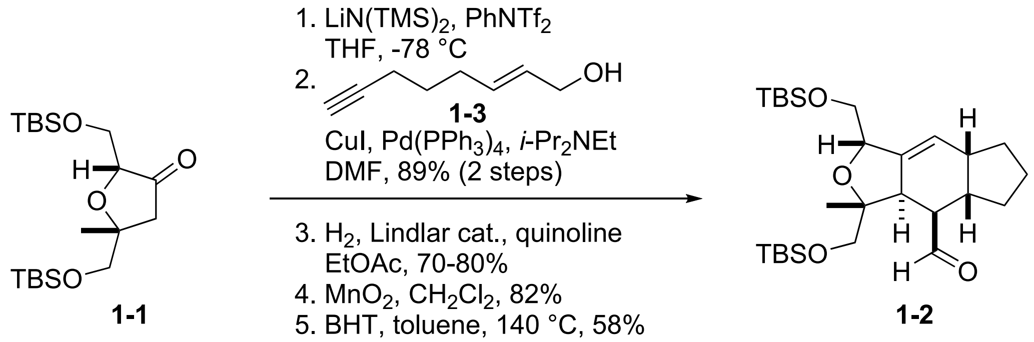
Problem Session (5)

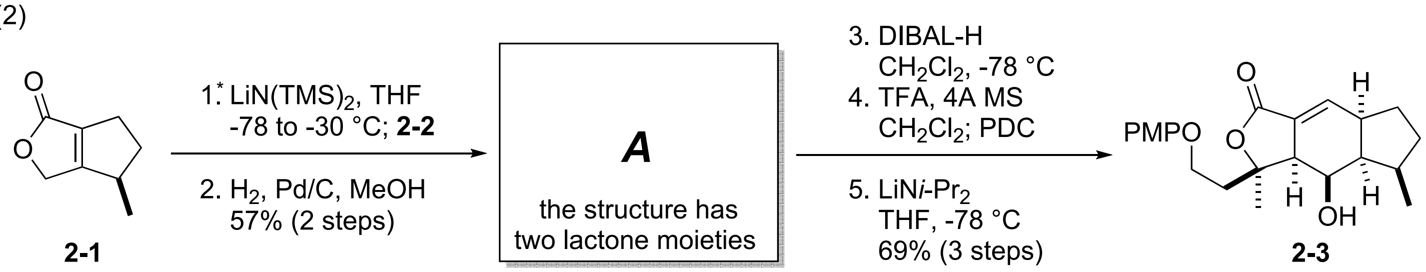
2016.7.4. Takahiro Kawamata

Please provide the reaction mechanisms and fill in the blank.

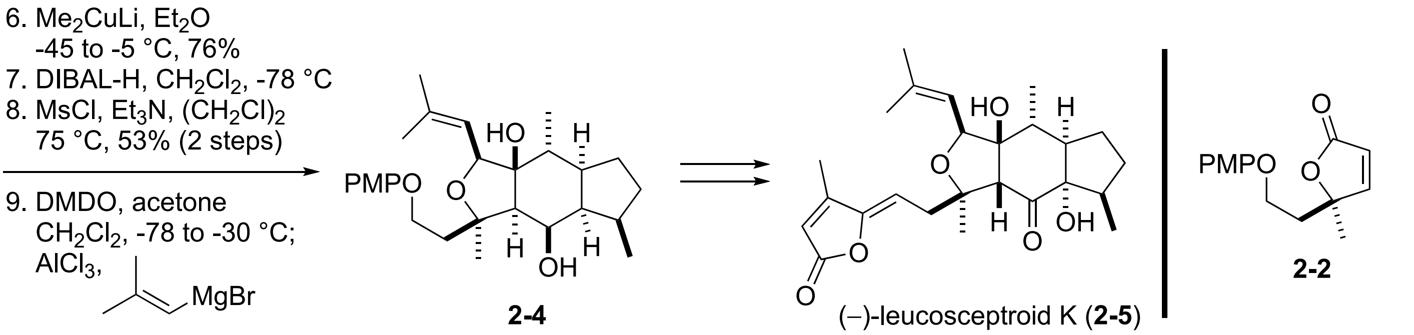
(1)



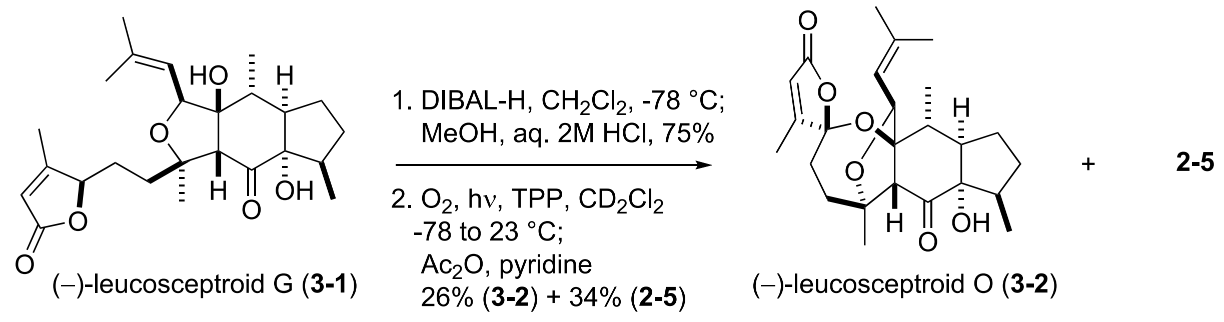
(2)



* The product of 1st step is 5/6/5-membered ring compound.



(3)



Abbreviations

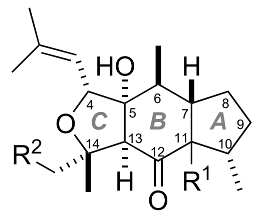
BHT = butylated hydroxytoluene PDC = pyridinium dichromate DMDO = dimethyldioxirane TPP = tetraphenylporphyrin

Problem Session Answer (5)

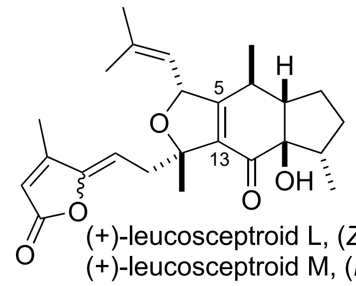
2016.7.4. Takahiro Kawamata

Topic : **Strategies for the synthesis of leucosceptroids**

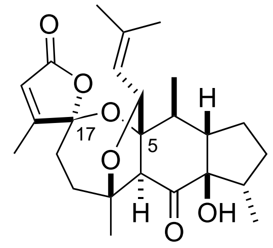
Introduction



(+)-leucosceptroid A-K
(shown in Table 1)

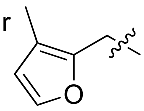
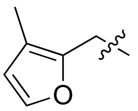
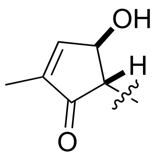
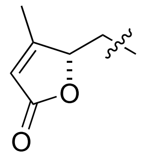
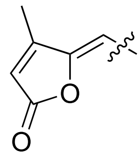


(+)-leucosceptroid L, (*Z*)
(+)-leucosceptroid M, (*E*)



(+)-leucosceptroid O

Table 1. leucosceptroid A-K

leucosceptroids	A	B	C	G	K
R^1	β-OH	α-H	β-OH	β-OH	β-OH
R^2	r 				

(0-1) Isolation[1]
trichomes, flowers and whole leaves of *Leucosceptrum canum Smith* which is a native plant in China and Nepal

(0-2) Biological activity[1]
nanomolar antifeedant activity againt both the cotton bollworm and the beet armyworm

(0-3) Structural features of leucosceptroid natural products[2]

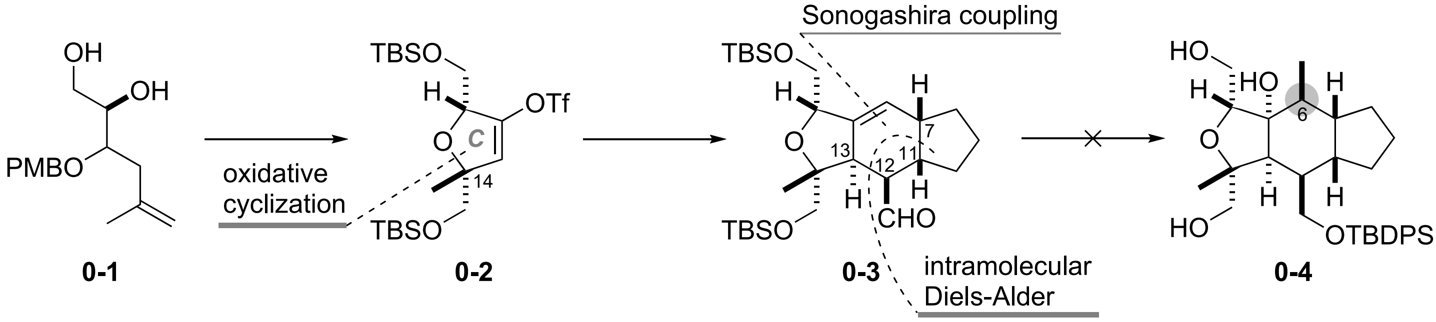
Common points
1. highly functionalized tricyclic framework
2. eight contiguous stereogenic centers

Different points
1. oxidation state at C11 (OH or H)
2. substitution of the southern hemisphere side chain (C14 linkage)
3. hydration/dehydration of the C5–C13 bond

(0-4) Synthetic approaches[2]

Asymmetric core struture synthesis by Horne and co-workers in 2011[3]

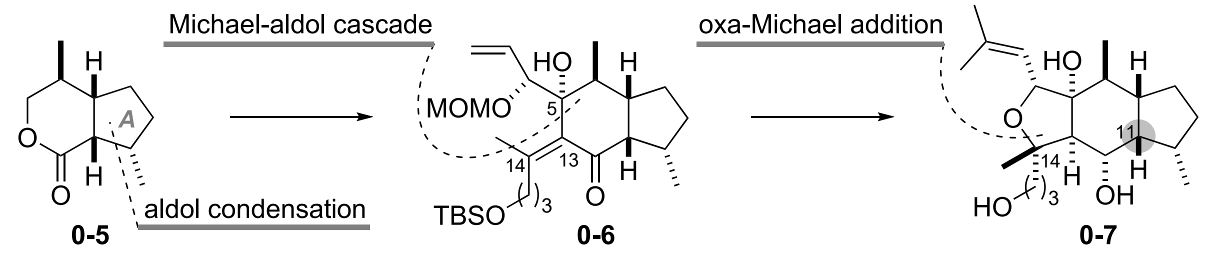
key : 1. oxidative cylization (C ring formation)
2. intramolecular Diels-Alder reaction (A and B ring formation) ⟹ problem 1



(1) (a) Luo, S.-H.; Luo, Q.; Niu, X.-M.; Xie, M.-J.; Zhao, X.; Schneider, B.; Gershenzon, J.; Li, S.-H. *Angew. Chem. Int. Ed.* **2010**, *49*, 4471. (b) Luo. S.-H.; Weng, L.-H.; Xie, M.-J.; Li, X.-N.; Hua, J.; Zhao, X.; Li, S.-H.; *Org. Lett.* **2011**, *13*, 1864. (c) Luo, S.-H.; Hua, J.; Niu, X.-M.; Liu, Y.; Li, C.-H.; Zhou, Y.-Y.; Jing, S.-X.; Zhao, X.; Li, S.-H. *Phitochemistry* **2013**, *86*, 29. (d) Luo, S.-H.; Hua, J.; Li, C.-H.; Liu, Y.; Li, X.-N.; Zhao, X.; Li, S.-H. *Tetrahedron Lett.* **2013**, *54*, 235.
(2) review: Hugelshofer, C. L.; Magauer, T. *Synlett* **2015**, *26*, 572.
(3) Xie, J.; Ma, Y.; Horne, D. A. *J. Org. Chem.* **2011**, *76*, 6169.

First total synthesis of leucosceptroid B by Liu and co-workers in 2013[4)]

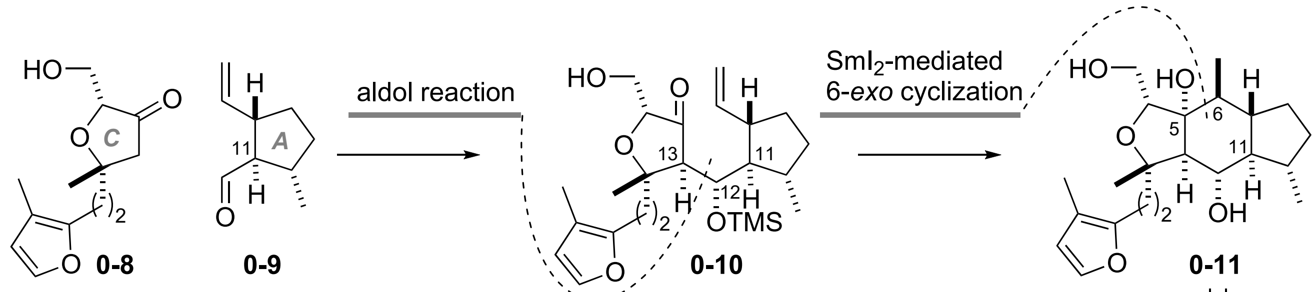
key : 1. aldol condensation (A ring formation)
2. Michael-aldol cascade reaction (B ring formation)
3. oxa-Michael addition (C ring formation)



(+)-leucosceptroid B (19 steps, 2.7%)

Total synthesis of leucosceptroid A and B by Ma and co-workers in 2015[5)]

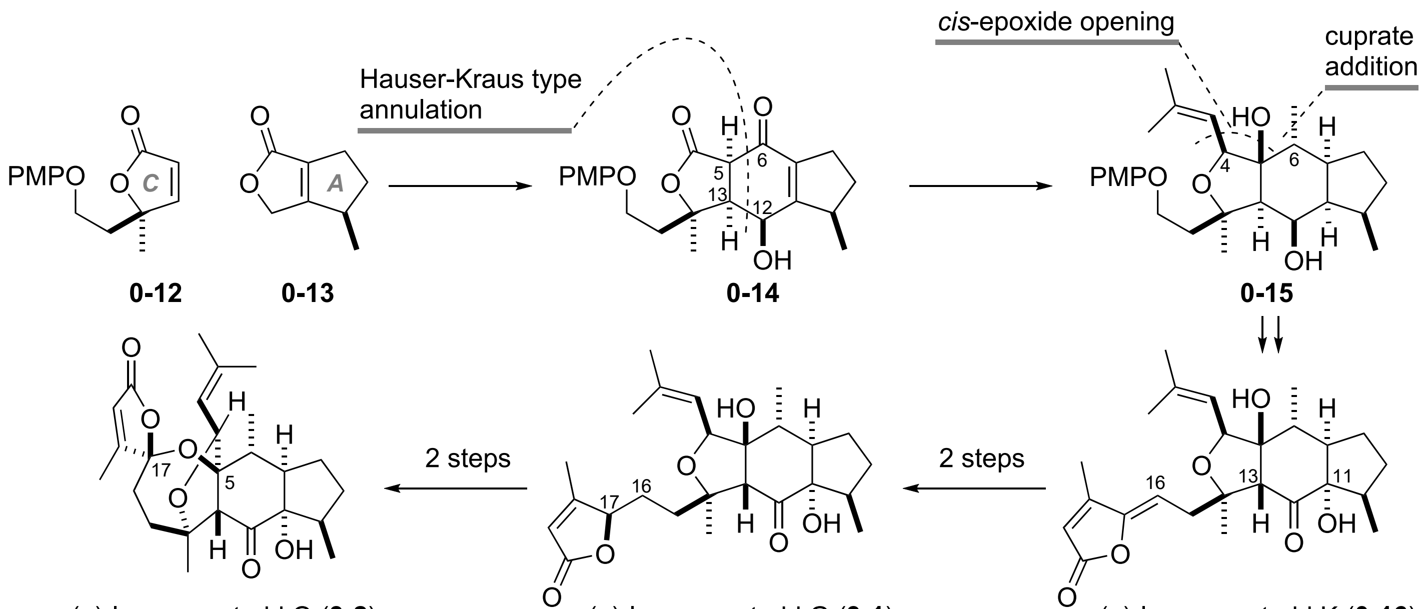
key : 1. aldol reaction (connection between A and C rings)
2. late-stage intramolecular ketyl-olefin radical cyclization (B ring formation)



oxidation at C11 → (+)-leucosceptroid B (18 steps, 5.6%)
(+)-leucosceptroid A

Collective synthesis of leucosceptroid natural products by Magauer and co-workers in 2014-2015[6)]

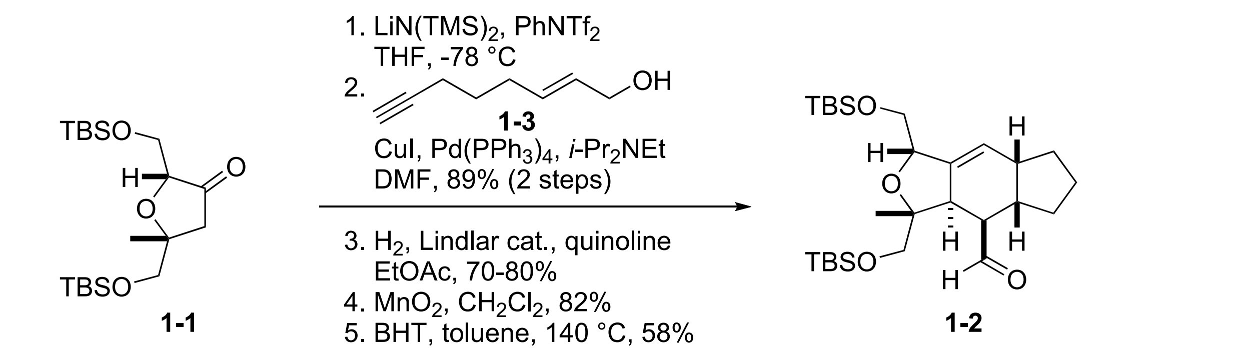
key : 1. Hauser-Kraus type annulation (B ring formation)
2. *cis*-epoxide opening and cuprate addition (introduction of C4- and C6-carbon units) ⟹ problem 2
3. bioinspired photo-oxidation (synthesis of leucosceptroid O from G) ⟹ problem 3



(–)-leucosceptroid O (**3-2**) (–)-leucosceptroid G (**3-1**) (–)-leucosceptroid K (**0-16**)
(19 steps, 0.14%)

(4) Huang, X.; Song, L.; Xu, J.; Zhu, G.; Liu, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 952.
(5) Guo, S.; Liu, J.; Ma, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 1298.
(6) (a) Hugelshofer, C. L.; Magauer, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 11351. (b) Hugelshofer, C. L.; Magauer, T. *J. Am. Chem. Soc.* **2015**, *137*, 3807.

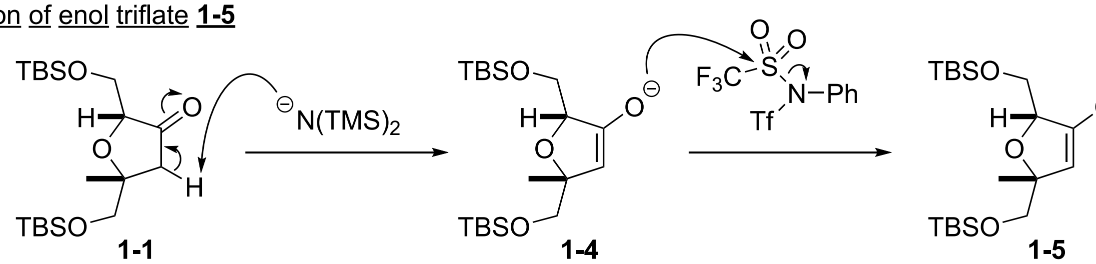
(1)



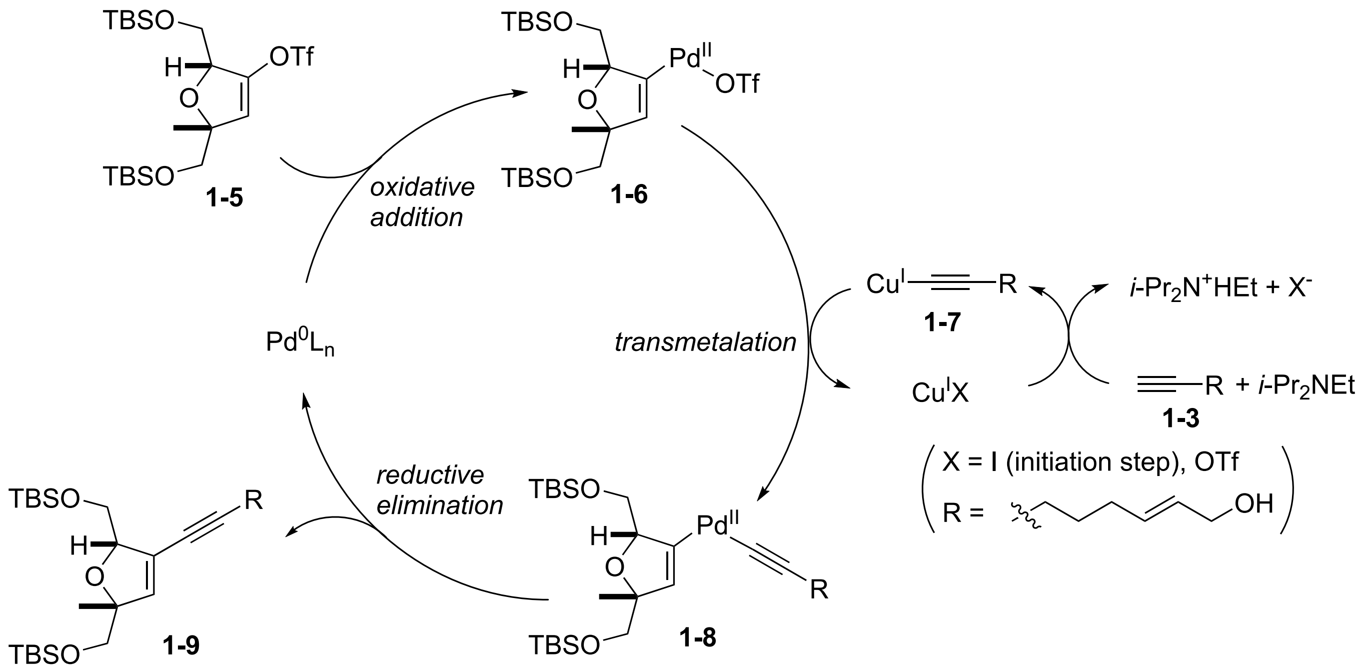
Xie, J.; Ma, Y.; Horne, D. A. *J. Org. Chem.* **2011**, *76*, 6169.

(1-1) Proposed mechanisms

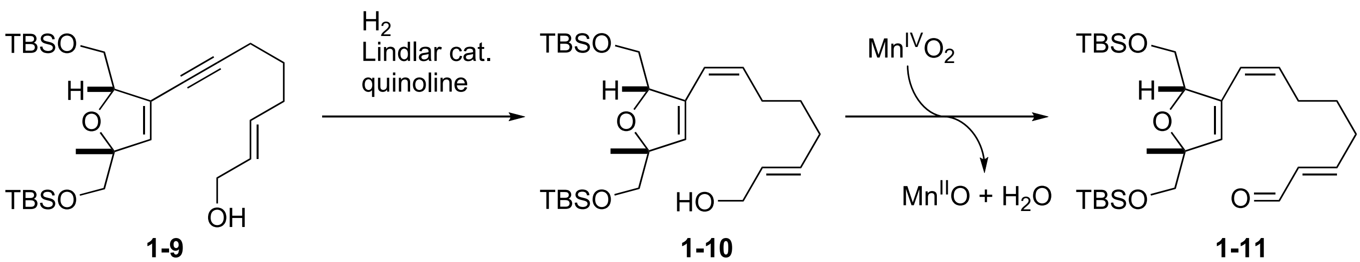
Formation of enol triflate **1-5**

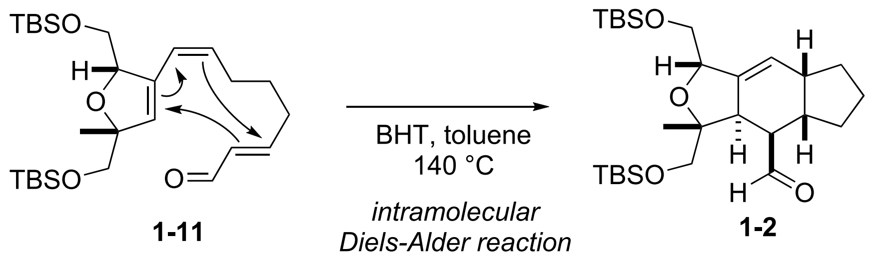


Sonogashira coupling



Formation of aldehyde **1-11**





1-11 → **1-2**

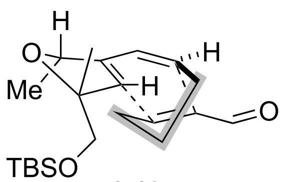
(1-2) Discussion

(1-2-1) Selectivity in Diels-Alder reaction

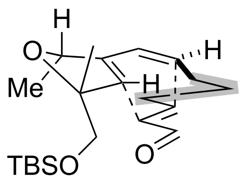
1. *endo/exo* selectivity
2. regioselectivity
3. face selectivity

} 2^3 = 8 isomers

(1-2-2) Consideration abount *exo*-type transition state

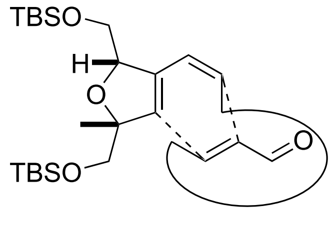
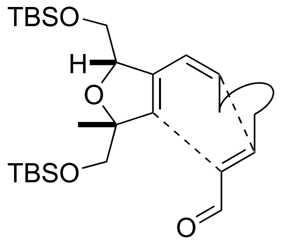
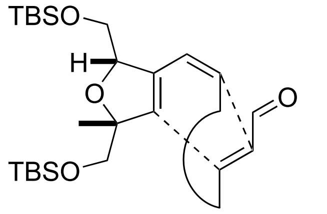
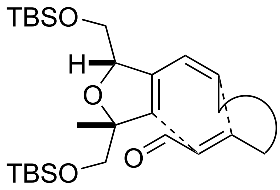


1-13a
(**1-12-exo-A** type)



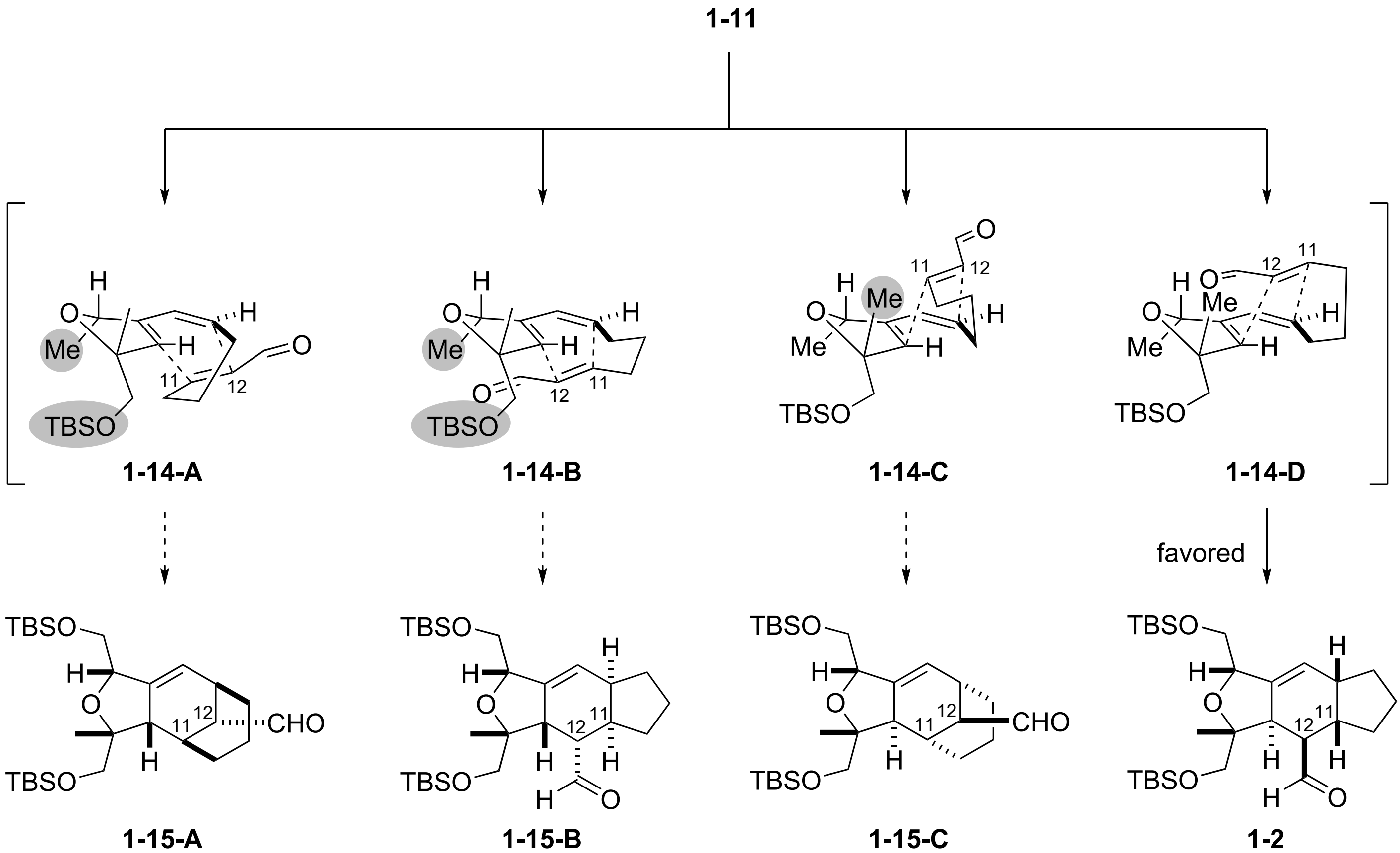
1-13b
(**1-12-exo-B** type)

These transition states are impossible because the highlitened 3-carbon chains are too short.

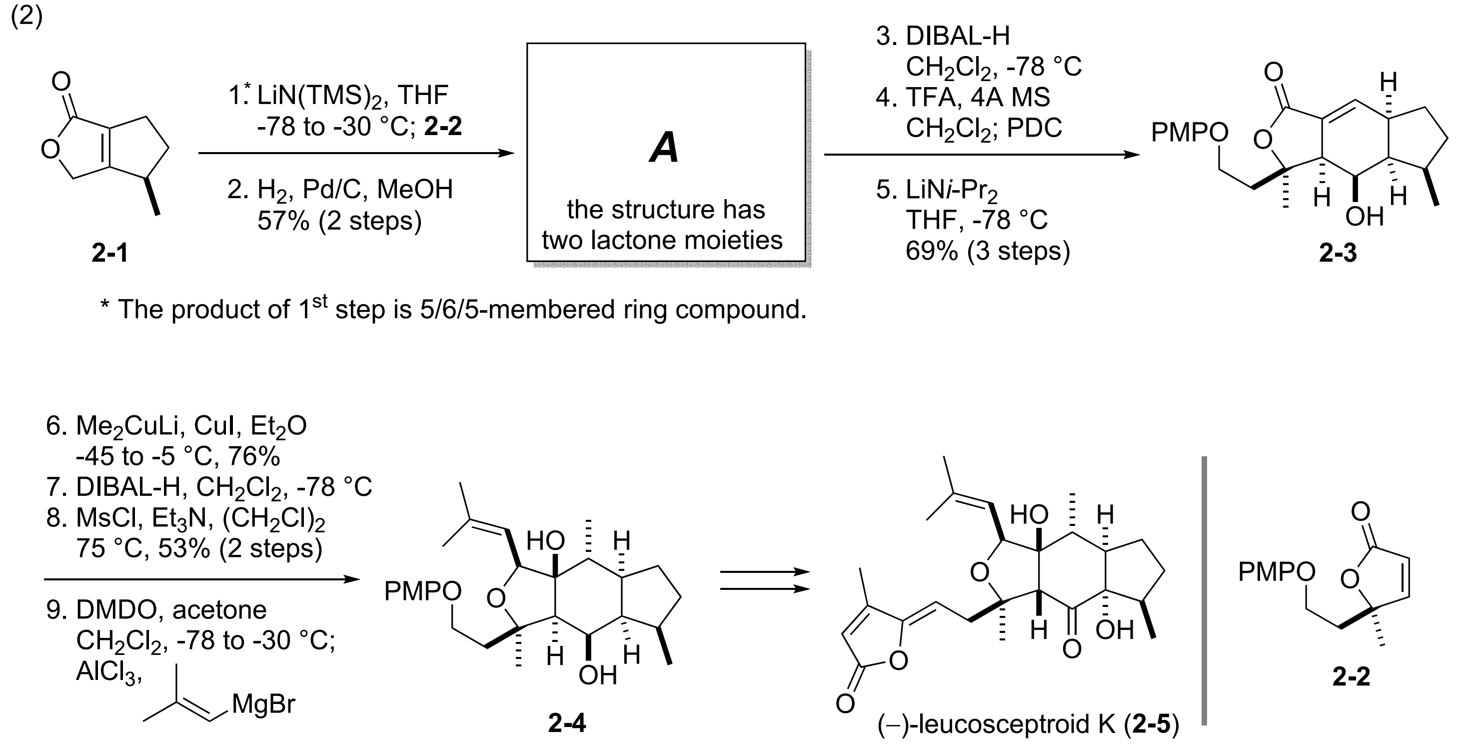
	regioselectivity	
exo	 **1-12-exo-A**	 **1-12-exo-B**
endo	 **1-12-endo-A**	 **1-12-endo-B**

face selectivity (x 2)

(1-2-2) Consideration abount *endo*-type transition state

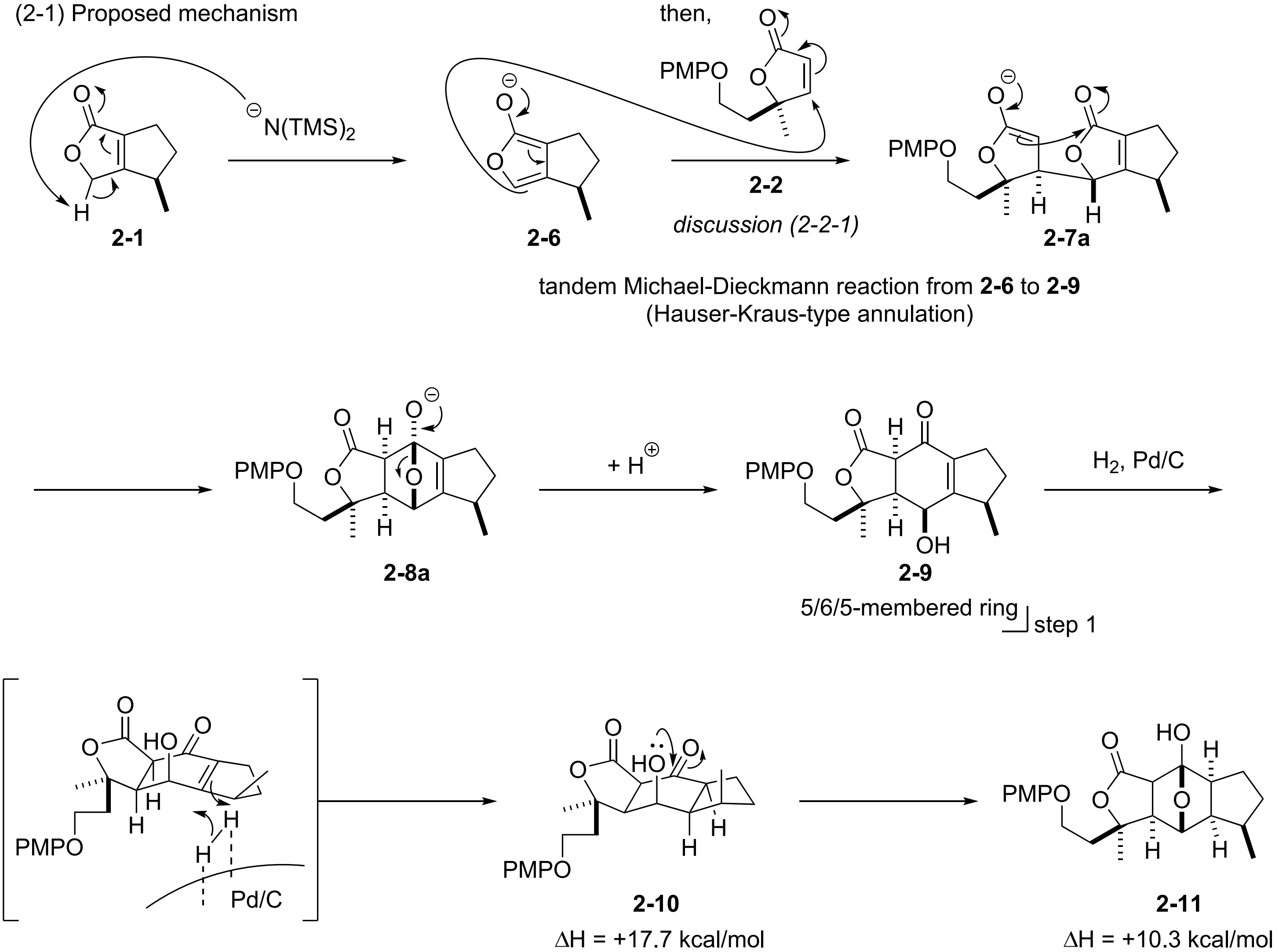


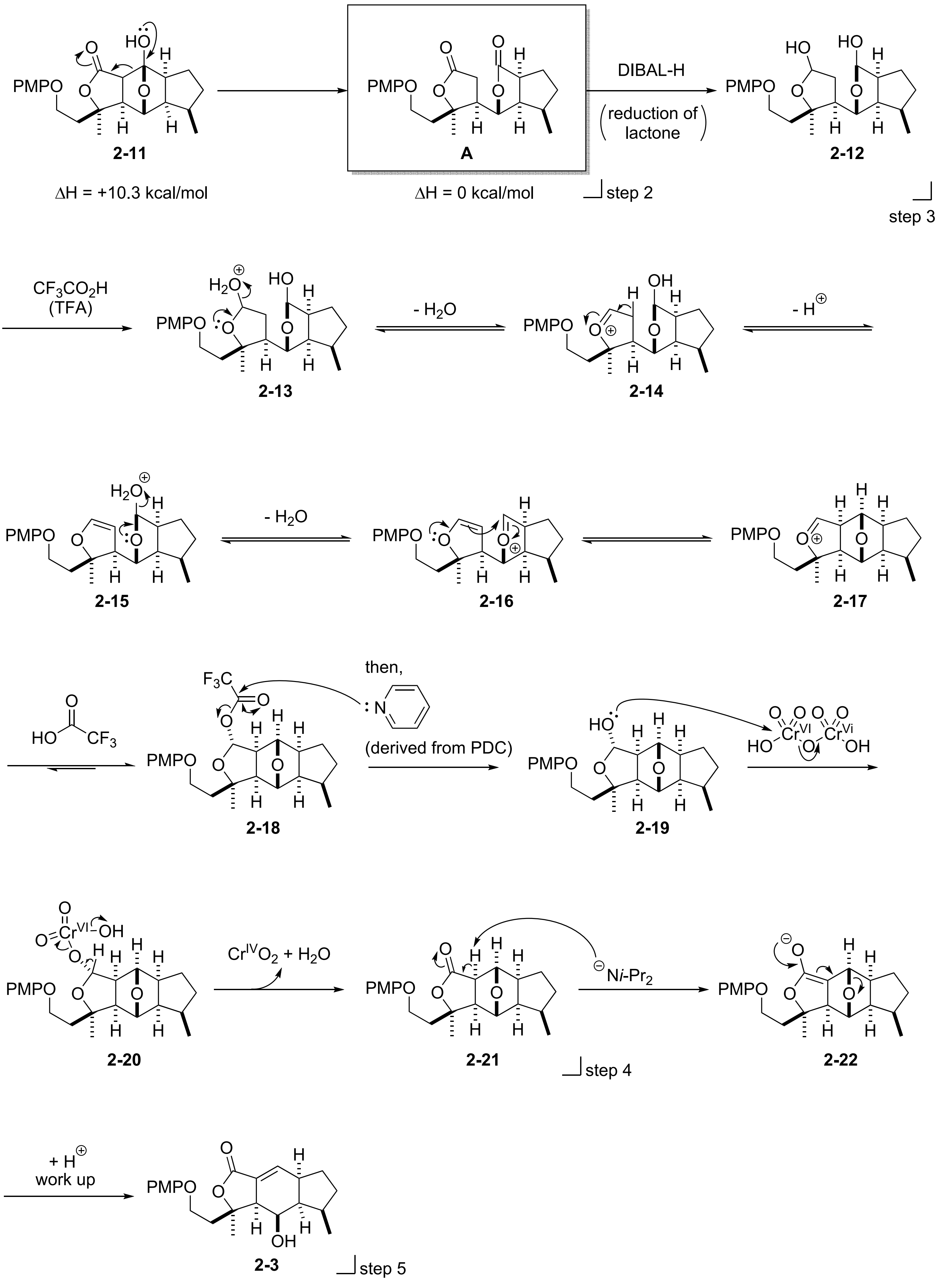
(2)

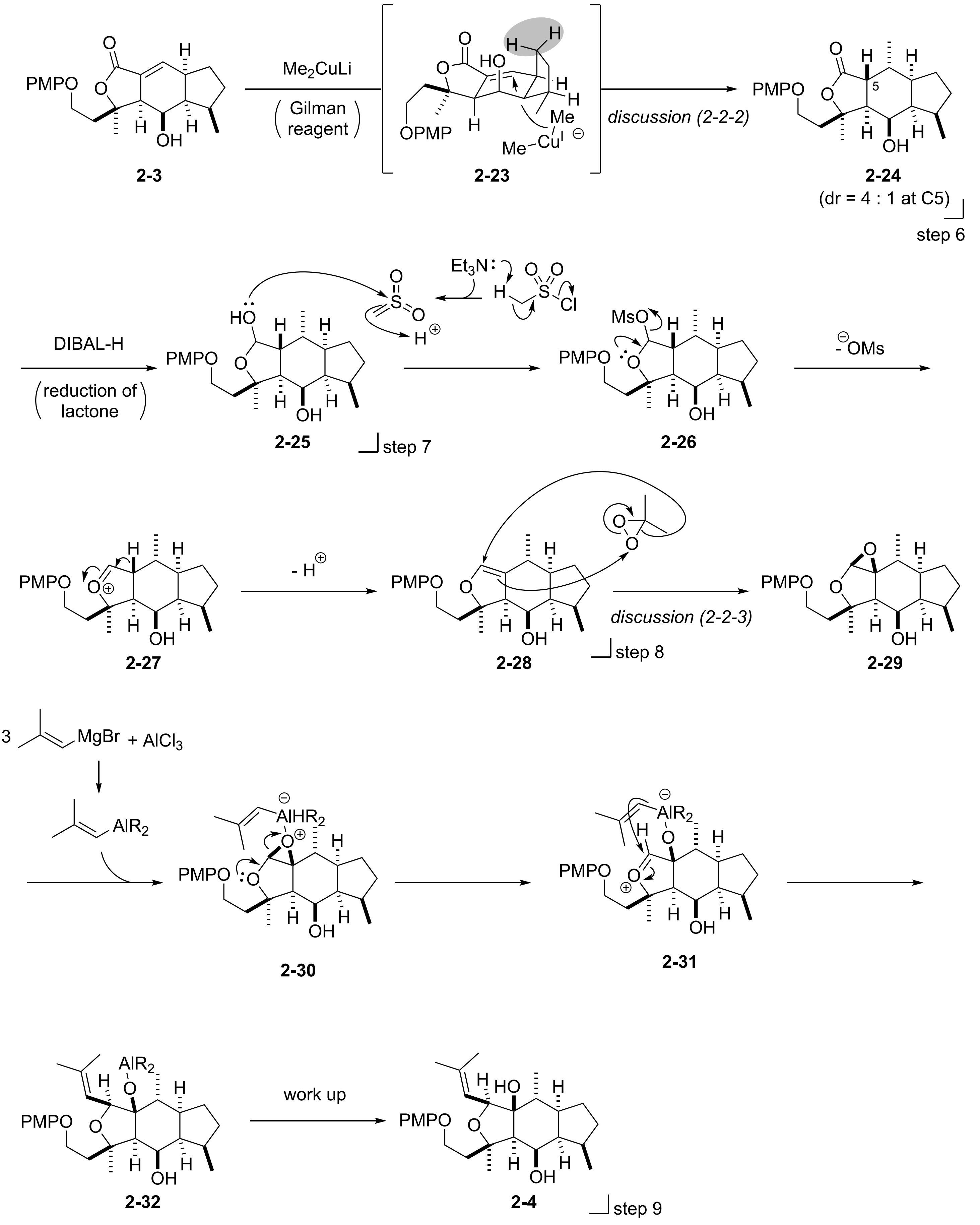


Hugelshofer, C. L.; Magauer, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 11351.

(2-1) Proposed mechanism

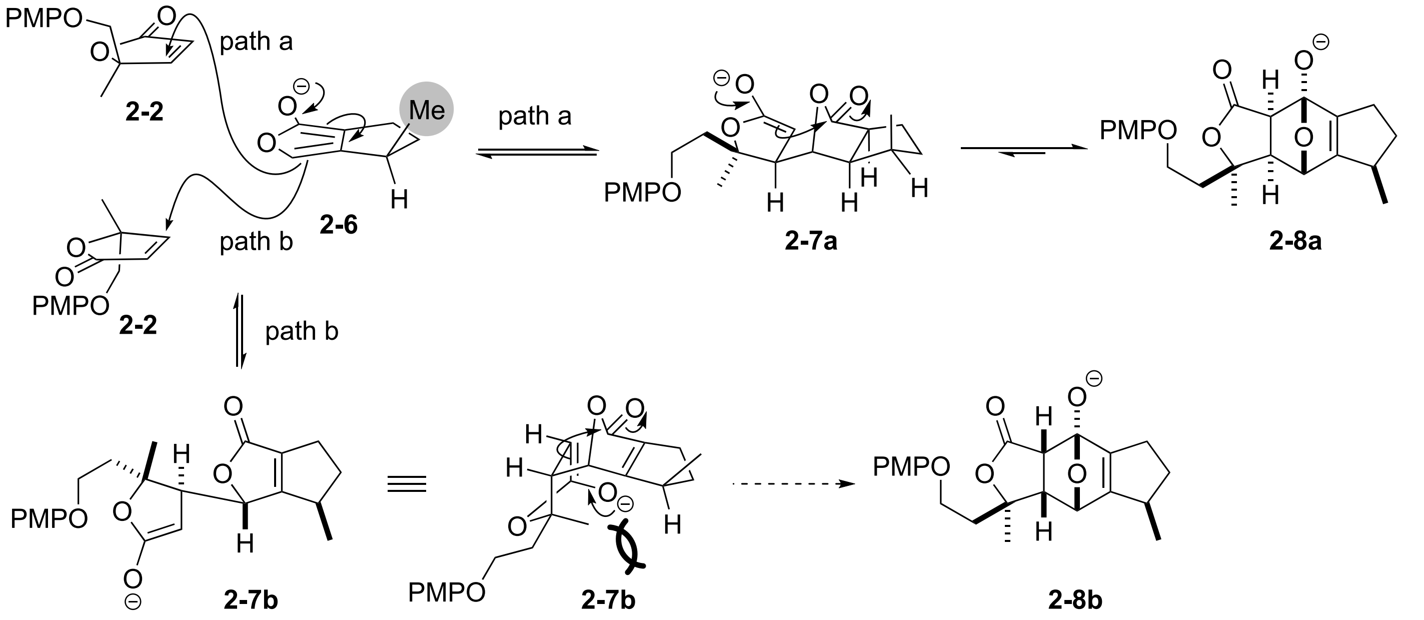



2-11
ΔH = +10.3 kcal/mol
A
ΔH = 0 kcal/mol
DIBAL-H
(reduction of lactone)
step 2
2-12
step 3
CF3CO2H (TFA)
2-13
- H2O
2-14
- H
2-15
- H2O
2-16
2-17
2-18
then,
(derived from PDC)
2-19
2-20
CrIVO2 + H2O
2-21
step 4
Ni-Pr2
2-22
+ H
work up
2-3
step 5
PMPO

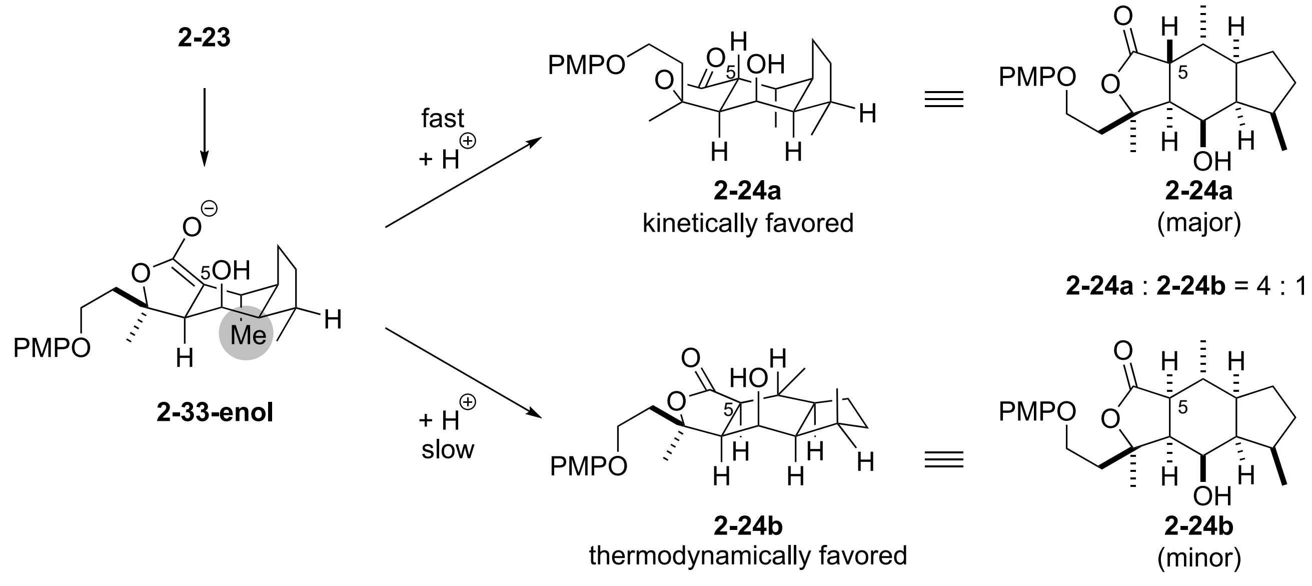

Me2CuLi
Gilman reagent
discussion (2-2-2)
2-3
2-23
2-24
(dr = 4 : 1 at C5)
step 6
DIBAL-H
reduction of lactone
2-25
step 7
Et3N
2-26
- OMs
- H
2-27
2-28
step 8
discussion (2-2-3)
2-29
3 MgBr + AlCl3
AlR2
AlHR2
2-30
2-31
2-32
work up
2-4
step 9

(2-2) Discussion

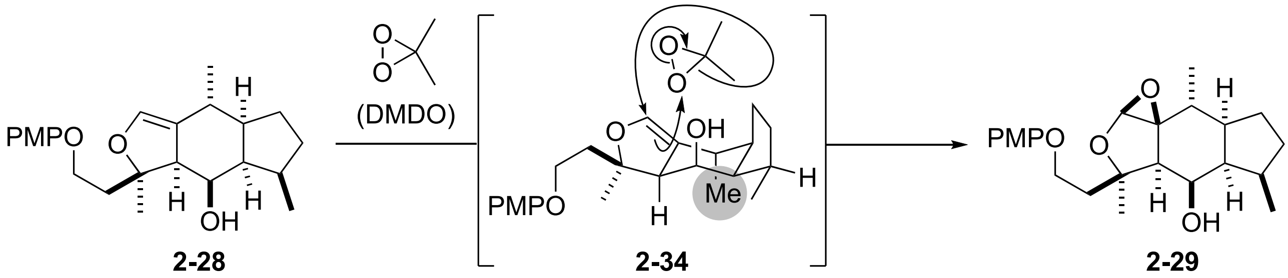
(2-2-1) Regioselectivity in tandem Michael-Dieckmann reaction from **2-6** to **2-8a**



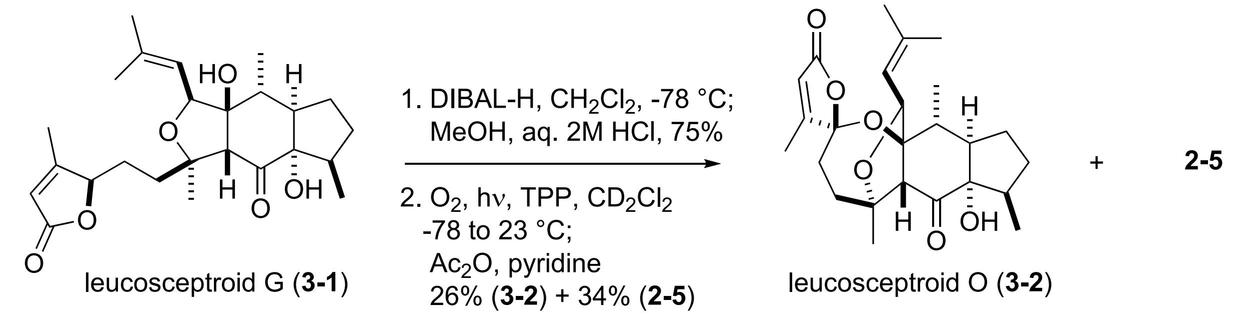
(2-2-2) Regioselectivity at C5 position of **2-24**



(2-2-3) Regioselectivity in epoxidation from **2-28** to **2-29**



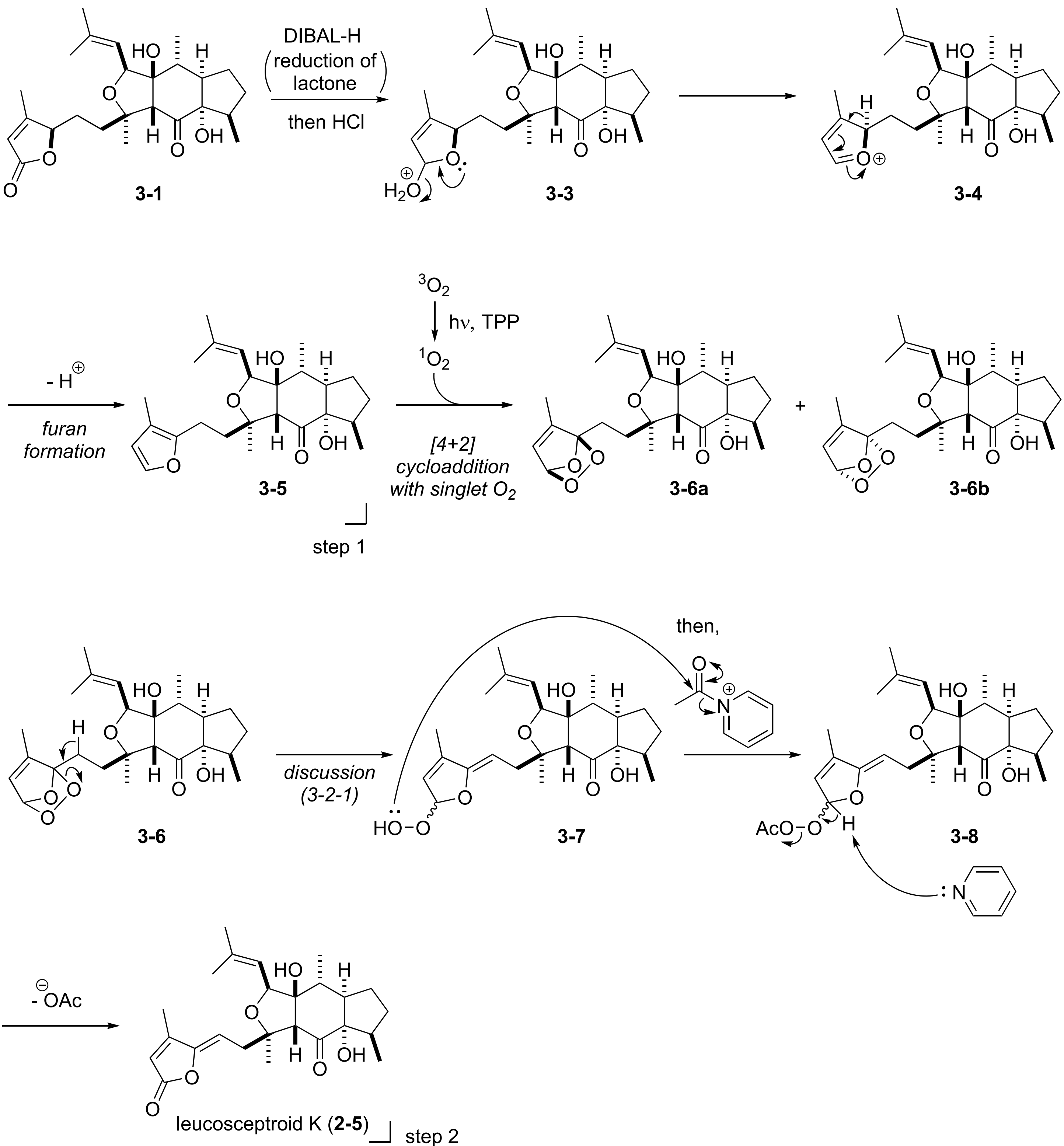
(3)



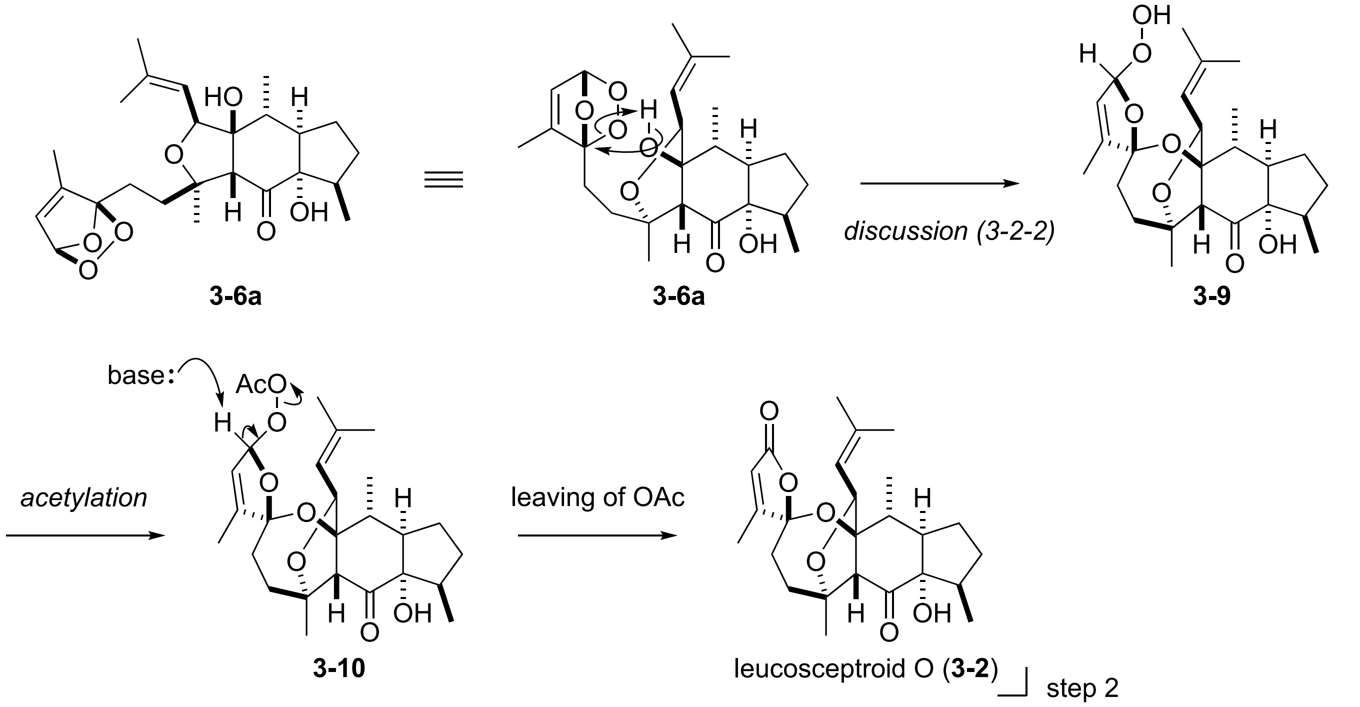
Hugelshofer, C. L.; Magauer, T. *J. Am. Chem. Soc.* **2015**, *137*, 3807.

(3-1) Proposed machanism

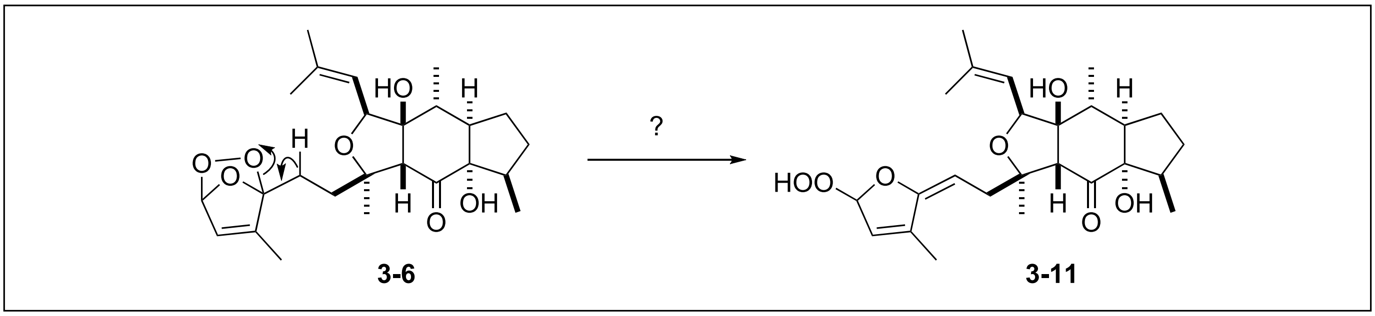
(3-1-1) Pathway from **3-1** to **2-5**



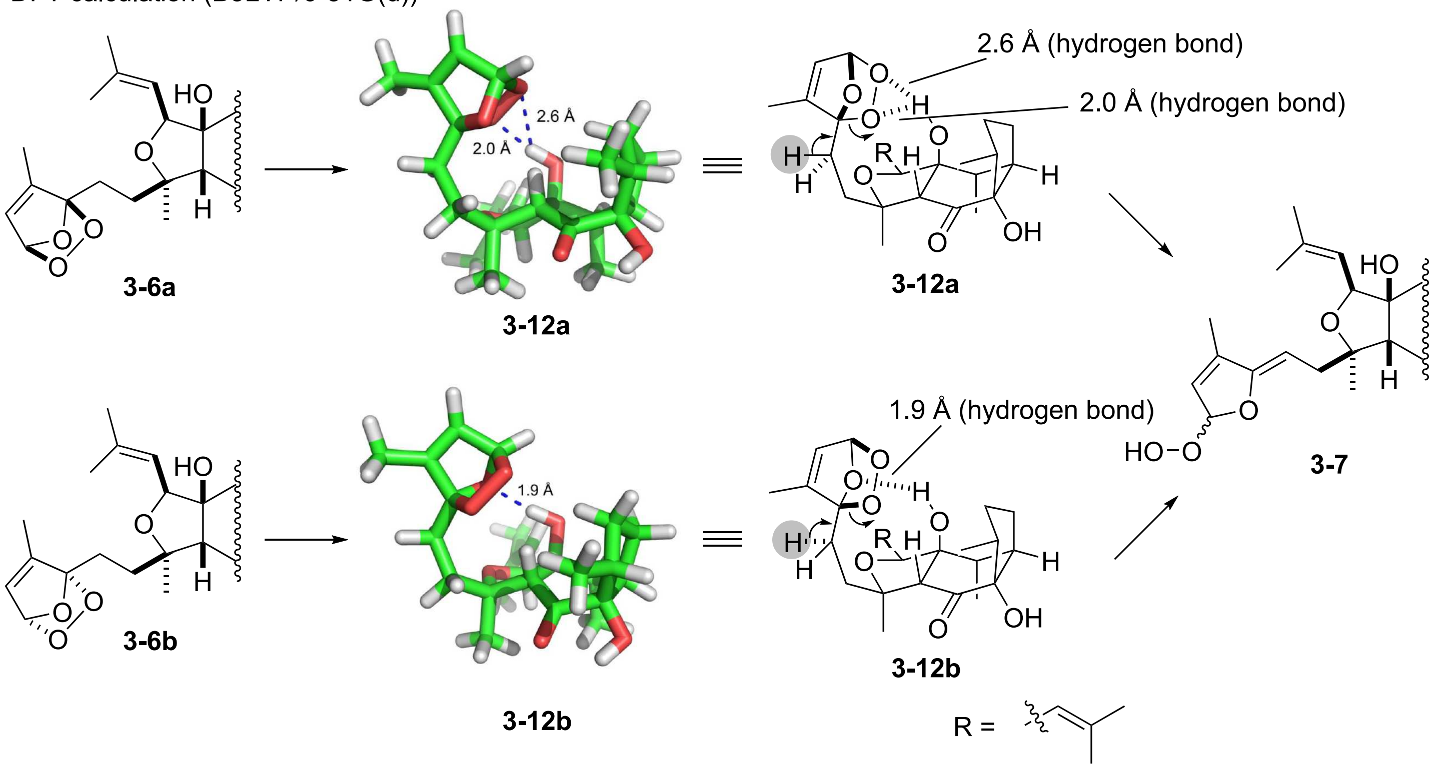
(3-1-2) Pathway from **3-1** to **3-2**



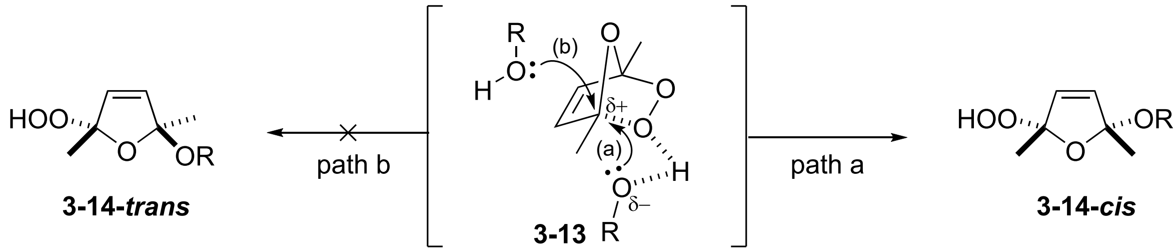
(3-2) Discussion
(3-2-1) Possibility of olefin isomer **3-11**



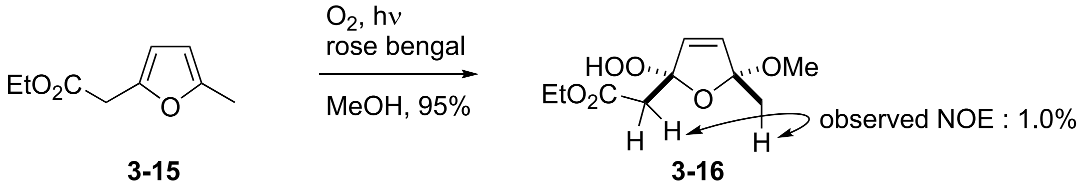
DFT calculation (B3LYP/6-31G(d))



(3-2-2) Reactions of ozonides with alcohols



Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057.



Kalaitzakis, D.; Triantahyllakis, M.; Alexopoulou, I.; Sofiadis, M.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 13201.

<u>Possibility of the formation of the isomer **3-17** at C17 position</u>