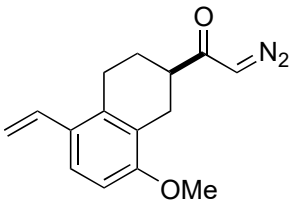
Problem Session (3)

2023.4.22 Yuya Shiga

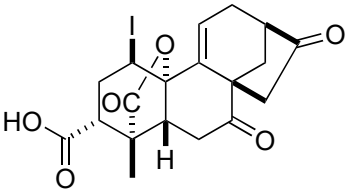
Please provide the reaction mechanism and stereoselectivity.

1

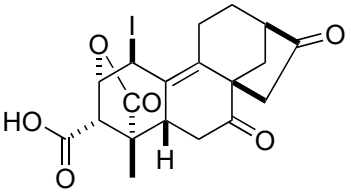


1-1

1. $Cu(acac)_2$ (3.0 mol%), $ClCH_2CH_2Cl$, reflux;
   1-4 (3.0 eq), 22 °C, 75%
2. pyridine•HBr (3.0 eq), DMF, reflux
3. 1 M KOH (3.7 eq), THF, 22 °C;
   6 M HCl (5.0 eq), 0 °C;
   NIS (1.7 eq), 22 °C,
   1-2 : 54% (2 steps), **1-3** : 13% (2 steps)

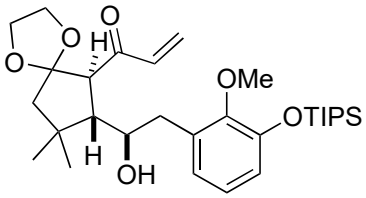


1-2



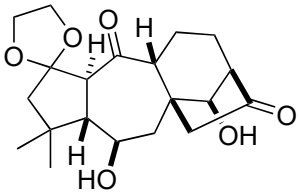
1-3

2



2-1

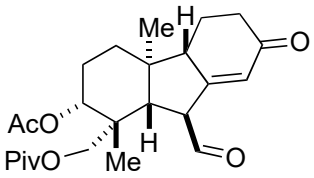
1. *n*-Bu_4NF (1.1 eq), THF, 0 °C;
   $PhI(OAc)_2$ (1.5 eq), THF/MeOH (1/10), 65 °C, 70%
2. SmI_2 (3.0 eq)*, THF/MeOH (10/1)
   25 °C, 90%
3. DMDO (4.0 eq), CH_2Cl_2, 25 °C, 92%
4. Cp_2TiCl_2 (10 mol%), Mn (9.0 eq), 2,4,6-collidine•HCl (6.0 eq), $ClCH_2CH_2Cl$, 50 °C, 61%



2-2

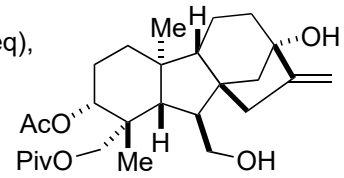
*It is likely that 4 equivalents of SmI_2 are necessary for this step

3

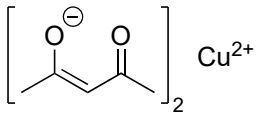


3-1

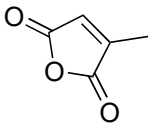
1. Mg (932 eq), **3-3** (620 eq), hv, THF, −100 °C;
   $NaBH_4$ (1 eq), CH_2Cl_2/EtOH (3/1), −78 °C,
   65%, dr = 4 : 1
2. SmI_2 (10 eq), *n*-Bu_4NBr (20 eq), HMPA (40 eq),
   THF, reflux, 70 %



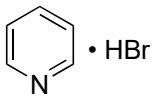
3-2



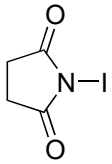
$Cu(acac)_2$



1-4

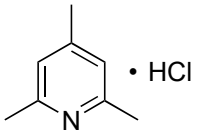


pyridine•HBr

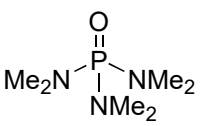


NIS

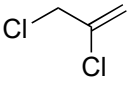
DMDO



2,4,6-collidine•HCl



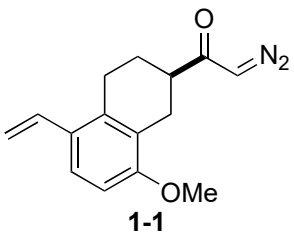
HMPA



3-3

topic: Construction of bicyclo [3.2.1] octane skeleton

1



1-1

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   1-4 (3.0 eq), 22 °C, 75%
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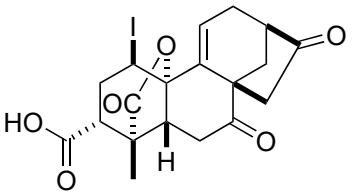
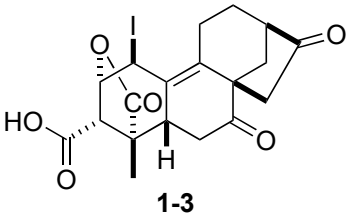
3. 1 M KOH (3.7 eq), THF, 22 °C;
   6 M HCl (5.0 eq), 0 °C;
   NIS (1.7 eq), 22 °C,
   1-2 : 54% (2 steps), **1-3** : 13% (2 steps)



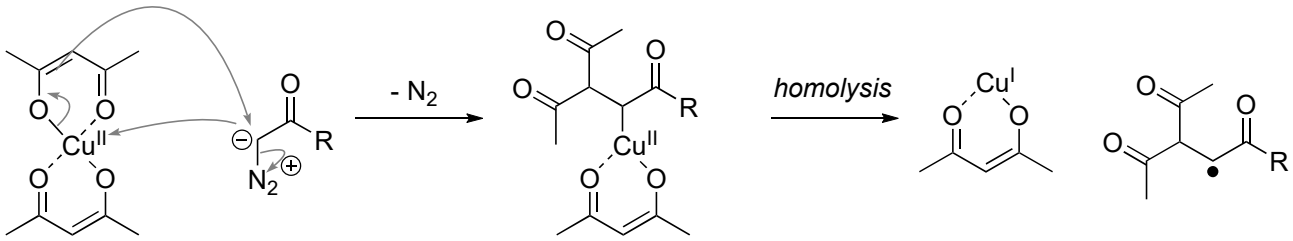
1-2



1-3

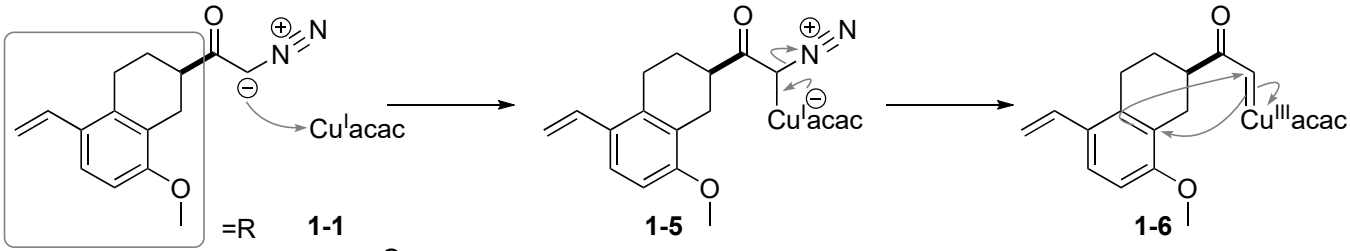
King, R. G.; Mander, N. L.; Monck, J. T.; Morris, J. C.; Zhang, H. *J. Am. Chem. Soc.* **1997**, *119*, 3828.

1-1. reaction mechanism

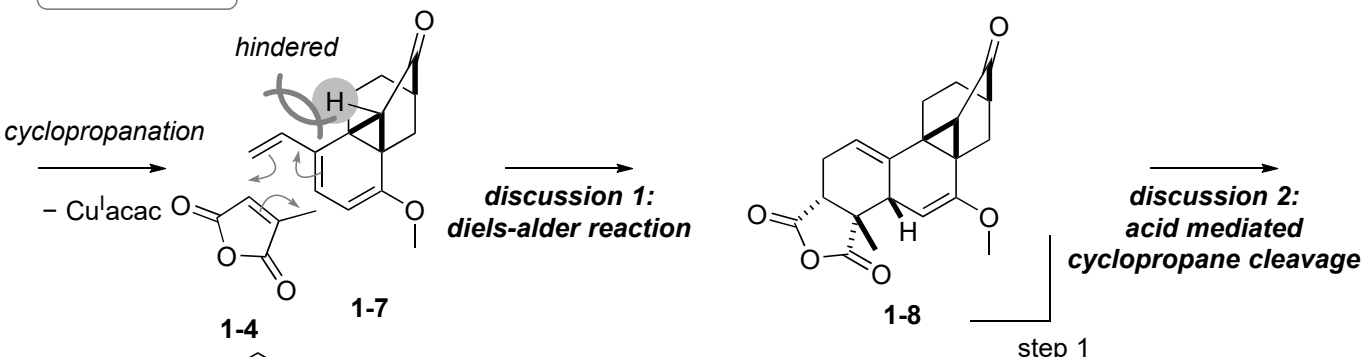


$Cu^{II}(acac)_2$ **1-1** **1-0** $Cu^{I}acac$

Shirafumi, T.; Yamamoto, Y.; Nozaki, H. *Tetrahedron,* **1971**, *27*, 5353.
Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.



=R **1-1** **1-5** **1-6**

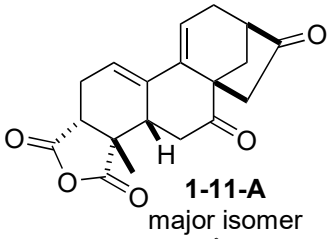


1-4 **1-7** **1-8**

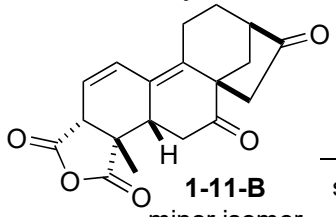
discussion 1: diels-alder reaction

discussion 2: acid mediated cyclopropane cleavage

step 1

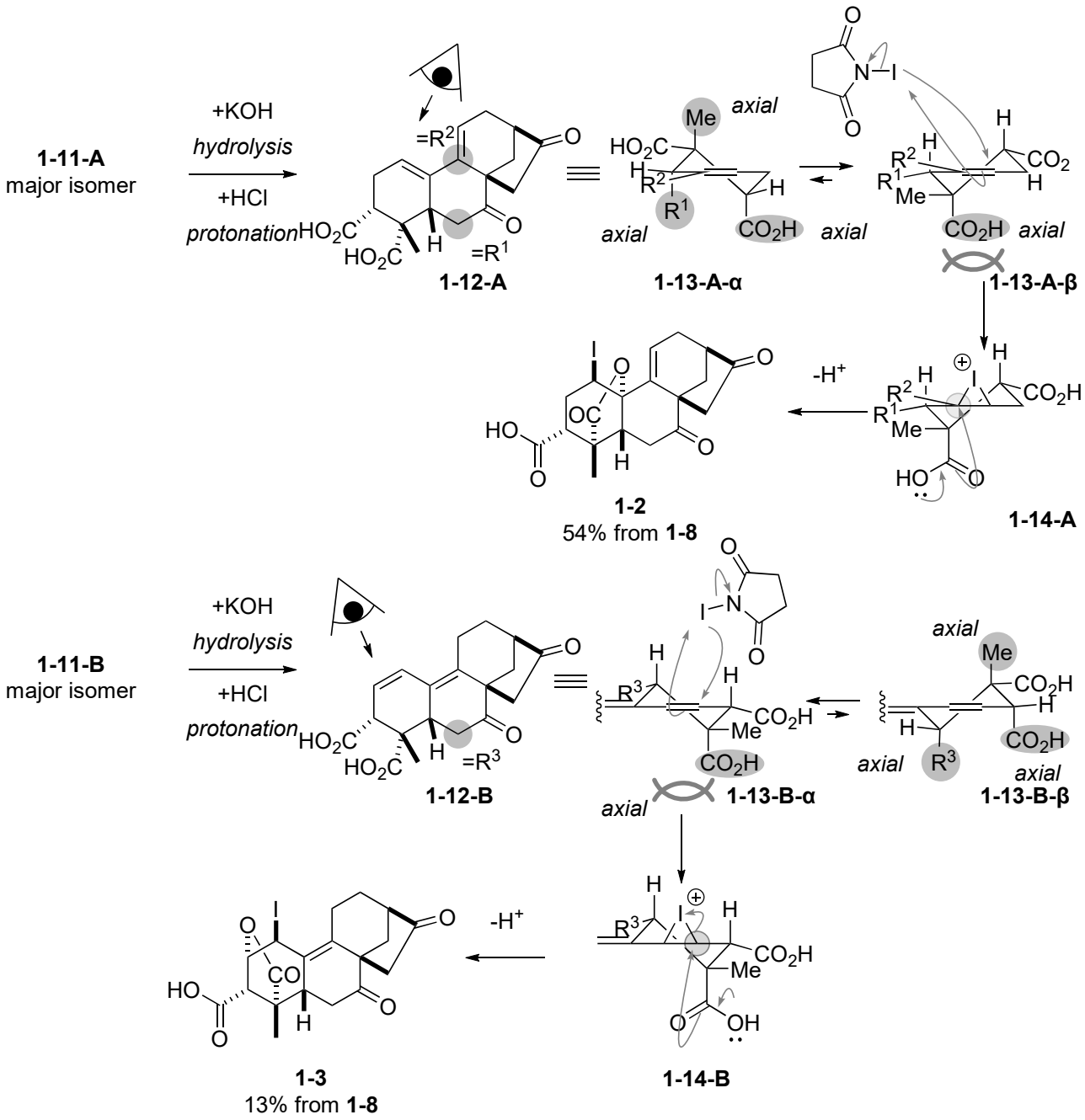


1-11-A
major isomer



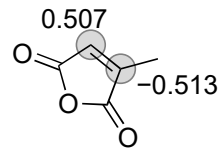
1-11-B
minor isomer

step 2

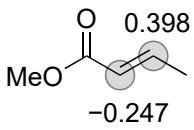


1-2. **discussion 1: Diels-Alder reaction**

calculated LUMO coefficients of dienophile



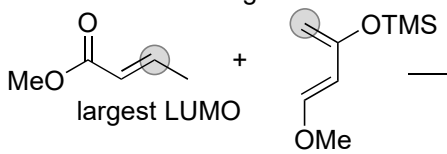
1-4



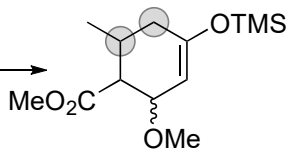
1-15

calc. level B3LYP/6-31G(d)

largest HOMO



1-15 **1-16**



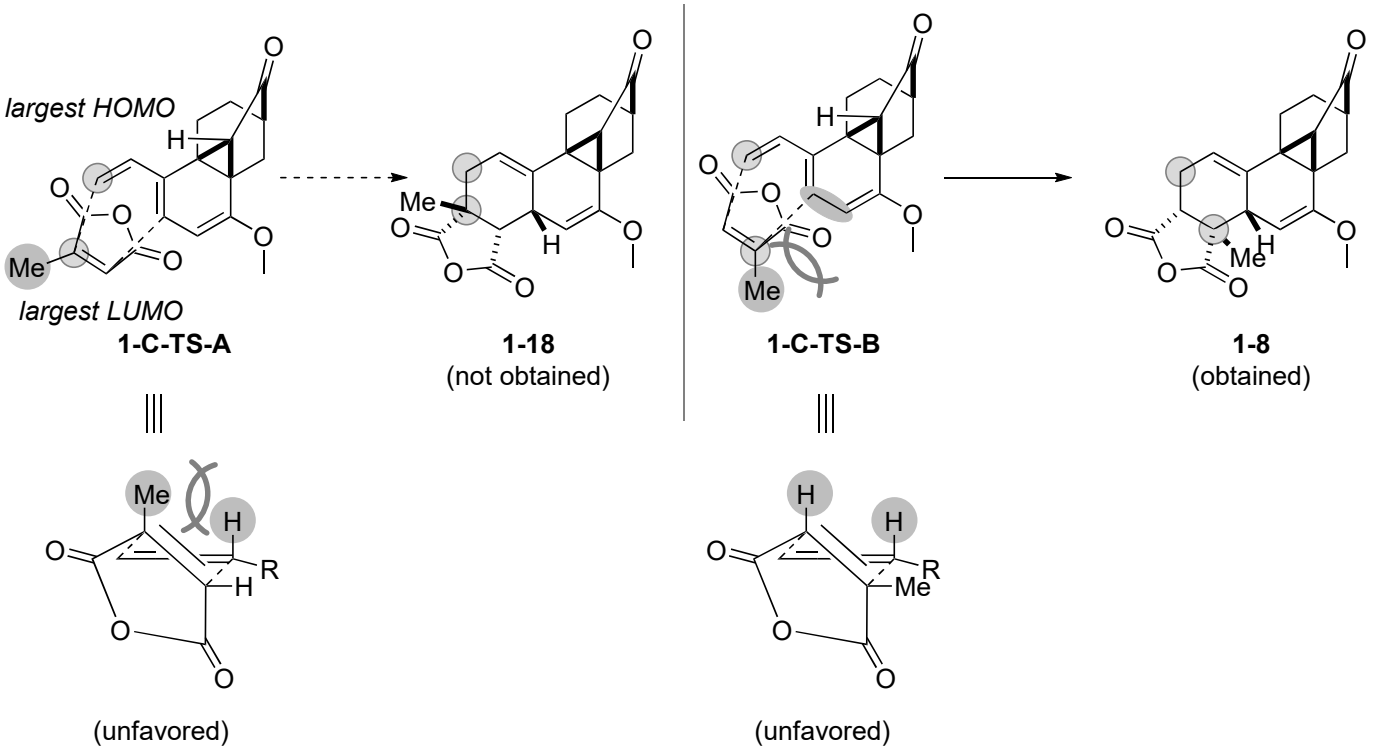
1-17

regioselectively obtained

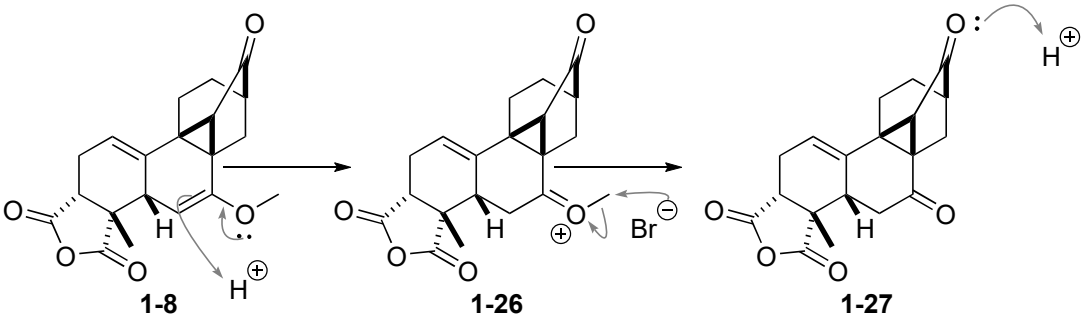
→In case of **1-4**, the difference of LUMO coefficients is small, so the other factors should also be considered.

Wel, H. V. D.; Nibbering, N. M. M.; Kayser, M. M. *Can. J. Chem.* **1988**, *66*, 2587.
Marakchi, K.; Ghailane, R.; Kabbaj, O. K.; Komiha, N. *J. Chem. Sci.* **2014**, *126*, 283.
Inokuchi, T.; Okano, M.; Miyamoto, T.; Madon, H. B.; Takagi, M. *Synlett,* **2000**, *11*, 1549.

・concerted pathway

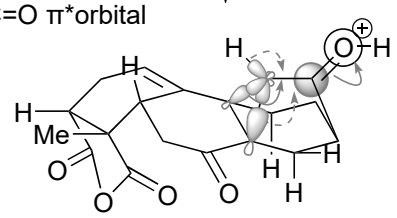


1-3. ***discussion 2: acid mediated cyclopropane cleavage***



1-8 **1-26** **1-27**

C-H σ orbital→poor orbital overlap with C=O π*orbital



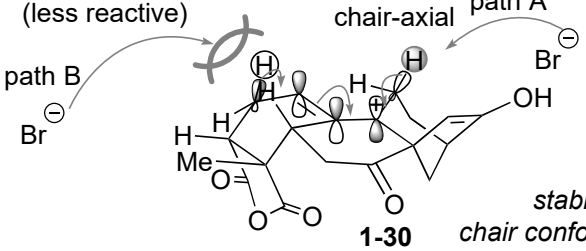
1-28

boat-axial
(less reactive)

path B

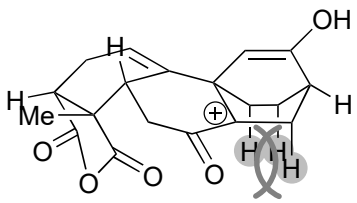
chair-axial

path A



1-30

stable
chair conformation

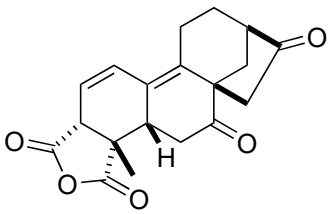


1-29

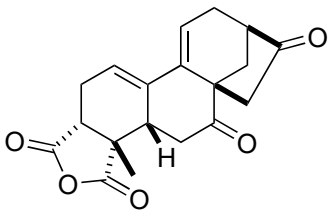
unstable
boat conformation
and
α carbonyl cation

path B

path A



1-9-B
minor isomer



1-9-A
minor isomer

2

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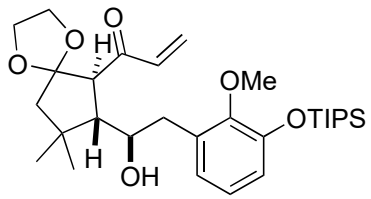
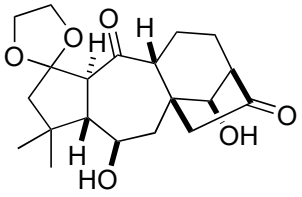
2. SmI_2 (3.0 eq), THF/MeOH (10/1) 25 °C, 90%
3. DMDO (4.0 eq), CH_2Cl_2, 25 °C, 92%
4. Cp_2TiCl_2 (10 mol%), Mn (9.0 eq), 2,4,6-collidine•HCl (6.0 eq), $ClCH_2CH_2Cl$, 50 °C, 61%



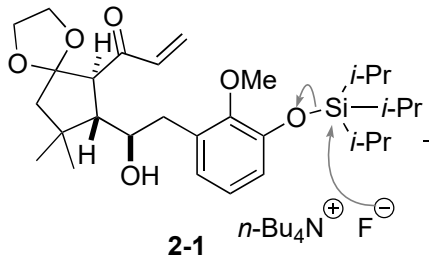
2-1



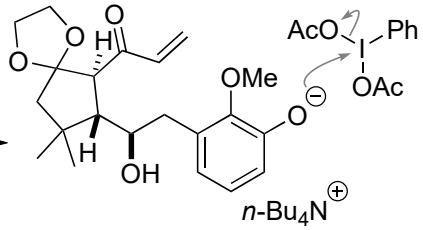
2-2

Yu, K.; Yang, Z.; Liu, C.; Wu, S.; Hong, X.; Zhao, X.; Ding, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 8556.

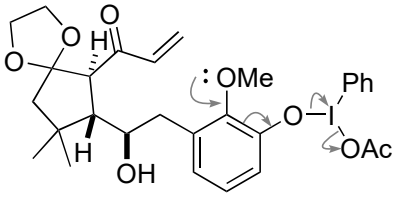
2-1. reaction mechanism



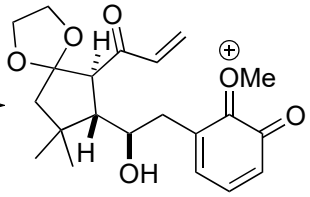
2-1



2-3

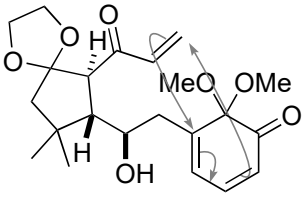


2-4



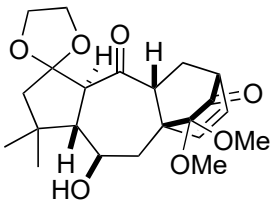
2-5

+MeOH



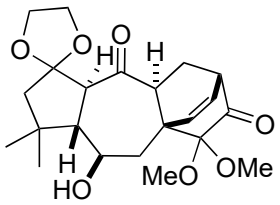
2-6

discussion 3:
Diels-alder reaction



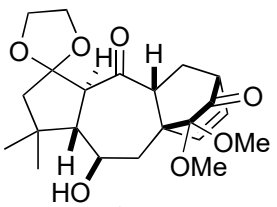
2-7
70%

+



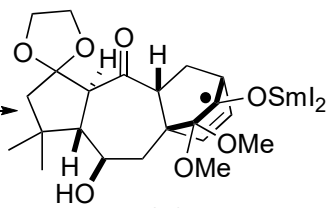
2-8
25%

step 1



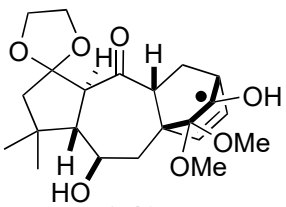
2-7

SmI_2
SET



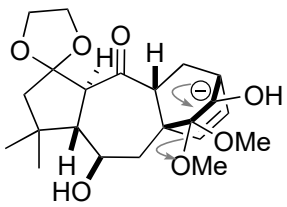
2-9

MeOH

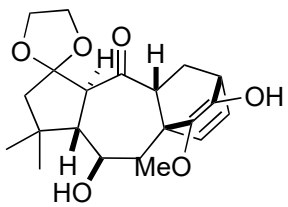


2-10

SmI_2
SET

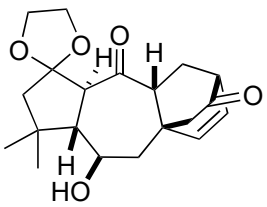


2-11



2-12

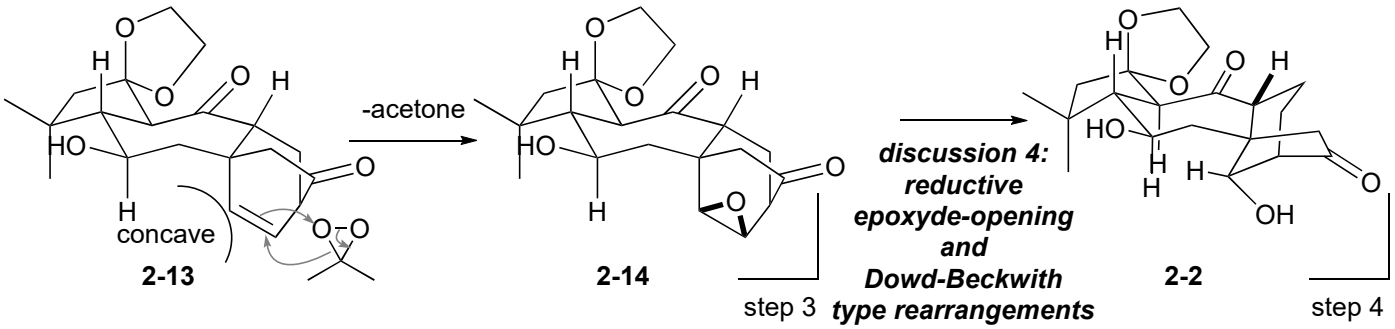
2×SmI_2



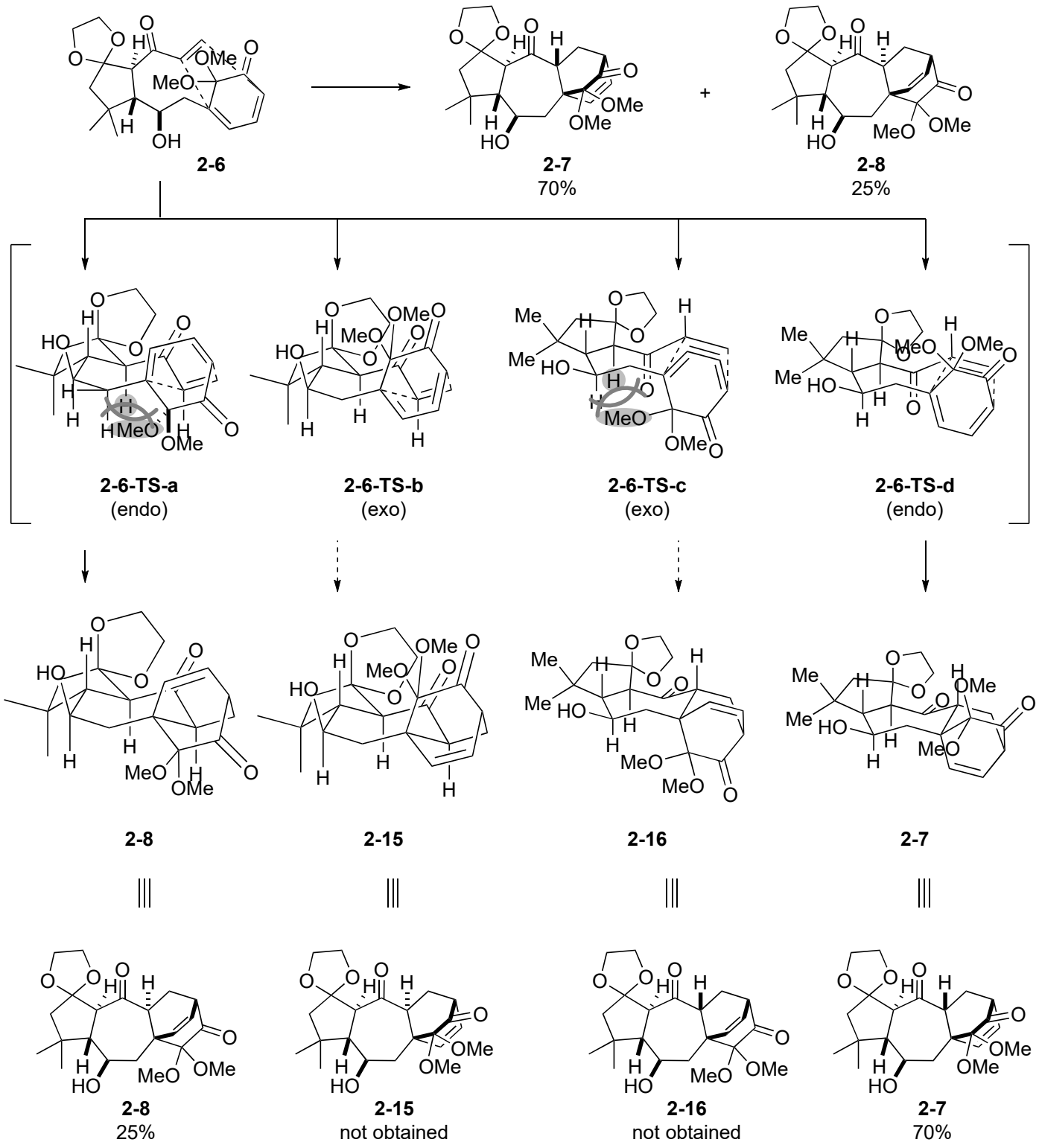
2-13

A total of 4 equivalents of SmI_2 is necessary....

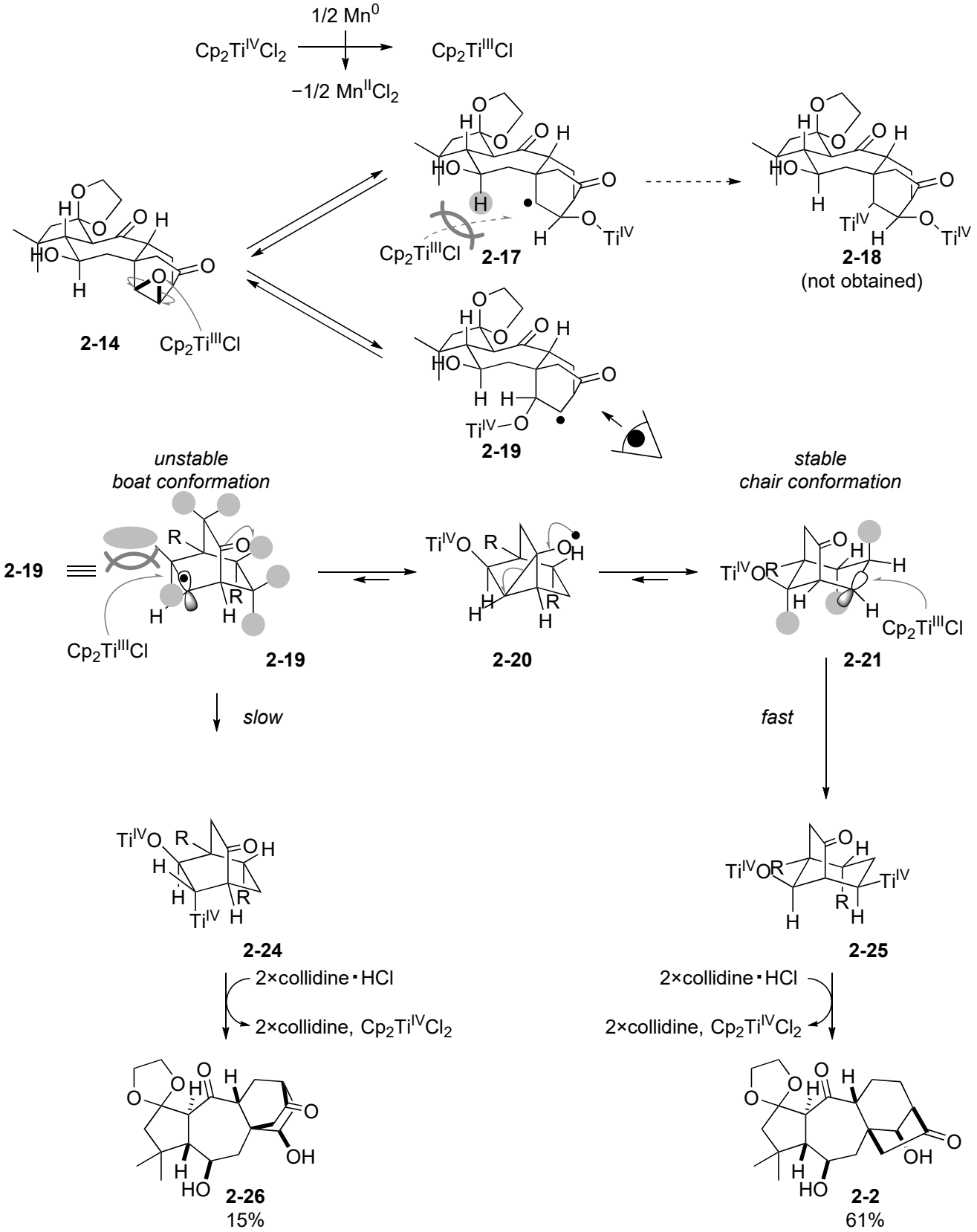
step 2



2-2. ***discussion 3: Diels-alder reaction***

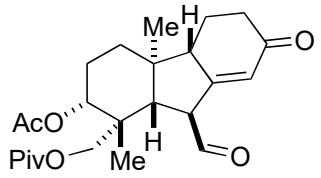


2-3. ***discussion 4:reductive epoxyde-opening and Dowd-Beckwith type rearrangements***



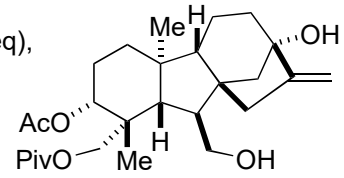
In the ring rearrangement, the stable bicyclo [3.2.1]octane skeleton is thermodynamically favored and the one-electron reduction from **2-21** is the fastest, **2-2** is obtained as the major compound.

3



3-1

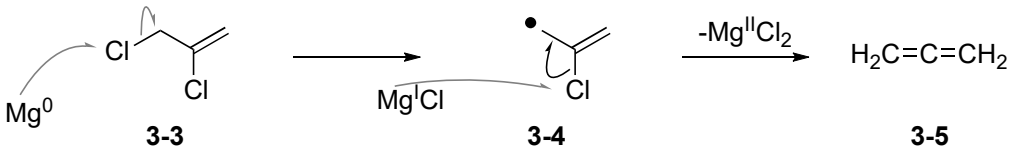
1. Mg (932 eq), **3-3** (620 eq), hv, THF, −100 °C;
   $NaBH_4$ (1 eq), CH_2Cl_2/EtOH (3/1), −78 °C,
   65%, dr = 4 : 1
2. SmI_2 (10 eq), *n*-Bu_4NBr (20 eq), HMPA (40 eq),
   THF, reflux, 70 %



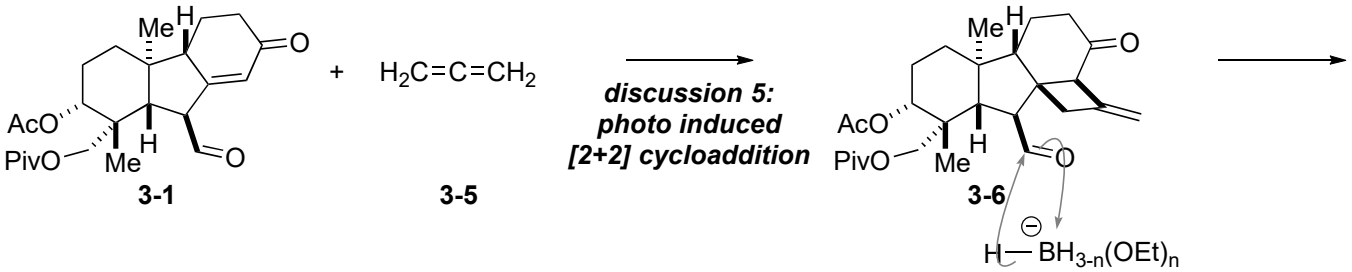
3-2

Li, L.; Liang, W.; Rivera, M.; Wang, Y. Dai, M. *J. Am. Chem. Soc.* **2023**, *145*, 53.

3-1. reaction mechanism



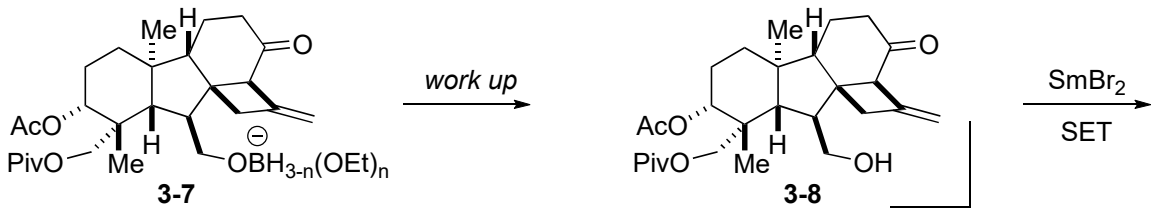
3-3 **3-4** **3-5**



3-1 **3-5** **3-6**

discussion 5: photo induced [2+2] cycloaddition

SmI_2 + 2 *n*-Bu_4NBr ⟶ $SmBr_2$ + 2 *n*-Bu_4NI

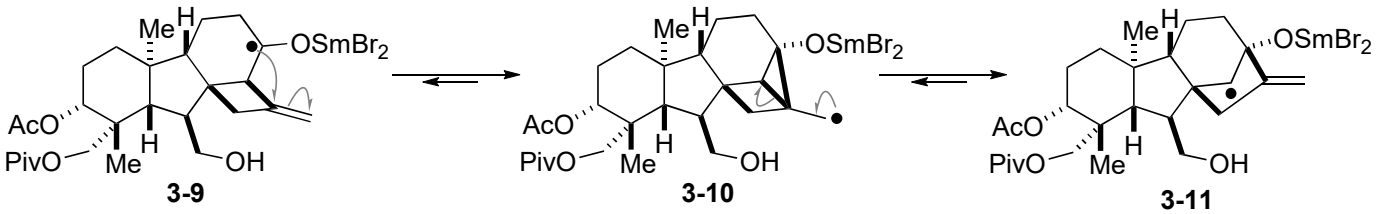


3-7 **3-8**

work up

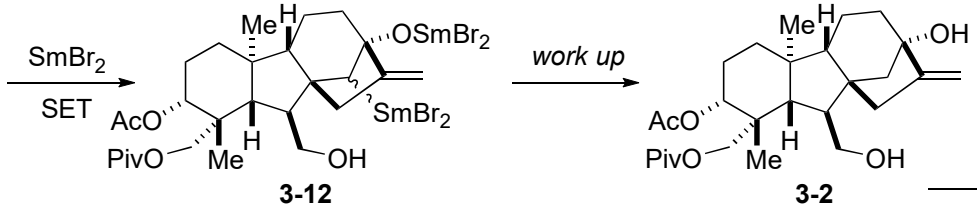
$SmBr_2$, SET

step 1



3-9 **3-10** **3-11**

The strain release of four-membered ring and the formation of stable bicyclo [3.2.1] octane skeleton are driving forces.



3-12 **3-2**

$SmBr_2$, SET

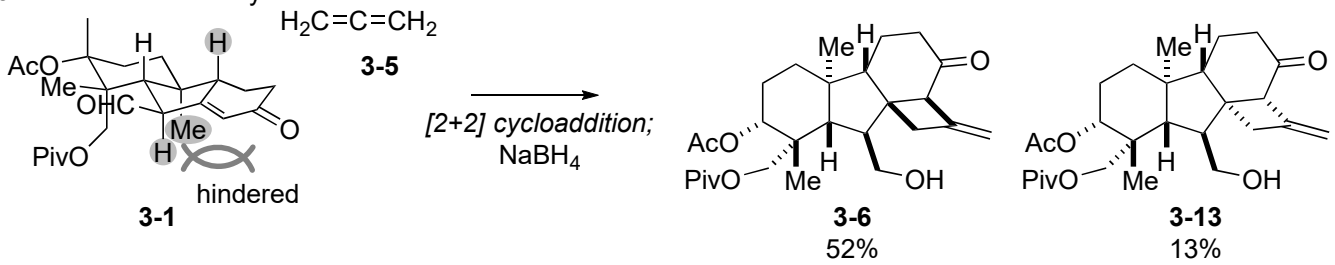
work up

step 2

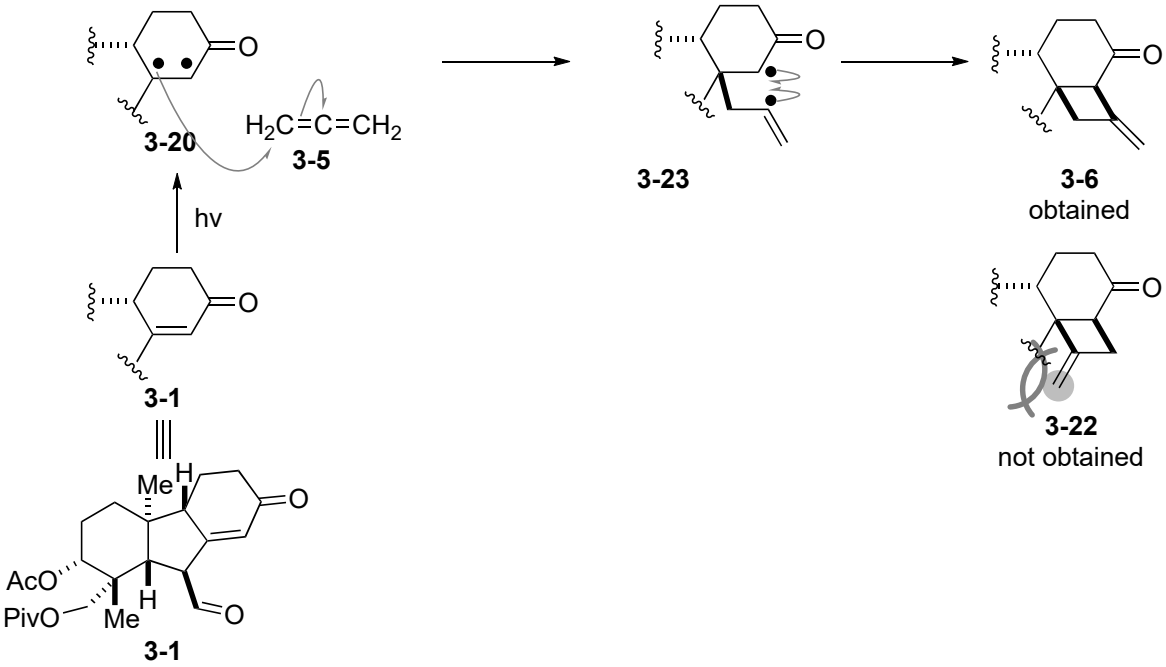
c.f. appendix 1, 2: The reaction mechanism study for SET promoted skeleton rearrangement

3-2. ***discussion 5:photo induced [2+2] cycloaddition***

3-2-1. stereoselectivity

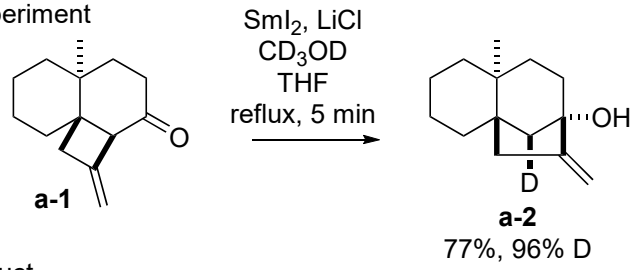


3-2-2. regioselectivity



appendix

1. Deuteration experiment



2. Isorated byproduct