Tetrahedron Letters,Vol.23,No.26,pp 2631-2634,1982 0040-4039/82/262631-04$03.00/0
Printed in Great Britain

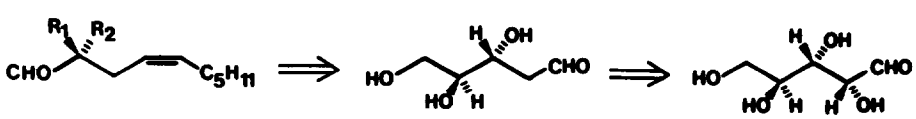
SIMPLE EFFICIENT SYNTHESIS OF LTB_4 AND 12-epi-LTB_4

Robert Zamboni and Joshua Rokach*
Merck Frosst Canada Inc. P.O. Box 1005, Pointe Claire-Dorval, Quebec, H9R 4P8

Summary: Using L-and D-arabinose respectively as the source of chirality at C-12 in LTB_4, efficient new syntheses of LTB_4 and 12-epi-LTB_4 have been realized.

LTB_4, a metabolite of arachidonic acid, has recently been isolated and characterized.[1] The biological activity of LTB_4[2] (potent chemotactic and chemokinetic properties and induction of vascular permeablity) and the availability of only µg quantities from biological sources has resulted in the synthesis of this important mediator of allergic and inflammatory states.[3,4] In our first synthesis of LTB_4 1a[4] (Scheme 2) 2-deoxy D-ribose was used in a chirally economic manner to provide the two synthons 2 and 3b which were coupled to yield the natural product. The present approach, which is also entirely stereospecific in nature, was designed to allow more flexibility and versatility in our overall approach to the synthesis of metabolites of arachidonic acid and some of their isomers. This strategy is illustrated below for the synthesis of LTB_4 1a (natural isomer) and 12-epi LTB_4 1b. The selection of 1b as target molecule was dictated by our desire to investigate the pharmacology, biochemistry and receptor binding properties of this isomer of LTB_4 in which the only difference with the natural product is the stereochemistry at carbon 12. Our plan was to develop stereospecific routes to both R and S isomers of 4. The two compounds could then be combined with 2[4] through an appropriate 4 carbon unit to form the desired LTB_4 isomers 1a and 1b. Retrosynthetic analysis for Synthon 4a (Scheme 1) shows that L-arabinose 5 is an appropriate starting material.

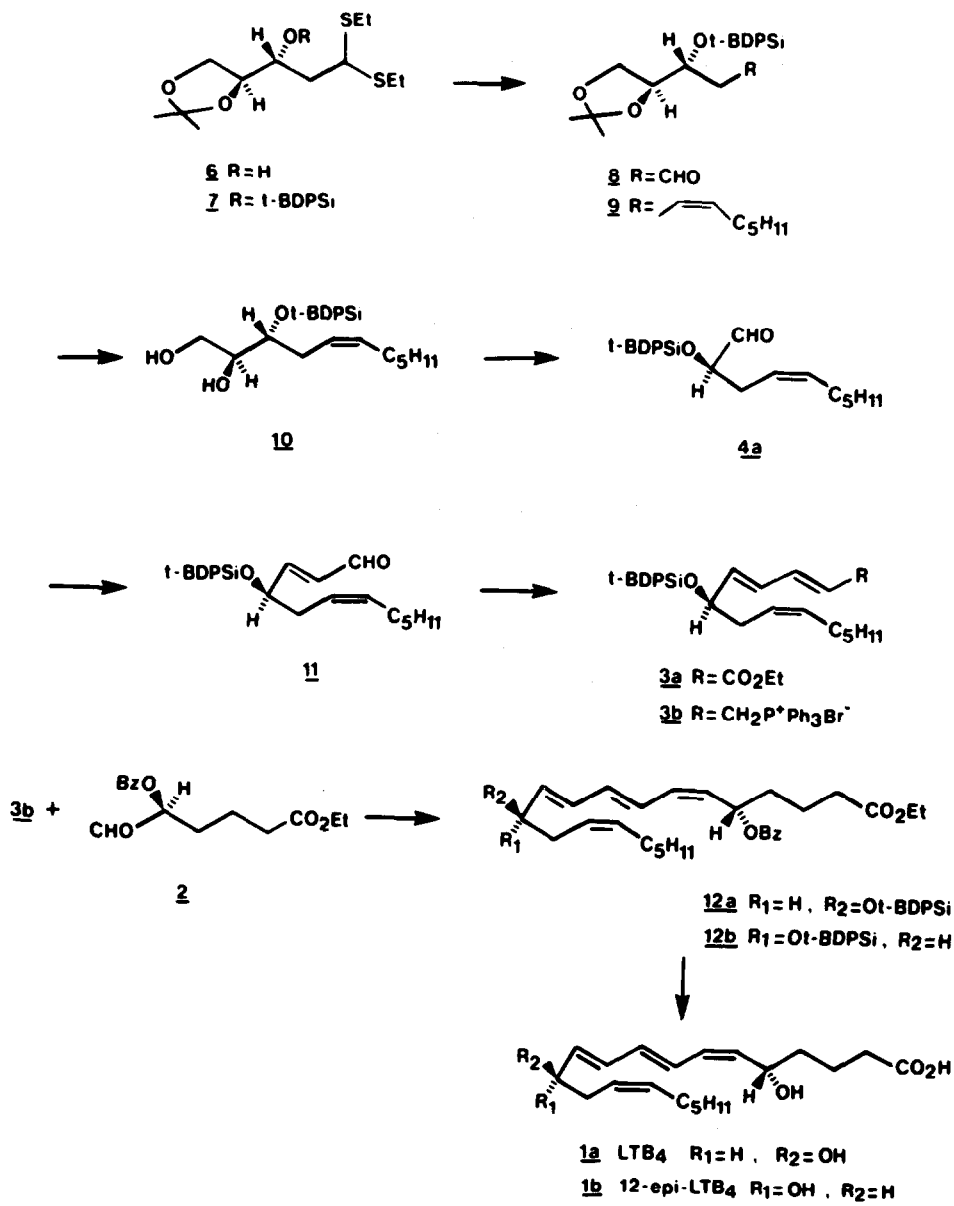
SCHEME 1



4a R_1=H, R_2=Ot-BDPSi
4b R_1=Ot-BDPSi, R_2=H

5

SCHEME 2


6 R=H
7 R= t-BDPSi
8 R=CHO
9 R=
10
4a
11
3a R=CO2Et
3b R=CH2P+Ph3Br-
3b +
2
12a R1=H, R2=Ot-BDPSi
12b R1=Ot-BDPSi, R2=H
1a LTB4 R1=H, R2=OH
1b 12-epi-LTB4 R1=OH, R2=H

The hydroxyl groups at C-4 and C-5 of 5 could be considered as precursors of an aldehyde function while the hydroxyl group at C-3 will provide the desired chiral center in 4a and ultimately the 12R center in LTB_4 1a. Equally the use of D-arabinose would yield the required 12S configuration of 12-epi LTB_4 1b.

Examination of the literature revealed a simple and efficient way to prepare 6 from L-arabinose in 4 steps which was used as our starting material.[5]

Thus silylation of acetonide 6 (t-Buϕ_2SiCl/DMAP/Et_3N)[6] afforded silylether 7, $[\alpha]_D$=-14.9° (c=2.5, $CHCl_3$) in 80% yield. Removal of the dithioacetal (NCS/$AgNO_3$ in CH_3CN/H_2O at 0°)[7] afforded the sensitive aldehyde 8[8] in 60% yield. Condensation of aldehyde 8 with hexylidene triphenylphosphorane in THF at -78° gave olefin 9 in 55-60% yield. Selective removal of the acetonide group (TFA/THF/H_2O,16 hrs) afforded diol 10 $[\alpha]_D$=-45.1°(c=3,$CHCl_3$) in 80% yield. Cleavage of the diol with $Pb(OAc)_4$ in the presence of finely ground Na_2CO_3 gave aldehyde 4a $[\alpha]_D$=-18°,(c=2.0,$CHCl_3$) in 70-80% yield. Repeating the sequence, but starting from D-arabinose we obtained the S isomer 4b $[\alpha]_D$=+18.5° (c=3.0,$CHCl_3$).

Treatment of aldehyde 4a with 1.2 eq of formylmethylene triphenylphosphorane in benzene at 75-80° afforded α,β-unsaturated aldehyde 11 in virtually quantitative yield. Condensation of 11 with excess triethylphosphonoacetate (NaH, benzene, rt, 1 hr)[9] afforded dienester 3a $[\alpha]_D$=+45°(c=3.0,$CHCl_3$) in >75% overall yield from 4a. We have found this two step procedure for chain elongation by 4 carbons of aldehyde 4a superior to other methods tried (Ph_3P=CH-CHO[10], Ph_3P=CH-CH=CH-CHO[11], $(EtO)_2PO-CH_2-CH=CH-CO_2Et$/NaH[12]) both in yield and ease of purification. Ester 3a was transformed (1.AlH_3, 2.CBr_4/Ph_3P, 3.Ph_3P/CH_3CN)[4] to phosphonium salt 3b and then coupled with 2 (n-BuLi/THF/HMPA)[4] to obtain 12a, $[\alpha]_D$=+202°, (c=1.0,$CHCl_3$). Deprotection ($nBu)_4NF$,THF) and hydrolysis afforded LTB_4 1a.[13,14] Repeating the above sequence starting with aldehyde 4b afforded 12b $[\alpha]_D$=+100° (c=.5,$CHCl_3$) which was deprotected and hydrolyzed to 12-epi-LTB_4 1b.[15] 12-epi-LTB_4 was found to be approximately 16 times less potent than natural LTB_4 in the rat neutrophil aggregation assay.[14]

ACKNOWLEDGMENTS

We take this opportunity to thank the National Sciences and Engineering Research Council Canada for an Industrial Postdoctoral Fellowship to R. Zamboni. The authors would like to extend their thanks to Dr. J. Atkinson and Dr. Y. Guindon for helpful discussions during the preparation of this manuscript.

REFERENCES and FOOTNOTES:

1. P. Borgeat and B. Samuelsson, J. Biol. Chem., 254, 2643 (1979).
2. a) A.W. Ford-Hutchinson, M.A. Bray, M.V. Doing, M.E. Shipley and M.S.H. Smith, Nature (London), 286, 264 (1980); b) R.M.J. Palmer, R.J. Stepley, G.A. Higgs, and K.E. Eakins, Prostaglandins, 20, 411 (1980); c) M.A. Bray, A.W. Ford-Hutchinson and M.J.H. Smith, Br. J. Pharmac., 73, 259 (1981); d) G.A. Higgs and K.E. Eakins, Prostaglandins, 20, 411 (1980) and e) M.A. Bray, F.M. Cunningham, A.W. Ford-Hutchinson and M.J.H. Smith, Br. J. Pharmac. 72, 483 (1981).
3. a) E.J. Corey, A. Marfat, G. Goto and F. Brion, J. Am. Chem. Soc., 102, 7984 (1980); b) E.J. Corey, A. Marfat, J. Monroe, K.S. Kim, P.B. Hopkins and F. Brion, Tetrahedron Lett., 22 1077 (1981).
4. Y. Guindon, R. Zamboni, C.K. Lau and Joshua Rokach, Tetrahedron Lett., 23, 739 (1982).
5. M.Y.H. Wong, and G.R. Gray, J. Am. Chem. Soc., 100, 3548 (1978).
6. S.K. Chandhary and O. Hernandez, Tetrahedron Lett., 21, 835 (1980).
7. E.J. Corey and B.W. Erickson, J. Org. Chem., 36, 3553 (1971).
8. The aldehyde was purified by quick filtration through SiO_2 column using 25% ethylacetate in hexane and used directly.
9. W.S. Wadsworth, Jr., and W.D. Emmons, Org. Syn. 45, 44 (1965).
10. a) J. Rokach, R.N. Young, M. Kakushima, C.K. Lau, R. Sequin, R. Frenette and Y. Guindon, Tetrahedron Lett., 22, 979 (1981); b) J. Rokach, R. Zamboni, C.K. Lau and Y. Guindon, Tetrahedron Lett., 22, 2759 (1981); c) J. Rokach, C.K. Lau, R. Zamboni and Y. Guindon, Tetrahedron Lett., 22, 2763 (1981).
11. I. Ernest, A.J. Main and R. Menassé, Tetrahedron Lett., 23, 167 (1982).
12. P.J. Vanden Tempel and H.O. Huisman, Tetrahedron, 22, 293 (1966).
13. Identical in all respects to natural LTB_4 and synthetic (5S,12R) LTB_4 previously prepared by us.

14. We would like to thank Dr. A.W. Ford-Hutchinson, Kings College, for the biological comparisons.

15. LTB_4 and 12-epi LTB_4 could easily be differentiated on a Waters C_{18} μbondapak column using 70% MeOH/30% H_2O/.01% AcOH as solvent. The purity of the 12-epi LTB_4 was > 99% by HPLC.

(Received in USA 18 March 1982)