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SYNTHESIS OF (E)-β-FLUOROMETHYLENEGLUTAMIC ACID

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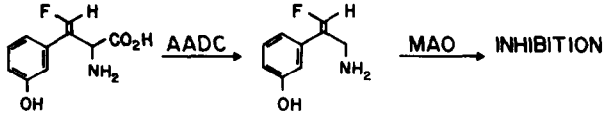
Abstract: A potential dual-enzyme activated inhibitor of γ-aminobutyric acid transaminase, (E)-β-fluoromethyleneglutamic acid, was prepared from ethyl 3,3-dimethylacrylate in 11 steps.

The dual enzyme-activated approach to the design of enzyme inhibitors has led to the synthesis of inhibitors possessing both enzyme specificity and site selectivity[1]. For example, (E)-β-fluoromethylene-meta-tyrosine (1) is decarboxylated by the metabolic enzyme aromatic L-amino acid decarboxylase (AADC) to generate (E)-β-fluoromethylene-meta-tyramine (2), a classic enzyme-activated inhibitor of the catabolic enzyme monoamine oxidase (MAO)[2]. The predominant neuronal location of AADC resulted in selective MAO inhibition in nerve endings. Similarly, α-fluoromethyl-para-tyrosine (3) is activated by an enzyme coming earlier in the metabolic pathway, in this case tyrosine hydroxylase (TH), leading to AADC inhibition preferentially in catecholaminergic neurones[3].



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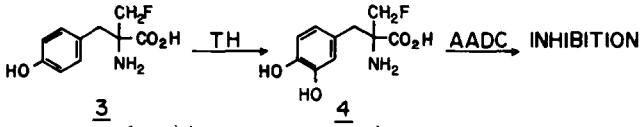

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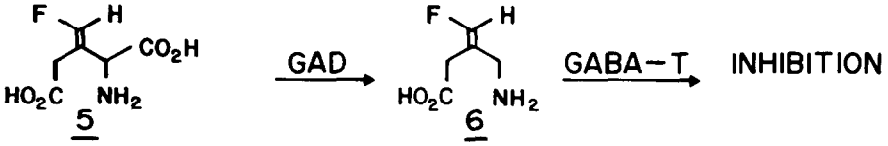
In an attempt to apply this concept to other enzyme systems, γ-aminobutyric acid transaminase (GABA-T) was chosen as a suitable target. Of the large number of GABA-T inhibitors synthesized to date, (E)-β-fluoromethyleneGABA (6), recently reported by our group[4], appeared to be a suitable starting point. Since GABA is synthesized from glutamic acid by the enzyme glutamate decarboxylase (GAD)[5], (E)-β-fluoromethyleneglutamic acid (5) could be envisaged as a dual enzyme-activated inhibitor of GABA-T.



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The synthesis of 5 is outlined in the Scheme. Bromination of ethyl 3,3-dimethylacrylate (7) followed by fluoride exchange afforded known[6] 8 as a mixture of isomers (b.p. 60-72 °C/

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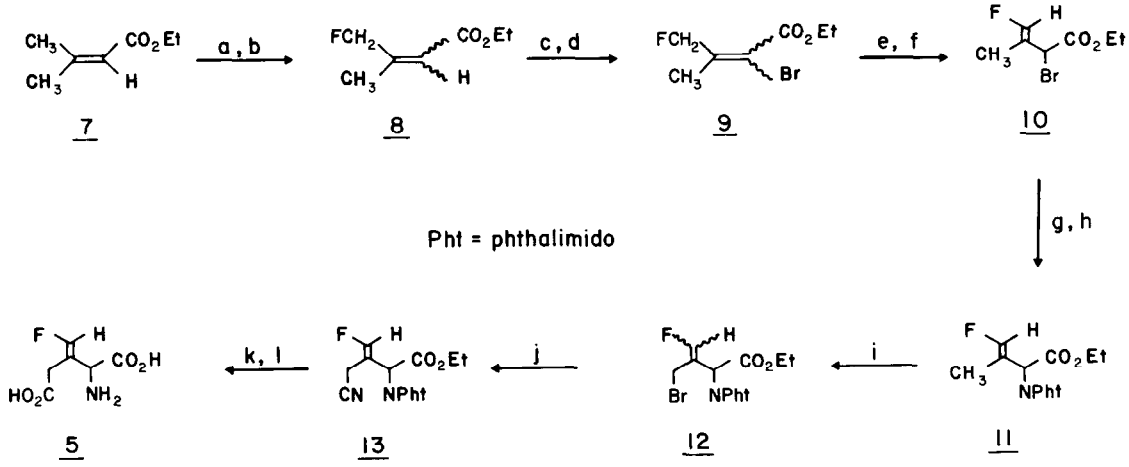
12 mm). This substance was converted to 9 (b.p. 92-104 °C/13 mm) by a bromination-dehydrobromination sequence. Deconjugation of 9 proceeded, as in previous cases[2], to afford almost exclusively the E isomer 10. Bromine displacement with NH_3 in dimethyl sulfoxide (DMSO) followed by treatment with phthaloyl dichloride and 4-dimethylaminopyridine gave the protected amino acid 11 (m.p. 70-71 °C)[7]. This method of introducing the phthaloyl group seems well suited for hindered amines where more conventional means (eg N-carbethoxyphthalimide) often fail[8]. While allylic bromination of 11 apparently occurred predominantly at the methyl group, isomerization of the double bond could be detected by proton NMR. The ratio of 12Z to 12E was approximately 2:1. The crude mixture was treated with sodium cyanide in DMSO then 13E (m.p. 98-99 °C) was separated by silica chromatography from the minor Z-isomer. Conversion to 5 (dec. 156-158 °C) was achieved by acid hydrolysis followed by treatment with propylene oxide in isopropanol. When tested with mammalian GAD, this substance was not a substrate of the enzyme, but a weak inhibitor[10].



7 8 9 10 11 12 13 5

Scheme: a) NBS, CCl_4, reflux 2 h; 67% yield; b) KF, triethylene glycol, 70 °C, 1 h; 50% yield; c) Br_2, CCl_4, 2 h; d) DABCO, EtOH, 1.5 h; 69% yield from 8 ; e) LDA, THF, - 70 °C, 1 h; f) 10% aq. HCl; g) NH_3-saturated DMSO, overnight; h) phthaloyl dichloride, 4-dimethylaminopyridine, CH_2Cl_2, reflux 30 min; 13% yield from 9; i) NBS, CCl_4, reflux 30 min; j) NaCN, DMSO, 3 h; 42% yield from 11; k) conc. aq. HCl, reflux 5.5 h; l) propylene oxide, isopropanol, several days, then ether; 95% yield from 13.

References and Notes

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7. Deprotection of 11 afforded (E)-2-amino-3-fluoromethylenebutyric acid, an amino acid with interesting antibacterial properties[9].
8. We thank Dr. F. Gerhart for suggesting this procedure.
9. W. Higgins, personal communication.
10. M. Jung, unpublished data.

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