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D. Misiti [a] , M. Santaniello [b] & G. Zappia [a]

[a] Dip. Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive , Universita "La Sapienza" , P.le A. Moro 5, 00185, Roma, Italy

[b] Lab. Ricerca Chimica , Sigma Tau S.p.A. , Via Pontina km 30.400, 00040, Pomezia, Italy

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SYNTHESIS OF (3R)- AND (3S)-3,4-DIAMINO-BUTYRIC ACID FROM L-ASPARTIC ACID

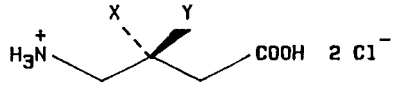
D. Misiti[a]*, M. Santaniello[b], G. Zappia[a]

a) Dip. Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza", P.le A. Moro 5, 00185 Roma (Italy)
b) Lab. Ricerca Chimica, Sigma Tau S.p.A., Via Pontina km 30.400, 00040 Pomezia (Italy)

Abstract

A short and convenient synthesis for both enantiomers of GABOB amino-analogue **1a,b** is reported, starting from L-aspartic acid. The protected diester **3** is the common intermediate for the synthetic pathway.

γ-Amino-β-hydroxy butyric acid (GABOB) has great pharmacological importance because of its biological function as a neuromodulator in the mammalian nervous system [1,2].



1 a (R) : X = NH_3^+ Y = H

1 b (S) : X = H Y = NH_3^+

Furthermore the (3R)- enantiomer has been shown to be more active[3] than the corresponding (3S)- enantiomer, and both have been

(*) To whom correspondence should be addressed.

used chemically as synthons for γ-amino-butyric acid (GABA)-receptor agonists[4] with heterocyclic structure.

The growing interest in aminoacids as a tool to clarify biochemical mechanisms or as "chiral pool" in asymmetric synthesis[5], prompted us to develope a simple and flexible route to both enantiomers of the GABOB amino-analogue **1**.

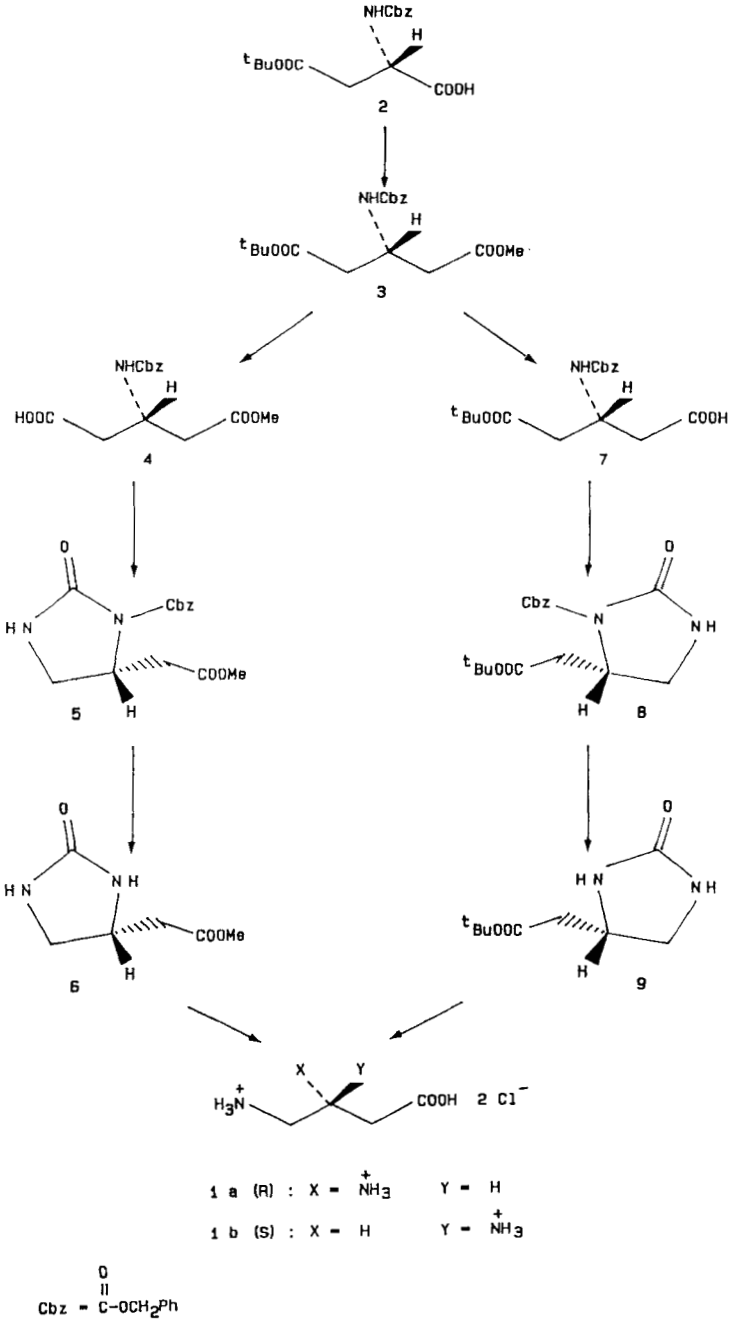
The present communication [6] deals with the synthesis of the (3R)- and (3S)-3,4-diamino-butyric acid, **1a** and **1b** respectively, starting from L-aspartic acid as common precursor.

Commercially available Cbz-L-aspartic acid 4-t-butyl ester[7] **2** was converted into the chiral diester **3** according to the Wakamiya method[8]: conversion of **2** in the α-diazoketone followed by Wolff rearrangement with silver benzoate in MeOH affords **3** (85% yield) which can be used without further purification as key intermediate in our synthetic pathway.

Really, it is possible to direct the reaction sequence towards the preparation of both enantiomers of **1** by taking advantage of the different reactivity of the two ester groups of **3** in alkaline and acid medium, respectively. So, the crude diester **3** was treated under acid conditions at room temperature to yield the monoacid **4** which was then converted to the intermediate crystalline azide "*via*" mixed anhydride with an aqueous solution of NaN_3; the above azide was then rearranged to the chiral imidazolidin-2-one **5** by reflux in toluene.

Attempts to convert **5** directly to the final product **1a** did not give any satisfactory result. Finally, when **5** was first hydrogenated to **6**[10] and then heated (80°C) overnight with 3N HCl, the (R)- enantiomer **1a** was obtained as crystalline hydrochloride[10] in 45% overall yield from **2**.

The (S)-enantiomer **1b** was prepared by treating the crude diester **3** with NaOH in MeOH to obtain the monoacid **7** in 85% yield. When the



monoacid was subjected to the same reactions sequence used to prepare the (R)-enantiomer, the intermediates **8** and **9** were obtained in satisfactory yield. Finally **1b** was obtained from **9**, as the crystalline dichloridrate in 43% overall yield from **2**.

Experimental Section

All reagents and anhydrous solvents were obtained from Fluka Chemie A.G. Proton magnetic resonance spectra were recorded on a Varian FT80 in $CDCl_3$, unless otherwise indicated, containing tetramethylsilane as internal standard and chemical shift (δ) expressed in ppm. Melting points were taken on a Buchi melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (0.25 mm). Chromatographic separations were carried out using silica gel E. Merck (Kieselgel 60).

Methyl (3R)-3-N-(benzyloxycarbonyl)-amino-4-(t-butoxycarbonyl)--butyrate 3

To a cold (0°C) solution of Z-L-aspartic acid 4-t-butyl ester (6.83 g, 20 mmol) in ethyl acetate (60 ml), dry N-methylmorpholine (2 ml, 20 mmol) and i-butyl chloroformate (2.61 ml, 20 mmol) were added under vigorous stirring. After 15 min, the precipitated salt was filtered off through a pad of celite, and an excess of an ethereal solution of diazomethane (30 mmol) was added with stirring at 0°C in 20 min. The mixture was then stirred for 4 h at the same temperature and concentrated under reduced pressure; the residue was dissolved in methanol (100 ml) and treated with silver benzoate (1 g, 4 mmol) and Et_3N (10 ml) under a positive pressure of nitrogen. After 2 h of stirring at room temperature, the mixture was

concentrated under reduced pressure and the residue was dissolved in AcOEt (100 ml), washed with a saturated solution of $NaHCO_3$ (2 x 100 ml), water (100 ml), 1M aqueous $KHSO_4$ (2 x 100 ml), brine and dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure to give the crude **3**, which can be used without further purification. Yield: 85%. An analytical sample was obtained by flash chromatography (AcOEt/n-hexane 1:1). $[\alpha]_D$ = -1.12° (c = 3.5 in $CHCl_3$); Lit[9]: $[\alpha]_D^{24}$ = -1.15° (c = 3.4 in $CHCl_3$). ^1H NMR δ: 7.25 (5H, m, CH_2-C_6H_5), 5.70- 5.30 (1H, bs, CH_2-NH-CO), 5.10 (2H, s, CH_2-C_6H_5), 4.60-4.10 (1H, m, -C*H-), , 3.65 (3H, s, OCH_3), 2.55-2.40 (4H, m, centrated at 2.50, -CH_2-C*H- CH_2-, J = 6 Hz), 1.40 (9H, s, O-t-Bu).

(3S)-3-(Benzyloxycarbonyl)-amino-4-(methoxycarbonyl)-butyric acid 4

Compound **3** (2.0 g, 5.7 mmol) was dissolved in 50% CF_3COOH in CH_2Cl_2 (60 ml), stirred at room temperature and followed by TLC (AcOEt/n-hexane 1:1). The solution was then concentrated and the residue dissolved in diethyl ether (25 ml) followed by evaporation under reduced pressure. The procedure was repeated twice to give **4** as an oil. Yield: 94%, mp 94-95°C (Et_2O/n-hexane) $[\alpha]_D^{25}$ = +0.70° (c = 5 in $CHCl_3$); Lit[9]: mp = 97.0-97.5°C (Et_2O/n-hexane); $[\alpha]_D^{24}$ = +0.72° (c = 7.5 in $CHCl_3$). ^1H NMR δ: 8.00- 7.90 (1H, bs, COOH), 7.20 (5H, m, CH_2-C_6H_5), 5.90- 5.45 (1H, bs, -NH-), 5.10 (2H, s, CH_2-C_6H_5), 4.70-4.15 (1H, m, -C*H-), 3.60 (3H, s, OCH_3), 2.70-2.50 (4H, d, -CH_2-C*H- CH_2-, J = 6 Hz).

3-N-(benzyloxycarbonyl)-(4R)-4-(carbomethoxymethyl)-imidazolidin-2-one 5

i-Butylchloroformate (0.53 ml, 5,5 mmol) was dropwised to a cooled (0°C) solution of **4** (1.6 g, 5.0 mmol) in dry THF (18 ml) added of Et_3N (0.8 ml, 5.7 mmol). After stirring at the same temperature for 30 min 5M aqueous NaN_3 (11.5 ml) was dropwised and stirred for additional 30 min at 0°C. The solution was then diluted with AcOEt (50 ml) and the two phases were separated. The organic phase was dried and concentrated under reduced pressure to afford the crude acyl-azide (IR 2140 cm^{-1}). The so obtained acyl-azide was dissolved in dry toluene (50 ml), heated at 90°C overnight and finally concentrated under reduced pressure. The crude product was purified by chromatography (silica gel: AcOEt/n-hexane 6:4) to give crystals of **5**. Yield: 80%; mp 108-109°C (AcOEt/n-hexane); $[\alpha]_D$ = -69.6° (c = 2 in MeOH) . ^1H NMR δ: 7.50-6.95 (5H, m, CH_2-$C_6\underline{H}_5$), 6.30-6.05 (1H, bs, CH_2-N$\underline{H}$-CO), 5.20 (2H, s, $C\underline{H}_2$-C_6H_5), 4.75-4.20 (1H, m, AB$\underline{C}$XY, -CO-NH-C*$\underline{H}$C-), 3.60 (3H, s, O$C\underline{H}_3$), 3.80-3.35 (1H, t, centrated at 3.55, $\underline{A}$BCXY, NH-C$\underline{H}_A$$H_B$-C*HC-, J_{AB} = J_{AC} = 9 Hz), 3.25-2.95 (1H, dd, A$\underline{B}$CXY, -NH-C$H_A\underline{H}_B$-C*HC-, J_{BA} = 9 Hz, J_{BC} ≅ 3-4 Hz), 2.90-2.30 (2H, m, ABC$\underline{X}\underline{Y}$, -C*HC-C$\underline{H}_X\underline{H}_Y$-COOMe).

(4R)-4-(Carbomethoxymethyl)-imidazolidin-2-one 6

Compound **5** (2.92 g, 10 mmol) was dissolved in absolute ethanol (25 ml) and hydrogenated over 10% Pd/C. The mixture was filtered on celite and concentrated under reduced pressure to give **6** (1.50 g). Yield: 90%. $[\alpha]_D$ = +20.3° (c = 1 in MeOH). ^1H NMR δ: 5.80-5.60 (2H, bs, N$\underline{H}$-CO-N$\underline{H}$), 4.60-3.85 (1H, m, AB$\underline{C}$XY, -CO-NH-C*$\underline{H}$C-), 3.65 (3H, s, O$C\underline{H}_3$), 3.80-3.45 (1H, t, centrated at 3.60, $\underline{A}$BCXY, NH-C$\underline{H}_A$$H_B$-C*HC-, J_{AB} = J_{AC} = 9 Hz), 3.25-2.95 (1H, dd, A$\underline{B}$CXY, -NH-C$H_A\underline{H}_B$-C*HC-, J_{BA} = 9 Hz, J_{BC} = 6 Hz), 2.85-2.30 (2H, m, ABC$\underline{X}\underline{Y}$, -C*HC-C$\underline{H}_X\underline{H}_Y$-COOMe).

(3R)-3,4-diaminobutyric acid hydrochloride 1a

Compound **6** (1.58 g, 10 mmol) was dissolved in HCl 3N (15 ml) and heated at 80°C overnight. The solution was then concentrated under reduced pressure to give the crude hydrochloride; recrystallization from EtOH/H_2O affords **1a** in 78 % yield. Mp 222-223°C (H_2O/EtOH); $[\alpha]_D$ = +7.9°C (c = 1 in H_2O). ^1H NMR (D_2O) δ: 4.30-3.85 (1H, m, -C*H-), 3.60-3.35 (2H, d, H_3N^+-CH_2-C*H-, J = 6 Hz), 3.15-2.80 (2H, d, -CH_2-COOH, J = 6 Hz).

(3R)-3-(Benzyloxycarbonyl)-amino-4-(t-butoxycarbonyl)-butyric acid 7

To a stirred solution of the diester **3** (3.15 g, 9 mmol) in MeOH (30 ml) 1M NaOH (11 mmol) was added and stirred for 3 h at room temperature. The mixture was diluted with water (50 ml), extracted with CH_2Cl_2 (3 x 25 ml), acidified to pH 2 with 1N HCl, and finally extracted with AcOEt (3 x 100 ml). The last combined extracts were washed with brine, water, dried and concentrated under reduced pressure to give the monoester **7** as a colourless gum. Yield: 85%. $[\alpha]_D$ = -1.5° (c = 3.0 in $CHCl_3$); Lit[9]: $[\alpha]^{20}$ = -1.4° (c = 2.6 in $CHCl_3$). ^1H NMR δ: 7.20 (5H, m, CH_2-C_6H_5), 5.70-5.55 (1H, bs, -NH-), 5.05 (2H, s, CH_2-C_6H_5), 4.30-4.10 (1H, m, -C*H-), 2.70-2.50 (4H, m, -CH_2-C*H- CH_2-), 1.40 (9H, s, O-t-Bu).

3-N-(Benzyloxycarbonyl)-(4S)-4-(carbo-t-butoxymethyl)- imidazolidin--2-one 8

The compound **8** was obtained from **7** following the same procedure used for **5**. Yield: 80%. mp 159-160°C (Et_2O/hexane); $[\alpha]_D$ = +61.6° (c=

1 in MeOH). ^{1}H NMR δ: 7.50-7.20 (5H, m, CH_2-C_6H_5), 6.30-6.10 (1H, bs, -NH-CO), 5.20 (2H, s, CH_2-C_6H_5), 4.70-4.30 (1H, m, ABCXY, -CONCO-C*HC-), 3.70-3.45 (1H, t, centrated at 3.60, ABCXY, NH-C-HAHB-C*H-, J_{AB} = J_{AC} = 9 Hz), 3.30-2.95 (1H, dd, ABCXY, -NH-CH_AH_B-C*HC-, J_{BA} = 9 Hz, J_{BC} ≅ 3-4 Hz), 3.05-2.45 (2H, m, ABCXY, -C*HC-C-HXHY-COO-t-Bu), 1.40 (9H, s, COO-t-Bu).

(4S)-4-(Carbo-t-butoxymethyl)-imidazolidin-2-one 9

The compound **9** has been prepared from **8** in the same way used for **6**. Yield: 93%; mp 104-105°C (Et_2O/n-hexane); $[\alpha]_D$ = -19.2° (c = 0.5 in MeOH). ^{1}H NMR δ: 5.75-5.70 (2H, 2bs partially overlapped, NH-CO-NH), 4.35-3.85 (1H, m, ABCXY, -NH-C*HC-), 3.85-3.50 (1H, t, centrated at 3.65, ABCXY, NH-CH_AH_B-C*HC-, J_{AB} = J_{AC} = 9 Hz), 3.35-3.00 (1H, dd, ABCXY, -NH-CH_AH_B-C*HC-, J_{BA} = 9 Hz, J_{BC} = 6 Hz), 2.80-2.20 (2H, m, ABCXY, -C*HC-CHXHY- COO-t-Bu), 1.40 (9H, s, COO-t-Bu).

(3S)-3,4-Diaminobutyric acid hydrochloride 1b

The compound **1b** has been prepared from **9** in the same way for **1a** from **6**. Yield: 70%; mp 221-222°C (H_2O/EtOH); $[\alpha]_D$ = - 7.2° (c = 1 in H_2O).

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