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TOTAL SYNTHESIS OF 5(S),12(S)- and 5(S),12(R)-DIHYDROXYEICOSA-6(Z),8(E),14(Z)-TRIENOIC ACIDS, METABOLITES OF LEUKOTRIENE B_4

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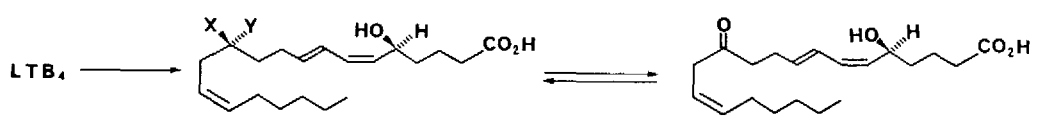
Summary: The recently identified dihydro-leukotriene B_4 metabolite 1 and its C(12)-epi analogue 2 were prepared by Wittig coupling of segments derived from 2-deoxy-D-ribose and L-glutamic acid.

Leukotriene B_4 (LTB_4), a 5-lipoxygenase metabolite of arachidonic acid, is a potent endogenous mediator of macrophage and neutrophil activity and, consequently, may play a major role in inflammation and acute hypersensitivity.[1] Human neutrophils rapidly metabolize LTB_4 to biologically less active ω-oxidized products.[2] In contrast, other cell types[3] primarily convert LTB_4 to a dihydro derivative recently assigned structure 1.[4a] Stable isotope studies suggest that the reductase acts directly on LTB_4 without activation of the triene system via a keto intermediate.[4] It is also possible that the 12(R)-stereoisomer 2 is present since dihydro-LTB_4 (1) can be further metabolized[4] in a reversible reaction to 12-oxo-dihydro-LTB_4 (3).



1: X=OH, Y=H
2: X=H, Y=OH

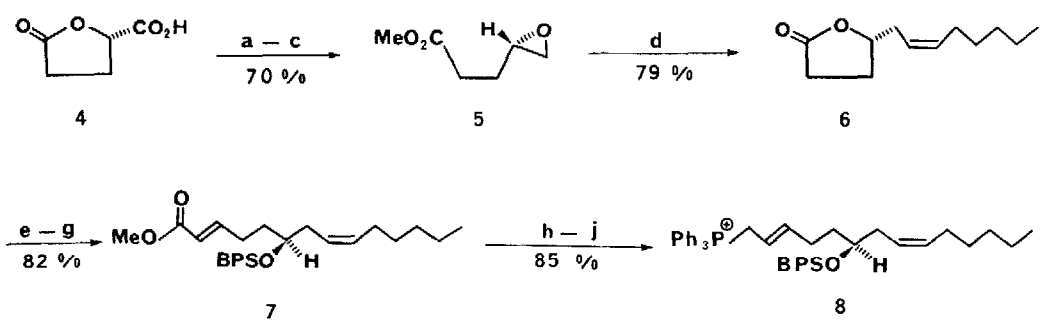
3

It is not known whether the reductase pathway plays a regulatory role[5] leading to biologically inactive catabolites or is the source of a new family of eicosanoids with unique physiological properties. Support for the latter view is provided by the recent

characterization[6] of dihydro-12-HETE in bovine cornea where it displays potent pro-inflammatory activity. To help address this and other urgent questions concerning dihydro metabolites as well as to clarify structure assignments, we report herein the asymmetric total synthesis of 1 and 2 using commercially available, chiral precursors.

Our synthesis of the fragment corresponding to C(7)-C(20) (Scheme I) commenced with borane-methyl sulfide reduction of carboxylic acid 4, readily accessible from L-glutamic acid[7], followed by methanolysis of the derived primary tosylate to give epoxy-ester 5[8] (70%). Addition of the higher order cuprate[9] (1.1 equiv) generated from (Z)-1-iodo-1-heptene[7] (9) to a 0.1 M solution of 5 with concomitant lactonization furnished 6 (79%), $[\alpha]_D^{23}$ + 17.7° (c 3.7, MeOH); lit.[10] $[\alpha]_D^{24}$ + 16.5° (c 2.6, MeOH). Diisobutylaluminum hydride (DIBAL-H) reduction of 6 and trans-specific homologation of the resultant lactol[6] with methyl (triphenylphosphoranylidene)acetate yielded ester 7[11] (82%) after silylation [TLC of 7: SiO_2, Et_2O/hexanes (1:6), R_f ~ 0.41]. The allylic alcohol obtained from 7 upon hydride reduction was transformed by standard procedures to Wittig salt 8[12] (85%) [TLC of 8: SiO_2, MeOH/CH_2Cl_2 (1:9), R_f ~ 0.29].

SCHEME I



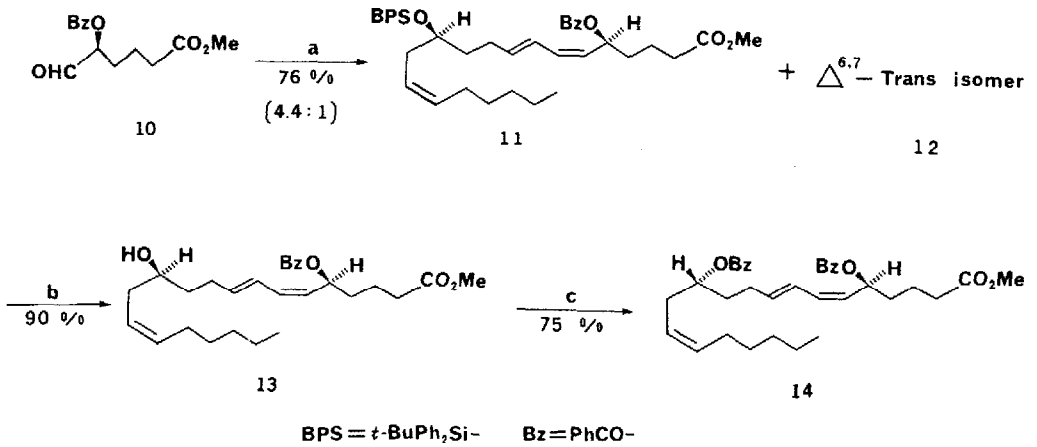
BPS = *t*-BuPh$_2$Si

[a]BH_3·Me_2S, THF, 0° to 23°C over 2h. [b]TsCl, C_5H_5N/CH_2Cl_2 (1:2.5), 24°C, 6h. [c]NaOMe, MeOH, 20 min; AcOH to pH 7. [d]9, n-BuLi, Et_2O, -60°C, 20 min; CuCN, -78° to -45°C, 30 min; 5, -50°C, 10 min. [e]DIBAL-H, $PhCH_3$, -78°C, 3h. [f]Ph_3PCHCO_2Me (1.5 equiv), $PhCH_3$, 23°C, 15h. [g]*t*-$BuPh_2SiCl$, Et_3N, DMAP, CH_2Cl_2, 45°C, 26h. [h]DIBAL-H, $PhCH_3$, -78°C, 1h. [i]CBr_4, Ph_3P, CH_2Cl_2, 1h. [j]Ph_3P, CH_3CN, 6h.

Union of methyl 5(S)-benzoyloxy-5-formylpentanoate[13] (10) with the ylide of 8 (1.2 equiv) afforded 11 (62%) and its $\Delta^{6,7}$-*trans* isomer 12 (14%) after chromatographic purification [HPLC:Altex Ultrasphere Si (4.6 x 250 mm, 5 μ), EtOAc/hexane (5:95), 1 ml/min flow rate, R_t ~ 7.32 and 9.51 min for 11 and 12, respectively]. Desilylation of

11 with fluoride ion gave rise to alcohol 13[14] (90%), $[\alpha]_D^{23}$ +160° (c 1.68, $CHCl_3$), which was smoothly inverted to the 12(R)-isomer 14 (75%), $[\alpha]_D^{23}$ +141.7° (c 1.2, $CHCl_3$), by the Mitsunobu procedure.[15]

SCHEME II



[a] 8, n-BuLi, THF/HMPA (4:1), -78°C, 1h; add 10 -78° to -50°C over 1.5h. [b] n-Bu_4NF, THF, 12h. [c] $PhCO_2H$, Ph_3P, EtO_2CNNCO_2Et, $PhCH_3$/pentane (1:1), 0°C, 1.5h.

Esters 13 and 14 were converted to 1 and 2, respectively, by saponification (LiOH, THF/H_2O 3:1), adjustment to pH 4.5, and extractive isolation[16]. Initial chromatographic comparisons revealed that natural dihydro-LTB_4 was an approximate 2:1 mixture of 1 and 2; none of the $\Delta^{6,7}$-trans isomers of 1 was detected [SP-HPLC: Altex ROSIL (4.6 x 300 mm, 5 μ), hexane/isopropanol/acetic acid (933/66/1), 2 ml/min flow rate, R_t ~ 16.0, 15.4, and 20.8 min for 1, 2, and $\Delta^{6,7}$-trans 1, respectively].[4a] Additional results from investigations into the occurrence and pharmacological profile of this novel class of eicosanoids will be reported elsewhere.

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16. Mass spectrum of 1 as its TMS ether, methyl ester (PICI, CH_4): m/e 203, 229, 267, 285, 295, 317 (base), 345, 385, 407, 481, 495, 497 (M^+1), 525 (M^+29), 537 (M^+41); MS (EI, 70 ev): m/e 147, 159, 203, 213, 229 (base), 265, 295, 305, 316, 338, 385, 395, 406, 481. The MS of 2 was virtually identical to that of 1.

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