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Stereoselective Synthesis of (11R,12S)-(5Z,7E,9E,14Z)-11,12-dihydroxy-5,7,9,14-eicosatetraenoic acid from 'Diacetone Glucose'

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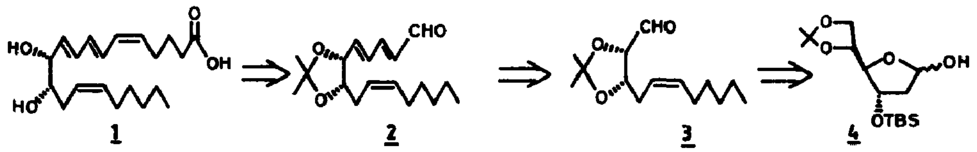
Abstract : A stereoselective total synthesis of (11R,12S)-diHETE is described. The strategy is based on the use of a 'sugar' derived 'chiron' for the incorporation of 'vic-diol' stereocentres, while Wittig reactions for the assembly of requisite carbon frame work of the target molecule.

(11R,12S)-diHETE[1], an enzymatic metabolite, belonging to a novel class of oxygenated eicosanoids, is found in leucocytes from arachidonic acid from the lipoxygenase pathway by the conversion of (11,12)-LTA_4 by an epoxide hydrolase derived from guinea pig liver cystol. In continuation of our programme[2] on the synthesis of hydroxy fatty acids, herein, we report the total synthesis[3] of (11R,12S)-diHETE (**1**), by making use of the 'chiron' derived from 'diacetone glucose' as the source of 'vic-diol' system present in **1**, which will enable to procure the material in larger quantities for biological screening.

From the disconnection approach (Scheme 1), it was reasoned that the dissection at C-5 and C-6 bond of **1**, would lead to dienal **2**, which inturn could come from **3**. Aldehyde **3**, could be envisioned from lactol **4**, which inturn could be easily made from D-glucose.

Scheme - 1



1 2 3 4

The known[2a] furanoid glycal **5** (Scheme 2) prepared from D-glucose was subjected to hydration[4] ($Hg(OAc)_2$, aq. THF, KI, $NaBH_4$) to afford the lactol **4**[5] (76%) which on Wittig olefination with n-hexyltriphenylphosphonium bromide (n-BuLi, THF, -78°C) furnished **6** (68%). Fluoride catalysed desilylation of **6** and subsequent treatment of diol **7** with dimethoxypropane in presence of PTSA gave **8** (62%). Hydrolysis of **8** (0.8% H_2SO_4, MeOH, RT) followed by $NaIO_4$ (aq. THF) cleavage of the resulting diol afforded **3** (73%), $[\alpha]_D$ -18.9° (c 1.25, $CHCl_3$). Aldehyde **3** on reaction with 2.3 equivalents of (formylmethylene)triphenylphosphorane (toluene, 80°C) afforded **2** (72%) along with its lower vinylogue[6]. **2** without purification was subjected to second Wittig reaction with (4-carboxybutyl)triphenylphosphonium bromide (LiHMDS, THF-HMPA, -78°C) and purified by column chromatography to give **9** (62%) $[\alpha]_D$ -15.4° (c 0.85, $CHCl_3$) which on treatment with ethereal diazomethane furnished ester **10**[7] (85%) $[\alpha]_D$ -5.3° (c 0.8,

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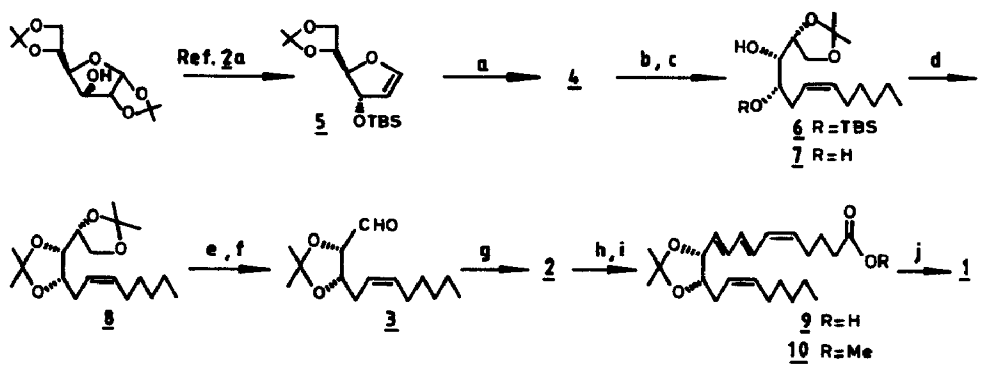
$CHCl_3$). Finally acid **9** on exposure to CF_3CO_2H in DCM at 0° furnished (+)(11R,12S)-diHETE (**1**), whose spectral data was in full agreement with reported[3b] data.

Scheme - 2



a) $Hg(OAc)_2$, KI, $NaBH_4$, aq. THF; b) $Ph_3PBr(CH_2)_5CH_3$, n-BuLi, THF, -78°; c) Bu_4NF, THF; d) dimethoxypropane, PTSA, DCM; e) 0.8% H_2SO_4, MeOH; f) $NaIO_4$, aq. THF; g) $Ph_3P{=}CH-CHO$, Toluene, 80°; h) $Ph_3PBr(CH_2)_4COOH$, LiHMDS, THF-HMPA (4:1), -78°C; i) CH_2N_2, ether; j) CF_3COOH, DCM.

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5. All the new compounds gave satisfactory elemental analysis.
6. See ref: Spur, B. and Jendralla, H. *Arch. Pharm.* **1986**, 319, 140.
7. ^1H NMR data (200 MHz, $CDCl_3$, TMS, δ in ppm): **10** - 0.9 (t, 3H), 1.2-1.45 (m, 8H), 1.4, 1.5 (2s, 6H), 1.7 (t, 2H), 1.95-2.4 (m, 6H), 3.65 (s, 3H), 4.05-4.2 (m, 1H), 4.5-4.65 (m, 1H), 5.25-5.7 (m, 6H), 5.94-6.1 (m, 1H), 6.4-6.6 (m, 1H).

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