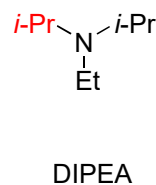
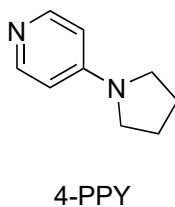
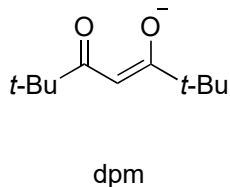
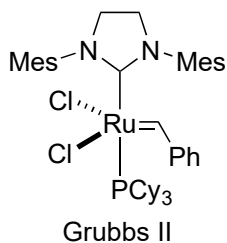
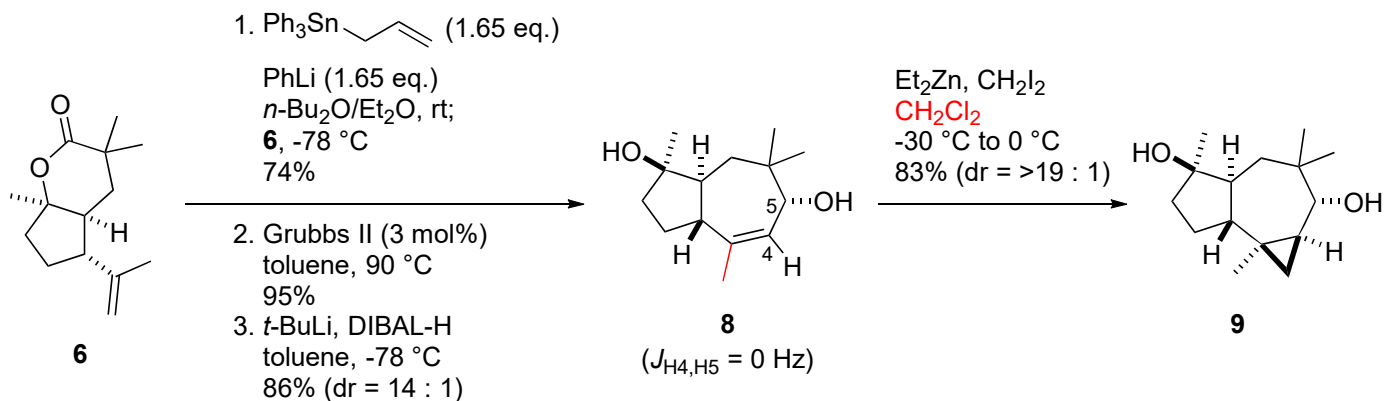
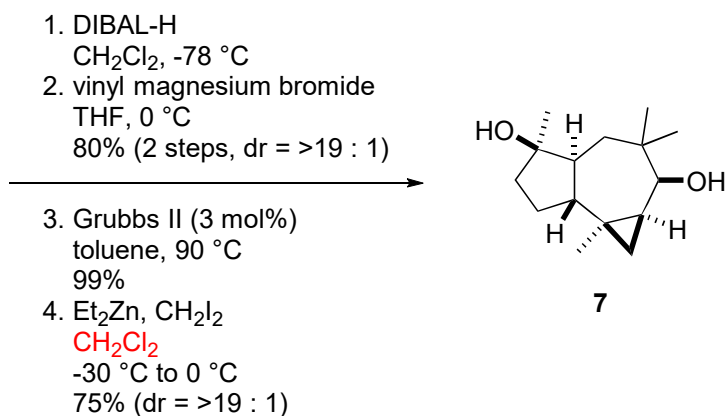
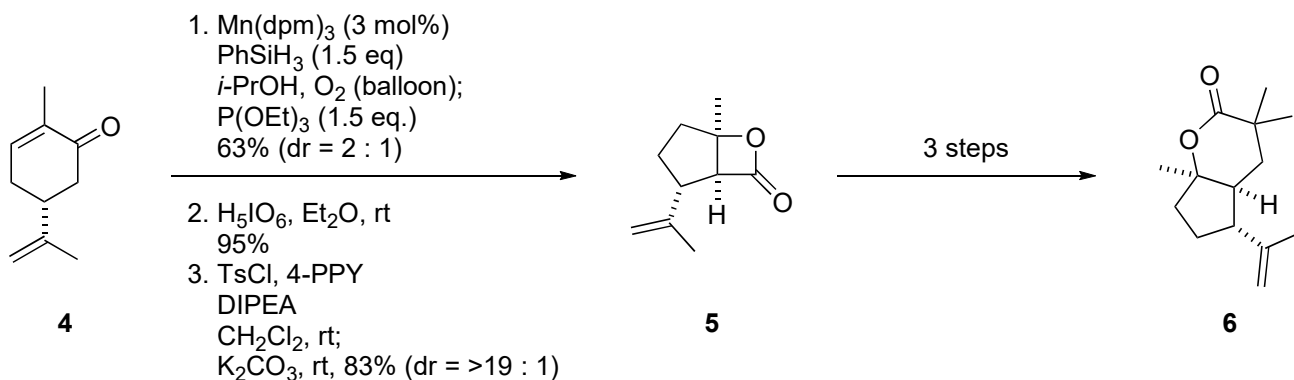
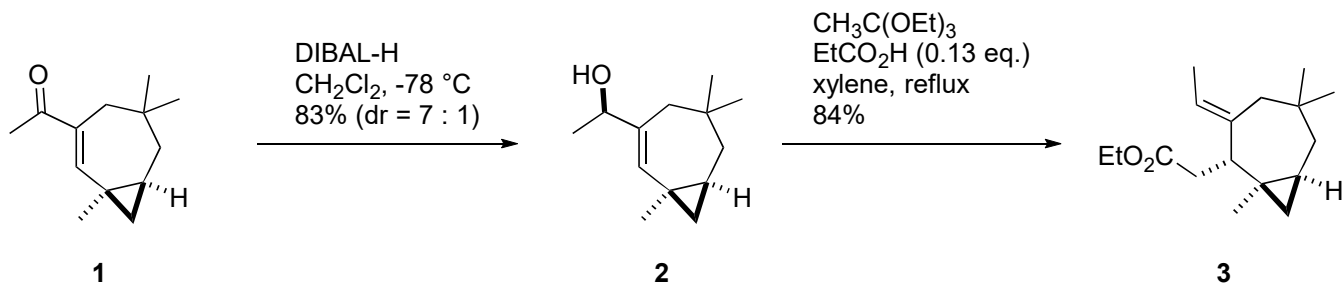


## Problem Session (6)

2017/09/16 Hiroki Fujisawa

- Please provide the reasonable reaction mechanisms of each reaction.
- Please explain the stereoselectivity (1→2, 2→3, 3rd step of 4→5, 6→7, 6→8, 8→9)



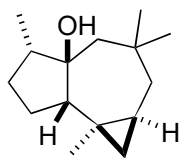
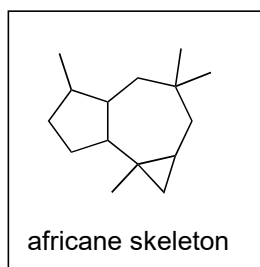
# Problem Session ~ Answer ~

2017/9/16 Hiroki Fujisawa

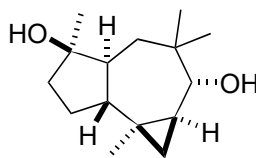
## Topic: Synthetic Studies of Africanane sesquiterpenoids

### 0. Introduction

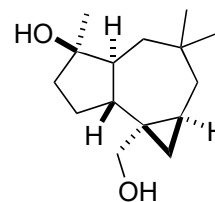
#### 0-1. Africanane sesquiterpenoid.



africanol



omphadiol



pyxidatol C

isolation:

africanol: *Lemnalia africana* (soft coral) *Tetrahedron Lett.* **1974**, 747.

omphadiol: *Omphalotus illudens* or *clavicorna pyxidata* *J. Nat. Prod.* **2000**, 63, 1557.

pyxidatol C: *clavicorna pyxidata* *Helv. Chim. Acta.* **2008**, 91, 2174.

biological activity: not reported.

structural features:

-5-7-3 tricyclic skeleton (africanane skeleton)

total syntheses:

- africanol

Matsumoto's group (racemic; *Tetrahedron Lett.* **1980**, 21, 4835.)

L. A. Paquette's group (racemic; *J. Am. Chem. Soc.* **1987**, 109, 3025. **problem 1**)

J. B. White's group (racemic; *J. Org. Chem.* **1993**, 58, 3557.)

F. A. Marques' group (racemic; *J. Braz. Chem. Soc.* **2000**, 11, 502.)

A. H. Hoveyda's group (asymmetric; *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5805.)

- omphadiol

D. Romo's group (asymmetric; *Angew. Chem. Int. Ed.* **2011**, 50, 7537. **problem 2**)

G. Liang's group (racemic; *J. Org. Chem.* **2014**, 79, 5345.)

M. Kalesse's group (asymmetric; *Org. Lett.* **2016**, 18, 2320.)

- pyxidatol C

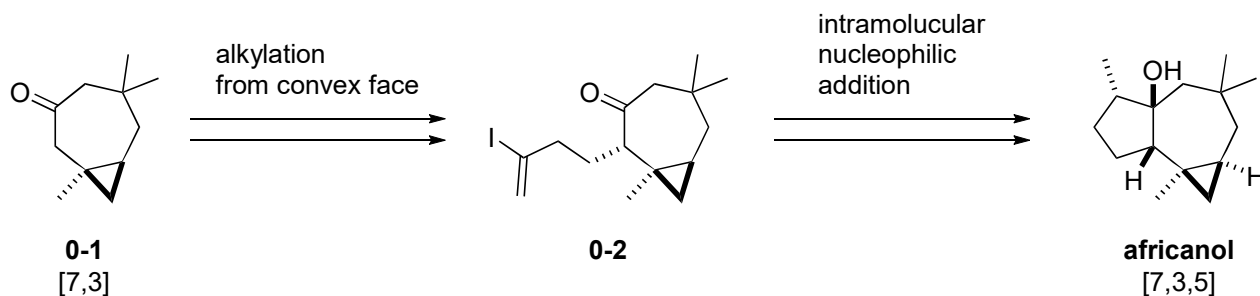
G. Liang's group (racemic; *J. Org. Chem.* **2014**, 79, 5345.)

M. Kalesse's group (asymmetric; *Org. Lett.* **2016**, 18, 2320.)

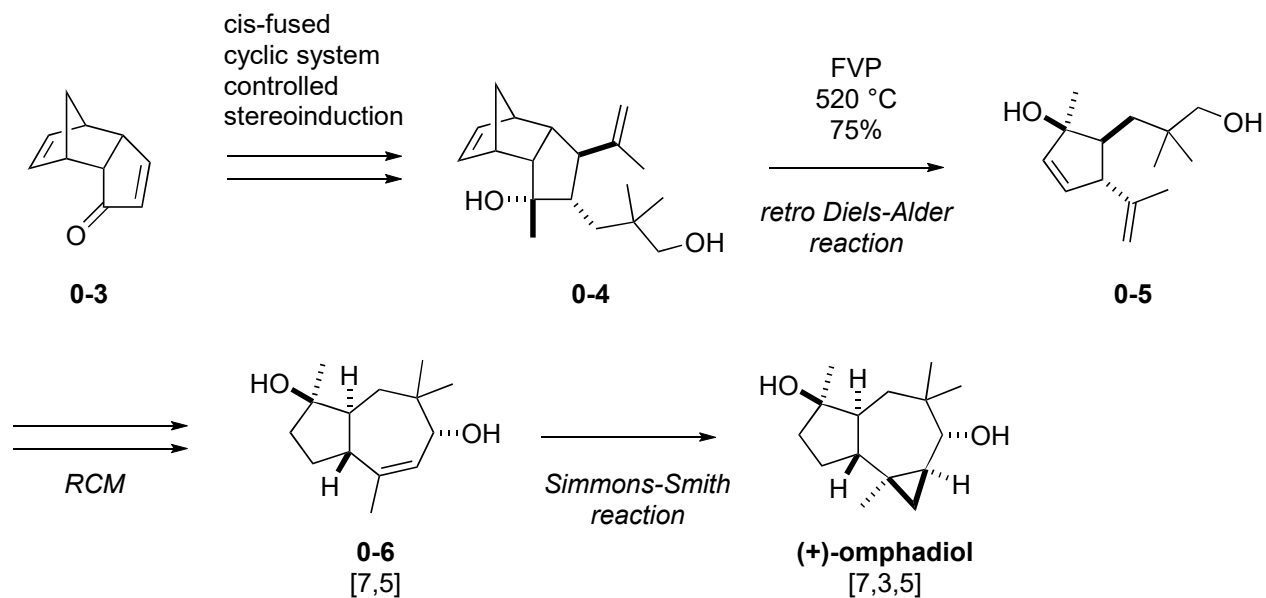
### 0-2. Synthetic strategy

#### 0-2-1. (7→3→5) **problem 1**

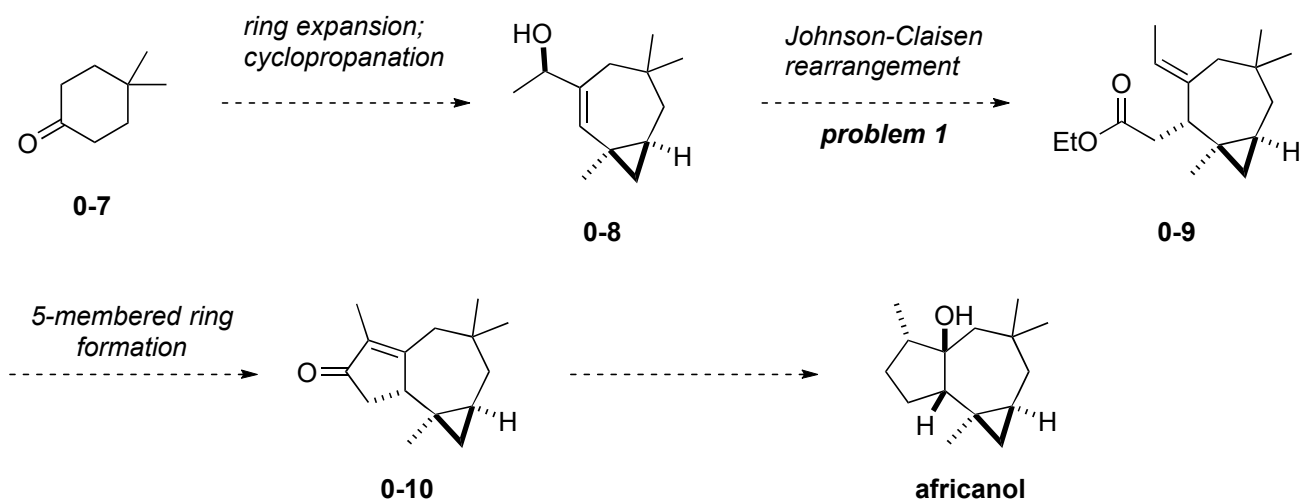
ex. Marques' synthesis of africanol

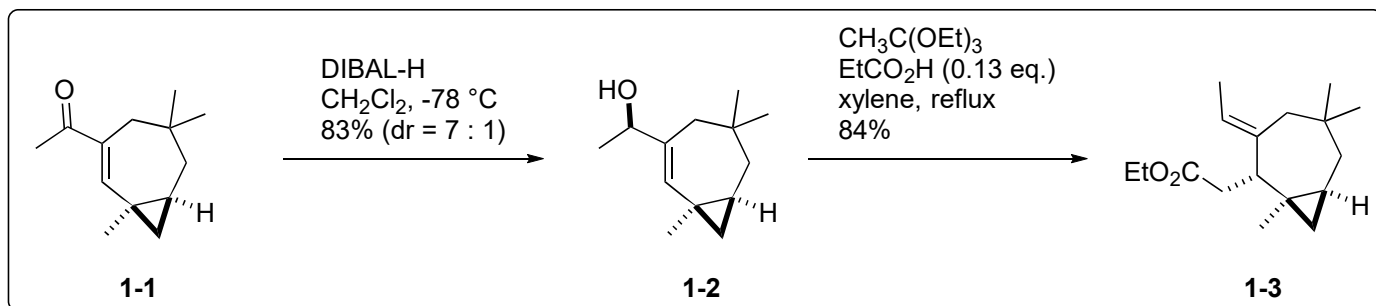


0-2-2. (5→7→3) **problem 2, 3**  
 ex. Kalesse's synthesis of (+)-omphadiol



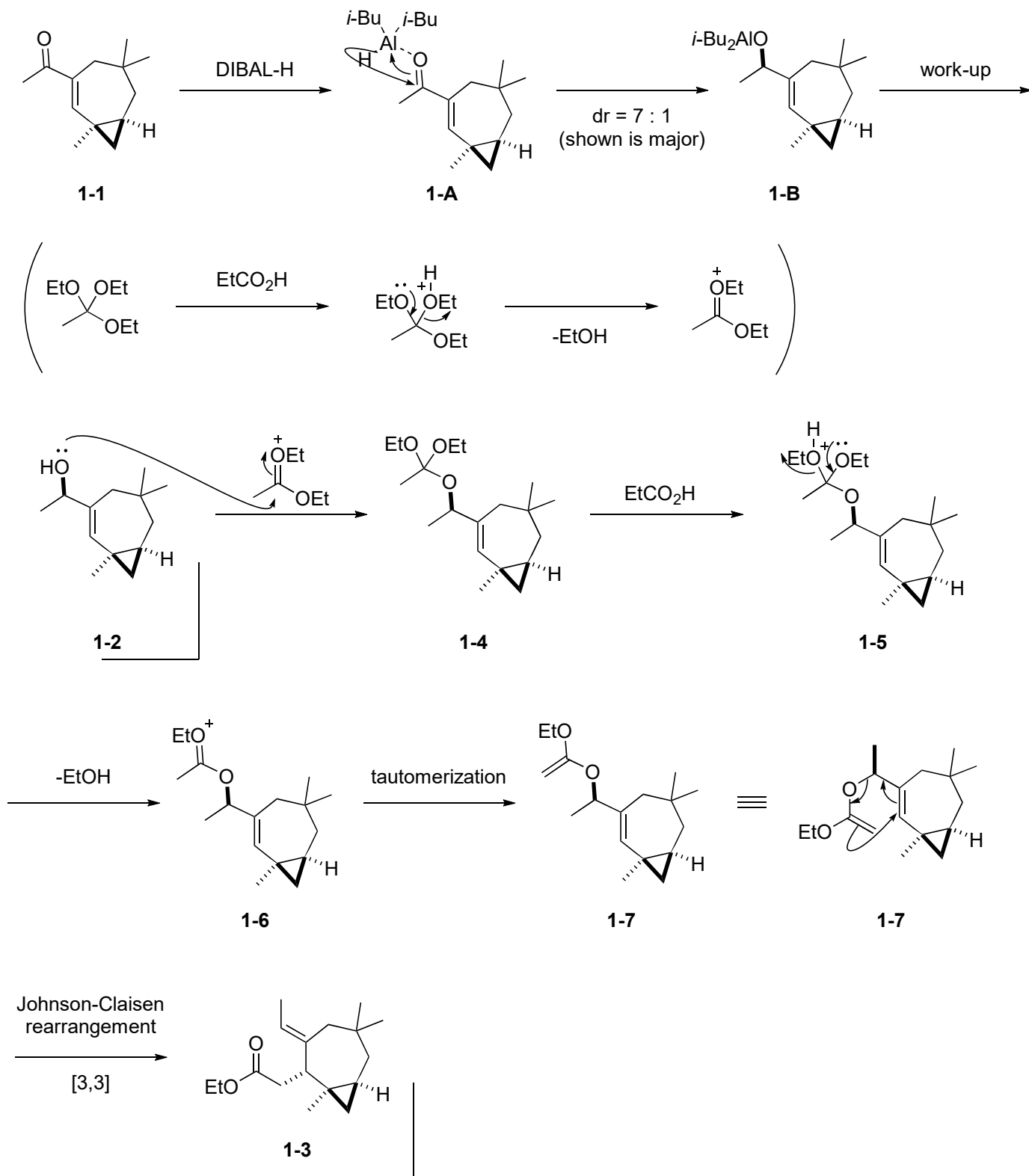
Problem 1: Paquette's synthesis of africanol  
 1-0. Synthetic plan





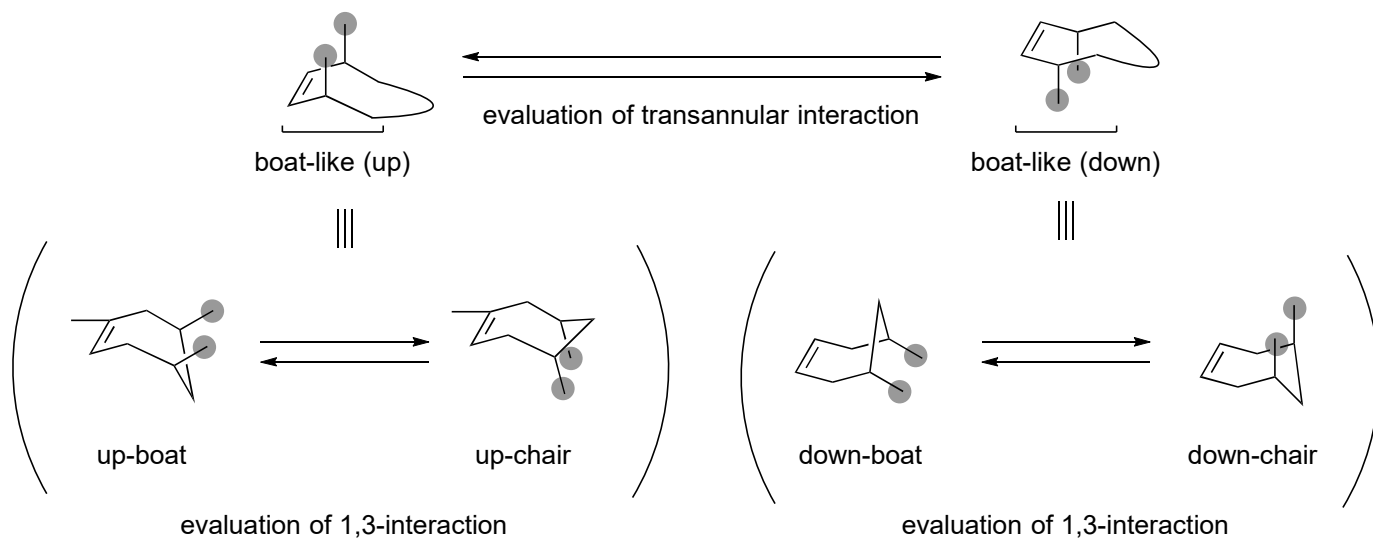
Paquette, L. A.; Ham, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 3025.

Answer:

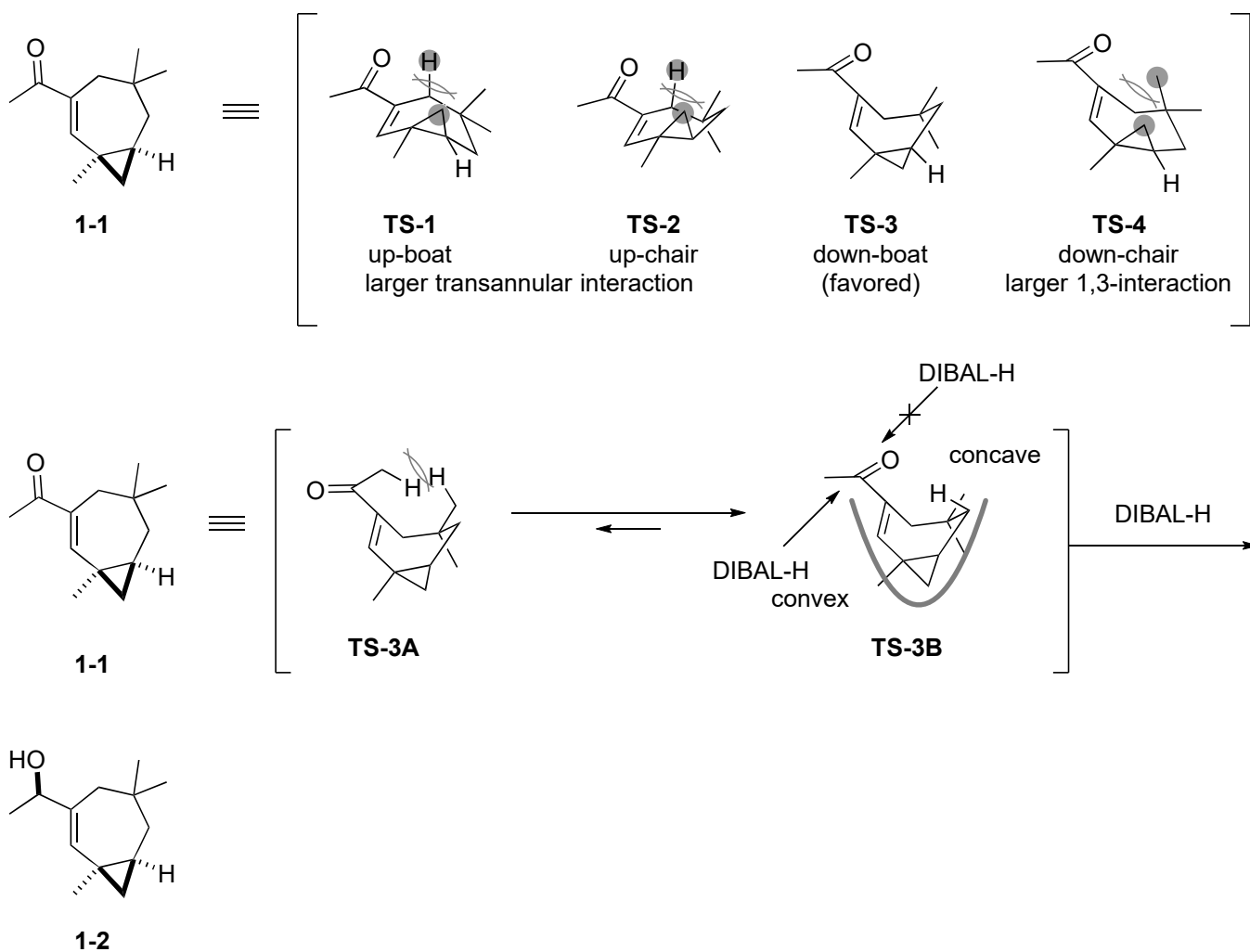


**Discussions:**

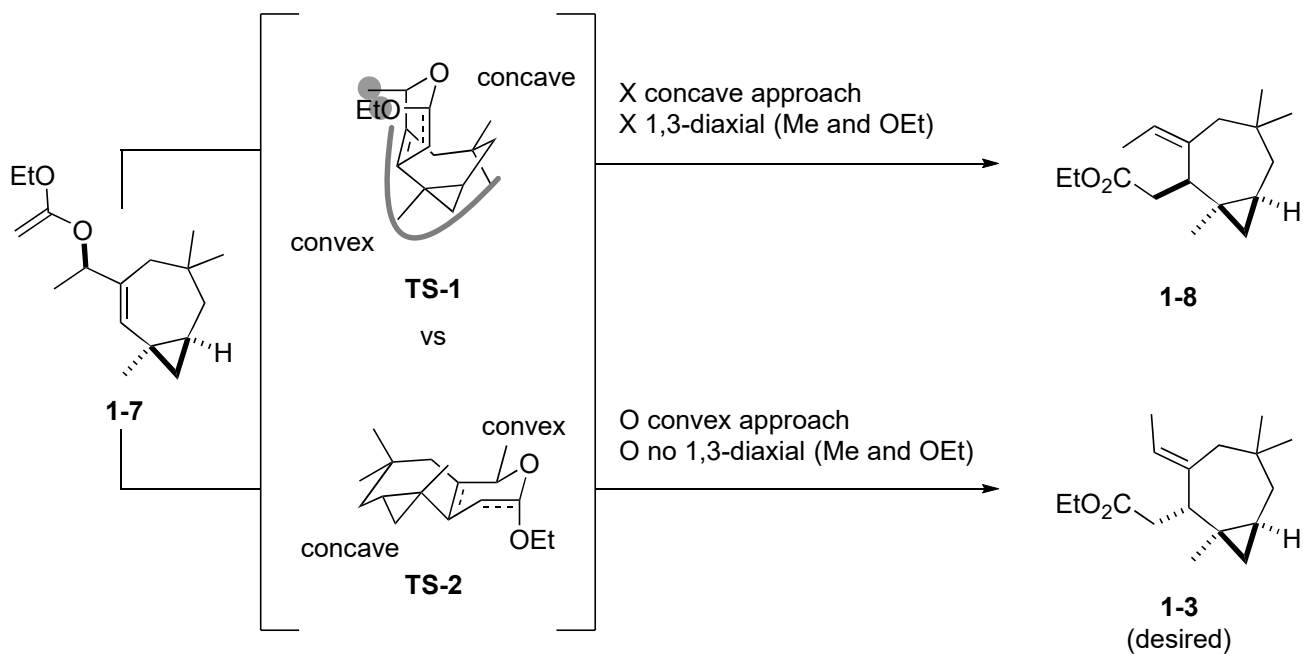
1. Conformation of cycloheptene ring.



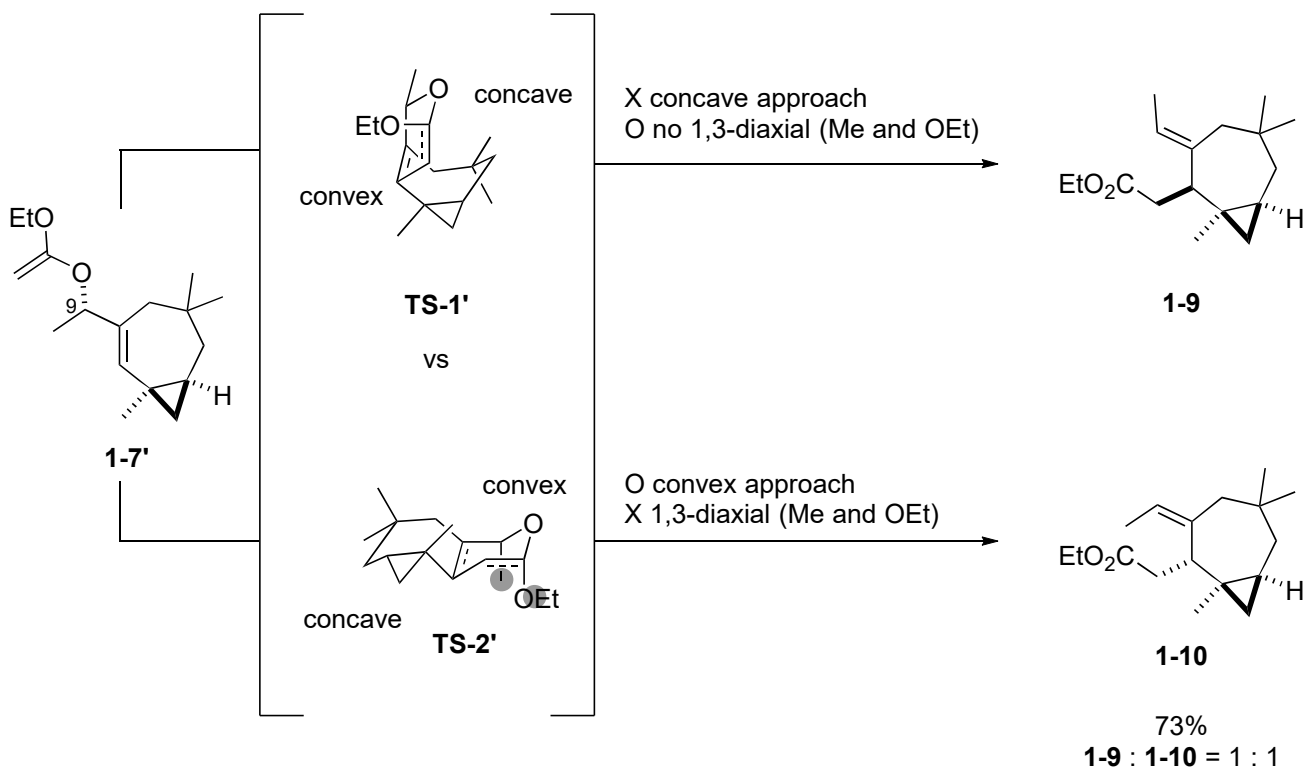
2. Stereoselectivity in DIBAL-H reduction.

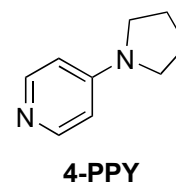
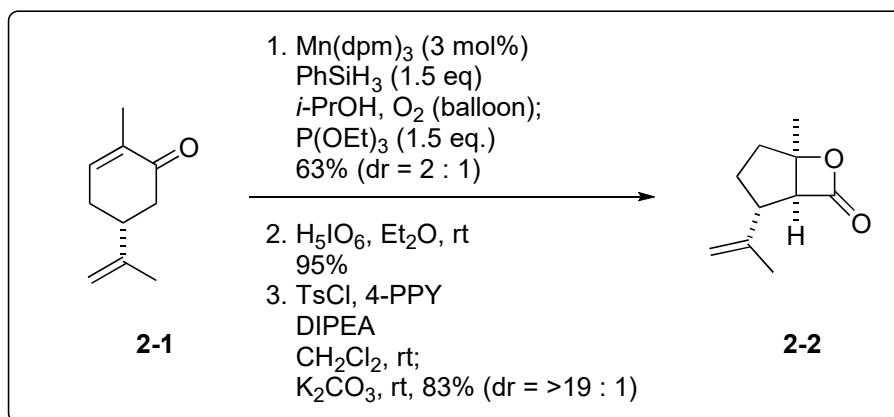


2. Stereoselectivity in Johnson-Claisen rearrangement.



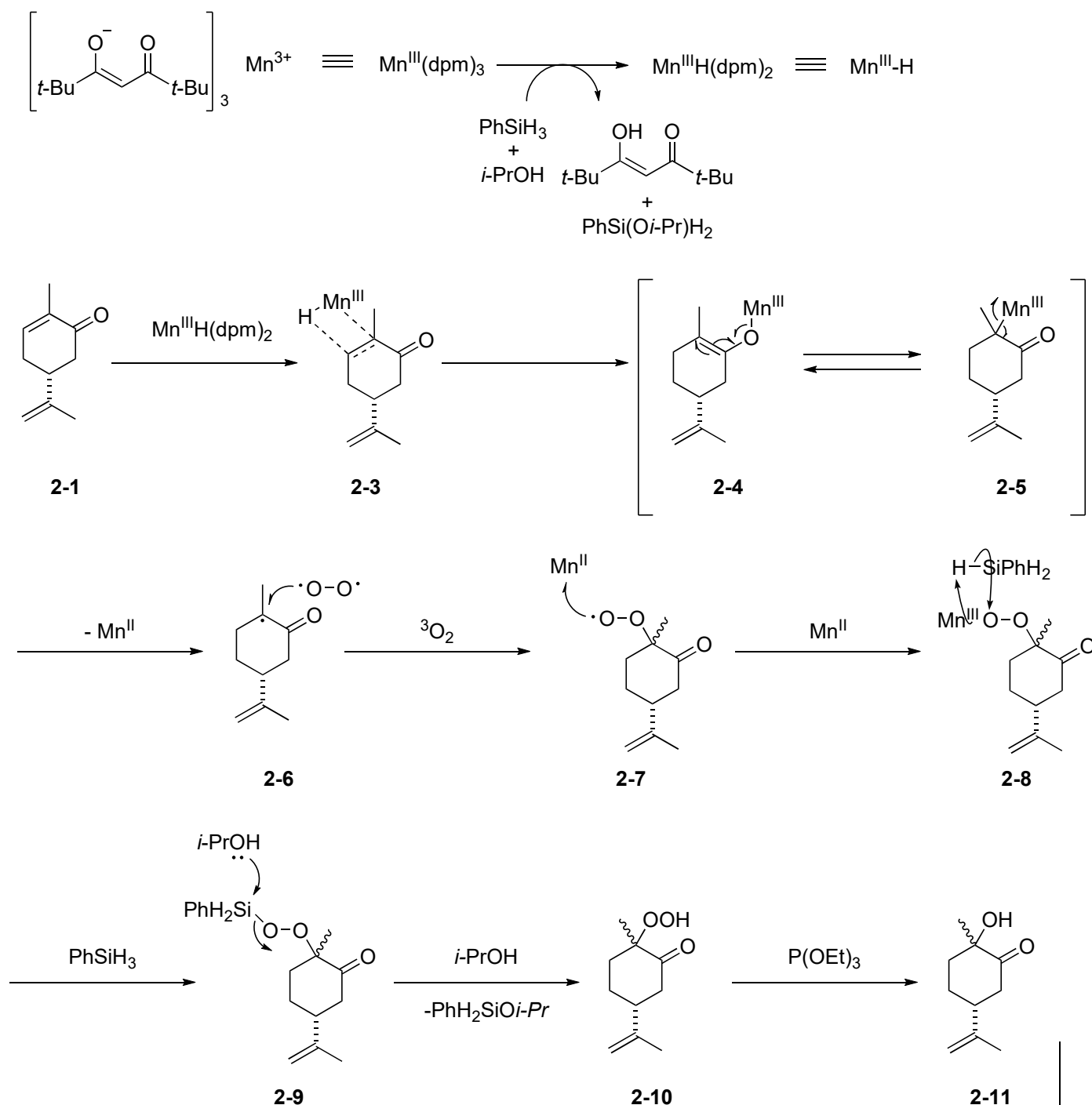
cf. in the case of C9 epimer



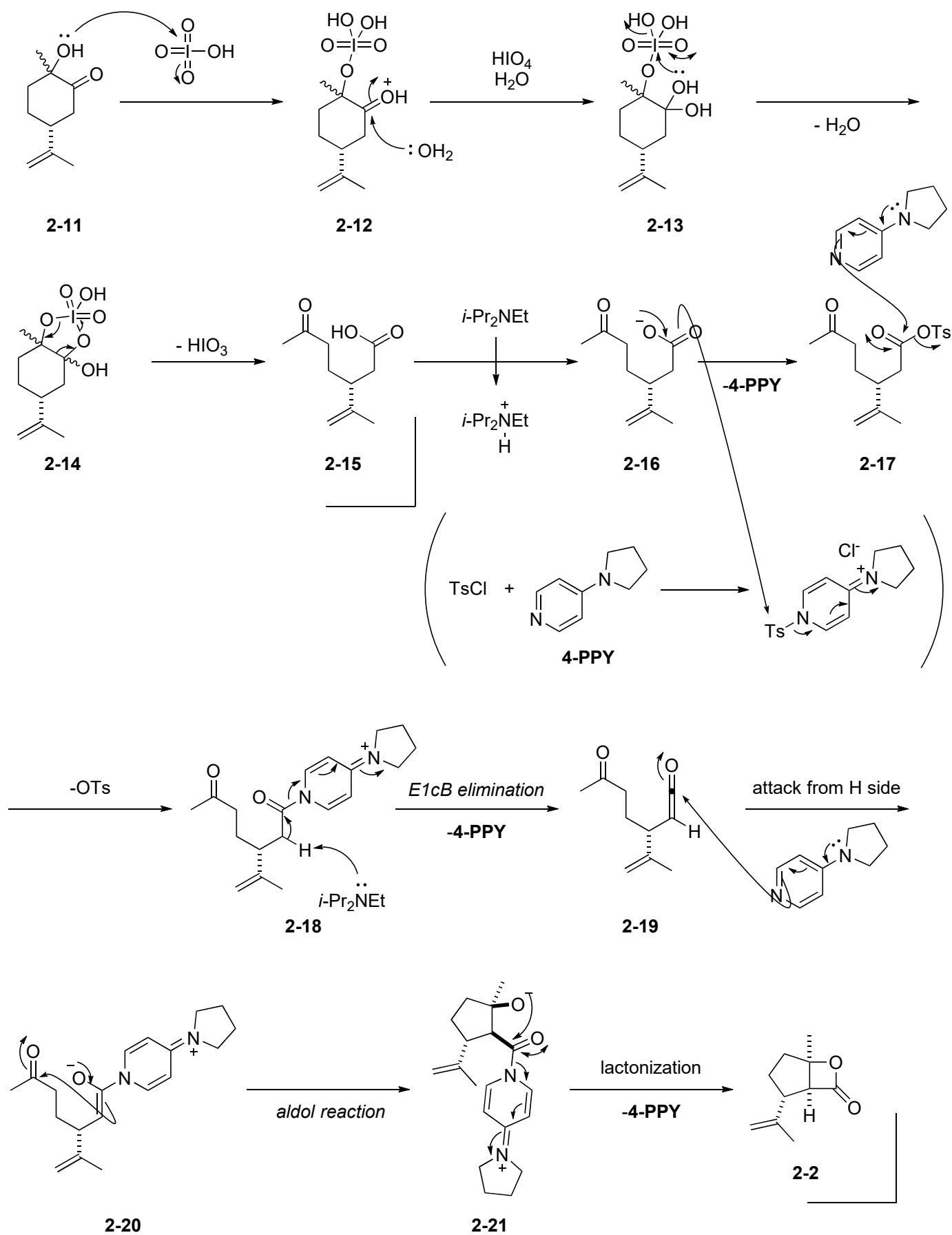
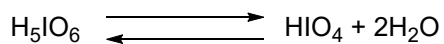


Liu, Gang, Romo, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 7537.

Answer:



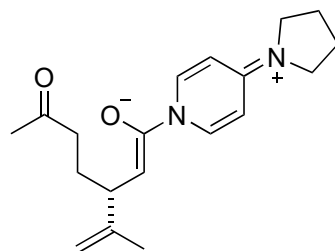
Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595.  
 See also Dr. Koshimizu's master thesis and Dr. Nagatomo's LS on 140308.



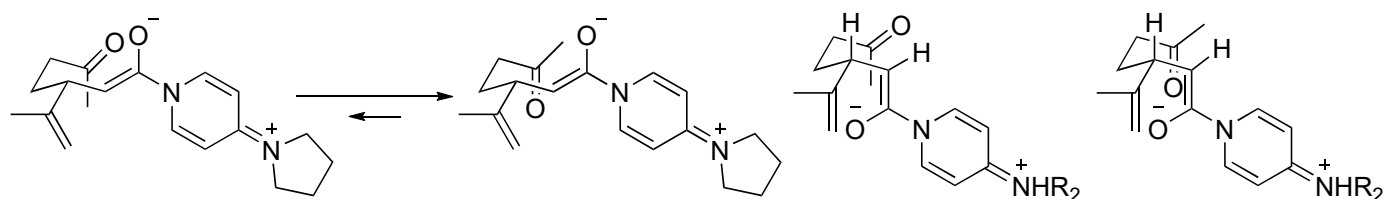


**Discussions:**

1. Stereoselectivity in the aldol-lactonization reaction.



**2-20**

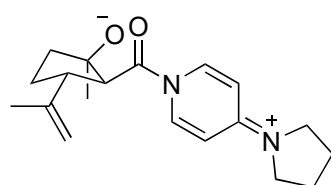


**TS-1**  
favored

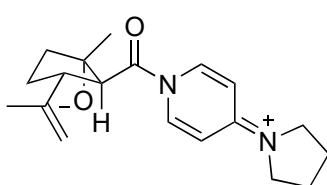
**TS-2**  
most favored

**TS-3**  
disfavored

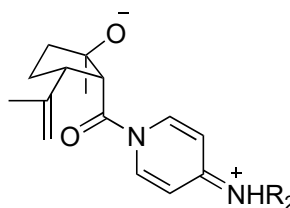
**TS-4**  
disfavored



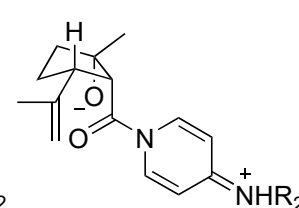
**2-2**



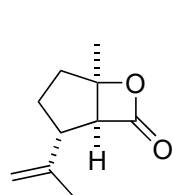
**2-22**  
*trans*-[5,4]



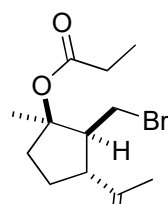
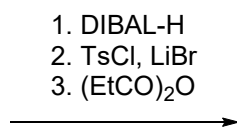
**2-23**



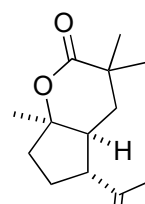
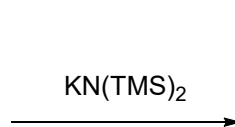
**2-24**



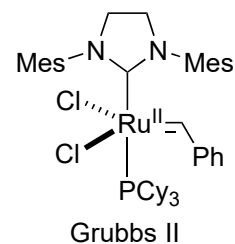
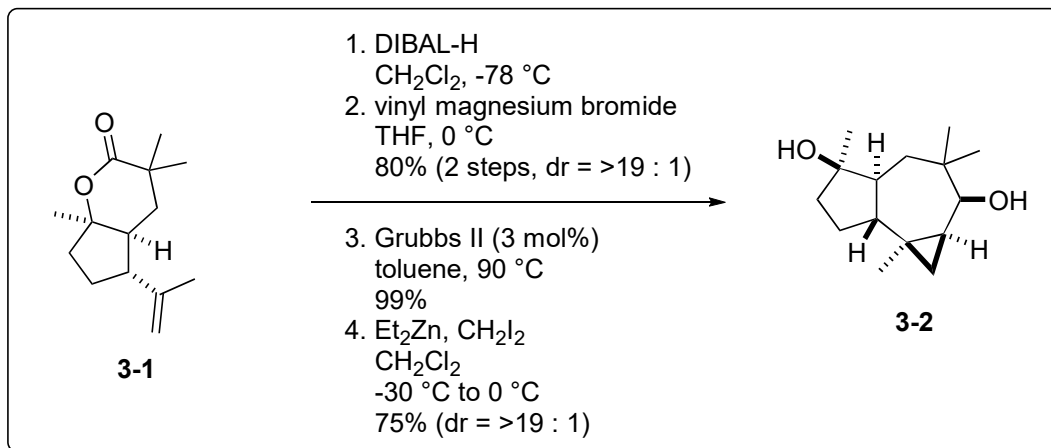
**2-2**



**2-25**

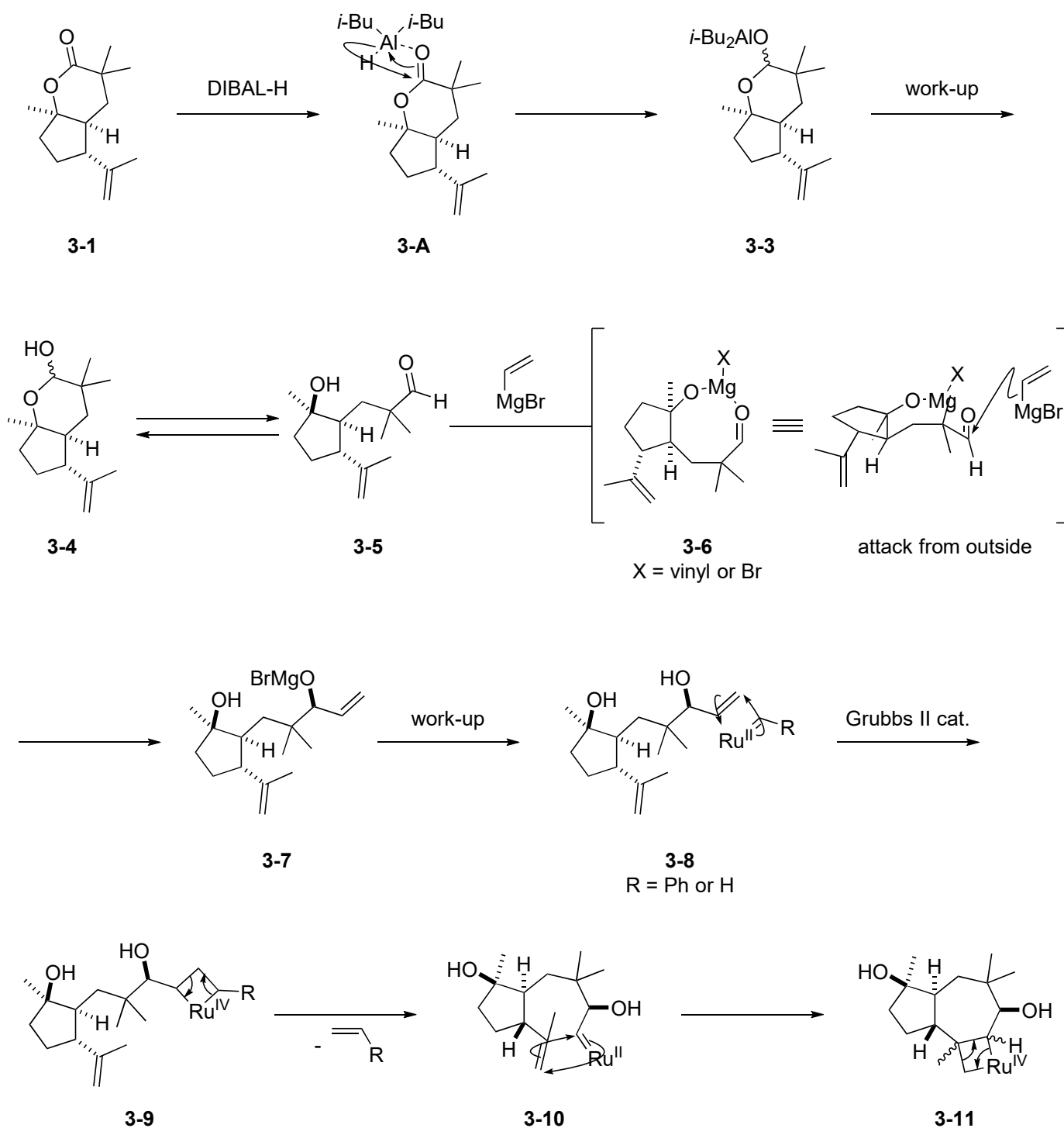


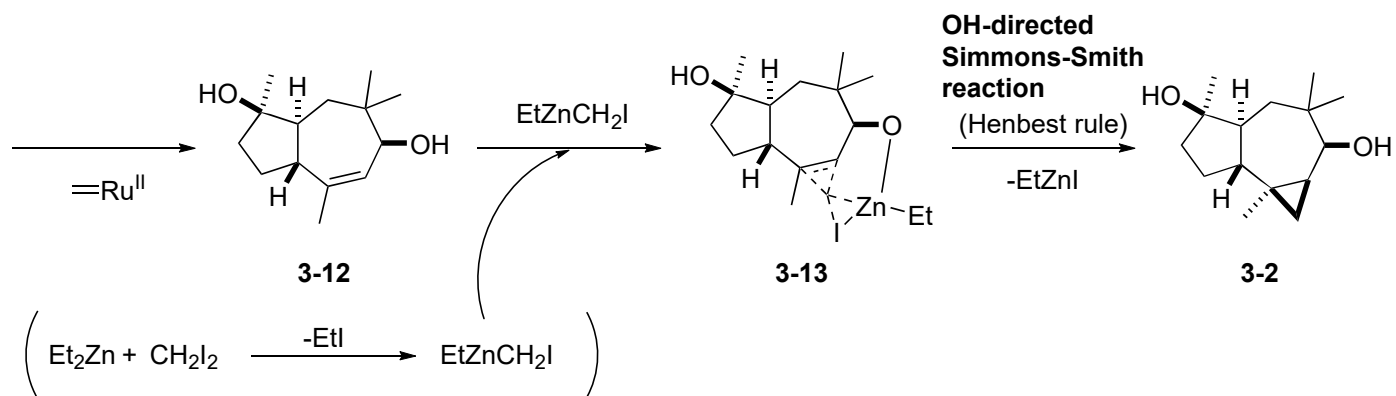
**3-1**



Liu, Gang, Romo, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 7537.

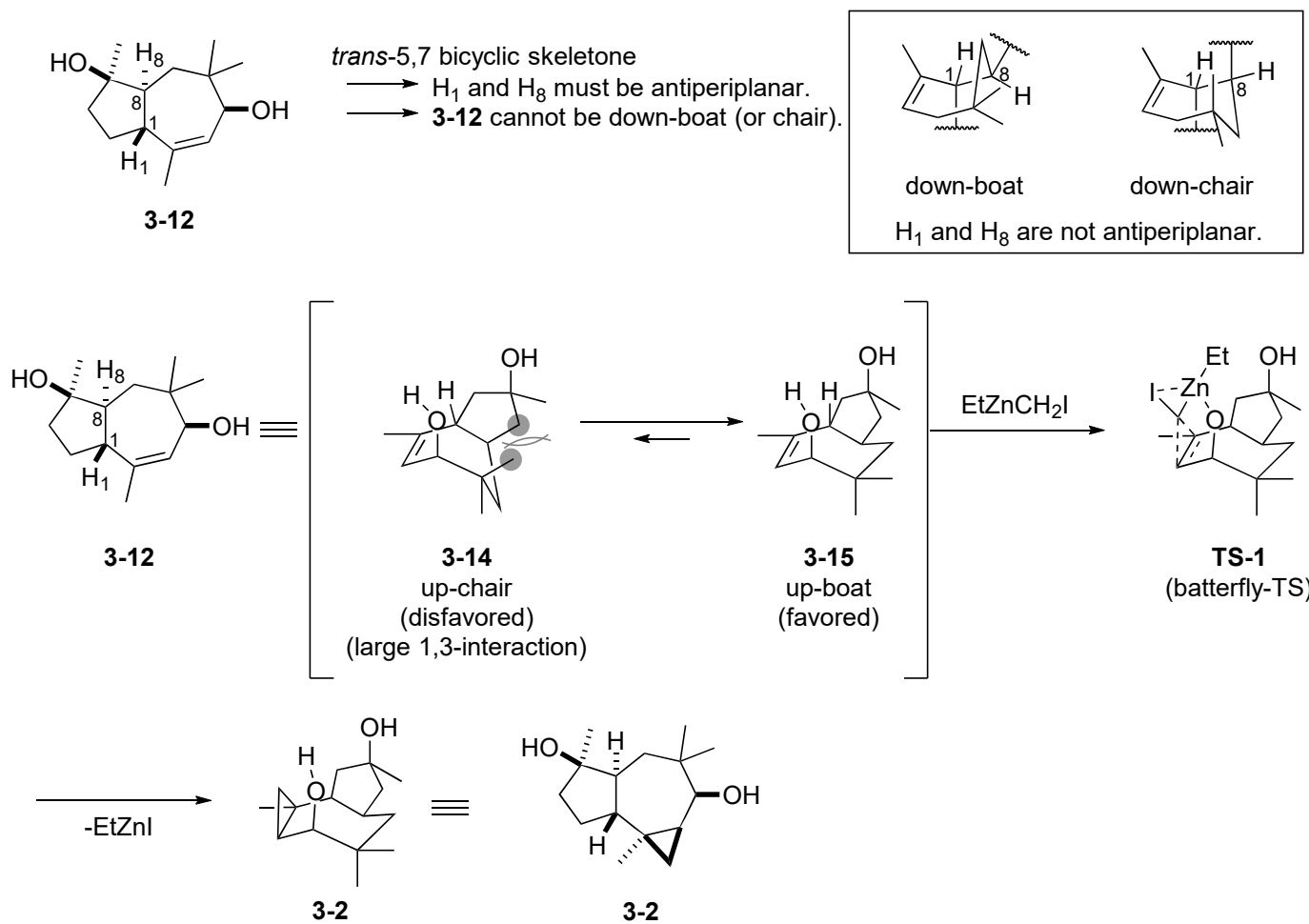
**Answer:** (If not mentioned, Ru = Ru<sup>II</sup>)

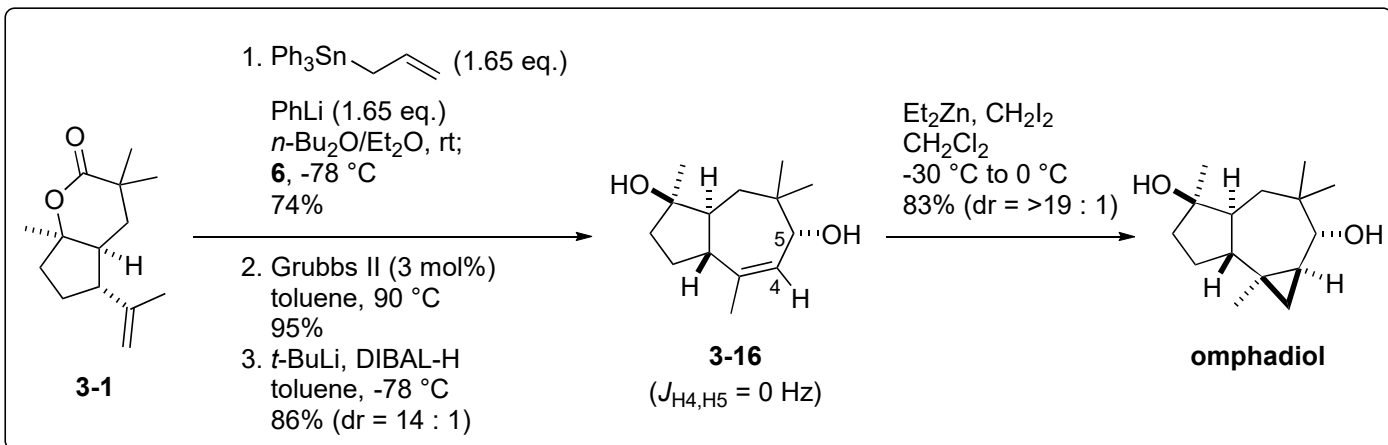




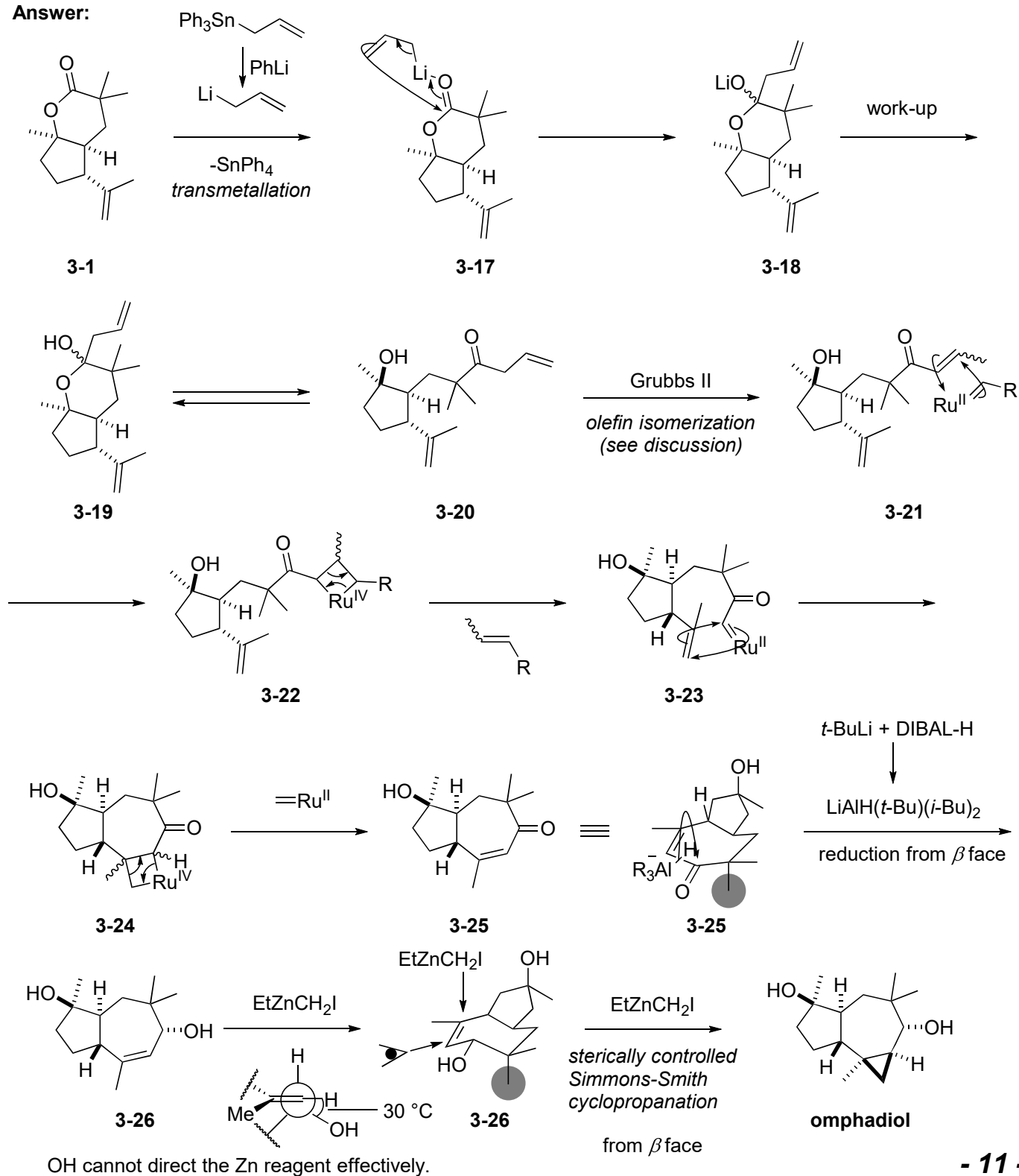
### Discussions:

1. Conformation of cycloheptene and stereoselectivity in Simmons-Smith cyclopropanation.





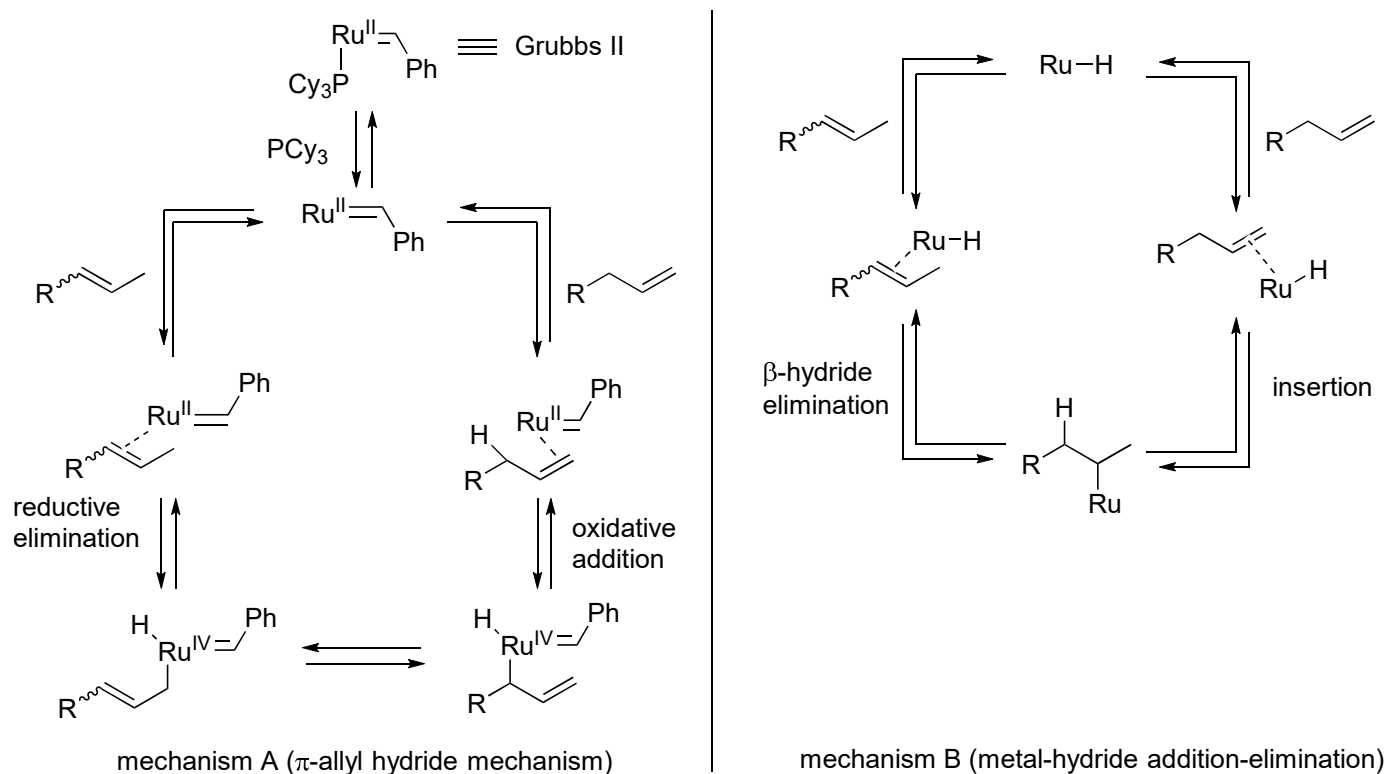
**Answer:**



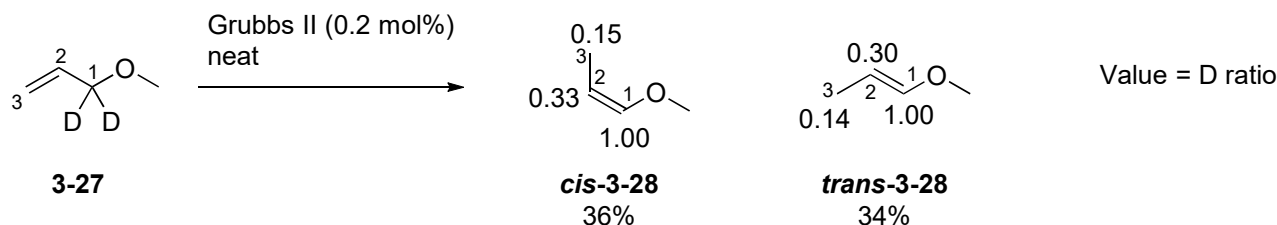
## Discussions:

### 1. Grubbs second generation catalyst catalyzed olefin isomerization.

#### 1-1. Two possible mechanisms.



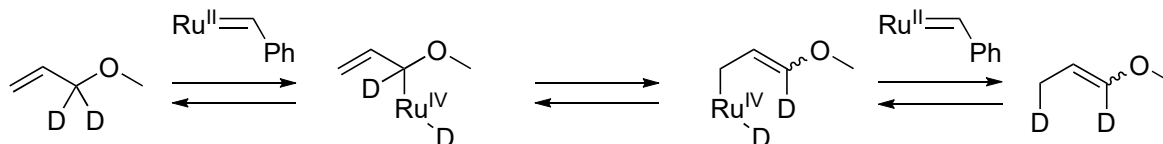
#### 1-2. Deuterium labeling study



Deuteration at C2 position occurred.

→ Mechanism B is correct.

(If mechanism A, deuteration should occur at C1 or C3 position only as shown below.)



Courchay F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074.

#### 1-3. Where did ruthenium hydride come from?

- decomposition of Grubbs catalyst (Grubbs et al.)

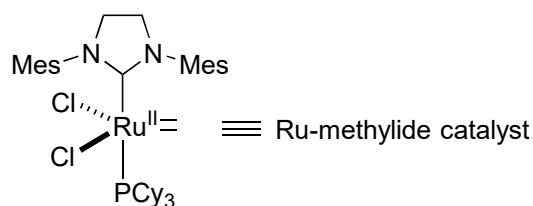
Grubbs isolated Ru-hydride when using Ru-methylidene catalyst.

(Grubbs et al. *J. Am. Chem. Soc.* **2004**, *126*, 7414.)

- impurity in the commercial Grubbs catalyst (Fürstner et al.)

Fürstner detected Ru-hydride when synthesizing Grubbs second catalyst from Grubbs first catalyst.

(Fürstner et al. *Chem. Eur. J.* **2001**, *7*, 3236.)



cf. 1,4-benzoquinone is thought to serve as Ru-hydride scavenger to prevent olefin isomerization.