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SYNTHESIS OF 19-HYDROXY LTB_4, AN ASSUMED METABOLITE OF LEUKOTRIENE B_4.

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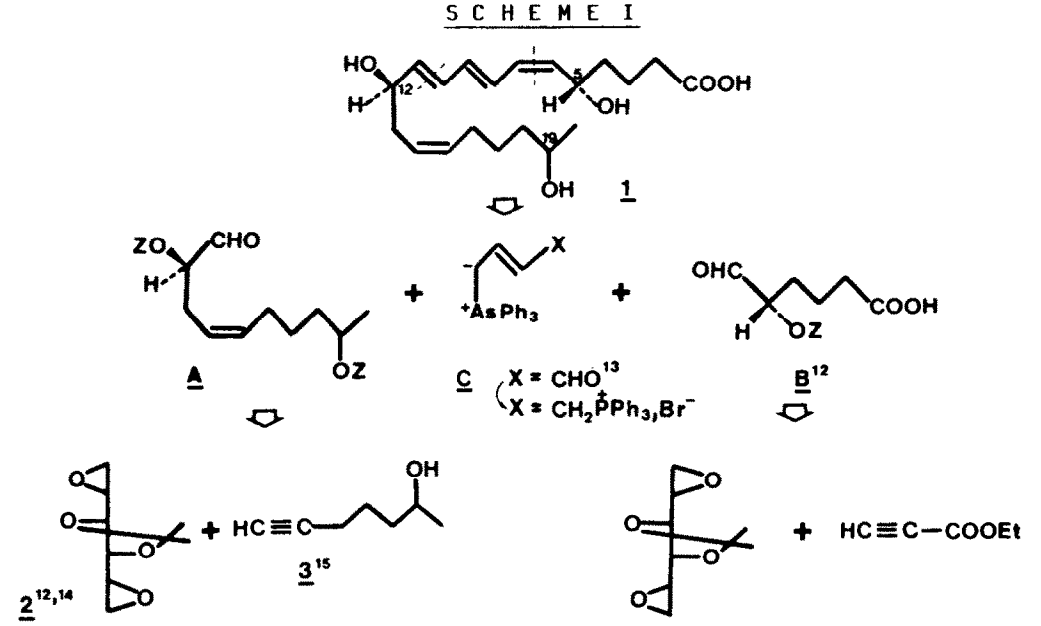
Summary : From D-mannitol, the total convergent synthesis of 19-hydroxy LTB_4, an assumed metabolite of LTB_4, has been carried out via α-hydroxyaldehydes. Connection at a four carbon atoms interval uses conjugated arsonium ylide.

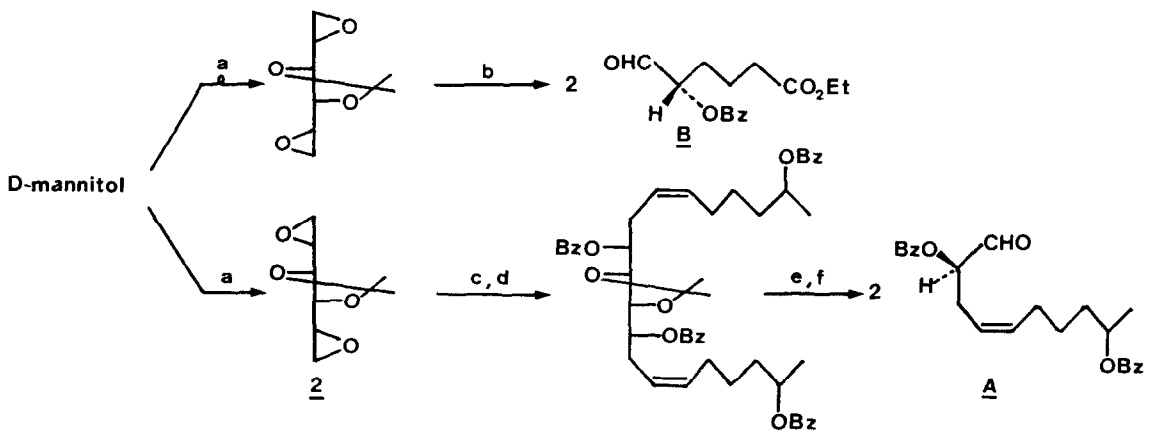
In leucocytes, oxygenation of arachidonic acid in presence of 5-lipoxygenase produces 5-HPETE which is the precursor of leukotrienes (1). Among them, LTB_4 is considered as an important mediator of inflammation (2,3). Biological activity of LTB_4 is reduced by metabolic oxidations. ω-Hydroxy and ω-carboxy LTB_4 have been reported to be the major products of catabolism of LTB_4 in human polymorphonuclear leukocytes (4-7) and have been targets for synthesis (8,9). Recently, preliminary evidence has been provided for the formation of another hydroxylated metabolite of LTB_4 in rat liver microsomes (10) and in rat leucocytes (11). On the basis of mass spectral data, a 19-hydroxy LTB_4 structure was proposed for this metabolite. To confirm the structure we have undertaken the synthesis of this assumed metabolite. Absolute configurations of carbon atoms 5 and 12 are supposed to be respectively S and R as for LTB_4 but the 19-C absolute configuration is unknown, therefore a mixture of the two 19-epimers is required for metabolite identication.

Scheme I outlines the retrosynthetic route to 19-hydroxy LTB_4 **1**.

S C H E M E I

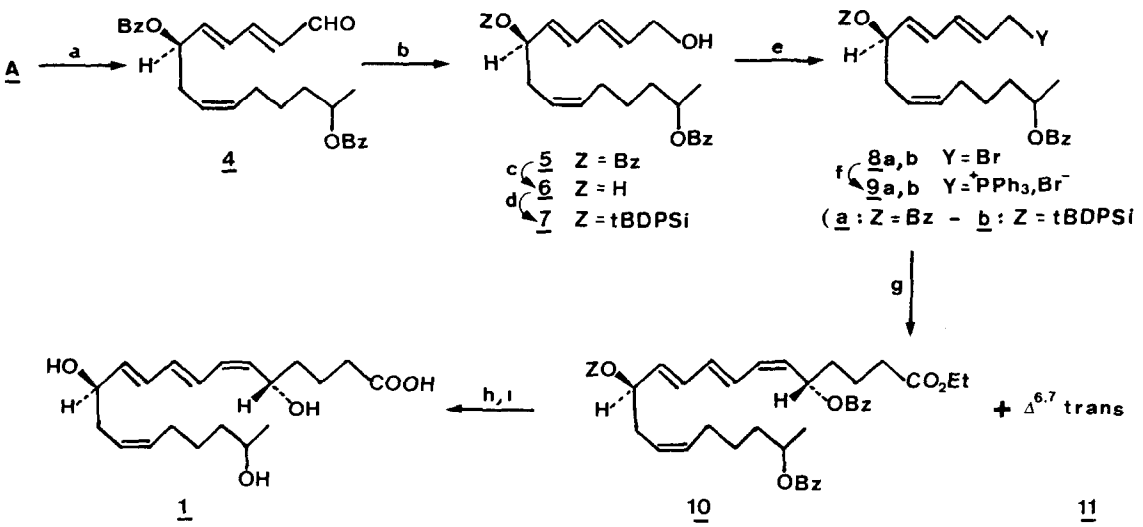


SCHEME II - Synthesis of aldehydes



a : ref.14 - b : ref. 12 - c : $Li\text{-}C{\equiv}C\text{-}(CH_2)_3CH(OLi)CH_3$, THF, HMPT, 65°C, 6h then PhCOCl, 0°C, 0.5h ; 55%
d : Lindlar cat., H_2, C_6H_6 ; 74% - e : TFA, H_2O 9/1, 0°C, 1h ; 99% - f : $Pb(OAc)_4$, CH_2Cl_2, -10°C, 1.25h ; 86%

SCHEME III - Synthesis of 19-hydroxy LTB_4 + $\Delta^{6.7}$ trans isomer (21)



a : $Ph_3As\text{-}CH_2CH{=}CHCHO$, K_2CO_3, THF, Et_2O, H_2O, 23h ; then I_2, CH_2Cl_2, 6h ; 91% - b : $NaBH_4$, $CeCl_3$, iPrOH, 3.5h ; 84% - c : 0.33eq.K_2CO_3, CH_3OH, 50°C, 4h ; 63% - d : 1/ $(CH_3OPh)Ph_2CCl$, pyr., 110°C, 2min ; 77% 2/ 2eq.tBDPSiCl, 5eq.Im., DMF, 72h 3/ HCO_2H, H_2O, THF, 1.5h, 20°C ; (2+3) 70% - e : 3.3eq.CBr_4, 1.5eq. DIPHOS, CH_2Cl_2, -35°C, 50min ; 100% - f : 1.2eq.Ph_3P, CH_3CN, 2h, 96% - g : 1eq.Buli, THF, -100°C, then B, HMPT, -100°C ⟶ RT ; 61% - h : 10eq.nBu_4NF, THF - i : 20eq.K_2CO_3, MeOH.

This synthesis is related to the chemistry developped by us for (+)-LTB_4 (12) with regard to the obtention of the two α-hydroxyaldehydes **A** and **B**, key intermediates prepared from D-mannitol. To prepare the connection between aldehydes **A** and **B**, four atoms are then introduced in one step by a Wittig type condensation using a conjugated arsonium ylide **C** (13).

From D-mannitol, the synthesis of enantiomerically pure aldehyde **B** has been previously described (12,14). The synthesis of protected dihydroxy aldehyde **A** (scheme II) involves diepoxyde **2** (12,14) and 1-heptyn-6 ol **3** (15). Nucleophilic opening of enantiomerically pure diepoxyde **2** (12,14) by the dilithio-derivative of **3** is followed *in situ* by tetrabenzoylation, controlled hydrogenation of the triple bonds, removal of the acetonide group and oxidative cleavage of the 3,4-diol. Since these transformations preserve the C2 axis of symmetry of **2**, two moles of **A** are obtained from one mole of D-mannitol. Condensation of aldehyde **A** with arsonium ylide **C** (13) (scheme III) leads to the E,E-dienal **4** (yield 91% after adjusting experimental conditions). Aldehyde **4** is carefully reduced (16), the primary alcohol **5** obtained is transformed into the phosphonium salt **9a** (Z=Bz) from which, even at -100°C, a stable ylide could not be obtained (elimination of the allylic benzoate) (17). To prevent this elimination the secondary allylic alcohol is protected by a silyl group (**6**→**7**) (18,19). The ylide prepared from phosphonium salt **9b** (Z=tBBPSi) is stable at -100°C and condensation occurs with aldehyde **B**. Protected 19-hydroxy LTB_4 **10** is obtained with its $\Delta^{6,7}$ trans isomer **11** (ratio **10**:**11**, ca 9/8). The compounds are easily separated by column chromatography and fully characterised (21). Sequential deprotection of **19** leads to the potassium salt of 19-hydroxy LTB_4, which is currently compared with metabolites of LTB_4 produced by different cellular systems (human and rat PMNL) (20).

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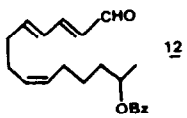
17. To prevent benzoate elimination use of phosphonium ylide without protection of secondary allylic alcohol should be a solution, but dienal 12 is obtained instead of primary bromide during transformations of 6 (-CH_2OH ⟶ -CH_2Br using CBr_4-DIPHOS at room temperature)



12

18. tBDP-silyl group could also be introduced when diepoxyde 2 is opened by lithium acetylide, but removal of the acetonide group is easier in the presence of benzoate (see ref. 12).
19. J. Adams, J. Rokach, Tetrahedron Lett., 25,35 (1984).
20. Drs J-L Boucher and M. Delaforge of our department are presently carrying out biological and analytical investigations. Results will be published elsewhere.
21. All new compounds exhibited satisfactory spectra and analytical data.

A : ^{1}H NMR (250MHz, $CDCl_3$) : 1.3(2d,3H,J=7Hz), 1.45(m,2H), 1.65(m,2H), 2.1(m,2H,H_6), 2.7(t,2H,H_3,$J_{2,3}=J_{3,4}=6.5$Hz), 5.15(m,1H,H_9), 5.25(t,1H, H_2), 5.45(m,1H, H_4, $J_{4,5}$ =11Hz), 5.55(m,1H,H_5), 8.2-7.3(2m,10H), 9.6(s,1H,H_1)-^{13}C NMR($CDCl_3$) : 198.0(C_1), 166.2(PhCO) ; 133.7, 133.5, 132.6, 129.8, 129.5, 128.4, 128.2, 122.5(Ph, C_4,C_5) ; 78.2(C_2) ; 74.3(C_9) ; 35.7(C_3) ; 32.5, 27.3, 25.2(C_6, C_7, C_8) ; 20.1(C_{10}).

4 : ^{1}H NMR(250MHz, $CDCl_3$) : 1.3(2d,3H,J=6Hz), 1.8-1.3(m,4H), 2.1(m,2H, H_{10}), 2.6(m,2H, H_7), 5.15(m,1H,H_{13}), 5.45, 5.55(2m,2H,H_8.H_9), 5.6(m,1H,H_6,$J_{5,6}$=6Hz), 6.15(dd,1H,H_2, $J_{1,2}$=8Hz, $J_{2,3}$=15.5Hz), 6.25(dd,1H,H_5,$J_{4,5}$=15Hz), 6.5(dd,1H,$J_{3,4}$=10.5Hz), 7.05(dd,1H,H_3), 8.1-7.4(2m,10H), 9.55(d,1H)- ^{13}C NMR : 193.3(C_1) ; 166.1, 165.5(PhCO) ; 150.3, 141.5, 133.2, 132.7, 129.6, 129.4, 128.4, 128.2, 123.3(Ph, C_2, C_3, C_4, C_5, C_8, C_9) ; 73.3(C_6); 71.3 (C_{13}) ; 35.4 (C_7) ; 32.2, 27.2, 25.1(C_{10}, C_{11}, C_{12}) ; 20.0(C_{14}).

10 : ^{1}H NMR(250MHz, CDCl3) : 1.05(s,9H,tBu), 1.2(t,3H, CO_2Et), 1.3(d,3H, H20, $J_{19,20}$=6.5Hz), 1.35(m,2H,H_{17}), 1.55(m,2H,H_{18}), 1.7(m,4H,H_3,H_4), 1.85(m,2H,H_{16}), 2.2(m,2H, H_2), 2.3(dd,2H,H_{13}), 4.1(t,2H,CO_2Et), 4.2(dt,1H,H_{12}), 5.1(tq,1H,H_{19}), 5.4-5.2(m,2H,H_{14}, H_{15}), 5.4(dd,1H,H_6), 5.66(dd,1H,H_{11}), 5.9(m,1H,H_5), 5.98(dd,1H,H_{10}), 6.1(dd,1H,H_7), 6.13(dd,1H,H_9), 6.48(dd,1H,H_8), 8.1-7.3(4m,20H) ; $J_{5,6}$=10, $J_{6,7}$=10.5,$J_{7,8}$=11, $J_{8,9}$ =14.5 $J_{9,10}$=10.5, $J_{10,11}$=15, $J_{11,12}$=6.5, $J_{14,15}$=11, $J_{18,19}=J_{19,20}$=6.5Hz - ^{13}C NMR : 165.8(PhCO) ; 137.6, 135.9, 135.2, 132.8, 131.9, 131.3, 130.0, 129.5, 128.3, 127.5, 126.8, 125.2(Ph,C_6, C_7,C_8,C_9,C_{10},C_{11},C_{14},C_{15}) ; 73.8(C_{12}) ; 71.6(C_{19}) ; 70.7(C_5) ; 60.3(CO_2Et) ; 36.0, 35.6, 34.4, 34.0, 29.7, 25.3, 20.6(C_2,C_3,C_4,C_{13},C_{16},C_{17}, C_{18}) ; 27.1, 19.4(tBu) ; 20.1(C_{20}) ; 14.3(CO_2Et)-SM(NH_3) : 844(M^++18) - UV(CH_3OH) : 282, 271, 262nm.

11 : ^{1}H NMR(250MHz, C_6D_6) : 4.35(q,1H,H_{12}), 5.2(m,1H,H_{19}), 5.45-5.3(m,2H,H_{14}, H_{15}), 5.5(dd,1H,H_6), 5.65(m,1H,H_5), 5.7(dd,1H,H_{11}), 5.95(m,1H,H_8), 6.0(m,1H,H_9), 6.1(dd,1H,H_{10}), 6.3(m,1H,H_7) ; $J_{5,6}$=7, $J_{6,7}$=15, $J_{7,8}$=$J_{9,10}$=9, $J_{10,11}$=14.5, $J_{11,12}$=6.5, $J_{14,15}$=11Hz - ^{13}C NMR($CDCl_3$) : 173.0(C_1) ; 165.5(PhCO) ; 136.9, 135.9, 133.0, 132.6, 131.2, 130.5, 129.6, 128.2, 127.7, 127.4, 125.1 (Ph, C_6,C_7,C_8,C_9, C_{10},C_{11},C_{14},C_{15}) ; 74.5(C_5) ; 73.6(C_{12}) ; 71.6(C_{19}) ; 60.5(CO_2Et); 36.0, 35.6, 34.0, 29.7, 25.3, 20.6(C_2,C_3,C_4,C_{13},C_{16},C_{17}.C_{18}); 27.1, 19.5(tBu); 20.0(C_{20}); 14.2(CO_2Et)- SM(NH_3) : 844(M^++18) - UV(CH_3OH); 282, 271, 262nm.

1 (potassium salt) : ^{1}H NMR(250MHz, D_2O) : 1.15(d,3H,H_{20}), 1.5-1.35(m,4H,H_{17},H_{18}), 1.7, 1.5(m,4H,H_3,H_4), 2.05(m,2H,H_{16}), 2.2(t,2H,H_2), 2.35(m,2H,H_{13}), 3.8(m,1H,H_{19}), 4.25(m,1H, H_{12}),4.65(m,1H,H_5), 5.45(m,2H,H_{14},H_{15}), 5.6(m,1H,H_6), 5.83(dd,1H,H_{11}), 6.2(dd,1H,H_7), 6.45-6.25(2dd,2H,H_9,H_{10}), 6.65(dd,1H,H_8) ; $J_{2,3}$=7.5, $J_{6,7}$=11, $J_{7,8}$=11.5, $J_{8,9}$=15, $J_{10,11}$=14.5, $J_{11,12}$=7, $J_{19,20}$=6.5Hz - UV (CH_3OH) : 281, 270.5, 260nm.

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