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SYNTHESIS OF (±)-EICOSA-CIS-8,9-(11,12- AND 14,15-) EPOXY-CIS-11,14-(8,14- AND 8,11-) DIENOIC ACIDS AND ATTEMPTED BIOCONVERSION TO PROSTAGLANDINS

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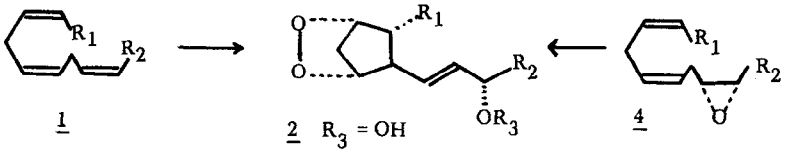
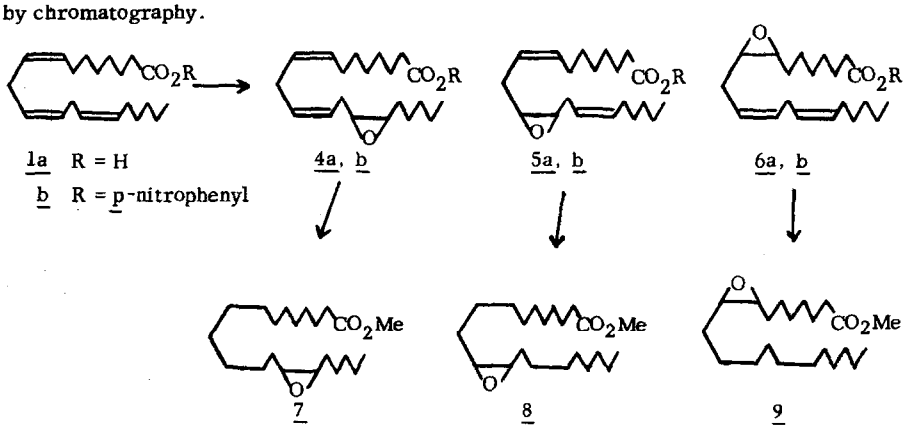
The endoperoxides 2 and 3 have been shown to be key intermediates in the bioconversion of polyunsaturated fatty acids to primary prostaglandins.[1] The possibility that epoxy polyunsaturated fatty acids might be other intermediates in the biosynthesis of prostaglandins has been proposed.[2] A recent report on the synthesis and metabolism of (±)-eicosa-cis-14,15-epoxy-cis-8,11-dienoic acid[3] prompted us to communicate our observations in this area.



1 2 R_3 = OH 3 R_3 = H 4

After some unsuccessful experiments on the selective epoxidation of polyunsaturated fatty acids[4], all cis-8,11,14-eicosatrienoic acid (1a) was randomly epoxidized and the mono-epoxy dienoic acid mixture was separated by chromatography.



1a R = H b R = p-nitrophenyl 4a, b 5a, b 6a, b 7 8 9

All cis-8,11,14-eicosatrienoic acid (1a) (kindly provided by Upjohn Co.) was esterified with excess p-nitrophenol and dicyclohexyl carbodiimide in dry pyridine at room temperature. The ester 1b, purified

by tlc, was carefully treated with 1 equivalent of m-chloroperbenzoic acid in CH_2Cl_2 (a slow addition of mCPBA) to give a mixture of mono-epoxy esters in 60% yield. The three epoxy esters (4b, 5b and 6b) were separated by preparative tlc on 0.5 mm Brinkmann silica gel plates (developed three times in 1% ethyl acetate in benzene), and hydrolyzed with 0.1N-NaOH in aqueous acetone (R_f: 0.34, 0.32 and 0.30 for 4a, 5a, and 6a respectively in ether/n-hexane/HOAc = 30/70/1).

After esterification with CH_2N_2 and hydrogenation, the identities of the three epoxy acids (4a, 5a and 6a) were confirmed by direct comparison (tlc and mass spectra) with the authentic samples 7 and 8 prepared from commercially available eicosa-11-cis-enoic acid and eicosa-all-cis-11,14-dienoic acid.

The radioactive epoxy dienoic acids ([1-^{14}C]-4a, 5a and 6a, specific activity 2.36μCi/μmol) were similarly prepared from [1-^{14}C]-all-cis-8,11,14-eicosatrienoic acid (obtained from New England Nuclear). When the labeled 4a, 5a and 6a were separately tested in the phenol activated sheep seminal vesicle microsome, acetone powder system for prostaglandin biosynthesis, none of the epoxy acids induced a detectable change in the rate of oxygen uptake or were converted to significant quantities of prostaglandin E or F.[7] Therefore, in agreement with the findings by Sih et al.[3], it is unlikely that the three epoxy acids are substrates or free intermediates in the prostaglandin synthetase system from sheep seminal vesicle.

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2. F. D. Gunstone, Chem. and Ind., 1551 (1966); E. J. Corey, G.W.J. Fleet and M. Kato, Tetrahedron Lett., 3963 (1973).
3. R. Sood, M. Nagasawa and C. J. Sih, Tetrahedron Lett., 423 (1974). These experiments utilized unlabeled epoxide.
4. When van Tamelen's conditions[5] were tried on arachidonic acid, some selectivity in favor of 14,15-epoxy-trienoic acid was obtained; in contrast benzonitrile-H_2O_2-$NaHCO_3$ conditions[6] seemed to favor the formation of 5,6-epoxy-trienoic acid.
5. E. E. van Tamelen and T. J. Curphey, Tetrahedron Lett., 121 (1962); E. E. van Tamelen and K. B. Sharpless, ibid., 2655 (1967).
6. G. B. Payne, Tetrahedron, 18, 763 (1962).
7. We would like to thank Drs. U. F. Axen and F. F. Sun of Upjohn Co. for carrying out these experiments.