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SYNTHESIS OF THE 9Z and 9Z,11E ISOMERS OF LEUKOTRIENE C_4

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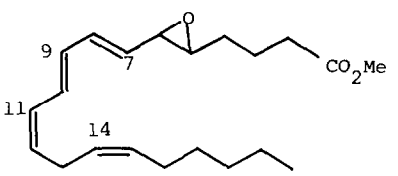
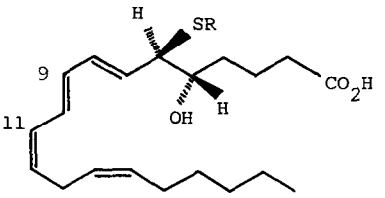
Summary: Synthesis of the 9Z and 9Z,11E isomers of leukotriene C_4 is described, the stereochemistry of the former was confirmed by its facile 1,7 hydride shift reaction.

Leukotriene C_4 (LTC_4) (2) is reported to be one of the biologically active components present in human slow reacting substance of anaphylaxis[1] (SRS-A), which is considered to be an important mediator in human asthma[2]. Corey and Samuelsson[3] showed that natural LTC_4 had the same UV, HPLC and biological characteristics as the synthetic compound 2 and thus concluded that the natural product had the 5S,6R,7,9E,11,14Z stereochemistry. They also reported the synthesis of 9Z LTC_4 (3) and showed that this compound differed from the natural product in both UV and HPLC characteristics. However, following the synthesis of the 9Z and 9Z,11E isomers of leukotriene A_4 (LTA_4) methyl ester[4], we became aware that the compound reported to be the 9Z isomer (3) might in fact have the 9Z,11E stereochemistry (4). In order to clarify the situation, we set out to prepare both the 9Z and 9Z,11E isomers of LTC_4.

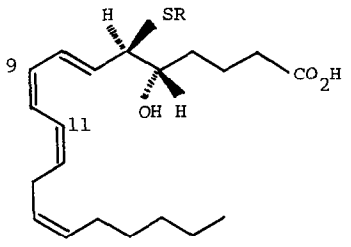
Racemic leukotriene A_4 methyl ester[4] (1) was reacted with glutathione in the presence of triethylamine[3]. The crude reaction product was then hydrolysed with aqueous 0.1M K_2CO_3 in methanol (3:1), (16 hours at 21°C) to give LTC_4 (2) and its 5R,6S isomer. Leukotrienes 3 and 4 were prepared in an analogous manner from the respective 9Z and 9Z,11E isomers of LTA_4 methyl ester[4]. The diastereoisomers were separated by reverse phase high performance liquid chromatography (RP-HPLC) and then bio-assayed on guinea pig ileum[5]. The second eluting isomer from the three separations proved to be considerably more biologically active than the first and was thus assumed to have the natural 5S,6R stereochemistry[5]. The double bond stereochemistry of the 9Z LTC_4 (3) was confirmed by its facile rearrangement to the tetraene 5; this reaction proceeding at an appreciable rate even at -78°C. This type of rearrangement was not observed for LTC_4 (2) or its 9Z,11E isomer (4) and is thought to be a 1,7 hydride shift reaction requiring a cyclic transition state[6] 6.



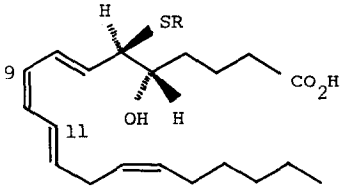
1
LTA_4 methyl ester



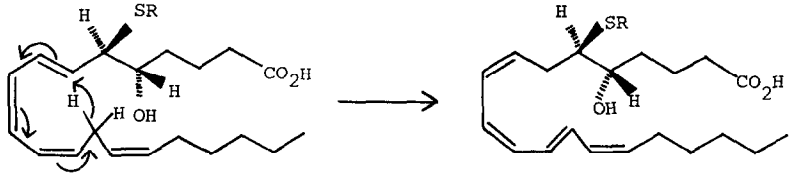
2
LTC_4



3
9Z LTC_4

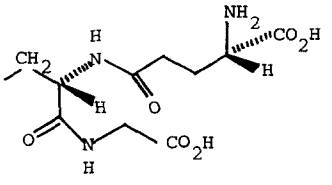


4
9Z,11E LTC_4



6 5

R =



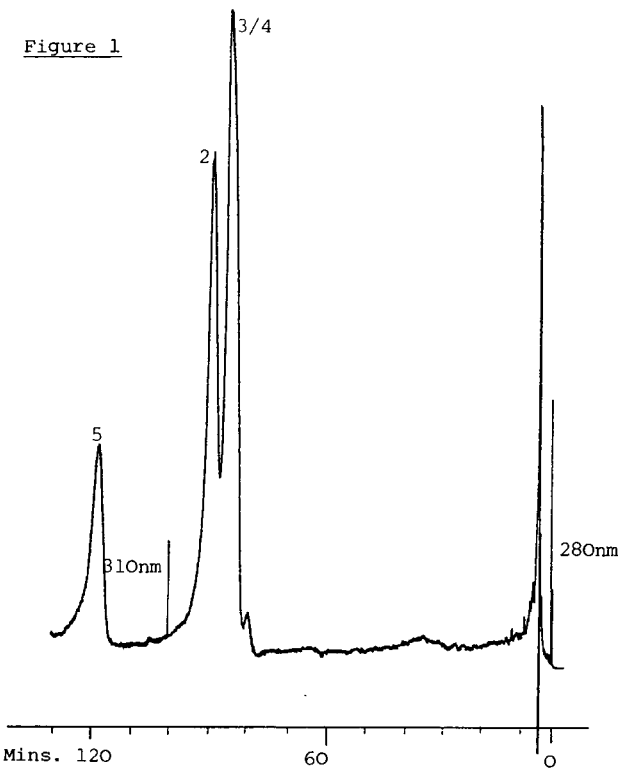
The table shows the full stereochemistry for compounds 2 - 5 together with their ultraviolet absorption maxima in methanol.

TABLE

Compound	Stereochemistry	λ max (nm)
2	7,9E,11,14Z	271, 281, 291
3	7E,9,11,14Z	271, 281, 291
4	7E,9Z,11E,14Z	269, 278, 291
5	8,10Z,12E,14Z	281, 293, 306, 322

9Z LTC_4 (3) is reported[3] as having λmax 277nm. However, we now conclude from the evidence presented above that the compound was probably the 9Z,11E isomer (4). RP-HPLC separation of leukotrienes 2 - 4 proved difficult but the fully conjugated tetraene 5 was well separated (Figure 1). We conclude that it is possible to distinguish between LTC_4 (2) and its 9Z isomer (3), and thus the 9Z compound (3) can be finally ruled out as a possible alternative structure for LTC_4 (2).

Figure 1



Acknowledgement

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7. The HPLC separations were all carried out using a 25 x 0.5 cm I.D. nucleosil 5 C_{18} column eluted with methanol: water: acetic acid (60:40:0.06).

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