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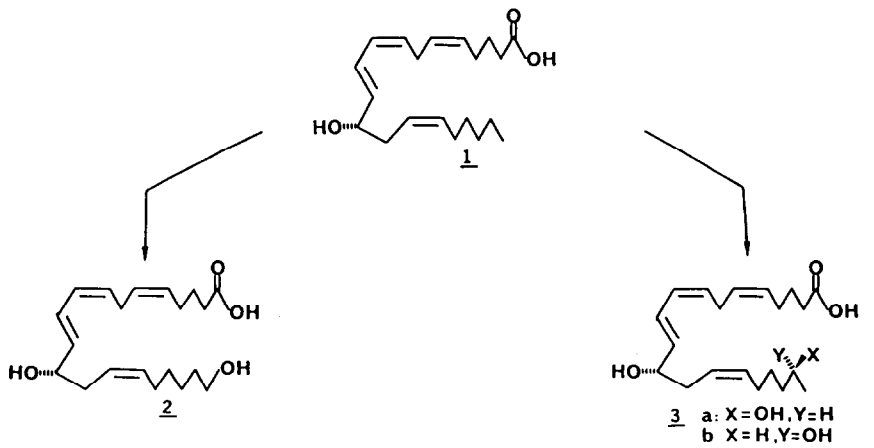
SYNTHESIS OF 12(S),20-, 12(S),19(R)-, AND 12(S),19(S)-DIHYDROXY-EICOSA-CIS-5,8,14-TRANS-10-TETRAENOIC ACIDS, METABOLITES OF 12(S)-HETE

Sukumar Manna, Jacques Viala[1], Pendri Yadagiri, and J.R. Falck*
Department of Molecular Genetics, University of Texas Health Science Center
Dallas, Texas 75235 USA

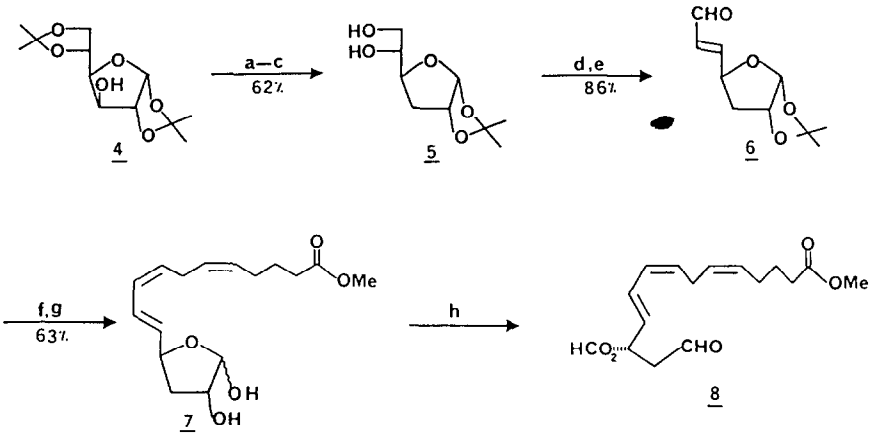
Summary: Enantiospecific syntheses of the 20- and both 19-hydroxy metabolites of 12(S)-HETE were accomplished using readily available, chiral precursors.

Recently, a new metabolite of 12(S)-hydroxyeicosatetraenoic (12-HETE) acid (1) was isolated from the coincubation of human platelets and neutrophils with arachidonic acid[2]. The metabolite, 12,20-dihydroxyeicosatetraenoic (12,20-DiHETE) acid (2), is produced from platelet derived 12-HETE by a monooxygenase ω-hydroxylation system such as cytochrome P-450 present in neutrophils. Individually, neither cell type is competent to produce 2 from arachidonic acid. Based on biogenetic considerations[3] and in vitro studies using microsomal cytochrome P-450, it may be anticipated that the corresponding ω-1 hydroxylated metabolite, i.e., 12,19-DiHETE 3, is also produced. As part of our current efforts to address the involvement and physiological significance of monooxygenases in eicosanoid metabolism as well as to provide confirmation of structure, we report herein the enantiospecific syntheses of 1-3.



The strategy for constructing the C-1 through C-14 moiety common to 1-3 is outlined in Scheme I. Deoxygenation[4] of di-O-isopropylidene-α-D-glucofuranose[5] (4) followed by selective removal of the 5,6-acetonide gave diol 5 (62%), mp. 84°C (lit.[6] 84°C). Sodium periodate cleavage and homologation of the resultant aldehyde with 1 equiv of formylmethyltriphenylphosphonium chloride in the presence of triethylamine at room temperature smoothly generated trans-enal 6[7,8] (86%) which was converted to 7 (63%) by condensation with the ylide of (7-carbomethoxyhepta-3-Z-en-1-yl)triphenylphosphonium bromide (9) under cis-olefination conditions and careful hydrolysis of the furanose acetonide. Anhydrous periodic acid cleavage of 7 afforded labile β-formyloxy aldehyde 8[9] which was used in situ following treatment (5 min) with powdered $CaSO_4$ and filtration over Celite[10].

Scheme I



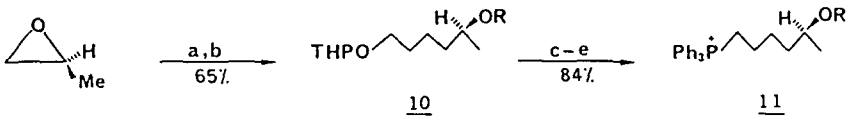
[a]NaH, CS_2, THF, 1h; MeI, 10 min. [b]Bu_3SnH, $PhCH_3$, 110°C, 16h. [c]0.8% H_2SO_4/MeOH (1:3), 24h; $NaHCO_3$. [d]$NaIO_4$, MeOH/H_2O (2:1), 0°C, 20 min. [e]$ClPh_3PCH_2CHO$, Et_3N, PhH, 20h. [f]9, $(Me_3Si)_2NLi$, THF/HMPA (4:1), -78°–> 24°C, 12h. [g]1mM TsOH, CH_3CN/H_2O (10:1), 60°C, 23h; $NaHCO_3$. [h]H_5IO_6, THF, 0°C, 5 min; $CaSO_4$.

A 0.1 M solution of 8 was transferred via canula to a -100°C solution of 6-(t-butyldiphenylsilyloxy)hexylidenetriphenylphosphorane[3a] (3 equiv, 0.11 M) in THF. Immediately after complete addition, the reaction was placed in a -78°C bath whereupon HMPA (20% v/v) was added and the mixture warmed to -15°C over 3.5-4 h, then quenched with methanol (10 min). Extractive isolation, chromatographic purification[11] to remove a variable amount of 8,10-E,E isomer, and desilylation (Bu_4NF, THF, 3.5 h) furnished the methyl ester of 2 (38-43% from 7).

For complete pharmacological evaluation and to help define the stereochemical consequences[12] of ω-1 hydroxylation, it was desirable to prepare both C-19 epimers of 3. Accordingly, copper cyanide catalyzed addition of 3-(tetrahydropyranyloxy)propylmagnesium

bromide to S-(-)-propylene oxide[13] and silylation gave 10 (65%) (Scheme II). Sequential THP removal, alcohol to bromide interchange, and treatment with excess triphenylphosphine yielded 11 (84%). Repetition of the sequence in Scheme II using R-(+)-propylene oxide[14] led to the enantiomeric phosphonium salt 12. Union of 8 with 11 and 12 under the conditions described above and desilylation (Bu_4NF, THF, 40h) afforded the methyl esters of 3a and 3b, respectively. The methyl ester of 1 was likewise made from 8 using n-hexylidenetriphenylphosphorane. Acids 1-3 were obtained quantitatively from their esters by saponification with NaOH in $MeOH/H_2O$ (3:1), acidification to pH 4, and extractive isolation[17].

Scheme II



10 11

R= t-BuPh$_2$Si

[a]THPO$(CH_2)_3$MgBr, CuCN, THF, -20°->0°C, 2hr. [b]t-BuPh_2SiCl, ImH, DMF. [c]Amberlyst 15, MeOH, 45°C, 1h. [d]CBr_4, Ph_3P, Et_2O. [e]Ph_3P, CH_3CN, 80°C, 5h.

The foregoing syntheses provide ready access to sufficient quantities of 1-3 for pharmacological testing. Investigations into their occurrence and physiological role will be reported in due course.

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References and Notes

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7. Unless otherwise noted, satisfactory nmr, ir and mass spectroscopic data were obtained for all new compounds using chromatographically homogeneous samples.

8. Physical data for 6: NMR ($CDCl_3$, 90 MHz) δ 1.33 (s,3H), 1.53 (s,3H), 1.62-2.41 (m,2H), 4.70-4.95 (m,2H), 5.82 (d, J ∿ 3.5Hz, 1H), 6.26 (ddd, J ∿ 16, 7, 1.5Hz, 1H), 6.74 (dd, J ∿ 16, 5Hz, 1H), 9.50 (d, J ∿ 7Hz, 1H); mass spec (PICI,CH_4) m/e 199,183,141,123; TLC, SiO_2, EtOAc/hexane (1:1) R_f ∿ 0.39; $[\alpha]^{24}_D$-61.8° (c 0.49, $CHCl_3$). 1,2-Acetonide of 7: NMR ($CDCl_3$, 90 MHz) δ 1.30 (s,3H), 1.51 (s,3H), 1.57-1.82 (m,2H), 1.98-2.37 (m,2H), 2.87 (apparent t, J ∿ 6Hz, 2H), 3.61 (s,3H), 4.51-4.80 (m, 2H), 5.14-6.05 (m,5H), 5.77 (d, J ∿ 3.5Hz, 1H), 6.52 (dd, J ∿ 15, 11Hz, 1H); mass spec (PICI,CH_4) m/e 337,319,279,261,247,229; $[\alpha]^{23}_D$-19.3° (c 1.57, $CHCl_3$); TLC, SiO_2, EtOAc/hexane (1:2), R_f ∿ 0.40. 7: NMR ($CDCl_3$, 90MHz) δ 1.57-2.37 (m,8H), 2.85 (apparent t, J ∿ 6Hz, 2H), 3.60 (s,3H), 4.20 (br s, 1H), 4.51-4.90 (m,1H), 5.14-6.17 (m, 7H), 6.45 (dd, J ∿ 15, 11Hz, 1H); TLC, SiO_2, MeOH/CH_2Cl_2 (1:9), R_f ∿ 0.37. 2 methyl ester: NMR ($CDCl_3$, 90MHz) δ 1.20-2.18 (m,14H), 2.30 (t, J ∿ 7Hz, 2H), 2.74-3.00 (m,2H), 3.58 (t, J ∿ 7Hz, 2H), 3.62 (s,3H), 4.00-4.34 (m,1H), 5.14-6.06 (m,7H), 6.48 (dd, J ∿ 15, 11Hz, 1H); mass spec (PICI, CH_4) of methyl ester TMS ether m/e 495,479,463,405,391,333,315, 295,283. 10: NMR ($CDCl_3$, 90MHz) δ 1.04 (s,9H), 1.06 (d, J ∿ 7Hz, 3H), 1.28-1.80 (m,12H), 3.16-4.00 (m,5H), 4.48 (br s, 1H), 7.20-7.36 (m,6H), 7.44-7.68 (m,4H); TLC, SiO_2, Et_2O/hexane (1:1), R_f ∿ 0.54. 3a methyl ester: NMR ($CDCl_3$, 90MHz) δ 1.16 (d, J ∿ 7Hz,3H), 1.28-2.16 (m,12H), 2.30 (t, J ∿ 7Hz, 2H), 2.76-3.00 (m, 2H), 3.62 (s,3H), 3.60-3.88 (m,1H), 4.00-4.32 (m, 1H), 5.12-6.08 (m, 7H), 6.50 (dd, J ∿ 15, 11Hz, 1H); mass spec (PICI, CH_4) of methyl ester TMS ether m/e 495,479,405,389,315,295,283; $[\alpha]^{24}_D$ 2.6° (c 1.65, $CHCl_3$); TLC, SiO_2, Et_2O, R_f ∿ 0.34. 3b methyl ester: NMR and mass spec were essentially identical to 3a; $[\alpha]^{24}_D$-3.17° (c 2.34, $CHCl_3$); TLC, SiO_2, Et_2O, R_f ∿ 0.40.

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10. Alternatively, $NaBH_4$ reduction of 7 and buffered $NaIO_4$ cleavage yielded the corresponding β-hydroxy aldehyde (90% crude yield). Subsequent Wittig coupling, however, gave variable results.

11. TLC: SiO_2, Et_2O/hexane (1:2), 3 elutions, Z,E/E,E-isomers R_f ∿ 0.35 and 0.32, respectively.

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14. In the R-(+)-propylene oxide series, the diol corresponding to 10 was converted to its di-4-nitrobenzoate derivative and found to have mp 109-110°C, $[\alpha]^{24}_D$-37° (c 1.5, $CHCl_3$); Lit.[15] mp 105-106°C, $[\alpha]_D$-33° (c 0.26, $CHCl_3$); Lit.[16] mp 110-110.5°C, $[\alpha]_D$-39.7° ($CHCl_3$).

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17. By HPLC, 2 was indistinguishable from enzymatically derived material. Prof. P.Y-K. Wong, New York Medical College, personal communication.

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