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SYNTHESIS, SEPARATION AND N.M.R. SPECTRA OF THREE DOUBLE BOND ISOMERS OF LEUKOTRIENE A METHYL ESTER

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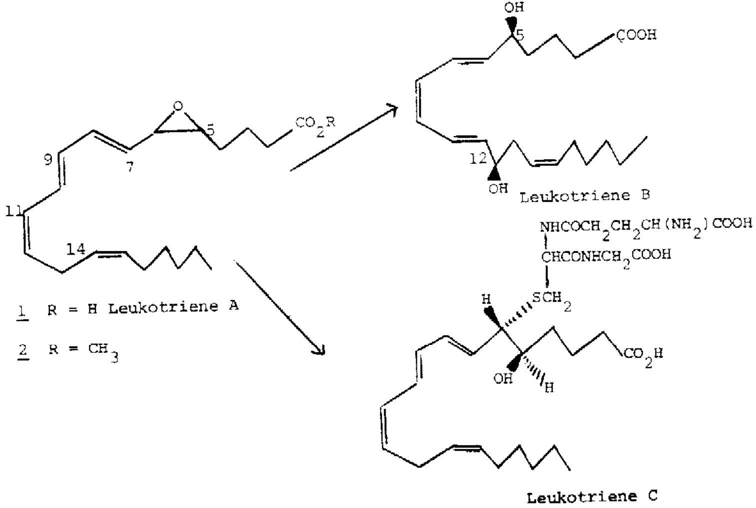
Summary: The synthesis and h.p.l.c. separation of three double bond isomers of leukotriene A methyl ester is described, their stereochemistry being assigned by ^{1}H N.M.R.

Samuelsson[1,2] has proposed that leukotriene A is a shortlived biosynthetic precursor to the biologically interesting leukotrienes B and C. Leukotriene B is a potent chemotactic factor[3] and leukotriene C shows spasmogenic activity in smooth muscle preparations similar to that of natural SRS-A, a mediator in human asthma[4]. However until recently the exact double bond stereochemistry of natural leukotriene A was unknown[5] so we set out to prepare a range of different double bond isomers.



A method that appeared to offer the greatest flexibility was the coupling of a 9 carbon enal epoxide 3[6] with an 11 carbon Z, Z diene phosphonium salt 4[6].

The reaction was shown by h.p.l.c. to yield three different double bond isomers of 2a-c the ratios being dependent on the solvent used (fig 1). Two very recent notes[5,7] describe similar reactions but they only report the formation of E and Z isomers about the 9,10 double bond.

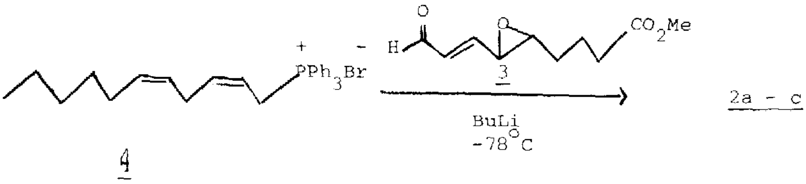


Figure 1

HPLC Separation of Leukotriene A methyl ester isomers[8]

Effect of solvent[9] on isomer ratios(%)

Isomer	THF+HMPA	THF
2a	41	12
2b	17	48
2c	42	40

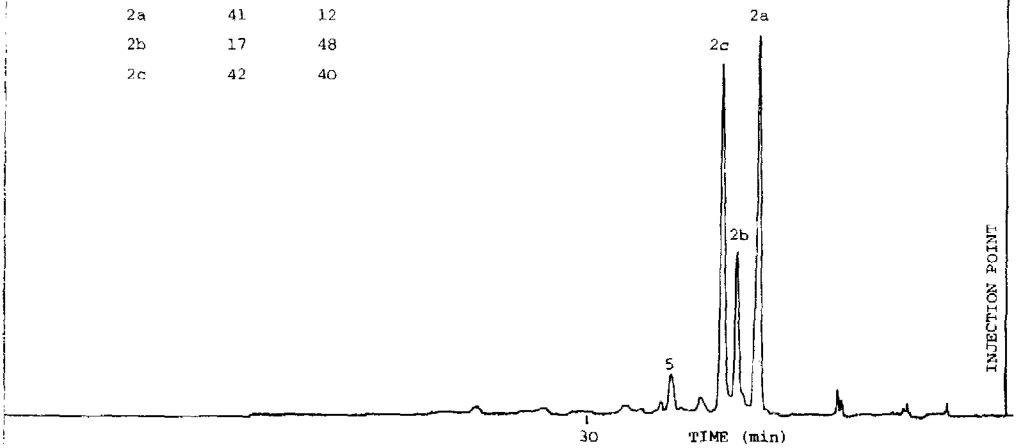
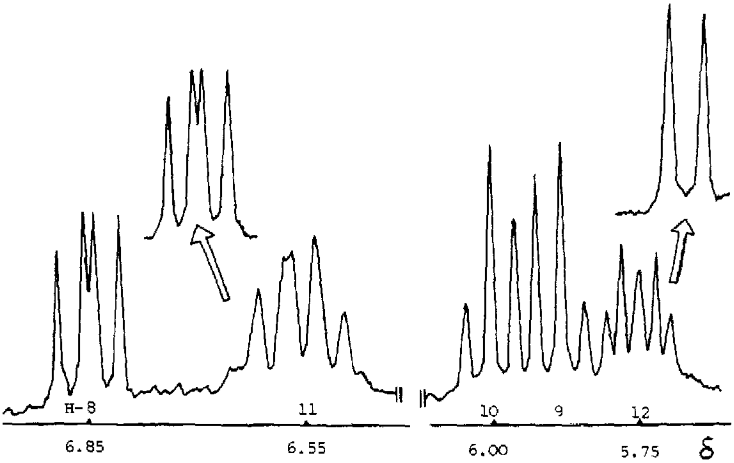


Figure 2

270 MHz 'H Spectrum of Isomer 2a(5.5-7.0δ)



Insets show the effect of decoupling at H-13

The three isomers of 2 were separated by preparative h.p.l.c. and their ^{1}H N.M.R. spectra examined at 80 MHz. The olefinic region was highly complex and only in 2c could one proton be seen to lowest field of the group. The stereochemistry of the triene system of 2 a-c was clearly revealed by ^{1}H N.M.R. analysis at superconducting (270 MHz) magnetic fields [10] and the chemical shifts found were as follows (Proton number then chemical shifts, in p.p.m., for 2a,b and c respectively).

H-2, 2.36, 2.36, 2.36; 3, 1.61, 1.61, 1.61; 4, 1.77, 1.77, 1.78; 5, 2.84, 2.84, 2.85; 6, 3.14, 3.11, 3.15; 7, 5.40, 5.41, 5.45; 8, 6.85, 6.48, 6.88; 9, 5.89, 6.21, 6.03; 10, 6.00, 6.56, 6.32; 11, 6.55, 6.03, 6.48; 12, 5.74, 5.49, 5.55; 13, 2.87, 2.93, 2.93; 14, 5.49, 5.45, 5.43; 15, 5.40, 5.37, 5.37; 16, 2.04, 2.04, 2.04; 17-19, 1.3-1.5, 1.3-1.5, 1.3-1.5; 20, 0.87, 0.87, 0.87.

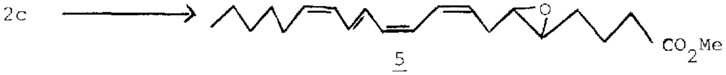
A representative ^{1}H N.M.R. spectrum for isomer 2a at 270MHz is shown in the Figure for the region δ= 5.5-7.0. the insets show the effect of decoupling at H-13 which removes three and four bond couplings to that methylene group. Five protons (H-8 to H-12) can readily be analysed by first order analysis (J trans = 14.5-15 Hz, Jcis = Jvic CH-$\overset{\|}{\mathrm{C}}$H = 10.5-11 Hz, Jvic CH-CH = 7.0 Hz). These couplings are identical to those measured in model hexatriene and heptatriene systems[11-13]. Thus the triene protons (e.g. H-9) with both cis (Z) and vicinal (vic) single bond couplings appear as triplets whereas those (e.g. H-8) with trans (E) and vic couplings are seen as double doublets.

Individual proton assignments were made by a series of homonuclear proton decoupling experiments starting at epoxide proton H-6 working through the triene system to H-13. The stereochemistry is thus seen to be 7-E, 9-Z, 11-E in isomer 2a. Even at 270 MHz the protons of the isolated (14) double bond (at 5.3-5.5δ) are not clearly resolved. We have simulated the spectrum for this region (at 270MHz) which clearly pointed to the Z configuration for the isolated double bond in all three isomers (as created in their synthesis). The Table shows the full double bond stereochemistry for 2a-c together with their ultraviolet absorption maxima in cyclohexane. (Pye Unicam SP8-100 spectrophotometer).

TABLE Double Bond Stereochemistry for Isomers 2a-c

Isomer	7-8	9-10	11-12	14-15	λmax(nm)[15]
2a	E	Z	E	Z	268(sh), 277.5,287(sh)
2b	E	E	Z	Z	271(sh), 280.5,292.5
2c	E	Z	Z	Z	271.5(sh), 280, 291.5

The 7E,9,11,14Z isomer 2c was found to readily undergo rearrangement at room temperature to give the tetraene 5, the structure being confirmed by the characteristic[14] U.V. (λmax = 281(sh),292,305,320 nm) mass and ^{1}H N.M.R. spectra. This reaction is probably a 1,7 hydrogen shift of the type reported by Rokach[16].



The synthesis and unambigious assignment of stereochemistry for these isomers of leukotriene A should be of great value in the synthesis of other leukotrienes and their isomers

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8. The h.p.l.c. separation was carried out using a 50 cm x 0.8 mm I.D. Spherisorb S5W column eluted with diethyl ether:hexane:triethylamine(5:95:0.5). The isomer ratios were measured from relative peak areas (U.V. detection λ = 276 nm).
9. The ylide was formed from 4 in THF using 1 eq of BuLi at -78°C and in one reaction 12 eq of cold H.M.P.A. was then added.
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