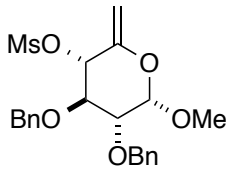
Problem Session (4)

2014. 7. 4. Keisuke Masuda

Please propose the reasonable reaction mechanism and fill in the blanks **1-2**.

1)



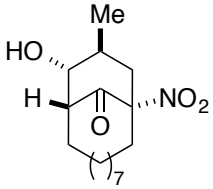
1-1
$C_{22}H_{26}O_7S$

1. $RuCl_3$ (cat.), $NaIO_4$
   $EtOAc/MeCN/H_2O$, rt
2. SiO_2, CH_2Cl_2, rt
3. DBU, THF

53% (3 steps)

1-2
$C_{20}H_{20}O_5$

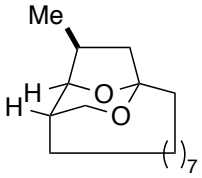
2)



2-1

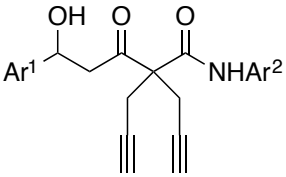
1. $NaBH_4$
   $MeCN/H_2O$, rt
2. HCl aq., rt

94% (2 steps)



2-2

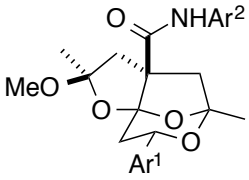
3)



3-1
$Ar^1 = 2\text{-}ClC_6H_4$
$Ar^2 = 4\text{-}EtOC_6H_4$

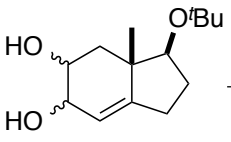
$AuCl_3$ (cat.)

$CH_2Cl_2/MeOH/H_2O$
41%



3-2

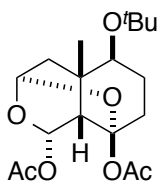
4)



4-1

$Pb(OAc)_4$

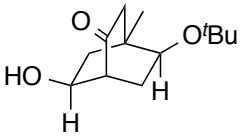
toluene
85%



4-2

K_2CO_3

$MeOH/H_2O$, rt
92%

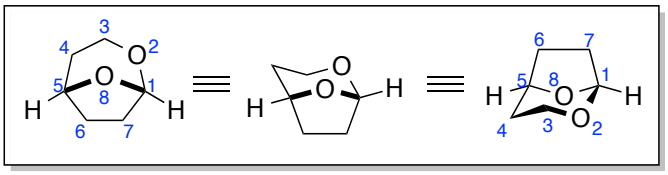


4-3

Problem Session Answer (4)

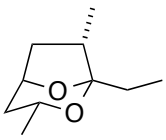
2014. 7. 4. Keisuke Masuda

Topic: synthesis of 2,8-dioxabicyclo[3,2,1]octane skeleton

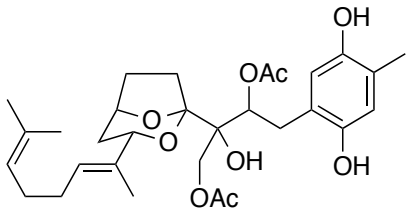


review of 2,8-diheterobicyclo[3,2,1]octane, see:
Flores, M.; Díez, D. *Synlett.* **2014**, *25*, 1643.

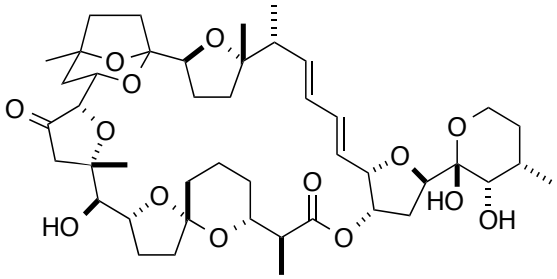
0-1. natural products containing 2,8-diheterobicyclo[3,2,1]octane



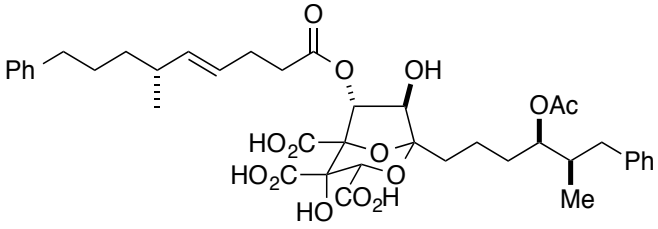
sordidine



sindurol

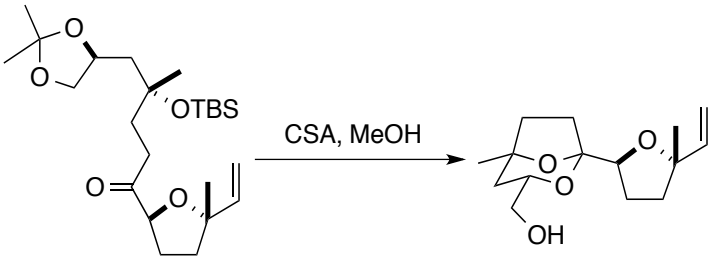


pectenotoxin 2



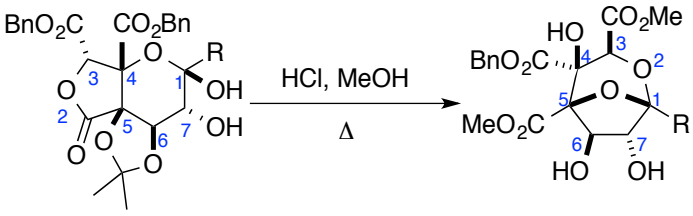
zaragozic acid C

0-2. construction of 2,8-diheterobicyclo[3,2,1]octane skeleton



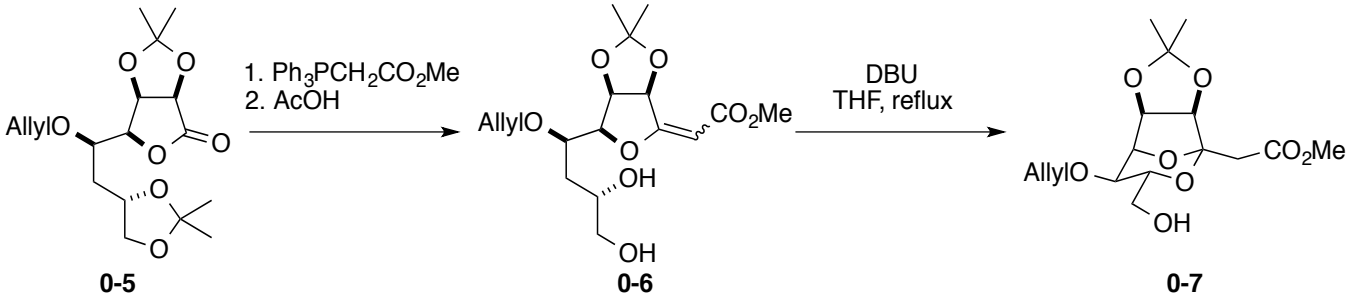
0-1 **0-2**

Micalizio, G. C. et. al. *Org. Lett.* **2011**, *13*, 2384.



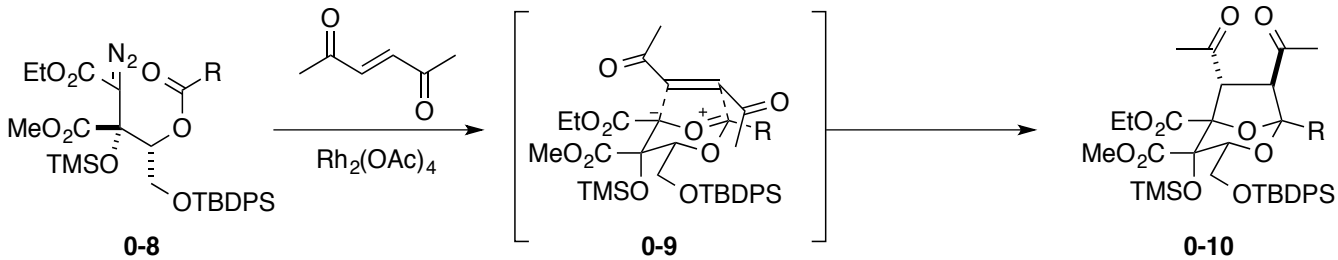
0-3 **0-4**

Nicolaou, K. C. et. al. *Chem. Eur. J.* **1995**, *1*, 467.



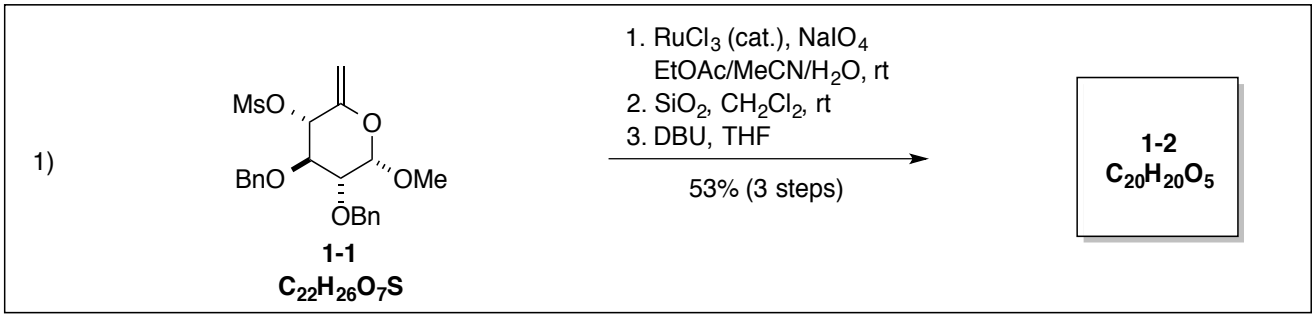
0-5 **0-6** **0-7**

Chapleur, Y. et. al. *Synlett.* **1999**, 697.



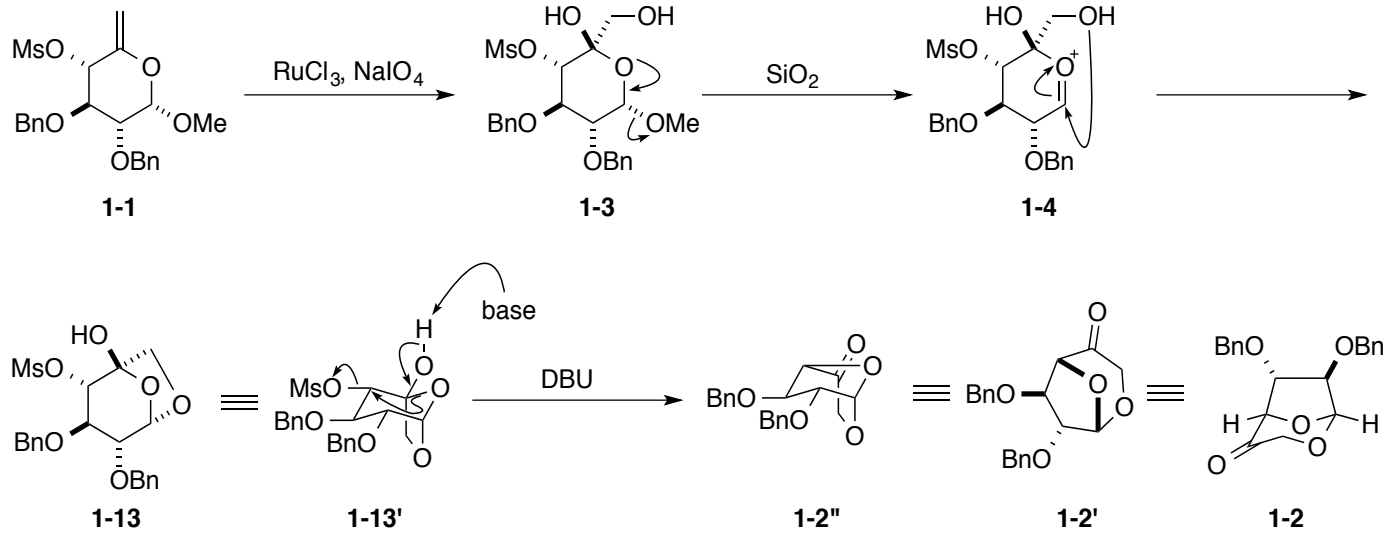
0-8 **0-9** **0-10**

Hashimoto, S. et. al. *Tetrahedron Lett.* **1998**, *39*, 2371.

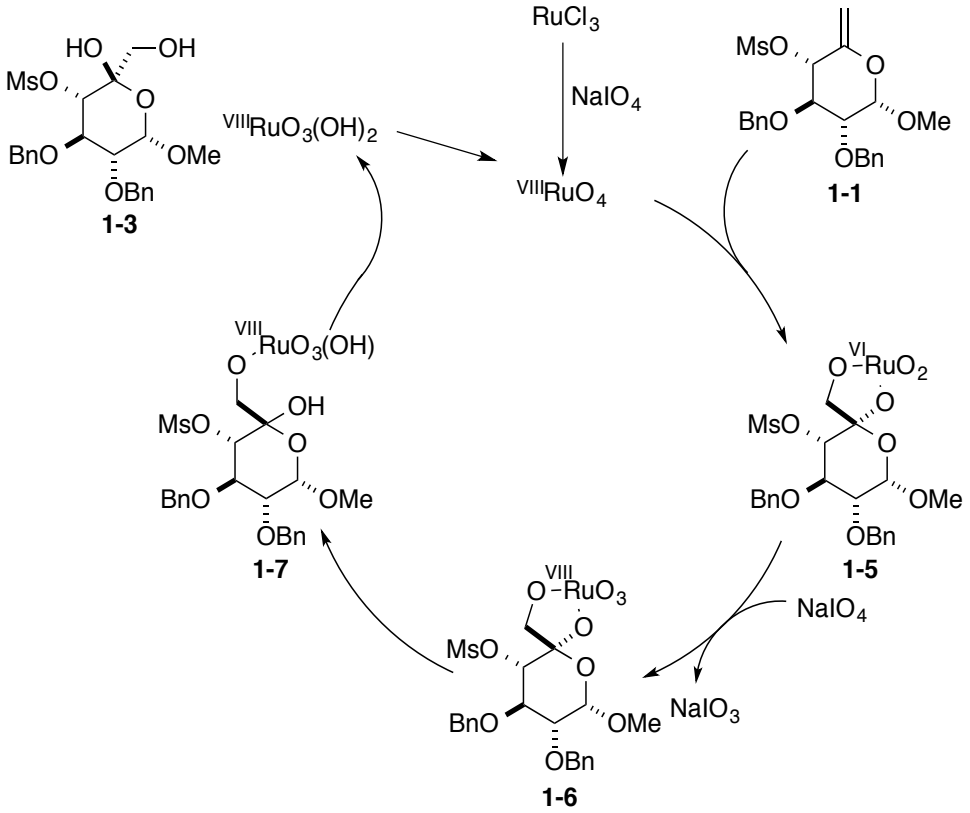


Chapleur, Y. et. al. *Synlett.* **1999**, 697.

1-1. proposed mechanism



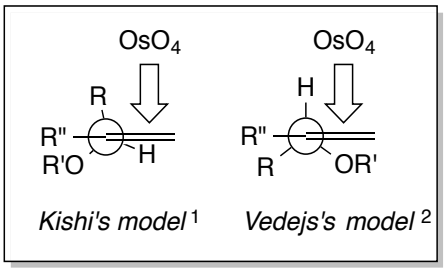
1-2. oxidation of olefin
1-2-1. proposed mechanism



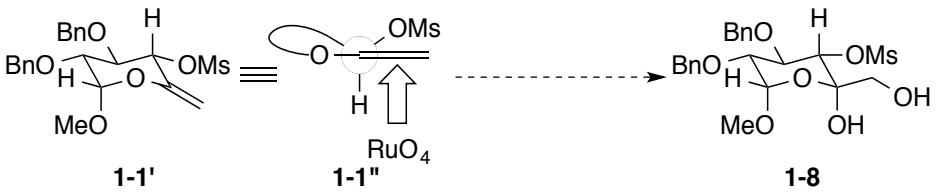
Plieker, B. et. al. *Tetrahedron:* Asymm. **2005**, *16*, 3453.

1-2-2. diastereoselectivity (Kishi's empirical rule vs steric hindrance)

1. Kishi's empirical rule

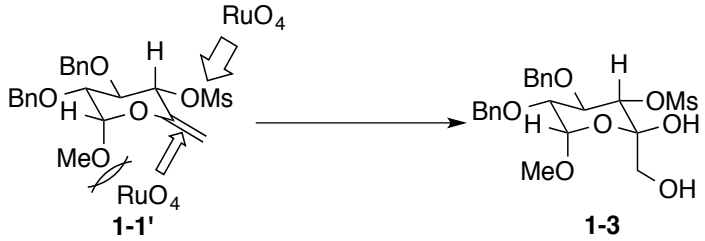


Addition of OsO_4 or RuO_4 occurs predominantly *anti* to an allylic EWG.



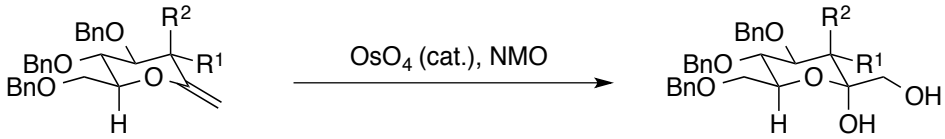
1. Kishi, Y. et. al. *Tetrahedron Lett.* **1983**, *24*, 3943.
Cha, J. K. et. al. *Chem. Rev.* **1995**, *95*, 1761.
2. Vedejs, E. et. al. *J. Am. Chem. Soc.* **1986**, *108*, 1094.

2. steric hindrance



α face is more hindered

1-3. other examples

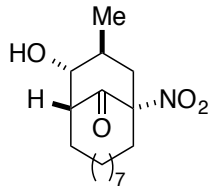


1-9 (R^1= OBn, R^2= H)
1-10 (R^1= H, R^2= OBn)

1-11 (R^1= OBn, R^2= H) 94%
1-12 (R^1= H, R^2= OBn) 90%

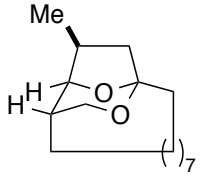
Wadouachi, A. et. al. *Tetrahedron:* Asymm. **2009**, *20*, 1817.

2)



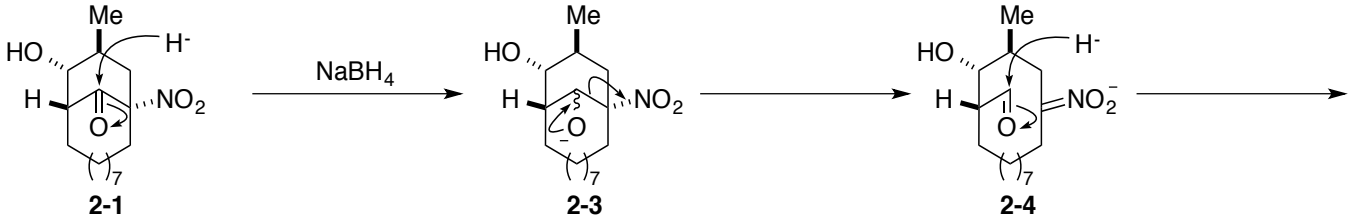
1. $NaBH_4$
$MeCN/H_2O$, rt
2. HCl aq., rt

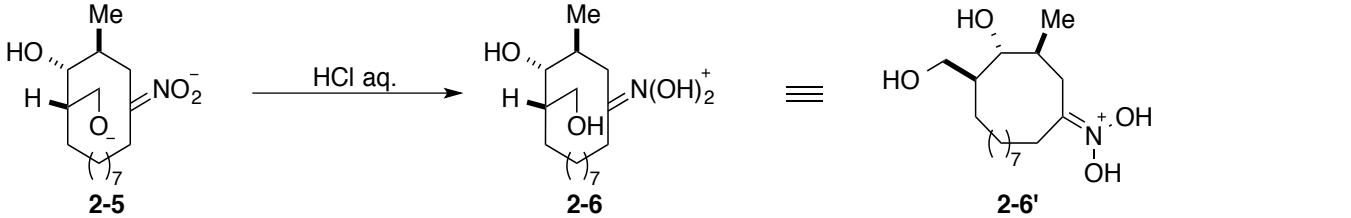
94% (2 steps)



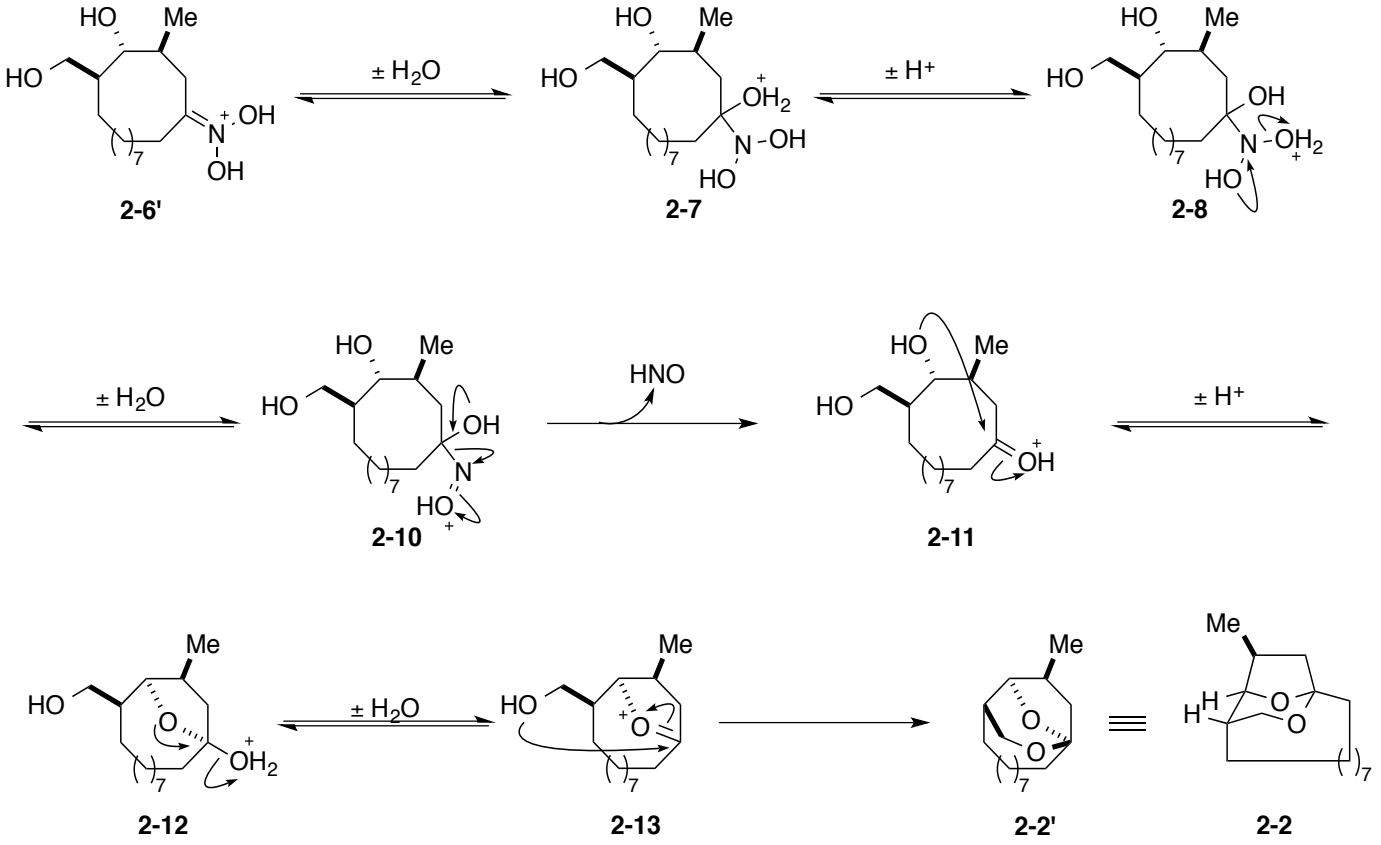
Menéndez, J. C. et. al. *Org. Biomol. Chem.* **2012**, 5131.

2-1. proposed mechanism

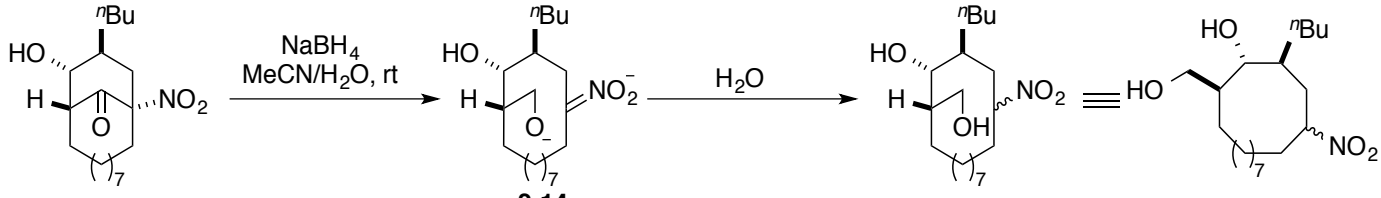




2-1. proposed mechanism (continued)



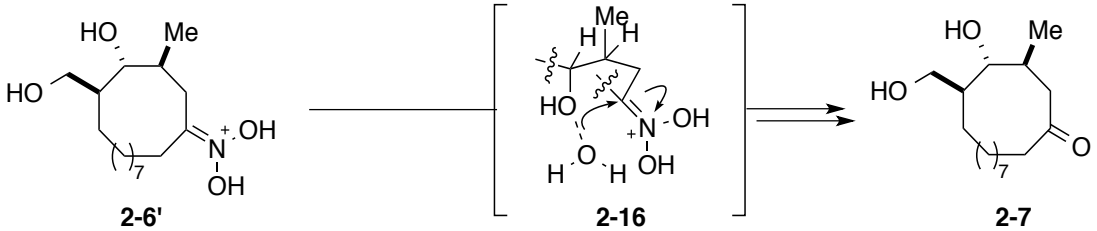
2-2. isolation of 14 membered ring **2-15**



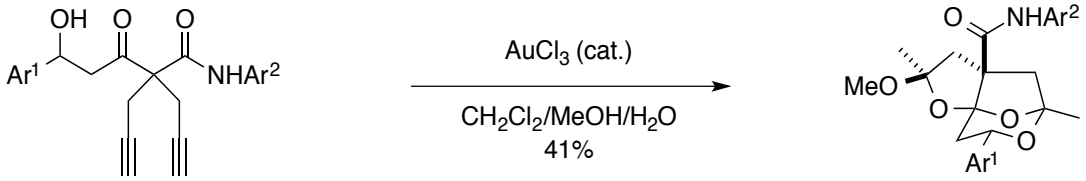
2-3. Nef reaction

Nef reaction is normaly requires strongy acidic conditions, long time, and/or high temp.

⇨ This condition is moderate acidic condition and room temp, so it can be attribute to assistance from intramolecular hydroxy group



3)

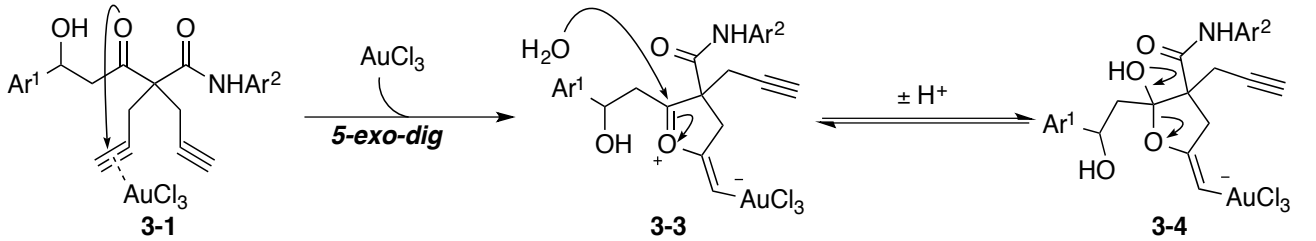


3-1
$Ar^1 = 2\text{-}ClC_6H_4$
$Ar^2 = 4\text{-}EtOC_6H_4$

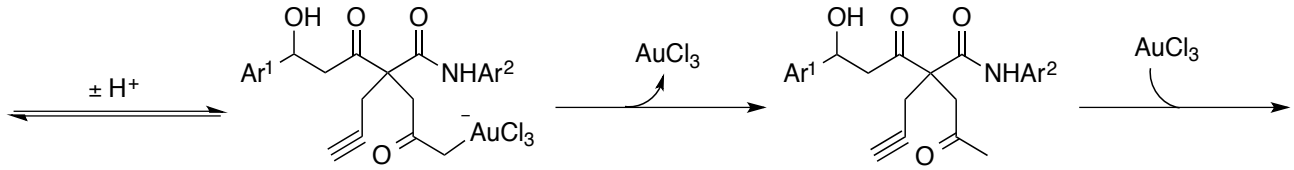
3-2

Liu, Q. et. al. *Chem. Eur. J.* **2009**, *15*, 1830.

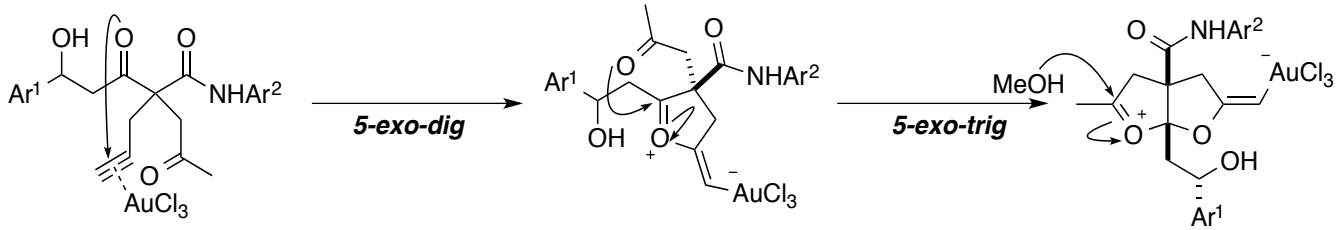
3-1. proposed mechanism



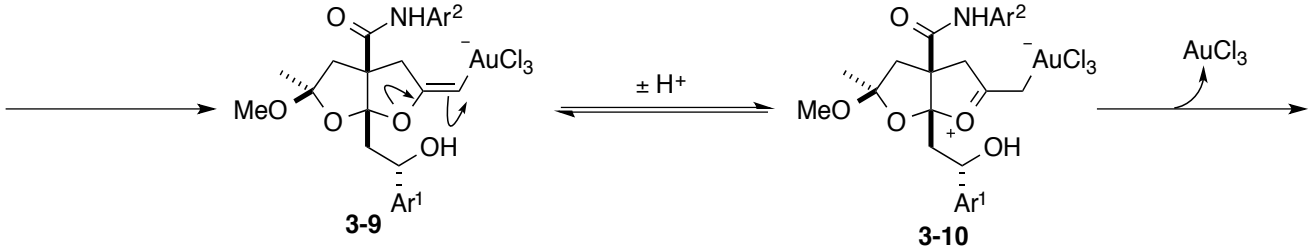
3-1 **3-3** **3-4**



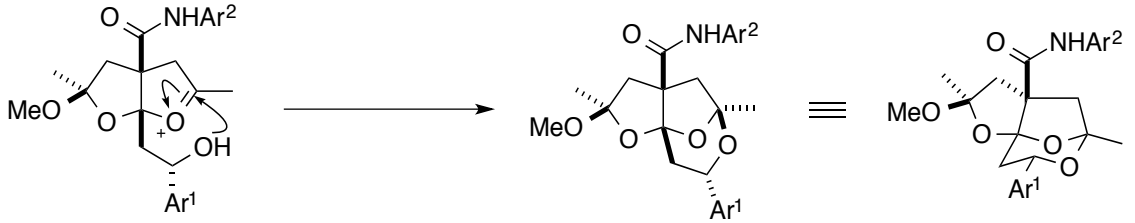
3-5 **3-6**



3-6' **3-7** **3-8**

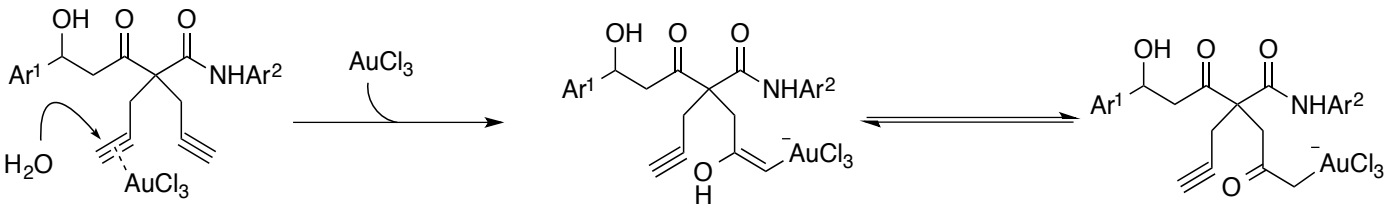


3-9 **3-10**

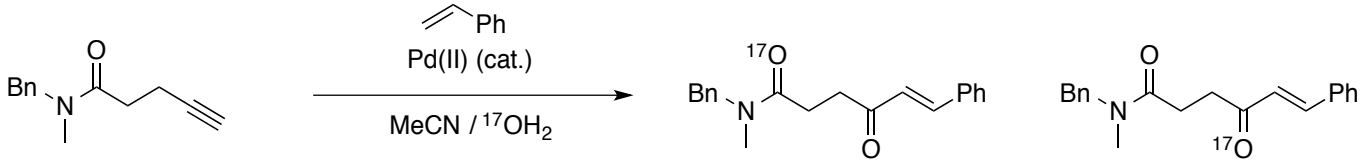


3-11 **3-2'** **3-2**

3-2. oxygen from intramolecular ketone or from H_2O



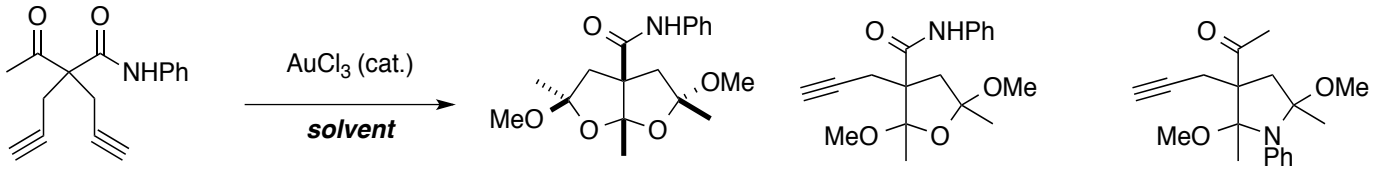
3-1 **3-12** **3-5**



3-13 **3-14** observed **3-15** NOT observed

Liu, A. R. et. al. *J. Am. Chem. Soc.* **2007**, *129*, 2230.

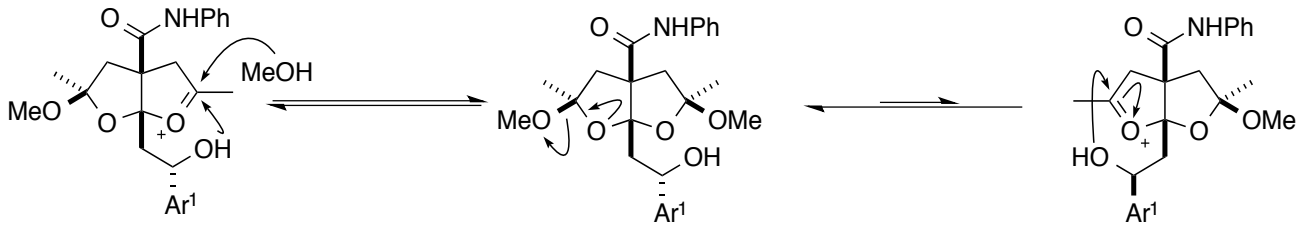
3-3. oxygen from ketone or from amide



3-16 **3-17** **3-18** a mixture of two diastereomers **3-19** NOT obtained

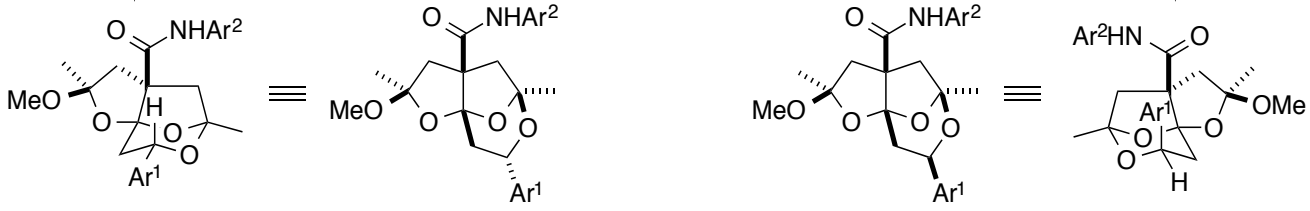
solvent	results
MeOH	**3-17**: 0%, **3-18**: 95%
MeOH/H_2O (50/1)	**3-17**: 8%, **3-18**: 89%
MeOH/H_2O (10/1)	**3-17**: 72%, **3-18**: 11%

3-3. stereoselectivity **3-11** to **3-2**



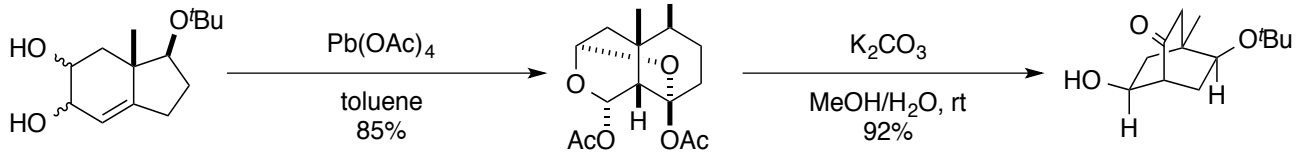
3-11 **3-20** **3-21**

fast ***slow***



3-2 **3-2'** **3-22'** **3-22**

4)

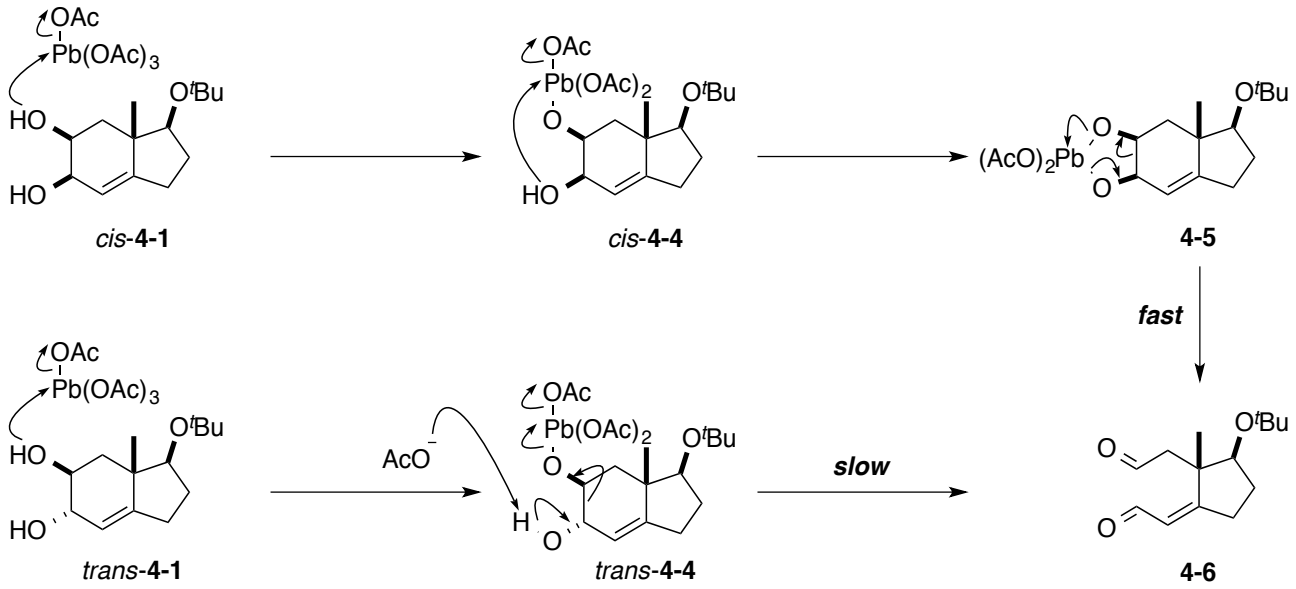


4-1 **4-2** **4-3**

Arsemoyados, S. et. al. *Chem. Eur. J.* **2003**, *9*, 3813.

4-1. proposed mechanism **4-1** to **4-6**

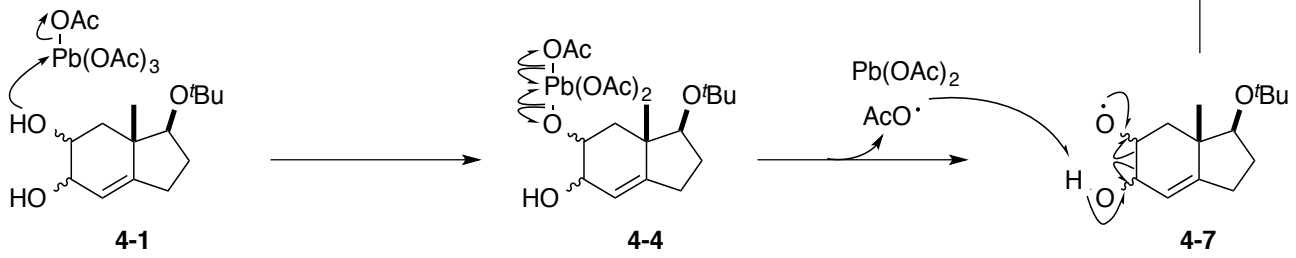
4-1-1. poler mechanism (favored in polar solvent)



cis-**4-1** *cis*-**4-4** **4-5**

trans-**4-1** *trans*-**4-4** **4-6**

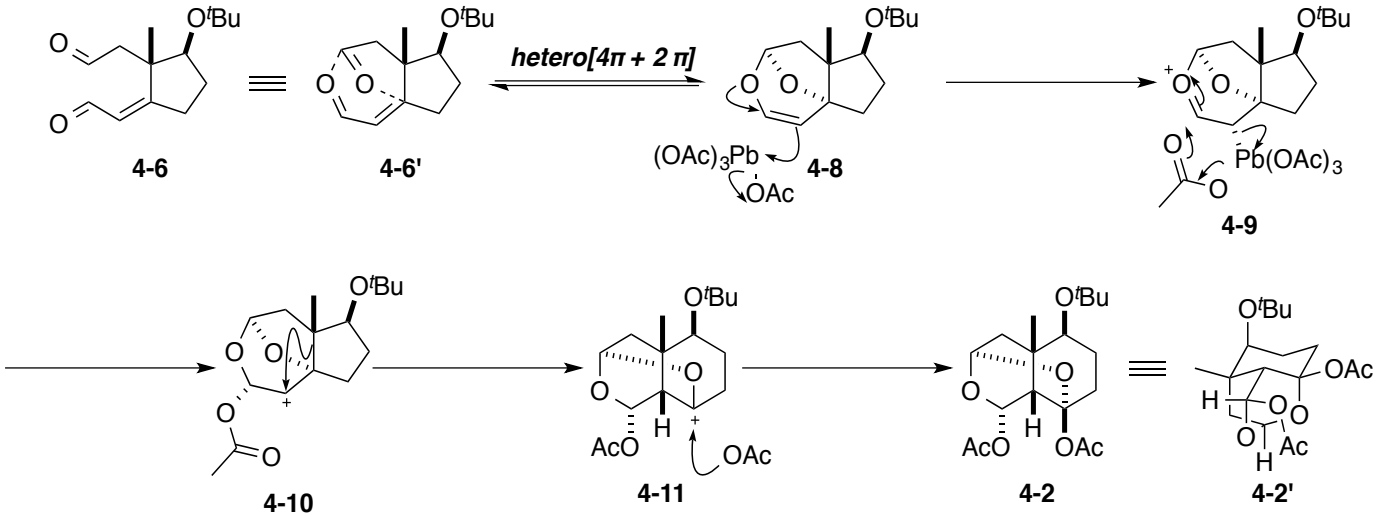
4-1-2. radical mechanism (favored in nonpolar solvent)



4-1 **4-4** **4-7**

Mihailovic, M. L. *Tetrahedron* **1965**, *21*, 1395.

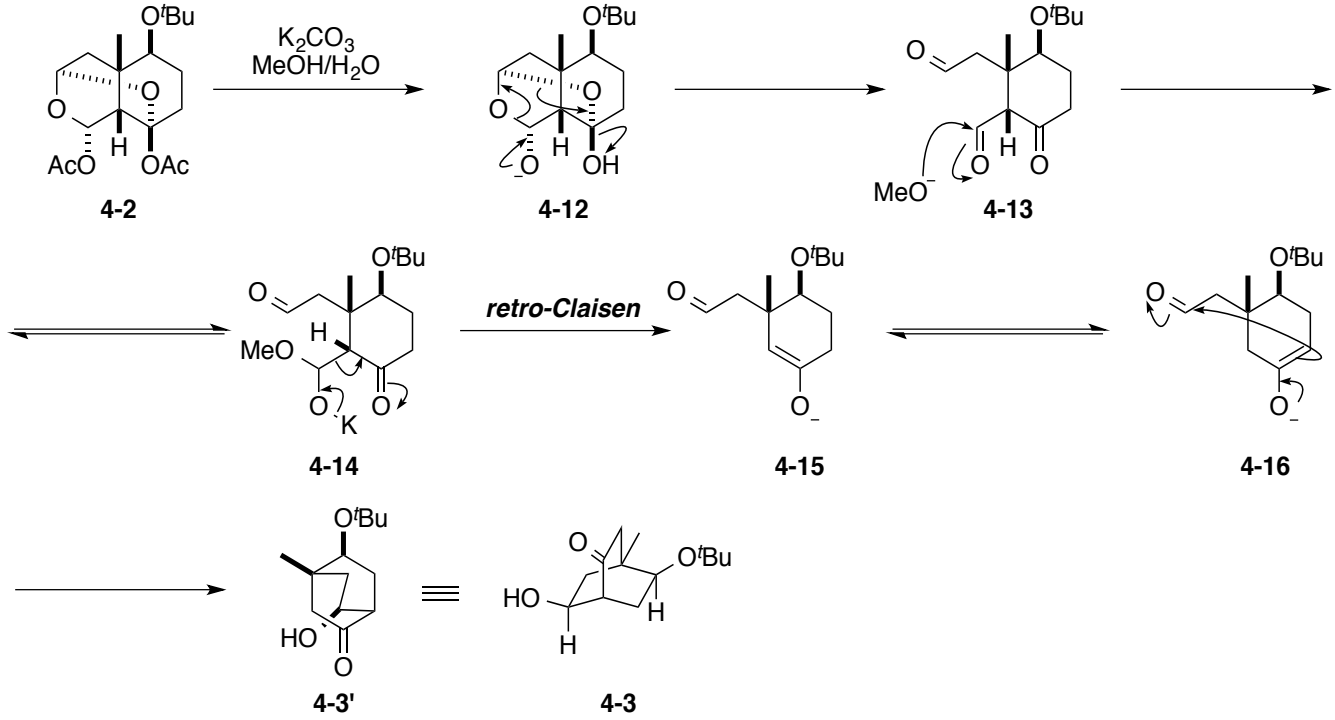
4-2. proposed mechanism **4-6** to **4-2**



4-6 **4-6'** **4-8** **4-9**

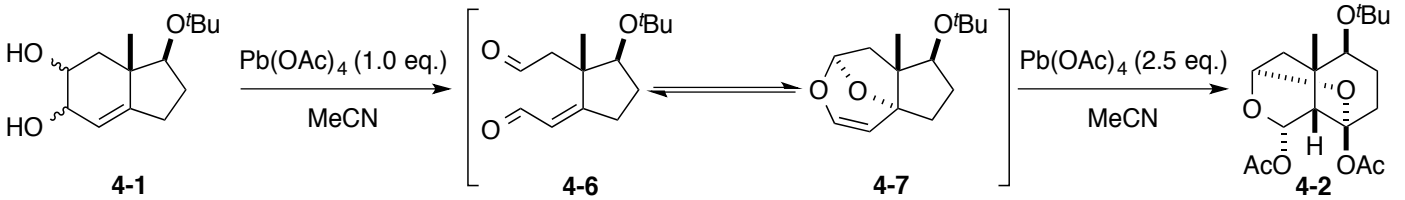
4-10 **4-11** **4-2** **4-2'**

4-3. proposed mechanism **4-2** to **4-3**



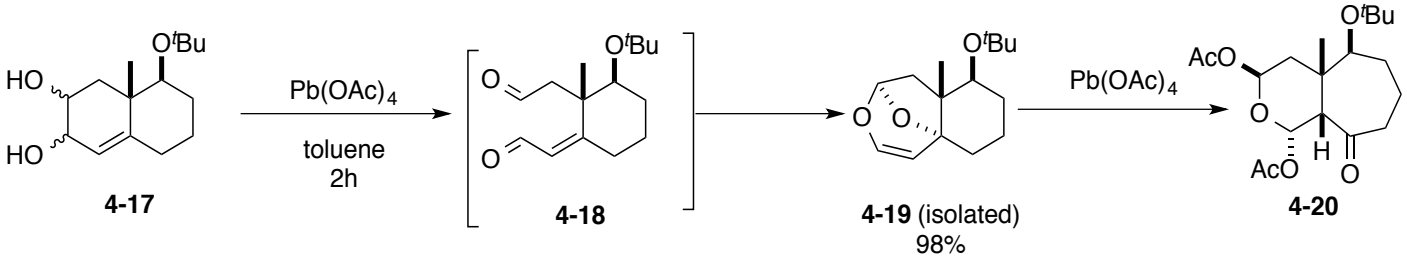
4-2 **4-12** **4-13** **4-14** **4-15** **4-16** **4-3'** **4-3**

4-4. isolation of intermediate **4-7**



4-1 **4-6** **4-7** **4-2**

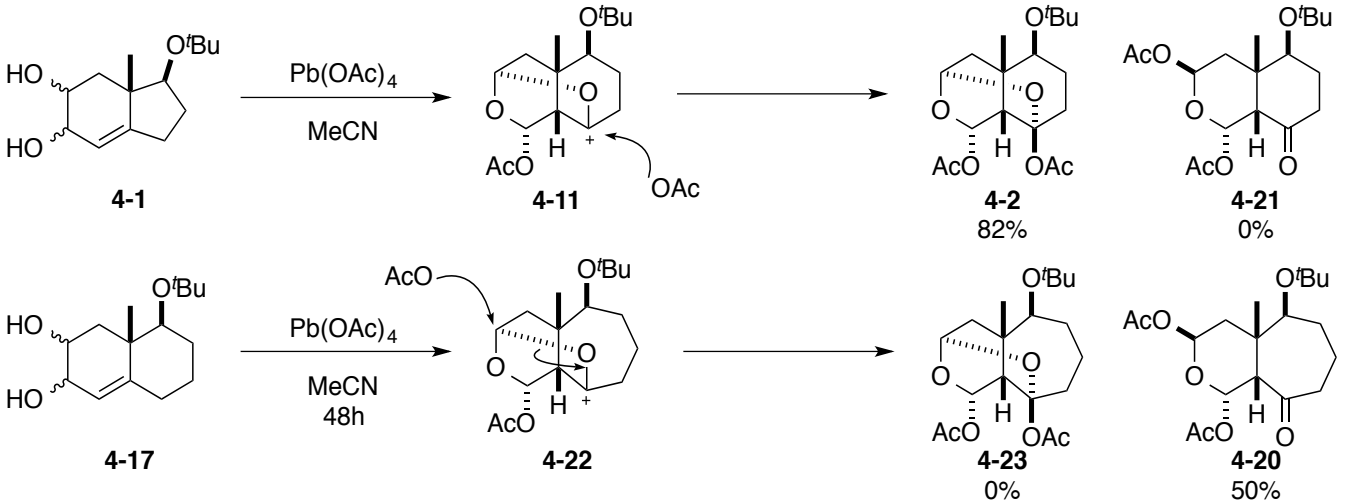
4-6 : **4-7** = 1 : 1
this mixture can be stored for weeks



4-17 **4-18** **4-19** (isolated) 98% **4-20**

Arsemoyados, S. et. al. *Tetrohedrone Lett.* **1995**, *36*, 8783.
Arsemoyados, S. et. al. *Eur. J. Org. Chem.* **2005**, 683.

4-5. regioselectivity of acetoxy group attack



4-1 **4-11** **4-2** 82% **4-21** 0%

4-17 **4-22** **4-23** 0% **4-20** 50%

 Arsemoyados, S. et. al. *Tetrohedrone Lett.* **1995**, *36*, 8783.

4-5-1. regioselectivity of acetoxy group attack to **4-11**

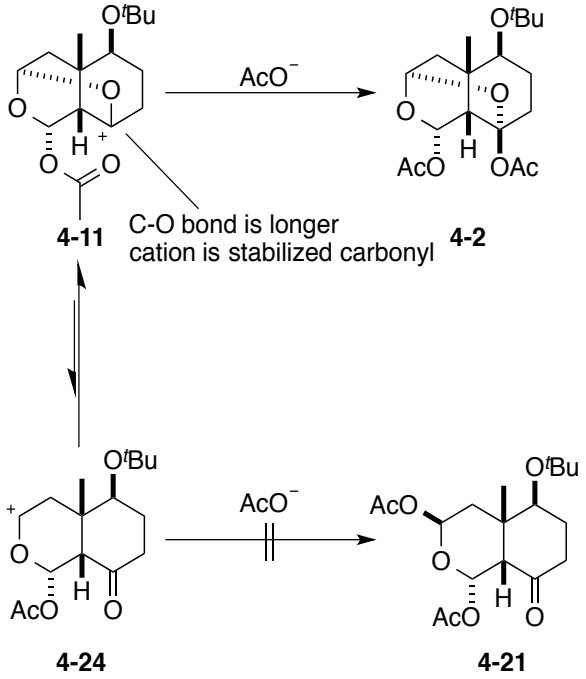
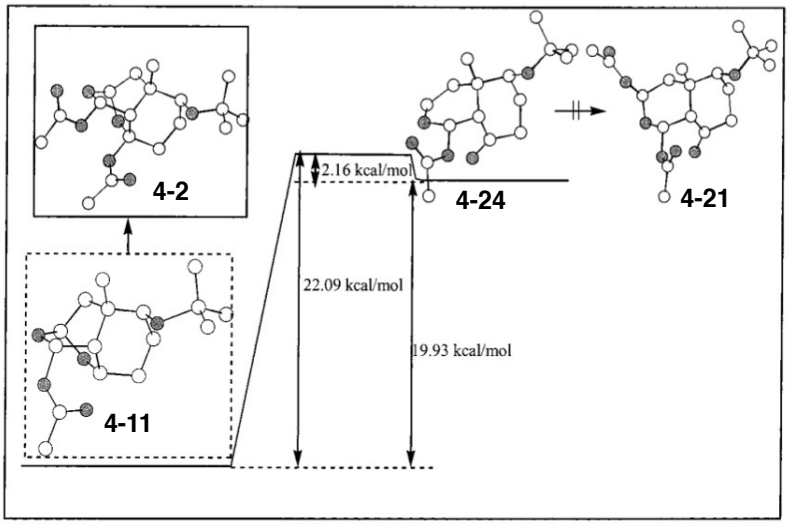


figure 4-5-1. energy plofile for **4-11** to **4-21**. (B3LYP/6-31G*)



4-5-2. regioselectivity of acetoxy group attack to **4-22**

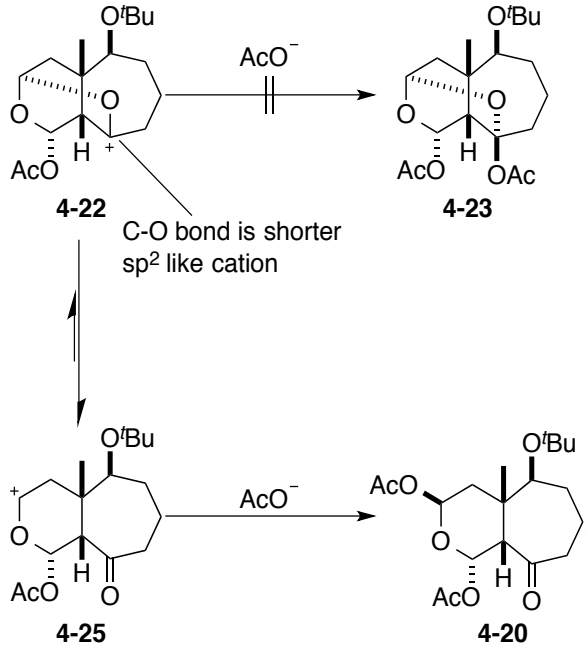
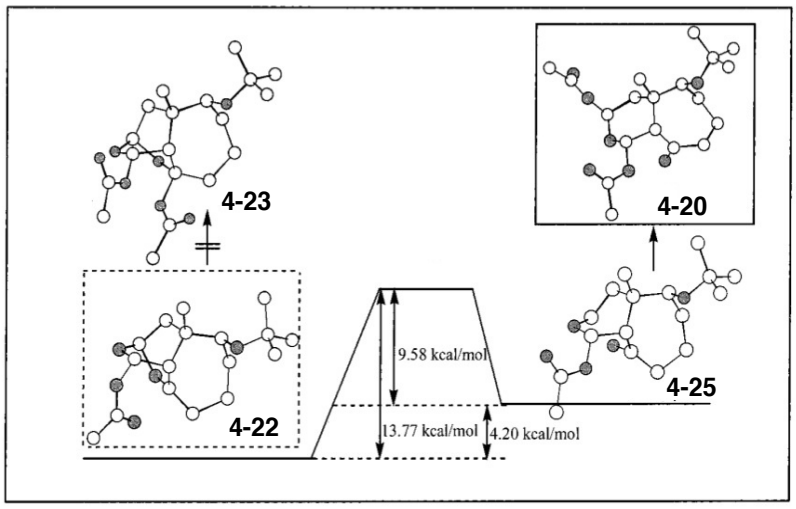


figure 4-5-2. energy plofile for **4-22** to **4-20**. (B3LYP/6-31G*)



Arsemoyados, S. et. al. *J. Org. Chem.* **2002**, *67*, 2447.

4-6. stereoselectivity of intramolecular aldol reaction