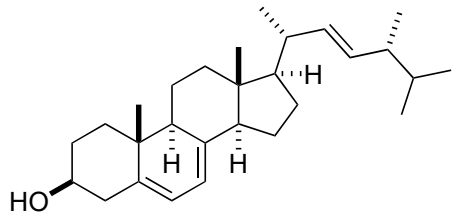
Problem Session (3) -Answer-

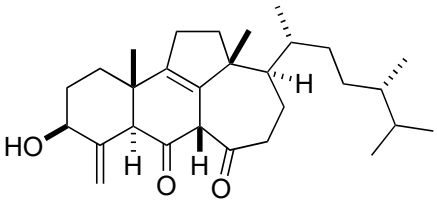
2023.4.28. Jaejoong Han

Topic: Construction of abeo- and diabeo-steroid framework from ergosterol



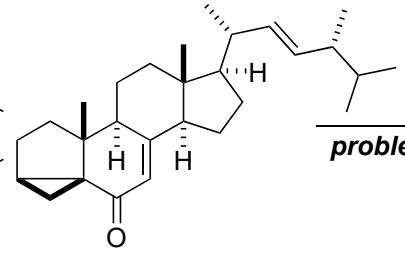
ergosterol

3 steps



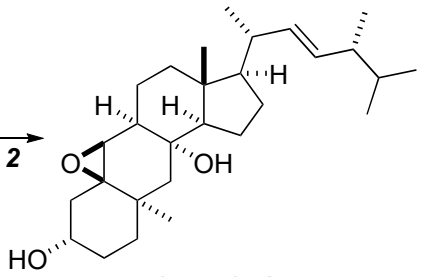
swinhoeisterol A
J. Am. Chem. Soc. **2020**, *142*, 104.

problem 1

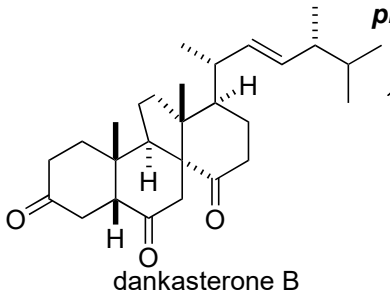


comon intermediate

problem 2

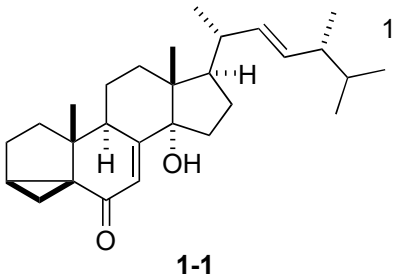


pleurocin A
J. Am. Chem. Soc. **2019**, *141*, 1222.



dankasterone B
J. Am. Chem. Soc. **2020**, *142*, 104.

1.



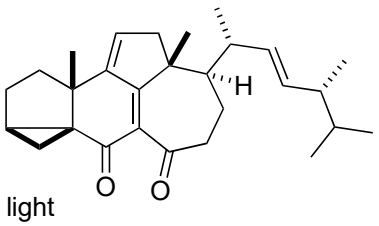
1-1

1. ***conditions A***: $PhI(OAc)_2$ (2 eq), I_2 (1 eq)
benzene, 25 ºC
1-2: 76%, **1-3:** not obtained

conditions B: HgO (2.7 eq), I_2 (2.4 eq)
benzene, 60 to 105 ºC
1-2: 2%, **1-3:** 68%

1-2
($C_{28}H_{41}IO_2$)

+

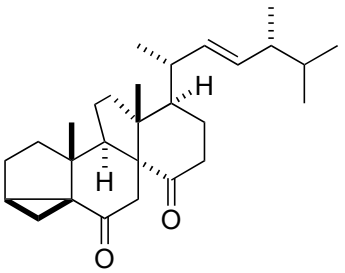


1-3

*In both conditions, probably the reaction was conducted under room light though not particularly mentioned .

1-2

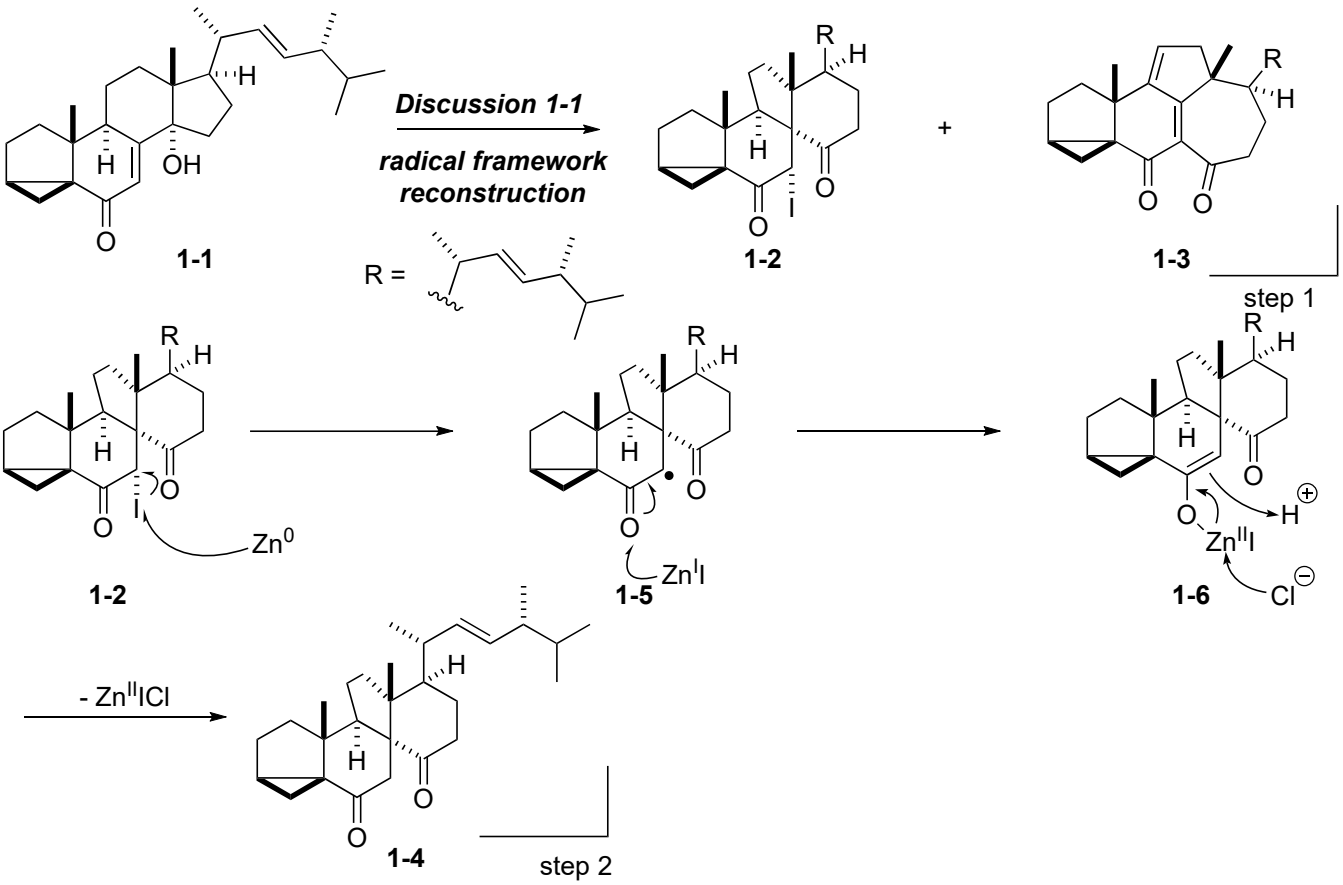
2. Zn (16 eq), NH_4Cl (4.7 eq), MeOH, 25 ºC
91%



1-4

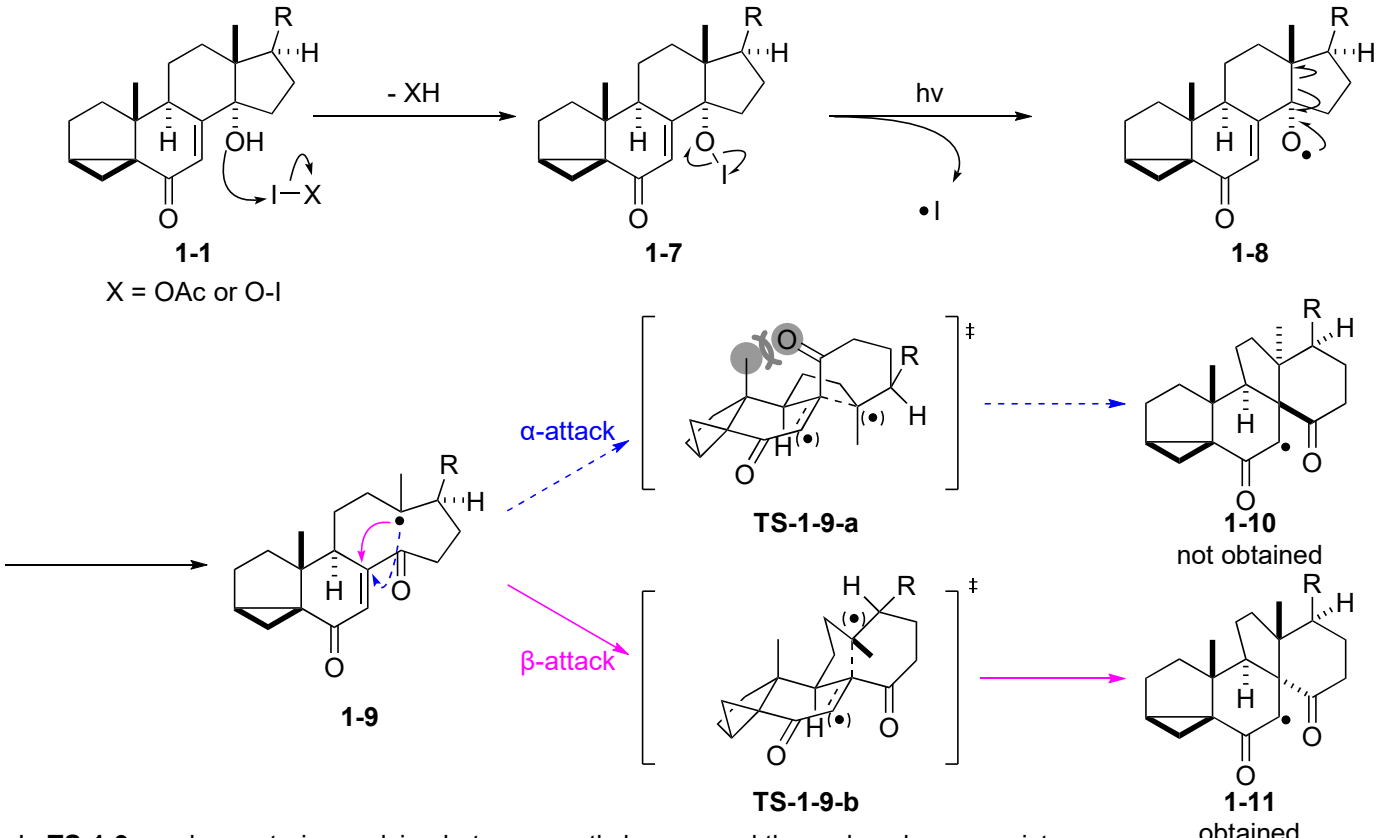
Duecker, F. L.; Heinze, R. C.; Heretsch, P. *J. Am. Chem. Soc.* **2020**, *142*, 104.

Answer

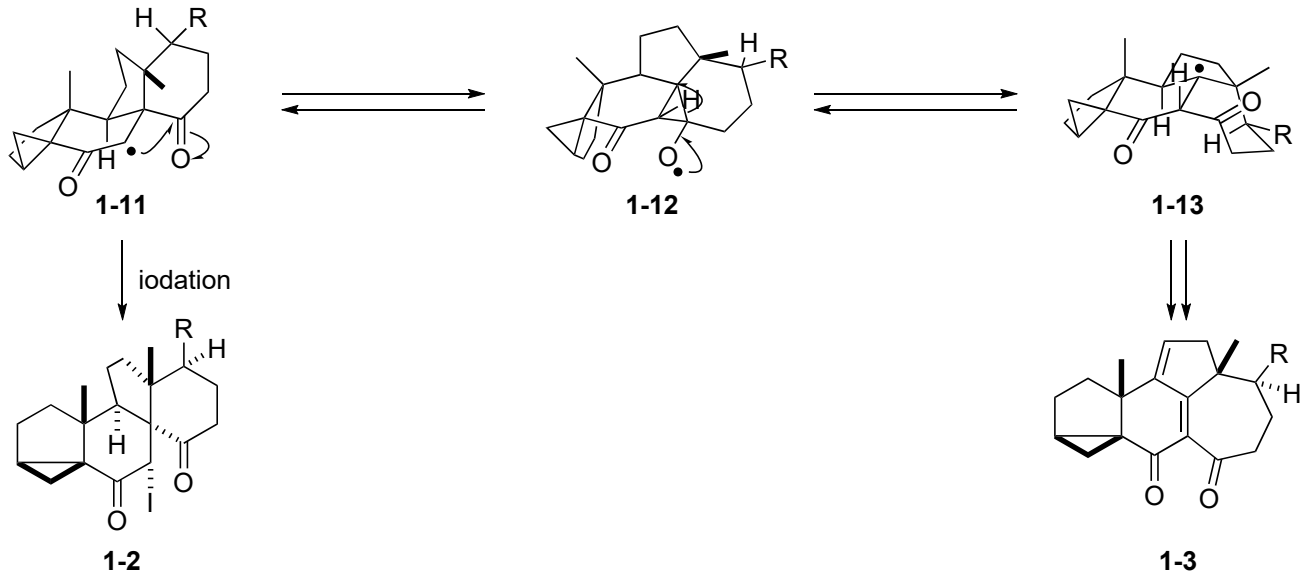


DIscussion 1-1: Radical framework reconstruction

1. Reaction overview



In **TS-1-9-a**, a large steric repulsion between methyl group and the carbonyl group exists. So raddical addition to enone occurs from β-face.



1-11 **1-12** **1-13**

1-2 **1-3**

From **1-11**, Dowd-Beckwith type rearrangement could occur.
Direct iodation from **1-11** gives **1-2**, while transformation from **1-13** gives **1-3**.

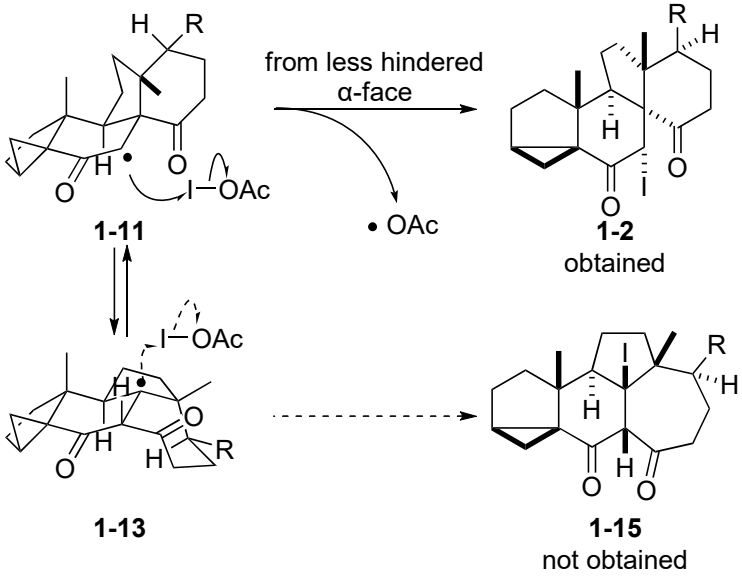
2. *Conditions A*
2-1. Iodation reagent

$PhI(OAc)_2 + I_2 \longrightarrow 2\ I{-}OAc + PhI$ (1 eq)

1-14

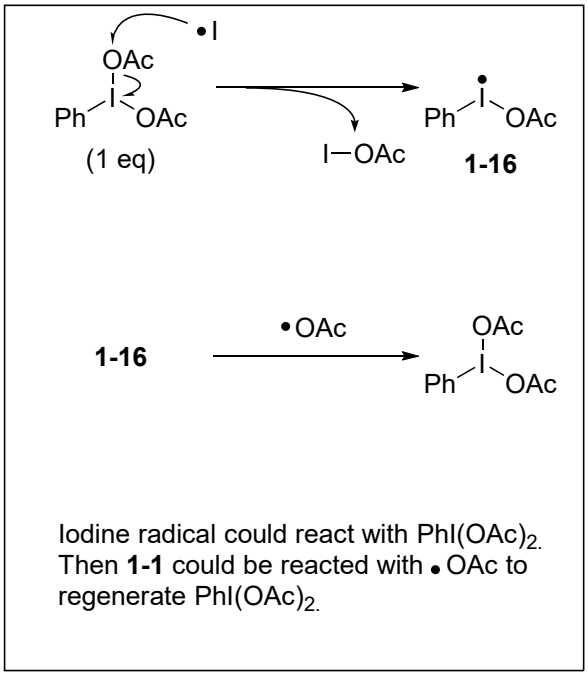
1 eq. of AcOH is generated after the formation of **1-7**.

2-2. Radical trap by iodine



1-11 **1-2** obtained

1-13 **1-15** not obtained



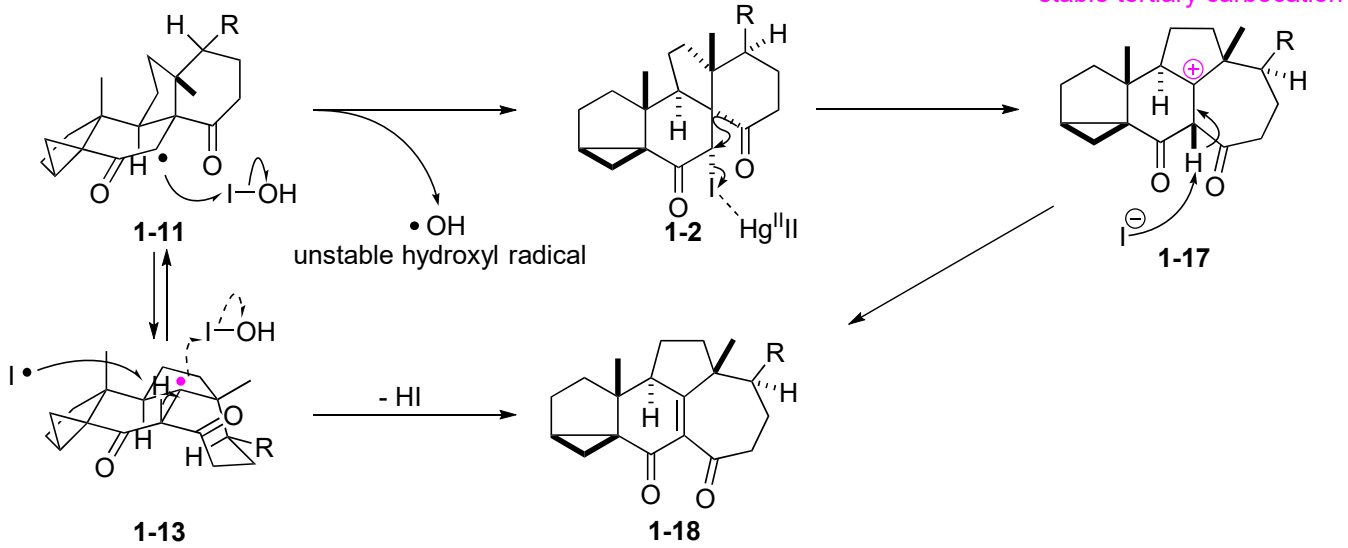
tertiary radical of **1-13** is too clouded for iodation.

3. *Conditions B*
3-1. Iodation reagent

$Hg^{II}O + 2I_2 \longrightarrow Hg^{II}I_2 + I{-}O{-}I$ (1.2 eq)[1)]

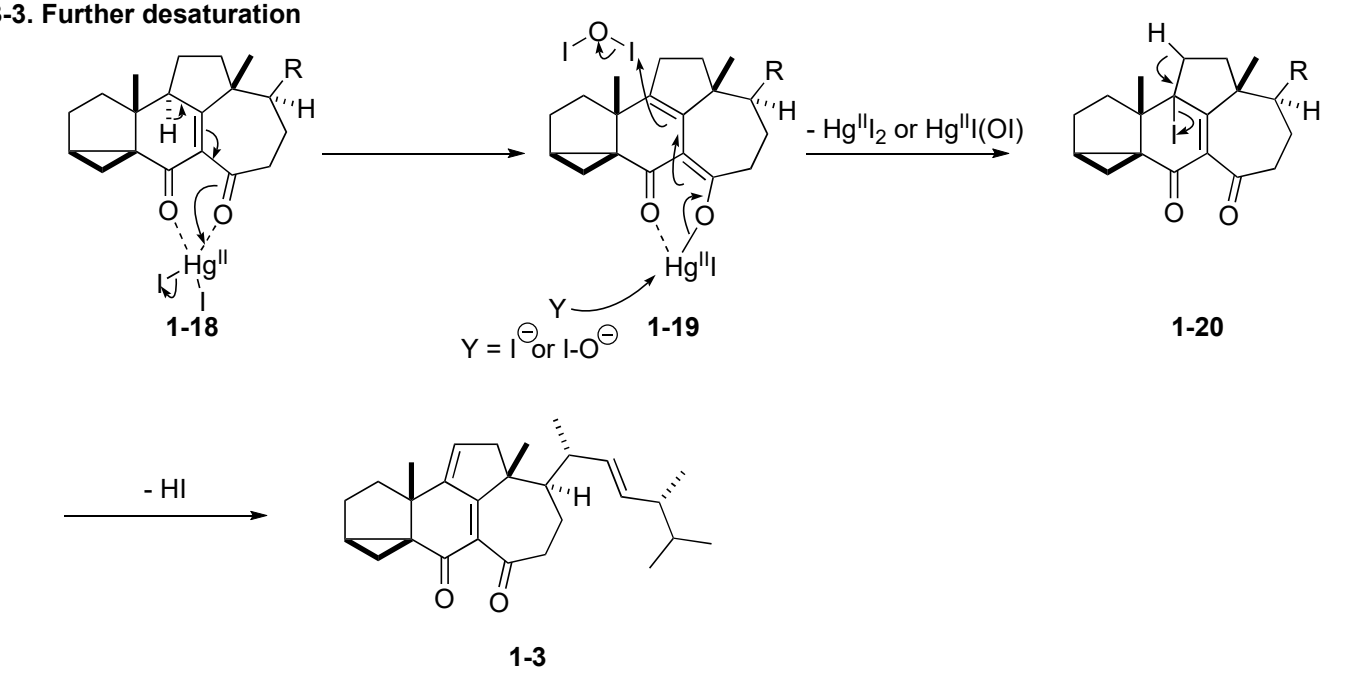
1 eq. of HIO is generated after the formation of **1-7**.

3-2. Generation of 1-18



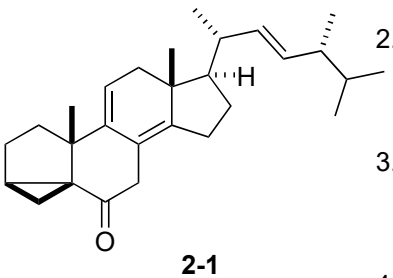
As hydroxyl radical is unstable, radical trap with iodine is slow.
As result, hydrogen abstract from **1-13** occurs.
Also, in the presence of Hg^{II}, rearrangement from **1-2** to **1-17** occurs to give **1-18**.

3-3. Further desaturation



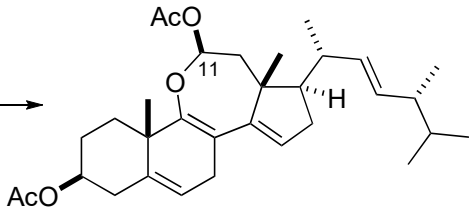
In the presence of Hg^{II} which has Lewic acidity, introduction of iodine via enolate form with highly reactive I_2O reagent and subsequent E2 elimination occures.
As a result, **1-3** is obtained.

2.



2-1

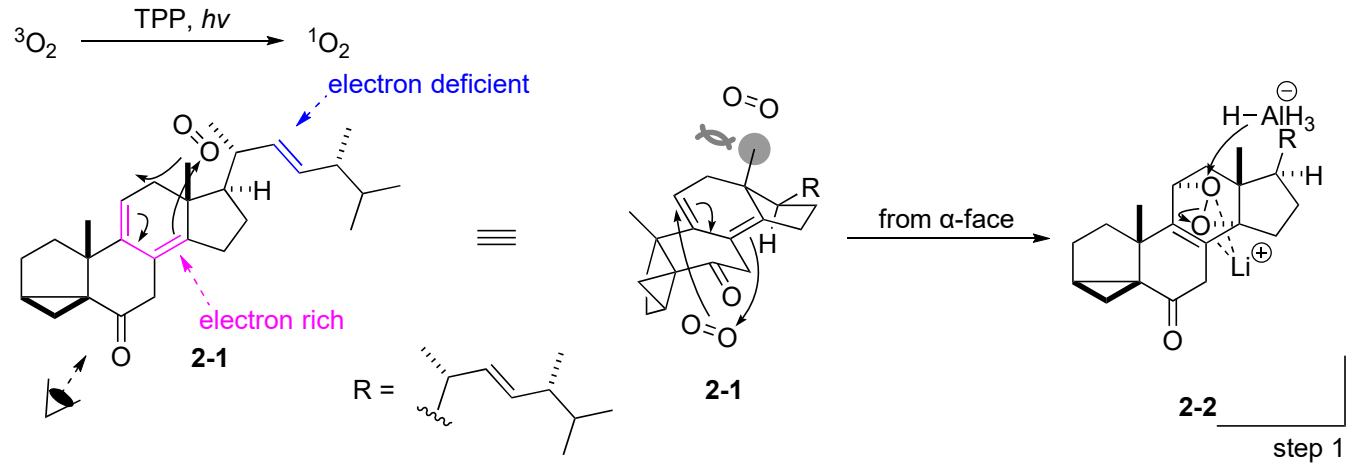
1. TPP (1.5 mol%), O_2 (bubbling)
   pyridine, hv (white light), 0 ºC
2. $LiAlH_4$ (3.3 eq), THF, 0 to 25 ºC;
   2.5 M aq. H_2SO_4, 25 ºC
   54% (3 steps from the former reaction)
3. $VO(acac)_2$ (5 mol%), TBHP (1.2 eq)
   benzene, 25 ºC;
   Raney Ni, EtOH, H_2 (bubbling);
   45 ºC, 57%
4. $PhI(OAc)_2$ (1.2 eq), CH_2Cl_2, 25 ºC, 94%
5. Ac_2O (13 eq), $BF_3 \cdot OEt_2$ (8 eq), AcOH (14 eq)
   Et_2O, 10 ºC, crude was used in the next reaction



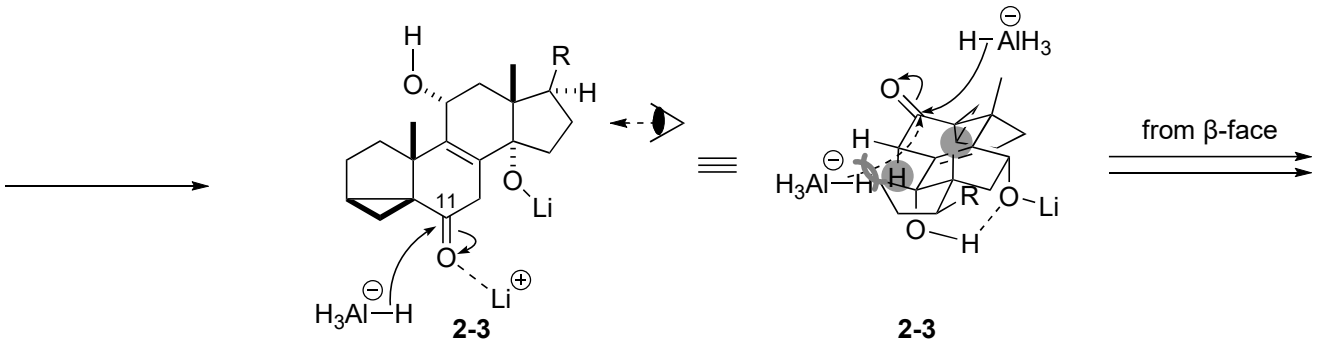
2-2
dr at C11 = 7:1

Heinze, R. C.; Heretsch, P. *J. Am. Chem. Soc.* **2019**, *141*, 1222.

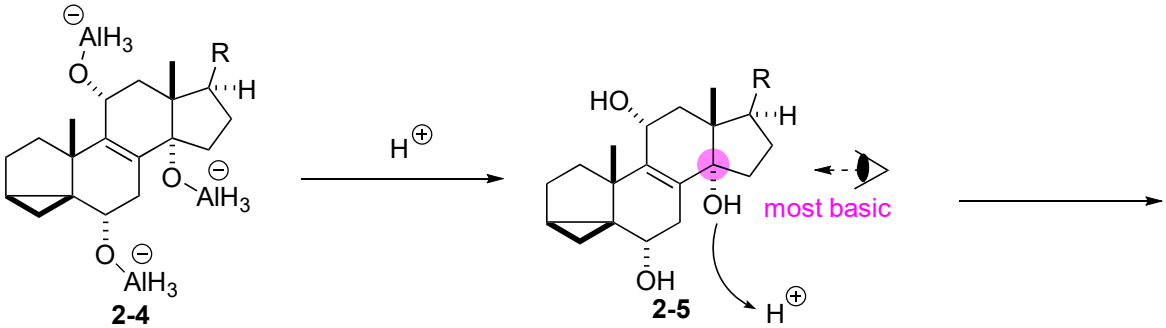
Answer



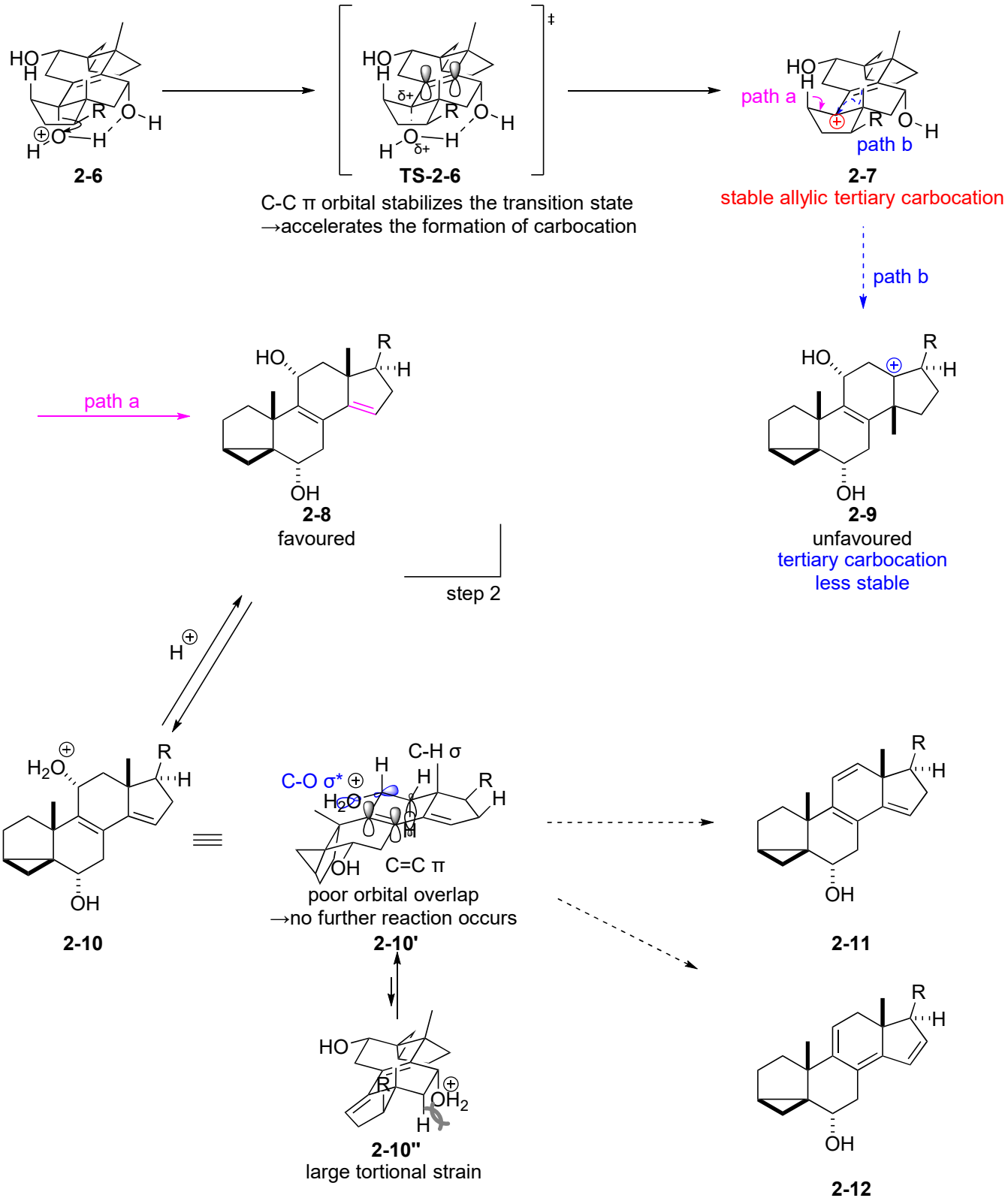
2-1 **2-1** **2-2**

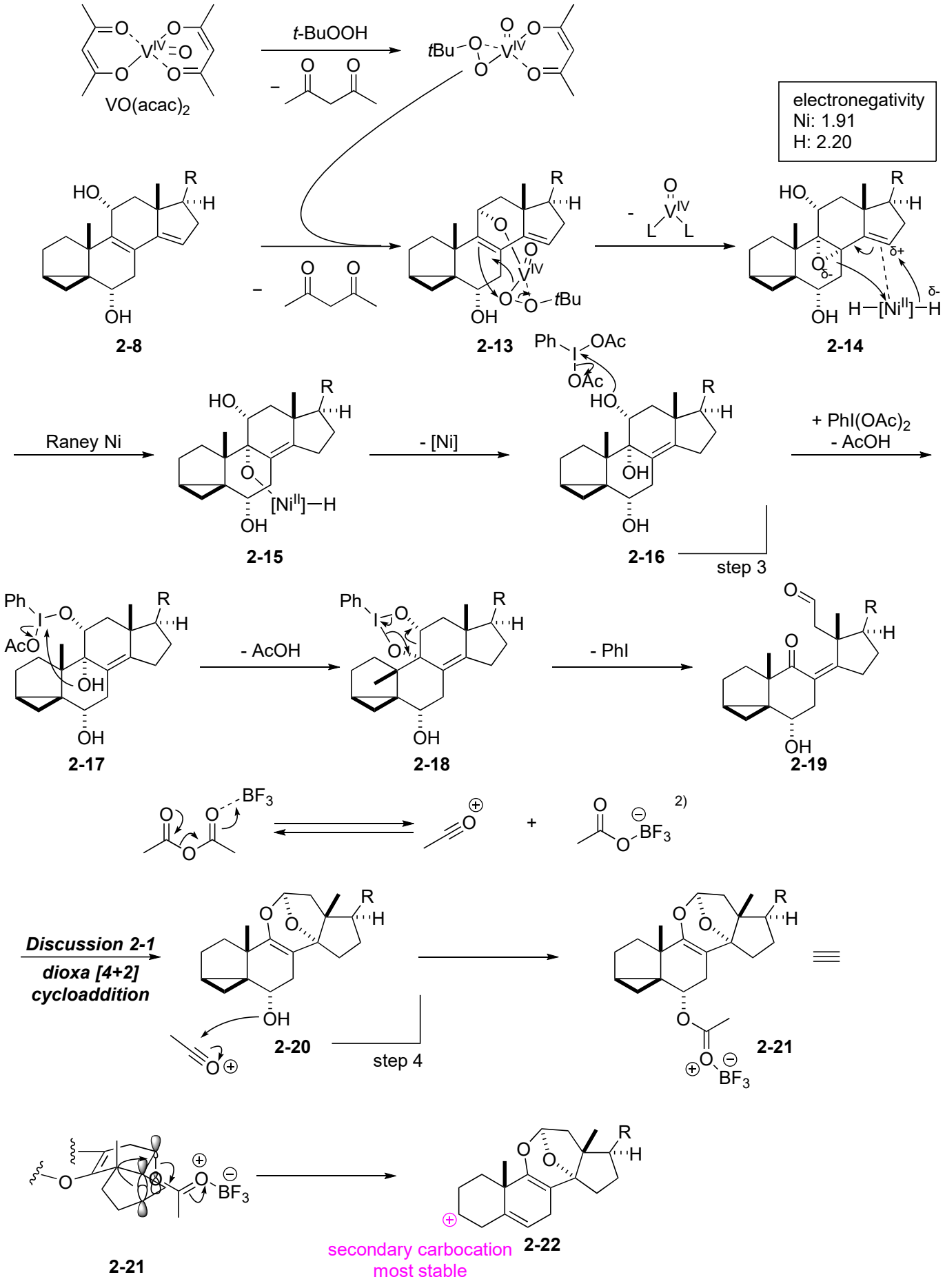


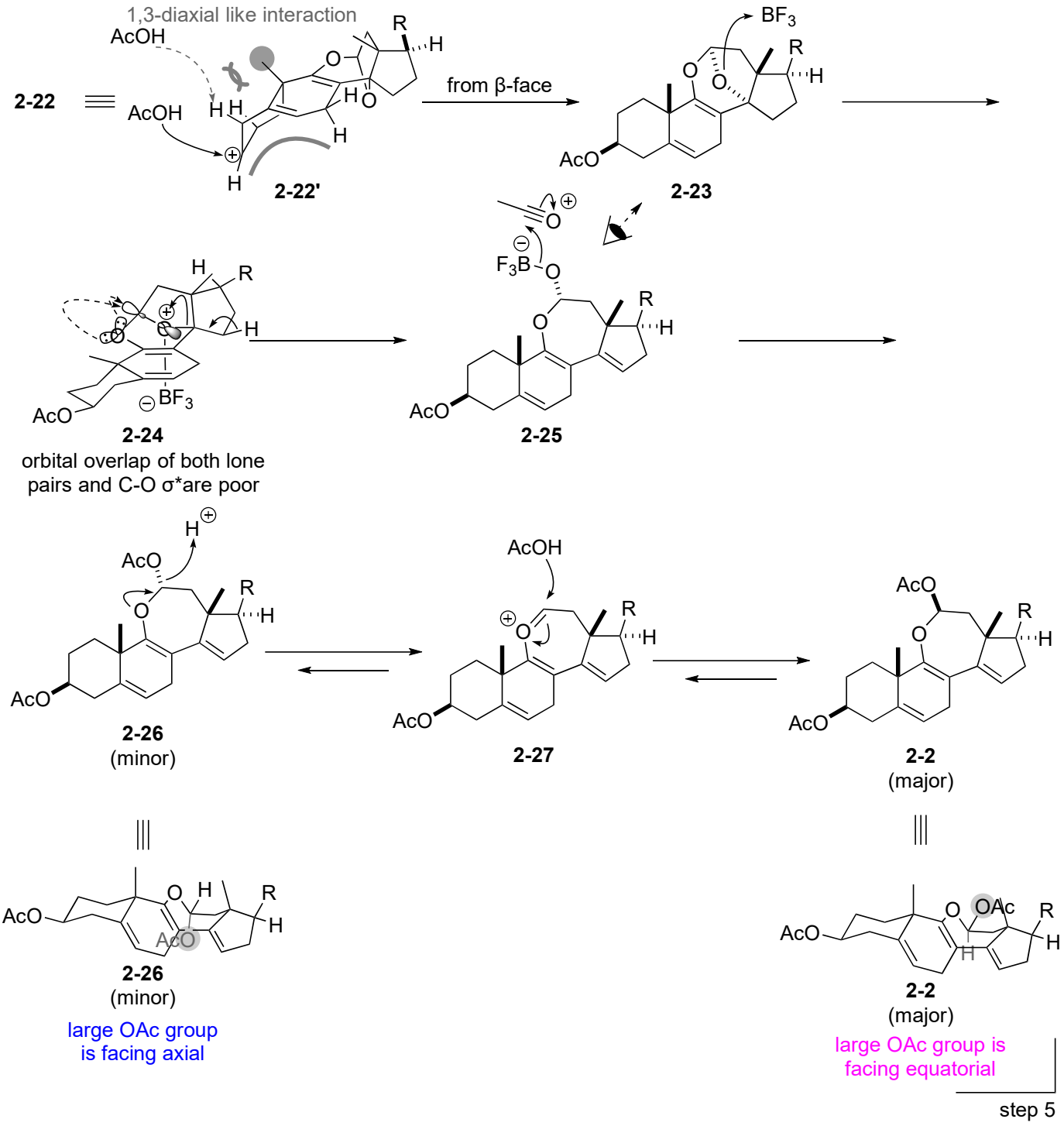
2-3 **2-3**



2-4 **2-5**

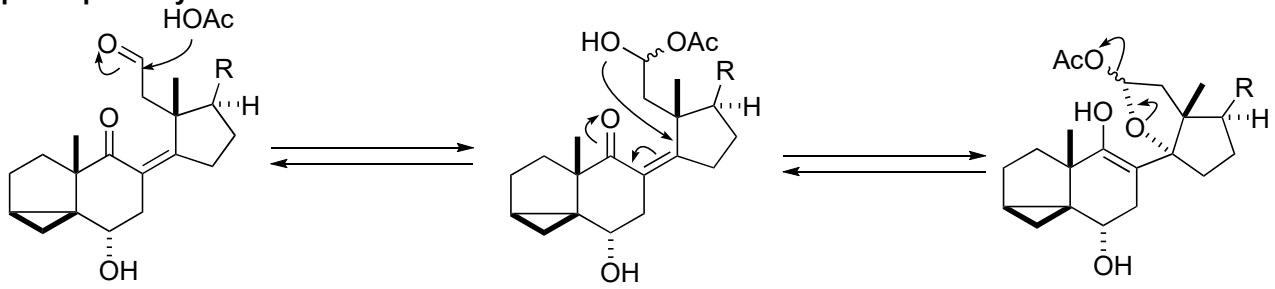

2-6
TS-2-6
C-C π orbital stabilizes the transition state
→accelerates the formation of carbocation
2-7
stable allylic tertiary carbocation
path a
path b
path b
path a
2-8
favoured
2-9
unfavoured
tertiary carbocation
less stable
step 2
2-10
C-O σ*
C-H σ
C=C π
poor orbital overlap
→no further reaction occurs
2-10'
2-10"
large tortional strain
2-11
2-12


VO(acac)2
t-BuOOH
electronegativity
Ni: 1.91
H: 2.20
2-8
2-13
2-14
Raney Ni
- [Ni]
+ PhI(OAc)2
- AcOH
2-15
2-16
step 3
- AcOH
- PhI
2-17
2-18
2-19
Discussion 2-1
dioxa [4+2]
cycloaddition
2-20
step 4
2-21
2-21
secondary carbocation
most stable
2-22

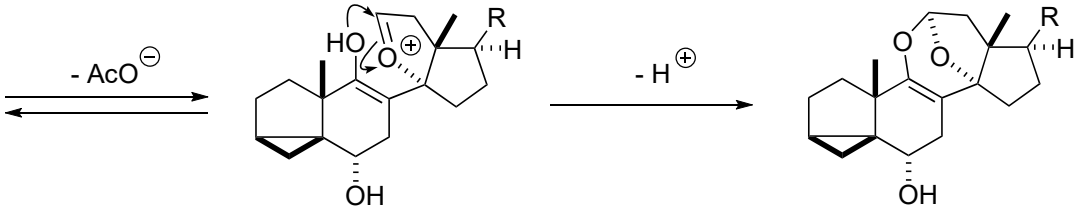

1,3-diaxial like interaction
2-22
AcOH
AcOH
2-22'
from β-face
BF3
2-23
2-24
orbital overlap of both lone pairs and C-O σ*are poor
2-25
2-26
(minor)
2-27
2-2
(major)
2-26
(minor)
large OAc group is facing axial
2-2
(major)
large OAc group is facing equatorial
step 5

Discussion 2-1: dioxa [4+2] cycloaddition

1. Stepwise pathway

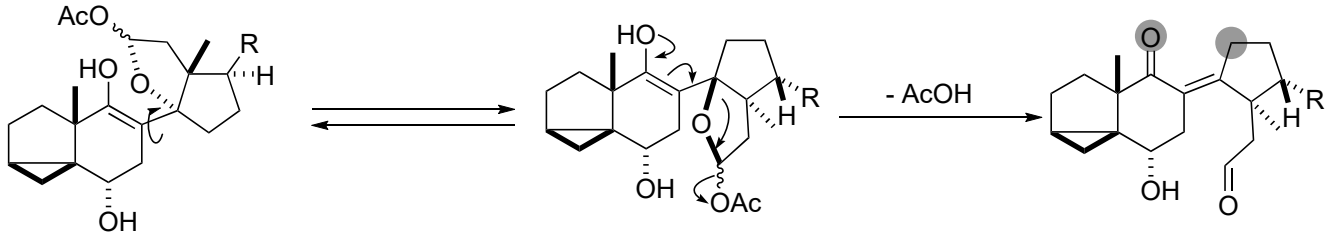


2-19 **2-28** **2-29**



2-30 **2-20**

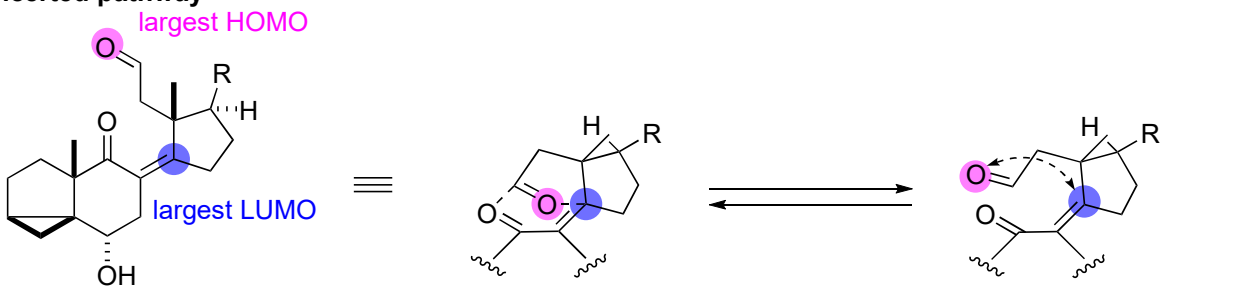
▪Possible side reaction[3)]



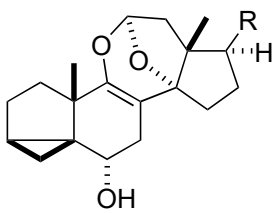
2-29 **2-31** **2-32**

steric repulsion is smaller than **2-21**

2. Concerted pathway



2-19 **2-19'** **2-19"**



2-20

The auther saids both pathway could be reasonable.
However, concerted pathway seemes to be more reasonable because geometrical isomerization of olefin could occur in the stepwise pathway.

Reference

1. Orito. K. et al. *Synthesis*. **1995**, 1273.
2. Zaytsev, V. P. et al. *Tetrahedron Lett*. **2019**, *60*, 151204.
3. Arseniyadis, S. et al. *Eur. J. Org. Chem.* **2005**, 683.