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ENANTIOSPECIFIC TOTAL SYNTHESIS OF 8- and 12-HYDROXYEICOSATETRAENOIC ACID

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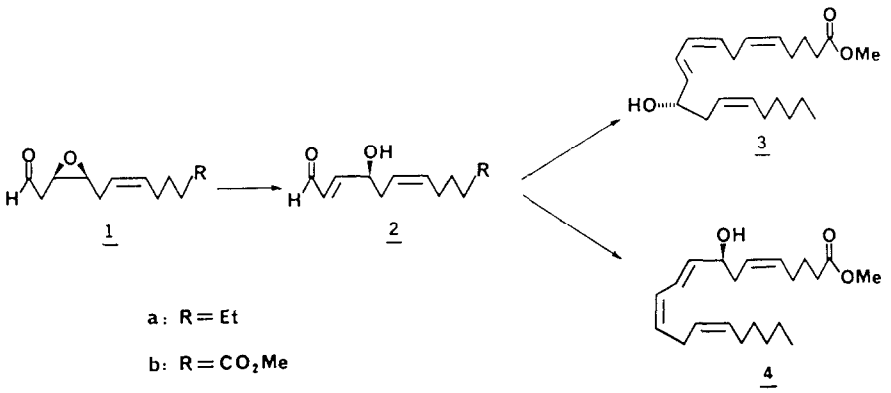
Summary: The R- and S-isomers of 8- and 12-hydroxyeicosatetraenoic acid (8- and 12-HETE) were synthesized from dimethyl malate derived precursors.

Recently, two of the six regioisomeric hydroxyeicosatetraenoic acids (HETEs) generated by monooxygenases[1], i.e., 8- and 12-HETE, have been found to occur naturally in either enantiomeric form[2-5]. The S-antipode of 12-HETE is produced by a variety of biological systems including human platelets[2] while the R-isomer predominates in human psoriatic scale[3]. Both 12-HETE enantiomers have engendered widespread attention[6] as putative mediators of inflammation or other pathophysiological conditions[7]. In contrast, little is known about the distribution and pharmacology[8] of the 8-HETE enantiomers, primarily as a consequence of the limited availability of authentic material. As an extension of our program[9] to develop synthetic strategies which would make monooxygenase metabolites of arachidonic acid readily available for chemical and biological study, we describe herein the convergent total syntheses of both enantiomers of 8- and 12-HETE.



Epoxy-aldehyde 1a, fabricated[9] from dimethyl L-malate, was smoothly isomerized to trans-enal 2a[10,11] (90-92%) by stirring with an ethereal suspension of silica gel (100 mg 1/g, E. Merck, 70-230 mesh) for 20-30 min, filtration and chromatographic purification (SiO_2:5% $MeOH/CH_2Cl_2$, R_f~0.50). Condensation of 2a with 7-carbomethoxyhepta-3-(Z)-en-1-ylidenetriphenylphosphorane (-78 to -15°C, 3h) in THF/HMPA (4:1), quenching with 25% aq NH_4OAc, extractive isolation, and chromatography (SiO_2:Et_2O/hexane 1:1, R_f~0.55) afforded methyl 12(S)-HETE (3) in 65-68% yield, $[\alpha]_D^{23}$ +12.8° (c 1.64, acetone); lit.[6b] $[\alpha]_D^{22}$ +13°

(c 1.5, acetone). Likewise, 1b furnished 2b (R_f~0.44) which in turn was coupled with 3-(7)-nonenylidenetriphenylphosphorane to give methyl 8(S)-HETE (4) in 71% yield following chromatography (R_f~0.35), $[\alpha]_D^{23}$ -4.75° (c 1.60, $CHCl_3$); reported[5] $[\alpha]_D^{22}$ -4.75° (c 0.4, $CHCl_3$). Starting with dimethyl D-malate[9], optically pure methyl 8(R)- and 12(R)-HETE were realized utilizing analogous procedures.

The HETE methyl esters were converted to the corresponding free acids with NaOH in MeOH/H_2O (3:1), acidification to pH 4, and extractive isolation. Results from current investigations into the occurrence, enzymatic origin, and pharmacology of HETE enantiomers will be reported in due course.

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10. Satisfactory nmr, ir, and mass spectral data were obtained for all new compounds using chromatographically homogeneous samples.
11. Spectral data for 2a: NMR ($CDCl_3$, 90 MHz) δ 0.88 (t, J~6Hz, 3H), 1.08-1.48 (m, 7H), 1.80-2.17 (m, 2H), 2.38 (t, J~6Hz, 2H), 4.20-4.57 (m, 1H), 5.14-5.71 (m, 2H), 6.23 (ddd, J~16,8,2Hz, 1H), 6.77 (dd, J~16,8Hz, 1H), 9.60 (d, J~8Hz, 1H). 2b: 1.54-2.60 (m, 8H), 3.62 (s, 3H), 4.27-4.57 (m, 1H), 5.22-5.67 (m, 2H), 6.24 (ddd, J~16,8,2Hz, 1H), 6.77 (dd, J~16,8Hz, 1H), 9.60 (d, J~8Hz, 1H). 3: 0.88 (t, J~6Hz, 3H), 1.06-1.44 (m, 6H), 1.51-2.37 (m, 10H), 2.87 (t, J~6Hz, 2H), 3.62 (s, 3H), 4.00-4.25 (m, 1H), 5.14-6.00 (m, 7H), 6.48 (dd, J~15,11Hz, 1H). The spectrum of 4 was virtually identical to that of 3.

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