

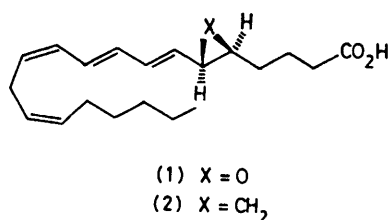
## 5,6-Methanoleukotriene A<sub>4</sub>. A Stable and Biologically Active Analogue of Leukotriene A<sub>4</sub>

By KYRIACOS C. NICOLAOU,\* NICOS A. PETASIS, and STEVEN P. SEITZ

(Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104)

**Summary** The total synthesis of 5,6-methanoleukotriene A<sub>4</sub>, a stable and biologically active analogue of leukotriene A<sub>4</sub> is described.

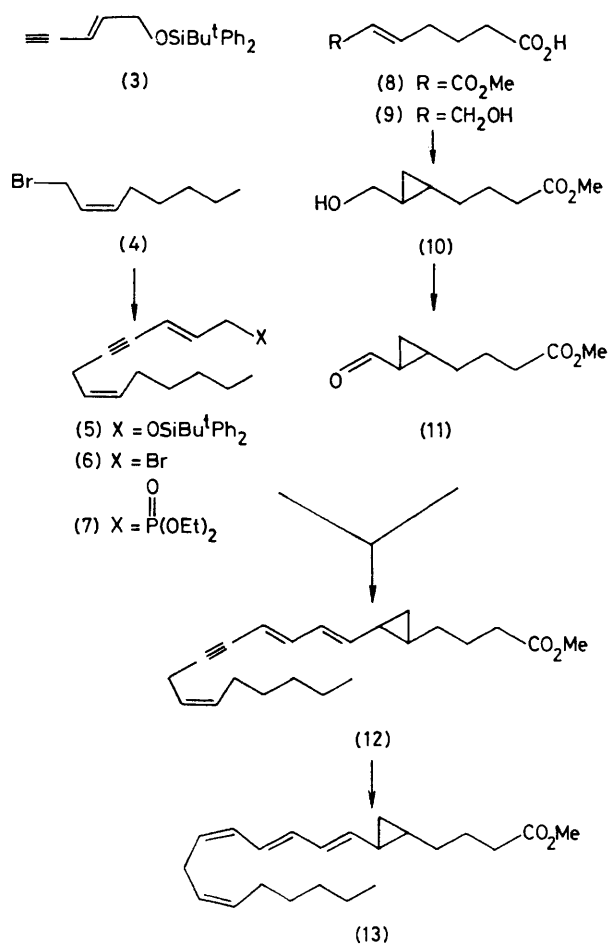
RECENT investigations into the lipoxygenase pathway of the arachidonic acid cascade led to the discovery of leukotrienes, a new class of biologically active eicosanoids.<sup>1-2</sup> The first leukotriene formed in this biosynthetic sequence is leukotriene A<sub>4</sub> (LTA<sub>4</sub>) (1), a relatively unstable substance



with an epoxide unit. This substance serves as a precursor to leukotrienes B<sub>4</sub>, 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.<sup>1-3</sup> Most of the natural leukotrienes and a number of their isomers have been synthesised chemically.<sup>3-5</sup> In this communication, we disclose the total synthesis of 5,6-methanoleukotriene A<sub>4</sub> (2), a stable and biologically active analogue of LTA<sub>4</sub>,<sup>6</sup> (Scheme).

Pent-2-en-4-yn-1-ol was converted into its *t*-butyldi-phenylsilyl ether (3)† (1.1 equiv. of Bu<sup>t</sup>Ph<sub>2</sub>SiCl, imidazole, *N,N*-dimethylformamide, 25 °C, 100%) and coupled to (2*E*)-1-bromo-oct-2-ene (4) [Bu<sup>n</sup>Li-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<sub>4</sub>-PPh<sub>3</sub> (1.2 equiv. of each, CH<sub>2</sub>Cl<sub>2</sub>, 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  $\delta$ -valerolactone as follows.  $\delta$ -Valerolactone was allowed to react with an excess of methyl (triphenylphosphoranylidene)acetate in benzene at 25 °C to afford after Jones' oxidation the  $\alpha\beta$ -unsaturated methylcarbonyloxy-carboxylic acid (8) (75% overall). Treatment of this monoester (8) with di-isobutyl-aluminium hydride (2.2 equiv., CH<sub>2</sub>Cl<sub>2</sub>, - 78 °C) followed by esterification with diazomethane gave the allylic alcohol (9) which was smoothly cyclopropanated (CH<sub>2</sub>I<sub>2</sub>-Zn-CuCl, diethyl ether, 35 °C, 75%) to afford (10), and oxidized with CrO<sub>3</sub>-pyridine-HCl-NaOAc (CH<sub>2</sub>Cl<sub>2</sub>, 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 stereo-controlled coupling, forming compound (12) [65% yield, (7*E*):(7*Z*)  $\geq$  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*<sub>f</sub> = 0.33, 10% diethyl ether in light petroleum). Hydrolysis of (13) with LiOH-THF-H<sub>2</sub>O at 25 °C gave 5,6-methanoleukotriene A<sub>4</sub> (2) in essentially quantitative yield (*R*<sub>f</sub> = 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.<sup>‡</sup> and the University of Pennsylvania for support of this work.

We thank Teijin Institute for Biomedical Research (Japan)

(Received, 12th August 1981; Com. 993)

<sup>‡</sup> Biological tests were performed by Drs. Y. Koshihara and S. Murota, Department of Pharmacology, Tokyo Metropolitan Institute of Gerontology through courtesy of Teijin Limited, Japan.

<sup>1</sup> B. Samuelsson, *Pure Appl. Chem.*, 1981, **53**, 1203.

<sup>2</sup> P. Borgeat and P. Sirois, *J. Med. Chem.*, 1981, **24**, 121.

<sup>3</sup> E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, and S. Hammarström, *J. Am. Chem. Soc.*, 1980, **102**, 1436.

<sup>4</sup> J. Rokach, R. N. Young, M. Kakushima, C.-K. Lau, R. Seguin, R. Frenette, and Y. Guindon, *Tetrahedron Lett.*, 1981, **22**, 979.

<sup>5</sup> M. Rosenberger and C. Neukom, *J. Am. Chem. Soc.*, 1980, **102**, 5425.

<sup>6</sup> The 5,6-thialeukotriene  $A_4$  has recently been reported: E. J. Corey, H. Park, A. Barton, and Y. Nii, *Tetrahedron Lett.*, 1980, **21**, 4243.