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TOTAL SYNTHESIS OF LEUKOTRIENE B_5

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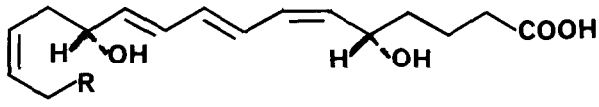
Abstract: A practical, stereocontrolled synthesis of leukotriene B_5 is described which makes this substance readily available for the first time.

Previous papers from this laboratory have described two total syntheses of leukotriene B_4 (1) which served the dual purpose of elucidating the stereochemistry of the conjugated triene unit and providing adequate material for biological study.[1,2] The analog of 1 which originates from eicosapentaenoic acid rather than arachidonic acid, LTB_5 (2), is of interest in connection with understanding the basis for the cardiovascular protective effect of dietary fish lipids.[3] Previously LTB_5 has only been obtained in minute amount (a few micrograms)[4] from biosynthetic experiments, and the study of its biological effects has been severely limited in consequence. We report here the first total synthesis of LTB_5 by a practical process which is stereocontrolled and does not require resolution.

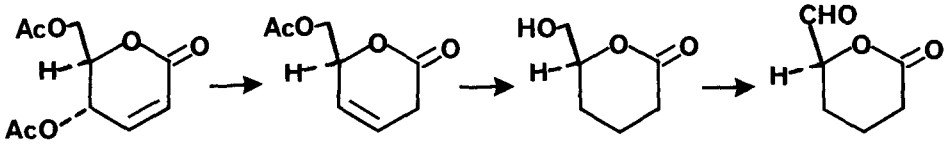
The known lactone 3,[5] which is readily available from commercial tri-O-acetyl-D-glucal,[6] was converted to the aldehyde 6 by the following sequence: (1) reduction of 3 (10 equiv. of zinc amalgum, anhydrous hydrogen chloride, ether, 0°, 2 hr., 90% yield) to give 4 ($[\alpha]_D^{20}$ -113.2° (c 1.25, $CHCl_3$)); (2) base-catalyzed double bond transposition (0.1 equiv. diazobicyclo[5.4.0]undecene, tetrahydrofuran (THF), 25°, 1 hr., 99% yield); (3) base hydrolysis (1M lithium hydroxide, dimethoxyethane (DME), 1 : 1, 25°, 2 hr.); (4) hydrogenation (1 atm.) over 10% Pd-C in ethyl acetate to give 5 ($[\alpha]_D^{20}$ + 34.68° (c 1.3, $CHCl_3$), 75% yield from 4); and (5) oxidation at 23° for 1.5 hr. with pyridinium dichromate[7] (5 equiv., anhydrous magnesium sulfate, powdered 4Å molecular sieves, CH_2Cl_2, 78%).

Octa-2,5-diyn-1-ol 7[8,9] was converted to the triphenylphosphonium iodide 12 (X= $\overset{+}{P}\phi_3I^-$) by the following sequence: (1) primary iodide formation[10] with triphenylphosphine, imidazole and iodine (1.5 equiv. of each reagent, ether-acetonitrile (CH_3CN), 3 : 1, 25°, 40 min., 97%); (2) copper (I) catalyzed alkylation with the bisbromomagnesium salt of propargyl alcohol[11] (5 equiv., THF, 65°, 12 hr., 7 → 8, 90%); (3) reduction with lithium aluminum hydride[12] in ether at 25° for 5 hr. (8 → 9, 91%); (4) enantioselective epoxidation[13] using dimethyl (S,S) (-) tartrate (9 → 10, 76%, 10: $[\alpha]_D^{23}$ + 8.3° (c 2.35, $CHCl_3$)); (5) hydrogenation (1 atm.) over Lindlar catalyst deactivated with triethylamine in THF (10 → 11 (X= H, OH), 90%, 11 (X= H,OH): $[\alpha]_D^{23}$ + 20.5° (c 1.73, $CHCl_3$)); (6) oxidation with Collins reagent (6 equiv., 11 (X= H,OH) → 11 (X=O), 84%); (7) exposure of 11 (X=O) to 1.25 equivalents of the ylide prepared from the 2-methoxy-2-propyl ether of (3-hydroxypropyl)triphenylphosphonium

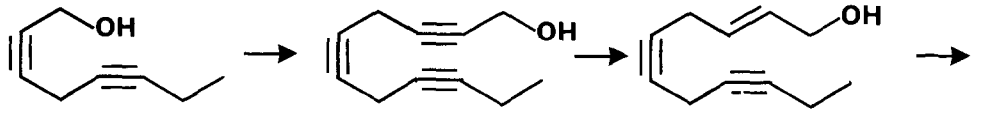


1 LTB_4 $R = nC_4H_9$

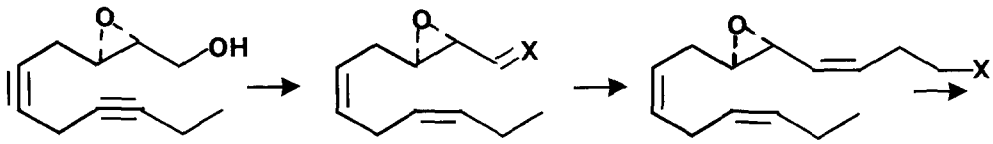
2 LTB_5 R =



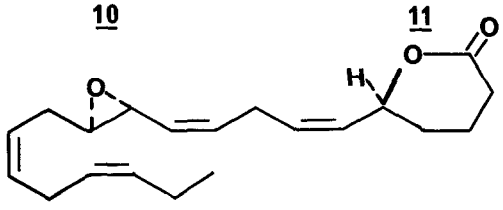
3 4 5 6



7 8 9



10 11 12



13

2

bromide[14] (using sodium hexamethyldisilazide,[15] THF-toluene, 1 : 2, 0°, 20 min.) at -78° for 10 min. and from -78° to 0° over 1 hr. (11 (X = O)⟶12 (X = OC $(OCH_3)(CH_3)_2$, 94%); (8) acidic hydrolysis (acetic acid-water-CH_3CN, 0.006 : 1 : 4, 25°, 6 hr., 12 (X = OC $(OCH_3)(CH_3)_2$ ⟶ 12 (X = OH), 84%); (9) primary iodide formation with triphenylphosphine, imidazole, iodine, diisopropylamine (1.5 equiv. of each reagent)[10] (ether - CH_3CN, 3 : 1, 25°, 40 min., 12 (X = OH)⟶12 (X = I); and (10) displacement of iodide with triphenylphosphine (1.5 M, 3 equiv., CH_3CN, 60°, 16 hr., 12 (X = I) ⟶ 12 (X = $P^+\phi_3I^-$), 92% from 12 (X = OH)).

The phosphonium iodide 12 (X = $P^+\phi_3I^-$) was converted to the corresponding ylide (0.95 equiv. of nBuLi, THF, -78°, 1.5 hr.) and treated sequentially with hexamethylphosphoric triamide (15 equiv.) and then the aldehyde 6 (1.2 equiv.). After 30 min. at -78° the reaction mixture was warmed to 0° over 1.5 hr. Extractive isolation and thin-layer chromatography gave the lactone 13 (45%) and the less mobile 6,7-trans isomer (5%) of 13. Exposure of 13 to potassium isopropoxide in isopropanol (10 equiv., 0.5 M, 0°, 1 hr.) followed by basic hydrolysis afforded LTB_5 (2) in 75% yield and >95% purity by RP-HPLC analysis. Both RP-HPLC retention volumes[16] (Dupont Zorbax ODS, 4.6mm x 25 cm, CH_3OH-H_2O-HOAc, 60 : 40 : 0.1, 2.0 ml/min., retention volume 21.5) and the UV spectra (UV_{max} (CH_3OH) 260.2, 269.3, 280.3 nm) of biosynthetic LTB_5 (2)[17] and synthetic 2 were identical. The synthetic LTB_5 (2) was fully characterized as its methyl ester diacetate by HPLC,[18] ^1H NMR,[19] UV,[20] and MS[21] analysis.

The availability of synthetic LTB_5 allowed comparative studies of its biological action on human polymorphonuclear leukocytes relative to LTB_4. Synthetic LTB_5 was found to be only ca. 5% as active as LTB_4 in leukocyte chemotaxis and aggregation.[22] LTC_4 and LTC_5, in contrast, appear to be similar in spasmogenic activity.[23] It is possible that part of the cardioprotective effect of fish lipid may be associated with the diminished activity of LTB_5 toward neutrophils relative to LTB_4.[24]

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9. Prepared from pent-2-yn-1-ol by conversion to the iodide[10] ($P\Phi_3$, I_2, imidazole, 1.5 equiv. of each reagent, ether-CH_3CN, 3 : 1, 25°, 40 min.) and then Cu(I) catalyzed alkylation with the bisbromomagnesium salt of propargyl alcohol[11] in 98% overall yield.
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16. RP-HPLC retention volumes for LTB_5 (2) and LTB_4 (1) were 8.6 and 12.6, respectively (Dupont Zorbax ODS, 4.6 mm x 25 cm., CH_3OH-H_2O-HOAc, 75 : 25 : 0.01, 2.0 ml./min.); cf. ref. 4.
17. We are grateful to Dr. Tak Lee of the Harvard Medical School for supplying biosynthetic LTB_5 (2).
18. Dupont Zorbax Sil 4.6 mm x 25 cm.; 0.3% iPrOH - 3% EtOAc - hexane; 2.0 ml./min., retention volume 16.
19. ^1H NMR (d^6-benzene, 270 MHz): 6.79 (dd, J = 11.53, 14.83 Hz, H - 8); 6.34 (dd, J = 10.55, 14.83 Hz, H - 10); 6.09 (dd, J = 10.87, 14.83 Hz, H - 9); 6.03 (t, J = 11.53 Hz, H - 7); 5.90 (dt, J = ca. 9.5, 11 Hz, H - 5); 5.63 (dd, J = 6.92, 14.82 Hz, H - 11); 5.60 - 5.38 (m, 5H, H - 12, H - 14, H - 15, H - 17, H - 18); 5.33 (t, J = 10.22 Hz, H - 6); 3.35 (s, 3H); 2.83 (m, 2H, H - 16), 2.47 (m, 1H, H - 13), 2.38 (m, 1H, H - 13); 1.74 (s, 3H); 1.68 (s, 3H); 0.95 (t, J = 7.5 Hz, 3H, H - 20). This spectrum was consistent with that of the methyl ester diacetate of LTB_4 (1), E. J. Corey, P. B. Hopkins, A. E. Barton, B. Bangerter, and P. Borgeat, Tetrahedron, 38, 2653 (1982).
20. UV_{max} (CH_3OH) 260.2, 269.3, 280.0 nm.
21. MS (CI, NH_3, 320°) 450 ($M + NH_4^+$, 100%), 392 ($M + NH_4^+$ - HOAc, 46%), 332 ($M + NH_4^+$ - 2 (HOAc), 53%).
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