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ENANTIOSPECIFIC SYNTHESIS OF ISOMERIC 8,9,12-TRIHYDROXYEICOSA-5(Z),10(E),14(Z)-TRIENOIC ACIDS

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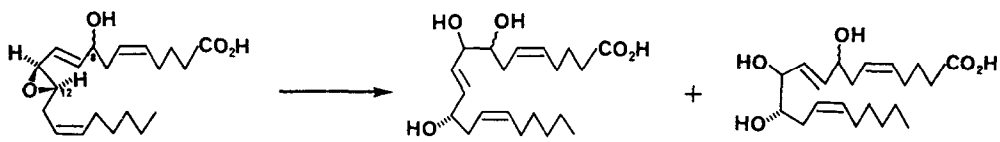
Summary: Five stereoisomers of triol 2, an arachidonic acid metabolite isolated from platelets, were prepared using a convergent strategy based on β-oxido ylide homologation of a carbohydrate-derived precursor.

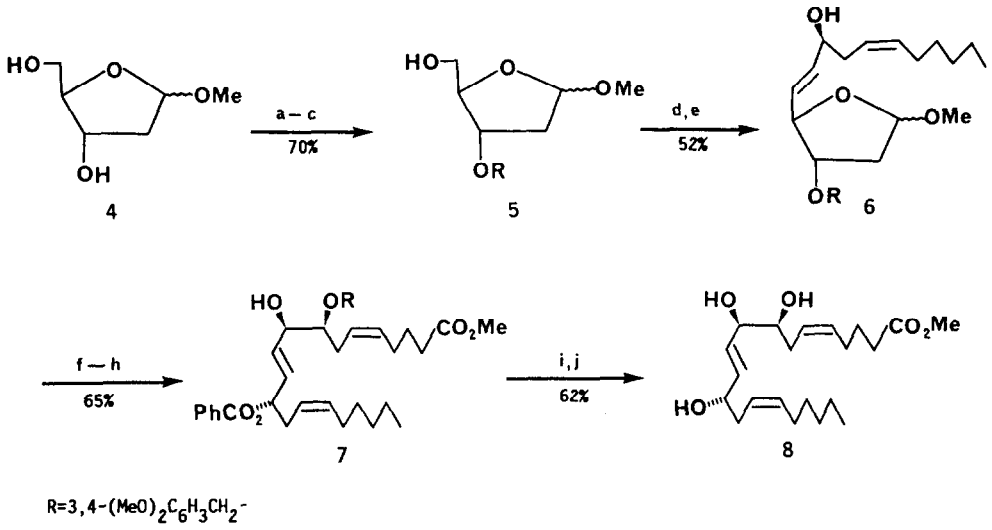
Trioxilins 2 and 3 were isolated initially from mammalian platelets by Jones *et al*[1] who proposed that they arise from 12(S)-hydroperoxyeicosatetraenoic acid via rearrangement to oxiranyl carbinol 1 and subsequent hydration. The structure of 1, now known as hepoxilin A_3, was established as 8(R/S)-hydroxy-11(S),12(S)-epoxyeicosa-5(Z),10(E),14(Z)-trienoic acid by total synthesis[2]. The configuration at C(12) is retained during hydroperoxide rearrangement[3] and epoxide hydrolysis[4]. Nevertheless, the complete stereochemical constitutions of the triols are unknown. Analogous metabolites derived from other polyunsaturated fatty acids have been identified in plants, marine organisms, and several animal species, although generally their stereochemistries are also obscure[5].



1 2 3

Metabolites of the hepoxilin/trioxilin pathway are of current interest as presynaptic messengers in **Aplysia** sensory cells[6] and as pancreatic insulin secretagogues[7]. However, due to the limited availability of natural material, further progress in defining the physiological role(s) of these metabolites and in clarifying their structural assignments is critically dependent on synthetic standards of known configuration. Consequently, we report herein the preparation of five stereoisomers of triol 2 by an unambiguous route utilizing a carbohydrate precursor. A synthesis of the biogenetically related 10,11,12-trihydroxyeicosatrienoic acids has been achieved recently[8].

SCHEME I



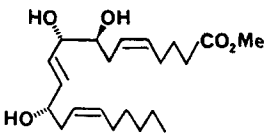
R=3,4-$(MeO)_2C_6H_3CH_2$-

[a] p-$MeOC_6H_4C(C_6H_5)_2Cl$, C_5H_5N/CH_2Cl_2 (1:2), DMAP, 40°C, 10 h. [b] 3,4-$(MeO)_2C_6H_3CH_2Cl$, KH, THF, 67°C, 6 h. [c] $ZnBr_2$ (10 equiv), $MeOH/CH_2Cl_2$ (1:20), 24°C, 0.3 h. [d] $(COCl)_2$/DMSO, CH_2Cl_2, -78°C, 1 h; Et_3N, -78°C → 23°C, 1 h. [e] **9**, THF, -78°C → 0°C, 3.5 h; 0°C, 10 h. [f] PhCOCl, C_5H_5N/CH_2Cl_2 (1:8), 0°C, 12 h. [g] $AcOH/H_2O$/THF (5:2:2), 70°C, 7 h. [h] **10** (3.6 equiv), THF/HMPA (3:1), -78°C → -20°C, 7 h; CH_2N_2. [i] NaOMe, MeOH, 23°C, 6 h. [j] 2% HCl-MeOH/THF (3:1), 23°C, 10 h.

Methyl furanoside **4**, prepared[9] as an anomeric mixture from commercial 2-deoxy-D-ribose (95%), was converted into **5**[10] by selective primary alcohol etherification, protection of the C(3) hydroxyl with 3,4-dimethoxybenzyl chloride, and zinc bromide mediated[11] detritylation (Scheme I). The aldehyde obtained by Swern oxidation of **5** was added in a minimum volume of tetrahydrofuran (THF) to a dark red, 75 mM solution of the β-oxido ylide **9** of 2(S)-hydroxydeca-4(Z)-en-1-yltriphenylphosphonium chloride[12] (1.8 equiv; generated at -30°C, THF, *sec*-BuLi, 30 min) in THF at -78°C. The mixture was gradually warmed to 0°C over 3.5 h where it was maintained for an additional 10 h. Quenching with ice-cold 25% aqueous NH_4OAc, extractive isolation, and chromatography [TLC:SiO_2, EtOAc/hexanes (3:1), $R_f \sim 0.52$] afforded **6** whose ^1H NMR (300 MHz) spectrum confirmed the newly created *trans*-olefin ($J \sim 15.7$Hz). Differentially protected triol **7** was obtained from **6** by benzoylation and mild acid hydrolysis to the corresponding lactol which was condensed with 4-carboxybutylidenetriphenylphosphorane (**10**) under Wittig *cis*-olefination conditions and esterified with diazomethane. TLC of **7** : SiO_2, hexanes/EtOAc (2:1), $R_f \sim$

0.32. Methanolysis of the benzoate and removal of the benzyl protecting group with 2% methanolic HCl furnished methyl 8(S),9(R),12(S)-trihydroxyeicosa-5(Z),10(E),14(Z)-trienoate[13] (**8**), $[\alpha]_D^{22}$ +10.5° (c 1.4, acetone); TLC:SiO_2, hexanes/EtOAc (1:1), $R_f \sim 0.27$.

Mitsunobu inversion[14] of **7** utilizing triphenylphosphine/diethyl azodicarboxylate (DEAD)/benzoic acid (2 equiv each) in THF at 0°C gave the corresponding epimeric C(9)-benzoate **11**. Benzoate solvolysis and debenzylation as described above generated methyl 8(S),9(S),12(S)-trihydroxy-5(Z),10(E),14(Z)-trienoate (**12**) in 59% overall yield from **7** accompanied by a variable amount of C(11)-diastereomeric triol **13**, the result of allylic transposition during the Mitsunobu reaction. TLC : SiO_2, hexanes/EtOAc (1:5), $R_f \sim 0.47$ and 0.33 for **12** and **13**, respectively. Likewise, stereoisomeric triols **14** and **15** were made in 21-23% overall yield by controlled inversion of **7** and **11**, respectively, by the sequence: benzoate solvolysis, protection of the C(9) and C(12) alcohols as their 2-(trimethylsilyl)ethoxymethyl ethers[15] (SEM-Cl, i-Pr_2NEt,CH_2Cl_2), debenzylation[16] (DDQ, CH_2Cl_2/H_2O), Mitsunobu inversion, benzoate solvolysis, and acidic SEM ether hydrolysis (2% methanolic HCl). For pharmacological comparison, triol **16** with the unnatural R-configuration at C(12) was produced by subjecting **6** to Mitsunobu inversion using benzoic acid and carrying the resultant epi-benzoate through the remaining steps in Scheme I.



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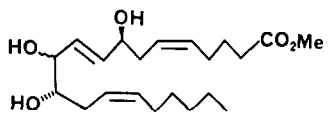

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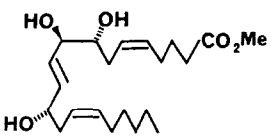

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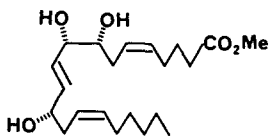

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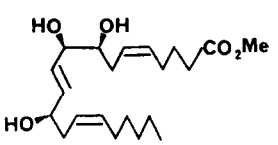

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Esters **8**,**12**, and **14-16** were converted to their free acids by saponification (LiOH,MeOH/H_2O 3:1), adjustment to pH 4.5, and extractive isolation. Results from our investigations into the occurrence and pharmacological profile of this novel class of eicosanoids will be reported elsewhere.

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13. Physical data for **8**: ^{1}H NMR($CDCl_3$, 300 MHz) δ 0.88 (t, J~7.0 Hz, 3H), 1.20-1.41 (m,6H), 1.68 (apparent p, 2H), 1.98-2.12 (m,4H), 2.17-2.37 (m,6H), 3.65 (s,3H), 3.63-3.71 (m,1H), 4.14-4.22 (m,2H), 5.32-5.60 (m,4H), 5.78 (dd, J~5.0, 15.6 Hz, 1H), 5.85 (dd, J~5.0, 15.6 Hz, 1H); MS (PICI,CH_4) of TMS ether m/e: 119, 139, 171, 213, 243 (base), 315, 405, 479, 495, 569, 585 (M^+), 613. **12**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, J~7.0 Hz, 3H), 1.22-1.35 (m, 6H), 1.66 (apparent p, 2H), 2.00 (q,2H), 2.07 (q, 2H), 2.15-2.35 (m, 6H), 3.48 (dt, J~5.2, 7.6 Hz, 1H), 3.64 (s, 3H), 3.96 (apparent t, 1H), 4.16 (apparent q, 1H), 5.33-5.58 (m, 4H), 5.72 (dd, J~6.1, 15.6 Hz, 1H), 5.83 (dd, J~5.4, 15.6 Hz, 1H); $[\alpha]_D^{22}$ - 13.8° (c 1.4, acetone). **13**: MS (PICI, CH_4) of TMS ether m/e: 213, 243 (base), 315, 405, 479, 495, 569, 585 (M^+), 613. **14**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, J~7.0 Hz, 3H), 1.23-1.33 (m, 6H), 1.67 (apparent p, 2H), 2.00 (q,2H), 2.07 (q, 2H), 2.15-2.35 (m, 6H), 3.48 (dt, J~5.1, 7.8 Hz, 1H), 3.64 (s, 3H), 3.96 (apparent t, 1H), 4.14 (apparent q, 1H), 5.30-5.57 (m, 4H), 5.70 (dd, J~6.0, 15.6 Hz, 1H), 5.81 (dd, J~6.0, 15.6 Hz, 1H),; $[\alpha]_D^{22}$ + 34° (c 1.5, acetone). **15**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, J~7.0 Hz, 3H), 1.20-1.35 (m, 6H), 1.66 (apparent p, 2H), 1.99-2.08 (m, 4H), 2.12-2.35 (m, 6H), 3.64 (s, 3H), 3.63-3.69 (m, 1H), 4.12 (apparent t, 1H), 4.17 (apparent q, 1H), 5.34-5.55 (m, 4H), 5.76 (dd, J~5.0, 15.5 Hz, 1H), 5.81 (dd, J~5.0, 15.5 Hz, 1H); $[\alpha]_D^{22}$ + 9.1° (c 1.1, acetone).
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