EX-CHIRAL POOL SYNTHESIS OF AMINOOXAZEPINONES AS CONFORMATIONALLY RESTRICTED ß-AMINO ACID ANALOGS

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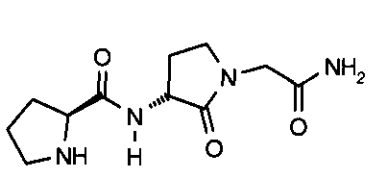
Abstract - Starting from natural asparagine, an efficient synthesis of the dibenzyl protected 6-amino-1,3-oxazepin-4-one (**7**) is reported. According to NMR based conformational studies, the lactam-bridged ß-amino acid analog (**7**) adopts preferentially a twisted boat structure. The incorporation of the described molecular scaffold to give a constrained ß-analog of the dopamine receptor modulating peptide Pro-Leu-Gly-NH_2 is described as an application in the field of medicinal chemistry.

In search for increased target selectivity and pharmakokinetics, great efforts in peptide-based drug design are made by developing non-peptidic structural modifications.[1-5] Among these, lactam-bridged peptidomimetics are of special relevance since their conformational constraints give interesting insights into the bioactive conformations of both, natural ligands and binding sites.[6-8] As an example, the γ-lactam restricted analog (**1**) of the dopamine receptor modulating peptide Pro-Leu-Gly-NH_2 (PLG) displayed modulating activities superior to PLG, indicating that a type-II ß-turn might be bioactive conformation.[9,10] Structure activity relationship studies in our laboratory are based on ß-amino acid derived PLG analogs including the incorporation of ß-proline as well as 4-aminopiperidin-2-one as a Homo-Freidinger lactam (**2**).[11,12]

As an extension of our efforts on the synthesis of conformationally restrained ß-amino acid equivalents, here we report the construction of enantiopure 6-amino-1,3-oxazepin-4-ones[13] from natural asparagine and the application of this novel molecular scaffold for the respective PLG analog (**3**).



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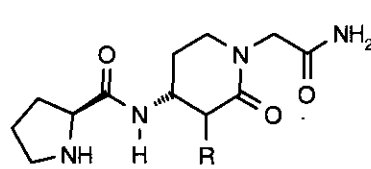

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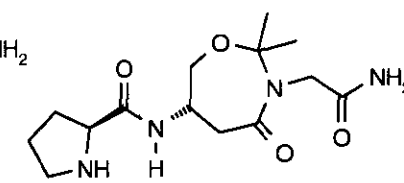
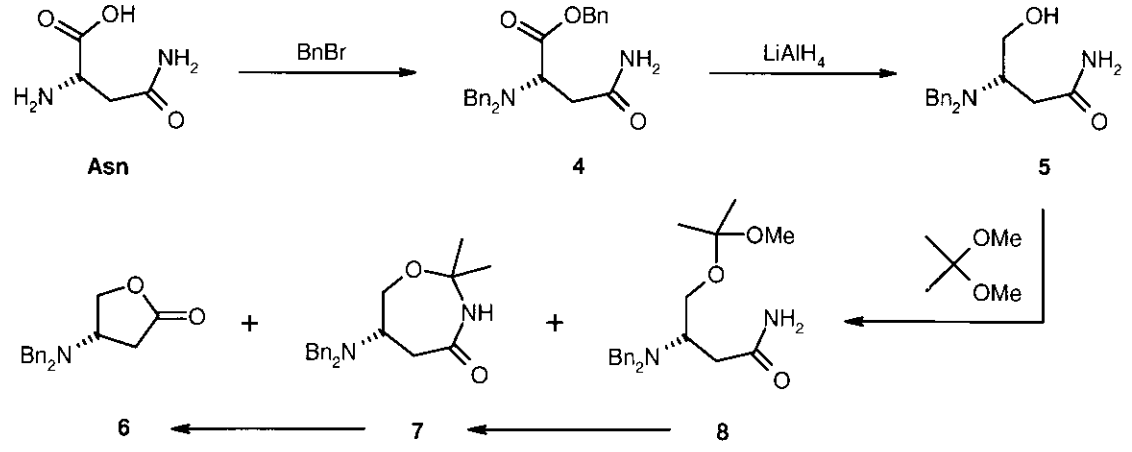


3

The synthesis of the *N,N*-dibenzyl protected chiral building block (**7**) was planned from natural asparagine employing the ß-homoserine derivative (**5**)[14] as a cyclization precursor. In practice, asparagine was readily tranformed into the protected ester (**4**) by reaction with benzyl bromide in aqueous K_2CO_3 solution. If the reaction is performed at room temperature benzylation of the amide function and formation of a cyclic imide can be precluded. Since most of the product precipitates under these conditions this one-pot preparation is superior to the earlier published two-step sequence including reductive alkylation and subsequent esterification.[15,16] Chemoselective reduction of the ester group of **4** by $LiAlH_4$ at 0°C gave the hydroxy amide (**5**). Formation of the cyclic *N/O*-acetal (**7**) could be accomplished by reaction of **5** with dimethoxypropane under acidic conditions. This transacetalization turned out to be very sensitive to the employed cyclization conditions. Thus, refluxing of **5** in neat dimethoxypropane using TsOH as a catalyst afforded the acyclic *O/O*-acetal (**8**) in 37 % yield. On the other hand, using toluene as a solvent gave a chromatographically separable mixture of the oxazepinone (**7**) (25 %) and the γ-lactone (**6**) (30 %) besides traces of **8** (1-2 %) after 4 h reflux. Lowering the reaction temperature resulted in 45 % of the lactone (**6**)[17] and a strongly decreased yield of the target compound (**7**). When heating the pure educts in toluene / TsOH, almost quantitative lactone formation could be observed directly from the ß-homoserine (**5**) as well as by ring-contraction of the oxazepinone (**7**). The selectivity of the reaction could be improved when pyridinium *p*-toluenesulfonate (PPTS) was used as a mild catalyst instead of TsOH. Under these conditions, only small amounts of the by-products were formed and 35 % of the pure building block (**7**) was isolated. In the presence of PPTS, selective cyclization of the *O/O*-acetal (**8**) to give **7** proved also possible.



Scheme 1

As the preferred conformation of compound (**7**), a twisted boat structure with C-2, N-3, C-4 and C-5 in one plane was deduced from NOE experiments (Figure 1) and the coupling constants measured for the couplings

between H-6 and its neighboured protons. A NOE was observed only between H-6 and H-5a but not between H-6 and H-5b. Considering the coupling constants ($J_{6,5a}$ = 3.5 Hz, $J_{6,5b}$ = 9.7 Hz), this indicated a dihedral angle of almost 180° formed by H-6 and H-5b with quasi axial orientation of these two protons. Furthermore, strong NOEs between the protons of one of the methyl groups and H-5b and the protons of the other methyl group and H-7a were measured, suggesting a conformation of **7** as shown in Figure 1, which is also in good agreement with all the other observed coupling constants and NOEs.

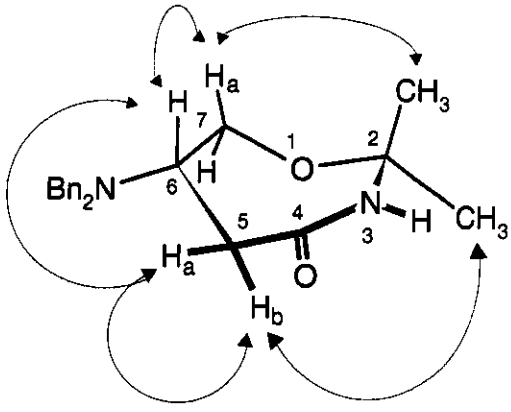
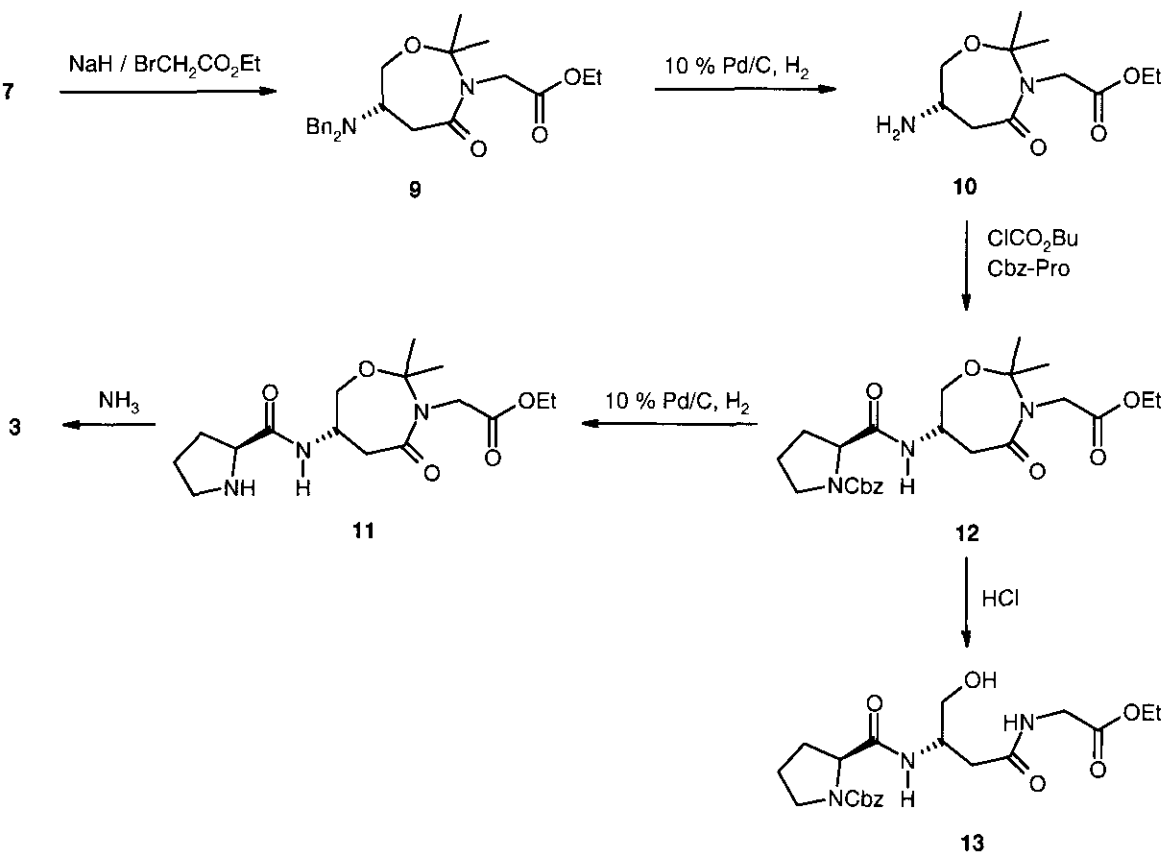


Figure 1 Conformational representation of compound (**7**) as derived from NOE experiments and ^{1}H NMR coupling constants

As an example for the incorporation of the chiral building block (**7**) into a constrained peptidomimetic, the synthesis of the PLG surrogate (**3**) was elaborated. Compound (**7**) was easily converted into the dipeptidomimetic (**9**) by deprotonation with NaH and subsequent reaction with ethyl bromoacetate. Hydrogenolytic cleavage of the dibenzylamine group of **9** with 10 % Pd/C as the catalyst afforded the primary amine (**10**), which was coupled with Cbz-proline to give the tripeptidomimetic (**12**) in good yield. Deprotection of the prolyl moiety followed by aminolysis of the glycine ester yielded the target compound (**3**). This pathway is superior to the reversed reaction sequence including aminolysis as the first step and subsequent hydrogenolytic deprotection of the tripeptidomimetic amide, which gave poorly separable mixtures.

Compound (**7**) also enables a simple but effective approach to peptidomimetics containing homo serine as an amino acid analog by hydrolysis of the cyclic *N*/*O*-acetal. Thus, treating (**12**) with diluted HCl resulted in the formation of the PLG analogue (**13**). However, as a building block of potential pharmaceutical use, the oxazepane (**7**) and especially its *N*-alkylated derivatives should resist hydrolysis under physiological conditions. It could be shown that treatment with aqueous citric acid (10%) resulted in rapid hydrolysis of unsubstituted **7**, whereas the rate of decomposition of 3-*N*-methyl-**7** was much slower. The glycine ester derivative (**9**) resisted the same conditions even for five days and more, demonstrating sufficiant stability of the oxazepane moiety in the aspired peptidomimetics. All oxazepanes were completely stable against water and mild bases.



Scheme 2

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. ^{1}H-NMR spectra were obtained on Bruker AC 200 (200 MHz) and AM 400 (400 MHz) spectrometers, if not otherwise stated in $CDCl_3$ relative to TMS; ^{13}C-NMR spectra on a Bruker AM 200 (50.3 MHz) in $CDCl_3$ relative to the solvent resonance (δ = 77.0). Chromatographic purification was performed using Silica gel 60 (Merck).

(*S*)-(-)-*N*,*N*-Dibenzylasparagine benzyl ester (4)

To a solution of L-asparagine (22.52 g, 0.15 mol) in H_2O (1 L), K_2CO_3 (100 g, 0.73 mol) and benzyl bromide (71.4 mL, 0.6 mol) were added and the mixture was stirred at rt for 10 d. The main part of the product precipitated. It was filtrated, washed with water and recrystallised from petrol-EtOAc 9:1. Evaporation of the filtrate and purification of the residue by flash chromatography (CH_2Cl_2-MeOH 19:1) gave an additional amount of pure **4** (39.2 g, 65%) as a colorless solid; $[\alpha]_D$ -93° (c = 0.5, $CHCl_3$), ref.14: $[\alpha]_D$ -93° (c = 0.5, $CHCl_3$).

(*S*)-(+)-*N*,*N*-Dibenzylamino-4-hydroxybutanecarboxamide (5)

Compound (**4**) (5.2 g, 12.9 mmol) was reduced with $LiAlH_4$ as erlier described to give **5** (2.3 g, 60.4%) as a colorless oil; $[\alpha]_D$ +8° (c = 1, $CHCl_3$), *ref. 14*: $[\alpha]_D$ +8° (c = 1, $CHCl_3$).

(*S*)-(+)-4-Dibenzylamino-γ-lactone (6)

A solution of **5** (149.2 mg, 0.5 mmol) in toluene (10 mL) was refluxed for 18 h. After evaporation of the solvent the residue was purified by column chromatography (petrol-EtOAc 3:1) to yield **6** (130 mg, 93%) as a colorless oil; $[\alpha]_D$ +17.5° (c = 1, $CHCl_3$), ref. 14: $[\alpha]_D$ +17.5° (c = 1, $CHCl_3$).

(*S*)-(+)-*N*,*N*-Dibenzylamino-2,2-dimethyl-1,3-oxazepan-4-one (7)

To a solution of **5** (232 mg, 0.78 mmol) in toluene (20 mL), dimethoxypropane (0.34 mL, 2.72 mmol) and PPTS (20 mg, 0.08 mmol) were added. After refluxing the mixture for 4 h, the toluene was evaporated and the residue was separated by column chromatography (EtOAc-petrol 2:1) into **7** (93 mg, 35%) as a colorless solid and **8** (4 mg, 1.5%) as a colorless oil.

Using the same reaction conditiones but *p*-toluenesulfonic acid hydrate as the catalyst, chromatographic separation of the products afforded **7** (66 mg, 25%), besides **6** (42 mg, 30%) and **8** (4 mg, 1.5%).

7: mp 108°C (petrol-EtOAc 2:1); $[\alpha]_D$ +18.8° (c = 0.5, $CHCl_3$); IR (KBr) υ 3270, 3200, 3050, 2970, 2910, 2840, 2800, 1645 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.33 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.57 (dd, J = 12.9, 3.6 Hz, 1H, H-5), 2.95 (dd, J = 12.9, 9.7 Hz, 1H, H-5), 3.24 (m, 1H, H-6), 3.57 (d, J = 14.0 Hz, 2H, NCH_2Ph), 3.78 (d, J = 14.0 Hz, 2H, NCH_2Ph), 3.88 (dd, J = 13.3, 5.2 Hz, 1H, H-7), 3.93 (dd, J = 13.3, 6.3 Hz, 1H, H-7), 5.85 (s, 1H, NH), 7.20-7.38 (m, 10H, Ph); ^{13}C-NMR δ 27.47 (CH_3), 28.96 (CH_3), 33.00 (C-5), 54.10 (2 NCH_2Ph), 54.65 (C-6), 63.61 (C-7), 85.29 (C-2), 127.01 (C-4'), 128.34 (C-2', C-6'), 128.50 (C-3', C-5'), 139.59 (C-1'), 173.89 (C-4). *Anal.* Calcd for $C_{21}H_{26}N_2O_2$: C, 74.51; H, 7.75; N, 8.28. Found: C, 74.37; H, 7.72; N, 8.12.

(*S*)-3-*N*,*N*-Dibenzylamino-4-(1-methyl-1-methoxyethyloxy)butanecarboxamide (8)

A solution of compound (**5**) (149.2 mg, 0.5 mmol) and *p*-toluenesulfonic acid hydrate (10 mg, 0.05 mmol) in dimethoxypropane (15 mL) was refluxed for 2 h. After evaporation the residue was purified by flash chromatography (EtOAc-petrol 2:1) to yield **8** (69 mg, 37%) as a colorless oil. ^{1}H-NMR (200 MHz) δ 1.35 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.37 (dd, J = 16.2, 4.0 Hz, 1H, H-2), 2.59 (dd, J = 16.2, 9.7 Hz, 1H, H-2), 3.21 (s, 3H, OCH_3), 3.26 (m, 1H, H-3), 3.44 (dd, J = 9.4, 6.8 Hz, 1H, H-4), 3.57 (d, J = 13.2 Hz, 2H, NCH_2Ph), 3.69 (dd, J = 9.4, 5.0 Hz, 1H, H-4), 3.87 (d, J = 13.2 Hz, 2H, NCH_2Ph), 5.25 (s, 1H, NH), 6.97 (s, 1H, NH), 7.21 - 7.34 (m, 10H, Ph).

(*S*)-(+)-6-(*N*,*N*-Dibenzylamino)-2,2-dimethyl-1,3-oxazepan-4-on-3-ylacetic acid ethyl ester (9)

A stirred solution of **8** (205 mg, 0.61 mmol) in THF (10 mL) was treated at 0°C with NaH (29.2 mg, 1.21 mmol, 50% in paraffin). After 1 h ethyl bromoacetate (0.135 mL, 1.21 mmol) was added dropwise and the mixture was allowed to warm up to 5°C during 4 h. After that EtOAc (15 mL) was added and the

reaction was quenched with saturated NaCl solution. The layers were separated and the water layer was extracted 3 times with EtOAc. The combined organic layers were dried with $MgSO_4$, evaporated and purified by column chromatography (petrol-EtOAc 3:1) to yield **9** (161 mg, 62%) as a colorless oil. $[\alpha]_D$ +6.1° (c = 0.5, $CHCl_3$); IR (film) υ 3050, 3010, 2970, 2930, 2820, 2800, 1735, 1635 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.18 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.43 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.68 (dd, J = 12.3, 5.0 Hz, 1H, H-5), 3.10 (dd, J = 12.3, 9.1 Hz, 1H, H-5), 3.35 (m, 1H, H-6), 3.58 (d, J = 14.0 Hz, 2H, $NC\underline{H}_2Ph$), 3.80 (m, 1H, H-7), 3.81 (d, J = 14.0 Hz, 2H, $NC\underline{H}_2Ph$), 3.95 (dd, J = 12.8, 4.4 Hz, 1H, H-7), 4.07-4.11 (4H, $NC\underline{H}_2CO$, $OC\underline{H}_2CH_3$), 7.19-7.35 (m, 10H, Ph). *Anal.* Calcd for $C_{25}H_{32}N_2O_4$: C, 70.72; H, 7.60; N, 6.60. Found: C, 70.47; H, 7.79; N, 6.57.

(*S*)-(-)-6-Amino-2,2-dimethyl-1,3-oxazepan-4-on-3-ylacetic acid ethyl ester (10)

A mixture of **9** (232 mg, 0.55 mmol) and 10 % Pd/C (56 mg) in MeOH (10 mL) was stirred under H_2 (1 bar) for 24 h at rt. The mixture was filtered, the filtrate evaporated and the residue was purified by column chromatography to give **10** (117 mg, 88%) as a colorless oil. $[\alpha]_D$ -7.6° (c = 0.5, $CHCl_3$); IR (film) υ 3600-2800, 3350, 2970, 2920, 1735, 1630 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.29 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.49 (s, 3H, CH_3), 1.50 (2H, NH_2), 1.51 (s, 3H, CH_3), 2.55 (dd, J = 12.8, 5.7 Hz, 1H, H-5), 3.05 (dd, J = 12.8, 4.6 Hz, 1H, H-5), 3.44 (m, 1H, H-6), 3.59 (dd, J = 12.6, 6.4 Hz, 1H, H-7), 3.80 (d, J = 17.5 Hz, 1H, $NC\underline{H}_2CO$), 4.10 (dd, J = 12.6, 7.1 Hz, 1H, H-7), 4.20 (m, 1H, $NC\underline{H}_2CO$), 4.20 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$).

(*S*)-(-)-6-(*N*-Benzyloxycarbonylprolylamino)-2,2-dimethyl-1,3-oxazepan-4-on-3-ylacetic acid ethyl ester (12)

To a solution of L-Cbz-proline (68.1 mg, 0.27 mmol) in THF (10 mL) *N*-methylmorpholine (0.03 mL, 0.27 mmol) was added. After cooling the solution to -10°C i-butyl chloroformiate (0.034 mL, 0.26 mmol) and a solution of **11** (63 mg, 0.26 mmol) in THF (5 mL) were added dropwise. The reaction mixture was kept at -10°C for 5 min and after stirring for 30 min at rt it was filtered and evaporated. The residue was dissolved in a mixture of $CHCl_3$ (1 mL), EtOAc (5 mL) and H_2O (1 mL), the mixture was separated and the organic layer was successively washed with a solution of 10 % Na_2CO_3 and H_2O. After drying with Na_2SO_4 and evaporation of the solvent the residue was purified by column chromatography (CH_2Cl_2-MeOH 19:1) to yield **12** (62 mg, 76%) as a colorless oil. $[\alpha]_D$ -50.0° (c = 1.0, $CHCl_3$); IR (film) υ 3960, 3600, 3540, 3490, 3440, 3350, 1960, 1790, 1675, 1610, 1560 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 1.19 (m, 3H, $OCH_2C\underline{H}_3$), 1.45 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.74-1.79 (m, 3H, 2 x H-γ Pro, H-β Pro), 2.08 (m, 1H, H-β Pro), 2.39 (m, 1H, H-5), 2.74 (m, 1H, H-5), 3.36-3.51 (m, 3H, 2 x H-δ Pro, H-6), 3.93 (m, 1H, NCH_2CO-), 4.02-4.19 (m, 6H, H-α Pro, 2 x H-7, NCH_2CO-, $OC\underline{H}_2CH_3$), 4.94-5.11 (m, 2H, OCH_2Ph), 7.28-7.38 (m, 5H, Ph), 8.03-8.15 (m, 1H, NH). *Anal.* Calcd for $C_{24}H_{33}N_3O_7$: C, 60.60; H, 7.00; N, 8.84. Found: C, 60.35; H, 7.48; N, 8.79.

(+)-*N*-Benzyloxycarbonylprolyl-β-homoserylglycine ethyl ester (13)

The same reaction but modified work-up by washing the organic layer after dissolving in $CHCl_3$ - EtOAc - H_2O 1:5:1 successively with a solution of 10 % Na_2CO_3, H_2O, 0.5N HCl and again H_2O yielded **13** (52%) as

a colorless solid. $[\alpha]_D$ +56.0° (c = 1.0, $CHCl_3$); IR (film) υ 3380, 3280, 3060, 2970, 2950, 2930, 2880, 1745, 1660 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.21 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.98 - 2.12 (4H, 2 x H-β Pro, 2 x H-γ Pro), 2.43 (dd, J = 13.0, 3.3 Hz, 1H, H-α hSer), 2.61 (dd, J = 13.0, 5.0 Hz, 1H, H-α hSer), 3.43 (m, 1H, H-β hSer), 3.54 - 3.59 (2H, 2 x H-δ Pro), 3.81 (dd, J = 11.8, 4.2 Hz, 1H, H-α Gly), 4.03 (m, 1H, H-γ hSer), 4.13 (m, 1H, H-α Gly), 4.13 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.23 - 4.29 (m, 2H, H-γ hSer, H-α Pro), 4.98 (d, J = 12.6 Hz, 1H, OCH_2Ph), 5.08 (d, J = 12.6 Hz, 1H, OCH_2Ph), 7.25 - 7.33 (6H, Ph, NH), 7.79 (s, 1H, NH). *Anal.* Calcd for $C_{21}H_{29}N_3O_7$: C, 57.90; H, 6.72; N, 9.65. Found: C, 57.80; H, 6.77; N, 9.58.

(*S*)-(+)-6-Prolylamino-2,2-dimethyl-1,3-oxazepan-4-on-3-ylglycine ethyl ester (11)

A mixture of **12** (250 mg, 0.53 mmol) and 10 % Pd/C (25 mg) in MeOH (10 mL) was stirred under H_2 (1 bar) for 12 h at rt. The mixture was filtered, the filtrate evaporated and the residue was purified by flash chromato-graphy (CH_2Cl_2-MeOH 9:1) to give **11** (147 mg, 81%) as a colorless oil. $[\alpha]_D$ +2.0° (c = 1.0, $CHCl_3$); IR (film) υ 3312, 2981, 1743, 1644cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 1.20 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.46 (s, 6H, 2 x CH_3), 1.55-1.69 (m, 3H, 2 x H-γ Pro, 1 x H-β Pro), 1.92 (m, 1H, H-β Pro), 2.55-2.82 (m, 4H, 2 x H-5, 2 x H-δ Pro), 3.51 (dd, J = 8.9, 5.2 Hz, 1H, H-6), 3.58 (dd, J = 12.6, 6.2 Hz, 1H, H-7), 3.98 (d, J = 17.7 Hz, 1H, H-α Gly), 4.04 (d, J = 17.7 Hz, 1H, H-α Gly), 4.10 (m, 1H, H-7), 4.10 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 7.97 (d, J = 8.6 Hz, 1H, CONH). *Anal.* Calcd for $C_{16}H_{27}N_3O_5 \cdot 1/2H_2O$: C, 54.84; H, 8.05; N, 11.99. Found: C, 54.76; H, 7.90; N, 11.86.

(*S*)-(+)-6-Prolylamino-2,2-dimethyl-1,3-oxazepan-4-on-3-ylglycine amide (3)

In an autoclave to a solution of **13** (63 mg, 0.20 mmol) in MeOH (2mL) liquid NH_3 (10 mL) was added at -50°C. The mixture was stirred at rt for 7 d. After evaporation the residue was separated by flash chromatography (CH_2Cl_2-MeOH 9:1) to yield **3** (31 mg, 50%) as a colorless solid and unchanged **13** (30 mg, 50%). $[\alpha]_D$ +23.5° (c = 1.2, MeOH); IR (KBr) υ 3405, 3199, 2983, 2949, 1679, 1632 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 1.44 (s, 6H, 2 x CH_3), 1.53-1.65 (m, 3H, 2 x H-γ Pro, 1 x H-β Pro), 1.94 (m, 1H, H-β Pro), 2.50-2.78 (m, 4H, 2 x H-5, 2 x H-δ Pro), 3.47 (m, 1H, H-6), 3.65 (dd, J = 12.3, 5.4 Hz, 1H, H-7), 3.80 (d, J = 16.8 Hz, 1H, H-α Gly), 3.89 (d, J = 16.8 Hz, 1H, H-α Gly), 4.05 (dd, J = 12.3, 6.7 Hz, 1H, H-7), 4.15 (m, 1H, H-α Pro), 6.98 (s, 1H, $CONH_2$), 7.31 (s, 1H, $CONH_2$), 8.01 (d, J = 8.4 Hz, 1H, CONH). *Anal.* Calcd for $C_{14}H_{24}N_4O_4 \cdot 2H_2O$: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.30; H, 7.67; N, 16.13.

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