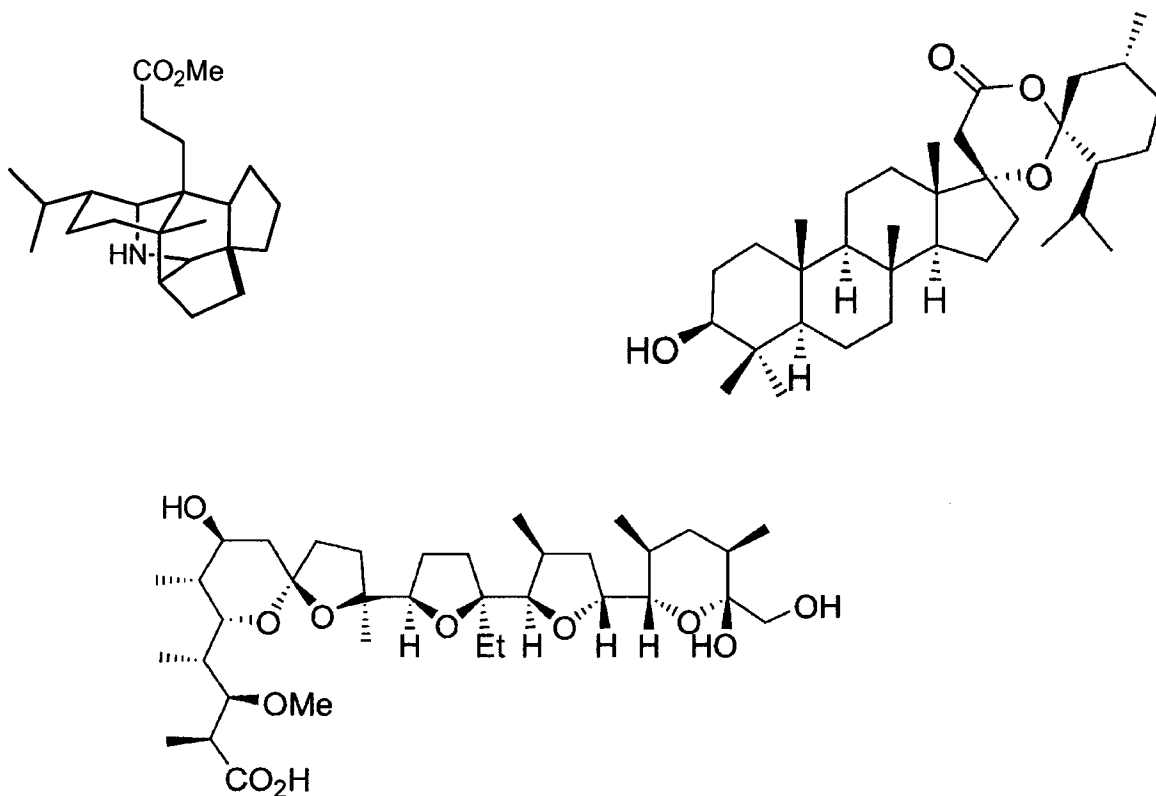


# Select Cascade Biomimetic Syntheses

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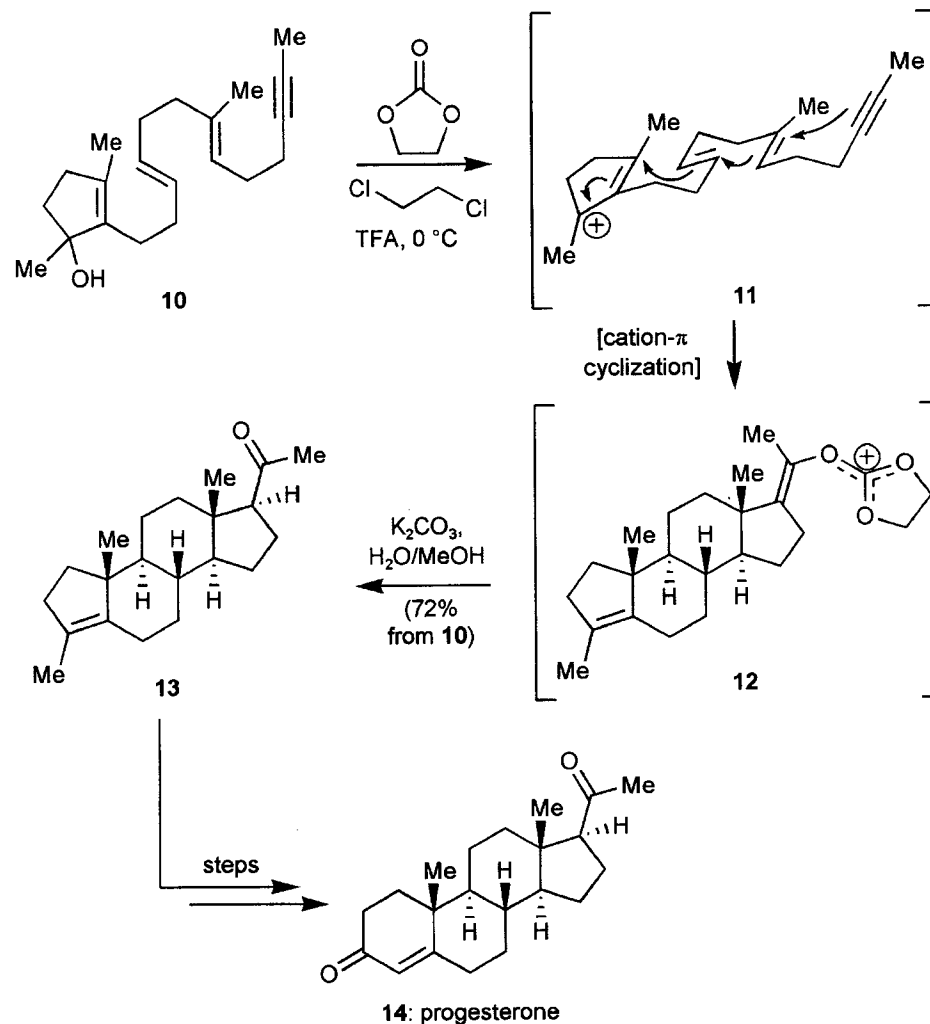
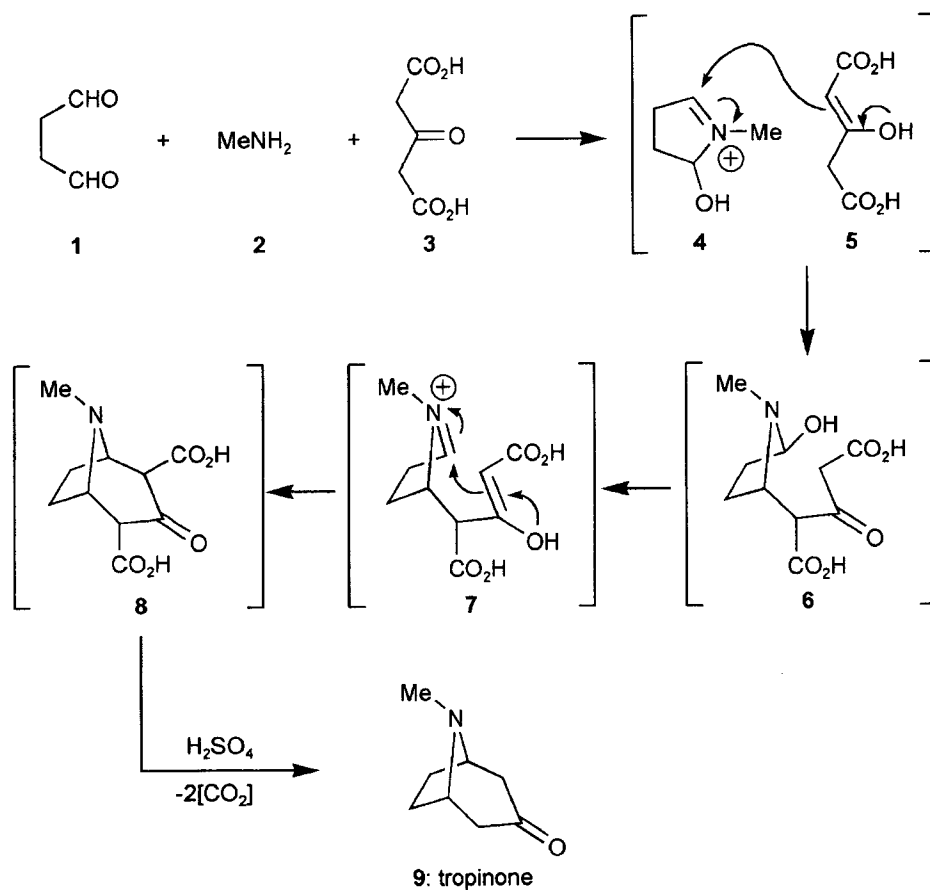
Justin Montgomery

1/27/4

# Introduction: Tropinone and Progesterone

2

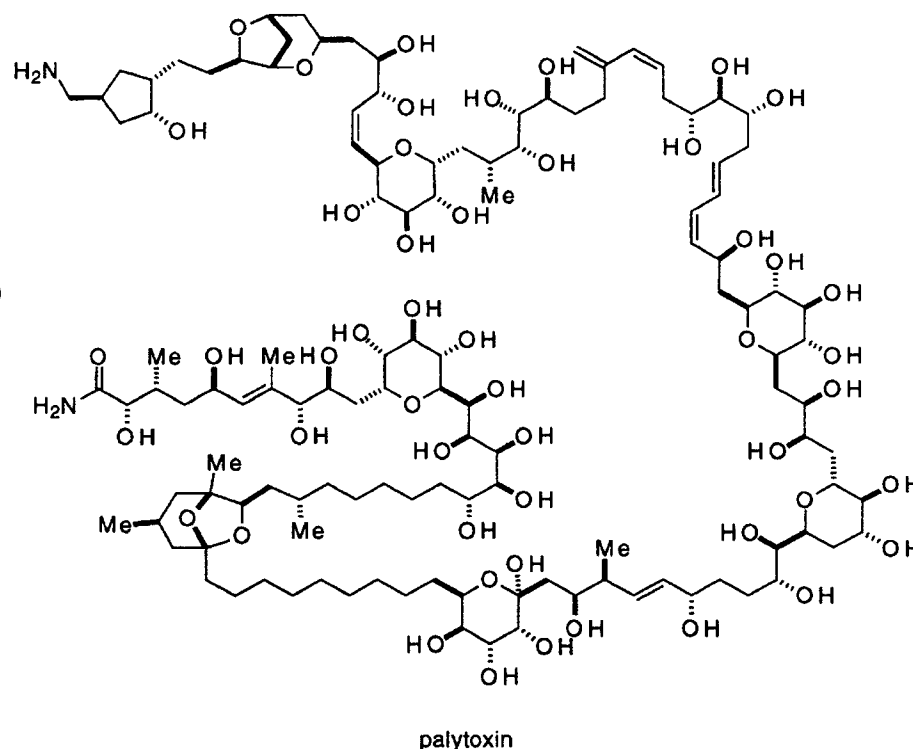
Sir Robert Robinson  
*J. Chem. Soc.* **1917**, 762.



W.S. Johnson  
*J. Am. Chem. Soc.* **1971**, 4330.

If you can draw it – we can make it...

- Organic chemists are capable of making pretty much anything for which a reasonable structure can be drawn
- Palytoxin – Kishi (1980's)
  - took a huge team of chemists many years to perform hundreds of reactions and put together only a few milligrams of synthetic material

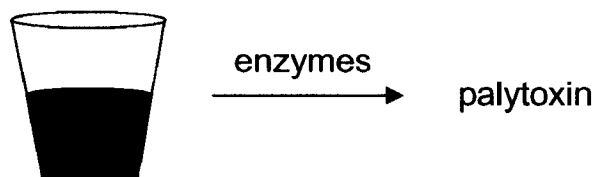


## Efficiency

- When large amounts of a complicated material have been needed quickly – chemists haven't been able to meet the demand!

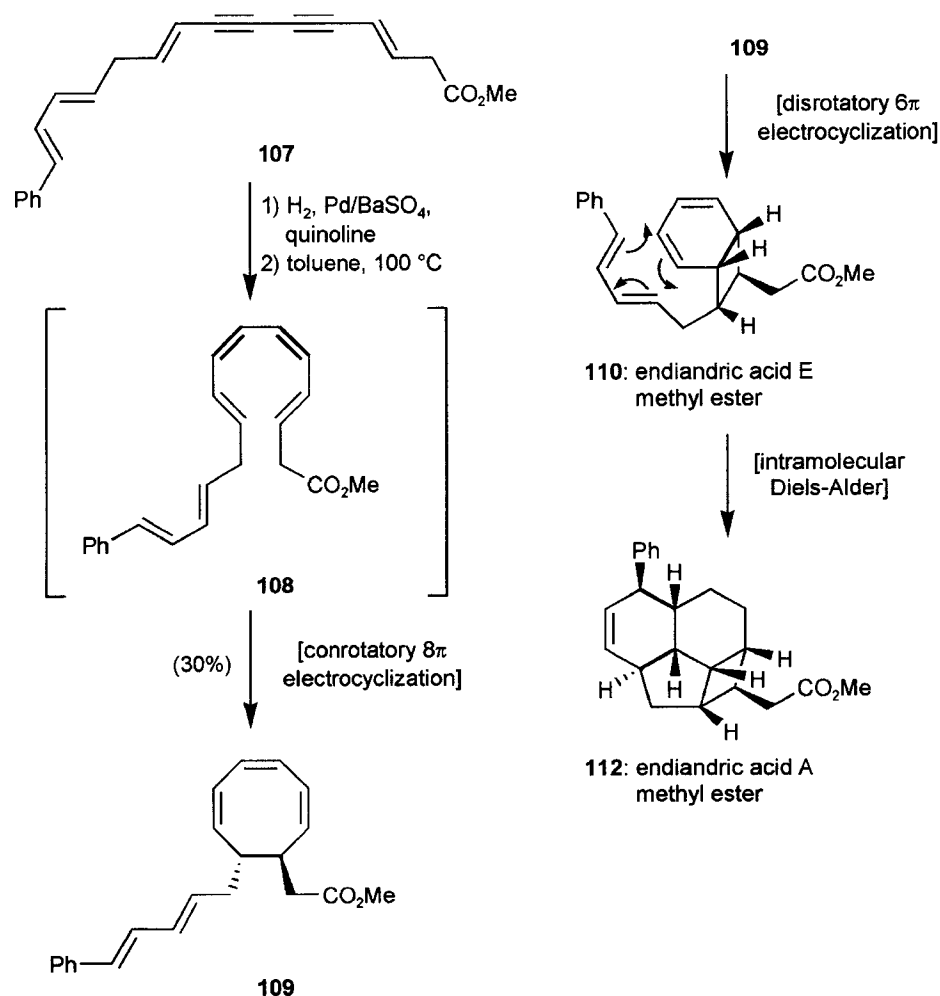
What can we learn from nature to increase our efficiency?

Enzymatic transformations – are there all powerful enzymes that cradle a substrate from all sides and enable transformations that are not possible in a laboratory?



# Minimal Enzymatic Participation

“...nature is the quintessential process development chemist. We think that the molecular frameworks of most natural products arise by intrinsically favorable chemical pathways—favorable enough that the skeleton could have arisen by a nonenzymic reaction in the primitive organism. If a molecule produced in this purely chemical manner was beneficial to the organism, enzymes would eventually have evolved to facilitate the production of this useful material.” C.H. Heathcock

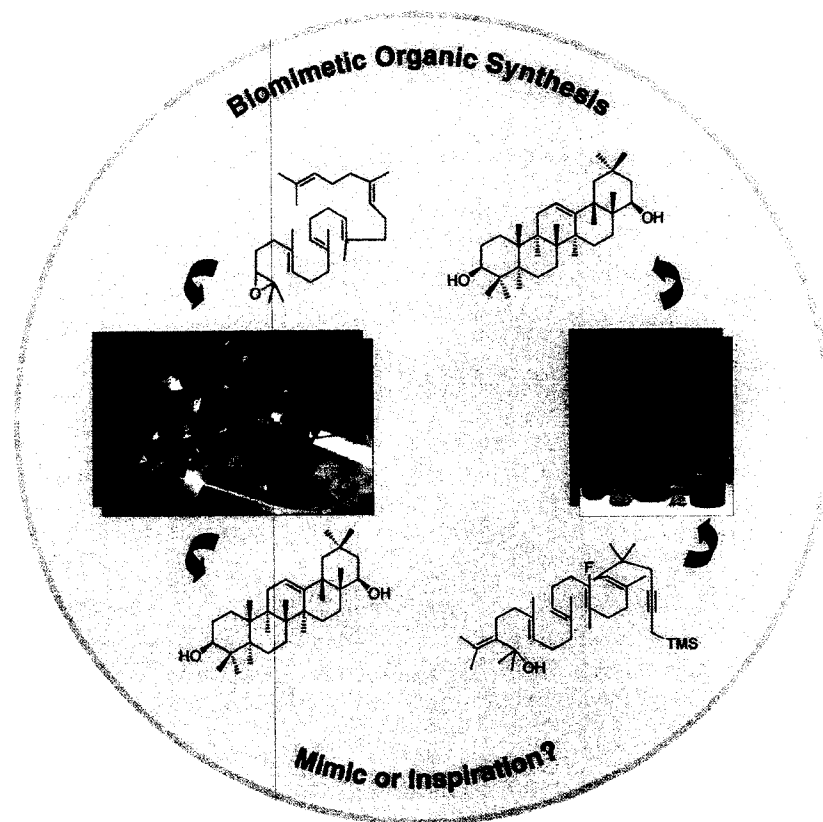


**112** is a racemic mixture in nature  
(nonenzymatic transformation)

Four new rings and eight  
stereogenic centers from an open  
chain precursor.

## Definitions

- “A specific reaction or a sequence of reactions that mimic a proposed biological pathway. The process being imitated usually has a solid biochemical background.”
- “...a sequence of reactions carried out to support a biogenetic hypothesis. In this case, a reaction is effected on a putative substrate of the transformation under study. Should the reaction succeed, the biosynthetic route would be generally accepted.”



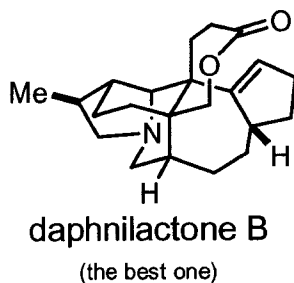
## All Powerful Enzymes vs. Minimal Enzymatic Participation

- biomimetic syntheses are more likely to succeed if involvement of enzymes in the biosynthesis is low
- allows us to ascertain which steps proceed due to reactivity that is intrinsic to a substrate's structure
  - steps that require external reagents suggest enzyme involvement

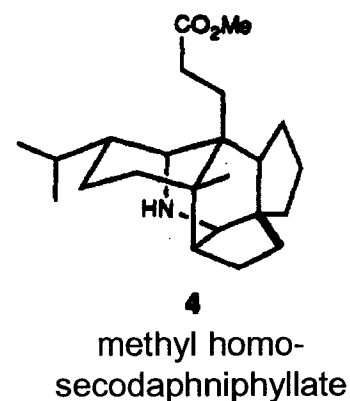
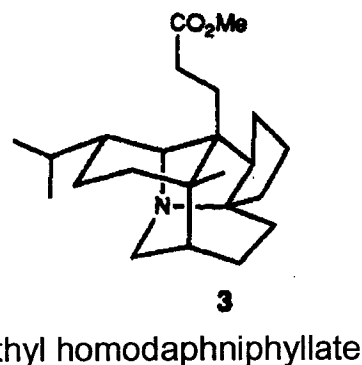
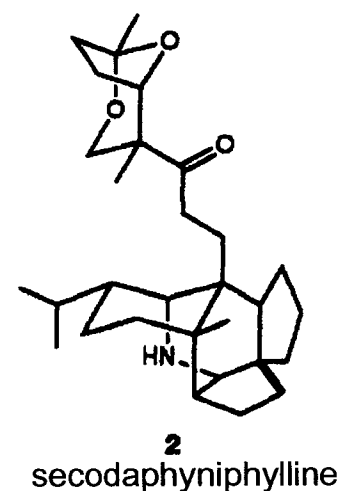
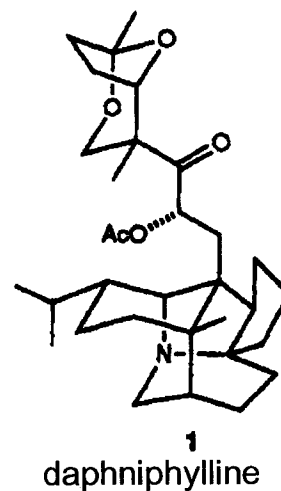
# *Daphniphyllum* Alkaloids: Background

6

- Isolated from *Daphniphyllum macropodum* (deciduous tree) and other sources
- 1966 – X-ray of **1** the “archetypal” example
- Derived from squalene
- >35 members of the family

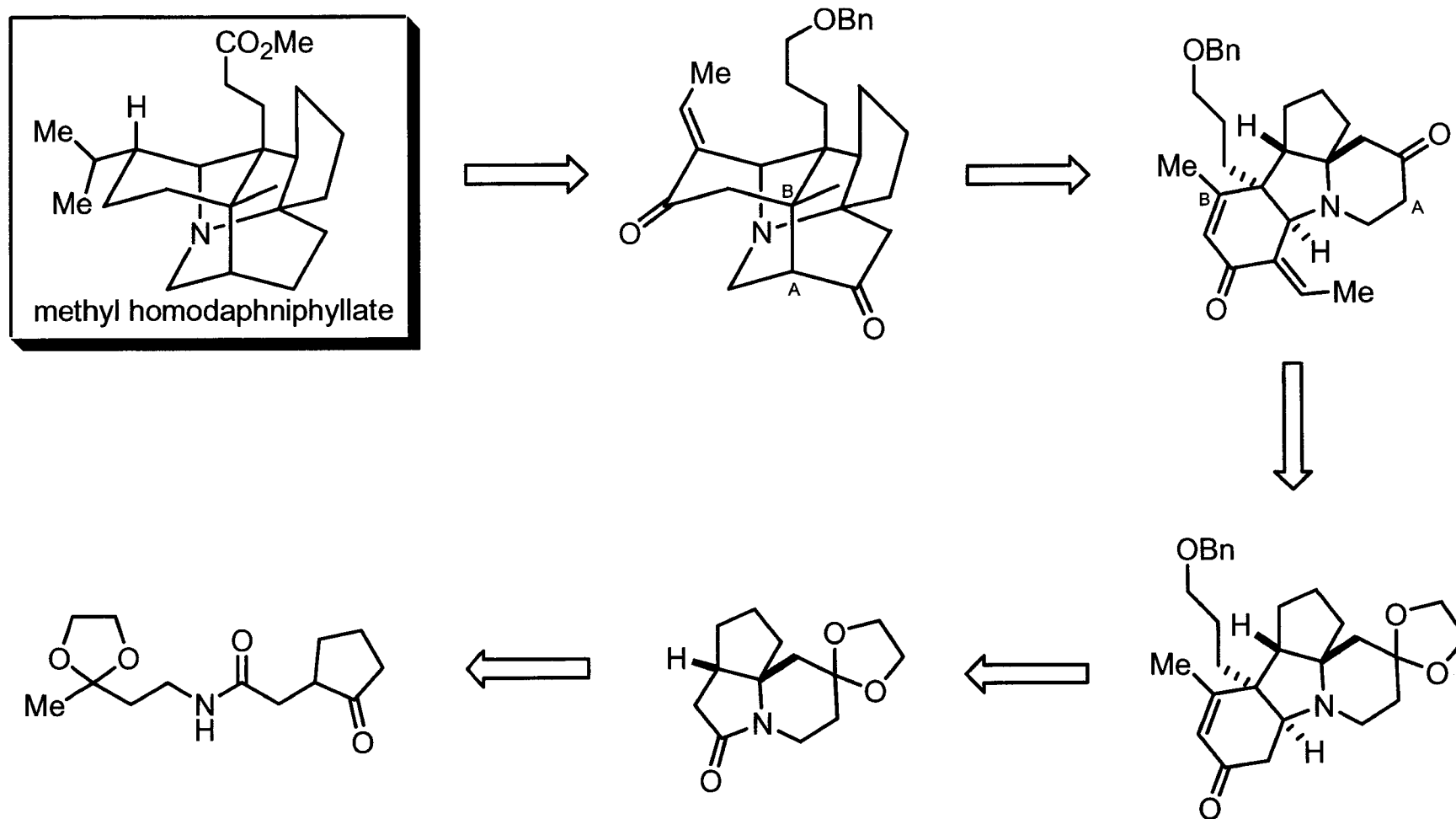


Classical and biomimetic approaches to members of the family have been reported



# *Daphniphyllum Alkaloids: Classical Synthesis Retro*

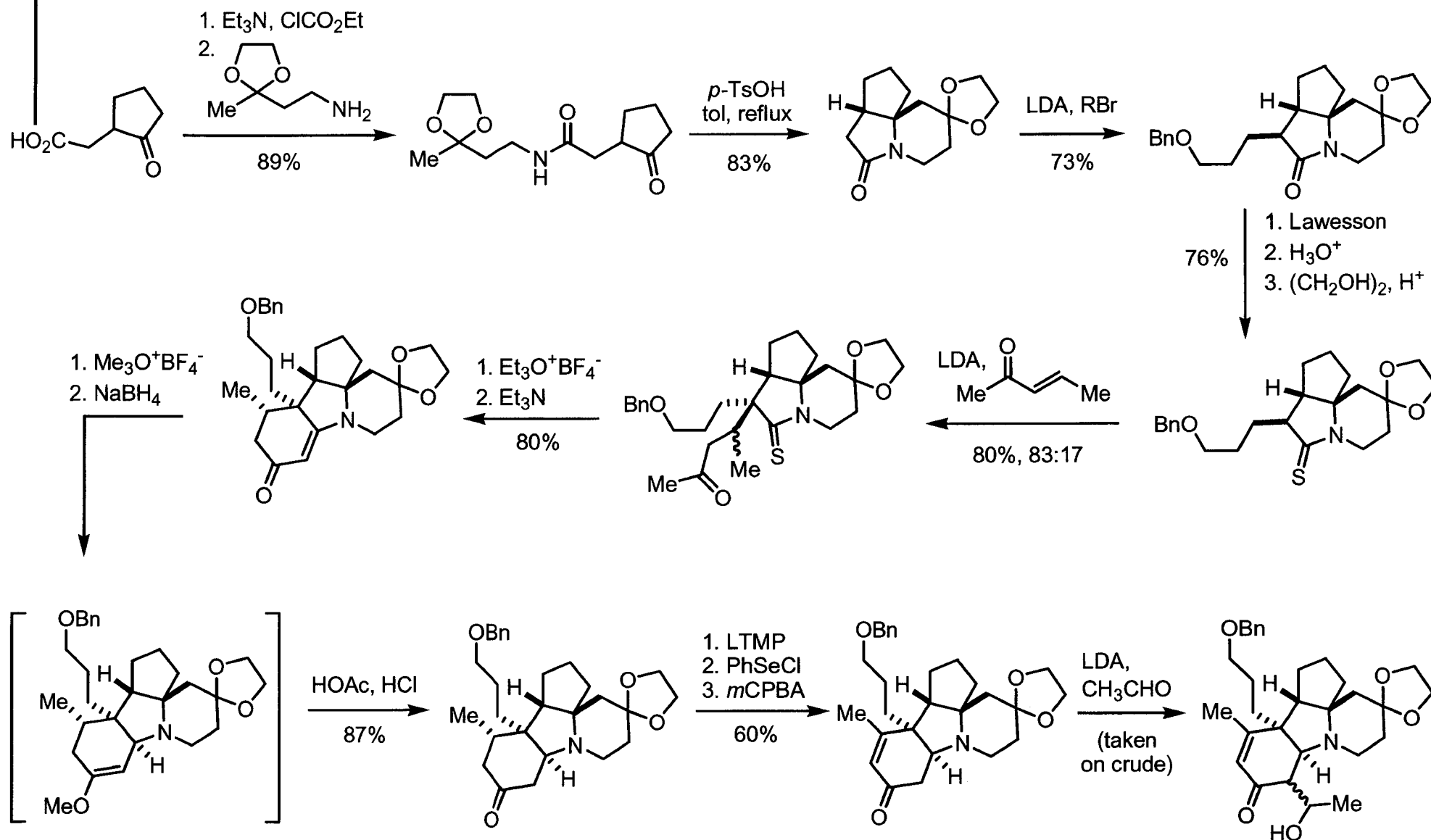
7



Key step (intra-Michael rxn) requires functionality not found in target molecule

# Daphniphyllum Alkaloids: Classical Synthesis (1)

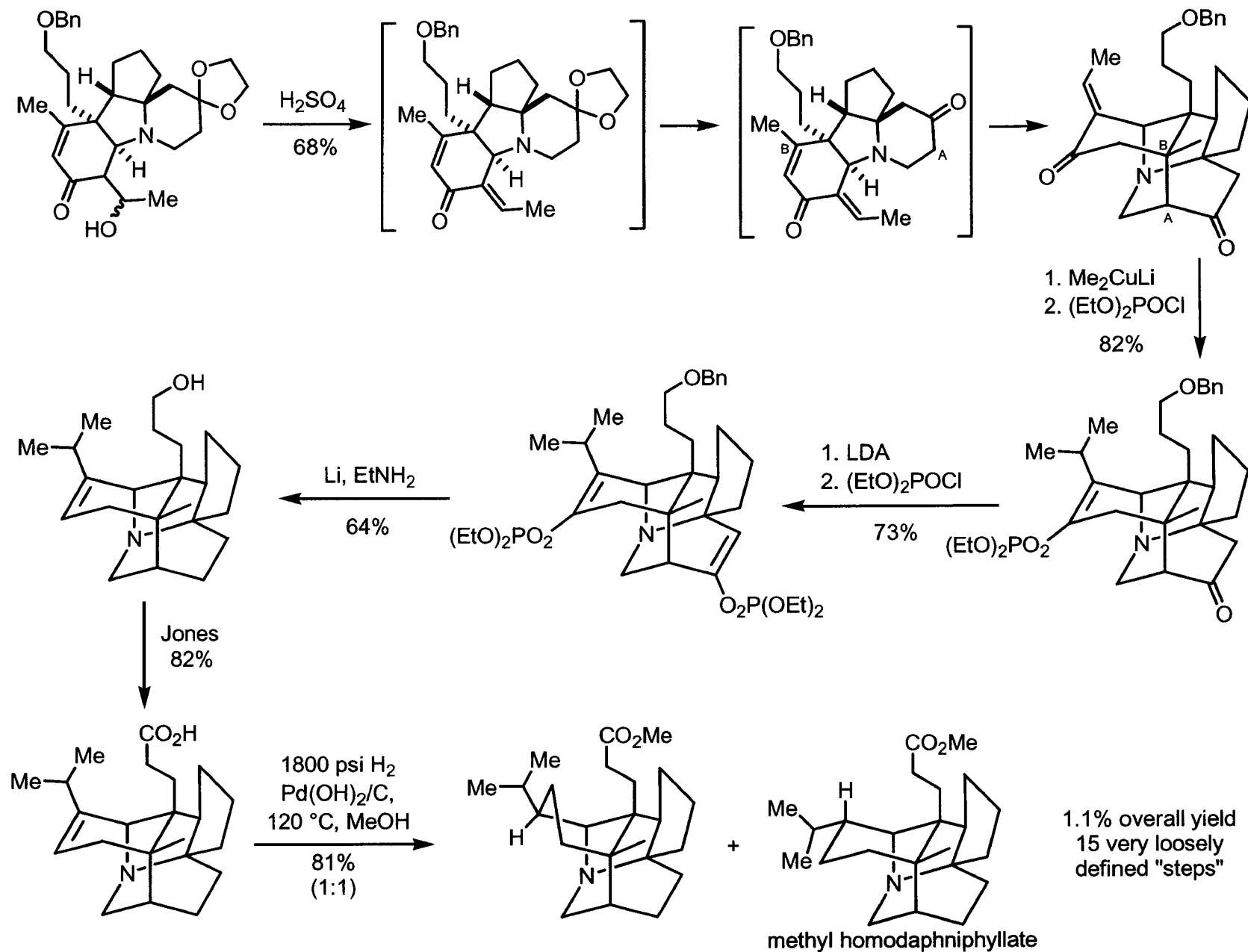
8





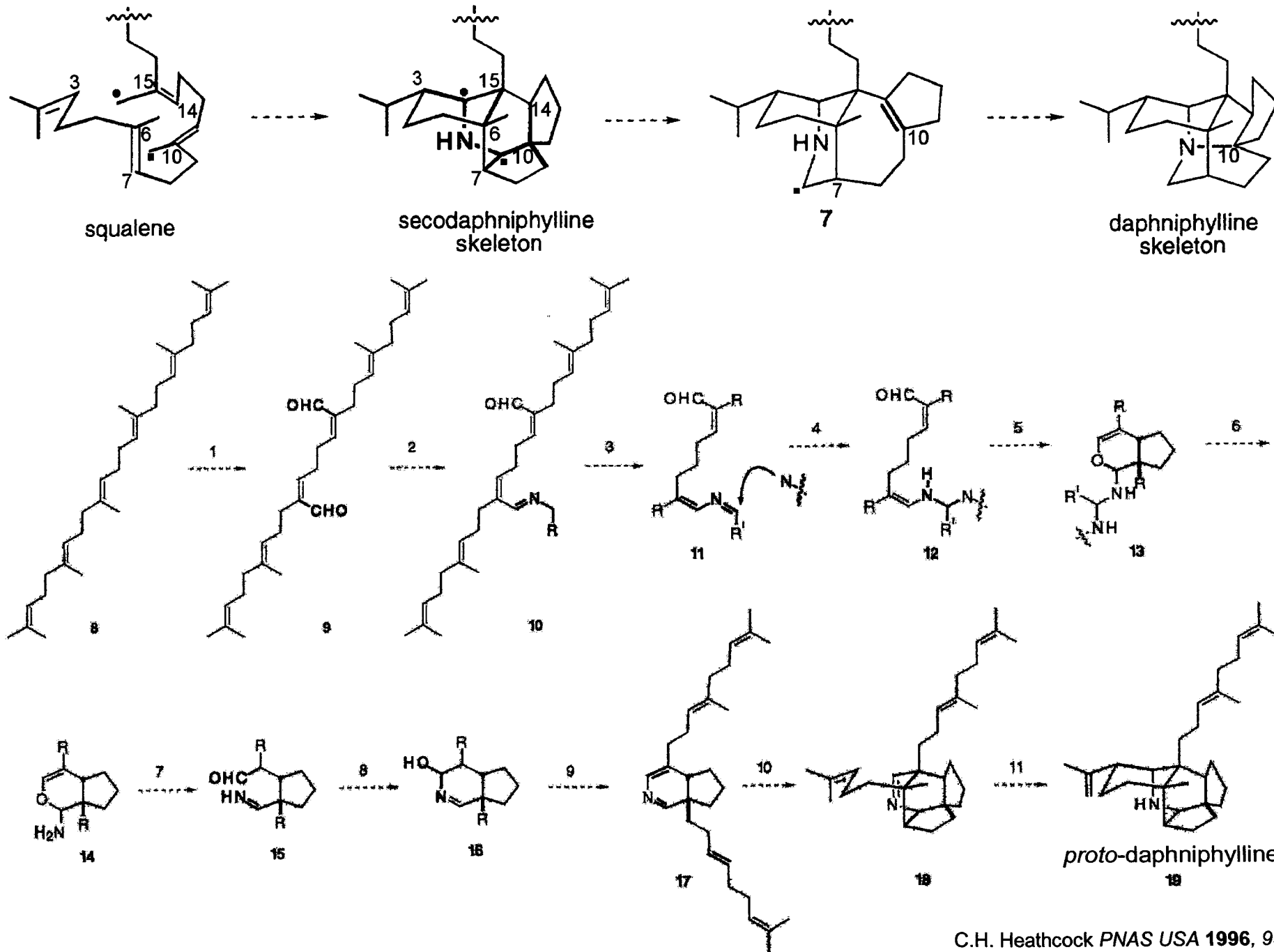
# Daphniphyllum Alkaloids: Classical Synthesis (2)

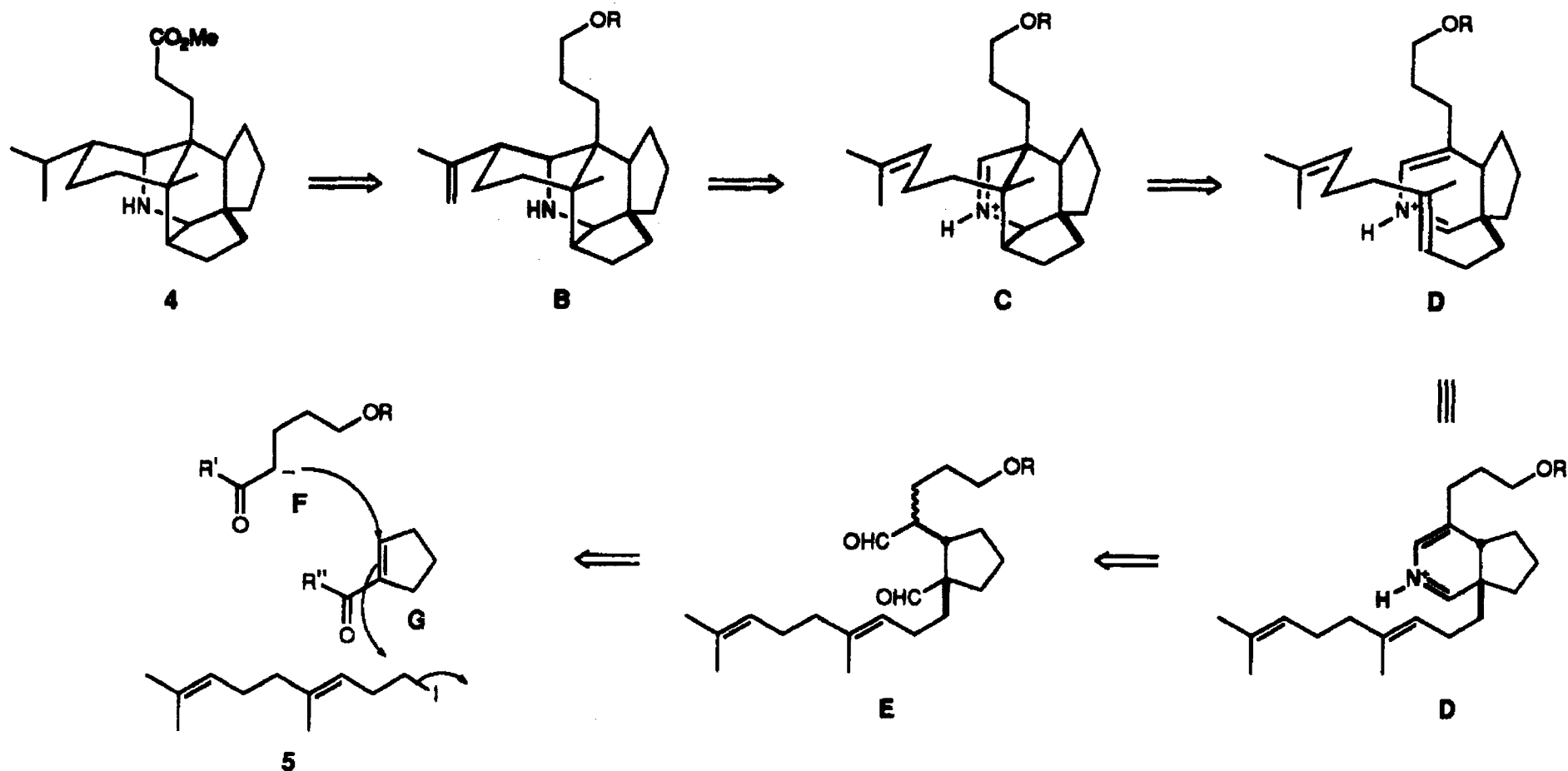
9



# Daphniphyllum Alkaloids: Biosynthesis

10

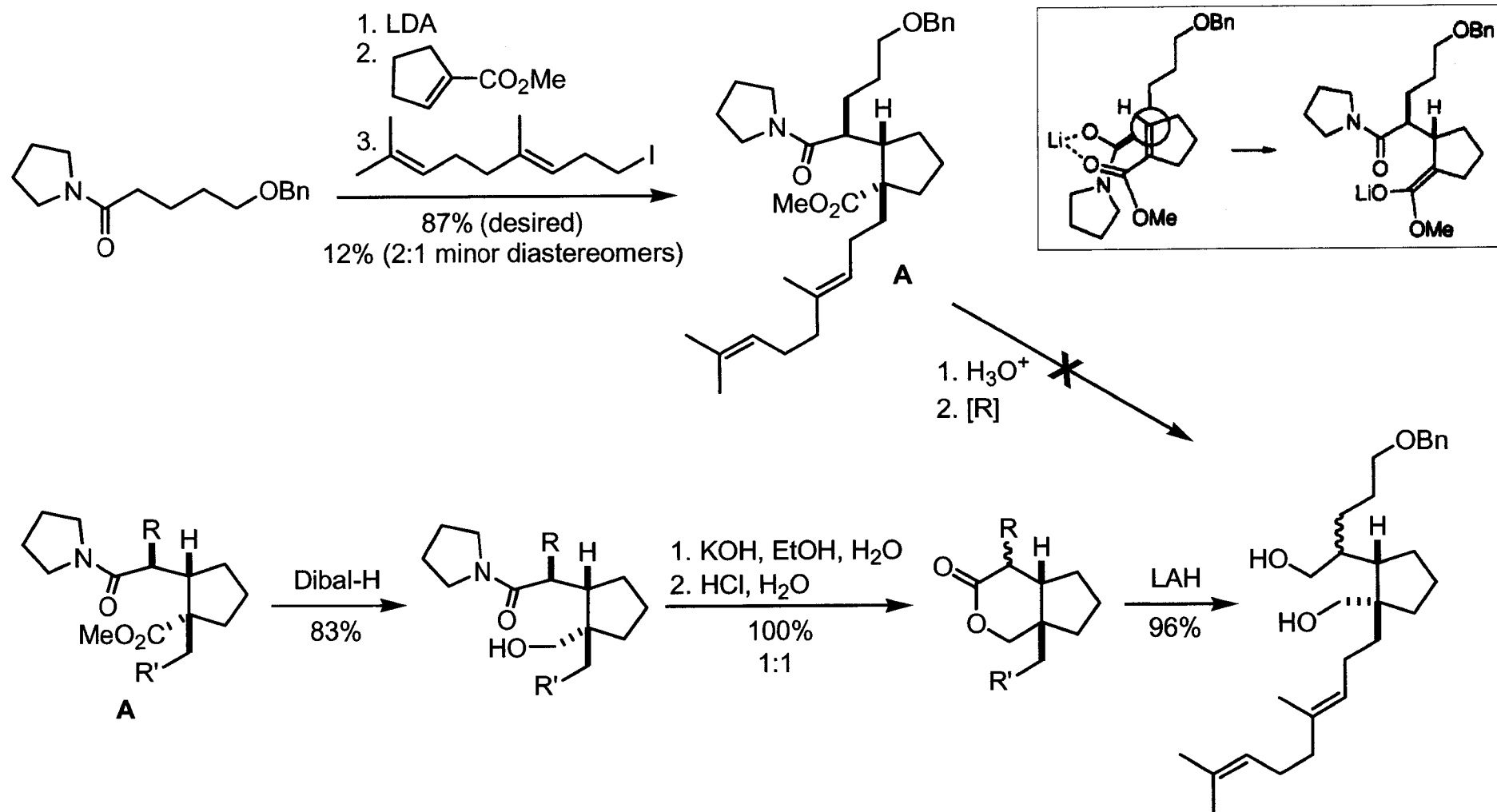




Biomimetic approach (D-C-B) intra-[4+2], intra-ene like cyclization

# Methyl Homosecodaphniphyllate: Biomimetic Synthesis

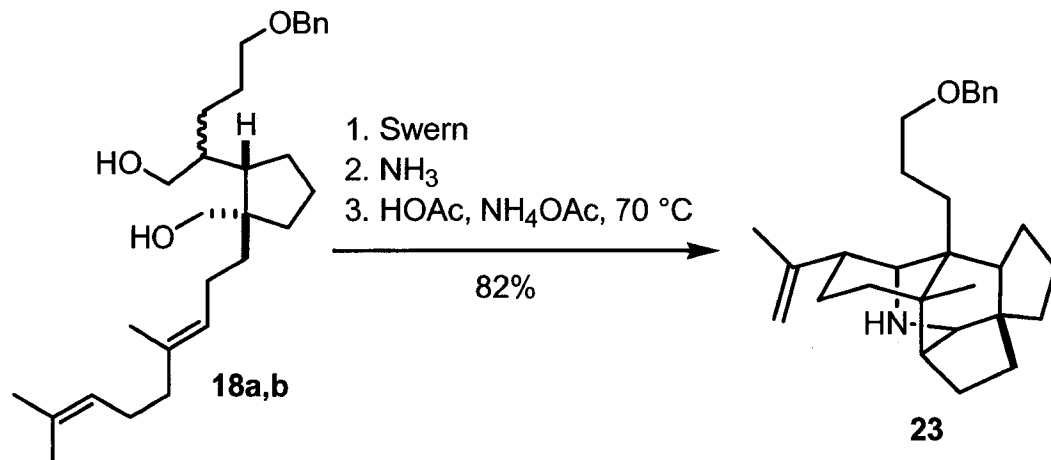
12



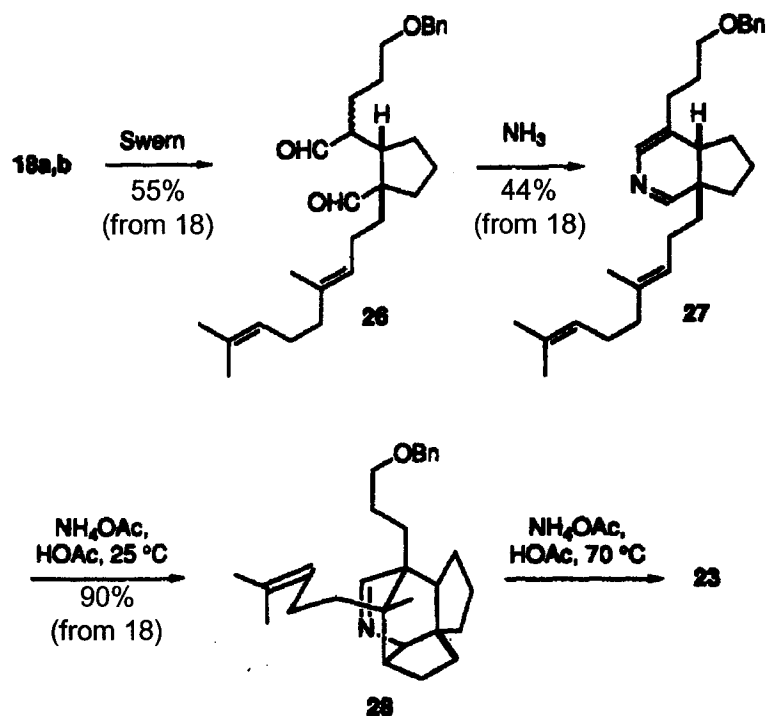
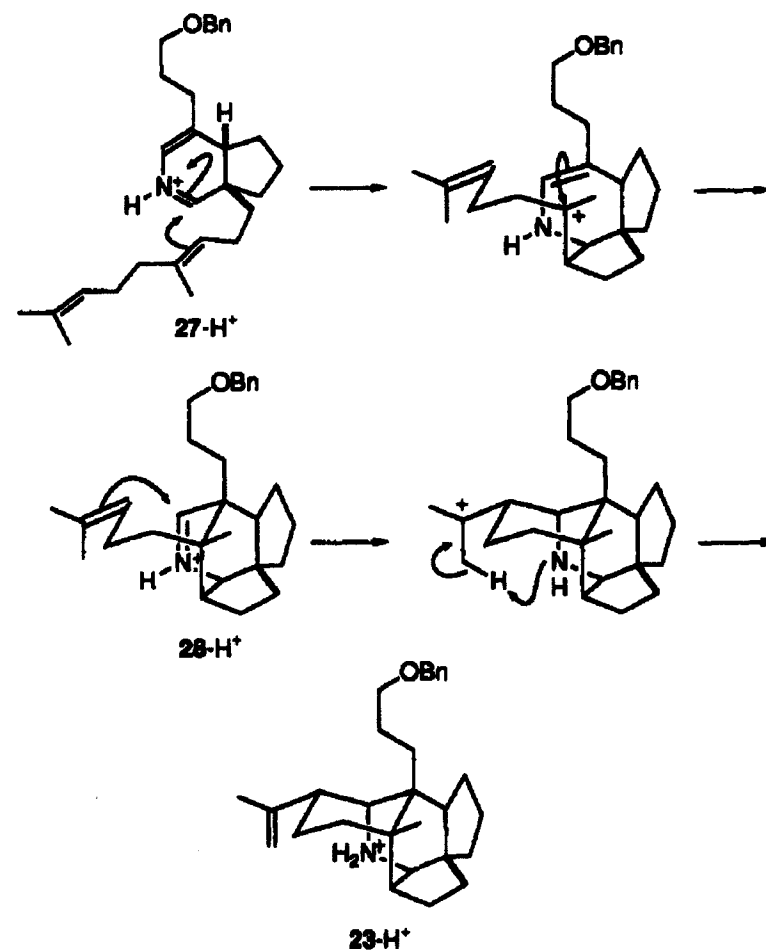
Three step sequence required for converting **A** to diol

# Tetracyclization of Diol **18**

13



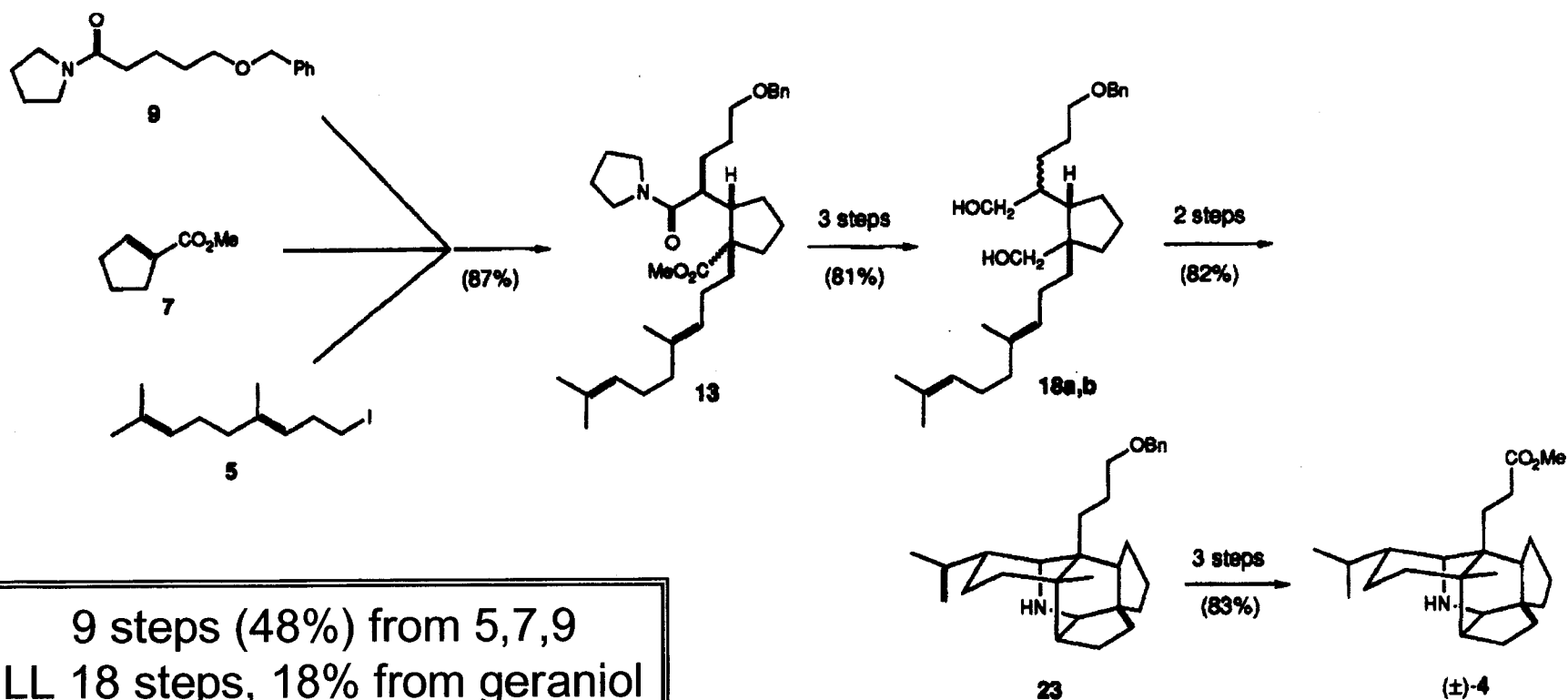
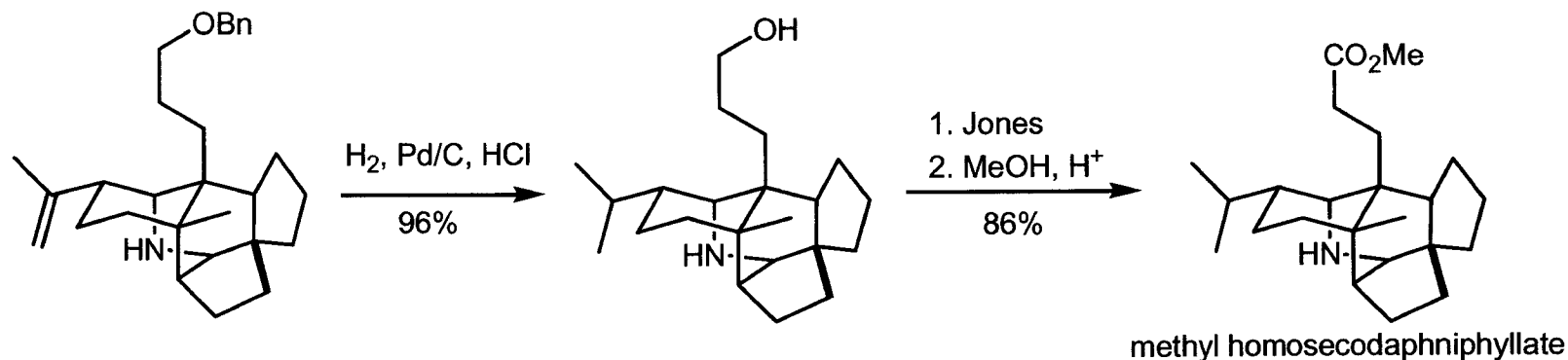
Possible mechanism:



**Tetracyclization proceeds in 82% yield!**

# Methyl Homosecodaphniphyllate: Completion

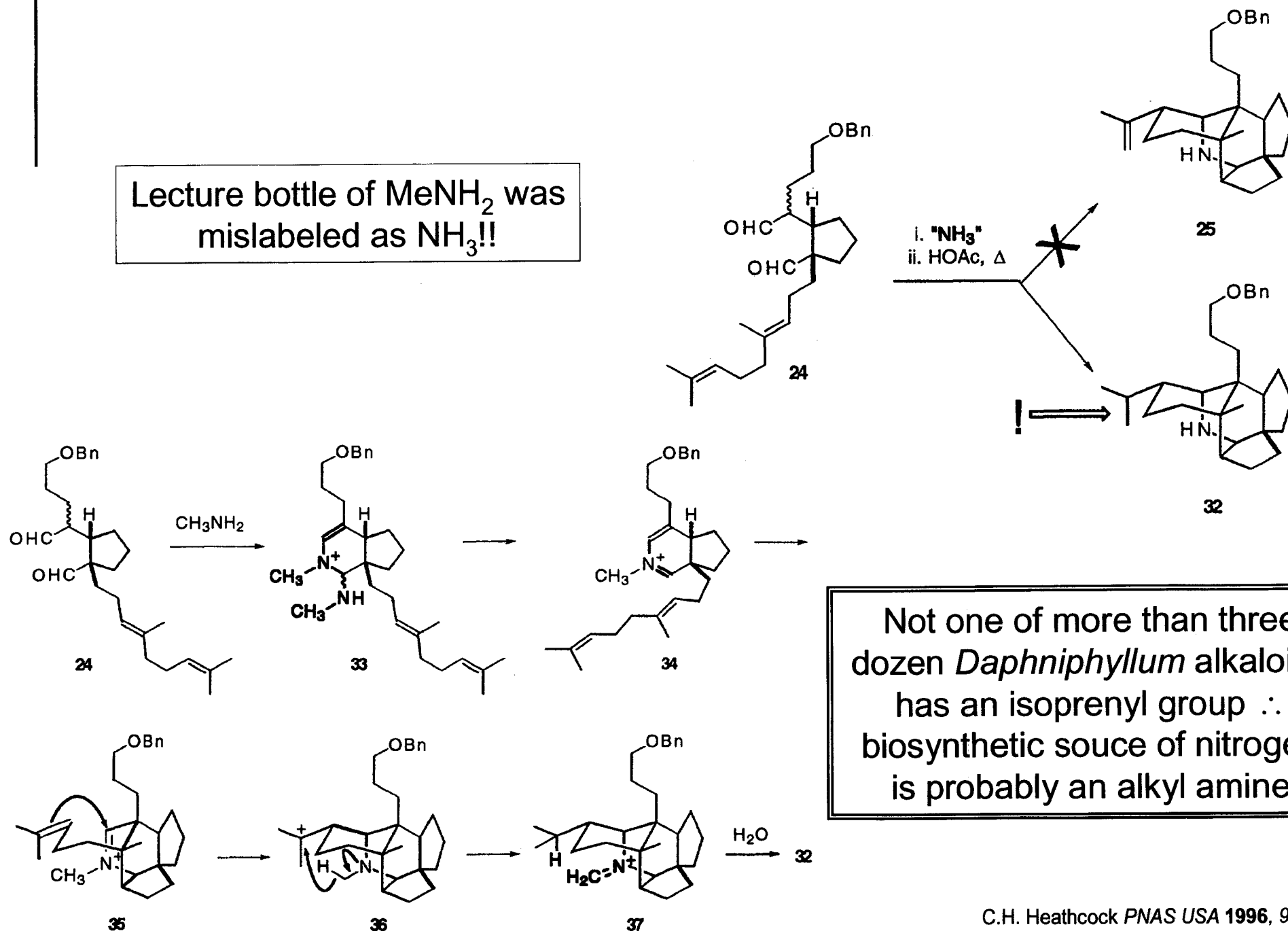
14



# Some people have all the luck...

15

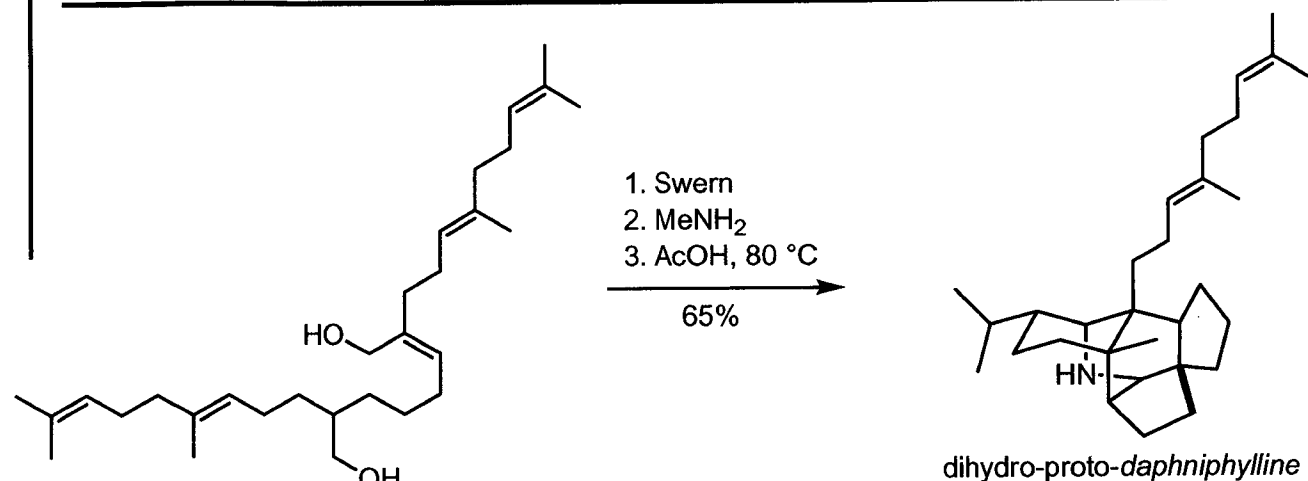
Lecture bottle of  $\text{MeNH}_2$  was mislabeled as  $\text{NH}_3$ !!



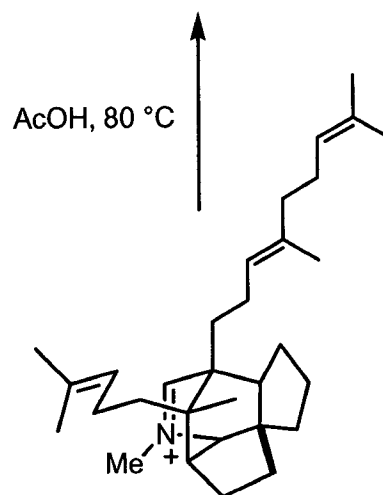
Not one of more than three dozen *Daphniphyllum* alkaloids has an isoprenyl group  $\therefore$  biosynthetic source of nitrogen is probably an alkyl amine

# Dihydro-Proto-Daphniphylline: Pentacyclization!!

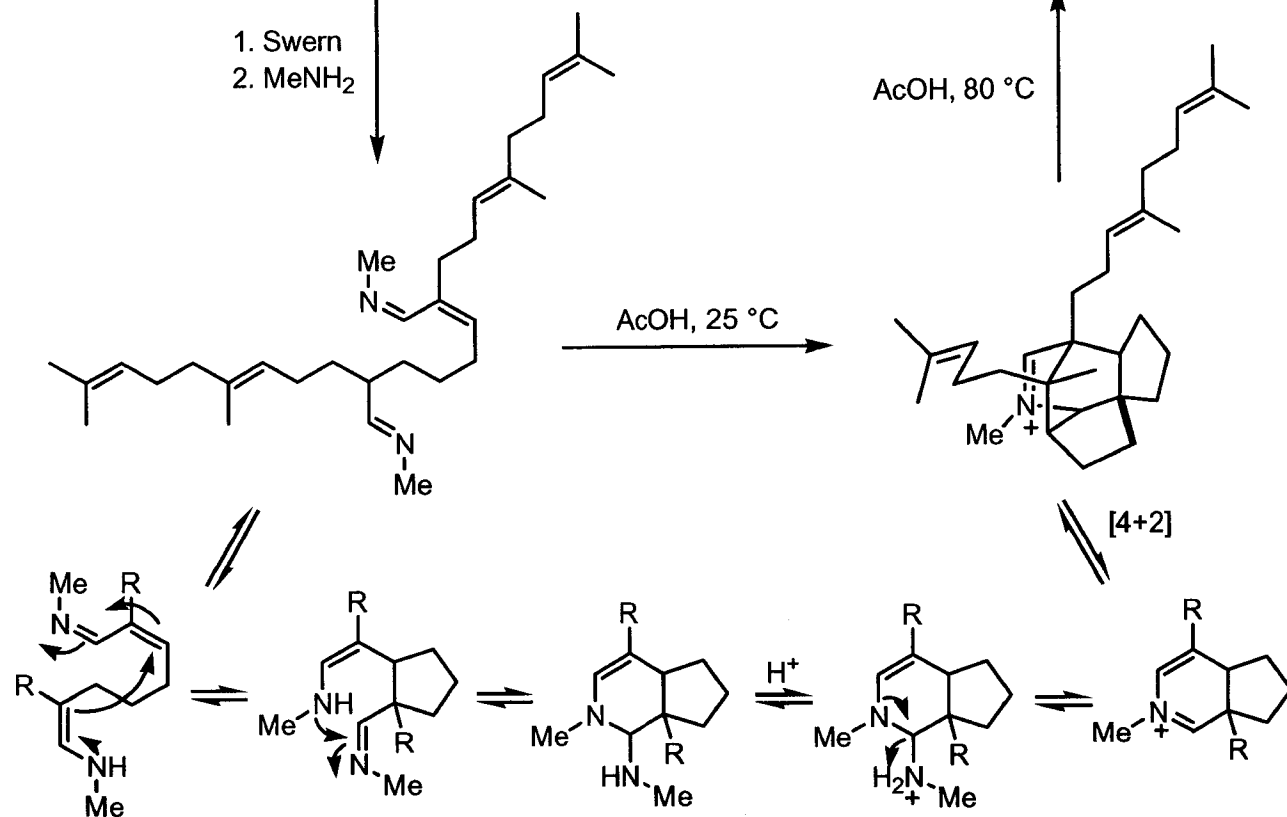
16



- 5 new rings
- 7 new  $\sigma$ -bonds
- Fully diastereoselective
- Fully regioselective in saturation of 1 of 4 similar C=C (consequence of mechanism)



Larger amines give lower yields  
(steric congestion)



- glycine – 38%
- alanine – 32%, 1-2% ee
- valine – 13%, 20-25% ee
- (+)-phenylethylamine – 0%

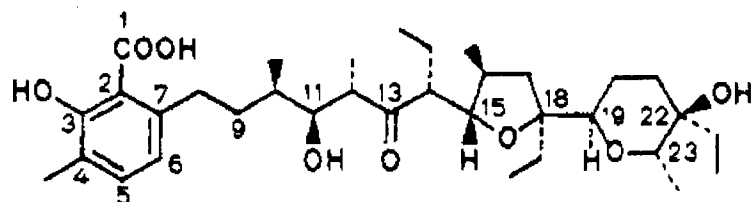
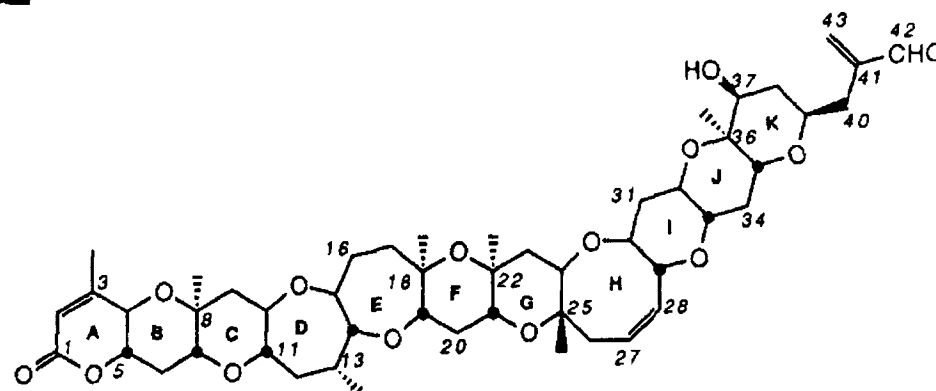
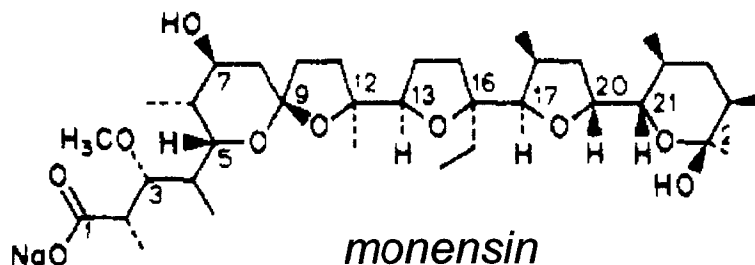


## Classical Synthesis

- Many problems along the way required changes from initial synthetic plan
- Steps wasted removing functionality needed for transformations but not in the target molecule
- Selectivity in the final step only 1:1
- Nice synthesis, but low overall yield

## Biomimetic Syntheses

- Biosynthetic hypothesis led to a successful and efficient synthesis
- Serendipity led to an improved synthesis and a modification of the proposed biosynthesis
- Demonstrated an amazing pentacyclization from acyclic starting material that proceeds in good overall yield
- Supports “minimal enzyme participation” theory although enantioselectivity in the natural process must come from enzymes
- Likely similar to what happens in nature



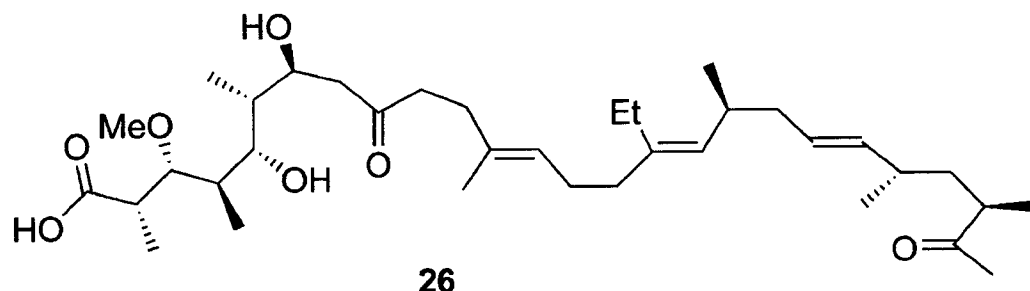
## *Polyether Antibiotics*

- from terrestrial microorganisms
- derived from acetate, propionate, and butyrate, but little is known about the chain-building steps

## *Polyether Marine Toxins*

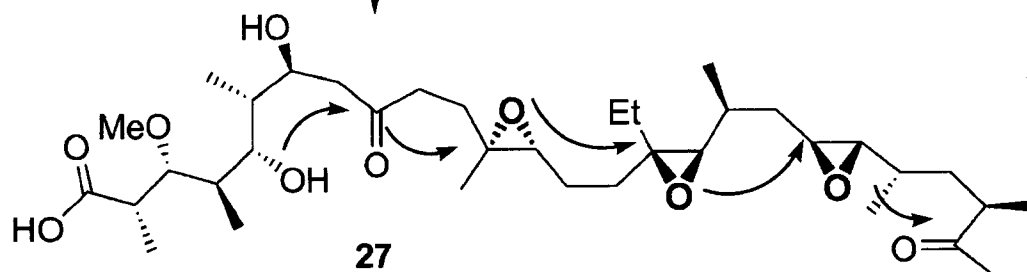
- neurotoxins responsible for harmful effects associated with “red tide”
- trans – fused “ladder-like” polyethers
  - biosynthesis is not of simple polyketide origin (citric acid cycle and CO<sub>2</sub> are involved)

# Polyether Antibiotics: Epoxide Biosynthetic Proposal



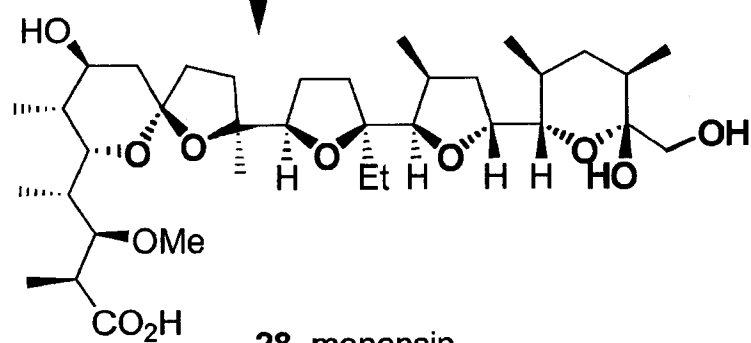
26

enzymatic polyepoxidation



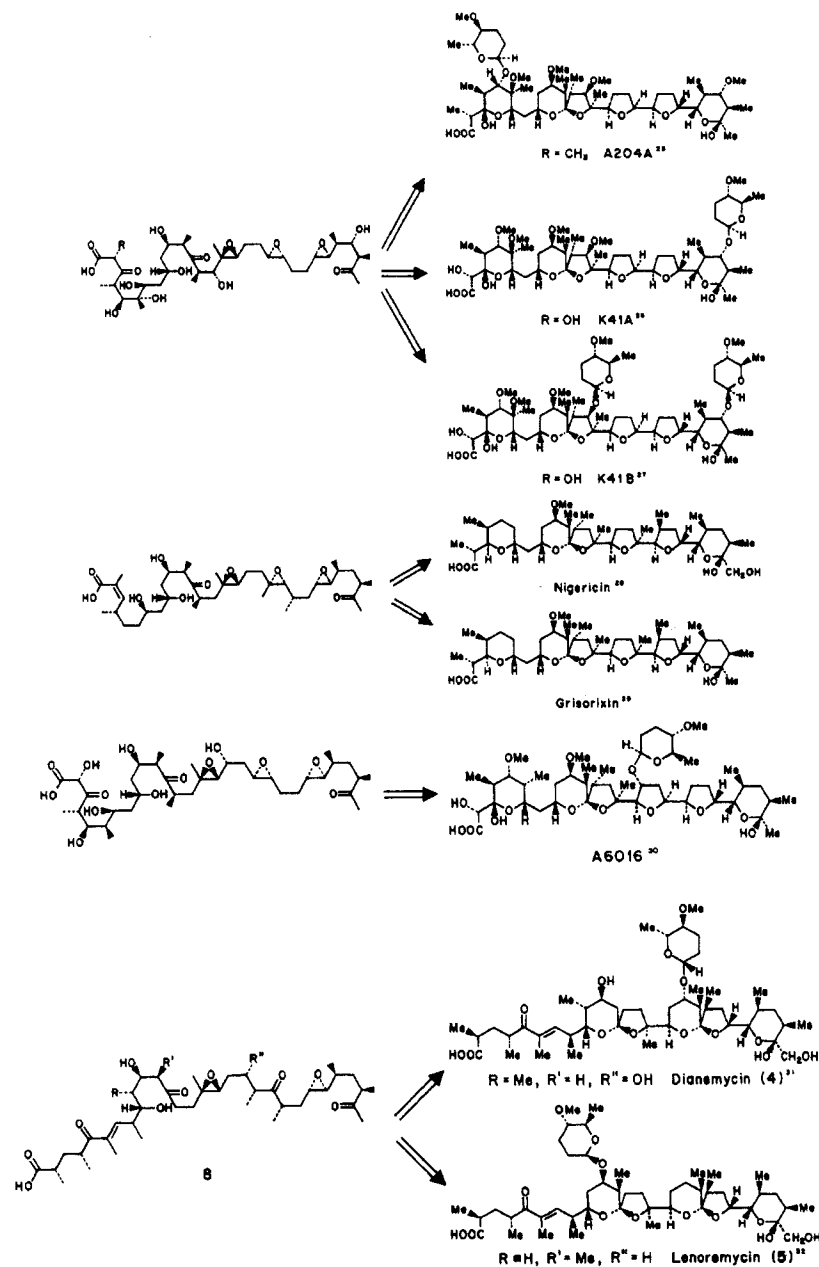
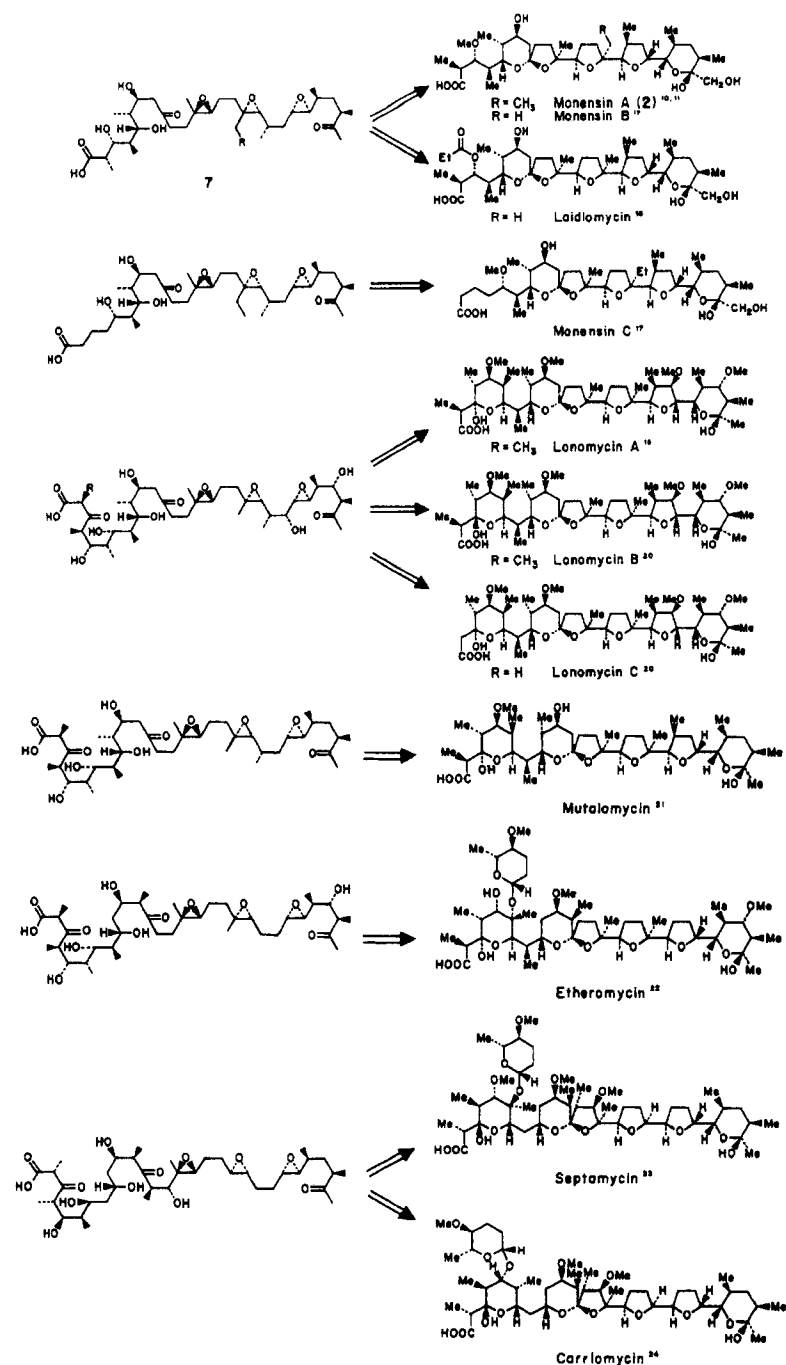
27

Yellow oxygens come from atmosphere,  
not polyketide precursors.

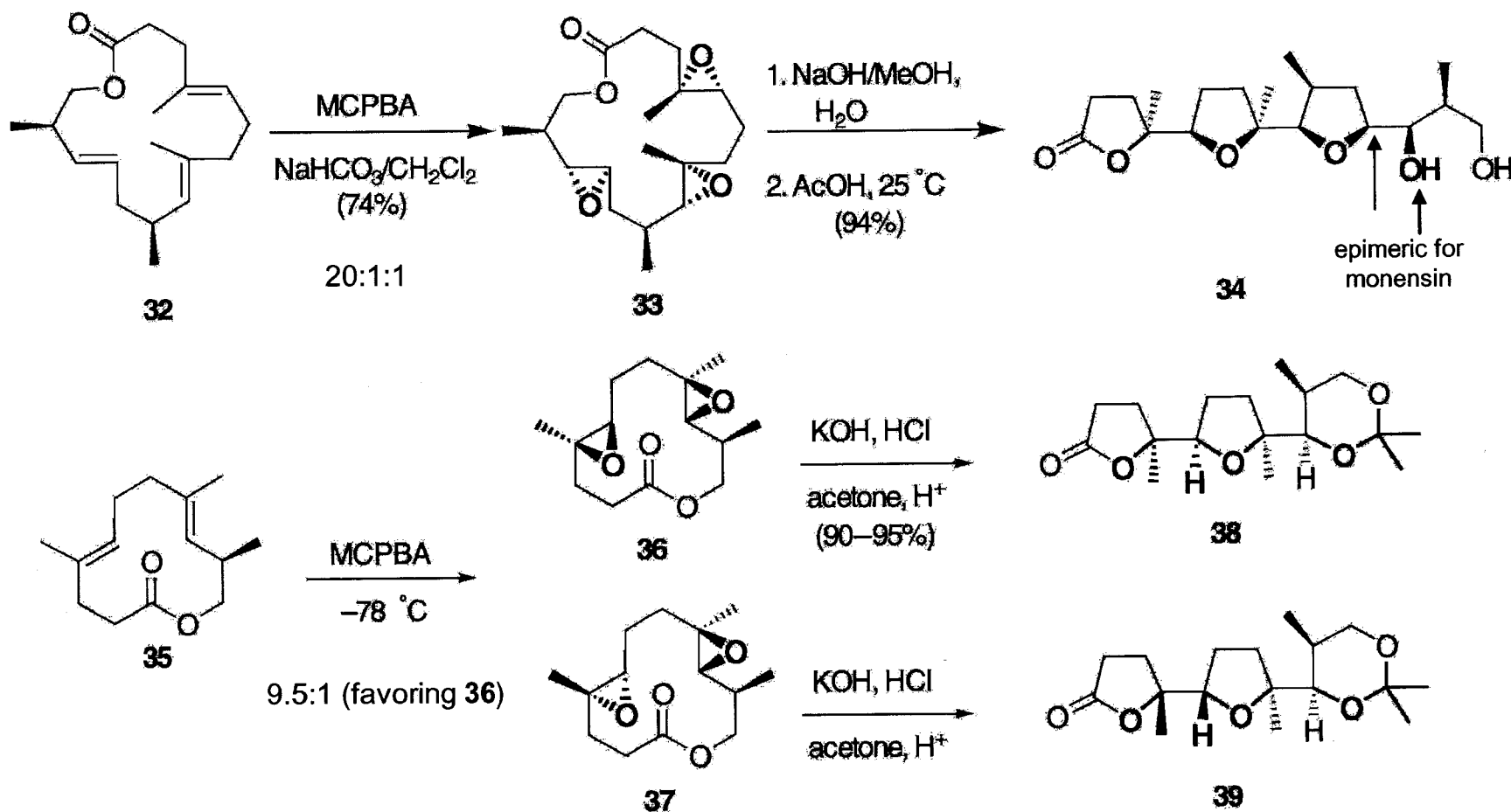


28 monensin

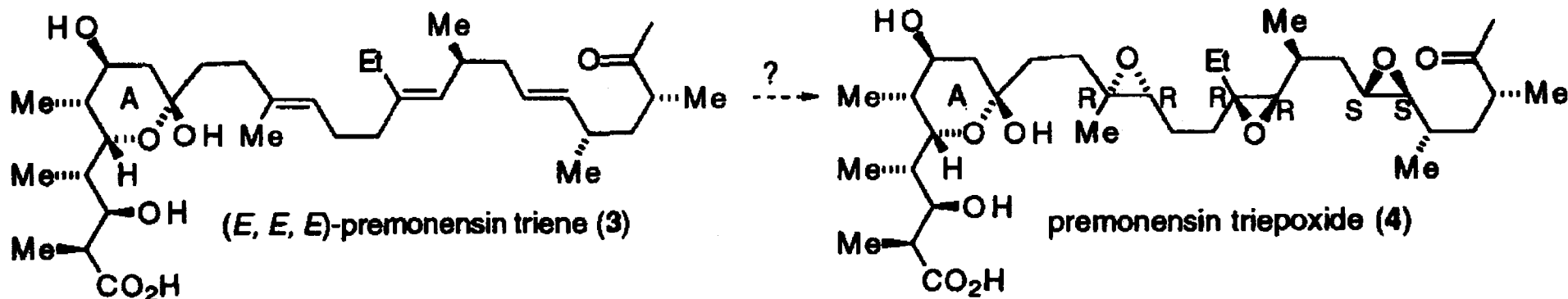
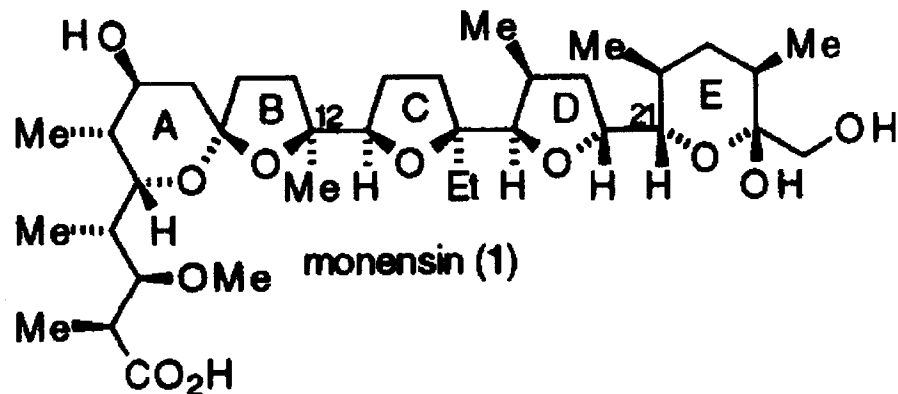
cascade of intramolecular  
epoxide-ring-opening reactions



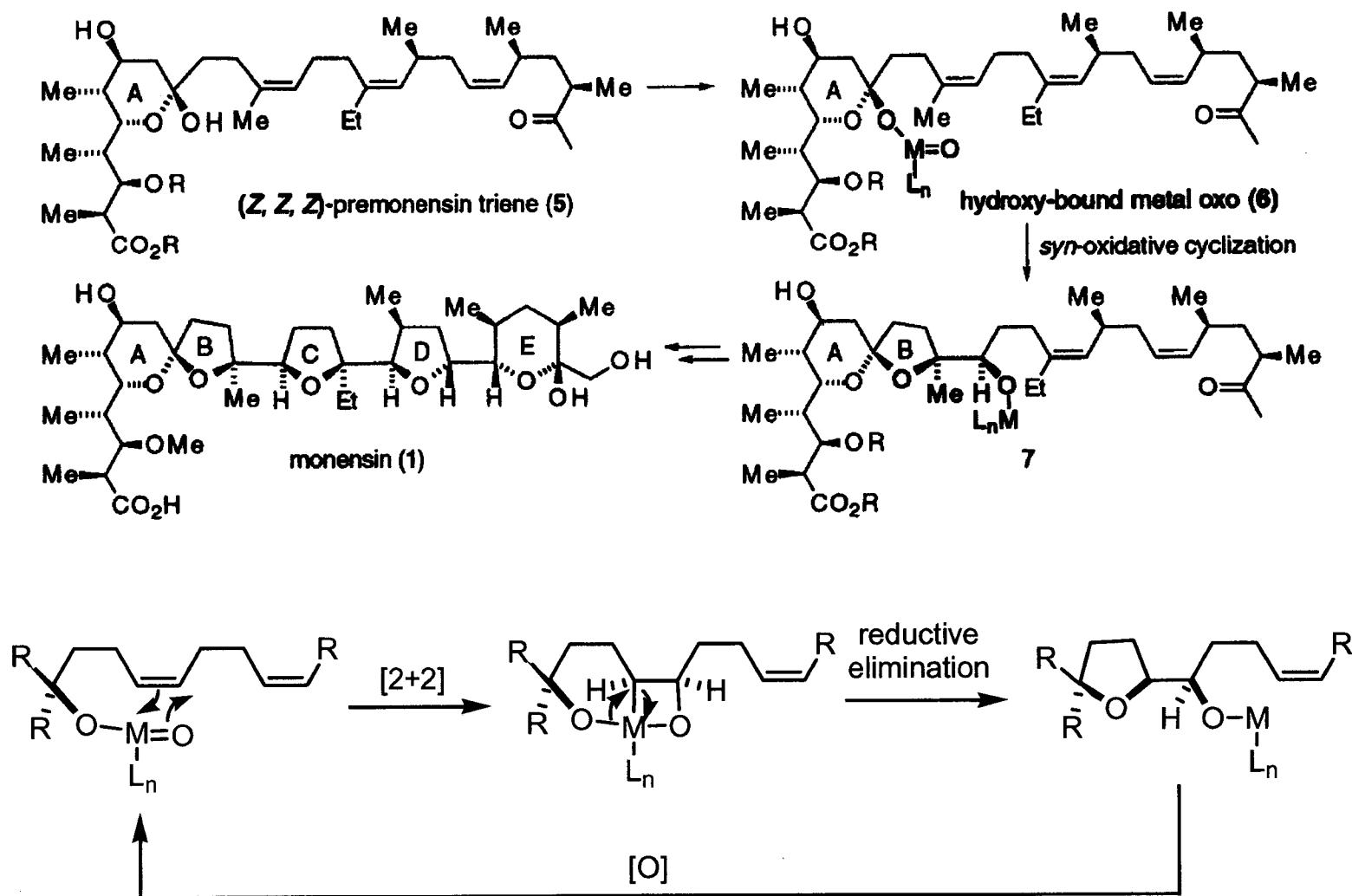
# Epoxide Method: Biomimetic Synthesis



- Stereoselective epoxidation through rigidity of macrocycles
- Cascade epoxide opening proposal is validated



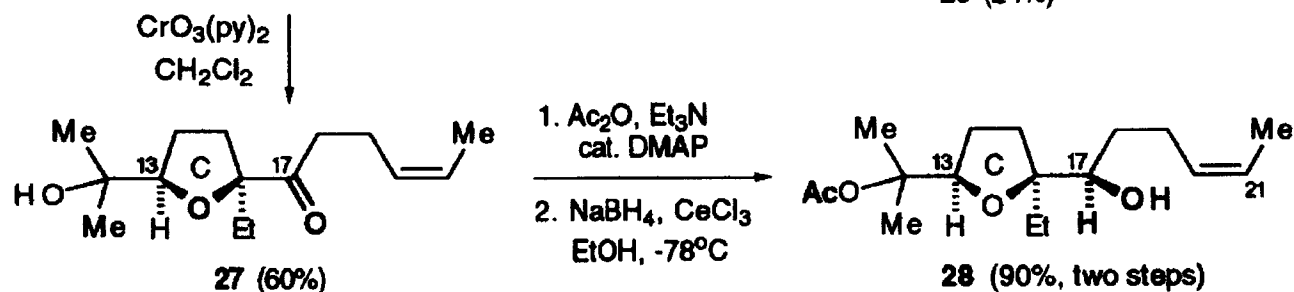
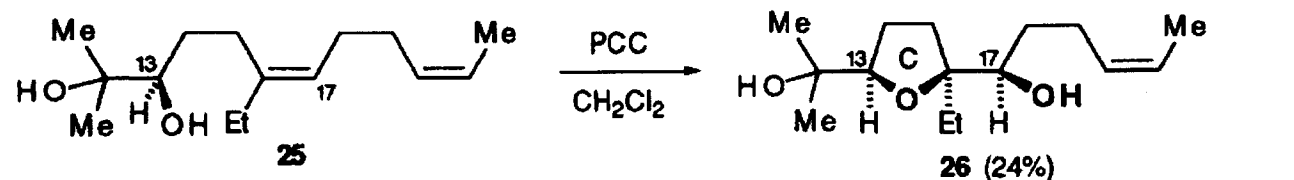
- 3 groups have prepared **3** – none have obtained **4**  
(epoxidation of *re* face for trisub. and *si* face for disub. required)
- Feeding studies with labeled **3** have not produced labeled **1**  
(could be solubility issue)



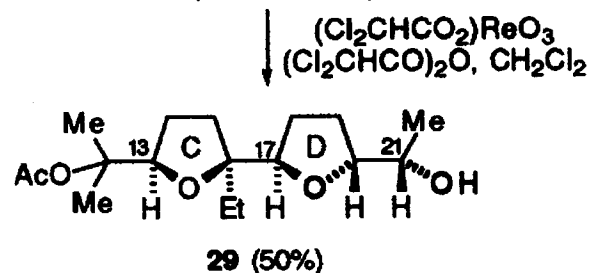
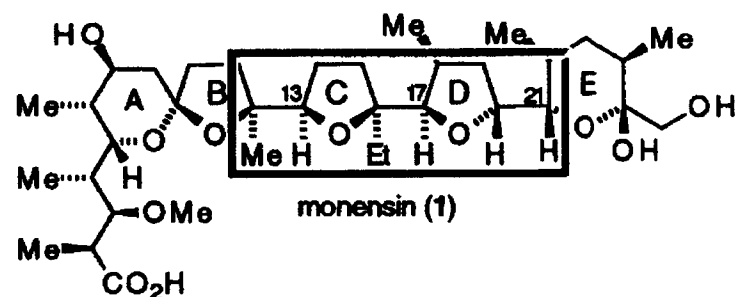
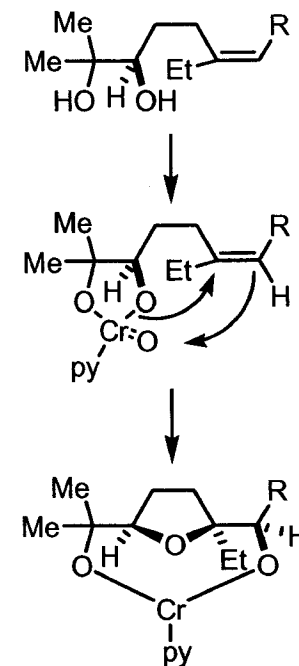
Townsend and Basak *syn*-oxidative cyclization requires *Z,Z,Z*-triene

# Polyethers: Stepwise Oxidative Cyclizations

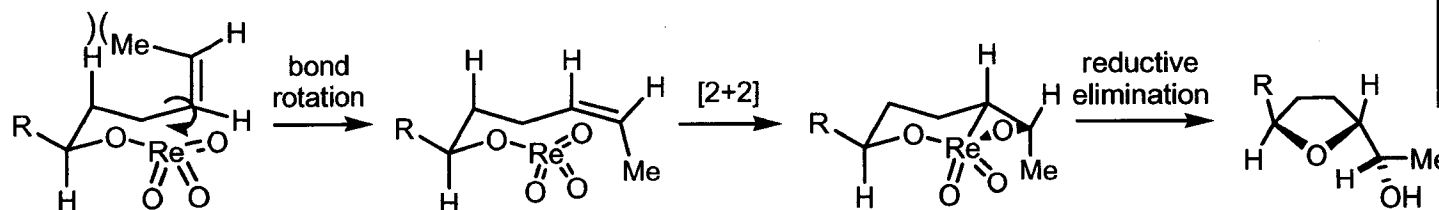
24



Cr promoted oxidative cyclization to *cis* THF

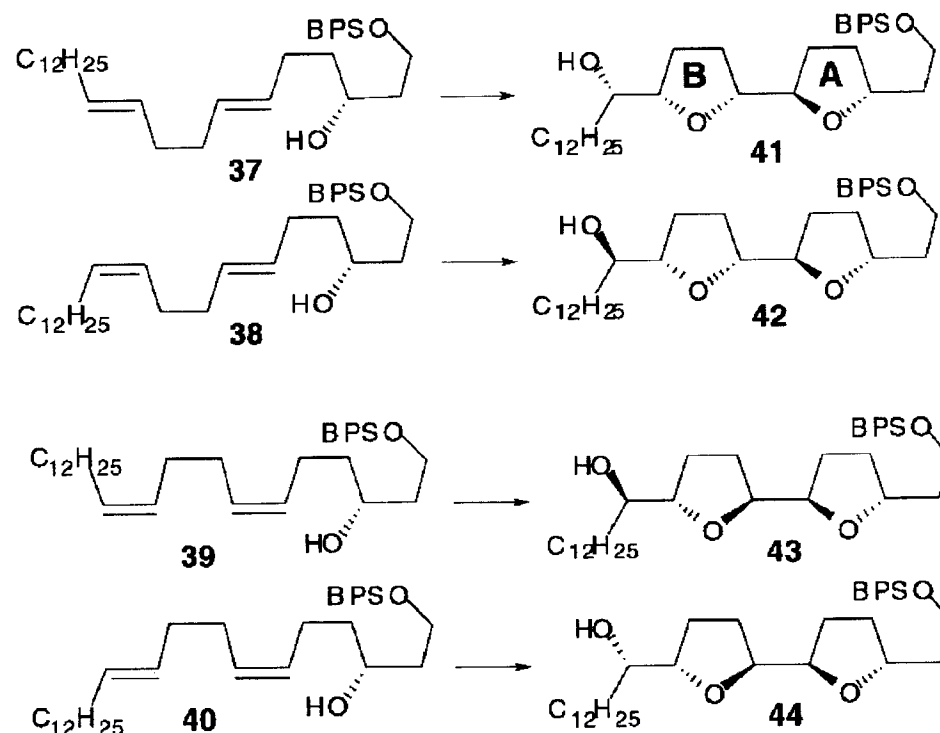
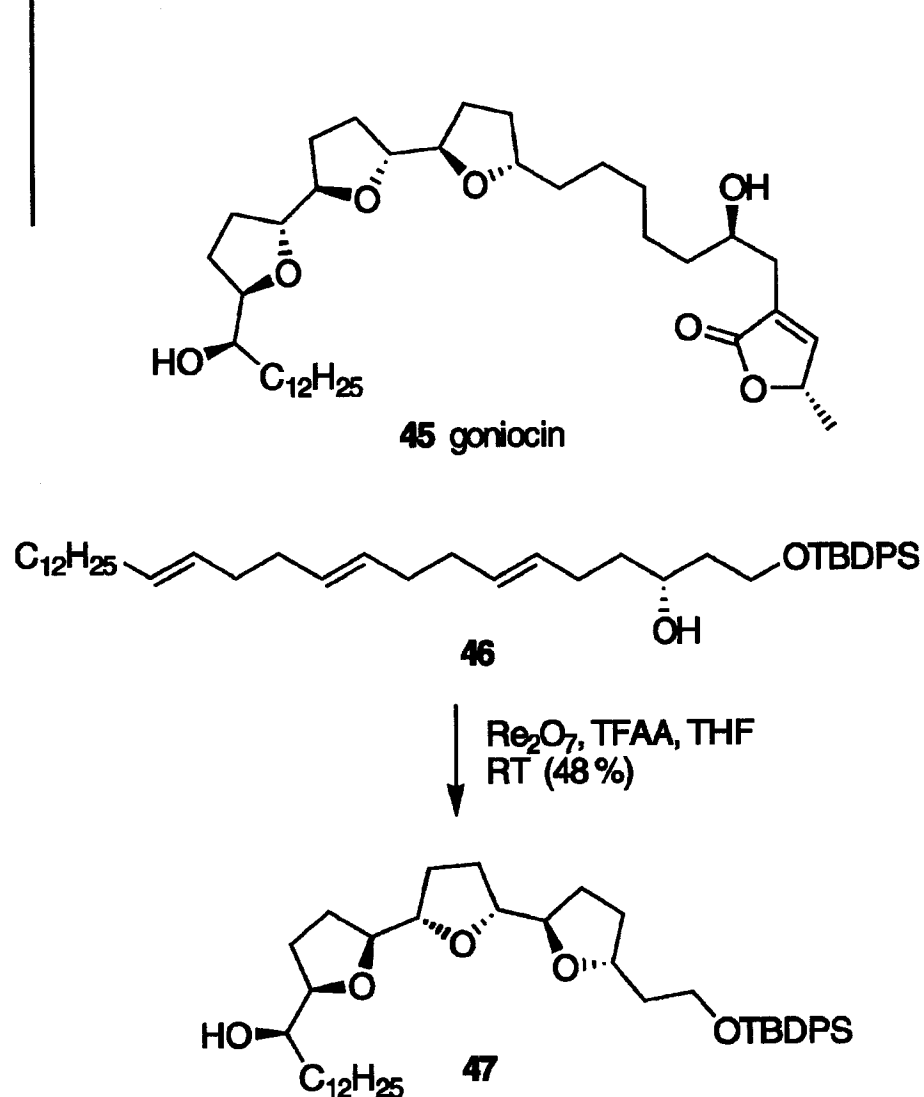


Re promoted oxidative cyclization to *trans* THF



Different transformations are required to obtain desired stereochemistry (or are they...?)

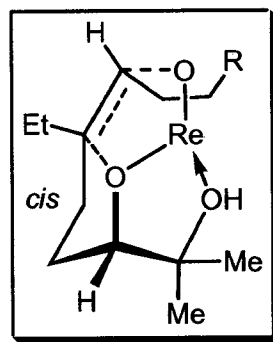
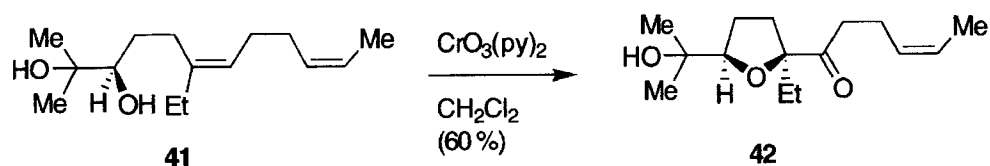
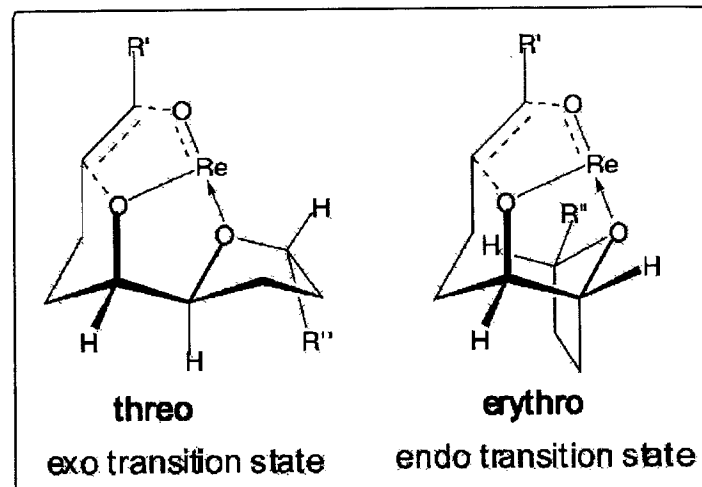
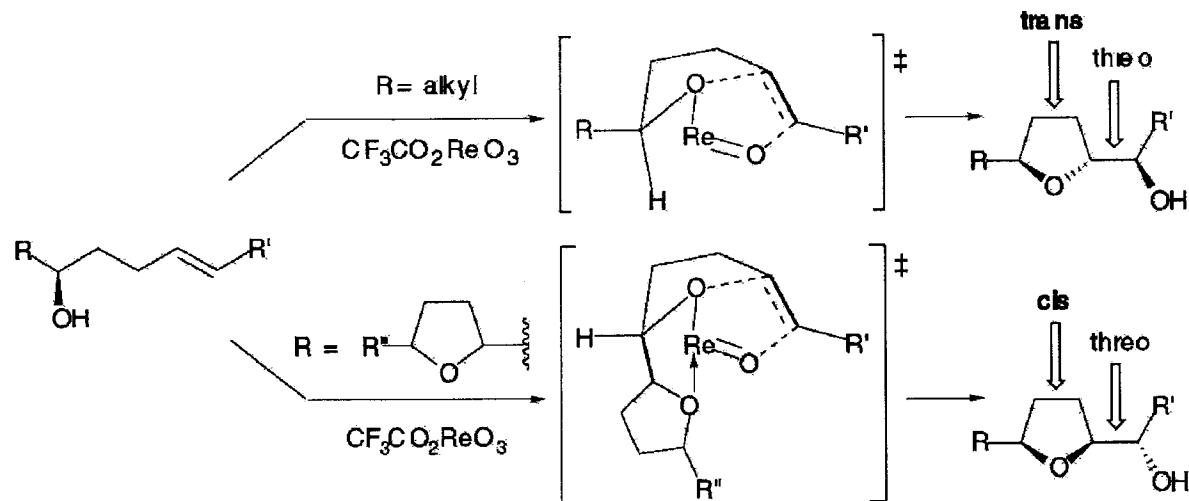




## Stereoselectivity Rules

- First THF – always *trans* (from *E* or *Z* alkene)
- Subsequent can be *cis* or *trans*
- When 1<sup>st</sup> is from *E* alkene – *threo* diol – 2<sup>nd</sup> gives *cis*
- When 1<sup>st</sup> is from *Z* alkene – *erythro* diol – 2<sup>nd</sup> gives *trans*

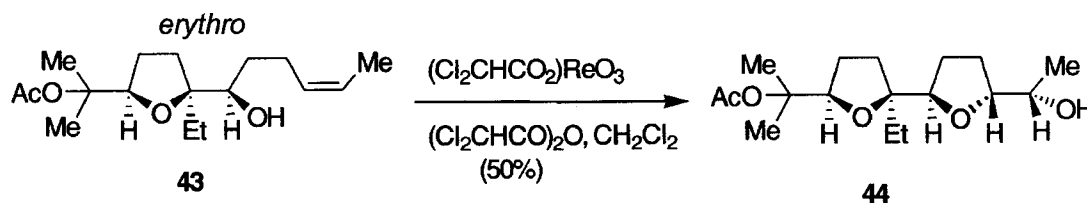
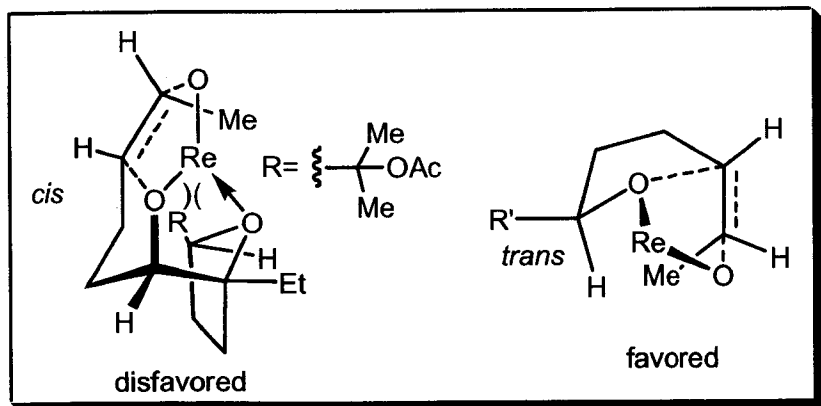
# Cascade Oxidative Cyclizations: Justification for Stereochem. <sup>26</sup>



Favors coordinated (lower) pathway for *threo* system

Favors uncoordinated (upper) pathway for *erythro* system

Applying Sinha analysis to the McDonald system suggests a cascade approach would work!



# *Polyether Biomimetic Synthesis: Conclusions*

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## Cascade epoxide opening proposal

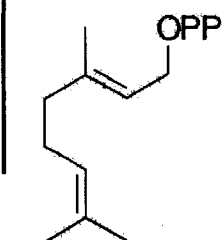
- Some synthetic support
- Difficulty of finding a stereoselective global epoxidation is the shortcoming in the lab since some natural products require different configurations at different double bonds within the same polyene (enzymes could do it)
- No proof yet from feeding experiments (one negative result)

## Cascade oxidative cyclization proposal

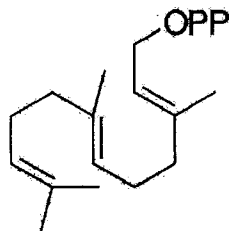
- Stepwise oxidative cyclizations have been achieved
- Cascade oxidative cyclizations are also possible but stereoselectivity is an issue
- A model for stereoselection has been proposed, but it will not allow for all permutations of stereochemistry that might be in natural products (enzymes could, again, probably overcome this shortcoming)
- No proof yet from feeding experiments (no studies were found)

To date, it is not clear which proposal is actually happening in nature

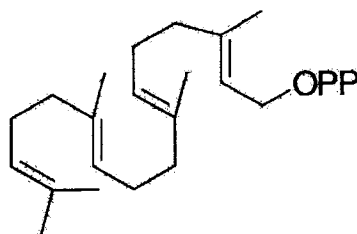
# Cascade Cyclizations of Isoprenoids



**68 GPP**  
geranyl  
pyrophosphate



**69 FPP**  
farnesyl PP



**70 GGPP**  
geranylgeranyl PP

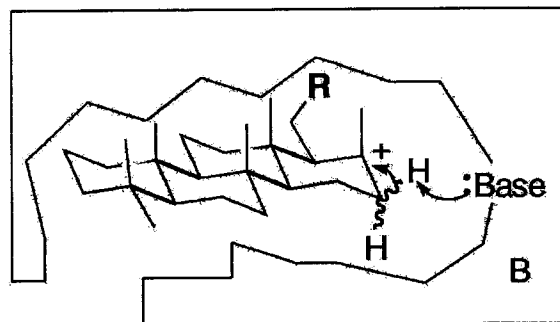
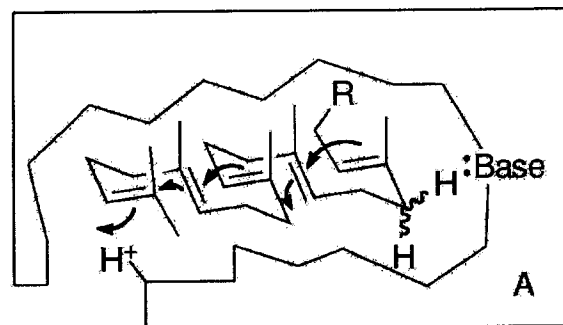
Cyclization involves:

1. generation of carbocation
2. control of conformation  
(Stork-Eschenmoser hypothesis)
3. stabilization of intermediates
4. quenching of final carbocation



achiral polyprenoids

+ cyclase



- cyclase



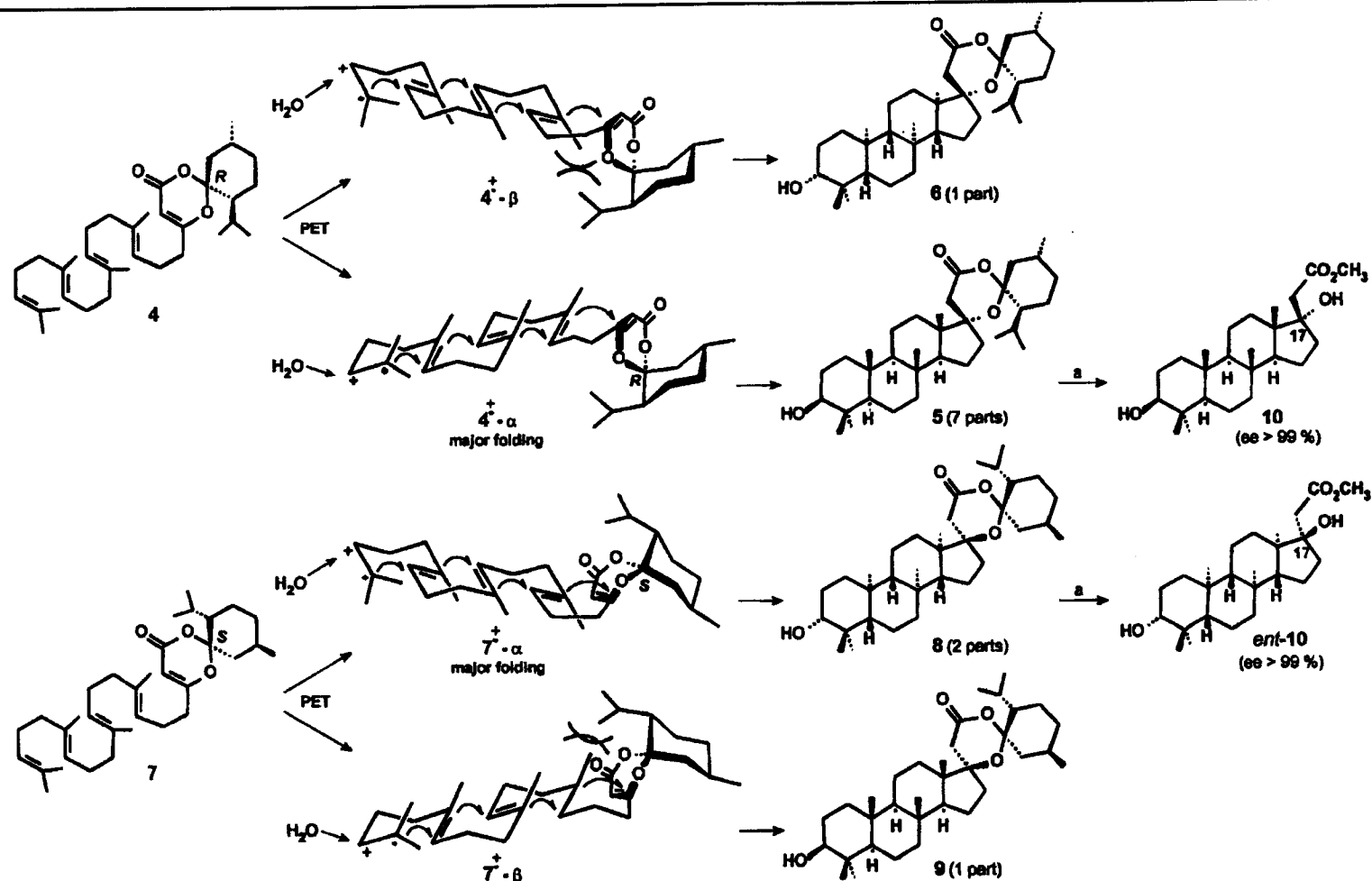
polycyclic chiral terpenoids

## Biomimetic Cyclization

How much are enzymes really  
involved in the cyclization  
process?

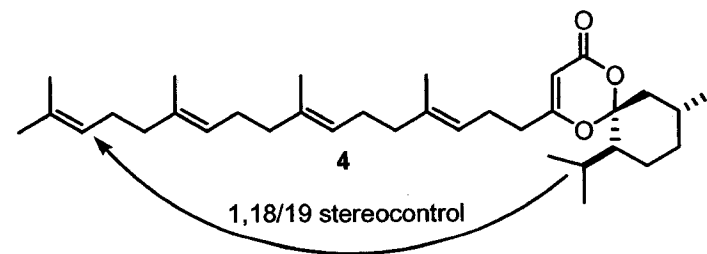
# Cyclizations of Isoprenoids: Remote Stereocontrol

29

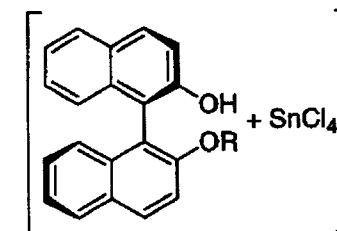
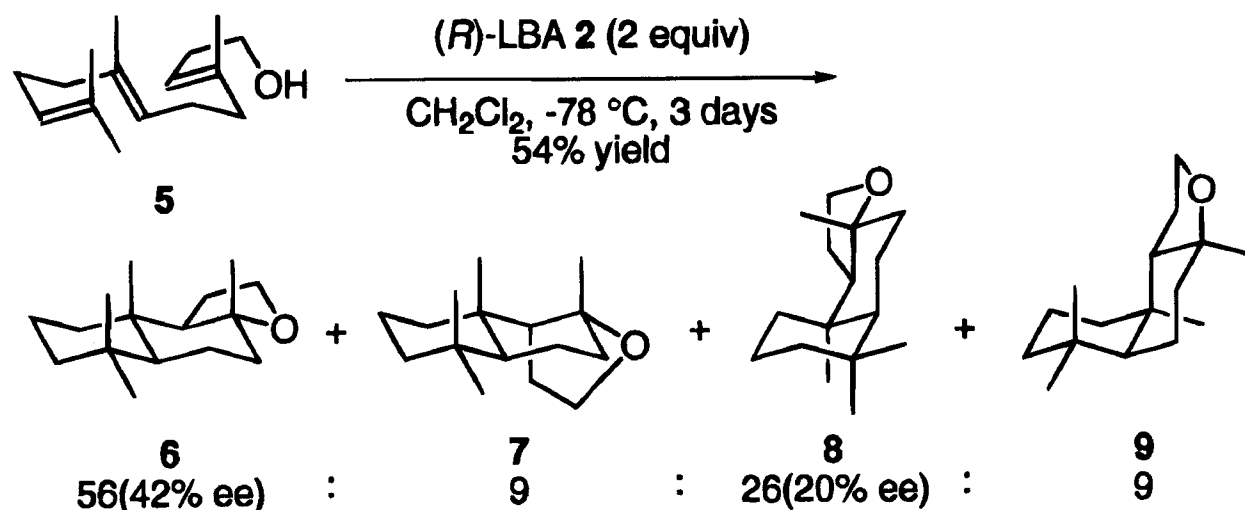


<sup>a</sup> Reagents and conditions: (PET) biphenyl, 1,4-dicyanotetramethylbenzene,  $h\nu$  (300 nm), MeCN/H<sub>2</sub>O 10:1, -25 °C, 10% (5 and 6), 12% (8 and 9);  
 (a) NaOMe, MeOH, 25 °C, 91% (10), 95% (*ent*-10).

- 8 stereogenic centers are formed in one step
- 2 of 256 possible isomers are formed selectively from control of distant stereogenic centers
- Supports "mimimal-enzymatic-assistance" theory

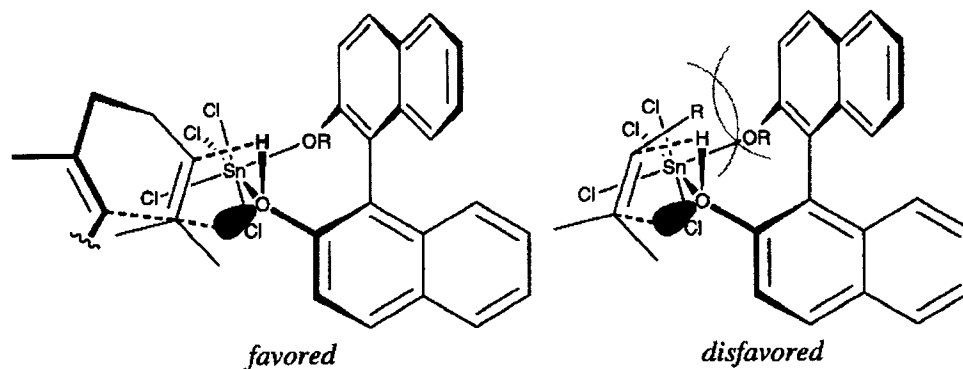


# Cyclizations of Isoprenoids: Artificial Cyclases



LBA 1 (R=H)  
 LBA 2 (R=Me)  
 LBA 3 (R=*i*-Pr)  
 LBA 4 (R=COPh)

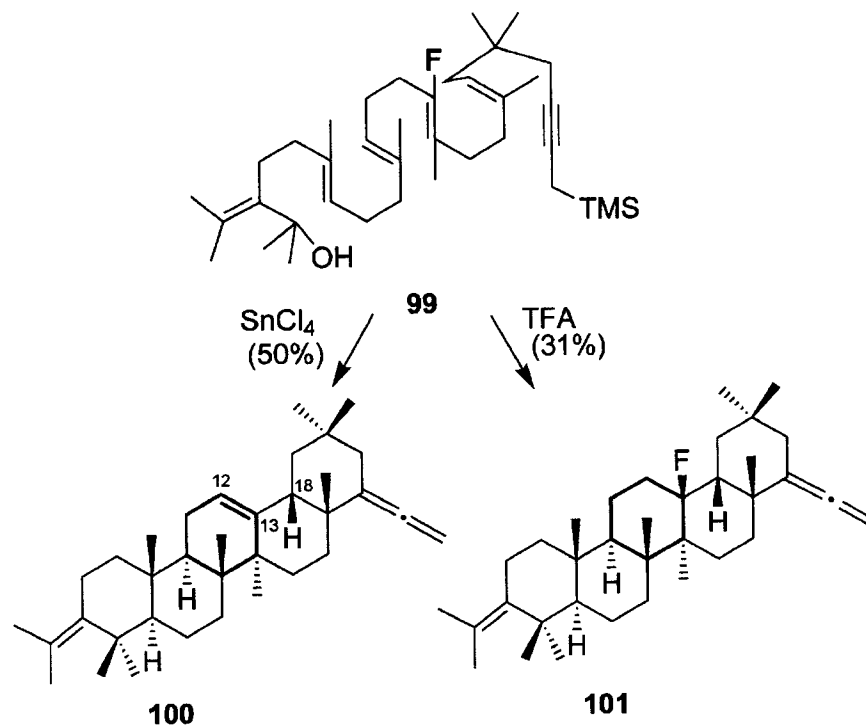
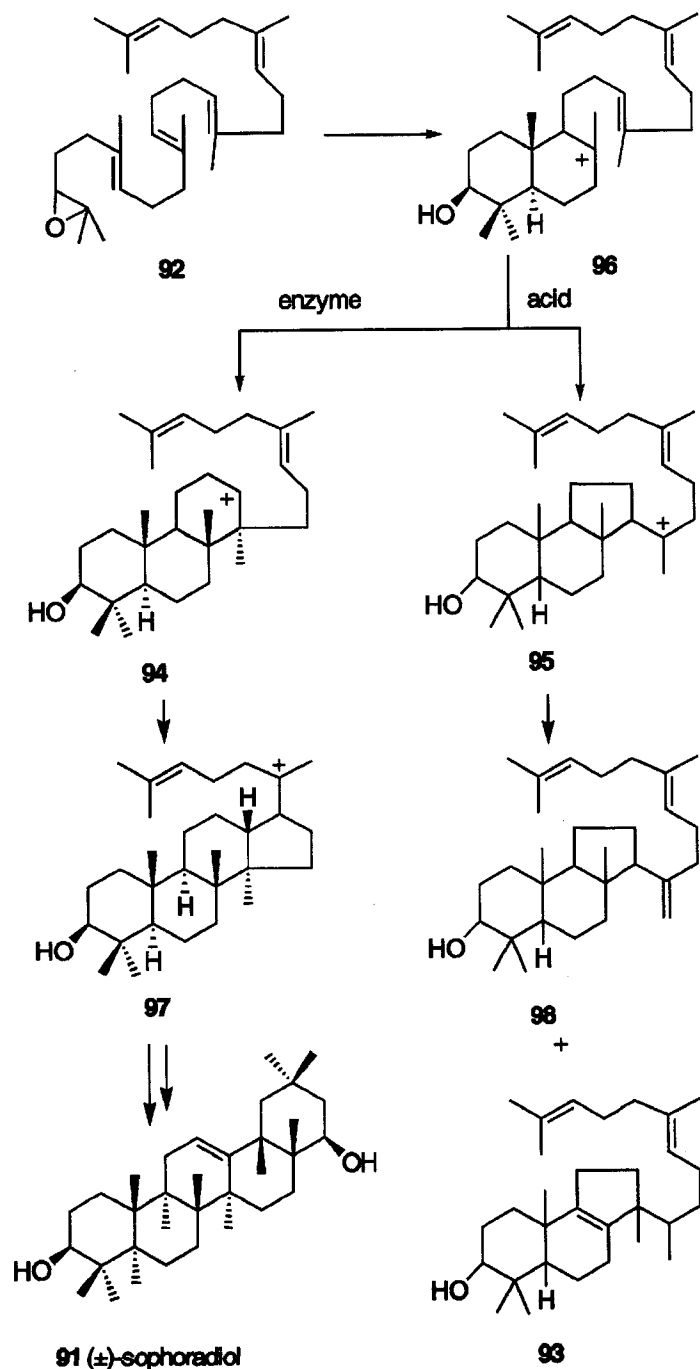
Lewis acid-assisted chiral  
 Brønsted acids = LBA's



“an  $n\text{-}\pi^*$  interaction between an oxygen lone pair (HOMO) of LBA and  $\pi^*$  (LUMO) of the terminal C=C bond of the substrates stabilizes the transition state of the cyclization (or the initial protonation step). The transition-state assembly proposed on the basis of the above assumption and the steric repulsion clearly would lead to the predominant approach of (R)-LBA to the *si* face of the terminal isoprenyl group.”

Mimics enzyme's ability to act as a chiral proton source

# Cyclizations of Isoprenoids: Stabilization of Intermediates



Fluorine stabilizes cation intermediate  
leading to complete regioselectivity

# Conclusions

---

## Cascade cyclizations of isoprenoids

- Possibility of remote stereocontrol by enzymes has been mimicked
- Possibility of enzymes acting as a chiral proton source has been mimicked
- Ability of enzymes to stabilize reactive intermediates has been mimicked

## Overall

- Cascade reaction sequences build up molecular complexity efficiently
- Biomimetic synthesis for three systems suggests differing levels of enzyme participation
  - *Daphniphyllum* alkaloids – cascade sequence of reactions that can happen in the laboratory (although without enantioselectivity) – enzyme probably functions as organization element or chiral amine source
  - Polyether proposals – enzymes are probably responsible for enantioselective epoxidations or enantioselective cyclization reactions
  - Isoprenoids – enzymes function as remote stereocontrol elements, chiral proton sources, and stabilize reactive intermediates
- These cascade reaction sequences work due to the inherent reactivity of substrates – using enzymes leads to specific regio- and stereochemical outcomes which probably can be (or already have been) mimicked in the lab