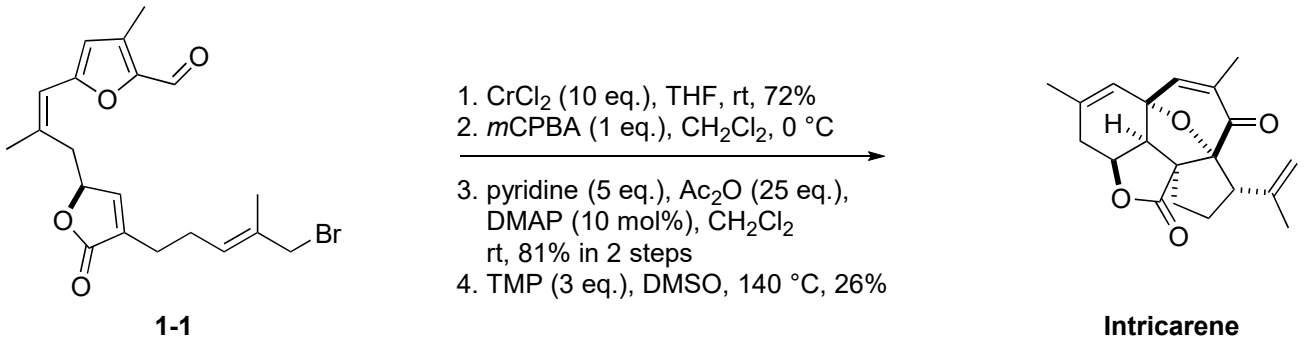
Problem Session (1) -revised-

2019/07/20 Ayumu Watanabe

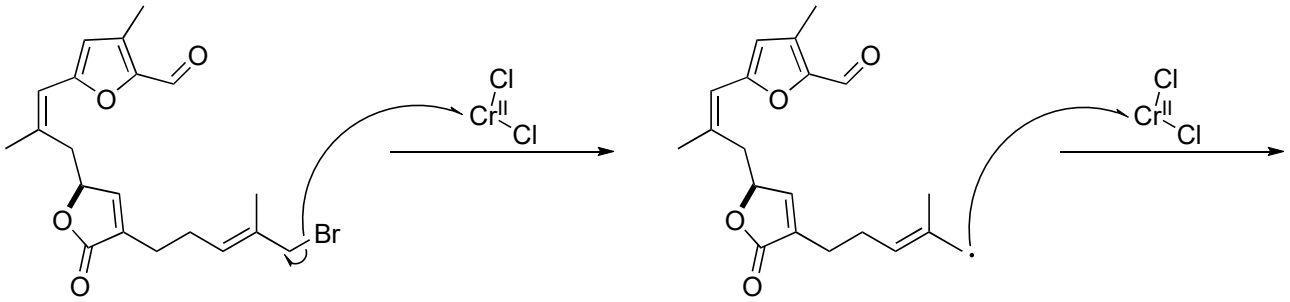
topic: Total synthesis by Trauner group

1. Total synthesis of (+)-Intricarene
1-1. Reaction mechanism

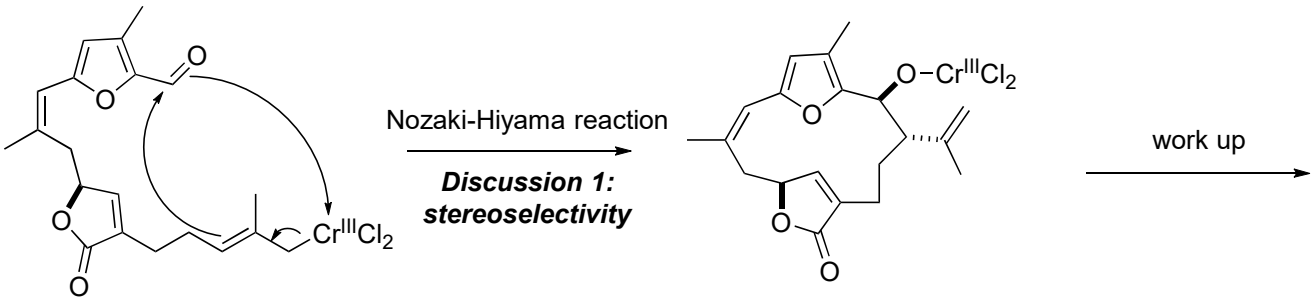


1-1 **Intricarene**

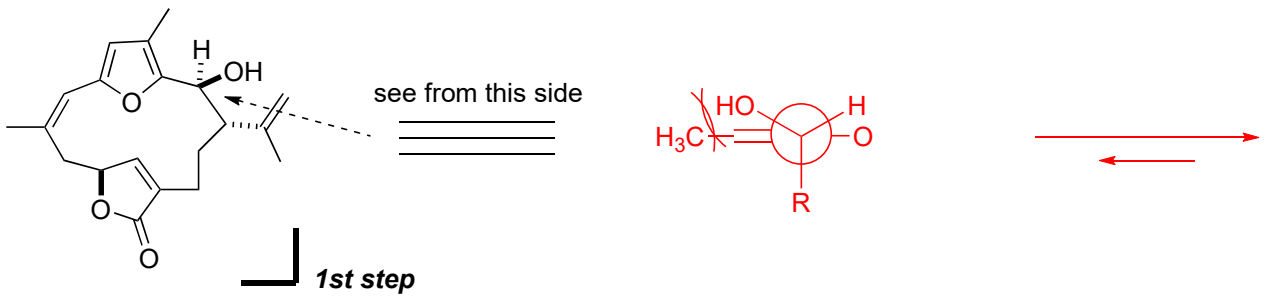
Roethle, P. A.; Hernandez, P. T.; Trauner D. *Org. Lett.* **2006**, *8*, 5901.



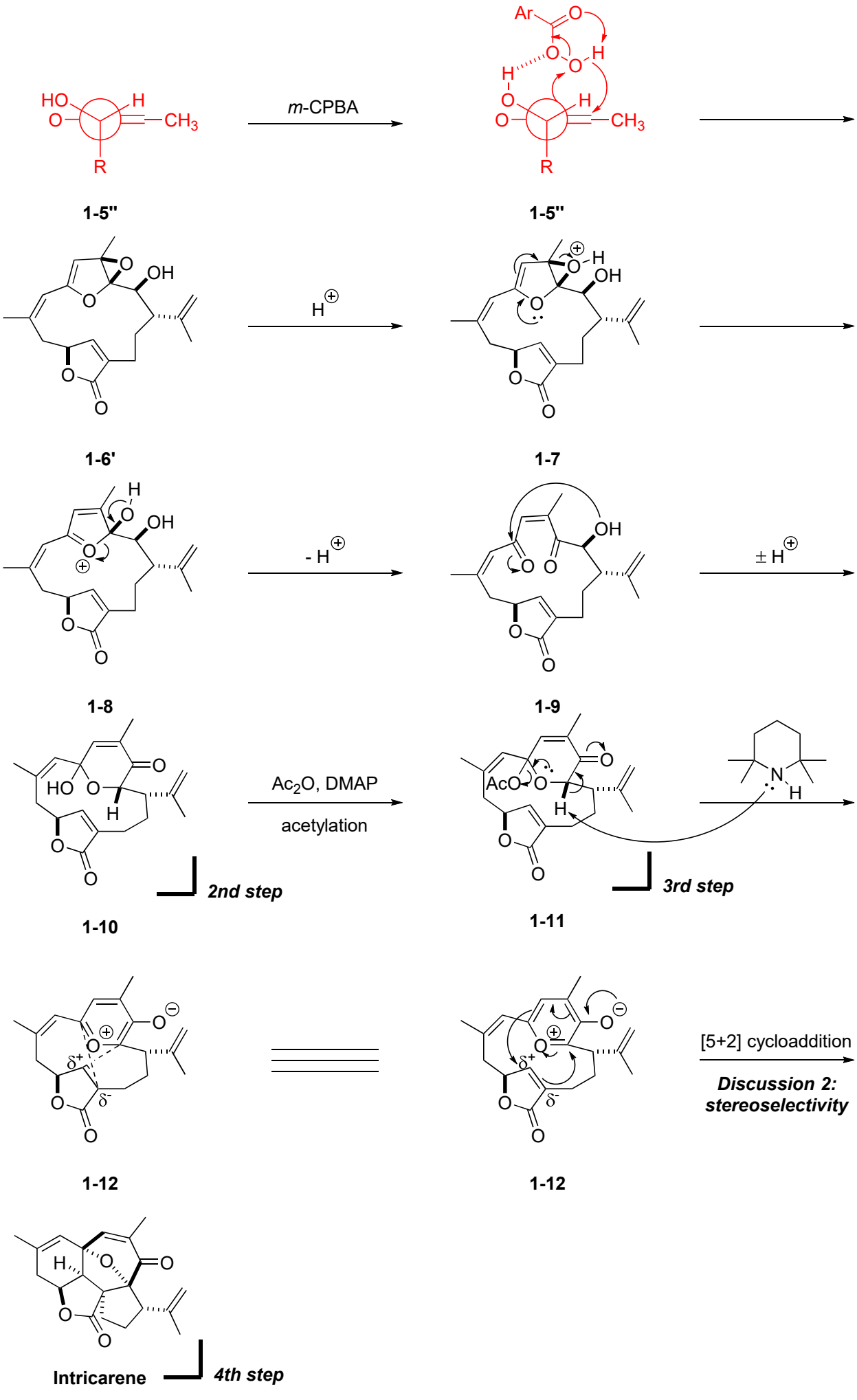
1-1 **1-2**



1-3 **1-4**

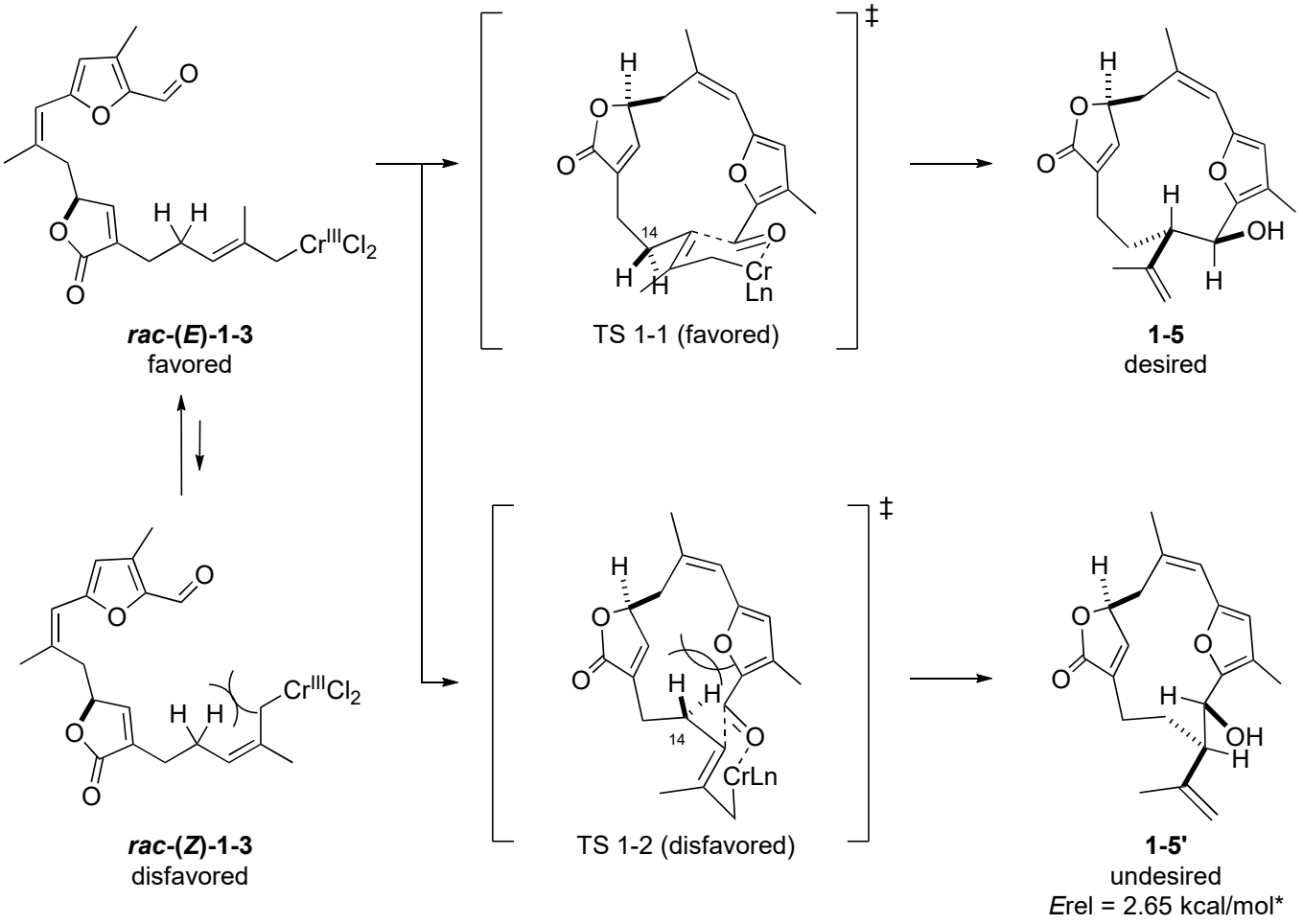


1-5 **1-5'**


m-CPBA
1-5''
1-5''
H⊕
1-6'
1-7
- H⊕
± H⊕
1-8
1-9
Ac2O, DMAP
acetylation
2nd step
3rd step
1-10
1-11
[5+2] cycloaddition
Discussion 2: stereoselectivity
1-12
1-12
Intricarene
4th step

1-2. Discussion

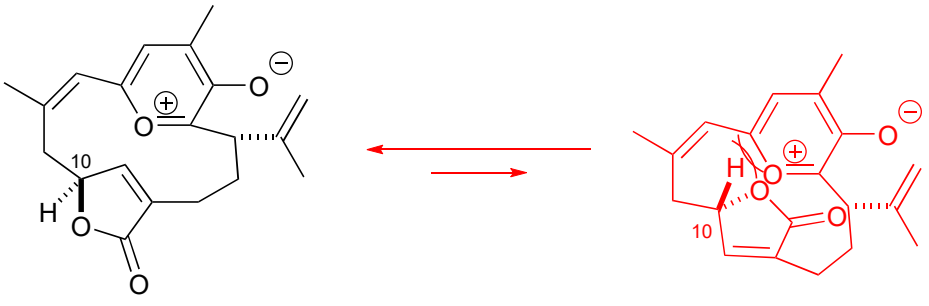
1-2-1. stereoselectivity of Nozaki-Hiyama reaction



* These calculations were performed with Macromodel version 8.1 (Schroedinger, LLC)
Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345.

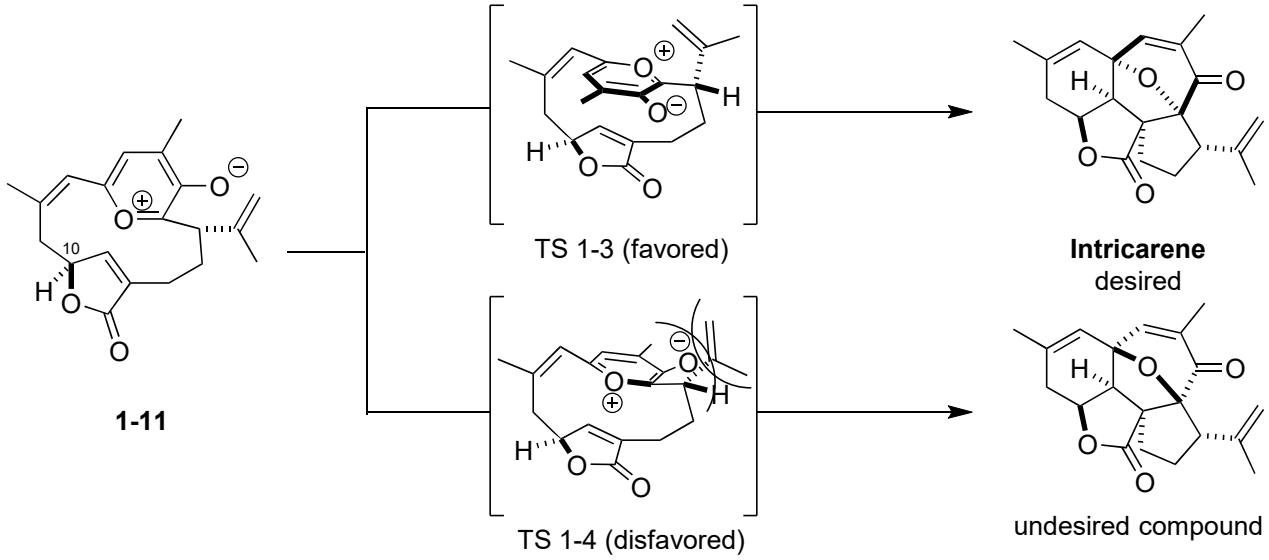
Molecular mechanics calculations suggest that **1-5'** is considerably higher in energy (*E*rel = 2.65 kcal/mol). This could be reflected in the relative energy of the chair-shaped tansition state. I think transannular interactions arise from a lack of space in the interior of the ring in TS-1-2. (ex. H of C14)

1-2-2. stereoselectivity of [5+2] cycloaddition



1-11 **1-11'**

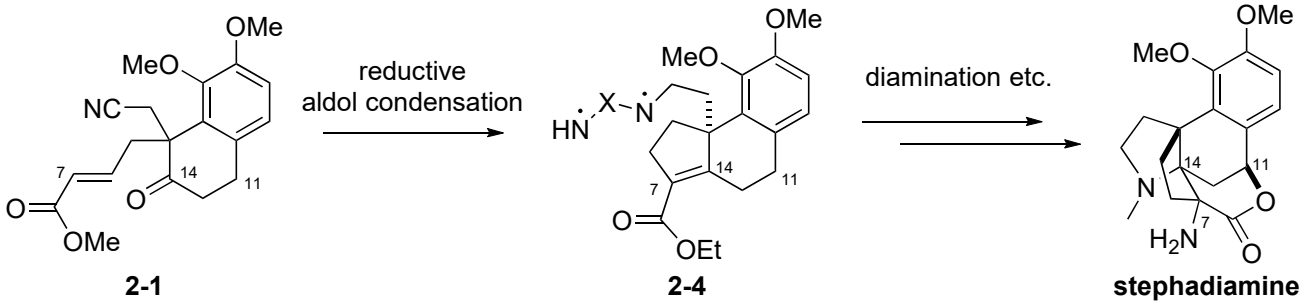
The hydrogen atom at C10 is oriented toward outside of the ring because **1-11'** has larger hindrance than **1-11** between the hydrogen atom of C10 and oxidepyrylium ion.
Thus, two likely transition states described in p.4 are considered.



In TS 1-4, the steric repulsion between oxidopyrylium ion and isopropenyl group is larger than that of TS 1-3. As a result, desired intricarene was stereoselectively obtained.

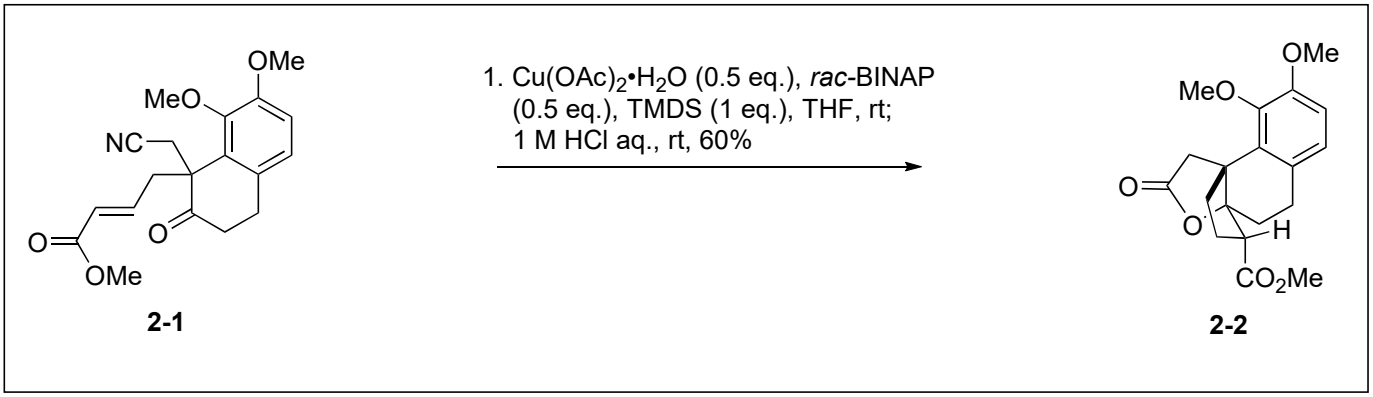
2. Total synthesis of Stephadiamine

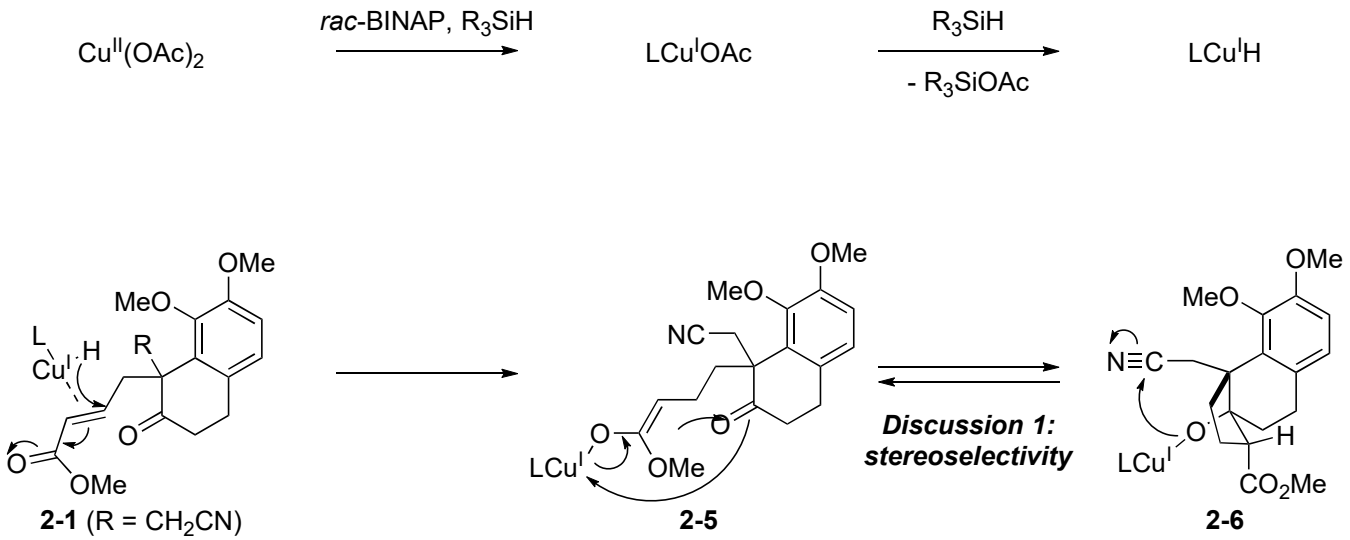
2-1. First Synthetic plan

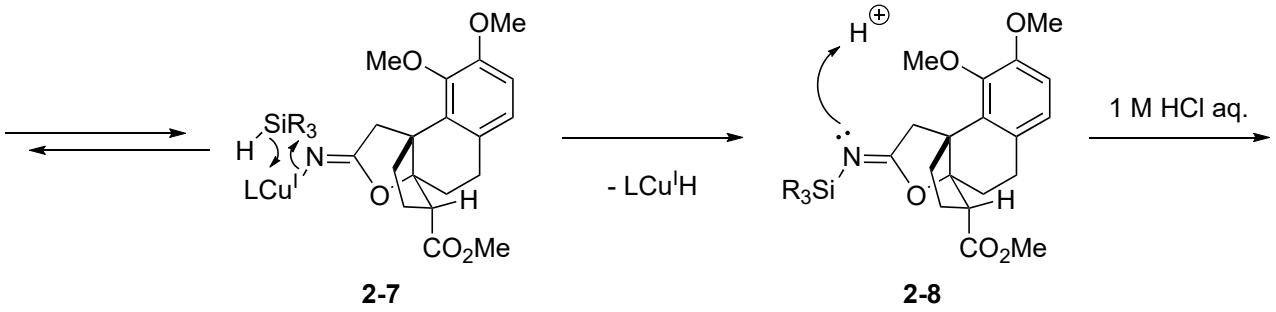


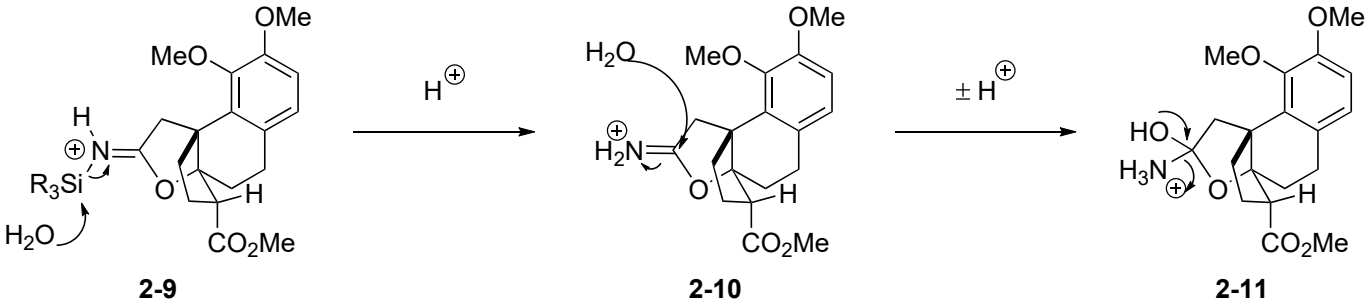
Hartrampf, N.; Winter, N.; Pupo, G.; Stoltz, B. M.; Trauner, D. *J. Am. Chem. Soc.* **2018**, *140*, 8675.

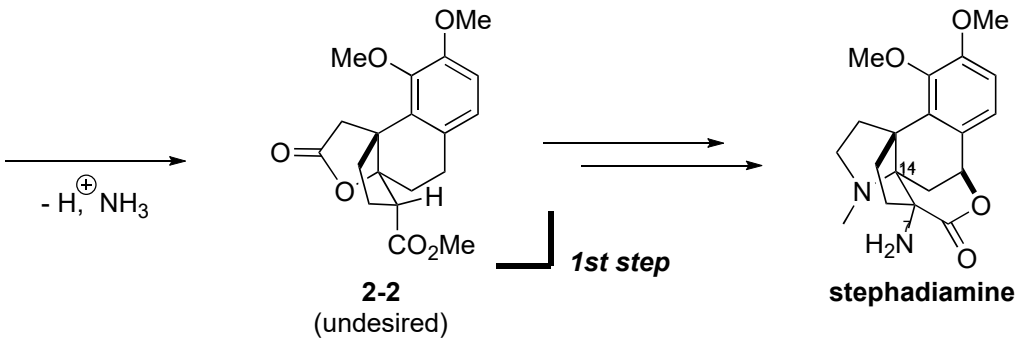
2-2. Reaction mechanism




Cu^II(OAc)2
rac-BINAP, R3SiH
LCu^IOAc
R3SiH
- R3SiOAc
LCu^IH
OMe
MeO
L
Cu^I
H
R
O
O
OMe
2-1 (R = CH2CN)
NC
LCu^I
OMe
2-5
Discussion 1:
stereoselectivity
N≡C
2-6

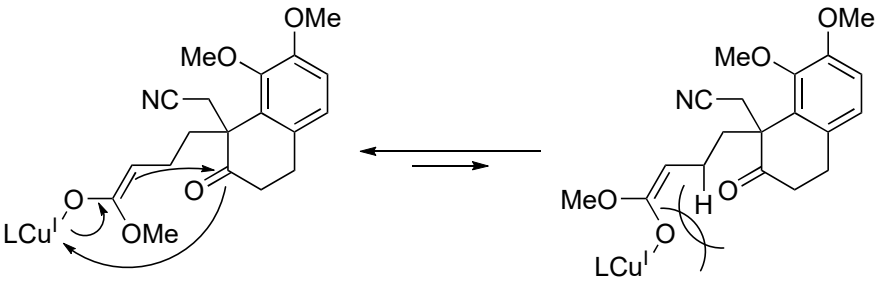

SiR3
H
N
LCu^I
2-7
- LCu^IH
H⊕
R3Si
2-8
1 M HCl aq.


H
⊕N
R3Si
H2O
2-9
H⊕
H2O
H2N
2-10
± H⊕
HO
H3N
2-11


- H,⊕ NH3
2-2
(undesired)
1st step
stephadiamine

2-3. Dicussion

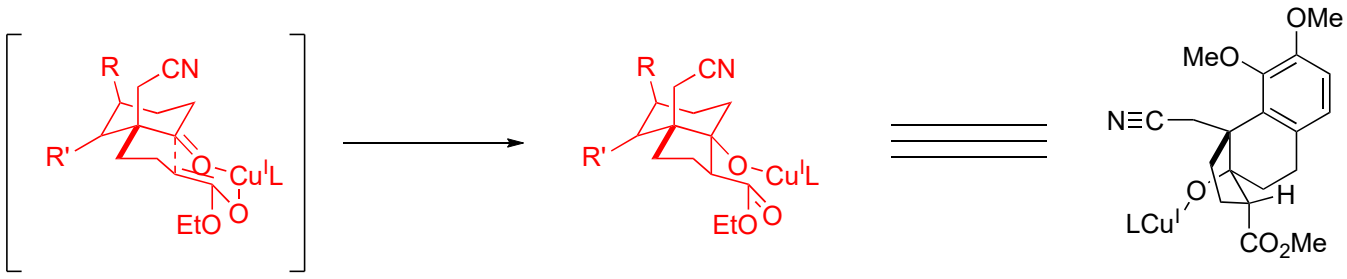
2-3-1. reductive aldol reaction



2-5
(*E*)-enolate
favored

2-5
(*Z*)-enolate
disfavored

6-membered
transition state

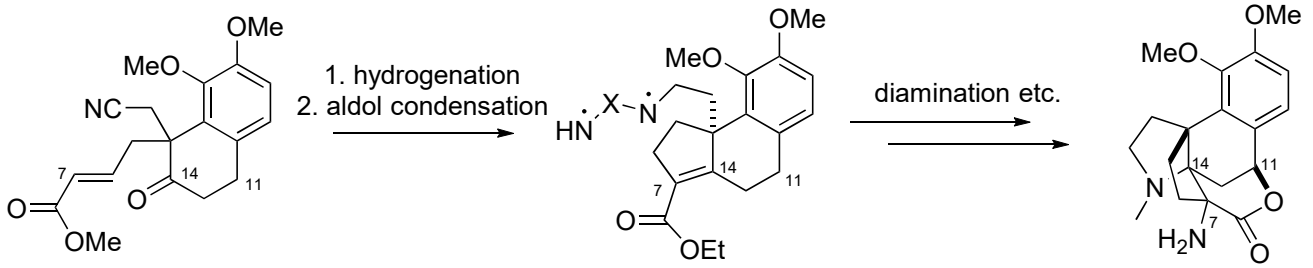


TS 2-1

2-6

The reaction proceeded highly regioselectively, which may be due to 6-membered cyclic transition state.
Regioselectivity: (*Z*)-olefin > (*E*)-olefin, the bigger substituent oriented equatorial position, via 6-membered cyclic transitionone.
→ One likely transition state was considered.

2-4. Second Synthetic plan

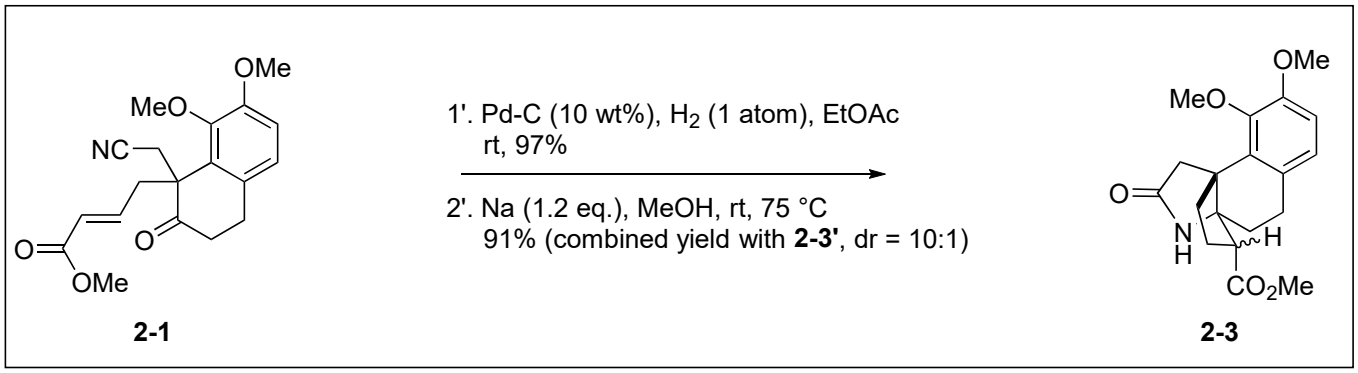


2-1

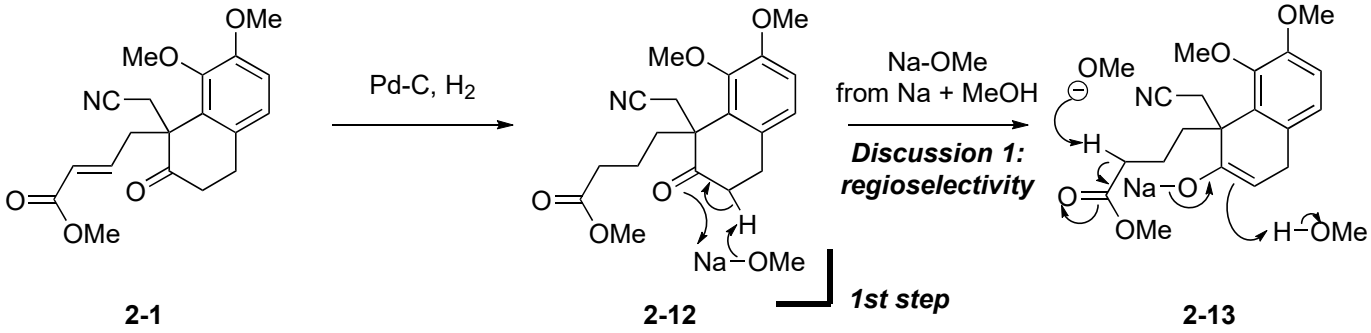
2-4

stephadiamine

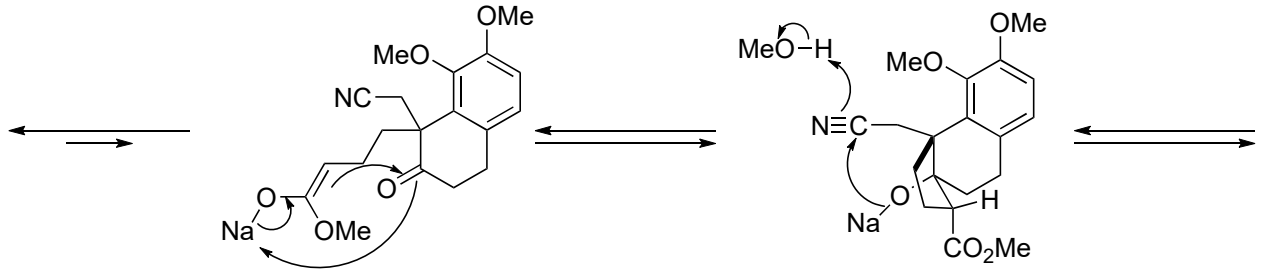
2-5. Reaction mechanism



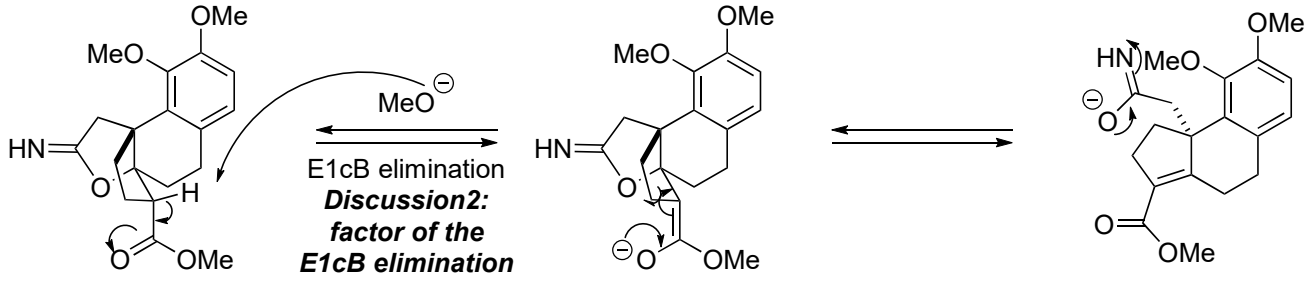
2-1 **2-3**



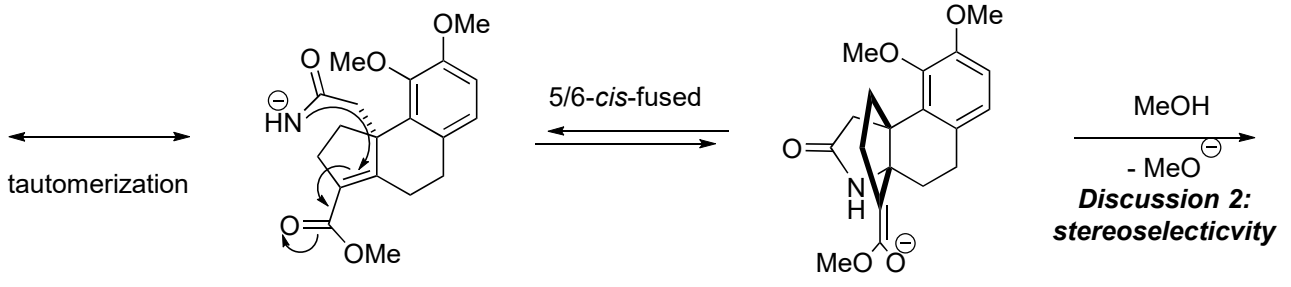
2-1 **2-12** **2-13**



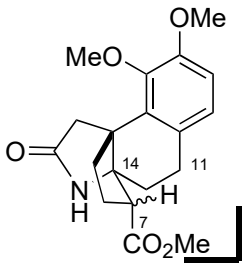
2-14 **2-15**



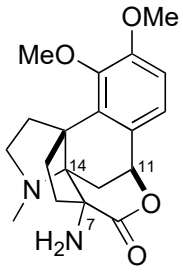
2-16 **2-17** **2-18**



2-19 **2-20**



Remaining Task
- *N*-methylation
- C-7 amination
- closure of the lactone
- reduction of the lactam

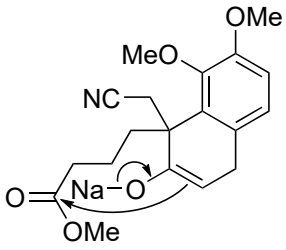


2nd step

2-3 (dr = 10:1)
undesired
but useful intermideate

stephadiamine

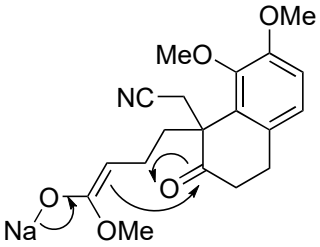
2-6. Discussion
2-6-1. regioselectivity of aldol reaction



2-13

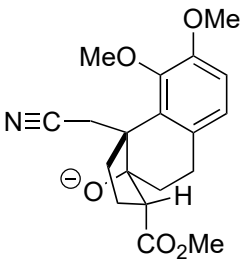
very slow
7-membered ring

Not obtained



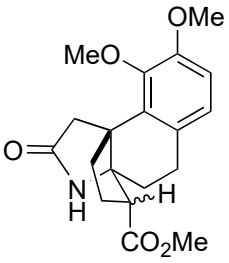
2-14

very fast
5-membered ring



2-12

the last step is
irreversible



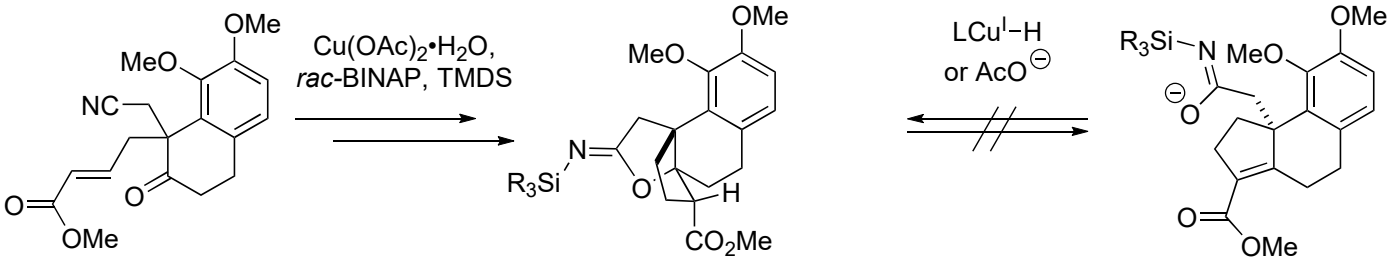
2-3 (dr = 10:1)

The ring closure rate of 5-membered ring is much faster than that of 7-membered ring.
cf. About anionic lactonization, the reaction rate of 5-membered ring is $1.5*10^4$ times faster than that of 7-membered ring.

The last step, which is the protonation of **2-20** is probably irreversible. Thus the equilibrium was biased and **2-3** was obtained in good yield.

2-6-2. factor of the E1cB elimination

(section 2-2.)



2-1 **2-8** **2-21**

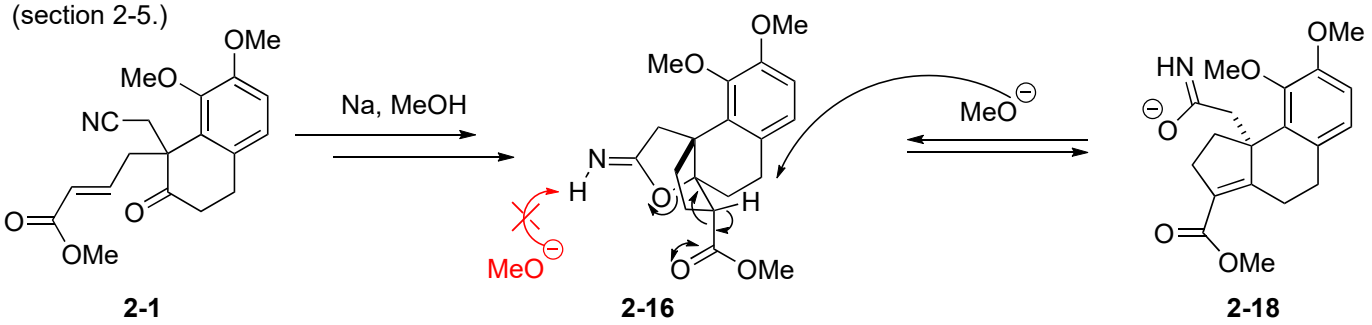
basicity: $MeO^{\ominus}$ > $LCu^{I}H$ or $AcO^{\ominus}$

cf.) pKa in H_2O: MeOH = 15.5, AcOH = 4.76

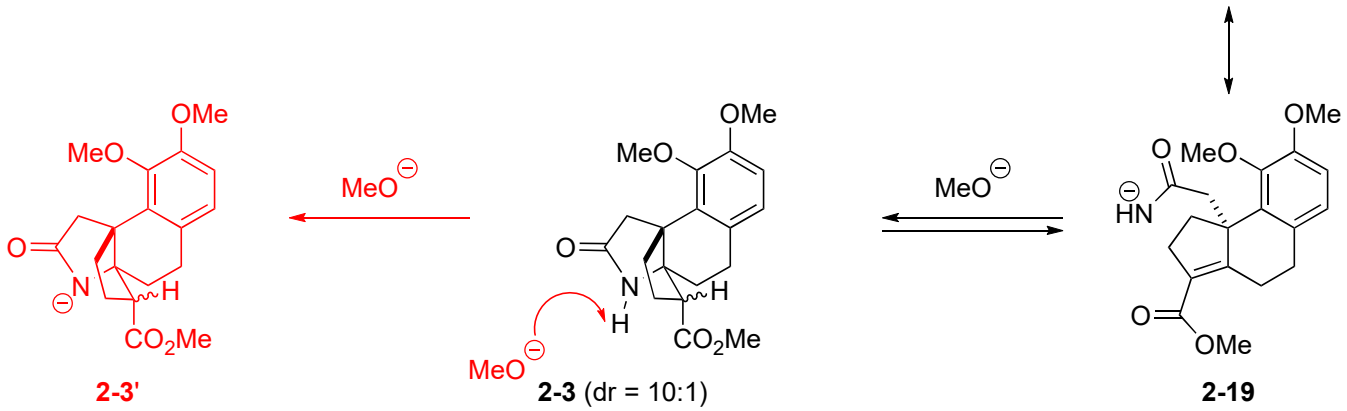
polarization: CuH = 0.30, NaH = 1.27

cf.) electronnegativity: H = 2.20, Na = 0.93, Cu =1.90

(section 2-5.)



2-1 **2-16** **2-18**

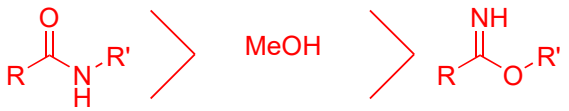


2-3' **2-3** (dr = 10:1) **2-19**

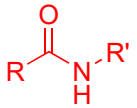
"all efforts to epimeriza the ester and to form silyl ketene acetal failed, suggesting that the deprotonation step was the source of our frustrations"

J. Am. Chem. Soc. **2018**, *140*, 8677, L. 26-29

pKa

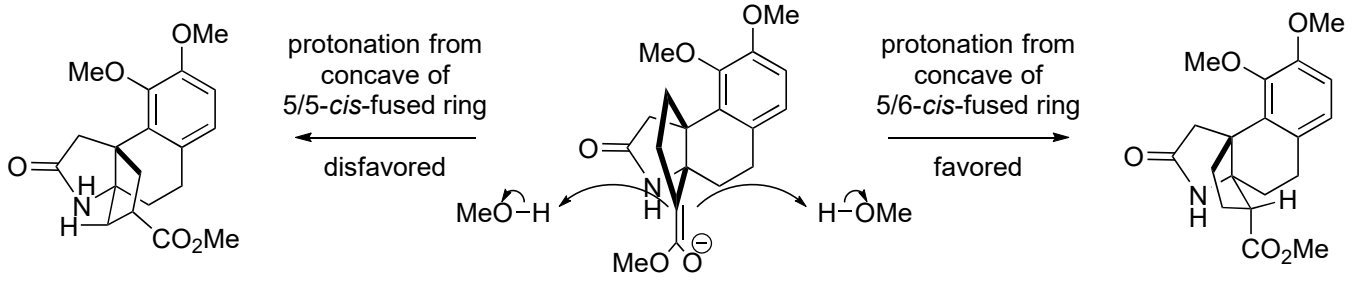


cf.) pKa in DMSO: MeOH = 27.9



= 25.9

2-6-3. regioselectiveity of protonation of **2-20**



2-3 **2-20** **2-3**
(dr = 10:1)