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DIMETHYLEICOSATRIENOIC ACIDS: INHIBITORS OF THE 5-LIPOXYGENASE ENZYME

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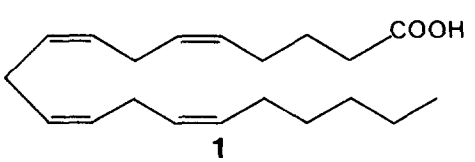
Summary: Syntheses of 7,7- and 10,10-dimethyleicosa-5(Z),8(Z),11(Z)-trienoic acids (5 and 6), which possess 5-lipoxygenase inhibitory activity, are described.

Arachidonic acid (1) is now well established as a key substance in the biosynthesis of the leukotrienes, a family of compounds that have been implicated as mediators of asthma and inflammation.[1] It is oxidized by a 5-lipoxygenase enzyme to 5-hydroperoxyeicosatetraenoic acid (5-HPETE, 2), which, in turn, is converted to Leukotriene A_4 (LTA_4, 3) by a second enzyme, "LTA_4 synthetase." LTA_4 serves as a precursor to Leukotrienes B, C, D, and E, the last three being integral components of Slow Reacting Substance of Anaphylaxis (SRS-A).

Other polyunsaturated fatty acids also serve as substrates for the 5-lipoxygenase enzyme system. In particular, Jakschik, et al.[2] have demonstrated that 5,8,11-eicosatrienoic acid (4) is converted to a material with SRS activity, and the work of Hammarstrom[3] strongly indicates that this material includes LTC_3 and LTD_3, which have biological activity comparable to their tetraene counterparts.



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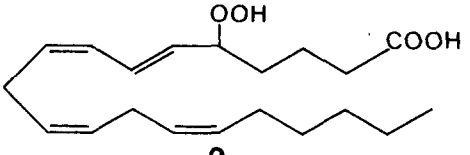

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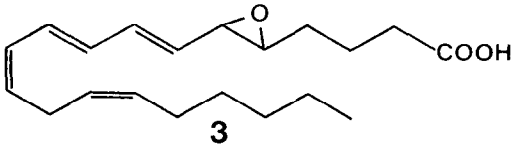

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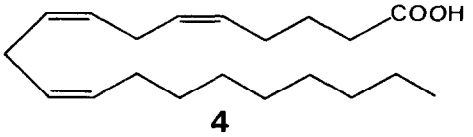

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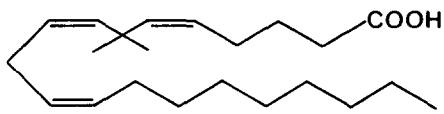
With a view toward the inhibition of leukotriene biosynthesis, we have prepared 7,7-dimethyleicosa-5(Z),8(Z),11(Z)-trienoic acid (5) and its 10,10-dimethyl isomer (6), in which the biochemically reactive 7 and 10 positions of 4 have been blocked by a gem-dimethyl group, and describe here the synthetic routes to these compounds.[4-6] The choice of the trienes as target compounds, as opposed to the corresponding tetraenes, was based in part on the expectation that, lacking the 14,15-double bond, they would not be substrates for the cyclooxygenase pathway of arachidonic acid metabolism.



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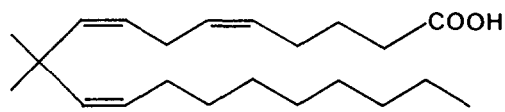

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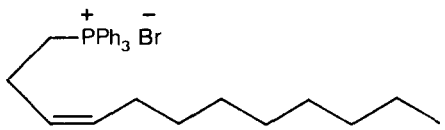
For the synthesis of 5, phosphonium salt 7[7] was prepared as follows. Alkylation of 3-butyn-1-ol with n-octyl bromide ($LiNH_2/NH_3$-Et_2O) afforded 3-dodecyn-1-ol in ca. 25% yield. Semi-hydrogenation of the acetylene (H_2/Pd-$BaSO_4$/quinoline/EtOAc) afforded a near quantitative yield of the cis olefin, which was converted to the corresponding bromide by treatment with 1.25 eq of CBr_4 and 1.50 eq of Ph_3P in CH_2Cl_2 (0°, 20 min; 83%). Reaction with 1.1 eq of triphenylphosphine in refluxing CH_3CN (72 h) then produced 7 (82%).

Wittig reaction of the ylide derived from 7 (n-BuLi/THF, 0°) with aldehyde 8[8] (-78° to RT) afforded, after silica gel chromatography, a 57% yield of 9. Acetal hydrolysis (HCl/H_2O-acetone, RT, 47 h; 47%), followed by a Wittig reaction with the ylide derived from (4-carboxybutyl) triphenylphosphonium bromide (KH/DMSO; RT, 1 h) then produced a 62% yield of 5 as a colorless oil, after purification on silica gel.



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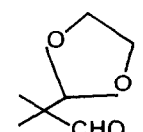

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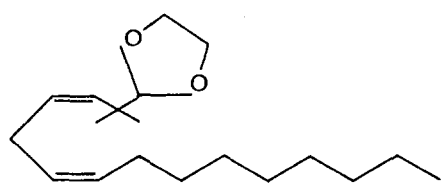

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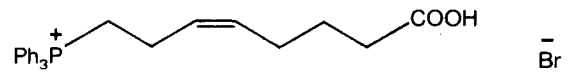
The preparation of 6 likewise employed 3-butyn-1-ol as the starting material. Alkylation with 1-bromo-3-chloropropane ($LiNH_2/NH_3$-Et_2O) gave 7-chloro-3-heptyn-1-ol in 57% yield. This was converted to the corresponding nitrile (NaCN-NaI/DMF, 100°, 3 h; 92%), and the acetylene was reduced to the cis olefin (H_2/Pd-$BaSO_4$/quinoline/EtOAc; 78%). Hydrolysis of the nitrile (KOH/CH_3OH-H_2O, reflux, 19 h; 89%), followed by bromination with CBr_4-Ph_3P (1.25 eq of each) in CH_2Cl_2 (0° to RT, 3 h; 72%) and reaction with 1.1 eq of triphenylphosphine (CH_3CN, reflux, 48 h) then afforded phosphonium salt 10 (63%).

11 was prepared by a Wittig reaction of aldehyde 8 with the ylide derived from (nonyl) triphenylphosphonium bromide (n-BuLi/THF, -78° to RT; 64%). Acetal hydrolysis (HCl/H_2O-acetone, RT, 22 h) produced the corresponding aldehyde (80%), which was then converted to 6 by a Wittig reaction with the ylide derived from 10 (n-BuLi/THF, -78° to RT).



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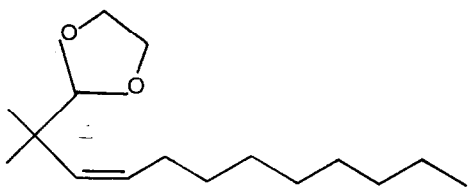

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The effect of compounds 5 and 6 on arachidonic acid metabolism in RBL-1 cells was investigated by a procedure[9] that allows an evaluation of action on the enzymes of both the 5-lipoxygenase and cyclooxygenase pathways. At 100 μM, 5 inhibited the formation of the 5-lipoxygenase products 5-HETE and 5,12-di-HETE by 50%, as well as the cyclooxygenase product PGD_2 by 30-40%. Compound 6 was more selective for the 5-lipoxygenase pathway, inhibiting the formation of 5-HETE and 5,12-di-HETE by 40% at 100 μM, while having little inhibitory activity on the formation of PGD_2.

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References and Notes

1. D. M. Bailey and L. W. Chakrin, Ann. Reports Med. Chem., 16, 213 (1981), and references cited therein.

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4. The syntheses of several dehydroarachidonic acids, which are position-selective lipoxygenase inhibitors, have been reported: a) E. J. Corey, H. Park, A. Barton, and Y. Nu, Tetrahedron Lett., 21, 4243 (1980); b) E. J. Corey and H. Park, J. Amer. Chem. Soc., 104, 1750 (1982); c) E. J. Corey and J. E. Munroe, Ibid., 104, 1752 (1982).

5. The carba-analog of LTA_4 has been synthesized and found to inhibit 5-lipoxygenase: a) K. C. Nicolaou, N. A. Petasis, and S. P. Seitz, J. Chem. Soc. Chem. Comm., 1195 (1981); b) Y. Arai, M. Konno, K. Shimogi, Y. Konishi, H. Niwa, M. Toda, and M. Hayashi, Chem. Pharm. Bull., 30, 379 (1982); c) Y. Arai, K. Shimoji, M. Konno, Y. Konishi, S. Okuyama, S. Iguchi, M. Hayashi, T. Miyamoto, and M. Toda, J. Med. Chem., 26, 72 (1983).

6. A carba-analog of 5-HPETE is reported to inhibit 5-lipoxygenase: references 5b and 5c.

7. Satisfactory IR, PMR, and mass spectra were obtained for all new compounds. 5 and 6 also afforded satisfactory CMR and 250 MHz PMR spectra, and correct elemental composition (combustion analysis or exact mass measurement).

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