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A concise synthesis of (*S*)-(–)-3-(2-carboxy-4-pyrrolyl)-alanine

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Abstract

A convergent synthesis of (*S*)-(–)-3-(2-carboxy-4-pyrrolyl)-alanine (CPA) **1**, a non-proteinogenic amino acid is described starting from a commercially available dimethyl L-aspartate **2** in good overall yield.

1. Introduction

The poisonous mushroom *Clitocybe acromelalga*, found exclusively in Japan, has been the source for a variety of potent neuroexcitatory amino acids related to the kainoid family.[1,2] (*S*)-(–)-3-(2-Carboxy-4-pyrrolyl)-alanine (CPA) **1** was isolated from the fruit bodies of this mushroom by a combination of ion-exchange column chromatography and paper electrophoresis.[3] The structure of CPA **1** was determined[3] by spectroscopic studies and confirmed by its racemic synthesis, which was achieved in seven steps starting from 2-carboxypyrrole. The synthetic (±)-CPA **1** was subsequently resolved on a chiral TLC plate and the faster moving isomer with R_f 0.65 (MeOH:H_2O:MeCN, 1:1:4 ratio), which exhibited the (+) Cotton effect, was identified to be (*S*)-**1**.[3] Intrigued by the novel structural features of this non-proteinogenic amino acid (*S*)-(–)-**1** and its potential applications in neuroscience research,[2] we decided to devise an efficient asymmetric synthesis of (*S*)-(–)-**1**, which would also be amenable for the preparation of its structural analogs. Our previous work in the area of 2-carboxypyrroles and their derivatives[4] has provided the foundation for the synthesis of amino acid (*S*)-(–)-**1**. In this paper, we describe a concise synthesis of (*S*)-(–)-**1** starting from a commercially available dimethyl L-aspartate **2**.

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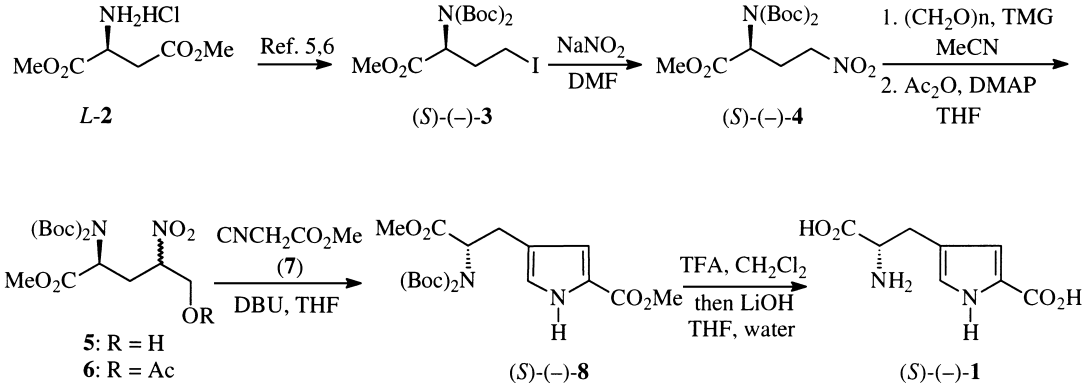
2. Results and discussion

The crucial step in the synthesis of (*S*)-(–)-**1** involves (Scheme 1) a base-promoted condensation–cyclization of α-acetoxynitro compound **6** with methyl isocyanoacetate **7** to afford the 2-carboxy-pyrrole derivative (*S*)-(–)-**9**. The α-acetoxynitro compound **6** was envisioned from a commercially available dimethyl L-aspartate **2**. Accordingly, the aspartic acid derivative **2** was transformed to the iodide (*S*)-(–)-**3** in three steps on a 13 g scale.[5,6] Subsequent treatment of iodide (*S*)-(–)-**3** with sodium nitrite in DMF afforded the nitro compound (*S*)-(–)-**4** in 52% yield after silica gel column chromatography. The nitro compound (*S*)-(–)-**4** was then treated with 37% aqueous formaldehyde in the presence of tetramethylguanidine (TMG) in acetonitrile to give the α-hydroxynitro compound **5** in 48% yield as a mixture of diastereomers (63:37 ratio). Since the new stereogenic center at the NO_2 group in compound **5** would be eventually eliminated during the pyrrole ring formation, the diastereomeric mixture of **5** as such was converted to the corresponding acetate derivative **6** by treatment with acetic anhydride in THF in 72% yield. The α-acetoxynitro compound **6** was then subjected to the crucial condensation–cyclization reaction[4,7] with methyl isocyanoacetate **7** in the presence of DBU in THF. Purification of the crude compound by silica gel column chromatography afforded the key intermediate 2-methoxycarbonyl-4-substituted pyrrole derivative (*S*)-(–)-**8** in 58% yield as a white solid. The synthesis of (*S*)-(–)-CPA **1** would only require unmasking both the *t*-butoxycarbonyl (Boc) and methyl ester protective groups. Thus, (*S*)-(–)-**8** was first treated with trifluoroacetic acid in methylene chloride to cleave the Boc groups and then the resulting crude amino compound subjected to the hydrolysis of methyl esters with lithium hydroxide. Purification of the crude product by preparative reversed phase HPLC followed by lyophilization afforded the desired (*S*)-(–)-3-(2-carboxy-4-pyrrolyl)-alanine-TFA salt (CPA) **1** in 59% yield as a white/pale pink powder.

In summary, a general and convergent synthesis of (*S*)-(–)-3-(2-carboxy-4-pyrrolyl)-alanine (CPA) **1** is described starting from a commercially available dimethyl L-aspartate **2** in good overall yield.



Scheme 1.

3. Experimental

3.1. General methods and materials

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz) and the chemical shifts (δ) reported in ppm relative to TMS. Electrospray ionization mass spectrometry (ESI-MS) was carried out on a Perkin–Elmer (Norwalk, CT) Sciex API 100 Benchtop system employing Turbo IonSpray ion source and the HRMS were obtained on a Nermang 3010 MS-50, JEOL SX102-A. Thin layer chromatography was performed on a pre-coated Whatman MK6F silica gel 60 Å plates (layer thickness: 250 μm) and visualized with UV light and/or using 0.2% ninhydrin in ethanol. Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). Anhydrous solvents were freshly distilled [(THF from a purple solution of sodium and benzophenone) and (CH_2Cl_2 from CaH_2)] under nitrogen. All reagents were purchased from the Aldrich Chemical Co. (Milwaukee, WI) or the Sigma Chemical Co. (St. Louis, MO). All the solvents employed were of HPLC grade purchased from EM Science (Gibbstown, NJ). Analytical reversed phase (RP) HPLC was performed using a Waters, Novapak, RCM C18, 7.0 μm (8×100 mm) column. Preparative reversed phase (RP) HPLC was performed using a Waters, Novapak RCM C18, 7.0 μm (40×100 mm) column. Optical rotations were measured on Autopol III polarimeter from Rudolph Research, Flanders, NJ.

3.2. (S)-(–)-Methyl 2-[bis(tert-butoxycarbonyl)amino]-4-iodobutanoate **3**

Triethylamine (12.4 mL, 89.1 mmol, 1.1 equiv.) and $(Boc)_2O$ (19.5 g, 89.3 mmol, 1.1 equiv.) were added sequentially to a suspension of dimethyl-L-aspartate HCl **2** (16.0 g, 81.0 mmol) in THF (120 mL) at room temperature under nitrogen. The mixture was stirred for 2.5 h and concentrated on a rotary evaporator. The residue was dissolved in EtOAc (200 mL), washed with water (200 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The resulting white solid, dimethyl *N*-(*tert*-butoxycarbonyl)-L-aspartate, was dissolved in THF (120 mL) and a solution of $(Boc)_2O$ (35.4, 162.0 mmol, 2.0 equiv.) in THF (80 mL) was added at room temperature under nitrogen. After stirring the mixture for 22 h, it was concentrated to dryness on a rotary evaporator and purified by silica gel column chromatography (30% EtOAc in hexanes) to afford 23.6 g of (–)-dimethyl *N*,*N*-bis(*tert*-butoxycarbonyl)-L-aspartate in 81% yield as a colorless viscous oil. R_f: 0.41 (30% EtOAc in hexanes); $[\alpha]_D^{23}$ –63.9 (*c* 2.01, MeOH); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 60:40, 2.0 mL/min at 215 nm, R_t: 4.03 min, 97%; ^{1}H NMR ($CDCl_3$): δ 5.45 (t, 1H, J=6.6 Hz), 3.73 (s, 3H), 3.71 (s, 3H), 3.25 (dd, 1H, J=16.5, 7.2 Hz), 2.73 (dd, 1H, J=16.5, 6.6 Hz), 1.51 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 170.9, 170.2, 151.5, 83.4, 54.8, 52.4, 51.8, 35.6, 27.9; ESI-MS (*m*/*z*): 362 $(M+H)^+$; HRMS (FAB, *m*/*z*) calcd for $C_{16}H_{27}NO_8$: 362.1815 $(M+H)^+$; observed: 362.1827.

DIBAL-H (1.0 M soln in toluene, 72.0 mL, 72.0 mmol, 1.1 equiv.) was added to a –78°C cooled solution of (–)-dimethyl *N*,*N*-bis(*tert*-butoxycarbonyl)-L-aspartate (23.5 g, 65.0 mmol) in ether (500 mL) over a 10 min period under nitrogen. After stirring the mixture for 15 min, water (17 mL) was added at –78°C and the mixture allowed to warm to room temperature. The resulting white precipitate was filtered through celite powder and washed with ether (3×100 mL). The filtrate was concentrated on a rotary evaporator and the residual water was azeotropically removed using toluene (3×100 mL). The crude compound was purified by silica gel column chromatography (30% EtOAc in hexanes) to afford 18.5 g of (*S*)-(–)-methyl-2-[bis(*tert*-

butoxycarbonyl)amino]-4-oxobutanoate in 86% yield as a colorless viscous oil. R_f: 0.30 (30% EtOAc in hexanes); $[\alpha]_D^{23}$ –52.5 (*c* 1.34, MeOH); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 60:40, 2.0 mL/min at 215 nm, R_t: 3.12 min, 92%; ^{1}H NMR ($CDCl_3$): δ 9.80 (s, 1H), 5.54 (t, 1H, $J=6.3$ Hz), 3.74 (s, 3H), 3.48–3.38 (m, 1H), 2.88–2.79 (m, 1H), 1.51 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 198.3, 170.2, 151.6, 83.6, 52.8, 52.6, 44.9, 27.9; ESI-MS (*m*/*z*): 332 $(M+H)^+$, 680 $(2\times M+NH_4)^+$.

Sodium borohydride (3.82 g, 101.0 mmol, 2.0 equiv.) was added to a 0°C cooled a solution of (*S*)-(–)-methyl-2-[bis(*tert*-butoxycarbonyl)amino]-4-oxobutanoate (16.8 g, 50.7 mmol) in MeOH (250 mL) under nitrogen. The mixture was stirred for 45 min, quenched with water (400 mL) and extracted with EtOAc (3×400 mL). The combined organic layers were dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 11.39 g of (*S*)-(–)-methyl-2-[bis(*tert*-butoxycarbonyl)amino]-4-hydroxybutanoate in 67% yield as colorless viscous oil. R_f: 0.31 (50% EtOAc in hexanes); $[\alpha]_D^{23}$ –36.6 (*c* 1.58, MeOH); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 50:50, 2.0 mL/min at 215 nm, R_t: 3.33 min, 97.1%; ^{1}H NMR ($CDCl_3$): δ 5.00 (dd, 1H, $J=9.9$, 4.5 Hz), 3.80–3.68 (m, 1H), 3.74 (s, 3H), 3.64–3.53 (m, 1H), 2.52 (dd, 1H, OH, $J=8.1$, 4.8 Hz), 2.48–2.36 (m, 1H), 2.08–1.97 (m, 1H), 1.51 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 171.2, 152.3, 83.5, 58.8, 55.3, 52.2, 32.9, 27.8; ESI-MS (*m*/*z*): 334 $(M+H)^+$; HRMS (FAB, *m*/*z*) calcd for $C_{15}H_{27}NO_7$: 334.1866 $(M+H)^+$; observed: 334.1850.

Triphenylphosphine (13.4 g, 51.0 mmol, 1.5 equiv.), imidazole (3.70 g, 54.4 mmol, 1.6 equiv.) and iodine (12.9 g, 51.0 mmol, 1.5 equiv.) were added sequentially to a solution of (*S*)-(–)-methyl-2-[bis(*tert*-butoxycarbonyl)amino]-4-hydroxybutanoate (11.34 g, 34.0 mmol) in THF (170 mL) at room temperature under nitrogen. After stirring the mixture for 2 h, it was diluted with 20% aq. NaCl (340 mL) and extracted with EtOAc (3×340 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed on a rotary evaporator. The crude product was purified by silica gel column chromatography (10% EtOAc in hexanes) to afford 13.63 g of (*S*)-(–)-methyl-2-[bis(*tert*-butoxycarbonyl)amino]-4-iodobutanoate (**3**) in 90% yield as a pale yellow viscous oil. R_f: 0.36 (20% EtOAc in hexanes); $[\alpha]_D^{23}$ –45.5 (c 1.44, MeOH); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 70:30, 2.0 mL/min at 215 nm, R_t: 5.00 min, >99%; ^{1}H NMR ($CDCl_3$): δ 5.00 (dd, 1H, $J=8.4$, 5.4 Hz), 3.73 (s, 3H), 3.34–3.15 (m, 2H), 2.76–2.64 (m, 1H), 2.44–2.34 (m, 1H), 1.51 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 170.4, 151.8, 83.5, 58.4, 52.3, 34.5, 27.9, 1.6; ESI-MS (*m*/*z*): 444 $(M+H)^+$, 904 $(2\times M+NH_4)^+$; HRMS (FAB, *m*/*z*) calcd for $C_{15}H_{26}NO_6I$: 444.0883 $(M+H)^+$; observed: 444.0869.

3.3. (S)-(–)-Methyl 2-[bis(tert-butoxycarbonyl)amino]-4-nitrobutanoate 4

Sodium nitrite ($NaNO_2$, 3.88 g, 56.2, mmol, 2.0 equiv.) was added to a solution of (*S*)-(–)-iodide **3** (12.46 g, 28.1, 1.0 equiv.) in DMF (140 mL) at room temperature under nitrogen. After stirring the mixture for 2 h, it was diluted with 20% aq. NaCl (300 mL) and extracted with EtOAc (3×300 mL). The combined organic layers were dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (20–30% EtOAc in hexanes) to afford 5.08 g of (*S*)-(–)-**4** in 50% yield as a colorless viscous oil. R_f: 0.30 (30% EtOAc in hexanes); $[\alpha]_D^{23}$ –29.5 (c 1.35, MeOH); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 60:40, 2.0 mL/min at 215 nm, R_t: 4.09 min, >99%; ^{1}H NMR ($CDCl_3$): δ 5.00 (dd, 1H, $J=8.7$, 5.4 Hz), 4.51 (t, 2H, $J=6.9$ Hz), 3.75 (s, 3H), 2.95–2.83 (m, 1H), 2.60–2.47

(s, 1H), 1.50 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 170.0, 151.6, 84.0, 72.1, 55.4, 52.5, 27.9, 27.6; ESI-MS (m/z): 363 $(M+H)^+$, 380 $(M+NH_4)^+$, 747 $(M+Na)^+$; HRMS (FAB, m/z) calcd for $C_{15}H_{26}N_2O_8$: 363.1767 $(M+H)^+$; observed: 363.1781.

3.4. *Methyl 2-[bis(*tert-*butoxycarbonyl)amino]-5-hydroxy-4-nitropentanoate* **5**

1,1,3,3-Tetramethyl guainidine (TMG, 0.005 mL, 0.04 mmol, 0.03 equiv.) was added to a mixture of (*S*)-(–)-methyl-2-[bis-(*tert*-butoxycarbonyl)amino]-4-nitrobutanoate (**4**, 4.332 g, 12.0 mmol) and 37% aq. formaldehyde (1.17 mL, 14.4 mmol, 1.2 equiv.) in MeCN (20 mL) at room temperature under nitrogen. After stirring the reaction mixture for 1.5 h, it was diluted with 20% aq. NaCl (100 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed on a rotary evaporator. The crude product was purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 2.273 g of α-hydroxynitro compound **5** in 48% yield as a mixture of diastereomers (ratio, 37:63, colorless viscous oil). R_f: 0.32 (40% EtOAc in hexanes); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 50:50, 2.0 mL/min at 215 nm, R_t: 4.37 and 4.70 min, 99%; ^{1}H NMR ($CDCl_3$): δ 5.02–4.96 (m, 1H), 4.82–4.74 and 4.72–4.63 (m, 1 H), 4.07–4.05 (m, 2H), 3.75 (s, 3H), 3.00–2.90 and 2.76–2.66 (m, 1H), 2.58–2.48 and 2.44–2.34 (m 1H), 2.24–2.14 (m, 1H, OH), 1.51 and 1.50 (two s, 18H); ESI-MS (m/z): 393 $(M+H)^+$, 400 $(M+NH_4)^+$, 802 $(M+NH_4)^+$; HRMS (FAB, m/z) calcd for $C_{16}H_{28}N_2O_9$: 393.1873 $(M+H)^+$; observed: 393.1880.

3.5. *Methyl 2-[bis(*tert-*butoxycarbonyl)amino]-5-acetoxy-4-nitropentanoate* **6**

Acetic anhydride (0.786 mL, 8.33 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (DMAP, 0.068 g, 0.56 mmol, 0.1 equiv.) were added sequentially to a solution of a diastereomeric mixture of α-hydroxy compound **5** (2.178 g, 5.55 mmol) in THF (50 mL) at room temperature under nitrogen. After stirring the mixture for 30 min, it was diluted with 20% aq. NaCl solution (100 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed on a rotary evaporator. The crude product was purified by silica gel column chromatography (25–30% EtOAc in hexanes) to afford 1.727 g of α-acetoxynitro compound **6** in 72% yield as a mixture of diastereomers (colorless viscous oil). R_f: 0.31 (30% EtOAc in hexanes); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid/60:40, 2.0 mL/min at 215 nm, R_t: 4.74 and 5.07 min, 98%; ^{1}H NMR ($CDCl_3$): δ 5.24–4.92 and 4.80–4.72 (m, 2H), 4.43–4.36 (m, 2H), 3.76 and 3.75 (two s, 3H), 3.20–2.24 (m, 2H), 2.08 and 2.06 (two s, 3H), 1.50 (s, 18H); ESI-MS (m/z): 435 $(M+H)^+$, 452 $(M+NH_4)^+$, 886 $(2\times M+NH_4)^+$, 891 $(M+Na)^+$; HRMS (FAB, m/z) calcd for $C_{18}H_{30}N_2O_{10}$: 435.1979 $(M+H)^+$; observed: 435.1990.

3.6. *(–)-Methyl 4-(2*S*)-2-[bis(*tert-*butoxycarbonyl)amino]-3-(methoxy)-3-oxopropyl]-1*H*-pyrrole-2-carboxylate* **8**

1,8-Diazabicyclo[5,4,0]undec-7-ene (DBU, 1.39 mL, 9.28 mmol, 2.5 equiv.) was added to a 0°C cooled solution of the diastereomeric mixture of α-acetoxynitro compound **6** (1.611 g, 3.71 mmol) and methyl isocyanoacetate (**7**, 0.438 mL, 4.82 mmol, 1.3 equiv.) in THF (30 mL) under nitrogen. After stirring the mixture for 30 min, the cooling bath was removed and the stirring continued for an additional 4.5 h. The reaction mixture was diluted with 20% aq. NaCl (100 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was

removed on a rotary evaporator. The crude product was purified twice by silica gel column chromatography (30–40% EtOAc in hexane) to afford 0.923 g of pyrrole derivative (*S*)-(–)-**8** in 58% yield as a white glassy material. R_f: 0.17 (30% EtOAc in hexanes); $[\alpha]_D^{23}$ –86.3 (*c* 1.18, MeOH); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 60:40, 2.0 mL/min at 215 nm, R_t: 3.49 min, 96%; ^{1}H NMR ($CDCl_3$): δ 8.23 (br s, 1H), 6.77–6.74 (m, 2H), 5.05 (dd, 1H, $J=10.2$, 5.1 Hz), 3.82 (s, 3H), 3.74 (s, 3H), 3.28 (dd, 1H, $J=14.7$, 5.1 Hz), 3.80 (dd, 1H, $J=14.7$, 10.2 Hz), 1.43 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 170.9, 161.5, 151.8, 122.3, 122.1, 121.2, 115.9, 83.0, 59.0, 52.2, 51.3, 27.8, 27.4; ESI-MS (*m*/*z*): 427 $(M+H)^+$, 444 $(M+NH_4)^+$, 870 $(M+NH_4)^+$; HRMS (FAB, *m*/*z*) calcd for $C_{20}H_{30}N_2O_8$: 426.2002 $(M)^+$; observed: 426.2008.

3.7. (S)-(–)-3-(2-Carboxy-4-pyrrolyl)-alanine (CPA) **1**

Trifluoroacetic acid (10 mL) was added to the pyrrole derivative (*S*)-(–)-**8** (0.548 g, 1.29 mmol) in CH_2Cl_2 (10 mL) at room temperature and stirred for 30 min. The mixture was concentrated on a rotary evaporator and the residual trifluoroacetic acid was removed azeotropically using toluene (5×10 mL). The resulting crude amine was dried on a vacuum pump (1.0 mm/Hg) for 20 min and dissolved in THF (30 mL). To this mixture, LiOH (monohydrate, 1.08 g, 25.8 mmol, 20.0 equiv.) and water (45 mL) were added at room temperature and the mixture was stirred for 1.5 h. Progress of the reaction was monitored by analytical RP HPLC (MeCN:0.1% aq. trifluoroacetic acid, 4:96, 2.0 mL/min at 215 nm). An additional amount of LiOH (monohydrate, 0.271 g, 6.45 mmol, 5.0 equiv.) was added to the reaction mixture and the stirring was continued at room temperature. After 1.5 h, pH of the mixture was adjusted to about 7.0 using 0.1% aq. trifluoroacetic acid and concentrated on a rotary evaporator. The residue (1.16 g) was dissolved in a mixture of MeCN:0.1% aq. trifluoroacetic acid (40 mL, 4:96 ratio) and purified by preparative RP HPLC (MeCN:0.1% aq. trifluoroacetic acid, 4:96, 40 mL/min at 215 nm). The product was concentrated on a rotary evaporator to about 100 mL volume and lyophilized to afford 0.235 g of (*S*)-(–)-CPA (**1**) as its TFA salt in 59% yield (white/pale pink powder). Analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid, 6:94, 2.0 mL/min at 215 nm, R_t: 2.80 min, >99%; $[\alpha]_D^{23}$ –2.98 (c 1.14, 1.0 M aq. NaOH); CD spectra: (23°C; c 0.00011 g/mL H_2O) $[\theta]_{215}$ +2835 L cm^{-1} mol^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.16 (brs, 3H), 6.83 (d, 1H, $J=1.5$ Hz), 6.63 (d, 1H, $J=1.5$ Hz), 4.14–4.06 (m, 1H), 3.41 (br s, 2H), 2.95 (d, 2H, $J=5.4$ Hz); ^{13}C NMR (DMSO-d_6): δ 170.6, 161.8, 123.1, 116.4, 115.3, 52.9, 27.4; ESI-MS (*m*/*z*): 199 $(M+H)^+$, 397 $(2\times M+H)^+$; HRMS (FAB, *m*/*z*) calcd for $C_8H_{10}N_2O_4$: 199.0719 $(M+H)^+$; observed: 199.0719.

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