Controlling the sign and magnitude of screw-sense preference from the C-terminus of an achiral helical foldamer

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General Experimental and Materials

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen using standard anhydrous techniques. All reagents were obtained from commercially available sources and used without further purification, or where indicated prepared internally. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Reactions performed at 0 °C were done so using an ice bath; those performed at -78 °C were done so using an acetone/dry ice bath. Anhydrous dichloromethane was obtained by distillation from calcium hydride. Other anhydrous reaction solvents were obtained from standard anhydrous solvent engineering system. Triethylamine was stored over potassium hydroxide. All products were dried on a rotary evaporator followed by connection to a high vacuum system to remove any residual solvent. Flash chromatography was performed on silica gel (Merck 60H, 40-60 nm, 230 – 300 mesh). Analytical thin layer chromatography was performed on aluminium backed silica (60 F254) plates.

Instrumentation

All \(^1\)H and \(^{13}\)C nuclear magnetic resonance spectra were obtained using Bruker Ultrashield 300, 400 or 500 MHz spectrometers. Chemical shifts are quoted in parts per million (ppm) and coupling constants (\(J\)) are quoted in Hz, given to the nearest 0.5 Hz. \(^1\)H-NMR were referenced to the residual deuterated solvent peak (CDCl\(_3\) 7.27; CD\(_2\)OD 3.31 ppm) and \(^{13}\)C-NMR were referenced to the carbon resonance of the solvent (CDCl\(_3\) 77.0; CD\(_2\)OD 49.05 ppm. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet), spt (septet) and m (multiplet) or denoted as br (broad), or some combination of these, where appropriate. Where \(^1\)H-NMR spectra were run in CD\(_2\)OD, D\(_2\)O exchangeable protons (NH, OH) are reported only where observed.

Infra-red spectra were recorded on an ATi Perkin Elmer Spectrum RX1 FT-IR spectrometer. Only absorption maxima (\(\lambda_{\text{max}}\)) of interest are reported and quoted in wavenumbers (cm\(^{-1}\)). Low and high resolution mass spectra were recorded by staff at the University of Manchester. Electrospray (ES) spectra were recorded on a Waters Platform II and high resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP and are accurate to \(\pm\) 0.001 Da. Melting points were determined on a GallenKamp apparatus and are uncorrected. Optical rotation measurements were taken on an AA-100 polarimeter at 20 °C with the solvent and concentration stated. Circular Dichroism (CD) measurements were performed at 20 °C on a JASCO J-815 spectropolarimeter, using a 1 mm cell with the solvent and concentration stated, where applicable.

Methods for the synthesis of H-Aib\(_2\)O\(_t\)Bu,\(^1\) HBr.H-(R)-Aib*OH,\(^2\) Z-\(\alpha\)MvOH,\(^3\) Z-\(\alpha\)MvO\(_t\)Bu,\(^4\) Z-AlaN(CH\(_2\))\(_4\) and H-TleO\(_t\)Bu\(^6\) have been reported previously.
Synthetic Procedures

General Procedure A: Coupling of Cbz-Aib*-Aib$_4$-OH and H-Xaa-Y

\[
\text{Ph} - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - R^1 \quad \text{i) EDC, HOBT, CH$_2$Cl$_2$} \\
\text{Ph} - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - R^1 \quad \text{ii) H-Xaa-Y, NEt$_3$, 72 h}
\]

(where $R^1 = H, Y = O'Bu$ or NH'Bu)

Z-(R)-Aib*-Aib$_4$-OH (1 eq.) and 1-Hydroxybenzotriazole hydrate (1.3 eq.) were dissolved in CH$_2$Cl$_2$ (60 mL/mmol) and the suspension cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (1.1 eq.) was added and the reaction was allowed to warm to room temperature and stirred until it was homogenous. The amino acid derivative "H-Xaa-Y" (prepared by the quantitative hydrogenolysis of Z-Xaa-Y)(2.5 eq.) and triethylamine (2 eq. if using the free amine, 3 eq. if using the HCl salt) were added and the reaction mixture stirred for 72 h. The solvent was removed in vacuo and EtOAc (400 mL/mmol) was added. The organic phase was washed with KHSO$_4$ (5%, 2 x 100 mL/mmol), NaHCO$_3$ (2 x 100 mL/mmol), brine (100 mL/mmol), dried (MgSO$_4$), filtered and concentrated. The pure peptide was isolated by column chromatography.

General Procedure B: Coupling of Cbz-Aib*-Aib$_4$-OH and H-Xaa-Y

\[
\text{Ph} - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - R^1 \quad \text{1) EDC, CH$_2$Cl$_2$, 4 h} \\
\text{Ph} - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - R^1 \quad \text{2) H-Xaa-Y, MeCN, $\Delta$, 5 d}
\]

(where $R^1 \neq H, Y = O'Bu, NH'Bu$ or αMv-NH'Bu)

Z-(R)-Aib*-Aib$_4$-OH (1 eq.) was dissolved in CH$_2$Cl$_2$ (60 mL/mmol) and the suspension cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (1.5 eq.) was added and the reaction was allowed to warm to room temperature and stirred for 4 h. The solvent was removed in vacuo and EtOAc (200 mL/mmol) was added. The organic phase was washed with KHSO$_4$ (2 x 75 mL/mmol), NaHCO$_3$ (2 x 100 mL/mmol), brine (75 mL/mmol), dried (MgSO$_4$), filtered and concentrated in vacuo. The crude azlactone was then placed under high vacuum (<0.1 mbar) before being dissolved in MeCN (60 mL/mmol). The amino acid derivative "H-Xaa-Y" (1.5 eq.) was added and the reaction stirred at reflux for 5 d. After removing the solvent in vacuo, the pure peptide was isolated by column chromatography.

General Procedure C: Synthesis of Cbz-Xaa-NH'Bu

\[
\text{Ph} - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - R^1 \quad \text{EDC.HCl, HOAt, NMM} \\
\text{Ph} - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - H^{\text{N}} - H - O - R^1 \quad \text{'BuNH$_2$, CH$_2$Cl$_2$, 16 h}
\]

Z-Xaa-OH (1 eq.), 'BuNH$_2$ (1.1 eq.) and 1-hydroxy-7-azabenzotriazole (1 eq.) were dissolved in CH$_2$Cl$_2$ (3 mL/mmol). 4-Methylmorpholine (3 eq.) and then N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1 eq.) were added and the reaction stirred for 16 h. EtOAC (7 mL/mmol) was then added and the organic phase washed with H$_2$O (2 x 3 mL/mmol), NaHCO$_3$ (sat., 2 x 3 mL/mmol), NH$_4$Cl (sat., 2 x 3 mL/mmol), dried (Na$_2$SO$_4$), filtered and concentrated. In all cases, the product was isolated as pure without further purification.
Z-(R)-Aib*-OH (R)-1

Benzyl chloroformate (0.64 mL, 4.47 mmol) was added to H-(R)-Aib*-OH (719 mg, 3.89 mmol) over 30 min in acetone/NaOH (2 M) (3.75 mL of each) at 0 °C. The pH was adjusted to 13 by the addition of NaOH (2 M) and the reaction stirred for 16 h at room temperature. A second portion of benzyl chloroformate (0.64 mL, 4.47 mmol) was added at 0 °C over 30 min and the reaction basified so that pH=13. After stirring for 6 h at room temperature, the acetone was removed in vacuo and the resulting mixture diluted with NaOH (2 M, 20 mL) then washed with EtO (2 x 20 mL). The aqueous phase was acidified so that pH=1 with HCl (conc.) and was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The crude reaction product was purified by column chromatography (1:1 PE:EtOAc) to give Cbz-(R)-Aib*-OH (751 mg, 81%) as a white solid.

Z-(R)-Aib*-Aib*-O'Bu 2

Cbz-(R)-Aib*-OH (72 mg, 0.30 mmol) and pyridine (24 µL, 0.30 mmol) were dissolved in CH₂Cl₂ (3 mL) and fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (119 mg, 0.45 mmol) was added. The solution was stirred for 3 h, then diluted with CH₂Cl₂ (7 mL) and washed with ice-cold water (4 x 10 mL). The organic phase was dried (MgSO₄), filtered and concentrated in vacuo. To a solution of H-Aib*O'Bu (149 mg, 0.36 mmol) and N,N-diisopropylethylamine (63 µL, 0.36 mmol) in CH₂Cl₂ (8 mL), a solution of the crude acid fluoride in CH₂Cl₂ (2 mL) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 6 d. The mixture was diluted with EtOAc (40 mL), washed with KHSO₄ (5%, 2 x 10 mL), NaHCO₃ (sat., 2 x 10 mL) and brine (10 mL), dried (MgSO₄), filtered and concentrated in vacuo to give Cbz-(R)-Aib*-Aib*-O'Bu (139 mg, 73%) as a white solid. 

1H-NMR (400 MHz, CDCl₃) δH 7.39 (1H, br s, NH), 7.38 (1H, br s, NH), 7.36 (5H, m, ArCH₃), 7.30-7.40 (5H, m, ArCH₂), 5.35 (1H, br d, 3J=129.0 Hz, CH₂), 1.59 (3H, d, 3J=4.5 Hz, CH₃), 1.59 (3H, d, 3J=130.0 Hz, CH₃). 13C-NMR (101 MHz, CDCl₃) δC 179.5 (CO), 155.3 (CO), 136.1 (ArC), 128.5 (ArCH), 128.1 (ArCH), 66.9 (CH₂), 56.3 (d, J=36.5, 6C-*CH₃), 25.1 (*CH₃). IR (neat) νmax/cm⁻¹ = 3238, 3036, 2989, 2932, 1716, 1683. HRMS (ES , CH₂Cl₂) Calc. for C₁₁H₁₄NO₄ [(M-H)⁺] = 237.0961, found 237.0968. Mp 69-71 °C. The e.r. of the product was determined by integration of the 13C-NMR spectrum of the crude mixture of Z-(R)-Aib*-PheOtBu diastereoisomers following coupling to H-PheO'Bu.
Z-(R)-Aib*-Aib$_2$-OBu (870 mg, 1.37 mmol) was dissolved in CH$_2$Cl$_2$ (8 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (5 mL) was added dropwise and the resulting solution was allowed to warm to room temperature and stirred for 16 h. The solvents were removed in vacuo and Et$_2$O (3 x 10 mL) was added to help co-evaporate any traces of trifluoroacetic acid. The crude reaction product was purified by recrystallisation in MeCN to give Z-(R)-Aib*-Aib$_2$-OH (595 mg, 75%) as a white solid.

1H-NMR (400 MHz, CD$_2$OD) $\delta$H 8.02 (1H, br s, NH), 7.75 (1H, br s, NH), 7.72 (1H, br s, NH), 7.65 (1H, br s, NH), 7.29-7.41 (5H, m, ArCH x5), 5.13 (2H, s, CH$_2$N). HRMS (ES$^+$, MeOH) Calc. for C$_{31}$H$_{54}$N$_2$O$_8$ ([M+H]$^+$) = 635.3844, found 635.3846. Mp 246-248 °C.

Z-(R)-Aib*-Aib$_2$-O'Bu was prepared according to general procedure A (0.17 mmol scale). The pure peptide (126 mg, 93%) was isolated as a white solid by column chromatography (2-5% MeOH in CH$_2$Cl$_2$). 1H-NMR (400 MHz, CD$_2$OD) $\delta$H 7.91 (1H, br s, NH), 7.85 (1H, br s, NH), 7.83 (1H, br s, NH), 7.73 (1H, br s, NH), 7.30 (10H, m, ArCH x10), 5.17 (1H, d, $J$=12.5, CH$_2$OH), 5.01 (1H, d, $J$=12.5, H$_A$ of AB system, CH$_2$OCCO), 5.10 (1H, d, $J$=12.5, H$_B$ of AB system, CH$_2$OCCO), 4.44 (1H, q, $J$=7.5, $^3$CH), 3.15 (1H, dd, $J$=14.0, 7.5, CH$_3$, H$_B$ of ABX system, CH$_3$Ph), 3.09 (1H, dd, $J$=14.0, 7.5, H$_B$ of ABX system, CH$_3$Ph), 1.49 (3H, s, CH$_3$), 1.47 (3H, s, CH$_3$), 1.44 (3H, s, CH$_3$), 1.43 (3H, s, CH$_3$), 1.43 (3H, s, CH$_3$), 1.42 (2.3H, d, $J$=4.0, CH$_3$ major), 1.42 (0.7H, d, $J$=129.0, $^3$CH$_3$ minor), 1.40 (0.7H, d, $J$=4.0, CH$_3$ minor), 1.40 (2.3H, d, $J$=129.0, $^3$CH$_3$ major), 1.38 (3H, s, CH$_3$), 1.35 (3H, s, CH$_3$), 1.35 (9H, s, C(CH$_3$)$_3$), 1.35 (9H, s, C(CH$_3$)$_3$), 1.35 (9H, s, C(CH$_3$)$_3$), 1.35 (9H, s, C(CH$_3$)$_3$), 1.35 (9H, s, C(CH$_3$)$_3$), $^{13}$C-NMR (126 MHz, CDCl$_3$) $\delta$C 177.6 (CO), 177.6 (CO), 177.3 (CO), 176.9 (CO), 176.9 (CO), 172.4 (CO), 158.1 (CO), 139.0 (ArC), 138.9 (ArC), 130.7 (ArC), 129.8 (ArC), 129.4 (ArC), 129.2 (ArC), 128.8 (ArC), 127.7 (ArC), 82.6 (CHMe$_3$), 67.8 (CH$_2$OCCO), 58.2 (CO), 58.1 (CO), 57.9 (CO), 57.8 (d, $J_c$ = 39.0, $^3$C-CH$_3$), 57.7 (CO), 56.9 (CO), 38.6 (CH$_2$Ph), 28.3 (C(CH$_3$)$_3$), 26.1 (CH$_3$), 25.9 (CH$_3$), 25.8 ($^3$CH$_3$ major and CH$_3$ x2), 25.6 (CH$_3$), 25.6 (CH$_3$), 25.0 (CH$_3$), 25.0 ($^3$CH$_3$ minor and CH$_3$). IR (neat) $\nu_{max}$/cm$^{-1}$ = 3310, 2983, 2934, 1703, 1660, 1530. HRMS (ES$^+$, MeOH) Calc. for C$_{40}$H$_{66}$N$_6$NaO$_9$ ([M+Na]$^+$) = 804.4348, found 804.4340. Mp 96-100 °C. [$\alpha$]$_D^{20}$ = -6.8 (c 1, CH$_2$Cl$_2$).
Z-(R)-Aib*-Aib*-PheNH′Bu 3-PheNH′Bu

Z-(R)-Aib*-Aib*-PheNH′Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (33 mg, 82%) was isolated as a white solid by column chromatography (1-2% MeOH in CH₂Cl₂). ¹H-NMR (500 MHz, CD₂OD) δH 8.06 (1H, br s, NH), 7.91 (1H, br s, NH), 7.75 (1H, br s, NH), 7.73 (1H, br s, NH), 7.71 (1H, br d, J=8.0, NH), 7.36 (7H, m, ArCH x7), 7.27 (1H, br s, NH), 7.18 (3H, m, ArCH x3), 5.21 (1H, d, J=12.5, CH₂-OCO, H₆ of AB system), 5.06 (1H, d, J=12.5, CH₂-OCO, H₆ of AB system), 4.38 (1H, ddd, J=11.5, 8.5, 3.0, *CH), 3.41 (1H, dd, J=14.5, 3.0, CH₂-Ph, H₆ of ABX system), 2.92 (1H, dd, J=14.0, 11.5, CH₂-Ph, H₆ of ABX system), 1.46 (6H, s, CH₃ x2), 1.44 (0.7H, d, J=4.5, CH₃ minor), 1.44 (2.3H, d, J=128.5, *CH₃ major), 1.40 (12H, m, CH₃ and C(CH₃)₃), 1.39 (0.7H, d, J=129.0, *CH₃ minor), 1.39 (2.3H, m, CH₃ major), 1.39 (3H, s, CH₃), 1.37 (3H, s, CH₃), 1.27 (3H, s, CH₃), 1.17 (3H, s, CH₃). ¹³C-NMR (126 MHz, CD₂OD) δC 177.9 (CO), 177.7 (CO), 177.3 (CO), 177.3 (CO), 176.9 (CO), 173.2 (CO), 158.0 (CO), 139.8 (Ar), 138.8 (Ar), 130.2 (Ar), 129.6 (Ar), 129.3 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 127.5 (ArCH), 67.7 (CH₂OCO), 58.0 (οC), 57.9 (οC), 57.9 (οC), 57.6 (οC), 57.6 (οC, J=39.0, *C-CH₃), 57.5 (οC), 52.6 (C(CH₃)₃), 38.1 (CH₂Ph), 29.0 (C(CH₃)₂), 27.4 (CH₃), 27.2 (CH₃), 26.9 (CH₃), 26.8 (CH₃), 26.3 (CH₃), 26.1 (*CH₃ major, 24.4 (*CH₃ major and CH₃), 24.2 (CH₃), 23.7 (CH₃). IR (neat) νmax/cm⁻¹ = 3308, 2925, 1656, 1533, 1454. HRMS (ES⁺, MeOH) Calc. for C₉₀¹³CH₂₋N₃O₈{[M+H]⁺} 781.4688, found 781.4673. Mp 120-122 °C. [α]⁺²⁰ = 7.2 (c 0.5, CH₂Cl₂).

Z-(R)-Aib*-Aib*-PheNHTs 3-PheNHTs

Z-(R)-Aib*-Aib*-PheNHTs was prepared according to general procedure A (0.052 mmol scale), except DMF (1 ml) was added to solubilise the amine. The pure peptide (35 mg, 77%) was isolated as a white solid by column chromatography (0.25-5% MeOH in CH₂Cl₂). ¹H-NMR (400 MHz, CDCl₃) δH 10.56 (1H, br s, NHTs), 8.01 (2H, d, J=8.5, ArCH x2), 7.78 (2H, br m, NH x2), 7.72 (1H, br s, NH), 7.49 (1H, br s, NH), 7.35 (5H, m, ArCH x5), 7.30 (2H, d, J=8.5, ArCH x2), 7.09 – 7.24 (5H, m, ArCH x5), 6.64 (1H, br s, NH), 5.82 (1H, br s, NH), 5.20 (1H, d, J=12.5, CH₂O, H₆ of AB system), 5.03 (1H, d, J=12.5, CH₂O, H₆ of AB system), 4.56 (1H, m, *CH), 3.44 (1H, d, J=14.0, CH₃), 2.97 (1H, dd, J=13.5, 13.5, CH₃), 2.42 (3H, s, CH₂-Ar), 1.63 (3H, s, CH₃), 1.52 (3H, s, CH₃), 1.49 (0.8H, d, J=3.5, CH₃ minor), 1.49 (2.2H, d, J=129.0, *CH₃ major), 1.46 (3H, s, CH₃), 1.43 (2.2H, d, J=4.0, CH₃ major), 1.43 (0.8H, d, J=130.0, *CH₃ minor), 1.41 (3H, s, CH₃), 1.39 (3H, s, CH₃), 1.36 (3H, s, CH₃), 1.20 (3H, s, CH₃), 1.19 (3H, s, CH₃). ¹³C-NMR (126 MHz, CDCl₃) δC 176.5 (CO), 175.6 (CO), 175.3 (CO), 174.4 (CO), 174.1 (CO), 171.6 (CO), 156.0 (CO), 144.2 (Ar), 137.9 (Ar), 136.5 (Ar), 129.3 (ArCH), 129.1 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.5 (Ar), 128.1 (ArCH), 127.9 (ArCH), 127.9 (ArCH), 126.3 (ArCH), 67.3 (CH₂O), 56.9 (οC), 56.9 (οC), 56.7 (οC), 56.5 (d, J=38.0, *C-CH₃), 56.4 (οC), 55.6 (οC), 36.4 (CH₂), 26.4 (*CH₃ minor), 25.9 – 26.9 (CH₃ x4), 23.6 (*CH₃ major), 22.8 – 24.3 (CH₃ x4), 21.6 (CH₂-Ar). IR (neat) νmax/cm⁻¹ = 3299,
Z-(R)-Aib*-Aib*-ValO'Bu 3-ValO'Bu

Z-(R)-Aib*-Aib*-ValO'Bu was prepared according to general procedure A (0.104 mmol scale). The pure peptide (69 mg, 91%) was isolated as a white solid by column chromatography (2-5% MeOH in CH2Cl2). 1H-NMR (500 MHz, CD2OD) δ 7.85 (1H, br s, NH), 7.79 (1H, br s, NH), 7.58 (1H, br s, NH), 7.34 (5H, m, ArCH x5), 5.18 (1H, d, J=12.5, CH2, HA of AB system), 5.09 (1H, d, J=13.0, CH2, HB of AB system), 4.03 (1H, d, J=7.0, 13C), 2.23 (1H, dq, J=7.0, 7.0, CH(CH3)2), 1.50 (3H, s, CH3), 1.49 (3H, s, CH3), 1.45 (12H, s, CH2 and C(CH3)3), 1.45 (3H, s, CH3), 1.42 (2.3H, d, J=4.5, CH2 major), 1.42 (0.7H, d, J=129.0, *CH3 minor), 1.40 (3H, s, CH3), 1.40 (0.7H, m, CH3 minor), 1.40 (2.3H, d, J=129.0, *CH3 major), 1.36 (6H, s, CH3 x2), 1.28 (3H, s, CH3), 1.04 (3H, d, J=7.0, CH2-CH), 1.00 (3H, d, J=6.5, CH2-CH). 13C-NMR (126 MHz, CD2OD) δ 177.7 (CO), 177.3 (CO), 177.2 (CO), 176.9 (CO), 176.7 (CO), 175.7 (CO), 173.5 (CO), 158.1 (CO), 138.9 (ArC), 129.7 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 82.4 (CMe3), 67.8 (CH2), 61.3 (CH2), 58.1 (CH), 58.0 (CH), 57.9 (3H, d, J=36.5, 13C-CH3), 57.7 (3C), 31.4 (CH), 28.5 (C(CH3)3), 27.4 (CH2), 26.9 (CH3), 26.4 (CH3), 26.2 (CH3), 25.9 (*CH3 major and CH3), 25.4 (*CH3 minor and CH3), 24.8 (CH3), 24.4 (CH3), 19.8 (CH3-CH), 19.5 (CH3-CH). IR (neat) νmax/cm⁻¹ = 3309, 2982, 2935, 2476, 1702, 1650, 1527, 1469, 1455, 1417. HRMS (ES', MeOH) Calc. for C43H59N7O15SNa ([M+Na]+) 756.4353, found 756.4327. Mp 200-204 °C. [d]20 D = −22.4 (c 1, CH2Cl2).

Z-(R)-Aib*-Aib*-ValNH'Bu 3-ValNH'Bu

Z-(R)-Aib*-Aib*-ValNH'Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (31 mg, 81%) was isolated as a white solid by column chromatography (2-5% MeOH in CH2Cl2). 1H-NMR (500 MHz, CD2OD) δ 8.07 (1H, br s, NH), 7.9 (1H, br s, NH), 7.82 (1H, br s, NH), 7.75 (1H, br s, NH), 7.55 (1H, br s, NH), 7.28 - 7.42 (5H, m, ArCH x5), 7.09 (1H, br s, NH), 5.21 (1H, d, J=13.0, CH2, HA of AB system), 5.06 (1H, d, J=13.0, CH2, HB of AB system), 3.99 (1H, d, J=6.0, 13C), 2.33 (1H, dq, J=6.5, 6.5 CH(CH3)2), 1.49 (3H, s, CH3), 1.48 (3H, s, CH3), 1.46 (3H, s, CH3), 1.45 (3H, s, CH3), 1.43 (2H, d, J=128.5, *CH3 major), 1.43 (0.8H, m, CH3 minor), 1.40 (2.2H, m, CH3 major), 1.40 (0.8H, d, J=128.5, *CH3 minor), 1.39 (3H, s, CH3), 1.37 (12H, s, CH3 and C(CH3)3), 1.36 (3H, s, CH3), 1.26 (3H, s, CH3), 1.04 (3H, d, J=7.0, CH2-CH), 0.98 (3H, d, J=7.0, CH2-CH). 13C-NMR (126 MHz, CD2OD) δ 178.1 (CO), 177.4 (CO), 177.3 (CO), 177.2 (CO), 177.0 (CO), 173.5 (CO), 158.1 (CO), 138.9 (ArC), 129.8 (ArCH), 129.2 (ArCH), 128.7 (ArCH), 67.8 (CH2), 62.0 (13C), 58.1 (13C), 57.9 (13C), 57.9 (13C), 57.7 (d, J=36.5, 13C-CH3), 52.6 (CMe3), 31.0 (CH), 29.2 (C(CH3)3), 28.0 (CH2), 27.2 (CH2), 27.0 (CH2), 26.7 (CH3), 26.2 (*CH3 minor), 24.8 (CH3), 24.5 (*CH3 major), 24.3 (CH3), 24.2 (CH3), 23.8 (CH3), 19.9 (CH3-CH), 18.5 (CH3-CH). IR (neat) νmax/cm⁻¹ = 3309, 2981, 2474, 1699, 1646, 1526, 1471, 1417.
Z-(R)-Aib*-Aib₂-αMvO'Bu 3-αMvO'Bu

Z-(R)-Aib*-Aib₂-αMvO'Bu was prepared according to general procedure B (0.052 mmol scale). The pure peptide (13 mg, 33%) was isolated as a white solid by column chromatography (0.5-5% MeOH in CH₂Cl₂). ¹H-NMR (400 MHz, CDCl₃) δH 7.44 (1H, br s, NH), 7.35 (6H, m, ArCH x5 and NH), 7.18 (1H, br s, NH), 6.37 (1H, br s, NH), 5.76 (1H, br s, NH), 5.73 (1H, br s, NH), 5.15 (1H, d, J=12.0, CH₂, H₄ of AB system), 5.08 (1H, d, J=12.0, CH₂, H₄ of AB system), 2.24 (1H, dq, J=6.5, 6.5, CH), 1.51 (3H, s, CH₃), 1.49 (3H, s, CH₃), 1.48 (3H, s, CH₃), 1.48 (0.7H, d, J=129.0, *CH₃ minor), 1.48 (2.3H, m, CH₃ major), 1.46 (3H, s, CH₃), 1.46 (2.3H, d, J=129.5, *CH₃ major), 1.46 (0.7H, m, CH₃ minor), 1.45 (12H, m, C(CH₃)₂ and CH₂), 1.43 (6H, s, CH₃ x2), 1.35 (3H, s, CH₃), 1.27 (3H, s, CH₃), 1.01 (3H, d, J=7.0, CH₃-CH), 0.98 (3H, d, J=7.0, CH₃-CH). ¹³C-NMR (101 MHz, CDCl₃) δC 174.5 (CO), 174.1 (CO), 174.0 (CO), 173.8 (CO), 173.7 (CO), 172.3 (CO), 155.9 (CO), 136.1 (Arc), 128.7 (Arc), 128.6 (Arc), 128.2 (Arc), 79.9 (CMe₃), 67.4 (CH₂), 62.3 (°C), 57.2 (d, J=37.0, °C-*CH₃), 56.7 (°C), 56.6 (°C), 56.6 (°C), 56.4 (°C), 34.8 (CH), 28.0 (C(CH₃)₂), 25.6 (*CH₃ major), 24.5 (*CH₃ minor), 24.2 – 25.9 (all other CH₃), 18.5 (CH₃), 17.9 (CH₃-CH), 17.6 (CH₃-CH). IR (neat) νmax/cm⁻¹ = 3319, 2981, 2934, 2481, 1703, 1651, 1523. HRMS (ES⁺, MeOH) Calc. for C₃₂H₃₅N₇O₉ ([M+H]+) = 748.4690, found 748.4701. Mp 125-127. [α]D₂⁰ = -16.8 (c 0.5, CH₂Cl₂).

Z-(R)-Aib*-Aib₂-αMvNH'Bu 3-αMvNH'Bu

Z-(R)-Aib*-Aib₂-αMvNH'Bu was prepared according to general procedure B (0.052 mmol scale). The pure peptide (21 mg, 54%) was isolated as a white solid by column chromatography (1% MeOH in CH₂Cl₂). ¹H-NMR (500 MHz, CD₂OD) δH 7.82 (1H, br s, NH), 7.82 (1H, br s, NH), 7.30-7.41 (5H, m, ArCH x5), 7.28 (1H, br s, NH), 7.03 (1H, br s, NH), 5.20 (1H, d, J=13.0, CH₂, H₄ of AB system), 5.06 (1H, d, J=13.0, CH₂, H₄ of AB system), 2.09 (1H, dq, J=6.5, 6.5, CH), 1.45 (3H, s, CH₃), 1.43 (2.3H, d, J=129.0, *CH₃ major), 1.43 (0.7H, m, CH₃ minor), 1.39 (0.7H, d, J=128.5, *CH₃ minor), 1.39 (2.3H, m, CH₃ major), 1.42 (3H, s, CH₃), 1.38 (9H, m, CH₃ x3), 1.38 (9H, s, C(CH₃)₂), 1.35 (3H, s, CH₃), 1.26 (3H, s, CH₃), 1.03 (3H, d, J=6.5, CH₂-CH), 0.94 (3H, d, J=6.5, CH₂-CH). ¹³C-NMR (126 MHz, CD₂OD) δC 177.3 (CO), 177.1 (CO), 176.8 (CO), 175.9 (CO), 158.1 (CO), 138.9 (Arc), 129.8 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 67.8 (CH₂), 64.6 (CMe₃), 58.1 (°C), 58.0 (°C), 57.8 (°C), 57.8 (°C-*CH₃), 57.7 (°C), 52.4 (°C), 37.2 (CH), 29.2 (C(CH₃)₂), 27.8 (CH₃), 27.3 (CH₃), 27.0 (CH₃), 26.7 (CH₃), 26.2 (*CH₃ minor), 24.8 (CH₃), 24.5 (*CH₃ major), 24.2 (CH₃), 24.0 (CH₃), 23.8 (CH₃), 18.6 (CH₃), 17.8 (CH₃-CH), 17.2 (CH₃-CH). IR (neat) νmax/cm⁻¹ = 3319, 2982, 2479, 1651, 1525, 1471, 1454, 1414, 1380, 1361.
HRMS (ES\(^+\), MeOH) Calc. for C\(_{37}\)\(^{13}\)CH\(_6\)N\(_7\)O\(_8\) ([M+H]\(^+\)) = 747.4850, found 747.4814. Mp 215-217 °C. \([\alpha\]\(^D\)\(^{20}\) = 16.0 (c 1, CH\(_2\)Cl\(_2\)).

**Z-(R)-Aib\(^*\)-Aib\(^*\)-\((\alpha\text{-Mv})\)\(_2\)NH\(_\text{Bu}\)** 3-\((\alpha\text{-Mv})\)_\(_2\)NH\(_\text{Bu}\)**

Z-(R)-Aib\(^*\)-Aib\(^4\)-\((\alpha\text{-Mv})\)_\(_2\)NH\(_\text{Bu}\) was prepared according to general procedure B (0.052 mmol scale). The crude reaction product was dissolved in CH\(_2\)Cl\(_2\) (20 mL) and washed with HCl (1 M, 2 x 5 mL). The organic phase was dried (MgSO\(_4\)), filtered and concentrated in vacuo. The pure peptide (26 mg, 58\%) was isolated as a white solid by column chromatography (1% MeOH in CH\(_2\)Cl\(_2\)). \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.85 (1H, br s, NH), 5.71 (1H, br s, NH), 5.04 (1H, d, \(J\) = 12.5, CH\(_3\), H\(^\beta\) of AB system), 5.04 (1H, d, \(J\) = 12.5, CH\(_3\), H\(^\beta\) of AB system), 2.12 (1H, dq, \(J\) = 7.0, 7.0, CH), 2.03 (1H, dq, \(J\) = 7.0, 7.0, CH), 1.52 (0.7H, d, \(J\) = 4.5, CH\(_3\) minor), 1.52 (2.3H, d, \(J\) = 129.0, \(*\text{CH}\(_3\)\) major), 1.49 (3H, s, CH\(_3\)), 1.47 (3H, s, CH\(_3\)), 1.47 (6H, s, CH\(_3\)x2), 1.46 (3H, s, CH\(_3\)), 1.45 (0.7H, d, \(J\) = 129.5, \(*\text{CH}\(_3\)\) minor), 1.45 (2.3H, m, CH\(_3\) major), 1.45 (3H, s, CH\(_3\)), 1.43 (3H, s, CH\(_3\)), 1.40 (9H, s, C(CH\(_3\))\(_3\)), 1.38 (3H, s, CH\(_3\)), 1.37 (3H, s, CH\(_3\)), 1.20 (3H, s, CH\(_3\)), 1.06 (3H, d, \(J\) = 7.0, CH\(_3\)-CH), 1.02 (3H, d, \(J\) = 7.0, CH\(_3\)-CH), 0.95 (3H, d, \(J\) = 7.0, CH\(_3\)-CH), 0.93 (3H, d, \(J\) = 7.0, CH\(_3\)-CH). \(^{13}\)C-NMR (126 MHz, CDCl\(_3\)) \(\delta\) 175.1 (CO), 175.0 (CO), 174.8 (CO), 174.2 (CO), 174.1 (CO), 173.9 (CO), 172.7 (CO), 156.0 (CO), 136.1 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.1 (ArCH), 67.4 (CH\(_3\)), 37.3 (CH\(_3\)), 29.7 (CH\(_3\)), 28.6 (C(CH\(_3\))\(_3\)), 27.4 (CH\(_3\)), 27.3 (CH\(_3\)), 26.9 (CH\(_3\)), 26.8 (\(*\text{CH}\(_3\)\) minor), 26.7 (CH\(_3\)), 23.2 (\(*\text{CH}\(_3\)\) major), 23.1 (CH\(_3\)), 22.9 (CH\(_3\)), 22.8 (CH\(_3\)), 18.0 (CH\(_3\)), 17.9 (CH\(_3\)), 17.3 (CH\(_3\)), 17.2 (CH\(_3\)), 16.6 (CH\(_3\)), 15.4 (CH\(_3\)). IR (neat) \(\nu_{\text{max}}/\text{cm}^{-1}\) = 3314, 2983, 1699, 1660, 1531, 1456, 1411. HRMS (ES\(^+\), MeOH) Calc. for C\(_{44}\)\(^{13}\)CH\(_7\)N\(_8\)O\(_9\) ([M+H]\(^+\)) 860.5685, found 860.5687. Mp 241-243 °C. \([\alpha\]\(^D\)\(^{20}\) = 15.2 (c 0.5, CH\(_2\)Cl\(_2\)).

**Z-(R)-Aib\(^*\)-Aib\(^-\)-TleO\(_\text{Bu}\)** 3-TleO\(_\text{Bu}\)**

Z-(R)-Aib\(^*\)-Aib\(^-\)-TleO\(_\text{Bu}\) was prepared according to general procedure A (0.052 mmol scale). The pure peptide (33 mg, 85\%) was isolated as a white solid by column chromatography (2% MeOH in CH\(_2\)Cl\(_2\)). \(^1\)H-NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.82 (1H, br s, NH), 7.80 (1H, br s, NH), 7.29-7.43 (6H, m, ArCH x5 and NH), 5.17 (1H, d, \(J\) = 13.0, CH\(_3\)OCO, H\(^\beta\) of AB system), 5.10 (1H, d, \(J\) = 13.0, CH\(_3\)OCO, H\(^\beta\) of AB system), 4.11 (1H, d, \(J\) = 8.0, CH), 1.49 (6H, s, CH\(_3\)x2), 1.46 (3H, s, CH\(_3\)), 1.46 (9H, s, C(CH\(_3\))\(_3\)), 1.45 (0.7H, d, \(J\) = 128.5, \(*\text{CH}\(_3\)\) minor), 1.45 (2.3H, d, \(J\) = 4.5, CH\(_3\) major), 1.45 (3H, s, CH\(_3\)), 1.42 (2.3H, d, \(J\) = 128.5, \(*\text{CH}\(_3\)\) major), 1.42 (0.7H, d, \(J\) = 4.5, CH\(_3\) minor), 1.39 (3H, s, CH\(_3\)), 1.39 (3H, s, CH\(_3\)), 1.36 (3H, s, CH\(_3\)), 1.29 (3H, s, CH\(_3\)), 1.07 (9H, s, C(CH\(_3\))\(_3\)). \(^{13}\)C-NMR (101 MHz, CD\(_3\)OD) \(\delta\) 177.6 (CO), 177.2 (CO), 177.0 (CO), 176.9 (CO), 176.8 (CO), 171.8 (CO), 158.0 (CO), 138.9 (ArC), 129.7 (ArCH), 129.2 (ArCH), 128.8
(ArCH), 82.5 (Me d, 3H), 67.8 (ArCH), 64.0 (ArCH), 58.2 (ArCH), 58.1 (ArCH), 58.0 (ArCH), 57.8 (d, J=44.0, *CH₂), 57.7 (ArCH), 35.1 (CH₃), 28.6 (CCl₃), 27.6 (CH₃), 27.1 (CH₃), 26.8 (CH₂), 26.2 (CH₃), 25.8 (*CH₃ major and CH₃ x2), 25.2 (CH₃), 24.9 (*CH₃ minor and CH₃), 24.6 (CH₂). IR (neat) νmax/cm⁻¹ = 3305, 2981, 2477, 2360, 1700, 1650, 1522, 1472, 1415. HRMS (ES⁺, MeOH) Calc. for C₃₇H₆₀N₈O₉Na ([M+Na]+) 770.4510, found 770.4541. Mp 126-128 °C. [α]D²⁰ = −18.4 (c 1, CH₂Cl₂).

Z-(R)-Aib*-Aib₂-TleNH²Bu 3-TleNH²Bu

Z-(R)-Aib*-Aib₂-TleNH²Bu was prepared according to general procedure A (0.055 mmol scale). The pure peptide (28 mg, 68%) was isolated as a white solid by column chromatography (25% MeOH in CH₂Cl₂). ¹H-NMR (500 MHz, CD₃OD) δH 8.05 (1H, br s, NH), 7.88 (1H, br s, NH), 7.82 (1H, br s, NH), 7.75 (1H, br s, NH), 7.46 (1H, d, J=8.0, NH-CH), 7.34 (5H, m, ArCH x5), 7.09 (1H, br s, NH), 5.20 (1H, d, J=12.5, CH₂), H² of AB system), 5.06 (1H, d, J=12.5, CH₂, H² of AB system), 3.93 (1H, d, J=8.0, CH), 1.48 (6H, s, CH₃ x2), 1.45 (6H, s, CH₃ x2), 1.43 (0.7H, d, J=4.5, CH₃ minor), 1.43 (2.3H, d, J=128.5, *CH₃ major), 1.39 (2.3H, d, J=4.0, CH₃ major), 1.39 (0.7H, d, J=129.0, *CH₃ minor), 1.38 (3H, s, CH₃), 1.37 (3H, s, CH₃), 1.36 (12H, s, CH₃ and C(CH₃)), 1.10 (9H, s, C(CH₃)). ¹³C-NMR (101 MHz, CD₃OD) δC 177.5 (CO), 177.4 (CO), 177.1 (CO), 177.0 (CO), 176.9 (CO), 172.5 (CO), 158.0 (CO), 138.7 (ArC), 129.6 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 67.7 (CH₃), 65.1 (ArCH), 58.1 (ArCH), 57.9 (ArCH), 57.8 (ArCH), 57.6 (d, J=40.5, *C-CH₃), 57.5 (ArCH), 52.5 (CMe₃), 34.8 (CMe₃), 29.0 (C(CH₃)), 27.8 (C(CH₃)), 27.7 (CH₃), 27.0 (CH₃), 26.7 (CH₃), 26.4 (CH₃), 26.0 (*CH₃ minor), 25.2 (CH₃), 24.5 (*CH₃ major and CH₃), 24.2 (CH₃), 23.8 (CH₃). IR (neat) νmax/cm⁻¹ = 3305, 2983, 2477, 1703, 1644, 1528, 1454. HRMS (ES⁺, MeOH) Calc. for C₃₇H₆₀N₈O₉Na ([M+Na⁺]⁺) 769.4664, found 769.4669. Mp 211-213. [α]D²⁰ = 16.8 (c 1, CH₂Cl₂).

Z-(R)-Aib*-Aib₂-AlaO²Bu 3-AlaO²Bu

Z-(R)-Aib*-Aib₂-AlaO²Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (32 mg, 87%) was isolated as a white solid by column chromatography (2% MeOH in CH₂Cl₂). ¹H-NMR (500 MHz, CD₃OD) δH 7.92 (1H, br s, NH), 7.76 (1H, br s, NH), 7.74 (1H, br s, NH), 7.71 (1H, br s, NH), 7.29-7.41 (5H, m, ArCH x5), 5.18 (1H, d, J=13.0, CH₂, H² of AB system), 5.08 (1H, d, J=13.0, CH₂, H² of AB system), 4.21 (1H, dt, J=7.0, 7.0, CH), 1.52 (3H, s, CH₃), 1.50 (3H, s, CH₃), 1.45 (3H, m, CH₃-CH), 1.44 (9H, s, C(CH₃)), 1.43 (H, s, CH₃ x2), 1.41 (0.66H, d, J₁=128.5, *CH₃ minor), 1.41 (2.34H, d, J₂=4.5, CH₃ major), 1.40 (3H, s, CH₃), 1.39 (2.34H, d, J₂=128.5, *CH₃ major), 1.39 (0.66H, d, J₂=4.5, CH₃ minor), 1.37 (3H, s, CH₃), 1.35 (3H, s, CH₃), 1.27 (3H, s, CH₃). ¹³C-NMR (126 MHz, CD₃OD) δC 177.6 (CO), 177.3 (CO), 177.3 (CO), 177.0 (CO), 176.9 (CO), 173.8 (CO), 158.1 (CO), 138.9 (ArC), 129.7 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 82.3 (CMe₃), 58.1 (ArCH), 58.1 (ArCH), 57.9 (ArCH), 57.8 (d, J=36.5, *C-CH₃), 57.7 (ArCH), 50.9 (ArCH), 28.4 (C(CH₃)), 27.7 (CH₃), 27.0 (CH₃), 26.5 (CH₃), 26.3 (CH₃), 26.0 (*CH₃ major and CH₃), 24.7 (*CH₃ minor and CH₃), 24.4 (CH₃), 24.1 (CH₃), 17.3 (CH₃CH).
Z-(R)-Aib*-Aib*-AlaNH*Bu 3-AlaNH*Bu

Z-(R)-Aib*-Aib*-AlaNH*Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (33 mg, 90%) was isolated as a white solid by column chromatography (2% MeOH in CH₂Cl₂). ¹H-NMR (500 MHz, CD₂OD) δₜ 8.04 (1H, br s, NH), 7.98 (1H, br s, NH), 7.88 (1H, d, J=7.0, NH), 7.74 (2H, br s, NH x2), 7.29-7.40 (5H, m, ArCH x5), 7.09 (1H, br s, NH), 5.20 (1H, d, J=13.0, CH₂, H₆ of AB system), 5.06 (1H, d, J=13.0, CH₃, H₈ of AB system), 4.11 (1H, dt, J=7.0, 7.0, CH), 1.56 (3H, s, CH₃), 1.46 (6H, s, CH₃ x2), 1.42 (3H, d, J=7.0, CH₃), 1.42 (2.36H, d, J=128.5, *CH₃ major), 1.42 (0.42H, m, CH₃ minor), 1.39 (0.64H, d, J=128.5, *CH₃ minor), 1.39 (2.36H, m, CH₃ major), 1.37 (9H, s, (CH₃)₃), 1.35-1.39 (9H, m, CH₃ x3), 1.26 3H, s, CH₃). ¹³C-NMR (126 MHz, CD₂OD) δC 177.7 (CO), 177.6 (CO), 177.3 (CO), 175.0 (CO), 159.1 (CO), 138.9 (ArC), 129.8 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 67.8 (CH₂), 58.1 (C), 58.1 (C), 57.8 (C), 57.8 (d, J=40.0, 0°, C-*CH₃), 57.7 (C), 52.6 (CMe₃), 52.2 (C), 29.2 (C(CH₃)₃), 27.8 (CH₂), 27.2 (CH₂), 27.0 (CH₃), 26.7 (CH₃), 26.3 (*CH₃ minor), 24.8 (CH₃), 24.5 (*CH₃ major), 24.0 (CH₃), 23.9 (CH₃), 23.8 (CH₃), 17.9 (CH₃-*CH). IR (neat) νmax/cm⁻¹ = 3305, 2982, 2475, 1650, 1526, 1452, 1382, 1361. HRMS (ES⁺, MeOH) Calc. for C₅₆H₄₅N₄O₄Na ([M+Na]⁺) 727.3994, found 727.3962. Mp 204-206 °C. [α]D²⁰ = 28.4 (c 1, CH₂Cl₂).

3-AlaO*Bu (17 mg) was dissolved in CH₂Cl₂ (1 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (200 µL) was added dropwise and the resulting solution was allowed to warm to room temperature and stirred for 45 min. The solvents were removed in vacuo and the crude reaction product was purified by column chromatography (2-10% MeOH in CH₂Cl₂) to give 3-AlaOH (15 mg, >99%) as a white solid. ¹H-NMR (500 MHz, CD₂OD) δₜ 8.02 (1H, br s, NH), 7.91 (1H, br s, NH), 7.77 (1H, br s, NH), 7.70 (1H, br s, NH), 7.34 (5H, m, ArCH x5), 5.18 (1H, d, J=13.0, CH₂, H₄ of AB system), 4.34 (1H, q, J=7.5, °CH), 1.50 (3H, s, CH₃), 1.49 (3H, s, CH₃), 1.47 (3H, d, J=7.5, CH₃*CH), 1.45 (3H, s, CH₃), 1.44 (3H, s, CH₃), 1.43 (2.4H, d, J=4.5, CH₃ major), 1.43 (0.6H, d, J=129.0, *CH₃ minor), 1.39 (0.6H, m, CH₃ minor), 1.39 (2.4H, d, J=129.0, *CH₃ major), 1.39 (3H, s, CH₃), 1.36 (3H, s, CH₃), 1.36 (3H, s, CH₃), 1.28 (3H, s, CH₃). ¹³C-NMR (126 MHz, CD₂OD) δC 177.6 (CO), 177.4 (CO), 177.2 (CO), 177.1 (CO), 176.9 (CO), 176.3 (CO), 176.0 (CO), 176.3 (CO), 175.0 (CO), 174.8 (CO), 173.6 (CO), 170.0 (CO), 158.0 (CO), 158.7 (ArC), 129.6 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 67.6 (CH₂), 58.1 (°C), 58.0 (°C), 57.9 (°C), 57.8 (d, J=37.0, °C-*CH₃), 57.7 (°C), 50.0 (°CH), 27.2 (CH₃), 26.3 (CH₃), 25.9 (*CH₃ major and CH₃ x2), 25.3 (CH₃), 24.7 (*CH₃ minor and CH₃) 24.4 (CH₃), 24.2 (CH₃), 17.5 (CH₃-*CH) IR (neat) νmax/cm⁻¹ = 3304, 2985, 2939, 1751, 1653,
3 mL), NaHCO₃ (2 3 mL), brine (3 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude reaction product was purified by column chromatography (1-5% MeOH in CH₂Cl₂) to give 3-AlaNHMe (10 mg, 75%) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δH 7.68 (1H, br s, NH), 7.61 (1H, br d, J=8.0, NH-CH), 7.57 (1H, br s, NH), 7.46 (1H, br s, NH), 7.42 (1H, q, J=4.5, NH-CH₂), 7.27 (5H, m, ArCH x5), 6.75 (1H, br s, NH), 6.15 (1H, br s, NH), 5.14 (1H, d, J=12.5, CH₁ major), 1.43 (3H, s, CH₃), 1.42 (4.2H, d, J=129.0, *CH₃ major), 1.44 (2.4H, d, J=4.5, CH₃-NH), 1.37 (3H, s, CH₃), 1.36 (0.6H, d, J=129.5, *CH₃ minor), 1.36 (2.4H, m, CH₃ major), 1.34 (3H, s, CH₃), 1.31 (3H, s, CH₃), 1.14 (3H, s, CH₃). ¹³C-NMR (126 MHz, CDCl₃) δC 176.4 (CO), 175.8 (CO), 175.2 (CO), 174.6 (CO), 174.5 (CO), 174.1 (CO), 156.1 (CO), 136.3 (ArC), 128.6 (ArCH), 128.4 (ArCH), 127.9 (ArCH), 67.2 (°C), 57.0 (d, J=39.5, °C-*CH₃), 57.0 (°C), 56.7 (°C), 56.6 (°C), 49.6 (°CH), 27.5 (CH₃), 26.9 (CH₃), 26.8 (CH₃), 26.6 (*CH₃ minor), 26.5 (CH₃), 26.2 (CH₃-NH), 25.9 (CH₃), 25.1 (CH₃), 23.2 (*CH₃ major), 22.7 (CH₃), 22.7 (CH₃), 17.3 (CH₃-CH). IR (neat) νmax/cm⁻¹ = 3298, 2984, 2936, 2472, 1698, 1647, 1528, 1414. HRMS (ES⁺, MeOH) Calc. for C₃₁H₅₃N₅O₈Na ([M+Na⁺]⁺) 685.3730, found 685.3713. Mp 230-232°C. [α]D²⁰ = 38.4 (c 0.5, CH₂Cl₂).

**Z-(R)-Aib*-Aib*-AlaNHMe 3-AlaNHMe**

Z-(R)-Aib*-Aib*-AlaNHMe was prepared according to general procedure A (0.026 mmol scale). The pure peptide (17 mg, 91%) was isolated as a white solid by column chromatography (1-5% MeOH in CH₂Cl₂). ¹H-NMR (400 MHz, CDCl₃) δH 7.67 (1H, br s, NH), 7.59 (1H, d, J=7.5, NH-CH₂), 7.53 (1H, br s, NH), 7.49 (1H, br s, NH), 7.33 (5H, m, ArCH x5), 6.89 (1H, br s, NH), 6.74 (1H, br s, NH), 6.29 (1H, br s, NH), 5.21 (1H, d, J=12.5, CH₃O, °C of AB system), 5.04 (1H, d, J=12.5, CH₂O, °H of AB system), 4.13 (1H, ddd, J= 11.0, 8.0, 3.5, CH), 2.13 (1H, m, CH₃), 1.79 (1H, m, CH₂), 1.58 (3H, s, CH₃), 1.51 (3H, s,
Z-(R)-Aib*-Aib*-AlaN(CH$_3$)$_4$ 3-AlaN(CH$_3$)$_4$

Z-(R)-Aib*-Aib*-AlaN(CH$_3$)$_4$ was prepared according to general procedure A (0.026 mmol scale). The pure peptide (14 mg, 77%) was isolated as a white solid by column chromatography (1-5% MeOH in CH$_2$Cl$_2$). $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$$_H$ 7.55 (1H, br s, NH), 7.52 (1H, br s, NH), 7.43 (1H, br s, NH), 7.41 (1H, br s, NH), 7.33 (5H, m, ArCH x5), 6.70 (1H, br m, NH), 5.99 (1H, br m, NH), 5.13 (1H, d, J=12.5, H$^a$ of AB system, CH$_2$O), 5.08 (1H, d, J=12.5, H$^b$ of AB system, CH$_2$O), 4.61 (1H, m, "CH$_3"$), 3.74 (1H, m, CH$_2$N), 3.43 (3H, m, CH$_3$N), 1.91 (2H, m, CH$_2$), 1.79 (2H, m, CH$_2$), 1.54 (3H, s, CH$_3$), 1.53 (3H, s, CH$_3$), 1.48 (3H, s, CH$_3$), 1.45 (3H, s, CH$_3$), 1.43 (3H, s, CH$_3$), 1.41 (3H, s, CH$_3$), 1.37 (3H, d, J=7.0, CH$_3$-CH$_2$), 1.32 (3H, s, CH$_3$), 1.29 (3H, s, CH$_3$). $^{13}$C-NMR (126 MHz, CDCl$_3$) $\delta$$_C$ 175.1 (CO), 174.9 (CO), 174.6 (CO), 174.31 (CO), 173.9 (CO), 170.90 (CO), 156.0 (CO), 136.3 (ArC), 128.7 (ArCH), 128.5 (ArCH), 128.0 (ArCH), 67.2 (CH$_2$OBn), 57.1 (d, J 37.0, "C-"CH$_3$), 56.8 ("C")x2), 56.7 ("C")x2), 56.4 ("C")x2), 47.6 ("C")x2), 46.1 (CH$_2$N), 29.7 (CH$_3$), 26.2 (CH$_2$), 25.2 ("CH$_3$" major), 24.8 ("CH$_3$" minor), 24.3-25.9 (CH$_3$ x7), 24.0 (CH$_3$), 17.0 (CH$_3$-"CH") IR (neat) $\nu$$_{max}$/cm$^{-1}$ = 3506, 2983, 2936, 1703, 1652, 1528. HRMS (ES$^+$, MeOH) Calc. for C$_{34}$H$_{53}$N$_7$O$_8$Na [(M+Na)$^+$] 725.4043, found 725.4030. Mp 197-199. [a]$^{20}_D$ = -21.6 (c 0.5, CH$_2$Cl$_2$).

Z-(R)-Aib*-Aib*-Ser(O'Bu)NH'Bu 3-Ser(O'Bu)NH'Bu

Z-(R)-Aib*-Aib*-Ser(O'Bu)NH'Bu was prepared according to general procedure A (0.026 mmol scale). The pure peptide (20 mg, 99%) was isolated as a white solid by column chromatography (1-5% MeOH in CH$_2$Cl$_2$). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$$_H$ 7.61 (1H, br s, NH), 7.58 (1H, br s, NH), 7.46 (1H, br s, NH), 7.34 (6H, m, ArCH x5 and NH), 7.01 (1H, br s, NH), 6.75 (1H, br s, NH), 6.27 (1H, br s, NH), 5.17 (1H, d, J=12.5, CH$_3$OCO, H$^a$ of AB system), 5.07 (1H, d, J=12.5, CH$_3$OCO, H$^b$ of AB system), 4.45 (1H, m, CH), 3.70 (2H, m, CH$_2$OCMe$_3$), 1.55 (3H, s, CH$_3$), 1.50 (6H, s, CH$_3$), 1.49 (3H, s, CH$_3$), 1.48 (2.3H, d, J=129.0, "CH$_3$" major), 1.48 (0.7H, m, CH$_3$ minor), 1.45 (2.3H, d, J=4.0, CH$_3$ major), 1.45 (0.7H, d, J=129.5, "CH$_3$" minor), 1.42 (3H, s, CH$_3$), 1.40 (3H, s, CH$_3$), 1.38 (12H, s, CH$_3$ and C(CH$_3$)$_3$), 1.25 (3H, s, CH$_3$), 1.13 (9H, s, C(CH$_3$)$_3$). $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$$_C$ 175.5 (CO), 175.4 (CO), 174.8 (CO), 174.3 (CO).
(CO), 174.2 (CO), 170.2 (CO), 156.1 (CO), 136.4 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.0 (ArCH), 72.8 (OCH₃), 67.1 (CH₂OCO), 61.8 (CH₂OCH₃), 57.0 (d, J=38.5, °C-*CH₃), 56.8 (°C), 56.7 (°C), 56.7 (°C), 56.4 (°C), 55.5 (°C), 51.2 (NHCH₃), 28.7 (C(CH₃)₃), 27.5 (C(CH₃)₃), 27.4 (CH₃), 25.9 (*CH₃ minor and CH₃ x3), 24.0 (*CH₃ major and CH₃ x3), 23.3 (CH₃). IR (neat) \( \nu_{\text{max}}/\text{cm}^{-1} = 3308, 2976, 2934, 1478, 1703, 1648, 1527. \) HRMS (ES⁺, MeOH) Calc. for \( \text{C}_{36}\text{H}_{58}\text{N}_{20}\text{O}_{39} \) ([M+H⁺]) 777.4956, found 777.4957. Mp 121-123. \( \left[ \alpha \right]_{D}^{20} = 21.2 \) (c 1, CH₂Cl₂).

**Z-(R)-Aib⁺⁻Aib⁺⁻ProNH'Bu 3-ProNH'Bu**

Z-(R)-Aib⁺⁻Aib⁺⁻ProNH'Bu was prepared according to general procedure A (0.031 mmol scale). The pure peptide (18 mg, 79%) was isolated as a white solid by column chromatography (1-5\% MeOH in CH₂Cl₂). \(^1\)H-NMR (400 MHz, CDCl₃) \( \delta_{H} = 7.34 \) (5H, m, ArCH x5 and NH), 7.13 (1H, br s, NH), 6.85 (1H, br s, NH), 6.66 (1H, br s, NH), 5.14 (1H, d, J=12.5, CH₂O, H° of AB system), 4.50 (1H, m, CH), 3.69 (2H, m, CH₂N), 1.82 – 2.05 (2H, m, CH₂), 1.63 – 1.92 (2H, m, CH₃), 1.56 (3H, s, CH₃), 1.50 (3H, s, CH₃), 1.49 (6H, s, CH₃ x2), 1.47 (2.3H, d, J=129.0, *CH₃ major), 1.46 (0.7H, m, CH₃ minor), 1.46 (2.3H, d, J=4.0, CH₃ major), 1.46 (0.7H, m, *CH₃ minor), 1.41 (9H, s, C(CH₃)₃), 1.39 (9H, s, C(CH₃)₃), 1.29 (3H, s, CH₃). \(^{13}\)C-NMR (101 MHz, CDCl₃) \( \delta_{C} = 175.2 \) (CO), 174.8 (CO), 174.7 (CO), 174.2 (CO), 172.9 (CO), 172.4 (CO), 156.1 (CO), 136.5 (ArC), 128.6 (ArCH), 128.3 (ArCH), 127.8 (ArCH), 67.0 (CH₂O), 62.8 (°CCH), 57.0 (d, J=39.0, °C-*CH₃), 57.0 (°C), 56.8 (°C), 56.6 (°C), 56.4 (°C), 51.0 (CMe₃), 48.1 (CH₃N), 29.1 (CH₂), 28.8 (C(CH₃)₃), 26.8 (CH₂), 25.9 (CH₃), 25.6 (*CH₃ minor and CH₃ x3), 24.2 (*CH₃ major and CH₃ x4). IR (neat) \( \nu_{\text{max}}/\text{cm}^{-1} = 3305, 2983, 2936, 1703, 1645, 1529. \) HRMS (ES⁺, MeOH) Calc. for \( \text{C}_{36}\text{H}_{58}\text{N}_{20}\text{O}_{39} \) ([M+Na⁺]) = 753.4356, found 753.4344. Mp 87-89. \( \left[ \alpha \right]_{D}^{20} = -11.2 \) (c 1, CH₂Cl₂).

**Z-ValNH'Bu**

Z-ValNH'Bu was prepared according to general procedure C (1 mmol scale). The pure product (251 mg, 82%) was isolated as a white solid. \(^1\)H-NMR (400 MHz, CDCl₃) \( \delta_{H} = 7.34 \) (5H, m, ArCH x5), 5.57 (1H, br s, NH), 5.37 (1H, br d, J=8.0, NH-CH), 5.11 (2H, s, CH₂O), 3.81 (1H, dd, J=8.5, 7.0, CH), 2.06 (1H, ddd, J=7.0, 7.0, 7.0), 1.35 (9H, s, C(CH₃)₃), 0.96 (3H, d, J=7.0, CH₃), 0.92 (3H, d, J=7.0, CH₃). \(^{13}\)C-NMR (101 MHz, CDCl₃) \( \delta_{C} = 170.2 \) (CO), 156.4 (CO), 136.3 (ArC), 128.5 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 66.9 (CH₂O), 60.9 (CH-NH), 51.5 (CMe₃), 31.4 (CH), 28.7 (C(CH₃)₃), 19.2 (CH₃), 17.9 (CH₃). IR (neat) \( \nu_{\text{max}}/\text{cm}^{-1} = 3333, 3231, 2963, 1698, 1651. \) HRMS (ES⁺, MeOH) Calc. for \( \text{C}_{13}\text{H}_{17}\text{N}_{2} \) ([M+H⁺]) = 307.2022, found 307.2009. Mp 108-111 °C. \( \left[ \alpha \right]_{D}^{20} = -8.8 \) (c 0.5, CH₂Cl₂).
Z-PheNH′Bu

Z-PheNH′Bu was prepared according to general procedure C (2 mmol scale). The pure product (517 mg, 71%) was isolated as a white solid. 1H-NMR (400 MHz, CDCl3) δ H 7.31 (10H, m, ArCH x 10) 5.47 (1H, br s, NH) 5.11 (2H, m, CH2) 4.21 (1H, br s, NH) 3.17 (1H, m, CH2) 2.90 (1H, m, CH2) 1.18 (9H, s, C(CH3)3). 13C-NMR (126 MHz, CDCl3) δC 169.4 (CO) 155.8 (CO) 136.8 (ArC) 136.3 (ArC) 129.4 (ArCH) 128.7 (ArCH) 128.5 (ArCH) 128.0 (ArCH) 127.0 (ArCH) 66.9 (CH2O) 56.9 (CMe3) 51.3 (CH) 39.4 (CH2) 28.4 (C(CH3)3).


Z-Phe-NHTs

p-Toluenesulfonyl isocyanate (0.17 mL, 1.1 mmol) was added dropwise to Z-Phe-OH (299 mg, 1 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h, then diluted with CHCl3 (20 mL) and washed with HCl (1 M, 10 mL). The aqueous phase was extracted with CHCl3 (2 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried (Na2SO4), filtered and concentrated in vacuo. The crude reaction product was purified by column chromatography (1:1 PE:EtOAc) to give Z-Phe-NHTs (201 mg, 44%) as a white solid. 1H-NMR (500 MHz, CDCl3) δ H 7.89 (2H, d, J=7.5, ArCH x2), 7.36 (7H, m, ArCH x7), 7.30 (1H, br s, NH) 7.20 (3H, m, ArCH x3), 6.98 (2H, d, J=7.5, ArCH x2), 5.20 (1H, d, J=7.5, NH), 5.08 (2H, m, CH2OCO), 4.47 (1H, m, CH), 3.02 (1H, dd, J=14.0, 6.0, CH2Ph, H of ABX system), 2.97 (1H, dd, J=14.0, 7.0, CH2Ph, H of ABX system), 2.46 (3H, s, CH3). 13C-NMR (126MHz, CDCl3) δC 169.1 (CO), 156.3 (CO), 145.2 (ArC), 135.6 (ArC), 135.3 (ArC), 134.9 (ArC), 129.5 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.4 (ArCH), 67.7 (CH2), 56.1 (CH), 37.5 (CH2), 21.7 (CH3). IR (neat) νmax/cm−1 = 3148, 1685, 1518, 1453, 1345, 1289, 1172. HRMS (ES+, CH2Cl2) Calc. for C24H22N4O5S ([M+Na]+) = 475.1298, found 475.1302. Mp 53-57 °C. [α]20D = −29.0 (c 1, CH2Cl2).

Z-(αMv)NH′Bu

Z-αMvOH (105 mg, 0.4 mmol) was dissolved in CH2Cl2 (5 mL) and the solution cooled to 0 °C. N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide (85 µL, 0.48 mmol) was added and the reaction was
allowed to warm to room temperature and stirred for 4 h. The solvent was removed in vacuo and EtOAc (20 mL) was added. The organic phase was washed with KHSO₄ (2 x 5 mL), brine (5 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude azlactone was then place under high vacuum (<0.1 mbar) before being dissolved in MeCN (8 mL). H-αMvNH₂Bu (prepared by the quantitative hydrogenolysis of Z-αMvNH₂Bu (62 mg, 0.33 mmol) was added and the reaction stirred at reflux for 5 d. After removing the solvent in vacuo, the crude reaction product was purified by column chromatography (1% MeOH in CH₂Cl₂) to give Z-αMv₂NH₂Bu (82 mg, 57%) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ_H 7.34 (5H, m, ArCH), 6.84 (1H, br s, NH), 6.34 (1H, br s, NH), 5.20 (1H, d, J=12.0, CH₂, Hα of AB system), 5.07 (1H, br s, NH), 5.01 (1H, d, J=12.0, CH₂, Hα of AB system), 1.97 (1H, spt, J=7.0, CH), 1.95 (1H, spt, J=7.0, CH), 1.48 (3H, s, CH₃), 1.45 (3H, s, CH₃), 1.38 (9H, s, C(CH₃)₃), 0.97 (3H, d, J=7.0, CH₂-CH), 0.96 (3H, d, J=7.0, CH₂-CH), 0.83 (3H, d, J=7.0, CH₂-CH), 0.77 (3H, d, J=7.0, CH₃-CH). ¹³C-NMR (75 MHz, CDCl₃) δ_C 171.8 (CO), 171.1 (CO), 155.5 (CO), 135.9 (ArC), 128.6 (ArCH), 128.5 (ArCH), 128.5 (ArCH), 67.2 (CH₂), 63.6 (CH), 63.1 (CH), 51.0 (CMe₂), 35.8 (CH), 35.4 (CH), 28.6 (C(CH₃)₃), 18.6 (CH₃), 18.5 (CH₃), 17.2 (CH₂-CH), 17.1 (CH₂-CH), 16.8 (CH₂-CH). IR (neat) νmax/cm⁻¹ = 3440, 3359, 3283, 2967, 1711, 1665, 1526, 1499, 1455. HRMS (ES⁺, CH₃Cl₂) Calc. for C₂₀H₂₉N₂O₃Na ([M+Na⁺], 456.2833, 456.2818. Mp 95-99 °C. [α]²₀°D = −5.2 (c 0.5, CH₂Cl₂).

Z-TleNH₂Bu

Z-TleNH₂Bu was prepared according to general procedure C (0.61 mmol scale). The pure product (181 mg, 93%) was isolated as a white solid. ¹H-NMR (500 MHz, CDCl₃) δ_H 7.34 (5H, m, ArCH), 5.54 (1H, d, J=9.0, NH), 5.38 (1H, br s, NH), 5.13 (1H, d, J=12.5, CH₂, Hα of AB system), 5.09 (1H, d, J=12.5, CH₂, Hα of AB system), 3.74 (1H, d, J=9.5, CH), 1.35 (9H, s, C(CH₃)₃), 0.99 (9H, s, C(CH₃)₃). ¹³C-NMR (126 MHz, CDCl₃) δ_C 169.5 (CO), 156.4 (CO), 156.3 (ArC), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 66.9 (CH₂OOC), 63.3 (CH), 51.7 (CMe₂), 34.8 (CMe₂), 28.7 (C(CH₃)₃), 26.6 (C(CH₃)₃). IR (neat) νmax/cm⁻¹ = 3341, 3276, 3065, 2961, 1702, 1653, 1537. HRMS (ES⁺, CH₃Cl₂) Calc. for C₁₈H₂₉N₂O₃Na ([M+H⁺]⁺) = 321.2173, found 321.2186. Mp 96-98 °C. [α]²₀°D = 12.8 (c 1, CH₂Cl₂).

Z-AlaNH₂Bu

Z-AlaNH₂Bu was prepared according to general procedure C (10 mmol scale). The pure product (2.61 g, 94%) was isolated as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ_H 7.33 (5H, m, ArCH), 5.80 (1H, br s, NH), 5.36 (1H, br s, NH), 5.12 (2H, s, CH₂), 4.11 (1H, m, CH), 1.35 (3H, d, J=7.0, CH₃), 1.33 (9H, s, C(CH₃)₃). ¹³C-NMR (101 MHz, CDCl₃) δ_C 171.3 (CO), 155.9 (CO), 136.3 (ArC), 128.5 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 66.9 (CH₂), 51.3 (CMe₂), 50.9 (CH), 28.6 (C(CH₃)₃), 18.7 (CH₃). IR (neat) νmax/cm⁻¹ = 3354, 3293, 2971, 1707, 1656, 1523, 1498, 1454. HRMS (ES⁺, CH₂Cl₂) Calc. for C₂₃H₃₂N₂O₃Na ([M+Na⁺]⁺) = 301.1523, found 301.1514. Mp 48-50 °C. [α]²₀°D = −16 (c 1, CH₂Cl₂).
Z-AbuNHtBu

Z-AbuNHtBu was prepared according to general procedure C (2 mmol scale). The pure product (536 mg, 92%) was isolated as a white solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$H 7.33 (5H, m, ArCH x5), 5.80 (1H, br s, NH), 5.46 (1H, br d, $J$ = 6.5, NH-CH), 1.83 (1H, m, CH$_2$), 1.13 (1H, m, CH$_2$), 1.34 (9H, s, C(CH$_3$)$_3$), 0.93 (3H, t, $J$ = 7.5, CH$_3$). $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$C 170.6 (CO), 156.1 (CO), 136.3 (ArC), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 66.8 (CH$_2$O), 56.5 (CH), 51.4 (CMe$_3$), 28.7 (C(CH$_3$)$_3$), 26.1 (CH$_2$), 9.7 (CH$_3$). IR (neat) $\nu_{max}$/cm$^{-1}$ = 3292, 2968, 1695, 1654, 1543. HRMS (ES$^+$, MeOH) Calc. for C$_{16}$H$_{25}$N$_2$O$_3$ ([M+H]$^+$) = 293.1865, found 293.1863. Mp 81-83°C. $[\alpha]_{D}^{20}$ = 6.0 (c 1, CH$_2$Cl$_2$).

Z-Ser(OtBu)NHtBu

Z-Ser(OtBu)NHtBu was prepared according to general procedure C (1 mmol scale). The pure product (318 mg, 91%) was isolated as a colourless oil. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$H 7.34 (5H, m, ArCH x5), 6.52 (1H, br s, NH), 5.75 (1H, br s, NH), 5.15 (1H, d, $J$ = 12.0, CH$_2$OBn), 5.09 (1H, d, $J$ = 12.5, CH$_2$OBn), 4.08 (1H, br s, CH), 3.77 (1H, br s, CH$_2$), 3.30 (1H, br dd, $J$ = 8.5, 8.5, CH$_2$), 1.34 (9H, s, C(CH$_3$)$_3$), 1.20 (9H, s, C(CH$_3$)$_3$). $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$C 169.1 (CO), 156.0 (CO), 136.3 (ArC), 128.5 (ArCH), 128.1 (ArCH), 128.1 (ArCH), 74.1 (OCMe$_3$), 66.9 (CH$_2$OBn), 62.0 (CH$_2$), 54.4 (CH), 51.2 (NCMe$_3$), 28.7 (C(CH$_3$)$_3$), 27.4 (C(CH$_3$)$_3$). IR (neat) $\nu_{max}$/cm$^{-1}$ = 3325, 2971, 1720, 1661, 1498, 1454. HRMS (ES$^+$, MeOH) Calc. for C$_{19}$H$_{30}$N$_2$O$_4$Na ([M+Na]$^+$) = 373.2103, found 373.2094. $[\alpha]_{D}^{20}$ = 16.4 (c 1, CH$_2$Cl$_2$).

Z-ProNHtBu

Z-ProNHtBu was prepared according to general procedure C (1 mmol scale). The pure product (289 mg, 95%) was isolated as a white solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$H 7.26 (5H, m, ArCH x5), 6.52 (1H, br s, NH), 5.75 (1H, br s, NH), 5.15 (1H, d, $J$ = 12.0, CH$_2$OBn), 5.09 (1H, d, $J$ = 12.5, CH$_2$OBn), 4.08 (1H, br s, CH), 3.77 (1H, br s, CH$_2$), 3.30 (1H, br dd, $J$ = 8.5, 8.5, CH$_2$), 1.75 – 2.30 (4H, br m, CH$_2$x2), 1.19 (9H, br m, C(CH$_3$)$_3$). $^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$C 128.5 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 67.2 (CH$_2$O), 61.3 (CH), 51.0 (CMe$_3$), 47.1 (CH$_3$N), 31.0 (CH$_2$), 28.6 (C(CH$_3$)$_3$), 24.5 (CH$_3$). ArC and CO (x2) signals not observed due to exchange broadening resulting from amide cis/trans isomerisation. IR (neat) $\nu_{max}$/cm$^{-1}$ = 3306, 2974, 2866, 1701, 1656, 1556. HRMS (ES$^+$, MeOH) Calc. for C$_{17}$H$_{24}$N$_2$O$_4$Na ([M+Na]$^+$) = 327.1685, found 327.1688. Mp 95-98°C. $[\alpha]_{D}^{20}$ = -68.4 (c 1, CH$_2$Cl$_2$).
$^1$H-NMR of Cbz-(R)-Aib*-OH

$^{13}$C-NMR of Cbz-(R)-Aib*-OH
$^1$H-NMR of Cbz-(R)-Aib*-Aib*-O'Bu

$^{13}$C-NMR of Cbz-(R)-Aib*-Aib*-O'Bu
$^1$H-NMR of Z-\((R)-\text{Aib}^*-\text{Aib}_4\)-OH

$^{13}$C-NMR of Z-\((R)-\text{Aib}^*-\text{Aib}_4\)-OH
$^1$H-NMR of $Z$-(R)-Aib*-Aib*-PheO'Bu

$^{13}$C-NMR of $Z$-(R)-Aib*-Aib*-PheO'Bu
\textsuperscript{1}H-NMR of Z-(R)-Aib*-Aib*-PheNH'Bu

\textsuperscript{13}C-NMR of Z-(R)-Aib*-Aib*-PheNH'Bu
$^1$H-NMR of $Z$-(R)-Aib*-Aib*-PheNHTs

$^{13}$C-NMR of $Z$-(R)-Aib*-Aib*-PheNHTs
$^1$H-NMR of Z-(R)-Aib*-Aib$_2$-ValO'Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib$_2$-ValO'Bu
H-NMR of Z-(R)-Aib*-Aib*-ValNH*Bu

\[ ^1\text{H-NMR of } Z-(R)-\text{Aib}^* \text{-Aib}^* \text{-ValNH}^*\text{Bu} \]

C-NMR of Z-(R)-Aib*-Aib*-ValNH*Bu

\[ ^{13}\text{C-NMR of } Z-(R)-\text{Aib}^* \text{-Aib}^* \text{-ValNH}^*\text{Bu} \]
$^1$H-NMR of Z-(R)-Aib*-Aib*-αMvO'Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib*-αMvO'Bu
$^1$H-NMR of Z-(R)-Aib*-Aib$_4$-αMvNH$_2$Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib$_4$-αMvNH$_2$Bu
$^1$H-NMR of Z-(R)-Aib*-Aib$_4$-(αMv)$_2$NH$^t$Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib$_4$-(αMv)$_2$NH$^t$Bu
$^1$H-NMR of Z-(R)-Aib*-Aib*-TleO'Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib*-TleO'Bu
$^1$H-NMR of Z-(R)-Aib*-Aib*-TleNH$^t$Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib*-TleNH$^t$Bu
$^1$H-NMR of $Z$-(R)-Aib*-Aib*-AlaO$^t$Bu

$^{13}$C-NMR of $Z$-(R)-Aib*-Aib*-AlaO$^t$Bu
$^1$H-NMR of $Z-(R)$-Aib*-Aib$_2$-AlaNH$^t$Bu

$^{13}$C-NMR of $Z-(R)$-Aib*-Aib$_2$-AlaNH$^t$Bu
$^1$H-NMR of Z-(R)-Aib*-Aib$_4$-AlaOH

$^{13}$C-NMR of Z-(R)-Aib*-Aib$_4$-AlaOH
$^1$H-NMR of $Z$-$(R)$-Aib*-Aib$_4$-AlaNHMe

$^{13}$C-NMR of $Z$-$(R)$-Aib*-Aib$_4$-AlaNHMe
$^1$H-NMR of Z-(R)-Aib*-Aib$_4$-AbuNH$^t$Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib$_4$-AbuNH$^t$Bu
$^1$H-NMR of $Z$-($R$)-Aib*-Aib$_4$-AlaN(CH$_2$)$_4$

$^{13}$C-NMR of $Z$-($R$)-Aib*-Aib$_4$-AlaN(CH$_2$)$_4$
$^1$H-NMR of Z-(R)-Aib*-Aib*-Ser(O'Bu)NH'Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib*-Ser(O'Bu)NH'Bu
$^1$H-NMR of Z-(R)-Aib*-Aib*$_4$-ProNH$^t$Bu

$^{13}$C-NMR of Z-(R)-Aib*-Aib*$_4$-ProNH$^t$Bu
$^1$H-NMR of Z-ValNH$^t$Bu

$^{13}$C-NMR of Z-ValNH$^t$Bu
$^1$H-NMR of Z-PheNH$^t$Bu

$^{13}$C-NMR of Z-PheNH$^t$Bu
$^1$H-NMR of Z-Phe-NHTs

$^{13}$C-NMR of Z-Phe-NHTs
$^1$H-NMR of Z-(αMv)$_2$NH$_2$Bu

$^{13}$C-NMR of Z-(αMv)$_2$NH$_2$Bu
$^1$H-NMR of Z-TleNH\textsuperscript{t}Bu

$^{13}$C-NMR of Z-TleNH\textsuperscript{t}Bu
$^1$H-NMR of Z-AlaNH$_2$Bu

$^{13}$C-NMR of Z-AlaNH$_2$Bu
$^1$H-NMR of Z-AbuNH$^t$Bu

$^{13}$C-NMR of Z-AbuNH$^t$Bu
$^1$H-NMR of Z-Ser(O\text{tBu})\text{NH}\text{tBu}$

$^{13}$C-NMR of Z-Ser(O\text{tBu})\text{NH}\text{tBu}$
$^1$H-NMR of Z-ProNH$^t$Bu

$^{13}$C-NMR of Z-ProNH$^t$Bu
Variable Temperature NMR Example (-70 to 40 °C) of Z-Aib*-Aib*-AlaNHBu in MeOD (zoomed in to CH₃ region)
X-ray Crystallographic Analysis of 3-AlaO‘Bu
Metrical parameters for the structure of 3-AlaO'Bu are available free of charge from the Cambridge Crystallographic Data Centre (reference number CCDC 994389).

References


