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AN EFFICIENT AND SIMPLE METHOD FOR THE CONVERSION OF 15-HPETE TO 14,15-EPETE (LIPOTRIENE A) AND 5-HPETE TO LEUKOTRIENE A AS THE METHYL ESTERS

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Summary: Simple new methodology is described for the synthesis from arachidonic acid of the important eicosanoids lipotriene A methyl ester (5) and leukotriene A methyl ester (10), a key feature being the use of a novel chemical method for effecting the allylic hydroperoxide ⟶ oxiranyl carbinol rearrangement.

Previous papers from this laboratory have described both chemical and enzymatic methods for the conversion of arachidonic acid to the methyl ester of leukotriene A (10) via the methyl ester of 5(S)-hydroperoxy-6(E)-8,11,14(Z)-eicosatetraenoic acid (5-HPETE) (6).[1,2] In addition a similar approach has been used for the transformation of arachidonic acid via the methyl ester of 15-HPETE (1) to the methyl ester of 14,15-EPETE (5),[3,4] which was recently given the name lipotriene A in recognition of its now apparent biological significance.[5] These processes, especially useful in biological laboratories where only microgram or milligram amounts of leukotrienes are needed, leave something to be desired since they require expertise which many biological workers do not possess. For this reason we have developed new methodology designed to be easily usable by workers who are not specialists in synthesis. The methyl ester of 15-HPETE (1) is easily prepared from arachidonate by the use of soybean lipoxygenase and air in aqueous medium[7] followed by esterification with ethereal diazomethane. The new synthesis of lipotriene A methyl ester (5) which has been developed starts with 1 and follows a three-step route. The key step process is a remarkably efficient hydroperoxide ⟶ oxiranyl carbinol rearrangement which can be effected via trifluoroacetylated intermediates. Reaction of 1 with trifluoroacetic anhydride in the presence of 2,6-lutidine in methylene chloride solution affords cleanly the epoxy trifluoroacetate 2 which upon exposure to potassium carbonate in methanol gives the hydroxy epoxide 3 in 99% overall yield. Mesylation of 3 with methanesulfonylchloride-triethylamine in methylene chloride at -78° produces the corresponding epoxy mesylate 4 which without isolation is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to effect elimination with the formation of lipotriene A (5) in 70-85% yield. The following procedure was used.

Methyl ester of Lipotriene A (5): 15-HPETE methyl ester (45 mg, 0.129 mmol) was dissolved in 20 ml of dry dichloromethane under nitrogen and cooled to -78°. To the resulting solution was added dry 2,6-lutidine (90 μl, 6 equiv) followed immediately by freshly distilled trifluoroacetic anhydride (55 μl, 3.0 equiv). After 30 min at -78° the reaction was quenched with 5% sodium bicarbonate (0.5 ml). The solution was diluted with 60 ml of ether and washed successively with sodium bicarbonate (5 ml), 1N

hydrochloric acid (5 ml) and saturated sodium chloride. Drying over magnesium sulfate, filtration, and concentration afforded crude trifluoroacetate.

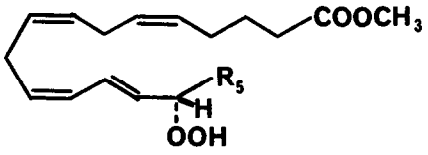
The trifluoroacetate was dissolved in 5 ml of dry methanol under nitrogen and cooled to 0°. Anhydrous potassium carbonate (~5.0 mg) was added under argon. The mixture was stirred vigorously at 0° for 30 min. Dilution with 10 ml of ether, filtration through silica gel (ca. 1 g) and evaporation in vacuo yielded the epoxy alcohol (44.5 mg, 99%). The epoxy alcohol was used in the next step without further purification. Tlc analysis of this alcohol revealed that it is the erythro isomer without detectable amounts (< 5%) of the threo epoxy alcohol, using authentic samples[7] for comparison.

The epoxy alcohol (44.5 mg, 0.127 mmol) was twice dried azeotropically with benzene (at 20 mm) and dissolved in 4 ml of dry dichloromethane under dry nitrogen. The resulting solution was cooled to -78° and triethylamine (71 μl, 4.0 equiv) was added with stirring. After 1 min at -78°, freshly distilled methanesulfonyl chloride (24.6 μl, 2.5 equiv) was added. After stirring at -78° to -60° for 1.0 hr, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 0.38 ml, 20 equiv) was added and then the reaction mixture was allowed to warm to 0° over a period of 3.0 hr. The reaction was quenched with 0.1 ml of saturated aqueous potassium bicarbonate solution and dried over sodium sulfate. Filtration through triethylamine deactivated silica gel (1 g), concentration and column chromatography on silica gel (20g, 230-400 mesh Merck 60) at 4° using 1 : 4 ether-hexane containing 5% triethylamine as eluent afforded pure methyl ester of lipotriene A (5). The yields ranged from 70% - 85% based on starting 15-HPETE.

Lipotriene A methyl ester shows UV_{max} in methanol at 268, 277 and 288 nm and an HPLC R_v of 3.83 using a DuPont Zorbax analytical column with 100 : 0.8 : 0.8 hexane-ethylacetate-triethylamine for elution.[8] The methyl ester 5 can be stored safely at -20° in frozen benzene containing a little triethylamine. Saponification of the methyl ester to give an alkaline solution of lipotriene A can be effected in 20 : 1 ethanol-1N aqueous sodium hydroxide (4 equiv) at 23° for 2.5 hr under nitrogen.

(±)-Leukotriene A (10) was synthesized in a similar way starting (±)-5-HPETE methyl ester (6).[9] The azeotropically dried methyl ester 6 under nitrogen was treated with 5 equiv of dry 2,6-lutidine and 3 equiv of trifluoroacetic anhydride in methylene chloride at -78° for 30 min to give after quenching with aqueous sodium bicarbonate and extractive workup 95% of the epoxy-trifluoroacetate 7. This was directly converted by methanolic potassium carbonate (0°, 30 min) to the epoxy alcohol 8, obtained as a mixture (ca. 1 : 1) of C(7) diastereomers as indicated by tlc analysis on a silica gel plate and also pmr. Chromatography on silica gel using 65 : 35 ether-hexane for development afforded 92% of pure epoxy alcohols 8. These diastereomers were dehydrated by conversion to epoxy mesylate (9) and subsequent DBU-catalyzed elimination essentially as described above. Preparative thin layer chromatography of the crude product on a silica gel plate at 4° using 25 : 75 : 5 ether-hexane-triethylamine for elution provided the methyl ester of leukotriene A (10) in 77% yield. The operations involved in this synthesis follow closely those indicated in the above described procedure for the preparation of 5.

It is noteworthy that whereas the trifluoroacetic anhydride promoted rearrangement of 1 to 2 was highly (> 95%) stereoselective for the erythro isomer, the corresponding rearrangement of (±)-5-HPETE methyl ester (6) to 7 was non-stereoselective. The reason for this difference is not clear at present.



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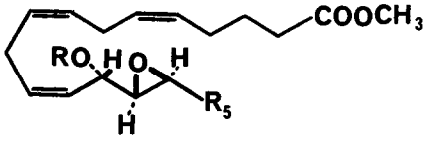
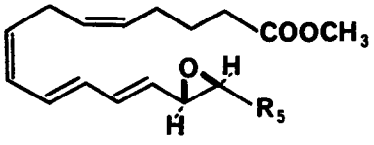


2 R=CF_3CO

3 R=H

4 R= $-SO_2CH_3$



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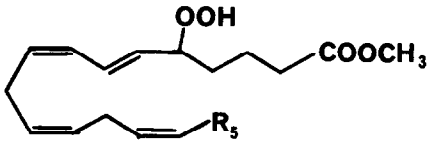

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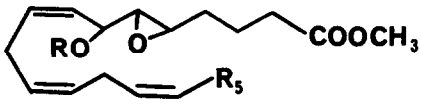
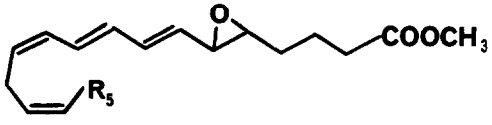


7 R=CF_3CO

8 R=H

9 R= $-SO_2CH_3$



10

$R_5 = C_5H_{11}$

The stereochemical sense of the trifluoroacetyl promoted rearrangement of 1 to 2 is opposite to that for the corresponding rearrangement catalyzed by soybean lipoxygenase.[7] In the trifluoroacetyl induced rearrangement two oxygens are added trans to the 13,14-double bond whereas in the lipoxygenase catalyzed process two oxygens are added cis to the 13,14-double bond.

A number of other catalysts were found to promote the hydroperoxide→oxiranyl carbinol rearrangement of 1. The following table summarizes the salient results. The trifluoroacetic anhydride induced rearrangement is clearly the method of choice.[10]

Rearrangement of 1 to 3

Reagent (1 eq)	Conditions	Yield	Erythro/Threo
$Zn(OSO_2CF_3)_2$	CH_2Cl_2, 4°, 48 hr	50%	0 : 100
$Zn(OSO_2CF_3)_2$	4 : 1 CH_2Cl_2 - CH_3NO_2, 4°, 14 hr	60%	25 : 75
$Zn(OCOCF_2CF_3)_2$	CH_2Cl_2, 4°, 24 hr	60%	10 : 90
SnF_4	4 : 1 CH_2Cl_2 - CH_3NO_2, 4°, 24 hr	55%	25 : 75
SeO_2	CH_2Cl_2, 4°, 6 hr	70%	35 : 65

References and Notes

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3. E. J. Corey, A. Marfat, and G. Goto, J. Am. Chem. Soc., 102, 6607 (1980).
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8. PMR data for 5 methyl ester (270 MHz in $CDCl_3$, δ): 6.50 (m, 2H); 6.21 (m, 1H); 6.00 (m, 1H); 5.40 (m, 5H); 3.67 (s, 3H); 3.15 (dd, 1H); 2.95 (dt, 1H); 2.85 (m, 2H); 2.33 (t, J 7.58Hz, 2H); 2.15 (m, 2H); 1.75 (m, 2H); 1.35 (m, 8H); 0.90 (t, 3H).
9. (a) E. J. Corey, J. O. Albright, A. E. Barton, and S. Hashimoto, J. Am. Chem. Soc., 102, 1435 (1980); (b) E. J. Corey and S. Hashimoto, Tetrahedron Letters, 22, 299 (1981).

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