"acid chloride–imine" method would also be applicable to the synthesis of bicyclic β-lactams from suitable tetrahydropyrimidine derivatives. The striking increase in stability in going from the 1-azadethiopenam to the corresponding cepham series, of course, facilitates the synthesis of cepham analogs. The extension of this general synthetic approach to other bicyclic β-lactams is in progress.

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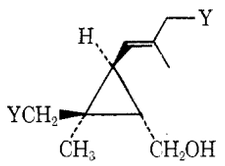
## Asymmetric Induction in a [2,3] Sigmatropic Rearrangement. A Biogenetic Model

*Summary:* Treatment of achiral *S*-methyl-*S*,*S*-bis(γ,γ-dimethylallyl)sulfonium fluoroborate with chiral bases produces artemisia methyl thioether with 5–12% asymmetric induction.

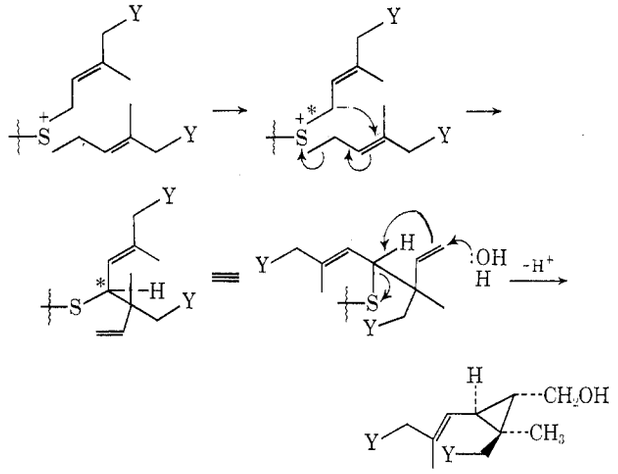
*Sir:* The discovery that the direct biological precursors of squalene[1,2] and phytoenes[3] possess the cyclopropane structures **1b** and **1c**, respectively, suggests a link to the monoterpene analog chrysanthemol (**1a**).



**1a**, Y = H
**b**, Y = geranyl
**c**, Y = farnesyl

Among the biogenetic schemes considered for the formation of these compounds,[4] that based on the [2,3] sigmatropic rearrangement of sulfur ylides possesses exceptional fascination (see Scheme I).[4g,5] In this scheme, the chirality of the biogenetic intermediates **1a–c** is determined by a single event—the conversion of an achiral sulfonium salt into a chiral ylide.

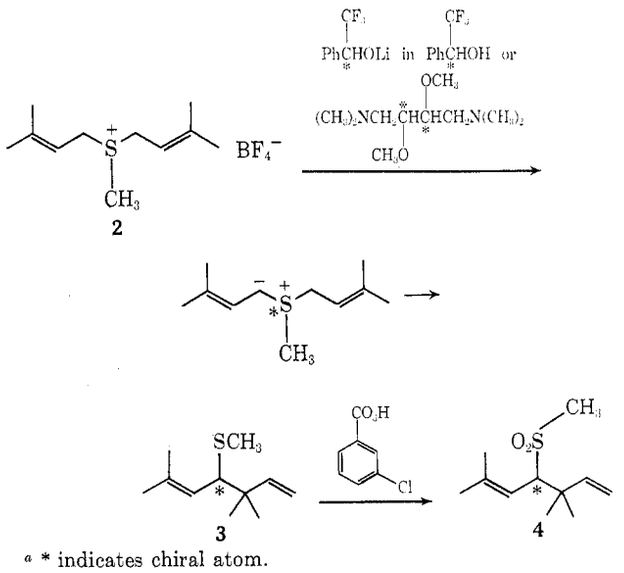
SCHEME I
[2,3] SIGMATROPIC REARRANGEMENT BIOGENETIC HYPOTHESIS



In experiments designed to examine various facets of this scheme, consideration of the stereochemistry of the process was undertaken to determine whether (1) simple chiral bases could discriminate between the enantiotopic[6] arms of the achiral sulfonium salt, (2) the ylide thus generated could rearrange faster than it loses its asymmetry, and (3) the chirality at sulfur could be faithfully translated into chirality at carbon.

Treatment of *S*-methyl-*S*,*S*-bis(γ,γ-dimethylallyl)-sulfonium fluoroborate (**2**) with *n*-butyllithium–sparteine complex[7] or lithium 1-(−)-menthoxide in tetrahydrofuran led to artemisia methyl thioether **3** with no observable optical rotation (see Scheme II). On the

SCHEME II
REARRANGEMENT IN MODEL SYSTEM[a]



[a] * indicates chiral atom.

(1) (a) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, **93**, 1782 (1971); (b) H. C. Rilling, C. D. Poulter, W. W. Epstein and B. Larsen, *ibid.*, **93**, 1783 (1971); (c) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **245**, 4597 (1979); (d) H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, **91**, 1041 (1969).

(2) (a) J. Edmond, G. Popjak, S.-M. Wong, and V. P. Williams, *J. Biol. Chem.*, **246**, 6254 (1971); (b) R. V. M. Campbell, L. Crombie, and G. Pattenden, *Chem Commun.*, 218 (1971); (c) R. M. Coates and W. H. Robinson, *J. Amer. Chem. Soc.*, **93**, 1785 (1971).

(3) L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, *J. Amer. Chem. Soc.*, **94**, 3257 (1972).

(4) (a) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, **93**, 1780 (1971); (b) R. M. Coates and W. H. Robinson, *ibid.*, **94**, 5920 (1972), and references therein; (c) C. D. Poulter, O. J. Muscio, C. J. Spillner, and R. G. Goodfellow, *ibid.*, **94**, 5921 (1972); (d) C. D. Poulter, *ibid.*, **94**, 5515 (1972); (e) L. Crombie, P. A. Frith, R. P. Houghton, D. A. Witing, and D. K. Woods, *J. Chem. Soc., Perkin Trans. 1*, 642 (1972); (f) A. F. Thomas and W. Pawlak, *Helv. Chim. Acta*, **54**, 1822 (1971); (g) B. M. Trost, P. Conway, and J. Stanton, *Chem. Commun.*, 1639 (1971); (h) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 4875 (1967).

(5) (a) J. E. Baldwin, R. E. Hackler, and D. P. Kelley, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (b) G. E. Risinger and H. D. Durst, *Tetrahedron Lett.*, 3133 (1968); (c) B. M. Trost and R. LaRochelle, *ibid.*, 3327 (1968); (d) G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969).

(6) In actuality, this terminology is incorrect. Since the carbanion may be tetrahedral the ylide may exist in one of four diastereomeric forms in which case the two arms are diastereotopic. Making the reasonable assumption that the carbanion center is at least "effectively" planar owing to rapid inversion simplifies the discussion. No conclusions are affected by this assumption.

(7) H. Nozaki, T. Aratani, and T. Toraya, *Tetrahedron Lett.*, 4097 (1968).

other hand, treatment of salt **1** with lithium (*R*)-(−)-2,2,2-trifluorophenylethoxide in 1:1 (*R*)-(−)-2,2,2-trifluorophenylethanol[8]–pentane at −10° led to thioether **3** in 54% yield with $[\alpha]^{25}D$ −1.45 ± 0.12° (*c* 4.12, $CHCl_3$). Use of (*S*)-(+)-alcoholate in its corresponding alcohol under the same conditions generated thioether **2** with $[\alpha[^{25}D$ +1.12 ± 0.54° (*c* 5.56, $CHCl_3$). To evaluate the optical purity of the thioethers, use of the chiral shift reagent tris[(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium[9] [henceforth abbreviated $Eu(CFP)_3$] was made. While separation of the signals for the *S*-$CH_3$ groups in the enantiomers could be achieved, cleaner results were obtained by oxidizing the thioether to the sulfone **4** (mp 38.5–40°) in 99% yield with *m*-chloroperbenzoic acid in ether at 0°. By addition of 21.7 mol % of $Eu(CFP)_3$ to a $CDCl_3$ solution of the racemic thioether, the $CH_3SO_2$ signal shifts from δ 2.74 to two singlets of equal intensity at 3.74 and 3.82. Treatment of the thioether of $[\alpha]^{25}D$ −1.45° in this way generated the corresponding sulfone, $[\alpha]^{25}_{365}$ −3.48 ± 0.18° (*c* 1.09, $CHCl_3$), in which the nmr spectrum showed a 5 ± 1% difference in the peak heights (average of 11 values) with the methyl singlet at highest field being the larger.

The use of optically active 1,4-bis(dimethylamino)-2,3-dimethoxybutane as solvent has been shown to enhance the optical yields in organometallic additions.[10] Rearrangement of the salt **2** with lithium (*S*)-(+)-2,2,2-trifluorophenylethoxide in a 1:1 mixture of dry tetrahydrofuran and (*S,S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane under nitrogen at −20° generated thioether **3** in 48% yield with $[\alpha]^{25}_{365}$ +2.90 ± 0.30° (*c* 0.62, $CHCl_3$). Oxidation with *m*-chloroperbenzoic acid as above gave the sulfone of $[\alpha]^{20}_{365}$ +6.33 ± 0.70° (*c* 1.43, $CHCl_3$) whose nmr spectrum in the presence of $Eu(CFP)_3$ indicated an enantiomeric purity of 12 ± 2% (average of 22 values) in which the downfield $CH_3SO_2$ singlet was the more intense. The net optical yield observed represents the optical yields for proton abstraction and ylide rearrangement.

In a related case, the [2,3] sigmatropic rearrangement has been found to proceed with >94% optical induction.[11] This observation suggests that in the present case the optical induction observed represents the preference in the proton abstraction step. The unusually high optical yields for such a process in this simple base system would clearly support a contention that in the highly asymmetric environment of an enzyme system such a process would exhibit complete optical induction. The demonstration that a great deal of the stereochemical control is inherent in the chemistry of such systems suggests more serious attention should be given to the hypothesis of Scheme I as a possible biogenetic model.

(8) W. H. Pirkle, S. D. Beare, and T. G. Burlingame, *J. Org. Chem.*, **34**, 470 (1968); H. M. Peters, D. M. Feigl, and H. S. Mosher, *ibid.*, **33**, 4245 (1968).

(9) (a) H. L. Goering and J. N. Eikenberry, unpublished results. For a related reagent, see H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Amer. Chem. Soc.*, **91**, 5913 (1971). (b) R. R. Fraser, M. A. Petit, and M. Miskow, *ibid.*, **94**, 3253 (1972). (c) R. R. Frazer, M. Petit, and J. K. Saunders, *Chem. Commun.*, 1450 (1971).

(10) D. Seebach, H. Dorr, B. Bostani, and V. Ehrig, *Angew. Chem., Int. Ed. Engl.*, **8**, 982 (1969).

(11) B. M. Trost and R. F. Hammen, *J. Amer. Chem. Soc.*, **95**, 962 (1973). For related work, see J. E. Baldwin and J. E. Patrick, *ibid.*, **93**, 3556 (1971); V. Rautenstrauch, *Chem. Commun.*, 4 (1970); R. K. Hill and T. H. Chan, *J. Amer. Chem. Soc.*, **88**, 866 (1966).

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## Rearrangement of Pyruvates to Malonates. β-Lactams by Ring Contraction

*Summary:* Periodate treatment of α-keto-γ-lactams results in rearrangement with ring contraction to β-lactams.

*Sir:* Numerous methods for the synthesis of β-lactams by ring closure or ring expansion have been developed,[1] but there are very few methods using ring contraction.[2] We have found that the oxidative rearrangement of α-ketoacyl derivatives with periodate, which has been reported for both acyclic and cyclic α-keto esters and amides,[3] appears to be generally extensible to the synthesis of β-lactams by oxidative ring contraction of α-keto-γ-lactams.

For example, the monocyclic α-ketolactam, 1-methyl-2,3-pyrrolidinedione (**2**), rearranges to 3-carboxy-1-methyl-2-azetidinone (**3**). The bicyclic compounds, **5a–c**, rearrange to bicyclic β-lactams, **6a–c**. When the β substituent, $R_1$ in **5**, is hydrogen or methyl, only one of the two possible isomers is obtained; however, when $R_1$ is bromine, both isomers are formed. The synthesis and rearrangement of these α-ketolactams, **2** and **5a–c**,[4] are presented below.

4-Ethoxycarbonyl-1-methyl-2,3-pyrrolidinedione (**1**),[5] heated in refluxing 2.9 *M* HCl (50 min), followed by extraction[6] and sublimation, gave 1-methyl-2,3-pyrrolidinedione (**2**, 63%, mp 89–91°). Reaction of **2** with periodate (pH 7.0, 24 hr), followed by destruction of excess periodate with bisulfite, extraction at pH 4.0, and chromatography on silica gel, gave 3-carboxy-1-methyl-2-azetidinone (**3**, 30%), ir 1745 (br) $cm^{-1}$.

1-Azabicyclo[4.3.0]nonane-8,9-dione (**5a**, 60%, mp 62–66°) was obtained from 7-ethoxycarbonyl-1-azabicyclo[3.2.0]nonane-8,9-dione (**4a**),[7] by an analogous

(1) Summarized in M. S. Manhas and A. K. Bose, "beta-Lactams: Natural and Synthetic," part 1, Wiley-Interscience, New York, N. Y., 1971.

(2) (a) S. N. Ege, *Chem. Commun.*, 759 (1968); (b) M. F. Chasle and A. Foucaud, *C. R. Acad. Sci., Ser. C*, **268**, 2034 (1969); (c) G. Lowe and D. D. Ridley, *Chem. Commun.*, 328 (1973).

(3) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 3877 (1972).

(4) All new compounds have been characterized spectrally (ir in $CHCl_3$ and nmr in $CDCl_3$). Elemental compositions were established by combustion analyses and mass spectra.

(5) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(6) Owing to high water solubility, most of the reported compounds were isolated from aqueous solution by continuous extraction with methylene chloride.

(7) R. Adams, S. Miyano, and M. D. Nair, *J. Amer. Chem. Soc.*, **83**, 3323 (1961).