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A short and convenient chemoenzymatic synthesis of both enantiomers of 3-phenylGABA and 3-(4-chlorophenyl)GABA (Baclofen)

Fulvia Felluga,* Valentina Gombac, Giuliana Pitacco and Ennio Valentin*

Dipartimento di Scienze Chimiche, Università di Trieste, via Licio Giorgieri 1, I-34127 Trieste, Italy

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Abstract—Both enantiomers of the pharmacologically active GABA analogues 4-amino-3-phenyl and 4-amino-3-(4-chlorophenyl)butyric acid (Baclofen) with high enantiomeric excesses were synthesized by a chemoenzymatic method involving α-chymotrypsin mediated kinetic resolutions of the corresponding 3-phenyl- and 3-(4-chlorophenyl)-4-nitrobutyric acid methyl ester precursors.

1. Introduction

GABA (γ-aminobutyric acid), is a major inhibitory neurotransmitter in the mammalian Central Nervous System (CNS),[1] and decreased GABA'ergic activity results in the excessive excitement of CNS (namely Neuronal Firing).[2] The disfunctioning of the central GABA system is responsible for the development and outbreak of epilepsy, Huntington's and Parkinson's diseases,[3] and other psychiatric disorders, such as anxiety and pain.

The direct administration of GABA is not an efficient therapy because due to its hydrophilic nature, it very poorly crosses the blood–brain barrier.[4] β-Aryl-γ-aminobutyric acids, particularly 4-amino-3-phenylbutyric acid[5] (β-phenylGABA) and 4-amino-3-(4-chlorophenyl)butyric acid (Baclofen)[6] are lipophilic analogues of GABA. Although very closely related in structure, β-phenylGABA and Baclofen show different pharmacological activities. The former is in fact a mood elevator and tranquillizer,[7] while Baclofen is widely used as a muscle relaxant in the treatment of spasticy[8] caused by diseases at the spinal cord, in particular following traumatic lesions or associated with multiple sclerosis.

Baclofen was first synthesized in 1962, and it is the most selective and the only therapeutically available $GABA_B$ agonist known. Although still commercialized in its racemic form, (Lioresal® and Baclon®), the biological activity of Baclofen, as well as that of β-phenylGABA, is known to reside in the (*R*)-enantiomer,[5,6] with the (*S*)-antipode showing a lower affinity to the same receptor site. Due to the increasing demand of enantiomerically pure drugs from the pharmaceutic industry, the enantioselective synthesis of compounds such as **3** and **4** in their enantiomerically pure, active form is an important target.

Some examples of optical resolution via diastereomeric compounds,[6,9] a number of stereoselective syntheses of the enantiomers of Baclofen have been reported in the literature,[10] some of which involve an enzymatic step.[11] Examples of enantioselective [10e,12] and chemoenzymatic syntheses[13] of (*R*)-(−)- and (*S*)-(+)-β-phenylGABA has also been published.

Herein we report a very short and convenient synthesis of both enantiomers of β-phenylGABA and Baclofen, obtained in excellent enantiomeric excess and good yield by a few step procedure, involving the use of α-chymotrypsin in the enantiodifferentiating step.

2. Results and discussion

The Michael addition of nitromethane to methyl cynnamate **1** and methyl *p*-chlorocynnamate **2**, respectively, catalyzed by 1,1,3,3-tetramethylguanidine,[14] proceeded smoothly within 48 h to give the corresponding racemic

* Corresponding authors. Tel.: +39 0405583924; fax: +39 0405583903; e-mail: felluga@dsch.units.it

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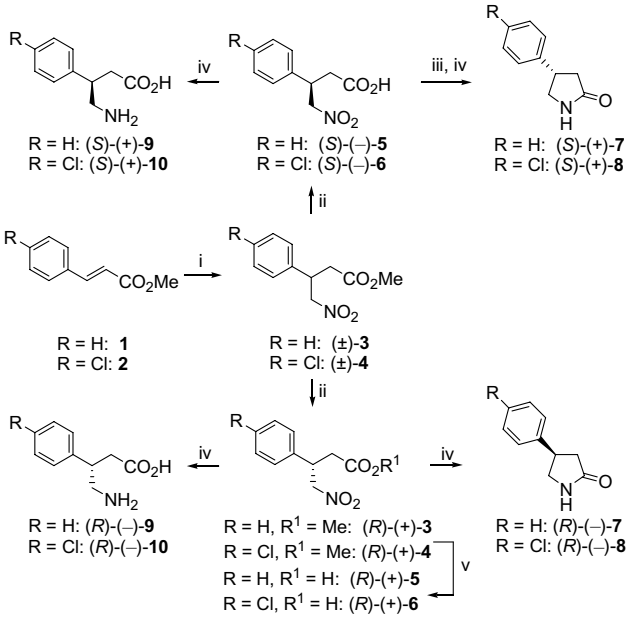
γ-nitroesters[15] **3** and **4** in excellent yields (Scheme 1). Due to the presence of the aromatic, hydrophobic substituent bonded to the stereogenic centre of these compounds, we considered them good substrates for the enzymic resolution mediated by α-chymotrypsin.

The preference of this enzyme for substrates bearing highly hydrophobic substituents close to the ester function is in fact well known,[16] and it relies on the presence in the active site of the protein of a hydrophobic binding pocket, in which the aromatic ring present on the substrate participates in favourable hydrophobic interactions with a number of apolar amino acid residues such as Phe, Tyr and Trp.

Racemic (±)-**3** and (±)-**4** were treated with α-chymotrypsin in a buffered solution at pH 7.4. The results obtained are summarized in the following Table 1, reporting the enantiomeric excesses of the acidic products (*S*)-(−)-**5** and (*S*)-(−)-**6** and those of the recovered unreacted substrates (*R*)-(+)-**3** and (*R*)-(+)-**4**, at different conversion values.



Scheme 1. Reagents and conditions: (i) CH_3NO_2 (5 equiv), 1,1,3,3-tetramethylguanidine (0.2 equiv), rt, overnight; (ii) 1.0 g substrate, 0.1 g enzyme, 0.1 phosphate buffer at pH 7.4 (5 mL/mmol), rt; (iii) CH_2N_2, diethyl ether; (iv) Raney Nickel, EtOH, 1 atm, rt; (v) refluxing CH_3COOH/HCl.

Hydrolyses of **3** and **4** proceeded with different enantioselectivities, as can be inferred from the values of the respective enantiomeric ratio *E*,[17] which was lower for **3** than for **4**. Accordingly, in the former case, hydrolysis product (*S*)-(−)-**5** was obtained with high enantiomeric excess (95% ee) at 23% conversion value, while the unreacted γ-nitroester (*R*)-(+)-**3** was recovered in an enantiomerically pure form (99.9% ee) at 70% conversion value. In the hydrolysis of (±)-**4**, owing to the high enantiomeric ratio, at 53% conversion value, the reaction did not practically proceed further, and both the acid (*S*)-(−)-**6** and the ester (*R*)-(+)-**4** could be obtained in enantiomerically pure forms, in 96% ee and 99.9% ee, respectively. After 10 min, at 16% conversion value, the ee of acid (*S*)-(−)-**6** was slightly better (98%) but a lower yield was obtained.

The dextrorotatory γ-nitroesters **3** and **4** are direct precursors of (*R*)-(−)-β-phenylGABA and (*R*)-(−)-Baclofen. In fact their acidic hydrolyses, carried out in a 1:1 mixture of 2 M HCl/AcOH[10k] under reflux, gave the corresponding acids (*R*)-(+)-**5** and (*R*)-(+)-**6**, which were reduced on Nickel Raney to the desired products (*R*)-(−)-**9** and (*R*)-(−)-**10**, respectively. The transformations described above were also carried out on the γ-nitroacids (*S*)-(−)-**5** and (*S*)-(−)-**6**, isolated from the enzymatic hydrolyses, thus allowing the availability of (*S*)-(+)-β-phenylGABA and (*S*)-(+)-Baclofen.

Moreover, the same substrates (*R*)-(+)-**3** and (*R*)-(+)-**4** were transformed into the corresponding 4-substituted γ-lactams (*R*)-(−)-**7** and (*R*)-(−)-**8**, by reduction of the nitro group under an atmospheric pressure of hydrogen, in the presence of the Raney Nickel as the catalyst (Scheme 1). The pyrrolidin-2-one derivative (*R*)-(−)-**8** is an important lipophilic pro-drug related with GABA, showing itself a muscle relaxant activity.[18]

3. Conclusion

In conclusion, a convenient enantioselective synthesis of the two pharmacologically active β-arylGABA (*R*)-(−)-**9** and (*R*)-(−)-**10**, together with their enantiomers, has been developed starting from the easily available racemic γ-nitroester precursors **3** and **4**, through their enzymatic kinetic resolution. As already observed in a previously reported example,[16] the presence of an aromatic substituent on the substrates proved to be crucial for the enantiopreference of α-chymotrypsin.

Table 1. Enzymatic resolutions of the γ-nitroesters (±)-**3** and (±)-**4**[a]

Substrate	*E*	Conv. (%)	Reaction time	Acid, ee (%),[b] [yield (%)][c]	Ester, ee (%),[b] [yield (%)][c]
3	50	23	2 h	(*S*)-(−)-**5**, 95, [18]	(*R*)-(+)-**3**, 29, [75]
		45	24 h	(*S*)-(−)-**5**, 91, [40]	(*R*)-(+)-**3**, 73, [48]
		70	72 h	(*S*)-(−)-**5**, 43, [62]	(*R*)-(+)-**3**, 99.9, [25]
4	120	16	10 min	(*S*)-(−)-**6**, 98, [15]	(*R*)-(+)-**4**, 18, [78]
		53	2 h	(*S*)-(−)-**6**, 96, [43]	(*R*)-(+)-**4**, 99.9, [42]

[a] Reaction conditions: 1.0 g substrate, 0.1 g enzyme, 0.1 phosphate buffer at pH 7.4 (5 mL/mmol), room temperature.
[b] Enantiomeric excesses were determined by chiral HRGC.
[c] Yields in isolated products.

4. Experimental

4.1. General

Mps were determined with a Büchi Apparatus and are uncorrected. IR spectra were recorded on a Jasco FT-IR 200 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 (400 MHz for proton, 100.1 MHz for carbon), using deuterochloroform as a solvent and tetramethylsilane as the internal standard, unless otherwise stated. *J* values are given in Hz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter, at 25 °C. ESI-MS spectra were obtained on a PE-API spectrometer at 5600 V by infusion of methanolic solutions. Mass spectra (EI, positive ions) were run on a VG 7070 spectrometer at 70 eV. Enzymatic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer, Copenhagen. High Resolution Chiral GLC (HRCGC) analyses were obtained on a Shimadzu 14B apparatus, using a Chiraldex™ column, type G-TA, trifluoroacetyl-γ-cyclodextrin (40 m × 0.25 mm) (carrier gas He, 180 kPa, split 1:100, 150 °C, isotherm). TLCs were performed on Polygram® Sil G/UV$_{254}$ silica gel pre-coated plastic sheets (eluent: light petroleum–ethyl acetate). Flash chromatography was run on silica gel, 230–400 mesh ASTM (Kieselgel 60, Merck), using mixtures of light petroleum 40–70 °C and ethyl acetate as the eluent. CHN analyses were run on a 1106 Carlo Erba Elemental Analyzer.

Raney® 2800 nickel, slurry in water, active catalyst, was purchased by Aldrich. α-Chymotrypsin (α-CT; 53.1 U/mg) was purchased from Fluka.

4.2. Synthesis of the reactants

Methyl 3-phenylpropenoate **1** (methyl cynnamate) and 3-(4-chlorophenyl)propenoate **2** (methyl *p*-chlorocynnamate) were obtained quantitatively from the corresponding commercially available acids (Aldrich), by esterification with MeOH used as a solvent, in the presence of trimethylchlorosilane.[19]

4.3. General procedure for the synthesis of methyl (±)-4-nitro-3-phenylbutanoate 3 and methyl (±) 3-(4-chlorophenyl)-4-nitrobutanoate 4

A mixture of nitromethane (18.3 g, 150 mmol), methyl cynnamate **1** (4.9 g, 30 mmol) or methyl *p*-chlorocynnamate **2** (5.9 g, 30 mmol) and 1,1,3,3-tetramethylguanidine[14] (0.6 g, 5 mmol) was stirred at room temperature. After 48 h, excess nitromethane was removed in vacuo and the residue dissolved in diethyl ether, washed with 5% HCl, the organic phase dried over Na_2SO_4 and chromatographed on column (eluent: light petroleum–ethyl acetate 9:1) to give **3** and **4** as pure compounds.

4.3.1. Methyl (±)-4-nitro-3-phenylbutanoate 3. Compound (±)-**3** was obtained in a 85% yield after purification by flash chromatography (eluent: light petroleum–ethyl acetate 9:1). Mp 37 °C; IR, cm^{-1} (neat): 3064, 3031 (Ph), 1736 (CO_2Et), 1552 and 1378 (NO_2), 1596, 1496, 1455, 1437, 767, 701 (Ph); ^{1}H NMR, δ, ppm: 7.36–7.21 (m, 5H, ArH), 4.73 (dd, *J* = 12.8 and 8.0, 1H, H-4), 4.63 (dd, *J* = 12.8 and 7.0, 1H, H-4), 3.98 (quint, *J* = 7.3, 1H, H-3), 3.62 (s, 3H, OMe), 2.77 (apparent d, *J* = 7.7, 2H, 2H-2); ^{13}C NMR, δ, ppm: 171.0 (s), 138.2 (s), 129.0 (2d), 128.0 (d), 127.2 (2d), 79.6 (t), 51.9 (q), 40.1 (d), 37.45 (t); ESI-MS (*m*/*z*): 224.1 [M+H]$^+$, 247.0 [M+Na]$^+$; MS (*m*/*z*): 223 (M+, 2%), 176 (45), 118 (100), 91 (12); Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.25; H, 5.9; N, 6.2. HRCGC t_R = 45 min (*S*)-enantiomer and 54 min (*R*)-enantiomer.

4.3.2. Methyl (±) 3-(4-chlorophenyl)-4-nitrobutanoate 4. Compound (±)-**4** was obtained in a 89% yield after flash chromatography (eluent: light petroleum–ethyl acetate 9:1). Mp 35 °C; IR, cm^{-1} (neat): 3030, 3002 (ArH), 1736 (CO_2Et), 1556, 1378 (NO_2), 1596, 1494, 1437, 1415, 830 (Ar); ^{1}H NMR, δ, ppm: 7.31 (d, 2H, ArH), 7.17 (d, 2H, ArH), 4.71 (dd, *J* = 12.8 and 7.0, 1H, H-4), 4.61 (dd, *J* = 12.8 and 8.0, 1H, H-4), 3.97 (quint, *J* = 7.3, 1H, H-3), 3.63 (s, 3H, OMe), 2.77 (dd, *J* = 4.4 and 7.3, 2H, 2H-2); ^{13}C NMR, δ, ppm: 170.7 (s), 136.7 (s), 133.9 (s), 128.7 (2d), 129.4 (2d), 79.05 (t), 52.0 (q), 39.4 (d), 37.3 (t); ESI-MS (*m*/*z*): 258.1 [M+H]$^+$, 260 [M+2+H]$^+$, 280.1 [M+Na]$^+$; MS (*m*/*z*): 257 (M$^+$), 210 (55), 152 (100), 115 (20); Anal. Calcd for $C_{11}H_{12}ClNO_4$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.3; H, 4.6; N, 5.5. HRGC: t_R = 139 (*S*)-enantiomer and 143 min (*R*)-enantiomer.

4.4. General procedure for enzymatic hydrolysis

A suspension of the γ-nitroester (±)-**3** (1.0 g, 4.5 mmol) and (±)-**4** (1.0 g, 3.9 mmol) in a 0.1 M KH_2PO_4/Na_2PO_4 buffer (pH 7.4) (20 mL) was hydrolyzed with α-chymotrypsine (0.050 g/0.500 g substrate) at room temperature under vigorous stirring. The pH was kept at its initial value by automatic continuous addition of 1 M NaOH. At the desired conversion value, the unreacted (+)-γ-nitroester was extracted from the suspension with ethyl acetate (3 × 10 mL) using a centrifuge for the separation of the layers.

For the isolation of the (−)-γ-nitroacid, the aqueous layer was acidified to pH 2 with 2 M HCl and extracted with chloroform (5 × 10 mL).

4.4.1. Methyl (*R*)-(+)-4-nitro-3-phenylbutanoate 3. Compound **3** was obtained with 99.9% ee by stopping the enzymatic hydrolysis of (±)-**3** at 70% conversion (25% yield). $[\alpha]_D^{25} = +8.7$ (*c* 2, $CHCl_3$).

4.4.2. (*S*)-(−)-4-Nitro-3-phenylbutanoic acid 5. Compound **5** was obtained with 95% ee by stopping the enzymatic hydrolysis of (±)-**3** at 23% conversion (18% yield). White solid, mp 103–104 °C; $[\alpha]_D^{25} = -15.2$ (*c* 0.6, MeOH); IR, cm^{-1} (Nujol): 3510–2500 (broad, CO_2H), 1711 (CO_2H), 1557, 1376 (NO_2), 1596, 1500, 721 (Ph); ^{1}H NMR, δ, ppm: 9.95 (broad, 1H, CO_2H), 7.31 (m, 3H, ArH), 7.20 (d, 2H, ArH), 4.70 (dd, *J* = 12.8 and 7.0, 1H, H-4), 4.60 (dd, *J* = 12.8 and 8.0, 1H, H-4), 3.94 (quint, *J* = 7.3, 1H, H-3), 2.79 (dd, *J* = 4.4 and

7.3, 2H, 2H-2); ^{13}C NMR, δ, ppm: 176.6 (s), 137.9 (s), 129.1 (2d), 128.1 (d), 127.2 (2d), 79.2 (t), 39.7 (d), 37.2 (t); ESI-MS (*m/z*): 210.0 $[M+H]^+$, 232.1 $[M+Na]^+$; MS (*m/z*): 162 (M−47, 73%), 134 (78), 115 (68), 105 (31), 92 (100), 78 (38); Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.3; H, 5.4; N, 6.75.

Enantiomer (*R*)-(+)-**5** was obtained by hydrolysis of (*R*)-(+)-**3** having 99.9% ee, in a refluxing 1:1 mixture of concd AcOH and 1 M HCl; $[\alpha]_D^{25} = +15.6$ (*c* 1, MeOH).

4.4.3. Methyl (*R*)-(+)-3-(4-chlorophenyl)-4-nitrobutanoate 4. Compound (*R*)-(+)-**4** with a 99.9% ee was isolated at the end of the enzymatic hydrolysis of (±)-**4** (53% conversion, 42% yield); $[\alpha]_D^{25} = +4.0$ (*c* 1, $CHCl_3$). {lit.[10h] for the ethyl ester: $[\alpha]_D^{25} = +3.9$ (*c* 0.1, $CHCl_3$)}.

4.4.4. (*S*)-(−)-4-Nitro-3-(4-chlorophenyl)butanoic acid 6. Compound (*S*)-(−)-**6** was obtained with 98% ee by stopping the enzymatic hydrolysis of (±)−**4** at 16% conversion (15% yield). White solid, mp 78–80 °C (lit[10k] 78–79 °C); $[\alpha]_D^{25} = -10.0$ (*c* 1, MeOH) {lit.[10k] $[\alpha]_D = -10.1$ (*c* 2, MeOH)}; IR, cm^{-1} (Nujol): 3500–2400 (broad, CO_2H), 1710 (CO_2H), 1558, 1376 (NO_2), 1596, 1500, 803 (Ph); ^{1}H NMR, δ, ppm: 8.40 (broad, 1H, CO_2H), 7.32 (d, 2H, ArH), 7.17 (d, 2H, ArH), 4.69 (dd, $J = 12.4$ and 7.0, 1H, H-4), 4.59 (dd, $J = 12.4$ and 7.7, 1H, H-4), 3.94 (quint, $J = 7.3$, 1H, H-3), 2.79 (dd, $J = 2.9$ and 7.0, 2H-2); ^{13}C NMR, δ, ppm: 176.0 (s), 136.4 (s), 134.1 (s), 129.3 (2d), 129.4 (2d), 79.0 (t), 39.2 (d), 37.2 (t); ESI-MS (*m/z*): 244.0 $[M+H]^+$, 246.0 $[M+2+H]^+$, 266.1 $[M+Na]^+$; MS (*m/z*): 225 $[(M-18)^+$, 49%], 194 (10), 155 (100), 139 (96), 103 (35); Anal. Calcd for $C_{10}H_{10}ClNO_4$: C, 49.30; H, 4.14; N, 5.75. Found: C, 49.3; H, 4.1; N, 5.65.

Enantiomer (*R*)-(+)-**6** was obtained by hydrolysis of (*R*)-(+)-**4** (99.9% ee) in refluxing AcOH/1 M HCl in a 1:1 ratio for 1 h, as described in the literature.[10k] $[\alpha]_D^{25} = +10.1$ (*c* 1.1, MeOH).

4.5. Reduction of the nitro compounds

4.5.1. (*R*)-(−)-4-Amino-3-phenylbutanoic acid 9. To a solution of (*R*)-(+)-**5** (0.200 g, 1 mmol, 99.9% ee) in ethanol (5 mL), Nickel Raney was added and the mixture hydrogenated at atm pressure until disappearance of the starting material (TLC, eluent: ethyl acetate). The catalyst was filtered off on a pad of Celite and the solvent removed in vacuo to give compound (*R*)-(−)-**9**. (0.15 g, 89% yield). Mp 190–191 °C [lit.[10e] 193 °C]; $[\alpha]_D^{25} = -6.25$ (*c* 0.25, H_2O, pH 7); {lit.[10e] $[\alpha]_D^{25} = -5.8$ (*c* 0.72, H_2O)}. The amino acid was converted into its hydrochloride by treatment of a methanolic solution with HCl(g). The hydrochloride had $[\alpha]_D^{25} = +2.0$ (*c* 2, 1 M HCl) {lit.[5] $[\alpha]_D^{25} = +2.3$ (*c* 1.3, H_2O, HCl)}; IR, cm^{-1} (Nujol): 3000–2000 (broad, CO_2H and NH_3^+), 1715 (CO_2H), 1590, 1520 (NH_3^+), 1490, 1411, 759, 700 (ArH); ^{1}H NMR, δ, ppm (D_2O): 7.43 (d, 2H, ArH), 7.37 (m, 3H, ArH), 3.40 (m, 2H, 2H-4), 3.25 (quint, 1H, H-3), 2.84 (dd, $J = 5.5$ and 16.1, H-2), 2.75 (dd, $J = 5.5$ and 9.8, 2H, H-2); ^{13}C NMR, δ, ppm (D_2O): 175.3 (s), 138.4 (s), 129.4 (2d), 128.4 (d), 128.0 (2d), 43.7 (t), 40.0. (d), 38.1 (t). ESI-MS: 180.1 $[M^+]$, 213.1 $[M+Na]^+$. The enantiomer (*S*)-(+)-**9**, obtained by reduction of (*S*)-(−)-**5** (95% ee) under the same conditions as above, had $[\alpha]_D^{25} = +5.8$ (*c* 0.5, H_2O, pH 7).

4.5.2. (*R*)-(−)-4-Phenylpyrrolidin-2-one 7. (*R*)-(−)-**7** was obtained by reduction of (*R*)-(+)-**3** (0.200 g, 0.9 mmol, 99.9% ee) over Raney Nickel under the conditions described above, followed by purification on column (eluent: ethyl acetate). The pure γ-lactam (0.12 g, 82% yield) had mp 97–99 °C [lit.[12] 101–104 °C; lit.[10e] 98–99 °C]; $[\alpha]_D^{25} = -36$ (*c* 0.5, MeOH) [lit.[10e] $[\alpha]_D = -37$ (*c* 1.09, MeOH)]; IR, cm^{-1} (neat): 3195 (NH), 1698 (CO); ^{1}H NMR, δ, ppm: 7.27 (m, 2H, ArH), 7.20 (m, 3H, ArH), 3.72 (dd, $J = 8.8$ and 8.4, 1H, H-5), 3.64 (quint, 1 H, H-4), 3.36 (dd, $J = 8.4$ and 6.7, 1H, H-5), 2.65 (dd, $J = 8.8$ and 16.8, 1H, H-3), 2.43 (dd, $J = 6.8$ and 16.8, 1H, H-3); ^{13}C NMR, δ, ppm: 178.0 (s); 142.0 (s), 128.6 (2d), 126.9 (d), 126.6 (2d), 49.5 (t), 40.1 (d), 38.35 (t). ESI-MS 162.1 $[M+H]^+$; MS (*m/z*): 161 (M^+, 20%), 132 (55), 104 (100), 78 (73); Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; O, 9.93. Found: C, 74.5; H, 6.8; N, 8.7.

The opposite enantiomer (*S*)-(+)-**7** was obtained starting from the γ-nitroacid (*S*)-(−)-**5** (95% ee), by esterification with CH_2N_2 to the corresponding (*S*)-(+)-**3** and subsequent reduction over Nickel Raney. $[\alpha]_D^{25} = +21.8$ (*c* 0.4, EtOH).

4.5.3. (*R*)-(−)-4-Amino-3-(4-chlorophenyl)butanoic acid 10. Compound (*R*)-(−)-**10** (0.170 g, 80% yield) was obtained from (*R*)-(+)-**6** (0.250 g, 1.0 mmol) by reduction over Nickel Raney. Its hydrochloride had mp 194–195 °C (dec); [lit.[10k] 195 °C]; $[\alpha]_D^{25} = -2.1$ (*c* 1, 1 M HCl) {lit.[10k] $[\alpha]_D^{25} = -2.0$ (*c* 0.60, H_2O)}; IR, cm^{-1} (Nujol): 3400–2500 (CO_2H, NH_3^+) 1716 (CO_2H), 1590, 1518 (NH_3^+), 1492, 1411, 758, 702 (ArH); ^{1}H NMR, δ, ppm (D_2O): 7.34 (m, 4H, ArH), 3.46 (m, 2H, 2H-4), 3.27 (t, $J = 10.6$, 1H, H-3), 2.90 (dd, $J = 4.0$ and 16.2, 2H, H-2), 2.73 (dd, $J = 7.3$ and 16.2, 1H, H-2); ^{13}C NMR, δ, ppm (D_2O): 175.1 (s), 137.4 (s), 133.4 (s), 129.6 (2d), 129.4 (2d), 43.9 (t), 39.3 (d), 38.2 (t). ESI-MS (*m/z*): 214.0 $[M^+]$, 215.0 $[M+H]^+$, 216.0 $[M+2]^+$ 217.0 $[M+2+H]^+$.

The enantiomer (*S*)-(+)-**10**, obtained from (*S*)-(−)-**6**, having a 98% ee, had $[\alpha]_D^{25} = +2.0$ (*c* 0.5, H_2O).

4.5.4. (*R*)-(−)-4-(4-Chlorophenyl)pyrrolidin-2-one 8. (*R*)-(−)-**8** was obtained (0.12 g, 80% yield) by reduction of (*R*)-(+)-**4** (0.200 g, 0.78 mmol, 99.9% ee) over Raney Nickel under the conditions described above, followed by purification on flash-chromatography (eluent: ethyl acetate). White solid, mp 110 °C [lit.[10k] 105–107 °C]; $[\alpha]_D^{25} = -38.0$ (*c* 1, EtOH) {lit.[10k] $[\alpha]_D^{25} = -38$ (*c* 1.02, EtOH)}; IR, cm^{-1} (Nujol): 3196 (NH), 1698 (CO). ^{1}H NMR, δ, ppm: 7.80 (s, 1H, NH), 7.27 (d, 2H, ArH), 7.17 (d, 2H, ArH), 3.76 (dd, $J = 9.8$ and 7.8, 1H, H-5), 3.63 (quint, 1H, H-4), 3.36 (dd, $J = 8.4$ and 7.8, 1H, H-5), 2.71 (dd, $J = 16.5$ and 6.8, 1H, H-3), 2.43 (dd, $J = 16.5$ and 8.4, 1H, H-3); ^{13}C NMR, δ, ppm: 177.7

(s), 140.5 (s), 132.3 (s), 128.6 (2d), 127.8 (2d), 49.25 (t), 39.2 (d), 37.9 (t). ESI-MS (*m*/*z*): 196.0 $[M+H]^+$, 198.0 $[M+2+H]^+$, 218.0 $[M+Na]^+$ 220.0 $[M+2+Na]^+$; MS (*m*/*z*): 195 (M^+, 41%), 167 (10), 138 (100), 103 (74); Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.4; H, 5.0; N, 7.3.

The opposite enantiomer was obtained starting from (*S*)-(−)-**6** (98% ee), by esterification with CH_2N_2 followed by reduction over Nickel Raney, $[\alpha]_D^{25} = +38$ (*c* 1, EtOH).

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