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SYNTHESIS OF TWO POSITION ISOMERS OF LEUKOTRIENE C HAVING THE S-PEPTIDE AT C(12)

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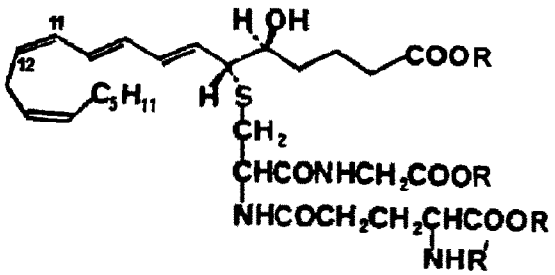
Summary: Two positional isomers of leukotriene C (1) (4a,4b), previously considered as possibly being members of the family of slow reacting substances, have been synthesized and found to be biological inactive.

During the course of our work on the elucidation of structure and total synthesis of slow reacting substances (SRS's), including the parent SRS leukotriene C (LTC) (1),[1,2] a method was developed for the synthesis of diastereomeric 5(S)-12-glutathionyl-6,8,10-trans-14-cis-eicosatetraenoic acid derivatives 4a, 4b. These isomers are of interest since Parker et al.[3] have suggested such a structure for an SRS produced from rat basophilic leukemia cells. In addition, the 12-glutathionyl positional isomers might well be formed from non-enzymatic reaction between glutathion and the biosynthetic SRS predecessor leukotriene A (2) (LTA). We now report on the method of synthesis of 4a and 4b and also the finding that the biological activity of these substances is so low as to preclude their playing a significant role as members of the family of SRS's.

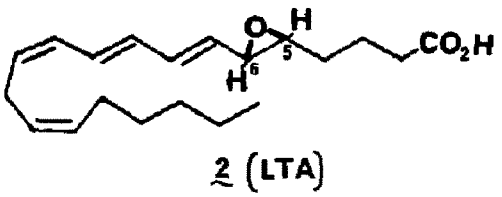
We have previously reported that the reaction of the methyl ester of 2 with N-trifluoroacetyl glutathione dimethyl ester and triethylamine in methanol produced in high yield the S_N2 product 3. In contrast, treatment of LTA methyl ester with N-trifluoroacetylglutathione dimethyl ester (6 equi and anhydrous lithium perchlorate[4] (20 equiv) in a mixture of tetrahydrofuran-ether (1:1) at 23°C f 12 h produced as the major products (~80% of crude) the two diastereomers 5a,b (ratio 1:1) along wi 4 minor adducts (2-8% each).[5] The diastereomers 5a,b were readily separated by preparative layer chromatography on silica gel at 4°C using 3:1 ethyl acetate-hexane (5a R_f 0.33, 5b R_f 0.27) and wer distinguished from 3, the N-trifluoroacetyl trimethyl ester of LTC, by reversed phase HPLC analysis [Waters Associates C_{18} methanol-water-acetic acid (74:26:0.074) buffered to pH 5.6; 5a ret. vol. 3. 5b ret. vol. 4.5, 3 ret. vol. 5.3]. The isomers 5a and 5b showed identical UV absorption, λ_{max}^{MeOH} 276 nm (ε = 40,000) with shoulders at 266 nm (ε = 31,000) and 286 nm (ε = 31,000). The pmr spectra ($CDCl_3$) were almost identical and showed the expected differences from 3 since the methylene at C_{1} appears at 2.3 δ (2.9 - 3.1 δ in 3) and the methine at C_5 appears at 4.15 δ (3.5 - 3.8 δ in 3).

Hydrolysis of the protecting groups in each of the purified derivatives 5a and 5b using 0.13 M K_2CO_3 in methanol-water (1:3) at 23°C for 15 h afforded each of the pure diastereomers 4a and 4b in

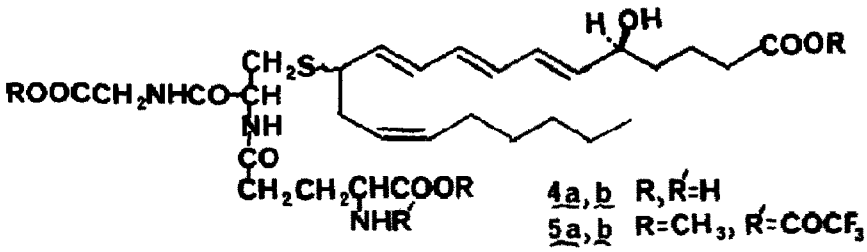
quantitative yield. The 12-glutathionyl diastereomers were differentiated from LTC by reversed HPLC analysis [methanol-water-acetic acid (65:35:0.1) buffered to pH 5.6; 4a ret. vol. 4.6, 4b vol. 5.4, LTC ret. vol. 6.4] as well as by UV absorption, λ_{max} at 277 nm (LTC λ_{max} 280 nm). Biological testing on guinea pig ileum and pulmonary strips[6] showed that each diastereomer was < as active as LTC.[7]



1 R,R′=H (LTC)
3 R=CH$_3$, R′=COCF$_3$



2 (LTA)



4a,b R,R′=H
5a,b R=CH$_3$, R′=COCF$_3$

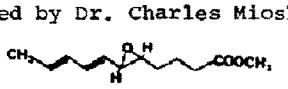
References and Notes

1. E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, S. Hammarström J. Am. Chem. Soc., 102, 1436, 3663 (1980).

2. (a) S. Hammarström, B. Samuelsson, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, and E. Corey, Biochem. Biophys. Res. Commun., 92, 946 (1980); (b) S. Hammarström, R. C. Murphy, B. Samuelsson, D. A. Clark, C. Mioskowski, and E. J. Corey, ibid., 91, 1266 (1979); (c) R. Murphy, S. Hammarström, and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 76, 4275 (1979) substance termed leukotriene C-1 in these papers is now referred to as leukotriene C; leul triene C-2 has been shown to be 11-trans-leukotriene C; see E. J. Corey, D. A. Clark, A. I and G. Goto, Tetrahedron Letters, in press.

3. C. W. Parker, M. M. Huber, M. K. Hoffman, S. F. Falkenheim, Prostaglandins, 18, 673 (1979

4. The use of lithium perchlorate-ether as catalyst for S_N1' reaction of thiols with the mod substrate i was first demonstrated by Dr. Charles Mioskowski in these laboratories.



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5. One of the minor products was identical to 3. The diastereomers 5a and 5b were each obta in 25% yield after purification by HPLC.

6. We thank Drs. R. A. Lewis and J. M. Drazen (Harvard Medical School) for these results.

7. This research was assisted financially by the National Institutes of Health and the Natio Science Foundation.

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