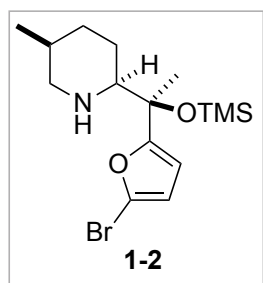
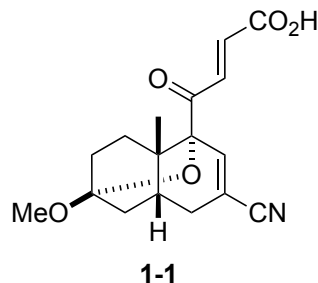


Problem session (2) -answer-

2024/02/10 Mizuki Sawada

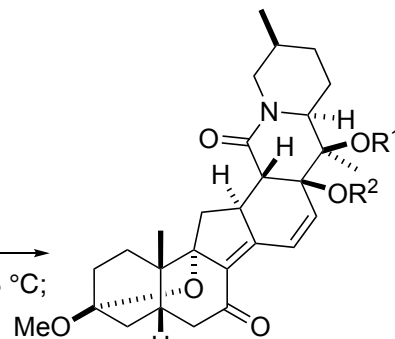
Topic: Skeleton construction of steroidal alkaloids.

Problem 1: Total synthesis of (-)-zygadenine



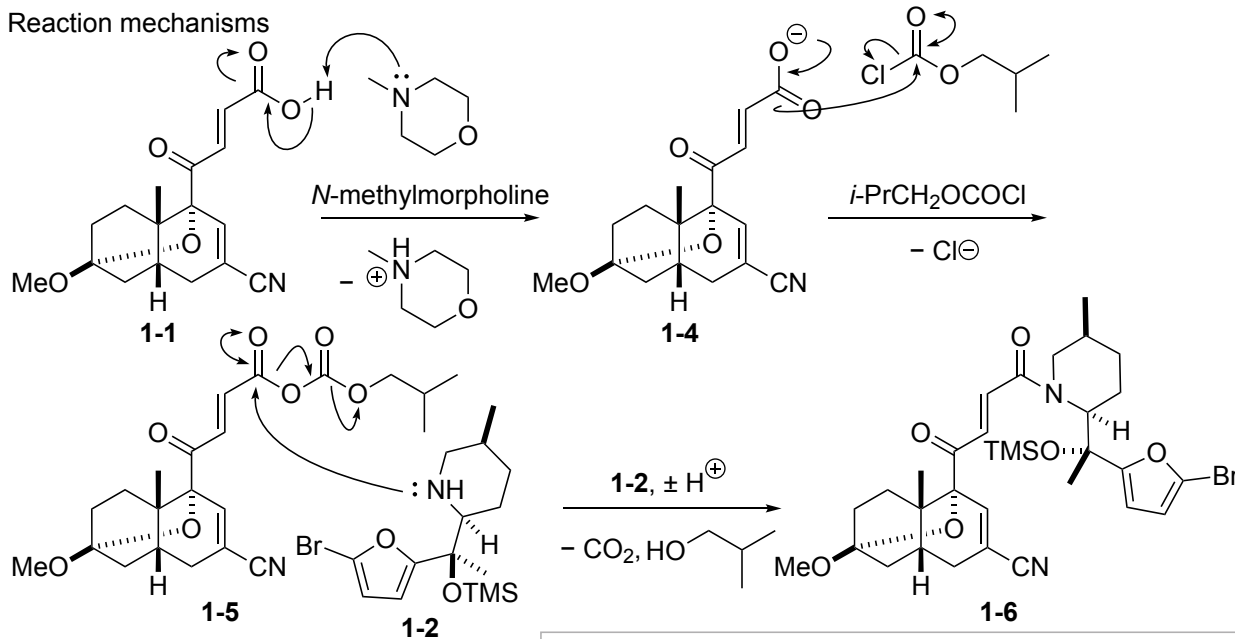
1. *i*-PrCH₂OCOCI (1.17 eq)
N-methylmorpholine (1.17 eq), THF, 0 °C;
1-2 (1.05 eq), Et₃N (2.5 eq), THF, 0 °C;
 H₂O (12 eq), reflux, 92%
2. AIBN (1.0 eq), *n*-Bu₃SnH (2.0 eq)
 benzene, reflux; concentrated;
 NaBH₄ (5.0 eq), MeOH, 0 °C, 89%

3. CS₂ (5.0 eq), NaN(TMS)₂ (3.0 eq), THF, -78 °C;
 MeI (5.0 eq), -78 °C, 66%
4. AIBN (2.0 eq), *n*-Bu₃SnH (5.0 eq)
 benzene, reflux, 85%
5. NaN(TMS)₂ (8.0 eq), THF, -78 °C;
 O₂ (bubbling), -78 °C;
 phosphate buffer (pH 7);
 sat. aq. Na₂SO₃, rt
1-3a + **1-3b**: 46% (**1-3a**:**1-3b** = ~2:1)
1-3c: 29%

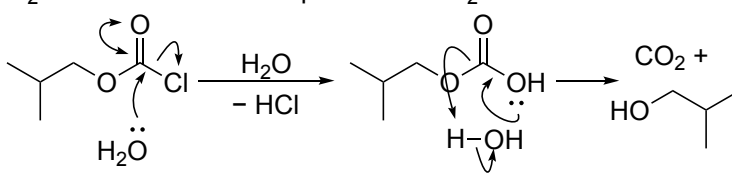


Guo, Y.; Lu, J.-T.; Fang, R.; Jiao, Y.; Liu, J.; Luo, T. *J. Am. Chem. Soc.* **2023**, *145*, 20202.

Reaction mechanisms

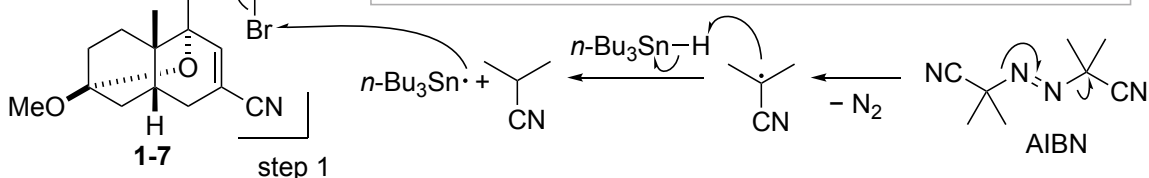


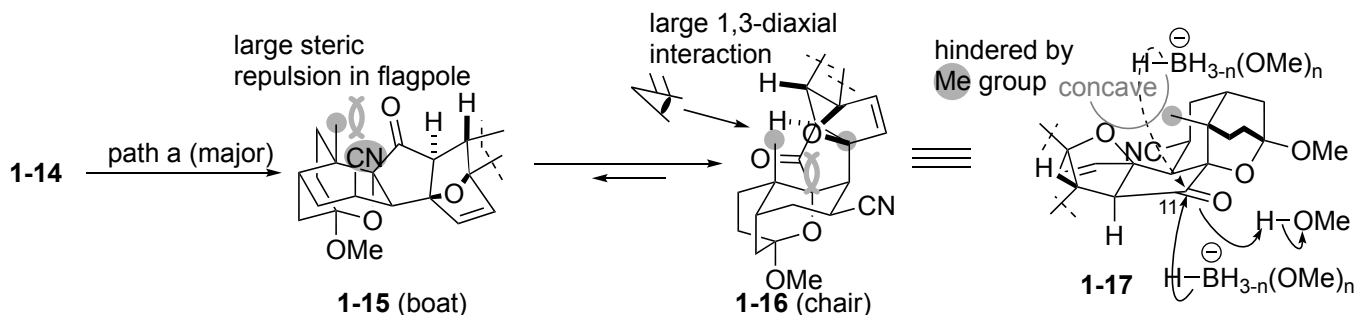
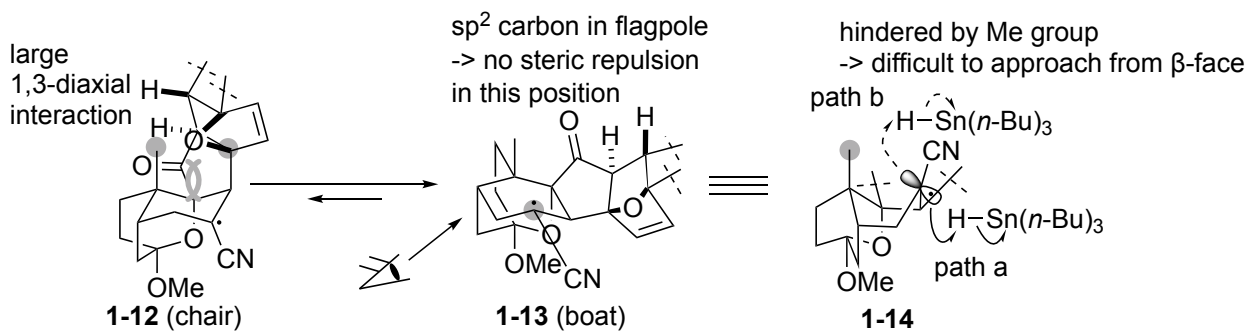
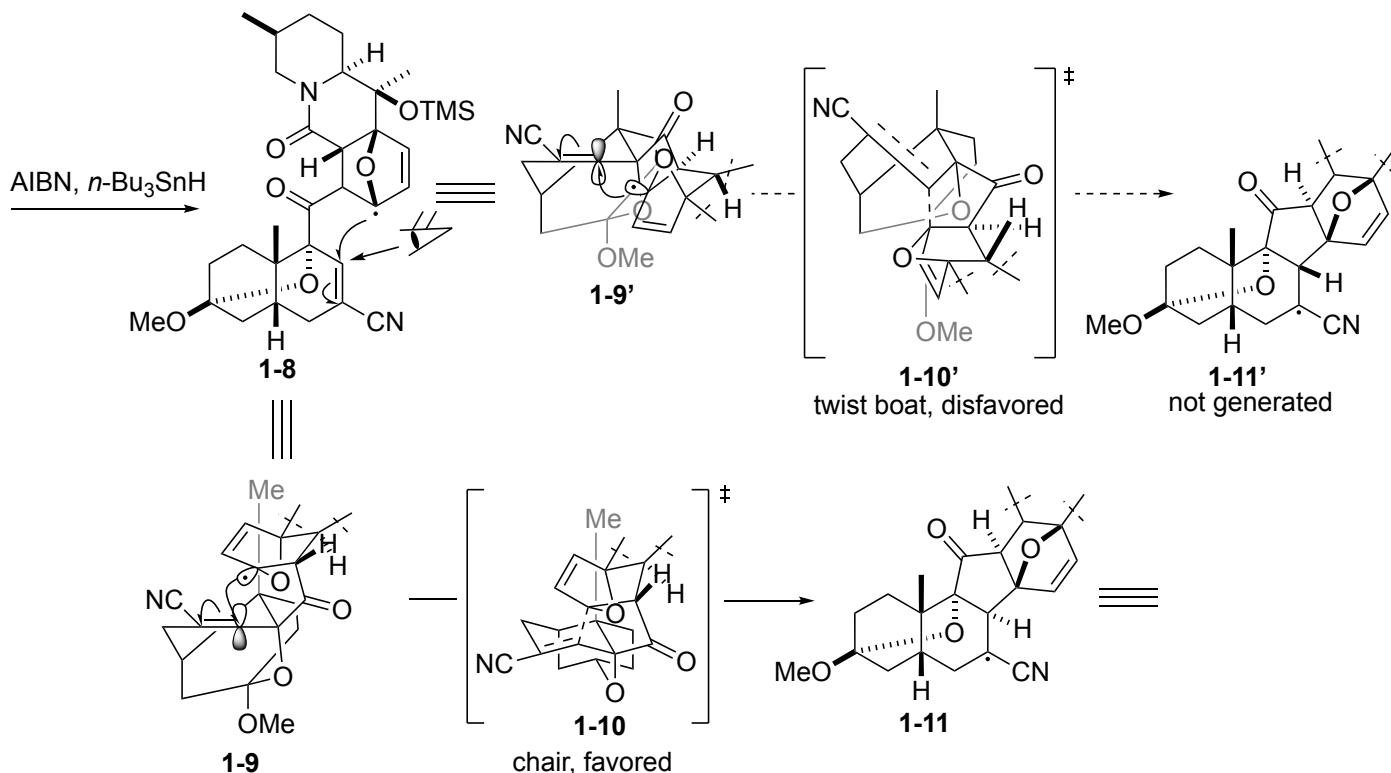
H₂O would be added to quench *i*-PrCH₂OCOCI.



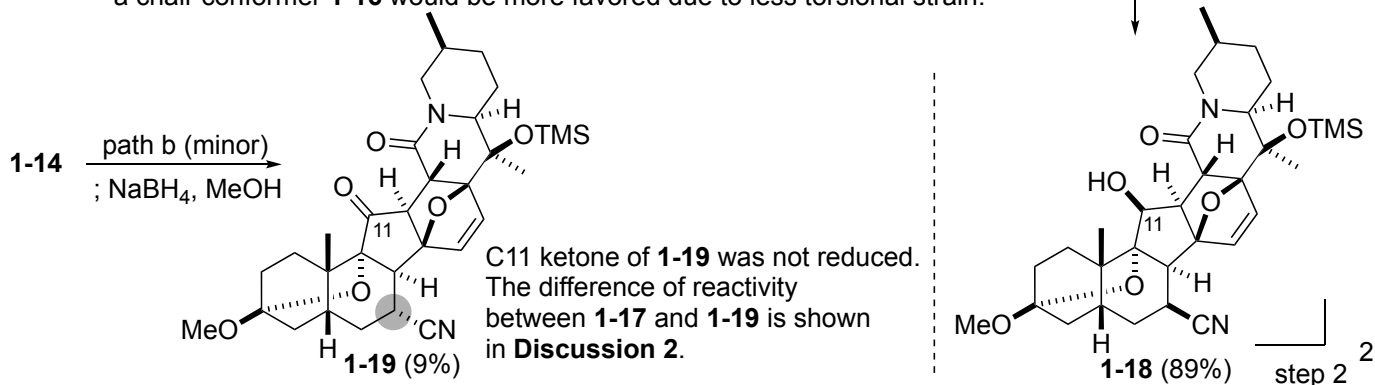
Diels-Alder reaction

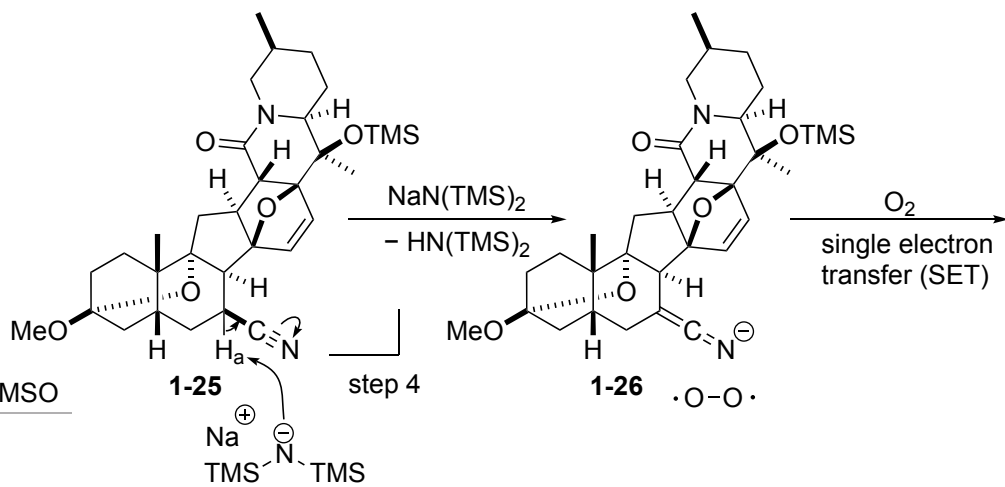
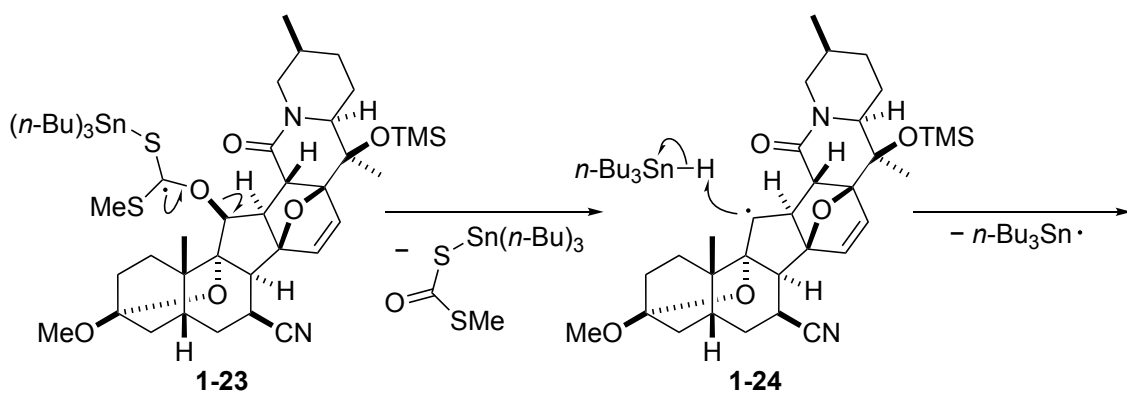
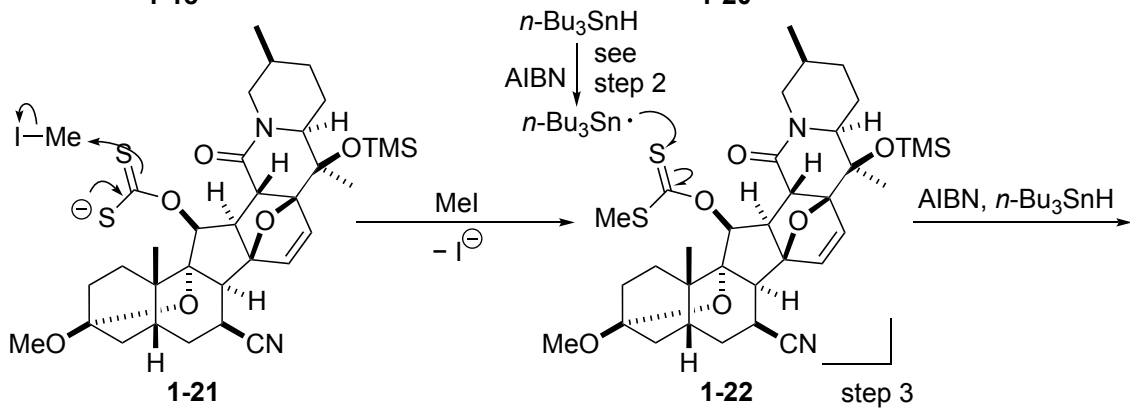
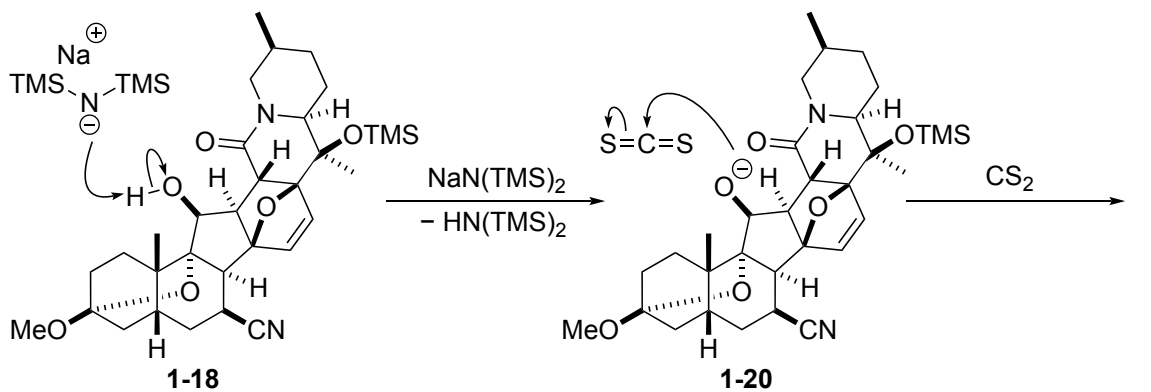
Discussion 1:
 stereoselectivity





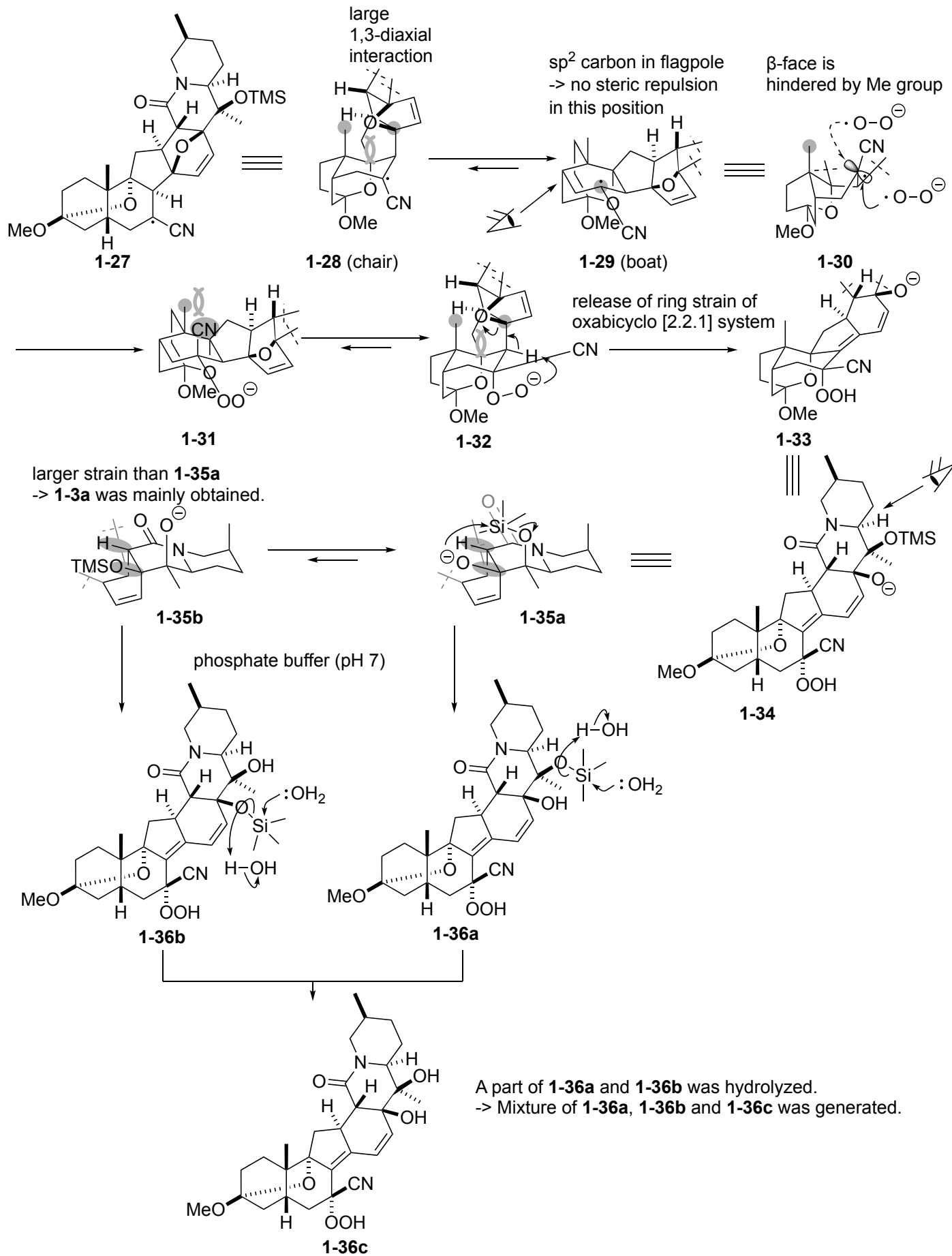
Although there is large steric repulsion both in **1-15** and **1-16**, a chair conformer **1-16** would be more favored due to less torsional strain.

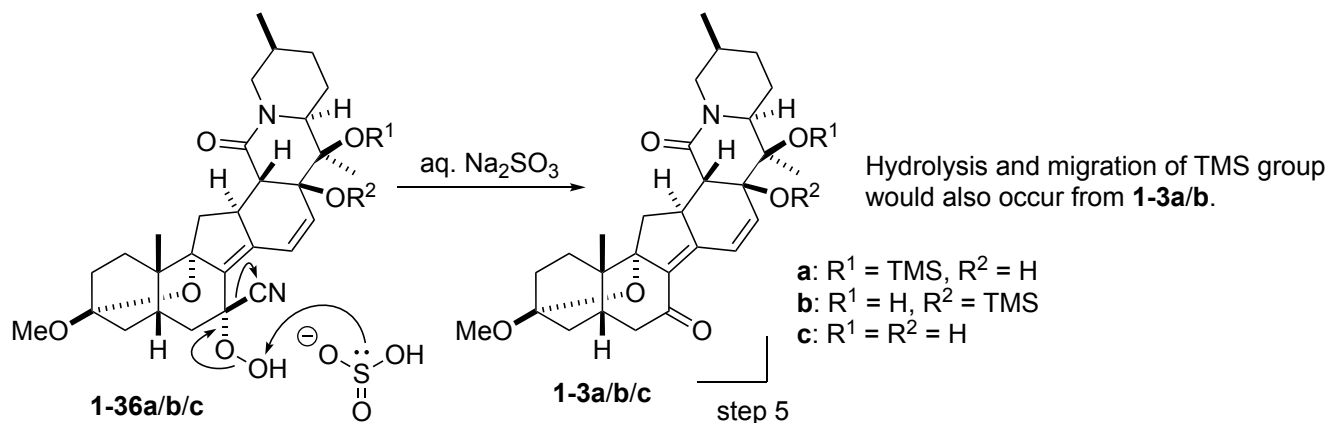




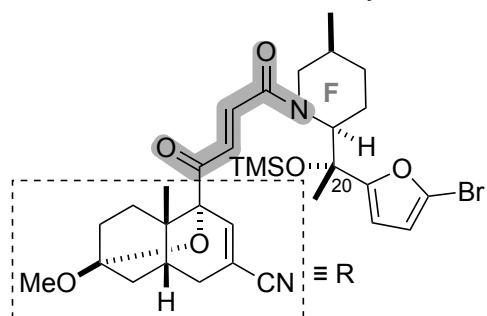
	pK _a in DMSO
	35
	32.5

H_a is expected to be the most acidic proton.





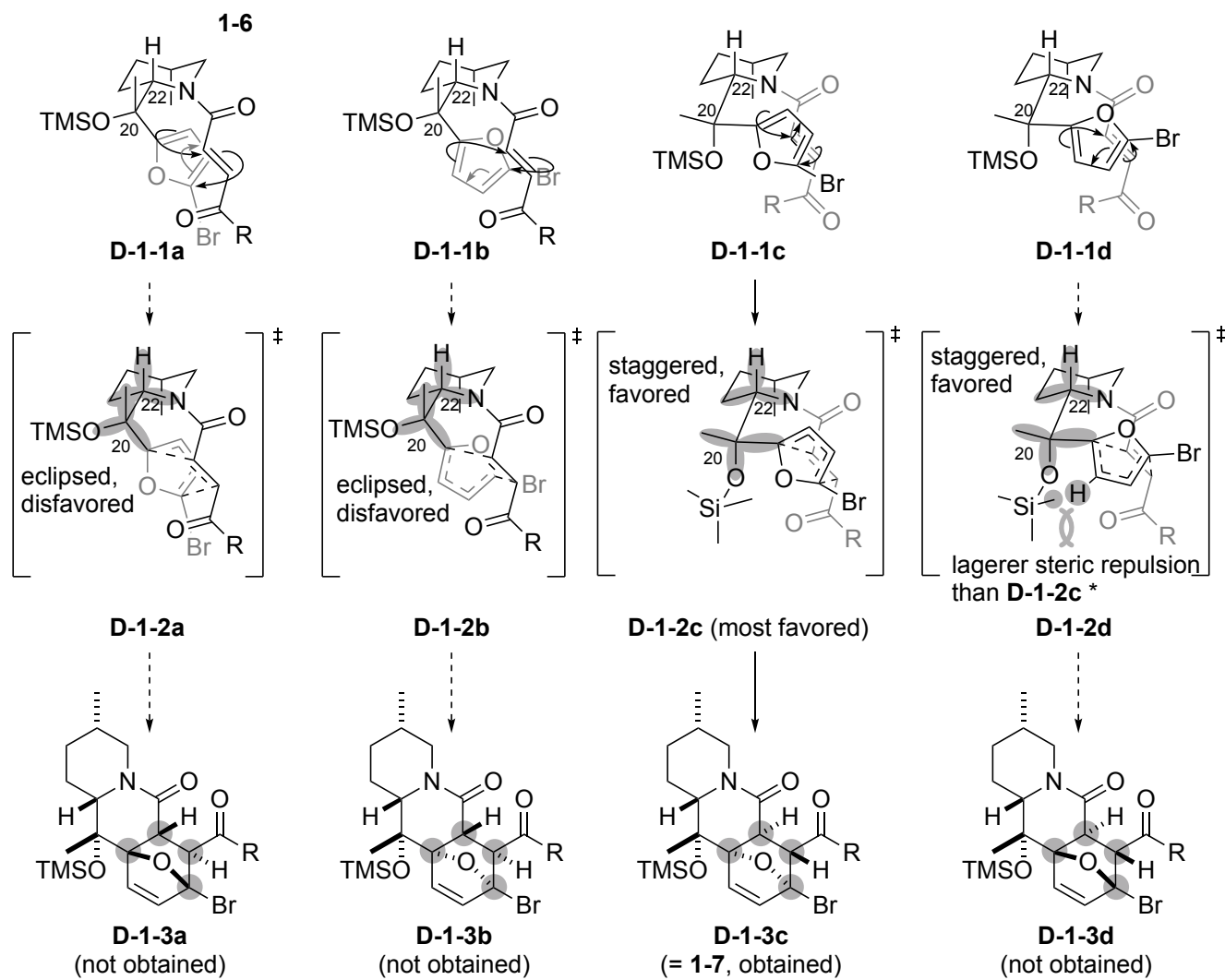
Discussion 1: Stereoselectivity of Diels-Alder reaction



Restrictions for conformation of **1-6**

- F-ring is chair-form.
- Tetrasubstituted C20 carbon should be oriented to equatorial position.
- Highlighted sp² atoms should be in the same plane to be conjugated.

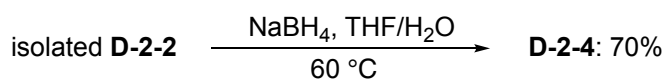
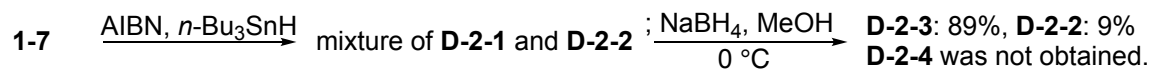
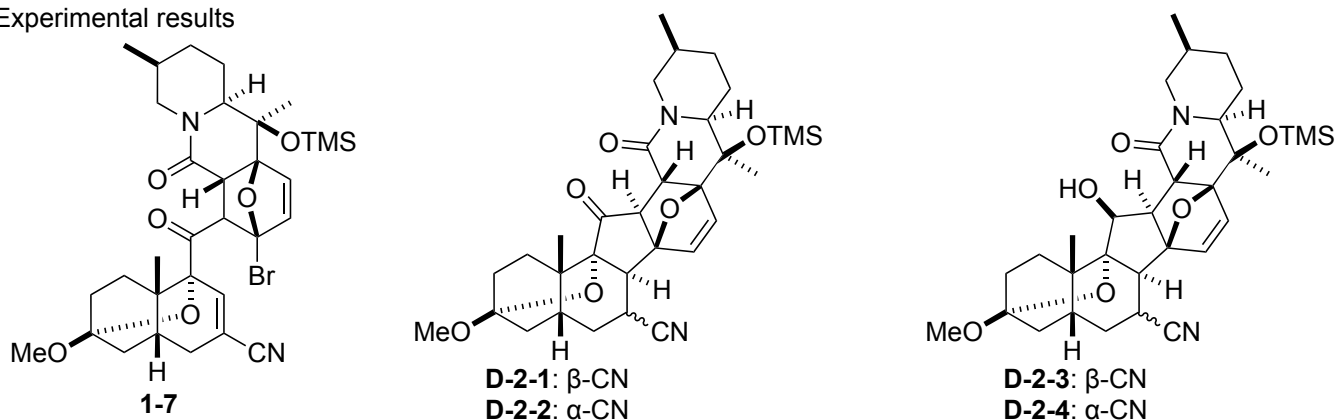
Under these promises, Diels-Alder reaction can proceed from conformers **D-1-1a/b/c/d**.



* The orientation of TMS group would be fixed to minimize repulsion with F-ring.

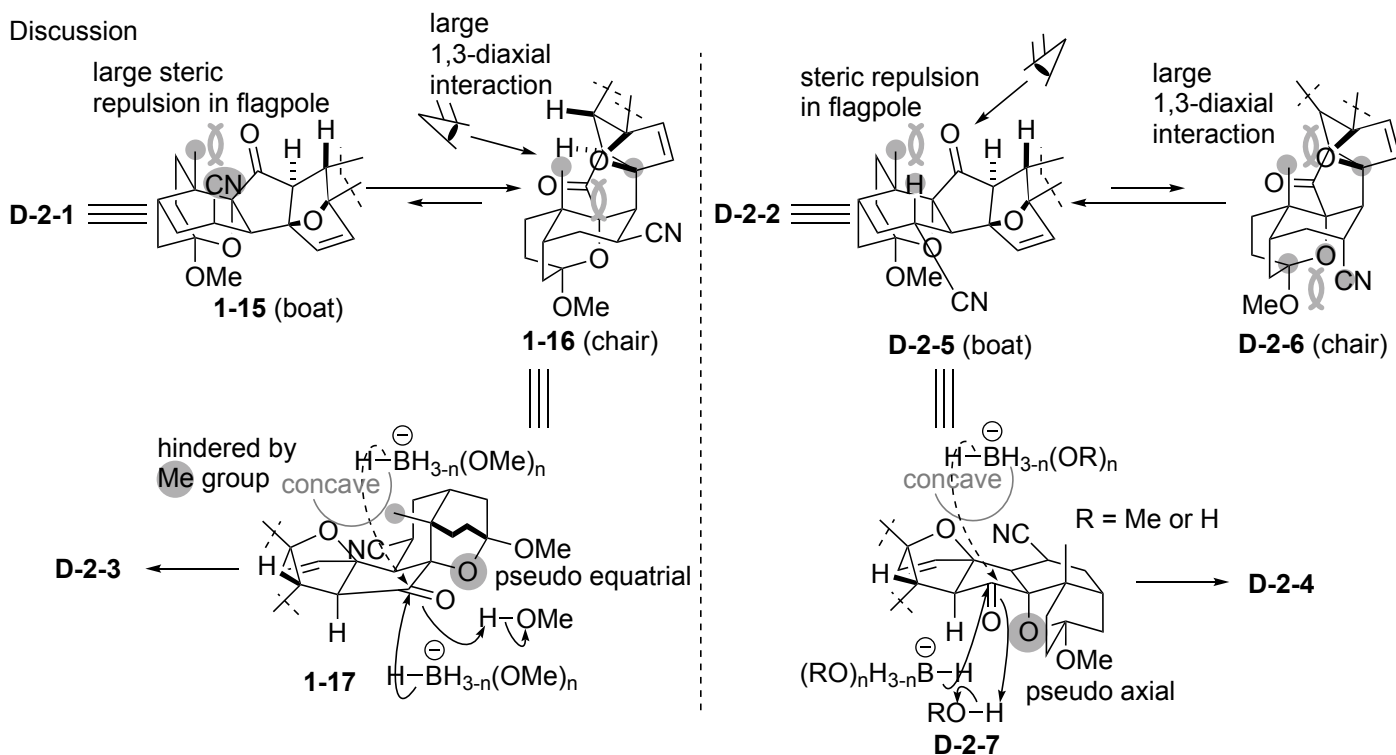
Discussion 2: The difference of reactivity between **D-2-1** and **D-2-2**

Experimental results



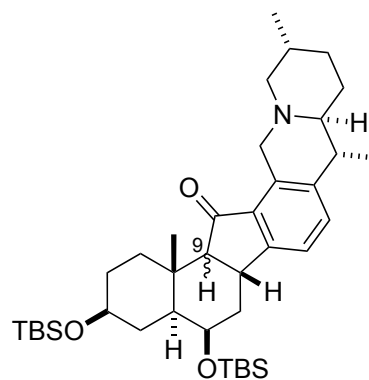
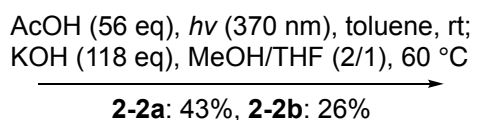
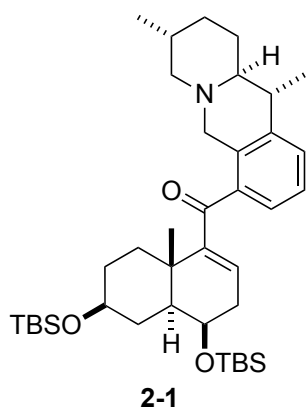
The higher temperature was required to reduce **D-2-2** than **D-2-1**.

Discussion



The convex face of **D-2-7** is more shielded than **1-17** due to pseudo axial oxygen atom of ether.

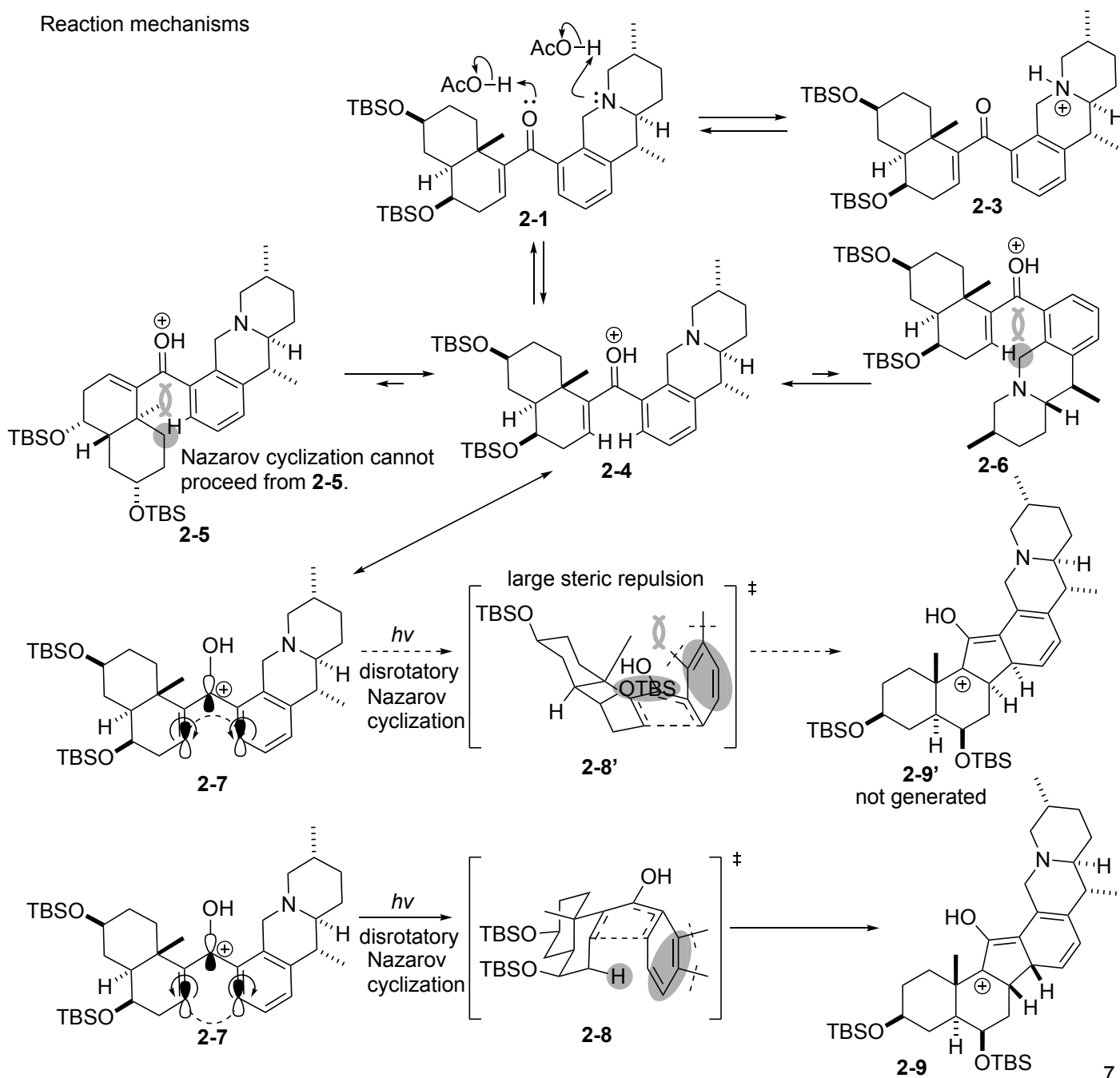
Problem 2: Total synthesis of (+)-heilonine

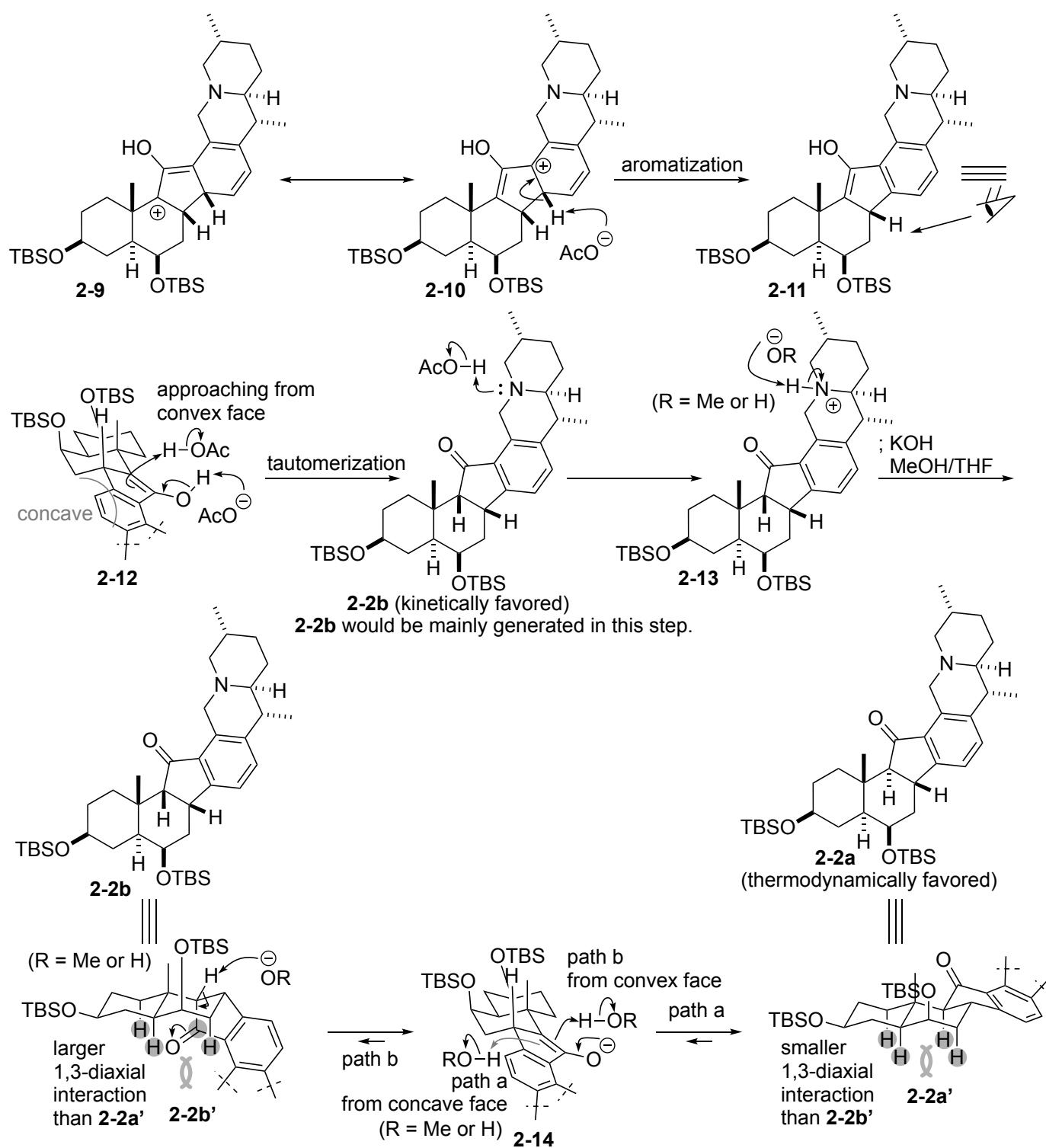


2-2a: α -H (S) at C9, 2-2b: β -H (R) at C9

Jin, Y.; Hok, S.; Bacsá, J. and Minji, D. *J. Am. Chem. Soc.* **2024**, *146*, 1825.

Reaction mechanisms





Epimerization of **2-2b** to **2-2a** in basic condition is experimentally confirmed.

