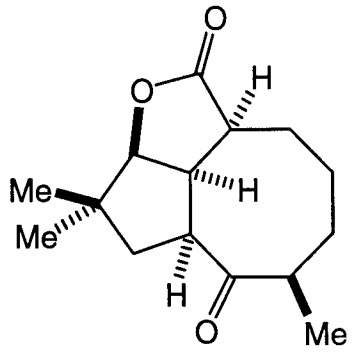
Total Syntheses of Asteriscanolide

Sam Pham, 27. Feb. 2001

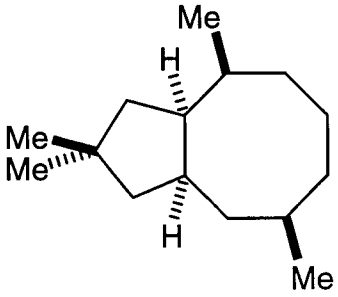


Isolated from the methanol/hexane extract of *Asteriscus aquaticus*

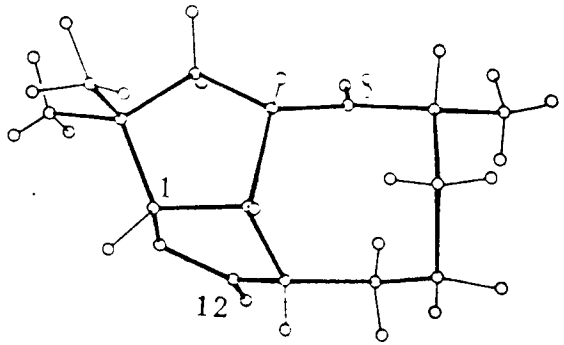
Relative configuration was determined by NMR experiments

Absolute configuration was determined through X-ray crystallographic analysis

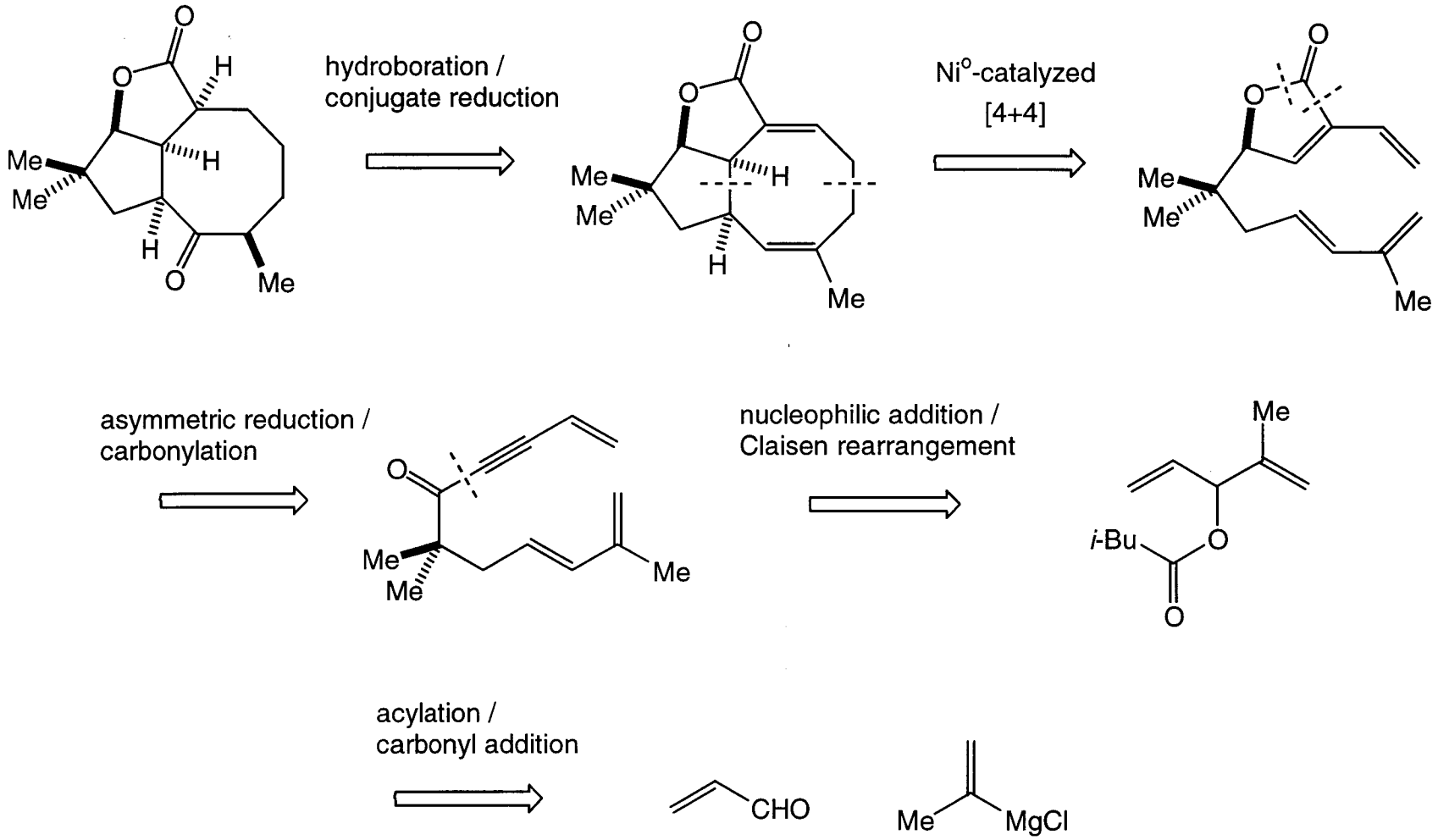
The natural compound contains 5 stereogenic centers, 4 of which are contiguous



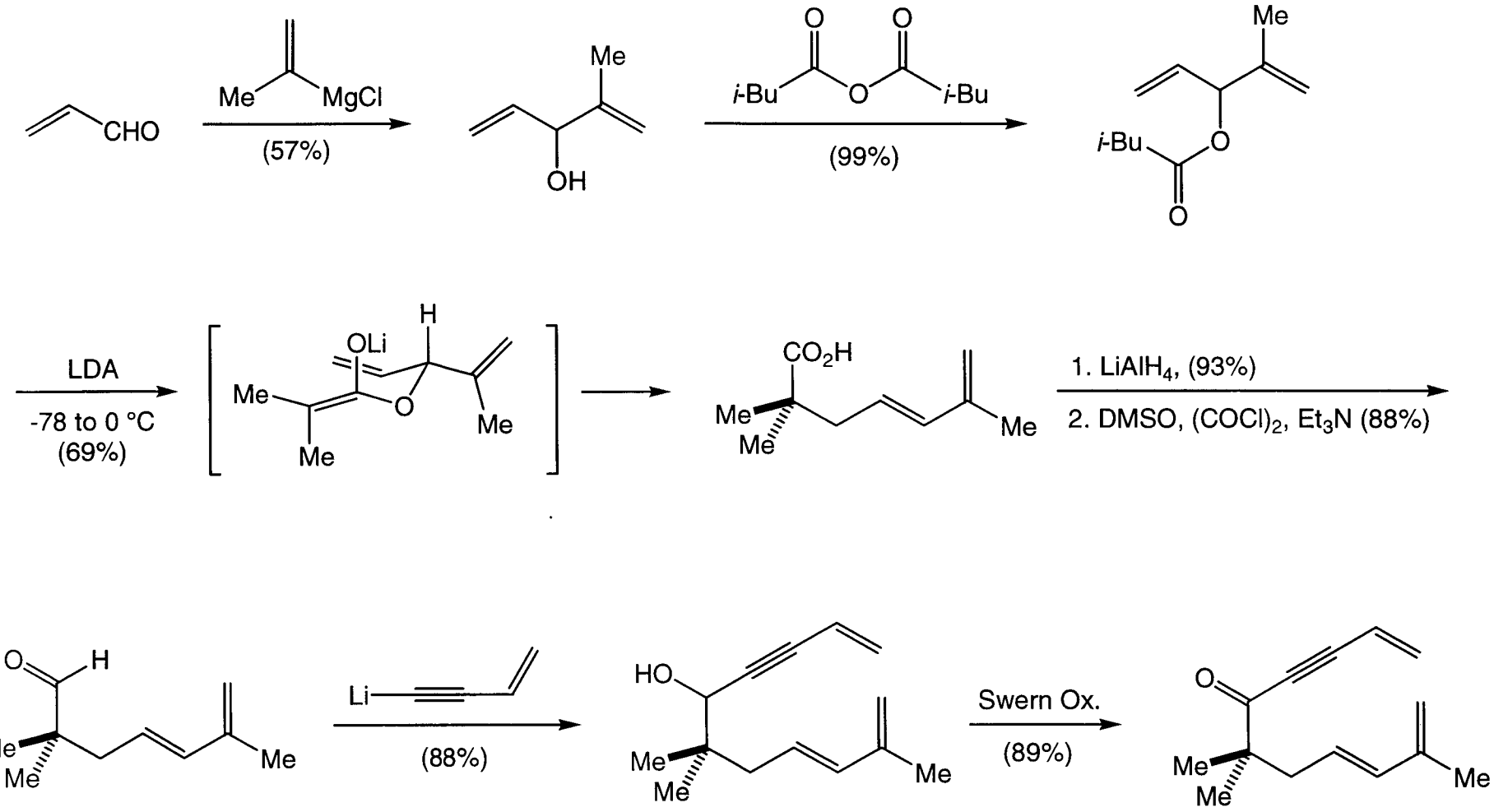
Related to a class of synthetic compounds, with the carbon backbone referred to as asteriscane



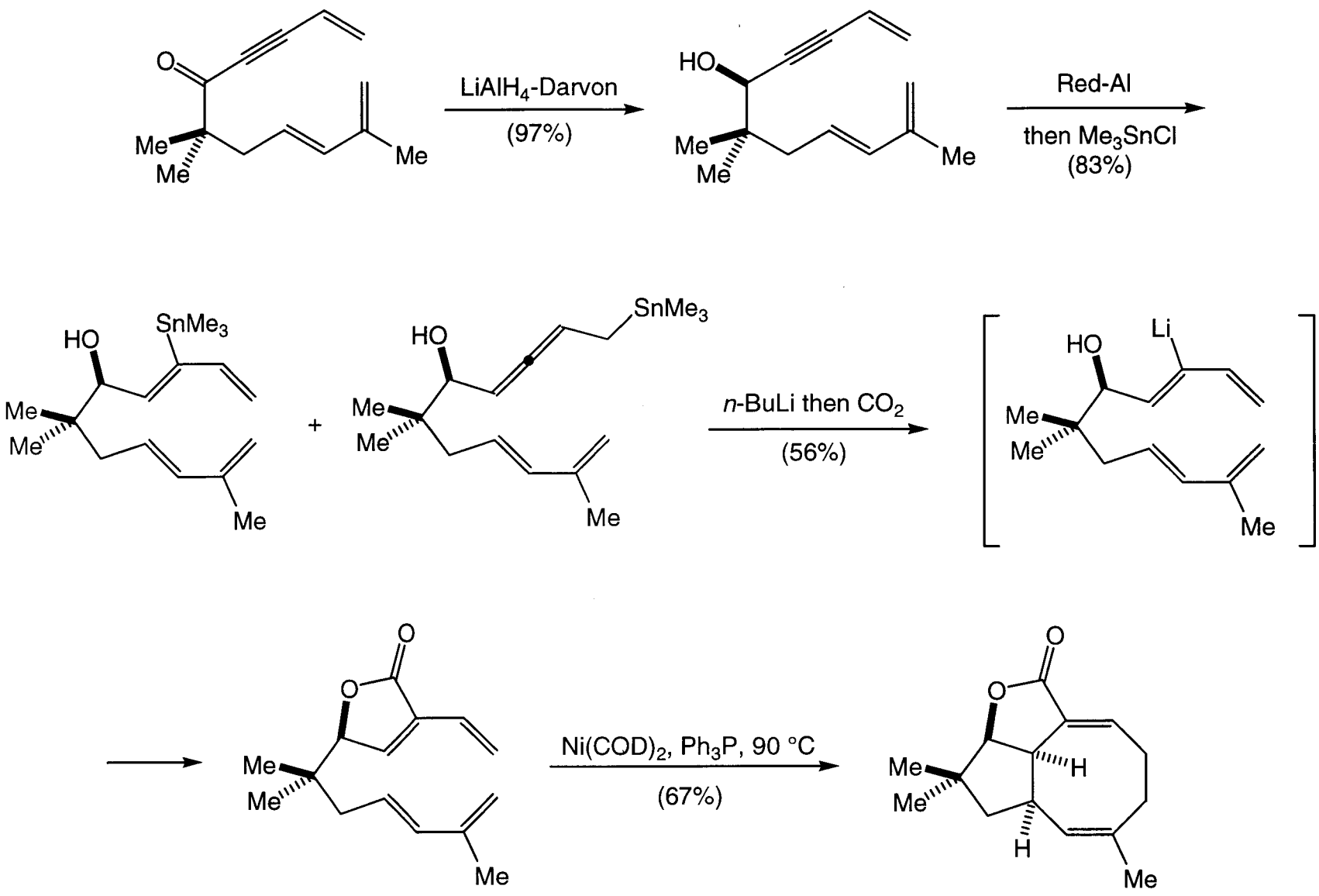
Wender: Retroanalysis



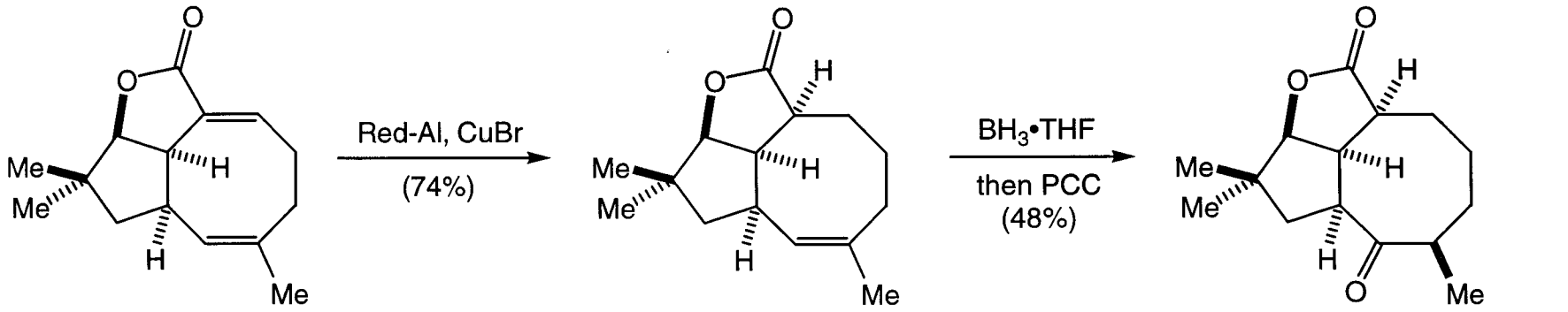
Wender: Total Synthesis



Wender: Total Synthesis, Part 2

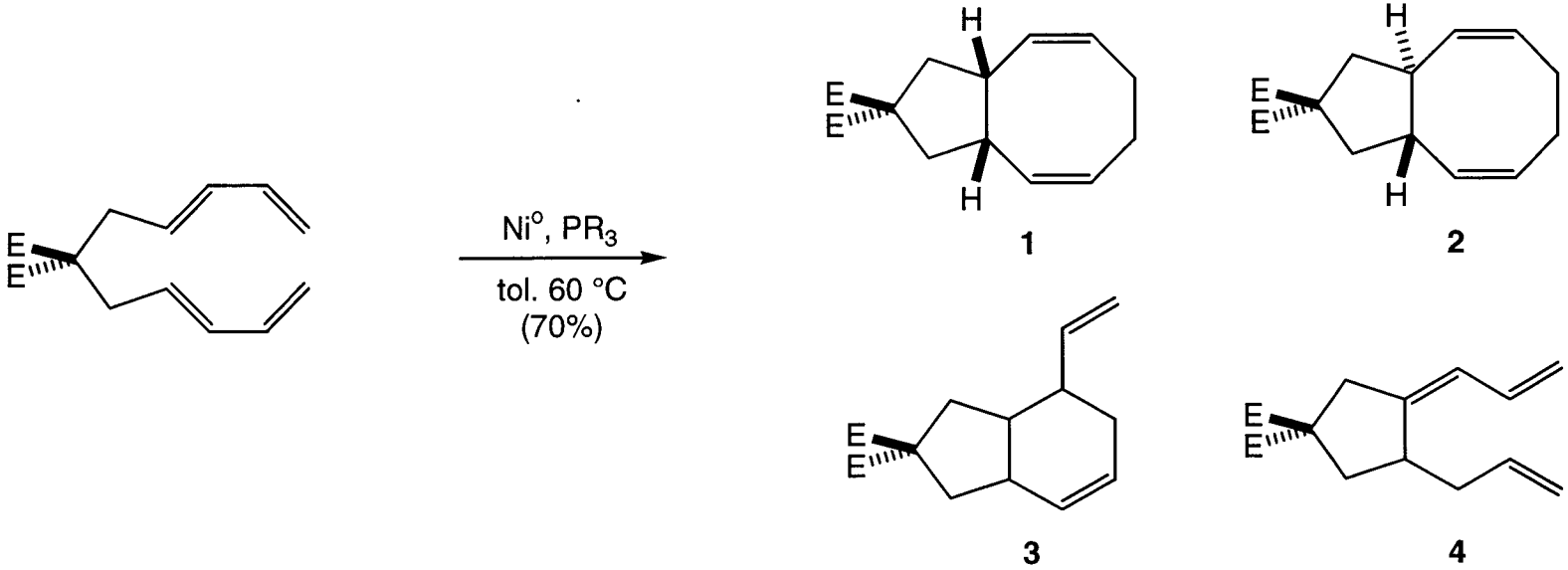


Wender: Total Synthesis, Part 3



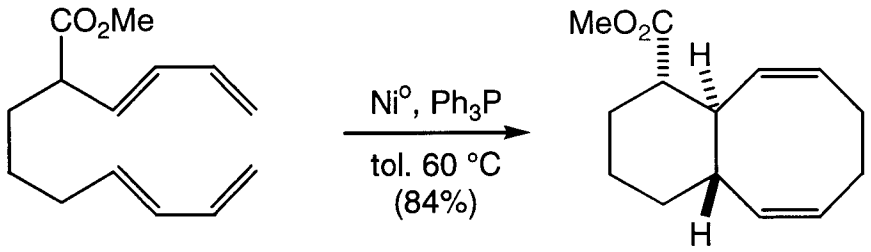
13 steps overall; 2.7% overall yield to afford (+)-Asteriscanolide

Early Studies on Ni(0)-Catalyzed [4+4] Cycloadditions



- When using $Ni(COD)_2$ and Ph_3P, 1:3, 11 mol % in Ni^0, **1** and **2** were the sole products in ratios as high as 40/1

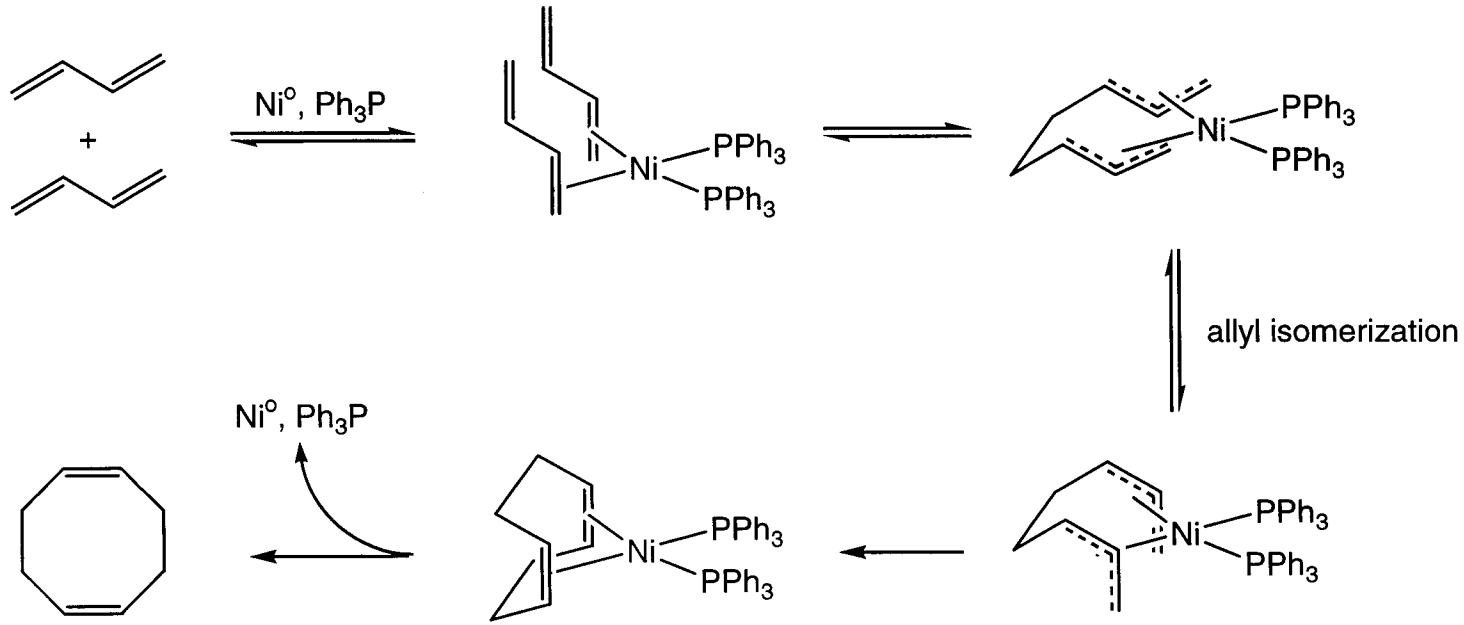
- Using more electron rich phosphines, ie: (o-Tol)$_3$P gave **3** or **4** as only products in low yields, depending upon the Ni^0/phosphine ratio



95/5 exo/endo, favoring trans-fusion
99/1 stereoinduction

When substituent is one carbon removed, cycloaddition still favors trans-fusion, but with only 2/1 stereoinduction

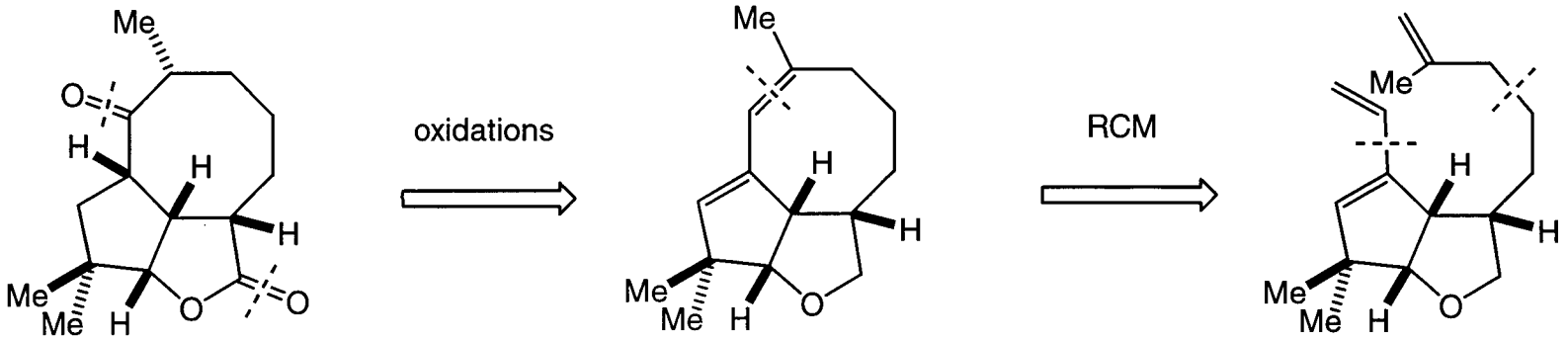
Mechanism of [4+4] Cycloaddition

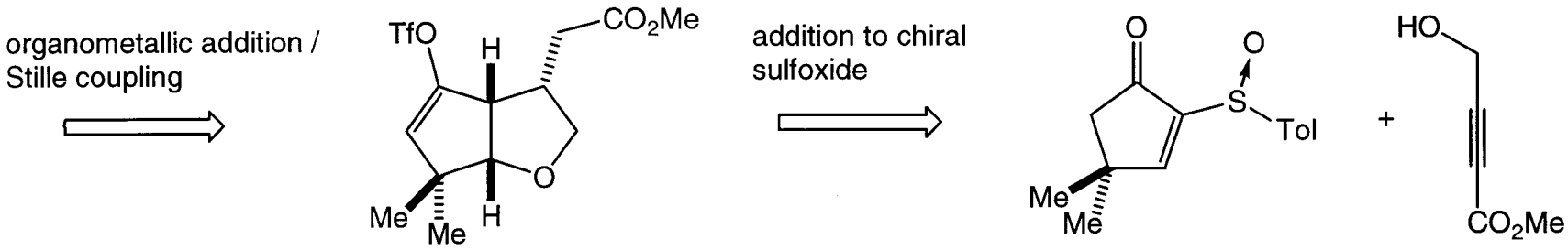


- Additional studies have determined the stereoselectivity to be thermodynamically governed through a series of reversible η^1, η^3 complexes

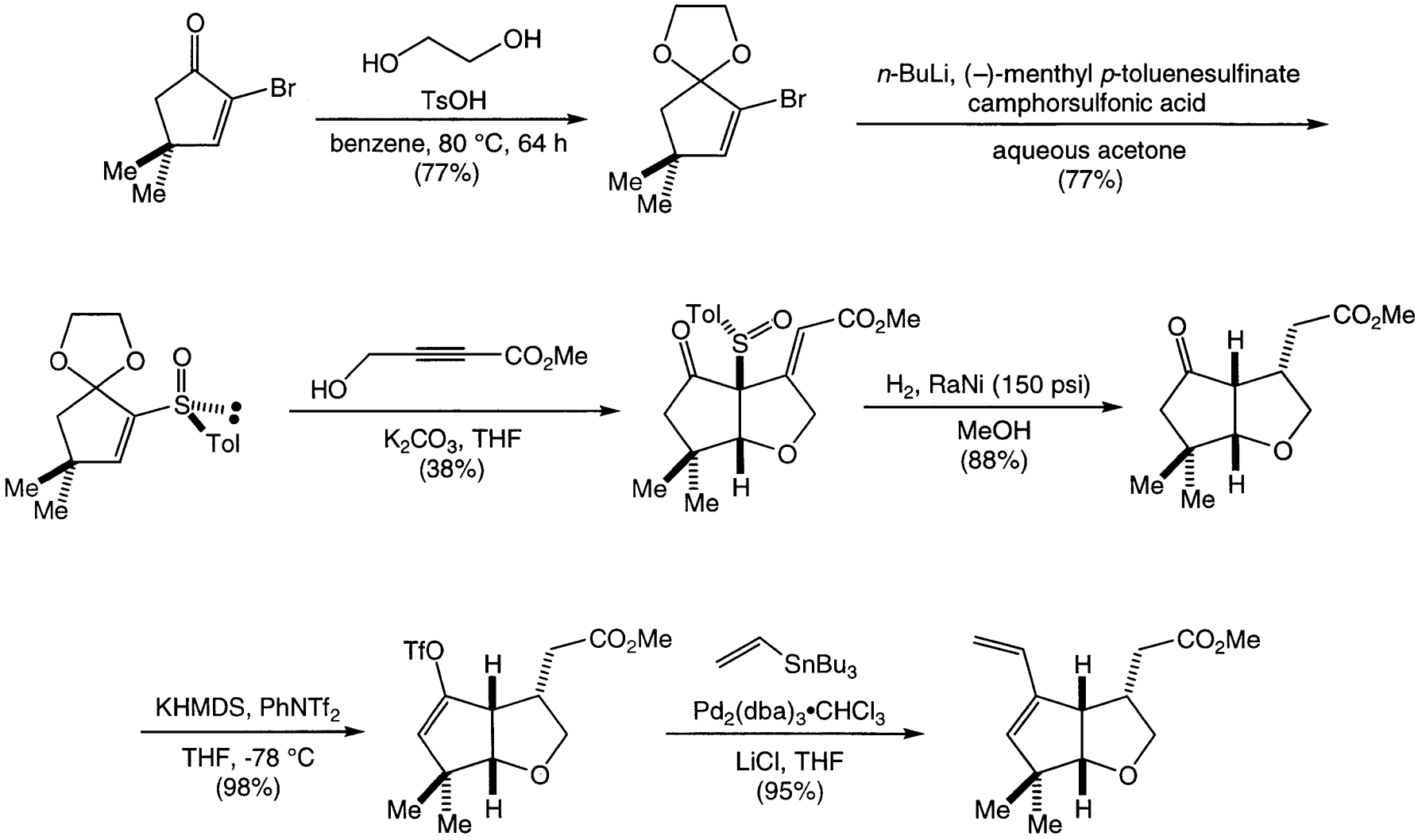
- The final σ-bond forming step is likely to be irreverisble since products cannot be further isomerized once formed

Paquette: Retroanalysis

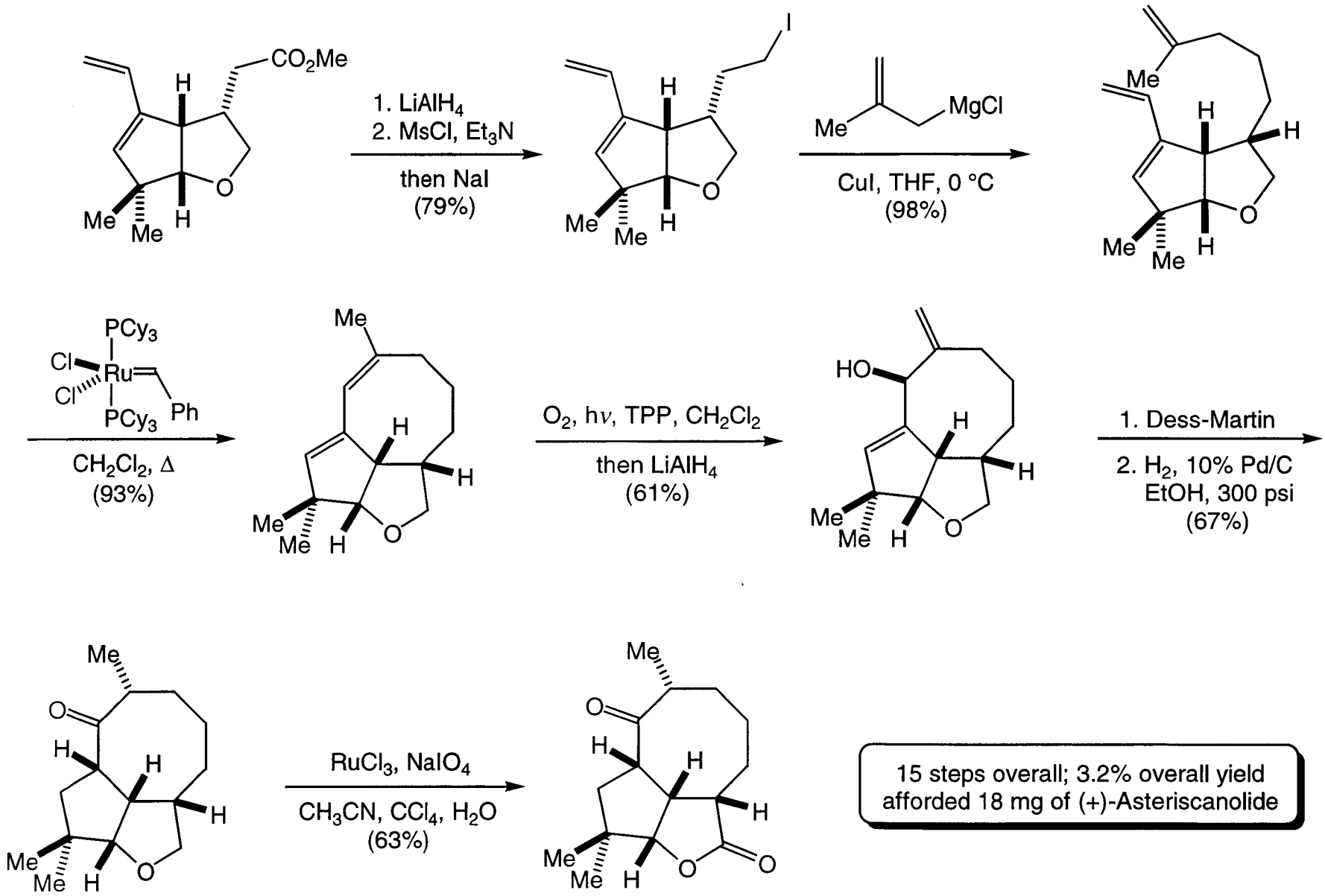




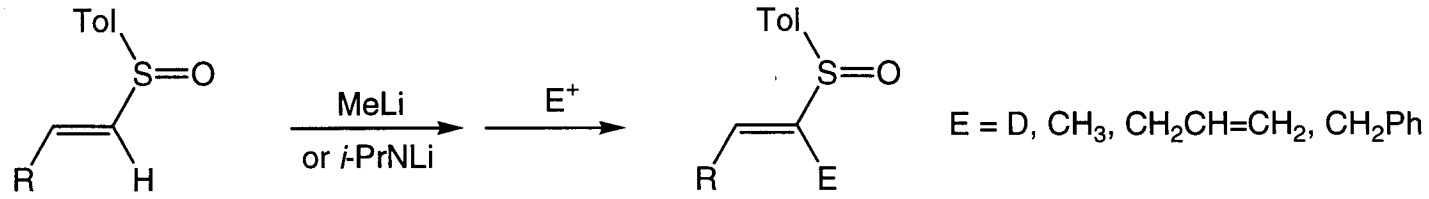
Paquette: Total Synthesis



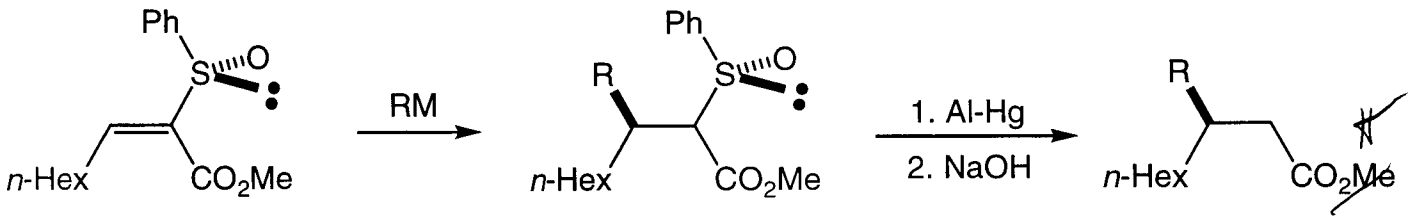
Paquette: Total Synthesis, Part 2



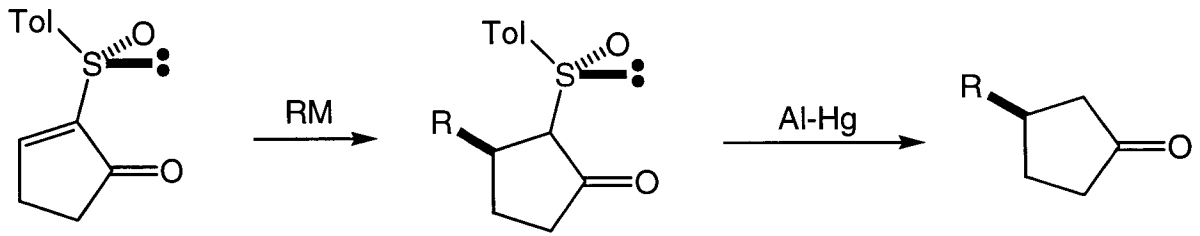
Additions to Chiral Vinyl Sulfoxides



Insufficient polarization of 2-alkenyl sulfoxides led to metallation followed by trapping with electrophiles over addition



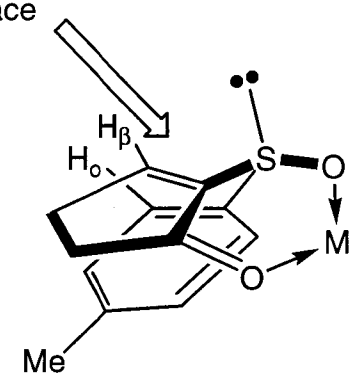
RM	ee, %
Me_2CuMgI	61
Me_2CuLi	65
$n\text{-}Bu_2CuLi$	59



RM	ee, %
$EtMgCl / ZnBr_2$	80
$EtTi(Oi\text{-}Pr)_3$	>98
$CH_2{=}CHMgBr$	>98
$PhMgCl / ZnBr_2$	92
2-NaphMgBr	>98

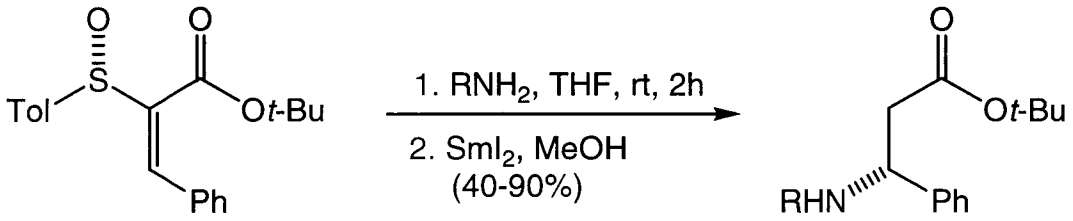
Transition State Model and Non-Carbon Nucleophiles

Addition on top face



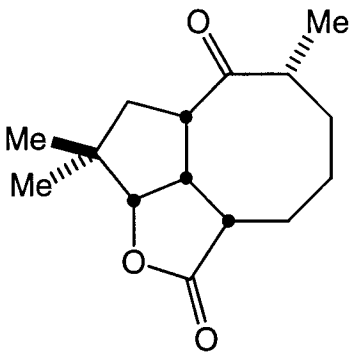
Observe downfield shift in H_β and C_β resonances when $ZnBr_2$ is added, suggestive of chelate. Also, a 7% NOE enhancement is observed between H_β and H_o in the presence of $ZnBr_2$.

Addition to chiral vinyl sulfoxides using nitrogen nucleophiles:

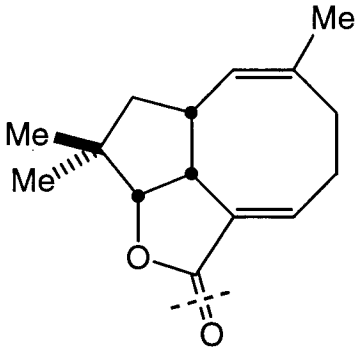


RNH_2	ee, %
NH_3	74
$C_6H_5CH_2NH_2$	52
$H_2N(CH_2)_3NH_2$	62
$H_2N(CH_2)_4NH_2$	89

Snapper: Retroanalysis

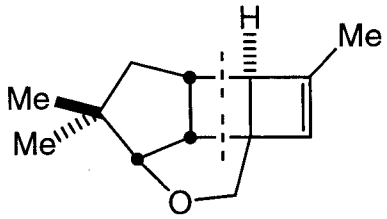


hydroboration /
conjugate reduction

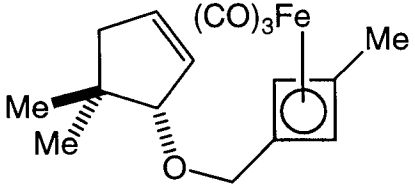


Wender Intermediate

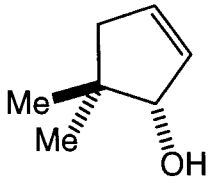
allylic oxidation /
[3,3]-rearrangement /
ROM

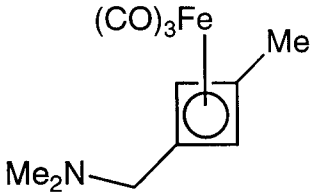


[2+2]

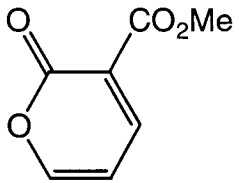


nucleophilic
addition

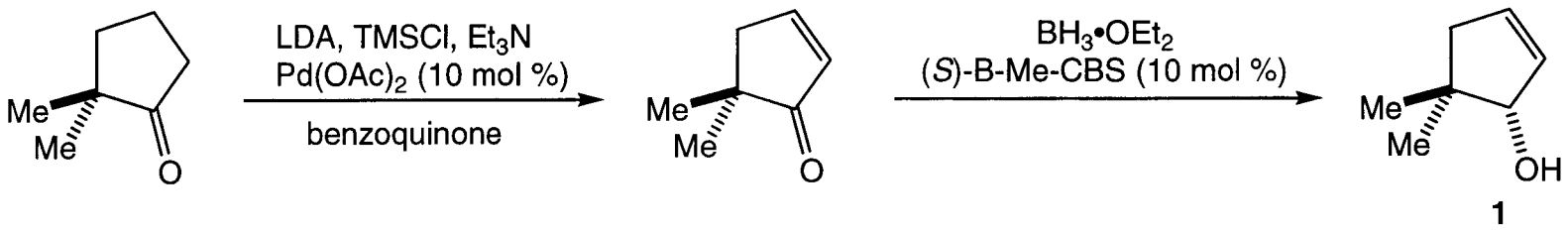


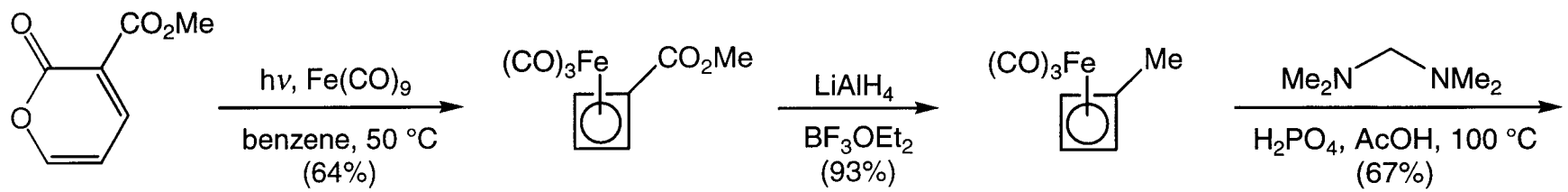


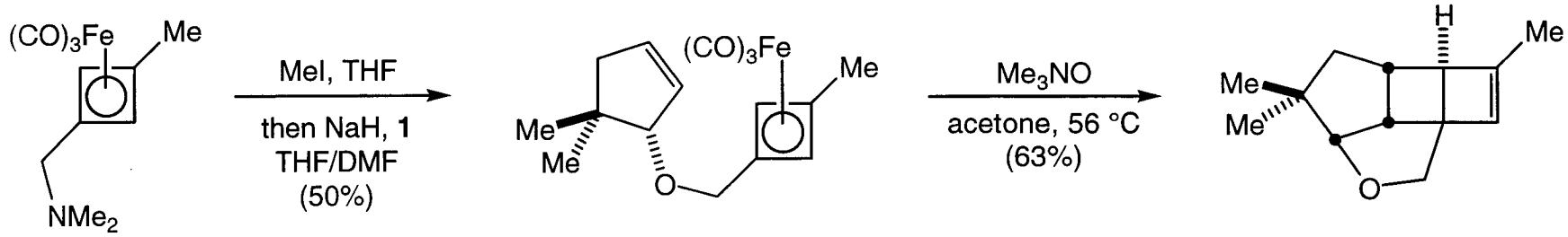
photolytic formation
of cyclobutadiene



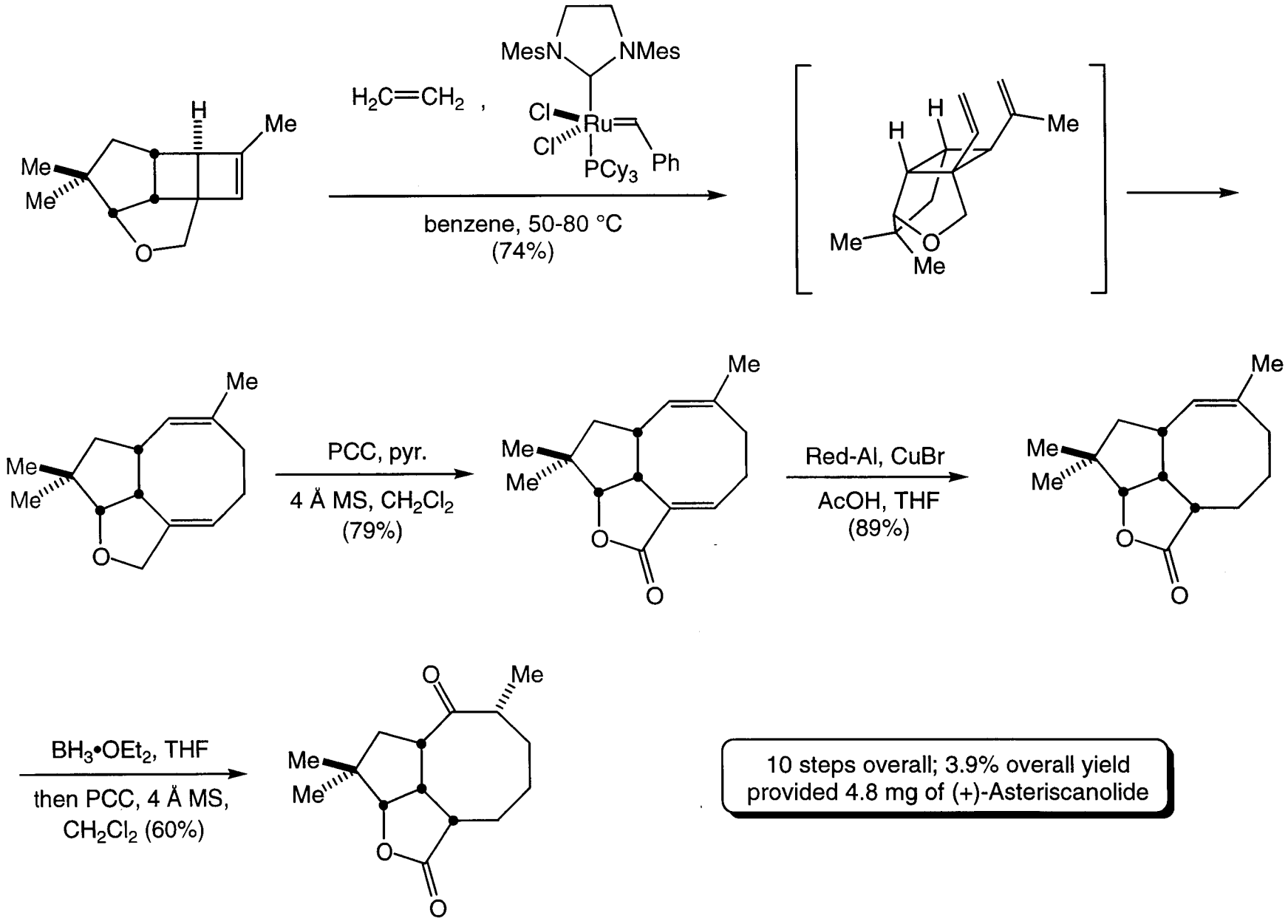
Snapper: Total Synthesis



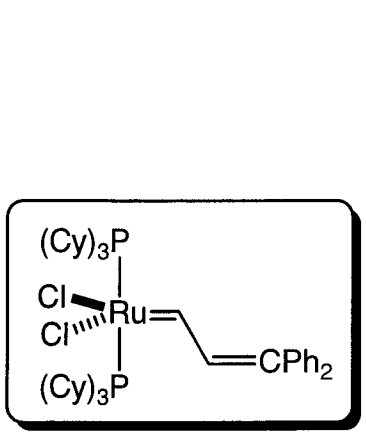


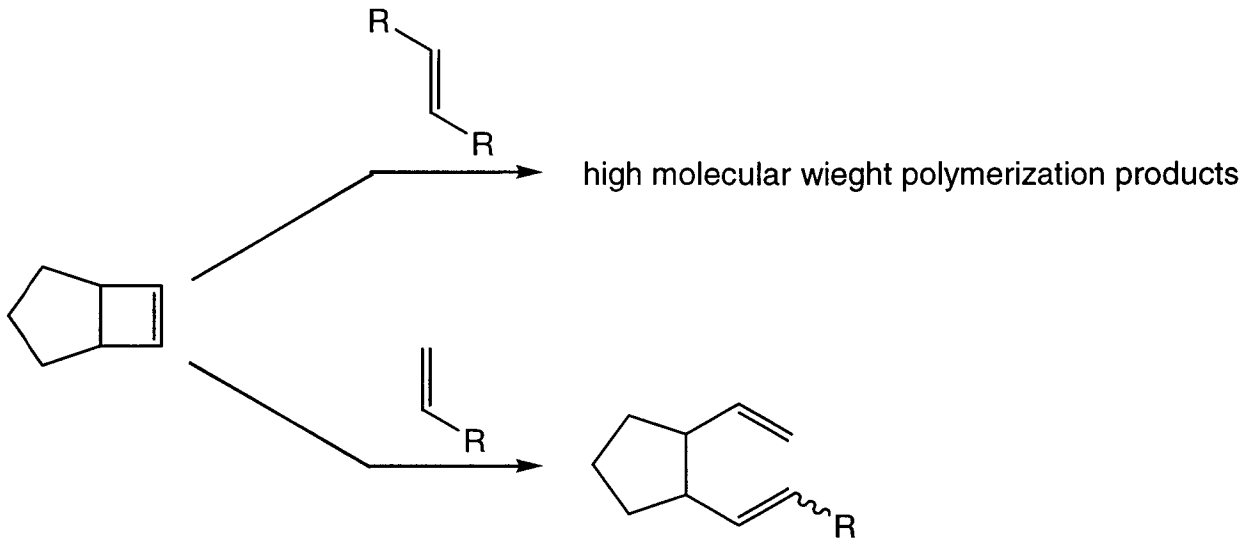


Snapper: Total Synthesis, Part 2

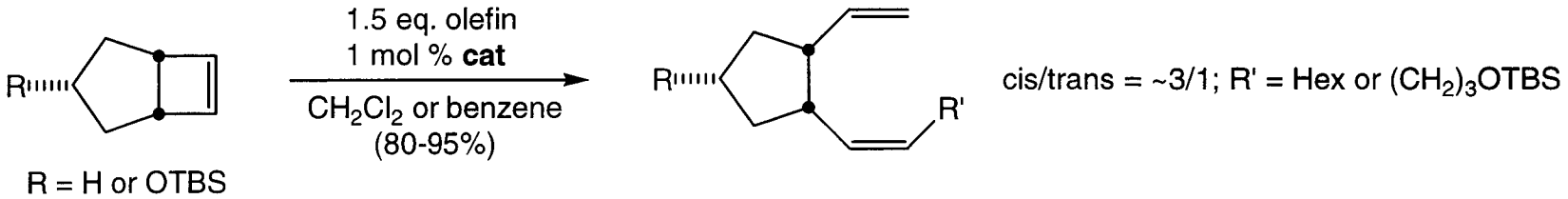


Early Studies on Ring Opening Cross-Metathesis

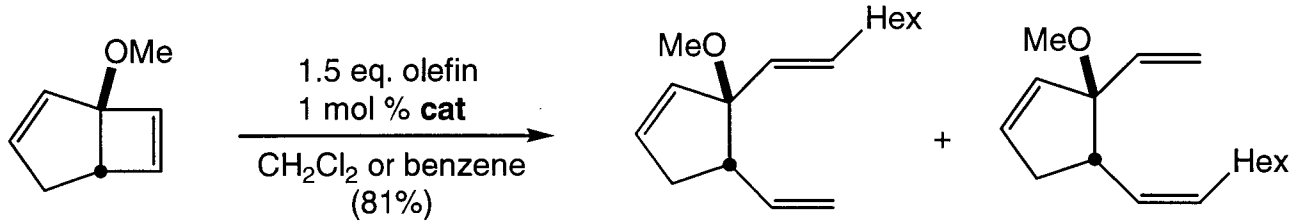




Use of terminal olefins afforded the monomeric cross-metathesis product; self-metathesis products were only observed once cyclobutene was consumed

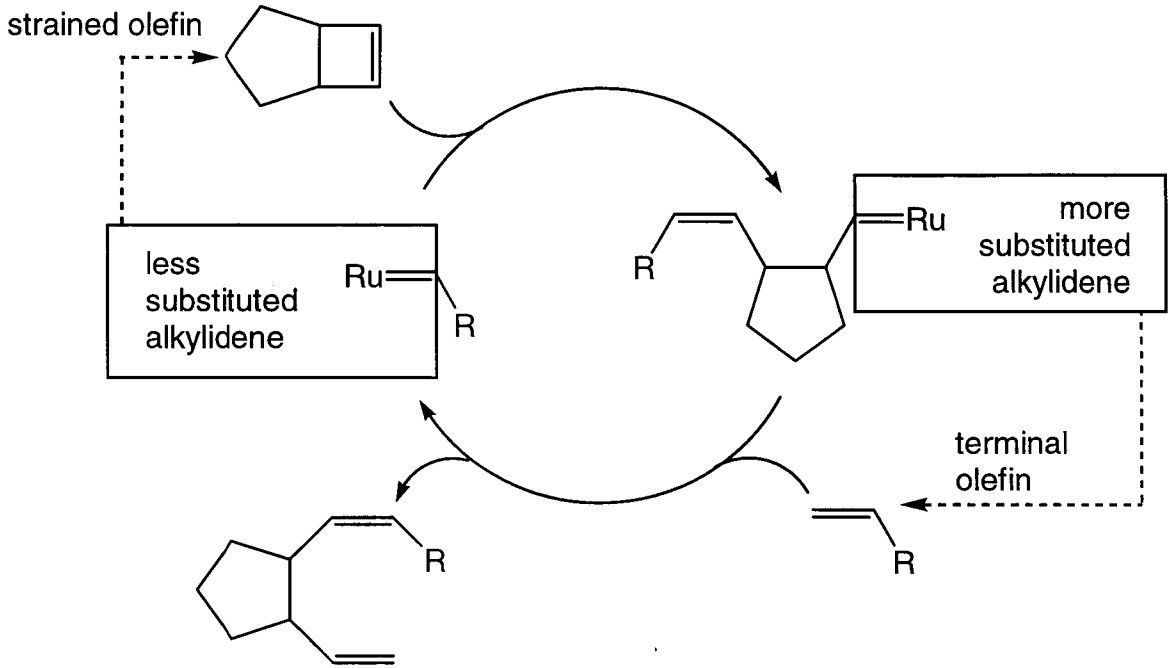


R = H or OTBS

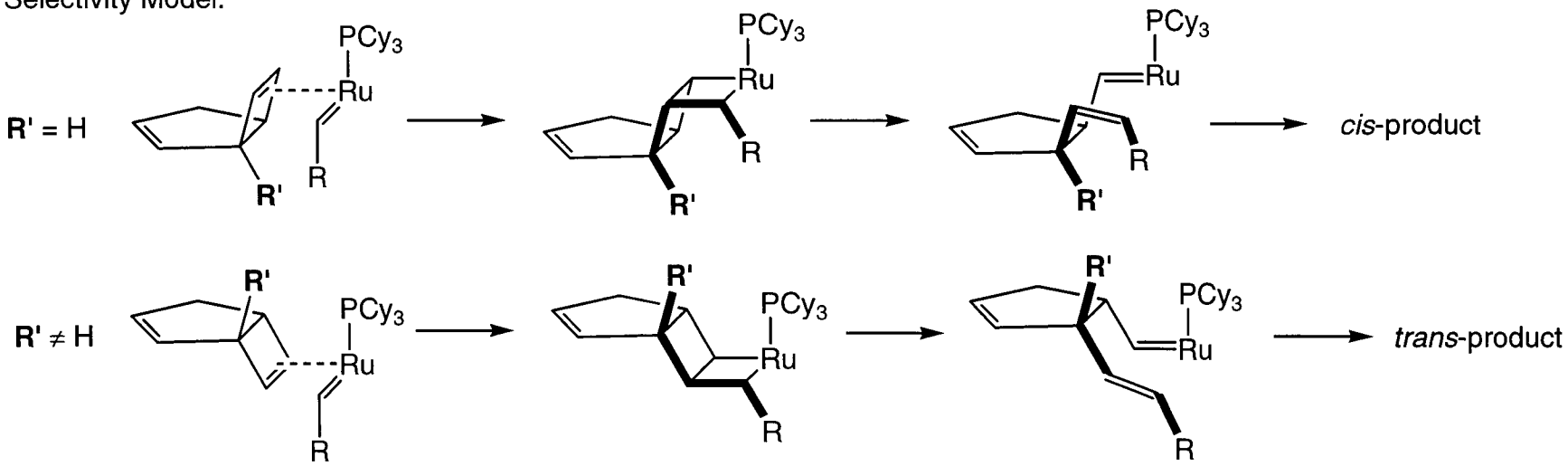


products formed in 4/1 with 9/1 trans/cis-selectivity

Mechanism and Selectivity Model



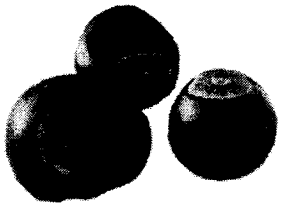
Selectivity Model:



Tale of the Tape

13 steps overall; 2.7% overall yield
Utilized an asymmetric $LiAlH_4$/Darvon reduction to set the first stereogenic center
Formed 8 membered ring via a formal [4+4] cycloaddition using Ni^0

10 steps overall; 3.9% overall yield afforded 4.8 mg
Utilized a CBS-borane reduction to set the first stereogenic center
Formed the 8 membered ring via a Ru-catalyzed ring opening cross-metathesis



15 steps overall; 3.2% overall yield afforded 18 mg
Utilized an asymmetric addition to a chiral vinyl sulfoxide to set the first stereogenic center
Formed the 8 membered ring via a Ru-catalyzed ring closing cross-metathesis

References

Isolation:

A. San Feliciano, A. F. Barrero, M. Medarde, J. M. Miguel del Corral and A. Aramburu *TL*, 1985, 26, 2369.

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Haruo Matsuyama, Nobuhiro Itoh, Masato Yoshida, Nobumasa Kamigata, Sigeru Sasaki and Masahiko Iyoda *Chem. Lett.* **1997**, 375.

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John A. Tallarico, Michele L. Randall and Marc L. Snapper *Tetrahedron* **1997**, *53*, 16511.