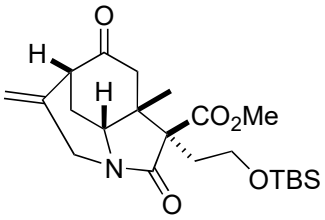
Problem Session (3)

2023/05/20 Hisahiro Morozumi

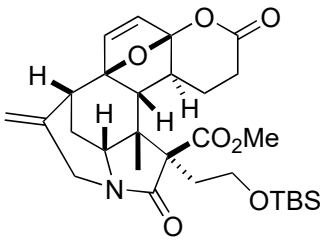
Please provide the reaction mechanism and stereoselectivity.

(1)



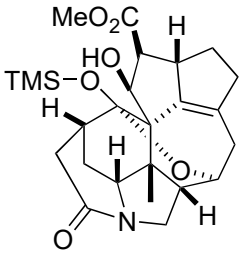
1-1

1. $KN(TMS)_2$ (1.2 eq), $PhNTf_2$ (1.1 eq)
   THF, −78 °C
2. **1-2** (1.2 eq), $Pd(PPh_3)_4$ (0.098 eq)
   K_2CO_3 (3.0 eq), 1,2-dimethoxyethane
   60 °C, 73% (2 steps)
3. hv (Hg lamp, 500W), benzene, air
   0 °C, 71%



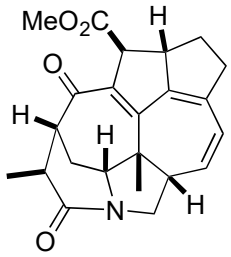
1-3

(2)

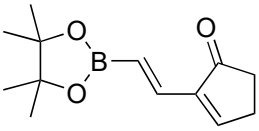


2-1

1. NaH (4.0 eq), CS_2 (6.0 eq), THF, 0 °C;
   MeI (8.0 eq), 25 °C
2. $LiN(TMS)_2$ (4.5 eq), THF, −78 °C;
   MeI (4.5 eq), 25 °C, 90% (2 steps)
3. *o*-dichlorobenzene, 180 °C;
   1 M aq. HCl (1.2 eq), MeOH, 25 °C, 88%
4. NaH (3.5 eq), CS_2 (5.0 eq), THF, 0 °C;
   MeI (7.0 eq), 45 °C
5. *o*-dichlorobenzene, 180 °C, 77% (2 steps)



2-2



1-2

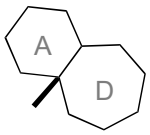
Problem Session (3) Answer

2023/05/20 Hisahiro Morozumi

Topic: Total synthesis of Alkaloids

0. Introduction

0-1. Daphniphyllum alkaloids[1)]

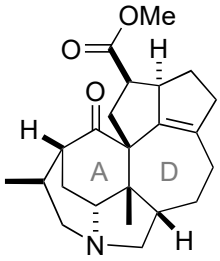


core structure of Daphniphyllum alkaloids

- More than 300 compounds are isolated.
- Classified into more than 13 subfamilies.

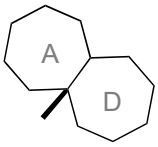
Total synthesis

- daphmanidin A-type (Carreira, Smith)
- yuzurimine-type (Xu)
- calyciphylline A-type (**A. Li (problem 1)**, Fukuyama, Dixon, Zhi, Qiu, Xu, Gao, Lu)



Calyciphylline A skeleton

0-2. Daphnicyclidin alkaloids[1)]



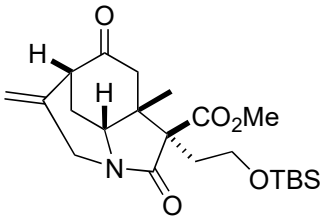
core structure of Daphnicyclidin alkaloids

- About 20 compounds are isolated.

Total synthesis

- Daphnicyclidin A,D,F,K (A. Li)
- Daphnicyclidin B (**Li, C.-C. (problem 2)**)

(1)



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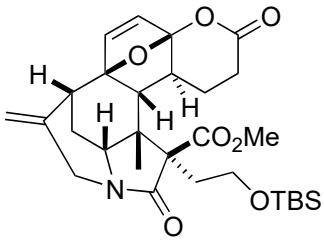
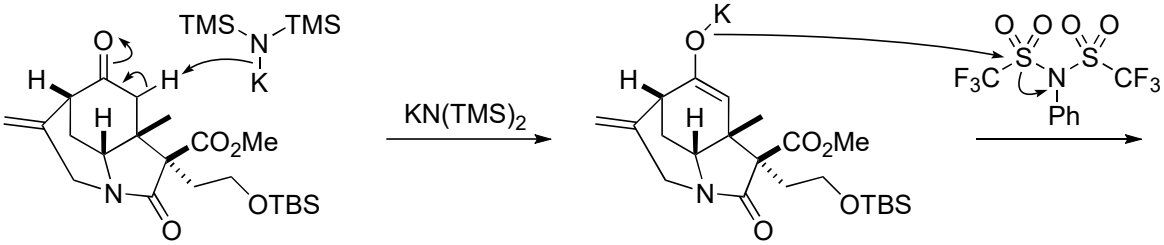


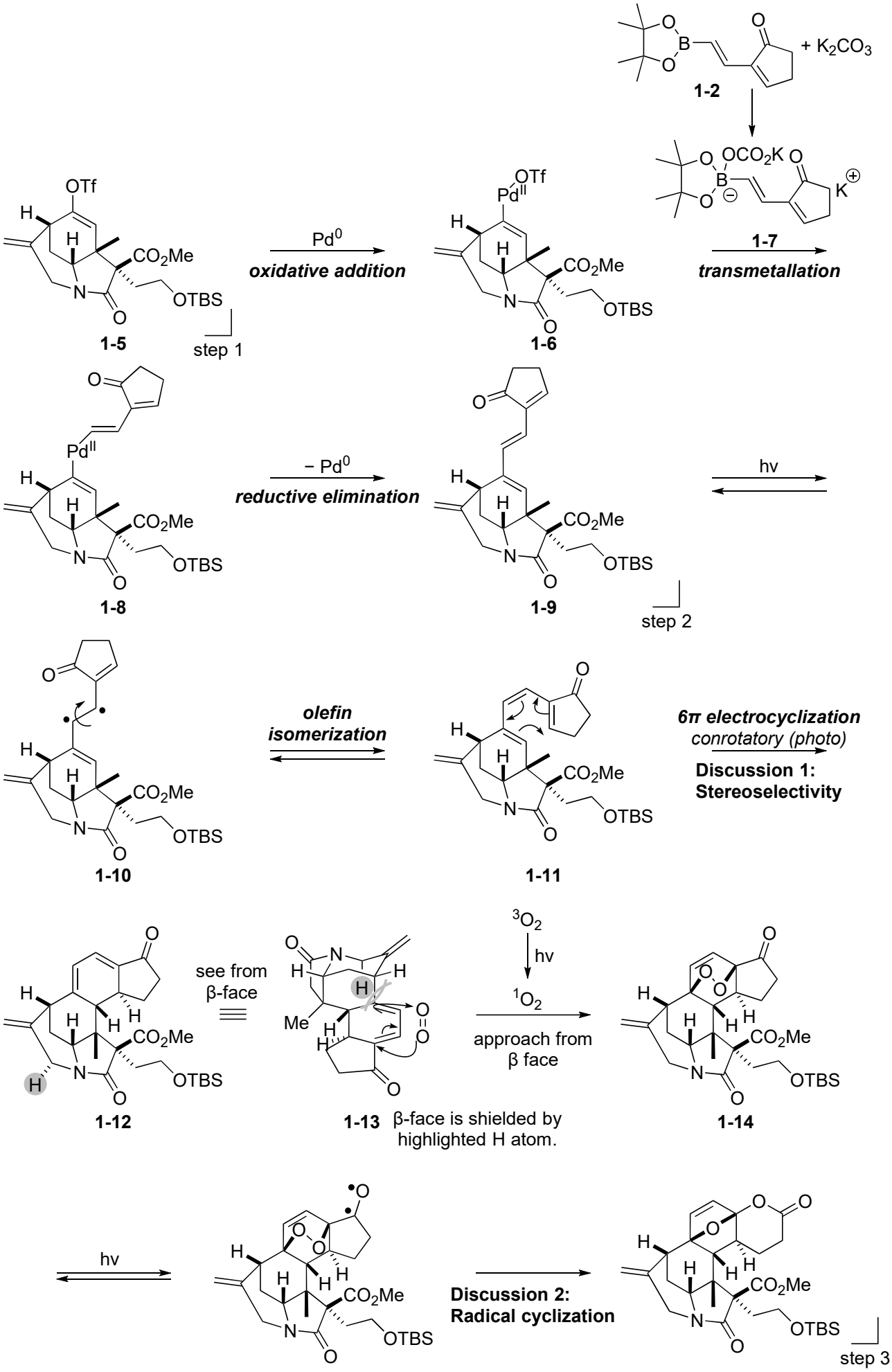
1-3

Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679-684[1)].

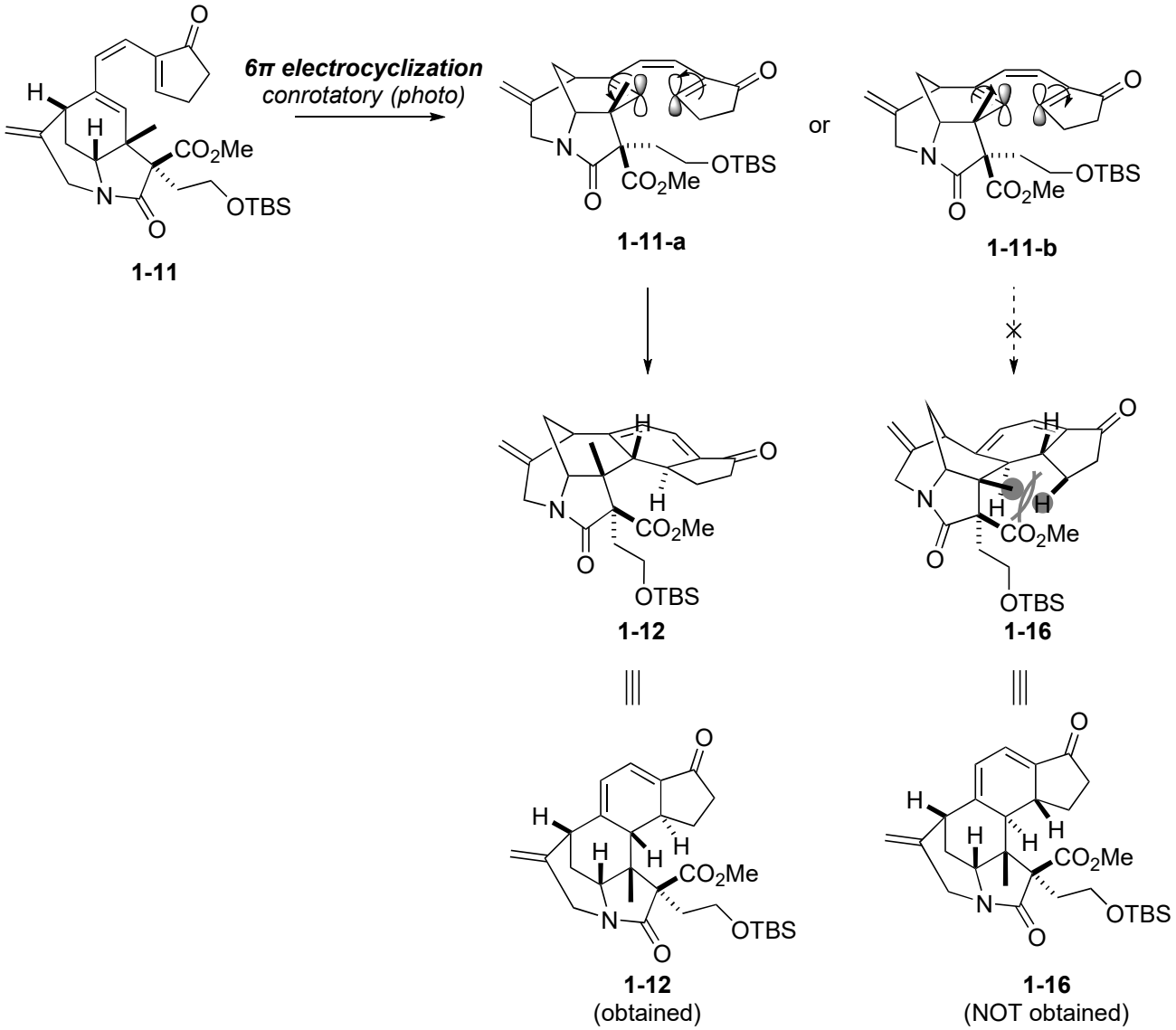
1-1: Reaction mechanism



1-1 **1-4**


+ K2CO3
1-2
1-7
Pd0
oxidative addition
transmetallation
1-5
1-6
step 1
− Pd0
reductive elimination
hv
1-8
1-9
step 2
olefin isomerization
6π electrocyclization
conrotatory (photo)
Discussion 1: Stereoselectivity
1-10
1-11
see from β-face
3O2
hv
1O2
approach from β face
1-12
1-13
β-face is shielded by highlighted H atom.
1-14
hv
1-15
Discussion 2: Radical cyclization
1-3
step 3

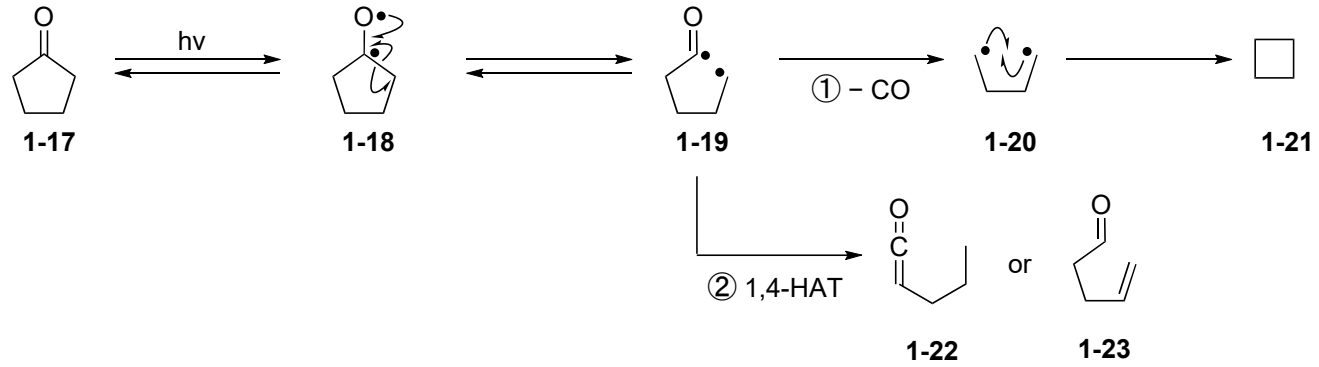
1-2: **Discussion 1**: Stereoselectivity of 6π electrocyclization



1-3. **Discussion 2**: Reaction mechanism of radical cyclization

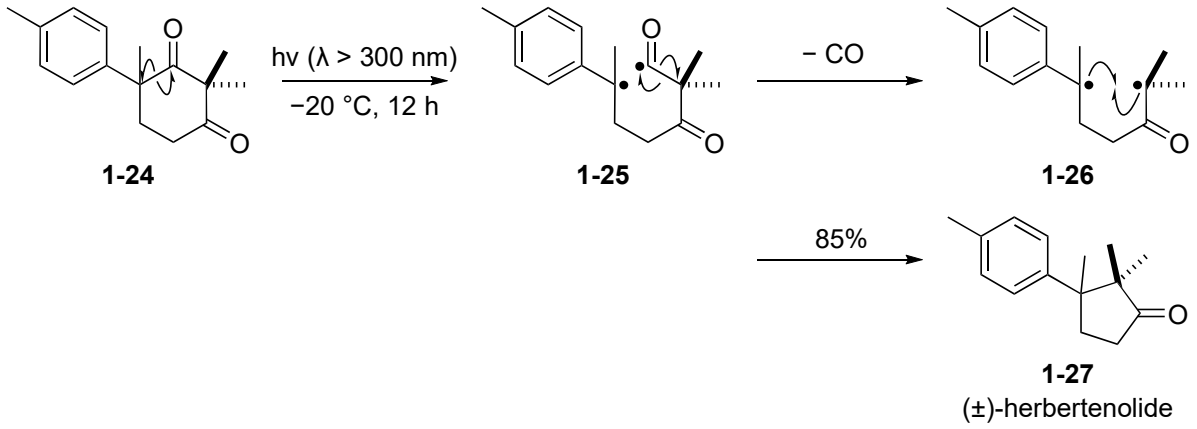
1-3-1. Proposed mechanism (by authors): a pathway involved Norrish type I fragmentation

<Norrish type I reaction>

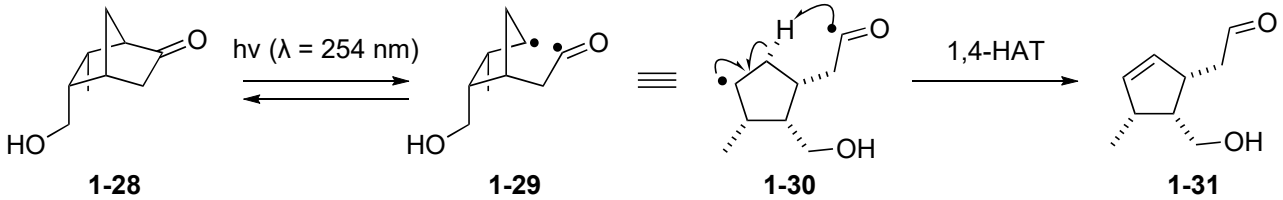


<Application of this reaction>

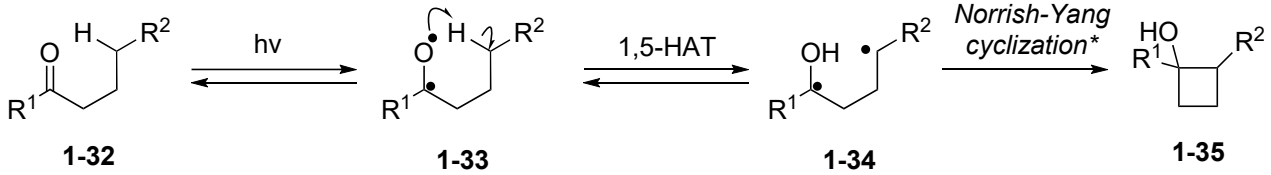
① − CO[2)]



② 1,4-HAT [3)]

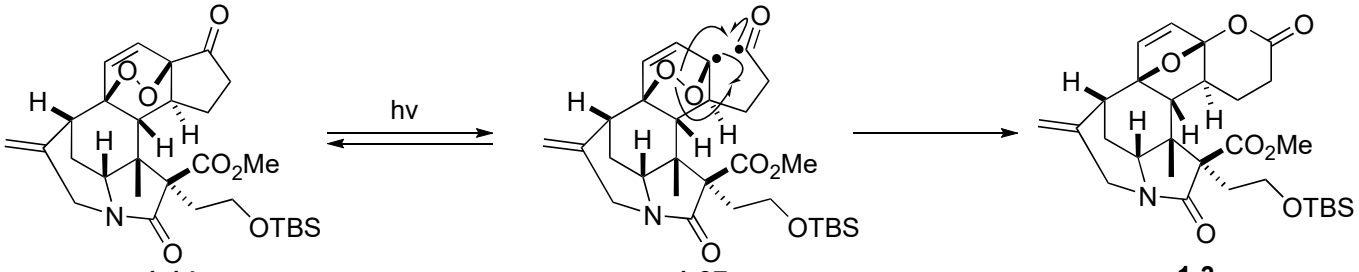


<Norrish type II reaction>



*For details, see: 220507_PS_Yuya_Shiga

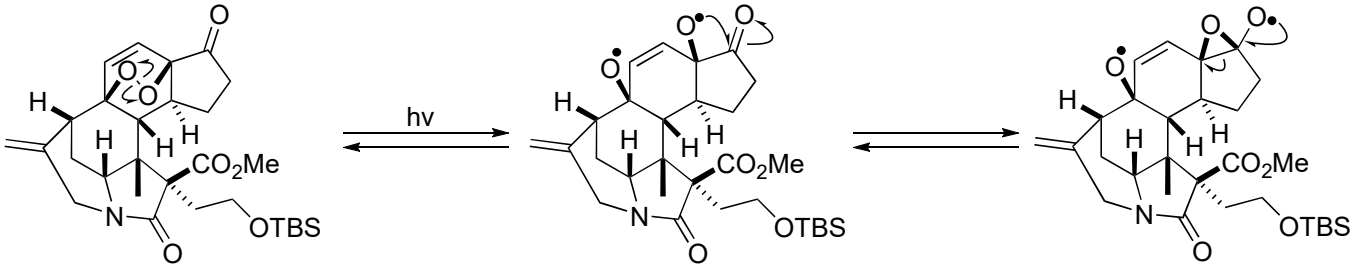
<proposed mechanism (by authors)>

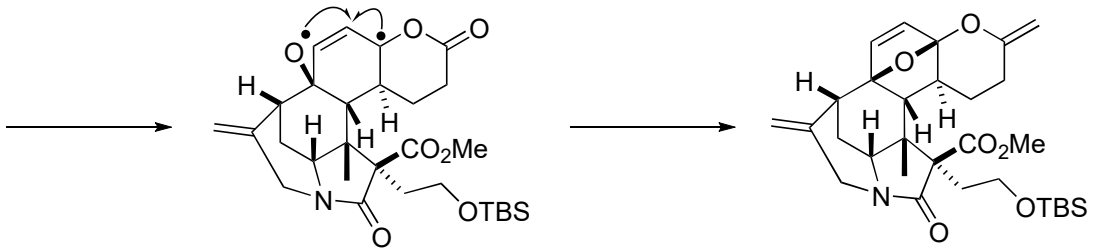


bridgehead radical
(no stablilization of olefin conjugation)

O-O bond is more easily cleaved?

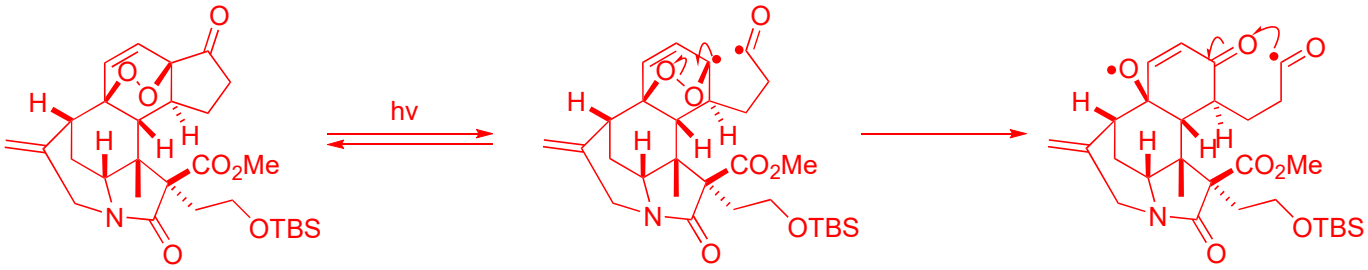
1-3-2. Proposed mechanism (my proposal): a pathway involved Dowd-Bechwith type rearrangement

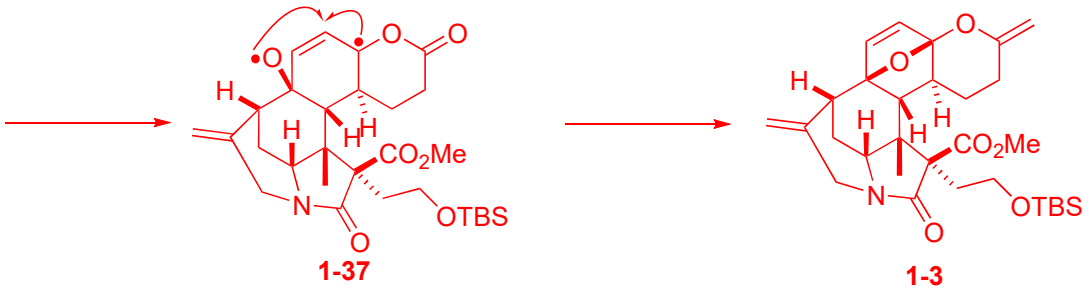




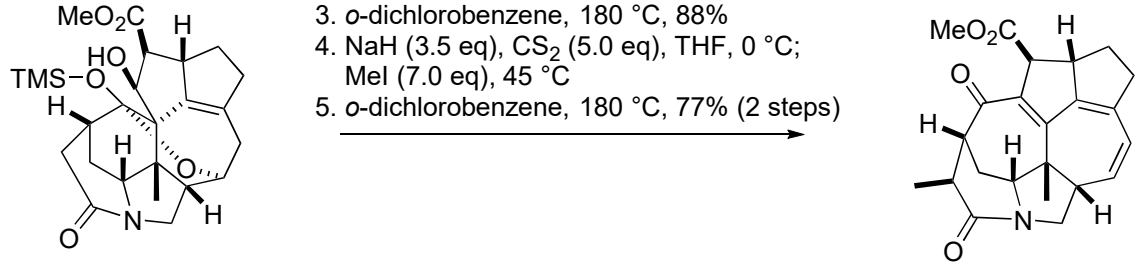
tertiary allylic radical
(more stable)

1-3-3. Another proposed mechanism: a pathway involved 6-endo radical cyclization



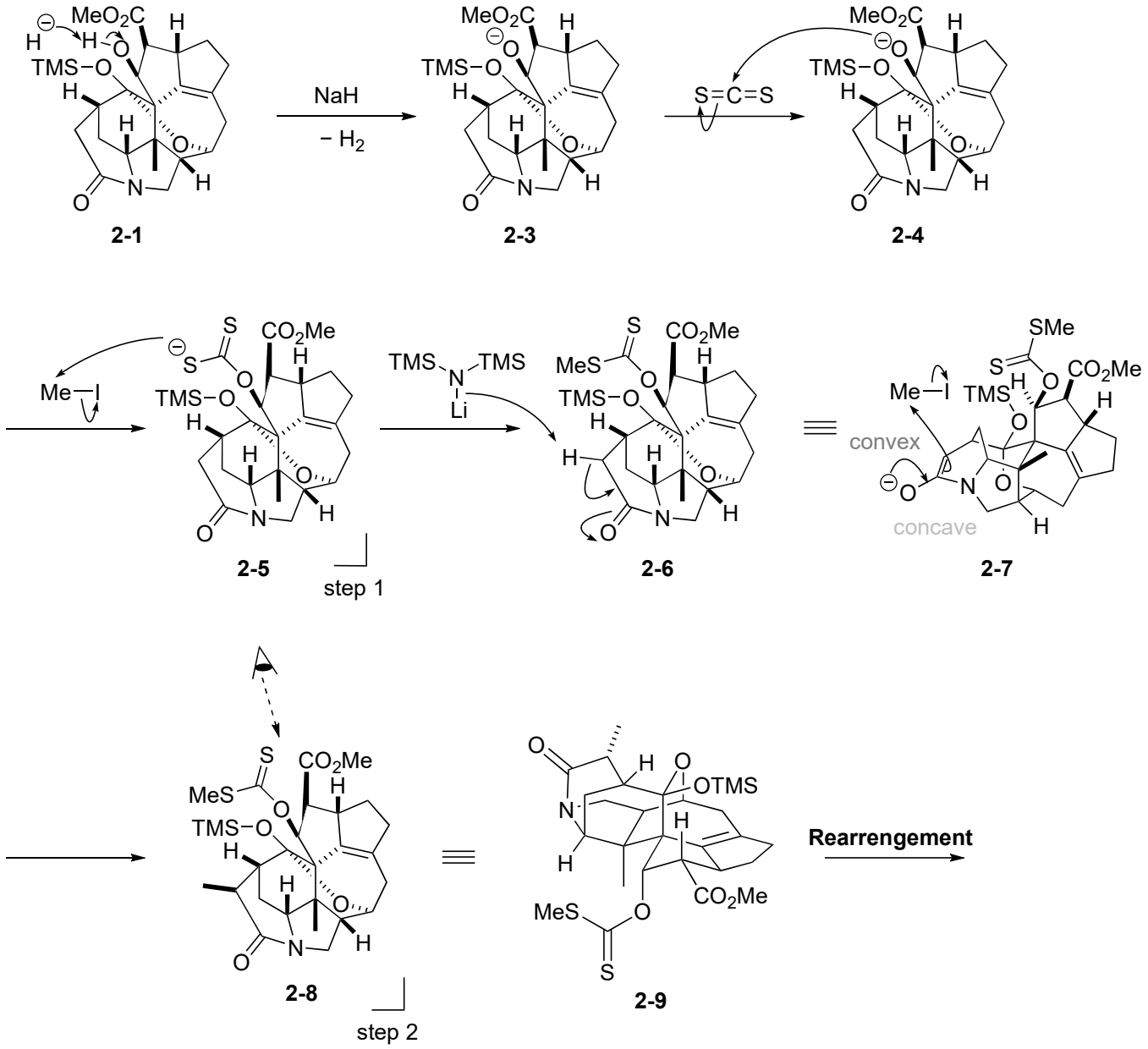


(2)

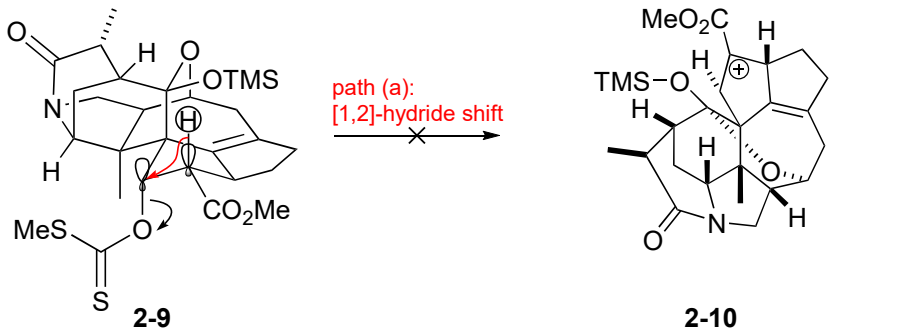


Zou, Y.-P.; Lai, Z.-L.; Zhang, M.-W.; Peng, J.; Ning, S.; Li, C.-C. *J. Am. Chem. Soc.* **2023**, *145*, 10998[4)].

2-1: Reaction mechanism



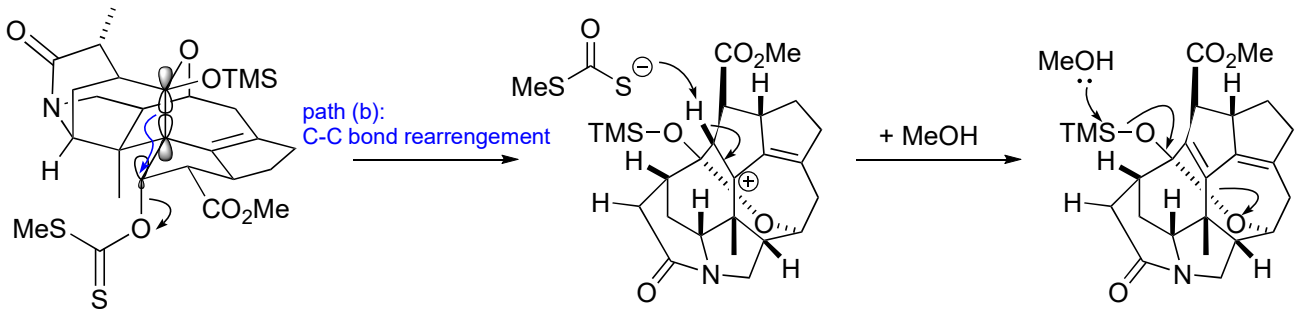
rearrengement path (a) from **2-9**



2-9 **2-10**

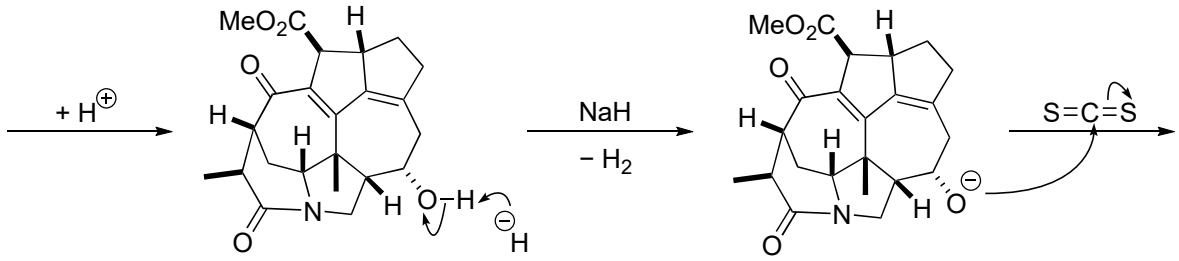
carbocation next to EWG group
(unstable)

rearrengement path (b) from **2-9**



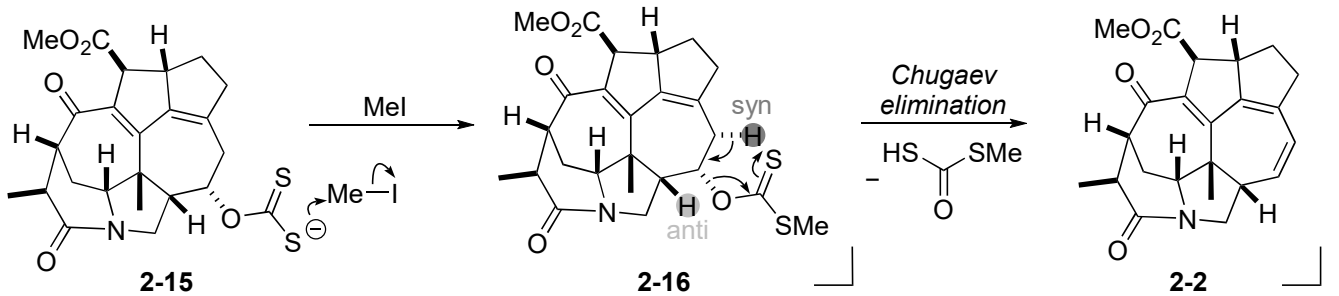
2-9 **2-11** **2-12**

tertiary allylic carbocation
(more stable)



2-13 **2-14**

step 3



2-15 **2-16** **2-2**

step 4 step 5

Reference

1) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679-684.
2) Natarajan, A.; Ng, D.; Yang, Z, Garcia-Garibay, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6485-6487.
3) Callent, P.; Storme, P.; Van der Ecyken, E.; Vandewalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797-5800.
4) Zou, Y.-P.; Lai, Z.-L.; Zhang, M.-W.; Peng, J.; Ning, S.; Li, C.-C. *J. Am. Chem. Soc.* **2023**, *145*, 10998.