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ON THE SYNTHESIS AND STRUCTURE OF LIPOXIN B

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Summary: A synthesis of lipoxin B, a recently discovered biologically active eicosanoid, and the assignment of stereoformula 2 is reported.

Serhan, Hamberg and Samuelsson have recently reported the isolation of two new eicosanoids described as 5,6,15(S)-trihydroxy 7,9,11,13-eicosatetraenoic acid (lipoxin A) and 5(S), 14,15(S)-trihydroxy 6,8,10,12-eicosatetraenoic acid (lipoxin B) from human leukocytes exposed to 15-HPETE (15-S-hydroperoxy-5Z,8Z,11Z,13E-eicosatetraenoic acid) in the presence of calcium ionophore A23187.[1,2] Supposedly formed by multiple lipoxygenations, these substances have been shown to possess interesting biological properties, viz., stimulation of elastase and superoxide ion release from neutrophils, an activity shared with leukotriene B_4.[2]

We have recently described the synthesis and assignment of the stereochemistry of lipoxin A (1).[3] Herein, we report the synthesis of two of the possible isomeric structures for lipoxin B and assign the stereoformula 2 to lipoxin B based on the comparison with a biologically produced sample.[4] Lipoxin B is available in submicrogram or microgram amounts only with difficulty (and biosynthesis requires access to human neutrophils). The availability of synthetic material should accelerate the study of the biological significance of this new eicosanoid.

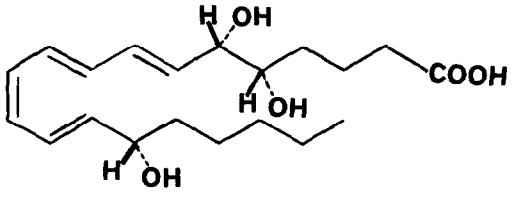
15(S)-HPETE methyl ester (4) on treatment with titanium tetraisopropoxide (1.1 equiv) in methylene chloride (-10 to 0°, 4 h) resulted in an easily separable mixture of threo epoxy alcohol (6) and the erythro isomer (5) in a ratio of ca. 3 : 1 (84% total yield; R_f values 0.29 and 0.36, respectively, using silica gel plates with 7 : 3 hexane - EtOAc for development).[5,6] Saponification of 6 with 4 equiv of

lithium hydroxide in 4 : 1 : 1 THF-methanol-water at 23° for 3 h afforded after acidification to pH 5 and extraction with ether the free acid (7) in 95% yield. Treatment of the hydroxy epoxide (7) with lithium bis(trimethylsilyl)amide (4 equiv, 0 to 23° over 1 h, 3 h at 23°) in THF followed by acidification to pH 4 and extractive isolation afforded cleanly 14(S), 15(S)-dihydroxy 5, 8-Z, 10, 12-E-eicosatetraenoic acid (8) (58% yield).[7]

With the 14- and 15-hydroxyl groups in place and the 8, 10, 12-conjugated triene unit in proper stereochemical order, the stage was set for the simultaneous introduction of the 5-hydroxyl and 6, 7-olefinic functions. This change was effected by the iodolactonization[8] method as follows.

Reaction of the dihydroxy tetraene acid (8) with 4.5 equiv of trimethylsilyl triflate and 8 equiv of 2, 6-lutidine in methylene chloride at 0° for 2 h followed by quenching with aqueous 1M - $CuSO_4$ and extractive isolation afforded the tetraene - di TMS ether (9). Treatment of 9 with iodine - potassium bicarbonate - potassium iodide for 10 h at 0° followed by reaction of the iodo δ-lactone with diazabicyclo-undecene (DBU) in methylene chloride for 2 h at 0° afforded the tetraene δ-lactone (10). Finally, methanolysis (methanol, triethylamine for 2 h at 23°) of 10 yielded lipoxin B methyl ester and its C(5) epimer in a ratio of ca. 1 : 1 (71% overall yield from 8) as determined by reversed phase HPLC analysis. Using 6 : 4 methanol - water as solvent with a Waters Associates 15 cm. NOVA PAC C_{18} column (flow rate 2 ml/min) retention times were measured as 9.64 min for lipoxin B methyl ester (2) and 7.52 min for its C-5 epimer. Both reversed phase HPLC mobilities and UV absorption (max. 288, 301, 316 nm) were identical for native lipoxin B and synthetic (2) as the methyl esters.

In a parallel sequence the erythro epoxy alcohol (5)[5] was transformed into 5(S), 14(R), 15(S)-trihydroxy-6, 10, 12-E, 8-Z-tetraenoic acid methyl ester (3). Although the UV absorption of this isomer was the same as that of native lipoxin B methyl ester (2), the reversed phase HPLC retention time was clearly different. Under the standard HPLC conditions described above the retention times were 8.10 min for erythro isomer (3) and 6.52 min for its C(5) epimer. Both reversed phase HPLC mobilities and UV absorption (max. 288, 301, 316 nm) were identical for the minor biological 15-HPETE metabolite[4] and synthetic (3) as the methyl esters. The biological properties of these lipoxin B isomers are at present under study and will be reported in a separate publication.[9,10]



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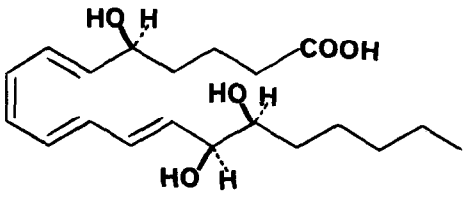

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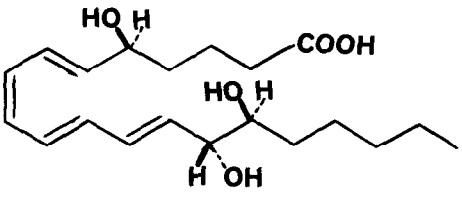

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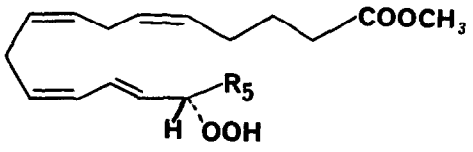

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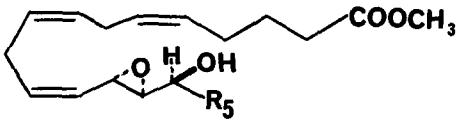

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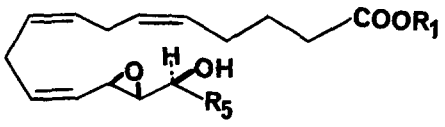
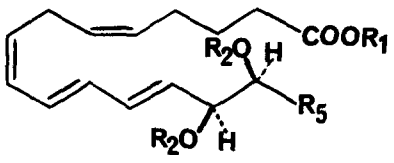


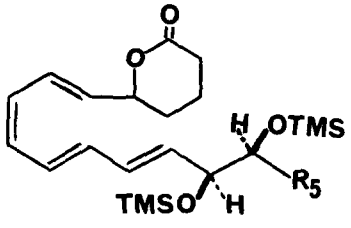
6 $R_1 = CH_3$

7 $R_1 = H$



8 $R_1 = R_2 = H$

9 $R_1 = H$ $R_2 = TMS$



10

$R_5 = C_5H_{11}$

References and Notes

1. C. N. Serhan, M. Hamberg and B. Samuelsson, Biochem. Biophys. Res. Commun., 118, 943 (1984).
2. C. N. Serhan, M. Hamberg and B. Samuelsson, Proc. Natl. Acad. Sci. USA, 81, 5335 (1984).
3. E. J. Corey and W. Su, Tetrahedron Lett., in press.
4. Biologically derived samples were prepared and purified exactly as described in refs. 1 and 2. The extractive isolation of the crude products from the incubation mixture was done at pH 7. HPLC analysis of the products after purification by preparative tlc also showed a minor peak corresponding to 5(S),14(R),15(S)-trihydroxy 6,10,12-E,8-Z-tetraenoic acid methyl ester (3). In one run when the incubation was carried out with a higher concentration of the ionophore (20 μM) and for a longer time (1 h), a substantial amount of this minor isomer was detected; however, the major product was still the threo compound (2).
5. The assignment of the stereochemistry was made by comparison with authentic samples prepared according to J. R. Falck, S. Manna, A. K. Siddhanta and J. Capdevila, Tetrahedron Lett., 24, 5715 (1983).
6. Satisfactory spectroscopic data (270 MHz PMR, infrared, ultraviolet and mass spectral) were obtained for each reaction product using a chromatographically purified and homogeneous sample.
7. J. R. Falck, S. Manna, J. Capdevila, and J. D. Buynak, Tetrahedron Lett., 24, 5719 (1983).
8. a) E. J. Corey and S. Hashimoto, Tetrahedron Letters, 22, 299 (1981); b) E. J. Corey, J. O. Albright, A. E. Barton and S. Hashimoto, J. Am. Chem. Soc., 102, 1435 (1980).

9. We are grateful to Drs. Robert A. Lewis, K. F. Austen, and R. A. Soberman of the Harvard Medical School for supplying a preparation of human neutrophils.
10. This work was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

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