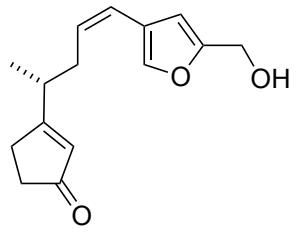
Problem Session (1)

2020.12.12 Junichi Taguchi

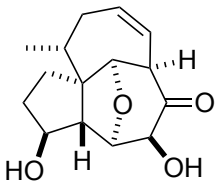
Please provide the reaction mechanism.

(1)



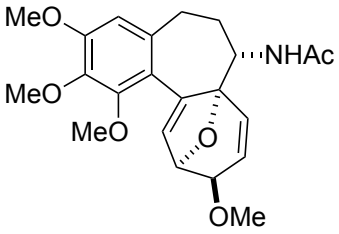
1-1

1. $VO(acac)_2$ (0.2 eq.), *t*-BuOOH (2.5 eq.), CH_2Cl_2, 0 °C to rt;
   Et_3N (3.8 eq.), Boc_2O (1.5 eq.), DMAP (0.5 eq.), 0 °C, 79% (2 steps)
2. TMP (1.5 eq.), MeCN, 150 °C, 38%
3. DIBAL-H (2.5 eq.), THF, -78 °C, 98 %
4. *m*-CPBA (1.1 eq.), CH_2Cl_2, rt, 79 %
5. $BF_3{\cdot}Et_2O$ (5 eq.), CH_2Cl_2, rt, 60 %



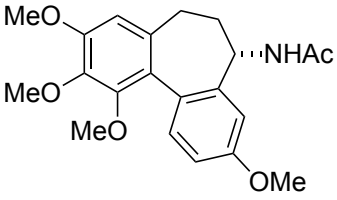
1-2

(2)



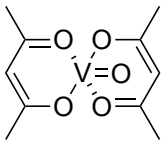
2-1

1. $PdCl_2$ (0.5 eq.), $Cu(OAc)_2$ (1.0 eq.), $MeCN/H_2O$ (9/1), O_2 (1 atm), 120 ºC, 70 %
2. TMSOTf (6.9 eq.), Me_2NEt (19 eq.), CH_2Cl_2, rt, 81 %
3*. hν (Hg lamp), MeCN/acetone (10/1), 68 %
4*. hν (Hg lamp), MeCN/acetone (10/1), 54 %

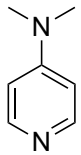


2-2

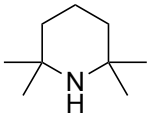
* The authors do not mention the temperature
** The authors tried to extend the time of irradiation for one-pot synthesis from step 3 to step 4, but a trace of **2-2** was detected.



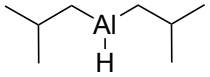
$VO(acac)_2$



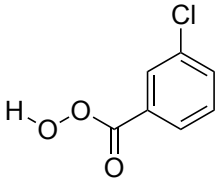
DMAP



TMP



DIBAL-H



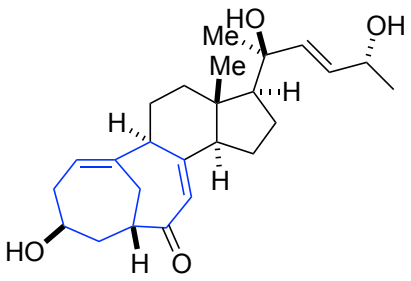
m-CPBA

Problem Session (1) -Answer-

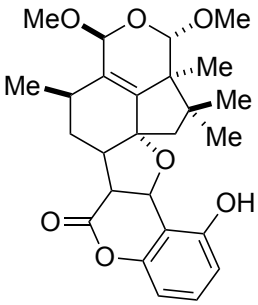
2020.12.12. Junichi Taguchi

Topic: Works by Prof. Chuang-Chuang Li

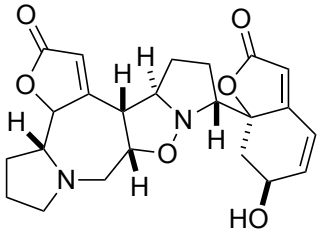
1997-2001 B.S. in Chemistry @ China Agricultural University (Prof. Dao-Quan Wang)
2001-2006 Ph.D. @ Peking University (Prof. Zhen Yang)
2006-2008 Postdoctoral Associate @ The Scripps Research Institute (Prof. Phil S. Baran)
2008-2013 Associate Professor @ Peking University
2014-2017 Research Professor (tenure-track) @ Southern University of Science and Technology (SUSTech)
2018- Full Professor with tenure @ SUSTech



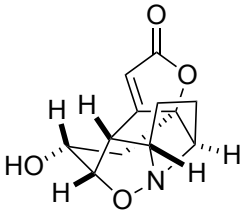
cyclocitrinol
J. Am. Chem. Soc. **2018**, *140*, 5365
See also 180421_PS_Yinghua_Wang



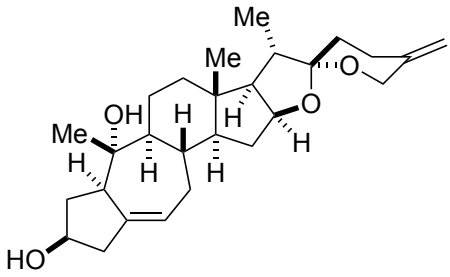
hypocrolide A
Org. Lett. **2016**, *18*, 4932



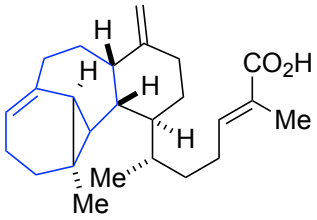
(-)-flueggine A



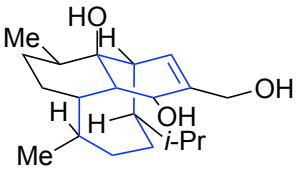
(+)-virosaine B
Angew. Chem. Int. Ed. **2013**, *52*, 620
See also 130112_PS_Satoshi_Hashimoto
190622_PS_Tsukasa_Shimakawa



bufospirostenin A
J. Am. Chem. Soc. **2020**, *142*, 12602

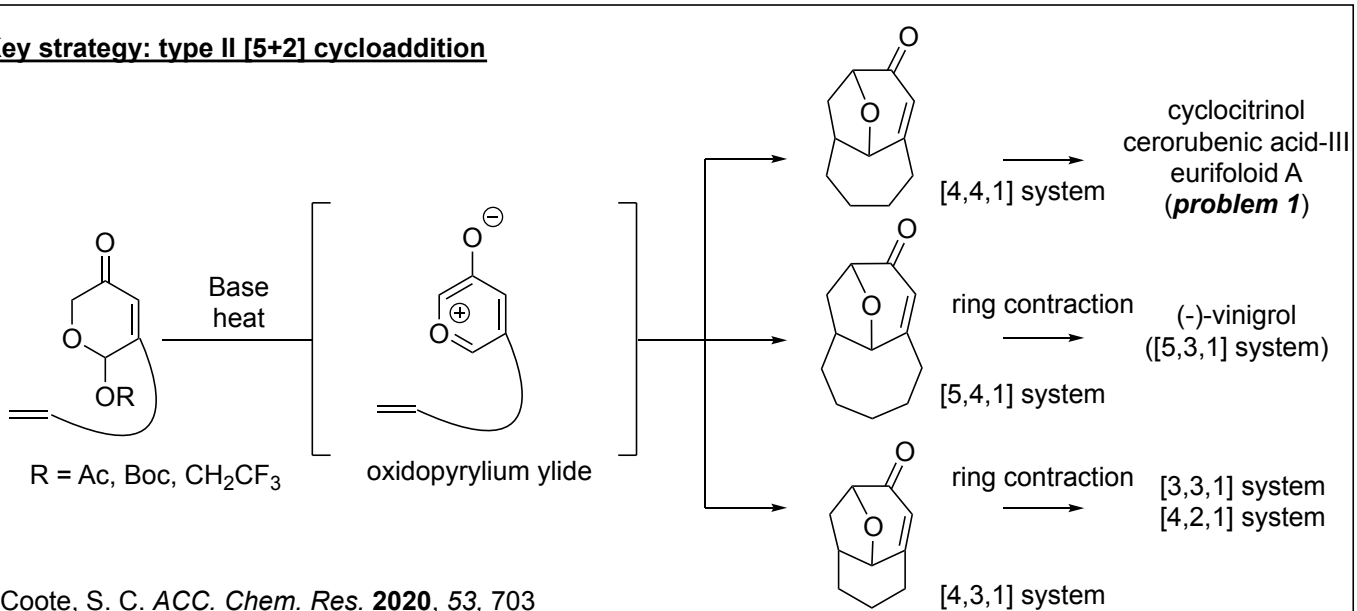


cerorubenic acid-III
J. Am. Chem. Soc. **2019**, *141*, 2872



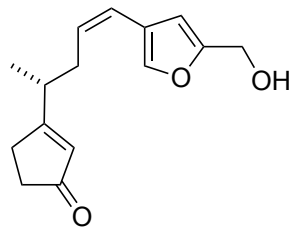
(-)-vinigrol
J. Am. Chem. Soc. **2019**, *141*, 15773
See also 191207_LS_Yuto_Hikone

Key strategy: type II [5+2] cycloaddition



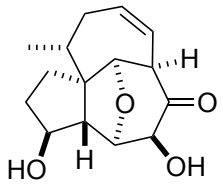
Coote, S. C. *ACC. Chem. Res.* **2020**, *53,* 703
Mei, G.; Liu, X.; Quo, C.; Chen, W.; Li, C. C. *Angew. Chem.* **2015**, *127*, 1774

(1)



1-1

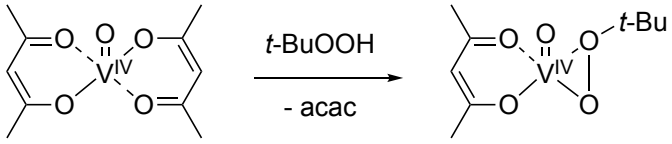
1. $VO(acac)_2$ (0.2 eq.), *t*-BuOOH (2.5 eq.), CH_2Cl_2, 0 °C to rt;
   Et_3N (3.8 eq.), Boc_2O (1.5 eq.), DMAP (0.5 eq.), 0 °C, 79% (2 steps)
2. TMP (1.5 eq.), MeCN, 150 °C, 38%
3. DIBAL-H (2.5 eq.), THF, -78 °C, 98 %
4. *m*-CPBA (1.1 eq.), CH_2Cl_2, rt, 79 %
5. $BF_3 \cdot Et_2O$ (5 eq.), CH_2Cl_2, rt, 60 %



1-2

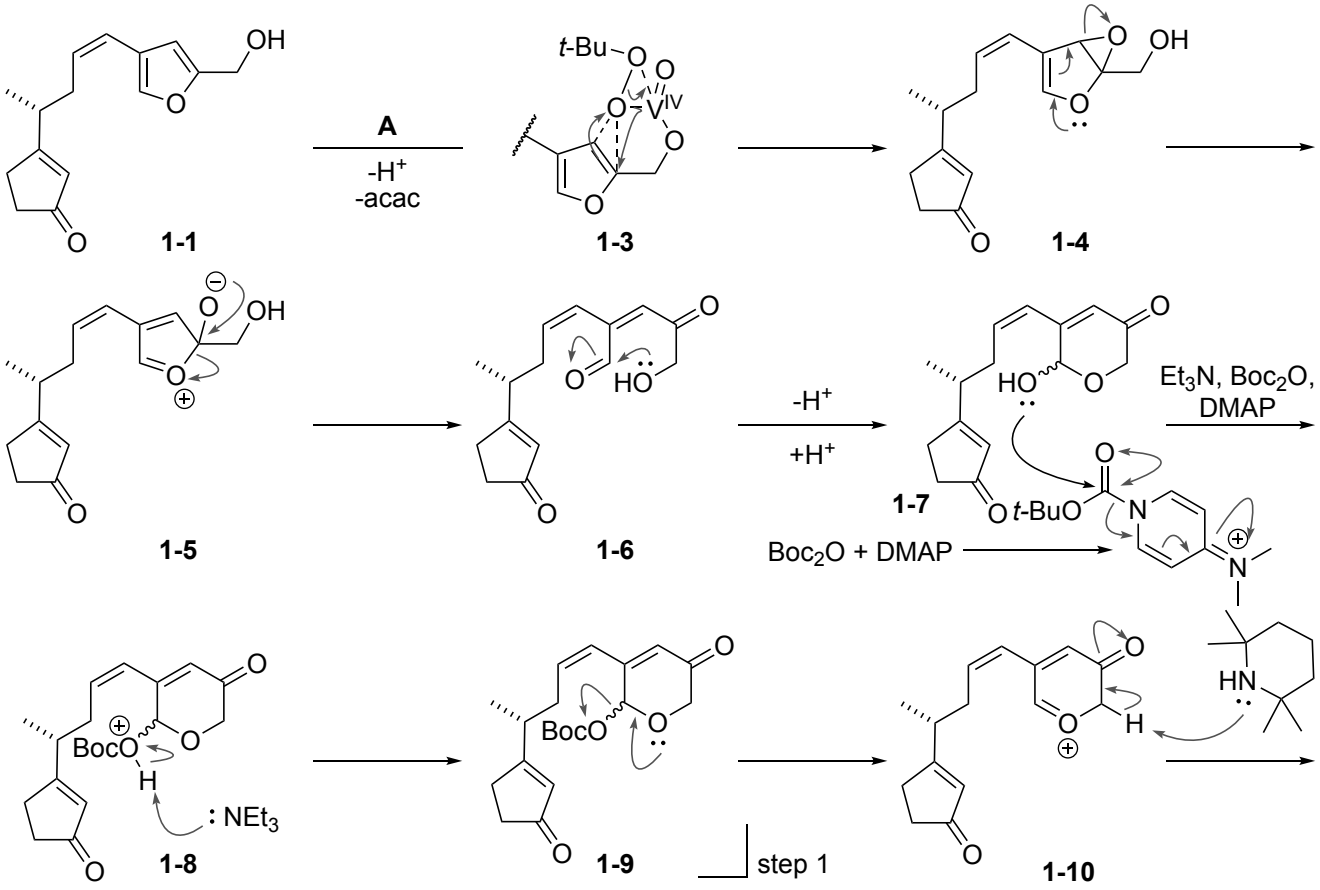
Liu, X.; Liu, J.; Zhao, J.: Li, S.; Li, C. C. *Org. Lett.* **2017**, *19*, 2742.

activation of vanadium catalyst



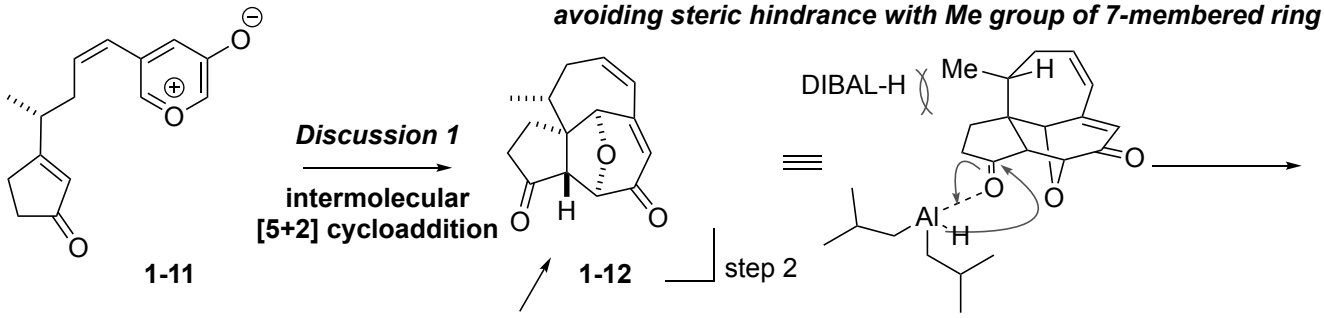
$VO(acac)_2$ *t*-BuOOH, - acac → **A**

Stepovik, L.; Gulenova, M. *Russ. J. Gen. Chem.* **2009**, *79*, 1663.



1-1 → (**A**, $-H^+$, -acac) → **1-3** → **1-4** → **1-5** → **1-6** → ($-H^+$, $+H^+$) → **1-7** → (Et_3N, Boc_2O, DMAP) → (Boc_2O + DMAP) → **1-8** (: NEt_3) → **1-9** → step 1 → **1-10**

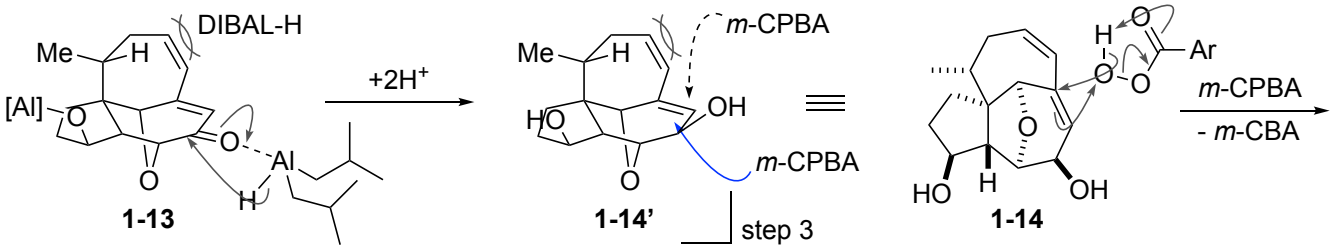
avoiding steric hindrance with Me group of 7-membered ring



1-11 → ***Discussion 1*** **intermolecular [5+2] cycloaddition** → **1-12** → step 2

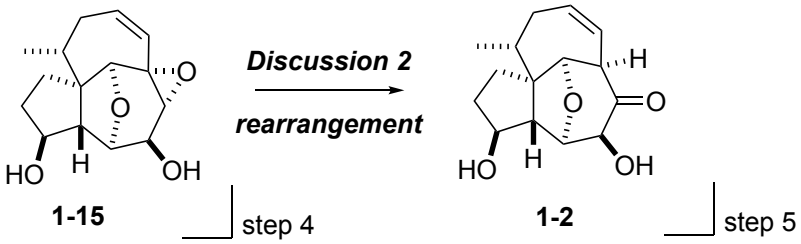
see from this side

approaching from the sterically accesible site



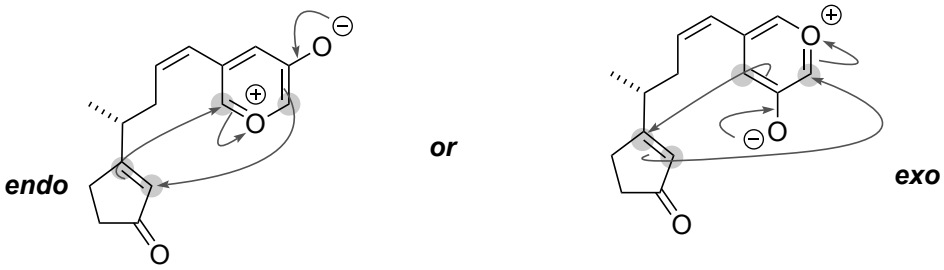
1-13 **1-14'** step 3 **1-14**

more electron-rich tri-substituted olefin reacts

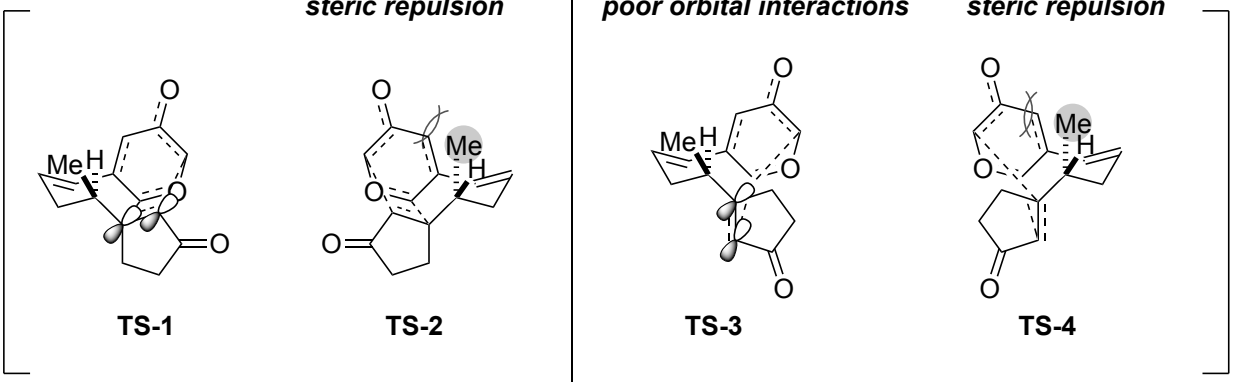


1-15 step 4 **1-2** step 5

Discussion 1: **intermolecular [5+2] cycloaddition**

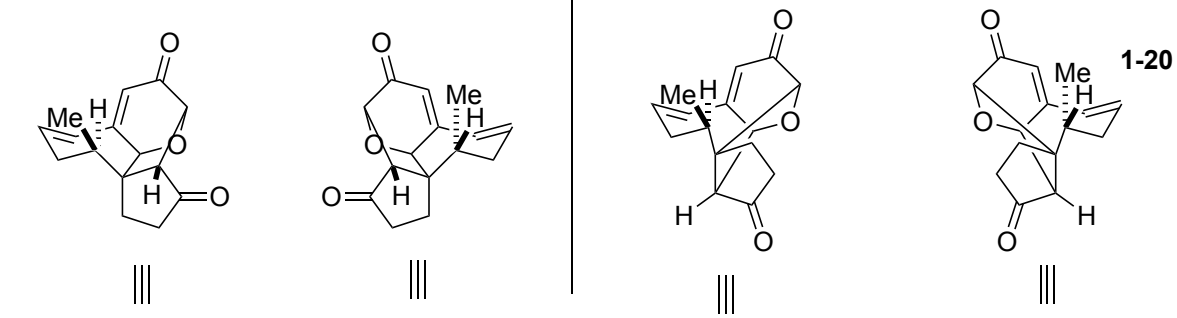


steric repulsion ***poor orbital interactions*** ***steric repulsion***

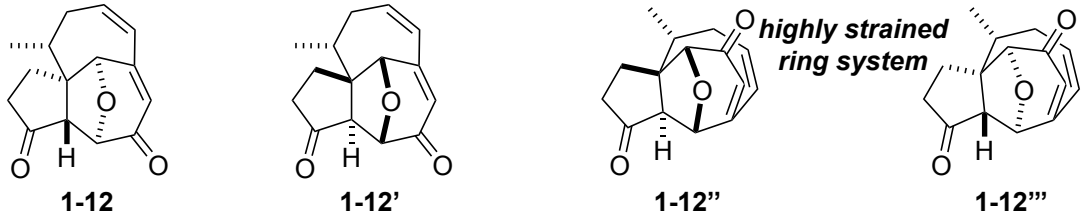


TS-1 **TS-2** **TS-3** **TS-4**

endo ***endo*** ***exo*** ***exo***



1-20



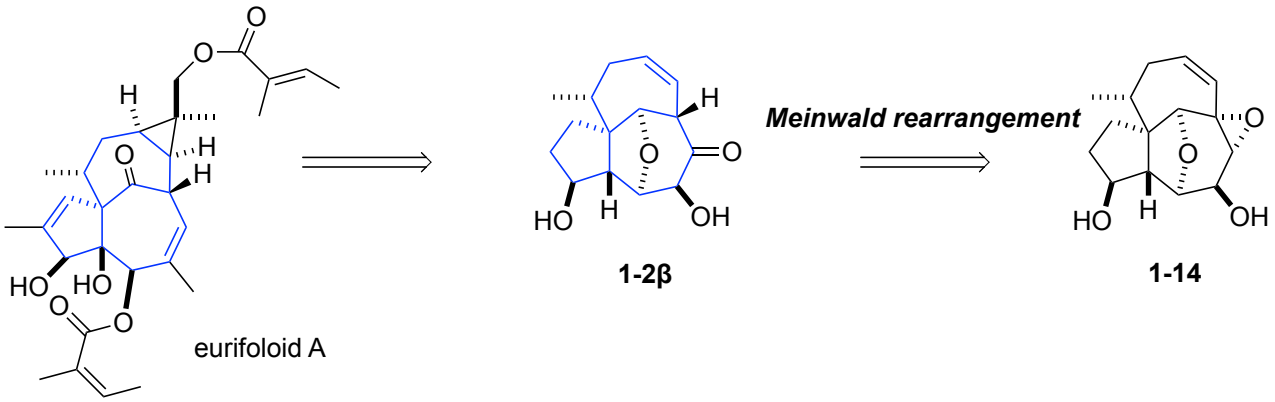
highly strained ring system

1-12 favored **1-12'** disfavored **1-12"** disfavored **1-12'"** disfavored

Discussion 2: **rearrangement**

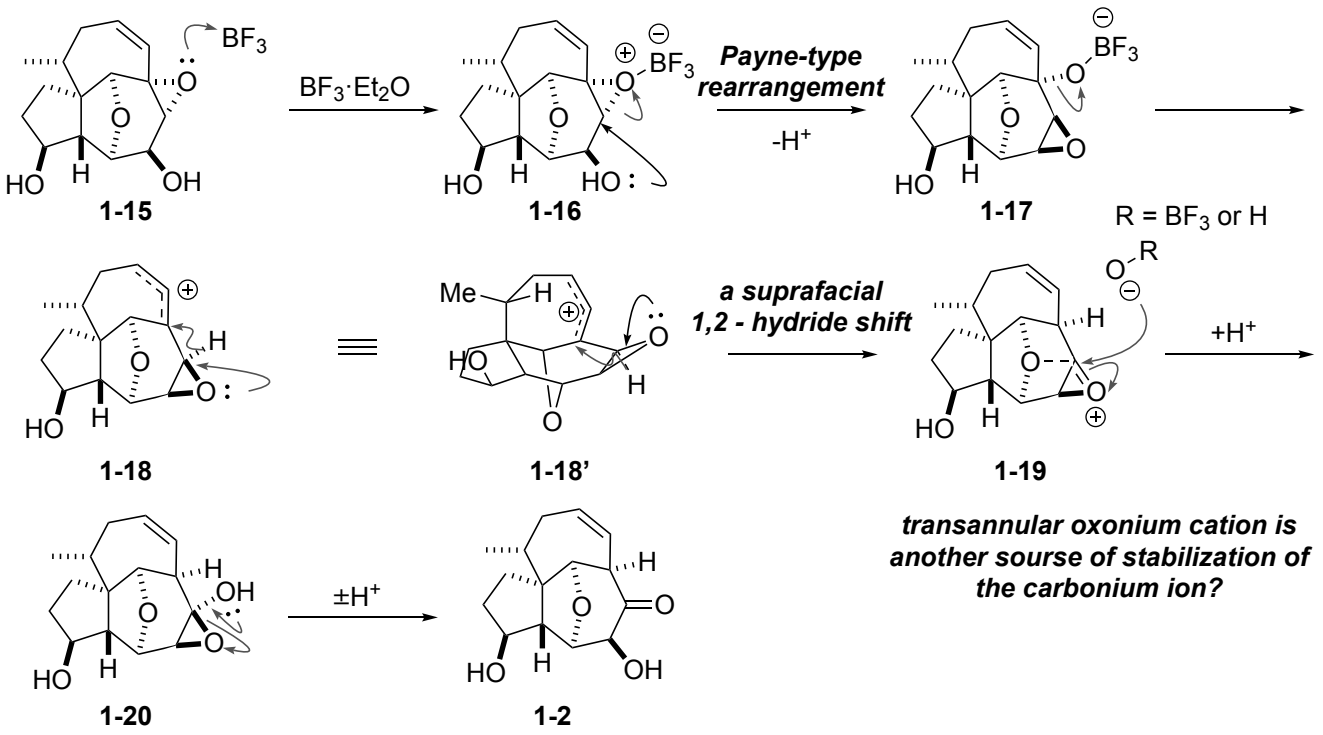
Background

The authors attempted Meinwald rearrangement reaction for the synthesis of **1-2β** through stereospecific intramolecular hydrogen transfer.



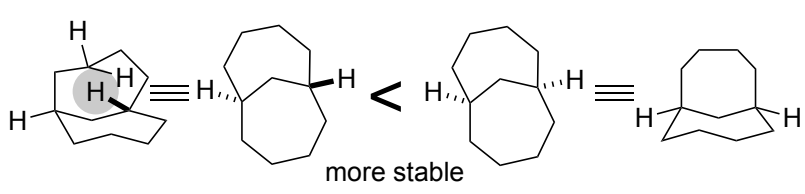
However, the desired product **1-2β** was not obtained and the undesired diastreomer **1-2** was obtained.

proposed mechanism 1 (by authors) : a pathway involved an initial inversion proceeding through a Payne-type rearrangement

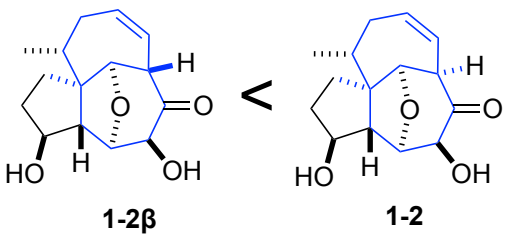


proposed mechanism 2 (my proposal): a pathway involved concerted Meinwald rearrangement

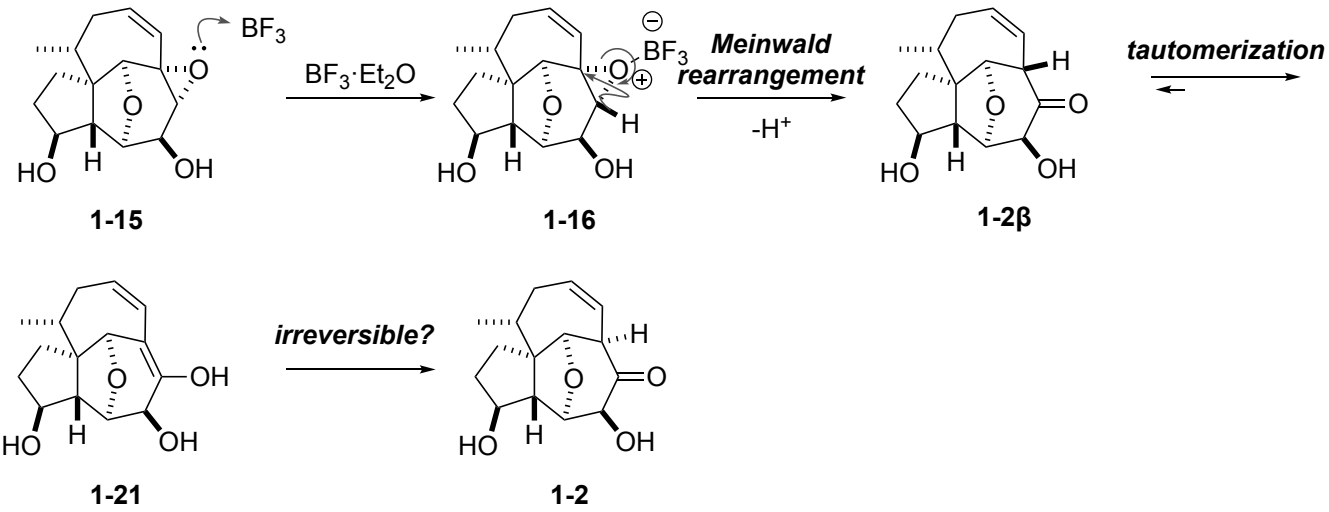
MM2 Calculated Steric Energies of Lowest Energy Conformations of bicyclo[4,4,1]undecane



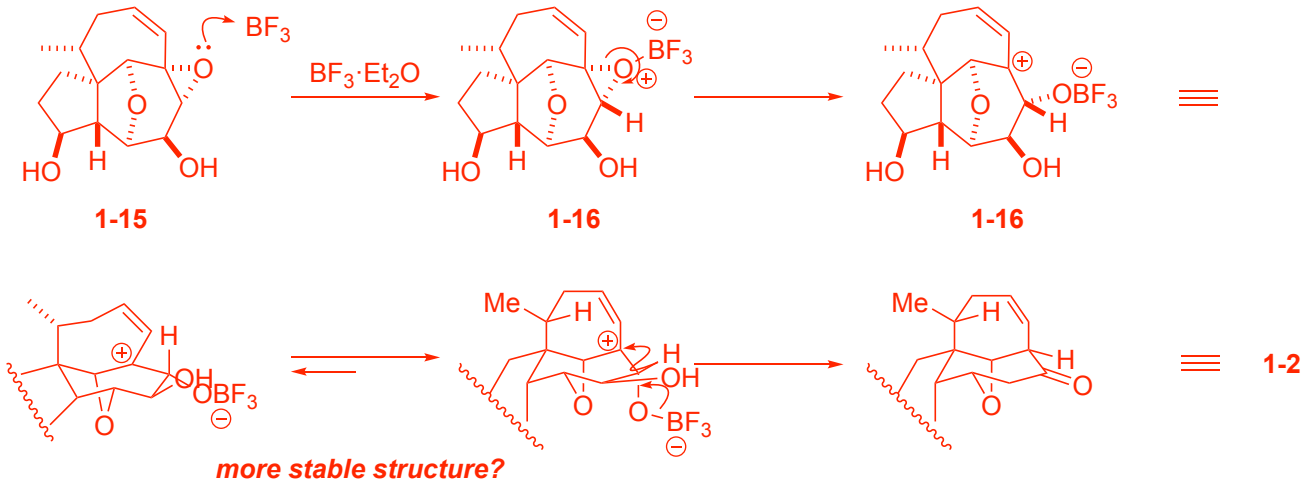
Saunders, M. *J. Comput. Chem.* **1989**, *10*, 203.



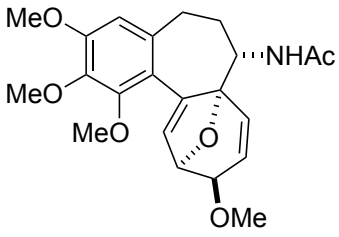
Considering form this result, **1-2** would be more stable than **1-2β**.



proposed mechanism 3 : a pathway involved stepwise Meinwald rearrangement



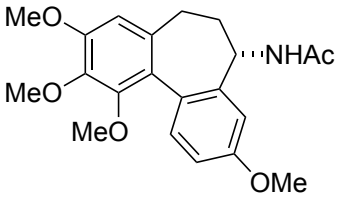
(2)



2-1

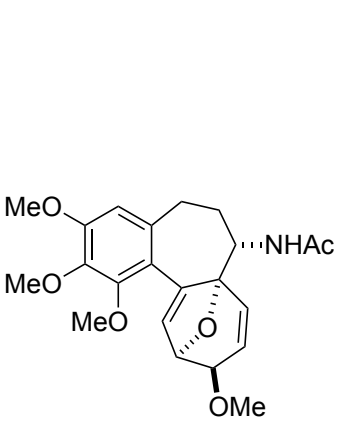
1. $PdCl_2$ (0.5 eq.), $Cu(OAc)_2$ (1.0 eq.), $MeCN/H_2O$ (9/1), O_2 (1 atm), 120 °C, 70 %
2. TMSOTf (6.9 eq.), Me_2NEt (19 eq.), CH_2Cl_2, rt, 81 %

3*. hν (Hg lamp), MeCN/acetone (10/1), 68 %
4*. hν (Hg lamp), MeCN/acetone (10/1), 54 %



2-2

Liu, X.; Hu, Y. -J.; Chen, B.: Min, L.; Peng, X, -S.; Zhao, J.; Li, S.; Wong, H. N. C.; Li, C. C. *Org. Lett.* **2017**, *19*, 4612.

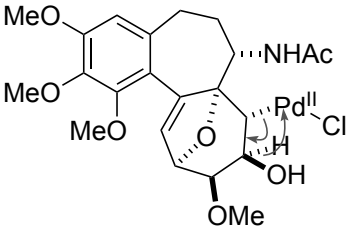


2-1

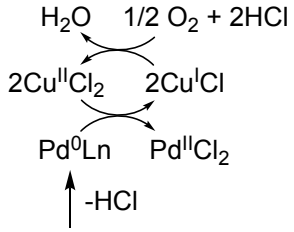
$Pd^{II}Cl_2$, H_2O

Wacker oxidation

Discussion 1: regioselectivity

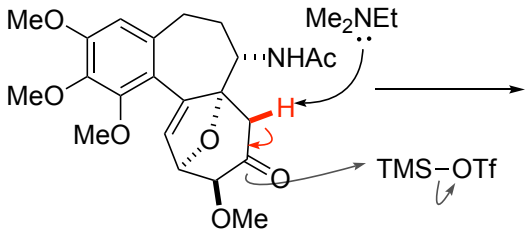


2-3



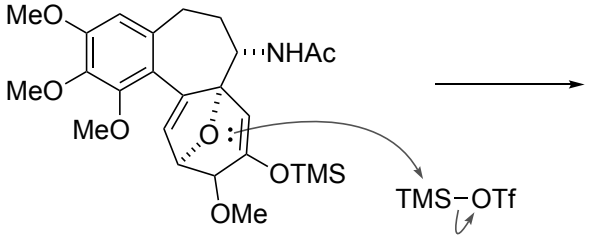
β elimination; keto-enol tautomerization

axial proton

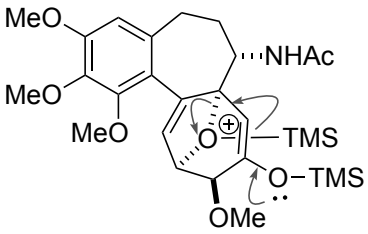


2-4

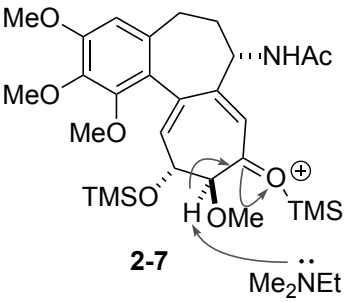
step 1



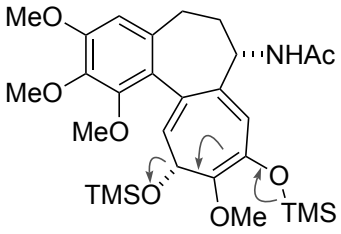
2-5



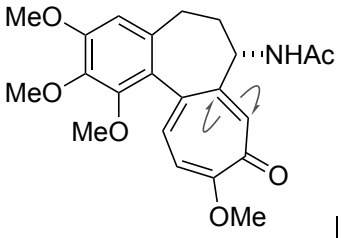
2-6



2-7



2-8



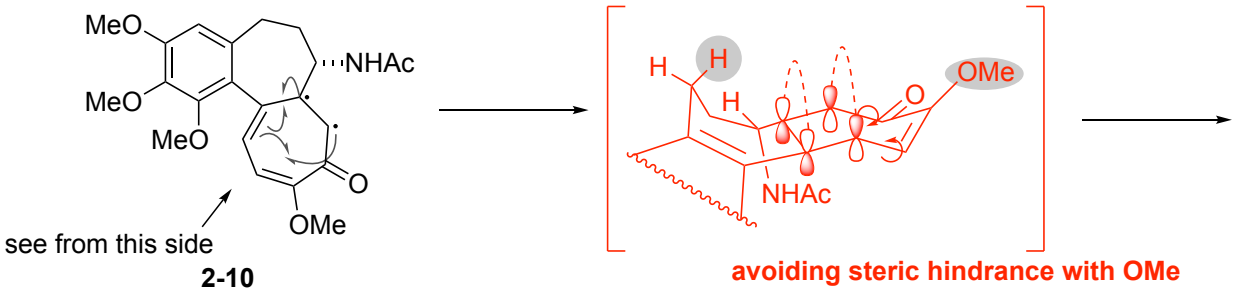
2-9 (colchicine)

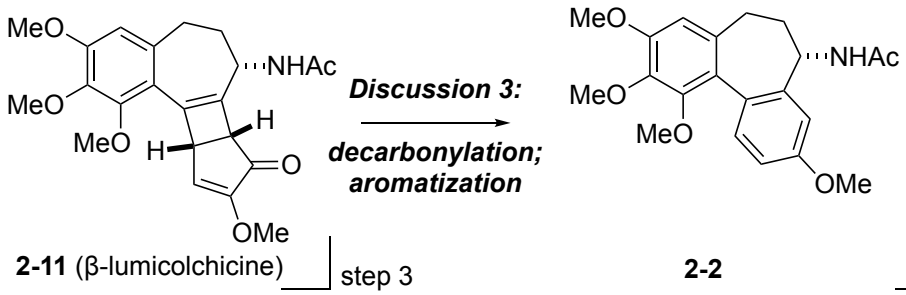
step 2

hν

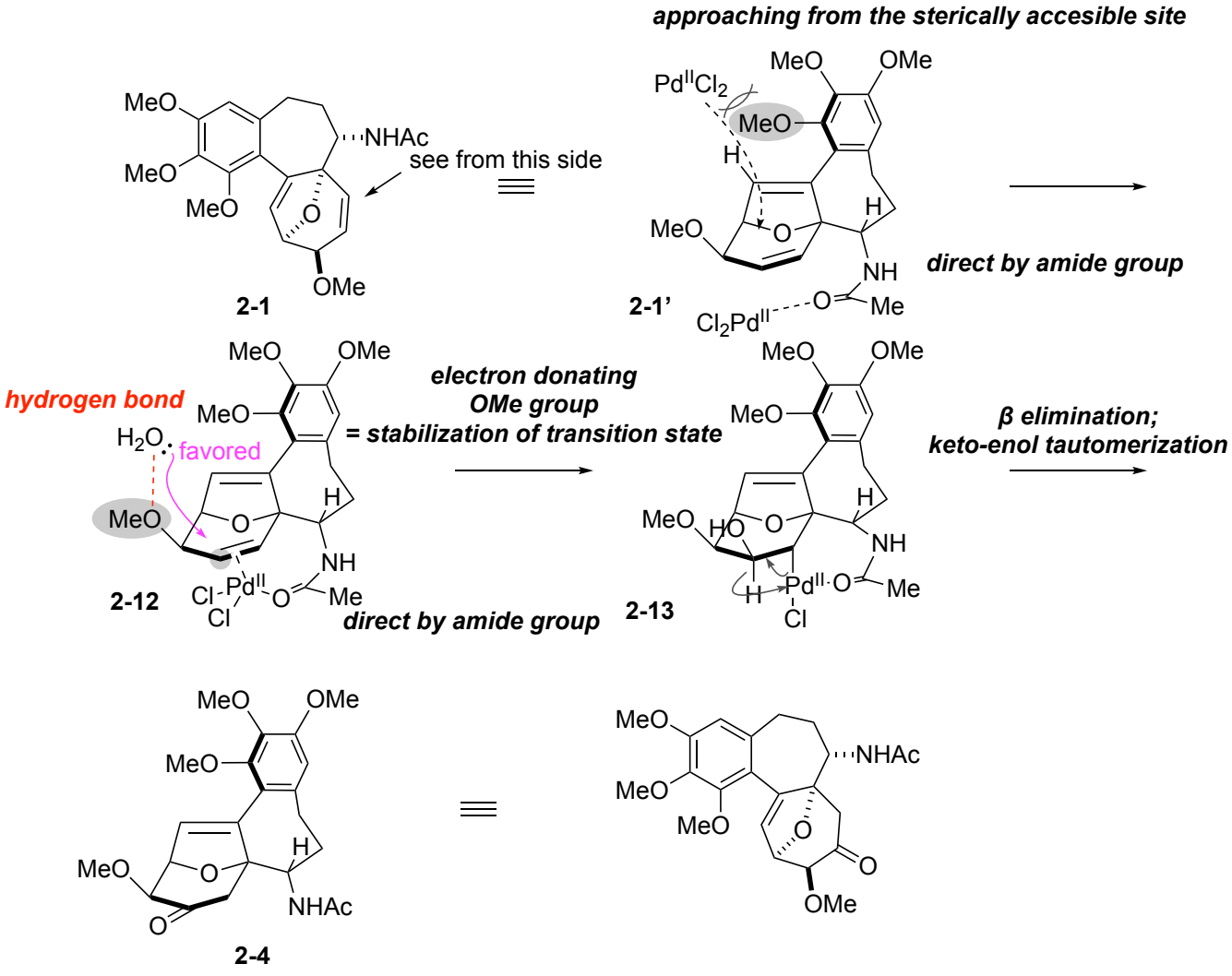
[2+2] cycloaddition

Discussion 2: regioselectivity



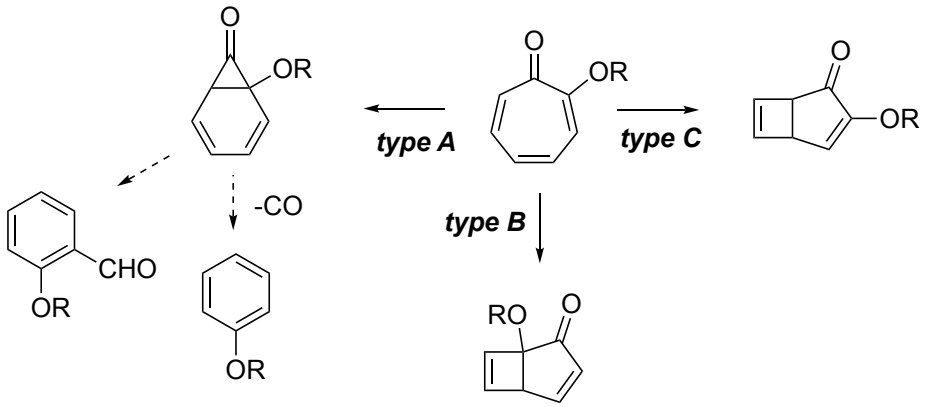


Discussion 1: regioselectivity



***Discussion 2: regioselectivity of* [2+2] cycloaddition**

3 possibilities for the electroisomerization of tropolone systems



Reaction type A rarely happens in the troponoid series, but is much more widespread in cycloheptatrienes.

Chapman, O. L.; Pasto, D. J. *J. Am. Chem. Soc.* **1960,** *82*, 3642

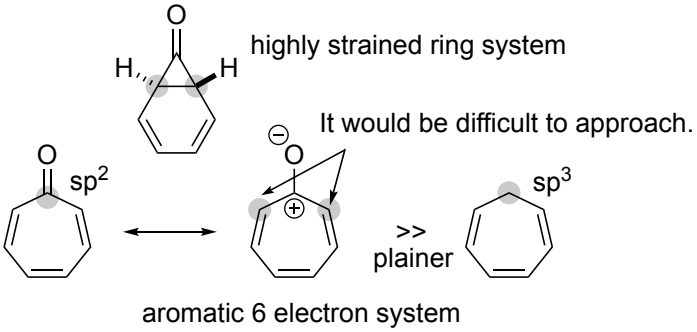
My proposal: the reasons why the reaction type A seldom happens are follows;

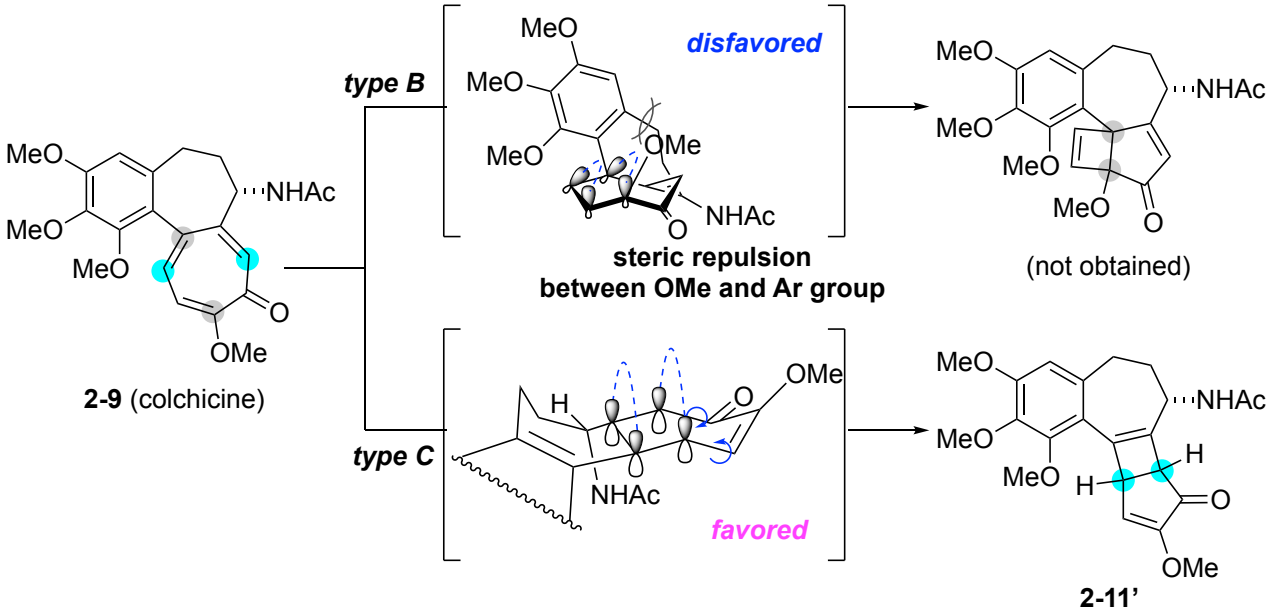
• trans 3/6 fused ring which is highly strained

• the poor overlap among π orbitals of tropolones

Since tropolones are aromatic, their structures are plainer than cycloheptatrienes. It causes difficult to close to each end of the conjugated triene.

In this problem, reaction type A is not expected to occur for the above reasons as well.



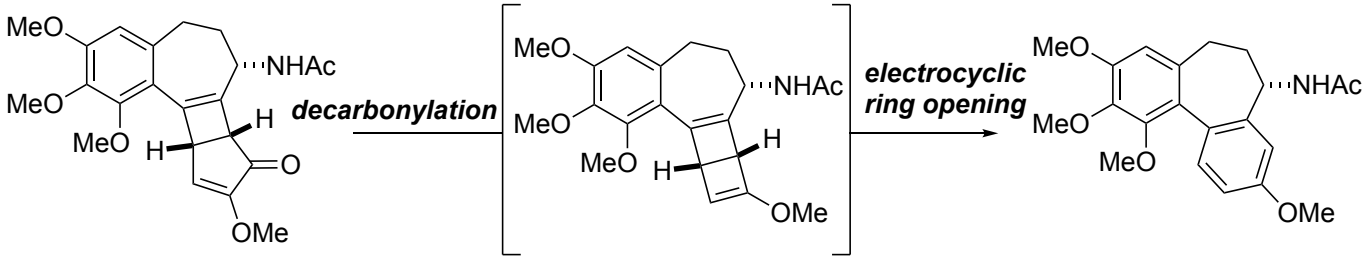


2-9 (colchicine)

2-11'

Discussion 3: decarbonylation; aromatization (reaction mechanism)

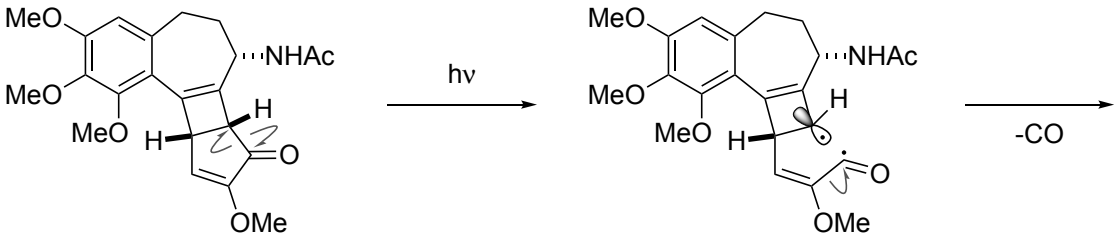
Authors' proposal



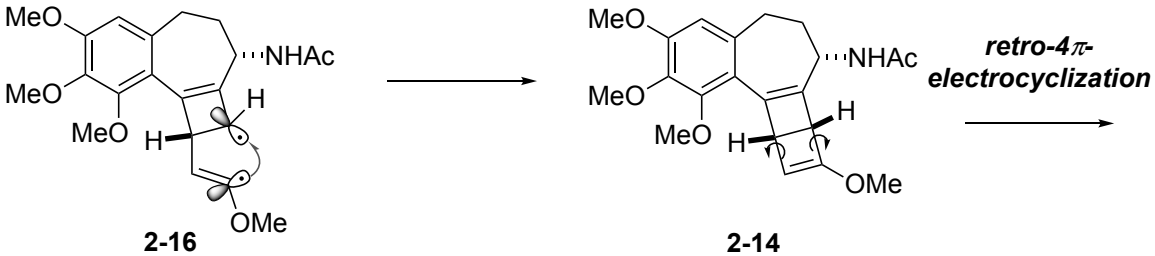
2-11 (β-lumicolchicine) **2-14** (not isolated) **2-2**

The authors does not show the reaction mechanism from **2-11** to **2-2**.

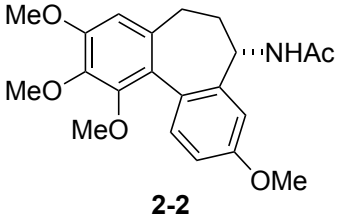
proposed mechanism 1 (based on authors' opinion): Norrish reaction type I



2-11 (β-lumicolchicine) **2-15**

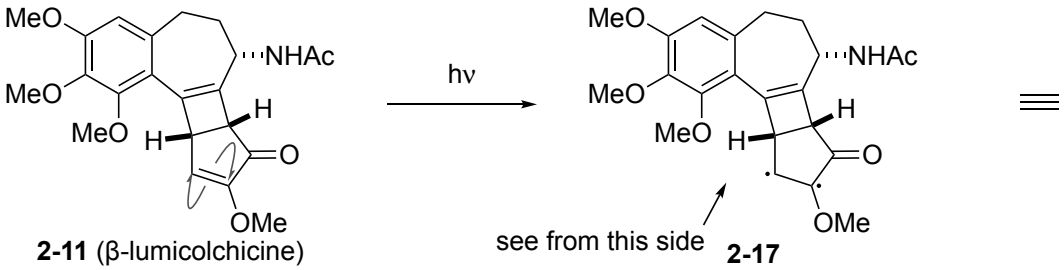


2-16 **2-14**

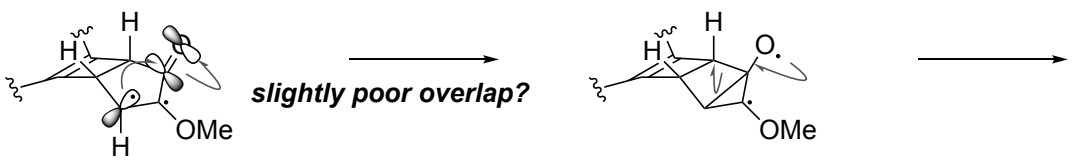


2-2

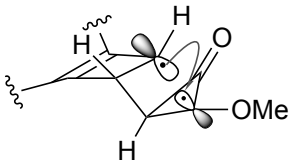
proposed mechanism 2 (based on authors' opinion)



2-11 (β-lumicolchicine) **2-17**

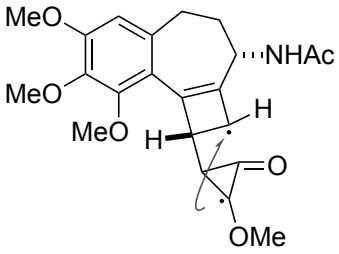


2-17' **2-18**

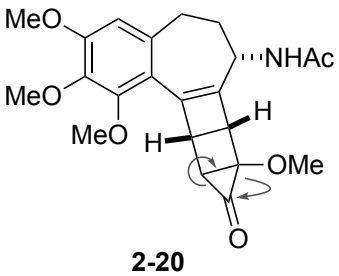


2-19

≡

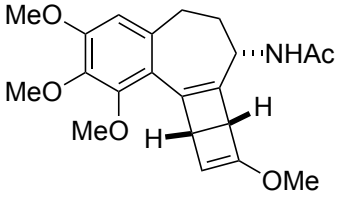


2-19'



2-20

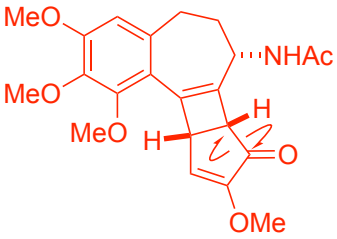
-CO



2-14

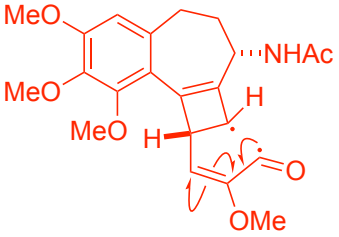
(same as the above) **2-2**

proposed mechanism 3

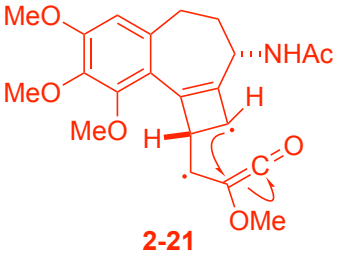


2-11 (β-lumicolchicine)

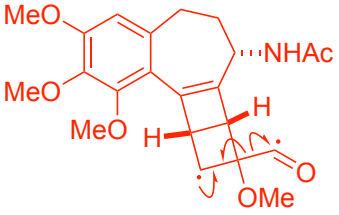
hν



2-15

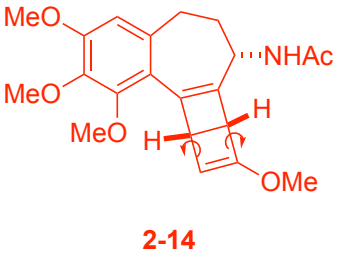


2-21



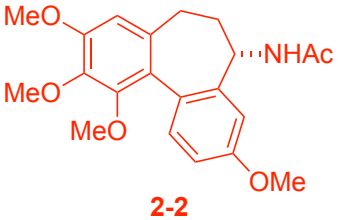
2-22

decarbonylation



2-14

retro-4π-electrocyclization

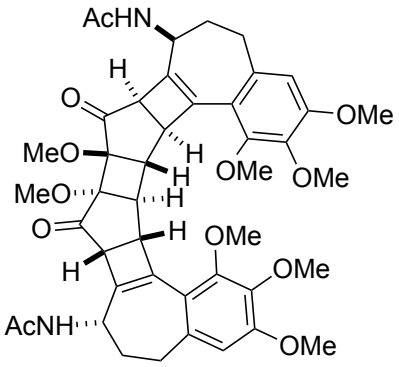


2-2

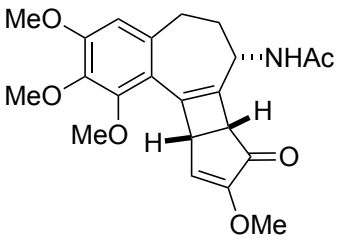
Discussion 4: The reason why one-pot synthesis of compound 2-2 was unsuccessful

Photoisomerization of Colchicine

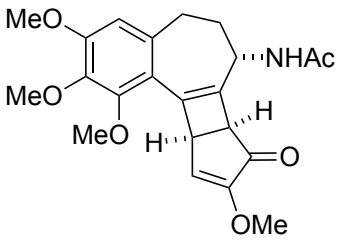
The irradiation of colchisine leads to the formation of β-lumicolchicine and γ-lumicolchicine.
Prolonged irradiation times lead to the formation of α-lumicolchicine (dimer of β-lumicolchicine).



α-lumicolchicine



β-lumicolchicine



γ-lumicolchicine

Bussotti, L.; Cacelli, I.; D'Auria, M.; Foggi, P.; Lesma, G.; Silvani, A.; Villani, V. *J. Phys. Chem. A.* **2003**, *107*, 9079

According to the main paper 2, α-lumicolchicine was NOT obtained in the step 3.

Although the authors does not mention, **α-lumicolchicine was thought to be a major product when the reaction time was extended.**

Discussion 5: The reason why β-lumicolchicine should be purified

The conditions of the two reactions are completely the same (including concentration and solvent, temperature).

The opinion of the authors:

- Probably, other unidentified compounds made the reaction more complex, with the time extend and the temperature of the solution increased.

→ γ-lumicolchicine??

My proposal:

Irradiation of colchicine utilized sunlight in H_2O solution for 2 months to **give α,β,γ-lumicolchicines together.**

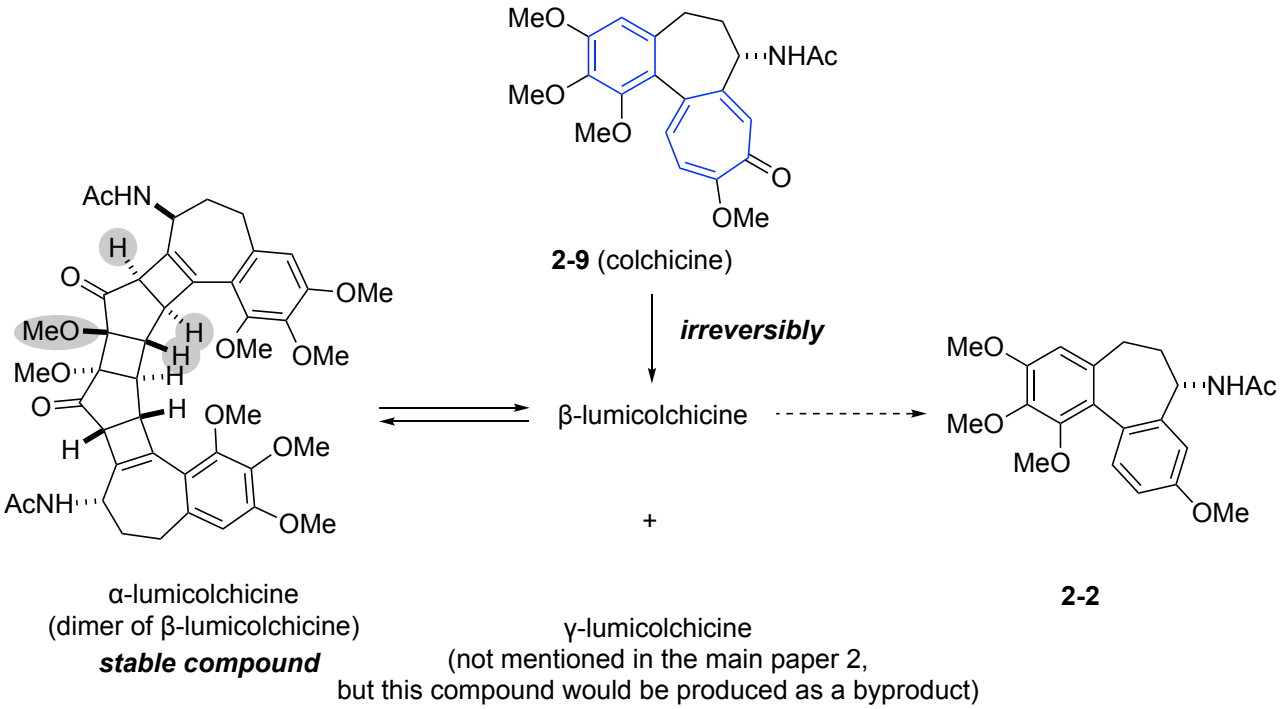
Grewe, R.; Wulf, W. *Chem. Ber.* **1951**, *84*, 621

→The three types of lumicolchicines are irreversibly generated from colchicine, so once the intramolecular cyclization reaction occurs, colchicine cannot be generated again.

α-Lumicolchicine is quantitatibely converted to β-Lumicolchicine on heating to the melting point or heating above 100 ºC in solution.

Chapman, O.L.; Smith, H. G. *J. Am. Chem. Soc.* **1961**, *83*, 3914

→β-lumicolchicines and α-lumicolchicines (dimer of β-lumicolchicine) would be formed by a reversible cyclization reaction and are in equilibrium in the solution. In addition, α-lumicolchicines would be relatively stable.



Colchicine has two aromatic rings and a long conjugation system. This suggests that colchicine would be a compound with strong intermolecular interactions to some extent.

It is thought that β-lumicolchicines formed a relatively stable dimer, α-lumicolchicine, before the decarbonylation. This would cause the result that a trace amount of the desired compound **2-2** was obtained when the reaction time was extended.

It is thought that β-lumicolchicines would not have such strong intermolecular interactions as colchicines. In my opinion, the purification is expected to reduce the rate of dimerization and cause aromatic cyclization by decarbonylation.