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STEREOSPECIFIC SYNTHESIS OF TWO METABOLITES OF LTB_4

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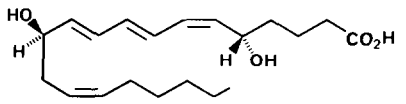
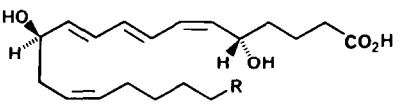
Summary: The stereospecific synthesis of the recently identified metabolites of LTB_4 1: 5(S),12(R),20-trihydroxy-6-cis,8,10-trans,14-cis-eicosatetraenoic acid 2 and 5(S),12(R),dihydroxy-6-cis,8,10-trans,14-cis-eicosatetraen-1,20-dioic acid 3, via the synthon 4 has been accomplished; identity of synthetic and natural products has been confirmed.

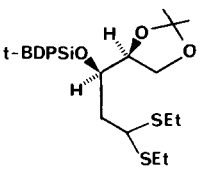
LTB_4 is a member of the arachidonic acid cascade recently identified by Borgeat and Samuelsson.[1] Arachidonic acid is transformed via the enzyme 5-lipoxygenase to 5-HPETE which in turn is transformed via a dehydrase step to LTA_4. LTA_4 is then diverted to two main pathways: action of glutathione transferase on LTA_4 leads to LTC_4, D_4 and E_4, components of the so-called slow reacting substances of anaphylaxis SRS-A. The other major known metabolitic transformation of LTA_4 is the enzymatic hydration to yield LTB_4. LTB_4 is a potent chemotactic agent and its implication in inflammatory processes is very likely and is being actively investigated.[2] The detailed metabolitic transformation of LTB_4 has not yet been elucidated. Preliminary reports have, however, identified two primary metabolites of LTB_4 namely, ω-hydroxy LTB_4 2[3,4] and ω-carboxy LTB_4 3.[4]



1 LTB_4



2 R = CH_2OH
3 R = CO_2H



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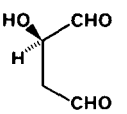

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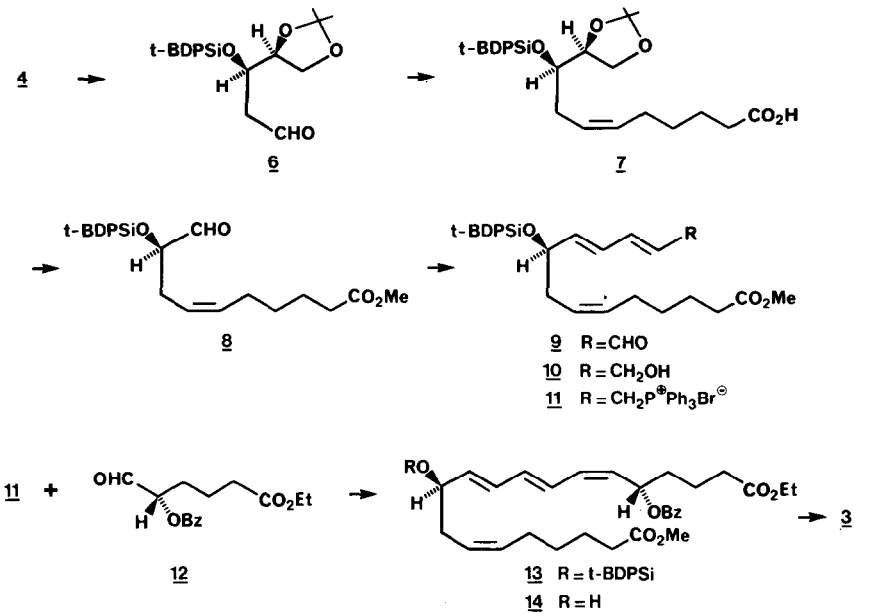
We have recently reported two stereospecific syntheses of LTB_4 and isomers[5,6] and we wish to describe now the first synthesis, completely stereospecific in nature, of metabolites 2 and 3. We had two main reasons for undertaking the synthesis of these metabolites. The first is the positive identification of the natural metabolites, and the second, perhaps more

important, is the large scale supply of these natural products for the study of their metabolism and pharmacological properties.

In our last synthesis of LTB_4[6] we used synthon 4 for the construction of the chiral center at C_{12}. The reason for this selection was its potential versatility.

Scheme 1



This synthon is an equivalent of the C_4 dialdehyde 5, which has the possibility for selective chain extension at either end of the molecule. We have now used this synthon to construct the chiral C_{12} in both 2 and 3.

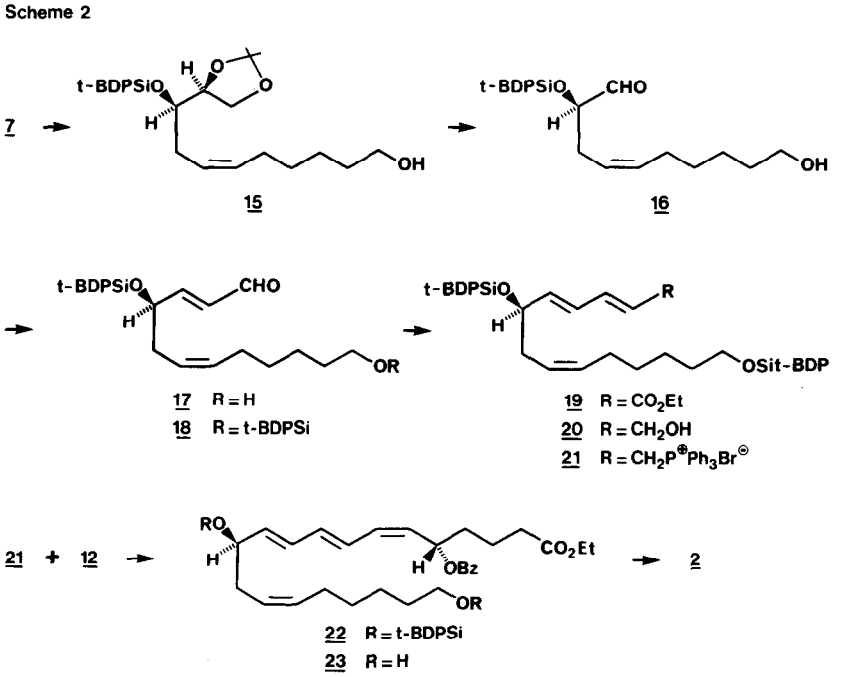
For the construction of the second asymmetric center at C_5, we used the synthon 12 described by us previously.[5] Schemes 1 and 2 summarize our strategy for the synthesis of the two metabolites. A different strategy was chosen for the chain extension of aldehydes 8 and 16 in order to avoid the possible interference of the 20-CO_2CH_3 group in 8.

Deprotection of dithiane 4 (NCS/$AgNO_3$ in CH_3CN at -10°)[7] afforded aldehyde 6 in 50-60% yield.[17] Treatment of 6 in THF/HMPA 10:1 with a slight excess of a solution of 6-carboxy hexylidene triphenylphosphorane at -78° afforded acid 7 $[\alpha]_D$ = -38° (c = 2, $CHCl_3$) in 60% yield. Esterification (CH_2N_2), removal of the acetonide group (TFA/THF/H_2O, 6 h r.t.) and cleavage of the resulting diol ($Pb(OAc)_4/Na_2CO_3$) afforded aldehyde 8. Condensation of 8 with formylmethylene triphenylphosphorane (3-4 eq) in benzene at 80° (16 h)[9,10] afforded diene-aldehyde 9, $[\alpha]_D$ = +42° (c = 1.0, $CHCl_3$) in 25-30% yield. Selective reduction of 9, ($NaBH_4$, $CeCl_3$, isopropanol, 0°)[11] afforded alcohol 10, $[\alpha]_D$ = +25° (c = 1.0, $CHCl_3$) in > 80% yield. The alcohol was transformed to the phosphonium salt 11 as previously described[5]

(1. CBr_4/Ph_3P; 2. Ph_3P/CH_3CN) in 40% yield. Treatment of the phosphonium salt 11 in THF/HMPA (5 eq) with .9 eq of LiHMDS[12] (.5M in THF) at -78° afforded the corresponding ylid which upon quenching with aldehyde 12 at -78° to -45° afforded 13 $[\alpha]_D$ = +187° (c = .6, $CHCl_3$) in 35-40% yield along with 8-10% of the 6,7 - trans isomer. Careful removal of the silyl ether ($(nBu)_4NF$ in THF, 0° to r.t.) gave alcohol 14,[13] $[\alpha]_D$ = +225° (c = 3, $CHCl_3$) in 70-80% yield. Hydrolysis of 14 (10 eq. LiOH, DME/H_2O), r.t.) afforded 20-CO_2H LTB_4 3 in 70% yield.

For the synthesis of 20-OH LTB_4 intermediate 7 was used as our starting material. Hence reduction of 7 ($LiAlH_4$, reflux THF) afforded alcohol 15, $[\alpha]_D$ = -43.5° (c = .5, $CHCl_3$) in 80% yield. Removal of the acetonide group (TFA/THF/H_2O, 16 h, r.t.) and cleavage of the resulting crude diol afforded aldehyde 16 in 60% yield. Condensation of aldehyde 16 with 1.2 eq of formylmethylene triphenylphosphorane in benzene at 80° (6 h) afforded α-β unsaturated aldehyde 17 in 45-50% yield, $[\alpha]_D$ = 8.5° (c = 2, $CHCl_3$). Protection of the alcohol in 17 (1.2 eq t-BDPSiCl/DMAP/Et_3N/CH_2Cl_2)[15] afforded silyl ether 18 in 80% yield. Condensation of aldehyde 18 ($(EtO)_2POCH_2CO_2Et$/NaH/toluene) afforded diene ester 19, $[\alpha]_D$ = +27° (c = .9, $CHCl_3$) in > 90% yield. Reduction of the ester (AlH_3/THF/0°) afforded alcohol 20, $[\alpha]_D$ = 13.3° (c = 3.2, $CHCl_3$) in > 90% yield. Alcohol 20 was transformed to phosphonium salt 21 (1. CBr_4/Ph_3P; 2. Ph_3P/CH_3CN) in 60% yield. Condensation of the phosphonium salt 21 with aldehyde 12 (.9 eq LiHMDS/THF/HMPA) afforded triene 22 in 30% yield, $[\alpha]_D$ = +150° (c = .6, $CHCl_3$) along with 7% of trans isomer . Removal of the silyl ether (excess $(nBu)_4NF$ in THF at 0° to r.t.) afforded diol 23[16], $[\alpha]_D$ = +250° (c = .2, $CHCl_3$) in 70% yield. Hydrolysis of 23 (K_2CO_3/MeOH/H_2O) afforded 20-OH LTB_4 2 in 70% yield. The synthetic 20-carboxy LTB_4 3 and 20-OH LTB_4 2 were compared with the natural products[14] and found to be identical (HPLC, UV).

Scheme 2



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7. E.J. Corey and B.W. Erickson, J. Org. Chem., 36, 3553 (1971).
8. Prepared by treatment of a suspension of the corresponding phosphonium salt in THF/HMPA at 0° with 1.9 eq of LiHMDS in THF and warming to r.t. (1 h).
9. There was also obtained 25% of the α-β unsaturated aldehyde which could be recycled (see also ref. 10).
10. J. Rokach, R.N. Young, M. Kakushima, C.K. Lau, R. Seguin, R. Frenette and Y. Guindon, Tetrahedron Lett., 22, 979 (1981).
11. Procedure of A.L. Gemal and J.L. Luche, Tetrahedron Lett., 22, 4077 (1981) modified by Dr. R. Perry in our laboratories.
12. Use of n-BuLi gave inferior results.
13. pmr (400MHz, $CDCl_3$): δ8.01 (q, 2H), 7.52 (t, 1H), 7.41 (t, 2H), 6.67 (q, 1H, H_8, $J_{7,8}$ = 11Hz, $J_{8,9}$ = 14Hz), 6.36 (q, 1H, J_1 = 11Hz, J_2 = 14.5Hz), 6.25 (q, 1H, J_1 = 11Hz, J_2 =14.5Hz), 6.16 (t, 1H, H_7, $J_{6,7}$ = $J_{7,8}$ = 11Hz), 5.90 (m, 1H, H_5), 5.77 (q, 1H, H_{11}, $J_{11,12}$ = 6.5Hz, $J_{10,11}$ = 14Hz), 5.55 (m, 1H), 5.43 (t, 1H, H_6), 5.39 (m, 1H), 4.23 (m, 1H, H_{12}), 4.1 (q, 2H, $O\underline{CH_2}CH_3$), 3.85 (s, 3H, OCH_3), 3.82 (m, 1H, OH), 2.30 (m, 6H), 2.08 (q, 2H), 1.90 (m, 1H), 1.75 (m, 3H), 1.65 (m, 2H), 1.40 (m, 2H), 1.24 (t, 3H, $OCH_2\underline{CH_3}$).
14. We would like to thank Dr. P. Borgeat for kindly providing us with samples of 20-OH LTB_4 and 20-CO_2H LTB_4 for comparison.
15. S.K. Chandhary and O. Hernandez, Tetrahedron Lett., 21, 835 (1980).
16. pmr (400MHz, $CDCl_3$): δ8.05 (q, 2H), 7.56 (t, 1H), 7.41 (t, 2H), 6.68 (q, 1H, H_8, $J_{8,9}$ = 14Hz, $J_{7,8}$ = 11Hz), 6.36 (q, 1H, J_1 = 11Hz, J_2 = 14.5Hz), 6.26 (q, 1H, J_1 = 11Hz, J_2 = 14.5Hz), 6.17 (t, 1H, H_7, $J_{6,7}$ = $J_{7,8}$ = 11Hz), 5.91 (m, 1H, H_5), 5.79 (q, 1H, H_{11}, $J_{11,12}$ = 6.5Hz, $J_{10,11}$ = 14Hz), 5.58 (m, 1H), 5.45 (t, 1H, H_6), 5.39 (m, 1H), 4.25 (m, 1H, H_{12}), 4.15 (q, 2H, $O\underline{CH_2}CH_3$), 3.65 (bt, 2H, $\underline{CH_2}OH$), 2.35 (m, 4H), 2.07 (bq, 2H), 1.90 (m, 1H), 1.65-1.80 (m, 4H), 1.40 (m, 4H), 1.25 (t, 3H, $OCH_2\underline{CH_3}$).
17. All yields reported have not been optimized.

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