5,6-Methanoleukotriene A_4. A Stable and Biologically Active Analogue of Leukotriene A_4

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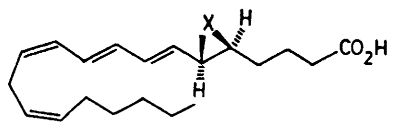
Summary The total synthesis of 5,6-methanoleukotriene A_4, a stable and biologically active analogue of leukotriene A_4 is described.

Recent investigations into the lipoxygenase pathway of the arachidonic acid cascade led to the discovery of leukotrienes, a new class of biologically active eicosanoids.[1–2] The first leukotriene formed in this biosynthetic sequence is leukotriene A_4 (LTA_4) (**1**), a relatively unstable substance

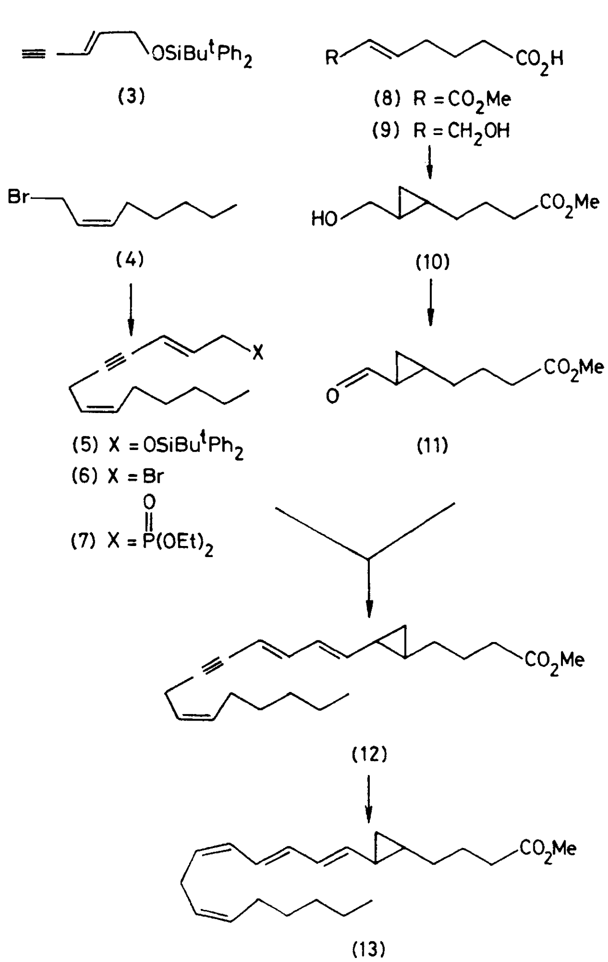


(**1**) X = O
(**2**) X = CH_2

with an epoxide unit. This substance serves as a precursor to leukotrienes B_4, which are potent chemotactic agents, and to a number of 'slow reacting substances of anaphylaxis' which have been implicated in asthma and other hypersensitivity reactions.[1–3] Most of the natural leukotrienes and a number of their isomers have been synthesised chemically.[3–5] In this communication, we disclose the total synthesis of 5,6-methanoleukotriene A_4 (**2**), a stable and biologically active analogue of LTA_4,[6] (Scheme).

Pent-2-en-4-yn-1-ol was converted into its t-butyldiphenylsilyl ether (**3**)† (1·1 equiv. of Bu^tPh_2SiCl, imidazole, *NN*-dimethylformamide, 25 °C, 100%) and coupled to (2*E*)-1-bromo-oct-2-ene (**4**) [Bu^nLi–LiCl–CuI–hexamethylphosphoramide, tetrahydrofuran (THF) − 78 °C, 60%] to afford product (**5**). Removal of the silyl ether (HF-pyridine, THF, 25 °C, 90%) followed by treatment with CBr_4–PPh_3 (1·2 equiv. of each, CH_2Cl_2, 0 °C, 98%) led to the bromide (**6**) which was converted into the desired phosphonate (**7**) by exposure to an excess of triethylphosphite in acetonitrile at 60 °C.

The other component required to assemble the leukotriene skeleton, aldehyde (**11**), was constructed from δ-valerolactone as follows. δ-Valerolactol was allowed to react with an excess of methyl (triphenylphosphoranylidene)acetate in benzene at 25 °C to afford after Jones' oxidation the αβ-unsaturated methylcarbonyloxy-carboxylic acid (**8**) (75% overall). Treatment of this monoester (**8**) with di-isobutylaluminium hydride (2·2 equiv., CH_2Cl_2, − 78 °C) followed by esterification with diazomethane gave the allylic alcohol (**9**) which was smoothly cyclopropanated (CH_2I_2–Zn–CuCl, diethyl ether, 35 °C, 75%) to afford (**10**), and oxidized with CrO_3–pyridine–HCl–NaOAc (CH_2Cl_2, 25 °C), leading to the aldehyde (**11**) (90%).



Scheme

Generation of the lithium salt of the phosphonate (**7**) (1·1 equiv. of lithium di-isopropylamide, THF, − 78 °C) and addition of the aldehyde (**11**) (− 78 °C) followed by stirring at 25 °C for 24 h resulted in a highly efficient and stereocontrolled coupling, forming compound (**12**) [65% yield, (7*E*) : (7*Z*) ⩾ 10] which was purified of the contaminating minor undesired isomers by flash column chromatography using silver nitrate-impregnated silica (10% diethyl ether in light petroleum). Finally, selective hydrogenation of the acetylenic linkage (Lindlar catalyst–hexane, 25 °C) led to the methyl ester (**13**) (90%, R_f = 0·33, 10% diethyl ether in light petroleum). Hydrolysis of (**13**) with LiOH–THF–H_2O at 25 °C gave 5,6-methanoleukotriene A_4 (**2**) in essentially quantitative yield (R_f = 0·38, 50% diethyl ether in light petroleum).

† All new compounds exhibited satisfactory spectral and analytical data.

Preliminary studies indicate that 5,6-methanoleukotriene A_4 is a potent and selective inhibitor of leukotriene biosynthesis.‡

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