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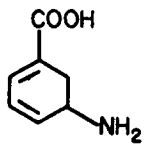
ENANTIOSPECIFIC SYNTHESIS OF (S)-4-AMINO-4,5-DIHYDRO-2-FURANCARBOXYLIC ACID, A NEW SUICIDE INHIBITOR OF GABA-TRANSAMINASE.

Joseph P. Burkhart, Gene W. Holbert* and Brian W. Metcalf

Merrell Dow Research Institute
2110 East Galbraith Road
Cincinnati, Ohio 45215

Abstract: The title compound has been prepared in optically pure form from (S)-glutamic acid.

In recent years there has been an increasing interest in suicide inhibitors of the enzyme 4-aminobutyrate:2-oxo-glutarate aminotransferase (GABA-T).[1,2] One such inhibitor, 4-aminohex-5-enoic acid (γ-vinyl GABA), has been demonstrated to have clinical potential in the treatment of epilepsy.[3] Based on the proven mechanism of action of the dihydroaromatic GABA-T inhibitors gabaculine (1)[4] and isogabaculine (2)[5] we decided to synthesize and test the dihydrofuran 3. It was hoped by analogy that 3, as a result of enzymatic processing by GABA-T, would be converted to the aromatic pyridoxamine-5'-phosphate adduct 4 which would not desorb from the active site. 3 has now been found to be a potent inactivator of GABA-T.[6] Here we describe syntheses of both the racemate and the individual enantiomers.



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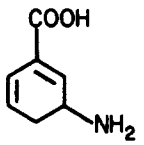

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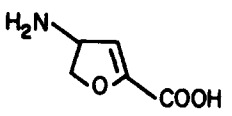

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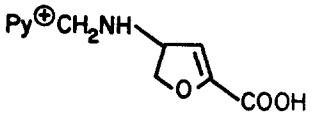

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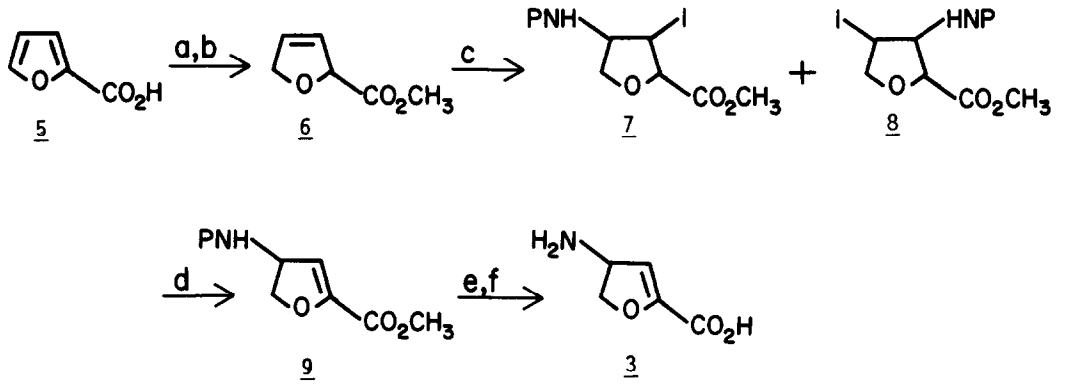
Our initial synthesis of racemic 3 is outlined in Scheme I and resembles the published syntheses of 1[7] and 2[5]. Dissolving metal reduction of 5[8] followed by esterification[9] yielded the ester 6. Treatment of 6 with iodine isocyanate followed by addition of p-methoxybenzyl alcohol produced a mixture of iodocarbamates 7 and 8. Chromatography followed by dehydrohalogenation furnished 9. Saponification of 9 followed by treatment with TFA in anisole and ion exchange chromatography produced pure racemic 3 in 10% overall yield.

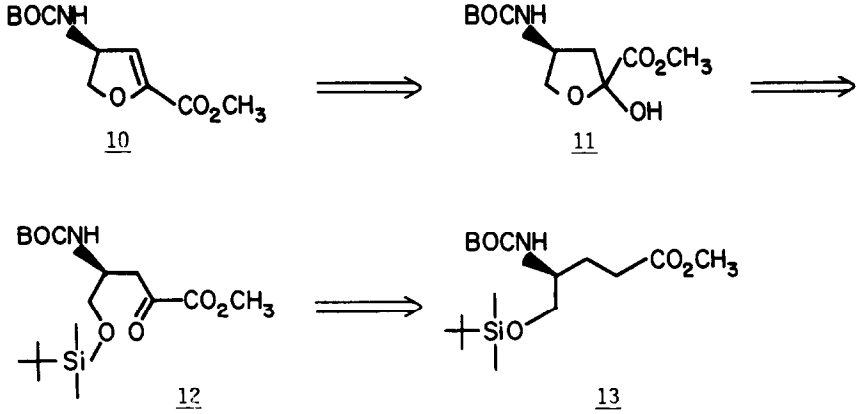
Scheme 1[10a]



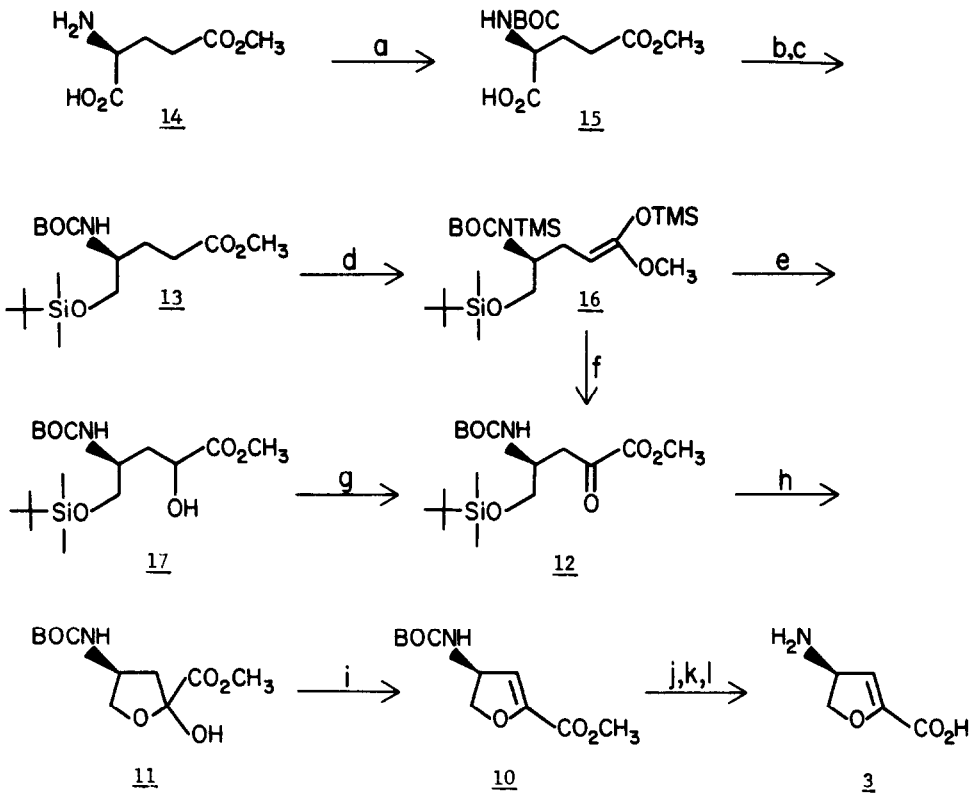
Reagents: (a) $Li/NH_3/C_2H_5OH$; (b) $CH_3I/DBU/CH_3CN$; (c) (i) $AgOCN/I_2/CH_2Cl_2$; (ii) $p\text{-}CH_3OC_6H_4CH_2OH$; (d) Dabco/acetone; (e) 1N aq. $LiOH/CH_3OH/THF$; (f) (i) TFA/anisole; (ii) ion exchange resin. P=p-methoxybenzyloxycarbonyl.

Although this route provided reasonable amounts of 3, it involved a very sensitive dissolving metal reduction and two difficult chromatographic separations. In addition, in view of the enzyme inhibitory activity found with racemic 3, we desired an enantiospecific synthesis so the individual optical isomers could be evaluated separately.

We envisioned (S)-10 as arising from dehydration of hemiketal 11 which we expected to form from 12 upon desilylation. We planned to generate 12 via α-oxidation of ester 13. The analysis was complete when we recognized 13 as a derivative of (S)-glutamic acid in which the α-carboxyl group had been reduced.



Scheme 2[10a,b]



Reagents: (a) BOC_2O/Et_3N/dioxane/H_2O; (b) (i) i-BuOCOCl/Et_3N/THF; (ii) aq. $NaBH_4$; (c) TBDMSCl/Et_3N/DMAP (cat)/CH_2Cl_2; (d) (i) 2 LDA/THF; (ii) TMSCl; (e) (i) m-CPBA/hexane; (ii) CH_3OH; (f) (i) O_2/hematoporphyrin/$h\mu$; (ii) Et_3N; (g) PDC/CH_2Cl_2; (h) 2% aq. $HClO_4$:THF, 1:4; (i) $SOCl_2/C_5H_5N/CH_2Cl_2$; (j) 1N LiOH/THF/CH_3OH; (k) TFA; (l) ion exchange resin.

Commercially available 14 (Scheme 2) was protected as the t-butoxycarbonyl derivative 15 (86%, m.p. 74-77°C) which was reduced via a mixed anhydride procedure[11] (82%) and silylated (80%) to yield 13. Treatment of 13 with excess LDA followed by TMSCl produced silyl ketene acetal 16 (100%) which was used without purification. When 16 was exposed to m-CPBA in hexane[12] and the crude product treated with methanol, hydroxyester 17 was isolated in 24% yield with 21% of 13 recovered.[13] PDC oxidation[14] of 17 furnished α-keto-ester 12 in 77% yield.

Alternatively, photooxygenation of 16 followed by treatment of the intermediate α-silyl hydroperoxide[15] with Et_3N led to 12 directly in 45% yield. Mild acid hydrolysis of 12 produced 11 (84%). No trace of the ketoalcohol was observable by NMR. Dehydration of 11 afforded 10 as a white solid (m.p. 94-96°C) in 71% yield after chromatography. Exposure of 10 to LiOH

produced the acid (m.p. 117-120°C, decomp.; 91%). Brief treatment of the acid with neat trifluoroacetic acid and subsequent ion exchange chromatography afforded (S)-3 as a white solid (m.p. 193-195°C, decomp.) in 70% yield upon concentration. (S)-3 exhibited $[\alpha]_D$=+101.6° (c=1.1, 0.1N NaOH). (R)-3 ($[\alpha]_D$=-109.0°, c=1.0, 0.1N NaOH) has also been prepared by this procedure from R-glutamic acid. This synthesis yields the individual enantiomers in optically pure form.[16]

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10. a. All compounds exhibited spectral characteristics in accord with their structures.
    b. Satisfactory elemental analyses were obtained for all compounds except 10.
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16. Optical purity has been demonstrated by the conversion to the diastereomeric leucine-aminodihydrofuran carboxylic acid dipeptides which are readily separable by HPLC. This procedure which was performed by T.-M. Chen of this Institute will be reported elsewhere.

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