Dibenzazepinyl ureas as dual NMR and CD probes of helical screw-sense preference in conformationally equilibrating dynamic foldamers

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**General Experimental and Materials**

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

**Instrumentation**

All $^1$H and $^{13}$C nuclear magnetic resonance spectra were obtained using Bruker AVANCE 300, 400 or 500 MHz spectrometers. Chemical shifts are quoted in parts per million (ppm), and coupling constants ($J$) are quoted in Hz to the nearest 0.5 Hz. $^1$H-NMR spectra were referenced to the residual deuterated solvent peak (CDCl$_3$ 7.26; CD$_3$OD 3.31) and $^{13}$C-NMR were referenced to the carbon resonance of the solvent (CDCl$_3$ 77.16; CD$_3$OD 49.00). Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintuplet), spt (septet) and m (multiplet) or denoted as br (broad), or some combination of these, where appropriate. Where $^1$H-NMR spectra were run in CD$_3$OD, D$_2$O or CD$_3$CD$_2$OD exchangeable protons (NH, OH) are reported only where observed.
Infra-red spectra were recorded on an ATi Perkin Elmer Spectrum RX1 FT-IR spectrometer. Only absorption maxima ($\lambda_{\text{max}}$) of interest are reported and quoted in wavenumbers (cm$^{-1}$). Low and high resolution mass spectra were recorded by staff at the University of Manchester. Electrospray (ES) spectra were recorded on a Waters Platform II and high resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP and are accurate to $\pm$ 0.001 Da. Melting points were determined on a GallenKamp apparatus and are uncorrected. Optical rotation measurements were taken on an AA-100 polarimeter at 20 °C with the solvent and concentration stated. Circular Dichroism (CD) measurements were performed at 20 °C on a JASCO J-815 spectropolarimeter, using a 1 mm cell with the solvent and concentration stated, where applicable.
Synthetic procedures and characterisation

Methods for the synthesis of NH$_2$-(L)-PheNH$_2$Bu,$^{[1]}$ NH$_2$-(L)-LeuNH$_2$Bu,$^{[1]}$ NH$_2$-(L)-AlaNH$_2$Bu,$^{[1]}$ 1 (as a free amine), $^{[2]}$ N$_3$Aib$_4$OH (3), $^{[3]}$ NH$_2$Aib$_4$OtBu (5x)$^{[3]}$ and oligoureas 7a$^{[4]}$ and 7b$^{[4]}$ were reported previously.

**General procedure A: Hydrogenolysis of N$_3$Aib$_n$-Xaa-Y (n = 4, 8, 12; Xaa = Ala, Phe, tLeu, Val; Y =NH$_2$Bu, OtBu)**

To a solution of N$_3$Aib$_n$-Xaa-Y (1 eq) in MeOH was added Pd/C (10%) and the resultant mixture was stirred under a H$_2$ atmosphere until completion of the reaction (TLC monitoring). After this time, the reaction mixture was filtered through a pad of Celite© under vacuum and the filtrate collected. The residue obtained after evaporation of the solvent under reduced pressure was dissolved in CH$_2$Cl$_2$ and the organic layer was washed with 0.5 M K$_2$CO$_3$ (2 ×) and dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, the residue containing the expected amine was used in the next step without further purification.

**General procedure B: azlactone synthesis**

To a solution of 3 (200 mg, 0.52 mmol) in CH$_2$Cl$_2$ (5 mL) was added EDC•HCl (197 mg, 1.03 mmol). The reaction mixture was stirred at RT for 16 h and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and the organic layer was successively washed with 5% KHSO$_4$ (2 × 25 mL), sat. NaHCO$_3$ (2 × 25 mL) and brine (25 mL) and was dried over MgSO$_4$. Evaporation of the solvent under reduced pressure provided the expected azlactone (153 mg) which was used in the next step without further purification.
**General procedure C: synthesis of AzeCl**

To a solution of triphosgene (158 mg, 0.53 mmol) in CH$_2$Cl$_2$ (1.2 mL) cooled at -78 °C was added dropwise a solution of 1 (226 mg, 1.16 mmol) in CH$_2$Cl$_2$ (1 mL). The reaction mixture was stirred at -78 °C for 30 min and was then warmed up to RT. After 3 h stirring, the reaction mixture was quenched with 1 M HCl (15 mL) and the resulting aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic layers were washed with sat. NaHCO$_3$ (10 mL) and were dried over MgSO$_4$. Evaporation of the solvent under reduced pressure provided **AzeCl** which was used in the next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48-7.58 (m, 4 H), 7.38-7.48 (m, 4 H), 4.52 (s, 2 H), 4.42 (s, 2 H) ppm.

**AzeAib$_4$-(L)-AlaNHtBu (2a)**

To a suspension of DSC (76 mg, 0.30 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added dropwise at 0 °C a solution of 5a (100 mg, 0.21 mmol, obtained by hydrogenolysis of 4a following general procedure A) in CH$_2$Cl$_2$ (3.0 mL). The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed with 5% KHSO$_4$ (2 × 25 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH$_3$CN (2.5 mL) and this solution was added dropwise to a mixture of 1·HCl (48 mg, 0.21 mmol) and DIPEA (0.82 mmol, 143 µL) in CH$_3$CN (1.5 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed successively with NaHCO$_3$ (2 × 30 mL), 5% KHSO$_4$ (2 × 30 mL) and brine (30 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO$_2$, EtOAc/CH$_2$Cl$_2$
75:25) provided the titled compound (86 mg, 59%) as a colourless solid. mp = 216-217 °C. IR (solid) ν\text{max} 3302, 2984, 1644, 1529, 1381, 1360, 1290, 1226, 1165 cm\(^{-1}\). [α]D\text{20} = +63.5 (c = 0.51, CH\(_2\)Cl\(_2\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 1.30 (s, 3 H, C\(_3\)H), 1.38 (s, 9 H, tBu), 1.43 (s, 3 H, CH\(_3\)), 1.44 (d, 3 H, J = 7.1 Hz, CH\(_2\)CH\(_3\)), 1.47 (s, 3 H, CH\(_3\)), 1.49 (s, 3 H, CH\(_3\)), 1.52 (s, 3 H, CH\(_3\)), 1.54 (s, 3 H, CH\(_3\)), 1.55 (s, 3 H, CH\(_3\)), 1.58 (s, 3 H, CH\(_3\)), 4.16 (d, 2 H, J = 12.7 Hz, A of AB, ArC\(_6\)H\(_5\)), 4.30-4.38 (m, 1 H, CH\(_3\)), 4.37 (d, 2 H, J = 12.7 Hz, B of AB, ArC\(_6\)H\(_5\)), 5.20 (s, 1H, NH), 6.48 (s, 1 H, NH), 6.95 (s, 1 H, NH), 7.37-7.42 (m, 4 H, 4 × H\(_{ar}\)), 7.47-7.57 (m, 5 H, 4 × H\(_{ar}\) + NH), 7.66 (d, 1 H, J = 7.9 Hz, NH), 8.29 (s, 1 H, NH) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 17.4 (CH\(_3\)), 23.2 (CH\(_3\)), 23.50 (CH\(_3\)), 23.53 (CH\(_3\)), 24.1 (CH\(_3\)), 27.2 (CH\(_3\)), 27.42 (CH\(_3\)), 27.44 (CH\(_3\)), 27.7 (CH\(_3\)) 28.8 (3 × CH\(_3\)), 48.1 (2 × CH\(_2\)), 50.1 (CH), 51.3 (C), 56.6 (C), 57.05 (C), 57.09 (C), 57.6 (C), 128.6 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH), 129.5 (2 × CH), 133.8 (2 × C), 140.5 (2 × C), 156.4 (CO), 173.0 (CO), 174.92 (CO), 174.95 (CO), 175.1 (CO), 175.5 (CO) ppm. MS (ES\(^+\), MeOH): 706.5 ([M+H]\(^+\), 20%), 728.6 ([M+Na]\(^+\), 50%). HRMS (ES\(^+\), MeOH) calced for C\(_{38}\)H\(_{56}\)N\(_7\)O\(_6\) = 706.4287; found 706.4279.

**AzeAib\(_4\)-(L)-PheNHtBu (2b)**

![Structure](image)

To a suspension of DSC (28 mg, 0.109 mmol) in CH\(_2\)Cl\(_2\) (0.5 mL) was added dropwise at 0 °C a solution of 5b (39 mg, 0.069 mmol, obtained by hydrogenolysis of 4b following general procedure A) in CH\(_2\)Cl\(_2\) (1.0 mL). The reaction mixture was stirred overnight at RT and was diluted with CH\(_2\)Cl\(_2\) (100 mL). The organic layer was washed with 5% KHSO\(_4\) (2 × 25 mL) and was dried over MgSO\(_4\). After evaporation of the solvent under reduced pressure, the
residue was dissolved in CH$_3$CN (0.5 mL) and this solution was added dropwise to a mixture of 1·HCl (25 mg, 0.108 mmol) and DIPEA (75 µL, 0.432 mmol) in CH$_3$CN (0.25 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (50 mL). The organic layer was washed successively with 5% KHSO$_4$ (2 × 20 mL), NaHCO$_3$ (2 × 20 mL) and brine (10 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO$_2$, EtOAc/CH$_2$Cl$_2$ 3:7→4:6) provided the titled compound (20 mg, 37%) as a colourless solid. mp = 219-221°C. IR (solid) $\nu_{max}$ 3294, 2981, 2930, 2868, 1651, 1632, 1529, 1148, 1383, 1360, 1227, 1169 cm$^{-1}$. $[\alpha]_D^{20}$ = +46.4° (c = 0.50, CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.18 (s, 3 H, C$_3$H$_3$), 1.30 (s, 3 H, C$_3$H$_3$), 1.41 (s, 9 H, tBu), 1.44 (s, 3 H, C$_3$H$_3$), 1.45 (s, 3 H, C$_3$H$_3$), 1.47 (s, 3 H, C$_3$H$_3$), 1.51 (s, 3 H, C$_3$H$_3$), 1.54 (s, 3 H, C$_3$H$_3$), 1.55 (s, 3 H, C$_3$H$_3$), 2.91 (dd, 1 H, $J$ = 14.3 and 12.3 Hz, PheC$_2$H), 3.63 (dd, 1 H, $J$ = 14.3 and 2.7 Hz, PheC$_2$H), 4.14 (d, 2 H, $J$ = 12.6 Hz, A of AB, ArC$_2$H$_2$N), 4.37 (d, 2 H, $J$ = 12.6 Hz, B of AB, ArC$_2$H$_2$N), 4.54-4.60 (m, 1 H, PheC$_2$H), 5.18 (s, 1H, N), 6.44 (s, 1 H, NH), 7.07-7.11 (m, 2 H, H$_{ar}$ + NH), 7.16 (t, 2 H, $J$ = 7.3 Hz, 2 × H$_{ar}$), 7.29 (d, 2 H, $J$ = 7.3 Hz, 2 × H$_{ar}$), 7.36-7.42 (m, 4 H, 4 × H$_{ar}$), 7.46-7.53 (m, 4 H, 2 × NH + 2 × H$_{ar}$), 7.55 (d, 2 H, $J$ = 7.2 Hz, 2 × H$_{ar}$), 8.19 (s, 1 H, NH) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.3 (CH$_3$), 23.4 (CH$_3$), 23.6 (CH$_3$), 24.0 (CH$_3$), 27.0 (CH$_3$), 27.1 (CH$_3$), 27.26 (CH$_3$), 27.30 (CH$_3$), 28.7 (3 × CH$_3$), 37.0 (CH$_2$), 48.0 (2 × CH$_2$), 51.2 (C), 55.4 (CH), 56.5 (C), 56.8 (C), 56.9 (C), 57.4 (C), 125.9 (CH), 128.0 (2 × CH), 128.48 (2 × CH), 128.85 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 133.5 (C), 139.3 (2 × C), 140.3 (2 × C), 156.1 (CO), 171.2 (CO), 174.4 (CO), 174.6 (CO), 174.97 (CO), 175.04 (CO) ppm. MS (ES$^+$, MeOH): 783 ([M+H]$^+$, 28%), 805 ([M+Na]$^+$, 100%); MS (ES$^-$, MeOH): 781 ([M-H]$^-$, 79%). HRMS (ES$^+$, MeOH) calcd for C$_{44}$H$_{60}$N$_7$O$_6$ = 782.4600; found 782.4602.
To a suspension of DSC (27 mg, 0.105 mmol) in CH$_2$Cl$_2$ (0.75 mL) was added dropwise at 0 °C a solution of 5c (39 mg, 0.074 mmol, obtained by hydrogenolysis of 4c following general procedure A) in CH$_2$Cl$_2$ (1.5 mL). The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed with 5% KHSO$_4$ (2 × 25 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH$_3$CN (1.5 mL) and this solution was added dropwise to a mixture of 1·HCl (17 mg, 0.073 mmol) and DIPEA (51 µL, 0.296 mmol) in CH$_3$CN (0.75 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed successively with 5% KHSO$_4$ (2 × 40 mL), NaHCO$_3$ (2 × 40 mL) and brine (20 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO$_2$, EtOAc/CH$_2$Cl$_2$ 5:5→4:6) provided the titled compound (38 mg, 69%) as a colourless solid. mp = 205-207 °C. IR (solid) $\nu_{max}$ 3283, 2981, 2933, 2872, 1652, 1644, 1626, 1531, 1451, 1383, 1360, 1287, 1260, 1166 cm$^{-1}$. $\{\alpha\}_{D}^{20}$ = +42.4 (c = 0.50, MeOH/CH$_2$Cl$_2$ 1:9). $^1$H NMR (400 MHz, CDCl$_3$/CD$_3$OH 97:3) $\delta$ 1.07 (s, 9 H, tBu), 1.27 (s, 3 H, CH$_3$), 1.33 (s, 9 H, tBu), 1.40 (s, 3 H, CH$_3$), 1.41 (s, 3 H, CH$_3$), 1.45 (s, 3 H, CH$_3$), 1.47 (s, 6 H, 2 × CH$_3$), 1.50 (s, 6 H, 2 × CH$_3$), 3.94 (d, 1 H, $J = 7.8$ Hz, CH$_2$Bu), 4.10 (d, 2 H, $J = 12.6$ Hz, A of AB, ArCH$_2$N), 4.35 (d, 2 H, $J = 12.6$ Hz, B of AB, ArCH$_2$N), 5.43 (s, 1H, NH), 6.65 (s, 1 H, NH), 6.78 (s, 1 H, NH), 7.26 (d, 1H, $J = 7.8$ Hz, NH), 7.31-7.41 (m, 4 H, 4 × H$_{ar}$), 7.44-7.50 (m, 2 H, 2 × H$_{ar}$), 7.52 (d, 2 H, $J = 7.4$ Hz, 2 × H$_{ar}$), 7.63 (s, 1 H, NH), 8.18 (s, 1 H, NH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$/CD$_3$OH 97:3) $\delta$ 23.4 (CH$_3$), 23.47 (CH$_3$), 23.51 (CH$_3$), 24.0 (CH$_3$), 27.0 (CH$_3$), 27.1
(CH₃), 27.2 (CH₃), 27.3 (3 × CH₃), 27.6 (CH₃), 28.6 (3 × CH₃), 33.8 (C), 47.9 (2 × CH₂), 51.3 (C), 56.5 (C), 56.87 (C), 56.95 (C), 63.5 (CH), 128.5 (4 × CH), 129.1 (2 × CH), 129.4 (2 × CH), 133.8 (2 × C), 140.4 (2 × C), 156.4 (CO), 171.1 (CO), 174.6 (CO), 175.3 (2 × CO), 175.6 (CO) ppm. MS (ES⁺, DCM): 748.7 ([M+H]⁺, 30%), 770.7 ([M+Na]⁺, 20%).

HRMS (ES⁺, MeOH) calcd for C₄₁H₆₀N₇O₆ = 748.4756; found 748.4756.

AzeAib₄-(L)-AlaOrBu (2d)

To a suspension of DSC (103 mg, 0.31 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise at 0 °C a solution of 5d (103 mg, 0.21 mmol, obtained by hydrogenolysis of 4d following general procedure A) in CH₂Cl₂ (3 mL). The reaction mixture was stirred overnight at RT and was diluted with CH₂Cl₂ (75 mL). The organic layer was washed with 5% KHSO₄ (2 × 25 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH₃CN (2.5 mL) and this solution was added dropwise to a mixture of 1·HCl (49 mg, 0.21 mmol) and DIPEA (0.84 mmol, 146 µL) in CH₃CN (1.5 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH₂Cl₂ (100 mL). The organic layer was washed successively with NaHCO₃ (2 × 25 mL), 5% KHSO₄ (2 × 25 mL) and brine (25 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO₂, EtOAc/CH₂Cl₂ 1:1) provided the titled compound (113 mg, 76%) as a colourless solid. Spectroscopic data of 2d (NMR, IR, MS) are identical to the spectroscopic data of 2e. [α]D²⁰ = -75.2 (c = 0.50, MeOH).
To a suspension of DSC (119 mg, 0.46 mmol) in CH$_2$Cl$_2$ (2.2 mL) was added dropwise at 0 °C a solution of 5e (157 mg, 0.32 mmol, obtained by hydrogenolysis of 4e following general procedure A) in CH$_2$Cl$_2$ (4.5 mL). The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (75 mL). The organic layer was washed with 5% KHSO$_4$ (2 × 25 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH$_3$CN (3.75 mL) and this solution was added dropwise to a mixture of 1·HCl (75 mg, 0.32 mmol) and DIPEA (1.28 mmol, 222 µL) in CH$_3$CN (2.2 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed successively with 5% KHSO$_4$ (2 × 25 mL), NaHCO$_3$ (2 × 25 mL) and brine (25 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO$_2$, EtOAc/CH$_2$Cl$_2$ 1:1) provided the titled compound (188 mg, 82%) as a colourless solid. mp = 217-218 °C. $[\alpha]_{D}^{20} = +80.0$ (c = 0.51, MeOH). IR (solid) $\nu_{\text{max}}$ 3305, 2981, 2935, 1656, 1629, 1528, 1454, 1382, 1361, 1228, 1151 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.33 (s, 3 H, CH$_3$), 1.42 (d, 3 H, J = 7.0 Hz, CH$_3$), 1.43 (s, 9 H, tBu), 1.45 (s, 3 H, CH$_3$), 1.47 (s, 3 H, CH$_3$), 1.51 (s, 3 H, CH$_3$), 1.53 (s, 3 H, CH$_3$), 1.54 (s, 3 H, CH$_3$), 1.55 (s, 3 H, CH$_3$), 1.56 (s, 3 H, CH$_3$), 4.18 (d, 2 H, J = 12.6 Hz, A of AB, ArCH$_2$N), 4.32 (d, 2 H, J = 12.6 Hz, B of AB, ArCH$_2$N), 4.31-4.38 (m, 1 H, CH$_3$-CH$_3$), 4.99 (s, 1 H, NH), 6.37 (s, 1 H, NH), 7.34-7.43 (m, 5 H, 4 × H$_{\text{Ar}}$ + NH), 7.44-7.53 (m, 3 H, 2 × H$_{\text{Ar}}$ + NH), 7.54-7.57 (m, 2 H, 2 × H$_{\text{Ar}}$), 8.10 (s, 1 H, NH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 17.1 (CH$_3$), 24.2-24.3 (m, 3 × CH$_3$), 24.8 (CH$_3$), 26.59 (CH$_3$), 26.65 (CH$_3$), 26.7 (CH$_3$), 27.2 (CH$_3$), 28.1 (3 × CH$_3$), 48.2 (2 × CH$_2$), 49.4 (CH), 56.6 (C), 57.0 (C),
57.1 (C), 57.5 (C), 80.6 (C), 128.6 (4 × CH), 129.1 (2 × CH), 129.5 (2 × CH), 133.9 (2 × C), 140.5 (2 × C), 156.4 (CO), 172.7 (CO), 174.4 (CO), 174.7 (CO), 174.8 (CO), 175.2 (CO) ppm. MS (ES⁺, MeOH): 707.5 ([M+H]⁺, 80%), 729.5 ([M+Na]⁺, 45%). HRMS (ES⁺, MeOH) calcd for C₃₈H₅₅N₆O₇ = 707.4127; found 707.4121.

**AzeAib₄-(L)-ValOrBu (2f)**

\[\text{To a suspension of DSC (66 mg, 0.258 mmol) in CH}_2\text{Cl}_2 (1.5 mL) was added dropwise at 0 °C a solution of 5f (91 mg, 0.177 mmol, obtained by hydrogenolysis of 4f following general procedure A) in CH}_2\text{Cl}_2 (3 mL). The reaction mixture was stirred overnight at RT and was diluted with CH}_2\text{Cl}_2 (100 mL). The organic layer was washed with 5% KHSO}_4 (2 × 25 mL) and was dried over MgSO}_4. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH}_3CN (3 mL) and this solution was added dropwise to a mixture of 1-HCl (41 mg, 0.177 mmol) and DIPEA (123 µL, 0.708 mmol) in CH}_3CN (1.5 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH}_2\text{Cl}_2 (50 mL). The organic layer was washed successively with 5% KHSO}_4 (2 × 20 mL), NaHCO}_3 (2 × 20 mL) and brine (10 mL) and was dried over MgSO}_4. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO}_2, EtOAc/CH}_2\text{Cl}_2 1:1) provided the titled compound (112 mg, 86%) as a colourless solid. mp = 215-217 °C. [α]D²⁰ = -35.9 (c = 0.58, CH}_2\text{Cl}_2). IR (solid) νmax 3288, 2980, 2934, 2873, 1726, 1653, 1629, 1524, 1454, 1382, 1361, 1228, 1161 cm⁻¹. ¹H NMR (400 MHz, CDCl)_3 δ 1.00 (d, 3 H, J = 6.9 Hz, CH(CH}_3)_2), 1.02 (d, 3 H, J = 6.9 Hz, CH(CH}_3)_2), 1.35 (s, 3 H, CH}_3), 1.43-1.47 (m, 12 H, tBu + CH}_3), 1.48 (s, 3 H, CH}_3), 1.51 (s, 3 H, CH}_3), 1.52-1.58 (m, 12 H, 4 × CH}_3), 2.16-2.28 (m, 1 H, CH(CH}_3)_2), 4.19 (d, 2 H, J = 12.7 Hz, A of AB, CH}_2Ar), 4.24 (br t, 1 H, J = 7.4 Hz,
CHCH(CH\(_2\)\(_3\)), 4.30 (d, 2 H, \(J = 12.7\) Hz, B of AB, CH\(_2\)Ar), 4.78 (s, 1 H, NH), 6.32 (s, 1 H, NH), 7.30 (d, 1 H, \(J = 8.2\) Hz, NH), 7.35-7.44 (m, 5 H, NH + 4 \(\times\) H\(_{\text{ar}}\)), 7.48-7.59 (m, 4 H, 4 \(\times\) H\(_{\text{ar}}\)), 7.98 (s, 1 H, NH) ppm. \({\text{\textsuperscript{13}C}}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 18.7 (CH\(_3\)), 19.3 (CH\(_3\)), 24.7 (3 \(\times\) CH\(_3\)), 25.1 (CH\(_3\)), 26.3 (CH\(_3\)), 26.4 (CH\(_3\)), 26.5 (CH\(_3\)), 26.9 (CH\(_3\)), 28.2 (3 \(\times\) CH\(_3\)), 30.4 (CH), 48.1 (2 \(\times\) CH\(_2\)), 56.7 (C), 57.0 (C), 57.1 (C), 57.5 (C), 59.5 (CH), 80.6 (C), 128.6 (4 \(\times\) CH), 129.2 (2 \(\times\) CH), 129.5 (2 \(\times\) CH), 133.8 (2 \(\times\) C), 140.4 (2 \(\times\) C), 156.2 (CO), 171.3 (CO), 174.06 (CO), 174.10 (CO), 174.5 (CO), 175.5 (CO) ppm. MS (ES\(^{+}\), MeOH): 735.6 ([M+H]\(^{+}\), 50%), 757.6 ([M+Na]\(^{+}\), 35%). HRMS (ES\(^{+}\), MeOH) calcd for C\(_{40}\)H\(_{59}\)N\(_6\)O\(_7\) = 735.4440; found 735.4437.

**AzeAib\(_4\)-(L)-PheOtBu (2g)**

To a suspension of DSC (40 mg, 0.156 mmol) in CH\(_2\)Cl\(_2\) (0.75 mL) was added dropwise at 0°C a solution of 5g (61 mg, 0.108 mmol, obtained by hydrogenolysis of 4g following general procedure A) in CH\(_2\)Cl\(_2\) (1.5 mL). The reaction mixture was stirred overnight at RT and was diluted with CH\(_2\)Cl\(_2\) (100 mL). The organic layer was washed with 5% KHSO\(_4\) (2 \(\times\) 25 mL) and was dried over MgSO\(_4\). After evaporation of the solvent under reduced pressure, the residue was dissolved in CH\(_3\)CN (1.5 mL) and this solution was added dropwise to a mixture of 1-HCl (25 mg, 0.108 mmol) and DIPEA (75 \(\mu\)L, 0.432 mmol) in CH\(_3\)CN (0.75 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH\(_2\)Cl\(_2\) (50 mL). The organic layer was washed successively with 5% KHSO\(_4\) (2 \(\times\) 15 mL), NaHCO\(_3\) (2 \(\times\) 15 mL) and brine (15 mL) and was dried over MgSO\(_4\). After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO\(_2\), EtOAc/CH\(_2\)Cl\(_2\))
4:6) provided the titled compound (61 mg, 72%) as a colourless solid. $\text{mp} = 197-199 \, ^{\circ} \text{C}$. $[\alpha]_\text{D}^{25} = -35.2$ (c = 1.00, MeOH). $\text{IR}$ (solid) $\nu_{\text{max}}$ 3304, 2981, 2932, 1651, 1629, 1527, 1454, 1382, 1361, 1228, 1153 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.32 (s, 9 H, tBu), 1.34 (s, 3 H, CH$_3$), 1.44 (s, 3 H, CH$_3$), 1.47 (s, 3 H, CH$_3$), 1.50 (s, 6 H, 2 × CH$_3$), 1.53 (s, 3 H, CH$_3$), 1.54 (s, 6 H, 2 × CH$_3$), 3.12 (dd, 1 H, J = 14.0 and 7.4 Hz, A of ABX, PhCH$_2$CH), 3.17 (dd, 1 H, J = 14.0 and 7.4 Hz, B of ABX, PhCH$_2$CH), 4.21 (d, 2 H, J = 12.6 Hz, A of AB, ArCH$_2$N), 4.30 (d, 2 H, J = 12.6 Hz, B of AB, ArCH$_2$N), 4.54 (q, 1 H, J = 7.4 Hz, PheCH$_2$CH), 5.07 (s, 1H, NH), 6.40 (s, 1 H, NH), 7.14 (tt, 1 H, J = 7.3 and 1.1 Hz, H$_{ar}$), 7.20-7.23 (m, 2 H, 2 × H$_{ar}$), 7.26-7.29 (m, 2 H, 2 × H$_{ar}$), 7.37 (s, 1 H, NH), 7.37-7.42 (m, 4 H, 4 × H$_{ar}$), 7.47-7.52 (m, 2 H, 2 × H$_{ar}$), 7.55 (d, 2 H, J = 7.4 Hz, 2 × H$_{ar}$), 7.61 (d, 1 H, J = 7.3 Hz, NH), 8.08 (s, 1 H, NH) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 24.77 (CH$_3$), 24.83 (2 × CH$_3$), 25.2 (CH$_3$), 26.2 (CH$_3$), 26.3 (CH$_3$), 26.4 (CH$_3$), 26.7 (CH$_3$), 28.0 (3 × CH$_3$), 37.8 (CH$_2$), 48.2 (2 × CH$_2$), 55.3 (CH), 56.7 (C), 57.1 (C), 57.2 (C), 57.6 (C), 80.8 (C), 126.3 (CH), 128.1 (2 × CH), 128.6 (4 × CH), 129.2 (2 × CH), 129.5 (2 × CH), 129.7 (2 × CH), 133.8 (2 × C), 138.0 (C), 140.5 (2 × C), 156.3 (CO), 171.2 (CO), 174.2 (CO), 174.4 (CO), 174.5 (CO), 175.4 (CO) ppm. $\text{MS}$ (ES$^+$, MeOH): 783.7 ([M+H]$^+$, 15%), 805.6 ([M+Na]$^+$, 100%). $\text{HRMS}$ (ES$^+$, MeOH) calcd for C$_{44}$H$_{59}$N$_6$O$_7$ = 783.4440; found 783.4436.

### AzeAib$_8$-(L)-AlaOrBu (2h)

![AzeAib$_8$-(L)-AlaOrBu](image)

To a suspension of DSC (45 mg, 0.18 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise at 0 °C a solution of 5h (100 mg, 0.12 mmol, obtained by hydrogenolysis of 4h following general procedure A) in CH$_2$Cl$_2$ (2 mL). The reaction mixture was stirred overnight at RT and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed with 5% KHSO$_4$ (2 × 25 mL)
and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, the residue was dissolved in DMF (2 mL) and this solution was added dropwise to a mixture of 1·HCl (28 mg, 0.12 mmol) and DIPEA (0.48 mmol, 85 µL) in DMF (1 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH₂Cl₂ (100 mL). The organic layer was washed successively with NaHCO₃ (2 × 30 mL), 5% KHSO₄ (2 × 30 mL) and brine (30 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO₂, EtOAc/CH₂Cl₂ 6:4) provided the titled compound (101 mg, 81%) as a colourless solid. mp = 208-211 °C. IR (solid) νmax 3287, 2983, 2936, 2870, 1735, 1650, 1529, 1454, 1383, 1361, 1289, 1227, 1166 cm⁻¹. [α]D²⁰ = -39.6 (c = 1.04, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 1.36 (s, 3 H, CH₃), 1.38-1.58 (m, 57 H, tBu + 16 × CH₃), 4.15-4.42 (m, 5 H, CHCH₃ + 2 × CH₂Ar), 5.49 (s, 1 H, NH), 6.61 (s, 1 H, NH), 7.36-7.42 (m, 4 H, 4 × HAr), 7.45-7.58 (m, 6 H, 4 × HAr + 2 × NH), 7.65 (s, 1 H, NH), 7.68 (s, 1 H, NH), 7.69 (s, 1 H, NH), 7.76 (s, 1 H, NH), 8.35 (s, 1 H, NH) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 17.0 (CH₃), 22.6-27.6 (m, 16 × CH₃), 28.1 (3 × CH₃, tBu), 48.1 (2 × CH₂), 49.6 (CH), 56.5 (C), 56.65 (C), 56.69 (C), 56.72 (C), 56.84 (C), 56.87 (C), 56.91 (C), 57.5 (C), 80.6 (C), 128.55 (2 × CH), 128.59 (2 × CH), 129.1 (2 × CH), 129.5 (2 × CH), 133.9 (2 × C), 140.5 (2 × C), 156.6 (CO), 172.8 (CO), 174.9 (CO), 175.3 (CO), 175.5 (CO), 175.6 (CO), 175.8 (CO), 176.03 (CO), 176.05 (CO), 176.1 (CO) ppm. MS (ES⁺, MeOH): 1047.7 ([M+H]⁺, 20%), 1069.7 ([M+Na]⁺, 100%). HRMS (ES⁺, MeOH) calcd for C₅₄H₈₃N₁₀O₁₁ = 1047.6237; found 1047.6239.

**Aze-Aib₁₂AlaO'Bu** (2j)
To a suspension of DSC (23 mg, 0.088 mmol) in CH₂Cl₂ (1 mL) was added dropwise at 0 °C a solution of 5j (74 mg, 0.063 mmol, obtained by hydrogenolysis of 4j following general procedure A) in CH₂Cl₂ (2 mL). The reaction mixture was stirred overnight at RT and was diluted with CH₂Cl₂ (100 mL). The organic layer was washed with 5% KHSO₄ (2 × 25 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, the residue was dissolved in DMF (1 mL) and this solution was added dropwise to a mixture of 1·HCl (15 mg, 0.065 mmol) and DIPEA (0.25 mmol, 44 µL) in DMF (0.5 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH₂Cl₂ (100 mL). The organic layer was washed successively with NaHCO₃ (2 × 30 mL), 5% KHSO₄ (2 × 30 mL) and brine (30 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO₂, EtOAc/CH₂Cl₂ 6:4) gave a mixture of 2i and 2j. Separation by HPLC provided an analytically pure sample of 2j.

\[ \text{mp} = 283-285 \degree C. \]  
\[ \text{IR (solid) } \nu_{\text{max}} \text{ 3291, 2984, 2931, 1651, 1531, 1455, 1384, 1362 cm}^{-1}. \]

\[ [\alpha]_{D}^{20} = -21.6 \text{ (c = 0.5, CH₂Cl₂).} \]

\[ ^{1}H \text{ NMR (400 MHz, CDCl₃)} \delta 8.39 (\text{br s, 1 H, NH}), 7.82 (\text{br s, 1H, NH}), 7.80 (\text{br s, 1H, NH}), 7.76 (\text{m, 4 H, 4 × NH}), 7.69 (\text{br s, 1 H, NH}), 7.67 (\text{br s, 1 H, NH}), 7.57 (\text{br s, 1H, NH}), 7.55 (\text{s, 2 H, 2 × H_Ar}), 7.51 (\text{m, 3 H, 3 × H_Ar}), 7.41 (\text{m, 3 H, 3 × H_Ar}), 7.40 (\text{br s, 1H, NH}), 6.71 (\text{br s, 1H, NH}), 5.63 (\text{br s, 1 H, NH}), 4.27 (\text{m, 5 H, 2 × ArCH₂ and CH}), 1.56 (\text{m, 9 H, 3 × CH₃}), 1.47-1.54 (\text{m, 54 H, 18 × CH₃}), 1.45 (\text{s, 3 H, CH₃}), 1.43 (\text{s, 12 H, CH₃ + C(CH₃)₃}), 1.41 (\text{m, 3 H, CH₃-CH}), 1.38 (\text{s, 3 H, CH₃}) \text{ ppm.} \]

\[ ^{13}C \text{ NMR (101 MHz, CDCl₃)} \delta 176.2 (2 × CO), 176.2 (CO), 176.1 (CO), 176.1 (CO), 176.0 (CO), 175.9 (CO), 175.7 (CO), 175.5 (CO), 175.4 (CO), 175.2 (CO), 174.8 (CO), 172.7 (CO), 156.5 (CO), 140.4 (2 × C), 133.7 (2 × C), 129.3 (2 × CH), 129.0 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 80.4 (C, tBu), 57.4 (C), 56.8 (C), 56.7 (C), 56.7 (C), 56.6 (C), 56.5 (6 × C), 56.4 (C), 49.5 (CH), 48.1 (2 × CH₂), 28.0 (3 × CH₃, tBu), 22.6-27.4 (24 × CH₃), 16.9 (CH₃) \text{ ppm. MS (ES⁺, CH₂Cl₂): 1388.4 (80%, [(M+H)⁺]), 1411.1 (100%, [M+Na]⁺).} \]
AzeAib$_{11}$AlaO'Bu (2i)

2i was obtained as a side product in the synthesis of 2j. An analytically pure sample of 2i was isolated by HPLC. IR (solid) $\nu_{\text{max}}$ 3273, 2984, 2935, 1738, 1650, 1538, 1455, 1383, 1361 cm$^{-1}$. $[\alpha]_b^{20} = -20.0$ (c = 0.5, CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.40 (br s, 1 H, NH), 7.82 (br s, 1 H, NH), 7.79 (br s, 1 H, NH), 7.77 (br s, 1 H, NH), 7.75 (br s, 2 H, $2 \times$ NH), 7.69 (br s, 1 H, NH), 7.67 (br s, 1 H, NH), 7.57 (br s, 1 H, NH), 7.55 (s, 2 H, $2 \times$ H$_A$), 7.51 (m, 3 H, 3 $\times$ H$_A$), 7.41 (m, 3 H, 3 $\times$ H$_A$), 7.40 (br s, 1 H, NH), 6.71 (br s, 1 H, NH), 5.68 (br s, 1 H, NH), 4.28 (m, 5 H, $2 \times$ ArCH$_3$N + CH), 1.55 (m, 12 H, 4 $\times$ CH$_3$), 1.47-1.53 (m, 45 H, 15 $\times$ CH$_3$), 1.45 (s, 3 H, CH$_3$), 1.43 (s, 12 H, CH$_3$ + C(CH$_3$)$_3$), 1.40 (m, 3 H, CH$_3$-CH), 1.37 (s, 3 H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.2 (CO), 176.1 (CO), 176.1 (CO), 176.0 (CO), 175.9 (CO), 175.7 (CO), 175.5 (CO), 175.4 (CO), 175.2 (CO), 174.7 (CO), 172.6 (CO), 156.5 (CO), 140.4 (2 $\times$ C), 133.8 (2 $\times$ C), 129.3 (2 $\times$ CH), 128.9 (2 $\times$ CH), 128.5 (2 $\times$ CH), 128.4 (2 $\times$CH), 80.4 (C, tBu), 57.3 (C), 56.8 (C), 56.7 (C), 56.7 (C), 56.6 (C), 56.5 (C), 56.5 (4 $\times$ C), 56.4 (C), 49.5 (CH), 48.1 (br, 2 $\times$ CH$_2$), 28.0 (3 $\times$ CH$_3$, tBu), 23.0-27.4 (m, 22 $\times$ CH$_3$), 16.9 (CH$_3$) ppm. MS (ES$^+$, CH$_2$Cl$_2$): 1303.1 (95%, [M+H]$^+$), 1325.1 (100%, [M+Na]$^+$).

AzeAib$_4$OtBu (2x)
To a suspension of DSC (107 mg, 0.42 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise at 0 °C a solution of 5x (120 mg, 0.29 mmol) in CH₂Cl₂ (3.0 mL). The reaction mixture was stirred overnight at RT and was diluted with CH₂Cl₂ (75 mL). The organic layer was washed with 5% KHSO₄ (2 × 25 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH₃CN (2.5 mL) and this solution was added dropwise to a mixture of 1·HCl (67 mg, 0.29 mmol) and DIPEA (222 µL, 1.16 mmol) in CH₃CN (1.25 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH₂Cl₂ (50 mL). The organic layer was washed successively with 5% KHSO₄ (2 × 15 mL), NaHCO₃ (2 × 15 mL) and brine (15 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO₂, EtOAc/CH₂Cl₂ 1:1) provided the tilted compound (146 mg, 79%) as a colourless solid. mp = 192-195 °C. IR (solid) νmax 3304, 2981, 2934, 1730, 1629, 1520, 1454, 1383, 1362, 1229, 1145 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.39 (s, 6 H, 2 × CH₃), 1.42 (s, 9 H, tBu), 1.47 (s, 6 H, 2 × CH₃), 1.51 (s, 6 H, 2 × CH₂), 1.56 (s, 6 H, 2 × CH₂), 4.24 (s, 4 H, 2 × ArCH₂N), 4.87 (s, 1H, NH), 6.35 (s, 1 H, NH), 7.30 (s, 1 H, NH), 7.37-7.42 (m, 4 H, 4 × H₆), 7.46-7.52 (m, 2 H, 2 × H₆), 7.55 (d, 2 H, J = 7.3 Hz, 2 × H₆), 7.77 (s, 1 H, NH) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 24.9 (2 × CH₃), 25.6 (2 × CH₃), 25.7 (2 × CH₃), 25.9 (2 × CH₃), 28.0 (3 × CH₃), 48.1 (2 × CH₂), 56.2 (C), 56.8 (C), 56.9 (C), 57.6 (C), 80.0 (C), 128.61 (2 × CH), 128.63 (2 × CH), 129.2 (2 × CH), 129.5 (2 × CH), 133.7 (2 × C), 140.4 (2 × C), 156.0 (CO), 173.1 (CO), 173.9 (CO), 174.2 (CO), 174.4 (CO) ppm. MS (ES⁺, MeOH): 658.5 ([M+Na]^+, 100%). HRMS (ES⁺, MeOH) calcd for C₃₅H₅₀N₅O₆ = 636.3756; found 636.3750.
N$_3$Aib$_4$-(L)-AlaNHtBu (4a)

To a mixture of EDC·HCl (900 mg, 4.70 mmol), HOBt·H$_2$O (719 mg, 4.70 mmol) and 3 (1.39 g, 3.62 mmol) in CH$_2$Cl$_2$ (25 mL) was added dropwise at 0 °C DIPEA (1.26 mL, 7.24 mmol). The reaction mixture was stirred at RT for 30 min and a solution of NH$_2$-(L)-AlaNHtBu (627 mg, 4.35 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise. The reaction mixture was stirred at RT for 4 days and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed successively with 5% KHSO$_4$ (2 × 50 mL), NaHCO$_3$ (2 × 50 mL) and brine (50 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO$_2$, MeOH/CH$_2$Cl$_2$ 3:97 → 5:95) provided the tilted compound (1.74 g, 94%) as a colourless solid. mp = 214 °C. IR (solid) $\nu$$_{max}$ 3307, 2977, 2936, 2111, 1648, 1526, 1454, 1382, 1362, 1221 cm$^{-1}$. [$\alpha$]$_{D}^{20}$ = +28.0 (c = 1.03, MeOH). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.37 (s, 12 H, tBu + CH$_3$), 1.41 (d, 3 H, $J$ = 7.3 Hz, CH$_3$CH), 1.45 (s, 6 H, 2 × CH$_3$), 1.47 (s, 3 H, CH$_3$), 1.48 (s, 3 H, CH$_3$), 1.53 (s, 3 H, CH$_3$), 1.55 (s, 3 H, CH$_3$), 1.57 (s, 3 H, CH$_3$), 4.33 (quin, 1 H, $J$ = 7.5 Hz, CH$_3$CH), 6.18 (s, 1H, NH), 6.77 (s, 1 H, NH), 6.74 (d, 1 H, $J$ = 7.9 Hz, NH) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 17.3 (CH$_3$), 23.46 (CH$_3$), 23.49 (CH$_3$), 23.7 (CH$_3$), 24.3 (CH$_3$), 24.6 (CH$_3$), 26.4 (CH$_3$), 27.4 (CH$_3$), 27.5 (CH$_3$), 28.8 (3 × CH$_3$), 50.1 (CH), 51.1 (C), 56.9 (C), 57.1 (C), 57.3 (C), 64.1 (C), 172.5 (CO), 173.3 (2 × CO), 173.6 (CO), 174.5 (CO) ppm. MS (ES$^+$, MeOH): 511.5 ([M+H]$^+$, 20%), 533.5 ([M+Na]$^+$, 100%). HRMS (ES$^+$, MeOH) calcd for C$_{23}$H$_{42}$N$_8$O$_5$Na = 533.3170; found 533.3183.

N$_3$Aib$_4$-(L)-PheNHtBu (4b)
To a mixture of HOBt·H₂O (204 mg, 1.33 mmol) and 3 (397 mg, 1.03 mmol) in CH₂Cl₂ (20 mL) was added dropwise at 0 °C EDC (200 µL, 1.13 mmol). The reaction mixture was stirred at RT for 30 min and a solution of NH₂-(L)-PheNH₂Bu (273 mg, 1.24 mmol) in CH₂Cl₂ (5 mL) and TEA (287 µL, 2.06 mmol) were successively added dropwise. The reaction mixture was stirred at RT for 2 days and was diluted with CH₂Cl₂ (100 mL). The organic layer was washed successively with 5% KHSO₄ (2 × 40 mL), NaHCO₃ (2 × 40 mL) and brine (20 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO₂, EtOAc/CH₂Cl₂ 4:6) followed by crystallisation from CH₃CN provided the tilted compound (323 mg, 53%) as a colourless solid. mp = 212 °C. IR (solid) νmax 3309, 2979, 2939, 2105, 1653, 1526, 1454, 1383, 1362, 1282, 1222, 1167 cm⁻¹. [α]D²⁰ = +22.3° (c = 0.52, MeOH). ¹H NMR (500 MHz, CDCl₃) δ 1.11 (s, 3 H, CH₃), 1.34 (s, 3 H, CH₃), 1.40 (s, 9 H, tBu), 1.455 (s, 3 H, CH₃), 1.46 (s, 3 H, CH₃), 1.47 (s, 6 H, 2 × CH₃), 1.52 (s, 3 H, CH₃), 1.53 (s, 3 H, CH₃), 2.88 (dd, 1 H, J = 12.0 and 14.5 Hz, PheCH₂CH), 3.61 (dd, 1 H, J = 3.2 and 14.5 Hz, PheCH₂CH), 4.55 (dd, 1 H, J = 11.9, 8.7 and 3.2 Hz, PheCH₂CH), 6.23 (s, 1 H, NH), 6.91 (s, 1 H, NH), 7.00 (s, 1 H, NH), 7.10 (t, 1 H, J = 7.3 Hz, H₆), 7.16 (t, 2 H, J = 7.3 Hz, 2 × H₅), 7.25-7.28 (m, 3 H, NH + 2 × H₆), 7.32 (d, 1 H, J = 8.7 Hz, NH) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 23.19 (CH₃), 23.24 (CH₃), 23.4 (CH₃), 24.1 (CH₃), 24.4 (CH₃), 26.5 (CH₃), 26.8 (CH₃), 27.4 (CH₃), 28.7 (3 × CH₃), 37.2 (CH₂), 51.2 (C), 55.3 (CH), 56.6 (C), 57.0 (C), 57.1 (C), 63.9 (C), 126.0 (CH), 128.0 (2 × CH), 129.1 (2 × CH), 139.1 (C), 171.0 (CO), 173.1 (CO), 173.2 (CO), 173.4 (CO), 174.6 (CO) ppm. MS (ES⁺, MeOH): 587 ([M+H]⁺, 100%), 609 ([M+Na]⁺, 75%). HRMS (ES⁺, MeOH) calcd for C₂⁹H₄⁷N₈O₅ = 587.3664; found 587.3654.
N$_3$-Aib$_4$-(L)-fLeuNHfBu (4c)

To a mixture of HOBt·H$_2$O (26 mg, 0.170 mmol), EDC·HCl (32 mg, 0.167 mmol) and 3 (50 mg, 0.130 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise at 0 °C DIPEA (67 µL, 0.387 mmol). The reaction mixture was stirred at RT for 30 min and NH$_3$-(L)-fLeu-NHfBu (29 mg, 0.156 mmol) was added portionwise. The reaction mixture was stirred at RT for 2 days and was diluted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed successively with 5% KHSO$_4$ (2 × 40 mL), NaHCO$_3$ (2 × 40 mL) and brine (20 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO$_2$, EtOAc/CH$_2$Cl$_2$ 6:4) provided the tilted compound (56 mg, 78 %) as a colourless solid. mp = 220-222 °C. IR (solid) $\nu_{max}$ 3374, 3335, 2969, 2937, 2873, 2112, 1683, 1642, 1525, 1454, 1383, 1361, 1219, 1172 cm$^{-1}$. $[^{[\alpha]}]_D^{20} = -4.1^\circ$ (c = 0.49, MeOH). $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.10 (s, 9 H, 3 $\times$ CH$_3$, tBu), 1.36 (s, 9 H, 3 $\times$ CH$_3$, tBu), 1.37 (s, 3 H, CH$_3$), 1.46 (s, 3 H, CH$_3$), 1.47 (s, 3 H, CH$_3$), 1.48 (s, 3 H, CH$_3$), 1.49 (s, 3 H, CH$_3$), 1.53 (s, 6 H, 2 $\times$ CH$_3$), 1.55 (s, 3 H, CH$_3$), 4.03 (d, 1 H, J = 8.1 Hz, CHC(CH$_3$)$_3$), 6.12 (s, 1 H, NH), 6.51 (s, 1 H, NH), 6.93 (s, 3 H, CH$_3$), 7.11 (d, 1 H, J = 8.1 Hz, NH), 7.35 (s, 1 H, NH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.63 (CH$_3$), 23.65 (CH$_3$), 23.8 (CH$_3$), 24.3 (CH$_3$), 24.6 (CH$_3$), 26.5 (CH$_3$), 27.38 (CH$_3$), 27.44 (3 $\times$ CH$_3$, tBu), 27.6 (CH$_3$), 28.8 (3 $\times$ CH$_3$, tBu), 34.0 (C), 51.2 (C), 56.9 (C), 57.2 (C), 57.3 (C), 63.0 (CH), 64.1 (C), 170.5 (CO), 172.6 (CO), 173.1 (CO), 173.3 (CO), 174.6 (CO) ppm. MS (ES$^+$, MeOH): 553.5 ([M+H]$^+$, 100 %). HRMS (ES$^+$, MeOH) calcd for C$_{26}$H$_{48}$N$_8$O$_5$ = 553.3820; found 553.3817.

N$_3$Aib$_4$-(L)-AlaOzBu (4d)

![Diagram of N$_3$Aib$_4$-(L)-AlaOzBu (4d)](image-url)
To a mixture of EDC·HCl (259 mg, 1.35 mmol), HOBt·H₂O (206 mg, 1.35 mmol) and 3 (400 mg, 1.04 mmol) in CH₂Cl₂ (10 mL) was added dropwise at 0 °C DIPEA (652 µL, 3.75 mmol). The reaction mixture was stirred at RT for 30 min and HCl·NH₂-(L)-AlaOtBu (227 mg, 1.25 mmol) was added portion wise. The reaction mixture was stirred at RT for 3 days and was diluted with CH₂Cl₂ (75 mL). The organic layer was washed successively with 5% KHSO₄ (2 × 25 mL), NaHCO₃ (2 × 25 mL) and brine (25 mL) and was dried over MgSO₄. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO₂, EtOAc/CH₂Cl₂ 5:5→7:3) provided the tilted compound (457 mg, 86%) as a colourless solid. mp = 161-162 °C. IR (solid) ν_max 3346, 3223, 2980, 2936, 2875, 2110, 1738, 1695, 1644, 1515, 1455, 1382, 1364, 1304, 1260, 1223, 1153 cm⁻¹. [α]D²⁰ = -51.0 (c = 1.02, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 1.38 (s, 3 H, CH₃), 1.39 (d, 3 H, J = 7.2 Hz, CH₃), 1.42 (s, 9 H, 3 × CH₃), 1.45 (s, 3 H, CH₃), 1.47 (s, 3 H, CH₃), 1.48 (s, 3 H, CH₃), 1.50 (s, 3 H, CH₃), 1.523 (s, 3 H, CH₃), 1.526 (s, 3 H, CH₃), 1.53 (s, 3 H, CH₃), 4.33 (quin, 1 H, J = 7.2 Hz, CH₃CH), 6.22 (s, 1 H, NH), 6.91 (s, 1 H, NH), 7.16 (s, 1 H, NH), 7.24 (d, 1 H, J = 7.0 Hz, NH) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 17.4 (CH₃), 24.2 (2 × CH₃), 24.3 (CH₃), 24.4 (CH₃), 24.5 (CH₃), 25.8 (CH₃), 26.7 (CH₃), 26.8 (CH₃), 28.1 (3 × CH₃), 49.2 (CH), 57.0 (C), 57.08 (C), 57.13 (C), 64.2 (C), 80.8 (C), 172.5 (CO), 172.8 (CO), 172.9 (CO), 173.0 (CO), 174.6 (CO) ppm. MS (ES⁺, MeOH): 534.5 ([M+Na]⁺, 100%). HRMS (ES⁺, MeOH) calcd for C₂₃H₄₁N₇O₆Na = 534.3011; found 534.3007.

N₃Aib₄-(D)-AlaOtBu (4e)

To a mixture of EDC·HCl (193 mg, 1.01 mmol), HOBt·H₂O (155 mg, 1.01 mmol) and 3 (300 mg, 0.78 mmol) in CH₂Cl₂ (8 mL) was added dropwise at 0 °C DIPEA (407 µL, 2.34 mmol). The reaction mixture was stirred at RT for 30 min and HCl·NH₂-(D)-AlaOtBu (170 mg, 0.94
mmol) was added portion wise. The reaction mixture was stirred at RT for 2 days and was
diluted with CH₂Cl₂ (100 mL). The organic layer was washed successively with 5% KHSO₄
(2 × 30 mL), NaHCO₃ (2 × 30 mL) and brine (30 mL) and was dried over MgSO₄. After
evaporation of the solvent under reduced pressure, purification of the crude by column
chromatography (SiO₂, EtOAc/CH₂Cl₂ 5:5→7:3) provided the titled compound (372 mg,
93%) as a colourless solid. Spectroscopic data of 4e are identical to those of 4d. [α]D²⁰ =
+51.4 (c = 1.02, MeOH).

N₃Alb₄-(L)-ValOₜBu (4f)

To a mixture of HOBt-H₂O (52 mg, 0.33 mmol), EDC·HCl (64 mg, 0.33 mmol) and 3
(100 mg, 0.26 mmol) in CH₂Cl₂ (3 mL) was added dropwise at 0 °C DIPEA (135 µL, 0.78 mmol).
The reaction mixture was stirred at RT for 30 min and HCl-NH₂-(L)-ValOₜBu (66 mg, 0.31
mmol) was added portion wise. The reaction mixture was stirred at RT for 2 days and was
diluted with CH₂Cl₂ (100 mL). The organic layer was washed successively with 5% KHSO₄
(2 × 40 mL), NaHCO₃ (2 × 40 mL) and brine (20 mL) and was dried over MgSO₄. After
evaporation of the solvent under reduced pressure, purification of the crude by column
chromatography (SiO₂, EtOAc/CH₂Cl₂ 6:4) provided the titled compound (134 mg, 95 %) as a
colourless solid. mp = 160-162 °C. IR (solid) νmax 3325, 2978, 2936, 2874, 2111, 1715, 1650,
1518, 1457, 1382, 1364, 1286, 1259, 1223, 1159 cm⁻¹. [α]D⁰ = -32.8 (c = 0.5, MeOH). ¹H
NMR (400 MHz, CDCl₃) δ 0.96 (d, 6 H, J = 6.8 Hz, CH(CH₃)₂), 1.41 (s, 3 H, CH₃), 1.44 (s, 9
H, tBu), 1.46 (s, 3 H, CH₃), 1.49 (s, 3 H, CH₃), 1.502 (s, CH₃), 1.504 (s, 3 H, CH₂), 1.53 (s, 9
H, 3 × CH₃), 2.18 (oct, 1 H, J = 6.4 Hz, CH(CH₃)₂), 4.27 (dd, 1 H, J = 6.0 and 8.2 Hz,
CHCH(CH₃)₂), 6.16 (s, 1H, NH), 6.87 (s, 1 H, NH), 7.09 (d, 1 H, J = 8.2 Hz, NH), 7.21 (s, 1
H, NH) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 18.3 (CH₃, iPr), 19.2 (CH₃, iPr), 24.4 (CH₃),
24.5 (CH$_3$), 24.6 (3 × CH$_3$), 25.6 (CH$_3$), 26.5 (CH$_3$), 26.6 (CH$_3$), 28.2 (3 × CH$_3$, tBu), 30.8 (CH, iPr), 57.0 (C), 57.2 (2 × C), 58.8 (CH), 64.2 (C), 80.9 (C), 171.2 (CO), 172.6 (CO), 172.7 (CO), 172.9 (CO), 174.9 (CO) ppm. MS (ES$^+$, MeOH): 540.4 ([M+H]$^+$, 100%), 562.5 ([M+Na]$^+$, 30%). HRMS (ES$^+$, MeOH) calcd for C$_{25}$H$_{46}$N$_7$O$_6$ = 540.3504; found 540.3496.

N$_3$Aib$_4$-(L)-PheOtBu (4g)

To a mixture of HOBt·H$_2$O (63 mg, 0.41 mmol) and 3 (120 mg, 0.31 mmol) in CH$_2$Cl$_2$ (6 mL) was added dropwise at 0 °C EDC (61 µL, 0.34 mmol). The reaction mixture was stirred at RT for 30 min and HCl·NH$_2$-(L)-PheOtBu (178 mg, 0.69 mmol) and TEA (131 µL, 0.94 mmol) were successively added. The reaction mixture was stirred at RT for 3 days and was diluted with CH$_2$Cl$_2$ (50 mL). The organic layer was washed successively with 5% KHSO$_4$ (2 × 25 mL), NaHCO$_3$ (2 × 25 mL) and brine (25 mL) and was dried over MgSO$_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (SiO$_2$, EtOAc/CH$_2$Cl$_2$ 4:6) provided the titled compound (156 mg, 85%) as a colourless solid.

mp = 68-72 °C. IR (solid) $\nu_{\text{max}}$ 3320, 2982, 2934, 2111, 1722, 1651, 1516, 1455, 1382, 1364, 1257, 1223, 1152 cm$^{-1}$. $[^{[a]}]D^{20} = -4.0^\circ$ (c = 0.50, MeOH). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.34 (s, 9 H, tBu), 1.41 (s, 3 H, CH$_3$), 1.42 (s, 3 H, CH$_3$), 1.46 (s, 3 H, CH$_3$), 1.48 (s, 3 H, CH$_3$), 1.49 (s, 6 H, 2 × CH$_3$), 1.52 (s, 3 H, CH$_3$), 1.53 (s, 3 H, CH$_3$), 3.09 (dd, 1 H, J = 14.2 and 7.2 Hz, A of ABX, PheCH$_2$CH), 3.11 (dd, 1 H, J = 14.2 and 7.2 Hz, B of ABX, PheCH$_2$CH), 4.59 (q, 1 H, J = 7.2 Hz, PheCH$_2$CH), 6.22 (s, 1 H, NH), 6.91 (s, 1 H, NH), 7.14 (s, 1 H, NH), 7.14-7.18 (m, 1 H, H$_{\text{Ar}}$), 7.20-7.28 (m, 5 H, NH + 4 × H$_{\text{Ar}}$) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 24.4 (CH$_3$), 24.5 (CH$_3$), 24.7 (CH$_3$), 24.8 (CH$_3$), 25.0 (CH$_3$), 25.3 (CH$_3$), 26.0 (CH$_3$), 26.1 (CH$_3$), 28.0 (3 × CH$_3$), 37.9 (CH$_2$), 54.8 (CH), 57.0 (C), 57.1 (C), 57.2 (C), 64.2 (C), 81.3 (C),

s23
126.5 (CH), 128.2 (2 × CH), 129.7 (2 × CH), 137.5 (C), 171.0 (CO), 172.8 (CO), 172.9 (2 × CO), 174.7 (CO) ppm. MS (ES⁺, MeOH): 588 ([M+H]+, 80%), 610 ([M+Na]+, 100%). HRMS (ES⁺, MeOH) calcd for C₂₉H₄₆N₇O₆ = 588.3504; found 588.3498.

N₃Aib₉-(L)-AlaOₜBu (4h)

5d (414 mg, 0.85 mmol) and the azlactone (312 mg, 0.85 mmol), synthesized respectively from 4d and 3 following general procedure A and B, were dissolved in dry acetonitrile (7 mL) and the mixture was heated at reflux for 5 days. The solvent was then evaporated under reduced pressure and purification of the crude by column chromatography (EtOAc/CH₂Cl₂ 7:3) provided the title compound (455 mg, 63%) as a white solid. mp = 229-230 °C. IR (solid) νmax 3303, 2983, 2938, 2873, 2109, 1736, 1657, 1644, 1526, 1526, 1455, 1383, 1363, 1276, 1227, 1168, 1153 cm⁻¹. [α]D²⁰ = -41.4 (c = 0.55, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 1.40 (s, 3 H, CH₃), 1.41-1.52 (m, 45 H, 15 × CH₃), 1.53-1.59 (m, 12 H, 4 × CH₃), 4.35 (quin, 1 H, J = 7.1 Hz, CHCH₃), 6.21 (s, 1 H, NH), 6.98 (s, 1 H, NH), 7.43 (s, 1 H, NH), 7.49-7.54 (m, 2 H, 2 × NH), 7.56 (s, 1 H, NH), 7.57 (s, 1 H, NH), 7.61 (s, 1 H, NH) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 175.8 (CO), 175.5 (CO), 175.4 (2 × CO), 174.7 (CO), 174.4 (CO), 173.7 (CO), 173.4 (CO), 172.7 (CO), 80.5 (C), 64.0 (C), 57.1 (C), 57.0 (C), 56.95 (C), 56.91 (C), 56.8 (2 × C), 56.7 (C), 49.6 (CH), 28.1 (3 × CH₃, tBu), 23.0-27.3 (m, 16 × CH₃), 17.1 (CH₃) ppm. MS (ES⁺, MeOH): 852.7 ([M+H]⁺, 90%), 874.7 ([M+Na]⁺, 100%). HRMS (ES⁺, MeOH) calcd for C₃₉H₆₉N₁₁O₁₀Na = 874.5127; found 874.5084.

N₃Aib₁₂-(L)-AlaOₜBu (4j)
5h (120 mg, 0.145 mmol) and the azlactone (58 mg, 0.16 mmol), synthesized respectively from 4h and 3 following general procedure A and B, were dissolved in dry acetonitrile (3 mL) and the mixture was heated at reflux for 4 days under N$_2$ atmosphere. The solvent was then evaporated under reduced pressure and the crude was purified by column chromatography (EtOAc/DCM from 6:4 to 7:3) to provide the title compound (78 mg, 45%) as a white solid. mp > 300 °C. IR (solid) $\nu_{\text{max}}$ 3287, 2984, 2936, 2872, 2113, 1660, 1530, 1455, 1383, 1362, 1294, 1227, 1168 cm$^{-1}$. $[\alpha]_{D}^{20} = -23.7$ (c = 0.54, CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.41 (s, 3 H, CH$_3$), 1.42-1.53 (m, 69 H, tBu + 20 × CH$_3$), 1.53-1.60 (m, 12 H, 4 × CH$_3$), 4.34 (quin, 1 H, $J$ = 7.1 Hz, CH$_3$CH), 6.33 (s, 1 H, NH), 7.07 (s, 1 H, NH), 7.47 (s, 1 H, NH), 7.54-7.57 (m, 2 H, 2 × NH), 7.646 (s, 1 H, NH), 7.654 (s, 1 H, NH), 7.661 (s, 1 H, NH), 7.67 (s, 1 H, NH), 7.71 (s, 1 H, NH), 7.73 (s, 2 H, 2 × NH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 17.1 (CH$_3$), 22.9-27.0 (24 × CH$_3$), 28.1 (3 × CH$_3$, tBu), 49.5 (CH), 56.6-56.7 (m, 4 × C), 56.7-56.8 (m, 3 × C), 56.94 (C), 56.97 (2 × C), 57.1 (C), 64.1 (C), 80.5 (C), 172.8 (CO), 173.46 (CO), 173.53 (CO), 174.3 (CO), 174.8 (CO), 175.4 (CO), 175.6 (CO), 175.7 (CO), 175.9 (CO), 176.0 (CO), 176.08 (CO), 176.14 (CO), 176.16 (CO) ppm. MS (ES$^+$, MeOH): 1192.8 ([M+H]$^+$, 35%), 1214.8 ([M+Na]$^+$, 100%). HRMS (ES$^+$, MeOH) calcd for C$_{58}$H$_{97}$N$_{15}$O$_{14}$Na = 1214.7237; found 1214.7215.
Scheme 1: Synthesis of 6a and 6b.

Aze-Aib\textsuperscript{\text{n}}-Aib\textsuperscript{\text{n}}-Val\textsuperscript{\text{n}}-Ala\textsuperscript{\text{n}}-Leu\textsuperscript{\text{n}}-NH\textsubscript{Pr} (6a)

Boc-protected oligoureia 7\text{a} (40 mg, 0.059 mmol) was dissolved in TFA (400 \(\mu\)L) and stirred for 45 min. The reaction mixture was then concentrated under reduced pressure and the resulting residue was co-evaporated 3 times with cyclohexane. The crude mixture was dissolved in CH\textsubscript{2}Cl\textsubscript{2} and treated with 1 M K\textsubscript{2}CO\textsubscript{3} aqueous solution and brine. The organic layer was then dried over MgSO\textsubscript{4} and evaporated. The crude product was dissolved in a stirred solution of AzeCl (20 mg, 0.077 mmol, synthesized from 1 following general procedure C) in anhydrous acetonitrile (150 \(\mu\)L). Et\textsubscript{3}N (11 \(\mu\)L) and a catalytic amount of DMAP were added and the resulting mixture was refluxed overnight. The reaction mixture was then diluted with DCM and quenched with water. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried.
over MgSO₄, filtered and concentrated in-vacuo. Purification by flash column chromatography (CH₂Cl₂-MeOH (v/v), 90:10) yielded the title compound as a white solid (20 mg, 0.023 mmol, 39%). **mp** = 170-172 °C. \(^1\)H NMR (500 MHz, CD₃OH) \(\delta\) 7.54 (2H, dd, \(J = 0.9\) and 7.6, 2 x CH₆ar), 7.48 (2H, dt, \(J = 1.5\) and 7.3, 2 x CH₆ar), 7.43 (2H, dd, \(J = 1.1\) and 7.4, 2 x CH₆ar), 7.38 (2H, dt, \(J = 1.3\) and 7.3, 2 x CH₆ar), 7.30 (1H, t, \(J = 5.2\), N₃H₄Aib₂), 6.44 (1H, s, N’H₃Aib₁ or Aib₂), 6.40 (1H, s, N’H₃Aib₁ or Aib₂), 6.38 (1H, dd, \(J = 2.8\) and 9.9, NH₄Val), 6.25-6.19 (2H, m, NH₃Val and NH₄Aib₁), 6.17 (1H, d, \(J = 10.7\), N’H₃Val), 5.92 (1H, dd, \(J = 5.2\) and 7.2, NH₄Val), 5.82 (1H, d, \(J = 10.0\), N’H₄Val), 5.67 (1H, d, \(J = 7.8\), NH₃Pr), 5.47 (1H, d, \(J = 9.6\), N’H₄Val), 4.24 (2H, d, \(J = 13.0\), 2 x CH₃H₄B, A part of AB pattern), 4.17 (2H, d, \(J = 13.0\), 2 x CH₃H₄B, B part of AB pattern), 4.07-3.96 (1H, m, NCH₃Val), 3.96-3.86 (1H, m, NCH₃Ala), 3.77 (1H, hept, \(J = 7.4\), NCH₃Pr), 3.74-3.68 (1H, m, NCH₃Val), 3.68-3.63 (1H, m, NCH₃H₄B₃Aib₂), 3.60 (1H, ddd, \(J = 2.7\), 10.6 and 16.5, NCH₃H₄B₃Aib₃), 3.52 (1H, ddd, \(J = 3.6\), 9.7 and 13.7, NCH₃H₄B₃Val), 3.48-3.35 (3H, m, NCH₂H₂Val and NCH₂H₄B₃Val), 3.26 (1H, dd, \(J = 9.9\) and 13.2, NCH₂H₄B₃Ala), 2.52-2.26 (3H, m, NCH₂H₂B₃Val, NCH₂H₄B₃Val and NCH₂H₄B₃Ala), 1.66 (1H, non, \(J = 7.0\), CH₃Val), 1.52 (1H, oct, \(J = 6.8\), CH₃Val), 1.34 (3H, s, CH₃₃Aib₁ or Aib₂), 1.31 (3H, s, CH₃₃Aib₁ or Aib₂), 1.27 (6H, s, CH₃₃Aib₁ or Aib₂), 1.19 (2H, t, \(J = 7.3\), CH₃₂Leu), 1.12 (3H, d, \(J = 6.6\), CH₃₃Pr), 1.11 (3H, d, \(J = 6.6\), CH₃₃Pr), 1.03 (3H, s, CH₃₃Aib₁ or Aib₂), 1.01 (3H, d, \(J = 6.9\), CH₃₃Ala), 0.91 (3H, d, \(J = 6.8\), CH₃₃Leu), 0.87 (3H, d, \(J = 6.7\), CH₃₃Leu), 0.84 (3H, d, \(J = 6.9\), CH₃₃Val), 0.80 (3H, d, \(J = 6.9\), CH₃₃Val) ppm. \(^{13}\)C NMR (125 MHz, CD₃OH) \(\delta\) 162.8 (C=O), 161.4 (C=O), 160.8 (C=O), 160.5 (2 x C=O), 159.6 (C=O), 141.8 (2 x =C₄), 135.4 (2 x =C₄), 130.5 (2 x =C₄), 129.7 (2 x =CH₃), 129.3 (2 x =CH₃), 128.9 (2 x =CH₃), 55.4 (NCH₃Val), 54.2 (C₃Aib₁ or Aib₂), 53.7 (C₃Aib₁ or Aib₂), 52.5 (NCH₂₃Aib₂), 46.7 (2 x NCH₂₃Ar), 48.6 (NCH₂₃Ala), 48.5 (NCH₃Leu), 47.4 (NCH₂₃Aib₁ and NCH₂₃Leu), 47.1 (NCH₃Val), 43.8 (NCH₂₃Val), 43.1 (NCH₃Pr), 42.9 (NCH₂₂Leu), 31.7 (CH₃Val), 26.8 (CH₃₃Aib₁ or Aib₂), 26.7 (CH₃₃Aib₁ or Aib₂), 26.3 (CH₃₃Aib₁ or Aib₂), 26.2 (CH₃Leu), 25.5 (CH₃₃Aib₁ or Aib₂), 23.5 (CH₃₃Pr), 23.5 (CH₃₃Pr), 23.5 (CH₃₃Val), 22.5 (CH₃₃Leu), 19.7 (CH₃₃Val), 527
18.8 (CH$_3$ala), 18.3 (CH$_3$Val) ppm. IR (film) ν 3343 (NH broad), 2965, 2930, 2868 (C-H), 1632 (C=O urea), 1220, 772 cm$^{-1}$. $[^{13}C]$$^2$$^H$3Ala, 18.3 ($[^{13}C]$$^2$$^H$3Val) ppm.

HRMS (ESI$^+$): m/z calcd for C$_{45}$H$_{75}$O$_6$N$_{12}$ [M+H]$^+$ 879.5927, found 879.5928.

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**Aze-Aib$^u$-Aib$^u$-Val$^u$-Ala$^u$-Leu$^u$-NH$i$Pr (6b)**

Boc-protected oligourea 7b (62 mg, 0.071 mmol) was dissolved in TFA (600 µL) and stirred for 45 min. The reaction mixture was then concentrated under reduced pressure and the resulting residue was coevaporated 3 times with cyclohexane. The crude mixture was dissolved in CH$_2$Cl$_2$ and treated with 1 M K$_2$CO$_3$ aqueous solution and brine. The organic layer was then dried over MgSO$_4$ and evaporated. The crude product was dissolved in a stirred solution of AzeCl (24 mg, 0.092 mmol, synthesized from 1 following general procedure C) in acetonitrile (180 µL). Et$_3$N (600 µL) and a catalytic amount of DMAP were added and the resulting mixture was refluxed overnight. The reaction mixture was then diluted with DCM and quenched with water. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over...
MgSO₄, filtered and concentrated in-vacuo. Purification by flash column chromatography (CH₂Cl₂-MeOH (v/v), 90:10) yielded the title compound as a white solid (49 mg, 0.049 mmol, 69.5%).  

**mp =** 192-194 °C;  
**¹H NMR** (500 MHz, CD₃OH) δ 7.55-7.51 (2H, m, 2 x CH₅), 7.50-7.45 (2H, m, 2 x CH₅), 7.44 -7.41 (2H, m, 2 x CH₅), 7.40-7.34 (2H, m, 2 x CH₅), 7.25 (1H, t, J = 5.1, NH₂), 6.43 (1H, s, N'NH₂), 6.38 (1H, dd, J = 2.7 and 9.9, NH₂), 6.25 (1H, dd, J = 3.0 and 9.5, NH₁), 6.20-6.17 (2H, m, NH₂ and N'NH₁), 6.12 (2H, brs, NH₂), 5.93 (1H, t, J = 6.1, NH₂), 5.83 (1H, d, J = 7.8, NH₁), 5.49 (1H, d, J = 9.5, NH₂), 4.21 (4H, AB system), 4.07-3.97 (1H, m, NH₂), 3.97-3.86 (1H, m, NH₂), 3.79 (1H, hept, J = 6.7, NH₁), 3.75-3.66 (1H, m, NH₁), 3.66-3.48 (3H, m, NCH₂, NCH₂, and NCH₂), 3.31-3.21 (1H, dd, J = 3.3 and 9.8, NCH);  

1H, s, CH₂, 1.28 (9H, s, C₃H₉), 1.04 (3H, s, CH₃);  

1.03 (3H, d, J = 7.0, CH₃), 0.92 (3H, d, J = 6.7, CH₃), 0.91 (3H, d, J = 6.9, CH₃), 0.88 (3H, d, J = 6.7, CH₃), 0.86 (3H, d, J = 7.0, CH₃) ppm.  

**¹³C NMR** (125 MHz, CD₃OH) δ 162.7 (C=O), 161.3 (C=O), 160.7 (2 x C=O), 160.5 (2 x C=O), 159.6 (C=O), 141.7 (2 x =C=O), 135.4 (2 x =C=O), 130.5 (2 x =C=O), 129.7 (2 x =C=O), 122.3 (2 x =C=O), 128.0 (2 x =C=O), 55.5 (NCH₃), 54.2 (CAib1 or Aib2 or Aib3), 53.7 (2 x CAib1 or Aib2 or Aib3), 52.4 (NCH₂Aib3), 49.0 (NCH₂Aib2), 48.6 (2 x NCH₂Ar), 48.5 (NCH₂Aib1), 48.4 (NCH₂), 47.4 (NCH₂Aib1 and NCH₂), 47.1 (NCH₂), 43.9 (NCH₂Val), 43.1 (NCH₁Pr), 42.9 (NCH₂Val), 31.7 (CH₂Val), 26.9 (CH₃Aib₁), 26.5 (CH₃Aib₂), 26.2 (CH₃Aib₁ or 2), 26.2 (CH₃Aib₁ or 2), 26.0 (CH₃Aib₁), 25.6 (CH₃Aib₁), 23.6 (2 x CH₃Pr), 23.5 (CH₃), 22.5 (CH₃), 20.0 (CH₃Val), 18.9 (CH₃Ala), 18.4 (CH₃Val) ppm.  

**IR** (film) ν 3339
(NH broad), 2965, 2930, 2871 (C-H), 1633 (C=O urea), 1249, 770 cm⁻¹. \([\alpha]_D^{20} = +3.6\) (c = 1.00; TFE). **HRMS** (ESI⁺): \(m/z\) calcd for C₅₀H₈₅O₇N₁₄ [M+H]⁺ 993.6720, found 993.6714.

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<th>β</th>
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NMR spectra of synthesized peptides

$^1$H NMR spectrum of $\text{AzeAib}_4$-(L)-$\text{AlaNH}t\text{Bu}$ (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{AzeAib}_4$-(L)-$\text{AlaNH}t\text{Bu}$ (100 MHz, CDCl$_3$):
\(^1\)H NMR spectrum of AzeAib\(_4\)-(L)-PheNH\(_t\)Bu (400 MHz, CDCl\(_3\)):

\(^{13}\)C NMR spectrum of AzeAib\(_4\)-(L)-PheNH\(_t\)Bu (125 Hz, CDCl\(_3\)):
$^1$H NMR spectrum of AzeAib$_4$-(L)-tLeuNHtBu (400 MHz, CDCl$_3$/CD$_3$OH 97:3):

$^{13}$C NMR spectrum of AzeAib$_4$-(L)-tLeuNHtBu (100 MHz, CDCl$_3$/CD$_3$OH 97:3):
$^1$H NMR spectrum of AzeAib$_4$-(D)-AlaOtBu (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of AzeAib$_4$-(D)-AlaOtBu (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of AzeAib$_4$-(L)-Val$^t$Bu (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of AzeAib$_4$-(L)-Val$^t$Bu (100 MHz, CDCl$_3$):
\(^1\)H NMR spectrum of \textit{AzeAib}_{4}-(L)-PheO{\textit{tBu}} (500 MHz, CDCl\textsubscript{3}):
$^1$H NMR spectrum of $\text{AzeAib}_8$-$\text{(L)}$-AlaO$t$_Bu (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{AzeAib}_8$-$\text{(L)}$-AlaO$t$_Bu (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of AzeAib$_{11}$AlaOrBu (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of AzeAib$_{11}$AlaOrBu (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of AzeAib$_{12}$AlaOtBu (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of AzeAib$_{12}$AlaOtBu (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of $N_3$Aib$_4$-(L)-AlaNHtBu (500 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $N_3$Aib$_4$-(L)-AlaNHtBu (125 MHz, CDCl$_3$):
$^1$H NMR spectrum of $\text{N}_3\text{Aib}_4$-(L)-PheNH$t\text{Bu}$ (500 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{N}_3\text{Aib}_4$-(L)-PheNH$t\text{Bu}$ (125 MHz, CDCl$_3$):
$^1$H NMR spectrum of $\text{N}_3\text{Aib}_4-(\text{L})-\text{tLeuNHtBu}$ (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{N}_3\text{Aib}_4-(\text{L})-\text{tLeuNHtBu}$ (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of $\text{N}_3\text{Aib}_4(\text{L})\text{-AlaO}t\text{Bu}$ (400 MHz, CDCl$_3$): 

$^{13}$C NMR spectrum of $\text{N}_3\text{Aib}_4(\text{L})\text{-AlaO}t\text{Bu}$ (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of $N_3$Aib$_4$-(L)-ValOtBu (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $N_3$Aib$_4$-(L)-ValOtBu (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of $\text{N}_3\text{Aib}_4(\text{L})\text{-PheO}t\text{Bu}$ (500 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{N}_3\text{Aib}_4(\text{L})\text{-PheO}t\text{Bu}$ (125 MHz, CDCl$_3$) :
$^1$H NMR spectrum of $\text{N}_3\text{Aib}_8$-(L)-AlaO$t$Bu (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{N}_3\text{Aib}_8$-(L)-AlaO$t$Bu (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of $\text{N}_3\text{Aib}_{12}\text{-(L)-AlaO}t\text{Bu}$ (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{N}_3\text{Aib}_{12}\text{-(L)-AlaO}t\text{Bu}$ (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of $\text{AzeAib}_4\text{OttBu}$ (400 MHz, CDCl$_3$):

$^{13}$C NMR spectrum of $\text{AzeAib}_4\text{OttBu}$ (100 MHz, CDCl$_3$):
$^1$H NMR spectrum of *Aze*-Aib$^u$-Aib$^u$-Val$^u$-Ala$^u$-Leu$^u$-NHPr (500 MHz, CD$_3$OH):

$^{13}$C NMR spectrum of *Aze*-Aib$^u$-Aib$^u$-Val$^u$-Ala$^u$-Leu$^u$-NHPr (125 MHz, CD$_3$OH):
COSY spectrum of Aze-Aib\textsuperscript{u}-Aib\textsuperscript{u}-Val\textsuperscript{u}-Ala\textsuperscript{u}-Leu\textsuperscript{u}-NH\textsubscript{i}Pr (500 MHz, CD\textsubscript{3}OH):
HSQC spectrum of Aze-Aib\textsuperscript{\textcircled{u}}-Aib\textsuperscript{\textcircled{u}}-Val\textsuperscript{\textcircled{u}}-Ala\textsuperscript{\textcircled{u}}-Leu\textsuperscript{\textcircled{u}}-NH\textsubscript{i}Pr (CD\textsubscript{3}OH):
$^1$H NMR spectrum of $\text{Aze-Aib}^u$-$\text{Aib}^u$-$\text{Val}^u$-$\text{Ala}^u$-$\text{Leu}^u$-$\text{NHPr}$ (500 MHz, CD$_3$OH):

$^{13}$C NMR spectrum of $\text{Aze-Aib}^u$-$\text{Aib}^u$-$\text{Val}^u$-$\text{Ala}^u$-$\text{Leu}^u$-$\text{NHPr}$ (125 MHz, CD$_3$OH):
COSY spectrum of Aze-Aib\textsuperscript{a}-Aib\textsuperscript{a}-Aib\textsuperscript{a}-Val\textsuperscript{a}-Ala\textsuperscript{a}-Leu\textsuperscript{a}-NHPr (500 MHz, CD\textsubscript{3}OH):
HSQC spectrum of Aze-Aib\textsuperscript{u}-Aib\textsuperscript{u}-Aib\textsuperscript{u}-Val\textsuperscript{u}-Ala\textsuperscript{u}-Leu\textsuperscript{u}-NH\textsubscript{ipr} (CD\textsubscript{3}OH):
$^{1}$H NMR spectrum of $\text{AzeCl}$ (500 MHz, CDCl$_3$):
Determination of the helical excess

The oligomers 8a-d and 8f-g (Figure S1) capped with an enantiomerically enriched $^{13}$C-monolabelled probe were previously used as model compounds to determine by NMR the effect of a chiral amino acid introduced at the C-terminus on the screw sense preference of the Aib helix in methanol.$^{[1]}$

![Figure S1: Peptides 8a-j.](image)

In this method, the local helical excess (h.e.), which quantifies the excess of the major helix ($M$ or $P$) at the probe, is determined for each chiral amino acid using the following formula:

$$h.e. = ([P]-[M])/([P]+[M]) = \Delta\delta_{\text{fast}}/\Delta\delta_{\text{slow}}$$

where $\Delta\delta_{\text{slow}}$ and $\Delta\delta_{\text{fast}}$ are the $^{13}$C labelled probe anisochronicity at slow and fast exchange regime of the helix, respectively measured at -70 °C and 20 °C.

Furthermore the relative intensity of the $^{13}$C signals of the enantioselectivity isotopically enriched probe provides the absolute screw sense of the helix ($M$ or $P$).

The helical excess as well as the absolute screw sense previously reported in methanol$^{[1]}$ are given Table S1 (Entries 1-7). A similar approach using the oligomers 8a-d and 8f-g was employed to determine the helical excess and the absolute screw in THF and the results are given Figure S2, Figure S3 and Table S1 (entries 1-7).
The local helical excesses of longer peptides (n = 8, 11 and 12; Figure S1) were estimated assuming an exponential decay of the helical excess with the number $n$ of Aib residues.[5] The helical excess $h.e.(n)$ were calculated by extrapolation of the helical excess of tetramer 8d ($n = 4$) using the following formula:

$$h.e.(n) = (1 - f)^{n-4} \times h.e.(4)$$

where $f$ is the per-residue decrease in h.e.

$f = 7.7\%$ in MeOH and $f = 1.3\%$ in THF. The results of the calculations for $n = 8, 11$ and 12 are furnished Table S1 (Entries 8-10).

Figure S2: DEPT-135 spectra of peptides 8b-d and 8f-g in THF-8d, showing the anisochronicity $\Delta\delta$ of the $^{13}$C-labelled probe.
**Figure S2**: Variation of the $^{13}$C-labelled probe anisochronicity $\Delta \delta$ measured in THF-8d with the temperature in the case of peptide 8a.

**Table S1**: Local helical excess and absolute screw sense of helix determined in MeOH and in THF.

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<tr>
<th>Entry</th>
<th>Peptide</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Y</th>
<th>n</th>
<th>h.e. (%)</th>
<th>$\Delta \delta_{\text{fast}}$ (ppb)</th>
<th>$\Delta \delta_{\text{slow}}$ (ppb)</th>
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<tr>
<td>1</td>
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<td>Me</td>
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<td>NHrBu</td>
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<td>70 (P)</td>
<td>2308</td>
<td>/</td>
</tr>
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<td>tBu</td>
<td>H</td>
<td>NHrBu</td>
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<td>65 (P)</td>
<td>2510</td>
<td>/</td>
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<td>8d</td>
<td>Me</td>
<td>H</td>
<td>OrBu</td>
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<td>55 (M)</td>
<td>1413</td>
<td>55 (M)</td>
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<tr>
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<td>8e</td>
<td>H</td>
<td>Me</td>
<td>OrBu</td>
<td>4</td>
<td>55 (P)</td>
<td>/</td>
<td>55 (P)</td>
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<td>iPr</td>
<td>H</td>
<td>OrBu</td>
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<td>46 (M)</td>
<td>1332</td>
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<td>12</td>
<td>29 (M)</td>
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a $\Delta \delta_{\text{slow}}$ determined at low temperature (-70 °C) and used as a constant value for the calculation of the helical excess whatever the chiral amino acid considered.
### NMR and CD analysis of peptides 2a-j and 2x

**Table S2:** Anisochronicity \( \Delta\delta \) of the methylene groups of the dibenzazepine probe and molar ellipticity \( \theta_{250\text{ nm}} \) measured in MeOH for peptides 2a-j and 2x.

<table>
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<th>Entry</th>
<th>Peptide</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Y</th>
<th>n</th>
<th>( \Delta\delta ) (ppm)</th>
<th>( \theta ) at 250 nm (deg.cm(^2).dm(^{-1}))</th>
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<td>OtBu</td>
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<td>Me</td>
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<td>OtBu</td>
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* Data not available due to the low solubility of peptide 2i in MeOH.

**Figure S4:** Portion of the \(^1\)H NMR in THF-8d of 2a-d and 2f-j, showing the anisochronicity \( \Delta\delta \) of the methylene proton of the dibenzazepine probe.
Table S3: Anisochronicity $\Delta\delta$ of the methylene groups of the dibenzazepine probe measured in THF for peptides 2a-d and 2f-j.

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<th>$R^2$</th>
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<th>n</th>
<th>$\Delta\delta$ (ppm)</th>
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<td>NH/TBu</td>
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Figure S2: CD spectra obtained by mixing peptides 2d and 2e in various proportions in methanol.
Table S3: Anisochronicity $\Delta\delta$ of the methylene groups of the dibenzazepine probe and molar ellipticity $\theta_{250\text{ nm}}$ measured in MeOH when peptides 2d and 2e are mixed in various proportions.

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<th>2e/2d</th>
<th>$\Delta\delta$ (ppm)</th>
<th>$\theta$ at 250 nm (deg cm$^2$ dm$^{-1}$)</th>
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<td>23500</td>
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<td>265</td>
<td>13700</td>
</tr>
<tr>
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</tr>
<tr>
<td>40/60</td>
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<td>/</td>
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</tr>
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References


