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STEREOCHEMISTRY OF THE LIPOXYGENASE-CATALYZED ALLYLIC HYDROPEROXIDE⟶OXIRANYLCARBINOL REARRANGEMENT

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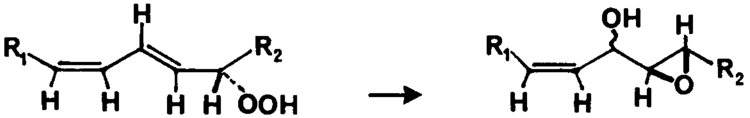
Summary: The anaerobic rearrangement of 15-(S)-HPETE (1) which is effected by the enzyme soybean lipoxygenase - type I leads stereospecifically to the hydroxy epoxide 2 by a cis addition of two oxygens to the 13,14-double bond.

The rearrangement of hydroperoxides produced by lipoxygenation of polyunsaturated fatty acids to isomeric hydroxy epoxides is known to be catalyzed by the same enzyme which effects the initial peroxidation, as follows:[1] .

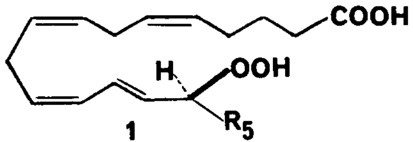


This interesting transformation is both a natural biosynthetic pathway[2] and a useful process for the synthesis of epoxyeicosatetraenoic acids (EPETE'S) which are metabolites of arachidonic acid.[3] The rearrangement does not seem to require molecular oxygen since it occurs under anaerobic conditions.[1] Further, it seems clear from labeling experiments that both oxygens of the hydroperoxy group are retained in the product, which from proton magnetic resonance (pmr) data is clearly a transoid oxirane (coupling constant between vicinal oxirane protons ca. 2.5 Hz).[1] As a step toward understanding the detailed mechanism of this unusual process it seemed important to determine unambiguously all stereorelationships in the oxiranylcarbinol unit. In this note we demonstrate that the anaerobic rearrangement of 15-(S)-HPETE (1) by soybean lipoxygenase (type I) produces 13-(R)-hydroxy-15-(S)-trans-14,15-epoxy-5,8,11-(Z)-eicosatetraenoic acid (2) by what amounts to a cis addition of two oxygens to the 13,14-double bond.

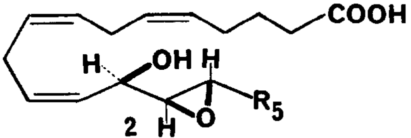
Rearrangement of 15-HPETE by type I soybean lipoxygenase was carried out as previously described (pH 7, argon atmosphere, in the presence of ethylenediamine tetraacetic acid)[3] to form 2 in ca. 50% yield. Esterification of 2 with ethereal diazomethane and hydrogenation (1 atm. H_2, Pd-C catalyst, methanol at 23°) provided (100%) the saturated hydroxy epoxide ester 3, m.p. 57° (from 1 : 9 ether-pentane), R_f 0.418 (silica gel plate, 2 : 1 ether-hexane), pmr peaks ($CDCl_3$, 270 MHz) due to C(13)-H at 3.44 δ (m, 1H), C(14)-H at 2.72 δ (dd, J = 2.6, 5.3 Hz, 1H) and C(15)-H at 2.90 δ (dt, J = 2.6, 5.3 Hz, 1H).[4] Oxidation of 3 (2 equiv. of pyridinium dichromate,[5] CH_2Cl_2, 2 hr.) afforded 91% of the corresponding 13-keto-14,15-epoxy ester, m.p. 33-34° (from pentane), which upon treatment with 0.3 mol equiv. of zinc borohydride in ether at 0° for 30 min.[6] gave 95% yield of the erythro carbinol epoxide 4, R_f 0.472 (silica gel plate, 2 : 1 ether-hexane), pmr peaks ($CDCl_3$, 270 MHz) due to C(13)-H at 3.80 δ (m, 1H), C(14)-H at 2.76 δ (dd, 2.6, 3.0 Hz, 1H) and C(15)-H at 2.99 δ (dt, J = 2.6, 5.2 Hz, 1H), in addition to a minor amount

(~ 3%) of the diastereomeric *threo* carbinol epoxide **3**. The assignments of *threo* and *erythro* C(13)/C(14) stereorelationships in **3** and **4**, respectively, follow from the known[6] highly selective formation of erythro α,β-epoxy carbinols by zinc borohydride reduction of α,β-epoxy ketones.[7] The nearly identical coupling constants for protons at C(13) and C(14) in the diastereomers **3** and **4** (5.3 and 3.0 Hz (±) 0.1 Hz), respectively) clearly vitiate the use[1b] of such pmr coupling in the assignment of *erythro* or *threo* geometry.

The elucidation of the stereospecific process **1**⟶**2** for the soybean lipoxygenase-catalyzed rearrangement of 15-(*S*)-HPETE raises the possibility that this *cis* oxygenation pathway might be generally favored for similar reactions of other substrates and other lipoxygenases. This point and other mechanistic questions are currently under study.[8]



1



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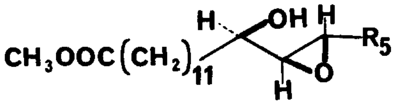
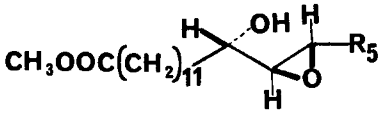


3

$R_5 = C_5H_{11}$



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1. (a) M. Hamberg and B. Gotthammar, *Lipids*, **8**, 737 (1973); (b) G. J. Garssen, G. A. Veldink, J. F. G. Vliegenthart and J. Boldingh, *Eur. J. Biochem.*, **62**, 33 (1976); (c) M. R. Egmond and R. J. P. Williams, *Biochim. Biophys. Acta*, **531**, 141 (1978).

2. (a) I. C. Walker, R. L. Jones, P. J. Kerry, and N. H. Wilson, *Adv. Prostaglandin Thromboxane Res.*, **6**, 107 (1980); (b) E. J. Corey, J. Kang, B. C. Laguzza, and R. L. Jones, foregoing paper.

3. E. J. Corey, M. M. Mehrotra and J. R. Cashman, *Tetrahedron Letters*, preceding paper.

4. Satisfactory spectral data were obtained.

5. E. J. Corey and G. Schmidt, *Tetrahedron Letters*, 399 (1979).

6. T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Letters*, **22**, 4723 (1981).

7. Sodium borohydride reduction of α,β-epoxy ketones also favors formation of *erythro* epoxy carbinols; see J. L. Pierre and P. Chautemps, *Tetrahedron Letters*, 4371 (1972).

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