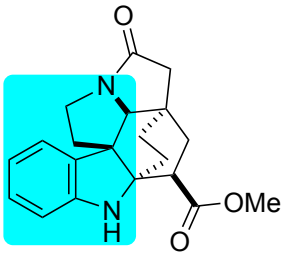
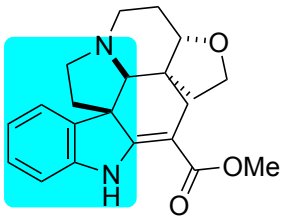
Problem Session (2) -Answer-

2024/12/07 Sota Mochizuki

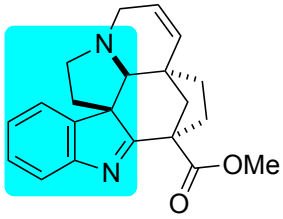
Topic: Skeleton construction of indoline and indole alkaloids



paucidirinine
(**problem 1**)



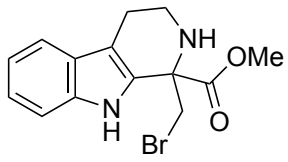
deoxoapodine
(**problem 2**)



kopsifoline D
(**problem 2**)

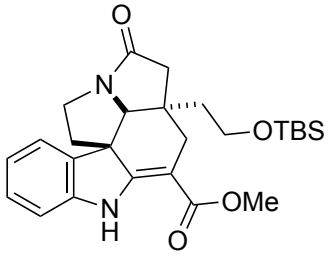
Problem:

(1)



1-1
(racemic)

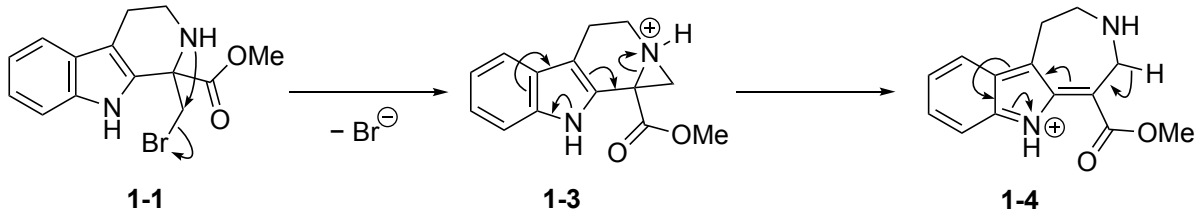
1. pyridine, reflux, 85%
2. $NaBH_3CN$ (2.8 eq), AcOH
   0 °C to rt, 98%
3. **A** (1.2 eq), benzene
   reflux, 66% (dr = 2 : 1)
4. *p*-TsOH (0.1 eq), toluene
   reflux, 50%



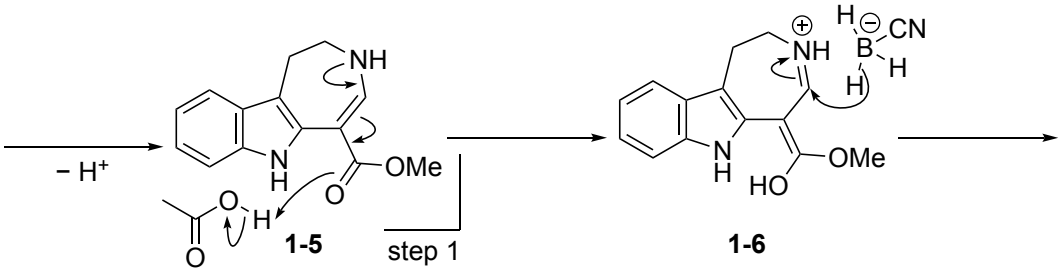
1-2
(racemic)

Zhang, W.; Lin, S.; Du, C.; Feng, S.; Liu, Z.; Zhang, J.; Xie, X.; Wang, X.; Li, H.; She, X. *J. Org. Chem.* **2019**, *84*, 1111.

Answer:

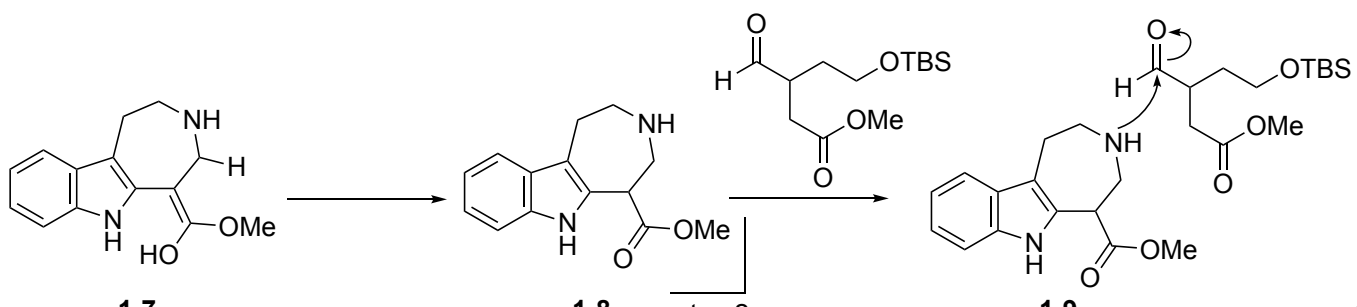


1-1 **1-3** **1-4**



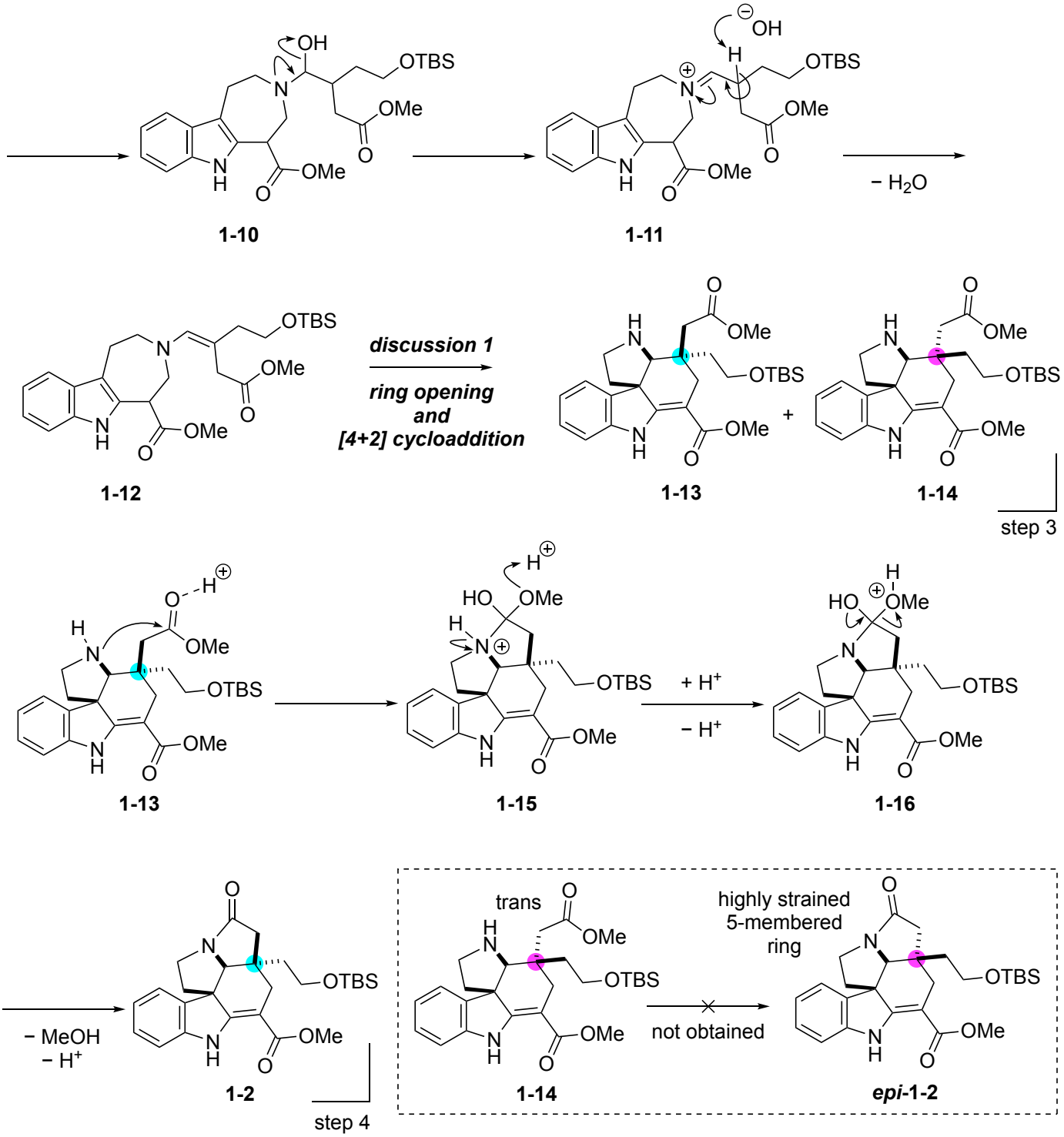
1-5 **1-6**

step 1

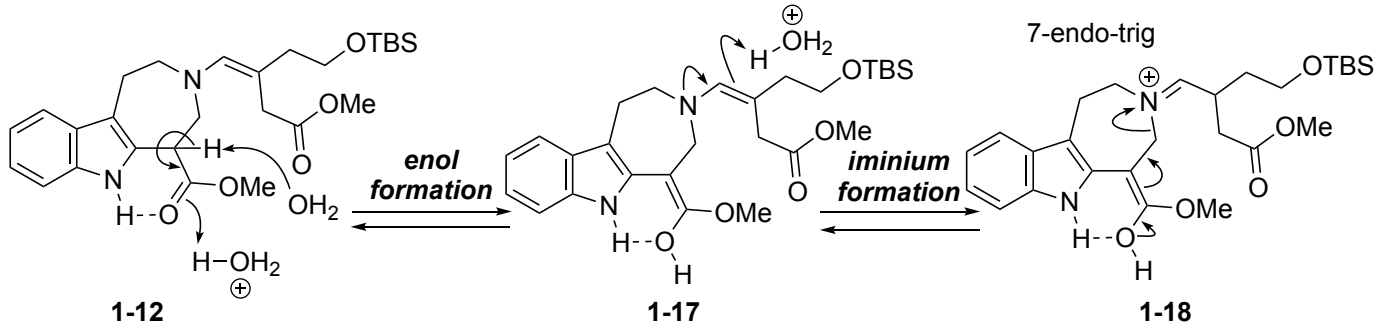


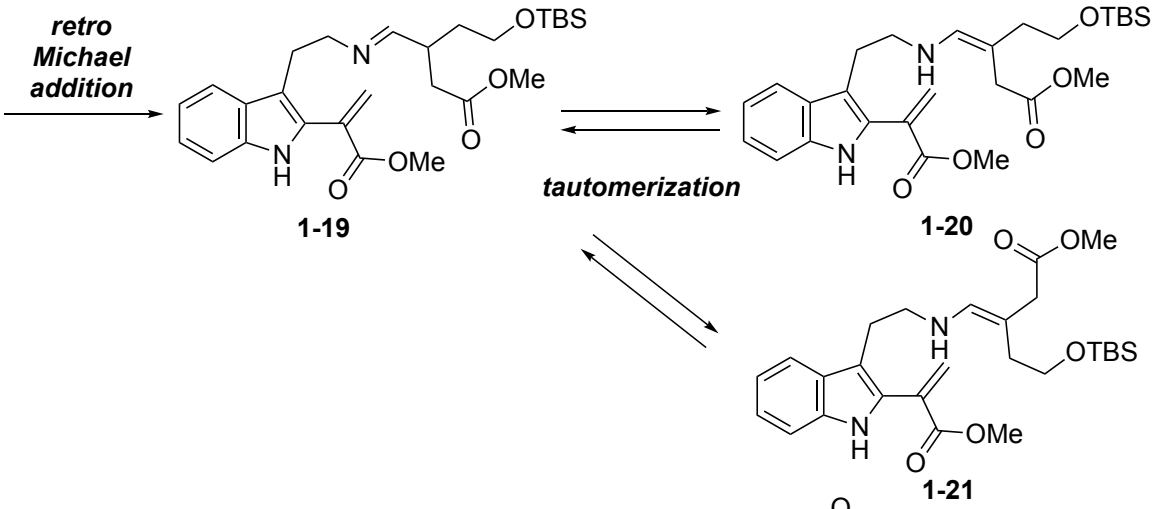
1-7 **1-8** **1-9**

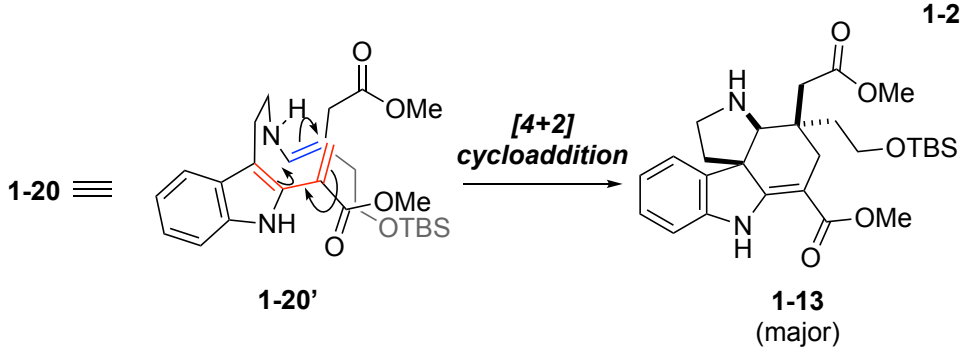
step 2

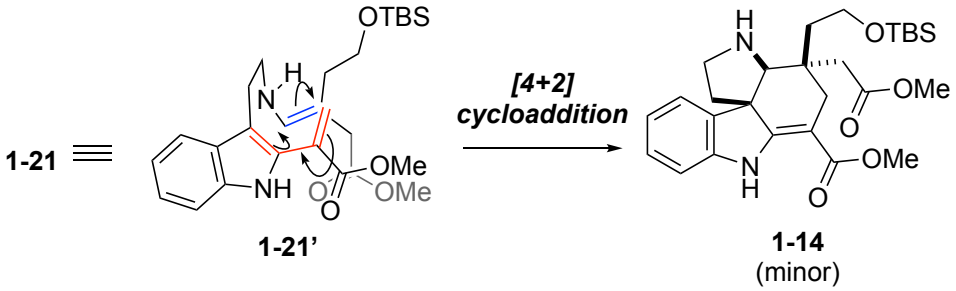


discussion 1 : **ring opening and [4+2] cycloaddition**

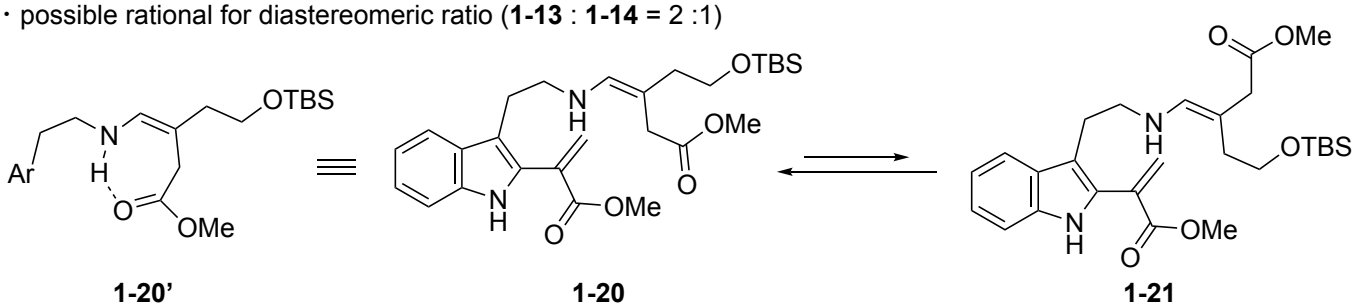








· possible rational for diastereomeric ratio (**1-13** : **1-14** = 2 :1)



small stabilization by hydrogen bond

Diastereomeric ratio would be determined by generation ratio of **1-20** and **1-21**, because of similar transition states (**1-20'** and **1-21'**).

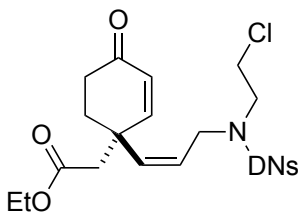
- Other possible rationale

Stabilization of transition state by hydrogen bond

Destabilization of transition state by electrostatic repulsion of 2 carbonyl groups

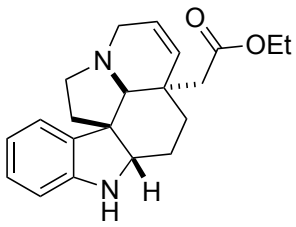
Problem:

(2)



2-1

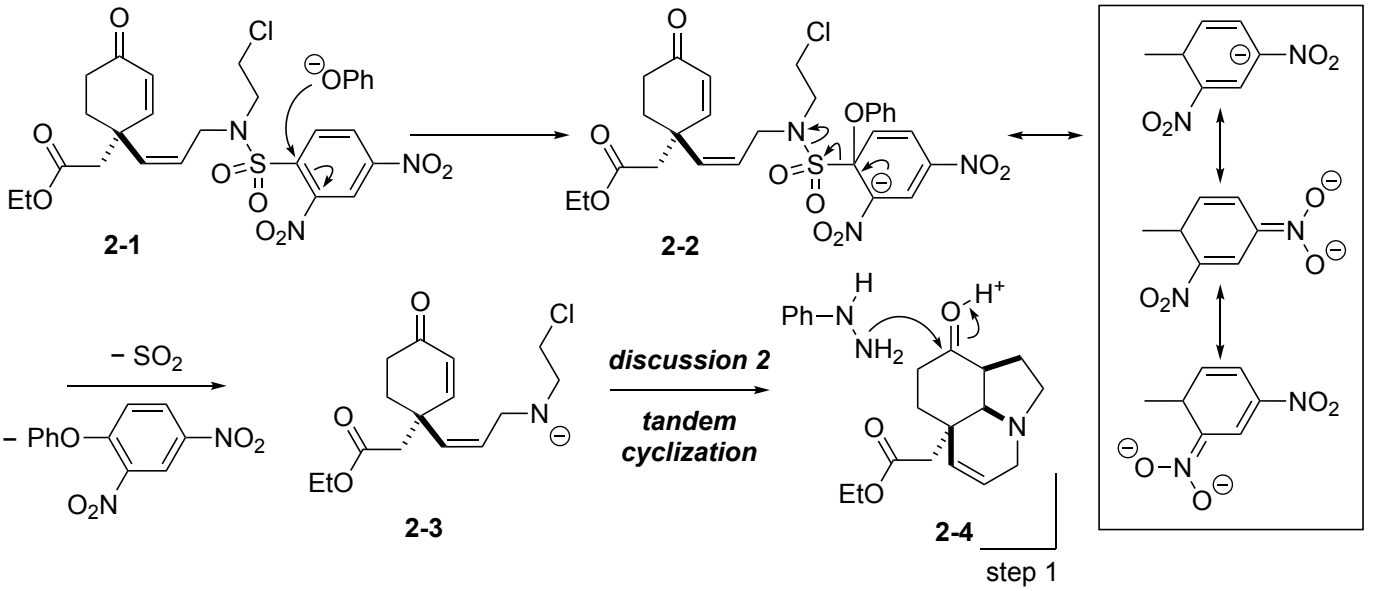
1. PhONa (4.0 eq), DMPU
   23 °C, 70%
2. $PhNHNH_2$ (1.5 eq), TFA (5.0 eq)
   $(CH_2Cl)_2$, 40 °C;
   TFA (60 eq), Et_3SiH (55 eq)
   23 °C, 67%

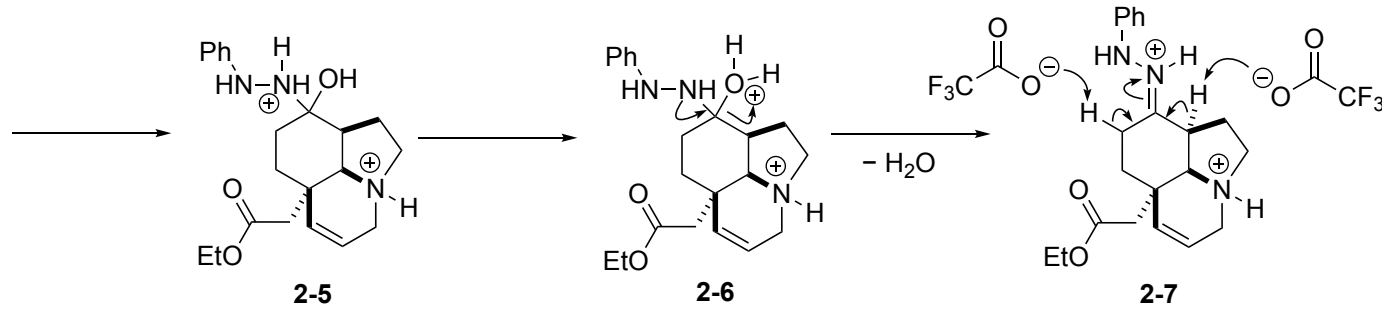


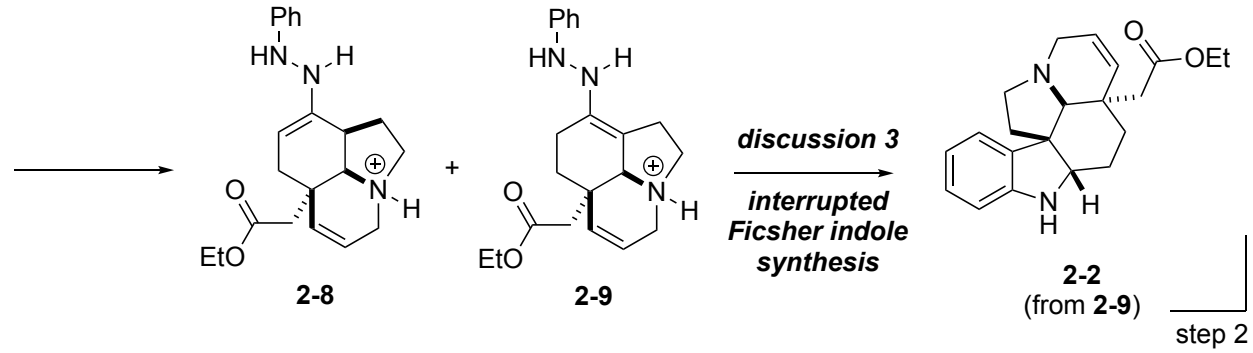
2-2

Zhou, Y.-G., Wong, H. N. C.; Peng, X.-S. *J. Org. Chem.* **2020**, *85*, 967.

Answer:

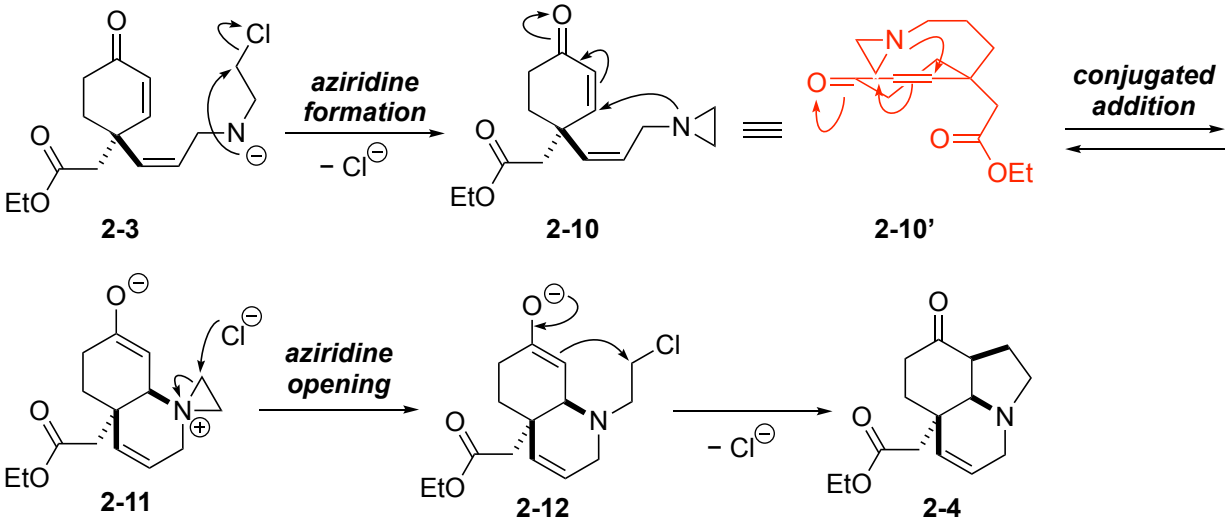




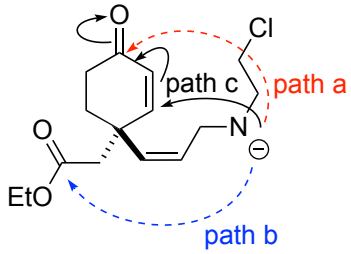


discussion 2: tandem cyclization

The author proposed the reaction mechanism below.



・rational for chemoselectivity

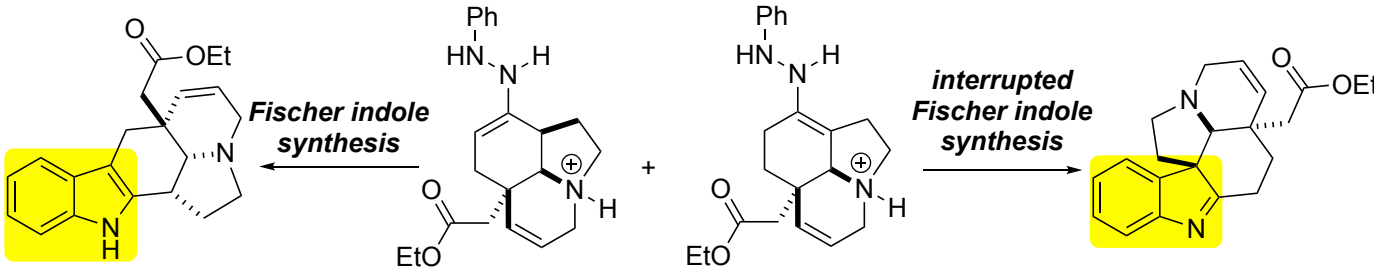


2-1

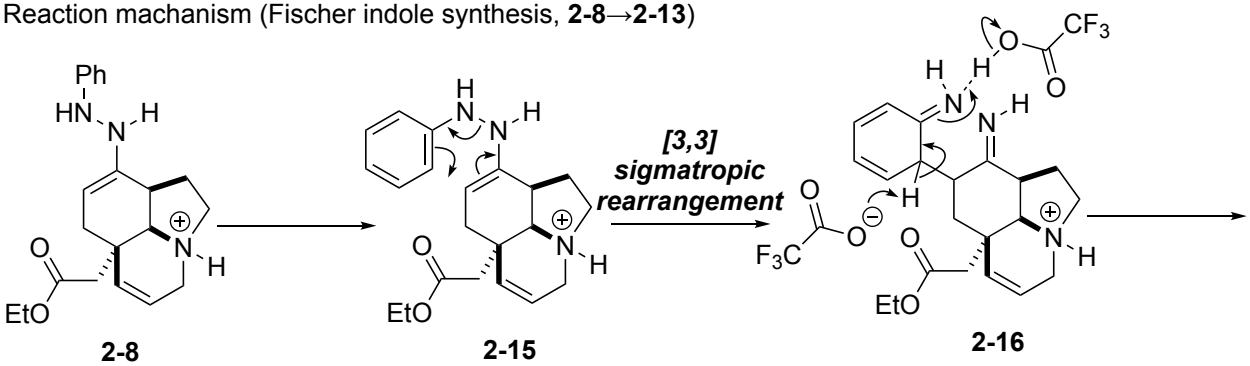
path a	8-membered ring formation	too far
path b	7-membered ring formation	ester is less electron defficient. (less reactive)
path c	6-membered ring formation	more reactive fast
aziridine formation	3-membered ring formation	most reactive irreversible

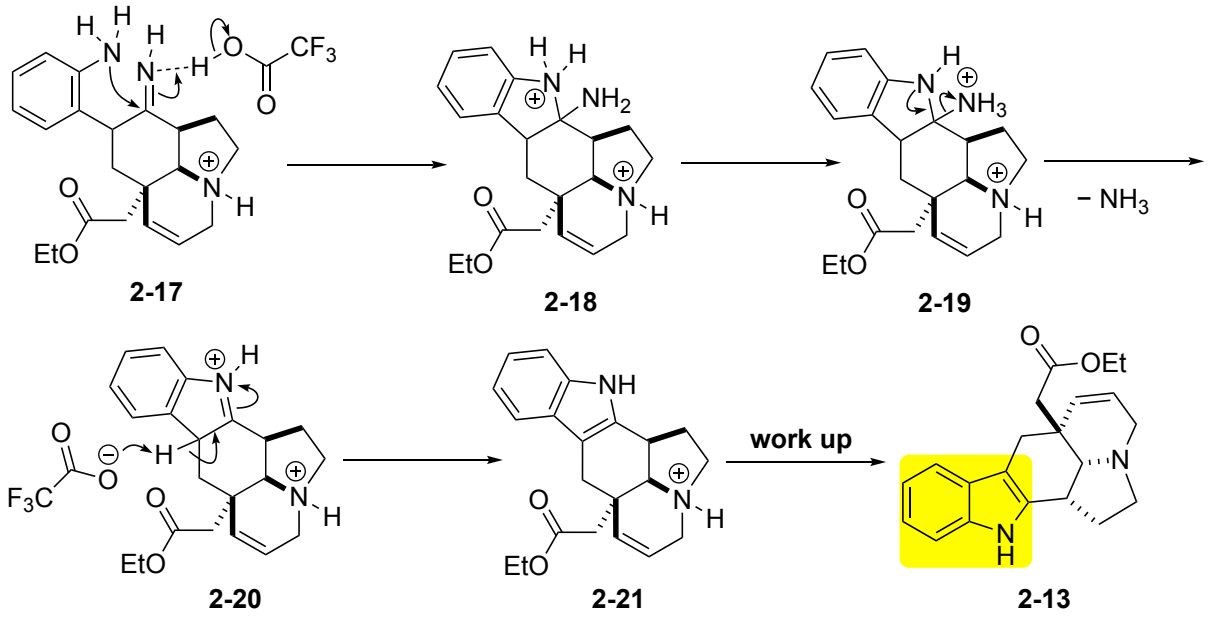
It would be suggested that path c and aziridine formation could be competitive.

discussion 3: interrupted Fischer indole synthesis

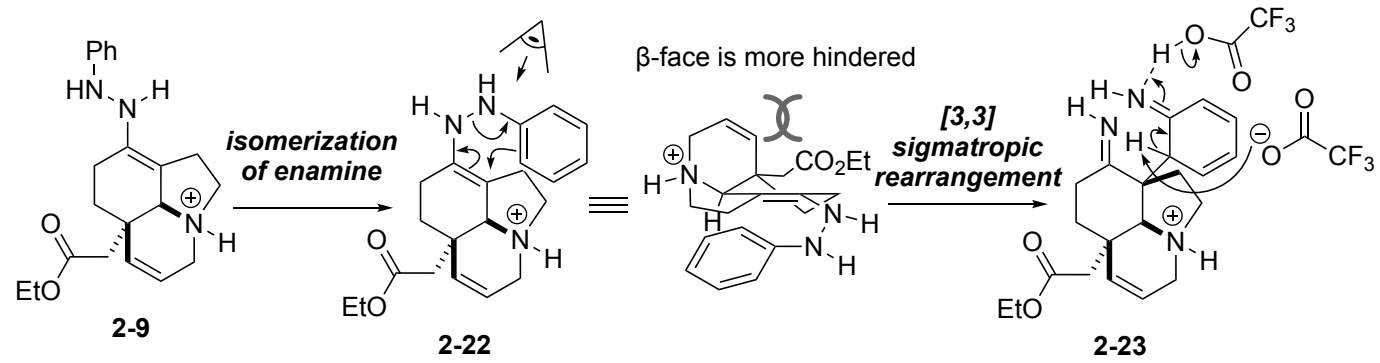


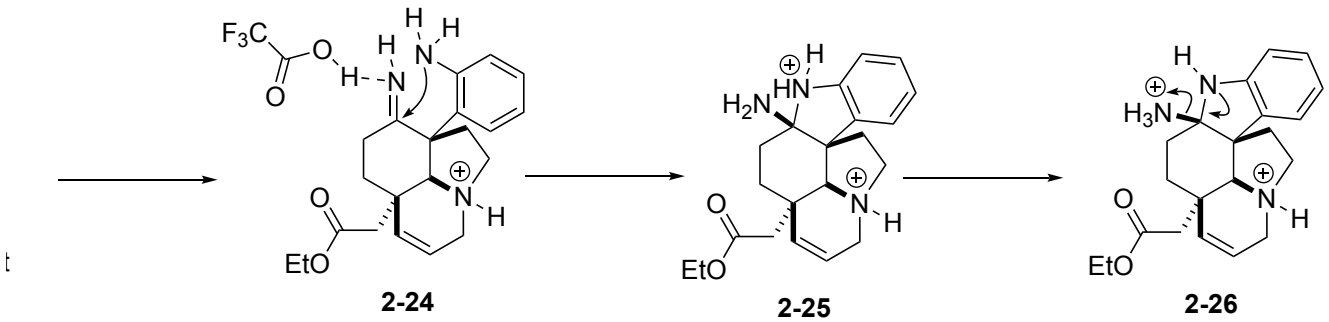
Reaction machanism (Fischer indole synthesis, **2-8**→**2-13**)

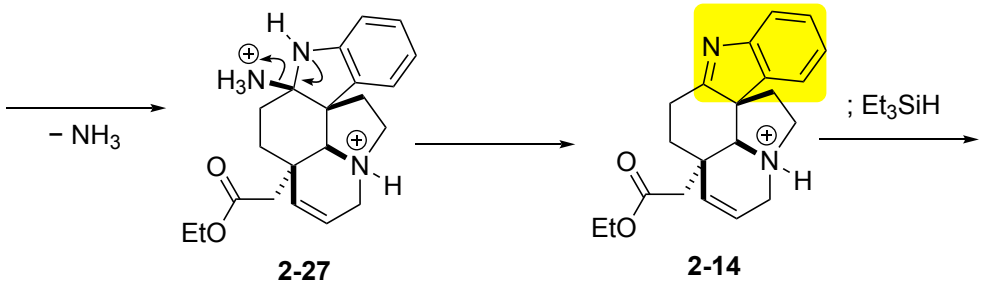


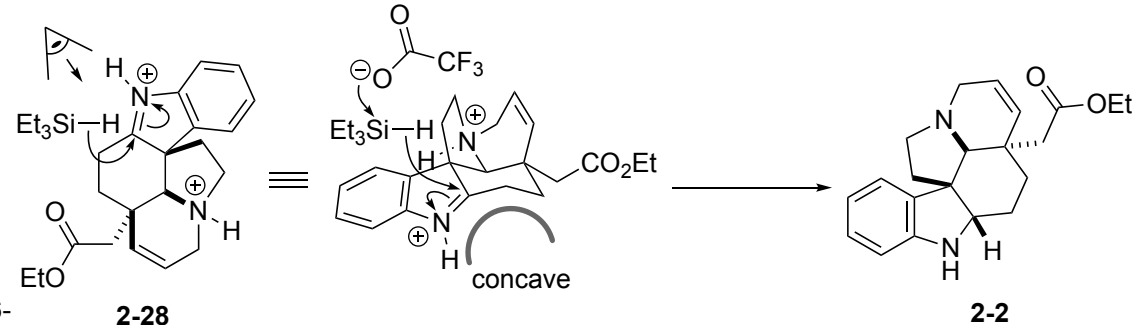


Reaction machanism (interrupted Fischer indole synthesis, **2-9**→**2-14**)

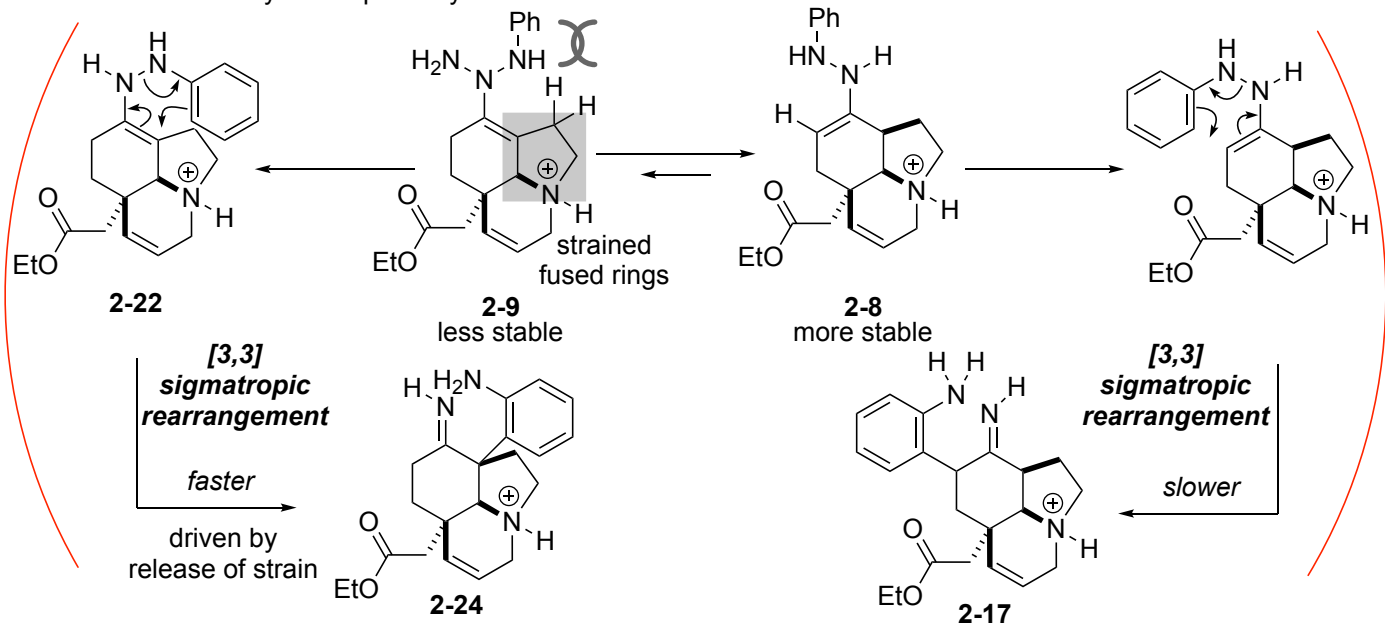


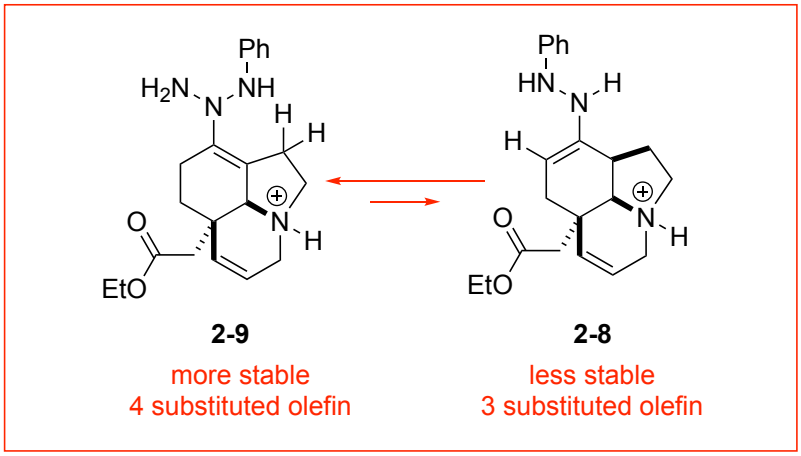




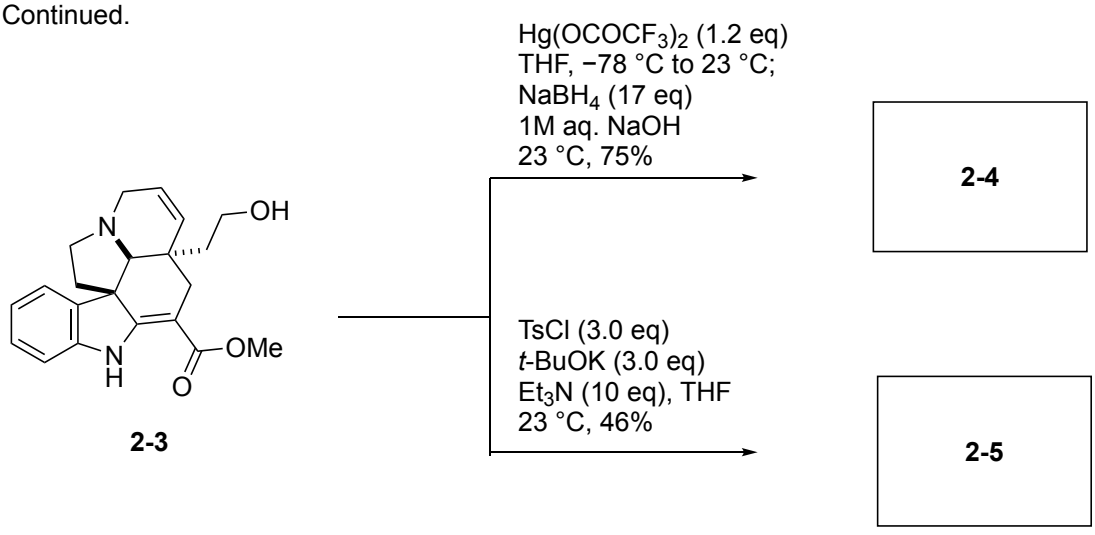


· rational for selectivity of two pathway





(2) Continued.



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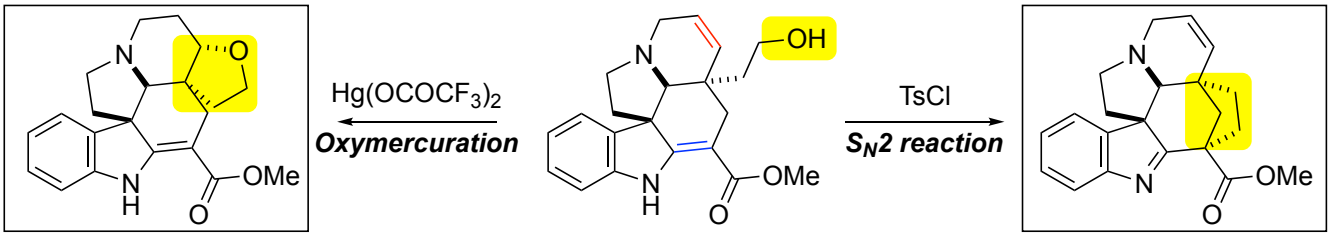
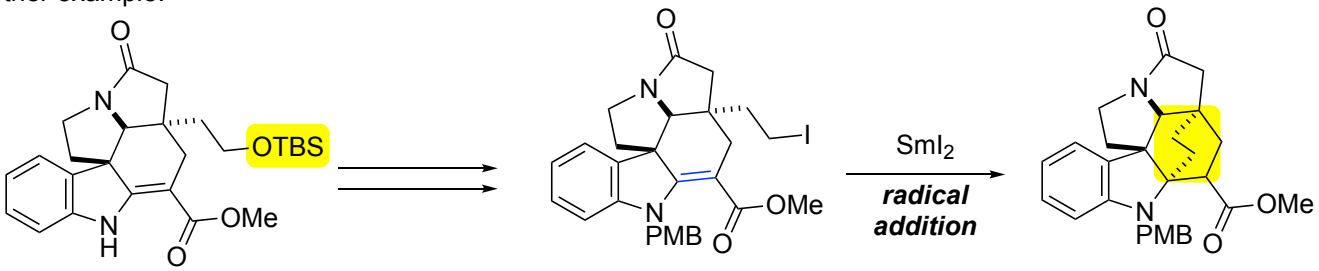
· **Chemoselective cyclization**



2-4 **2-3** **2-5**

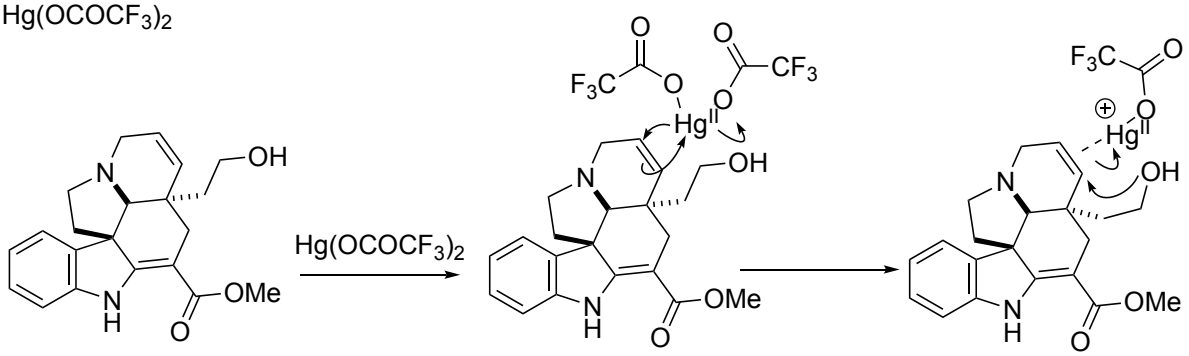
other example:



1-2 **1-22** **1-23**

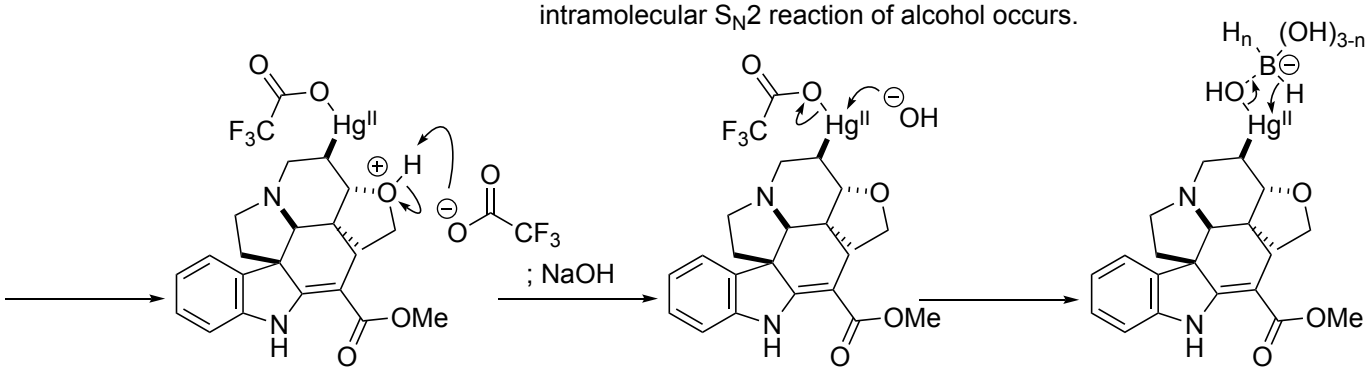
Answer

· $Hg(OCOCF_3)_2$

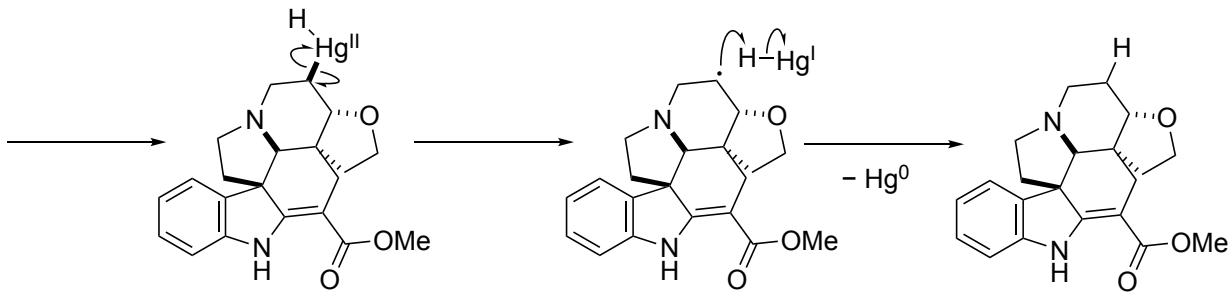


2-3 **2-29** **2-30**

Only when $Hg(OCOCF_3)_2$ reacts with olefin from β-face, intramolecular S_N2 reaction of alcohol occurs.

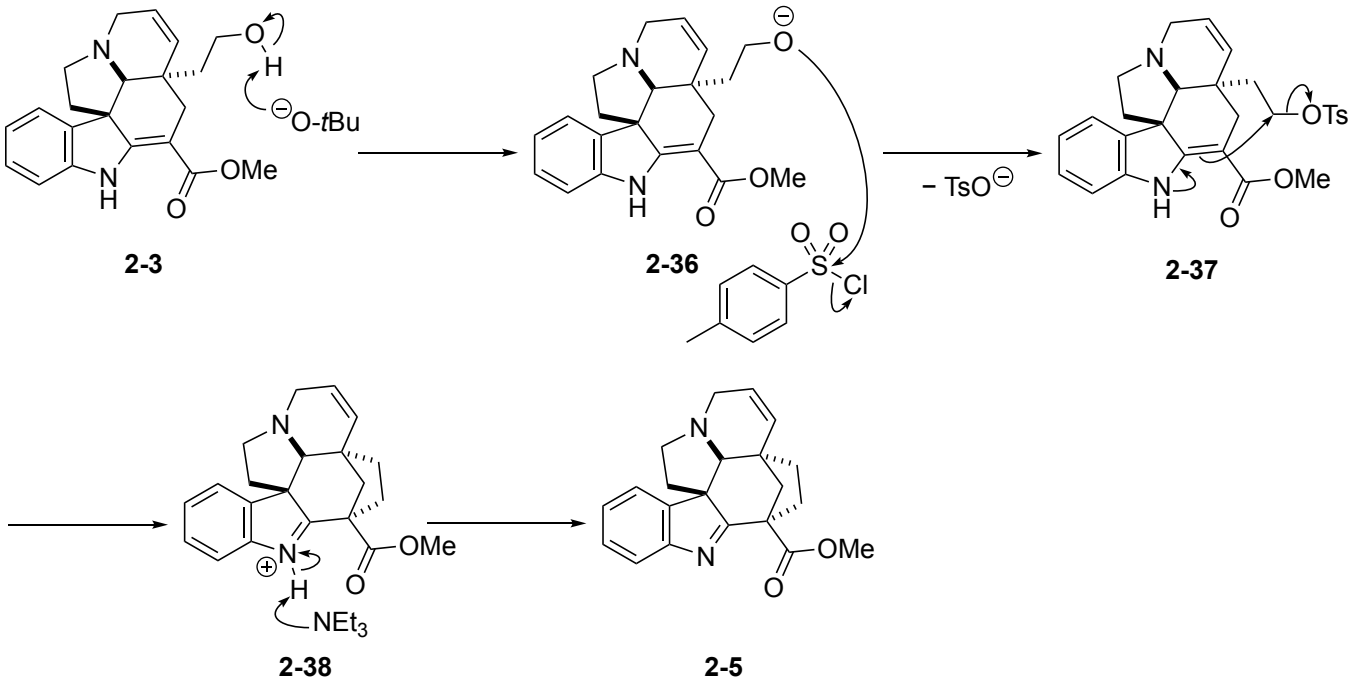


2-31 **2-32** **2-33**



2-34 **2-35** **2-3**

· TsCl. *t*-BuOK, Et_3N



Reference:

1) Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 719.