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SYNTHESIS OF THREE POTENTIAL INHIBITORS OF THE BIOSYNTHESIS OF LEUKOTRIENES A-E

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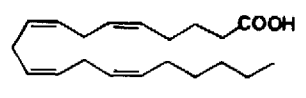
Summary: Simple synthetic routes are described to 5,6-dehydroarachidonic acid (5), cis-8-eicosen-5-ynoic acid (6) and the thio analog of (±)-leukotriene A (7), which are of value in the study of inhibition of the biosynthesis of leukotrienes and slow reacting substances.

The extraordinary importance of arachidonic acid (1) as a precursor of prostaglandins and thromboxanes has been appreciated for some time.[1] More recently another mode of biosynthesis from arachidonic acid via 5-HPETE (2) to leukotriene A (3) (LTA)[2] and thence to leukotriene B[2d] or to the "slow reacting substances of anaphylaxis" (SRS-A's) leukotrienes C (4, R = glu cys gly), D (4, R = cys gly) and E (4, R = cys) has been demonstrated.[3-7] The key role of LT's as agonists in immediate hypersensitivity and other pathological conditions has made it apparent that leukotriene biosynthesi inhibitors and leukotriene antagonists could be of medical value. We describe herein synthetic routes to three substances, 5, 6, and 7, which have been selected as rational candidates for initial biological studies on the inhibition of the biosynthesis of leukotrienes and SRS-A's.



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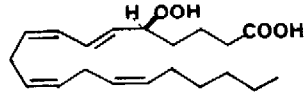

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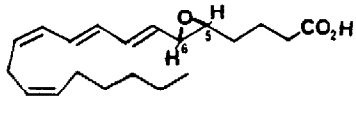

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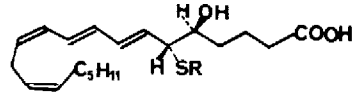

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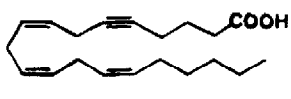

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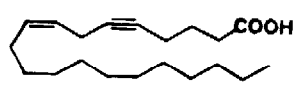

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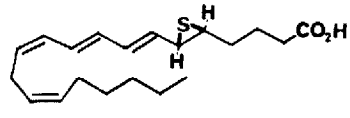

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The well known effectiveness of eicosa-5,8,11,14-tetraynoic acid (ETYNA) in blocking the first step of the bioconversion of arachidonic acid to prostaglandins suggests that both 5 and 6 could inhibit the transformation of arachidonic acid to 5-HPETE and leukotrienes. Further, although 5 could itself be converted to prostaglandins, 6 clearly cannot be. The episulfide 7, on the other hand, should inhibit the biosynthesis of LTB, LTC, etc. from arachidonic acid by blocking the enzymic reactions of LTA.[8]

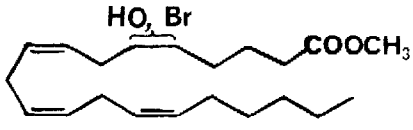
The synthesis of 5,6-dehydroarachidonic acid (5) was accomplished in an expeditious manner starting from arachidonic acid via the previously described 5,6-epoxide of methyl arachidonate[9] which could be converted to a 1:1 mixture of position isomeric bromohydrins 8 (94%) by exposure to a saturated solution of potassium bromide in HOAc-H_2O-THF[10] at 5° for 4 hr.[11,12] Treatment of the bromohydrin mixture with a small excess of Jones' reagent[13] at -20° for 15 min followed by extractive isolation with pentane gave a 1:1 mixture of 9 and the position isomeric bromo ketone (83%). Reaction of the mixture of bromo ketones with 1.5 equiv of 2,4-dinitrobenzenesulfonyl hydrazine[14] in 2:1 CH_2Cl_2-HOAc at 23° for 30 hr under argon afforded after extractive isolation with pentane and chromatographic purification the methyl ester of 5 directly (41%) (during the course of reaction the formation of the intermediate sulfonyl hydrazone was detected by TLC analysis). Saponification of the methyl ester using 10 equiv of lithium hydroxide in 1:1 THF-H_2O for 1.5 hr led cleanly to pure 5 (100%)[15] which was obtained as a colorless oil.

A simple, three-step synthesis of the methyl ester of cis-8-eicosen-5-ynoic acid (6) was carried out as follows. Reaction of 1-tridecyne with 1.3 equiv of iodine and 4.2 equiv of morpholine in benzene at 45° for 18 hr afforded 1-iodo-1-tridecyne (100%) which was converted by treatment with 1.9 equiv of potassium azodicarboxylate and acetic acid in 3:1 methanol-pyridine to cis-1-iodo-1-tridecene (10) (93%).[16] Lithiation of 10 was effected by treatment with 2 equiv of tert-butyllithium in THF at -110° for 1 hr under argon[17] and further reaction with cuprous iodide-dimethylsulfide complex at -78° for 1 hr and -50° for 0.5 hr generated the corresponding Gilman reagent which underwent coupling to methyl 7-iodo-5-heptynoate[18] (-110°, 0.5 hr, THF) containing 3 equiv of hexamethylphosphoric amide to give the desired methyl ester of 6 as a colorless oil in 26% yield after chromatography on silica gel.

The synthesis of the racemic methyl ester of the thio analog of leukotriene A (7) was readily effected by the following process. Methyl 7-hydroxy-5-heptynoate[18] was reduced to the corresponding cis olefin by hydrogenation (1 atm, 25°) in THF over Lindlar catalyst deactivated by triethylamine,

and that product was oxidized by pyridinium chlorochromate[19] (3 equiv, 23°, 2.5 hr) in methylene chloride (with concurrent isomerization) to the trans-α,β-unsaturated aldehyde which was then reduced with sodium borohydride in absolute ethanol at -30° to afford 60% overall yield of methyl 7-hydroxy-trans-5-heptenoate (11). Epoxidation of 11 with m-chloroperoxybenzoic acid in methylene chloride (0.14 M, 23°, 14 hr) afforded the corresponding epoxy alcohol (77%) which gave the epoxy aldehyde 12 (88%) by oxidation with pyridine-chromium trioxide complex in methylene chloride at 23° for 2 min. The epoxy aldehyde 12 was converted to the dienal 13 and thence to the methyl ester of (±)-LTA as previously described.[2b] Reaction of (±)-LTA with 14 equiv of sodium thiocyanate (0.05 M) in methanol containing 1 equiv of triethylamine at 23° for 1.5 hr, extractive isolation, and chromatography on silica gel deactivated with triethylamine (20% ether in pentane for elution) afforded the methyl ester of the racemic thiirane 7 in 60% yield, ultraviolet max (CH_3OH) 275, 286, and 295 nm.

The results of the biological studies of 5, 6, and 7 as inhibitors of SRS-A biosynthesis will be reported separately when these ongoing investigations[20] have been completed. Work is continuing on the synthesis of other potential inhibitors as well.[21]



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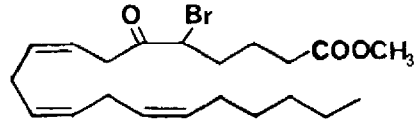

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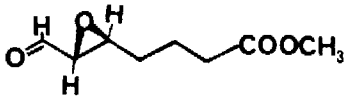

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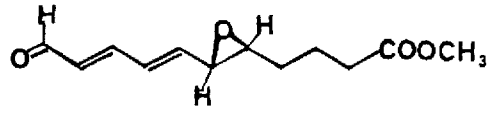

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References and Notes

1. See (a) K. C. Nicolaou and J. B. Smith, Ann. Reports Med. Chem., 14, 178 (1979); (b) T. K. Schaaf, ibid., 12, 182 (1977).
2. The structure of LTA (3) and its biosynthesis from 5-HPETE (first proposed by one of us, E.J.C., March 1977) in advance of its isolation, have been fully supported by a number of studies. See (a) E. J. Corey, Y. Arai, and C. Mioskowski, J. Am. Chem. Soc., 101, 6748 (1979) (b) E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, and S. Hammarström, ibid., 102, 1436, 3663 (1980); (c) E. J. Corey, A. E. Barton, and D. A. Clark, ibid., 102, 4278 (1980); (d) P. Borgeat and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 76, 3213 (1979); and (e) O. Rådmark, C. Malsten, B. Samuelsson, G. Goto, A. Marfat, and E. J. Corey, J. Biol. Chem., in press (1980).
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7. For nomenclature of LT's see, B. Samuelsson and S. Hammarström, Prostaglandins, 19, 645 (1980)
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10. Abbreviations: THF, tetrahydrofuran; TLC, thin layer chromatography.
11. Satisfactory infrared, proton magnetic resonance, and in the case of thermally stable compounds, mass spectral data were obtained for each new compound.
12. R_f values for the isomeric bromohydrins 8 by TLC on silica gel using 1:1 hexane-ether were 0.31 and 0.26 after two developments.
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15. The synthesis of 5, a lengthy and inefficient process, has previously been reported. See, L. Heslinga, R. v. d. Linde, H. J. J. Pabon, and D. A. van Dorp, Rec. Trav. Chim. Pays-Bas, 94, 262 (1975).
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18. E. J. Corey and H. S. Sachdev, ibid., 95, 8483 (1973).
19. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).
20. In collaboration with Drs. R. A. Lewis, J. M. Drazen and K. F. Austen of the Harvard Medical School.
21. Partial spectral data: for 5; pmr in $CDCl_3$ (δ) 5.27-5.52 (m, olefinic H, 6H), 3.67 (s, OCH_3, 3H), 2.58-2.98 (m, 7, 10, and 13-CH_2, 6H), 2.43 (t, J = 7.0 Hz, 2-CH_2, 2H), 2.23 (tt, J = 7.0 and 3.0 Hz, 4-CH_2, 2H), 2.00 (m, 14-CH_2, 2H), 1.79 (q, J = 7.0 Hz, 3-CH_2, 2H), 1.17-1.47 (m, CH_2, 6H), 0.80 (t, J = 7 Hz, CH_3, 3H), MS M^+ = 316 (.33), M^+-CH_3 (.13), M^+-OCH_3 (1.0), $M^+-C_5H_{11}$ (0.8); ror 6; pmr in $CDCl_3$ (δ) 5.30-5.50 (m, olefinic, 2H), 3.67 (s, OCH_3, 3H), 2.75-3.0 (m, 7-CH_2, 2H), 2.43 (t, J = 7.5 Hz, 2-CH_2, 2H), 2.05-2.30 (m, 4-CH_2, 2H), 1.90-2.05 (m, 10-CH_2, 2H); MS M^+ = 320 (.22), M^+-CH_3 (.04), M^+-OCH_3 (1.0); for 7; pmr in C_6D_6(δ) 6.15-7.0 (m, 8, 9, 10, 11-H, 4H), 5.4-5.7 (m, 7,12,11,14,15-H, 4H), 3.60 (s, OCH_3, 3H), 3.20 (m, 3H at 6 and 13), 2.60 (m, H at 5, 1H); MS M^+ = 348 (0.05), M^+-OCH_3 (0.1), M^+-CH_3OH (0.39), M^+-257 (1.0).

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