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THE TOTAL SYNTHESES OF SEVERAL 8, 15 DIHYDROXY ARACHIDONIC ACID DERIVATIVES (8,15, LTB's)

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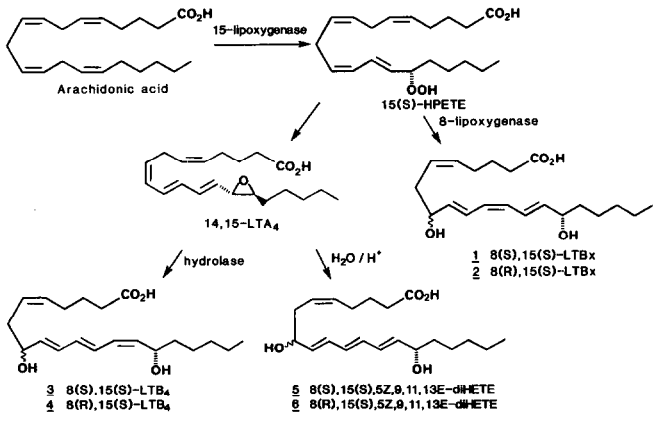
Abstract: The synthesis of the 8S, 15S and 8R, 15S diastereomers of 8,15 dihydroxy 5Z,9E,11E,13Z eicosatetraenoic acid (8,15-LTB_4) and of 8,15 dihydroxy 5Z,9E,11Z,13E eicosatetraenoic acid (8,15-LTB_X) from arabinose are described.

The initial step of the lipoxygenase pathway of arachidonic acid metabolism is its enzymatic oxidation at carbon 5, 8, 9, 11, 12 or 15 to yield the corresponding hydroperoxy derivative. These initial hydroperoxy products, termed HPETEs, are then metabolised further. Of the various arachidonic acid metabolites, those derived from the 5-lipoxygenase pathway have been the most thoroughly studied.

Of the 5-HPETE derived metabolites three types of dihydroxy metabolites, 5,12-diHETEs, have been isolated. The first type is derived from enzymtic hydrolysis of the LTA_4 epoxide to give the 5S,12R 6,8 E-10,13 Z-diHETE, LTB_4. The second type of 5,12-diHETE also arises from hydrolysis of LTA_4, however, in this case the hydrolysis is non-enzymatic giving the 5S, 8R and 5S, 8S-6,8,10 E-13 Z-diHETEs. The third type of 5,12-diHETE is derived from the action of 12-lipoxygenase on 5-HETE. This gives the 5S,12S-6,10 E-8,13Z-diHETE 5,12-LTB_X.

If the pathways of formation of the 5,12-diHETEs are general in nature, then the other HPETEs should give rise to analogous dihydroxy compounds. For example 15-HPETE should be metabolized further to the corresponding 8,15-diHETEs, as shown in Figure 1.

Figure 1



15-HETE has been isolated from many biological systems. For example it is a major metabolite of arachidonic acid in PMN's.[1] Recently 8S,15S-LTB_X 1, isolated from a soyabean lipoxygenase oxidation of arachidonic acid, has been reported to be a potent chemotactic factor.[2] The same compound and its 8R diastereomer 2 have been isolated from porcine leukocytes and human eosinophils.[3]

The 8R and 8S,15S 5Z-9,11,13 E-diHETEs 5 and 6 have been isolated by Samulesson and his collaborators and their presence put forward as proof of the existence of 14,15-LTA_4.[4]

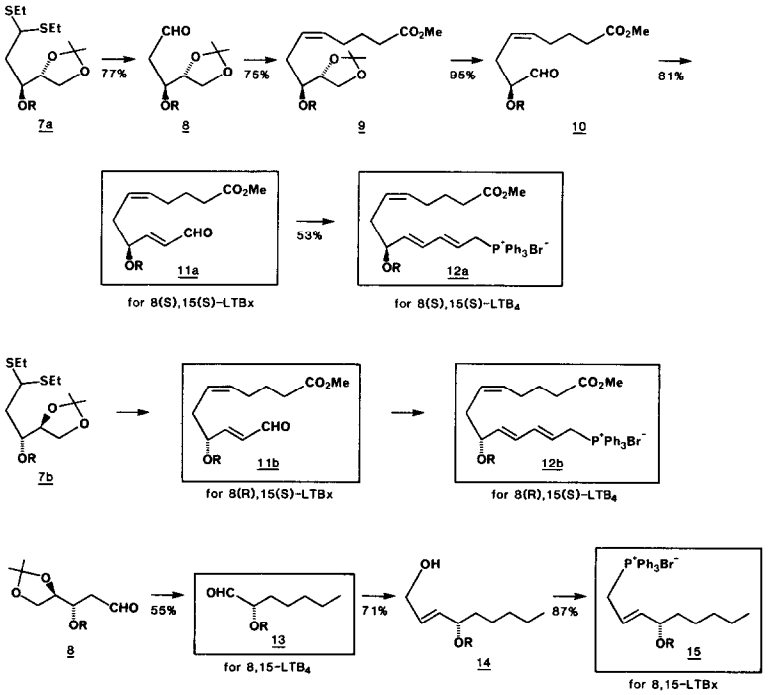
The 8,15-diHETE equivalent of LTB_4 (8,15-LTB_4), has not been reported to date. However, due to the extremely potent chemotactic activity of LTB_4[5] and the obvious structural similarity of the compounds the 8,15 LTB_4s 3 and 4 are compounds of considerable interest.

The 8,15-diHETEs have not been the subject of any reported synthetic effort to date. Due to the reported physiological activity of 8S,15S-LTB_X 1 and the general desire in these laboratories to thoroughly study all important lipoxygenase derived metabolites of arachidonic acid, the six possible 8,15 dihydroxy metabolites of arachidonic acid arising from initial oxidation at C-15 were prepared in optically and chemically pure form.

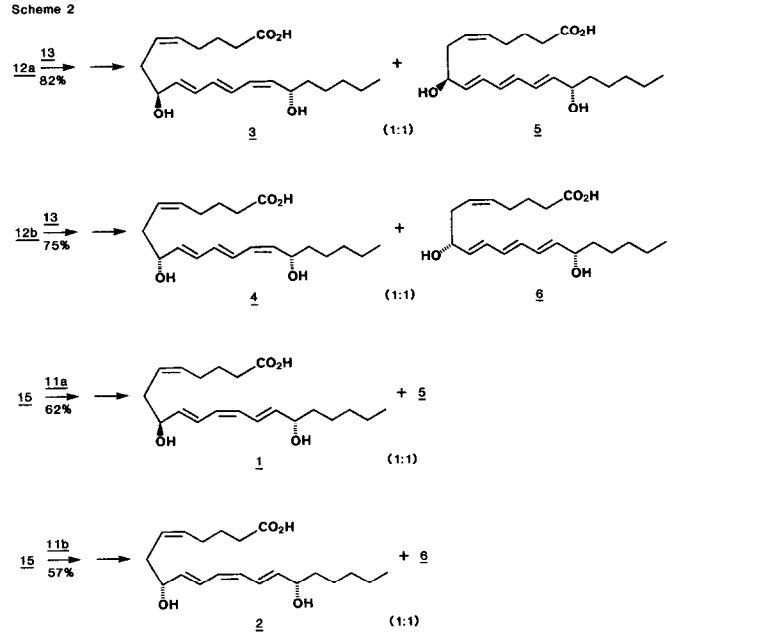
All six diHETEs were envisaged as being available from the enantiomeric arabinose derivatives 7a and 7b[6] as shown in Scheme 1. Hydrolysis of the thioacetal 7a using N-chlorosuccinimide and silver (I) nitrate[6] gave the aldehyde 8 in a 77% yield. Condensation of the aldehyde 8 with the ylide generated by treatment of 5-triphenylphosphium bromide pentanoic acid with 2 equivalents of lithium hexamethyldisilazide (LiHMDS) in THF/HMPA gave, after esterification with excess diazomethane, the ester 9 in a 75% yield. Hydrolysis of the acetonide of the ester 9 in aqueous acid gave the corresponding diol, in a 77% yield, which was treated with lead tetraacetate[6] in dichloromethane at -78°C to give the aldehyde 10 in a 95% yield. Treatment of the aldehyde 10 with 1.1 equivalents of formylmethylenetriphenylphosphorane[7] gave the corresponding , unsaturated aldehyde 11a necessary for the preparation of the 8S-LTB_X in an 81% yield. Homologation of the aldehyde by the method of Okyuama et al[8] and then reduction of the resulting diene aldehyde with sodium borohydride/ceric chloride in isopropanol[9] gave the corresponding diene alcohol in a 57% yield over the two steps. Treatment of the alcohol with DIPHOS and carbon tetrabromide and then treatment of the resulting bromide with excess triphenylphosphine gave the phosphonium salt 12a necessary for the preparation of the 8S,15S-LTB_4 in a 92% yield over the two steps. Similarly 7b was converted into the aldehyde 11b and the phosphonium salt 12b

Treatment of the aldehyde 8 with (1-propylidene)triphenylphosphorane and then hydrogenation of the resulting olefin afforded the alkylated product in a 71% yield. Aqueous hydrolysis of the acetonide and then lead tetraacetate cleavage[6] of the resulting diol gave the aldehyde 13 required for the preparation of the 8,15-LTB_4's in a 77% yield over the two steps. Homologation of the aldehyde 13 by the procedure of Okyuama et al[8] or by treatment with formylmethylenetriphenylphosphorane[7] followed by reduction of the resulting enal with sodium borohydride/ceric chloride[9] afforded the alcohol 14 in a 71% yield. Treatment of the alcohol 14 with DIPHOS and carbon tetrabromide and then treatment of the resulting bromide

Scheme 1



Scheme 2



with excess triphenylphosphine gave the phosphonium salt 15 required for the preparation of the 8,15 LTB_X's in an 87% yield over the two steps.

Condensation of the ylide generated from the phosphonium salt 12 a or b (Scheme 2), by treatment with one equivalent of LiHMDS in THF/HMPA at -78°C, with the aldehyde 13 gave the disilyl 8S,15S-LTB_4 and 8R,15S-LTB_4 methyl esters in 47% and 36% yields respectively plus, as anticipated, approximately equivalent amounts of the protected 8, 15S Z-9,11,13 E-diHETEs. Removal of the silyl protecting groups with tetrabutylammonium fluoride and hydrolysis of the methyl ester with aqueous potassium carbonate afforded the free acids of 8S,15S LTB_4 3 and 8R,15S-LTB_4 4 in yields of 86% and 82% respectively. Similarly the protected 9,11,13 E-diHETEs were converted to the acid diols 5 and 6.

Condensation of the aldehyde 11a or b with the ylide generated from the phosphonium salt 15 (Scheme 2), by treatment with one equivalent of n-butyllithium, at -78°C in THF/HMPA gave only a 12% yield of the desired products. However, if the ylide was generated in the absence of HMPA at -100°C in THF, condensed with the aldehyde and then 5 equivalents of HMPA were added the desired disilyl 8S,15S-LTB_X and 8R,15S-LTB_X methyl esters were obtained in 43% and 39% yields respectively, accompanied by equivalent amounts of the 8,15S 9,11,13 trans diHETEs. Removal of the silyl protecting groups from these compounds utilizing tetrabutylammonium fluoride with two equivalents of acetic acid to prevent decomposition and then hydrolysis of the ester with aqueous base gave the 8S,15S-LTB_X 1 and 8R,15S-LTB_X 2 in yields of 72% and 69% respectively and the 8,15S 5Z,9,11,13E-diHETEs 5 and 6.

In summary, the 8S,15S and 8R,15S diastereomers of 8,15 LTB_4, 8,15 LTB_X and 8,15,5Z 9,11,13E diHETE have been prepared to facilitate the determination of their physiological properties. It is worthwhile noting that all the asymmetric centers in the Six-8,15-diHETEs described here come from synthon 7a and 7b. The biological properties of these diHETEs are currently being investigated and the results will be reported at a later date.

Acknowledgement

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