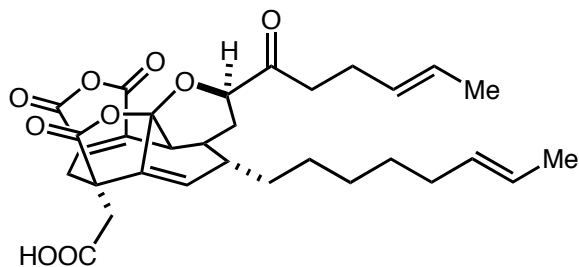
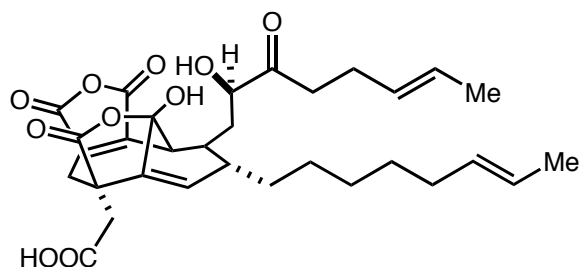


Comparative Syntheses of the CP-molecules: A focus on the Fukuyama and Shair strategies along with a brief look at key bond forming reactions developed by Nicolaou and Danishefsky



CP-263,114/phomoidride B



CP-225,917/phomoidride A

Jamie Tuttle  
MacMillan Group  
November 2, 2005

Lead Material: Spiegel, D. A.; Njardarson, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691.  
Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825.  
Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.

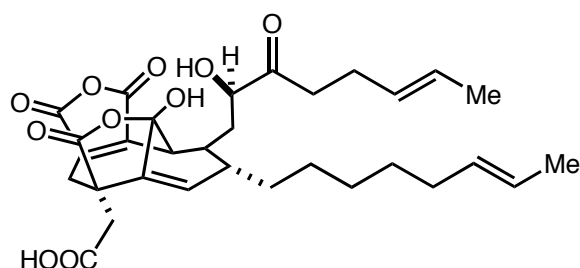
## A bit of background

### ■ Isolation of the molecules

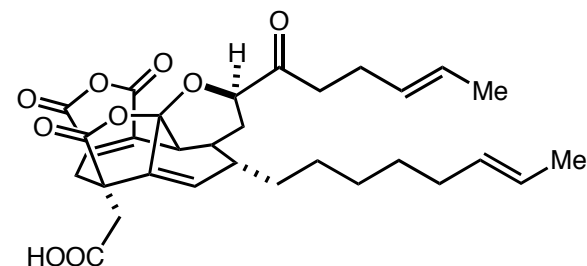
- Takushi Kaneko's group at Pfizer originally reported the structure determined via NMR.
- Derived from an unidentified fungus that afflicts the Texas juniper tree.



An afflicted twig



1, CP-225,917

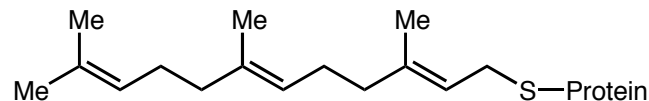


2, CP-263,114

- Only small amounts were obtainable using fermentation: 15 L broth produced 31 mg of CP-225,917 and 18 mg of CP-263,114 that were isolated by reverse HPLC.
- Characterization was achieved using NMR and mass spectrometry.

### ■ Therapeutic potential

- Molecules found to inhibit Ras farnesyl transferase: **1** IC<sub>50</sub> = 6 μM, **2** IC<sub>50</sub> 20 μM  
Importance: Farnesylation of ras protein induces membrane localization that causes cell growth.



Farnesylated Protein

- Inhibit squalene synthase: **1** IC<sub>50</sub> = 43 μM, **2** IC<sub>50</sub> = 160 μM  
Importance: Disrupts cholesterol biosynthesis starting from farnesyl pyrophosphate.

Dabrah, T. T.; Kaneko, T.; Masefski, Jr. Walter; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.  
Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70.

## The big players

- The following are the only souls to complete total syntheses of CP molecules to date



Prof. Tohru Fukuyama  
*J. Am. Chem. Soc.* **2000**, 122, 7825.  
21 linear steps, 2.2% overall yield



Prof. Matthew D. Shair  
*J. Am. Chem. Soc.* **2000**, 122, 7424.  
17 linear steps, 0.4% overall yield



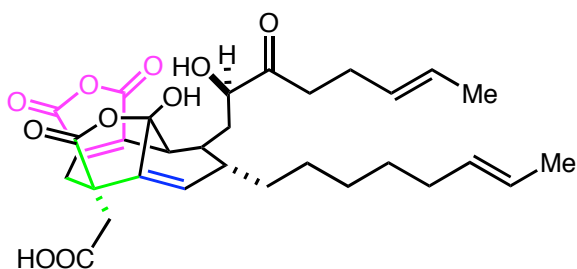
Prof. Kyriacos C. Nicolaou,  
first to publish the total synthesis  
review: *Angew. Chem. Int. Ed.* **2002**, 41, 2678.  
*Angew. Chem.* **1999**, 111, 1774.  
*Angew. Chem.* **1999**, 111, 1778.  
47 linear steps, 0.02% overall yield



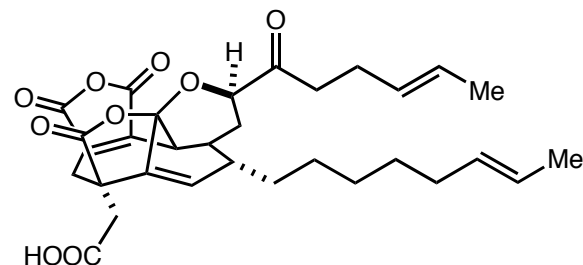
Prof. Samuel J. Danishefsky  
*Angew. Chem. Int. Ed.* **1998**, 37, 1877.  
*Angew. Chem. Int. Ed.* **1998**, 37, 1880.  
*Angew. Chem. Int. Ed.* **1999**, 38, 1485.  
*Angew. Chem. Int. Ed.* **1999**, 38, 3197.  
*Angew. Chem. Int. Ed.* **2000**, 39, 4509.  
47 linear steps, 0.003% overall yield

## A closer look at the unique molecular architecture

### ■ A potpourri of complexity



1, CP-225,917

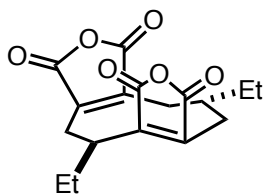


2, CP-263,114

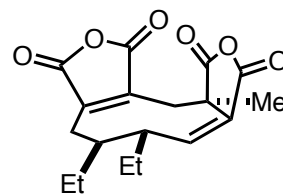
- A bridgehead olefin
- A quaternary carbon center held in a caged spirolactone
- A maleic anhydride moiety
- Two pendant olefinic side chains

### ■ Similar classes of molecules

- Shares structural homology with glauconic acid and byssochlamic acid



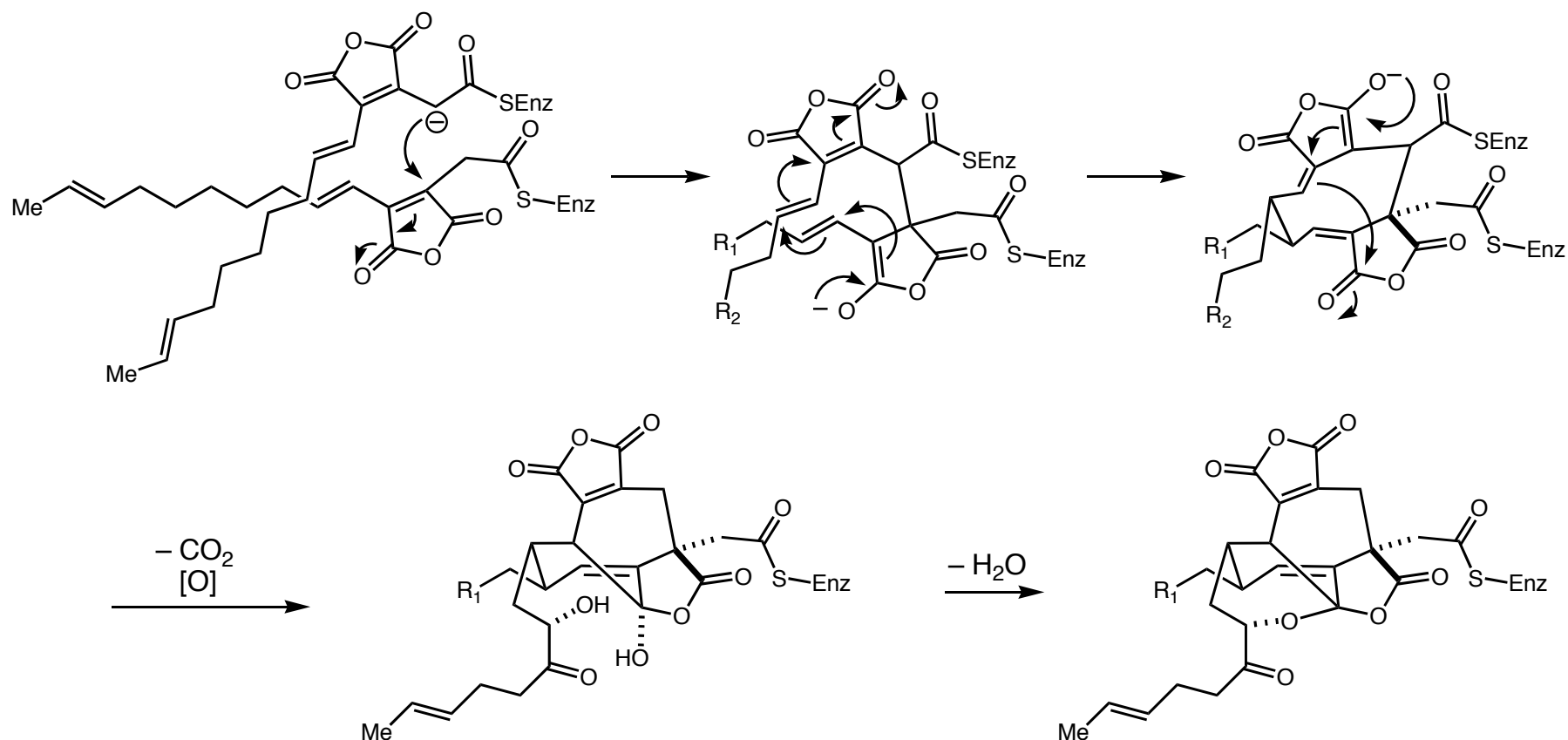
byssochlamic acid  
carcinogenic



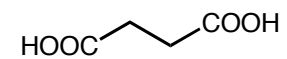
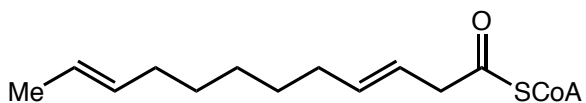
glauconic acid  
no known bioactivity

Spiegel, D. A.; Njardson, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691.

## Proposed Biosynthesis

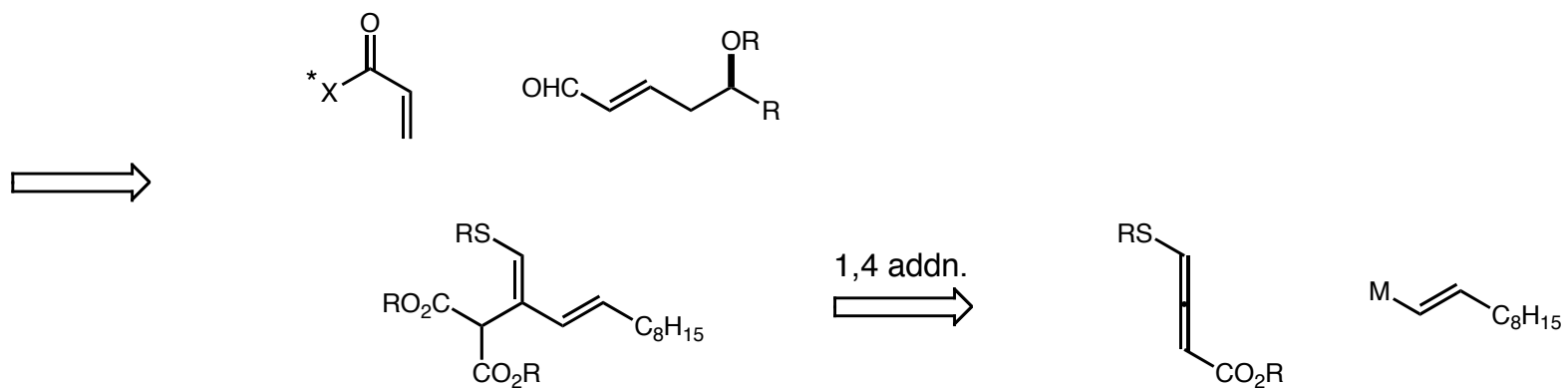
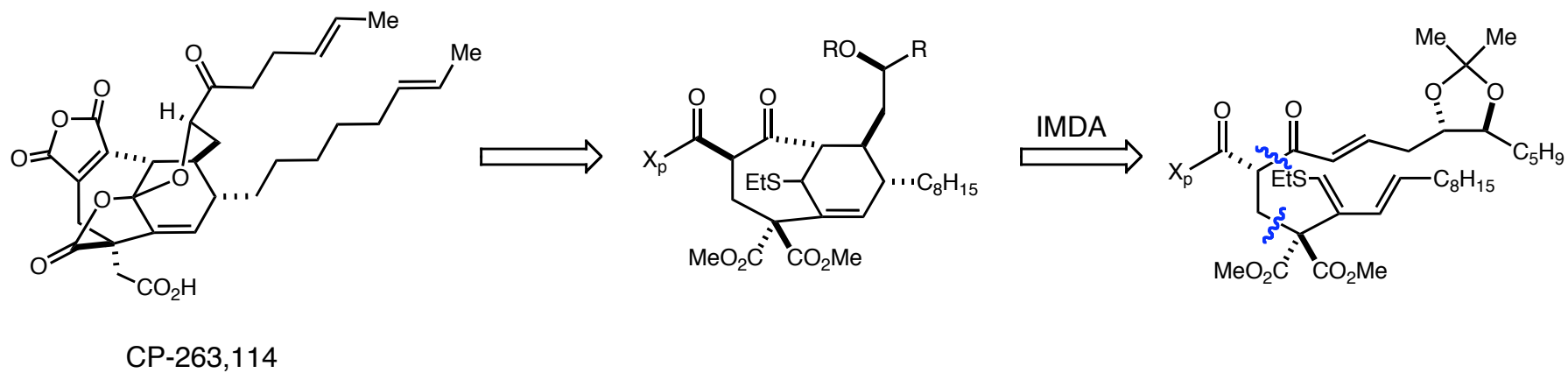


- A series of elegant labelling studies indicated all the carbons for the phomoidrides are derived from succinic acid and an acetyl-CoA derivative.



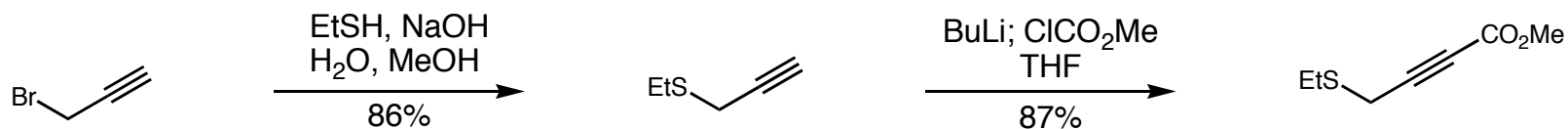
Sulikowski, G. A. *et al. J. Org. Chem.* **2000**, 65, 337.  
 Sulikowski, G. A. *et al. Org. Lett.* **2002**, 4, 1447.  
 Spencer, P. *et al. J. Am. Chem. Soc.* **2000**, 122, 420.

## Fukuyama's retrosynthetic analysis

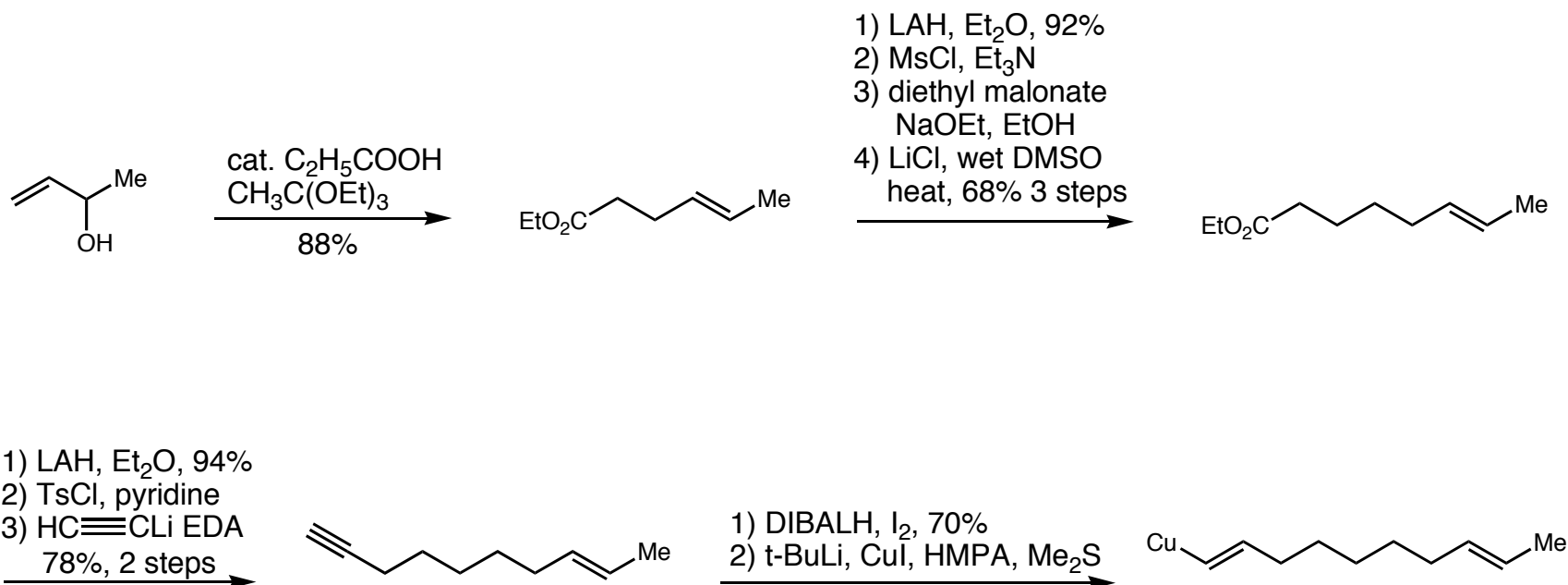


## Fukuyama's synthesis: Preparation of starting materials

### ■ Preparation of the alkynylester

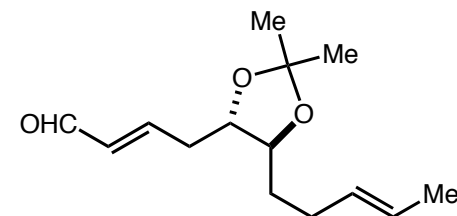
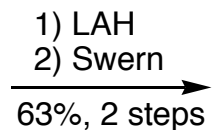
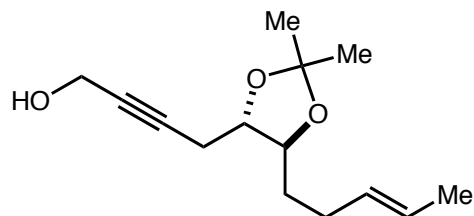
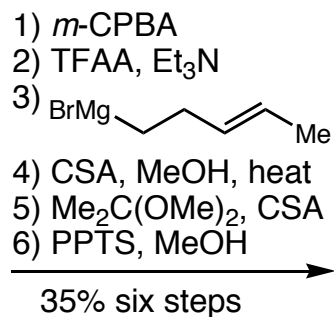
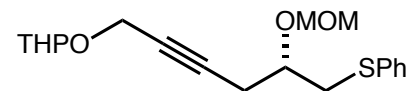
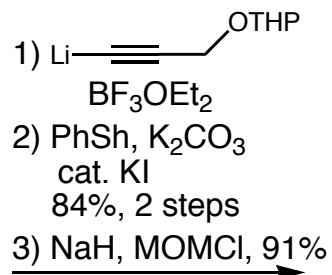
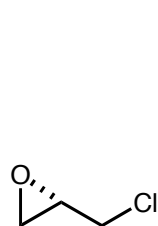


### ■ Preparation of the vinyl cuprate

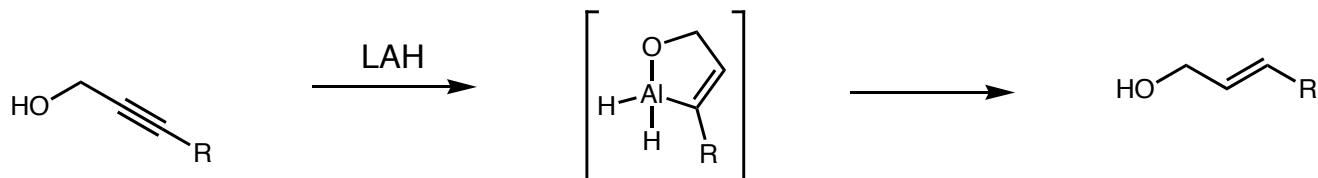


## Fukuyama's synthesis: Preparation of starting materials con't.

### ■ Preparation of the protected diol

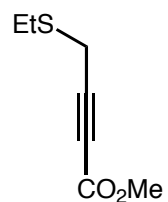


- Mechanism for *trans* selectivity

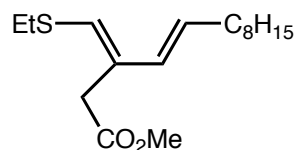
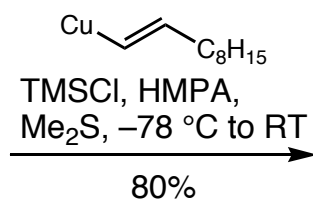
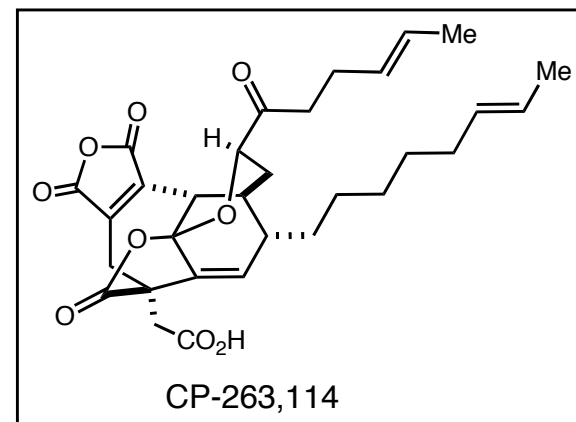
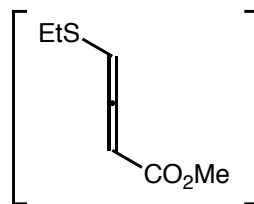




## Fukuyama's forward synthesis

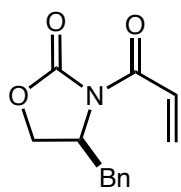
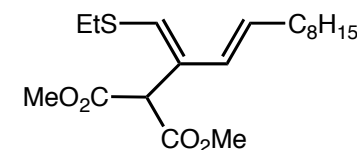


cat. DBU, THF, 0 °C



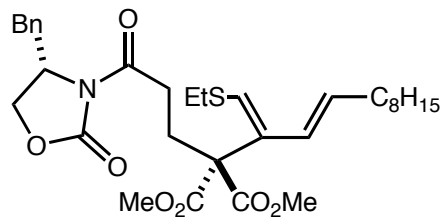
LiHMDS, THF;  
CICO2Me, -78 °C

84%

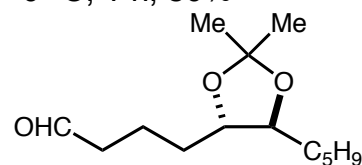


cat. Cs2CO3  
CH3CN

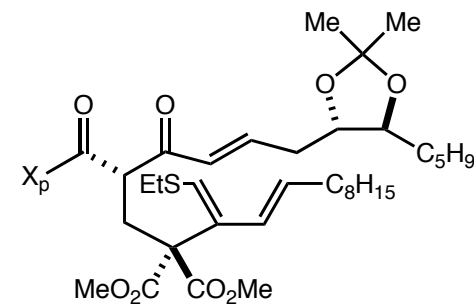
82%



1) Bu2BOTf, Et3N, CH2Cl2;  
 0 °C, 1 h, 80%



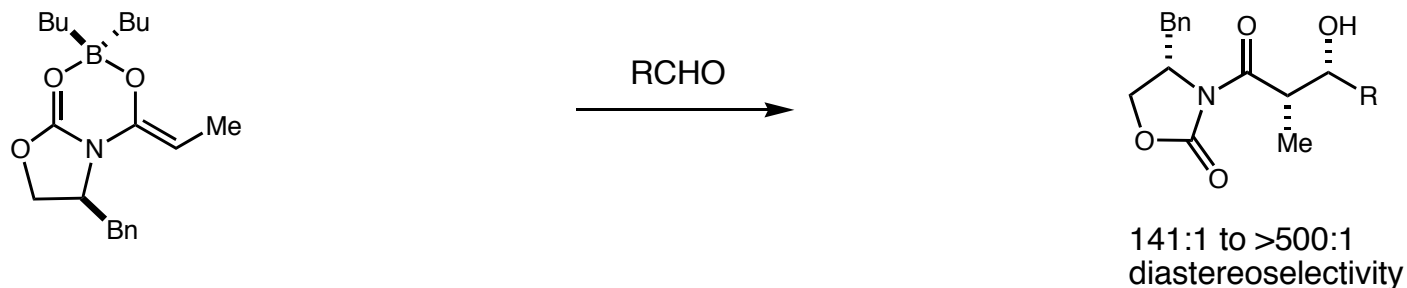
2) SO3-Py, DMSO-i-Pr2NEt  
 1 h 75%



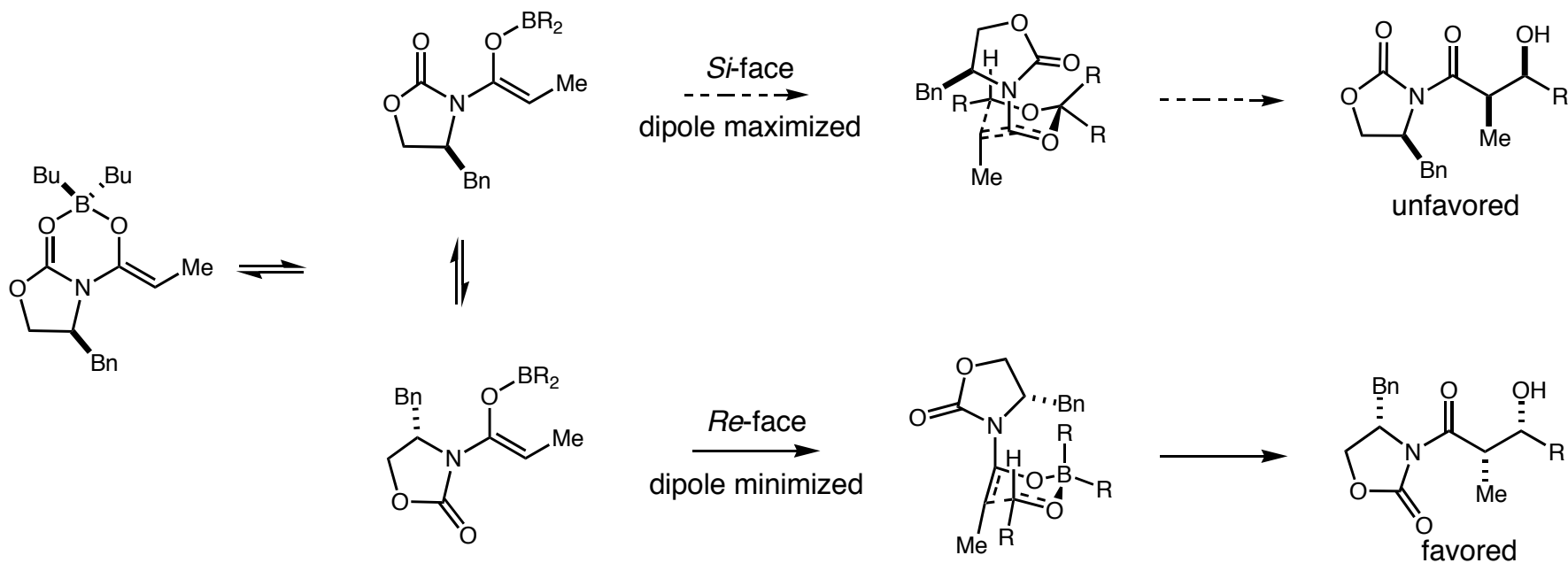
single diastereomer

## Fukuyama's forward synthesis

### General scheme for boron mediated diastereoselective aldol reaction using Evans' auxiliary



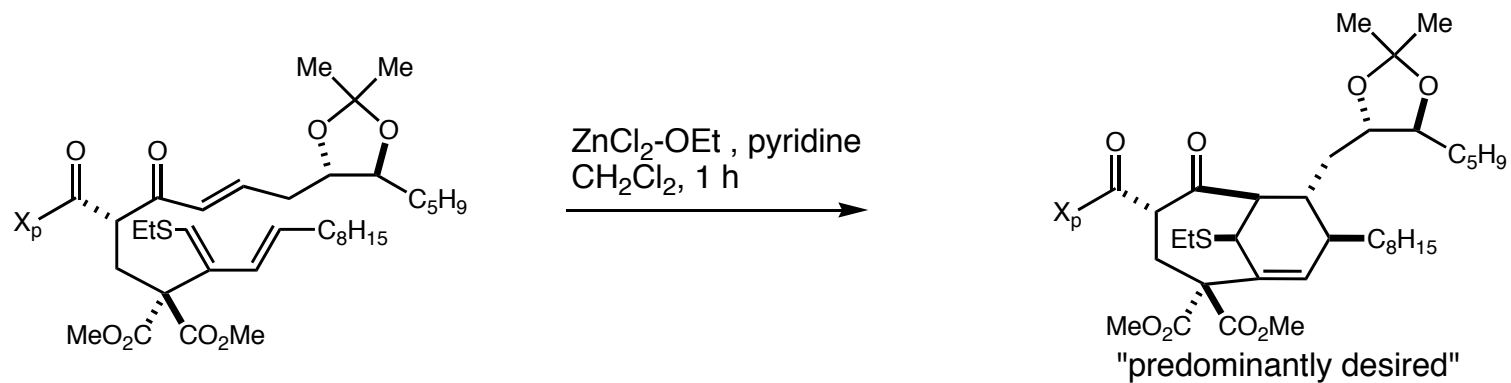
Why? Consider the proposed transition states.



Evans, D. A.; Bartroli, J. A.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

## Details of the key step

### ■ The key step

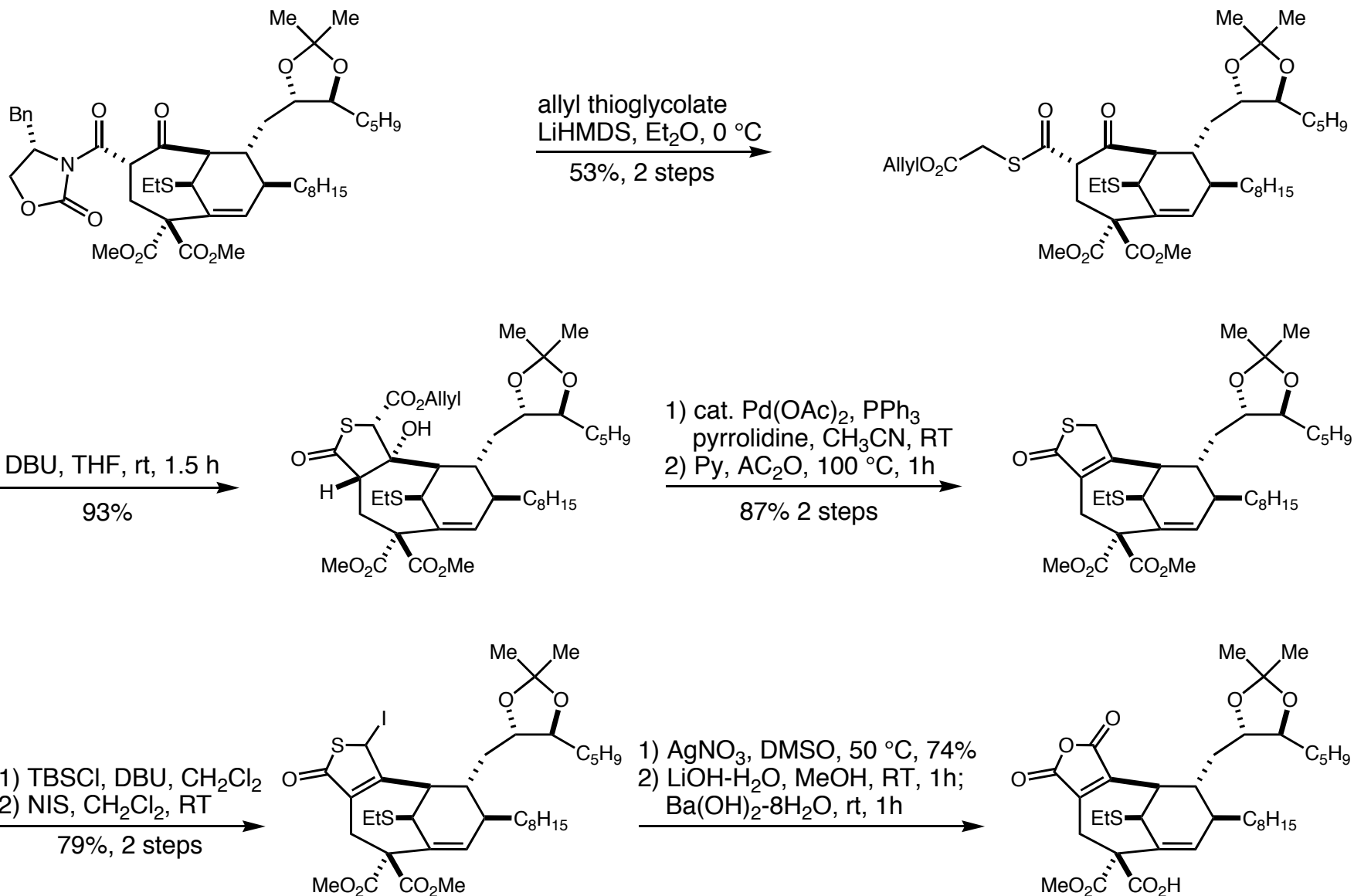


- Pyridine acts as a buffer to prevent diene isomerization during the Diels-Alder reaction.
- Presumably the C12 stereocenter provides remote stereocontrol.
- Yield not given for this step.
- First case in literature where acyclic stereocontrol produces a bridgehead adduct.

For other information regarding acyclic stereocontrol in Diels-Alder reaction see:  
Evans, D. A. *et al. Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2119. and references therein

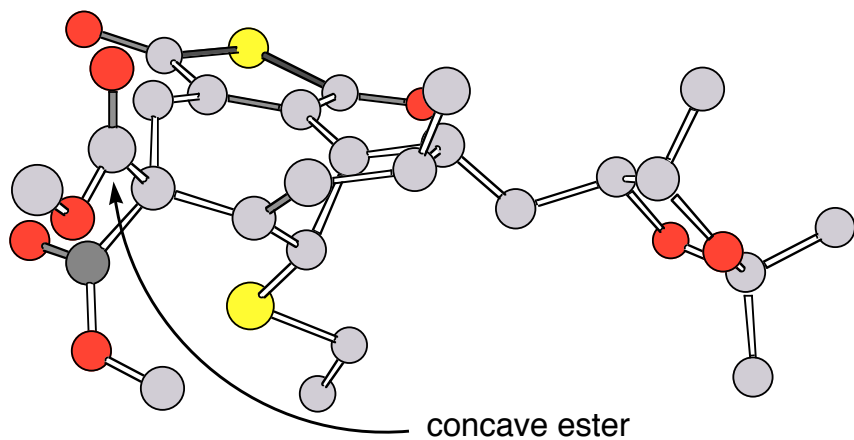
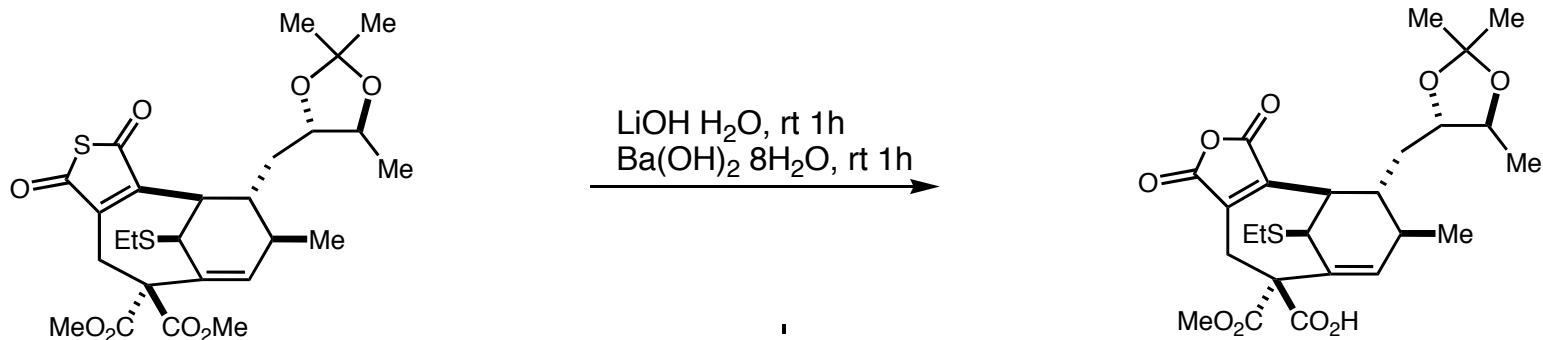
## Fukuyama's Synthesis

■ The synthesis continues. . .

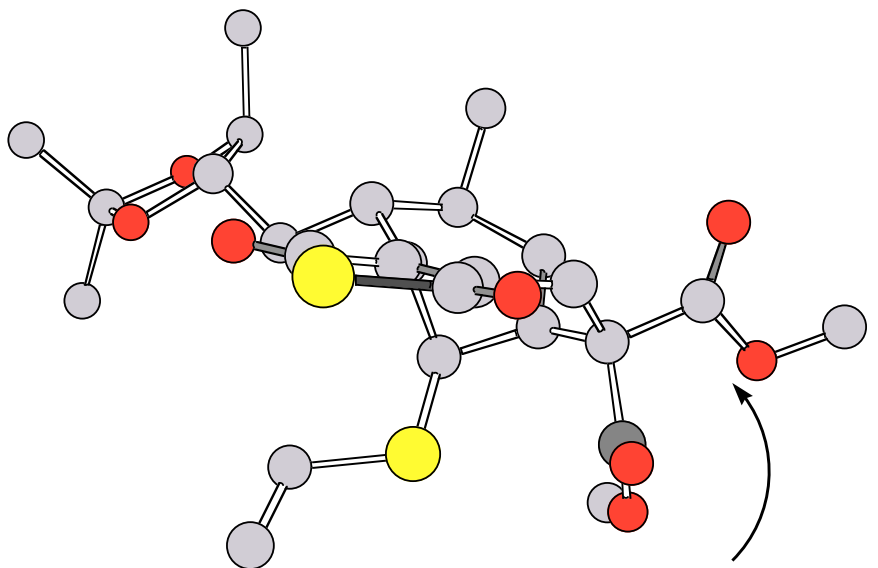


# Fukuyama's synthesis: 3-d analysis of the hydrolysis step

## ■ Concave versus convex ester



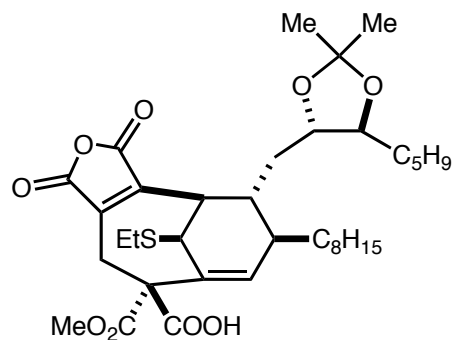
- This concave face ester is less sterically shielded
- The thioalkyl group shields the other ester



- Same molecule, different view

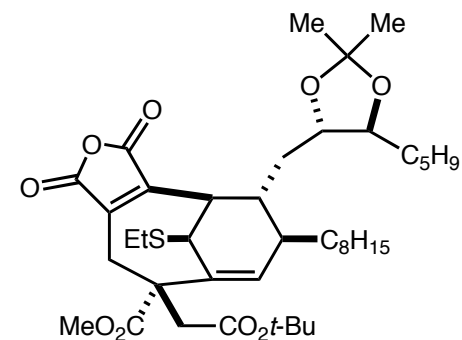
## Fukuyama's Synthesis

### The last transformations



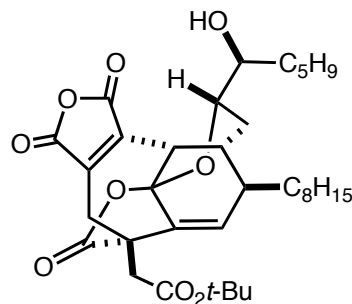
1)  $(\text{COCl})_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt;  
 $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ,  $-15\text{ }^\circ\text{C}$   
2)  $\text{PhCO}_2\text{Ag}$ ,  $t\text{-BuOH}$ ,  $50\text{ }^\circ\text{C}$

54%, 3 steps



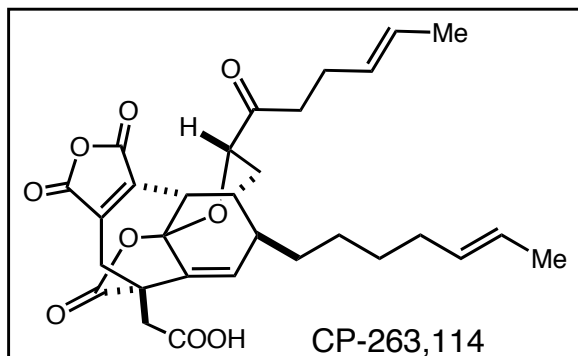
1) mCPBA,  $\text{CH}_2\text{Cl}_2$ ,  $-20\text{ }^\circ\text{C}$   
2) TFAA,  $i\text{-Pr}_2\text{NEt}$ , toluene,  $0\text{ }^\circ\text{C}$   
3) 80% aq. AcOH,  $70\text{ }^\circ\text{C}$

51%, 3 steps



Jones ox.,  $0\text{ }^\circ\text{C}$   
 $\text{HCO}_2\text{H}$ , rt

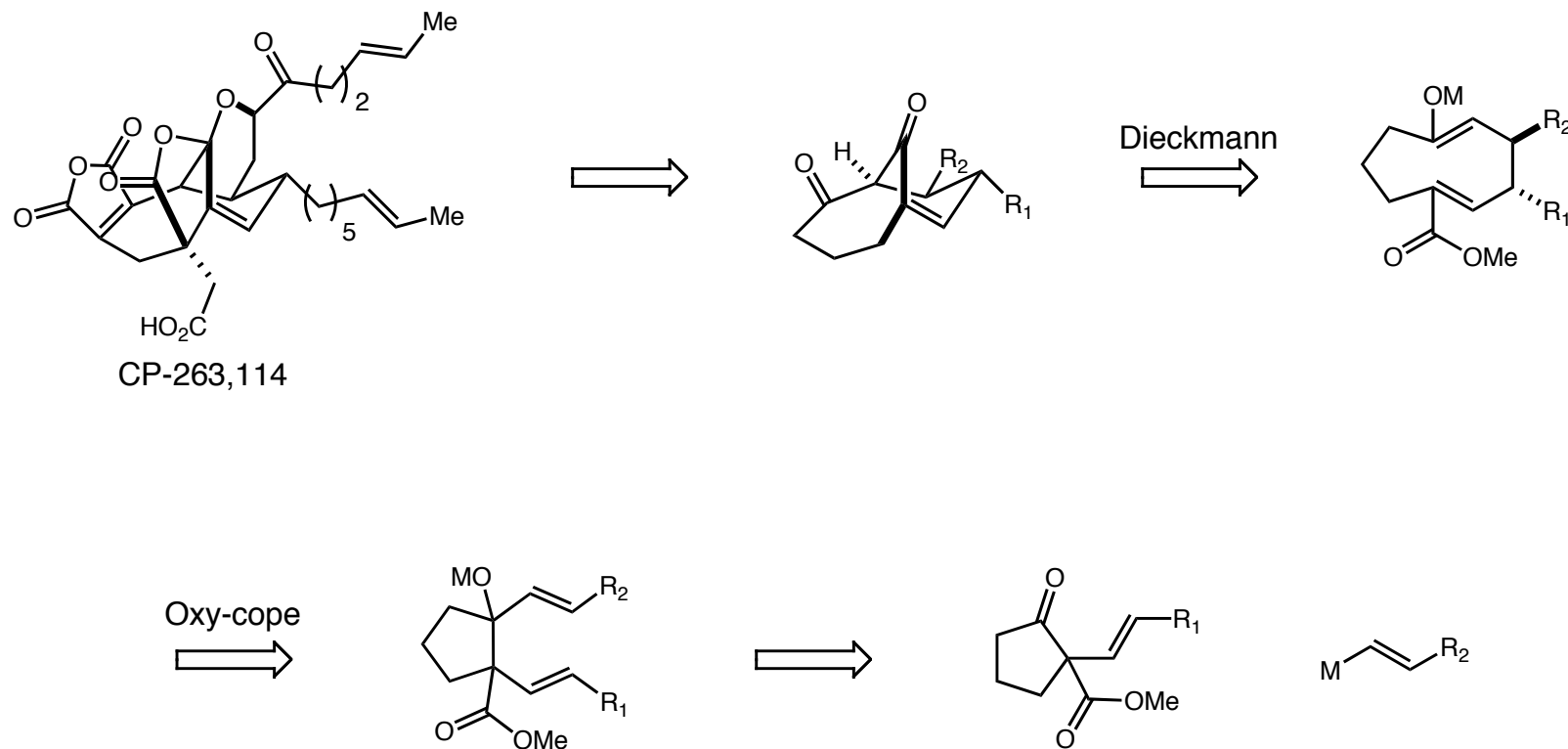
96% 2 steps



- Concluded that this absolute configuration is the same as the natural product.

## Shair's retrosynthesis

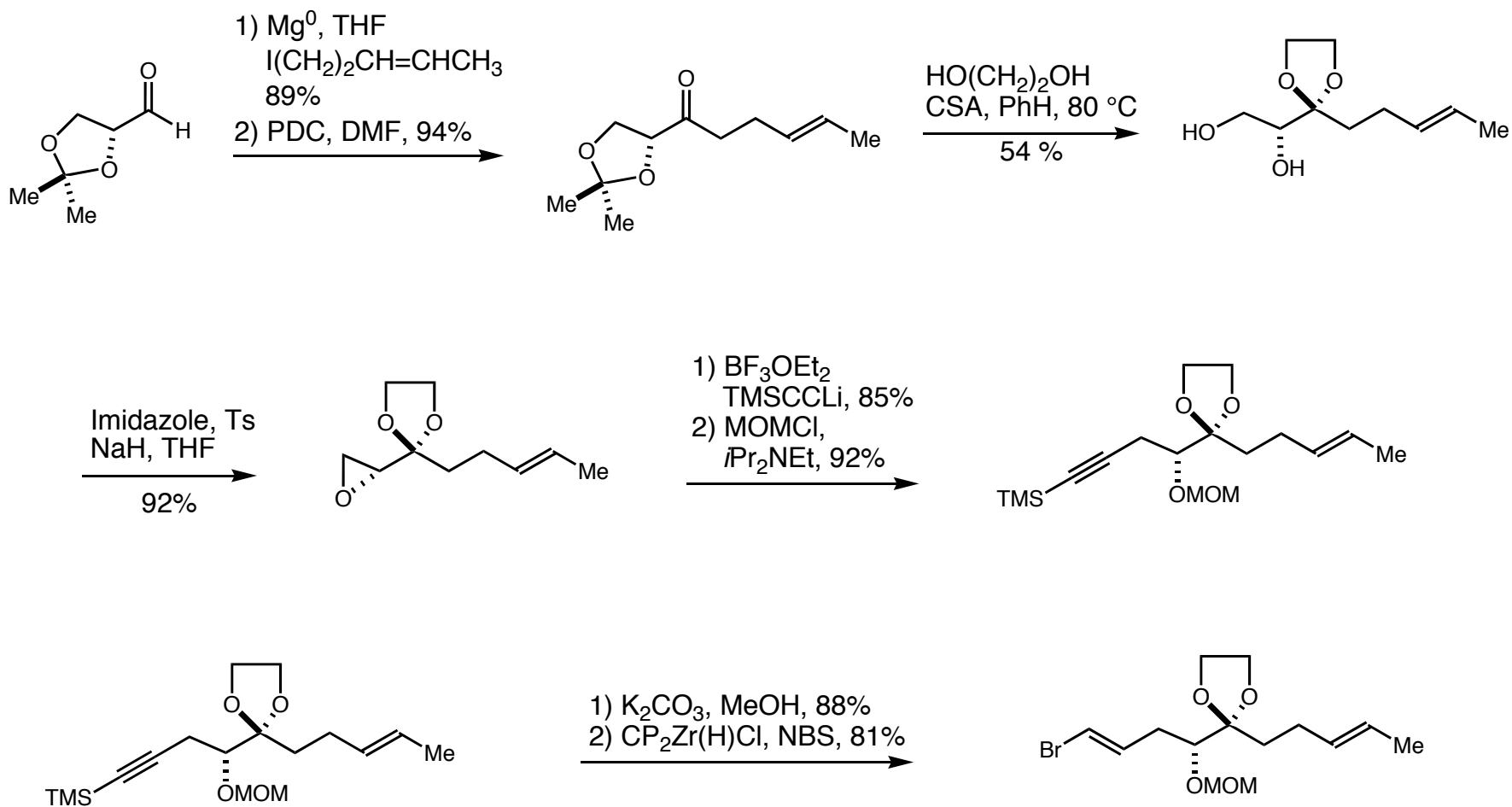
- Shair identifies an anion accelerated oxy-Cope rearrangement



Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.

## Shair's synthesis

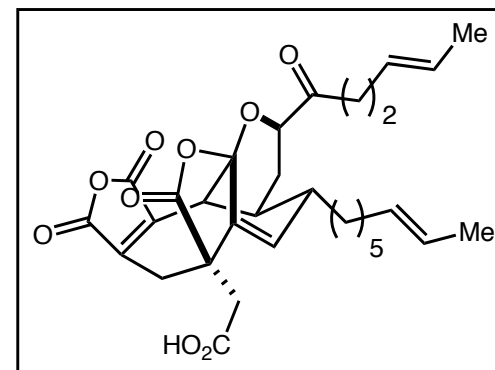
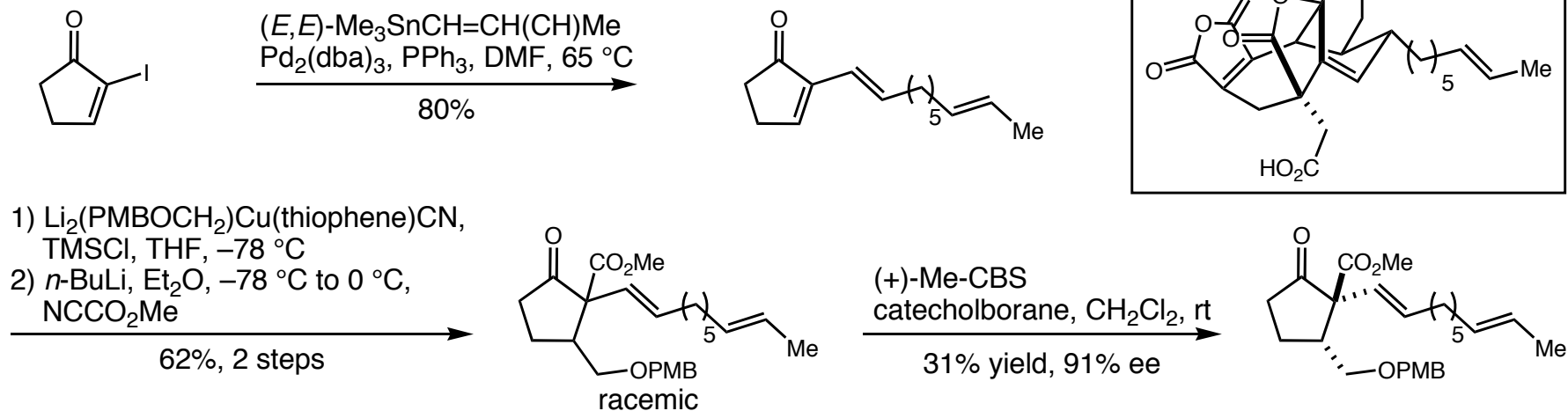
### ■ Preparation of starting materials



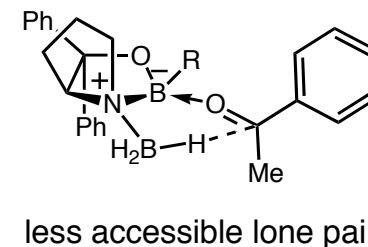
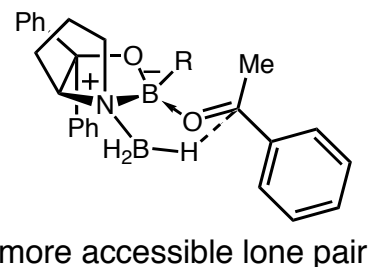
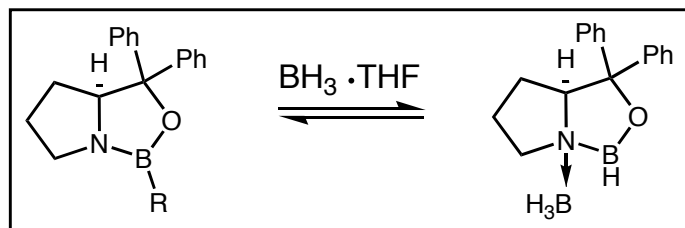


## Shair's Synthesis

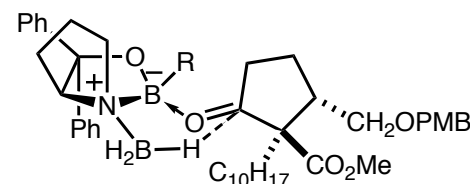
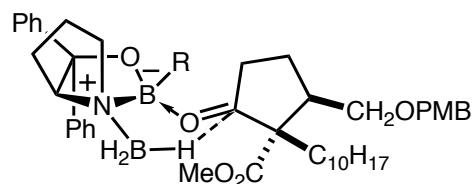
### Shair's preparation of the rearrangement precursor via kinetic resolution



### Mechanism and selectivity for CBS reduction



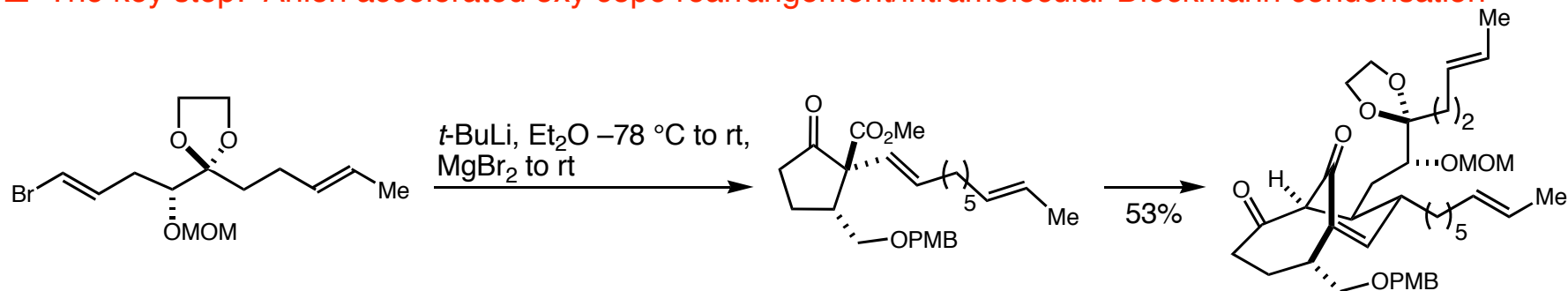
- Shair's intermediate



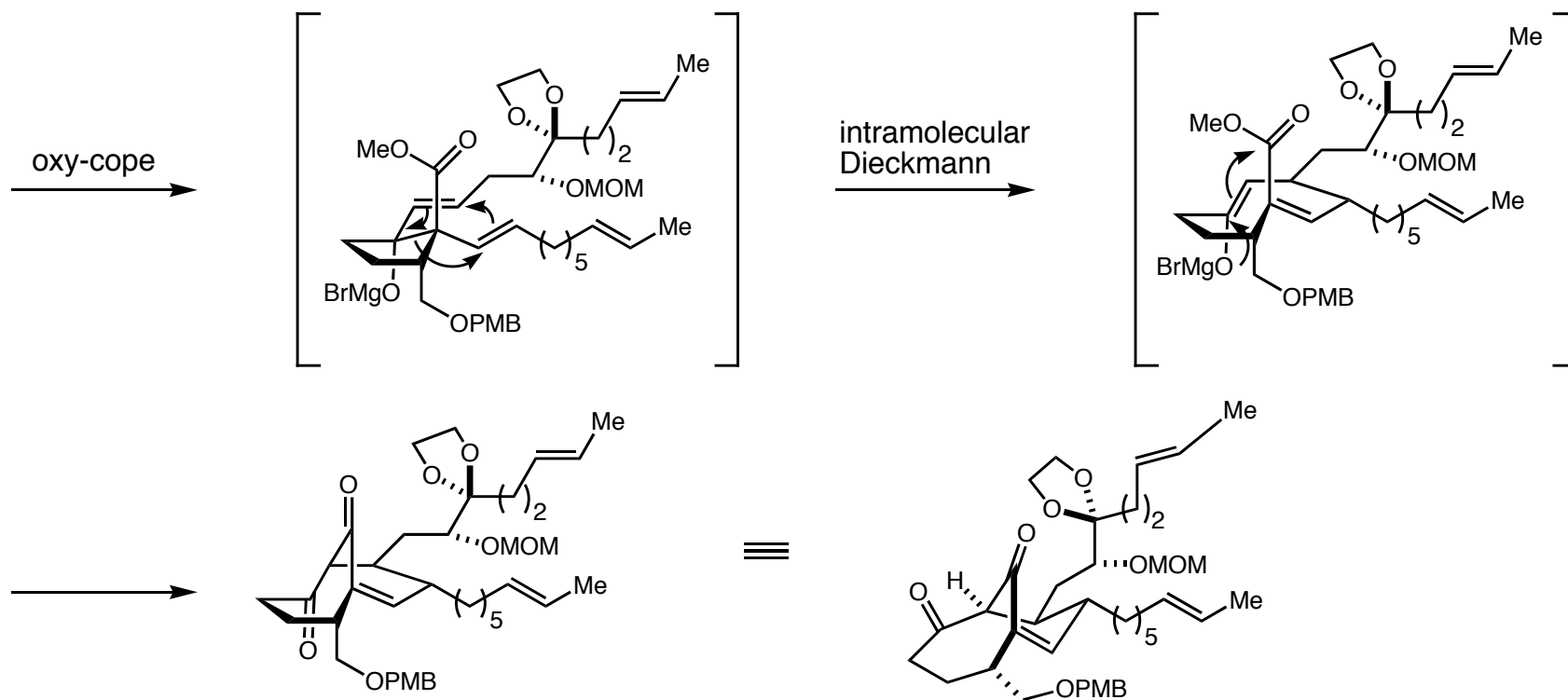
Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

## Shair's Synthesis

- The key step: Anion accelerated oxy cope rearrangement/intramolecular Dieckmann condensation



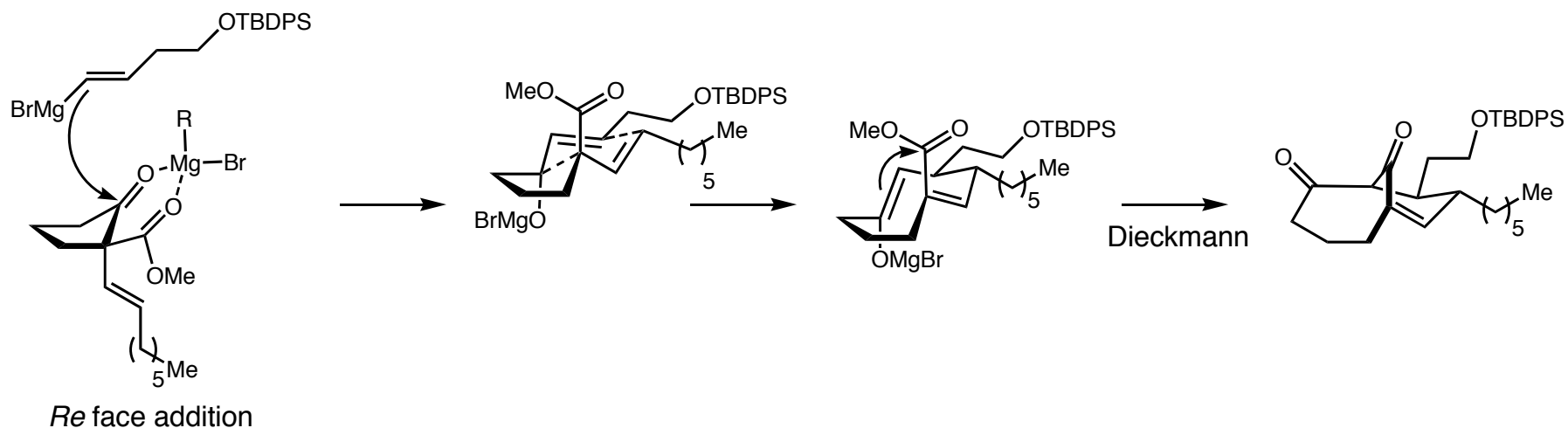
- The mechanism



For Anion Oxy-Cope: Evans, D. A.; Golob, A. M.; *J. Am. Chem. Soc.* **1975**, 97, 4765.

## Selectivity for the Shair Grignard Addition

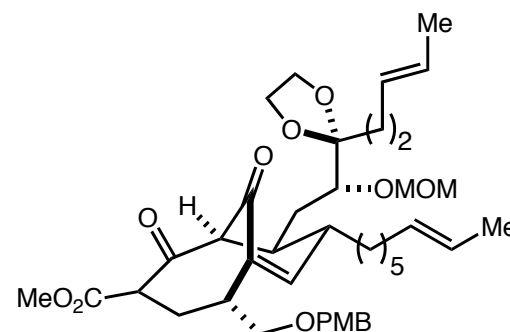
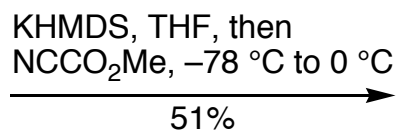
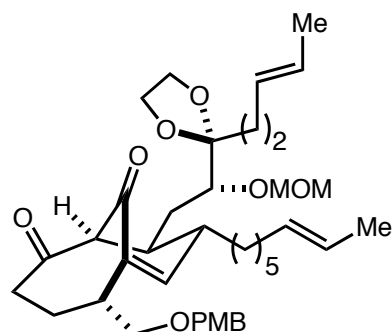
- A chelation model explains the approach of the nucleophile



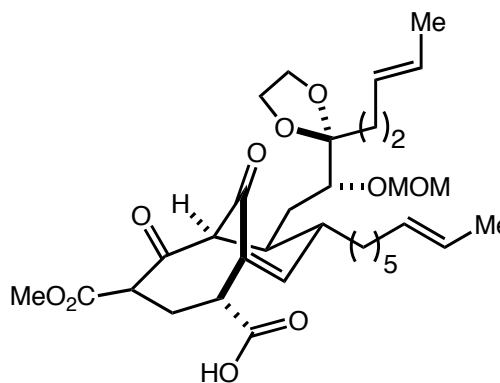
- Controls four stereochemical facets:
  - 1) C9 stereochemistry
  - 2) C10 stereochemistry
  - 3) C15-C16 trisubstituted double bond
  - 4) (*Z*) enolate geometry to afford transannular Dieckmann cyclization
- Interesting the analogous Li and Ce(III) based nucleophiles provided the 9 membered ring but did not effect the subsequent Dieckmann condensation.
- The olefin geometry of the alkene grignard reagent dicatates *cis/trans* relationship of alkyl chains.

# Shair's Synthesis

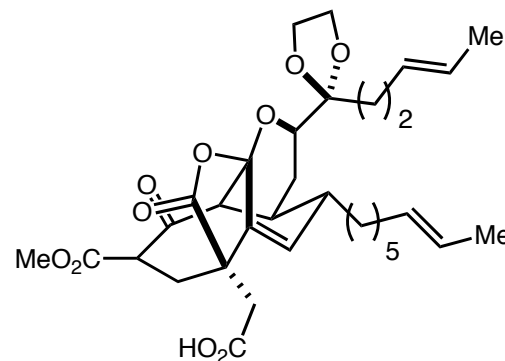
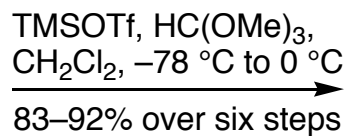
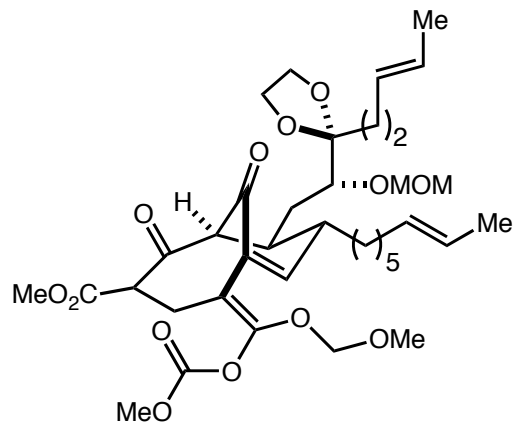
## Further into the synthesis



- 1) BCl<sub>3</sub>, -78 °C to -30 °C
- 2) Dess-Martin, pyr, H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, rt
- 3) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene, MeOH/H<sub>2</sub>O, rt

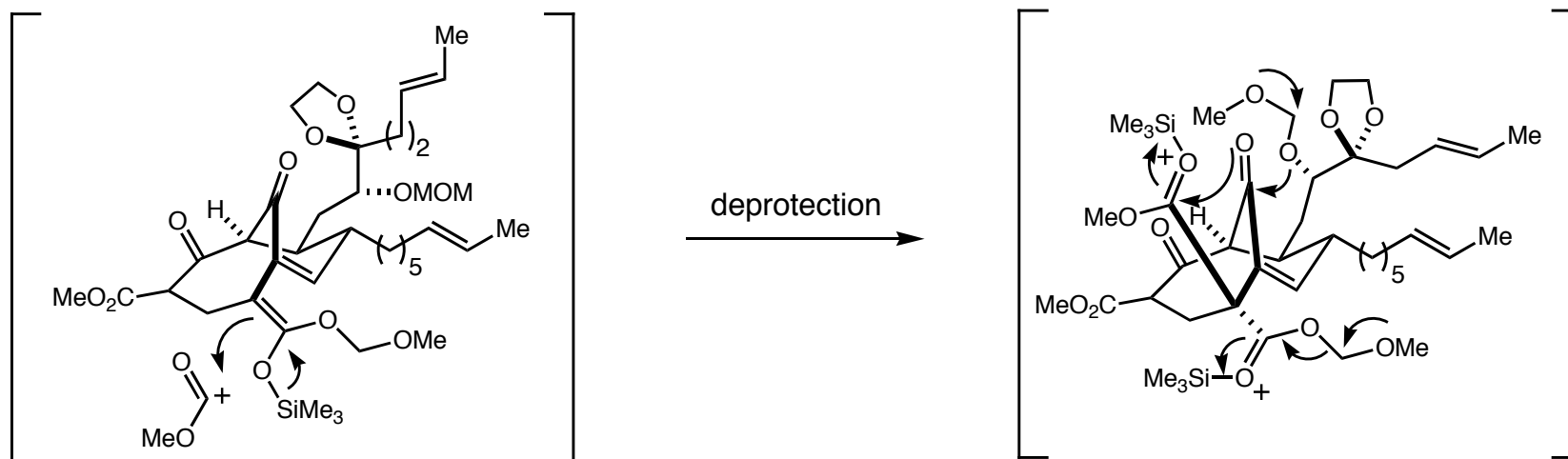
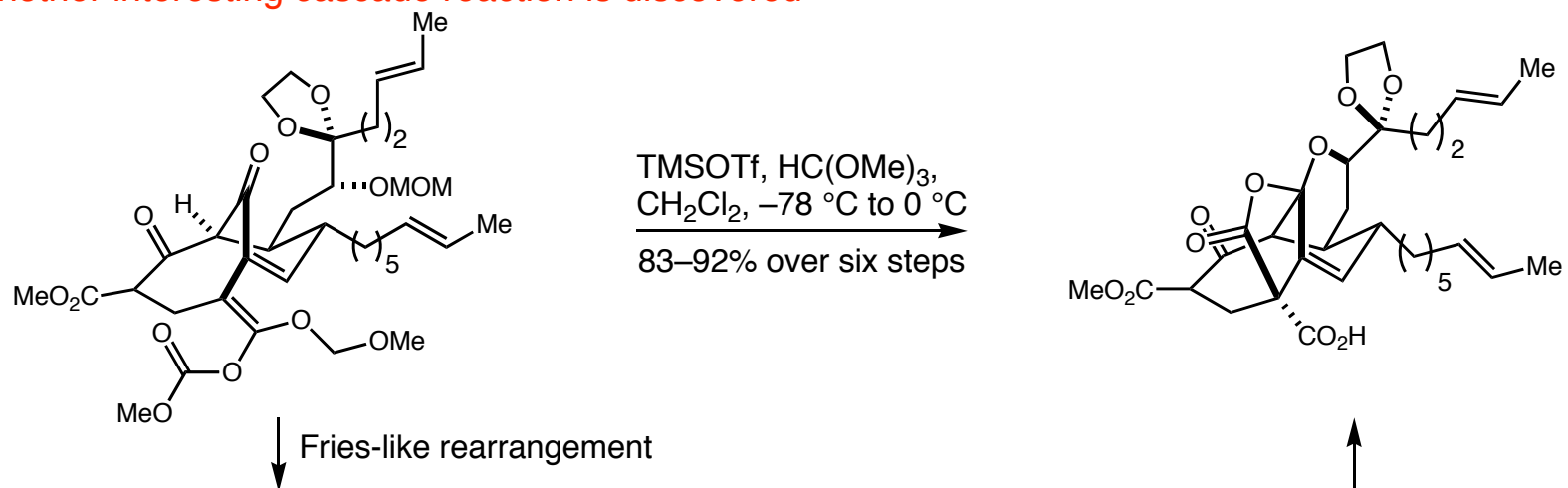


- 1) MOMCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt
- 2) KHMDS, THF, then NCCO<sub>2</sub>Me, -78 °C to 50 °C

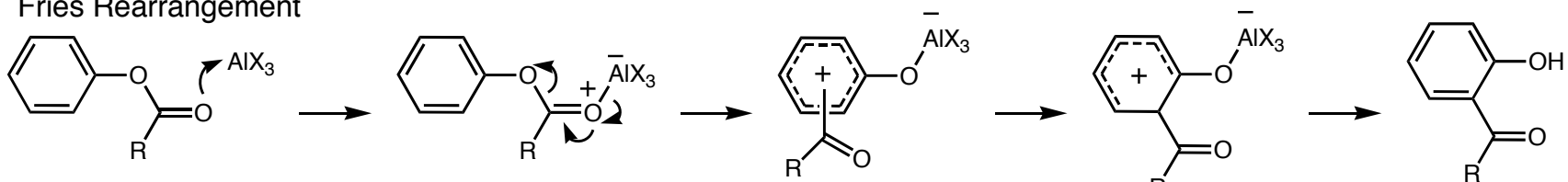


## Shair's Synthesis

■ Another interesting cascade reaction is discovered



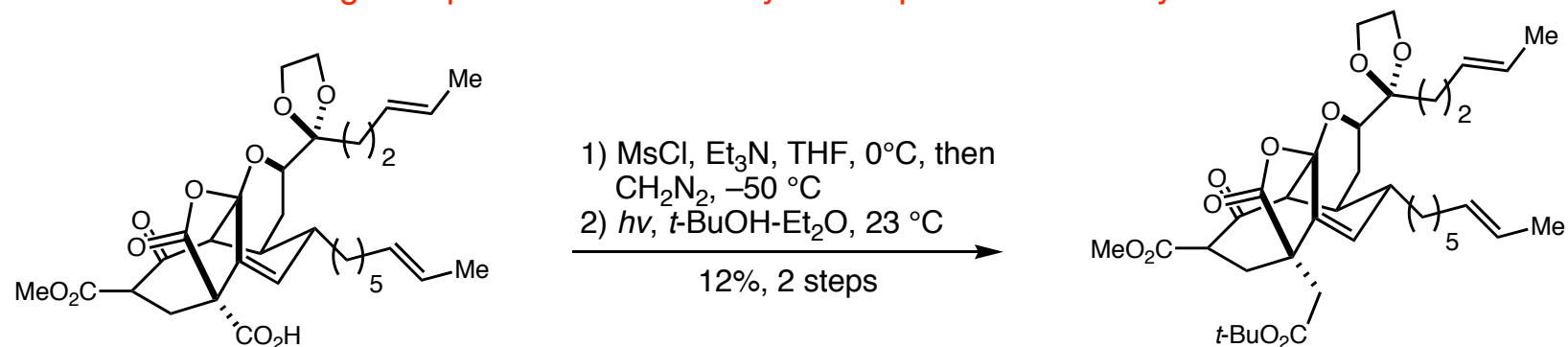
### Fries Rearrangement



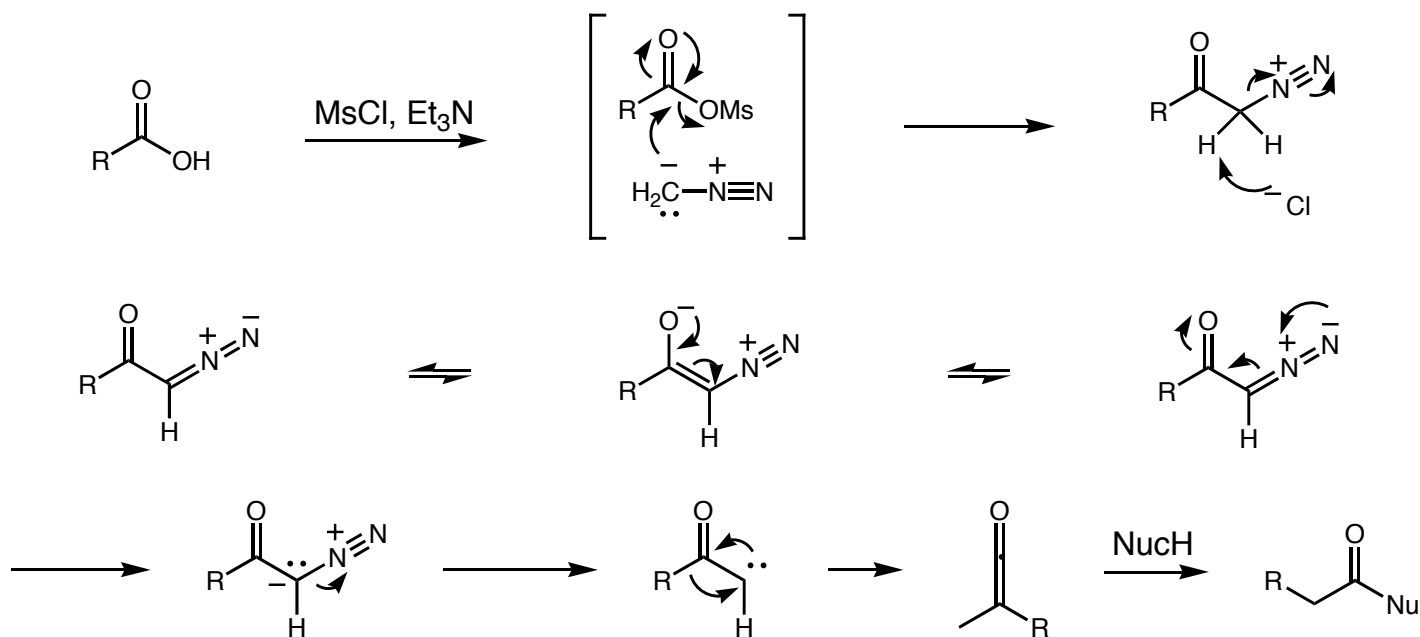
Cohen, N. *et al.* *J. Org. Chem.* **1978**, *43*, 3723.

## Shair's Synthesis

- Arndt-Eistert homologation proceeds inefficiently due to product instability



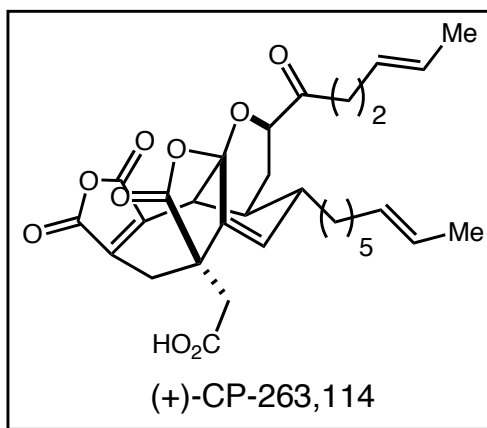
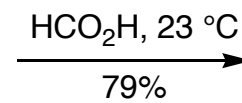
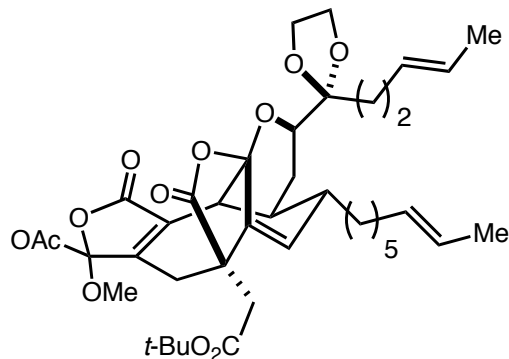
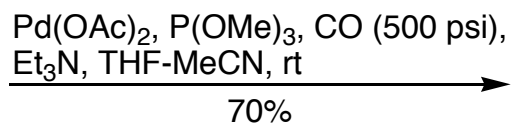
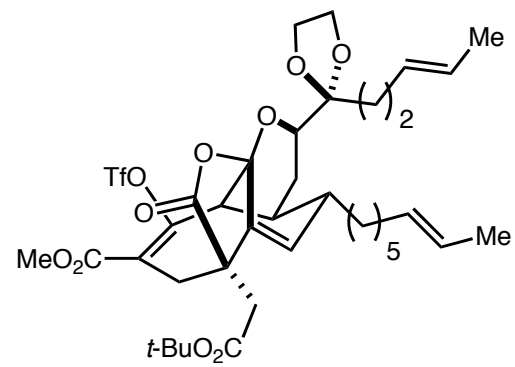
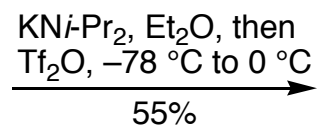
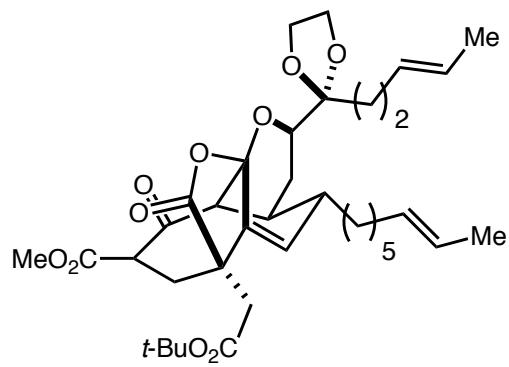
- Arndt-Eistert homologation mechanism



Arndt, F.; Eistert, B. *Org. React.* **1942**, 1, 38.

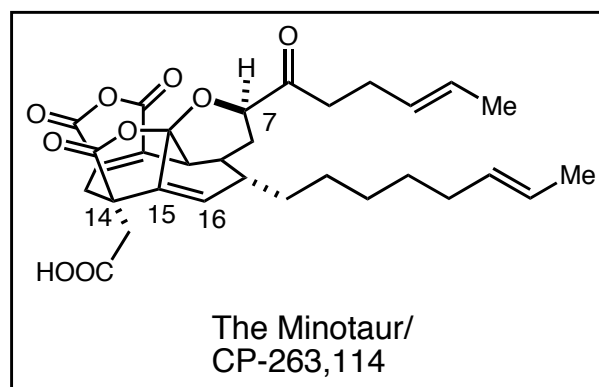
## Shair's Synthesis

### ■ The final steps of the synthesis



## Comparative analyses of key bond forming reactions

- A closer look at some interesting transformations derived from all the total syntheses



The four foci: C7 stereocenter, C15/C16 bridgehead double bond, carbocyclic core, C14 quaternary center

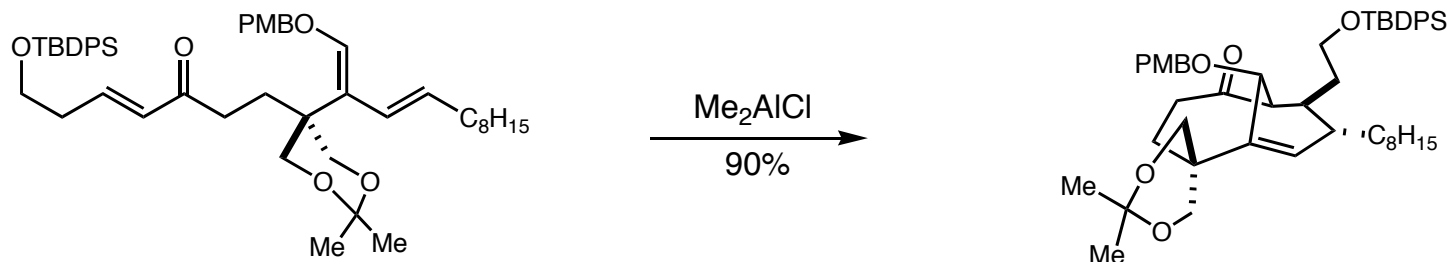
reminder:

	<u>Fukuyama</u>	<u>Shair</u>
1) C7 stereocenter	chiral starting materials	chiral starting materials
2) C15/C16 bridgehead	Diels Alder	oxy-cope/Dieckmann
3) carbocyclic core	Diels Alder	oxy-cope/Dieckmann
4) C14 quaternary carbon center	substrate control	stereoselective acyl transfer/ Arndt Eistert homologation



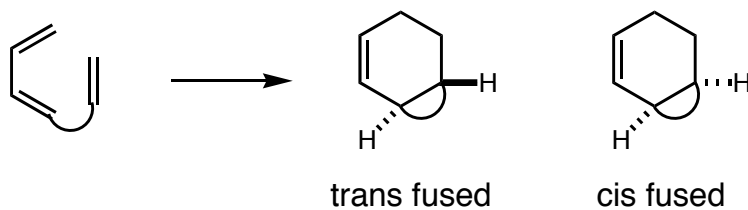
## Assembly of the carbocyclic core/bridgehead double bond

### ■ Nicolaou utilizes a type II intramolecular Diels-Alder Reaction

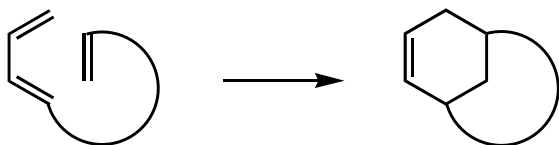


#### Type I

- tether is linked to 4-position



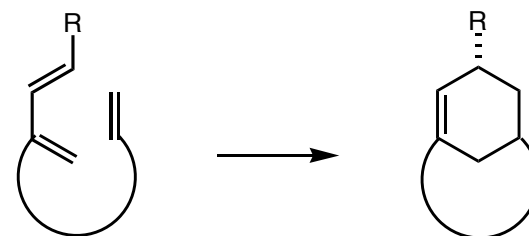
- fused products generally have 3-4 atom tethers



- bridged fused possible with tether >9 atoms

#### Type II

- tethered is linked to 3-position

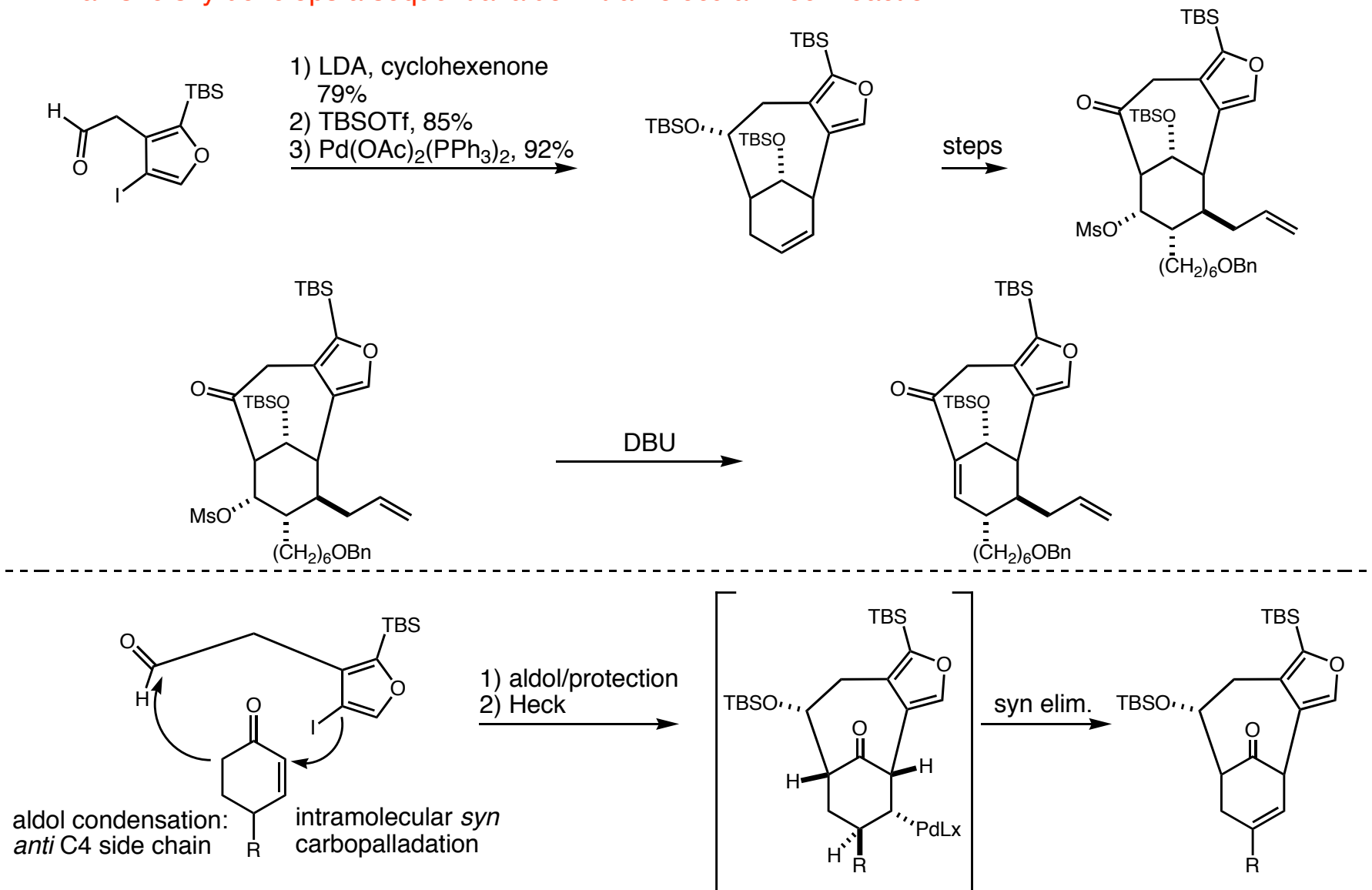


- always gives syn product

Nicolaou, K. C. *et al.* *J. Am. Chem. Soc.* **2002**, *124*, 2183.  
Shea, K. J. *Tet. Lett.* **1994**, *35*, 7311.  
Shea, K. J. *J. Am. Chem. Soc.* **1988**, *110*, 860.

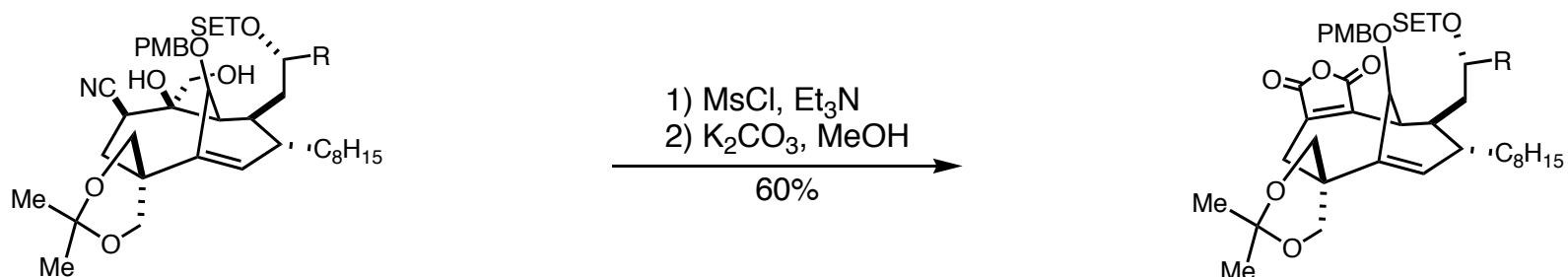
## Assembly of the carbocyclic core/bridgehead double bond

### Danishefsky develops a sequential aldol/intramolecular Heck reaction

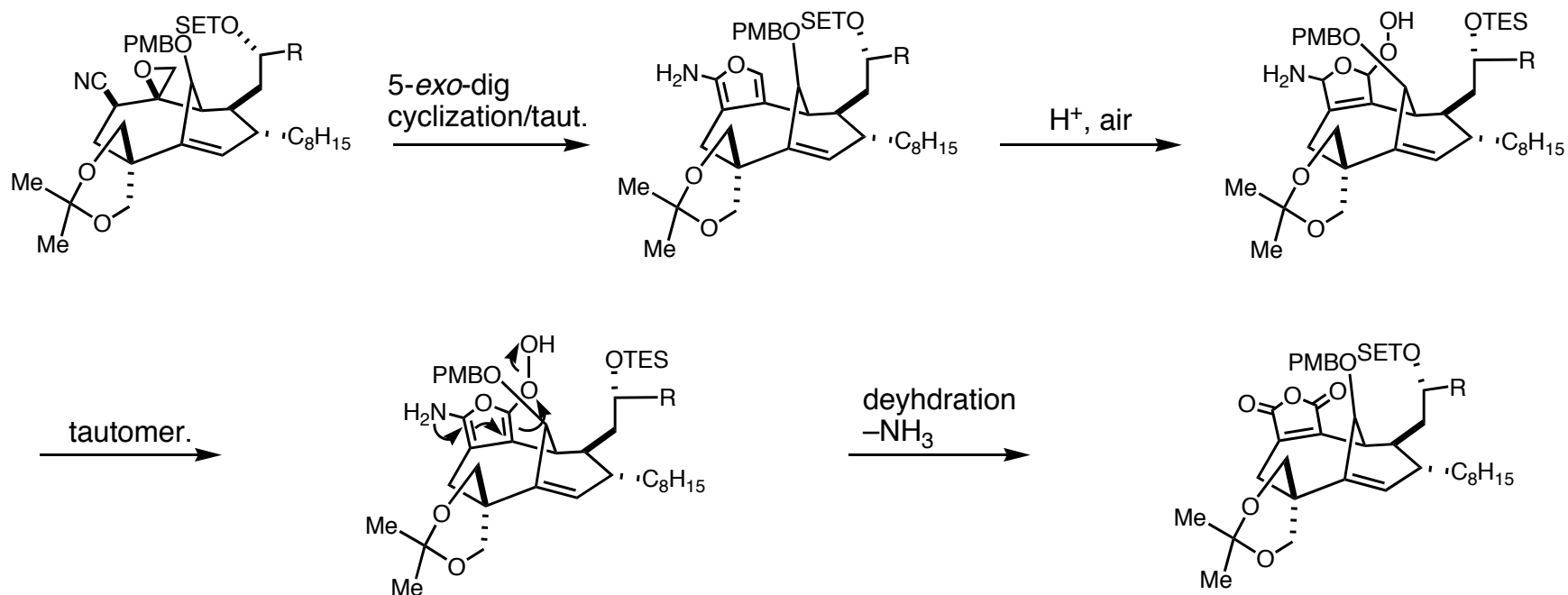


## Assembly of the maleic anhydride architecture

■ Nicolaou develops an interesting multi-step sequence



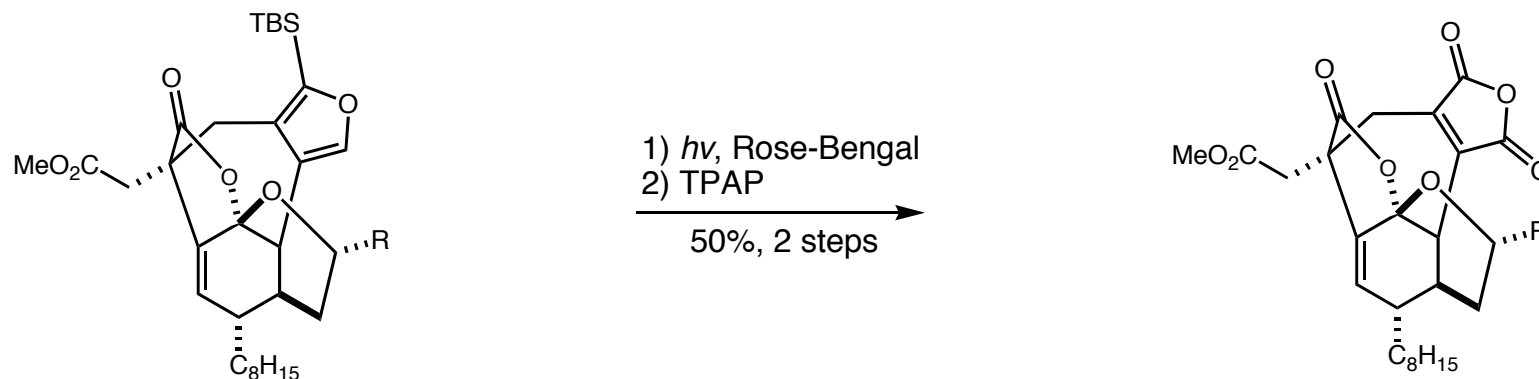
- Mechanism



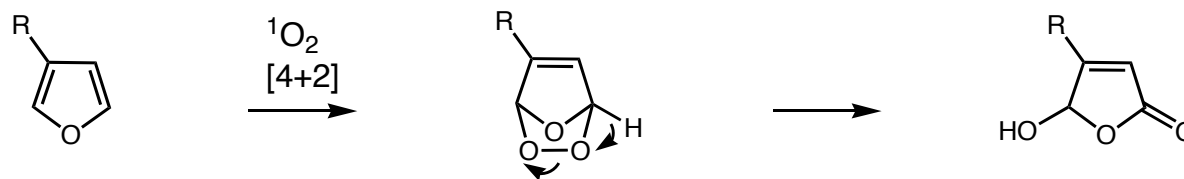
Spiegel, D. A. *et al. Chem. Rev.* **2003**, *103*, 2691.  
Nicolaou, K. C. *et al. J. Am. Chem. Soc.* **2002**, *124*, 2183.

## Assembly of the maleic anhydride architecture

- Danishefsky utilizes singlet oxygen to access the anhydride



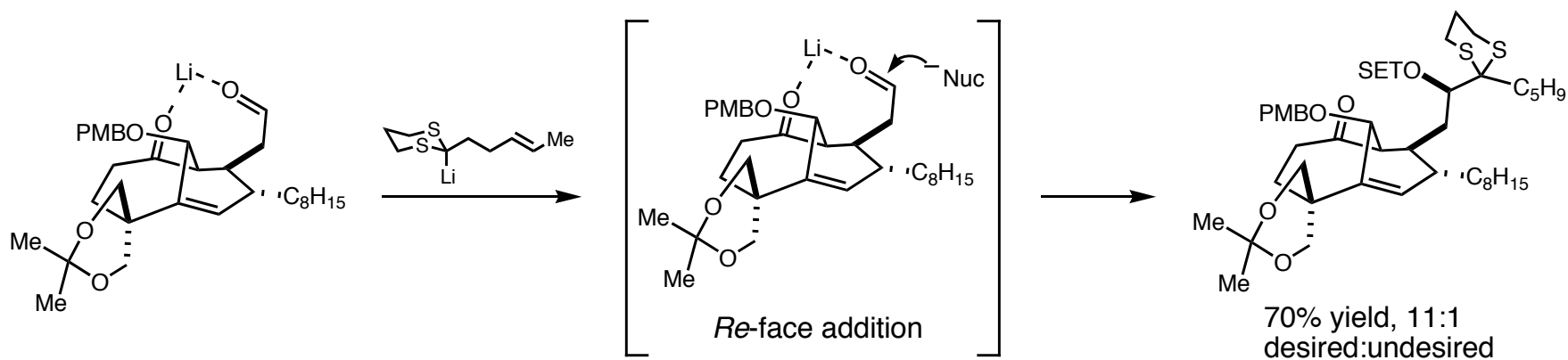
- General mechanism



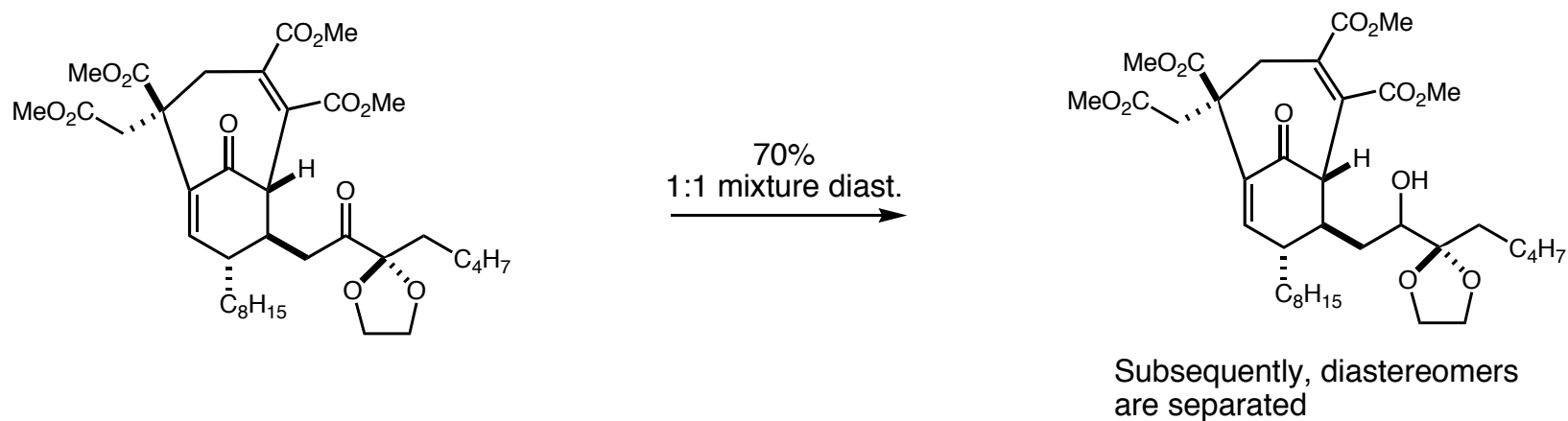
Kwon, O. *et al.* *Angew. Chem. Int. Ed.* **1998**, *37*, 1880  
Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773.

## Assembly of the C-7 stereocenter

- Nicolaou utilizes a diastereoselective aldehyde alkylation



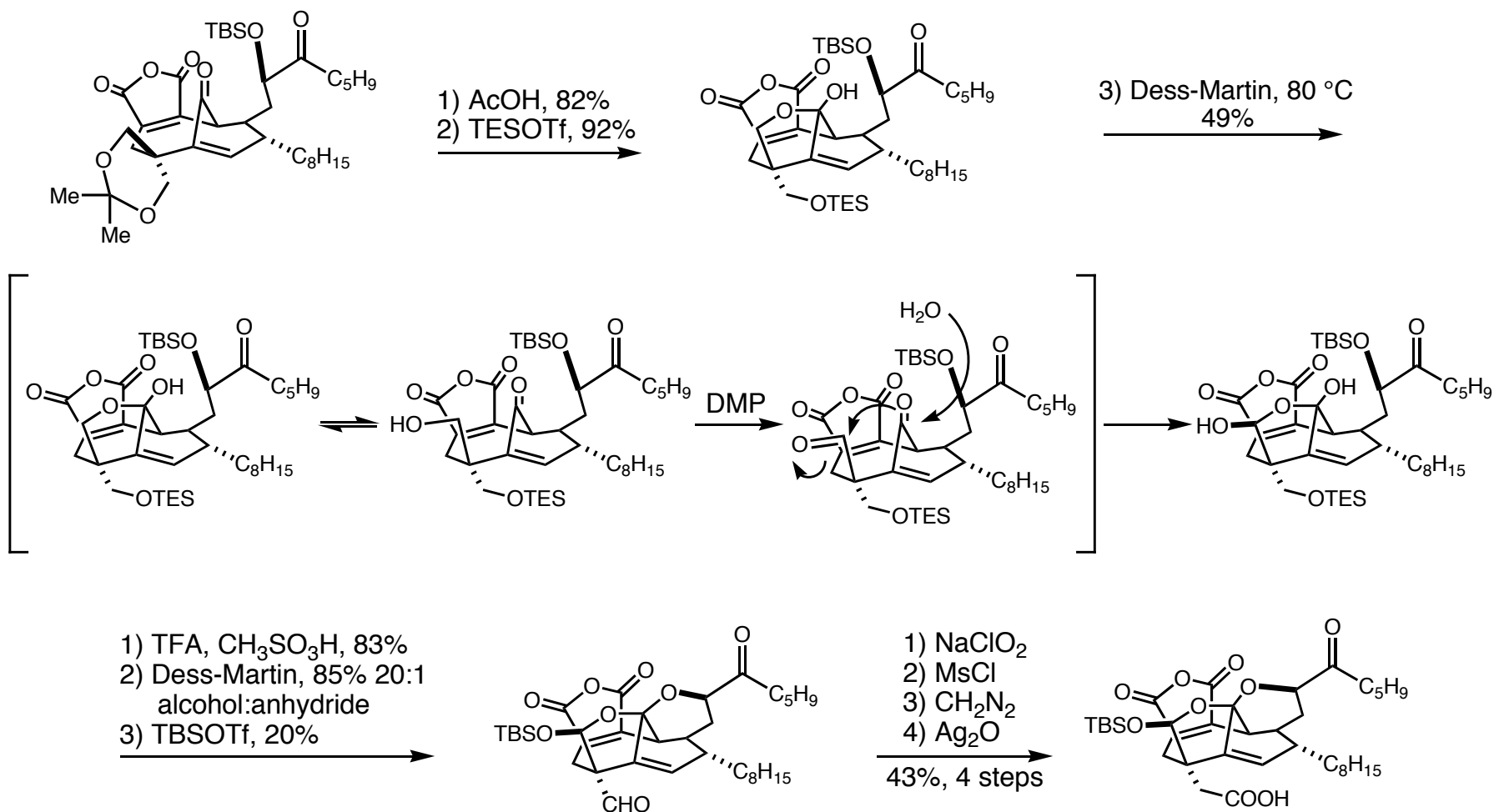
- Danishefsky attempted a similar alkylation but undesired diastereomer was favored. Here's route B.



Tan, Q.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 4509

## Assembly of the C14 quaternary carbon center

- Perhaps the most difficult problem
- Nicolaou, along with Fukuyama, rely upon the carbocycle to direct reactions to one diastereotopic center

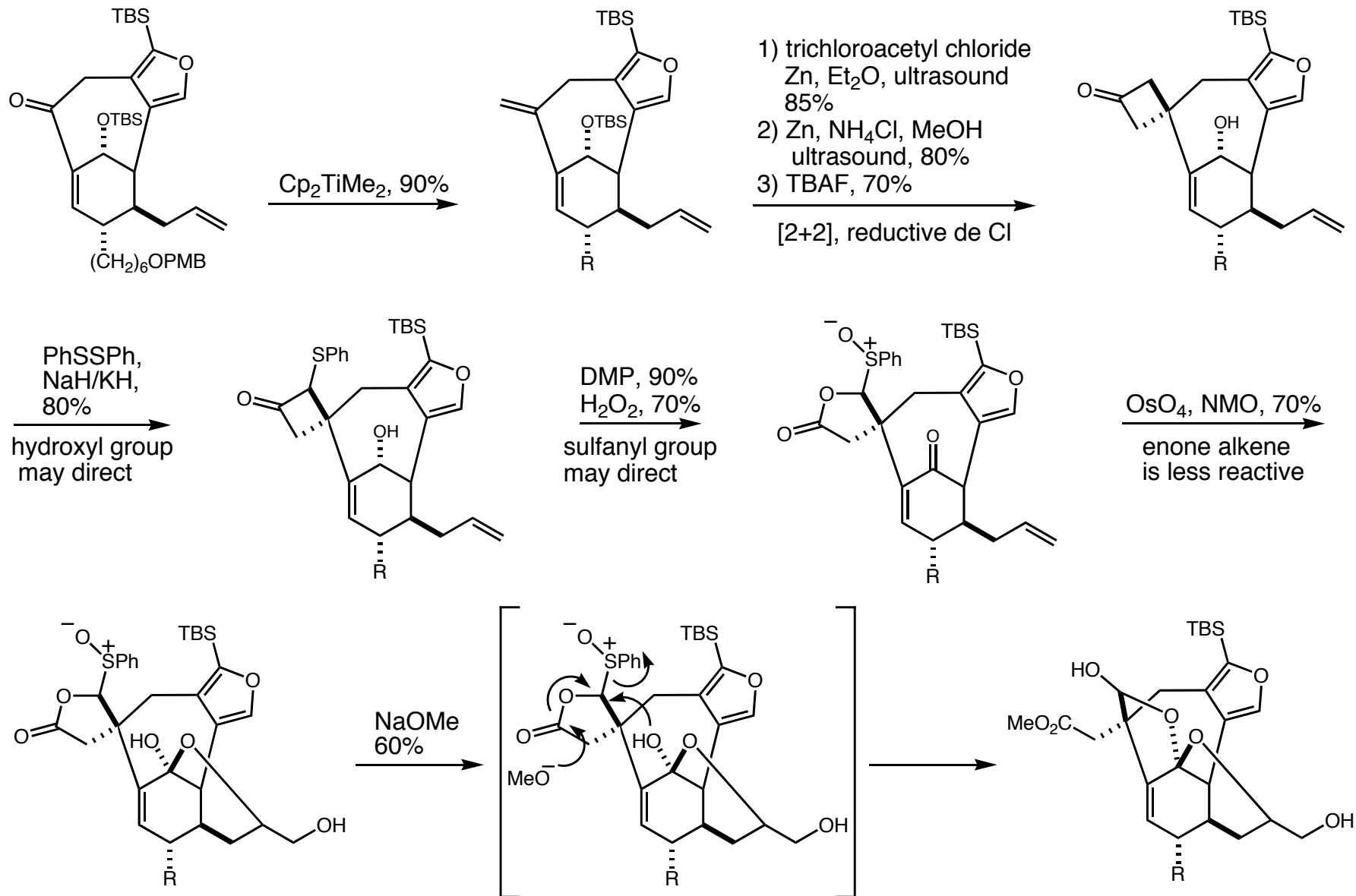


Nicolaou, K. C. *et al.* *J. Am. Chem. Soc.* **2002**, 124, 2202.

Nicolaou, K. C. *et al.* *J. Am. Chem. Soc.* **2002**, 124, 2190.

## Assembly of the C14 quaternary carbon center

■ Danishefsky utilizes an unusual desymmetrization reaction



Meng, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 1485.

## *Conclusions*

- These complex molecules have led to clever and creative methods for overcoming difficult problems.
- Persistence is the key success.
- Sigmatropic rearrangements provide the most powerful and efficient means of entry into phomoidride systems by generating the carbocycle and alkene in essentially one step.
- A good example that model systems, although useful, may not always be a good metric for actual system.