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TOTAL ENANTIOSPECIFIC SYNTHESIS OF 12(R)-HETE

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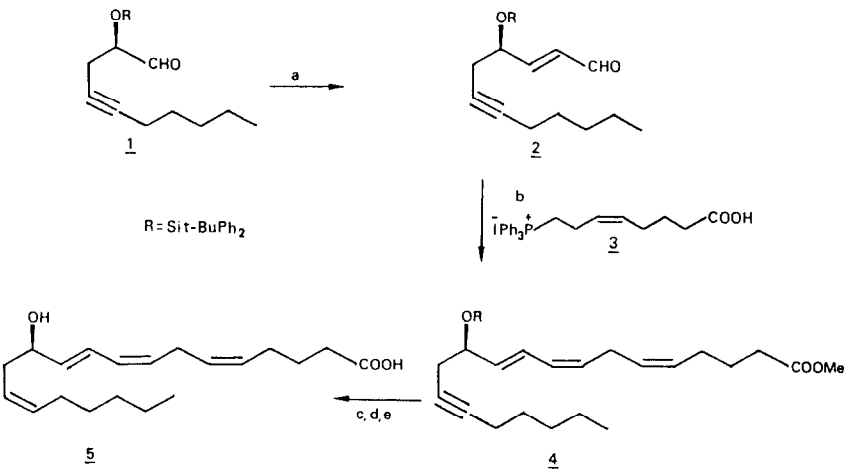
Summary: A total synthesis of 12(R)-hydroxy-5,8,14-cis-10-trans-eicosatetraenoic acid [12(R)-HETE] was accomplished via a short, efficient, enantiospecific route.

The recent report that 12-HETE from psoriatic lesions has the unusual R stereochemistry[1] has sparked numerous investigations into the biosynthesis and biological activity of this eicosanoid. Recent investigations have shown that 12(R)-HETE is more potent than its 12(S) enantiomer in a neutrophil chemokinesis assay[2] and shows an affinity ten times higher than that of 12(S)-HETE to the LTB_4 receptor[3]. In addition, it elicits an inflammatory response in cornea epithelial cells and inhibits Na^+,K^+-ATPase[4]. There has been much speculation as to its mode of biosynthesis including involvement of the cytochrome P-450 pathway[4,5], a 12-keto reductase[3] and a 12(R) lipoxygenase[11].

Recent reports[6] describing syntheses of 12(R)-HETE (5) have prompted us to report our short, efficient and enantiospecific synthesis starting from aldehyde 1. This aldehyde is readily prepared in both antipodes starting from R or S glycerol acetonide. Since we have previously prepared large quantities of 1 for the synthesis of leukotriene B_4[7] we herein demonstrate its straightforward conversion to 12(R)-HETE. Thus, reaction of 1 with formylmethylidenetriphenylphosphorane (3.5eq., CH_2Cl_2, 20°C) resulted in unsaturated aldehyde 2 (85%)[8]. Condensation of 2 with the phosphorane derived from 3[6c] ($NaN(TMS)_2$, THF, 0°→25°C) followed by diazomethane treatment provided ester 4 in 62% yield. Intermediate 4 was converted to 12(R)-HETE in three steps: a.) H_2, Lindlar catalyst, quinoline, hexane (96%); b.) nBu_4NF, THF (83%); c.) LiOH, THF, H_2O, 25°C (76%). The 12(R)-HETE thus obtained displayed identical physical properties[9] to those of 12(S)-HETE (with the exception of optical rotation) prepared by an alternative route[10] and co-eluted with 12(S)-HETE prepared from platelets (HPLC: Waters microporasil, 300 x 4.6mm, hexane:2-propanol:acetic acid (992:7:1, v/v), 1ml/min.). Analysis of the methyl ester using a Baker dinitrobenzoylphenylglycine (ionic) chiral phase HPLC column (250 x 4.6mm) eluting with n-hexane:2-propanol (100:0.5, v/v) and a flow rate of 0.5 ml/min. revealed the presence of a single enantiomer having a retention time of 37.4 min. (retention time for 12(S)-HETE was 36 min.).



Reagents: a) $Ph_3PCHCHO$, CH_2Cl_2. b) 3, $NaN(TMS)_2$, THF, CH_2N_2. c) H_2, Lindlar catalyst, quinoline, hexane. d) nBu_4NF, THF. e) LiOH, THF, H_2O.

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8. All chemical yields refer to chromatographically homogeneous products. All new compounds exibited satisfactory spectral (IR, NMR, and mass) data.

9. ^1H NMR (5), ($CDCl_3$, 250 MHz): 6.55 (dd, J=15.1Hz, 10.8Hz, 1H), 5.98(t, J=10.8Hz, 1H) 5.72(dd, J=15.1Hz, 6.8Hz, 1H). 5.62-5.32 (m, 5H), 4.21 (m, 1H),2.92 (t, J=6.0Hz, 2H), 2.30 (m, 4H), 2.05 (m, 4H), 1.80-1.20 (m, 9H), 0.85 (t, J=7.0Hz, 3H). UV: lambda max=237nm, ϵ=27,500.

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