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THE SYNTHESIS OF THIALEUKOTRIENE A_4

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Summary: A convenient method for synthesizing (±)-3-thialeukotriene A_4 and its derivatives has been developed.

The syntheses of (±)-3-thialeukotriene A_4 and its derivatives have been realized to carry on the studies into the synthesis of modified leukotrienes A_4-E_4. The key synthon was represented by (±)-methyl 10-formyl-3-thia-5,6E-epoxy-7E,9E-decadienoate <u>1</u> obtained as follows. The reaction of 1-chloro-4-acetoxy-2E-butene[1] with the equimolar amount of sodium methylthioglycolate (dimethyl formamide, 20°C, 24 h) led to the methyl 3-thia-7-acetoxy-5E-heptenoate <u>2</u> in a 85% yield. IR cm^{-1}: 980, 1250, 1680, 1735; ^1H NMR ($CDCl_3$) p.p.m.: 2.07 s(3H), 3.18 s(2H, C^2), 3.28 d(2H, C^4, J=7.5 Hz), 3.75 s(3H, OCH_3), 4.75 d(2H, C^7, J=8 Hz), 5.75 m(2H, $C^{5,6}$).

The treatment of <u>2</u> with 5% HCl in methanol (20°C, 30 min) resulted in a quantitative yield of hydroxy-ester <u>3</u>, further oxidized by CrO_3-2Pyr in CH_2Cl_2 (0°C, 1 h) into aldehydoester <u>4</u> in a 90% yield. IR cm^{-1}: 920, 980, 1620, 1700, 1730, 2750. ^1H NMR ($CDCl_3$) p.p.m.: 3.18 s(2H, C^2), 3.51 d(2H, C^4, J=8 Hz), 3.74 s(OCH_3), 6.12-7.05 m(2H, $C^{5,6}$), 9.66 d($\underset{\diagdown H}{C{=}O}$, J=10 Hz).

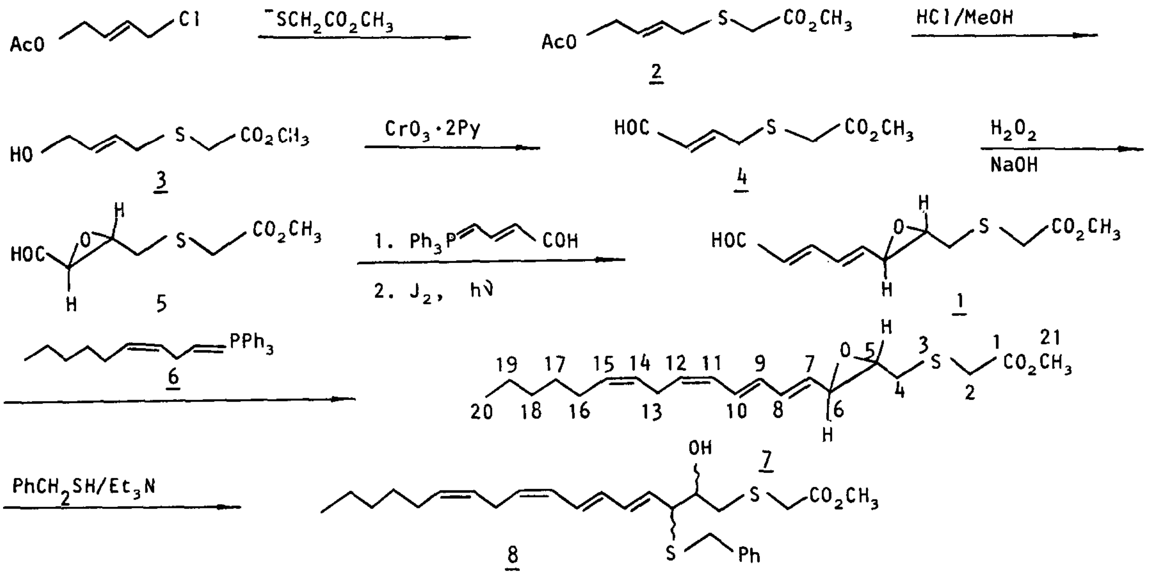
Epoxydation of the aldehydoester by alkaline hydrogen peroxide under standard conditions (30%, H_2O_2, 1N NaOH, in MeOH, at -25°C, 20 min, and at 20°C, 20 min) proceeds quite readily to give quantitatively methyl 3-thia-5,6E-epoxy-6-formyl-hexanoate <u>5</u>, ^1H NMR ($CDCl_3$) p.p.m.: 2.75-3.02 m(2H, $C^{5,6}$), 3.18 s(2H, C^2), 3.54 d(2H, C^4, J=6 Hz), 3.75 s(OCH_3), 9.54 d($\underset{\diagdown H}{C{=}O}$, J=11 Hz).

Condensation of <u>5</u> with triphenylphosphoronylidene-crotonaldehyde[2] leads to a mixture of 7Z- and 7E-epoxydienals (70%), which was then isomerized without any subsequent purification: the mixture (100 mg) with J_2 (3 mg) and CH_2Cl_2 (5 ml) was irradiated by a day-light lamp for 24 h. As a result, the key synthon <u>1</u> was produced in a practically quantitative yield. The product was purified by crystallization from the mixture of hexane-ether and was individual according to HPLC data; m.p. 78-80°C. UV λ_{max}^{EtOH}: 278 nm(ε 27500); IR cm^{-1}: 920, 980, 1650, 1700, 1740, 2745; ^1H NMR ($CDCl_3$) p.p.m.: 2.88 d(2H, C^4, J=6 Hz), 3.21 td(H, C^5, $J_{5,4}$=5.3 Hz, $J_{5,6}$=3 Hz), 3.39 s(2H, C^2), 3.48 dd(H, C^6, $J_{6,5}$=3 Hz, $J_{6,7}$=7 Hz), 3.78 s(OCH_3), 6.01 dd(H, C^7, $J_{7,6}$=7 Hz, $J_{7,8}$=15 Hz), 6.19 dd(H, C^{10}, $J_{10,9}$=15 Hz, $J_{10,11}$= 7.5 Hz), 6.69 dd(H, C^9, $J_{9,8}$=11 Hz, $J_{9,10}$= 15 Hz), 7.14 dd(H, C^8, $J_{8,9}$=11 Hz, $J_{8,7}$=15 Hz), 9.67 d(CHO , J=7.5 Hz).

Condensation of <u>1</u> with phosphorane <u>6</u> in THF-HMPTA with the use of n-C_4H_9Li (-78°C, 40 min) resulted in an almost quantitative yield of (±)-3-thialeukotriene A_4 <u>7</u>. The product was purified by HPLC[3] from the admixture of 11E-isomer. UV λ_{max}^{EtOH}: 274, 280, 292 nm(ε 29700, 34300, 25300); ^1H NMR ($CDCl_3$) p.p.m.: 0.89 t(3H, C^2, J=6 Hz), 1.64 m(6H, C^{17}, C^{18}, C^{19}), 2.30 m(2H, C^{16}), 2.85 d(2H, C^4, J=6 Hz), 3.12 m(2H, C^{13}), 3.20 td(H, C^5, $J_{5,4}$=6 Hz, $J_{5,6}$=2.5 Hz), 3.33 s(2H, C^2), 3.41 dd(H, C^6, $J_{6,5}$=2.5 Hz, $J_{6,7}$=7.5 Hz), 3.74 s(OCH_3), 5.16-6.74 m(8H, C^{7-12}, $C^{14,15}$).

^{13}C NMR JEOL-FX-90Q (22.50 MHz), ($CDCl_3$): 14.10 q(C^{20}), 22.58 t(C^{19}), 26.31 t(C^{13}), 27.29 t(C^{16}), 29.31 t(C^{17}), 31.53 t(C^{18}), 33.36 t, 33.75 t(C^2, C^4), 52.55 q(C^{21}), 58.36 d, 59.85 d(C^5, C^6), 126.83 d, 128.21 d, 128.79 d, 131.14 d, 131.99 d, 132.12 d, 135.38 d(C^7-C^{12}, C^{14}, C^{15}), 170.64 s(C^1).

The treatment of 7 with benzyl mercaptan gives rise to methyl ester of (±)-3-thia-5-oxy-6-thiobenzyl-7E, 9E, 11E, 14Z-eicosatetraene acid 8 [4] in a 90% yield as a mixture of diastereoisomers (1:1). UV λ_{max}^{EtOH}: 272, 284, 295 nm (ε 36600, 44300, 38100). ^1H NMR ($CDCl_3$) p.p.m.: 0.92 t (3H, C^{20}, J=6 Hz), 1.37 m($C^{17,18,19}$), 2.15 m(2H, C^{16}), 2.67-3.15 m(2H, $C^{5,6}$, 2H, C^{13}), 3.30 s (2H, C^2), 3.59 d(2H, C^4, J=6 Hz), 3.79 s(OCH_3), 5.20-6.58 m(8H, $C^{7,8,9,10,11,12,14,15}$), 7.30 s (5H, Ar).



REFERENCES

1. 1-Chloro-4-acetoxy-2E-butene was obtained by acetolysis of 1,4-dichlorobutene (AcONa, AcOH, 120°C, 5 h) in a 45% yield.
2. J.Ernest, A.J.Main, R.Menasse. Tetrahedron Letters, 167-170 (1982).
3. HPLC on a Du-Pont 8800. Zorbax-Sil column (25 x 0.45 cm); hexane ethyl acetate in a 8:2 ratio was employed as an eluent (retention vol.: 7.7 min).
4. Satisfactory results of the elemental analysis and of mass number were obtained for new compounds 2, 3, 4, 5, 7, and 8.

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