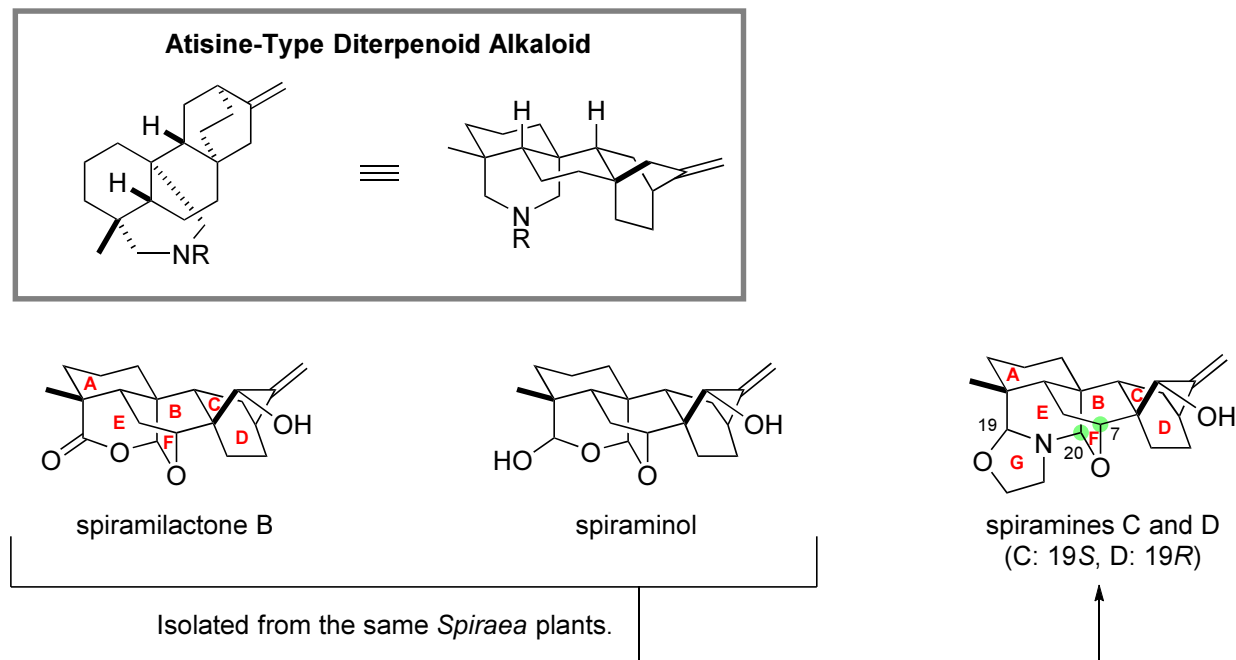


## Problem Session (5) - Answer -

15.11.14 Komei Sakata

### Collective Total Synthesis of Atisane-Type Diterpenes and Atisine-Type Diterpenoid Alkaloids: ( $\pm$ )-Spiramilactone B, ( $\pm$ )-Spiraminol, ( $\pm$ )-Dihydrojaconine, and ( $\pm$ )-Spiramines C and D

Cheng, H.; Zeng, F.-H.; Yang, X.; Meng, Y.-J.; Xu, L.; Wang, F.-P. *Angew. Chem. Int. Ed.* early view (DOI: 10.1002/anie.201508996)



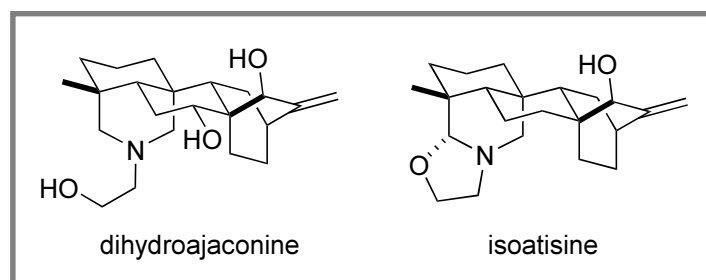
Spiraminol can be transformed to spiramines C and D.

\* Hao, X.-J. *et al*, *Curr. Med. Chem.* **2003**, *10*, 2253.

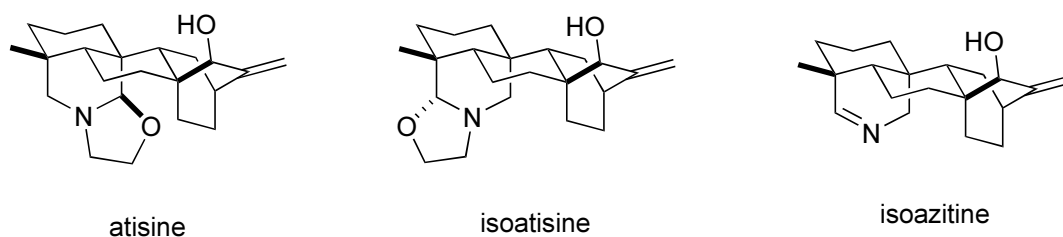
Hao, X.-J. *et al*, *J. Nat. Prod.* **2009**, *72*, 645.

#### Spiramines C and D:

- Heptacyclic ring framework
- Three bridged ring units (A/E, B/F, C/D)
- C7-C20 oxygen-bridge linkage

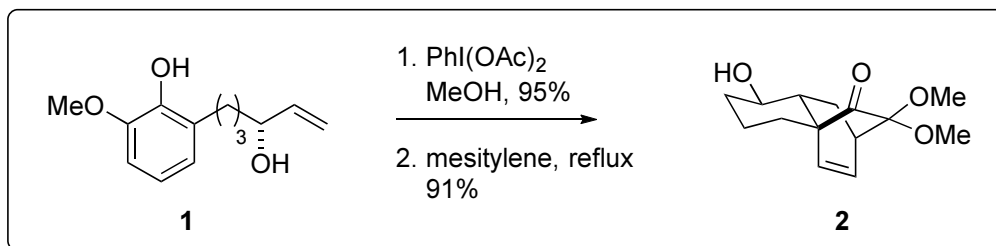


#### Total syntheses of other atisine-type diterpenoid alkaloids:

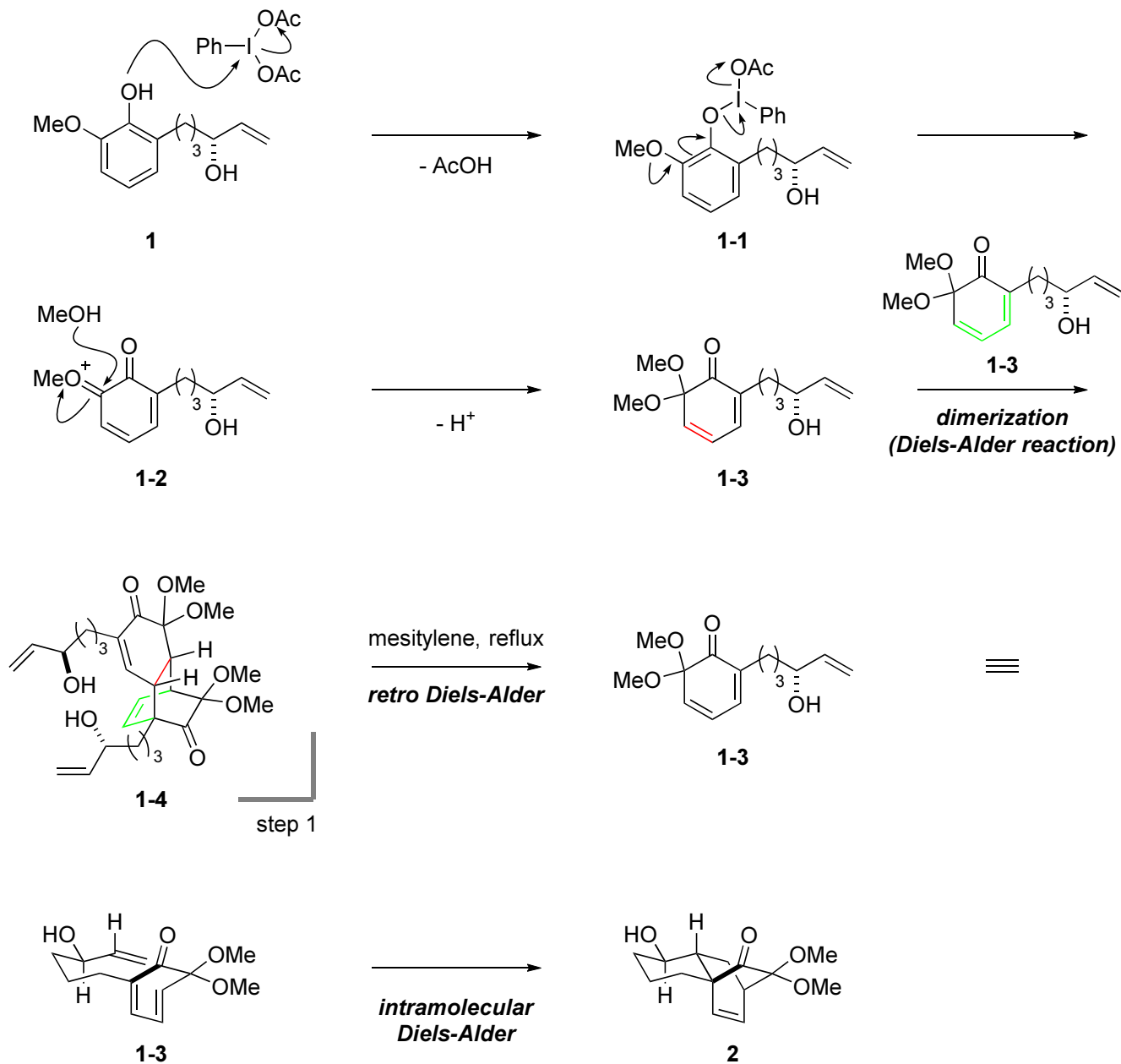


a) Baran, P. S. *et al*, *J. Am. Chem. Soc.* **2014**, *136*, 12592; b) Hayase, Y. *et al*, *J. Am. Chem. Soc.* **1963**, *85*, 2342; c) Hayase, Y., *J. Am. Chem. Soc.* **1967**, *89*, 1483; d) Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 291; e) Wiesner, K. *et al*, *Tetrahedron Lett.* **1966**, *7*, 4645; f) Kabuto, C. *et al*, *J. Am. Chem. Soc.* **1988**, *110*, 1963; g) Kabuto, C. *et al*, *J. Am. Chem. Soc.* **1990**, *112*, 1164; h) Chen, Q.-H.; Wang, F.-P. *et al*, *Org. Biomol. Chem.* **2012**, *10*, 1411.

1. Oxidative dearomatization, dimerization, retro DA/intramolecular DA

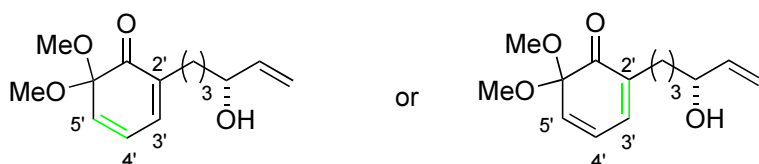


Proposed mechanism

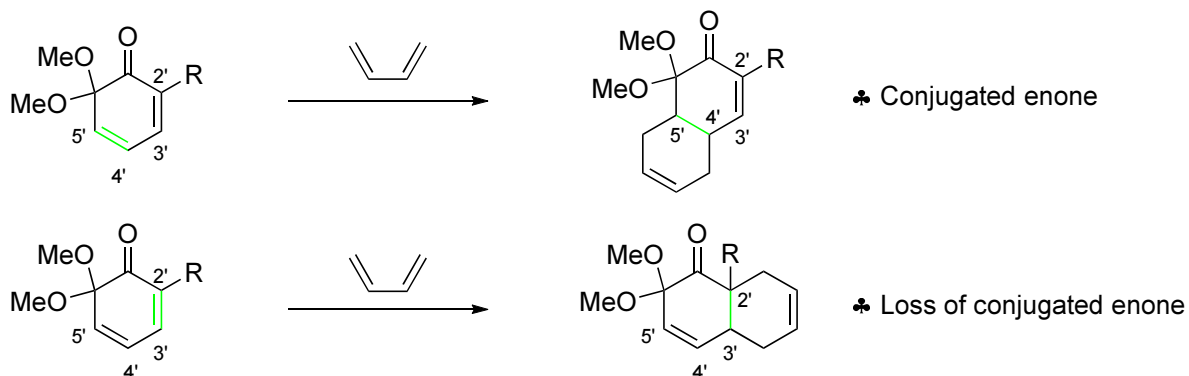


## Selectivities in dimerization

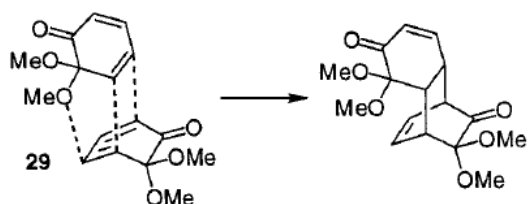
- Chemoselectivity of dienophile **1-3**



**C<sub>5'</sub>-C<sub>4'</sub> double bond selectively acted as an electrophile.**



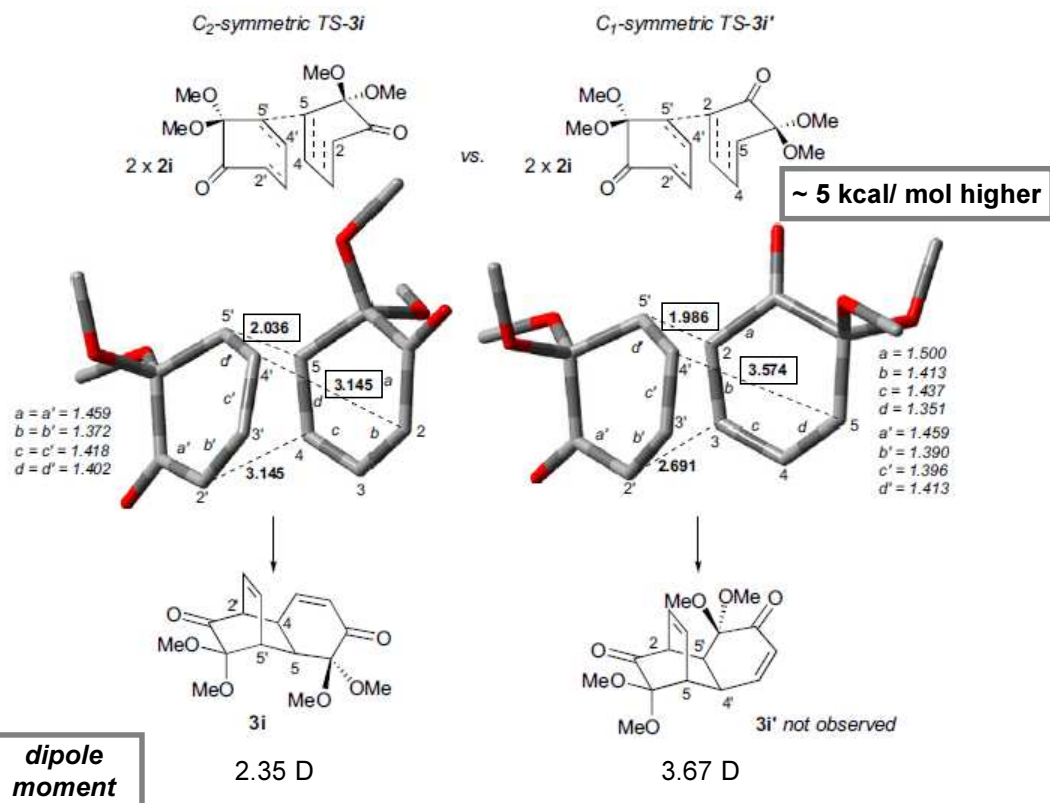
- Endo / exo selectivity



Liao, C.-C.; Chu, C.-C.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-H.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102.

- C<sub>2</sub>-symmetric vs C<sub>1</sub>-symmetric (site selectivity)

B3LTP/6-31G TS structure



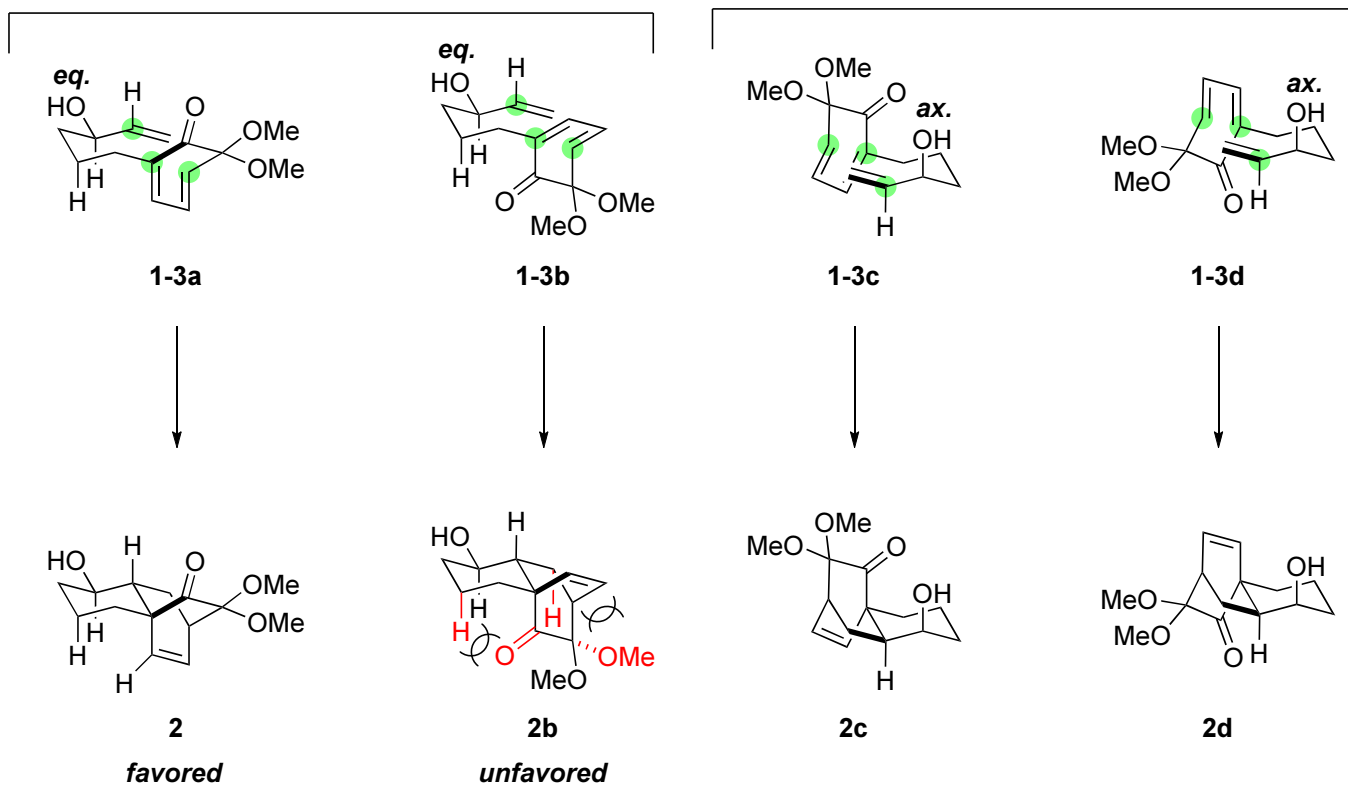
## Diastereoselectivity in Diels-Alder reaction

• 4 diastereomers could be generated from the conformers **1-3a-d**

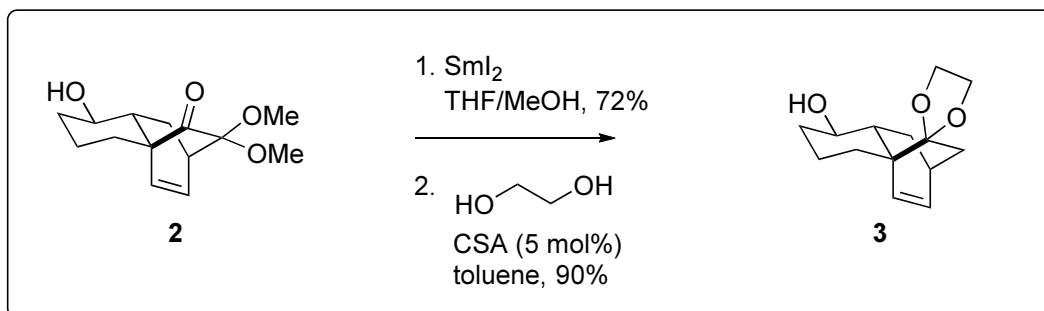
: Diastereoselectivities should be explained based on the thermodynamical aspect.

*equatorially oriented OH group (favored)*

*axially oriented OH group (unfavored)*

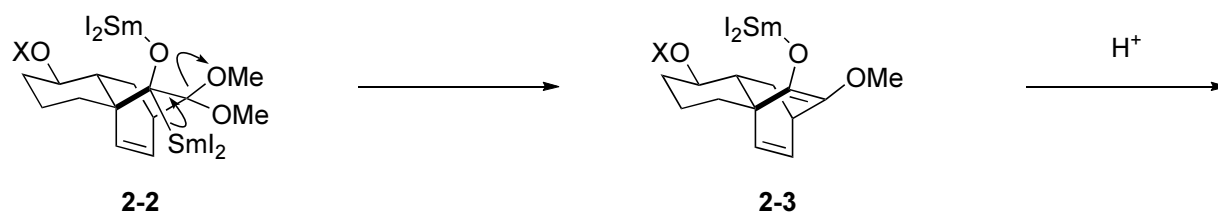
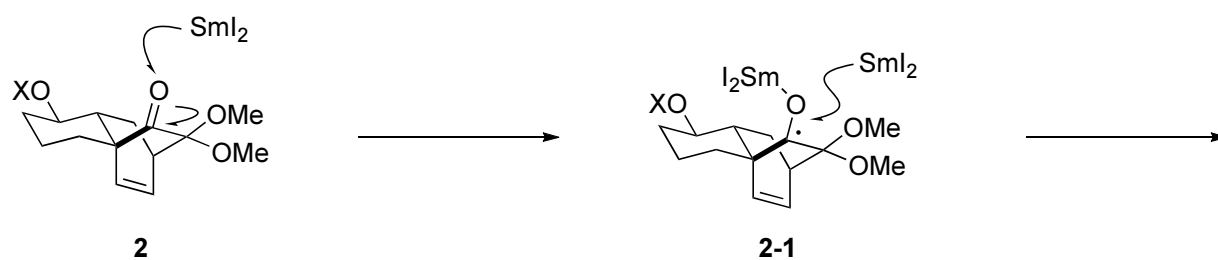


## 2. $\text{SmI}_2$ mediated deoxygenation, acetalization

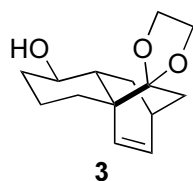
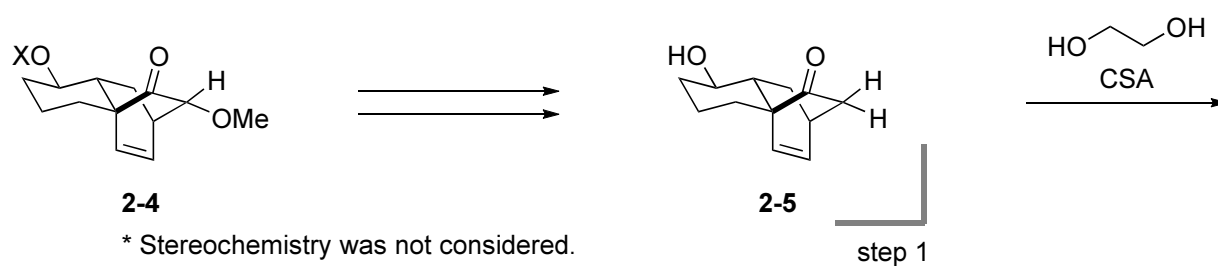


### Proposed mechanism

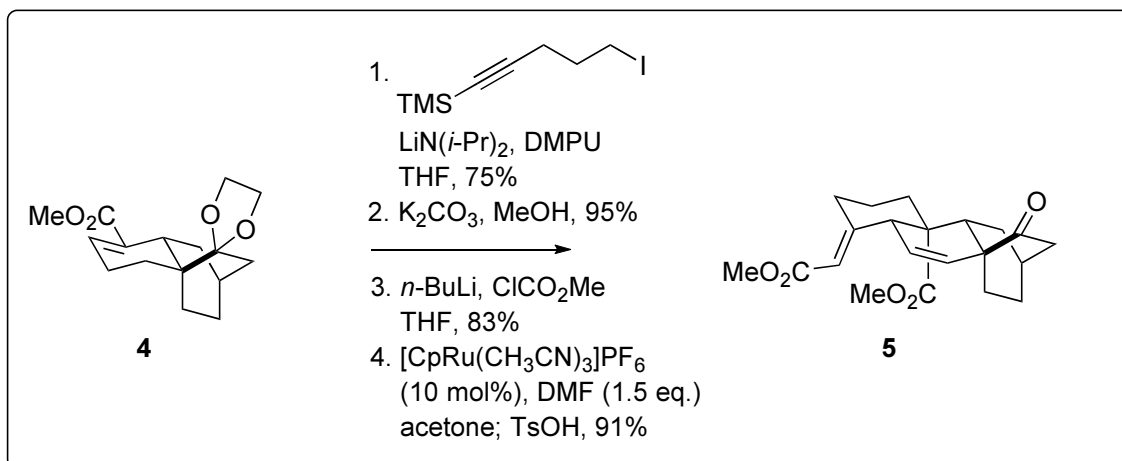
X = H or  $\text{SmI}_2$



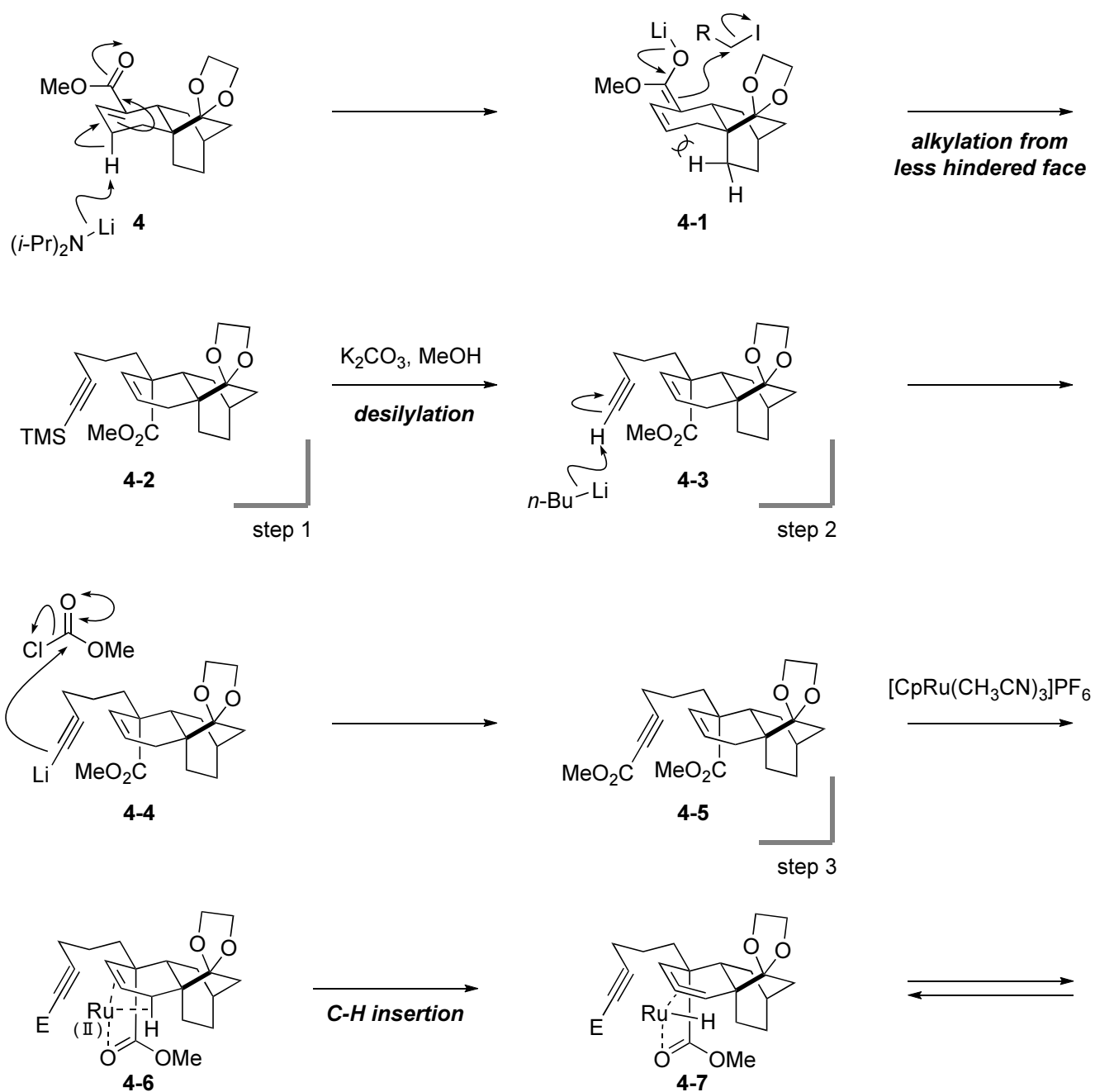
\* Stereochemistry was not considered.

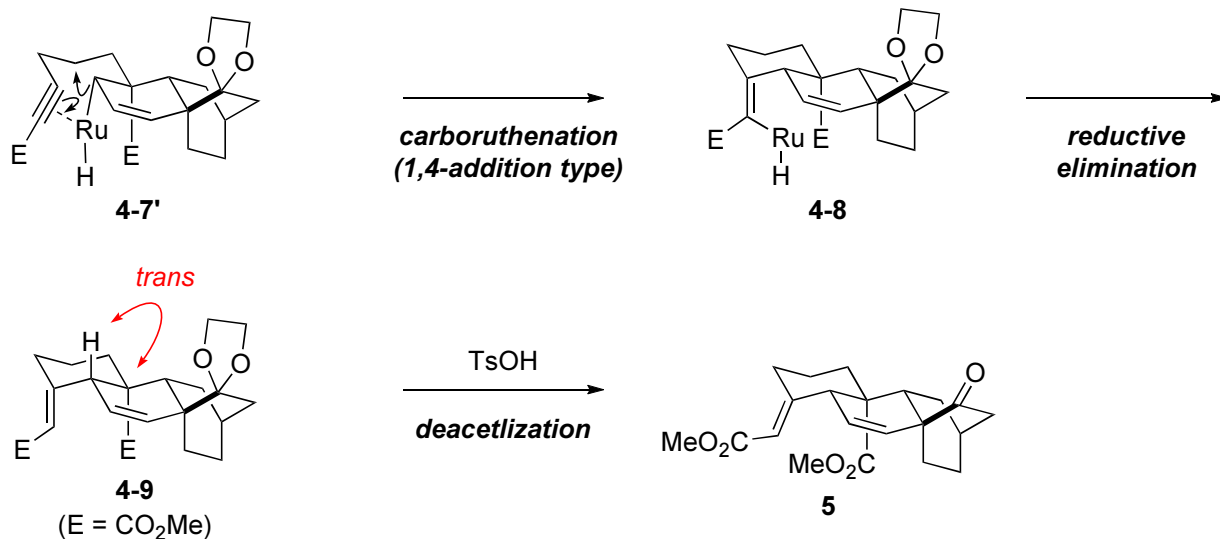


### 3. Alkylation, desilylation, acylation, cycloisomerization



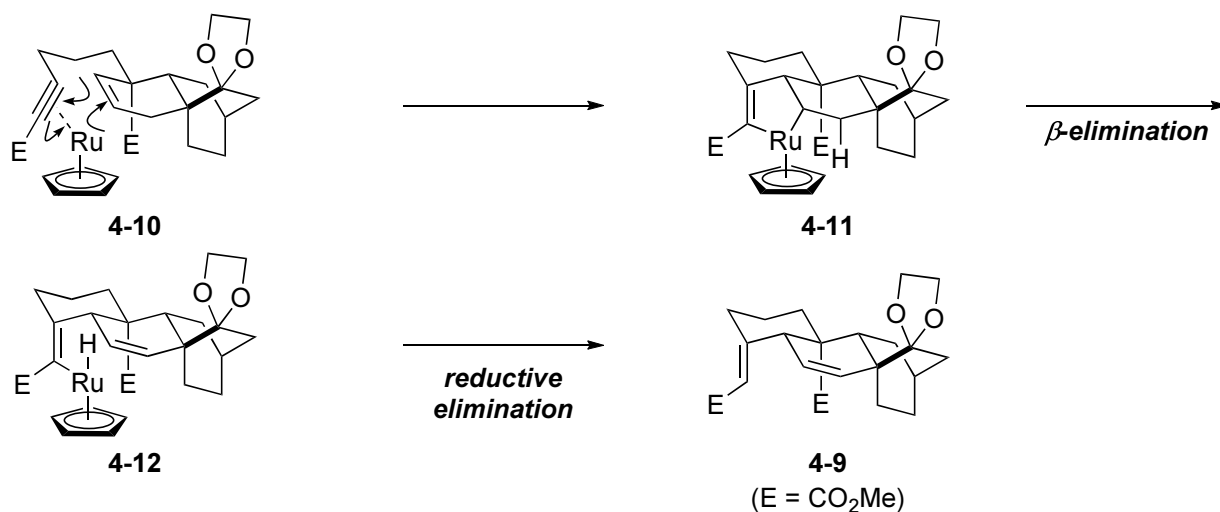
#### Proposed mechanism





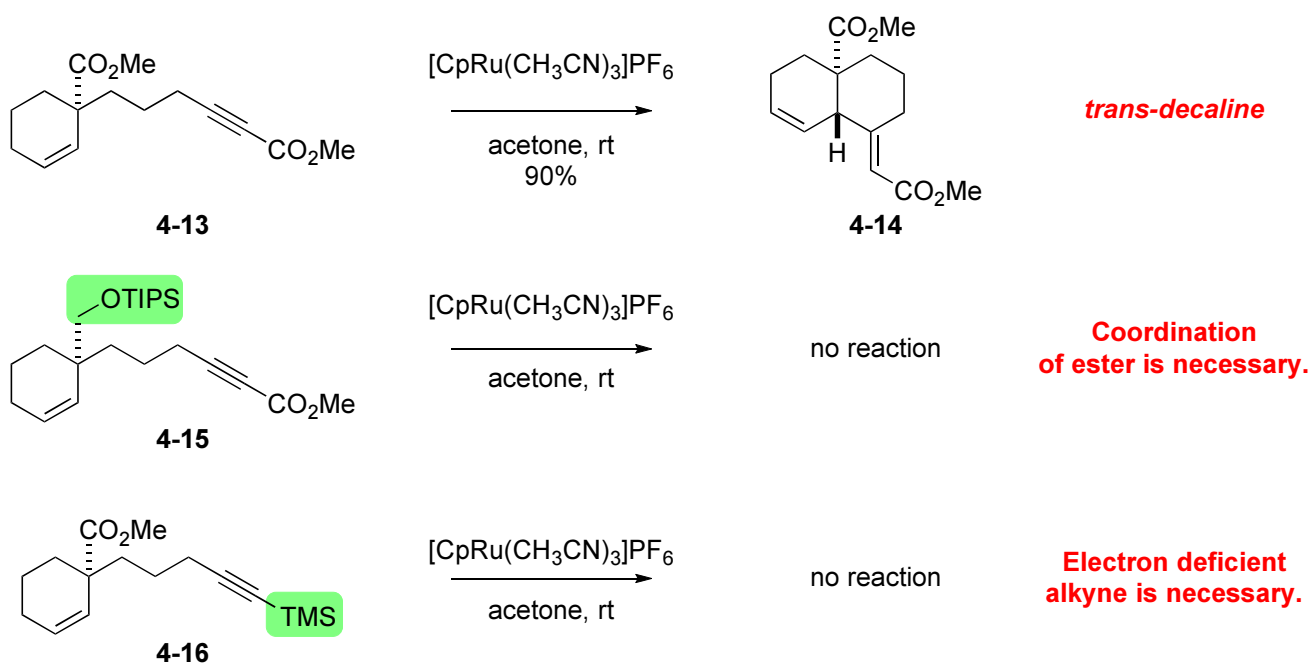
Alternative reaction mechanism for Ru-catalyzed cycloisomerization

- Metallacycle formation

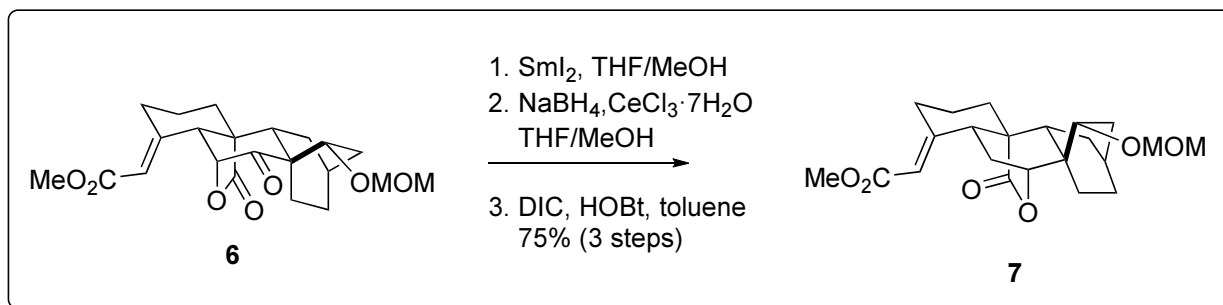


- Support for "C-H insertion" mechanism

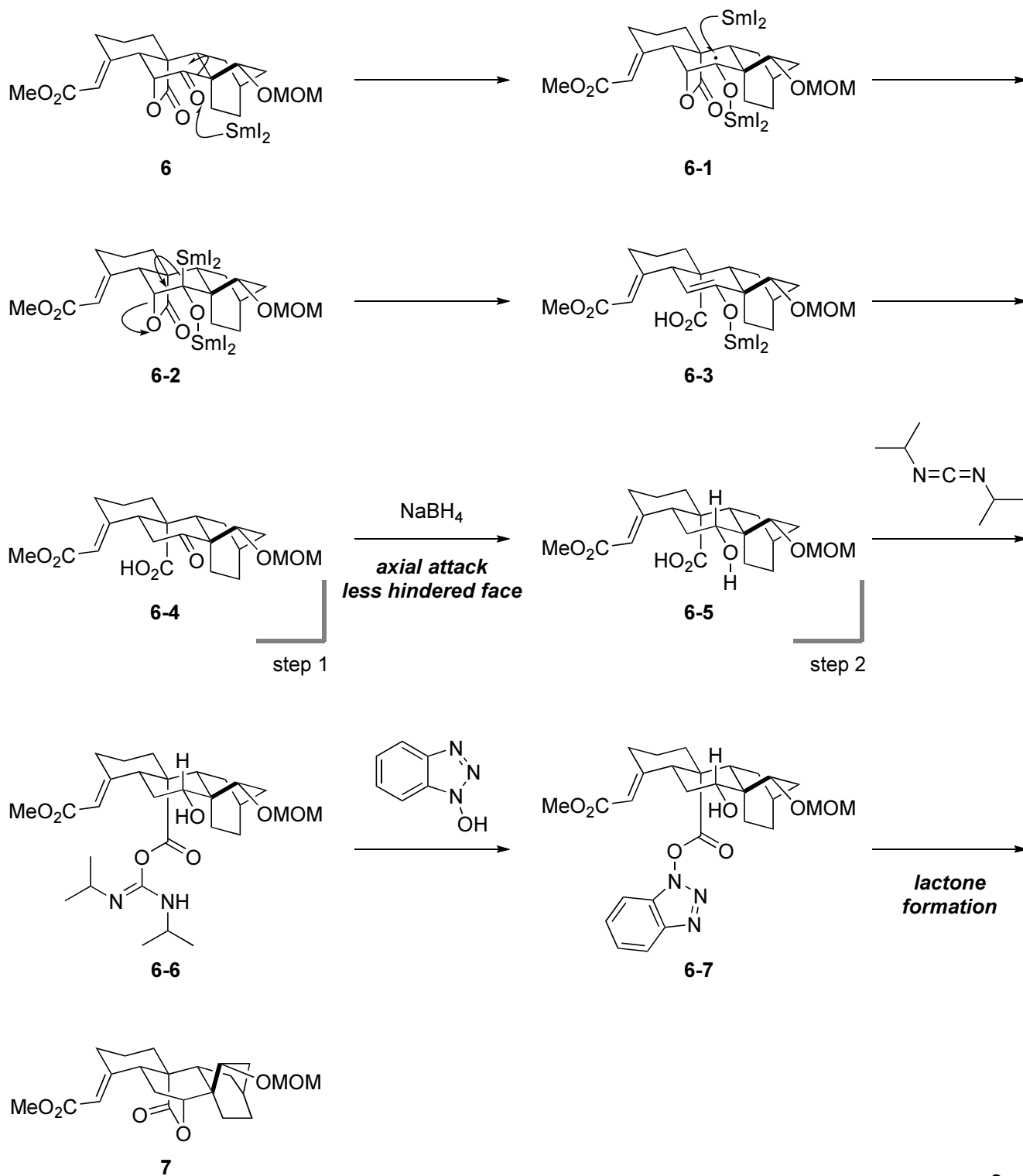
Trost, B. M.; Ferreira, E. M.; Gutierrez, A. C. *J. Am. Chem. Soc.* **2008**, *130*, 16176.



#### 4. Formal lactone migration

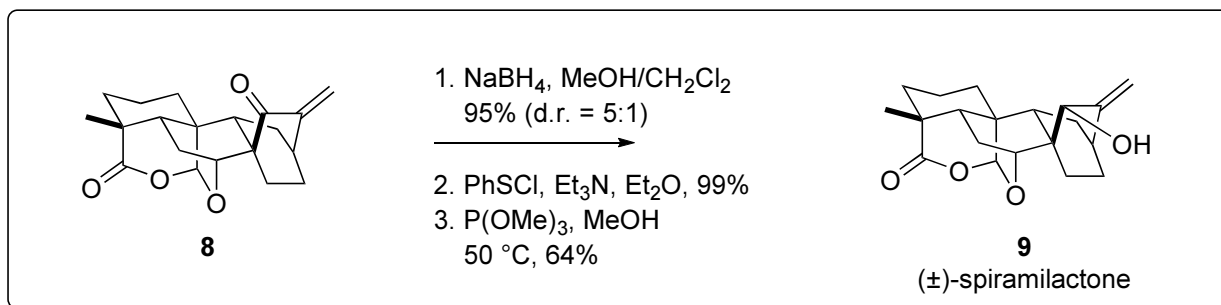


#### Proposed mechanism

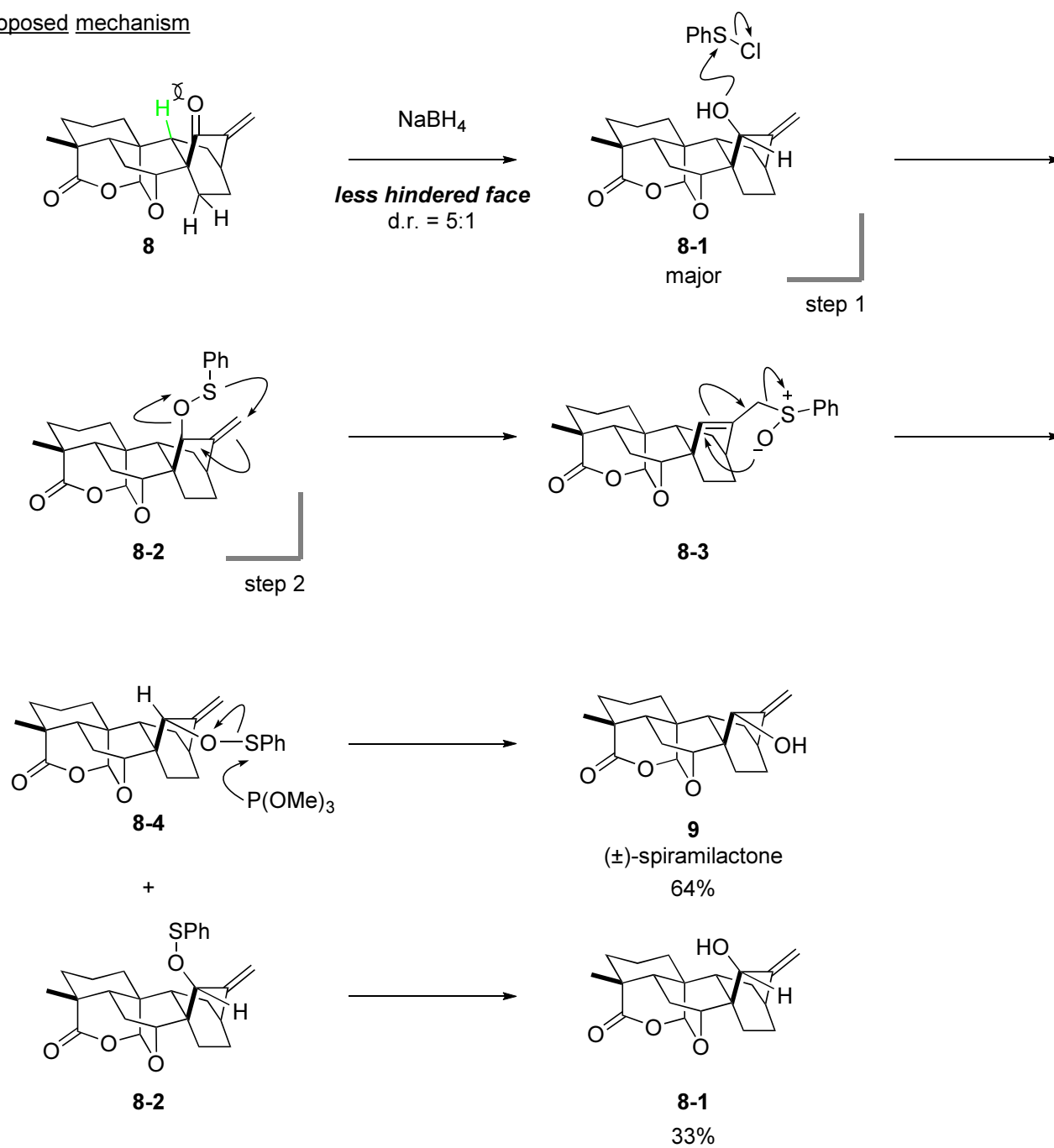




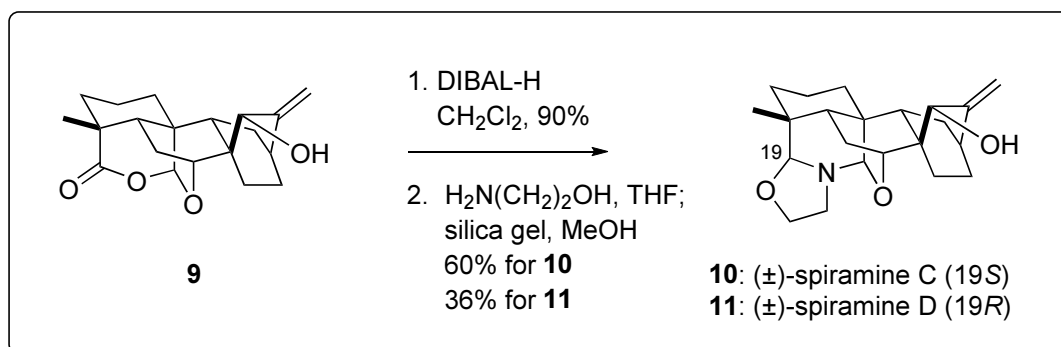
## 5. Reduction, Mislow-Evans rearrangement



### Proposed mechanism



## 6. Completion of total syntheses



### Proposed mechanism

