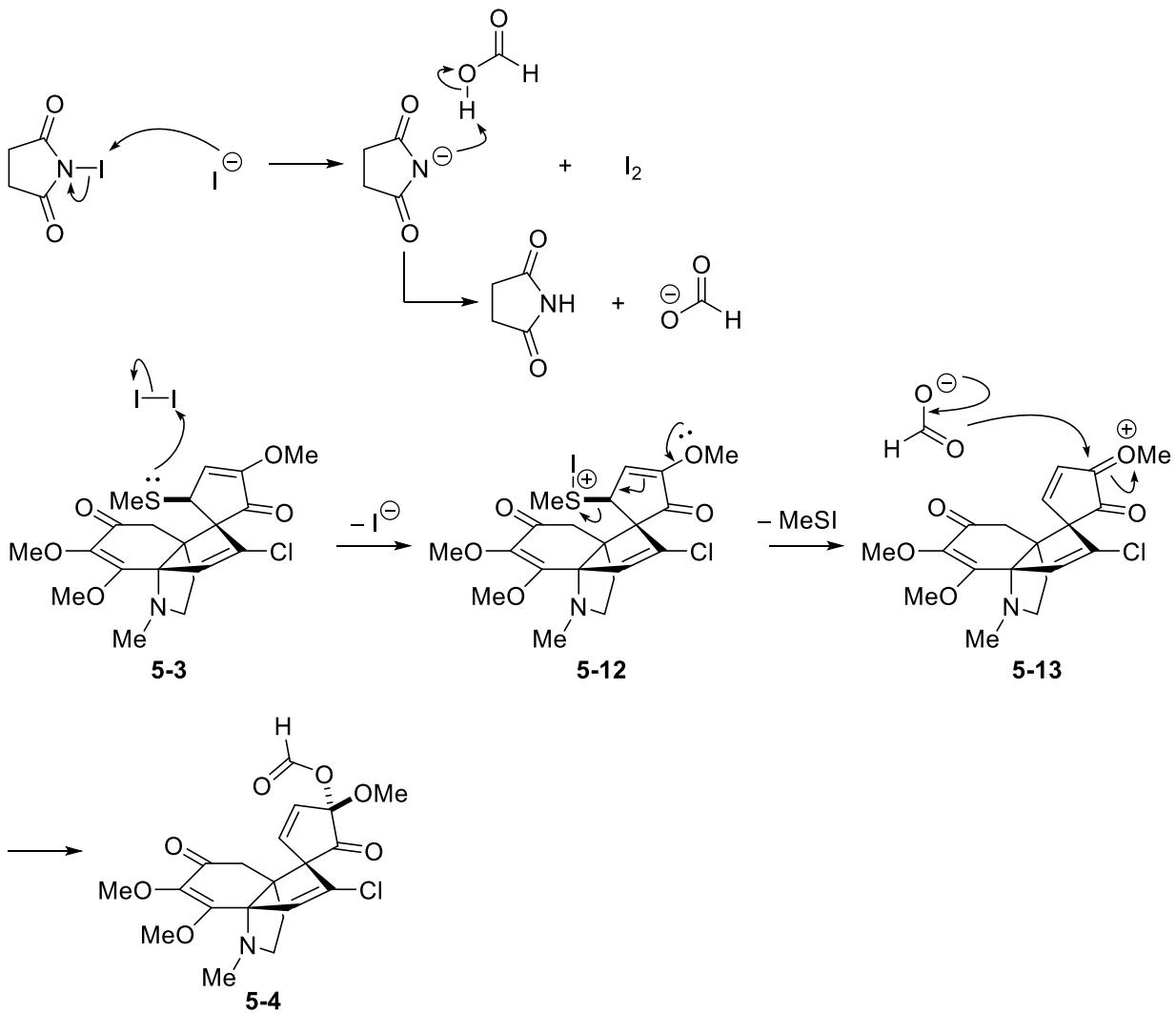
c. Swern oxidation followed by 1,4-addition of sodium thiomethoxide



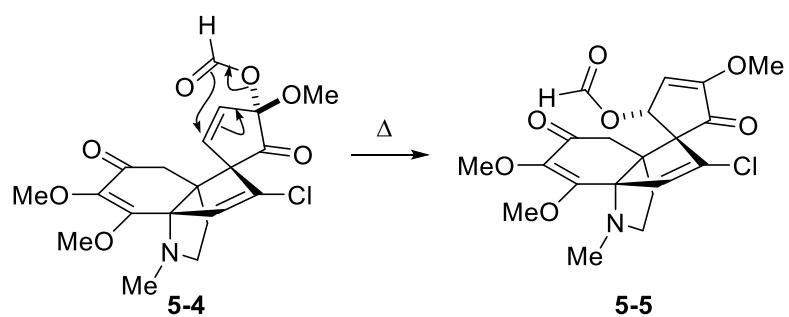
e. O-methylation



a. Oxidative elimination of methanethiol substituent followed by 1,2-addition to oxocarbenium ion



b. Thermal [3,3]-rearrangement



d. Cleavage of formyl group

