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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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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**.

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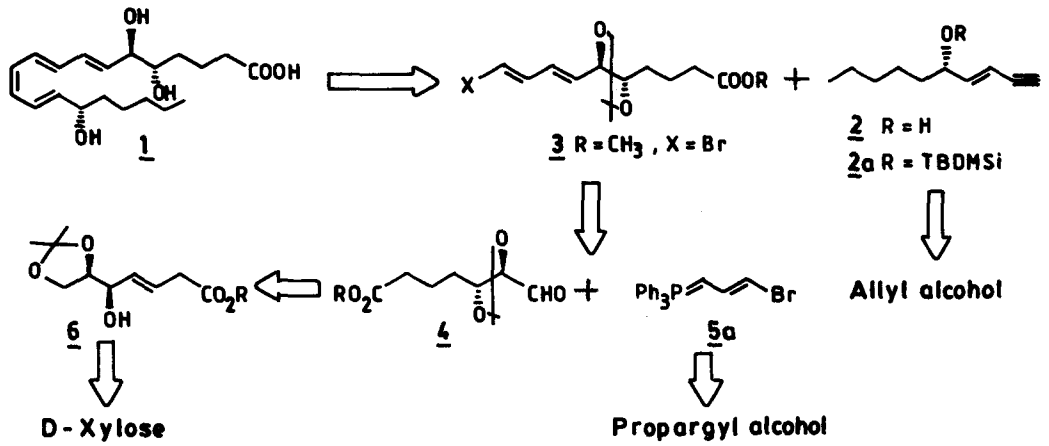
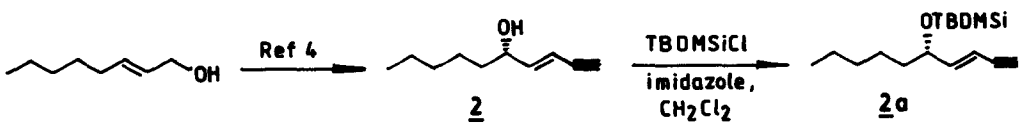
Scheme 1



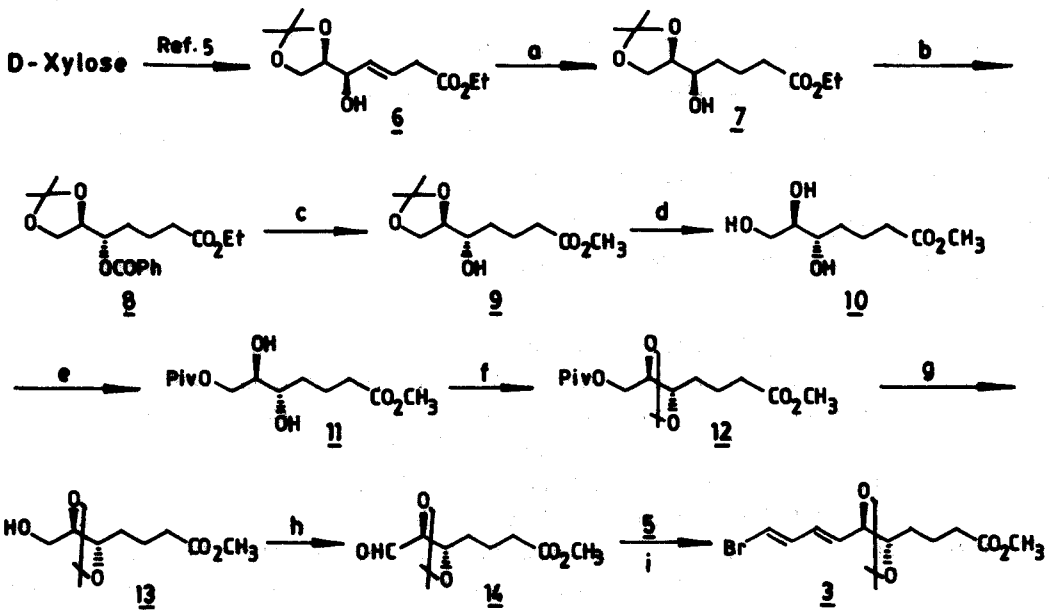
Accordingly retron **2a** was obtained from **2** by treatment with TBDMSiCl and imidazole and **2** inturn was obtained following the procedure reported earlier by us[5] as shown in **Scheme 2.**

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**.

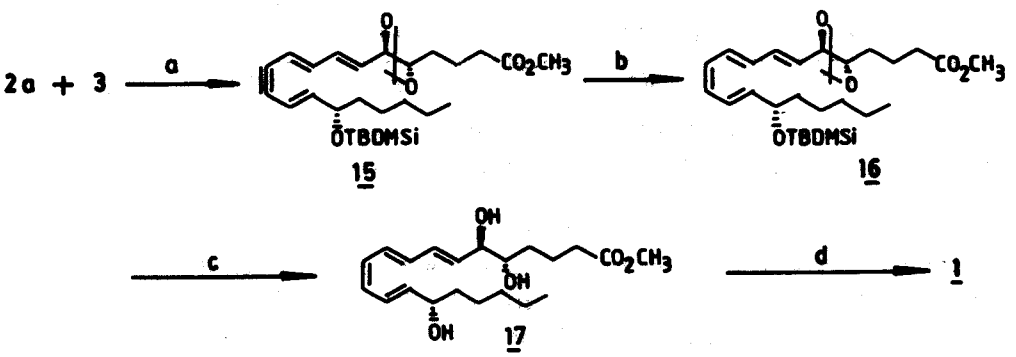
Scheme 3



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

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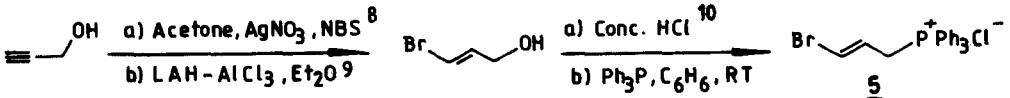
7. The Wittig salt **5** was prepared from propargyl alcohol as described below.



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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%).