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Stereoselective Synthesis of 10(S), 11(R), 12(R)-Trihydroxyeicosa-5(Z), 8(Z), 14(Z)-Trienoic Acid from D-Mannose

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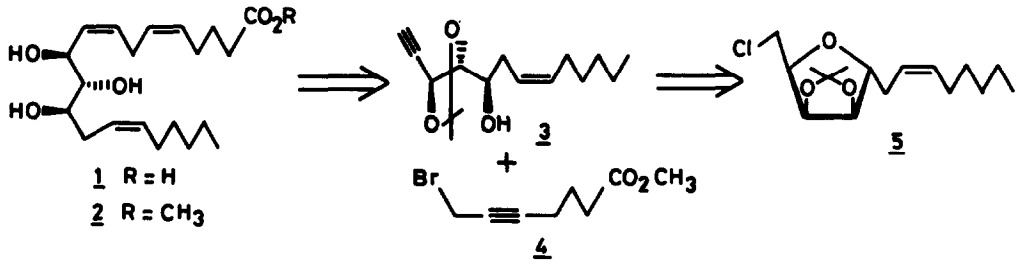
Abstract : A stereoselective synthesis of the title compound, from D-mannose using base induced double elimination of β-alkoxy chloride as key step is described.

Trioxilin B_3, which has been identified[1] as a mixture of 10(R/S), 11R, 12R-trihydroxy-eicosa-5(Z), 8(Z), 14(Z)-trienoic acids, is formed from hepoxilin B_3 by an epoxide hydratase enzyme present in rat lung homogenate[2]. Hepoxilins[3,4] are biologically active epoxy alcohols derived from 12(S)-hydroperoxyeicosatetraenoic acid [12(S)HPETE] formed[5] in the mammalian platelets via 12-lipoxygenation pathways of arachidonic acid which plays[6] a very crucial role in hemostasis and several respiratory disorders. Recent findings that the arachidonic metabolites of the hepoxilin/trioxilin pathways have insulin secretagogue activity[7] and their possible role as second messengers for presynaptic inhibitors of Aplysia sensory cells[8] have aroused renewed interest in their synthesis. The exact mode of action in their pharmacological profile is at present obscure because of their non-availability in larger quantities. To extend the scope of further exploration of the physiological importance of this novel class of eicosanoids, we report herein an enantiospecific total synthesis of 10(S)-diastereomer of trioxilin B_3 from D-mannose, a readily available chiral carbohydrate.

The retrosynthetic analysis of **1** (Scheme 1) indicates that acetylene **3** and the acetylenic bromide **4** are the ideal intermediates. The acetylenic functionality in **3** can be utilized for

Scheme 1

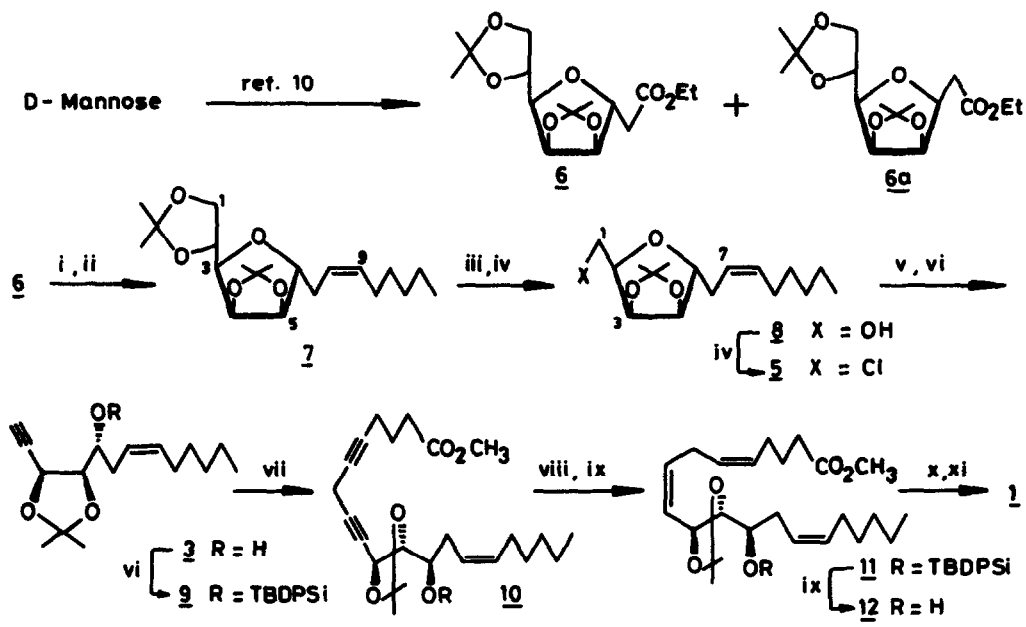


C-C bond formation and for the realisation of Z-olefin. **3** can be realised by β-alkoxy double elimination of the chloride **5** by the method recently demonstrated by us[9], which on alkylation with **4** and further transformations thereon would lead to the title compound.

5 was obtained from the known ester **6**[10] in a sequence of reactions as depicted in Scheme 2. Thus, DIBAL-H reduction of **6** provided the corresponding aldehyde, which was immediately treated with $Ph_3P{=}CH(CH_2)_4CH_3$ under cis olefination conditions to get the

Z-olefin **7**. Chemoselective cleavage of the 5,6-isopropylidene with 60% aq. AcOH followed by $NaIO_4$ cleavage of the resulting diol, furnished the corresponding aldehyde, which was

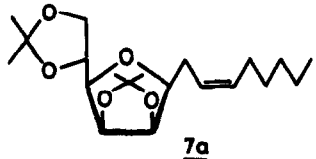
Scheme 2



Reagents and reaction conditions

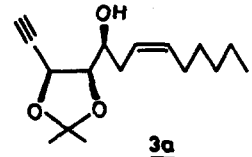
i) DIBAL-H, CH_2Cl_2, -78°C, 30 min, 95%; ii) $C_6H_{13}\overset{+}{P}Ph_3Br^-$, $NaNH_2$, THF-HMPA (4:1), -78°C to rt, 3h, 70%; iii) (a) 60% aq.AcOH, 28°C, 6h; b) $NaIO_4$, CH_3CN-H_2O (3:1), 3h; c) $NaBH_4$, EtOH, 30 min, 73% from **7**; iv) PPh_3, CCl_4, reflux, 6h; v) $LiNH_2$, liq. NH_3, -33°C, 30 min, 86%; vi) TBDPSiCl, Imidazole, DMF, 60°C, 8h, 94%; vii) n-BuLi, CuI, THF-HMPA (3:1), -78°C to 0°C, 30 min; **4** in THF, -78° to rt, 2h; viii) Pd-$CaCO_3$, H_2, EtOH; ix) 60% HF-Py, THF, 28°C, 36h; x) p-TSA (cat), MeOH, 28°C, 20h, 85%; xi) LiOH, MeOH-H_2O (2:1), 28°C, 10h,

reduced immediately to alcohol **8** in an overall yield of 49% from **6**. Treatment of alcohol **8** with triphenylphosphine in refluxing CCl_4 gave rise to **5** (90%). **5** was then subjected to double elimination with $LiNH_2$ in liquid NH_3 to produce the dianion of **3** on which attempted in situ C-alkylation with **4**[11] proved futile. In an attempt to utilize undesired diastereomer **6a**, it was converted to **3a** via **7a** and **8a** using the similar sequence of reactions described in the scheme 2 for **3** in 38% overall yield. However, the epimerisation of free hydroxyl group in **3a**, using Mitsunobu reaction, gave mostly the dehydrated product instead of required **3**.



7a

8a



3a

3 was converted into its silyl derivative **9** to facilitate the alkylation. The crucial coupling of **9** with **4** proved to be more difficult than anticipated. However, it was achieved in 95% yield via mixed Gillmann reagent formed from equimolar quantities of **9**, freshly prepared n-BuLi, CuI in THF-HMPA (3:1)(-78° to 0°C, 30 min) followed by dropwise addition of the bromide **4** (1 eq) in THF (-78° to rt, 2 hr). The resulting ester **10** was partially hydrogenated to **11**, and desilylated with 60% HF-PY to the alcohol **12** in 70% yield. Acid catalysed deketalization of **12** in methanol gave the known triol trienoate **2**, $[\alpha]_D$ +28.4° (c 2.0, acetone) (lit[1] $[\alpha]_D$ +29.2° (c 2.0, acetone) which was further saponified with LiOH to **1**[12] (76%), $[\alpha]_D$ +30.2° (c 1.8, acetone).

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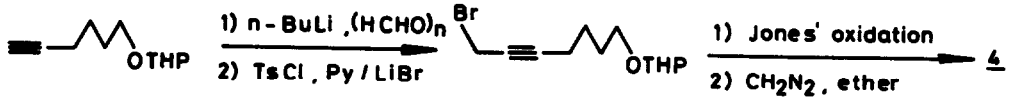
11. a) The acetylenic bromide **4** was prepared by totally different route[11b] as described below.



(b) E J Corey and H S Sachdev, J Am Chem Soc, 1973, **95**, 8483.

12. (a) All new compounds gave expected spectral data and exact mass (HRMS), (b) 200 MHz ^{1}H NMR ($CDCl_3$) and $[\alpha]_D$ of some selected compounds: **1**: δ 5.4-5.75 (m, 6H, olefinic), 4.67 (dd, 1H, H-10, J_1=5.9, J_2=9.8 Hz), 3.5-3.85 (m, 2H, H-11, H-12), 3.1-3.45 (br. hump, 4H, -OH and -COOH, exchangeable with D_2O), 2.89-3.05 (m, 2H, H-7), 2.01-2.65 (m, 8H, H-2 and allylic), 1.72 (dt, 2H, J_1=6, J_2=12 Hz), 1.19-1.5 (m, 8H, methylenes), 0.91 (t, 3H, $-CH_3$, J=6.64 Hz), **7**: δ 5.34 and 5.53 (2xtd, each 1H, H-8, H-9), 4.77 (dd, 1H, H-4, J_1=4, J_2=6.4 Hz), 4.53 (d, 1H, H-5, J=6.4 Hz), 4.01-4.14 (3H, 2dd, H-1 merged with t of H-6), 3.78 (dd, 1H, H-3, J_1=4, J_2=8 Hz), 2.19 (t, 2H, H-7,

J=8 Hz); $[\alpha]_D$ -4.0° (c 1.0, $CHCl_3$). **7a:** δ 5.37 and 5.46 (2xtd, each 1H, H-8, H-9), 4.72 (dd, 1H, H-3, J_1=4.2, J_2=6.8 Hz), 4.58 (dd, 1H, H-5, J_1=4.2, J_2=6.2 Hz), 3.96-4.09 (m, 3H, H-3, H-1), 3.45 (dt, 1H, H-6, J_1=6.2, J_2=7.2 Hz), 2.47 (t, 2H, H-7, J=7.2 Hz); $[\alpha]_D$ +6.75° (c 1.6, $CHCl_3$). **8:** δ 5.3 and 5.48 (2xtd, each 1H, H-7, H-8), 4.73 (dd, 1H, H-3, J_1=4.2, J_2=6.3 Hz), 4.48 (d, 1H, H-4, J=6.3 Hz), 4.06 (t, 1H, H-5, J=7.58 Hz), 3.87-3.94 (m, 1H, H-2), 3.76-3.87 (m, 2H, H-1), 2.05-2.21 (m, 2H, H-6), 1.87-2.02 (m, 2H, H-9); $[\alpha]_D$ +5.37° (c 1.6, $CHCl_3$). **8a:** δ 5.39 and 5.46 (2xtd, each 1H, H-7,H-8), 4.68 (dd, 1H, H-3, J_1=4.27, J_2=5.4 Hz), 4.56 (dd, 1H, H-4, J_1=3.6, J_2=5.4 Hz), 3.83-3.91 (m, 2H, H-1), 3.52-3.59 (m, 1H, H-2), 3.44 (dt, 1H, H-5, J_1=3.6, J_2=6.7 Hz), 2.45 (t, 2H, H-6, J=6.7 Hz), 1.91-2.12 (m, 2H, H-9); $[\alpha]_D$ +16.96° (c 1.45, $CHCl_3$). **3:** δ 5.47 and 5.65 (2xtd, each 1H, H-7, H-8), 4.9 (dd, 1H, H-3), 2.6 (d, 1H, H-1, J=2.4 Hz), 2.49-2.52 (m, 1H, H_a-6), 2.23-2.44 (m, 1H, H_b-6), 2.08 (dist.q, 2H, H-9); $[\alpha]_D$ -30.72° (c 1.1, $CHCl_3$). **3a:** δ 5.46 and 5.56 (2xtd, each 1H, H-7,H-8), 4.75 (dd, 1H, H-3), 2.56 (d, 1H, H-1), J=2.39 Hz), 2.22-2.38 (m, 2H, H-6), 2.05 (dist.q, 2H, H-9); $[\alpha]_D$ -57.73° (c 1.5, $CHCl_3$). **10:** δ 7.63-7.76 (m, 4H, aromatic), 7.28-7.42 (m, 6H, aromatic), 5.2-5.5 (m, 2H, H-14,H-15), 4.69 (d, 1H, H-10, J=5.5 Hz), 4.19 (td, 1H, H-12, J_1=7.7 and J_2=8.2 Hz), 4.0 (dd, 1H, H-11, J_1=5.5, J_2=7.7 Hz), 3.65 (s, 3H, $COOCH_3$), 2.85 (ABq, 2H, H-7); $[\alpha]_D$ +59.32° (c 1.1, $CHCl_3$).

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