A TOTAL SYNTHESIS OF LEUKOTRIENE F4 (LTF4)

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Abstract The synthesis of LTF $_{4}$ via the reaction of (\pm)-leukotriene A $_{4}$ (LTA $_{4}$), methyl ester 1 with the protected glutamylcysteine 2 is reported

The leukotrienes LTC4, D4 and E4 are a recently discovered family—of arachidonic acid metabolites which are thought to be involved in certain hypersensitivity reactions including allergic asthma 1 . It was recently disclosed 2 that incubation of LTE4 with σ -glutamyl transpeptidase, in the presence of glutathione, produces a new leukotriene (LTF4) possessing a σ -glutamylcysteine residue—The biological activity of this new leukotriene was, however, not given—We now wish to report a total synthesis of LTF4 via the reaction of (\pm)-leukotriene A4, methyl ester σ with the protected glutamylcysteine σ , thus making this new leukotriene accessible for further study—The ease of synthesis of σ is particularly noteworthy, and the methods described herein should be applicable to other areas of peptide chemistry in which the formation of a σ -glutamyl peptide bond is required

ROC NHCOCF₃

$$\overset{\bullet}{\overline{C}O_2R^1}$$
4 . R = OH R^1 = CH₃

$$\overset{\bullet}{\underline{C}O_2CH_3}$$
 $\overset{\bullet}{\overline{C}O_2CH_3}$

$$\overset{\bullet}{\underline{C}O_2CH_3}$$

$$\overset{\bullet}{\underline{C}O_2CH_3}$$

$$\overset{\bullet}{\underline{C}O_2CH_3}$$

$$\overset{\bullet}{\underline{C}O_2CH_3}$$

$$\overset{\bullet}{\underline{C}O_2CH_3}$$

$$\overset{\bullet}{\underline{C}O_2CH_3}$$

Treatment of L-glutamic acid with an excess of trifluoroacetic anhydride gave a 55% yield of the anhydride $3^{4,5}$ which was refluxed in dry methanol (20ml/g, 2 min) to afford a 5.2 mixture of the a-ester 4 [NMR/CDCl3 & 3 8 CO2CH3] and the 8 -ester 5 [NMR/CDCl3 & 3.7 CO₂CH₃] in 100% yield Without further purification, this mixture was dissolved in ether (10ml/g) and treated with 0.7 equivalents of dicyclohexylamine at 0° The resulting precipitate was recrystallised from dioxane to give the pure dicyclohexylamine salt of $\underline{\underline{u}}$ [m.p. 193-5-1940, $[\alpha]^{24}_{-21}$ 40, c=1.6 in H₂O] which was treated with 2M hydrochloric acid to give, after extraction into ethyl acetate, the pure α -ester 4 as a colourless oil in 36% overall yield from 3 [[α]²⁴ -31 9°, c=1 1 in H₂0] The preparation of $\frac{4}{3}$ from glutamic acid as described above can easily be accomplished in one day. Exposure of $\frac{4}{2}$ to 1 5 equivalents of thionyl chloride in ether-dimethylformamide (100:1, 10ml/g, 230, 2h) gave the acid chloride 6 which was treated with 0 5 equivalents of L-cystine, dimethyl ester, dihydrochloride which had previously been stirred with 2 equivalents of triethylamine in tetrahydrofuran for 15h at 23° The disulphide $\frac{7}{2}$ [m p 167-169°, $[\alpha]_{D}^{20}$ -82 9°, c=1.1 in CH₃OH] so obtained (60%) was reduced with an excess of zinc and acetic acid in ethyl acetate to give the thiol $\frac{2}{2}$ in 73% yield [m p 124-125°, [a] $_{\rm n}^{23}$ +26.6°, c=1.2 in CHCl3]. The coupling of 2 with 13 under standard conditions gave a 1:1 mixture of the trimethyl ester, N-trifluoroacetamide of LTF4 together with its 5(R),6(S)-diastereoisomer in 82% yield Hydrolysis of this mixture afforded the corresponding mixture of LTF4 and its diastereoisomer as their tripotass_um salts in 99% yield Initial studies indicate that the mixture of LTF4 and its 5(R).6(S)-diastereo.somer 8 is 282 times less active than LTDu in contracting the guinea pig ileum and has negligible contractile activity on the human bronchus in vitro

REFERENCES AND NOTES

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- 5. All stable intermediates were characterised by microanalysis, PMR, IR and, where applicable, UV spectroscopy.
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 7. HPLC retention times were 5.3 and 6.0 min on a 20x0 5cm Spherisorb, 5μ, C₁₈ column eluted at 2ml/min with MeOH H2O·AcOH (65 35 0 01) buffered to pH 5 7 with NH4OH Under these conditions LTE4 and its 5(R),6(S)diastereoisomer eluted at 11.4 and 12 8 min
- 8. Experience has shown that in the case of LTC4, D4 and E4 this diastereoisomer is as least two orders of magnitude less active than the natural diastereoisomer.