Problem session (1)

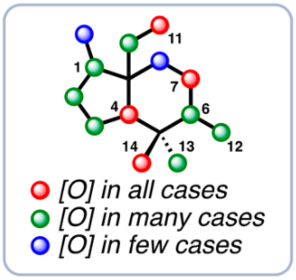
2025.1.31 B4 Shuntaro Kawai

topic: Synthesis of illicium sesquiterpenes

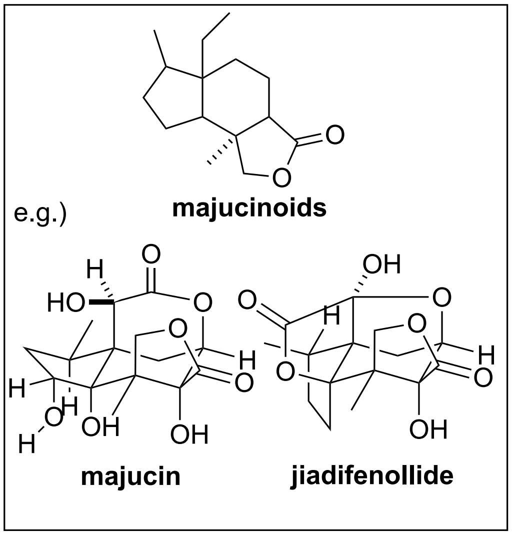
Main review: Hung, K.; Condakes, M. L.; Novaes, L. F. T.; Harwood, S. J.; Morikawa, T.; Yang, Z.; Maimone, T. J. *J. Am. Chem. Soc.* **2019**, *141*, 3083.

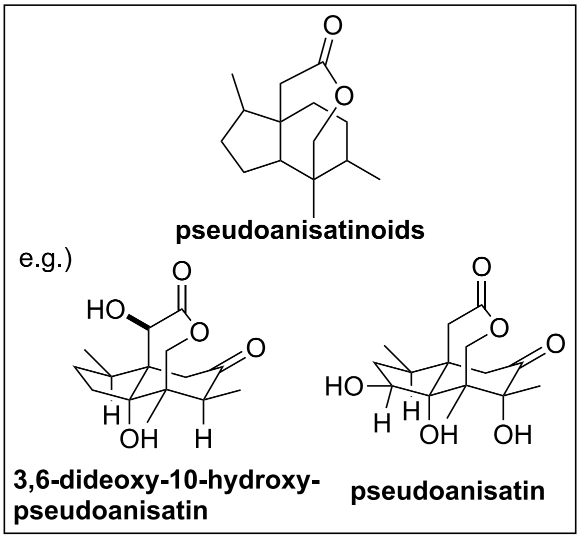
Introduction

0-1. illicium sesquiterpenes family



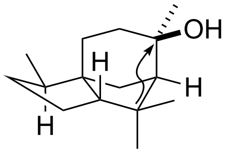
- ***>100 members***
- ***diverse [O] patterns***
- ***potent bioactivities***





The total synthesis of illicium sesquiterpenes was taken up in 171222_LS_Kohei_Ogino.

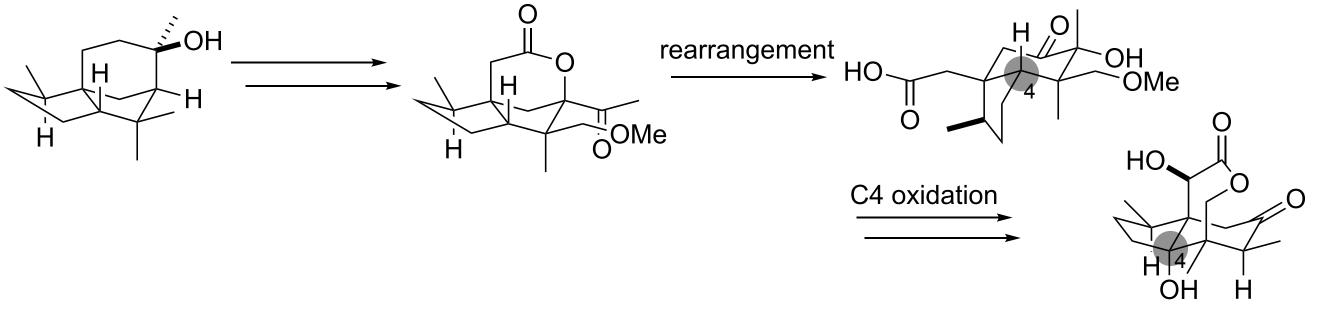
0-2. synthetic strategy



cedrol
(starting material)

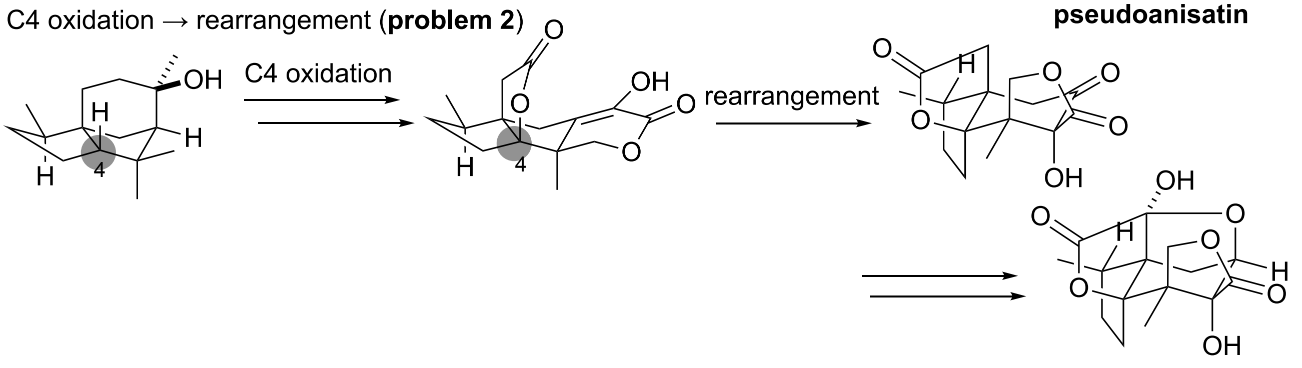
- siteselective oxidation
- skeletal rearrangement

rearrangement → C4 oxidation (**problem 1**)



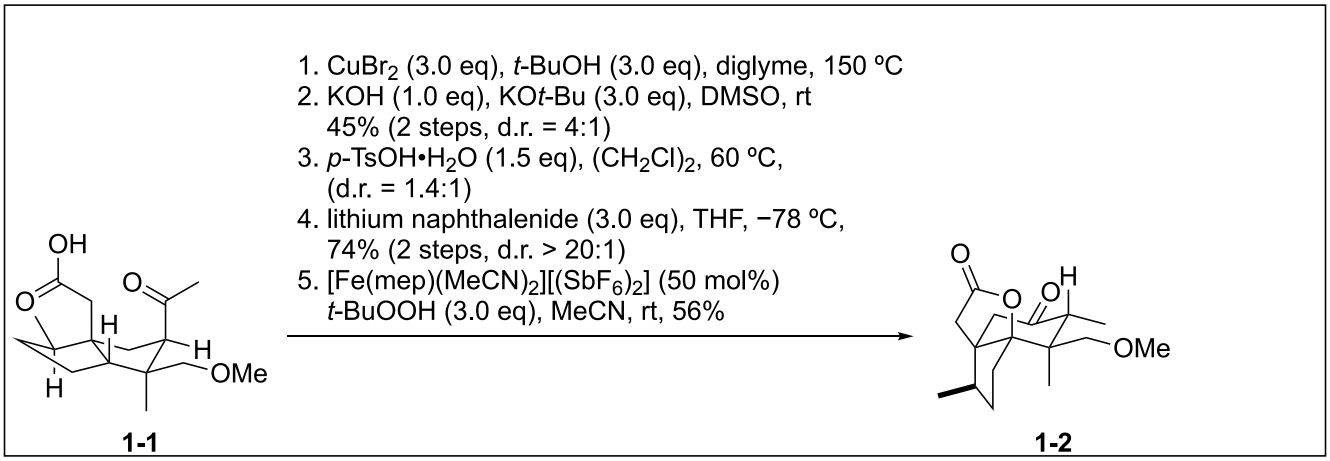
3,6-dideoxy-10-hydroxy-pseudoanisatin

C4 oxidation → rearrangement (**problem 2**)



jiadifenollide

1

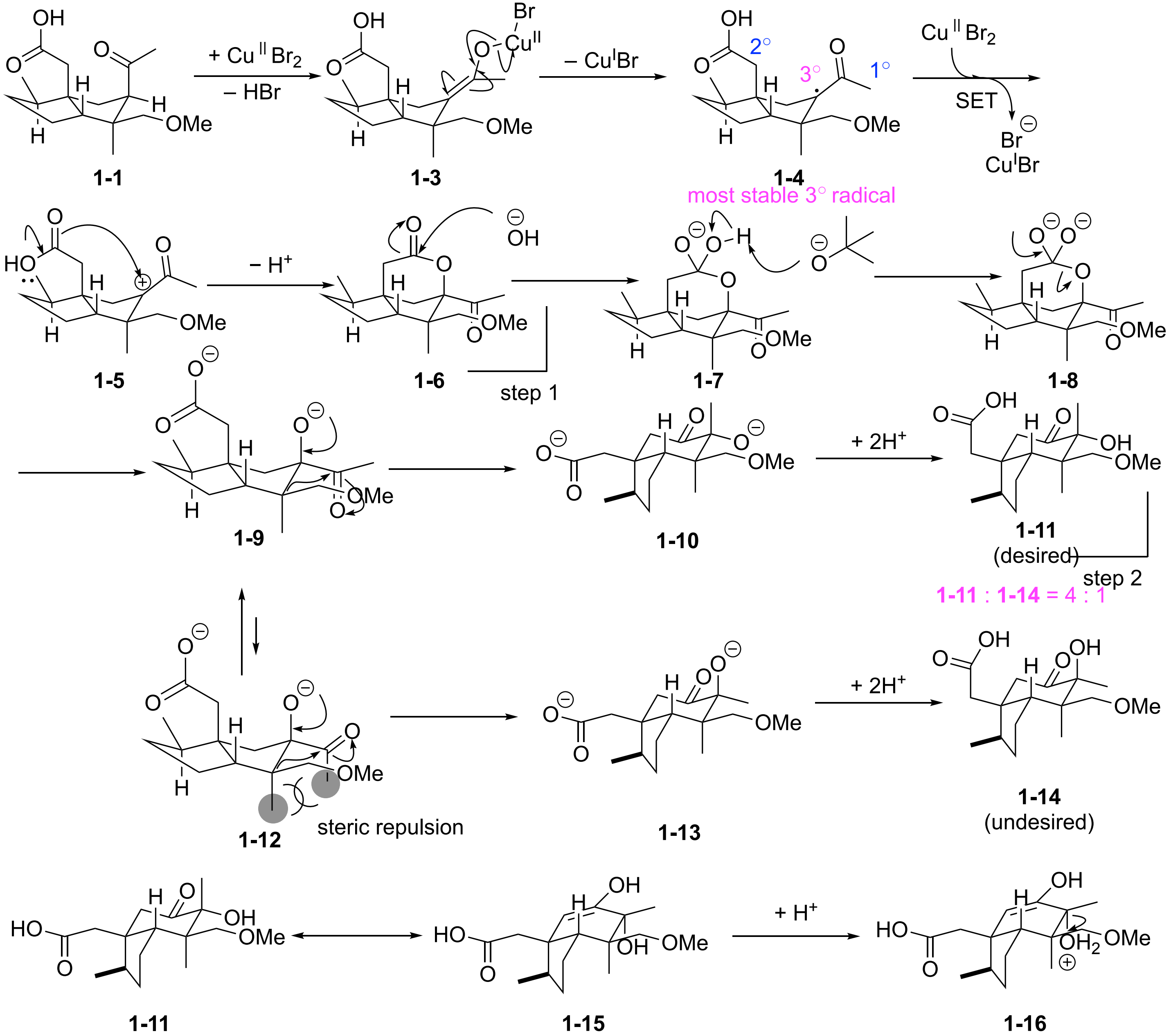

1. CuBr$_2$ (3.0 eq), *t*-BuOH (3.0 eq), diglyme, 150 ºC
2. KOH (1.0 eq), KO*t*-Bu (3.0 eq), DMSO, rt
   45% (2 steps, d.r. = 4:1)
3. *p*-TsOH•H$_2$O (1.5 eq), (CH$_2$Cl)$_2$, 60 ºC,
   (d.r. = 1.4:1)
4. lithium naphthalenide (3.0 eq), THF, −78 ºC,
   74% (2 steps, d.r. > 20:1)
5. [Fe(mep)(MeCN)$_2$][(SbF$_6$)$_2$] (50 mol%)
   t-BuOOH (3.0 eq), MeCN, rt, 56%

1-1

1-2

Reaction mechanisms

Hung, K.; Condakes, M. L.; Novaes, L. F. T.; Harwood, S. J.; Morikawa, T.; Yang, Z.; Maimone, T. J. *J. Am. Chem. Soc.* **2019**, *141*, 3083.



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

most stable 3° radical

1-5 **1-6** **1-7** **1-8**

step 1

1-9 **1-10** **1-11** (desired)

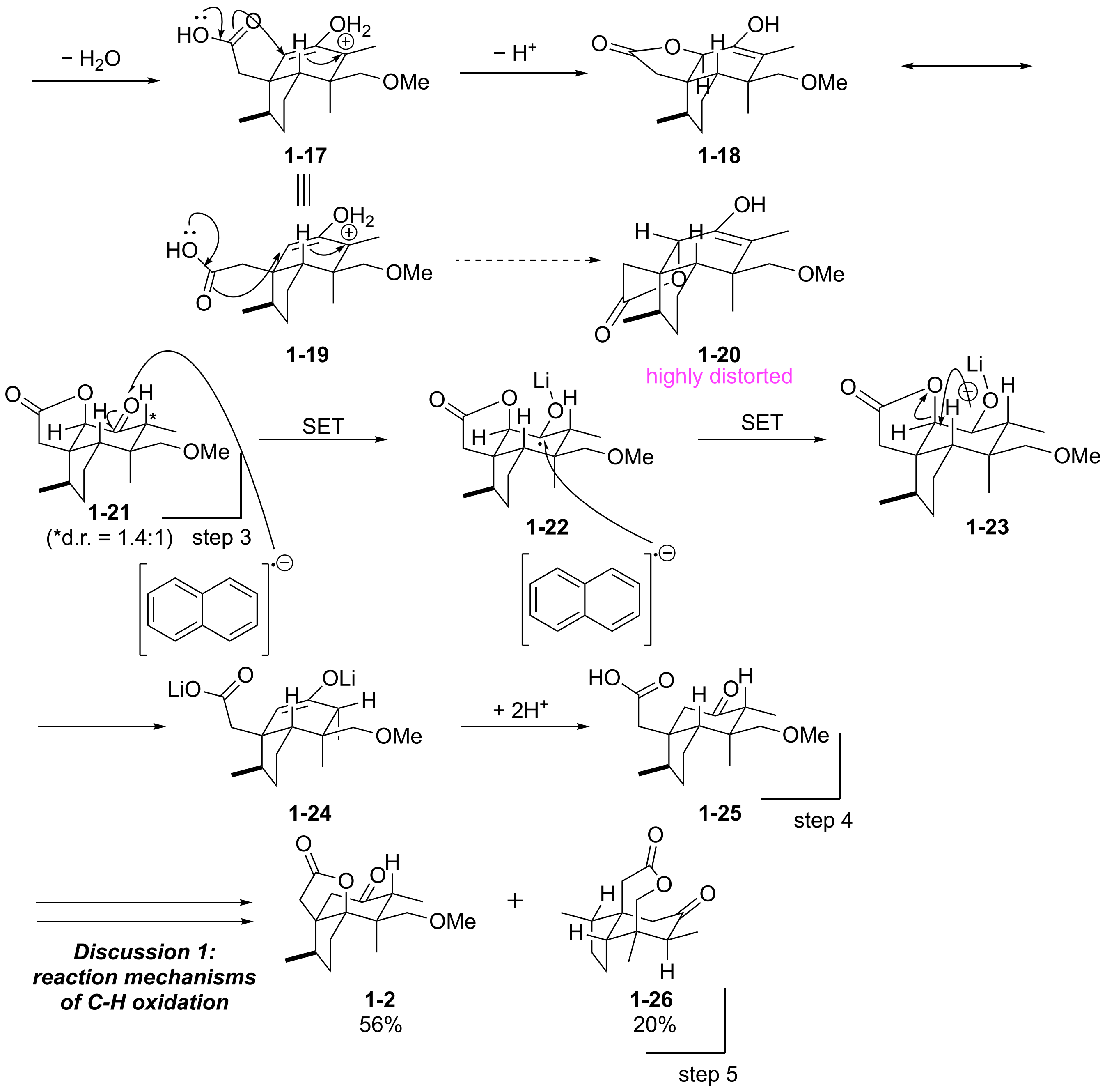
step 2

1-11 : **1-14** = 4 : 1

1-12 steric repulsion

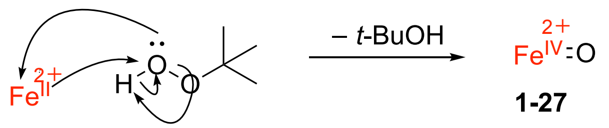
1-13 **1-14** (undesired)

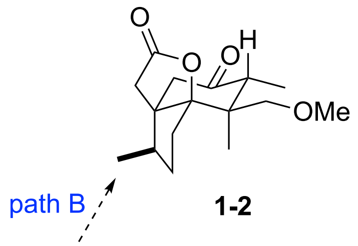
1-11 **1-15** **1-16**



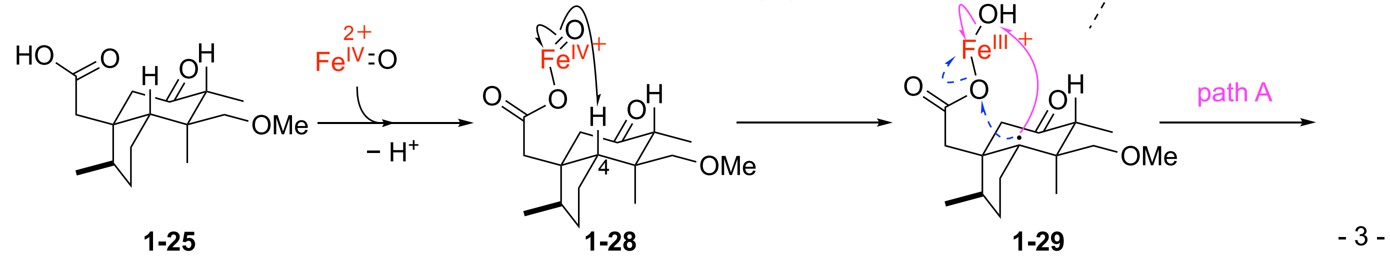
Discussion 1: reaction mechanisms of C-H oxidation

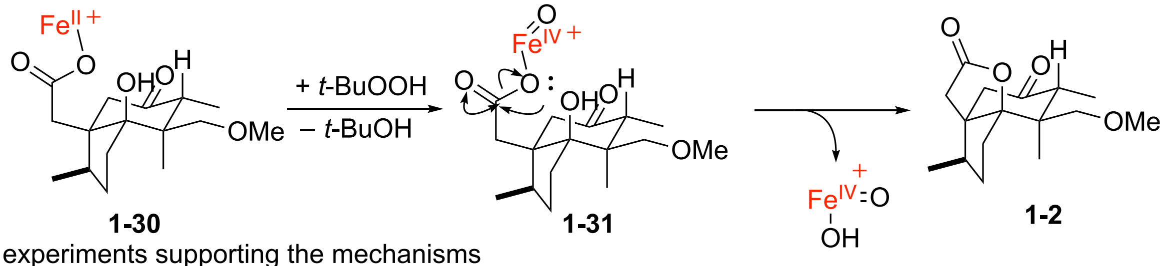
1. the generation of the Fe(IV)-oxo complex



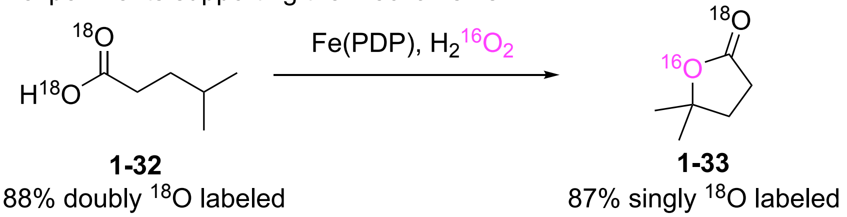


2. reaction mechanisms of lactone construction catalyzed by Fe(IV)-oxo complex



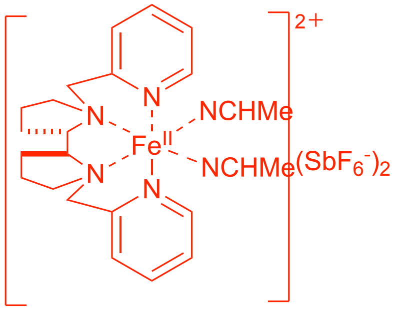


3. experiments supporting the mechanisms



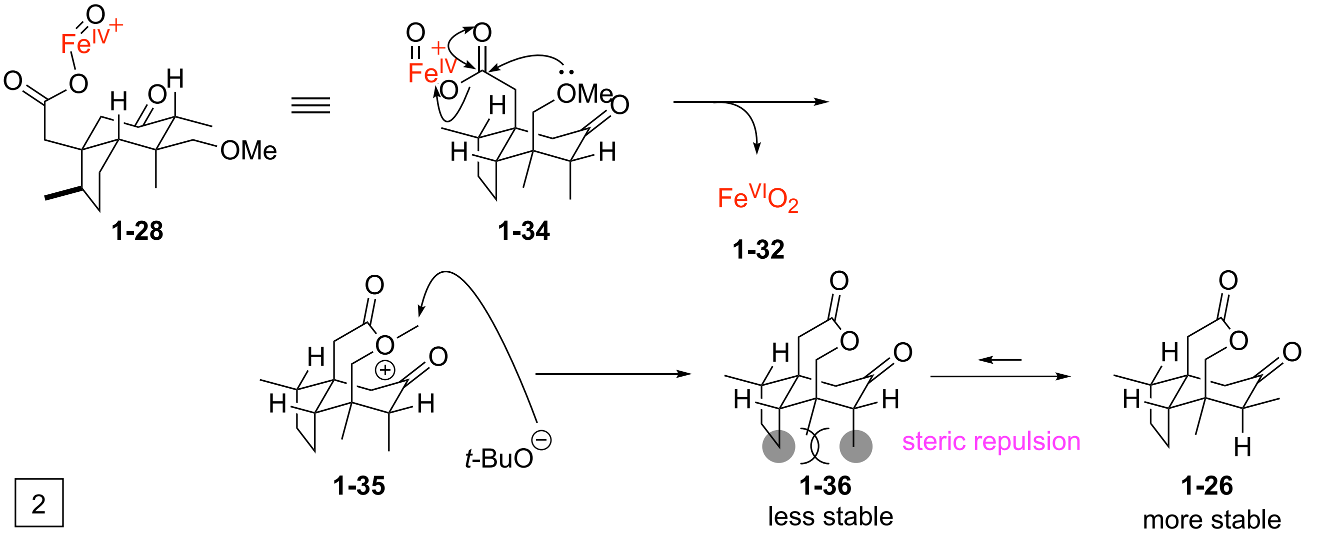
Bigi, A. M.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721.

Because path B is inconsistent with this result, so path A is more plausible.



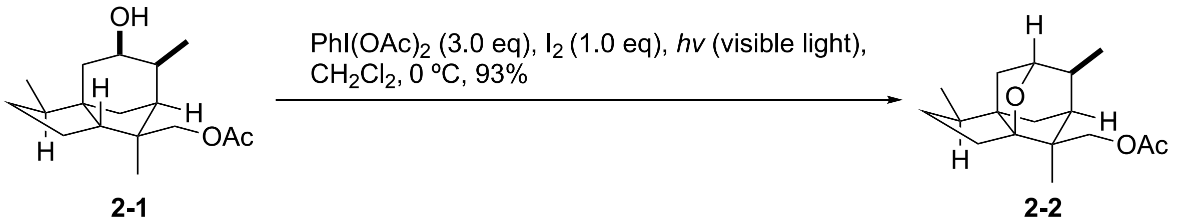
Fe(PDP)

4. generation of by-product



2

(1)



Reaction mechanisms

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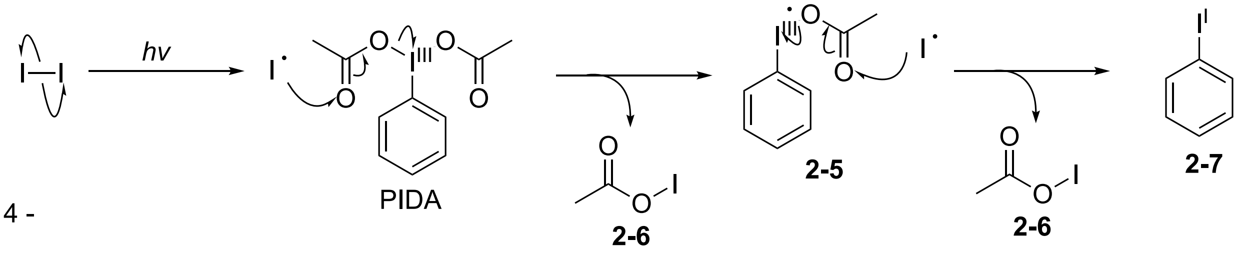
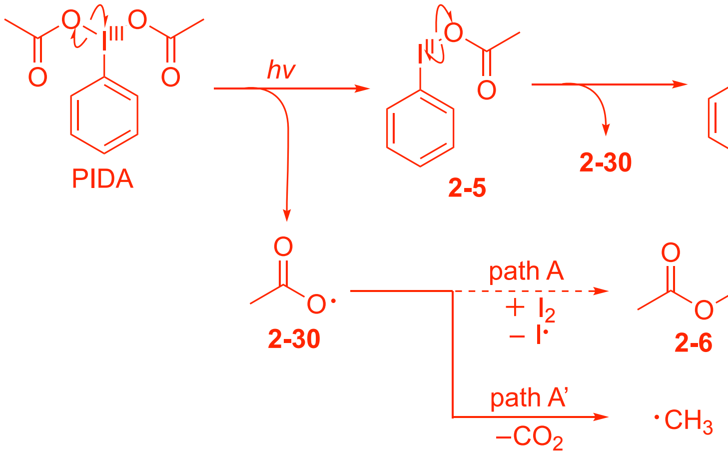
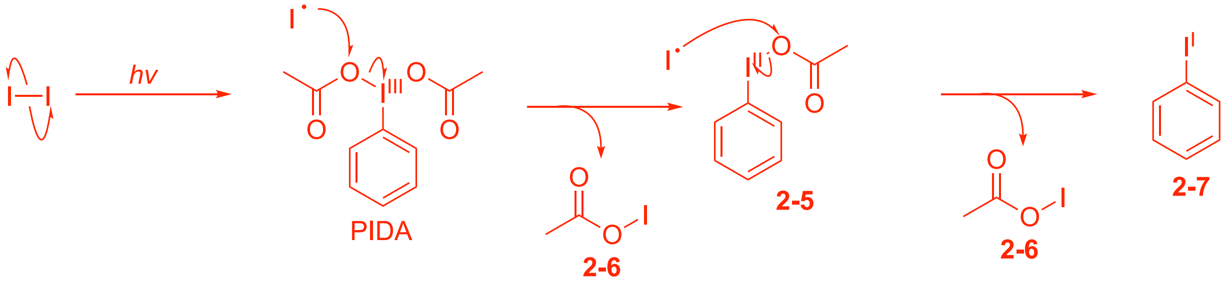


path A and path A’

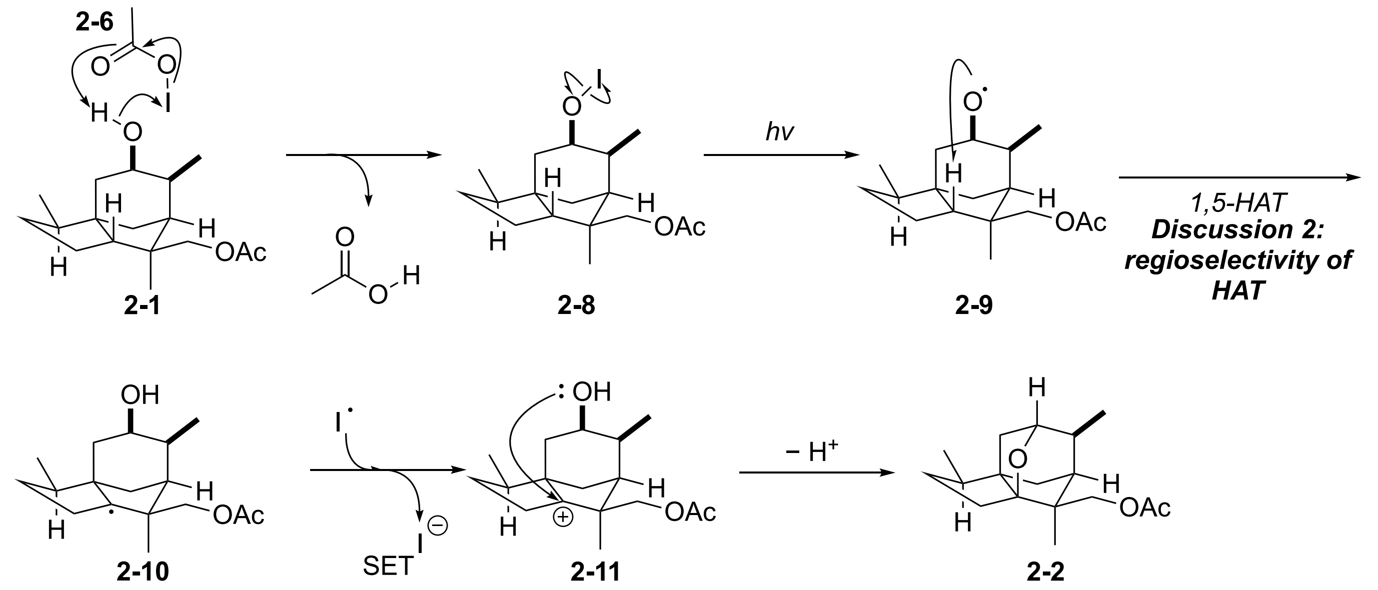


The homolysis of the C-O σ* orbital in a molecule containing hypervalent iodine was observed under photochemical conditions by Nemoto(2020).
On the other hand, **2-6** was observed under Suarez condition by Lusztyk(1994).
Thus, path A seems plausible.
However, the decarboxylation (path A’) which leads to the generation of methyl radical is more favored entropically and enthalpically than the attack to the iodine (path A).
The methyl radical was observed experimentally by Nemoto(2020) and Itami(2021).
Hence it is not likely that **2-6** is generated through path A.

path B

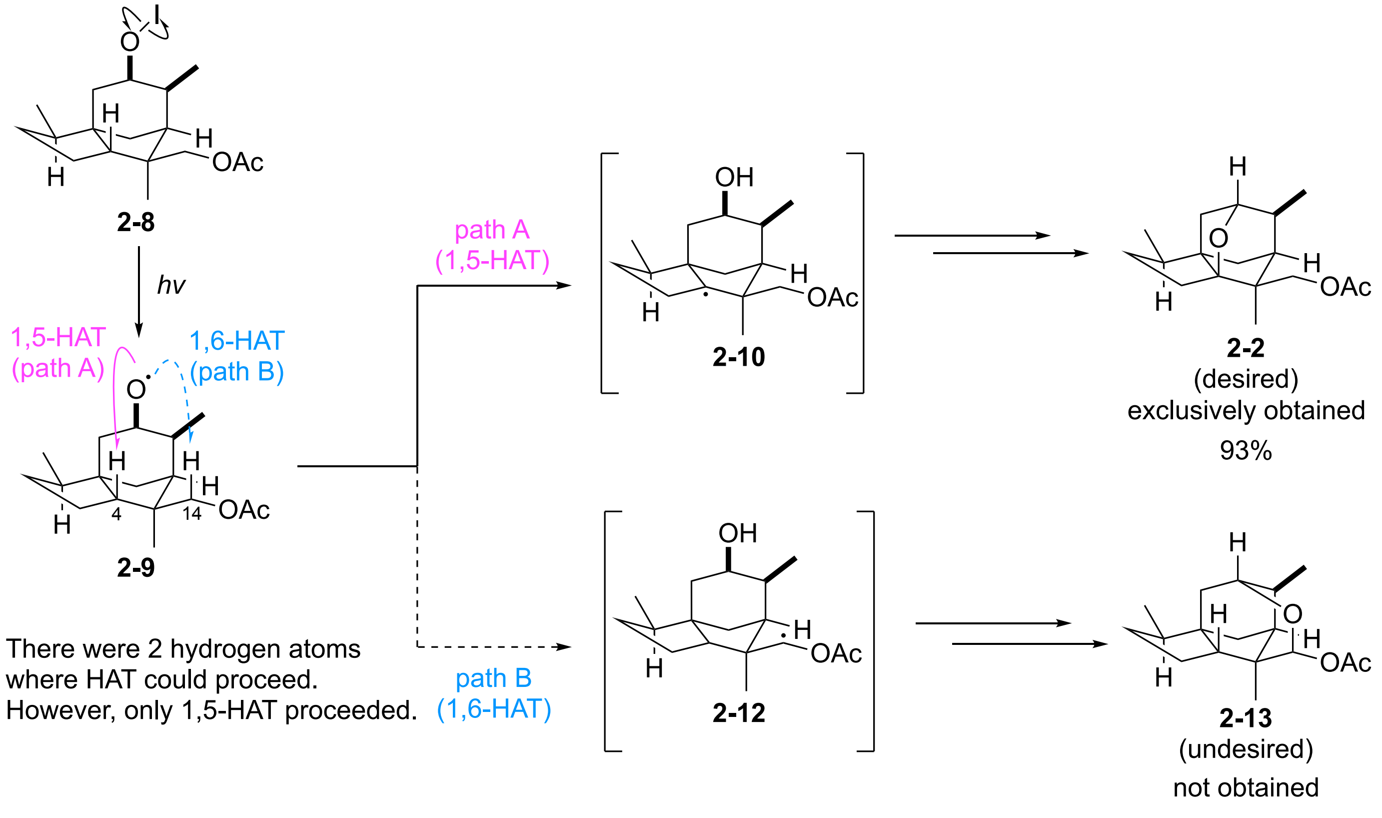


Path B, in which an iodine radical triggers the homolysis of the C-O σ* orbital in PIDA, is suggested.
This pathway is consistent with the fact that the iodine radical is more reactive with the C-O σ* orbital than with the carbonyl π* orbital.
Additionally, the decarboxylation cannot occur in this pathway.
Thus, path B is a more plausible route for the generation of **2-6**.
Because the condition is photochemical, the reaction via path A’ can proceed, but it is not the main pathway.



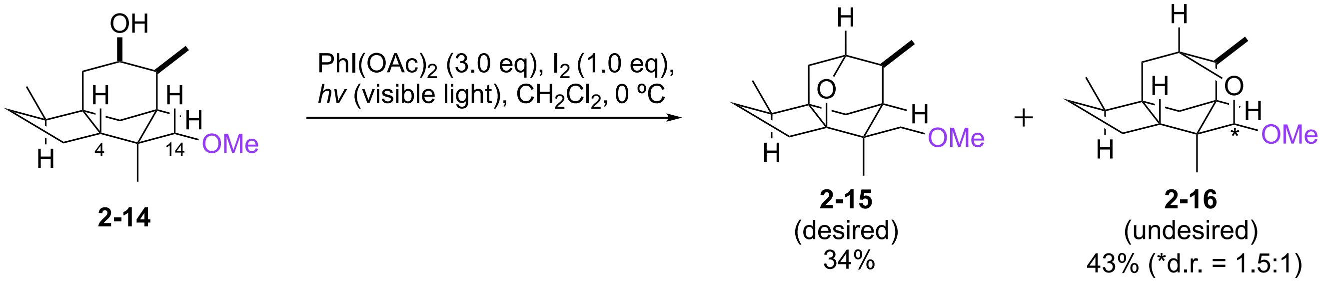
Discussion 2: regioselectivity of HAT

1. Mechanisms of possible pathways



There were 2 hydrogen atoms where HAT could proceed. However, only 1,5-HAT proceeded.

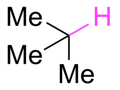
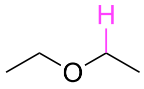
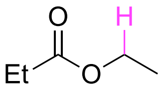
2. The role of protective group at C14-OH



When a methoxy group was the substituent at C14, the product of 1,6-HAT was obtained as the major product.

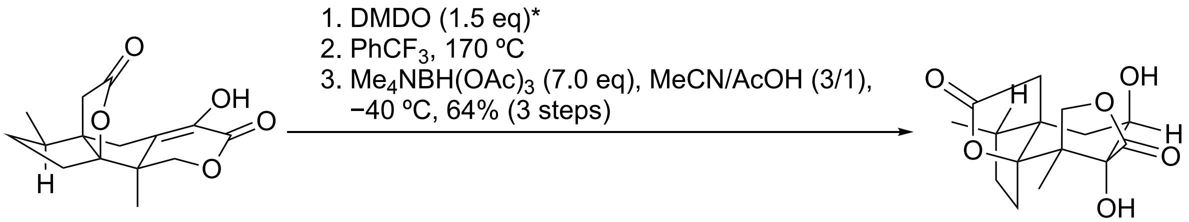
3. comparison of BDE

Table 1: The difference in BDE due to the substituent

structure	BDE (kcal/mol)
	96.5
	91.7
	97.3

The bond dissociation energy (BDE) of the C-H bond is one of the significant factors that determine the selectivity of HAT.
The substituent next to the C-H bond has influence on the strength of the C-H bond.
According to Table 1, it is estimated that the C-H bond adjacent to the acetyl group is stronger than the one adjacent to the methoxy group.
Thus, the selectivity of HAT when using **2-9** is attributed to the difference in BDE between the C-H bond at C4 and that at C14.

(2)



2-3 **2-4**

*The detailed conditions are not mentioned in the paper.

Reaction mechanisms

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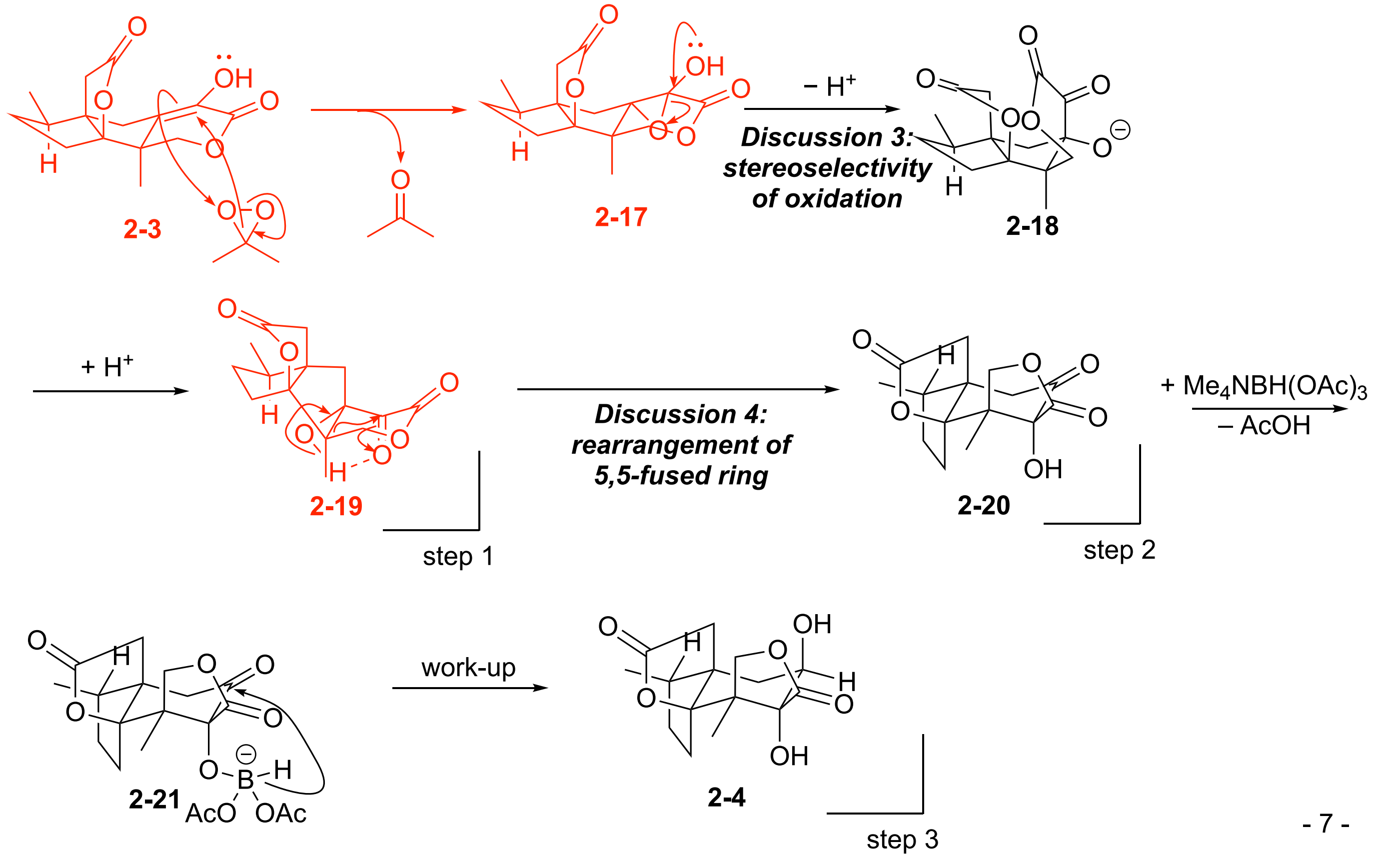
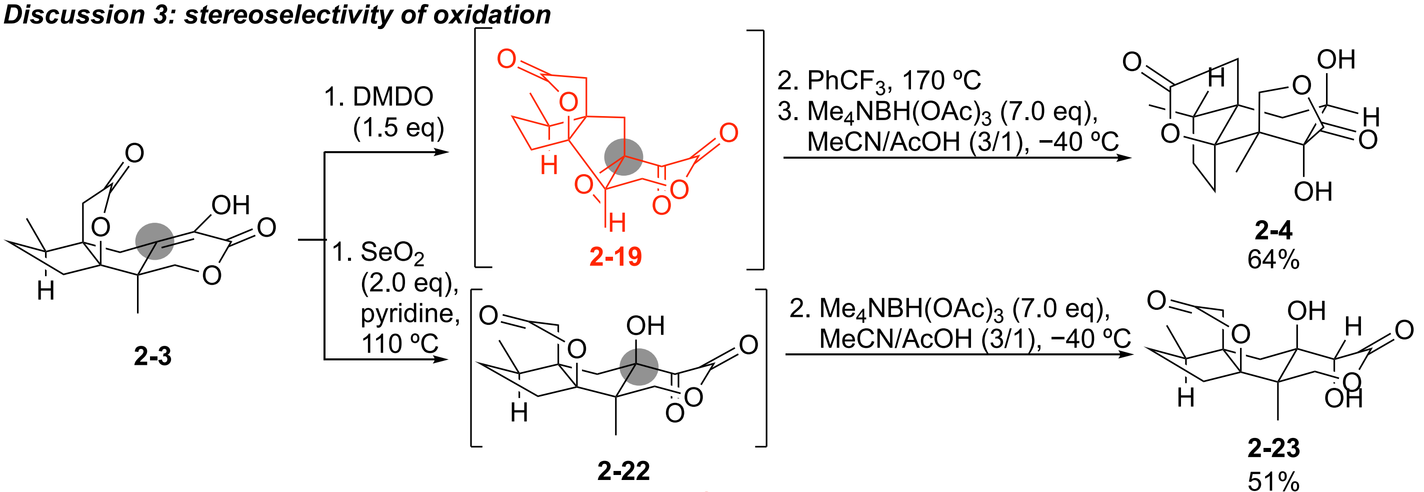
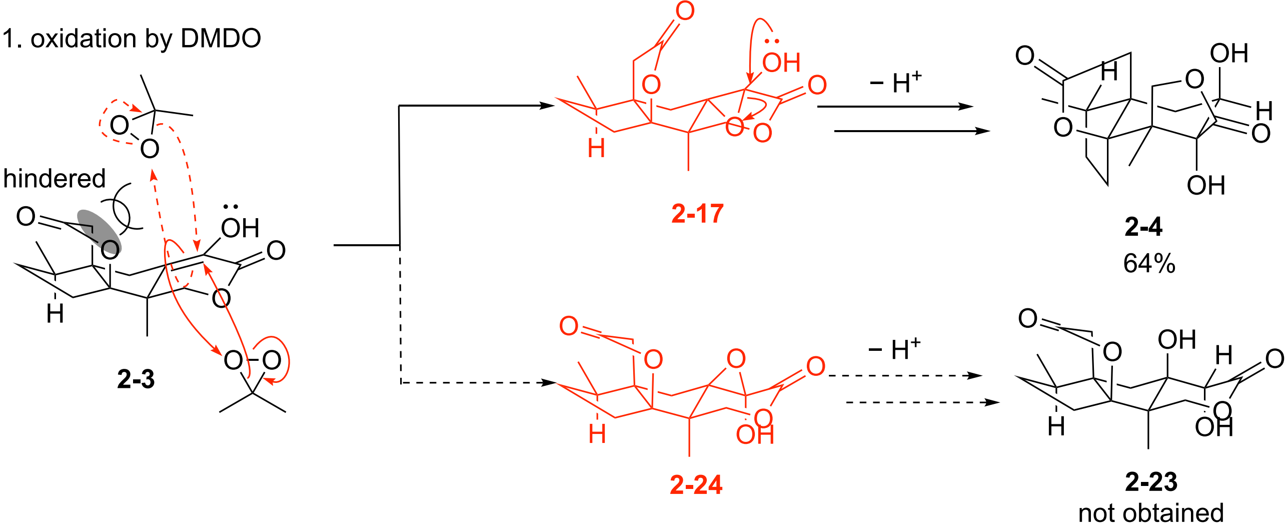


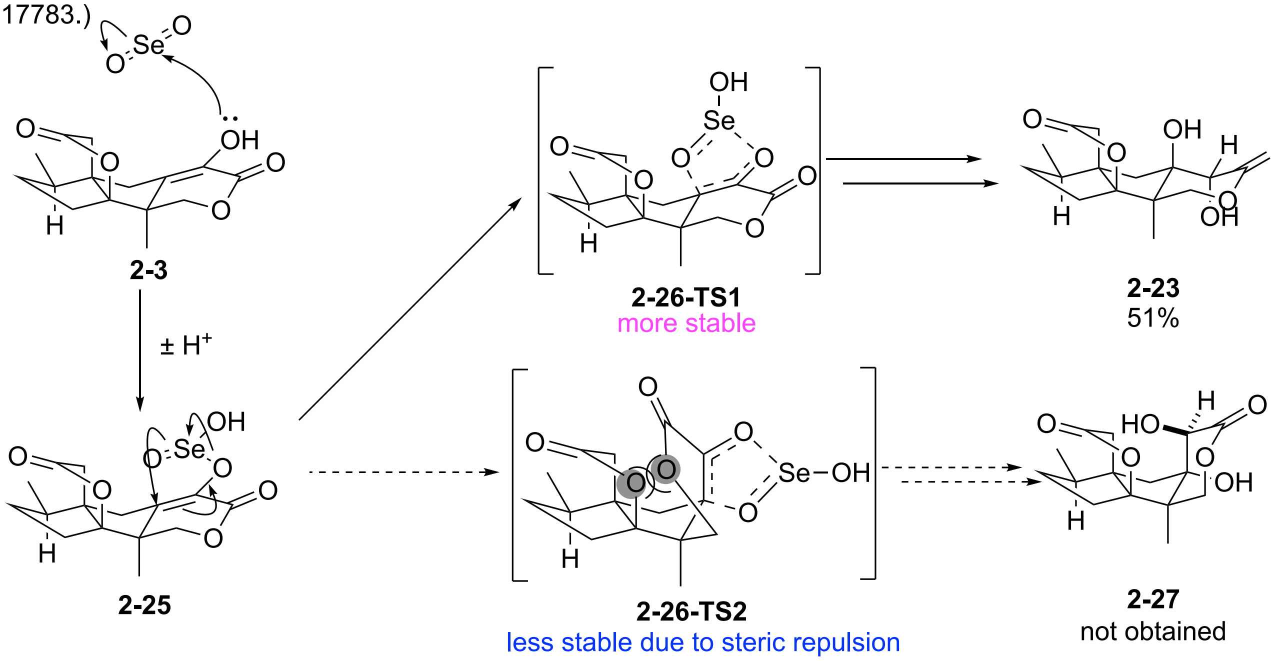
Discussion 3: stereoselectivity of oxidation



1. oxidation by DMDO



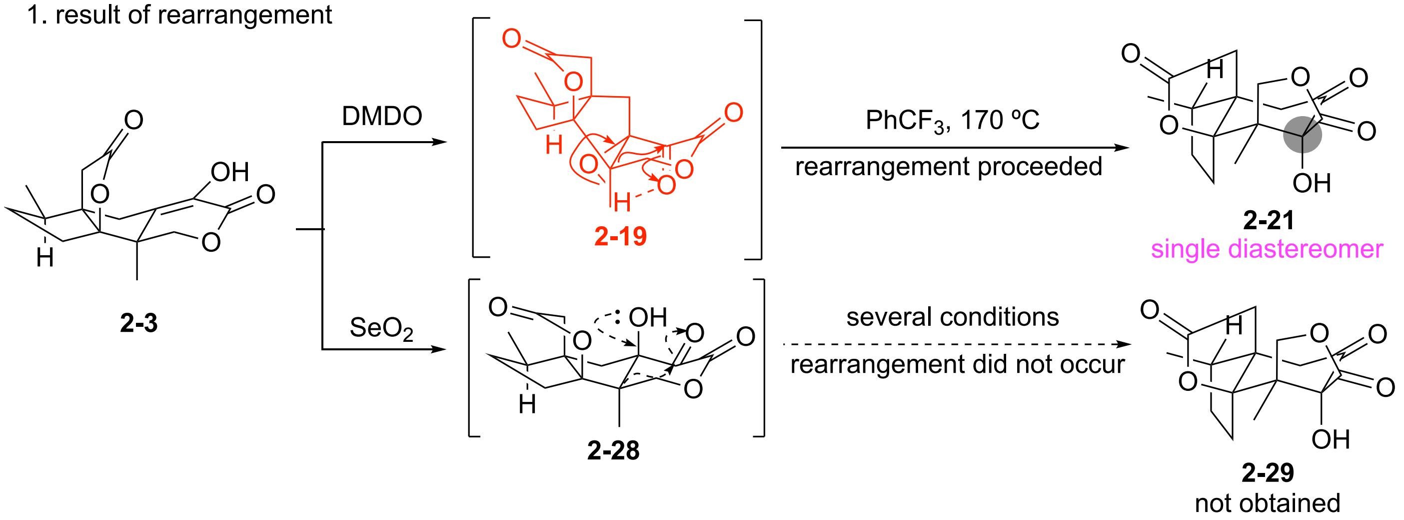
2. oxidation by SeO_2 (Condakes, M. L.; Hung, K.; Harwood, S. J.; Maimone, T. J. *J. Am. Chem. Soc.* **2017**, *139*, 17783.)



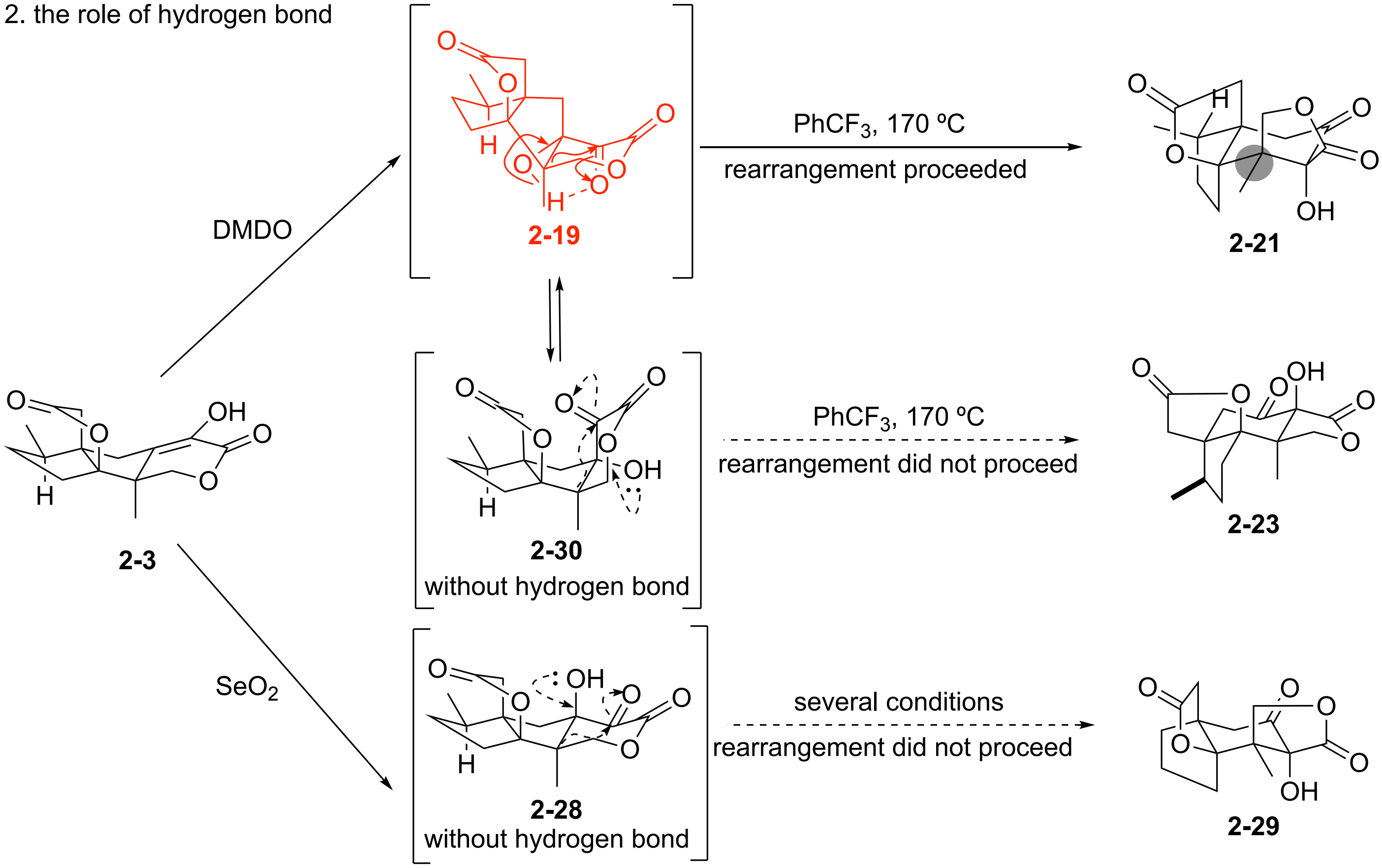
The difference of stability in the transition state determines the reaction pathway.

Discussion 4: rearrangement of 5,5-fused ring

1. result of rearrangement



2. the role of hydrogen bond



Hydrogen bond may activate the ketone and hydroxy group, leading to the rearrangement.

References

1) Hung, K.; Condakes, M. L.; Novaes, L. F. T.; Harwood, S. J.; Morikawa, T.; Yang, Z.; Maimone, T. J. *J. Am. Chem. Soc.* **2019**, *141*, 3083.
2) Bigi, A. M.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721.
3) Condakes, M. L.; Hung, K.; Harwood, S. J.; Maimone, T. J. *J. Am. Chem. Soc.* **2019**, *141*, 3083.
4) Maeda, B.; Sakakibara, Y.; Murakami, K.; Itami, K. *Org. Lett.* **2021**, *23*, 5113.
5) Nakajima, M.; Nagasawa, S.; Matsumoto, K.; Kuribara, T.; Muranaka, A.; Uchiyama, M.; Nemoto. T. *Angew. Chem.* **2020**, *132*, 6914.
6) Courtneidge, J. L.; Lusztyk, J.; Pagé, D. Tetrahedron. Lett. **1994**, *35*, 1003.