

Problem Session (1) -Answer-

2023/09/30 Sota Mochizuki

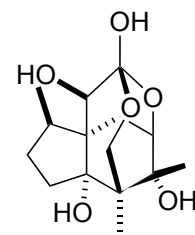
Topic: Divergent total synthesis of *illicium* sesquiterpenes

Introduction

Isolation: *illicium* genus of plants

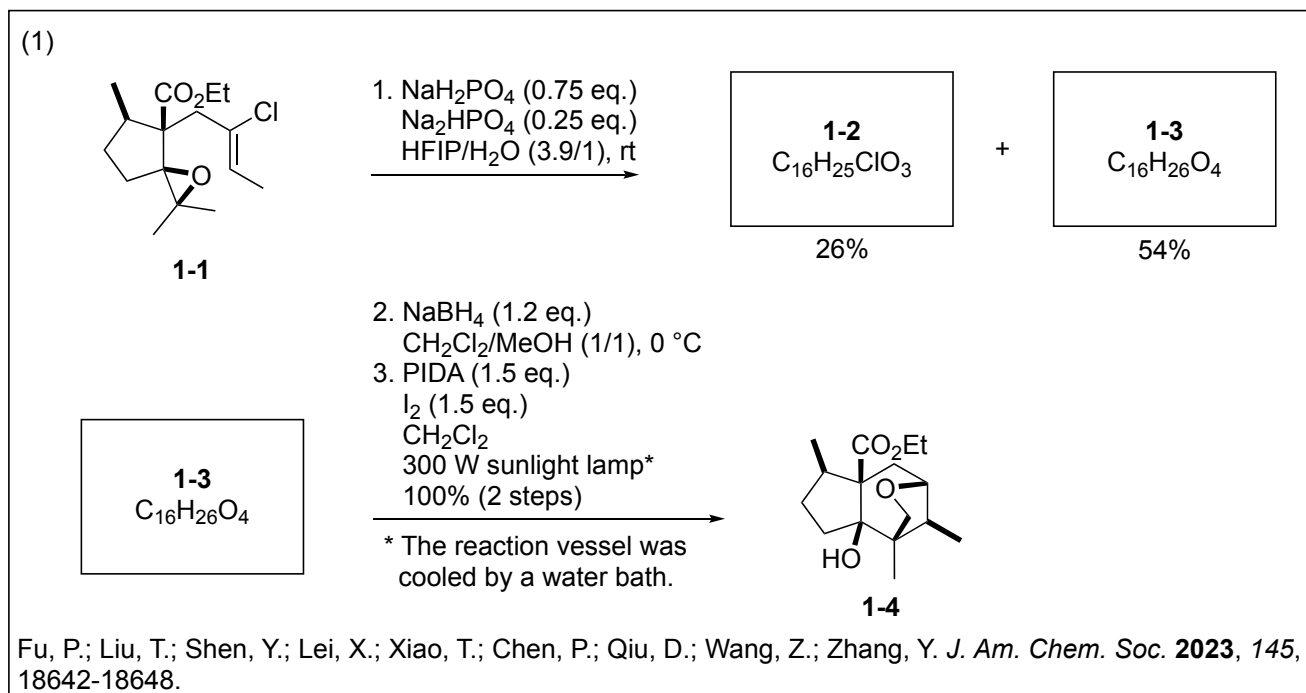
Bioactivity: anti-HBV activity (Henrylactone C, Anislactone B) ^{ref 1)}

Total synthesis: Maimone's group (*J. Am. Chem. Soc.* **2017**, *139*, 17783-17786.)

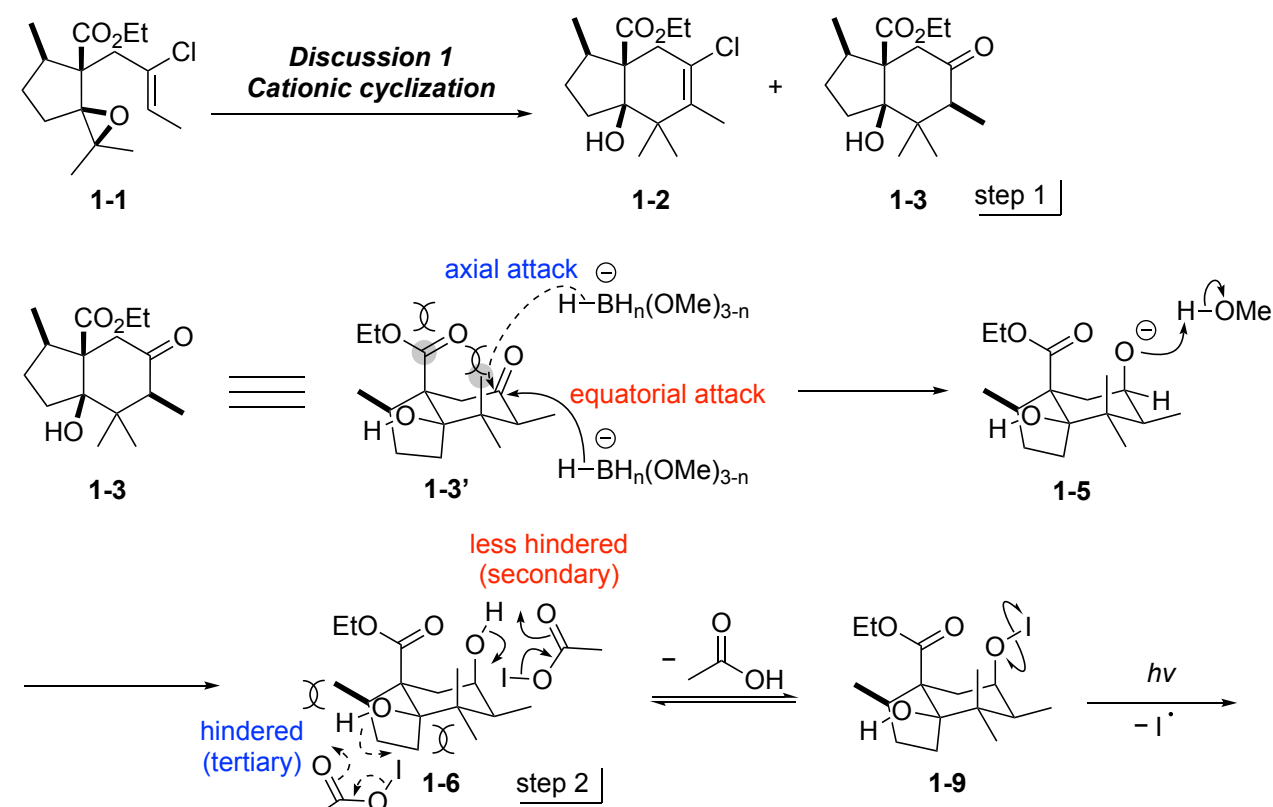


Henrylactone C

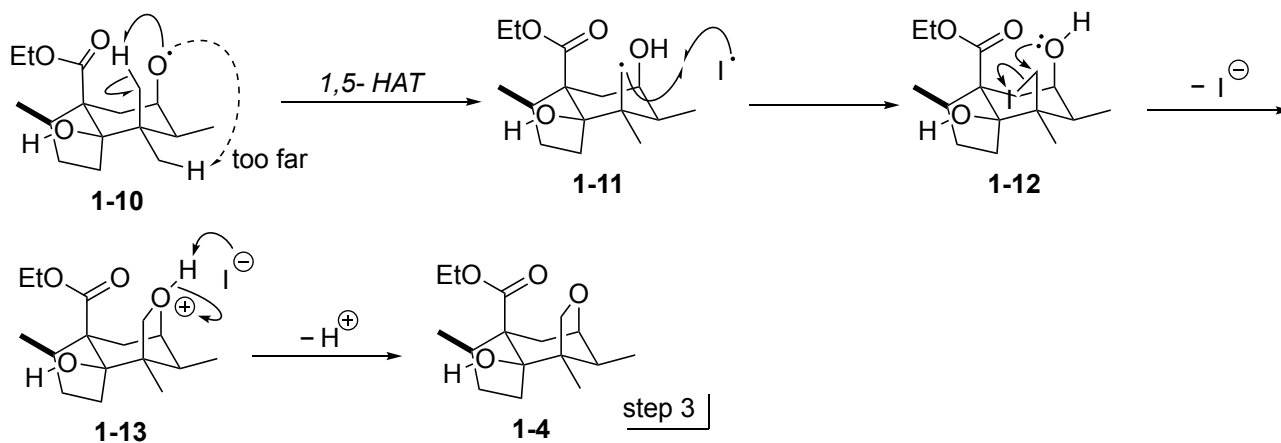
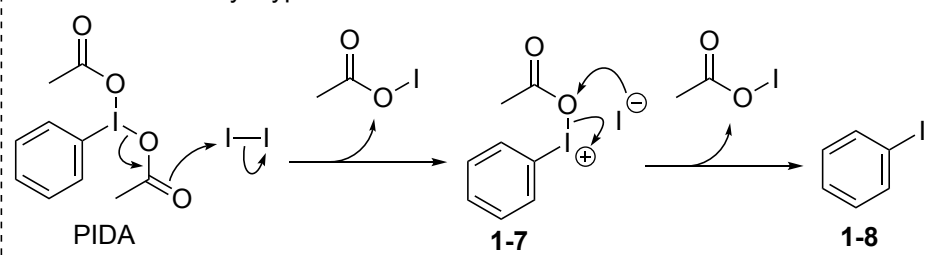
Problem



Answer:

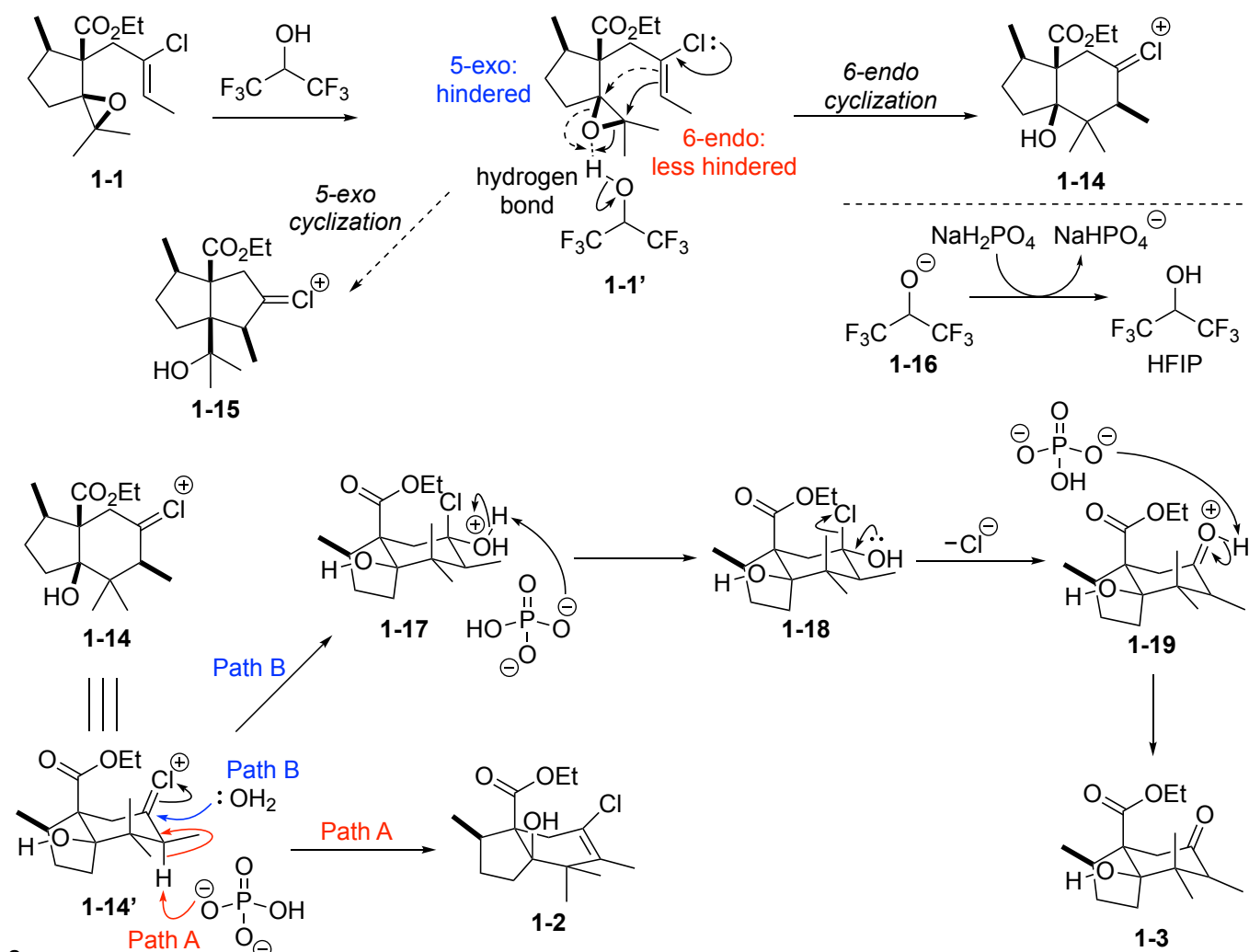


Generation of acetyl hypoiodite ^{ref 2)}



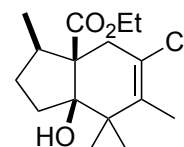
Discussion 1: Cationic cyclization

1-1. Reaction mechanism

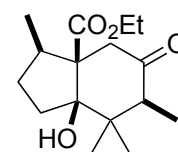


1-2. Conditions

entry	additive and solvent	time (h)	yields (%)	
			1-2	1-3
1	HFIP, THF/H ₂ O	24	21	31
2	Na ₂ HPO ₄ , NaH ₂ PO ₄ , H ₂ O	96	0	0
3	HFIP, Na ₂ HPO ₄ , NaH ₂ PO ₄ , H ₂ O	48	26	54
4	<i>n</i> -Bu ₂ BOTf	1	58	0



1-2



1-3

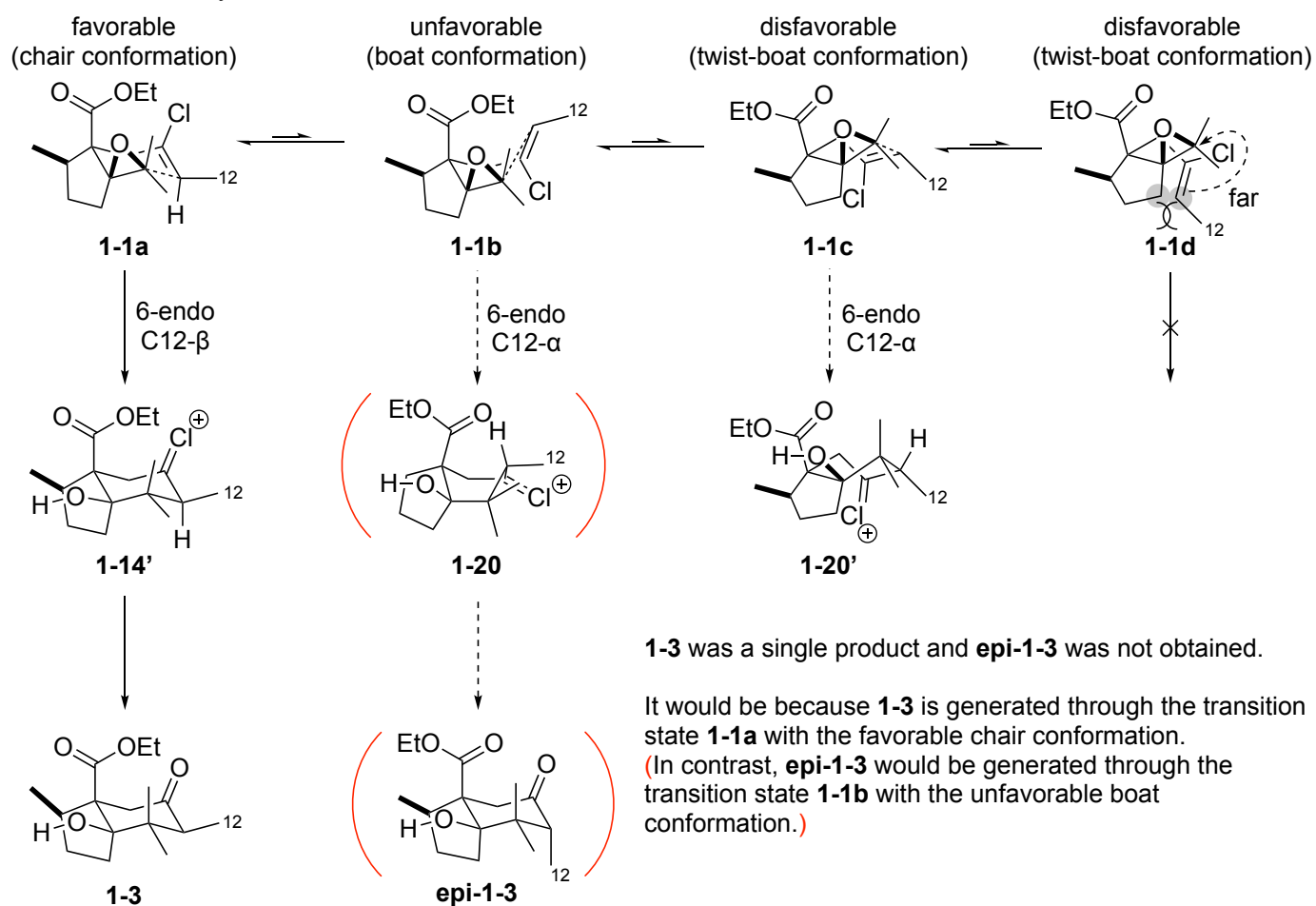
Comparing entry 2 and entry 3, it is suggested that epoxide of **1-1** is activated by a hydrogen bond with HFIP, and the activation is necessary for cationic cyclization.

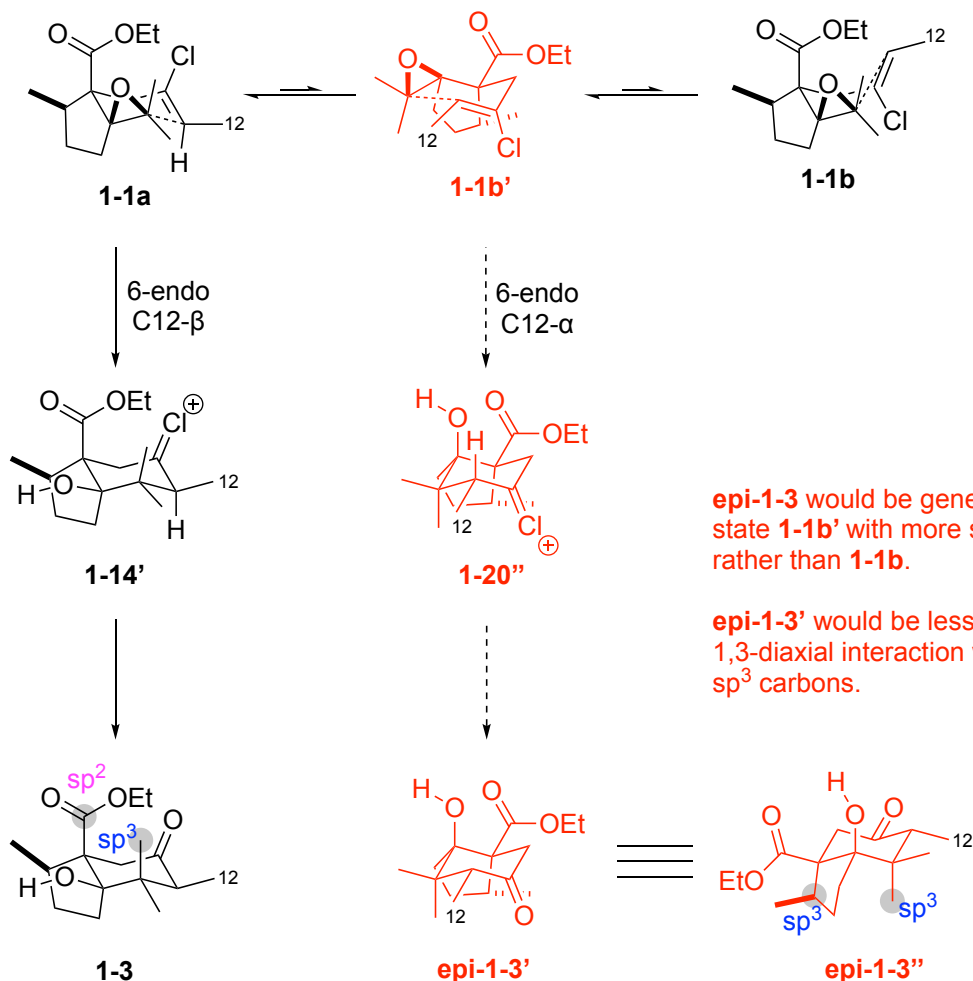
Comparing entry 1 and entry 3, the yield of **1-3** was improved by adding a buffer. This could be explained by neutralizing HCl released during the generation of **1-3**. Lower concentration of H⁺ may suppress side reactions.

buffer: pH = 6.72

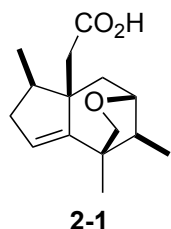
In entry 4, Lewis acid was used instead of Brønsted acid without H₂O, and only **1-2** was generated. This indicates that the activation by Lewis acid also can proceed cyclization, but generation of **1-3** needs H₂O.

1-3. Stereoselectivity

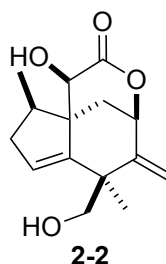




(2)

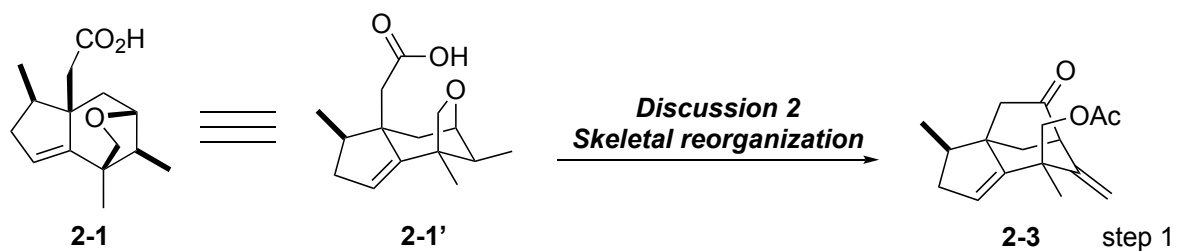


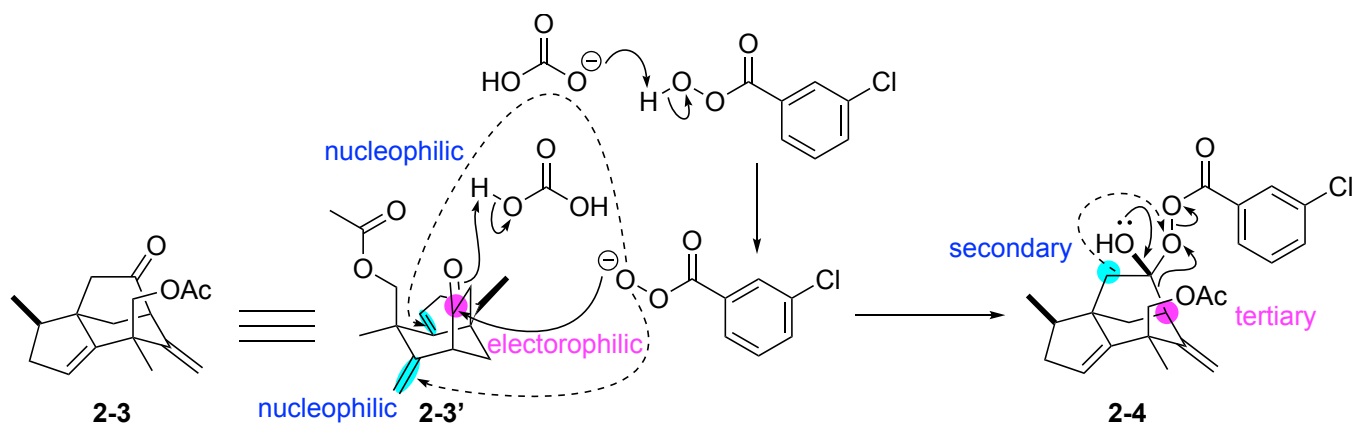
1. TMSOTf (2.0 eq.)
(±)-BINAP (1.0 eq.)
Ac₂O, -78 °C to rt, 61%
2. *m*-CPBA (1.35 eq.)
NaHCO₃ (10 eq.)
CH₂Cl₂, 0 °C to rt, 83%
3. KN(TMS)₂ (2.0 eq.)
THF, rt;
Davis reagent (2.0 eq.)
-78 °C to rt, 71%



Fu, P.; Liu, T.; Shen, Y.; Lei, X.; Xiao, T.; Chen, P.; Qiu, D.; Wang, Z.; Zhang, Y. *J. Am. Chem. Soc.* **2023**, *145*, 18642-18648.

Answer:

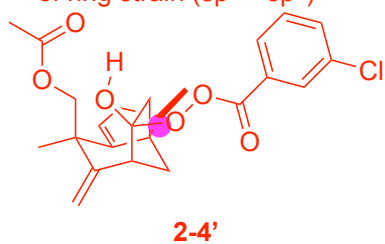
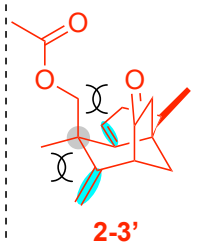




Another factors of chemoselectivity

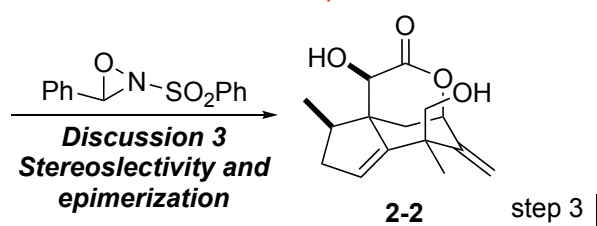
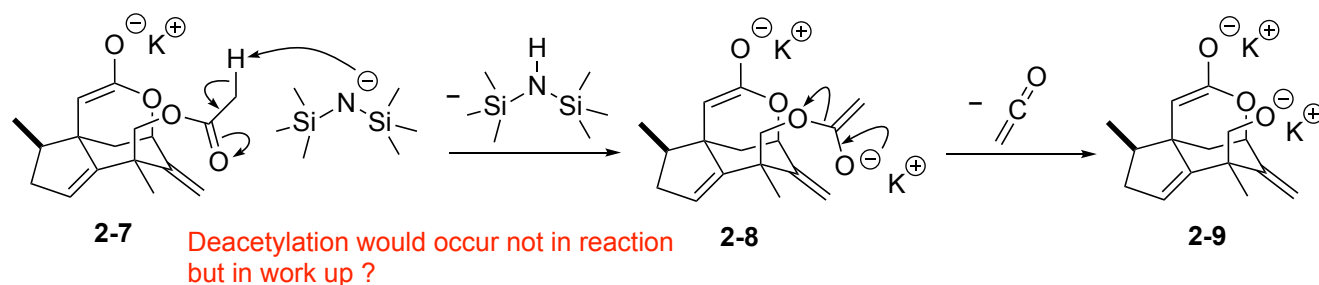
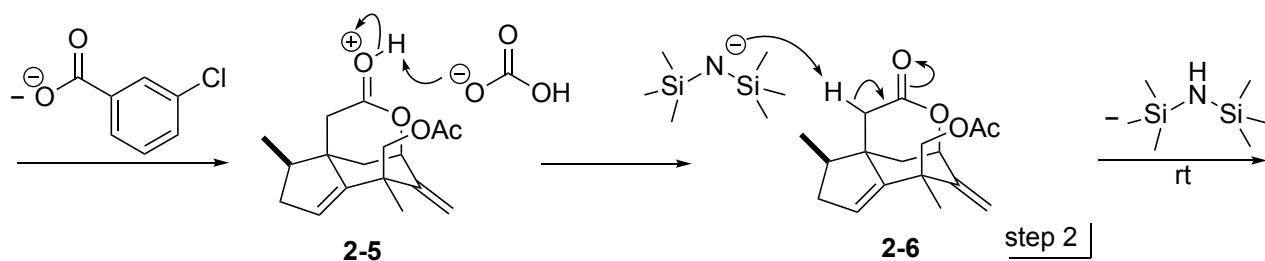
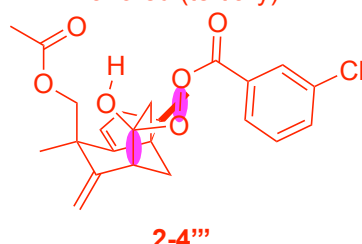
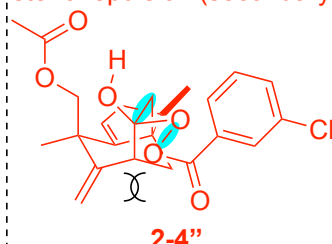
steric repulsion

acceleration by elimination of ring strain ($sp^2 \rightarrow sp^3$)



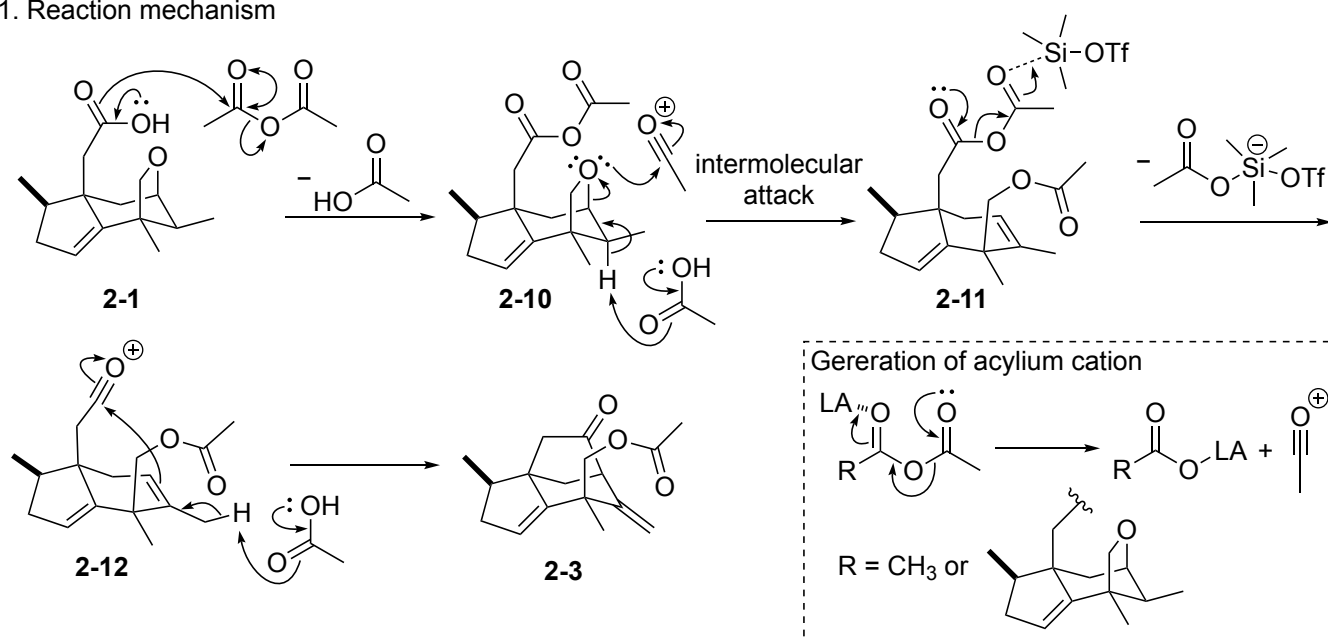
Another factors of stereoselectivity

anti-periplanar conformations for rearrangement:
steric repulsion (secondary) favored (tertiary)

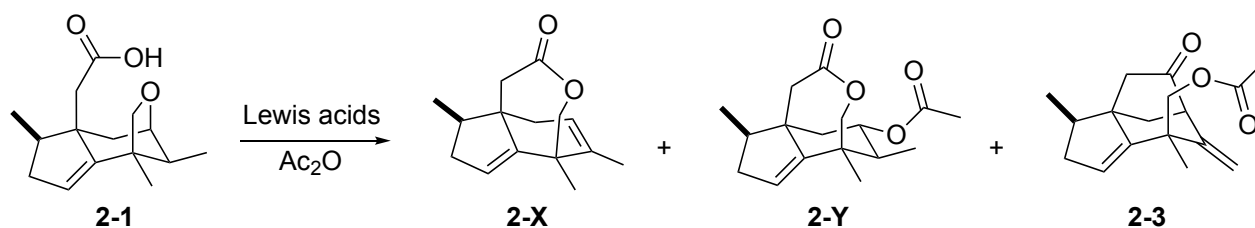


Discussion 2: Skeletal reorganization

2-1. Reaction mechanism



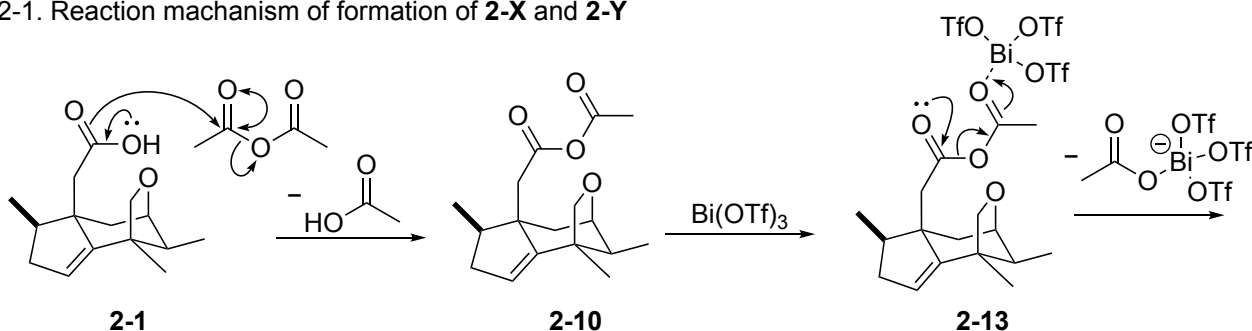
2-2. Conditions

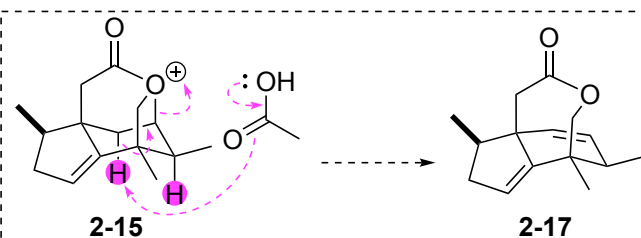
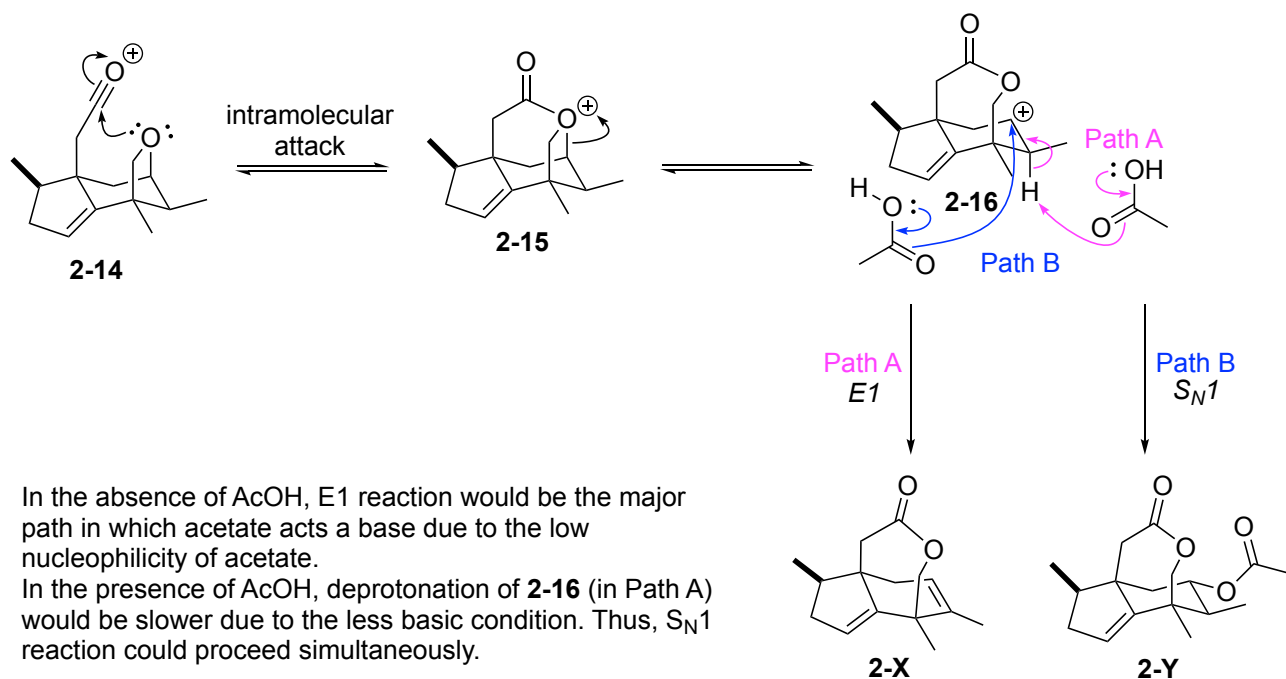


entry	Lewis acid	additive & solvent & temperature	time (h)	yield (%)		
				2-X	2-Y	2-3
1	Bi(OTf) ₃ (2 eq.)	Ac ₂ O, 0 °C	0.5	80	10	2
2	Bi(OTf) ₃ (2 eq.)	Ac ₂ O/AcOH (1:1), 0 °C	0.5	47	50	2
3	TMSOTf (2 eq.)	Ac ₂ O (8 eq.), CH ₂ Cl ₂ , 0 °C	1.0	75	12	0
4	TMSOTf (2 eq.)	Ac ₂ O, -78 °C to 23 °C	8.0	19	6	30
5	TMSOTf (2 eq.)	(±)-BINAP (1 eq.), Ac ₂ O, -78 °C to 23 °C	8.0	3	4	61
6	TMSOTf (2 eq.)	PPh ₃ (1 eq.), Ac ₂ O, -78 °C to 23 °C	8.0	34	15	30

In entries 1-3, with no additive, **2-X** was the major product. In the presence of AcOH, the yield of **2-Y** increased. In entries 4-6, reactions were conducted at -78 °C to 23 °C, and there was a tendency for the yield of **2-3** to increase. Adding (±)-BINAP reduced the yield of **2-X** and **2-Y**, and increased the one of **2-3**.

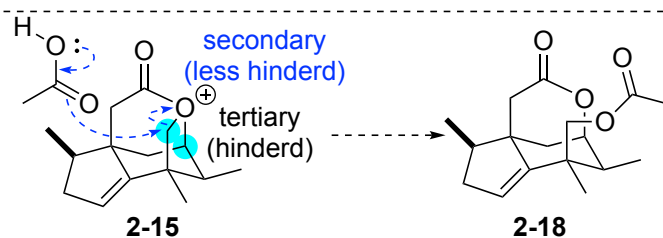
2-2-1. Reaction mechanism of formation of **2-X** and **2-Y**





If path A is E2 reaction, there would be two hydrogen atom which could be deprotonated in E2 reaction. Thus, two pathways would be competitive, and the compound **2-17** could also be generated.

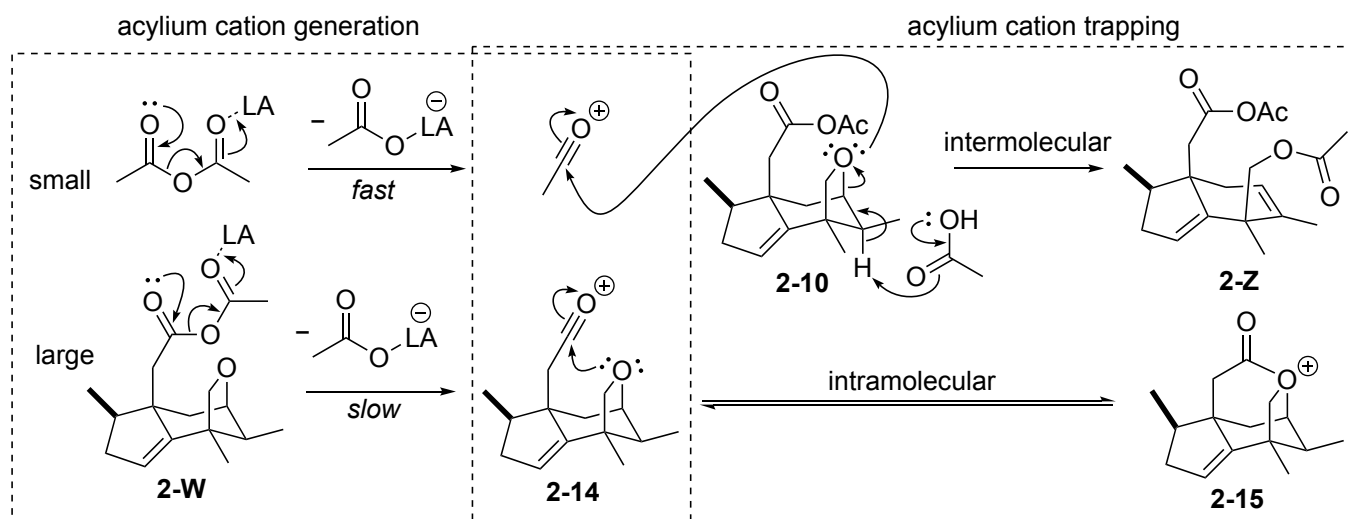
If path B is E1 reaction, on the other hand, generation of **2-X** would be preferred because **2-X** has a more substituted olefin which could stabilize the carbocation **2-16** more.



If path B is S_N2 reaction, there would be two carbon atom which could be attacked by acetate in S_N2 reaction. Thus, two pathways would be competitive, and the compound **2-18** could be generated rather than **2-Y** because the less hindered secondary carbon could be attacked more easily.

If path B is S_N1 reaction, on the other hand, only **2-Y** would be generated because only more stable secondary carbocation **2-15** could be generated stereoselectively.

2-2-2. Reactivity difference in acylium cation generation and trapping

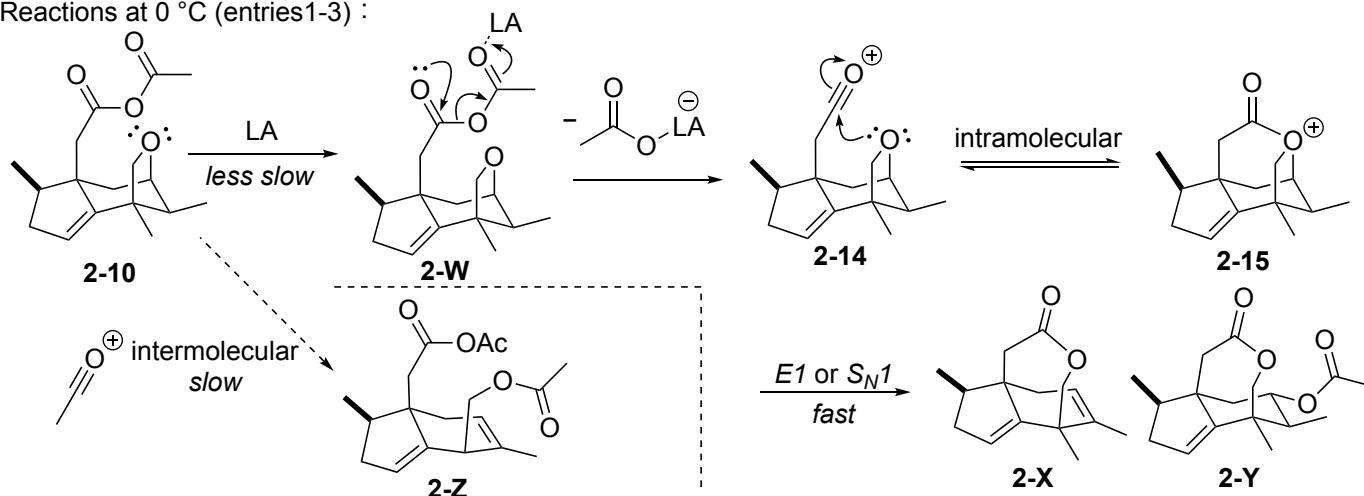


Acetic anhydride and acid anhydride **2-W** could produce corresponding acylium cations by activation by Lewis acid respectively.

If Lewis acid coordinates acetic anhydride and acylium cation is generated, it would be trapped by **2-10** intermolecularly, and then **2-Z** would be produced.

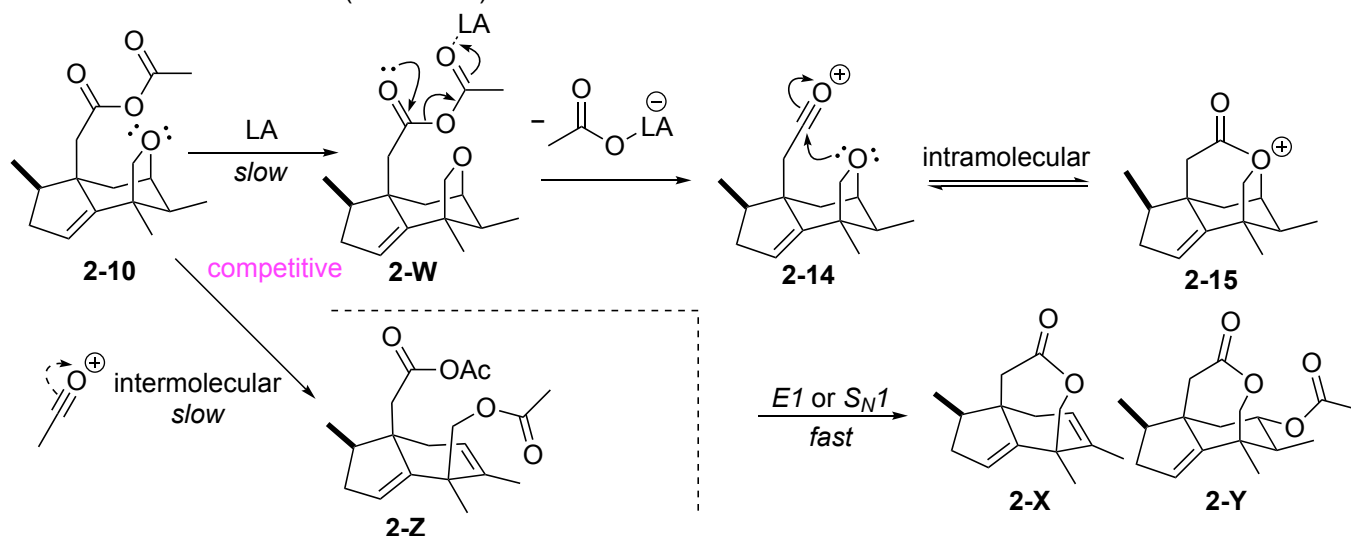
Acylium cation **2-14** could be produced more slowly because **2-W** has a large substituted group.

Reactions at 0 °C (entries 1-3) :



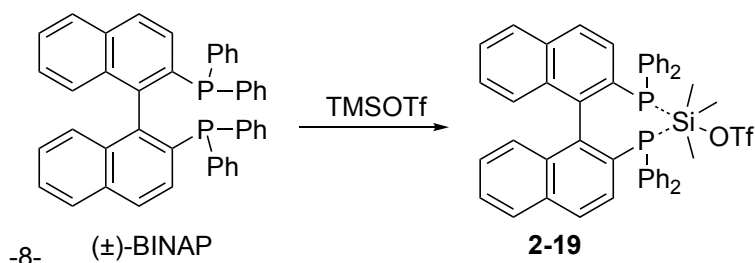
Due to higher temperature, coordination of Lewis acid with large **2-10** and production of **2-14** could occur relatively fast. Once **2-14** is generated, acylium cation would be trapped intramolecularly and following E1 or S_N1 reaction would occur fast. Thus, **2-X** and **2-Y** would be generated selectively.

Reactions at -78 °C to 23 °C (entries 4-6):



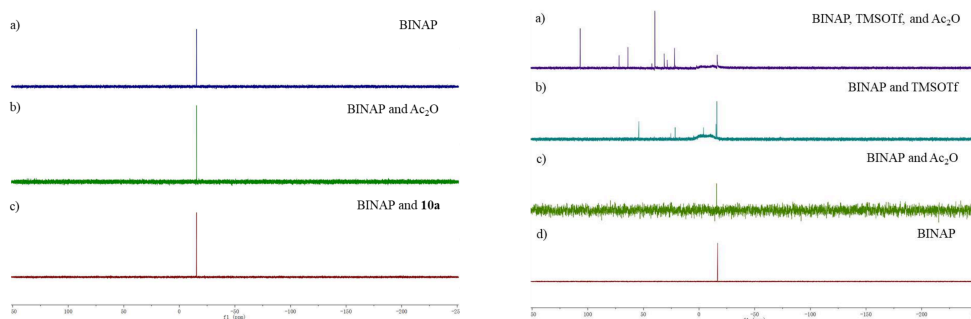
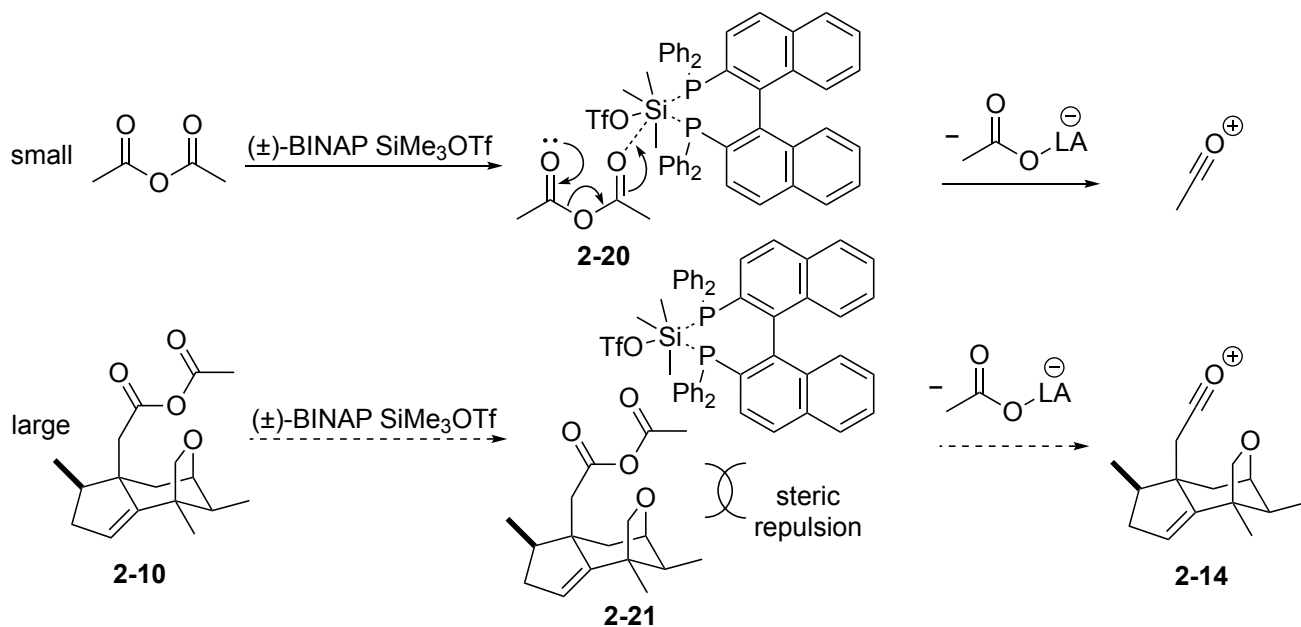
Due to lower temperature, the difference in reaction rate of generation of acylium cation between larger **2-10** and smaller acetic anhydride would be more remarkable. Thus, production of **2-W** and **2-14** (acylium cation generation) and production of **2-Z** (intermolecular acylium cation trapping) would become competitive, and **2-12** could also become generated.

2-3. Role of (±)-BINAP

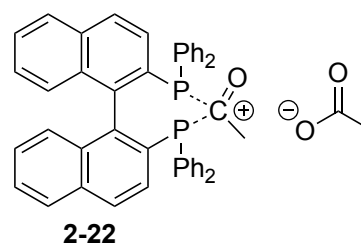


According to P³¹ NMR, it is suggested that (±)-BINAP would chelate Si atom of TMSOTf, and an active species generated by it would newly act as Lewis acid.

Due to large substituted groups of (±)-BINAP, the active species could coordinate acetic anhydride, but could not coordinate **2-10**. Thus, acetic cation and **2-3** would be selectively generated.

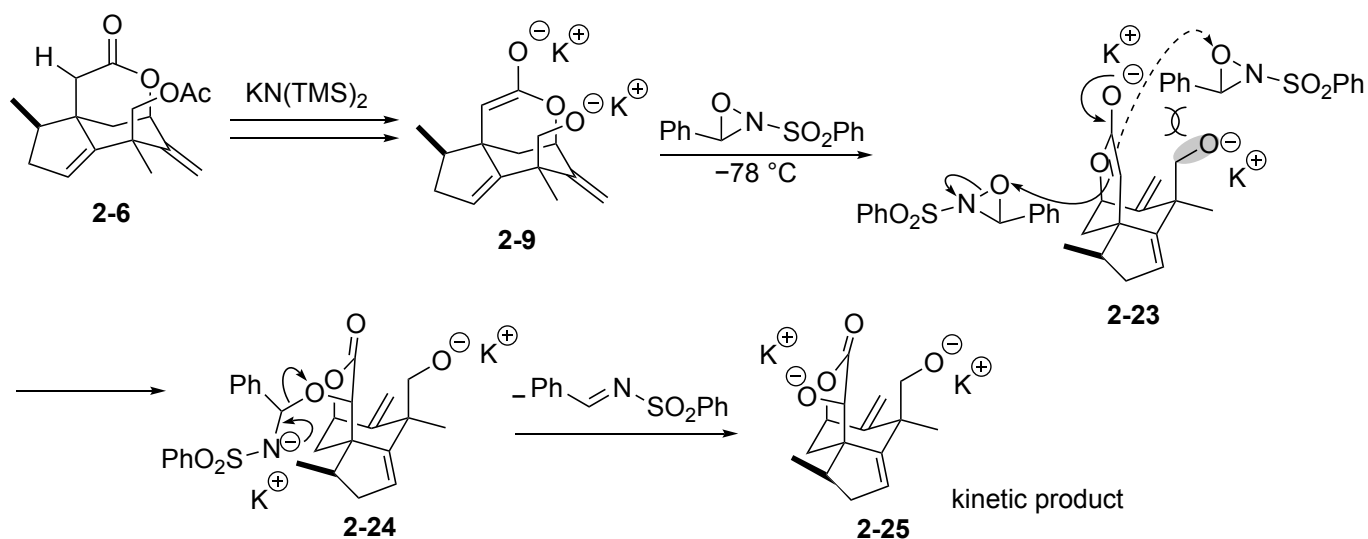


It is suggested that not only TMSOTf but acyl cation would be chelated by (\pm) -BINAP according to the fact that Bu_3P could catalyze acylation with acetic anhydride. *ref 3)*
The active species could also act as Lewis acid.

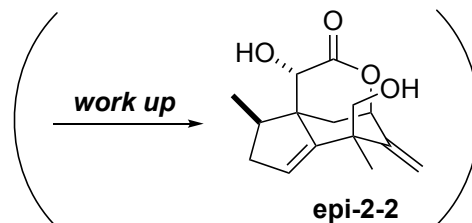


Discussion 3: Stereoslectivity and epimerization

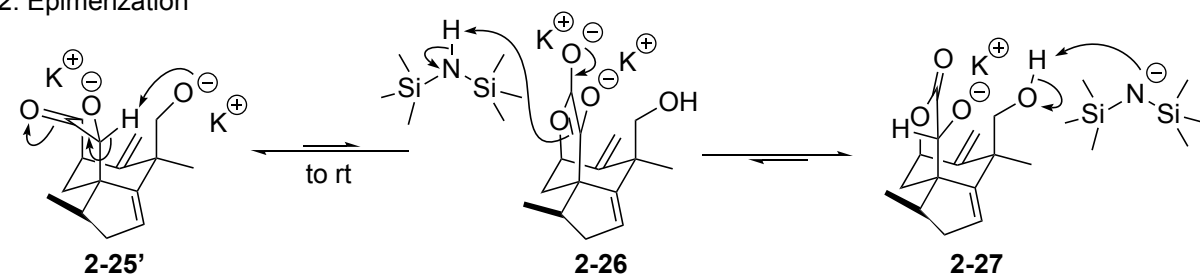
3-1. Stereoselectivity on α -hydroxylation



Davis reagent would react from the sterically less hindered face, and **2-24** would be generated kinetically. In fact, after work up at -78°C , **epi-2-2** was obtained.

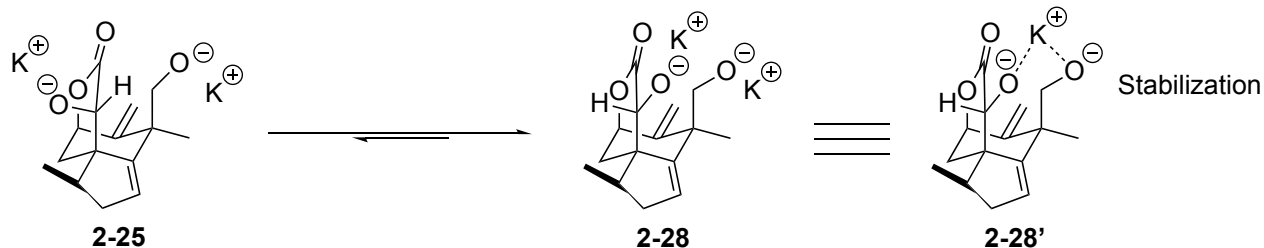


3-2. Epimerization



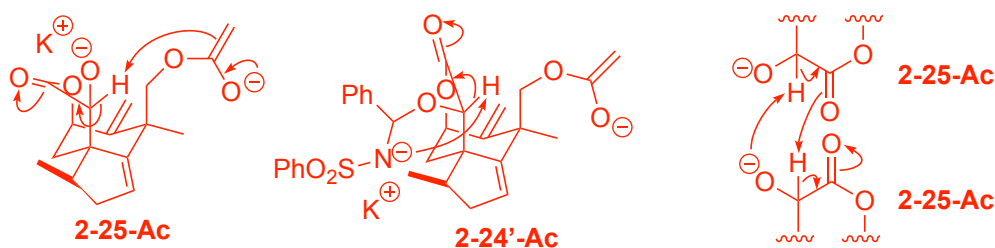
After generation of **2-25**, reaction temperature was raised to room temperature. Equilibrium in deprotonation, formation of elolate, and protonation would come to occur.

Thereby thermodynamically stable **2-28** would be generated, and a single diastereomer **2-2** would be obtained.



2-28 might be stabilized by cation chelation in two alcoxide.

In case that deacetylation would occur in work up, different deprotonation steps would be considered.



Reference

- 1) Ji-Feng, L.; Zhi-Yong, J.; Quan, Z.; Yao, S.; Yun-Bao, M.; Ming-Jin, X.; Xue-Mei, Z.; Ji-Jun, C. *Planta Med.* **2010**, *76*, 152-158.
- 2) Himabindu, G.; Thottumkara, V. *J. Org. Chem.* **2011**, *76*, 974-977.
- 3) Vedejs, E.; Bennet, N.; Conn, L.; Diver, S.; Gingras, M.; Lin, S.; Oliver, P.; Peterson, M. *J. Org. Chem.* **1993**, *58*, 7286-7288.