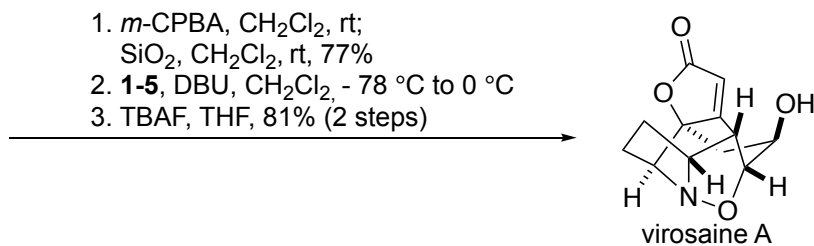
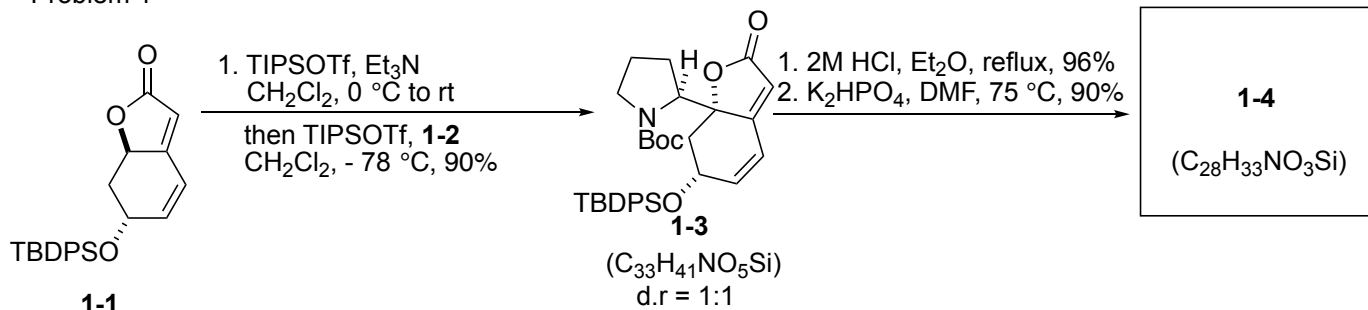


Problem Session (1)

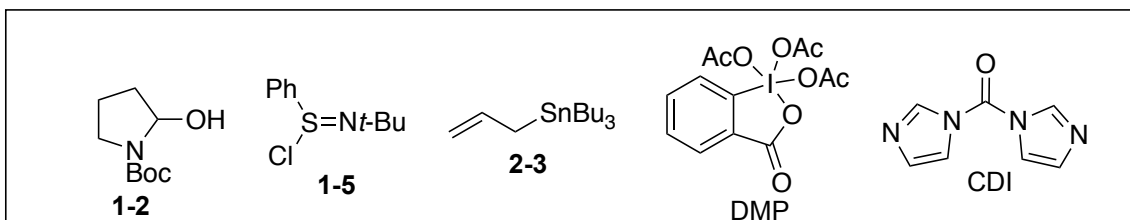
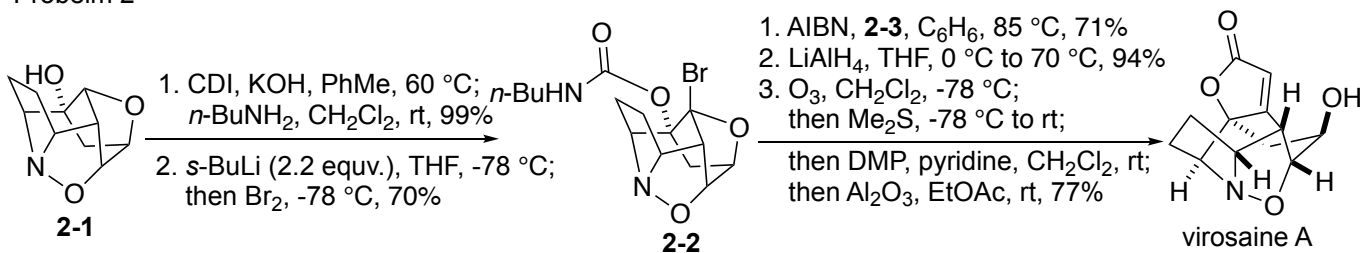
2018. 1. 20. Kensuke Miura

Please fill in the blank and explain the reaction mechanism.

Problem 1



Problem 2



Problem Session (1) - Answer -

2018. 1. 20. Kensuke Miura

Topic: (-)-virosaine A

isolation and bioactivity:

from the twigs and leaves of *Flueggea virosa*

activities on cytotoxicity and the central nervous system

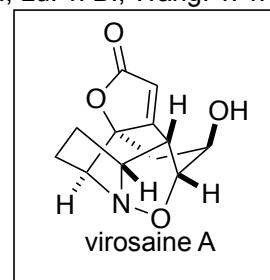
(Zhao. B. X.; Wang. Y.; Zhang. D. M.; Huang. X. J.; Bai. L. L.; Yan. Y.; Chen. J. M.; Lu. T. B.; Wang. Y. T. Zhang. Q. W.; Ye. W. C. *Org. Lett.* **2012**, 14, 3096.)

structural feature:

the presence of multiple bridged bicycles

six congested stereocenters

an isoxazolidine ring embedded in the penta cyclic framework

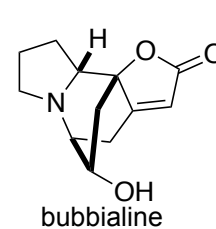
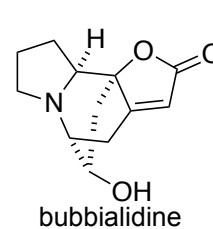
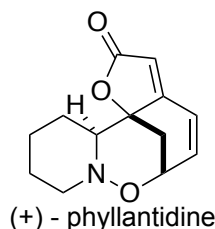
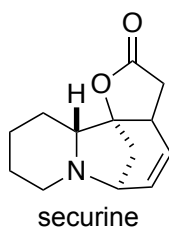
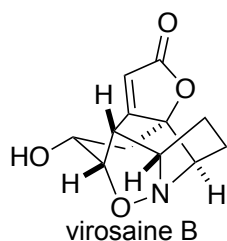


total synthesis:

Miyatake. H. B.; Bannwart. L. M.; Gademann. K. *Chem. Commun.* **2013**, 49, 1921. (Problem 1)

Hughes. J. M. E.; Gleason. J. L. *Angew. Chem., Int. Ed.* **2017**, 56, 10830. (Problem 2)

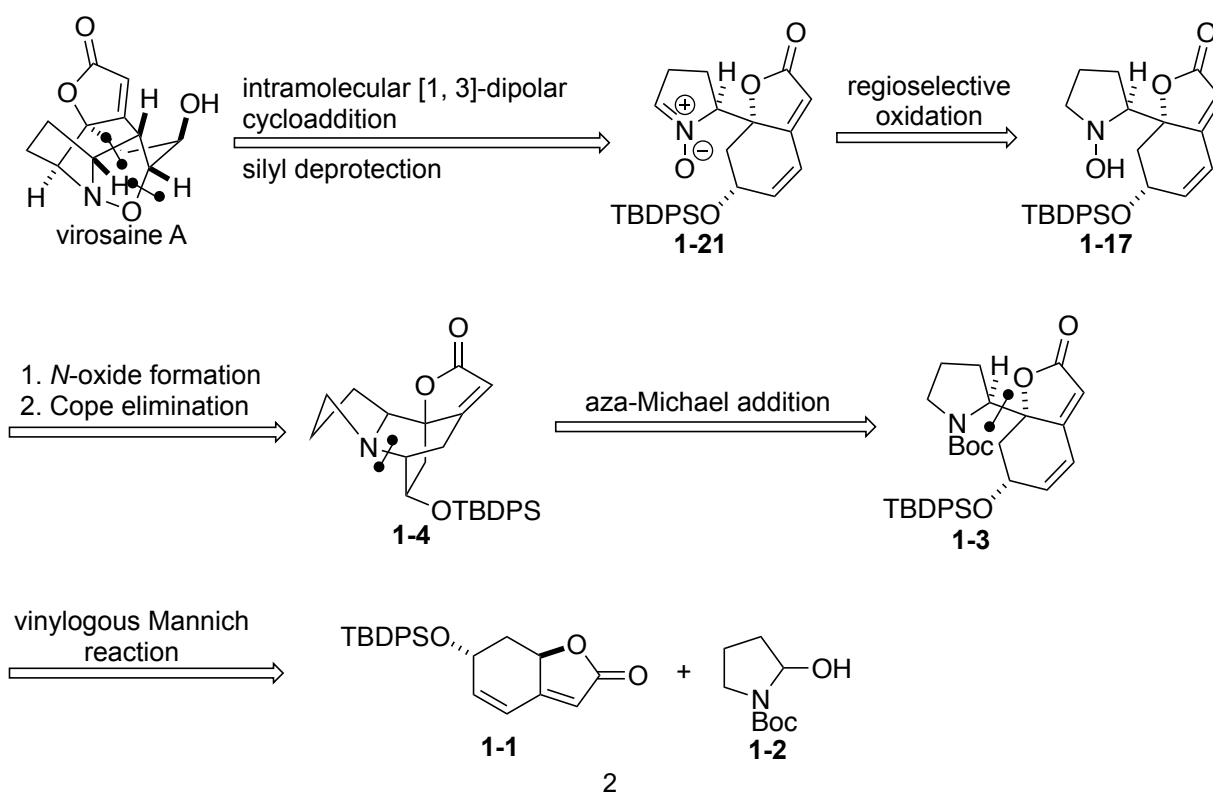
related alkaloids:

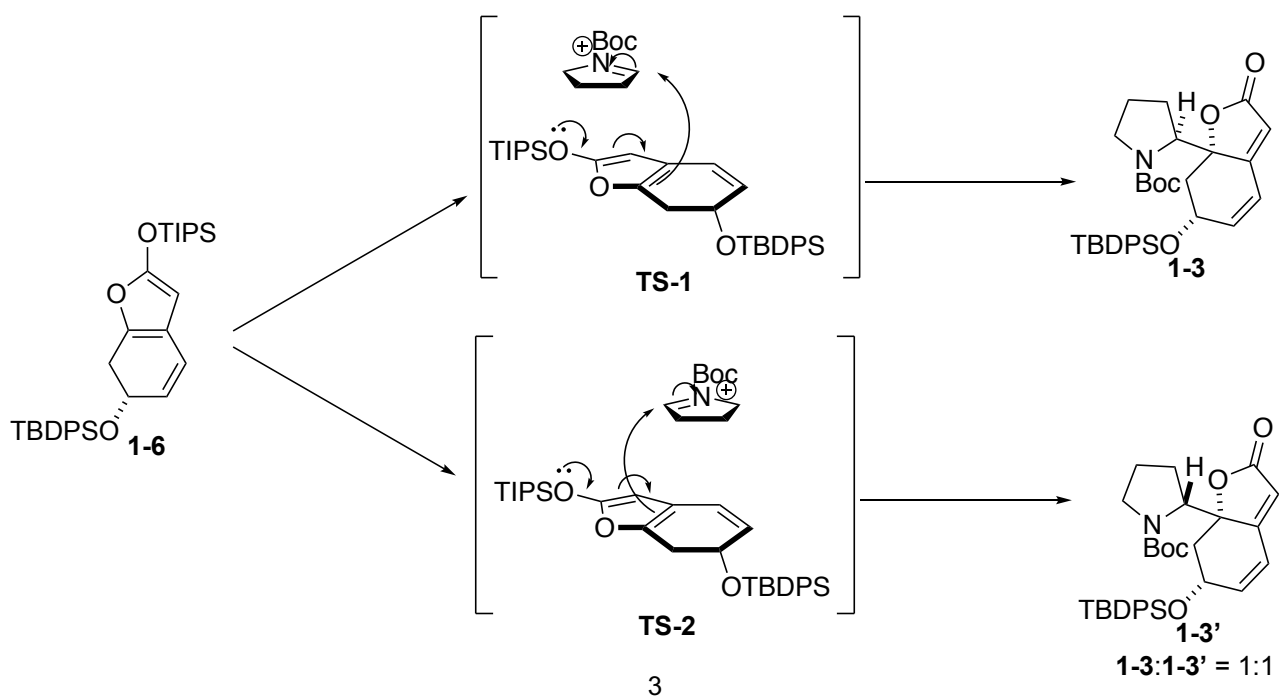
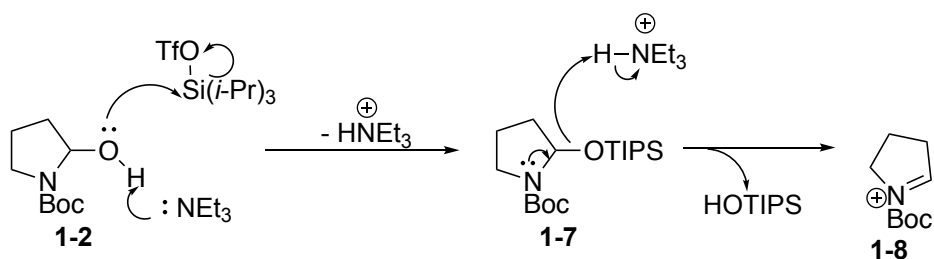
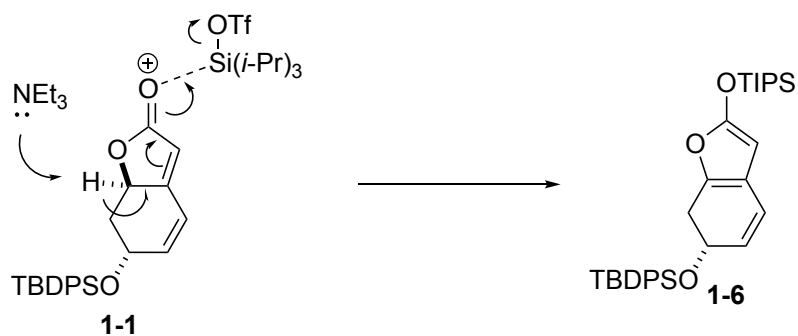
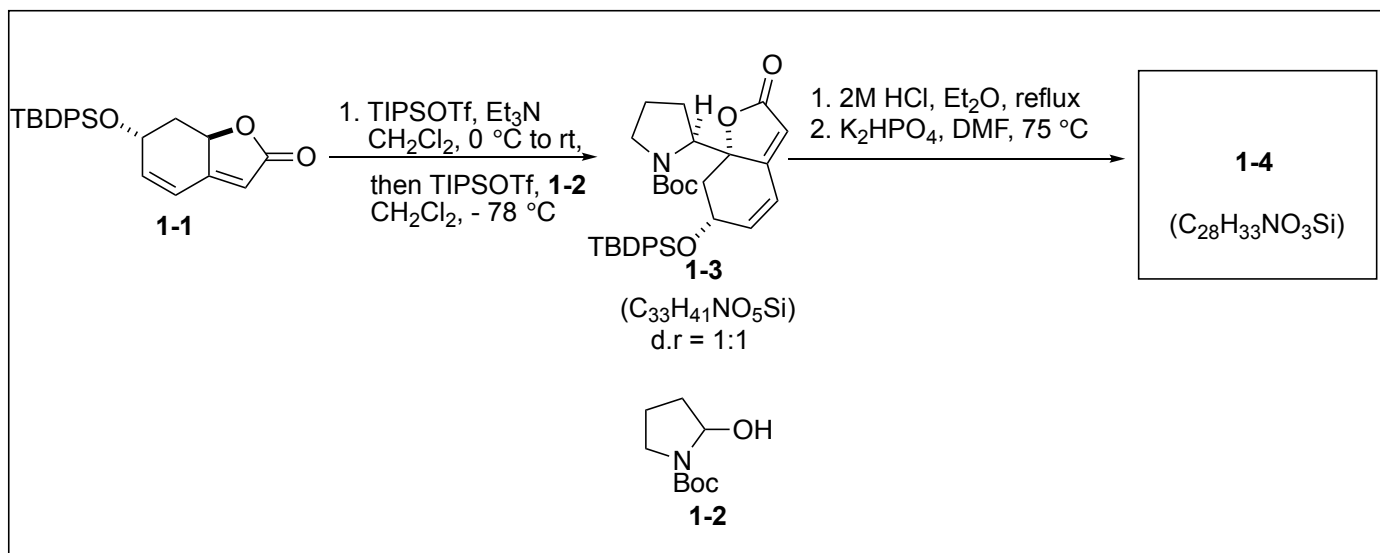


130112_PS_Satoshi_HASHIMOTO

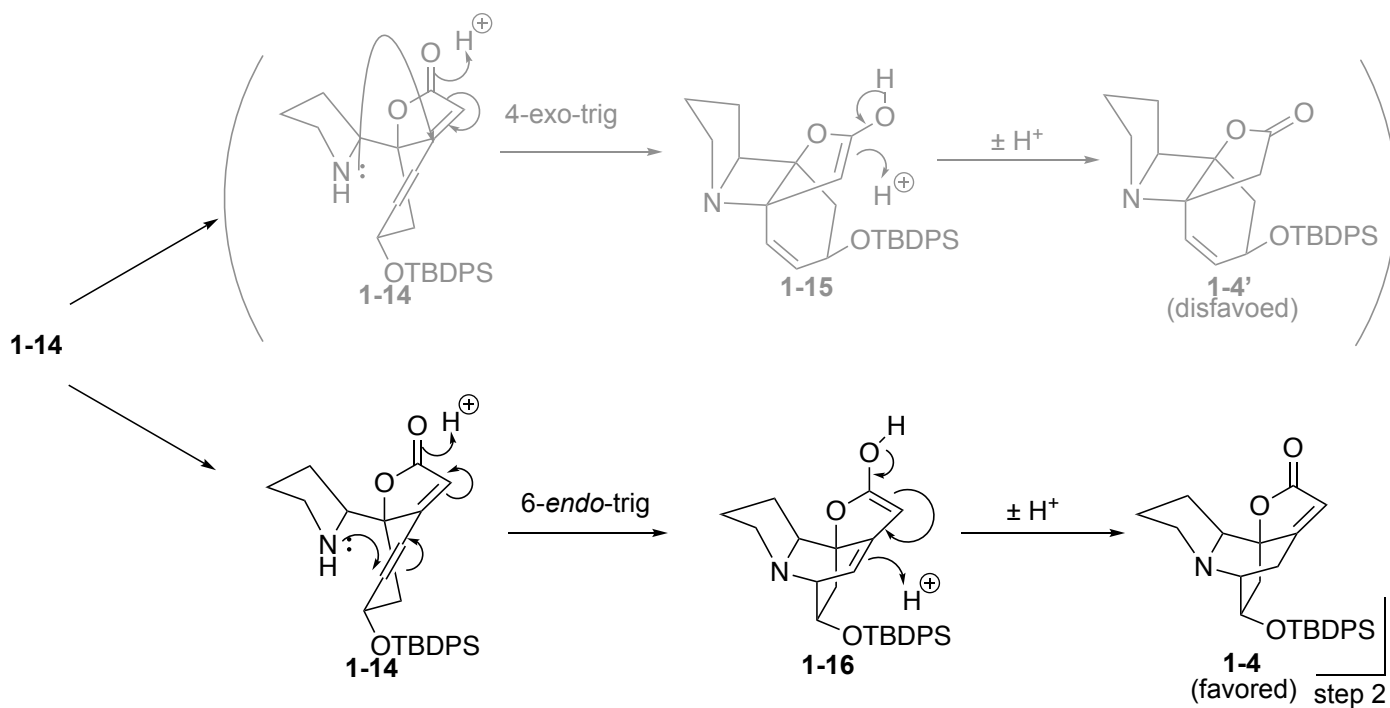
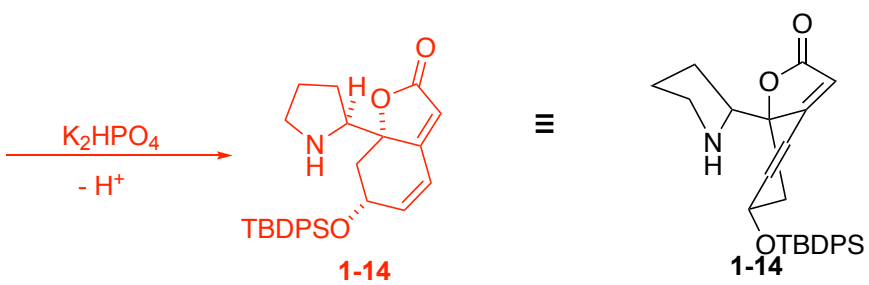
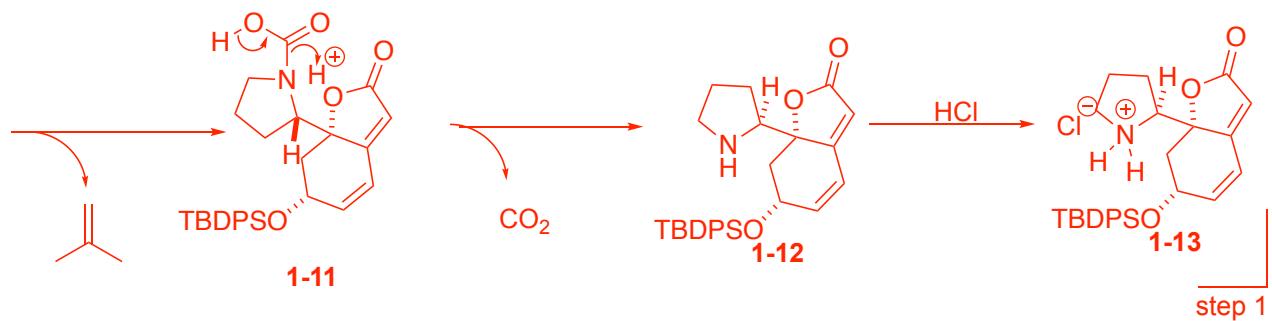
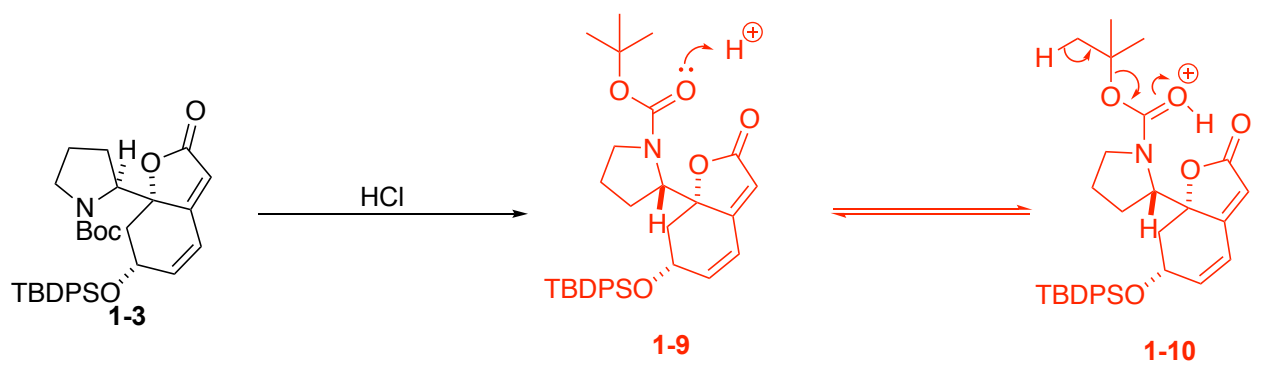
Problem 1. Total synthesis of (-)-virosaine A by Gademann

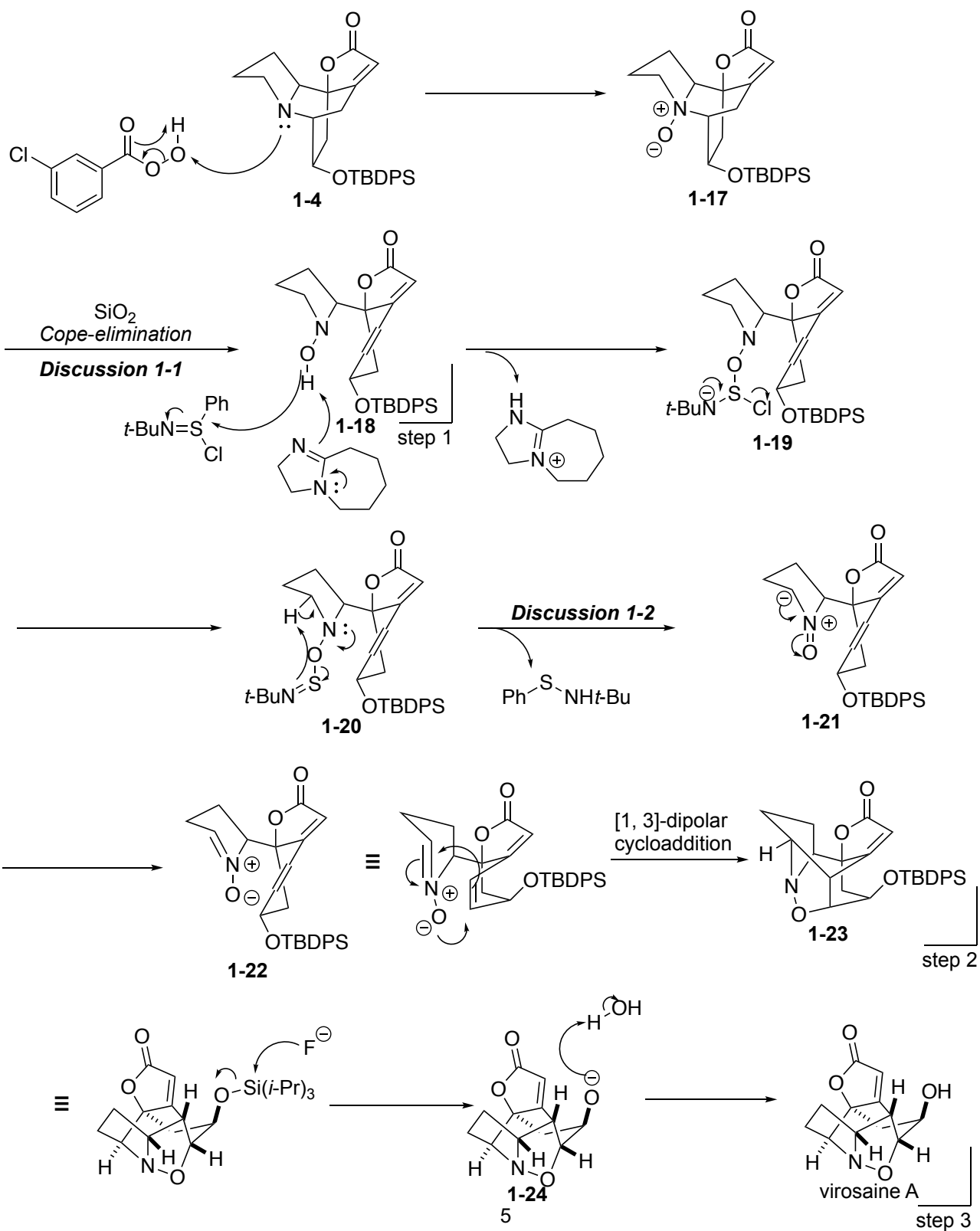
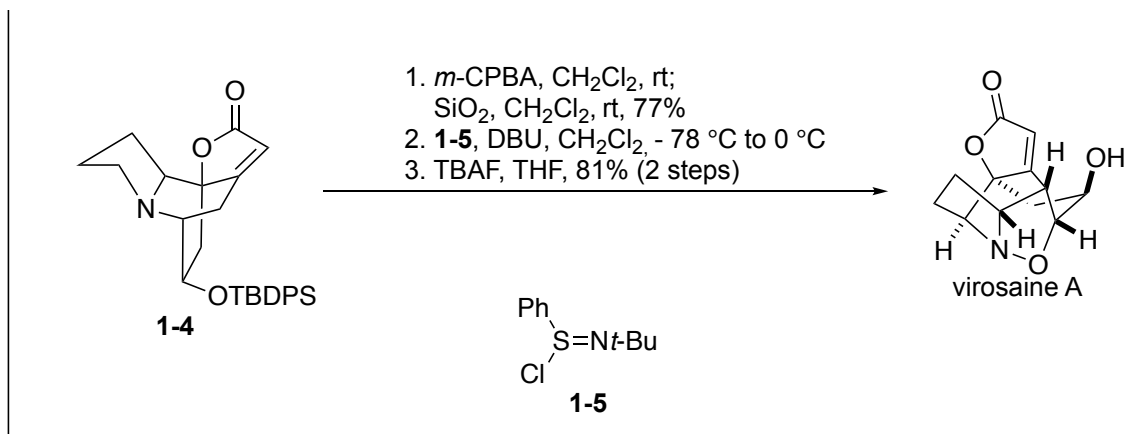
retrosynthetic analysis





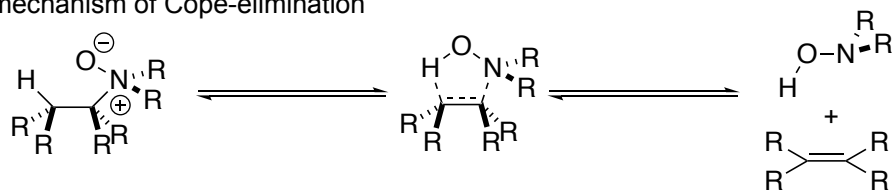
step 1





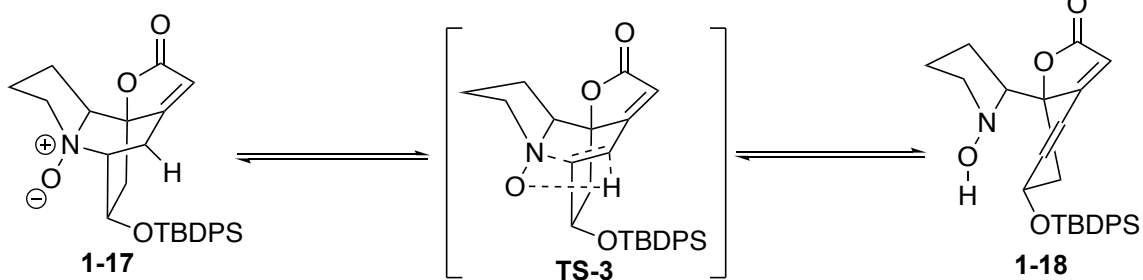
Discussion 1-1: reaction mechanism from **1-17** to **1-18**

Reaction mechanism of Cope-elimination



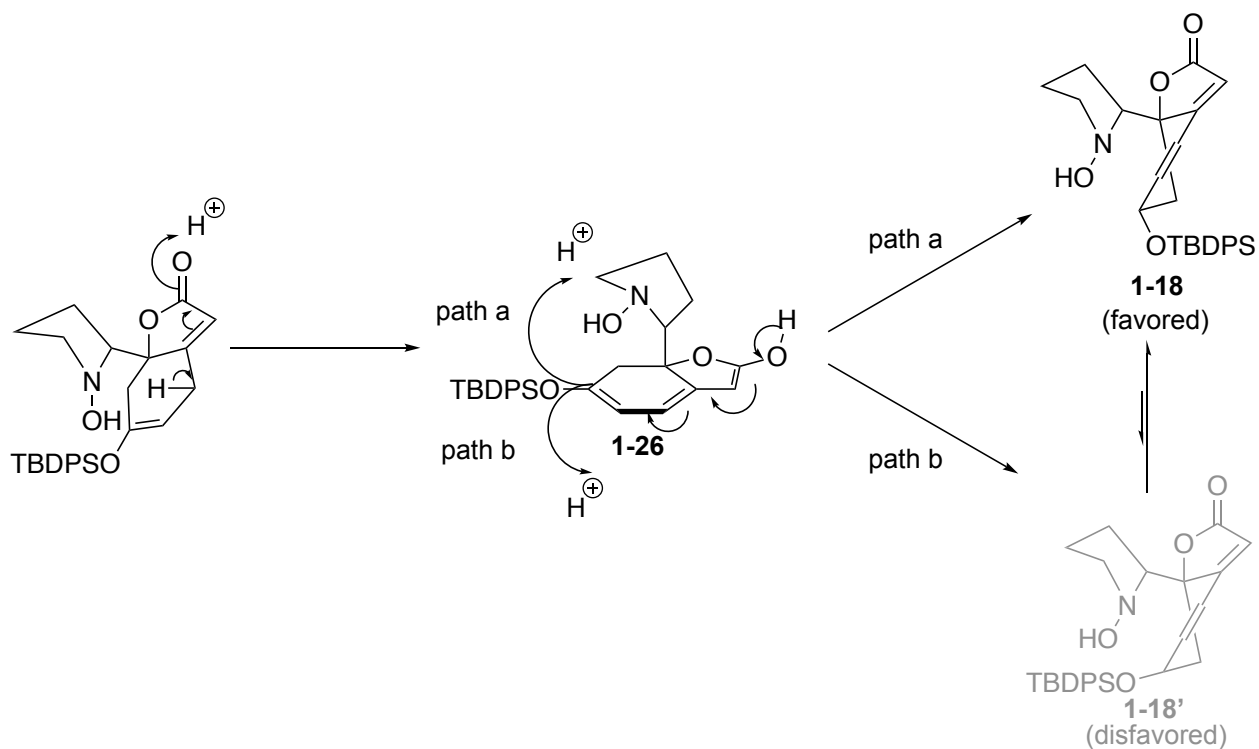
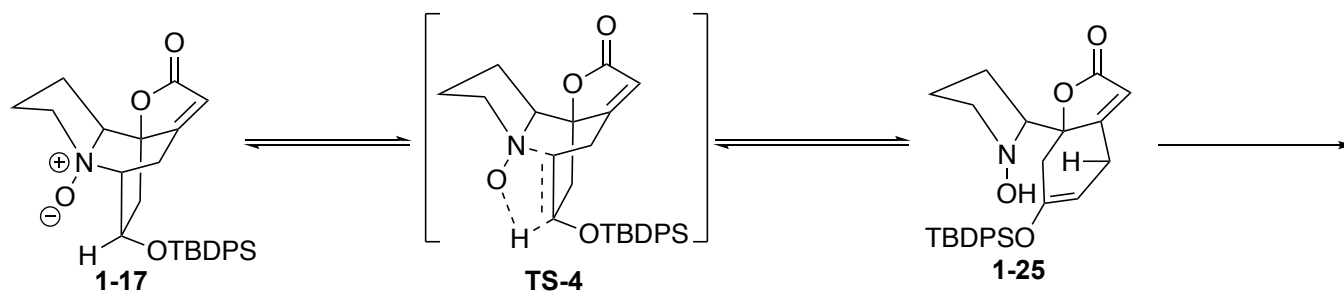
intramolecular proton-transfer via five-membered cyclic transition state

possible mechanism from **1-17** to **1-18**



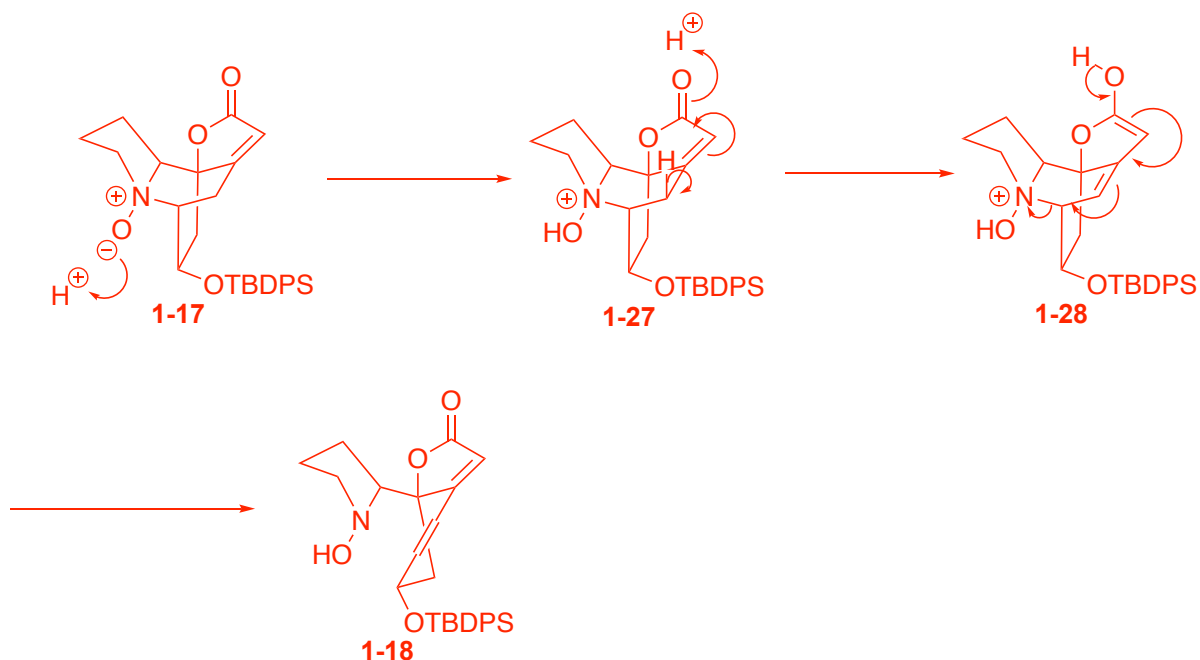
but oxygen and hydrogen might be too far \longrightarrow it is possible **TS-3** cannot form

another possible mechanism from **1-16** to **1-17** (my proposal)



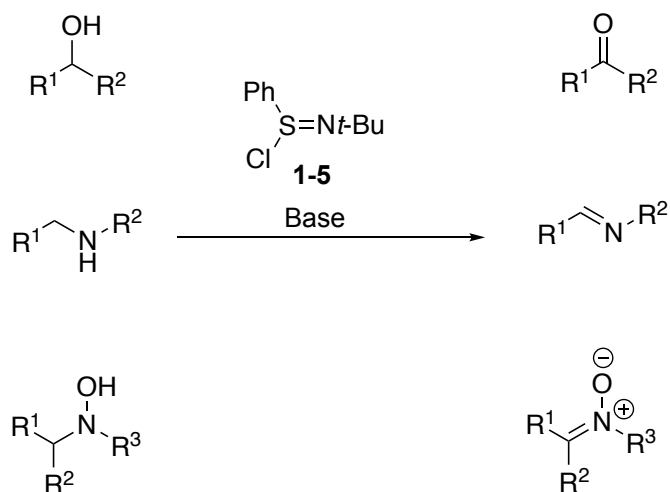
1-18 was thermodynamically more stable than **1-18'**

most reasonable mechanism from 1-17 to 1-18



Discussion 1-2: regioselectivity of deprotonation

N-*t*-Butylbenzenesulfinimidoyl (**1-5**)

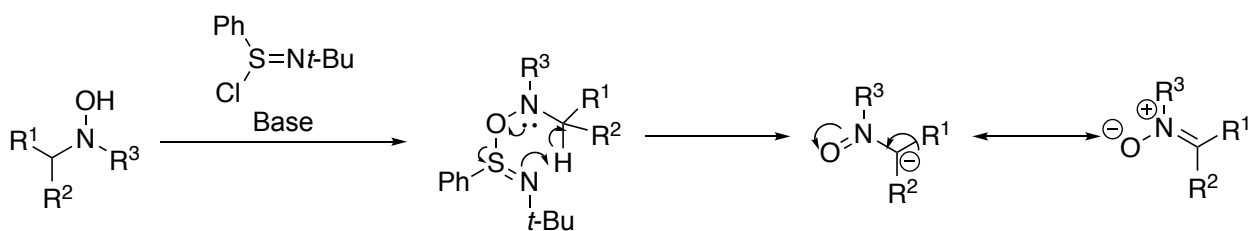


Matsuo. J.; Iida. D; Tatani. K.; Mukaiyama. T. *Bull. Chem. Soc. Jpn.* **2002**, 75, 223.

Matsuo. J.; Fukuda Y; Kuwana A.; Mukaiyama. T. *Chem. Lett.* **2001**, 30, 390.

Matsuo. J.; Shibata T.; Kitagawa. H.; Mukaiyama. T. *Arkivok.* **2006**, 58.

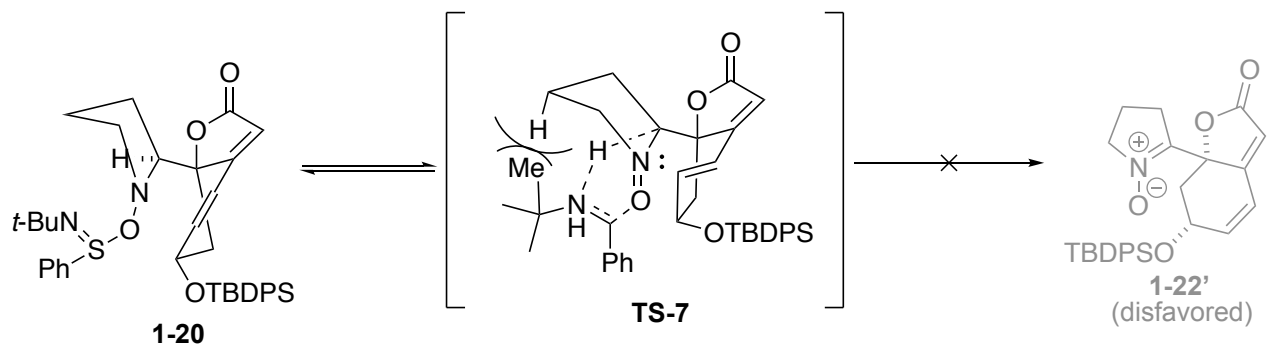
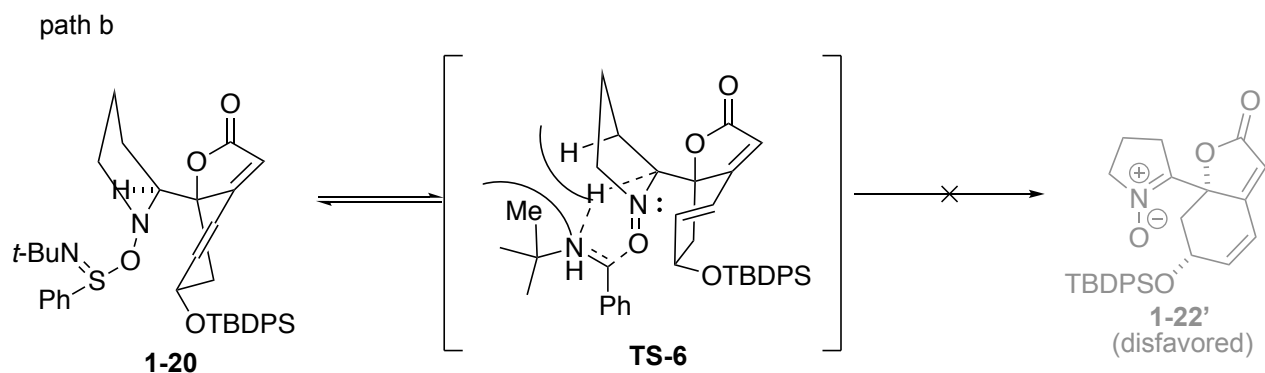
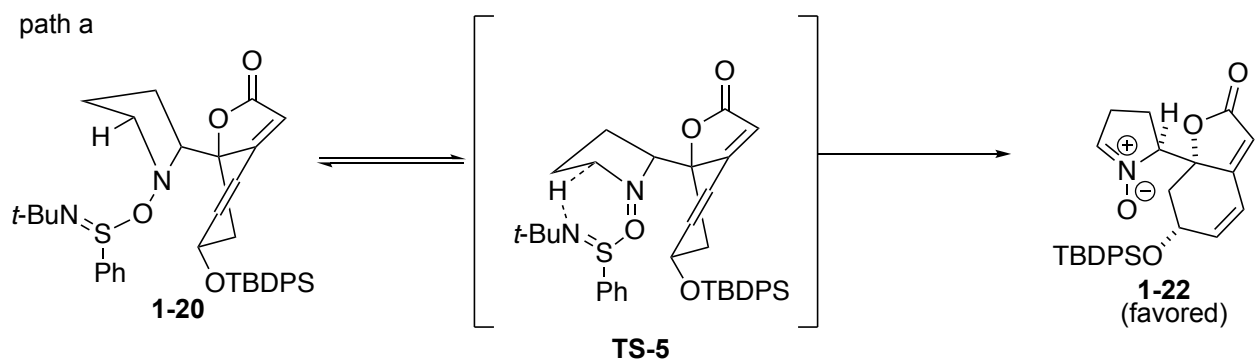
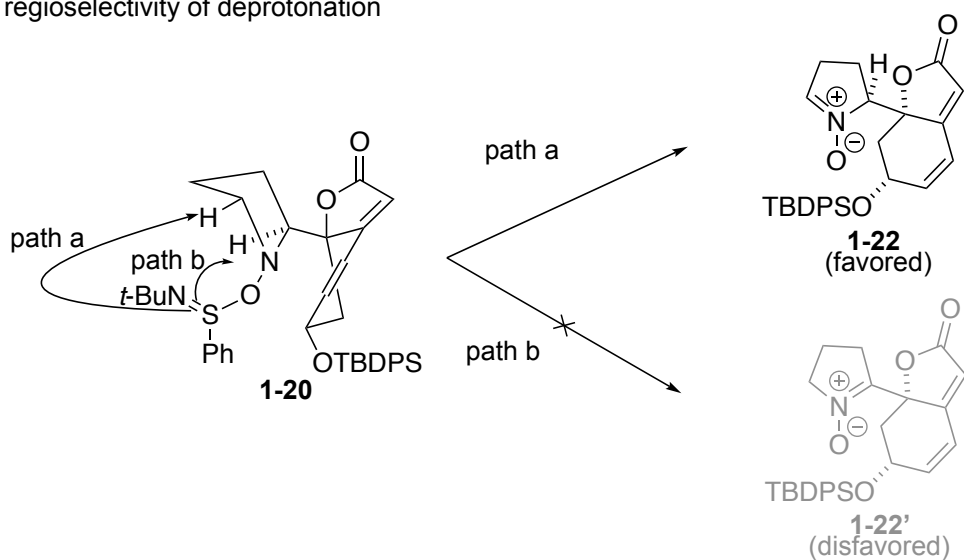
reaction mechanism of author's proposal



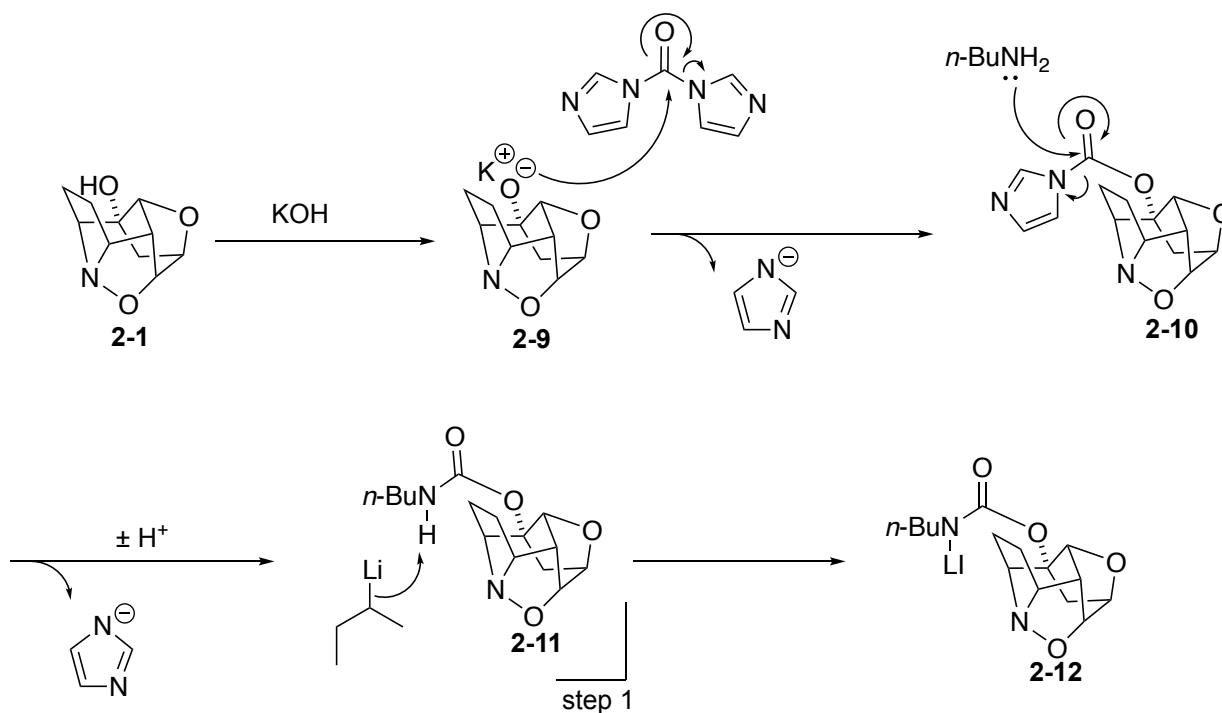
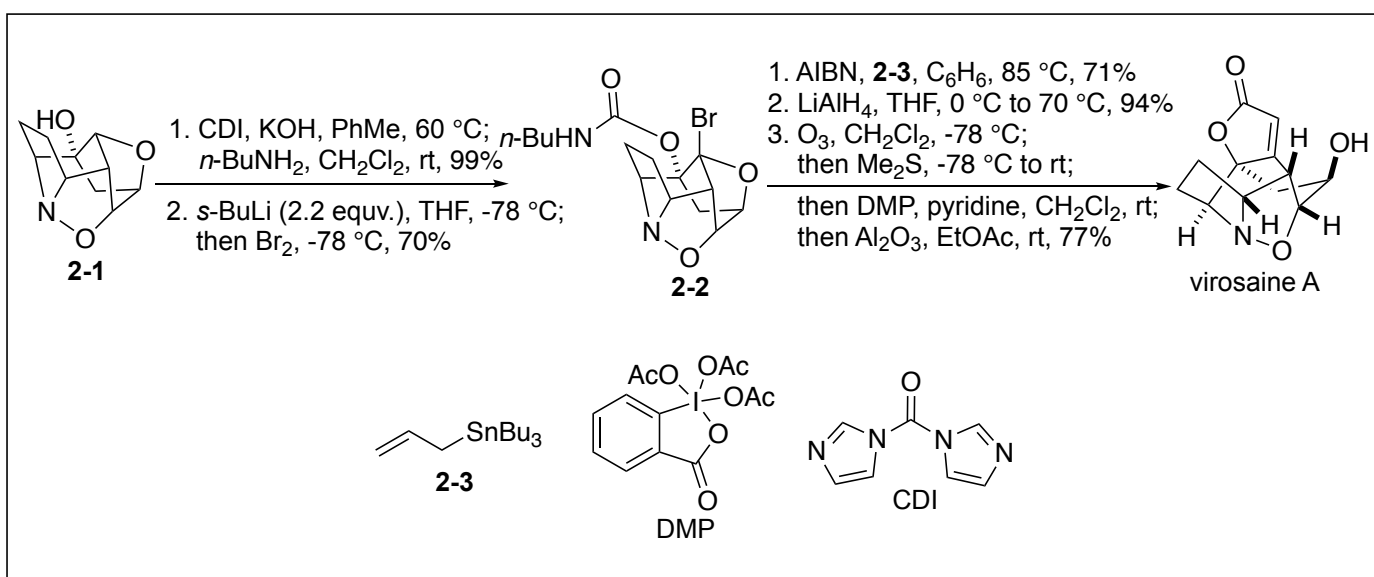
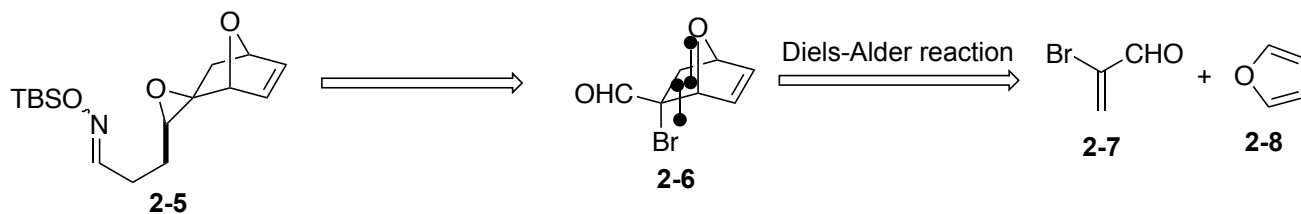
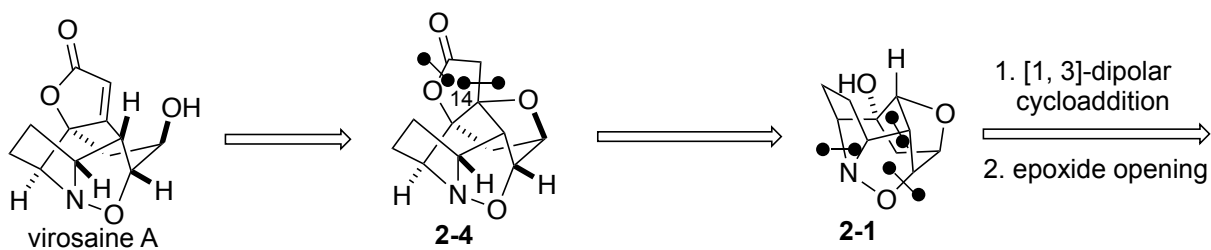
intramolecular proton-transfer via six-membered cyclic transition state

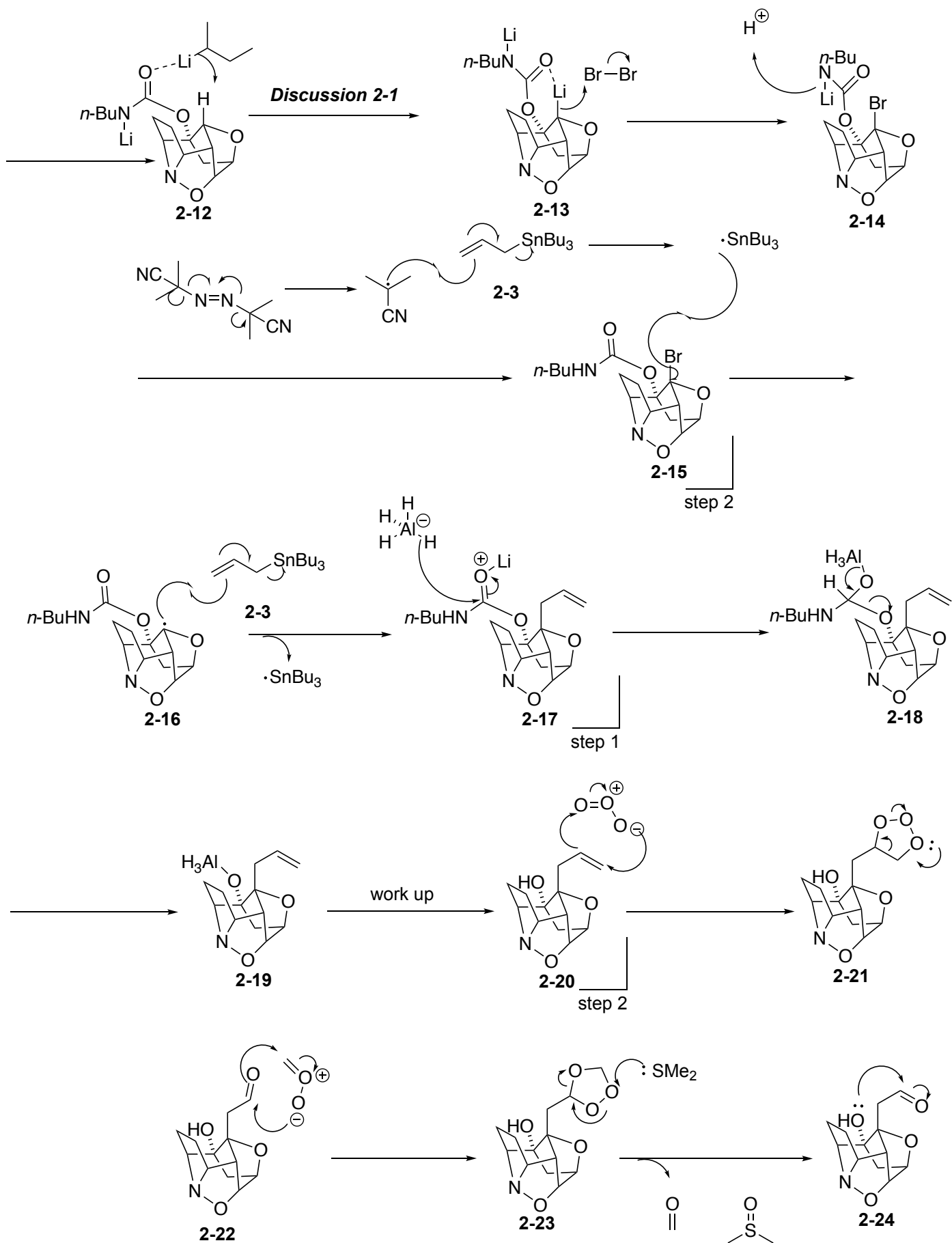
→ reaction from **1-20** to **1-22** is assumed to progress via six-member cyclic transition state

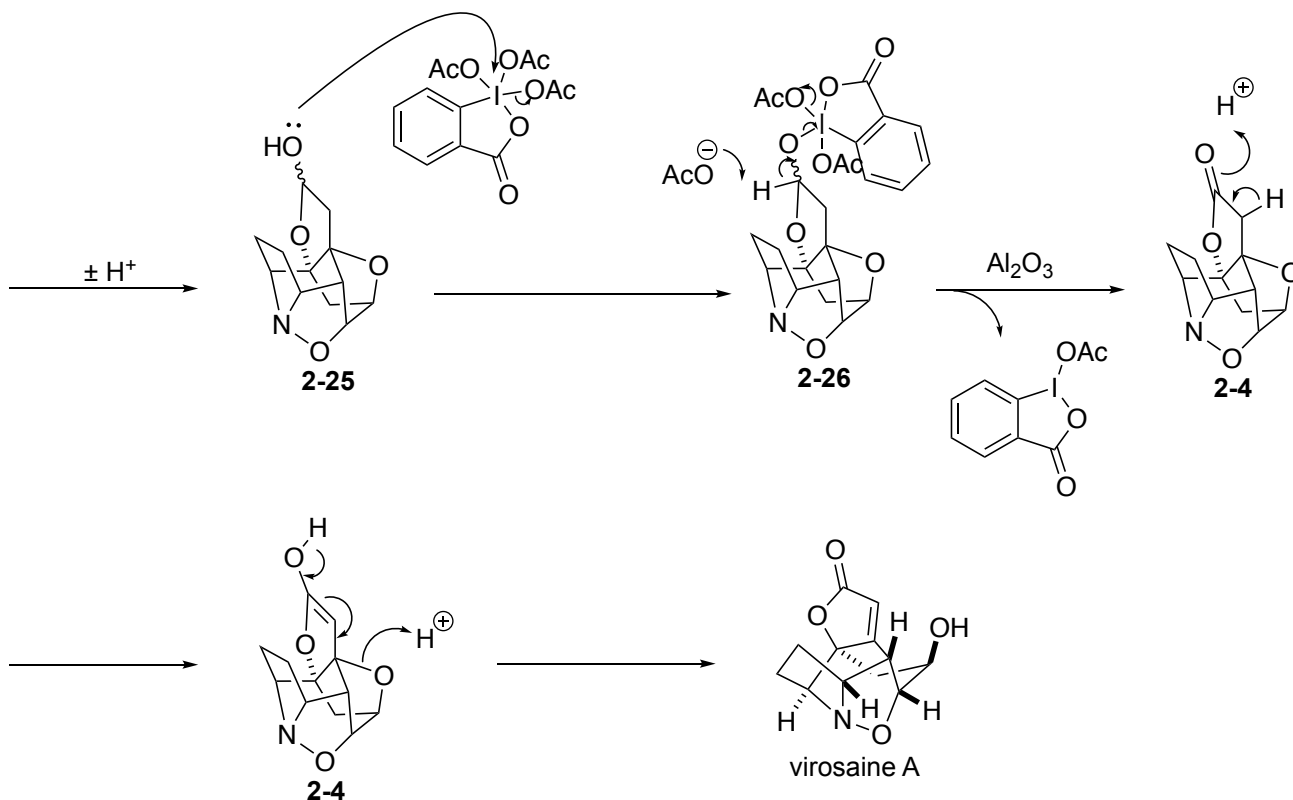
regioselectivity of deprotonation



retrosynthetic analysis







Discussion 2-1: regioselectivity of lithiation

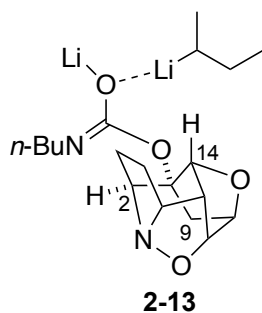


Table 1.

Site	¹ H (δ , ppm)	¹³ C (δ , ppm)	NPA partial atomic charge on carbon*
2	3.59	66.8	-0.037
9	1.73	45.5	-0.423
14	4.72	85.7	+0.095

* this value was determined by B3LPY/6-311++G**

- 2C, 9C and 14C were possible to be lithiated.
- **Table 1.** shows 14H and 14C were the most downfield signals.
- **Table 1.** shows NPA (natural population analysis) partial atomic charge on 14C was calculated to be most positive.

my proposal for these observations:

- inductive effect of oxygen vicinal to 14C
- possibility of the higher s-character of C-H bonds (14C)