Tetrahedron Letters,Vol.27,No.48,pp 5853-5856,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

OPTICALLY ACTIVE PROPARGYLIC ALCOHOLS FROM D-XYLOSE USEFUL PRECURSORS FOR LTB_4 SYNTHESIS

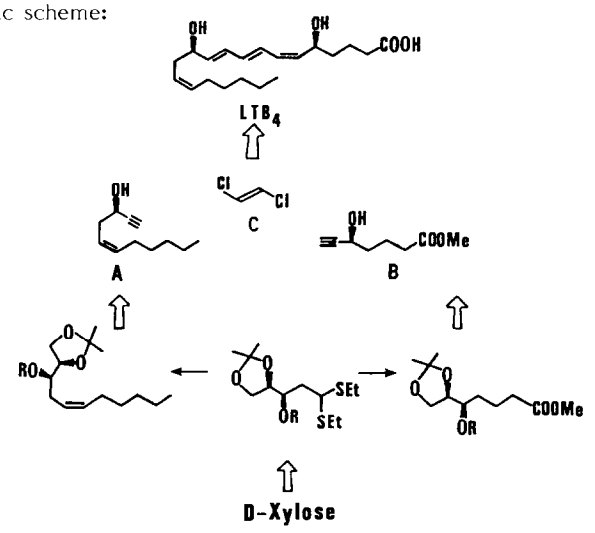
P. Pianetti, P. Rollin and J.R. Pougny*

Laboratoire de Biochimie Structurale, UA 499, UFR de Sciences
Fondamentales et Appliquées, BP 6759, 45067 Orléans Cédex 2, France

Summary Using D-Xylose as a source of chirality at C-5 and C-12 in LTB_4, an efficient synthesis of the optically active propargylic alcohols **A** and **B**, chiral precursors for the LTB_4 synthesis, has been achieved.

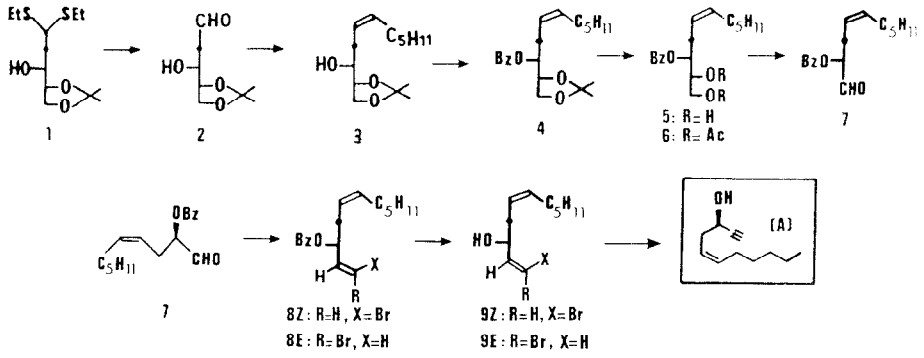
Leukotriene B_4 (LTB_4), a member of the arachidonic cascade identified by Borgeat and Samuelsson[1], is a potent chemotactic agent and its implication in inflammatory processes is very likely and is being actively investigated.

Since 1980, several syntheses of LTB_4 have been published[2a-g] and one report describes the preparation of chiral intermediates[3]. In every case, a common approach was used, based on a final Wittig reaction step. We are now describing a new approach to the synthesis of LTB_4, based on the following retrosynthetic scheme:



Cleavage of C_7-C_8 and C_9-C_{10} bonds leads to chiral fragments C_1-C_7 [**B**] and C_{10}-C_{20} [**A**] and a single olefin [**C**]. Fragments [**A**] and [**B**] are chiral propargylic alcohols which can be prepared from a common precursor: D-xylose. The final carbon-carbon bond could be formed by coupling of fragments [**A**] and [**B**] with [**C**] according to a method developed by Linstrumelle[4,5].

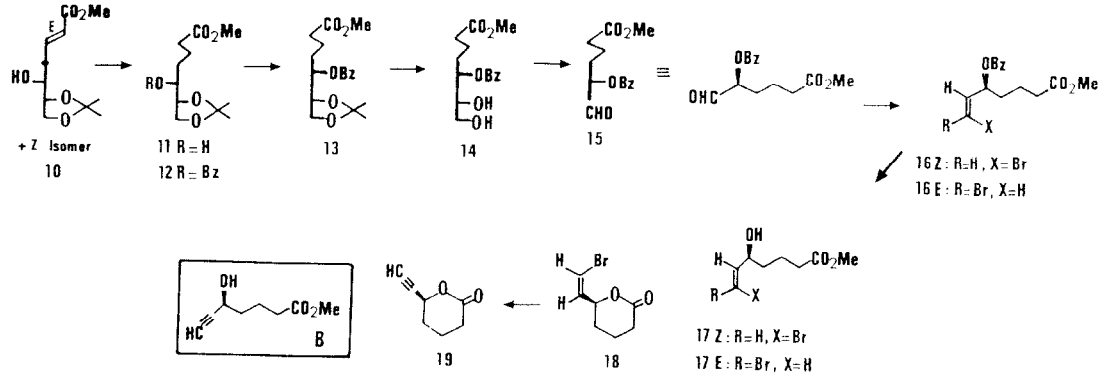
The deoxy compound **1** could be easily obtained from D-xylose[6]. Removal of the dithioacetal (red HgO/BF_3-Et_2O in THF-H_2O)[7] afforded the ß-hydroxy aldehyde **2** in 90% yield. Reaction of



the crude aldehyde **2** with hexylidenetriphenylphosphorane (4.0 eq., -78°C) generated from n-hexyltriphenylphosphonium bromide[8] ($NaNH_2$, THF/HMPT, 1 h, r.t.) gave the olefin **3**, b.p. 70°C/0.1 mm Hg, $[\alpha]_D$ = +8° (c, 1.35, CCl_4) in 71% yield[9]. Benzoylation of the homoallylic alcohol **3** (1.2 eq. BzCl in pyridine) yielded to the ester **4** (98%), $[\alpha]_D$ = +15° (c, 2.25, CCl_4). Cleavage of the acetonide group (TFA/H_2O, 9:1, 30 min, -10°C) gave the diol ester **5** (95%) which was fully characterized as the triester **6**, $[\alpha]_D$ = +23° (c, 1.80, CCl_4). Cleavage of the vic-diol **5** with $Pb(OAc)_4$ (1.1 eq.) in the presence of finely ground Na_2CO_3 (2.0 eq.) in CH_2Cl_2 (30 min, 0°C) gave the aldehyde **7** (70%)[2g], b.p.: 100°C/0.08 mm Hg, $[\alpha]_D$ = +32° (c, 1.50, CCl_4).

A convenient synthesis of 1-bromoolefins and acetylenes by chain extension of aldehydes was reported by Matsumoto and Kuroda[10], and used for the total synthesis of (±)-dicranenones[11]. Wittig reaction of aldehyde **7** with bromomethylenetriphenylphosphorane (1.5 eq. $Ph_3P^+CH_2Br,Br^-$; 1.4 eq. t-BuOK in dry THF, 30 min, -78°C) gave the bromoolefin **8** (73%) as a mixture of the Z and E isomers which could not be separated. After debenzoylation of bromoolefin **8** (catalytic MeONa in MeOH), the alcohols **9** were obtained and separated by flash chromatography (54%, **Z:E** ratio = 9:1)[12]. By treatment with base, Z-haloolefins generally undergo elimination more rapidly than the E-isomers[10]. Indeed, while the isomer **9E** reacted quite smoothly, the isomer **9Z** yielded propargylic alcohol [A] (92% after purification)[13] when treated with t-BuOK (2 eq. in dry THF, -78°C to 0°C).

According to our retrosynthetic analysis, chirality at C-3 of the D-xylose can be transferred to the C-5 of LTB_4. A direct transfer of chirality would lead to the 5(R) epimer of LTB_4. It was therefore necessary to effect inversion of configuration at the C-3 position of the sugar moiety.



β-Hydroxy aldehyde **2** was reacted with methyl (triphenylphosphoranylidene) acetate (1.02 eq., AcOEt, 1 h, reflux) to give the crude unsaturated ester **10** as a mixture of the **Z** and **E** isomers (**Z:E** = 1:10) which could be separated by silica gel column chromatography: **10Z** (7%), $[\alpha]_D$ = +9.5° (c, 1.84, CCl_4); δ H_3 = 6.45 ppm ($J_{3,2}$ = 11.3 Hz); **10E** (72%), $[\alpha]_D$ = +16° (c, 2.25, CCl_4); δ H_3 = 6.97 ppm ($J_{3,2}$ = 16.0 Hz). Catalytic hydrogenation of the mixture of isomers **10** (10% Pd/C, AcOEt, 15 psi, 24 h) gave the saturated ester **11** (95%), $[\alpha]_D$ = +11.5° (c, 3.28, CCl_4)[14] which was benzoylated (1.1 eq. BzCl, pyridine, r.t.) to give 5(R) **12** (84%), $[\alpha]_D$ = +23° (c, 3.40, CCl_4).

The 5(S) benzoylated compound **13**, could be obtained using a methodology first proposed by Still[15]. Reaction of the alcohol **11** with 3.0 eq. Ph_3P and 1.5 eq. $Zn(OBz)_2$, (toluene, 0°C, then dropwise addition of 3.0 eq. of diethylazodicarboxylate, r.t.)[16] yielded benzoate **13** (70% after purification)[17], $[\alpha]_D$ = +0.5° (c, 2.04, CCl_4). Cleavage of the acetonide (TFA/H_2O, 9:1, 30 min, 0°C) gave the diol **14** (91%), $[\alpha]_D$ = -4° (c, 1.50, CCl_4) which was converted into the aldehyde **15** (1.2 eq. $Pb(OAc)_4$, CH_2Cl_2, 2.0 eq. Na_2CO_3, 30 min, 0°C) in 75% yield, $[\alpha]_D$ = -37° (c, 2.45, CCl_4)[18].

The aldehyde **15** was then treated with bromomethylenetriphenylphosphorane (1.5 eq. $Ph_3P^+CH_2$ Br,Br^-, 1.3 eq. t-BuOK, THF, -78°C), to give the bromovinyl derivative **16** (70%) as a mixture of **Z** and **E** isomers[19] which could not be separated.

Debenzoylation of compound **16** (catalytic MeONa, MeOH, r.t.) gave a mixture of the **(Z,E)**-bromovinyl alcohols **17** and **Z**-bromovinyl lactone **18** in a 4:1 ratio[20] (65% overall yield) which could be separated. Reaction of the **Z**-bromovinyl lactone **18** with t-BuOK (1.05 eq. t-BuOK, THF -78°C to -20°C) produced the acetylenic lactone **19** in only moderate yield[21]. Finally, dehydrohalogenation of the **(Z,E)** mixture of bromovinyl alcohols **17E** (2.0 eq. t-BuOK, DME, -78°C to r.t.) yielded the **E**-bromovinyl alcohol **17** and the propargylic alcohol **[B]** in a 1:3 ratio (92% overall yield) which could be separated by flash chromatography and fully characterized[22].

Acknowledgments This work was supported by the Centre National de Recherche Scientifique within the framework of the PIRMED-ASP "Lipides Pharmacologiquement Actifs". We thank Prof. P. Sinaÿ for his interest and Mr. G. Keravis for mass spectrometry.

References

1. P. Borgeat and B. Samuelsson, J. Biol. Chem., 254, 2643 (1979).
2. 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. Munroe, K.S. Kim, P.B. Hopkins and F. Brion, Tetrahedron Lett., 22, 1077 (1981); c) Y. Guindon, R. Zamboni, C.K. Lau and J. Rokach, Tetrahedron Lett., 23, 739 (1982); d) R. Zamboni and J. Rokach, Tetrahedron Lett., 23, 2631 (1982); e) L.S. Mills and P.C. North, Tetrahedron Lett., 24, 409 (1983); f) K.C. Nicolaou, R.E. Zipkin, R.E. Dolle and B.D. Harris, J. Am. Chem. Soc., 106, 3548 (1984); g) Y. Le Merrer, A. Duréault, C. Gravier, D. Languin-Micas and J.C. Depezay, Journées de la Division Chimie Organique, Société Française de Chimie, Paris, March 3-4, 1986; Tetrahedron Lett., 27, 4161 (1986).
3. C. Fuganti, S. Servi and C. Zirotti, Tetrahedron Lett., 24 5285 (1983).
4. V. Ratovelomanana and G. Linstrumelle, Tetrahedron Lett., 25, 6001 (1984).
5. D. Guillerm and G. Linstrumelle: see preceding paper.
6. M.Y.H. Wong and G.R. Gray, J. Am. Chem. Soc., 100, 3548 (1978).
7. E. Vedejs and P.L. Fuchs, J. Org. Chem., 36, 367 (1971).

8. C.F. Hauser, Th. W. Brooks, M.L. Miles, M.A. Raymond and G.B. Butler, J. Org. Chem., 28, 372 (1963).

9. Fully satisfactory spectroscopic and analytical data for the new compounds were obtained. ^{1}H-N.m.r. spectra (300 MHz, $CDCl_3$), m.s. (NH_3, C.I.), i.r. (neat, cm^{-1}) were entirely consistent with the assigned structures.

10. M. Matsumoto and K. Kuroda, Tetrahedron Lett., 21, 4021 (1980).

11. K. Sakai, T. Fujimoto, M. Yamashita and K. Kondo, Tetrahedron Lett., 26, 2089 (1985).

12. **9Z**-isomer: $[\alpha]_D$ = +65° (c, 1.07, CCl_4), ^{1}H-n.m.r.: δ 6.26 (1 H, d, $J_{1,2}$ = 7.0 Hz, H_1), 6.20 (1 H, dd, $J_{2,3}$ = 7.0 Hz, H_2); **9E**-isomer: $[\alpha]_D$ = +35° (c, 2.20, CCl_4, ^{1}H-n.m.r.: δ 6.36 (1 H, d, $J_{1,2}$ = 15.0 Hz, H_1) 6.25 (1 H, dd, $J_{2,3}$ = 5.8 Hz, H_2).

13. Compound [**A**]: $[\alpha]_D$ = + 26° (c, 1.13, CCl_4), m.s.: ($C_{11}H_{18}O$, M.W.: 166), 184 (100) [M+18], i.r.: 3400 (broad OH), 3300 and 2100 (HC≡C), ^{1}H-n.m.r.: δ 5.64 (1 H,m, $J_{6,5}$ = 11.4 Hz, J_6, $^7CH_2$ = 7.0 Hz, J_6, $^4CH_2$ = 1.4 Hz, H_6)*, 5.47 (1 H, m, J_5, $^4CH_2$ = 6.5 Hz, J_5, $^7CH_2$ = 1.8 Hz, H_5), 4.40 (1 H, td, J_3, $^4CH_2$ = 6.5 Hz, $J_{3,1}$ = 1.8 Hz, H_3), 2.50 (1 H, dd, $^4CH_2$), 2.47 (1 H, d, H_1), 2.07 (2 H, td, J $^7CH_2$, $^8CH_2$ = 7.0 Hz, $^7CH_2$), 1.39-1.26 [6 H, m, $(CH_2)_3$], 0.89 (3 H, t, J CH_3, $^{10}CH_2$ = 6.7 Hz, CH_3).

14. J. Rokach, R. Zamboni, C.K. Lau and Y. Guindon, Tetrahedron Lett., 22, 2759 (1981).

15. I. Galynker and W.C. Still, Tetrahedron Lett., 23 4461 (1982).

16. P. Rollin, Synth. Commun., 16, 611 (1986).

17. **12**: δ 4.30 (1 H, ddd, $J_{6,7}$ = 6.8 Hz, $J_{6,7'}$ = 6.4 Hz, $J_{6,5}$ = 4.5 Hz, H_6), 3.80 (1 H, dd, $J_{7,7'}$ = 8.7 Hz, H_7), 1.35 and 1.45 (6 H, 2s, isopropylidene CH_3); **13**: δ 4.26 (1 H, ddd, $J_{6,7}$ = 6.5 Hz, $J_{6,7'}$ = 6.3 Hz, $J_{6,5}$ = 5.4 Hz, H_6), 3.91 (1 H, dd, $J_{7,7'}$ = 8.0 Hz, H_7), 1.35 and 1.36 (6 H, 2s, isopropylidene CH_3).

18. Aldehyde **15** was previously synthesized from 2-deoxy-D-ribose, $[\alpha]_D$ = -33° (c, 2.50, $CHCl_3$) 2a, 2b; $[\alpha]_D$ = -34° (c, 1.30, $CHCl_3$) 2e; $[\alpha]_D$ = -46° (c, 0.50, $CHCl_3$) 2c; $[\alpha]_D$ = -39° (c, 1.20, $CHCl_3$) 2g. In a non-carbohydrate based synthesis of this compound, $[\alpha]_D$ = -34° (c, 2.50, $CHCl_3$) 3a.

19. **16**: $[\alpha]_D$ = +62° (c, 1.88, CCl_4); **16Z**-isomer, ^{1}H-n.m.r.: δ 6.38 (1 H, d, $J_{7,6}$ = 7.3 Hz, H_7), 6.23 (1 H, dd, $J_{6,5}$ = 7.3 Hz, H_6), 3.70 (3 H, s, OMe); **16E**-isomer, ^{1}H-n.m.r.: δ 6.51 (1 H, d, $J_{7,6}$ = 14.0 Hz, H_7), 6.25 (1H, dd, $J_{6,5}$ = 7.2 Hz, H_6), 3.70 (3 H, s, OMe). These values were taken from the n.m.r. spectrum of the mixture of isomers **16**.

20. **17**: $[\alpha]_D$ = +18°(c, 0.98, CCl_4); **17Z**-isomer: ^{1}H-n.m.r.: δ 6.27 (1 H, d, $J_{7,6}$ = 7.5 Hz, H_7), 6.16 (1 H, dd, $J_{6,5}$ = 7.5 Hz, H_6), 3.70 (3 H, s, OMe); Z-bromovinyl lactone **18**: $[\alpha]_D$ = +41° (c, 1.59, CCl_4); ^{1}H-n.m.r.: δ 6.36 (1 H, dd, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.3 Hz, H_7), 6.28 (1 H, dd, $J_{6,5}$ = 7.5 Hz, H_6), 5.23 (1 H, ddd, $J_{5,4ax}$ = 10.6 Hz, $J_{5,4eq}$ = 3.4 Hz, H_5).

21. **19**: m.s.: ($C_7H_8O_2$, M.W.: 124), 125 (72) (M+1), 142 (100) (M+18), i.r.: 3300 (HC≡C), 1750 (OCO); ^{1}H-n.m.r.: δ 5.13 (1 H, ddd, $J_{5,4ax}$ = 6.4 Hz, $J_{5,4eq}$ = 4.0 Hz, $J_{5,7}$ = 1.7 Hz, H_5), 2.27 (1 H, d, H_7).

22. **17E**: ^{1}H-n.m.r.: δ 6.36 (1 H, d, $J_{7,6}$ = 13.0 Hz, H_7), 6.22 (1 H, dd, $J_{6,5}$ = 6.0 Hz, H_6), 3.70 (3 H, s, OMe); Compound [**B**]: $[\alpha]_D$ = -9° (c, 1.56, CCl_4), m.s.: ($C_8H_{12}O_3$, M.W.: 156), 157 (100) (M+1), 174 (40) (M+18), i.r.: 3400 (broad, OH), 3300 (HC≡C), 1750 (OCO), ^{1}H-n.m.r.: δ 4.40 (1 H, broad m, H_5), 3.70 (3 H, s, OMe), 2.48 (1 H, d, $J_{7,5}$ = 2.0 Hz, H_7), 2.39 (2 H, t, J $^2CH_2$, $^3CH_2$ = 6.7 Hz, $^2CH_2$), 1.90-1.60 (4 H,m, $^3CH_2$ and $^4CH_2$).

*Superior figures refer to the number of the carbon atom in the aliphatic chain.

(Received in France 28 July 1986)