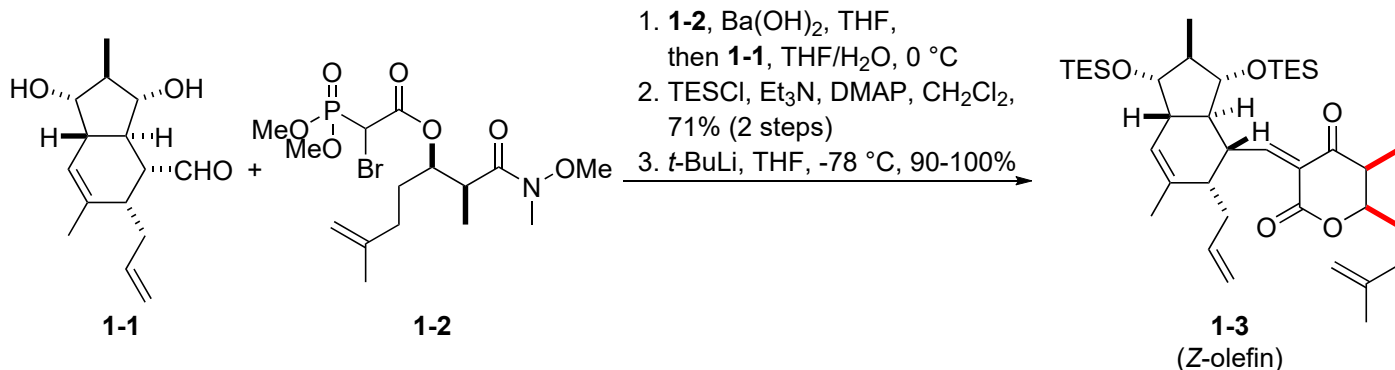


# Problem Session (3)

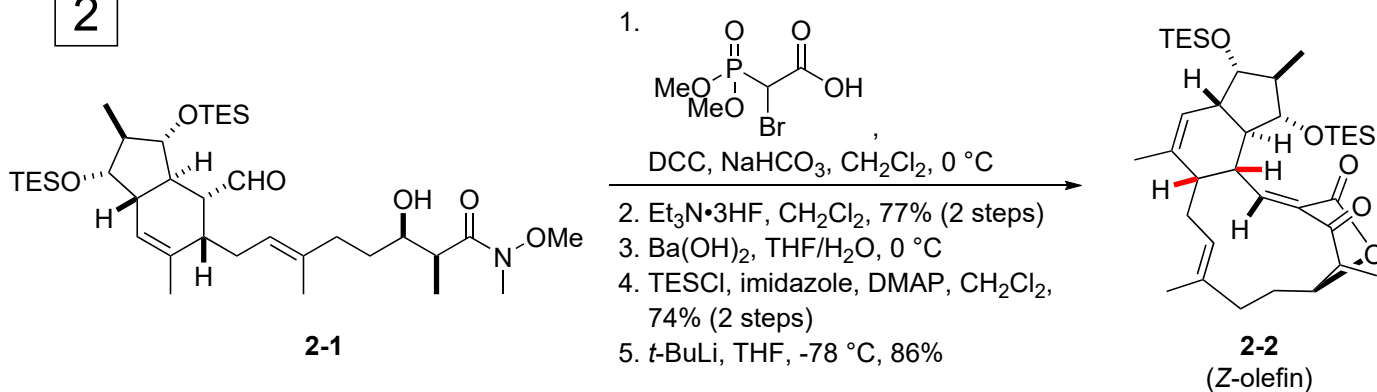
18/12/15 Koichi Kamiya

Please provide plausible mechanisms for each reaction and explain stereoselectivities.

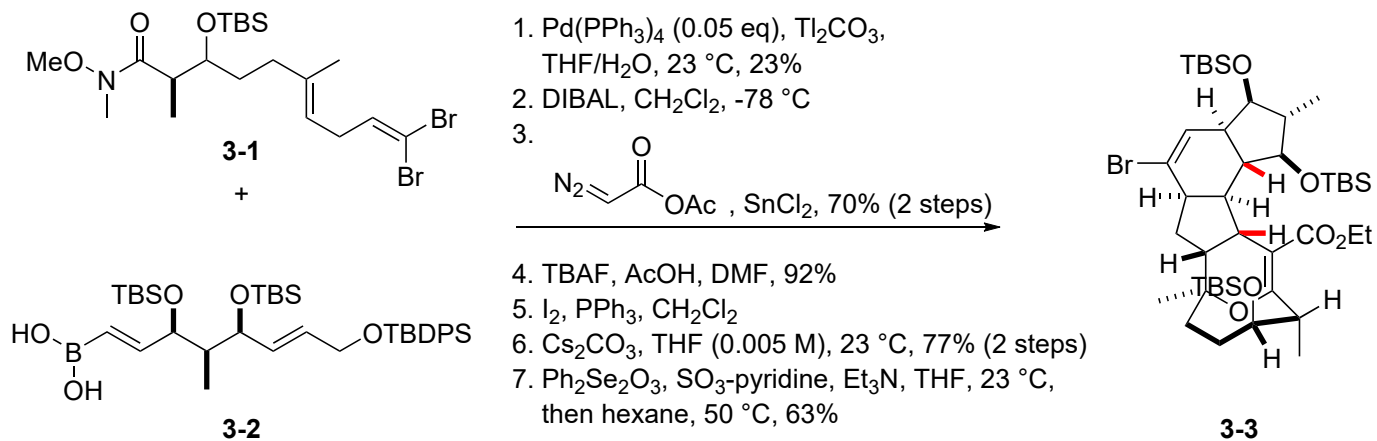
1



2



3

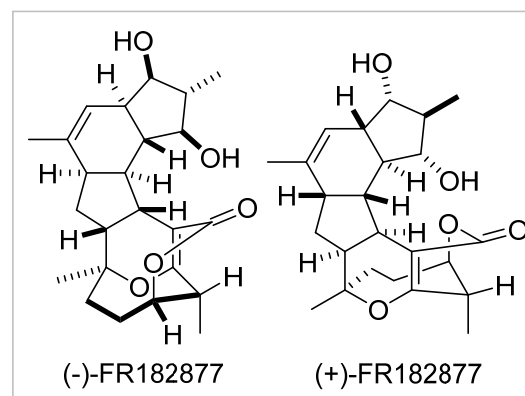


Topic: Total synthesis of FR182877

0. Introduction

■ Isolation

- from the culture broth of *Streptomyces* sp. No. 9885
- Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123.
- Sato, B.; Nakajima, H.; M.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204.
- Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.



■ Biological activity

- anticancer activity against MCF-7 ( $IC_{50} = 27$  ng/mL), A549 ( $IC_{50} = 73$  ng/mL), HT-29 ( $IC_{50} = 73$  ng/mL), Jurkat ( $IC_{50} = 33$  ng/mL), P388 ( $IC_{50} = 21$  ng/mL), B16 ( $IC_{50} = 67$  ng/mL)
- promoting the microtubule assembly in vitro and inducing G<sub>2</sub>/M phase arrest in the cell cycle

■ Structural feature

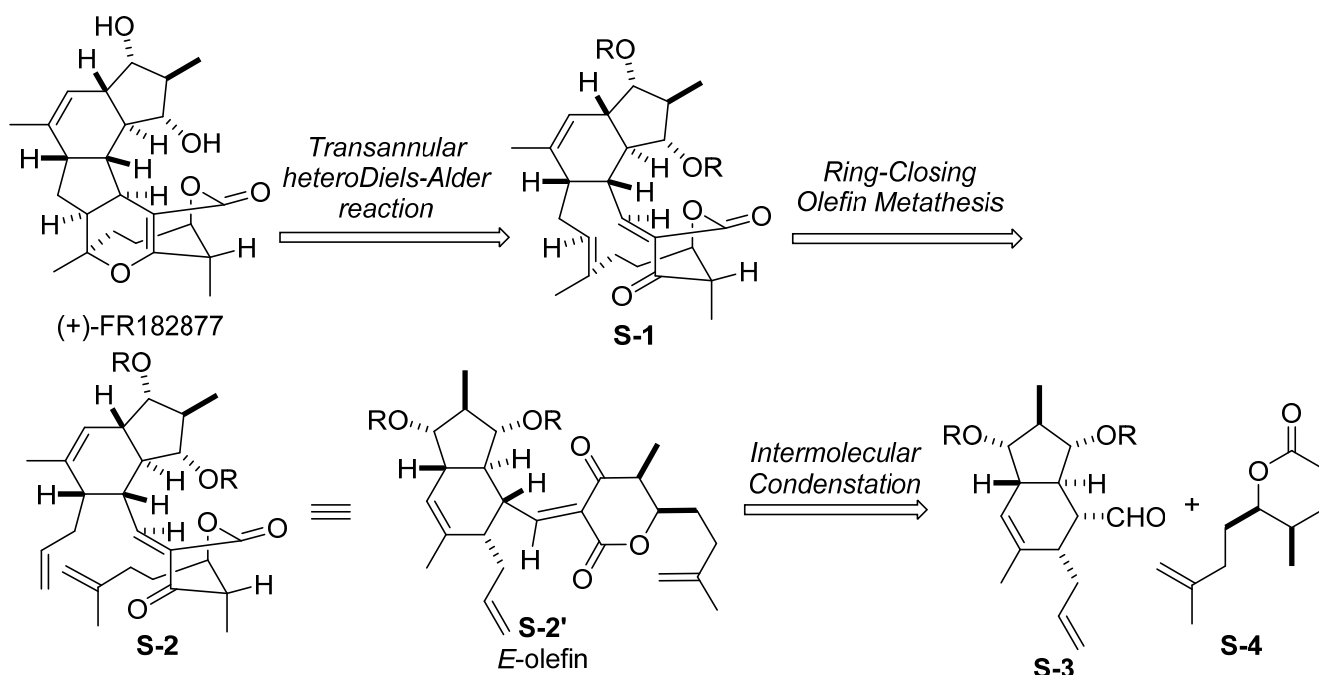
- 19-membered Hexacyclic carbomacrocycle featuring 12-stereocenter
- vinyllogous carbonate embedded in a fused 6-6-7 ring system

■ Total synthesis

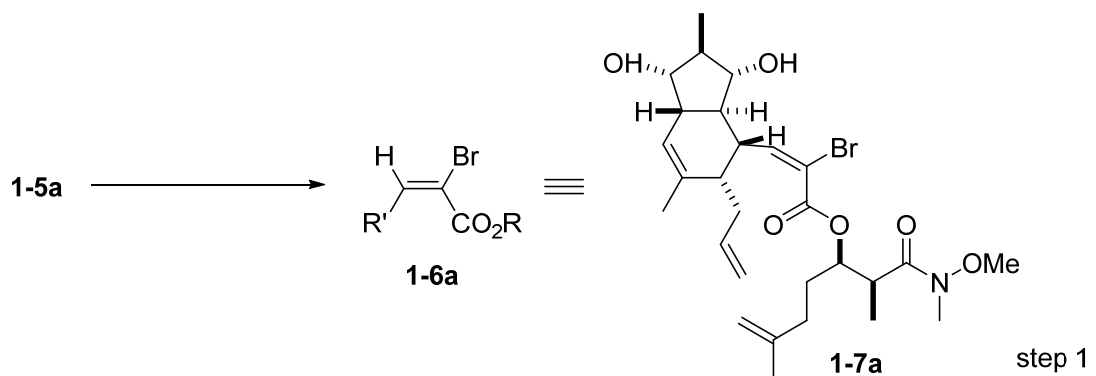
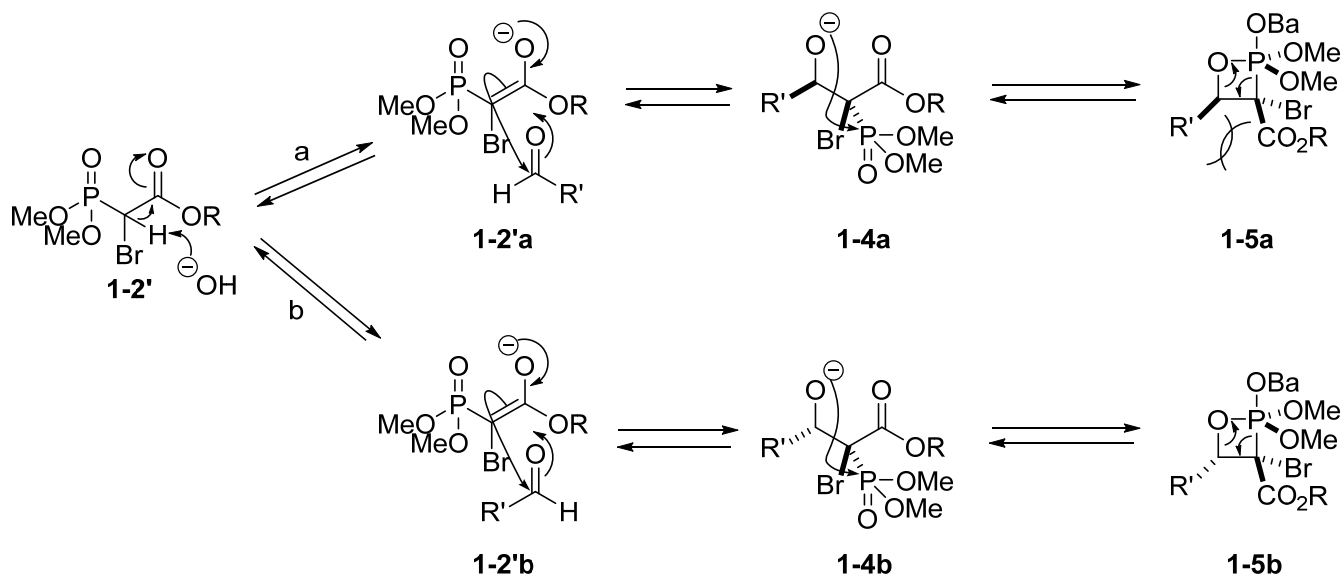
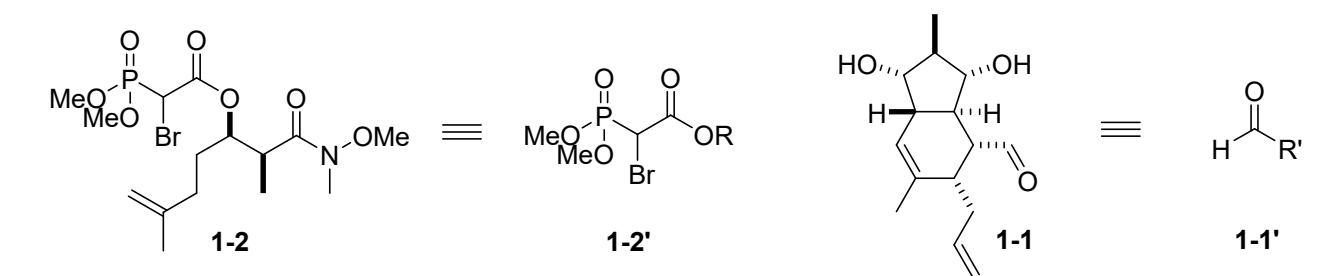
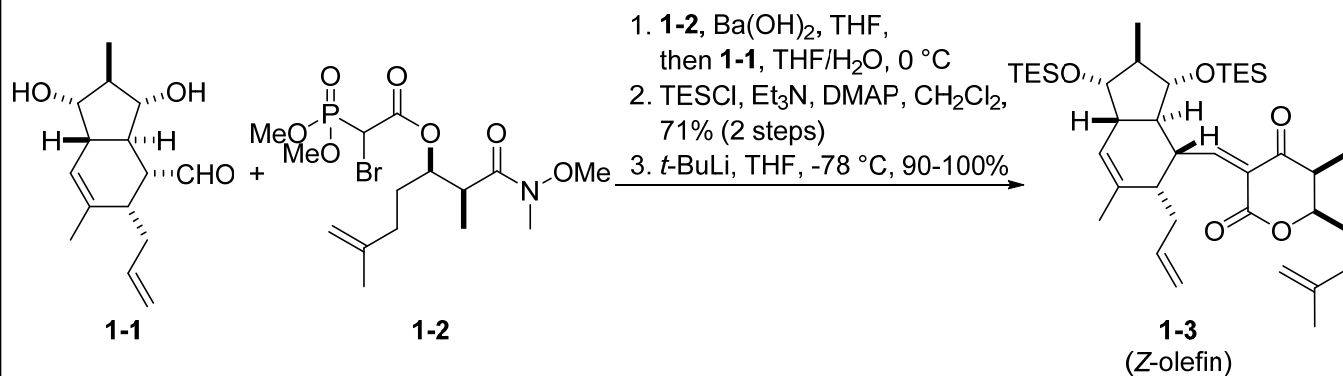
- Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552.
- Vosberg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393. (**Problem 1, 2**)
- Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787.
- Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531. (**Problem 3**)
- Tanaka, N.; Suzuki, T.; Matsumura, T.; Hosoya, Y.; Nakada, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2580.

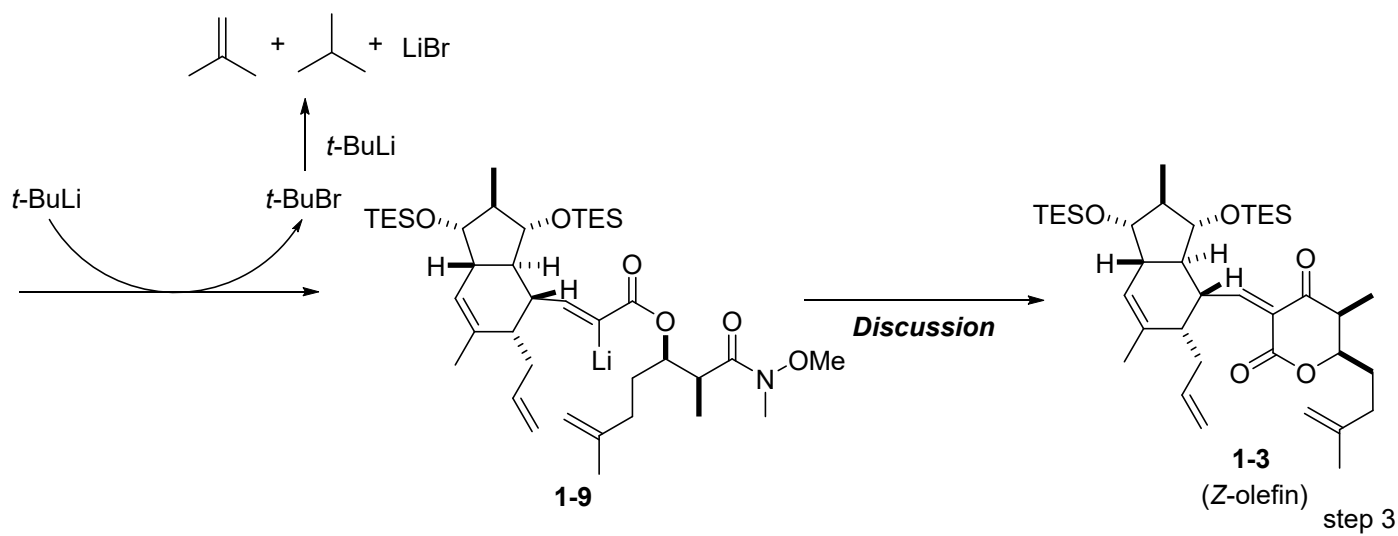
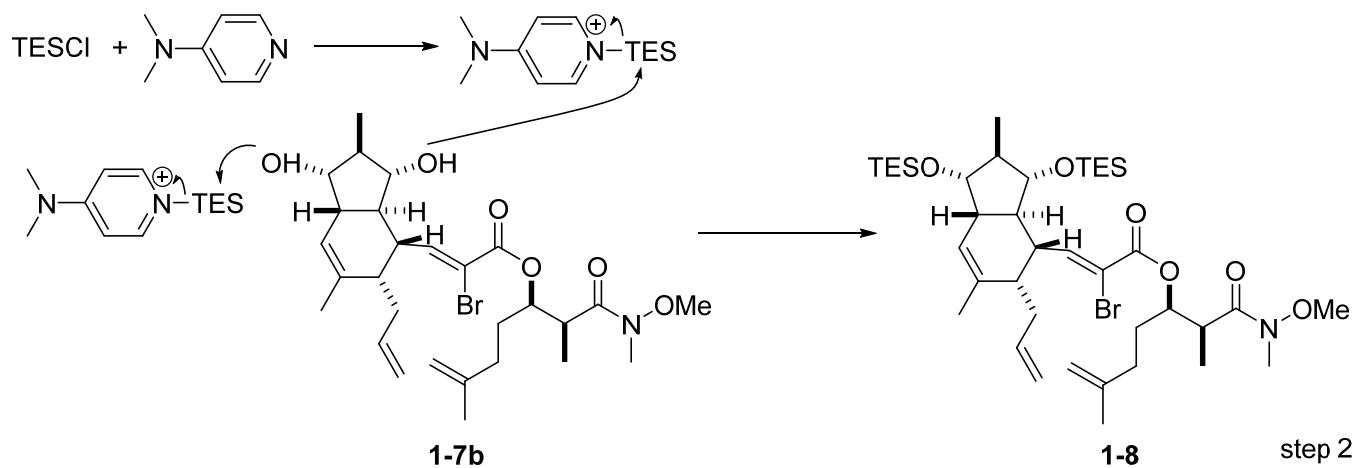
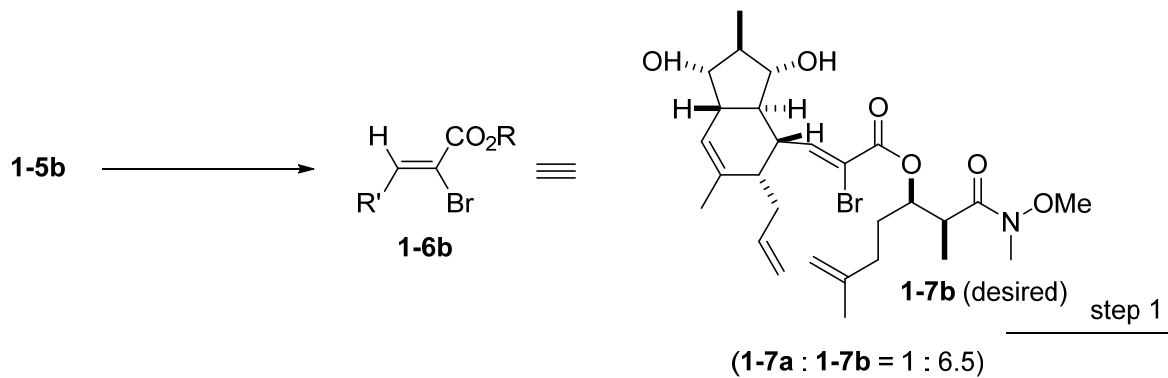
1. Sorensen's synthesis

Retro synthetic route toward (+)-FR182877



1

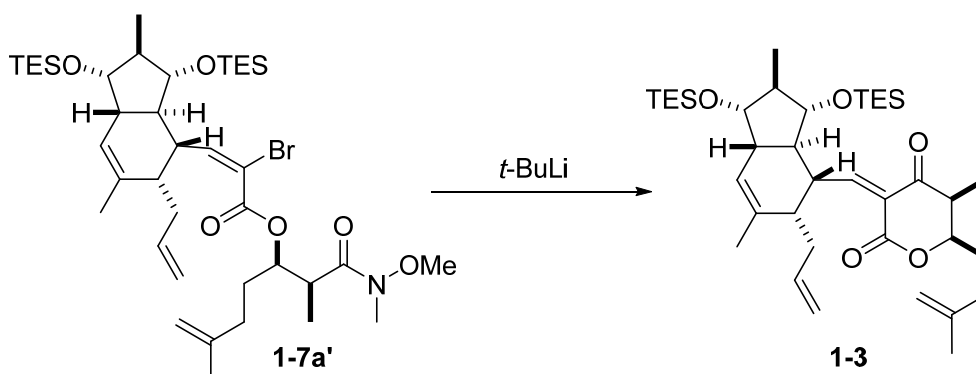




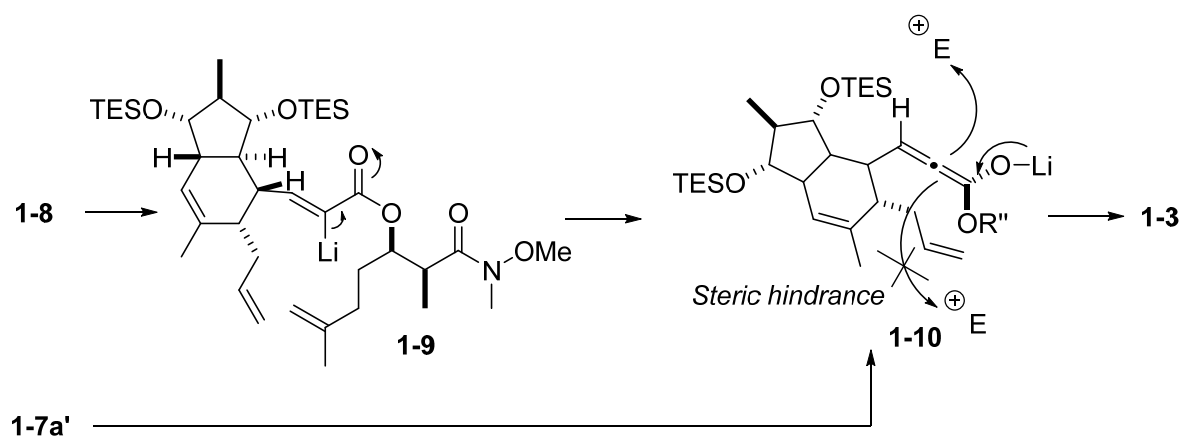
## Discussion

Mechanism to produce undesired *Z*-olefin

Minor olefination product was exposed to the reducing action of *t*-BuLi under the same condition

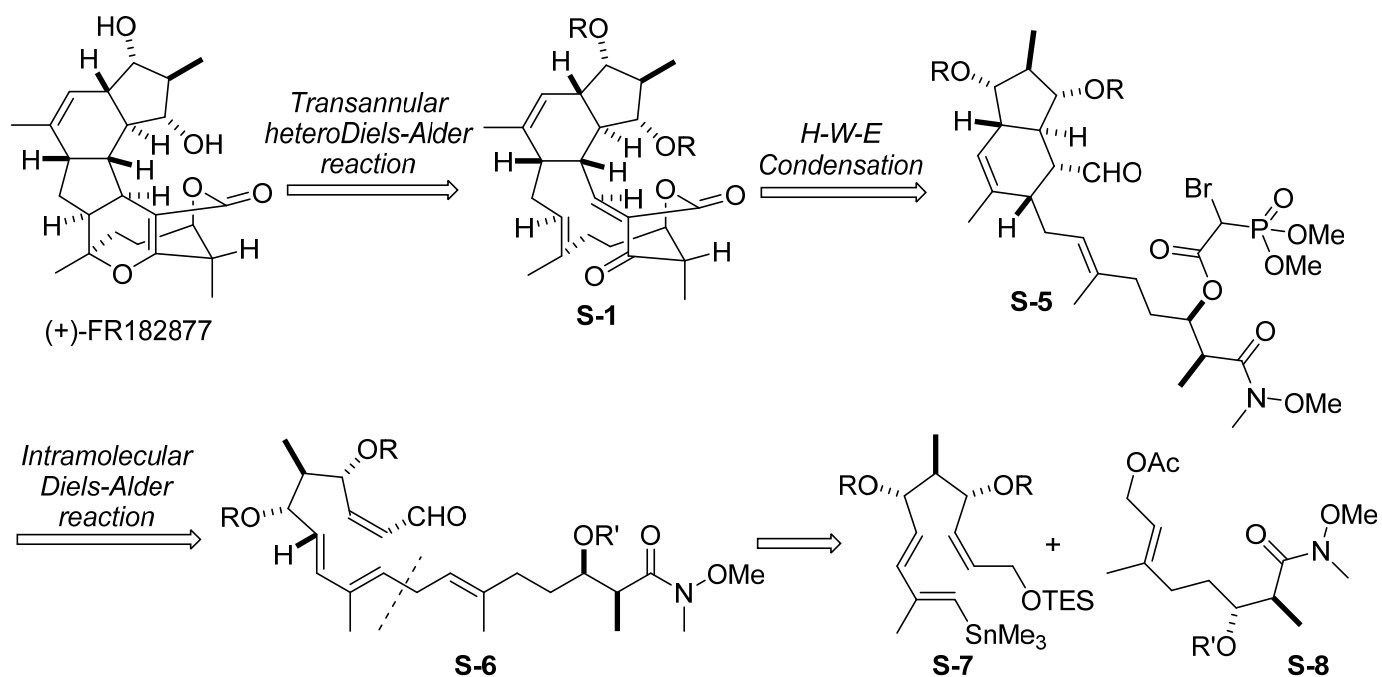


→ The same product **1-3** was obtained. Conceivable mechanism is shown below.

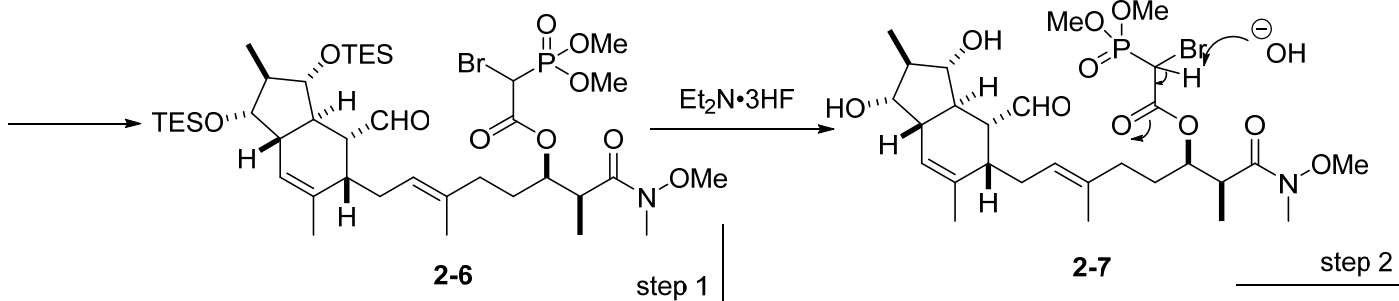
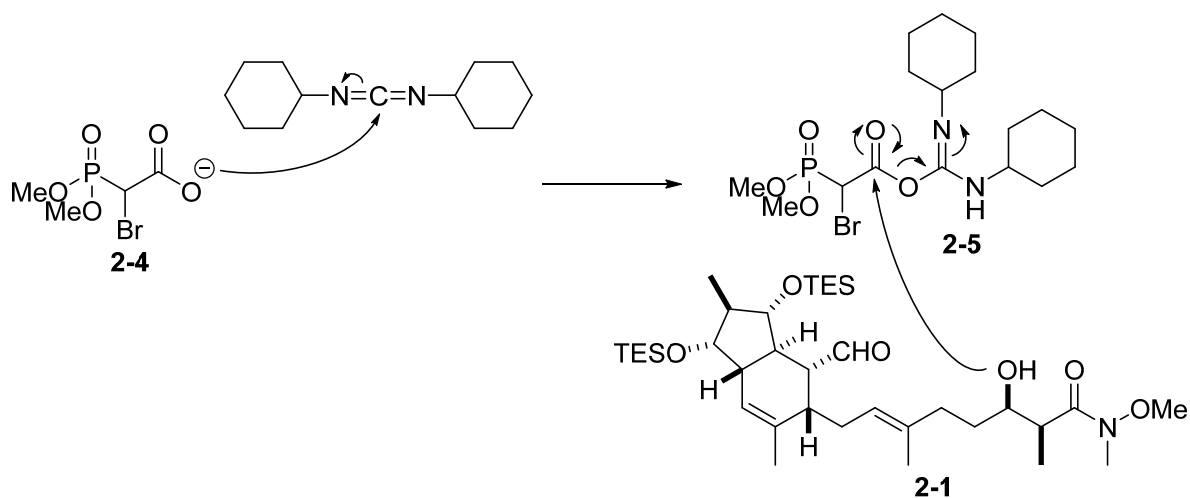
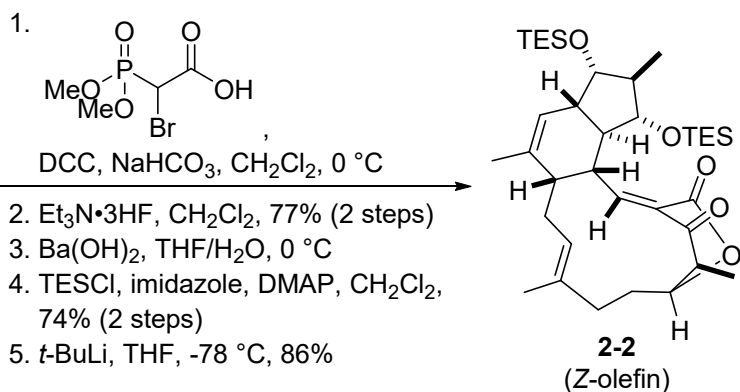
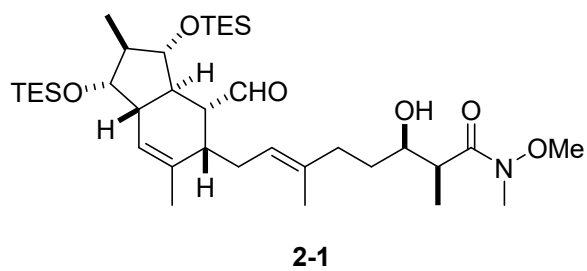


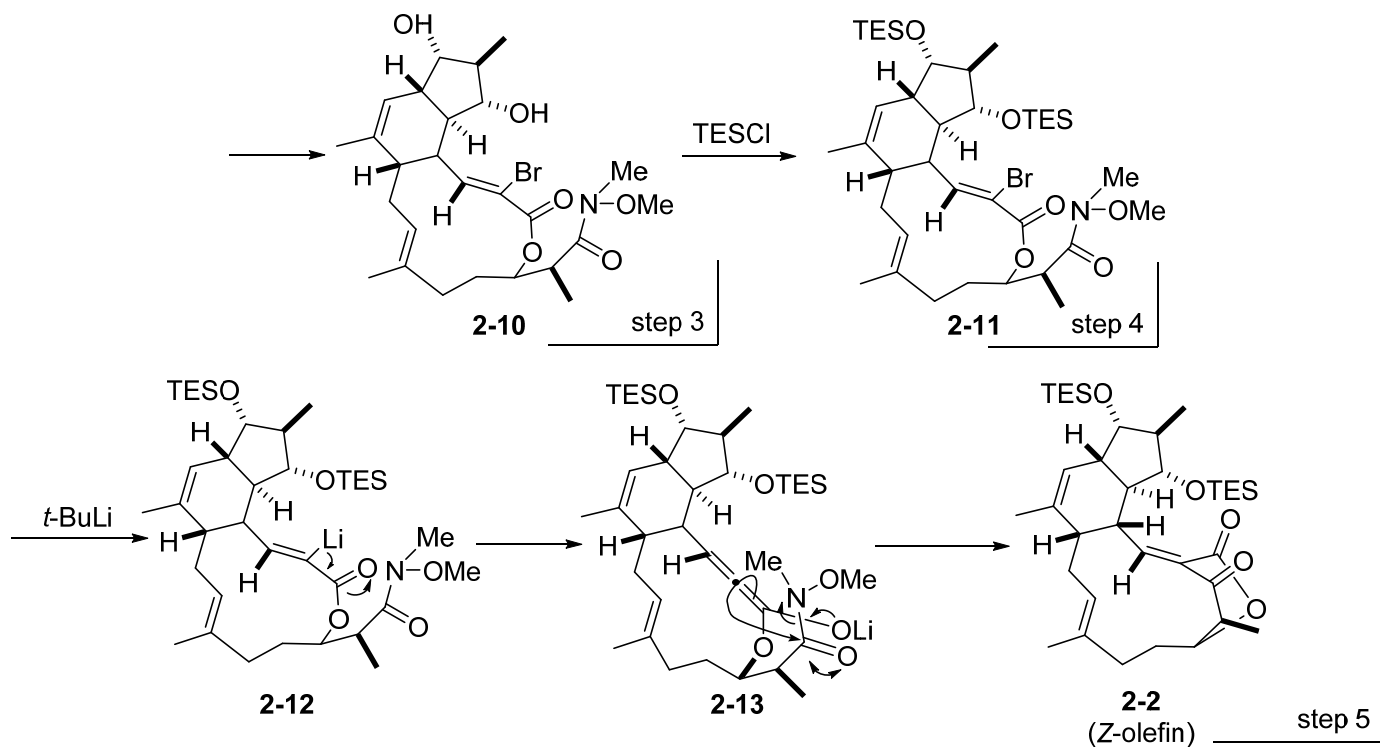
## 2. Sorensen's synthesis

Another retro synthetic route toward (+)-FR182877

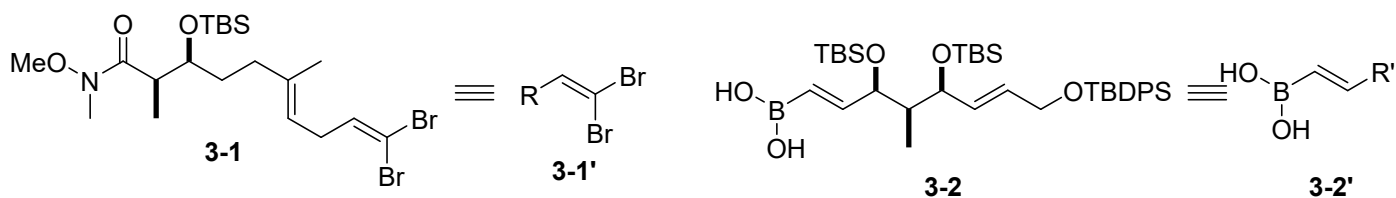
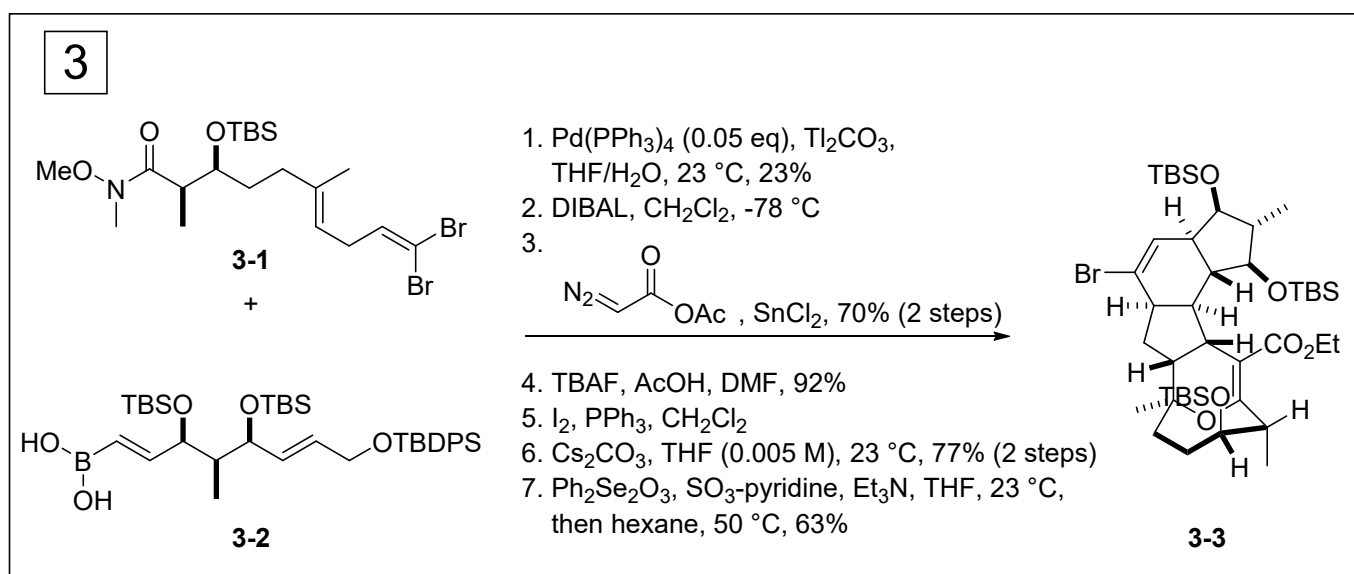


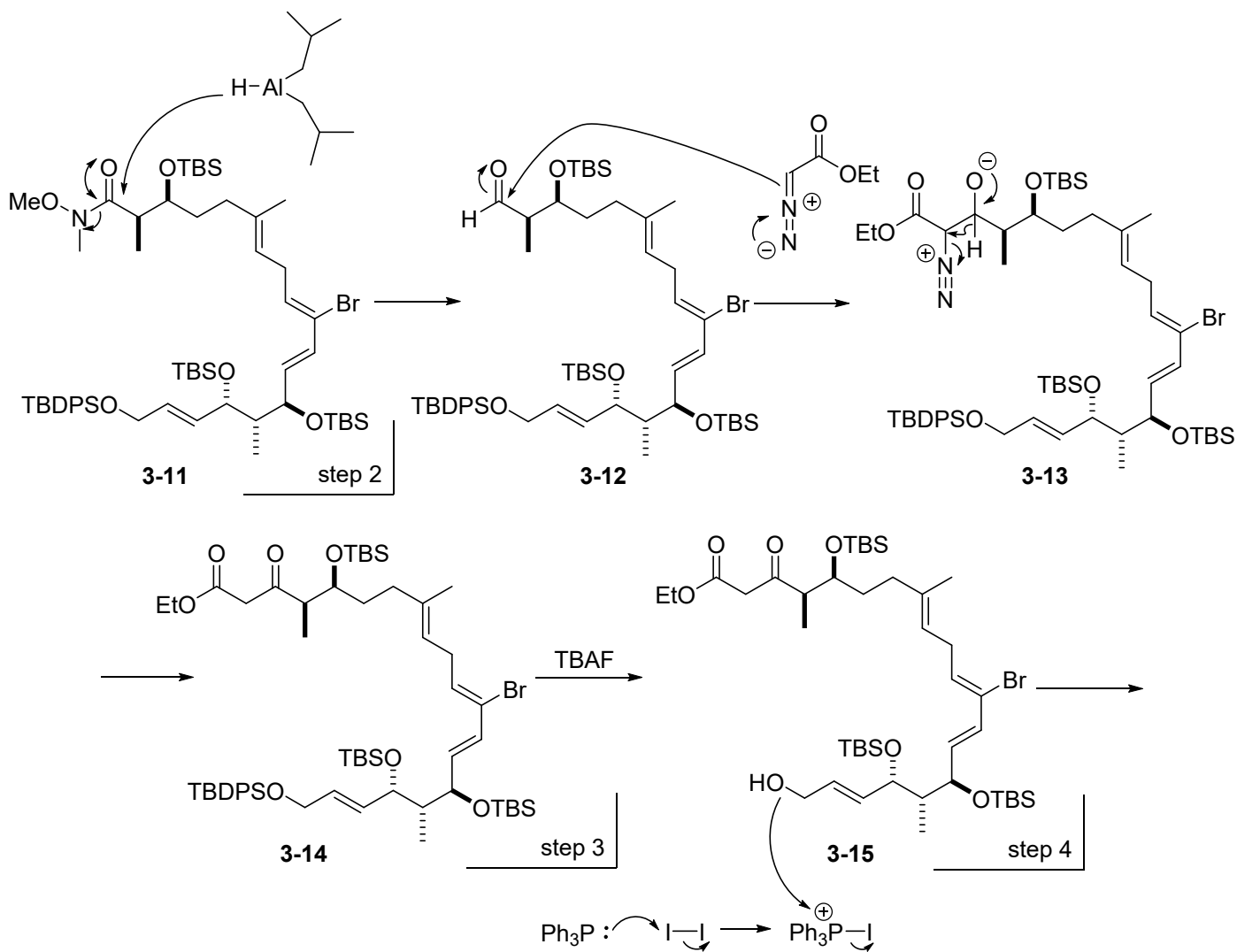
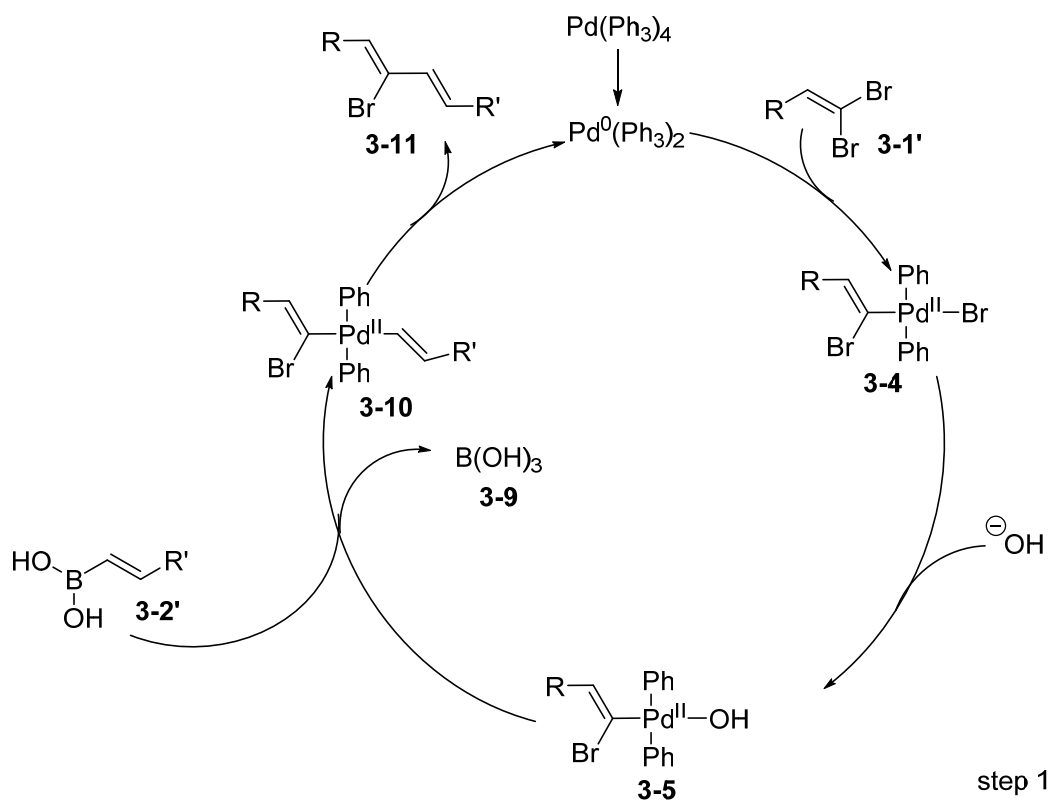
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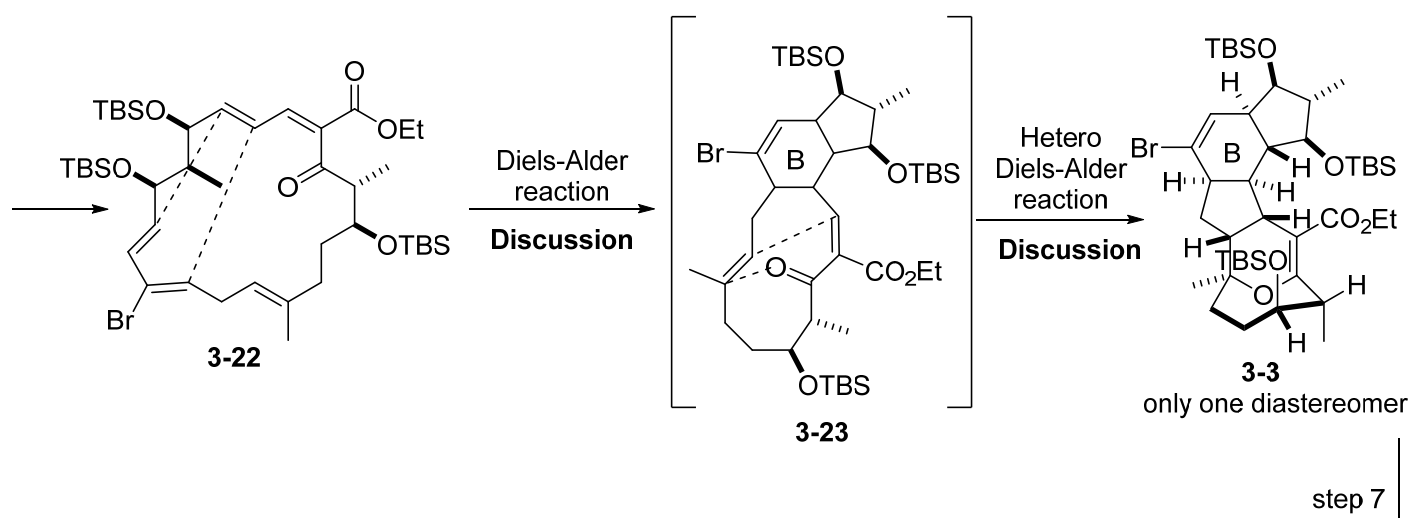
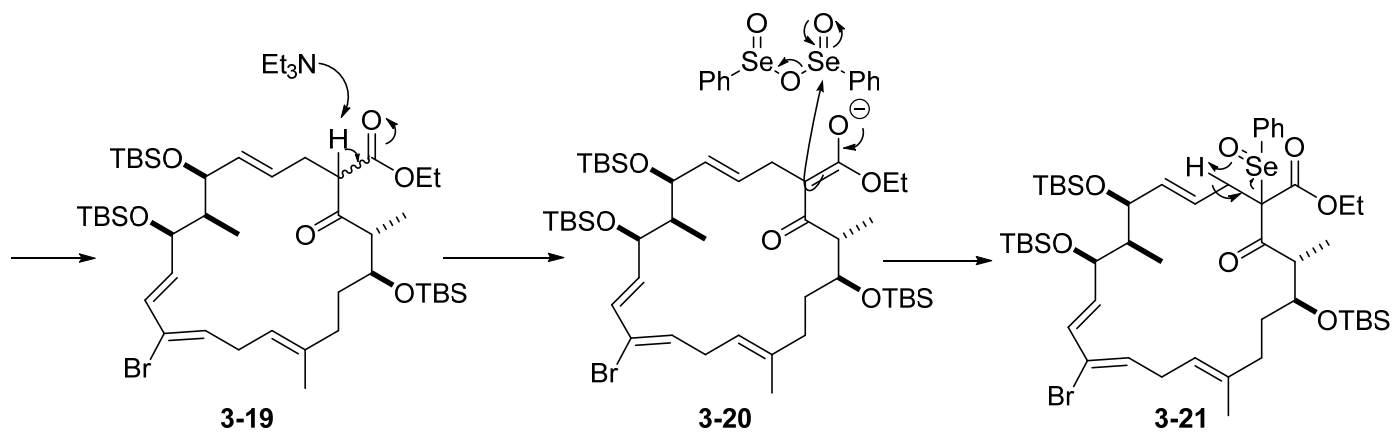
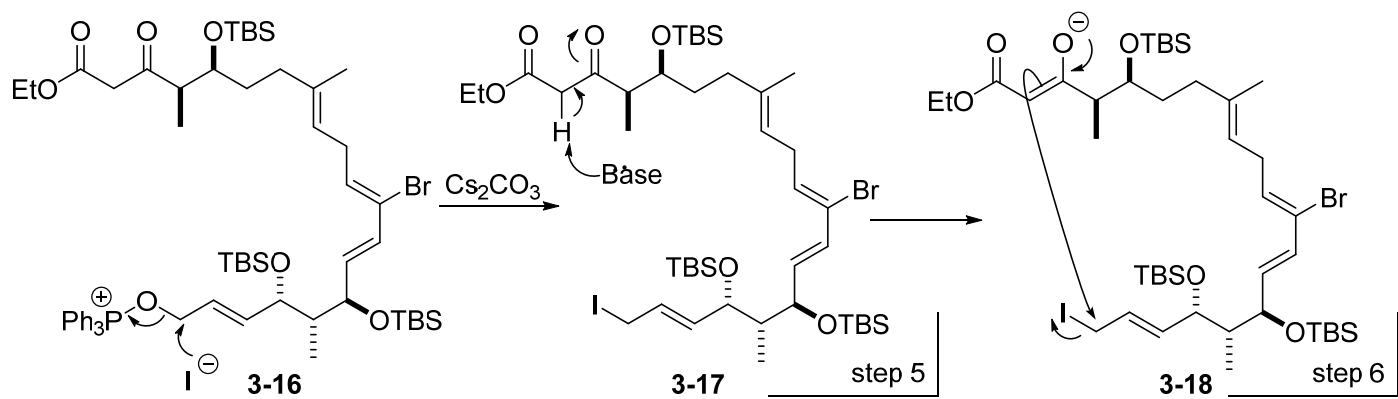


### 3. Evan's synthesis



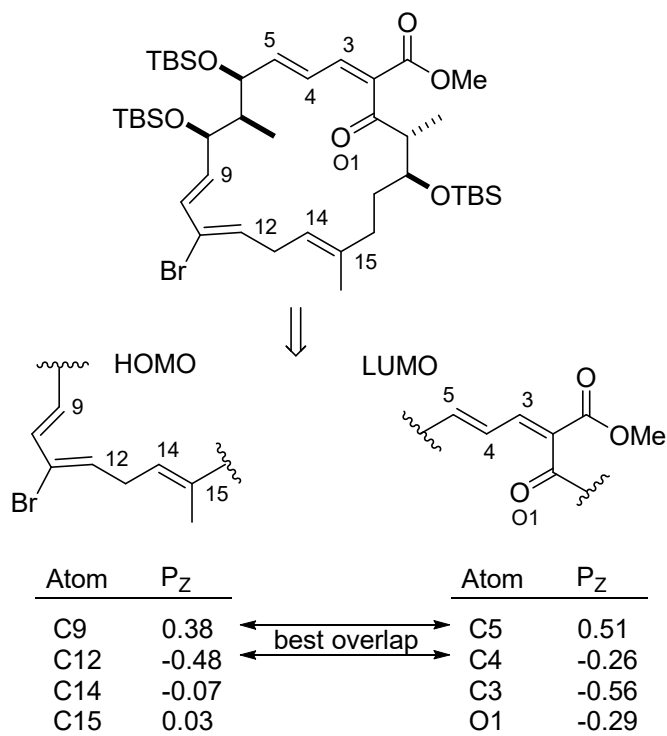






## Discussion

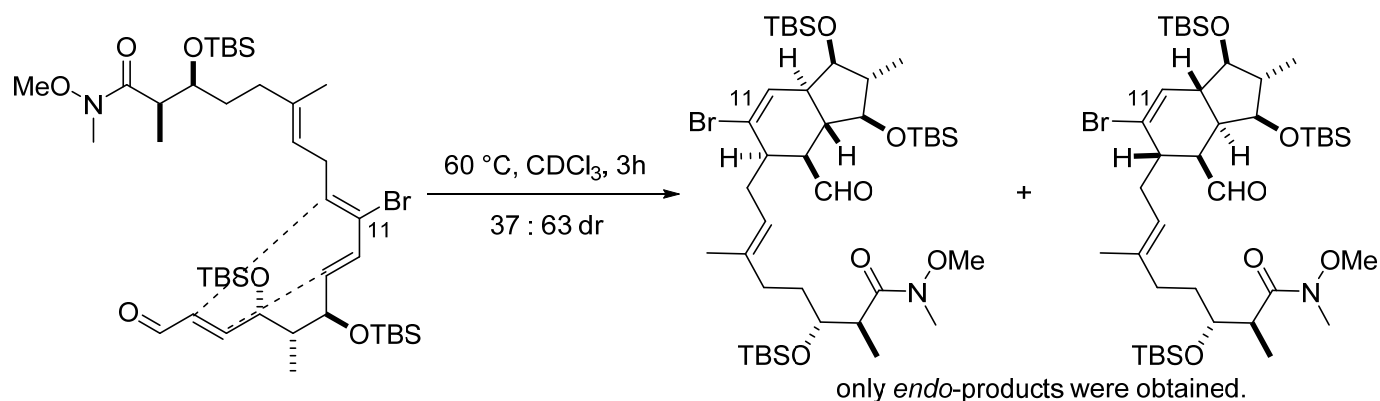
### 1. Cyclization order (Which one is faster, DA or HAD?)



FMO analysis using calculated (Spartan 5.1 running on an SGI Indigo computer) P<sub>Z</sub> orbital coefficients of the HOMO and LUMO predicts DA to occur first.

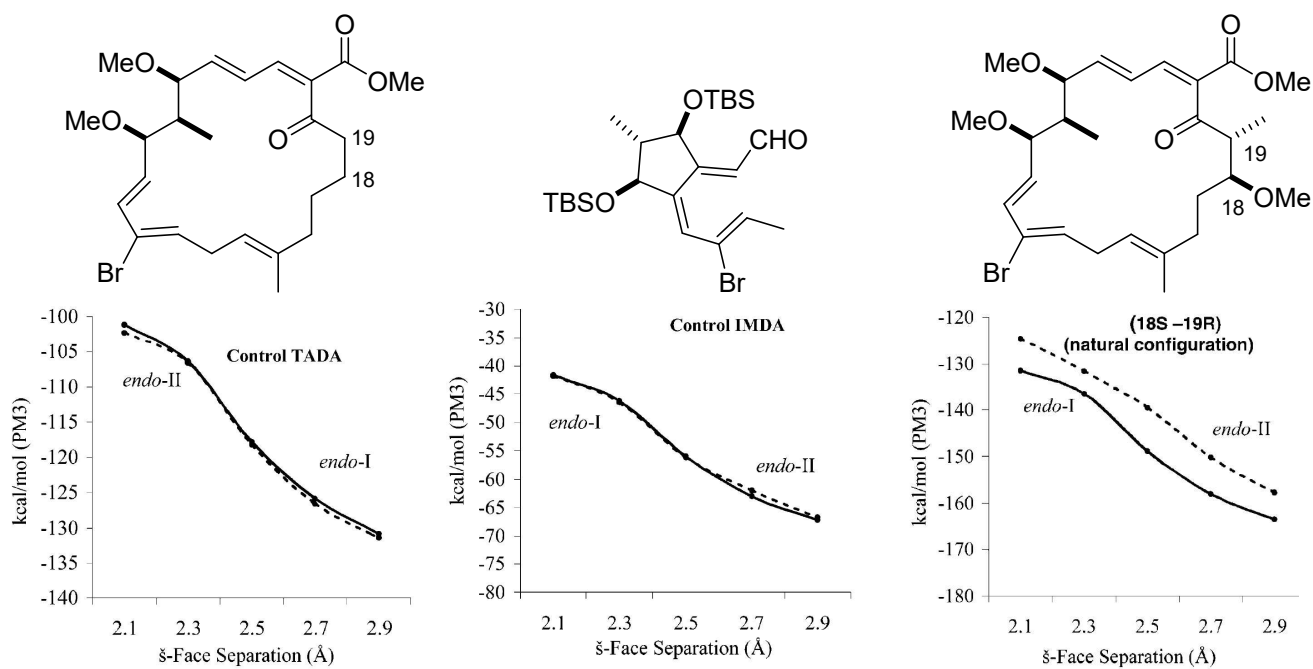
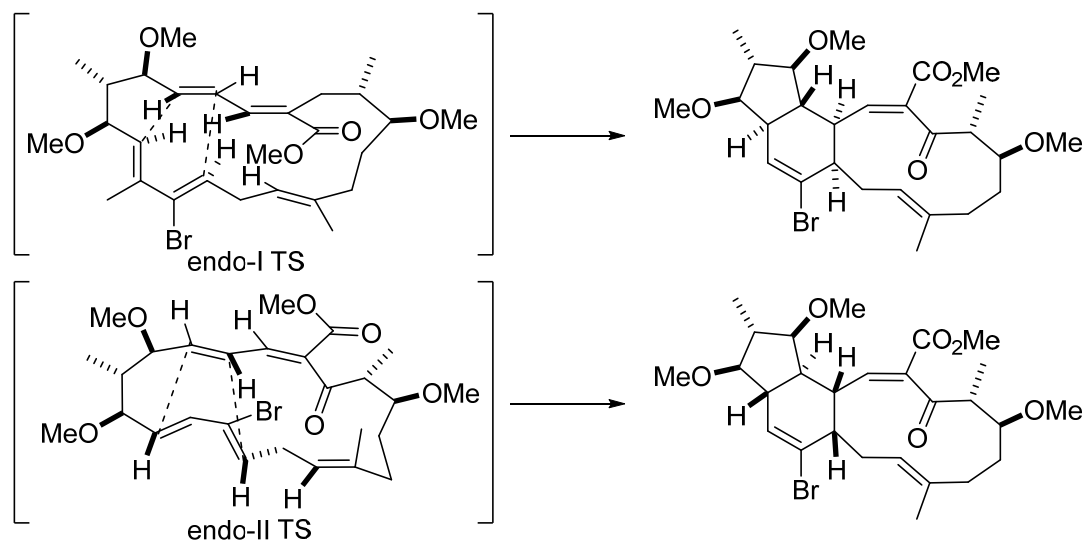
### 2. Reason of the high diastereoface selection in the Diels-Alder reaction in the construction of ring-B

#### Model experiment



- Model IMDA study shows high *endo* selectivity with poor diastereofacial selectivity.
- Sorensen's system, the enantiomer which differs only in silyl protecting groups and the Me at C11 (Br→Me), also observed high *endo* selectivity and the opposite dr (61:31 dr).

## Modeling the DA endo transition state



✓ The high face-selectivity of the DA cycloaddition is affected by C18,C19 stereocenters

### 3. Analysis of Hetero Diels-Alder Cycloaddition

