

2,3-Sigmatropic Rearrangements in Organic Synthesis

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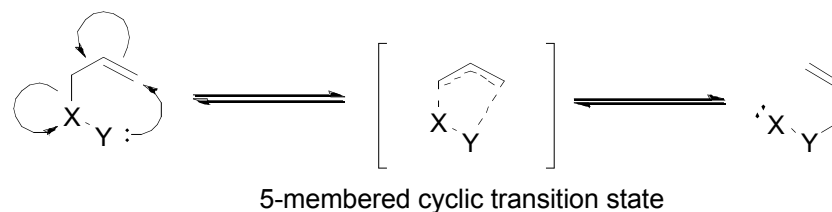
Crimmins Group

Sigmatropic Rearrangements

- concerted pericyclic reactions traditionally thought to be governed by orbital symmetry
- a group attached by a sigma bond migrates to the terminus of an adjacent pi-electron system

2,3-sigmatropic rearrangements:

- can be defined as a thermal isomerization that proceeds through a six-electron, five-membered cyclic transition state
- thermally allowed sigmatropic process according to the Woodward-Hoffman Rule*

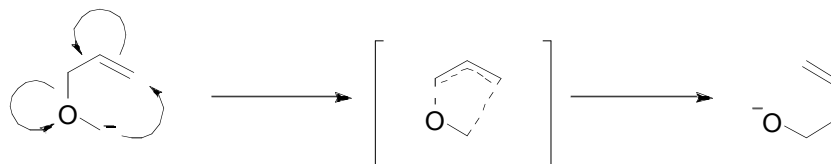


2,3-sigmatropic rearrangements discussed:

- 2,3-Wittig rearrangements
- Mislow-Evans rearrangement
- Additional 2,3 rearrangements

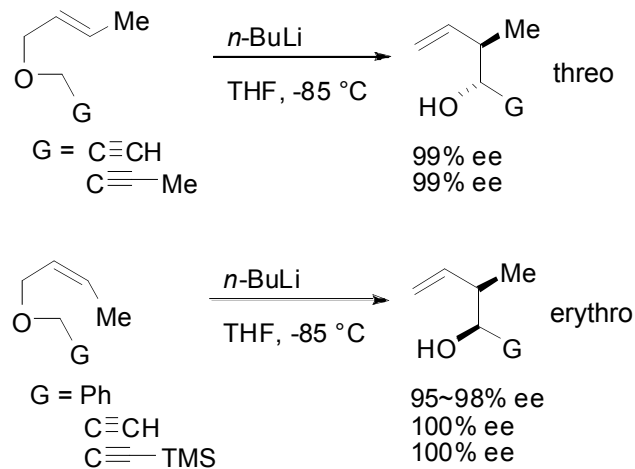
Chem. Rev.* **1986, *86*, 885-902

2,3-Wittig Rearrangement (anionic)

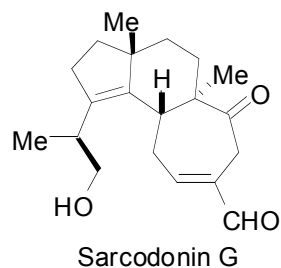


- regiospecific carbon-carbon bond formation and allylic transposition of oxygen function
- generation of specific olefin geometries
- stereoselective creation of vicinal chiral centers
- transfer of chirality
- competition is seen with 1,2-shift, dependent on substrate structure and rxn temperature

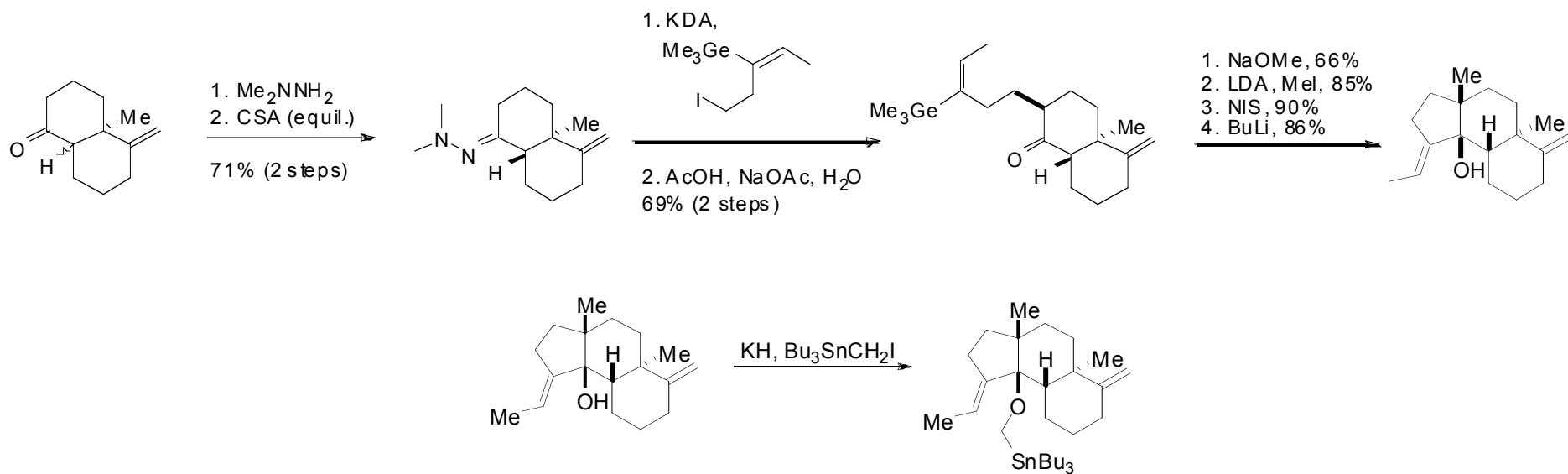
Diastereoselection Study

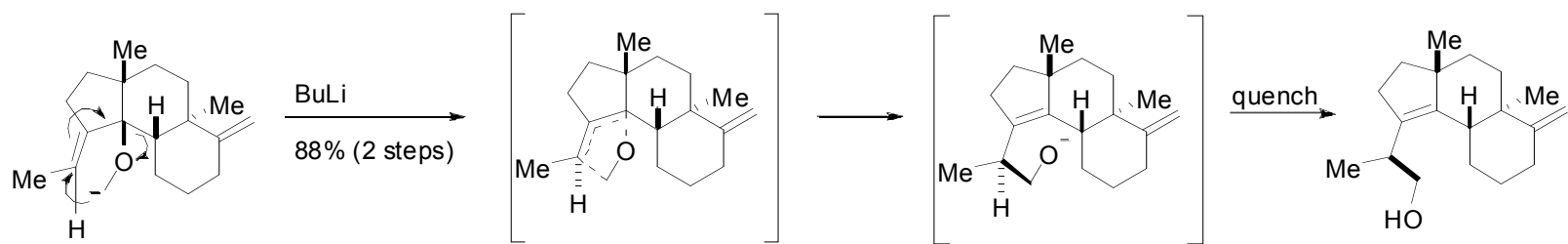


A general trend is observed that *E*-alkenes show threo selection and *Z*-alkenes show Erythro selection. Exceptions include Substrates where G = CO₂H and Ph

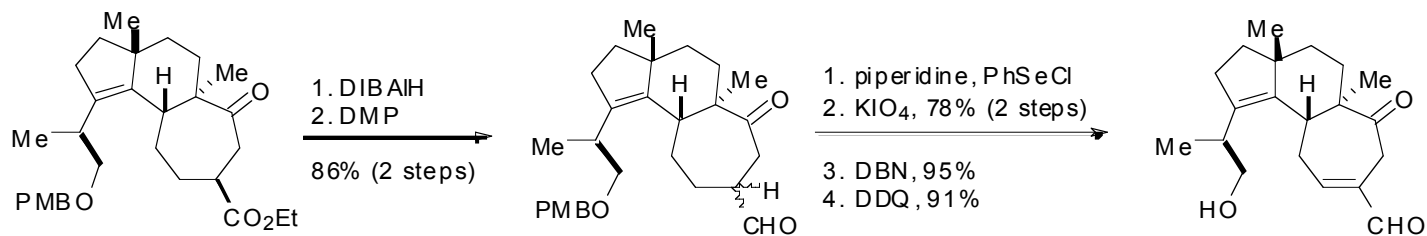
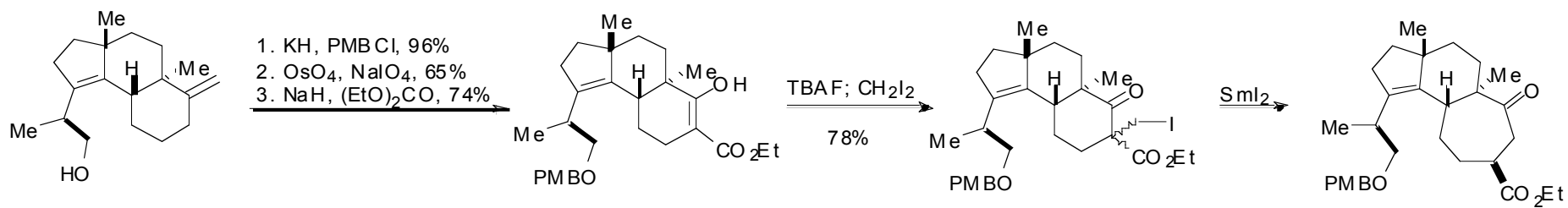


- diterpenoid from the cyathane family
- characterized by Ayer and Taube in 1972
- anti-fungal and promotes synthesis of nerve growth factor

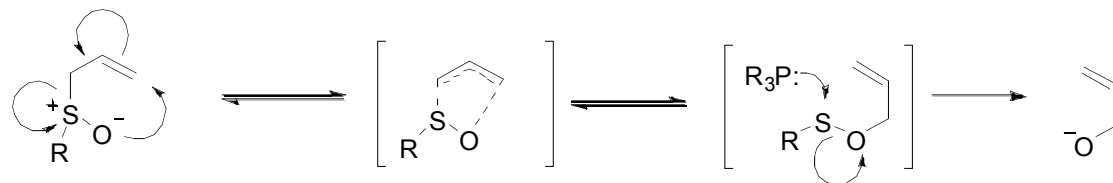




Completion of Sarcodonin G



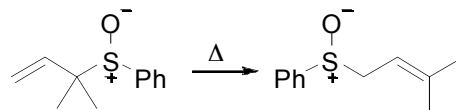
Mislow-Evans (neutral)



-it is proposed that the rearrangement proceeds exclusively through a concerted mechanism

-equilibrium lies largely to the left, sulfonate not detectable by NMR

-increased heating can result in 1,3-shift of sulfoxide:

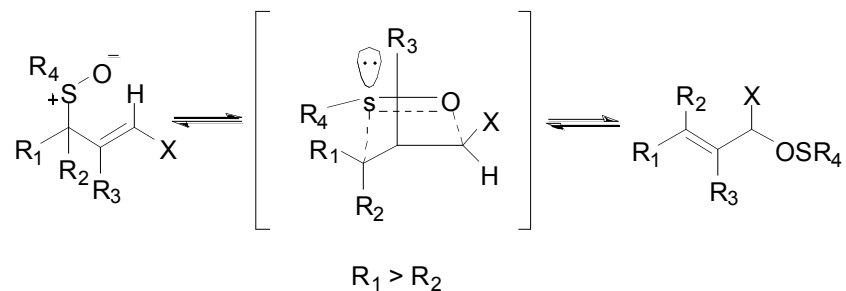


Olefin Geometry

Table I. Conversion of 2 into 3^a

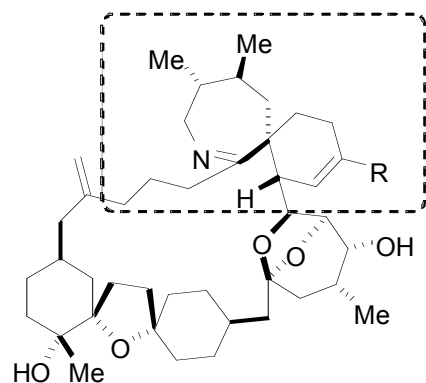
entry	2 ^b	reactn time, h	3	yield ^c	<i>E:Z</i> of 5 ^d
1		20		81	94:6
2		1.5		93	99:1
3		4		97	99:1
4		1 ^g		75	99:1
5		1.5		75	95:5
6		1.5 ^f		60	95:5
7		2.5 ^f		36 ^g	93:7

^a Reaction conditions unless otherwise noted: NaIO₄ (2 equiv), 5:1 dioxane-water, room temperature. ^b Diastereomeric mixtures (ca. 1:1) were obtained for the aldehyde adducts. ^c Isolated yields as pure (*E*)-3 after column chromatography. ^d Determined by capillary GC. ^e MoOPH (2 equiv), CH₂Cl₂, 0 °C. ^f NaHCO₃ (2 equiv) was added. ^g Yield based on 1 since 2 was used without purification due to its instability.



There is a very high *E*-olefin selectivity when there is substitution β to the sulfoxide (substitution at R₁)

Synthesis of the Imine Ring System of Pinnatoxins

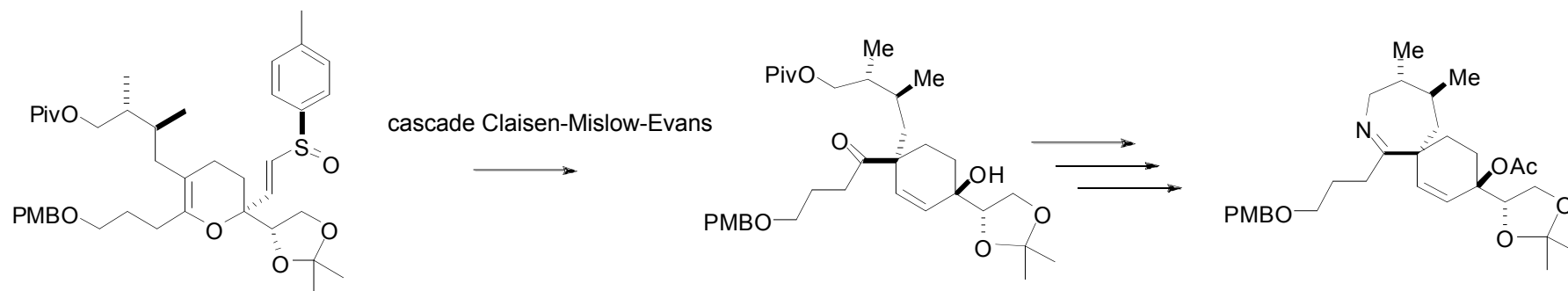


Pinnatoxins: A: R = CO₂H

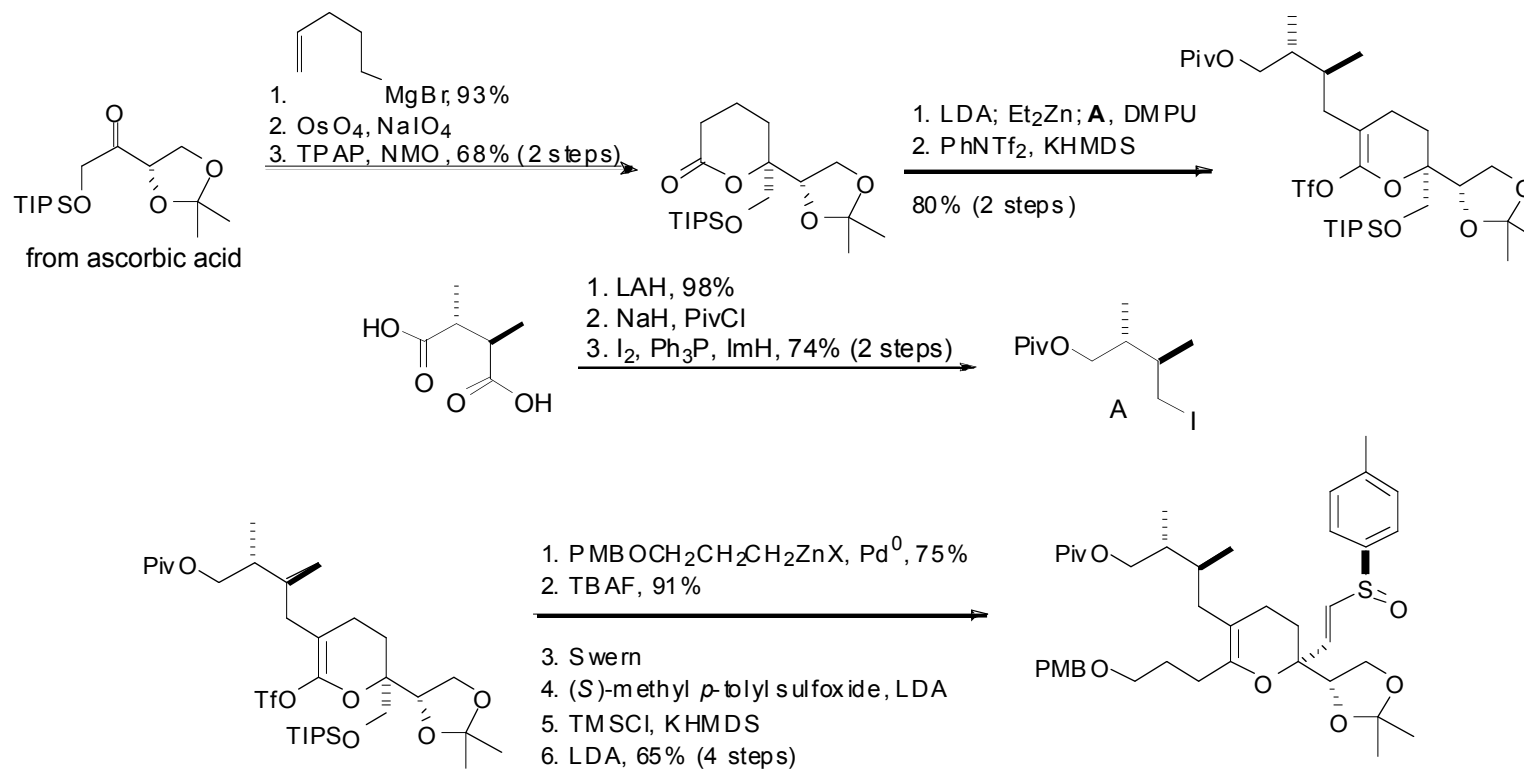
C: R =

B: R =

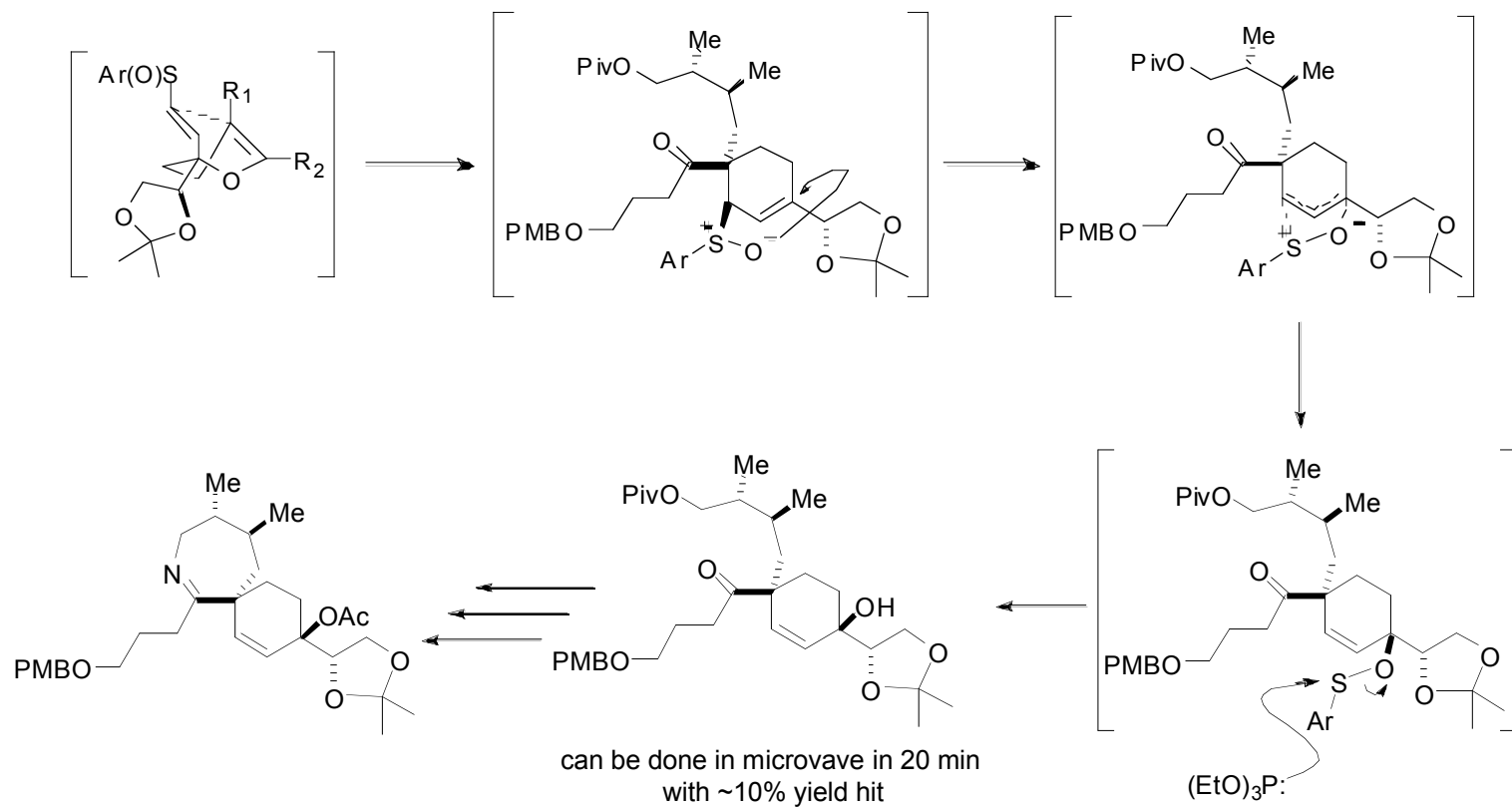
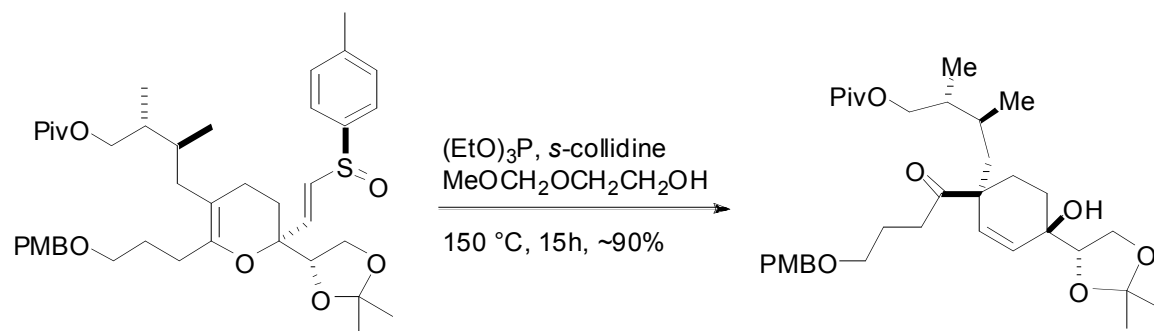
- pinnatoxins structurally elucidated by Uemura et al. in 1995
- structurally unique cyclic imine, stable to aqueous acids



Construction of Cascade Reaction Precursor



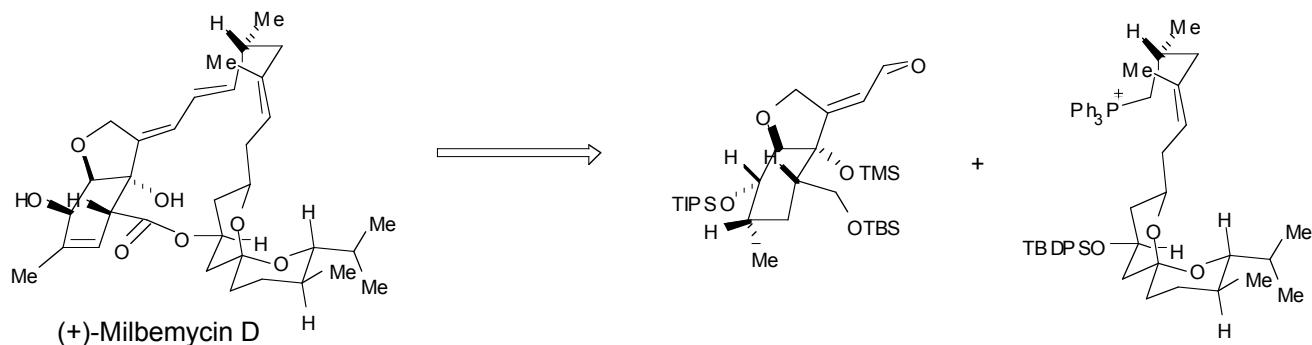
Cascade Claisen-Mislow-Evans



Organic Letters, **2005**, *7*, 1629-1631

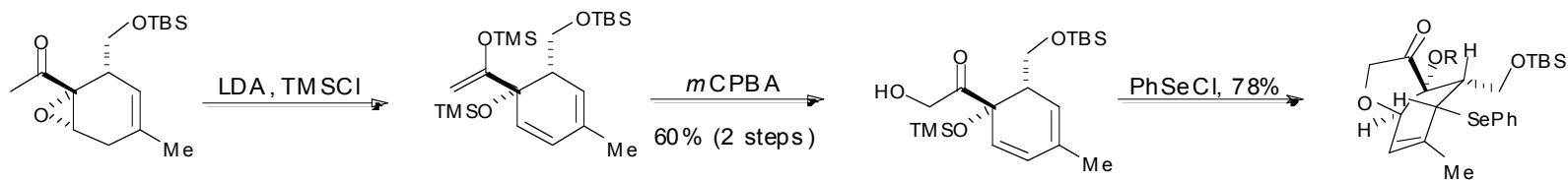
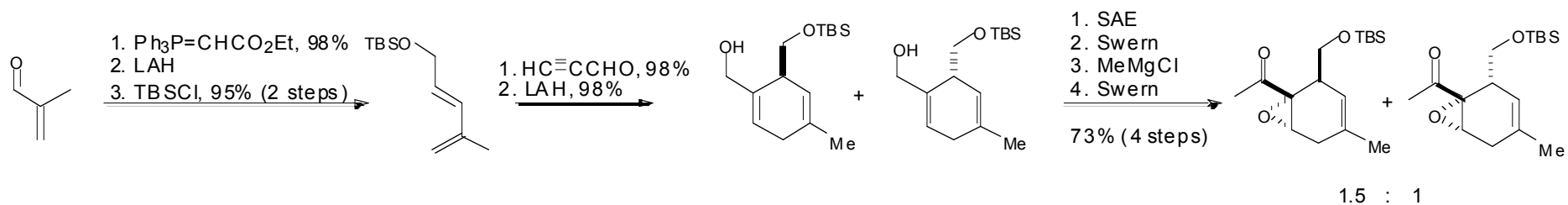
Additional 2,3-Sigmatropic Rearrangements

Synthesis of (+)-Milbemycin D



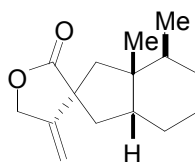
- milbemycins first reported in 1975 by Mishima
- among the most potent antiparasitic and insecticidal agents known
- notable synthetic challenges include spiroketal moiety and hexahydrobenzofuran

Preparation of 2,3-Rearrangement Precursor



Additional 2,3-Sigmatropic Rearrangements Cont'd

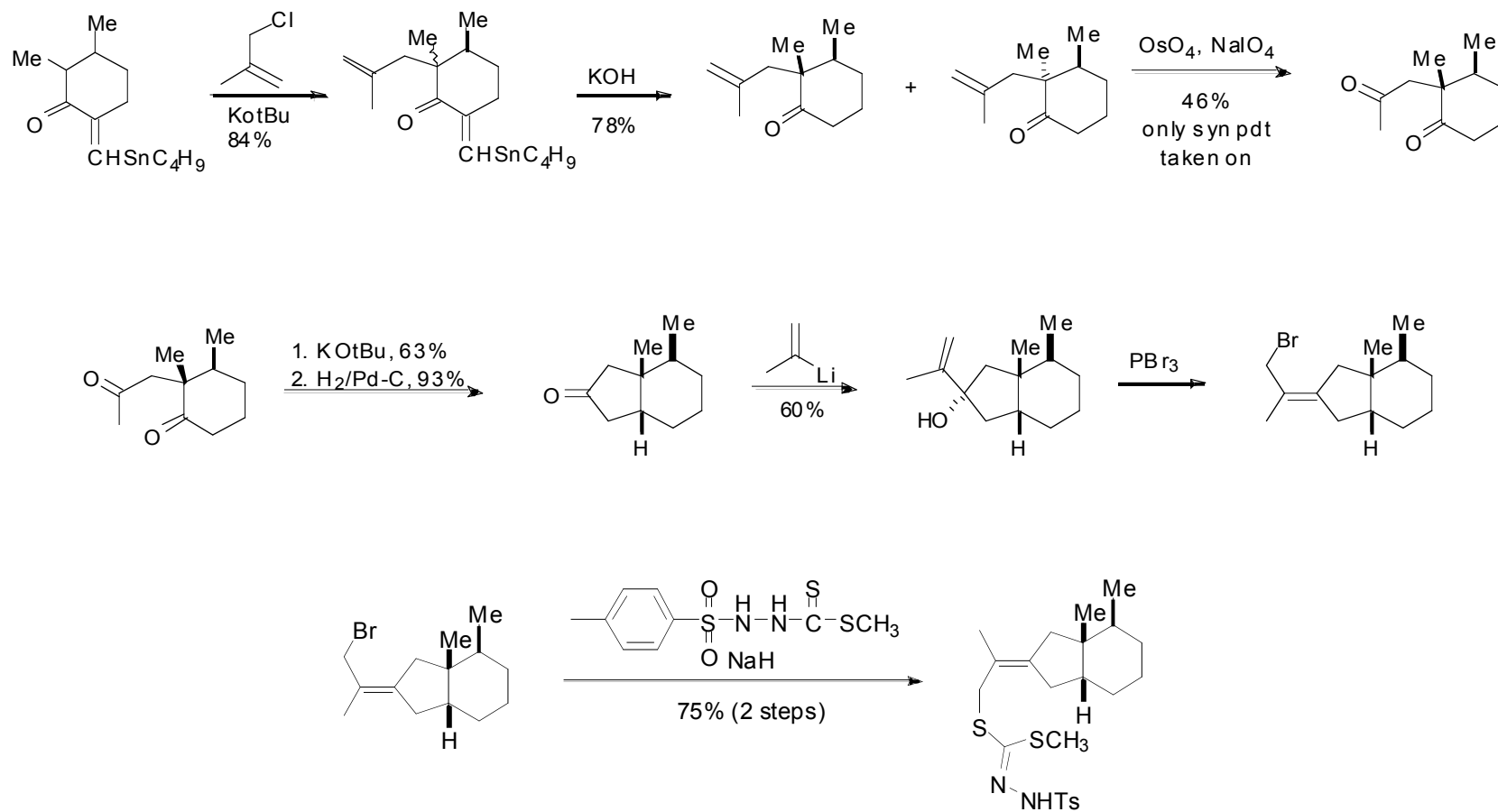
Synthesis of Bakkenolide A



Bakkenolide A

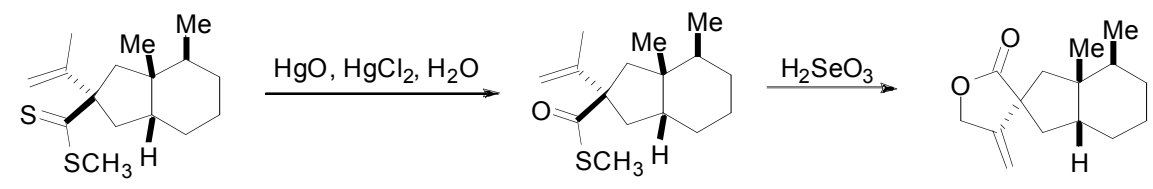
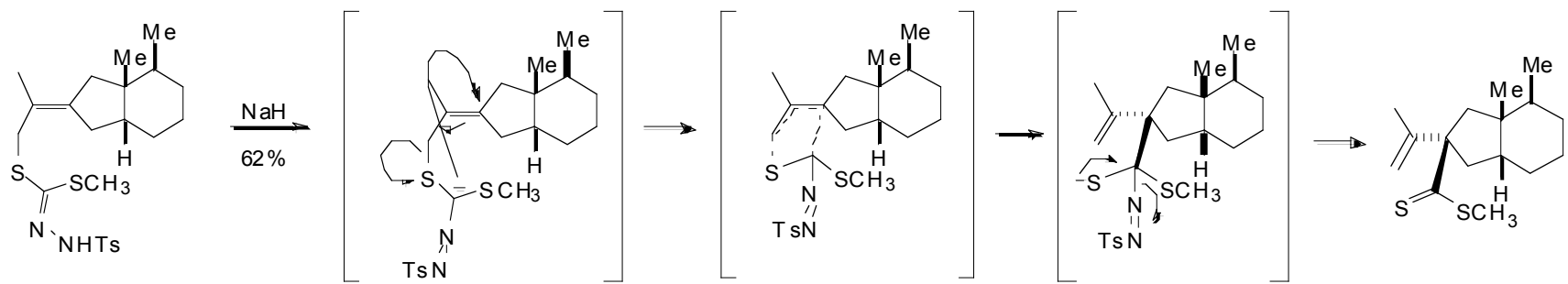
- Approximately 50 bakkanes isolated from plants to date
- they are sesquiterpenoids possessing a *cis*-hydrindane skeleton with two quat. centers
- biological activities include selective cytotoxicity, antifeedant effects and inhibition of platelet aggregation

Synthesis of Bakkenolide A



2,3-Sigmatropic Rearrangement

Synthesis of Bakkenolide A



Additional Interesting 2,3 Rearrangements

