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SYNTHESIS OF TRIOXILIN B_3

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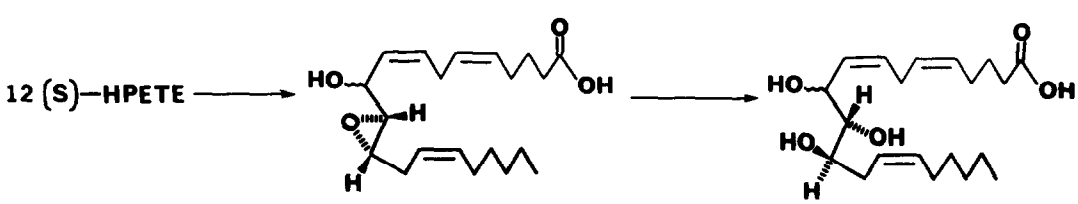
Summary: Both C(10) diastereomers of trioxilin B_3, presumed to be a mixture of 10(R/S), 11(R),12(R)-trihydroxyeicosa-5(Z),8(Z),14(Z)-trienoic acids, were prepared from a carbohydrate derived precursor by Wittig homologation and Mitsunobu inversion.

Hepoxilin B_3, first identified by Walker et al[1] in 1979, arises via intramolecular rearrangement[2] of 12(S)-hydroperoxyeicosatetraenoic acid [12(S)-HPETE] and is now known to consist of two isomeric 10-hydroxy-11,12-epoxyeicosatrienoic acids (1) whose exact stereochemical constitution has been confirmed by total chemical synthesis[3]. Stable isotope studies[4] revealed 1 is regiospecifically hydrated at C(12) to the corresponding triols 2, designated trioxilin B_3, by an epoxide hydratase present in rat lung homogenate. Based on the well precedented[5] expectation of stereochemical inversion at the site of hydration, 2 can be formulated as 10(R/S),11(R),12(R)-trihydroxyeicosa-5(Z),8(Z), 14(Z)-trienoic acid.

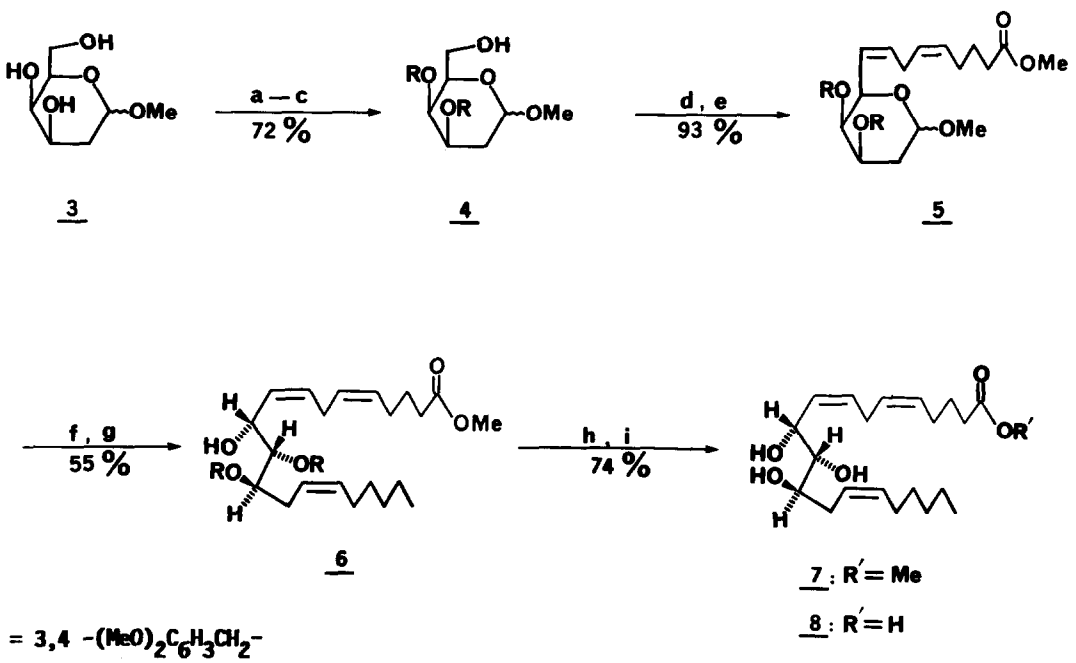


1 2

Interest in the arachidonate metabolites of the hepoxilin/trioxilin pathway has been heightened recently by reports of their insulin secretagogue activity[6] and possible role as second messengers for presynaptic inhibition of **Aplysia** sensory cells[7]. Related metabolites originating from linoleic, linolenic, eicosatrienoic, and eicosapentaenoic

acids have been observed previously, although generally their stereochemistries remain obscure[8]. To expedite the further study of the occurrence and pharmacological profile of this novel class of eicosanoids, we report herein the enantiospecific total synthesis of both C(10) diastereomers of trioxilin B_3.

Scheme I



3 4 5

6

7: R′ = Me

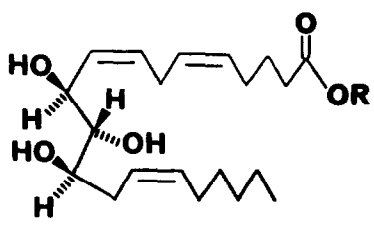
8: R′ = H

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

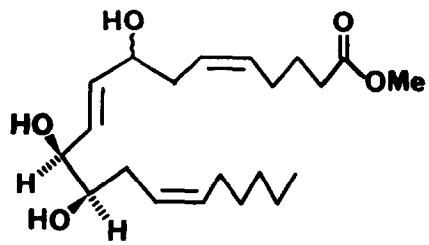
[a] Ph_3CCl, CH_2Cl_2/C_5H_5N (8:1), DMAP, 40°C, 12h. [b] 3,4-$(MeO)_2C_6H_3CH_2Cl$, KH, THF, 45°C, 3h. [c] $ZnBr_2$ (5 equiv), CH_2Cl_2/MeOH (20:1), 24°C, 2h. [d] $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1h; ET_3N, -20°C, 0.5h. [e] **9**, THF/HMPA (10:1), -40°→0°C, 0.5h. [f] AcOH/THF/H_2O (3:1:1), 70°C, 3h. [g] **10**, THF/$PhCH_3$ (1:3), -78°→0°C, 2h; 0°C, 40 min. [h] 2% HCl/MeOH, 45°C, 3h. [i] LiOH, MeOH/H_2O (2:1), 24°C, 5h.

Methyl pyranoside **3**, prepared[9] as an anomeric mixture from commercial 2-deoxy-D-galactose (88%), was converted to **4**[10] (72%) by primary selective tritylation, protection of the secondary alcohols with 3,4-dimethoxybenzyl chloride, and zinc bromide mediated[11] detritylation (Scheme I). Swern oxidation[12] of **4** and condensation of the

resultant aldehyde with 1.2 equiv of 7-carbomethoxyhepta-3(Z)-en-1-ylidenetriphenylphosphorane[13] (**9**) under *cis*-olefination conditions furnished ester **5** (93%) after chromatographic purification (SiO_2: EtOAc/hexanes 3:1, $R_f \sim 0.53$). The lactol obtained from **5** by mild acid hydrolysis was added dropwise in a minimum volume of toluene to a 36mM solution of hexylidenetriphenylphosphorane (**10**) [2.7 equiv; generated at -78°C, THF, 0.5h, $LiN(SiMe_3)_2$] in toluene/THF (3:1) at -78°C. The mixture was gradually warmed to 0°C over 2h where it was maintained for an additional 40 min. Quenching with ice-cold 50% aqueous NH_4OAc, extractive isolation, and flash chromatography afforded **6** (55% overall from **5**) accompanied by a small amount of its 14(E)-isomer. TLC:SiO_2, EtOAc/hexanes (1:1), two elutions, $R_f \sim 0.55$ and 0.61 for **6** and 14(E)-**6**, respectively. Removal of the benzyl protecting groups with 2% methanolic HCl yielded methyl 10(R),11(R),12(R)-trihydroxyeicosa-5(Z),8(Z),14(Z)-trienoate[14] (**7**), $[\alpha]_D^{22}$-16.4° (c 3.5, acetone), which was saponified to free acid **8** (74% overall from **6**); TLC: SiO_2, $MeOH/CH_2Cl_2$ (1:9), $R_f \sim 0.35$.



11: R = Me
12: R = H



13

Mitsunobu inversion[15] of **6** utilizing triphenylphosphine/diethyl azodicarboxylate/benzoic acid (2 equiv each) in THF at 0°C followed by benzoate solvolysis (NaOMe/MeOH, 22°C, 10h) and debenzylation as described above generated methyl 10(S),11(R),12(R)-trihydroxyeicosa-5(Z),8(Z),14(Z)-trienoate (**11**), $[\alpha]_D^{22}$+29.2° (c 2.0, acetone). Saponification gave free acid **12** in 30% overall yield from **6**; TLC: SiO_2, $MeOH/CH_2Cl_2$ (1:9), $R_f \sim 0.38$. Unexpectedly, triol **13**, the result of allylic transposition during the Mitsunobu reaction, was also isolated and found to be an approximate 1:5 diastereomeric mixture at C(8); TLC: SiO_2, $MeOH/CH_2Cl_2$ (5:95), $R_f \sim 0.15$ and 0.17.

Details of current investigations into the production and physiological relevance of trioxilins will be reported elsewhere.

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14. Physical data for 7: ^{1}H NMR($CDCl_3$, 300 MHz) δ 0.88 (t, J~6Hz, 3H), 1.17-1.40 (m,6H), 1.68 (dt, J~6, 12Hz, 2H), 1.95-2.15 (m,4H), 2.22-2.42 (m,4H), 2.73-3.01 (m,2H), 3.45 (dd, J~6, 6Hz, 1H), 3.65 (s,3H), 3.73 (dt, J~4, 6Hz, 1H), 4.69 (dd, J~4, 10Hz, 1H), 5.32-5.48 (m,3H), 5.52-5.74 (m,3H); MS (EI, 70ev) of TMS ether m/e: 103, 129 (base), 147, 159, 186, 213, 225, 269, 282, 315, 342; RP-HPLC: μBondapak C_{18} (3.9 x 300 mm), CH_3CN/H_2O (35:65), 1 ml/min flow rate, R_t ~ 13.5 min, monitored at 210 nm.11: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J~6Hz, 3H), 1.17-1.42 (m, 6H), 1.68 (dt, J~6, 12Hz, 2H), 1.93-2.58 (complex m, 11H), 2.74-3.03 (m, 2H), 3.42-3.55 (m, 1H), 3.56-3.72 (m with methyl ester singlet at 3.65, 4H), 4.65 (dd, J~6, 10Hz, 1H), 5.32-5.75 (m, 6H); MS (PICI, CH_4) of TMS ether m/e: 213 (base), 269, 287, 315, 343, 355, 405, 429, 479, 511, 555, 569, 585.

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