CHEMO- AND REGIOSELECTIVE SYNTHESES OF ENANTIOPURE AMINOPYRROLIDINONES AS BUILDING BLOCKS FOR CONSTRAINED PEPTIDOMIMETICS

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Abstract - Starting from natural asparagine the synthesis of the N-protected enantiomerically pure 3- and 4-aminopyrrolidinones (1) and (3) was accomplished. The incorporation of these building blocks into conformationally constrained peptidomimetics was demonstrated by the synthesis of the potential dopamine receptor modulator (14b) (β-PAOPA). Furthermore, Freidinger γ-lactams including the protected dipeptide mimetics (8a-c) and (9) were prepared. The optical integrity of the synthesis was established by NMR analysis of the ureas (10a,b).

Conformationally constrained peptide analogs represent an important family of compounds employed for the development of enzyme inhibitors and receptor ligands. Additionally, interesting insights into the biologically active conformation of natural peptides are provided. Because of their ability to serve as conformationally rigidized surrogates of peptide secondary structures, lactam-bridged peptidomimetics including Freidinger lactams (I) have proven particularly useful. As an extension to these studies, the first investigations on the incorporation of β-amino acid derived lactams (Homo-Freidinger lactams, II) were reported, very recently.
So far, only few synthetic methods for the construction of these molecular scaffolds in enantiomerically pure form are described in the literature.\(^7\)\(^8\)

In this paper, we present a practical ex-chiral pool approach to 3- and 4-dibenzylaminopyrrolidinones which can serve as useful and flexible synthetic intermediates for the preparation of \(\gamma\)-lactam bridged peptidomimetics of type I and II, respectively. Our strategy was based on selective transformations of asparagine as a versatile bifunctional amino acid. Thus, cyclic imide formation of the benzyl protected asparagine derivative (2)\(^6\)\(^9\)\(^10\) followed by regioselective reduction of the sterically less hindered carbonyl function should lead to the \(\alpha\)-amino lactam (1). On the other hand, the \(\beta\)-amino regioisomer should be approached by chemoselective reduction of the ester group of 2, followed by activation of the thus formed primary alcohol and cyclization.

In practice, refluxing of the central intermediate (2) in toluene afforded the projected imide (4a) in high 91\% yield (Scheme I). Regioselective reduction of 4a was attempted by a two-step procedure involving reduction with LiEt\(_3\)BH and treatment of the thus formed hydroxylactam with a mixture of Et\(_3\)SiH and BF\(_3\)/Et\(_2\)O.
Actually, product formation was observed, however, 1 could be isolated in only 8% yield. Employing BH$_3$/Et$_2$O as the reducing agent and CH$_2$Cl$_2$ as a solvent gave substantial improvement resulting in the formation of 1 in 48% yield. The synthesis of the regioisomer (3) as a side product could not be detected. Complete regioselectivity of the reduction was also observed for the N-alkylated imide (4b), readily available by benzylation of asparagagine under more drastic conditions. In this case, the two-step reduction procedure turned out to be advantageous affording the respective lactam (5) in 74% yield compared to 48% for the borane-reduction. As an alternative, a synthesis of 1 from natural glutamine involving a modified Hofmann degradation was elaborated. Using our benzylation protocol described for asparagagine, the glutamine derivative (6) as well as the enantiomer (ent-6) could be readily prepared from (S)- and (R)-glutamine, respectively. Subsequent treatment of 6 with bis-trifluoroacetoxylidobenzene resulted in formation of the primary amine (7) in 37% yield, which was converted into the lactam (1) upon refluxing in toluene.

To verify whether the building block (1) is suitable as a central intermediate for lactam-bridged peptidomimetics, further reactions including lactam N-alkylation and deprotection as well as the optical integrity were investigated (Scheme 2). Thus, preparation of the protected lactam-bridged dipeptide analog (8a) containing a glycine moiety was done by NaH induced deprotonation of 1 followed by lactam N-alkylation with ethyl bromoacetate. Subsequent hydrogenolytic deprotection afforded the primary amine (9). Starting from the commercially available amino acids (R)-asparagagine and (R)-glutamine the enantiomeric building block (ent-9) can be approached which is known as a synthetic intermediate of PAOPA, a highly bioactive surrogate of the dopamine D2 receptor modulating peptide Pro-Leu-Gly-NH$_2$. The amino function of 9 was also used to determine the optical integrity of the synthesis. Thus, coupling of the dipeptide surrogate (9) with (R)- and (S)-1-phenylethyl isocyanate afforded the isomerically pure ureas (10a) and (10b), respectively. No diastereomeric impurity could be detected by careful $^1$H NMR spectroscopic analysis of the crude products.
For the incorporation of an alanine substructure the α-amino lactam (1) was deprotonated and alkylated with the commercially available (S)- and (R)-configured ethyl 2-trifluormethylsulfonyloxypropionates to afford the dipeptide surrogates (8b) and (8c), respectively. In accordance to previous alkylation studies on Boc-protected α-amino-ε-caprolactams, a partial epimerization at the acidic ester α-position was observed. Thus, the reaction of 1 with the (S)-configured malic acid equivalent resulted in formation of a 3.7:1 mixture of the diastereomers (8b) and (8c), which could be separated and purified by MPLC. On the other hand, employment of the (R)- configured electrophile resulted in a preferred formation of 8c (8b:8c = 1:3).

The protected asparagine ester (2) was also chosen as the precursor of the 4-aminopyrrolidinone (3) representing a building block for Homo-Freidinger lactams (Scheme 3). Following our previously described protocol, chemoselective reduction of 2 afforded the N,N-dibenzylasparaginol (11) which we attempted to cyclize under Mitsunobu conditions or by O-mesylation and subsequent ring closure. However, due to side reactions including lactone formation, migration of the amino functionality and β-elimination, these reactions failed. Synthesis of the γ-lactam (3) was achieved by activation of the primary alcohol with dimethylformamide dimethyl acetal. Using p-TosOH as a catalyst and toluene as a solvent, pure product was formed in moderate yield (24%). However, due to the short reaction pathway and the inexpensive starting materials the synthesis is still very practical.

The incorporation of the β-amino-γ-lactams (3) into conformationally constrained peptide surrogates was representatively demonstrated by the synthesis of the tripeptide mimetic (14b) which can be regarded as a β-amino isomer of the dopamine receptor modulator PAOPA (3R-[(2S-pyrrolidiny)carbonyl]amino]-2-oxo-1-pyrrolidineacetamide). N-deprotonation of 3 with NaH, followed by reaction with ethyl bromoacetate resulted in the formation of 12, which was hydrogenolytically debenzylated to give the amine (13) (Scheme 4). Proceeding through a mixed anhydrid, 13 was reacted with Cbz-Pro to afford the coupling product (15), which was transformed into 14a by aminolysis of the glycine ester functionality. Subsequent hydrogenolytic N-deprotection gave the final product (14b) in 33% overall yield.
**Experimental**

**General:** Solvents were purified and dried by standard procedures. Optical rotation was measured on a Perkin-Elmer Polarimeter 241 at 23°C. IR spectra were recorded on a Perkin-Elmer 1420. If not otherwise stated MS were run by EI ionization (70 eV) with solid inlet. ¹H-NMR spectra were obtained on Bruker AC 200 (200 MHz), AM 360 (360 MHz) and AM 400 (400 MHz) spectrometers, if not otherwise stated in CDCl₃ relative to TMS; ¹³C-NMR spectra were run on a Bruker AC 250 (63 MHz) in DMSO-d₆ relative to the solvent resonance (δ = 39.5). Chromatographic purification was performed using Silica gel 60 (Merck).

**(S)-(−)-N,N-Dibenzylasparagine benzyl ester (2)**

L-Asparagine (22.5 g, 0.15 mol) was benzylated as earlier described⁶ to give 2 (39.2 g, 65%) as a colorless solid; [α]D -93° (c = 0.5, CHCl₃), ref. 6: [α]D -93° (c = 0.5, CHCl₃).

**(S)-(−)-3-N,N-Dibenzylaminopyrrolidine-2,5-dione (4a)**

A solution of 2 (5 g, 12 mmol) in toluene (100 mL) was refluxed for 6 h. Evaporation of the solvent followed by flash chromatographic purification (petroleum ether-EtOAc 4:1) afforded 4a (3.34 g, 91%) as colorless crystals; mp 93-95°C (petroleum ether); [α]D -12.6° (c = 0.5, CHCl₃); IR (KBr) ν 3030, 2930, 1780, 1705, 1600 cm⁻¹; ¹H-NMR (200 MHz) δ 2.59 (dd, J = 18.6, 6.1 Hz, 1H, H-4a), 2.73 (dd, J = 18.6, 8.7 Hz, 1H, H-4b), 3.58 (d, J = 13.6 Hz, 2H, NCH₂Ph), 3.78 (d, J = 13.4 Hz, 2H, NCH₂Ph), 3.91 (dd, J = 8.7, 6.1 Hz, 1H, H-3), 7.14-7.35 (m, 10H, ar). Anal. Calcd for C₁₈H₁₈N₂O₄: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.35; H, 6.16; N,
†(S)-(−)-1-Benzyl-3-\(N,N\)-dibenzylaminopyrrolidine-2,5-dione (4b)

To a solution of L-asparagine (7.5 g, 0.05 mmol) and \(\text{K}_2\text{CO}_3\) (25 g) in \(H_2O\) (100 mL) benzyl bromide (35.63 mL, 0.3 mol) was added. The mixture was stirred under reflux for 2 h, then extracted 4 times with \(Et_2O\). The combined organic layers were dried (\(\text{MgSO}_4\)) and evaporated and the residue was separated by flash chromatography (petroleum ether-\(EtOAc\) 9:1) to give 4b (5.1 g, 26%) as colorless crystals; mp 66-67°C (petroleum ether); \([\alpha]_D -18^\circ\) (\(c = 0.5, \text{CHCl}_3\)), ref. 10: mp 65-66°C; \([\alpha]_D -19^\circ\) (\(c = 0.5, \text{CHCl}_3\)). As a further product \(N,N\)-dibenzylasparaginic acid dibenzyl ester (6.8 g, 27%) was isolated.

(S)-(−)-3-\(N,N\)-Dibenzylaminopyrrolidin-2-one (1)

a) To a solution of 4a (1.0 g, 3.4 mmol) in \(CH_2Cl_2\) (30 mL) a solution (1 M) of \(\text{BH}_3\) (20.4 mL, 20.4 mmol) in THF was added dropwise at 0°C under \(N_2\). After 1 h the temperature was raised to rt and finally the reaction mixture was refluxed for 4 h. The reaction was quenched by acidifying to pH 1 with 6N HCl, the mixture was alkalized to pH 12 with 2N \(\text{NaOH}\) and extracted 4 times with \(Et_2O\). The combined organic layers were dried (\(\text{MgSO}_4\)) and evaporated and the residue was purified by flash chromatography (petroleum ether-\(EtOAc\) 3:2) to give 1 (462 mg, 48%) as a colorless oil; \([\alpha]_D -24.7^\circ\) (\(c = 0.5, \text{CHCl}_3\)); CI-MS (isobutane) \(m/\epsilon 4281\) (\(MH^+\)); \(R(film) v 3246, 3028,2927,2870,1695\) cm\(^{-1}\); \(^1\)H-NMR (360 MHz) \(\delta 2.04-2.23\) (m, 2H, H-4) \(3.15-3.24\) (m, 1H, H-5), \(3.27-3.35\) (m, 1H, H-5), \(3.58\) (dd, \(J = 9.3, 9.3\) Hz, 1H, H-3), \(3.66\) (d, \(J = 13.9\) Hz, 2H, NC&Ph), \(3.95\) (d, \(J = 13.9\) Hz, 2H, NCH\(_2\)Ph), \(6.50\) (s, 1H, NH), \(7.19-7.24\) (m, 2H, Ar), \(7.27-7.33\) (m, 4H, Ar), \(7.41-7.46\) (m, 4H, Ar). Anal. Calcd for \(C_{30}H_{29}N_2O\): C, 77.1; H, 7.19; N, 9.99. Found: C, 76.78; H, 7.29; N, 9.91.

b) To 4a (150 mg, 0.51 mmol) dissolved in \(CH_2Cl_2\) (20 mL) a solution (1 M) of \(\text{LiEt}_3\)BH (0.61 mL, 0.61 mmol) in THF was added at -78°C under \(N_2\). After 1 h a second portion of \(\text{LiEt}_3\)BH (0.61 mL, 0.61 mmol) was added and the mixture was stirred for further 30 min before the reaction was quenched with a saturated solution of \(\text{NaHCO}_3\) (5 mL). At 0°C \(H_2O_2\) (0.15 mL) was added and after stirring for 30 min the mixture was brought to rt. Extraction with \(CH_2Cl_2\), drying of the combined organic layers (\(\text{MgSO}_4\)) and evaporation of the solvent afforded a crude product (176 mg) which was used without purification for the following reaction.

To a solution of the crude product (176 mg) and \(Et_3\)SiH (0.32 mL, 2.24 mmol) in \(CH_2Cl_2\) (20 mL) \(BF_3/ Et_2O\) (8 M, 0.28 mL, 2.24 mmol) was added at -78°C under \(N_2\). After 1 h a second portion of \(Et_3\)SiH (0.16 mL, 1.02 mmol) and \(BF_3/ Et_2O\) (8 M, 0.14 mL, 1.12 mmol) was added. The mixture was stirred for 2 h brought to rt and after further 2 h stirring the reaction was quenched by adding a saturated solution of \(\text{NaHCO}_3\) (10 mL). Extraction with \(CH_2Cl_2\), drying of the combined extracts (\(\text{MgSO}_4\)), evaporation and subsequent separation by flash chromatography afforded 1 (11.5 mg, 8%) as a colorless oil; \([\alpha]_D -25^\circ\) (\(c = 0.5, \text{CHCl}_3\)); identical with the product described above.

c) Crude 7 (1.8 g, 4.64 mmol) was refluxed in toluene (40 mL) for 17 h. To the reaction mixture a saturated solution of \(\text{NaHCO}_3\) was added and the water layer was extracted with \(Et_2O\). The combined organic layers were dried (\(\text{MgSO}_4\)), evaporated and purified by flash chromatography (petroleum ether-\(EtOAc\) 1:1) to give 1 (0.5 g, 38.5%) as a colorless oil; \([\alpha]_D -25.4^\circ\) (\(c = 1.0, \text{CHCl}_3\)); identical with the product described above.
(S)-(−)-1-Benzyl-3-N,N-dibenzylaminopyrrolidin-2-one (5)
Starting from 4b (80 mg, 0.21 mmol) the above described reaction sequence a) afforded 5 (37.4 mg, 48%) as a colorless oil; reaction sequence b), starting from 4b (1 g, 2.59 mmol) gave 5 (671 mg, 74%) as a colorless oil, too; [α]D -13.5° (c = 0.5, CHCl3); IR (film) v 3020, 2920, 1680, 1490, 1450 cm⁻¹; 1H-NMR (400 MHz) δ 1.88 (m, 1H, H-4), 2.02 (m, 1H, H-4), 2.97 (ddd, J = 9.6, 8.1, 8.1 Hz, 1H, H-5), 3.08 (ddd, J = 9.6, 9.6, 2.4 Hz, 1H, H-3), 3.61 (m, 1H, H-3), 3.61 (d, J = 13.8 Hz, 2H, NCH2Ph), 3.92 (d, J = 13.8 Hz, 2H, NCH2Ph), 4.31 (d, J = 14.5 Hz, 1H, NCH2Ph), 4.43 (d, J = 14.5 Hz, 1H, NCH2Ph), 7.14-7.39 (m, 15H, Ar). Anal. Calcd for C63H47N2O: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.25; H, 7.12; N, 7.29.

(S)-(−)-N,N-Dibenzylglutamine benzyl ester (6)
To a solution of L-glutamine (12.5 g, 85 mmol) in H2O (575 mL), K2CO3 (57.5 g, 0.42 mol) and benzyl bromide (58.5 g, 0.34 mol) were added. After stirring for 10 d at rt the mixture was extracted with Et2O, the combined organic layers were dried (MgSO4) and evaporated. The crude product was purified by flash chromatography (petroleum ether-EtOAc 3:2 to 2:3) to yield 6 (15.9 g, 46%) as a colorless oil; [α]D -100.3° (c = 1.0, CHCl3); IR (film) v 3459, 3343, 3191, 3029, 2939, 2846, 1727, 1672, 1605 cm⁻¹; 1H-NMR (250 MHz) δ 1.99-2.35 (m, 4H, H-3, H-4), 3.36 (dd, J = 7.5, 6.5 Hz, 1H, H-2), 3.52 (d, J = 13.5 Hz, 2H, NCH2Ph), 3.87 (d, J = 13.5 Hz, 2H, NCH2Ph), 5.16 (d, J = 12.0 Hz, 1H, OCH2Ph), 5.27 (d, J = 12.0 Hz, 1H, OCH2Ph), 7.17-7.46 (m, 15H, Ar). Anal. Calcd for C32H32N2O3: C, 74.98; H, 6.78; N, 6.73. Found: C, 74.89; H, 6.72; N, 6.73.

Starting from D-glutamine the same procedure afforded ent-6 as a colorless oil; [α]D +100° (c = 1.0, CHCl3).

(S)-(−)-4-Amino-2-N,N-dibenzylaminobutanoic acid benzyl ester (7)
To a solution of bis-trifluoroacetoxyiodobenzene (7 g, 16.3 mmol) in DMF (30 mL) and H2O (45 mL), compound (6) (4.5 g, 10.8 mmol) in DMF (15 mL) was added slowly. After stirring at rt for 15 min pyridine (1.71 g, 21.6 mmol) was added, the reaction mixture was stirred for further 4 h at rt and then evaporated. The residue was mixed with a saturated solution of NaHCO3 and extracted with EtOAc. The combined organic layers were dried (MgSO4) and evaporated. The crude product was purified by flash chromatography (CH2Cl2-MeOH 4:1) to yield pure 7 as a colorless oil; [α]D -29.7° (c = 0.6, CHCl3); CI-MS (methane) m/z 389 (MH⁺); IR (film) v 3500-3100, 3027, 2929, 2844, 1730 cm⁻¹; 1H-NMR (360 MHz) δ 1.94-2.35 (m, 4H, H-3, H-4), 3.36 (dd, J = 7.5, 6.5 Hz, 1H, H-2), 3.52 (d, J = 13.5 Hz, 2H, NCH2Ph), 3.87 (d, J = 13.5 Hz, 2H, NCH2Ph), 5.16 (d, J = 12.0 Hz, 1H, OCH2Ph), 5.27 (d, J = 12.0 Hz, 1H, OCH2Ph), 7.17-7.46 (m, 15H, Ar). Anal. Calcd for C32H32N2O2·½H2O: C, 75.54; H, 7.35; N, 7.05. Found: C, 75.23; H, 7.07; N, 6.94.

(S)-(−)-3,N,N-Dibenzylaminopyrrolidin-2-on-1-ylacetic acid ethyl ester (8a)
A solution of 1 (150 mg, 0.535 mmol) in THF (5 mL) was treated at 0°C with 50% NaH in paraffin (21 mg, 0.535 mmol). After stirring at 0°C for 30 min bromoacetic acid ethyl ester (222 mg, 1.338 mmol) was added. The mixture was stirred for 4 h at 0°C, then 14 h at rt. After that EtOAc (15 mL) and a saturated NaHCO3...
solution (30 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (MgSO₄) and evaporated and the residue was purified by flash chromatography (petrol-EtOAc 7:3 to 3:7) to yield the product (140 mg, 72%) as a colorless oil; \([\alpha]_D^{24.3°} (c = 1.0, \text{CHCl}_3); \text{IR (film)} v 3326, 2981, 2927, 1737, 1691 \text{ cm}^{-1}; \text{H-NMR (360 MHz)} \delta = 1.25 (t, J = 7.2 Hz, 3H, CH₂CH₂O), 2.00 - 2.23 (m, 2H, H-4), 3.31 (ddd, J = 9.1, 8.8, 8.8 Hz, 1H, H-5), 3.37 (ddd, J = 9.1, 9.1, 2.8 Hz, 1H, H-5), 3.68 (d, J = 13.9 Hz, 2H, NCH₂Ph), 3.69 (ddd, J = 9.3, 9.3 Hz, 1H, H-3), 3.95 (d, J = 13.9 Hz, 2H, NCH₂Ph), 3.98 (d, J = 17.5 Hz, 1H, NCH₂CO), 4.09 (d, J = 17.5 Hz, 1H, NCH₂CO), 4.17 (q, J = 7.2 Hz, 2H, CH₂CH₂O), 7.19 - 7.25 (m, 2H, Ar), 7.27 - 7.33 (m, 4H, Ar), 7.41 - 7.47 (m, 4H, Ar). Anal. Calcd for C₂₂H₂₈N₂O₅: 1/4 H₂O: C, 71.23; H, 7.20; N, 7.55. Found: C, 71.25; H, 7.26; N, 7.43.

\((-\)-2R-(3S,N,N-Dibenzyaminopyrrolidin-2-on-1-yl)propionic acid ethyl ester (8b) and \((-\)-2S-(3S,N,N-dibenzylaminopyrrolidin-2-on-1-yl)propionic acid ethyl ester (8c)

A solution of 1 (36 mg, 0.13 mmol) in THF (5 mL) was treated at 0°C with 60% NaH in paraffin (36 mg, 0.13 mmol). After stirring for 30 min (S)-2-trifluoromethanesulfonyloxypropionic acid ethyl ester (32 mg, 0.128 mmol) was added. The mixture was stirred for 4 h at 0°C and then for 14 h at rt. EtOAc (5 mL) and a saturated solution of NaHCO₃ (10 mL) were added, the layers were separated and the water layer was extracted with EtOAc. After drying (MgSO₄) and evaporation of the solvent the mixture was separated by MPLC (petroleum ether-EtOAc 7:3 to 3:7) to yield 8b (18 mg, 37%) and 8c (5 mg, 10%) as colorless oils together with 1 (17 mg). The same reaction starting from 1 (106 mg, 0.378 mmol) and (R)-2-trifluoromethanesulfonyloxypropionic acid ethyl ester (95 mg, 0.378 mmol) afforded 8b (20 mg, 14%), 8c (61 mg, 42%), and 1 (33 mg).

8b: \([\alpha]_D^{28.8°} (c = 1.0, \text{CHCl}_3); \text{IR (film)} v 3326, 2981, 2938, 1738, 1692 \text{ cm}^{-1}; \text{H-NMR (C₆D₆, 360 MHz)} \delta = 0.83 (t, J = 7.1 Hz, 3H, CH₃CH₂O), 1.10 (d, J = 7.4 Hz, 3H, CH₃CH), 1.45 - 1.73 (m, 2H, H-4), 2.70 (ddd, J = 9.0, 9.0, 2.6 Hz, 1H, H-5), 2.90 (ddd, J = 9.0, 8.4, 8.4 Hz, 1H, H-5), 3.67 (d, J = 13.9 Hz, 2H, NCH₂Ph), 3.68 (dd, J = 9.2, 9.2 Hz, 1H, H-3), 3.82 (q, J = 7.1 Hz, 2H, CH₂CH₂O), 4.13 (d, J = 13.9 Hz, 2H, NCH₂Ph), 4.92 (q, J = 7.4 Hz, 2H, CH₃CH), 7.06 - 7.12 (m, 2H, ar), 7.14 - 7.21 (m, 4H, ar), 7.46 - 7.51 (m, 4H, ar). Anal. Calcd for C₂₂H₂₈N₂O₅: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.53; H, 7.51; N, 7.27.

8c: \([\alpha]_D^{22.5°} (c = 1.0, \text{CHCl}_3); \text{IR (film)} v 3326, 2981, 2927, 1737, 1691 \text{ cm}^{-1}; \text{H-NMR (C₆D₆, 360 MHz)} \delta = 0.82 (t, J = 7.1 Hz, 3H, CH₃CH₂O), 1.04 (d, J = 7.5 Hz, 3H, CH₃CH), 1.49 - 1.81 (m, 2H, H-4), 2.43 (ddd, J = 9.0, 8.4, 8.4 Hz, 1H, H-5), 2.97 (ddd, J = 9.0, 9.0, 2.6 Hz, 1H, H-5), 3.59 (dd, J = 9.0, 9.0 Hz, 1H, H-3), 3.72 (d, J = 13.9 Hz, 2H, NCH₂Ph), 3.81 (q, J = 7.1 Hz, 2H, CH₂CH₂O), 4.19 (d, J = 13.9 Hz, 2H, NCH₂Ph), 4.98 (q, J = 7.5 Hz, 2H, CH₃CH), 7.06 - 7.13 (m, 2H, ar), 7.15 - 7.23 (m, 4H, ar), 7.50 - 7.55 (m, 4H, ar). Anal. Calcd for C₂₂H₂₈N₂O₅: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.45; H, 7.26; N, 7.23.

(5)-(-)-3-Aminopyrrolidin-2-on-1-ylacetic acid ethyl ester (9)

A mixture of 8a (138 mg, 0.377 mmol) and 10% Pd/C (30 mg) in EtOH (30 mL) was stirred under H₂ (1 bar) at rt for 4 h. The mixture was filtered, the filtrate evaporated and the residue purified by flash chromatography (CH₂Cl₂-MeOH 9:1) to yield the product (60 mg, 86%) as a colorless oil; \([\alpha]_D^{245.3°} (c = 1.0, \text{CHCl}_3); \text{MS} m/z 186 (M⁺); \text{IR (film)} v 3600 - 3000, 3370, 2982, 2931, 1741, 1681 \text{ cm}^{-1}; \text{H-NMR (360 MHz)} \delta = 1.28 (t,
J = 7.1 Hz, 3H, CH$_3$CH$_2$O), 1.80 (dddd, J = 12.6, 9.7, 9.3, 9.3 Hz, 1H, H-4), 2.47 (dddd, J = 12.6, 8.4, 6.8, 1.9 Hz, 1H, H-4), 3.36 (ddd, J = 9.3, 9.3, 1.9 Hz, 1H, H-5), 3.45 (ddd, J = 9.3, 9.3, 6.8 Hz, 1H, H-5), 3.57 (dd, J = 9.7, 8.4 Hz, 1H, H-3), 3.97 (d, J = 17.5 Hz, 1H, NCH$_2$CO), 4.15 (d, J = 17.5 Hz, 1H, NCH$_2$CO), 4.20 (q, J = 7.1 Hz, 2H, CH$_3$CH$_2$O).

(-)-3S-[3-(1S-Phenylethyl)ureido]pyrrolidin-2-on-l-ylacetic acid ethyl ester (10a)

To a solution of 9 (10 mg, 0.054 mmol) in THF (1 mL) (S)-1-phenylethyl isocyanate (8 mg, 0.054 mmol) was added at 0°C. After 3 h the solvent was evaporated and the residue purified by flash chromatography (CH$_2$Cl$_2$:MeOH 19:1) to give 10a as a colorless oil; [$\alpha$]$_D$ -26.4° (c = 0.4, CHCl$_3$); MS m/z 333 (M$^+$); IR (film) ν 3342, 2963, 2928, 1747, 1695, 1643 cm$^{-1}$; $^1$H-NMR (360 MHz) δ 1.26 (t, J = 7.1 Hz, 3H, CH$_3$CH$_2$O), 1.44 (d, J = 7 Hz, 1H, CHCH$_3$), 1.89 (dddd, J = 12.5, 9.9, 9.5, 9.5 Hz, 1H, H-4), 2.65 (dddd, J = 12.5, 8.0, 6.6, 1.2 Hz, 1H, H-4), 3.35 (ddd, J = 9.5, 9.5, 1.2 Hz, 1H, H-5), 3.46 (ddd, J = 9.5, 9.5, 6.6 Hz, 1H, H-5), 3.94 (d, J = 17.8 Hz, 1H, NCH$_2$CO), 4.10 (d, J = 17.8 Hz, 1H, NCH$_2$CO), 4.17 (q, J = 7.1 Hz, 2H, CH$_3$CH$_2$O), 4.38 (ddd, J = 9.9, 8.0, 4.8 Hz, 1H, H-3), 4.88 (dq, J = 7.0, 7.0 Hz, 1H, CH$_2$CH$_3$), 5.41 (br d, J = 4.8 Hz, 1H, NHCH), 5.58 (br d, J = 7.0 Hz, 1H, NHCH), 7.19 - 7.35 (m, 5H, ar). Anal. Calcd for C$_{17}$H$_{23}$N$_2$O$_4$: C, 61.25; H, 6.95; N, 12.60. Found: C, 60.97; H, 7.11; N, 12.56.

(-)-3S-[3-(1R-Phenylethyl)ureido]pyrrolidin-2-on-1-ylacetic acid ethyl ester (10b)

The same reaction as described above using (R)-1-phenylethyl isocyanate (8 mg, 0.054 mmol) afforded 10b (17 mg, 94%) as a colorless oil; [$\alpha$]$_D$ -2.1° (c = 0.5, CHCl$_3$); MS m/z 333 (M$^+$); IR (film) ν 3345, 2978, 2932, 1744, 1695, 1642 cm$^{-1}$; $^1$H-NMR (360 MHz) δ 1.26 (t, J = 7.1 Hz, 3H, CH$_3$CH$_2$O), 1.43 (d, J = 7.0 Hz, 1H, CHCH$_3$), 1.90 (ddd, J = 12.7, 10.0, 9.6, 9.6 Hz, 1H, H-4), 2.65 (ddd, J = 12.7, 8.0, 6.8, 1.2 Hz, 1H, H-4), 3.35 (ddd, J = 9.6, 9.6, 1.2 Hz, 1H, H-5), 3.45 (ddd, J = 9.6, 9.6, 6.8 Hz, 1H, H-5), 3.94 (d, J = 17.5 Hz, 1H, NCH$_2$CO), 4.12 (d, J = 17.5 Hz, 1H, NCH$_2$CO), 4.17 (q, J = 7.1 Hz, 2H, CH$_2$CH$_3$), 4.26 (ddd, J = 10.0, 8.0, 4.7 Hz, 1H, H-3), 4.87 (dq, J = 7.0, 7.0 Hz, 1H, CH$_2$CH$_3$), 5.48 (br d, J = 4.7 Hz, 1H, NHCH), 5.66 (br d, J = 7.0 Hz, 1H, NHCH), 7.19 - 7.35 (m, 5H, ar). Anal. Calcd for C$_{17}$H$_{23}$N$_2$O$_4$: C, 61.25; H, 6.95; N, 12.60. Found: C, 60.97; H, 7.11; N, 12.56.

(S)-(+)N,N-Dibenzylamino-4-hydroxybutanecarboxamide (11)

Compound 2 (5.2 g, 12.9 mmol) was reduced with LiAlH$_4$ as earlier described$^{10}$ to give 11 (2.3 g, 60%) as a colorless oil; [$\alpha$]$_D$ +8° (c = 1, CHCl$_3$), ref. 10: [$\alpha$]$_D$ +8° (c = 1, CHCl$_3$).

(S)-(+)4-N,N-Dibenzylaminopyrrolidin-2-one (3)

A solution of 11 (298.4 mg, 1 mmol) in toluene (20 mL) was refluxed with N,N-dimethylformamide dimethyl acetal (0.67 mL, 5 mmol) and p-toluenesulfonic acid (19 mg, 0.1 mmol) for 3.5 h. After evaporation of the solvent the residue was purified by column chromatography (CH$_2$Cl$_2$:MeOH 19:1) to yield 3 (67 mg, 24%) as a colorless solid; mp 139°C (MeOH); [$\alpha$]$_D$ +26.2° (c = 0.5, CHCl$_3$); IR (KBr) v 3600-3100, 3460, 3400, 1670 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 2.31 (dd, J = 17.3, 8.6 Hz, 1H, H-3), 2.38 (dd, J = 17.3, 6.6 Hz, 1H, H-3), 3.30
(S)-4-N,N-Dimethylaminopyrrolidin-2-on-1-ylacetic acid ethyl ester (12)

A solution of 3 (65.8 mg, 0.24 mmol) in THF (10 mL) was treated at 0°C with a suspension of 50% NaH (23.2 mg, 0.591 mmol) in paraffin. After stirring 1 h at 0°C bromoacetic acid ethyl ester (79.7 mg, 0.48 mmol) was added and the mixture was stirred at 0°C for further 3 h. Adding EtOAc (5 mL) and a saturated solution of NaCl quenched the reaction. The layers were separated and the aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried (MgSO₄) and evaporated, and the crude product was purified by column chromatography (petroleum ether-EtOAc 3:2) to yield 12 (47.3 mg, 54%) as a colorless oil; MS m/z 366 (M⁺); IR (film) ν 3500-3100, 1730, 1680 cm⁻¹; ¹H-NMR (400 MHz) δ 1.23 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.66 (br s, 2H, NH₂), 2.19 (dd, J = 16.7, 3.5 Hz, 1H, H-3), 2.71 (dd, J = 16.7, 6.4 Hz, 1H, H-3), 3.13-3.18 (m, 1H, H-4), 3.60-3.74 (m, 2H, H-5), 3.80-4.06 (m, 2H, H-6), 4.17 (q, J = 7.1 Hz, 2H, CH₂CH₃). HR-MS m/z 186.0999 (M⁺) calcd for C₉H₁₄N₂O₂: 186.0904.

(S)-4-Aminopyrrolidin-2-on-1-ylacetic acid ethyl ester (13)

A mixture of 12 (381 mg, 1.04 mmol) and 10% Pd/C (50 mg) in MeOH (15 mL) was stirred under H₂ (1 bar) at rt for 24 h. The mixture was filtered and the filtrate evaporated to give 13 (192 mg, 99%) as an unstable colorless oil. ¹H-NMR (400 MHz) δ 1.25 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.66 (br s, 2H, NH₂), 2.19 (dd, J = 16.7, 3.5 Hz, 1H, H-3), 2.71 (dd, J = 16.7, 6.4 Hz, 1H, H-3), 3.13-3.18 (m, 1H, H-4), 3.60-3.74 (m, 2H, H-5), 3.80-4.06 (m, 2H, H-6), 4.17 (q, J = 7.1 Hz, 2H, CH₂CH₃). HR-MS m/z 186.0999 (M⁺) calcd for C₉H₁₄N₂O₂: 186.0904.

(S)-(−)-4-(N-Benzoylbromoprolyl)aminopyrrolidin-2-on-1-ylacetic acid ethyl ester (15)

To a solution of L-Cbz-proline (267.0 mg, 1.08 mmol) in THF (15 mL) N-methylmorpholine (0.12 mL, 1.08 mmol) was added. After cooling the solution to -15°C i-butyl chloroformiate (0.134 mL, 1.03 mmol) and a solution of 13 (192 mg, 1.03 mmol) in THF (15 mL) were added dropwise. The reaction mixture was kept at -15°C for 5 min and after stirring at rt for 30 min it was filtered and evaporated. The residue was dissolved in a mixture of CHCl₃ (5 mL), H₂O (5 mL) and EtOAc (25 mL). The layers were separated and the organic layer was successively washed with a saturated solution of Na₂CO₃ and H₂O. Drying (MgSO₄), evaporation of the solvent and subsequent purification of the residue by column chromatography (CH₂Cl₂-MeOH 19:1) afforded 15 (312 mg, 73%) as a colorless oil; [α]₀D -198° (c = 0.5, CHCl₃); CI-MS (methane) m/z 418 (MH⁺); IR (film) ν 3320, 2980, 2940, 2880, 1750, 1700 cm⁻¹; ¹H-NMR (DMSO-d₆, 360 MHz, 100°C) δ 1.21 (t, J = 7.0 Hz, 3H, OCH₂CH₃), 1.73-1.93 (m, 3H, 2 x H-8 Pro, H-β Pro), 2.12 (m, 1H, H-β Pro), 2.20 (dd, J = 17.0, 5.5 Hz, 1H, H-3), 2.53 (dd, J = 17.0, 8.5 Hz, 1H, H-3), 3.18 (dd, J = 10.0, 5.0 Hz, 1H, H-5), 3.37-3.50 (m, 2H, 2 x H-δ Pro), 3.63 (dd, J = 10.0, 7.5 Hz, 1H, H-5), 3.93 (d, J = 17.0 Hz, 1H, H-α Gly), 3.99 (d, J = 17.0 Hz, 1H, H-α Gly), 4.13 (q, J = 7.0 Hz, 2H, OCH₂CH₃), 4.17 (dd, J = 8.5, 4.0 Hz, 1H, H-α Pro), 4.32 (m, 1H, H-4), 5.01 (d,
J = 13.0 Hz, 1H, OCH₂Ph), 5.07 (d, J = 13.0 Hz, 1H, OCH₂Ph), 7.24-7.37 (m, 5H, Ph), 7.96 (d, J = 5.5 Hz, 1H, CONH). At temperatures below 60°C a double set of signals was observed. Anal. Calcd for C₂₁H₂₇N₃O₆·H₂O: C, 57.92; H, 6.71; N, 9.65. Found: C, 58.05; H, 6.90; N, 9.45.

(S)-(-)-4-(N-Benzoyloxycarbonylprolyl)aminopyrrolidin-2-on-1-yacetic acid amide (14a)

A solution of 15 (295 mg, 0.71 mmol) in MeOH (10 mL) was treated at rt for 16 h with NH₃. The solvent was removed and the residue purified by flash chromatography (CH₂Cl₂-MeOH 9:1) to give 14a (259 mg, 94%) as a colorless oil; [α]D -58.1° (c = 0.3, MeOH); IR (KBr) ν 3387, 2957, 2884, 1680, 1551 cm⁻¹; ¹H-NMR (DMSO-d₆, 360 MHz, 100°C) δ 1.75-1.90 (m, 3H, 2 x H-8 Pro, H-13 Pro), 2.11 (m, 1H, H-β Pro), 2.17 (dd, J = 17.0, 5.5 Hz, 1H, H-3), 2.54 (dd, J = 17.0, 8.5 Hz, 1H, H-3), 3.14 (dd, J = 10.0, 4.5 Hz, 1H, H-5), 3.37-3.51 (m, 2H, 2 x H-β Pro), 3.61 (dd, J = 10.0, 7.5 Hz, 1H, H-5), 3.72 (d, J = 17.0 Hz, 1H, H-α Gly), 3.77 (d, J = 17.0 Hz, 1H, H-α Gly), 4.15 (m, J = 8.5, 3.5 Hz, 1H, H-α Pro), 4.30 (m, 1H, H-4), 5.01 (d, J = 13.0 Hz, 1H, OCH₂Ph), 5.07 (d, J = 13.0 Hz, 1H, OCH₂Ph), 6.85 (br s, 2H, CONH₂), 7.24-7.37 (m, 5H, Ph), 7.95 (br d, J = 5.5 Hz, 1H, CONH). At temperatures below 60°C a double set of signals was observed.

(S)-(-)-4-Prolylaminopyrrolidin-2-on-1-yacetic acid amide (14b)

A mixture of 14a (194.3 mg, 0.5 mmol) and 10% Pd/C (19 mg) in MeOH (15 mL) was stirred under H₂ (1 bar) at rt for 12 h. The mixture was filtered, the filtrate evaporated and the residue purified by column chromatography (CH₂Cl₂-MeOH-Me₂NH 9:1:0.1) to yield the product (90 mg, 71%) as a colorless oil; [α]D -58.1° (c = 0.1, MeOH); IR (film) ν 3329, 2971, 2878, 1675, 1551 cm⁻¹; ¹H-NMR (DMSO-d₆, 360 MHz) δ 1.53-1.69 (m, 3H, 2 x H-γ Pro, H-β Pro), 1.92 (m, 1H, H-β Pro), 2.22 (dd, 1H, J = 16.5, 5.0 Hz, H-3), 2.57 (dd, 1H, J = 16.5, 8.5 Hz, H-3), 2.80 (m, 2H, H-δ Pro), 3.13 (dd, 1H, J = 10.0, 4.5 Hz, H-5), 3.27 (s, 1H, NH), 3.48 (dd, 1H, J = 9.0, 5.5 Hz, H-α Pro), 3.64 (dd, 1H, J = 10.0, 7.5 Hz, H-5), 3.72 (1H, d, J = 17 Hz, H-α Gly), 3.78 (1H, d, J = 17 Hz, H-α Gly), 4.35 (m, 1H, H-4), 7.11 (s, 1H, CONH₂), 7.39 (s, 1H, CONH₂), 8.28 (d, 1H, J = 7.5 Hz, CONH(CH); ¹³C-NMR δ = 25.7 (C-β Pro), 30.4 (C-γ Pro), 36.8 (C-3), 41.8 (C-4), 44.7 (C-α Gly), 46.7 (C-β Pro), 53.7 (C-5), 60.1 (C-α Pro), 169.6 (C=O Gly), 172.3 (C-2), 174.6 (C=O Pro). Anal. Calcd for C₁₁H₁₉N₂O₇·H₂O: C, 48.52; H, 7.40; N, 20.53. Found: C, 48.31; H, 7.76; N, 20.85.

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