

# Vicinal Quaternary Stereogenic Centers: A Dauting Challenge in Natural Product Synthesis

Gérald Lelais  
MacMillan Group Meeting  
October 26, 2005

## Lead References:

E. A. Peterson, L. E. Overman, *PNAS* **2004**, *101*, 11943-11948.

K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, 1996, Chapters 14, 25, 26.

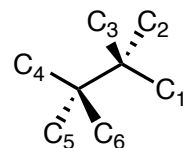
K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, 2003, Chapters 11, 14, 19.

# Asymmetric Vicinal Quaternary Centers Construction

*Applied to natural product synthesis*

## ■ Definition of vicinal quaternary carbons:

two carbon centers attached to each other, each of them having three carbon substituents



## ■ Contents:

- Nature's way of building vicinal quaternary stereocenters
- Biomimetic cascade cyclizations (Dammarenediol II, Secodaphniphylline)
- Diels–Alder cycloadditions (Maritimol, Colombiasin A)
- Other cycloadditions (Retigeranic acid, Valerane)
- Other pericyclic reactions (Trichodiene)
- Intramolecular Heck-cyclization (Chimonanthine)
- Intermolecular alkylation (Chimonanthine)
- Intermolecular Michael addition (Aphidicolin)
- Decarbonylation reaction

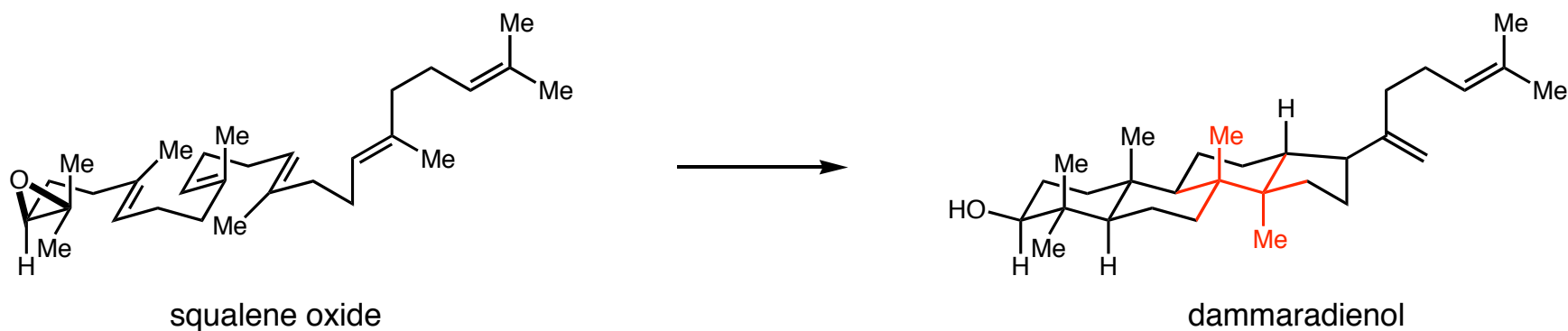
## Nature's Way of Constructing Vicinal Quaternary Stereocenters

### ■ Quaternary carbons are a common feature of terpenes and related natural products

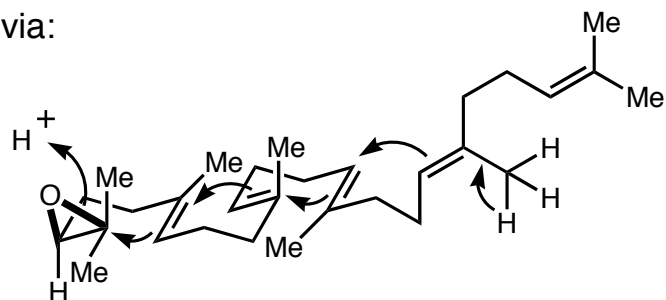
Quaternary stereocenters are biosynthetically assembled by using carbocation chemistry:

- polyene cyclizations
- cationic rearrangements

### ■ Enzyme-catalyzed polyene cyclization:

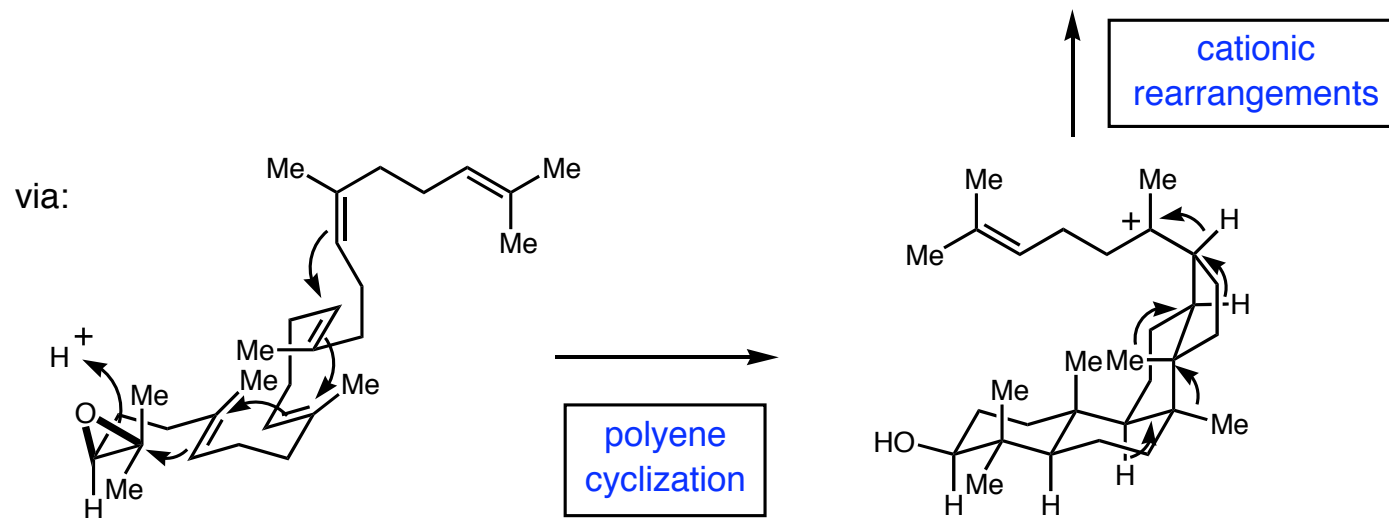
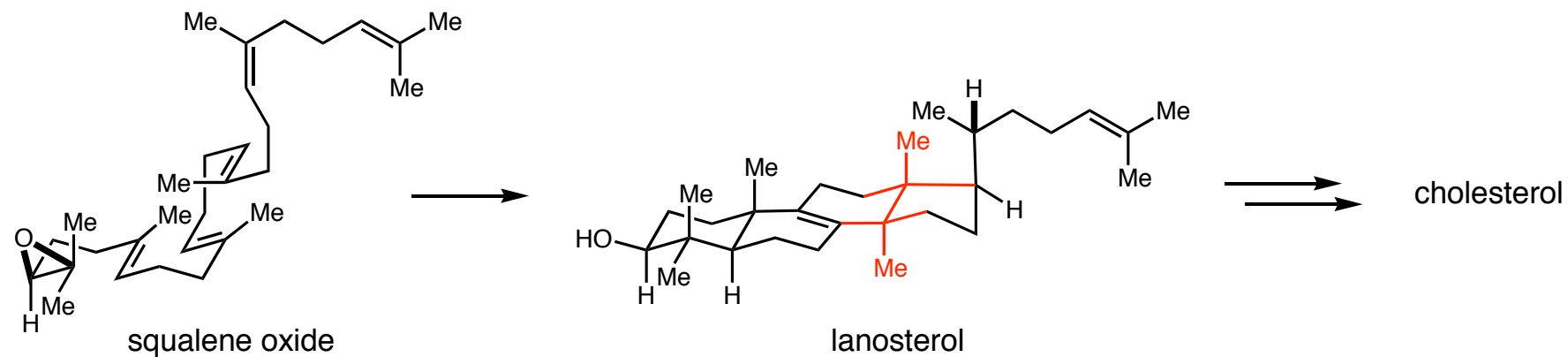


via:



# Nature's Way of Constructing Vicinal Quaternary Stereocenters

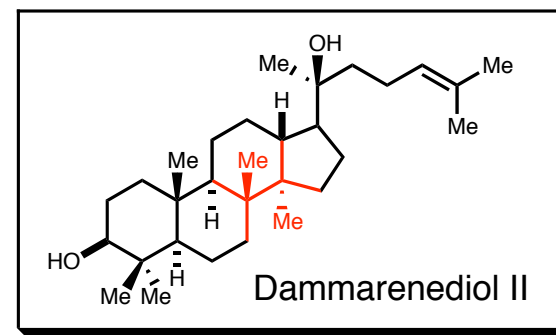
## ■ Lanosterol/cholesterol biosynthesis:



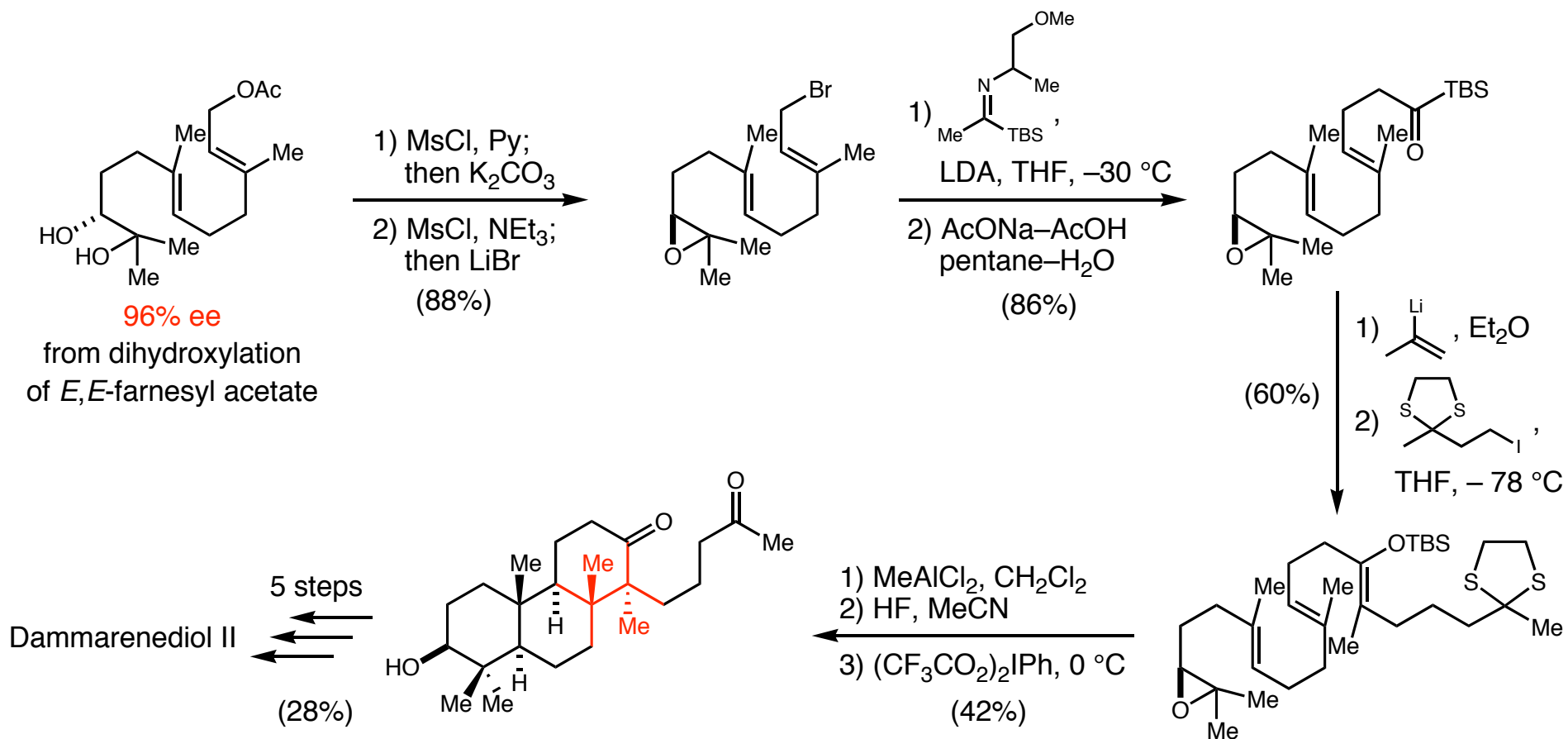
Eschenmoser: *Helv. Chim. Acta* **1955**, *38*, 1890-1904.  
Stork: *JACS* **1955**, *77*, 5068-5077.  
Johnson: *JACS* **1987**, *109*, 5852-5853.

# Biomimetic Total Syntheses

## Cascade cyclizations



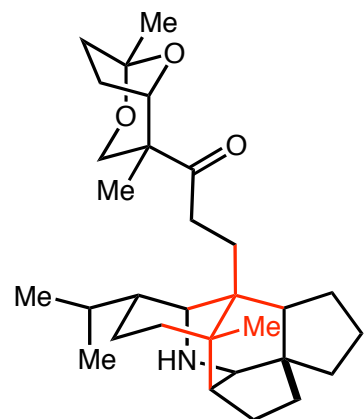
### ■ Enantioselective synthesis of Dammarenediol II



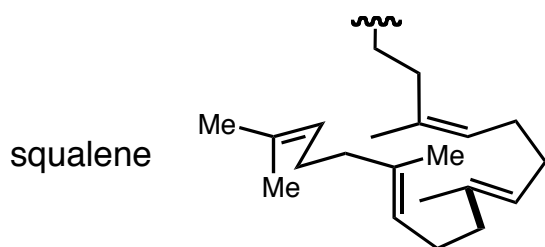
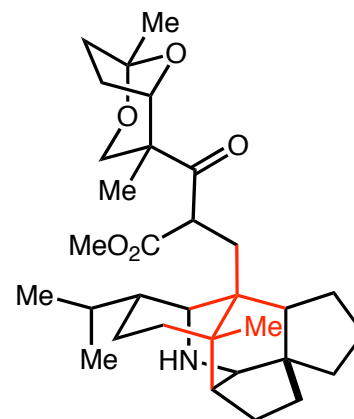
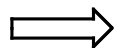
# Biomimetic Total Syntheses II: (-)-Secodaphniphylline

## Cascade cyclizations

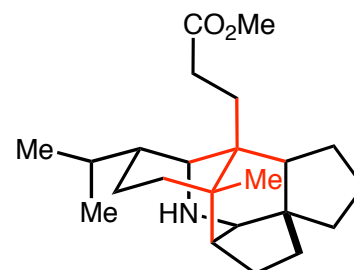
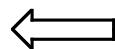
### ■ Retrosynthetic analysis



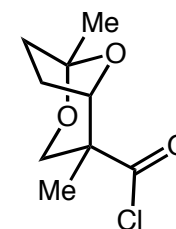
(-)-Secodaphniphylline



squalene



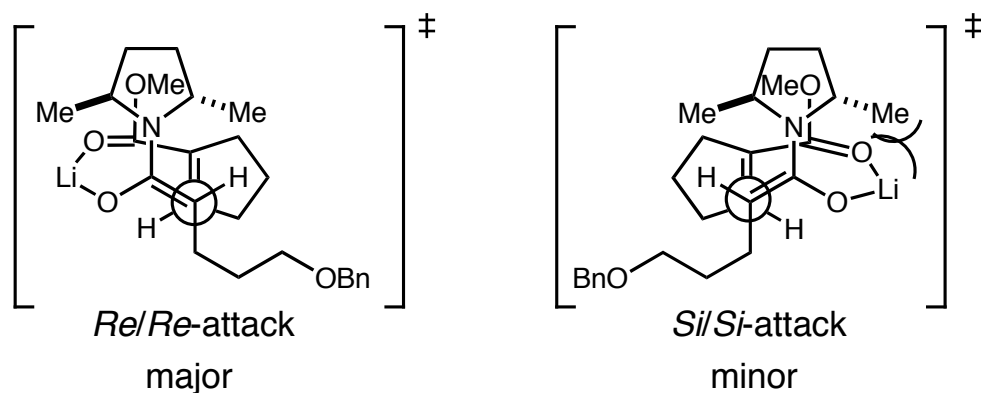
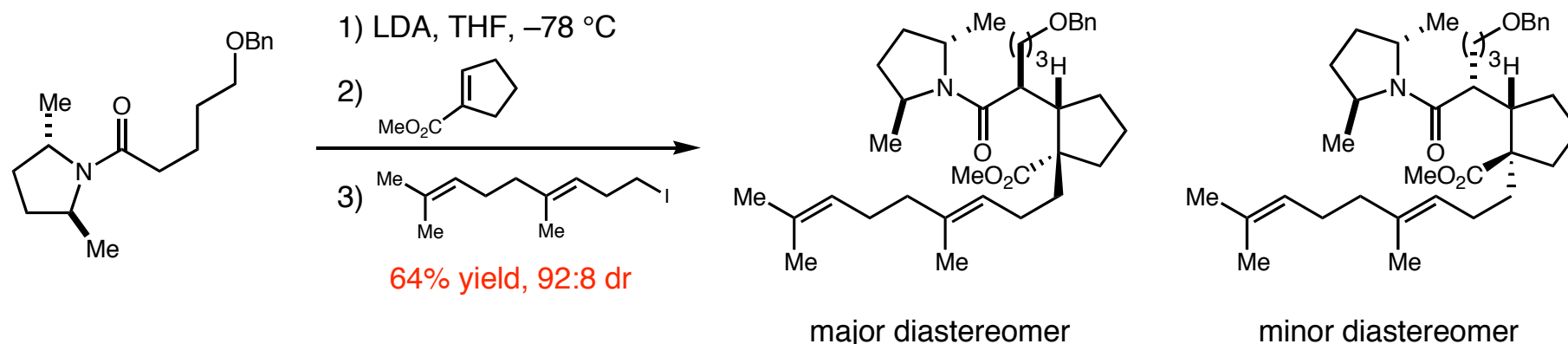
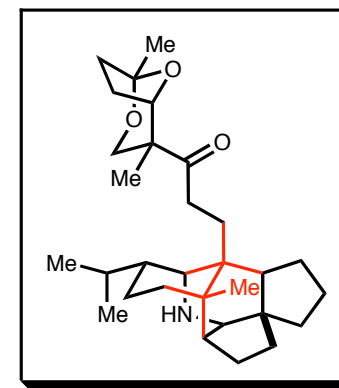
+



# Biomimetic Total Syntheses II: (-)-Secodaphniphylline

## Cascade cyclizations

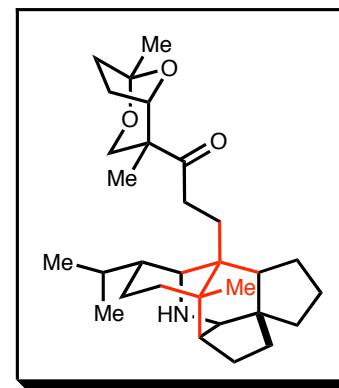
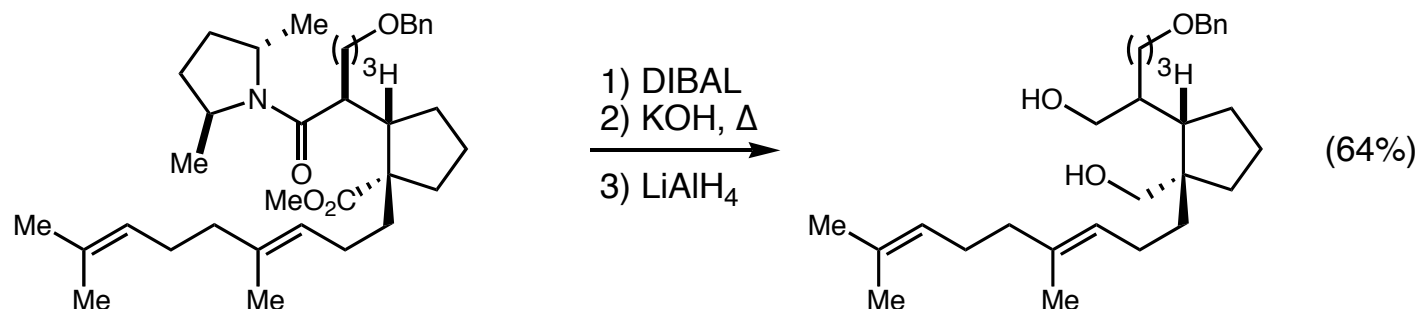
### Asymmetric induction using a $C_2$ -symmetric *N*-acyl pyrrolidine



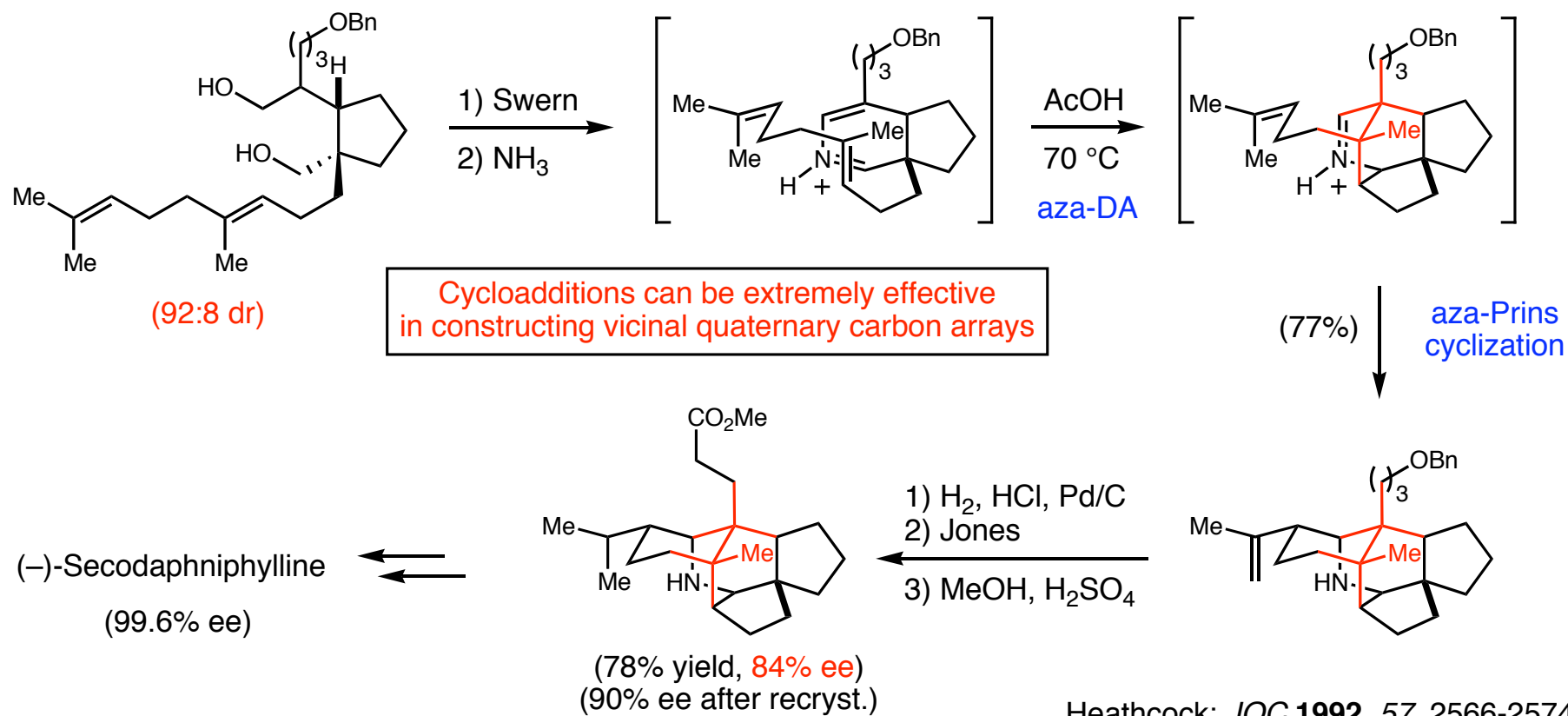
repulsive interaction between the pyrrolidine methyl and the cyclopentane ring is favored over that with the enolate cluster

## (-)-Secodaphniphylline: Key cyclization steps

### ■ Preparation of the key intermediate



### ■ Cascade cyclization with installment of vicinal quaternary stereogenic centers

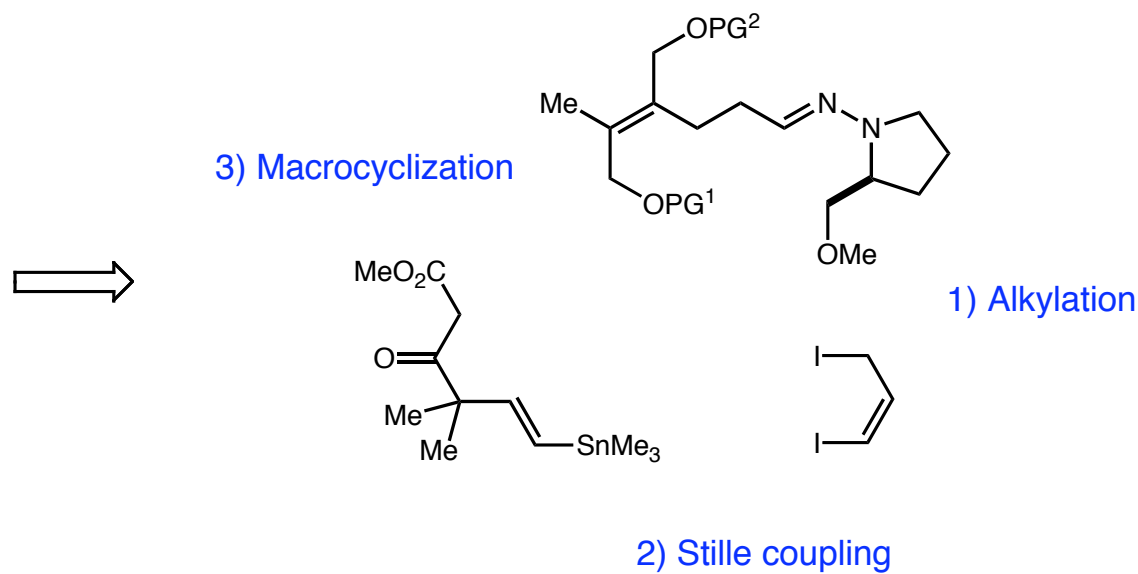
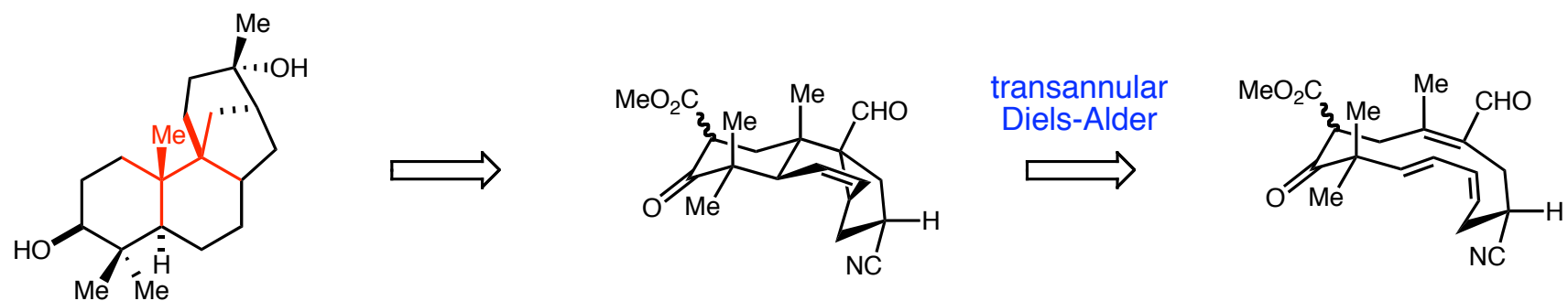




# Diels-Alder Cycloadditions to Assemble Contiguous Quaternary Carbons

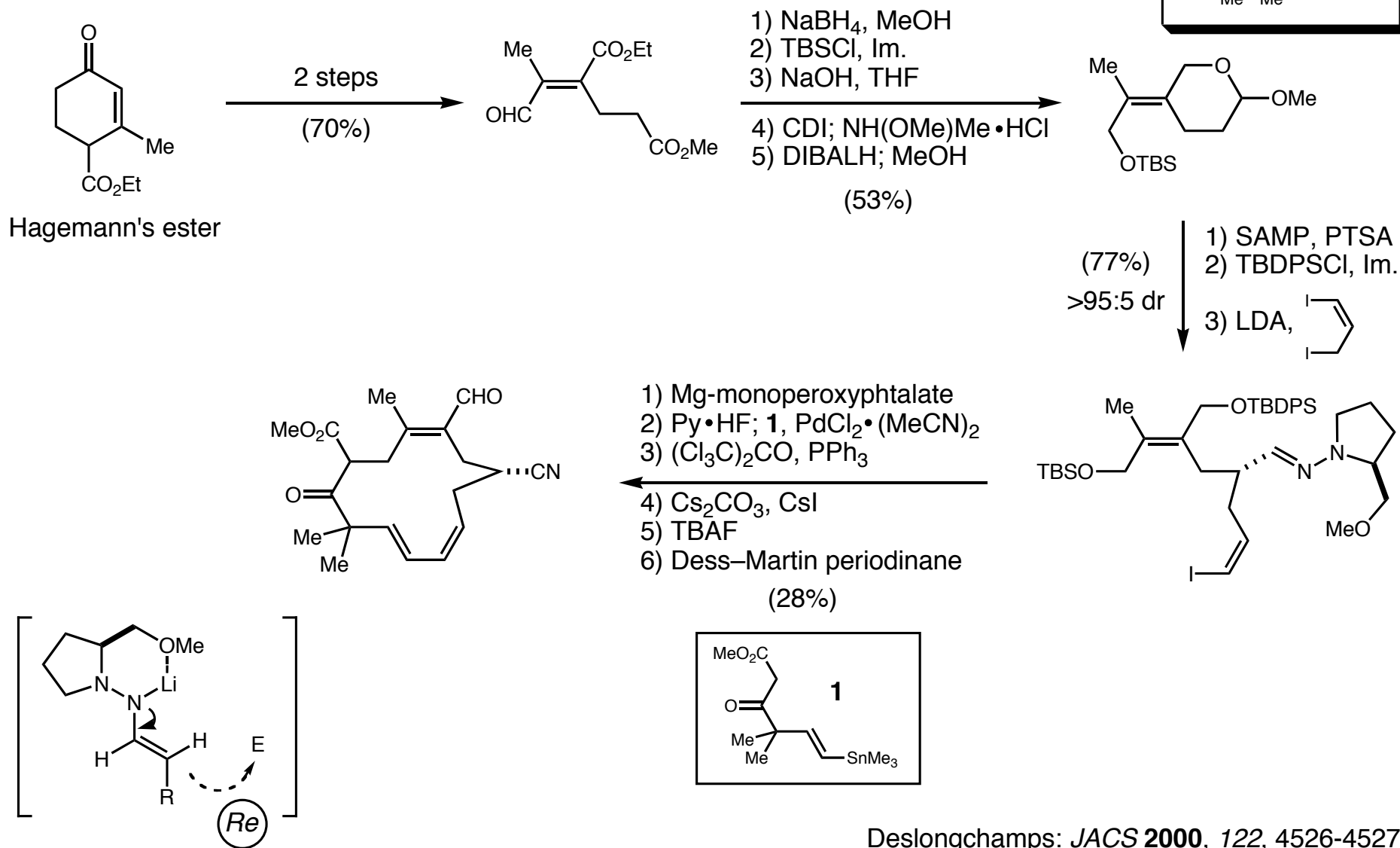
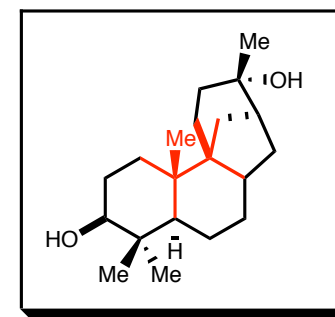
Enantioselective synthesis of (+)-Maritamol

## Retrosynthetic analysis



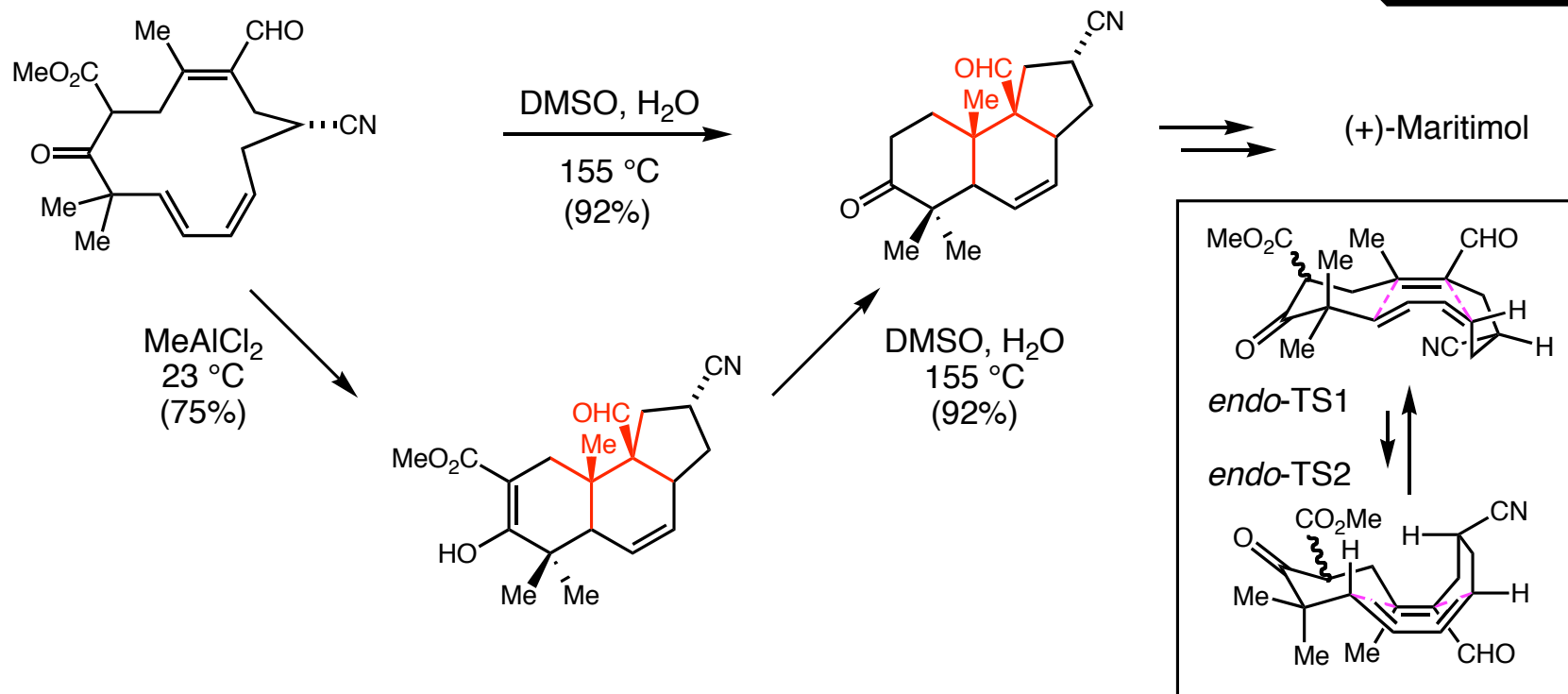
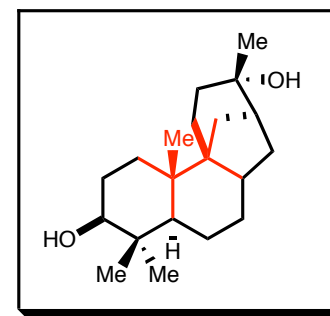
# Enantioselective Synthesis of (+)-Maritamol

## Asymmetric synthesis of the macrocycle



## Enantioselective Synthesis of (+)-Maritamol

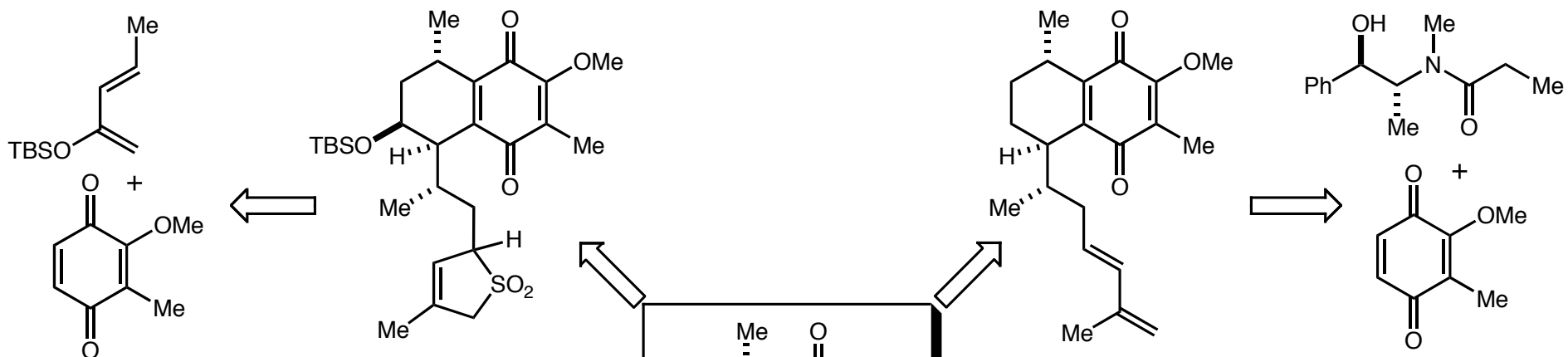
- Vicinal quaternary centers formation by transannular Diels–Alder reaction (TADA)



- Both Lewis acid-catalyzed and thermal TADA exhibit similar complete stereoface- and diastereospecificity induced by a small remote nitril group
- Intensive decomposition was observed when demethoxycarbonylated macrocycle was subjected to TADA reaction

# Diels–Alder Cyclization II

## Enantioselective synthesis of (–)-Colombiasin A

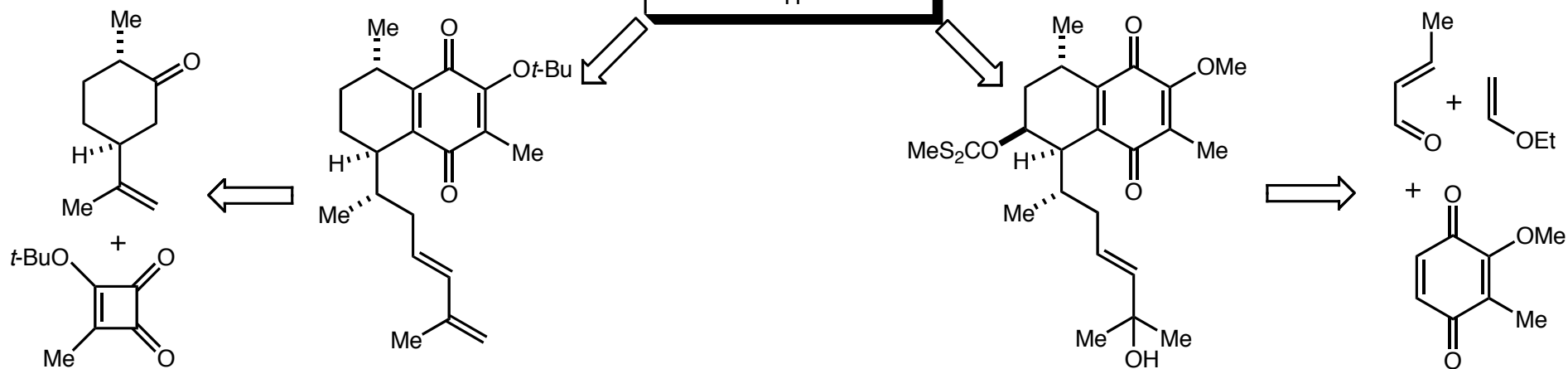


Nicolaou, 2001

(first enantioselective synthesis)

*Chem. Eur. J.* **2001**, *7*, 5359-5371

Richnovsky, 2003  
(17 steps, 3.9% yield)  
*Angew. Chem. Int. Ed.* **2003**, *42*, 1267-1270



Harrowven, 2005

(12 steps, 1.5% yield)

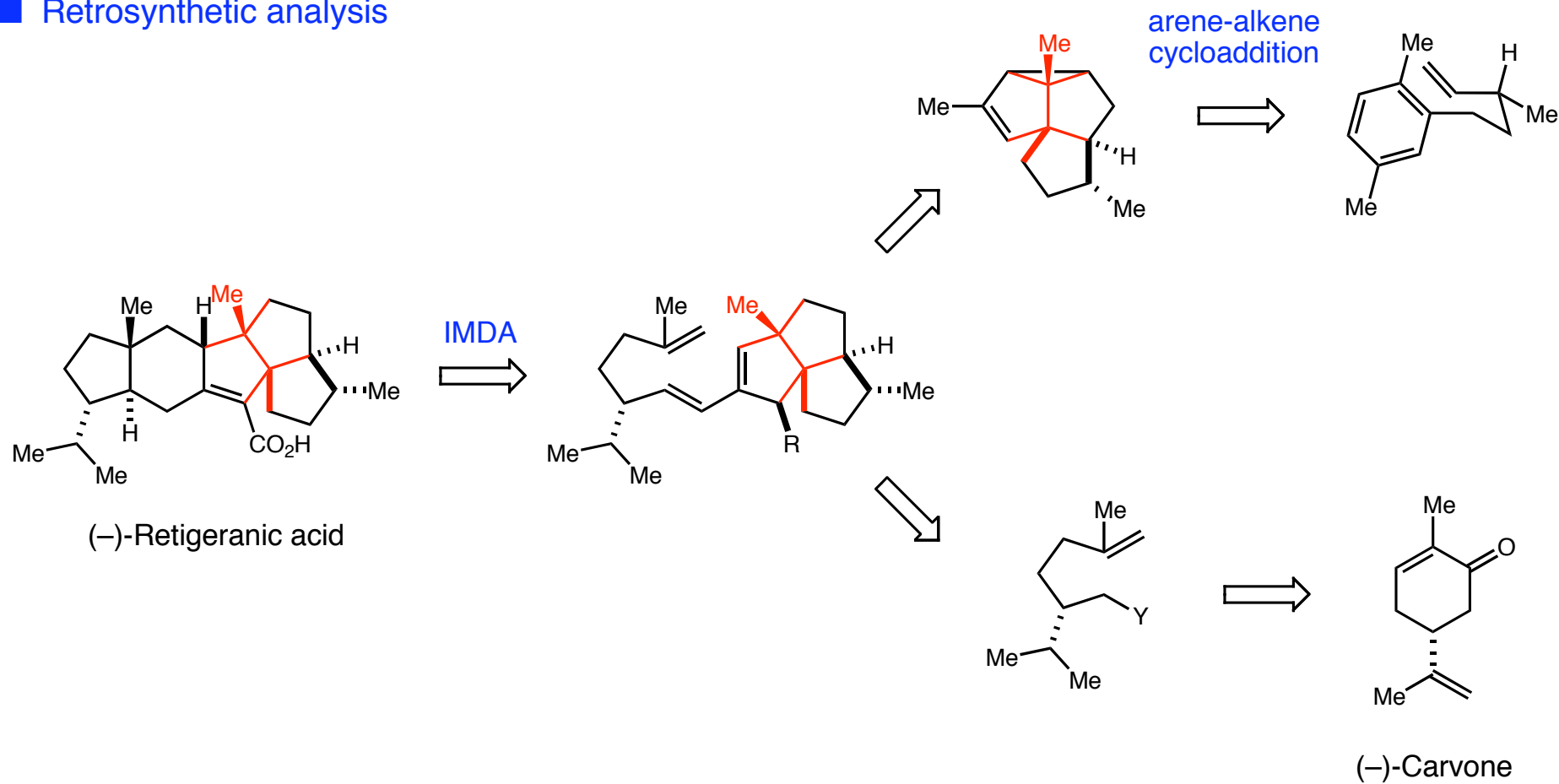
*Angew. Chem. Int. Ed.* **2005**, *44*, 1221-1222

Jacobsen, 2005  
(12 steps, 11.5% yield)  
*Angew. Chem. Int. Ed.* **2005**, *44*, 6046-6050

# Alternative Cycloadditions: Arene-Alkene meta-Cycloadditions

Enantioselective synthesis of (-)-Retigeranic acid

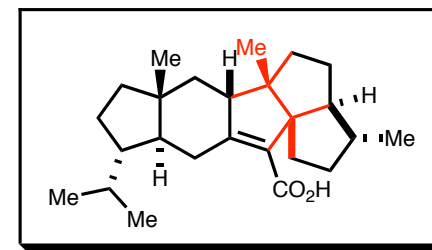
## Retrosynthetic analysis



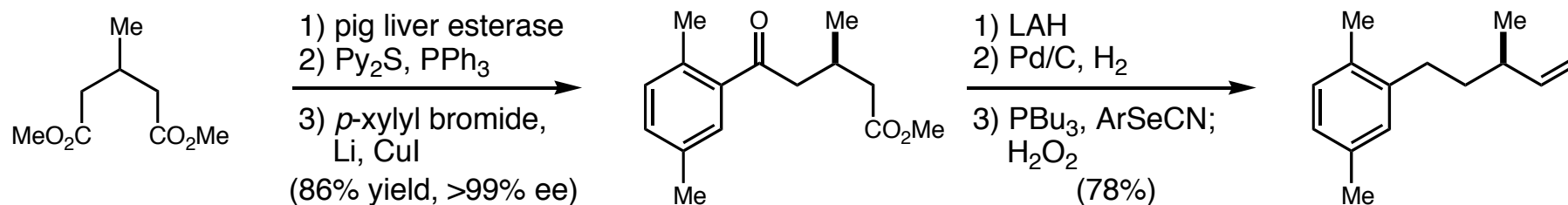
Wender: *Tetrahedron Letters* **1990**, 31, 2517-2520.  
Wender: *Pure & Appl. Chem.* **1990**, 62, 1597-1602.

# (-)-Retigeranic Acid

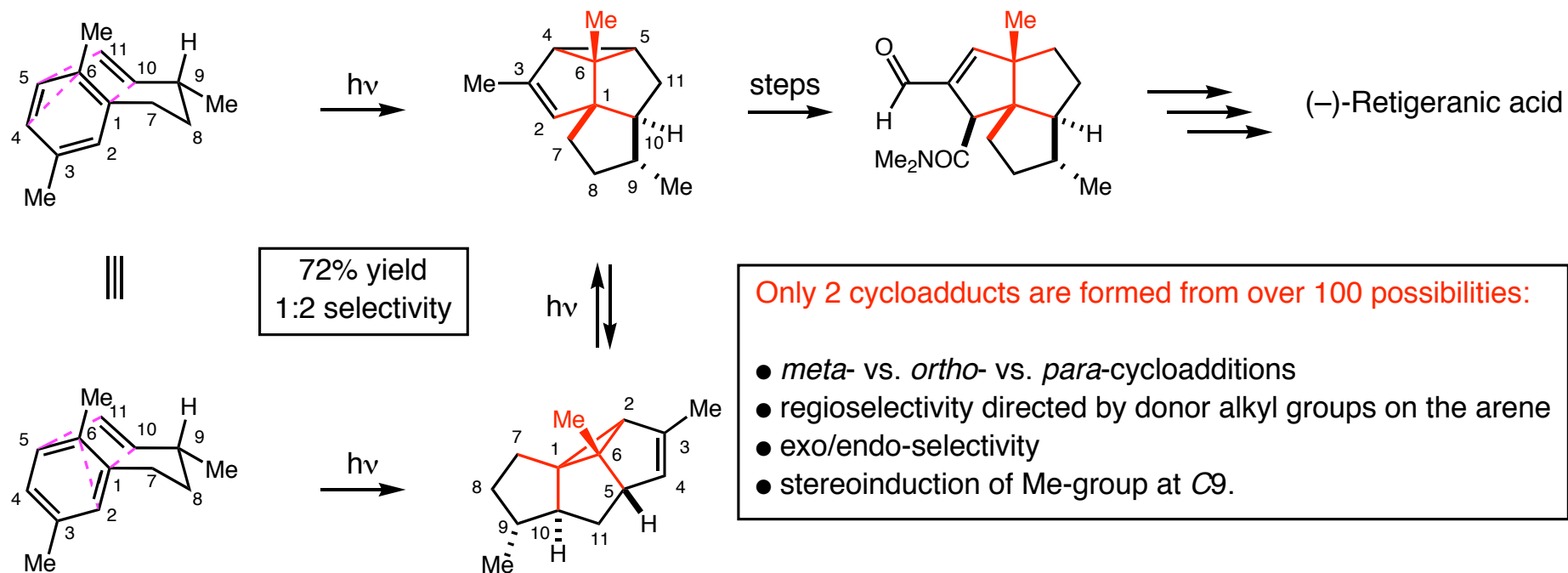
Highly selective photo-cycloaddition as key step



## Preparation of the cycloaddition precursor



## Key photo-cycloaddition reaction

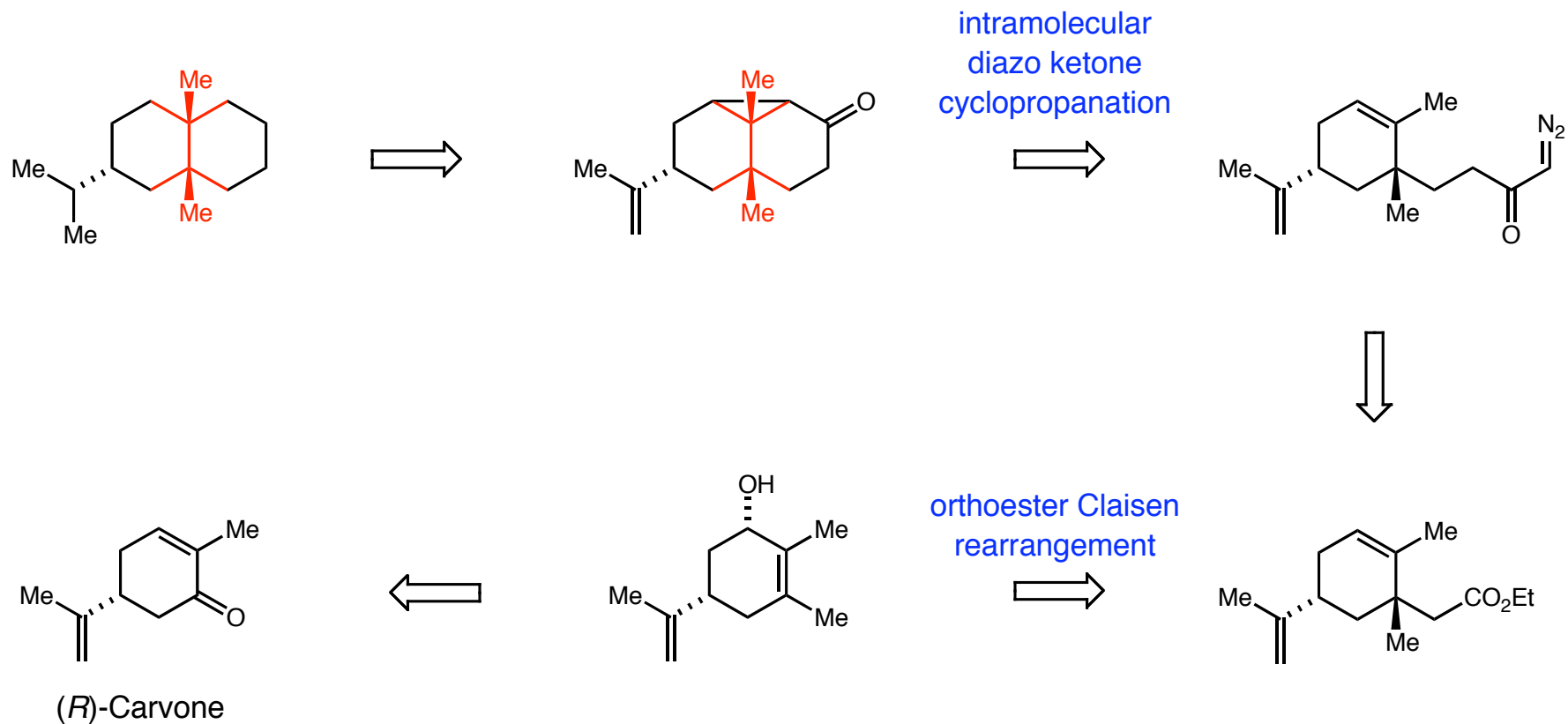


Wender: *Tetrahedron Letters* **1990**, 31, 2517-2520.  
Wender: *Pure & Appl. Chem.* **1990**, 62, 1597-1602.

# Claisen Rearrangement/Intramolecular Diazo Ketone Cyclopropanation

Enantioselective synthesis of (+)-Valerane

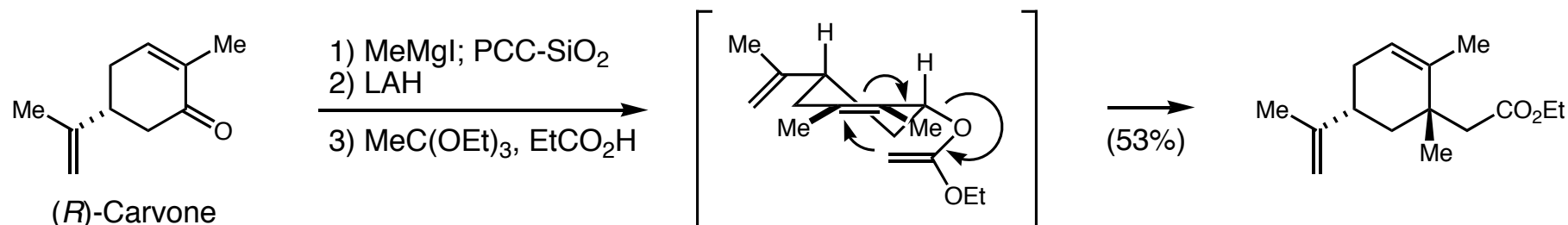
## Retrosynthetic analysis



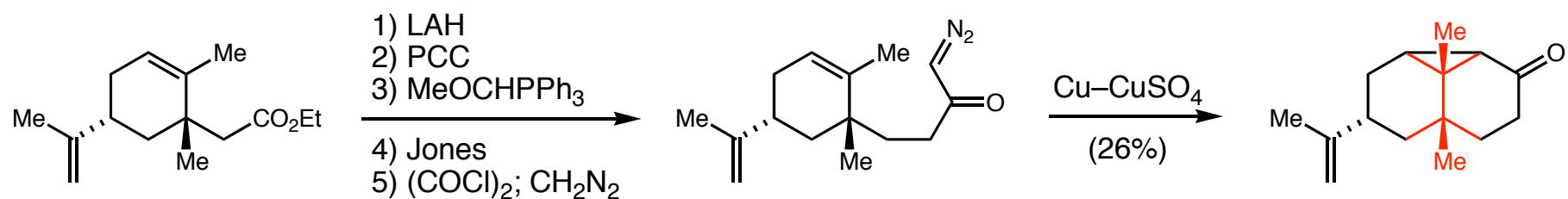
Combination of 2 pericyclic reactions for the stepwise construction of vicinal quaternary carbons

## Enantioselective Synthesis of (+)-Valerane

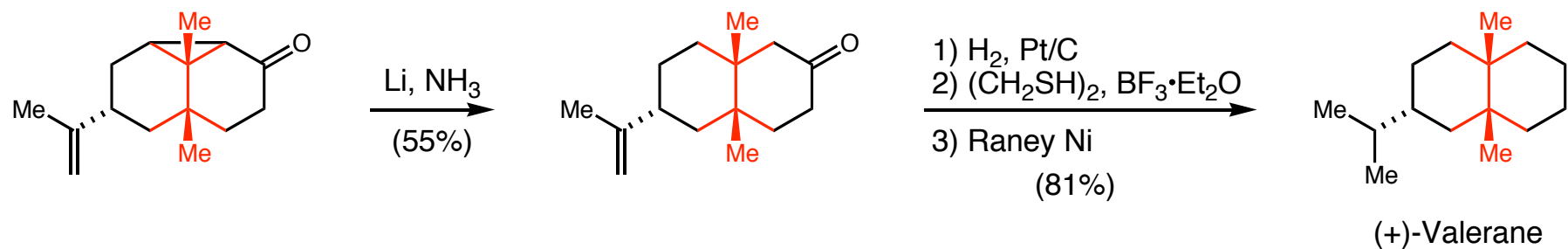
### ■ Diastereoselective installment of the first quaternary carbon stereocenter



### ■ Diastereoselective installment of the second quaternary carbon stereocenter



### ■ Endgame

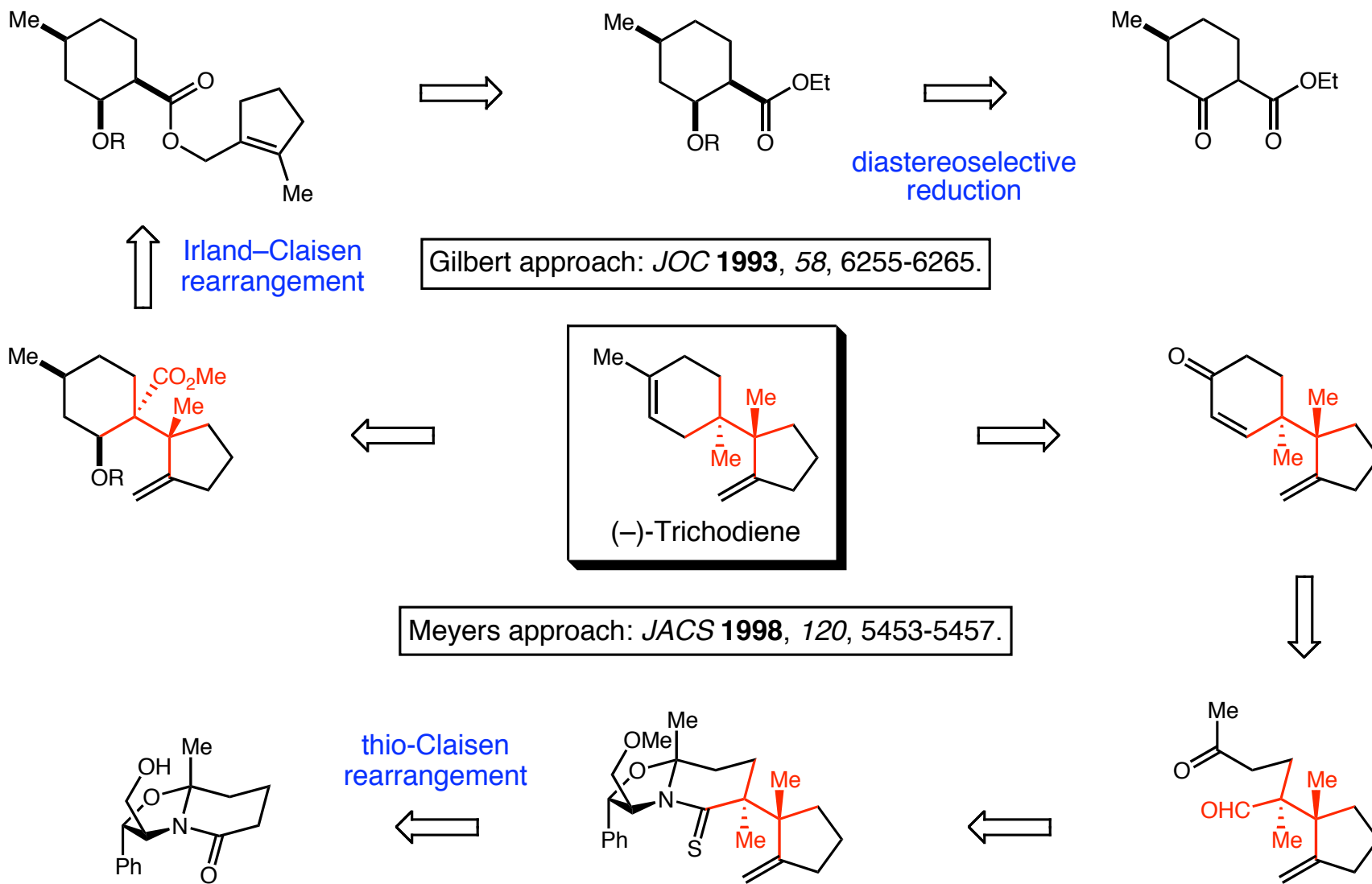




# Other Pericyclic Reactions: Ireland–Claisen and Thio-Claisen Rearrangements

Enantioselective synthesis of (–)-Trichodiene

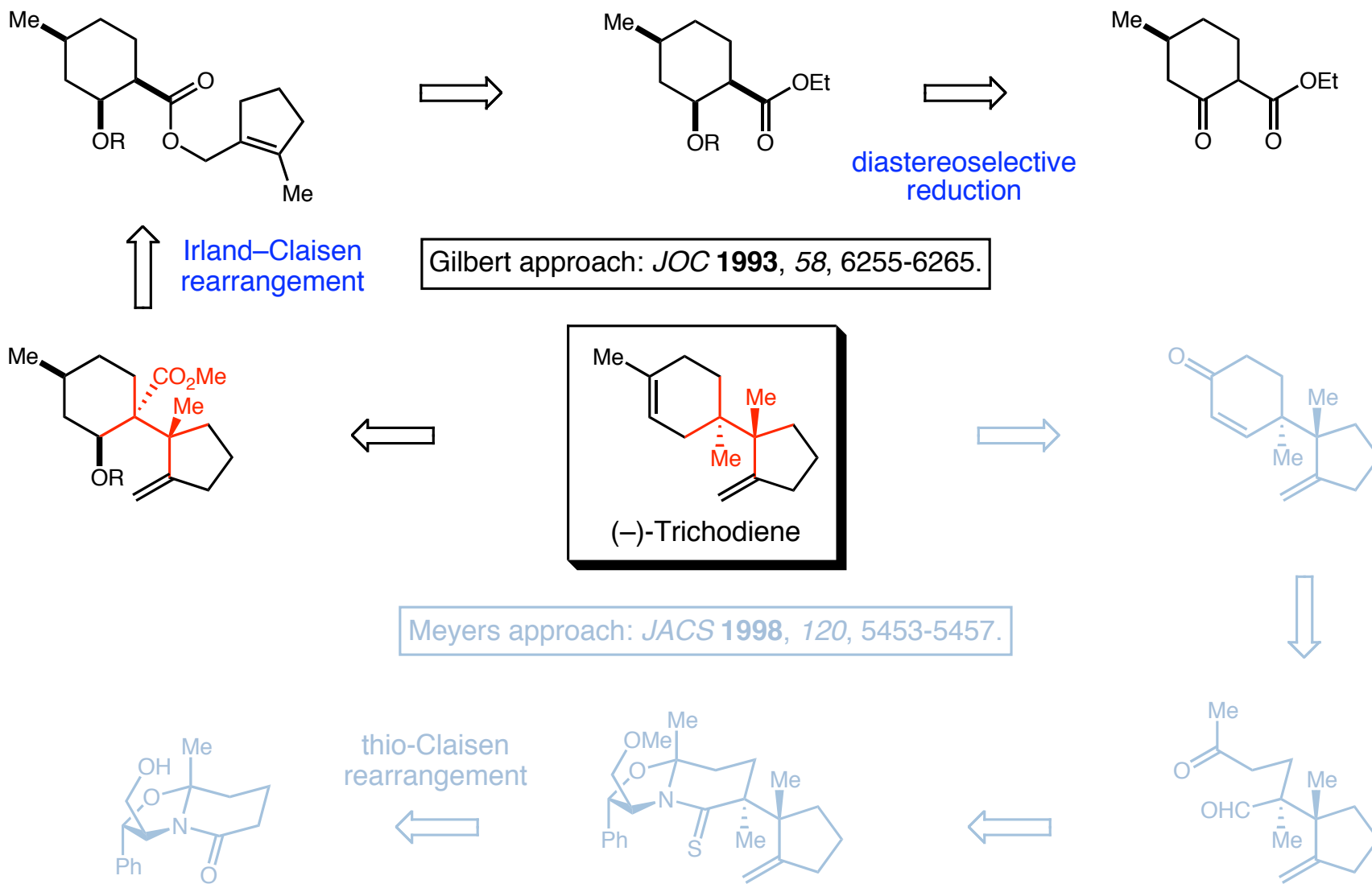
## Retrosynthetic analysis



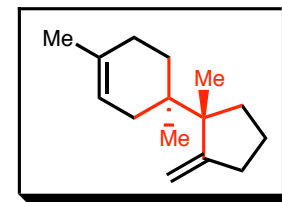
# Other Pericyclic Reactions: Ireland–Claisen and Thio-Claisen Rearrangements

Enantioselective synthesis of (–)-Trichodiene

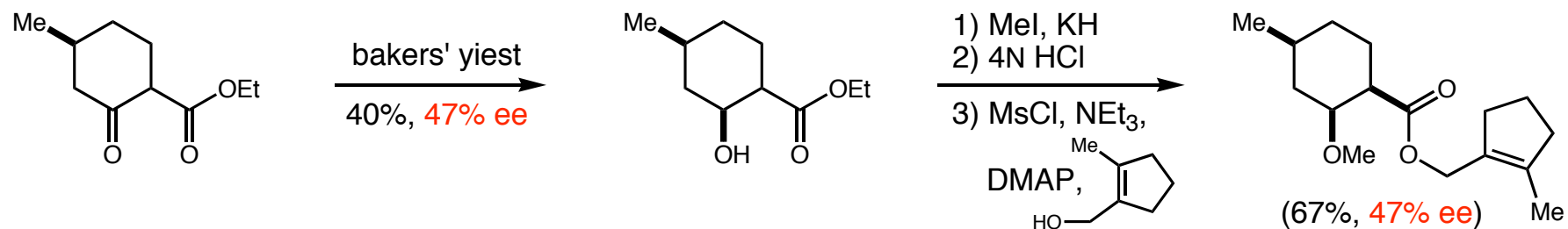
## Retrosynthetic analysis



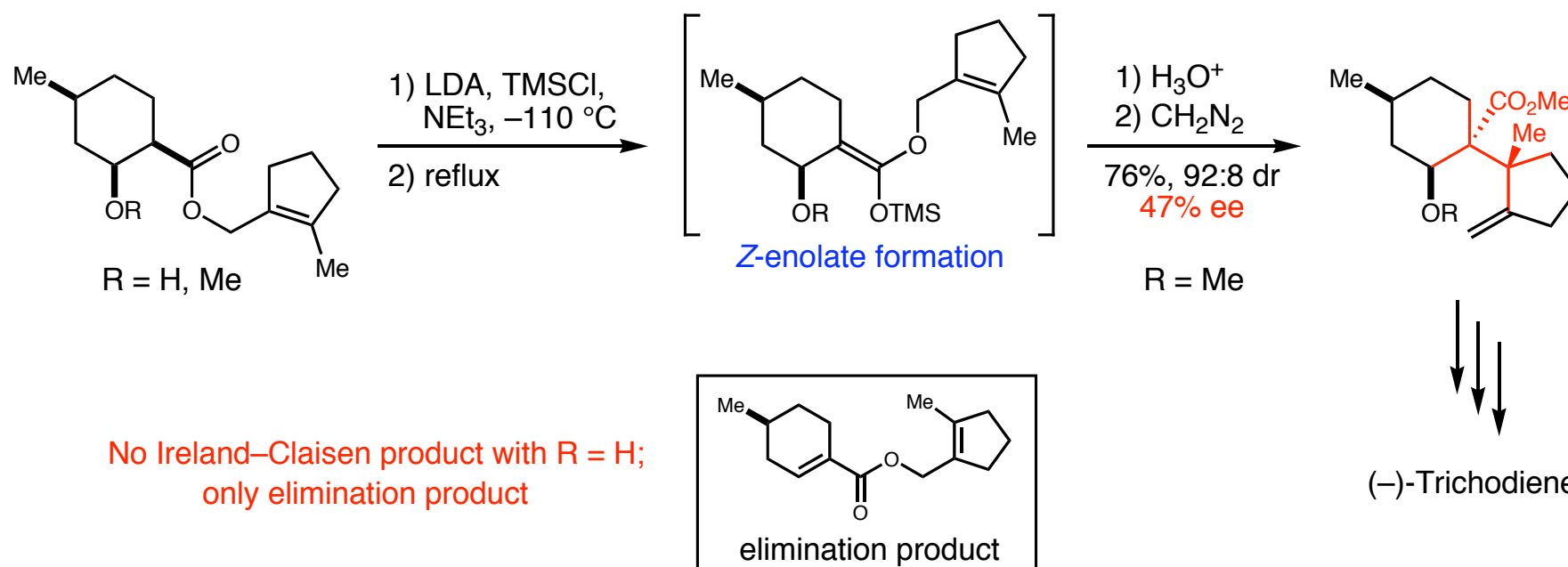
## (-)-Trichodiene: Gilbert Synthesis



### Preparation of the Ireland–Claisen-precursor

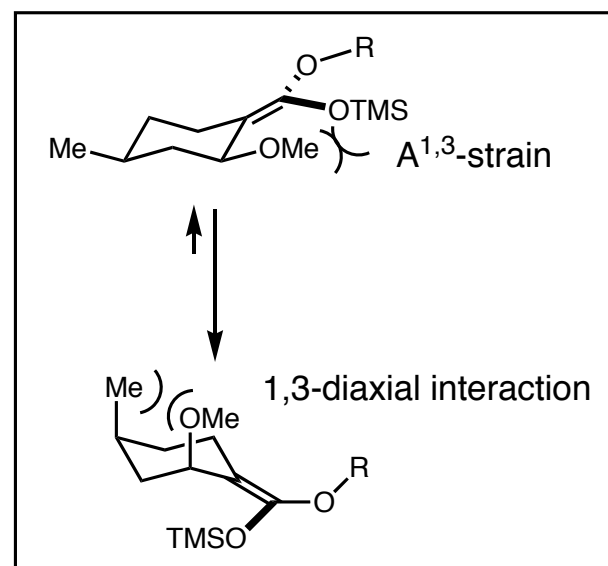
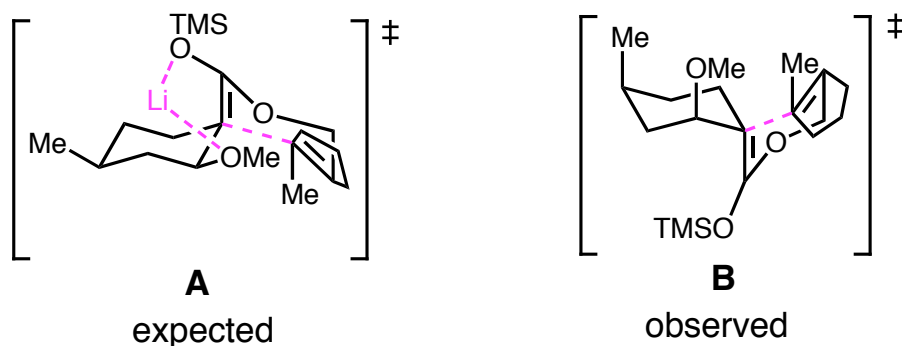
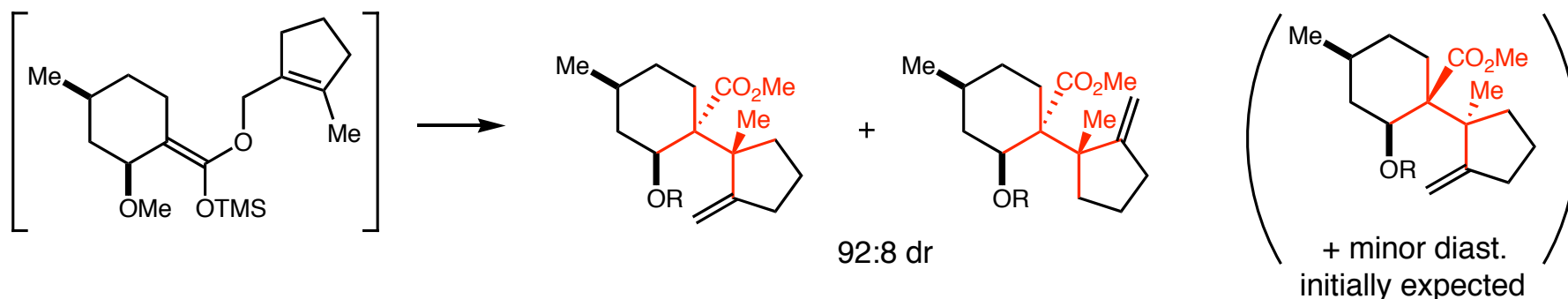


### Ireland–Claisen rearrangement



## Ireland–Claisen Rearrangement in More Detail: Gilbert Synthesis

### Ireland–Claisen rearrangement



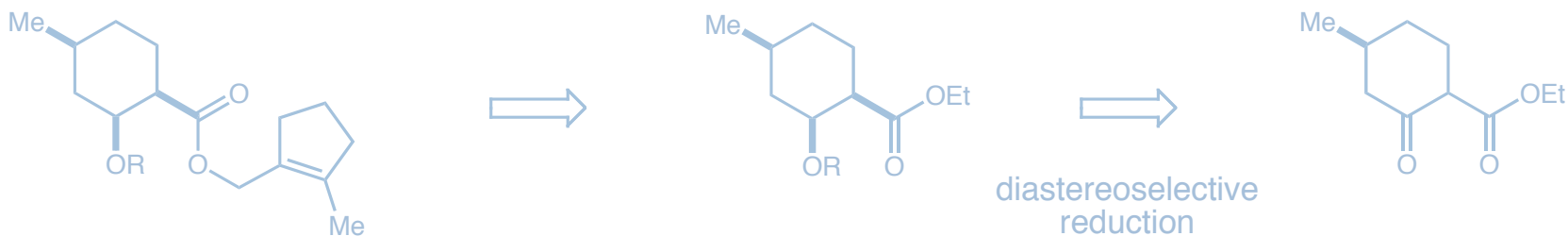
### Stereoselectivity rationale

- Rearrangement was expected to proceed through chair TS
- Only TS where methylcyclopentenyl group occupy an equatorial position in the product should be formed
- The reaction was expected to proceed under Li-chelation of OMe- and OTMS-groups ( → expected product)
- However,  $A^{1,3}$ -strain is responsible for rearrangement selectivity (TS-B preferred vs. TS-A)

# Other Pericyclic Reactions: Ireland–Claisen and Thio-Claisen Rearrangements

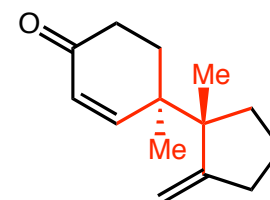
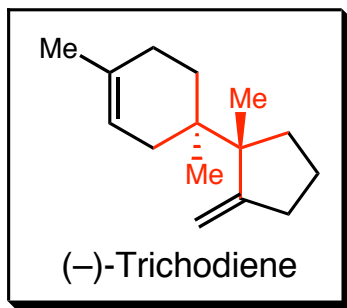
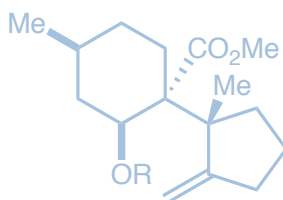
Enantioselective synthesis of (–)-Trichodiene

## Retrosynthetic analysis

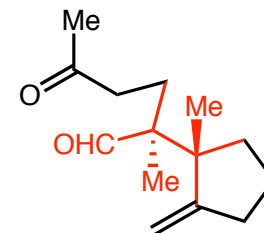
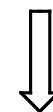


Ireland–Claisen rearrangement

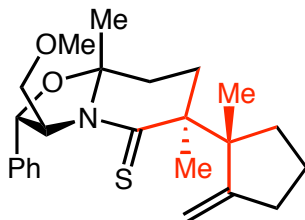
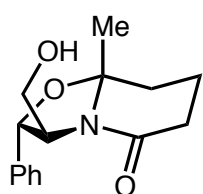
Gilbert approach: *JOC* **1993**, *58*, 6255-6265.



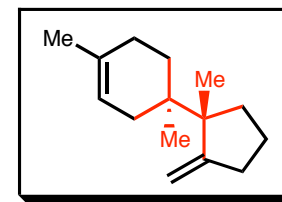
Meyers approach: *JACS* **1998**, *120*, 5453-5457.



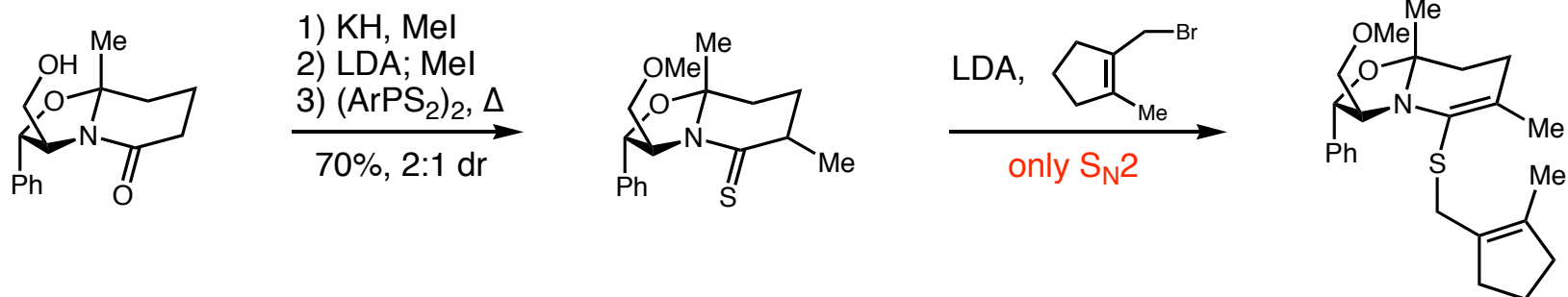
thio-Claisen rearrangement



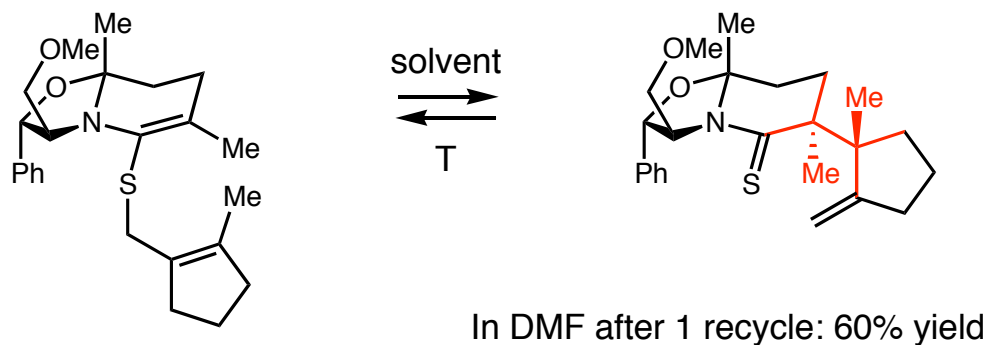
## (-)-Trichodiene: Meyers Synthesis



### ■ Preparation of the rearrangement precursor



### ■ Thio-Claisen rearrangement



solvent	T (°C)	SM:Prod
xylene	140	100:0
MeCN	80	65:35
DME	83	60:40
dioxane	101	60:40
HMPA	100	48:52
DMF	90	36:64
DMSO	80	dec
EtOH	78	dec

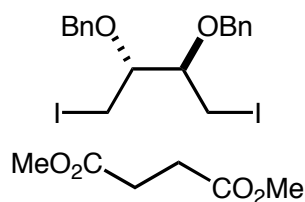
### ■ (-)-Trichodiene is synthesized in 10 steps from bicyclic lactam in 14% overall yield and >99% ee!

# Intramolecular Heck Reaction vs. Intermolecular Alkylation

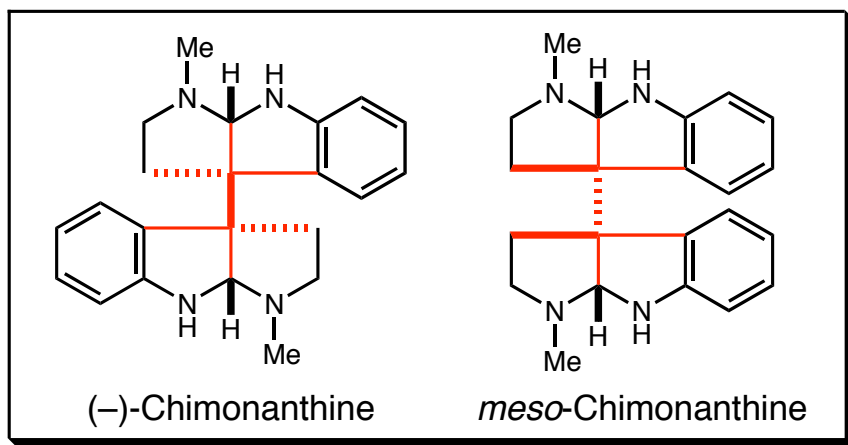
Total synthesis of Chimonanthe by Overman

## Retrosynthetic analysis

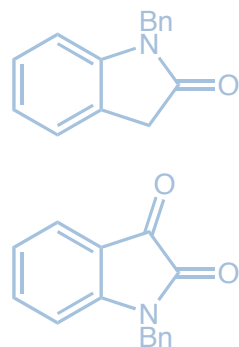
Intramolecular  
Heck-Reaction



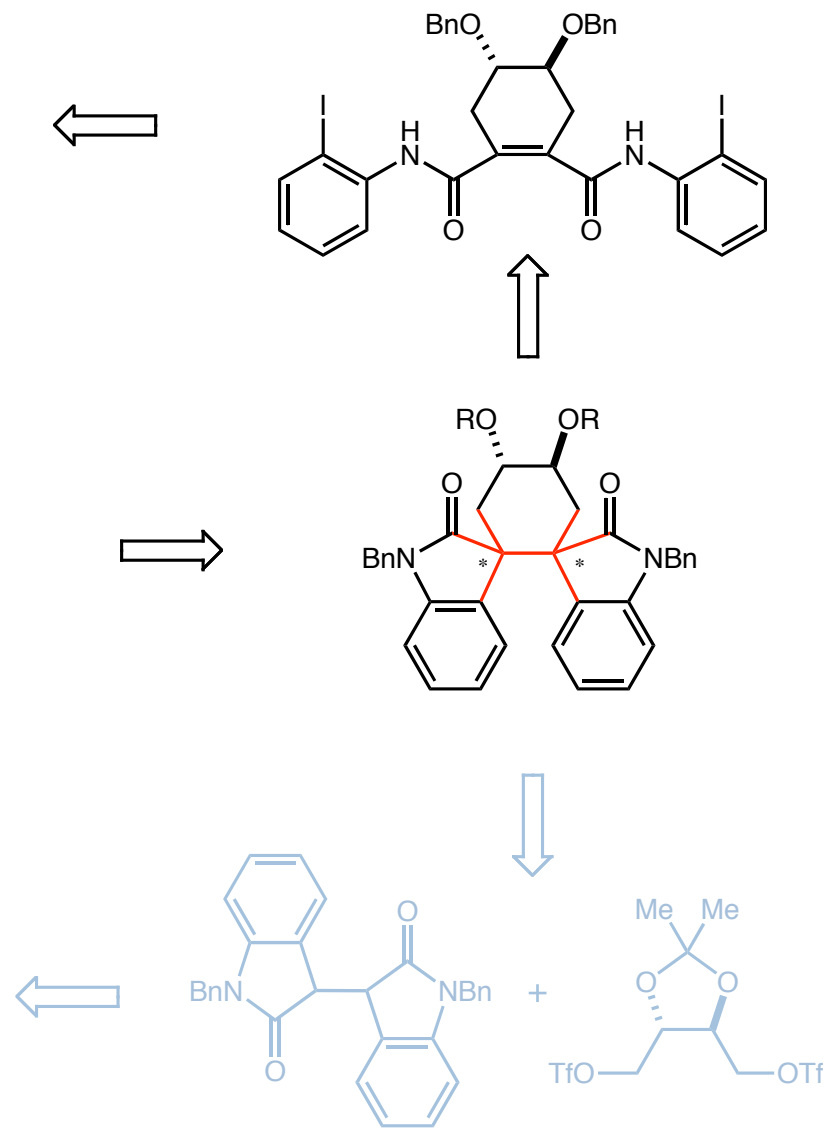
JACS 1999, 121, 7702-7703.



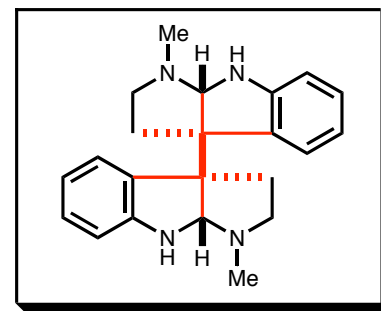
Intermolecular  
Alkylation



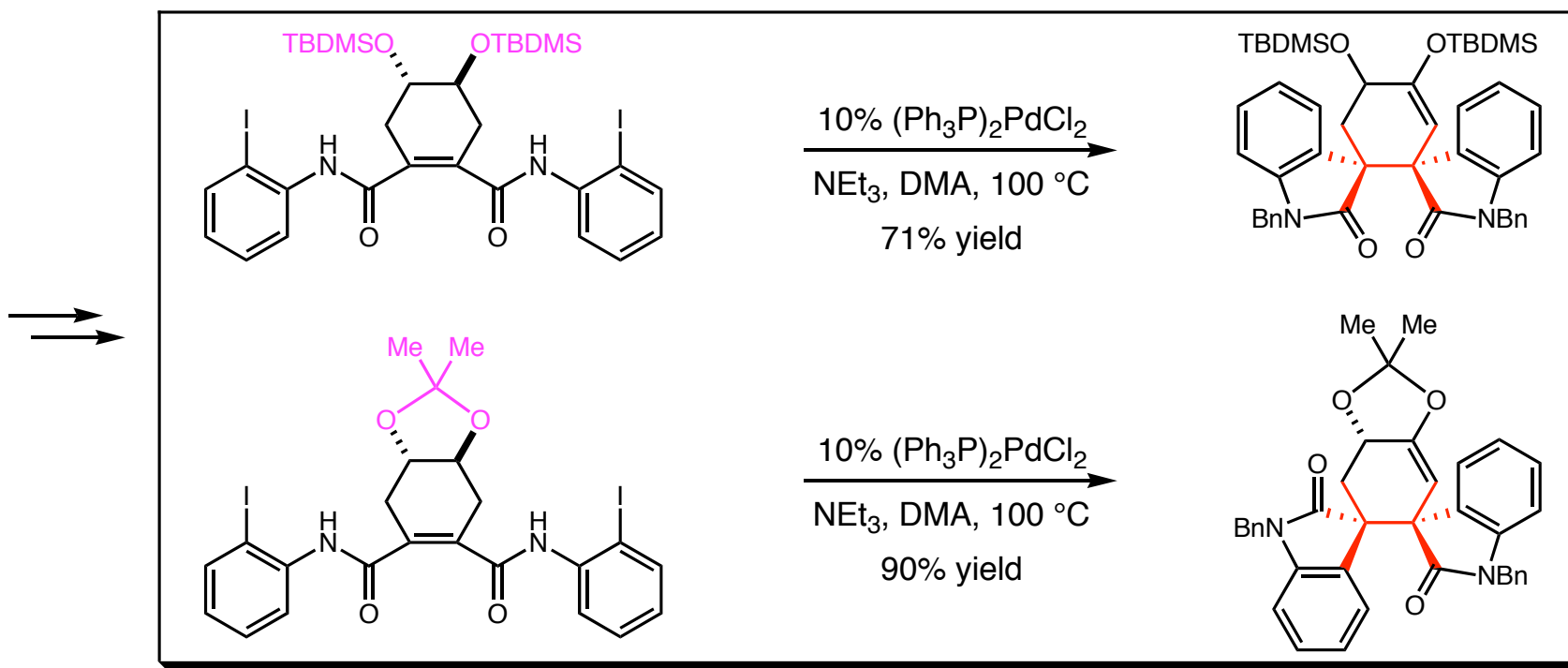
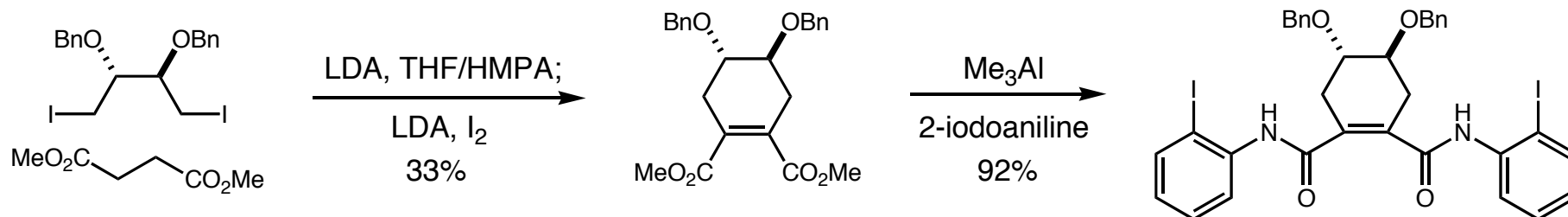
Angew. Chem. Int. Ed. 2000, 39, 213-215.  
OL 2000, 2, 3241-3244.



# Intramolecular Heck-Reaction Cascade: Enantioselective synthesis of Chimonanthine

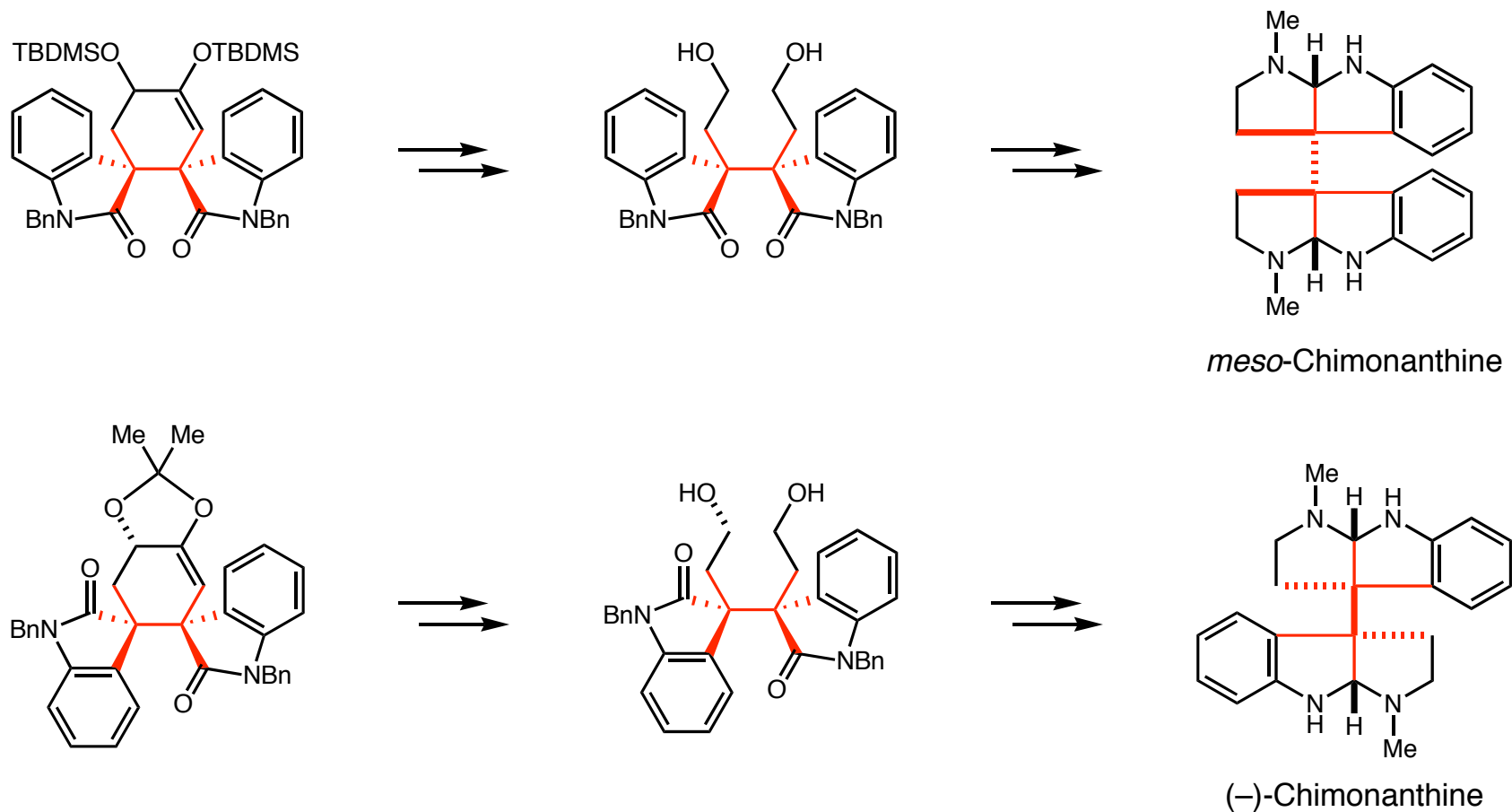


## Construction of the vicinal stereogenic quaternary carbon centers





## Intramolecular Heck-Reaction Cascade: Endgame



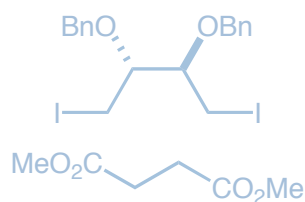
- Both products are formed with complete stereocontrol
- Variation in protecting group allows access to both stereogenic products
- To date, this represents the only example of catalytic asymmetric approach to vicinal quaternary stereocenters

# Intramolecular Heck Reaction vs. Intermolecular Alkylation

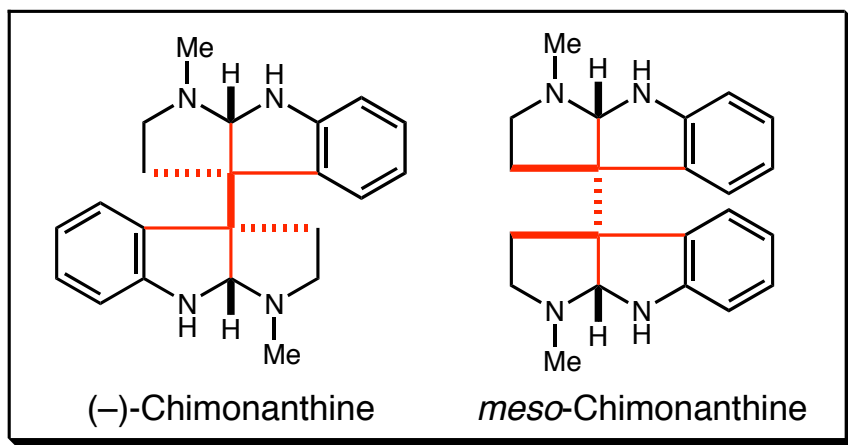
Total synthesis of Chimonanthe by Overman

## Retrosynthetic analysis

Intramolecular  
Heck-Reaction



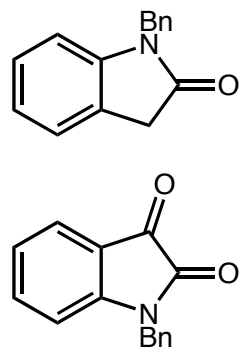
JACS 1999, 121, 7702-7703.



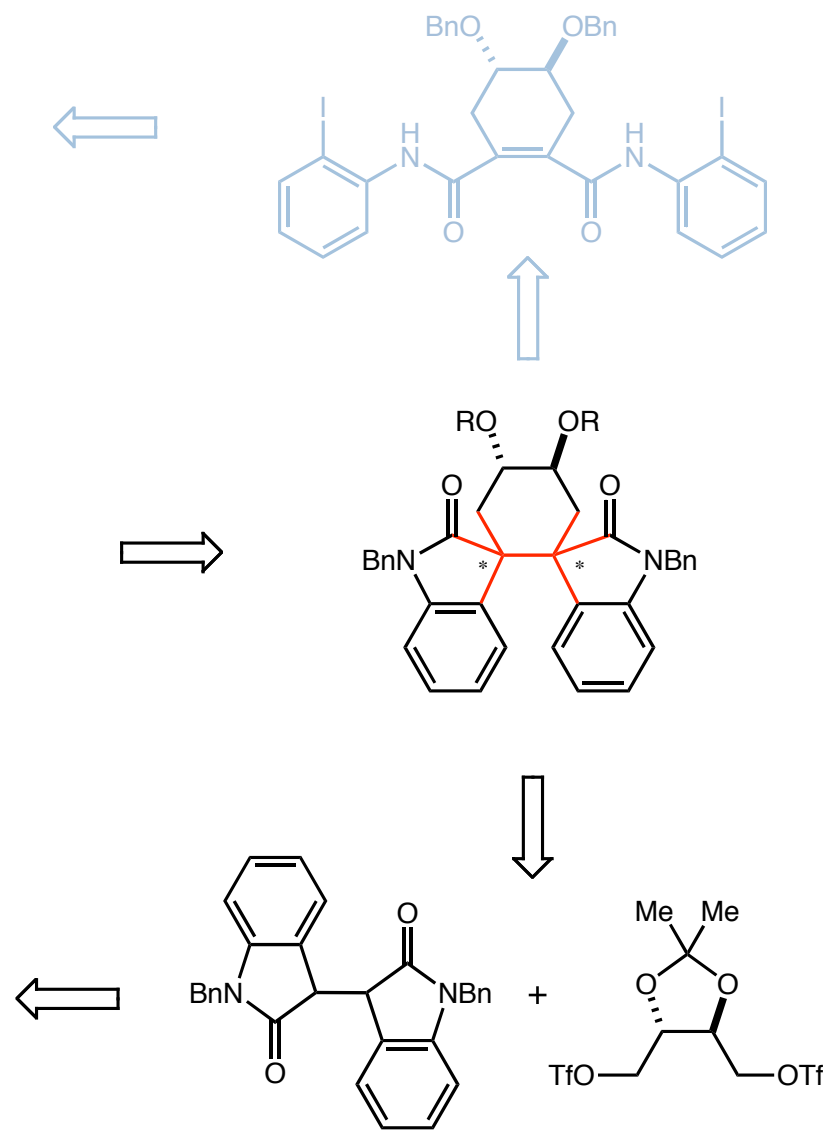
(-)-Chimonanthine

meso-Chimonanthine

Intermolecular  
Alkylation



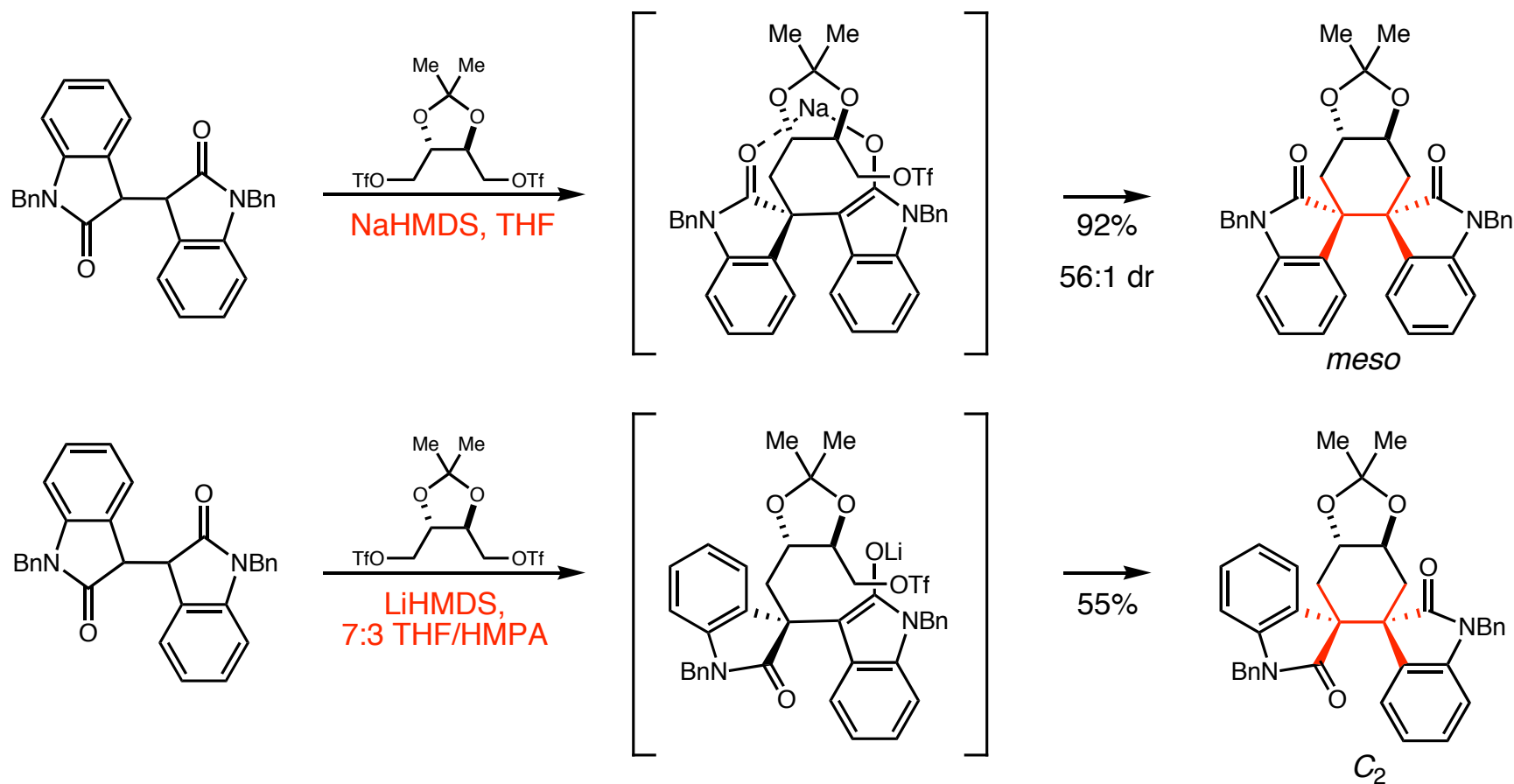
Angew. Chem. Int. Ed. 2000, 39, 213-215.  
OL 2000, 2, 3241-3244.



# Intermolecular Transformation to Install Vicinal Quaternary Stereogenic Centers

Stereoselective dianion dialkylation: an alternative route to Chimonanthine

## ■ Stereoselective dialkylation: Metal- and solvent-dependence



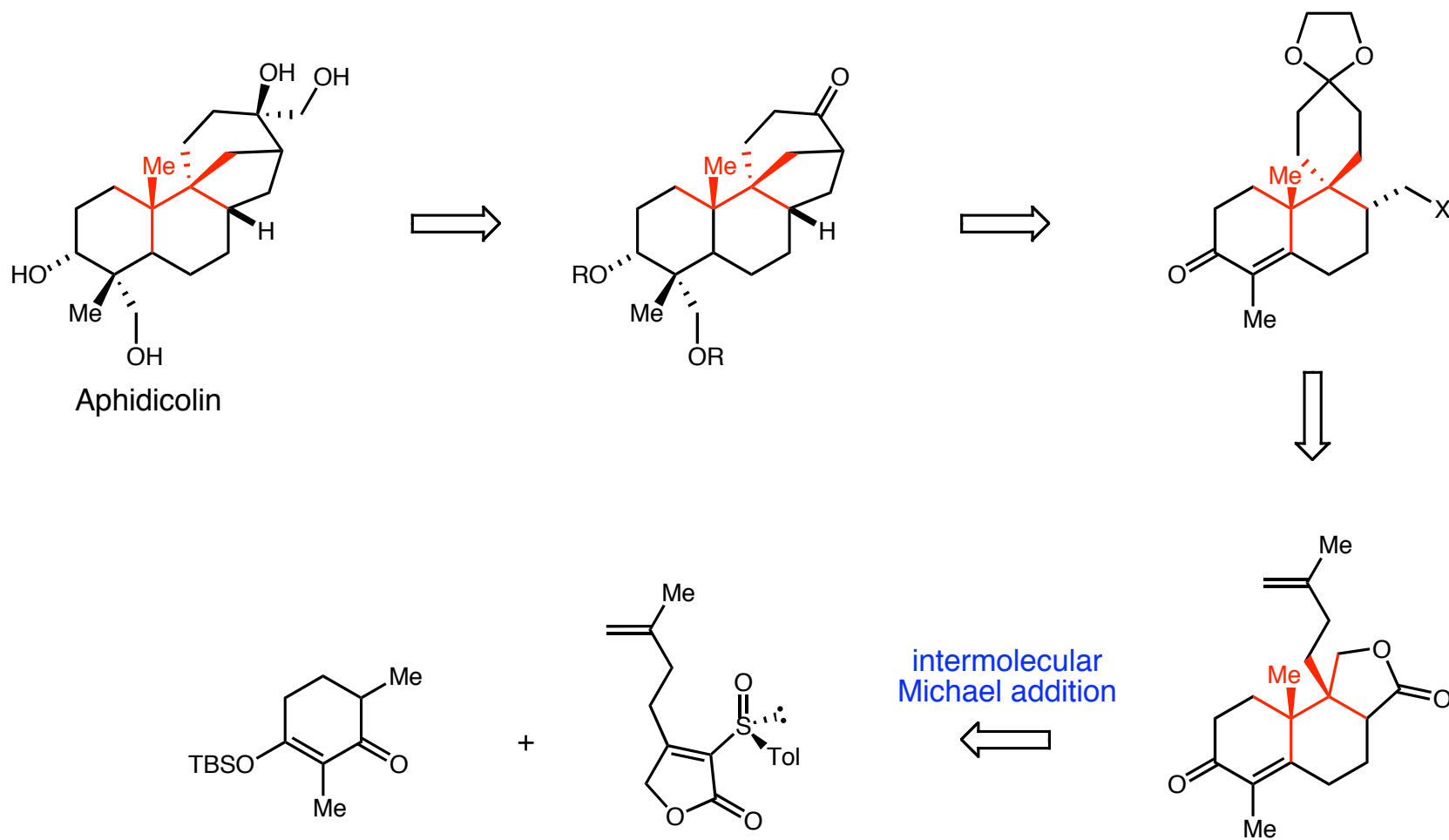
- The *C*<sub>2</sub>-symmetric derivative was obtained with very high enantio- (100:1) and good diastereoselectivity (8:1)
- This represents a rare example of high stereoselection resulting from the reaction of a prostereogenic enolate with a chiral, sp<sup>3</sup>-hybridized electrophile

Overman: *Angew. Chem. Int. Ed.* **2000**, 39, 213-215.  
Overman: *OL* **2000**, 2, 3241-3244.

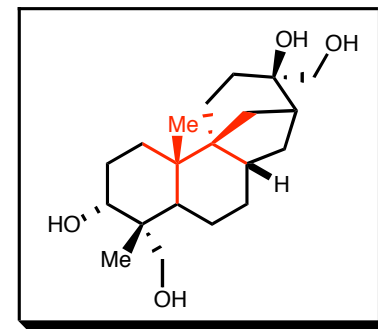
# Intermolecular Michael Reaction

## Enantioselective synthesis of Aphidicolin

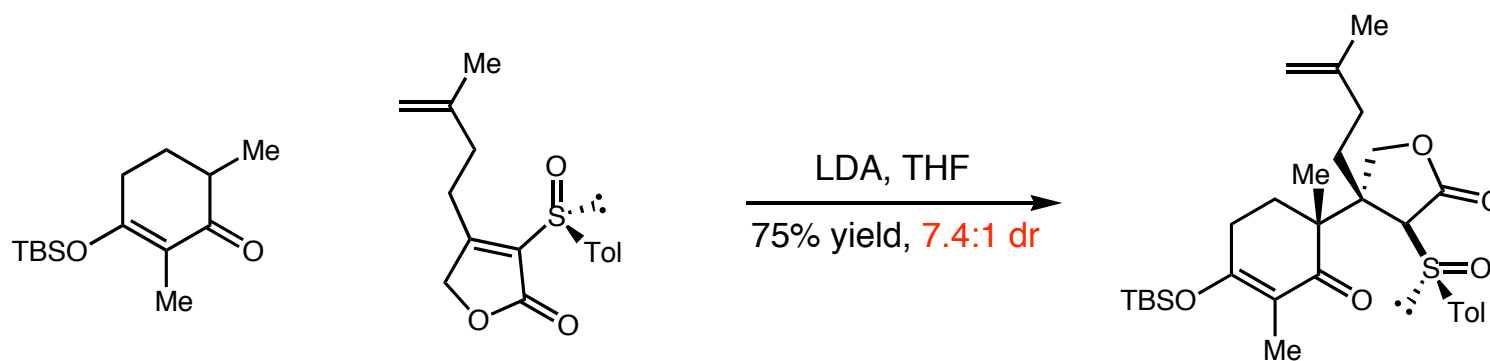
### Retrosynthetic analysis



## Intermolecular Michael Reaction: Total Synthesis of Aphidicolin

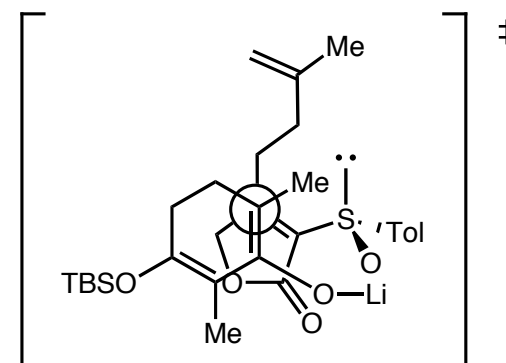


### ■ Vicinal quaternary stereocenter construction

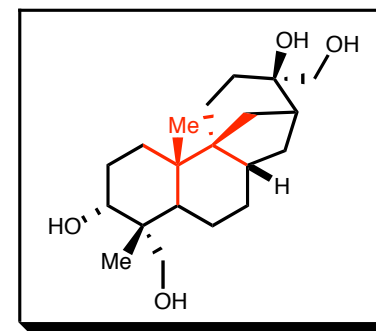


- The Michael addition may be carried out under aprotic conditions, provided that the enolate formed in the addition reaction is more stabilized than that of which acts as the nucleophilic addend

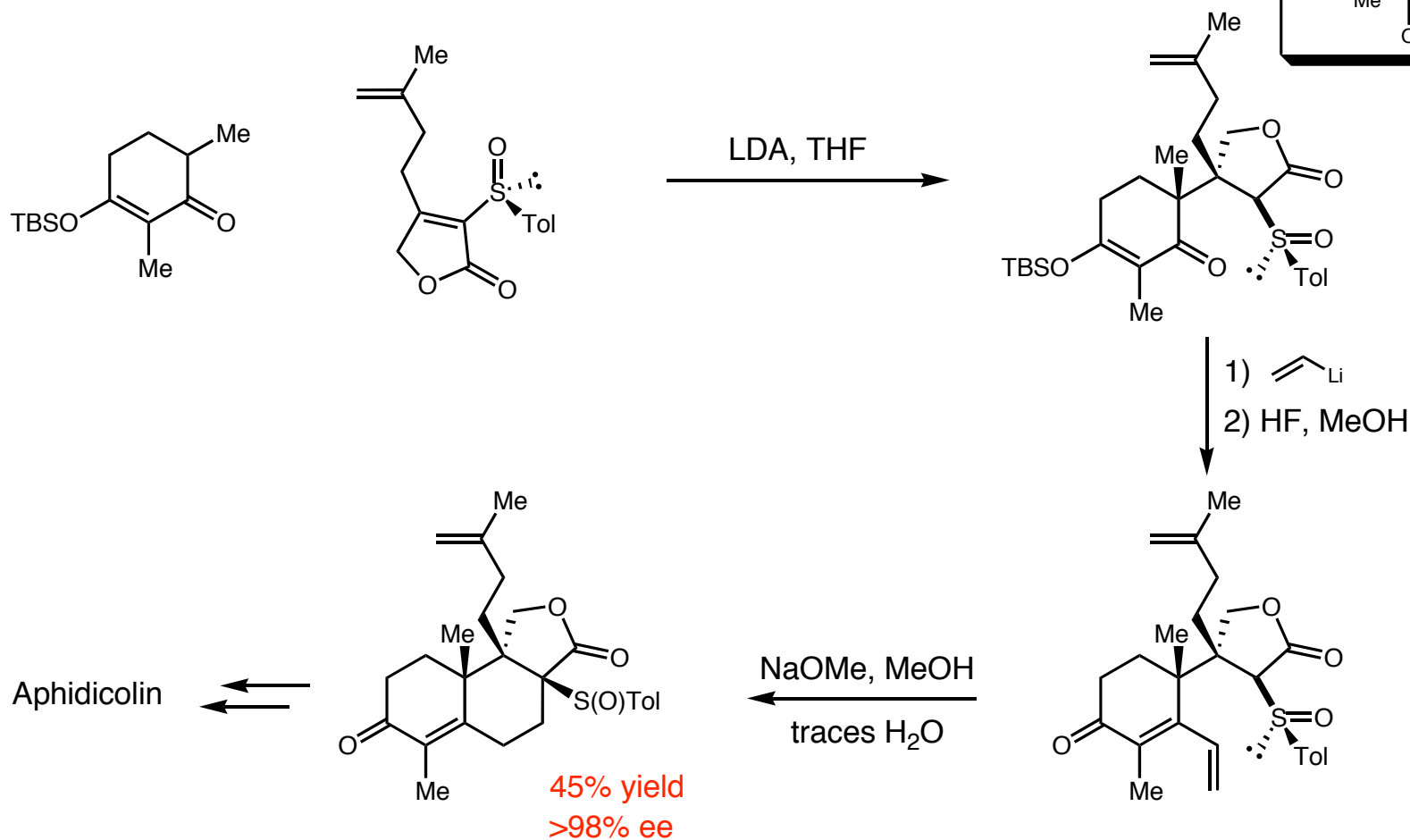
⇒ Two electron-withdrawing groups attached to the Michael acceptor are enough to compensate the steric bulk originated by the formation of the vicinal quaternary carbons



# Intermolecular Michael Reaction: Total Synthesis of Aphidicolin



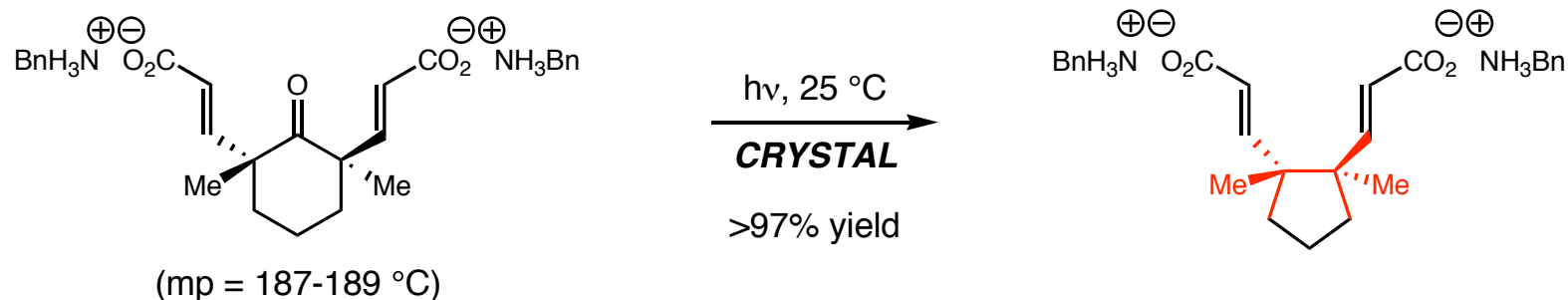
- One-pot procedure for the construction of the core system of aphidicolin



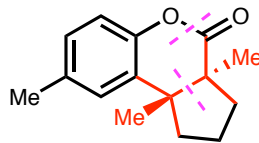
# Green Chemistry Strategies: Decarbonylation Reactions

Photochemical crystal-to-crystal reactions

## ■ Proof of concept



- Reaction run on 1.5 g scale: microcrystals suspended in hexane and irradiated with a medium-pressure Hg lamp using a pyrex jacket ( $\lambda \geq 290\text{ nm}$ ) for 12 h. Product was simply collected by filtration.
- A robust crystal lattice is needed to ensure stereochemistry transfer from reactant to product
- Reaction relies on the high energy content of the ketone  $n,\pi^*$  excited state (ca. 80 kcal/mol)
- Reaction relies on the effects of the  $\alpha$ -substituents, which lower the bond dissociation energies of the two  $\alpha$ -bonds
- Substituents with radical-stabilizing energies (RSE) > 12–15 kcal/mol should enable the solid-state reaction (e.g., crystalline ketones with secondary, tertiary, and quaternary  $\alpha$ -carbons bearing phenyl, carbonyl, dialkoxy, and  $\alpha$ -alkenyl groups)
- Applied to the total synthesis of ( $\pm$ )-Herbertenolide



Garcia-Garibay: *OL* **2004**, *6*, 645-647.  
Garcia-Garibay: *OL* **2005**, *7*, 371-374.  
Garcia-Garibay: *JACS* **2005**, *127*, 7994-7995.

## *Conclusions*

- At present, only limited number of chemical synthesis strategies have been devised for directly assembling vicinal quaternary carbon centers
- Mainly intramolecular approaches such as biomimetic polyene cycloadditions, cycloaddition reactions, and sigmatropic rearrangements have been used to control the stereochemistry of adjacent quaternary centers
- Only two types of intermolecular transformations have been realized. In both cases, the alkylation diastereoselectivity results from the union of a chiral electrophile with an achiral nucleophile (extremely rare!)
- To date, only one diastereoselective catalytic reaction has been developed (Heck-reaction) and no catalytic asymmetric approach has been disclosed!