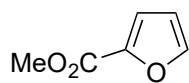


# Problem Session (3)

2017.11.18. Yinghua Wang

Please fill in the blank and provide each reaction mechanisms.

1



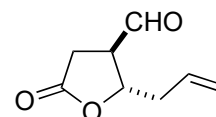
1-1

1.  $\text{N}_2\text{CHCO}_2\text{Et}$  (1.67 eq.),  $\text{Cu}(\text{OTf})_2$  (0.75 mol%)  
 $S,S$ -*i*-Pr-BOX (1 mol%),  $\text{PhNHNH}_2$  (0.9 mol%)  
 $\text{CH}_2\text{Cl}_2$ , 0 °C, 44%

2.  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ , -78 °C;  $\text{Me}_2\text{S}$ , 91%

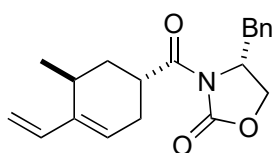
3. ,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , -78 °C

4.  $\text{Et}_3\text{N}$ ,  $\text{MeOH}$ , 68% (2 steps)



1-2

2



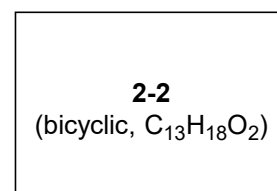
2-1

1.  $\text{LiBH}_4$ ,  $\text{MeOH}$ ,  $\text{THF}$ , 0 °C

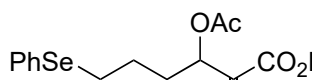
2.  $(\text{COCl})_2$ ,  $\text{DMSO}$ ,  $\text{CH}_2\text{Cl}_2$ , -78 °C;  $\text{Et}_3\text{N}$ , 0 °C

3.  $\text{LiClO}_4$ , *i*- $\text{Pr}_2\text{NEt}$ ,  $\text{TMSQ}$  (10 mol%),  $\text{EtCOCl}$   
 $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ , -40 °C, 55% (3 steps)

4.  $\text{EtAlCl}_2$ , toluene, 67-75%

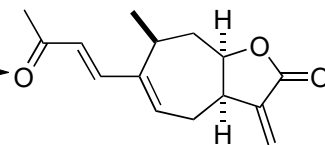


3



3-1

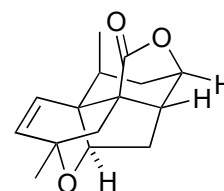
1.  $(\text{pinB})_2$ ,  $\text{CuCl}$ ,  $\text{LiCl}$   
 $\text{KOAc}$ ,  $\text{DMF}$   
 80% (E/Z = 4/1)  
 2. **A**, *p*- $\text{TsOH}$  (30 mol%)  
 toluene  
 80% (dr = 1.6:1)  
 3.  $\text{TBAF}$ ,  $\text{THF}$ , 74%  
 4.  $\text{H}_2\text{O}_2$ ,  $\text{THF}$ , 83%  
 5.  $\text{MVK}$  (10 eq)  
 $\text{HG2}$  (20 mol%)  
 $\text{CH}_2\text{Cl}_2$ , reflux, 81%



3-2

$h\nu$  (Hg lamp),  $\text{DBU}$   
 $\text{CH}_2\text{Cl}_2/\text{pentane}$   
 2.5 h, quartz flask;  
 45 °C, 4.5 h

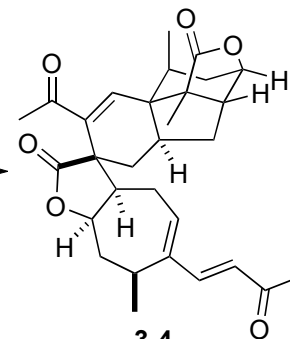
40%



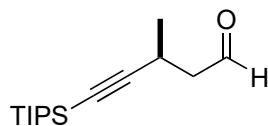
3-3

BHT,  $\text{EtOH}$   
 180 °C

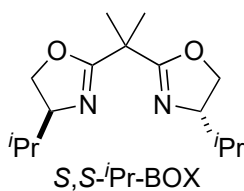
40%



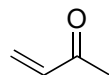
3-4



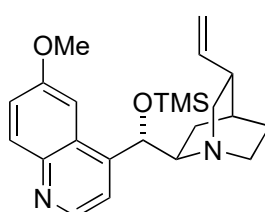
**A** (95% ee)



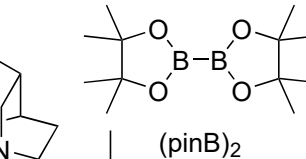
$S,S$ -*i*-Pr-BOX



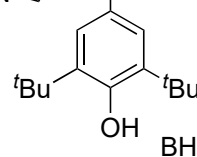
MVK



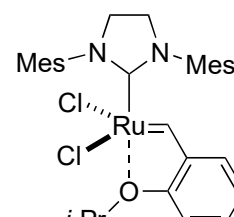
TMSQ



(pinB)<sub>2</sub>



BHT



HG2

(Hoveyda-Grubbs 2<sup>nd</sup> catalyst)

## Problem Session (3) -Answer-

2017.11.18. Yinghua Wang

### Topic: Total Syntheses of Xanthanolides

#### 0. Introduction

##### 0-1. Isolation

primarily isolated from genus *Xanthium*, family *Compositae*

xanthatin: Little, J. E.; Foote, D. B.; Johnstone, D. B. *Arch. Biochem.* **1950**, *27*, 247.

review: Vasas, A.; Hohmann, J. *Nat. Prod. Rep.* **2011**, *28*, 824.

##### 0-2. Biological activity

Many varieties of biological activities are reported; antimicrobial, antiviral, antibacterial, antitumor activity and so on.

review: Vasas, A.; Hohmann, J. *Nat. Prod. Rep.* **2011**, *28*, 824.

##### 0-3. Structural feature

a bicyclic sesquiterpene lactone

five-membered  $\gamma$ -butyrolactone ring is fused to a seven-membered carbocycle

generally unsaturated at C1-C5 and C2-C3 positions

##### 0-4. Total synthesis of xanthanolides

• *cis*-fused series:

Martin et. al. *Org. Lett.* **2005**, *7*, 4621. ((+)-8-*epi*-xanthatin, 5.5%, 14 steps)

Shishido et. al. *Org. Lett.* **2007**, *9*, 969. ((+)-sundiversifolide, 13%, 21 steps)

Takikawa et. al. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 2046. (( $\pm$ )-sundiversifolide, 3.5%, 14 steps)

Shishido et. al. *Org. Lett.* **2008**, *10*, 1247. ((+)- and (-)-sundiversifolide, 25%, 20 steps)

Shishido et. al. *Heterocycles* **2009**, *77*, 773. ((-)-sundiversifolide, 2.5%, 26 steps)

Shindo et. al. *Tetrahedron* **2010**, *66*, 8407. ((+)-8-*epi*-xanthatin, 6.5%, 24 steps)

Tang et. al. *Angew. Chem. Int. Ed.* in press ((+)-8-*epi*-xanthatin, 15%, 7 steps, **Problem 3**)

• *trans*-fused series:

Morken et. al. *Org. Lett.* **2005**, *7*, 3371. ((-)-11 $\alpha$ ,13-dihydroxanthatin, 5.6%, 19 steps)

Shishido et. al. *Tetrahedron Lett.* **2008**, *49*, 3504. ((-)-xanthatin, 5.6%, 30 steps)

Shindo et. al. *Tetrahedron* **2010**, *66*, 8407. ((-)-xanthatin, 2.3%, 28 steps)

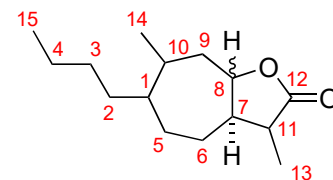
Tang et. al. *Angew. Chem. Int. Ed.* **2012**, *51*, 6984. ((-)-xanthatin, 9.4%, 9 steps, **Problem 2**)

Reiser et. al. *Chem. Eur. J.* **2014**, *20*, 7613. ((-)-xanthatin, 9.7%, 19 steps, **Problem 1**)

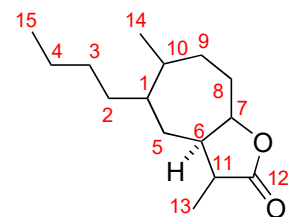
• Dimer of xanthanolides:

Tang et. al. *Angew. Chem. Int. Ed.* **2014**, *53*, 14494. (Dimer of (-)-xanthatin)

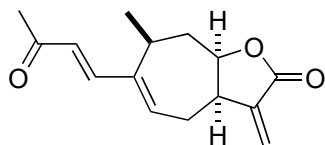
Tang et. al. *Angew. Chem. Int. Ed.* in press (Dimer of (+)-8-*epi*-xanthatin, **Problem 3**)



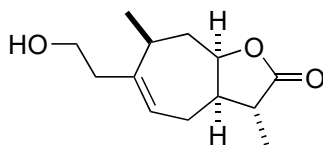
12,8-Xanthanolides (0-1)



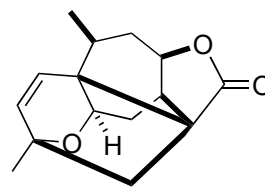
12,6-Xanthanolides (0-2)



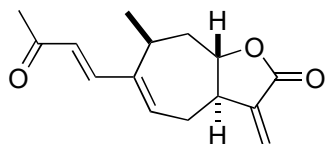
(+)-8-*epi*-xanthatin (0-3)



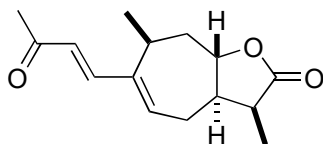
(+)-sundiversifolide (0-4)



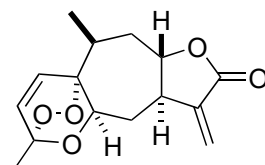
xanthipungolide (0-4)



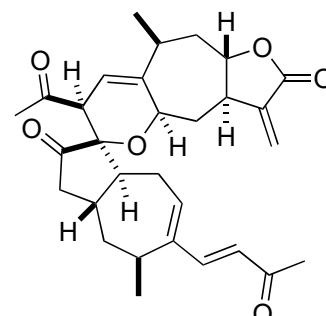
(-)-xanthatin (0-5)



(-)-11 $\alpha$ ,13-dihydroxanthatin (0-6)

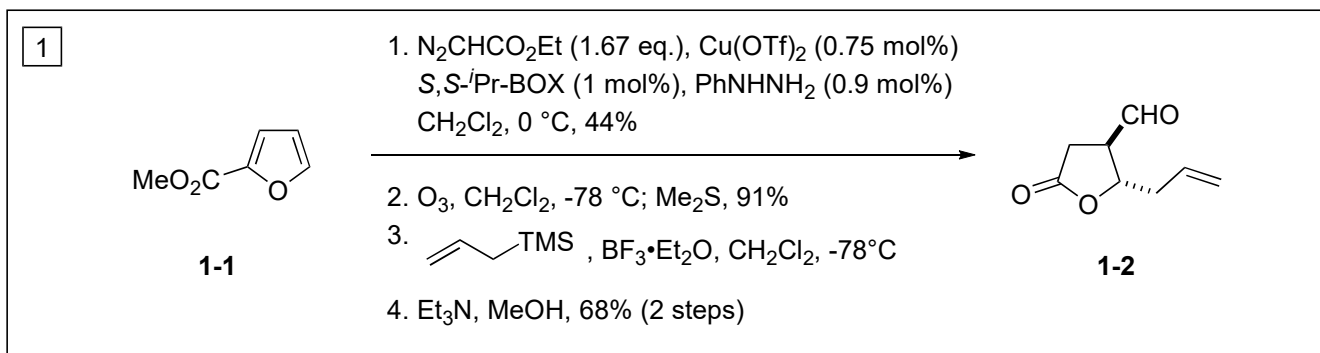


4 $\beta$ ,5 $\beta$ -epoxyxanthatin-1 $\alpha$ ,4 $\alpha$ -endoperoxide (0-7)



mogolide B (0-8)

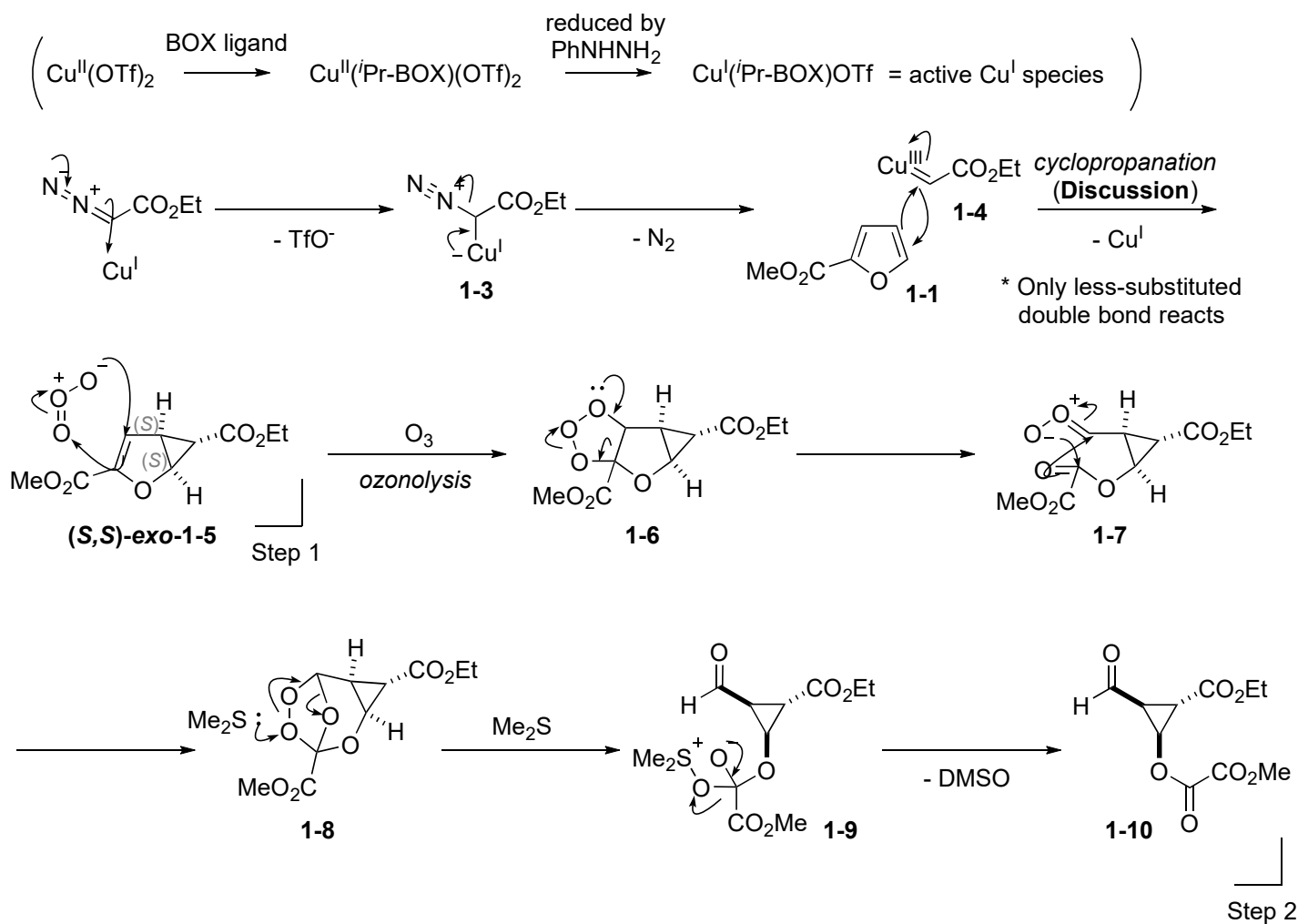
**-Answer-**



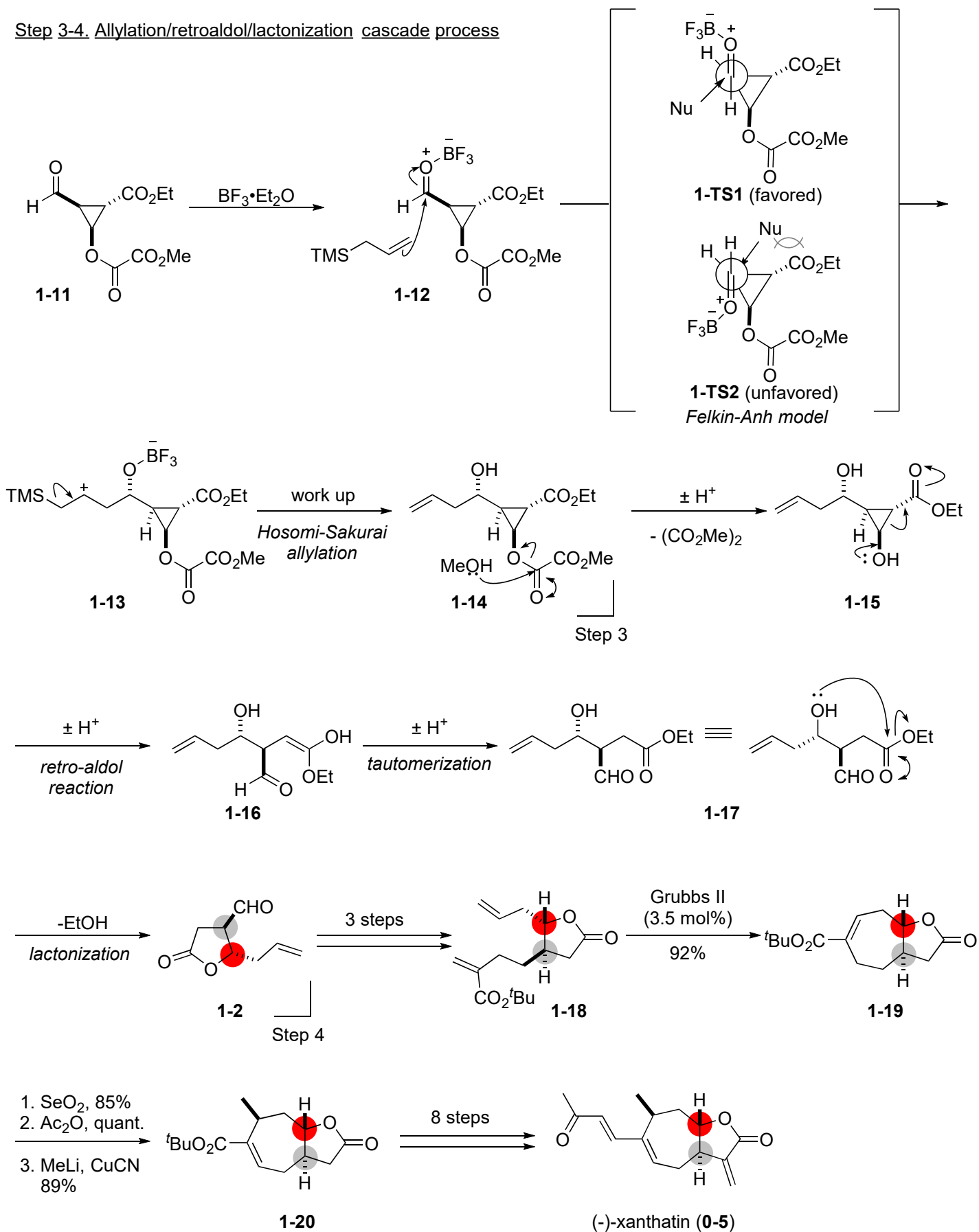
Nosse, B.; Chhor, R. B.; Jeong, W. B.; Bohm, C.; Reiser, O. *Org. Lett.* **2003**, 5, 941.  
 Bergmann, A.; Reiser, O. *Chem. Eur. J.* **2014**, 20, 7613.

- Reiser constructed the bicyclic core nucleus of xanthanolides the first time in 2003
- Synthesis of a chiral lactone from furans via asymmetric cyclopropanation as the key step.

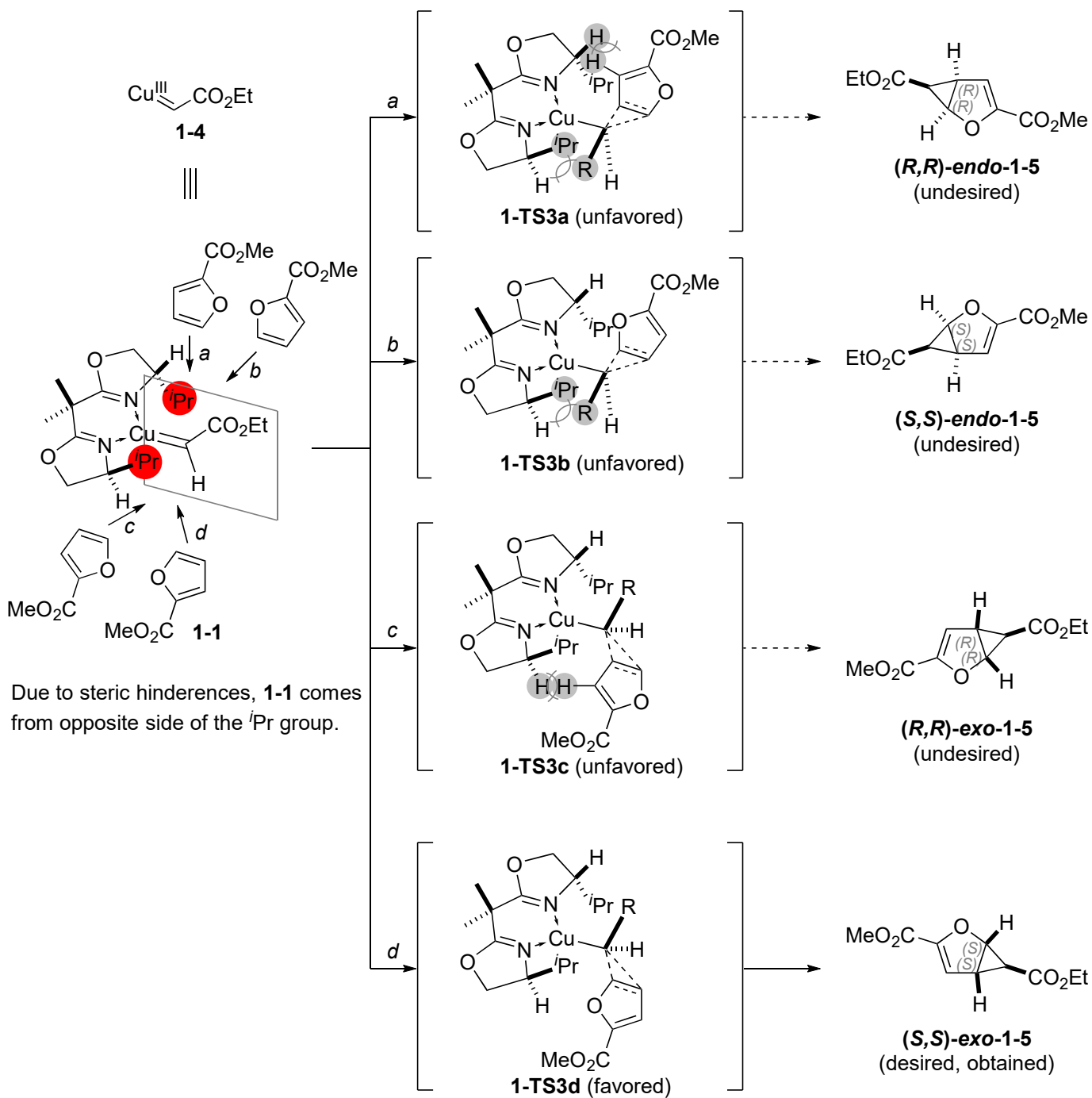
Step 1-2. Formation of cyclopropane carbaldehyde via asymmetric cyclopropanation and ozonolysis.



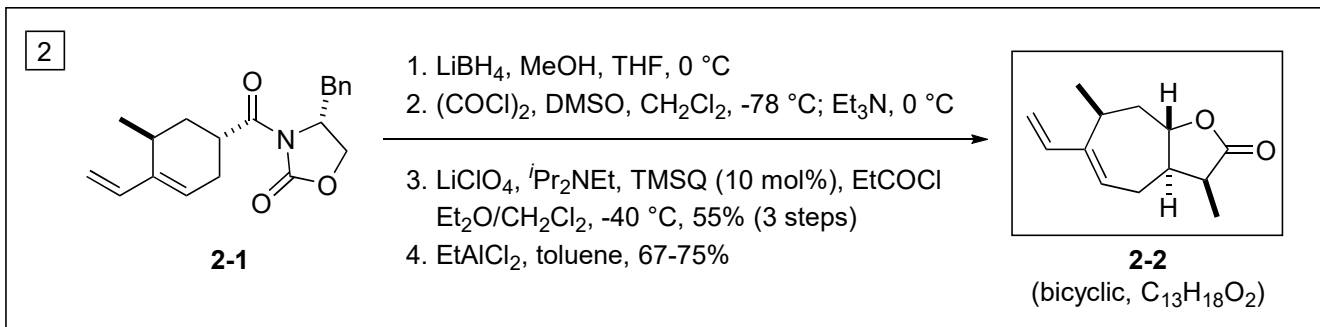
Step 3-4. Allylation/retroaldol/lactonization cascade process



**Discussion:** Stereo- and enantio-selectivity of cyclopropanation.



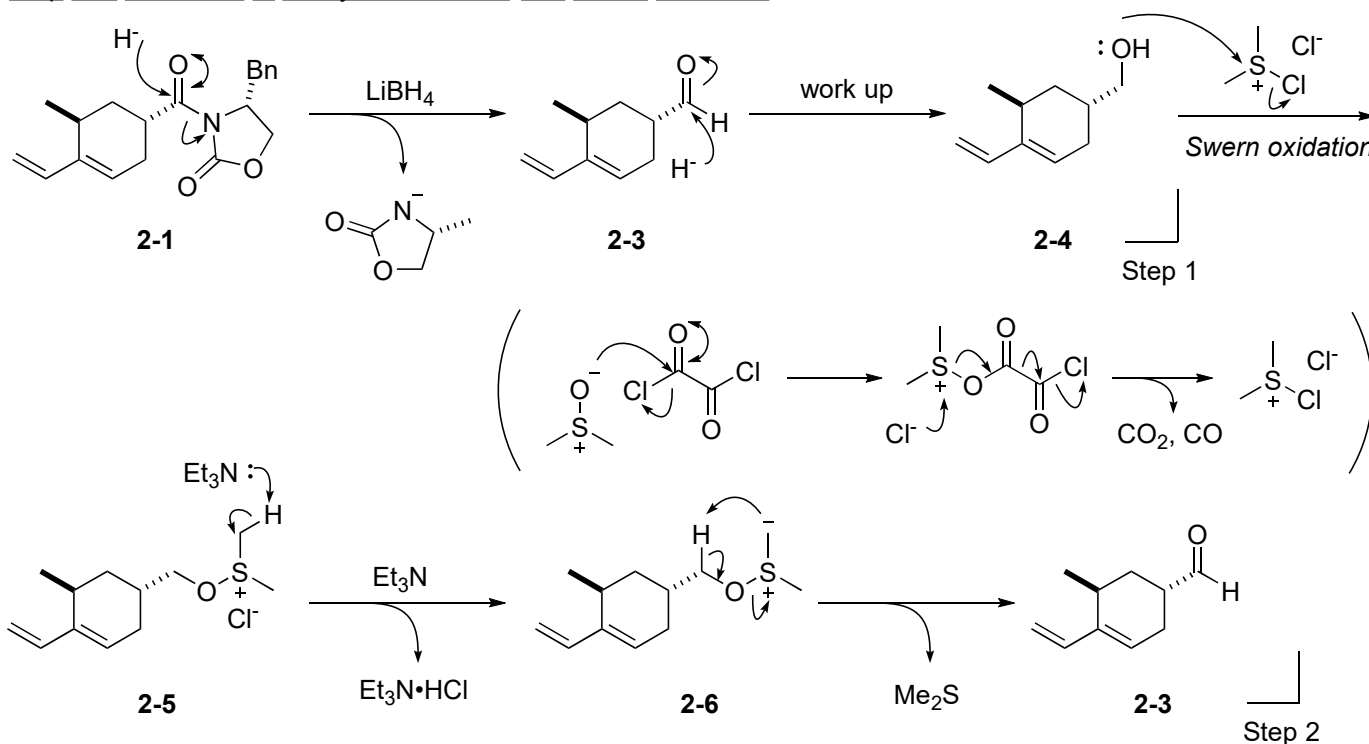
Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta.* **1988**, *71*, 1553.



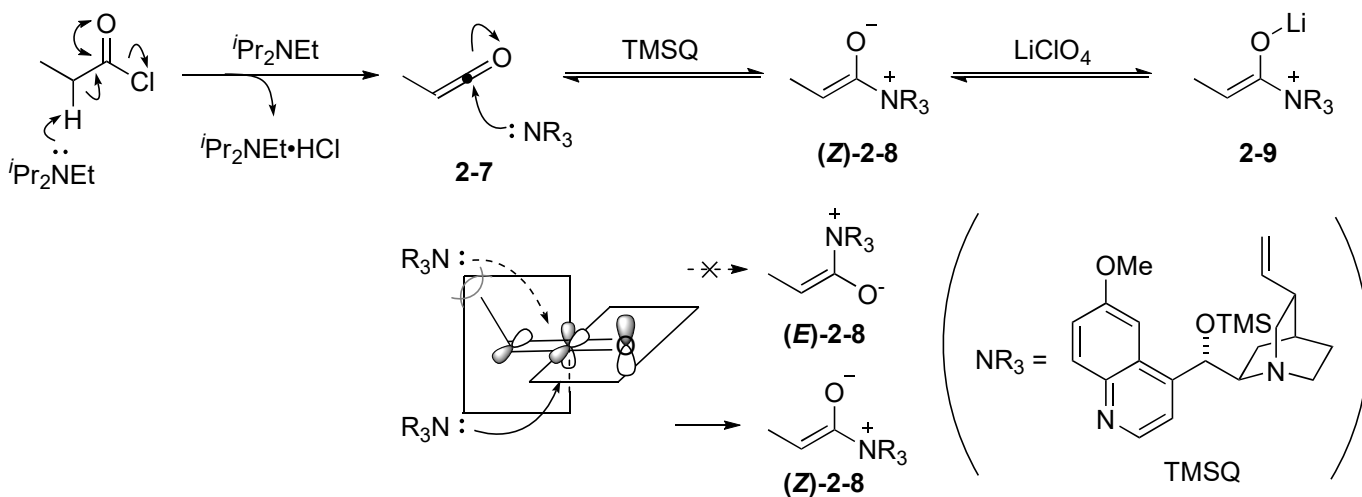
Ren, W.; Bian, Y.; Zhang, Z.; Shang, H.; Zang, P.; Chen, Y.; Yang, Z.; Luo, T.; Tang, Y.  
*Angew. Chem. Int. Ed.* **2012**, *51*, 6984.

• Construction of *trans*-fused 7/5-bicyclic system via dyotropic rearrangement as the key step.

Step 1-2. Reduction of benzyloxazolidinone and Swern oxidation.

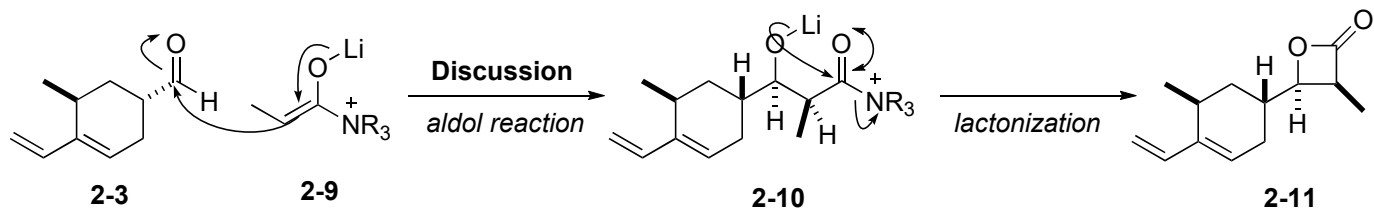


Step 3. Formation of *cis*- $\beta$ -lactone by cinchona alkaloid-lewis acid catalyzed cycloaddition.

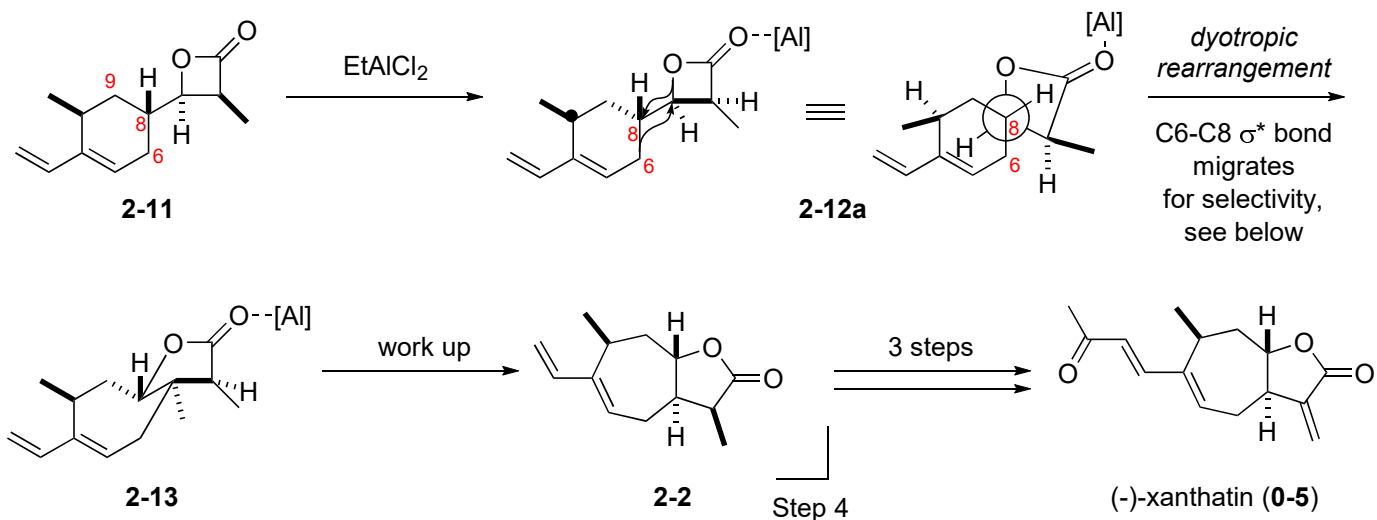


Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352.

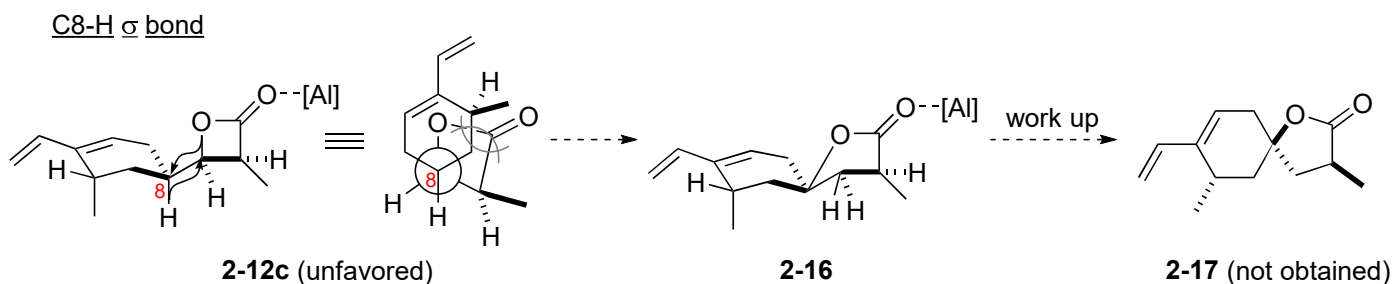
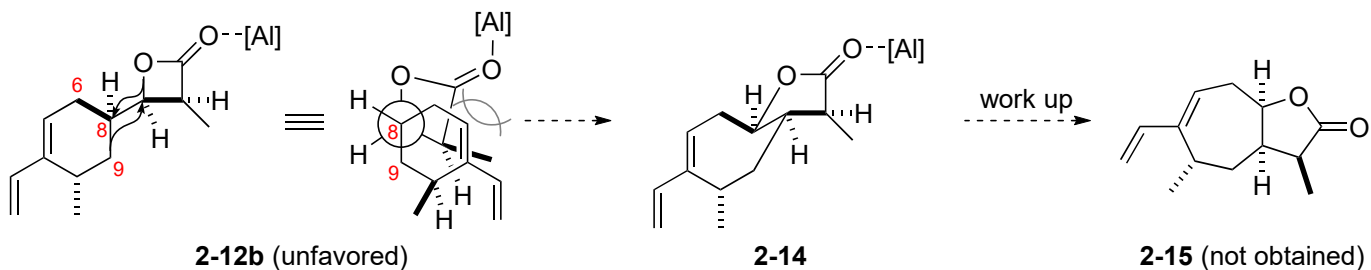
Step 3. Formation of *cis*- $\beta$ -lactone by cinchona alkaloid-lewis acid catalyzed cycloaddition. (continued)



Step 4. Wagner-Meerwein-type *dyotropic* rearrangement of *cis*- $\beta$ -lactone

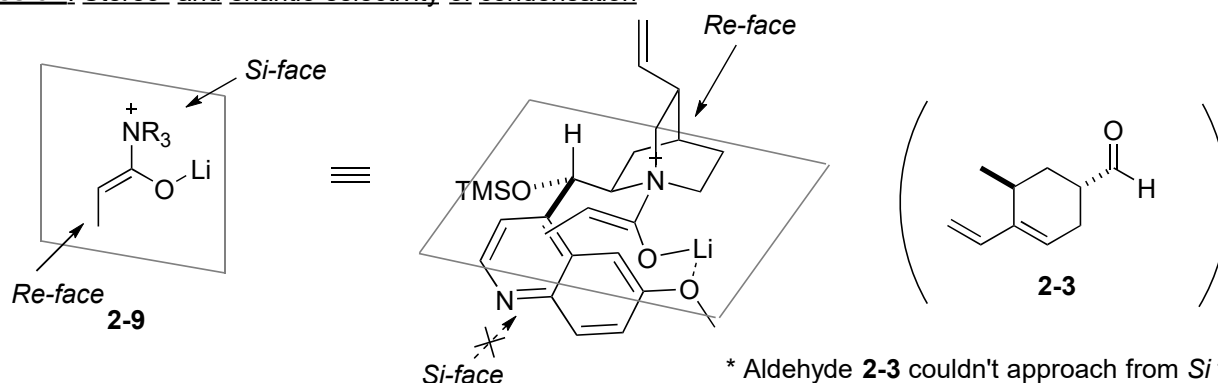


- Selectivity of *dyotropic* rearrangement  
C8-C9  $\sigma^*$  bond

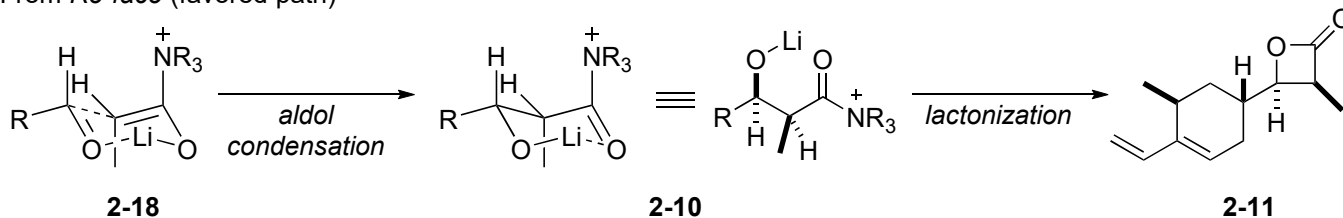


For more information about *dyotropic* rearrangement, see: 100501\_PS\_Koichi\_MURAI and references in it.

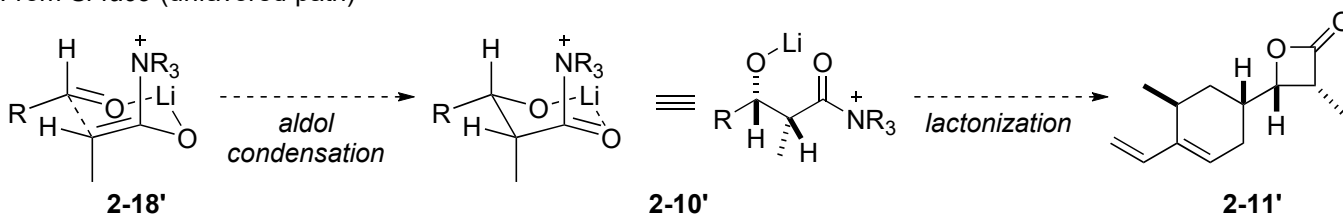
**Discussion: Stereo- and enantio-selectivity of condensation**



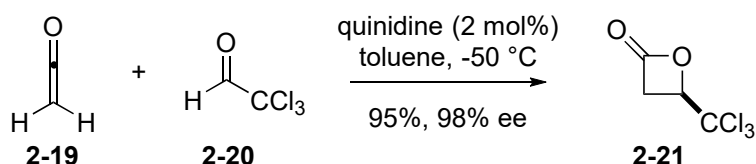
- From *Re-face* (favored path)



- From *Si-face* (unfavored path)

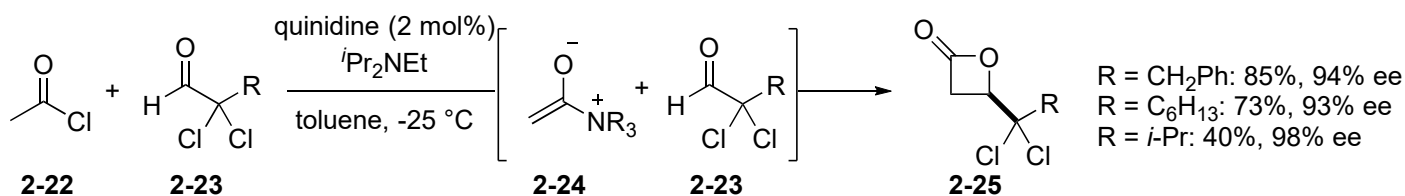


- The first asymmetric alkaloid-catalyzed ketene-chloral cycloaddition by Wynberg.



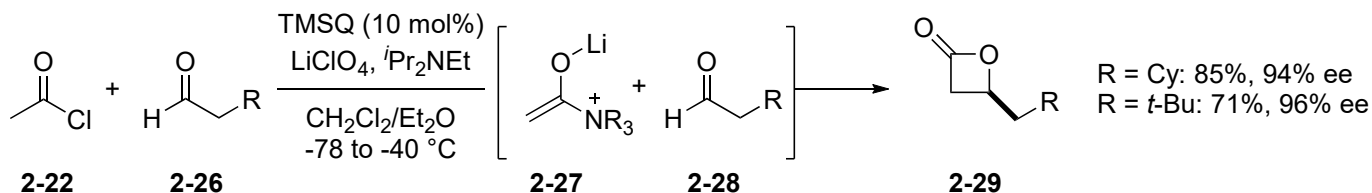
Wynberg, H.; Staring, E. M. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.

- Alkaloid-catalyzed cycloaddition of *in situ* generated ketenes and to activated aldehydes.



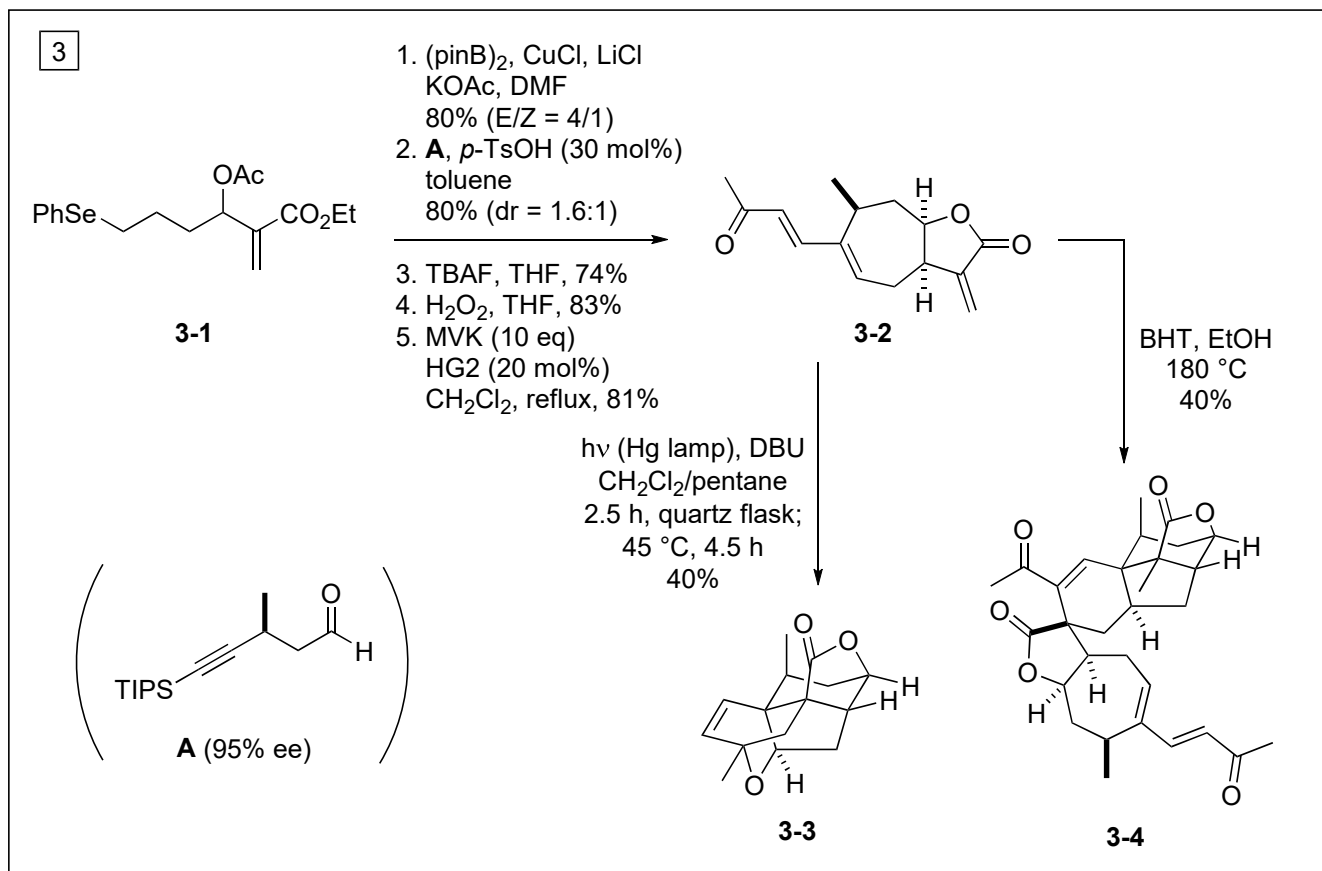
\* Activated aldehydes are needed due to the limited nucleophilicity of ammonium enolate **2-24**  
Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248.

- Cinchona alkaloid-Lewis acid catalyzed ketene-aldehyde cycloaddition.



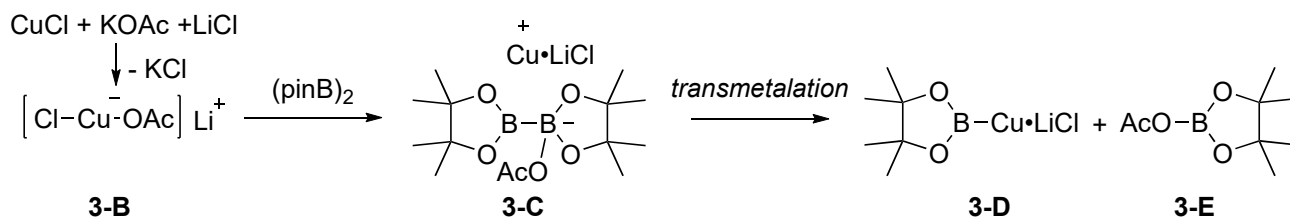
\* Metal-stabilized ammonium enolate **2-27** enables metal-templated six-membered transition state aldol reaction.  
Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352.



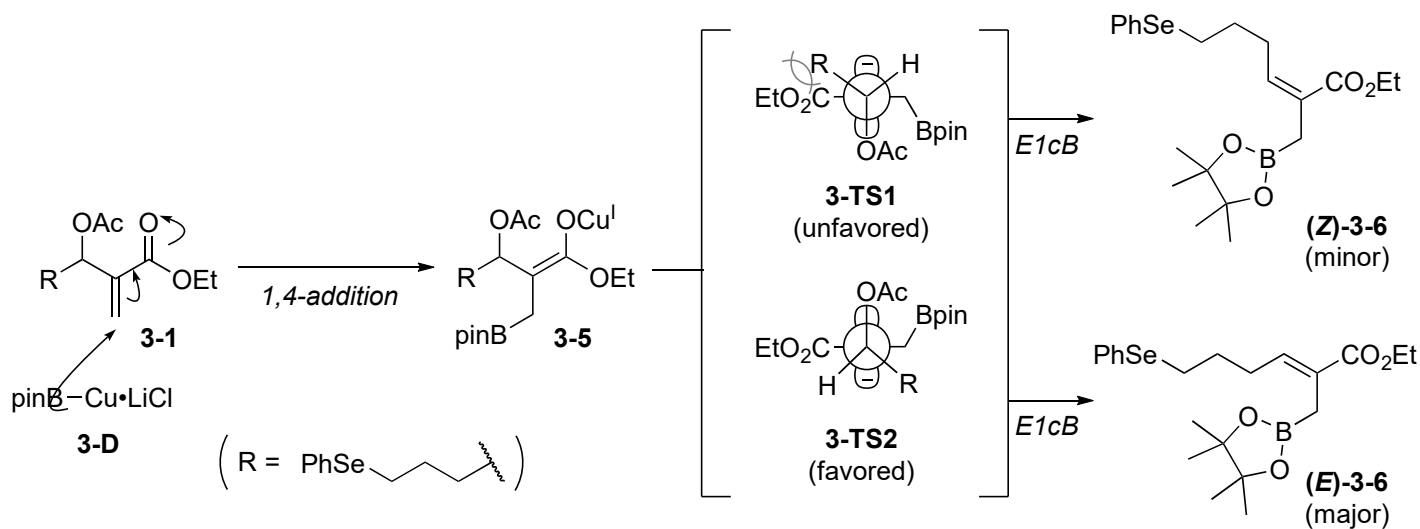


Feng, J.; Lei, X.; Bao, R.; Li, Y.; Xiao, C.; Hu, L.; Tang, Y. *Angew. Chem. Int. Ed.* DOI: 10.1002/anie.201710846

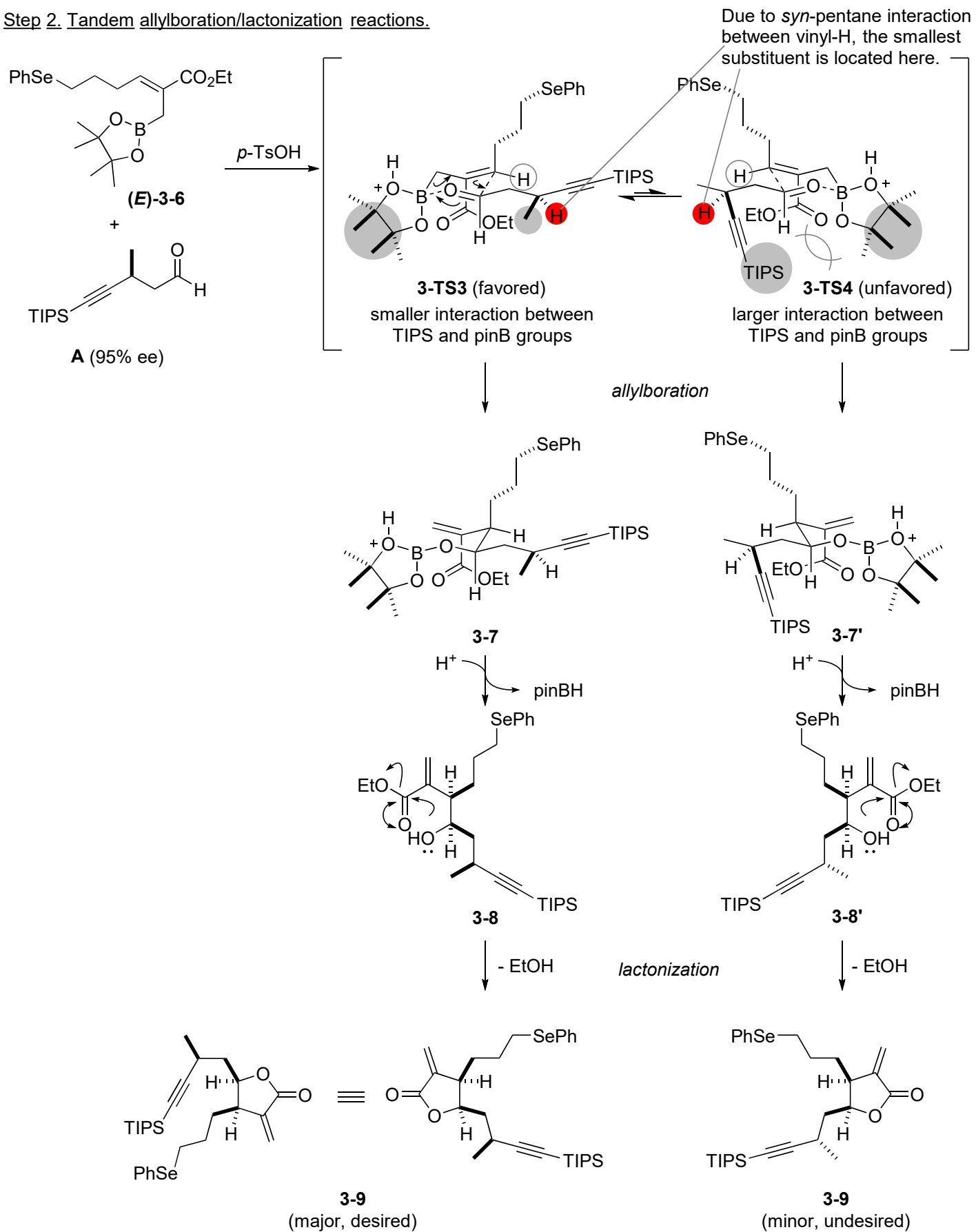
Step 1. Synthesis of the allylboronate via Hosomi-Miyaura borylation.



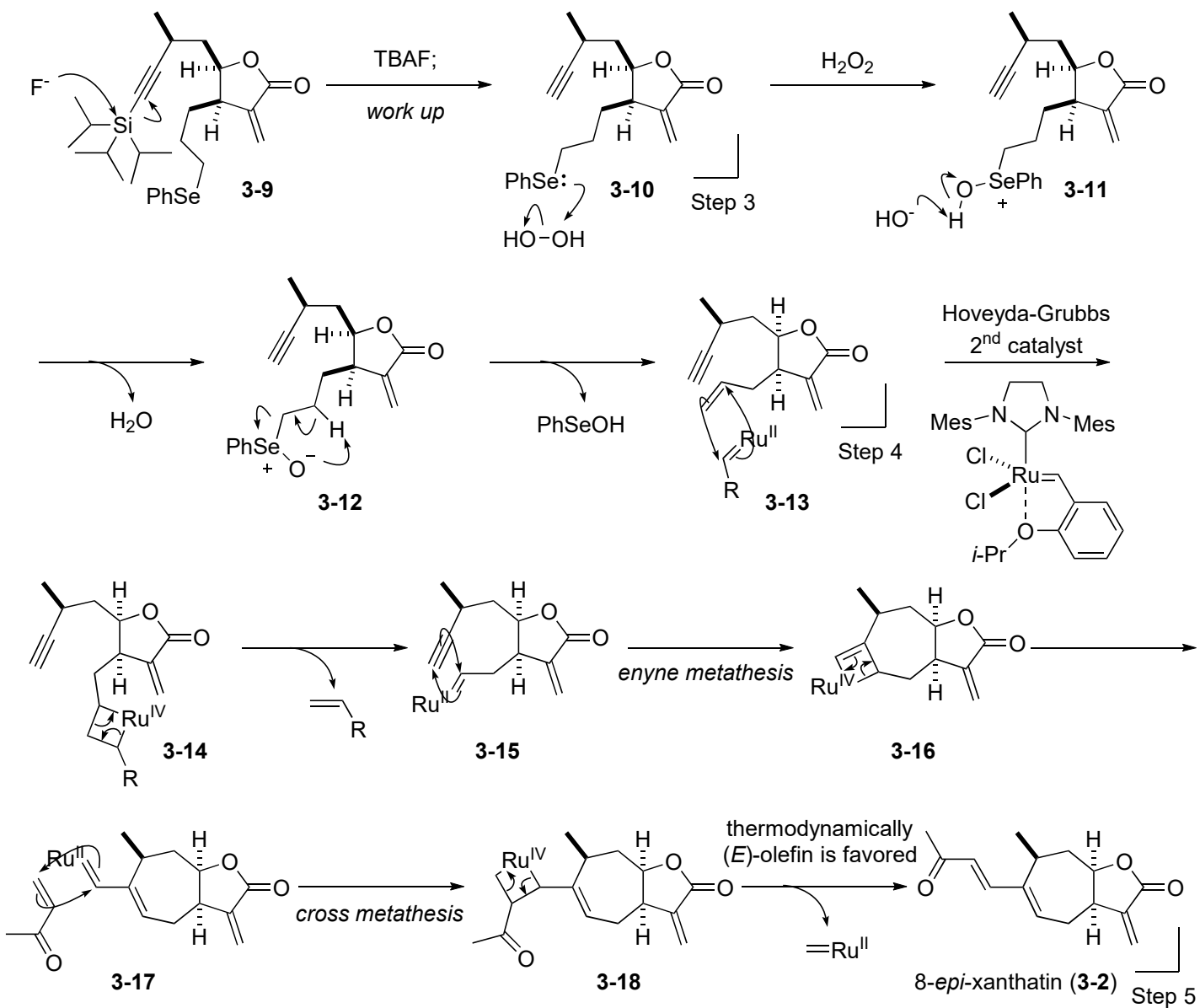
Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, 625, 47.



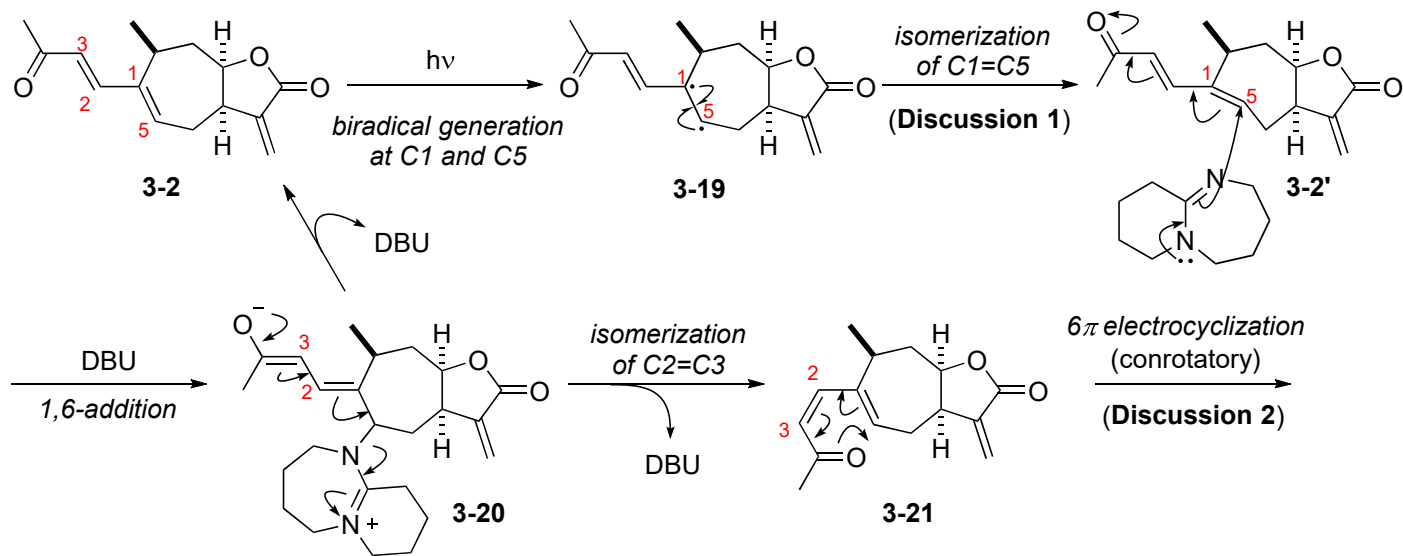
Step 2. Tandem allylboration/lactonization reactions.



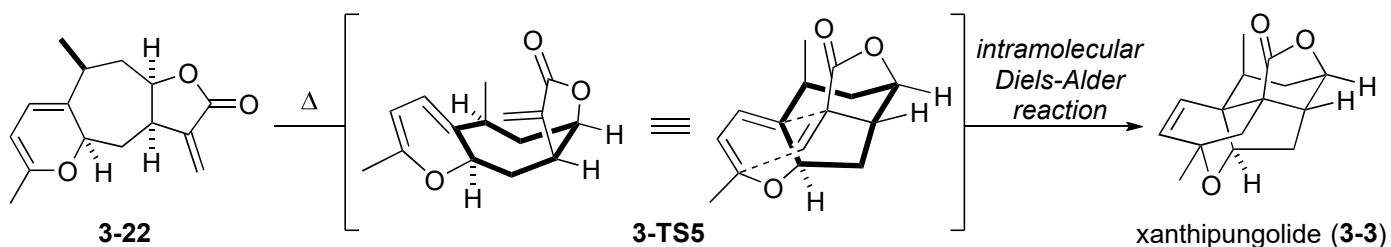
Step 3-5. Complete synthesis of 8-*epi*-xanthatin.



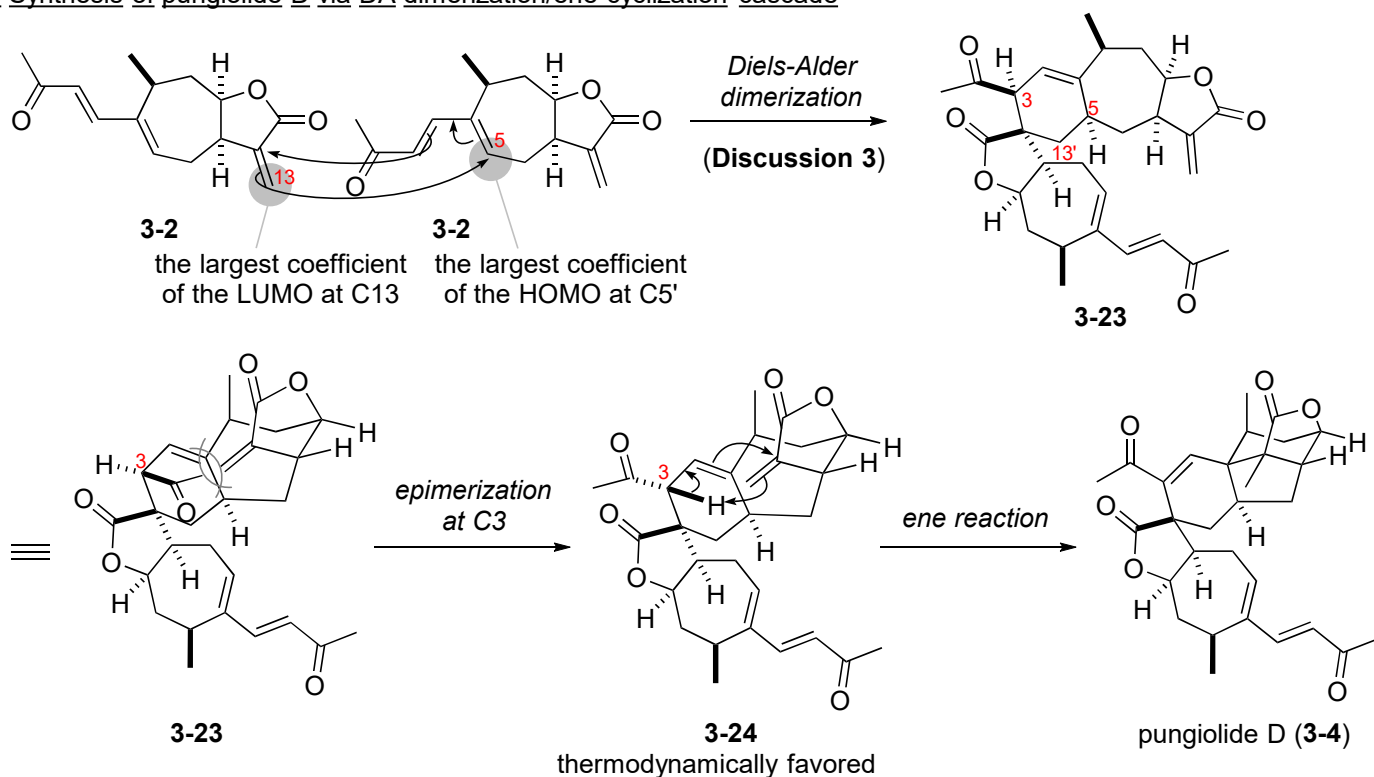
• Synthesis of xanthipungolide via double bond isomerization/  $6\pi$  electrocyclozation/IDA cascade



• Synthesis of xanthipungolide via double bond isomerization/ $6\pi$  electrocyclicization/IDA cascade (continued)

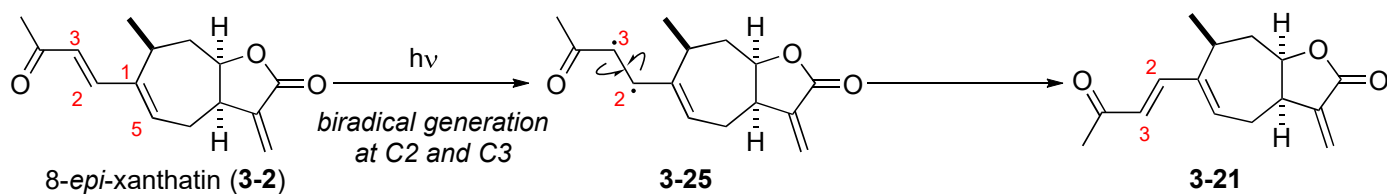


• Synthesis of pungiolide D via DA dimerization/ene-cyclization cascade

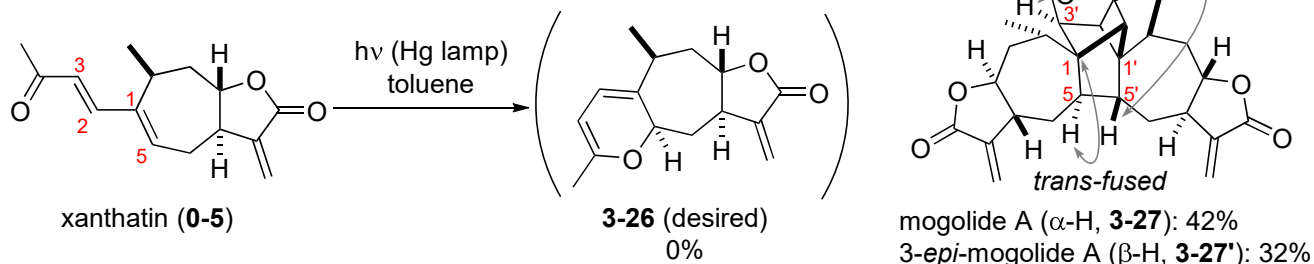


**Discussion 1: Reaction mechanism of double bond isomerization**

- Another possible pathway for isomerization of C2=C3 bond (minor path)

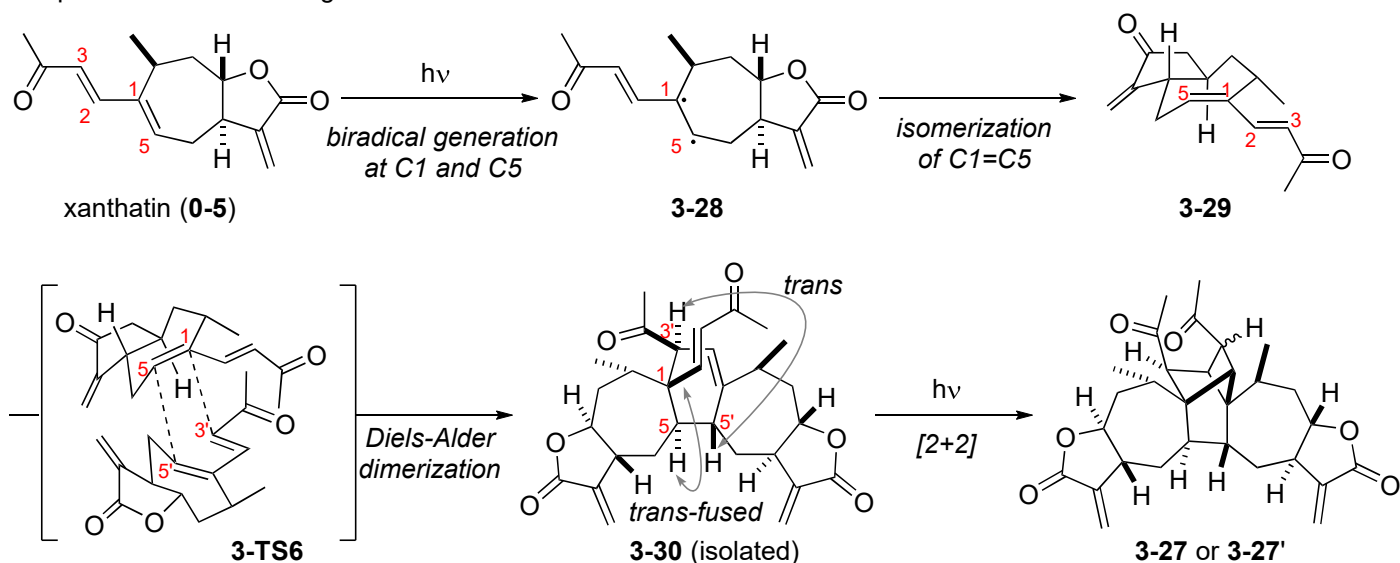


- Experimental results for biradical generation at C1 and C5

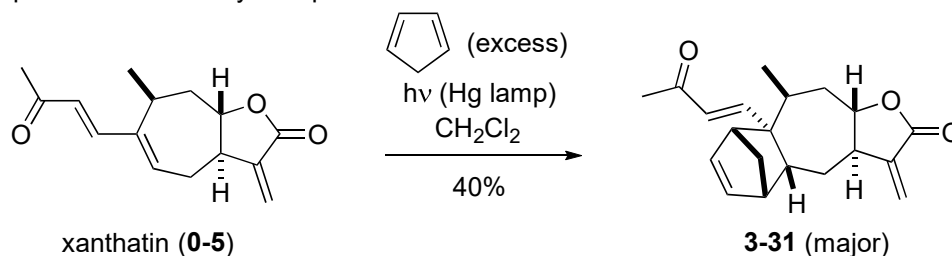


\* When the reaction was conducted in  $\text{CH}_2\text{Cl}_2$  with DBU and  $h\nu$  irradiation, 3-26 was obtained in 60% yield (dr = 5:1).

- Proposed mechanism for generation **3-27** and **3-27'**



- Trapping experiment of *trans*-cycloheptene



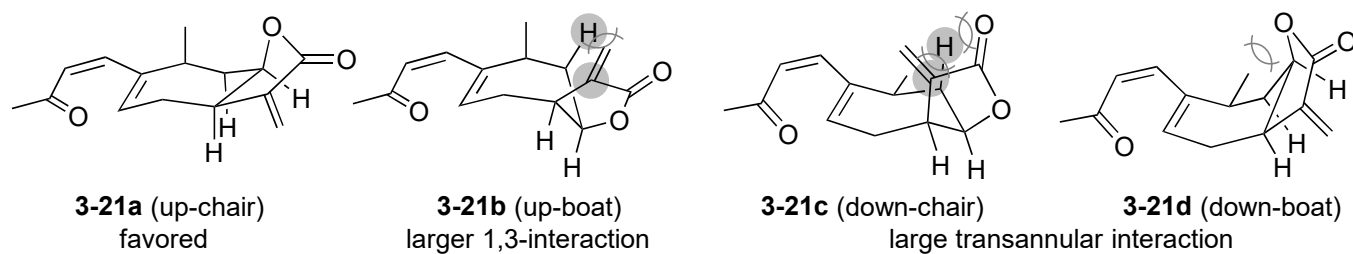
\* **3-31** was not obtained without  $h\nu$  irradiation.

Shang, H.; Liu, J.; Bao, R.; Cao, Y.; Zhao, K. Xiao, C.; Zhou, B.; Hu, L.; Tang, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 14494.

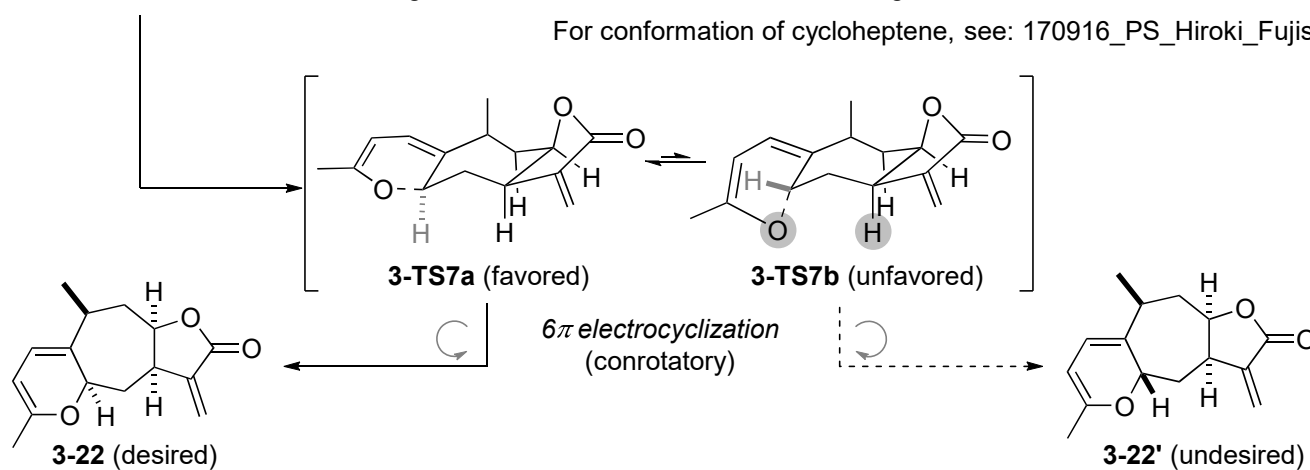
For more information about *trans*-cycloalkenes, see: 150613\_PS\_Takahiro\_Kawamata and references in it.

## Discussion 2: Stereoselectivity of electrocyclization

- Proposed conformation of **3-21**



For conformation of cycloheptene, see: 170916\_PS\_Hiroki\_Fujisawa



**Discussion 3:** Face- and endo/exo-selectivity of Diels-Alder dimerization.

