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First stereoselective synthesis and assignment of the absolute configuration of the nebracetam eutomer and derivatives

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Abstract—(−)-Nebracetam **1** was stereoselectively prepared for the first time, allowing the determination of its absolute configuration as (*R*). The pivotal intermediate in the synthesis, 1-benzyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-pyrrolidin-2-one **6**, was previously obtained in 60% yield and 90% ee from an enoate derived from D-mannitol. Two approaches were investigated to synthesize (*R*)-(−)-nebracetam **1** and analogues **4** and **5** from **6**. Compound **6** was transformed into WEB-1868 **2**. Mesylation of the hydroxyl group in **2**, followed by nucleophilic substitution with azide and reduction led to target **1**. Compounds **4** and **5** were synthesized by using morpholine and *N*-methyl piperazine as nucleophiles. Compounds **4** and **5** were also prepared, in higher yields and similar ee, through the reductive amination of aldehyde **10**, obtained in two steps from **6**.

1. Introduction

The pyrrolidin-2-one nucleus is embedded in the structure of several bioactive compounds.[1a–e] Some of these substances substituted at C-4 display outstanding biological activities, such as (*R*)-rolipram, a potent and selective PDE4 inhibitor[2a–c] and a HIV-1 replication inhibitor.[2d] 4-Substituted derivatives have also been used as intermediates in the synthesis of pyrrolidines, such as a selective agonist of HT_3 histaminic receptors,[1b] and γ-amino acids, such as (*R*)-baclofen.[1c–e] Nebracetam **1**,[3a–e] its fumarate salt (WEB-1881),[3f] as well as WEB-1868 **2**[3g] and **3** (Fig. 1) act as nootropic agents[3h] and are hailed as smart drugs. These increase the faculties of the mind like bolstering cognition, lucidity, memory and mood.[3h,i] Nebracetam **1** is awaiting marketing approval in Japan to be used as a cognitive enhancer[3a,b] and acts as a partial agonist at the presynaptic muscarinic receptor. Dopaminergic and serotonergic uptakes are also reduced by **1**, and intracellular calcium flux is inhibited in response to glutaminergic stimulation.[3b] These pyrrolidones are promising for the prevention and symptomatic treatment of degenerative senior's diseases, and were patented as antidepressant drugs.[4] The enantiomers of **1** were obtained by chemical resolution and the *levo* isomer proved to be 10 times more active than the *dextro* one,[3b,j] but its absolute configuration was not determined. On the other hand, the enantiomers of **2** were

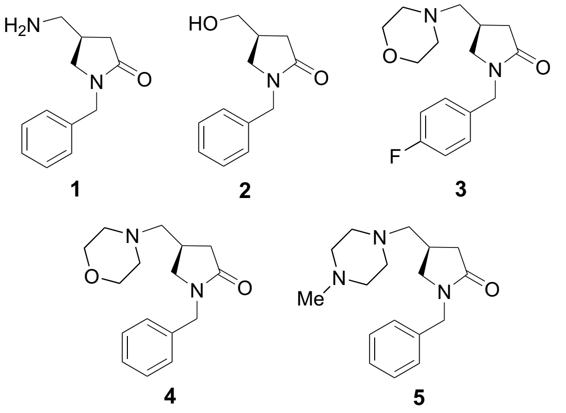

Figure 1. Nebracetam, (*R*)-(−)-**1**, and analogues.

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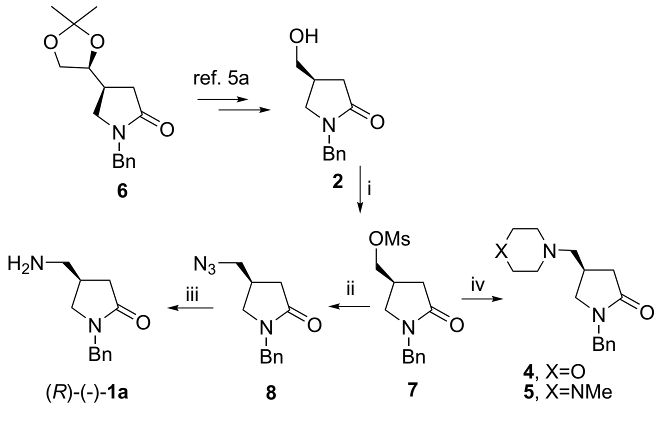
almost equipotent[3e] and for compound **3**, no correlation between biological activity and configuration was done.

Herein, we report the first stereoselective synthesis of (−)-**1**, allowing the determination of its configuration as *R*. New derivatives of **1** (Fig. 1), (*R*)-(−)-**4** and (*R*)-(−)-**5**, were also stereoselectively synthesized by two different approaches.

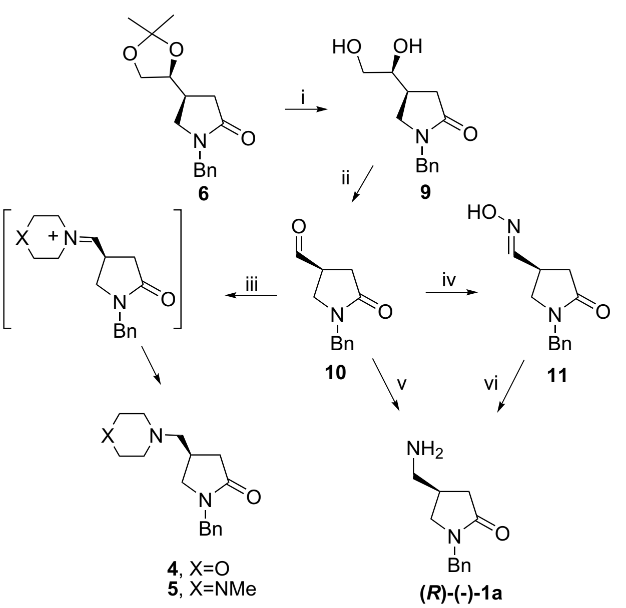
2. Results and discussion

We had previously reported the synthesis of homochiral compound **6** from a *Z*-enoate derived from D-(+)-mannitol, in three steps and 52% overall yield. This compound was used as an intermediate in the synthesis of (*S*)-(−)-WEB-1868 **2**.[5a] In Scheme 1, the use of this alcohol as a precursor of (−)-nebracetam **1** and derivatives[5b] (−)-**4**, (−)-**5** is shown. Alcohol **2** was mesylated under the standard conditions, leading to **7** in 96% yield.[6] Nucleophilic substitution of the mesylate group in **7** by azide[6] in DMF (90%), followed by the reduction of the crude resulting intermediate **8** with Na_2S[6] in solution of methanol–water (79%), led to the most active enantiomer (eutomer) of (−)-nebracetam **1**, and to the establishment of its absolute configuration as (*R*). Once alcohol **2** was obtained in good enantiomeric excess, (95:5 as determined by Mosher ester analysis) and as its transformation into (−)-**1** does not involve the stereogenic centre, we can conclude that both products have the same enantiomeric purity.[7] Compound **4** was obtained from **7** in 55% yield by reflux in dioxan in the presence of morpholine for long periods of time (~20 h). The yield was improved (86%) when the reaction was carried out in the absence of the solvent. Compound **5** was prepared by the same strategy in 70% yield (Scheme 1).

We attempted to shorten the synthesis and improve the overall yield by directly using aldehyde **10** as a precursor of the target molecules. The hydrolysis of the dimethylketal group at **6**, followed by the oxidation of the resulting diol **9** with $NaIO_4$ led to **10**, which was immediately used in the next step (Scheme 2). Under the conditions of reductive amination,[8] **10** reacted either with morpholine or with *N*-methylpiperazine leading directly to **4** or **5**, respectively, in 87% and 93% yield. Unfortunately, under modified Leukart condition, **10** led to **1** in poor yields (<10% by GC–MS). Attempts at partial reduction of oxime **11** to *N*-hydroxinebracetam furnished nebracetam, instead, in low yields. The yield of **1** could not be improved using excess $NaBH_3CN$.



Scheme 1. Synthesis of (−)-**1**, (−)-**4** and (−)-**5** from chiral compound **6**. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 96%; (ii) NaN_3, DMF, 100 °C, 90%; (iii) Na_2S, MeOH, H_2O, 79%; (iv) morpholine, neat, 86% or *N*-methylpiperazine, neat, 70%.



Scheme 2. Alternative synthesis of **1**, **4** and **5**. Reagents and conditions: (i) HCl 6 M, MeOH, 84%; (ii) $NaIO_4$, H_2O–MeOH, 94%; (iii) HCl, MeOH, $NaBH_3CN$ and morpholine (**4**, 87%) or *N*-methylpiperazine (**5**, 93%); (iv) $NH_2OH{\cdot}HCl$, $NaHCO_3$, Na_2SO_4, CH_2Cl_2, 89%, (*E*:*Z*, 84:16); (v) $AcONH_4$, $NaBH_3CN$, MeOH, <10%; (vi) $NaBH_3CN$, MeOH, pH 3, <10%.

The specific rotations of compounds **4** and **5** prepared by reductive amination from **10** were found to be very similar to those obtained for these compounds when synthesized from alcohol **2**, showing that the reductive amination of **10** occurs without racemization.

3. Conclusion

Herein, we have reported the first enantioselective synthesis of nebracetam (−)-**1**, allowing the (*R*)-configuration to be established for this compound. Analogues (−)-**4** and (−)-**5** were also enantioselectively prepared from **6**, in either four steps, via nucleophilic substitution (Scheme 1, 45–55% overall yield), or, more conveniently and efficiently, in three steps by means of reductive amination (Scheme 2, 73–87% overall yield).

Since key compound **6** can also be obtained in its enantiomeric form from vitamin C,[9] the disclosed synthetic strategy represents a broad access to pyrrolidin-2-ones with different patterns of substitution and configuration at the 4-position.

4. Experimental

4.1. *N*-Benzyl-(4*S*)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-pyrrolidin-2-one 6

To a mixture of the *syn*-nitroadduct obtained by conjugate addition of nitromethane to the enoate derived from D-mannitol[10] (260 mg, 1.0 mmol) and Pd/C 10% (65 mg, 25% w/w) in methanol was added ammonium formate (760 mg, 12.0 mmol).[11] The reaction mixture was submitted to sonication for 2 h (total disappearance of the starting material detected by TLC). The crude mixture was filtered through Celite and the solvent evaporated in vacuo. The resulting material was purified by flash column chromatography with methanol–ethyl acetate (5:95) to give a solid in 86% yield (160 mg). A solution of this compound in dry THF (1.8 mL) was added dropwise to a suspension of NaH (31 mg, 1.3 mmol) in THF (6.5 mL). After 1 h, BnBr was added (192.0 mg, 1.12 mmol) in THF (1.1 mL) and the mixture was stirred at rt for 24 h. The excess of NaH was destroyed by the addition of brine (10.0 mL) and the resulting mixture was extracted with CH_2Cl_2 (5 × 15.0 mL). The organic phases were mixed, dried over Na_2SO_4, filtered and concentrated in vacuo to give a pale solid in 87% yield (206 mg). $[\alpha]_D = -4.4$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.39–7.19 (s, 5H), 4.47 (d, 1H, $J = 14.7$ Hz), 4.24 (d, 1H, $J = 14.7$ Hz), 3.60–3.16 (s, 5H), 2.60–2.10 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 173.0, 135.9–127.4, 109.1, 77.4, 67.4, 48.7, 46.3, 34.3, 33.3, 26.3, 25.0. MS (EI, 70 eV): *m*/*z* 275 (11), 218 (11), 202 (26), 173 (36), 91 (100), 65 (13).

4.2. *N*-Benzyl-(4*S*)-4-[(1′*S*)-1′,2′-dihydroxyethyl]pyrrolidin-2-one 9

To a solution of **5** (140 mg, 0.51 mmol) in MeOH (4.5 mL) was added aqueous 6 N HCl (0.04 mL) at room temperature. After stirring for 3 h, the solvent was removed in vacuo and the material obtained was dissolved in CH_2Cl_2 (10.0 mL), dried with K_2CO_3 and filtered. Removal of solvent gave **9** as a solid (106 mg, 84%), which was used for the next step without purification. $[\alpha]_D = -15.0$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.34–7.10 (m, 5H), 4.47 (d, 1H, $J = 14.7$ Hz), 4.24 (d, 1H, $J = 14.7$ Hz), 3.65–3.16 (m, 5H), 2.58–2.20 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 174.2, 135.5–127.3, 73.4, 64.4, 48.7, 46.2, 33.7, 33.5. MS (EI, 70 eV): *m*/*z* 235 (%) (21, M^+), 146 (14), 119 (9), 91 (100), 65 (18).

4.3. *N*-Benzyl-(4*S*)-4-hydroxymethyl pyrrolidin-2-one (2, WEB-1868)

To a solution of diol **9** (70 mg, 0.30 mmol) in H_2O–MeOH (3:1, 3.2 mL) was added $NaIO_4$ (90 mg, 0.40 mmol). After stirring for 1.5 h at room temperature, the mixture was cooled to 0 °C and $NaBH_4$ (15 mg, 0.39 mmol) was added. After stirring for 3 h, the mixture was extracted with CH_2Cl_2 (5 × 12 mL). The organic layers were dried over sodium sulfate, the solvent was removed in vacuo and the residue was purified by flash column chromatography (MeOH–ethyl acetate, 1:9) affording alcohol **2** as an oil (42 mg, 79%). $[\alpha]_D = -10.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.39–7.05 (m, 5H), 4.45 (d, 1H, $J = 14.6$ Hz), 4.33 (d, 1H, $J = 14.6$ Hz), 3.61–3.50 (m, 2H), 3.37 (dd, 1H, $J = 9.8$ Hz; 8.2 Hz), 3.09 (dd, 1H, $J = 9.8$ Hz; 4.8 Hz), 2.60–2.39 (m, 2H), 2.36–2.18 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 174.2, 135.8–127.3, 63.9, 49.1, 46.3, 33.7, 32.8. MS (EI, 70 eV): *m*/*z* 205 (%) (43, M^+), 174 (6), 146 (28), 114 (23), 104 (26), 91 (100), 65 (31), 55 (13).

4.4. *N*-Benzyl-(4*S*)-4-methanesulfonylmethyl-pyrrolidin-2-one 7

A solution of **2** (0.10 g, 0.48 mmol) and triethylamine (0.06 mL, 0.58 mmol) in CH_2Cl_2 (4.8 mL) was cooled to 0 °C. Mesyl chloride (0.08 g, 0.55 mmol) was added dropwise over 15 min to the vigorously stirred solution. The reaction mixture was allowed to stir for an additional 15 h at rt after the addition of mesyl chloride had been completed. To this solution was added 15.0 mL of CH_2Cl_2 and the resulting slurry was washed with 3 × 8.0 mL portions of saturated aqueous sodium bicarbonate, followed by 3 × 8.0 mL portions of water. The organic layer was dried, filtered and evaporated to an orange oil**,** mesylate **7** (0.13 g, 96%). Mesylate **7** was converted to azide **8**, without further purification. $[\alpha]_D = -3.0$ (*c* 2.36, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.38–7.20 (m, 5H), 4.42 (s, 2H), 4.16 (dd, 1H, $J = 9.9$ Hz; 5.9 Hz), 4.09–4.04 (m, 1H), 3.41 (dd, 1H, $J = 10.2$ Hz; 8.1 Hz), 3.09 (dd, 1H, $J = 10.2$ Hz; 4.8 Hz), 2.94 (s, 3H), 2.80–2.72 (m, 1H), 2.62 (dd, 1H, $J = 16.5$ Hz; 9.2 Hz), 2.26 (dd, 1H, $J =$ 16.5 Hz; 5.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 172.2, 135.6–127.3, 70.1, 48.2, 46.0, 36.8, 33.1, 30.2; MS (EI, 70 eV): *m*/*z* 283 (%) (26, M^+), 254 (5), 146 (20), 119 (33), 96 (33), 91 (100), 65 (25), 55 (13).

4.5. *N*-Benzyl-(4*S*)-4-azidomethyl-pyrrolidin-2-one 8

Mesylate **7** (93 mg, 0.33 mol) was dissolved in 2.0 mL of DMF, followed by the addition of sodium azide (33 mg, 0.50 mmol) and the resulting solution was heated at 100 °C for 7 h, leading to a complete consumption of **7**. The reaction mixture was cooled to rt, after which 8.0 mL of saturated brine was added and the solution was extracted with 5 × 15 mL portions of ethyl acetate. The combined organic layer was washed with 2 × 8.0 mL portions of water, dried and then evaporated, furnishing a yellow oil, azide **8** (70 mg, 90%). The crude product was used to prepare **(−)-1**. $[\alpha]_D = +2.2$ (*c* 0.90, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.39–7.15 (m, 5H), 4.44 (s, 2H), 3.42–3.23 (m, 3H), 3.02 (dd, 1H, $J =$ 10.1 Hz; 5.13 Hz), 2.68–2.45 (m, 2H), 2.32–2.10 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 172.9, 135.8–127.4, 54.1, 49.2, 46.3, 34.6, 30.9; (EI, 70 eV): *m*/*z* 230 (%) (8, M^+), 202 (4), 173 (15), 118 (12), 91 (100), 65 (27), 56 (16).

4.6. *N*-Benzyl-(4*R*)-4-aminomethyl pyrrolidin-2-one (−)-1 (nebracetam)

Azide **8** (54 mg, 0.24 mmol) was dissolved in 0.6 mL of CH_3OH and a solution of Na_2S (24 mg, 0.31 mmol) in

1.2 mL of H_2O was added. The two-phase mixture was heated to 65 °C and stirred at that temperature overnight. The resulting homogeneous orange solution was saturated with NaCl and extracted with 5 × 6.0 mL portions of CH_2Cl_2. The combined organic layers were dried, filtered and evaporated to furnish the (*R*)-nebracetam (−)-**1** (40 mg, 79%), as an oil. $[\alpha]_D = -6.3$ (*c* 1.90, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) *δ* (ppm): 7.38–7.20 (m, 5H), 4.44 (s, 2H), 3.38 (dd, 1H, *J* = 9.9 Hz; 7.9 Hz), 3.00 (dd, 1H, *J* = 9.9 Hz; 5.4 Hz), 2.76 (dd, 1H, *J* = 12.5 Hz; 6.7 Hz), 2.66 (dd, 1H, *J* = 12.5 Hz; 7.1 Hz), 2.61 (dd, 1H), 2.48–2.28 (m, 1H), 2.20 (dd, 1H, *J* = 16.1 Hz; 6.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* (ppm): 173.8, 136.2–127.3, 54.8, 50.0, 45.7, 35.6, 35.2, 34.1; MS (EI, 70 eV): *m*/*z* (%) 204 (3, M^+), 187 (56), 174 (9), 106 (9), 91 (100), 65 (24), 56 (12).

4.7. *N*-Benzyl-4-[(1′*S*)-carboxyaldehyde]pyrrolidin-2-one 10

To a solution of diol **9** (70 mg, 0.30 mmol) in H_2O–MeOH (3:1, 3.2 mL) was added $NaIO_4$ (90 mg, 0.40 mmol). After stirring for 1.5 h, the mixture was extracted with CH_2Cl_2 (5 × 15 mL), dried with Na_2SO_4 and filtered. Removal of solvent afforded **10** (54 mg, 94%), which was used for the reductive amination and formation of oxime **11** without purification.

4.8. *N*-Benzyl-(4*R*)-4-morpholylmethyl-pyrrolidin-2-one 4

4.8.1. Procedure A, nucleophilic substitution. A mixture of **7** (34 mg, 0.12 mmol) and morpholine (0.5 mL) was stirred for 38 h at rt. The reaction mixture was partitioned between 15 mL of ethyl acetate and water (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to furnish **4** as an oil (28 mg, 86%). $[\alpha]_D = -4.0$ (*c* 2.76, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) *δ* (ppm): 7.34–7.22 (m, 5H), 4.44 (s, 2H), 3.64 (t, 4H, *J* = 4.7); 3.34 (dd, 1H, *J* = 9.8 Hz; 7.7 Hz), 3.06 (dd, 1H, *J* = 9.8 Hz; 4.9 Hz); 2.64–2.03 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* (ppm): 173.9, 136.3–127.4, 66.7, 53.6, 50.5, 46.4, 35.7, 29.6, 28.3. MS (EI, 70 eV): *m*/*z* % 274 (1, M^+), 243 (7), 100 (100), 91 (27), 65 (6), 56 (19).

4.8.2. Procedure B, reductive amination. To a solution of 79.3 mg (0.91 mmol) of morpholine in 1.0 mL of absolute MeOH was added 0.06 mL (0.302 mmol) of 5 N HCl–methanol, followed by a solution of 30.7 mg (0.151 mmol) of aldehyde **10** in 0.5 mL of MeOH and 9.5 mg (0.151 mmol) of $NaBH_3CN$. The mixture was stirred 30 h at room temperature. Concentrated HC1 was added until pH < 2, and the methanol was then removed in vacuo. The residue was taken up in 10 mL of water and extracted with three 12-mL portions of CH_2Cl_2. The aqueous solution was brought to pH > 10 with solid KOH, saturated with NaCl and extracted with five 15-mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated to give 36.2 mg (87%) of **4** pure (analyzed by GC–MS, ^1H and ^{13}C NMR). $[\alpha]_D = -4.9$ (*c* 0.30, $CHCl_3$).

4.9. *N*-Benzyl-(4*R*)-4-*N*-methyl-piperazylmethyl pyrrolidin-2-one 5

4.9.1. Procedure A, nucleophilic substitution. A mixture of **7** (33.8 mg, 0.12 mmol) and *N*-methyl piperazine (0.5 mL) was stirred for 38 h at rt. The reaction mixture was partitioned between 15 mL of ethyl acetate and water (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to furnish **5** (24,2 mg, 70%). $[\alpha]_D = -5.7$ (c 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) *δ* (ppm): 7.37–7.21 (m, 5H), 4.45 (s, 2H), 3.37 (dd, 1H, *J* = 9.9 Hz; 7.6 Hz), 3.04 (dd, 1H, *J* = 9.9 Hz; 4.8 Hz), 2.40–2.20 (m, 12H), 2.20–2.08 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* (ppm): 173.9, 136.4, 128.5–127.4, 62.1, 54.7, 52.8, 50.6, 46.4, 45.6, 35.8, 29.5, 28.7; MS (EI, 70 eV): *m*/*z* % 287 (6, M^+), 243 (2), 174 (7), 113 (100), 91 (17), 70 (57).

4.9.2. Procedure B, reductive amination. To a solution of 57.1 mg (0.57 mmol) of *N*-methyl piperazine in 0.7 mL of absolute MeOH was added 0.04 mL (0.19 mmol) of 5 N HCl–methanol, followed by a solution of 19.4 mg (0.095 mmol) of aldehyde **10** in 0.5 mL of MeOH and 6.0 mg (0.095 mmol) of $NaBH_3CN$. The mixture was stirred 30 h at room temperature. Concentrated HC1 was added until pH < 2, and the methanol was removed in vacuo. The residue was taken up in 10 mL of water and extracted with three 12-mL portions of CH_2Cl_2. The aqueous solution was brought to pH > 10 with solid KOH, saturated with NaCl, and extracted with five 15-mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated to give 25.5 mg (93%) of **5** pure (analyzed by GC–MS, ^1H and ^{13}C NMR). $[\alpha]_D = -5.0$ (*c* 0.17, $CHCl_3$).

4.10. *N*-Benzyl-(4*S*)-4-carbadolxime-pyrrolidin-2-one 11

To a solution of **10** (50 mg, 0.26 mmol) in CH_2Cl_2 were added $NH_2OH{\cdot}HCl$ (20 mg, 0.30 mmol), $NaHCO_3$ (30 mg, 0.30 mmol) and Na_2SO_4. This mixture was stirred for 18 h, filtered and evaporated to furnish oxime **11** as an oil (50 mg, 89%, *E*:*Z* = 84:16) which was used for the reduction step without further purification. $[\alpha]_D = +14.0$ (*c* 1.00, $CHCl_3$) ^1H NMR (200 MHz, $CDCl_3$) *δ* (ppm): 7.40–7.04 (m, 11H), 6.68 (d, 1H, *J* = 5.9), 4.49 (d, 2H, *J* = 15.6 Hz), 4.39 (d, 2H, *J* = 15.6 Hz), 3.75–3.60 (m, 2H), 3.59–3.38 (m, 2H), 3.27–3.06 (m, 2H), 2.79 (dd, 2H, *J* = 17.2 Hz; 9.2 Hz), 2.42 (dd, 2H, *J* = 17.2 Hz; 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* (ppm): 173.5, 151.7 and 150.0, 135.6–127.6, 49.9 and 49.4, 46.5, 35.2 and 34.8, 31.9 and 27.4. MS (EI, 70 eV): *Z*-oxime *m*/*z* (%) 218 (6, M^+), 201 (13), 146 (6), 118 (9), 91 (100), 65 (21), 51 (7); *E*-oxime *m*/*z* (%) 200 (42), 160 (2), 146 (44), 132 (5), 118 (20), 104 (43), 91 (100), 65 (39), 51 (19).

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References

1. (a) Gouliaev, A. H.; Senning, A. *Brain Res. Rev.* **1994**, *19*, 180; (b) Aslanian, R. *Tetrahedron: Asymmetry* **2000**, *11*, 3867; (c) Corey, E. J.; Zhang, F. Y. *Org. Lett.* **2000**, *2*, 4257; (d) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synt. Catal* **2007**, *349*, 2660; (e) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 4907.
2. (a) Palfreyman, M. N. *Prog. Med. Chem.* **1996**, *33*, 2; (b) Anada, M. et al. *Synlett* **1999**, *11*, 1775; (c) Enderes, S.; Angel, J. B.; Saget, B. M.; Walsh, S. P.; Greten, T. F.; Dinarello, C. A.; Skolnik, P. R. *AIDS* **1995**, *9*, 1137; (d) Connolly, N. C.; Riddler, S. A.; Rinaldo, C. R. *AIDS Rev.* **2005**, *7*, 168; (e) Albrecht, D.; Bach, T. *Synlett* **2007**, *10*, 1557.
3. (a) Shorvon, S. *Lancet* **2001**, *358*, 1885; (b) Gualtieri, F.; Manetti, D.; Romanelli, M. N.; Ghelardini, C. *Curr. Pharm. Des.* **2002**, *8*, 125; (c) Weber, K.-H. et al. U.S. Patent 5,073,671, 1991.; (d) Weber, K.-H. et al. U.S. Patent, 4,581,364, 1986; (e) Yamada, K.; Ren, X.; Nabeshima, T. *Jpn. J. Pharmacol.* **1999**, *80*, 9; (f) Prous, J.; Castañer, R. M.; Graul, A. *Drugs Future* **1993**, *18*, 18; (g) Weber, K.-H. et al. U.S. Patent, 4,581,364, April 8, 1986; (h) Balaraman, R.; Shingala, J. *Indian J. Pharmacol* **2002**, *34*, 439; (i) Mashkovskii, M. D.; Glushkov, R. G. *Pharm. Chem. J.* **2001**, *35*, 179; (j) Yamada, H.; Kushiko, K.; Kohno, Y.; Furukawa, T. *Oyo Yakuri* **1996**, *51*, 29.
4. Lehr, E. et al. U.S. Patent, 4,954,516, 1990.
5. (a) Domingos, J. L. O.; Lima, E. C.; Dias, A. G.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2313; (b) Weber, K.-H. et al. U.S. Patent 4,767,759, 1988.
6. Gibson, F. S.; Park, M. S.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 7503.
7. The $[\alpha]_D$ reported in literature (Ref. 1c) for **1a** in water was −8.4. In our work $[\alpha]_D$ was measured in $CHCl_3$ (c, 1.90) and a smaller value was obtained (−6.3).
8. (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897; (b) Lane, C. F. *Synthesis* **1975**, 135.
9. Hubschwerlin, C. *Synthesis* **1986**, 962.
10. Pinto, A. C.; Freitas, C. B. L.; Dias, A. G.; Pereira, V. L. P.; Tinant, B.; Declercq, J.-P.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2002**, *13*, 1025.
11. Ehrenkaufer, R. E.; Ram, S. *Tetrahedron Lett.* **1984**, *25*, 415.