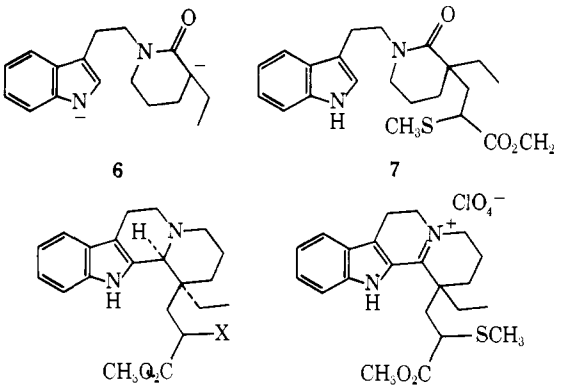
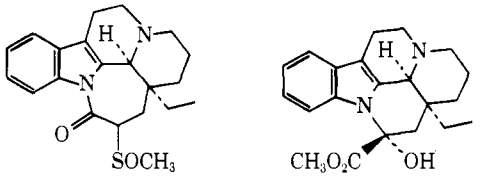


6 7

9, X = SCH_3
10, X = $SOCH_3$ 8



11

12

Cyclization of **7** (1 equiv) was carried out in refluxing acetonitrile (0.1 M) containing phosphorus oxychloride (30 equiv) for 14 hr. The crude reaction mixture was treated with lithium perchlorate (2 equiv) in water to give the immonium perchlorate **8** (mp 88–96°, 93% yield from **7**). Stereospecific reduction of **8** to the tetracyclic amine ester **9** (mp 102–104°) could be realized in 98% yield using lithium tri-*tert*-butoxyaluminum hydride (3.0 equiv) in THF solution (0.3 *M*) at 0°.[9]

The final ring of vincamine was introduced by oxidation of **9** (1 equiv) to the sulfoxide **10** (mp 110–115°, 96% yield) with *m*-chloroperbenzoic acid (1.3 equiv) in methylene chloride solution (0.1 *M*). Treatment of **10** (1.0 equiv) with sodium hydride (2 equiv) in THF solution (0.1 *M*) gave the lactam sulfoxide **11** (mp 75–77°) in 98% yield. Direct conversion of **11** into vincamine may be accomplished by reaction of the lactam sulfoxide (1.0 equiv) with acetyl chloride (2.2 equiv) at 0° for 20 min followed by addition of sodium methoxide (4.0 equiv) in methanol (0.1 *M*).[10] After stirring 14 hr at 22°, dilution of the reaction mixture with water gave pure *dl*-vincamine (**1**) (mp 225–227°) in 80% yield.[11] The same reaction using 2.5 equiv of sodium methoxide in methanol for 6 hr afforded pure *dl*-epivincamine (**12**) (mp 203–204°) in 85% yield.[12]

at 105–106° and 82–83°. The epimeric mixture was used in the actual synthesis thus accounting for the melting point ranges reported for compounds **7** to **11** inclusive.

(9) Sodium borohydride reduction of **8** gave a mixture of *cis* and *trans* isomers of **9** (4:1) which are easily separated by liquid chromatography. Less than 0.5% of the *trans* isomer of **9** is formed when lithium tri-*tert*-butoxyaluminum hydride is used.

(10) Presumably this reaction sequence involves acid chloride induced rearrangement of the sulfoxide functionality into the α-acetoxysulfide followed by methoxide conversion of this intermediate into its α-keto lactam analog. Ring opening of the lactam with methoxide affords the corresponding methyl pyruvate derivative which is known to undergo ring closure into vincamine (ref 2e).

(11) We thank Professor M. P. Cava, Department of Chemistry, University of Pennsylvania for a sample of naturally occurring *dl*-vincamine. The synthetic *dl*-vincamine was identical in all respects to the natural material.

(12) Epivincamine is apparently a kinetic product in this reaction since prolonged refluxing or the use of excess methoxide quantitatively converts epivincamine into vincamine. A similar experiment is described in ref 2e.

Use of the dianion **6** as an intermediate in the synthesis of other indole alkaloids is currently under investigation.

Acknowledgment. We thank the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Hoffmann-LaRoche Company, Nutley, N. J., for support of this work.

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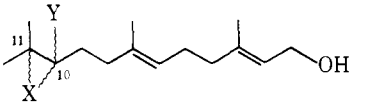
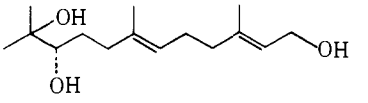
Trans and Cis Hydration of Racemic 10,11-Epoxyfarnesol into Optically Active Glycols by Fungus

Sir:

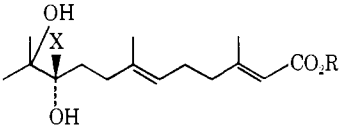
We have recently established the fungal transformation of a racemic mixture of 10,11-epoxyfarnesol (I)



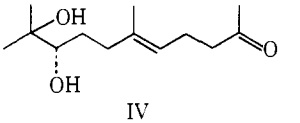
I, X = >O; Y = H
Ia (10-*R*), X = >O; Y = H
Ib (10-*S*), X = >O; Y = H
Ic, X = $>^{18}O$; Y = H
Id, X = >O; Y = ^{2}H
Ie (10-*S*), X = $>^{18}O$; Y = H



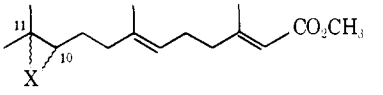
II



III, X = H; R = H
IIIa, X = H; R = CH_3
IIIb, X = ^{2}H; R = CH_3



IV



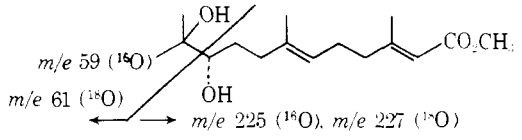
Va (10-*R*), X = >O
Vb (10-*S*), X = >O

into three optically minus glycollic metabolites, *i.e.*, (*S*)-(−)-10,11-dihydroxyfarnesol (II), (*S*)-(−)-10,11-di-

hydroxyfarnesic acid (III), and (*S*)-(−)-9,10-dihydroxygeranylacetone (IV),[1] and have successfully converted the former two compounds into two enantiomeric pairs, that of the original epoxide (Ia and Ib)[2] and that of its ester analog (Va and Vb).[3] In this communication we describe novel trans and cis hydration of a racemic epoxide by which both enantiomers of I are converted into the same optically minus metabolites.

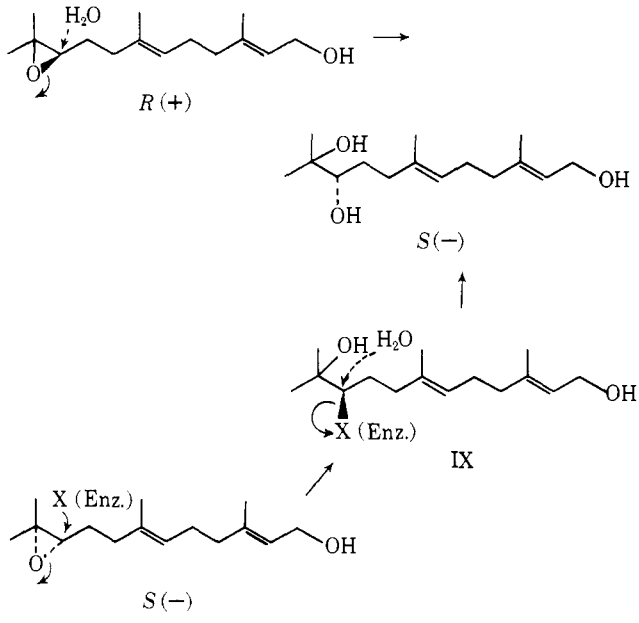
Two main problems to be solved are (1) whether both or either one of the enantiomers of I are converted to *S*-(−)-glycols and (2) the mechanism of the epoxy-ring opening. The first was experimentally accounted for by quantitatively analyzing by glc the respective products of the action of *Helminthosporium sativum* on (*R*)-(+)- and (*S*)-(−)-epoxyfarnesol (Ia and Ib) and the racemate (I). The summed yields of three glycollic metabolites from each substrate were 60.1, 81.7, and 78.4%, respectively, for these three substrates, clearly indicating that *the optically minus metabolites are produced efficiently from either of the enantiomers of the racemic substrate.* Although a rate study was not carried out, *R*(+) enantiomer (Ia) seems to be consumed more readily as compared with the *S*(−) one (Ib), based on our earlier observation[2] that the latter, whose optical value, $[\alpha]_D$ −1.2°, suggested it to be partially racemic, could be recovered after interruption of the fermentation of the racemate (I). One of the metabolites, II, showed the identical optical rotation, $[\alpha]_{400}$ −25.3° (*c* 0.1, MeOH), regardless of its source, supporting the above conclusion.

The second problem, the site of epoxide cleavage, was examined by subjecting (±)-[^{18}O]epoxyfarnesol (Ic) to fungal metabolism. Ic was prepared from farnesyl acetate by oxidation (NBS in $H_2{}^{18}O$–*t*-BuOH) followed by base treatment, being determined from mass spectrometry to contain 72% of ^{18}O in the epoxide oxygen. [^{18}O]-II and -III were produced by incubating Ic (the purely isolated yield; 19.3 and 21.7%, respectively), and the ^{18}O distribution between C_{10} and C_{11} hydroxyl groups was determined by Nakanishi's method.[4] On the basis of the relative peak intensities for the couples of isotopic ions due to fission of the C_{10}–C_{11} bond the distribution was estimated as 64–66% on C_{11} and 6–8% on the C_{10} hydroxyl group. Therefore, the main part (89–92%) of the nucleophillic attack has occurred on C_{10} of I, while a minor attack (8–11%) has also occurred at C_{11}. In additional support of

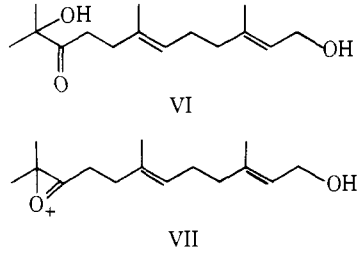


this, Va derived from [^{18}O]-IIIa by the procedure[2] known to eliminate the C_{10} but not the C_{11} oxygen was found to retain the same ^{18}O content as that of the C_{11}-hydroxyl of the latter. These results, coupled with our further observation on racemic 10,11-epoxyhomofarnesol,[5] allow us to present a *trans opening process for the major hydration of R-(+)-epoxide into S-(−)-glycols as the result of an attack on* C_{10} (Scheme I).

Scheme I



The process from *S*-(−)-epoxide (Ib) to *S*-(−)-glycols is supposed to be more complex than that from Ia. Among the conceivable routes, the two, *i.e.*, that through 10-keto intermediate (VI) and that *via*



isomerization at C_{10} through an oxirenium cation (VII), require elimination of C_{10}-methine proton. (±)-[10-^{2}H]-epoxyfarnesol (Id) was prepared for a substrate from (±)-dihydroxyfarnesyl acetate by oxidation (DMSO–Ac_2O),[6] reduction ($LiAl^2H_4$), and finally the epoxide formation.[2] Involvement of VI or VII is unlikely since IIIb produced enzymatically from Id showed no proton signal due to C_{10}-methine, indicating that deuterium in Id was not replaced by hydrogen during the hydration.

That the cis opening operated in the hydration of Ib was shown by further metabolic experiment using (*S*)-(−)-[^{18}O]epoxyfarnesol (Ie). Ie with 34% ^{18}O content was prepared by hydrolysis of Ib with sulfuric acid in THF–$H_2{}^{18}O$ followed by the epoxide formation.[2] Mass spectrometric analysis of [^{18}O]-glycols obtained as the metabolite of Ie revealed that 29–30% of ^{18}O was located in the C_{11}-hydroxyl group. This result undoubtedly indicates that the predominant part of the attack (85–88%) has occurred at C_{10} of Ie. This hydration is clearly cis opening in contrast to trans in Ia. Presentation of the precise mechanism from these

(1) Y. Suzuki and S. Marumo, *Tetrahedron Lett.*, 1887 (1972).
(2) Y. Suzuki and S. Marumo, *Chem. Commun.*, 1199 (1971).
(3) Y. Suzuki, K. Imai, S. Marumo, and T. Mitsui, *Agr. Biol. Chem.*, 36, 1849 (1972).
(4) K. Nakanishi, D. S. Schooley, M. Koreeda, and J. Dillon, *Chem. Commun.*, 1235 (1971).
(5) (10*R*,11*S*)-Epoxyhomofarnesol has been metabolized by the same fungus into (10*S*,11*S*)-dihydroxyhomofarnesic acid. The hydration of this compound analogous to *R*-(+)-epoxide (Ia) in this communication occurred clearly in trans opening.
(6) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 87, 4214 (1965).

results should be careful, because the present studies were conducted only on incubation with an intact fungus. In Scheme I we speculate on one of the possible mechanisms to explain the cis opening, which proceeds presumably in two steps. First the *S*-(−)-epoxide may be trans opened by a backside attack of a nucleophillic center of an enzyme to form an intermediate complex IX, which is then solvolyzed, also enzymatically, in an SN2 type reaction into the *S*-(−)-glycol.

In connection with the less dominant attack (8–11%) on C_{11}, optical purity of the glycollic metabolites was examined by nmr using chiral lanthanide shift reagent.[7] IIIa, showing $[\alpha]_D$ −14.1° (*c* 0.7, MeOH), was found to consist of 86.5% of *S*(−) and 13.5% of *R*(+) enantiomer.[8] This partial racemization is probably accounted for by the above minor route of hydration.[9]

The enzymatic hydration of racemic epoxides into a single stereoisomer has been reported on several compounds,[10] in every case occurring as a trans opening. The present studies suggested the operation of two different pathways, trans and cis opening, in the fungal hydration of racemic epoxyfarnesol, the latter pathway being quite novel. Further refined study on the level of the enzyme *in vitro* will be necessary to elucidate the precise mechanism of this interesting hydration.

(7) H. L. Goering, J. N. Eikenberry, and G. S. Koemer, *J. Amer. Chem. Soc.*, **93**, 5913 (1971).

(8) Enantiomeric composition of IIIa (0.23 *M*) was determined in CCl_4 in the presence of 0.07 *M* tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III). Under these conditions, some of the signals of the *S* enantiomer shift downfield more than those of *R* enantiomer. The signals used for the determination were those for C_{10}-methine ($\Delta\Delta\delta$ 0.3 ppm) and either one of C_{11}-methyls ($\Delta\Delta\delta$ 0.09 ppm).

(9) Nonenzymatic hydration of an epoxide during the incubation was prevented by powdered calcium carbonate added into the medium. In the controlled experiment with heat-inactivated fungus, the substrate did not produce a glycollic compound (II).

(10) (a) D. M. Jerina, J. W. Daly, B. Witkop, P. Z. Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90**, 6525 (1968); (b) T. Tanabe, S. Kanehira, K. Kiyinaga, and S. Hara, 2nd Symposium on Drug Metabolism and Action, K. Kakemi, Ed., Hirokawa Publishing Co., Tokyo 1970, p 59; (c) W. G. Niehaus, Jr., A. Kisic, A. Torkelson, D. J. Bednarczyk, and G. J. Schroepfer, Jr., *J. Biol. Chem.*, **245**, 3802 (1970).

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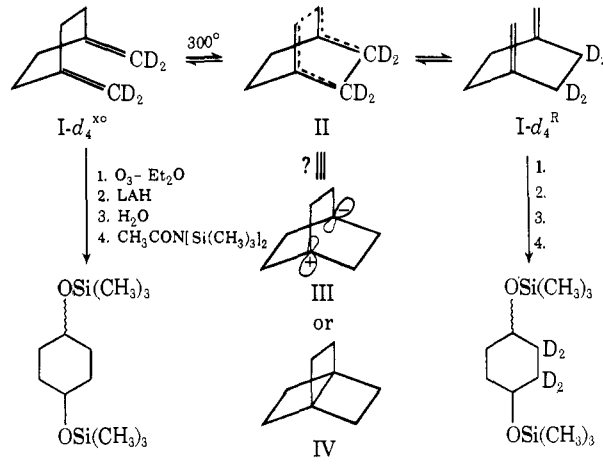
Hydrocarbon Thermal Degenerate Rearrangements. VI. A Boat Cope Transition State in the Self-Interconversion of 1,4-Dimethylenecyclohexane

Sir:

Concern over the energetics of the high temperature Cope rearrangement in comparison with the "chair" process[1] prompts us to report the energetics of the necessarily boat-like 3,3-sigmatropic rearrangement of 1,4-dimethylenecyclohexane (I) the transition state of which, II, has the added feature of resembling [2.2.2]propellane.[2]

Lithium aluminum deuteride reduction of 1,4-dicarbomethoxycyclohexane followed by tosylation, iodide displacement, and *tert*-butoxide–*tert*-butyl alcohol elimination gave 1,4-bis(dideuteriomethylene)cyclohexane (*I*-d_4^{xo}).



Pyrolysis of this material in a well-conditioned bulb at 333° for 35 min (100 μl in a 2-l. vessel with 40 Torr of N_2) gave only I[3] with 30% of total protium on the exomethylene position. Ozonolysis of recovered I in Et_2O at −78° followed by lithium aluminum hydride reduction gave a cyclohexane-1,4-diol which was converted to the bis(trimethylsilyl) ether whose mass spectrum (in the M − 15 region) revealed the presence of d_0, d_2, and d_4 materials in the ratio, 1:<0.02:0.46. Thus the rearrangement is best interpreted as a 3,3-sigmatropic shift as depicted above.

The temperatures necessary to affect the Cope rearrangement were 50–75° higher than that for reaction of 1,5-hexadiene *via* the chair process[1] and provided impetus for determination of the activation parameters. Examination of the kinetics over a temperature range of 42° (to ±0.3°) gave $\Delta S^{\ddagger} = -13.8 \pm 2$ eu and $\Delta H^{\ddagger} = 39.0 \pm 1.0$ kcal/mol for the conversion of I-d_4^{xo} to I-d_4^{R} ($K_{eq} = 2.1$ at 300°).[4]

As a result of the partial, but elegant, stereochemical labeling studies of Doering and Roth,[5] the lowest energy Cope process has been accepted as that involving the chair transition state; a higher energy (5.7 kcal/mol) process also occurred with stereochemistry consistent with a boat-like transition state. Indeed, Dewar has calculated, by the MINDO technique, this energy difference but has poorly reproduced the absolute heats of formation of individual species.[6] Other symmetry allowed[7] transition states of the antara–antara variety have been recognized by ourselves[8] and Goldstein,[9] namely the "helix" or twist and the "plane" with C_2h symmetry. The observed partial stereochemistry of the low energy pathway can be explained by either the chair or helix;[8] however, an important, but occasionally overlooked[8] study by Hill[10] clearly reveals the chair to

(1) (a) W. von E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971); (b) M. J. Goldstein and M. S. Benzon, *J. Amer. Chem. Soc.*, **94**, 7147 (1972).

(2) P. E. Eaton and G. H. Temme III, *J. Amer. Chem. Soc.*, **95**, 7508 (1973).

(3) Without prior conditioning with dimethyldichlorosilane, *p*-xylene was a major product.

(4) (a) For comparison, Humski, *et al.*,[4b] reported K_{eq} for conversion of 1,1,6,6-tetradeuterio-1,5-hexadiene to 3,3,4,4-tetradeuterio-1,5-hexadiene as 1.23 at 200°. (b) K. Humski, R. Malojčić, S. Borčić, and D. E. Sunko, *J. Amer. Chem. Soc.*, **92**, 6534 (1970), and references contained therein.

(5) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(6) A. Brown, M. J. S. Dewar, and W. Schoeller, *J. Amer. Chem. Soc.*, **92**, 5517 (1970).

(7) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(8) J. J. Gajewski, *Mech. Mol. Migr.*, **4**, 1 (1972).

(9) M. J. Goldstein and M. J. Benzon, *J. Amer. Chem. Soc.*, **94**, 7149 (1972).

(10) R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).