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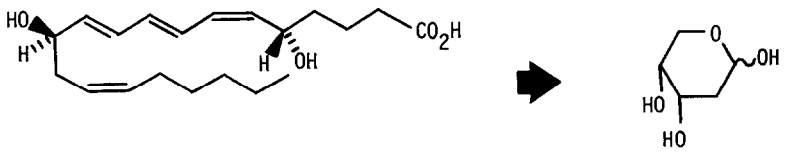
STEREOSPECIFIC SYNTHESIS OF LEUKOTRIENE B_4 (LTB_4)

By Yvan Guindon*, Robert Zamboni, Cheuk-Kun Lau and Joshua Rokach
Merck Frosst Laboratories, P.O. Box 1005,
Pointe-Claire/Dorval, Québec, Canada H9R 4P8

Summary: A stereospecific and chirally economical synthesis of LTB_4 starting from 2-deoxy-D-ribose is reported as part of a comprehensive and efficient approach to the Leukotrienes (A, B, C, D, E). The process includes a novel approach to chiral dienic synthons.

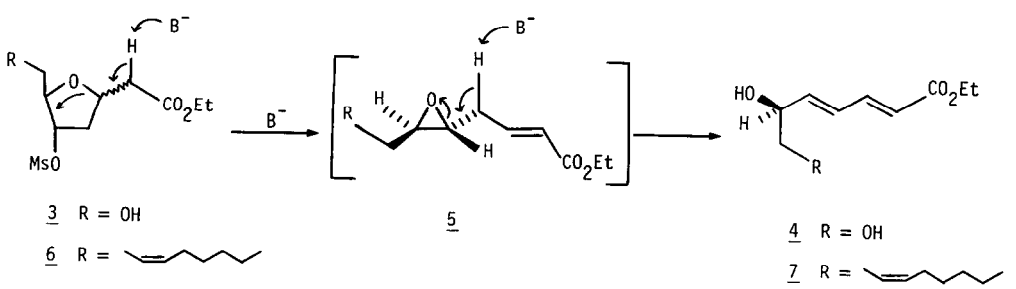
Leukotriene B_4 (1) is a component of the arachidonic acid cascade which has been recently isolated[1] and characterized[2]. This local hormone stimulates leukocyte functions[3] (chemotaxis, chemokinesis), induces an increase in capillary permeability[3] and causes smooth muscle contraction[4]. The potential importance of LTB_4 in allergic and inflammatory states and the need for a better supply to investigate its properties prompted us to embark on the synthesis of this mediator which we are now reporting.



1, LTB_4 2

Our approach is based on the realization that the common synthetic precursor, 2-deoxy-D-ribose (2), which has been used in the stereospecific synthesis[5,6] of LTA_4, 5-epi-LTA_4, 6-epi-LTA_4 and 5-epi,6-epi-LTA_4 could also be utilized in the preparation of LTB_4. In particular, we recognized the potential stereochemical and functional overlap between the hydroxyls at C-5 and C-12 of LTB_4 (1) and those at C-3 and C-4 of 2, respectively.

The key step in our synthesis is based on our finding that some C-glycosides which possess a leaving group on the tetrahydrofurane ring, could be considered as masked dienic precursors, as illustrated in the stereospecific conversion of 3 to 4. (The structure of 4 was secured by sodium periodate oxidation to yield ethyl (E, E)-6-oxo-2,4-hexadienoate and comparison with authentic material[7]). The formation of compound 4 can be explained by a β-elimination to give the corresponding α,β-unsaturated ester derivative 5 which rearranges under the basic conditions to 4.

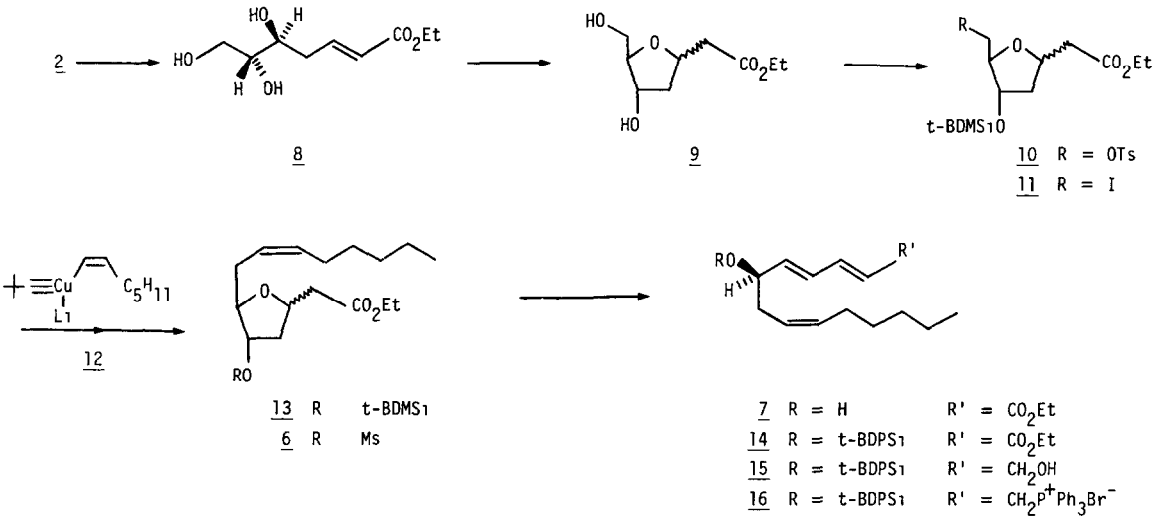


3 R = OH
6 R = 5 4 R = OH
7 R =

Based on this observation, it was envisaged that replacement of the primary hydroxyl group in the C-glycoside 3 with an alkyl side chain (e.g. compound 6) and subsequent treatment with base will give the corresponding chiral diene alcohol (7) bearing the desired R configuration. The condensation of this C-14 fragment with the C-6 piece, 19, would give LTB_4, 1, stereospecifically.

The preparation of the key intermediates 7 and 19 was carried out as follows. Reaction of 2 with 1.2 equivalent of (carbethoxymethylene)triphenylphosphorane in refluxing THF for 6 hours gave the triol 8 in 80% yield[5,6]. The C-glycoside (α/β:1/1) 9 were then obtained by treating 8 with a catalytic amount of sodium ethoxide in ethanol (95% yield).

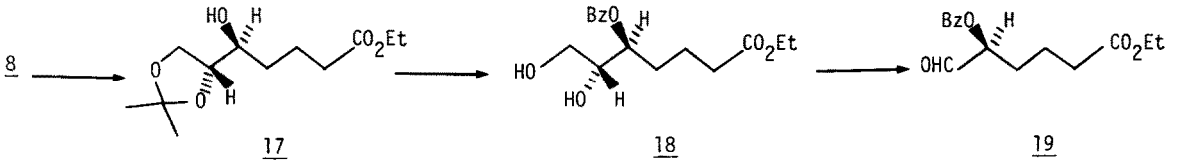
Selective tosylation of the primary alcohol 9 (1.1 equivalent TsCl, pyr.) and subsequent treatment with 2 equivalents of tert-butyldimethylsilyl chloride (CH_2Cl_2, Et_3N, DMAP) gave the derivative 10 (82%). Displacement of the tosylate with sodium iodide in refluxing acetone (18 hours) led to the 7-iodo-C-glycoside 11 in 70% yield. The chain extension was then realized by adding the iodide 11 (at -25°) to the heterocuprate reagent 12[8] (in ether), in the presence of 0.3 equivalent excess of $CuBr \cdot Me_2S$[9], to obtain, after 16 hours, the C-14 unit 13 (36% isolated yield with 25% recovered starting material)[10].



Removal of the silyl group (nBu_4NF, THF) and subsequent mesylation (MsCl, Et_3N, CH_2Cl_2) of the resulting alcohol gave the key intermediates 6 in 71% yield. Treatment of 6 with 2.5 equivalents of sodium ethoxide in ethanol (0.5 hours, R.T.) led cleanly to the dienic synthon 7 in 90% yield, $[\alpha]_D$ = +11.4° (c 1.31, $CDCl_3$) which was transformed into 14 (90% yield), $[\alpha]_D$ = +44.8° (c 1.25, $CDCl_3$) using tert-butyldiphenylsilylchloride[11] (EtN, CH_2Cl_2). The ester 14 was then reduced by AlH_3 (THF) to the alcohol 15, $[\alpha]_D$ = +21.9° (c 1.67, $CDCl_3$). Bromination of the primary alcohol (CBr_4, 2.5 equiv., Ph_3P, 2 equiv., 0°) and its displacement with Ph_3P (5 equiv.) in acetonitrile (R.T., 1.5 hrs) provided the C-7 to C-20 segment, in the form of the Wittig reagent 16.

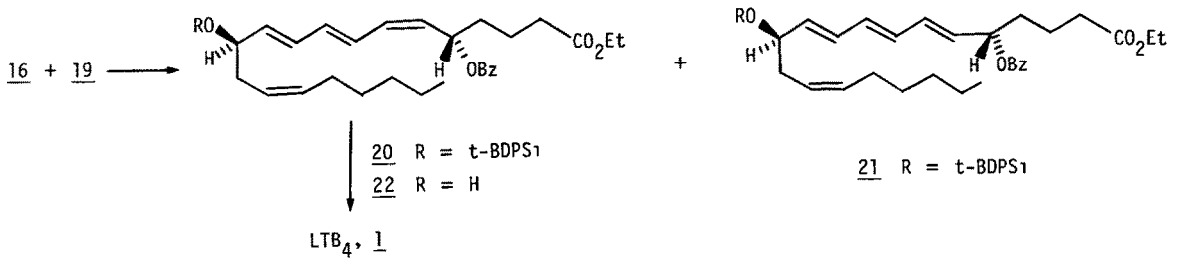
Since the stereochemistry at C-3 of the starting sugar, 2, was identical to that at C-5 of LTB_4, the synthesis of the C-1 to C-6 segment of 1 was done using the same intermediates. Hydrogenation of the α,β-unsaturated ester 8 and formation of the kinetically favored acetonide,

as we previously reported[5], gave the alcohol 17 in good yield. Benzoylation of 17 (BzCl, Et_3N, CH_2Cl_2, DMAP) and a subsequent treatment with 1N HCl in MeOH (2 hrs, 60°) gave in 50% yield the corresponding diol 18. The oxidative cleavage of the vicinal diol using 1.1 equiv. of lead tetraacetate in CH_2Cl_2 containing 2 equiv. of sodium carbonate[2] led to the aldehyde 19 in 65% yield $[\alpha]_D$ = -46° (c 0.5, $CHCl_3$) (lit.[2]: -33° for the corresponding methyl ester, $CHCl_3$).



17 18 19

The synthesis of LTB_4 was then completed as follows. The phosphonium salt, 16, in THF was treated with 1.1 equiv. of BuLi at -78° to which 1.3 equiv. of aldehyde 19 was added. The reaction was allowed to proceed at -40° for 15 min. Extractive isolation and purification by HPLC[12] gave the $\Delta^{6,7}$ cis compound 20 (30% yield from 15), $[\alpha]_D$ = +202° (c 1.2, $CHCl_3$) and $\Delta^{6,7}$ trans isomer 21[13] (12% yield from 15), $[\alpha]_D$ = +106° (c 1.0, $CHCl_3$). The compound 22, $[\alpha]_D$ = +260° (c 1.0, $CHCl_3$)[14], obtained in 80% yield from 20 (nBu_4NF, 10 equiv.) was then treated with K_2CO_3 (10 equiv.) in MeOH-H_2O (4.1) to give LTB_4[15] (1) cleanly in 60% yield, U.V. (max.) CH_3OH·260, 270.5, 281.



20 R = t-BDPSi
22 R = H

LTB_4, 1

21 R = t-BDPSi

The identity of the synthetic material with native LTB_4[16] was assured by comparison of their HPLC behaviour[17] and their biological activities[18].

The present synthesis of LTB_4 can be considered as being chirally economical since all the chiral centers of the synthetic precursor are maintained as chiral centers in the final target molecule. As such, it constitutes part of our comprehensive approach to the Leukotrienes, since from the same precursor, 2-deoxy-D-ribose (2), one can also obtain optically active LTA_4, LTC_4, LTD_4 and LTE_4 and their respective isomers[5,6].

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9. The yield of the substitution product 14 relative to that of the elimination products was improved by the addition of excess $CuBr \cdot Me_2S$. Although the role of excess $CuBr \cdot Me_2S$ is not yet known, it is possible that the reactive species is no longer the stoichiometric RR'CuLi but rather $R_3R_3'Cu_4Li_2$ which may be less basic hence decreases the yield of elimination compounds.
10. The cuprate reaction on both the α and β C-glycosides was investigated separately and each gave the corresponding substitution product 11 in comparable yields.
11. S. Hanessian, P. Lavallée, Can. J. Chem., 53, 2975 (1975).
12. Waters μ-Porasil column; 98.5% hexane/.5% EtOAc/1% Et_3N as solvent.
13. 400 MHz pmr: cis isomer, H_6 appeared as a quartet at δ5.43 ppm. $J_{5,6}$ = 7Hz, $J_{6,7}$ = 11Hz; trans isomer, H_6 appeared as a quartet at δ5.65 ppm. $J_{5,6}$ = 7Hz, $J_{6,7}$ = 14.5Hz.
14. The methyl ester analog of 22 has surprisingly a reported $[\alpha]_D$ of +164°, see ref. 2.
15. pmr (400 MHz, CD_3SOCD_3, of syn. LTB_4) δ6.59 (q, 1H, H_8, $J_{8,9}$ = 14Hz, $J_{7,8}$ = 12Hz), 6.31 (m, 2H, H_9 + H_{10}), 6.02 (t, 1H, H_7, $J_{6,7}$ = $J_{7,8}$ = 11Hz), 5.80 (q, 1H, H_{11}, $J_{11,12}$ = 6.5Hz, $J_{10,11}$ = 14Hz), 5.50 (m, 3H, H_{14}, H_{15}, OH), 5.48 (q, 1H, H_6, $J_{6,7}$ = 11Hz, $J_{5,6}$ = 7.0Hz), 4.96 (m, 1H, OH), 4.46 (m, 1H, H_5), δ4.10 (m, 1H, H_{12}) ppm.
16. We would like to thank Dr. A.W. Ford-Hutchinson (King's College Hospital Medical School, London, England) and Dr. P. Borgeat (Centre Hospitalier Université Laval, Québec, Canada) for kindly supplying us with samples of natural LTB_4 for HPLC comparison.
17. Synthetic LTB_4 was identical to natural LTB_4 in two solvent system (40% CH_3CN / 60% H_2O / .01% AcOH, 65% MeOH / 35% H_2O / .01% AcOH; on a Waters C_{18} μ-bondapak column.
18. Biological activities comparisons were performed by Dr. A.W. Ford-Hutchinson and by Dr. M. Springer, Dr. P. Davies and Dr. A. Rosenthal, Merck & Co., Rahway, New Jersey.

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