Tetrahedron Letters, Vol.32, No.9, pp 1165-1168, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

TOTAL SYNTHESIS OF LIPOXINS A4 and B4 FROM D-ISOASCORBIC ACID

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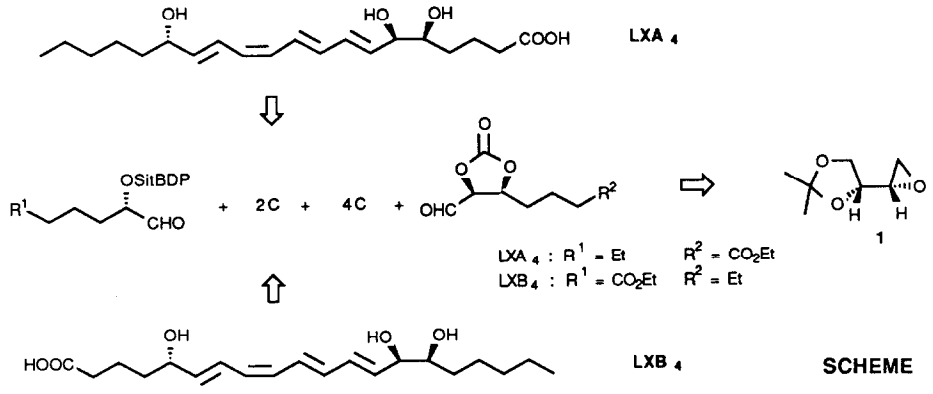
Summary : A total convergent synthesis of lipoxins A4 and B4 has been carried out via four optically pure α-hydroxy and α,β-dihydroxyaldehydes, obtained from D-isoascorbic acid as a single starting material. Connection by a six carbons unit uses Wittig-type reactions notably involving a stabilized arsonium ylide.

We have previously reported a general method for the preparation of enantiomerically pure α-hydroxy and α,β-dihydroxyaldehydes, for which all configurations are available starting either from D-isoascorbic or L-ascorbic acids[1]. We decided to embark on the synthesis of the most biologically active lipoxins LXA4 and LXB4[2,3] depicted in scheme I.

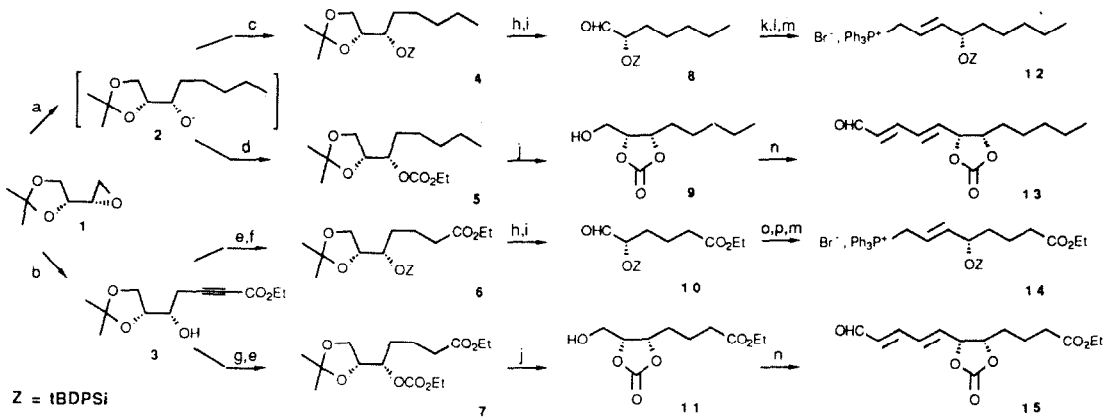


SCHEME I

The four key synthons required can be prepared from the same epoxytetrol **1**, readily available from D-isoascorbic acid [1](5 steps, 40% overall yield) without wasting chiral centers. The six missing carbon atoms are introduced via successive Wittig-type reactions.

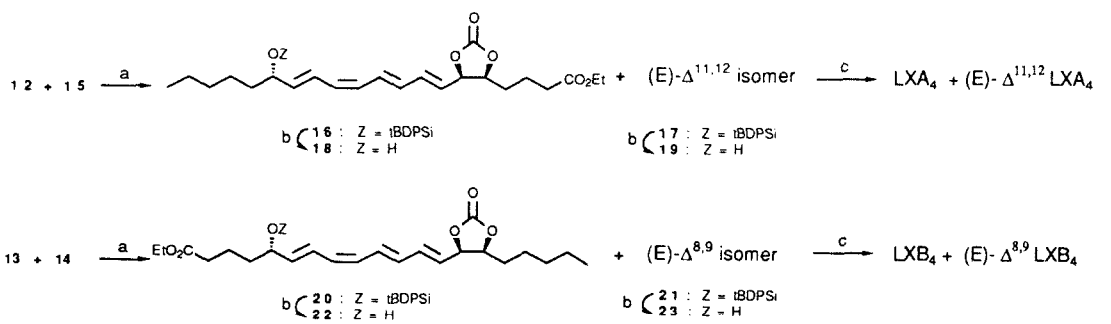
The preparation of the key precursors **12-15** is outlined in scheme II[4].

SCHEME II



a) Bu_2CuLi, THF, - 30°C, 15 min. b) Li-C≡C-CO_2Et, $BF_3.Et_2O$, -100°C, 1h, 75%. c) tBDPSiCl, catal. DMAP, overnight reflux, 70% from **1**. d) EtOCOCl, 0°C--->RT, 70% from **1**. e) H_2, catal. PtO_2, EtOH, 95%. f) tBDPSiCl, Im., DMF, 80°C, 18h. g) EtOCOCl 10 eq., pyr., RT, 81%. h) TFA, H_2O, THF 1:1:3, RT, 4h, 80% from **4**, 64% from **3**. i) $Pb(OAc)_4$, CH_2Cl_2, 0°C, 1h, 95%. j) TFA/H_2O 1:1, 0°C, 1h, then PTSA 0.3 eq., tol., RT, 6h, 50%. k) $(EtO)_2POCH_2CO_2Et$, CH_3CN, LiCl, DBU, RT, 3h, 83%. l) DIBAH, CH_2Cl_2, - 78°C ---> - 20°C, 93%. m) CBr_4, DIPHOS, CH_2Cl_2, - 30°C, 1h, then Ph_3P. CH_3CN, RT, 90%. n) $(COCl)_2$, DMSO, THF, - 60°C then Et_3N, 0°C, then (E)-OHC-CH = CH-CH_2-$AsPh_3^+$, Br^-, then catal. I_2, CH_2Cl_2, 55-62%. o) Ph_3P = CH-CHO, tol., 80°C, 5h, 50%. p) $NaBH_4$, $CeCl_3$, iPrOH, 0°C ---> RT, 97%.

SCHEME III



a) KHMDS, THF, - 105°C then HMPA - 100°C ---> - 40°C, 55%. b) TBAF/THF 5 eq. RT, 4h. c) K_2CO_3, MeOH, H_2O, 4°C, overnight.

The alcoxide **2** resulting from dibutyl cuprate addition on epoxytetrol **1** (THF, -30°C, 15 min.) can be protected by addition *in situ* of either tert-butyldiphenylchlorosilane (DMAP, overnight, reflux) or ethylchloroformate (0°C ---> RT, 1h). The two protected triols **4** and **5** are obtained in 70% isolated yield from **1**. Mild ketal hydrolysis of **4**, followed by cleavage of the resulting diol afforded enantiomerically pure aldehyde **8** in 76% yield from **4**. We realized a two carbons chain extension by treatment of **8** with triethylphosphonoacetate (DBU, LiCl, CH_3CN)[5] thus affording the corresponding pure (E)-α,β-unsaturated ester (83% yield) which was converted to the phosphonium salt **12** in three steps (DIBAH reduction to the allylic alcohol, bromination with CBr_4/DIPHOS and triphenylphosphine substitution [3b], 84% overall yield).

On the other hand, acyclic carbonate **5** was converted into the cyclic carbonate **9** as previously described[1] by us. We carried out the transformation of **9** into **13** by an original one-pot procedure : Swern oxidation[6] of **9** in THF afforded the corresponding unstable aldehyde which was submitted to alkylidenation by addition of formylenyl triphenylarsonium bromide [7]. The triethylammonium hydrochloride/triethylamine buffer present at the end of the Swern oxidation generates the arsorane, thus allowing the Wittig-type reaction with the highly reactive aldehyde issued from **9** to occur. The dienal **13** of pure (E, E)-stereochemistry is obtained after iodide catalyzed isomerization and chromatographic purification in 55-62% yield from **9**.

The preparation of both precursors **14** and **15**, functionnalized by an ester group started with the regiospecific opening of **1** by 3-lithioethylpropiolate, in the presence of $BF_3.Et_2O$ in Et_2O[8] (75% yield). *In situ* protection during this reaction proved unsuccessful. Homopropargylic alcohol **3** was hydrogenated and then silylated under rather drastic conditions (3 eq. tBDPSiCl, 6 eq. Im., DMF, 80°C, 18h, 80% from **3**)[9]. The silyl ether **6** was converted into the aldehyde **10** as described above for the transformation of **4** into **8**. According to a classical method [3a] the phosphonium salt **14** was obtained from **10** in four steps (Wittig reaction with formylmethylene triphenylphosphorane, regioselective carbonyl reduction under Luche conditions [10], bromination with CBr_4/DIPHOS and triphenylphosphine substitution, 44% overall yield).

Alternately, protection of **3** by a large excess of ethyl chloroformate in pyridine, followed by hydrogenation, afforded the acyclic carbonate **7** in 77% yield from **3**. The dienal **15** was obtained from **7** using the same reagents and conditions as described above for the transformation of **5** into **13**, in similar overall yield.

The ylide derived from **12** (KHMDS, THF, - 105°C, 5 min.) was reacted with the dienic aldehyde **15** (Scheme III) and afforded after HMPA addition, workup and chromatography the fully protected lipoxin A_4 **16** and its (E)-$\Delta^{11,12}$ isomer **17** (55% yield, 1:1 mixture). These two isomers were easily separated by HPLC (hexane/ethyl acetate 80:20). The pure isolated isomers **16**[11] and **17** were subjected to desilylation (5 eq.TBAF, THF, RT, 4h) and respectively afforded **18** and **19**. However, **18** was contaminated by its all trans isomer **19** which could be easily removed by HPLC[12] (hexane/ethyl acetate 60:40). Subsequent saponification of **18** and **19** (K_2CO_3, MeOH, H_2O, 4°C overnight) respectively afforded LXA_4 potassium salt[13], and its (E)-$\Delta^{11,12}$ isomer[13] (>95% purity on RP-HPLC analysis).

The LXB_4 potassium salt[13] and its (E)-$\Delta^{8,9}$ isomer[13] were obtained from the dienic aldehyde **13** and the phosphonium salt **14** with a similar selectivity using the same protocol[11].

Studies on the biological activity of LXA_4 and LXB_4 will be reported in due course.

All possible stereoisomers of our starting material, epoxytetrol **1**, being easily available from D-isoascorbic or L-ascorbic acids, the flexible strategy we develop allows the total synthesis of all stereoisomers of LXA_4 or LXB_4 and of modified analogues.

The financial support of MRT in the section "Chimie Nouvelle : Ingénierie Moléculaire" is gratefully acknowledged.

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9. No lactonization occured during this transformation.
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11. Data for **16** and **20** :

    16 : UV(EtOH) : 293, 305, 319 nm ; $[\alpha]_D^{20}$= - 5 (c 0.55, CH_2Cl_2) ; δ_H(250 MHz, $CDCl_3$) 0.83(3H, t, 7Hz, H20), 1.08(9H, s, tBu), 1.10-1.90(15H, m), 2.38(2H, m, H2), 4.12(2H, q, 7Hz, OEt), 4.21 (1H, q, 6.5Hz, H15), 4.70(1H, m, H5), 5.15(1H, t, 8Hz, H6), 5.61(1H, dd, 8Hz, 15Hz,H7), 5.67 (1H, dd, 6.5Hz, 15Hz, H14), 5.90 & 5.93(2H, AB from ABMN system, 10Hz, H11,12), 6.17(1H, dd, 11Hz, 15Hz, H9), 6.25-6.42(2H, m, H8,13), 6.51(1H, dd, 11Hz, 15Hz, H10), 7.30-7.45(6H, m Ph), 7.60-7.70(4H, m, Ph) ; δ_C($CDCl_3$) 14.0, 14.2 (C20, OEt), 19.4, 27.1(tBu), 21.0, 22.5, 24.3, 29.5, 31.8, 33.4, 37.8(C2-4, C16-19), 60.5(OEt), 74.1(C15), 79.9, 80.1 (C5, C6) 122.3, 124.9, 127.7, 130.2, 131.6, 137.0, 138.9 (C7-14),127.4, 129.5, 134.2 (Ph), 154.2 (C=O), 172.8 (C1)

    HRMS Calcd. for $C_{35}H_{43}O_6Si$: 587.2829 (M^+-tBu), found : 587.2824.

    20 : UV(EtOH) : 291, 304, 320 nm ; $[\alpha]_D^{20}$ = -10 (c 0.38, CH_2Cl_2) ; δ_H(250MHz, $CDCl_3$) 0.87(3H, m, H20), 1.10(9H, s, tBu), 1.18-1.90(15H, m), 2.18(2H, m, H2), 4.10(2H, q, 7Hz, OEt), 4.25(1H, m, H5), 4.69(1H, m, H15), 5.15(1H, t, 7.5Hz, H14), 5.62(1H, dd, 7.5Hz, 15Hz, H13),5.66(1H, dd, 6Hz, 15Hz, H6), 5.83-6.02(2H, AB from ABMN system, 10Hz, H8,9), 6.11-6.55(4H, m), 7.30-7.50(6H, m, Ph), 7.60-7.75(4H, m, Ph) ; δ_C($CDCl_3$) 13.9, 14.2 (C20, OEt), 19.4, 27.1(tBu), 20.1, 22.4, 25.1, 30.1, 31.3, 34.2, 37.1(C2-4, C16-19), 60.2(OEt), 73.6(C5), 80.3(C14-15), 122.8, 125.3 128.2, 130.5, 131.3, 131.4, 136.7, 138.1, (C6-13), 127.5, 129.6, 134.1 (Ph), 173.5 (C1).
12. To avoid repetitive HPLC purification, it is not necessary to separate **16** from **17**, but only **18** from **19** after the desilylation step.
13. Data for LXA_4 potassium salt (and its (E)-$\Delta^{11,12}$ isomer) and LXB_4 potassium salt (and its (E)-$\Delta^{8,9}$ isomer) : UV (MeOH) : λmax 289, 302, 317 ± 1 nm for each isomer.

    RP-HPLC analysis (column 250x4.6mm, Nucleosil C_{18} 5µ, eluent CH_3CN : H_2O + H_3PO_4 0.05M = 15:85 to100:0 in 35 min, flow rate : 1mL/min, detection at both 270 and 302nm), retention time (min.) : LXA_4 (23.7), LXA_4-(E)-$\Delta^{11,12}$ isomer (23.4), LXB_4 (22.3), and LXB_4-(E)-$\Delta^{8,9}$ isomer (22.1). The purity is over than 95% for each isomer
    In the same HPLC conditions, our sythetic LXA_4 coelutes with a sample supplied by Euromedex; an identical result was also obtained for their methyl esters (retention time : 25.9 min.).

(Received in France 8 October 1990)