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TRANSFORMATION OF 15-HETE TO 14,15-DIHYDROXYEICOSATRIENOIC ACID AND 11,14,15- AND 13,14,15-TRIHYDROXYEICOSATRIENOIC ACID

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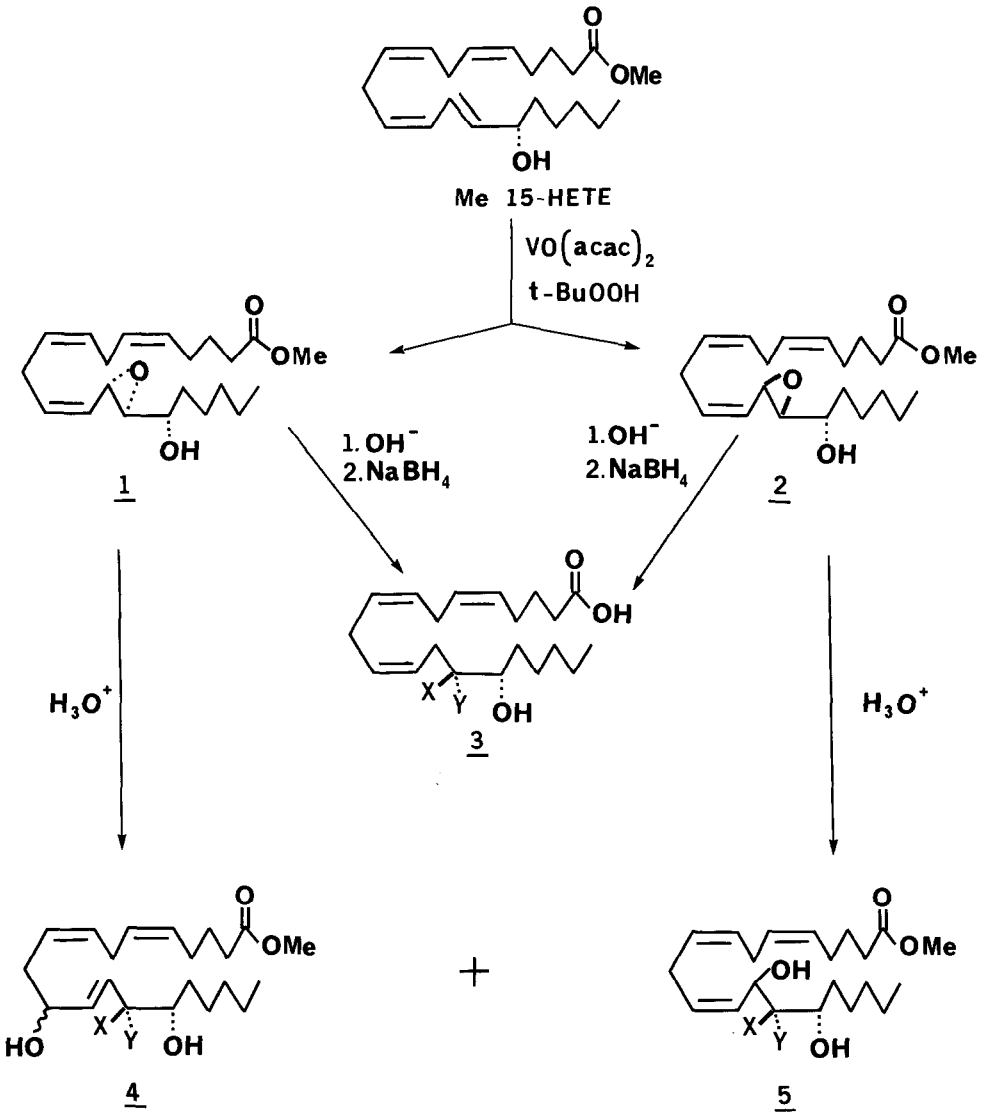
Summary: The erythro and threo 13,14-epoxides of 15(S)-HETE were transformed to 14,15-dihydroxyeicosatrienoic acid (14,15-DHET) by regiospecific reduction and to a mixture of 11,14,15- and 13,14,15-trihydroxyeicosatrienoic acids (THET) by hydrolysis.

In the past decade, a wide variety of biologically active, oxygenated arachidonate metabolites have been isolated[1]. Recent additions to this list include several di- and trihydroxylic eicosanoids derived enzymatically and non-enzymatically from primary oxidation products of the lipoxygenase and epoxygenase pathways[2]. Because these metabolites are present in only minute amounts, structure confirmation and biological evaluation must in many instances rely on the availability of synthetic material. An expeditious approach to some of these eicosanoids which exploits a readily available starting material is described herein and in the following paper[3].

Vanadium catalyzed allylic epoxidation[4] of methyl 15(S)-hydroxyeicosatetraenoate[5] (Me 15-HETE) generated a separable mixture of 1 and 2 (82%, 2.3:1 ratio)[6]. TLC:SiO_2, Et_2O/hexane (1:1) containing 1% Et_3N, $R_f \sim 0.32$ and 0.24, respectively[7]. Their stereochemistries were established by saturation (Pt/H_2, MeOH) with concomitant allylic hydrogenolysis, silylation, and gas chromatographic comparison[2d] with silylated erythro/threo dihydroxyeicosanoate[8] standards (3% SP-2100 DOH, 9 ft., 205°C).

The epoxygenase pathway[2d,9] of arachidonate metabolism produces four regioisomeric epoxyeicosatrienoic acids (EETs) which are in turn converted to vic-diols (DHETs) by cytosolic epoxide hydrolase[10]. Both the EETs and DHETs have been detected in vivo[11] and show potent biological activity in vitro[2a,12]. The absolute configuration of the EETs has been



a: X = H, Y = OH

b: X = OH, Y = H

determined[11], however, for the DHETs only the relative configuration of 14,15-DHET is known[2d]. To gain access to a 14,15-DHET of known configuration, 1 was saponified (NaOH, THF/H_2O, rt, 10h) and the sodium salt reduced regiospecifically with $NaBH_4$ (DMSO, 90°C, 1.5h). Acidification (pH 4) and extractive isolation afforded 14(R),15(S)-DHET, 3a (54%) after chromatography [SiO_2:5% $MeOH/CH_2Cl_2$, R_f ~0.34; methyl ester Et_2O/hexane (2:1), R_f ~0.30][7]. Epoxide 2 furnished 14(S),15(S)-DHET 3b[7].

Mild acid hydrolysis [1% aq. $HClO_4$/THF (1:3), 0°C, 2h] of 1 gave 4a (48%) as a mixture of C-11 epimers[13] whose chromatographic and mass spectral properties were in agreement with a 11,14,15-trihydroxy-5,8,12-eicosatrienoic acid (THET) of unknown geometry isolated from leukocytes[2b]. Additionally, regioisomeric THET 5a (20%) was obtained. While 5a appeared homogeneous in several chromatographic systems, the stereochemistry at C-13 is unknown. Given the recent isolation of a 13-hydroxy-14,15-oxido-5,8,11-eicosatrienoic acid[2b] and precedent for conversion of related epoxy-alcohols to triols[2c], it is likely that THETs such as 5a will be isolated. The 12,13-olefin in 4a and 11,12-olefin in 5a were trans (15.4 Hz) and cis (11.2 Hz), respectively, by nmr analysis (200 MHz). Finally, in some instances, minor amounts of 14(R),15(S)-DiHETE[3] were also found. TLC:SiO_2, 5% $MeOH/CH_2Cl_2$, 3 elutions, R_f ~0.17, 0.19, 0.34, and 0.56 for 4a (2 isomers), 5a, and 14,15-DiHETE, respectively. Hydrolysis of 2 gave a similar product profile of 4b, 5b and a small amount of 14(S),15(S)-DiHETE.

With recent advances in the enzymatic and synthetic preparation of HETE enantiomers[14], the procedures described here should provide access to other polyhydroxylic eicosanoids[2].

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ratio of >13:1 and 2:1, respectively. See, T. Katsuki and K.B. Sharpless, J. Amer. Chem. Soc. 102: 5974-5976, 1980.

5. Preparation and random epoxidation of methyl 15-HETE, J.E. Baldwin, D.I. Davies, L. Hughes, and N.J.A. Gutteridge, J.C.S. Perkin I 1979: 115-121. The 15-HETE prepared by this procedure was 85% S (15% R). All products described in the text are assumed to reflect this enantiomeric composition.

6. Satisfactory spectral data (nmr, ir, mass spectroscopy) were obtained for all new compounds using chromatographically homogeneous samples.

7. NMR of 1 (90 MHz, $CDCl_3$): δ0.92 (3H,t), 1.16-2.20 (13H,complex m), 2.32 (2H,t,J~7Hz), 2.68-3.12 (5H,m), 3.64 (3H,s), 3.72-3.96 (2H,m), 4.92-5.80 (6H,m); 2:0.90 (3H,t), 1.12-2.20 (13H,complex m), 2.32 (2H,t,J~7Hz), 2.68-3.12 (5H,m), 3.40-3.76 (5H,m, ester singlet at 3.64), 4.92-5.80 (6H,m); 3a methyl ester:0.96 (3H,t), 1.10-2.24 (16H,m), 2.38 (2H,t,J~7Hz), 2.68-3.08 (4H,m), 3.50-3.80 (5H,m, ester singlet at 3.68), 5.20-5.76 (6H,m); 3b methyl ester:0.96 (3H,t), 1.08-2.24 (16H,m), 2.37 (2H,t,J~7Hz), 2.58-2.98 (4H,m), 3.22-3.74 (5H,m, ester singlet at 3.68), 5.14-5.74 (6H,m).

8. Erythro standard from partial cis-hydroxylation of methyl 11,14-eicosadienoate (Sigma) with OsO_4, separation of regioisomers, and catalytic reduction. Threo standard from catalytic reduction of methyl 14,15-dihydroxyeicosatrienoate prepared according to S. Manna, J.R. Falck, N. Chacos, and J. Capdevila, Tetrahedron Lett. 24: 33-36, 1983.

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13. NMR of 4a more polar isomer (90 MHz, $CDCl_3$): δ0.95 (3H,t), 1.15-2.67 (19H,complex m), 2.83 (2H,t,J~5.5 Hz), 3.30-3.56 (1H,m), 3.66 (3H,s), 3.77-3.96 (1H,m), 4.02-4.32 (1H,m), 5.16-5.60 (4H,m), 5.64-5.92 (2H,m); 4a less polar isomer was superimposable with other isomer at 90 MHz; 5a: δ0.88 (3H,t), 1.14-2.21 (12H,complex m), 2.33 (2H,t,J~7Hz), 2.65-3.03 (4H,m), 3.28-3.44 (1H,m), 3.68 (3H,s), 3.70-3.94 (1H,m), 4.60 (1H,dd,J~5,7 Hz), 5.15-5.76 (6H,m).

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