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TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE METABOLITES OF ARACHIDONIC ACID. THE TWO 8-HYDROXY-11,12(S,S)-EPOXYEICOSA-5,14(Z),9(E)-TRIENOIC ACIDS.

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Summary: An efficient and simple total synthesis of the two C(8) diastereomers of 3, of interest as possible hormonal releasing agents, is described.

A previous publication from this laboratory has described the synthesis of the two diastereomeric 10-hydroxy-11,12(S,S)-epoxyeicosa-5,9,14(Z)-trienoic acids (1) and their identity with two new metabolites of arachidonic acid produced in mammalian blood platelets.[1] These substances are evidently produced from 12-(S)-HPETE (2) by a hydroperoxide → oxiranylcarbinol rearrangement.[2,3] A supernatant protein fraction from rat lung has been found recently to convert arachidonate or 2 to a mixture of what is probably the two diastereomers of 1 and another pair of isomeric epoxides which have been formulated as 8-hydroxy-11,12-epoxyeicosa-5,9,14-trienoic acids.[4] The latter pair of metabolites are of considerable interest since they are also produced in pancreatic islet cells where they are capable of stimulating insulin release in the presence of glucose.[5] These substances, termed "hepoxylins," which on biogenetic grounds are surmised to be the 8-diastereomeric 8-hydroxy-11,12(S,S)-epoxyeicosa-5,14(Z),9(E)-trienoic acids (3), have not been obtainable in sufficient amount for rigorous chemical identification or detailed biological study and hence their synthesis assumes some urgency. A simple and practical synthesis of 3 is described herein. This convergent route uses as one component a now standard intermediate for the synthesis of leukotriene B_4,[6] the chiral epoxy aldehyde 9, and as the other achiral bromo ketone 7.

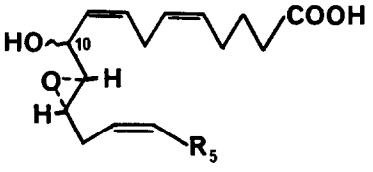
5-Hexynoic acid (from commercially available 5-hexyn-1-ol in 76% yield by oxidation with a small excess of Jones reagent at 0°) was converted in 88% overall yield to methyl non-5-yn-8-enoate (4) by the sequence: (1) treatment with two equiv of ethyl magnesium bromide in tetrahydrofuran (THF)[7] at 0° to form the magnesio acetylide of magnesium 5-hexynoate, (2) addition of 0.05 equiv of purified cuprous bromide, (3) reaction with 1 equiv of allyl bromide at 0° for 15 min and then at reflux for 8 hr, (4) extractive isolation and esterification of the resulting acid with diazomethane, and (5) removal of solvent and column chromatography on silica gel using 4 : 1 hexane - ether as eluent. The ester 4 was epoxidized selectively to the corresponding 8,9-oxide (89%) by reaction with m-chloroperbenzoic acid in methylene chloride (2 equiv, 23°, 4 hr) and this was reduced by exposure to hydrogen (1 atm) in the presence of Lindlar catalyst

(5% Pd on $CaCO_3$) in THF solution at 23° for 45 min to give the Z-olefinic epoxy ester 5 in 99% yield. The hydrogenation was monitored by silica gel thin layer chromatography (sg-tlc) with the olefin 5 (blue spot with anisaldehyde-sulfuric acid stain) having higher R_f than the starting epoxy acetylene (green spot) using 1 : 1 hexane-ether as eluent. The epoxide 5 was converted cleanly to methyl 9-bromo-8-hydroxy-non-5(Z)-enoate (6, 99%) by reaction with 2 : 1 : 1 acetic acid-saturated aqueous potassium bromide-THF for 10 hr at 0°. Oxidation of the bromohydrin 6 by Jones reagent at 23° for 1.5 hr afforded the sensitive bromo ketone 7 in 92% yield (R_f 0.67, sg-tlc using 9 : 1 methylene chloride-ether), IR $_{max}$ at 1740, 1720 $cm.^{-1}$ (film). The bromo ketone 7 was transformed into the corresponding triphenylphosphonium salt (8) using 1 equiv of triphenylphosphine in chloroform at reflux for 3 hr. The solution of 8 in chloroform was shaken with 1 N aqueous sodium hydroxide at 23° for 3 min and the resulting ylide was isolated by removal of solvent from the chloroform layer and then without delay allowed to react in benzene solution with the aldehyde 9[6] at 23° for 10 hr. Removal of solvent and column chromatography at 0° on silica gel using 3 : 2 hexane-ether as eluent gave the epoxy enone 10 as an oil in 80% yield, UV_{max} 232 nm in methanol, $[\alpha]_D^{23}$ - 32.7° (c = 1.94 in benzene), IR $_{max}$ 1740, 1680, 1635 $cm.^{-1}$ (film). The proton magnetic resonance spectrum of 10 (in C_6D_6 at 270 MHz) showed characteristic peaks for the proton at C(10) (6.52 δ, dd, J 15.8, 6.6 Hz, 1H) and that at C(9) (6.35 δ, d, J 15.8 Hz, 1H) confirming the expected E geometry of the newly formed double bond. The four 5,14Z olefinic protons which appeared as a multiplet at 5.80 - 5.40 δ were absent in the spectrum of 5,6,14,15-tetradeuterio 10. The 7-methylene protons appeared as a doublet (3.03 δ, J 6.6 Hz) in 10 but as a singlet in 5,6,14,15-tetradeuterio 10.

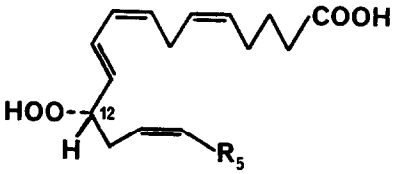
Reduction of epoxy enone 10 with sodium borohydride in methanol at -40° for 10 min afforded after extractive isolation and chromatography the 8-epimeric alcohols of 3 methyl ester having sg-tlc R_f values of 0.38 and 0.33 using 85 : 15 benzene-ether containing 1% triethylamine and three developments.[8] The two diastereomers were separated preparatively by flash column chromatography on 230-400 mesh Merck silica gel 60 using 85 : 15 benzene-ether for elution.[9] The EI mass spectrum of the trimethylsilyl ether of 3 methyl ester showed in addition to the molecular ion at (m/e) 422, fragments at 243 and 281 as previously reported for the native metabolite.[4] These peaks were shifted in the spectrum of the 5,6,14,15-tetradeuteriated compound to 426, 245, and 283.

The synthesis of 5,6,14,15-tetradeuterio 3 methyl ester was carried out to provide a standard for the quantitative determination of hepoxylins in biological samples by GC-MS analysis. The same process was used as for the preparation of unlabeled 3 except for the substitution of deuterium gas in the generation of 5 from the corresponding acetylene and in the synthesis of 9 which also involved Lindlar reduction of a triple bond to the Z double bond.

Biological studies using the two C(8) diastereomers of 3 are currently underway in the laboratories of Dr. Pace-Asciak. If biological activity is confirmed, as we expect, much interesting research should follow.[10]



1



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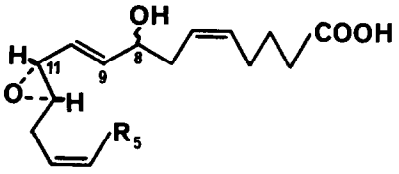


3

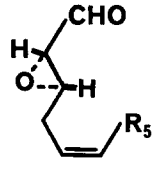
4

5

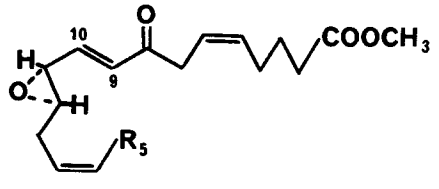
6

7 X = Br

8 X = $\overset{+}{P}Ph_3$



9



10

$R_5 = C_5H_{11}$

References and Notes

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7. All reactions involving air or moisture sensitive substances were conducted with the usual exclusionary precautions. Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained on chromatographically purified samples of each isolated intermediate.
8. R_f values of the two diastereomers of 3 were approximately the same by sg-tlc using 9 : 1 benzene-ethyl acetate with three developments.
9. The following proton magnetic resonance data (270 MHz, C_6D_6 solvent, δ) were obtained for 3 methyl ester: 5.88 (dd, J 5.61, 15.5 Hz, 1H); 5.52 (m, 5H); 4.00 (m, 1H); 3.38 (s, 3H); 3.10 (d, J 7.61 Hz, 1H); 2.78 (m, 1H); 2.25 (m, 4H); 2.12 (t, J 7.25 Hz, 2H); 2.00 (m, 2H); 1.60 (m, 2H); 1.27 (m, 6H); 0.92 (t, J 6.26 Hz, 3H). 5,6,14,15-Tetradeuterio 3 methyl ester should absorption at 5.52 δ as dd, J 7.91, 15.2 Hz, 1H.

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