A General Strategy for the Total Synthesis of the Presumed Lipoxin Structures

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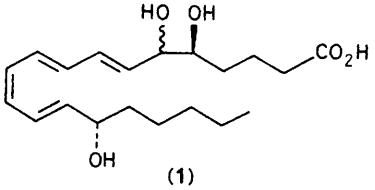
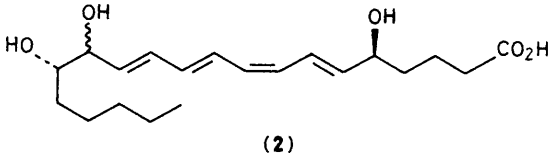
Stereocontrolled total syntheses of four possible isomers of lipoxin B by a Pd^0–Cu^I catalysed coupling reaction as a key step are described.

The lipoxins are a series of newly discovered, biologically active compounds formed from arachidonic acid in human leukocytes.[1,2] Recently, structures (**1**) and (**2**) have been tentatively assigned to lipoxins A (LX-A) and B (LX-B) by Samuelsson's group.[1,2] Owing to the biological importance[1,2] of these molecules and the remaining stereochemical uncertainties we undertook their total synthesis. In this communication we report the construction of four possible isomers of lipoxin B by a general strategy applicable for the total synthesis of all members of the lipoxin family.

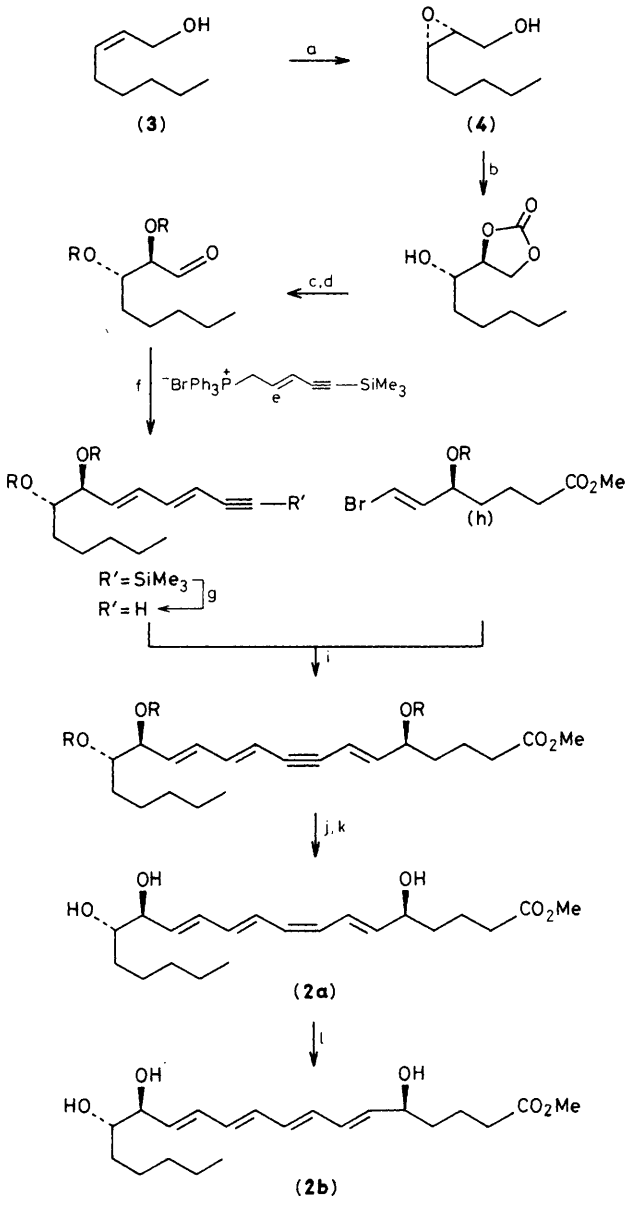
Since not only the stereochemistry at C-14 was in question but also the geometry of the C(8)–C(9) double bond, our synthesis was designed to accommodate the four possible



(**1**)

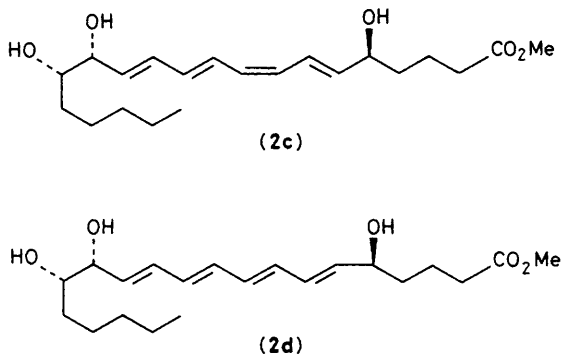


(**2**)



R = $SiBu^tMe_2$

Scheme 1. *Reagents and conditions*: a, Sharpless:[3] Bu^tOOH (2.0 equiv.); $Ti(OPr^i)_4$ (1.2 equiv.), (−)-diethyl tartrate (1.0 equiv.); CH_2Cl_2, −20 °C, 78%; b, PhNCO (2.5 equiv.), pyridine (2.2 equiv.), CH_2Cl_2, 90%, then $BF_3{\cdot}Et_2O$ (1.1 equiv.), Et_2O, 0 °C, then 0.5 M H_2SO_4, 95% overall; c, NaOMe (3.0 equiv.), 0.5 M in MeOH, 25 °C, 95%, then Bu^tCOCl (1.1 equiv.), pyridine, 90%, then Bu^tMe_2SiCl (2.4 equiv.), imidazole (5.0 equiv.), 95%; d, Bu^i_2AlH (2.5 equiv.), CH_2Cl_2, −78 °C, 95%, then $CrO_3 \cdot$ pyridine $\cdot$ HCl (1.5 equiv.), CH_2Cl_2, 0—25 °C, 84%; e, prepared from the corresponding alcohol in two steps: *N*-bromosuccinimide (1.1 equiv.), PPh_3 (1.2 equiv.), CH_2Cl_2, 0—25 °C, then PPh_3 (1.2 equiv.), benzene, 25 °C, 80% overall; f, Wittig: phosphonium salt (1.5 equiv.), Bu^nLi (1.4 equiv.), tetrahydrofuran, −78 to 25 °C, 83%, *ca.* 1 : 1 *E*–*Z* mixture, isomerised exclusively to *E* with I_2 (0.1 equiv.), benzene, 85%; g, excess of $AgNO_3$–KCN, EtOH–tetrahydrofuran–H_2O, 0—25 °C, 97%; h, prepared as described in ref. 4; i, coupling:[5] $(Ph_3P)_4Pd$ (0.04 equiv.), CuI (0.16 equiv.), Pr^nNH_2 (1.4 equiv.), benzene, 25 °C, 82%; j, excess of HF·pyridine, tetrahydrofuran, 0—25 °C, then aq. $NaHCO_3$, 70%; k, H_2–Lindlar catalyst, CH_2Cl_2, 25 °C, 80% based on *ca.* 50% conversion; l, I_2 (0.01 equiv.), CH_2Cl_2, 25 °C, 80%.



isomers of lipoxin B. Scheme 1† details the total synthesis of the (5*S*,14*S*,15*S*)-5,14,15-trihydroxy-(6*E*,8*Z*,10*E*,12*E*)-icosa-6,8,10,12-tetraenoic methyl ester (**2a**) [R_f 0.14, silica, 10% MeOH in CH_2Cl_2; ^1H n.m.r. ($CDCl_3$; 250 MHz): δ 0.86 (3H, t, *J* 6.4 Hz, 20-H), 1.19—1.8 (12H, m, 3-, 4-, 16-, 17-, 18-, and 19-H), 2.18 (3H, br. s, 3 × OH), 2.34 (2H, t, *J* 7.1 Hz, 2-H), 3.48 (1H, m, 15-H), 3.65 (3H, s, CO_2Me), 3.98 (1H, m, 5-H), 4.21 (1H, m, 14-H), 5.65—5.77 (2H, m, 6- and 13-H), and 7—12-H at 5.93—6.06 (2H, m), 6.17—6.43 (2H, m), and 6.63—6.70 (2H, m)] and its all-*trans* isomer (**2b**) [R_f 0.17, silica, 10% MeOH in CH_2Cl_2; ^1H n.m.r.; differences from (**2a**) only: δ 3.96 (1H, m, 5-H), 4.18 (1H, m, 14-H), 5.6—5.8 (2H, m, 6- and 13-H), and 6.15—6.42 (6H, m, 7—12-H)]. The corresponding (14*R*) compounds (**2c**) and (**2d**) were also synthesized by a similar route utilizing the *E* isomer of (**3**). All four methyl esters (**2a—d**) could be hydrolysed to give the corresponding sodium salts (NaOH) or carboxylic acids (alkaline hydrolysis followed by acidification). The key features in this rather general synthesis include: (a) stereocontrolled construction of all chiral centres and double bonds, (b) flexibility for selective formation of isomers and analogues, and (c) a Pd^0–Cu^I-catalysed coupling reaction involving terminal acetylenes and vinyl bromides according to our recently proposed general strategy towards linear icosanoids.[4]

Comparisons of these synthetic lipoxins with naturally derived materials and the synthesis of other members of this family of bioactive compounds by this strategy are in progress.

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† All new compounds exhibited satisfactory spectra and analytical data.