Supporting Information
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Foldamer-Mediated Remote Stereocontrol: > 1,60 Asymmetric Induction**
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Supplementary Materials for
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1. Experimental Section

1.1 General Methods

All reactions were conducted in flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Anhydrous dichloromethane and tetrahydrofuran were obtained by distillation over calcium hydride and sodium/benzophenone respectively. Anhydrous toluene was obtained from a PureSolve™ solvent purification system (Innovative Technologies PS-MP-5). Petrol refers to the fraction of light petroleum ether boiling between 40 and 65 °C. All other solvents and commercially available reagents were used as received. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Ultrashield 300, 400, 500 or 800 MHz spectrometer. $^1$H and $^{13}$C spectra were referenced relative to the solvent residual peaks and chemical shifts (δ) reported in ppm downfield of tetramethylsilane (CDCl$_3$ δ H: 7.26 ppm, δ C: 77.16 ppm; CD$_3$OD δ H: 3.31 ppm, δ C 49.05 ppm; d$_8$-THF δ H: 3.58, 1.73 ppm, δ C: 67.57, 25.37 ppm). Coupling constants (J) are reported in Hertz and rounded to 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (spt), multiplet (m), broad (br) or some combination of these. In $^1$H NMR spectra, amide NH signals that exchange with deuterated solvent are not reported. Assignments were made using DEPT-135, 2D $^1$H-COSY and HMQC experiments. 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 ± 0.001 Da. Infrared spectra were recorded on a Thermo Scientific Nicolet iS5 FTIR spectrometer. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram. Sil G/UV254) and visualized under UV light at 254 nm and/or by staining with phosphomolybdic acid solution. Flash column chromatography was carried out on Fluorochem Davisil 40-63 μm 60 Å silica with the eluent quoted. Optical rotation measurements were taken on an AA-100 polarimeter using a cell with a pathlength of 0.25 dm at 24 °C with the solvent and concentration (g/100 mL) stated. Circular dichroism (CD) spectra were recorded on a Jasco J-815 spectrometer using a 1 mm cell at 20 °C with the solvent and concentration stated. Analytical HPLC analysis was
performed on a Hewlett-Packard series 1050 system, using the column and eluent stated, with UV detection at 254, 230 and 210 nm.

Methods for the synthesis of $N_3\text{Aib}_4\text{OH}$,$^1$ $H_2\text{NAib}_4\text{Or-Bu}$,$^1$ Z-L-(αMe)ValAlb$_4$GlyNH$_2$,$^2$ (S)-2,2-dimethyl-4-methyl-3-(1-naphthoyl)-oxazolidin-5-one$^3$ and Z-L-(αMe)Val-F$^4$ have been reported previously.

1.2 Abbreviations

Aib aminoisobutyric acid; Aib* singly labelled ($^{13}\text{C}$) Aib; Aib** doubly labelled ($^{13}\text{C}_2$) Aib; DIPEA $N,N$-diisopropylethylamine; EDC $N$-(3-dimethylaminopropyl)-$N'$-ethylcarbodiimide; HBTU $O$-(benzotriazol-1-yl)-$N,N,N',N'$-tetramethyluronium hexafluorophosphate; HOBt 1-hydroxybenzotriazole; KHMDS potassium hexamethyldisilazide; TFA trifluoroacetic acid.

1.3 Synthetic Procedures

Synthesis of HCl·H-Aib*OEt

A flame-dried pear-shaped flask was charged with KHMDS (5 mL; 1 M in THF, 5.03 mmol) and diluted with anhydrous THF (15 mL). The solution was cooled to −78 ºC and added portionwise (5 x 4 mL portions over 4 min) to a stirred solution of (S)-2,2-dimethyl-4-methyl-3-(1-naphthoyl)-oxazolidin-5-one (712 mg, 2.52 mmol) in THF (20 mL) at −78 ºC. After a further 4 min $^{13}\text{CH}_3\text{I}$ (780 µL, 12.60 mmol) was added (colour change from deep red to light yellow over ~2 min). After stirring for a further 30 min, the reaction was quenched by addition of 1 M HCl (10 mL) and allowed to warm to room temperature. The mixture was partitioned between water (50 mL) and EtOAc (50 mL) and the organic phase concentrated under reduced pressure. HBr (47% in water, 20 mL) was added and the resulting suspension heated at reflux for 18 h. The reaction was allowed to cool to room temperature, diluted with water (35 mL) and washed with CH$_2$Cl$_2$ (2 x 15 mL) and Et$_2$O (15 mL). The aqueous phase was concentrated under reduced pressure and the residual solid re-dissolved in EtOH (20 mL). Thionyl chloride (2 mL) was added and the reaction mixture heated at reflux overnight. The reaction
mixture was concentrated under reduced pressure and excess SOCl₂ removed by co-
evaporation with PhMe. Trituration with Et₂O gave the title compound as a pale yellow
solid (394 mg, 2.35 mmol, 93%) as a 2.4:1 mixture of enantiomers (R:S; determined by
EDC/HOBt coupling with Z-L-Phe-OH). m.p. 150-154 °C; ¹H NMR (400 MHz, CDCl₃)
δH 8.83 (brs, 3H, H₃N⁺R), 4.28 (q, J = 7.0, 2H, CH₂), 1.74 (d, ¹JCH = 130.5, 3H, ¹³CH₃),
1.57 (d, ³JCH = 3.5, 3H, ¹³CH₃(C)CH₃), 1.33 (t, J = 7.0, 3H, CH₂CH₃) ppm; ¹³C NMR
(100 MHz, CDCl₃) δC 171.2 (C=O), 63.0 (C₂H₂), 57.8 (d, J = 35.5, C), 24.1 (¹³CH₃ + CH₃),
14.2 (CH₃) ppm; IR νmax = 2924, 2852, 2781, 2645, 2573, 1742, 1590, 1519 cm⁻¹; MS
(ES⁺, MeOH) m/z = 133 (M⁺, 100%); HRMS (ES⁺, MeOH) Calcd for C₅¹³CH₁₄NO₂ =
133.1053, found 133.1053.

Synthesis of N₃Aib₄Aib*OEt
To a stirred solution of N₃Aib₄OH (857 mg, 2.23 mmol) in anhydrous CH₂Cl₂ (10 mL) at
0 °C was added EDC (590 μL, 3.35 mmol) dropwise. The mixture was stirred at room
temperature for 3 h then concentrated under reduced pressure. The residue was dissolved
in EtOAc (30 mL) and washed with 5% KHSO₄ solution (2 × 15 mL) and brine (15 mL).
The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give
the crude azlactone as a white solid (739 mg, 2.02 mmol), which was re-dissolved in dry
MeCN (15 mL). HCl·H-Aib*OEt (390 mg, 2.32 mmol) and Et₃N (420 μL, 3.03 mmol)
were added and the resulting suspension heated at reflux for 5 d. The solvents were
removed under reduced pressure and the residue purified by column chromatography
(SiO₂; CH₂Cl₂:EtoH; 98:2→90:10) to give the title compound as a white solid (449 mg,
0.90 mmol, 45%). m.p. 153-156 °C; ¹H NMR (400 MHz, CDCl₃) δH 7.09 (s, 1H, NH),
6.84 (s, 1H, NH), 6.11 (s, 1H, NH), 4.13 (q, J = 7.0, 2H, CH₂), 1.55 (s, 6H, 2 × CH₃),
1.49 (d, ¹JCH = 129.0, 3H, ¹³CH₃), 1.49 (d, ³JCH = 4.5, 3H, ¹³CH₃(C)CH₃), 1.49 (s, 6H, 2 ×
CH₃), 1.48 (s, 6H, 2 × CH₃), 1.42 (s, 6H, 2 × CH₃), 1.22 (t, J = 7.0, 3H, CH₂CH₃) ppm;
¹³C NMR (100 MHz, CDCl₃) δC 175.0 (CO), 174.2 (CO), 173.0 (CO), 172.9 (CO), 172.4
(CO), 64.2 (C), 60.8 (CH₂), 57.02 (C), 56.98 (C), 56.9 (C), 55.8 (d, J = 37.0, C), 25.5
(CH₃), 25.4 (CH₃), 25.0 (¹³CH₃), 24.8 (CH₃), 24.5 (CH₃), 14.3 (CH₃) ppm; IR νmax =
3312, 2984, 2938, 2112, 1722, 1651, 1514, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 499
(\([\text{M+H}]^+, 45\%\), 521 (\([\text{M+Na}]^+, 100\%\)); HRMS (ES\(^+\), MeOH): Calcd for C\(_{21}^{13}\)H\(_{40}\)N\(_7\)O\(_6\) = 499.3069, found 499.3059.

**Synthesis of N\(_3\)Aib\(_4\)Aib*-OH**

A stirred solution of N\(_3\)Aib\(_4\)Aib*OEt (444 mg, 0.89 mmol) and LiOH (150 mg, 6.24 mmol) in THF/H\(_2\)O (4:1; 5 mL) was heated at 70 °C for 24 h. The reaction was allowed to cool to room temperature, acidified to pH = 1 with 1 M HCl and extracted with EtOAc (2 × 25 mL). The organic phase was washed with 1 M HCl (5 mL) and brine (5 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give the title compound as a white solid (393 mg, 0.84 mmol, 94%). m.p. 222-225 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.56 (s, 1H, NH), 7.49 (s, 1H, NH), 7.01 (s, 1H, NH), 6.36 (s, 1H, NH), 1.58 (d, \(^1\)J\(_{\text{CH}}\) = 129.5, 3H, \(^{13}\)CH\(_3\)), 1.58 (d, \(^3\)J\(_{\text{CH}}\) = 4.5, 3H, \(^{13}\)CH\(_3\)(C)CH\(_3\)), 1.54 (s, 6H, 2 × CH\(_3\)), 1.49 (s, 6H, 2 × CH\(_3\)), 1.42 (s, 6H, 2 × CH\(_3\)) ppm; \(^{13}\)C NMR (125 MHz, MeOD) \(\delta\) C 178.2 (CO), 176.7 (CO), 176.22 (CO), 176.16 (CO), 174.6 (CO), 64.8 (C), 57.93 (C), 57.86 (C), 57.8 (C), 57.0 (d, J = 37.0, C), 25.6 (CH\(_3\)), 25.32 (CH\(_3\)), 25.3 (\(^{13}\)CH\(_3\)), 24.8 (CH\(_3\)), 24.5 (CH\(_3\)) ppm; IR \(\nu_{\text{max}}\) = 3284, 2987, 2938, 2112, 1742, 1663, 1646, 1523, 1460 cm\(^{-1}\); MS (ES\(^-\), MeOH) \(m/z\) = 469 ([M−H]\(^-\), 100%).

**Synthesis of N\(_3\)Aib\(_4\)Aib*Aib*O\(_t\)Bu**

A stirred solution of N\(_3\)Aib\(_4\)Aib*OH (346 mg, 0.74 mmol) in Ac\(_2\)O (3 mL) was heated at 120 °C for 3 h. The reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The last traces of Ac\(_2\)O were removed by co-evaporation with anhydrous PhMe to give the crude azlactone as an off-white solid (326 mg, 0.72 mmol), which was re-dissolved in anhydrous MeCN (6.5 mL). H-Aib\(_4\)O\(_t\)Bu (328 mg, 0.79 mmol) was added and the mixture heated at reflux for 3 d. The reaction was allowed to cool to room temperature and the solvents removed under reduced pressure. The residual solid was re-dissolved in CH\(_2\)Cl\(_2\) (30 mL) and washed with 5% KHSO\(_4\) solution (2 × 20 mL), sat. NaHCO\(_3\) solution (20 mL) and brine (20 mL). The organics were dried (MgSO\(_4\)) and concentrated under reduced pressure. Trituration with Et\(_2\)O gave the title compound as a white solid (438 mg, 0.51 mmol, 69%). m.p. 223-226 °C; \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 7.98 (s, 1H, NH), 7.90 (s, 1H, NH), 7.89 (s, 1H,
Purification by column chromatography (SiO$_2$ 5.09 (d, 1H, $J_{CH} = 129.5$), 3H, $^{13}$CH$_3$)), 1.46 (m, 18H, 3 × CH$_3$) 1.43 (s, 9H, (CH$_3$)$_3$), 1.41 (s, 6H, 2 × CH$_3$) ppm; $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta_C$ 177.57 (CO), 177.50 (CO), 177.46 (CO), 177.0 (CO), 176.8 (CO), 176.4 (CO), 176.3 (CO), 175.5 (CO), 174.8 (CO), 81.5 (C(CH$_3$)$_3$), 58.0 (C), 57.91 (C), 57.89 (C), 57.86 (C), 57.82 (C), 57.78 (d, $J = 37.0$, C), 57.65 (C), 57.62 (C), 57.5 (C), 28.2 ((CH$_3$)$_3$), 25.4 ($^{13}$CH$_3$ + 7 × CH$_3$), 24.5 (CH$_3$) ppm; IR $\nu_{max} = 3282, 2983, 2938, 2113, 1741, 1653, 1534, 1457$ cm$^{-1}$; MS (ES$^+$, MeOH) $m/z = 889$ ([M+Na]$^+$, 100%); HRMS (ES$^+$, MeOH): Calcd for C$_{39}$H$_{72}$N$_{10}$O$_{10}$ = 867.5492, found 867.5528.

Synthesis of Z-L-(αMe)ValAib$_4$Aib*Aib$_4$O‘Bu 4

To a stirred solution of H-Aib$_4$Aib*O‘Bu (375 mg, 0.45 mmol; obtained in quantitative yield by hydrogenolysis of N$_3$Aib$_4$Aib*O‘Bu) and DIPEA (270 μL, 1.56 mmol) in CH$_2$Cl$_2$ (3 mL) was added a solution of Z-L-(αMe)Val-F (417 mg, 1.56 mmol) in CH$_2$Cl$_2$ (2 mL) and the reaction stirred at room temperature for 5 d. The solvents were removed under reduced pressure and the residue re-dissolved in CH$_2$Cl$_2$ (20 mL) and washed with 5% KHSO$_4$ solution (2 × 15 mL), sat. NaHCO$_3$ solution (15 mL) and brine (15 mL). The organics were dried (MgSO$_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:EtOH; 99:1→95:5) gave the title compound as a white solid (353 mg, 0.33 mmol, 73%) as a 2:4:1 mixture of isotopically labelled diastereoisomers. m.p. 242-245 °C; [α]$_D$ = + 29.4 (c = 1.0; CHCl$_3$); $^1$H NMR (400 MHz, CD$_3$OD) $\delta_H$ 8.00 (s, 1H, NH), 7.94-7.87 (m, 4H, 4 x NH), 7.73 (s, 1H, NH), 7.68 (s, 1H, NH), 7.44-7.29 (m, 5H, 5 × ArH, Cbz), 5.21 (d, 1H, $J = 12.5$, HA of AB), 5.09 (d, 1H, $J = 12.5$, HB of AB), 2.03 (spt, 1H, $J = 7.0$, CH(CH$_3$)$_2$), 1.50 (m, 6H, 2 × CH$_3$), 1.49-1.45 (m, 36H, 11 × CH$_3$ + $^{13}$CH$_3$(C)CH$_3$, maj. + min.), 1.48 (d, $^1J_{CH} = 129.0$, 3H, $^{13}$CH$_3$, maj. + min.), 1.44 (s, 9H, (CH$_3$)$_3$), 1.43 (s, 3H, CH$_3$), 1.40 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_3$), 1.37 (s, 3H, CH$_3$), 1.31 (s, 3H, CH$_3$), 1.00 (d, $J = 7.0$, 3H, CH(CH$_3$)), 0.94 (d, $J = 7.0$, 3H, CH(CH$_3$)) ppm; $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta_C$ 177.64 (CO), 177.60 (CO), 177.55 (CO), 177.51 (CO), 177.47 (CO), 177.0 (CO), 176.8 (CO), 176.4 (CO), 175.9 (CO), 175.5 (CO), 158.1 (CO, Cbz), 138.7 (ArC), 129.6 (ArCH), 129.1 (ArCH), 128.7 (ArCH), 81.5 (C(CH$_3$)$_3$), 67.7 (CH$_2$, Cbz), 63.9 (C), 58.06 (C), 58.01 (C), 57.90
Synthesis of Z-L-(αMe)Val₂Aib₄Aib*Aib₄O'Bu 5

To a stirred solution of H-(αMe)ValAib₄Aib*Aib₄O'Bu (171 mg, 0.18 mmol; obtained in quantitative yield by hydrogenolysis of Z-L-(αMe)ValAib₄Aib*Aib₄O'Bu) and DIPEA (80 μL, 0.45 mmol) in CH₂Cl₂ (1.5 mL) was added a solution of Z-L-(αMe)Val-F (120 mg, 0.45 mmol) in CH₂Cl₂ (1.5 mL) and the reaction stirred at room temperature for 7 d. The mixture was diluted with CH₂Cl₂ (15 mL) and washed with 5% KHSO₄ solution (2 x 10 mL), sat. NaHCO₃ solution (10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:EtOH; 99:1→95:5) gave the title compound as a white solid (164 mg, 0.14 mmol, 76%) as a 2:4:1 mixture of isotopically labelled diastereoisomers. m.p. 255-258 °C; [α]D = +38.0 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, CD₃OD) δH 8.072 (s, 1H, NH), 8.065 (s, 1H, NH), 7.99 (s, 1H, NH), 7.925 (s, 1H, NH), 7.917 (s, 1H, NH), 7.908 (s, 1H, NH), 7.896 (s, 1H, NH), 7.78 (s, 1H, NH), 7.73 (s, 1H, NH), 7.68 (s, 1H, NH), 7.44-7.31 (m, 5H, 5 × ArH, Cbz), 5.20 (d, 1H, J = 10.0, HA of AB), 5.06 (d, 1H, J = 10.0, HB of AB), 1.95 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.61 (m, 1H, CH(CH₃)₂), 1.51 (s, 3H, CH₃), 1.50 (s, 6H, 2 × CH₃), 1.497-1.47 (27H, 9 × CH₃), 1.48 (d, JCH = 128.5, 3H, ¹³CH₃, maj. + min.), 1.47-1.46 (12H, 4 × CH₃), 1.456 (s, 3H, CH₃), 1.44 (s, 9H, (CH₃)₃), 1.414 (s, 3H, CH₃), 1.405 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.95 (d, J = 7.0, 3H, CH(CH₃)), 0.86 (d, J = 7.0, 3H, CH(CH₃)), 0.80 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, CD₃OD) δC 177.66 (CO), 177.65 (CO), 177.62 (CO), 177.60 (CO), 177.5 (2 × CO), 176.8 (CO), 176.4 (CO), 175.5 (CO), 175.2 (CO), 174.3 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.3 (ArCH), 81.5 (C(CH₃)₃), 68.0 (CH₂, Cbz), 64.4 (C), 63.7 (C) 58.1 (C), 58.02 (C), 57.96 (C), 57.91 (d, J = 37.0, C), 57.90 (C), 57.86 (C), 57.8 (C), 57.78 (C), 57.5 (C), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 28.2 ((CH₃)₃), 27.61 (CH₃), 27.55 (CH₃), 27.4 (CH₃), 27.1 (¹³CH₃, min.),

(C), 57.85 (C), 57.74 (C), 57.71 (C), 57.69 (C), 57.67 (d, J = 37.0, C), 57.66 (C), 57.5 (C), 36.0 (CH(CH₃)₂), 28.2 ((CH₃)₃), 26.6 (¹³CH₃, min.), 24.5 (CH₃), 24.3 (¹³CH₃, maj.), 18.0 (CH(CH₃)₂), 17.7 (CH(CH₃)₂) ppm; IR vₑₓₐₓ = 3296, 2983, 2938, 1656, 1528, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1110 ([M+Na]⁺, 100%); HRMS (ES⁺, MeOH): Calcd for C₅₅¹³CH₉₁N₁₀O₁₃ = 1088.6796, found 1088.6824.
26.0 (CH₃), 24.4 (CH₃), 24.2 (CH₃), 24.14 (CH₃), 24.07 (CH₃), 23.8 (¹³CH₃, maj.), 23.54 (CH₃), 23.46 (CH₃), 18.7 (CH₃), 18.1 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; IR νmax = 3295, 2981, 2937, 1654, 1528, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1223 ([M+Na]⁺, 100%).

**Synthesis of Z-L-(αMe)Val₂Aib₂GlyNH₂ 6a**

To a stirred solution of H-(αMe)ValAib₄GlyNH₂ (104 mg, 0.20 mmol; obtained in quantitative yield by hydrogenolysis of Z-L-(αMe)ValAib₄GlyNH₂) and DIPEA (137 μL, 0.79 mmol) in CH₂Cl₂ (3 mL) was added a solution of Z-L-(αMe)Val-F (185 mg, 0.70 mmol) in CH₂Cl₂ (2 mL) and the reaction stirred at room temperature for 4 d. The mixture was diluted with CH₂Cl₂ (20 mL) and washed with 5% KHSO₄ solution (2 × 15 mL), sat. NaHCO₃ solution (15 mL) and brine (15 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:EtOH; 95:5) gave the title compound as a white solid (99 mg, 0.13 mmol, 65%).

**m.p.** 206-208 °C; [α]D = +60.0 (c = 0.4; CHCl₃); **¹H NMR** (300 MHz, CD₃OD) δH 8.08 (s, 2H, 2 × NH), 7.93 (s, 1H, NH), 7.78 (s, 1H, NH), 7.44-7.30 (m, 5H, 5 × ArH, Cbz), 5.20 (d, 1H, J = 12.5, HA of AB, Cbz), 5.05 (d, 1H, J = 12.5, HB of AB, Cbz), 4.03 (d, 1H, J = 17.5, HA of AB', Gly), 3.64 (d, 1H, J = 17.5, HB of AB', Gly), 1.94 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.59 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.52 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.46 (m, 6H, 2 × CH₃), 1.45 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.79 (d, J = 7.0, 3H, CH(CH₃)) ppm; **¹³C NMR** (75 MHz, CD₃OD) δC 178.3 (CO), 178.2 (CO), 178.1 (CO), 177.5 (CO), 175.4 (CO), 175.2 (CO), 174.5 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.3 (ArCH), 68.0 (CH₂, Cbz), 63.8 (C) 58.3 (C), 58.2 (C), 58.13 (C), 58.06 (C), 57.9 (C), 43.7 (CH₂, Gly), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 27.5 (CH₃), 27.3 (2 × CH₃), 27.2 (CH₃), 24.1 (CH₃), 23.52 (CH₃), 23.46 (CH₃), 23.4 (CH₃), 18.7 (CH₃), 18.1 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; **IR** νmax = 3296, 2981, 2937, 1653, 1526, 1455 cm⁻¹; **MS** (ES⁺, MeOH) m/z = 775 ([M+H]⁺, 20%), 792 ([M+NH₄]⁺, 100%), 798 ([M+Na]⁺, 100%); **HRMS** (ES⁺, MeOH): Calcd for C₃₈H₇₅N₈O₉ = 775.4713, found 775.4742.
Synthesis of N$_3$Aib$_4$PhSer-OMe

To a stirred suspension of N$_3$Aib$_4$-OH (250 mg, 0.65 mmol), HBTU (296 mg, 0.78 mmol), HOBt (145 mg, 0.98 mmol) and DIPEA (340 µL, 1.95 mmol) in CH$_2$Cl$_2$ (8 mL) was stirred at room temperature for 2 h. H-D,L-PhSer-OMe (180 mg, 0.78 mmol) was added in a single portion and the reaction stirred for an additional 18 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (30 mL) and washed with 5% KHSO$_4$ solution (2 × 20 mL), sat. NaHCO$_3$ solution (2 × 20 mL) and brine (20 mL). The organics were dried (MgSO$_4$) and concentrated under reduced pressure. Trituration with Et$_2$O gave the title compound as a white solid (325 mg, 0.58 mmol, 89%). m.p. 183-187 °C; $^1$H NMR (500 MHz, MeOD) δ $^H$ 7.40 (d, $^J$ = 7.5, 2H, Ar$^H$), 7.31 (dd, $^J$ = 7.5, 7.5, 2H, Ar$^H$), 7.25 (dd, $^J$ = 7.0, 7.0, 1H, Ar$^H$), 5.15 (d, $^J$ = 5.5, 1H, C$^H$OH), 4.73 (d, $^J$ = 5.5, 1H, $^a$C$^H$), 3.59 (s, 3H, OCH$_3$), 1.55 (s, 3H, CH$_3$), 1.54 (s, 3H, CH$_3$), 1.48 (s, 3H, CH$_3$), 1.46 (s, 3H, CH$_3$), 1.41 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_3$), 1.36 (s, 3H, CH$_3$) ppm; $^{13}$C NMR (125 MHz, MeOD) δ $^C$ 177.7 (C$^O$), 176.7 (C$^O$), 176.3 (C$^O$), 174.8 (CO), 171.9 (CO), 141.4 (ArC), 129.2 (ArCH), 128.9 (ArCH), 127.7 (ArCH), 75.1 (CHOH), 64.8 (C), 60.7 ($^a$C$^H$), 58.3 (C), 58.03 (C), 58.01 (C), 52.5 (OCH$_3$), 26.2 (CH$_3$), 26.1 (CH$_3$), 25.2 (CH$_3$), 25.0 (CH$_3$), 24.6 (CH$_3$), 24.5 (3 × CH$_3$) ppm; IR $\nu_{\text{max}}$ = 3424, 3260, 2995, 2114, 1731, 1646, 1533, 1467 cm$^{-1}$; MS (ES$^+$, MeOH) m/z = 562 ([M+H]$^+$, 50%), 584 ([M+Na]$^+$, 100%); HRMS (ES$^+$, MeOH): Calcd for C$_{26}$H$_{40}$N$_7$O$_7$ = 562.2984, found 562.2978.

Synthesis of N$_3$Aib$_4$DpeAib$_4$O$^t$Bu

A solution of N$_3$Aib$_4$PhSer-OMe (306 mg, 0.55 mmol) and K$_2$CO$_3$ (301 mg, 2.18 mmol) in MeOH/H$_2$O (3:1; 4 mL) was stirred at room temperature for 18 h. The reaction was quenched with 1 M HCl (10 mL), diluted with H$_2$O (5 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organics were washed with brine (20 mL), dried (MgSO$_4$) and concentrated. The resulting white solid (282 mg, 0.52 mmol) and NaOAc (63 mg, 0.77 mmol) were suspended in Ac$_2$O (4 mL) and the reaction stirred at room temperature for 3 d. The solvents were removed and the residue re-dissolved in CH$_2$Cl$_2$ (25 mL) and washed with 5% KHSO$_4$ solution (2 × 15 mL), sat. NaHCO$_3$ solution (2 × 15 mL) and brine (15 mL). The organics were dried (MgSO$_4$) and concentrated under reduced

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pressure to give a white solid. The crude azlactone (205 mg, 0.40 mmol) and H-Aib₄-O'Bu (166 mg, 0.40) were dissolved in CH₂Cl₂ (4 mL) and the mixture stirred at room temperature for 10 d. The solution was diluted with CH₂Cl₂ (25 mL) and washed with 5% KHSO₄ solution (2 × 20 mL), sat. NaHCO₃ solution (2 × 20 mL) and brine (20 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (255 mg, 0.28 mmol, 69%). m.p. 270-271 °C; ¹H NMR (500 MHz, MeOD) δH 7.56 (d, J = 7.5 Hz, 2H, ArH), 7.35 – 7.25 (m, 4H, ArH + C=C), 1.60 (s, 6H, 2 × C₃H₃), 1.57-1.51 (m, 18H, 6 × C₃H₃), 1.47 (m, 12H, 4 × C₃H₃), 1.42 (s, 9H, (C₃H₃)₃), 1.42 (m, 6H, 2 × C₃H₃), 1.15 (s, 6H, 2 × C₃H₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 178.2 (CO), 177.1 (CO), 176.83 (CO), 176.76 (CO), 176.2 (CO), 176.1 (CO), 175.5 (CO), 174.6 (CO), 166.9 (CO), 134.8 (ArC), 131.8 (ArCH), 130.8 (ArCH), 130.0 (C=CH), 129.7 (C=CH), 129.5 (ArCH), 81.4 (C(CH₃)₃), 64.5 (C), 58.1 (C), 57.9 (C), 57.8 (C), 57.7 (C), 57.6 (C), 57.5 (C), 57.2 (C), 28.2 (CH₃), 25.7-24.9 (6 × CH₃), 24.5 (CH₃) ppm; IR vₚ = 3292, 2981, 2104, 1732, 1653, 1536, 1457 cm⁻¹; MS (ES⁺, CH₂Cl₂) m/z = 926 ([M+H]⁺, 20%), 943 ([M+NH₄]⁺, 100%); HRMS (ES⁺, CH₂Cl₂): Calcd for C₄₅H₇₂N₁₁O₁₀ = 926.5459, found 926.5452.

Synthesis of Z-L-(αMe)ValAib₄-PheAib₄-O'Bu 7
A stirred solution of N₃Aib₄-PheAib₄-O'Bu (120 mg, 0.13 mmol) and PPh₃ (51 mg, 0.20 mmol) in THF/H₂O (2:1; 3 mL) was heated at reflux for 14 d. The mixture was allowed to cool to room temperature and the solvents removed under reduced pressure. The residue was purified directly by column chromatography (SiO₂; CH₂Cl₂:MeOH:NEt₃; 95:4:9:0.1→90:9:9:0.1) to give a white solid (55 mg, amine contaminated with small quantities of PPh₃=O). The impure amine was dissolved in dry CH₂Cl₂ (1.5 mL) and added to a solution of Z-L-(αMe)Val-F (49 mg, 0.18 mmol) in CH₂Cl₂ (0.5 mL). DIPEA (32 μL, 0.18 mmol) was added and the reaction stirred at room temperature for 5 d. The solvents were removed and the residue re-dissolved in EtOAc (20 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (15 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound...
as a white solid (34 mg, 0.030 mmol, 23% over 2 steps). m.p. 224-227 °C; \([\alpha]_D^\circ = + 97.0 (c = 0.47; \text{CH}_2\text{Cl}_2)\); \(^1\text{H NMR}\) (500 MHz, MeOD) \(\delta_H^\circ 8.04\) (s, 1H, NH), 7.97 (s, 1H, NH), 7.96 (s, 1H, NH), 7.76 (s, 1H, NH), 7.75 (s, 1H, NH), 7.55 (d, \(J = 7.0, 2H, 2 \times \text{ArH}, \alpha^\circ\)-Phe), 7.40-7.30 (m, 9H, 8 \times \text{ArH}, Cbz), 5.17 (d, \(J = 13.0, 1H, \text{HA of AB, Cbz}\)), 5.03 (d, 1H, J = 13.0, HB of AB, Cbz), 2.02 (spt, 1H, J = 7.0, CH(CH\(_3\))\(_2\)), 1.62 (s, 3H, CH\(_3\)), 1.59 (s, 3H, CH\(_3\)), 1.57 (s, 3H, CH\(_3\)), 1.56 (s, 3H, CH\(_3\)), 1.54 (s, 3H, CH\(_3\)), 1.52 (s, 3H, CH\(_3\)), 1.48-1.47 (m, 15H, 5 \times C\(_3\)H), 1.44 (s, 3H, CH\(_3\)), 1.42 (s, 3H, CH\(_3\)), 0.99 (d, \(J = 7.0, 3H, \text{CH(CH}_3\))\(_2\)), 0.94 (d, \(J = 7.0, 3H, \text{CH(CH}_3\))\(_2\)) ppm; \(^{13}\text{C NMR}\) (125 MHz, MeOD) \(\delta_C 178.4\) (CO), 177.9 (CO), 177.1 (CO), 177.0 (CO), 176.8 (CO), 176.5 (CO), 176.4 (CO), 175.9 (CO), 175.6 (CO), 175.1 (CO, Cbz), 138.6 (ArC), 135.0 (ArC), 132.0 (C=CH), 130.9 (ArCH), 130.1 (ArCH), 129.7 (ArCH), 129.6 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 81.5 (C(CH\(_3\))\(_3\)), 67.6 (CH\(_2\), Cbz), 63.9 (C), 58.4 (C), 58.3 (C), 58.1 (C), 57.9 (C), 57.7 (C), 57.6 (C), 57.5 (C), 36.0 (CH(CH\(_3\))\(_2\)), 28.2 (C(CH\(_3\))\(_3\)), 26.5 (CH\(_3\)), 26.4 (3 \times CH\(_3\)), 26.0 (CH\(_3\)), 25.4 (CH\(_3\)), 24.8 (3 \times CH\(_3\)), 24.2 (CH\(_3\)), 23.9 (CH\(_3\)), 23.7 (CH\(_3\)), 18.0 (CH\(_3\)), 17.9 (CH(CH\(_3\))\(_2\)), 17.6 (CH(CH\(_3\))\(_2\)) ppm; \(\text{IR } \nu_{\text{max}} = 3305, 2982, 2932, 1651, 1526, 1417\) cm\(^{-1}\); MS (ES\(^+\), MeOH) \(m/z = 1147\) ([M+H\(^+\), 50 %), 1169 ([M+Na\(^+\), 100 %).

**Synthesis of Z-L-(\(\alpha\)Me)ValAib\(_4\)O'Bu**

To a stirred solution of H-Aib\(_4\)O'Bu (1.10 g, 2.65 mmol) and DIPEA (920 \(\mu\)L, 5.29 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added a solution of Z-L-(\(\alpha\)Me)Val-F (1.41 g, 5.29 mmol) in CH\(_2\)Cl\(_2\) (5 mL) and the reaction stirred at room temperature for 4 d. The mixture was diluted with CH\(_2\)Cl\(_2\) (50 mL) and washed with 5% KHSO\(_4\) solution (2 \times 20 mL), sat. NaHCO\(_3\) solution (2 \times 20 mL) and brine (20 mL). The organics were dried (MgSO\(_4\)) and concentrated under reduced pressure. Trituration of the resulting oily solid with Et\(_2\)O gave the title compound as a white solid (1.55 g, 2.34 mmol, 89%). m.p. 215-217 °C; \([\alpha]_D = + 32.0 (c = 0.5; \text{CHCl}_3)\); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta_H 7.42\) (s, 1H, NH), 7.40-7.33 (m, 5H, 5 \times ArH, Cbz), 7.30 (s, 1H, NH), 7.25 (s, 1H, NH), 6.21 (s, 1H, NH), 5.18 (d, 1H, J = 12.0, HA of AB), 5.03 (d, 1H, J = 12.0, HB of AB), 1.91 (spt, 1H, J = 7.0, CH(CH\(_3\))\(_2\)), 1.59 (s, 3H, CH\(_3\)), 1.54 (s, 3H, CH\(_3\)), 1.50 (s, 3H, CH\(_3\)), 1.47 (s, 6H, 2 \times
CH₂), 1.45 (s, 3H, CH₃), 1.42 (s, 9H, (CH₃)₃), 1.41 (s, 3H, CH₃), 1.20 (s, 3H, CH₃), 0.97 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δc 174.2 (CO), 174.1 (CO), 173.80 (CO), 173.77 (CO), 172.5 (CO), 156.1 (CO, Cbz), 136.1 (ArC), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 79.9 (C(CH₃)₃), 67.6 (CH₂, Cbz), 63.1 (C), 57.1 (C) 56.84 (C), 56.81 (C), 56.2 (C), 35.7 (CH(CH₃)₂), 27.9 ((CH₃)₃), 27.3 (CH₃), 27.02 (CH₃), 26.95 (CH₃), 25.6 (CH₃), 24.2 (CH₃), 23.9 (CH₃), 23.6 (CH₃), 23.5 (CH₃), 17.7 (CH₃), 17.4 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), ppm; IR νmax = 3319, 2980, 2938, 1730, 1702, 1668, 1643, 1530, 1456 cm⁻¹; MS (ES⁺, MeOH) m/z = 662 ([M+H]⁺, 20%), 684 ([M+Na]⁺, 100%); HRMS (ES⁺, MeOH): Calcd for C₃₄H₅₆N₅O₈ = 662.4124, found 662.4114.

**Synthesis of Z-L-(αMe)Val₂Aib₂O'Bu**

To a stirred solution of H-L-(αMe)ValAib₂O'Bu (1.21 g, 2.29 mmol; obtained in quantitative yield by hydrogenolysis of Z-L-(αMe)ValAib₂O'Bu) and DIPEA (795 μL, 4.57 mmol) in CH₂Cl₂ (15 mL) was added a solution of Z-L-(αMe)Val-F (1.22 g, 4.57 mmol) in CH₂Cl₂ (7 mL) and the reaction stirred at room temperature for 5 d. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (30 mL) and washed with 5% KHSO₄ solution (2 × 20 mL), sat. NaHCO₃ solution (2 × 20 mL) and brine (20 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (1.58 g, 2.05 mmol, 90%). m.p. 174-176 °C; [α]b = + 40.8 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.06 (s, 1H, NH), 7.79 (s, 1H, NH), 7.71 (s, 1H, NH), 7.70 (s, 1H, NH), 7.43-7.31 (m, 5H, 5 × ArH, Cbz), 5.20 (d, 1H, J = 12.5, HA of AB), 5.05 (d, 1H, J = 12.5, HB of AB), 1.93 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.58 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.493 (s, 3H, CH₃), 1.490 (s, 3H, CH₃), 1.46 (s, 9H, 3 × CH₃), 1.45 (s, 6H, 2 × CH₃), 1.44 (s, 3H, CH₃), 1.42 (s, 9H, (CH₃)₃), 1.40 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)), 0.84 (d, J = 7.0, 3H, CH(CH₃)), 0.78 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δc 177.3 (CO), 176.7 (CO), 176.3 (CO), 175.5 (CO), 175.0 (CO), 174.0 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.33 (ArCH), 129.30 (ArCH), 81.5 (C(CH₃)₃), 68.0 (CH₂, Cbz), 64.4 (C), 63.7 (C) 58.0 (C), 57.9 (C), S13
57.8 (C), 57.4 (C), 36.7 (CH(CH_3)_2), 36.5 (CH(CH_3)_2), 28.2 ((CH_3)_3), 28.1 (CH_3), 27.53 (CH_3), 27.50 (CH_3), 26.3 (CH_3), 24.0 (CH_3), 23.63 (CH_3), 23.59 (CH_3), 23.5 (CH_3), 18.8 (CH_3), 18.2 (CH_3), 17.9 (CH(CH_3)_2), 17.8 (CH(CH_3)_2), 17.5 (CH(CH_3)_2), 17.4 (CH(CH_3)_2) ppm; IR _v_max_ = 3310, 2980, 1700, 1660, 1525, 1455 cm⁻¹; MS (ES⁻, MeOH) _m/z_ = 773 ([M−H]⁻, 30%), 819 ([M+HCO_2]⁻, 100%); HRMS (ES⁺, MeOH): Calcd for C_{40}H_{67}N_6O_9 = 775.4964, found 775.4957.

**Synthesis of Z-L-(αMe)Val_2Aib_4-OH 16**

A solution of Z-L-(αMe)Val_2Aib_4O'Bu (1.53 g, 1.98 mmol) in CH_2Cl_2 (6 mL) and TFA (3 mL) was stirred at room temperature for 18 h. The solvents were removed under reduced pressure and the last traces of TFA removed by co-evaporation with Et_2O. Purification by column chromatography (SiO_2; CH_2Cl_2:MeOH; 95:5→90:10) gave the title compound as a white solid (1.33 g, 1.85 mmol, 93%). _m.p._ 217-220 °C; [α]D = +72.3 (c = 1.0; CH_2Cl_2); ^1H NMR (500 MHz, MeOD) δ_H 8.05 (s, 1H, NH), 7.82 (s, 1H, NH), 7.75 (s, 1H, NH), 7.69 (s, 1H, NH), 7.43-7.31 (m, 5H, 5 × ArH, Cbz), 7.08 (s, 1H, NH), 5.20 (d, 1H, J = 12.5, HA of AB), 5.05 (d, 1H, J = 12.5, HB of AB), 1.93 (spt, 1H, J = 7.0, CH(CH_3)_2), 1.58 (spt, 1H, J = 7.0, CH(CH_3)_2), 1.52 (s, 6H, 2 × CH_3), 1.472 (s, 3H, CH_3), 1.469 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.45 (s, 6H, 2 × CH_3), 1.44 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.00 (d, J = 7.0, 3H, CH(CH_3)), 0.94 (d, J = 7.0, 3H, CH(CH_3)), 0.84 (d, J = 7.0, 3H, CH(CH_3)), 0.79 (d, J = 7.0, 3H, CH(CH_3)) ppm; ^13C NMR (125 MHz, MeOD) δ_C 178.3 (CO), 177.4 (CO), 177.0 (CO), 176.8 (CO), 175.2 (CO), 158.3 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.34 (ArCH), 129.30 (ArCH), 68.0 (CH_2, Cbz), 64.5 (C), 63.8 (C) 58.1 (C), 58.0 (C), 57.9 (C), 36.7 (CH(CH_3)_2), 36.5 (CH(CH_3)_2), 27.7 (CH_3), 27.6 (CH_3), 27.5 (CH_3), 26.3 (CH_3), 26.2 (CH_3), 24.5 (CH_3), 23.62 (CH_3), 23.55 (CH_3), 23.5 (CH_3), 18.8 (CH_3), 18.1 (CH_3), 17.9 (CH(CH_3)_2), 17.8 (CH(CH_3)_2), 17.5 (CH(CH_3)_2), 17.4 (CH(CH_3)_2) ppm; IR _v_max_ = 3292, 2981, 1745, 1698, 1656, 1526, 1456 cm⁻¹; MS (ES⁺, MeOH) _m/z_ = 719 ([M+H]⁺, 100%), 741 ([M+Na]⁺, 20%); HRMS (ES⁺, MeOH): Calcd for C_{36}H_{59}N_6O_9 = 719.4339, found 719.4333.
Synthesis of Z-L-(αMe)Val₂Aib₄PhSer-OMe

To a stirred suspension of Z-L-(αMe)Val₂Aib₄-OH (215 mg, 0.30 mmol), HBTU (136 mg, 0.36 mmol), HOBt (67 mg, 0.45 mmol) and DIPEA (156 µL, 0.90 mmol) in CH₂Cl₂ (4 mL) was stirred at room temperature for 2 h. H-D,L-PhSer-OMe (83 mg, 0.36 mmol) was added in a single portion and the reaction stirred for an additional 18 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (30 mL) and washed with 5% KHSO₄ solution (2 x 20 mL), sat. NaHCO₃ solution (2 x 20 mL) and brine (20 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as an off-white solid (238 mg, 0.27 mmol, 89%) as an inseparable 1:1 mixture of diastereomers. m.p. 122-124 °C; [α]D = + 96.6 (c = 0.6; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 7.43-7.22 (m, 10H, 10 × ArH, Cbz + PhSer), 5.21 (m, 1.5H, HA of AB + CH(OH)), 5.14 (d, J = 5.5, 0.5H, CH(OH)), 5.06 (d, 1H, J = 12.5, HB of AB), 4.77 (d, J = 5.0, 0.5H, aCH), 4.73 (d, J = 5.5, 0.5H, aCH), 3.65 (s, 1.5H, OCH₃), 3.56 (s, 1.5H, OCH₃), 1.95 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.60 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.53-1.48 (m, 12H, 4 × C₃), 1.47-1.44 (m, 9H, 3 × CH₃), 1.41-1.31 (m, 9H, 3 × CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)₂), 0.95 (m, 3H, CH(CH₃)), 0.85 (m, 3H, CH(CH₃)), 0.80 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δC 178.2 (CO), 178.1 (CO), 178.0 (CO), 177.9 (CO), 177.7 (CO), 177.42 (CO), 177.35 (CO), 177.2 (CO), 176.61 (CO), 176.60 (CO), 175.2 (CO), 174.3 (CO), 171.94 (CO), 171.88 (CO), 158.38 (CO, Cbz), 158.37 (CO, Cbz), 141.9 (ArC), 141.2 (ArC), 138.3 (ArC), 129.6 (ArCH), 129.34 (ArCH), 129.32 (ArCH), 129.25 (ArCH), 129.14 (ArCH), 128.9 (ArCH), 128.7 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 75.2 (CHOH), 74.9 (CHOH), 68.05 (CH₂, Cbz), 68.03 (CH₂, Cbz) 64.47 (C), 64.44 (C), 63.73 (C) 63.70 (C) 61.0 (aCH), 60.3 (aCH), 58.34 (C), 58.32 (C), 58.28 (C), 58.27 (C), 58.11 (C), 58.07 (C), 57.99 (C), 57.97 (C), 52.53 (OCH₃), 52.46 (OCH₃), 36.70 (CH(CH₃)₂), 36.67 (CH(CH₃)₂), 36.51 (CH(CH₃)₂), 36.46 (CH(CH₃)₂), 27.64 (CH₃), 27.59 (CH₃), 27.5 (CH₃), 27.44 (CH₃), 27.35 (CH₃), 27.2 (CH₃), 27.1 (CH₃), 26.8 (CH₃), 24.8 (CH₃), 24.2 (CH₃), 24.0 (CH₃), 23.9 (CH₃), 23.6 (CH₃), 23.50 (CH₃), 23.47 (CH₃), 23.4 (CH₃), 18.81 (CH₃), 18.75 (CH₃), 18.2 (CH₃), 18.1 (CH₃), 17.92 (CH(CH₃)₂), 17.90 (CH(CH₃)₂), 17.52 (CH(CH₃)₂), 17.49 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; IR νmax = 3297, 2980, 1743,
Synthesis of Z-L-(αMe)Val$_2$Aib$_4$ΔPheAib$_4$O'Bu 8

A solution of Z-L-(αMe)Val$_2$Aib$_4$PhSer-OMe (235 mg, 0.26 mmol) and K$_2$CO$_3$ (144 mg, 1.04 mmol) in MeOH/H$_2$O (3:1; 4 mL) was stirred at room temperature for 18 h. The reaction was quenched with 1M HCl (5 mL), diluted with H$_2$O (5 mL) and extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organics were washed with brine (20 mL), dried (MgSO$_4$) and concentrated. The resulting white solid (220 mg, 0.25 mmol) and NaOAc (25 mg, 0.30 mmol) were suspended in Ac$_2$O (1.5 mL) and the reaction stirred at room temperature for 3 d. The solvents were removed and the residue re-dissolved in EtOAc (25 mL) and washed with 5% KHSO$_4$ solution (2 × 10 mL), sat. NaHCO$_3$ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO$_4$) and concentrated under reduced pressure to give a white solid. The crude azlactone (191 mg, 0.23 mmol) and H-Aib$_4$-O'Bu (112 mg, 0.27 mmol) were dissolved in CH$_2$Cl$_2$ (5 mL) and the mixture stirred at room temperature for 13 d. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (30 mL) and washed with 5% KHSO$_4$ solution (2 × 20 mL), sat. NaHCO$_3$ solution (2 × 20 mL) and brine (20 mL). The organics were dried (MgSO$_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:MeOH; 99:1→95:5) gave the title compound as a white solid (226 mg, 0.18 mmol, 79%).

**m.p.** 260-262 °C; [α]$_D$ = + 41.6 (c = 0.8; CHCl$_3$); **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta_{H}$ 9.00 (s, 1H, NH), 8.04 (s, 1H, NH), 7.95 (s, 1H, NH), 7.87 (s, 1H, NH), 7.79 (s, 1H, NH), 7.62 (s, 2H, 2 × NH), 7.56 (d, $J$ = 7.5, 2H, 2 × ArH, o-ΔPhe), 7.47 (s, 1H, NH), 7.41 (s, 1H, NH), 7.40-7.34 (m, 5H, 5 × ArH, Cbz), 7.30-7.27 (m, 3H, 2 × ArH + C=CH), 7.56 (m, 1H, ArH), 6.37 (s, 1H, NH), 5.47 (s, 1H, NH), 5.19 (d, $J$ = 12.0, 1 H, HA of AB, Cbz), 5.03 (d, 1H, $J$ = 12.0, HB of AB, Cbz), 1.86 (spt, 1H, $J$ = 7.0, CH(CH$_3$)$_2$), 1.65 (s, 3H, CH$_3$), 1.62-1.58 (m, 7H, 2 × CH$_3$ + CH(CH$_3$)$_2$), 1.56 (s, 3H, CH$_3$), 1.55 (s, 6H, 2 × CH$_3$), 1.521 (s, 3H, CH$_3$), 1.515 (s, 3H, CH$_3$), 1.49 (s, 9H, 3 × CH$_3$), 1.45 (m, 15H, 5 × CH$_3$), 1.41 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$), 1.06 (s, 3H, CH$_3$), 0.97 (d, $J$ = 7.0, 3H, CH(CH$_3$)), 0.95 (d, $J$ = 7.0, 3H, CH(CH$_3$)), 0.78 (m, 6H, 2 × CH(CH$_3$)) ppm; **$^{13}$C NMR** (125 MHz, CDCl$_3$) $\delta_{C}$ 176.9 (CO), 176.7 (CO), 1653, 1526, 1454 cm$^{-1}$; **MS** (ES$^+$, MeOH) $m/z$ = 897 ([M+H]$^+$, 100%); **HRMS** (ES$^+$, MeOH): Calcd for C$_{46}$$H_{70}$$N_{7}$$O_{11}$ = 896.5128, found 896.5132.
Synthesis of Z-L-PheAib₄O'Bu

To a stirred solution of Z-L-Phe-OH (57 mg, 0.19 mmol) and HOBT (34 mg, 0.23 mmol) in CH₂Cl₂ (2 mL) was added EDC (40 μL, 0.23 mmol) and the mixture stirred at room temperature for 30 min. H-Aib₄-OtBu (95 mg, 0.23 mmol) and DIPEA (40 μL, 0.23 mmol) were added and the reaction stirred for an additional 48 h. The solvents were removed under reduced pressure and the residue redissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→96:4) gave the title compound as a white solid (81 mg, 0.12 mmol, 61%). m.p. 213-215 °C; [α]D = −13.6 (c = 1.0; CHCl₃);

¹H NMR (500 MHz, CDCl₃) δH 7.38-7.27 (m, 9H, 8 × ArH + NH), 7.19 (d, J = 7.0, 2H, ArH), 7.13 (s, 1H, NH), 6.95 (s, 1H, NH), 6.21 (s, 1H, NH), 5.47 (s, 1H, NH), 5.09 (m, 2H, CH₂, Cbz), 4.11 (s, 1H, aCH), 3.14 (dd, J = 13.0, 5.0, 1H, βCH₃CH₃, Phe), 3.00 (m, 1H, βCH₃CH₃, Phe), 1.50 (s, 6H, 2 × CH₃), 1.46 (s, 6H, 2 × CH₃), 1.43 (s, 9H, (CH₃)₃), 1.41 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 1.27 (s, 3H, CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δC ¹³C NMR (126 MHz, CDCl₃) δ 174.2 (CO), 173.9 (CO), 173.5 (CO), 173.3 (CO), 171.2 (CO), 156.9 (CO, Cbz), 136.0 (ArC), 135.9 (ArC), 129.3 (ArCH), 129.2 (ArCH), 128.84 (ArCH), 128.75 (ArCH), 128.3 (ArCH), 127.6 (ArCH), 80.0 (C(CH₃)₃), 67.7 (CH₂, Cbz), 57.7 (aCH), 57.1 (C), 57.0 (C), 56.8 (C), 56.2 (C), 36.8
Synthesis of Z-D-PheAib₄O’Bu
Prepared by the same procedure described for Z-L-PheAib₄O’Bu from Z-D-Phe-OH (57 mg, 0.19 mmol). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→96:4) gave the title compound as a white solid (73 mg, 0.11 mmol, 55%). m.p. 214-216 °C; [α]D = +11.0 (c = 0.9; CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.27 (m, 9H, 8 × ArH + NH), 7.19 (d, J = 6.8, 2H, ArH), 7.10 (s, 1H, NH), 6.91 (s, 1H, NH), 6.10 (s, 1H, NH), 5.39 (d, J = 4.5, 1H, PheN), 5.10 (d, J = 12.0, 1H, HA of AB, Cbz), 5.07 (d, J = 12.0, 1H, HB of AB, Cbz), 4.09 (dd, J = 12.0, 7.0, 1H, βCH₂), 3.14 (dd, J = 14.0, 6.5, 1H, βCH₂CH₂, Phe), 3.00 (dd, J = 14.0, 8.0, 1H, βCH₂CH₂, Phe), 1.51 (s, 6H, 2 × CH₃), 1.46 (s, 6H, 2 × CH₃), 1.43 (s, 9H, (CH₃)₃), 1.42 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 1.27 (s, 3H, CH₂) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 174.2 (CO), 173.9 (CO), 173.3 (CO), 173.2 (CO), 171.1 (CO), 156.9 (CO, Cbz), 135.91 (ArC), 135.87 (ArC), 129.3 (ArCH), 129.2 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 127.7 (ArCH), 80.0 (C(CH₃)₃), 67.7 (CH₂, Cbz), 57.7 (αCH), 57.1 (C), 57.0 (C), 56.9 (C), 56.2 (C), 36.8 (βCH₂), 28.0 (C(CH₃)₃), 25.8 (CH₃), 25.5 (2 × CH₃), 25.4 (CH₃), 25.2 (CH₃), 25.0 (CH₃), 24.9 (CH₃), 24.8 (CH₃) ppm; IR νmax = 3316, 2983, 2936, 1699, 1672, 1650, 1530, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 697 ([M+H]⁺, 100%); HRMS (ES⁺, MeOH): Calcd for C₃₇H₅₃N₅NaO₈ = 718.3786, found 718.3777.

Synthesis of Z-L-(αMe)ValAib₄-OH
A solution of Z-L-(αMe)ValAib₄O’Bu (150 g, 0.23 mmol) in CH₂Cl₂ (1 mL) and TFA (1 mL) was stirred at room temperature for 18 h. The solvents were removed under reduced pressure and the last traces of TFA removed by co-evaporation with Et₂O. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 95:5→90:10) gave the title compound as a white solid (105 mg, 0.17 mmol, 76%). m.p. 232-234 °C; [α]D = +48.2 (c = 1.0;
CHCl₃); ¹H NMR (500 MHz, MeOD) δ  7.79 (s, 1H, NH), 7.67 (s, 2H, 2 × NH), 7.38-7.27 (m, 5H, 5 × ArH, Cbz), 5.18 (d, 1H, J = 12.5, HA of AB, Cbz), 5.04 (d, 1H, J = 12.5, HB of AB, Cbz), 1.97 (spt, 1H, J = 6.5, CH(CH₃)₂), 1.50 (s, 6H, 2 × CH₃), 1.46 (s, 6H, 2 × CH₃), 1.40 (s, 3H, CH₃), 1.36 (s, 3H, CH₃), 1.35 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 1.24 (s, 3H, CH₃), 0.97 (d, J = 6.5, 3H, CH(CH₃)), 0.94 (d, J = 6.5, 3H, CH(CH₃)), ppm; ¹³C NMR (125 MHz, MeOD) δC 176.5 (CO), 175.1 (CO), 174.9 (CO), 173.8 (CO), 156.1 (CO, Cbz), 136.5 (ArC), 127.8 (ArCH), 127.3 (ArCH), 126.9 (ArCH), 66.0 (CH₂, Cbz), 62.1 (C), 56.1 (C), 56.0 (C), 55.2 (C), 34.1 (CH(CH₃)₂), 25.5 (CH₃), 25.3 (CH₃), 25.1 (CH₃), 24.2 (CH₃), 23.1 (CH₃), 22.5 (CH₃), 22.4 (CH₃), 22.3 (2 × CH₃), 16.3 (CH(CH₃)₂), ppm; IR νmax = 3311, 2987, 2937, 1725, 1707, 1648, 1529, 1445 cm⁻¹; MS (ES⁺, MeOH) m/z = 607 ([M+H]⁺, 100%); HRMS (ES⁺, MeOH): Calcd for C₃₀H₄₇N₅NaO₈ = 628.3317, found 628.3310.

Synthesis of Z-L-(αMe)ValAib₄-L-PheAib₄O'Bu 9a
To a stirred solution of Z-L-(αMe)ValAib₄-OH (36 mg, 0.060 mmol) and HOBt (11 mg, 0.071 mmol) in CH₂Cl₂ (1.5 mL) was added EDC (13 μL, 0.071 mmol) and the mixture stirred at room temperature for 30 min. H-L-PheAib₄O'Bu (40 mg, 0.071 mmol; obtained in quantitative yield by hydrogenolysis of Z-L-PheAib₄O'Bu) and DIPEA (12 μL, 0.071 mmol) were added and the reaction stirred for an additional 48 h. The solvents were removed under reduced pressure and the residue redissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (42 mg, 0.037 mmol, 61%). m.p. 231-232 °C; [α]D = + 23.7 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.054 (s, 1H, NH), 8.046 (s, 1H, NH), 7.94 (s, 1H, NH), 7.85 (d, J = 7.0, 1H, NH, Phe), 7.80 (s, 1H, NH), 7.76 (s, 1H, NH), 7.71 (s, 1H, NH), 7.67 (s, 1H, NH), 7.62 (s, 1H, NH), 7.42-7.17 (m, 11H, 10 × ArH + NH), 5.22 (d, J = 13.0, 1H, HA of AB, Cbz), 5.07 (d, J = 13.0, 1H, HB of AB, Cbz), 4.35 (m, 1H, aCH), 3.32 (dd, J = 14.5, 4.0, 1H, bCH²CH³, Phe), 3.03 (dd, J = 14.5, 11.0, 1H, bCH²CH³, Phe), 2.00 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.52 (s, 3H, CH₃), 1.50 (s, 15H, 5 × CH₃), 1.46 (m, 6H, 2 × CH₃), 1.45 (s, 3H, CH₃), 1.43 (m, 15H, 2 × CH₃ + (CH₃)₃), 1.42 (s, 3H, CH₃),
1.38 (s, 3H, CH₃), 1.37 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 1.32 (s, 3H, CH₃), 1.27 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δC 178.5 (CO), 178.2 (CO), 177.7 (CO), 177.0 (CO), 176.9 (CO), 176.4 (CO), 175.9 (CO), 175.6 (CO), 174.1 (CO), 174.0 (CO), 158.2 (CO, Cbz), 139.2 (ArC), 138.7 (ArC), 130.1 (ArCH), 129.6 (ArCH), 129.4 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 127.6 (ArCH), 81.5 (C(CH₃)₃), 67.7 (CH₂, Cbz), 64.0 (C), 58.2 (C), 58.1 (C), 58.0 (C), 57.93 (C), 57.89 (C), 57.8 (C), 57.7 (αCH), 57.5 (C), 36.7 (βCH₂), 35.8 (CH(CH₃)₂), 28.2 (C(CH₃)₃), 27.1 (CH₃), 26.9 (CH₃), 26.5 (CH₃), 26.2 (CH₃), 25.8 (CH₃), 25.5 (CH₃), 25.1 (CH₃), 25.0 (CH₃), 24.9 (CH₃), 24.4 (CH₃), 24.1 (CH₃), 23.9 (CH₃), 23.1 (CH₃), 18.2 (CH(CH₃)₂), 18.0 (CH₃), 17.7 (CH(CH₃)₂) ppm; IR νmax = 3305, 2982, 2930, 1651, 1526, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1150 ([M+H]⁺, 100%)

**Synthesis of Z-L-(αMe)ValAib₄-D-PheAib₄O'Bu 9b**

Prepared by the same procedure described for 9a from Z-L-(αMe)ValAib₄-OH (36 mg, 0.060 mmol) and H-D-PheAib₄O'Bu (43 mg, 0.077 mmol; obtained in quantitative yield by hydrogenolysis of Z-D-PheAib₄O'Bu). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (60 mg, 0.052 mmol, 87%). m.p. 234-235 °C; [α]D = + 49.1 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.01 (s, 1H, NH), 7.74 (s, 1H, NH), 7.71 (s, 1H, NH), 7.43-7.29 (m, 5H, 5 × ArH), 7.27-7.12 (m, 5H, 5 × ArH), 5.19 (d, J = 12.5, 1H, HA of AB, Cbz), 5.09 (d, J = 12.5, 1H, HB of AB, Cbz), 4.18 (dd, J = 10.5, 5.0, 1H, βCH), 3.32 (1H, m, βCH₃CHβ, Phe; overlapping with MeOD), 3.15 (dd, J = 14.0, 10.5, 1H, βCH₃CHβ, Phe), 2.07 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.52 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 1.48-1.46 (m, 15H, 5 × CH₃), 1.45 (s, 9H, 3 × CH₃), 1.44 (s, 9H, (CH₃)₃), 1.40 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.374 (s, 3H, CH₃), 1.366 (s, 3H, CH₃), 1.33 (s, 3H, CH₃), 1.28 (s, 3H, CH₃), 1.23 (s, 3H, CH₃), 0.99 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δC 178.2 (CO), 178.1 (CO), 177.1 (CO), 177.0 (CO), 176.7 (CO), 176.6 (CO), 176.4 (CO), 176.0 (CO), 175.6 (CO), 173.7 (CO), 158.1 (CO, Cbz), 139.5 (ArC), 138.6 (ArC), 130.3 (ArCH), 129.6 (ArCH), 129.4 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 127.6 (ArCH), 81.5 (C(CH₃)₃), 67.7 (CH₂, Cbz), 63.8 (C), 58.04 (C), 57.98 (C), 57.96 (C), 57.94 (C), 57.90 (C), 57.68 (2 × C), 57.65 (αCH), 57.49 (C), 36.7 (βCH₂), 35.8

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(CH(CH$_3$)$_3$), 28.2 (C(CH$_3$)$_3$), 26.3-26.0 (3 × CH$_3$), 25.6 (CH$_3$), 25.1-24.6 (4 × CH$_3$), 18.2 (CH$_3$), 18.0 (CH(CH$_3$)$_2$), 17.7 (CH(CH$_3$)$_2$) ppm; IR $\nu_{\text{max}}$ = 3293, 2982, 2936, 1655, 1530, 1455 cm$^{-1}$; MS (ES$^+$, MeOH) $m/z$ = 1150 ([M+H]$^+$, 100%).

**Synthesis of Z-L-(αMe)Val$_2$Aib$_4$-L-PheAib$_4$O’Bu 10a**

To a stirred solution of Z-L-(αMe)Val$_2$Aib$_4$-OH (31 mg, 0.043 mmol) and HOBT (8 mg, 0.056 mmol) in CH$_2$Cl$_2$ (1 mL) was added EDC (9 μL, 0.051 mmol) and the mixture stirred at room temperature for 30 min. H-L-PheAib$_4$O’Bu (48 mg, 0.086 mmol; obtained in quantitative yield by hydrogenolysis of Z-L-PheAib$_4$O’Bu) and DIPEA (15 μL, 0.086 mmol) were added and the reaction stirred for an additional 72 h. The solvents were removed under reduced pressure and the residue redissolved in EtOAc (15 mL) and washed with 5% KHSO$_4$ solution (2 × 10 mL), sat. NaHCO$_3$ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO$_4$) and concentrated. Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:MeOH; 99:1→95:5) gave the title compound as a white solid (43 mg, 0.034 mmol, 80%). *m.p.* 250-252 °C; [α]$_D$ = +37.3 (c = 0.4; CHCl$_3$); 

$^1$H NMR (500 MHz, MeOD) $\delta_{H}$ 8.09 (s, 1H, NH), 8.05 (s, 1H, NH), 7.85 (s, 1H, NH), 7.77 (s, 1H, NH), 7.72 (s, 1H, NH), 7.68 (s, 1H, NH), 7.43-7.31 (m, 7H, 7 × ArH), 7.25-7.17 (m, 3H, 3 × ArH), 5.21 (d, $J$ = 12.5, 1H, HA of AB, Cbz), 5.06 (d, $J$ = 12.5, 1H, HB of AB, Cbz), 4.38 (dd, $J$ = 10.0, 3.5, 1H, $\alpha$CH), 3.38 (dd, $J$ = 14.5, 3.5, 1H, $\beta$CH$_2$CH$_2$Phe), 3.02 (m, 1H, $\beta$CH$_2$CH$_2$Phe), 1.94 (spt, 1H, $J$ = 6.5, CH(CH$_3$)$_2$), 1.59 (spt, 1H, $J$ = 6.5, CH(CH$_3$)$_2$), 1.59-1.49 (m, 24H, 8 × C(CH$_3$)$_3$), 1.46 (m, 15H, 5 × CH$_3$), 1.43 (s, 15H, 2 × CH$_3$ + (CH$_3$)$_3$), 1.41 (s, 6H, 2 × CH$_3$), 1.33 (s, 3H, CH$_3$), 1.00 (d, $J$ = 6.5, 3H, CH(CH$_3$)), 0.95 (d, $J$ = 6.5, 3H, CH(CH$_3$)), 0.86 (d, $J$ = 6.5, 3H, CH(CH$_3$)), 0.80 (d, $J$ = 6.5, 3H, CH(CH$_3$)) ppm; $^{13}$C NMR (125 MHz, MeOD) $\delta_{C}$ 178.5 (CO), 178.2 (CO), 177.8 (CO), 177.7 (CO), 177.4 (CO), 176.7 (CO), 176.4 (CO), 175.6 (CO), 175.3 (CO), 174.4 (CO), 174.0 (CO), 158.4 (CO, Cbz), 139.2 (ArC), 138.3 (ArC), 130.1 (ArCH), 129.6 (ArCH), 129.4 (ArCH), 129.3 (ArCH), 127.7 (ArCH), 81.5 (C(CH$_3$)$_3$), 68.1 (CH$_2$, Cbz), 64.5 (C), 63.8 (C), 58.09 (C), 58.05 ($\alpha$CH), 57.9 (C), 57.8 (C), 57.5 (C), 37.7 ($\beta$CH$_2$), 36.7 (CH(CH$_3$)$_2$), 36.5 (CH(CH$_3$)$_2$), 28.2 (C(CH$_3$)$_3$), 27.65 (CH$_3$), 27.60 (CH$_3$), 27.56 (CH$_3$), 27.5 (CH$_3$), 27.4 (CH$_3$), 27.3 (CH$_3$), 26.7 (CH$_3$), 26.4 (CH$_3$), 26.0 (CH$_3$), 25.6 (CH$_3$), 24.9 (CH$_3$), 24.8 (CH$_3$), 23.8 (CH$_3$), 23.7 (CH$_3$), 23.5 (CH$_3$), 23.4 (CH$_3$), 18.7 (CH$_3$), 18.1
(CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; IR νₘₐₓ = 3306, 2981, 2936, 1651, 1526, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1263 ([M+H]⁺, 100%).

**Synthesis of Z-L-(αMe)Val₂Aib₄-D-PheAib₄O’Bu 10b**

Prepared by the same procedure described for 10a from Z-L-(αMe)Val₂Aib₄-OH (31 mg, 0.043 mmol) and H-D-PheAib₄O’Bu (48 mg, 0.086 mmol; obtained in quantitative yield by hydrogenolysis of Z-D-PheAib₄O’Bu). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (44 mg, 0.035 mmol, 82%). m.p. 251-253 °C; [α]_D = + 70.6 (c = 0.8; CHCl₃); ¹H NMR (500 MHz, MeOD) δ_H 7.96 (s, 1H, NH), 7.76 (s, 1H, NH), 7.71 (s, 1H, NH), 7.43-7.32 (m, 6H, 5 × ArH + NH), 7.26-7.16 (m, 5H, 5 × ArH + NH), 5.20 (d, J = 12.5, 1H, HA of AB, Cbz), 5.06 (d, J = 12.5, 1H, HB of AB, Cbz), 4.13 (dd, J = 10.0, 5.0, 1H, ⁶CH₂), 3.29 (1H, m, ¹⁰CH⁴CH₂, Phe; overlapping with MeOD), 3.15 (dd, J = 14.0, 10.5, 1H, ¹⁰CH⁴CH₂, Phe), 1.94 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.60 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.53 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.49 (s, 6H, 2 × CH₃), 1.47 (s, 9H, 3 × CH₃), 1.46 (s, 9H, 3 × CH₂), 1.44 (s, 12H, CH₃ + (CH₃)₃), 1.42-1.41 (m, 9H, 3 × CH₃), 1.40-1.38 (m, 9H, 3 × CH₂), 1.26 (s, 3H, CH₃), 0.99 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.79 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δ_C 178.1 (CO), 177.56 (CO), 177.55 (CO), 177.2 (CO), 177.1 (CO), 176.6 (CO), 176.4 (CO), 175.6 (CO), 175.2 (CO), 174.3 (CO), 173.6 (CO), 158.4 (CO, Cbz), 139.6 (ArC), 138.3 (ArC), 130.4 (ArCH), 129.6 (ArCH), 129.4 (ArCH), 129.3 (ArCH), 127.5 (ArCH), 81.5 (C(CH₃)₃), 68.0 (CH₂, Cbz), 64.4 (C), 63.7 (C), 58.0 (C), 57.94 (C), 57.91 (C), 57.86 (C), 57.8 (C), 57.7 (C), 57.64 (C), 57.5 (C), 57.4 (⁶CH), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 36.3 (¹⁰CH₂), 28.2 (C(CH₃)₃), 27.4 (CH₃), 27.2 (CH₃), 27.10 (CH₃), 27.06 (CH₃), 26.8 (CH₃), 26.6 (CH₃), 25.8 (CH₃), 24.6 (CH₃), 24.4 (CH₃), 24.3 (CH₃), 24.2 (CH₃), 24.0 (CH₃), 23.7 (CH₃), 23.5 (CH₃), 18.7 (CH₃), 18.2 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.5 (CH(CH₃)₂) ppm; IR νₘₐₓ = 3293, 2981, 2938, 1733, 1652, 1530, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1263 ([M+H]⁺, 100%).
**Typical procedure for the hydrogenation of ΔPhe-containing peptides**

A solution of Z-L-(αMe)Val₂Aib₄ΔPheAib₄O'Bu 8 (20 mg, 0.016 mmol) and Crabtree’s catalyst ((1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)-iridium(I) hexafluorophosphate; 2 mg, 10% w/w) in anhydrous CH₂Cl₂ was stirred under an atmosphere of H₂ at room temperature for 48 h. The mixture was filtered through a plug of SiO₂ (eluting with CH₂Cl₂) and the filtrate concentrated under vacuum giving a yellow oily solid as a >95:5 mixture of diastereomers (See ¹H NMR expansion; Section 4).

**Synthesis of Z-L-(αMe)Val₂Aib₄-NHAllyl 11**

To a stirred solution of Z-L-(αMe)₂ValAib₄-OH (144 mg, 0.20 mmol) and HOBt (44 mg, 0.30 mmol) in CH₂Cl₂ (2.5 mL) was added EDC (55 μL, 0.30 mmol) and the mixture stirred at room temperature for 30 min. Allylamine (45 μL, 0.60 mmol) was added and the reaction stirred for an additional 18 h. The solvents were removed under reduced pressure and the residue redissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (142 mg, 0.19 mmol, 94%). m.p. 197-199 °C; [α]D = + 43.6 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.06 (s, 1H, NH), 8.01 (s, 1H, NH), 7.77 (s, 1H, NH), 7.42-7.30 (m, 5H, 5 × ArH, Cbz), 5.86 (app. ddt, J = 17.0, 10.5, 5.0, 1H, NHCH₂CH=CH₂), 5.24 (dd, J = 17.0, 1.5, 1H, NHCH₂CH=CH₂), 5.20 (d, 1H, J = 12.5, HA of AB, Cbz), 5.07-5.03 (m, 2H, NHCH₂CH=CH₂+ HB of AB, Cbz), 3.89 (dd, J = 16.0, 5.0, 1H, NHCH₂CH=CH₂), 3.77 (dd, J = 16.0, 5.1, 1H, NHCH₂CH=CH₂), 1.94 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.59 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.55 (s, 3H, CH₃), 1.52 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 1.441 (s, 3H, CH₃), 1.437 (s, 6H, 2 × CH₃), 1.41 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.79 (d, J = 7.0, 3H, CH(CH₃)) ppm;¹³C NMR (125 MHz, MeOD) δC 178.0 (CO), 177.5 (CO), 177.4 (CO), 177.0 (CO), 175.2 (CO), 174.7 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 135.6 (NHCH₂CH=CH₂), 129.6 (ArCH), 129.3 (ArCH), 115.7 (NHCH₂CH=CH₂), 68.0 (CH₂, Cbz), 64.5 (C), 63.7 (C) 58.4 (C), 58.2 (C), 58.1 (C), 58.0 (C), 57.9 (C), 42.8
(NHCH₂CH=CH₂), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 28.2 (CH₃), 27.5 (CH₃), 27.3 (CH₃), 24.0 (CH₃), 23.6 (CH₃), 23.5 (CH₃), 18.8 (CH₃), 18.1 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; IR 𝜈ₘₚₓ = 3304, 2981, 1654, 1526, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 758 ([M+H]+, 10%), 780 ([M+Na]+, 100%); HRMS (ES⁺, MeOH): Calcd for C₃₉H₆₄N₇O₈ = 758.4811, found 758.4809.

**Synthesis of Z-L-(αMe)Val₂Aib₄-NHCH=CHCH₃ 12**

A stirred solution of Z-L-(αMe)Val₂Aib₄-NHAllyl (132 mg, 0.17 mmol) and carbonylchlorohydridotris(triphenylphosphine)ruthenium (17 mg, 0.017 mmol) in THF (2 mL) was heated at reflux for 19 h. The solvents were removed under reduced pressure and the residue purified by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) to give the title compound as a white solid (126 mg, 0.166 mmol, 96%) as an inseparable 2:1 mixture of E:Z isomers. m.p. 211-213 °C; [α]D = +24.3 (c = 1.0; CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δH 8.95 (d, J = 10.0, 0.66H, NHCH=CHCH₃; E), 8.55 (d, J = 10.0, 0.34H, NHCH=CHCH₃; Z), 7.74 (s, 1H, NH), 7.56 (s, 1H, NH), 7.40 (s, 1H, NH), 7.39-7.35 (m, 5H, 5 × ArH, Cbz), 6.76 (dd, J = 13.0, 11.0, 0.66H, NHCH=CHCH₃; E), 6.76 (dd, J = 10.0, 9.0, 0.34H, NHCH=CHCH₃; Z), 6.37 (s, 0.66H, NH; E), 6.35 (s, 0.34H, NH; Z), 5.51 (dq, J = 13.5, 6.5, 0.66H, NHCH=CHCH₃; E), 5.34 (s, 0.66H, NH; E), 5.31 (s, 0.34H, NH; Z), 5.18 (d, 1H, J = 12.0, HA of AB, Cbz), 5.02 (d, 1H, J = 12.0, HB of AB, Cbz), 4.78 (m, 0.34H, NHCH=CHCH₃; Z), 1.87 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.81 (dd, J = 7.0, 1.5, 1H, NHCH=CHCH₃; Z), 1.66-1.58 (m, 7H, 2 × CH₃ + NHCH=CHCH₃; E), 1.54-1.43 (m, 22H, 7 × CH₃ + CH(CH₃)₂), 1.40 (s, 3H, CH₃), 0.99 (d, J = 7.0, 3H, CH(CH₃)), 0.96 (d, J = 7.0, 3H, CH(CH₃)), 0.79 (d, J = 7.0, 3H, CH(CH₃)), 0.77 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, CDCl₃) δC 176.0 (CO), 175.1 (CO), 174.7 (CO), 173.8 (CO), 172.9 (CO), 172.4 (CO), 156.4 (CO, Cbz), 135.8 (ArC), 128.9 (ArCH), 128.7 (ArCH), 124.7 (NHCH=CHCH₃; E), 123.2 (NHCH=CHCH₃; Z), 107.5 (NHCH=CHCH₃; E), 106.9 (NHCH=CHCH₃; Z), 67.9 (CH₂, Cbz), 63.6 (C), 62.5 (C), 57.1 (C), 57.0 (C), 56.9 (C), 56.8 (C), 36.2 (CH(CH₃)₂), 35.9 (CH(CH₃)₂), 28.3 (CH₃), 27.5 (CH₃), 27.3 (CH₃), 27.2 (CH₃), 23.5 (CH₃), 23.1 (CH₃), 23.0 (CH₃), 22.9 (CH₃), 18.2 (CH₃), 18.1 (CH₃), 17.4 (CH(CH₃)₂), 17.3 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 17.1 (CH(CH₃)₂), 15.3 (NHCH=CHCH₃; E), 11.4 (NHCH=CHCH₃; Z) ppm; IR 𝜈ₘₚₓ = 3304,
Synthesis of (S)-2-methyl-N-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide

To a stirred solution of 2,4,6-trimethoxybenzaldehyde (392 mg, 2.00 mmol) and (S)-tert-butanesulfinamide (242 mg, 2.00 mmol) in THF (8 mL) was added titanium(IV) ethoxide (838 µL, 4.00 mmol) and the reaction heated at reflux for 4 h. The mixture was allowed to cool to room temperature and sat. NaHCO₃ solution (25 mL) and CH₂Cl₂ (50 mL) added. The biphasic solution was filtered through a pad of Celite (eluting with CH₂Cl₂) and the layers separated. The organic phase was washed with brine (50 mL) then dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; EtOAc:Petrol; 50:50→80:20) gave the title compound as a white solid (476 mg, 1.59 mmol, 80%). 

**m.p.** 159-161 °C; \([\alpha]_D = −77.1 \ (c = 1.0; \text{CHCl}_3)\); **¹H NMR** (500 MHz, CDCl₃) δH 8.91 (s, 1H, ArC=H=N), 6.12 (s, 2H, 2 × ArCH), 3.86 (s, 9H, 3 x OC₃H₃), 1.24 (s, 9H, (C₃H₃)₃) ppm; **¹³C NMR** (125 MHz, CDCl₃) δC 164.8 (ArC), 162.3 (ArC), 156.2 (ArCH=N), 106.3 (ArC), 90.6 (ArCH), 57.2 (C(CH₃)₃), 56.1 (OCH₃), 55.6 (OCH₃), 22.6 ((CH₃)₃) ppm; **IR** νmax = 3010, 2980, 1950, 1586, 1457 cm⁻¹; **MS** (ES⁺, CH₂Cl₂) m/z = 300 ([M+H]⁺, 100%), 322 ([M+Na]⁺, 10%); **HRMS** (ES⁺, CH₂Cl₂): Calcd for C₁₄H₂₂NO₄S = 300.1265, found 300.1263.

Synthesis of (R)-2-methyl-N-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide

Prepared by the same procedure described for (S)-2-methyl-N-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide from 2,4,6-trimethoxybenzaldehyde (392 mg, 2.00 mmol) and (R)-tert-butanesulfinamide (242 mg, 2.00 mmol). Purification by column chromatography (SiO₂; EtOAc:Petrol; 50:50→80:20) gave the title compound as a white solid (445 mg, 1.49 mmol, 74%). **m.p.** 163-165 °C; \([\alpha]_D = +76.5 \ (c = 1.0; \text{CHCl}_3)\); **¹H NMR** (500 MHz, CDCl₃) δH 8.90 (s, 1H, ArC=H=N), 6.11 (s, 2H, 2 × ArCH), 3.86 (s, 9H, 3 x OCH₃), 1.24 (s, 9H, (CH₃)₃) ppm; **¹³C NMR** (125 MHz, CDCl₃) δC 164.7 (ArC), 162.2 (ArC), 156.1 (ArCH=N), 106.1 (ArC), 90.4 (ArCH), 57.1 (C(CH₃)₃), 56.0 (OCH₃), 55.5 (OCH₃), 22.4 ((CH₃)₃) ppm; **IR** νmax = 3010, 2980, 1950, 1586, 1457 cm⁻¹;
Synthesis of (S)-2-methyl-N-((R)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfinamide

To a stirred solution of (S)-2-methyl-N-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide (299 mg, 1.00 mmol) in CH$_2$Cl$_2$ (6 mL) at −78 °C was added ethylmagnesium bromide (3M in Et$_2$O; 666 µL, 2.00 mmol) dropwise and the mixture stirred at −78 °C for 5 h. The reaction was allowed to warm to room temperature, quenched by the addition of sat. NH$_4$Cl (5 mL) and diluted with CH$_2$Cl$_2$ (10 mL) and sat. NH$_4$Cl (5 mL). The layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO$_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO$_2$; EtOAc:Petrol; 80:20) gave the title compound as a white solid (288 mg, 0.88 mmol, 88%) as a > 95:5 mixture of diastereoisomers. m.p. 92-93 °C; [α]$_D$ = −2.3 (c = 1.0; CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) major diastereomer: δ$_H$ 6.11 (s, 2H, 2 × ArCH), 4.75 (ddd, $J$ = 10.0, 9.0, 6.5, HNCHCH$_2$CH$_3$), 4.51 (d, $J$ = 10.5, HNCHCH$_2$CH$_3$), 3.80 (s, 3H, OC$_3$H$_3$), 3.79 (s, 6H, 2 × OC$_3$H$_3$), 2.01 (m, 1H, HNCHCH$_2$CH$_3$), 1.88 (m, 1H, HNCHCH$_2$CH$_3$), 1.08 (s, 9H, (C$_3$H$_3$)$_3$), 0.81 (t, $J$ = 7.5, HNCHCH$_2$C$_3$) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$) major diastereomer δ$_C$ 160.2 (ArC), 111.8 (ArC), 91.1 (ArCH), 55.9 (OCH$_3$), 55.7 (C(CH$_3$)$_3$), 55.4 (OCH$_3$), 55.0 (HNCHCH$_2$CH$_3$), 30.3 (HNCHCH$_2$CH$_3$), 22.6 ((CH$_3$)$_3$), 11.4 (HNCHCH$_2$CH$_3$) ppm; IR $\nu_{\text{max}}$ = 3306, 2969, 1589, 1496, 1461 cm$^{-1}$; MS (ES$^+$, CH$_2$Cl$_2$) $m/z$ = 330 ([M+H]$^+$, 50%), 352 ([M+Na]$^+$, 100%); HRMS (ES$^+$, CH$_2$Cl$_2$): Calcd for C$_{16}$H$_{27}$NNaO$_4$S = 352.1554, found 352.1555.

Synthesis of (R)-2-methyl-N-((S)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfinamide

Prepared by the same procedure described for (S)-2-methyl-N-((R)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfinamide from (R)-2-methyl-N-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide (299 mg, 1.00 mmol) and ethylmagnesium bromide (3M in Et$_2$O; 666 µL, 2.00 mmol). Purification by column chromatography
(SiO$_2$; EtOAc:Petrol; 80:20) gave the title compound as a white solid (285 mg, 0.87 mmol, 87%) as a > 95:5 mixture of diastereoisomers. m.p. 94-96 °C; [$\alpha$]$_D$ = + 1.2 (c = 1.0; CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) major diastereomer: $\delta$H 6.11 (s, 2H, 2 × ArCH), 4.75 (ddd, J = 10.0, 9.0, 6.5, HNCHCH$_2$CH$_3$), 4.53 (d, J = 10.5, HNCHCH$_2$CH$_3$), 3.80 (s, 3H, OCH$_3$), 3.79 (s, 6H, 2 × OCH$_3$), 2.01 (m, 1H, HNCHCH$_2$CH$_3$), 1.88 (m, 1H, HNCHCH$_2$CH$_3$), 1.08 (s, 9H, (CH$_3$)$_3$), 0.81 (t, J = 7.5, HNCHCH$_2$CH$_3$) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$) major diastereomer $\delta$C 160.1 (ArC), 111.7 (ArC), 91.0 (ArCH), 55.8 (OCH$_3$), 55.7 (C(CH$_3$)$_3$), 55.4 (OCH$_3$), 30.3 (HNCHCH$_2$CH$_3$), 22.6 ((CH$_3$)$_3$), 11.4 (HNCHCH$_2$CH$_3$) ppm; IR $\nu_{\text{max}}$ = 3306, 2969, 1589, 1496, 1461 cm$^{-1}$; MS (ES$^+$, CH$_2$Cl$_2$) m/z = 330 ([M+H]$^+$, 50%), 352 ([M+Na]$^+$, 100%); HRMS (ES$^+$, CH$_2$Cl$_2$): Calcd for C$_{16}$H$_{27}$NNaO$_4$S = 352.1554, found 352.1555.

**Synthesis of (R)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (R)-15**

To a stirred solution of (S)-2-methyl-N-[(R)-1-(2,4,6-trimethoxyphenyl)propyl]propane-2-sulfinamide (250 mg, 0.76 mmol) in anhydrous MeOH (3.8 mL) was added HCl (2M in Et$_2$O; 3.8 mL, 7.60 mmol) and the reaction stirred at room temperature for 18 h. The solvents were removed under reduced pressure and the residue redissoved in 1M HCl (20 mL) and washed with Et$_2$O (2 × 15 mL). The aqueous layer was basified to pH = 13 by the addition of 2M NaOH and extracted with Et$_2$O (3 × 20 mL). The combined organics were washed with brine (20 mL), dried (MgSO$_4$) and concentrated to give the title compound as a yellow oil (155 mg, 0.69 mmol, 91%). [$\alpha$]$_D$ = − 2.9 (c = 1.0; CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.12 (s, 2H, 2 × ArCH), 4.22 (t, J = 7.5, H$_2$NCHCH$_2$CH$_3$), 3.80 (s, 3H, OCH$_3$), 3.78 (s, 6H, 2 × OCH$_3$), 1.89 (br s, 2H, NH$_2$), 1.77 (m, 2H, H$_2$NCHCH$_2$CH$_3$), 0.81 (t, J = 7.5, H$_2$NCHCH$_2$CH$_3$) ppm; $^{13}$C NMR (125 MHz, MeOD) $\delta$C 159.7 (ArC), 159.0 (ArC), 114.9 (ArC), 91.1 (ArCH), 55.7 (OCH$_3$), 55.4 (OCH$_3$), 49.0 (HNCHCH$_2$CH$_3$), 30.0 (HNCHCH$_2$CH$_3$), 11.8 (HNCHCH$_2$CH$_3$) ppm; IR $\nu_{\text{max}}$ = 3378, 2959, 2837, 1607, 1591, 1461 cm$^{-1}$; MS (ES$^+$, MeOH) m/z = 209 ([M-NH$_2$]$^+$, 100%), 226 ([M+H]$^+$, 10%), 451 ([2M-H]$^+$, 40%); HRMS (ES$^+$, MeOH): Calcd for C$_{16}$H$_{19}$NNaO$_4$S = 248.1258, found 248.1248.
Synthesis of (S)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (S)-15
Prepared by the same procedure described for (R)-15 from (R)-2-methyl-N-((S)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfonamide (250 mg, 0.76 mmol) and HCl (2M in Et₂O; 3.8 mL, 7.60 mmol) to give the title compound as a yellow oil (152 mg, 0.68 mmol, 89%). [α]D = +2.5 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 6.12 (s, 2H, 2 × ArCH), 4.22 (t, J = 7.5, H₂NCH₂CH₂CH₃), 3.80 (s, 3H, OCH₃), 3.78 (s, 6H, 2 × OCH₃), 1.93 (br s, 2H, NH₂), 1.77 (m, 2H, H₂NCH₂CH₂CH₃), 0.81 (t, J = 7.5, H₂NCH₂CH₂CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δC 159.7 (ArC), 159.0 (ArC), 114.9 (ArC), 91.1 (ArCH), 55.7 (OCH₃), 55.4 (OCH₃), 49.0 (HNCH₂CH₂CH₃), 30.0 (HNCH₂CH₂CH₃), 11.8 (HNCH₂CH₂CH₃) ppm; IR ν max = 3376, 2959, 2836, 1607, 1591, 1464 cm⁻¹; MS (ES⁺, MeOH) m/z = 209 ([M-NH₂]⁺, 100%), 226 ([M+H]⁺, 10%), 451 ([2M-H]⁺, 40%); HRMS (ES⁺, MeOH): Calcd for C₁₂H₁₀N₂NaO₃ = 248.1258, found 248.1257.

Synthesis of Z-L-(αMe)Val₂Aib₄-(R)-N-(1-(2,4,6-trimethoxyphenyl)propyl)amide 14a
To a stirred solution of Z-L-(αMe)Val₂Aib₄-OH (50 mg, 0.070 mmol) and HOBt (13 mg, 0.091 mmol) in CH₂Cl₂ (1.5 mL) was added EDC (16 μL, 0.091 mmol) and the mixture stirred at room temperature for 30 min. (R)-1-(2,4,6-Trimethoxyphenyl)propan-1-amine XX (20 mg, 0.091 mmol) and DIPEA (16 μL, 0.091 mmol) were added and the reaction stirred for an additional 48 h. The solvents were removed under reduced pressure and the residue redissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (59 mg, 0.064 mmol, 91%). m.p. 122-124 °C; [α]D = +30.5 (c = 1.5; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.08 (s, 1H, NH), 8.07 (s, 1H, NH), 7.77 (s, 1H, NH), 7.73 (s, 1H, NH), 7.49 (s, 1H, NH), 7.48 (s, 1H, NH), 7.43-7.31 (m, 5H, 5 × ArH, Cbz), 6.17 (s, 2H, 2 × ArH), 5.37 (dd, 1H, J = 16.0, 8.0, NHCH(Ar)Et), 5.21 (d, 1H, J = 12.5, HA of AB, Cbz), 5.05 (d, 1H, J = 12.5, HB of AB, Cbz), 3.81 (s, 6H, 2 × OCH₃), 3.78 (s, 3H, OCH₃), 1.94 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.87 (m, 1H, CHA⁺CHB⁺CH₃), 1.74 (m, 1H, CHA⁺CHB⁺CH₃), 1.59 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.50 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 1.47 (s, 3H, CH₃),
1.46 (s, 3H, CH₃), 1.451 (s, 3H, CH₃), 1.447 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.401 (s, 3H, CH₃), 1.95 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.95 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.82 (t, J = 7.0, 3H, CH₂CH₃), 0.80 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δC 177.3 (CO), 176.9 (CO), 176.1 (CO), 174.3 (CO), 161.8 (ArC), 160.3 (ArC), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.35 (ArCH), 129.33 (ArCH), 111.5 (ArC), 92.1 (ArCH), 68.0 (CH₂, Cbz), 64.5 (C), 63.7 (C), 58.1 (C), 58.0 (2 × C), 57.9 (C), 56.3 (OCH₃), 55.7 (OCH₃), 48.1 (NHCH(Ar)Et), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 28.5 (CH₂CH₃), 28.0 (CH₃), 27.5 (CH₃), 25.7 (CH₃), 25.5 (CH₃), 23.7 (CH₃), 23.6 (2 × CH₃), 18.8 (CH₃), 18.2 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.51 (CH(CH₃)₂), 17.47 (CH(CH₃)₂), 11.5 (CH₂CH₃) ppm; IR νmax = 3314, 2972, 1658, 1607, 1522, 1456 cm⁻¹; MS (ES⁻, MeOH) m/z = 924 ([M–H]⁻, 20%), 970 ([M+HCO₂]⁻, 100%); HRMS (ES⁺, MeOH): Calcd for C₄₈H₇₆N₇O₁₁ = 926.5598, found 926.5580.

**Synthesis of Z-L-(αMe)Val₂Aib₄-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 14b**

Prepared by the same procedure described for 14a from Z-L-(αMe)Val₂Aib₄-OH (50 mg, 0.070 mmol) and (S)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (20 mg, 0.091 mmol). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (62 mg, 0.067 mmol, 96%). m.p. 133-136 °C; [α]D = +23.5 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.05 (s, 1H, NH), 7.83 (s, 1H, NH), 7.62 (s, 1H, NH), 7.54 (s, 1H, NH), 7.53 (s, 1H, NH), 7.43-7.32 (m, 5H, 5 × ArH, Cbz), 6.19 (s, 2H, 2 × ArH), 5.45 (dd, 1H, J = 17.0, 8.0, NHCH(Ar)Et), 5.20 (d, 1H, J = 12.5, HA of AB, Cbz), 5.05 (d, 1H, J = 12.5, HB of AB, Cbz), 3.80 (s, 6H, 2 × OCH₃), 3.79 (s, 3H, OCH₃), 1.93 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.78 (m, 1H, CHACHBCH₃), 1.66 (m, 1H, CHAÇH₃CHB), 1.60 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.56 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 1.47 (s, 9H, 3 × CH₃), 1.46 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 1.42 (s, 6H, 2 × CH₃), 1.39 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.95 (d, J = 7.0, 3H, CH(CH₃)), 0.86 (d, J = 7.0, 3H, CH(CH₃)), 0.82-0.79 (m, 6H, CH(CH₃) + CH₂CH₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 177.4 (CO), 177.3 (CO), 176.9 (CO), 176.1 (CO), 175.2 (CO), 174.3 (CO), 161.9 (ArC), 160.2 (ArC), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.3 (ArCH), 111.4 (ArC), 92.1 (ArCH), 68.0 (CH₂, Cbz), 64.5 (C), 63.7 (C), 58.1 (C), 58.0 (C), 57.9
(C), 57.8 (C), 56.4 (OCH₃), 55.8 (OCH₃), 47.6 (NHCH(Ar)Et), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 29.0 (CH₂CH₃), 28.2 (CH₃), 27.5 (CH₃), 27.1 (CH₃), 24.2 (CH₃), 23.6 (CH₃), 23.5 (CH₃), 23.4 (CH₃), 18.9 (CH₃), 18.2 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.50 (CH(CH₃)₂), 17.49 (CH(CH₃)₂), 17.49 (CH(CH₃)₂), 11.4 (CH₂C₃H₇) ppm; IR ν max = 3312, 2973, 1658, 1609, 1521, 1454 cm⁻¹; MS (ES⁺, MeOH) m/z = 926 ([M+H]+, 10%), 948 ([M+Na]+, 100%); HRMS (ES⁺, MeOH): Calcd for C₄₈H₇₆N₇O₁₁ = 926.5598, found 926.5605.

**Synthesis of Z-L-(αMe)Val₂Aib₄-N-(1-(2,4,6-trimethoxyphenyl)propylamide (Addition to N-acyliminium)**

To a stirred solution of Z-L-(αMe)Val₂Aib₄-NHCH=CHCH₃ (49 mg, 0.065 mmol) and 1,3,5-trimethoxybenzene (54 mg, 0.32 mmol) in anhydrous THF (320 μL) at −50 °C was added TfOH (6 μL, 0.065 mmol) and the mixture stirred at −50 °C for 17 h. The reaction was quenched at low temperature with sat. NaHCO₃ solution (1 mL) and allowed to warm to room temperature. The mixture was diluted with sat. NaHCO₃ solution (9 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organics were dried (MgSO₄) and concentrated to give a 92.7:7.3 mixture of 14a:14b (See ¹H NMR expansion; Section 4). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (50 mg, 0.054 mmol, 84%).

**Synthesis of Z-L-(αMe)Val₂Aib₄OMe 17**

To a stirred solution of Z-L-(αMe)ValAib₄-OH (180 mg, 0.25 mmol) in Et₂O/MeOH (3:2; 15 mL) was added (trimethylsilyl)diazomethane (2M in hexanes; 375 μL, 0.75 mmol) dropwise and the resulting yellow solution stirred at room temperature for 16 h. The reaction was quenched by the addition of AcOH and the solvents removed under reduced pressure. Purification by column chromatography (SiO₂; EtOAc:Petrol; 66:34→80:20) gave the title compound as a white solid (160 mg, 0.22 mmol, 87%). m.p. 186-188 °C; [α]D = + 40.9 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.05 (s, 1H, NH), 7.79 (s, 1H, NH), 7.75 (s, 2H, 2 × NH), 7.43-7.31 (5 H, m, 5 × ArH, Cbz), 7.06 (s, 1H, NH), 5.20 (d, 1H, J = 12.5, HA of AB), 5.05 (d, 1H, J = 12.5, HB of AB), 3.67 (s, 3H, OCH₃), 1.93 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.59 (spt, 1H, J = 7.0, CH(CH₃)₂), 1.50 (s,
3H, CH₃), 1.49 (s, 3H, CH₃), 1.465 (s, 3H, CH₃), 1.461 (s, 3H, CH₃), 1.454 (s, 3H, CH₃), 1.451 (s, 6H, 2 × CH₃), 1.44 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.80 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δC 177.4 (CO), 176.94 (CO), 176.91 (CO), 176.8 (CO), 175.1 (CO), 174.1 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.33 (ArCH), 129.31 (ArCH), 68.0 (CH₂, Cbz), 64.5 (C), 63.7 (C) 58.1 (C), 58.0 (C), 57.9 (C), 57.1 (C), 52.6 (OCH₃), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 27.9 (CH₃), 27.54 (CH₃), 27.50 (CH₃), 26.1 (CH₃), 24.4 (CH₃), 23.6 (CH₃), 23.48 (CH₃), 23.46 (CH₃), 18.8 (CH₃), 18.2 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; IR νmax = 3310, 2981, 1739, 1657, 1525, 1454 cm⁻¹; MS (ES⁺, MeOH) m/z = 733 ([M+H]⁺, 100%); HRMS (ES⁺, MeOH): Calcd for C₃₇H₆₁N₆O₉ = 733.4500, found 733.4502.

**Synthesis of N₃Aib₄NHAllyl 18**

To a stirred solution of N₃Aib₄-OH (150 mg, 0.39 mmol) and HOBt (87 mg, 0.59 mmol) in CH₂Cl₂ (4 mL) was added EDC (105 µL, 0.59 mmol) and the mixture stirred at room temperature for 30 min. Allylamine (88 µL, 1.17 mmol) was added and the reaction stirred for an additional 72 h. The solvents were removed under reduced pressure and the residue redissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (79 mg, 0.19 mmol, 48%). m.p. 189-191 °C; ¹H NMR (500 MHz, MeOD) δH 5.85 (ddt, J = 17.0, 10.5, 5.0, 1H, NHCH₂CH=CH₂), 5.23 (dd, J = 17.0, 1.5, 1H, NHCH₂CH=CH₂), 5.04 (dd, J = 10.5, 1.5, 1H, NHCH₂CH=CH₂), 3.77 (dt, J = 5.0, 1.5, 2H, NHCH₂CH=CH₂), 1.52 (s, 6H, 2 × CH₃), 1.51 (s, 6H, 2 × CH₃), 1.43 (s, 6H, 2 × CH₃), 1.37 (s, 6H, 2 × CH₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 177.5 (CO), 176.6 (CO), 176.3 (CO), 174.7 (CO), 135.5 (NHCH₂CH=CH₂), 115.7 (NHCH₂CH=CH₂), 64.7 (C), 58.3 (C), 57.94 (C), 57.89 (C), 42.8 (NHCH₂CH=CH₂), 26.0 (CH₃), 25.3 (CH₃), 24.8 (CH₃), 24.5 (CH₃) ppm; IR νmax = 3289, 2979, 2937, 2109, 1655, 1515, 1454 cm⁻¹; MS (ES⁺, MeOH) m/z = 367
([M−NC3H6]⁺, 100%), 424 ([M+H]⁺, 70%), 446 ([M+Na]⁺, 90%); HRMS (ES⁺, MeOH): Calcd for C19H34N7O4 = 424.2667, found 424.2669.

**Synthesis of N₃Aib₄-NHCH=CH₃**

A stirred solution of N₃Aib₄-NHAllyl (66 mg, 0.16 mmol) and carbonylchlorohydridotris(triphenylphosphine)ruthenium (15 mg, 0.016 mmol) in THF (2 mL) was heated at reflux for 18 h. The solvents were removed under reduced pressure and the residue purified by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) to give the title compound as an off-white solid (40 mg, 0.095 mmol, 61%) as an inseparable 2:1 mixture of E:Z isomers. m.p. 171-173 °C; ¹H NMR (500 MHz, CDCl₃) δH 8.70 (d, J = 10.0, 0.66H, NHCH=CHCH₃; E), 8.43 (d, J = 10.0, 0.34H, NHCH=CHCH₃; Z), 7.21 (s, 0.34H, NH), 7.08 (s, 0.66H, NH), 6.86 (s, 1H, NH), 6.72 (dd, J = 12.5, 11.5, 0.66H, NHCH=CHCH₃; E), 6.66 (dd, J = 9.5, 9.0, 0.34H, NHCH=CHCH₃; Z), 6.14 (s, 0.66H, NH; E), 6.07 (s, 0.34H, NH; Z), 5.41 (dq, J = 13.5, 6.5, 0.66H, NHCH=CHCH₃; E), 4.79 (m, 0.34H, NHCH=CHCH₃; Z), 1.75 (d, J = 7.0, 1H, NHCH=CHCH₃; Z), 1.65 (d, J = 6.5, 1H, NHCH=CHCH₃; E), 1.54-1.49 (m, 18H, 6 × CH₃), 1.44 (s, 6H, 6 × CH₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 173.4 (CO, E), 173.1 (CO, E), 173.03 (CO, Z), 172.95 (CO, Z), 172.9 (CO, Z), 172.74 (CO, E), 172.74 (CO, Z), 172.1 (CO, E), 124.5 (NHCH=CHCH₃; E), 123.0 (NHCH=CHCH₃; Z), 107.7 (NHCH=CHCH₃; E), 106.8 (NHCH=CHCH₃; Z), 64.2 (E + Z), 57.32 (C, Z), 57.27 (C, E), 57.14 (C, E), 57.07 (C, Z), 57.0 (C, Z), 56.9 (C, E), 25.85 (CH₃, Z), 25.78 (CH₃, E), 25.6 (CH₃, Z), 25.5 (CH₃, E), 25.1 (CH₃, Z), 25.0 (CH₃, E), 24.43 (CH₃, Z), 24.41 (CH₃, E), 15.2 (NHCH=CHCH₃; E), 11.2 (NHCH=CHCH₃; Z) ppm; IR νmax = 3291, 2980, 2932, 2110, 1655, 1517, 1455 cm⁻¹; MS (ES⁻, CH₂Cl₂) m/z = 458 ([M+Cl]⁻, 100%), 881 ([2M+Cl]⁻, 30%); HRMS (ES⁺, CH₂Cl₂): Calcd for C₁₉H₃₃N₇O₄ = 446.2487, found 446.2503.

**Synthesis of N₃Aib₄-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide (R)-19**

To a stirred solution of N₃Aib₄-OH (40 mg, 0.10 mmol) and HOBt (20 mg, 0.14 mmol) in CH₂Cl₂ (1.5 mL) was added EDC (24 μL, 0.14 mmol) and the mixture stirred at room temperature for 30 min. (R)-1-(2,4,6-Trimethoxyphenyl)propan-1-amine (30 mg, 0.14
mmol) and DIPEA (24 μL, 0.14 mmol) were added and the reaction stirred for an additional 72 h. The solvents were removed under reduced pressure and the residue redissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (61 mg, 0.10 mmol, 98%). m.p. 72-74 °C; [α]D = + 20.4 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 7.55 (d, 1H, J = 9.0, NHCH(Ar)Et), 6.18 (s, 2H, 2 × ArH), 5.38 (dd, 1H, J = 7.5, 8.0, NHCH(Ar)Et), 3.81 (s, 6H, 2 × OCH₃), 3.78 (s, 3H, OCH₃), 1.87 (m, 1H, CH²CH³CH₃), 1.72 (m, 1H, CH⁴CH⁵CH₃), 1.521 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.46 (s, 6H, 2 × CH₃), 1.42 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.36 (s, 3H, CH₃), 0.82 (t, 3H, J = 7.5, CH₂CH₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 176.3 (CO), 176.0 (CO), 175.5 (CO), 174.6 (CO), 161.8 (ArC), 160.3 (ArC), 111.6 (ArC), 92.1 (ArC), 64.8 (CO), 58.00 (C), 57.7 (C), 56.3 (OCH₃), 55.7 (OCH₃), 48.1 (NHCH(Ar)Et), 28.5 (CH₂CH₃), 26.2 (CH₃), 25.9 (CH₃), 25.14 (CH₃), 25.10 (CH₃), 24.9 (CH₃), 24.7 (CH₃), 24.51 (CH₃), 24.49 (CH₃), 11.5 (CH₂CH₃) ppm; IR νmax = 3335, 2974, 2936, 2111, 1651, 1608, 1592, 1513, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 592 ([M+H]⁺, 70%), 614 ([M+Na]⁺, 100%); HRMS (ES⁺, MeOH): Calcd for C₂₈H₄₆N₇O₇ = 592.3454, found 592.3463.

**Synthesis of N₃Aib₄-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide (S)-19**

Prepared by the same procedure described for (R)-19 from N₃Aib₄-OH (40 mg, 0.10 mmol) and (S)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (30 mg, 0.14 mmol). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (60 mg, 0.10 mmol, 99%). m.p. 75-77 °C; [α]D = − 22.1 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 7.55 (d, 1H, J = 9.0, NHCH(Ar)Et), 6.18 (s, 2H, 2 × ArH), 5.38 (dd, 1H, J = 16.5, 8.0, NHCH(Ar)Et), 3.81 (s, 6H, 2 × OCH₃), 3.78 (s, 3H, OCH₃), 1.87 (m, 1H, CH²CH³CH₃), 1.72 (m, 1H, CH⁴CH⁵CH₃), 1.520 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.36 (s, 3H, CH₃), 0.82 (t, 3H, J = 7.5, CH₂CH₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 176.3 (CO), 176.0 (CO), 175.5 (CO), 174.6 (CO), 161.8 (CO), 157.8 (CO), 156.3 (OCH₃), 155.7 (OCH₃), 48.1 (NHCH(Ar)Et), 28.5 (CH₂CH₃), 26.2 (CH₃), 25.9 (CH₃), 25.14 (CH₃), 25.10 (CH₃), 24.9 (CH₃), 24.7 (CH₃), 24.51 (CH₃), 24.49 (CH₃), 11.5 (CH₂CH₃) ppm; IR νmax = 3335, 2974, 2936, 2111, 1651, 1608, 1592, 1513, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 592 ([M+H]⁺, 70%), 614 ([M+Na]⁺, 100%); HRMS (ES⁺, MeOH): Calcd for C₂₈H₄₆N₇O₇ = 592.3454, found 592.3463.
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(ArC), 160.3 (ArC), 111.6 (ArC), 92.1 (ArCH), 64.8 (C), 58.00 (C), 57.98 (C), 57.7 (C),
56.3 (OCH₃), 55.7 (OCH₃), 48.1 (NHCH(Ar)Et), 28.5 (CH₂CH₃), 26.2 (CH₃), 25.9 (CH₃),
25.13 (CH₃), 25.10 (CH₃), 24.9 (CH₃), 24.7 (CH₃), 24.51 (CH₃), 24.48 (CH₃), 11.5
(CH₂CH₃) ppm; IR νmax = 3335, 2974, 2936, 2111, 1651, 1608, 1592, 1512, 1455 cm⁻¹;
MS (ES⁺, MeOH) m/z = 592 ([M+H]⁺, 100%), 614 ([M+Na]⁺, 80%); HRMS (ES⁺,
MeOH): Calcd for C₂₈H₄₆N₇O₇ = 592.3454, found 592.3453.

Synthesis of N₃Aib₄-N-(1-(2,4,6-trimethoxyphenyl)propylamide 19 (Control)

To a stirred solution of N₃Aib₄-NHCH=CHCH₃ (27 mg, 0.065 mmol), Z-L-(αMe)Val₂Aib₄OMe (47 mg, 0.065 mmol) and 1,3,5-trimethoxybenzene (54 mg, 0.32
mmol) in anhydrous THF (320 μL) at −50 °C was added TfOH (6 μL, 0.065 mmol) and
the mixture stirred at −50 °C for 20 h. The reaction was quenched at low temperature
with sat. NaHCO₃ solution (1 mL) and allowed to warm to room temperature. The
mixture was diluted with sat. NaHCO₃ solution (9 mL) and extracted with CH₂Cl₂ (3 ×
10 mL). The combined organics were dried (MgSO₄) and concentrated to give a 48:52
mixture of (R)-19:((S)-19. Analytical HPLC (Chiralcel OD-H; hexane:2-propanol:
90:10; 1.0 mL/min; 5 μL injection of a 1 mg/mL solution): (R)-19 tR = 11.05 min, (S)-19
tR = 12.11 min.

Synthesis of Z-Ac₆c-OH

Prepared by the procedure of Brimble et al.⁵ from 1-amino-1-cyclohexanecarboxylic
acid (715 mg, 5.00 mmol), benzyl chloroformate (780 μl, 5.50 mmol) and Na₂CO₃ (1.59
g, 15.00 mmol). The title compound was obtained as a white solid (1.182 g, 4.27 mmol,
85%). m.p. 156-158 °C; ¹H NMR (500 MHz, MeOD) δH 7.37-7.26 (5 H, m, 5 × ArH,
Cbz), 5.06 (s, 2H, CH₂, Cbz), 2.06 (m, 2H, 2 × CH, cyclohexyl), 1.81 (m, 2H, 2 × CH,
cyclohexyl) 1.63-1.48 (m, 5H, 5 × CH₂, cyclohexyl), 1.33 (m, 1H, CH, cyclohexyl) ppm;
¹³C NMR (125 MHz, MeOD) δC 178.5 (CO), 157.8 (CO, Cbz), 138.4 (ArC), 129.4
(ArCH), 128.9 (ArCH), 128.7 (ArCH), 67.1 (CH₂, Cbz), 60.2 (C), 33.5 (CH₂,
cyclohexyl), 26.5 (CH₂, cyclohexyl), 22.4 (CH₂, cyclohexyl) ppm; IR νmax = 3334, 3066
(br), 2938, 2857, 1719, 1662, 1529, 1456 cm⁻¹; MS (ES⁺, MeOH) m/z = 300 ([M+Na]⁺,
100%).
Synthesis of Z-Ac\textsubscript{6}cAib\textsubscript{4}O\textsubscript{t}Bu

To a stirred solution of Z-Ac\textsubscript{6}C-OH (232 mg, 0.84 mmol) and HO\textsubscript{Bt} (186 mg, 1.26 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (4.5 mL) was added EDC (222 \textmu L, 1.26 mmol) and the mixture stirred at room temperature for 1 h. H-Aib\textsubscript{4}O\textsubscript{t}Bu (231 mg, 0.56 mmol) was added and the reaction stirred for an additional 48 h. The mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (40 mL) and washed with 5\% KHSO\textsubscript{4} solution (2 \times 20 mL), sat. NaHCO\textsubscript{3} solution (2 \times 20 mL) and brine (20 mL). The organics were dried (MgSO\textsubscript{4}) and concentrated under reduced pressure. Trituration with Et\textsubscript{2}O gave the title compound as a white solid (182 mg, 0.27 mmol, 48\%). m.p. 253-255 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \delta \text{H} 7.39-7.34 (5 H, m, 5 \times ArH, Cbz), 7.33 (s, 1H, NH), 7.31 (s, 1H, NH), 7.20 (s, 1H, NH), 6.29 (s, 1H, NH), 5.36 (s, 1H, NH), 5.12 (s, 2H, CH\textsubscript{2}, Cbz), 1.90-1.83 (m, 4H, 4 \times CH, cyclohexyl), 1.73-1.64 (m, 4H, 4 \times CH, cyclohexyl), 1.51 (s, 6H, 3 \times CH\textsubscript{3}), 1.47 (s, 6H, 3 \times CH\textsubscript{3}), 1.43 (s, 9H, (CH\textsubscript{3})\textsubscript{3}), 1.42 (s, 6H, 3 \times CH\textsubscript{3}), 1.38-1.33 (m, 2H, 2 \times CH, cyclohexyl), 1.30 (s, 6H, 3 \times CH\textsubscript{3}) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta \text{C} 174.2 (CO), 174.0 (CO), 173.9 (CO), 173.8 (CO), 173.6 (CO), 155.6 (CO, Cbz), 136.1 (ArC), 128.90 (ArCH), 128.85 (ArCH), 128.4 (ArCH), 79.9 (C(CH\textsubscript{3})\textsubscript{3}), 67.6 (CH\textsubscript{2}, Cbz), 59.6 (C), 57.0 (C), 56.8 (C), 56.6 (C), 56.1 (C), 31.8 (CH\textsubscript{2}, cyclohexyl), 31.1 (CH\textsubscript{3}), 28.0 (C(CH\textsubscript{3})\textsubscript{3}), 25.7 (CH\textsubscript{3}), 25.3 (CH\textsubscript{3}), 25.2 (CH\textsubscript{3}), 25.0 (CH\textsubscript{2}, cyclohexyl), 24.9 (CH\textsubscript{3}), 21.3 (CH, cyclohexyl) ppm; IR \nu\text{max} = 3323, 3244, 2981, 2940, 1731, 1705, 1670, 1640, 1533, 1498, 1456 cm\textsuperscript{-1}; MS (ES\textsuperscript{+}, MeOH) \textit{m/z} = 674 ([M+H]\textsuperscript{+}, 80\%), 696 ([M+H]\textsuperscript{+}, 100\%); HRMS (ES\textsuperscript{+}, MeOH): Calcd for C\textsubscript{35}H\textsubscript{56}N\textsubscript{5}O\textsubscript{8} = 674.4124, found 674.4102.

Synthesis of Z-L-(\alpha Me)Val\textsubscript{2}Aib\textsubscript{4}Ac\textsubscript{6}cAib\textsubscript{4}O\textsubscript{t}Bu

A stirred solution of Z-L-(\alpha Me)Val\textsubscript{2}Aib\textsubscript{4}-OH (359 mg, 0.50 mmol) in Ac\textsubscript{2}O (3 mL) was heated at 120 °C for 3 h. The reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The last traces of Ac\textsubscript{2}O were removed by co-evaporation with anhydrous PhMe to give the crude azlactone as an off-white solid (350 mg, 0.50 mmol), which was re-dissolved in anhydrous MeCN (2 mL). H-Ac\textsubscript{6}cAib\textsubscript{4}O\textsubscript{t}Bu (270 mg, 0.50 mmol; obtained in quantitative yield by hydrogenolysis of Z-Ac\textsubscript{6}cAib\textsubscript{4}O\textsubscript{t}Bu) was added and the mixture heated at reflux for 7 d. The reaction was allowed to cool to room temperature and the solvents removed under reduced pressure.
The residual solid was re-dissolved in EtOAc (25 mL) and washed with 5% KHSO₄ solution (2 × 20 mL), sat. NaHCO₃ solution (20 mL) and brine (20 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (302 mg, 0.24 mmol, 49%). m.p. 246-248 °C; [α]D = +39.3 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.09 (s, 1H, NH), 8.00 (s, 1H, NH), 7.95 (s, 2H, 2 × NH), 7.77 (s, 1H, NH), 7.69 (s, 1H, NH), 7.68 (s, 1H, NH), 7.55 (s, 1H, NH), 7.43-7.31 (m, 5H, 5 × ArH, Cbz), 5.21 (d, J = 12.5, 1 H, HA of AB, Cbz), 5.06 (d, 1H, J = 12.5, HB of AB, Cbz), 2.33 (m, 1H, CH, cyclohexyl), 2.06 (m, 1H, CH, cyclohexyl), 1.98-1.85 (m, 3H, CH(CH₃)₂ + 2 × CH, cyclohexyl), 1.72-1.60 (m, 5H, CH(CH₃)₂ + 4 × CH, cyclohexyl), 1.56 (s, 3H, CH₃, cyclohexyl), 1.52 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 1.48 (s, 15H, 5 × CH₃), 1.47-1.46 (m, 18H, 6 × C(CH₃)₃), 1.45 (s, 3H, CH₃), 1.44 (s, 9H, (CH₃)₃), 1.42 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.38-1.32 (m, 2H, 2 × CH, cyclohexyl), 1.01 (d, J = 7.0, 3H, CH(CH₃)), 0.95 (d, J = 7.0, 3H, CH(CH₃)), 0.86 (d, J = 7.0, 3H, CH(CH₃)), 0.81 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹³C NMR (125 MHz, MeOD) δC 177.8 (CO), 177.7 (CO), 177.64 (CO), 177.56 (CO), 177.5 (CO), 176.8 (CO), 176.4 (CO), 175.6 (CO), 175.2 (CO), 174.34 (CO), 174.25 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.3 (ArCH), 81.5 (C(CH₃)₃), 68.0 (CH₂, Cbz), 64.5 (C), 63.7 (C), 60.9 (C), 58.1 (C), 58.01 (C), 57.99 (C), 57.96 (C), 57.94 (C), 57.88 (C), 57.7 (C), 57.5 (C), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 35.2 (br, CH₂, cyclohexyl), 30.1 (br, CH₂, cyclohexyl), 28.2 (C(CH₃)₃), 27.62 (CH₃), 27.56 (CH₃), 27.1 (CH₃), 26.6 (CH₂, cyclohexyl), 26.0 (CH₃), 24.4 (CH₃), 24.0 (CH₃), 23.8 (CH₃), 23.6 (CH₃), 23.5 (CH₃), 23.1 (CH₂, cyclohexyl), 22.6 (CH₂, cyclohexyl), 18.7 (CH₃), 18.2 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; IR νmax = 3302, 2980, 2935, 1656, 1526, 1447 cm⁻¹; MS (ES⁺, MeOH) m/z = 1240 ([M+H]⁺, 10%), 1257 ([M+NH₄]⁺, 100%), 1262 ([M+Na]⁺, 70%); (ES⁻, MeOH) m/z = 1238 ([M–H]⁻, 20%), 1284 ([M+HCO₃]⁻, 100%).

Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-OH 21

A solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄O’Bu (282 mg, 0.23 mmol) in CH₂Cl₂ (1 mL) and TFA (1 mL) was stirred at room temperature for 18 h. The solvents were removed.
under reduced pressure and the last traces of TFA removed by co-evaporation with Et$_2$O. Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:MeOH; 98:2→90:10) gave the title compound as a white solid (203 mg, 0.17 mmol, 75%). m.p. 243-246 °C; [α]$_D$ = + 50.2 (c = 0.9; CHCl$_3$); $^1$H NMR (500 MHz, MeOD) δ$_H$ 8.08 (s, 1H, NH), 8.00 (s, 1H, NH), 7.95 (s, 1H, NH), 7.94 (s, 1H, NH), 7.76 (s, 2H, 2 × NH), 7.69 (s, 1H, NH), 7.54 (s, 1H, NH), 7.43-7.31 (m, 5H, 5 × ArH, Cbz), 7.11 (s, 1H, NH), 5.21 (d, $J = 12.5$, 1 H, HA of AB, Cbz), 5.06 (d, 1H, $J = 12.5$, HB of AB, Cbz), 2.34 (m, 1H, C$_H$, cyclohexyl), 2.06 (m, 1H, C$_H$, cyclohexyl), 1.99-1.85 (m, 3H, C$_H$(CH$_3$)$_2$+ 2 × C$_H$, cyclohexyl), 1.71-1.60 (m, 5H, CH(CH$_3$)$_2$ + 4 × CH, cyclohexyl), 1.56 (s, 3H, CH$_3$), 1.52 (s, 6H, 2 × CH$_3$), 1.51 (s, 3H, CH$_3$), 1.50 (s, 3H, CH$_3$), 1.48-1.46 (m, 33H, 11 × CH$_3$), 1.42 (s, 3H, CH$_3$), 1.41 (s, 3H, CH$_3$), 1.38-1.32 (m, 2H, 2 × CH, cyclohexyl), 1.01 (d, $J = 7.0$, 3H, CH(CH$_3$)), 0.95 (d, $J = 7.0$, 3H, CH(CH$_3$)), 0.86 (d, $J = 7.0$, 3H, CH(CH$_3$)), 0.81 (d, $J = 7.0$, 3H, CH(CH$_3$)) ppm; $^{13}$C NMR (125 MHz, MeOD) δ$_C$ 177.8 (CO), 177.73 (CO), 177.69 (CO), 177.67 (CO), 177.6 (CO), 177.5 (CO), 177.0 (CO), 176.93 (CO), 176.87 (CO), 175.3 (CO), 174.4 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.3 (ArCH), 68.0 (CH$_2$, Cbz), 64.5 (C), 63.8 (C), 60.9 (C), 58.07 (C), 58.06 (C), 58.01 (C), 57.94 (C), 57.91 (C), 57.7 (C), 36.7 (CH(CH$_3$)$_2$), 36.5 (CH(CH$_3$)$_2$), 35.2 (CH$_2$, cyclohexyl), 29.9 (CH$_2$, cyclohexyl), 27.6 (2 × CH$_3$), 27.4 (CH$_3$), 27.2 (CH$_3$), 26.6 (CH$_2$, cyclohexyl), 25.9 (CH$_3$), 24.0 (CH$_3$), 23.7 (CH$_3$), 23.6 (CH$_3$), 23.5 (CH$_3$), 23.1 (CH$_2$, cyclohexyl), 22.6 (CH$_2$, cyclohexyl), 18.7 (CH$_3$), 18.1 (CH$_3$), 17.9 (CH(CH$_3$)$_2$), 17.8 (CH(CH$_3$)$_2$), 17.5 (CH(CH$_3$)$_2$), 17.4 (CH(CH$_3$)$_2$) ppm; IR $\nu_{\text{max}}$ = 3304, 2983, 2937, 1655, 1526, 1448 cm$^{-1}$; MS (ES$^+$, MeOH) m/z = 1201 ([M+NH$_4$]$^+$, 30%), 1206 ([M+Na]$^+$, 100%); (ES$^-$, MeOH) m/z = 1182 ([M−H]$^-$, 100%), 1228 ([M+HCO$_2$]$^-$, 50%).

**Synthesis of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-NHAllyl 24**

To a stirred solution of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-OH (183 mg, 0.15 mmol) and HOBt (34 mg, 0.23 mmol) in CH$_2$Cl$_2$ (2 mL) was added EDC (41 μL, 0.23 mmol) and the mixture stirred at room temperature for 30 min. Allylamine (35 μL, 0.46 mmol) was added and the reaction stirred for an additional 48 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (20 mL) and washed with 5% KHSO$_4$ solution (2 × 10 mL), sat. NaHCO$_3$ solution (2 × 10 mL) and brine (10 mL). The
organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (137 mg, 0.11 mmol, 73%). m.p. 237-239 °C; [α]D = + 38.4 (c = 0.25; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.09 (s, 1H, NH), 7.96 (s, 1H, NH), 7.95 (s, 1H, NH), 7.78 (s, 1H, NH), 7.70 (s, 1H, NH), 7.55 (s, 1H, NH), 7.43-7.32 (m, 5H, 5 × ArH, Cbz), 5.87 (ddt, J = 17.0, 10.5, 5.0, 1H, NHCH₂CH=CH₂), 5.25 (dd, J = 17.0, 1.5, 1H, NHCH₂CH=CH₂), 5.21 (d, J = 12.5, 1H, HA of AB, Cbz), 5.07-5.05 (m, 2H, NHCH₂CH=CH₂ + HB of AB, Cbz), 3.88 (dd, J = 16.0, 5.0, 1H, NHCH₂CH=CH₂), 2.34 (m, 1H, CH, cyclohexyl), 2.07 (m, 1H, CH, cyclohexyl), 1.98-1.86 (m, 3H, CH(CH₃)₂ + 2 × CH, cyclohexyl), 1.71-1.60 (m, 5H, CH(CH₃)₂ + 4 × CH, cyclohexyl), 1.56-1.53 (m, 9H, 3 × CH₃), 1.50 (s, 6H, 2 × CH₃), 1.49 (s, 12H, 4 × CH₃), 1.471-1.465 (m, 18H, 6 × CH), 1.44 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.39-1.32 (m, 2H, 2 × CH, cyclohexyl), 1.01 (d, J = 7.0, 3H, CH(CH₃)), 0.95 (d, J = 7.0, 3H, CH(CH₃)), 0.86 (d, J = 7.0, 3H, CH(CH₃)), 0.81 (d, J = 7.0, 3H, CH(CH₃))) ppm; ¹³C NMR (125 MHz, MeOD) δC 180.0 (CO), 177.72 (CO), 177.67 (CO), 177.63 (CO), 177.58 (CO), 177.55 (CO), 177.5 (CO), 177.4 (CO), 177.1 (CO), 175.2 (CO), 174.3 (CO), 158.4 (CO, Cbz), 138.3 (ArC), 135.6 (NHCH₂CH=CH₂), 129.6 (ArCH), 129.3 (ArCH), 115.6 (NHCH₂CH=CH₂), 68.0 (CH₂, Cbz), 64.5 (C), 63.7 (C), 60.9 (C), 58.4 (C), 58.1 (C), 57.97 (C), 57.95 (C), 57.91 (C), 57.88 (C), 57.85 (C), 57.7 (C), 42.8 (NHCH₂CH=CH₂), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 35.3 (CH₂, cyclohexyl), 30.0 (CH₂, cyclohexyl), 27.61 (CH₃), 27.55 (CH₃), 27.4 (CH₃), 27.3 (CH₃), 26.6 (CH₂, cyclohexyl), 24.6 (CH₃), 23.9 (CH₃), 23.7 (CH₃), 23.6 (CH₃), 23.5 (CH₃), 23.1 (CH₂, cyclohexyl), 22.6 (CH₂, cyclohexyl), 18.8 (CH₃), 18.2 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂) ppm; IR νmax = 3299, 2981, 2936, 1652, 1525, 1452 cm⁻¹; MS (ES⁺, MeOH) m/z = 1241 ([M+NH₄]⁺, 30%), 1246 ([M+Na]⁺, 100%); (ES⁻, MeOH) m/z = 1268 ([M+HCO₂⁻], 100%).

**Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-NHCH=CHCH₃ 27**

A stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-NHAllyl (123 mg, 0.10 mmol) and carbonylchlorohydridotrisc(triphenylphosphine)ruthenium (10 mg, 0.010 mmol) in THF (1.5 mL) was heated at reflux for 19 h. The solvents were removed under reduced
pressure and the residue purified by column chromatography (SiO2; CH2Cl2;MeOH; 99:1→95:5) to give the title compound as a white solid (109 mg, 0.089 mmol, 89%) as an inseparable 1.5:1 mixture of E:Z isomers. m.p. 249-251 °C; [α]D20 = + 41.9 (c = 0.9; CHCl3); 1H NMR (500 MHz, CDCl3) δH 8.96 (d, J = 10.0, 0.60H, NHCH=CHCH3, E), 8.55 (d, J = 10.0, 0.40H, NHCH=CHCH3, Z), 7.87 (s, 1H, NH), 7.84 (s, 1H, NH), 7.82 (s, 1H, NH), 7.78 (s, 1H, NH), 7.61 (s, 1H, NH), 7.42-7.36 (m, 7H, 2 × NH + 5 × ArH, Cbz), 6.75 (dd, J = 13.0, 11.0, 0.60H, NHCH=CHCH3, E), 6.68 (dd, J = 8.5, 8.5, 0.40H, NHCH=CHCH3, Z), 6.41 (s, 1H, NH), 5.52 (dq, J = 13.5, 6.5, 0.60H, NHCH=CHCH3, E), 5.39 (s, 1H, NH), 5.19 (d, J = 12.0, 1H, HA of AB, Cbz), 5.04 (d, J = 12.0, 1H, HB of AB, Cbz), 4.78 (m, 0.40H, NHCH=CHCH3, Z), 2.36 (m, 1H, CH, cyclohexyl), 2.01-1.85 (m, 4H, CH(CH3)2 + 3 × CH, cyclohexyl), 1.82 (dd, J = 7.0, 1.5, 1.2H, NHCH=CHCH3, Z), 1.71-1.64 (m, 3.8H, 2 × CH, cyclohexyl + NHCH=CHCH3, E), 1.62-1.55 (s, 14H, 4 × CH3 + 2 × CH, cyclohexyl), 1.53-1.46 (m, 36H, 12 × CH3), 1.45 (s, 3H, CH3), 1.40 (s, 3H, CH3), 1.37-1.27 (m, 2H, 2 × CH, cyclohexyl), 0.99 (d, J = 7.0, 3H, CH(CH3)), 0.97 (d, J = 7.0, 3H, CH(CH3)), 0.80 (d, J = 7.0, 3H, CH(CH3)), 0.79 (d, J = 7.0, 3H, CH(CH3)) ppm; 13C NMR (125 MHz, CDCl3) δC 176.4 (CO, Z), 176.33 (CO, Z), 176.25 (CO, Z), 176.11 (CO, Z), 176.10 (CO, Z), 176.03 (CO, Z), 176.01 (CO, E), 175.8 (CO, E), 175.42 (CO, E), 175.36 (CO, Z), 174.8 (CO, E), 174.7 (CO, E), 173.8 (CO, E), 172.9 (CO, E), 172.5 (CO, E), 156.3 (CO, Cbz), 135.7 (ArC), 128.7 (ArCH), 128.5 (ArCH), 124.6 (NHCH=CHCH3, E), 123.2 (NHCH=CHCH3, Z), 107.3 (NHCH=CHCH3; E), 106.7 (NHCH=CHCH3; Z), 67.7 (CH2, Cbz), 63.5 (C), 62.4 (C), 59.5 (C), 56.93 (C), 56.87 (C), 56.83 (C), 56.79 (C), 56.67 (C), 56.61 (C), 57.4 (C), 36.0 (CH(CH3)2), 35.8 (CH(CH3)2), 34.9 (CH2, cyclohexyl), 28.0 (CH2, cyclohexyl), 27.33 (CH3), 27.31 (CH3), 27.28 (CH3), 27.2 (CH3), 25.6 (CH2, cyclohexyl), 23.0 (CH3), 22.8 (CH3), 22.74 (CH3), 22.69 (CH3), 21.8 (CH2, cyclohexyl), 21.5 (CH2, cyclohexyl), 18.04 (CH3), 17.96 (CH3), 17.3 (CH(CH3)2), 17.2 (CH(CH3)2), 17.03 (CH(CH3)2), 16.98 (CH(CH3)2) 15.1 (NHCH=CHCH3, E), 11.3 (NHCH=CHCH3, Z) ppm; IR νmax = 3296, 2981, 2935, 1652, 1524, 1451 cm−1; MS (ES+, CH2Cl2) m/z = 1241 ([M+NH4]+, 100%), 1246 ([M+Na]+, 50%); (ES−, CH2Cl2) m/z = 1258 ([M+Cl]−, 100%), 1268 ([M+HCO3]−, 20%).
Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-(R)-N-(1-(2,4,6-
trimethoxyphenyl)propylamide 30

To a stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-OH (25 mg, 0.021 mmol) and 
HOBt (4 mg, 0.028 mmol) in CH₂Cl₂ (1.5 mL) was added EDC (5 μL, 0.028 mmol) and 
the mixture stirred at room temperature for 1 h. (R)-1-(2,4,6-Trimethoxyphenyl)propan-1-
amine (6 mg, 0.028 mmol) and DIPEA (5 μL, 0.028 mmol) were added and the reaction 
stirred for an additional 48 h. The solvents were removed under reduced pressure and the 
residue re-dissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 
ml), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried 
(MgSO₄) and concentrated under reduced pressure. Purification by column 
chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white 
solid (27 mg, 0.019 mmol, 92%). m.p. 180-183 °C; [α]D = + 31.6 (c = 1.0; CHCl₃); ¹H NMR 
(500 MHz, MeOD) δH 8.11 (s, 1H, NH), 8.02 (s, 1H, NH), 8.00 (s, 1H, NH), 7.97 
(s, 1H, NH), 7.81 (s, 1H, NH), 7.78 (s, 2H, 2 × NH), 7.76 (s, 1H, NH), 7.71 (s, 1H, NH), 
7.56 (s, 1H, NH), 7.50 (s, 1H, NH), 7.48 (s, 1H, NH), 7.44-7.31 (m, 5H, 5 × ArH, Cbz), 
7.15 (s, 1H, NH), 6.18 (s, 2H, 2 × ArH), 5.38 (dd, 1H, J = 16.5, 8.0, NHCH(Ar)Et), 5.21 
(d, 1H, J = 12.5, HA of AB, Cbz), 5.06 (d, 1H, J = 12.5, HB of AB, Cbz), 3.82 (s, 6H, 2 
× OCH₃), 3.78 (s, 3H, OCH₃), 2.36 (m, 1H, CH, cyclohexyl), 2.08 (m, 1H, CH, cyclohexyl), 1.98-1.83 (m, 4H, CH²CH₃, CH(CH₃)₂ + 2 × CH, cyclohexyl), 1.78-
1.59 (m, 6H, CH²CH₃, CH(CH₃)₂, + 4 × CH, cyclohexyl), 1.56 (s, 3H, CH₃), 1.50 (s, 
6H, 2 × CH₃), 1.49-1.48 (m, 27H, 9 × CH₃), 1.47 (s, 6H, 2 × CH₃), 1.44 (s, 3H, CH₃), 
1.42 (s, 3H, CH₃), 1.412 (s, 3H, CH₃), 1.408 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, 
CH(CH₃)), 0.95 (d, J = 7.0, 3H, CH(CH₃)), 0.86 (d, J = 7.0, 3H, CH(CH₃)), 0.84-0.79 (m, 
6H, CH₂CH₃ + CH(CH₃)) ppm; ¹H NMR (800 MHz, d₈-THF) δH 8.12 (s, 1H, NH), 8.08 
(s, 1H, NH), 7.98 (s, 1H, NH), 7.95 (s, 1H, NH), 7.86 (s, 1H, NH), 7.75 (s, 1H, NH), 7.58 
(s, 1H, NH), 7.444 (s, 1H, NH), 7.441 (s, 1H, NH), 7.41-7.30 (m, 5H, 5 × ArH, Cbz), 
7.27 (s, 1H, NH), 7.26 (d, J = 8.8, 1H, NHCH), 6.94 (s, 1H, NH), 6.12 (s, 2H, 2 × ArH), 
5.39 (dd, 1H, J = 7.5, 7.5, NHCH(Ar)Et), 5.17 (d, 1H, J = 12.5, HA of AB, Cbz), 5.09 (d, 
1H, J = 12.5, HB of AB, Cbz), 3.82 (s, 6H, 2 × OCH₃), 3.73 (s, 3H, OCH₃), 2.37 (m, 1H, 
CH, cyclohexyl), 2.03-1.99 (m, 4H, CH(CH₃)₂ + 3 × CH, cyclohexyl), 1.88 (m, 1H, 
CH²CH₃, CH(CH₃)₂, + 4 × CH, cyclohexyl), 1.56
Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-(S)-N-(1-(2,4,6-
trimethoxyphenyl)propylamide epi-30

Prepared by the same procedure described for 30 from Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-OH (25 mg, 0.021 mmol) and (S)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (6 mg, 0.028 mmol). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOD; 99:1→95:5) gave the title compound as a white solid (26 mg, 0.019 mmol, 89%). m.p. 175-178 °C; [α]D = + 38.0 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, MeOD) δH 8.10 (s, 1H, NH), 8.02 (s, 1H, NH), 8.00 (s, 1H, NH), 7.96 (s, 1H, NH), 7.79 (s, 2H, 2 × NH), 7.78 (s, 1H, NH), 7.69 (s, 1H, NH), 7.56 (s, 1H, NH), 7.54 (s, 1H, NH), 7.52 (s, 1H, NH), 7.44-7.32 (m, 5H, 5 × ArH, Cbz), 7.15 (s, 1H, NH), 6.19 (s, 2H, 2 × ArH), 5.45 (dd, 1H, J = 17.0, 7.5, NHCH(Ar)Et), 5.20 (d, 1H, J = 12.5, HA of AB, Cbz), 5.06 (d, 1H, J = 12.5, HB of AB, Cbz), 3.82 (s, 6H, 2 × OCH₃), 3.78 (s, 3H, OCH₃), 2.36 (m, 1H, CH, cyclohexyl), 2.09 (m, 1H, CH, cyclohexyl), 1.99-1.85 (m, 3H, CH(CH₃)₂ + 2 × CH, cyclohexyl), 1.81 (m, 1H, CH²CH₃), 1.72-1.59 (m, 6H, CH²CH₃, CH(CH₃)₂, + 4 × CH, cyclohexyl), 1.52 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 1.50-1.47 (m, 24H, 8 × CH₂), 1.46-1.45 (m, 9H, 3 × CH₂), 1.43 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.35-1.31 (m, 5H, CH₃ + 2 × CH, cyclohexyl), 1.01 (d, J = 7.0, 3H, CH(CH₃)), 0.98 (d, J = 7.0, 3H, CH(CH₃)), 0.88 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.81 (t, J = 7.5, 3H, CH₂CH₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 177.9 (CO), 177.8 (CO), 177.7 (2 × CO), 177.6 (CO), 177.1 (CO), 176.9 (CO), 176.1 (CO), 175.34 (CO), 175.25 (CO), 174.3 (CO), 161.8 (ArC), 160.3 (ArC), 158.4 (CO, Cbz), 138.3 (ArC), 129.7 (ArCH), 129.3 (ArCH), 111.4 (ArC), 92.0 (ArCH), 68.0 (CH₂, Cbz), 64.5 (C), 63.8 (C), 63.7 (C), 60.9 (C), 58.1 (C), 58.01 (C), 58.00 (C), 57.98 (C), 57.96 (C), 57.9 (C), 57.7 (C), 56.4 (OCH₃), 55.7 (OCH₃), 48.1 (NHCH(Ar)Et), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 35.4 (CH₂, cyclohexyl), 30.0 (CH₂, cyclohexyl), 28.6 (CH₂CH₃), 27.7 (CH₃), 27.5 (CH₃), 27.3 (CH₃), 27.2 (CH₃), 26.7 (CH₂, cyclohexyl), 26.0 (CH₃), 25.3 (CH₃), 24.1 (CH₃), 23.8 (CH₃), 23.5 (CH₃), 23.1 (CH₂, cyclohexyl), 22.7 (CH₂, cyclohexyl), 18.8 (CH₃), 18.1 (CH₃), 18.0 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂), 11.5 (CH₂CH₃) ppm; IR νmax = 3298, 2933, 1652, 1610, 1525, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1392 ([M+H]⁺, 100%); 1414 ([M+Na]⁺, 80%).
1.58 (s, 3H, CH₃), 1.56 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 1.49-1.48 (m, 2H, 2 x CH), 1.47 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.413 (s, 3H, CH₃), 1.408 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.34-1.26 (m, 2H, 2 x CH, cyclohexyl), 1.01 (d, J = 7.0, 3H, CH(CH₃)), 0.95 (d, J = 7.0, 3H, CH(CH₃)), 0.86 (d, J = 7.0, 3H, CH(CH₃)), 0.82 (t, J = 7.5, 3H, CH₂CH₃), 0.80 (d, J = 7.0, 3H, CH(CH₃)) ppm; \(^1\)H NMR (800 MHz, d₈-THF) δ H 8.14 (s, 1H, NH), 8.08 (s, 1H, NH), 8.01 (s, 1H, NH), 7.96 (s, 1H, NH), 7.86 (s, 1H, NH), 7.68 (s, 1H, NH), 7.58 (s, 1H, NH), 7.51 (s, 1H, NH), 7.41-7.28 (m, 8H, 3 x NH + 5 x ArH, Cbz), 7.02 (s, 1H, NH), 6.13 (s, 2H, 2 x ArH), 5.45 (dd, 1H, J = 17.0, 7.5, NHCH(Ar)Et), 5.16 (d, 1H, J = 12.5, HA of AB, Cbz), 5.10 (d, 1H, J = 12.5, HB of AB, Cbz), 3.81 (s, 6H, 2 x OCH₃), 3.73 (s, 3H, OCH₃), 2.39 (m, 1H, CH, cyclohexyl), 2.05-1.97 (m, 4H, CH(CH₃)₂ + 3 x CH, cyclohexyl), 1.81 (m, 1H, CH₂CH₂CH₃), 1.67-1.60 (m, 6H, CH₂CH₂CH₃, CH(CH₃)₂, + 4 x CH, cyclohexyl), 1.56 (s, 3H, CH₃), 1.52-1.51 (m, 9H, 3 x CH₃), 1.49-1.46 (m, 30H, 10 x CH₃), 1.45 (m, 9H, 3 x CH₃), 1.36 (s, 3H, CH₃), 1.35-1.25 (m, 2H, 2 x CH, cyclohexyl), 1.02 (d, J = 7.0, 3H, CH(CH₃)), 0.98 (d, J = 7.0, 3H, CH(CH₃)), 0.88 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.79 (t, J = 7.5, 3H, CH₂CH₃) ppm; \(^13\)C NMR (125 MHz, MeOD) δ C 177.9 (CO), 177.8 (CO), 177.7 (2 x CO), 177.5 (CO), 177.3 (CO), 176.9 (CO), 176.1 (CO), 175.3 (CO), 175.2 (CO), 174.3 (CO), 161.9 (ArC), 160.2 (ArC), 158.4 (CO, Cbz), 138.3 (ArC), 129.6 (ArCH), 129.3 (ArCH), 111.3 (ArC), 92.1 (ArCH), 68.0 (CH₂, Cbz), 64.4 (C), 63.8 (C), 63.7 (C), 60.9 (C), 58.07 (C), 58.05 (C), 57.99 (C), 57.96 (C), 57.9 (C), 57.6 (C), 56.4 (OCH₃), 55.7 (OCH₃), 47.7 (NHCH(Ar)Et), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 35.3 (CH₂, cyclohexyl), 30.8 (CH₂, cyclohexyl), 28.9 (CH₂CH₃), 27.6 (CH₃), 27.4 (CH₃), 27.2 (CH₃), 27.00 (CH₃), 27.95 (CH₃), 26.6 (CH₂, cyclohexyl), 24.4 (CH₃), 24.1 (CH₃), 23.8 (CH₃), 23.7 (CH₃), 23.5 (CH₃), 23.0 (CH₂, cyclohexyl), 22.6 (CH₂, cyclohexyl), 18.8 (CH₃), 18.1 (CH₃), 17.9 (CH(CH₃)₂), 17.8 (CH(CH₃)₂), 17.5 (CH(CH₃)₂), 17.4 (CH(CH₃)₂), 11.5 (CH₂CH₃) ppm; IR νmax = 3296, 2932, 1652, 1610, 1525, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1392 ([M+H]⁺, 100%); 1414 ([M+Na]⁺, 90%); (ES⁻, MeOH) m/z = 1390 ([M–H]⁻, 100%).
Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-N-(1-(2,4,6-trimethoxyphenyl)propylamide (Addition to N-acyliminium)

To a stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-NHCH=CHCH₃ (50 mg, 0.041 mmol) and 1,3,5-trimethoxybenzene (34 mg, 0.21 mmol) in anhydrous THF (210 μL) at −50 °C was added TfOH (4 μL, 0.041 mmol) and the mixture stirred at −50 °C for 18.5 h. The reaction was quenched at low temperature with sat. NaHCO₃ solution (1 mL) and allowed to warm to room temperature. The mixture was diluted with sat. NaHCO₃ solution (9 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organics were dried (MgSO₄) and concentrated to give a 91.5:8.5 mixture of 30:epi-30 (See ¹H NMR expansion; Section 4). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (52 mg, 0.037 mmol, 91%).

Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄OᵗBu

To a solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄-OH (191 mg, 0.16 mmol) in CH₂Cl₂ (2 mL) was added EDC (43 μL, 0.24 mmol) and the mixture stirred at room temperature for 3 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL) and brine (15 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure giving the crude azlactone as a white solid (186 mg, 0.16 mmol). A solution of H-Ac₆cAib₄OᵗBu (95 mg, 0.18 mmol) in MeCN/ CH₂Cl₂ (1:1; 2 mL) was added and the mixture heated at reflux for 7 d. The reaction was allowed to cool to room temperature and the solvents removed under reduced pressure. The residual solid was re-dissolved in EtOAc (20 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (163 mg, 0.096 mmol, 60%). m.p. >300 °C (decomp.); [α]D = + 35.3 (c = 0.8; CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 7.90 (s, 1H, NH), 7.89 (s, 1H, NH), 7.86 (s, 2H, 2 × NH), 7.80 (s, 1H, NH), 7.78 (s, 1H, NH), 7.72 (s, 1H, NH), 7.67 (s, 1H, NH), 7.63 (s, 1H, NH), 7.53 (s, 1H, NH), 7.42 (s, 1H, NH), 7.40 (s, 1H, NH), 7.38 (m, 7H, 2 × NH + 5 × ArH, Cbz), 6.39 (s, 1H, NH), 5.45 (s, 1H, NH), 5.19 (d, J = 12.5, 1 H, HA of AB, Cbz), 5.03 (d, 1H, J = 12.5, HB of AB, Cbz), 2.35 (br m,
2H, 2 × CH, cyclohexyl), 2.02-1.79 (m, 7H, CH(CH₃)₂ + 6 × CH, cyclohexyl), 1.74-1.56 (m, 15H, CH(CH₃)₂ + 8 × CH, cyclohexyl + 2 × CH₃), 1.55 (s, 3H, CH₃), 1.54 (s, 3H, CH₃), 1.52 (s, 6H, 2 × CH₃), 1.51 (s, 3H, CH₃), 1.50 (s, 6H, 2 × CH₃), 1.49-1.46 (m, 45H, 15 × CH₃), 1.45 (s, 3H, CH₃), 1.43 (s, 9H, (CH₃)₃), 1.40 (s, 3H, CH₃), 1.37-1.16 (m, 4H, 4 × CH, cyclohexyl), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.97 (d, J = 7.0, 3H, CH(CH₃)), 0.80-0.78 (m, 6H, 2 × CH(CH₃)) ppm; ¹³C NMR (125 MHz, CDCl₃) δC 176.6 (CO), 176.6 (CO), 176.4 (CO), 176.34 (CO), 176.29 (CO), 176.26 (CO), 176.2 (CO), 176.12 (CO), 176.08 (CO), 175.6 (CO), 174.5 (CO), 174.4 (CO), 174.3 (CO), 172.7 (CO), 172.6 (CO), 156.4 (CO, Cbz), 135.8 (ArC), 128.90 (ArCH), 128.86 (ArCH), 128.7 (ArCH), 79.7 (C(CH₃)₃), 67.9 (CH₂, Cbz), 63.6 (C), 62.5 (C), 59.6 (C), 57.0 (2 × C), 56.92 (C), 56.90 (C), 56.88 (C), 56.87 (C), 56.8 (C), 56.73 (C), 56.70 (C), 56.5 (2 × C), 56.1 (C), 56.0 (C), 36.2 (CH(CH₃)₂), 35.9 (CH(CH₃)₂), 35.0 (br, 2 × CH₂, cyclohexyl), 30.1 (br, 2 × CH₂, cyclohexyl), 28.0 (C(CH₃)₃), 27.9-27.3 (12 × CH₃), 25.6 (2 × CH₂, cyclohexyl), 23.3-22.7 (12 × CH₃), 21.9 (2 × CH₂, cyclohexyl), 21.6 (2 × CH₂, cyclohexyl), 18.2 (CH₃), 18.1 (CH₃), 17.5 (CH(CH₃)₂), 17.3 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 17.1 (CH(CH₃)₂) ppm; IR νmax = 3299, 2981, 2935, 1653, 1525, 1452 cm⁻¹; MS (ES⁺, MeOH) m/z = 1723 ([M+NH₄]⁺, 100%), 1726 ([M+Na]⁺, 70%); (ES⁻, MeOH) m/z = 1750 ([M+HCO₂]⁻, 100%).

**Synthesis of Z-L-(αMe)Val₅Aib₅Ac₆cAib₅Ac₆cAib₅-OH 22**

A solution of Z-L-(αMe)Val₅Aib₅Ac₆cAib₅Ac₆cAib₅O'Bu (157 mg, 0.092 mmol) in CH₂Cl₂ (1 mL) and TFA (1 mL) was stirred at room temperature for 18 h. The solvents were removed under reduced pressure and the last traces of TFA removed by co-evaporation with Et₂O. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 98:2→90:10) gave the title compound as a white solid (146 mg, 0.089 mmol, 96%). m.p. >300 °C (decomp.); [α]D = + 35.8 (c = 0.8; CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 7.90 (m, 3H, 3 × NH), 7.86 (m, 3H, 3 × NH), 7.82 (s, 1H, NH), 7.73 (s, 1H, NH), 7.67 (s, 1H, NH), 7.65 (s, 1H, NH), 7.62 (s, 2H, 2 × NH), 7.41 (s, 2H, 2 × NH), 7.38 (m, 5H, 5 × ArH, Cbz), 6.51 (s, 1H, NH), 5.53 (s, 1H, NH), 5.18 (d, J = 12.0, 1 H, HA of AB, Cbz), 5.04 (d, 1H, J = 12.0, HB of AB, Cbz), 2.35 (m, 2H, 2 × CH, cyclohexyl), 2.02-1.79 (m, 7H, CH(CH₃)₂ + 6 × CH, cyclohexyl), 1.74-1.57 (m, 24H, CH(CH₃)₂ + 8 × CH, cyclohexyl +
5 × CH₃), 1.56-1.42 (m, 60H, CH(CH₃)), 1.40 (d, J = 7.0, 3H, CH(CH₃)), 0.96 (d, J = 7.0, 3H, CH(CH₃)), 0.80 (m, 6H, 2 × CH(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δC 176.73 (CO), 176.67 (2 × CO), 176.58 (CO), 176.5 (CO), 176.42 (CO), 176.39 (CO), 176.37 (3 × CO), 176.28 (CO), 176.27 (CO), 176.1 (CO), 175.7 (CO), 172.9 (CO), 172.8 (CO), 156.4 (CO, Cbz), 136.0 (ArC), 128.9 (ArCH), 128.81 (ArCH), 128.77 (ArCH), 67.9 (CH₂, Cbz), 63.6 (C), 62.5 (C), 59.61 (C), 59.59 (C), 57.8 (C), 57.01 (C), 56.98 (C), 56.91 (2 × C), 56.87 (C), 56.8 (C), 56.7 (2 × C), 56.5 (2 × C), 36.2 (CH(CH₃)₂), 36.0 (CH(CH₃)₂), 34.9 (br, 2 × CH₃, cyclohexyl), 30.3 (br, 2 × CH₂, cyclohexyl), 27.7-26.9 (12 × CH₃), 25.6 (br, 2 × CH₂, cyclohexyl), 23.4-22.7 (12 × CH₃), 21.9 (br, 2 × CH₂, cyclohexyl), 21.6 (br, 2 × CH₂, cyclohexyl), 18.3 (CH₃), 18.0 (CH₃), 17.60 (CH(CH₃)₂), 17.57 (CH(CH₃)₂), 17.45 (CH(CH₃)₂), 17.43 (CH(CH₃)₂) ppm; IR νmax = 3294, 2980, 2937, 1654, 1527, 1448 cm⁻¹; MS (ES⁻, MeOH) m/z = 1648 ([M−H]⁻, 50%), 1694 ([M+HCO₂]⁻, 50%).

**Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-NHAllyl 25**

To a stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-OH (262 mg, 0.16 mmol) and HOBt (35 mg, 0.24 mmol) in CH₂Cl₂ (2 mL) was added EDC (42 μL, 0.24 mmol) and the mixture stirred at room temperature for 30 min. Allylamine (36 μL, 0.48 mmol) was added and the reaction stirred for an additional 96 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (15 mL) and washed with 5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (241 mg, 0.14 mmol, 90%). m.p. 289-291 °C; [α]D = + 40.3 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 7.90 (s, 1H, NH), 7.89 (s, 1H, NH), 7.87 (s, 1H, NH), 7.86 (s, 1H, NH), 7.84 (s, 1H, NH), 7.80 (s, 1H, NH), 7.73 (s, 1H, NH), 7.69 (s, 1H, NH), 7.67 (s, 1H, NH), 7.62 (s, 1H, NH), 7.58 (s, 1H, NH), 7.42 (s, 1H, NH), 7.41 (s, 2H, 2 × NH), 7.38 (m, 5H, 5 × ArH, Cbz), 6.44 (s, 1H, NH), 5.88 (ddt, J = 17.0, 10.0, 5.0, 1H, NHCH₂CH=CH₂), 5.47 (s, 1H, NH), 5.28 (dd, J = 17.5, 1.5, 1H, NHCH₂CH=CH₂), 5.19 (d, J = 12.0, 1 H, HA of AB, Cbz), 5.05 (dd, J = 10.5, 1.5, 1H, NHCH₂CH=CH₂), 5.04 (d, J = 12.0, 1 H, HB of AB, Cbz), 3.99 (d, J = 16.0, 1H, NHCH₂CH=CH₂), 3.82 (d,
Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-NHCH=CH₃ 28

A stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-NHAllyl (200 mg, 0.12 mmol) and carbonylchlorohydridotris(triphenylphosphine)ruthenium (11 mg, 0.012 mmol) in THF (2 mL) was heated at reflux for 19 h. The solvents were removed under reduced pressure and the residue purified by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) to give the title compound as a white solid (186 mg, 0.11 mmol, 93%) as an inseparable 1.5:1 mixture of E:Z isomers. m.p. >300 °C (decomp.); [α]D = +41.7 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 8.97 (d, J = 10.0, 0.60H, NHCH=CHCH₃, E), 8.55 (d, J = 10.0, 0.40H, NHCH=CHCH₃, Z), 7.901 (s, 1H, NH), 7.895 (s, 1H, NH), 7.87 (s, 1H, NH), 7.86 (s, 1H, NH), 7.85 (s, 1H, NH), 7.80 (s, 1H, NH), 7.73 (s, 1H, NH), 7.69 (s, 1H, NH), 7.63 (s, 1H, NH), 7.59 (s, 1H, NH), 7.56 (s, 1H, NH), 7.42 (s, 1H, NH), 7.41 (s, 1H, NH), 7.37 (m, 5H, 5 × ArH, Cbz), 7.45 (dd, J = 6.5, 1H, Cyclohexyl), 27.8-27.0 (12 × C, cyclohexyl), 18.2 (2 × CH₂), cyclohexyl), 12.7-12.0 (2 × CH₂, cyclohexyl), 23.2-22.7 (12 × CH₃), 21.9 (2 × CH₂, cyclohexyl), 21.6 (2 × CH₂, cyclohexyl), 18.2 (CH₃), 18.0 (CH₃), 17.5 (CH(CH₃)₂), 17.3 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 17.1 (CH(CH₃)₂) ppm; IR νmax = 3295, 2983, 2936, 1652, 1526, 1454 cm⁻¹; MS (ES⁺, MeOH) m/z = 845 ([M+2H]²⁺, 50%), 856 ([M+H+Na]²⁺, 100%), 867 ([M+2Na]²⁺, 40%), 1689 ([M+H]+, 60%), 1711 ([M+Na]⁺, 50%).
10.0, 0.60H, NHCH=CHCH₃, E), 6.67 (m, 0.40H, NHCH=CHCH₂, Z), 6.43 (s, 1H, NH), 5.56-4.45 (m, 1.60H, NH + NHCH=CHCH₃, E), 5.19 (d, J = 12.0, 1H, HA of AB, Cbz), 5.03 (d, J = 12.0, 1H, HB of AB, Cbz), 4.78 (dq, J = 14.5, 7.0, 0.40H, NHCH=CHCH₃, Z), 2.36 (m, 2H, 2 × CH, cyclohexyl), 2.04-1.84 (m, 7H, CH(CH₃)₂ + 6 × CH, cyclohexyl), 1.82 (dd, J = 7.0, 1.5, 1.2H, NHCH=CHCH₃, E), 1.74-1.59 (m, 22.8H, CH(CH₃)₂ 8 × CH, cyclohexyl + NHCH=CHCH₃, E + 4 × CH₃), 1.55-1.45 (s, 60H, 20 × CH₃), 1.46 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.36-1.26 (m, 4H, 4 × CH, cyclohexyl), 0.99 (d, J = 7.0, 3H, CH(CH₃)), 0.96 (d, J = 7.0, 3H, CH(CH₃)), 0.79 (m, 6H, 2 × CH(CH₃)) ppm;¹³C NMR (125 MHz, CDCl₃) δC 176.73 (CO), 176.66 (CO), 176.6 (CO), 176.5 (CO), 176.42 (CO), 176.38 (CO), 176.3 (CO), 176.1 (CO), 175.64 (CO), 175.58 (CO), 175.0 (CO), 174.0 (CO), 173.0 (CO), 172.7 (CO), 172.6 (CO), 156.5 (CO, Cbz), 135.8 (ArC), 128.9 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 124.7 (NHCH=CHCH₃, E), 123.3 (NHCH=CHCH₃, Z), 107.5 (NHCH=CHCH₃, E), 106.9 (NHCH=CHCH₃; Z), 67.8 (CH₂, Cbz), 63.6 (C), 62.5 (C), 59.6 (C), 57.1 (C), 56.98 (2 × C), 56.97 (C), 56.91 (C), 56.90 (C), 56.87 (C), 56.7 (2 × C), 56.5 (2 × C), 56.1 (CH(CH₃)₂), 35.9 (CH(CH₃)₂), 35.0 (br, 2 × CH₂, cyclohexyl), 28.0 (2 × CH₂, cyclohexyl), 27.7-27.1 (12 × CH₃), 25.6 (2 × CH₂, cyclohexyl), 23.2-22.7 (12 × CH₃), 21.9 (2 × CH₂, cyclohexyl), 21.6 (2 × CH₂, cyclohexyl), 18.2 (CH₃), 18.0 (CH₃), 17.5 (CH(CH₃)₂), 17.3 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 17.1 (CH(CH₃)₂), 15.3 (NHCH=CHCH₃, E), 11.4 (NHCH=CHCH₃, Z) ppm; IR νmax = 3292, 2983, 2935, 1651, 1525, 1454 cm⁻¹; MS (ES⁺, CH₂Cl₂) m/z = 1706 ([M+NH₄]⁺, 100%), 1711 ([M+Na⁺], 30%); (ES⁻, CH₂Cl₂) m/z = 1723 ([M+Cl⁻], 100%).

Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-(R)-N-(1-(2,4,6-trimethoxyphenyl)propan-1-amine 31

To a stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-OH (25 mg, 0.015 mmol) and HOBt (3 mg, 0.020 mmol) in CH₂Cl₂ (1 mL) was added EDC (4 μL, 0.020 mmol) and the mixture stirred at room temperature for 1 h. (R)-1-(2,4,6-Trimethoxyphenyl)propan-1-amine (5 mg, 0.023 mmol) and DIPEA (4 μL, 0.023 mmol) were added and the reaction stirred for an additional 48 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (15 mL) and washed with
5% KHSO₄ solution (2 × 10 mL), sat. NaHCO₃ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (27 mg, 0.019 mmol, 92%). m.p. 212-214 °C; [α]D = +37.3 (c = 1.0; CDCl₃); ¹H NMR (500 MHz, MeOD) δH 8.04 (s, 1H, NH), 7.93 (s, 2H, 2 × NH), 7.91 (s, 2H, 2 × NH), 7.87 (s, 1H, NH), 7.78 (s, 1H, NH), 7.73 (s, 1H, NH), 7.72 (s, 1H, NH), 7.68 (s, 1H, NH), 7.66 (s, 1H, NH), 7.48 (s, 2H, 2 × NH), 7.40-7.30 (m, 5H, 5 × ArH, Cbz), 6.13 (s, 2H, 2 × ArH), 5.38 (dd, 1H, J = 16.5, 8.0, NHCH(Ar)Et), 5.19 (d, 1H, J = 12.5, HA of AB, Cbz), 5.03 (d, 1H, J = 12.5, HB of AB, Cbz), 3.81 (s, 6H, 2 × OCH₃), 3.77 (s, 3H, OCH₃), 2.36 (m, 2H, 2 × CH, cyclohexyl), 2.08 (m, 2H, 2 × CH, cyclohexyl), 1.98-1.81 (m, 6H, 6 × C₃H₈), 1.51-1.46 (m, 51H, 17 × C₃H₈), 1.53 (s, 6H, 2 × CH₃), 1.51-1.462 (m, 51H, 17 × CH₂), 1.466 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 1.41 (s, 6H, 2 × CH₃), 1.39 (s, 3H, CH₃), 1.31-1.21 (m, 4H, 4 × CH, cyclohexyl), 0.99 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)), 0.83 (d, J = 7.0, 3H, CH(CH₃)), 0.81 (t, J = 7.5, 3H, CH₂CH₃), 0.79 (d, J = 7.0, 3H, CH(CH₃)) ppm; ¹H NMR (800 MHz, d₈-THF) δH 8.14 (s, 1H, NH), 8.10 (s, 1H, NH), 8.09 (s, 1H, NH), 8.04 (s, 1H, NH), 7.99 (s, 1H, NH), 7.97 (s, 1H, NH), 7.90 (s, 1H, NH), 7.86 (s, 1H, NH), 7.77 (s, 1H, NH), 7.62 (s, 1H, NH), 7.59 (s, 1H, NH), 7.47 (s, 1H, NH), 7.41-7.31 (m, 5H, 5 × ArH, Cbz), 7.28 (s, 1H, NH), 7.14 (br m, 1H, NH), 6.12 (s, 2H, 2 × ArH), 5.38 (dd, 1H, J = 7.5, 7.5, NHCH(Ar)Et), 5.16 (d, 1H, J = 12.5, HA of AB, Cbz), 5.09 (d, 1H, J = 12.5, HB of AB, Cbz), 3.82 (s, 6H, 2 × OCH₃), 3.73 (s, 3H, OCH₃), 2.36 (m, 2H, 2 × CH, cyclohexyl), 2.05-1.96 (m, 6H, 6 × CH, cyclohexyl), 1.88 (spt, 1H, J = 7.0, CH(CH₃)), 1.71-1.54 (m, 17H, CH⁴CH³CH₃ + CH³CH⁵CH₃, CH(CH₃)₂ + 8 × CH, cyclohexyl + 2 × CH₃), 1.52-1.47 (m, 54H, 18 × CH₃), 1.46 (m, 6H, 2 × CH₃), 1.44 (s, 3H, CH₃), 1.43 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 1.32-1.24 (m, 4H, 4 × CH, cyclohexyl), 1.01 (d, J = 7.0, 3H, CH(CH₃)), 0.97 (d, J = 7.0, 3H, CH(CH₃)), 0.89 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.81 (t, J = 7.5, 3H, CH₂CH₃) ppm; ¹³C NMR (125 MHz, MeOD) δC 177.6 (CO), 177.5 (CO), 177.4 (2 × CO), 177.33 (CO), 177.30 (2 × CO), 177.26 (CO), 177.0 (CO), 176.6 (CO), 176.5 (CO), 175.7 (CO), 174.6 (CO), 173.9 (CO), 173.8 (CO), 161.2 (ArC), 159.9 (ArC), 157.9 (CO, Cbz), 137.6 (ArC), 129.3 (ArCH),
Synthesis of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide epi-31

Prepared by the same procedure described for 31 from Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-OH (25 mg, 0.015 mmol) and (S)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (5 mg, 0.023 mmol). Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:MeOH; 99:1→95:5) gave the title compound as a white solid (24 mg, 0.013 mmol, 85%). m.p. 209-211 °C; [α]$_D$ = + 28.5 (c = 1.0; CHCl$_3$); $^1$H NMR (500 MHz, MeOD) δ$_H$ 8.07 (s, 1H, NH), 8.95 (s, 1H, NH), 7.93 (s, 1H, NH), 7.90 (s, 1H, NH), 7.81 (s, 1H, NH), 7.77 (s, 1H, NH), 7.74 (s, 1H, NH), 7.65 (s, 1H, NH), 7.52 (s, 1H, NH), 7.50 (s, 1H, NH), 7.42-7.31 (m, 5H, 5 × ArH, Cbz), 6.16 (s, 2H, 2 × ArH), 5.43 (dd, 1H, $J = 17.0$, 7.5, NHCH(Ar)Et), 5.20 (d, 1H, $J = 12.5$, HA of AB, Cbz), 5.04 (d, 1H, $J = 12.5$, HB of AB, Cbz), 3.82 (s, 6H, 2 × OCH$_3$), 3.78 (s, 3H, OCH$_3$), 2.35 (m, 2H, 2 × CH, cyclohexyl), 2.11 (m, 2H, 2 × CH, cyclohexyl), 1.99-1.76 (m, 6H, CH(CH$_3$)$_2$ + CH$_{\alpha}$CH$_{\beta}$CH$_3$ + 4 × CH, cyclohexyl), 1.75-1.60 (m, 10H, CH$_{\alpha}$CH$_{\beta}$CH$_3$, CH(CH$_3$)$_2$, + 8 × CH, cyclohexyl), 1.57 (br s, 9H, 3 × CH$_3$), 1.53 (s, 6H, 2 × CH$_3$), 1.53-1.43 (s, 54H, 18 × CH$_3$), 1.42 (s, 3H, CH$_3$), 1.40 (s, 6H, 2 × CH$_3$), 1.35-1.27 (m, 4H, 4 x CH, cyclohexyl), 1.00 (d, $J = 7.0$, 3H, CH(CH$_3$)), 0.95 (d, $J = 7.0$, 3H, CH(CH$_3$)), 0.85 (d, $J = 7.0$, 3H, CH(CH$_3$)), 0.83-0.79 (m, 6H, CH$_2$CH$_3$ + CH(CH$_3$)) ppm; $^1$H NMR (800 MHz, d$_8$-THF) δ$_H$ 8.17 (s, 1H, NH), 8.11 (s, 1H, NH), 8.04 (s, 1H, NH), 8.03 (s, 1H, NH), 7.99 (s, 1H, NH), 7.90 (s, 1H, NH), 7.86 (s, 1H, NH), 7.71 (s, 1H, NH), 7.62 (s, 1H, NH), 7.59 (s, 1H, NH), 7.53 (s, 1H, NH), 7.42-7.30 (m, 8H, 3 × NH + 5 × ArH, Cbz), 7.26 (s, 1H, NH),
6.14 (s, 2H, 2 × ArH), 5.45 (dd, 1H, J = 8.0, 8.0, NHCH(ArEt)), 5.16 (d, 1H, J = 12.5, HA of AB, Cbz), 5.10 (d, 1H, J = 12.5, HB of AB, Cbz), 3.81 (s, 6H, 2 × OCH3), 3.73 (s, 3H, OCH3), 2.37 (m, 2H, 2 × CH, cyclohexyl), 2.02 (m, 6H, 6 × CH, cyclohexyl), 1.81 (spt, 1H, J = 7.0, CH(CH3)2), 1.76 (m, 1H, CH2CH2CH3), 1.69-1.57 (m, 10H, CH2CH2CH3, CH(CH3)2, + 8 × CH, cyclohexyl), 1.57 (s, 6H, 2 × CH3), 1.53-1.46 (m, 66H, 22 × CH3), 1.44 (s, 3H, CH3), 1.36 (s, 3H, CH3), 1.31-1.21 (m, 4H, 4 × CH, cyclohexyl), 1.02 (d, J = 7.0, 3H, CH(CH3)), 0.97 (d, J = 7.0, 3H, CH(CH3)), 0.89 (d, J = 7.0, 3H, CH(CH3)), 0.86 (d, J = 7.0, 3H, CH(CH3)), 0.79 (t, J = 7.5, 3H, CH2CH3) ppm;

13C NMR (125 MHz, MeOD) δC 178.0 (CO), 177.74 (CO), 177.69 (CO), 177.57 (2 × CO), 177.53 (CO), 177.46 (CO), 177.3 (CO), 177.2 (CO), 177.0 (CO), 176.7 (CO), 176.0 (CO), 174.9 (CO), 174.0 (CO), 161.5 (ArC), 160.0 (ArC), 158.1 (CO, Cbz), 137.9 (ArC), 129.5 (ArCH), 129.2 (ArCH), 111.3 (ArC), 91.9 (ArCH), 67.9 (CH2, Cbz), 64.3 (C), 63.5 (C), 60.7 (C), 60.6 (C), 57.91 (C), 57.88 (C), 57.85 (C), 57.83 (C), 57.78 (C), 57.76 (C), 57.72 (C), 57.5 (C), 56.3 (OCH3), 55.7 (OCH3), 47.5 (NHCH(ArEt)), 36.5 (CH(CH3)2), 36.4 (CH(CH3)2), 35.6 (br, CH2, 2 × cyclohexyl), 30.6 (CH2, 2 × cyclohexyl), 28.7 (CH2CH3), 27.7-26.7 (12 × CH3), 26.4 (CH2, 2 × cyclohexyl), 24.4-22.8 (12 × CH3), 23.5 (CH2, 2 × cyclohexyl), 22.5 (CH2, 2 × cyclohexyl), 18.7 (CH3), 18.2 (CH3), 17.9 (CH(CH3)2), 17.7 (CH(CH3)2), 17.5 (CH(CH3)2), 17.4 (CH(CH3)2), 11.4 (CH2CH3) ppm;

IR νmax = 3296, 2931, 1651, 1609, 1525, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 1857 ([M+H]⁺, 100%); 1879 ([M+Na]⁺, 40%).

**Synthesis of Z-L-(αMe)Val2Aib4Ac6cAib4Ac6cAib4cAib4b-N-(1-(2,4,6-trimethoxyphenyl)propylamide (Addition to N-acyliminium)**

To a stirred solution of Z-L-(αMe)Val2Aib4Ac6cAib4Ac6cAib4cAib4b-NHCH=CHCH3 (68 mg, 0.040 mmol) and 1,3,5-trimethoxybenzene (33 mg, 0.20 mmol) in anhydrous THF (200 μL) at −50 °C was added TfOH (4 μL, 0.040 mmol) and the mixture stirred at −50 °C for 18 h. The reaction was quenched at low temperature with sat. NaHCO3 solution (1 mL) and allowed to warm to room temperature. The mixture was diluted with sat. NaHCO3 solution (9 mL) and extracted with CH2Cl2 (3 × 10 mL). The combined organics were dried (MgSO4) and concentrated to give a **90.2:9.8** mixture of **31:epi-31** (See ¹H NMR
expansion; Section 4). Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:MeOH; 99:1→95:5) gave the title compound as a white solid (58 mg, 0.031 mmol, 78%).

**Synthesis of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$O'Bu**

To a solution of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-OH (125 mg, 0.076 mmol) in CH$_2$Cl$_2$ (2 mL) was added EDC (17 μL, 0.099 mmol) and the mixture stirred at room temperature for 3 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (15 mL) and washed with 5% KHSO$_4$ solution (2 × 10 mL) and brine (15 mL). The organics were dried (MgSO$_4$) and concentrated under reduced pressure giving the crude azlactone as a white solid (120 mg, 0.074 mmol). A solution of H-Ac$_6$cAib$_4$O'Bu (59 mg, 0.11 mmol) in MeCN/CH$_2$Cl$_2$ (1:1; 2 mL) was added and the mixture heated at reflux for 10 d. The reaction was allowed to cool to room temperature and the solvents removed under reduced pressure. The residual solid was re-dissolved in EtOAc (20 mL) and washed with 5% KHSO$_4$ solution (2 × 10 mL), sat. NaHCO$_3$ solution (10 mL) and brine (10 mL). The organics were dried (MgSO$_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:MeOH; 99:1→95:5) gave the title compound as a white solid (75 mg, 0.035 mmol, 47%).

m.p. >300 °C (decomp.); [α]$_D$ = +38.6 (c = 0.5; CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$

7.90-7.87 (m, 5H, 5 × NH), 7.80 (s, 1H, NH), 7.79 (s, 1H, NH), 7.74 (s, 1H, NH), 7.73 (s, 1H, NH), 7.68-7.64 (m, 3H, 3 × NH), 7.54 (s, 1H, NH), 7.42-7.41 (m, 3H, 3 × NH), 7.40-7.34 (m, 7H, 2 × NH + 5 × ArH, Cbz), 6.40 (s, 1H, NH), 5.50 (s, 1H, NH), 5.19 (d, J = 12.0, 1 H, HA of AB, Cbz), 5.03 (d, 1H, J = 12.0, HB of AB, Cbz), 2.36 (br m, 3H, 3 × C, cyclohexyl), 2.10-1.80 (m, 10H, CH(CH$_3$)$_2$ + 9 × CH, cyclohexyl), 1.79-1.57 (m, 25H, CH(CH$_3$)$_2$ + 12 × CH, cyclohexyl + 4 × CH$_3$), 1.55-1.46 (m, 84H, 28 × CH$_3$), 1.45 (s, 3H, CH$_3$), 1.43 (s, 9H, (CH$_3$)$_3$), 1.40 (s, 3H, CH$_3$), 1.35-1.16 (m, 6H, 6 × CH, cyclohexyl), 1.00 (d, J = 6.5, 3H, CH(CH$_3$)), 0.97 (d, J = 6.5, 3H, CH(CH$_3$)), 0.80-0.78 (m, 6H, 2 × CH(CH$_3$)) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ$_C$ 176.80 (CO), 176.76 (CO), 176.6 (CO), 176.5 (CO), 176.40 (3 × CO), 176.37 (CO), 176.32 (CO), 176.28 (CO), 176.2 (CO), 176.15 (CO), 176.10 (CO), 175.9 (CO), 175.6 (CO), 174.50 (CO), 174.47 (CO), 174.4 (CO), 172.7 (CO), 172.6 (CO), 156.5 (CO, Cbz), 135.8 (ArC), 128.89 (ArCH), 128.86 (ArCH), 128.7 (ArCH), 79.7 (C(CH$_3$)$_3$), 67.9 (CH$_2$, Cbz), 63.6 (C), 62.5
(C), 59.63 (C), 59.60 (C), 59.58 (C), 57.0 (2 × C), 56.92 (2 × C), 56.90 (3 × C), 56.86 (C), 56.8 (C), 56.7 (2 × C), 56.53 (2 × C), 56.1 (C), 36.2 (CH(CH₃)₂), 35.9 (CH(CH₃)₂), 35.0 (br, 3 × CH₂, cyclohexyl), 29.8 (br, 3 × CH₂, cyclohexyl), 28.0 (C(CH₃)₃), 27.9-27.2 (16 × CH₃), 25.6 (3 × CH₂, cyclohexyl), 23.2-22.7 (16 × CH₃), 21.9 (3 × CH₂, cyclohexyl), 21.6 (3 × CH₂, cyclohexyl), 18.2 (CH₃), 18.1 (CH₃), 17.5 (CH(CH₃)₂), 17.3 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 17.1 (CH(CH₃)₂) ppm; IR νmax = 3294, 2982, 2935, 1652, 1526, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 2171 ([M+H]+, 100%), 2188 ([M+NH₄]+, 20%), 2193 ([M+Na]+, 50%).

**Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄Aib₄Ac₆c-OH 23**

A solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄Ac₆cAib₄Ac₆cO'Bu (74 mg, 0.034 mmol) in CH₂Cl₂ (1 mL) and TFA (0.5 mL) was stirred at room temperature for 3 h. The solvents were removed under reduced pressure and the last traces of TFA removed by co-evaporation with Et₂O. Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 98:2→90:10) gave the title compound as a white solid (62 mg, 0.029 mmol, 86%). **m.p. >300 °C (decomp.); [α]D = +32.1 (c = 1.0; CHCl₃); **¹H NMR (400 MHz, MeOD) δH 8.01 (m, 1H, NH), 7.93-7.84 (m, 7H, 7 × NH), 7.75-7.66 (m, 5H, 5 × NH), 7.62 (s, 1H, NH), 7.58 (s, 1H, NH), 7.51-7.42 (m, 3H, 3 × NH), 7.39-7.29 (m, 5H, 5 × ArH, Cbz), 6.84 (s, 1H, NH), 5.19 (d, J = 12.0, 1 H, HA of AB, Cbz), 5.02 (d, 1H, J = 12.0, HB of AB, Cbz), 5.01 (d, J = 12.0, 1H, Cbz), 2.33 (m, 3H, 3 × CH, cyclohexyl), 2.08 (m, 3H, 3 × CH, cyclohexyl), 1.98-1.77 (m, 7H, CH(CH₃)₂ + 6 × CH, cyclohexyl), 1.75-1.55 (m, 25H, CH(CH₃)₂ + 12 × CH, cyclohexyl + 4 × CH₃), 1.54-1.39 (m, 84H, 28 × CH₃), 1.41 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.35-1.25 (m, 6H, 6 × CH, cyclohexyl), 0.98 (d, J = 6.5, 3H, CH(CH₃)), 0.94 (d, J = 6.5, 3H, CH(CH₃)), 0.82 (d, J = 6.5, 3H, CH(CH₃)), 0.78 (d, J = 6.5, 3H, CH(CH₃)) ppm; **¹³C NMR (100 MHz, MeOD) δC 177.43 (2 × CO), 177.39 (CO), 177.31 (2 × CO), 177.27 (2 × CO), 177.25 (CO), 177.23 (2 × CO), 177.19 (CO), 177.17 (2 × CO), 177.1 (CO), 177.0 (CO), 176.9 (CO), 174.4 (2 × CO), 173.7 (CO), 157.7 (CO, Cbz), 137.3 (ArC), 129.2 (ArCH), 128.95 (ArCH), 128.87 (ArCH), 67.7 (CH₂, Cbz), 64.0 (C), 63.2 (C), 60.23 (2 × C), 60.21 (C), 57.6 (C), 57.5 (5 × C), 57.43 (C), 57.40 (2 × C), 57.36 (C), 57.3 (2 × C), 57.2 (3 × C), 36.3 (CH(CH₃)₂), 36.2 (CH(CH₃)₂), 35.3 (br, 3 × CH₂, cyclohexyl), 30.2 (br, CH₂, cyclohexyl), 27.7-26.9 (16 × CH₃), 26.1 (3 × CH₂, cyclohexyl), 23.9-23.3 (16 × C).
CH$_3$), 22.5 (CH$_2$, cyclohexyl), 22.2 (3 × CH$_2$, cyclohexyl), 18.5 (CH$_3$), 18.2 (CH$_3$), 17.7 (CH(CH$_3$)$_2$), 17.5 (CH(CH$_3$)$_2$), 17.4 (CH(CH$_3$)$_2$), 17.3 (CH(CH$_3$)$_2$) ppm; IR $\nu_{\text{max}}$ = 3292, 2982, 2932, 1652, 1526, 1454 cm$^{-1}$; MS (ES$^+$, MeOH) $m/z$ = 2115 ([M+H]$^+$, 50%), 2132 ([M+Na]$^+$, 100%).

**Synthesis of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHAllyl 26**

To a stirred solution of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-OH (60 mg, 0.028 mmol) and HOBt (8 mg, 0.57 mmol) in CH$_2$Cl$_2$ (1 mL) was added EDC (10 µL, 0.57 mmol) and the mixture stirred at room temperature for 1 h. Allylamine (21 µL, 0.28 mmol) was added and the reaction stirred for an additional 120 h. The solvents were removed under reduced pressure and the residue re-dissolved in EtOAc (15 mL) and washed with 5% KHSO$_4$ solution (2 × 10 mL), sat. NaHCO$_3$ solution (2 × 10 mL) and brine (10 mL). The organics were dried (MgSO$_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$:MeOH; 99:1 → 95:5) gave the title compound as a white solid (47 mg, 0.022 mmol, 77%). m.p. >300 °C; $\alpha$ = +34.2 (c = 1.0; CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$ 7.90-7.80 (m, 7H, 7 × NH), 7.74 (s, 1H, NH), 7.68-7.62 (m, 4H, 4 × NH), 7.58 (s, 1H, NH), 7.43 (s, 1H, NH), 7.41 (s, 2H, 2 × NH), 7.38 (m, 5H, 5 × ArH, Cbz), 6.45 (s, 1H, NH), 5.88 (ddt, $J$ = 17.0, 10.0, 5.0, 1H, NHCH$_2$CH=CH$_2$), 5.53 (s, 1H, NH), 5.27 (dd, $J$ = 17.0, 1.5, 1H, NHCH$_2$CH=CH$_2$), 5.19 (d, $J$ = 12.0, 1 H, HA of AB, Cbz), 5.05-5.03 (m, 2H, NHCH$_2$CH=CH$_2$ + HB of AB, Cbz), 3.98 (d, $J$ = 16.0, 1H, NHCH$_2$CH=CH$_2$), 3.81 (d, $J$ = 16.0, 1H, NHCH$_2$CH=CH$_2$), 2.36 (m, 3H, 3 × CH, cyclohexyl), 2.03 (m, 3H, 3 × CH, cyclohexyl), 1.96-1.79 (m, 7H, CH(CH$_3$)$_2$ + 6 × CH, cyclohexyl), 1.75-1.57 (m, 28H, CH(CH$_3$)$_2$ + 12 × CH, cyclohexyl + 5 × CH$_3$), 1.56-1.43 (m, 84H, 28 × CH$_3$, Cbz), 1.37-1.17 (m, 2H, 6 × CH, cyclohexyl), 1.00 (d, $J$ = 6.5, 3H, CH(CH$_3$)), 0.97 (d, $J$ = 6.5, 3H, CH(CH$_3$)), 0.80 (m, 6H, 2 × CH(CH$_3$)), ppm; $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$ 176.81 (CO), 176.76 (CO), 176.7 (CO), 176.64 (CO), 176.61 (CO), 176.5 (2 × CO), 176.42 (3 × CO), 176.40 (CO), 176.37 (CO), 176.3 (CO), 176.2 (CO), 176.1 (2 × CO), 175.73 (CO), 175.65 (CO), 175.0 (CO), 172.8 (CO), 172.7 (CO), 156.5 (CO, Cbz), 135.9 (ArC), 135.2 (NHCH$_2$CH=CH$_2$), 128.9 (ArCH), 128.7 (ArCH), 114.9 (NHCH$_2$CH=CH$_2$), 67.9 (CH$_2$, Cbz), 63.6 (C), 62.5 (C), 59.63 (C), 59.61 (C), 57.4 (C), 57.1 (C), 57.00 (2 ×
C), 56.97 (C), 56.92 (3 × C), 56.9 (C), 56.76 (2 × C), 56.74 (2 × C), 56.6 (2 × C), 56.5 (C), 42.0 (NHCH₂CH=CH₂), 36.1 (CH(CH₃)₂), 35.9 (CH(CH₃)₂), 35.1 (br, 3 × CH₂, cyclohexyl), 29.8 (br, 3 × CH₂, cyclohexyl), 28.4-27.1 (16 × CH₃), 25.7 (3 × CH₂, cyclohexyl), 23.3-22.6 (16 × CH₃), 21.9 (3 × CH₂, cyclohexyl), 21.6 (3 × CH₂, cyclohexyl), 18.2 (CH₃), 18.1 (CH₃), 17.5 (CH(CH₃)₂), 17.3 (CH(CH₃)₂), 17.20 (CH(CH₃)₂), 17.16 (CH(CH₃)₂) ppm; IR νmax = 3292, 2982, 2934, 1651, 1526, 1454 cm⁻¹; MS (ES⁺, MeOH) m/z = 2154 ([M+H]⁺, 100%), 2173 ([M+NH₄]⁺, 20%), 2178 ([M+Na]⁺, 30%).

**Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄Ac₆cAib₄-NHCH=CHCH₃ 29**

A stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄Ac₆cAib₄-NHAllyl (45 mg, 0.021 mmol) and carbonylchlorohydridotris(triphenylphosphine)ruthenium (4 mg, 0.0042 mmol) in THF (0.5 mL) was heated at reflux for 19 h. The solvents were removed under reduced pressure and the residue purified by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) to give the title compound as an off-white solid (34 mg, 0.016 mmol, 76%) as an inseparable 1:1 mixture of E:Z isomers. m.p. >300 °C (decomp.); [α]D = + 28.4 (c = 1.0; CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 8.98 (d, J = 10.0, 0.5H, NHCH=CHCH₃, E), 8.55 (d, J = 10.0, 0.5H, NHCH=CHCH₃, Z), 7.95-7.83 (m, 5H, 5 × NH), 7.81 (m, 2H, 2 × NH), 7.74 (m, 2H, 2 × NH), 7.69 (m, 2H, 2 × NH), 7.64 (s, 2H, 2 × NH), 7.60 (s, 1H, NH), 7.57 (s, 1H, NH), 7.49-7.40 (s, 3H, 3 × NH), 7.37 (m, 5H, 5 × ArH, Cbz), 6.74 (m, 0.5H, NHCH=CHCH₃, E), 6.67 (m, 0.5H, NHCH=CHCH₃, Z), 6.46 (s, 1H, NH), 5.59-5.50 (m, 1.5H, NH + NHCH=CHCH₃, E), 5.18 (d, J = 12.0, 1H, HA of AB, Cbz), 5.04 (d, J = 12.0, 1H, HB of AB, Cbz), 4.77 (m, 0.5H, NHCH=CHCH₃, Z), 2.36 (m, 3H, 3 × CH, cyclohexyl), 2.04-1.84 (m, 10H, CH(CH₃)₂ + 9 × CH, cyclohexyl), 1.82 (d, J = 7.0, 1.5H, NHCH=CHCH₃, Z), 1.77-1.57 (m, 29.5H, CH(CH₃)₂, 12 × CH, cyclohexyl + NHCH=CHCH₃, E + 5 × CH₃), 1.55-1.45 (s, 8H, 28 × CH₃), 1.41 (s, 3H, CH₃), 1.36-1.26 (m, 6H, 6 × CH, cyclohexyl), 0.99 (d, J = 6.5, 3H, CH(CH₃)), 0.96 (d, J = 6.5, 3H, CH(CH₃)), 0.80 (m, 6H, 2 × CH(CH₃)) ppm; ¹³C NMR (125 MHz, CDCl₃) δC 176.82 (CO), 176.77 (CO), 176.7 (CO), 176.62 (CO), 176.59 (CO), 176.52 (CO), 176.43 (5 × CO), 176.30 (2 × CO), 176.1 (CO), 175.7 (CO), 175.6 (CO), 174.1 (CO), 173.1 (CO), 172.78 (2 × CO), 172.7 (CO), 156.5 (CO, Cbz), S54
135.9 (ArC), 128.8 (ArCH), 128.7 (ArCH), 124.7 (NHCH=CHCH₃, E), 123.3 (NHCH=CHCH₃, Z), 107.4 (NHCH=CHCH₃; E), 106.9 (NHCH=CHCH₃; Z), 67.8 (CH₂, Cbz), 63.6 (C), 62.5 (C), 59.62 (C), 59.60 (C), 57.1 (C), 56.99 (3 × C), 56.97 (C), 56.92 (3 × C), 56.87 (C), 56.8 (C), 56.7 (3 × C), 56.54 (3 × C), 56.50 (C), 36.1 (CH(CH₃)₂), 35.9 (CH(CH₃)₂), 35.0 (br, 3 × CH₂, cyclohexyl), 29.8 (br, 3 × CH₂, cyclohexyl), 28.1-27.1 (16 × CH₃), 25.7 (3 × CH₂, cyclohexyl), 23.3-22.7 (16 × CH₃), 21.9 (3 × CH₂, cyclohexyl), 21.6 (3 × CH₂, cyclohexyl), 18.2 (CH₃), 18.0 (CH₃), 17.5 (CH(CH₃)₂), 17.3 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 17.1 (CH(CH₃)₂) 15.3 (NHCH=CHCH₃, E), 11.4 (NHCH=CHCH₃, Z) ppm; IR νmax = 3290, 2983, 2935, 1651, 1526, 1455 cm⁻¹; MS (ES⁺, MeOH) m/z = 2154 ([M+H]+, 70%), 2173 ([M+NH₄]+, 100%), 2178 ([M+Na]+, 20%).

Iminium: Synthesis of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-N-(1-(2,4,6-trimethoxyphenyl)propylamide 32 (Addition to N-acyliminium)

To a stirred solution of Z-L-(αMe)Val₂Aib₄Ac₆cAib₄Ac₆cAib₄-NHCH=CHCH₃ (32 mg, 0.015 mmol) and 1,3,5-trimethoxybenzene (12 mg, 0.074 mmol) in anhydrous THF (100 μL) at −50 °C was added TfOH (2 μL, 0.022 mmol) and the mixture stirred at −50 °C for 18 h. The reaction was quenched at low temperature with sat. NaHCO₃ solution (1 mL) and allowed to warm to room temperature. The mixture was diluted with sat. NaHCO₃ solution (9 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organics were dried (MgSO₄) and concentrated to give a 88.3:11.7 mixture of 32:epi-32 (See ¹H NMR expansion; Section 4). Purification by column chromatography (SiO₂; CH₂Cl₂:MeOH; 99:1→95:5) gave the title compound as a white solid (27 mg, 0.012 mmol, 78%). ¹H NMR (800 MHz, d₈-THF; Major diastereoisomer) δH 8.13 (s, 1H, NH), 8.10 (m, 2H, 2 × NH), 8.07-8.03 (m, 3H, 3 × NH), 7.99 (s, 1H, NH), 7.97 (s, 1H, NH), 7.91 (m, 2H, 2 × NH), 7.87 (s, 1H, NH), 7.83 (s, 1H, NH), 7.76 (s, 1H, NH), 7.64-7.60 (m, 3H, 3 × NH), 7.45 (s, 1H, NH), 7.44 (s, 1H, NH), 7.41-7.31 (m, 5H, 5 × ArH, Cbz), 7.27 (m, 2H, 2 × NH), 6.94 (m, 1H, NH), 6.12 (s, 2H, 2 × ArH), 5.39 (dd, J = 15.5, 7.5, 1H, NHCH(ArEt)), 5.17 (d, J = 12.5, 1H, HA of AB, Cbz), 5.09 (d, J = 12.5, 1H, HB of AB, Cbz), 3.82 (s, 6H, 2 × OCH₃), 3.73 (s, 3H, OCH₃), 2.37 (m, 3H, 3 × CH, cyclohexyl), 2.11-1.94 (m, 10H, 9 × CH, cyclohexyl + CH(CH₃)₂), 1.88 (m, 1H, CH₃CH₂CH₃), 1.71-1.54 (m, 26H, + CH₃CH₂CH₂, CH(CH₃)₂, + 12 × CH, cyclohexyl +...
4 × CH₃), 1.52-1.47 (m, 81H, 27 × CH₃), 1.43 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.33 (s, 3H, CH₃), 1.32-1.24 (m, 6H, 6 × CH, cyclohexyl), 1.02 (d, J = 7.0, 3H, CH(CH₃)), 0.98 (d, J = 7.0, 3H, CH(CH₃)), 0.89 (d, J = 7.0, 3H, CH(CH₃)), 0.85 (d, J = 7.0, 3H, CH(CH₃)), 0.81 (t, J = 7.5, 3H, CH(CH₃)) ppm; ¹³C NMR (200 MHz, d₈-THF) δC 177.5 (2 × CO), 177.4 (CO), 177.3 (CO), 177.19 (CO), 177.16 (CO), 177.13 (2 × CO), 177.07 (CO), 177.06 (CO), 177.03 (CO), 176.97 (CO), 176.95 (2 × CO), 176.8 (CO), 176.5 (CO), 175.0 (CO), 174.6 (CO), 174.4 (CO), 173.7 (2 × CO), 161.0 (ArC), 160.4 (ArC), 158.2 (CO, Cbz), 137.8 (ArC), 129.5 (ArCH), 129.4 (ArCH), 129.3 (ArCH), 113.8 (ArC), 92.2 (ArCH), 68.0 (CH₂, Cbz), 64.5 (C), 63.6 (C), 60.6 (C), 60.53 (C), 60.51 (C), 57.9 (C), 57.78 (C), 57.75 (3 × C), 57.71 (C), 57.69 (C), 57.66 (C), 57.59 (2 × C), 57.40 (C), 57.38 (C), 57.3 (C), 56.5 (3 × C), 55.4 (OCH₃), 55.1 (OCH₃), 47.3 (NHCH(Ar)Et), 36.7 (CH(CH₃)₂), 36.5 (CH(CH₃)₂), 35.7 (br, 3 × CH₂, cyclohexyl), 29.2 (3 × CH₂, cyclohexyl), 28.6 (CH₂CH₃), 28.2-27.3 (16 × CH₃), 26.6 (3 × CH₂, cyclohexyl), 24.1-23.2 (16 × CH₃), 23.0 (3 ×CH₂, cyclohexyl), 22.7 (3 × CH₂, cyclohexyl), 19.2 (CH₃), 18.6 (CH₃), 18.1 (CH(CH₃)₂), 18.0 (CH(CH₃)₂), 17.64 (CH(CH₃)₂), 17.56 (CH(CH₃)₂), 11.8 (CH₂CH₃) ppm; MS (ES⁺, MeOH/CH₂Cl₂) m/z = 2322 ([M+H]⁺, 100%), 2324 ([M+Na]⁺, 70%).
2. Comparison of compounds containing one, two and three αMv residues

S1: Z-L-(αMe)Val8Aib**GlyNH2
S2: Z-L-(αMe)Val7Aib**GlyNH2
S3: Z-L-(αMe)Val6Aib**GlyNH2

Standard preparative methods were used to synthesise three peptides S1-S3 bearing one, two or three L-α-methylvaline residues and two pairs of diastereotopic NMR reporter groups: namely, a doubly $^{13}$C-labelled Aib** for analysis by $^{13}$C NMR (17) and a C-terminal glycinamide GlyNH2 for analysis by $^1$H NMR (24). Comparison of the $^{13}$C NMR chemical shift separations (in MeOD) in the slow and fast exchange regimes allowed us to estimate the helical excess (h.e.) at the position of the isotopic label of each peptide (see Table S1). Increasing the number of α-methylvaline residues from one in S1 to two in S2 gave rise to a significant increase in h.e. (39→60%), consistent with results reported in Table 1. However, the addition of a third α-methylvaline residue in S3 gave only a small improvement in h.e. (60→65%). This is also reflected in the $\Delta\delta_{fast}$ values for the glycinamide reporters, which again show a much lower proportional increase upon addition of the third α-methylvaline residue. Set against the apparent increase in h.e. is the fact that as the number of the α-methylvaline residues increases by one the distance between the chiral controller and the NMR reporter is reduced by one, itself accounting for a ca. 3% increase in helical excess in MeOD (16,17). Thus we conclude that no significant gain in conformational control is achieved in compounds bearing an N-terminal L-(αMe)Val3 trimer over those bearing an N-terminal L-(αMe)Val2 dimer.

Table S1.

<table>
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<th>Cpd</th>
<th>αMv</th>
<th>$\Delta\delta_{fast}$ (Aib**) /ppb</th>
<th>$\Delta\delta_{slow}$ (Aib**) /ppb</th>
<th>h.e. a /%</th>
<th>P/M b</th>
<th>$\Delta\delta_{fast}$ (Gly) /ppb</th>
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<td>3900</td>
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<td>70:30</td>
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<tr>
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<td>60</td>
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<tr>
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<td>3900</td>
<td>65</td>
<td>83:17</td>
<td>292</td>
</tr>
</tbody>
</table>

aThe value $\Delta\delta_{fast}/\Delta\delta_{slow}$ interpreted as ‘helical excess’ (i.e. [P]–[M] / [P]+[M]);
bCalculated ratio of P and M conformers derived from h.e.
**Z-L-(αMe)ValAib₅Aib** **GlyNH₂ S1**

**m.p.** 249-251 °C; **¹H NMR** (500 MHz, MeOD) δₜ 8.00 (s, 1H, NH), 7.99 (s, 1H, NH), 7.93 (s, 1H, NH), 7.91 (s, 1H, NH), 7.90 (s, 1H, NH), 7.89 (s, 1H, NH), 7.44-7.29 (m, 5H, 5 × ArH, Cbz), 5.21 (d, J = 13.0, 1H, HA of AB, Cbz), 5.09 (d, J = 13.0, 1H, HB of AB, Cbz), 3.96 (d, J = 17.0, 1H, HA of AB', Gly), 3.75 (d, J = 17.0, 1H, HB of AB', Gly), 2.03 (m, 1H, CH(CH₃)₂), 1.65 (m, 3H, CH₃), 1.50 (s, 6H, 2 × CH₃), 1.49 (s, 12H, 4 × CH₃), 1.48 (s, 18H, 6 × CH₃), 1.43 (s, 3H, CH₃), 1.40 (s, 6H, 2 × CH₃), 1.38 (s, 3H, CH₃), 1.37 (s, 3H, CH₃), 1.29 (s, 3H, CH₃), 1.01 (d, J = 7.0, 3H, CH(CH₃)), 0.95 (d, J = 6.6, 3H, CH(CH₃)) ppm; **¹³C NMR** (125 MHz, MeOD) δ_C 179.3 (CO), 179.2 (CO), 178.3 (CO), 178.3 (CO), 178.1 (CO), 177.7 (CO), 177.61 (CO), 177.58 (CO), 177.0 (CO), 176.0 (CO), 175.5 (CO), 158.2 (CO, Cbz), 138.7 (ArC), 129.7 (ArCH), 129.1 (ArCH), 128.7 (ArCH), 67.7 (CH₂, Cbz), 64.0 (C), 58.1-57.7 (9 × C), 43.8 (CH₂, Gly), 36.1 (CH(CH₃)₂), 26.4 (¹³CH₃), 26.7-26.1 (overlapping signals CH₃), 24.9 (¹³CH₃), 25.1-24.7 (overlapping signals CH₃), 18.1 (CH₃), 18.0 (CH(CH₃)₂) 17.7 (CH(CH₃)₂) ppm; **IR** ν_max = 3290, 2956, 1650, 1534, 1450, cm⁻¹; **MS** (ES⁺, MeOH) m/z = 1111 ([M+Na]⁺, 100%).

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**Z-L-(γMe)Val₂Aib₇Aib** **GlyNH₂ S2**

**m.p.** 260-262 °C; **¹H NMR** (400 MHz, MeOD) δₜ 8.08 (s, 1H, NH), 8.01 (s, 1H, NH), 7.98 (s, 1H, NH), 7.94 (s, 1H, NH), 7.93 (s, 1H, NH), 7.78 (s, 1H, NH), 7.45-7.29 (m, 5H, 5 × ArH, Cbz), 7.13 (s, 1H, NH), 5.21 (d, J = 12.5, 1H, HA of AB, Cbz), 5.06 (d, J = 12.5, 1H, HB of AB, Cbz), 3.98 (d, J = 17.5, 1H, HA of AB', Gly), 3.70 (d, J = 17.5, 1H, HB of AB', Gly), 1.95 (m, 1H, CH(CH₃)₂), 1.69 (m, 3H, CH₃), 1.60 (m, 1H, CH(CH₃)₂), 1.51 (s, 6H, 2 × CH₃), 1.50 (s, 6H, 2 × CH₃), 1.48 (s, 15H, 5 × CH₃), 1.48 (s, 6H, 2 × CH₃), 1.47 (s, 9H, 3 × CH₃), 1.46 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.36 (s, 3H, CH₃), 1.00 (d, J = 7.0, 3H, CH(CH₃)), 0.94 (d, J = 7.0, 3H, CH(CH₃)), 0.86 (d, J = 7.0, 3H, CH(CH₃)), 0.80 (d, J = 7.0, 3H, CH(CH₃)) ppm; **¹³C NMR** (100 MHz, CDCl₃) δ_C 176.5 (CO), 176.4 (CO), 176.1 (CO), 176.1 (CO), 175.8 (CO), 175.9 (2 × CO), 175.4 (CO), 173.3 (CO), 172.5 (CO), 172.4 (CO), 156.3 (CO, Cbz), 135.7 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 67.7 (CH₂, Cbz), 63.4 (C), 62.2 (C), 56.8-56.3 (8 × C), 43.0 (CH₂, Gly), 36.0 (CH(CH₃)₂), 35.7 (CH(CH₃)₂), 27.3 (¹³CH₃), 27.3-26.9 (overlapping signals CH₃), 23.3 (¹³CH₃), 22.9-22.5 (overlapping signals CH₃), 18.0
(CH₃), 17.9 (CH₃), 17.3 (CH(CH₃)₂), 17.1 (CH(CH₃)₂), 17.0 (CH(CH₃)₂), 17.0 (CH(CH₃)₂) ppm; **IR** νₘₐₓ = 3289, 2985, 1649, 1526 cm⁻¹; **MS** (ES⁺, MeOH) m/z = 1139 ([M+Na]⁺, 100%).

**Z-L-(αMe)Val₃Aib₆Aib**GlyNH₂S₃

m.p. 270-272 °C; **¹H NMR** (500 MHz, MeOD) δH 8.04 (s, 1H, NH), 7.98 (brs, 1H, NH), 7.94 (s, 1H, NH), 7.92 (s, 1H, NH), 7.48-7.30 (m, 5H, 5 × ArH, Cbz), 5.17 (d, J = 12.5, 1H, HA of AB, Cbz), 5.12 (d, J = 12.5, 1H, HB of AB, Cbz), 3.99 (d, J = 17.5, 1H, HA of AB’, Gly), 3.70 (d, J = 17.5, 1H, HB of AB’, Gly), 2.06 (m, 1H, CH(CH₃)₂), 1.96 (m, 1H, CH(CH₃)₂), 1.80 (m, 1H, CH(CH₃)₂), 1.66 (s, 3H, CH₃), 1.51 (s, 6H, 2 × CH₃), 1.50 (s, 9H, 3 × CH₃), 1.49 (s, 6H, 2 × CH₃), 1.48 (s, 6H, 2 × CH₃), 1.47 (s, 6H, 2 × CH₃), 1.44 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.29 (s, 6H, 2 × CH₃), 1.07 (d, J = 7.0, 3H, CH(CH₃)), 1.01 (d, J = 7.0, 3H, CH(CH₃)), 0.97 (d, J = 7.0, 3H, CH(CH₃)), 0.96 (d, J = 7.0, 3H, CH(CH₃)), 0.91 (d, J = 7.0, 3H, CH(CH₃)), 0.89 (d, J = 7.0, 3H, CH(CH₃)) ppm; **NMR** (125 MHz, CD₂OD) δC 178.3 (CO), 178.2 (CO), 178.1 (CO), 177.7 (3 × CO), 176.0 (CO), 175.9 (CO), 175.5 (CO), 175.0 (CO), 174.3 (CO), 158.2 (CO, Cbz), 138.2 (ArC), 129.7 (ArCH), 129.3 (ArCH), 129.0 (ArCH), 67.9 (CH₂, Cbz), 64.7 (C), 64.5 (C), 64.0 (C), 58.1 (C), 58.0 (C), 57.9 (C), 57.9-57.7 (4 × C), 43.8 (CH₂, Gly), 37.0 (CH(CH₃)₂), 36.7 (2 × CH(CH₃)₂), 26.9 (¹³CH₃), 27.6-26.2 (overlapping signals CH₃), 24.4 (¹³CH₃), 24.8-23.3 (overlapping signals CH₃), 19.7 (CH₃), 18.7 (CH₃), 18.4 (CH₃), 18.0 (2 × CH(CH₃)₂), 18.0 (CH(CH₃)₂), 17.6 (2 × CH(CH₃)₂), 17.2 (CH(CH₃)₂) ppm. **IR** νₘₐₓ = 3297, 2975, 1663, 1550 cm⁻¹; **MS** (ES⁺, MeOH) m/z = ([M+Na]⁺, 100%).

3. NMR Spectra
$^1$H NMR (400 MHz, CDCl$_3$) of HCl·H-Aib*OEt

$^{13}$C NMR (100 MHz, CDCl$_3$) of HCl·H-Aib*OEt
$^1$H NMR (400 MHz, CDCl$_3$) of N$_3$Aib$_4$Aib*OEt

$^{13}$C NMR (100 MHz, CDCl$_3$) of N$_3$Aib$_4$Aib*OEt
$^1$H NMR (300 MHz, CDCl$_3$) of N$_3$Aib$_4$Aib*OH

$^{13}$C NMR (125 MHz, MeOD) of N$_3$Aib$_4$Aib*OH
$^1$H NMR (500 MHz, MeOD) of N$_3$Aib$_4$Aib*Aib$_4$O'Bu

$^{13}$C NMR (125 MHz, MeOD) of N$_3$Aib$_4$Aib*Aib$_4$O'Bu
$^1$H NMR (400 MHz, MeOD) of Z-L-(αMe)ValAib$_4$Aib*Aib$_4$O'Bu 4

$^{13}$C NMR (100 MHz, MeOD) of Z-L-(αMe)ValAib$_4$Aib*Aib$_4$O'Bu 4
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Aib*Aib$_4$O$^t$Bu 5

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Aib*Aib$_4$O$^t$Bu 5
$^1$H NMR (300 MHz, MeOD) of Z-L-(αMe)Val₂Aib₄GlyNH₂ 6

$^{13}$C NMR (75 MHz, MeOD) of Z-L-(αMe)Val₂Aib₄GlyNH₂ 6
$^1$H NMR (500 MHz, MeOD) of N$_3$Aib$_4$PhSer-OMe

$^{13}$C NMR (125 MHz, MeOD) of N$_3$Aib$_4$PhSer-OMe
$^{1}H$ NMR (500 MHz, MeOD) of $N_{3}Aib_{4}^\Delta$PheAib$_{4}O^t$Bu

$^{13}C$ NMR (125 MHz, MeOD) of $N_{3}Aib_{4}^\Delta$PheAib$_{4}O^t$Bu
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)ValAib₄PheAib₄OTBu 7

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)ValAib₄PheAib₄OTBu 7
$^1$H NMR (400 MHz, CDCl$_3$) of Z-L-(αMe)ValAib$_4$O'Bu

$^{13}$C NMR (100 MHz, CDCl$_3$) of Z-L-(αMe)ValAib$_4$O'Bu
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$O'Bu

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$O'Bu
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$PhSer-OMe

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$PhSer-OMe
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$PheAib$_4$O'Bu 8

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$PheAib$_4$O'Bu 8
$^1\text{H NMR (500 MHz, CDCl}_3\text{)}$ of Z-L-PheAib$_4$O'Bu

$^{13}\text{C NMR (125 MHz, CDCl}_3\text{)}$ of Z-L-PheAib$_4$O'Bu
$^1$H NMR (500 MHz, CDCl$_3$) of Z-D-PheAib$_4$O'Bu

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-D-PheAib$_4$O'Bu
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)ValAib$_4$-OH

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)ValAib$_4$-OH
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Valib$_4$-L-Pheib$_4$O'Bu 9a

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Valib$_4$-L-Pheib$_4$O'Bu 9a
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)ValAib$_4$-D-PheAib$_4$O'Bu 9b

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)ValAib$_4$-D-PheAib$_4$O'Bu 9b
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$L-PheAib$_4$O'Bu 10a

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$L-PheAib$_4$O'Bu 10a
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$-D-PheAib$_4$O'Bu 10b

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$-D-PheAib$_4$O'Bu 10b
$^1$H NMR (500 MHz, MeOD) of Z-L-($\alpha$Me)Val$_2$Aib$_4$-NHAllyl 11

$^{13}$C NMR (125 MHz, MeOD) of Z-L-($\alpha$Me)Val$_2$Aib$_4$-NHAllyl 11
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$-NHCH=CHCH$_3$ 12

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$-NHCH=CHCH$_3$ 12
$^1$H NMR (500 MHz, CDCl$_3$) of (S)-2-methyl-$N$-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide

$^{13}$C NMR (125 MHz, CDCl$_3$) of (S)-2-methyl-$N$-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide
$^1$H NMR (500 MHz, CDCl$_3$) of (R)-2-methyl-$N$-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide

$^{13}$C NMR (125 MHz, CDCl$_3$) of (R)-2-methyl-$N$-(2,4,6-trimethoxybenzylidene)propane-2-sulfinamide
$^1$H NMR (500 MHz, CDCl$_3$) of (S)-2-methyl-N-((R)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfinamide

$^{13}$C NMR (125 MHz, CDCl$_3$) of (S)-2-methyl-N-((R)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfinamide
$^1$H NMR (500 MHz, CDCl$_3$) of (R)-2-methyl-N-((S)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfinamide

$^{13}$C NMR (125 MHz, CDCl$_3$) of (R)-2-methyl-N-((S)-1-(2,4,6-trimethoxyphenyl)propyl)propane-2-sulfinamide
$^1$H NMR (500 MHz, CDCl$_3$) of (R)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (R)-15

$^{13}$C NMR (125 MHz, CDCl$_3$) of (R)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (R)-15
$^1$H NMR (500 MHz, CDCl$_3$) of (S)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (S)-15

$^{13}$C NMR (125 MHz, CDCl$_3$) of (S)-1-(2,4,6-trimethoxyphenyl)propan-1-amine (S)-15
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 14a

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 14a
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 14b

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 14b
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$OMe 17

$^{13}$C NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$OMe 17
$^1$H NMR (500 MHz, MeOD) of N$_3$Aib$_4$NHAllyl 18

$^{13}$C NMR (125 MHz, MeOD) of N$_3$Aib$_4$NHAllyl 18
$^1$H NMR (500 MHz, CDCl$_3$) of N$_3$Aib$_4$-NHCH=CHCH$_3$

$^{13}$C NMR (125 MHz, CDCl$_3$) of N$_3$Aib$_4$-NHCH=CHCH$_3$
$^1$H NMR (500 MHz, MeOD) of N$_3$Aib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide (R)-19

$^{13}$C NMR (125 MHz, MeOD) of N$_3$Aib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide (R)-19
$^1$H NMR (500 MHz, MeOD) of N$_3$Aib$_4$-(S)-N-(1-(2,4,6-
trimethoxyphenyl)propylamide (S)-19

$^{13}$C NMR (125 MHz, MeOD) of N$_3$Aib$_4$-(S)-N-(1-(2,4,6-
trimethoxyphenyl)propylamide (S)-19
$^1$H NMR (500 MHz, MeOD) of Z-Ac$_6$c-OH

$^{13}$C NMR (125 MHz, MeOD) of Z-Ac$_6$c-OH
$^1$H NMR (500 MHz, CDCl$_3$) of Z-Ac$_6$C$_4$Aib$_4$O$^t$Bu

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-Ac$_6$C$_4$Aib$_4$O$^t$Bu
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$OtBu

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$OtBu
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-OH 21

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-OH 21
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-NHAllyl 24

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-NHAllyl 24
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-NHCH=CHCH$_3$ 27

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-NHCH=CHCH$_3$ 27
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 30

$^1$H NMR (800 MHz, d$_8$-THF) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 30
$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 30

$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide epi-30
\(^{1}\text{H NMR} (800 \text{ MHz, d}_8\text{-THF})\) of \(Z-L-(\alpha\text{Me})\text{Val}_2\text{Aib}_4\text{Ac}_6\text{cAib}_4-(S)-N-(1-(2,4,6-\text{trimethoxyphenyl})\text{propylamide} \text{ epi-30}\)

\(^{13}\text{C NMR} (125 \text{ MHz, MeOD})\) of \(Z-L-(\alpha\text{Me})\text{Val}_2\text{Aib}_4\text{Ac}_6\text{cAib}_4-(S)-N-(1-(2,4,6-\text{trimethoxyphenyl})\text{propylamide} \text{ epi-30}\)
\(^1\)H NMR (500 MHz, MeOD) of Z-L-(\(\alpha\)Me)Val2Aib4Ac5cAib4Ac5cAib4\(\alpha\)Bu

\(^{13}\)C NMR (125 MHz, MeOD) of Z-L-(\(\alpha\)Me)Val2Aib4Ac5cAib4Ac5cAib4\(\alpha\)Bu
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-OH 22

$^{13}$C NMR (100 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-OH 22
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHAllyl 25

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHAllyl 25
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHCH=CHCH$_3$ 28

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHCH=CHCH$_3$ 28
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 31

$^1$H NMR (800 MHz, d$_8$-THF) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 31
$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-(R)-N-(1-(2,4,6-trimethoxyphenyl)propylamide 31

$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide epi-31
$^1$H NMR (800 MHz, d$_8$-THF) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide epi-31

$^{13}$C NMR (125 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-(S)-N-(1-(2,4,6-trimethoxyphenyl)propylamide epi-31
$^1$H NMR (400 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$OtBu

$^{13}$C NMR (100 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$OtBu
$^1$H NMR (400 MHz, MeOD) of Z-L-(\(\alpha\)Me)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-OH 23

$^{13}$C NMR (100 MHz, MeOD) of Z-L-(\(\alpha\)Me)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-OH 23
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHAllyl 26

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHAllyl 26
$^1$H NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHCH=CHCH$_3$ 29

$^{13}$C NMR (125 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-NHCH=CHCH$_3$ 29
$^1$H NMR (800 MHz, d$_8$-THF) of Z-L-(αMe)Val$_2$Aib$_2$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-N-(1-(2,4,6-trimethoxyphenyl)propylamide 32

$^{13}$C NMR (200 MHz, d$_8$-THF) of Z-L-(αMe)Val$_2$Aib$_2$Ac$_6$cAib$_4$Ac$_6$cAib$_4$Ac$_6$cAib$_4$-N-(1-(2,4,6-trimethoxyphenyl)propylamide 32
$^1$H NMR (500 MHz, MeOD) of Z-L-($\alpha$Me)ValAib$_8$Aib**GlyNH$_2$

$^{13}$C NMR (125 MHz, MeOD) of Z-L-($\alpha$Me)ValAib$_8$Aib**GlyNH$_2$
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_2$Aib$_7$Aib**GlyNH$_2$

$^{13}$C NMR (500 MHz, CDCl$_3$) of Z-L-(αMe)Val$_2$Aib$_7$Aib**GlyNH$_2$
$^1$H NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_3$Aib$_6$Aib**GlyNH$_2$

$^{13}$C NMR (500 MHz, MeOD) of Z-L-(αMe)Val$_3$Aib$_6$Aib**GlyNH$_2$
4. $^1$H NMR expansions: determination of diastereomeric ratios

Diastereomeric ratios were determined by $^1$H NMR analysis of the crude reaction mixtures via integration of diagnostic signals identified from the preparation of authentic samples. Baseline resolution of the diagnostic signals of 30, 31 and 32 was achieved using $d_8$-THF as the NMR solvent. A broadband homodecoupled $^1$H NMR (pure shift) spectrum for 32 was acquired using a band-selective pure shift sequence with interferrogram based data collection. The sequence used is based on that of Zangger and Sterk,\cite{6} with extensive modification.\cite{7} To maximise the signal-to-noise ratio for the diagnostic region, no magnetic field gradient was applied during the 14.575 ms (160 Hz bandwidth) $rsnob$ frequency selective refocusing pulse, which was centred on the diagnostic signals. To generate the high resolution pure shift $^1$H NMR spectrum, 80 chunks of data, each of duration 19.968 ms, were acquired to give a total of 20480 complex points. 4 transients were acquired for each chunk, and 8 steady state scans were used with a total recycle time of 9.3 s. The total experiment time was 55 min. The multiplets are reduced to singlets, resolving the distinct species in the diagnostic region. The identity of the major diastereomer 32 was assigned by comparison with the lower homologues 14, 30 and 31.
$^1$H NMR (500 MHz, MeOD; expansion) of 9a

$^1$H NMR (500 MHz, MeOD; expansion) of 9b
$^1$H NMR (400 MHz, MeOD; expansion) of 9a/9b (crude reaction mixture; EtOH)

$^1$H NMR (400 MHz, MeOD; expansion) of 9a/9b (crude reaction mixture; CH$_2$Cl$_2$)
$^1$H NMR (500 MHz, MeOD; expansion) of 10a

$^1$H NMR (500 MHz, MeOD; expansion) of 10b
$^1$H NMR (400 MHz, MeOD; expansion) of 10a/10b (crude reaction mixture; EtOH)

$^1$H NMR (500 MHz, MeOD; expansion) of 10a/10b (crude reaction mixture; CH$_2$Cl$_2$)
$^1$H NMR (500 MHz, MeOD; expansion) of 14a

$^1$H NMR (500 MHz, MeOD; expansion) of 14b
$^1$H NMR (500 MHz, MeOD; expansion) of 14a/14b (crude reaction mixture)

$^1$H NMR (800 MHz, $d_8$-THF; expansion) of 30
$^1$H NMR (800 MHz, $d_8$-THF; expansion) of epi-30

$^1$H NMR (800 MHz, $d_8$-THF; expansion) of 30/epi-30 (crude reaction mixture)
$^1$H NMR (800 MHz, $d_8$-THF; expansion) of 31

$^1$H NMR (800 MHz, $d_8$-THF; expansion) of epi-31
\(^1\)H NMR (800 MHz, d\(_8\)-THF; expansion) of 31/epi-31 (crude reaction mixture)

\(^1\)H NMR (800 MHz, d\(_8\)-THF; expansion) of 32/epi-32 (crude reaction mixture)
Pure shift $^1$H NMR (800 MHz, $d_8$-THF; expansion) of 32/epi-32 (crude reaction mixture)
5. Circular dichroism spectra of peptides 4 and 5 in MeOH

![Circular dichroism spectra of peptides 4 and 5 in MeOH](image)

- Molar ellipticity (deg cm$^2$ dmol$^{-1}$)
- Wavelength (nm)
6. d<sub>6</sub>-DMSO titration: evidence for adoption of 3<sub>10</sub> helicity in THF

In a 3<sub>10</sub> helix two N-terminal N–H bonds do not participate in intramolecular hydrogen bonding; in an α helix three N-terminal N–H bonds are in this position. We added 2, 4, 6 and 8 mol% d<sub>6</sub>-DMSO successively to a d<sub>8</sub>-THF solution of 5 and noted that only two of the NH signals underwent a downfield shift (See Fig S1), consistent with their non-participation in intramolecular hydrogen bonding. [1,8]

Fig. S1.
Chemical shift (ppm) vs vol% d<sub>6</sub>-DMSO in d<sub>8</sub>-THF added to a 17 mM solution of 5 in d<sub>8</sub>-THF.
7. Computational Details

All calculations were carried out using the Gaussian 09 package [Revision A.02, Gaussian, Inc., Wallingford CT (2009).] Full geometry optimizations were performed with the B3LYP density functional using the 6-31G(d,p) basis set.\textsuperscript{[9-13]} For peptide 6b, 36 conformers were fully optimized corresponding to all possible combinations of: a) Type II/Type III initial turn (x2); b) $P/M$ helicity (x2); c) rotameric arrangements of the two isopropyl groups (x9). Single-point calculations on the optimized structures were then carried out with the B3LYP and the M06-2X density functionals,\textsuperscript{[14,15]} using the 6-311+G(2d,2p) basis set (See Table S2).
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<th>$B3LYP \ E_{\text{rel}}$ [kcal/mol]</th>
<th>$M06-2X \ E_{\text{rel}}$ [kcal/mol]</th>
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<td>6.2</td>
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</table>
8. X-ray crystallographic analysis of 6

Metrical parameters for the structure of 6 are available free of charge from the Cambridge Crystallographic Data Centre (reference number CCDC 954033)
9. Details of line-shape modeling for 4 (MeOD) and 5 (MeOD and d₈-THF)

After 1 Hz line broadening, phased ¹³C data for the spectral regions containing the two labelled signals were transferred to the program Mathematica 8 [Wolfram Research, Inc., Mathematica, Version 8.0, Champaign, IL (2010).] and downsampled to a digitization of 0.91 Hz/pt. For each solvent, global nonlinear least squares fitting of the complete set of data as a function of temperature was performed using the analytical solutions of the steady-state Bloch-McConnell equations for asymmetric two-site exchange with negligible saturation, assuming (i) Arrhenius temperature dependences for the forward and back rate constants, (ii) negligible transverse relaxation compared to the applied line broadening, and (iii) a linear dependence of weighted average chemical shift on temperature. The parameters iterated on were the activation energy \( E_a \), the enthalpy of interconversion \( \Delta H \), the enantiomeric excess \( ee \) of ¹³C label, the chemical shift difference \( \Delta \delta_{\text{slow}} \), the average chemical shift \( \delta \), the temperature coefficient \( d\delta/dT \) of the shift, the rate and equilibrium constants at –50 °C \( k_{223} \) and \( K_{223} \) and the signal intensity. The fitted parameters obtained are listed below (see Table S3); the estimated standard errors quoted are those reported by the Mathematica function NonlinearModelFit, for the fitting alone. They do not include the effects of systematic errors, which in most cases will be substantially larger. The Mathematica notebooks below illustrate the analysis, in which initial manual adjustment of parameters was used to generate starting guesses from which full automated iterative fitting could proceed. Calculations were performed on a Mac Pro computer with 2 x 2.4 GHz quad-core Xeon processors and 24 Gb of memory; calculation times (‘Cumulative time’) in seconds are given in the notebooks.
### Table S3.

<table>
<thead>
<tr>
<th></th>
<th>4 (MeOD)</th>
<th>5 (MeOD)</th>
<th>5 (d₈-THF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_a$</td>
<td>$32.4 ± 0.2$</td>
<td>$35.7 ± 0.2$</td>
<td>$30.8 ± 0.2$</td>
</tr>
<tr>
<td>$\Delta H$</td>
<td>$-3.3 ± 0.1$</td>
<td>$-2.3 ± 0.1$</td>
<td>$-6.3 ± 0.1$</td>
</tr>
<tr>
<td>$ee$</td>
<td>$0.45 ± 0.01$</td>
<td>$0.49 ± 0.01$</td>
<td>$0.51 ± 0.01$</td>
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<tr>
<td>$\Delta \delta_{\text{slow}}$</td>
<td>$4.488 ± 0.002$</td>
<td>$4.471 ± 0.002$</td>
<td>$4.413 ± 0.001$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>$25.216 ± 0.002$</td>
<td>$25.254 ± 0.002$</td>
<td>$25.589 ± 0.001$</td>
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<tr>
<td>$d\delta/dT$</td>
<td>$-6.7 ± 0.2 \times 10^{-4}$</td>
<td>$-3.9 ± 0.1 \times 10^{-4}$</td>
<td>$-2.1 ± 0.1 \times 10^{-4}$</td>
</tr>
<tr>
<td>$k_{223}$</td>
<td>$360 ± 9$</td>
<td>$580 ± 8$</td>
<td>$630 ± 23$</td>
</tr>
<tr>
<td>$K_{223}$</td>
<td>$4.9 ± 0.1$</td>
<td>$9.5 ± 0.1$</td>
<td>$60 ± 1$</td>
</tr>
</tbody>
</table>
Fig. S2.
Variable-temperature $^{13}$C NMR (500 MHz, MeOD) spectra of 4 between 193K (bottom) and 313K (top)
Fig. S3.
Variable-temperature $^{13}$C NMR (500 MHz, MeOD) spectra of 5 between 193K (bottom) and 313K (top)
Fig. S4.
Variable-temperature $^{13}$C NMR (500 MHz, $d_8$-THF) spectra of 5 between 213K (bottom) and 313K (top)
Fit Liam Byrne data for αMeVal monolabelled Aib in methanol using analytical asymmetric 2 - site exchange solution

Reduction temperature range from -60 °C, downsample only 4x
Normalise spectra to constant integral

```
alldata = Join[{atemps[[1]], sp2[[1, 1]], sp2[[1, 2]]}, alldata = AppendTo[alldata, {atemps[[i temp]], sp2[[j, 1]], sp2[[j, 2]]}];
}
];
]
];
alldataorig = alldata;
(* Normalise spectra to constant integral *)
ints = Table[0, {i, nt}];
j = 0; int = 0; k = 0; max = 0; For[i = 1, i <= Length[temps], i++, int = 0;
For[j = 2, j <= ns, j++, k = j + (i - 1) ns; int = int + (alldataorig[[k, 3]] + alldataorig[[k - 1, 3]]) (alldataorig[[k, 2]] - alldataorig[[k - 1, 2]]) / 2;
];
For[j = 1, j <= ns, j++, k = j + (i - 1) ns; alldata[[k, 3]] = 1200.0 alldataorig[[k, 3]] / (int (alldataorig[[ns, 2]] - alldataorig[[1, 2]]));
If[alldata[[k, 3]] > max, max = alldata[[k, 3]]];
];
ints[[i]] = int;
]
];

marker = Graphics[{Gray, Disk[{0, 0}, 0.1]}, 0.015];
ns = Length[alldata] / nt;
pos = 0;
offset = 1; For[i = 1, i <= Length[temps], i++,
exp = ListPlot[Table[{0, pos}, {j, ns}] + Take[Transpose[Take[Transpose[alldata], {2, 3}]], {1 + (i - 1) ns, i ns}],
Axes -> None, PlotRange -> All, PlotMarkers -> marker, PlotStyle -> PointSize[0.001]];
plot[i] = Show[exp];
pos = pos + offset;
]
];
Show[Table[plot[i], {i, Length[temps]}], ImageSize -> {840, 600}]
starttime = TimeUsed[];
offset = 0.024;
ti = alldata[[1, 1]]; tf = alldata[[ns + (nt - 1) + 1, 1]];
Clear[δ, f, ff, f0, ea, dh, i, netshift, allmodel, params, assumptions];
r = 8.3144; lineb = 2;

eag = 2.5; K223g = 4.2; og = 42; k223g = 120; dhsg = -1.6; δg = 4.55; eeg = 4.2; f0g = -25.21; netshiftg = 0.07;
params = {{ea, eag}, {K223, K223g}, {a, og}, {k223, k223g}, {dhsg, dhsg}, {δg, δg}, {eeg, eeg}, {f0, f0g}, {netshift, netshiftg}};
assumptions = {
{dh -> 1000 dhsg, λ -> Pi lineb, kmp -> k223 Exp[-(10000 ea / r) (1 / ttemp - 1 / 223.15)], kpm -> kmp / K223} Exp[(dh / r) (1 / ttemp - 1 / 223.15)];
allmodel = spec //. assumptions;

sol = NonlinearModelFit[alldata, (allmodel // (f -> sfq (ff - f0 + netshift + (ttemp - ti) / (tf - ti)))), params, {ttemp, ff}, MaxIterations -> 5000];
sol["ParameterConfidenceIntervalTable"]
sol["ANOVATable"]
sol["EstimatedVariance"]
```
sol[ "EstimatedVariance"]
Clear[ plots ];
plots = Array[ plot, Length[ temps ]]; pos = 0;
offset = 1;
nt = Length[ temps ]; ns = Length[ alldata ] / nt;
For[ i = 1, i ≤ Length[ temps ], i++,
    fit = Plot[ pos + sol[ attemps[[i]] ], ff ],
    { ff, alldata[[1, 2]], alldata[[ns, 2]] },
    PlotRange → All, PlotStyle → ( Red, Thick ),
    Axes → None; exp = ListPlot[
        Table[ {{0, pos}, {j, ns}} + Take[ Transpose[ Take[ Transpose[ alldata ], {2, 3} ] ],
            (1 + (i - 1) ns, i ns ) ],
        Axes → None, PlotRange → All, PlotStyle → PointSize[ 0.01 ] ];
    plot[ i ] = Show[ exp, fit ];
    pos = pos + offset;
]
Show[ Table[ plot[ i ], {i, Length[ temps ]} ], ImageSize → {840, 600} ];
Export[ rootfilename <> "_finalplot.eps", Show[ Table[ plot[ i ], {i, Length[ temps ]} ] ] ];
Print[ "Cumulative time = ", TimeUsed[] - starttime ];
NonlinearModelFit::sszero : The step size in the search has become less than the tolerance prescribed by the PrecisionGoal option, but the gradient is larger than the tolerance specified by the AccuracyGoal option. There is a possibility that the method has stalled at a point that is not a local minimum. ➔
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<th>Confidence Interval</th>
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<td>k223</td>
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<td>(351.335, 369.269)</td>
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0.000476956

0.933658
Cumulative time = 255.424
Fit Liam Byrne data for αMeVal2 monolabelled Alb in methanol using analytical asymmetric 2-site exchange solution

Use data only from -60 °C, downsample only 4x

Correct temperature values

```
In[392]:= Clear[Context][D]

itemp = D; ns tempin = D;

spec = spec; smyr = smyr; spy = spy; sssol = Solve[ssseqs, {px, py, mx, my}];
smy = my / sssol[[1]]; spy = py / sssol[[1]]; smyr = smy /.(δ -> δ);
spyr = spy /.(δ -> δ);
spec = (ee (smy + spy) + smyr + spyr) / (1 + ee);
spec = ((1 + ee) (smy + spy) + (1 - ee) (smyr + spyr)) / 2;
Plot[spec/.(δ -> 25, α -> 1, kmp -> 0.6, kpm -> 0.2, λ -> 3), (f -> -50, 50), PlotRange -> All]
Plot[(smyr + spyr)/.(δ -> 25, α -> 1, kmp -> 0.6, kpm -> 0.2, λ -> 3), (f -> -50, 50), PlotRange -> All]
Plot[spec/.(δ -> 25, α -> 1, kmp -> 0.6, kpm -> 0.2, λ -> 3, ee -> 3.5), (f -> -50, 50), PlotRange -> All]

rootfilename = "2012-06-15-jpc-62-tr";
downsamp = 4;
linelb = 1; sw = 29761.9; rfl = 8295.4; rfp = 6162.7; sfrq = 125.783;
marker = {Graphics[{Gray, Disk[{0, 0}, 0.1]}], 0.03};
atemps = 273.15 + {-60.1, -50, -39.9, -30, -20, -9.9, 0, 10, 20, 30.1, 40};
temps = atemps; nt = Length[temps];

(* read data *)

For[itemp = 1, itemp <= nt, itemp++,
    tempin = temps[[itemp]];
    filename = rootfilename <> ToString[itemp + 2];
    filein = OpenRead[filename];
    Read[filename, String];
    dum = Read[filename, Real];
    np = Read[filename, Real];
    Read[filename, String];
    sp = Table[{0, 0}, {i, np}];
    int = 0;
    Read[filename, String];
    For[j = 1, j <= np, j++,
        sp[[j, 1]] = -(sw/2 + rfp - rfl - Read[filename, Number]) / sfrq; sp[[j, 2]] = Read[filename, Number];
    ]
    Close[filename];
    sp2 = Take[sp, {106260, 107100, downsamp}]; n1 = Length[sp2]; sp2[[n1 + 2]] = 0;
    sp2 = Join[sp2, Take[sp, {108000, 109200, downsamp}]]; ns = Length[sp2]; sp2[[n1 + 1, 2]] = 0;
    (* Print[ListPlot[sp2,PlotRange->All,PlotStyle->PointSize[0.015],Joined->True, Axes->(True,False)]; *)
    For[j = 1, j <= Length[sp2], j++,
        If[(itemp == 1) && (j == 1),
            ,
        ]
    ]
```

S147
```mathematica
alldata = {{atemps[[1]], sp2[[1, 1]], sp2[[1, 2]]}};

alldata = AppendTo[alldata, {atemps[[itemp]], sp2[[j, 1]], sp2[[j, 2]]}];

alldataorig = alldata;

(* Normalise spectra to constant integral *)

int = Table[0, {i, nt}];
j = 0; int = 0; k = 0; max = 0;
For[i = 1, i <= Length[temps], i++, int = 0; 
For[j = 2, j <= ns, j++, k = j + (i - 1) ns; int = int + (alldataorig[[k, 3]] + alldataorig[[k - 1, 3]]) (alldataorig[[k, 2]] - alldataorig[[k - 1, 2]])/2; 
}
For[j = 1, j <= ns, j++, k = j + (i - 1) ns; alldata[[k, 3]] = 1200.0 alldataorig[[k, 3]]/(int (alldataorig[[ns, 2]] - alldataorig[[1, 2]])); 
If[alldata[[k, 3]] > max, max = alldata[[k, 3]]]; 
]

ints[[i]] = int;
}

For[i = 1, i <= Length[temps], i++, int = 0; 
For[j = 1, j <= ns, j++, k = j + (i - 1) ns; alldata[[k, 3]] = alldata[[k, 3]]/max; 
]

marker = {Graphics[{Gray, Disk[{0, 0}, 0.1]}, 0.015];
	ns = Length[alldata]/nt;

pos = 0;
	ns = Length[alldata]/nt;

offset = 1; For[i = 1, i <= Length[temps], i++, 

exp = ListPlot[Table[{0, pos}, {j, ns}] + Take[Transpose[Take[Transpose[alldata], {2, 3}]], {1 + (i - 1) ns, i ns}], 

Axes -> None, PlotRange -> All, PlotMarkers -> marker, PlotStyle -> PointSize[0.001];
plot[i] = Show[exp];
pos = pos + offset;
]

Show[Table[plot[i], {i, Length[temps]}], ImageSize -> {840, 600}]

starttime = TimeUsed[];

offset = 0.024;
ti = alldata[[1, 1]]; tf = alldata[[ns*(nt - 1) + 1, 1]];

Clear[δ, f, ff, f0, ea, dh, i, netshift, allmodel, params, assumptions];
r = 8.3144; lineb = 2;

```

Try guess for lowest temperature

\[
\begin{align*}
eag &= 3.6; \\
K223g &= 8.9; \\
ag &= 15; \\
k223g &= 580; \\
dhsg &= -1.6; \\
deeg &= 0.5; \\
f0g &= -25.3; \\
\text{netshiftg} &= 0.02; \\
ti &= \text{alldata}[[1, 1]]; \\
tf &= \text{alldata}[[\text{ns}*(\text{nt}-1)+1, 1]]; \\
r &= 8.3144; \quad \text{lineb} = 2; \\
tests &= \{ea \rightarrow \text{eag}, \\
K223 \rightarrow K223g, \\
\alpha \rightarrow ag, \\
k223 \rightarrow k223g, \\
dhs \rightarrow dhsg, \\
\delta \rightarrow \delta g, \\
eeeg \rightarrow eeg, \\
f0 \rightarrow f0g, \\
\text{netshift} \rightarrow \text{netshiftg}; \}
\end{align*}
\]

\[
\begin{align*}
\text{assumptions} &= \{dh \rightarrow 1000 \text{ dhs}, \lambda \rightarrow \text{Pi lineb}, \\
kmp \rightarrow \text{k223 Exp}[-(10000 \text{ ea} / r) \left(1 / (\text{tttemp} - 1) / 223.15\right)], \\
kmp \rightarrow \text{k223 Exp}[(\text{dh} / r) \left(1 / (\text{tttemp} - 1) / 223.15\right)]; \}
\end{align*}
\]

\[
\begin{align*}
\text{allmodel} &= \text{spec} //. \text{assumptions}; \\
i &= 1; \\
\text{Show}[\text{Plot}[(\text{allmodel} //. (\text{tttemp} \rightarrow \text{atemps}[[1]]), f \rightarrow \text{sfrq} (\text{ff} - f0 + \text{netshift} \ast (\text{tttemp} - \text{ti}) / (\text{tf} - \text{ti}))) / . \text{tests}, \\
\{\text{ff, alldata}[[1, 2]], \text{alldata}[[\text{ns}, 2]]\}, \text{PlotRange} \rightarrow \text{All}, \text{Axes} \rightarrow \{\text{True, False}\}, \text{PlotStyle} \rightarrow \{\text{Red, Thick}\}], \text{ListPlot}[ \\
\text{Take}[\text{Transpose}[\text{Take}[\text{Transpose}[\text{alldata}], \{2, 3\}]], \{1 + (i-1) \text{ ns}, i \text{ ns}\}], \text{Axes} \rightarrow \{\text{True, False}\}, \text{PlotRange} \rightarrow \text{All}, \text{PlotStyle} \rightarrow \text{PointSize}[0.01]]
\end{align*}
\]
Try guess for highest temperature

```mathematica
In[431]:= eag = 3.6; K223g = 8.9; \[alpha]g = 15; k223g = 580; dhsg = -1.6; \[delta]g = 4.52; eeg = 0.5; f0g = -25.3; netshiftg = 0.02;
ti = alldata[[1, 1]]; tf = alldata[[ns + (nt - 1) + 1, 1]];
r = 8.3144; lineb = 2;
tests = (ea -> eag, K223 -> K223g, \[alpha] -> \[alpha]g, k223 -> k223g, dh -> dhsg, \[delta] -> \[delta]g, ee -> eeg, f0 -> f0g, netshift -> netshiftg);
assumptions = 
  {dh -> 1000 dh, \[lambda] -> Pi lineb, kmp -> k223 Exp[-(10000 ea / r) (1 / (ttemp - 1 / 223.15))], kpm -> (kmp / K223) Exp[(dh / r) (1 / (ttemp - 1 / 223.15))];
  allmodel = spec //. assumptions;

i = nt;
Show[Plot[(allmodel //. {ttemp -> atemps[[i]], f -> sfrq (ff - f0 + netshift * (ttemp - ti) / (tf - ti))) //. tests, 
{ff, alldata[[1, 2]], alldata[[ns, 2]]}, PlotRange -> All, Axes -> {True, False}, PlotStyle -> {Red, Thick}], ListPlot[
  Take[Transpose[Take[Transpose[alldata], {2, 3}]], (1 + (i - 1) ns, i ns)], Axes -> {True, False}, PlotRange -> All, PlotStyle -> PointSize[0.01]]]```
Out[440]=

Out[444]=

In[449]=

JPC_LB_fit_aMvM2_NLMF_ds4_ee_14iii13.nb

netshift 0.0390607 0.000923922
f0 - ee 0.492983 0.00429279
4.4711 0.00172744
dhs - k223 580.703 7.62313
a 15.0539 0.0749725
K223 9.50769 0.0364729
Error 5623 0.88389 0.000157192
Model 9 13.3332 1.48147
Uncorrected Total 5623 0.88389 0.000157192
Corrected Total 5631 11.7839

params = (ea, eeg, (K223, K223g), (a, ag), (k223, k223g), (dhs, dhsg), (ee, eeg), (f0, f0g), (netshift, netshiftg));
assumptions = {dh -> 1000 dhs, \(\lambda\) -> Pi lineb, kmp -> k223 Exp[-(10 000 ea / r) (1 / ttemp - 1 / 223.15)], kpm -> (kmp / K223) Exp[(dh / r) (1 / ttemp - 1 / 223.15)]};
allmodel = spec //. assumptions;
sol = NonlinearModelFit[alldata, (allmodel //. (f -> sfrq (ff - f0 + netshift + (ttemp - ti) / (tf - ti))))], params, {ttemp, ff}, MaxIterations -> 5000];
sol["ParameterConfidenceIntervalTable"]
sol["ANOVAtable"]
sol["EstimatedVariance"]
sol["AdjustedRSquared"]
Clear[plots];
plots = Array[plot, Length[temps]]; pos = 0;
offset = 1;
nt = Length[temps]; ns = Length[alldata] / nt;
For[i = 1, i < Length[temps], i++,
  fit = Plot[pos + sol[atemps[[i]], ff], (ff, alldata[[1, 2]], alldata[[ns, 2]]), PlotRange -> All, PlotStyle -> (Red, Thick), Axes -> None];
  exp = ListPlot[Table[{0, pos}, {j, ns}) + Take[Transpose[Take[Transpose[alldata], {2, 3}]], 1 + (i - 1) ns, i ns]],
  Axes -> None, PlotRange -> All, PlotStyle -> PointSize[0.01];
  plot[i] = Show[exp, fit];
  pos = pos + offset;
];
Show[Table[plot[i], {i, Length[temps]]}], ImageSize -> (840, 600)]
Export[rootfilename <> ".finalplot-eps", Show[Table[plot[i], {i, Length[temps]]]]];
sol["ANOVAtable"]
sol["EstimatedVariance"]
sol["AdjustedRSquared"]
Print["Cumulative time = ", TimeUsed[] - starttime];

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<th>Confidence Interval</th>
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<td>k223g</td>
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<td>dhs</td>
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<td>eeg</td>
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<th>SS</th>
<th>MS</th>
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<td>1.48147</td>
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<tr>
<td>Error</td>
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<td>0.88389</td>
<td>0.000157192</td>
</tr>
<tr>
<td>Uncorrected Total</td>
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<td>14.2171</td>
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<tr>
<td>Corrected Total</td>
<td>5631</td>
<td>11.7839</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative time = 320.486

Out[456]=

Out[457]= 0.93773
Fit Liam Byrne data for $\alpha$MeVal2 monolabelled Alb in THF using analytical asymmetric 2-site exchange solution

Full temperature range from -60 °C, downsample only 4x

SetDirectory["/Users/qam/Documents/Collaborations/JPC Liam Byrne xii12/2012-12-11-jpc-61-tr"]; Clear[Evaluate[Context[] <> "*"]]

sseqs = (0 == -px km + mx km - λ px - (2 Pi f - Pi δ sfrq) py, 0 == -py km + my km - λ py + (2 Pi f - Pi δ sfrq) px + α, 0 == -mx km + px km - λ mx - (2 Pi f + Pi δ sfrq) my, 0 == -my km + py km - λ my + (2 Pi f + Pi δ sfrq) mx + α km / kmp); sssol = Solve[sseqs, \{px, py, mx, my\}];
smy = my / sssol[[1]]; spy = py / sssol[[1]]; smyr = smy / δ + δ; spyr = spy / δ - δ;

spec = (ee (smy + spy) + smyr + spyr) / (1 + ee); spec = ((1 + ee) (smy + spy) + (1 - ee) (smyr + spyr)) / (2);

Plot[spec[[smy + spy]] / ((δ - 25, α - 1, kmp → 0.6, kmp → 0.2, λ → 3), {f, -50, 50}, PlotRange → All]
Plot[spec[[smyr + spyr]] / ((δ - 25, α - 1, kmp → 0.6, kmp → 0.2, λ → 3), {f, -50, 50}, PlotRange → All]
Plot[spec[[spec]] / ((δ - 25, α - 1, kmp → 0.6, kmp → 0.2, λ → 3), {f, -50, 50}, PlotRange → All]

(* read in data *)

rootfilename = "2012-12-11-jpc-61-tr";
downsample = 4;
lineb = 1; sw = 29.761.9; rfl = 8295.4; rfp = 6162.7; sfrq = 125.783;
marker = {Graphics[{Gray, Disk[{0, 0}, 0.03]}];

atemps = 273.15 + (-59.6, -49.8, -39.9, -29.8, -19.8, -9.9, 0.2, 10.1, 20, 30.1, 40.1);
temps = atemps; nt = Length[temps];

For[i = 1, itemp ≤ nt, itemp++,
	tempin = temps[[itemp]];
	filename = rootfilename <> ToString[itemtemp];
	filein = OpenRead[filename];
	Read[filein, String];
	dum = Read[filein, Real];
	np = Read[filein, Real];
	Read[filein, String];
	sp = Table[{0, 0}, \{i, np\}];
	int = 0;
	Read[filein, String];

For[j = 1, j ≤ np, j++,
	sp[[j, 1]] = -(sw/2 + rfp - rfl - Read[filein, Number]) / sfrq; sp[[j, 2]] = Read[filein, Number];
]
Close[filein];

sp2 = Take[sp, {106 000, 106 500, downsample}]; n1 = Length[sp2]; sp2[[n1, 2]] = 0;
sp2 = Join[sp2, Take[sp, {108 200, 108 900, downsample}]]; ns = Length[sp2]; sp2[[n1 + 1, 2]] = 0;

(* Print[ListPlot[sp2,PlotRange→All,PlotStyle→PointStyle→0.015,Joined→True, Axes→(True,False)]; *)

For[j = 1, j ≤ Length[sp2], j++,
	If[(itemp = 1) \&\& (j = 1),
	alldata = (atemps[[1]], sp2[[1, 1]], sp2[[1, 2]]); alldata = AppendTo[alldata, (atemps[[itemp]], sp2[[j, 1]], sp2[[j, 2]])];

S155
alldata = 88
atemps @@ 1, 1 DD, sp2 @@ 1, 2 DD
alldata = AppendTo @ alldata, 8 itemp, sp2 @@ i, 1 DD, sp2 @@ j, 2 DD; 
H* Normalise spectra to constant integral 
H* Lints = Table @ 0, 8 i, nt D, i = 0; int = 0; k = 0; max = 0; 
For[i = 1, i ≤ Length[temps], i++, int = int + (alldataorig[[k, 3]] + alldataorig[[k - 1, 3]]) (alldataorig[[k, 2]] - alldataorig[[k - 1, 2]]) / 2; ];
For[j = 1, j ≤ ns, j++, k = j + (i - 1) ns; int = int + (alldataorig[[k, 3]] - alldataorig[[k - 1, 3]])];
If[alldataorig[[k, 3]] > max, max = alldataorig[[k, 3]]];
ints[[i]] = int;
]
}
For[i = 1, i ≤ Length[temps], i++, int = 0;
For[j = 1, j ≤ ns, j++, k = j + (i - 1) ns; alldata[[k, 3]] = 1200.0 alldataorig[[k, 3]] / (int (alldataorig[[ns, 2]] - alldataorig[[1, 2]])))
If[alldataorig[[k, 3]] > max, max = alldataorig[[k, 3]]];
ints[[i]] = int;
]
}
marker = {Graphics[{Gray, Disk[{0, 0}, 0.1]}], 0.015};
ns = Length[alldata] / nt;
pos = 0;
offset = 1; For[i = 1, i ≤ Length[temps], i++,
exp = ListPlot[Table[{0, pos}, {j, ns}] + Take[Transpose[Take[Transpose[alldata], {2, 3}]], {1 + (i - 1) ns, i ns}], Axes -> None, PlotRange -> All, PlotMarkers -> marker, PlotStyle -> PointSize[0.001]];
plot[i] = Show[exp];
pos = pos + offset;
]
Show[Table[plot[i], {i, Length[temps]}], ImageSize -> {840, 600}]
starttime = TimeUsed[];
offset = 0.024;
ti = alldata[[1, 1]]; tf = alldata[[ns + (nt - 1) + 1, 1]];
Clear[δ, f, ff, f0, ea, dh, i, netshift, allmodel, params, assumptions];
r = 8.3144; lineb = 2;
Try guess for lowest temperature

eag = 3.2; K223g = 60; ag = 23; k223g = 630; dhsg = -1.6; δg = 4.45; eeg = 0.5; f0g = -25.6; netshiftg = 0.07;
ti = alldata[[1, 1]]; tf = alldata[[ns + (nt - 1) + 1, 1]]; 
r = 8.3144; lineb = 2;
tests = (ea → eag, K223 → K223g, α → ag, k223 → k223g, dhsg → dhsg, δ → δg, ee → eeg, f0 → f0g, netshift → netshiftg);
asumptions = 
{ dh → 1000 dh, λ → Pi lineb, kmp → k223 Exp[-(10 000 ea / r) (1 / ttemp - 1 / 223.15)], kpm → (kmp / K223) Exp[(dh / r) (1 / ttemp - 1 / 223.15)]; allmodel = spec //. assumptions;
i = 1;
Show[Plot[(allmodel //. {ttemp → atemps[[1]], f → sfrq (ff - f0 + netshift * (ttemp - ti) / (tf - ti))) / tests, 
(ff, alldata[[1, 2]], alldata[[ns, 2]]), PlotRange -> All, Axes -> {True, False}, PlotStyle -> {Red, Thick}], ListPlot[
Take[Transpose[Take[Transpose[alldata], {2, 3}], {1 + (i - 1) ns, i ns}], Axes -> {True, False}, PlotRange -> All, PlotStyle -> PointSize[0.01]]]
Try guess for highest temperature

eag = 3.0; K223g = 60.2; ag = 23; k223g = 630; dhsg = -1.6; δg = 4.45; eeg = 0.5; f0g = -25.6; netshiftg = 0.15;
ti = alldata[[1, 1]]; tf = alldata[[ns + (nt - 1) + 1, 1]];
r = 8.3144; lineb = 2;
tests = (ea → eag, K223 → K223g, α → ag, k223 → k223g, dhsg → dhsg, δ → δg, ee → eeg, f0 → f0g, netshift → netshiftg);
assumptions =
{ dh → 1000 dh, λ → Pi lineb, kmp → k223 Exp[(-10000 ea/r) (1/ttemp - 1/223.15)], kpm → (kmp / K223) Exp[(dh/r) (1/ttemp - 1/223.15)];
allmodel = spec //. assumptions;
i = nt;
Show[Plot[(allmodel // . ttemp → atemps[[i]], f → sfq ((f - f0 + netshift * (ttemp - ti) / (tf - ti))) / . tests,
{ff, alldata[[1, 2]], alldata[[ns, 2]]}, PlotRange → All, Axes → {True, False}, PlotStyle → {Red, Thick}], ListPlot[
Take[Transpose[Take[Transpose[alldata], {2, 3}]], (1 + (i - 1) ns, i ns)], Axes → {True, False}, PlotRange → All, PlotStyle → PointSize[0.01]]]
eag = 3.2; K223g = 30.2; ag = 23; k223g = 30; dhsg = -1.6; δg = 4.45; eeg = 3; f0g = -25.6; netshiftg = 0.15;
params = {ea, eag}, (K223, K223g), {α, αg}, (k223, k223g), (dh, dhsg), (δ, δg), (ee, eeg), (f0, f0g), (netshift, netshiftg));
assumptions =
{dh → 1000 dh, λ → Pi lineb, kmp → K223 Exp[-(10000 ea / r) (1 / ttemp - 1 / 223.15)], kmp → (kmp / K223) Exp[(dh / r) (1 / ttemp - 1 / 223.15)]};
allmodel = spec //. assumptions;
sol = NonlinearModelFit[alldata, (allmodel //. (f → sfrq (ff - f0 + netshift * (ttemp - ti) / (tf - ti))))], params, {ttemp, ff}, MaxIterations → 5000];

NonlinearModelFit::sszero:
The step size in the search has become less than the tolerance prescribed by the PrecisionGoal option, but the gradient is larger than the tolerance specified by the AccuracyGoal option. There is a possibility that the method has stalled at a point that is not a local minimum. »

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<th>Standard Error</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
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<td>ea</td>
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<td>[3.03996, 3.11779]</td>
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<tr>
<td>K223</td>
<td>60.4204</td>
<td>[59.2961, 61.5448]</td>
</tr>
<tr>
<td>α</td>
<td>13.2382</td>
<td>[12.8877, 13.1542]</td>
</tr>
<tr>
<td>k223g</td>
<td>630.252</td>
<td>[607.149, 653.355]</td>
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<td>dhsg</td>
<td>-6.25385</td>
<td>[6.12641, 6.38128]</td>
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<td>δg</td>
<td>4.41252</td>
<td>[4.1151, 4.1153]</td>
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<td>[0.497681, 0.516517]</td>
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<td>[-25.5893, -25.5883]</td>
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<td>netshift</td>
<td>0.206838</td>
<td>[0.206051, 0.207624]</td>
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Cumulative time = 226.183

0.000241133
0.953805
10. References and Notes