Problem Session (2) -Answer-

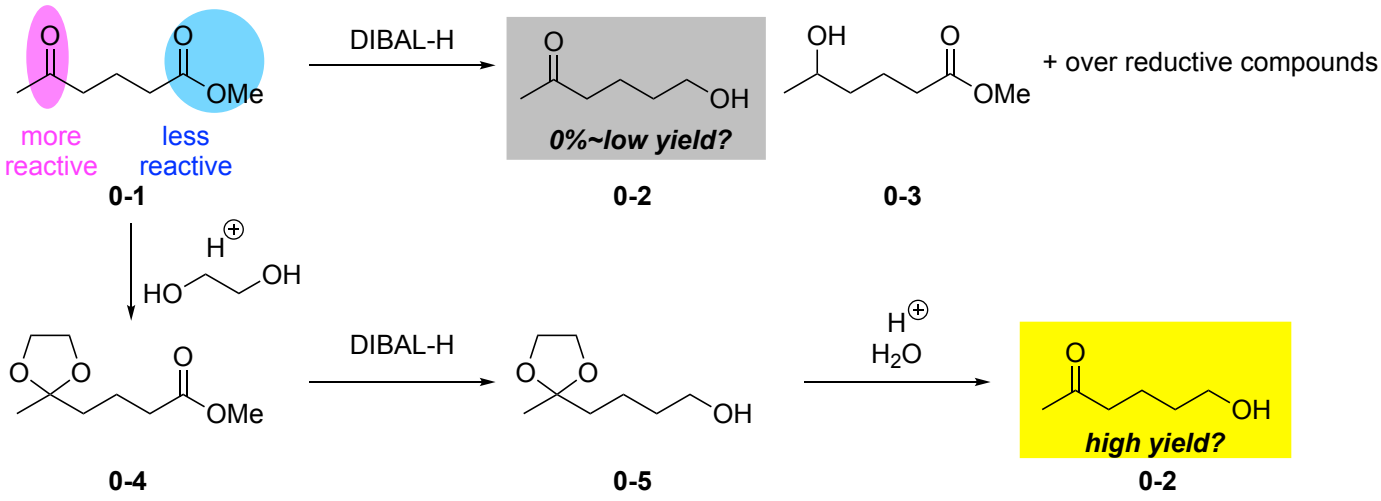
2020. 10. 24. Yuuki Watanabe

Topic: The effective use of protective groups -the case of total synthesis of (-)-Rhodomollanol A-
Gao, J.; Rao, P.; Xu, K.; Wang, S.; Wu, Y.; He, C.; Ding, H. *J. Am. Chem. Soc.* **2020**, *142*, 4592.

0. Introduction

0-1. Protective groups

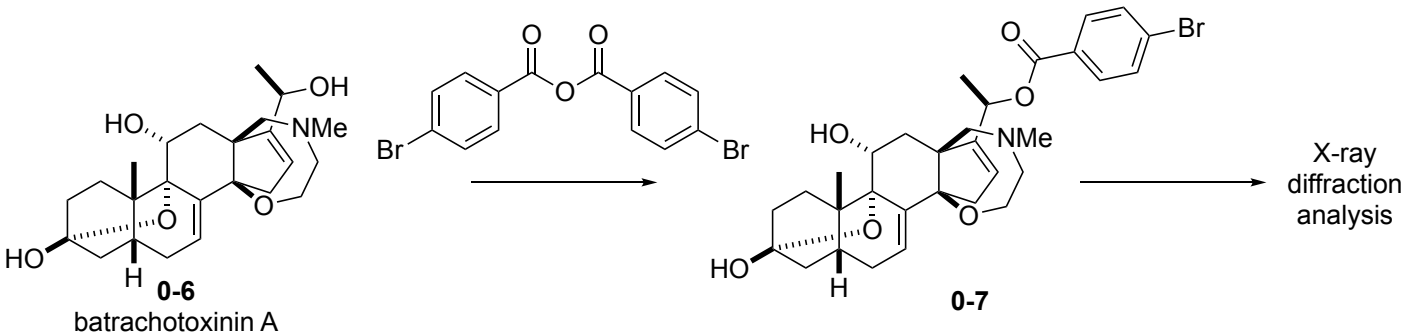
Protective groups: Functional groups used for changing the reactivity. (mainly for block the reactive sites)
Properties: Selective installation, selective removal, minimum of additional functionality…



0-2. The aim and disadvantage of protective groups

0-2-1. Aim

1. Inactivate the functional groups
2. Higher crystallinity
   Tokuyama, T.; Daly, J.; Wiktop, B.; Karle, I. L.; Karle, J. *J. Am. Chem. Soc.* **1968**, *90*, 1917.



3. Easier to determine the structure
4. Changing the properties of compounds

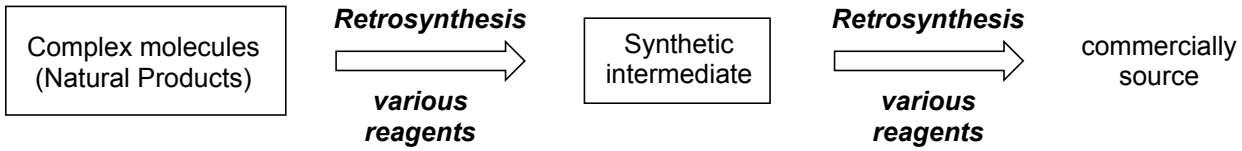
0-2-2. Disadvantage

1. Increasing number of steps (protection, deprotection) → lower over-all yield
2. Installation or removal of protective groups are often problematic in the syntheses.
3. Low atom economy

0-3. The selection of proper protective group

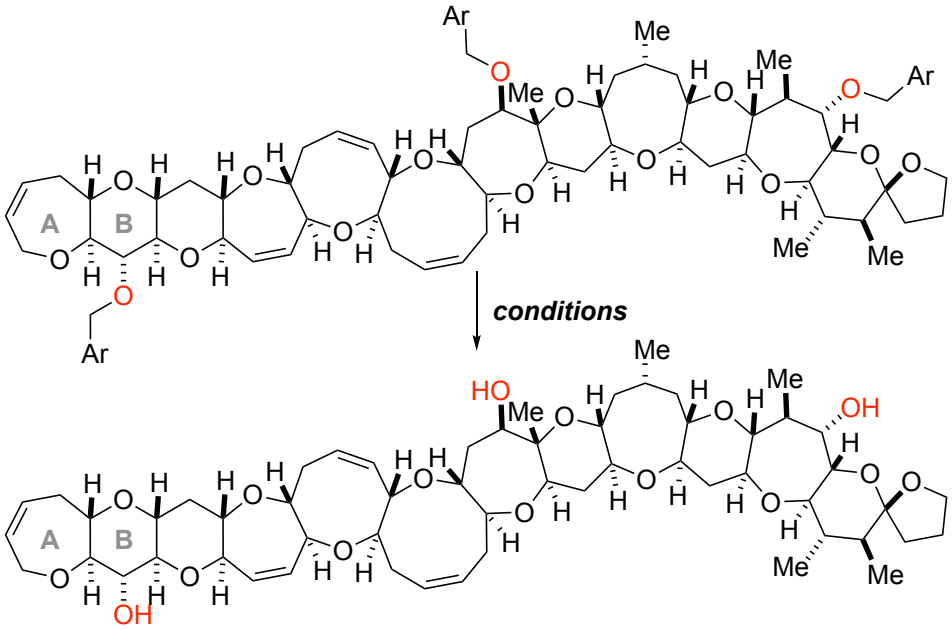
"Greene's Protective Groups in Organic Synthesis" (accesible on Wiley Online Library)

"All things considered, no one protective group is the best."



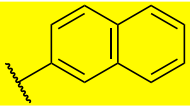
In retrosynthesis,
we must consider in detail all the reactants, reagents and intermediates to select a specific, proper protective group.

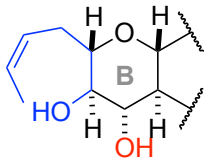
· The strategy of protective group -total synthesis of ciguatoxin CTX3C-
Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.
Inoue, M.; Uehara, H.; Maruyama, M.; Hirama, M. *Org. Lett*. **2002**, *4*, 4551.



0-8

0-9: CTX3C

entry	Ar	*conditions*	result
1		DDQ 45 ºC	complex mixture
2		Na, NH_3 -90 ºC	**0-9**: ~7%
3		DDQ rt	**0-9**: 63%



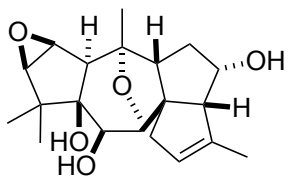
0-10

Reductive cleavage of A-ring occurred.

As shown, the choice of proper protective groups is very important for the achievement of desired reaction.

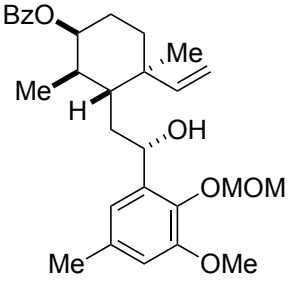
0-4. Introduction of (-)-Rhodomollanol A

Isolation: from the leaves of *Rhododendron molle*.
Zhou, J.; Zhan, G.; Zhang, H.; Zhang, Q.; Li, Y.; Xue, Y.; Yao, G. *Org. Lett*. **2017**, *19*, 3935.
Biological activity: PTP1B inhibitory activity (preliminary)
Structural features: [3,5,7,5,5,5] hexacyclic framework, 11 contiguous stereocenters
Total synthesis: Ding's group (2020)



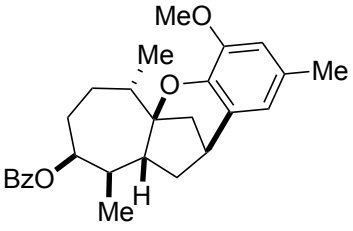
(-)-Rhodomollanol A

(1) **Desired reaction**: Oxidative dearomatization-induced cycloaddition and pinacol-type migration



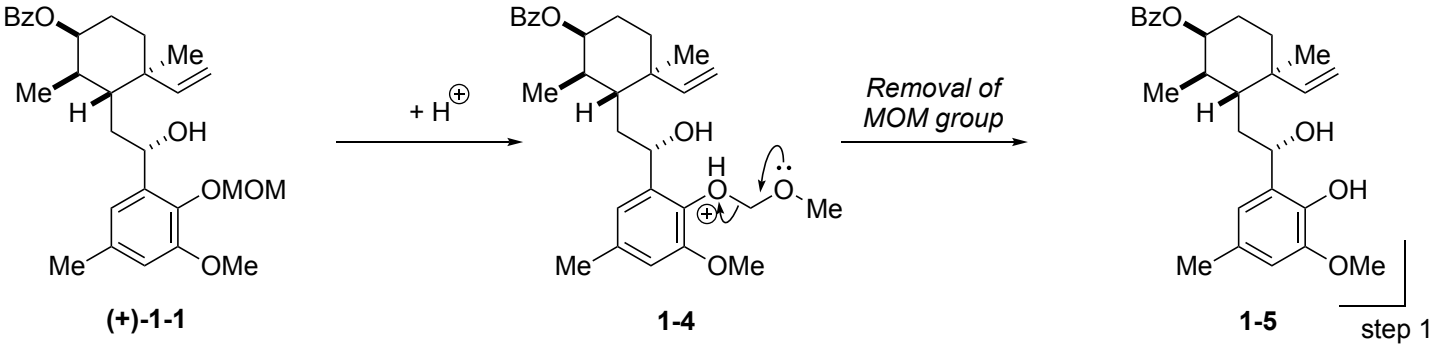
(+)-1-1

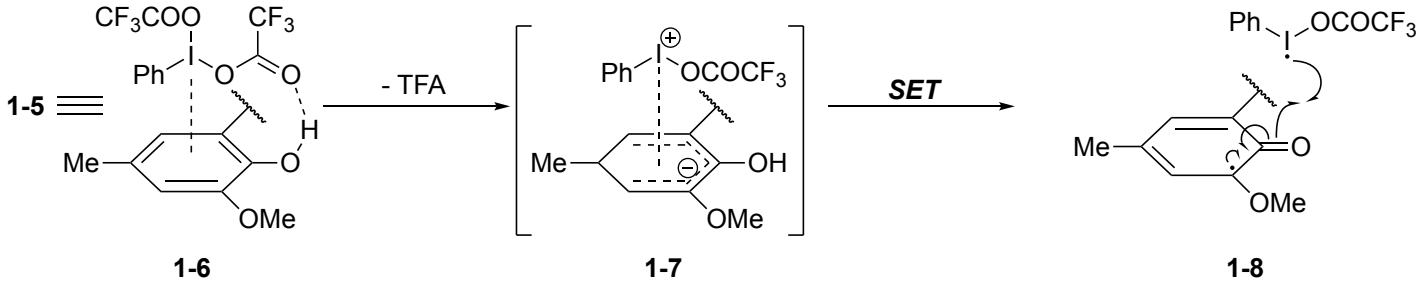
1. *p*-TsOH·H_2O (0.5 eq.), CH_2Cl_2, rt
2. $PhI(OCOCF_3)_2$ (1.2 eq.), Na_2CO_3 (3.0 eq.)
Na_3PO_4 (2.0 eq.), $(CF_3)_2CHOH$
0 ºC, 45% (2 steps)

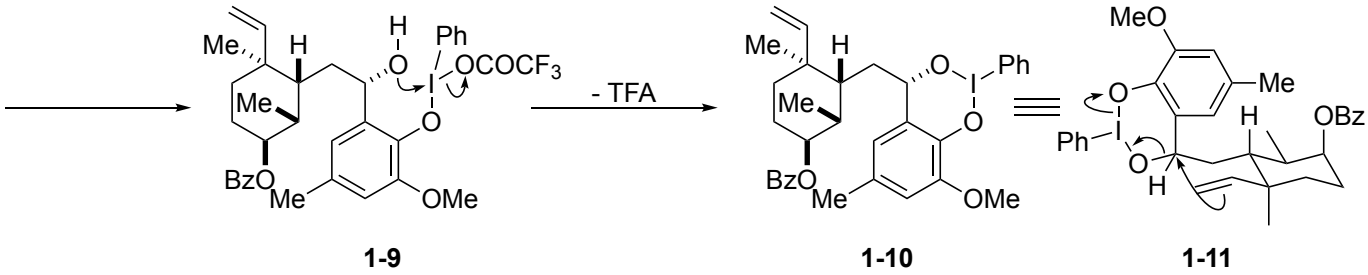


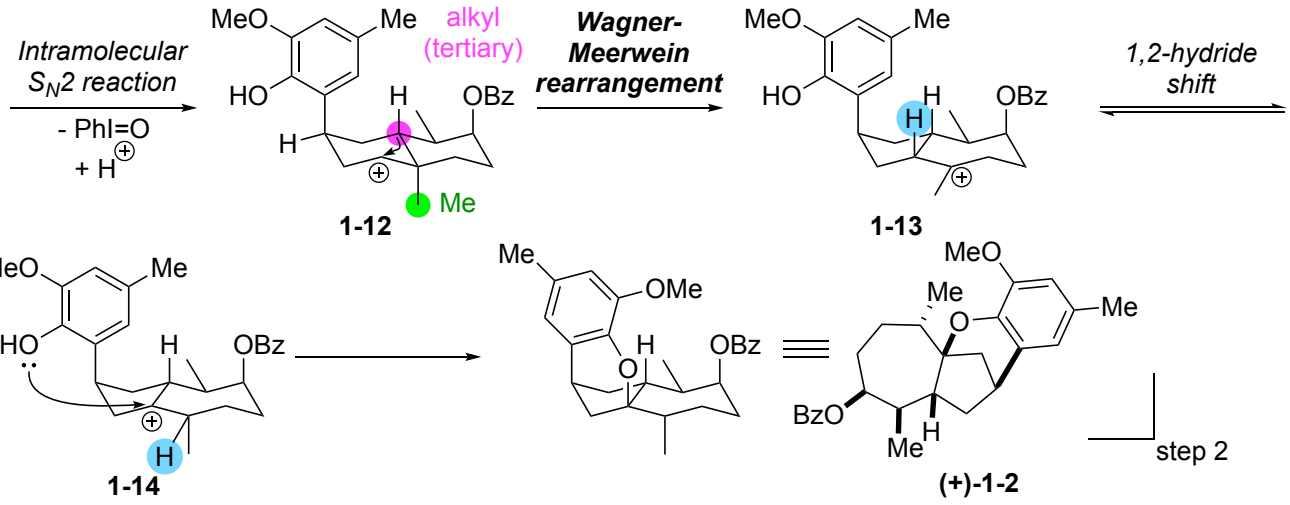
(+)-1-2

Answer:

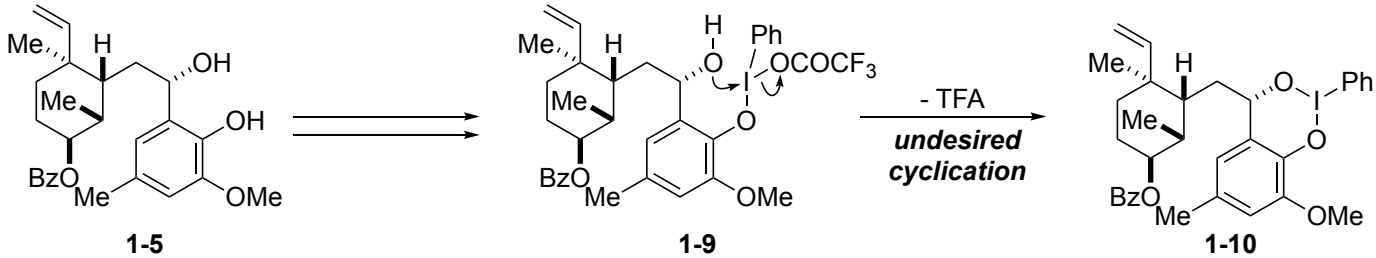






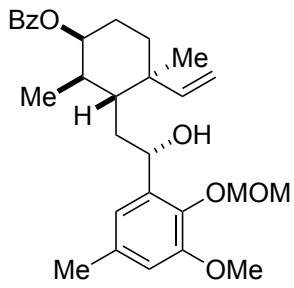


· For desired reaction



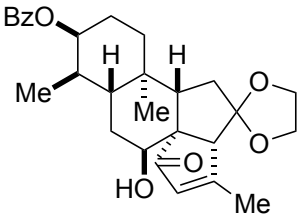
To supress the attack of hydroxy group, the protection is necessary.

· In synthetic plan…
To decrease the number of steps, the protection should be conducted with the removal of MOM group.
Also, the deprotection should be conducted in one-pot.



(+)-1-1

1. **Reagent X** (2.5 eq.)
   p-TsOH·H_2O (1.0 eq.), CH_2Cl_2, rt
2. $PhI(OCOCF_3)_2$ (1.2 eq.), Na_2CO_3 (3.0 eq.)
   Na_3PO_4 (2.0 eq.), $(CF_3)_2CHOH$, 0 ºC;
   TFA (25 eq.), rt, 58% (2 steps)
3. $(TMSOCH_2)_2$ (3.1 eq.), TMSOTf (1.2 eq.)
   CH_2Cl_2, rt, 72%



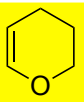
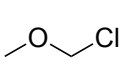
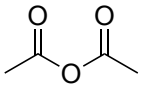
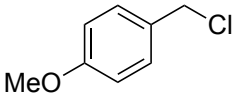
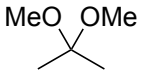
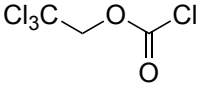
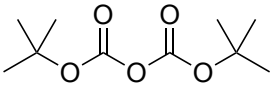
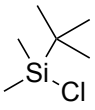
(+)-1-3

· Protection conditions: *p*-TsOH·H_2O (Brønsted acid)
· Deprotection conditions: TFA (acid), $(CF_3)_2CHOH$ (low-nucleophilicity, polar solvent)
= Acetal (**A** or **B**) or acetonide (**F**) protective group should be used.

· In the reaction 1, the protection of hydroxy group and the removal of MOM group occurred.
= **B** would be inappropriate. (Also, protection would be difficult under acidic conditions.)

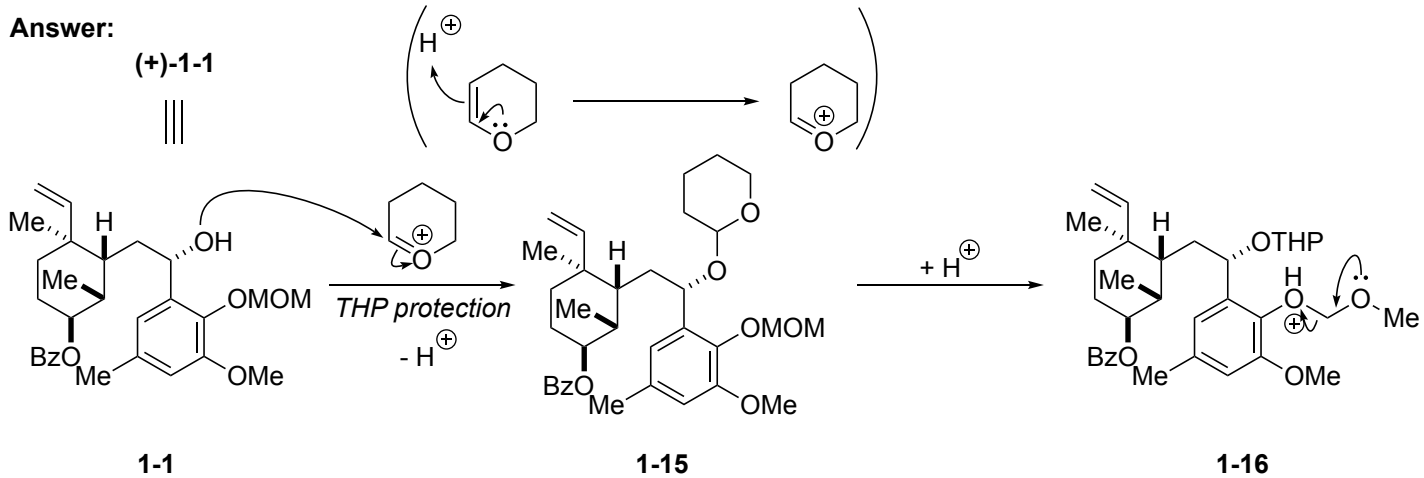
· In the reaction 2, phenol should react with $PhI(OCOCF_3)_2$.
= Phenol hydroxy group should not be protected, so **F** would be inappropriate.
= **DHP** (**A**) should be used as **Reagent X**.

C, D: Deprotection would be difficult. / **E, H, I, J**: Protection would be difficult.
G: Elimination of $MsO^{\ominus}$ would occur.

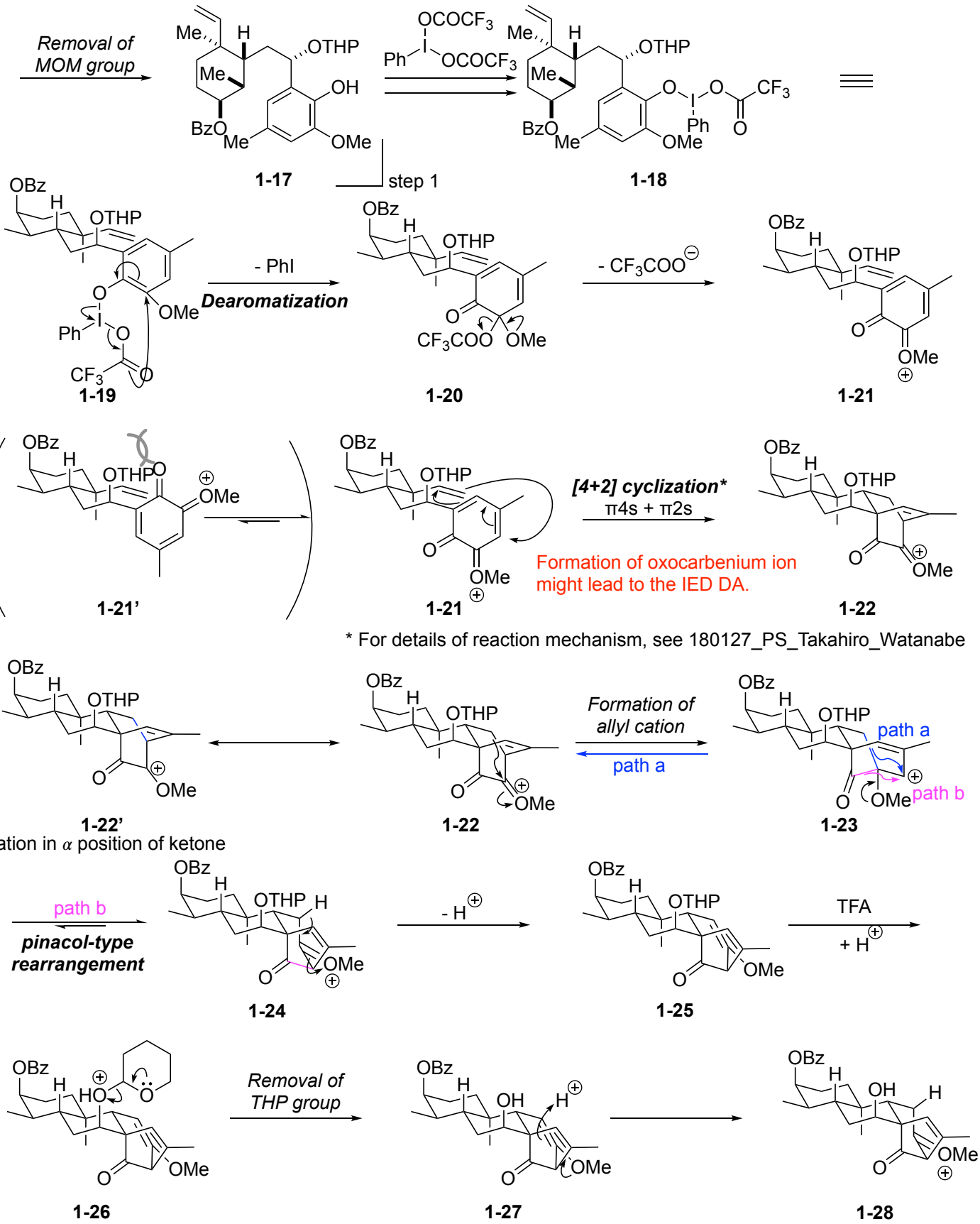
	 **A**: DHP	 **B**: MOMCl	 **C**: Ac_2O	 **D**: PMBCl	 **E**: TMSCl
introduction	Brønsted acid	base	base	base	base
removal	acid	strong acid	solvolysis/reduction	strong acid/H_2/DDQ	various conditions
	 **F**: DMP (2,2-dimethoxypropane)	 **G**: MsCl	 **H**: Troc-Cl	 **I**: Boc_2O	 **J**: TBSCl
introduction	strong acid	weak base	base	base	base
removal	strong acid	strong base	Zn, AcOH	strong Brønsted acid	acid/$F^{\ominus}$

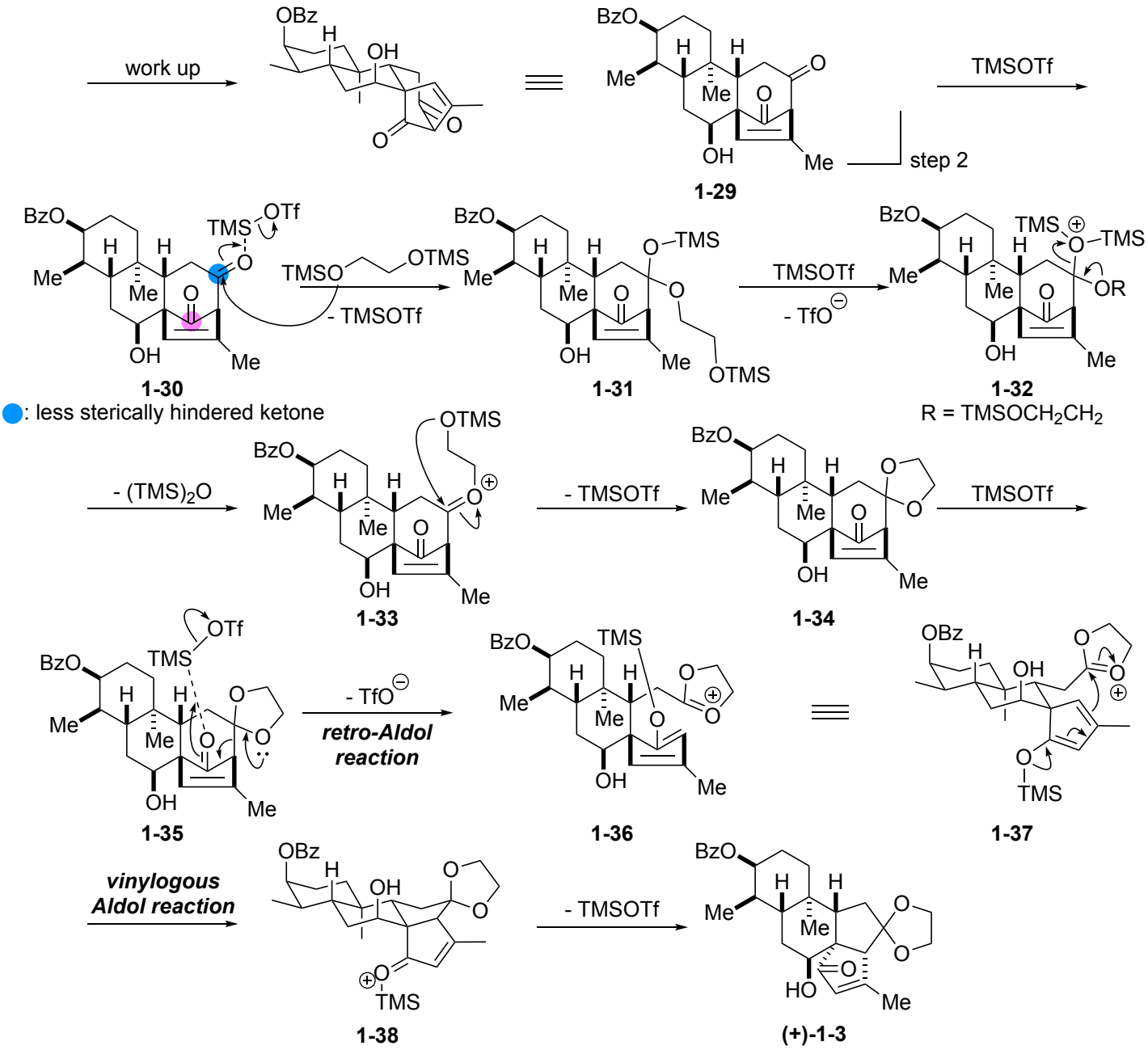
Answer:

(+)-1-1



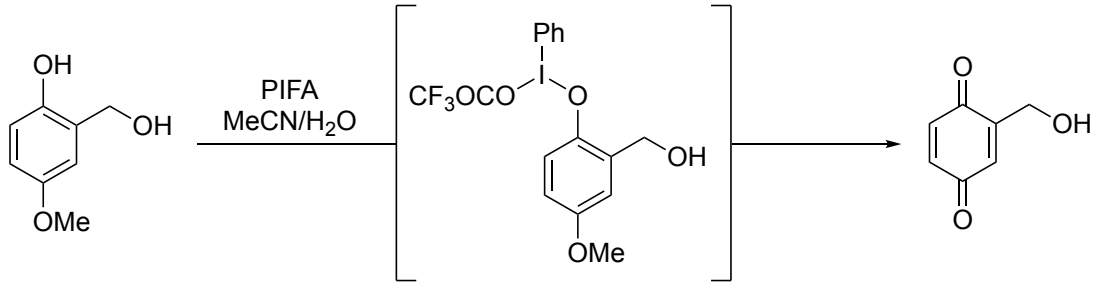
1-1 **1-15** **1-16**


Removal of MOM group
1-17
step 1
1-18
- PhI
Dearomatization
1-19
1-20
- CF3COO
1-21
1-21'
[4+2] cyclization*
π4s + π2s
Formation of oxocarbenium ion might lead to the IED DA.
1-22
* For details of reaction mechanism, see 180127_PS_Takahiro_Watanabe
1-22'
cation in α position of ketone
Formation of allyl cation
path a
path b
1-23
pinacol-type rearrangement
1-24
- H
1-25
TFA
+ H
Removal of THP group
1-26
1-27
1-28



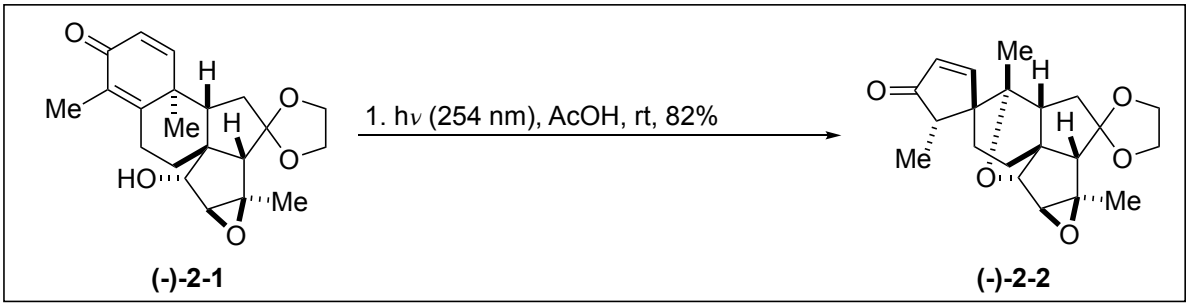
Discussion 1: Reaction of PhI(OCOCF$_3$)$_2$ (PIFA)

Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 126.



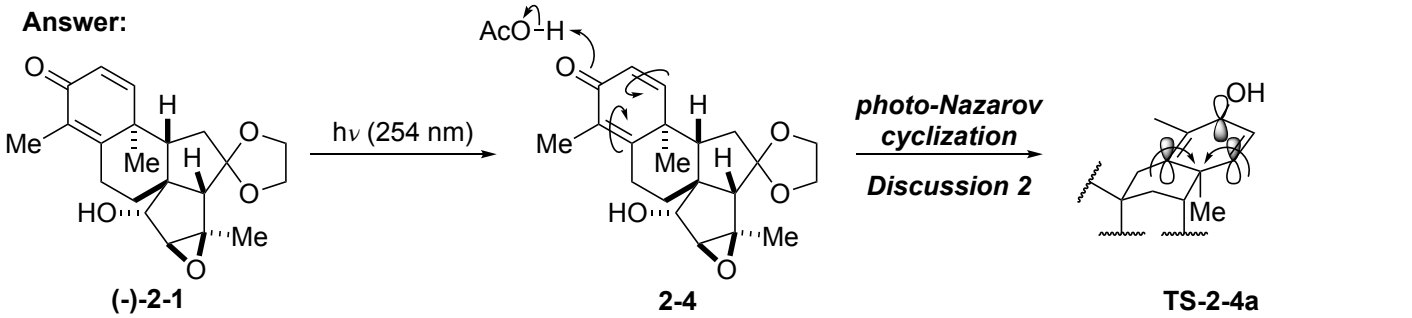
From this result, I assume that PhI(OCOCF$_3$)$_2$ reacts with phenolic hydroxy group rather than OH at benzyl position.

(2) **Desired reaction**: photo-Nazarov cyclization and intramolecular ether cyclization

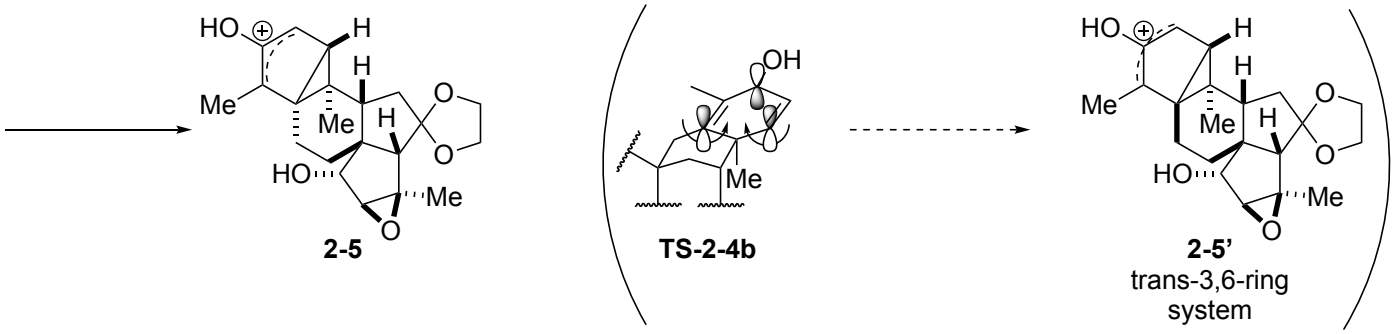


(-)-2-1 **(-)-2-2**

Answer:

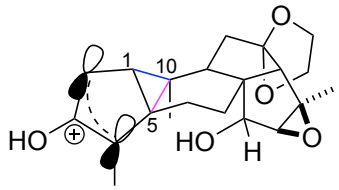


(-)-2-1 **2-4** **TS-2-4a**



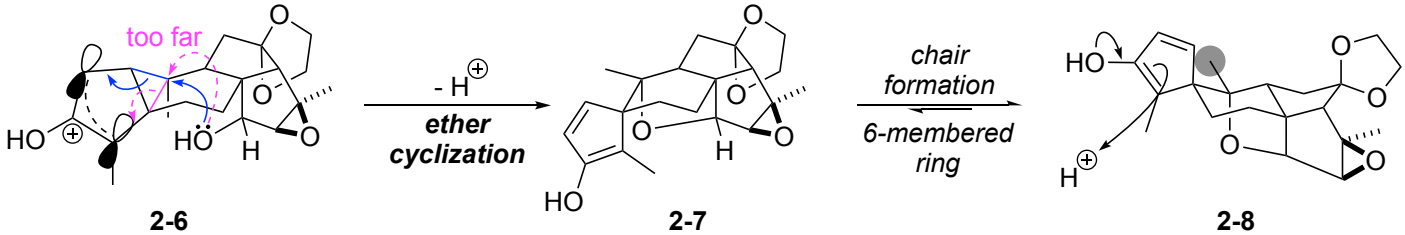
2-5 **TS-2-4b** **2-5'** trans-3,6-ring system

2-5 ≡

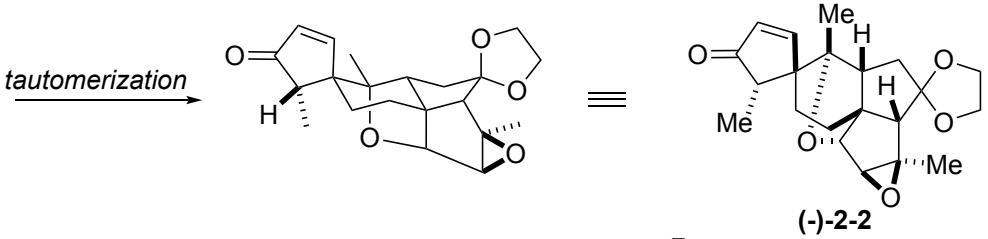


2-6

π-orbital : orthogonal to this paper
= C1-C10 bond (shown in blue) or
C5-C10 bond (shown in magenta) may cleave.
(C1-C5 bond should not cleave.)



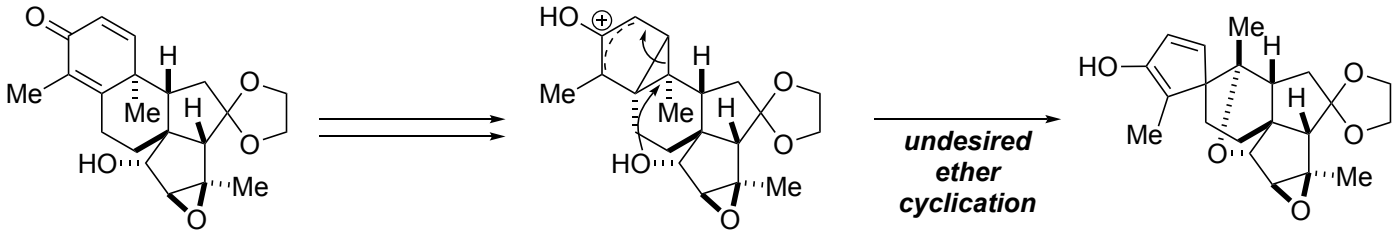
2-6 **2-7** **2-8**



(-)-2-2

●: sterically shielding the back side of cyclodiene

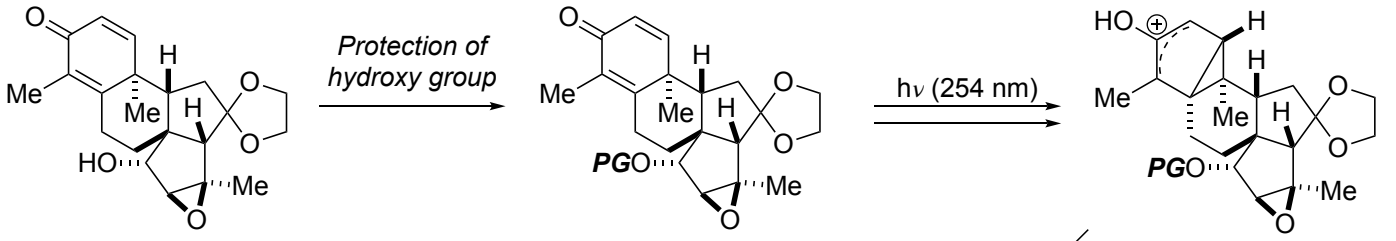
·For desired reaction



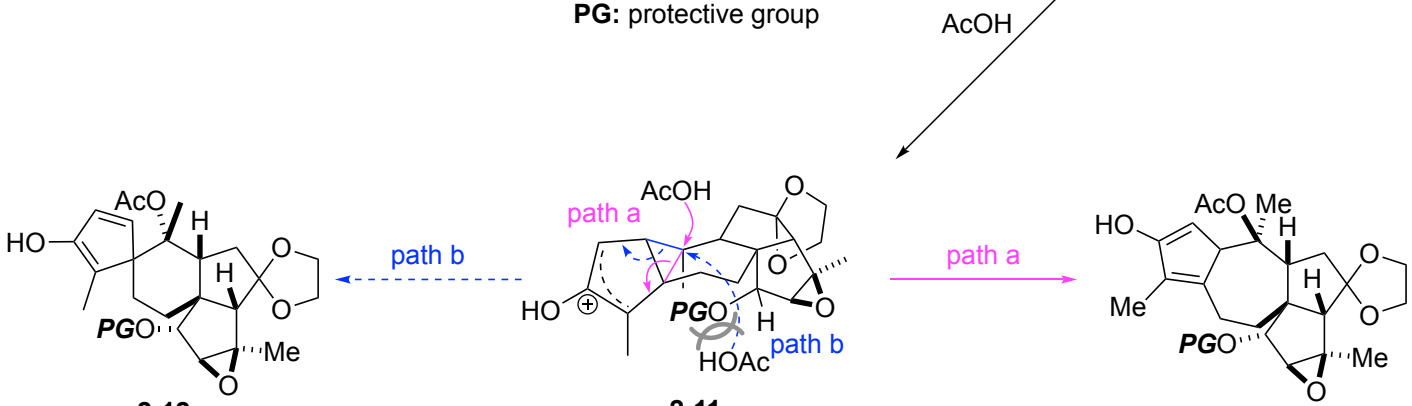
(-)-2-1 **2-5** **2-8**

In this condition, intramolecular ether cyclization was fast and undesired **2-8** was formed.
To supress the attack of hydroxy group, the protection is necessary.

· Detour

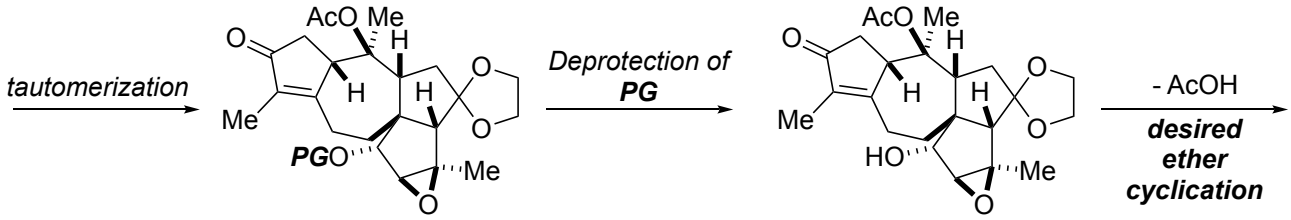


2-1 **2-9**
PG: protective group **2-10**

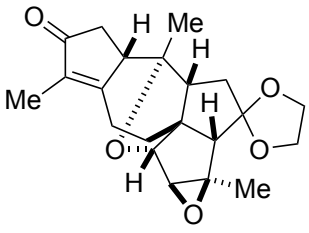


2-12 **2-11** **2-13**

The protection of hydroxy group would result in the desired opening of cyclopropane by AcOH.



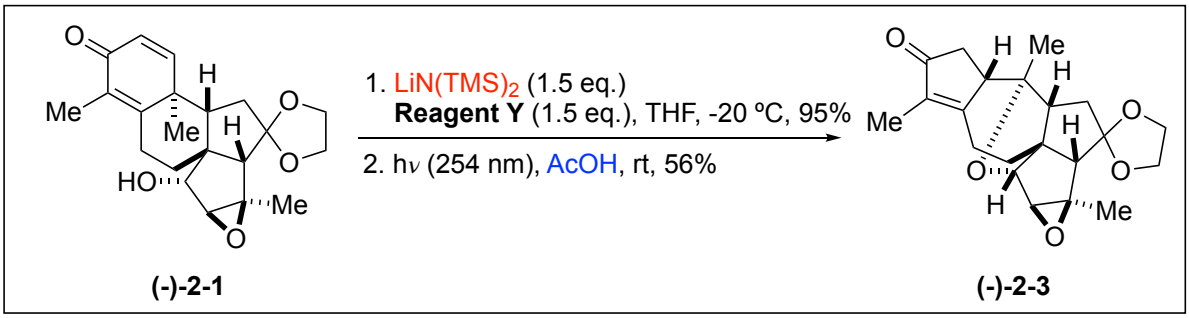
2-14 **2-15**



(-)-2-3

For the desired reaction…
1st. Photo Nazarov cyclization (PG should not be removed at this time.)
2nd. **Removal of PG**
3rd. Ether cyclization

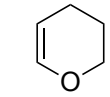
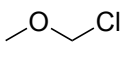
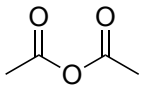
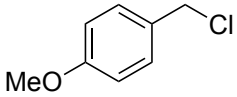
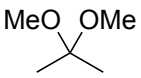
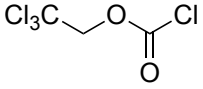
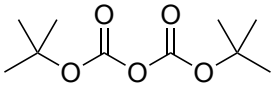
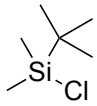
· In synthetic plan…
Considering AcOH is used as a solvent in this reaction, deprotection should be occurred by AcOH.



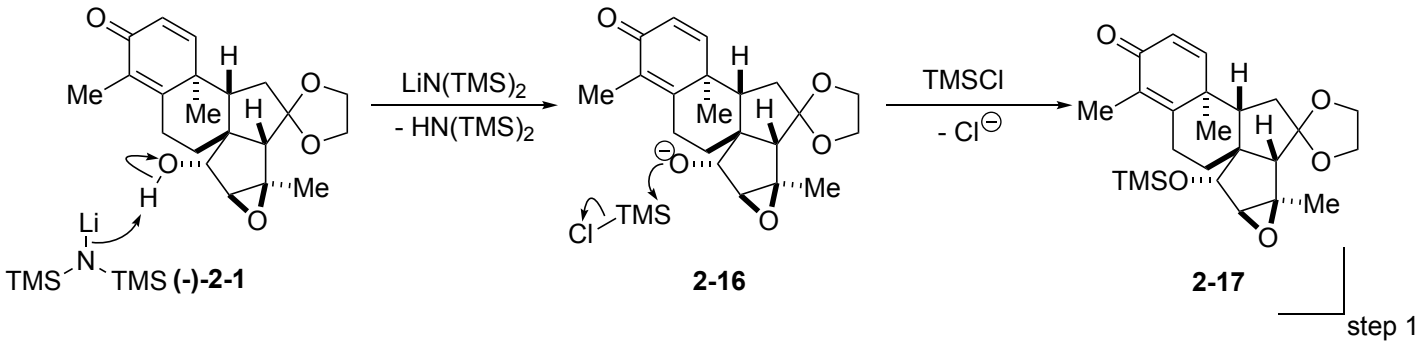
(-)-2-1 **(-)-2-3**

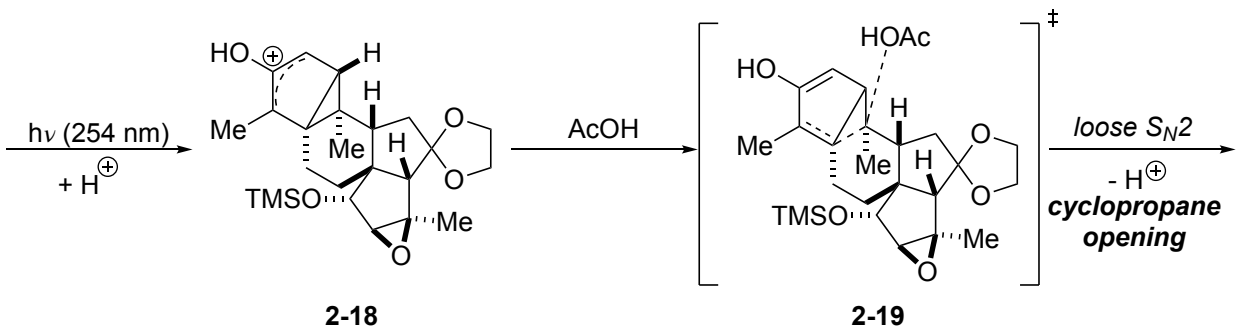
・Protection conditions: $LiN(TMS)_2$ (strong base)
・Deprotection conditions: AcOH (weak acid), room temperature
= TMSCl (**E**) should be used as **Reagent Y**.

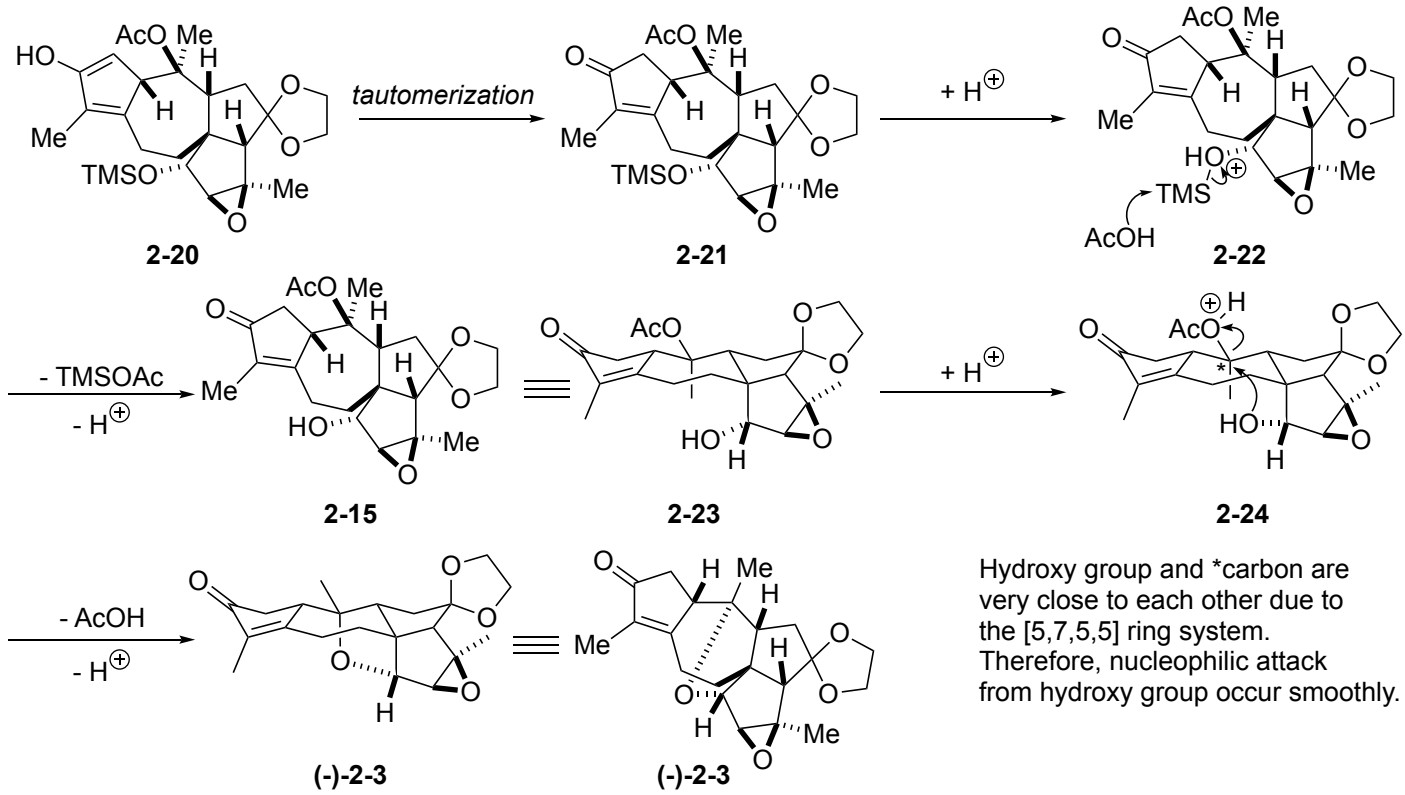
B, C, D, H, I, J: Removal would be difficult.
A, F: Installation would be difficult.
G: Other reaction (such as rearrangement) would be occurred.

					
	A: DHP	**B**: MOMCl	**C**: Ac_2O	**D**: PMBCl	**E**: TMSCl
introduction	Brønsted acid	base	base	base	base
removal	acid	strong acid	solvolysis/reduction	strong acid/H_2/DDQ	various conditions
					
	F: DMP (2,2-dimethoxypropane)	**G**: MsCl	**H**: Troc-Cl	**I**: Boc_2O	**J**: TBSCl
introduction	strong acid	weak base	base	base	base
removal	strong acid	strong base	Zn, AcOH	strong Brønsted acid	acid/$F^{\ominus}$

Answer:





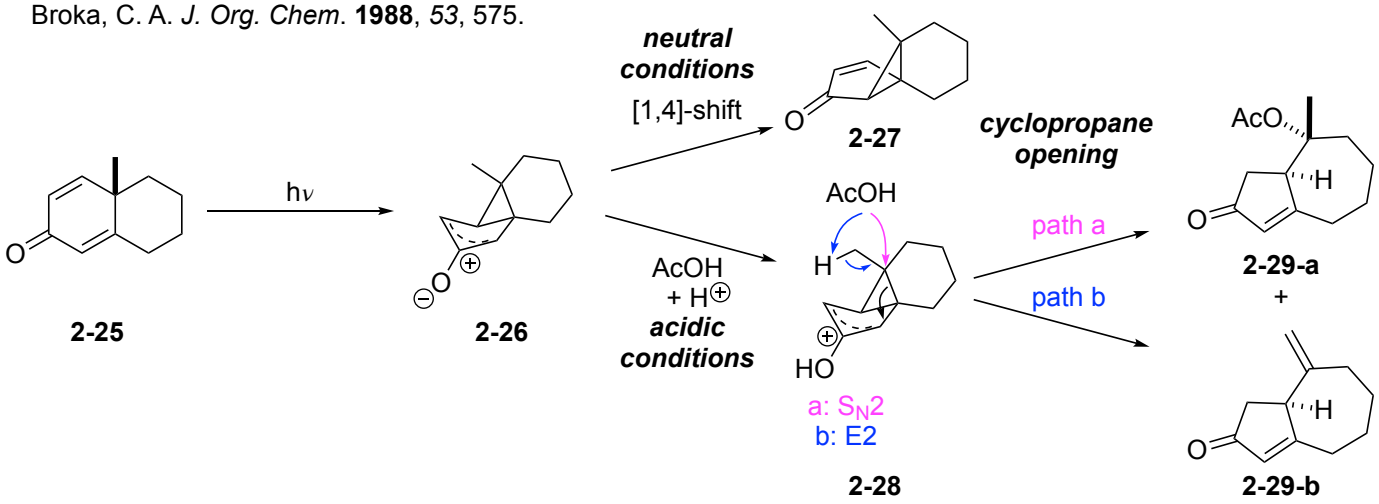


Hydroxy group and *carbon are very close to each other due to the [5,7,5,5] ring system. Therefore, nucleophilic attack from hydroxy group occur smoothly.

Discussion 2: photo-Nazarov cyclization of tetrahydronaphtalenone

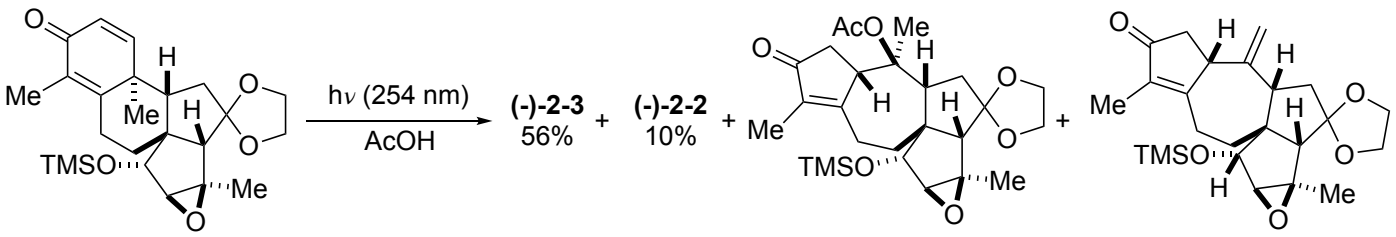
1. Reaction mechanism

The products of photo-Nazarov cyclization with 2-20 were different depending on the acidity of conditions.
Broka, C. A. *J. Org. Chem*. **1988**, *53*, 575.



Based on these results, protonation of ketone and following ring-opening would occur in **conditions for 2-2 and 2-3**.

2. Results of cyclization of **2-17**



2-21 and **2-30** were obtained as byproducts.