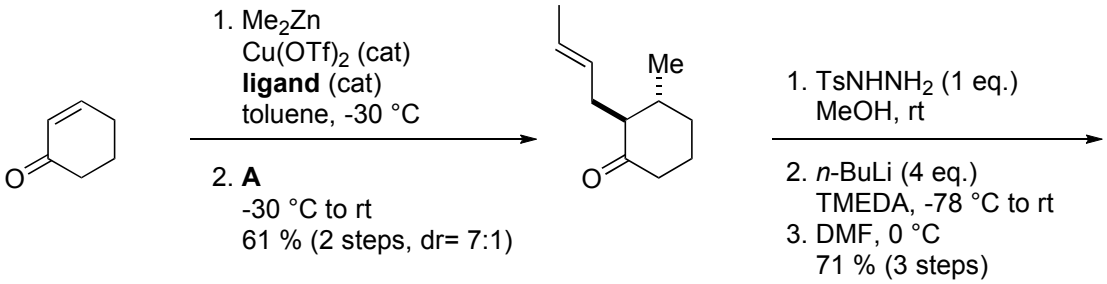
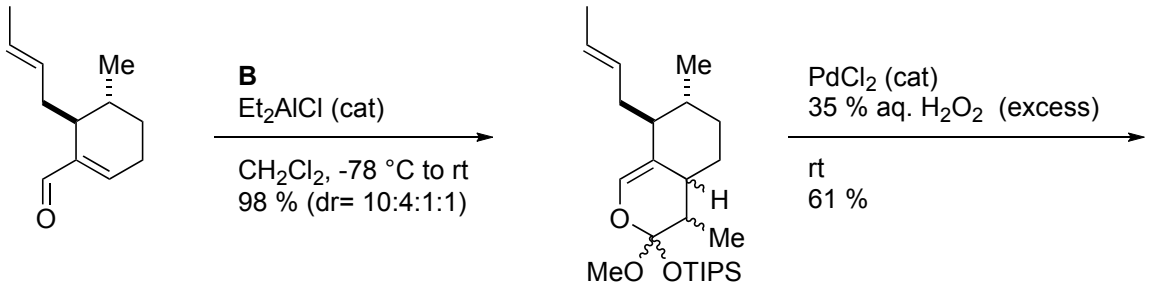
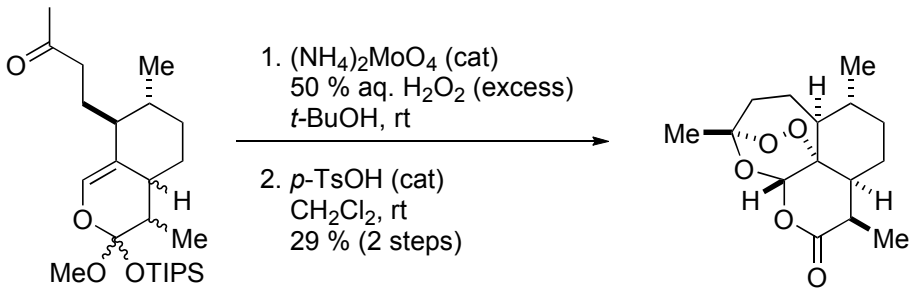
Problem Session (1)

15/11/7 Yuki Fujimoto

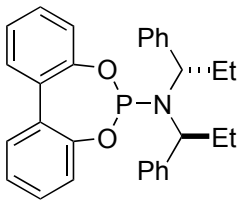
please provide each reaction mechanisms



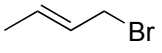




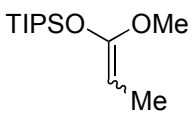
ligand



A



B



(*E*:*Z*= 3:1)

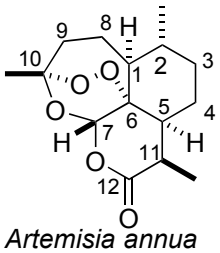
Problem Session (1) Answer

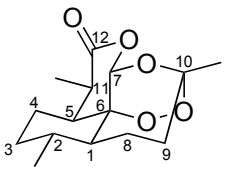
15/11/07 Yuki Fujimoto

Topic: A total synthesis of (+)-artemisinin by S. P. Cook et al.

Introduction

1. about artemisinin





CCDC-691593

Isolation: *Artemisia annua*

Klayman, D. L. *Science.* **1985**, *228*, 1049.

Bioligical activity: antimararia

peroxide bridge can be cleavaged and form free radical

Meshnick, S. R., Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301.

Structural feature: endo-peroxide

lacton

tetracyclic structure includes seven stereocenters

2. total synthesis

Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc*. **1983**, *105*, 624.

Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron* **1986**, *42*, 819.

Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *Tetrahedron Lett*. **1987**, *28*, 4629

Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc*. **1992**, *114*, 974.

Liu, H. J.; Yeh, W. L.; Chew, S. Y. *Tetrahedron Lett*. **1993**, *34*, 4435.

Constantino, M. G.; Beltrame, M.; daSilva, G. V. J. *Synth. Commun*. **1996**, *26*, 321.

Liu, H. J.; Yeh, W. L. *Heterocycles* **1996**, *42*, 493.

Yadav, J. S.; Babu, R. S.; Sabitha, G. *Tetrahedron Lett*. **2003**; *44*: 387

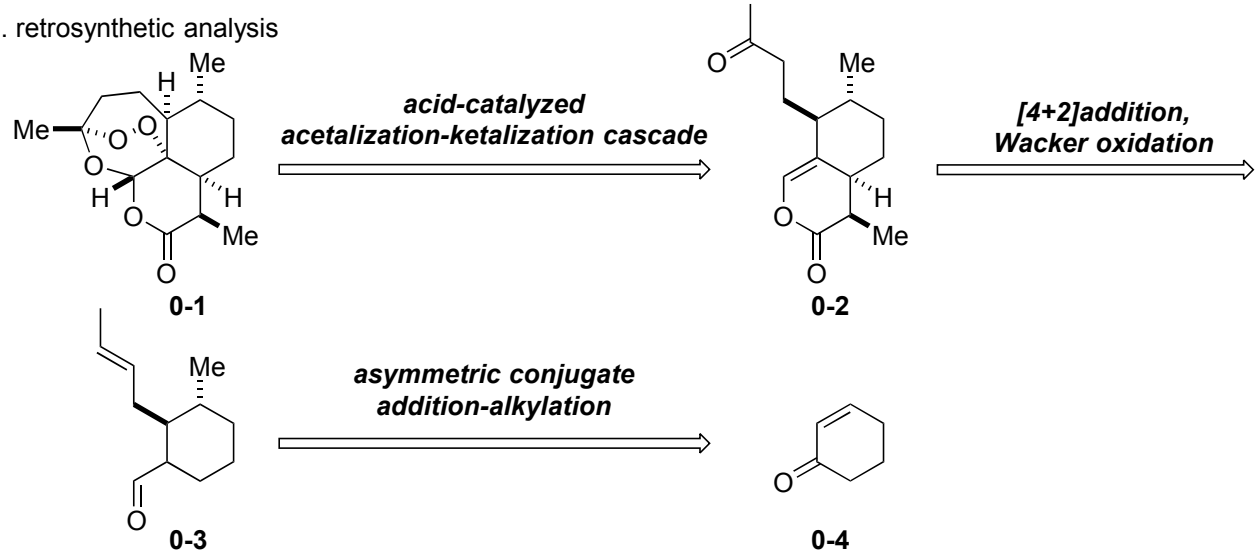
Yadav, J. S.; Thirupathaiah, B.; Srihari, P. *Tetrahedron* **2010**; *66*: 2005

formal total synthesis

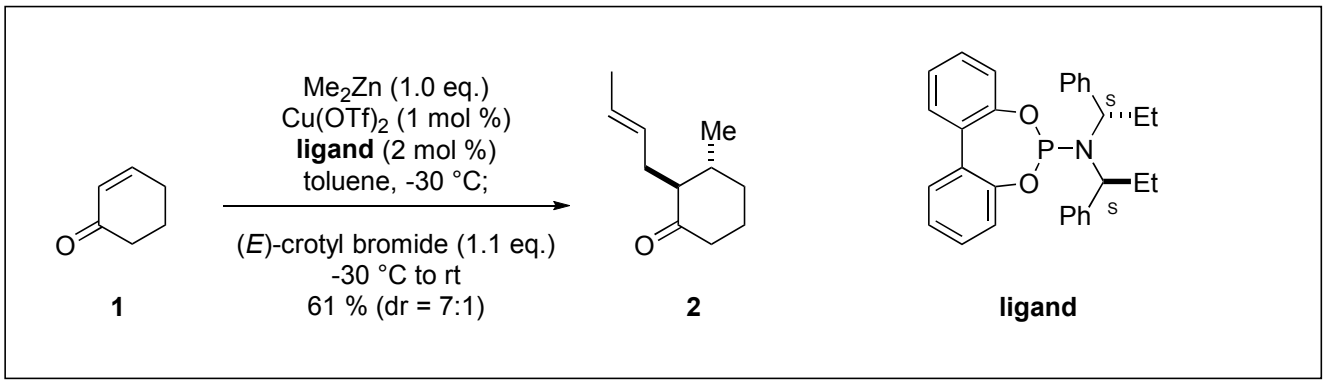
Ravindranathan, T.; Kumar, M. A.; Menon, R. B.; Hiremath, S. V. *Tetrahedron Lett*. **1990**, *31*, 755

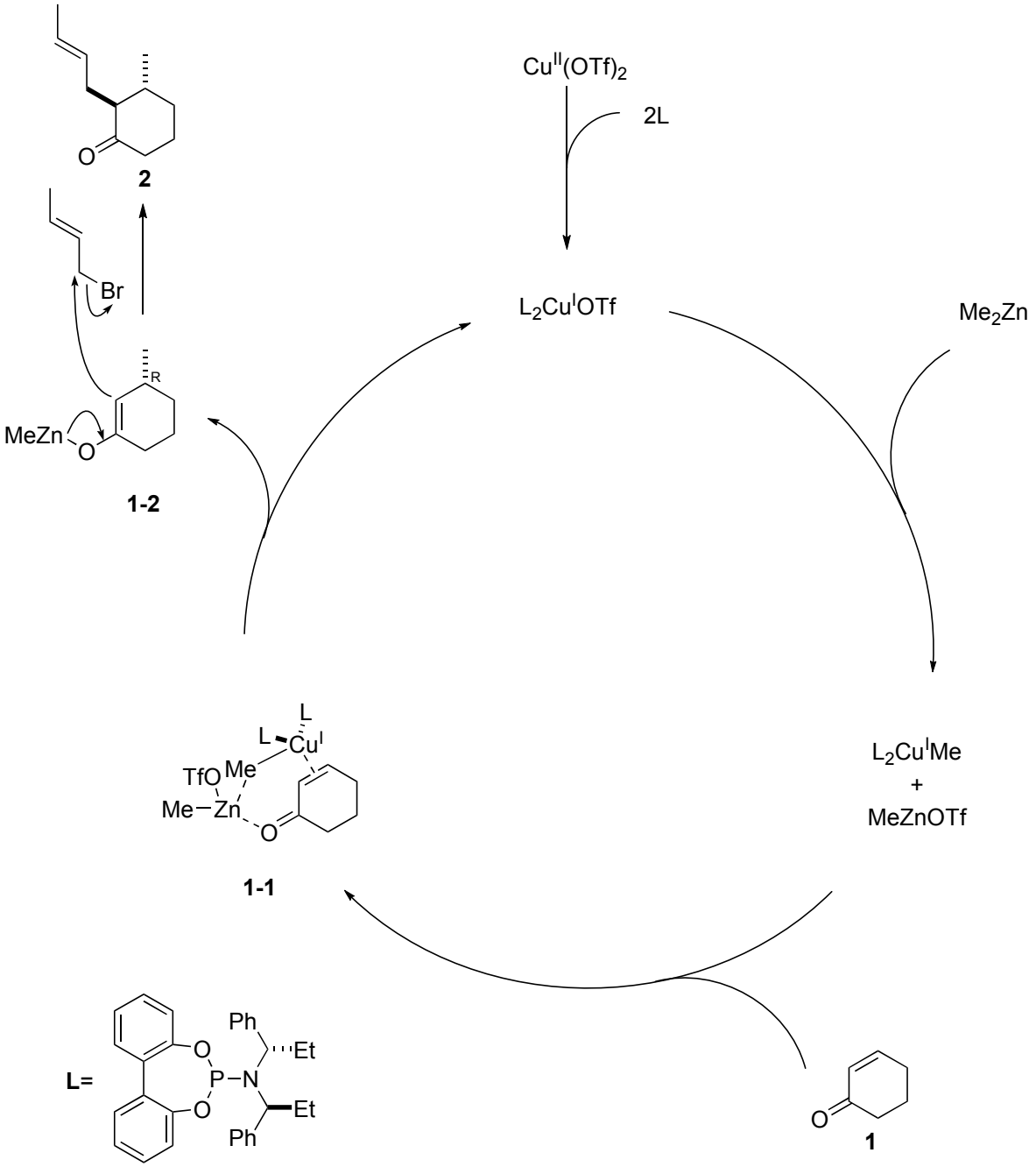
Bhonsle, J. B.; Pandey, B.; Deshpande, V. H.; Ravindranathan, T. *Tetrahedron Lett*. **1994**, *35*, 5489

3. retrosynthetic analysis

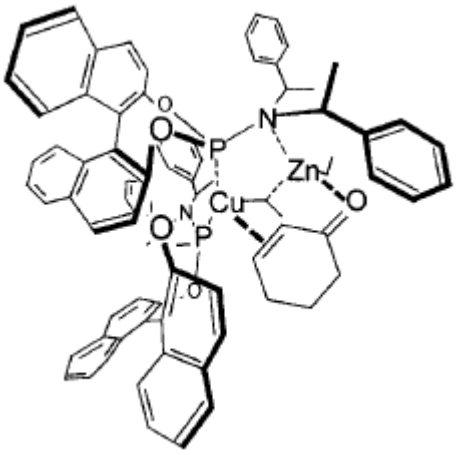


1→**2**: Copper and phosphoramidite catalyzed enantioselective conjugate addition of dialkyl zinc

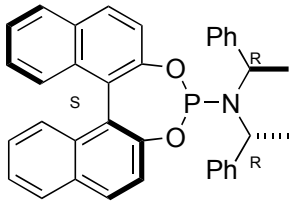




enantioselectivity of conjugate addition



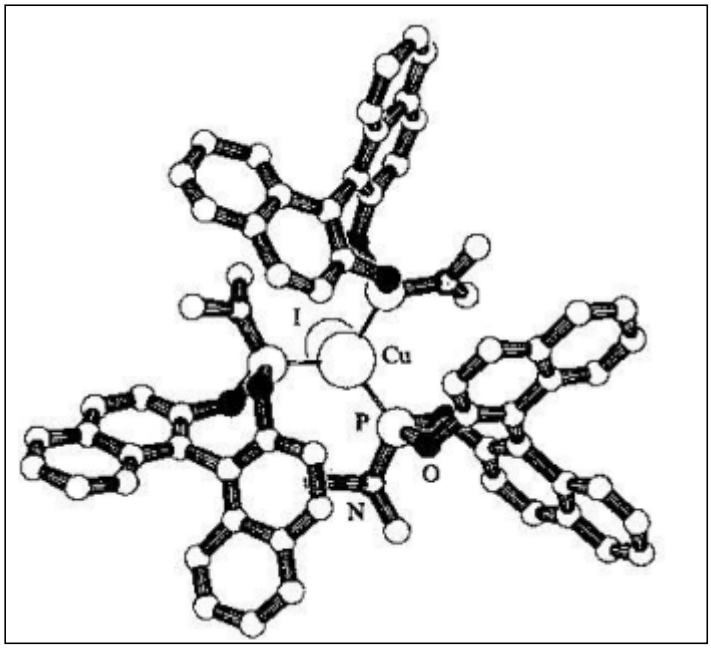
1-1 (L→(S, R, R)-L-1)

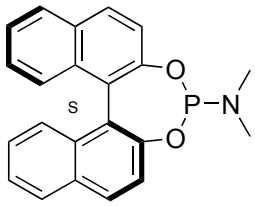


(S, R, R)-L-1

Figure1. proposed structure of **1-1** (**L→(S, R, R)-L-1**)

Modern Organocopper Chemistry; ed. by Krause, N.; Wiley-VCH, **2001**, chapter 7.





L-2

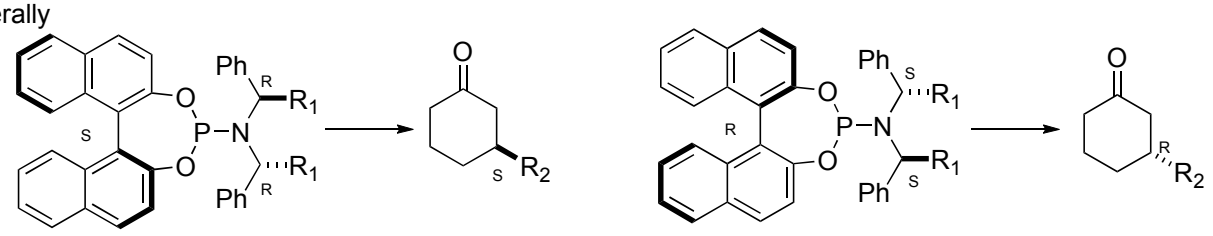
Figure 2. X-ray structure of CuI(**L-2**)$_3$

de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 2374.

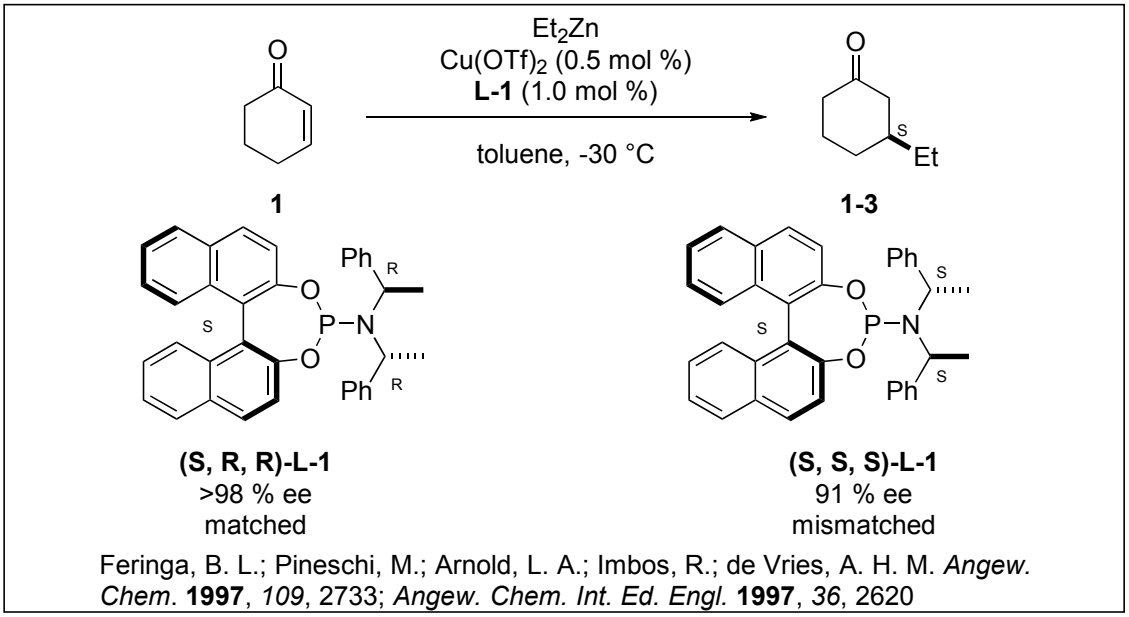
I →Et
one of **L-2** →enone ⟶ the skelton of Figure 1.

However this structure is not **L**, but **(S, R, R)-L-1**

generally

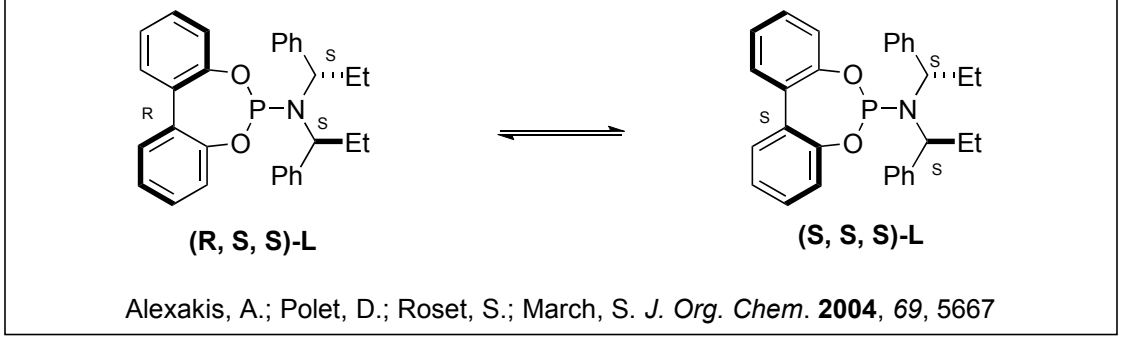


(S, R, R) (S) (R, S, S) (R)



Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem*. **1997**, *109*, 2733; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620

(S, R, R)-L-1 provide **1-3(S)**
(S, S, S)-L-1 provide **1-3(S)** ⟶ binaphtyl is more important than amine



Alexakis, A.; Polet, D.; Roset, S.; March, S. *J. Org. Chem*. **2004**, *69*, 5667

L provide **1-2 (R)→(R, S, S)-L** is major

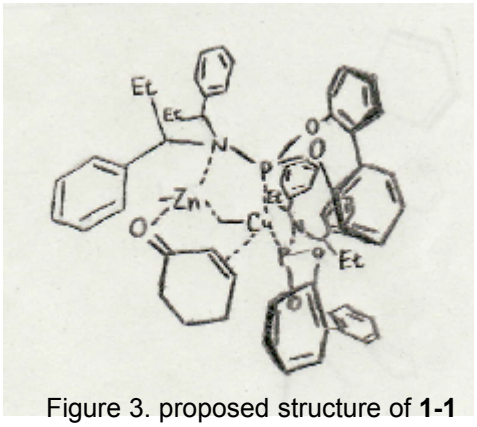
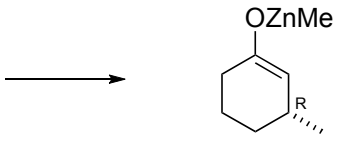
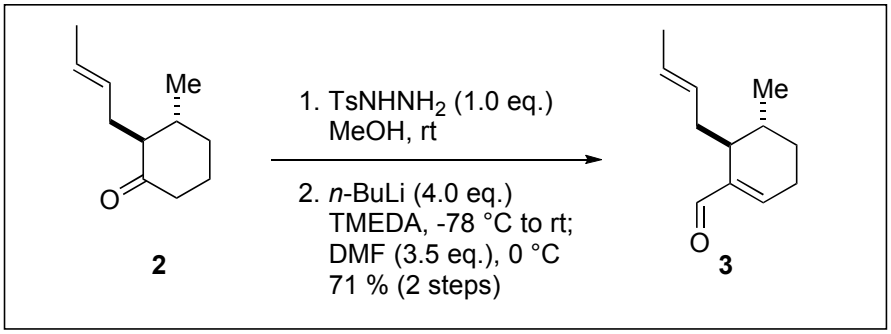


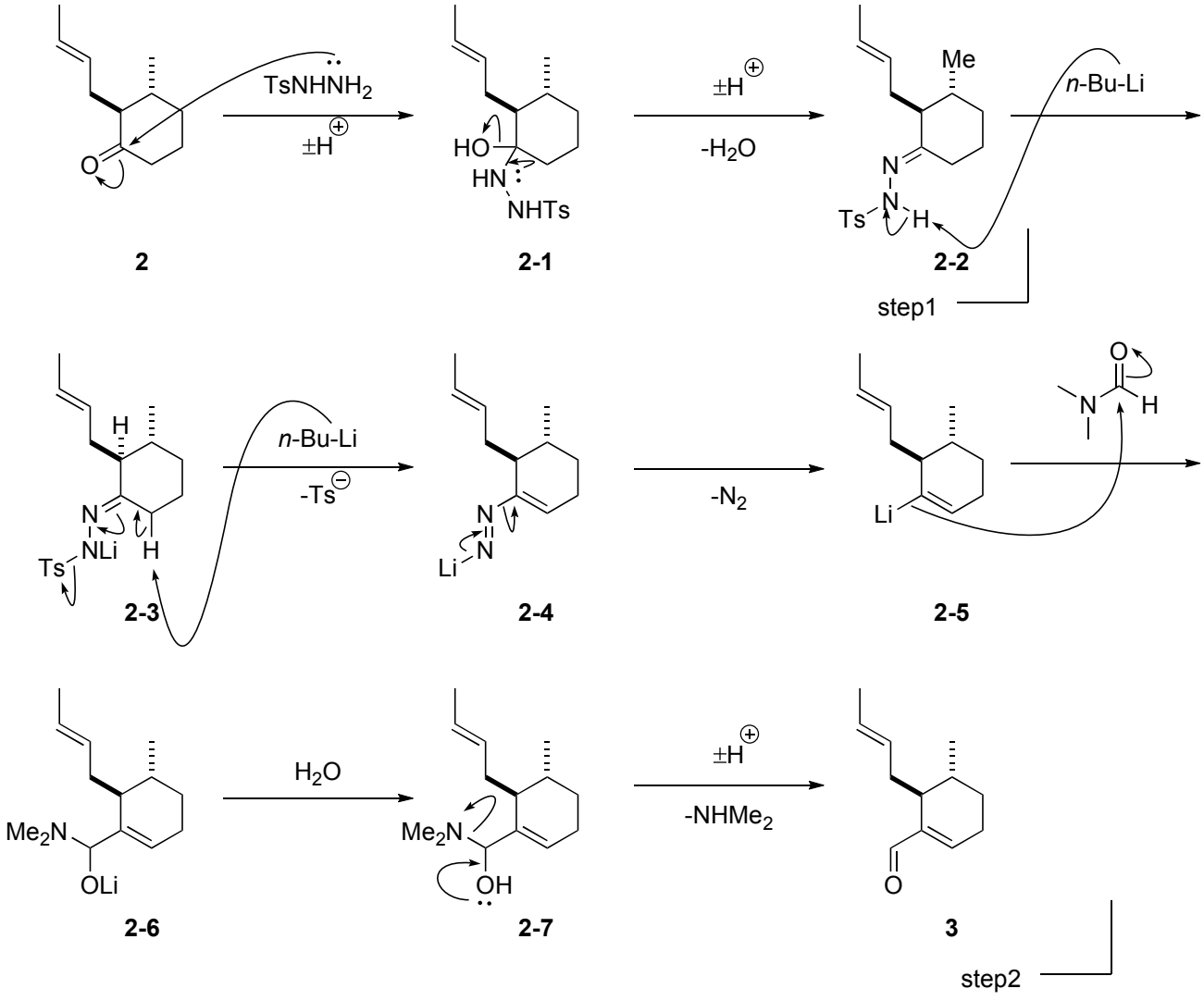
Figure 3. proposed structure of **1-1**



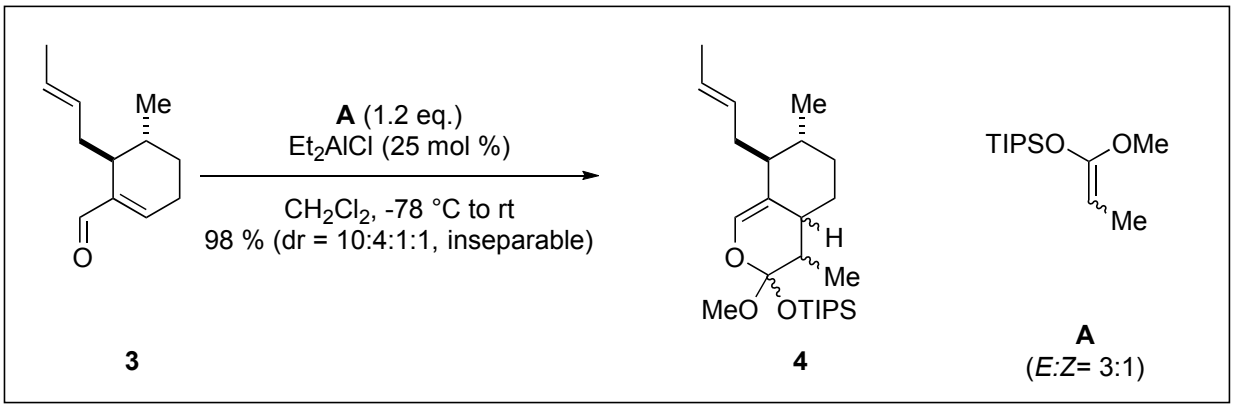
1-2

2→3: Shapiro reaction

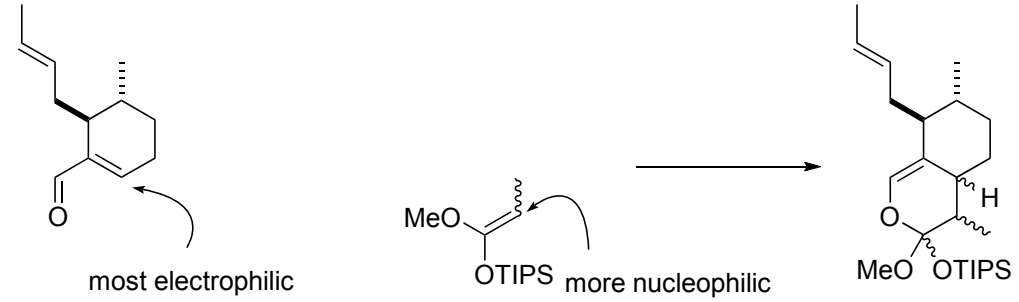




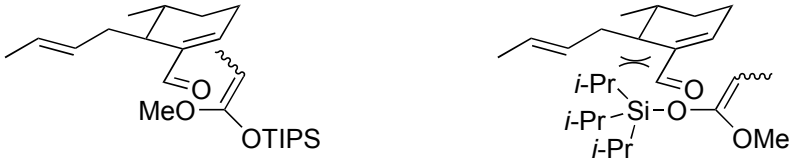
3→4 :Hetero Diels- Alder reaction



regioselectivity

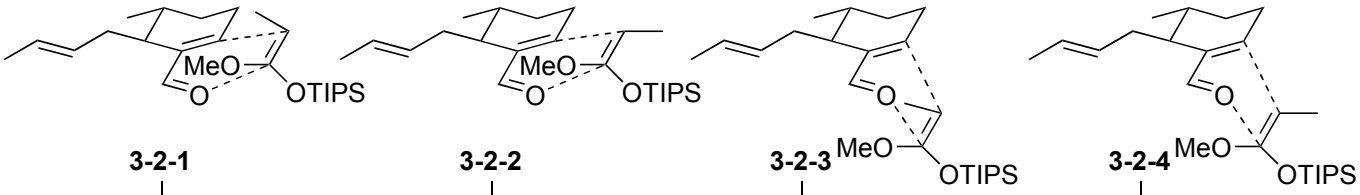


stereoselectivity



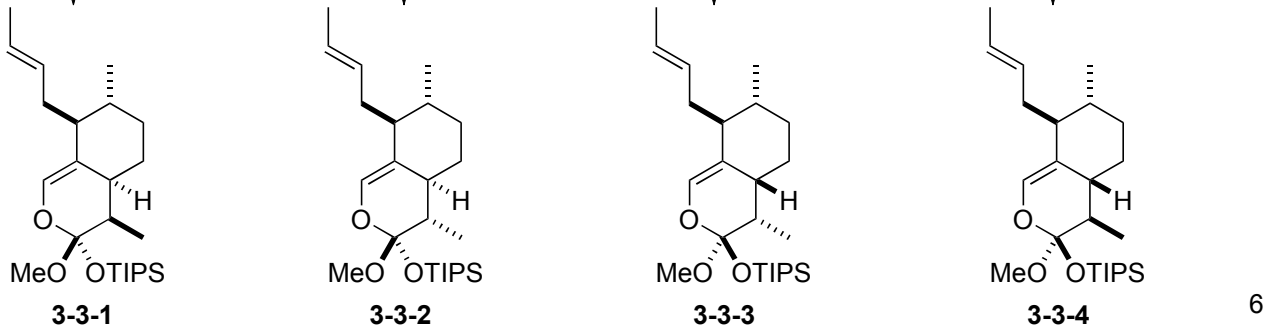
3-1-1
favored

3-1-2
unfavored

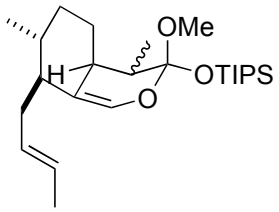


3-2-1 **3-2-2** **3-2-3** **3-2-4**

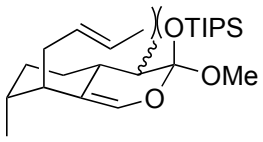
(*E*) (*Z*) (*E*) (*Z*)

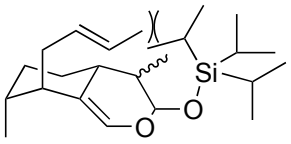


3-3-1 **3-3-2** **3-3-3** **3-3-4**



3-3-1, 3-3-2
favored



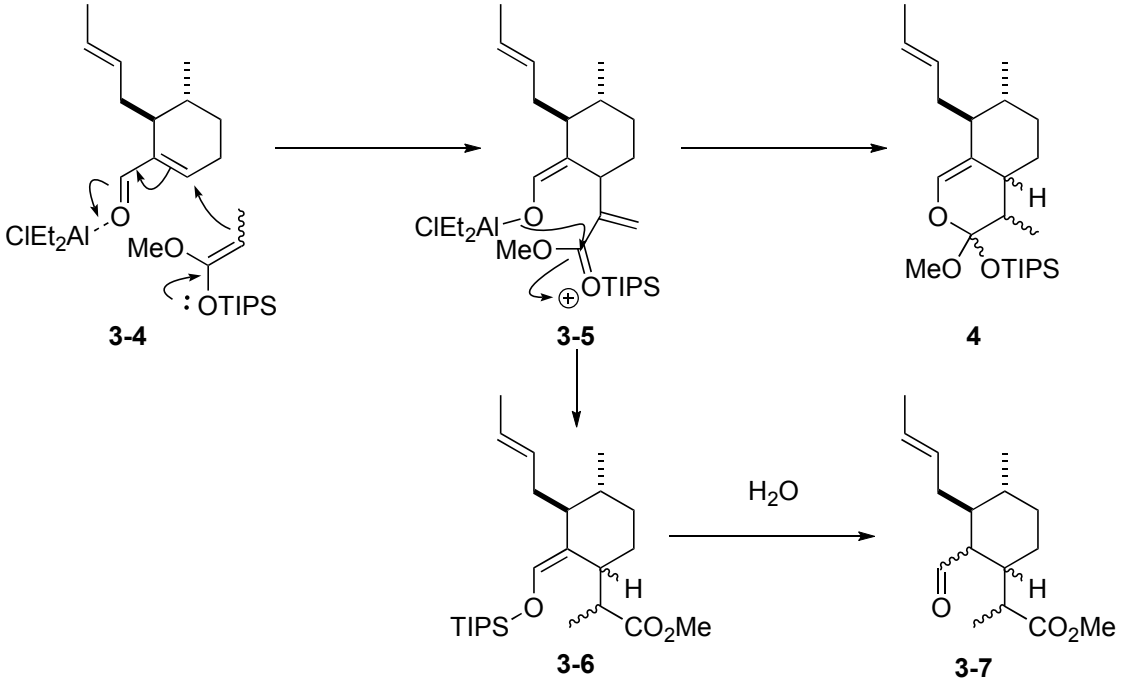


3-3-3, 3-3-4
unfavored

-OMe was omitted for clarification

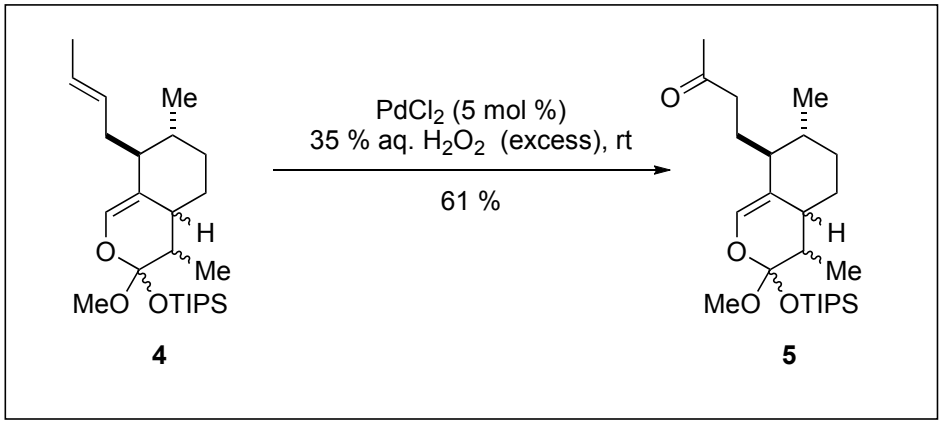
3-3-1:**3-3-2**:**3-3-3**:**3-3-4** = 10:4:1:1

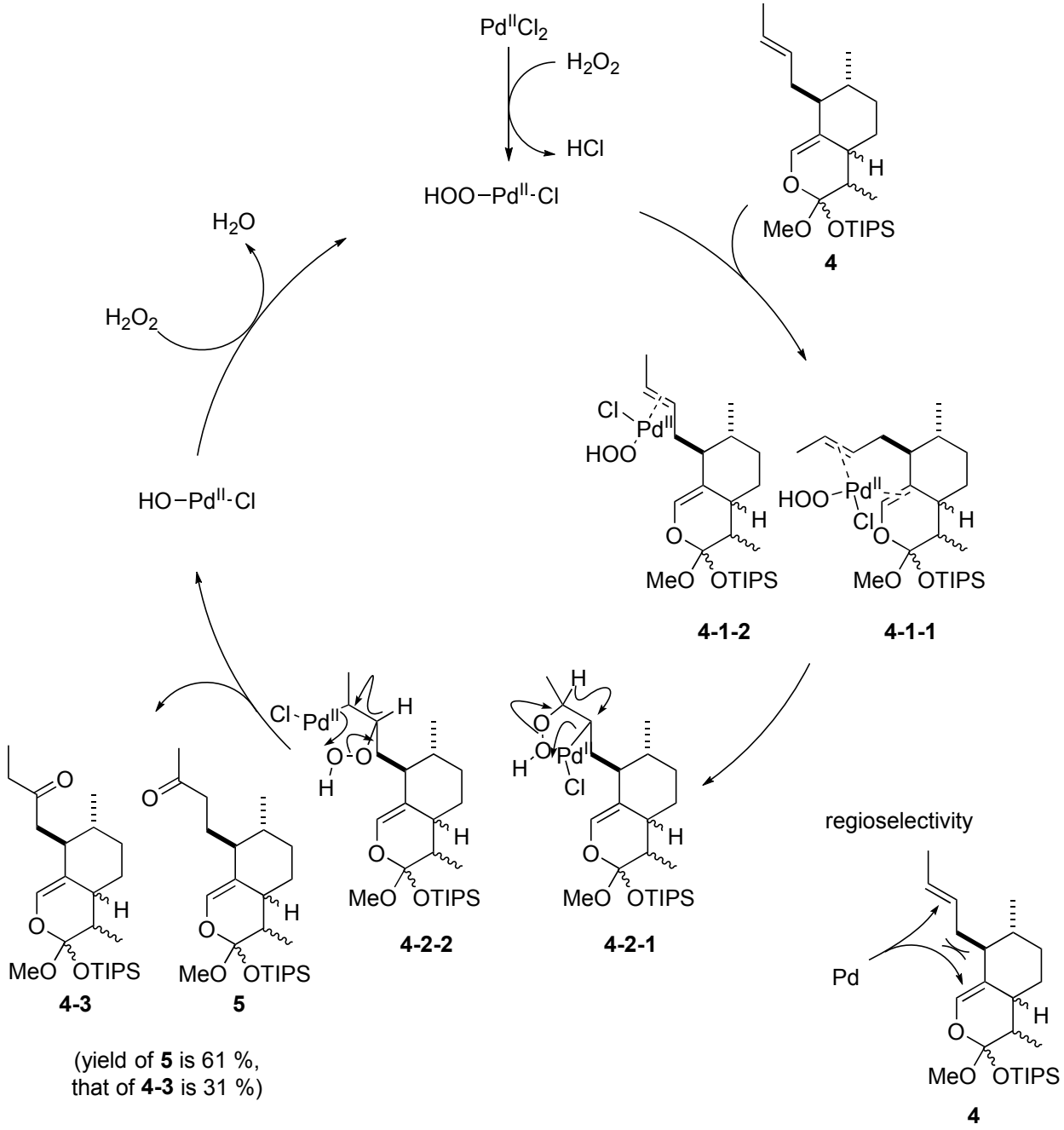
stepwise path



If the cyclization proceed through stepwise path, desilylation or Michael addition can proceed. But **4** is silyl acetal, so I presume that this reaction proceed through hetero Diels Alder path

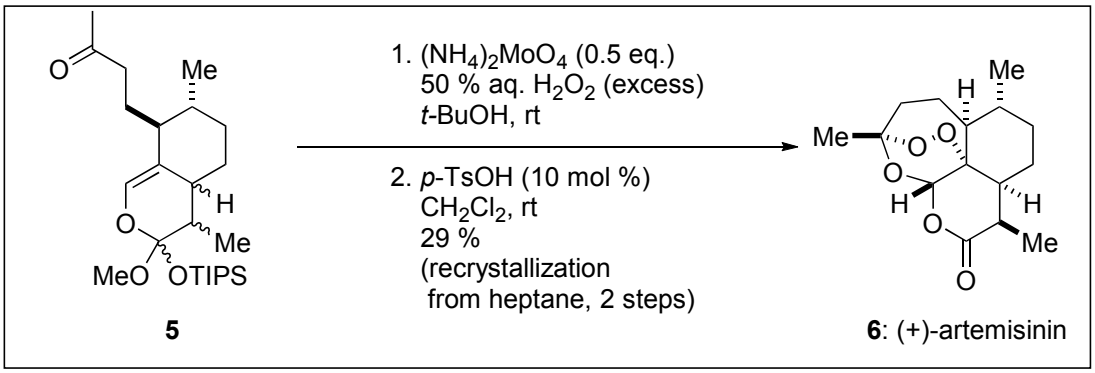
4→5: Wacker type oxidation of internal olefin





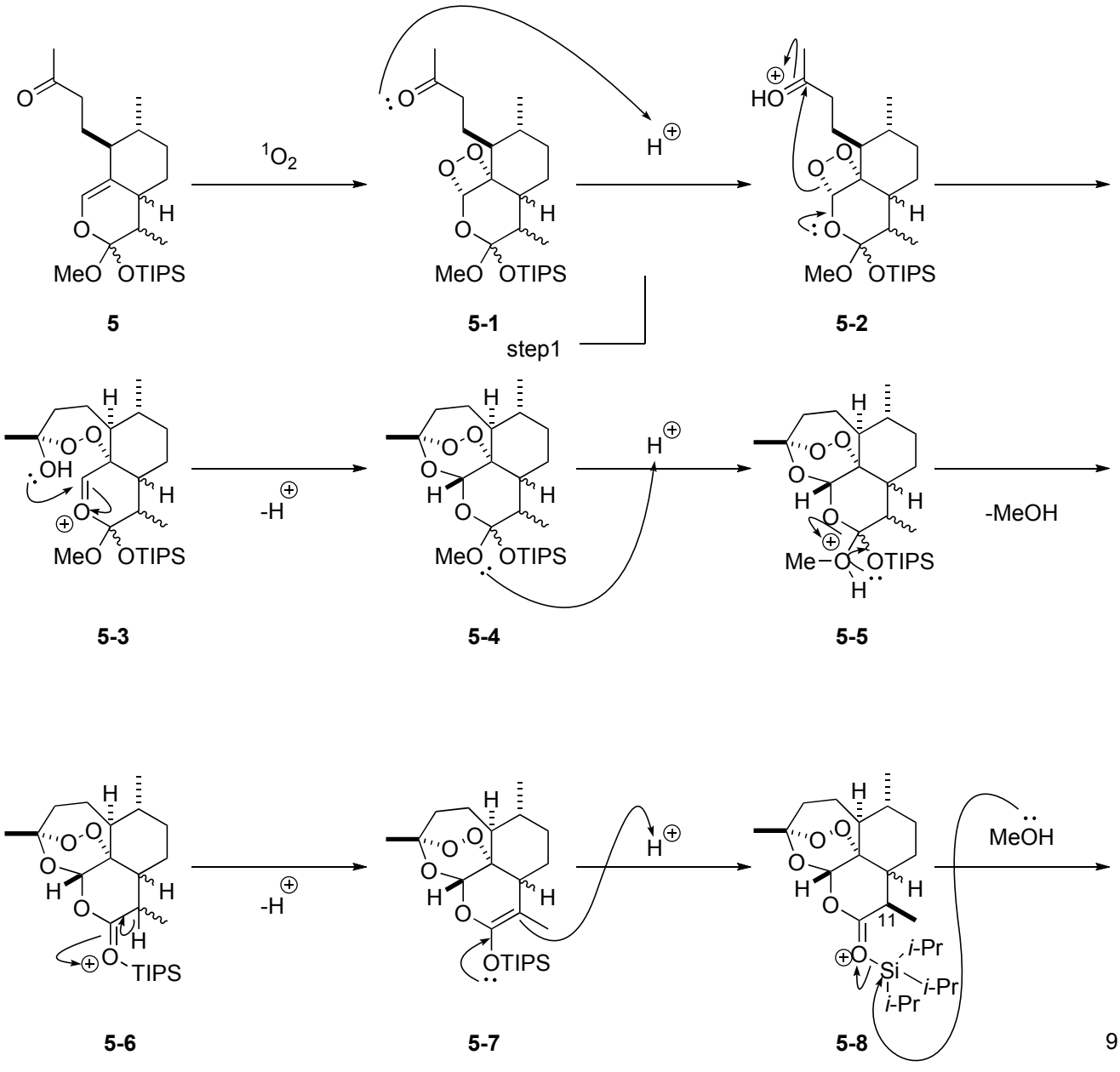
(yield of **5** is 61 %,
that of **4-3** is 31 %)

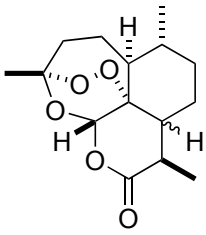
5→**6**: singlet oxigen oxidation



$MoO_4^{2-} + 2H_2O_2 \rightarrow MoO_6^{2-} + 2H_2O$

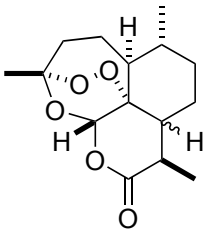
$MoO_6^{2-} \rightarrow MoO_4^{2-} + {}^1O_2$





5-9

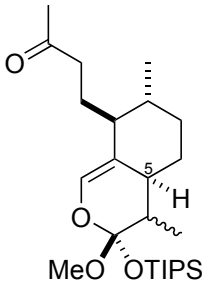
recrystallization



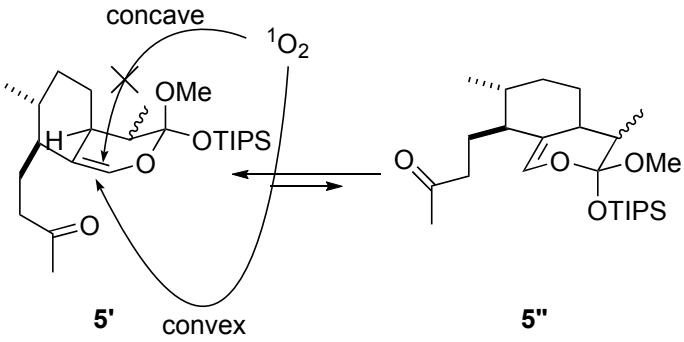
5-10

step2

stereoselectivity of seven-membered ring formation

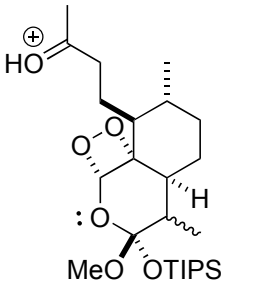


5

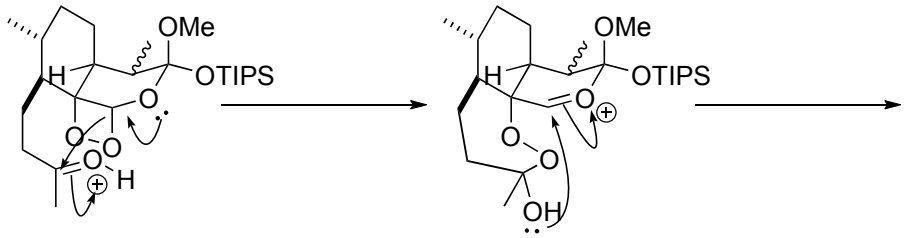


5' **5"**

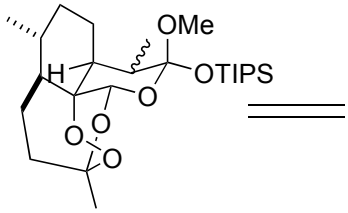
silyl ether is pseudo equatrial in major conformation



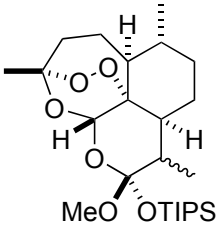
5-2



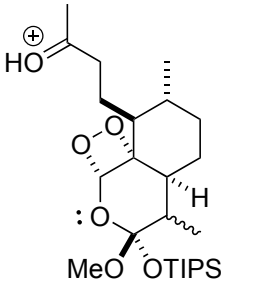
5-2-1 **5-3-1**



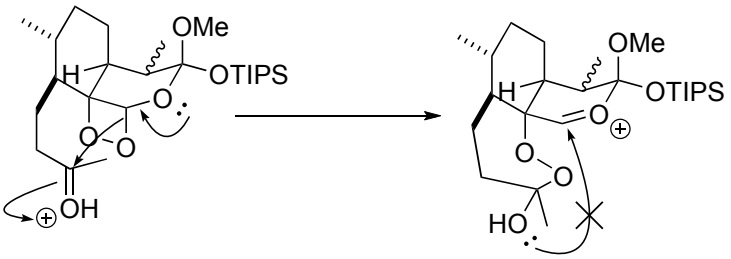
5-4-1



5-4



5-2



5-2-2 **5-3-2**