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SYNTHESIS OF 14(R),15(S)- AND 14(S),15(S)-DIHYDROXY-5,8-Z-10,12-E - EICOSATETRAENOIC ACID

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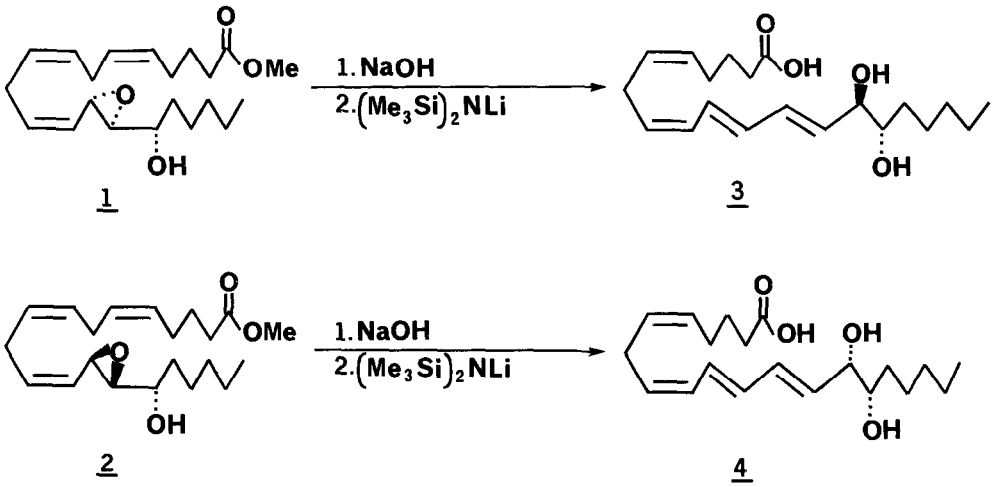
Summary: 14(R),15(S)- and 14(S),15(S)-dihydroxy-5,8-Z-10,12-E-eicosatetraenoic acids were prepared from 15(S)-HETE by allylic epoxidation and base induced isomerization.

Recently, two epimeric 14,15-dihydroxyeicosatetraenoic acids, designated 14,15-DiHETE or 14,15-LTB_4 depending upon their enzymatic origin, have been isolated from incubations of arachidonic acid or 15(S)-hydroperoxyeicosatetraenoic acid (15-HPETE) with platelets and leukocytes[1]. A similar transformation of 15-HPETE is catalyzed by hemoglobin and methemoglobin[2]. Although available in only minute amounts from natural sources, the biogenesis and complete structure of these eicosanoids have been elucidated[1e]. Described herein is a stereospecific synthesis of the individual epimers in sufficient quantity for pharmacological evaluation and comparison with biologically derived material.

We have shown that erythro and threo methyl 15(S)-hydroxy-13,14-E-oxido-5,8,11-Z-eicosatrienoates, 1 and 2, respectively, provide ready access to products derived from lipoxygenase and epoxygenase metabolites of the arachidonate cascade[3]. To exploit this approach for the preparation of 14(R),15(S)-dihydroxy-5,8-Z-10,12-E-eicosatetraenoic acid 3, epoxy-alcohol 1 was saponified (NaOH,rt,10h) in tetrahydrofuran (THF)/H_2O (3:1) and the resultant salt isolated by adsorption (1-2h) onto BioRad SM-2 beads[4] after thorough evaporation of the organic solvent. The product was removed from the resin with methanol, dried azeotropically, and treated with lithium bis(trimethylsilyl)amide (4-5 equiv, 0°C→rt over 1h, 2h at rt) in THF[5]. The dark yellow mixture was quenched at 0°C and adjusted to pH 4. Extractive isolation and chromatography (SiO_2:5% MeOH/CH_2Cl_2, $R_f \sim 0.30$) yielded 3[6] (55%). The 14(S),15(S)-epimer 4 was obtained from 2[3] in an analogous manner.



1 3

2 4

Both 3 and 4 had uv and CI/EI mass spectra consistent with published data[1]. The assigned 8-Z-10,12-E-triene geometry was confirmed with the methyl esters by appropriate nmr decoupling experiments. NMR (200 MHz, C_6D_6) for both were very similar: δ 1.31(3H,t), 1.54-2.20(12H, complex m), 2.25-2.40(2H, m), 2.46(2H,t,J~7Hz), 3.14-3.27(2H, m), 3.64(3H, s), 3.83(1H,br s), 4.21(1H,br s), 5.38-5.72(3H, m), 5.84(1H,dd,J~7,15Hz), 6.13-6.42(2H, m), 6.47(1H,dd,J~15,15Hz), 6.70(1H,dd,J~11,15Hz).

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1. (a) U. Lundberg, O. Radmark, C. Malmsten, and B. Samuelsson, FEBS Letters 126: 127-132, 1981. (b) W. Jubiz, O. Radmark, J.A. Lindgren, C. Malmsten, and B. Samuelsson, Biochem. Biophys. Res. Comm. 99: 976-986, 1981. (c) D.-E. Sok, C.-O. Han, W.-R. Shieh, B.-N. Zhou, and C.J. Sih, ibid. 104: 1363-1370, 1982. (d) J. Turk, R.L. Maas, A.R. Brash, L.J. Roberts, II, and J.A. Oates, J. Biol. Chem. 257: 7068-7076, 1982. (e) R.L. Maas and A.R. Brash, Proc. Natl. Acad. Sci. USA 80: 2884-2888, 1983, also corrects earlier report.

2. D.-E. Sok, T. Chung, and C.J. Sih, Biochem. Biophys. Res. Comm. 110: 273-279, 1983.

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4. A spherical, macroreticular styrene-divinylbenzene copolymer (20-50 mesh). The beads were prepared prior to use by three sequential washings with 0.01 N NH_4OH, 0.01 N ammoniacal methanol, and distilled H_2O.

5. For a closely related transformation see, E.J. Corey, P.B. Hopkins, J.E. Munroe, A. Marfat, and S.-I. Hashimoto, J. Amer. Chem. Soc. 102: 7986-7987, 1980.

6. Occasionally, minor amounts of isomeric trienes could be detected and were removed by HPLC: Waters μ-Bondapak C-18 (30x1.2 cm), gradient CH_3CN/H_2O/HOAc 40:60:0.1 to 70:30:0.1 over 30 min, flow rate 3 ml/min; retention time 21 and 23.5 min for 3 and 4, respectively. Waters μ-Porasil, hexane/2-propanol/HOAc 99:1:0.1 to 97:3:0.1 over 30 min, flow rate 3 ml/min; retention time 24 and 26 min for 3 and 4, respectively.

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