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FORMATION AND STRUCTURE DETERMINATION OF 5,6-EPOXY-8,11,14-Z-EICOSATRIENOIC ACID AND 5-OXO-8,11,14-Z-EICOSATRIENOIC ACID

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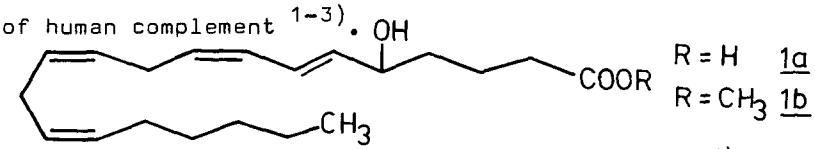
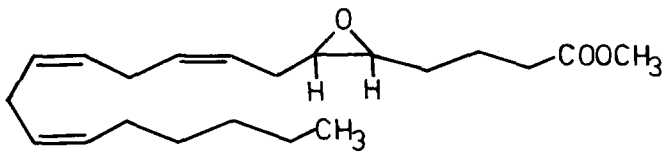
Abstract: The formation of 5,6-epoxy-8,11,14-Z-eicosatrienoic acid and 5-oxo-8,11,14-Z-eicosatrienoic acid as by-products in the synthesis of 5-hydroxy-6-E-8,11,14-Z-eicosatetraenoic acid is described.

5-Hydroxy-6-E-8,11,14-Z-eicosatetraenoic acid (5-HETE) 1a is an important biological mediator which is strongly chemotactic for human eosinophils and neutrophils comparable in magnitude to the peptide factor C5a derived from the fifth component of human complement [1-3].



The methyl ester 1b was prepared essentially as described by Corey [4,5]. However, we modified his work up procedure by using HPLC throughout [6]. HPLC-analysis of the crude reaction mixture showed the presence of 1b (90%) as well as the intact 5-HETE-δ-lactone (8%) and one or two unknown products (1%). GC-MS produced an M^+ peak of 334 ($C_{21}H_{34}O_3$) [7] indicating isomeric 1b or LTA_3 methyl ester [8]. The 250 MHz ^1H NMR spectrum, however, showed the presence of two methoxy groups (ratio 70:30), a fact incompatible with the assumption of one unknown product. On further investigation we found that indeed two products 2, 3 could be isolated by HPLC using hexane/ethyl acetate (95:5) a solvent system known to be suitable for the separation of LTA_4 isomers [9]. On the basis of the ^1H- (Table 1) and ^{13}C-NMR (Table 2) data we suggest the

following structures of 2 and 3 .



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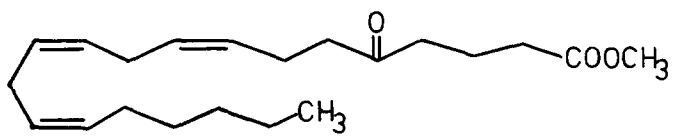

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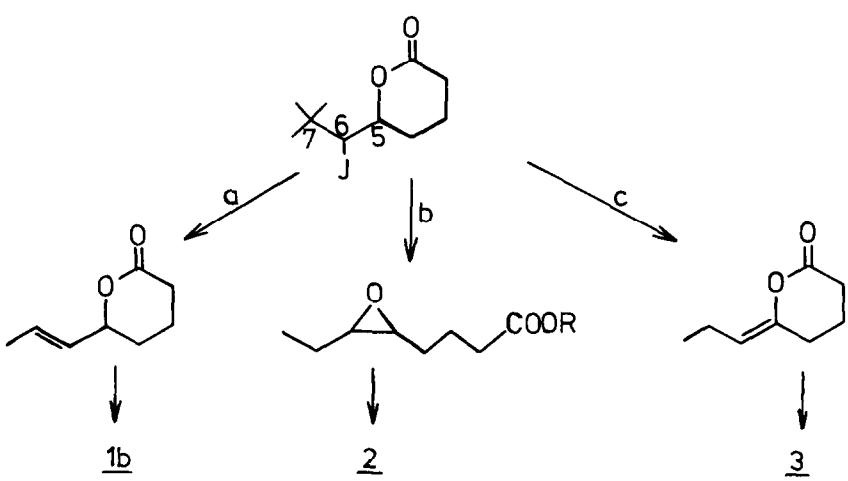
The assignment of ^{13}C- and ^{1}H- signals is straightforward and follows known additivity rules [10]. The relatively high value of $^{3}J_{5,6}$, the downfield shift of H-5,6 and the marked upfield shift of C-4 (see Table 1,2) confirm the cis - stereochemistry at C-5,6 in 2 [11-13]. Only little is known about the magnitude of the electric field effect due to the carbonyl- or oxirane-group and its influence on a sequence of non conjugated double bonds. Nevertheless we have made a tentative assignment based on the spectral analysis of related or analogous compounds which is almost certainly correct [11-13]. The formation of 1b, 2, 3 can be explained by three different ways a - c of HI-elimination from the intermediate iodolactone 4 [5].



1b 2 3

Table 1: ^{1}H NMR Data of 2 and 3, δ ppm (250 MHz)

H-Assignment	2	3
H- 2	2.41	2.35m +)
H- 3	1.59	1.90
H- 4	1.84m	2.48m +)
H- 5	2.95	--
H- 6	2.95	2.48m +)
H- 7	2.41	2.35 +)
H- 8	5.48m	5.36m
H- 9	5.48m	5.36m
H-10	2.82 +)	2.81 +)
H-11	5.36m	5.36m
H-12	5.36m	5.36m
H-13	2.84 +)	2.83 +)
H-14	5.36m	5.36m
H-15	5.36m	5.36m
H-16	2.06	2.06
H-17	1.31m	1.30m
H-18	1.31m	1.30m
H-19	1.31m	1.30m
H-20	0.90	0.90
OCH_3	3.70	3.69

Table 2: ^{13}C NMR Data of 2 and 3, δ ppm (50.3 MHz)

C-Assignment	2	3
C- 1	173.65	173.69
C- 2	33.65	33.12
C- 3	22.10	18.94
C- 4	26.23	42.56 +)
C- 5	56.57 +)	209.42
C- 6	56.24 +)	41.70 +)
C- 7	26.23	21.71
C- 8	124.23	129.21
C- 9	130.70	127.87
C-10	25.93	25.66
C-11	127.50	128.24
C-12	128.40	128.72
C-13	25.69	25.66
C-14	127.50	127.59
C-15	130.62	130.57
C-16	27.26	27.28
C-17	29.33	29.37
C-18	31.54	31.56
C-19	22.58	22.61
C-20	14.06	14.08
OCH_3	51.55	51.54

m: multiplet, +): ambiguity remains; $^3J_{5,6}$ = 3.5 Hz; H-7, $^2J_{a,b}$ = 14.5 Hz.

Our results demonstrate that NMR spectroscopy is a valuable method for rapid determination of structures of known or unknown leukotriene isomers and other lipoxygenase products.

Compound 2 and 3 as well as the free acids show only a weak histamine release and no chemotaxis for human granulocytes.

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