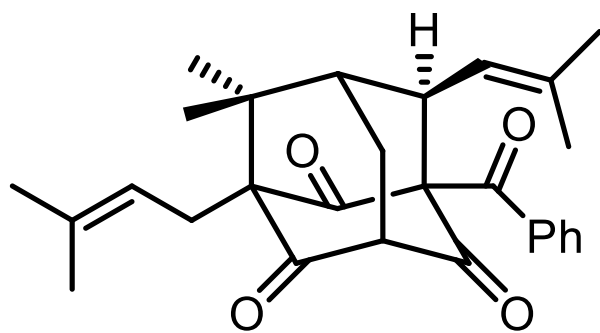
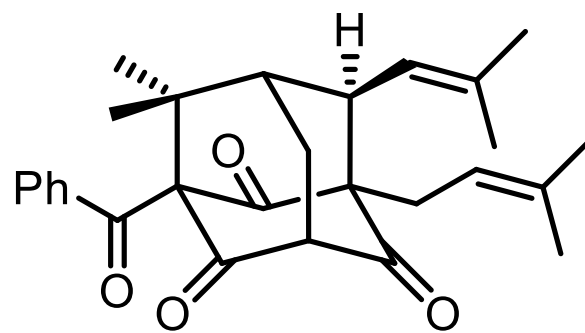


# Research Progress of Polycyclic Polyprenylated Acylphloroglucinols

## —Total synthesis of adamantane-PPAPs



hyperibone K



plukenetione A

Group Seminar  
Zhepei Lu  
2022-09-29



John A. Porco, Jr.  
CMD director and Professor of Chemistry  
Boston University

## Curriculum Vitae:

### 1. Education:

1981-1985, B.A. in Chemistry(summa cum laude, with Honors), **College of the Holy Cross**

1985-1988, M.S. in Organic Chemistry, **Yale University**

1988-1992, Ph.D. in Organic Chemistry, **Harvard University**

(Director: **Prof. Stuart Schreiber**)

### 2. Work experience:

1992, postdoctoral fellow, **Scripps Research Institute**  
(Director: **Prof. Chi Huey Wong**)

1992-1999, Associate of Avalon Ventures

1999-current, **Boston University**

## Representative Chinese PI educated in Porco group



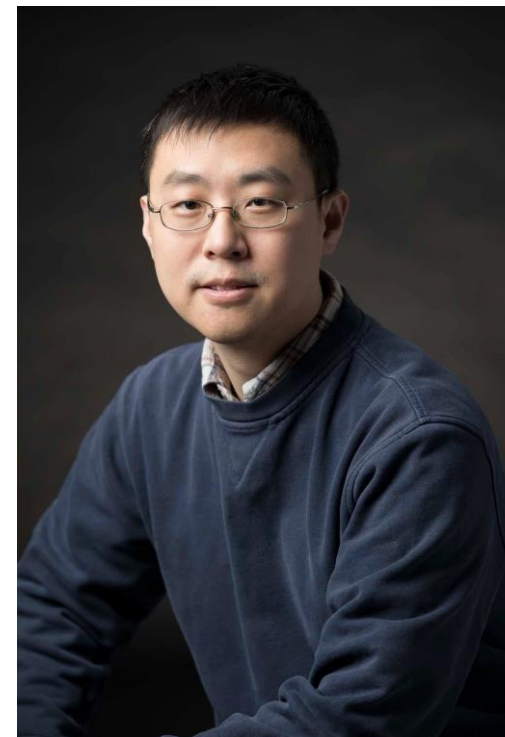
Prof. Xiaoguang Lei  
Peking University

**(+)-Panepophenanthrin**, Angew, 2003  
**(-)-Kinamycin C**, JACS, 2006



Prof. Suwei Dong  
Peking University

**(+)-Chamaecypanone C**, Angew, 2009



Prof. Huan Cong  
Tech Inst Phys & Chem, CAS

**(+/-)-Sorocenol B**, OL, 2012

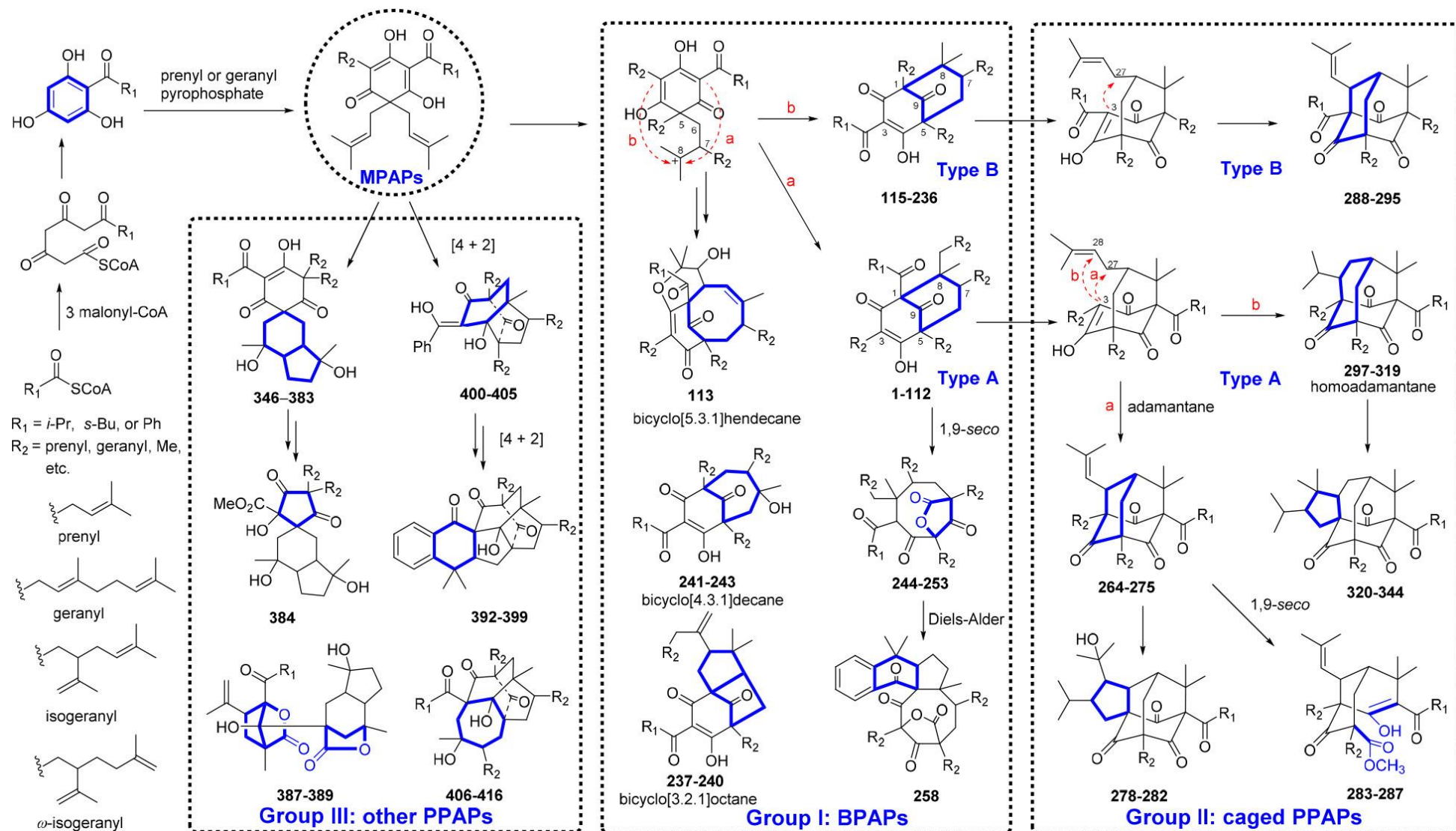
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# Introduction and Classification of Diverse PPAPs

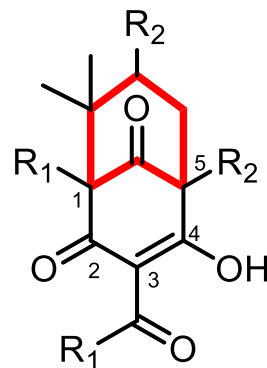




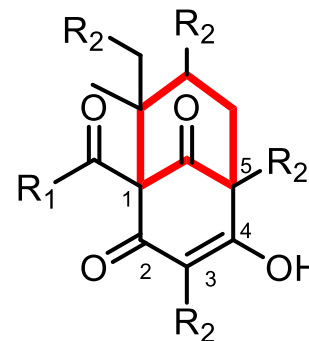
# Structural features of representative Type A and Type B BPAPs

## Type B BPAPs:

- Obtained from the **genus *Garcinia***
- Acyl group located at C-3 position
- Most of them share a characteristic hydroxylated benzoyl group
- Benzene group further oxidized and cyclized with O-2 or O-4



Type B BPAPs



Type A BPAPs

R<sub>1</sub>=*i*-Pr, *s*-Bu or Ph  
R<sub>2</sub>=prenyl, geranyl, Me, etc.

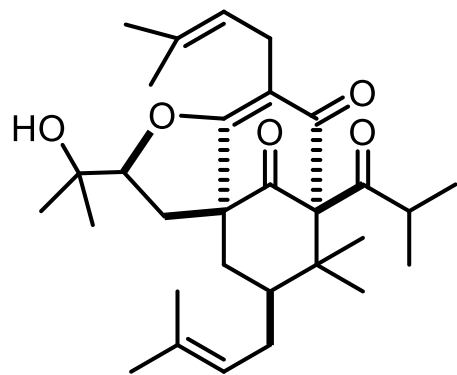
## Type A BPAPs:

- Obtained from the **genus *Hypericum***
- Acyl group located at C-1 position
- Usually obtained as keto-enol tautomeric mixtures
- C-3 and C-5 oxidized and further cyclized with O-2 or O-4 to form furan, pyran, etc..

## Common features:

1. [3.3.1] nonane skeleton
2. Quaternary center at both bridge head
3. Enolic  $\beta$ -diketone system

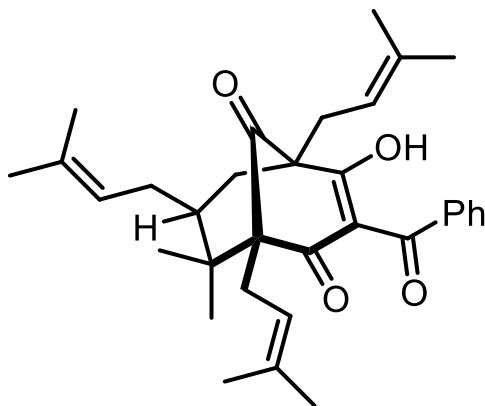
# Representative total synthesis of BPAPs



Garsubellin A

Shibasaki, JACS, 2005

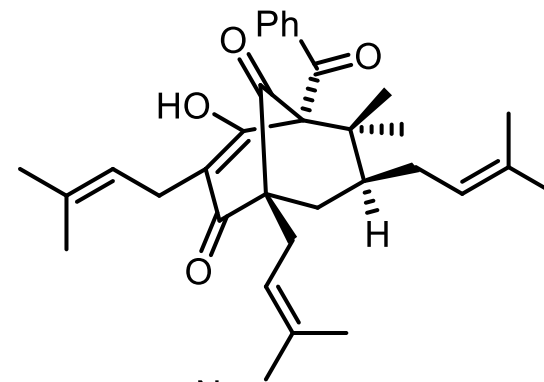
Strategy: **RCM**



Clusianone

Simpkins, JOC, 2007

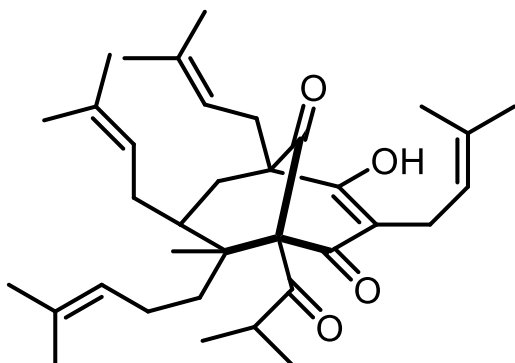
Strategy: **Effenberger  
Cyclization**



Nemorosone

Nakada, JOC, 2012

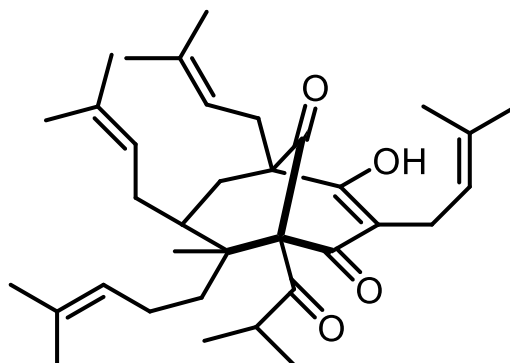
Strategy: **Cyclopropanation&Ring  
opening**



Hyperforin

Barriault, Angew, 2014

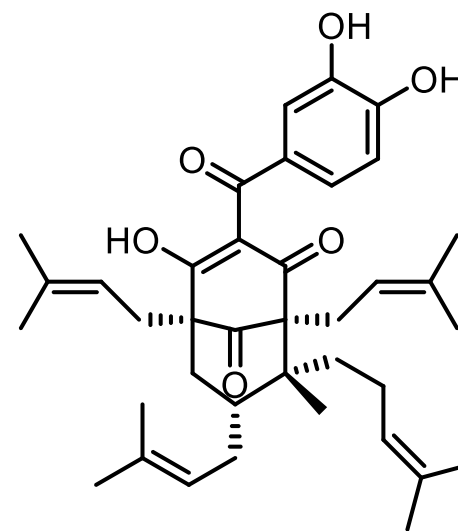
Strategy: **Gold-  
Catalyzed Cyclization**



Hyperforin

Maimone, JACS, 2015

Strategy: **Oxidative  
ring expansion**



6-epi-guttiferone A

Plietker, JACS, 2014

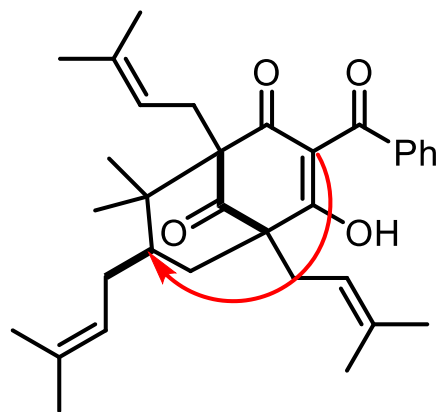
Strategy: **Ester  
condensation**<sup>8</sup>



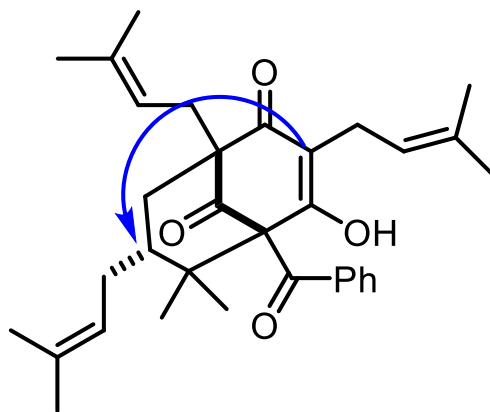
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## Target PPAPs of Porco group



clusianone



7-*epi*-nemerosone

clusianone

### **Type B BPAPs**

Isolated from the floral resins of *Clusia* species

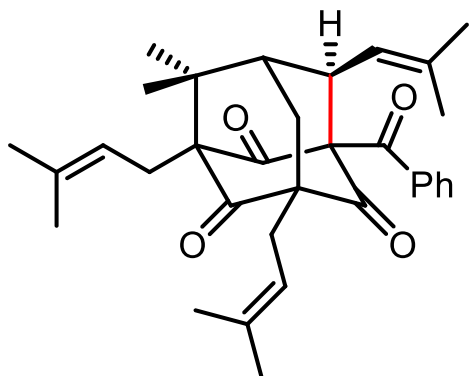
7-*epi*-nemerosone

### **Type A BPAPs**

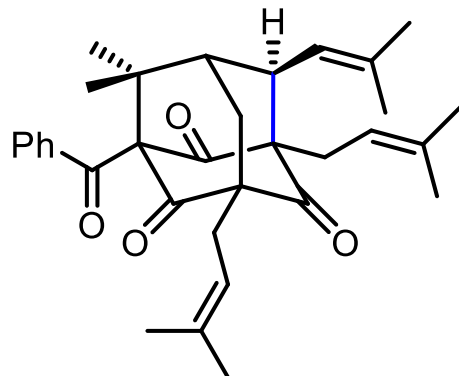
hyperibone K:

### **Type B adamantane PPAPs**

isolated from the aerial parts of *Hypericum scabrum*



hyperibone K



plukenetione A

plukenetione A:

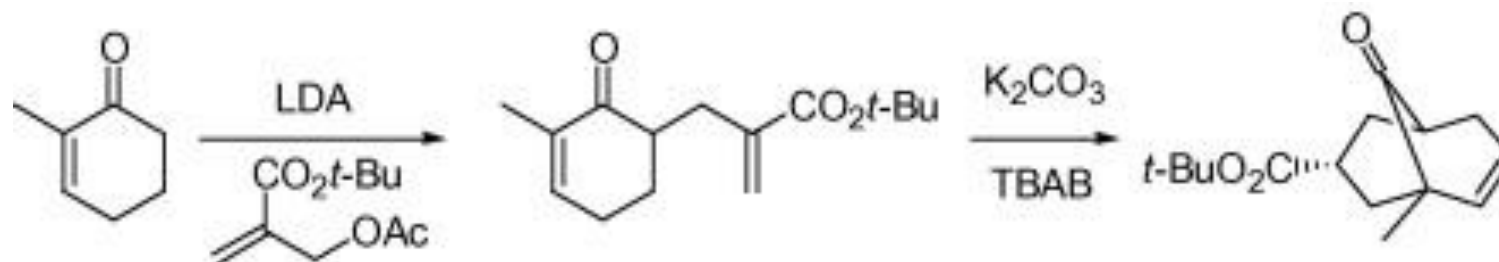
### **Type A adamantane PPAPs**

isolated from *Clusia plukenetii* (Guttiferae)

the **first natural product bearing an adamantane framework** isolated from plant sources

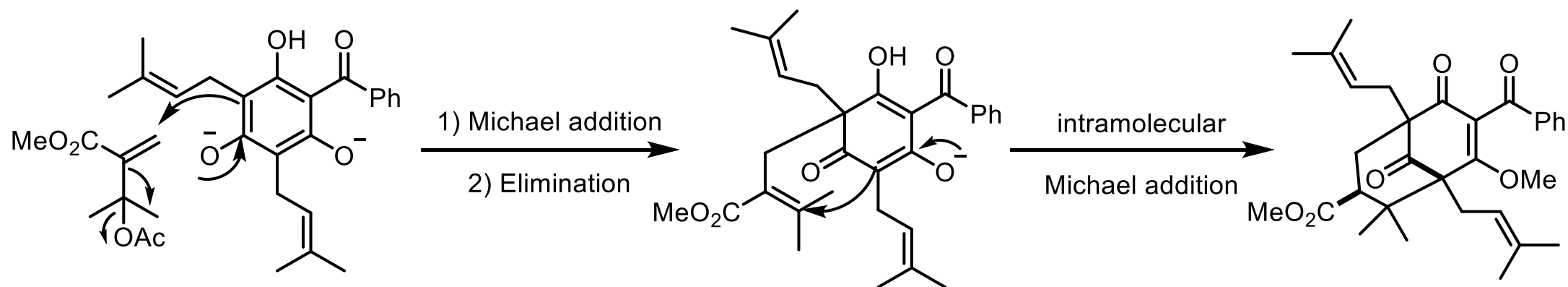
*Acta Cryst.* **1976**, B32, 1793  
*Phytochemistry* **1999**, 50, 1073  
*J. Nat. Prod.* **2004**, 67, 1870  
*Tetrahedron Lett.* **1996**, 37, 8663

## Ohkata's construction of bicyclo[3.3.1] ring system

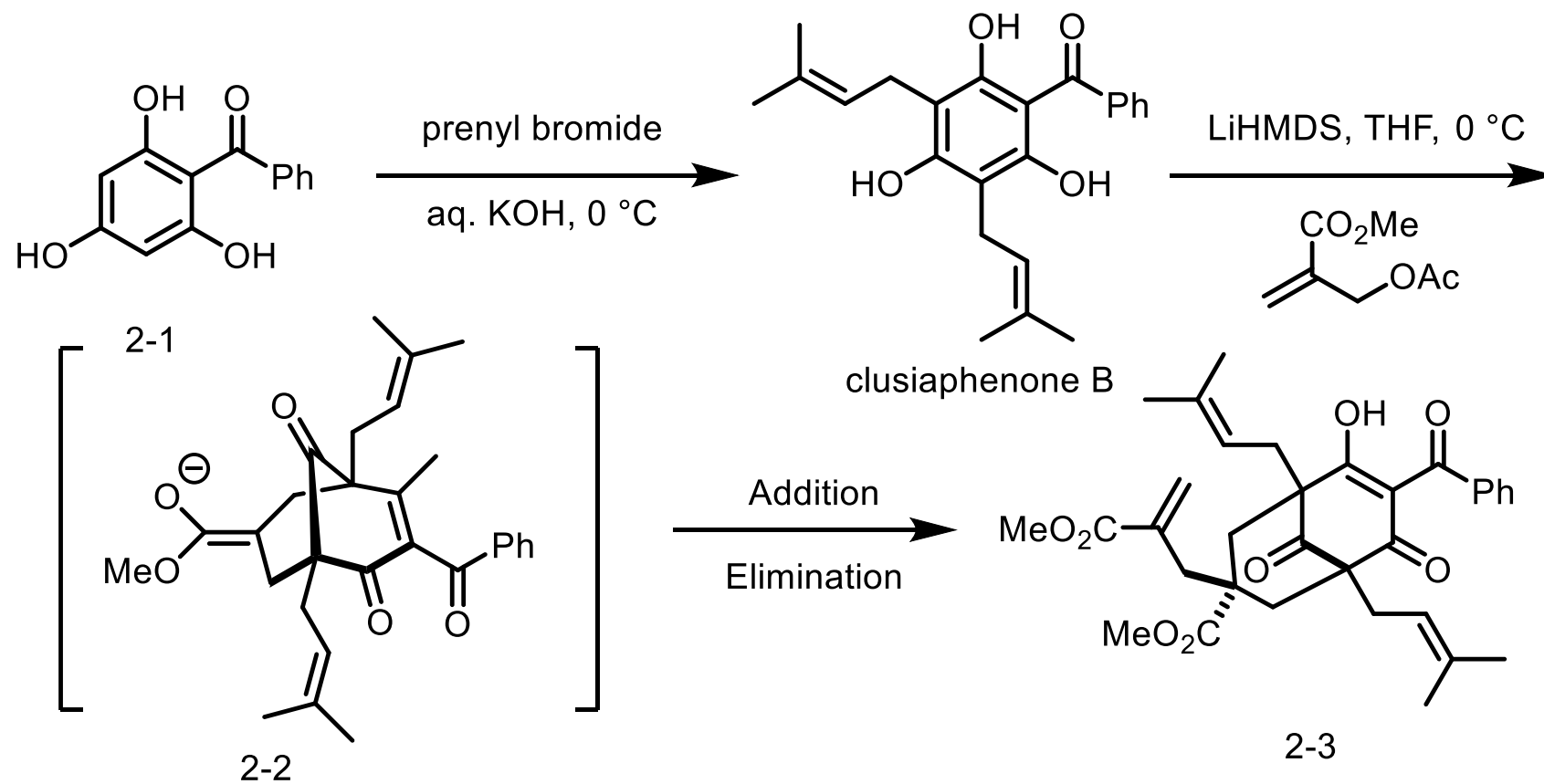


*Tetrahedron Lett.* **2004**, 45, 7401

## Porco's idea: Alkylative Dearomatization-Annulation



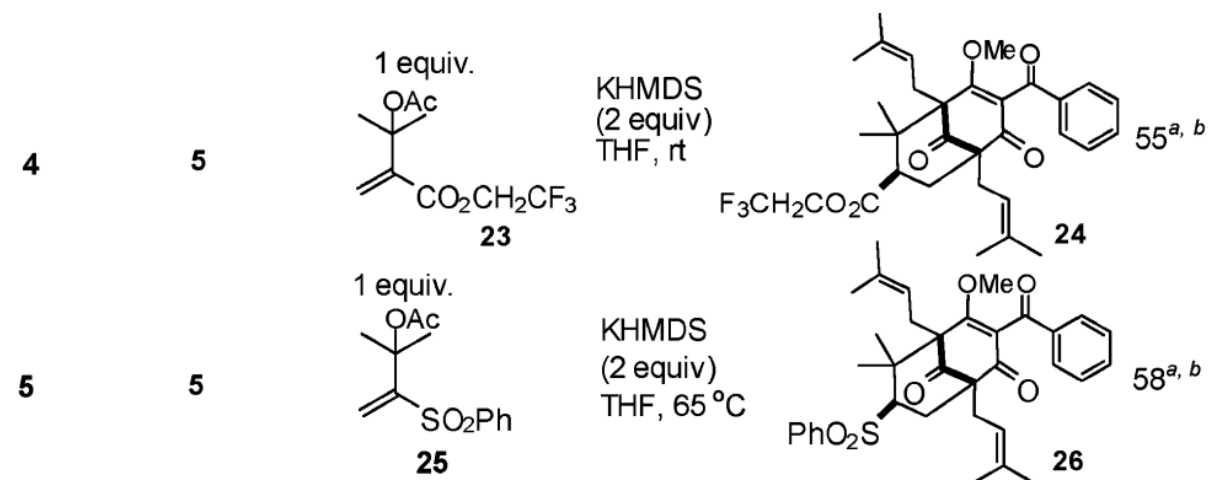
Model studies:



*J. Am. Chem. Soc.* **2007**, *129*, 12682-12683

# Scope evaluation of Alkylative Dearomatization-Annulation

entry	substrates	Michael acceptors	conditions	products	yield(%)
1		2 equiv. 	LiHMDS (3 equiv) THF, 0 °C		84
2		1 equiv. 	KHMDS (2 equiv) THF, 65 °C		41 <sup>a</sup>
3	5	1 equiv. 	KHMDS (2 equiv) THF, 65 °C		63 <sup>a, b</sup> ( $\beta:\alpha=4:1$ )

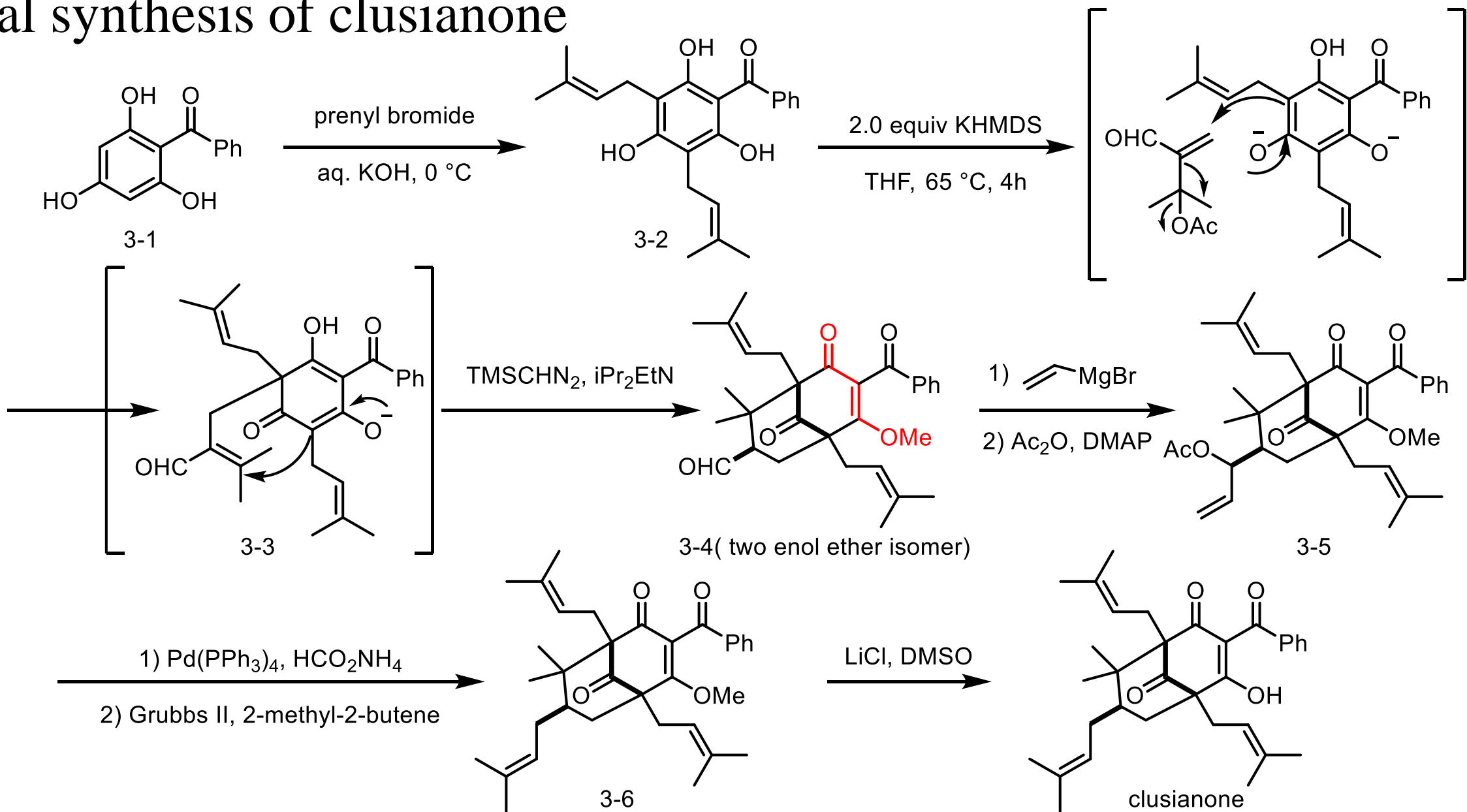


<sup>a</sup> Yield after enol methylation using TMSCHN<sub>2</sub> (2 equiv) and *i*Pr<sub>2</sub>EtN (1.5 equiv). <sup>b</sup> Mixture of enol ether isomers produced, one shown for clarity.

# Content

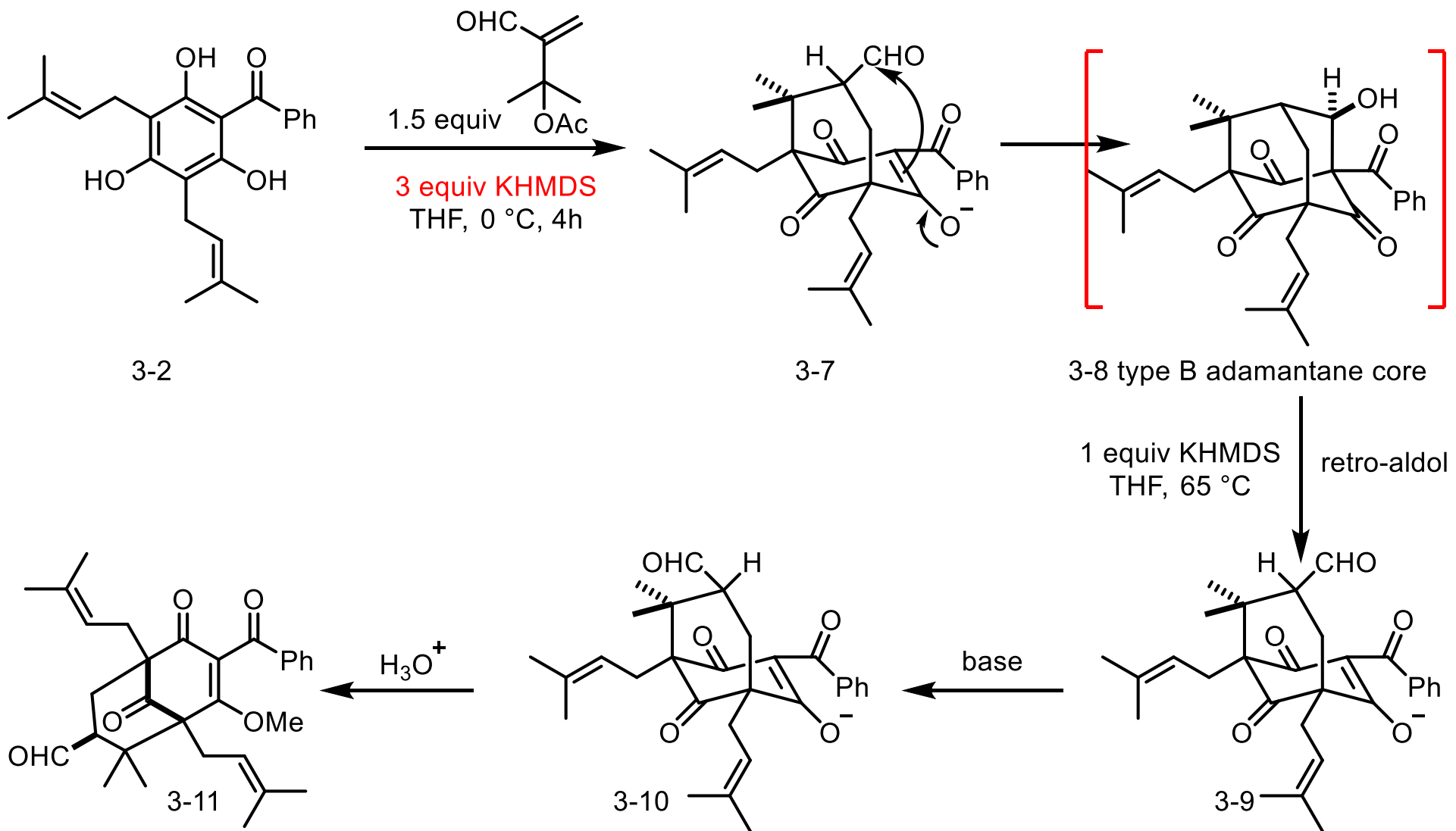
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# Total synthesis of clusianone





## An unexpected discovery: access to an adamantane core

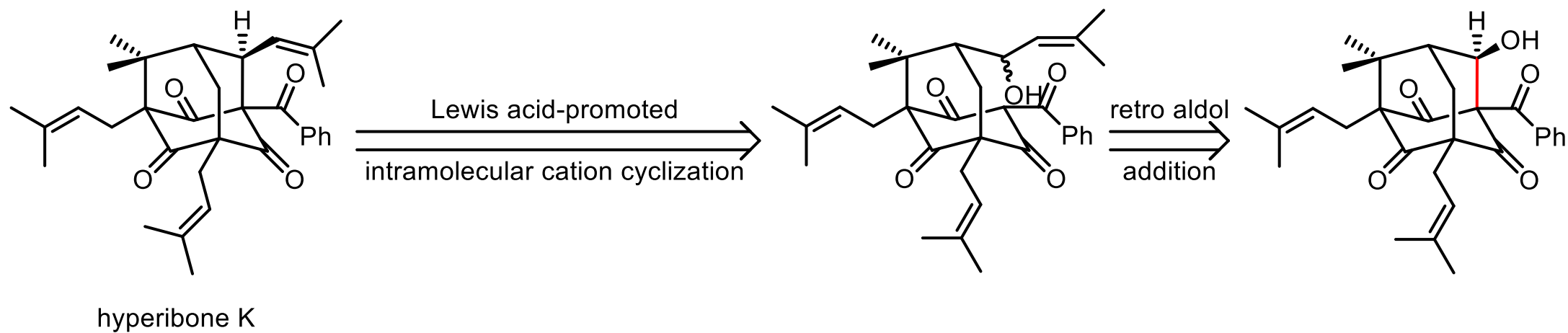


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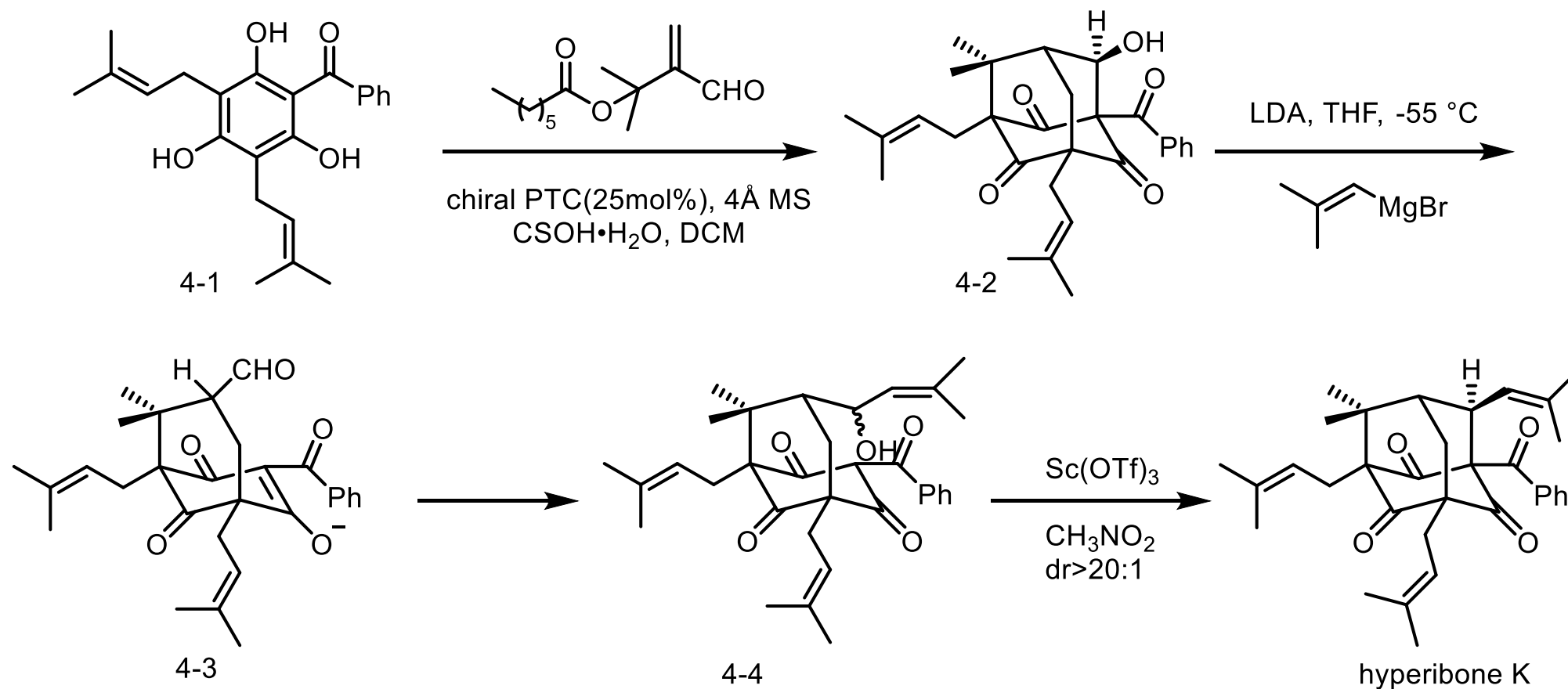
# Total synthesis of hyperibone K

## Retrosynthetic analysis



*J. Am. Chem. Soc.* **2010**, *132*, 13642–13644

# Total synthesis of hyperibone K

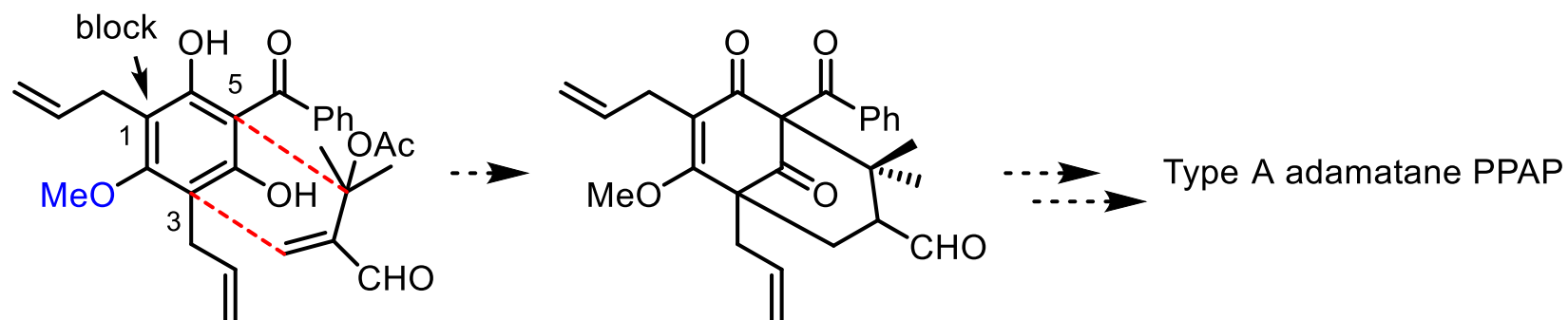


*J. Am. Chem. Soc.* **2010**, *132*, 13642–13644

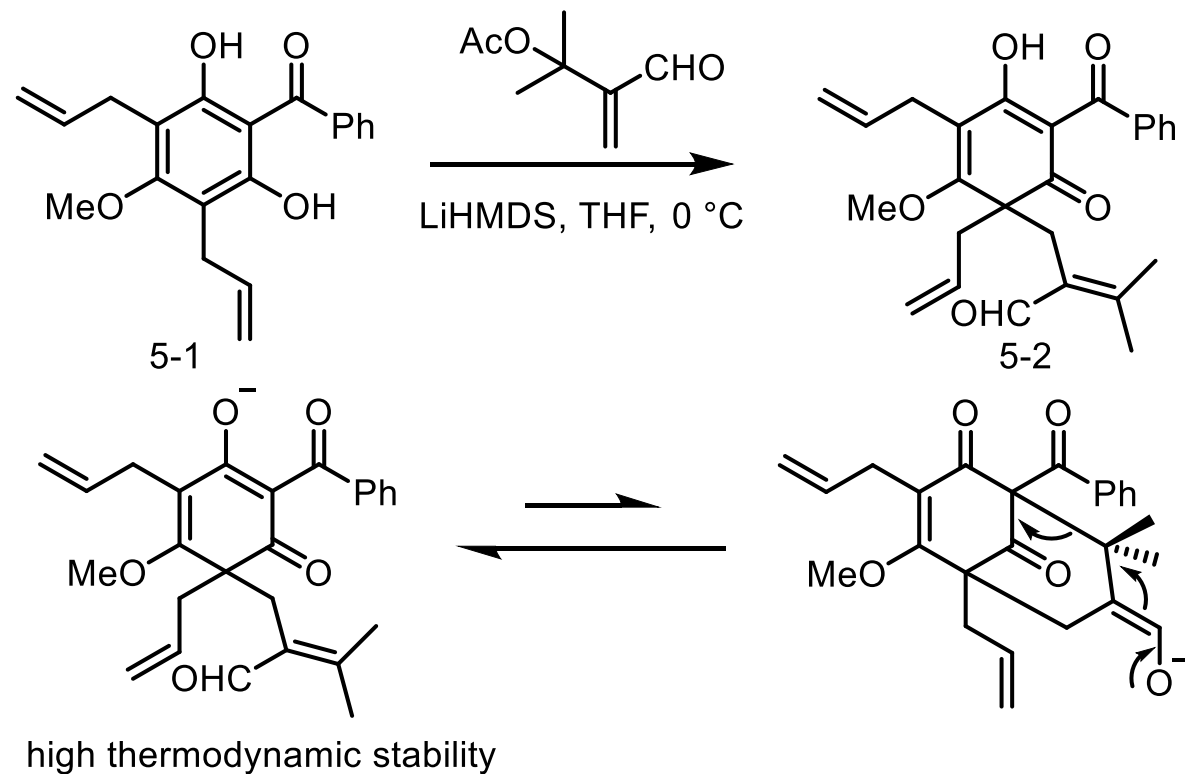
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## Synthetic plan

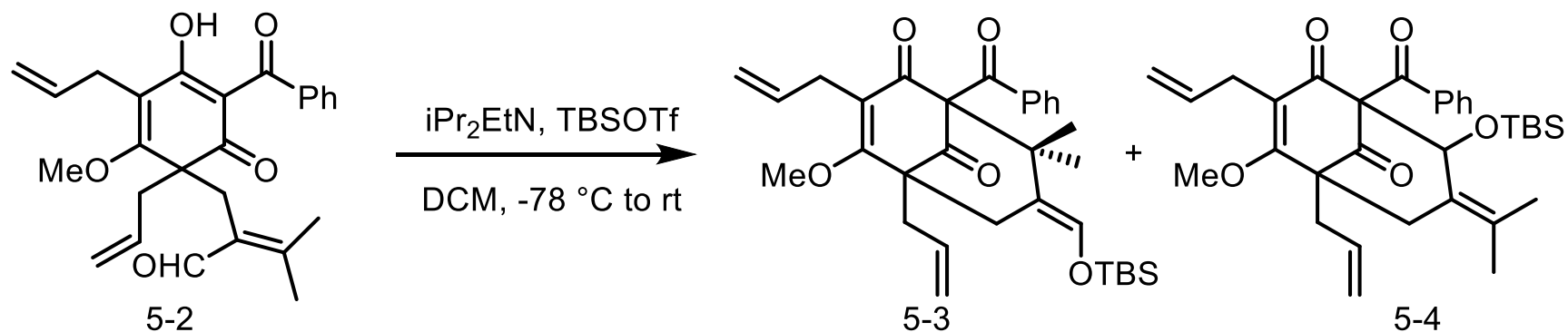


## Attempted alkylative dearomatization-annulation

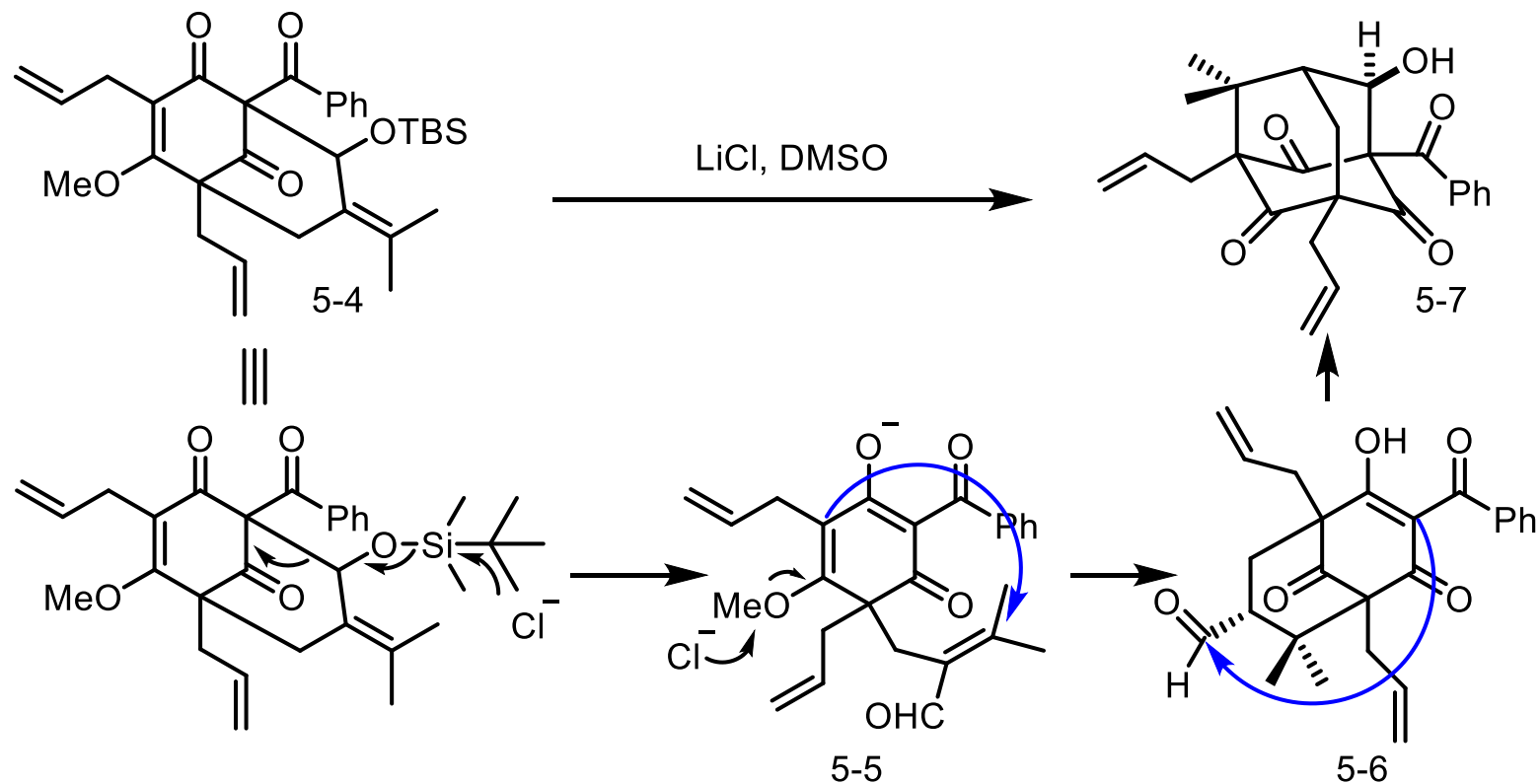


*J. Am. Chem. Soc.* **2010**, *132*, 14212–14215

## Silylative cyclization to the bicyclo[3.3.1] ring system

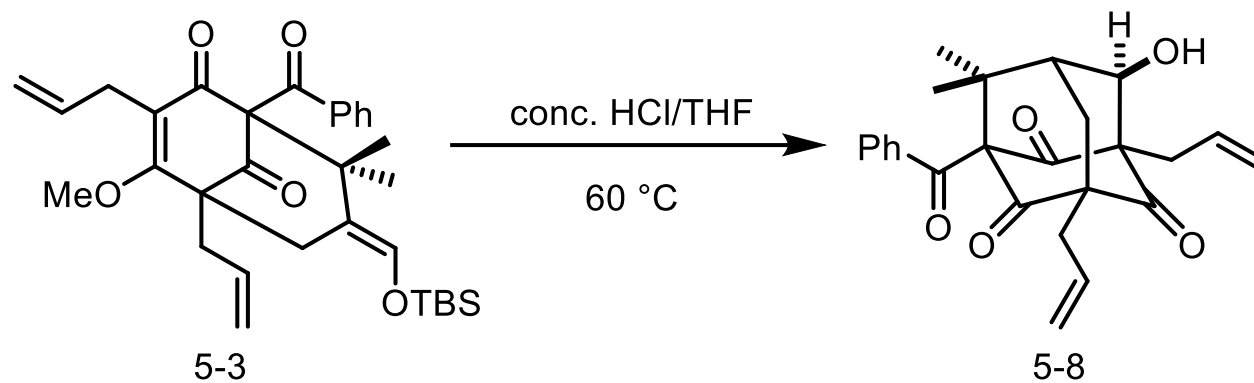


## Unexpected production of the Type B Adamantane Core

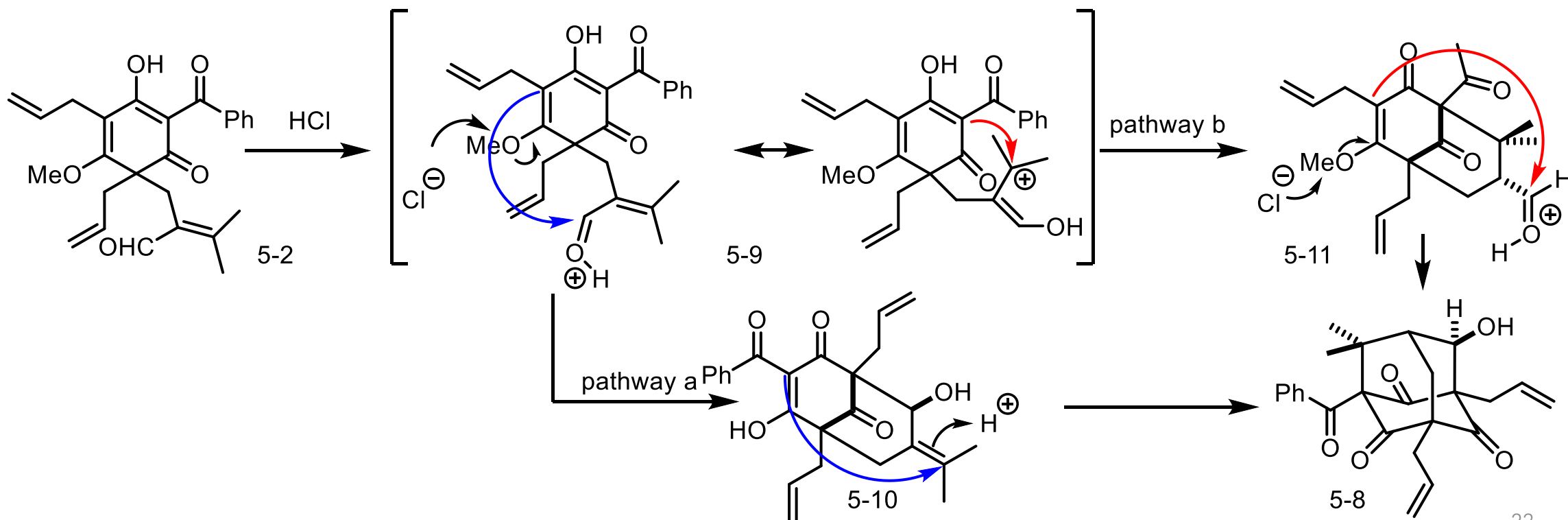




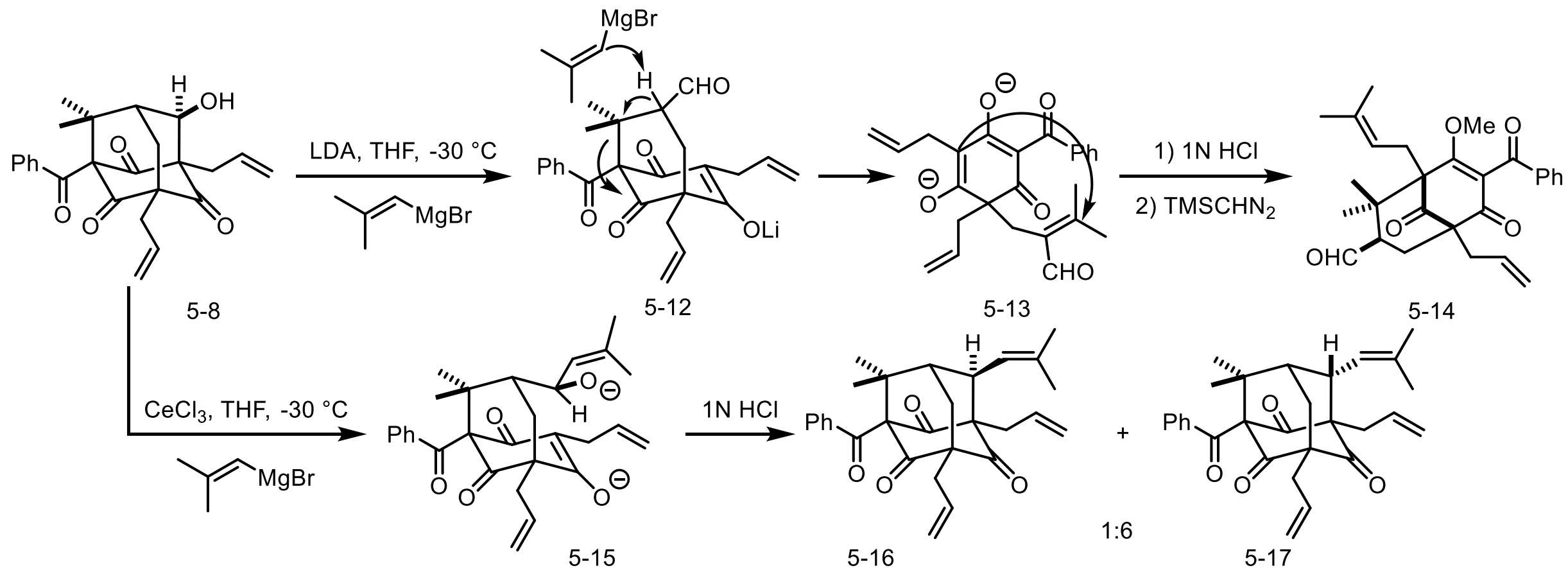
# Synthesis of the Type A Adamantane Framework



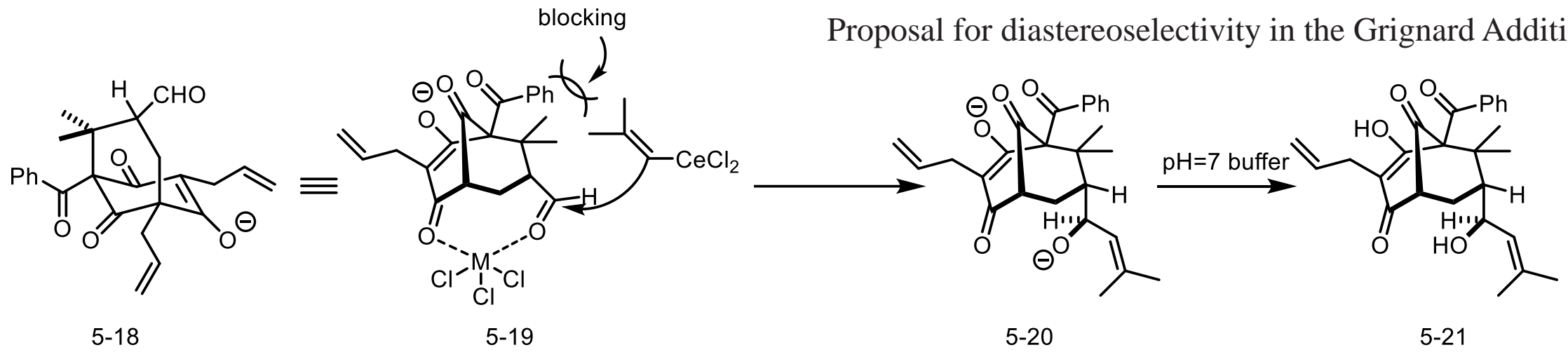
## Possible reaction mechanisms for adamantane formation



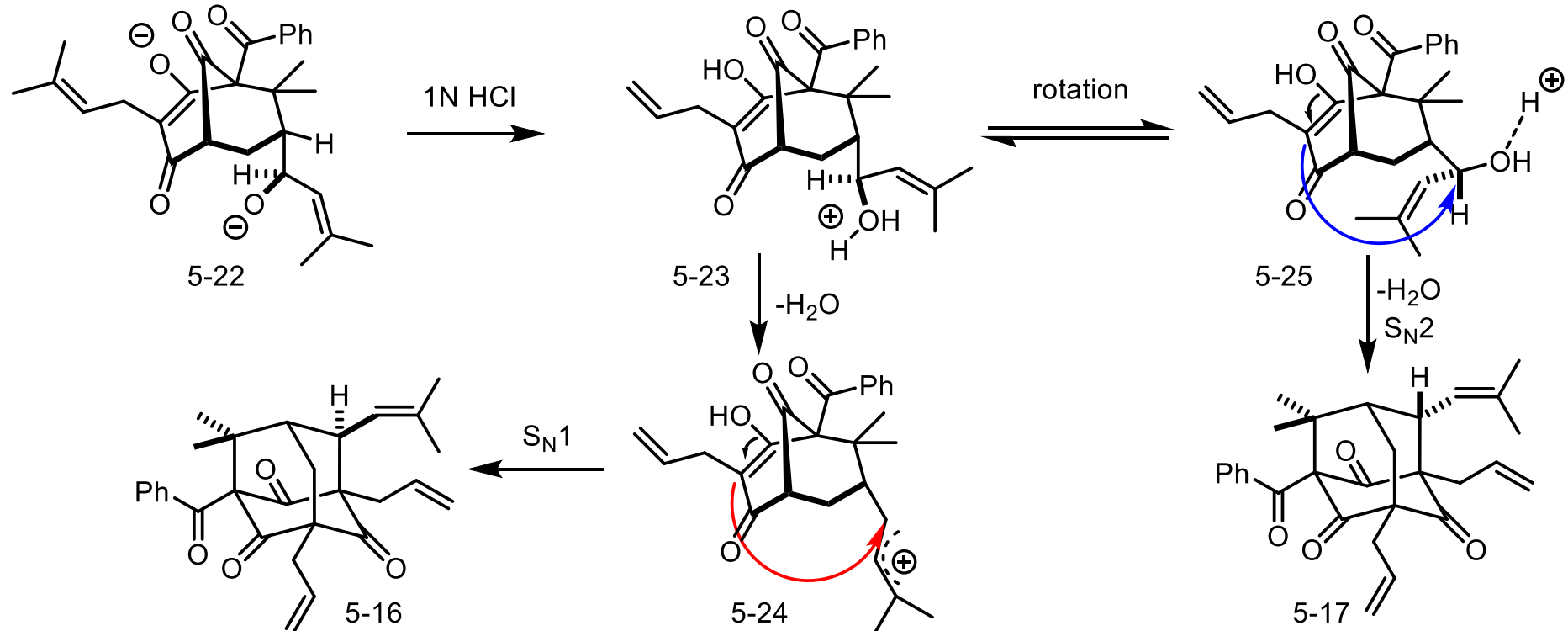
# Retro-Aldol/Addition attempt



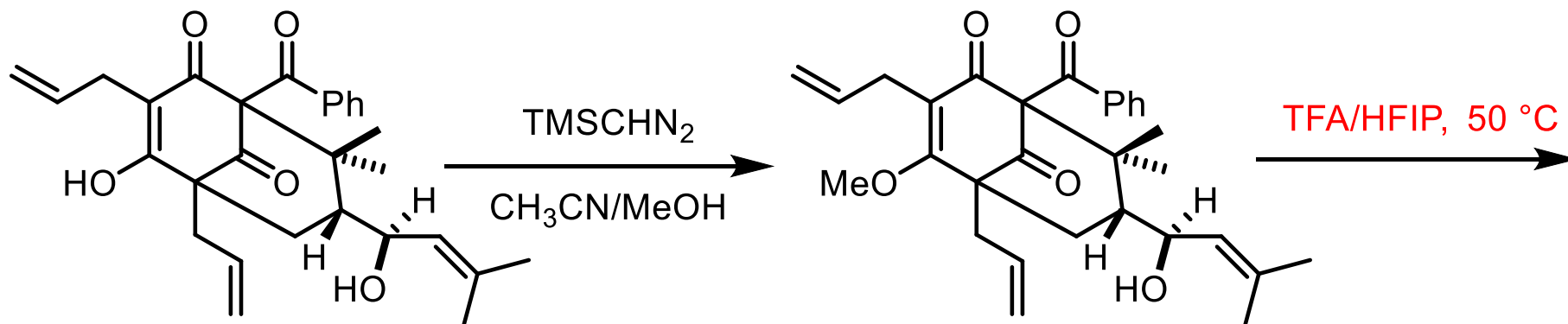
# Proposal for diastereoselectivity in the Grignard Addition



## Rationale for stereoselectivity

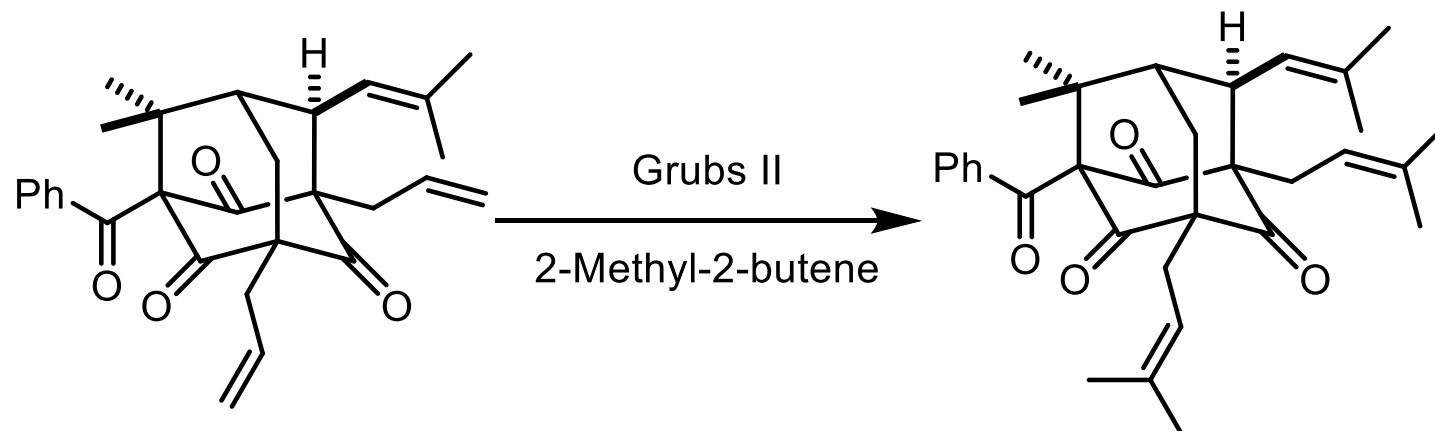


## Completion of the synthesis of plukenetione A



5-26(enol ether isomer of 5-21)

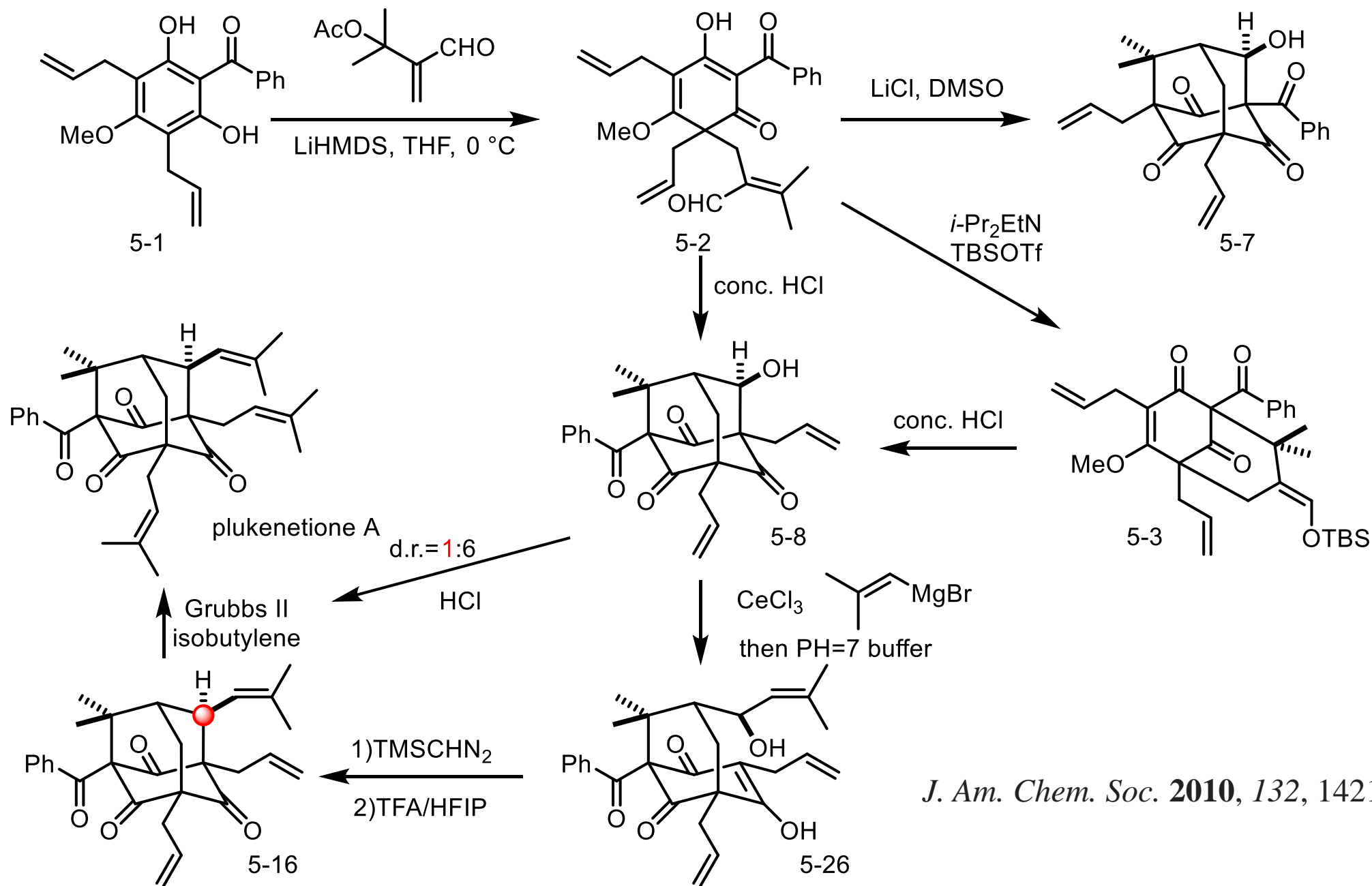
5-27



5-16

plukenetione A

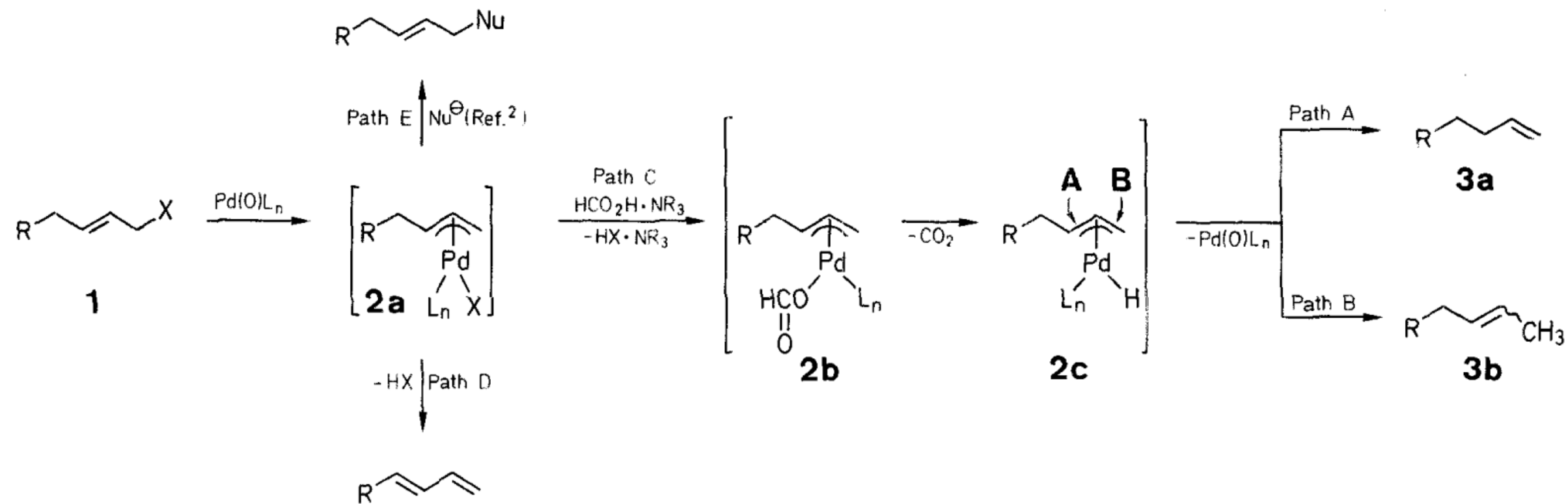
# Synthetic route of plukenetione A



*J. Am. Chem. Soc.* **2010**, *132*, 14212–14215

supplements

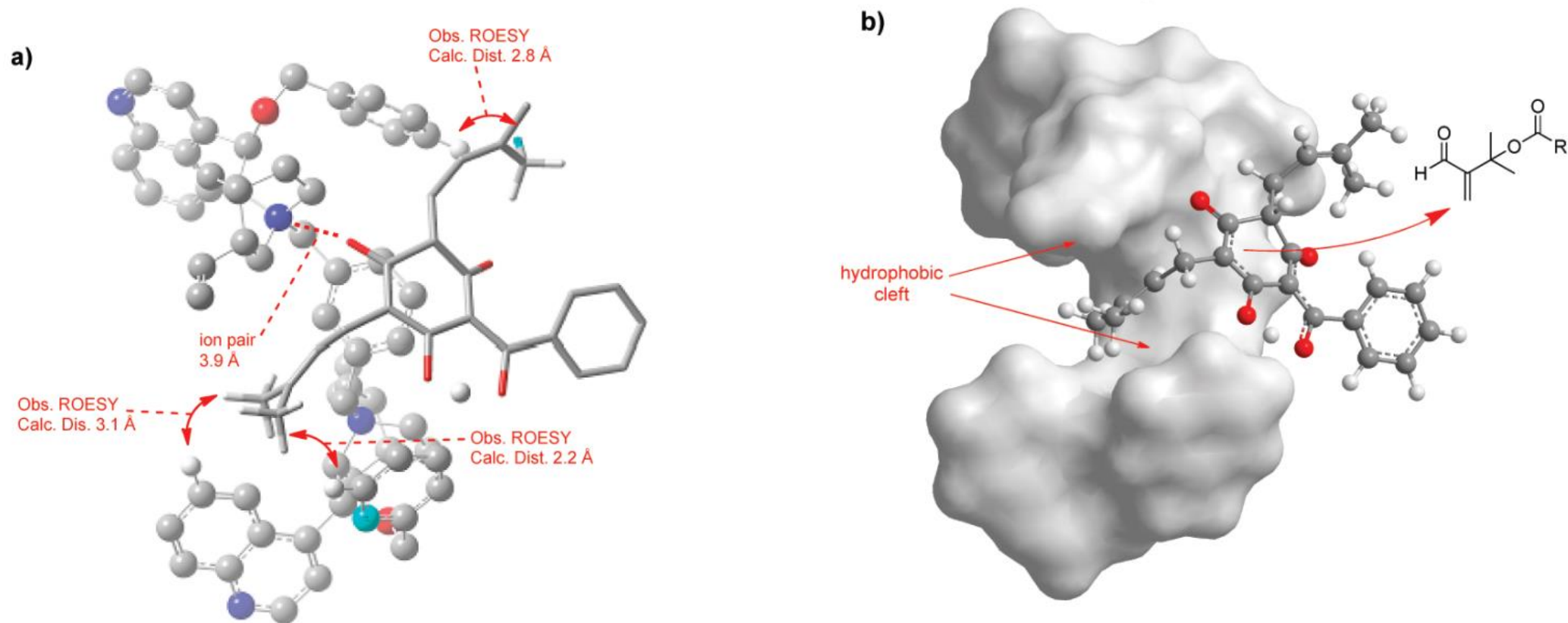
# Palladium-catalyzed formate reduction:



*Synthesis* **1986**, 623  
*Org. Lett.* **2000**, 2, 107



## Proposed Binding Model of chiral PTC and compound 4-1



*J. Am. Chem. Soc.* **2010**, *132*, 13642–13644