Stereoselective Total Synthesis of the Presumed Biosynthetic Precursor to Lipoxins A and B: Methyl (7*E*,9*E*,11*Z*,13*E*,5*S*,6*S*,15*S*)-5,6-Epoxy-15-hydroxyicosa-7,9,11,13-tetraenoate and its 5,6-Methano Analogue

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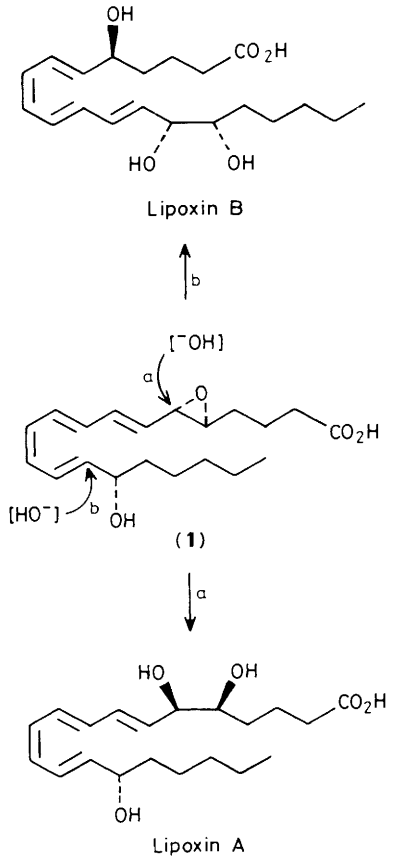
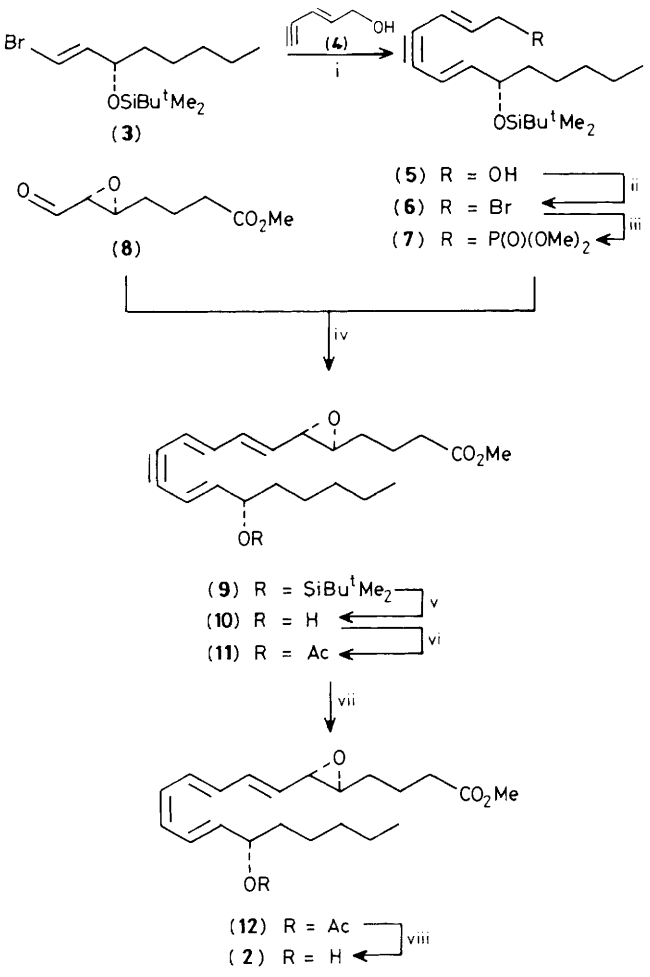
Stereoselective and highly efficient total syntheses of the presumed biosynthetic precursor of lipoxins A and B and its 5,6-methano analogue are described.

(7*E*,9*E*,11*Z*,13*E*,5*S*,6*S*,15*S*)-5,6-Epoxy-15-hydroxyicosa-7,9,11,13-tetraenoic acid (**1**) has been suggested as a biosynthetic precursor to lipoxins A and B (Scheme 1).[1,2] In order to aid biogenetic studies in this area, we decided to undertake a chemical synthesis of the methyl ester (**2**) of this presumed intermediate[3] and its 5,6-methano analogues (**13**) and (**14**). In this communication, we report a stereoselective and highly efficient total synthesis of these biologically interesting molecules.

Scheme 2 details the construction of the titled compound from the readily available fragments (**3**)[4] and (**4**) (commercially available from Farchan). Thus, Pd^0–Cu^I catalysed coupling[5] of the vinyl bromide (**3**) with (*E*)-1-hydroxypent-2-en-4-yne (**4**) proceeded smoothly to afford the alcohol (**5**)† which was converted sequentially into the bromide (**6**) and the phosphonate (**7**). Generation of the lithio derivative of this phosphonate with lithium di-isopropylamide (LDA) at low temperature followed by condensation with the optically active epoxy-aldehyde (**8**)[6] furnished the epoxide (**9**) in 72% yield (7*E*:7*Z* 3:1). Before further manipulations, this mixture was enriched further in the 7*E* isomer by treatment with catalytic amounts of iodine to a ratio of 7*E*:7*Z* ≥ 9:1 (quantitative yield). Difficulties in reducing the derivative (**9**)



Scheme 1. Biosynthesis of lipoxins A and B.

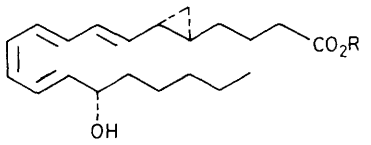


Scheme 2. *Reagents and conditions:* i, (**4**) (2.0 equiv.), $(Ph_3P)_4Pd$ (0.04 equiv.), CuI (0.16 equiv.), Et_2NH, 25 °C (91%); ii, CBr_4 (1.25 equiv.), Ph_3P (1.3 equiv.), CH_2Cl_2, −20 → 25 °C (89%); iii, $(MeO)_3P$ (10.0 equiv.), MeCN, 60 °C (100%); iv, LDA (1.0 equiv.), THF, −78 → 25 °C (72%) 7*E*:7*Z* *ca.* 3:1, then I_2 cat., PhH, 25 °C, 5 min (100%, 7*E*:7*Z* ≥9:1); v, Bu^n_4NF (1.2 equiv.), THF, 0 °C (89%); vi, Ac_2O (1.3 equiv.), 2-*N*,*N*-dimethylaminopyridine (DMAP) cat., Et_3N (3.0 equiv.), CH_2Cl_2, 25 °C (85% pure 7*E* after h.p.l.c.); vii, H_2–Lindlar cat., quinoline, hexane–EtOAc (3:1), 25 °C (44%); viii, K_2CO_3 cat., MeOH–THF (1:1), 25 °C (84%).

† All new compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

led us to exchange the silyl ether with an acetate group leading to (**11**) *via* (**10**). Purification of (**11**) (removal of 7*Z* isomer) was carried out by h.p.l.c. (Whatman Particil-10 normal phase-Prep; 250 × 25.4 mm; 12% EtOAc, 2% Et_3N, 86% hexane; 11 ml/min; $\lambda_{max.}$ 330 nm). Selective hydrogenation of the acetylenic compound (**11**) under carefully controlled conditions (10% by weight of Lindlar catalyst, quinoline poisoning; hexane–EtOAc, 3 : 1; 25 °C) furnished compound (**12**) which was purified by h.p.l.c. according to the above conditions (44% yield). Finally, deacetylation of (**12**) in MeOH–tetrahydrofuran (THF) with catalytic amounts of K_2CO_3 under anhydrous conditions followed by addition of ether, filtration through a short pad of anhydrous $MgSO_4$, and evaporation led to the desired hydroxy epoxide methyl ester (**2**)‡ in 84% yield. This labile compound can be stored with a trace of Et_3N in benzene at −40 °C for several days.

The corresponding 5,6-methano analogues of (**1**) and (**2**), compounds (**13**)‡ and (**14**) were also synthesized from the phosphonate (**7**) and the optically active 5,6-methano analogue[7] of the aldehyde (**8**) by a similar sequence. The biochemistry of (**2**) and the possible inhibition of various enzymes of the arachidonic acid cascade by (**13**) and (**14**) are currently under investigation and results will be reported later.



(**13**) R = Me

(**14**) R = H

‡ N.m.r. (250 MHz, $CDCl_3$, $SiMe_4$). (**2**): δ 6.96—6.27 (m, 2H, 10-H, 13-H), 6.46 (dd, $J_{7,8}$ 15.1, $J_{8,9}$ 10.8 Hz, 1H, 8-H), 6.21 (dd, $J_{9,10}$ 14.6, $J_{8,9}$ 10.8 Hz, 1H, 9-H), 6.00 (m, 2H, 11-H, 12-H), 5.74 (dd, $J_{13,14}$ 15.0, $J_{14,15}$ 6.6 Hz, 1H, 14-H), 5.40 (dd, $J_{7,8}$ 15.1, $J_{6,7}$ 8.0 Hz, 1H, 7-H), 4.19 (m, 1H, 15-H), 3.65 (s, 3H, CO_2Me), 3.13 (dd, $J_{6,7}$ 8.0, $J_{5,6}$ 2.0 Hz, 1H, 6-H), 2.85 (ddd, $J_{4,5}$ 5.9, $J_{4',5}$ 5.1, $J_{5,6}$ 2.0 Hz, 1H, 5-H), 2.36 (t, $J_{2,3}$ 7.0 Hz, 2H, 2-H), 1.78 (m, 2H, 3-H), 1.70—1.40 (m, 5H, 4-H, 16-H, OH), 1.28 (m, 6H, 17-H, 18-H, 19-H), and 0.87 (t, $J_{19,20}$ 6.4 Hz, 3H, 20-H). (**13**): δ 6.66 (dd, $J_{13,14}$ 15.0, $J_{12,13}$ 10.0 Hz, 1H, 13-H), 6.61—6.44 (m, 1H, 8-H), 6.16 (m, 2H, 11-H, 12-H), 5.96 (m, 3H, 9-H, 10-H), 5.68 (dd, $J_{13,14}$ 15.0, $J_{14,15}$ 6.8 Hz, 1H, 14-H), 5.36—5.21 (m, 1H, 7-H), 4.17 (m, 1H, 15-H), 3.64 (s, 3H, CO_2Me), 2.32 (t, 2H, $J_{2,3}$ 7.5 Hz, 2-H), 1.69 (m, 2H, 3-H), 1.61—1.45 (m, 3H, 16-H, OH), 1.43—1.21 (m, 8H, 4-H, 17-H, 18-H, 19-H), 1.20—1.10 (m, 1H, 6-H), 0.87 (t, $J_{19,20}$ 6.5 Hz, 3 H, 20-H), 0.78 (m, 1H, 5-H), and 0.59 (m, 2H, 6′-H).

We thank Dr. C. N. Serhan for valuable discussions and Drs. G. Furst and J. Dykins for spectroscopic assistance. This work was financially supported by the National Institutes of Health, Merck Sharp & Dohme, and Smith Kline Beckman.

Received, 30th July 1986; Com. 1087

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6 This key intermediate, previously used in the synthesis of leukotriene A_4 (E. J. Corey, D. A. Clark, G. Goto, A. I. Marfat, C. Mioskowski, B. Samuelsson, and S. Hammarstrom, *J. Am. Chem. Soc.*, 1980, **102**, 1436; J. Rokach, R. Zamboni, C.-K. Lau, and Y. Guindon, *Tetrahedron Lett.*, 1981, **22**, 2759; N. Cohen, B. L. Banner, R. J. Lopresti, F. Wong, M. Rosenberger, Y.-Y. Liu, E. Thom, and A. A. Liebman, *ibid.*, 1983, **105**, 3661, and references cited therein) was prepared by a new method from (*E*)-1-benzyloxy-7-hydroxy-hept-5-ene by Sharpless asymmetric epoxidation followed by a series of steps along the lines given in ref. 4.
7 This key intermediate previously used by us in racemic form in the synthesis of 5,6-methanoleukotriene A_4 (K. C. Nicolaou, N. A. Petasis, and S. P. Seitz, *J. Chem. Soc., Chem. Commun.*, 1981, 1195) was prepared in optically active form following Yamamoto's method (I. Arai, A. Mori, and H. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 8254).