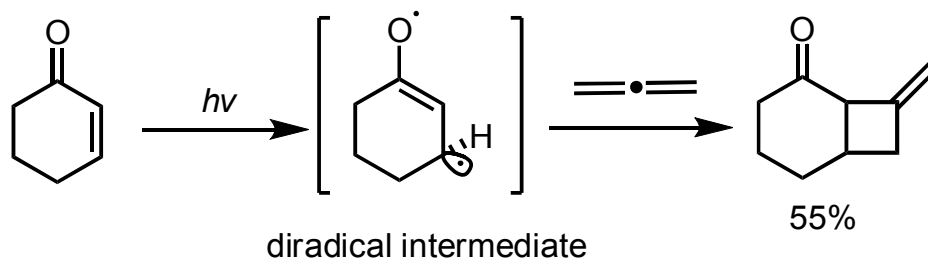

Cycloaddition Reactions of Allenes: Examples in Natural Product Synthesis

Miriam Inbar
Leighton Group Literature Seminar
May 4 2007

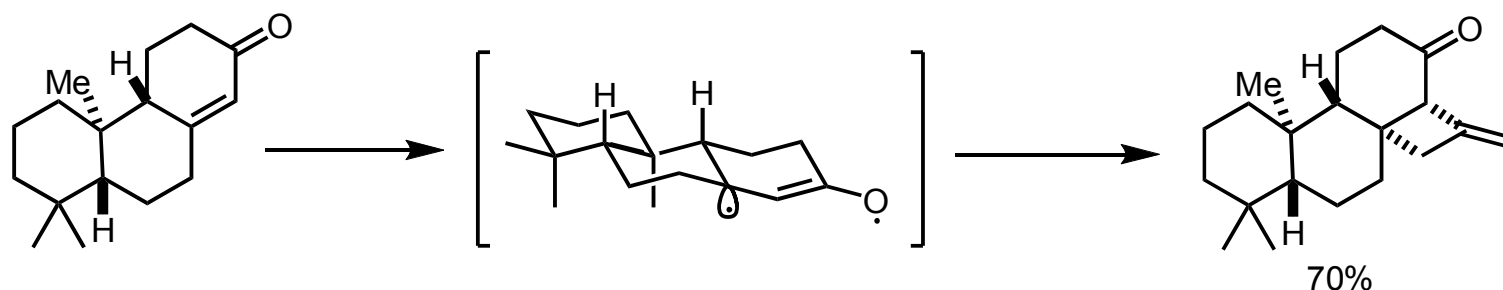
Summary

- I. [2+2] Cycloadditions of Enones and Allenes
- II. [4+2] Cycloadditions with Allenes as Dienophiles
- III. [4+2] Cycloadditions with Allenes as Dienes
- IV. Rh-catalyzed [5+2] Cycloadditions
- V. Allenic Nazarov Cyclizations

[2+2] Photocycloadditions of Allenes and Enones

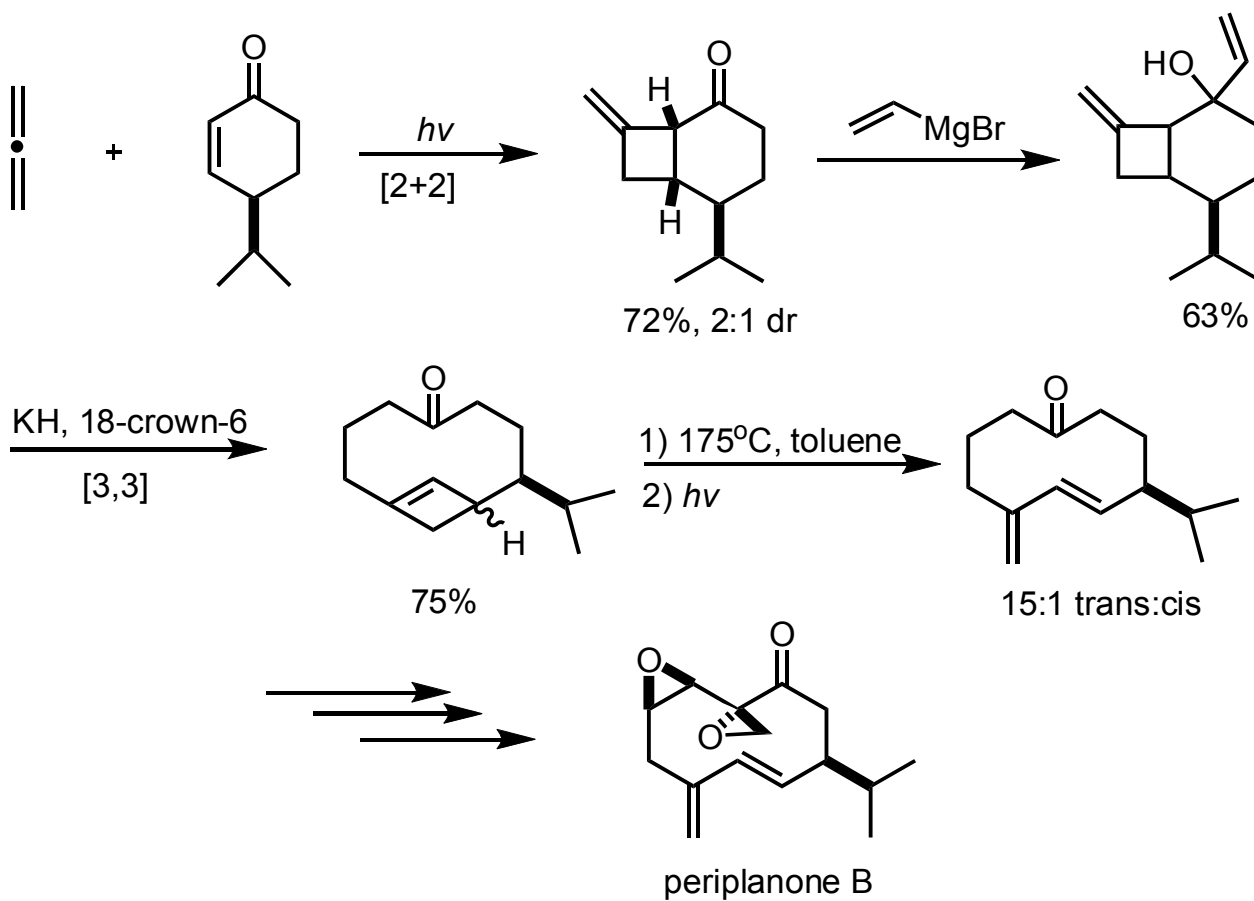


- Diradical intermediate forms from a triplet enone
- Triplet diradical cyclizes to product after spin inversion to singlet state
- Configuration of the diradical determines stereochemistry of the product



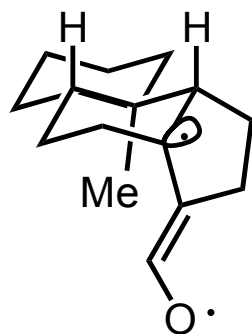
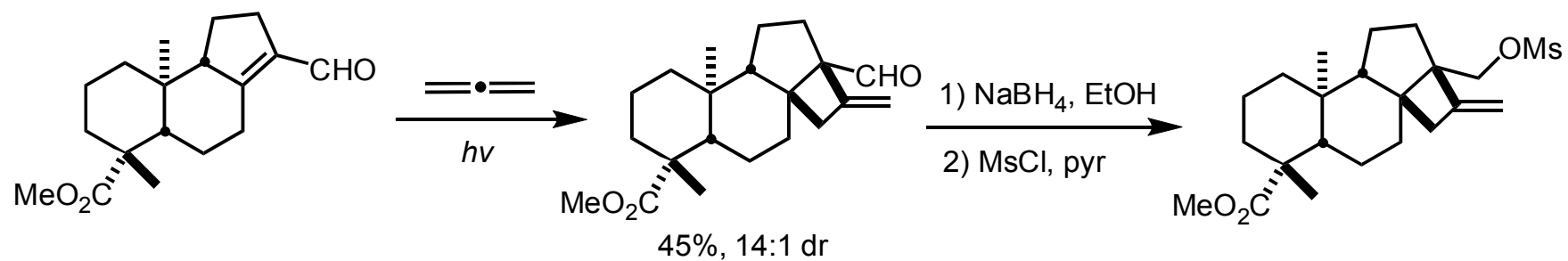
Corey et al. *J. Am. Chem. Soc.*, **1964**, *86*, 5570-5583

Synthesis of periplanone B



Schreiber, S.L. et al. *J. Am. Chem. Soc.*, **1984**, *106*, 4038

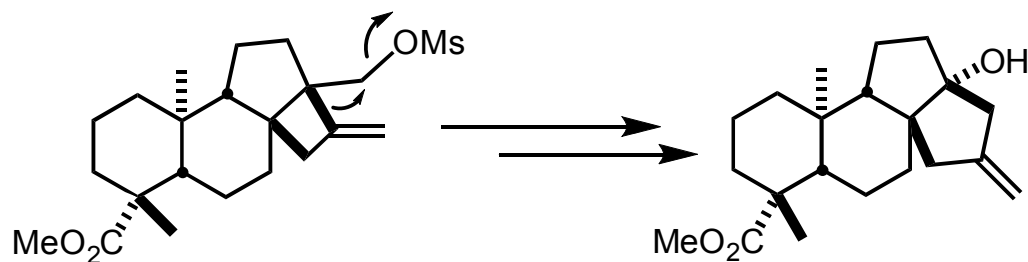
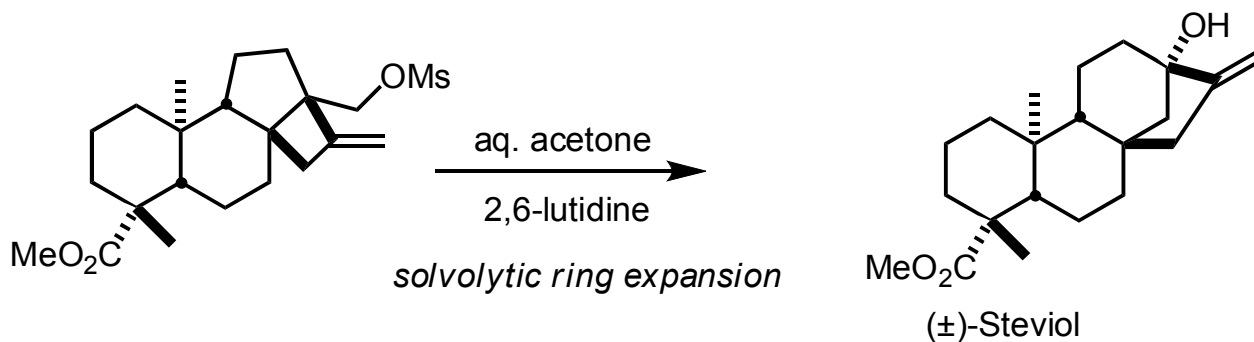
Synthesis of (\pm)-Steviol



[2+2] addition occurs preferentially from less-hindered top face

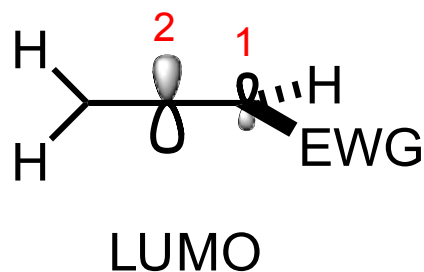
Ziegler, Frederick and Kloek, James A. *Tetrahedron*, **1977**, 33, 373-380

Synthesis of (±)-Steviol



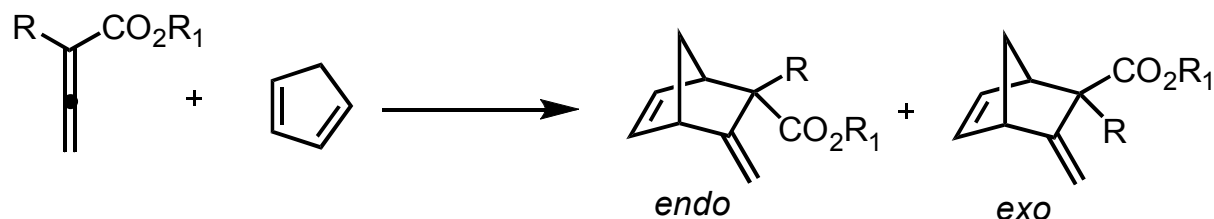
A substantial amount of a second rearrangement product was also observed.

[4+2] Cycloadditions of Allenes



- Allenes usually participate in Diels-Alder reactions as electron deficient dienophiles
- LUMO energy of the allene is lowered by EWG
- Largest LUMO coefficient rests on C2
- Diels-Alder will take place at the internal C=C bond

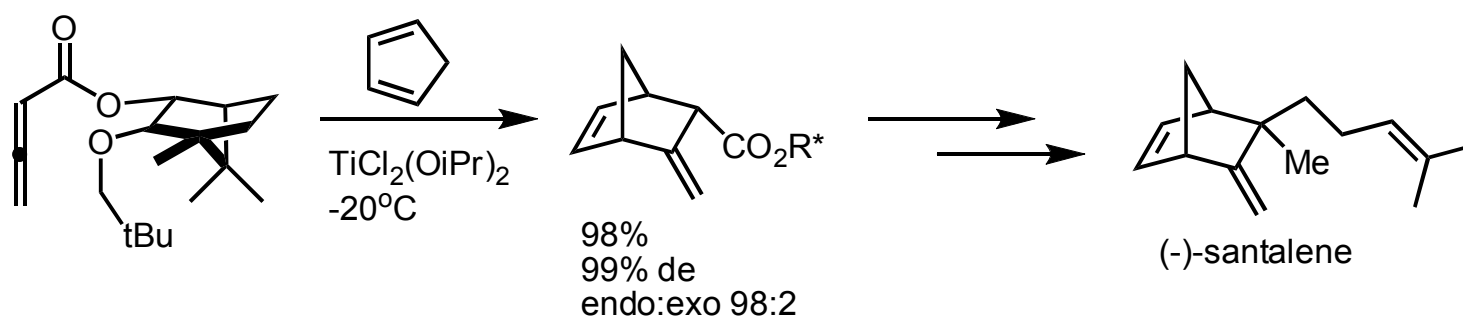
Allenic Esters Generally Show *Endo* Selectivity



R	R1	Conditions	Yield (%)	endo:exo
H	Et	Benzene, 80°C	90	64:36
H	Et	AlCl ₃ , benzene, RT	95	86:14
Me	Me	Benzene, 80°C	80	40:60
Me	Me	AlCl ₃ , benzene, RT	90	76:24

- Lewis acids increase efficiency of the reaction as well as *endo/exo* selectivity
- Other EWGs also show preference for *endo*

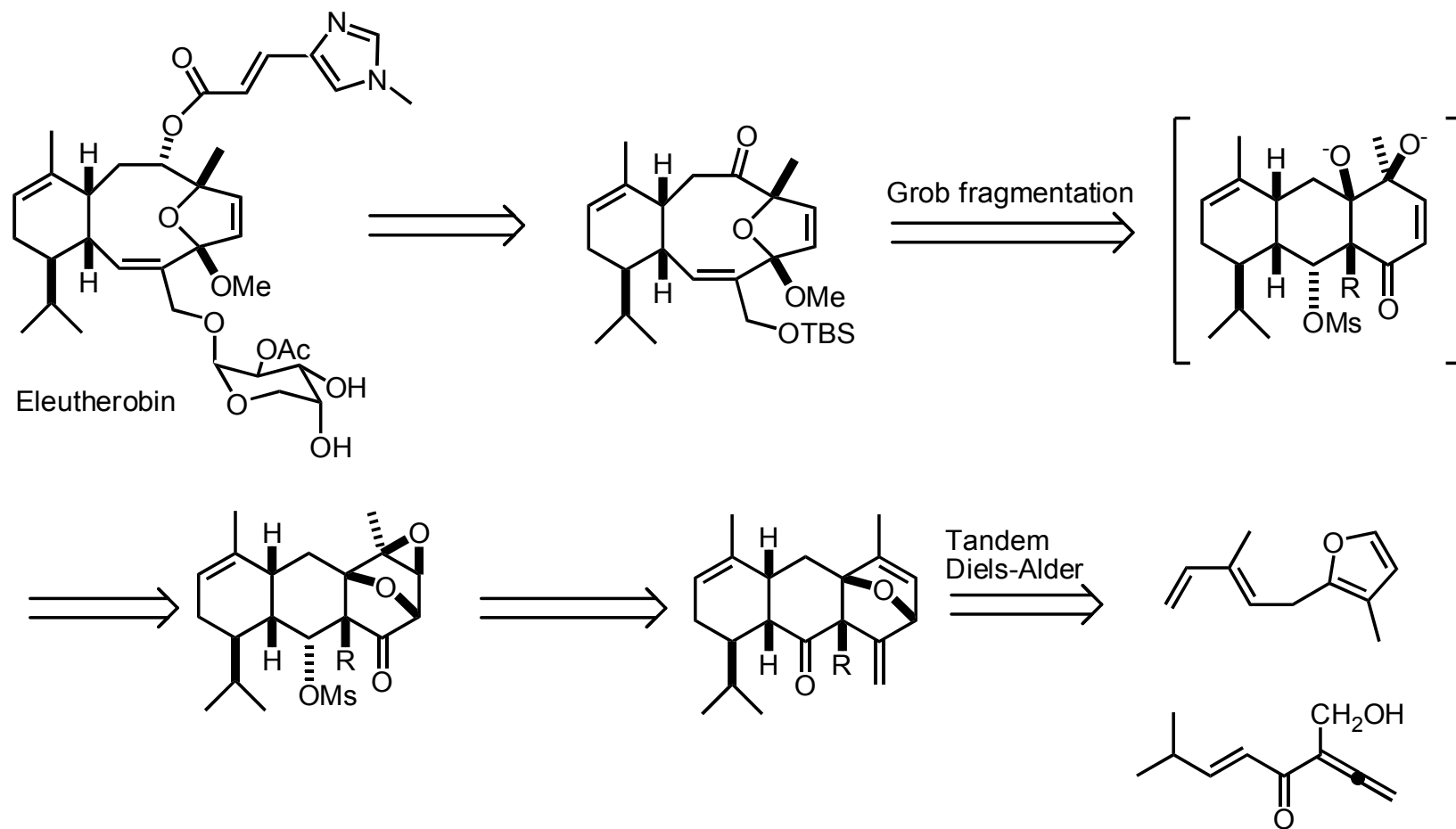
Enantioselective Synthesis of (-)-santalene



Use of camphor-derived chiral auxiliaries leads to excellent facial selectivity

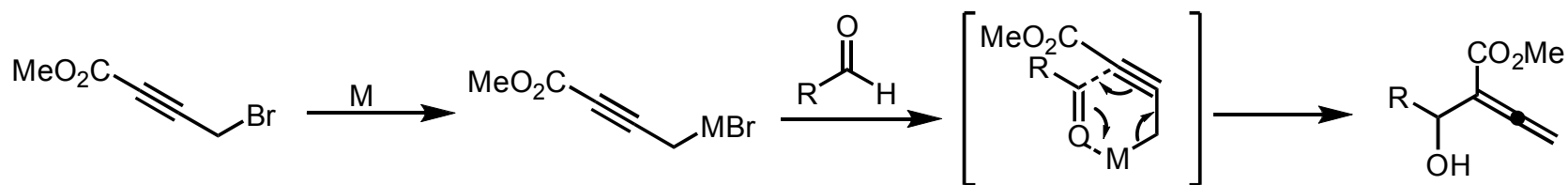
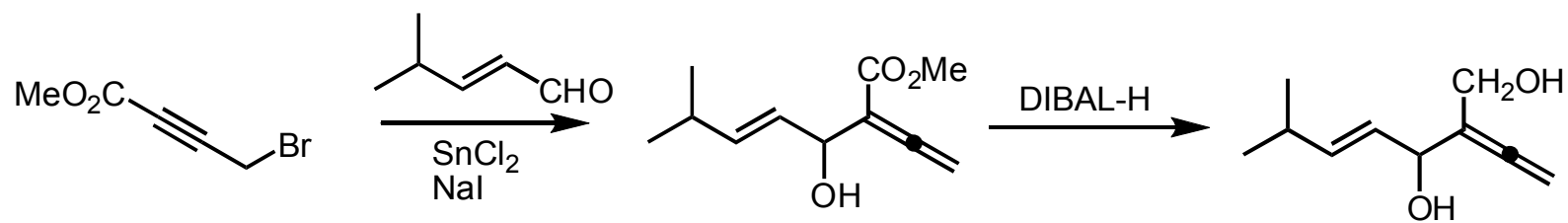
Oppolzer et al. *Tetrahedron Lett.* **1983**, 24, 4665-4668.

Towards Eleutherobin: Retrosynthetic Analysis



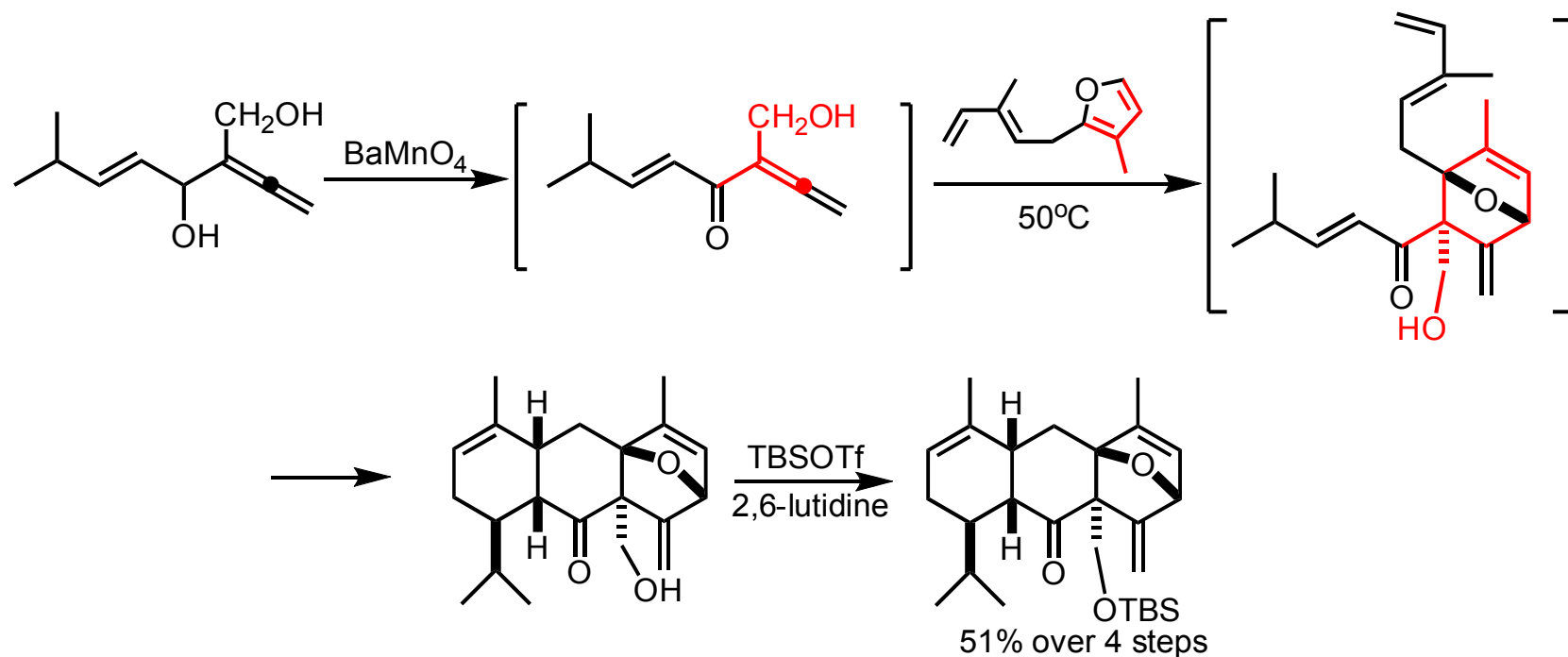
Winkler et al. *Org. Lett.* **2003**, 5, 1805-1808.

Synthesis of Allenyldienophile



Walls et al. *J. Chem. Soc.* **1950**, 3646-3650.

Tandem Diels-Alder Reaction

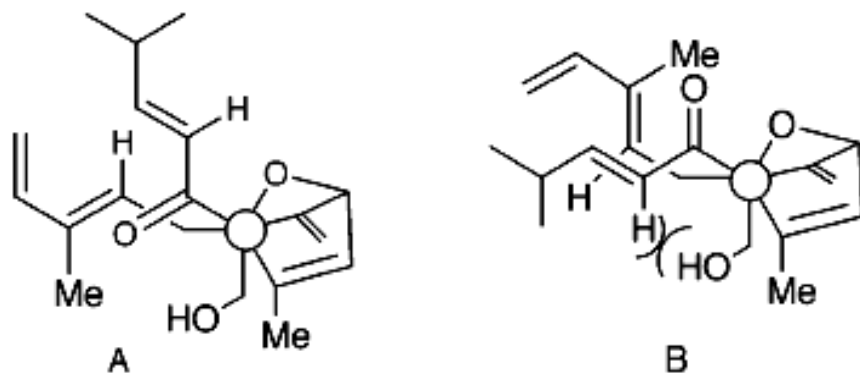


- Single stereoisomeric product; creation of six new stereogenic centers and three new rings
- Exclusively *exo* selectivity observed in first cycloaddition step
- Second Diels-Alder reaction is exclusively *endo*

Winkler et al. *Org. Lett.* **2003**, 5, 1805-1808.

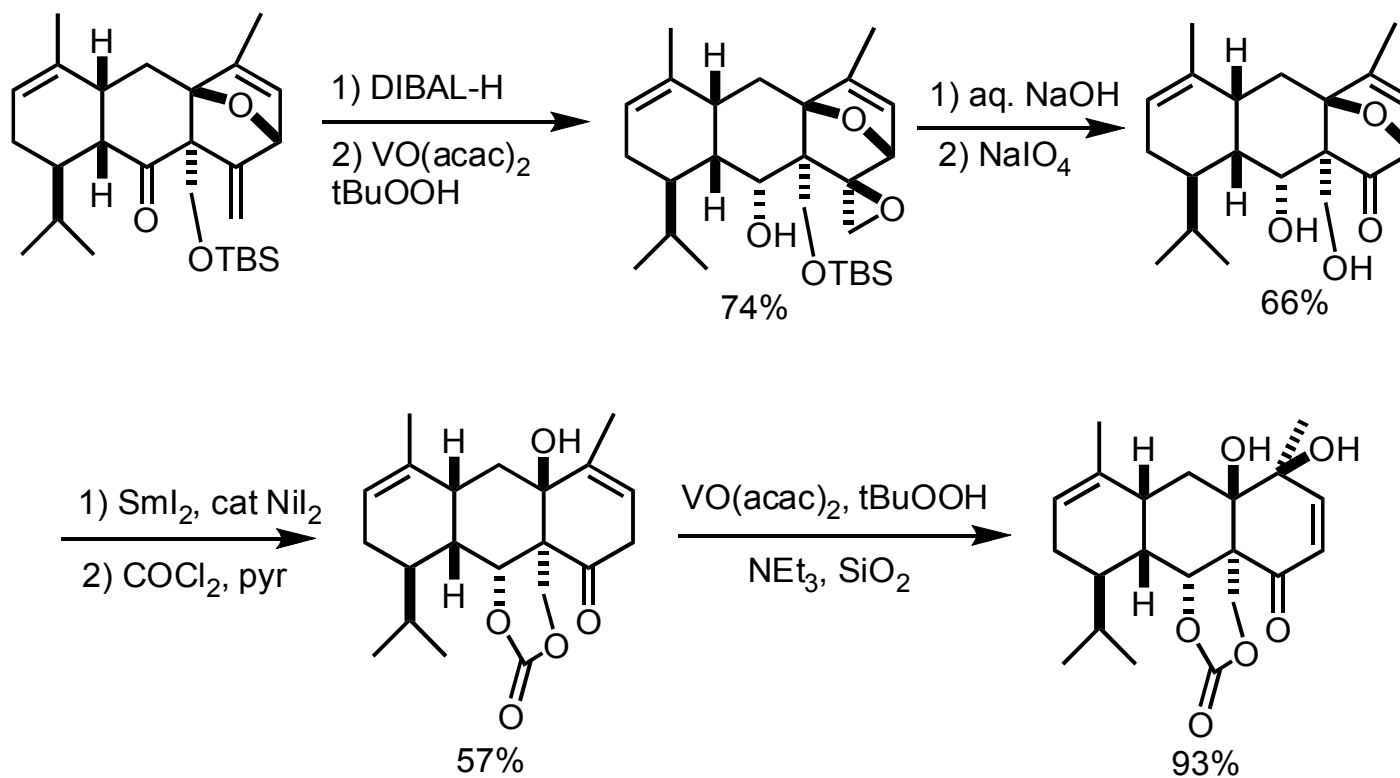
Conformational Analysis of Second Cycloaddition

Relative stereochemistry of the second Diels-Alder may be explained by examining the two possible conformers A vs. B:

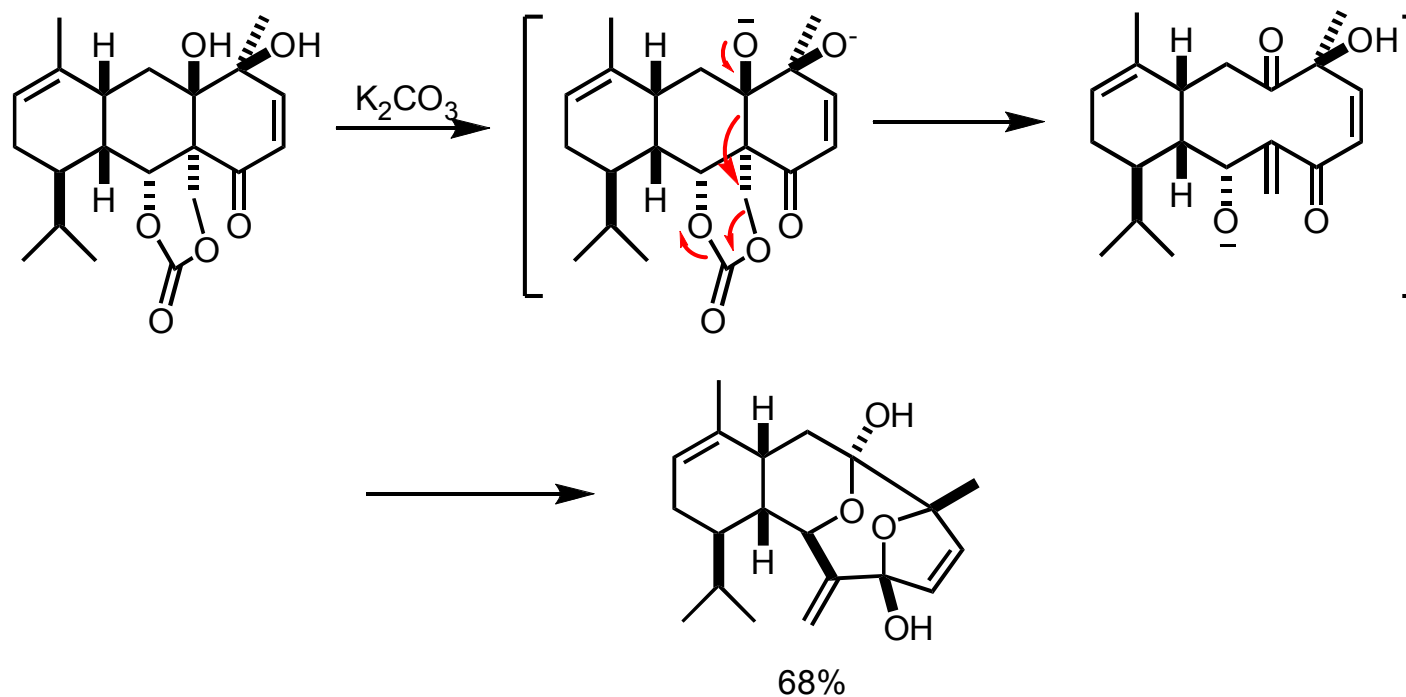


Reaction of A avoids the unfavorable steric interaction shown in B

Preparation for Grob Fragmentation

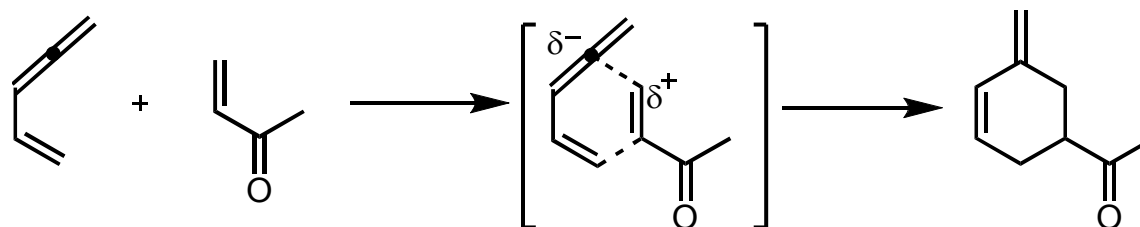


Grob Fragmentation

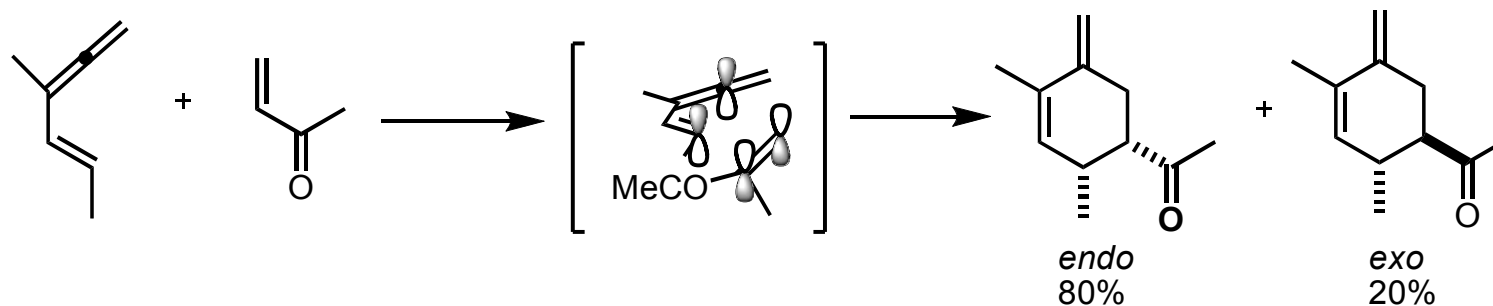


- Undesired bond was fragmented with subsequent extrusion of CO_2
- Double hemiketalization
- Currently looking into isomerization of *exo*-methylene

Vinylallenes as Dienes

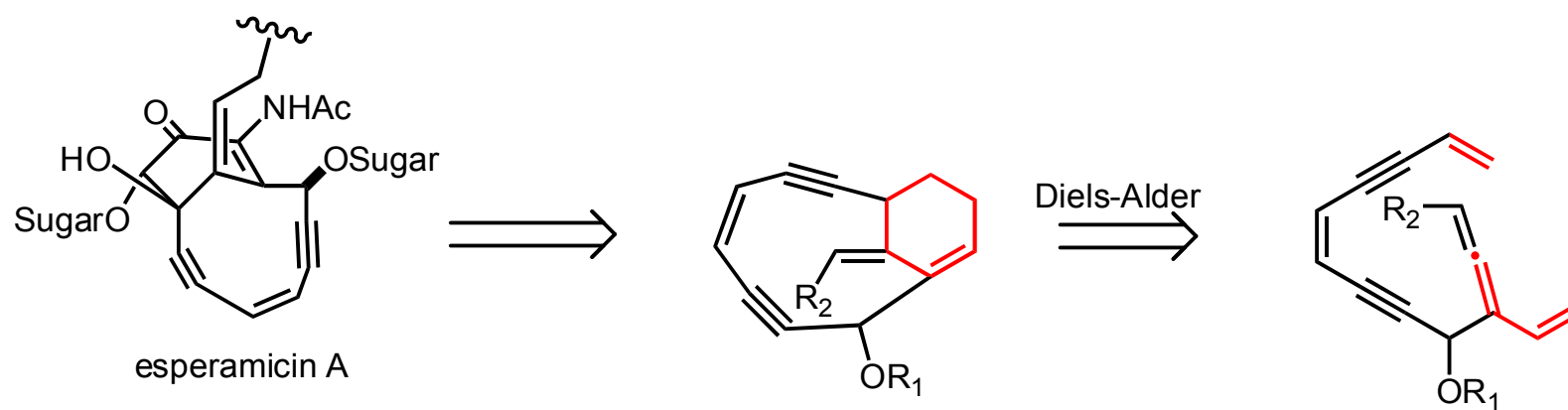


Electron-rich central carbon of the allene preferentially adds to the more electron-deficient carbon of the dienophile



Endo selectivity is generally observed

Vinylallenes as Biosynthetic Intermediates

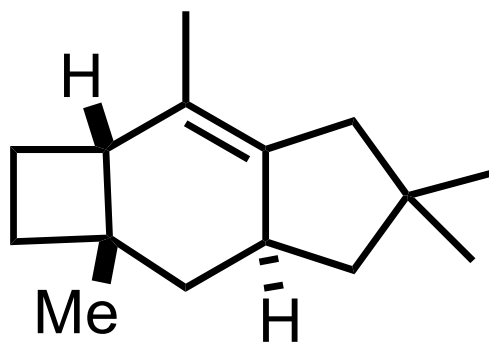


A vinylallene has been proposed as a biogenetic intermediate in the biosynthesis of esperamicin A.

Schreiber, S.L. et al. *J. Am. Chem. Soc.*, **1988**, *110*, 631.

Synthesis of (+)-sterpurene

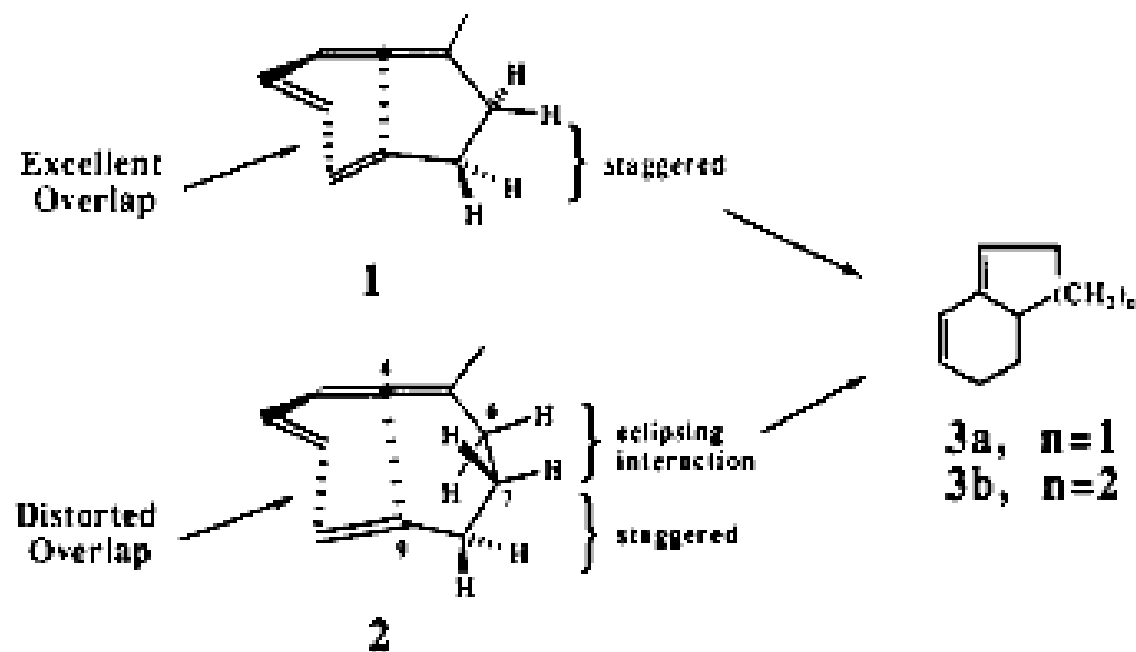
- An example of a [4+2] cycloaddition with the allene as the diene
- Demonstrated the feasibility of chiral transfer from an asymmetric allene to an sp^3 carbon in a natural product synthesis



(+)-Sterpurene

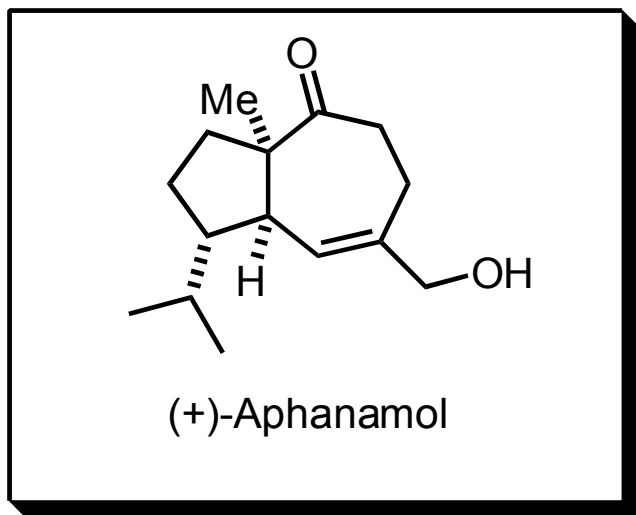
Tether Length Affects Facility of DA

Scheme 1



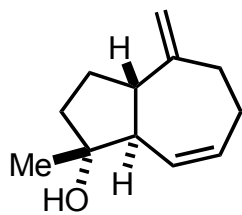
Molecular modeling suggests a shorter tether facilitates the Diels-Alder reaction due to better orbital overlap and the absence of eclipsing hydrogens.

Total Synthesis of (+)-Aphanamol

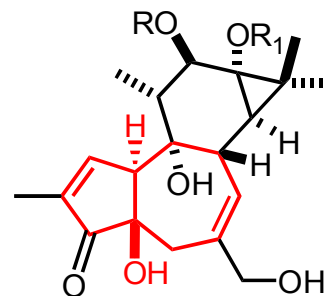


Constructed via rhodium catalyzed [5+2] cycloaddition of an allene and a vinylcyclopropane

Rh [5+2] cycloadditions as a general route to 5,7 ring systems:

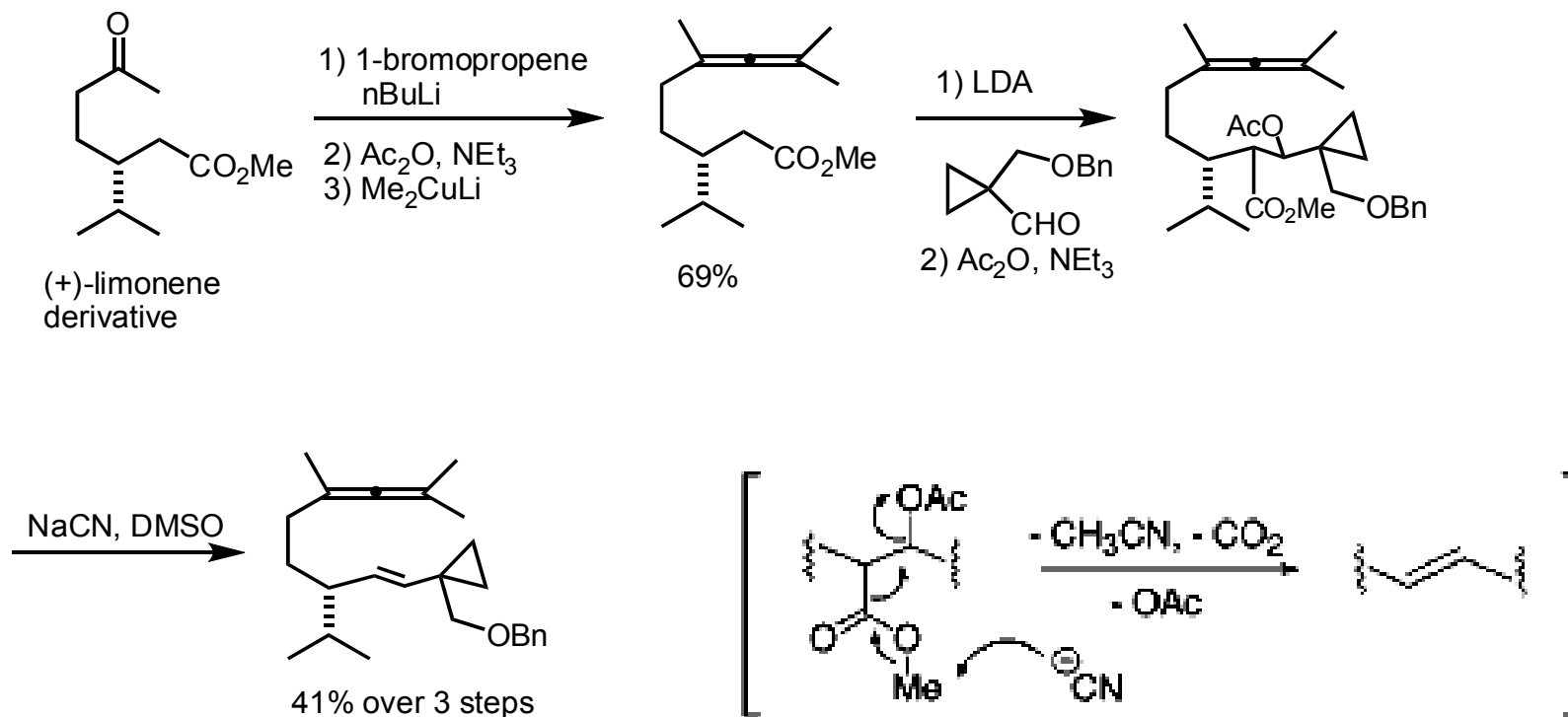


Dictamnol



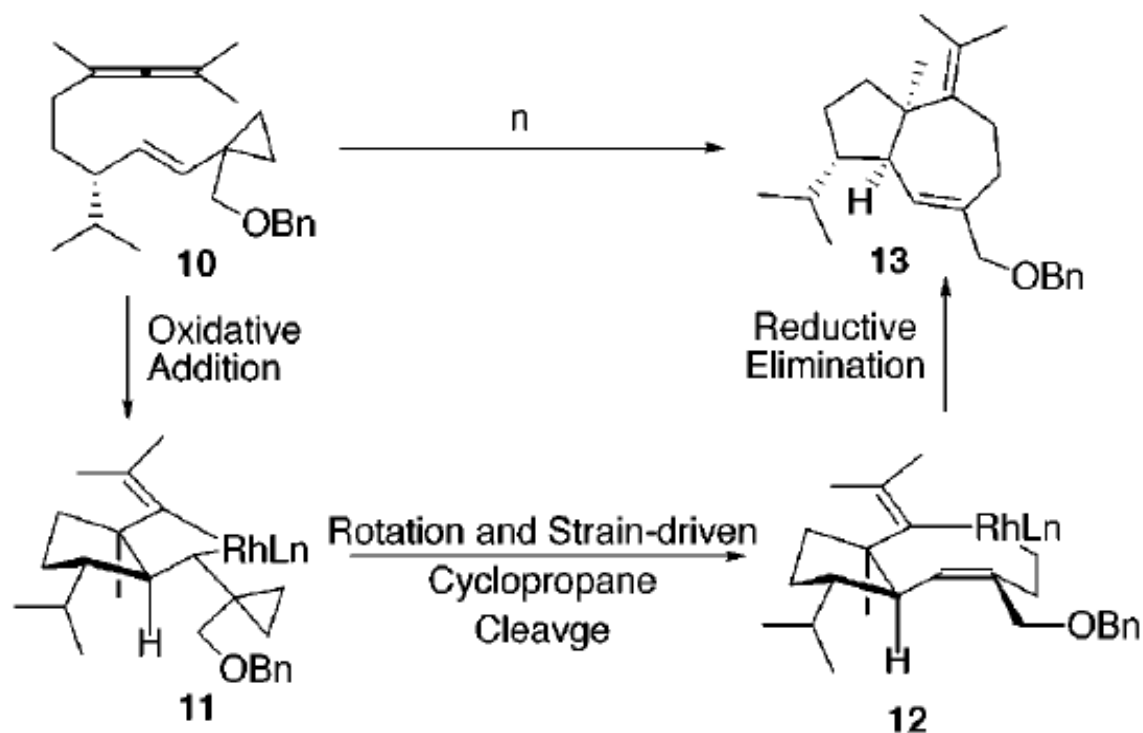
Phorbol Esters

Total Synthesis of (+)-Aphanamol



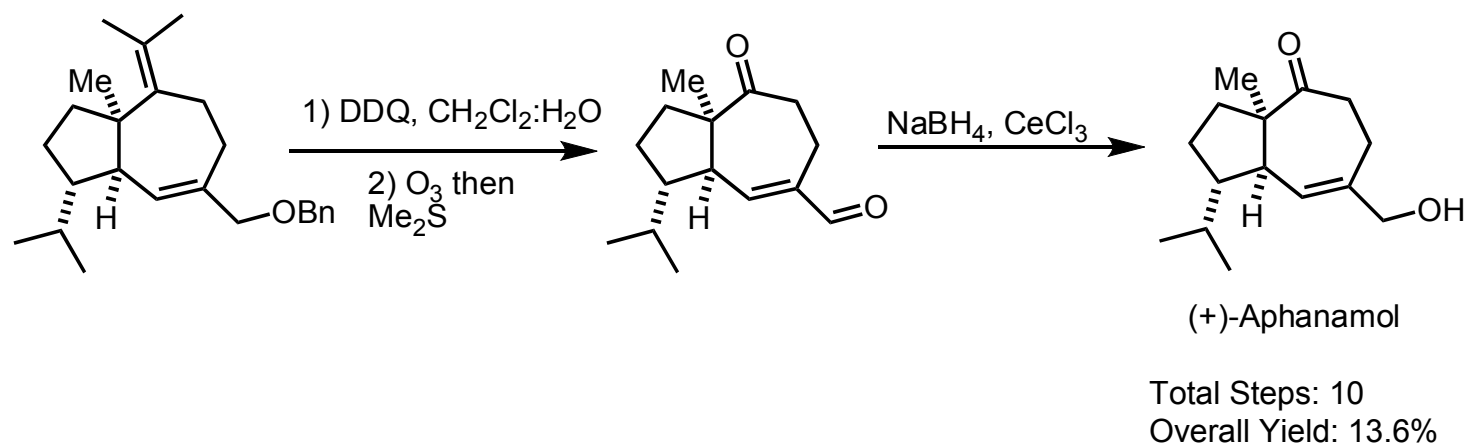
Wender et al. *Org. Lett.* **2000**, 2, 2323-2326.

[5+2] Reaction Mechanism



- Catalyst may reversibly coordinate either *pi* face of alkene
- One of two diastereomeric complexes produces cis-fused metallocycle with isopropyl substituent pseudoequatorial
- Strain-driven cleave of cyclopropyl bond furnished a new metallocycle
- Reductive elimination results in 5,7 cis ring fusion

Final Steps

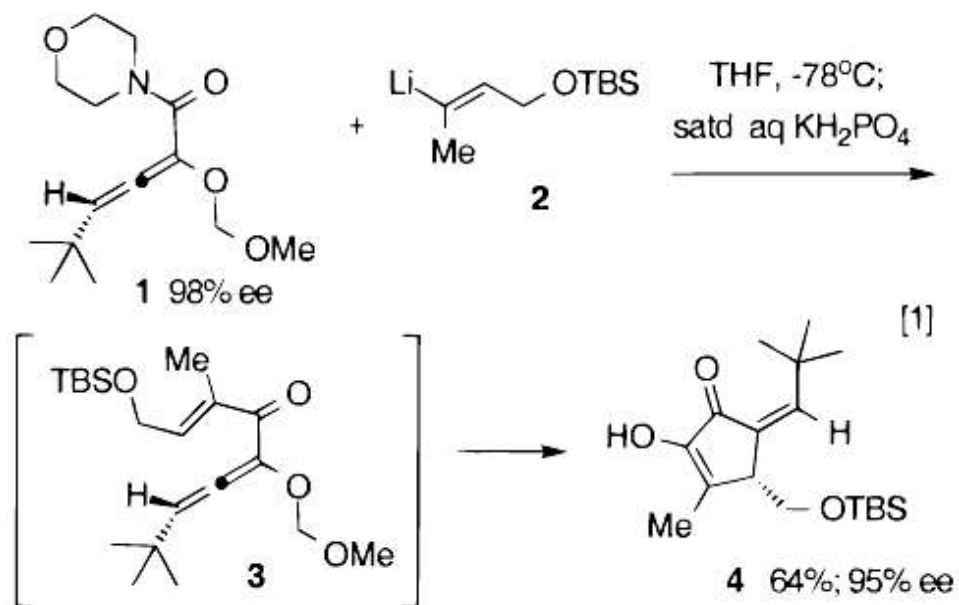


Synthesis Highlights:

- First use of tetrasubstituted allene in [5+2] cycloaddition
- Control of stereochemistry was achieved with tether substituent

Wender et al. *Org. Lett.* **2000**, 2, 2323-2326.

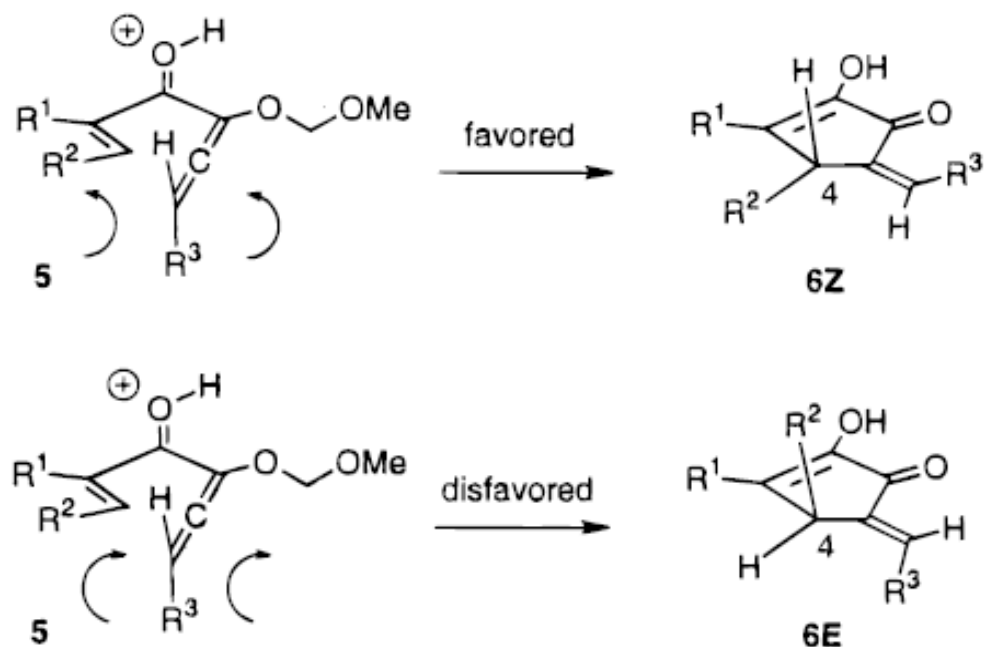
Allenes in Nazarov Cyclizations



- Axial chirality of the allene component transferred to the tetrahedral ring carbon of product
- Allene must be stereogenic (γ -substituted)

Tius et al. *J. Am. Chem. Soc.*, **1999**, *121*, 9895-9896.

Allenes in Nazarov Cyclizations

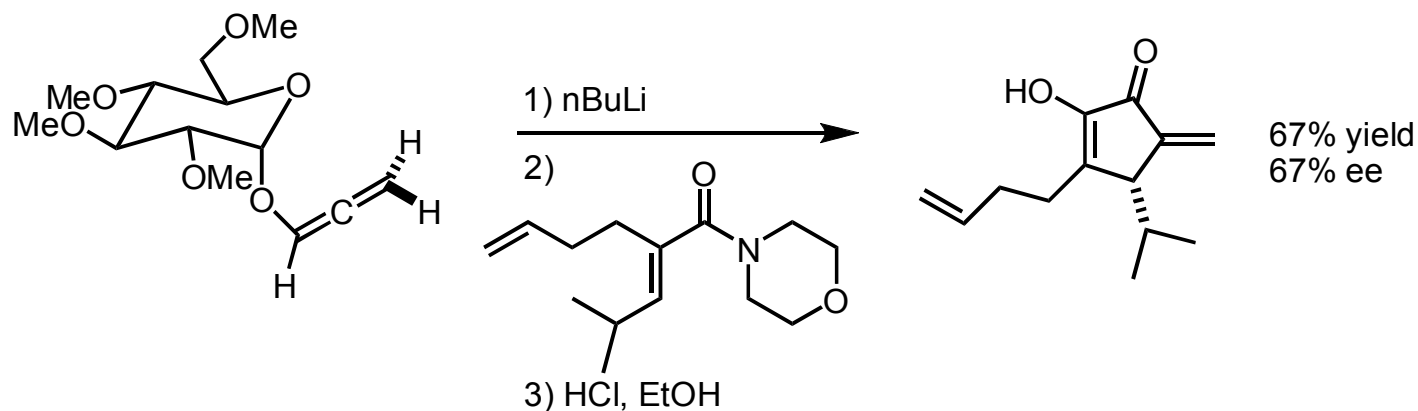


- Two allowed modes for conrotatory ring closure
- Steric bias favors route to **6Z**
- Strong kinetic preference observed for Z exocyclic double bond in product

Chiral Auxillary on the Allene

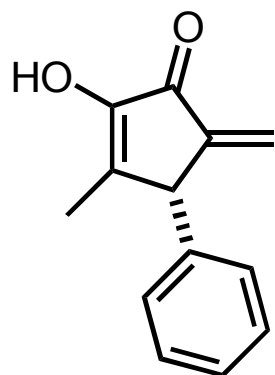
Goal: Development of an enantioselective Nazarov that generates an unsubstituted double bond in the product

Strategy: Use a chiral carbohydrate auxillary on the allene

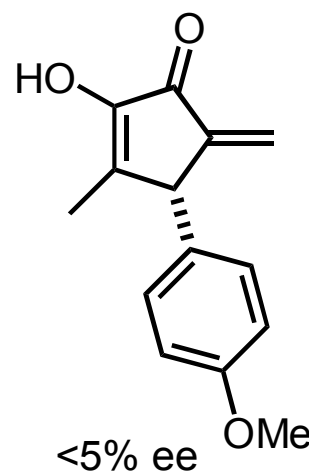


Tius et al. *Org Lett.* **2000**, 2, 2447-2450.

Some Curious Results



42% ee

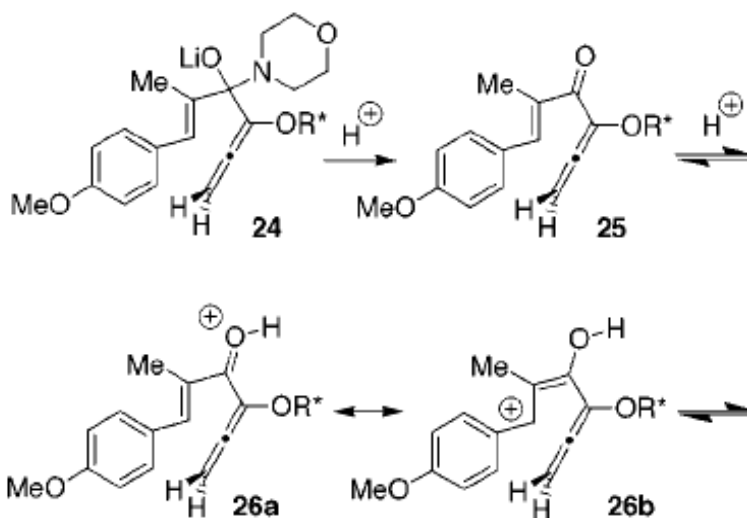


<5% ee

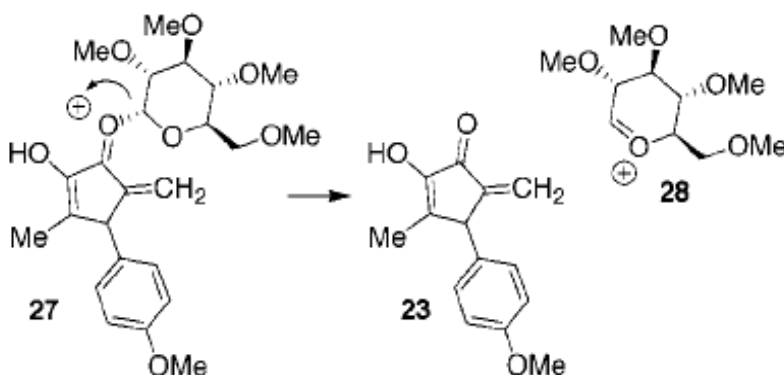
Use of *p*-methoxy substituted substrate resulted in racemic Nazarov product!

Enhanced Stability of Intermediate Cation Results in Loss of Enantioselectivity

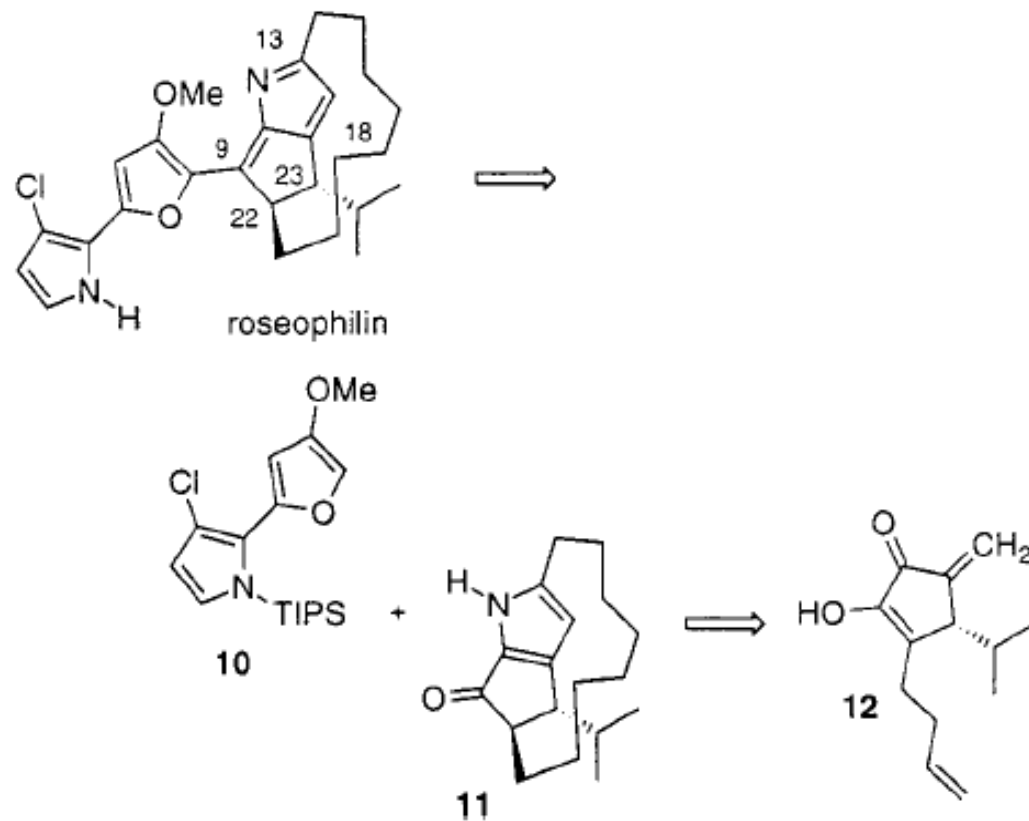
Longer lifetime of cationic intermediate **26** results in reduced enantioselectivity



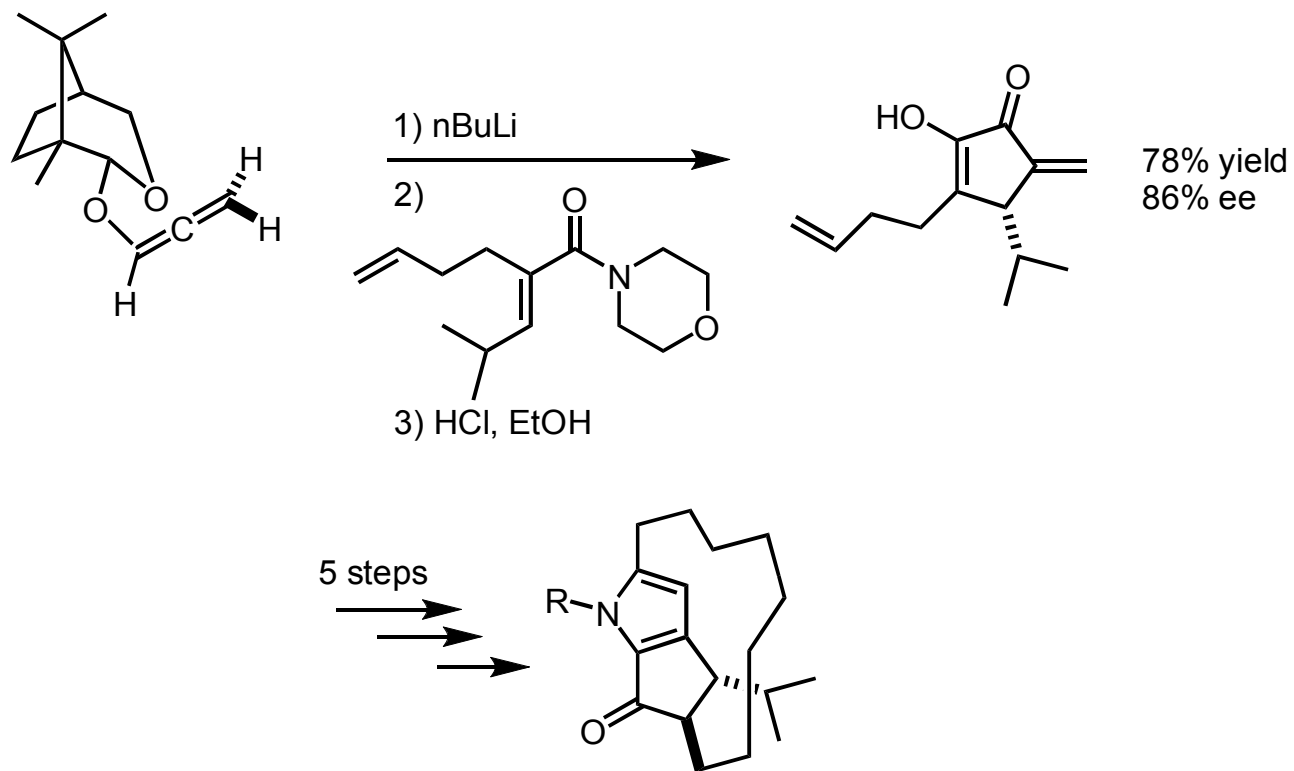
Switching the solvent from THF to EtOH fixed this issue.



Application to Synthesis of Roseophilin



Application to Synthesis of Roseophilin



Tius et al. *J. Am. Chem. Soc.*, **2001**, *123*, 8509-8514.

Suggested Reviews

Krause and Hashmi. *Modern Allene Chemistry Vol I: Synthesis of Allenes*. Wiley-VCH, Weinheim: 2004.

Krause and Hashmi. *Modern Allene Chemistry Vol II: Reactions of Allenes*. Wiley-VCH, Weinheim: 2004.