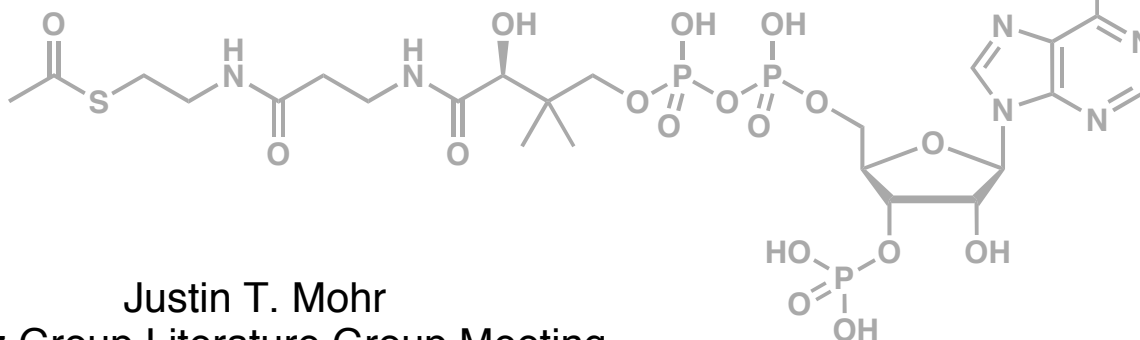
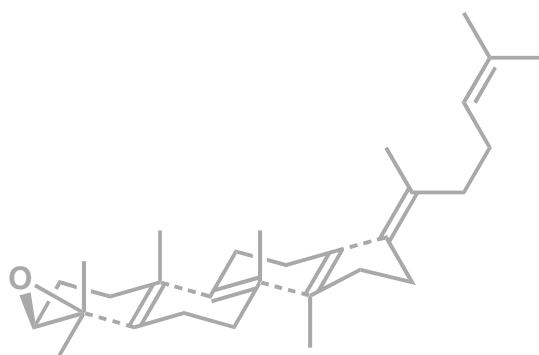
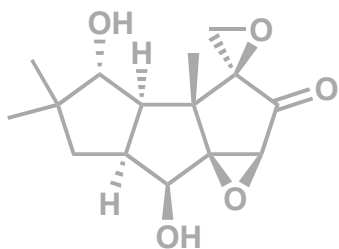


Sesquiterpenoids

Biosynthesis and Total Synthesis



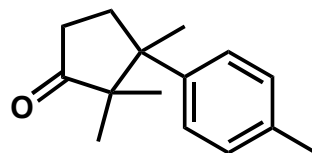
Justin T. Mohr
Stoltz Group Literature Group Meeting
2 April 2007

Outline

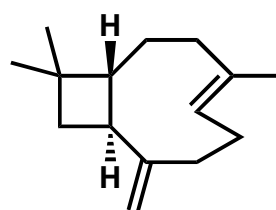
- Introduction to terpenes and terpenoids
- Traditional isolation of terpenoids
- The Isoprene Rule
- Terpenoid biosynthesis
 - Coenzymes
 - The mevalonate pathway
- Cyclization examples
- Case studies in biosyntheses and laboratory total syntheses

General References

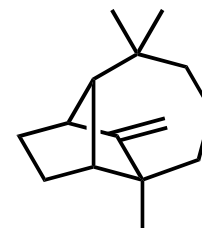
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- Newman, *Chemistry of Terpenes and Terpenoids*, Academic: London, 1972.
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- Cane, "Isoprenoid Biosynthesis. Stereochemistry of the Cyclization of Allylic Pyrophosphates" *Acc. Chem. Res.* **1985**, 18, 220-226.
- Roberts, "Sesquiterpene Biogenesis" *Q. Rev., Chem. Soc.* **1967**, 21, 331-363.
- Roberts, "Sesquiterpenoids" *Terpenoids and Steroids* **1982**, 11, 3-90.
- Roberts, "Sesquiterpenoids" *Nat. Prod. Rep.* **1984**, 1, 105-169.
- Roberts, "Sesquiterpenoid Synthesis" *Nat. Prod. Rep.* **1985**, 2, 97-145.
- Dewick, "The Biosynthesis of C₅-C₂₅ Terpenoid Compounds" *Nat. Prod. Rep.* **2002**, 19, 181-222.



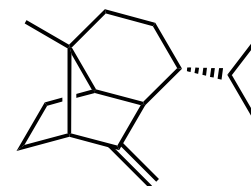
α-Cuparenone
(Noyori, 1978)



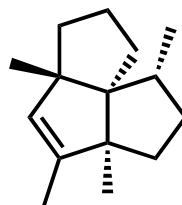
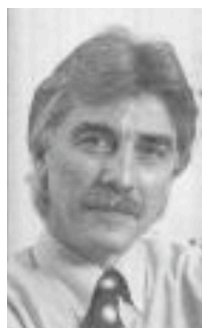
β-Caryophyllene
(Corey, 1963)



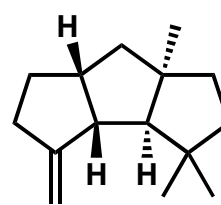
Longifolene
(Oppolzer, 1978)



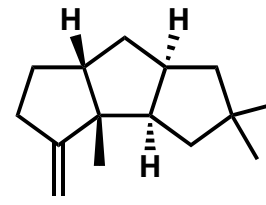
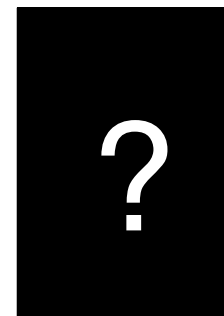
Sinularene
(Oppolzer, 1982)



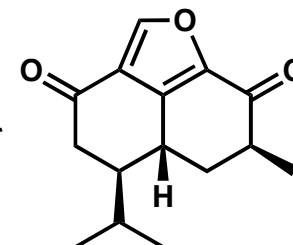
α-Isocomene
(Wender, 1981)



Δ⁹⁽¹²⁾-Capnellene
(Curran, 1985)



Hirsutene
(Oda, 1986)

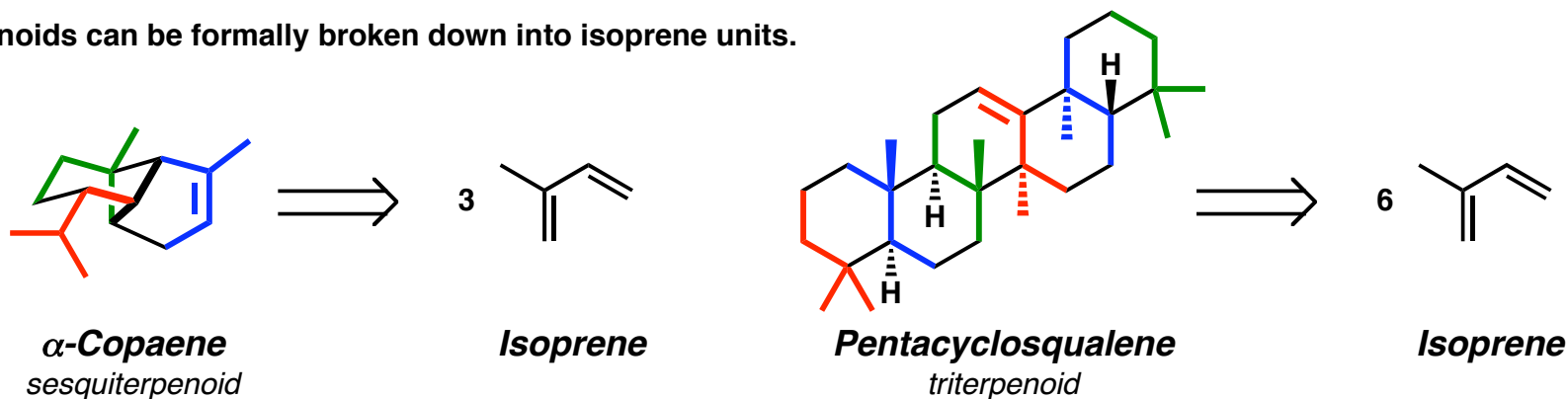


Hibiscone C
(Smith, 1982)

Terpenoids

An Introduction

All terpenoids can be formally broken down into isoprene units.



Class names are derived from the number of isoprene units incorporated:

# of isoprenes	# of carbons	class name
1	5	hemiterpenoids
2	10	monoterpenoids
3	15	sesquiterpenoids
4	20	diterpenoids
5	25	sesterterpenoids
6	30	triterpenoids
8	40	tetraterpenoids
∞	$5^*\infty$	rubber

} often dimers of lower terpenoids

Prefixes (many of these are now antiquated):

- α , β , γ – usually olefin isomers, occasionally stereochemistry
- *seco* – designates cleavage of one bond
- *cyclo* – with one additional bond forming a ring
- *abeo* – designates a rearranged bond
- *nor* – lacking one carbon
- *homo* – with one additional carbon

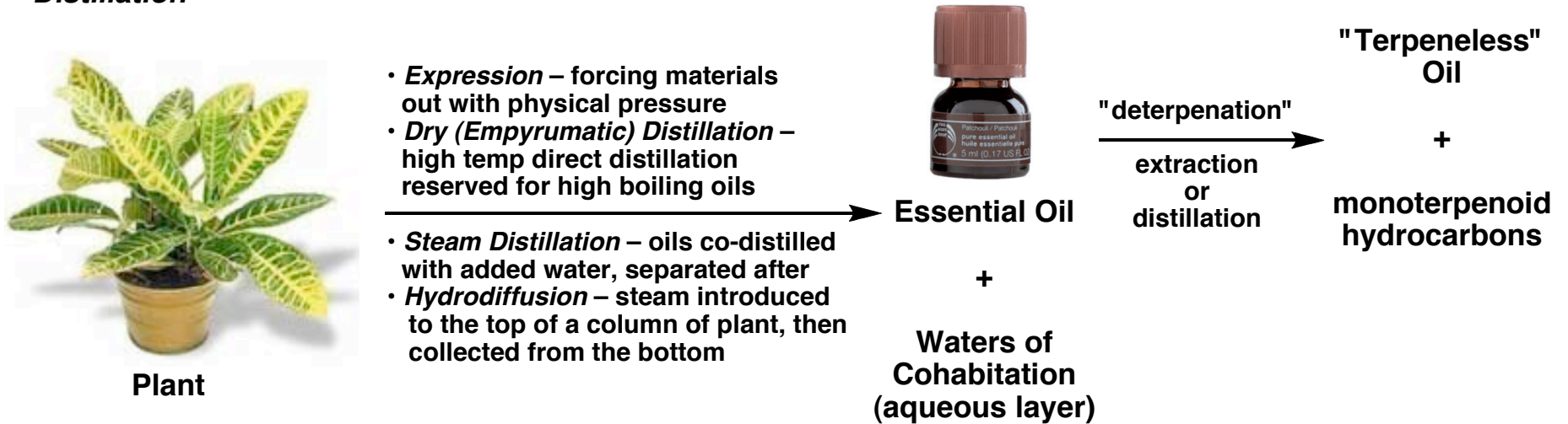


Turpentine
terpenoids distilled from sap
(largely pinene) are the only
compounds correctly called terpenes

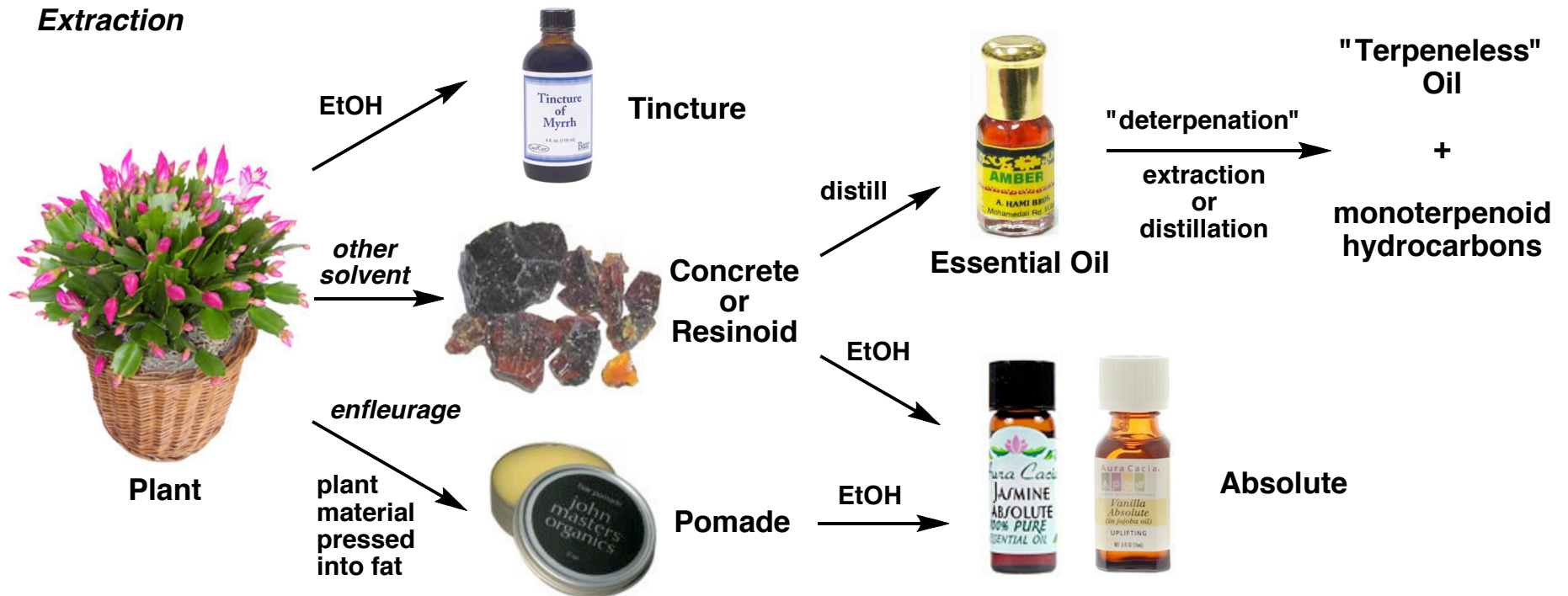
Terpenoids

Methods of Extraction

Distillation

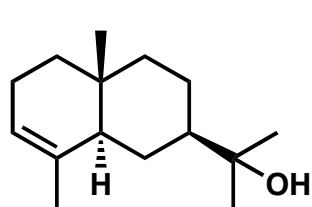


Extraction

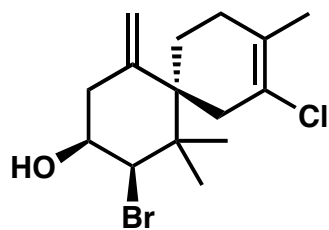


Terpenoids and You

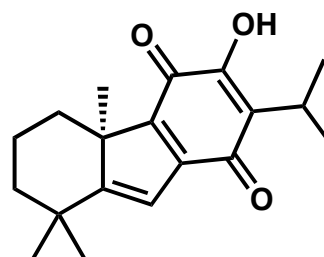
Terpenoid structures are very diverse, incorporating many unique ring systems, functionalities, and molecular architectures.



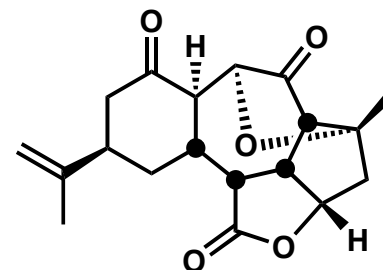
α-Eudesmol
sesquiterpenoid



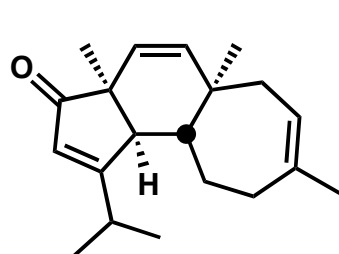
Elatol
sesquiterpenoid



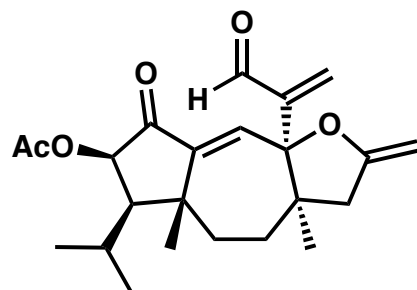
Dichroanone
norditerpenoid



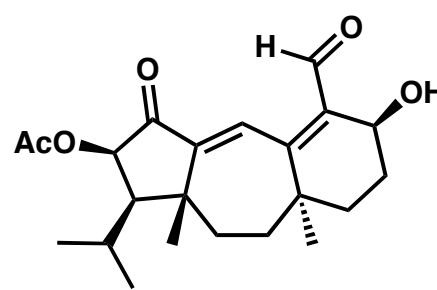
Ineleganolide
diterpenoid



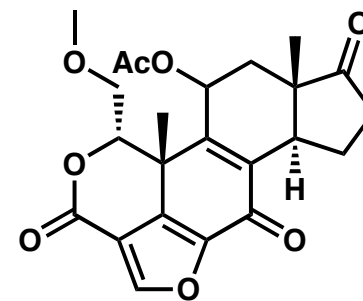
Cyanthiwigin G
diterpenoid



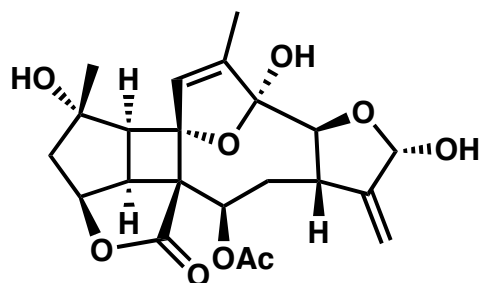
Lepistal
diterpenoid



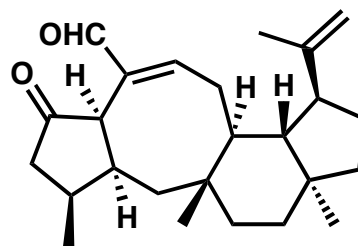
Guanacastepene
diterpenoid



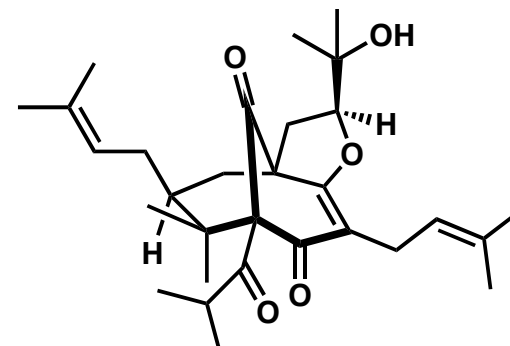
Wortmannin
diterpenoid



Bielschowskysin
diterpenoid



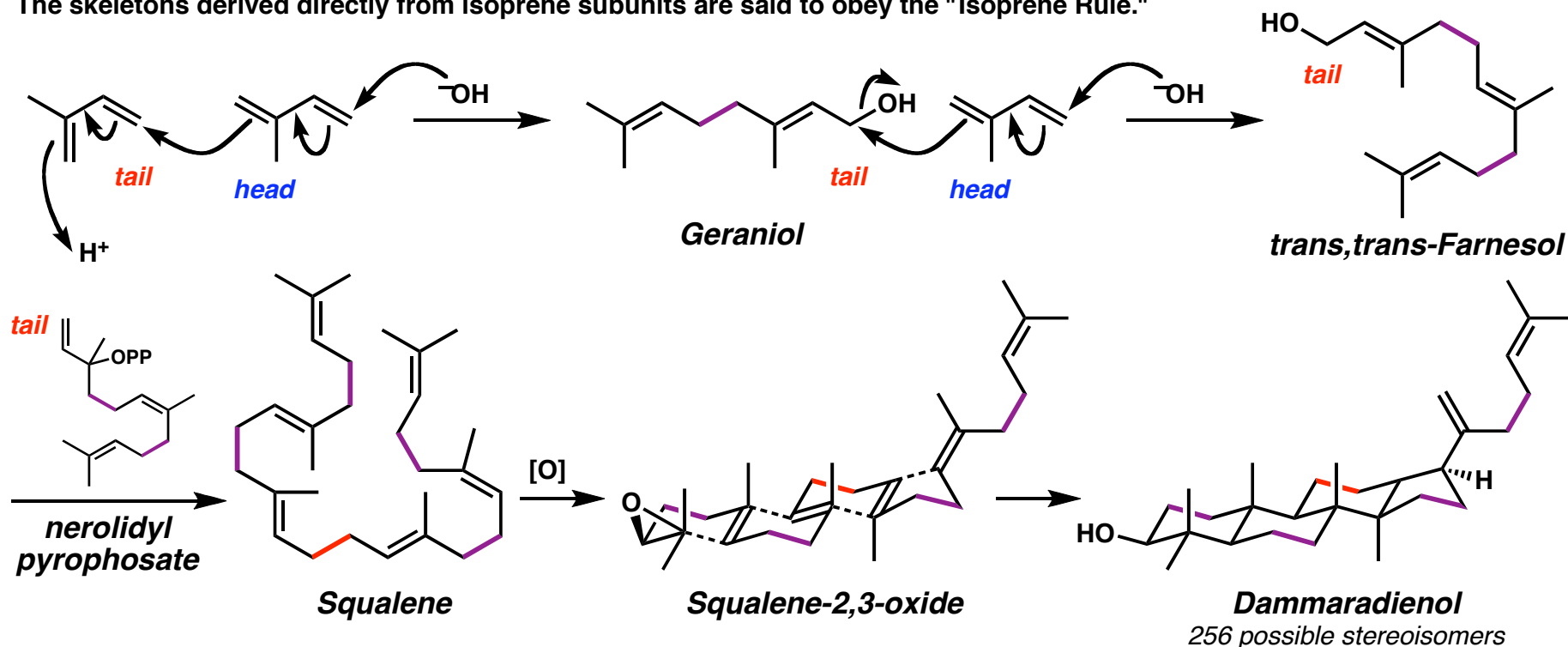
Variocolin
Sesterterpenoid



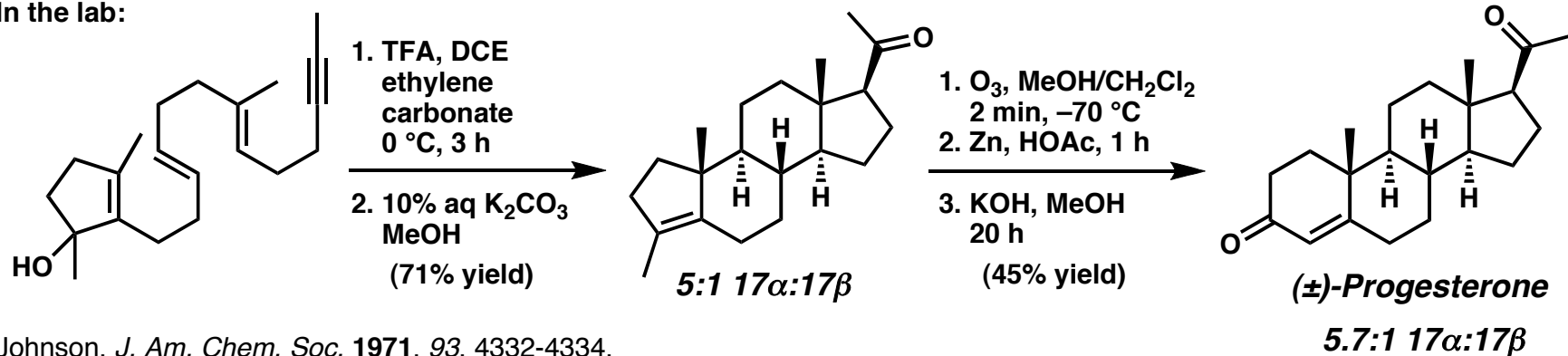
Garsubellin A
triterpenoid

Isoprene to Terpenoids

Isoprene units can (formally) combine in two ways to make higher terpenoids.
The skeletons derived directly from isoprene subunits are said to obey the "Isoprene Rule."



In the lab:



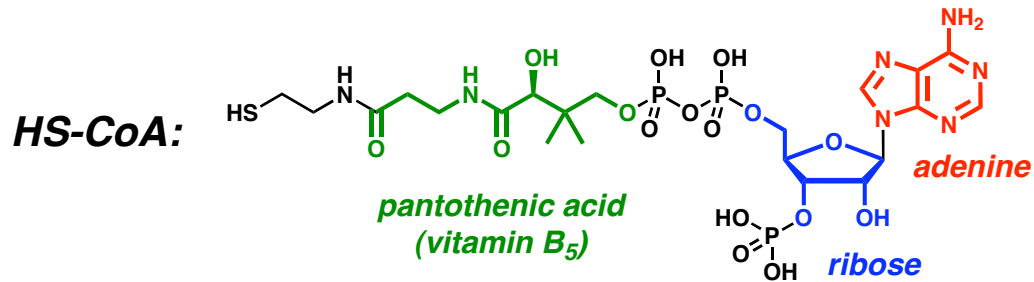
Johnson, *J. Am. Chem. Soc.* **1971**, 93, 4332-4334.
Johnson, *J. Am. Chem. Soc.* **1978**, 100, 4274-4282.

Johnson, *Acc. Chem. Res.* **1968**, 1, 1-8.

Terpenoid Biosynthesis

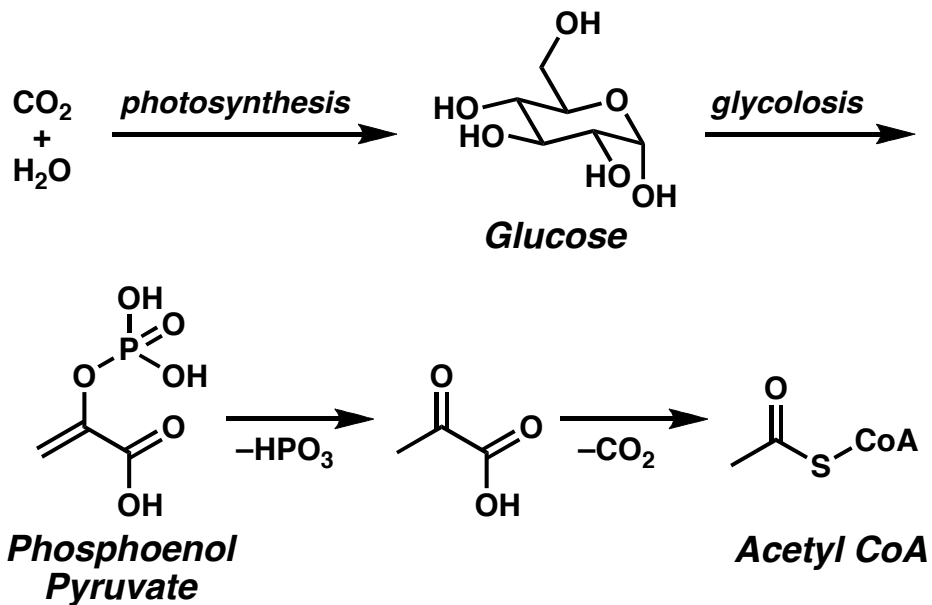
An Overview

Acetyl Coenzyme A – A versatile biosynthetic intermediate

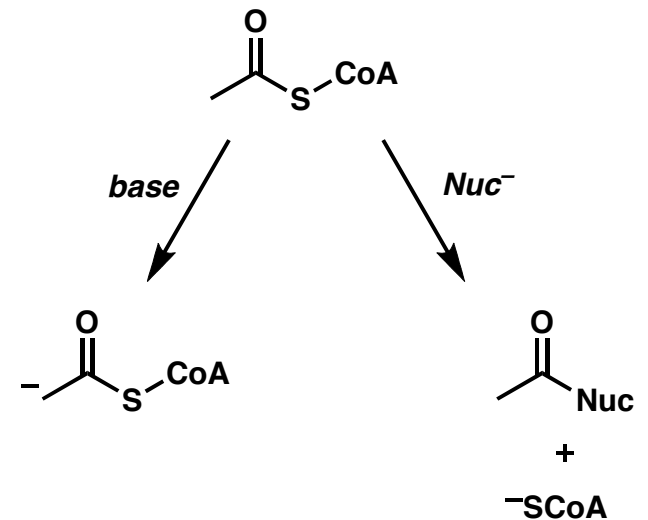


- While not directly functional, the sugar and nucleotide fragments are important for selective binding to the enzyme.

Origin of Acetyl CoA:



Depending on the enzyme, acetyl CoA can be an electrophilic or nucleophilic partner:

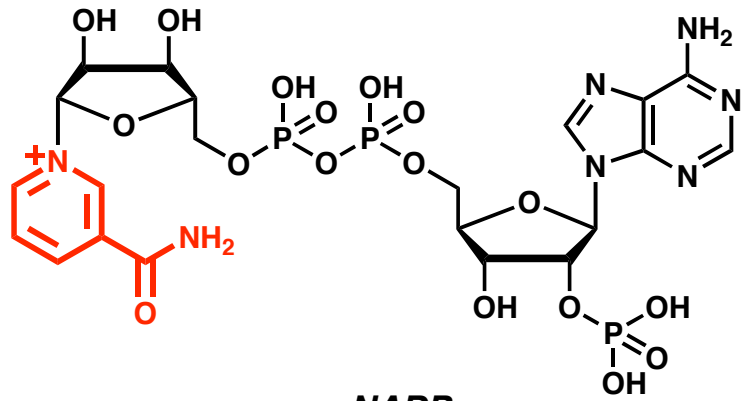


* Disclaimer: All intermediates are shown in neutral forms. At physiological pH, most acidic FGs are deprotonated.

Terpenoid Biosynthesis

An Overview

Other Important Coenzymes:

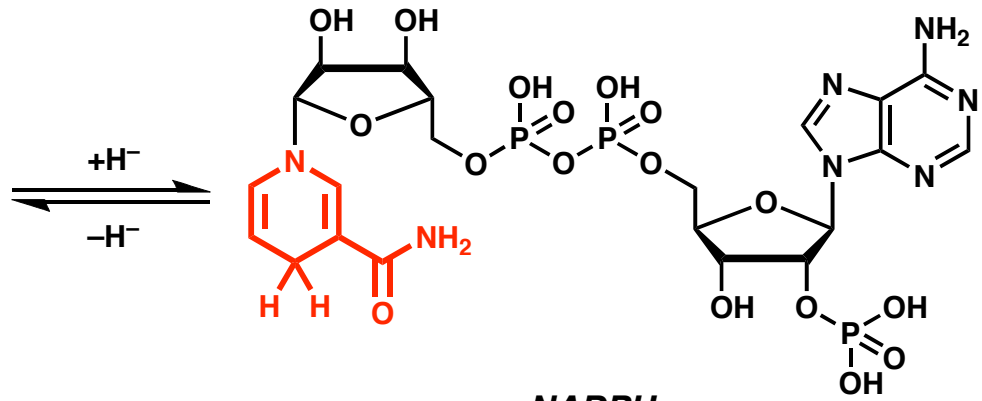


NADP

(Nicotinamide Adenine Dinucleotide Phosphate)

biosynthetic hydride acceptor (oxidizing agent)

- Nicotinamide is aromatic, but charged

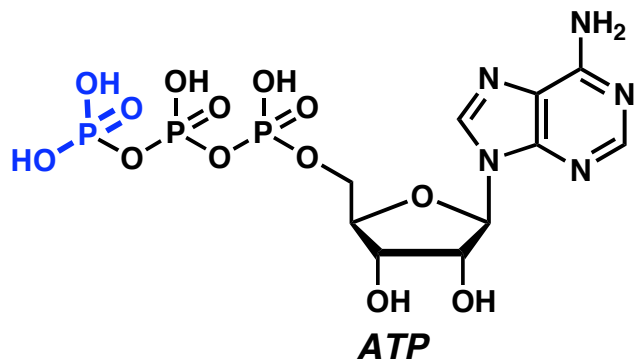


NADPH

biosynthetic hydride donor (reducing agent)

- Nicotinamide neutral, but not aromatic

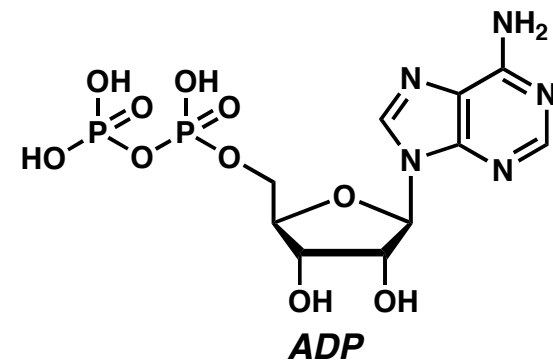
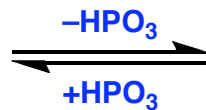
* Related coenzymes NAD and NADH (lacking the 2' phosphate) have similar function in *degradation*.



ATP

(Adenosine Triphosphate)

phosphorylating agent



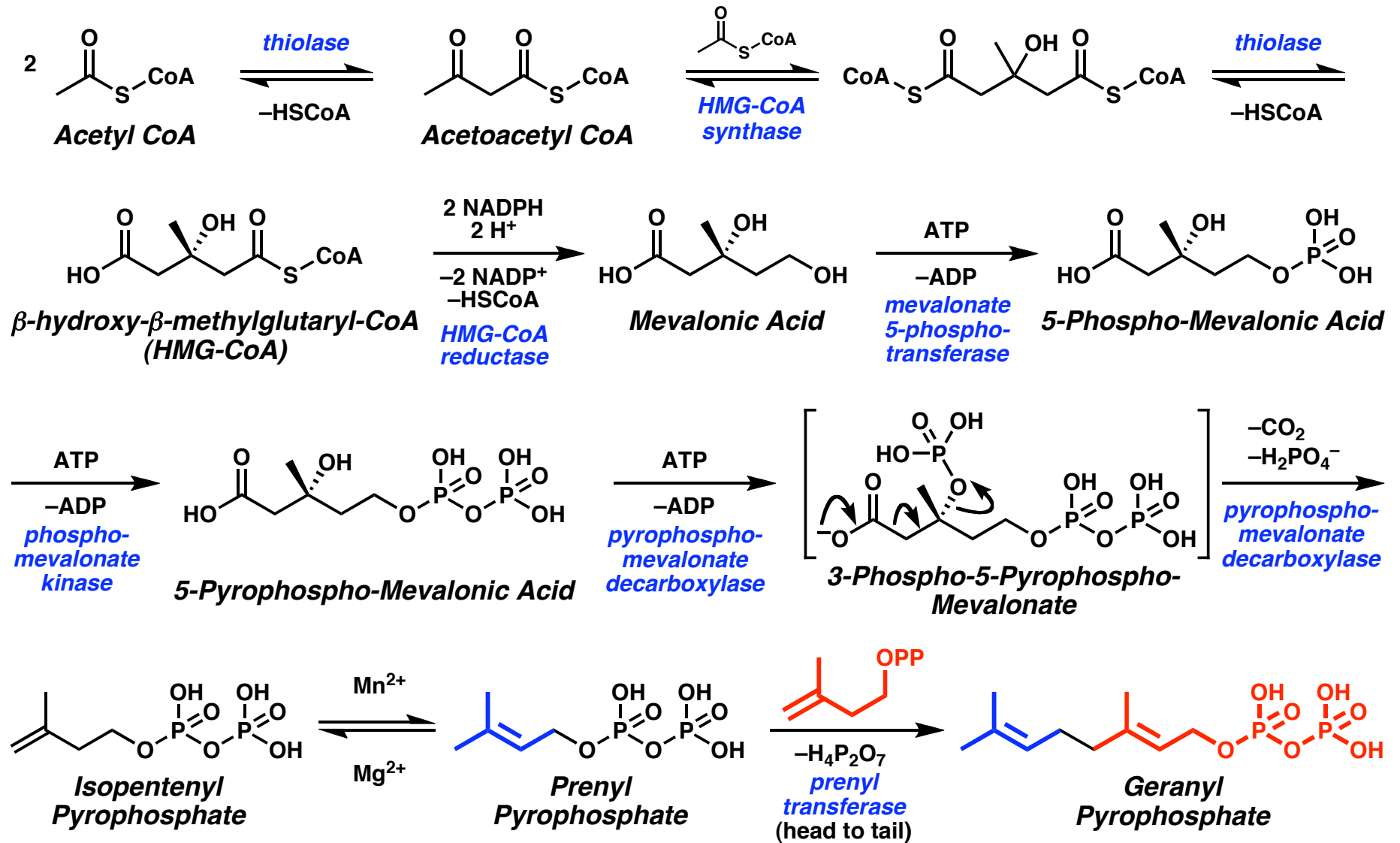
ADP

(Adenosine Diphosphate)

- Triphosphate is relatively high energy, so phosphate transfer to nucleophiles (e.g., alcohols) is favorable

Terpenoid Biosynthesis

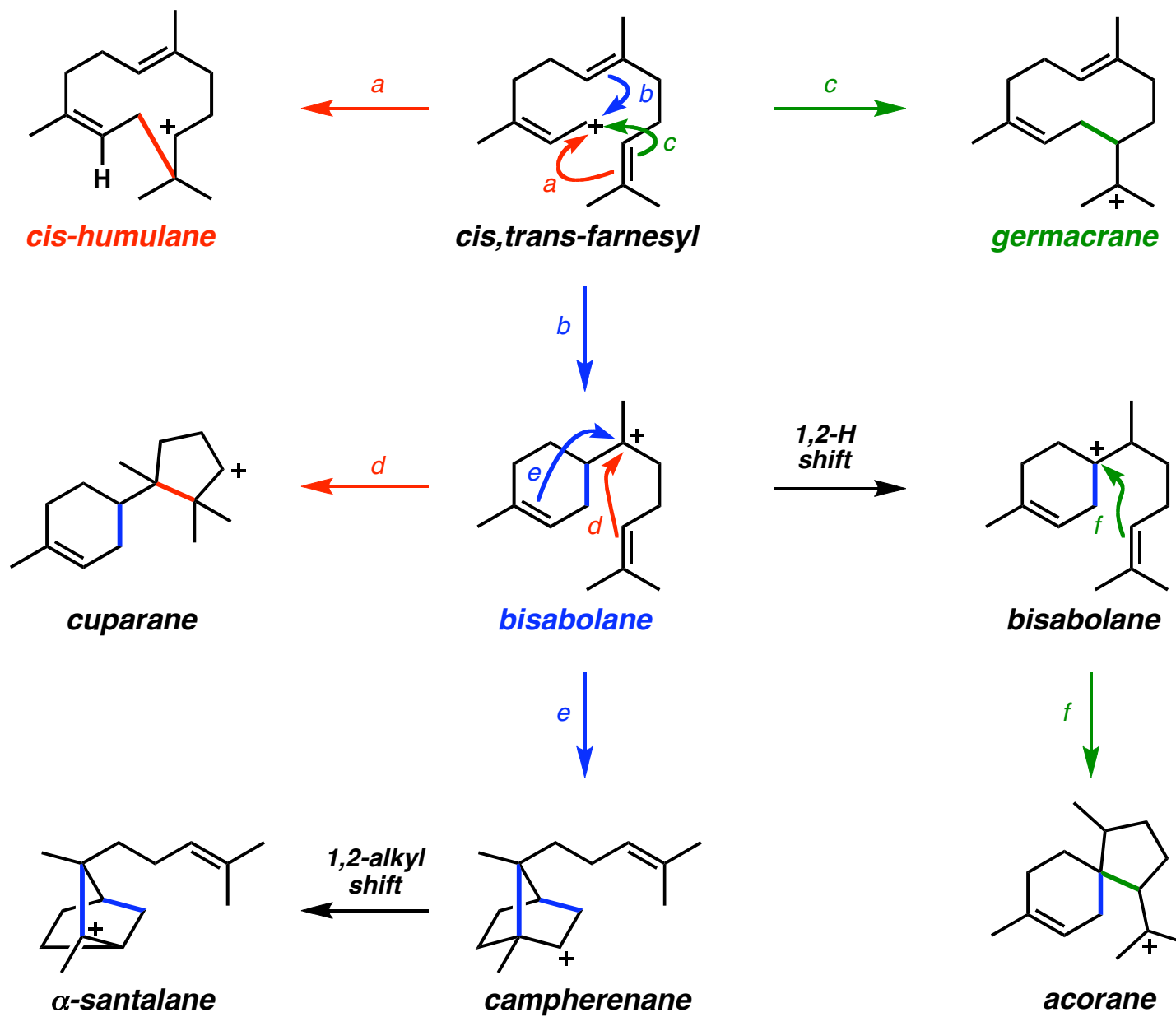
An Overview



* The mevalonate pathway is shown. This occurs in plant cytoplasm and all animals. A mevalonate independent pathway is known to occur in plant chloroplasts and in many bacteria.

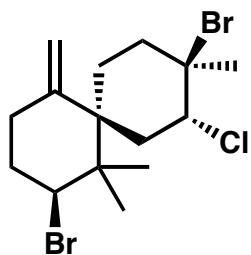
Terpenoids

Linear to Cyclic Terpenoids

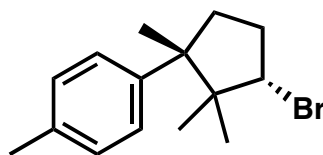
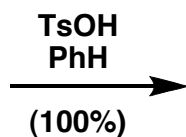


Terpenoids

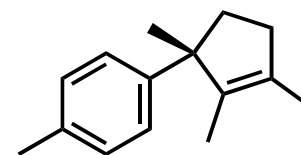
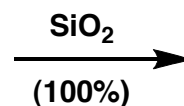
Biogenetic Relationship of Various Architectures



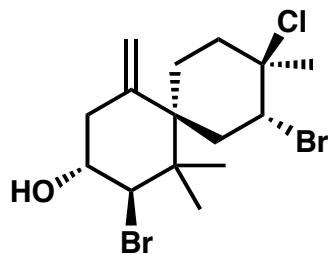
Obtusane
chamigrane



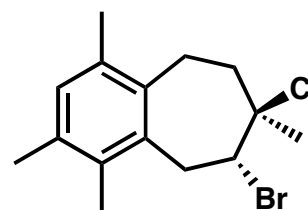
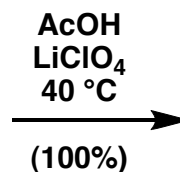
Iso-bromocuparane
cuparane



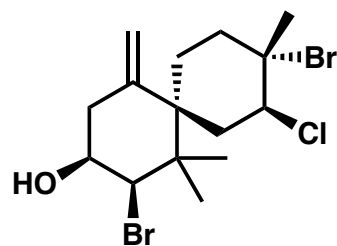
Isolaurene
rearranged cuparane



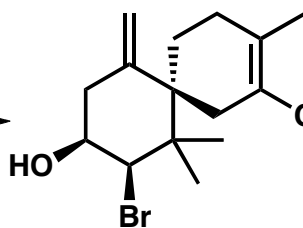
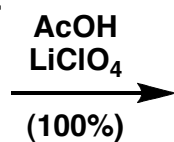
*a chamigrane
natural product*



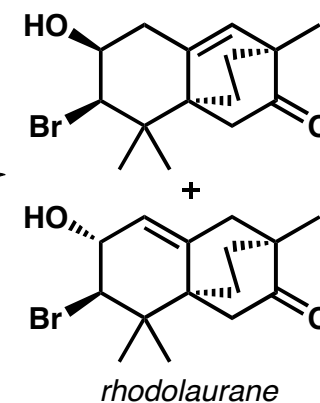
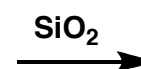
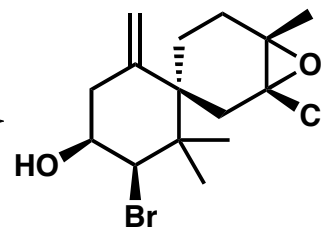
Perforene



**9-Hydroxy-
Iso-Obtusene**
chamigrane



Elatol
chamigrane

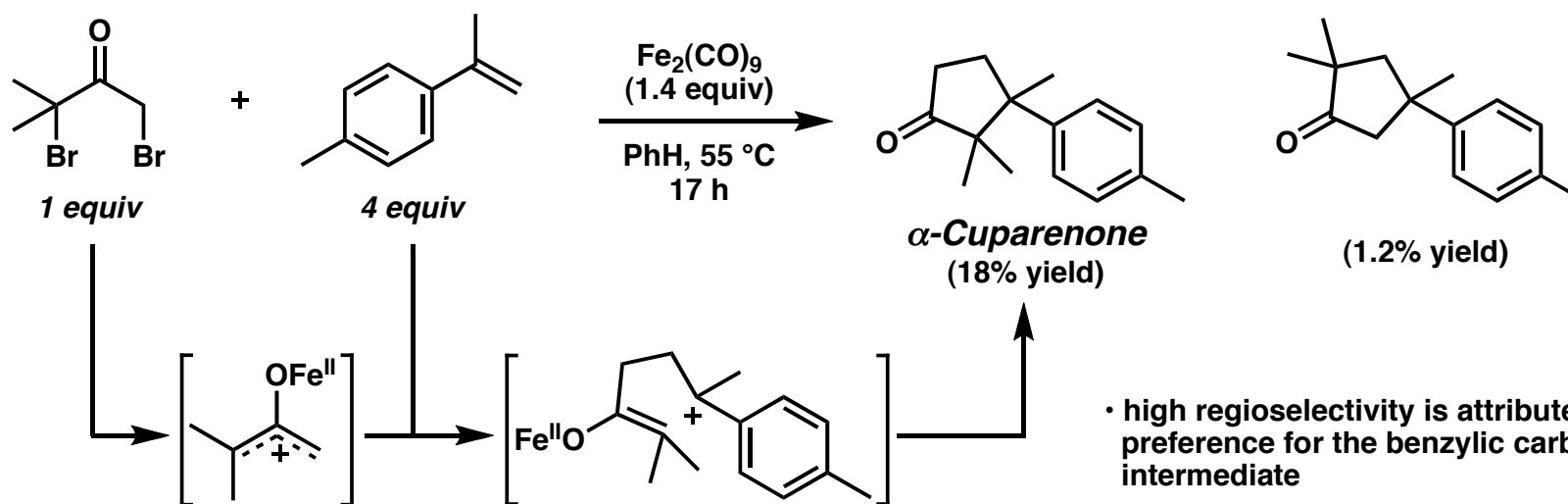
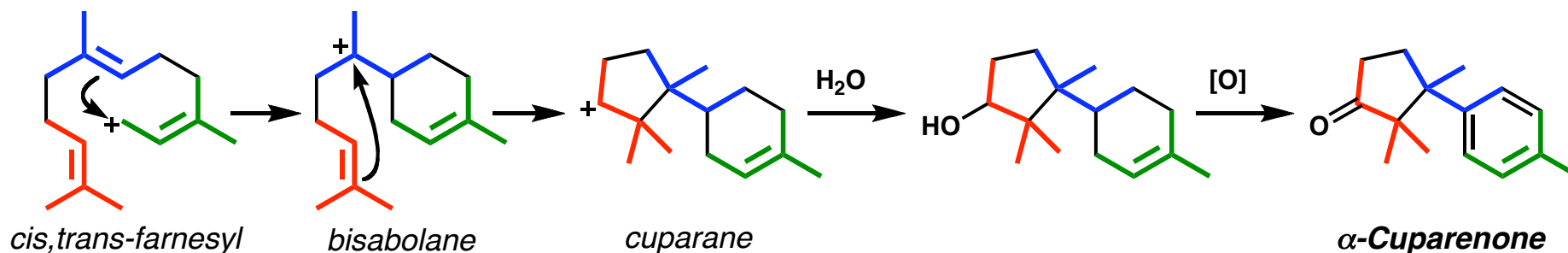


González, *Tetrahedron Lett.* **1980**, 21, 1151-1154.
González, *Tetrahedron Lett.* **1982**, 23, 2395-2398.

Synthesis of Sesquiterpenoids

α -Cuparenone

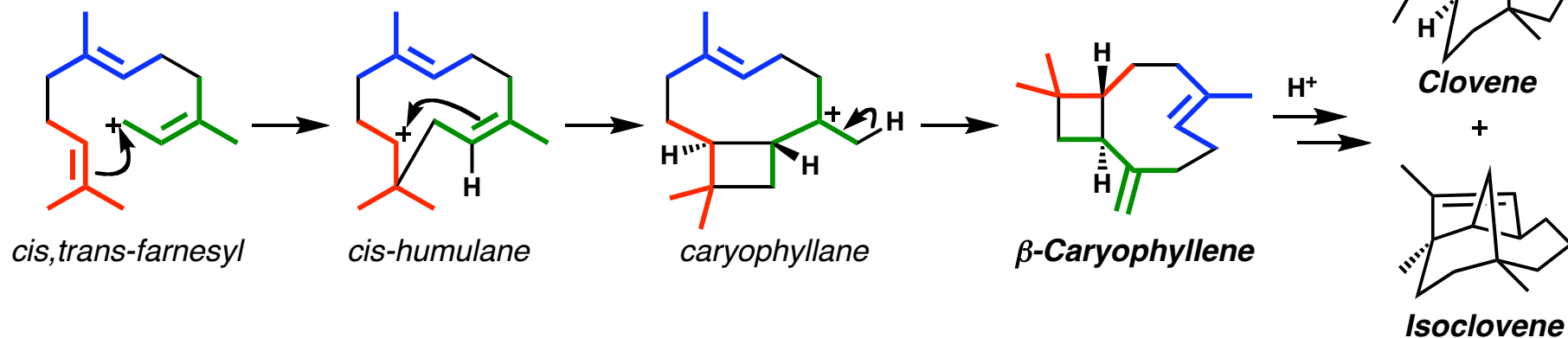
Biosynthesis



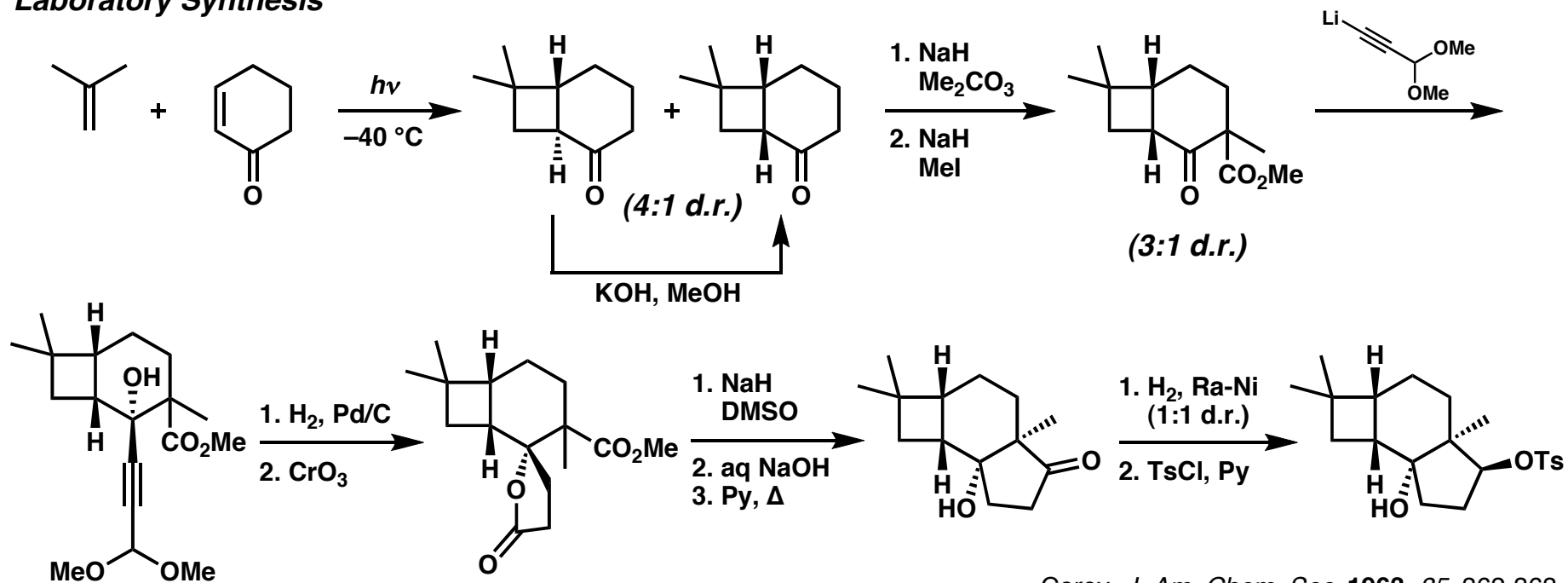
Synthesis of Sesquiterpenoids

β-Caryophyllene

Biosynthesis



Laboratory Synthesis

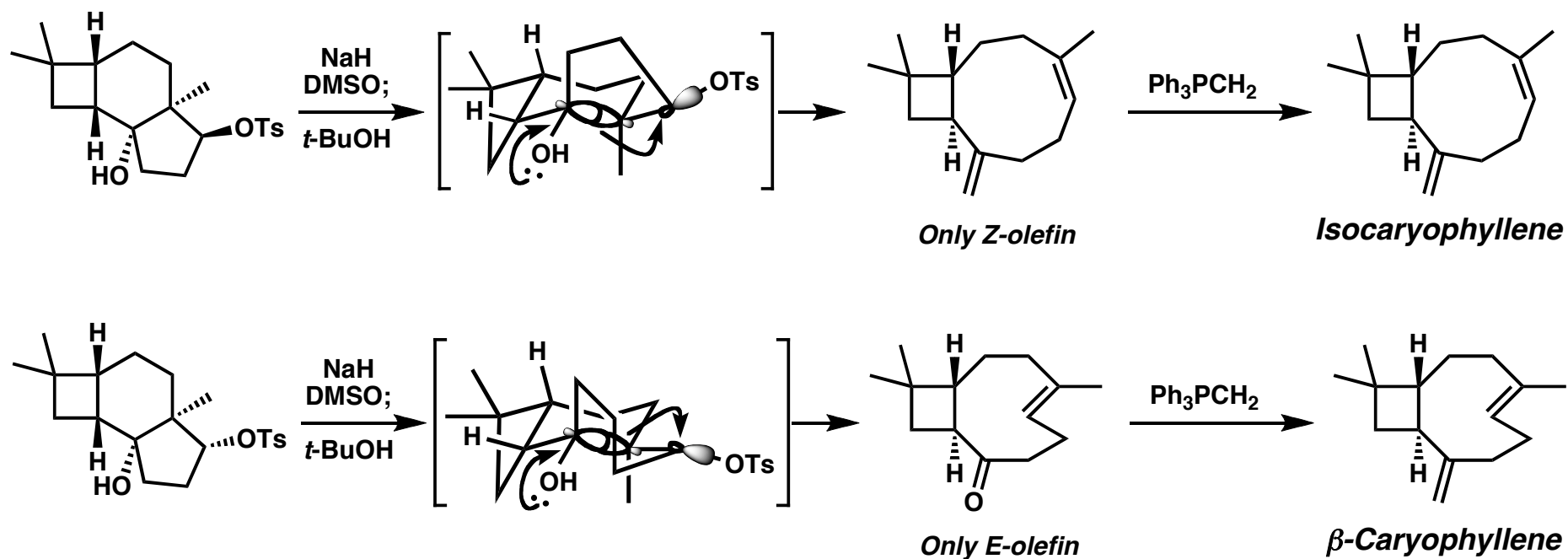


Corey, *J. Am. Chem. Soc.* **1963**, *85*, 362-363.
 Corey, *J. Am. Chem. Soc.* **1964**, *86*, 485-492.

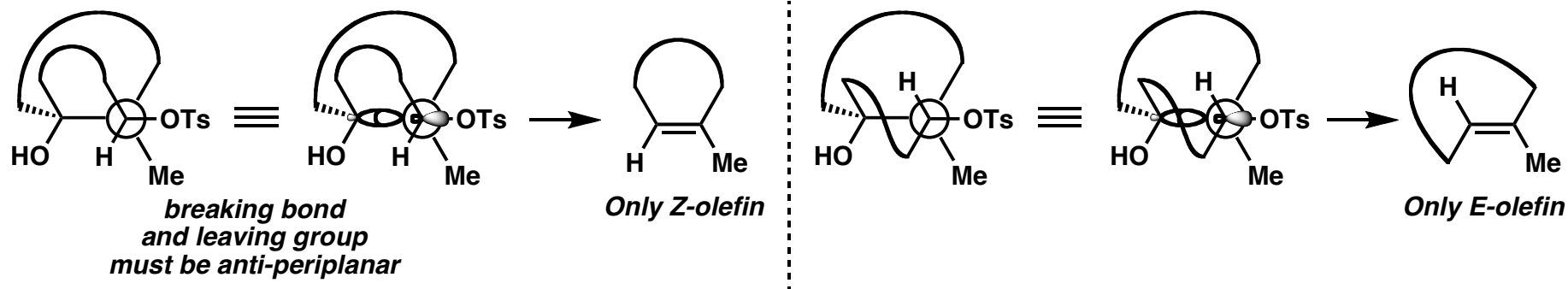
Synthesis of Sesquiterpenoids

β-Caryophyllene

A stereospecific fragmentation reaction:



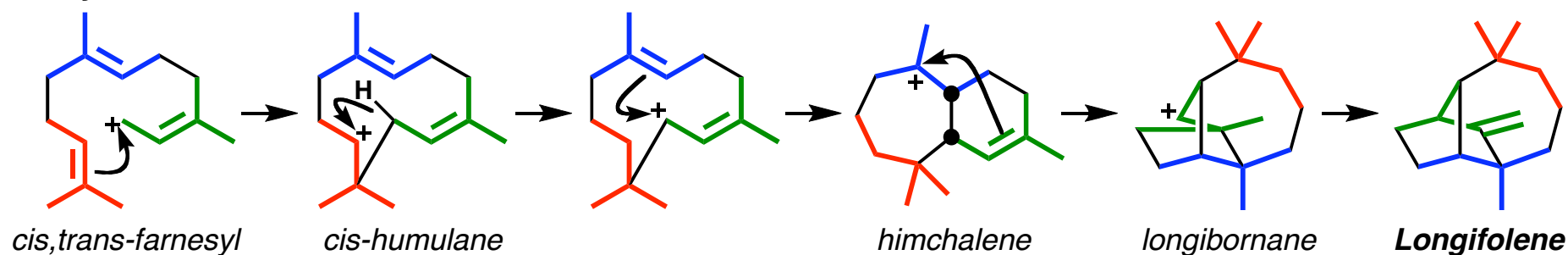
Stereospecificity can also be viewed by Newman projection:



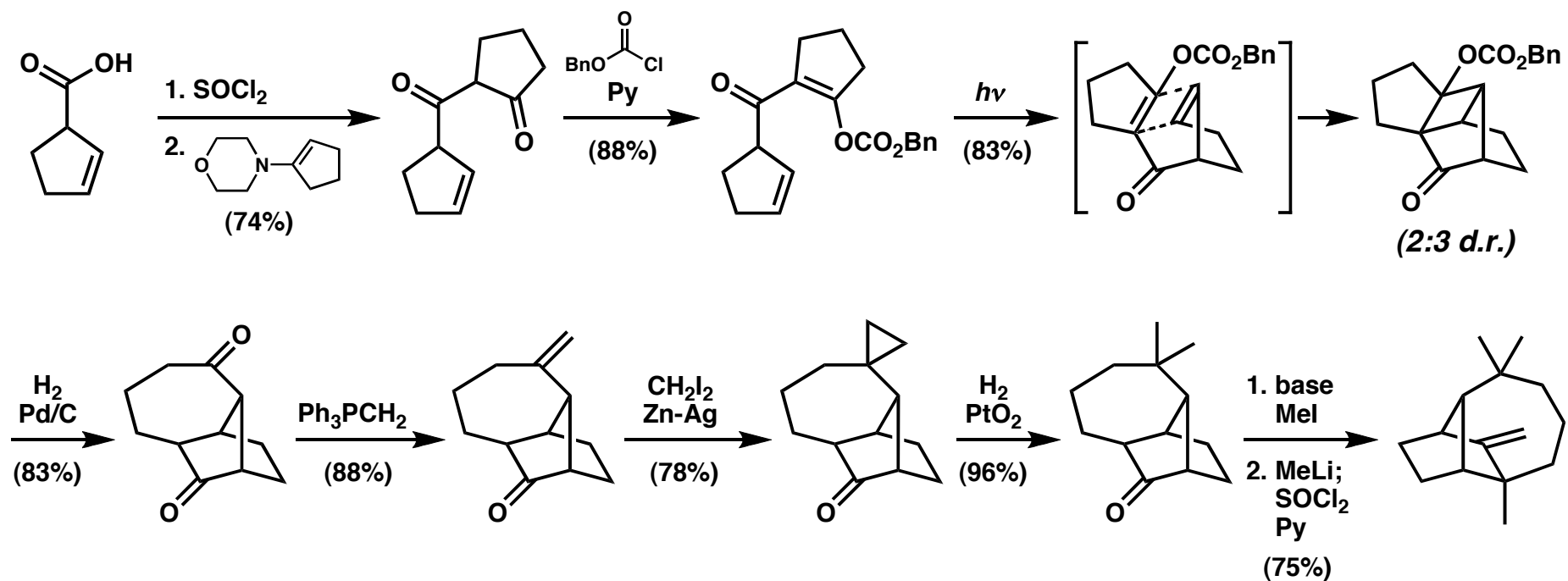
Synthesis of Sesquiterpenoids

Longifolene

Biosynthesis



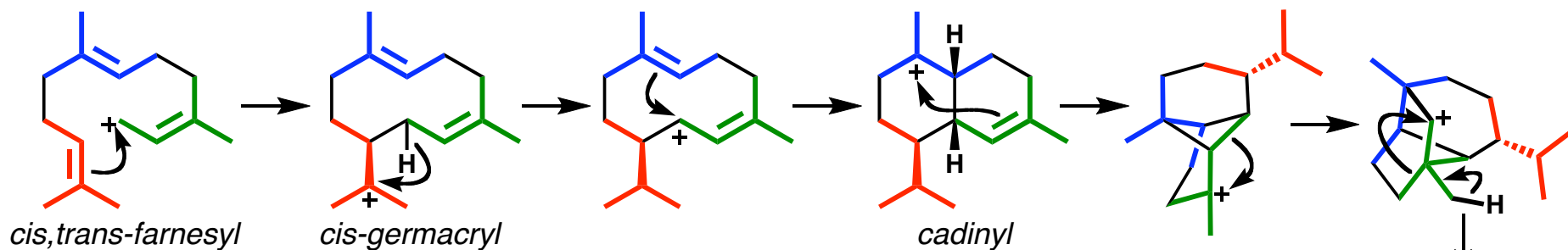
Laboratory Synthesis



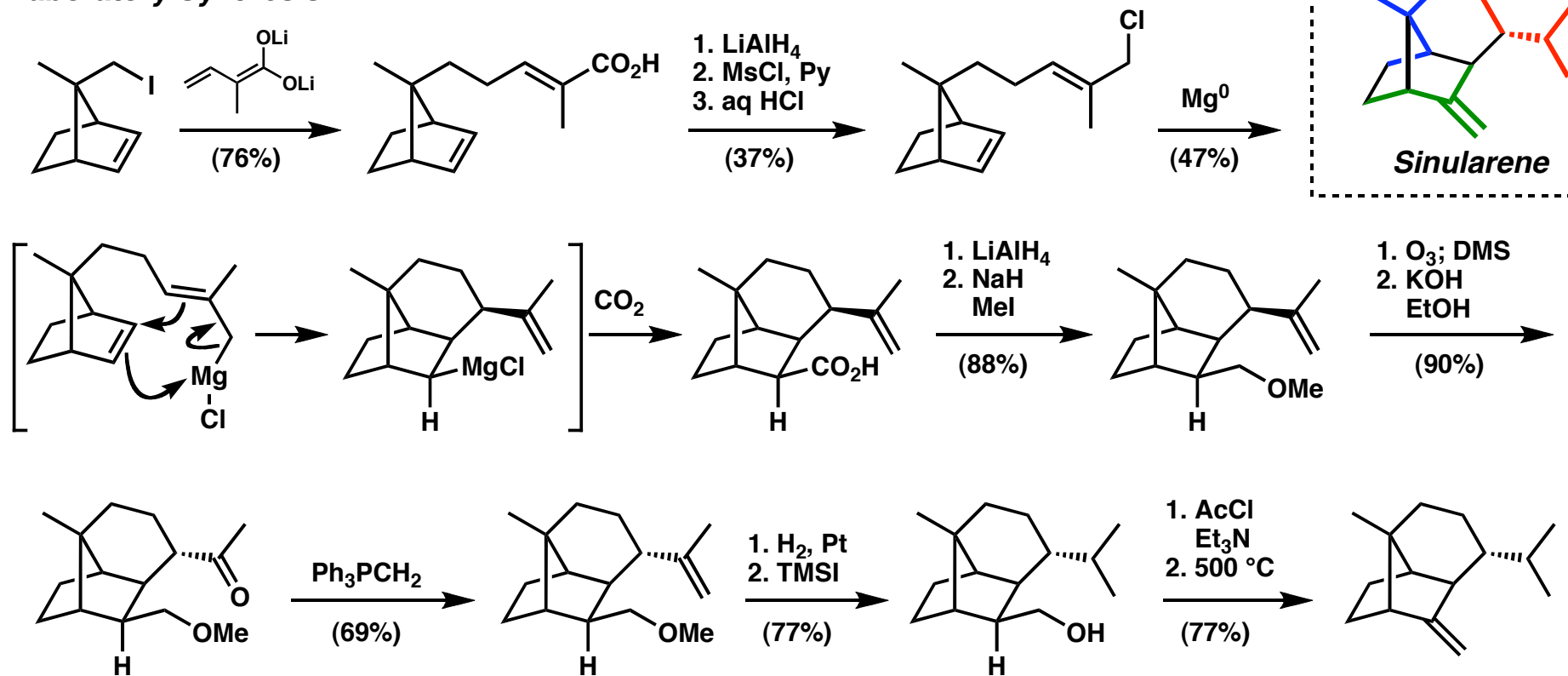
Synthesis of Sesquiterpenoids

Sinularene

Biosynthesis



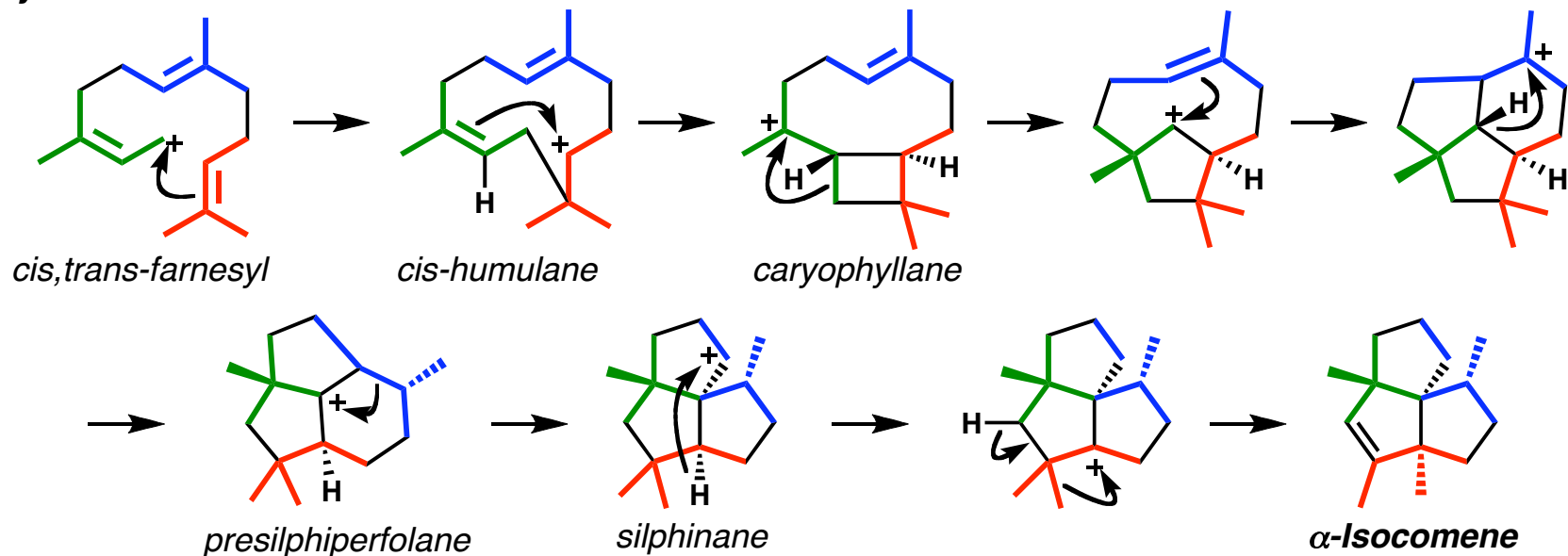
Laboratory Synthesis



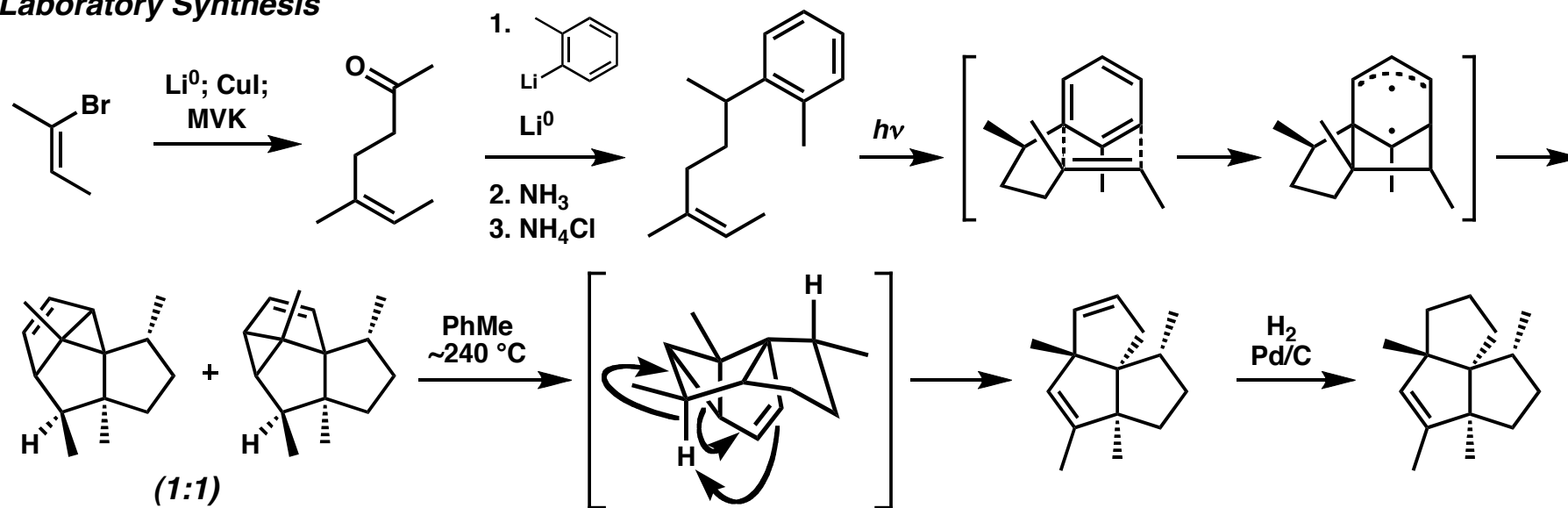
Oppolzer, *Tetrahedron Lett.* **1982**, 23, 4673-4676.

Synthesis of Sesquiterpenoids

Biosynthesis



Laboratory Synthesis

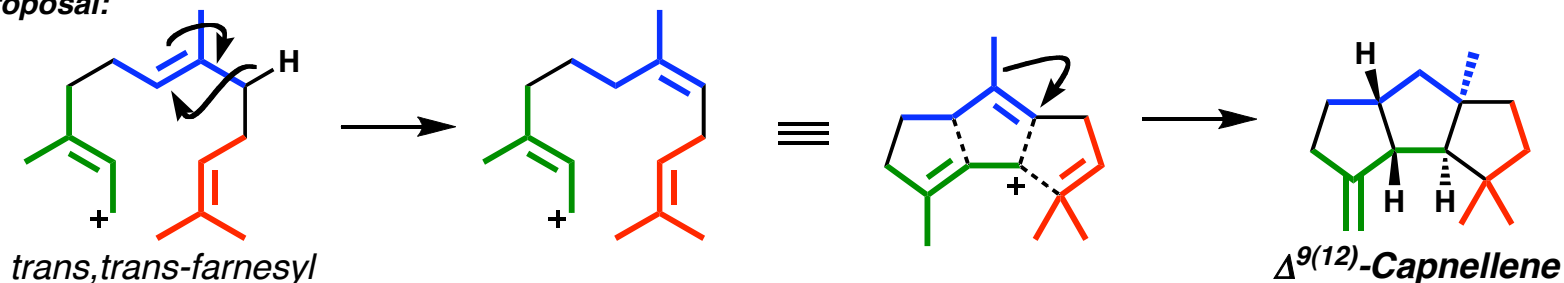


Wender, *Tetrahedron* **1981**, 37, 4445-4450.

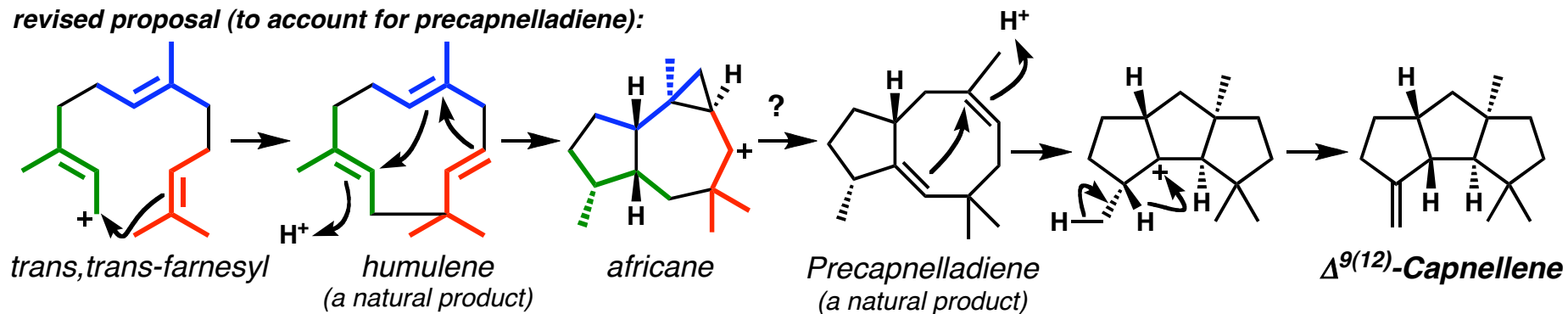
Synthesis of Sesquiterpenoids

Biosynthesis

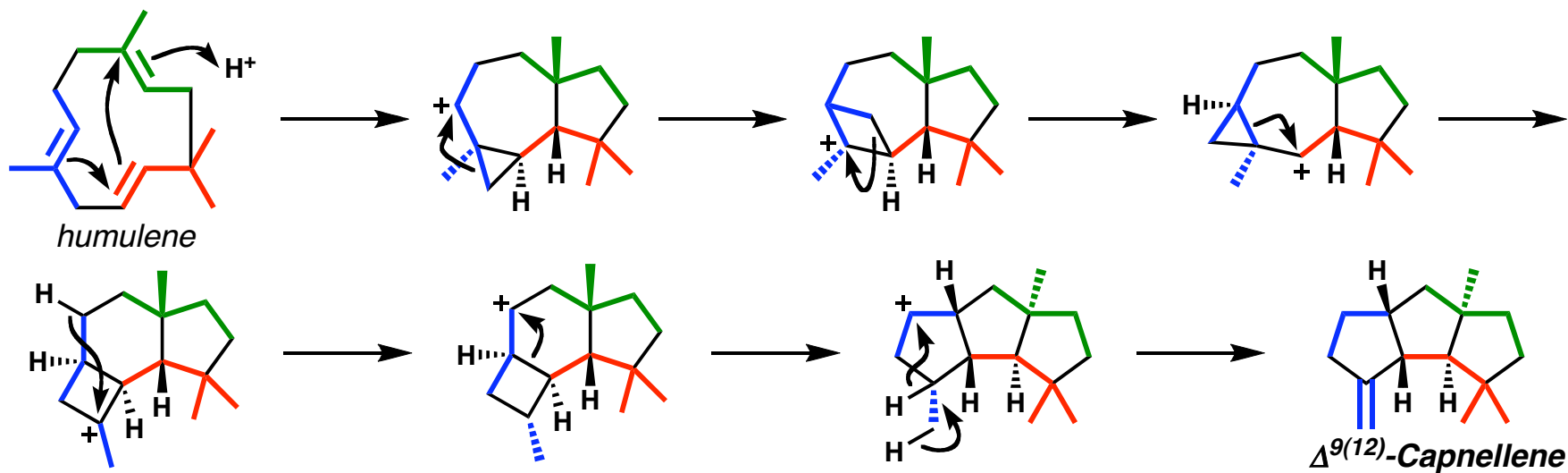
initial proposal:



revised proposal (to account for precapnelladiene):



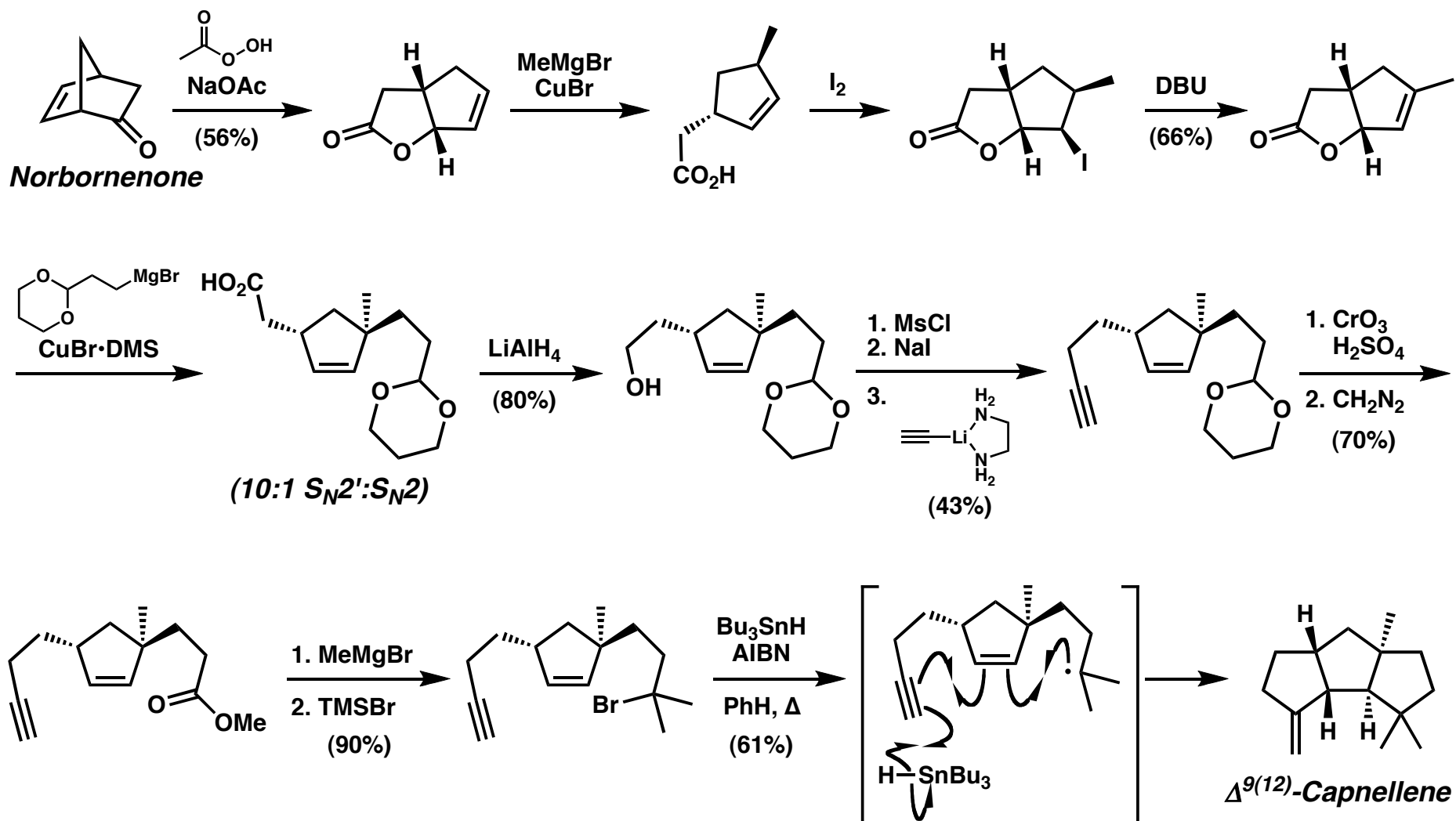
another proposal ("cyclopropane sliding"):



Synthesis of Sesquiterpenoids

$\Delta^{9(12)}$ -Capnellene

Laboratory Synthesis

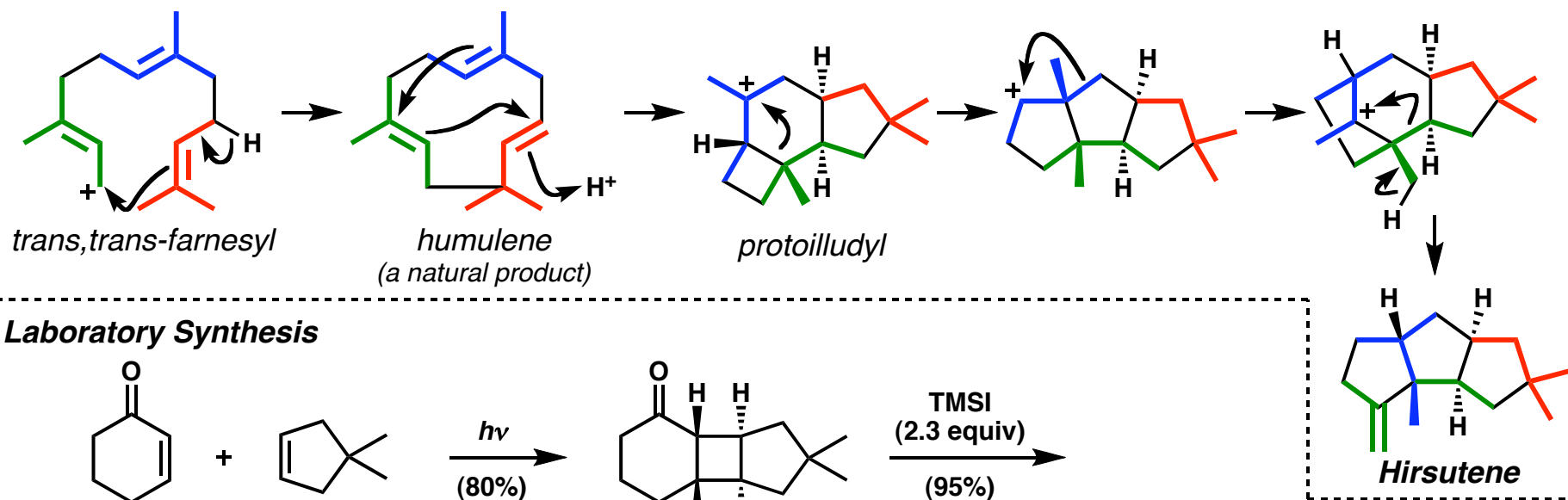


Curran, *Tetrahedron Lett.* **1985**, 26, 4991-4994.

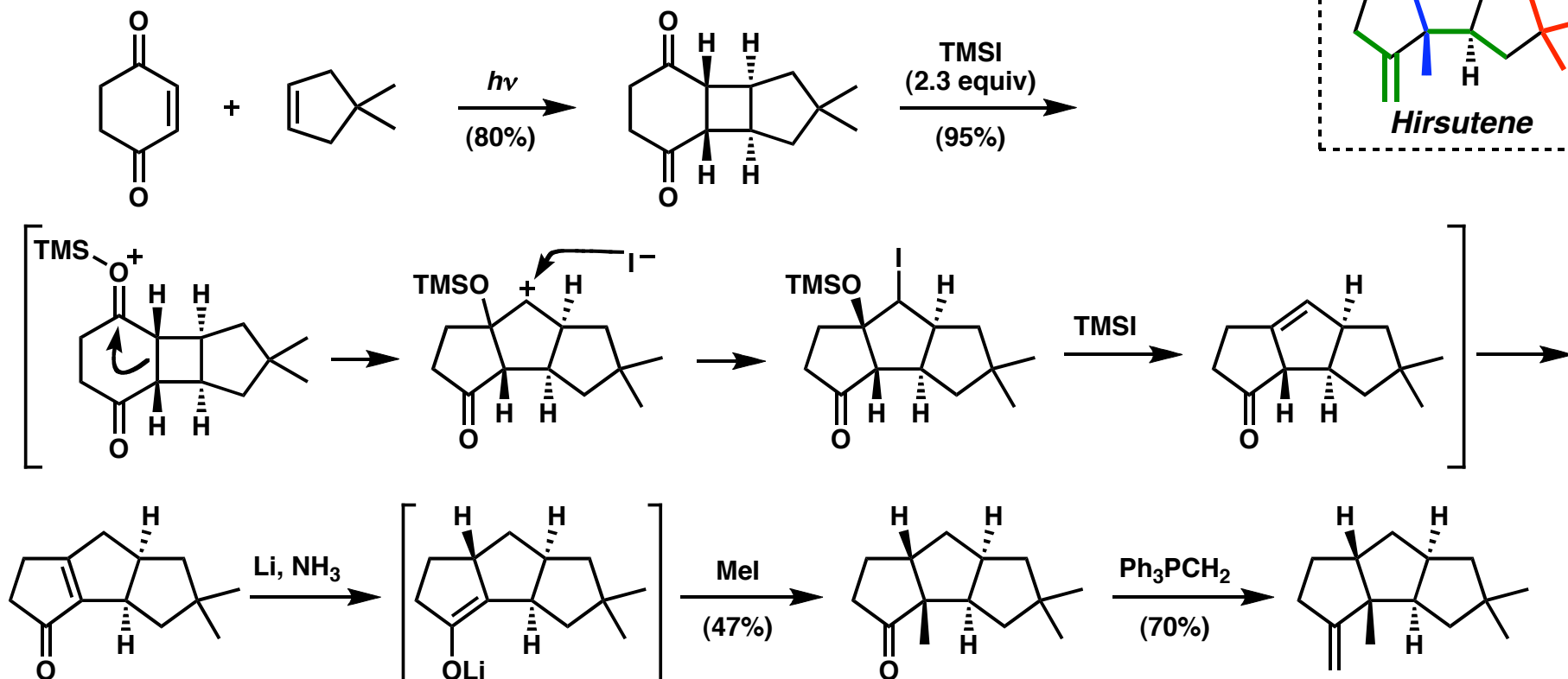
Synthesis of Sesquiterpenoids

Biosynthesis

Hirsutene



Laboratory Synthesis

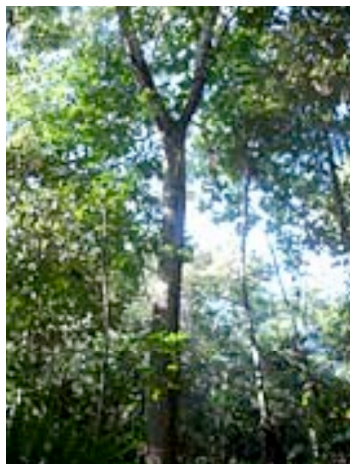


Oda, *J. Chem. Soc., Chem. Commun.* **1986**, 1049-1050.

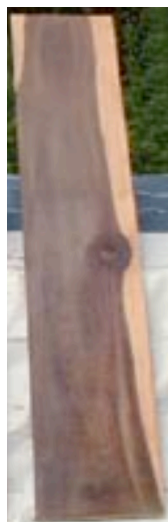
Sesquiterpenoids in Nature

Blue Mahoe

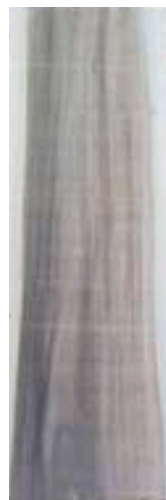
- Blue Mahoe is the national tree of Jamaica. The wood has interesting photochemical properties.



Blue Mahoe
(*Hibiscus elatus*)



fresh cut

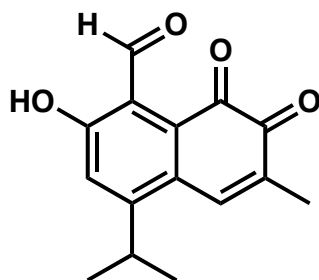


after 1 week

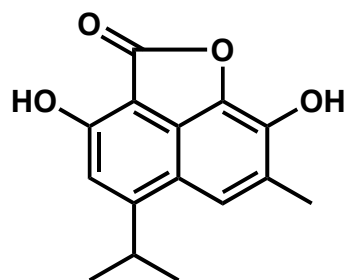
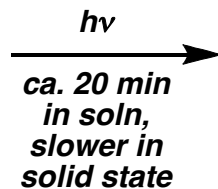


enlarged blue-hued woodgrain
(after polishing)

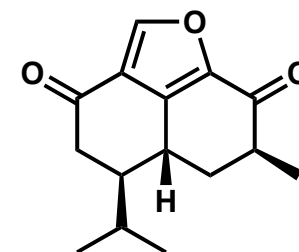
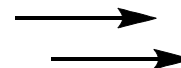
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- Some sesquiterpenoid isolates may be responsible



Hibiscoquinone A
purple crystal
red in soln
 $\lambda_{\max} = 484 \text{ nm}$



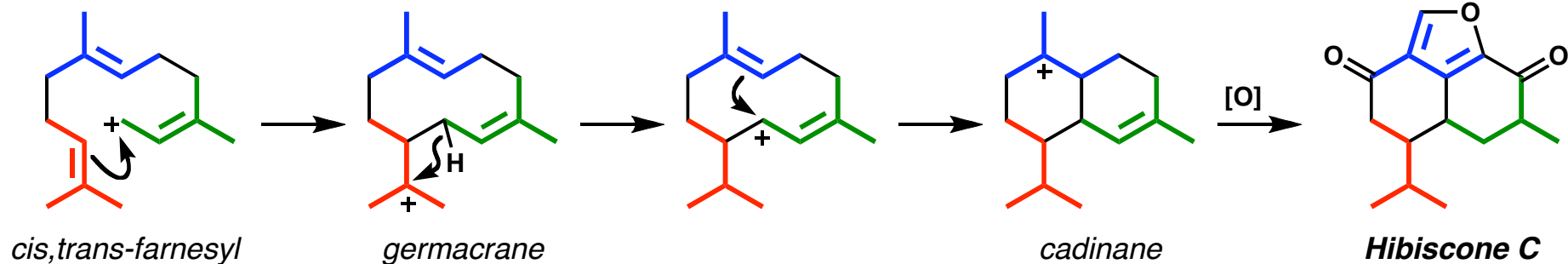
Hibiscolactone A
colorless
 $\lambda_{\max} = 356 \text{ nm}$



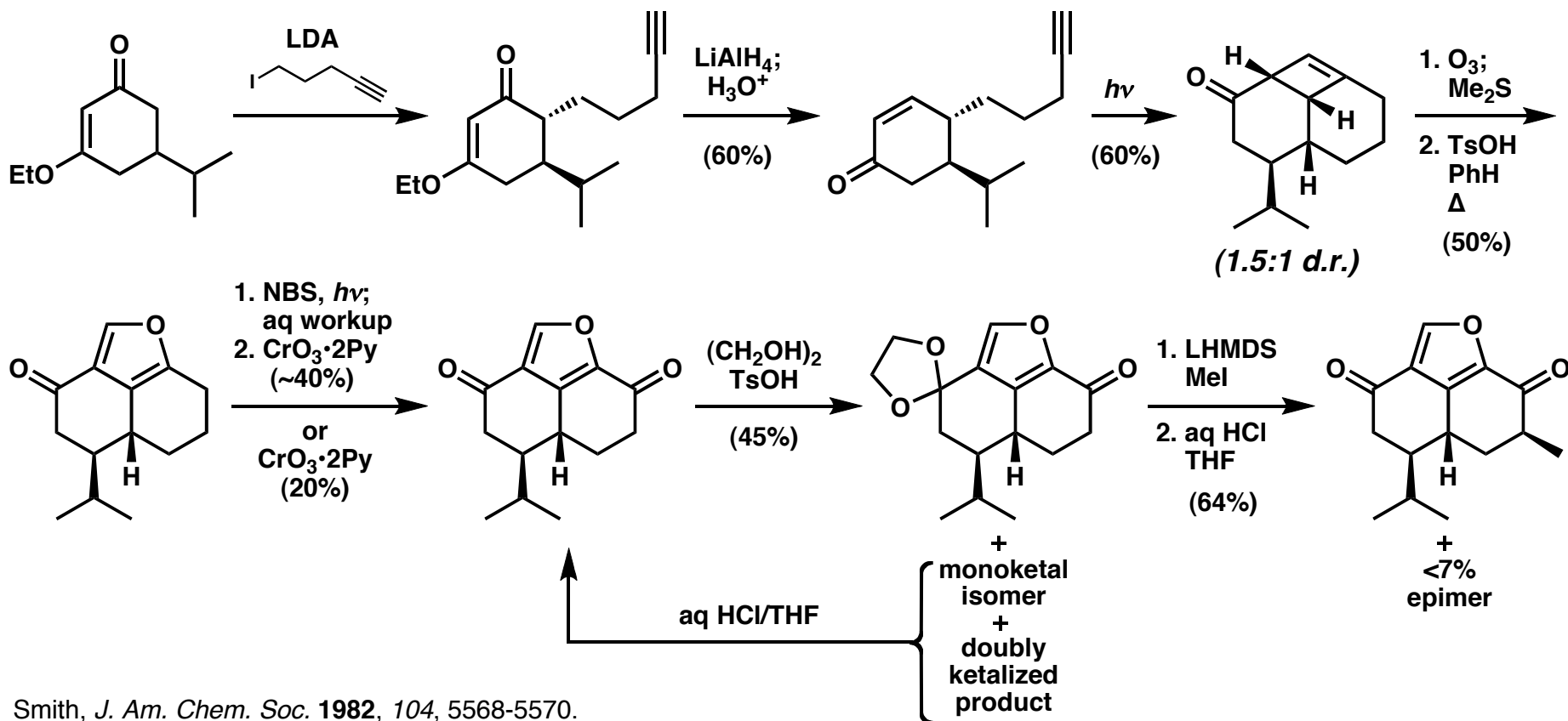
Hibiscone C
major component
 $\lambda_{\max} = 232 \text{ and } 267 \text{ nm}$

Synthesis of Sesquiterpenoids

Biosynthesis

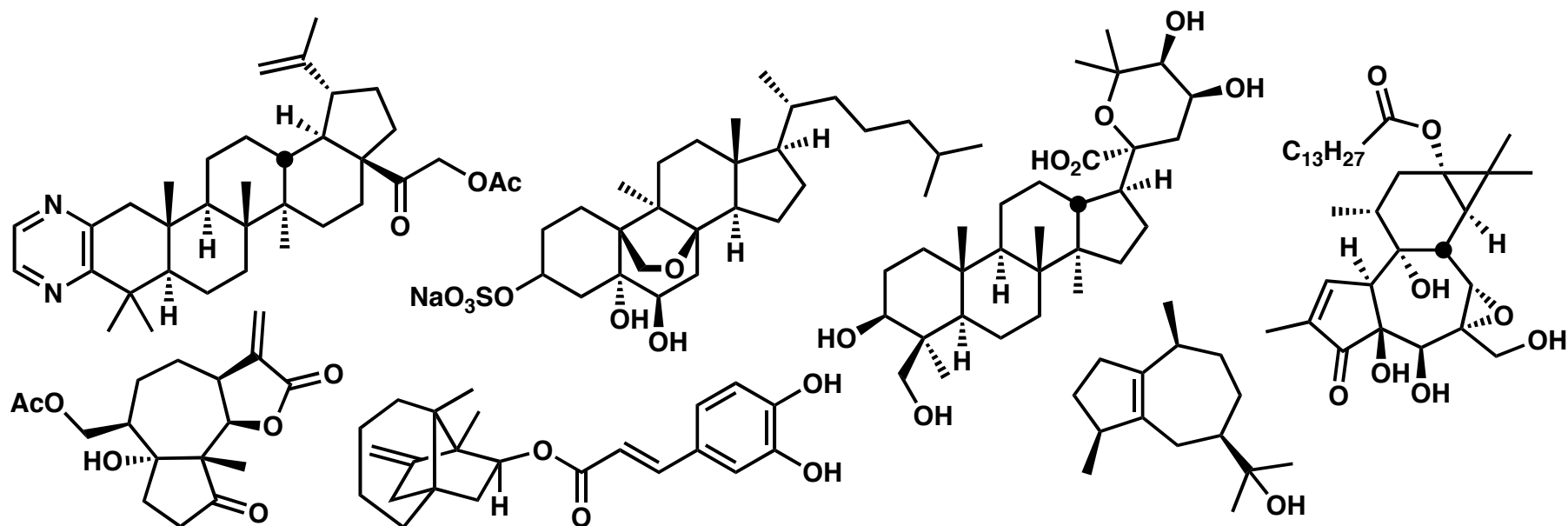


Laboratory Synthesis

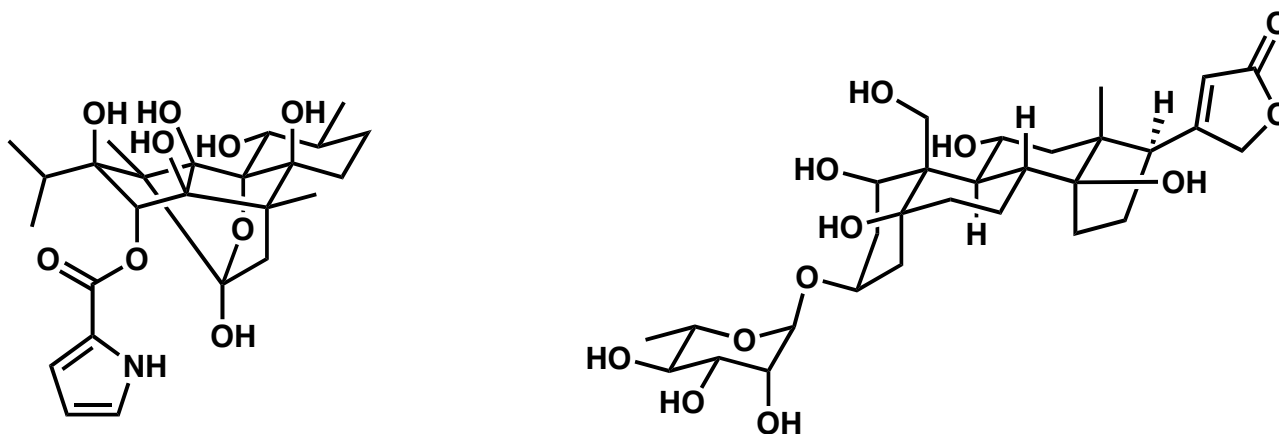


Conclusion and Outlook

More naturally occurring terpenoids are constantly isolated. Here is a sample of some on *J. Nat. Prod.* ASAP:



Others remain as standing challenges to synthetic chemistry:



The important bioactivity of these molecules ensures continued interest in synthesis. Understanding the biosynthesis of these molecules may aid in the development of new approaches and a better understanding of the relationship to function.

