Pergamon

Tetrahedron Letters 39 (1998) 143–146

TETRAHEDRON LETTERS

Stereoselective Total Synthesis of 5(S), 6(R), 15(S)-Trihydroxy-7(E), 9(E), 11(Z),13(E)-Eicosatetraenoic Acid (Lipoxin A)

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Received 22 September 1997; revised 21 October 1997; accepted 24 October 1997

Abstract : A stereoselective synthesis of the title compound from D-xylose using zinc mediated deoxygenation of 4-hydroxy-2-butenoic acid moiety and base induced double elimination of 4,5-epoxy allyl chloride as key steps is described.

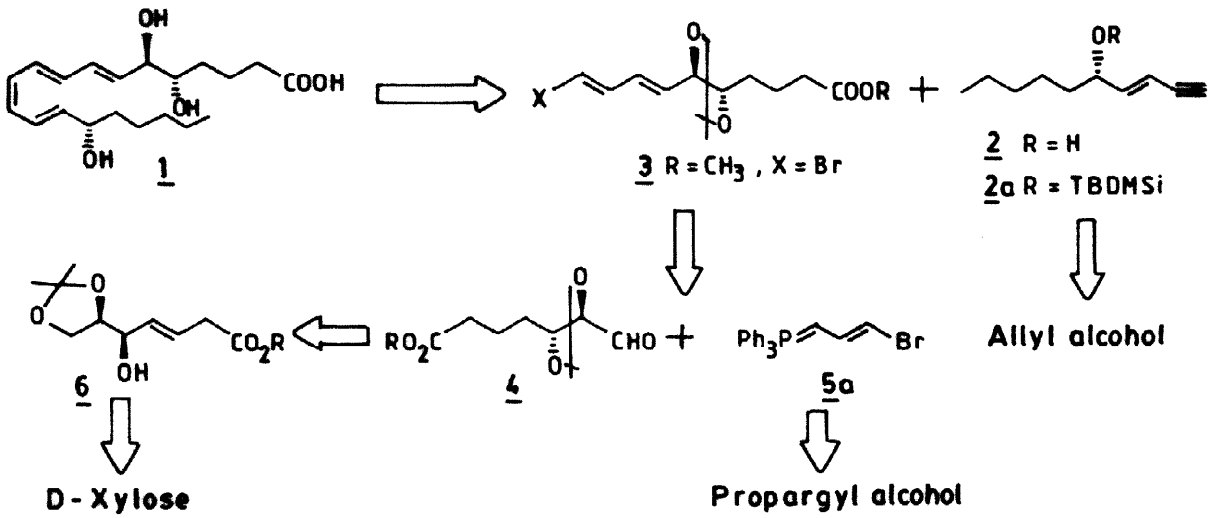
The isolation of a new class of arachidonic acid metabolites was reported in 1984 by Serhan, Hamberg and Samuelsson and the names Lipoxin A and Lipoxin B were assigned to the two substructural groups identified.[1] These oxygenated derivatives containing a tetraene structure, represent the first natural products, derived from arachidonic acid, containing four conjugated double bonds as a distinguishing feature. These are also produced by incubation of human leukocytes with 15-HPETE and A 23187.[2] In addition, it was reported that, these tetraene eicosanoids possess intriguing biological properties[2] and very few syntheses were reported.[3] In continuation of our efforts[4] towards the total synthesis of this class of polyhydroxy fatty acids, because of their non-availability in larger quantities and also to extend the scope of further exploration of the physiological importance of this novel class of eicosanoids, we report herein a convenient practical stereoselective total synthesis of lipoxin A from D-xylose, a readily available chiral carbohydrate.

The following retrosynthetic analysis (**Scheme1**) dictates the convergent approach where the molecule can be disassembled into its retrons **2** and **3**.

IICT Communication No. 3900

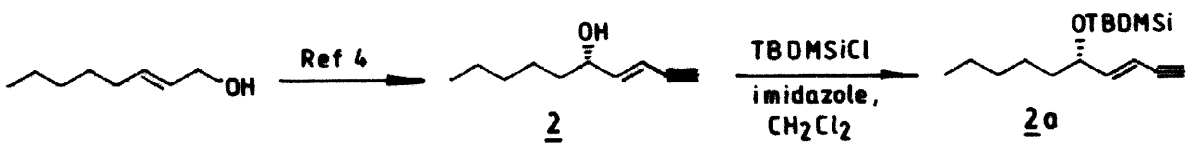
0040-4039/98/$19.00
PII: S0040-4039(97)10471-3

Scheme 1



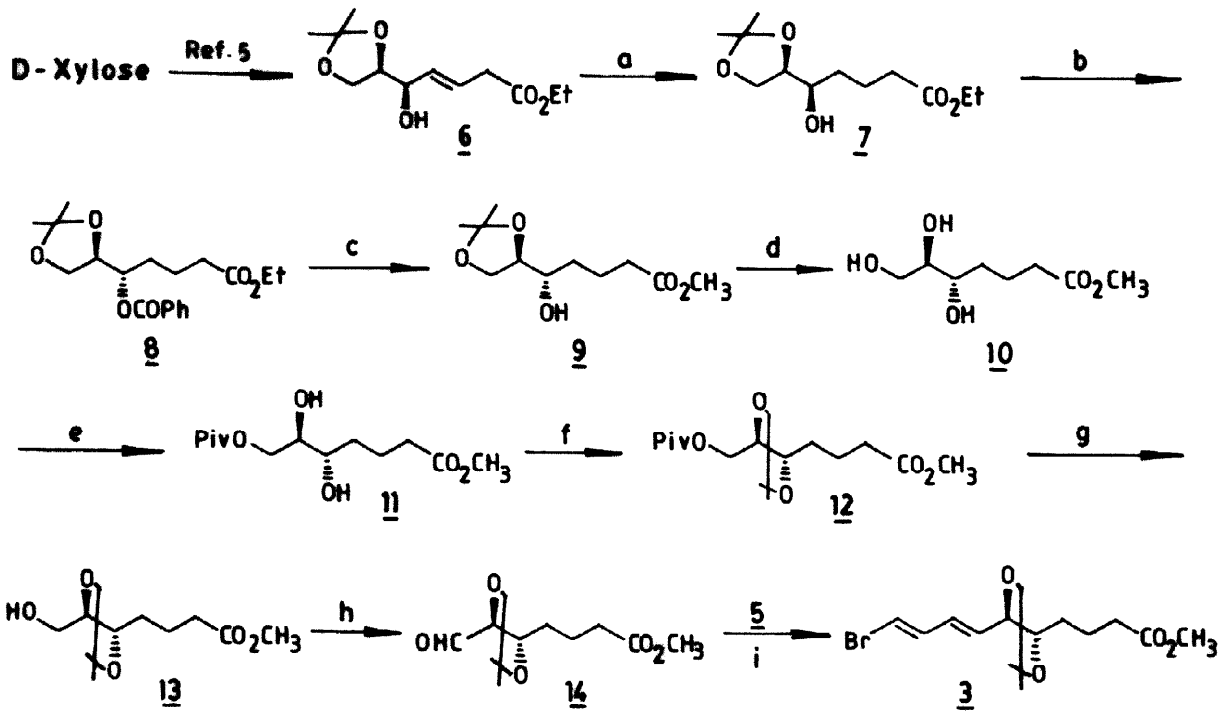
Accordingly retron **2a** was obtained from **2** by treatment with TBDMSiCl and imidazole and **2** inturn was obtained following the procedure reported earlier by us[5] as shown in **Scheme 2.**

Scheme 2



Similarly in order to synthesize the retron **3**, we have developed yet another methodology, wherein D-xylose was converted to 5-hydroxy-3,4-unsaturated ester[6] **6** (**Scheme 3**). Pd/C, H_2 reduction of **6** provided the corresponding saturated hydroxy ester **7**, which was further treated with DEAD, Ph_3P, C_6H_5COOH at -30°C to afford **8**. The Mitsunobu product **8** was treated with NaOMe in MeOH to afford hydroxy ester **9**, which was treated with 2N HCl in MeOH to give trihydroxy ester **10**. The primary alcohol in **10** was selectively protected by using pivCl in pyridine to give **11**, and 1,2 diol of **11** was further protected as acetonide to yield **12**. The deprotection of pivolyl group in **12** with NaOMe in MeOH afforded **13** and Swern oxidation of **13** with $(COCl)_2$, DMSO, Et_3N gave **14**. Finally **14** was treated with Wittig ylide **5a** at -78° C in THF, which was generated from Wittig salt **5**[7] by treating with n-BuLi as base in THF at -78° C to afford **3**.

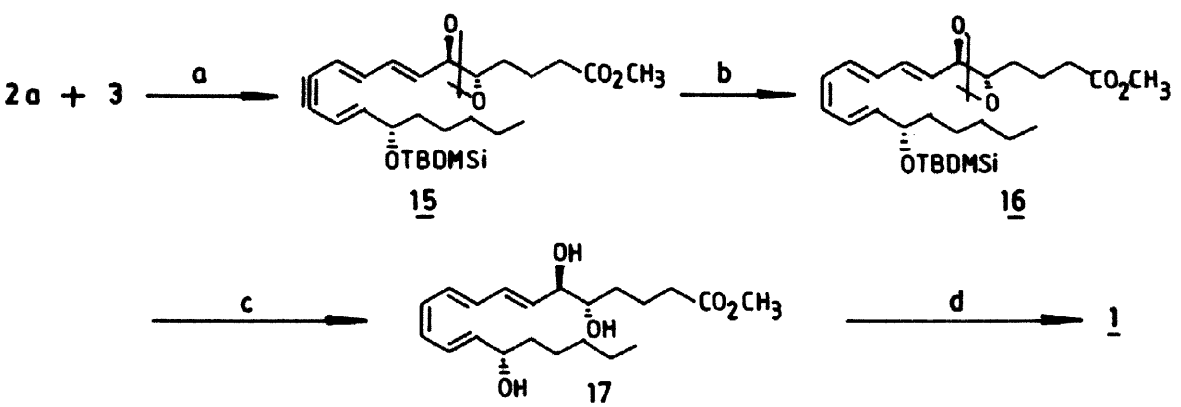
Scheme 3



Reagents : (a) Pd/C, H_2 ; (b) DEAD, Ph_3P, C_6H_5COOH; (c) NaOMe, MeOH; (d) 2N HCl in MeOH; (e) PivCl, pyr, CH_2Cl_2; (f) CH_3COCH_3, H_2SO_4, $CuSO_4$; (g) NaOMe, MeOH; (h) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C, (i) nBuLi, THF, -78°C.

Coupling of retrons **2a** and **3** and finally to the target molecule is illustrated in **Scheme 4**.

Scheme 4



Reagents: (a) $(Ph_3P)_4Pd$, $nPrNH_2$, CuI, C_6H_6, RT;[11] (b) Pd-$CaCO_3$, H_2, EtOH; (c) 2N HCl, THF; (d) LiOH, H_2O, THF.

Protected hydroxy enyne **2a** was coupled with vinyl bromide **3** in the presence of Pd^0-Cu^I to generate acetylene **15**. Then Lindlar hydrogenation of triple bond of **15** to afford **16**, which on deprotecting both the acetonide and TBDMS groups using 2N HCl in THF to afford trihydroxy ester **17** followed by ester hydrolysis to the title compound **1**, whose data were superimposible with the reported values.[3]

Thus the synthesis of Lipoxin A has been demonstrated by a concise and convenient route involving zinc mediated deoxygenation and base induced reductive elimination reactions developed by us as key steps.

Acknowledgements

Two of the authors (DKB) and (DD) wish to thank CSIR, New Delhi for financial assistance.

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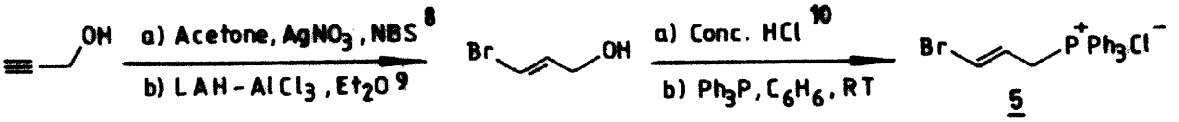
7. The Wittig salt **5** was prepared from propargyl alcohol as described below.



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12. All the new compounds were characterised by spectral data and HRMS. Selected data for some compounds. **3** : **^{1}H NMR** ($CDCl_3$, 200 MHz) : δ 1.30 (s, 3H); 1.43 (s, 3H); 1.52-1.90 (m, 4H); 2.30 (t,2H, J=6.77 Hz); 3.67 (s,3H); 4.03-4.20 (m, 1H); 4.80-4.91 (m, 1H); 5.40-5.51 (m, 1H); 6.0-6.2 (m,1H); 6.4 (d, 1H, J=12.95Hz); 7.0 (t, 1H, J=12.50Hz). [α]$_D$ -35.72 (c 0.90, $CHCl_3$). **15** : **^{1}H NMR** ($CDCl_3$, 200 MHz) : δ 0.05 (s, 6H); 0.90 (s, 9H); 1.20-1.55 (m, 17H); 1.56-1.90 (m, 4H); 2.35 (t, 2H, J=7.23Hz); 3.65 (s, 3H); 4.11-4.25 (m, 2H); 4.91-5.05 (dd, 1H); 5.40-5.50 (m, 1H); 5.75 (d, 2H, J=15.85); 6.04-6.28 (m, 2H); 6.71-6.90 (m, 1H). [α]$_D$ -79.47 (c 0.50, $CHCl_3$). Mass m/z 517 (M^+-1), 461, 329, 317, 303, 273, 256, 215 (100%).