Supplementary Material

Experimental

General

NMR spectra were recorded on 400 MHz or 300 MHz Bruker instruments Chemical shifts were reported in ppm (parts per millions) using the solvent residual peak as the internal reference. IR spectra were recorded on a Perkin Elmer 1600 series. Chemical shifts are referenced to the residual solvent peak. Quin = quintet, sext = sextuplet, Septuplet = sept, double septuplets = dsept, octuplet = oct. TLC was performed on Merck TLC aluminium sheets, silica gel 60, F_{254} and visualizing was effected with UV−light and/or 1 % ninhydrin in n-BuOH/AcOH. High resolution mass spectra were provided by the Department of Bioorganic Chemistry, Royal Veterinary and Agricultural University, Denmark. Elemental analysis was provided by the Department of Chemistry, University of Copenhagen, Denmark. Dry Flash Chromatography was performed with silica gel using Merck Silica gel 60 (0.015−0.040 mm). PtO_2 (surface area ≥60 m^2/g) was purchased from SigmaAldrich Denmark. All solvents were purchased from VWR and used without further purification and kept under MS and a nitrogen atmosphere. *Pyr*rolidinediones were synthesized as previously described[i]. Molecular sieves was purchased from VWR and used as received with no activation.

*py*Ala-Ala-NH_2 (**3a**)

To a solution of (S)−5−methylpyrrolidine-2,4−dione (*py*Ala-OH)[i] (226 mg, 2.0 mmol) in i−PrOH (9 mL) was added AcOH (1 mL), alanine amide (125 mg, 1.0 mmol) and 3Å molecular sieves (5 mL). The mixture was heated to 55 °C and stirred for 24h. The red−brown mixture was filtered through celite and evaporated to a brown oil. Purification by dry flash chromatography using a gradient eluent of 0−10 vol% MeOH in EtOAc (150 ml fractions) provided the title product as an off−white solid (174 mg, 95%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.52 (s, 1H), 4.10 (q, *J* = 6.6 Hz, 1H), 3.81 (q, *J* = 7.1 Hz, 1H), 1.44 (d, *J* = 7.1 Hz, 3H), 1.36 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 18.6, 19.8, 55.0, 55.3, 87.3, 170.3, 177.9, 179.1. IR (KBr): 3297 (br) 1681 (s), 1606 (s), 1608 (s), 1206 (w), 792 (w). Mp 89−90 °C. $[\alpha]^{20}_D$ 35.7 (*c* 0.1, MeOH). HRMS (EI^+): Calcd. for $C_8H_{14}N_3O_2$ [M+H^+] 184.1086 Found 184.1085.

*py*Ala-Val-NH_2 (**3b**)

Following the procedure for **3a** (186 mg, 88%).

^{1}H NMR (300 MHz, DMSO) δ 7.36 (bs, 1H), 7.07 (bs, 1H), 6.73 (bs, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 4.34 (s, 1H), 3.87 (q, *J* = 6.4 Hz, 1H), 1.95 (sept, *J* = 6.8 Hz, 1H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.93−0.87 (m, 6H). ^{13}C NMR (75 MHz, DMSO) δ 19.0, 19.2, 19.9, 30.2, 52.0, 64.0, 86.1, 167.8, 172.9, 174.9. IR (KBr): 3413 (br) 2926 (w), 1676 (s), 1608 (s), 1207 (s), 1137 (s). $[\alpha]^{20}_D$ −88.0 (*c* 0.3, MeOH). HRMS (EI^+): Calcd. for $C_{10}H_{18}N_3O_2$ [M+H^+] 212.1399 Found 212.1409.

*py*Ala-Leu-NH_2 (**3c**)

Following the procedure for **3a** (191 mg, 85%).

^{1}H NMR (400 MHz, CD_3OD) δ 4.49 (s, 1H), 4.12 (q, *J* = 6.6 Hz, 1H), 3.73 (dd, *J* = 5.1, 8.6 Hz, 1H), 1.65−1.47 (m, 3H), 1.24 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 19.9, 22.3, 23.5, 26.1, 42.5, 54.8, 58.5, 87.0, 170.7, 177.9, 179.0. IR (KBr): 3391 (br), 1674 (s), 1605 (s), 1203 (w), 722 (w). Mp 127−129 °C. $[\alpha]^{20}_D$ −150.0 (*c* 0.4, MeOH). HRMS (EI^+): Calcd. for $C_{11}H_{20}N_3O_2$ [M+H^+] 226.1559 Found 226.1557.

*py*Val-Ala-NH_2 (**3d**)

Following the procedure for **3a** (186 mg, 88%).

^{1}H NMR (400 MHz, CD_3OD) δ 0.71 (m, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H), 1.43 (d, *J* = 6.6 Hz, 3H), 2.14 (dsept, *J* = 7.1, 2.5 Hz, 1H), 3.82 (q, *J* = 7.1 Hz, 1H), 4.03 (d, *J* = 2.5 Hz, 1H), 4.56 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 13.9, 18.4, 20.7, 31.5, 49.5, 54.9, 64.1, 88.5, 167.9, 177.8, 180.1. IR (KBr): 3400 (br), 1679 (s), 1642 (s), 1609 (s), 729 (w). Mp 102−104 °C. $[\alpha]^{20}_D$ −22.4 (*c* 0.7, MeOH). HRMS (EI^+): Calcd. for $C_{10}H_{18}N_3O_2$ [M+H^+] 212.1399 Found 212.1396.

*py*Val-Val-NH_2 (**3e**)

Following the procedure for **3a** (196 mg, 82%).

^{1}H NMR (400 MHz, CD_3OD) δ 0.67 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 2.04 (sept, *J* = 6.9 Hz, 1H), 2.16 (dsept, *J* = 6.8, 2.8 Hz, 1H), 3.45 (d, *J* = 8.6 Hz, 1H), 4.07 (d, *J* = 3.0 Hz, 1H), 4.63 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 13.8, 19.5, 19.6, 20.8, 31.5, 32.0, 63.9, 65.7, 88.1, 168.7, 176.3,

180.3. IR (KBr): 3429 (br), 2976 (w), 1670 (s), 1288 (w). Mp 102−104 °C. $[\alpha]^{20}_{D}$ −84.4 (*c* 1.2, MeOH). HRMS (EI^+): Calcd. for $C_{12}H_{22}N_3O_2$ $[M+H^+]$ 240.1712 Found 240.1708.

*py*Val-Leu-NH_2 (**3f**)
Following the procedure for **3a** (231 mg, 91%).
^{1}H NMR (400 MHz, CD_3OD) δ 0.69 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.1 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.54 −1.62 (m, 1H), 1.66−1.67 (m, 2H), 2.17 (dsept, *J* = 6.9, 2.8 Hz, 1H), 3.79 (dd, *J* = 8.6, 5.6 Hz, 1H), 4.04 (d, *J* = 2.5 Hz, 1H), 4.62 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 13.8, 20.8, 22.3, 23.3, 26.0, 31.4, 42.5, 58.1, 64.0, 88.1, 168.5, 177.6, 180.2. IR (KBr): 3273 (br), 2398 (m), 1655 (s), 1602 (s), 155 (w). Mp 118−119 °C. $[\alpha]^{20}_{D}$ −21.6 (*c* 0.9, MeOH). HRMS (EI^+): Calcd. for $C_{13}H_{24}N_3O_2$ $[M+H^+]$ 254.1869 Found 254.1866.

*py*Val-D-Ala-NH_2 (**3g**)
Following the procedure for **3a** (177 mg, 84%).
^{1}H NMR (300 MHz, DMSO) δ 7.42 (bs, 1H), 7.08 (bs, 1H), 6.86 (bs, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 4.31 (s, 1H), 3.84 (bs, 1H), 3.60 (quin, *J* = 7.1 Hz, 1H), 2.06 (dsept, *J* = 6.8, 2.6 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 0.95 Hz, 3H), 0.56 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ 13.4, 18.2, 20.2, 29.2, 53.0, 61.3, 88.0, 164.6, 174.4, 175.8. IR (KBr): 3292 (br) 2963 (w), 1648 (s), 1609 (s), 1158 (w). Mp 232−234 °C.
$[\alpha]^{20}_{D}$ −31.8 (*c* 0.7, MeOH). HRMS (EI^+): Calcd. for $C_{10}H_{18}N_3O_2$ $[M+H^+]$ 212.1393 Found 212.1399.

*py*Val-Ala-OMe (**3h**)
Following the procedure for **3a** (198 mg, 88%)
^{1}H NMR (400 MHz, CD_3OD) δ 4.48 (s, 1H), 4.02 (d, *J* = 3.0 Hz, 1H), 3.98 (dq, *J* = 2.5, 7.1 Hz, 1H), 2.14 (dsept, *J* = 3.0, 6.6 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (100 MHz, CD_3OD) δ 13.7, 17.5, 17.6, 20.7, 31.4, 52.7, 54.0, 64.0, 88.1, 168.0, 174.7, 180.1.
IR (KBr): 3435 (br), 1640 (m), 1635 (m), 1120 (w). Mp 181−182 °C. $[\alpha]^{20}_{D}$ −101.9 (*c* 0.5, MeOH).
HRMS (EI^+): Calcd. for $C_{11}H_{21}N_2O_3$ $[M+H^+]$ 226.1552 Found 226.1552.

*py*Val-Ala-O*t*-Bu (**3i**)
Following the procedure for **3a** (250 mg, 93%).
^{1}H NMR (400 MHz, CD_3OD) δ 4.51 (s, 1H), 4.01 (d, *J* = 2.5 Hz, 1H), 3.79 (q, *J* = 7.1 Hz, 1H), 2.15 (dsept, *J* = 2.5, 7.1 Hz, 1H), 1.46 (s, 9H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.75 (d, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, CD_3OD) δ 4.0, 17.62, 17.57, 20.7, 28.2, 31.4, 55.0, 55.1, 63.9, 64.0, 82.8, 88.00, 88.05, 168.0, 168.1, 173.7, 180.2. IR (KBr): 3392 (w), 2980 (w), 1604 (s), 1369 (m), 1148 (m). Mp 164−165 °C. $[\alpha]^{20}_{D}$ 177.5 (*c* 0.5, MeOH). HRMS (EI^+): Calcd. for $C_{14}H_{25}N_2O_3$ $[M+H^+]$ 269.1865 Found 269.1854.

*py*Val-Pro-NH_2 (**3j**)
Following the procedure for **3a** (209 mg, 88%).
^{1}H NMR (400 MHz, DMSO) δ 4.29 (bs, 1H), 3.50−3.31 (m, 3H), 2.25−2.09 (m, 2H), 1.97−1.68 (m, 2H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.58 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 13.1, 20.1, 23.7, 28.0, 30.2, 49.3, 61.0, 62.4, 90.5, 164.3, 173.2, 174.7. IR (KBr): 3479 (w), 2964 (w), 1658 (s), 1592 (s), 1399 (m).
Mp 93−94 °C. $[\alpha]^{20}_{D}$ −33.3 (*c* 0.5, MeOH). HRMS (EI^+): Calcd. for $C_{12}H_{20}N_3O_2$ $[M+H^+]$ 238.1556 Found 238.1556.

*py*Leu-Ala-NH_2 (**3k**)
Following the procedure for **3a** (198 mg, 88%).
^{1}H NMR (400 MHz, CD_3OD) δ 4.52, (s, 1H), 4.11 (dd, *J* = 3.0, 10.6 Hz, 1H), 3.81 (q, *J* = 6.6 Hz, 1H), 1.85−1.74 (m, 1H), 1.85−1.72 (m, 1H), 1.42 (d, *J* = 7.1 Hz, 3H), 1.40−1.34 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.6 Hz).
^{13}C NMR (100 MHz, CD_3OD) δ 18.4, 21.6, 24.4, 26.4, 40.4, 44.1, 55.2, 57.6, 169.6, 177.9, 179.3. IR (KBr): 3398 (br) 2963 (w), 1682 (s), 1607 (s), 1207 (s), 1140 (s). Mp 132−135 °C. $[\alpha]^{20}_{D}$ −15.8 (*c* 0.4, MeOH). HRMS (EI^+): Calcd. for $C_{11}H_{20}N_3O_2$ $[M+H^+]$ 226.1556 Found 226.1547.

*py*Leu-Val-NH_2 (**3l**)
Following the procedure for **3a** (218 mg, 86%)
^{1}H NMR (400 MHz, CD_3OD) δ 4.55 (s, 1H), 4.12−4.08 (m, 1H), 4.42−3.38 (m, 1H), 2.05−1.91 (m, 1H), 1.75−1.59 (m, 2H), 1.32−1.15 (m, 1H), 1.01−0.85 (m, 12H). ^{13}C NMR (100 MHz, CD_3OD) δ 19.4, 19.6, 21.7, 24.4, 26.3, 32.0, 44.0, 57.5, 66.0, 87.1, 170.3, 170.4, 176.4, 179.3. IR (KBr): 3403 (br), 2966 (w), 1677 (s), 1603 (s), 1415 (m). Mp 105−106 °C. $[\alpha]^{20}_{D}$ −27.7 (*c* 0.3, MeOH). HRMS (EI^+): Calcd. for $C_{13}H_{24}N_3O_2$ $[M+H^+]$ 254.1869 Found 254.1873.

*py*Leu-Leu-NH_2 (**3m**)
Following the procedure for **3a** (233 mg, 87%).

^{1}H NMR (400 MHz, CD_3OD) δ 4.60 (s, 1H), 4.14 (dd, *J* = 2.5, 10.1 Hz, 1H), 3.79 (dd, *J* = 8.6, 5.6 Hz, 1H), 1.83−1,67 (m, 4H), 1.64−1.56 (m, 1H), 1.02−0.91 (m, 12H). ^{13}C NMR (100 MHz, CD_3OD) δ 21.6, 22.2, 23.3, 24.4, 25.9, 26.3, 42.3, 44.0, 57.6, 57.6, 58.3, 87.1, 170.0, 177.8, 179.3. IR (KBr): 3420 (br) 2962 (w), 1677 (s), 1606 (s), 1202 (s), 1142 (s). Mp 132−133 °C. $[\alpha]^{20}_D$ −25.6 (*c* 0.3, MeOH). HRMS (EI^+): Calcd. for $C_{14}H_{26}N_3O_2$ [M+H$^+$] 268.2025 Found 268.2012.

*py*Phe-Leu-NH_2 (**3n**)
Following the procedure for **3a** (1592 mg, 88%).
^{1}H NMR (300 MHz, CD_3OD) δ 7.30−7.20 (m, 5H), 4.50 (s, 1H), 4.33 (dd, *J* = 3.8, 7.1 Hz, 1H), 3.76 (dd, *J* = 5.6, 8.5 Hz, 1H), 2.24 (dd, *J* = 4.1, 13.8 Hz, 1H), 2.82 (dd, *J* = 7.0, 13.8 Hz, 1H), 1.81−1.56 (m, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (75 MHz, CD_3OD) δ 22.1, 22.8, 24.3, 38.5, 41.0, 56.3, 57.0, 87.3, 126.1, 127.7, 129.9, 136.8, 164.9, 173.9, 175.0. IR (KBr): 3459 (br), 2925 (m), 1675 (m), 1601 (m). Mp 168−169 °C.
$[\alpha]^{20}_D$ 86.9 (*c* 0.6, MeOH). Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69. N, 13.94 Found: C, 67.40; H, 7.54; N, 13.58.

^{cis}*py*Ala-Ala-NH_2 (**4a**)
To a solution of **3a** (0.109mmol, 20 mg) in *t*-BuOH (2 mL) was added PtO_2 (6 mg, 0.026mmol). The mixture was heated to 25 °C and stirred under 60 bar H_2 for 24 h. Filtration of the catalyst followed by evaporation provided the title product as a white solid (18 mg, 89%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.81 (quint, *J* = 6.6 Hz, 1H), 3.53−3.46 (m, 1H), 3.18 (q, *J* = 7.1 Hz, 1H), 2.39 (dd, *J* = 8.1, 16.7 Hz, 1H), 2.22 (dd, *J* = 9.6, 16.7 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (75 MHz, CD_3OD) δ 181.1, 177.5, 56.9, 56.2, 53.6, 36.6, 19.6, 15.2. IR (KBr): 3435 (br) 2860 (w), 1650 (m). $[\alpha]^{20}_D$ −52.2 (*c* 0.4, MeOH). HRMS (EI^+): Calcd. for $C_8H_{16}N_3O_2$ [M+H$^+$] 186.1243 Found 186.1234.

^{cis}*py*Ala-Val-NH_2 (**4b**)
To a solution of **3d** (0.095mmol, 20 mg) in *t*-BuOH (2 mL) was added PtO_2 (5 mg, 0.022mmol). The mixture was heated to 25 °C and stirred under 60 bar H_2 for 36h. Filtration of the catalyst followed by column chromatography (EtOAc/MeOH, 9:1) (18 mg, 89%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.78 (quint, *J* = 6.6 Hz, 1H), 3.47−3.39 (m, 1H), 2.23 (d, *J* = 6.6 Hz, 1H), 2.37 (dd, *J* = 8.8, 16.7 Hz, 1H), 2.24 (dd, *J* = 9.6, 16.7 Hz, 1H), 1.81 (oct, *J* = 6.6 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 15.7, 19.4, 19.9, 33.0, 37.1, 54.2, 56.9, 68.1, 178.2, 180.1. IR (KBr): 3435 (br) 2925 (w), 1677 (s), 1435 (w), 1206 (w). $[\alpha]^{20}_D$ 32.6 (*c* 0.7, MeOH). HRMS (EI^+): Calcd. for $C_{10}H_{20}N_3O_2$ [M+H$^+$] 215.1556 Found 215.1559.

^{cis}*py*Ala-Leu-NH_2 (**4c**)
Following the procedure for **4a** (19 mg, 94%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.79 (quint, *J* = 6.6 Hz, 1H), 3.45−3.42 (m, 1H), 3.15 (t, *J* = 7.1 Hz, 1H), 2.38 (dd, *J* = 8.1, 16.7 Hz, 1H), 2.22 (dd, *J* = 9.6, 16.7 Hz, 1H), 1.77 (sept, *J* = 6.6 Hz, 1H), 1.48−1.40 (m, 2H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 M Hz, CD_3OD) δ 15.8, 23.3, 23.4, 26.2, 37.3, 44.9, 54.4, 56.9, 61.0, 178.3, 181.3. IR (KBr): 3439 (br), 2960 (w), 1672 (s), 1435 (w), 1204 (m). $[\alpha]^{20}_D$ −32.0 (*c* 0.05, MeOH). HRMS (EI^+): Calcd. for $C_{11}H_{22}N_3O_2$ [M+H$^+$] 228.1712 Found 228.1720.

^{cis}*py*Val-Ala-NH_2 (**4d**)
To a solution of **3d** (0.095mmol, 20 mg) in *t*-BuOH (2 mL) was added PtO_2 (5 mg, 0.022mmol). The mixture was heated to 55 °C and stirred under 60 bar H_2 for 24h. Filtration of the catalyst followed by evaporation provided the title product as a white solid (19 mg, 94%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.62 (q, *J* = 7 Hz, 1H), 3.52 (t, *J* = 7 Hz, 1H), 3.30 (q, *J* = 7 Hz, 1H), 2.45 (dd, *J* = 6 Hz, 16 Hz, 1H), 2.20 (dd, *J* = 6, 16 Hz, 1H), 2.93 (oct. *J* = 6 Hz, 1H), 1.25 (d, *J* = 7 Hz, 3H), 0.93 (d, *J* = 7 Hz, 3H), 0.85 (d, *J* = 7 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 17.7, 21.7, 25.3, 29.8, 32.2, 36.8, 55.5, 64.1, 65.6, 67.7, 178.7, 181.6. IR (KBr): 3390 (br), 2966 (w), 1682 (s), 1385 (w). $[\alpha]^{20}_D$ 37.5 (*c* 0.5, MeOH). HRMS (EI^+): Calcd. for $C_{10}H_{20}N_3O_2$ [M+H$^+$] 214.1556 Found 214.1548.

^{cis}*py*Val-Val-NH_2 (**4e**)
Following the procedure for **4d** (20 mg, 99%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.50−3.43 (m, 2H), 2.79 (d, *J* = 7.6 Hz, 1H), 2.39 (dd, *J* = 7.1, 16.7 Hz, 1H), 2.25 (dd, *J* = 7.1, 16.2 Hz, 1H), 2.14−2.03 (m, 1H), 1.78 (oct, *J* = 6.6 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.1 Hz, 6H).
^{13}C NMR (100 MHz, CD_3OD) δ 18.3, 19.3, 19.9, 20.7, 29.3, 33.1, 38.9, 57.2, 64.9, 68.7, 179.3, 180.5. IR (KBr): 3429 (br) 2976 (w), 1670 (s), 1209 (w), 672 (w). Mp 178−179 °C. $[\alpha]^{20}_D$ −25.2 (*c* 0.5, MeOH). HRMS (EI^+): Calcd. for $C_{12}H_{24}N_3O_2$ [M+H$^+$] 242.1869 Found 242.1859.

cis-*py*Val-Leu-NH_2 (**4f**)
Following the procedure for **4d** (19 mg, 94%).
^{1}H NMR (400 MHz, D_2O) δ 3.61 (q, *J* = 7.1 Hz, 1H), 3.59−3.52 (m, 1H), 3.10 (t, *J* = 7.6 Hz, 1H), 2.46 (dd, *J* = 7.1, 16.7 Hz, 1H), 2.21 (dd, *J* = 7.6, 16.7 Hz, 1H), 1.91 (quint, *J* = 6.6 Hz, 1H), 1.55 (quint, *J* = 6.6 Hz, 1H), 1.47−1.40 (m, 1H), 0.91−0.83 (m, 12H). ^{13}C NMR (100 MHz, CD_3OD) δ 18.4, 20.7, 22.9, 23.4, 25.9, 29.3, 38.9, 44.7, 57.0, 61.2, 64.9, 179.3, 181.5. IR (KBr): 3378 (br), 2964 (w), 1639 (s), 1390 (w). Mp 170−172 °C $[\alpha]^{20}_D$ 162.6 (*c* 0.5, MeOH). HRMS (EI^+): Calcd. for $C_{13}H_{26}N_3O_2$ [M+H^+] 256.2025 Found 256.2028.

cis-*py*Val-D−Ala-NH_2 (**4g**)
Following the procedure for **4d** (20 mg, 99%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.41−3.35 (m, 2H), 3.24 (q, *J* = 6.6 Hz, 1H), 2.46 (dd, *J* = 6.6, 16.7 Hz, 1H), 1.97 (sext, *J* = 7.1 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.02−0.97 (m, 6H). ^{13}C NMR (400 MHz, CD_3OD) δ 18.66, 18.73, 19.4, 26.6, 37.5, 53.7, 54.1, 65.0, 180.1, 180.2. IR (KBr): 3351 (br), 2976 (w), 1670 (s), 1385 (w), 1209 (w). $[\alpha]^{20}_D$ 40.1 (*c* 0.2, MeOH). HRMS (EI^+): Calcd. for $C_{10}H_{20}N_3O_2$ [M+H^+] 214.1556 Found 214.1558.

cis-*py*Val-Ala-OMe (**4h**)
Following the procedure for **4d** (20 mg, 99%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.72 (s, 3H), 3.54−3.33 (m, 3H), 2.39 (dd, *J* = 8.1, 16.7 Hz, 1H), 2.21 (dd, *J* = 7.1, 16.7, 1H), 2.05−1.96 (m, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 6H).
^{13}C NMR (100 MHz, CD_3OD) δ 18.5, 19.2, 20.6, 29.3, 38.8, 52.5, 56.3, 56.7, 65.0, 177.8, 179.3.
IR (KBr): 3435 (s), 2923 (w), 1732 (m), 1688 (m), 1175 (w).
Mp 68−70 °C. $[\alpha]^{20}_D$ −51.5 (*c* 0.6, MeOH), HRMS (EI^+): Calcd. for $C_{11}H_{20}N_2NaO_3$ [M+Na^+] 251.1372 Found 251.1369.

cis-*py*Val-AlaOt−Bu (**4i**)
Following the procedure for **4d** (19 mg, 94%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.64−3.54 (m, 2H), 3.32 (q, *J* = 6.6 Hz, 1H), 2.43 (dd, *J* = 7.6, 16.8 Hz, 1H), 2.23 (dd, *J* = 8.1, 17.2 Hz, 1H), 1.97−1.86 (m, 1H), 1.42 (s, 9H), 1.23 (dd, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (400 MHz, D_2O) δ 17.4, 17.9, 20.2, 27.4, 27.5, 37.1, 54.9, 56.4, 63.2, 83.8, 176.8, 179.7. IR (KBr): 3436 (br), 2975 (m), 1699 (s), 1368 (w), 1152 (m). $[\alpha]^{20}_D$ 177.5 (*c* 0.5, MeOH). HRMS (EI^+): Calcd. for $C_{14}H_{26}N_2O_3Na$ [M+Na^+] 293.1841 Found 293.1842.

cis-*py*Val-Pro-NH_2 (**4j**)
Following the procedure for **4d** (20 mg, 99%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.51 (dd, *J* = 2.1, 7.1 Hz, 1H), 3.45−3.36 (m, 1H), 3.29−3.21 (m, 2H), 2.50−2.41 (m, 3H), 1.86−1.79 (m, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 17.7, 21.7, 25.3, 29.8, 32.2, 36.7, 55.5, 64.1, 65.6, 67.7, 178.7, 181.6. IR (KBr): 3435 (br), 2963 (w), 1672 (s), 1317 (w), 1094 (w). Mp 81−82 °C. $[\alpha]^{20}_D$ −33.3 (*c* 0.7, MeOH). HRMS (EI^+): Calcd. for $C_{12}H_{22}N_3O_2$ [M+H^+] 240.1710 Found 240.1712.

cis-*py*Leu-Ala-NH_2 (**4k**)
To a solution of **3k** (0.089 mmol, 20 mg) in *t*-BuOH (2 mL) was added PtO_2 (5 mg, 0.022mmol). The mixture was heated to 35 °C and stirred under 60 bar H_2 for 36h. Filtration of the catalyst followed by column chromatography (EtOAc/MeOH, 9:1) (18 mg, 89%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.79−3−72 (m, 1H), 3.57−3.49 (m, 1H), 3.17 (q, *J* = 6.6 Hz, 1H), 2.38 (dd, *J* = 7.6, 16.7 Hz, 1H), 2.23 (dd, *J* = 9.6, 16.7 Hz, 1H), 1.74−1.64 (m, 1H), 1.47−1.40 (m, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 19.6, 21.3, 24.3, 25.4, 37.0, 39.2, 56.0, 56.7, 57.0, 178.0, 180.9. IR (KBr): 3435 (br), 2924 (w), 1677 (m), 1206 (w). $[\alpha]^{20}_D$ −103.6 (*c* 0.3, MeOH). HRMS (EI^+): Calcd. for $C_{11}H_{22}N_3O_2$ [M+H^+] 228.1712 Found 228.1717.

cis-*py*Leu-Val-NH_2 (**4l**)
Following the procedure for **4k** (17 mg, 84%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.81 (quint, *J* = 6.6 Hz, 1H), 3.52−3.46 (m, 1H), 3.18 (q, *J* = 6.6 Hz, 1H), 2.39 (dd, *J* = 8.1, 16.7 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 19.4, 19.9, 21.8, 24.4, 25.6, 33.1, 37.5, 39.5, 56.7, 57.5, 68.2, 178.5, 180.2. IR (KBr): 3434 (br), 2964 (w), 1676 (m), 1209 (m). 1140 (m). $[\alpha]^{20}_D$ 86.0 (*c* 0.4, MeOH). HRMS (EI^+): Calcd. for $C_{13}H_{26}N_3O_2$ [M+H^+] 256.2025 Found 256.2036.

cis-*py*Leu-Leu-NH_2 (**4m**)
Following the procedure for **4k** (20 mg, 99%).

^{1}H NMR (400 MHz, CD_3OD) δ 3.83−3.78 (m, 1H), 3.66−3.61 (m, 1H), 2.42 (dd, *J* = 7.6, 16.2 Hz, 1H), 2.31 (d, *J* = 9.2, 16.2 Hz, 1H), 1.87−1.64 (m, 2H), 1.58−1.38 (m, 3H), 1.36−1.22 (m, 1H), 1.02−0.88 (m, 12H). ^{13}C NMR (100 MHz, CD_3OD) δ 21.5, 23.0, 23.1, 24.5, 25.6, 25.8, 36.5, 39.4, 43.7, 56.0, 56.8, 60.6, 163.0, 163.4, 177.5. IR (KBr): 3413 (br), 2962 (w), 1677 (s), 1206 (m). 1142 (m). $[\alpha]^{20}_D$ −91.8 (*c* 0.5, MeOH). HRMS (EI^+): Calcd. for $C_{14}H_{28}N_3O_2$ [M+H$^+$] 270.2182 Found 270.2181.

^{cis}*py*Cha-Leu-NH_2 (**4n**)
Following the procedure for **4a** (20 mg, 99%).
^{1}H NMR (400 MHz, CD_3OD) δ 3.79 −3.73 (m, 1H), 3.46 (q, *J* = 7.1 Hz, 1H), 3.11 (t, *J* = 7.1 Hz, 1H), 2.35 (dd, *J* = 7.6, 16.2 Hz, 1H), 2.22 (dd, *J* = 9.6, 16.7, 1H), 1.90 − 1.65 (m, 6H), 1.44−1.25 (m, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 23.0, 23.4, 25.9, 27.1, 27.4, 27.7, 33.4, 35.1, 35.8, 37.5, 38.0, 44.7, 55.8, 57.2, 60.7, 178.3, 181.2. IR (KBr): 3435 (br) 2922 (m), 1656 (s), 1449 (w).
$[\alpha]^{20}_D$ −100.0 (*c* 0.33, MeOH). Mp. 267 ^{o}C (decomp.)
HRMS (EI^+): Calcd. for $C_{11}H_{20}N_3O_2$ [M+H$^+$] 310.2495 Found 310.2494.

^{cis}*py*Val-Ala-OH (**5**)
To a solution of **4i** (36 mg, 0.13 mmol) was added TFA (3 mL) and the mixture was stirred for 6 hours and evaporated in vacuo to provide ^{cis}*py*Val-AlaOH·TFA (42 mg, 96%).
^{1}H NMR (300 MHz, CD_3OD) δ 4.24 (q, *J* = 7.5 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 2.70 (q, *J* = 7.9, 17.3 Hz, 1H), 2.56 (q, *J* = 6.8, 17.3 Hz, 1H), 1.89 (sext, *J* = 6.4 Hz, 1H), 1.53 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ 13.8, 17.6, 17.6, 20.2, 27.2, 33.6, 54.3, 55.7, 61.7, 61.8, 61.8, 116.7 (q, *J* = 36 Hz), 163.1 (q, *J* = 291 Hz), 172.0, 176.4. IR (KBr): 3430 (s), 1754 (w), 1673 (s), 1201 (s), 1136 (m). Mp 134−135^{o}C. $[\alpha]^{20}_D$ 91.8 (*c* 0.7, MeOH). HRMS (EI^+): Calcd. for $C_{10}H_{19}N_2O_3$ [M+H$^+$−TFA] 215.1396 Found 215.1389.

Preparation of the crystal.

To a solution of ^{cis}*py*Val-Pro-NH_2 in MeOH (2 mL) was added heptane (1 mL) and the mixture was allowed to evaporate over three days. The formed crystals were washed with Heptane (2 x 3 mL) and dried in a vacuum oven (50 ^{o}C).

X-ray Crystal Structure Determinations.

The crystal of the compound, $C_{12}H_{21}N_3O_2{\cdot}1.5\ H_2O$, was cooled to 120 K using a Cryostream nitrogen gas cooler system. The data were collected on a Bruker SMART 1K diffractometer with a CCD area sensitive detector. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 of all data. The temperature factors of N1, C3, C4 and C10 are rather large and may indicate that the atoms are disordered. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms of the water molecules were all refined isotropically. All the other hydrogen atoms were at calculated positions using a riding model with C-H = 0.98-1.00 Å, N-H = 0.88 Å. For all hydrogen atoms the thermal parameters were fixed [U_{iso}(H) = 1.5 U_{iso}(C) for methyl and water and U_{iso}(H) = 1.2 U_{iso}(C,N) for the remaining H atoms.]. The absolute configuration of the structure could not be determined due to the lack of heavy atoms. In the refinement of the structure 2 restraints were used to fix the origin and 4 were used to keep the O-H bonds around 0.9 Å for the water molecules. Programs used for data collection, data reduction and absorption were SMART, SAINT and SADABS.[ii,iii] The program SHELXTL 95[iv] was used to solve the structures and for molecular graphics.

Crystal data: *M*= 266.34, tetragonal, *a* = 12.9386(8)Å, *b* = 12.9386(8) (8)Å, *c* = 8.5628(7) Å, *V* =1433.48(17)Å^3, *T* = 120(2) K, space group $P4_2$, *Z* = 4, D_x = 1.234 g cm^{-3}, crystal size = 0.46 x 0.08 x 0.04 mm^3, μ(MoKα) = 0.091 mm^{-1}, 20006 reflections measured, 1858 unique (R_{int} = 0.08(4)) and 1779 reflections with $I > 2\sigma(I)$ wich were used in all calculations. Friedel pairs were merged before refinement. The final *R*1 was 0.1025 (observed data) and $wR(F^2)$ was 0.2087 (all data).

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