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BIOMIMETIC ENTRY TO CHIRAL EPOXIDE SYNTHESIS
NOVEL ASYMMETRIC INDUCTION USING CHIRAL ANCHIMERIC ASSISTANCE

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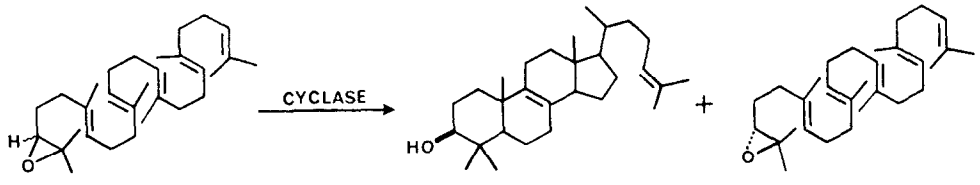
Summary: Stannic chloride promotes the cyclization of the epoxide 1 at low temperature to give the recovered epoxide in ca. 60% ee. The result suggests a new evidence for the chiral anchimeric assistance of the olefinic cyclization process.

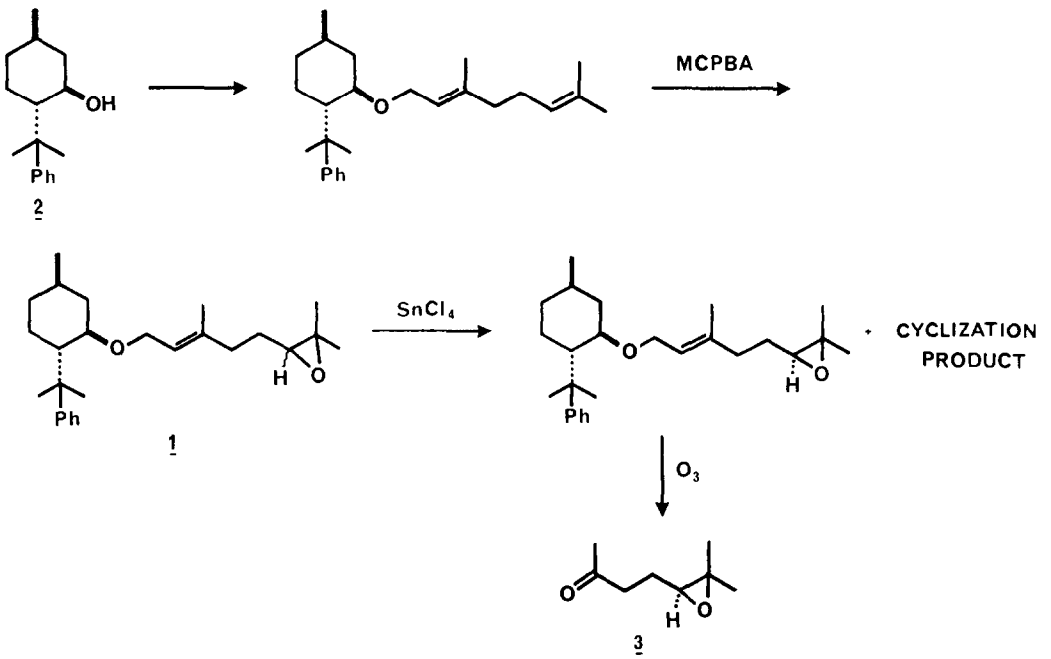
The sterol biosynthetic pathway from 2,3-oxidosqualene is truly unique in the number of asymmetric centers it produces in a single operation.[1] Carbon-carbon bonds are formed by intramolecular cyclization, and there is evidence the reactions occur by attack of electrophilic carbocations on neighboring π-electron functional groups.[2,3,6] It was shown that racemic C^{14}-2,3-oxidosqualene prepared by chemical synthesis was converted to lanosterol in up to 50% yield when incubated anaerobically with rat liver homogenates. The unchanged epoxide was thus recovered in 50% yield.[7] This represents essentially 100% conversion of one optical isomer. This reaction seems to be an impressive example of a complete kinetic resolution. Can asymmetric induction of the similar type be observed in a purely non-biochemical reaction? The present paper addresses realization of this enterprise and attempts to provide an understanding of the underlying steric and electronic factors.



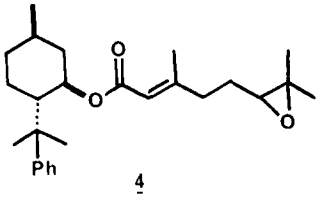
1 : 1

The requisite ether 1 could be prepared conveniently from the readily available phenylmenthol 2[8] by alkylation followed by selective terminal epoxidation. When treated with a catalytic amount of stannic chloride (0.45 mmol, 0.5 M solution in dichloromethane) in nitroethane (15 ml) at -90°C, the epoxide 1 (1.5 mmol) was partially consumed. Termination of the reaction by the addition of pyridine followed by extraction and purification

by column chromatography on silica gel gave the recovered epoxide in 20-30% yield. Ozonolysis of this epoxide in methyl acetate (10 ml) and subsequent treatment with triethylamine at room temperature for several hours furnished the chiral epoxy ketone 3. Optical purity of the epoxide was determined by NMR assay using the chiral shift reagent.[9] As indicated in Table 1, good to excellent stereoselection were obtained with the epoxide 1. In comparable

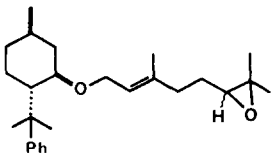
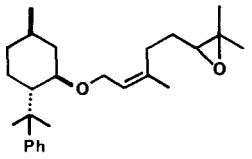
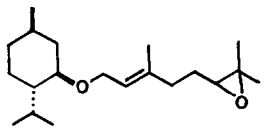
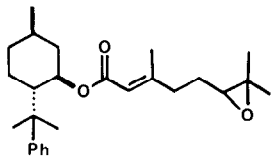
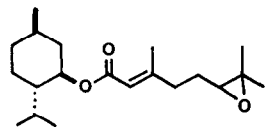


experiments using the ester 4 under the similar conditions, no significant asymmetric induction was observed as is also indicated in Table 1. Obviously, the central olefinic linkage of the substrate 4 should have the less electronic interaction to the oxirane ring.

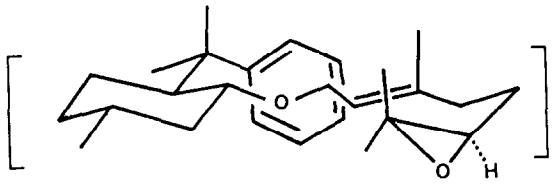


Thus, the stereochemical control achieved in the substrate 1 should not be attributed merely to the steric bulk of phenylmenthol. The conformation which allows these results is shown below. In the conformation 5 there is a high degree of participation of the adjacent π-bond during S_N2-like epoxide ring opening. Thus, the R oxirane reacts faster than the S isomer.

Table 1[a]

Entry	Epoxide	Reaction Conditions				Unreacted Epoxide
		Solvent	°C	h	Conversion (%)	% ee[10]
1		$EtNO_2$	-78	1	60	58 (S)
2		$EtNO_2$	-78	1.7	70	64 (S)
3		$CFCl_3$	-40	0.25	70	42 (S)
4		CH_2Cl_2	-78	0.25	80	50 (S)
5		$EtNO_2$	-78	1.5	85	44 (R)
6		$EtNO_2$	-50	0.15	80	6 (S)
7		$EtNO_2$	-78	13.5	80	8 (S)
8		$EtNO_2$	-50	0.1	80	8 (S)

[a]Typically performed as follows: To a solution of the epoxide (1.5 mmol) diluted with nitroethane (15 ml) at -90°C was added a 0.5 M dichloromethane solution of tin (IV) chloride (0.45 mmol) over a period of 5 min. The reaction mixture was heated at the temperature listed above and stirred there. The progress of the reaction was monitored by tlc analyses. The reaction was terminated by the addition of pyridine (1.5 ml) and treated with aq. sodium hydroxide. The product was extracted with ether repeatedly and the combined ether layers were washed with brine, dried, and concentrated in vacuo. Purification by column chromatography on silica gel gave the recovered epoxide. The recovered epoxide in methyl acetate (10 ml) was treated with exess ozone at -78°C followed by triethylamine (0.5 ml) at room temperature. The mixture was stirred for 4 h at room temperature to give the ketone 3 after extractitive workup and chromatographic purification.



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On the basis of the studies described above, it would seem that the chiral anchimeric assistance in the epoxide ring opening process is possible and should provide the route to optically active epoxide with the remote asymmetric induction. Another noteworthy aspect of our results is that a high degree of chiral neighboring π-bond participation during S_N2-like epoxide ring opening should play an important role for the formation of A ring during the biological construction of steroid.

References and Notes

1) P. Manitto and P. G. Sammes, "Biosynthesis of Natural Product," John Wiley & Sons, New York, 1981.

2) Recent excellent review: P. A. Bartlett, In "Asymmetric Synthesis," J. D. Morrison, Ed., Academic Press, New York, Vol. 3, 341, 1984.

3) For a stepwise mechanism of biomimetic polyene cyclizations, each step involving the formation of a cyclic π-complex by electrophilic addition to a C==C bond was established theoretically[4] and experimentally.[5]

4) M. J. S. Dewar and C. H. Reynols, J. Am. Chem. Soc., 106, 1744 (1984).

5) M. Nishizawa, H. Takenaka, and Y. Hayashi, J. Am. Chem. Soc., 107, 522 (1985).

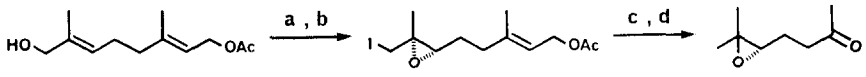
6) E. E. van Tamelen, D. R. James, J. Am. Chem. Soc., 104, 6480 (1982).

7) P. R. Ortiz de Montellano, Ph. D. Thesis, Harvard University, 1968.

8) E. J. Corey, H. E. Ensley, J. Am. Chem. Soc., 96, 6908 (1975).

9) ^1H NMR analysis in the presence of $Eu(hfc)_3$ in $CDCl_3$.

10) The absolute configuration of the epoxide 3 was proven by chemical correlations as follows:

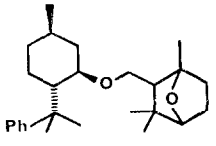


a: Sharpless oxidation[11] b: 1) TsCl; 2) NaI c: $NaBH_3CN$ d: O_3

See also: W. Eschenmoser, P. Uebelhalt, C. H. Eugster, Helv. Chim. Acta, 66, 82 (1983).

11) T. Katsuki, K. B. Sharpless, J. Am. Chem. Soc., 102, 5976 (1980).

12) On treatment of the epoxide 1 with excess stannic chloride gave the bicyclic ether as shown below:



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