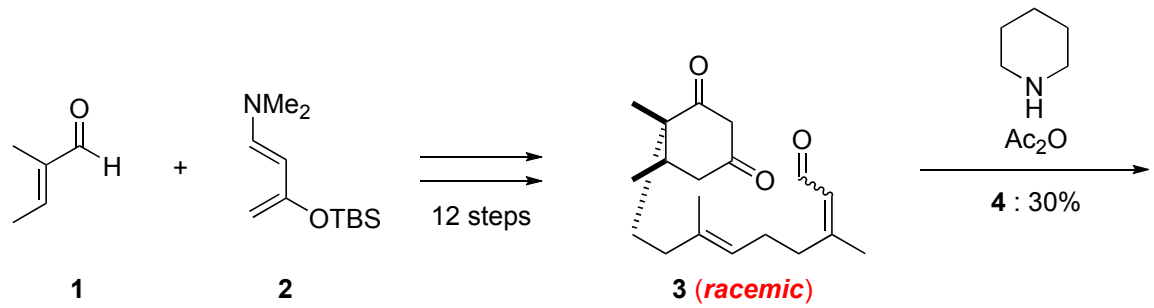
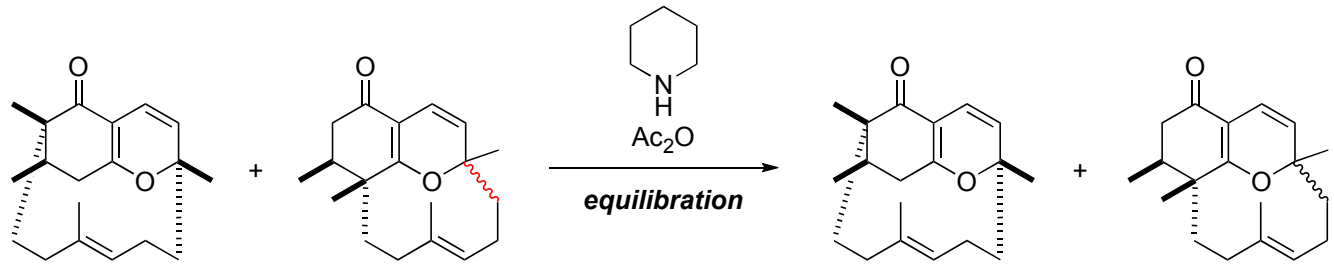
Problem Session (2)

2015.5.16 Akinori Yamaguchi

(1) Please provide the reaction mechanism of **3** to **4,5**. You ***do not*** have to explain the ratios of **4** to **5**.



1 **2** **3** (***racemic***)



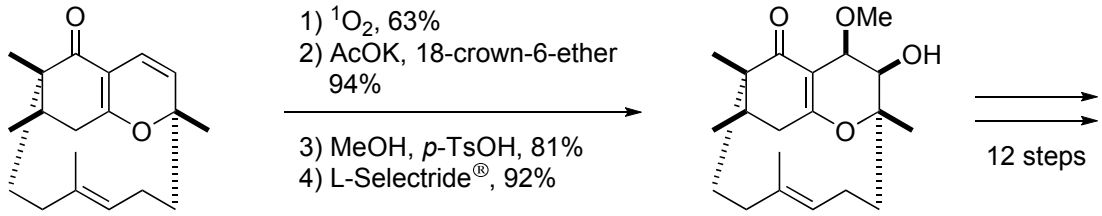
4 (desired) **5**

4 : 5 = 1 : 1
kinetic

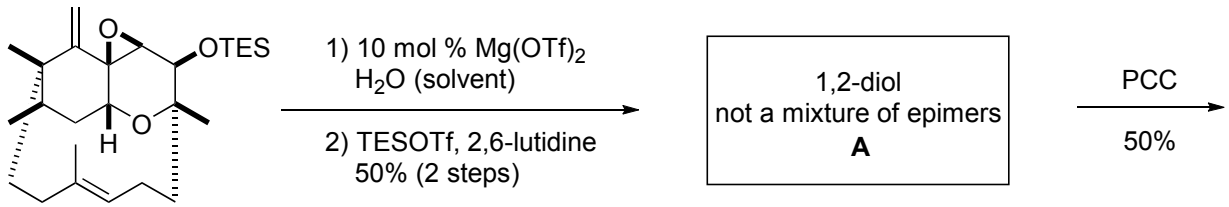
4 **5**

4 : 5 = 1 : 2.2
thermodynamic

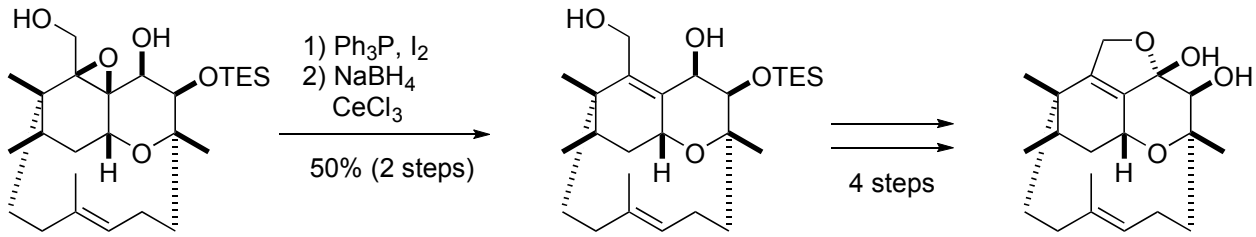
(2) Please explain the selectivity of **4** to **6**, fill in the blank **A**, and provide the reaction mechanism of **A** to **9**.



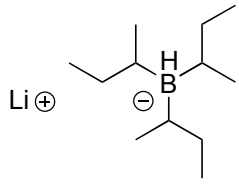
4 **6**



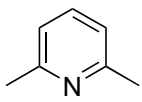
7



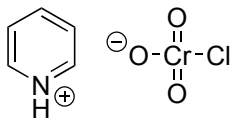
8 **9** **(±)-phomactin A**



L-Selectride®



2,6-lutidine



PCC

Problem Session (2) Answer

2015.5.16 Akinori Yamaguchi

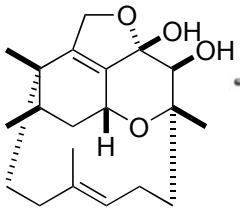
Total synthesis of phomactin A by Hsung [1,2)]

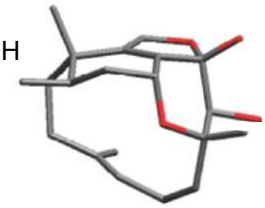
Introduction

0-1 Isolation

a marine fungus *Phoma simplex*

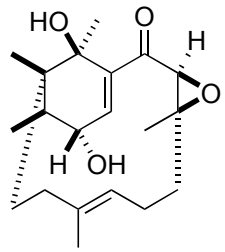
Sugano *et al.* in 1991, 1994, 1995 [3,4,5)]



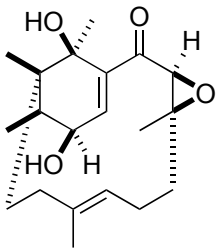


X-ray

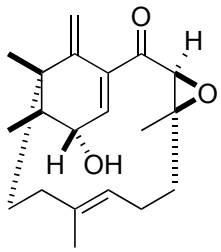
(+)-phomactin A



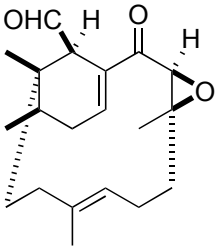
(+)-phomactin B



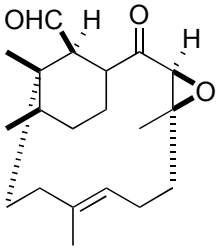
(+)-phomactin B1



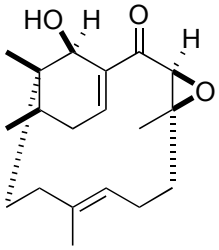
(+)-phomactin B2



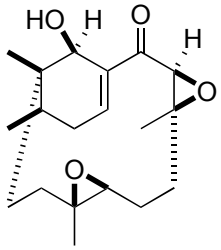
(+)-phomactin C



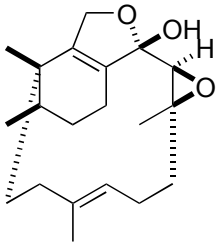
(+)-phomactin D



(+)-phomactin E

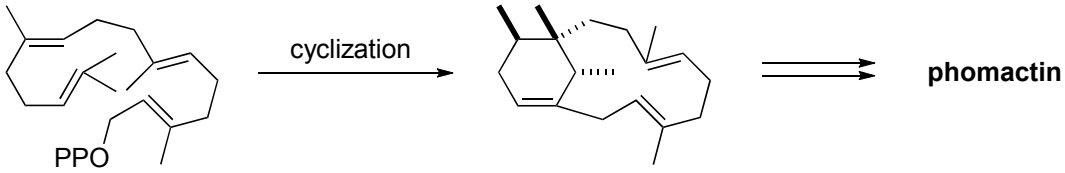


(+)-phomactin F



(+)-phomactin G

0-2 Biosynthesis [6)]



0-1

geranylgeranyl diphosphate

0-2

phomactatriene

0-3 Bioactivity [3)]

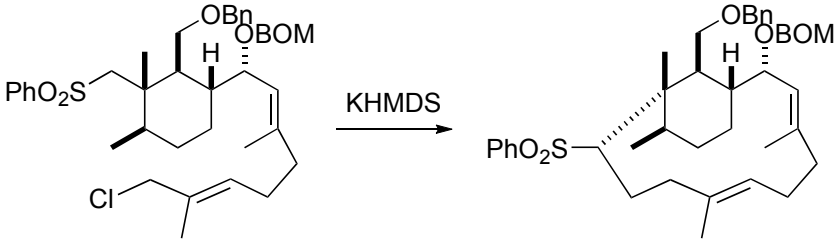
a pletelet-activating factor antagonst

The mechanism is unknown but unique relative to other known inhibitors.

0-4 Synthesis

(+)-phomactin D: Yamada in 1996 [7)]
(±)-phomactin A: Pattenden in 2002 [8)]
(+)-phomactin A: Halcomb in 2003 [9)]
(±)-phomactin G: Pattenden in 2004 [10)]
(±)-phomactin B2: Wulff in 2007 [11)]

Yamada's sysnthesis

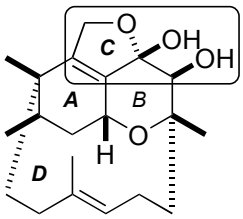


0-3

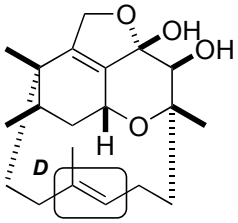
0-4

1) Hsung, R. P. *et al. Org. Lett.* **2003**, *5*, 4843.
2) Hsung, R. P. *et al. Org. Lett.* **2009**, *11*, 1591.
3) Sugano, M. *et al. J. Am. Chem. Soc.* **1991**, *113*, 5463.
4) Sugano, M. *et al. J. Org. Chem.* **1994**, *59*, 564.
5) Sugano, M. *et al. J. Antibiot.* **1995**, *48*, 1188.
6) Oikawa, H. *et al. Chem. Commun.* **2004**, 1324.
7) Yamada, Y. *et al. Tetrahedron. Lett.* **1996**, *37*, 7107.
8) Pattenden, G. *et al. Chem. Commun.* **2002**, 1736.
9) Halcomb, RL. *et al. J. Am. Chem. Soc.* **2003**, *125*, 1712.
10) Pattenden, G. *et al. Org. Biomol. Chem.*. **2004**, *2*, 466.
11) Wulff, WD. *et al.J. Am. Chem. Soc.* **2007**,*129*, 13366.

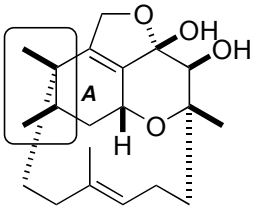
0-5 Structural furtures and challenges for total synthesis[2]



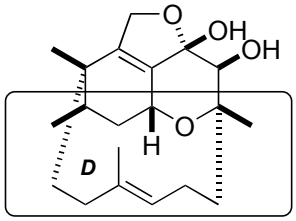
0-5
highly sensitive
hydrated furan



0-6
strained and twisted
electron-rich
double bond

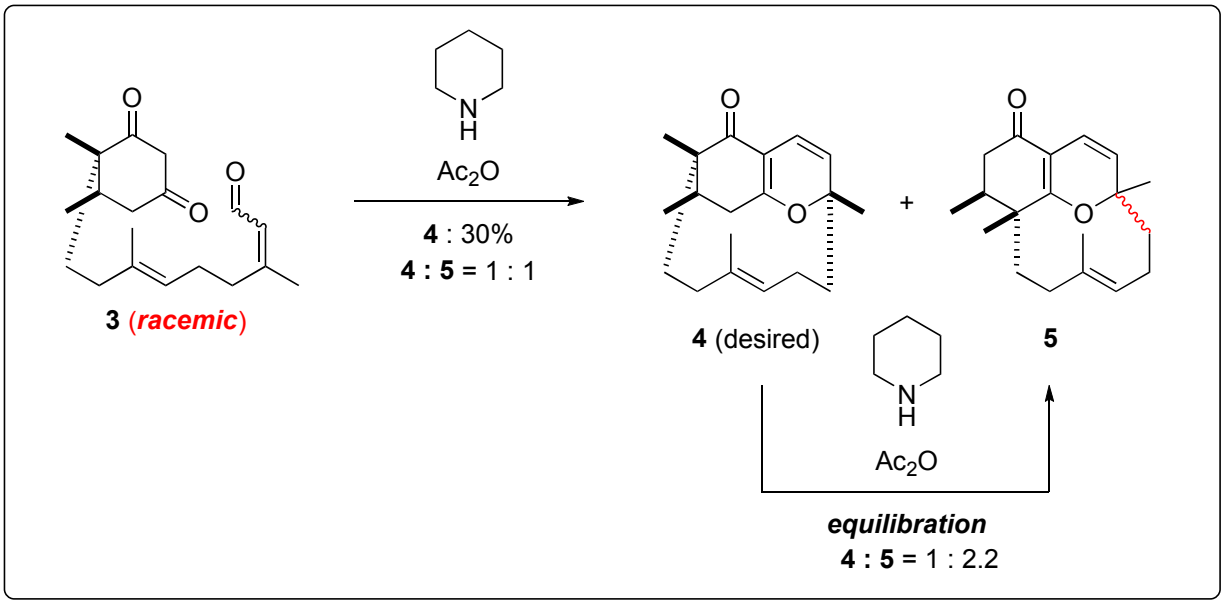


0-7
extremely hindered
quaternary center
and axial Me

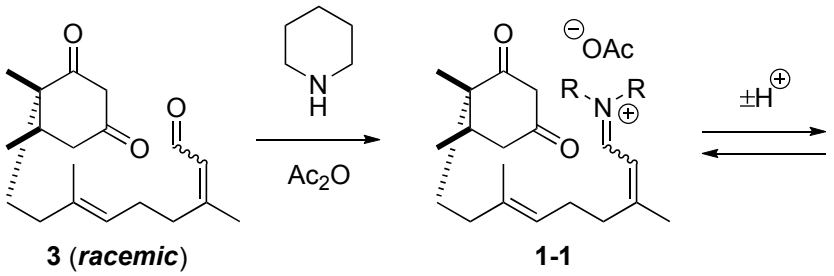


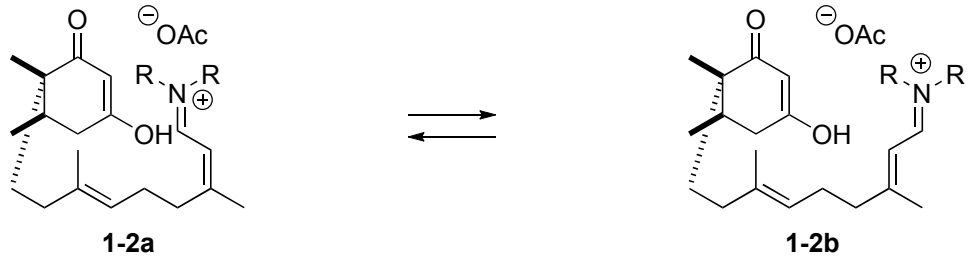
0-8
12-membered ring system
blocking the bottom face

Ploblem 1

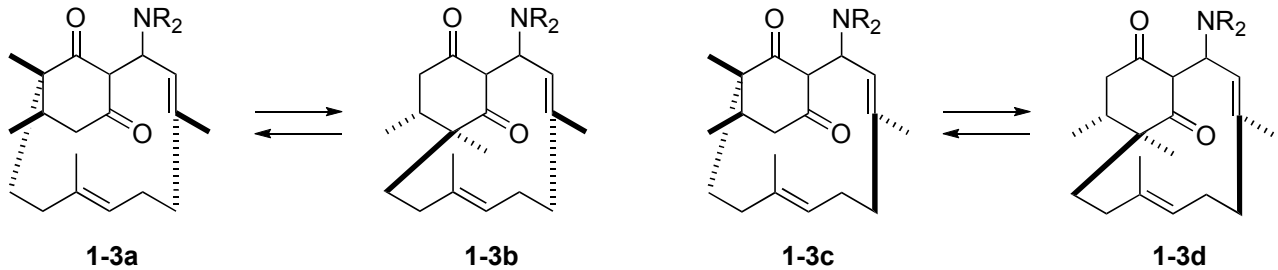


1-1 reaction mechanism

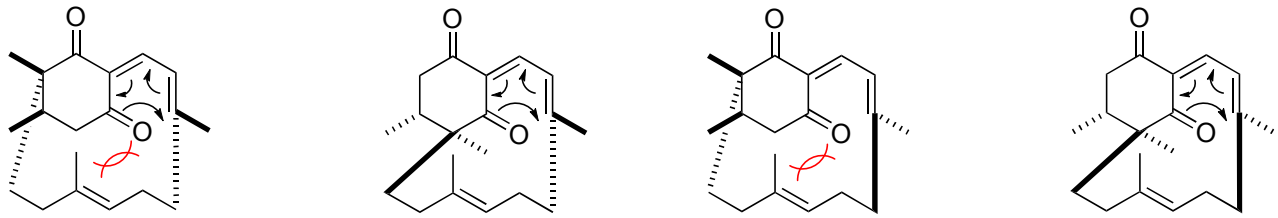




C-1,2-addition



β-elimination

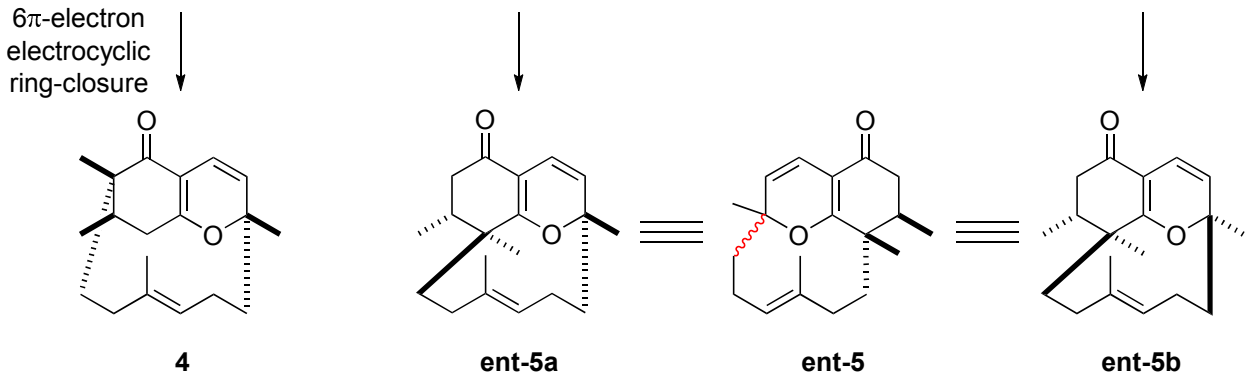


1-4a cis 12-membered ring steric hindrance

1-4b trans 12-membered ring less steric hindrance

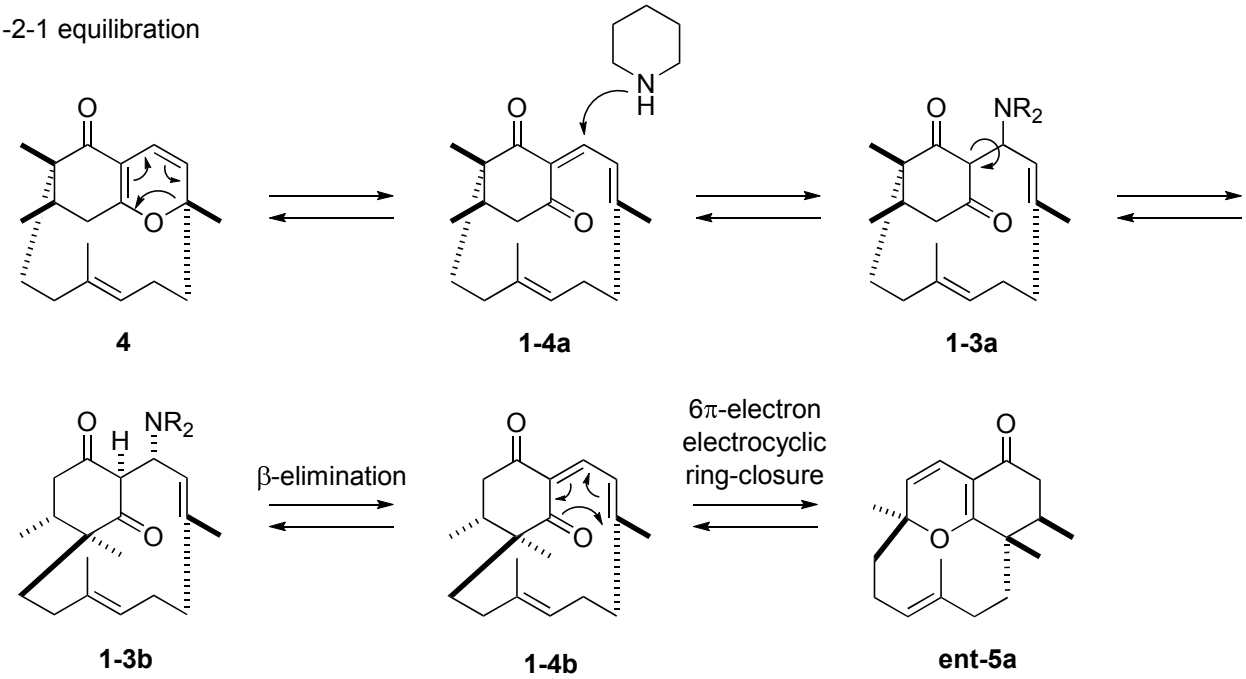
1-4c trans 12-membered ring steric hindrance

1-4d cis 12-membered ring less steric hindrance

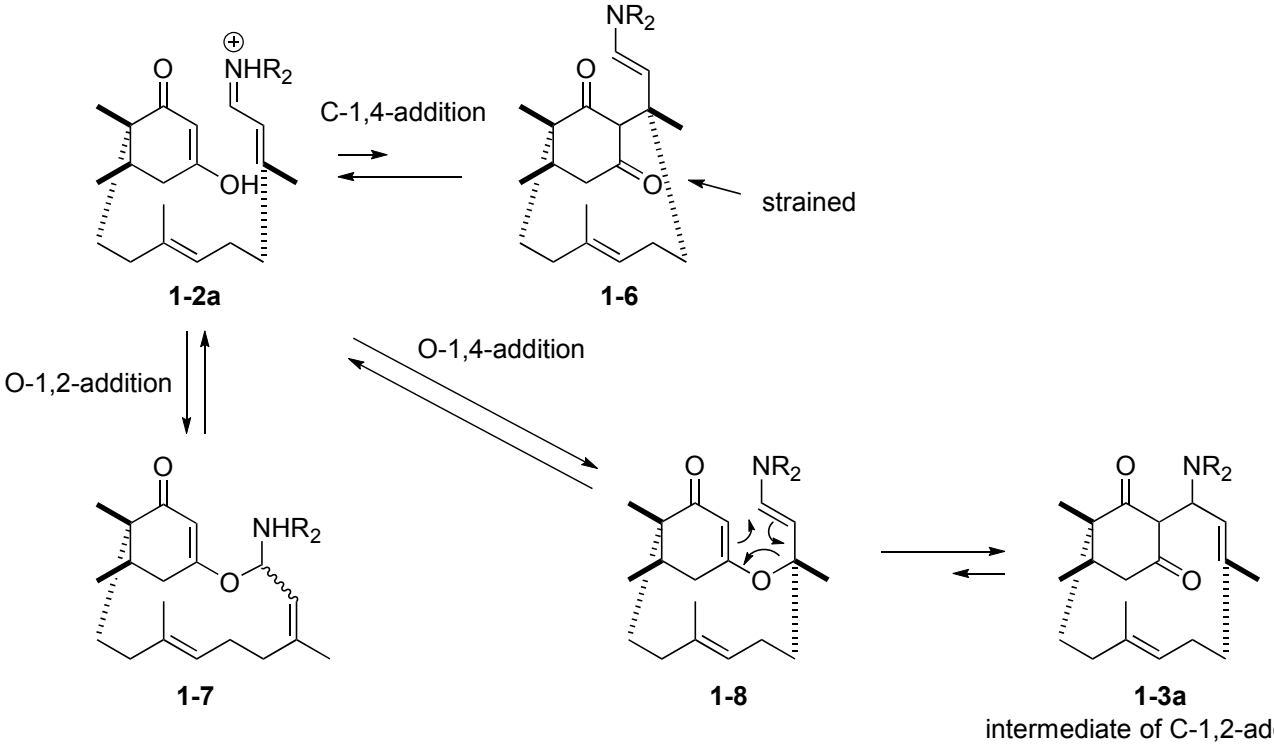


1-2 discussion

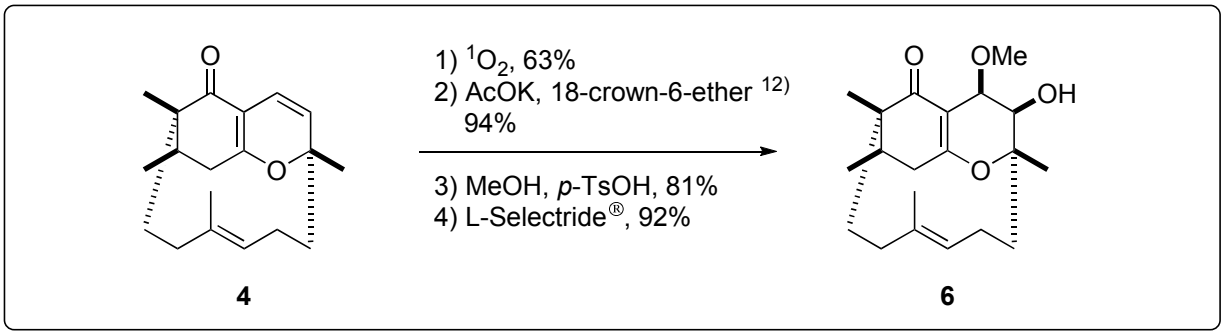
1-2-1 equilibration



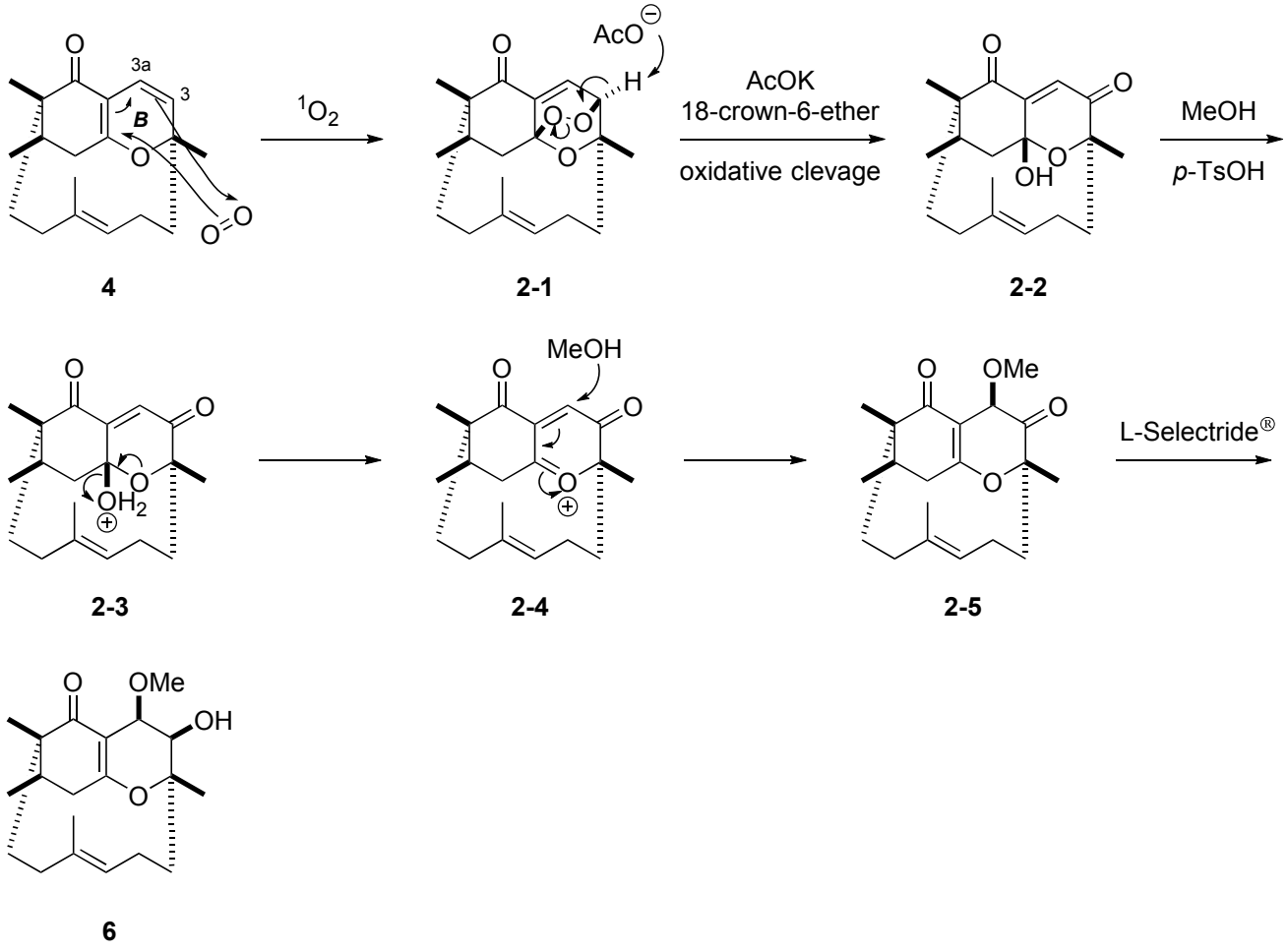
1-2-2 competing reaction pathways



Ploblem 2



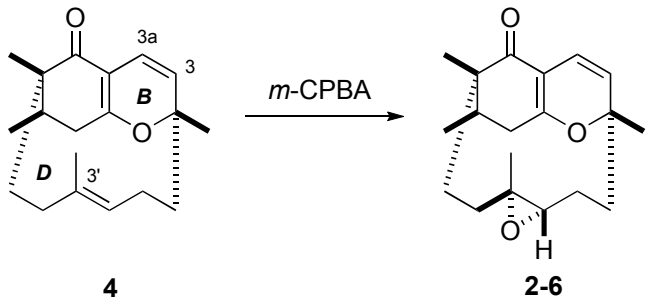
2-1 reaction mechanism



2-2 discussion

2-2-1 the reason for using $^1O_2$

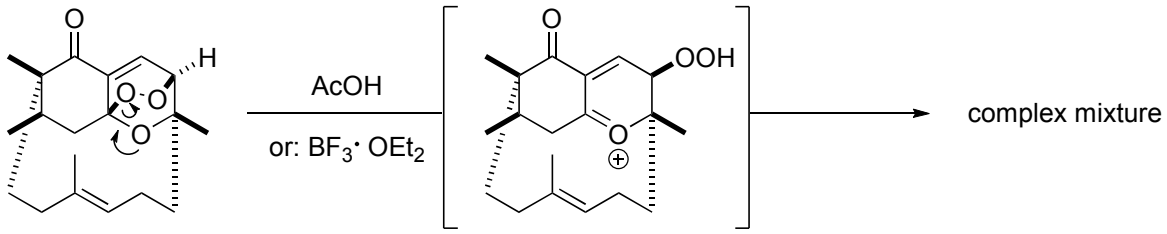
・erectrophilic epoxidation at 3'-orefin



12) Kornblm, N. *et al. J. Am. Chem. Soc.* **1951**, *73*, 880.

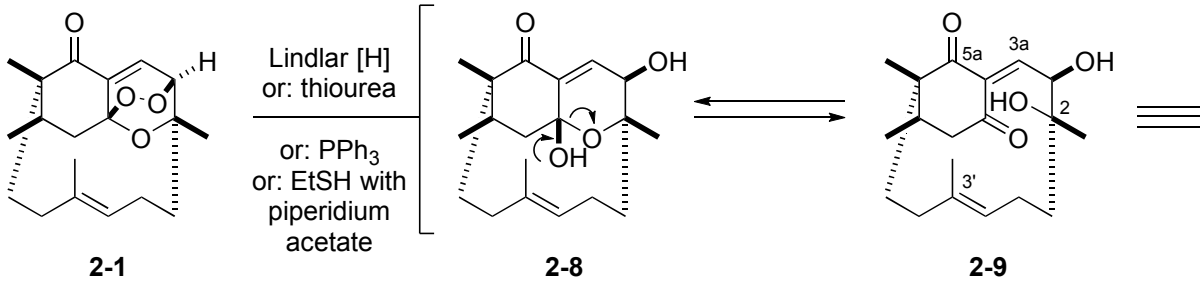
2-2-2 the reason for using AcOK in the presence of 18-crown-6-ether

・acidic condition

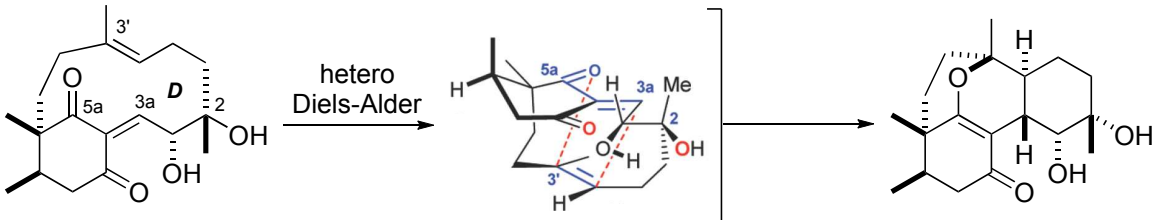


2-1 **2-7** proposed

・other conditions

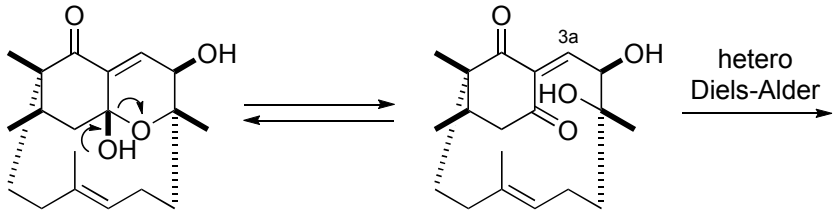


2-1 **2-8** **2-9**

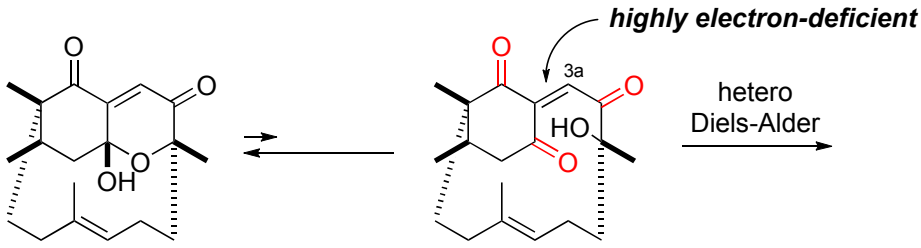


2-10 **2-11** **2-12** 50% (in the use of thiourea)

・the comparison of the equilibration in **2-8** with that in **2-2**

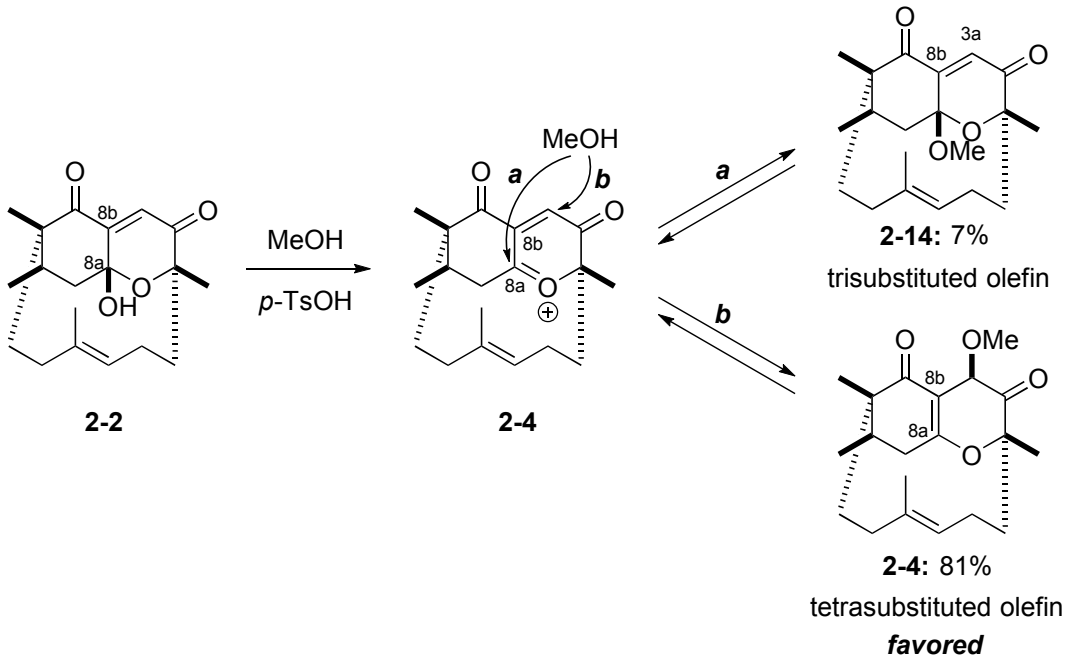


2-8 **2-9**



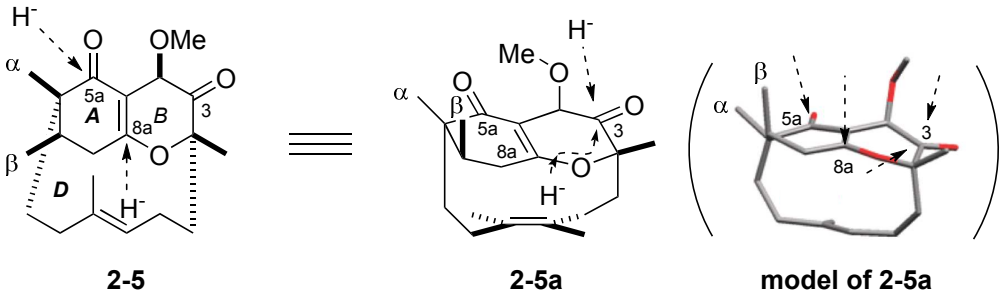
2-2 **2-13**

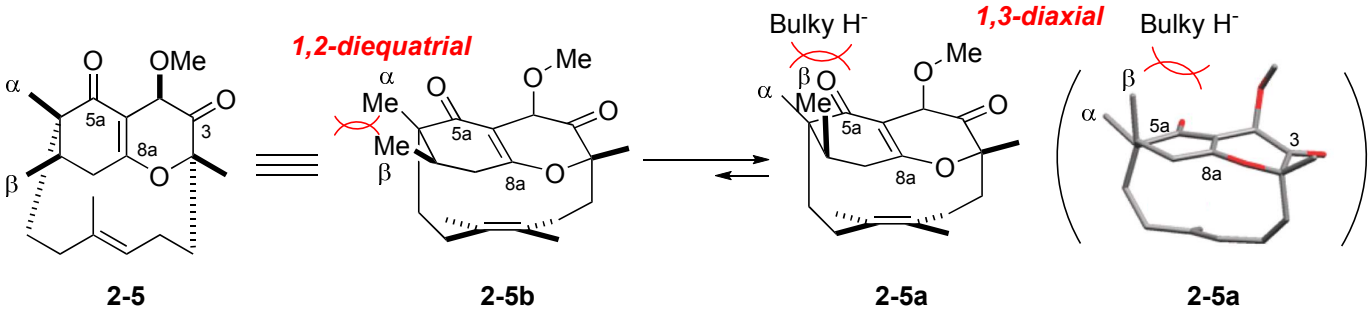
2-2-3 the redioselectivity in the solvolysis by MeOH



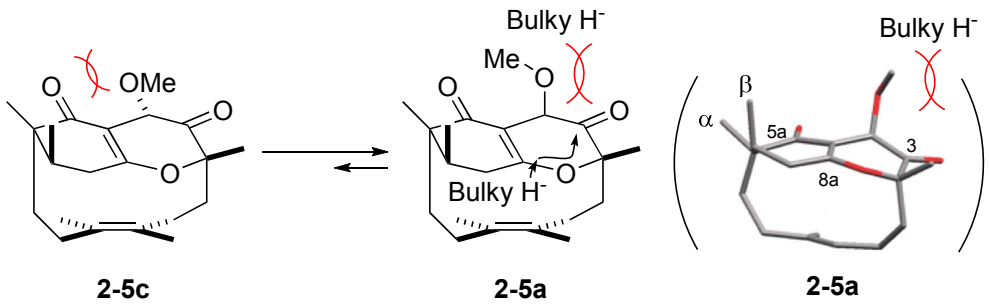
2-2-4 the selectivitiy in the reduction of **2-5**

· possible directions



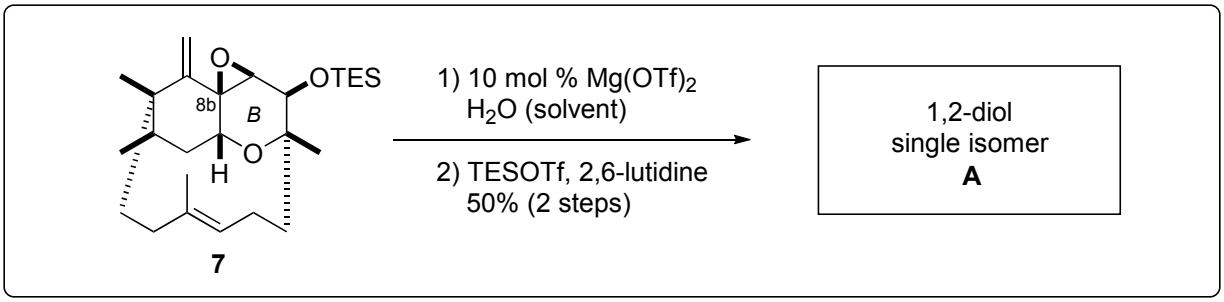


That axial β-Me is shielding the top face of **A** ring.

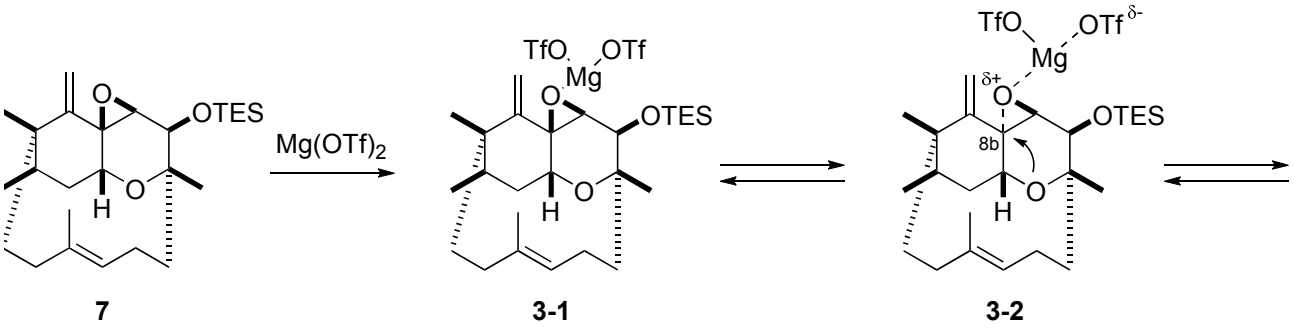


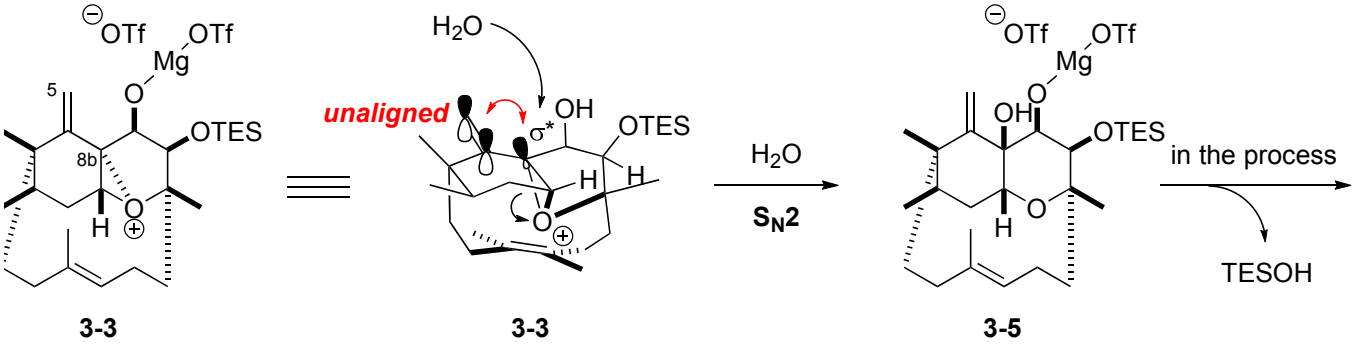
That axial OMe is shielding the top face of **B** ring.

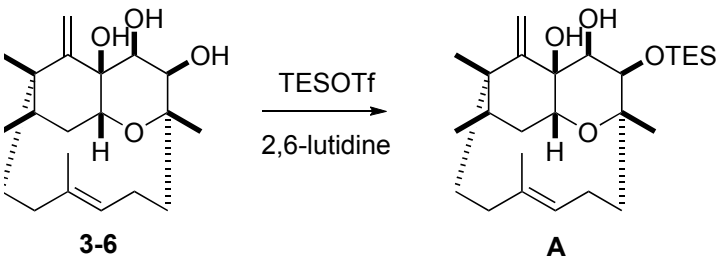
›blem 3



reaction mechanism

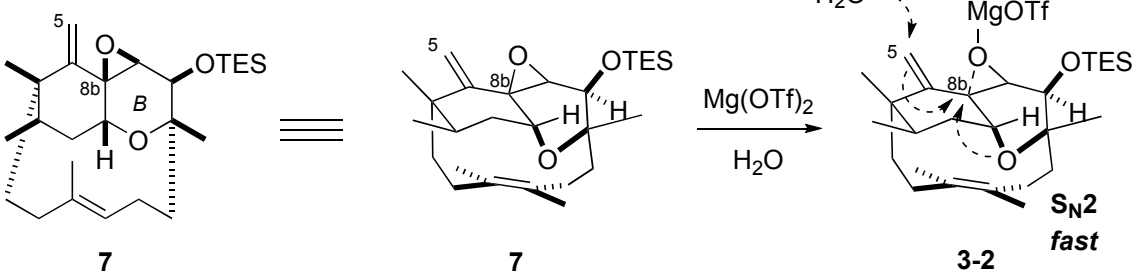




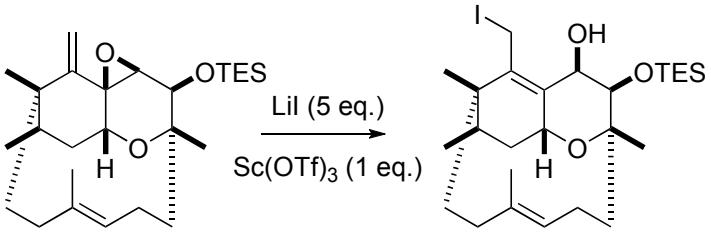


2 discussion

3-2-1 S_N2' *vs* S_N2



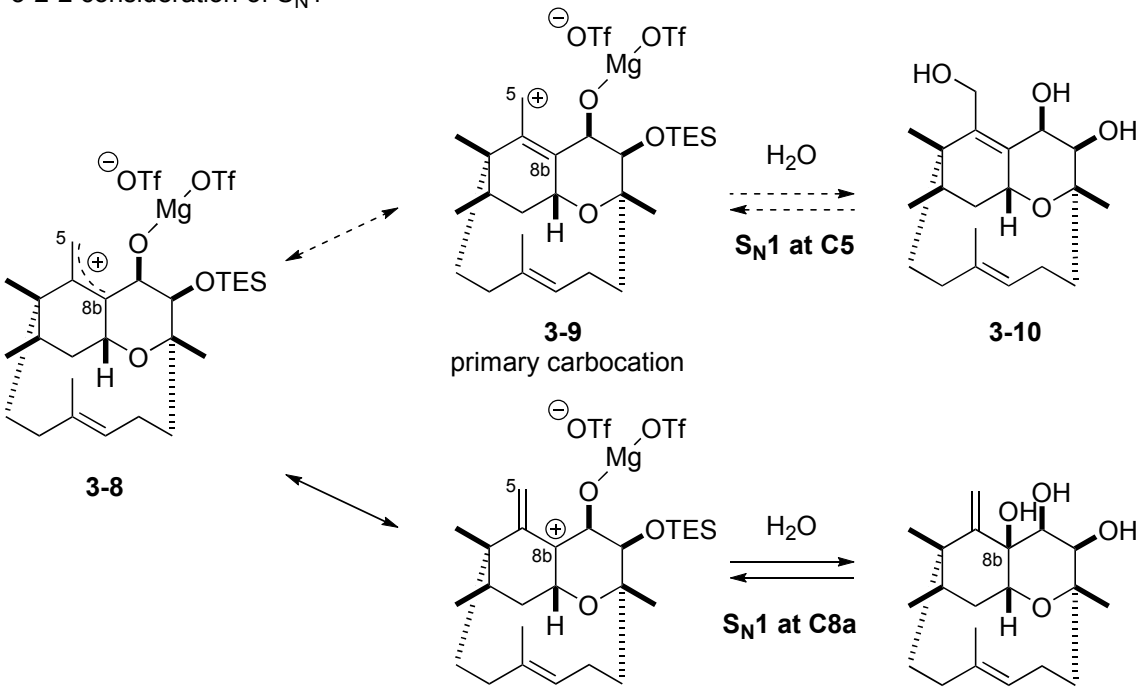
S_N2' by H_2O is slower than intramorecular S_N2 probably because insufficient nucleophilicity of H_2O.



7 **3-7**

- I^- reacts via S_N2'.
- nucleophilicity: I^- > H_2O

- 3-2-2 consideration of S_N1



3-8

3-9
primary carbocation

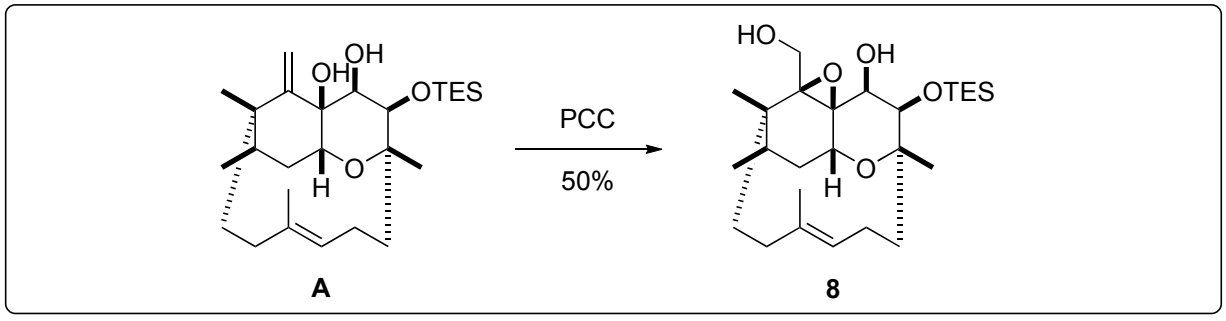
3-10

3-11
tertiary carbocation

3-6

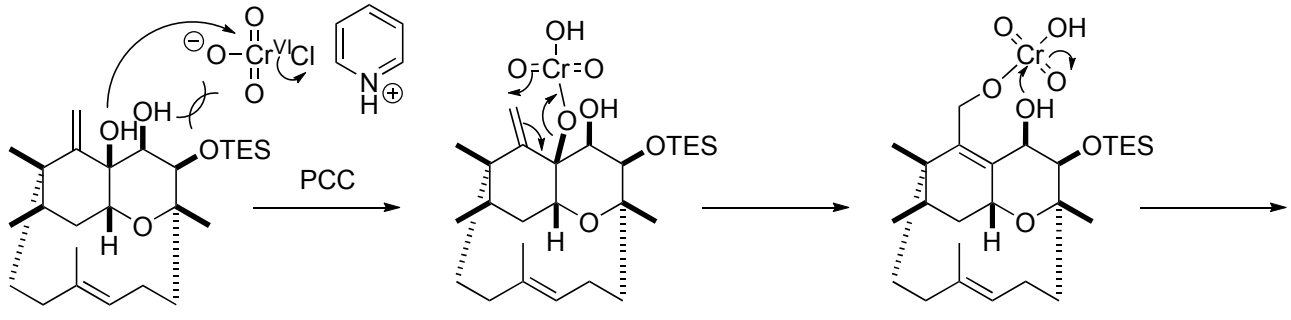
If iodine ion cannot access the C8b just because of its bulkiness in the above-mentioned reaction, this tertiary carbocation **3-11** can explain the redioserectivity.

Ploblem 4

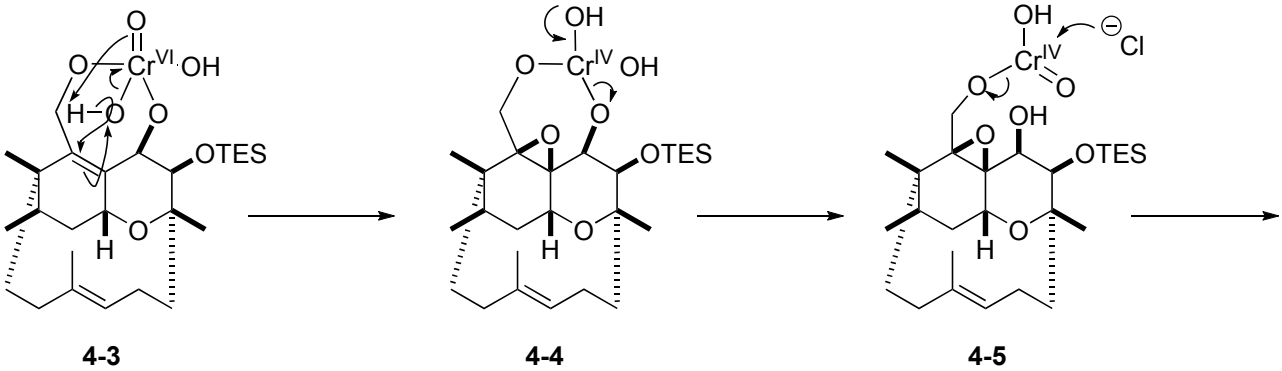


A **8**

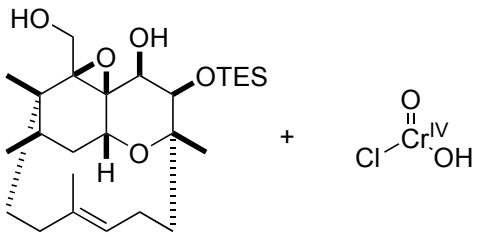
4-1 reaction mechanism



A **4-1** **4-2**



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

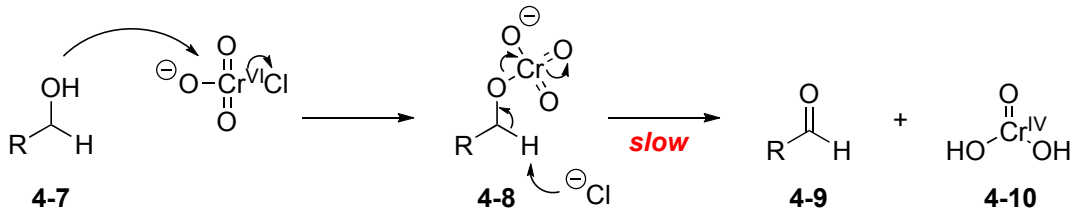


8 **4-6**

4-2 discussion

4-2-1 epoxidation *vs* oxidation of the alcohol

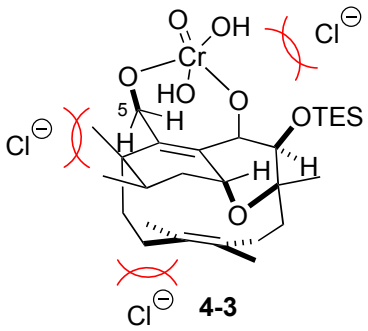
・typical PCC oxidation



4-7 **4-8** **4-9** **4-10**

rate-determining step

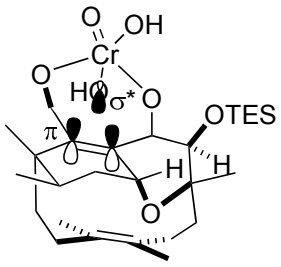
・highly-shielded hydrogen at C5



4-3

→ The oxidation of the alcohol could be slow.

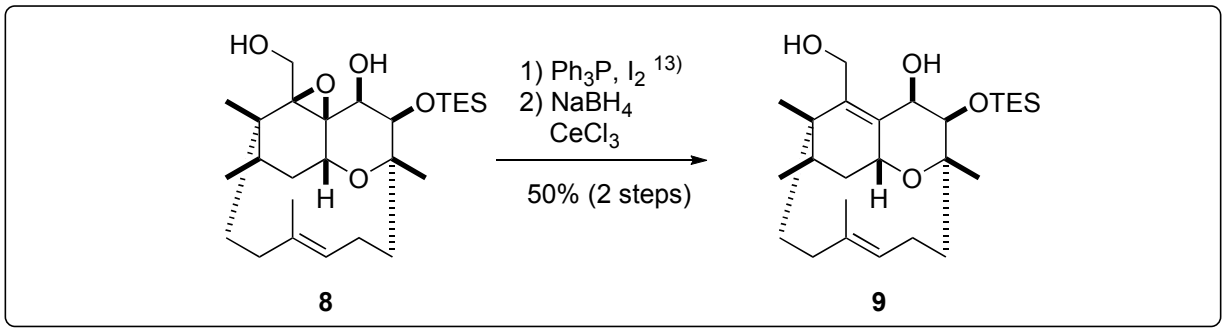
・trap of Cr by C3a-oxygen



4-3

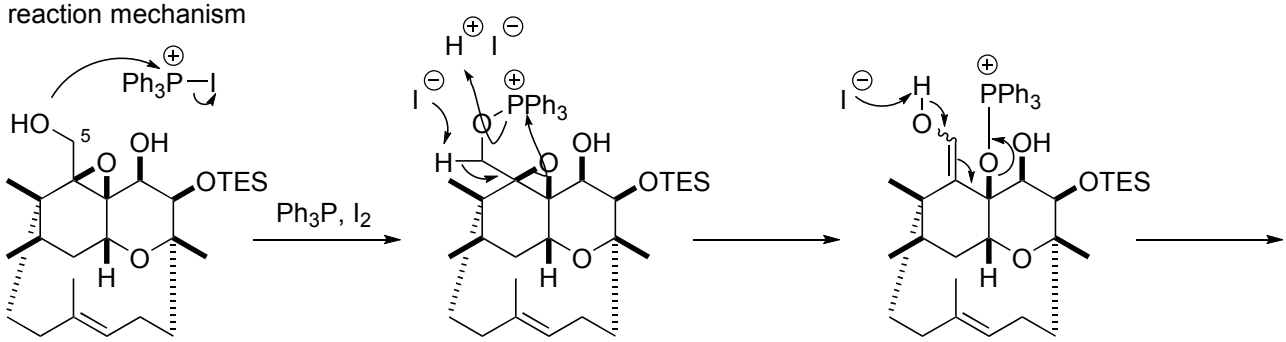
→ Good orbital lapping for electrophilic epoxidation

Ploblem 5

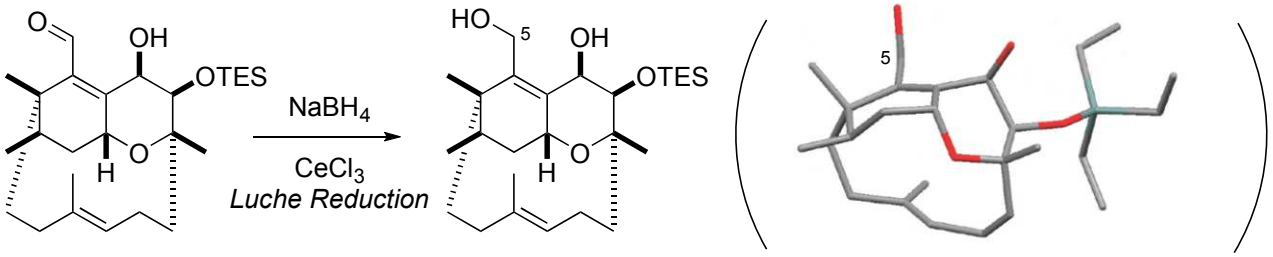


8 **9**

5-1 reaction mechanism



8 **5-1** **5-2**

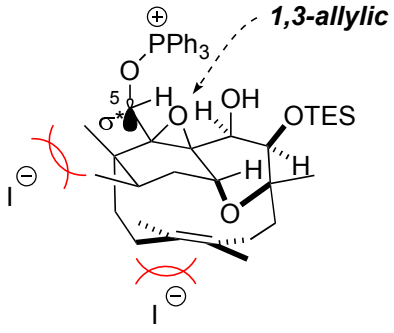


5-3 **9** **X-ray of 9**

5-2 discussion

5-2-1 chemoserectivity of I^-

- highly-shielded C-Oσ* at C5 (neopentyl, D ring)



5-1

→ S_N2 at C5 (Appel reaction) could not occur.

13)Paryzek, Z. *et al. Tetrahedron. Lett.* **1984**, *25*, 2601.