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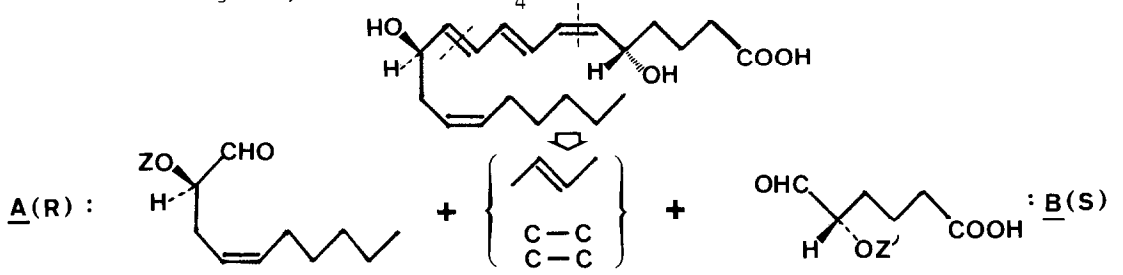
TOTAL SYNTHESIS OF LEUKOTRIENE (+)-LTB_4 FROM D-MANNITOL[1]

Y. Le Merrer, C. Gravier, D. Languin-Micas and J.C. Depezay*

Université René Descartes, Laboratoire de Chimie et Biochimie
Pharmacologiques et Toxicologiques (Unité Associée au CNRS n° 400)
45 rue des Saints Pères, 75270 PARIS Cedex 06, FRANCE.

Abstract : A total convergent synthesis of leukotriene (+)-LTB_4 has been carried out via two enantiomerically pure α-hydroxyaldehydes,chiral key intermediates both obtained from D-mannitol and connected at a four carbon atoms interval by Wittig reactions.

We have previously reported [2] a general method to prepare enantiomerically pure α-hydroxyaldehydes of R or S configuration from D-mannitol. These aldehydes are chiral key intermediates for the synthesis of arachidonic acid metabolites. The strategy is based on nucleophilic opening of diastereoisomeric diepoxides 1 and 2. We have now used this approach for a total convergent synthesis of (+)-LTB_4 [3] :

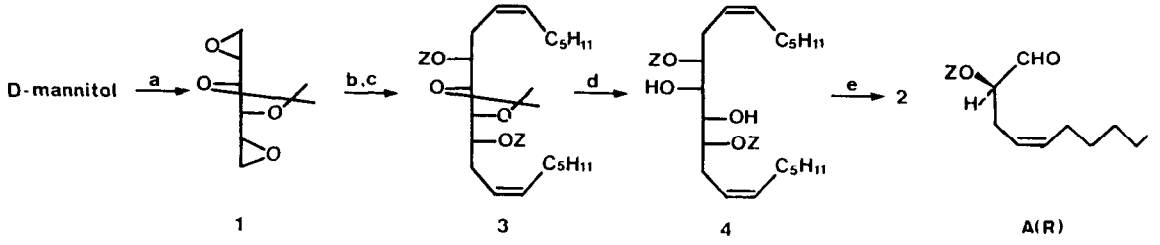


The first part of our work is concerned with the preparation of suitably protected (Z = tBDPSi, Z'= C_6H_5CO) enantiomerically pure aldehydes A (R) and B (S). Two moles of each are obtained from one mole of D-mannitol without "wastage of carbons".

Suitably protected α-hydroxyaldehyde A results (Scheme I)from nucleophilic opening of the diepoxide [2] 1 (1,2 : 5,6-dianhydro-3,4-O-methylethylidene-D-mannitol) by lithium heptynide followed by silylation in situ, controlled hydrogenation of the triple bonds (1→3), removal of the acetonide group (3→4) and oxidative cleavage of the 3,4-diol (4→A).

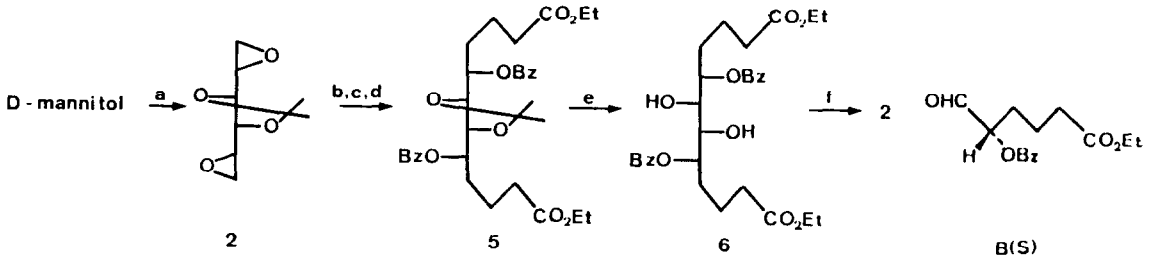
In the presence of bulky tert-butyldiphenylsilyl (tBDPSi) protecting groups, hydrolysis of the acetonide using aqueous trifluoroacetic acid is not complete at 0°C and silicium-oxygen bond cleavage occurs at higher temperatures. Indeed deprotection of the glycol by transthioketalisation[4] affords crude diol 4. Aldehyde A (R) is obtained with 33 % overall yield

Scheme I - Synthesis of aldehyde A(R)[10]



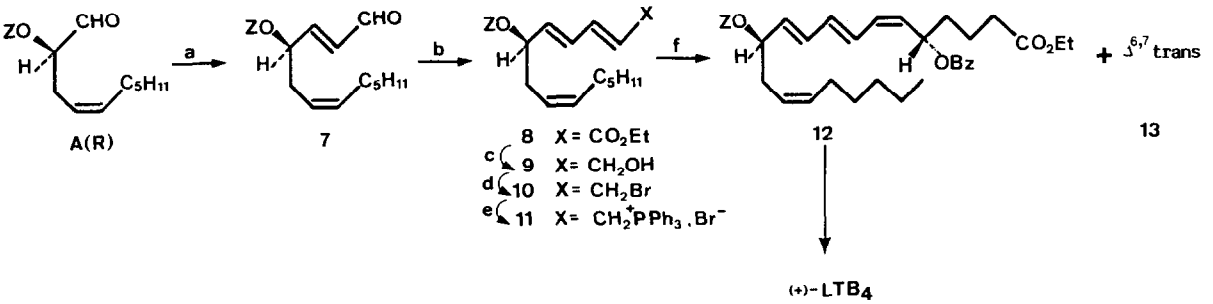
a : ref. 1 - b : 2,2eq.C_5H_4-C≡C-Li, THF, HMPT, 65°C, 2h30 then tBDPSiCl, 65°C, 16h30 ; 60 % - c : Lindlar cat., H_2, C_6H_6 ; 100 % - d : 7eq.$(CH_2SH)_2$, 0,2eq. TSOH, $CHCl_3$, 60°C, 3h - e: 1,1eq. $Pb(OAc)_4$, C_6H_6, RT, 1h ; d + e : 55 %

Scheme II - Synthesis of aldehyde B(S)[10]



a : ref. 1 - b : 6eq. LiC≡C-CO_2Et, 6eq. $BF_3.OEt_2$, THF, - 78°C, 2h then NH_4Cl aq.Sat. - c : 2,5eq. PhCOCl, pyr, 20°C, 2h ; b + c : 80 % - d : H_2, Pt, C_2H_5OH ; 100 % - e : TFA, H_2O 9/1, -5°C, 3h30 ; 90 % - f : 1,1eq. $Pb(OAc)_4$, CH_2Cl_2, - 10°C, 1h ; 65 %

Scheme III - Synthesis of conjugated triene-LTB$_4$ + $\Delta^{6,7}$ trans isomer[10]



a : 1,2eq. Ph_3P=CH-CHO, C_6H_6, 80°C, 6h ; 60 % - b : 1,2eq. $(EtO)_2POCH_2CO_2Et$, 1eq. DBU, 1,2eq. LiCl, CH_3CN, RT, 1h ; 65 % c : 1,3eq. AlH_3, THF, 0°C, 2h30 - d : 3,3eq. CBr_4, 1,5eq. DIPHOS, CH_2Cl_2, - 35°C, 2h30 - e : 1,2eq. Ph_3P, CH_3CN, RT, 2h30 ; c + d + e : 75 % - f : 1eq. BuLi, THF, - 100°C, 2mn then 1,5eq. HMPT, - 100°C→RT ; 80 % - g : 10eq. nBu_4NF, THF - h : 10eq. K_2CO_3, MeOH.H_2O 4/1.

from diepoxide 1.

The synthesis of the protected aldehyde B (S) (Scheme II) begins with the nucleophilic opening of the diepoxide [2] 2 (1,2 : 5,6-dianhydro-3,4-O-methylethylidene-L-iditol) by lithio ethylpropiolate (large excess) in the presence of boron trifluoride-etherate at -78 °C [5]. The diol is then benzoylated and triple bonds are reduced (2→5). Hydrolysis of the acetonide 5 and cleavage of the 3,4-diol 6 leads to aldehyde B (S) in 47 % of overall yield from diepoxide 2.

In the second part of the synthesis (Scheme III), a four carbon atom junction between the two aldehydes A and B is realized by succesive Wittig condensations according to a scheme previously described [3d]. We have modified some experimental conditions. In particular during the Horner-Wadsworth-Emmons reaction (7→8) we used conditions [6] more appropriate for base sensitive aldehydes. For the transformation of allylic alcohol 9 into bromide 10 use of DIPHOS [7] $(Ph_2CH_2)_2$ instead of triphenylphosphine facilitates purification since "diphos monoxyde" is more easily separated than triphenylphosphine oxide.

The last Wittig reaction leads to a mixture of the two diastereoisomers $\Delta^{6,7}$ cis and $\Delta^{6,7}$ trans (double bond isomers ; ratio 12 : 13, ca. 7 : 3). These compounds are easily separated by HPLC [8] and fully characterised. Each isomer has been sequentially deprotected and the potassium salt of (+)-LTB_4 obtained is identical (HPLC, UV) [9] with a sample supplied by J. Rokach.

The study of LTB_4 metabolism by different systems (P.M.N.L. and hepatic microsomes of rat) shows that the metabolic profile obtained is superposable to the one obtained from Rokach's sample of LTB_4.

Starting from an inexpensive chiral natural compound, via diepoxides, this synthesis of (+)-LTB_4 has been accomplished according to a flexible strategy which is easily applicable to synthesis of analogs or modified LTB_4 and of hydroxy eicosatetraenoïc acids (HETE).

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REFERENCES AND NOTES

1. Presented in "Société Française de Chimie", organic division meeting, Paris March 1986, oral communication ; "1st Belgian Organic Synthesis Symposium", Belgian Chemical Society, Namur May 1986, poster.
2. Y. Le Merrer, A. Dureault, C. Gravier, D. Languin, J.C. Depezay, Tetrahedron Lett., 1985, 26, 319.
3. a) E.J. Corey, A. Marfat, G. Goto, F. Brion, J. Am. Chem. Soc., 1980, 102, 7984.
b) E.J. Corey, A. Marfat, J. Munroe, K.S. Kim, P.B. Hopkins, F. Brion, Tetrahedron Lett., 1981, 22, 1077.
c) Y. Guindon, R. Zamboni, C.K. Lau, J. Rokach, Tetrahedron Lett., 1982, 23, 739.
d) R. Zamboni, J. Rokach, Tetrahedron Lett. 1982, 23, 2631.
e) K.C. Nicolaou, R.E. Zipkin, R.E. Dolle, B.D. Harris, J. Am. Chem. Soc., 1984, 106, 3548.

f) J. Rokach, J. Adams. Acc. Chem. Res., 1985, 18, 87.
g) Chao-Qi Han , D. Di Tullio, Yi-Fong Wang, C.J. Sih, J. Org. Chem., 1986, 51, 1253.
4. D.R. Williams, Sing-Yuen Sit, J. Am. Chem. Soc., 1984, 106, 2949.
5. M.J. Eis, J.E. Wrobel, B. Ganem, J. Am . Chem. Soc., 1984, 106, 3693.
6. S. Masamune, W.R. Roush, Tetrahedron Lett., 1984, 25, 2183.
7. J. Rokach, J. Adams, R. Perry, Tetrahedron Lett., 1983, 24, 5185.
8. Waters μ- Porasil column ; 98.5 % hexane /.5 % AcOEt / 1 % Et_3N as solvent, retention volumes : 12, 11.60 ; 13, 13.60.
9. HPLC : solvent gradient system (CH_3CN / H_2O with .1 % AcOH) on a Spherisorb ODS 2 5 μcolumn . UV : 261, 269, 281 nm.
10. All new compounds exhibited satisfactory spectra and analytical data.
A (R) : $Eb_{0.05} \sim 168°C$ (Büchi) - $[\alpha]_D^{20°}$ = -14.5° (c 2.2, $CHCl_3$) [Litt : -16.5° (c 3.0, $CHCl_3$)[3g]; -18° (c 2, $CHCl_3$)[2d]] - ^1H NMR (90 MHz, $CDCl_3$) : 0.85 (t,3H), 1.10 (s, 9H), 1.25, (m, 6H), 1.9 (m, 2H), 2.4 (m, 2H), 4.1 (dt, 1H, 6Hz, 1.8Hz), 5.4 (m, 2H), 7.4-7.7 (2m, 10H), 9.5 (d, 1H, 1.8 Hz) - ^{13}C NMR ($CDCl_3$) : 202.2 (d), 135.4 (d), 133.0 (d), 132.8 (s), 132.6 (s),129.6 (d), 127.4 (d), 122.3 (d), 77.7 (d), 37.3 (t), 31.5 (t), 29.1 (t), 27.3 (t), 27.0 (q), 22.6 (t), 19.4 (s), 14.1 (q). SM (NH_3) : 426 ($M^{\cdot+}$+18).
B (S) : $Eb_{0.02} \sim 100°C$ (Büchi) - $[\alpha]_D^{25°}$ = -39° (c 1.2, $CHCl_3$) [Litt : -46° (c0.5, $CHCl_3$)[3c]; enantiomer : +35° (c 2, $CHCl_3$)[3d]] - ^1H NMR (90 MHz, $CDCl_3$) : 1.25 (t, 3H, 7.5Hz); 1.95 (m, 4H), 2.40 (t, 2H, 7.25Hz), 4.15 (q,2H), 5.30 (t, 1H, 7Hz), 7.60-8.15 (2m, 5H), 9.75 (s, 1H) - ^{13}C NMR ($CDCl_3$) : 197.8 (d), 172.6 (s), 165.9 (s), 133.5 (d), 129.8 (d), 129.1 (s), 128.5 (d), 78.3 (d), 60.4 (t), 33.6 (t), 28.3 (t), 20.5(t), 14.1 (q).
7 $[\alpha]_D^{25°}$ = -13° (c 1.55, $CHCl_3$) [Litt[3g]: -14.4° (c 2.0, $CHCl_3$)] .
8 $[\alpha]_D^{20°}$ = 43° (c 2.2, $CHCl_3$) [Litt : 40,6°(c 2.0, $CHCl_3$)[3g] , 45° (c 3.0, $CHCl_3$)[3d]] .
12 ^1H NMR (C_6D_6, 250 MHz) : 0.80 (t, 3H), 0.90 (t, 3H), 1.10-1.40 (m, 15H), 1.60 (m, 4H), 1.85 (m, 2H), 2.10 (m, 2H), 2.35 (m, 2H), 3.80 (q, 2H), 4.30 (m, 1H, H_{12}), 5.30 (dd, 1H, H_6), 5.45 (ddd, 1H, H_{15}), 5.47 (ddd, 1H, H_{14}),5.70 (dd, 1H, H_{11}), 5.95 (dd, 1H, H_{10}), 6.0 (dd, 1H, H_7), 6.05 (m, 1H, H_9), 6.10 (ddd, 1H, H_5), 6.70 (dd, 1H, H_8), 7.0-8.10 (2m, 5H), 7.20-7.80 (2m, 10H), $J_{4,5}$ = 5.5, $J_{5,6}$ = 9.5, $J_{6,7}$ =10.5, $J_{7,8}$ = 11.5, $J_{8,9}$ = 14, $J_{9,10}$ = 10.2, $J_{10,11}$ = 14.5, $J_{11,12}$ = 7.2, $J_{14,15}$ = 11Hz - ^{13}C NMR (C6D6) : 172.3 (C_1) ; 165.6 (BzCO) ; 137.6, 136.4, 135.3, 132.6, 132.3, 130.9, 130.7, 129.9, 128.9, 128.4, 128.2 125.0 (Ph, C_6, C_7, C_8, C_9, C_{10} , C_{11} , C_{14} , C_{15}) ; 74.7 (C_{12}) ; 70.7 (C_5) ; 60.0 ($CO_2\underline{CH_2}CH_3$) ; 36.6, 34.7, 34.0, 31.8, 29.6, 27.8, 22.9, 20.9, (C_2, C_3, C_4, C_{13} , C_{16} , C_{17} , C_{18} , C_{19}) ; 27.3, 19.6 (tBu) ; 14.1 ($CO_2CH_2\underline{CH_3}$, C_{20}) - SM (NH_3) : 724 ($M^{\cdot+}$+18) - UV (C_2H_5OH) : 263, 272, 283 nm.
13 ^1H NMR (C_6D_6, 400MHz) : 0.80 (t, 3H), 0.90 (t, 3H), 1.10-1.40 (m, 15H), 1.60 (m, 4H), 1.85 (m, 2H), 2.05 (t,2H), 2.40 (m, 2H), 3.90 (q, 2H), 4.40 (ddd, 1H, H_{12}), 5.45 (m, 2H, H_{14} , H_{15}), 5.50 (ddd, 1H, H_6), 5.70 (dd, 1H, H_{11}), 5.95 (m, 1H, H_8), 6.0 (m, 1H, H_9), 6.10 (dd, 1H, H_{10}), 6.30 (ddd, 1H, H_7), 7.05-8.20 (2m, 5H), 7.20-7.80 (2m, 10H), $J_{4,5}$ = 5.5, $J_{5,6}$ = 7.5, $J_{6,7}$ = 14, $J_{6,8}$ = 2, $J_{7,8}$ = 9,5, $J_{7,9}$ = 2.5, $J_{9,10}$ = 9, $J_{10,11}$ = 15, $J_{11,12}$ = 7, $J_{12,13}$ = 5.5, $J_{14,15}$ = 11Hz - ^{13}C NMR (C_6D_6) : 172.3 (C_1) ; 165.3 (BzCO) ; 137.0, 136.3, 133.8, 133.2, 132.8, 132.4, 131.8, 131.2, 130.4, 129.9, 124.9 (Ph, C_6, C_7, C_8, C_9, C_{10} , C_{11} , C_{14} , C_{15}) ; 74.6 (C_{12}) ; 74.4 (C_5) ; 60.0 ($CO_2CH_2CH_3$) ; 36.6, 34.2, 33.9, 31.8, 29.6, 27.8, 23.0, 21.0 (C_2, C_3, C_4, C_{13} , C_{16} , C_{17} , C_{18} , C_{19}) ; 27.3, 19.6 (tBu) ; 14.3 ($CO_2CH_2\underline{CH_3}$, C_{20}) - SM (NH_3) : 724 ($M^{\cdot+}$+18) - UV (C_2H_5OH) : 262, 270, 282 nm.

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