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SYNTHESIS OF THE SULFONES OF LEUKOTRIENE C_4, D_4, and E_4

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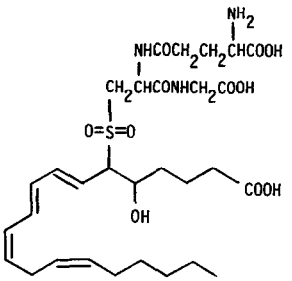
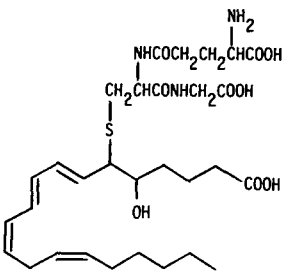
Summary: A simple one-step preparation of the sulfones of Leukotriene C_4, D_4 and E_4 has been developed by the direct oxidation of the parent compounds. An alternative synthesis of these sulfones has also been carried out by reduction of an acetylenic precursor.

Slow reacting substance of anaphylaxis (SRS-A) has for many years been implicated as an important mediator of anaphylactic reactions[1]. Interest in the role of SRS in these reactions and other biological responses has been stimulated in recent years by the elucidation of its structure[2] and its chemical synthesis[3]. Syntheses of its three major components: LTC_4, LTD_4, and LTE_4, has allowed more precise studies of its biological properties. However, in 1980, Ohnishi and coworkers[4] reported the structure of SRS-A isolated from rat peritoneal cells in which the sulfur of the thioether linkage is present as a sulfone (structure A) rather than a sulfide (structure B) as proposed by Samuelsson[2].



A



B

The biological activity of LTC_4 sulfone was reported to be comparable to the activity of LTC_4 itself, thus setting up an intriguing and possibly disturbing situation with regard to the proposed structures for the components of SRS-A. As there have been no further reports clarifying these contrasting structural assignments, we decided to carry out the synthesis of LTC_4 sulfone. We report herein a surprisingly facile solution to this objective, and extended it to the preparation of the sulfones of LTD_4 and LTE_4.

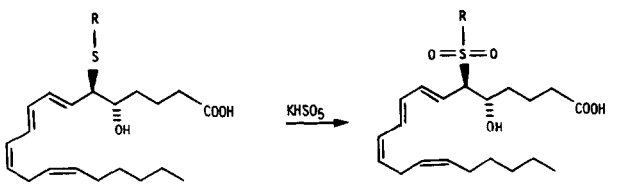
In order to synthesize the Leukotriene sulfones 2 we had at first considered opening LTA_4 methyl ester with the appropriate sulfinic acid. Although this proposal was the most attractive from the view point of ascertaining the identity of the product, the preliminary experiments with a model sulfinic acid were not very encouraging.

The oxidation of Leukotrienes C_4, D_4 and E_4, as well as that of various protected derivatives also appeared to be an attractive alternative. This approach suffered from the disadvantages of having to prove the integrity of the molecule since the double bonds are also

susceptible to oxidation. We reasoned however that, of the four double bonds in the molecule, the conjugated triene would be easily recognized by its characteristic U.V. absorption. The isolated double bond at C_{14} would present more of a problem. Not only would it be difficult to detect but it is the most susceptible to oxidation. So, in our overall strategy, we needed a complementary synthetic method which would take into account this potential problem, provide an alternative to the direct oxidation and more importantly, allow for confirmation and proof of structure.

After a number of unsuccessful attempts to oxidize Leukotrienes and their derivatives with different oxidizing agents, the reagent of choice was found to be potassium hydrogen persulfate. Trost et al.[5] successfully used this reagent to prepare sulfones and they have shown that the oxidation could be performed in the presence of double bonds. Using 7.5 equivalents of $KHSO_5$[6] and 1 equivalent of LTC_4 and monitoring the reaction by HPLC for the disappearance of starting material, the desired sulfone 2a was obtained. In fact, the reaction is slightly more complicated as three types of products are formed. The two sulfoxide diastereoisomers are formed first and are seen on HPLC as two close peaks (a certain asymmetric induction occurred since the two peaks were in a ratio of 4:1). In a slower second step oxidation, the concentration of the sulfoxides diminished and that of the sulfone increased. As this was happening a third much more polar new compound starts appearing which has not as yet been completely characterized, but has the characteristic triene chromophore in the U.V. spectrum (λ_{max}^{MeOH} 266, 276, 287 nm). This compound may have resulted from an epoxidation at the 14-15 positions followed by hydrolysis to the diol under the conditions of the reaction. In a typical run, 8.5 mg of LTC_4 will yield, after purification by HPLC[7], 2.5 mg (25%) of LTC_4 sulfone 2a. Similarily LTD_4 and LTE_4, when oxidized under the same experimental conditions, afforded a 20-25% yield of the corresponding sulfones 2b and 2c respectively. It is interesting to note that the U.V. spectra of the sulfones with λ_{max}^{MeOH} 270, 280 and 292 nm are almost identical to those of the parent sulfides. Proton assignments have been made on the 400 MHz NMR spectra of these sulfones[8] and we observe as expected a downfield shift of 0.6-0.7 ppm for the protons α to the sulfones as compared to the sulfides.

SCHEME 1:



1 2

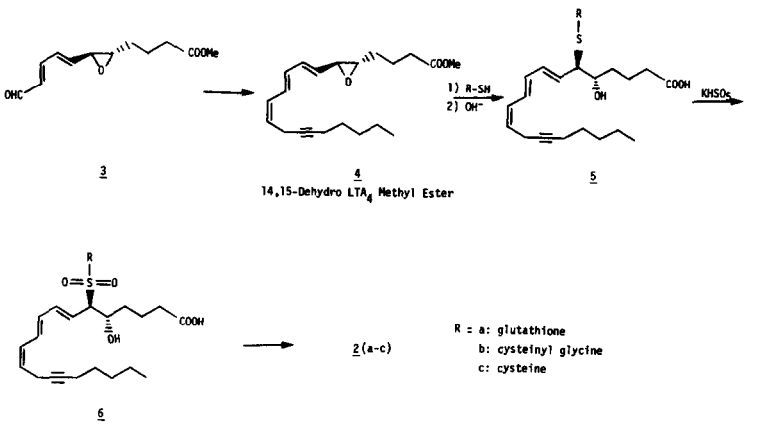
R

LTC_4 (1a)	a: glutathione	LTC_4 sulfone (2a)
LTD_4 (1b)	b: cysteinyl glycine	LTD_4 sulfone (2b)
LTE_4 (1c)	c: cysteine	LTE_4 sulfone (2c)

The main strategy used in our second synthesis (Scheme 2) is the incorporation of a group at the 14 position not susceptible to oxidation under experimental conditions and which would be subsequently transformed to a cis olefin. Hence the diene aldehyde 3[9] was converted to 14,15-dehydro LTA_4 methyl ester by a Wittig reaction with triphenyl (non-3-yn-1-yl)phosphonium

bromide[3a] in 70% yield. The opening of the epoxide 4 with the appropriate protected amino acid followed by basic hydrolysis to afford 5 was carried out in 50% yield under previously described conditions[3a]. The oxidation of 5 to the sulfones 6 was carried out with $KHSO_5$[6] as described above for the oxidation of Leukotrienes C_4, D_4, and E_4 in 50-70% yield. Finally, the reduction of 6 with Lindlar catalyst led to the sulfones of Leukotrienes C_4, D_4, and E_4 2 in 10-30% yield.[10]

SCHEME 2:



The pD_2 values of the sulfones 2a, 2b and 2c on the non-tonal guinea pig trachea (0.5 µg/mL indomethacin present) are 8.2, 8.1, and 7.9, respectively. The comparative data for LTC_4, D_4, and E_4, determined previously by us, are 8.7, 8.6, and 8.1 respectively. It is clear from these data that the sulfones are very potent compounds and their activity, while slightly lower than the corresponding sulfides, is in the same range. Since the retention times on reverse-phase HPLC[11] of the sulfones 2 are different (more polar) than the corresponding sulfides 1 it follows that the natural product previously compared[12,13] with synthetic material was indeed a sulfide and not a sulfone.

While it is possible that the sulfones 2 will be shown to be natural products, the evidence presented by the Japanese workers is not enough to support their claim. Careful controls will have to be developed, e.g., by recycling pure synthetic leukotrienes through all the steps of the isolation procedure. Final comparison of the results with authentic LT's and their sulfones will have to be made. Without such comparison it will be difficult to know how much of the sulfone isolated by the Japanese group is an artifact of oxidation during the isolation procedure. Since no HPLC work seems to have been done, it is even difficult to know if their samples are not contaminated to varying degrees with LTC_4.

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REFERENCES and NOTES

1. K.F. Austen, J. Immunol., 121, 793-805 (1978).
2. For a recent review of the chemistry and properties of the Leukotrienes see: B. Samuelsson, Pure Appl. Chem., 53, 1203-1213 (1981).
3. a) J. Rokach, Y. Girard, Y. Guindon, J.G. Atkinson, M. Larue, R.N. Young, P. Masson and G. Holme, Tetrahedron Lett., 21, 1485-1488 (1980). b) E.J. Corey, D.A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson and S. Hammarstrom, J. Am. Chem. Soc., 102, 1436-1439 (1980). c) M. Rosenberger and C. Newkom, J. Am. Chem. Soc. 102, 5425-5426 (1980).
4. H. Ohnishi, H. Kosuzume, Y. Kitamura, K. Yamaguchi, M. Nobuhara and Y. Suzuki, Prostaglandins 20, 655-666 (1980).
5. B.M. Trost and D.P. Curran, Tetrahedron Lett., 22, 1287-1290 (1981).
6. Potassium hydrogen persulfate is commercially available from Alfa Division of the Ventron Corp. under the trade name oxone (mixture of 2 moles $KHSO_5$, 1 mole K_2SO_4 and 1 mole $KHSO_4$).
7. The reverse phase (μ-Bondapak C_{18}) solvent system used for this purpose is a mixture of acetonitrile:water:acetic acid (35:65:0.1) buffered at pH 5.8 with ammonium hydroxide. The polarity of LTC_4, LTC_4 sulfone and the LTC_4 sulfoxides are in the expected order, with retention times of 13.8 min., 11.7 min, 8.7 min. and 8.4 min. respectively, when eluted at 1 mL/min.
8. The sulfones of Leukotrienes C_4, D_4, and E_4 have the same characteristic data. LTE_4 ^1H NMR (D_2O) δ 0.93 (3H, CH_3, m), 1.25-1.80 (10 H, methylenes, m), 2.13 (2H, H_{16}, quartet, J = 7Hz), 2.21 (2H, H_2, m), 3.04 (2H, H_{13}, m), 3.64 and 3.73 (2H, $SO_2\underline{CH_2}CH$, m), 3.89 (1H, H_5, m), 4.02 (1H, H_6, d, J = 9Hz), 4.50 (1H, $SO_2CH_2\underline{CH}$, m), 5.49 (1H, H_{14}, dT, J = 11Hz and 7Hz), 5.55 (1H, H_{15}, dT, J = 11Hz and 7Hz), 5.66 (1H, H_{12}, dT, J = 11Hz and 8Hz), 5.84 (1H, H_7, dd, J = 9Hz and 15Hz), 6.17 (1H, H_{11}, T, J = 11Hz), 6.46 (1H, H_9, dd, J = 11Hz and 15Hz), 6.69 (1H, H_8, dd, J = 11Hz and 15Hz) and 6.85 (1H, H_{10}, dd, J = 11Hz and 15Hz).
9. a) J. Rokach, R.N. Young, M. Kakushima, C.K. Lau, R. Seguin, R. Frenette and Y. Guindon, Tetrahedron Lett. 22, 979-982 (1981). b) J. Rokach, R. Zamboni, C.K. Lau, and Y. Guindon, Tetrahedron Lett. 22, 2759-2762 (1981). c) J. Rokach, C.K. Lau, R. Zamboni and Y. Guindon, Tetrahedron Lett. 22, 2763-2766 (1981).
10. This reduction step led also to an important amount of 11-trans isomer by HPLC. The reaction conditions were not optimized.
11. This reverse phase HPLC comparison was done using the solvent system of reference 12 [methanol:water:acetic acid (65:35:0.01)].
12. H.R. Morris, G.W. Taylor, J. Rokach, Y. Girard, P.J. Piper, J.R. Tippins and M.N. Samhoun, Prostaglandins, 20, 601-607 (1980).
13. S. Hammarstrom, B. Samuelsson, D.A. Clark, G. Goto, A. Marfat, C. Mioskowski and E.J. Corey, Biochem. Biophys. Res. Commun. 92, 946-953 (1980).

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