

# Total Syntheses of FR182877



MacMillan Group Meeting  
October 5, 2005  
Sandra Lee

## Key Articles:

**Isolation Papers:** (a) Sato, B.; *et. al. J. Antibiot.* **2000**, *53*, 123; (b) Sato, B.; *et. al. J. Antibiot.* **2000**, *53*, 204; (c) Yoshimura, S.; *et. al. J. Antibiot.* **2000**, *53*, 615.

**Sorensen Synthesis:** (a) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552; (b) Vanderwal, C. D.; Vosberg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.

**Evans Synthesis:** (a) Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787; (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531.

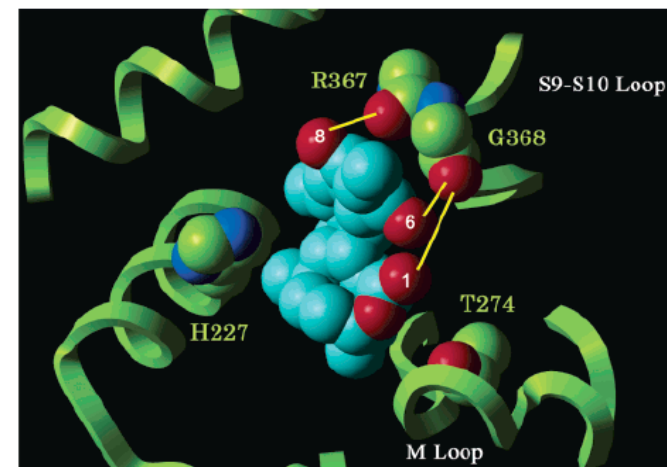
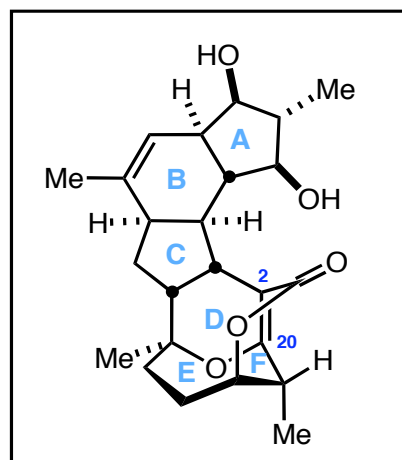
# FR182877 : Taxol-type

## Cytotoxicity and Antimitotic Activity

### ■ Isolation—Fujisawa Pharmaceutical Co.

Isolated from the fermentation broth of *Streptomyces* in 1998 with  $IC_{50} = 28-75$  ng/mL cytotoxicity against several cell lines.

Structurally similar natural products: Hexacyclic Acid, Macquaimicin A, and Cochleamycin A

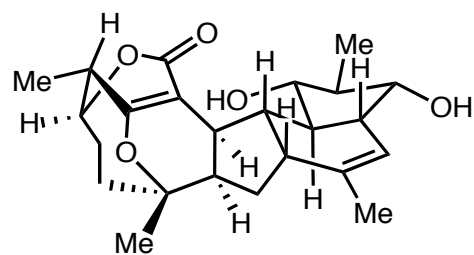


### ■ Synthetic challenges

- 19-membered Hexacyclic carbomacrocyclic featuring 12 stereocenters
- Vinlogous carbonate embedded in a 6-6-7 fused ring system
- Instability to air oxidation (C2-C21) to form a biologically inactive epoxide

### ■ Completed syntheses

- (+)-FR182877 by Sorensen in 2002
- (-)-FR182877 by Evans in 2002
- (+)-FR182877 by Sorensen in 2003



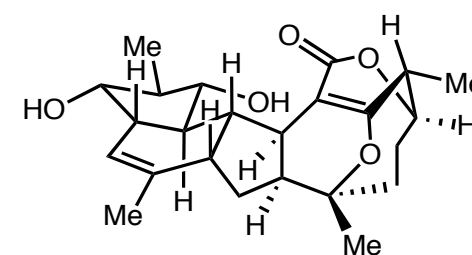
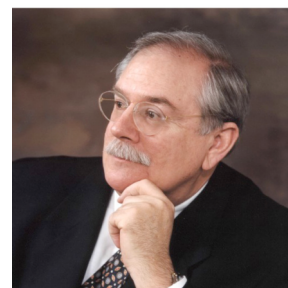
(+)-FR182877



### ■ Ongoing synthetic efforts

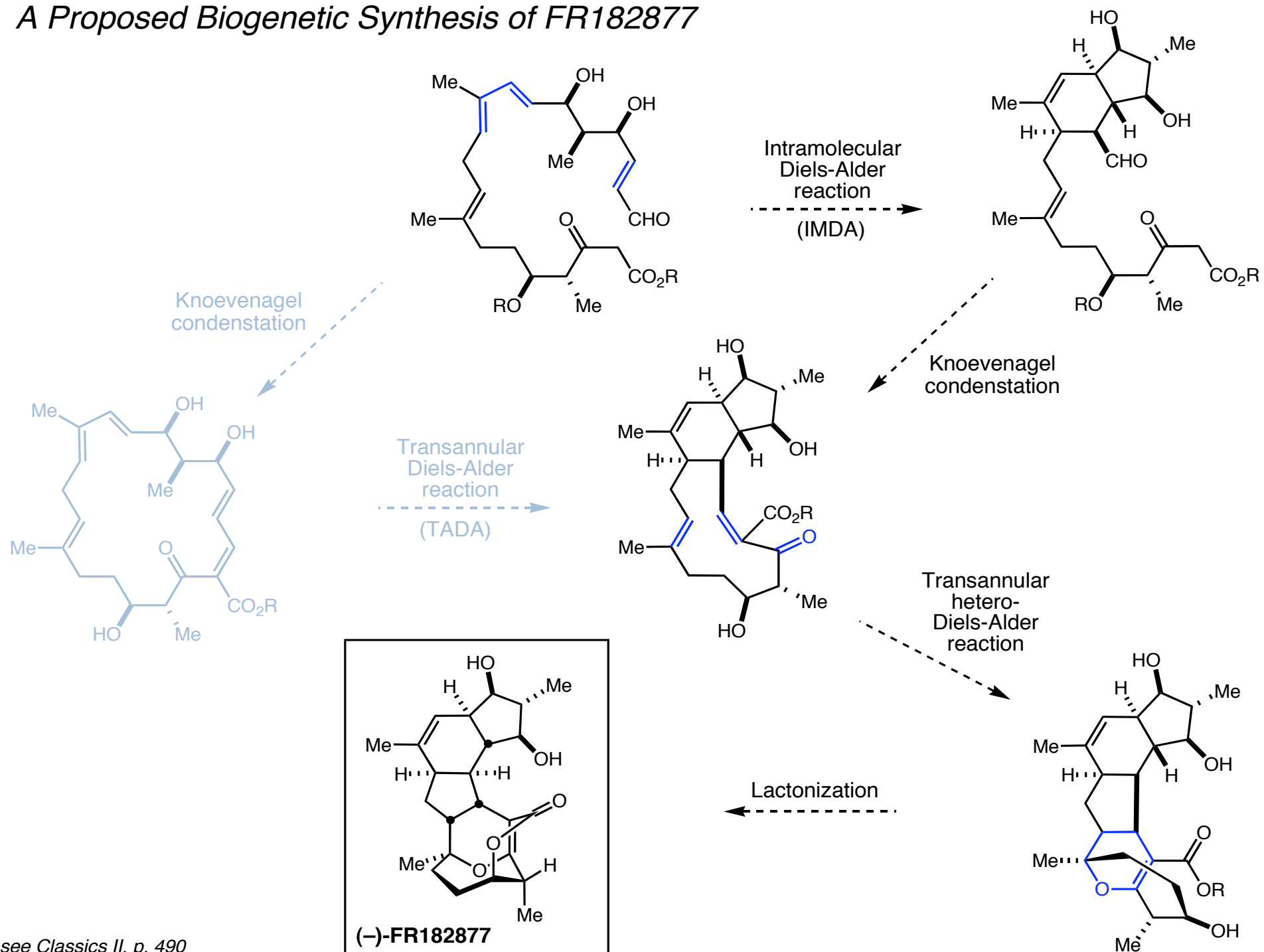
- Armstrong in 2001: Model DF ring system
- Nakada in 2002: AB bicycle
- Roush in 2003: ABC tricycle
- Prunet in 2004: A ring
- Clarke in 2005: DEF ring system, B ring

vs.

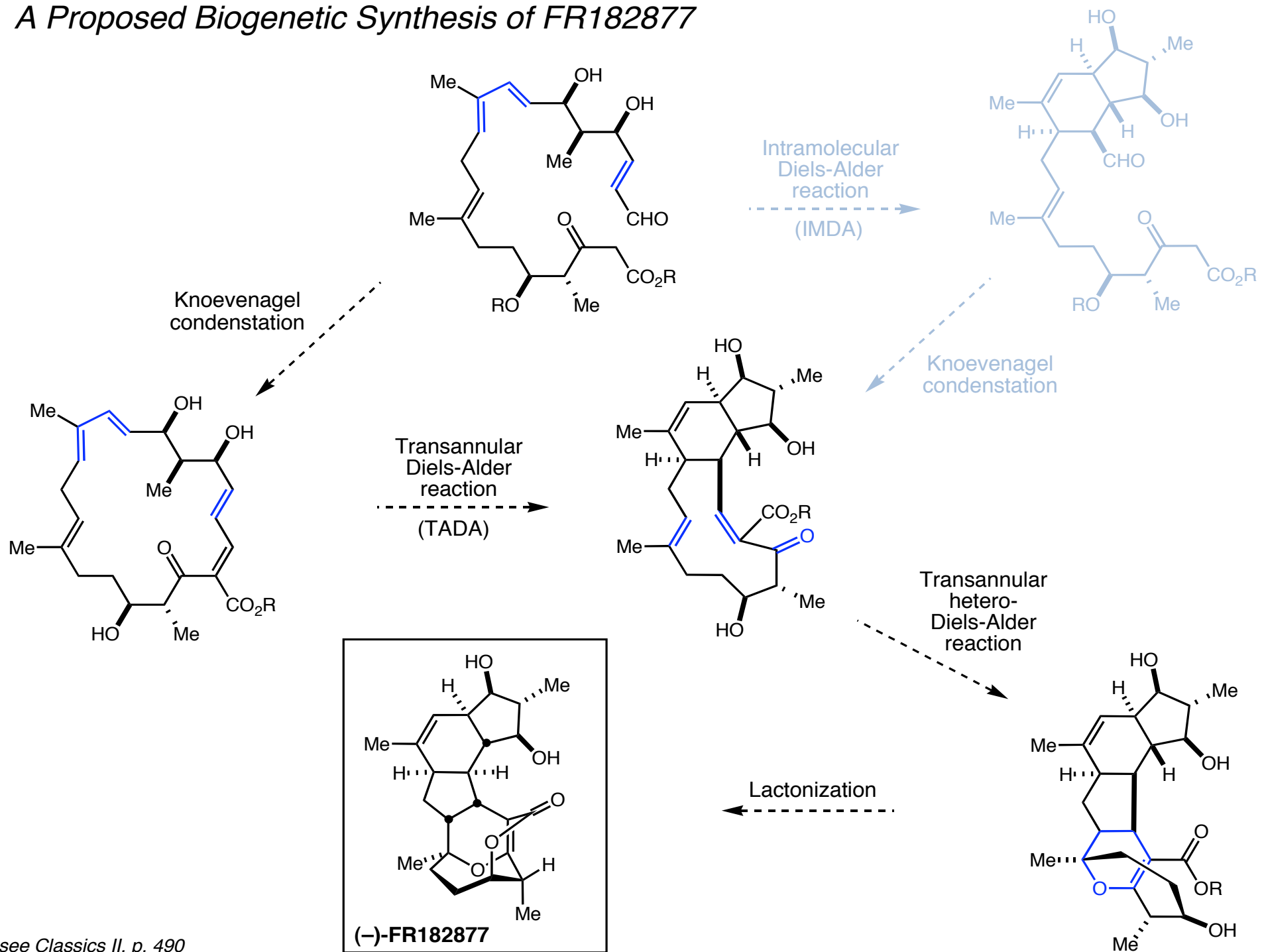


(-)-FR182877

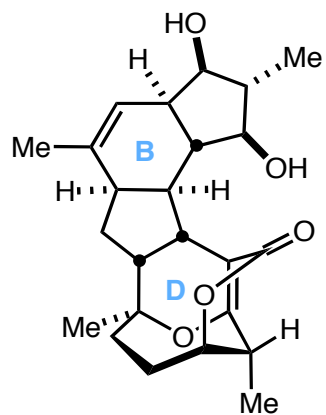
# A Proposed Biogenetic Synthesis of FR182877



# A Proposed Biogenetic Synthesis of FR182877

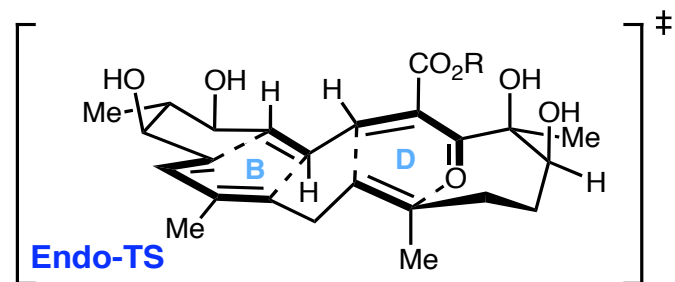


# The Pivotal Transformation: Endo vs. Exo

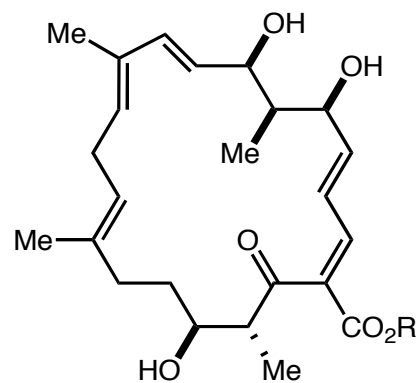


**(-)-FR182877**

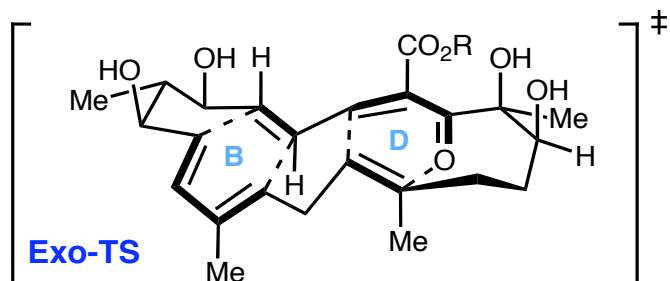
Cascade TADA  
←



**Endo-TS**

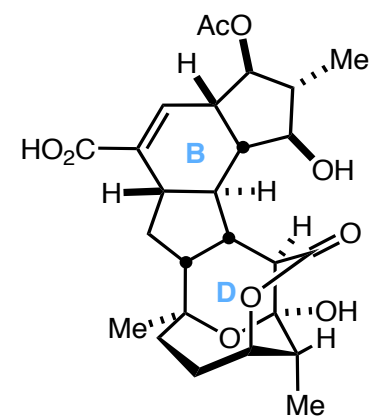


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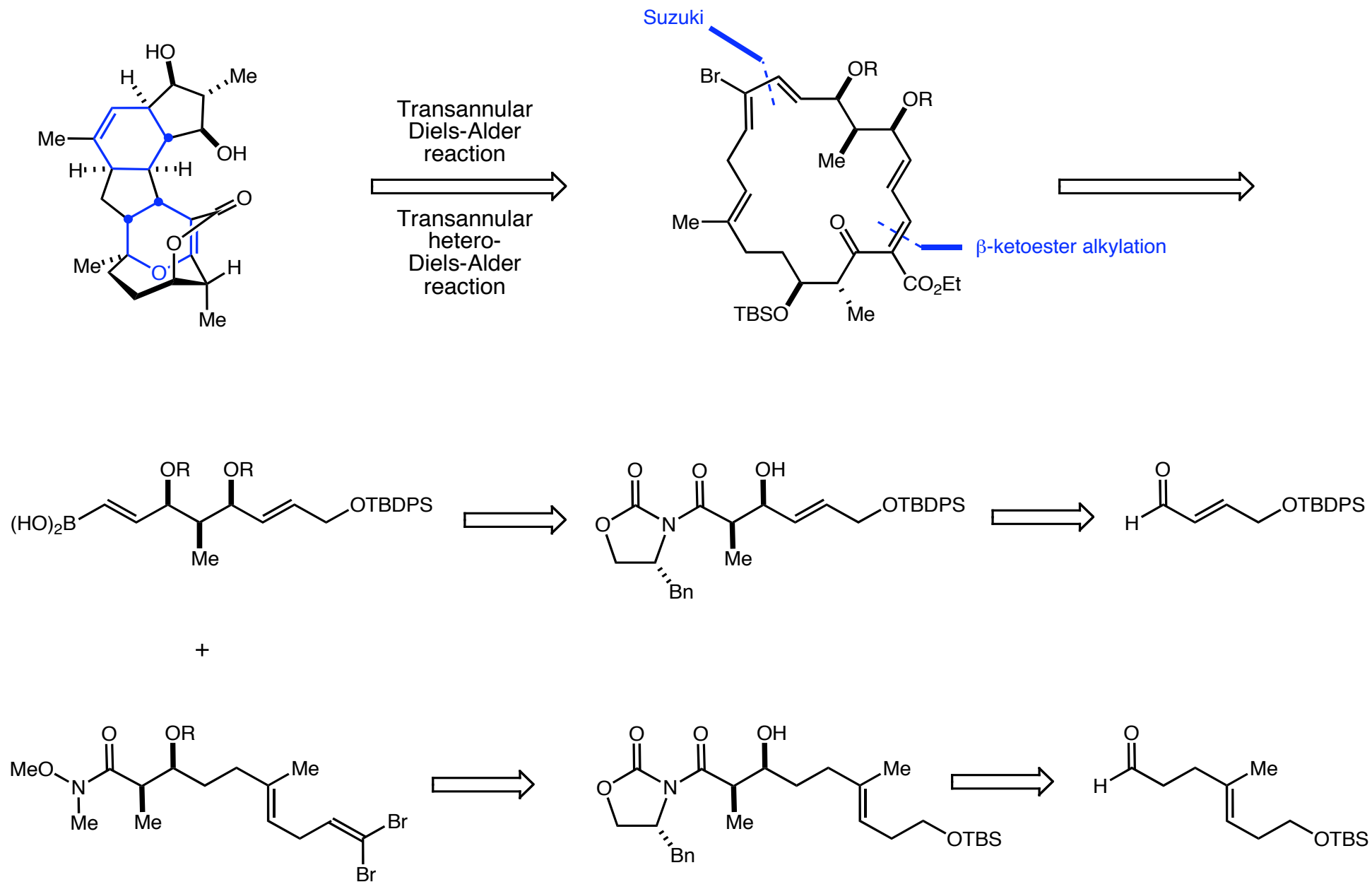
**Exo-TS**

Cascade TADA  
→

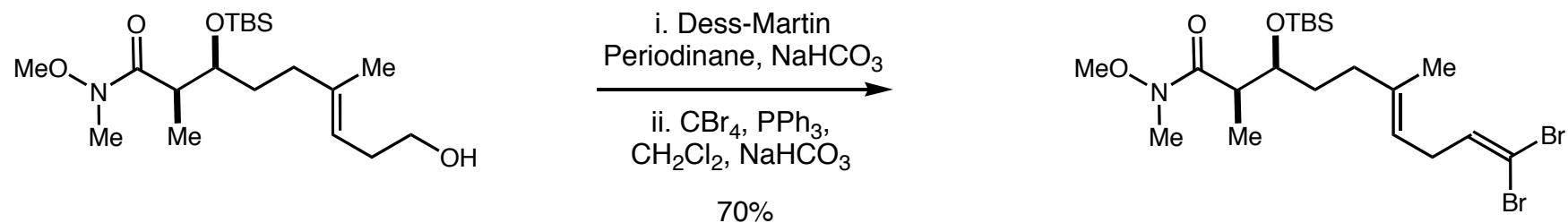
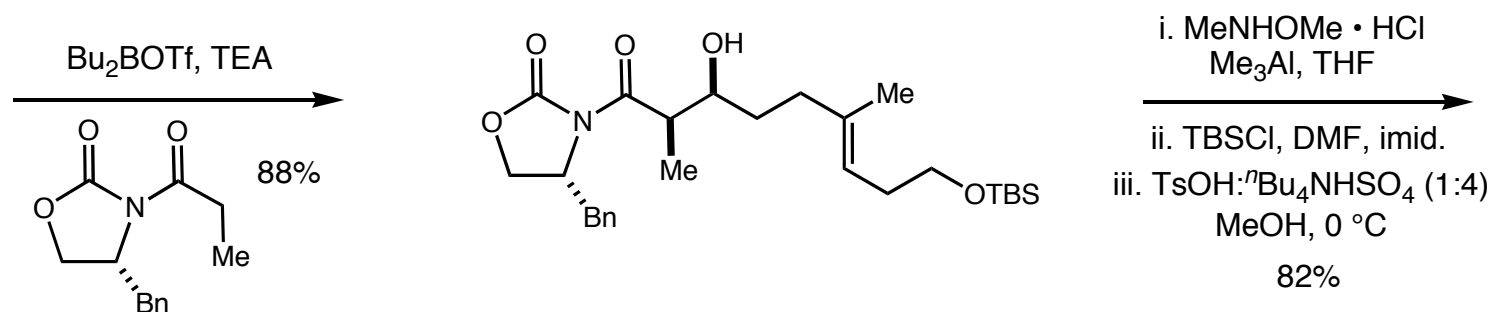
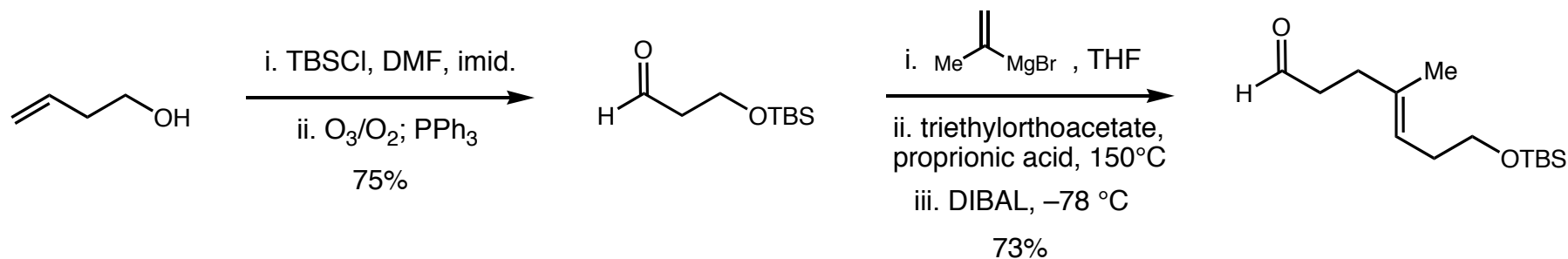


**Hexacyclinic Acid**

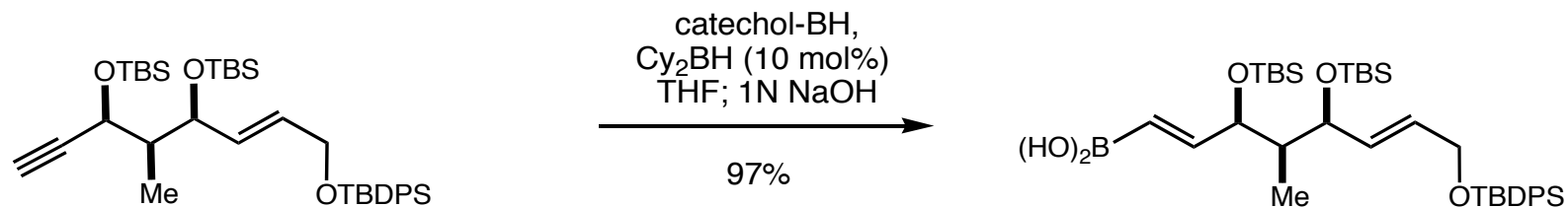
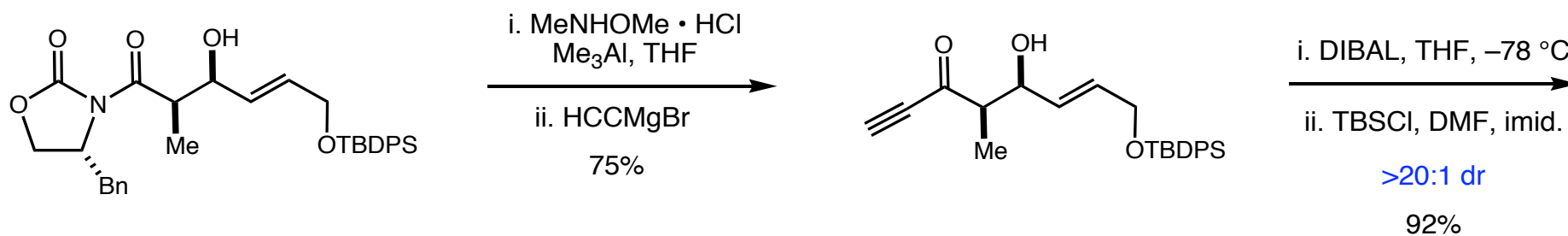
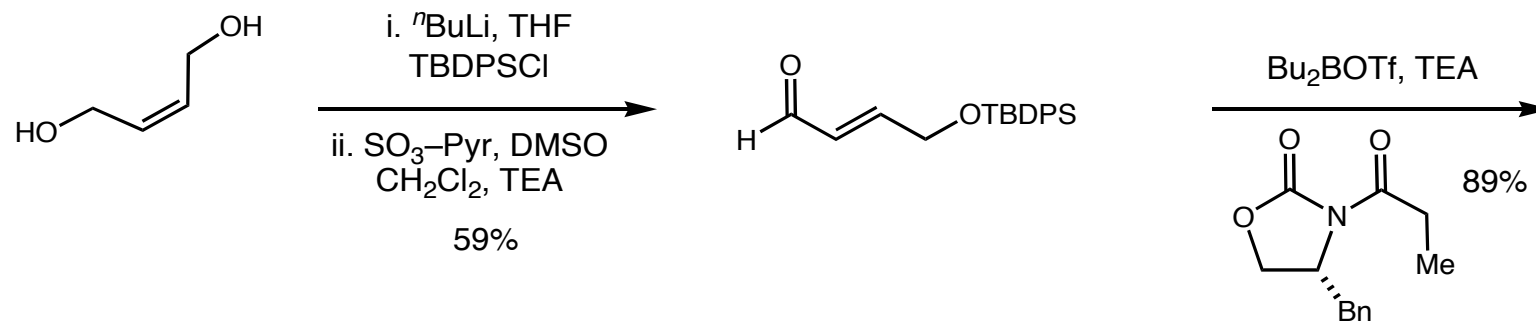
# Evans: A Diels-Alder Cascade Strategy



## Aldol Fragment Synthesis: Dibromide Fragment

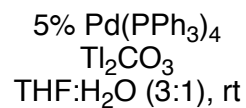
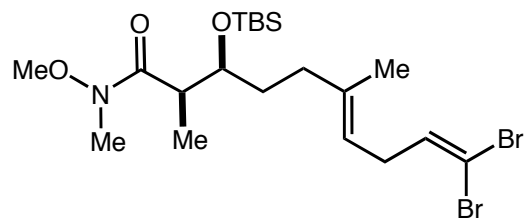


## Aldol Fragment Synthesis: Boronic Acid Fragment

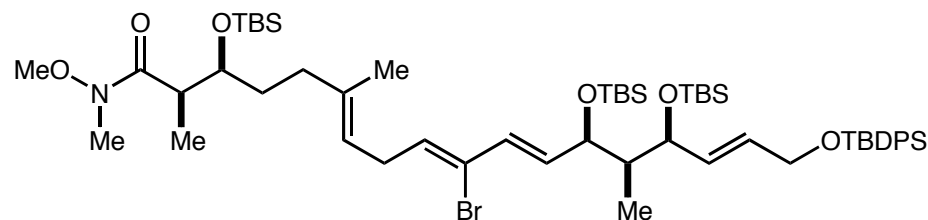
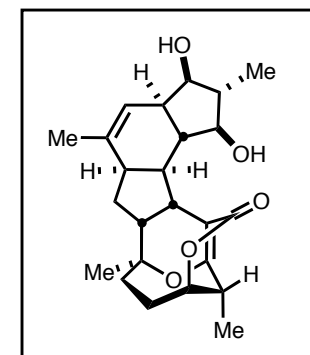
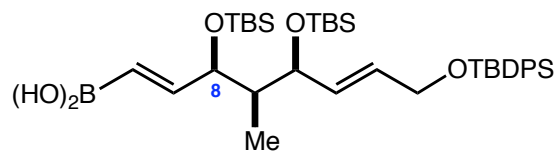




## Suzuki Coupling of the "Aldol" Fragments



84% desired pdt

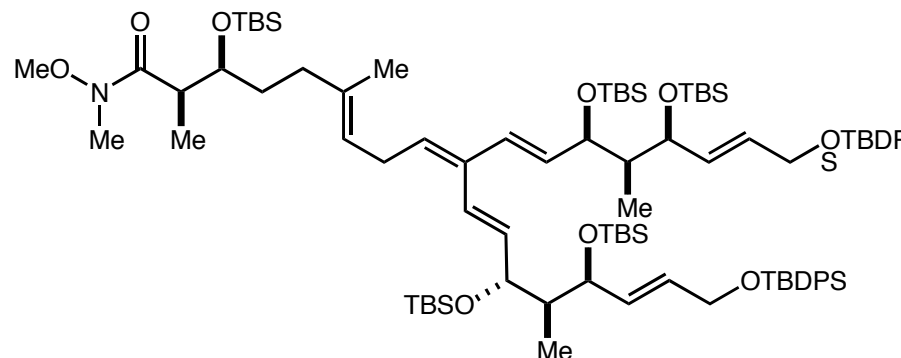


+ *undesired double  
addition product*

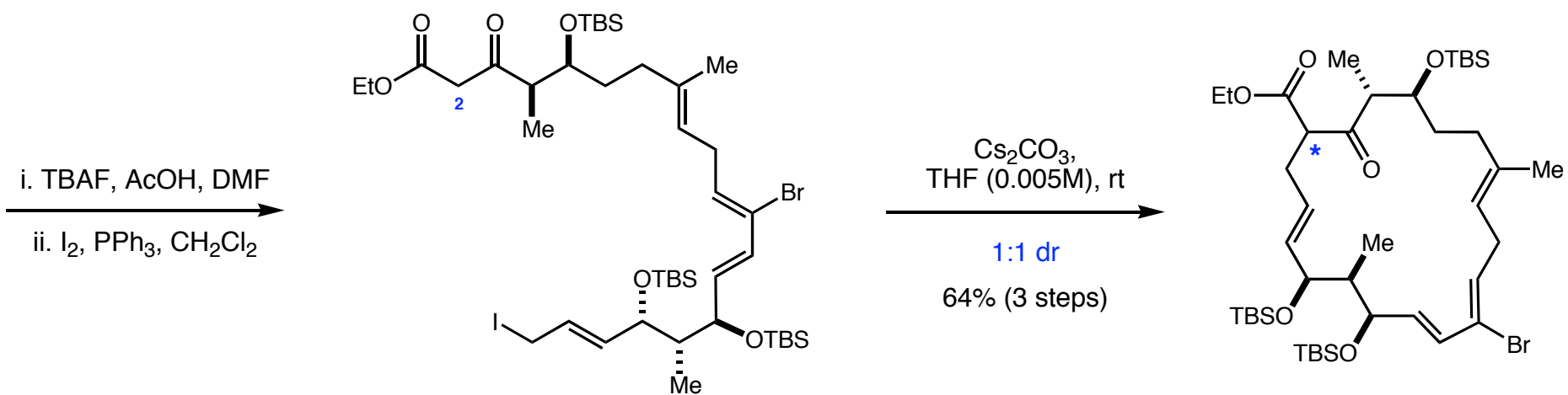
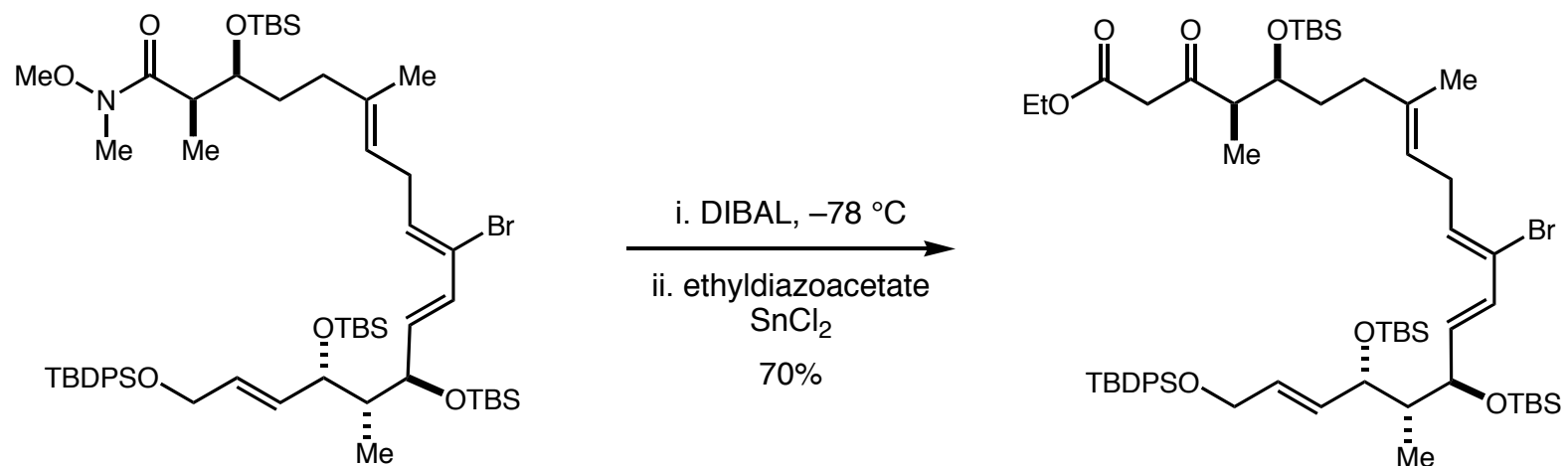
### Highly Optimized Suzuki Coupling Conditions

The coupling was sensitive to the choice of base:

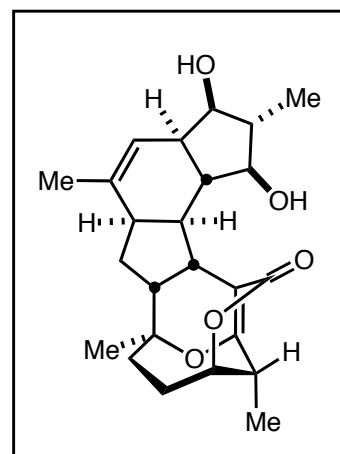
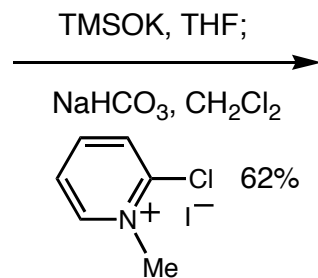
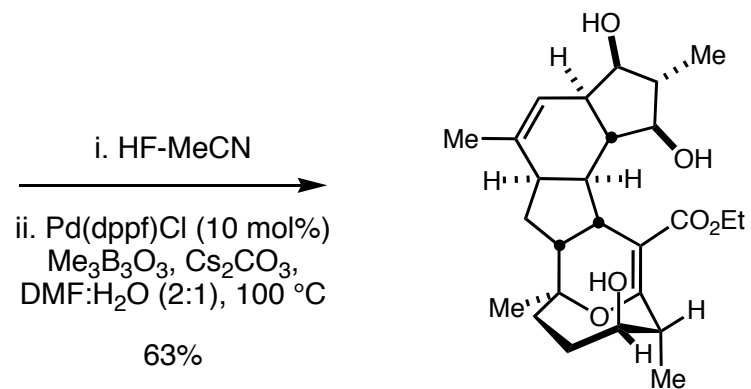
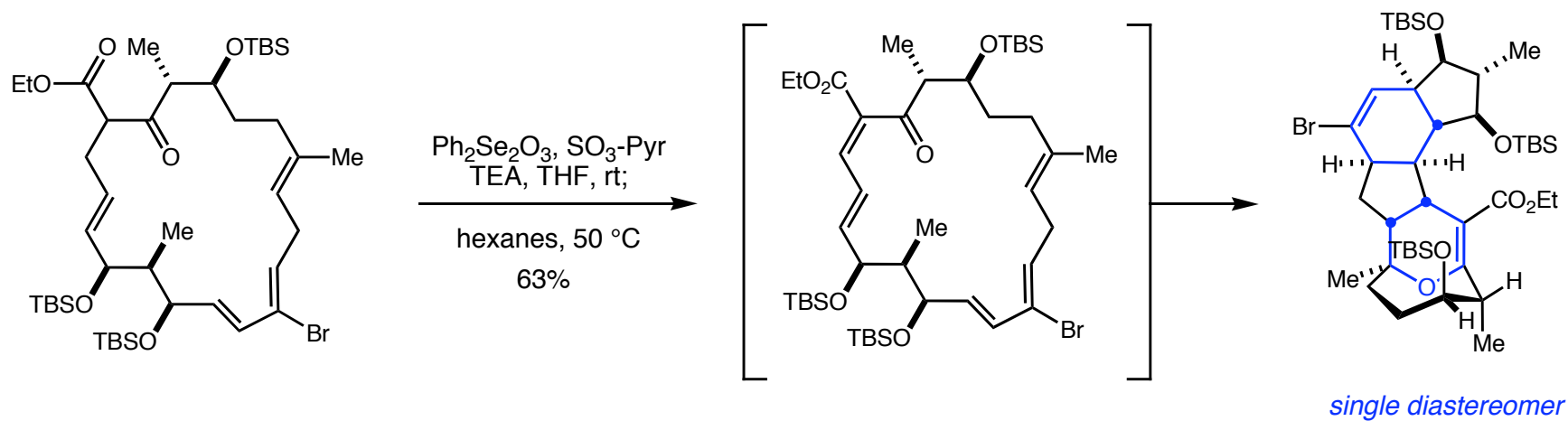
- (1) strong bases (i.e. hydroxides, oxides) or less halophilic cations resulted in slower rates and competitive decomposition of SM via protodeborylation, oxidation, elimination, etc.
- (2) silver bases completely decomposed products'
- (3) carbonates had the best selectivity and only Tl<sub>2</sub>CO<sub>3</sub> gave good reaction at rt



## Synthesis of the Pivotal Macrocycle



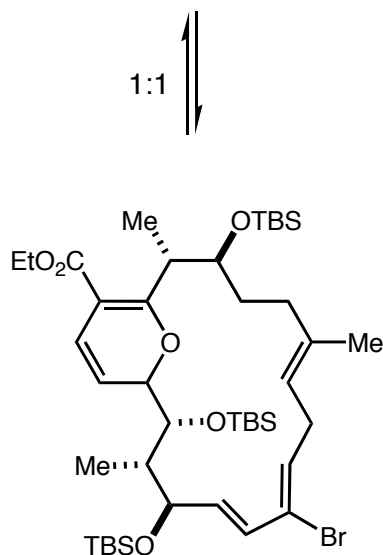
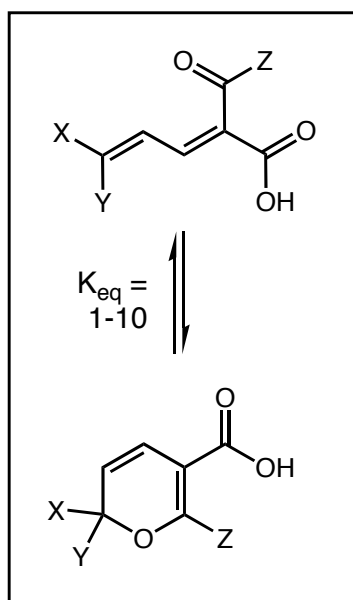
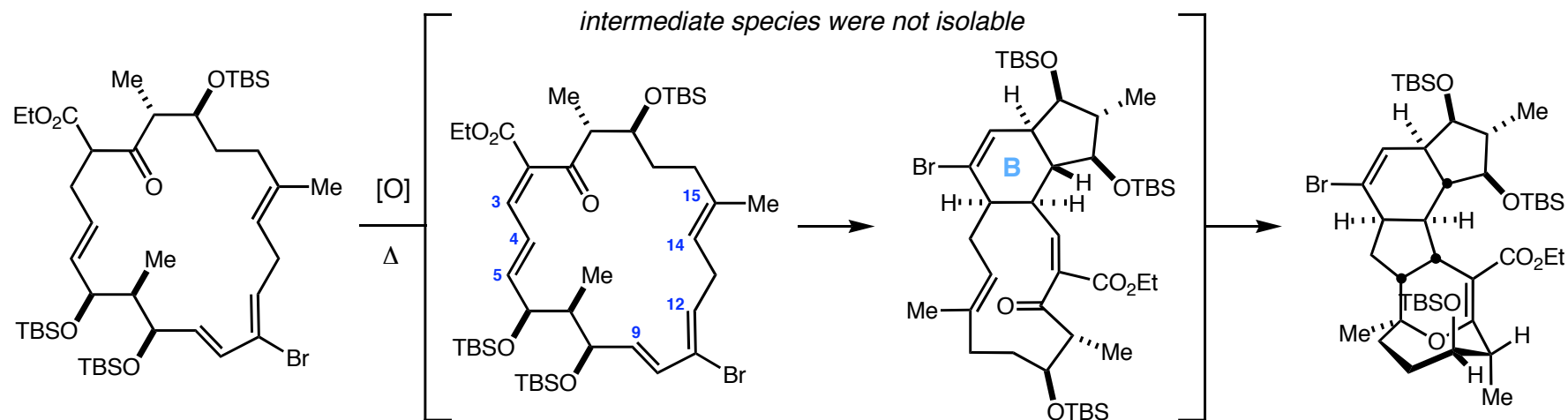
## The Diels-Alder Cascade in Action



Evans:  $[\alpha]_D^{23} = -5$

Fujisawa:  $[\alpha]_D^{23} = -3.5$

## A Closer Look at the Cyclization Sequence



■ NMR analysis shows 2H-pyran equilibrium

■ Cyclization order? The Normal-demand DA (NDA) or inverse-demand hetero DA (HDA)?

FMO analysis using calculated (Spartan 5.1)  $P_z$  orbital coefficients of the HOMO and LUMO predicts B-ring cyclization to occur first.

HOMO		LUMO	
Atom	$P_z$	Atom	$P_z$
C9	0.38	C5	0.51
C12	-0.48	C4	-0.26
C14	-0.07	C3	-0.56
C15	0.03	O1	-0.29

best overlap (pink line) connects C9 to C5 and C12 to C4.

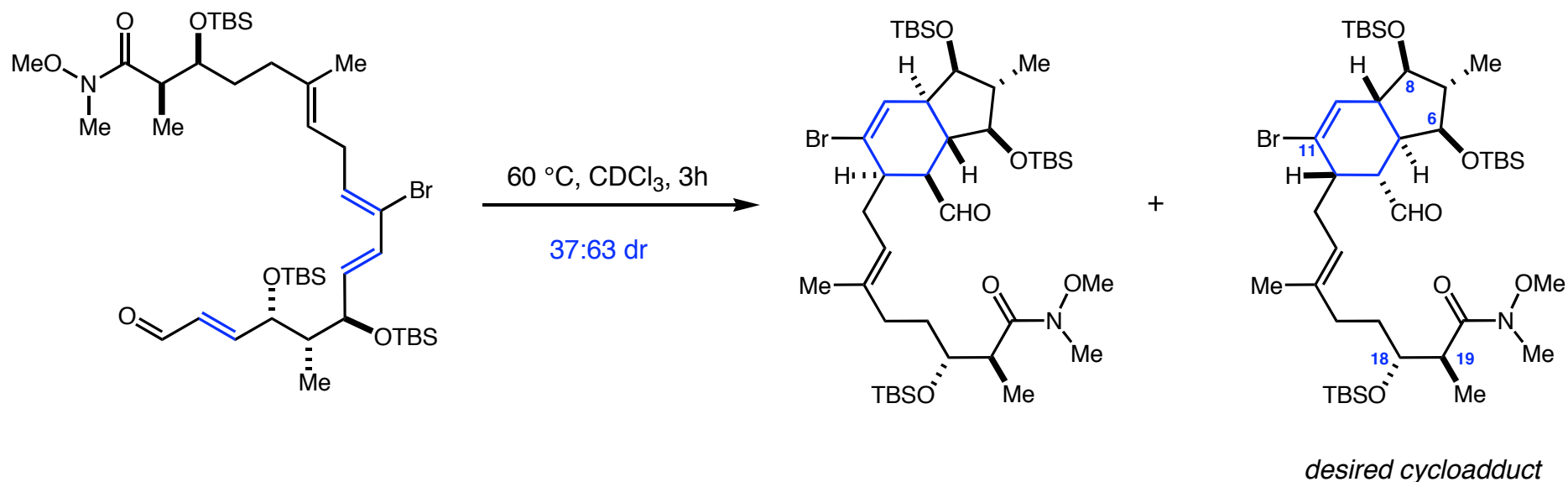
Moorhoff (*Syn* **1997**, 685):  $6\pi$ -cyclization to pyran tautomer

## Studying the Inherent Stereoselectivity of the TADA Cascade

### ■ 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 @ C11, also observed high endo selectivity and the opposite dr 61:31 dr.

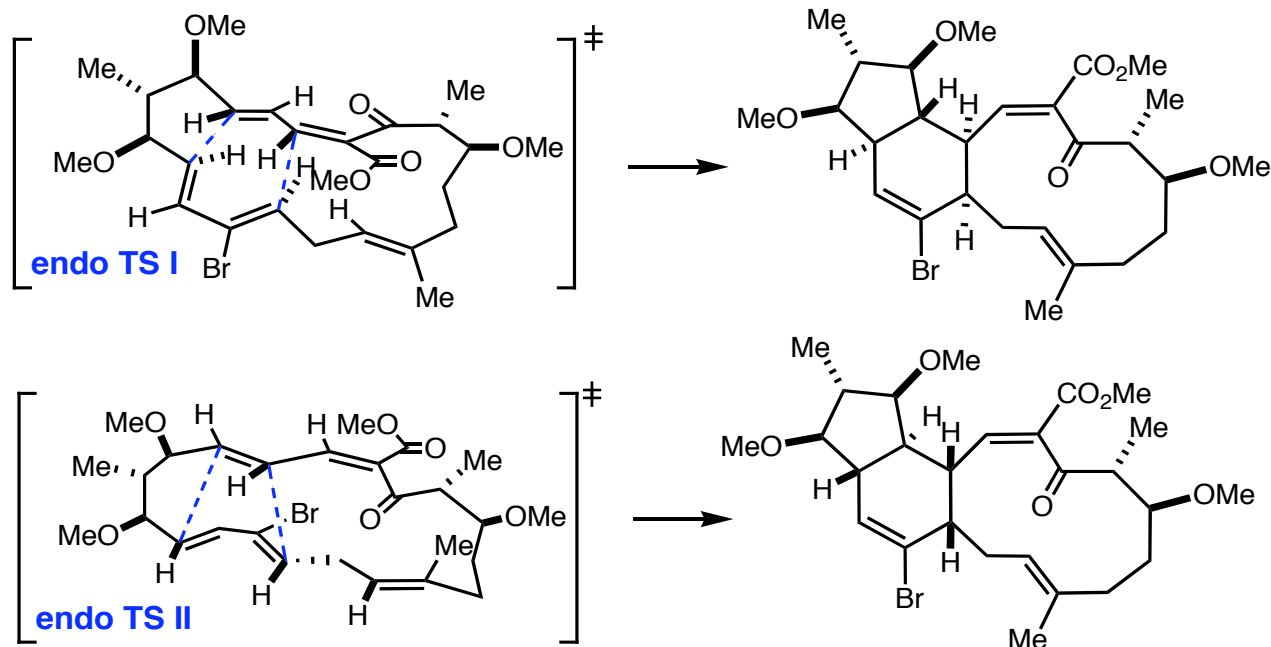
This suggests that the C6-C8 stereotriad only modestly differentiates  $\pi$ -faces in the B-ring cyclization



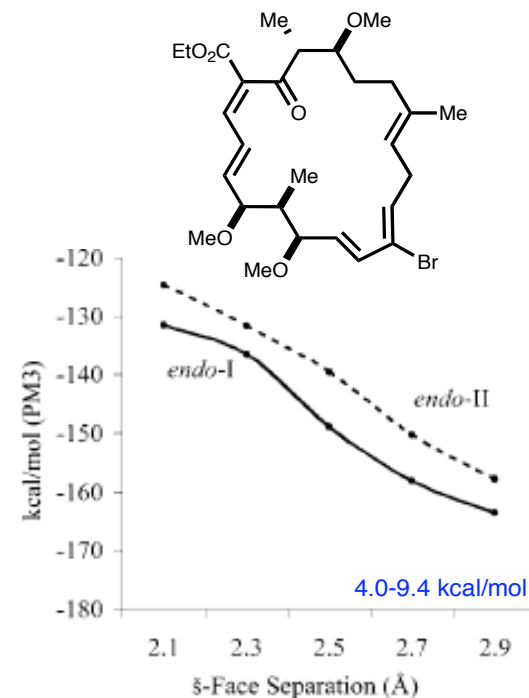
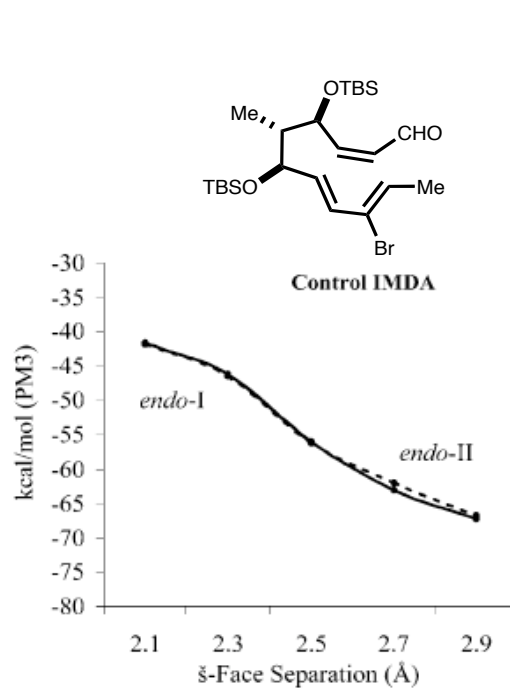
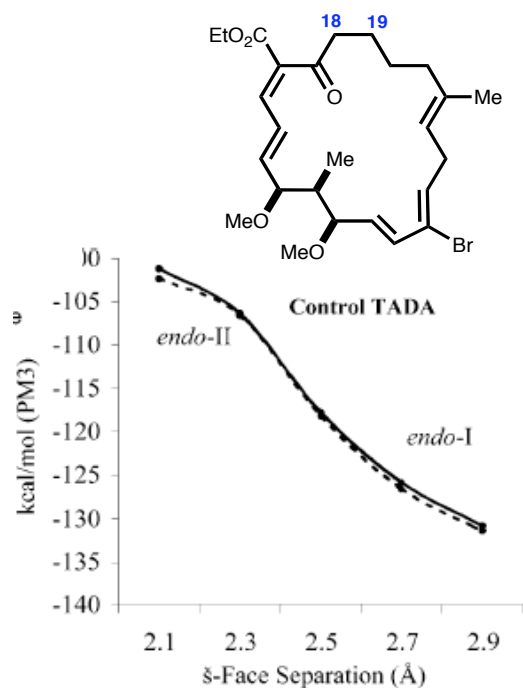
### ■ The high face-selectivity of the TADA cycloaddition is conjectured to arise from C18,C19 stereocenters

# Modeling the TADA Endo Transition States

Nine simplified macrocycles (varied at C18 and C19) were energy-minimized (PM3) with distance constraints (of 2.9-2.1 Å) leading to the observed natural product (via endo TS I) or it's endo diastereomer (via endo TS II).

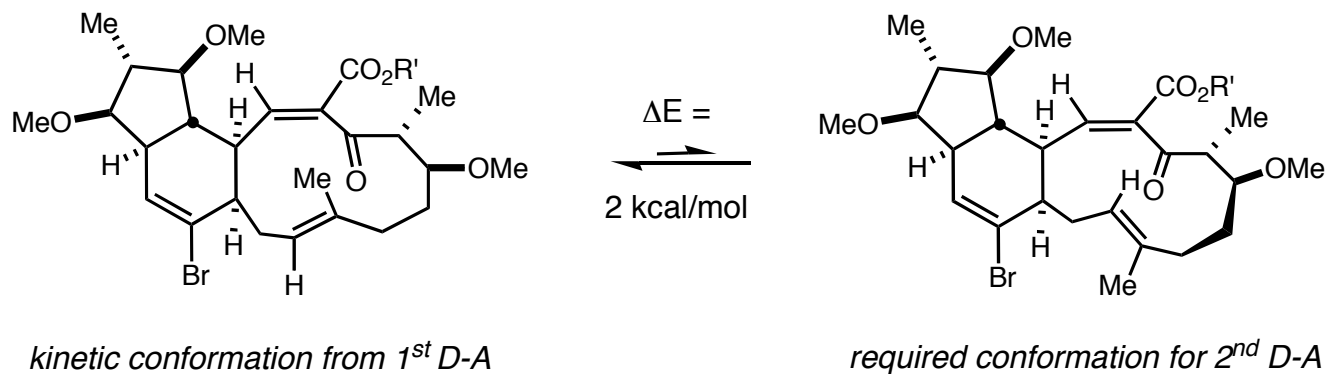


For each macrocycle, five energy-minimized geometries were obtained and two energy curves were generated plotting the increasing energy penalty for  $\pi$ -face alignment of the approaching TS ( I and II).

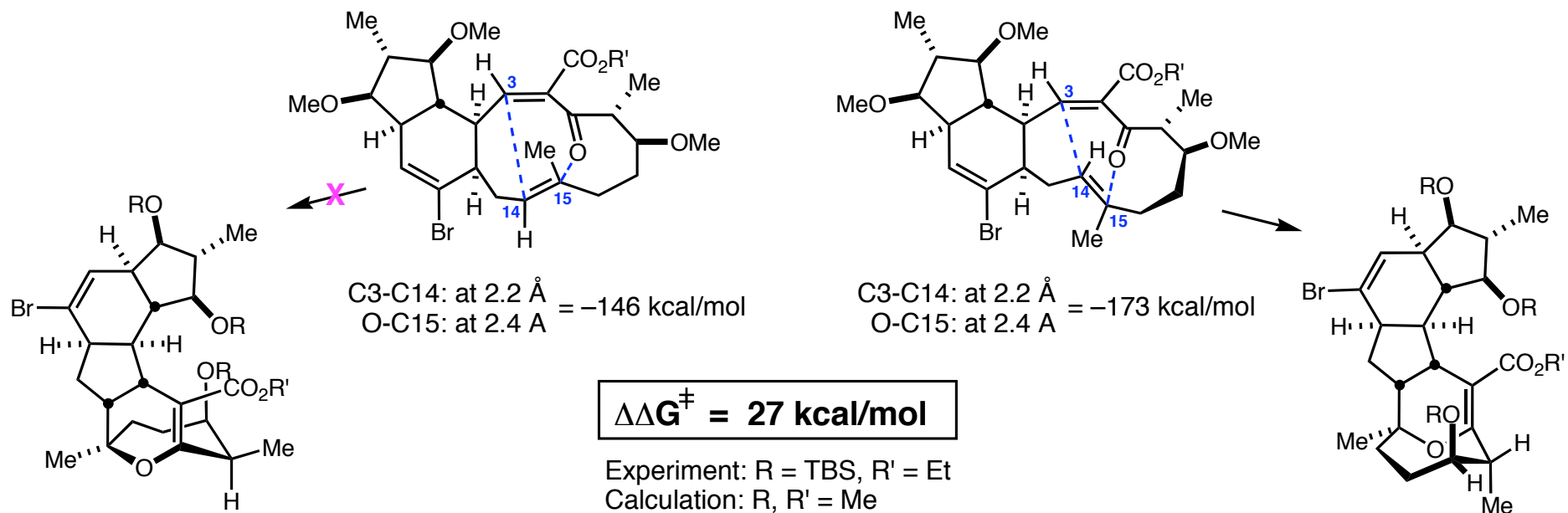


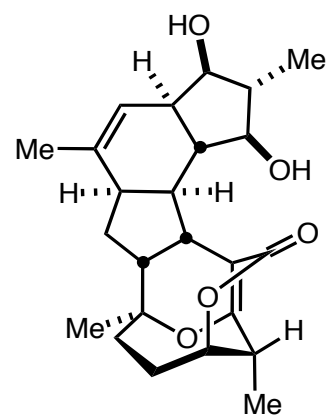
# Analysis of the Transannular Hetero Diels-Alder Cycloaddition

- Tricyclic intermediate has two low-energy conformations

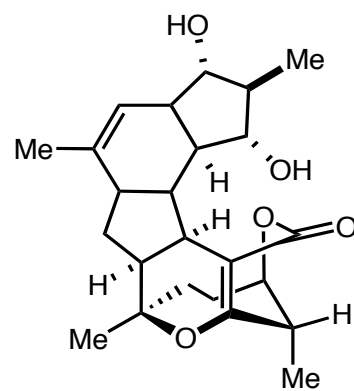


- Application of transition state bond constraints energetically favors desired cyclization





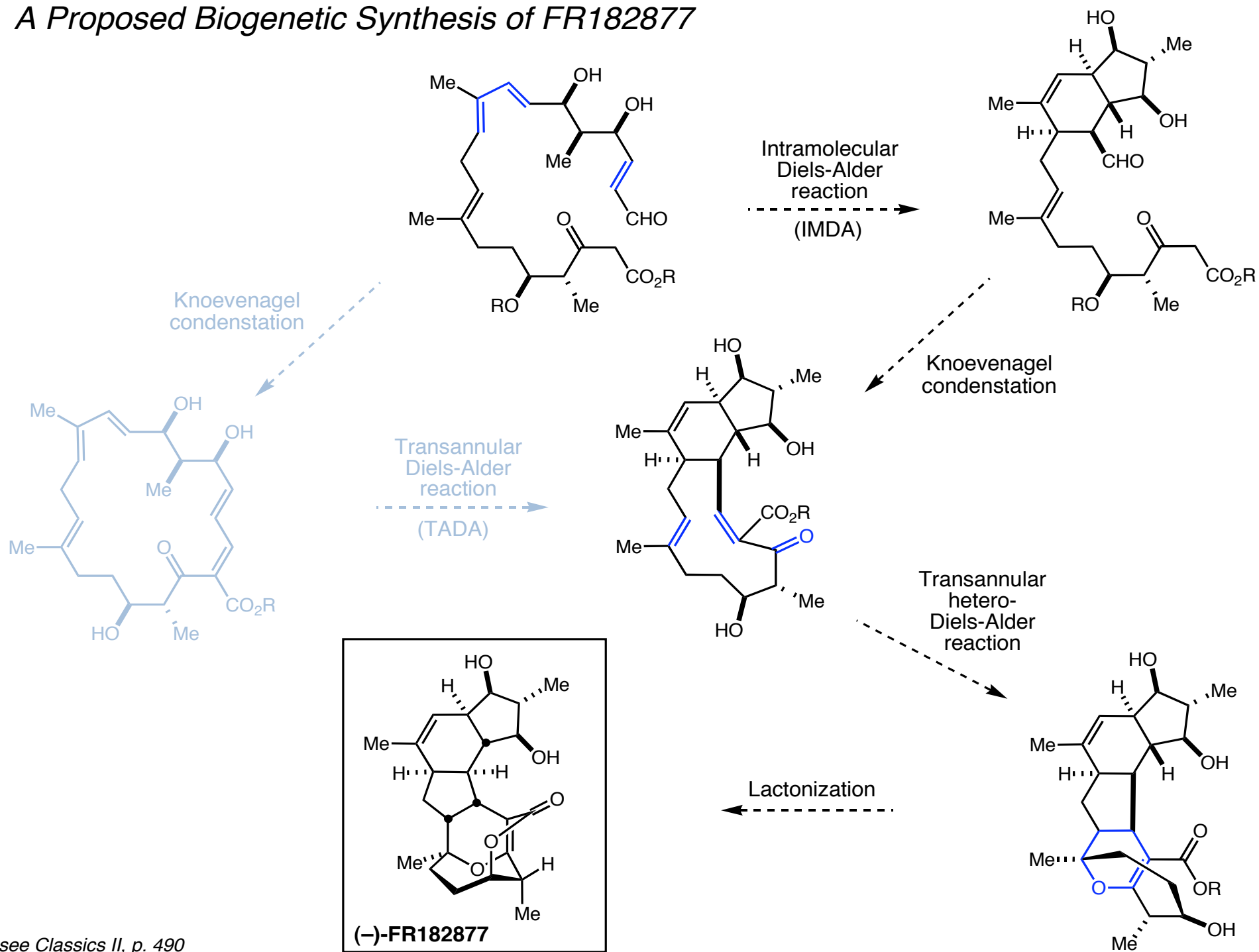
**(-)-FR182877**



**(+)-FR182877**

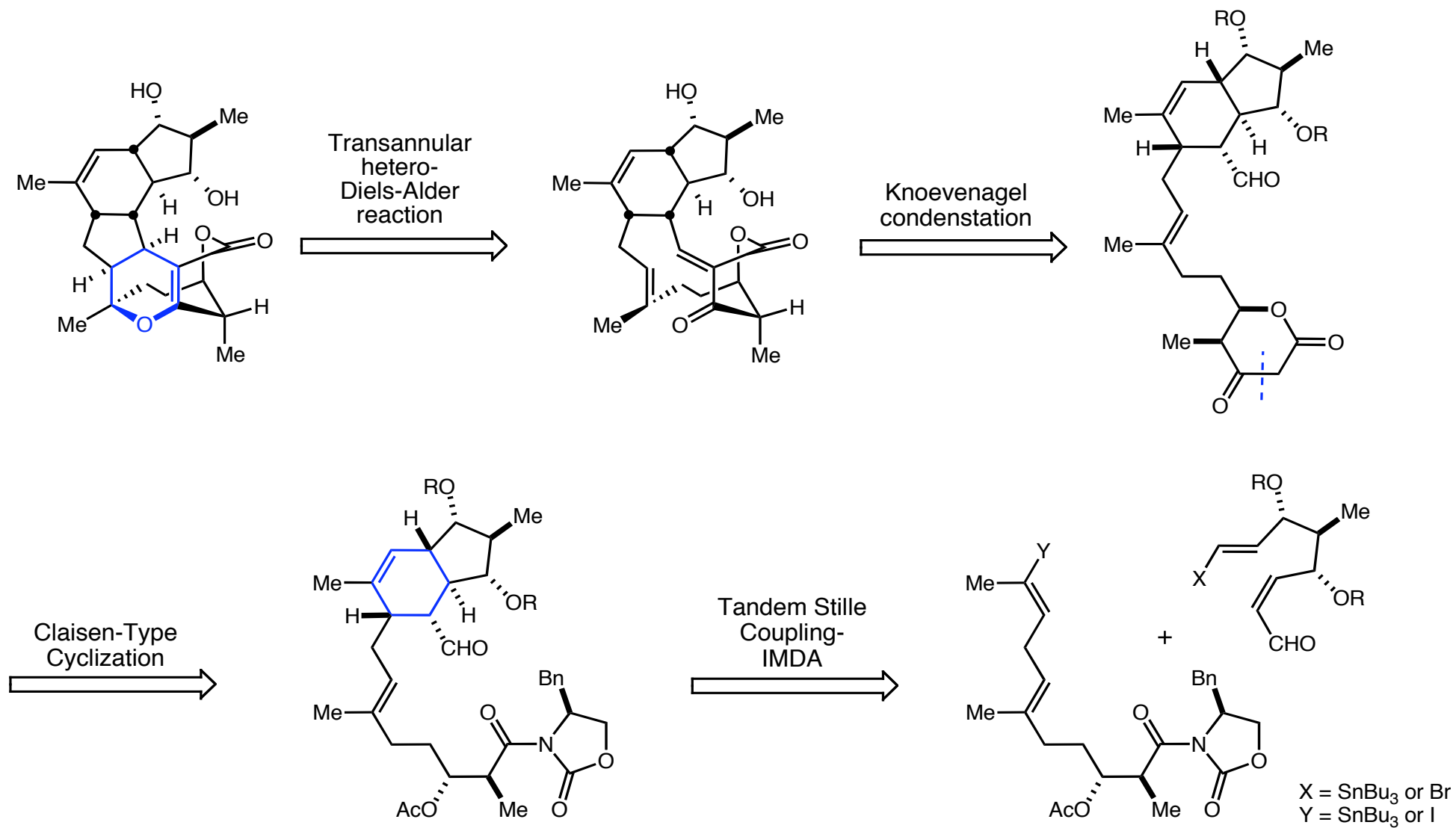


# A Proposed Biogenetic Synthesis of FR182877



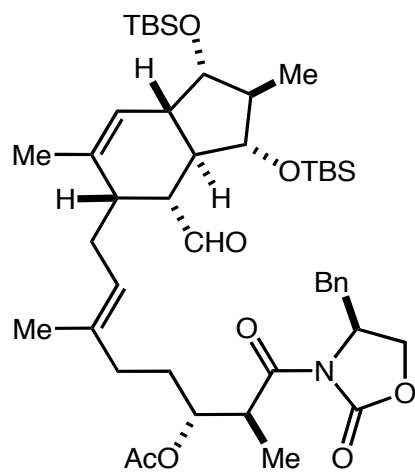
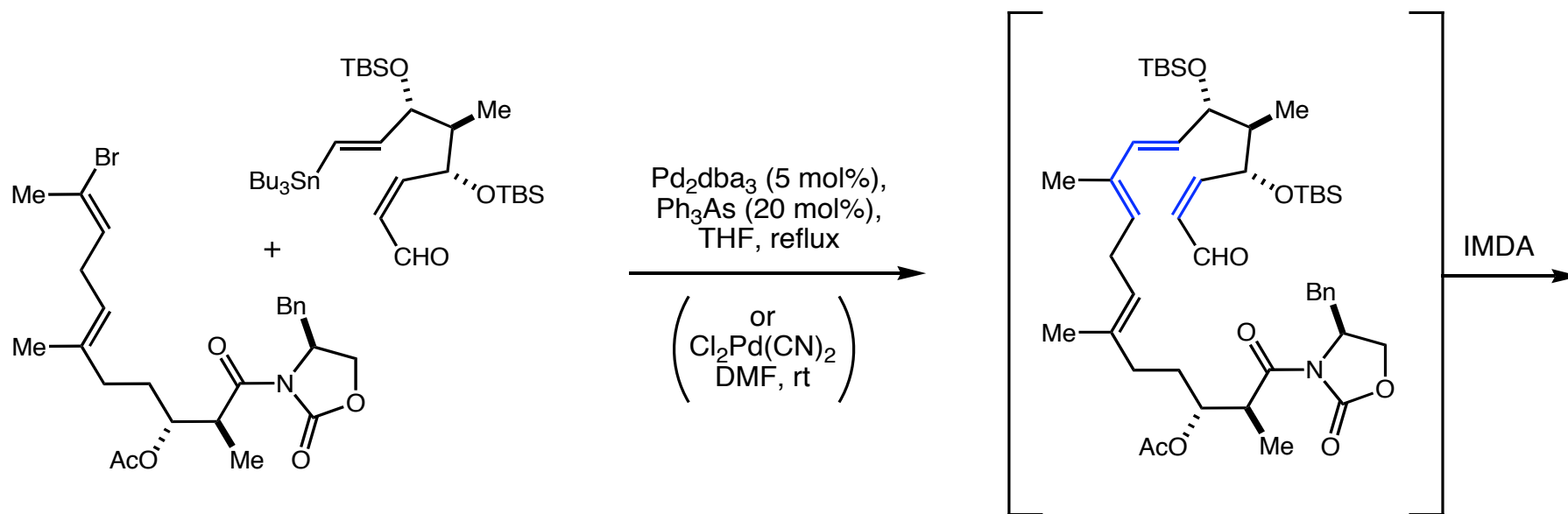
# Sorensen: Initial Retrosynthetic Strategy Towards (+)-FR182877

featuring a D-A / Knoevenagel / D-A sequence

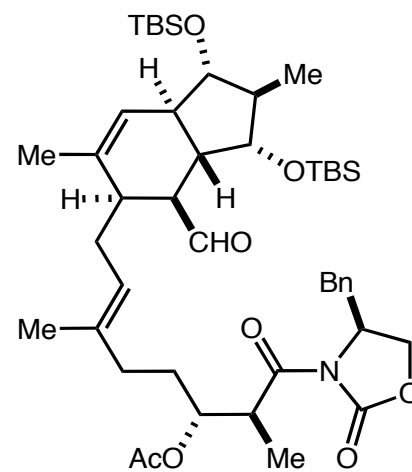


# Highlighted Issues in the Initial Strategy Towards (+)-FR182877

selectivity in the tandem Stille/IMDA sequence



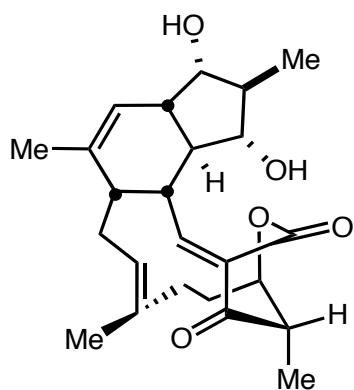
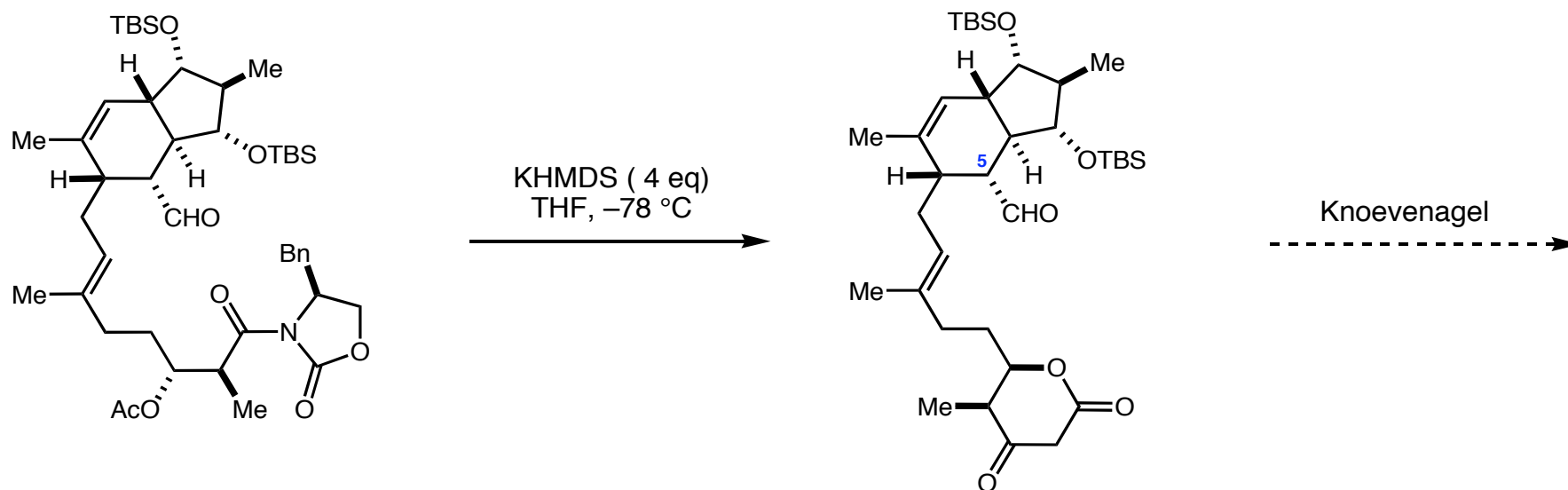
+



*undesired endo cycloadduct*

## Highlighted Issues in the Initial Strategy Towards (+)-FR182877

forming the  $\beta$ -keto lactone and Knoevenagel condensation



### ■ Issues encountered in this approach:

The desired  $\beta$ -keto lactone substrate was unstable to Stille coupling, as such the acetate imide was used.

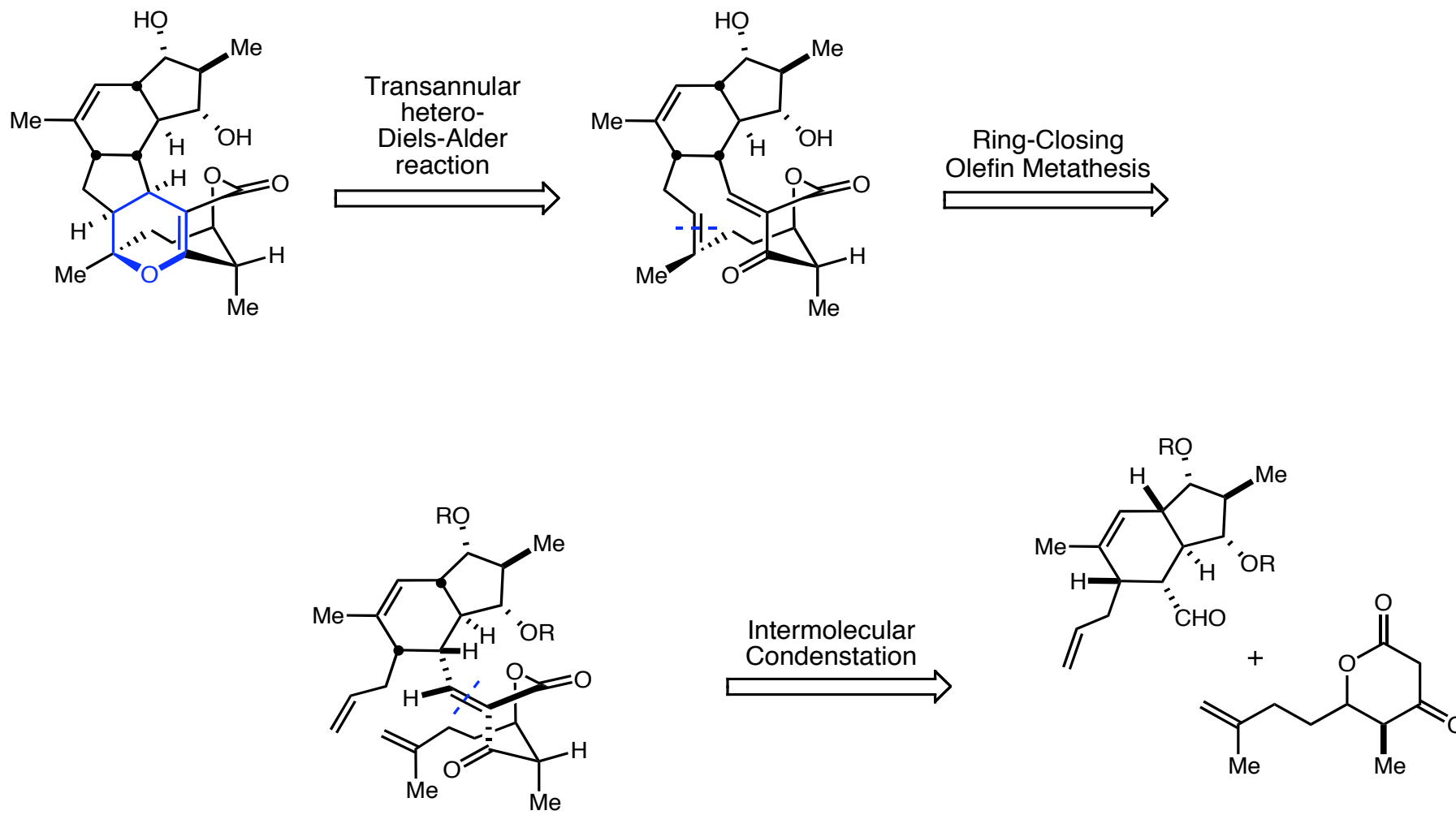
The IMDA was not diastereoface-selective and gave 2 endo cycloadducts (separable by chromatography)

The Knoevenagel condensation to form the tetracycle ring was unsuccessful

⇒ revise strategy to an intermolecular Knoevenagel condensation

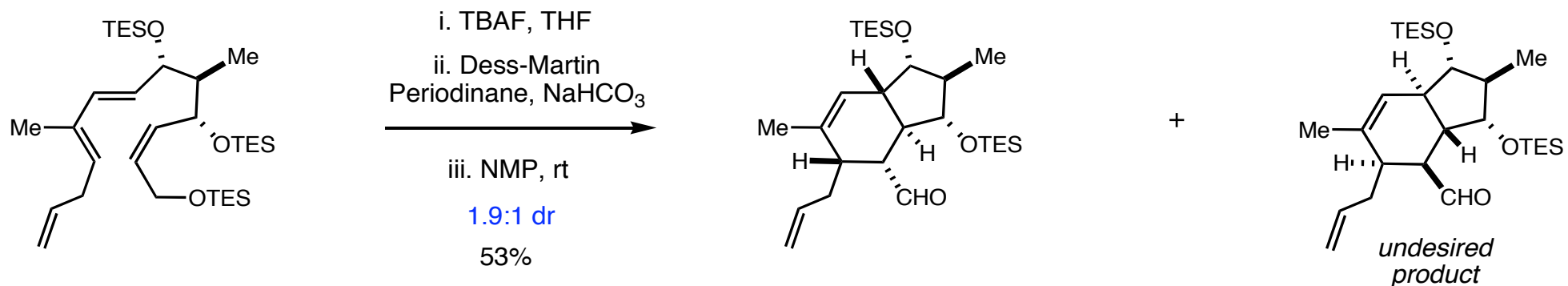
# A Revised Retrosynthetic Strategy Towards (+)-FR182877

featuring a Knoevenagel / RCM approach

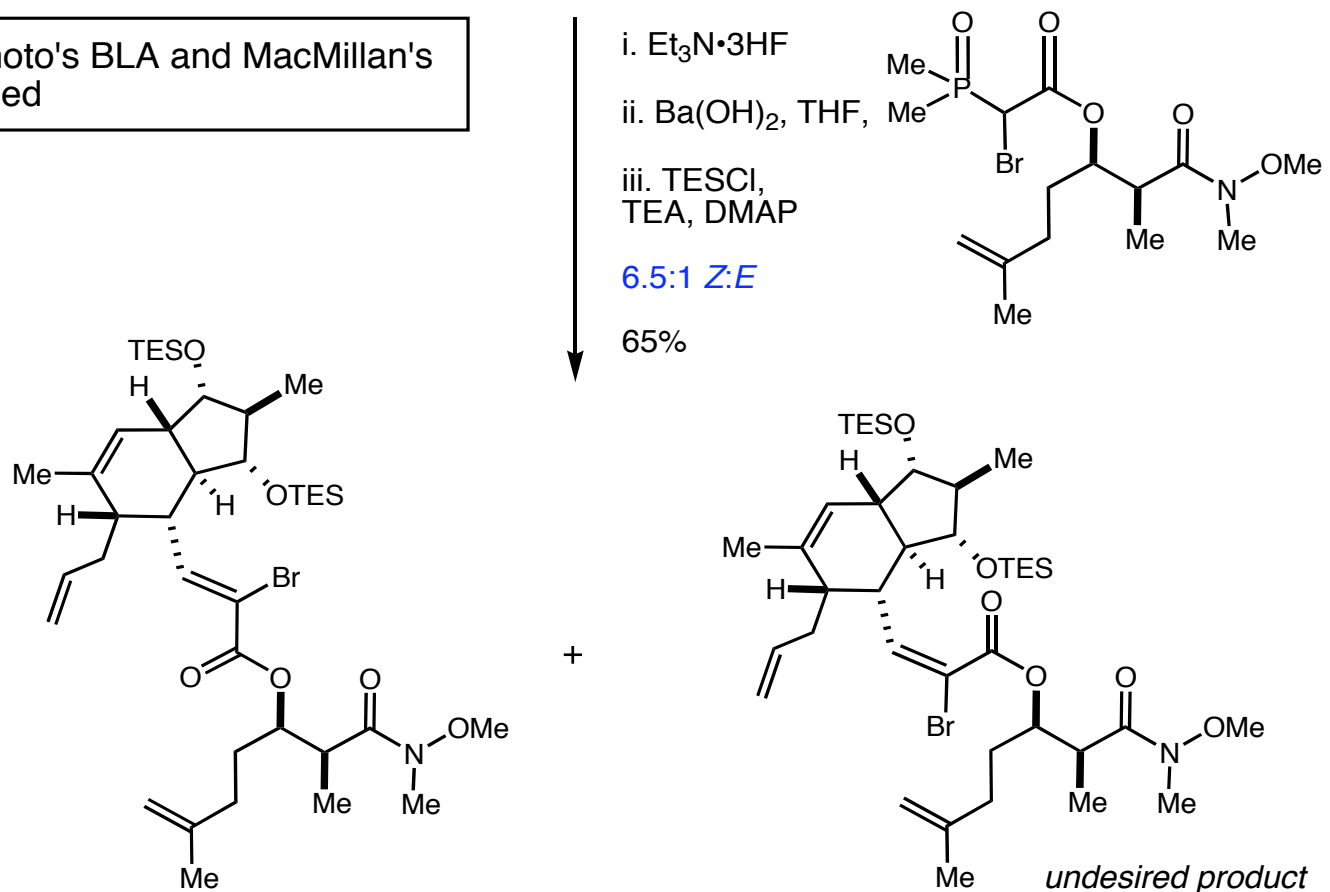


# Highlighted Issues in the Revised Strategy Towards (+)-FR182877

unfruitful condensation reactions are circumvented via a HWE

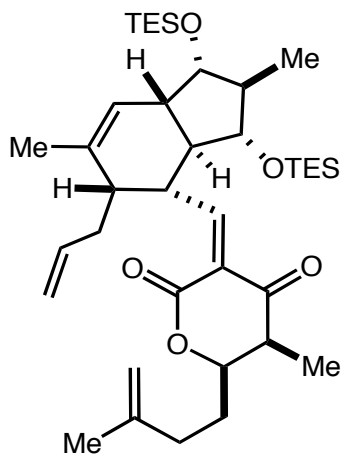
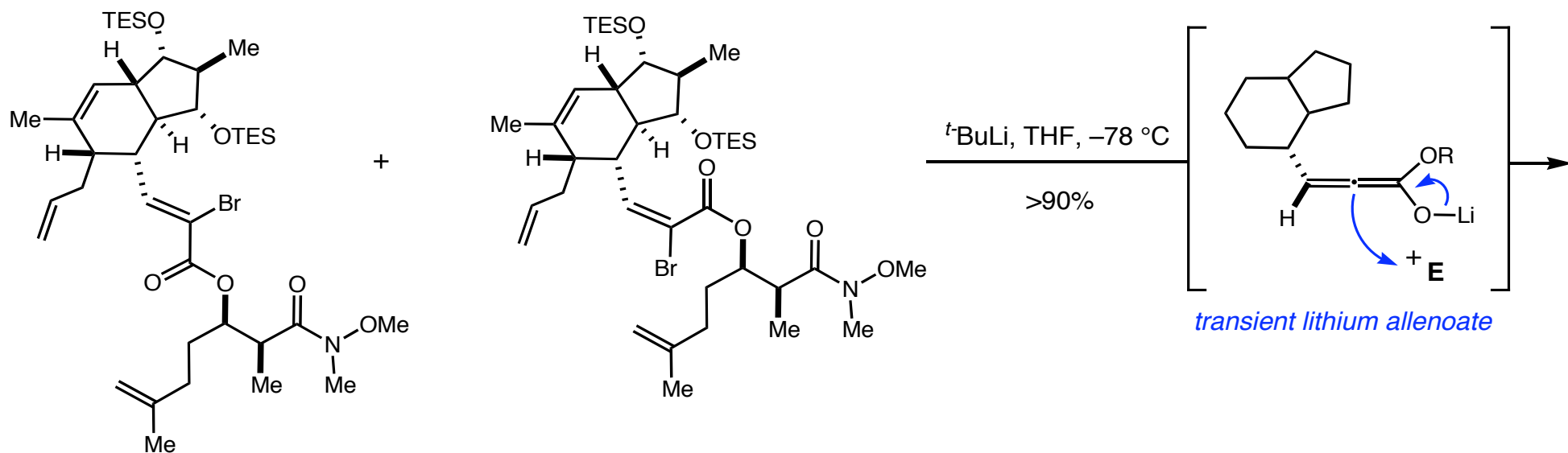


⇒ for IMDA rxn: Yamamoto's BLA and MacMillan's catalysts were also tried



# Highlighted Issues in the Revised Strategy Towards (+)-FR182877

an unexpected olefin geometry in alkyldiene formation



*undesired Z-olefin geometry*

## ■ Issues Encountered in this Approach:

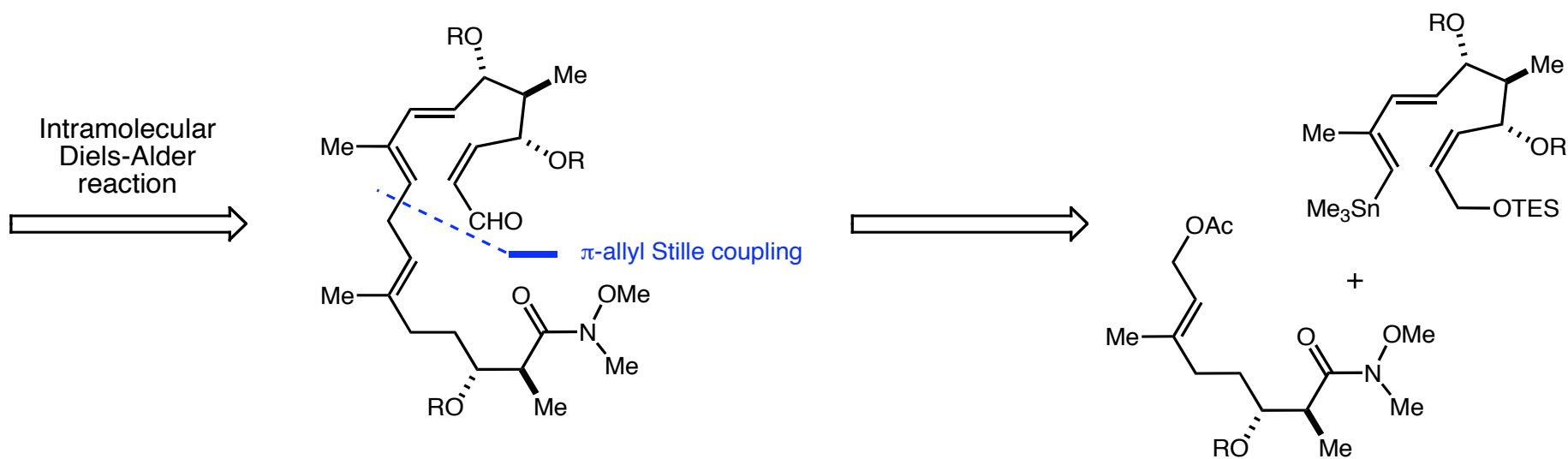
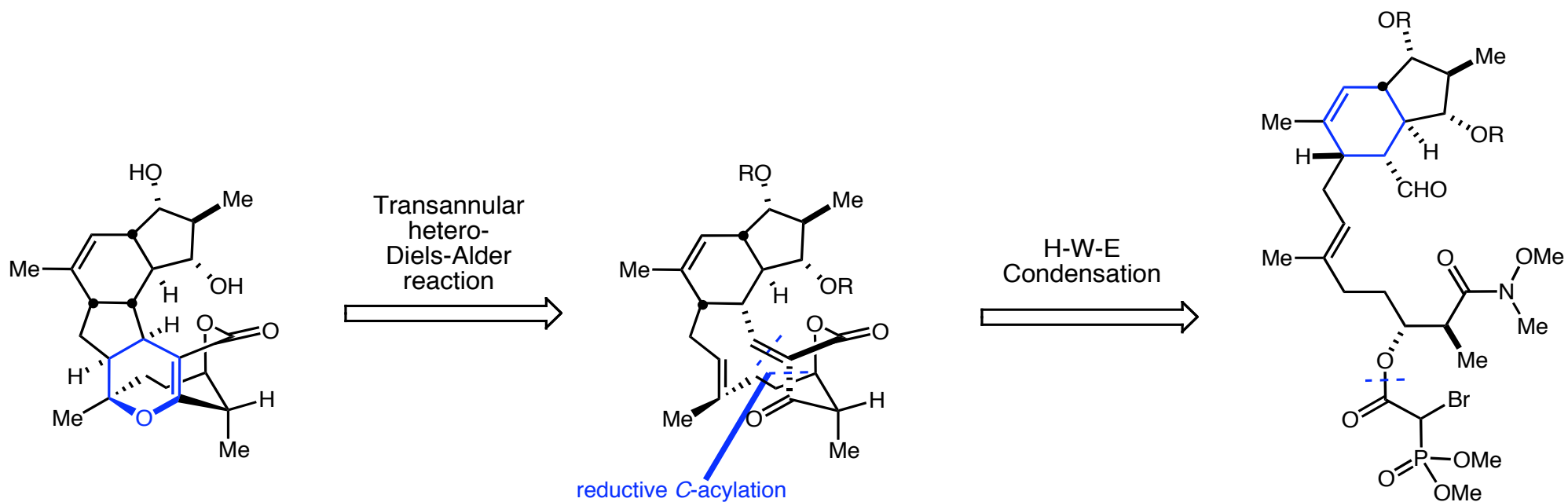
IMDA to form the first fragment was moderately diastereoface-selective (1.9:1 desired:undesired)

The desired  $\beta$ -keto lactone and the acyclic  $\beta$ -keto ester were not amenable to the Knoevenagel condensation

Isomerization to the needed *E* geometry of alkyldiene ketolactone was not realized though various methods

⇒ revise strategy to form *E*-geometry alkyldiene dicarbonyl

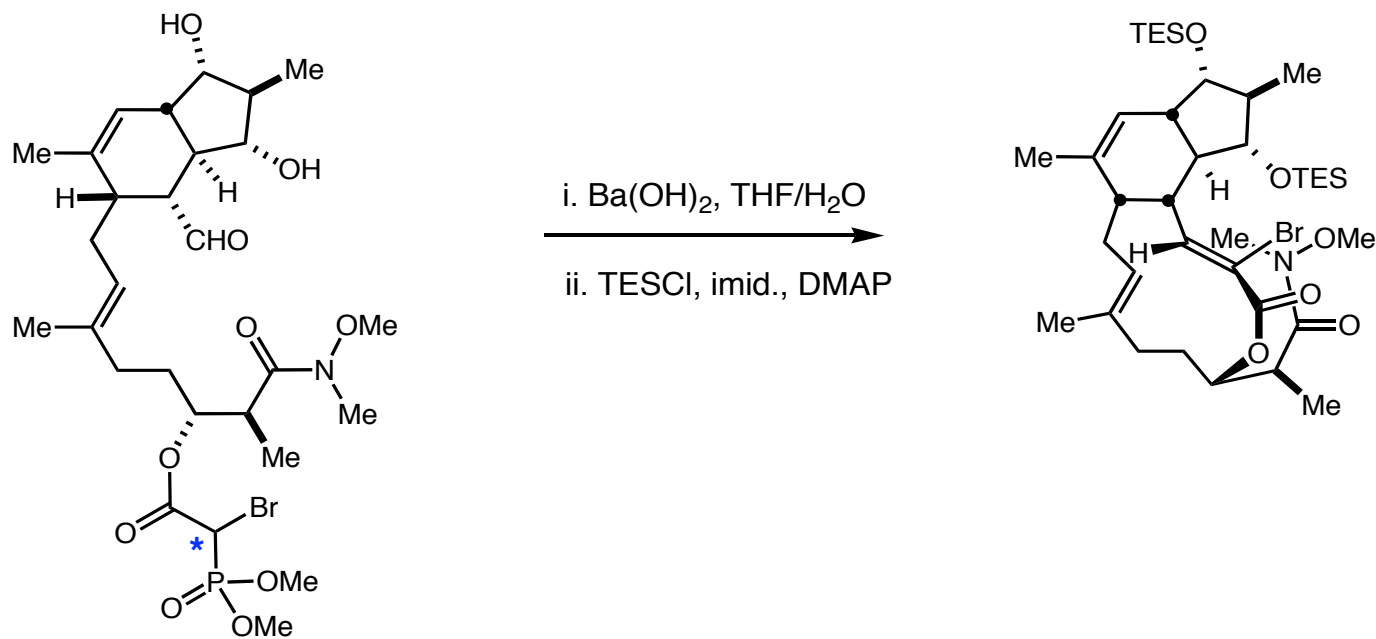
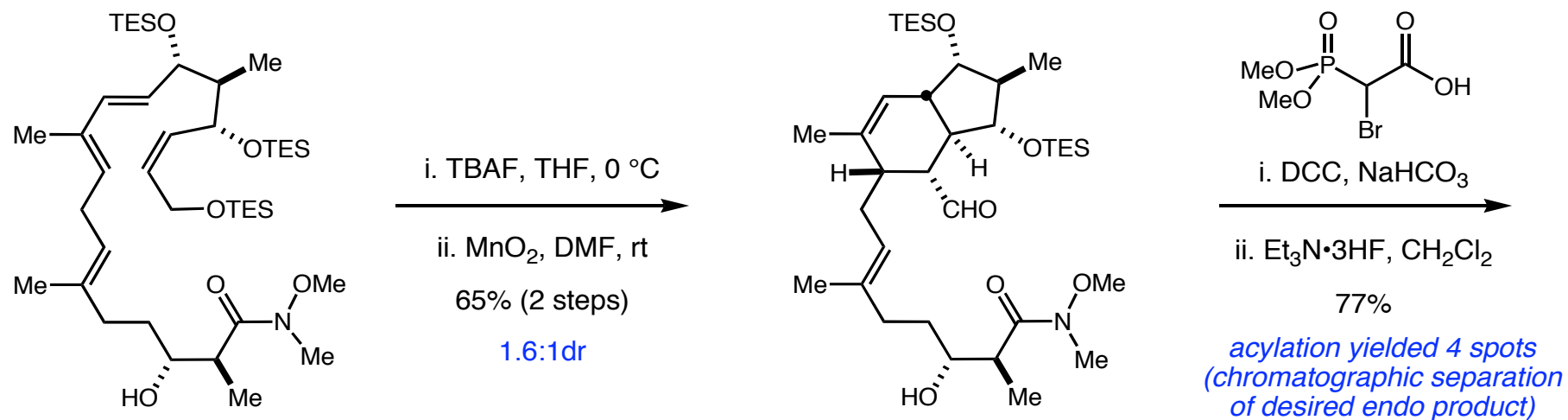
# A Re-revised Retrosynthetic Strategy Towards (+)-FR182877





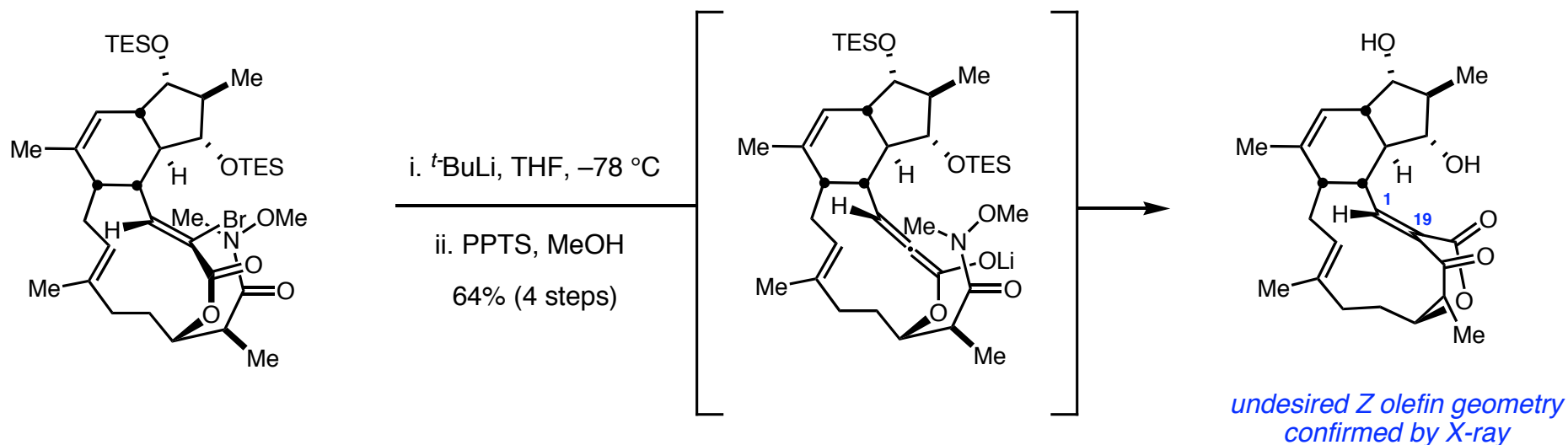
# Highlighted Issues in the Re-revised Strategy Towards (+)-FR182877

IMDA and the HWE sequence



## Highlighted Issues in the Re-revised Strategy Towards (+)-FR182877

haunted by the formation of the *E*-alkylidene



### ■ Issues Encountered in this Approach:

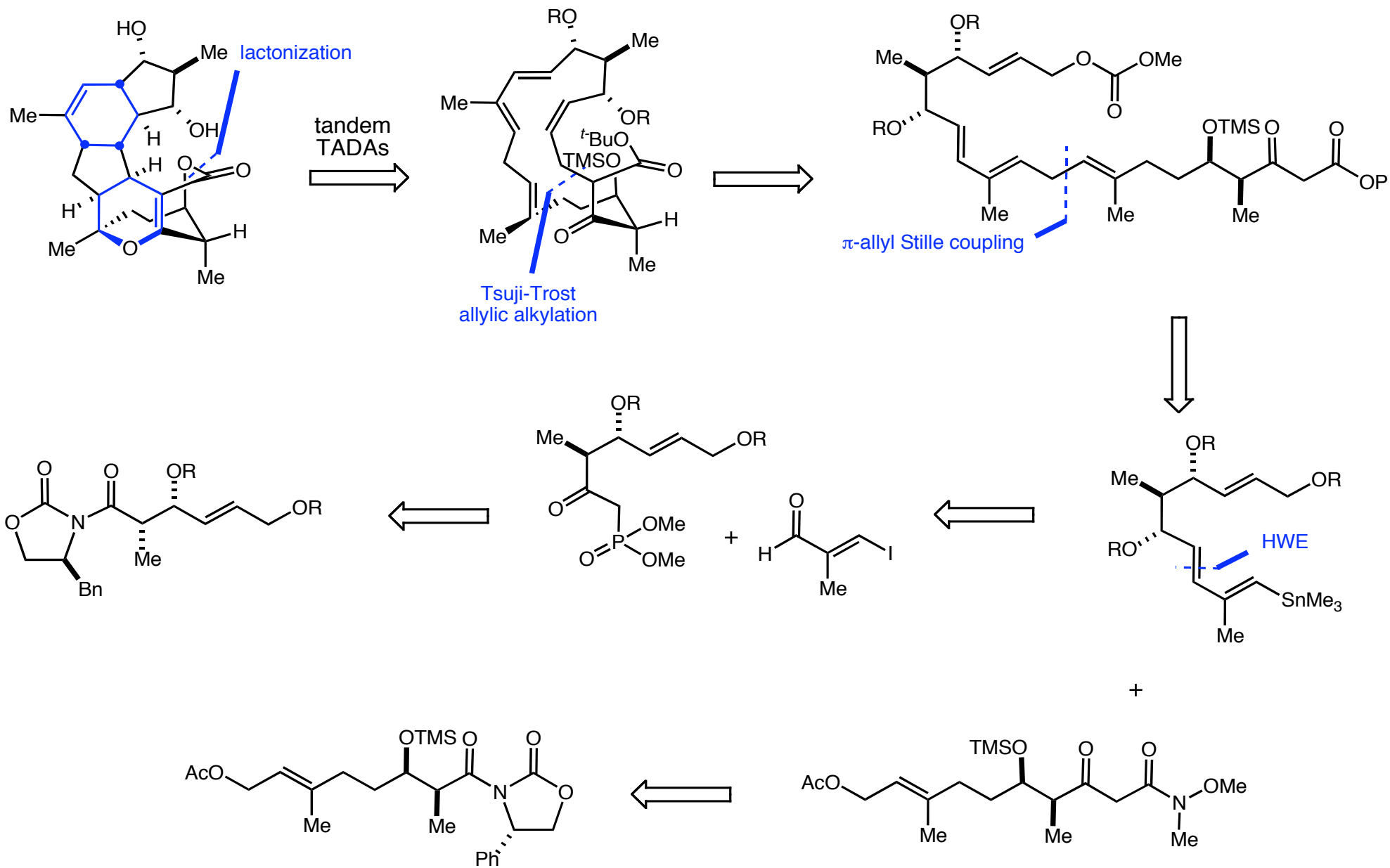
IMDA gave poor diastereofacial selectivity (1.6:1 of desired:undesired cycloadduct)

Key reductive lithiation cyclization step resulted in the formation of an undesired *Z* alkylidene dicarbonyl tetracycle. It was conjectured that the geometrical constraints of the 12-membered ring would have favored the *Z* isomer

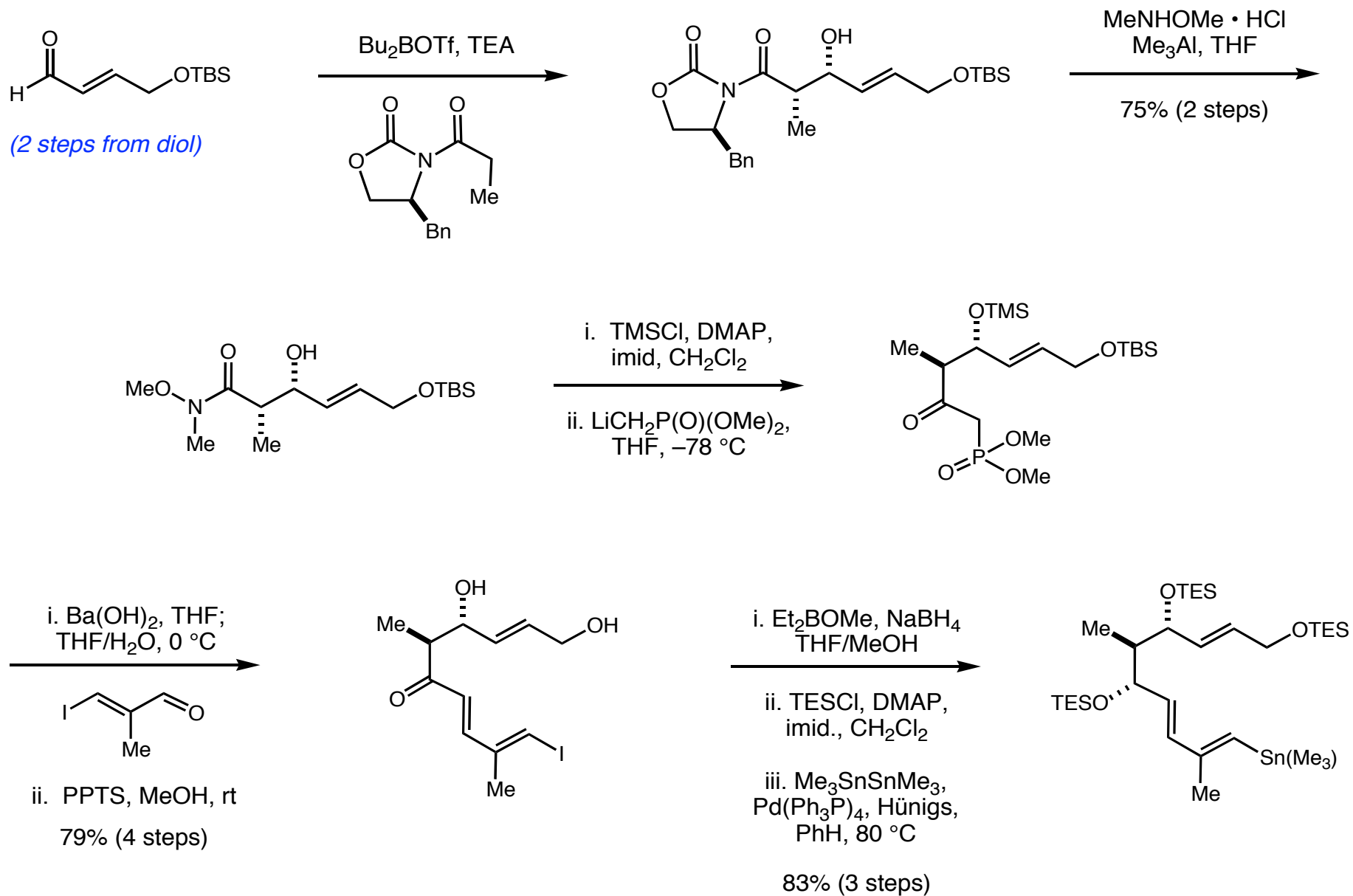
⇒ revise strategy in forging the C1-C19 bond and forming the  $\beta$ -keto lactone

# Sorensen: The Retrosynthetic Strategy that Worked

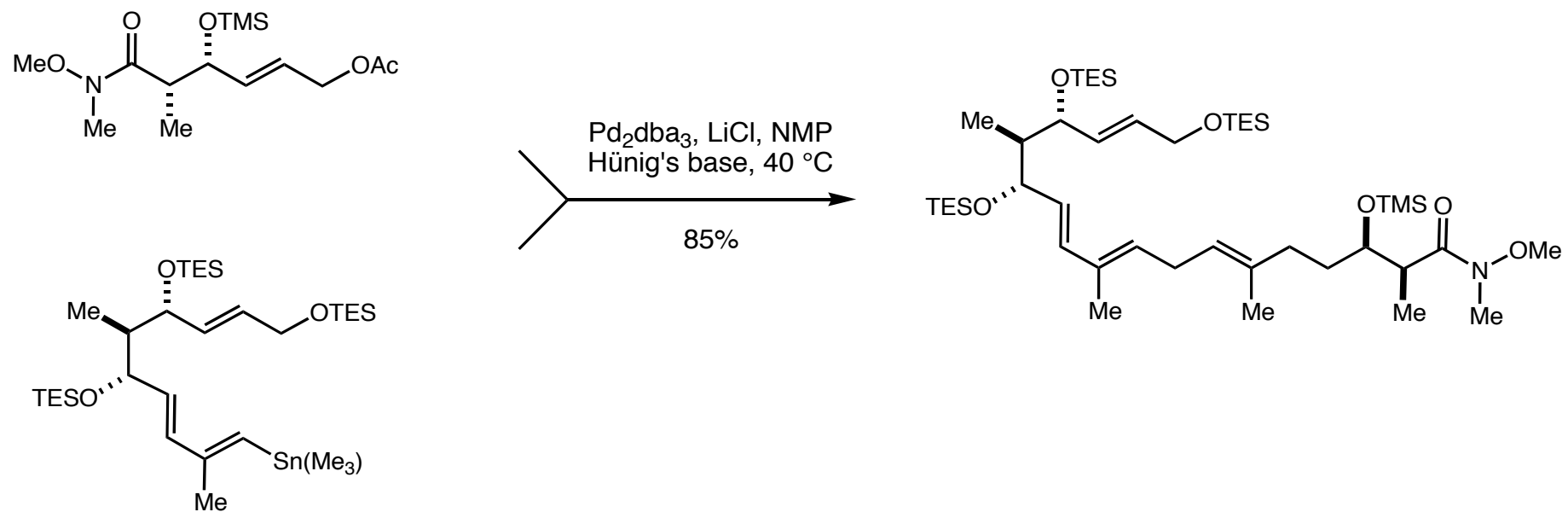
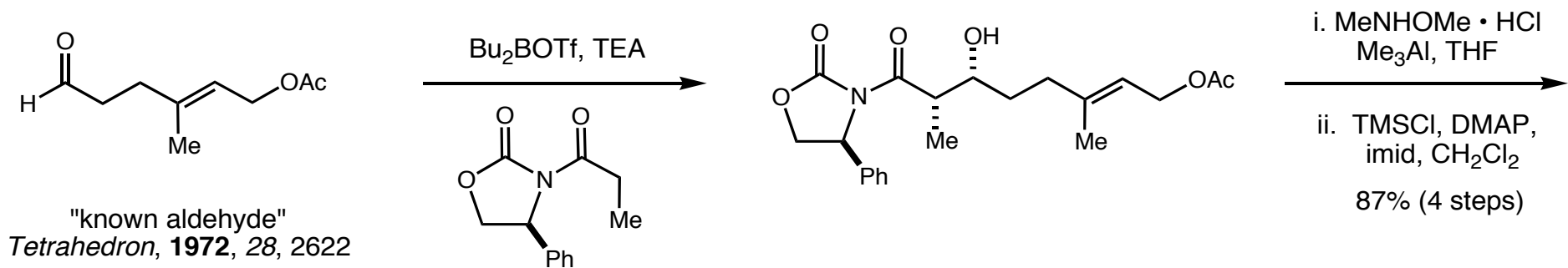
featuring tandem TADA reactions



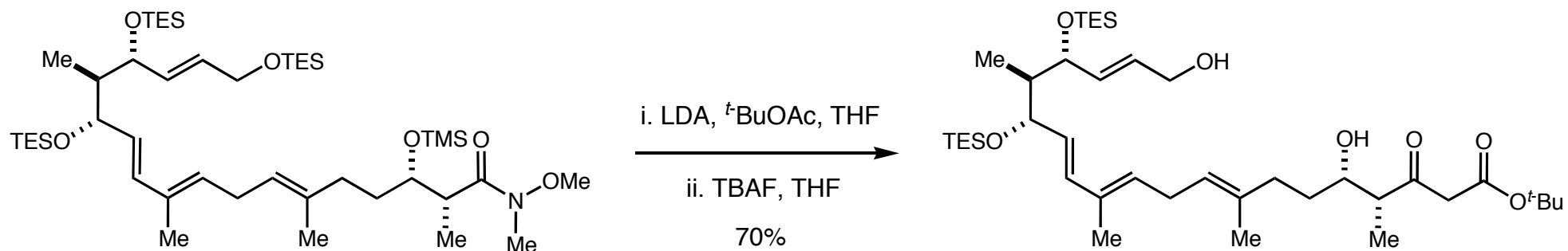
## Synthesis of $\pi$ -allyl Stille Coupling Fragment



## The $\pi$ -allyl Stille Coupling of the Aldol Fragments



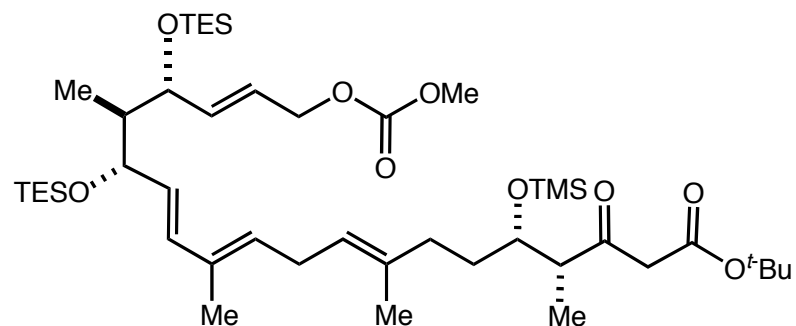
## Trost-Tsuji Coupling to the 19-Membered Macrocycle



i. MeOCOCl, pyridine

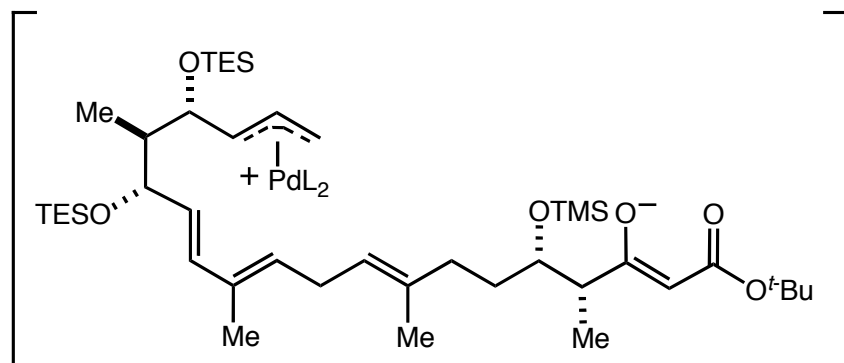
ii. TMS, imid,  $\text{CH}_2\text{Cl}_2$

88%

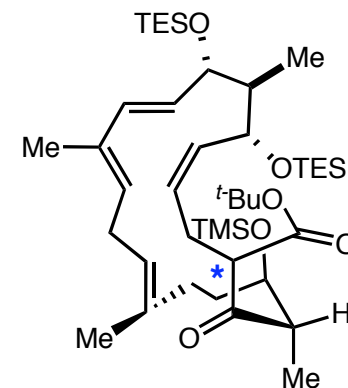


$\text{Pd}_2\text{dba}_3$  (10 mol%)  
THF (0.005 M), 40 °C

$\text{CO}_2, ^-\text{OMe}$

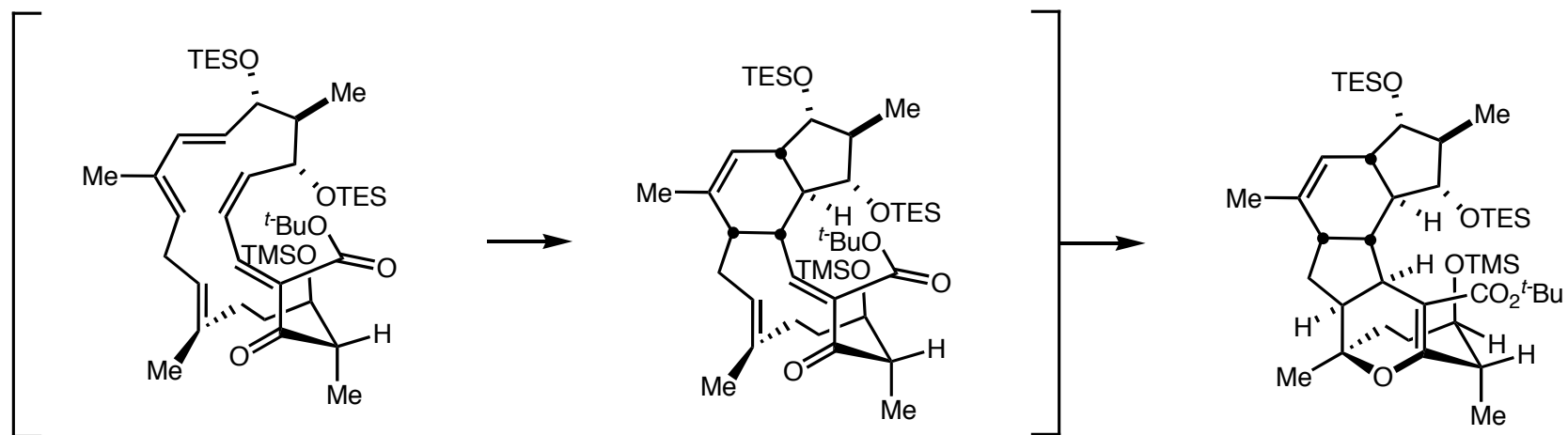
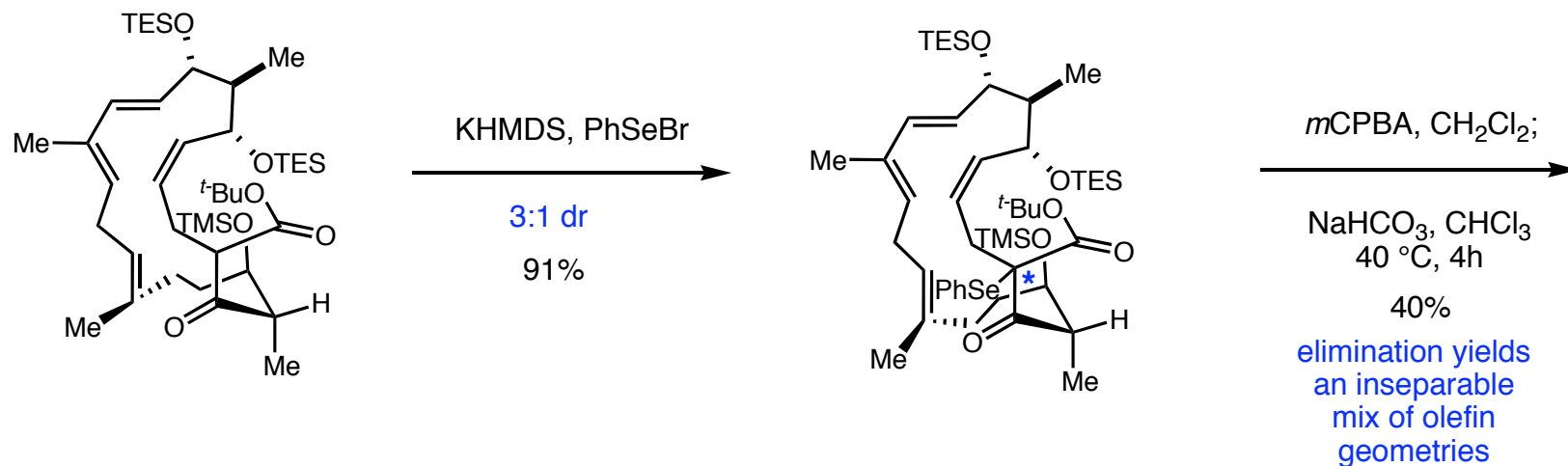


80%



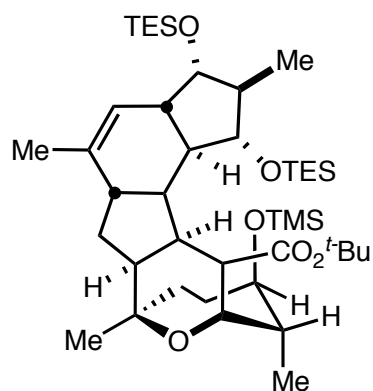
single diastereomer  
(configuration at C19 was not determined)

## Tandem Diels-Alder Sequence



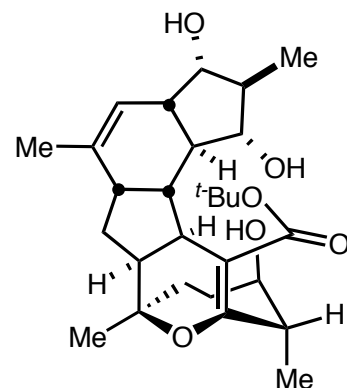
"two byproducts...the majority of the mass balance, are presumably formed from the Z-isomer"

## Completion of the Synthesis of (+)-FR182877



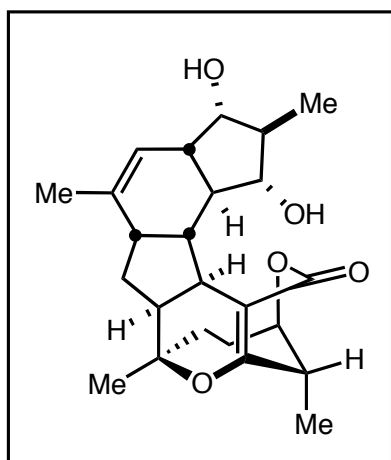
i. PPTS, MeOH, rt

ii. TFA:CH<sub>2</sub>Cl<sub>2</sub> (1:9)



EDC, DMAP,  
CH<sub>2</sub>Cl<sub>2</sub>, rt

63% (3 steps)



### ■ Demonstrated the gram scale synthesis of the natural enantiomer (-)-FR182877

Limitation of this synthesis was the undesired Z-isomer in the selenium-based desaturation

60g of dienyl stannane and 47g the allylic acetate were used to synthesize 3.2g of the natural product

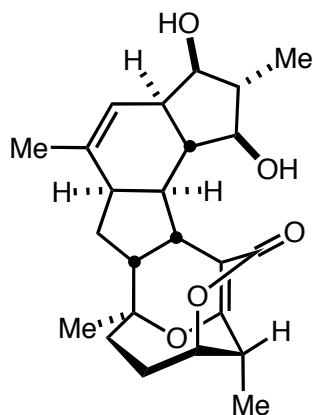
Sorensen:  $[\alpha]_D^{23} = +5.7$

Fujisawa:  $[\alpha]_D^{23} = -3.5$



## *Adventures in Synthesis: Comparative Syntheses of FR182877*

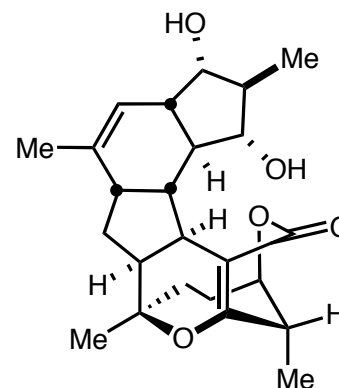
- Both successful strategies included a cascade Diels-Alder sequence to yield the hexacyclic frame of the natural product



**(-)-FR182877**

### **Evans Synthesis**

17 linear steps  
6.04% yield  
84.8% avg.yield/step



**(+)-FR182877**

### **Sorensen Synthesis**

22 linear steps  
2.09% yield  
83.9% avg.yield/step