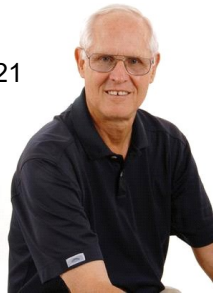
## Problem Session (4) -Answer

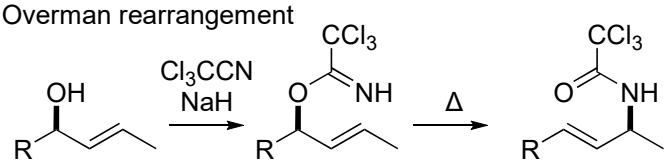
2024.4.13 Kyohei Oga

Topic: Prof. Larry E. Overman
1. https://doi.org/10.1021/ol902373m
2. https://doi.org/10.1021/jo00061a021



**Research Area**
1. Total sythesis of natural products
2. Invention of new reaction and strategies

Overman rearrangement

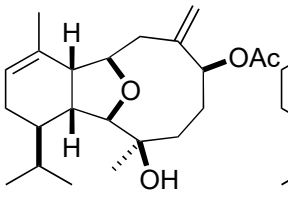


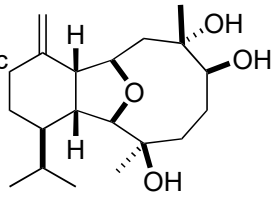

0. Introduction
0-1. Prof. Larry Overman

**Educatioin**

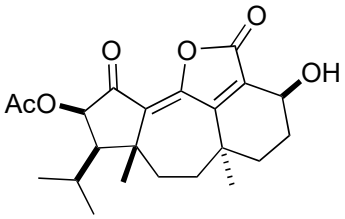
1965, B.S., Earlham College
1969, Ph.D., the University of Wisconsin (Prof. Howard W. Whitlock. Jr.)
1971, Post. Doct., Columbia University (Prof. Ronald, Breslow)
1971-2021, Professor, University of California, Irvine

0-2. Total synthesis of natural product (1971~2021)

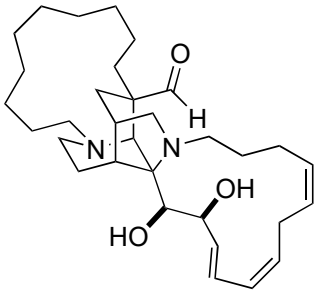


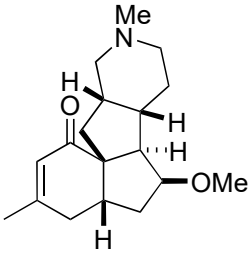

(-)-7-Deacetoxyalcyonin acetate
**MacMillan, D. W. C**; Overman, L. E.
*J. Am. Chem. Soc.* **1995**, *117*, 10391.
090224_PS_Koichi_Murai



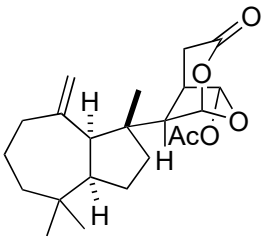

(+)-Guanacastepene N
Limura, S.; Overman, L. E.; Paulini, R.; **Zakarian, A.**
*J. Am. Chem. Soc.* **2006**, *128*, 13095.



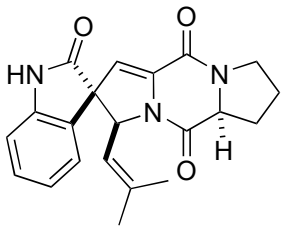

Sarain A
**Garg, N. K.**; Hiebert, S.; Overman, L. E.
*Angew. Chem. Int. Ed.* **2006**, *45*, 2912.



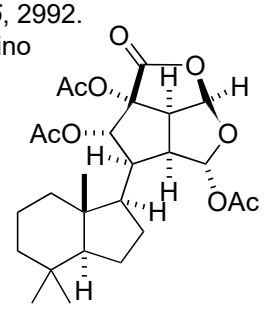

Magellanine
Hirst, G. C; Johnson, T. O. Overman, L. E.
*J. Am. Chem. Soc.* **1993**, *115*, 2992.
131102_PS_Haruka_Fujino



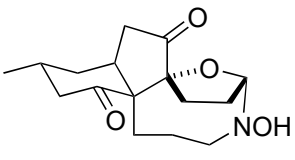

Aplyviolene
Shnermann, M. J; Overman, L. E.
*J. Am. Chem. Soc.* **2011**, *133*, 16425.
131221_LS_Hiroaki_Matoba



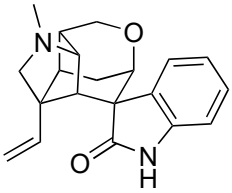

Spirotryprostatin B
Overman, L. E.; Rosen, M. D.
*Angew. Chem. Int. Ed.* **2000**, *39*, 4596.
170210_PS_Yuki_Fujimoto




Chromodorolide B
Tao, D. J.; Yuriy, S.; Overman, L. E.
*J. Am. Chem. Soc.* **2016**, *138*, 2186.
202003_PS_Keshu_Zhang

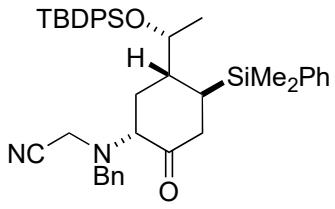



(+)-Sieboldine A
Canham, S. M.; France, D. J.; Overman, L. E.
*J. Am. Chem. Soc.* **2010**, *132*, 7876.
101111_PS_Taro_Asaba



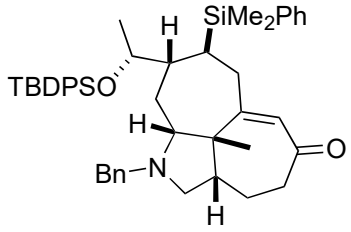

Gelsemine
Madin, A.; O'Donnell, C. J.; Oh, T.; Oldd, D. W.; Overman, L. E.
*Angew. Chem. Int. Ed.* **1999**, *38*, 2934.
160227_LS_Yuki_Fujimoto

1.



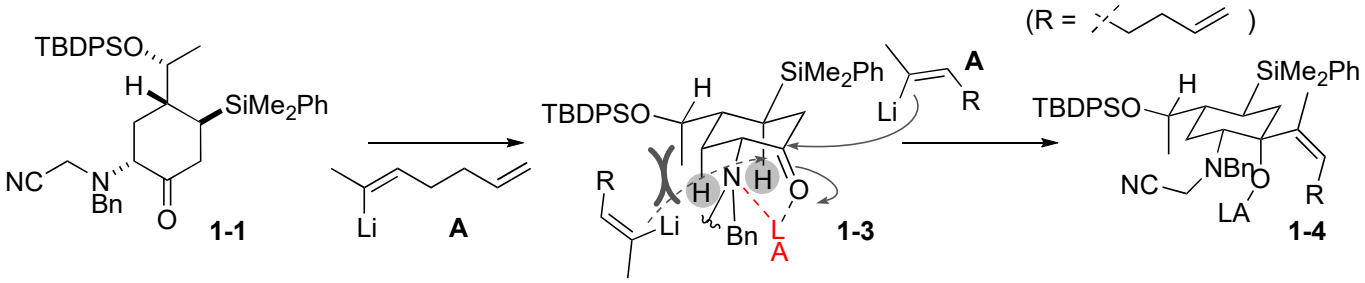

**1-1**

1. **A** (est.1.4 eq)
   $CeCl_3$ (1.5 eq), LiCl (3.0 eq)
   THF, −78 ºC, 73%
2. $AgNO_3$ (1.2 eq), EtOH, rt, 89%
3. **B** (10.5 eq)
   $CeCl_3$ (10 eq), LiCl (20 eq)
   THF, −78 ºC, 72%
4. Grubbs 2nd (5 mol%)
   $CH_2Cl_2$, 40 ºC, 96%
5. $SOCl_2$ (2.0 eq), pyridine (2.5 eq)
   THF, −40 ºC;
   $Al_2O_3/H_2O$/THF (1/1/2, excess), −40 ºC to rt, 66%
6. Dess-Martin periodinane (1.05 eq)
   pyridine (2.5 eq), $CH_2Cl_2$, rt, 68%



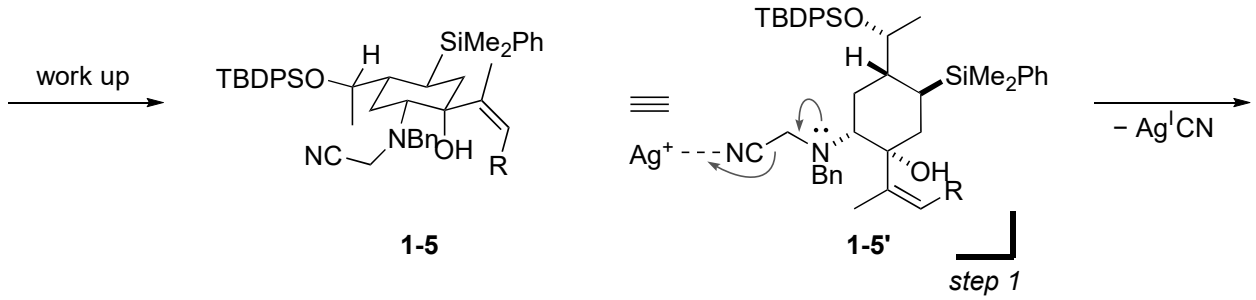

**1-2**

Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**. *11*, 5658.

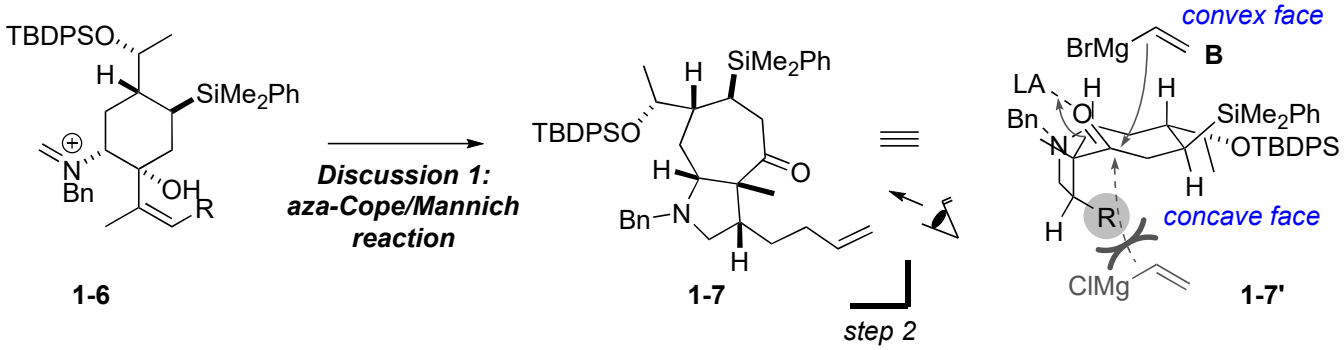


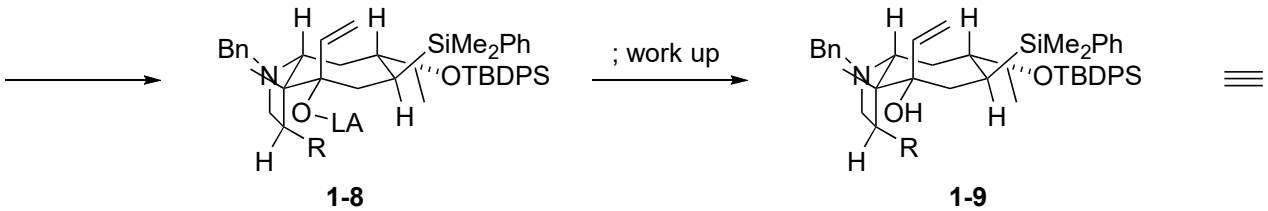

$CeCl_3$ + 2 LiCl ⟶ $CeCl_3 \cdot 2LiCl$

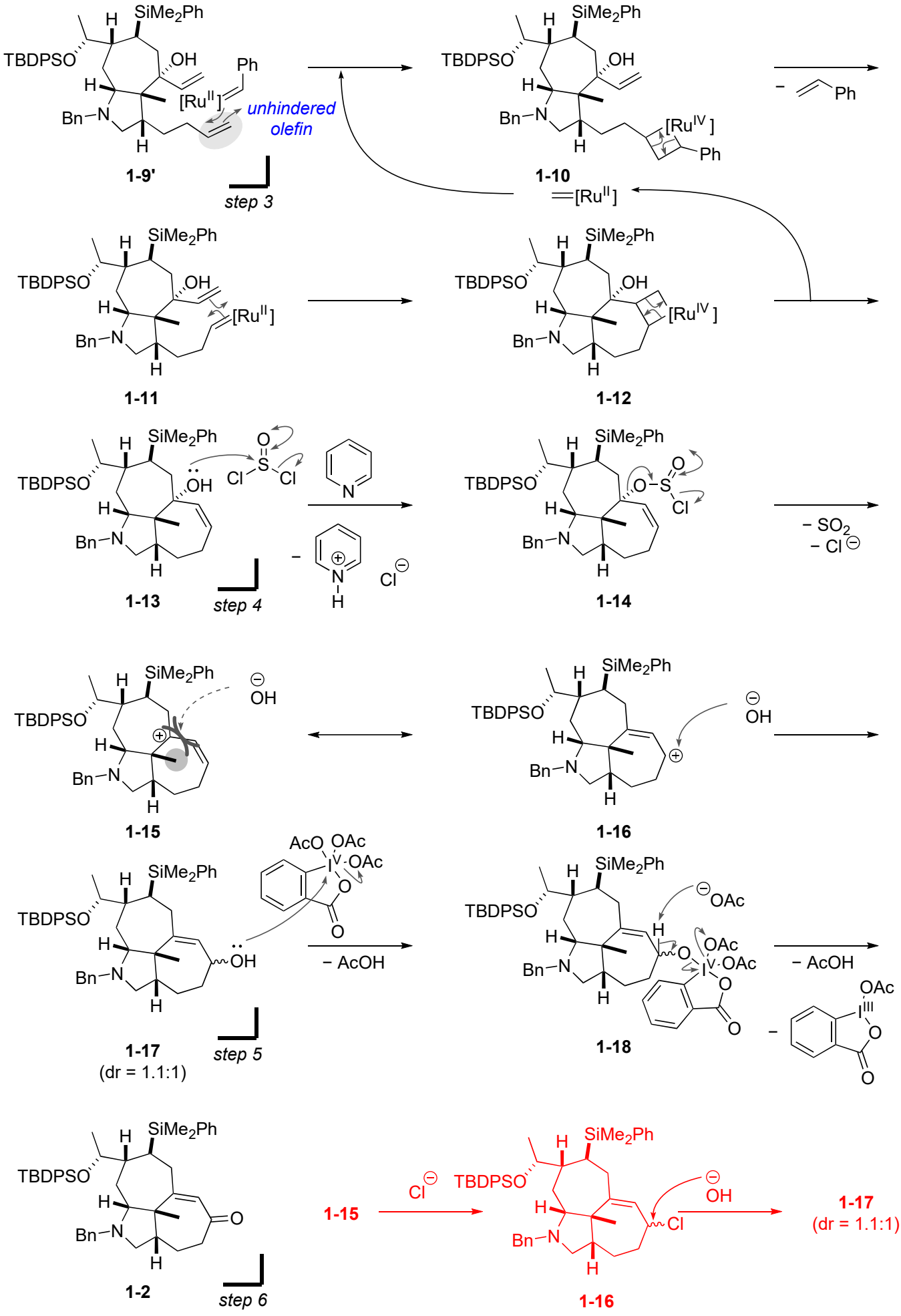
Knochel, P. *et al. Angew. Chem. Int. Ed*. **2006**, *45*, 497.




Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc*. **1979**, *101*, 1310.

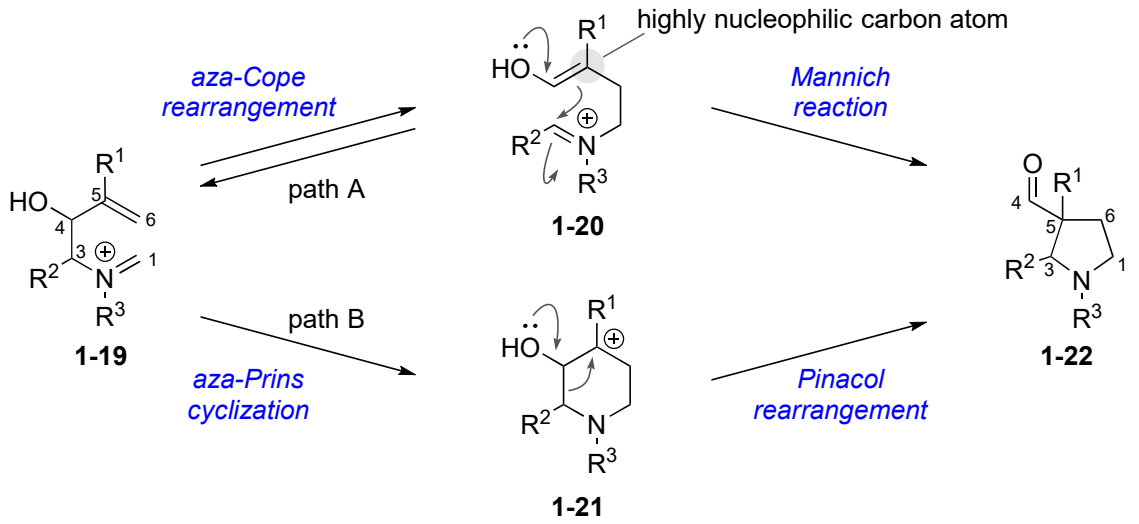



SiMe2Ph
TBDPSO
OH
Ph
[RuII]
Bn–N
unhindered olefin
1-9'
step 3
[RuIV]
1-10
– Ph
=[RuII]
1-11
1-12
Cl
S
O
Cl
N
1-13
step 4
– Cl
1-14
– SO2
– Cl
1-15
1-16
AcO
OAc
I
1-17
(dr = 1.1:1)
step 5
– AcOH
1-18
1-2
step 6
1-15
1-16
1-17
(dr = 1.1:1)

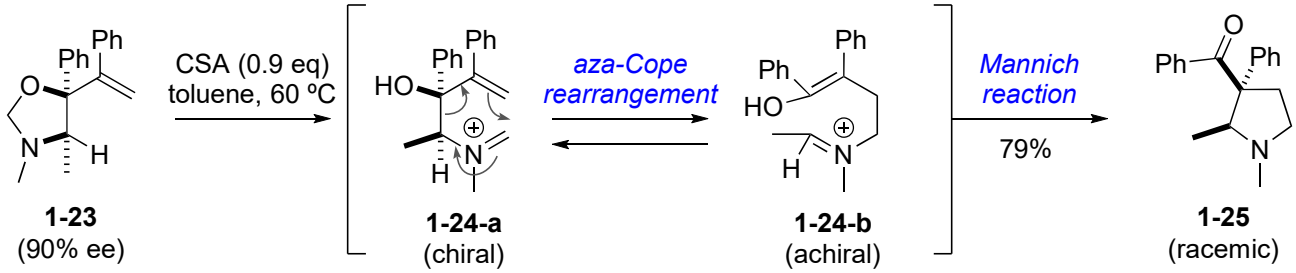
***Discussion 1:*** aza-Cope rearrangement and Mannich reaction

1. Introductioin of aza-Cope/Mannich reaction



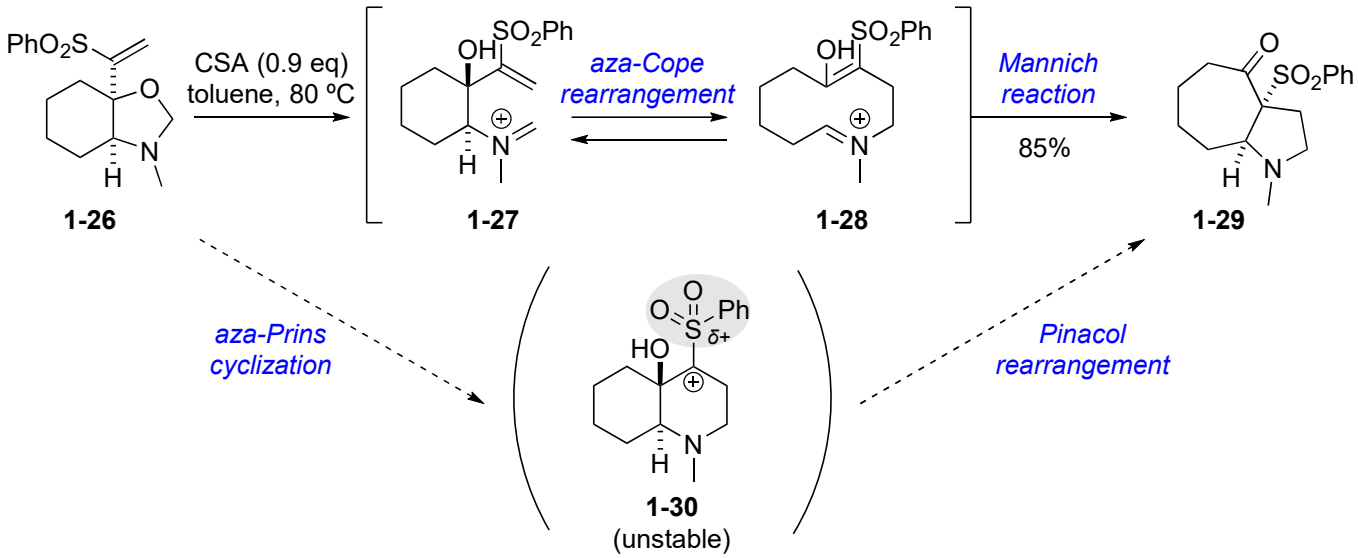

2. Mechanistic study

2-1. Investigation of the fate of a chirality



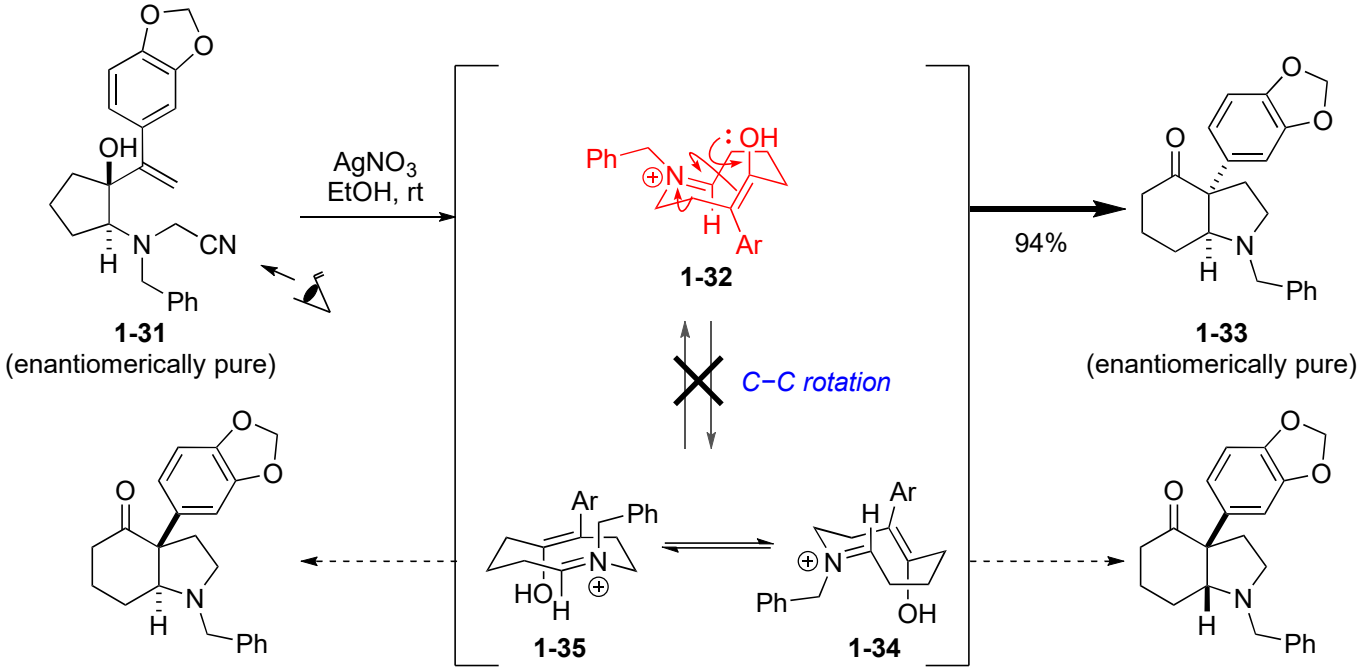

Aza-Cope rearrangement step produces lacking stereogenic center intermediate **1-24**.

2-2. Additional evidence for aza-Cope/Mannich reaction




In this case, **1-26** olefin with sulfone, a highly strong electron-withdrawing group, are electron-deficient. Furthermore, the positive charge of **1-30** produced by cyclization is considered to be highly unstable.

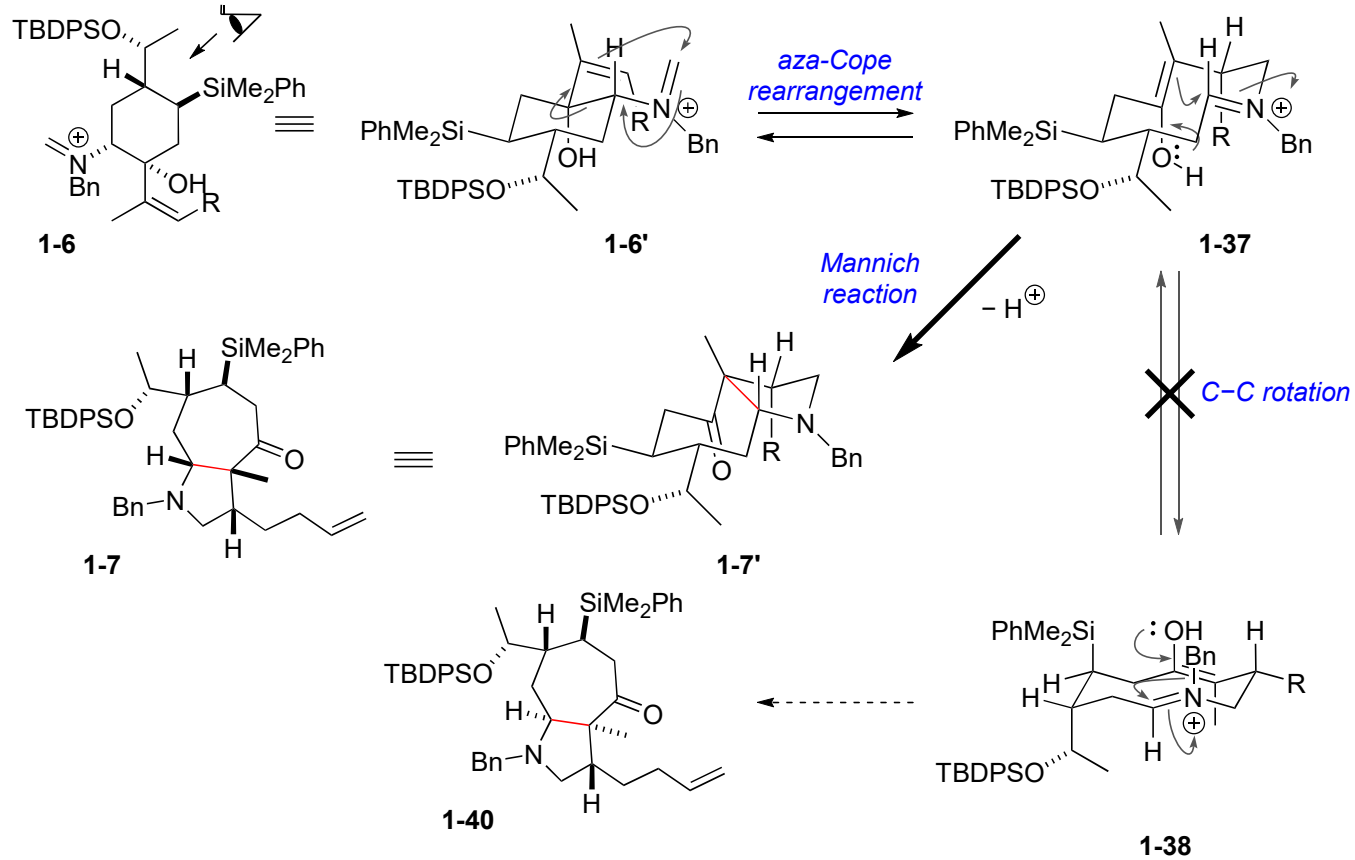
2-3. Retention of enantiomeric purity

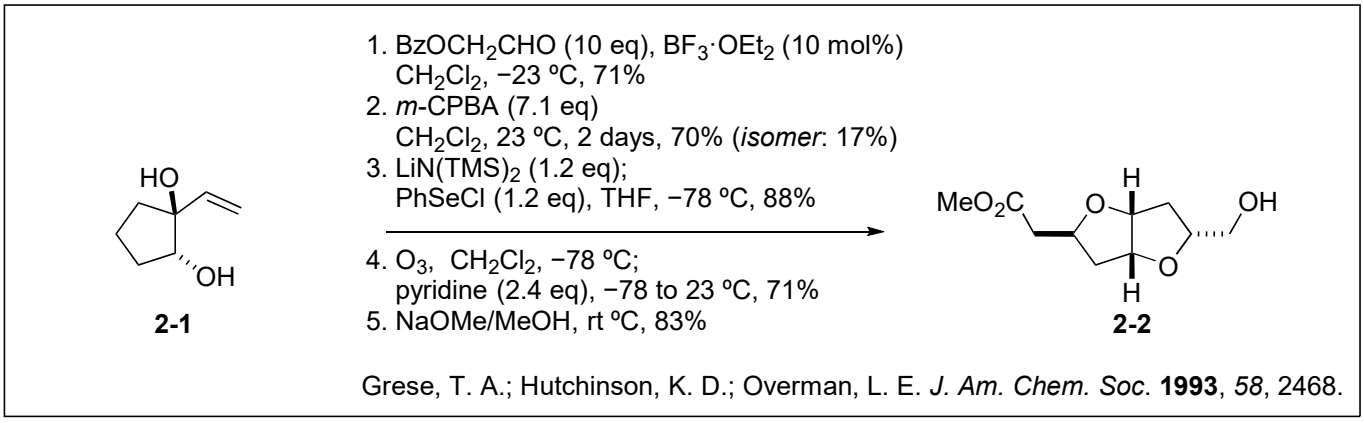



In this case, racemization of the likely intermediate in this sequence, **1-32**, is retarded by the conformational constraints of the medium-size ring due to high energy of C-C rotation.

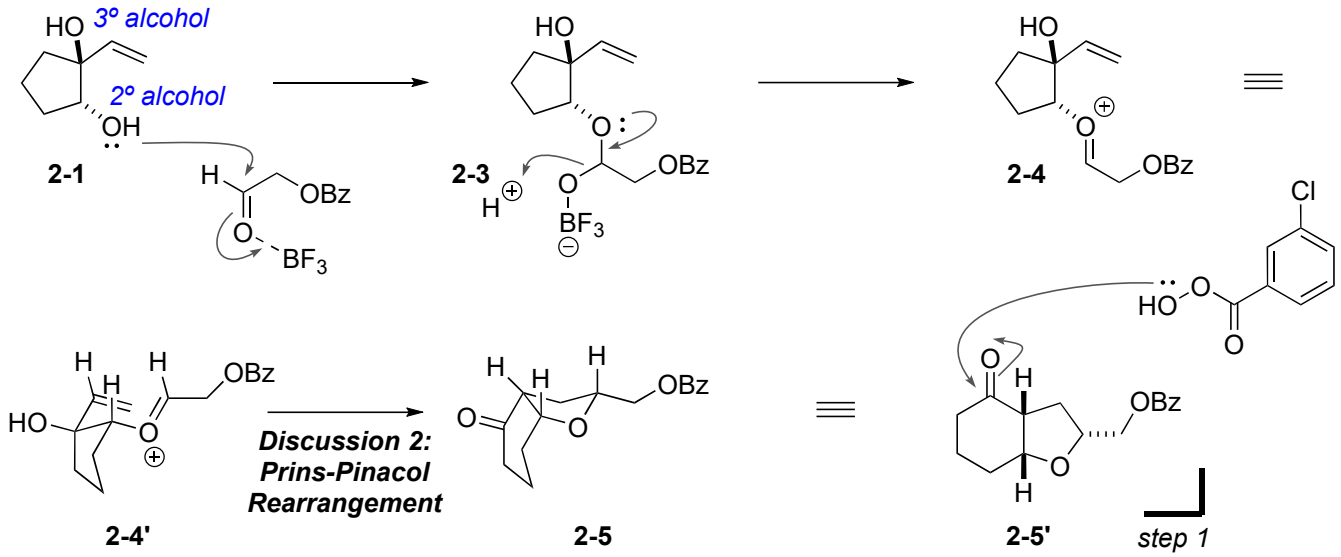
Jacobsen, E. J.; Jeremy, L.; Overman, L. E. *J. Am. Chem. Soc*. **1988**, *110*, 4329.

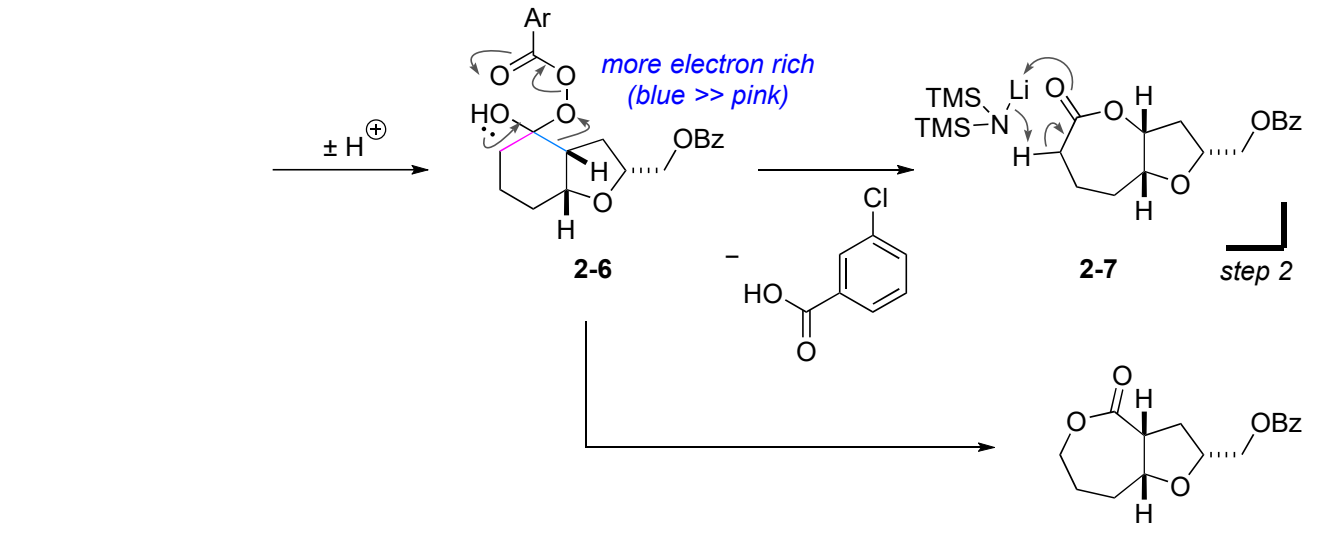
3. Proposed mechanism

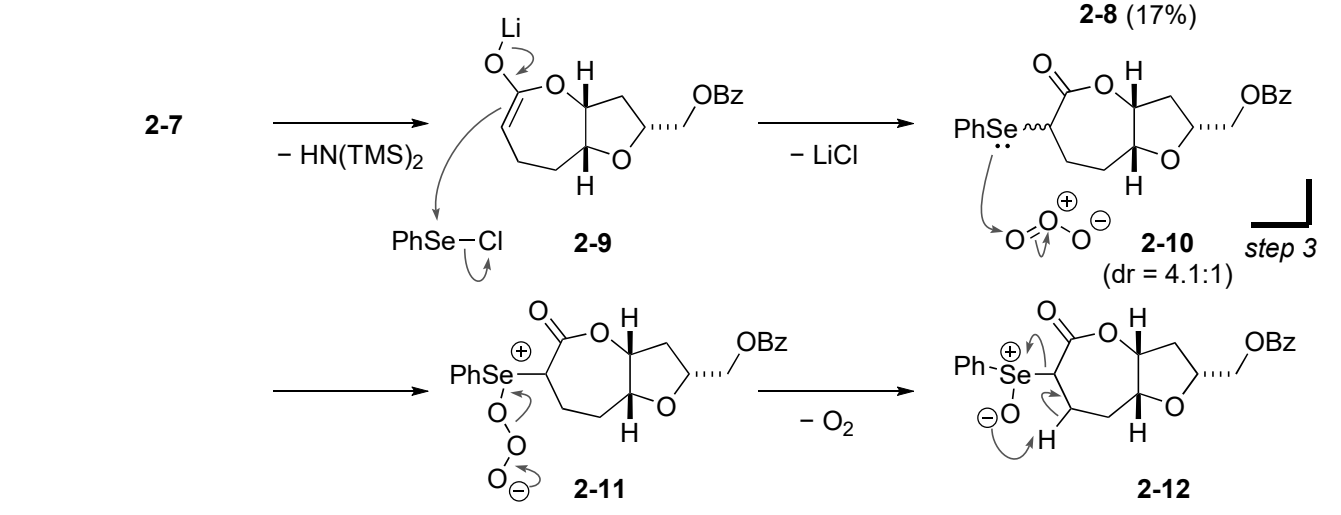


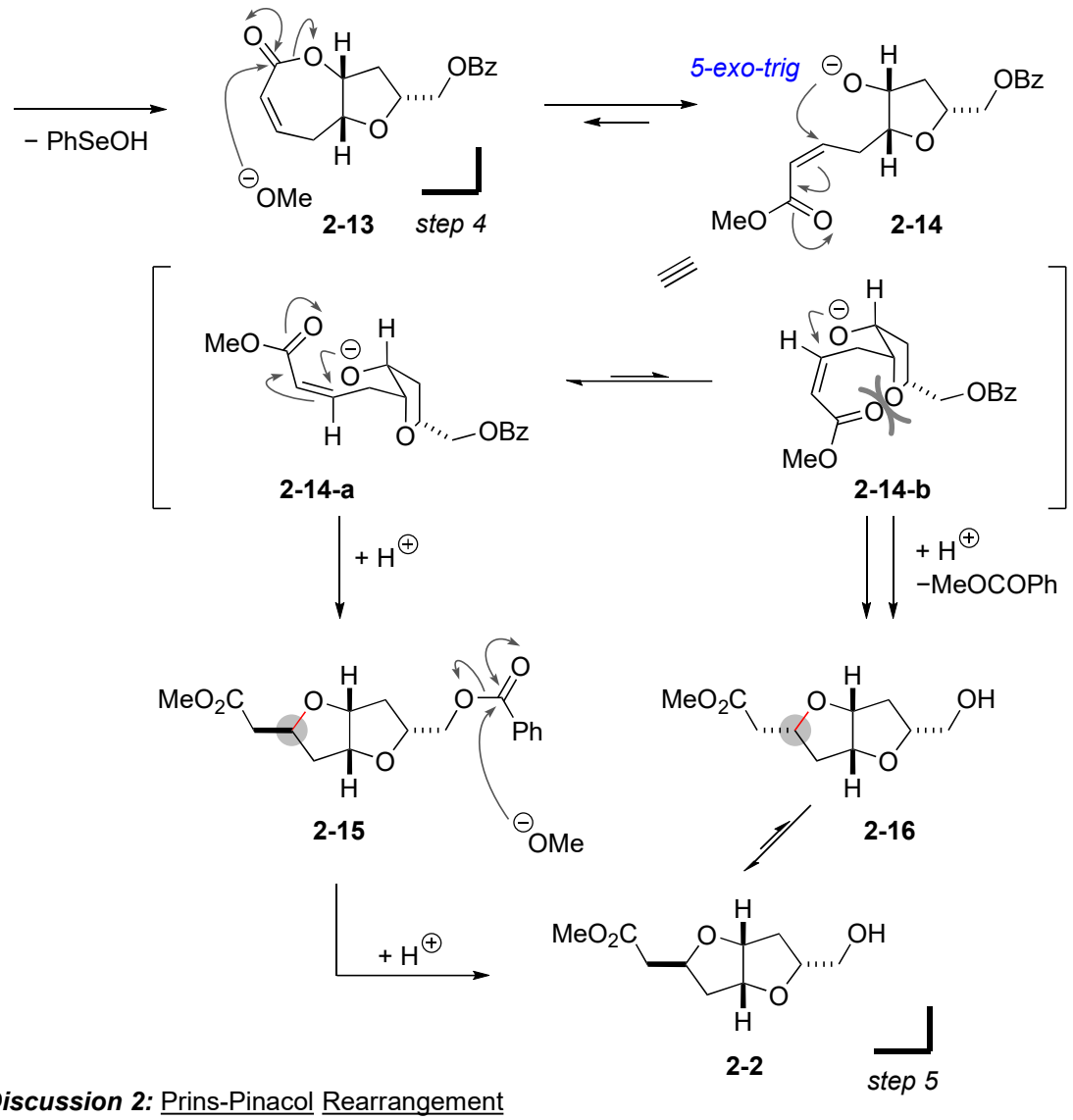



Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *58*, 2468.



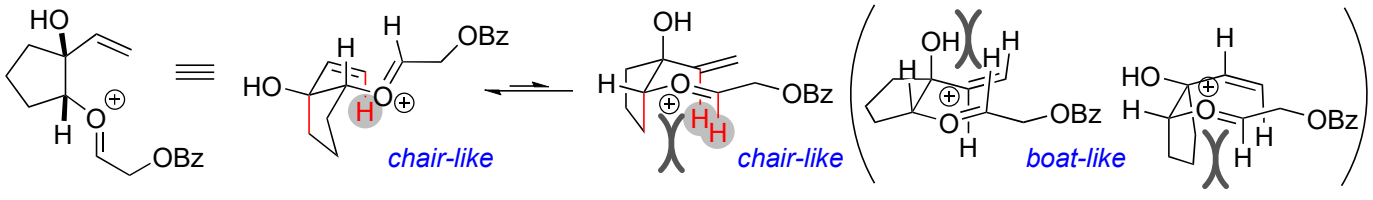



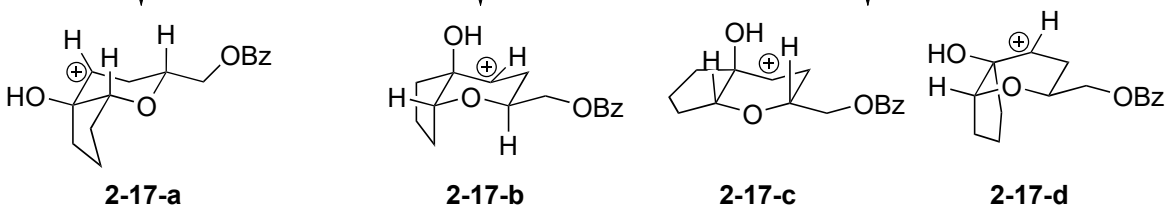



***Discussion 2:*** Prins-Pinacol Rearrangement

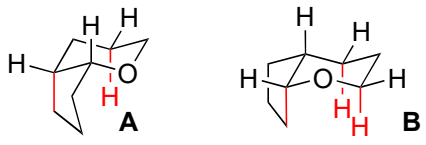
1. Mechanism of Prins Cyclization




(small $A^{1,3}$ allylic interaction) large $A^{1,3}$ allylic interaction)




The lowest energy comformations of cis-2-oxabicyclo[4.2.0]nonane calculated by molecular mechanics calculation

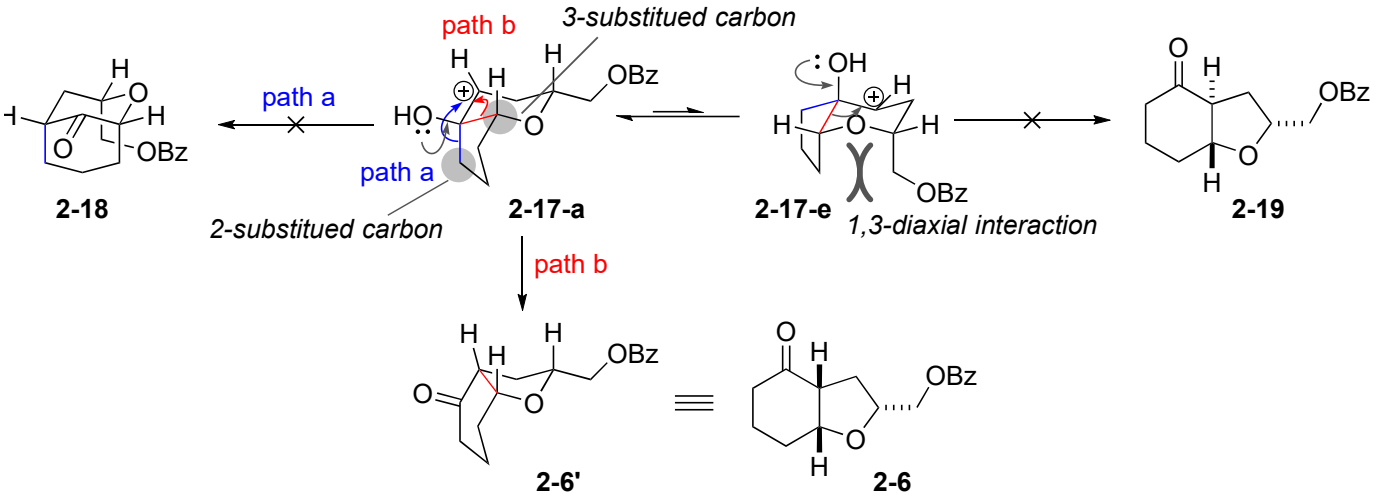



20.0 kcal/mol 22.6 kcal/mol

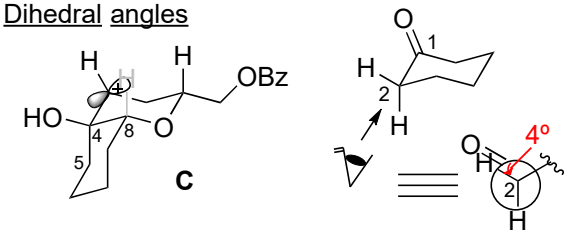
These energy differences are reasonable since two 1,3-diaxial interactions are removed when oxygen atom occupies an axial orientation on the cyclohexane ring.

Overman, L. E. *et al. J. Am. Chem. Soc.* **1991**, *113*, 5365.

## 2. Mechanism of Pinacol Rearrangement




Dihedral angles

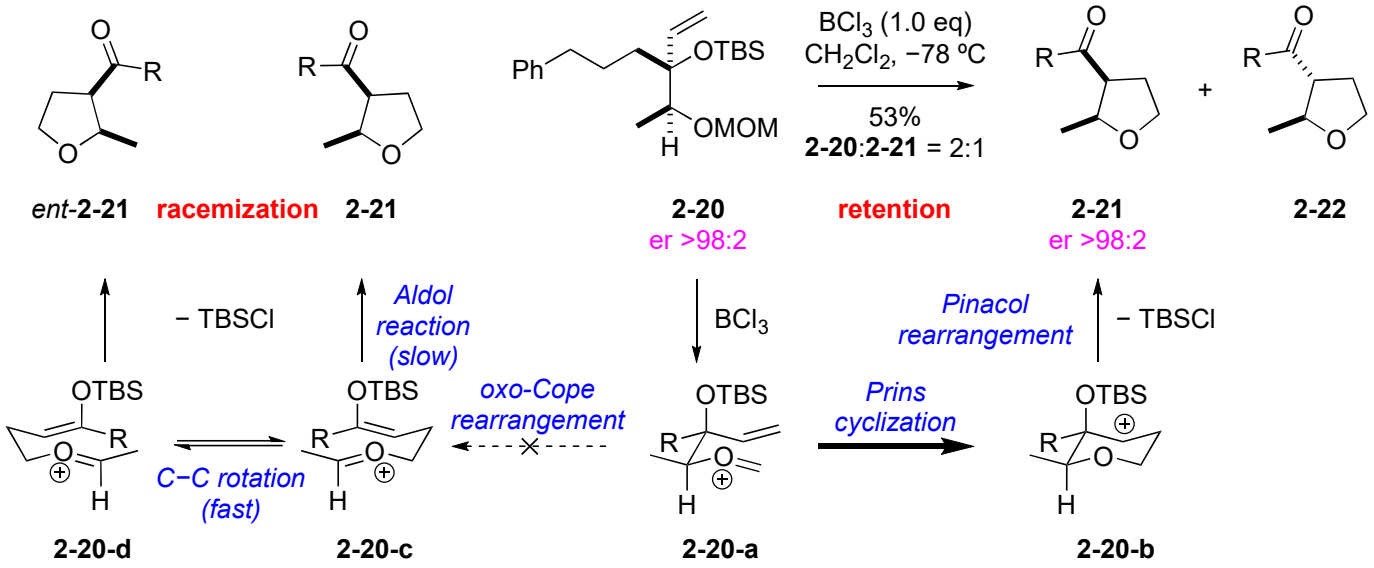



> The C(4)−C(5) and C(4)−C(8) σ bond have similar overlap with the vacant p orbital of carbenium ion **C**.

> The dihedral angle between C=O and $C_2$−H (eq) is 4° in cyclohexanone.

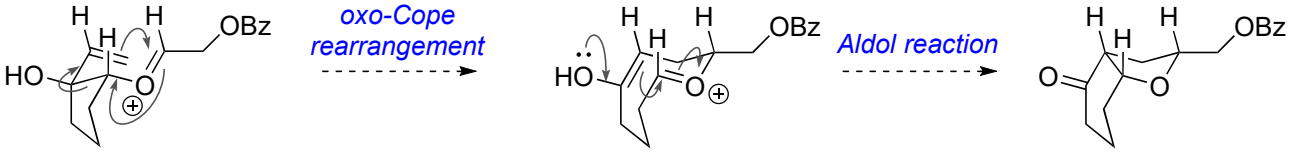
Overman, L. E. *et al. J. Am. Chem. Soc.* **1991**, *113*, 5365.
Woodward, R. B. et al. *J. Am. Chem. Soc.* **1961**, *83*, 4013.

## 3. Other possible mechanism ([3,3]-rearrangement and aldol-type cyclization)




> a [3,3]-sigmatropic rearrangement-aldol process would yield racemic products if the rearranged oxonium ion (**2-20-c, 2-20-d**) contained no stereogenic centers.
> The barrier for aldol cyclization was higher than that of C−C singe bond rotation.

Overman, L. E. *et al. Tetrahedron Lett.* **2000**, *41*, 9431.




>These transformations more likely proceeds by Prins-Pinacol rearrangement than [3,3] rearrangement and aldol reaction.