2,3-Sigmatropic Rearrangements in Organic Synthesis

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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

Chem. Rev. 1986, 86, 885-902
Diastereoselectivity:
Proposed Transition States

Nakai and Mikami

Marshall, Houk, and Wu

Transition structure based on MP2/6-31+G computations:

π-acceptors like carbonyls and electropositive groups like silyl ethers prefer endo position

Cation plays large role

stersics place substituents preferentially in the exo position

Chem. Rev. 1986, 86, 885-902

J. Org. Chem. 1990, 55, 1421-1423
-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

-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:

There is a very high $E$-olefin selectivity when there is substitution $\beta$ to the sulfoxide (substitution at $R_1$)
Synthesis of the Imine Ring System of Pinnatoxins

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

Organic Letters, 2005, 7, 1629-1631
Construction of Cascade Reaction Precursor

from ascorbic acid

1. LAH, 98%
2. NaH, PivCl
3. I2, Ph3P, ImH, 74% (2 steps)

PivO

1. LDA; Et2Zn; A, DMPU
2. PhNTf2, KHMDS
80% (2 steps)

PivO

1. Pd0, 75%
2. TBAF, 91%
3. S-wern
4. (S)-methyl p-tolyl sulfoxide, LDA
5. TMSCl, KHMDS
6. LDA, 65% (4 steps)

Organic Letters, 2005, 7, 1629-1631
Cascade Claisen-Mislow-Evans

can be done in microwave in 20 min with ~10% yield hit

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

Rearrangement and Endgame

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

Organic Letters, 2004, 6, 3345
J. Am. Chem. Soc. 1977, 99, 5453
Synthesis of Bakkenolide A

J. Am. Chem. Soc. 1977, 99, 5453
2,3-Sigmatropic Rearrangement
Synthesis of Bakkenolinde A
Additional Interesting 2,3 Rearrangements

Angew. Chem. Int. Ed. 2000, 39, 3740