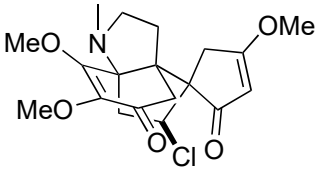
Problem Session (5) -Answer-

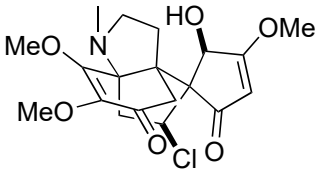
2023/08/05 Yuuki Watanabe

Topic: Synthetic study of acutuminine
Grunenfelder, D. C.; Navarro, R.; Wang, H.; Fastuca, N. J.; Butler, J. R.; Reisman, S. E.
Angew. Chem. Int. Ed. **2022**, *61*, e202117480.

0. Introduction
0-1. Outline of acutumine and acutuminine



0-1
(-)-acutuminine

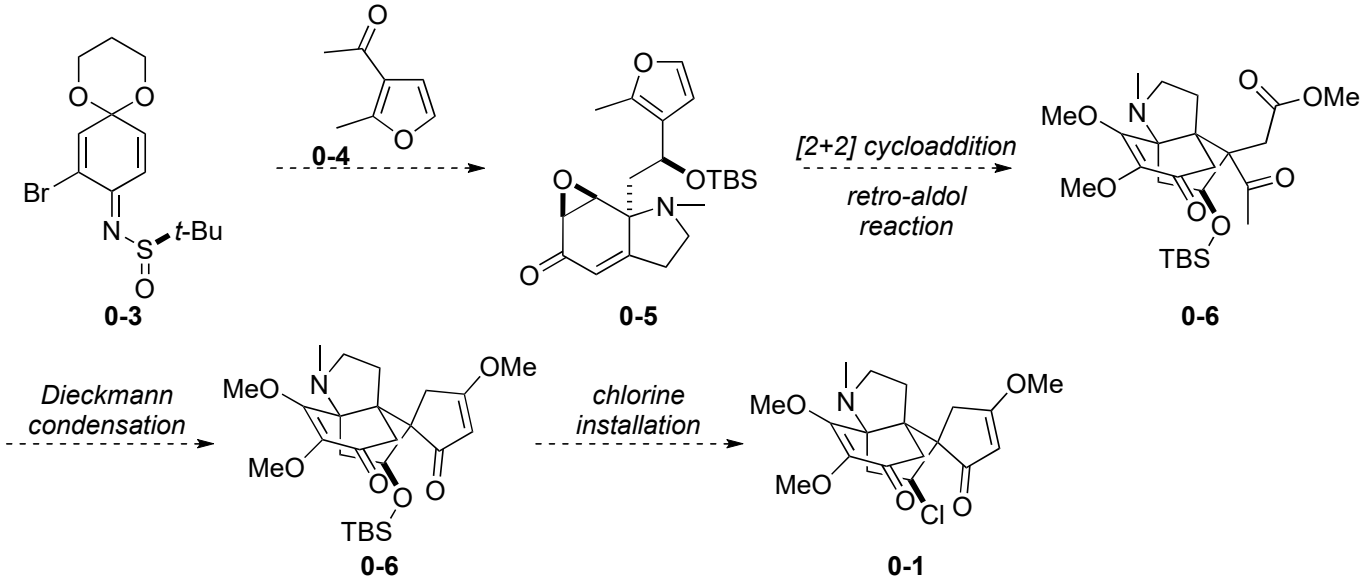


0-2
(-)-acutumine

Isolation:
medicinal herb Sinomenium acutum[1)]
Structural features:
[4.3.3]propellane cores
spirofused cyclopentenone
tertially amine
chlorine atom

0-2. Synthetic study
acutumine: Castle, J. *J. Am. Chem. Soc*. **2009**, *131*, 6674.
Herzon, S. B. *Angew. Chem. Int. Ed*. **2013**, *52*, 3642.
See 100106_LS_Yuuki_Amaoka, 151016_PS_Kotaro_Tokumoto

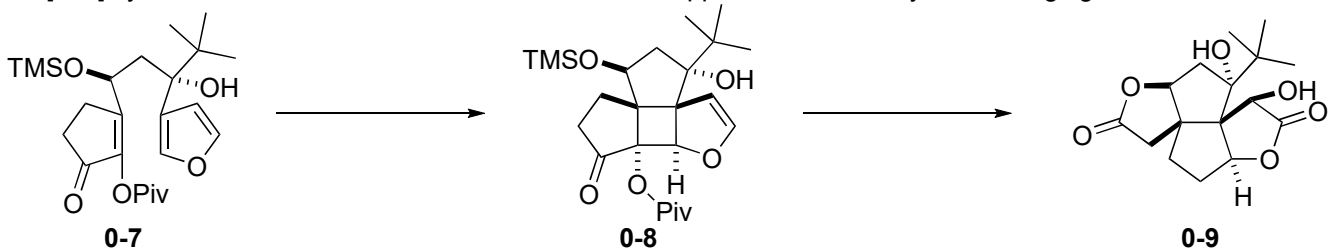
0-3. Reisman's initial synthetic approach



0-3 **0-5** **0-6** **0-6** **0-1**

For the model study of [2+2]-cycloaddition: Navarro, R.; Reisman, S. E. *Org. Lett*. **2012**, *14*, 4354.
See 181208_PS_Yusuke_Imamura

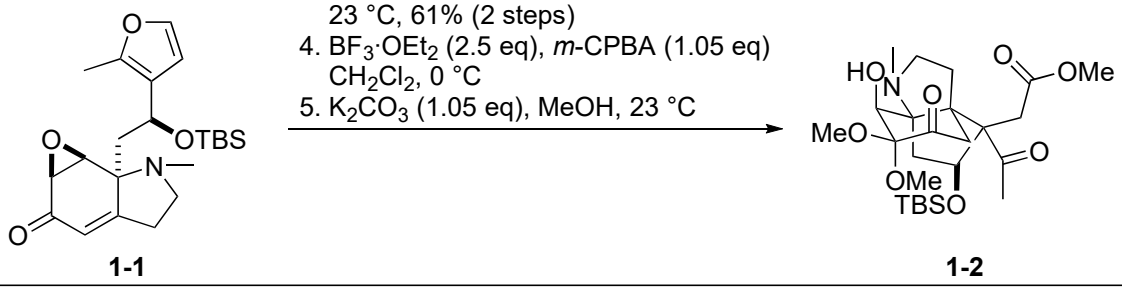
The [2+2] cyclization with the enone and the furan is also applied in the total synthesis of gingkolide B and bilobalide



0-7 **0-8** **0-9**
rac-bilobalide

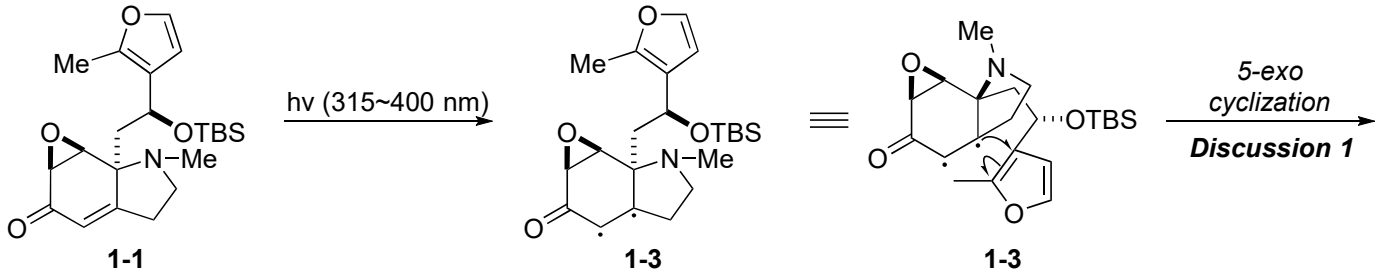
Bilobilide:
Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc*. **1993**, *115*, 3146. See 180901_PS_Masanori_Nagatomo.
Ginkgolide B:
Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S.
J. Am. Chem. Soc. **2000**, *122*, 8453. See 150206_LS_Kosuke_Minagawa, 221105_LS_Shintaro_Fukaya.

(1) Please provide the reaction mechanism and explain the stereoselectivity.

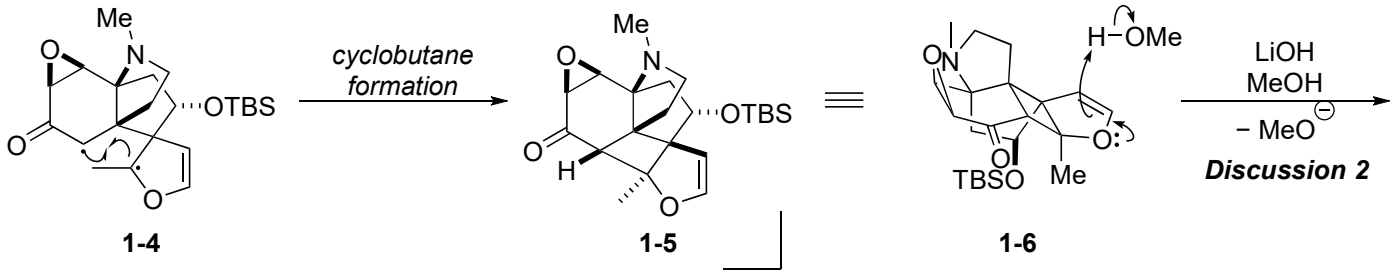


1-1 **1-2**

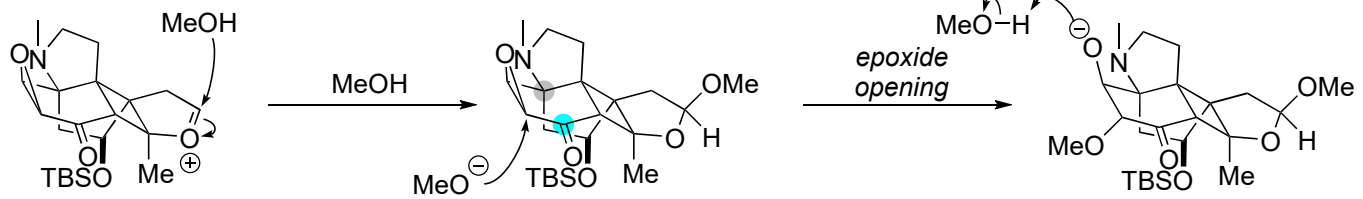
Answer:



1-1 **1-3** **1-3**



1-4 **1-5** **1-6**

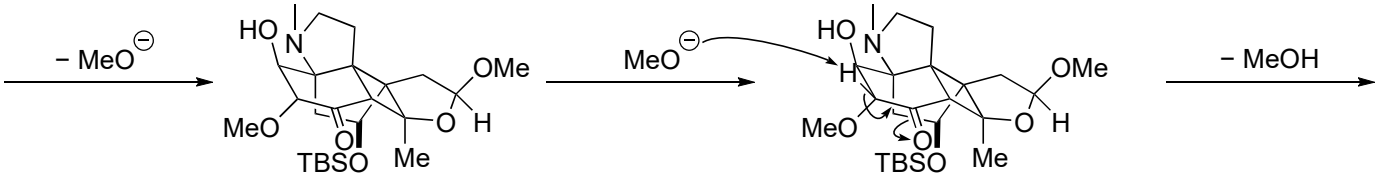


1-7 **1-8** **1-9**

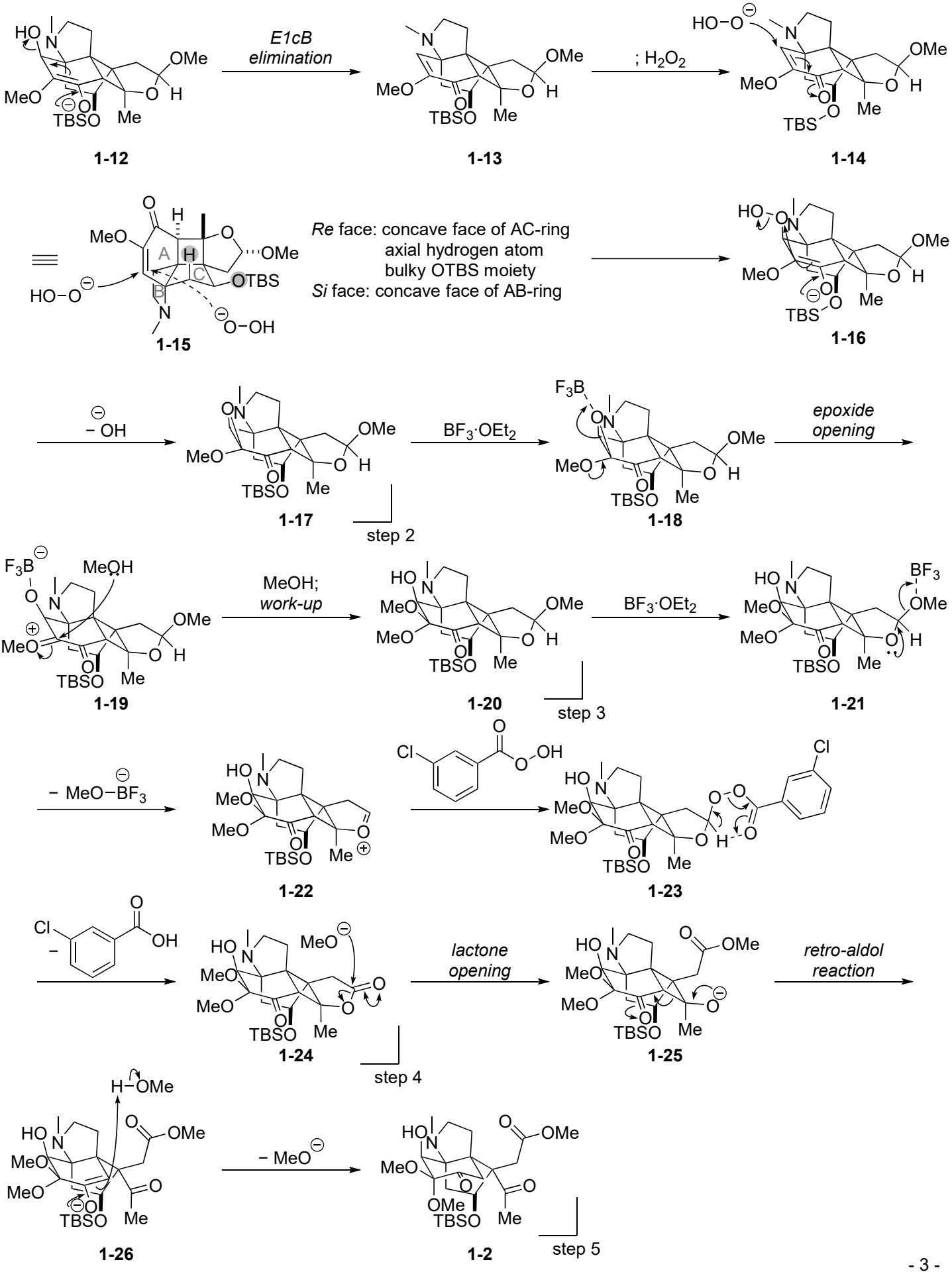
● : sp^2 carbon

● : sp^3 tetra-substituted carbon

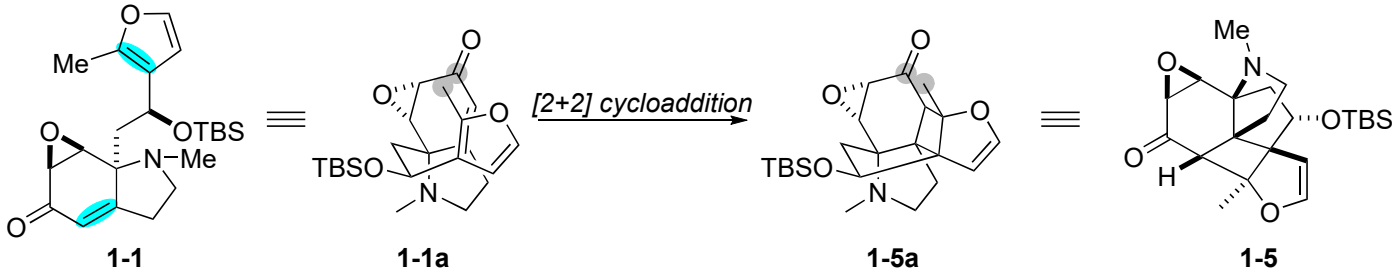
The authors indicated the obtained **1-17** was a single diastereomer. However, they didn't determine the stereochemistry. I thought the reaction would be thermodynamically controlled (LiOH (10 eq), MeOH, 70 °C).
MeO group would be oriented at the opposite side of sterically bulky TBSO group and the axial-oriented Me groups. Therefore, the stereochemistry was proposed as described from **1-9**.



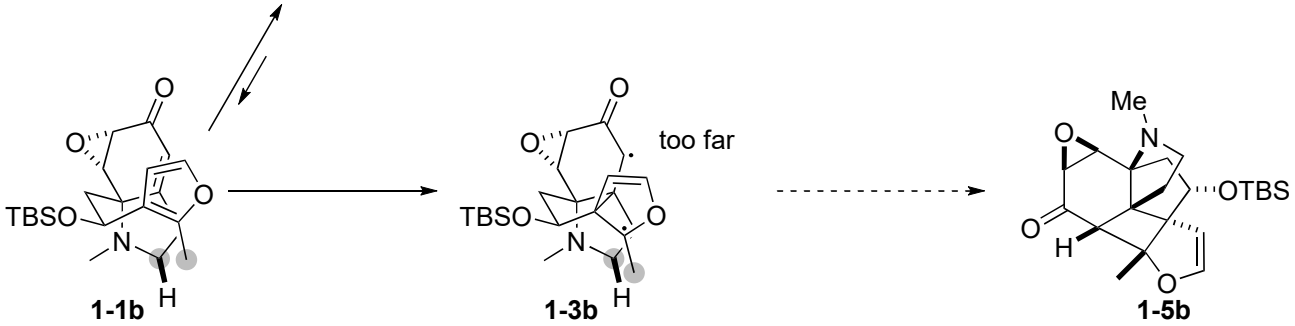
1-10 **1-11**


E1cB elimination
; H_2O_2
1-12
1-13
1-14
Re face: concave face of AC-ring
axial hydrogen atom
bulky OTBS moiety
Si face: concave face of AB-ring
1-15
1-16
$BF_3{\cdot}OEt_2$
epoxide opening
1-17
1-18
step 2
MeOH; work-up
1-19
1-20
1-21
step 3
1-22
1-23
lactone opening
retro-aldol reaction
1-24
1-25
step 4
1-26
1-2
step 5

Discussion 1: [2+2] cycloaddition

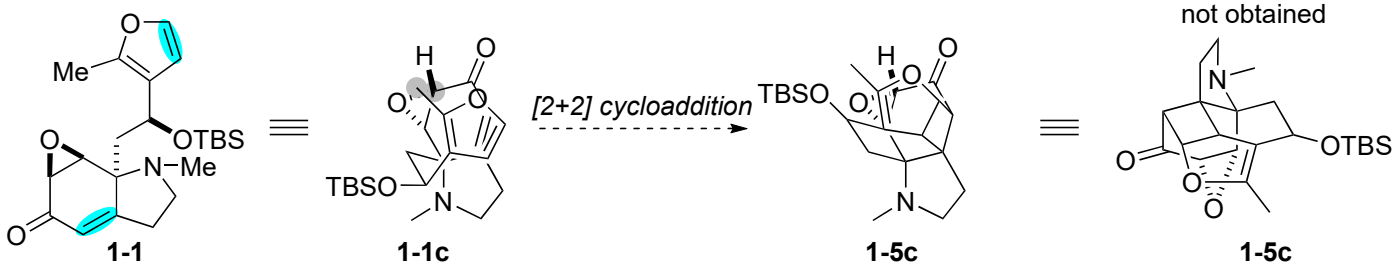


1-1 **1-1a** **1-5a** **1-5**



1-1b **1-3b** **1-5b**

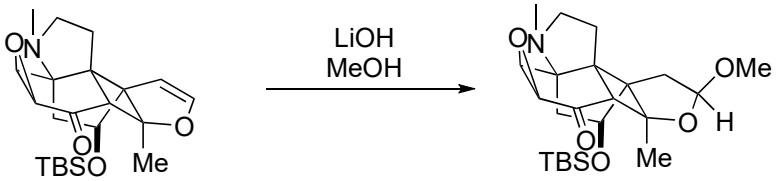
not obtained



1-1 **1-1c** **1-5c** **1-5c**

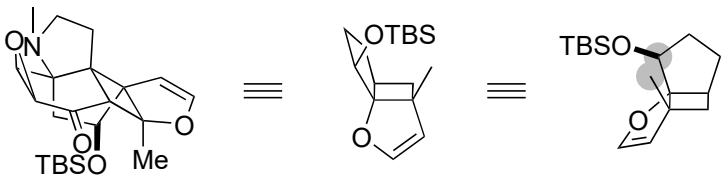
not obtained

Discussion 2: Acetal formation



1-6 **1-8**

The formation of acetal from vinyl ether proceeded even in the basic conditions probably due to the release of the strong ring strain of oxabicyclo[3.2.0]heptene.

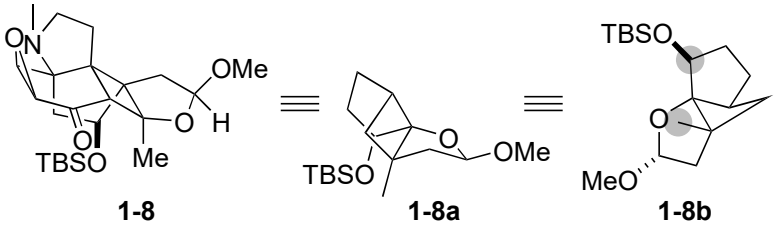


1-6 **1-6a** **1-6b**

eclipsed conformation
unsaturated ether ring: planar

6-membered ring/pyrrolidine ring are omitted for clarity.

Due to the vinyl ether moiety, all atoms in the ether ring are on the same plane.
As a result, the cyclobutane moiety also gets planner→strong steric repulsion

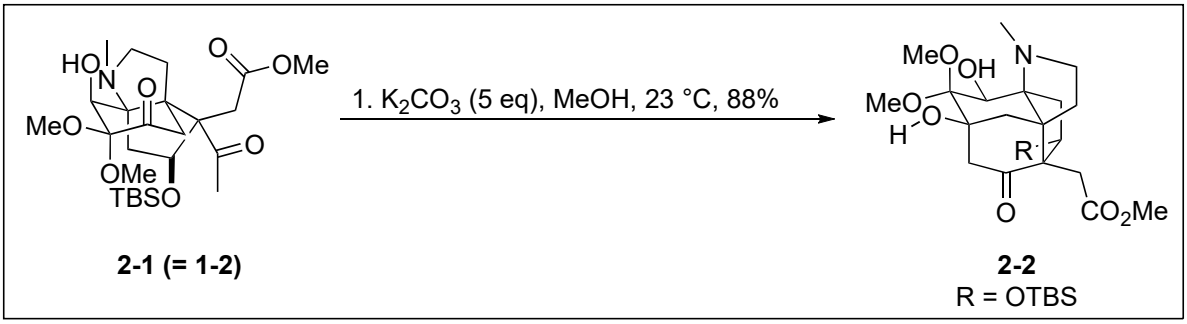


1-8 **1-8a** **1-8b**

gauche conformation
saturated ether ring: envelope

6-membered ring/pyrrolidine ring are omitted for clarity.

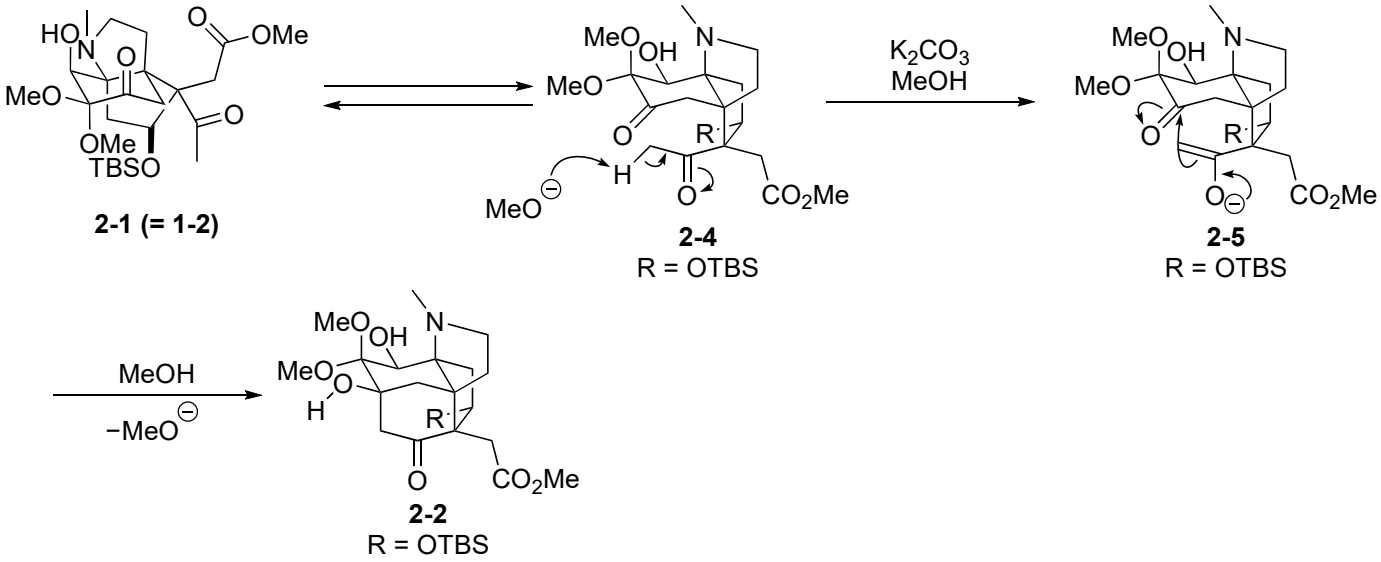
The saturated ether ring can form the envelope structure, which induces the puckered conformation of cyclobutane.
→relatively low steric repulsion.



2-1 (= 1-2)

2-2
R = OTBS

Answer:

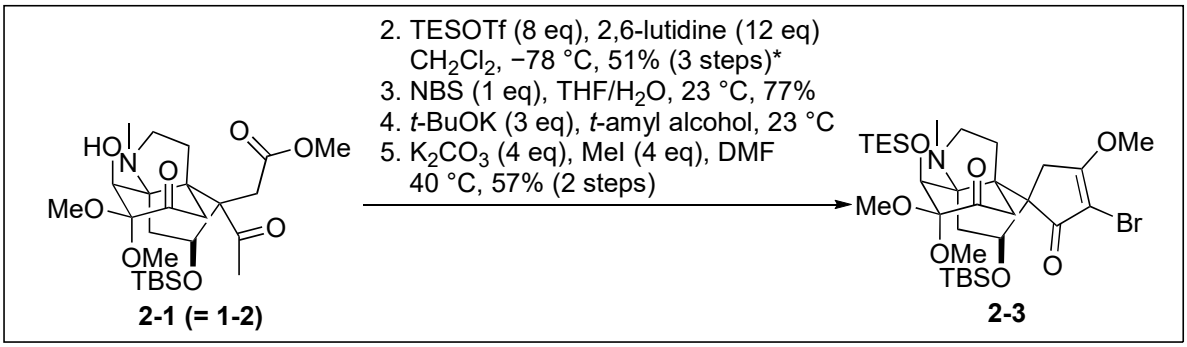


2-1 (= 1-2)

2-4
R = OTBS

2-5
R = OTBS

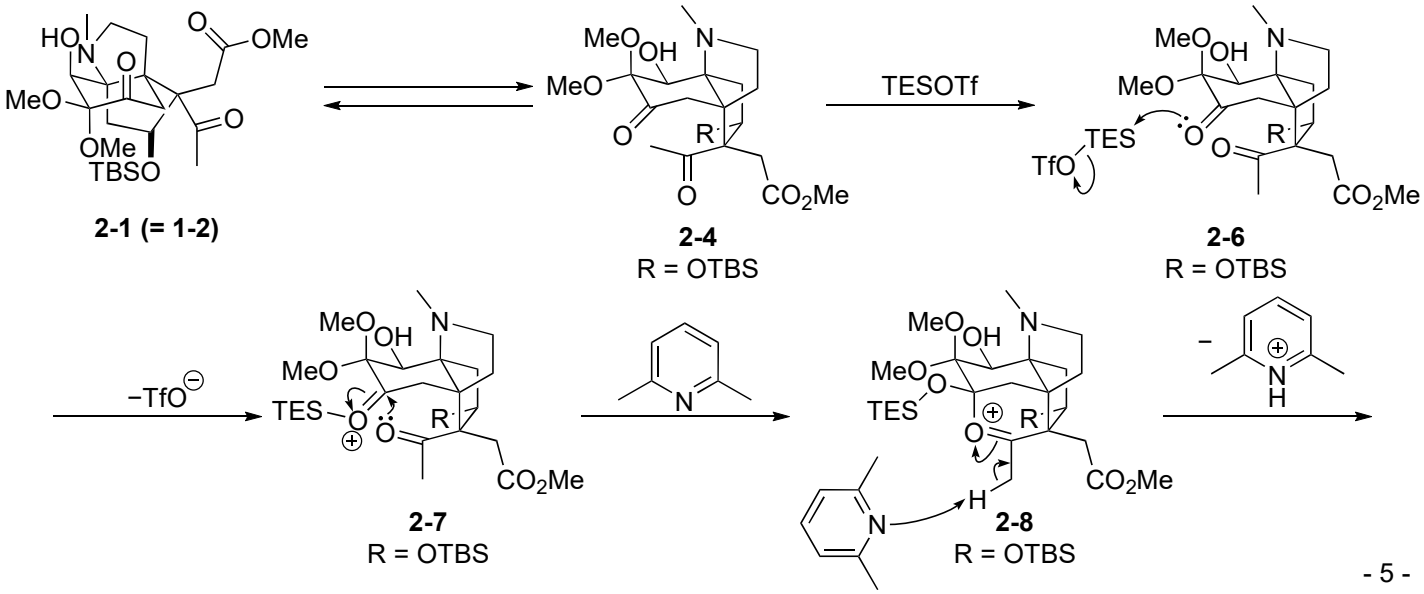
2-2
R = OTBS



2-1 (= 1-2)

2-3

Answer:



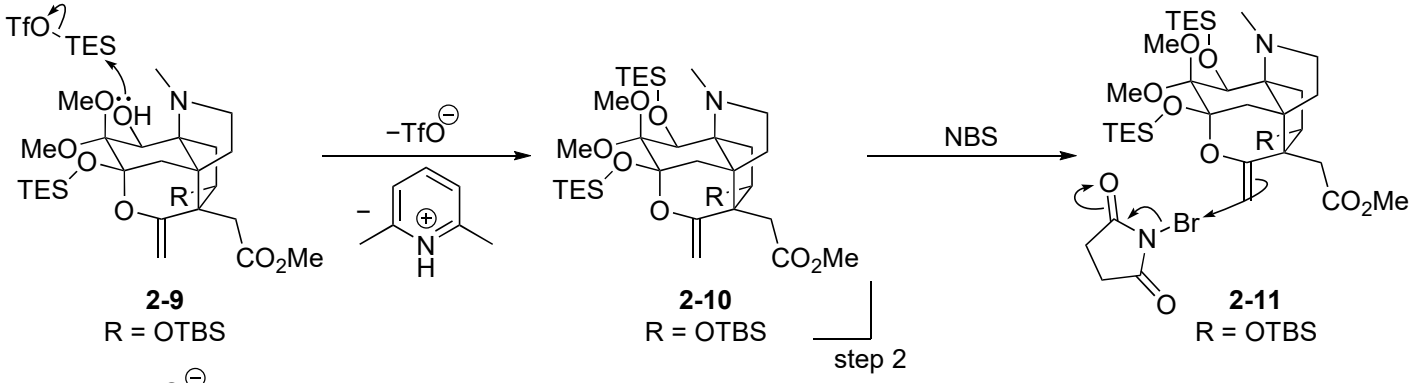
2-1 (= 1-2)

2-4
R = OTBS

2-6
R = OTBS

2-7
R = OTBS

2-8
R = OTBS



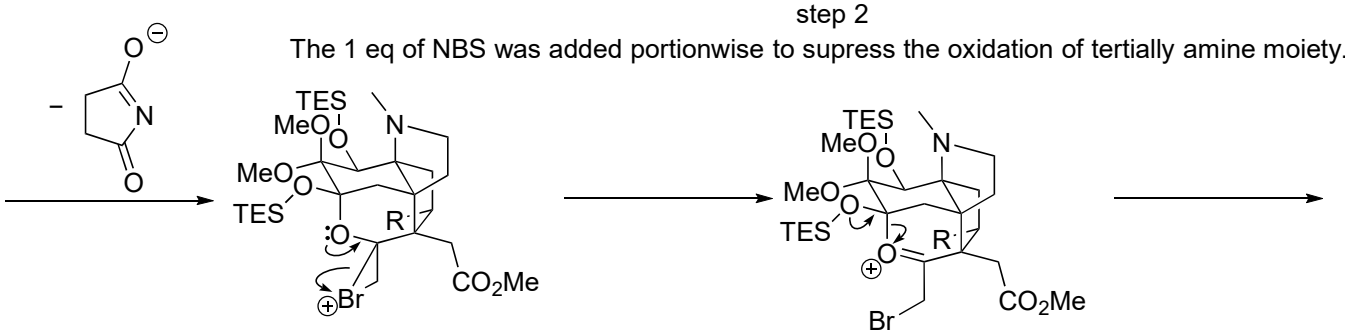
2-9
R = OTBS

2-10
R = OTBS

step 2

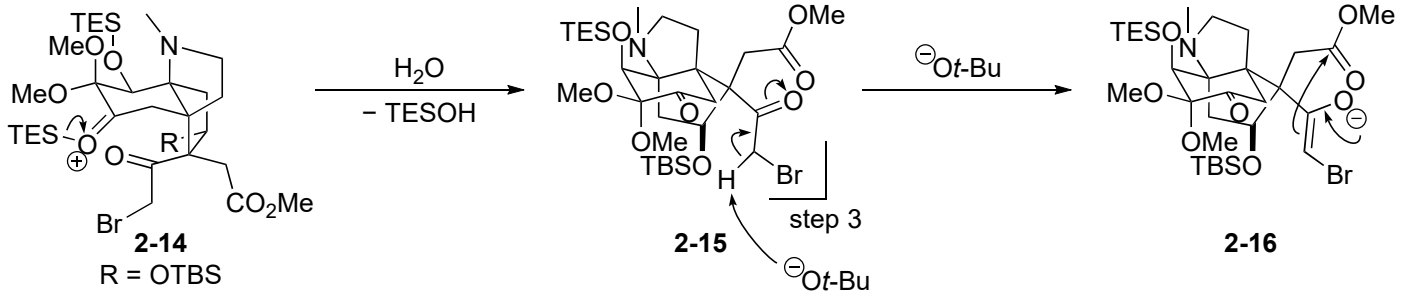
2-11
R = OTBS

The 1 eq of NBS was added portionwise to supress the oxidation of tertially amine moiety.



2-12
R = OTBS

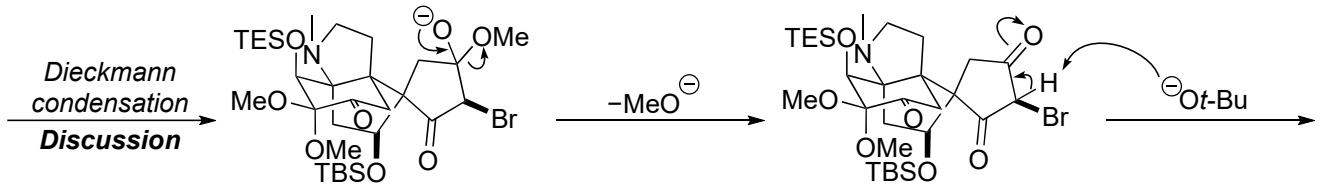
2-13
R = OTBS



2-14
R = OTBS

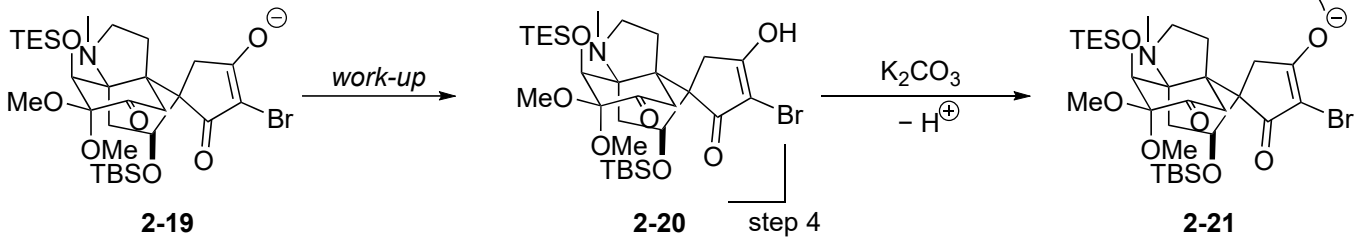
2-15

2-16



2-17

2-18

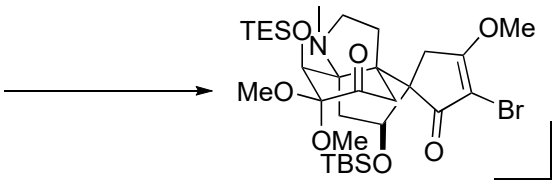


2-19

2-20

step 4

2-21

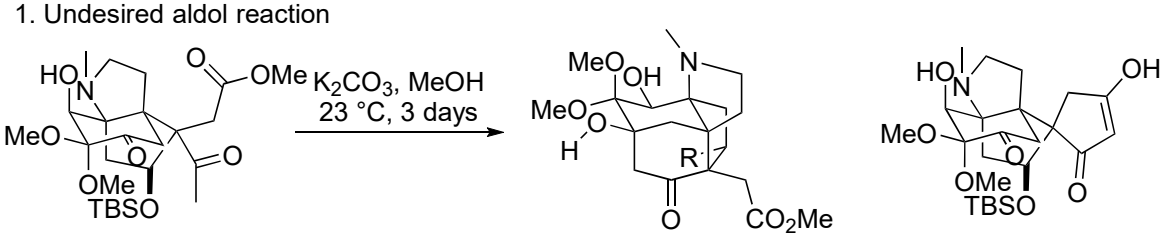


2-3

step 5

Discussion: Dieckmann condensation

1. Undesired aldol reaction

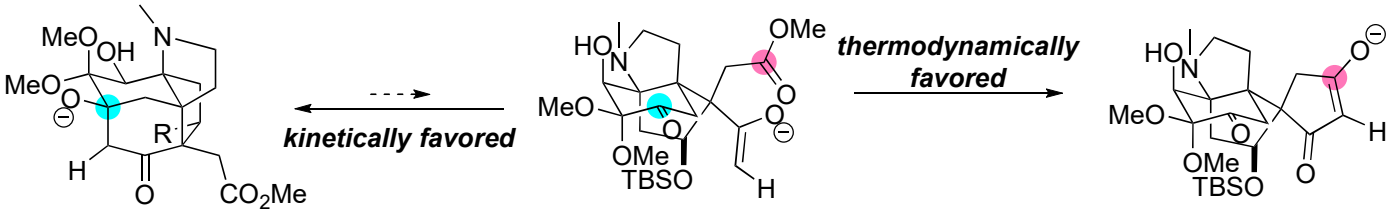


2-1 (= 1-2)

2-2 (undesired)
R = OTBS
88%

2-22 (desired)
R = OTBS
not obtained

The authors planned Dieckmann condensation from **2-1** to **2-22**.
However, the aldol product **2-2** was obtained even under the thermodyamic-control reaction conditions.



2-23
R = OTBS

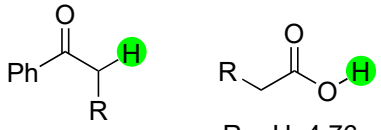
2-24

2-25

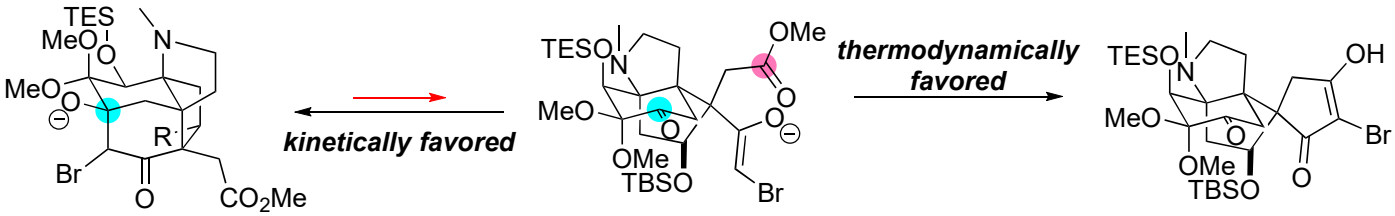
:α, α-bis-methoxy ketone
:ester

The enolate **2-24** will attack to the α-bis-methoxy ketone (the most electron deficient carbonyl group) kinetically.
If the aldol reaction is reversible, Dieckmann condensation (thermodyanically favored reaction) could occur.
In this case, the aldol product **2-23** may be too stable to proceed the retro-aldol reaction.

<The authors' detour>
The installation of halogen atom leads to lowering the pKa value.



The pKa value of highlighted hydrogen atom would be lowered by the bromine atom.
Therefore, the generated enolate **2-16** might be stable compared to enolate **2-24**.



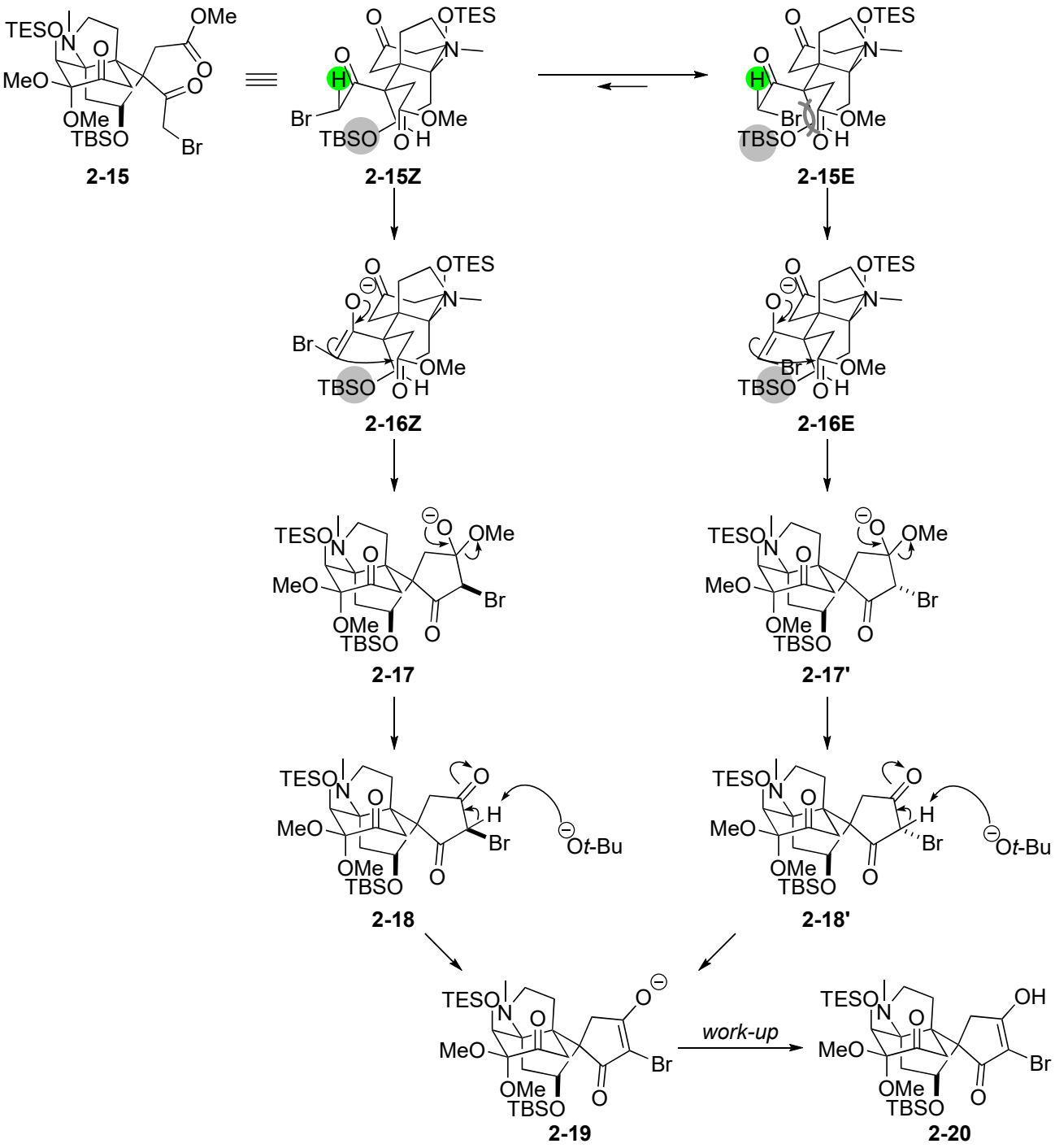
2-26
R = OTBS

2-16

2-20

Due to the lower energy of enolate **2-16** than **2-24**, the retro aldol reaction would become possible.
On the other hand, Dieckmann condensation from **2-16** to **2-20** is irreversible.
Therefore, the obtained **2-26** might be converted to **2-20** through **2-16**, and finally **2-20** was obtained selectively.

2. E/Z selectivity of enolate



The authors didn't mention the E/Z of enolate **2-16** and the stereoselectivity of Dieckmann condensation. These mechanism and the structures of the intermediates are my proposal.

Reference:

1. Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn*. **1929**, *4*, 220.
2. Okamoto, Y,; Yuge, E.; Nagai, Y.; Katsuta, R.; Kishimoto, A.; Kobayashi, Y.; Kikuchi, T.; Tomita, M. *Tetrahedron Lett*. **1969**, *10*, 1933.