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SYNTHESIS OF LIPOXINS: TOTAL SYNTHESIS OF CONJUGATED TRIHYDROXY EICOSATETRAENOIC ACIDS

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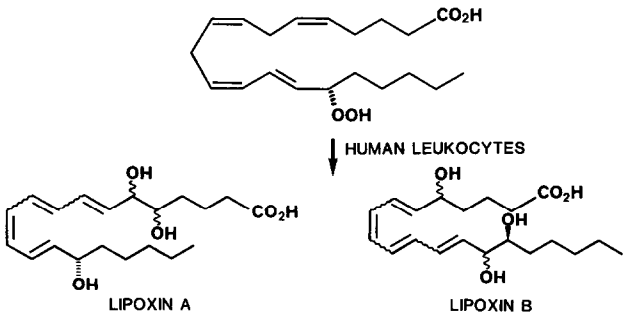
Summary: The first synthesis of a conjugated trihydroxy eicosatetraenoic acid, a possible structure for Lipoxin A is described. A biomimetic approach was utilized.

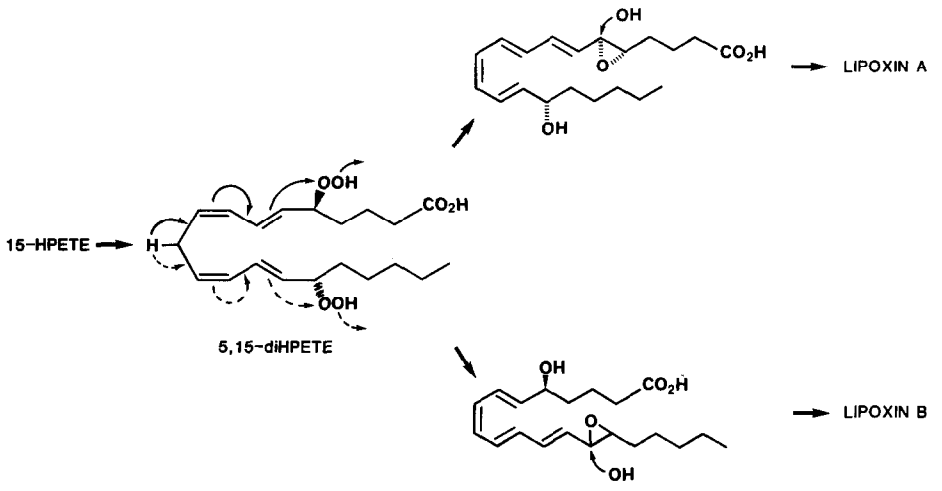
Recently, the Samuelsson group reported the isolation of a new series of natural products derived from oxidative metabolism of arachidonic acid.[1] Incubation of 15-HPETE with human leukocytes produced Lipoxins A and B, conjugated tetraene triols (characteristic UV spectra; λmax = 301 nm). The Samuelsson group performed a very elegant structural elucidation to determine the skeletal connectivity of the Lipoxins. However, the geometric configuration of the conjugated double bonds and the absolute stereochemistry of the vicinal alcohols at C_5 and C_6 for Lipoxin A, and the alcohol at C_{14} for Lipoxin B remains unknown.[1b]

Scheme I

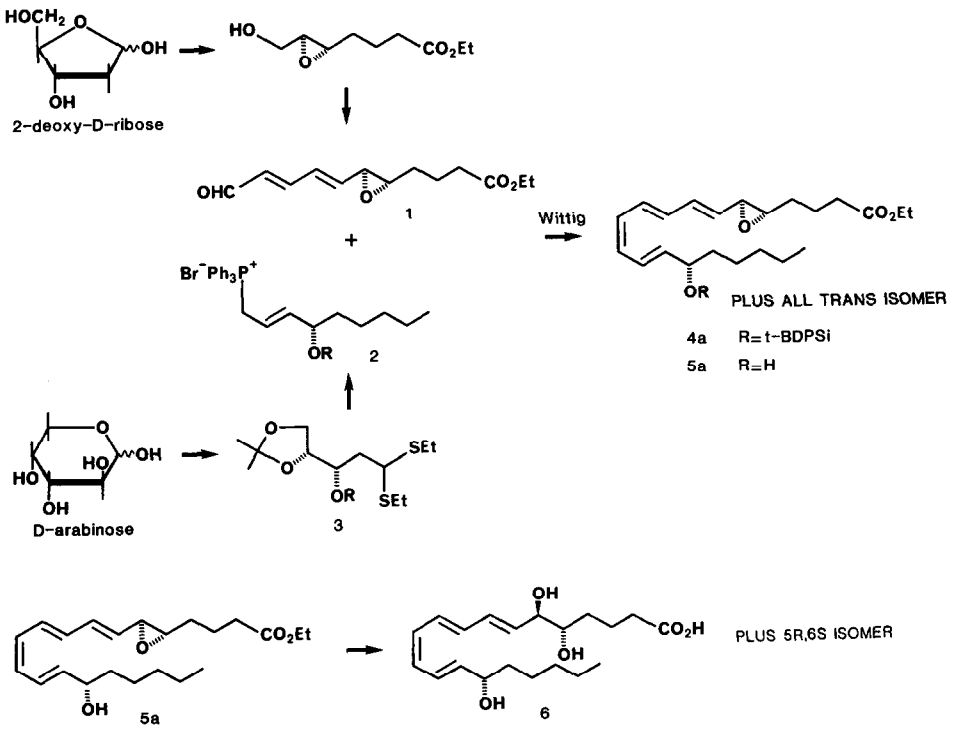


Upon examination of these natural products we carried out a bio-retrosynthetic analysis in an effort to define the biochemical origins of these compounds. Scheme II depicts a plausible cascade whereby 15-HPETE undergoes a second oxidation via a 5-lipoxygenase enzyme to produce the well known 5,15-diHPETE. We envisaged an enzymatic dehydration step, strictly analgous to the formation of LTA_4, in which a stereospecific abstraction of a porton between the skipped diene unit occurs to form the polyene epoxide. The solid arrows in the scheme lead to the formation of an epoxide at C_5-C_6 with a tetraene bearing the 7-trans, 9-trans, 11-cis, 13-trans

Scheme II



Scheme III



geometry. This epoxy tetraene would be expected to show the same metabolic instability as LTA_4. Enzymatic hydrolysis of the epoxide to form the 5S, 6R, 15S triol, or the 5S, 6S, 15S triol depends upon whether the hydrolysis occurs with inversion or retention respectively at C_6, the more electrophilic carbon of the epoxide. This gives rise to Lipoxin A. Similarly, the broken arrows in Scheme II lead to a 14,15 epoxy tetraene followed by hydrolysis giving Lipoxin B.

Guided by this reasoning we designed a convergent synthesis of the putative epoxide ester precursor to Lipoxin A which upon hydrolysis of the epoxide under basic conditions should produce a vicinal diol as in the natural product.

Commencing with 2-deoxy-D-ribose we prepared the optically pure diene aldehyde 1, an intermediate used for our LTA_4 synthesis.[2] The chiral phosphonium bromide 2, which was utilized in our very recent synthesis of 8,15-diHETEs was derived from D-arabinose via the versatile masked dialdehyde synthon 3.[3] It remained for us to couple these two intermediates using a Wittig reaction to form the conjugated polyene. The phosphorane of 2 was generated at -100°C[4] (2, 1 eq BuLi, THF, 2 min) and aldehyde 1 was added. The reaction was stirred for one minute and HMPA (4 eq) was added in order to promote the rapid decomposition of the intermediate oxy-phosphetane to the olefin. The reaction was gradually allowed to warm to RT over a period of one hour then quenched with 25% NH_4OAc. Extractive workup was followed by purification by flash chromatography on silica gel (5:1 hexanes/EtOAc, 5% TEA) and normal phase HPLC (μporasil column hexanes, 2% TEA) afforded a 2:1 ratio of pure 11-cis and trans epoxy tetratenes 4a and 4b respectively in 50% yield. The silyl protecting group was removed (5 eq nBu_4NF, THF) to give the free 11-cis and trans 15S alcohols 5a and 5b) respectively in 75% yield.These epoxy tetraenes exhibit similar chemical sensitivity as LTA_4, and are stored in hexanes/TEA at -70°C. In addition the UV spectra portray a similar bathochromic shift with respect to the hydrolyzed products (λmax = 309, hexanes).

Finally, conversion of the 11-cis epoxy tetraene to a trihydroxy eicosatetrenoic acid 6 a possible structure for Lipoxin A was achieved via a sequential saponification, and nucleophilic SN_2 opening at C_6 of the epoxide. (0.8N KOH/DMSO, 60°C, 2h)[5,6]. Two products were obtained (ratio 4:1, ≈ 60% yield) and purified by reverse phase HPLC (3:2 $MeOH/H_2O$, 0.1% HOAc). The major compound was treated with diazomethane and isolated as its methyl ester 7, for purposes of characterization.[7] The identical chemical sequence was carried out on the all-trans epoxide isomer to form the corresponding trihydroxy tetraenes.

The work described here represents the first synthesis of two 5, 6, 15S trihydroxy 7-trans, 9-trans, 11-cis, 13-trans eicosatetraenoic acid, and two all-trans isomers, potential structures for Lipoxin A. The natural product described by Samuelsson and co-workers[1b], possesses interesting biological properties including the initiation of superoxide release, inhibition of natural killer cells, and contractile

activity on smooth muscle tissue. Our synthetic product is currently being evaluated with regards to its biological profile and these results will be reported at a later date.

We are currently in the process of synthesizing other geometric and diastereomeric isomers in order to resolve the stereochemical nature of the Lipoxins.

There are of course other bio-synthetic possibilities which we are considering to account for the formation of Lipoxins A and B. With the help of synthetic materials we hope to establish the pathways for the formation of Lipoxins.

References and Notes

1. a) C.N. Serhan, M. Hamberg and B. Samuelsson, Biochem. Biophys. Res. Commun. 118, 943 (1984).
   b) B. Samuelsson and C.N. Serhan, Oral presentations at Prostaglnadins and Leukotrienes '84 meeting, Washington, D.C. May 8 - 11, 1984.
2. J. Rokach, R. Zamboni, C.-K. Lau and Y. Guindon, Tetrahedron Lett. 2759 (1981).
3. B.J. Fitzsimmons and J. Rokach, Tetrahedron Lett. 3043, (1984).
4. The same reaction to from the phosphorane at -78°C occurs with substantial elimination of the vinylogous silyloxy group.
5. The reaction proceeds via an SN_2 mechanism. Ring opening by hydroxide with inversion at C_6 occurs, by analogy to reactions of nucleophiles with LTA_4. However, epoxide opening via an internal displacement by the carboxylate and subsequent hydrolysis of the lactone, inverts the center at C_5 furnishes the 5R, 6S diastereomer. This possibility for the major isomer is being considered.
6. The reaction can be monitored by UV whereby the epoxide acid (λmax = 306 MeOH) is slowly converted to the triol acid (λmax = 301).
7. Spectral characterization of all purified intermediates was obtained using TLC, IR, HPLC, UV and NMR.

UV: Compounds 6 and 7 as well as the all-trans isomers have identical UV profiles to the published spectrum.[1a] (316, 301 λmax, 287 nm; MeOH).

G.C. - M.S. Compound 7 was converted to its tri-TMS derivative and the G.C. - mass spectrum obtained was identical in all respects to the published spectrum.[1a] (M^+ m/e = 582; 100% peak m/e = 203).

^{1}H NMR (250 MHz) The spectra of the tetraenes were diagnostic in the olefin region distinguishing the trans, trans, cis, trans pattern from the all-trans pattern.

Data for 7: (CD_3COCD_3) δ2.30, t, 2H ($\underline{CH_2}CO_2CH_3$, J = 7.5 Hz) δ3.50, m, 1H; δ3.58, s, 3H (Me-ester), δ4.01, m, 1H; δ4.11, m, 1H; δ5.7-5.9, 2 dd, 2H (trans J = 15 and 17 Hz); δ5.93-6.06, AA'BB', 2H (cis); δ6.2-6.4, m, 2H (trans); δ6.6-6.8,m, 2H, (trans).

8. We gratefully acknowledge N.S.E.R.C. Canada for an industrial post-doctoral fellowship to Dr. Fitzsimmons.

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