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A SHORT SYNTHESIS OF A KEY LEUKOTRIENE B_4 SYNTHON

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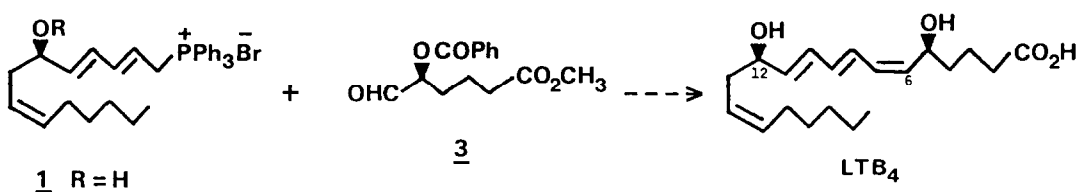
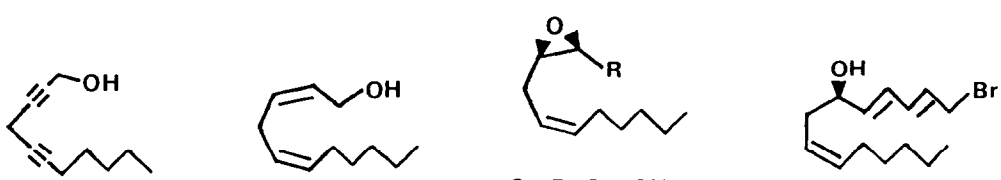
Abstract: The enantioselective epoxidation of the diene 5 is reported as the key step in a short synthesis of the LTB_4 synthon 1.

Leukotriene B_4 (LTB_4), a recently characterised metabolite of arachidonic acid, is thought to be an important mediator in inflammatory and allergic diseases because of its potent chemotactic and smooth muscle contractile actions[1,2]. To date, four syntheses of LTB_4 have been reported[2-5], and three of these have utilised the Wittig coupling of either 1 or 2 with the aldehyde 3 as a means of constructing the LTB_4 skeleton. Thus, 1 has been prepared in fourteen steps from D-(+)-mannose[2] whilst 2 has been prepared in thirteen steps from 2-deoxy-D-ribose[3] and in fourteen steps from L-arabinose[4]. We now wish to report a six step synthesis of 1 starting from the diyne 4 which is easily prepared on a large (1 Mole) scale in three steps from propargyl alcohol[6].



1 R = H
2 R = $SiPh_2Bu^t$

3



4

5

6 R=CH_2OH
7 R=CHO
8 R=CH=CHCH=CH_2 Z/E

9

Catalytic hydrogenation of 4 (Pd on $BaSO_4$ in pyridine) cleanly gave the Z,Z-diene 5[7] (70%) which was subjected to an enantioselective epoxidation[8] (1.1 equiv. each of $Ti(OPr^i)_4$ and natural (+)-dimethyl tartrate, 2 equiv. of Bu^tO_2H, CH_2Cl_2, -25°, 18h) to give the epoxide 6 [$[\alpha]_D^{25}$ -10.2° (C=1.5, $CHCl_3$)] in 71% yield and 94% enantiomeric excess[9]. Collins oxidation of 6 (CrO_3, pyridine, CH_2Cl_2, 23°, 0.5h) afforded the aldehyde 7 (77%) which was elaborated essentially as described previously[2]. Thus, reaction of 7 with allylidenetriphenylphosphorane (1.1 equiv., THF, -78°, 1.5h) gave the conjugated diene 8 [67%, Z:E=4:1, $[\alpha]_D^{24}$ +40.6° (C=1.5, $CHCl_3$), lit.[2] $[\alpha]_D^{25}$ +40.4° (C=3.5, $CHCl_3$)] which was treated with dry HBr[10] to give exclusively the labile E,E-conjugated diene 9. Without purification, 9 was treated with triphenylphosphine (3 equiv., CH_2Cl_2, 23°, 24h) to give, after concentration and trituration with ether, the salt 1 as a white hygroscopic solid in 58% yield from 8. The reaction of 1 with 3[11] afforded the corresponding Wittig coupled product [29%, 6Z:6E=7:3, $[\alpha]_D^{25}$ +152.6° (C=0.85, $CHCl_3$), lit.[2] $[\alpha]_D^{25}$ +164.4° (C=1.4, $CHCl_3$)] which on hydrolysis (NaOH/H_2O/MeOH) afforded a 7:3 mixture of LTB_4 and 6E-LTB_4 together with a trace of the corresponding C-12 epimers[12] which inevitably arise from the intermediate 6 (94%e.e.). Preparative RP-HPLC[12] effected a very clean separation of this mixture to give LTB_4 with >99% purity and with characteristic biological activity.

References and notes

1. E.J. Goetzel, New Eng.J.Med., 1980, 303, 822.
2. E.J. Corey, A. Marfat, G. Goto and F. Brion, J.Amer.Chem.Soc., 1980, 102, 7984.
3. Y. Guindon, R. Zamboni, C-K. Lau and J. Rokach, Tetrahedron Letters, 1982, 23, 739.
4. R. Zamboni and J. Rokach, Tetrahedron Letters, 1982, 23, 2631.
5. E.J. Corey, A. Marfat, J. Munroe, K.S. Kim, P.B. Hopkins and F. Brion, Tetrahedron Letters, 1981, 22, 1077.
6. Prepared by (a) C-alkylation of di-lithio propargyl alcohol with 1-bromopentane see D.E. Ames, A.N. Covell and T.G. Goodburn, J.Chem.Soc., 1963, 5889. (b) PBr_3 bromination. (c) Reaction with the di-Grignard complex of propargyl alcohol see J.M. Osbond, P.G. Philpot and J.C. Wickens, J.Chem.Soc., 1961, 2779.
7. All stable intermediates were purified and characterised by microanalysis, 250 MHz PMR, IR and, where applicable, UV spectroscopy.
8. T. Katsuki and K.B. Sharpless, J.Amer.Chem.Soc., 1980, 102, 5974.
9. As determined by 250 MHz PMR using $Eu(hfbc)_3$ chiral shift reagent.
10. HBr gas (ex cylinder) was bubbled into dry CH_2Cl_2 over 4A-molecular sieves for 30 sec. This solution (conc. unknown) was added to 8 in CH_2Cl_2 at 23° until TLC [silica, cyclohexane-ether (5:1)] indicated conversion of 8 (Rf 0.84) into 9 (Rf 0.47).
11. Prepared essentially as described in ref. 5 except the epoxybenzoate (intermediate 6 in ref. 5) was treated with $HIO_4.2H_2O$ in ether (23°, 24h) to give 3 $[[\alpha]_D^{23}$-34.4° (C = 1.3, $CHCl_3$)] directly in 67% yield.
12. HPLC retention times were 9.5min (LTB_4), 7.8min (6E-LTB_4), 8.3min (12-epi-LTB_4) and 8.5min (12-epi-6E-LTB_4) using a 0.5 x 20cm Spherisorb 5μ, C_{18} column eluted (2ml/min) with MeOH:H_2O:AcOH (65:35:0.01), UV detection 270nm.

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