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TOTAL SYNTHESIS OF 20-HYDROXY- AND 20-CARBOXY-LEUKOTRIENES B_4

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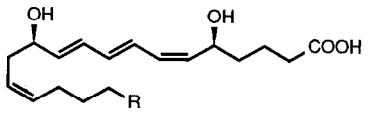
Summary. *The total synthesis of 20-hydroxy- and 20-carboxy-leukotrienes B_4 (1 and 2) from key intermediates 13, 14 and 15 is described.*

20-Hydroxy- and 20-carboxy-leukotrienes B_4 (1 and 2) are important metabolites of leukotriene B_4.[1-4] Their low natural abundance coupled with their important biological properties make these molecules prime targets for synthesis.[5] In this communication, we report chemistry leading to stereocontrolled total syntheses of both 1 and 2 in their naturally occuring forms.



1, R=CH_2OH
2, R=COOH
3, R=COOMe

Scheme 1[6] outlines the synthetic routes to these compounds which rely on the chemistry developed by us for LTB_4.[7] Thus, 6-heptyn-1-ol (3) was converted to the silylether 4 (1.1 equiv. $^tBuPh_2SiCl$, 1.2 equiv. imidazole, DMF, 0→25°C, 98%), the lithioderivative (2.5 equiv. nBuLi, 2.5 equiv. TMEDA, THF, -78°C) of which reacted with (R)-glycidol-THP ether (6) (THF, -78→25°C) to afford hydroxyacetylene 7 in 69% yield. Introduction of a second $^tBuPh_2Si$ group in 7 as above (95%) followed by removal of the THP protection (pyridinium p-toluene sulphonate, MeOH, 48°C, 88%) led to the hydroxy compound 9 via 8. Oxidation of 9 (excess $CrO_3 \cdot 2pyr.$, celite, CH_2Cl_2, 0°C) then furnished aldehyde 13 (90%) which reacted with the lithioanion of 15 (1.1 equiv. LDA, THF, -78→25°C) to afford the coupling product 16 in 62% yield.[8] Hydrogenation of the diacetylene 16 over Lindlar catalyst gave, as the major product (66%) tetraene 18.[9] Exposure of 18 to excess nBu_4NF (THF, 0→25°C) removed all protecting groups including the methylester (presumably by anchimeric assistance from the 5-OH group) giving 20-LTB_4 (1) in 95% yield. The methylester 19 (CH_2N_2, ether, 0°C, 95% yield) and the methylester triacetate 20 (Ac_2O, DMAP, pyridine, CH_2Cl_2, 0→25°C, 90% yield) were also prepared and fully characterized.

For the synthesis of the 20-carboxy-LTB_4 (2), the acetylene orthoester 5 was prepared from 3' as follows: (a) CBr_4-PPh_3 (1.2 equiv each, CH_2Cl_2, -40→25°C); (b) KCN (excess)-18-Crown-6 (0.01 equiv), DMF, 25°C; and (c) MeOH-Et_2O-HCl gas, 0→25°C (78% overall yield). The rest of the sequence followed similar reactions and yields as for the synthesis of 1 leading to 20-carboxy-LTB_4 (2) and its dimethylester 23 via intermediates 10-12, 14, 17, 21 and 22. The described chemistry renders these and related biomolecules readily available

for further investigations in biomedical research.

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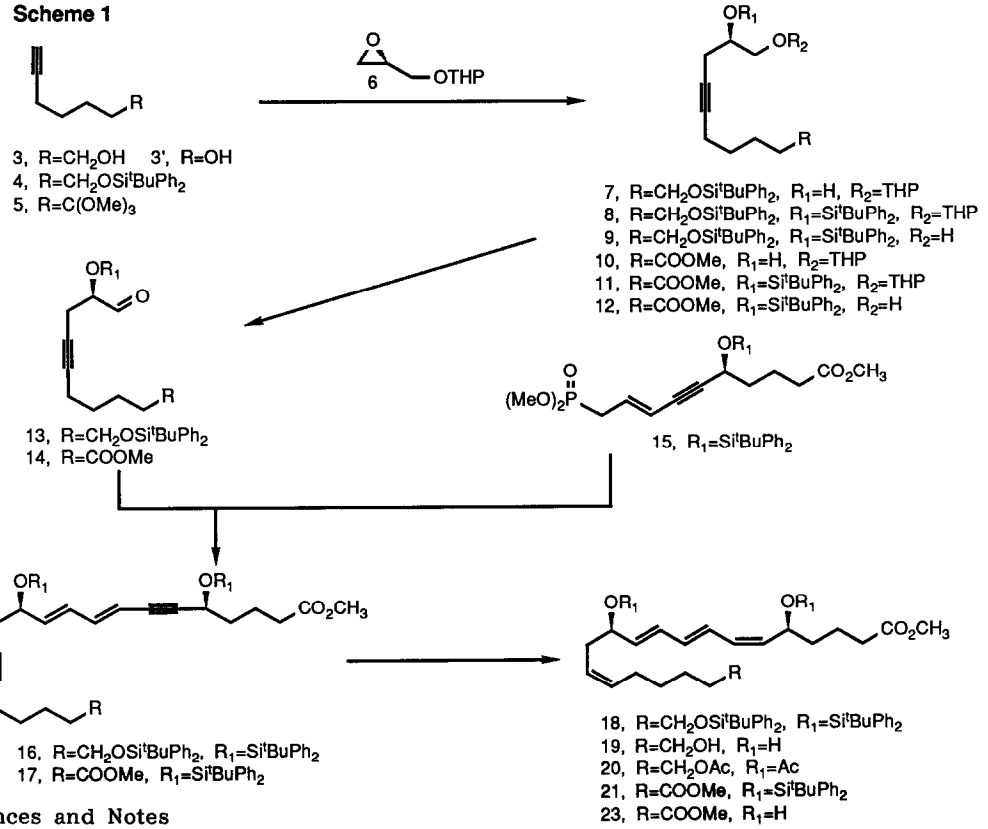
Scheme 1



References and Notes

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2. W.S. Powell, J. Biol. Chem., 1984, 259, 3082.
3. S.J. Feinmark, J.A. Lindgren, H.-E. Claesson, C. Malmsten, , B. Samuelsson, FEBS Lett., 1981, 136, 141.
4. G. Hansson, J.A. Lindgren, S.-E. Dahlen, P. Hedquist, B. Samuelsson, FEBS Lett. 1981, 130, 107.
5. For a previous synthesis of these metabolites see: R. Zamboni, J. Rokach, Tetrahedron Lett., 1982, 23, 4751.
6. All new compounds in Scheme 1 were characterized by spectroscopic (IR, MS, UV, NMR) and analytical and/or exact mass measurements.
7. K.C. Nicolaou, R.E. Zipkin, R.E. Dolle, B.D. Harris, J. Am. Chem. Soc., 1984, 106, 3548.
8. Small amounts (5-7%) of the corresponding Z-isomer was formed and removed chromatographically.
9. Selected spectroscopic data. 18: ^{1}H NMR (250MHz, $CDCl_3$, TMS) δ 7.64 (m, 12H, aromatic), 7.35 (m, 18H, aromatic), 5.97-5.20 (m, 8H, olefinic), 4.49-4.43 (m, 1H, H-5), 4.17-4.14 (m, 1H, H-12), 3.63 (m, 2H, H-20), 3.60 (s, 3H, $COOCH_3$), 2.28-2.05 (m, 4H, CH_2), 1.92-1.72 (m, 2H, CH_2), 1.65-1.00 (m, 10H, CH_2), 1.04 (singlet, 27H, ^{t}Bu), IR (neat) ν_{max} 1745 cm^{-1} ($COOCH_3$); UV (MeOH) λ_{max} 285, 275, 265nm. 21: ^{1}H NMR (250MHz, $CDCl_3$, TMS) δ 7.60 (m, 8H, aromatic), 7.30 (m, 12H, aromatic), 5.95-5.20 (m, 8H, olefinic), 4.42 (m, 1H, H-5), 4.10 (m, 1H, H-12), 3.65 and 3.60 (singlets, 3H each, $COOCH_3$), 2.30-2.05 (m, 6H, CH_2), 1.85-1.70 (m, 2H, CH_2), 1.70-1.00 (m, 8H, CH_2), 1.10 and 1.06 (singlets, 9H each, ^{t}Bu); IR (neat) ν_{max} 1745 cm^{-1} ($COOCH_3$); UV (MeOH) λ_{max} 285, 275, 265nm.

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