

**New Approach toward
Biomimetic Total Synthesis:
Artificial "Tail-to-Head"
Terpene cyclization**

2017/07/29
M2 Akira Hirose

Contents

- 1. Introduction about Biosynthesis of Terpenes**

- 2. Synthetic Application of
"Tail-to-Head" Terpene Cyclization by Shenvi**

- 3. "Tail-to-Head" Terpene Cyclization
inside a Supramolecular Catalyst (main paper)**

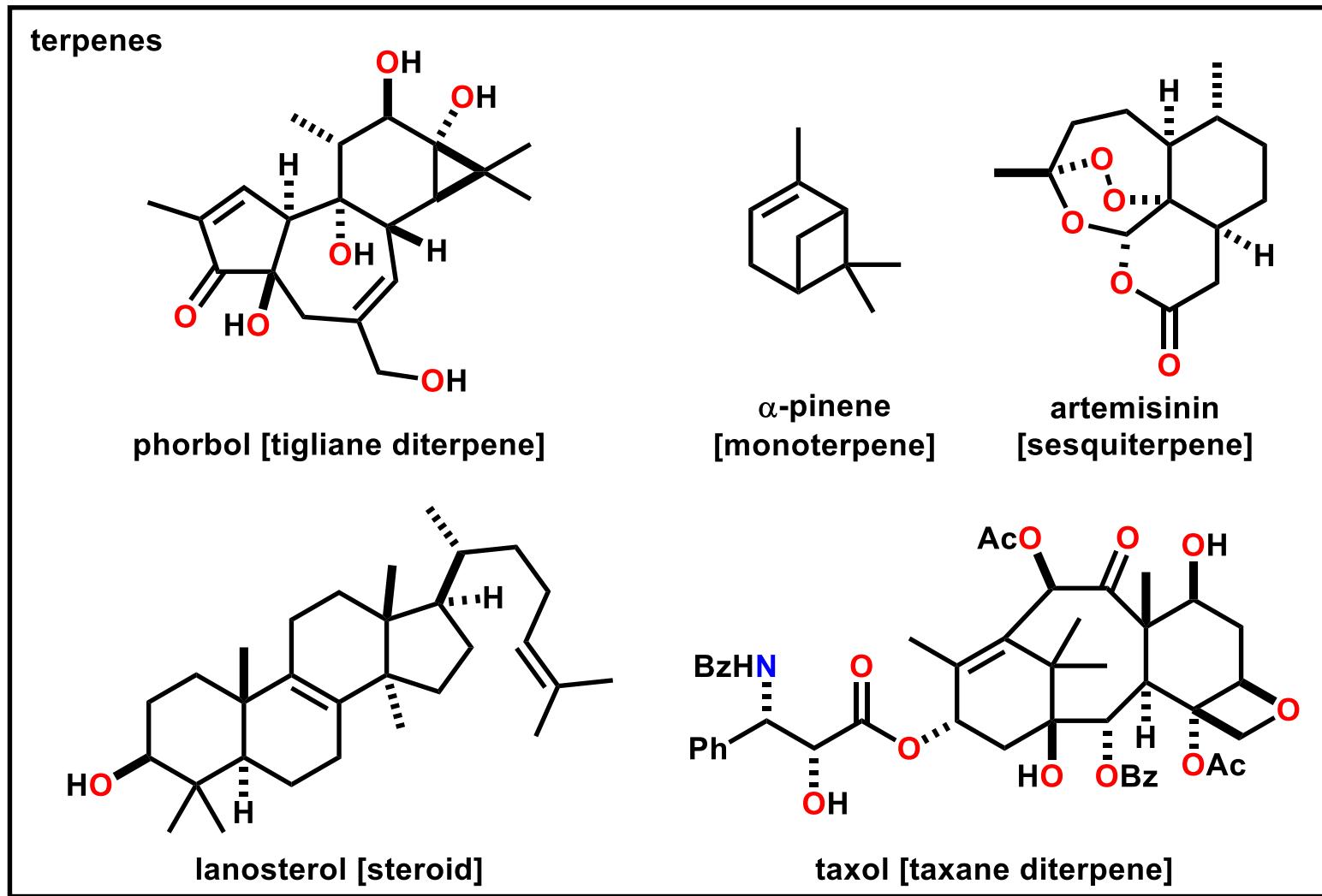
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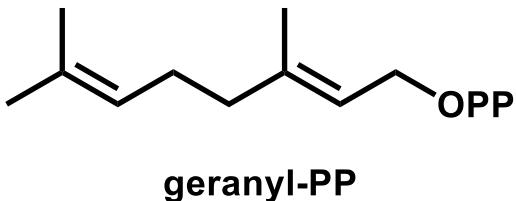
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Biosynthesis of Terpenes



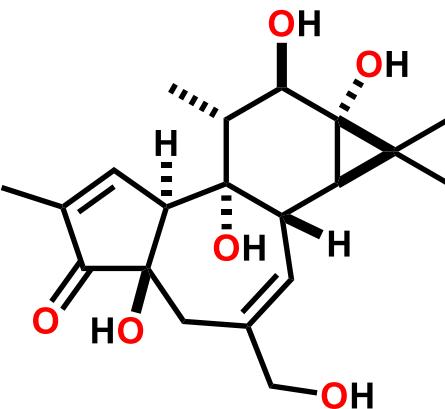
Difference in Cyclization Pathway



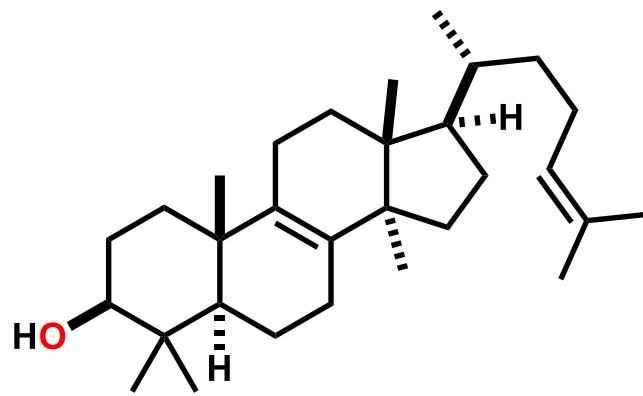
- farnesyl-PP
- geranylgeranyl-PP
- squalene
- etc.

cyclase enzyme
(oxydase enzyme)

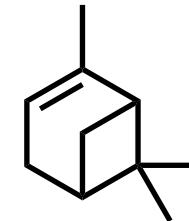
"head-to-tail" terpene (HTT) cyclization



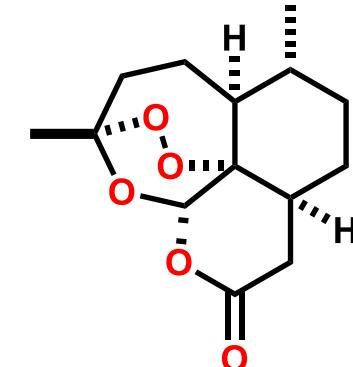
phorbol [tigliane diterpene]



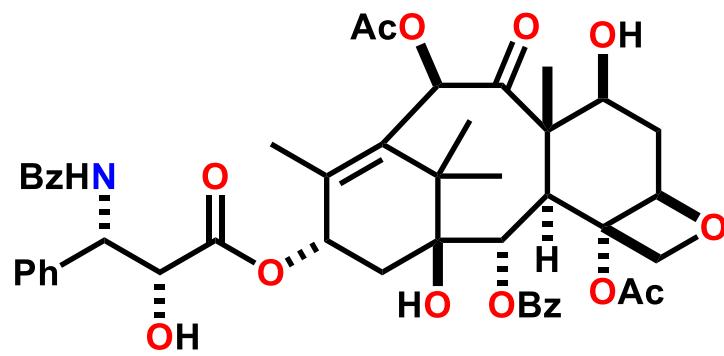
"tail-to-head" terpene (THT) cyclization



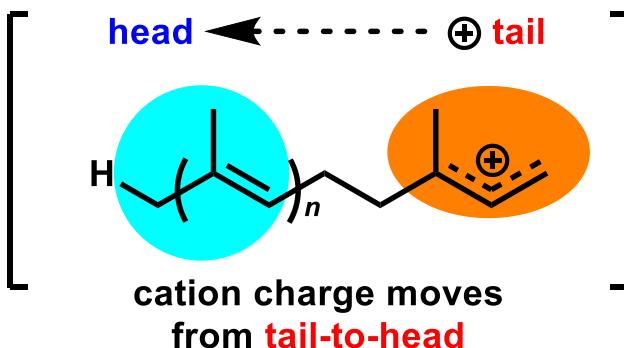
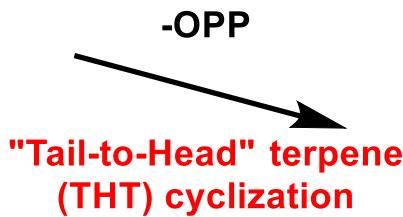
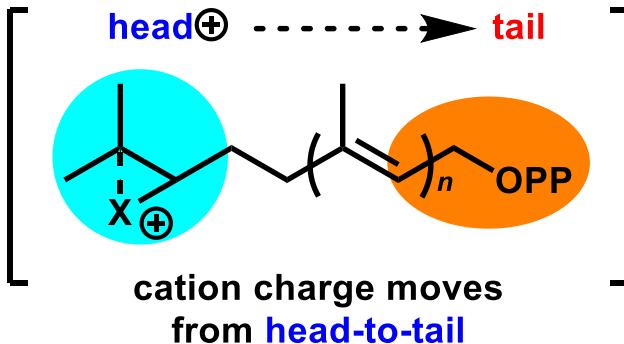
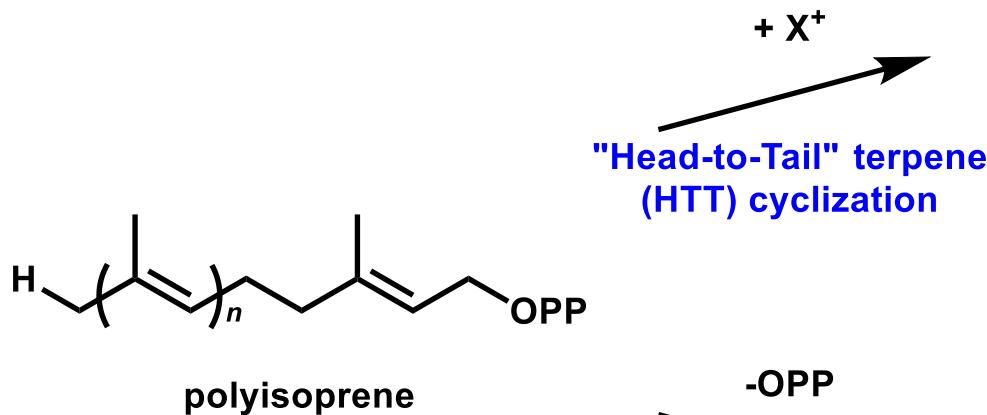
α -pinene
[monoterpene]



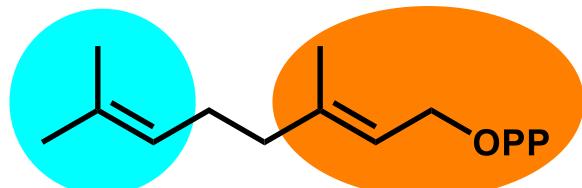
artemisinin
[sesquiterpene]



"Head-to-Tail" or "Tail-to-Head"

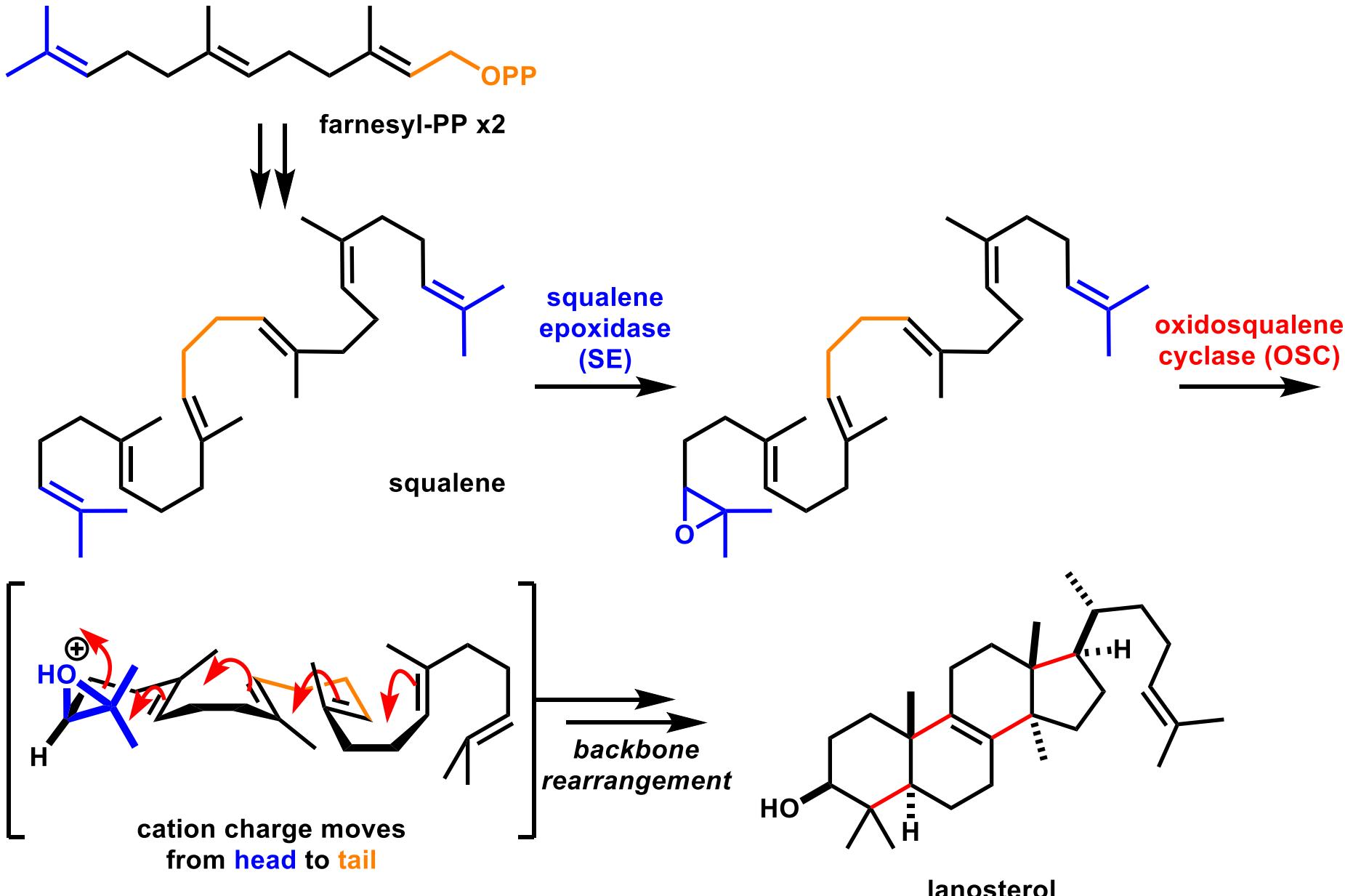


head:
terminal prenyl unit

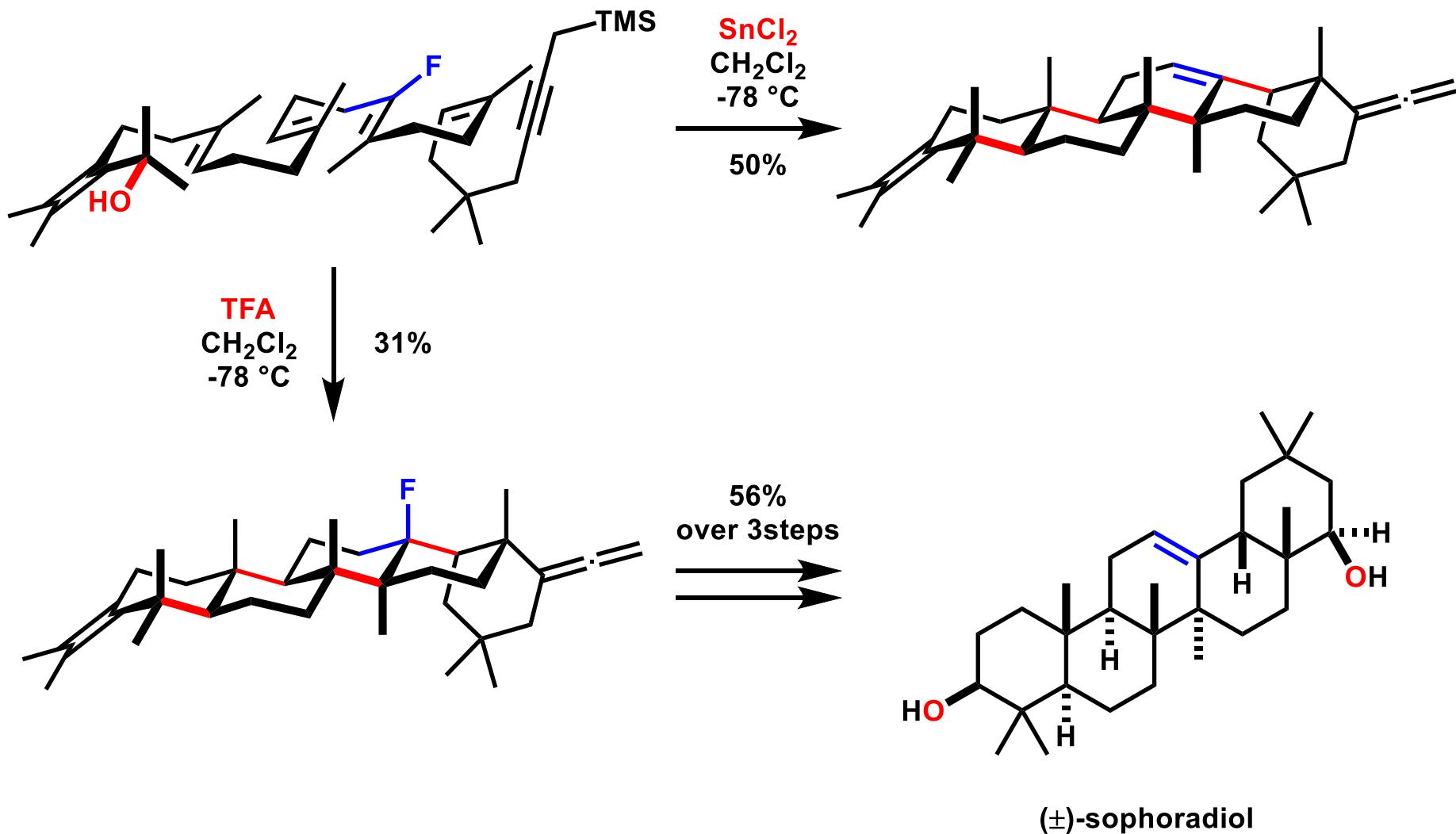


-> Most "biomimetic total syntheses" employ head-to-tail cyclization

HTT Cyclization in Biosynthesis



HTT Cyclization-mimetic Total Synthesis



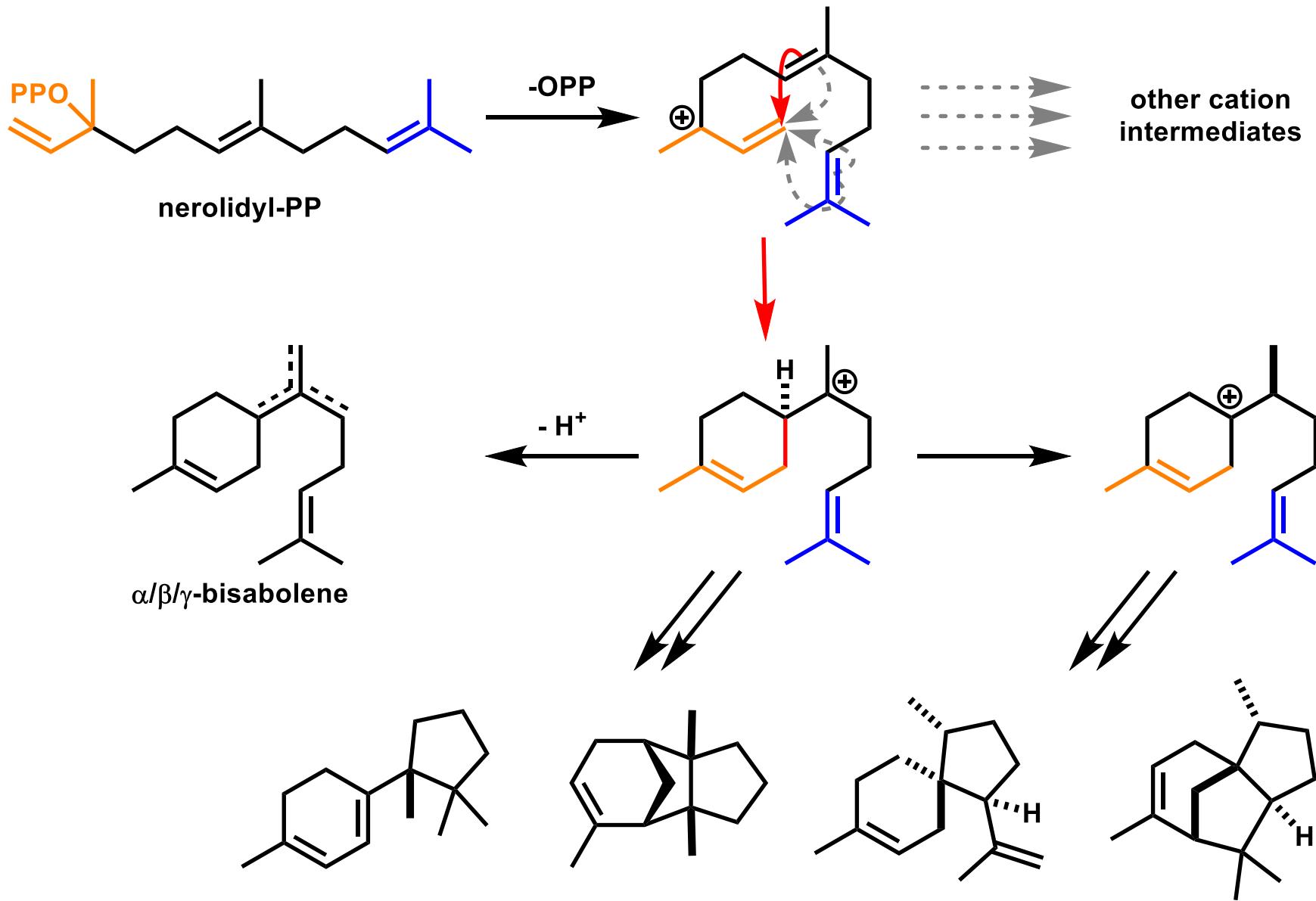
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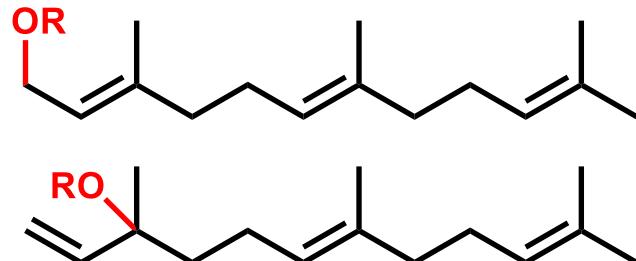
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THT Cyclization in Biosynthesis

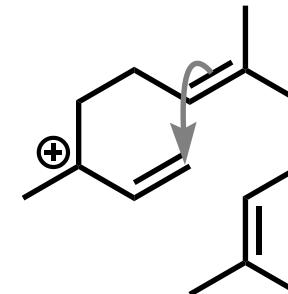


Problems of THT Cyclization-mimetic Synthesis

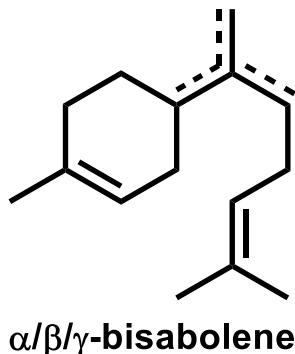


farnesol or nerolidol

Bronsted
or Lewis
acid
- OR

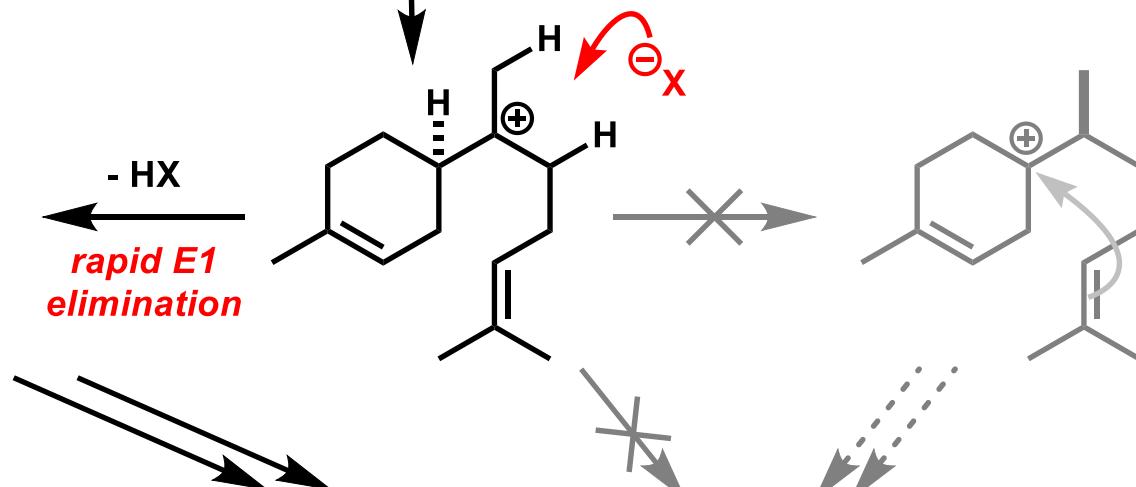


X^- and cation intermediate
are in close proximity
by Coulombic forces.
-> E1 elimination or
SN₁ anion capture is rapid.

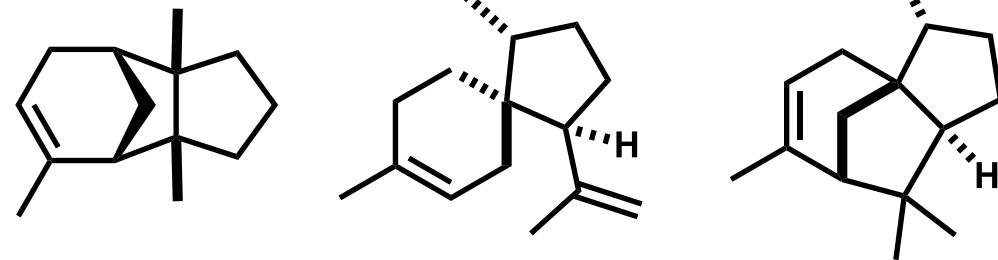


$\alpha/\beta/\gamma$ -bisabolene

- HX
rapid E1
elimination

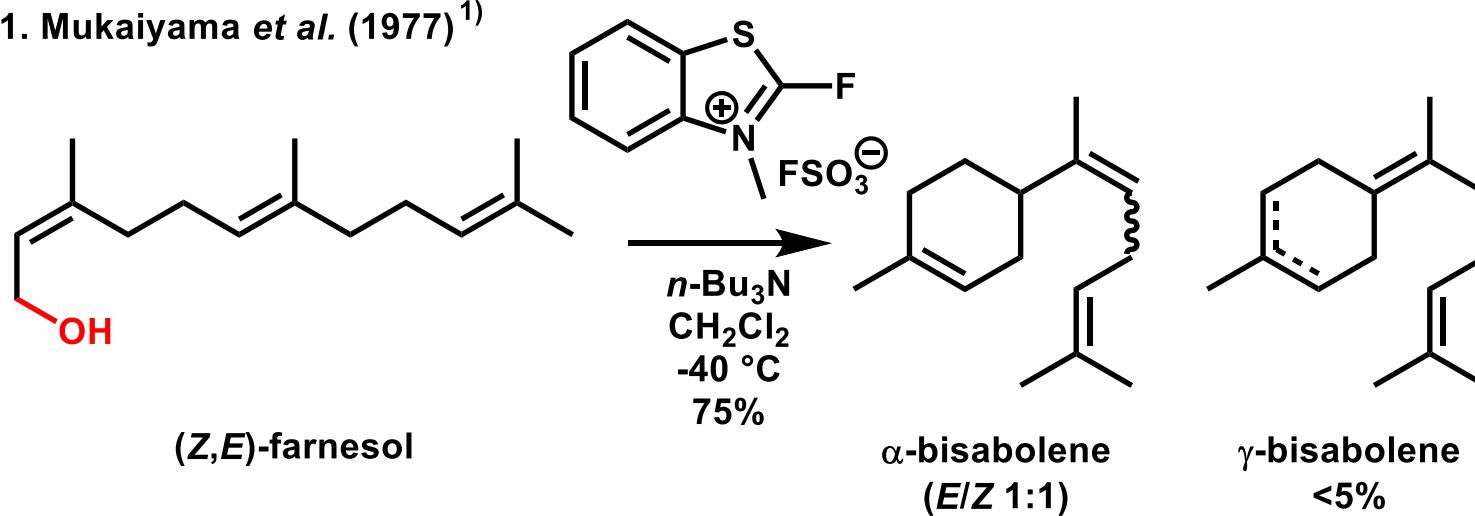


Bisabolenes are reprotonated
non-selectively.
-> Complex mixture of
sesquiterpenes.

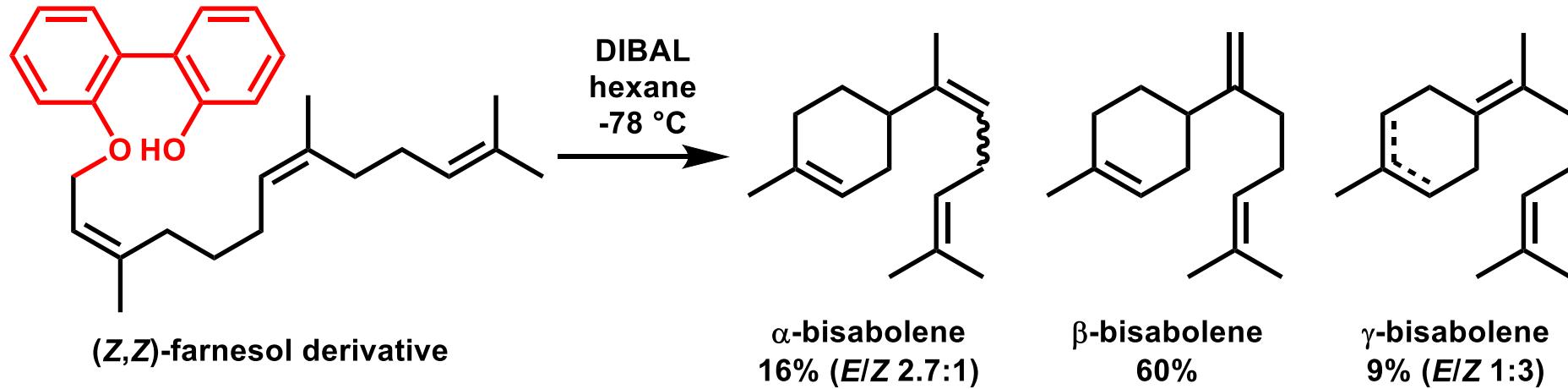


Previous THT Cyclization-mimetic Synthesis

1. Mukaiyama et al. (1977)¹⁾



2. Yamamoto et al. (1983)²⁾

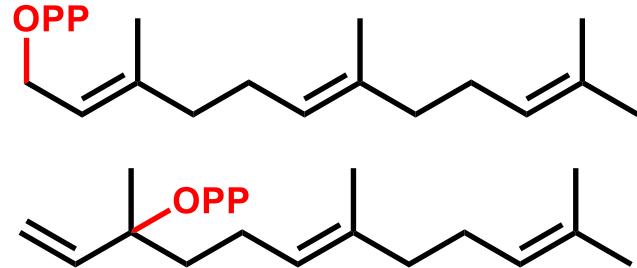


1) Kobayashi, S.; Tsutsui, M.; Mukaiyama, T. *Chem. Lett.* 1977, 1169.

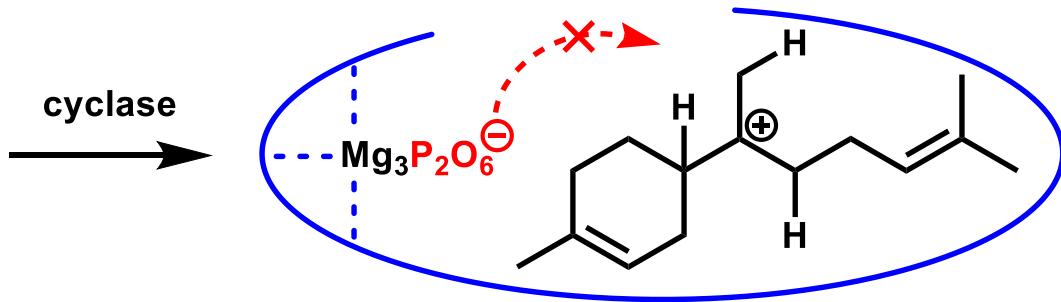
2) Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* 1983, 105, 6154.

Shenvi's Working Hypothesis

Anion immobilization by **Cyclase** enzymes



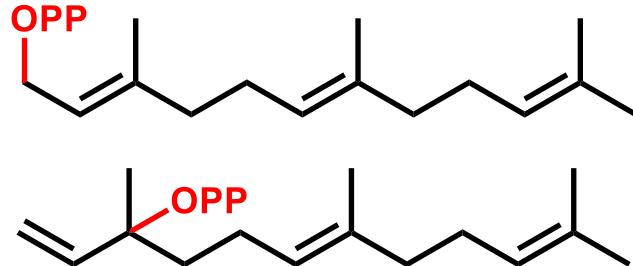
farnesol-PP or nerolidyl-PP



Enzymes immobilizes counteranion
and keeps it far from cation

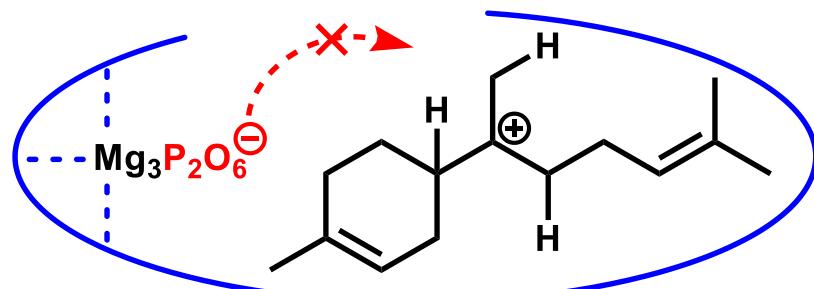
Shenvi's Working Hypothesis

Anion immobilization by **Cyclase enzymes**



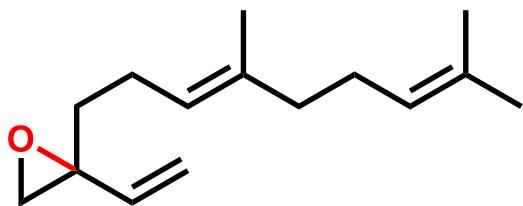
farnesol-PP ir nerolidyl-PP

cyclase

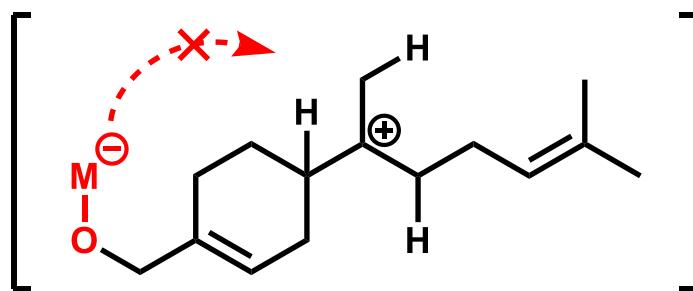


Enzymes immobilizes counteranion
and keeps it far from cation

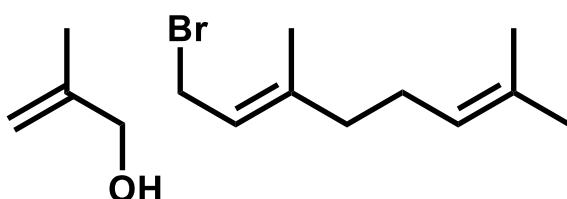
Mimicking of cyclase active site



nerolidol-mimic epoxide



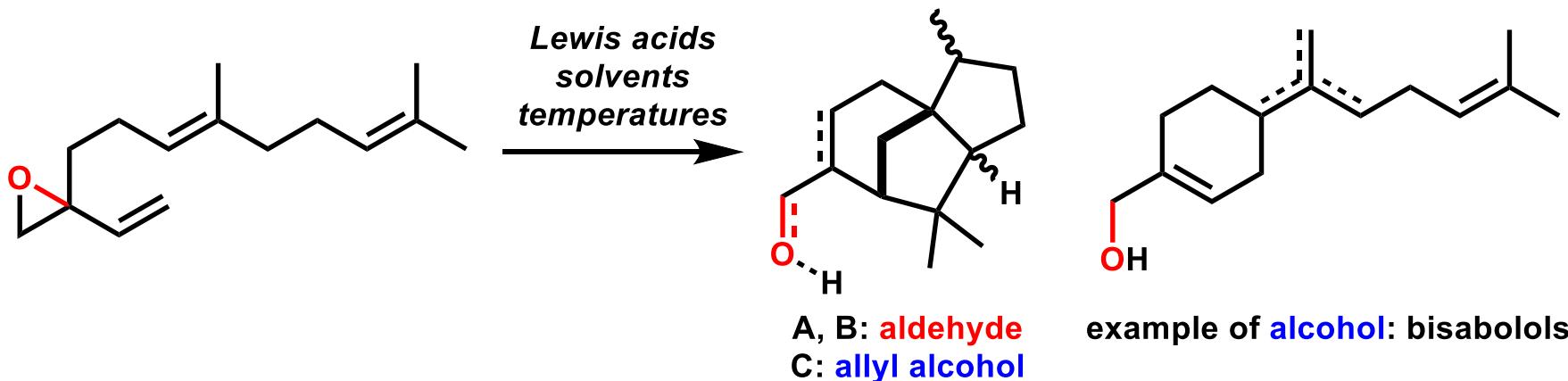
↑↑ 42% over 4 steps



Similar anion sequestration

- substrate control
(carbocation and Lewis base are distal)
- by using **Lewis acid with non-dissociating ligands**

Screening of Lewis Acid

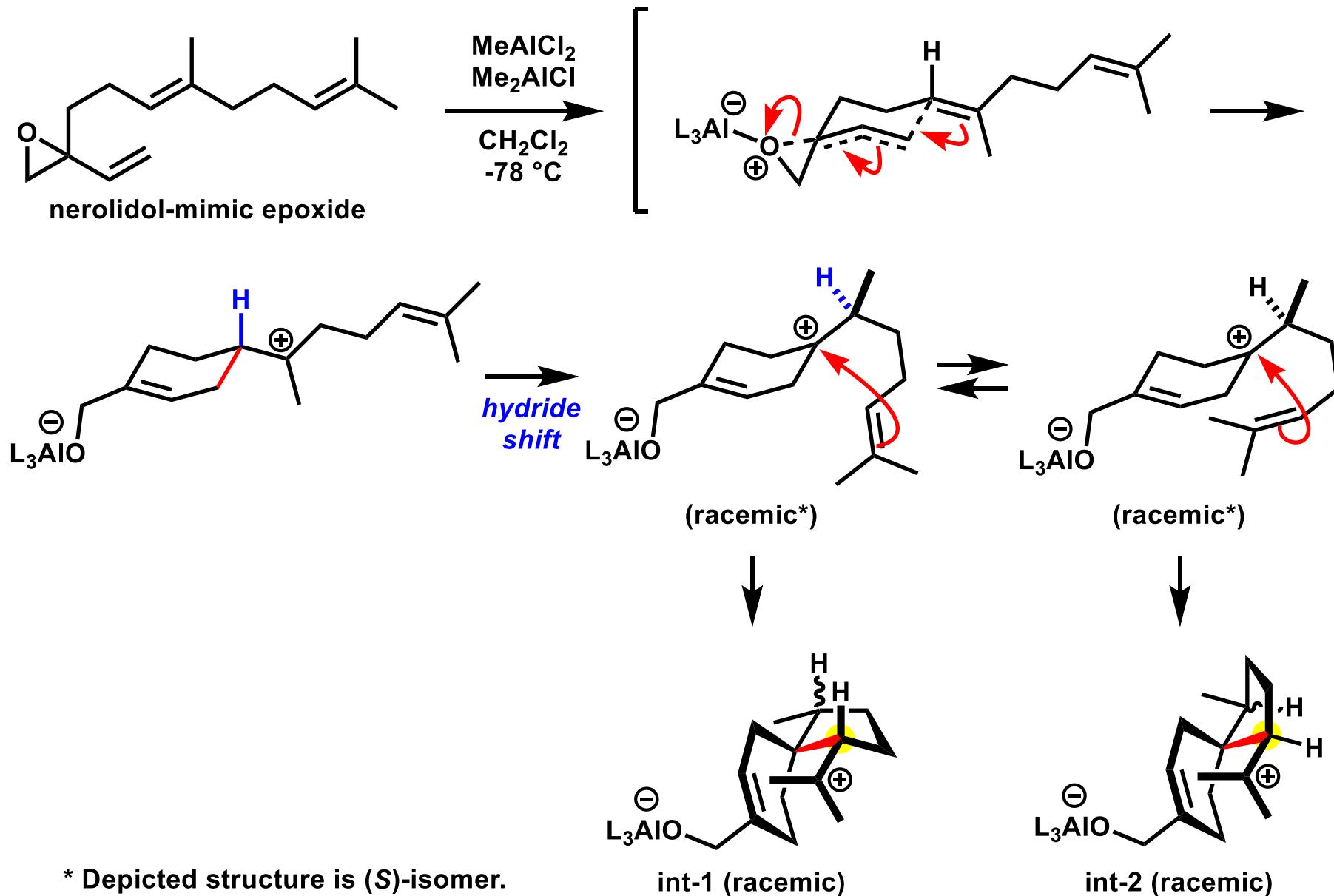


Entry	Lewis acids	solvents, temperatures	aldehyde:alcohol*	isolated yield (A-C)
1	TiCl ₄	CH ₂ Cl ₂ (1 mM), -78 °C	1:11.6	n/d
2	TiCl ₃ (O <i>i</i> -Pr)	CH ₂ Cl ₂ (1 mM), -78 °C	1:12.7	n/d
3	SnCl ₄	CH ₂ Cl ₂ (1 mM), -78 °C	1:7.0	n/d
4	SnCl ₄	C ₆ H ₁₄ (1 mM), -78 °C	1:15.0	n/d
5	SiCl ₄	CH ₂ Cl ₂ (1 mM), -78 °C	0:1	n/d
6	Sc(OTf) ₃	CH ₂ Cl ₂ (1 mM), -78 °C	1:9.8	n/d
7	EtAlCl ₂	CH ₂ Cl ₂ (1 mM), -78 °C	1:3.1	n/d
8	EtAlCl ₂ /Me ₂ AlCl	CH ₂ Cl ₂ (1 mM), -78 °C	1:3.3	n/d
9	EtAlCl ₂	CF ₃ Cl (1 mM), -78 °C	1:16.0	n/d
10	EtAlCl ₂	CH ₂ Cl ₂ (5 mM), -78 °C	1:2.8	35%
11	EtAlCl ₂	CH ₂ Cl ₂ (25 mM), -78 °C	1:3.5	30%
12	MeAlCl ₂ /Me ₂ AlCl	CH ₂ Cl ₂ (2.5 mM), -78 °C	1:2.6**	44%
13	TfOH	CH ₂ Cl ₂ (1 mM), -78 °C	0:1	n/d

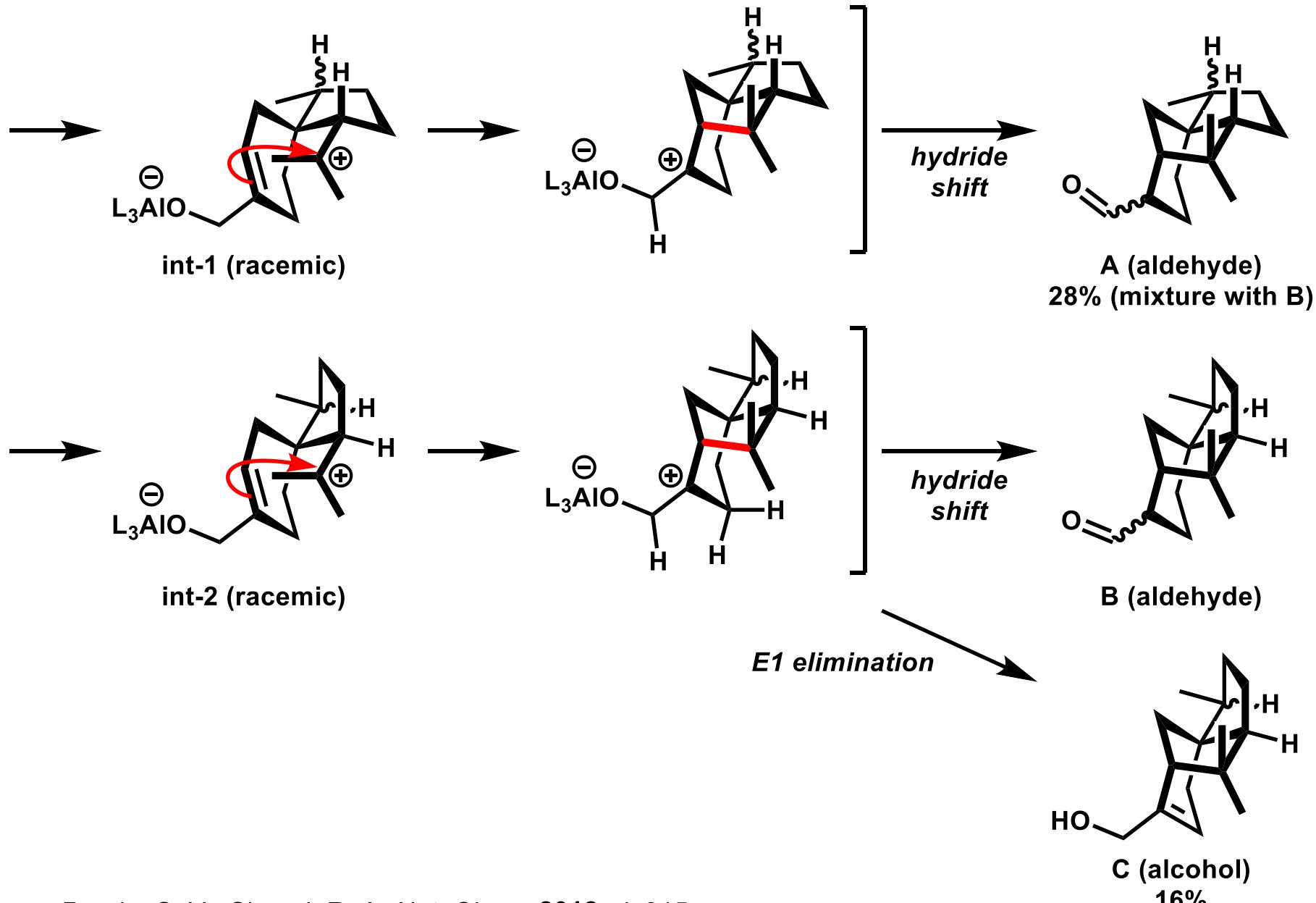
* Determined by ¹H NMR.

** No monocyclic compound (e.g. bisabolols) was observed by GC.

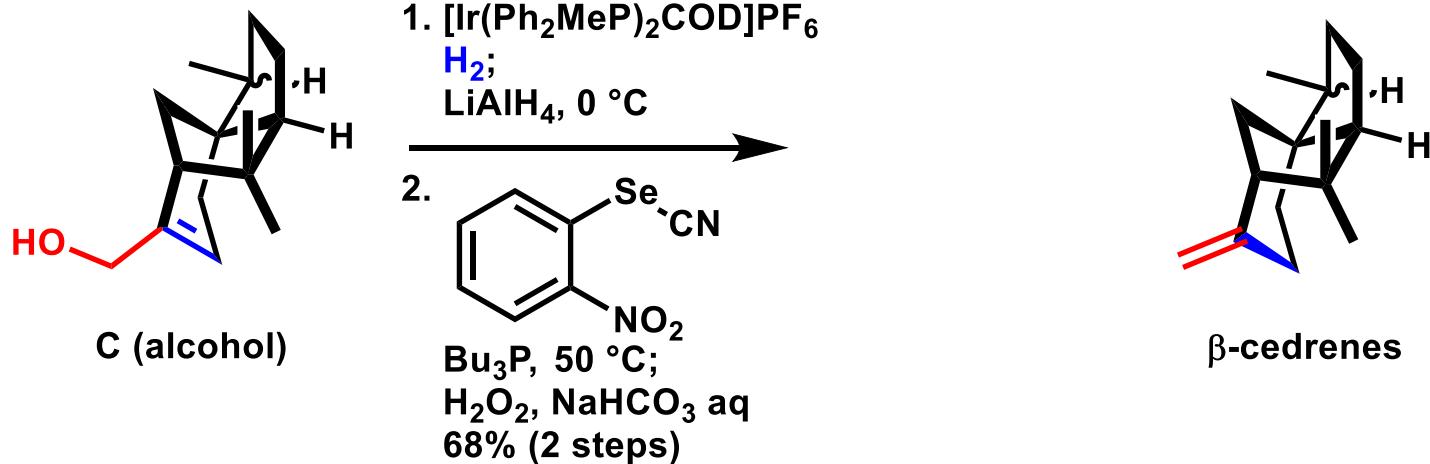
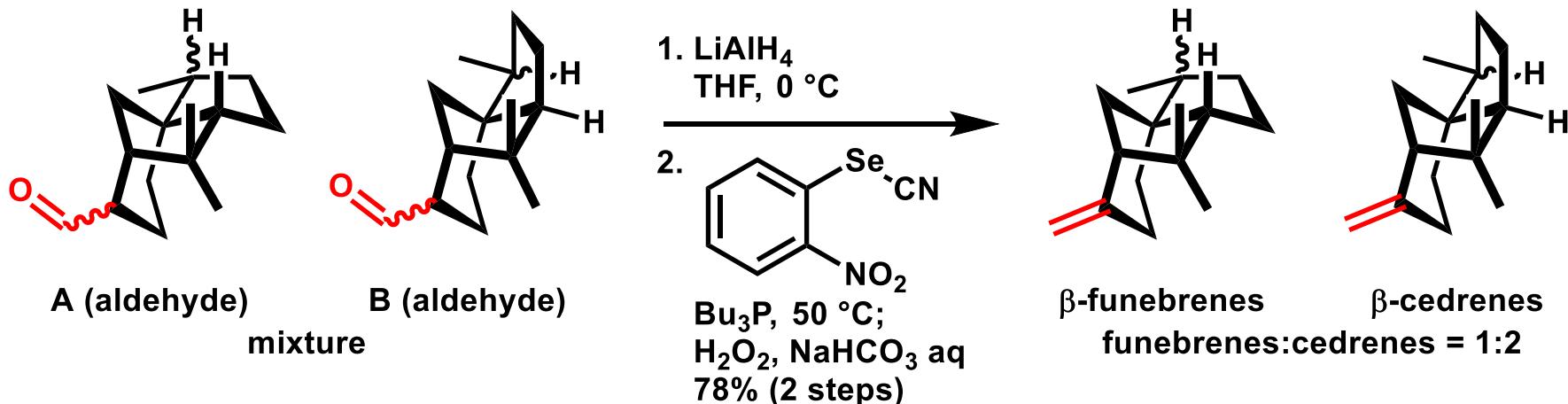
Proposed Reaction Pathway of THT Cyclization (1)



Proposed Reaction Pathway of THT Cyclization (2)



Total Synthesis of β -Funebrenes/ β -Cedrenes



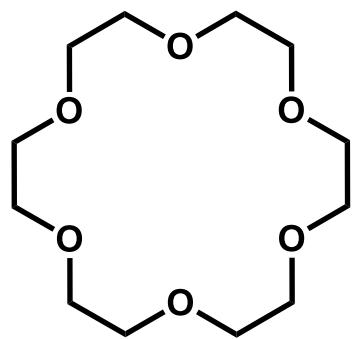
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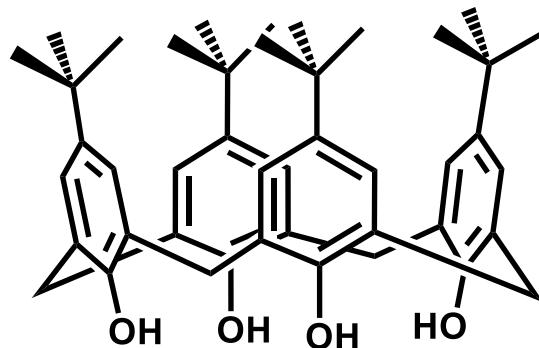
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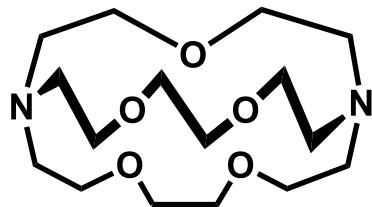
Supramolecules: Host-Guest Chemistry



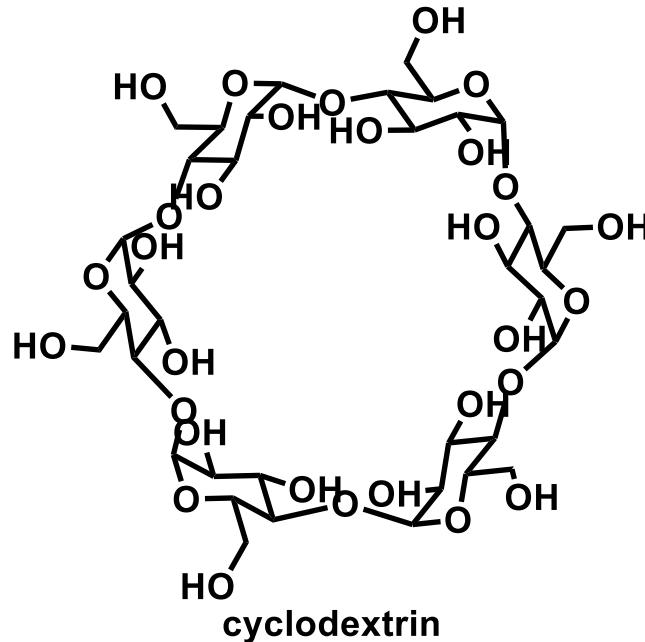
crown ether



calixarene

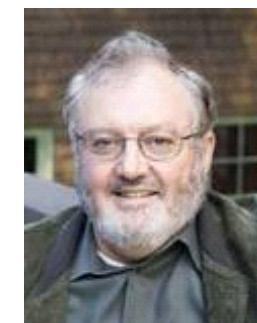
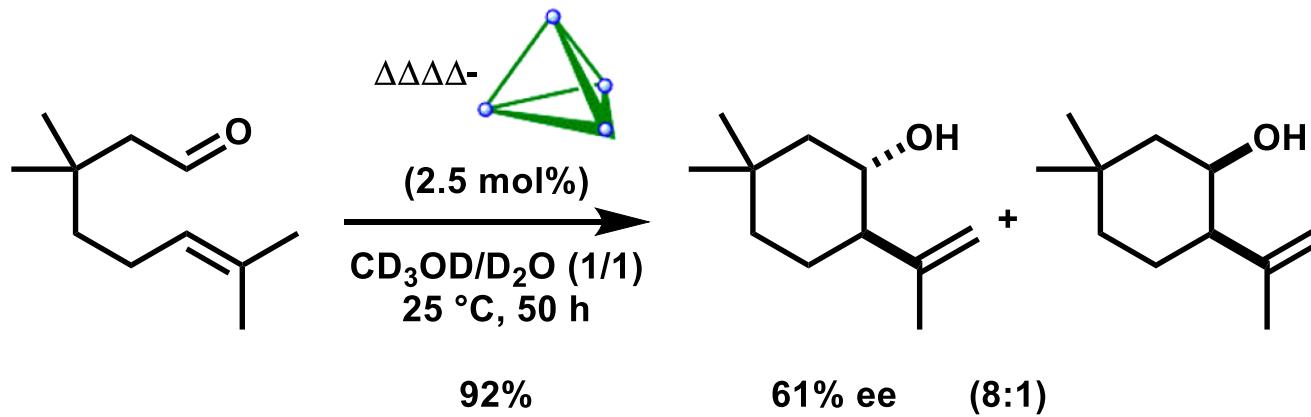
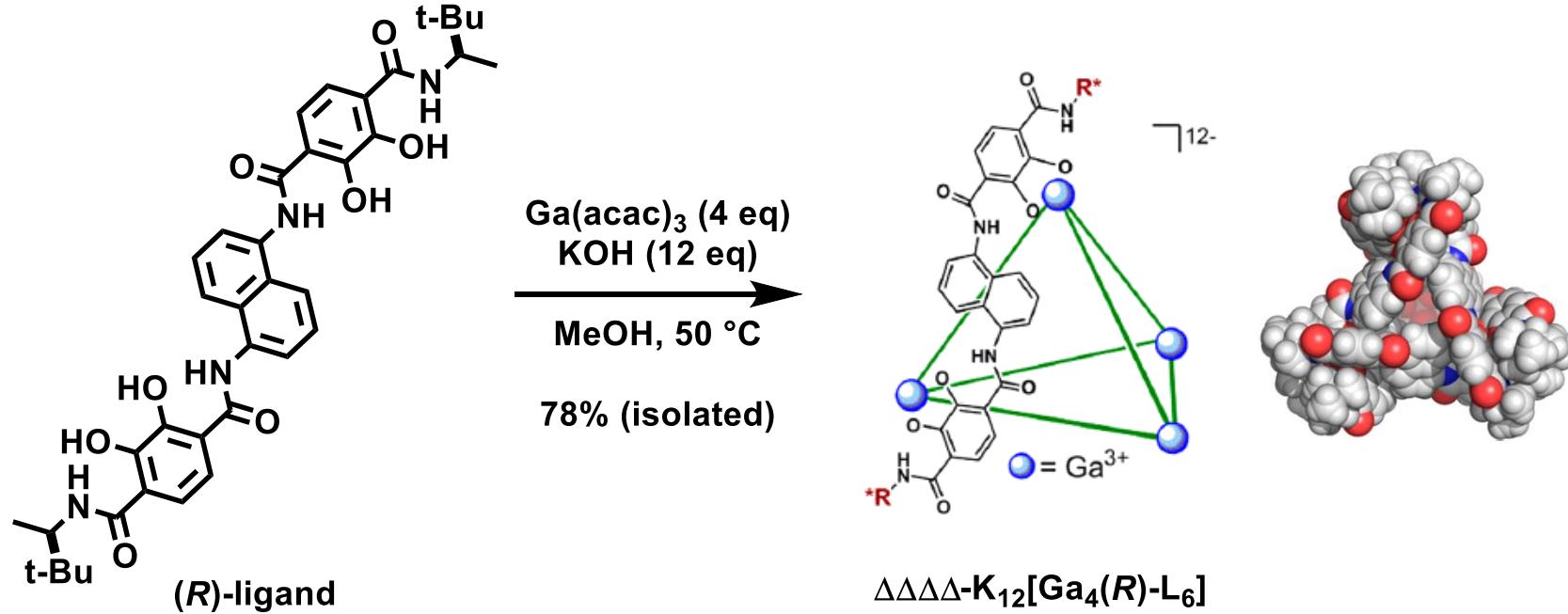


cryptand



cyclodextrin

Self-assembly Sulramolecular as Catalyst



Prof. Ken Raymond

1) Raymond, K. N. et al. *J. Am. Chem. Soc.* **2013**, *135*, 18802.

2) 141101_LS_Satoshi_HASHIMOTO

Prof. Konrad Tiefenbacher

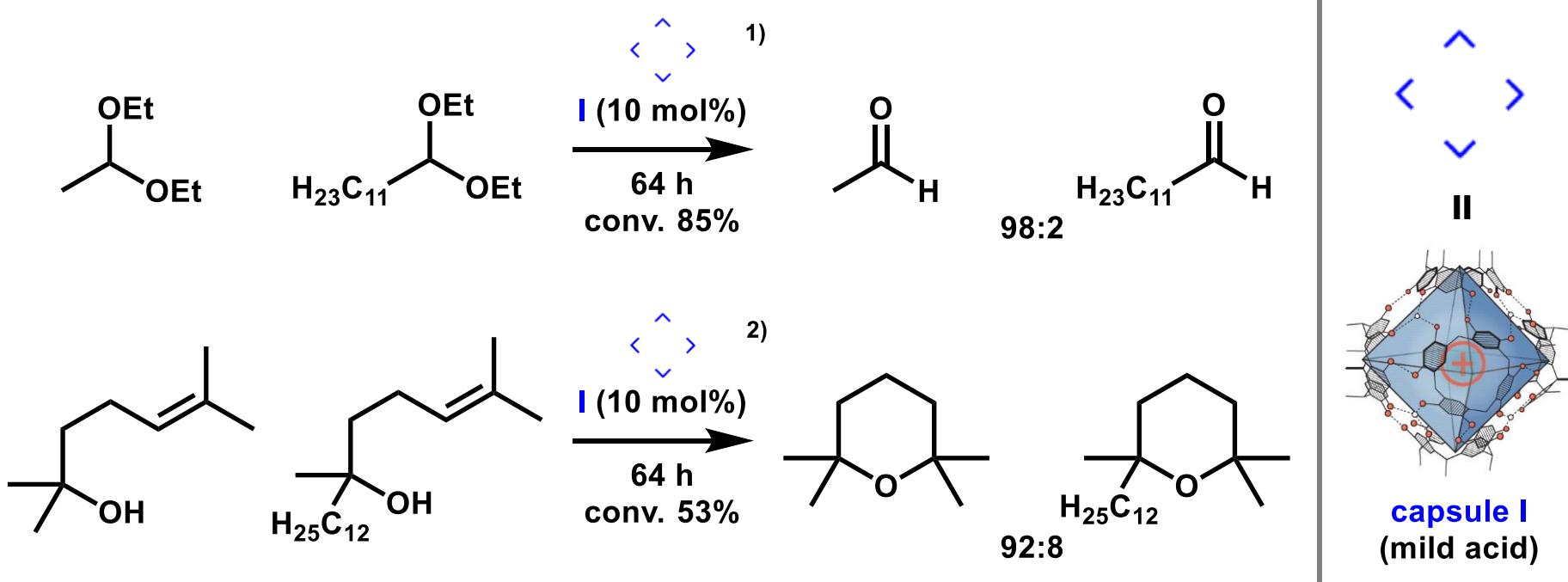


career:

M.S. Technical University of Vienna (Austria) with Prof. Fröhlich
Ph.D Technical University of Vienna with Prof. Mulzer
P. D. The Scripps Research Institute (La Jolla, USA) with Prof. Rebek
2011-2016 Juniorprofessor at the Technical University Munich
2016- a dual tenure track assistant professorship
at the University of Basel and the ETH Zurich

Research Projects:

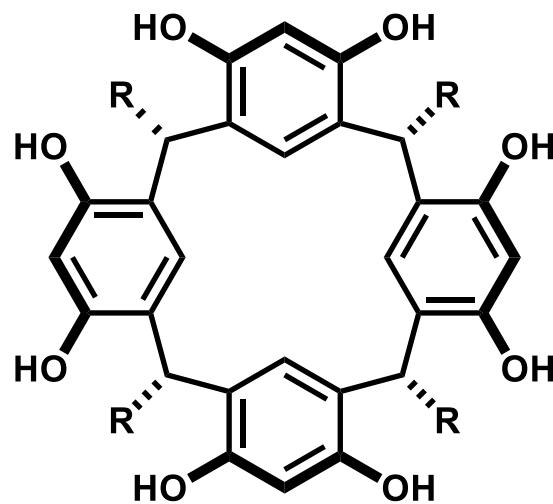
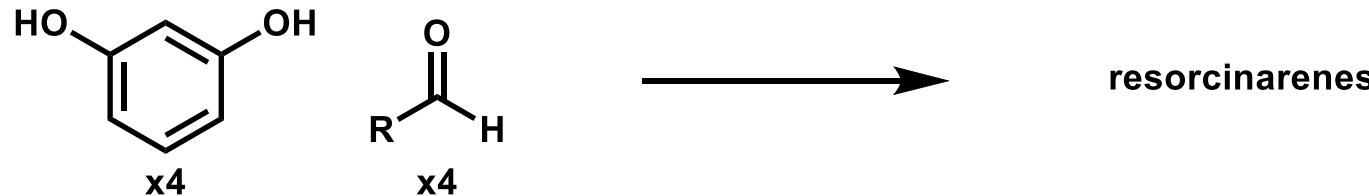
investigation of **supramolecular host structures** for their potential as catalysts



1) Zhang, Q.; Tiefenbacher, K. *J. Am. Chem. Soc.* **2013**, *135*, 16213.

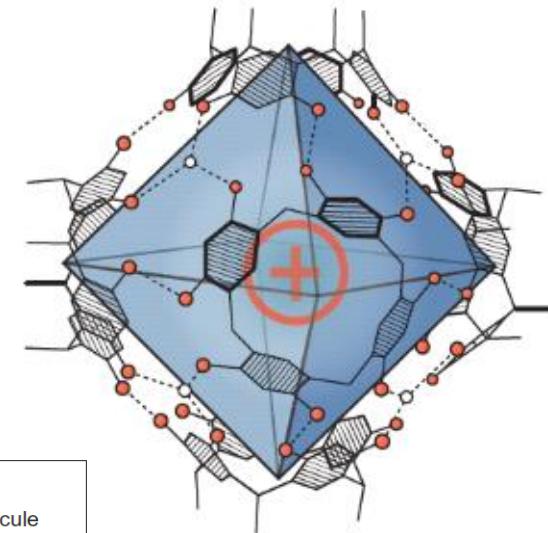
2) Catti, L.; Tiefenbacher, K. *Chem. Commun.* **2015**, *51*, 892.

Resorcinarene Hexamer



self-assembly¹⁾
in apolar solvents

- = OH group
- = H₂O molecule
- = Intermolecular hydrogen bonding



capsule I = $L_6(H_2O)_8$

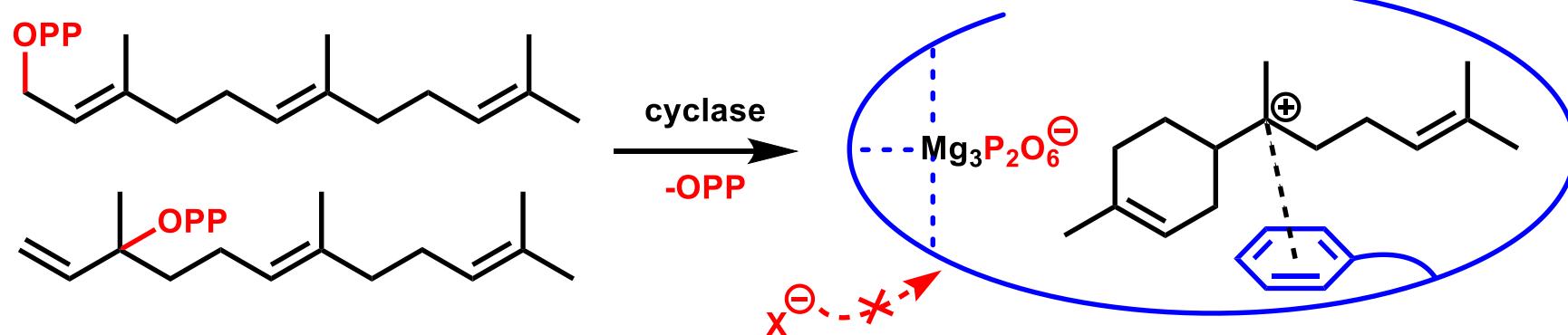
- Cationic guests are bound inside the cavity²⁾ ($\sim 1400 \text{ \AA}^3$) via cation- π interactions.
- Mild Brønsted acid ($pK_a \sim 5.5-6$)
- Guest exchange is facile.

1) MacGilivray, L.; Atwood, J. L. *Nature* **1997**, 389, 469.

2) Zhang, Q.; Tiefenbacher, K. *Nat. Chem.* **2015**, 7, 197.

Tiefenbacher's Working Hypothesis

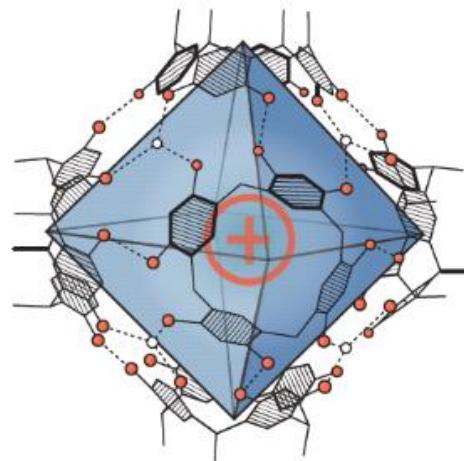
Advantage of THT cyclization in the enzyme pocket



1. OPP is removed under non-harsh conditions (pH 6-7).
2. Cationic Intermediate is stabilized by cation- π /cation-dipole interaction.
3. Undesired nucleophilic attacks are blocked.
4. Conformation of the substrate is defined.

Mimicking of the enzyme pocket

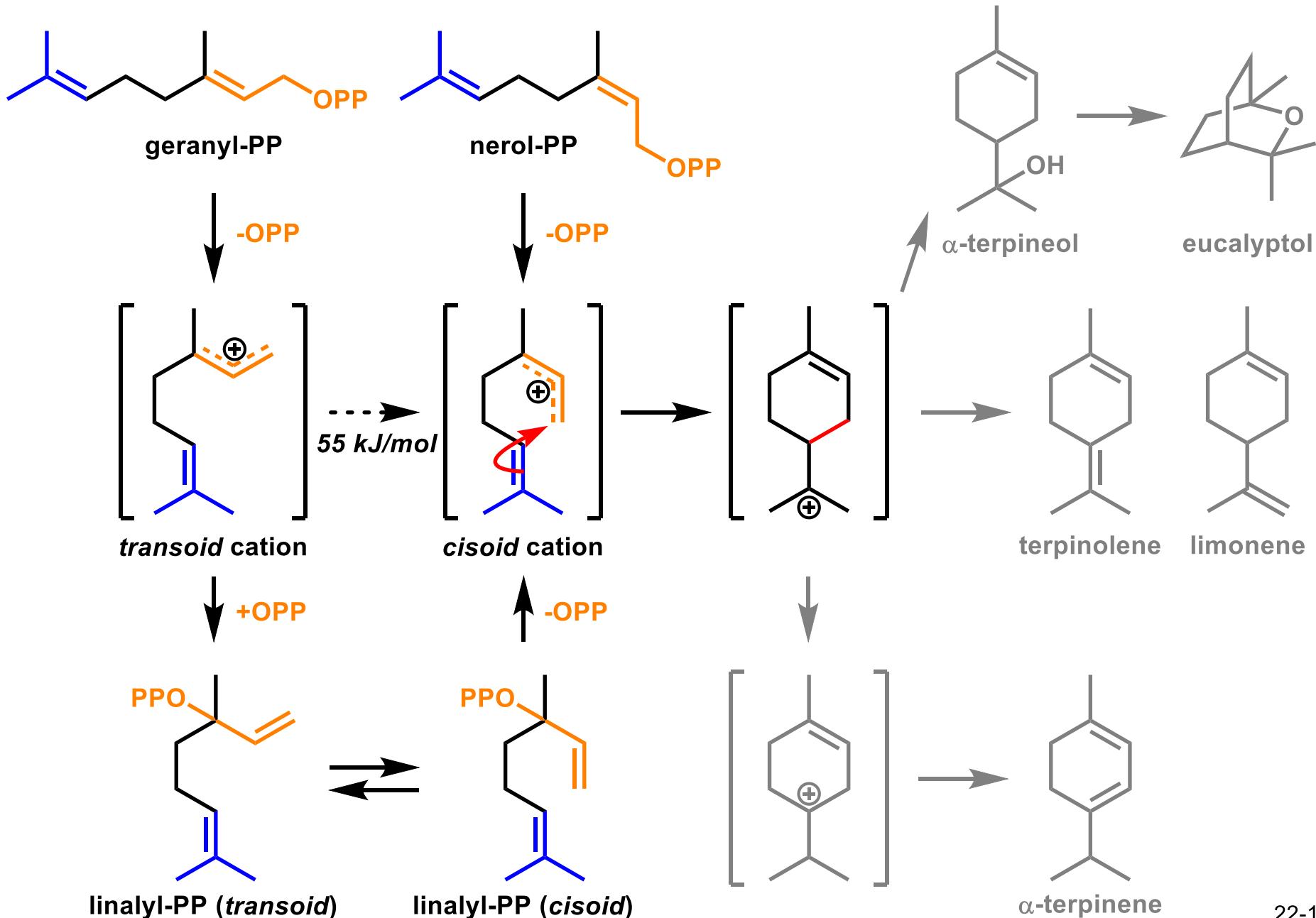
- Cationic guests are bound inside the cavity ($\sim 1400 \text{ \AA}^3$) via cation- π interactions.
 - Mild Brønsted acid ($\text{pK}_a \sim 5.5-6$)
 - > Trace acid (DCI or HCl) is required for reaction.¹⁾
 - Guest exchange is facile.
- > Capsule I-catalyzed THT cyclizations were investigated.



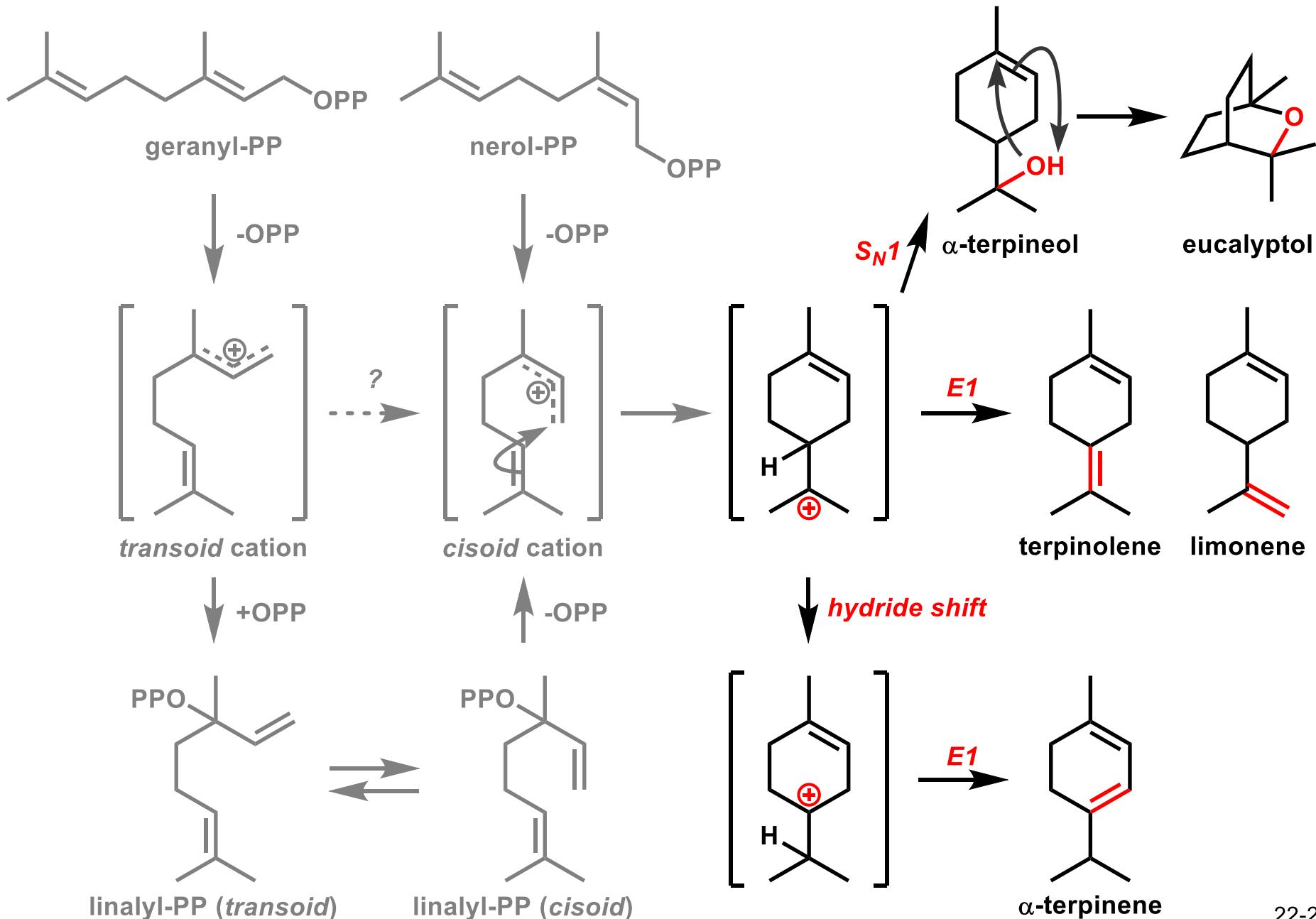
$$\text{capsule I} = \text{L}_6(\text{H}_2\text{O})_8$$

1) Zhang, Q.; Catti, L.; Pleiss, J.; Tiefenbacher, K. *J. Am. Chem. Soc.* **2017**, ASAP.

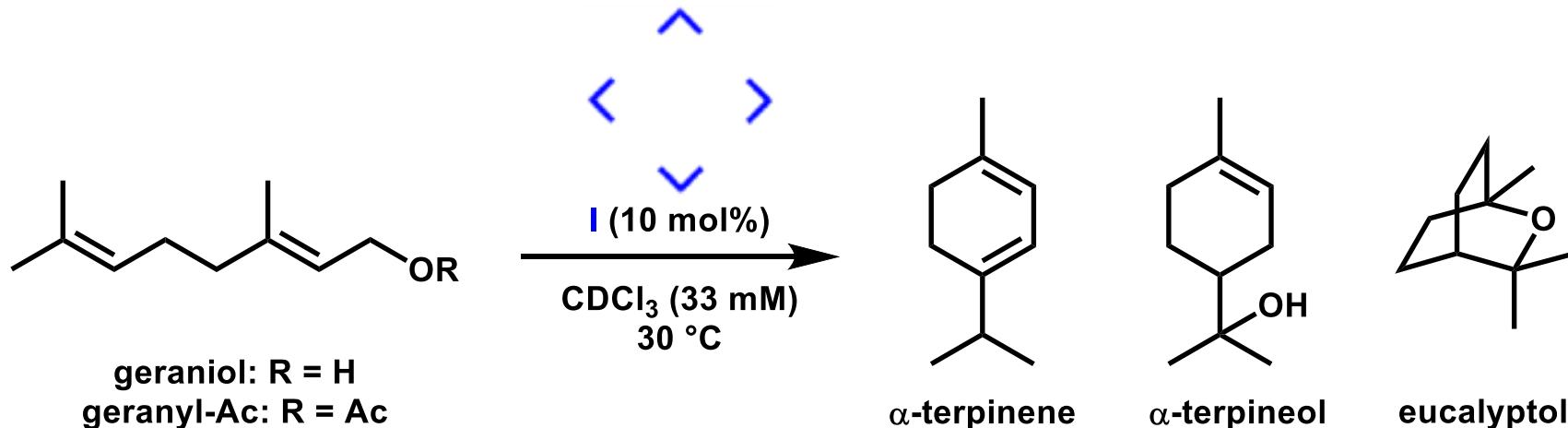
Biosynthetic Pathways toward Cyclic Monoterpenes



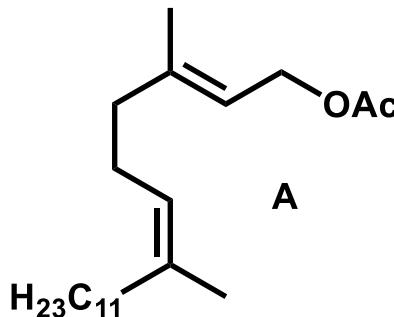
Biosynthetic Pathways toward Cyclic Monoterpenes



THT Cyclization and Control Experiment



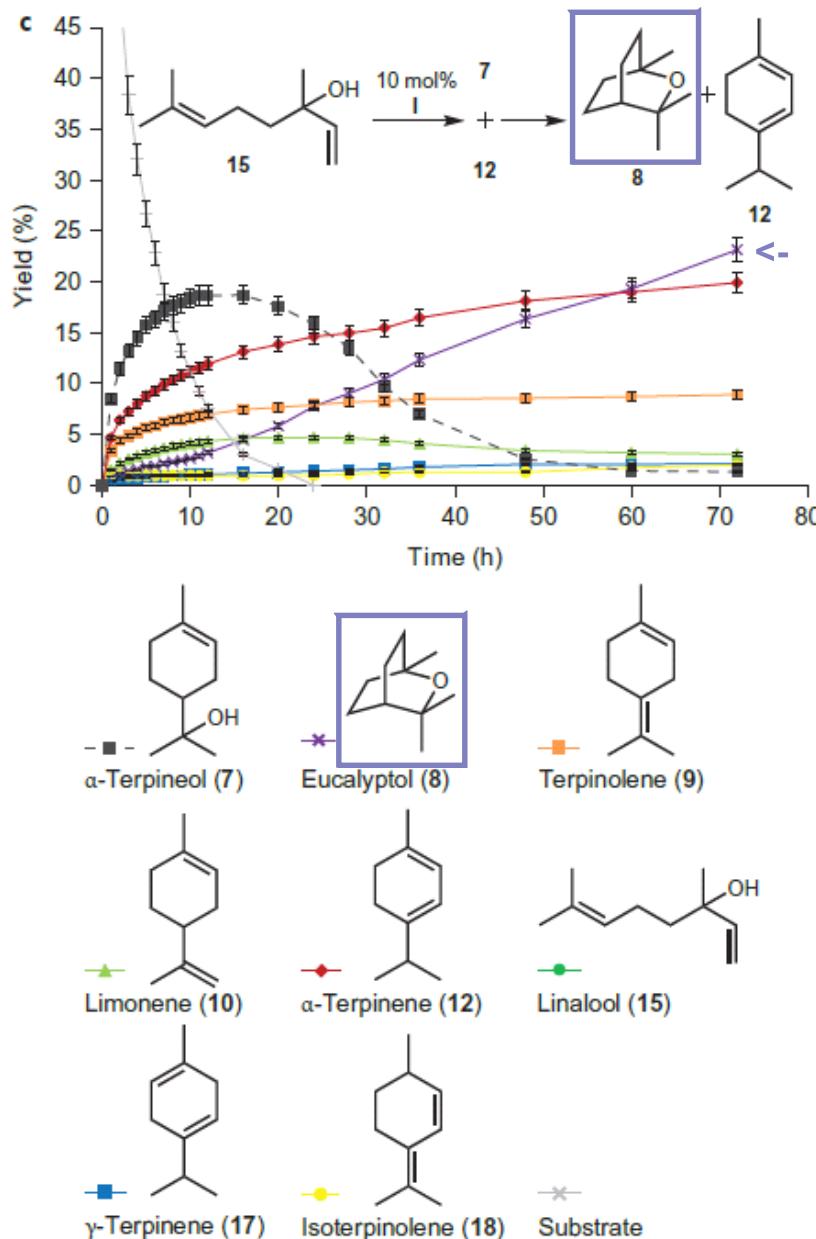
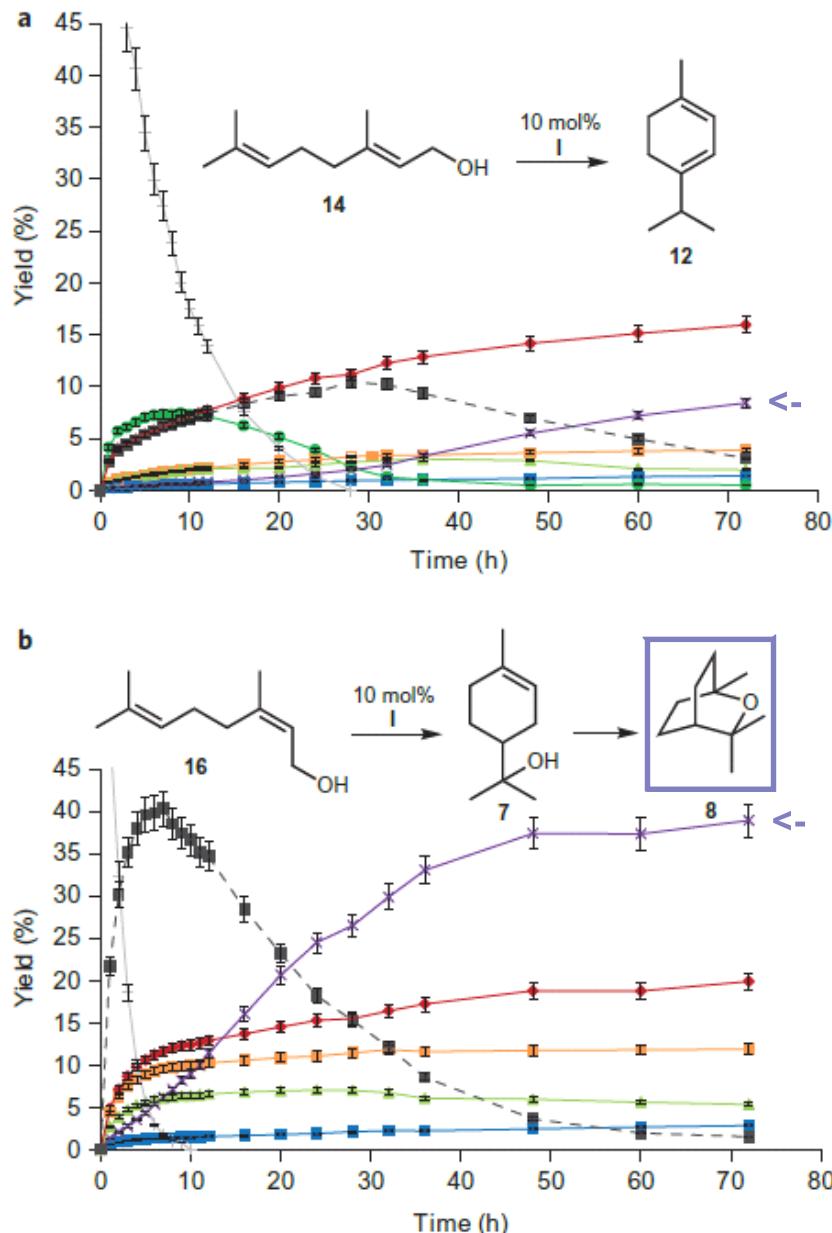
R	I	additive	conversion
H	10 mol%	none	100% (1 d)
Ac	10 mol%	none	95% (1 d)
Ac	10 mol%	15 mol% Bu_4NBr	4% (3d, no THT product)
Ac (0.5 eq)	10 mol%	A (0.5 eq)	geranyl-Ac: 81% (1 d) A: 2% (1 d)
Ac	10 mol%	DMSO (10 eq)	0% (7 d)
Ac	none	none	0% (20 d)



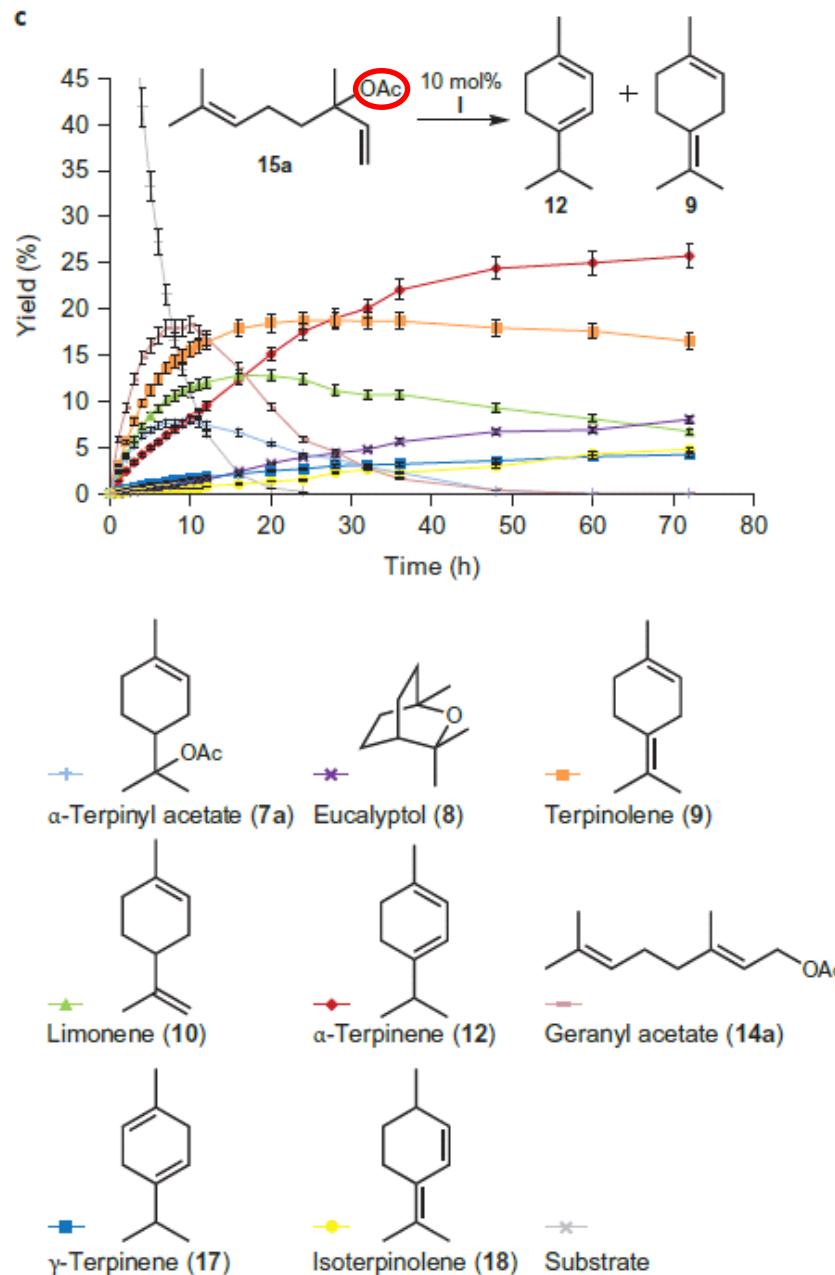
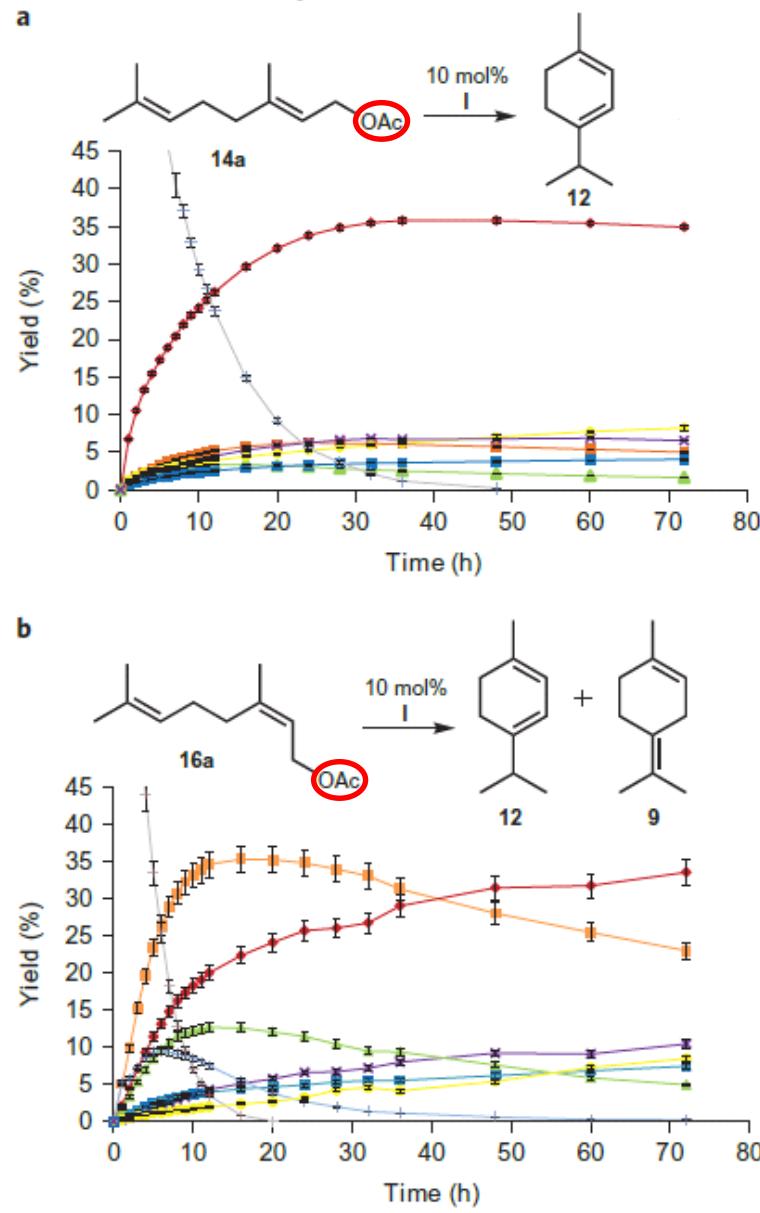
1) Zhang, Q.; Tiefenbacher, K. *Nat. Chem.* **2015**, 7, 197.

2) Zhang, Q.; Catti, L.; Pleiss, J.; Tiefenbacher, K. *J. Am. Chem. Soc.* **2017**, ASAP.

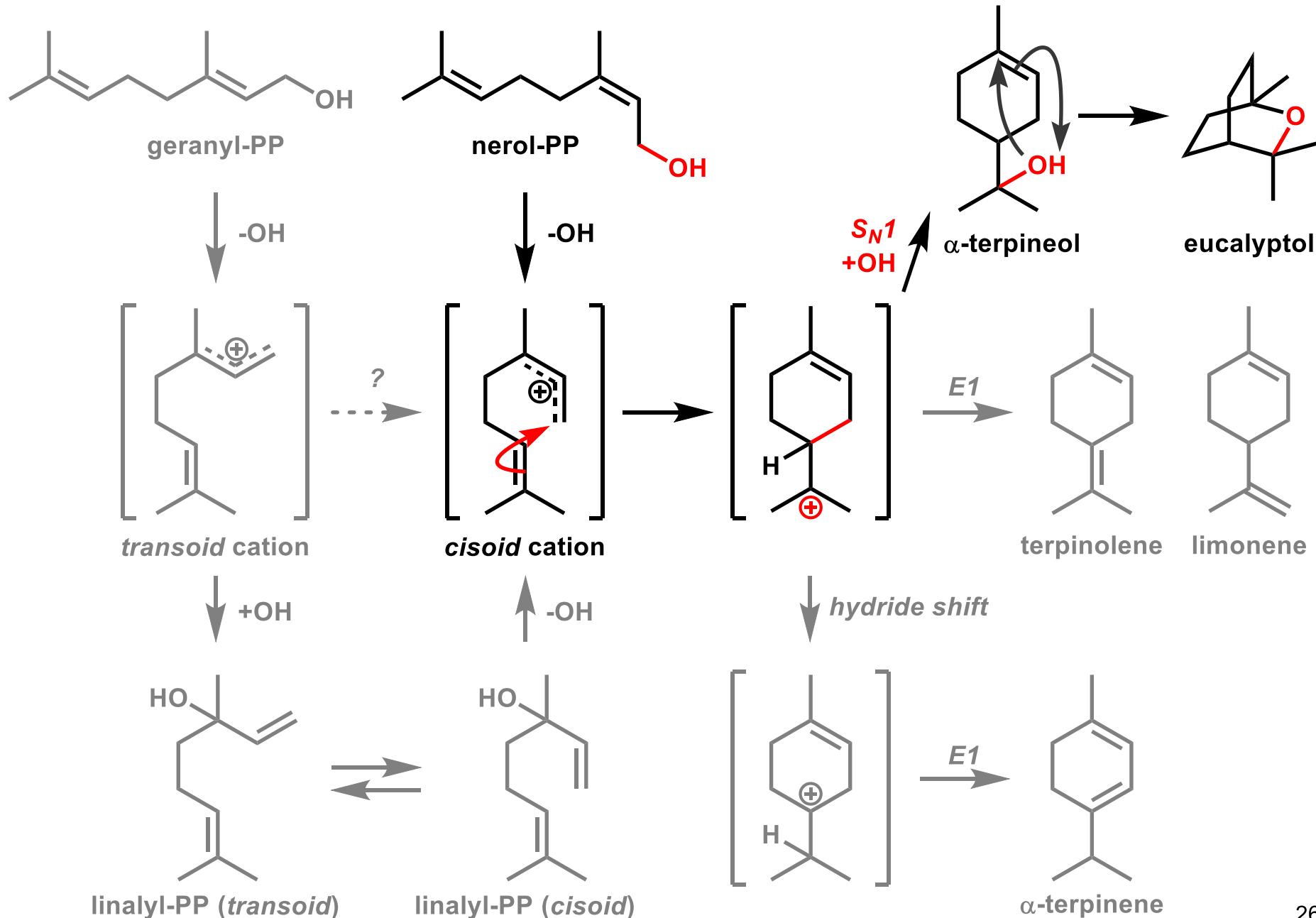
THT Cyclization of Alcohol Substrate with I



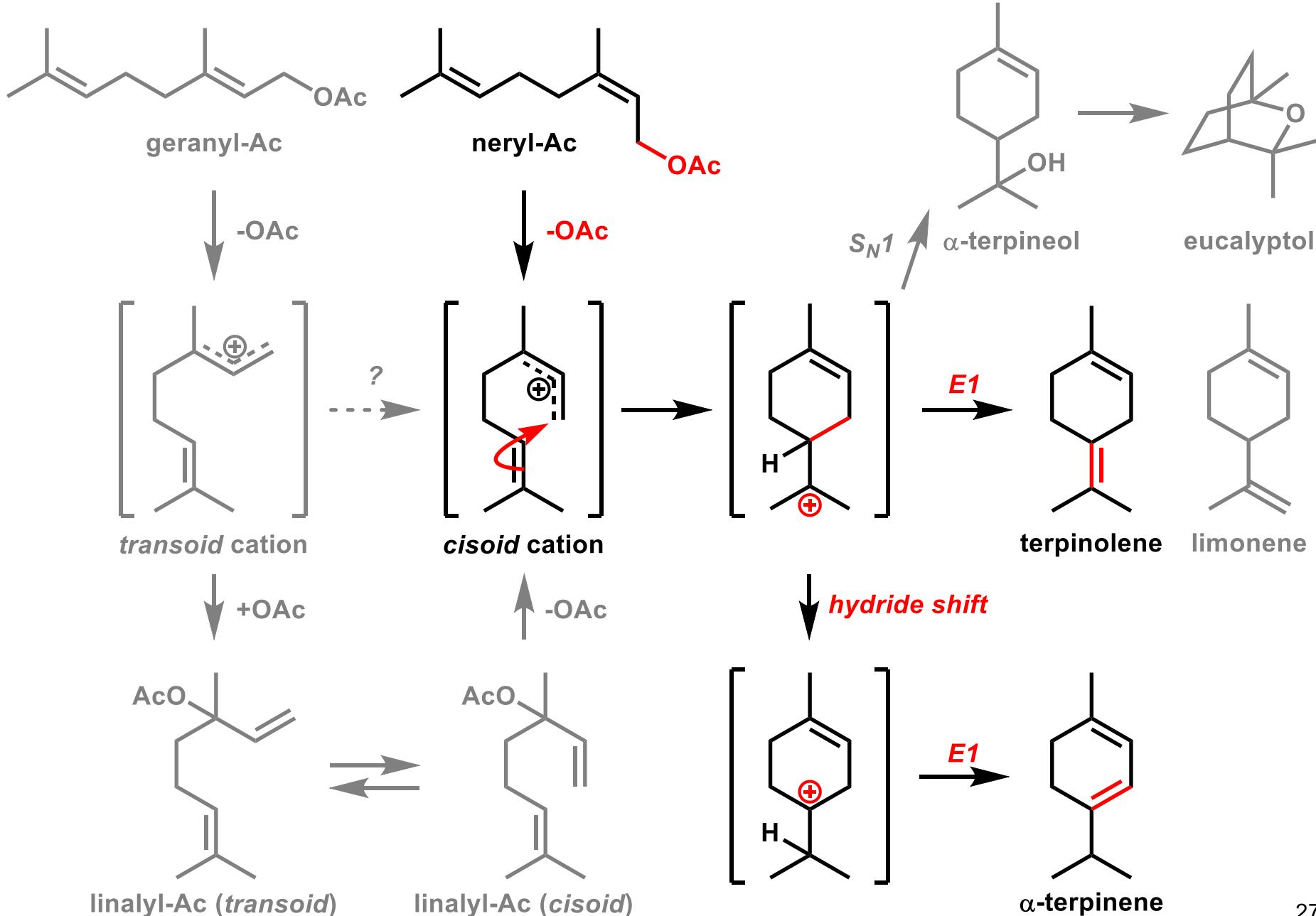
THT Cyclization of Acetate Substrate with I_n



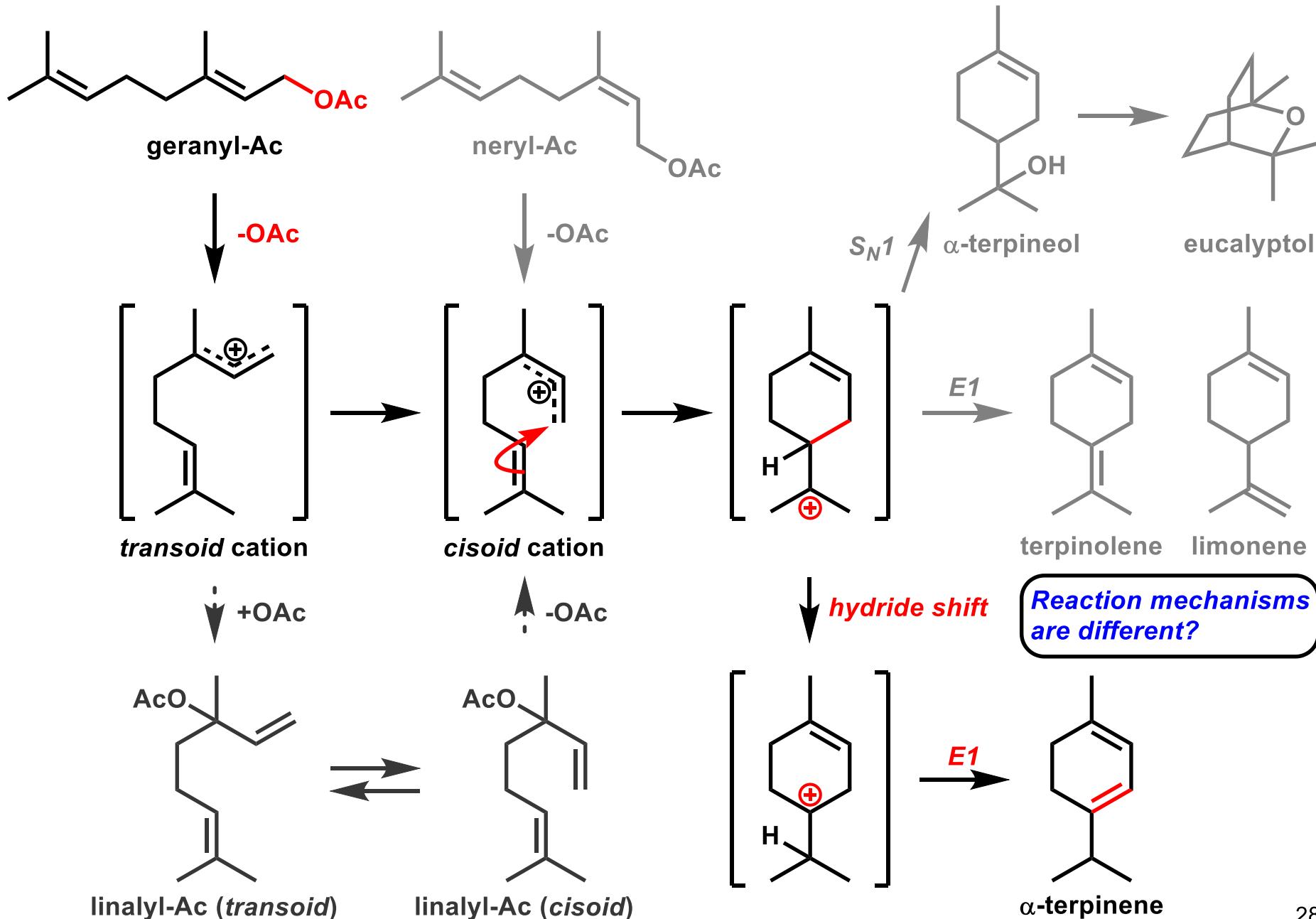
THT Cyclization of Nerol with I



THT Cyclization of Neryl-Ac with I

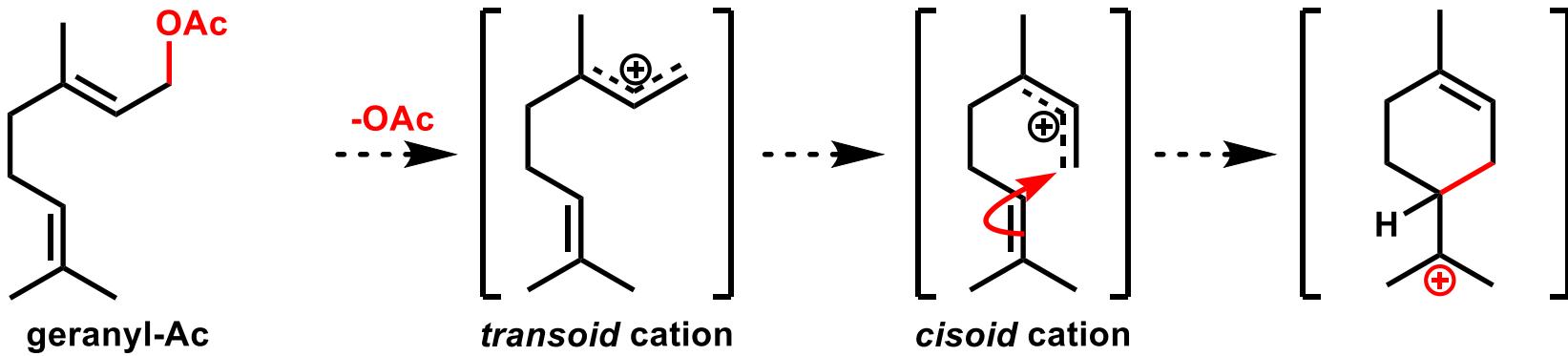


"non-stop" THT Cyclization of Geranyl-Ac with I



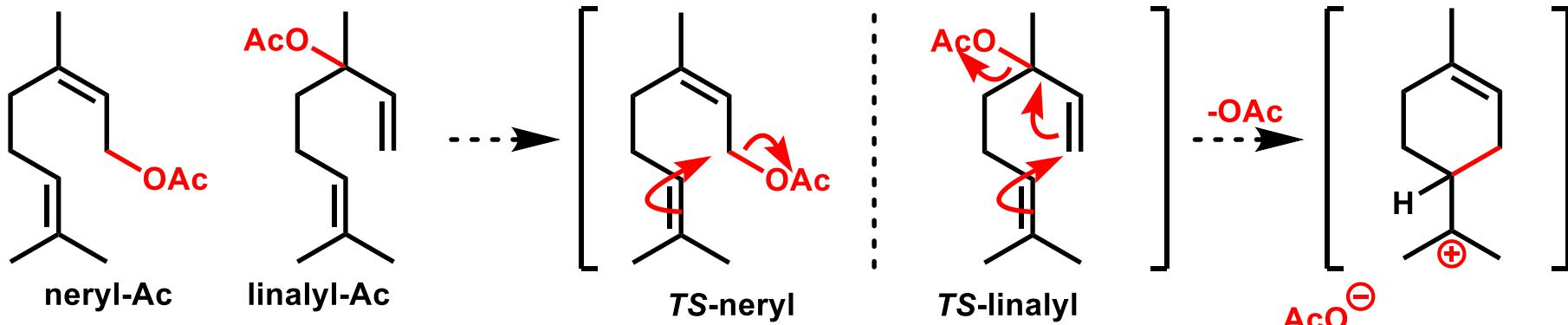
Hypothesis: S_N1 or S_N2/S_N2'

In the reaction of Geranyl-Ac, ring closing cannot occur without olefin isomerization (S_N1-like).



During the isomerization,
AcO⁻ may be diffused away
from cation intermediate.

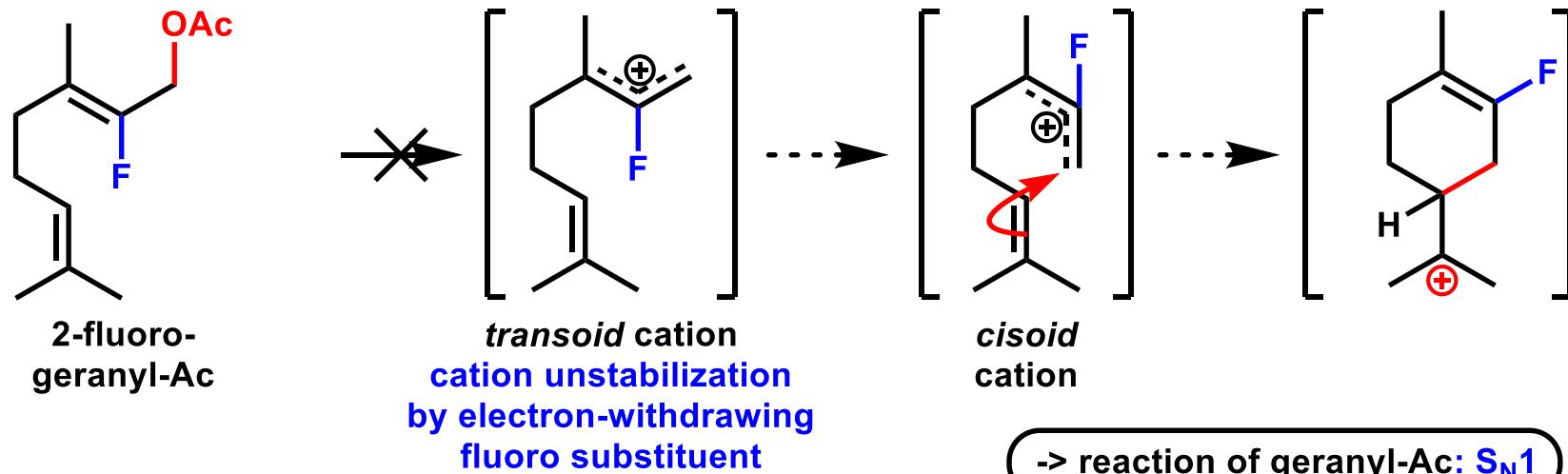
Neryl-Ac/linalyl-Ac both can react in a concerted fashion (S_N2/S_N2'-like).



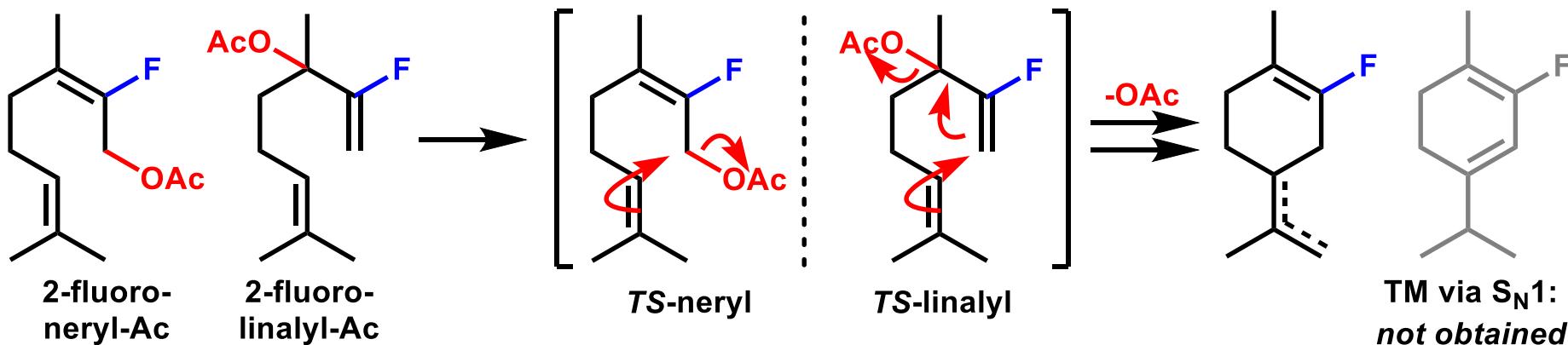
AcO⁻ group and cation
would be in close proximity.

Examination: Cyclization of 2-Fluoro Derivatives

2-fluorogeranyl-Ac: no reaction

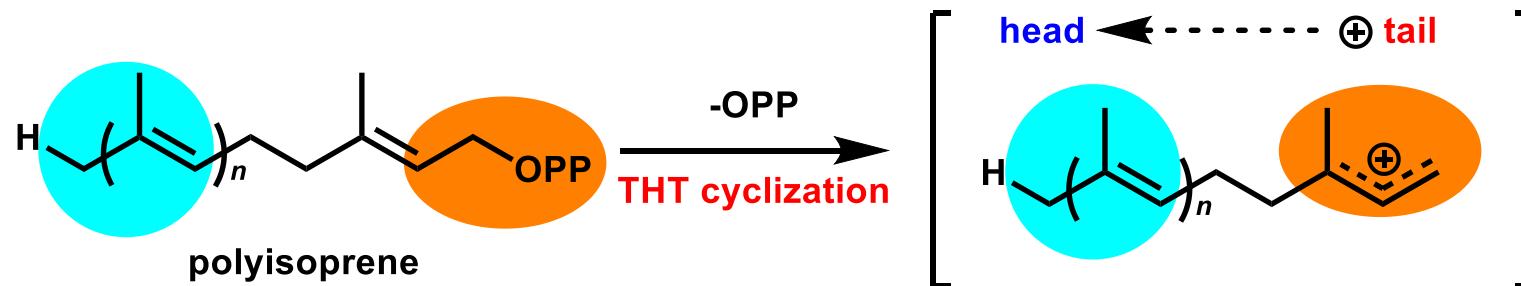


neryl-Ac/linalyl-Ac: reaction proceeded (but low yields)

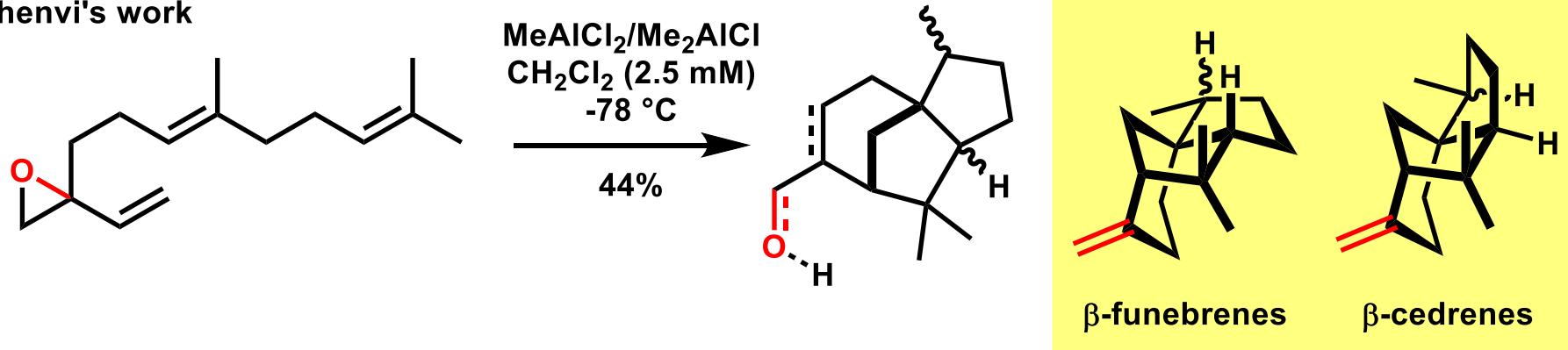


Summary (1)

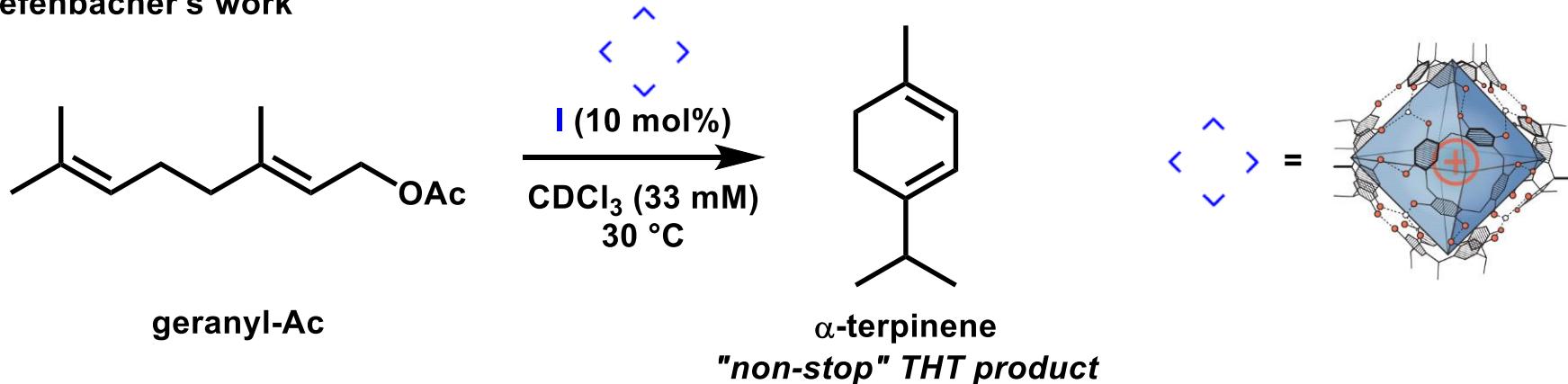
"Tail-to-Head" cyclization competes with E1 elimination/S_N1 reaction; difficult in solvent



Shenvi's work

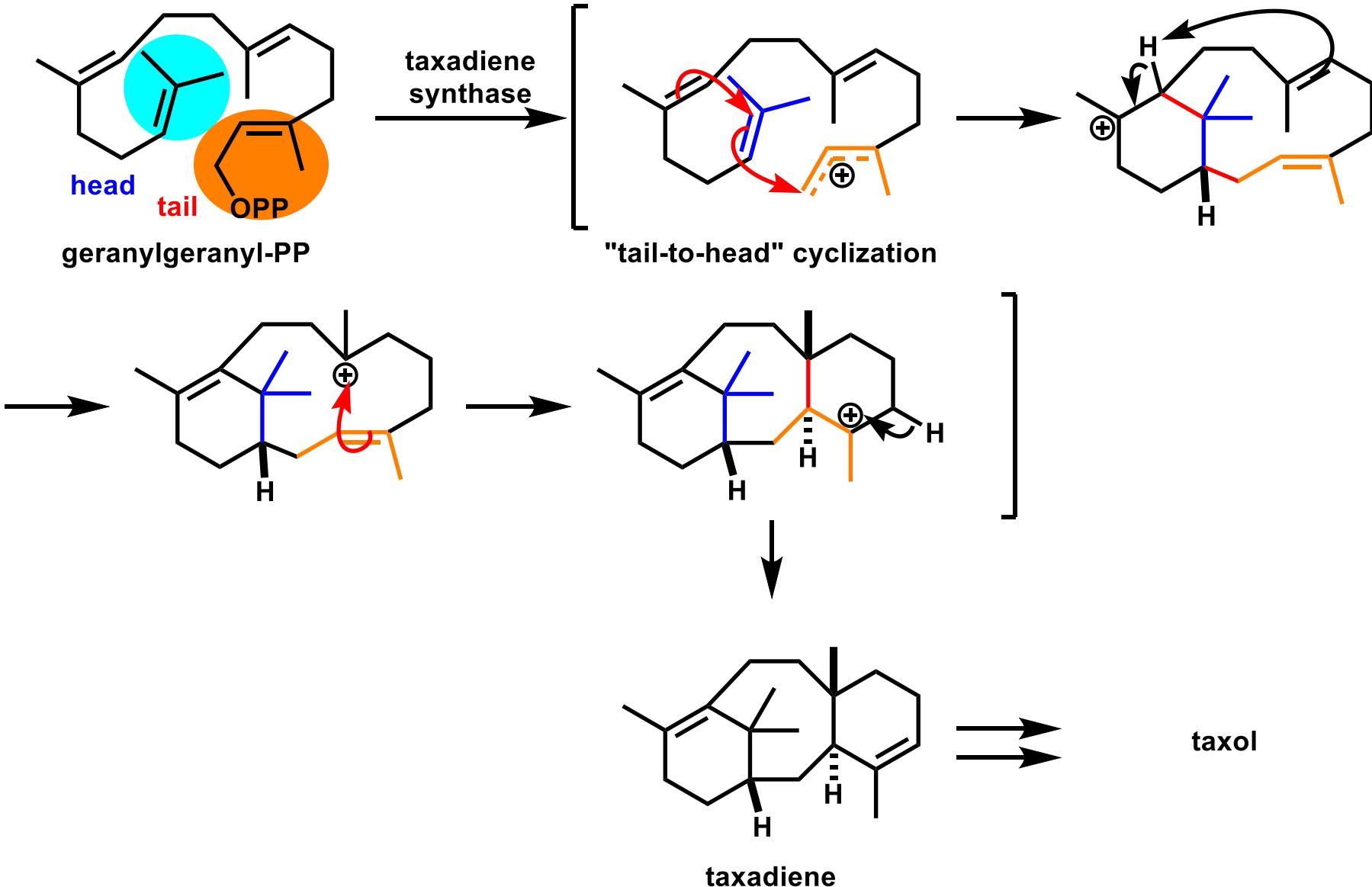


Tiefenbacher's work



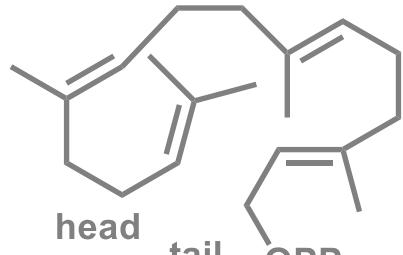
Summary (2)

Taxol biosynthetic route

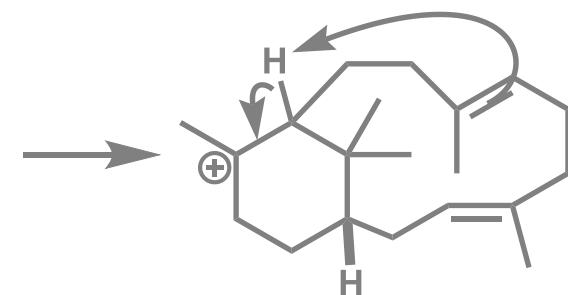


Summary (2)

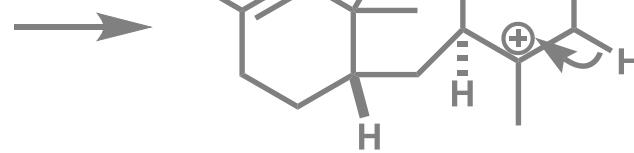
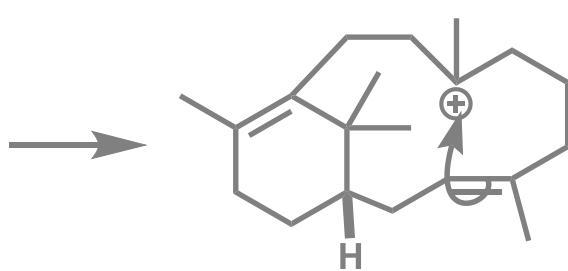
Taxol biosynthetic route



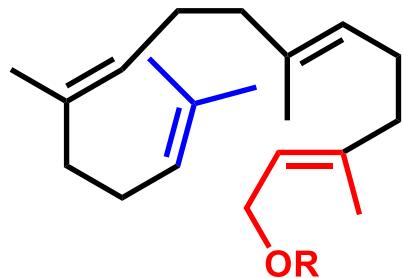
taxadiene synthase



"tail-to-head" cyclization

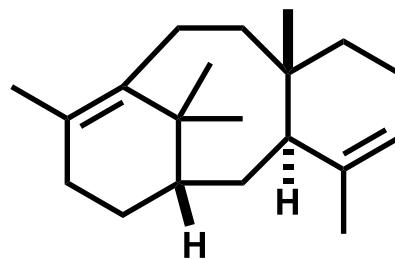


Biomimetic THT cyclization toward taxane skeleton



geranylgeraniol-mimic

?



taxadiene

taxol

Appendix

Preparation of Nerolidol-mimic Epoxide

