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SYNTHESIS OF LIPOXIN B

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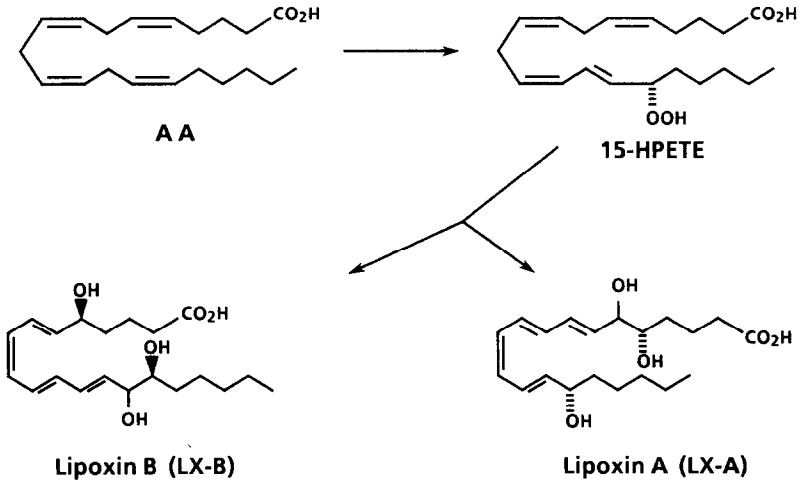
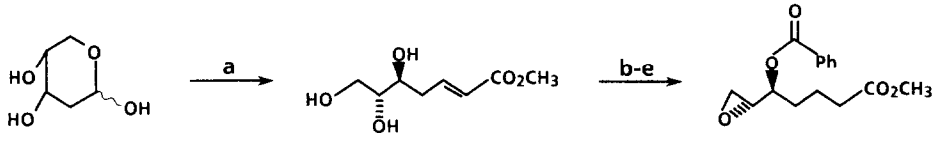
ABSTRACT: *The synthesis of four isomers of 5,14,15-triHETE is reported. The key step is the coupling of acetylene 11 (or 19) with epoxide 7 to afford alcohol 12 (or 20). Natural lipoxin B is found to correspond to a mixture of 14R-8-cis-1, 14R-8-trans-3 and 14S-8-trans-4.*

While studying the relationship between the 5- and 15-lipoxygenase pathways in 1983, Serhan, Hamberg and Samuelsson isolated a novel series of oxygenated arachidonic acid derivatives produced when human leukocytes were treated with exogenous 15-hydroperoxy-5,8,11,13-eicosatetraenoic acid (15-HPETE) in the presence of the calcium ionophore A-23187[1]. Initially, two generic isomeric structures were identified from these studies, namely 5,6,15-trihydroxy-7,9,11,13-eicosatetraenoic acid (5,6,15-triHETE) and 5,14,15-trihydroxy-6,8,10,12-eicosatetraenoic acid (5,14,15-triHETE). Because of their potential formation via multiple lipoxygenation reactions, these metabolites were given the trivial names lipoxin A (LX-A) and lipoxin B (LX-B), respectively. Encouraged by reports of interesting biological activities for these compounds[1,2], much attention has focused on the elucidation of their absolute stereochemistry and olefin geometry[3,4]. With regards to lipoxin B, two different structural assignments have been made[4a,d]. In this paper, we disclose our findings in this area and report the synthesis of four isomers of 5,14,15-triHETE. In contrast with both of the previous claims we find that natural lipoxin B corresponds to a mixture of three of these synthetic isomers.



In choosing specific isomers of 5,14,15-triHETE for total synthesis, we considered a variety of potential biosynthetic pathways for the formation of lipoxin B, all of which assume an initial 5-lipoxygenation of 15-HPETE to produce 5S,15S-diHPETE as a common intermediate[5]. On the basis of this analysis four isomers were targeted for total synthesis, namely, 5S,14R,15S-6,10,12-*trans*-8-*cis*-triHETE (1), 5S,14S,15S-6,10,12-*trans*-8-*cis*-triHETE (2) and the corresponding all *trans* derivatives 3 and 4, respectively. Our strategy was to assemble these molecules via the coupling of an appropriately functionalized C_1-C_7 epoxide with a suitably protected conjugated acetylene (C_8-C_{20}) in which the hydroxyl stereocenters at C-5,14 and 15 were derived from optically pure carbohydrates. Epoxide 7 was synthesized in 5 steps starting from 2-deoxy-D-ribose (5) (scheme 1). This compound, previously described as an intermediate in total syntheses of leukotrienes A_4 and B_4[6], was the C_1-C_7 fragment for all of the lipoxin B isomers.

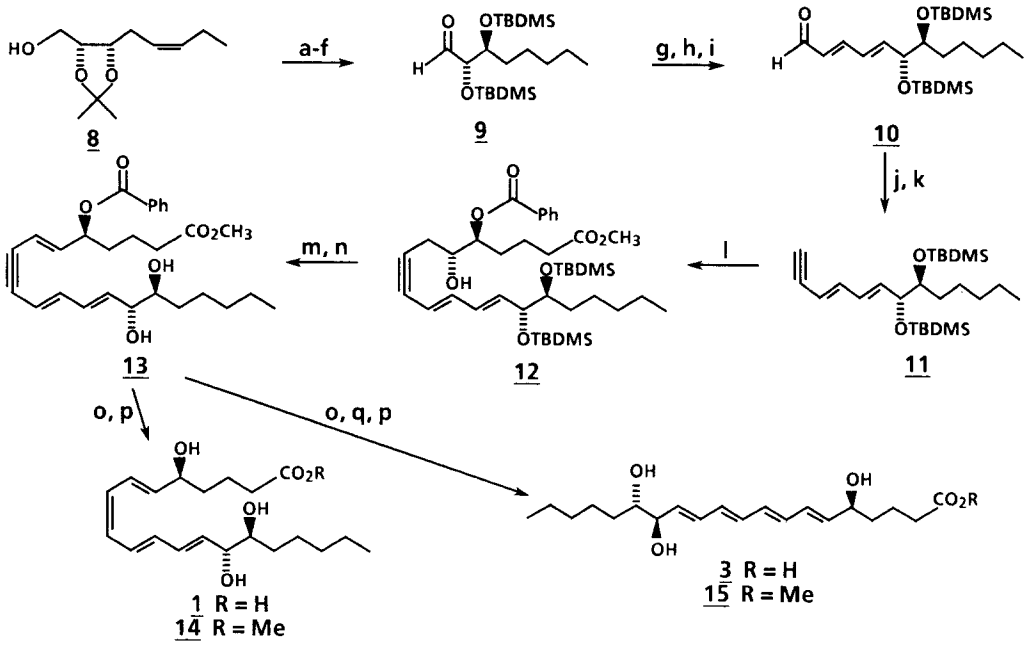


5 6 7

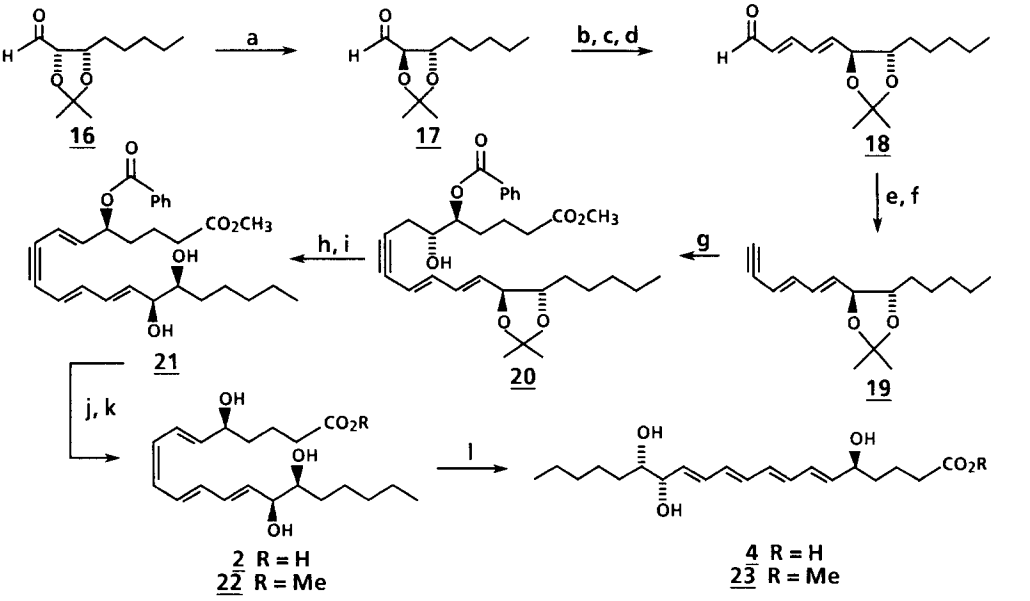
SCHEME 1[17]: *a. $Ph_3P=CHCO_2Me$ b. $C_9H_{11}SO_2Cl$, pyr. c. H_2, Pd/C d. K_2CO_3, MeOH e. PhCOCl, pyr.*

Compound 5 was also the starting material for the synthesis of the C_8-C_{20} acetylenes 11 and 19. Wittig reaction of the acetonide of 2-deoxy-D-ribose with the ylid derived from $nPrPh_3P^+Br^-$ afforded alcohol 8 (82%) which was converted to aldehyde 9 in 69% overall yield (scheme 2)[7]. Treatment of 9 with the lithium anion of *cis*-1-methoxy-1-buten-3-yne (THF, -78°C) afforded the corresponding propargylic alcohol (99%). Reduction with with Red-Al ($PhCH_3$,-78 to 0°C)[9,10] gave the diene (*cis, trans*) which upon treatment with MsCl (Et_3N, THF, -40°C) followed by aqueous hydrolysis afforded dienealdehyde 10 in 30% yield[8]. Wittig reaction of 10 with the ylid prepared from $ClCH_2Ph_3P^+Cl^-$ (THF, 0°C) gave a mixture of chloroolefins (96%) which when exposed to LDA (THF,0°C) produced acetylene 11 (87%). Following the conditions described by Yamaguchi[11], succesive treatment of acetylene 11 with *n*BuLi and $BF_3{\cdot}OEt_2$ followed by the addition of epoxide 7 (THF, -78°C) afforded a 60% yield of alcohol 12 along with 23% of unreacted 11. Reaction of 12 with MsCl (Et_3N, THF, -10 to 23°C) followed by treatment of the corresponding mesylate in situ with DBU gave an 8:1 mixture of 6-*trans*/6-*cis* olefins in which the major isomer was isolated in 57% yield (>98% purity). Deprotection with nBu_4NF (3 eq. THF, 25°C) afforded diol 13 in 73% yield. Semihydrogenation of 13 was carried out using 5% $Pd/CaCO_3$ (Lindlar) in 5% pyridine/EtOAc to give a 50% yield of the 8-*cis* tetraene after purification by RP-HPLC. Removal of the benzoate with K_2CO_3 in methanol afforded methyl ester 14. Alternatively, hydrolysis of the benzoate methyl ester with LiOH followed by acidification to pH 3.5 with aqueous $KHSO_4$ gave acid 1 (89%). Isomerization of the 8-*cis* olefin with iodine (CH_2Cl_2) afforded the corresponding all *trans* benzoate methyl ester. Hydrolysis as above gave the all *trans* methyl ester 15 and acid 3, respectively.

In order to use this same methodology to synthesize the corresponding 14S isomers, acetylene 19 was required. Hydrogenation (5%Pd/C, EtOAc) of alcohol 8 followed by Swern[12] oxidation afforded aldehyde 16 (80%). Following a similar example reported by Sharpless[13], treatment of 16 with K_2CO_3 in methanol resulted in a clean epimerization of the α-alkoxy center giving aldehyde 17. Conversion of 17 to dienealdehyde 18 (73%) and on to acetylene 19 (53%) was accomplished by the same sequence as described for the 14R case (scheme 3). Sequential treatment of 19 with n-BuLi and $BF_3{\cdot}OEt_2$ as before followed by the addition of epoxide 7 gave a 63% yield of the coupled product 20 along with 22% un-



SCHEME 2[17]: *a. PhCOCl, pyr. b. H_2, Pd/C c. aq. HCl d. TBDMsCl, imd., DMF e. Dibal, CH_2Cl_2, -78°C f. CrO_3·2 pyr. g. LiC≡CCH=CHOMe, THF, -78°C h. Red-Al i. MsCl, Et_3N, H_2O j. $ClCH_2PPh_3Cl$, nBuLi k. LDA, THF, 0°C l. nBuLi, BF_3·OEt_2; 7, -78°C m. MsCl, Et_3N; DBU n. nBu_4NF o. H_2, Lindlar, 5% pyr/EtOAc p. K_2CO_3, MeOH or LiOH; $KHSO_4$ q. I_2, CH_2Cl_2*



SCHEME 3[17]: *a. K_2CO_3, MeOH b. LiC≡CCH=CHOMe c. Red-Al d. MsCl, Et_3N; H_2O e. $ClCH_2PPh_3Cl$, nBuLi f. LDA, THF, 0°C g. nBuLi, BF_3·OEt_2; 7, -78°C h. MsCl, Et_3N; DBU i. 80% HOAc, H_2O j. H_2, Lindlar, 5% pyr/EtOAc k. K_2CO_3, MeOH or LiOH; $KHSO_4$ l. I_2, CH_2Cl_2*

reacted 19. Elimination of the C-6 hydroxyl group (MsCl, THF; DBU) gave the enyne (85%) as a 9:1 mixture of 6-*trans*/6-*cis* isomers. Removal of the acetonide with 80% aqueous acetic acid (55°C, 84%) afforded diol 21. Semihydrogenation as above produced a 30% yield of the desired 8-*cis* tetraene after purification by RP-HPLC. Hydrolysis with LiOH followed by acidification to pH 3.3 (aq. $KHSO_4$) gave acid 2 in 87% yield. Alternatively, the benzoate was removed with K_2CO_3 in methanol to afford methyl ester 22. Isomerization of 22 with iodine (CH_2Cl_2) produced the corresponding all *trans* methyl ester 23.

Comparisons of the methyl esters of the synthetic lipoxin B isomers were made by RP-HPLC with a sample of natural lipoxin B methyl ester prepared by Dr. Charles Serhan of the Karolinska Institutet[14]. In 65/35 methanol/water (Ultrasphere-ODS, 250x10mm, 3.0mL/min, 300nm) natural lipoxin B appears as a mixture of three components at 34.3, 36.1 and 37.0 min in a relative ratio of 3:5:2, respectively. In coinjection experiments with the synthetic isomers, 5S,14S,15S-6,8,10,12-*trans*-triHETE methyl ester (23) was found to coelute with the natural material at 34.3 min. Similarly, 5S,14R,15S-6,8,10,12-*trans*-triHETE methyl ester (15) coeluted with the natural material at 36.1 min and 5S,14R,15S-6,10,12-*trans*-8-*cis*-triHETE methyl ester (14) matched the third natural component at 37.0 min[15]. These results strongly suggest the structures for the natural lipoxin B isomers as indicated[16]. The discrepancy between our assignments and those previously reported clearly must reside in the source of the natural material. There is recent evidence to suggest that the 14R-8-*cis* isomer 1 undergoes at least partial isomerization during the isolation process[5]. This may explain the failure of at least one group[4a,b] from detecting significant amounts of 1 in their sample of natural lipoxin B.

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14. We thank Drs: C.N. Serhan and B. Samuelsson for providing a sample of natural lipoxin B.

15. By comparison, 5S,14S,15S-6,10,12-*trans*-8-*cis*-triHETE methyl ester (22) had a retention time of 61.0 min. under these RP-HPLC conditions.
16. The possibility that other 5,14,15-trihydroxytetraenes may have similar retention times cannot be ruled out.
17. Satisfactory spectroscopic data were obtained for each reaction product.

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