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

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Supporting Information

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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_3OD 3.31) and ^{13}C-NMR were referenced to the carbon resonance of the solvent ($CDCl_3$ 77.16; CD_3OD 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_3OD, D_2O or CD_3CD_2OD 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 (λ_{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 ± 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*t*Bu**,[1] **NH_2-(L)-*t*LeuNH*t*Bu**,[1] **NH_2-(L)-AlaNH*t*Bu**, [1] **1** (as a free amine), [2] **N_3Aib$_4$OH** (**3**), [3] **NH_2Aib$_4$OtBu** (**5x**) [3] and oligoureas **7a** [4] and **7b** [4] were reported previously.

General procedure A: Hydrogenolysis of N_3Aib$_n$-X$_{aa}$-Y (n = 4, 8, 12; Xaa = Ala, Phe, *t*Leu, Val; Y =NH*t*Bu, O*t*Bu)

To a solution of **N_3Aib$_n$-X$_{aa}$-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_2Cl_2 and the organic layer was washed with 0.5 M K_2CO_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.

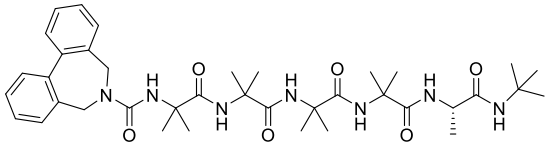
General procedure B: azlactone synthesis

To a solution of **3** (200 mg, 0.52 mmol) in CH_2Cl_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_2Cl_2 (1.2 mL) cooled at –78 °C was added dropwise a solution of **1** (226 mg, 1.16 mmol) in CH_2Cl_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_2Cl_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.

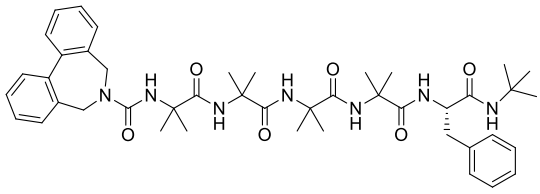
AzeAib_4-(L)-AlaNH*t*Bu (2a)



To a suspension of DSC (76 mg, 0.30 mmol) in CH_2Cl_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_2Cl_2 (3.0 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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 (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_3CN (1.5 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_2Cl_2

75:25) provided the titled compound (86 mg, 59%) as a colourless solid. **mp** = 216-217 °C. **IR** (solid) ν_{max} 3302, 2984, 1644, 1529, 1452, 1381, 1360, 1290, 1226, 1165 cm^{-1}. $\mathbf{[\alpha]_D^{20}}$ = +63.5 (c = 0.51, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.30 (s, 3 H, C$\underline{H}_3$), 1.38 (s, 9 H, *t*Bu), 1.43 (s, 3 H, C$\underline{H}_3$), 1.44 (d, 3 H, *J* = 7.1 Hz, CHC$\underline{H}_3$), 1.47 (s, 3 H, C$\underline{H}_3$), 1.49 (s, 3 H, C$\underline{H}_3$), 1.52 (s, 3 H, C$\underline{H}_3$), 1.54 (s, 3 H, C$\underline{H}_3$), 1.55 (s, 3 H, C$\underline{H}_3$), 1.58 (s, 3 H, C$\underline{H}_3$), 4.16 (d, 2 H, *J* = 12.7 Hz, A of AB, ArC$\underline{H}_2$), 4.30-4.38 (m, 1 H, $CH_3C\underline{H}$), 4.37 (d, 2 H, *J* = 12.7 Hz, B of AB, ArC$\underline{H}_2$), 5.20 (s, 1H, N$\underline{H}$), 6.48 (s, 1 H, N$\underline{H}$), 6.95 (s, 1 H, N$\underline{H}$), 7.37-7.42 (m, 4 H, 4 × $\underline{H}_{ar}$), 7.47-7.57 (m, 5 H, 4 × $\underline{H}_{ar}$ + N$\underline{H}$), 7.66 (d, 1 H, *J* = 7.9 Hz, N$\underline{H}$), 8.29 (s, 1 H, N$\underline{H}$) 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) calcd for $C_{38}H_{56}N_7O_6$ = 706.4287; found 706.4279.

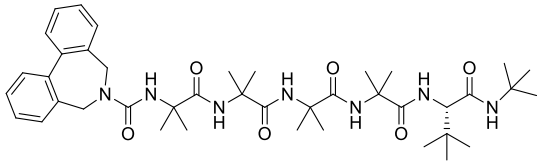
AzeAib$_4$-(L)-PheNH*t*Bu (2b)



To a suspension of DSC (28 mg, 0.109 mmol) in CH_2Cl_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_2Cl_2 (1.0 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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 (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_3CN (0.25 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_2Cl_2 3:7→4:6) provided the titled compound (20 mg, 37%) as a colourless solid. **mp** = 219-221 °C. **IR** (solid) ν_{max} 3294, 2981, 2930, 2868, 1651, 1632, 1529, 1148, 1383, 1360, 1227, 1169 cm^{-1}. $[\alpha]_D^{20}$ = +46.4° (c = 0.50, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.18 (s, 3 H, C$\underline{H}_3$), 1.30 (s, 3 H, C$\underline{H}_3$), 1.41 (s, 9 H, *t*Bu), 1.44 (s, 3 H, C$\underline{H}_3$), 1.45 (s, 3 H, C$\underline{H}_3$), 1.47 (s, 3 H, C$\underline{H}_3$), 1.51 (s, 3 H, C$\underline{H}_3$), 1.54 (s, 3 H, C$\underline{H}_3$), 1.55 (s, 3 H, C$\underline{H}_3$), 2.91 (dd, 1 H, *J* = 14.3 and 12.3 Hz, PheC$\underline{H}_2$CH), 3.63 (dd, 1 H, *J* = 14.3 and 2.7 Hz, PheC$\underline{H}_2$CH), 4.14 (d, 2 H, *J* = 12.6 Hz, A of AB, ArC$\underline{H}_2$N), 4.37 (d, 2 H, *J* = 12.6 Hz, B of AB, ArC$\underline{H}_2$N), 4.54-4.60 (m, 1 H, PheCH$_2$C$\underline{H}$), 5.18 (s, 1H, N$\underline{H}$), 6.44 (s, 1 H, N$\underline{H}$), 7.07-7.11 (m, 2 H, $\underline{H}_{ar}$ + N$\underline{H}$), 7.16 (t, 2 H, *J* = 7.3 Hz, 2 × $\underline{H}_{ar}$), 7.29 (d, 2 H, *J* = 7.3 Hz, 2 × $\underline{H}_{ar}$), 7.36-7.42 (m, 4 H, 4 × $\underline{H}_{ar}$), 7.46-7.53 (m, 4 H, 2 × N$\underline{H}$ + 2 × $\underline{H}_{ar}$), 7.55 (d, 2 H, J = 7.2 Hz, 2 × $\underline{H}_{ar}$), 8.19 (s, 1 H, N$\underline{H}$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 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), 128.52 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 129.3 (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 $C_{44}H_{60}N_7O_6$ = 782.4600; found 782.4602.

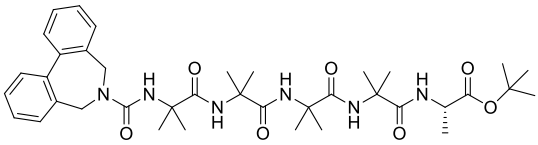
AzeAib$_4$-(L)-*t*LeuNH*t*Bu (2c)



To a suspension of DSC (27 mg, 0.105 mmol) in CH_2Cl_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_2Cl_2 (1.5 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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 (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_3CN (0.75 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_2Cl_2 5:5→4:6) provided the titled compound (38 mg, 69%) as a colourless solid. **mp** = 205-207 °C. **IR** (solid) ν_{max} 3283, 2981, 2933, 2872, 1652, 1644, 1626, 1531, 1451, 1383, 1360, 1287, 1260, 1166 cm^{-1}. **[α]$_D^{20}$** = +42.4 (c = 0.50, MeOH/CH_2Cl_2 1:9). **^{1}H NMR** (400 MHz, $CDCl_3$/CD_3OH 97:3) δ 1.07 (s, 9 H, *t*Bu), 1.27 (s, 3 H, C$\underline{H}_3$), 1.33 (s, 9 H, *t*Bu), 1.40 (s, 3 H, C$\underline{H}_3$), 1.41 (s, 3 H, C$\underline{H}_3$), 1.45 (s, 3 H, C$\underline{H}_3$), 1.47 (s, 6 H, 2 × C$\underline{H}_3$), 1.50 (s, 6 H, 2 × C$\underline{H}_3$), 3.94 (d, 1H, *J* = 7.8 Hz, C$\underline{H}$*t*Bu), 4.10 (d, 2 H, *J* = 12.6 Hz, A of AB, ArC$\underline{H}_2$N), 4.35 (d, 2 H, *J* = 12.6 Hz, B of AB, ArC$\underline{H}_2$N), 5.43 (s, 1H, N$\underline{H}$), 6.65 (s, 1 H, N$\underline{H}$), 6.78 (s, 1 H, N$\underline{H}$), 7.26 (d, 1H, *J* = 7.8 Hz, N$\underline{H}$), 7.31-7.41 (m, 4 H, 4 × $\underline{H}_{ar}$), 7.44-7.50 (m, 2 H, 2 × $\underline{H}_{ar}$), 7.52 (d, 2 H, *J* = 7.4 Hz, 2 × $\underline{H}_{ar}$), 7.63 (s, 1 H, N$\underline{H}$), 8.18 (s, 1 H, N$\underline{H}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$/CD_3OH 97:3) δ 23.4 (CH_3), 23.47 (CH_3), 23.51 (CH_3), 24.0 (CH_3), 27.0 (CH_3), 27.1

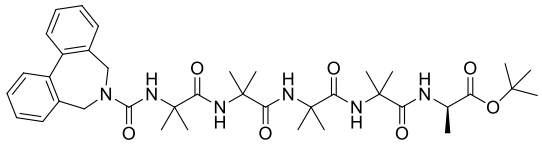
(CH_3), 27.2 (CH_3), 27.3 (3 × CH_3), 27.6 (CH_3), 28.6 (3 × CH_3), 33.8 (C), 47.9 (2 × CH_2), 51.3 (C), 56.5 (C), 56.87 (C), 56.95 (C), 57.3 (C), 63.5 (CH), 128.5 (4 × CH), 129.1 (2 × CH), 129.4 (2 × CH), 133.8 (2 × C), 140.4 (2 × C), 156.4 (CO), 171.1 (CO), 174.6 (CO), 175.3 (2 × CO), 175.6 (CO) ppm. **MS** (ES^+, DCM): 748.7 ($[M+H]^+$, 30%), 770.7 ($[M+Na]^+$, 20%). **HRMS** (ES^+, MeOH) calcd for $C_{41}H_{62}N_7O_6$ = 748.4756; found 748.4756.

AzeAib$_4$-(L)-AlaO*t*Bu (2d)



To a suspension of DSC (103 mg, 0.31 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (3 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_3CN (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 CH_3CN (1.5 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_2 (100 mL). The organic layer was washed successively with $NaHCO_3$ (2 × 25 mL), 5% $KHSO_4$ (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_2Cl_2 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**. $[\alpha]_D^{20}$ = -75.2 (c = 0.50, MeOH).

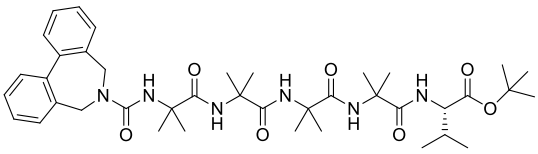
AzeAib$_4$-(D)-AlaO*t*Bu (2e)



To a suspension of DSC (119 mg, 0.46 mmol) in CH_2Cl_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_2Cl_2 (4.5 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_3CN (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_3CN (2.2 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_2Cl_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) ν_{max} 3305, 2981, 2935, 1656, 1629, 1528, 1454, 1382, 1361, 1228, 1151 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (s, 3 H, C$\underline{H}_3$), 1.42 (d, 3 H, *J* = 7.0 Hz, C$\underline{H}_3$), 1.43 (s, 9 H, *t*Bu), 1.45 (s, 3 H, C$\underline{H}_3$), 1.47 (s, 3 H, C$\underline{H}_3$), 1.51 (s, 3 H, C$\underline{H}_3$), 1.53 (s, 3 H, C$\underline{H}_3$), 1.54 (s, 3 H, C$\underline{H}_3$), 1.55 (s, 3 H, C$\underline{H}_3$), 1.56 (s, 3 H, C$\underline{H}_3$), 4.18 (d, 2 H, *J* = 12.6 Hz, A of AB, ArC$\underline{H}_2$N), 4.32 (d, 2 H, *J* = 12.6 Hz, B of AB, ArC$\underline{H}_2$N), 4.31-4.38 (m, 1 H, C$\underline{H}$-CH$_3$), 4.99 (s, 1H, N$\underline{H}$), 6.37 (s, 1 H, N$\underline{H}$), 7.34-7.43 (m, 5 H, 4 × $\underline{H}_{Ar}$ + N$\underline{H}$), 7.44-7.53 (m, 3 H, 2 × $\underline{H}_{Ar}$ + N$\underline{H}$), 7.54-7.57 (m, 2 H, 2 × $\underline{H}_{Ar}$), 8.10 (s, 1 H, N$\underline{H}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 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 $C_{38}H_{55}N_6O_7$ = 707.4127; found 707.4121.

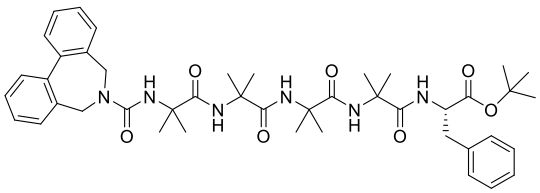
AzeAib_4-(L)-Val$O$*t*Bu (2f)



To a suspension of DSC (66 mg, 0.258 mmol) in CH_2Cl_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_2Cl_2 (3 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_2Cl_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_2Cl_2 1:1) provided the titled compound (112 mg, 86%) as a colourless solid. **mp** = 215-217 °C. $[\alpha]_D^{20}$ = -35.9 (c = 0.58, CH_2Cl_2). **IR** (solid) ν_{max} 3288, 2980, 2934, 2873, 1726, 1653, 1629, 1524, 1454, 1382, 1361, 1228, 1161 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.00 (d, 3 H, *J* = 6.9 Hz, $CH(C\underline{H}_3)_2$), 1.02 (d, 3 H, *J* = 6.9 Hz, $CH(C\underline{H}_3)_2$), 1.35 (s, 3 H, $C\underline{H}_3$), 1.43-1.47 (m, 12 H, *t*Bu + $C\underline{H}_3$), 1.48 (s, 3 H, $C\underline{H}_3$), 1.51 (s, 3 H, $C\underline{H}_3$), 1.52-1.58 (m, 12 H, 4 × $C\underline{H}_3$), 2.16-2.28 (m, 1 H, $C\underline{H}(CH_3)_2$), 4.19 (d, 2 H, *J* = 12.7 Hz, A of AB, $C\underline{H}_2Ar$), 4.24 (br t, 1 H, *J* = 7.4 Hz,

C<u>H</u>CH(CH_3)$_2$), 4.30 (d, 2 H, *J* = 12.7 Hz, B of AB, C<u>H</u>$_2$Ar), 4.78 (s, 1H, N<u>H</u>), 6.32 (s, 1 H, N<u>H</u>), 7.30 (d, 1 H, *J* = 8.2 Hz, N<u>H</u>), 7.35-7.44 (m, 5 H, N<u>H</u> + 4 × <u>H</u>$_{ar}$), 7.48-7.59 (m, 4 H, 4 × <u>H</u>$_{ar}$), 7.98 (s, 1 H, N<u>H</u>) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.7 (CH_3), 19.3 (CH_3), 24.7 (3 × 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 × CH_3), 30.4 (CH), 48.1 (2 × CH_2), 56.7 (C), 57.0 (C), 57.1 (C), 57.5 (C), 59.5 (CH), 80.6 (C), 128.6 (4 × CH), 129.2 (2 × CH), 129.5 (2 × CH), 133.8 (2 × C), 140.4 (2 × 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 $C_{40}H_{59}N_6O_7$ = 735.4440; found 735.4437.

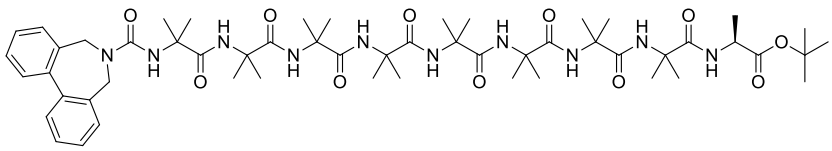
AzeAib$_4$-(L)-PheO*t*Bu (2g)



To a suspension of DSC (40 mg, 0.156 mmol) in CH_2Cl_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_2Cl_2 (1.5 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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 (1.5 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_3CN (0.75 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_2 (50 mL). The organic layer was washed successively with 5% $KHSO_4$ (2 × 15 mL), $NaHCO_3$ (2 × 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_2Cl_2

4:6) provided the titled compound (61 mg, 72%) as a colourless solid. **mp** = 197-199 °C. $[\alpha]_D^{25}$ = -35.2 (c = 1.00, MeOH). **IR** (solid) ν_{max} 3304, 2981, 2932, 1651, 1629, 1527, 1454, 1382, 1361, 1228, 1153 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.32 (s, 9 H, *t*Bu), 1.34 (s, 3 H, C$\underline{H}_3$), 1.44 (s, 3 H, C$\underline{H}_3$), 1.47 (s, 3 H, C$\underline{H}_3$), 1.50 (s, 6 H, 2 × C$\underline{H}_3$), 1.53 (s, 3 H, C$\underline{H}_3$), 1.54 (s, 6 H, 2 × C$\underline{H}_3$), 3.12 (dd, 1 H, *J* = 14.0 and 7.4 Hz, A of ABX, PhC$\underline{H}_2$CH), 3.17 (dd, 1 H, *J* = 14.0 and 7.4 Hz, B of ABX, PhC$\underline{H}_2$CH), 4.21 (d, 2 H, *J* = 12.6 Hz, A of AB, ArC$\underline{H}_2$N), 4.30 (d, 2 H, *J* = 12.6 Hz, B of AB, ArC$\underline{H}_2$N), 4.54 (q, 1 H, *J* = 7.4 Hz, PheCH$_2$C$\underline{H}$), 5.07 (s. 1H, N$\underline{H}$), 6.40 (s, 1 H, N$\underline{H}$), 7.14 (tt, 1 H, *J* = 7.3 and 1.1 Hz, $\underline{H}_{ar}$), 7.20-7.23 (m, 2 H, 2 × $\underline{H}_{ar}$), 7.26-7.29 (m, 2 H, 2 × $\underline{H}_{ar}$), 7.37 (s, 1 H, N$\underline{H}$), 7.37-7.42 (m, 4 H, 4 × $\underline{H}_{ar}$), 7.47-7.52 (m, 2 H, 2 × $\underline{H}_{ar}$), 7.55 (d, 2 H, *J* = 7.4 Hz, 2 × $\underline{H}_{ar}$), 7.61 (d, 1 H, *J* = 7.3 Hz, N$\underline{H}$), 8.08 (s, 1 H, N$\underline{H}$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 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. **MS** (ES^+, MeOH): 783.7 ($[M+H]^+$, 15%), 805.6 ($[M+Na]^+$, 100%). **HRMS** (ES^+, MeOH) calcd for $C_{44}H_{59}N_6O_7$ = 783.4440; found 783.4436.

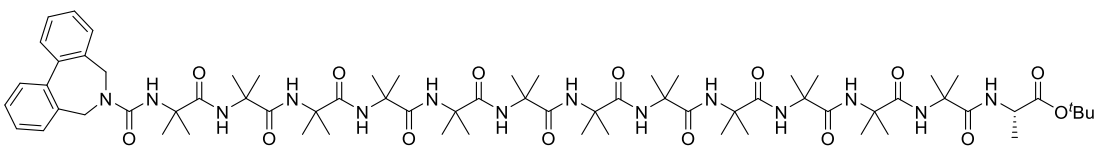
AzeAib$_8$-(L)-AlaO*t*Bu (2h)



To a suspension of DSC (45 mg, 0.18 mmol) in CH_2Cl_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_2Cl_2 (2 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with 5% $KHSO_4$ (2 × 25 mL)

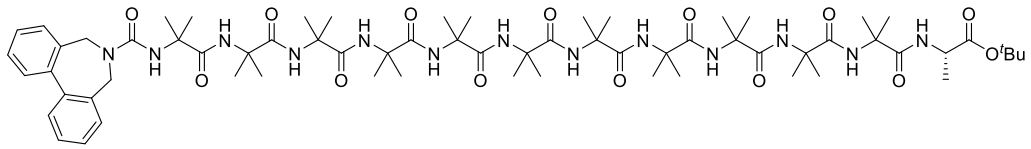
and was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in DMF (2 mL) and this solution was added dropwise to a mixture of **1**·HCl (28 mg, 0.12 mmol) and DIPEA (0.48 mmol, 85 µL) in DMF (1 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_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_2Cl_2 6:4) provided the titled compound (101 mg, 81%) as a colourless solid. **mp** = 208-211 °C. **IR** (solid) ν_{max} 3287, 2983, 2936,2870, 1735, 1650, 1529, 1454, 1383, 1361, 1289, 1227, 1166 cm^{-1}. $[\alpha]_D^{20}$ = -39.6 (c = 1.04, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (s, 3 H, CH_3), 1.38-1.58 (m, 57 H, *t*Bu + 16 × CH_3), 4.15-4.42 (m, 5 H, C<u>H</u>CH_3 + 2 × C<u>H</u>$_2$Ar), 5.49 (s, 1 H, N<u>H</u>), 6.61 (s, 1 H, N<u>H</u>), 7.36-7.42 (m, 4 H, 4 × <u>H</u>$_{Ar}$), 7.45-7.58 (m, 6 H, 4 × <u>H</u>$_{Ar}$ + 2 × N<u>H</u>), 7.65 (s, 1 H, N<u>H</u>), 7.68 (s, 1 H, N<u>H</u>), 7.69 (s, 1 H, N<u>H</u>), 7.76 (s, 1 H, N<u>H</u>), 8.35 (s, 1 H, N<u>H</u>) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.0 (CH_3), 22.6-27.6 (m, 16 × CH_3), 28.1 (3 × CH_3, *t*Bu), 48.1 (2 × CH_2), 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 $C_{54}H_{83}N_{10}O_{11}$ = 1047.6237; found 1047.6239.

Aze-Aib$_{12}$AlaO^{t}Bu (2j)



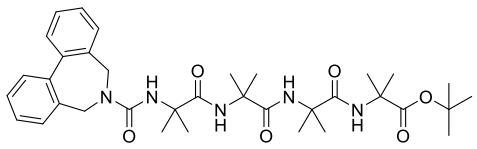
To a suspension of DSC (23 mg, 0.088 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 0 °C a solution of **5j** (74 mg, 0.063 mmol, obtained by hydrogenolysis of **4j** following general procedure A) in CH_2Cl_2 (2 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_2 (100 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 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 CH_2Cl_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_2Cl_2 6:4) gave a mixture of **2i** and **2j**. Separation by HPLC provided an analytically pure sample of **2j**. **mp** = 283-285 °C. **IR** (solid) ν_{max} 3291, 2984, 2931, 1651, 1531, 1455, 1384, 1362 cm^{-1}. $\mathbf{[\alpha]_D^{20}} = -21.6$ (c = 0.5, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (br s, 1 H, NH), 7.82 (br s, 1H, NH), 7.80 (br s, 1H, NH), 7.76 (m, 4 H, 4 × 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 × H_{Ar}), 7.51 (m, 3 H, 3 × H_{Ar}), 7.41 (m, 3 H, 3 × H_{Ar}), 7.40 (br s, 1H, NH), 6.71 (br s, 1 H, NH), 5.63 (br s, 1 H, NH), 4.27 (m, 5 H, 2 × ArCH_2 and CH), 1.56 (m, 9 H, 3 × CH_3), 1.47-1.54 (m, 54 H, 18 × CH_3), 1.45 (s, 3 H, CH_3), 1.43 (s, 12 H, CH_3 + C(CH_3)$_3$), 1.41 (m, 3 H, CH_3-CH), 1.38 (s, 3 H, CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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, *t*Bu), 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 × CH_2), 28.0 (3 × CH_3, *t*Bu), 22.6-27.4 (24 × CH_3), 16.9 (CH_3) ppm. **MS** (ES^+, CH_2Cl_2): 1388.4 (80%, $[(M+H)^+]$), 1411.1 (100%, $[M+Na]^+$).

AzeAib$_{11}$AlaO^{t}Bu (2i)



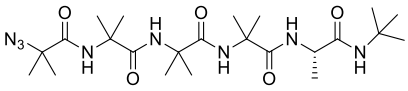
2i was obtained as a side product in the synthesis of **2j**. An analytically pure sample of **2i** was isolated by HPLC. **IR** (solid) ν_{max} 3273, 2984, 2935, 1738, 1650, 1538, 1455, 1383, 1361 cm^{-1}. **[α]$_D^{20}$** = −20.0 (c = 0.5, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (br s, 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 × 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 × H_{Ar}), 7.51 (m, 3 H, 3 × H_{Ar}), 7.41 (m, 3 H, 3 × H_{Ar}), 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 × ArCH_2N + CH), 1.55 (m, 12 H, 4 × CH_3), 1.47-1.53 (m, 45 H, 15 × 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, $CDCl_3$) δ 176.2 (CO), 176.1 (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 × C), 133.8 (2 × C), 129.3 (2 × CH), 128.9 (2 × CH), 128.5 (2 × CH), 128.4 (2 ×CH), 80.4 (C, *t*Bu), 57.3 (C), 56.8 (C), 56.7 (C), 56.7 (C), 56.6 (C), 56.5 (C), 56.5 (4 × C), 56.4 (C), 49.5 (CH), 48.1 (br, 2 × CH_2), 28.0 (3 × CH_3, *t*Bu), 23.0-27.4 (m, 22 × CH_3), 16.9 (CH_3) ppm. **MS** (ES^+, CH_2Cl_2): 1303.1 (95%, [(M+H]$^+$), 1325.1 (100%, [M+Na]$^+$).

AzeAib$_4$OtBu (2x)



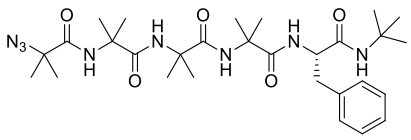
To a suspension of DSC (107 mg, 0.42 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise at 0 °C a solution of **5x** (120 mg, 0.29 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_2 (75 mL). The organic layer was washed with 5% $KHSO_4$ (2 × 25 mL) and was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH_3CN (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 CH_3CN (1.25 mL) cooled at 0°C. The reaction mixture was stirred overnight at RT and was diluted with CH_2Cl_2 (50 mL). The organic layer was washed successively with 5% $KHSO_4$ (2 × 15 mL), $NaHCO_3$ (2 × 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_2Cl_2 1:1) provided the tilted compound (146 mg, 79%) as a colourless solid. **mp** = 192-195 °C. **IR** (solid) ν_{max} 3304, 2981, 2934, 1730, 1629, 1520, 1454, 1383, 1362, 1229, 1145 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.39 (s, 6 H, 2 × C$\underline{H}_3$), 1.42 (s, 9 H, *t*Bu), 1.47 (s, 6 H, 2 × C$\underline{H}_3$), 1.51 (s, 6 H, 2 × C$\underline{H}_3$), 1.56 (s, 6 H, 2 × C$\underline{H}_3$), 4.24 (s, 4 H, 2 × ArC$\underline{H}_2$N), 4.87 (s, 1H, N$\underline{H}$), 6.35 (s, 1 H, N$\underline{H}$), 7.30 (s, 1 H, N$\underline{H}$), 7.37-7.42 (m, 4 H, 4 × $\underline{H}_{ar}$), 7.46-7.52 (m, 2 H, 2 × $\underline{H}_{ar}$), 7.55 (d, 2 H, *J* = 7.3 Hz, 2 × $\underline{H}_{ar}$), 7.77 (s, 1 H, N$\underline{H}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.9 (2 × CH_3), 25.6 (2 × CH_3), 25.7 (2 × CH_3), 25.9 (2 × CH_3), 28.0 (3 × CH_3), 48.1 (2 × CH_2), 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 $C_{35}H_{50}N_5O_6$ = 636.3756; found 636.3750.

N_3Aib$_4$-(L)-AlaNH*t*Bu (4a)



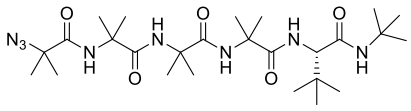
To a mixture of EDC·HCl (900 mg, 4.70 mmol), HOBt·H_2O (719 mg, 4.70 mmol) and **3** (1.39 g, 3.62 mmol) in CH_2Cl_2 (25 mL) was added dropwise at 0 °C DIPEA (1.26 mL, 7.24 mmol). The reaction mixture was stirred at RT for 30 min and a solution of **NH_2-(L)-AlaNH*t*Bu** (627 mg, 4.35 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at RT for 4 days and was diluted with CH_2Cl_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_2Cl_2 3:97→5:95) provided the tilted compound (1.74 g, 94%) as a colourless solid. **mp** = 214 °C. **IR** (solid) ν_{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, $CDCl_3$) δ 1.37 (s, 12 H, *t*Bu + C$\underline{H}_3$), 1.41 (d, 3 H, *J* = 7.3 Hz, C$\underline{H}_3$CH), 1.45 (s, 6 H, 2 × C$\underline{H}_3$), 1.47 (s, 3 H, C$\underline{H}_3$), 1.48 (s, 3 H, C$\underline{H}_3$), 1.53 (s, 3 H, C$\underline{H}_3$), 1.55 (s, 3 H, C$\underline{H}_3$), 1.57 (s, 3 H, C$\underline{H}_3$), 4.33 (quin, 1 H, *J* = 7.5 Hz, CH_3C$\underline{H}$), 6.18 (s, 1H, N$\underline{H}$), 6.77 (s, 1 H, N$\underline{H}$), 6.91 (s, 1 H, N$\underline{H}$), 7.27 (s, 1 H, N$\underline{H}$), 7.45 (d, 1 H, *J* = 7.9 Hz, N$\underline{H}$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 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 $C_{23}H_{42}N_8O_5Na$ = 533.3170; found 533.3183.

N_3Aib$_4$-(L)-PheNH*t*Bu (4b)



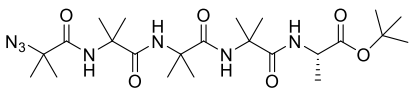
To a mixture of HOBt·H_2O (204 mg, 1.33 mmol) and **3** (397 mg, 1.03 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C EDC (200 µL, 1.13 mmol). The reaction mixture was stirred at RT for 30 min and a solution of **NH_2-(L)-PheNH*t*Bu** (273 mg, 1.24 mmol) in CH_2Cl_2 (5 mL) and TEA (287 µL, 2.06 mmol) were successively added dropwise. The reaction mixture was stirred at RT for 2 days and was diluted with CH_2Cl_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_2Cl_2 4:6) followed by crystallisation from CH_3CN provided the tilted compound (323 mg, 53%) as a colourless solid. **mp** = 212 °C. **IR** (solid) ν_{max} 3309, 2979, 2939, 2105, 1653, 1526, 1454, 1383, 1362, 1282, 1222, 1167 cm^{-1}. $[\alpha]_D^{20}$ = +22.3° (c = 0.52, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.11 (s, 3 H, C$\underline{H}_3$), 1.34 (s, 3 H, C$\underline{H}_3$), 1.40 (s, 9 H, *t*Bu), 1.455 (s, 3 H, C$\underline{H}_3$), 1.46 (s, 3 H, C$\underline{H}_3$), 1.47 (s, 6 H, 2 × C$\underline{H}_3$), 1.52 (s, 3 H, C$\underline{H}_3$), 1.53 (s, 3 H, C$\underline{H}_3$), 2.88 (dd, 1 H, *J* = 12.0 and 14.5 Hz, PheC$\underline{H}_2$CH), 3.61 (dd, 1 H, *J* = 3.2 and 14.5 Hz, PheC$\underline{H}_2$CH), 4.55 (ddd, 1 H, *J* = 11.9, 8.7 and 3.2 Hz, PheCH_2C$\underline{H}$), 6.23 (s. 1H, N$\underline{H}$), 6.91 (s, 1 H, N$\underline{H}$), 7.00 (s, 1 H, N$\underline{H}$), 7.10 (t, 1 H, *J* = 7.3 Hz, $\underline{H}_{ar}$), 7.16 (t, 2 H, *J* = 7.3 Hz, 2 × $\underline{H}_{ar}$), 7.25-7.28 (m, 3 H, N$\underline{H}$ + 2 × $\underline{H}_{ar}$), 7.32 (d, 1 H, *J* = 8.7 Hz, N$\underline{H}$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 23.19 (CH_3), 23.24 (CH_3), 23.4 (CH_3), 24.1 (CH_3), 24.4 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 27.4 (CH_3), 28.7 (3 × CH_3), 37.2 (CH_2), 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 $C_{29}H_{47}N_8O_5$ = 587.3664; found 587.3654.

N_3-Aib$_4$-(L)-*t*LeuNH*t*Bu (4c)



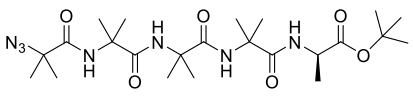
To a mixture of HOBt·H_2O (26 mg, 0.170 mmol), EDC·HCl (32 mg, 0.167 mmol) and **3** (50 mg, 0.130 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 0 °C DIPEA (67 µL, 0.387 mmol). The reaction mixture was stirred at RT for 30 min and **NH_2-(L)-*t*Leu-NH*t*Bu** (29 mg, 0.156 mmol) was added portionwise. The reaction mixture was stirred at RT for 2 days and was diluted with CH_2Cl_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_2Cl_2 6:4) provided the tilted compound (56 mg, 78 %) as a colourless solid. **mp** = 220-222 °C. **IR** (solid) ν_{max} 3374, 3335, 2969, 2937, 2873, 2112, 1683, 1642, 1525, 1454, 1383, 1361, 1219, 1172 cm^{-1}. **$[\alpha]_D^{20}$** = -4.1° (c = 0.49, MeOH). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (s, 9 H, 3 × C$\underline{H}_3$, *t*Bu), 1.36 (s, 9 H, 3 × C$\underline{H}_3$, *t*Bu), 1.37 (s, 3 H, C$\underline{H}_3$), 1.46 (s, 3 H, C$\underline{H}_3$), 1.47 (s, 3 H, C$\underline{H}_3$), 1.48 (s, 3H, C$\underline{H}_3$), 1.49 (s, 3 H, C$\underline{H}_3$), 1.53 (s, 6 H, 2 × C$\underline{H}_3$), 1.55 (s, 3 H, C$\underline{H}_3$), 4.03 (d, 1 H, *J* = 8.1 Hz, C$\underline{H}$C$(CH_3)_3$), 6.12 (s, 1 H, N$\underline{H}$), 6.51 (s, 1 H, N$\underline{H}$), 6.93 (s, 3 H, C$\underline{H}_3$), 7.11 (d, 1 H, *J* = 8.1 Hz, N$\underline{H}$), 7.35 (s, 1 H, N$\underline{H}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 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 × CH_3, *t*Bu), 27.6 (CH_3), 28.8 (3 × CH_3, *t*Bu), 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 $C_{26}H_{49}N_8O_5$ = 553.3820; found 553.3817.

N_3Aib$_4$-(L)-AlaO*t*Bu (4d)



To a mixture of EDC·HCl (259 mg, 1.35 mmol), HOBt·H_2O (206 mg, 1.35 mmol) and **3** (400 mg, 1.04 mmol) in CH_2Cl_2 (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·NH$_2$-(L)-AlaO*t*Bu** (227 mg, 1.25 mmol) was added portion wise. The reaction mixture was stirred at RT for 3 days and was diluted with CH_2Cl_2 (75 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_2Cl_2 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}. **$[\alpha]_D^{20}$** = -51.0 (c = 1.02, MeOH). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 3 H, C<u>H</u>$_3$), 1.39 (d, 3 H, *J* = 7.2 Hz, C<u>H</u>$_3$), 1.42 (s, 9 H, 3 × C<u>H</u>$_3$), 1.45 (s, 3 H, C<u>H</u>$_3$), 1.47 (s, 3 H, C<u>H</u>$_3$), 1.48 (s, 3 H, C<u>H</u>$_3$), 1.50 (s, 3 H, C<u>H</u>$_3$), 1.523 (s, 3 H, C<u>H</u>$_3$), 1.526 (s, 3 H, C<u>H</u>$_3$), 1.53 (s, 3 H, C<u>H</u>$_3$), 4.33 (quin, 1 H, *J* = 7.2 Hz, CH_3C<u>H</u>), 6.22 (s, 1 H, N<u>H</u>), 6.91 (s, 1 H, N<u>H</u>), 7.16 (s, 1 H, N<u>H</u>), 7.24 (d, 1 H, *J* = 7.0 Hz, N<u>H</u>) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.4 (CH_3), 24.2 (2 × CH_3), 24.3 (CH_3), 24.4 (CH_3), 24.5 (CH_3), 25.8 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 28.1 (3 × CH_3), 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 $C_{23}H_{41}N_7O_6Na$ = 534.3011; found 534.3007.

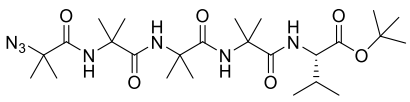
N$_3$Aib$_4$-(D)-AlaOtBu (4e)



To a mixture of EDC•HCl (193 mg, 1.01 mmol), HOBt•H_2O (155 mg, 1.01 mmol) and **3** (300 mg, 0.78 mmol) in CH_2Cl_2 (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•NH$_2$-(D)-AlaO*t*Bu** (170 mg, 0.94

mmol) was added portion wise. The reaction mixture was stirred at RT for 2 days and was diluted with CH_2Cl_2 (100 mL). The organic layer was washed successively with 5% $KHSO_4$ (2 × 30 mL), $NaHCO_3$ (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_2Cl_2 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**. $[\alpha]_D^{20}$ = +51.4 (c = 1.02, MeOH).

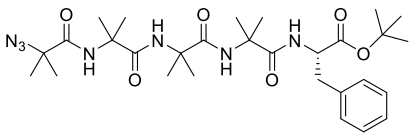
N_3Aib$_4$-(L)-ValO*t*Bu (4f)



To a mixture of HOBt·H_2O (52 mg, 0.33 mmol), EDC·HCl (64 mg, 0.33 mmol) and **3** (100 mg, 0.26 mmol) in CH_2Cl_2 (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·NH_2-(L)-ValO*t*Bu** (66 mg, 0.31 mmol) was added portion wise. The reaction mixture was stirred at RT for 2 days and was diluted with CH_2Cl_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_2Cl_2 6:4) provided the titled compound (134 mg, 95 %) as a colourless solid. **mp** = 160-162 °C. **IR** (solid) ν_{max} 3325, 2978, 2936, 2874, 2111, 1715, 1650, 1518, 1457, 1382, 1364, 1286, 1259, 1223, 1159 cm^{-1}. $[\alpha]_D^{20}$ = -32.8 (c = 0.5, MeOH). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.96 (d, 6 H, *J* = 6.8 Hz, CH(C$\underline{H}_3$)$_2$), 1.41 (s, 3 H, C$\underline{H}_3$), 1.44 (s, 9 H, *t*Bu), 1.46 (s, 3 H, C$\underline{H}_3$), 1.49 (s, 3 H, C$\underline{H}_3$), 1.502 (s, C$\underline{H}_3$), 1.504 (s, 3 H, C$\underline{H}_3$), 1.53 (s, 9 H, 3 × C$\underline{H}_3$), 2.18 (oct, 1 H, *J* = 6.4 Hz, C$\underline{H}$(CH$_3$)$_2$), 4.27 (dd, 1 H, *J* = 6.0 and 8.2 Hz, C$\underline{H}$CH(CH$_3$)$_2$), 6.16 (s. 1H, N$\underline{H}$), 6.87 (s, 1 H, N$\underline{H}$), 7.09 (d, 1 H, *J* = 8.2 Hz, N$\underline{H}$), 7.21 (s, 1 H, N$\underline{H}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.3 (CH$_3$, *i*Pr), 19.2 (CH$_3$, *i*Pr), 24.4 (CH$_3$),

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, *t*Bu), 30.8 (CH, *i*Pr), 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 $C_{25}H_{46}N_7O_6$ = 540.3504; found 540.3496.

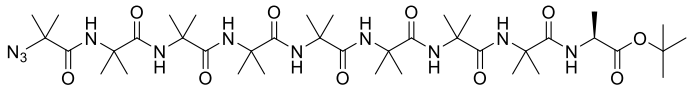
N_3Aib$_4$-(L)-PheO*t*Bu (4g)



To a mixture of HOBt·H_2O (63 mg, 0.41 mmol) and **3** (120 mg, 0.31 mmol) in CH_2Cl_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)-PheO*t*Bu** (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_2Cl_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_2Cl_2 4:6) provided the titled compound (156 mg, 85%) as a colourless solid. **mp** = 68-72 °C. **IR** (solid) ν_{max} 3320, 2982, 2934, 2111, 1722, 1651, 1516, 1455, 1382, 1364, 1257, 1223, 1152 cm^{-1}. **$[\alpha]_D^{20}$** = -4.0° (c = 0.50, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.34 (s, 9 H, *t*Bu), 1.41 (s, 3 H, C<u>H</u>$_3$), 1.42 (s, 3 H, C<u>H</u>$_3$), 1.46 (s, 3 H, C<u>H</u>$_3$), 1.48 (s, 3 H, C<u>H</u>$_3$), 1.49 (s, 6 H, 2 × C<u>H</u>$_3$), 1.52 (s, 3 H, C<u>H</u>$_3$), 1.53 (s, 3 H, C<u>H</u>$_3$), 3.09 (dd, 1 H, *J* = 14.2 and 7.2 Hz, A of ABX, PheC<u>H</u>$_2$CH), 3.11 (dd, 1 H, *J* = 14.2 and 7.2 Hz, B of ABX, PheC<u>H</u>$_2$CH), 4.59 (q, 1 H, *J* = 7.2 Hz, PheCH$_2$C<u>H</u>), 6.22 (s. 1H, N<u>H</u>), 6.91 (s, 1 H, N<u>H</u>), 7.14 (s, 1 H, N<u>H</u>), 7.14-7.18 (m, 1 H, <u>H$_{ar}$</u>), 7.20-7.28 (m, 5 H, N<u>H</u> + 4 × <u>H$_{ar}$</u>) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 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),

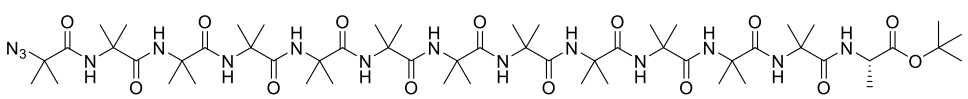
126.5 (CH), 128.2 (2 × CH), 129.7 (2 × CH), 137.5 (C), 171.0 (CO), 172.8 (CO), 172.9 (2 × CO), 174.7 (CO) ppm. **MS** (ES^+, MeOH): 588 ($[M+H]^+$, 80%), 610 ($[M+Na]^+$, 100%). **HRMS** (ES^+, MeOH) calcd for $C_{29}H_{46}N_7O_6$ = 588.3504; found 588.3498.

N_3Aib$_8$-(L)-AlaO*t*Bu (4h)

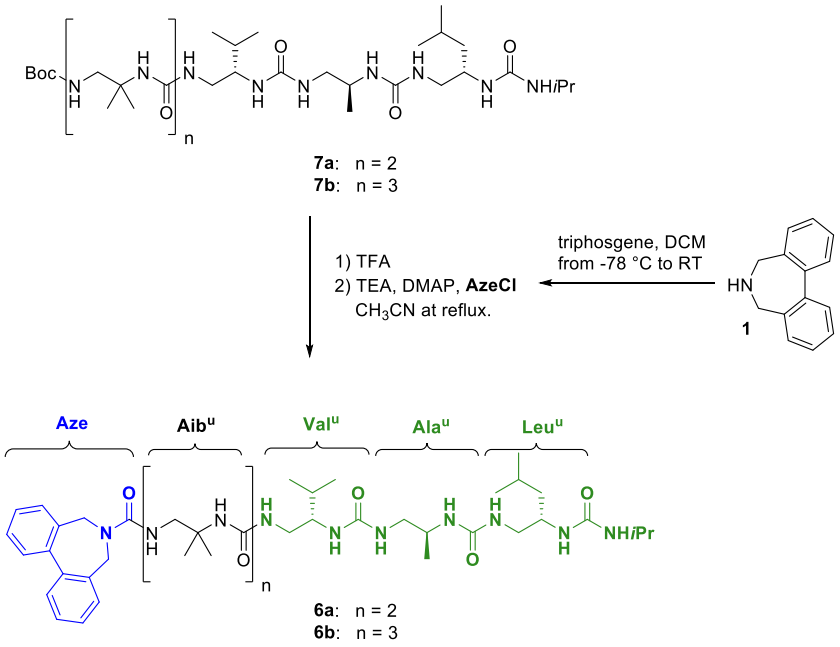


5d (414 mg, 0.85 mmol) and the azlactone (312 mg, 0.85 mmol), synthesized respectively from **4d** and **3** following general procedure A and B, were dissolved in dry acetonitrile (7 mL) and the mixture was heated at reflux for 5 days. The solvent was then evaporated under reduced pressure and purification of the crude by column chromatography (EtOAc/ CH_2Cl_2 7:3) provided the title compound (455 mg, 63%) as a white solid. **mp** = 229-230 °C. **IR** (solid) ν_{max} 3303, 2983, 2938, 2873, 2109, 1736, 1657, 1644, 1526, 1455, 1383, 1363, 1276, 1227, 1168, 1153 cm^{-1}. **$[\alpha]_D^{20}$** = -41.4 (c = 0.55, MeOH). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.40 (s, 3 H, CH_3), 1.41-1.52 (m, 45 H, 15 × CH_3), 1.53-1.59 (m, 12 H, 4 × CH_3), 4.35 (quin, 1 H, *J* = 7.1 Hz, C<u>H</u>CH_3), 6.21 (s, 1 H, N<u>H</u>), 6.98 (s, 1 H, N<u>H</u>), 7.43 (s, 1 H, N<u>H</u>), 7.49-7.54 (m, 2 H, 2 × N<u>H</u>), 7.56 (s, 1 H, N<u>H</u>), 7.57 (s, 1 H, N<u>H</u>), 7.61 (s, 1 H, N<u>H</u>) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) 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 × CH_3, *t*Bu), 23.0-27.3 (m, 16 × CH_3), 17.1 (CH_3) ppm. **MS** (ES^+, MeOH): 852.7 ($[M+H]^+$, 90%), 874.7 ($[M+Na]^+$, 100%). **HRMS** (ES^+, MeOH) calcd for $C_{39}H_{69}N_{11}O_{10}Na$ = 874.5127; found 874.5084.

N_3Aib$_{12}$-(L)-AlaOtBu (4j)

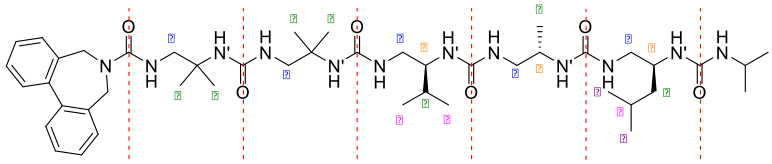


5h (120 mg, 0.145 mmol) and the azlactone (58 mg, 0.16 mmol), synthesized respectively from **4h** and **3** following general procedure A and B, were dissolved in dry acetonitrile (3 mL) and the mixture was heated at reflux for 4 days under N_2 atmosphere. The solvent was then evaporated under reduced 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) ν_{max} 3287, 2984, 2936, 2872, 2113, 1660, 1530, 1455, 1383, 1362, 1294, 1227, 1168 cm^{-1}. $\mathbf{[\alpha]_D^{20}}$ = -23.7 (c = 0.54, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.41 (s, 3 H, C$\underline{H}_3$), 1.42-1.53 (m, 69 H, *t*Bu + 20 × C$\underline{H}_3$), 1.53-1.60 (m, 12 H, 4 × C$\underline{H}_3$), 4.34 (quin, 1 H, *J* = 7.1 Hz, $CH_3C\underline{H}$), 6.33 (s, 1 H, N$\underline{H}$), 7.07 (s, 1 H, N$\underline{H}$), 7.47 (s, 1 H, N$\underline{H}$), 7.54-7.57 (m, 2 H, 2 × N$\underline{H}$), 7.646 (s, 1 H, N$\underline{H}$), 7.654 (s, 1 H, N$\underline{H}$), 7.661 (s, 1 H, N$\underline{H}$), 7.67 (s, 1 H, N$\underline{H}$), 7.71 (s, 1 H, N$\underline{H}$), 7.73 (s, 2 H, 2 × N$\underline{H}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.1 (CH_3), 22.9-27.0 (24 × CH_3), 28.1 (3 × CH_3, *t*Bu), 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 $C_{55}H_{97}N_{15}O_{14}Na$ = 1214.7237; found 1214.7215.



Scheme 1: Synthesis of **6a** and **6b**.

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



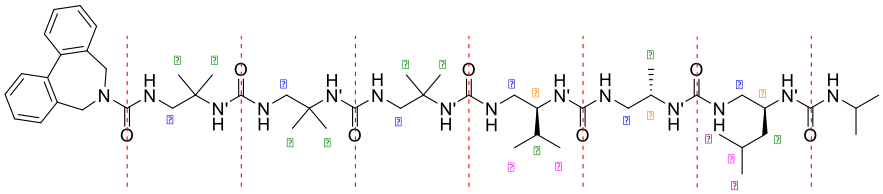
Boc-protected oligourea **7a** (40 mg, 0.059 mmol) was dissolved in TFA (400 µL) and stirred for 45 min. The reaction mixture was then concentrated under reduced pressure and the resulting residue was co-evaporated 3 times with cyclohexane. The crude mixture was dissolved in CH_2Cl_2 and treated with 1 M K_2CO_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** (20 mg, 0.077 mmol, synthesized from **1** following general procedure C) in anhydrous acetonitrile (150 µL). Et_3N (11 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 $MgSO_4$, filtered and concentrated *in-vacuo*. Purification by flash column chromatography (CH_2Cl_2-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, CD_3OH) δ 7.54 (2H, dd, J = 0.9 and 7.6, 2 x CH_{ar}), 7.48 (2H, dt, J = 1.5 and 7.3, 2 x CH_{ar}), 7.43 (2H, dd, J = 1.1 and 7.4, 2 x CH_{ar}), 7.38 (2H, dt, J = 1.3 and 7.3, 2 x CH_{ar}), 7.30 (1H, t, J = 5.2, NH_{Aib2}), 6.44 (1H, s, N'$H_{Aib1\ or\ Aib2}$), 6.40 (1H, s, N'$H_{Aib1\ or\ Aib2}$), 6.38 (1H, dd, J = 2.8 and 9.9, NH_{Ala}), 6.25-6.19 (2H, m, NH_{Val} and NH_{Aib1}), 6.17 (1H, d, J = 10.7, N'H_{Val}), 5.92 (1H, dd, J = 5.2 and 7.2, NH_{Leu}), 5.82 (1H, d, J = 10.0, N'H_{Ala}), 5.67 (1H, d, J = 7.8, NH_{iPr}), 5.47 (1H, d, J = 9.6, N'H_{Leu}), 4.24 (2H, d, J = 13.0, 2 x CH_AH$_B$, A part of AB pattern), 4.17 (2H, d, J = 13.0, 2 x CH_AH$_B$, B part of AB pattern), 4.07-3.96 (1H, m, NCH_{Leu}), 3.96-3.86 (1H, m, NCH_{Ala}), 3.77 (1H, hept, J = 7.4, NCH_{iPr}), 3.74-3.68 (1H, m, NCH_{Val}), 3.68-3.63 (1H, m, NCH_AH$_B$*Aib1*), 3.60 (1H, ddd, J = 2.7, 10.6 and 16.5, NCH_AH$_B$*Ala*), 3.52 (1H, ddd, J = 3.6, 9.7 and 13.7, NCH_AH$_B$*Val*), 3.48-3.35 (3H, m, NCH_AH$_B$*Leu* and NCH_{2Aib2}), 3.26 (1H, dd, J = 9.9 and 13.2, NCH$_A$$H_{BAib1}$), 2.52-2.26 (3H, m, NCH$_A$$H_{BVal}$, NCH$_A$$H_{BLeu}$ and NCH$_A$$H_{BAla}$), 1.66 (1H, non, J = 7.0, CH_{Leu}), 1.52 (1H, oct, J = 6.8, CH_{Val}), 1.34 (3H, s, C$H_{3Aib1\ or\ Aib2}$), 1.31 (3H, s, C$H_{3Aib1\ or\ Aib2}$), 1.27 (6H, s, C$H_{3Aib1\ or\ Aib2}$), 1.19 (2H, t, J = 7.3, CH_{2Leu}), 1.12 (3H, d, J = 6.6, CH_{3iPr}), 1.11 (3H, d, J = 6.6, CH_{3iPr}), 1.03 (3H, s, C$H_{3Aib1\ or\ Aib2}$), 1.01 (3H, d, J = 6.9, CH_{3Ala}), 0.91 (3H, d, J = 6.8, CH_{3Leu}), 0.87 (3H, d, J = 6.7, CH_{3Leu}), 0.84 (3H, d, J = 6.9, CH_{3Val}), 0.80 (3H, d, J = 6.9, CH_{3Val}) ppm. **^{13}C NMR** (125 MHz, CD_3OH) δ 162.8 (*C*=O), 161.4 (*C*=O), 160.8 (*C*=O), 160.5 (2 x *C*=O), 159.6 (*C*=O), 141.8 (2 x =C_{Ar}), 135.4 (2 x =C_{Ar}), 130.5 (2 x =CH_{Ar}), 129.7 (2 x =CH_{Ar}), 129.3 (2 x =CH_{Ar}), 128.9 (2 x =CH_{Ar}), 55.4 (NC$_\beta$$H_{Val}$), 54.2 ($C_{Aib1\ or\ Aib2}$), 53.7 ($C_{Aib1\ or\ Aib2}$), 52.5 (NC$_\alpha$$H_{2Aib2}$), 46.7 (2 x NC$H_2$Ar), 48.6 (NC$_\alpha$$H_{2Ala}$), 48.5 (NC$_\beta$$H_{Leu}$), 47.4 (NC$_\alpha$$H_{2Aib1}$ and NC$_\alpha$$H_{2Leu}$), 47.1 (NC$_\beta$$H_{Ala}$), 43.8 (NC$_\alpha$$H_{2Val}$), 43.1 (NC$H_{iPr}$), 42.9 (NC$_\gamma$$H_{2Leu}$), 31.7 (C$_\gamma$$H_{Val}$), 26.8 (C$_\gamma$$H_{3Aib1\ or\ Aib2}$), 26.7 (C$_\gamma$$H_{3Aib1\ or\ Aib2}$), 26.3 (C$_\gamma$$H_{3Aib1\ or\ Aib2}$), 26.2 (C$_\delta$$H_{Leu}$), 25.5 (C$_\gamma$$H_{3Aib1\ or\ Aib2}$), 23.5 (C$H_{3iPr}$), 23.5 (C$H_{3iPr}$), 23.5 (C$_\epsilon$$H_{3Leu}$), 22.5 (C$_\epsilon$$H_{3Leu}$), 19.7 (C$_\delta$$H_{3Val}$),

18.8 (C_sH_{3Ala}), 18.3 (C_sH_{3Val}) ppm. **IR** (film) ν 3343 (NH broad), 2965, 2930, 2868 (C-H), 1632 (C=O urea), 1220, 772 cm^{-1}. $[\alpha]_D^{20}$ = + 8.2 (c = 0.50, TFE). **HRMS (ESI$^+$)**: *m/z* calcd for $C_{45}H_{75}O_6N_{12}$ $[M+H]^+$ 879.5927, found 879.5928.

Residue	NH	N'H	α	β	γ	δ	ε	CH_2	CH	Δδ(Hα)
Aze								4.24 / 4.17		
Aib_2	7.30	6.44	3.45 / 3.40		/					0.05
Aib_1	6.19	or 6.40	3.68 / 3.28		/					0.40
Val	6.24	6.17	3.53 / 2.41	3.71	1.52	0.80 / 0.84				1.12
Ala	6.38	5.82	3.61 / 2.37	3.93	1.01					1.24
Leu	5.92	5.47	3.44 / 2.43	4.02	1.20	1.66	0.91 / 0.87			1.01
iPr	5.67							1.12 / 1.11	3.77	

Aze-Aib^u-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_2Cl_2 and treated with 1 M K_2CO_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_3N (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

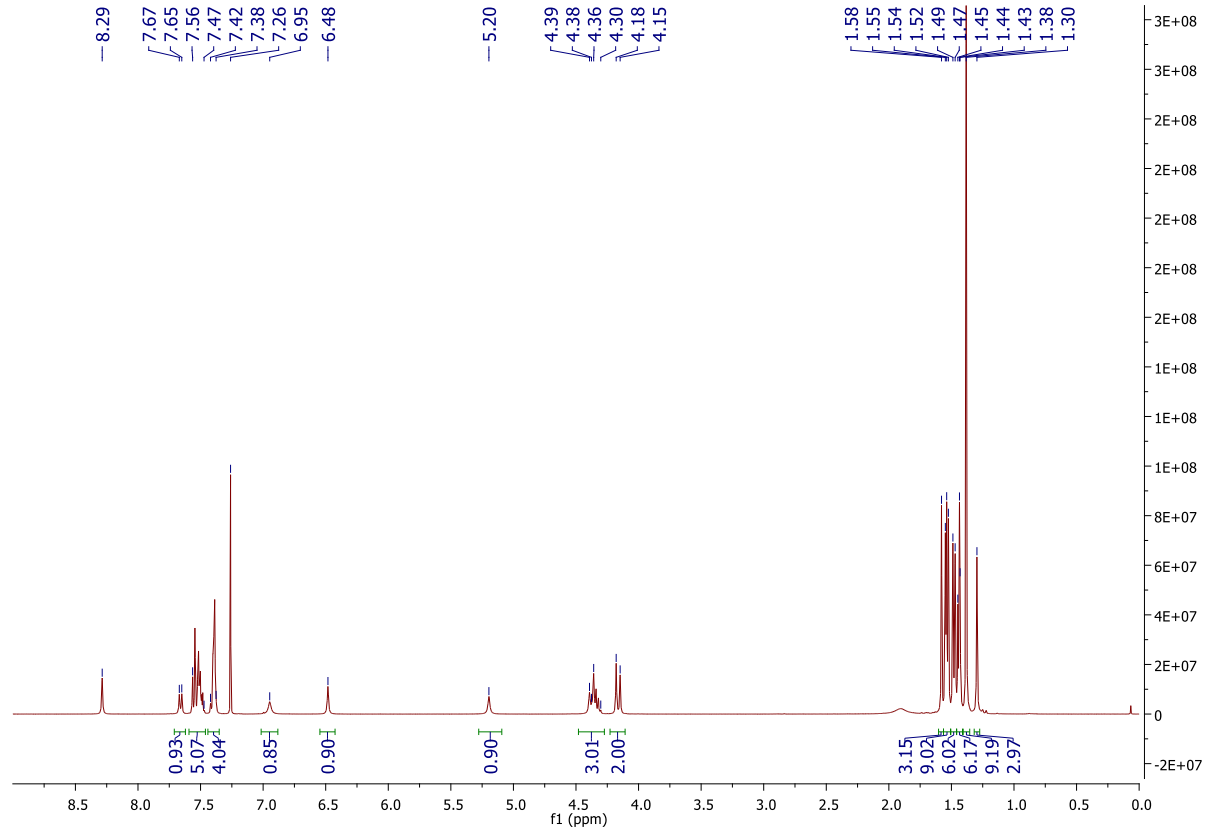
$MgSO_4$, filtered and concentrated *in-vacuo*. Purification by flash column chromatography (CH_2Cl_2-MeOH (v/v), 90:10) yielded the title compound as a white solid (49 mg, 0.049 mmol, 69.5%). **mp** = 192-194 ^oC; **^{1}H NMR** (500 MHz, CD_3OH) δ 7.55-7.51 (2H, m, 2 x CH_{ar}), 7.50-7.45 (2H, m, 2 x CH_{ar}), 7.44 -7.41 (2H, m, 2 x CH_{ar}), 7.40-7.34 (2H, m, 2 x CH_{ar}), 7.25 (1H, t, J = 5.1, NH_{Aib3}), 6.43 (1H, s, N'$H_{Aib1\ or\ Aib2\ or\ Aib3}$), 6.38 (1H, dd, J = 2.7 and 9.9, NH_{Ala}), 6.25 (1H, dd, J = 3.0 and 9.5, NH_{Val}), 6.20-6.17 (2H, m, NH_{Aib1} and N'H_{Val}), 6.12 (2H, brs, N'$H_{Aib1\ and/or\ Aib2\ and/or\ Aib3}$), 6.03 (1H, t, J = 6.1, NH_{Aib2}), 5.93 (1H, t, J = 5.4, NH_{Leu}), 5.83 (1H, d, J = 10.0, N'H_{Ala}), 5.69 (1H, d, J = 7.8, NH_{iPr}), 5.49 (1H, d, J = 9.5, N'H_{Leu}), 4.21 (4H, AB system), 4.07-3.97 (1H, m, NCH_{Leu}), 3.97-3.86 (1H, m, NCH_{Ala}), 3.79 (1H, hept, J = 6.7, NCH_{iPr}), 3.75-3.66 (1H, m, NCH_{Val}), 3.66-3.48 (3H, m, NCH_AH$_{BAib1}$, NCH_AH$_{BAla}$ and NCH_AH$_{BVal}$), 3.47-3.33 (4H, m, NCH_AH$_{BLeu}$, NCH_{2Aib3} and NCH_AH$_{BAib2}$), 3.29 (1H, dd, J = 7.5 and 13.3, NCH$_A$$H_{BAib2}$), 3.21 (1H, dd, J = 9.8 and 13.1, NCH$_A$$H_{BAib1}$), 2.50-2.39 (2H, m, NCH$_A$$H_{BVal}$ and NCH$_A$$H_{BLeu}$), 2.39-2.28 (1H, m, NCH$_A$$H_{BAla}$), 1.67 (1H, non, J = 6.9, CH_{Leu}), 1.59 (1H, oct, J = 6.8, CH_{Val}), 1.28 (9H, s, C$H_{3Aib1\ and/or\ Aib2\ and/or\ Aib3}$), 1.27 (3H, s, C$H_{3Aib1\ or\ Aib2\ or\ Aib3}$), 1.20 (2H, t, J = 7.5, CH_{2Leu}), 1.17 (3H, s, C$H_{3Aib1\ or\ Aib2\ or\ Aib3}$), 1.12 (6H, d, J = 6.6, CH_{3iPr}), 1.04 (3H, s, C$H_{3Aib1\ or\ Aib2\ or\ Aib3}$), 1.03 (3H, d, J = 7.0, CH_{3Ala}), 0.92 (3H, d, J = 6.7, CH_{3Leu}), 0.91 (3H, d, J = 6.9, CH_{3Leu}), 0.88 (3H, d, J = 6.7, CH_{3Val}), 0.86 (3H, d, J = 7.0, CH_{3Val}) ppm. **^{13}C NMR** (125 MHz, CD_3OH) δ 162.7 (*C*=O), 161.3 (*C*=O), 160.7 (2 x *C*=O), 160.5 (2 x *C*=O), 159.6 (*C*=O), 141.7 (2 x =C_{Ar}), 135.4 (2 x =C_{Ar}), 130.5 (2 x =CH_{Ar}), 129.7 (2 x =CH_{Ar}), 129.3 (2 x =CH_{Ar}), 129.0 (2 x =CH_{Ar}), 55.5 (NC$_\beta$H$_{Val}$), 54.2 ($C_{Aib1\ or\ Aib2\ or\ Aib3}$), 53.7 (2 x $C_{Aib1\ or\ Aib2\ or\ Aib3}$), 52.4 (NC$_\alpha$H$_{2Aib3}$), 49.0 (NC$_\alpha$H$_{2Aib2}$), 48.6 (2 x NCH$_2$Ar), 48.5 (NC$_\alpha$H$_{2Ala}$), 48.4 (NC$_\beta$H$_{Leu}$), 47.4 (NC$_\alpha$H$_{2Aib1}$ and NC$_\alpha$H$_{2Leu}$), 47.1 (NC$_\beta$H$_{Ala}$), 43.9 (NC$_\alpha$H$_{2Val}$), 43.1 (NCH$_{iPr}$), 42.9 (NC$_\gamma$H$_{2Leu}$), 31.7 (C$_\gamma$H$_{Val}$), 26.9 (C$_\gamma$H$_{3Aib1}$), 26.5 (C$_\gamma$H$_{3Aib2}$), 26.2 (C$_\delta$H$_{Leu}$), 26.2 (C$_\gamma$H$_{3Aib1\ or\ 2}$), 26.2 (C$_\gamma$H$_{3Aib1\ or\ 2}$), 26.0 (C$_\gamma$H$_{3Aib3}$), 25.6 (C$_\gamma$H$_{3Aib3}$), 23.6 (2 x *C*H$_{3iPr}$), 23.5 (C$_\epsilon$H$_{3Leu}$), 22.5 (C$_\epsilon$H$_{3Leu}$), 20.0 (C$_\delta$H$_{3Val}$), 18.9 (C$_\delta$H$_{3Ala}$), 18.4 (C$_\delta$H$_{3Val}$) 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 $C_{50}H_{85}O_7N_{14}$ $[M+H]^+$ 993.6720, found 993.6714.

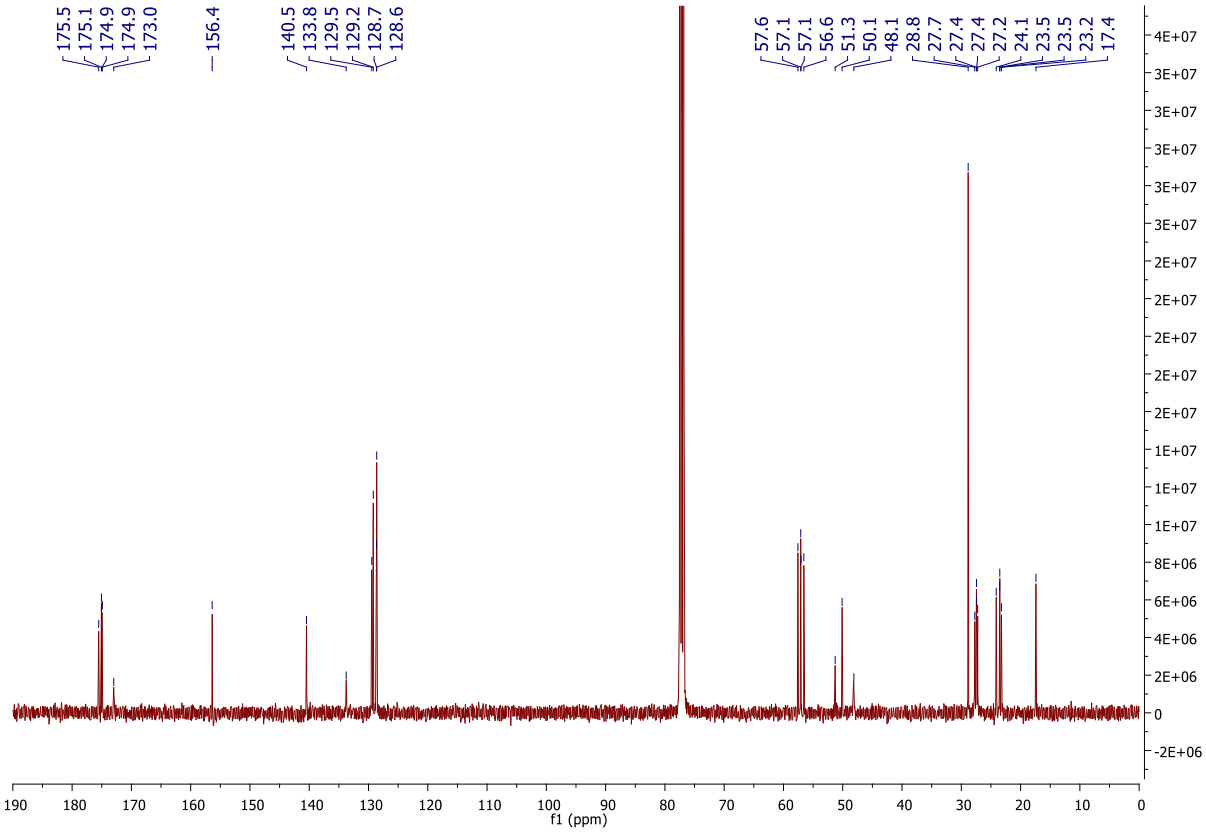
Residue	NH	N'H	α	β	γ	δ	ε	CH_2	CH	Δδ
Aze								4.21		
Aib_3	7.25	/	3.41 / 3.36		/					0.05
Aib_2	6.03	/	3.42 / 3.29		/					0.13
Aib_1	6.18	/	3.63 / 3.21		/					0.42
Val	6.25	6.19	3.54 / 2.43	3.70	1.59	0.92 / 0.91				1.11
Ala	6.38	5.83	3.56 / 2.34	3.92	1.03					1.22
Leu	5.93	5.49	3.44 / 2.43	4.00	1.20	1.67	0.88 / 0.86			1.01
***i*Pr**	5.69							1.12	3.79	

NMR spectra of synthesized peptides

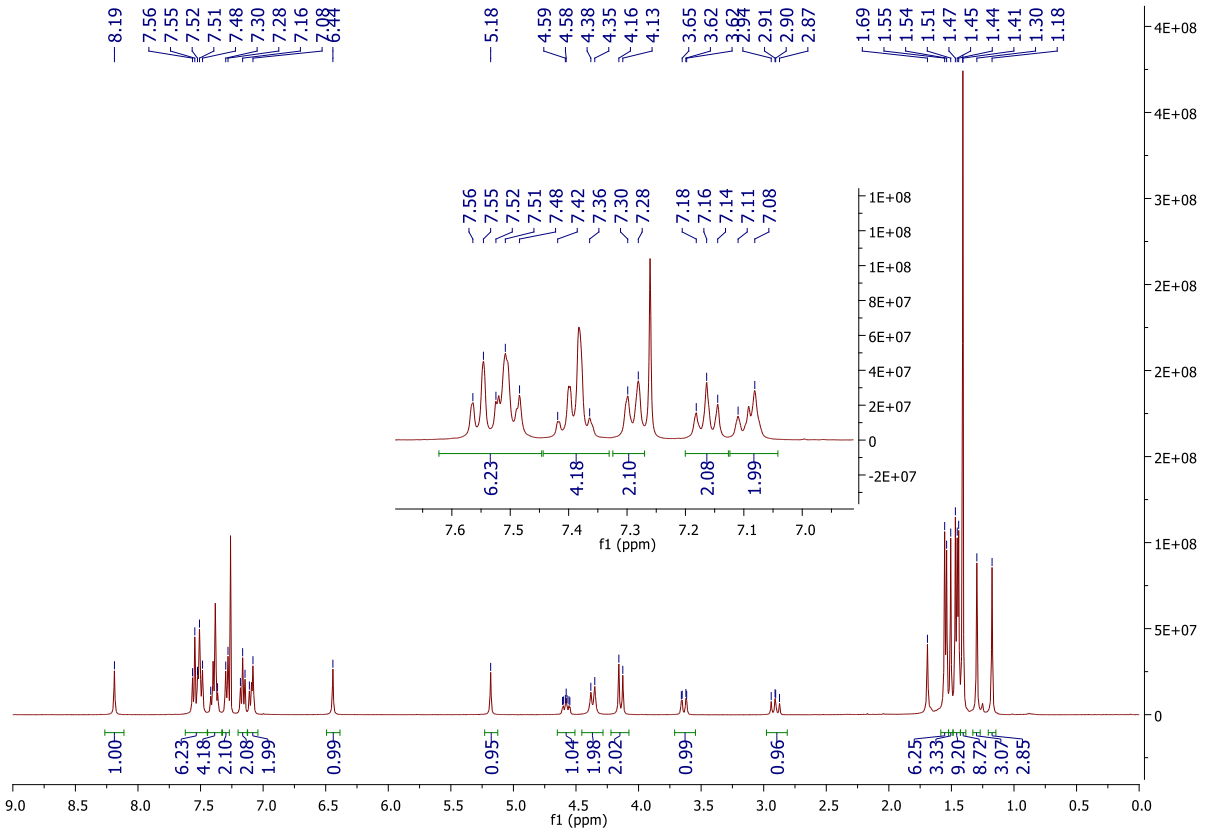
^{1}H NMR spectrum of **AzeAib$_4$-(L)-AlaNH*t*Bu** (400 MHz, $CDCl_3$) :



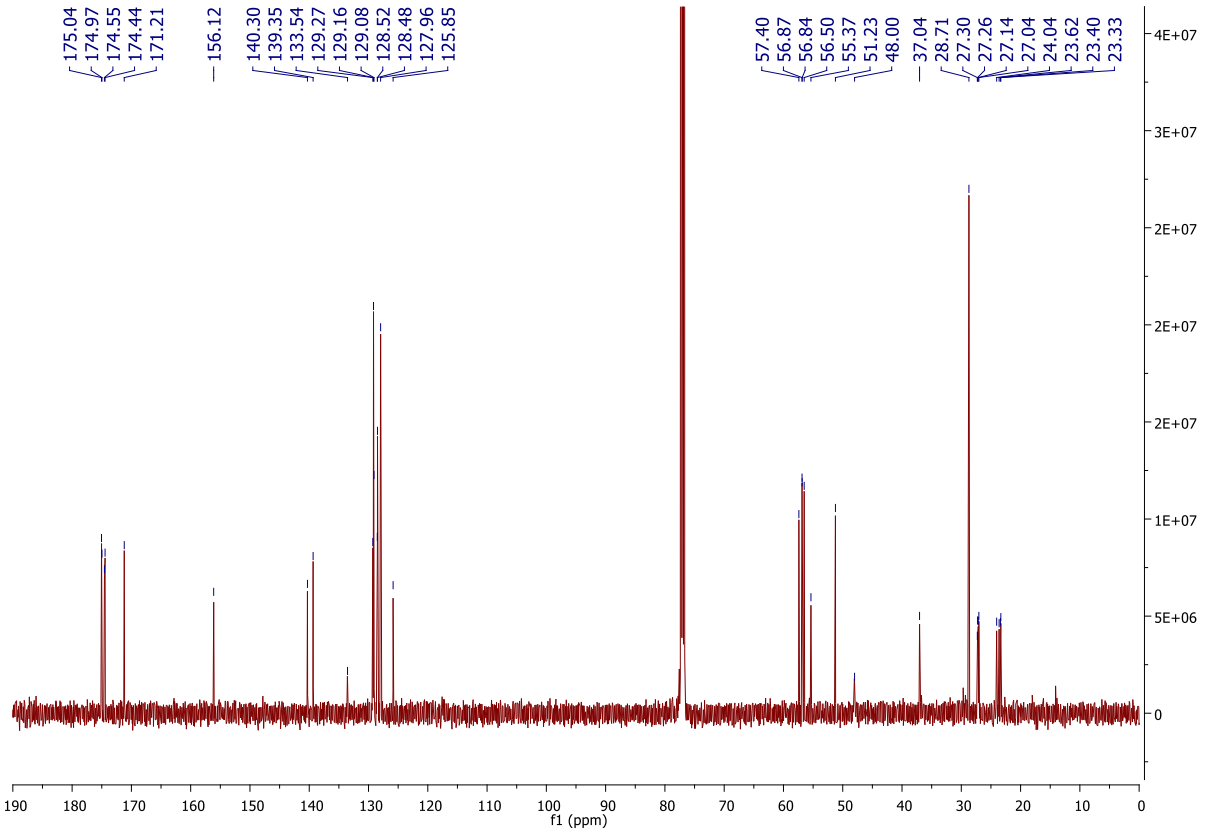
^{13}C NMR spectrum of **AzeAib$_4$-(L)-AlaNH*t*Bu** (100 MHz, $CDCl_3$) :



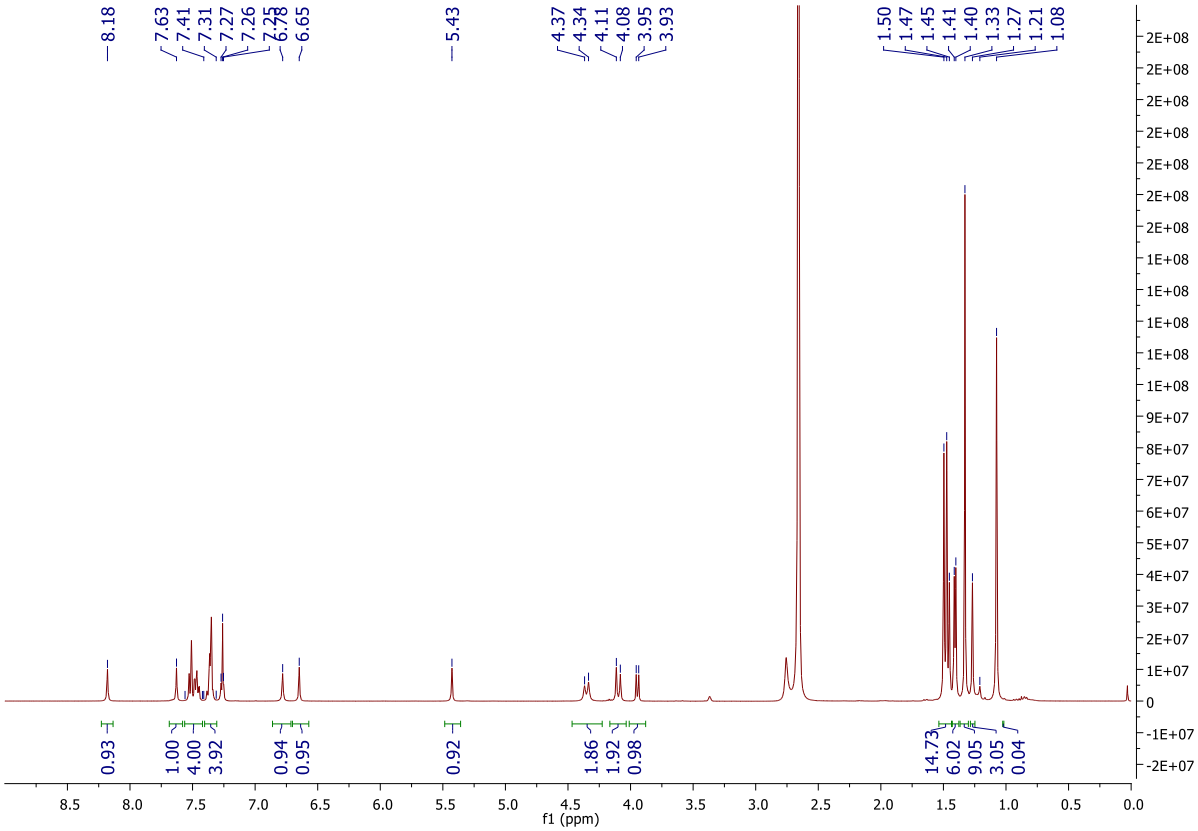
^{1}H NMR spectrum of **AzeAib4-(L)-PheNH*t*Bu** (400 MHz, $CDCl_3$):



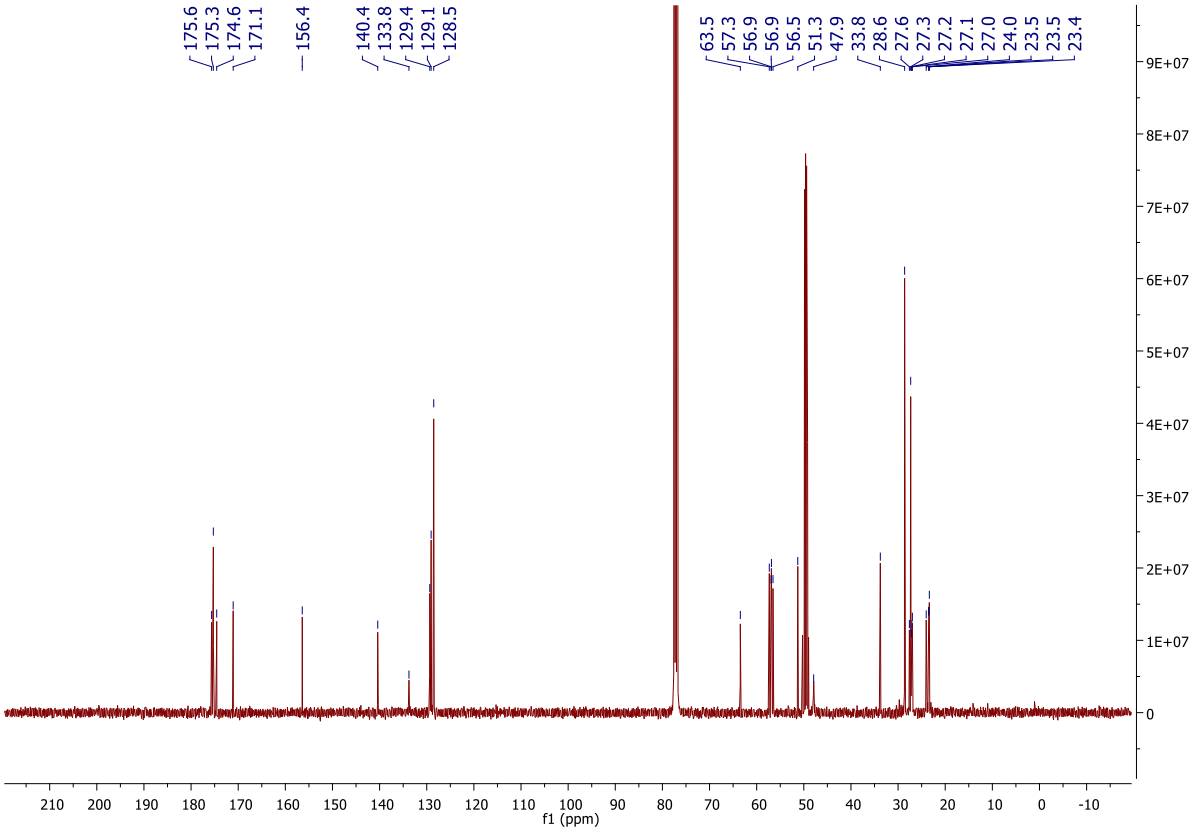
^{13}C NMR spectrum of **AzeAib4-(L)-PheNH*t*Bu** (125 Hz, $CDCl_3$):



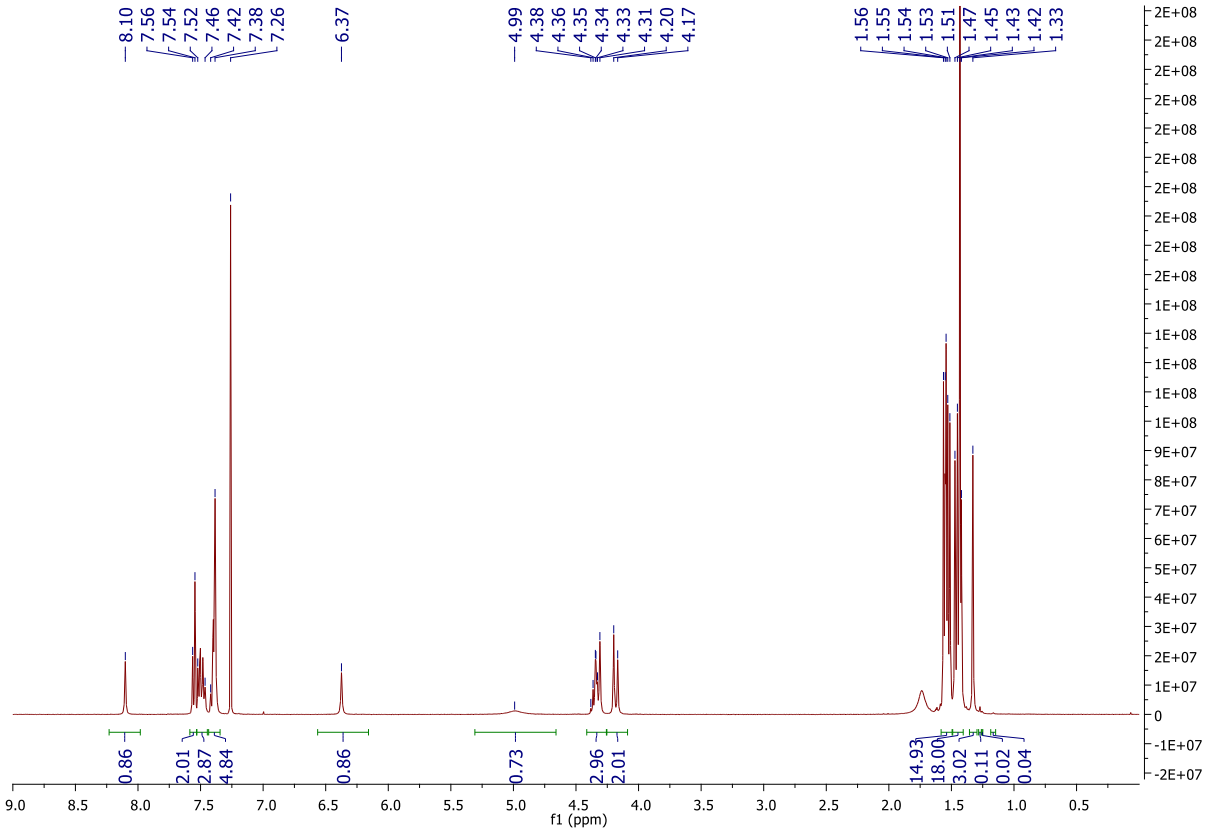
^{1}H NMR spectrum of **AzeAib$_4$-(L)-*t*LeuNH*t*Bu** (400 MHz, $CDCl_3/CD_3OH$ 97:3):



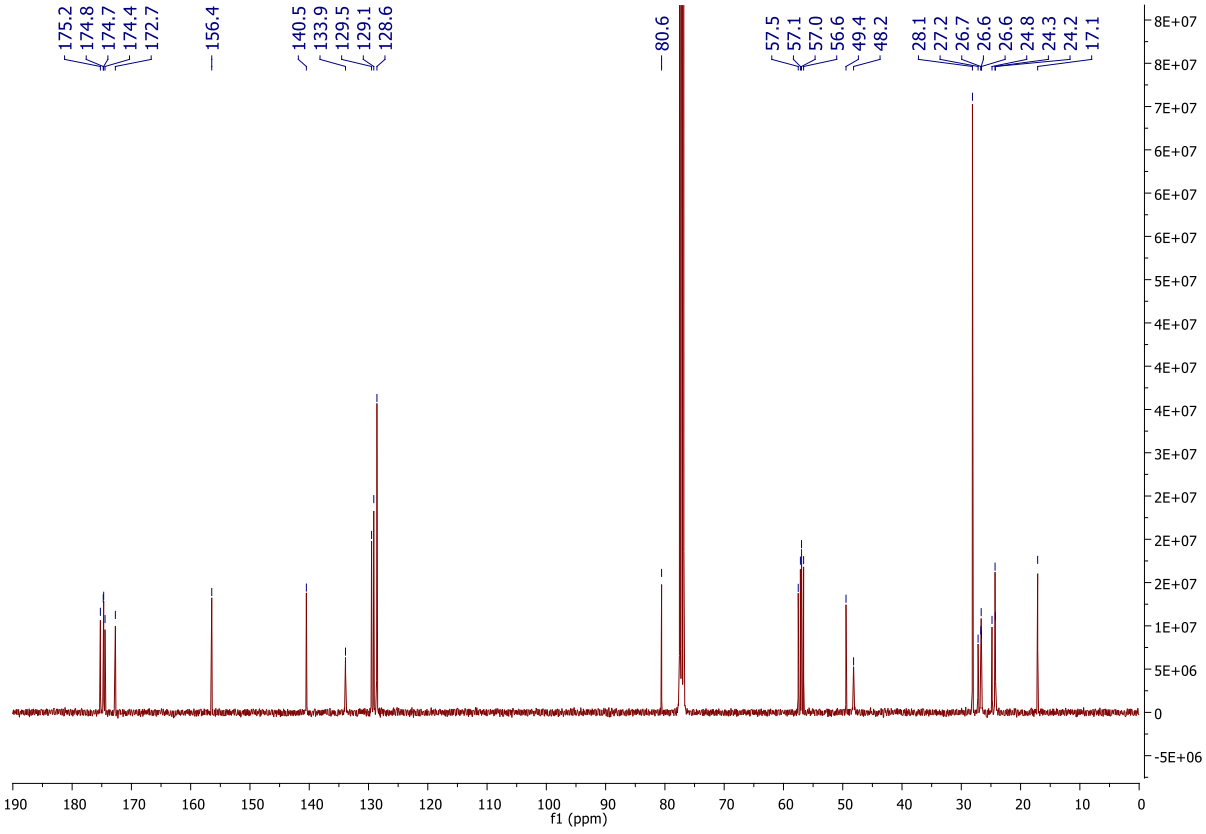
^{13}C NMR spectrum of **AzeAib$_4$-(L)-*t*LeuNH*t*Bu** (100 MHz, $CDCl_3/CD_3OH$ 97:3):



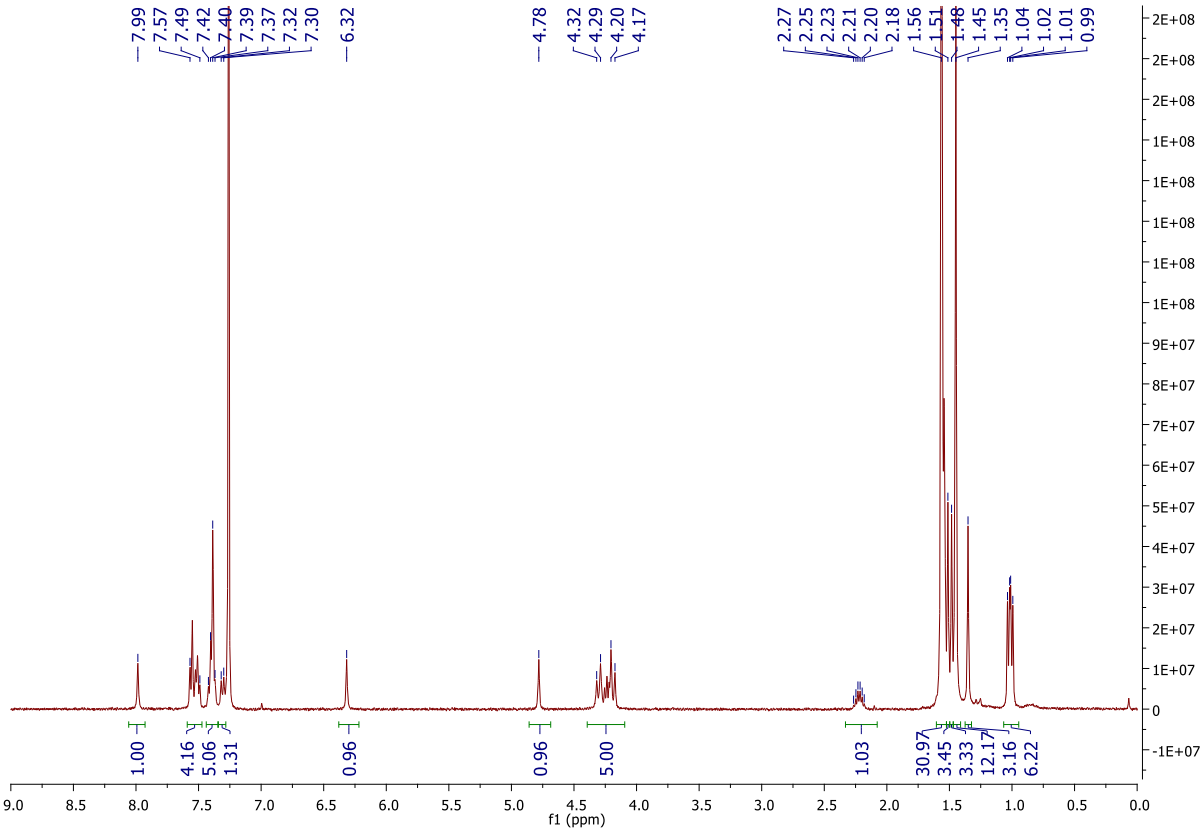
^{1}H NMR spectrum of **AzeAib$_4$-(D)-AlaOtBu** (400 MHz, $CDCl_3$):



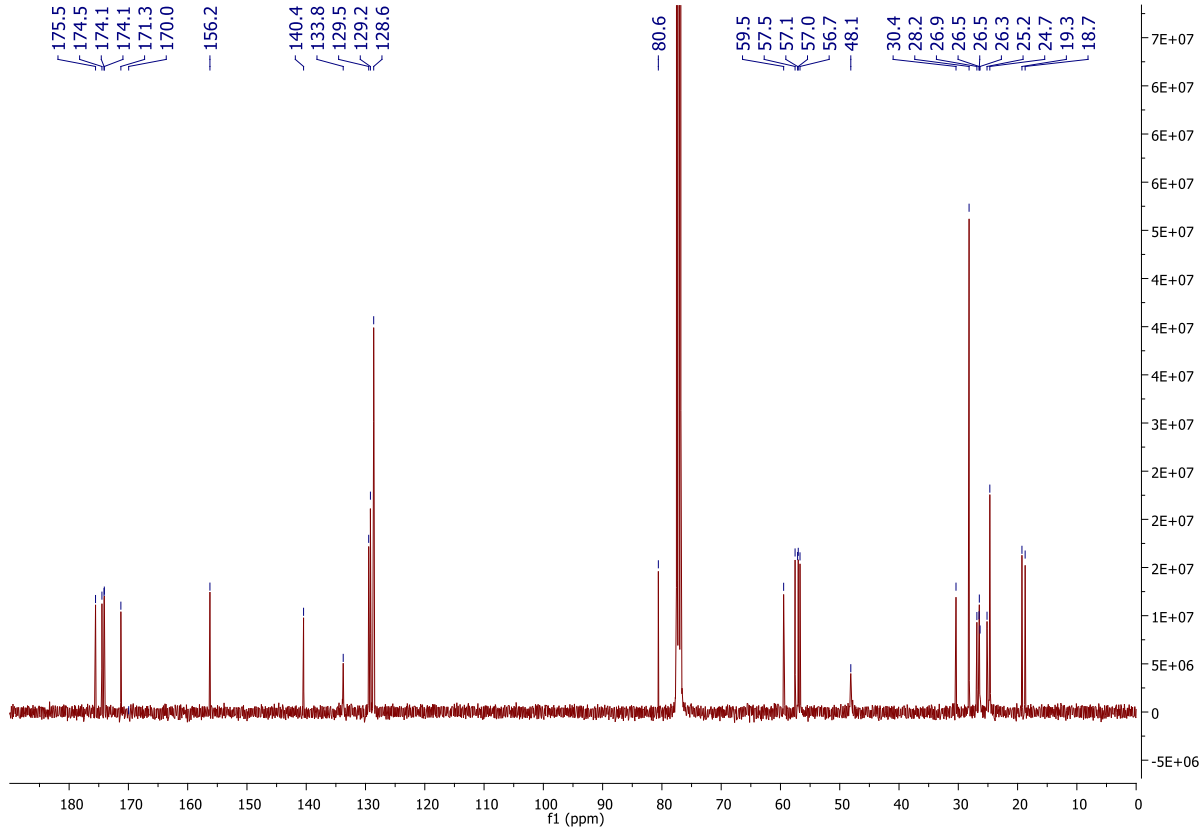
^{13}C NMR spectrum of **AzeAib$_4$-(D)-AlaO*t*Bu** (100 MHz, $CDCl_3$):



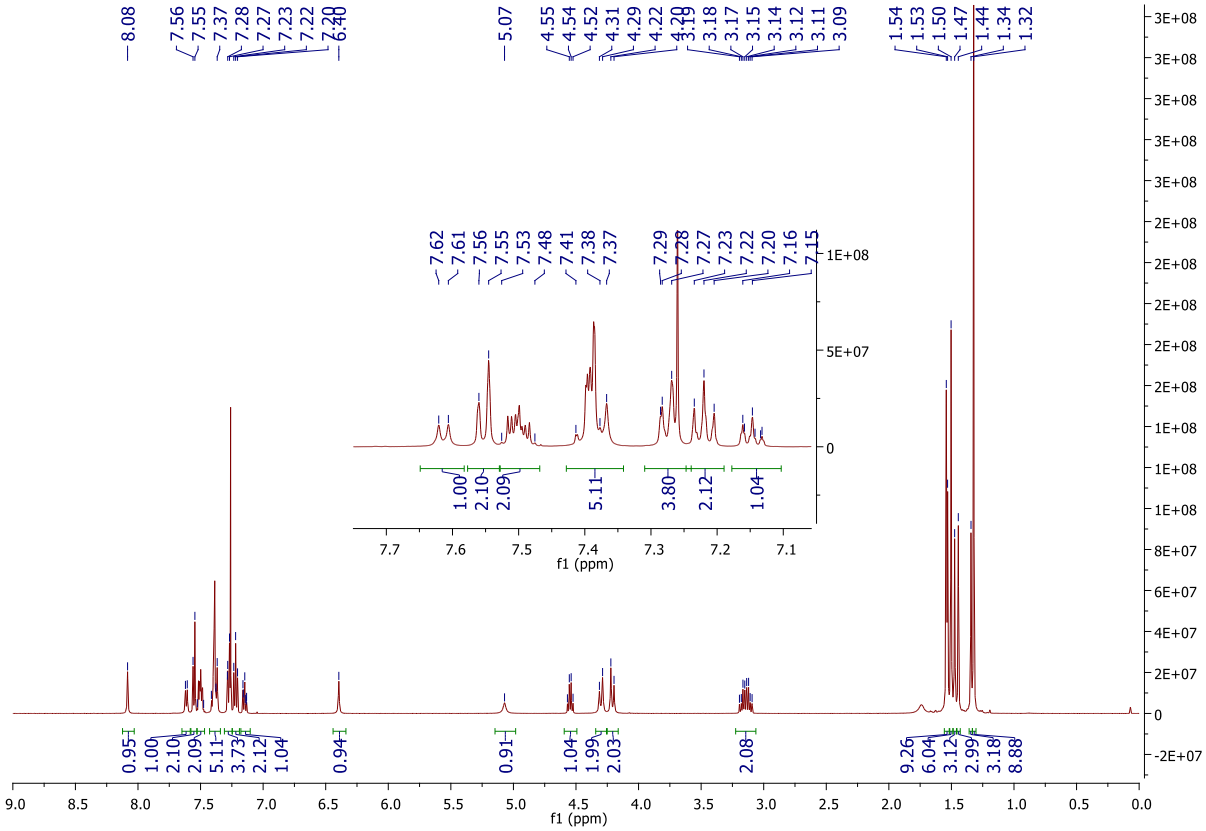
^{1}H NMR spectrum of **AzeAib$_4$-(L)-ValO*t*Bu** (400 MHz, $CDCl_3$):



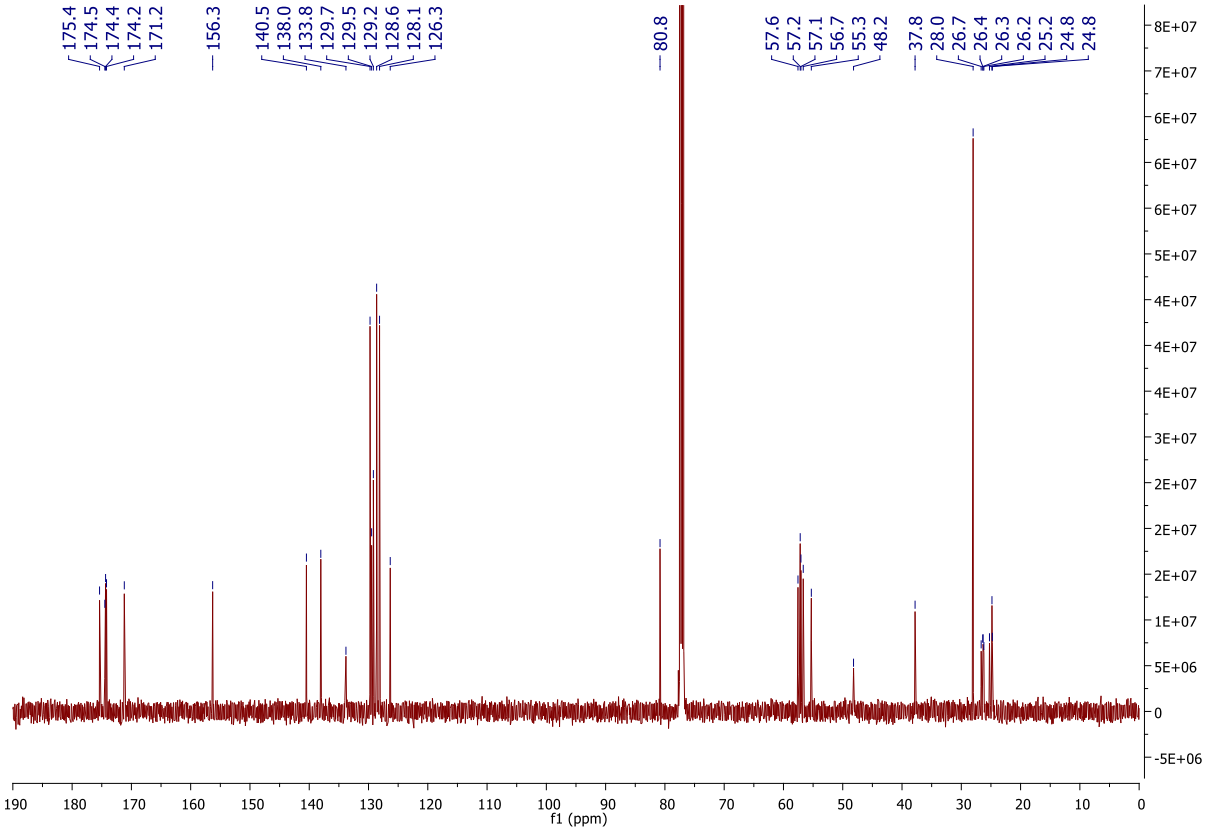
^{13}C NMR spectrum of **AzeAib$_4$-(L)-ValO*t*Bu** (100 MHz, $CDCl_3$):



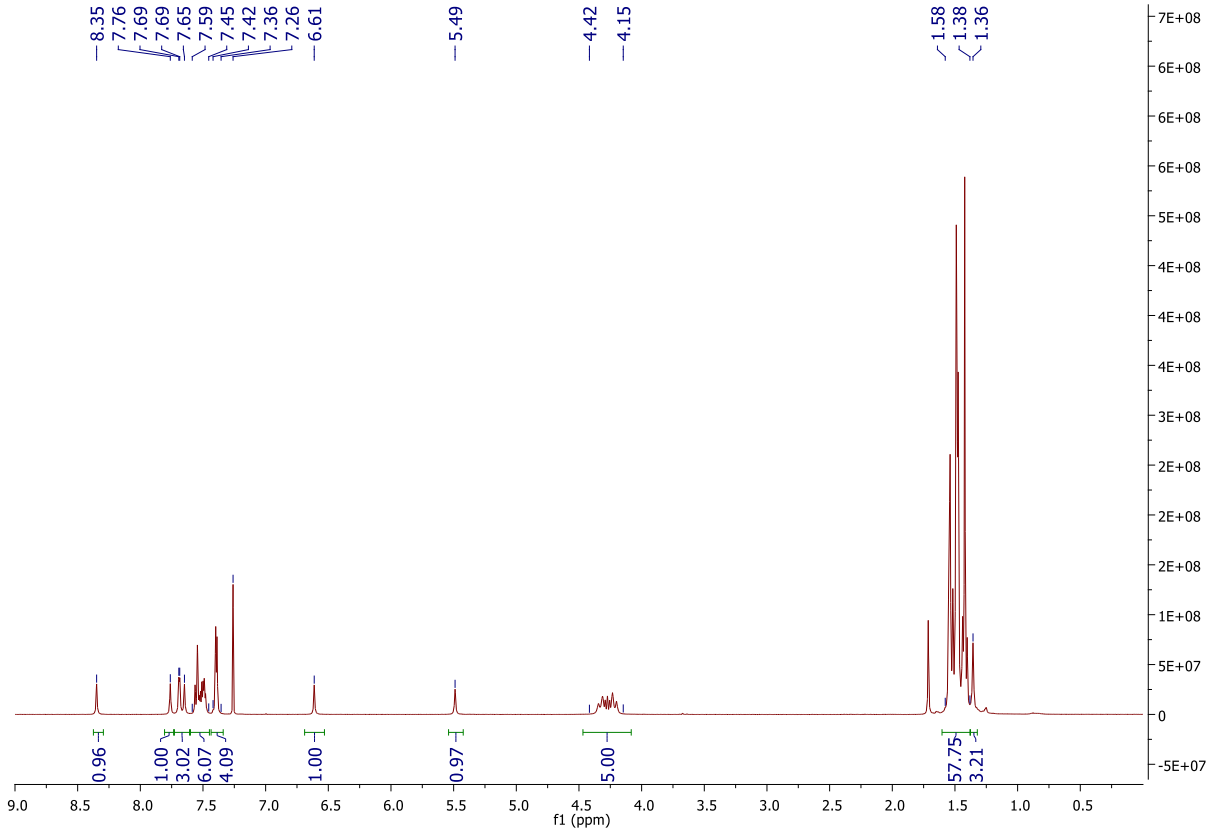
^{1}H NMR spectrum of **AzeAib$_4$-(L)-PheO*t*Bu** (500 MHz, $CDCl_3$):



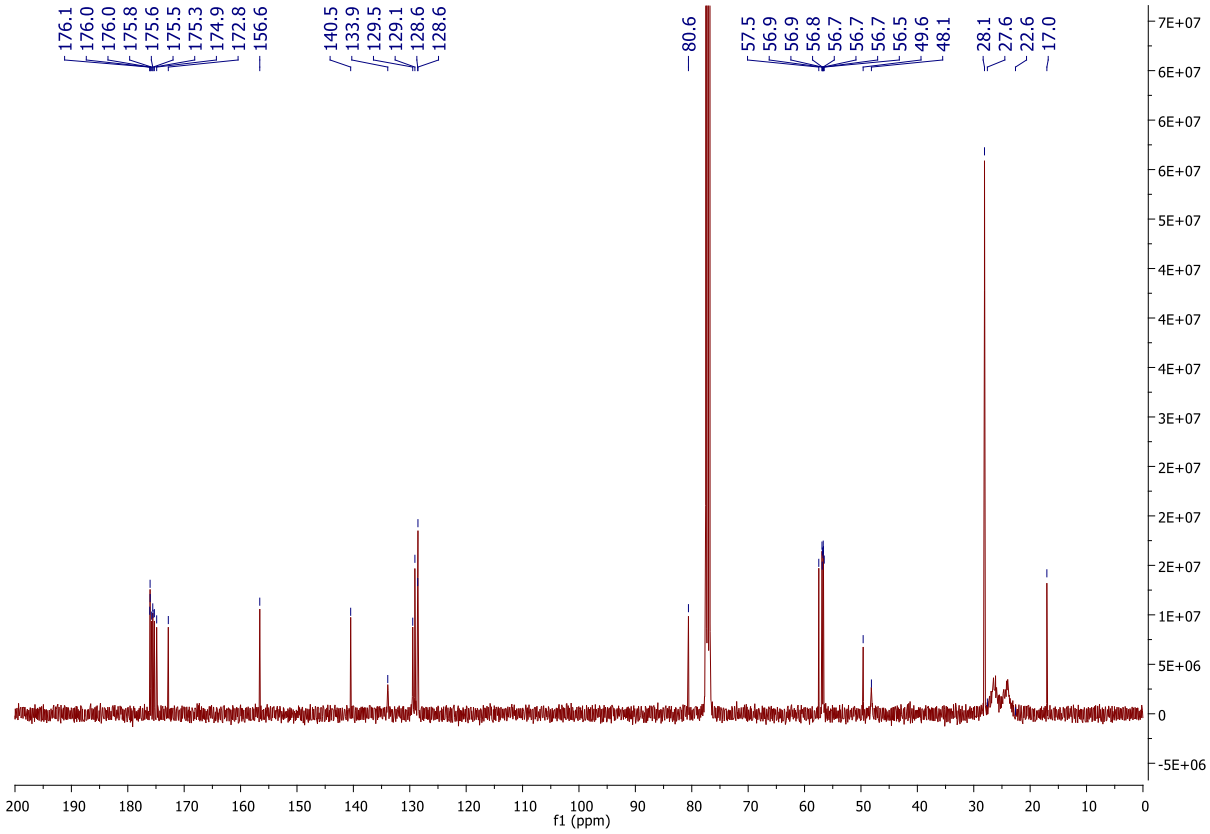
^{13}C NMR spectrum of **AzeAib$_4$-(L)-PheO*t*Bu** (125 MHz, $CDCl_3$):



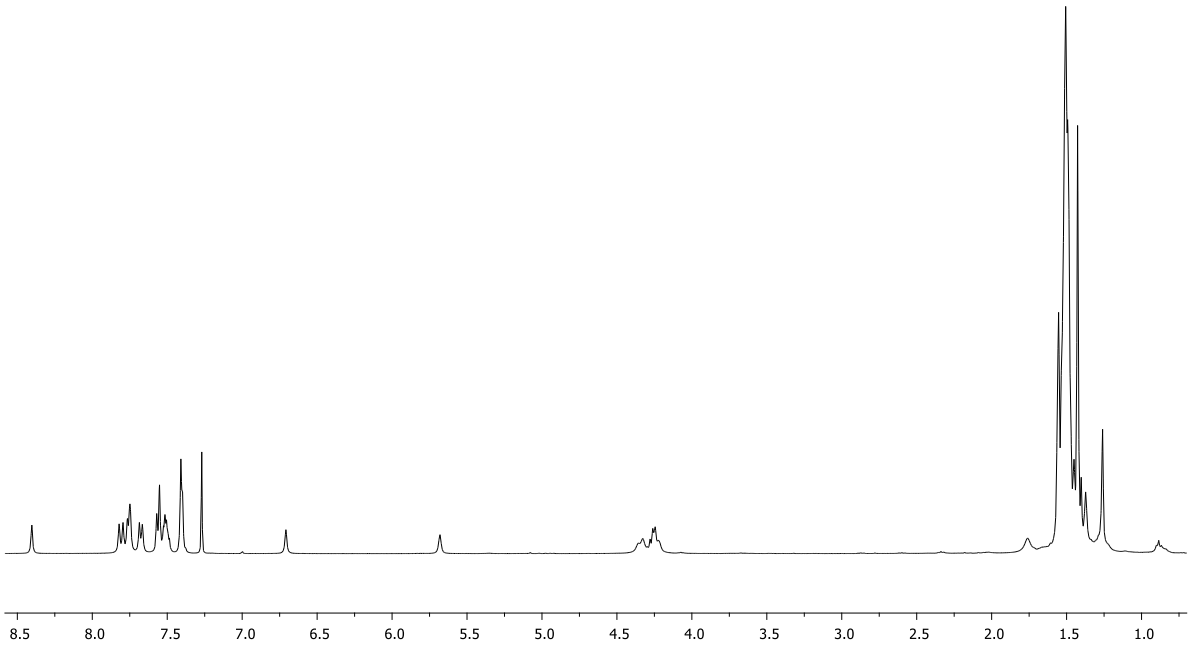
^{1}H NMR spectrum of **AzeAib$_8$-(L)-AlaO*t*Bu** (400 MHz, $CDCl_3$):



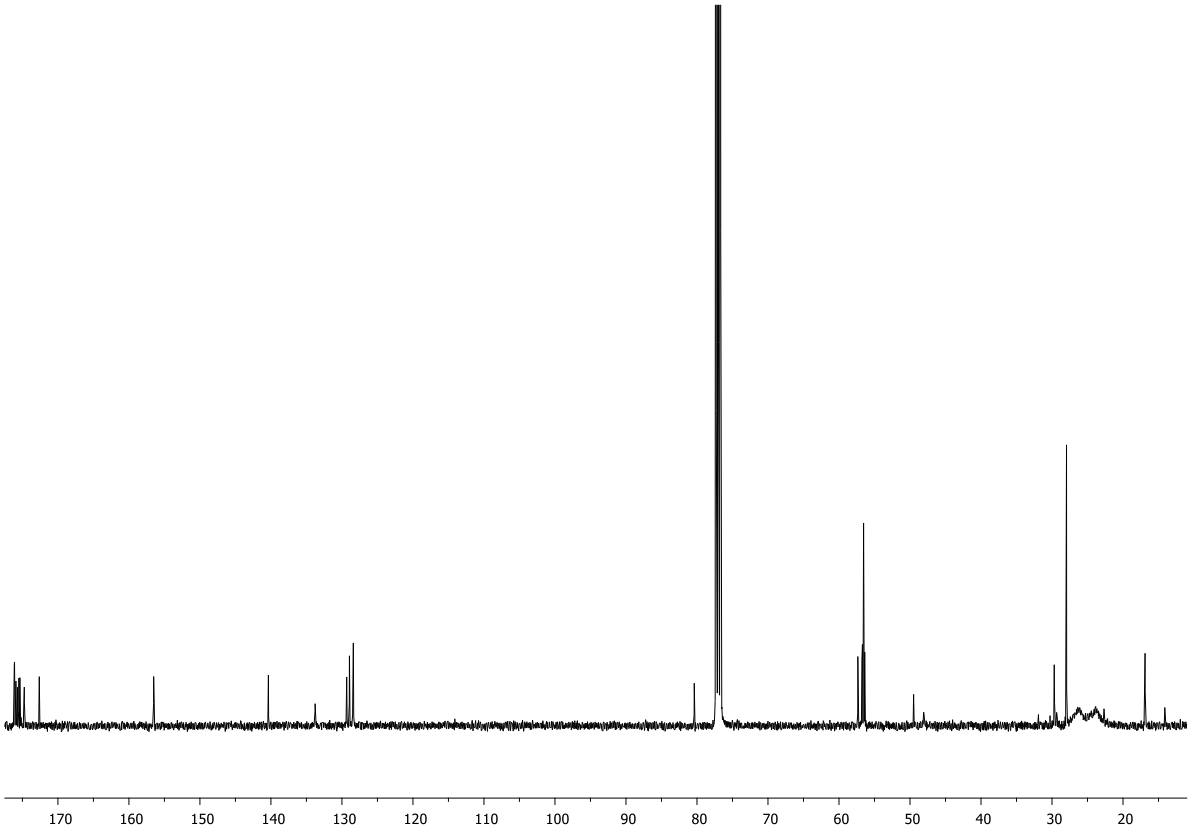
^{13}C NMR spectrum of **AzeAib$_8$-(L)-AlaO*t*Bu** (100 MHz, $CDCl_3$):



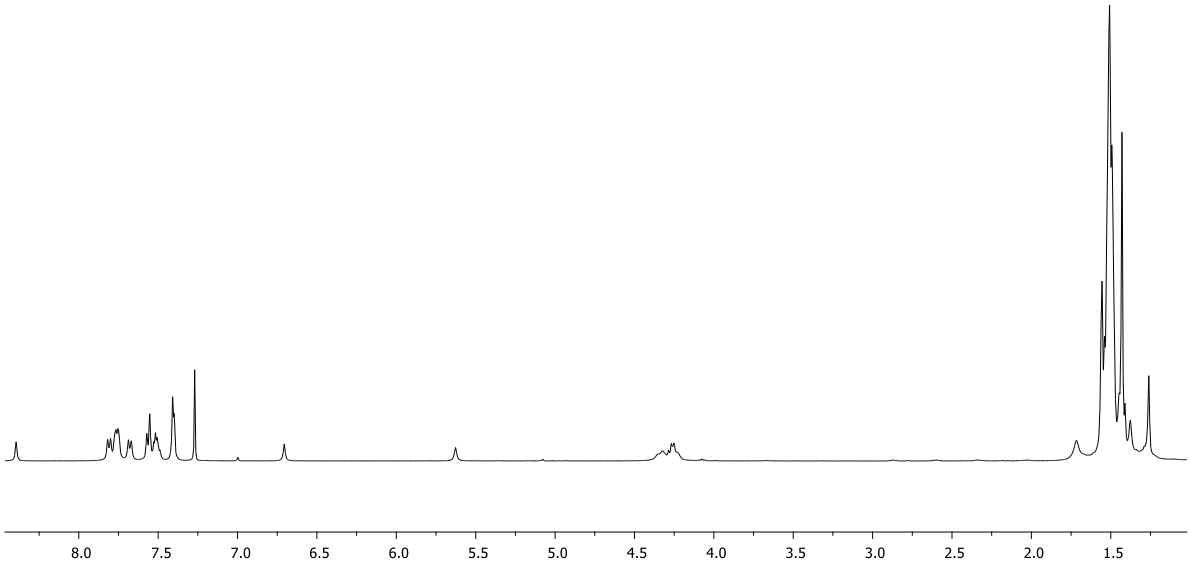
^{1}H NMR spectrum of **AzeAib$_{11}$AlaO*t*Bu** (400 MHz, $CDCl_3$):



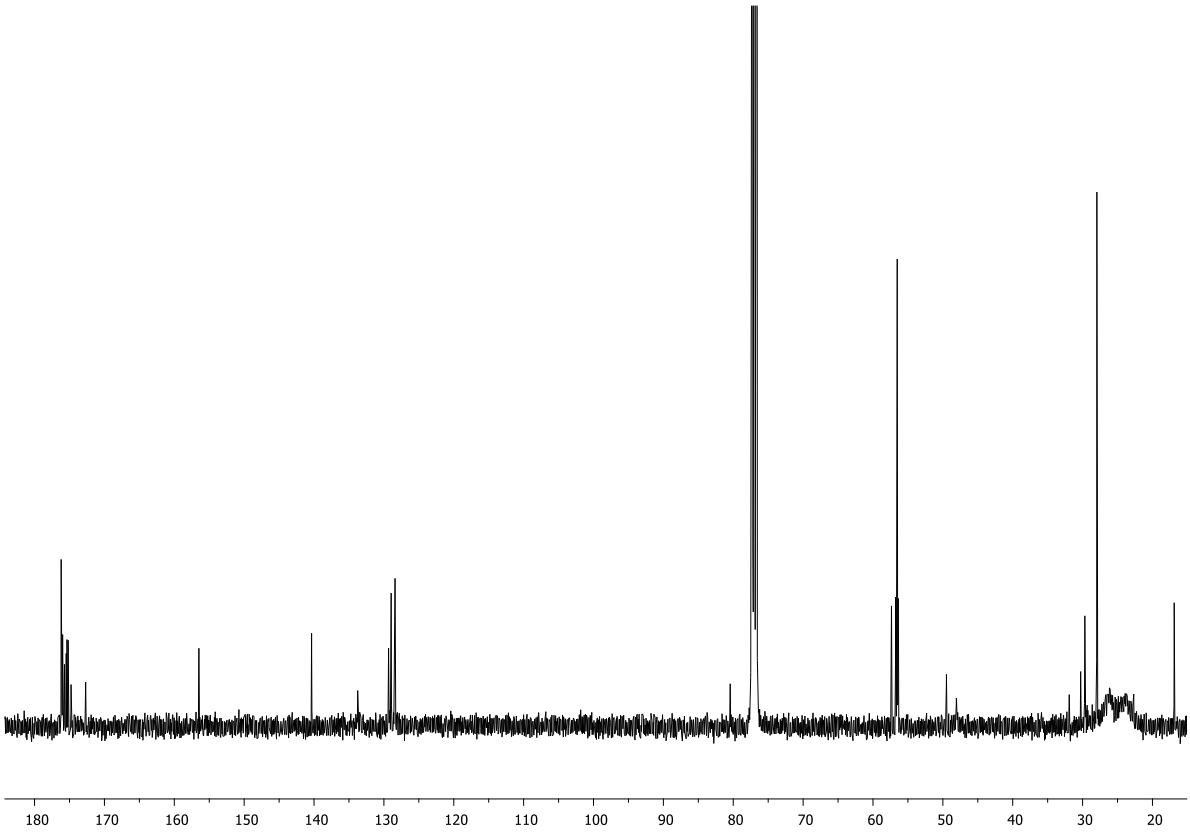
^{13}C NMR spectrum of **AzeAib$_{11}$AlaO*t*Bu** (100 MHz, $CDCl_3$):



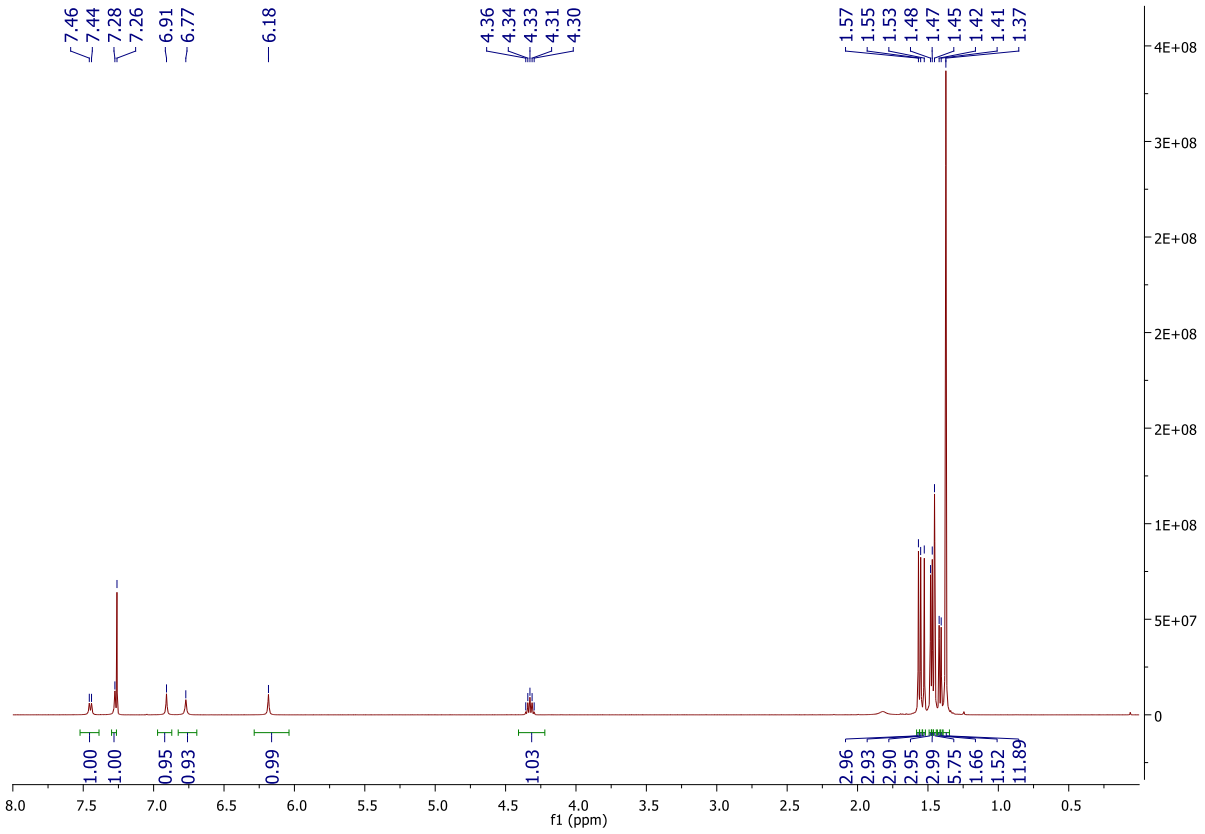
^{1}H NMR spectrum of **AzeAib$_{12}$AlaO*t*Bu** (400 MHz, $CDCl_3$) :



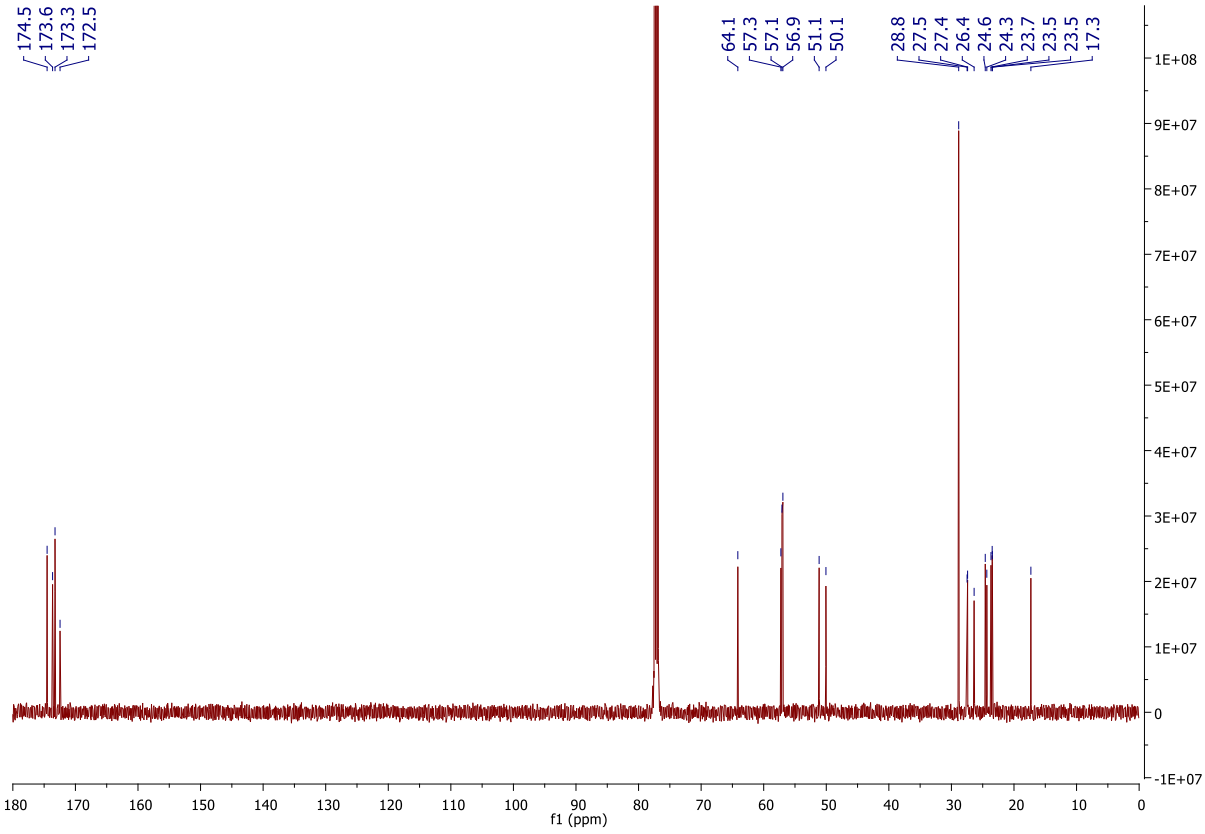
^{13}C NMR spectrum of **AzeAib$_{12}$AlaO*t*Bu** (100 MHz, $CDCl_3$):



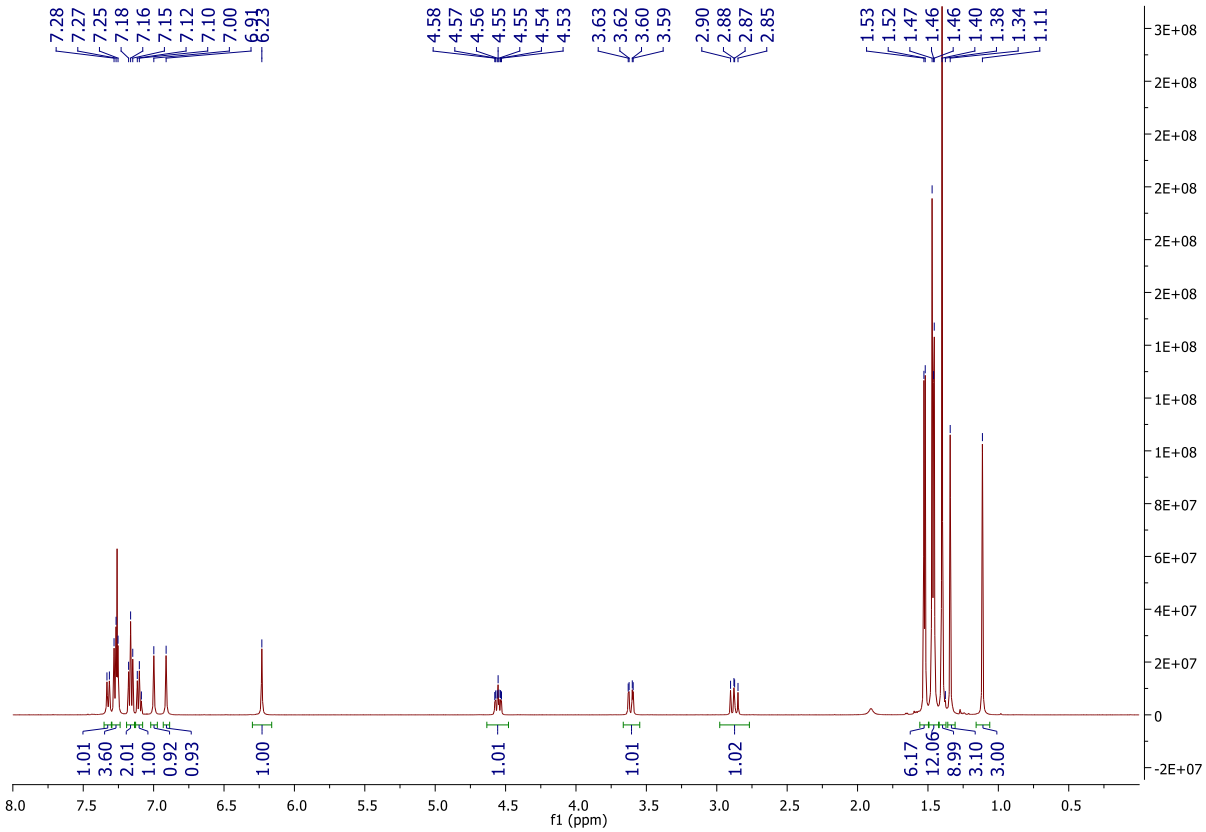
^{1}H NMR spectrum of **N_3Aib$_4$-(L)-AlaNH*t*Bu** (500 MHz, $CDCl_3$):



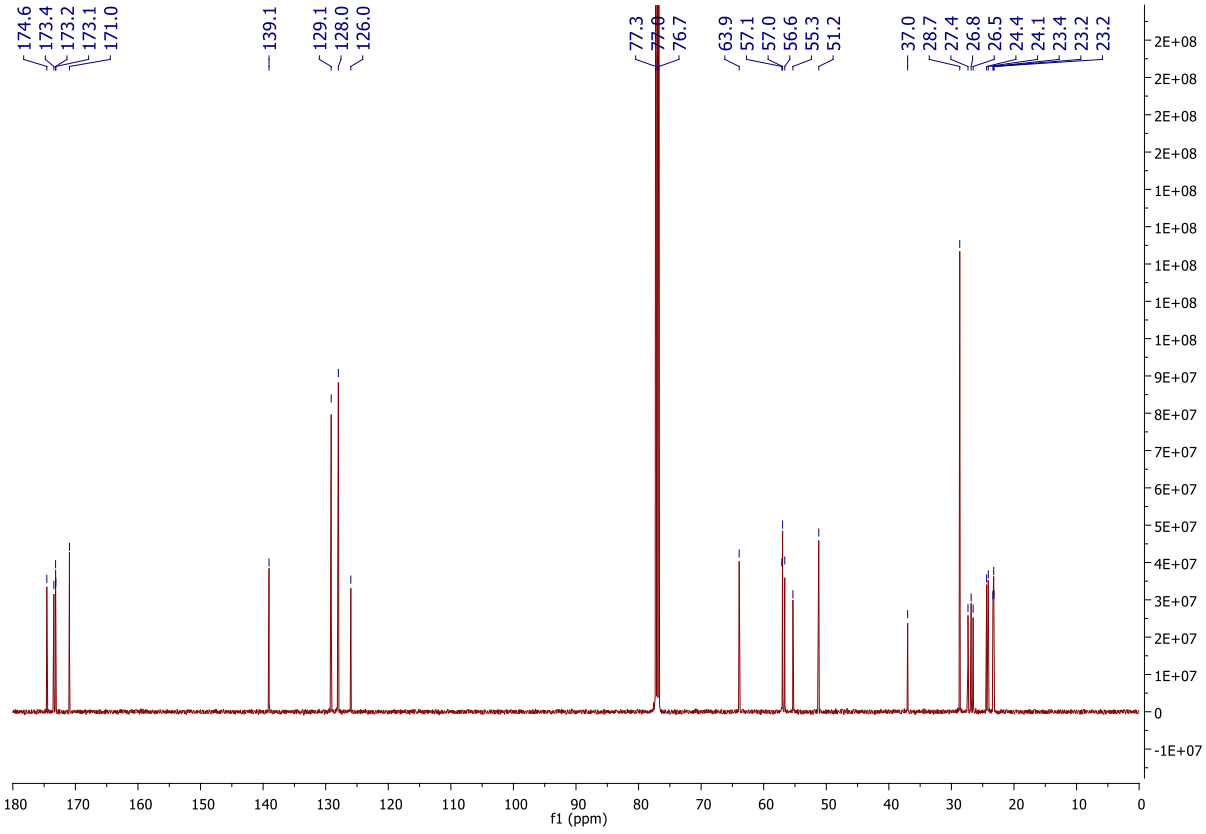
^{13}C NMR spectrum of **N_3Aib$_4$-(L)-AlaNH*t*Bu** (125 MHz, $CDCl_3$):



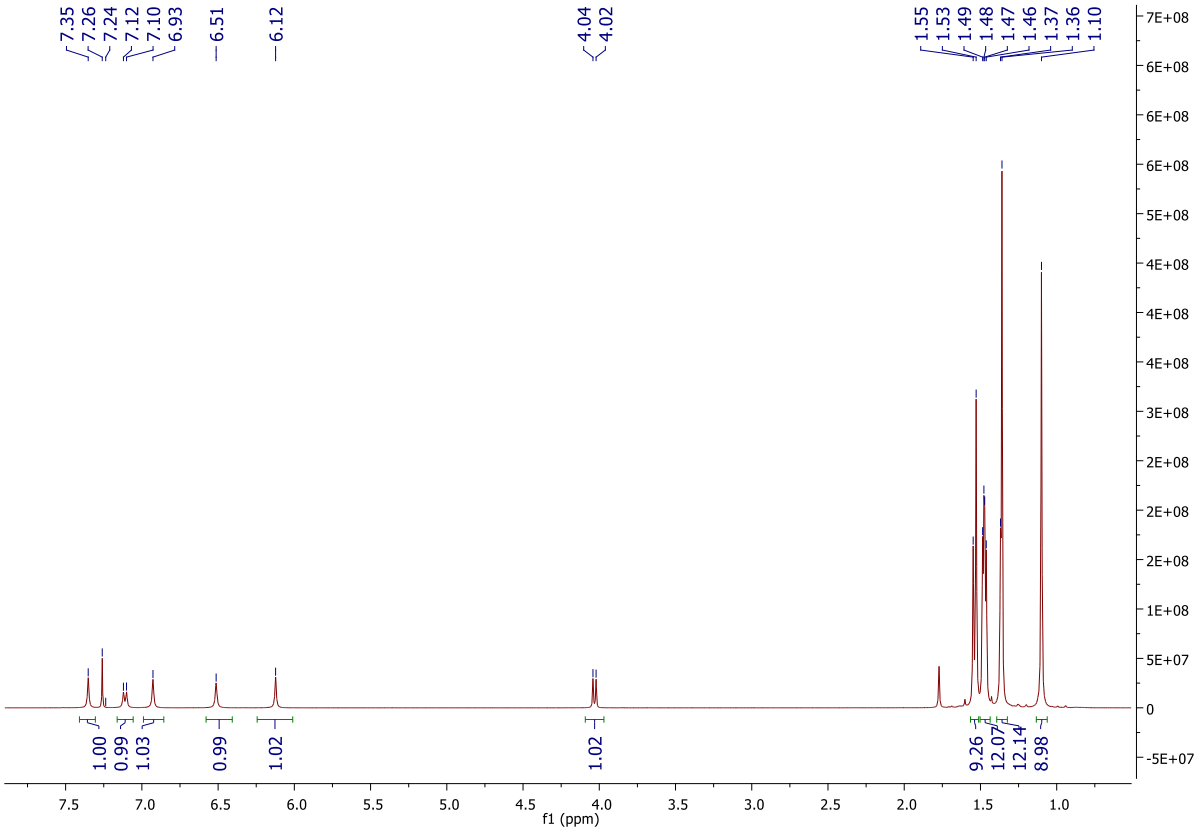
^{1}H NMR spectrum of **N_3Aib$_4$-(L)-PheNH*t*Bu** (500 MHz, $CDCl_3$):



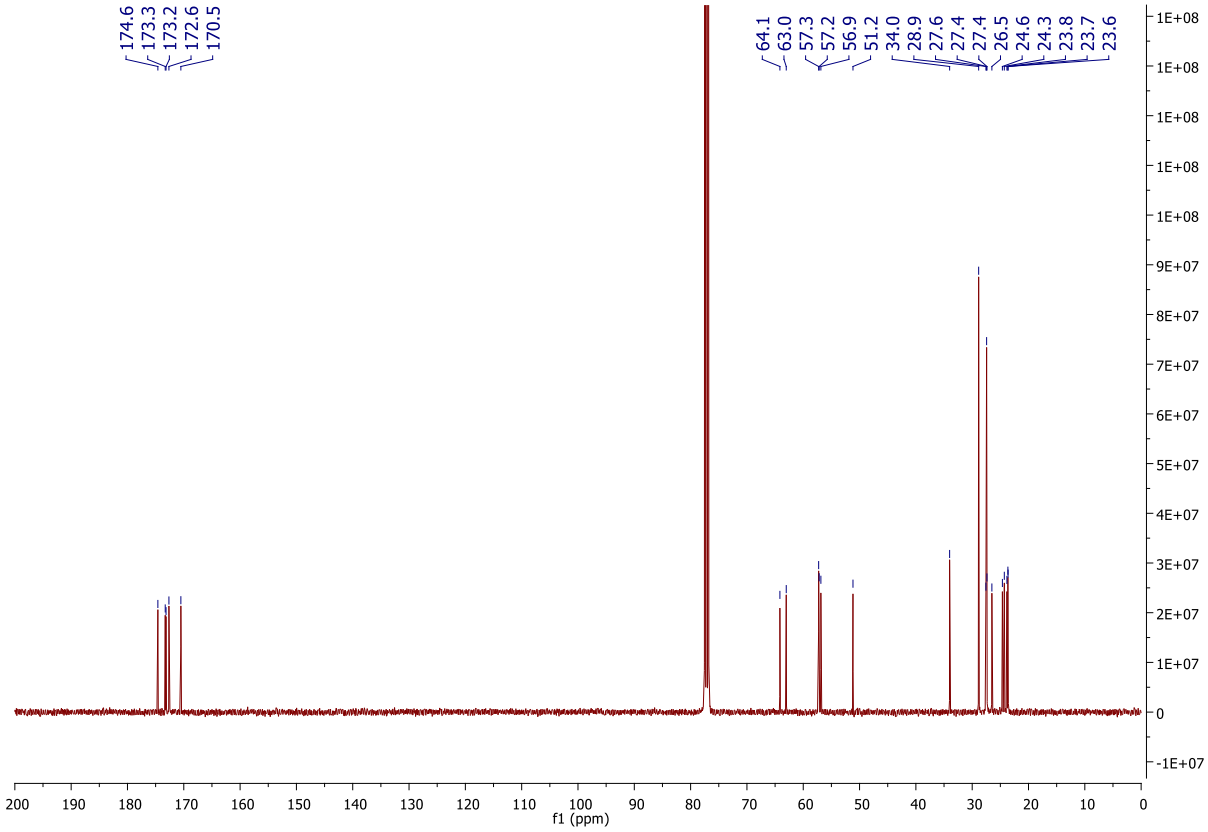
^{13}C NMR spectrum of **N_3Aib$_4$-(L)-PheNH*t*Bu** (125 MHz, $CDCl_3$):



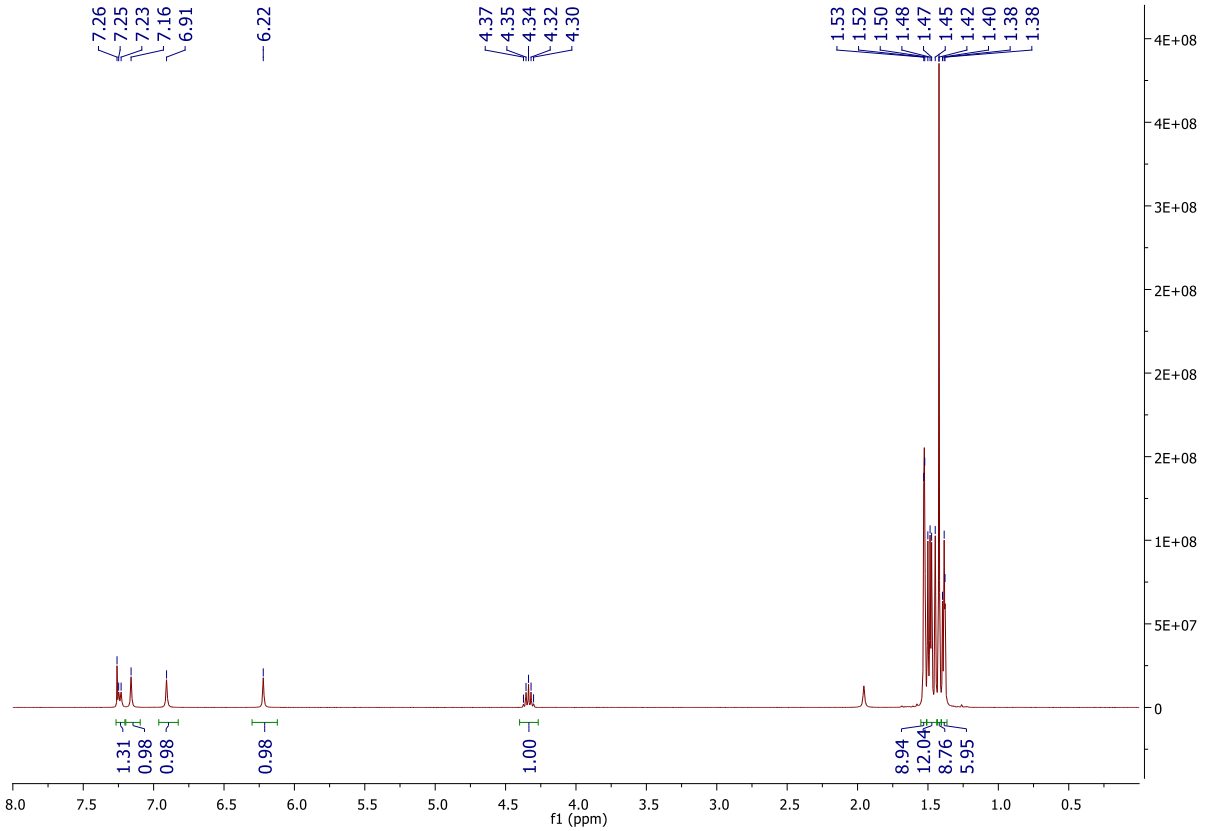
^{1}H NMR spectrum of **N_3Aib$_4$-(L)-*t*LeuNH*t*Bu** (400 MHz, $CDCl_3$):



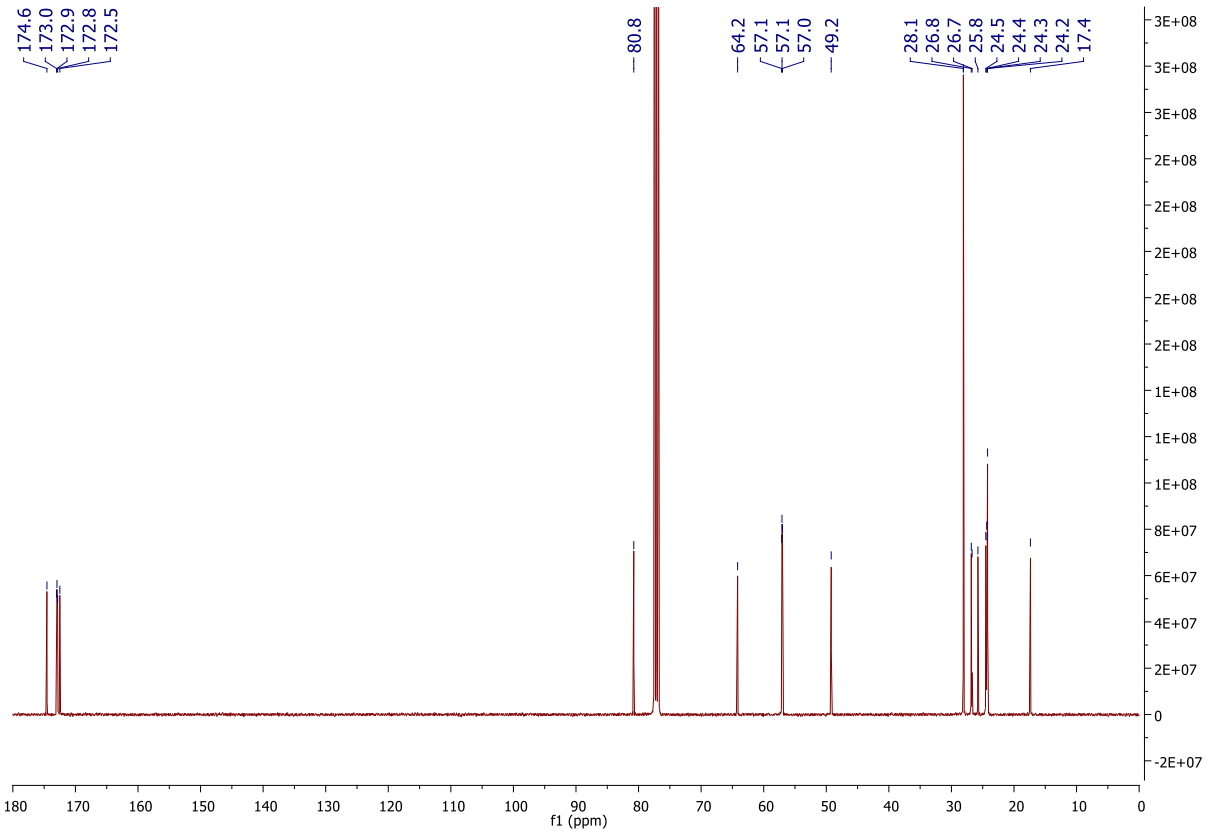
^{13}C NMR spectrum of **N_3Aib$_4$-(L)-*t*LeuNH*t*Bu** (100 MHz, $CDCl_3$):



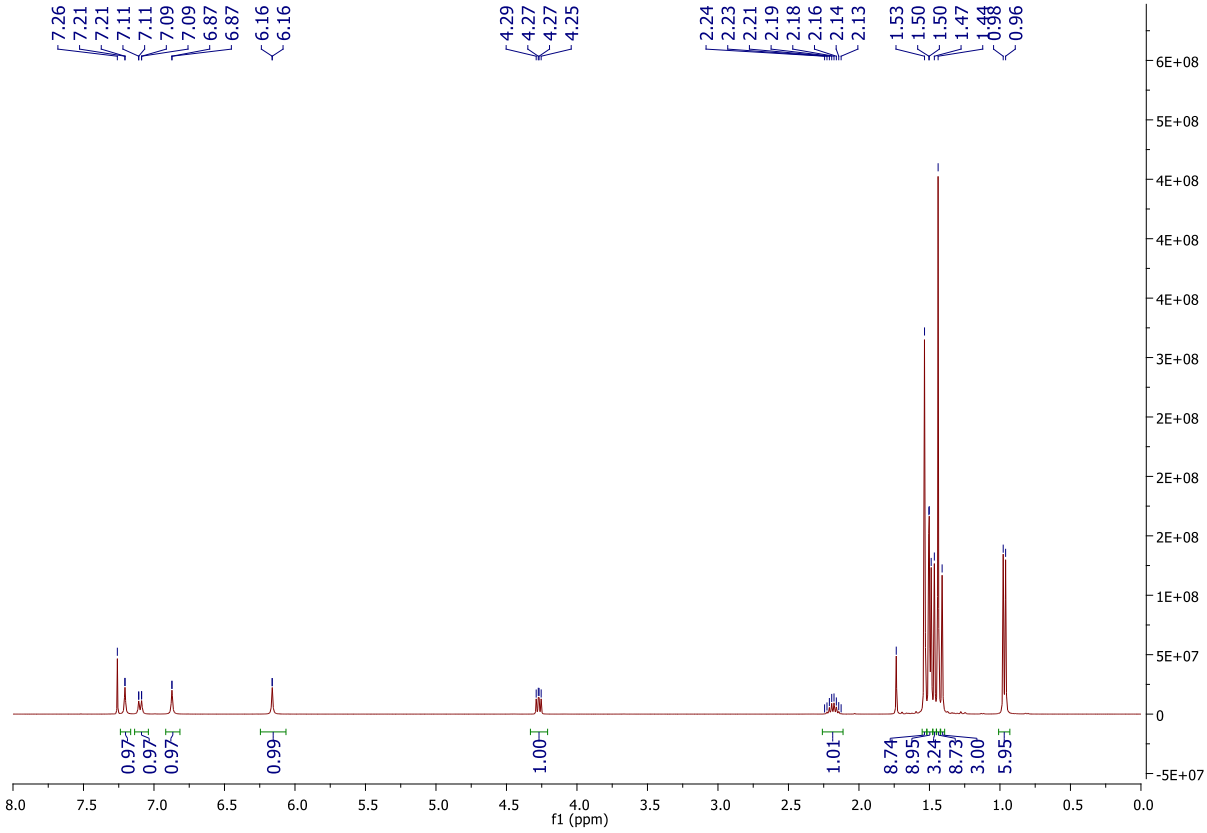
^{1}H NMR spectrum of **N_3Aib$_4$-(L)-AlaO*t*Bu** (400 MHz, $CDCl_3$):



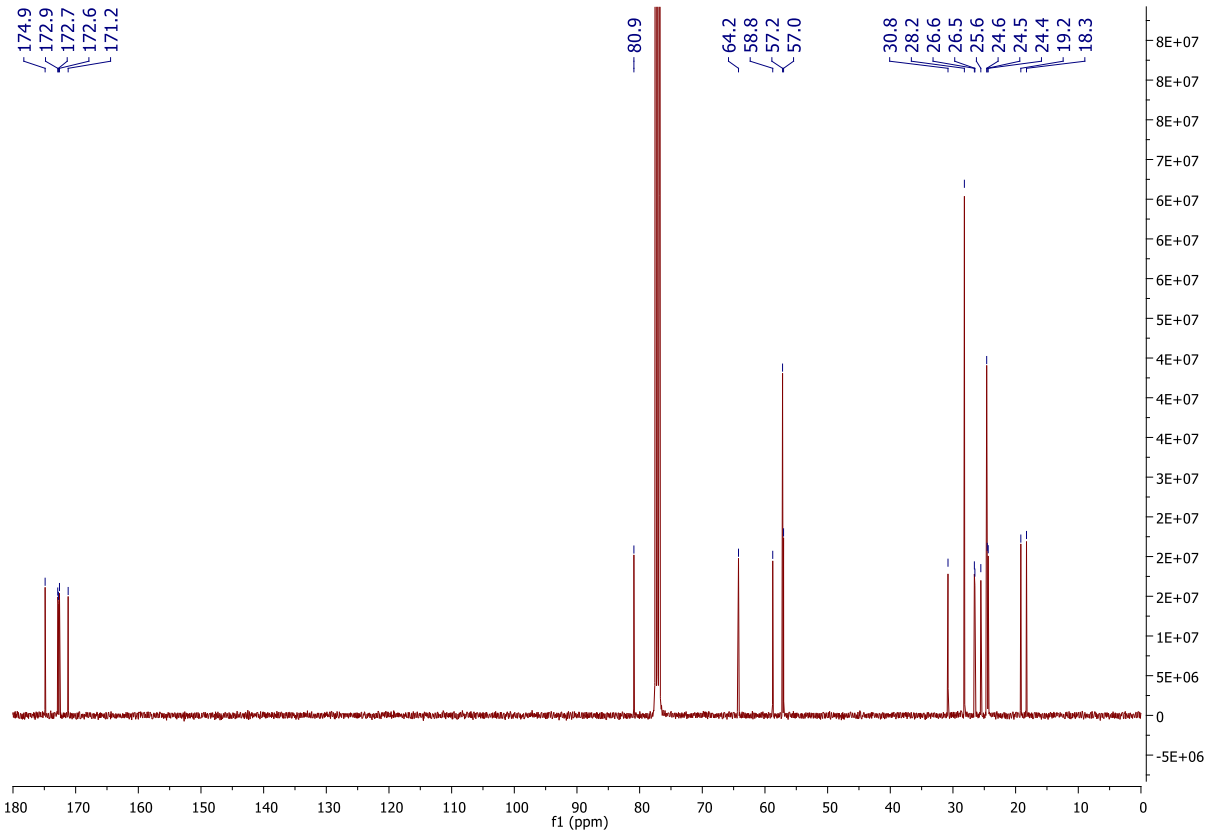
^{13}C NMR spectrum of **N_3Aib$_4$-(L)-AlaO*t*Bu** (100 MHz, $CDCl_3$):



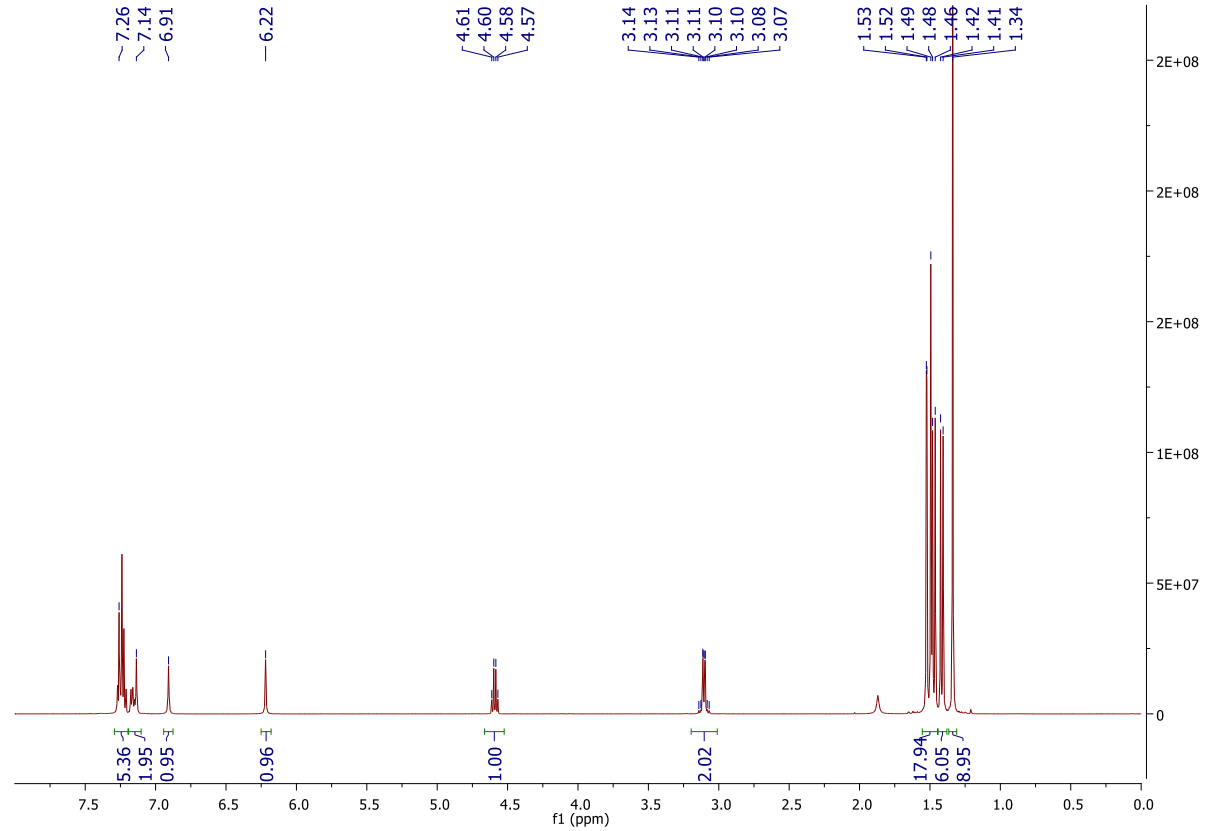
^{1}H NMR spectrum of **N_3Aib$_4$-(L)-ValO*t*Bu** (400 MHz, $CDCl_3$):



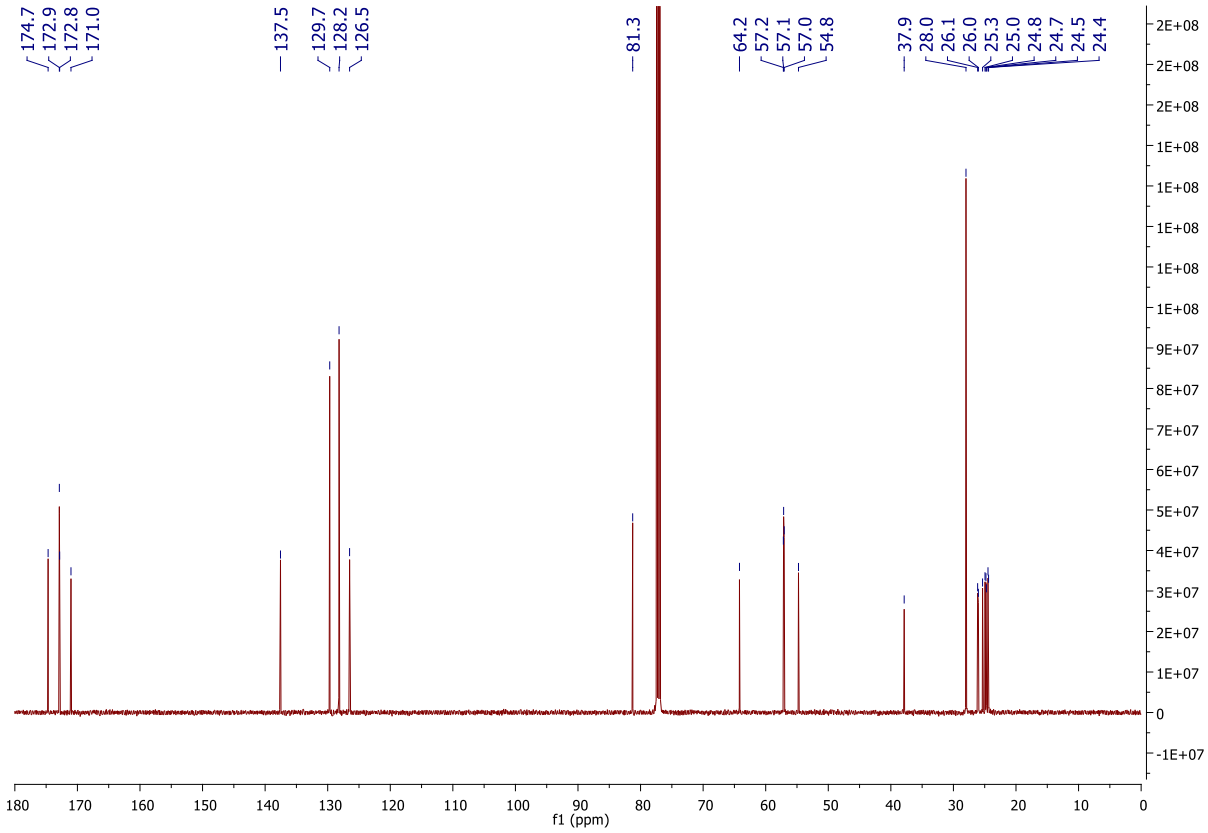
^{13}C NMR spectrum of **N_3Aib$_4$-(L)-ValO*t*Bu** (100 MHz, $CDCl_3$):



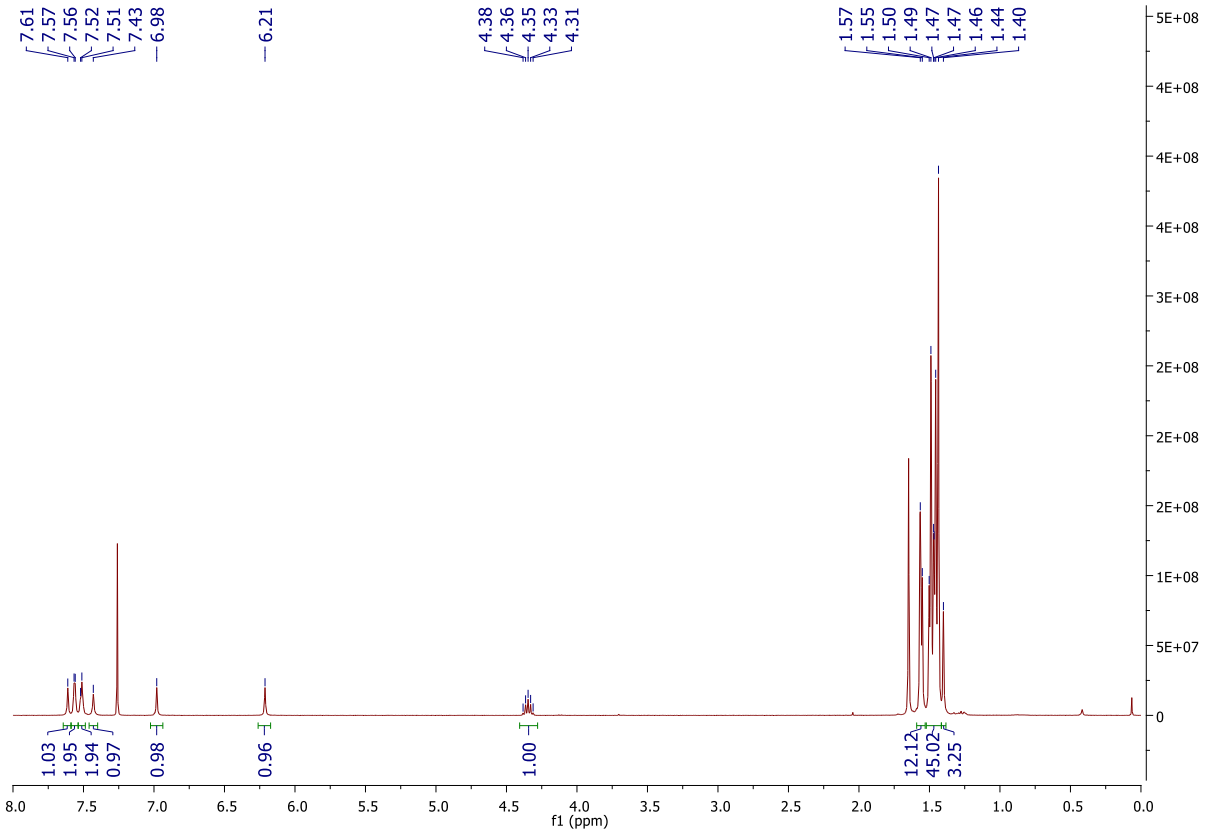
^{1}H NMR spectrum of **N_3Aib$_4$-(L)-PheO*t*Bu** (500 MHz, $CDCl_3$):



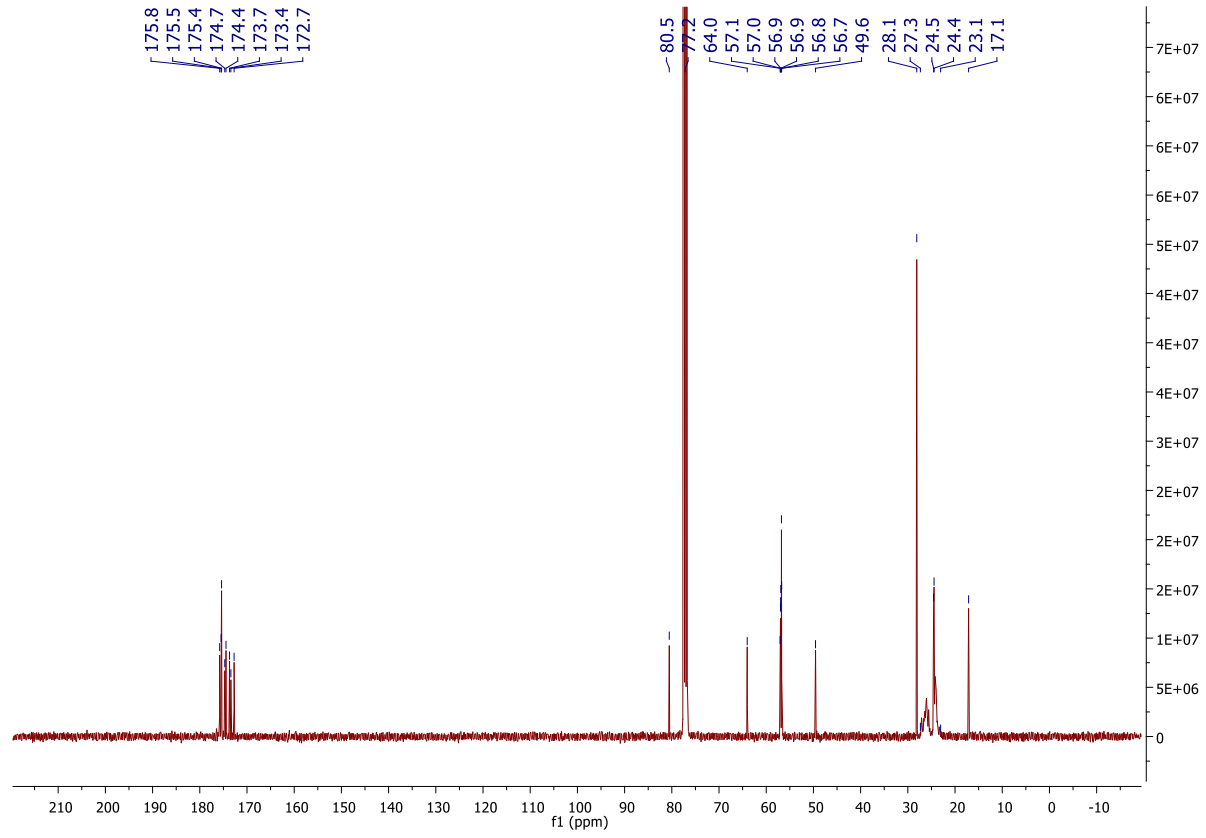
^{13}C NMR spectrum of **N_3Aib$_4$-(L)-PheO*t*Bu** (125 MHz, $CDCl_3$) :



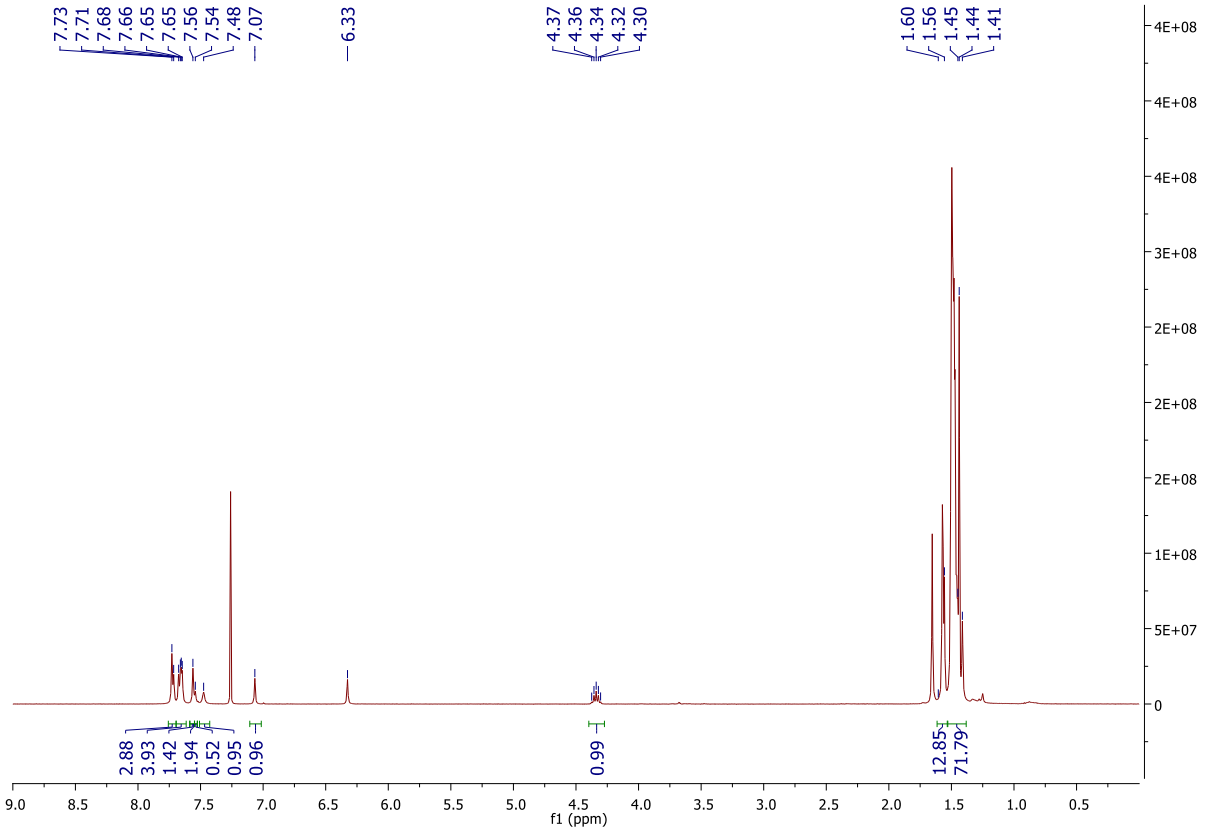
^{1}H NMR spectrum of **N_3Aib$_8$-(L)-AlaO*t*Bu** (400 MHz, $CDCl_3$):



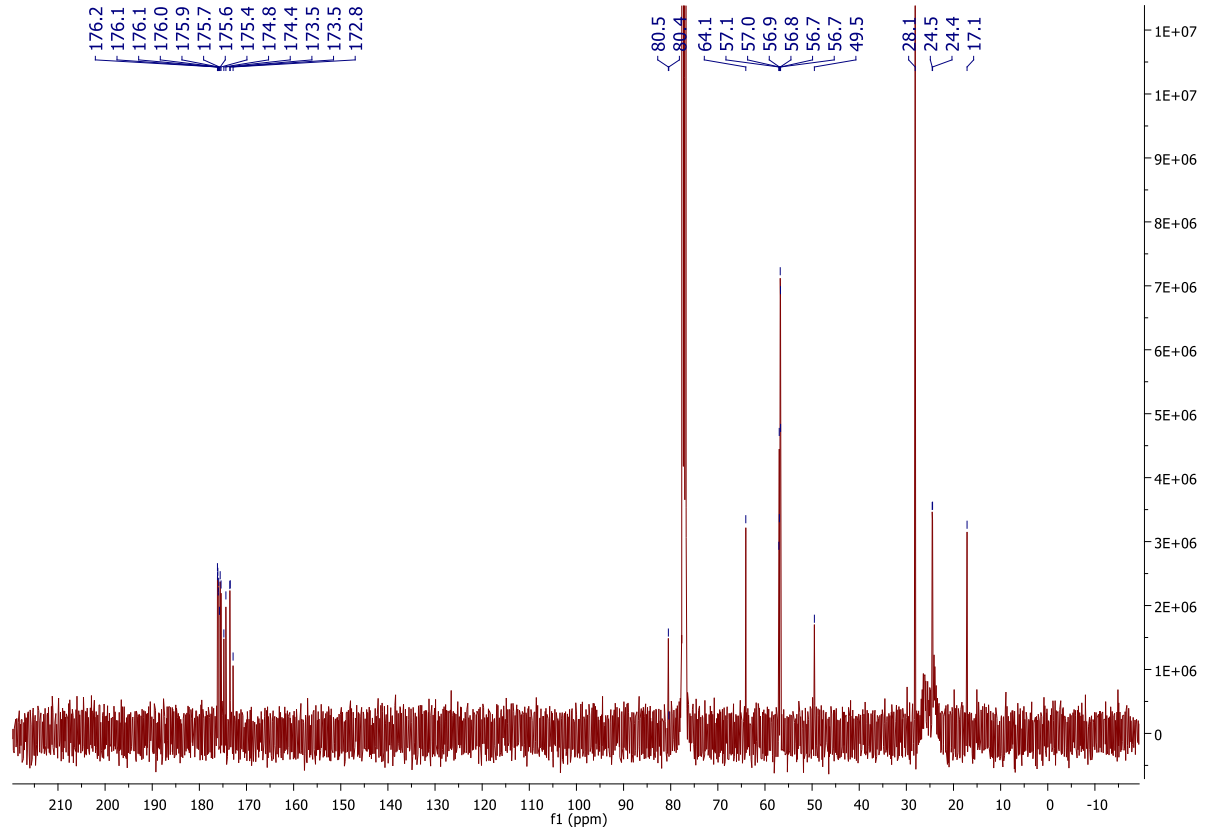
^{13}C NMR spectrum of **N_3Aib$_8$-(L)-AlaO*t*Bu** (100 MHz, $CDCl_3$):



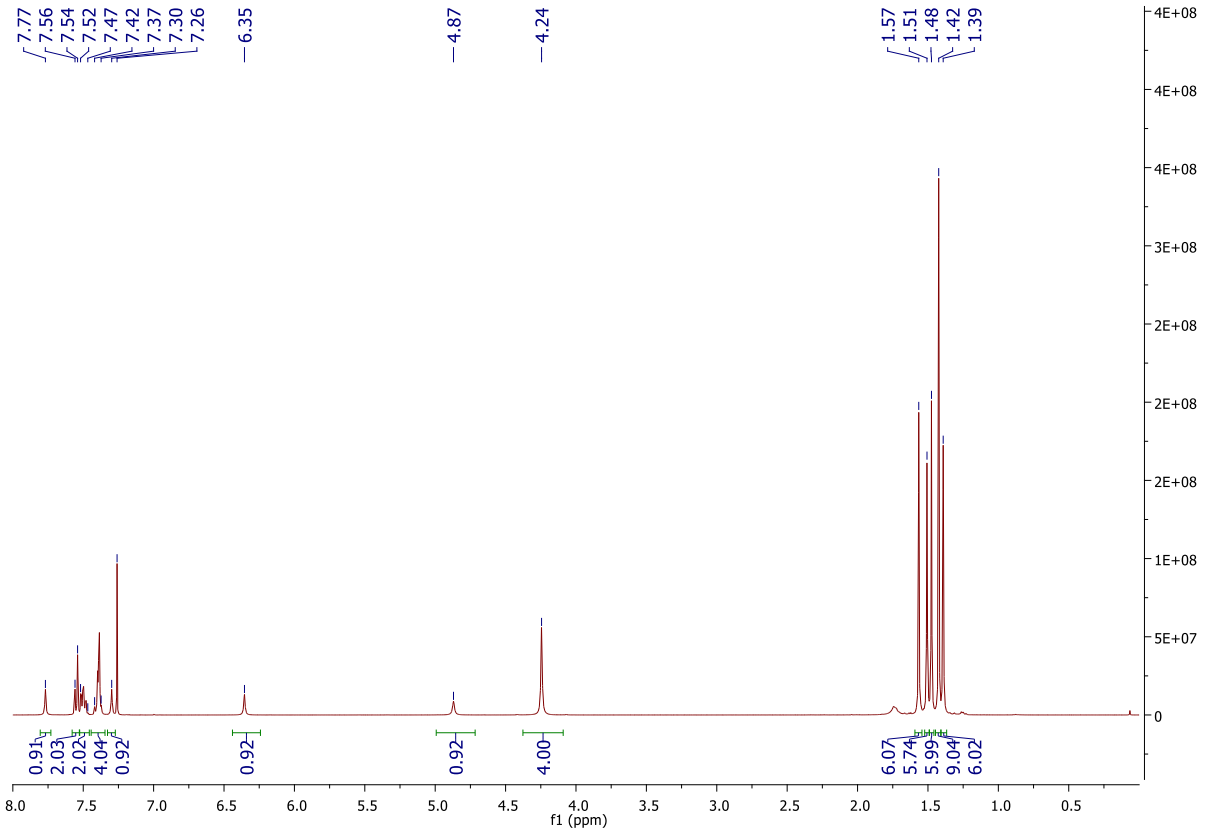
^{1}H NMR spectrum of **N_3Aib$_{12}$-(L)-AlaO*t*Bu** (400 MHz, $CDCl_3$):



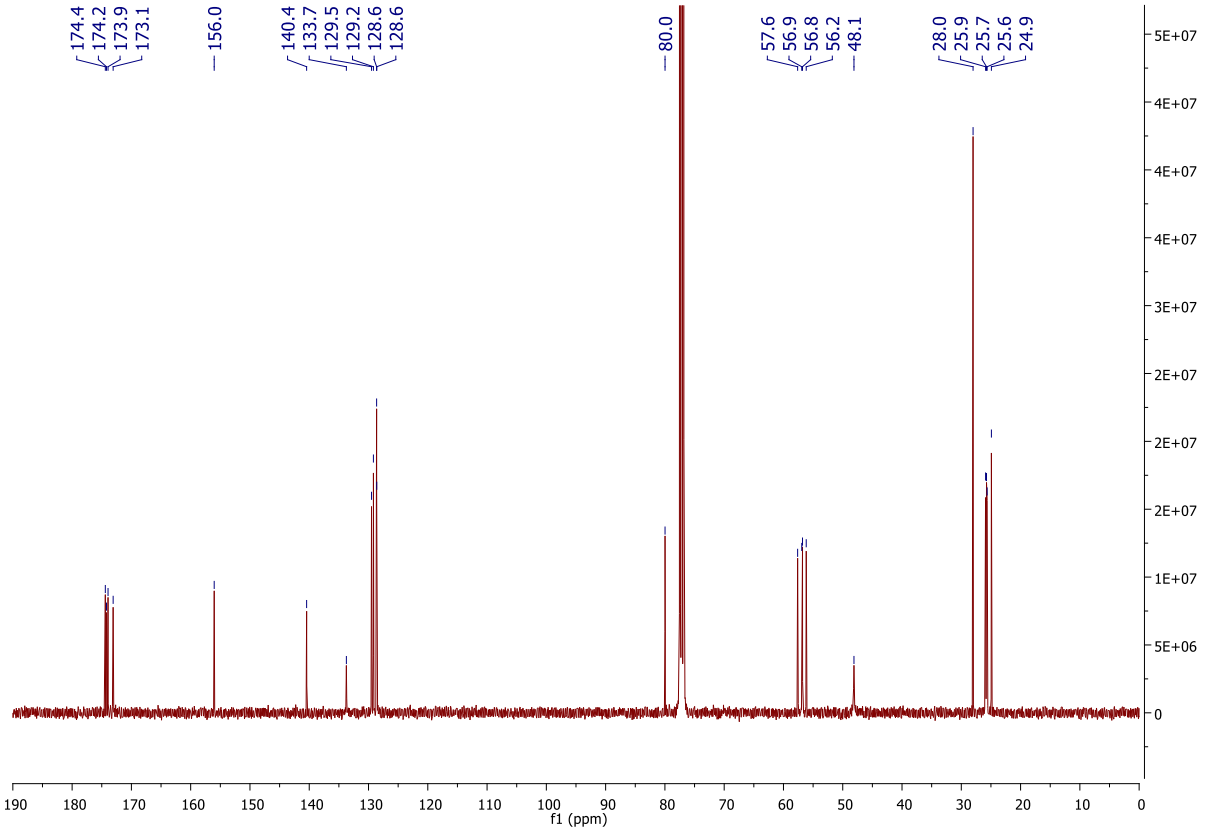
^{13}C NMR spectrum of **N_3Aib$_{12}$-(L)-AlaO*t*Bu** (100 MHz, $CDCl_3$):



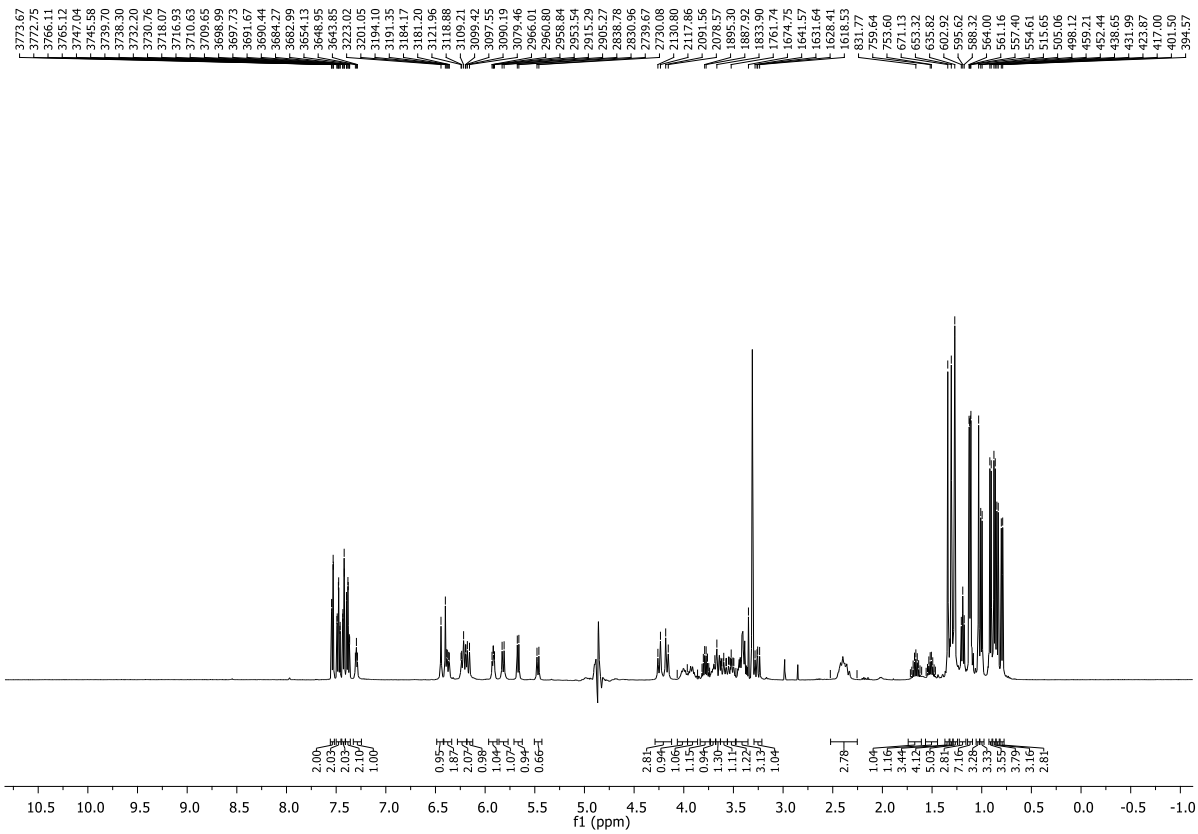
^{1}H NMR spectrum of **AzeAib$_4$O*t*Bu** (400 MHz, $CDCl_3$):



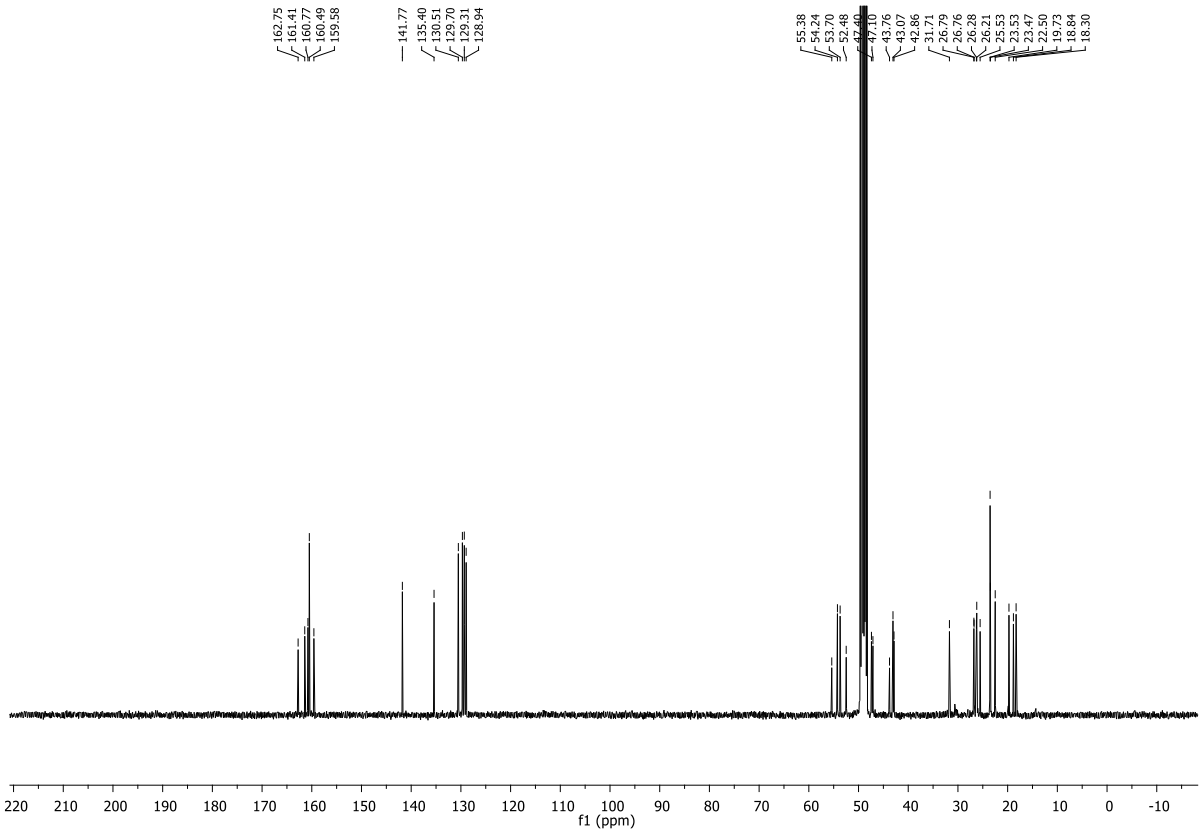
^{13}C NMR spectrum of **AzeAib$_4$O*t*Bu** (100 MHz, $CDCl_3$):



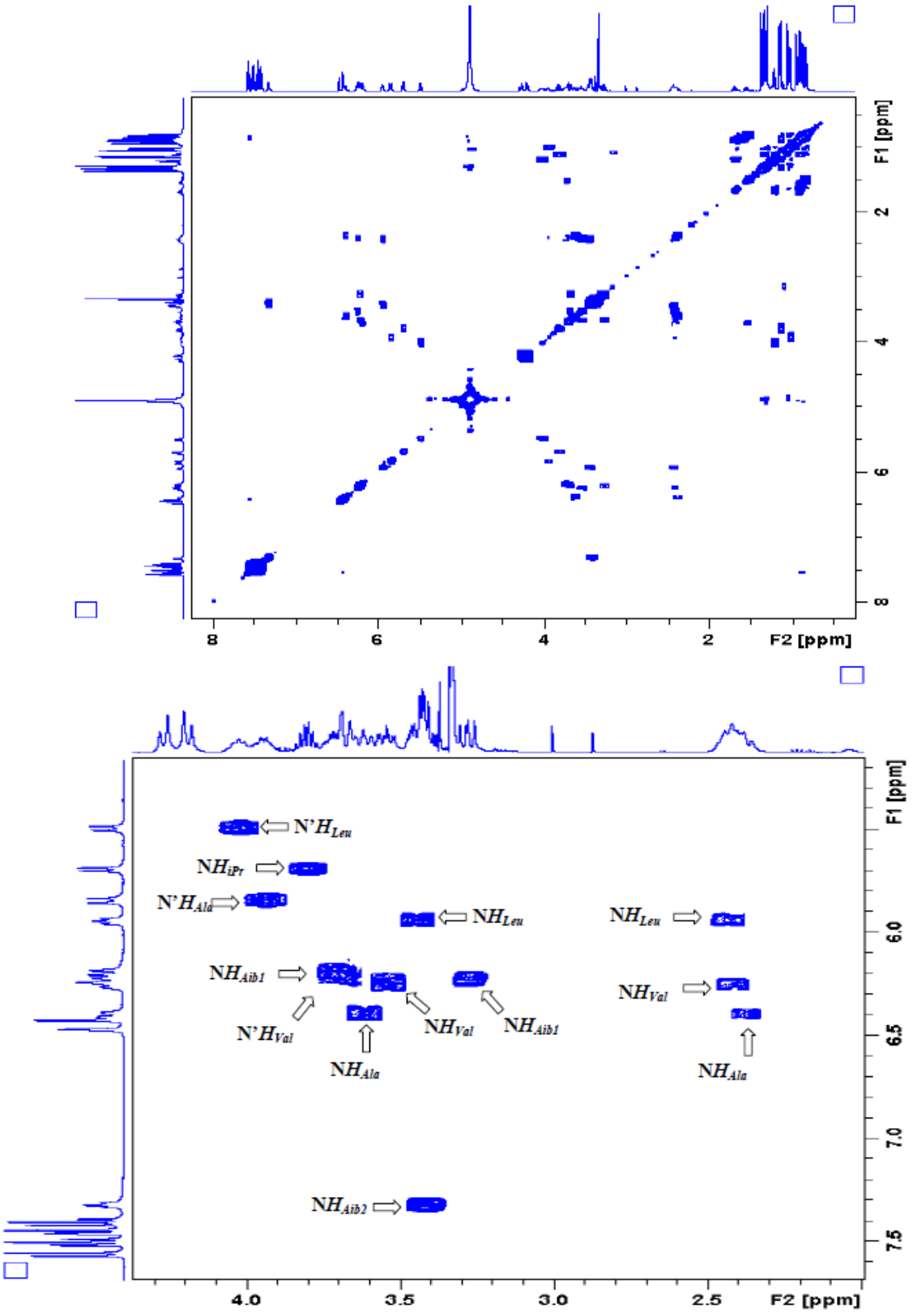
^{1}H NMR spectrum of **Aze-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (500 MHz, CD_3OH) :



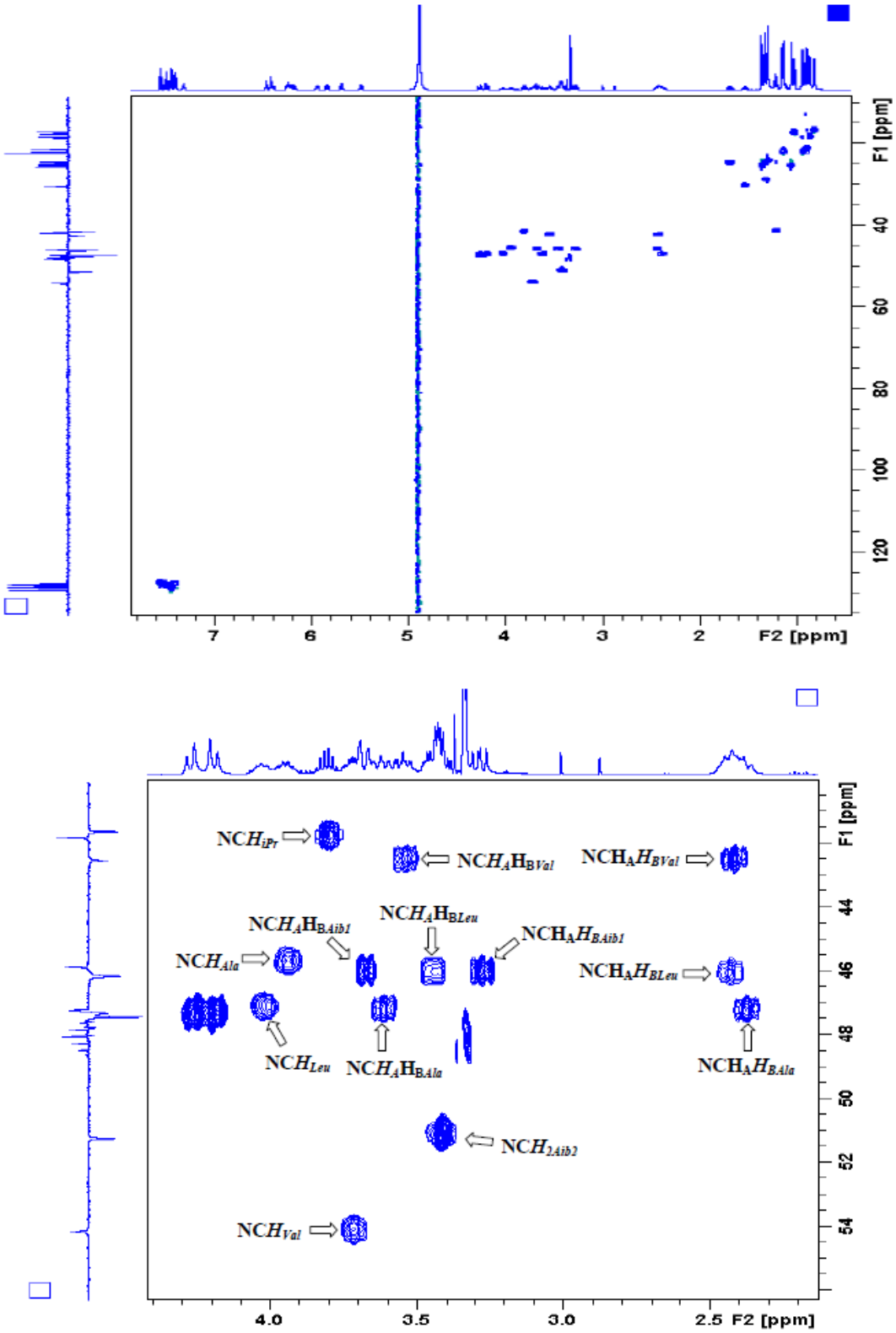
^{13}C NMR spectrum of **Aze-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (125 MHz, CD_3OH) :



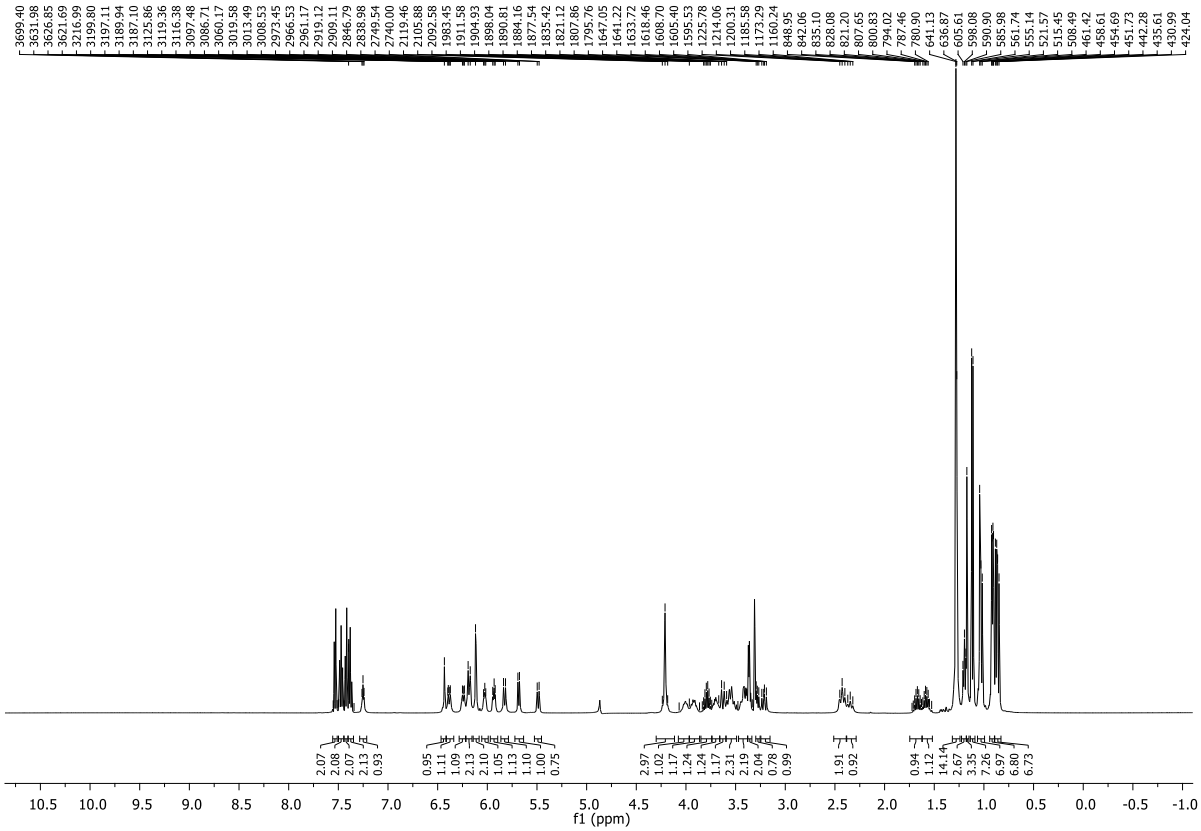
COSY spectrum of **Aze-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (500 MHz, CD_3OH):



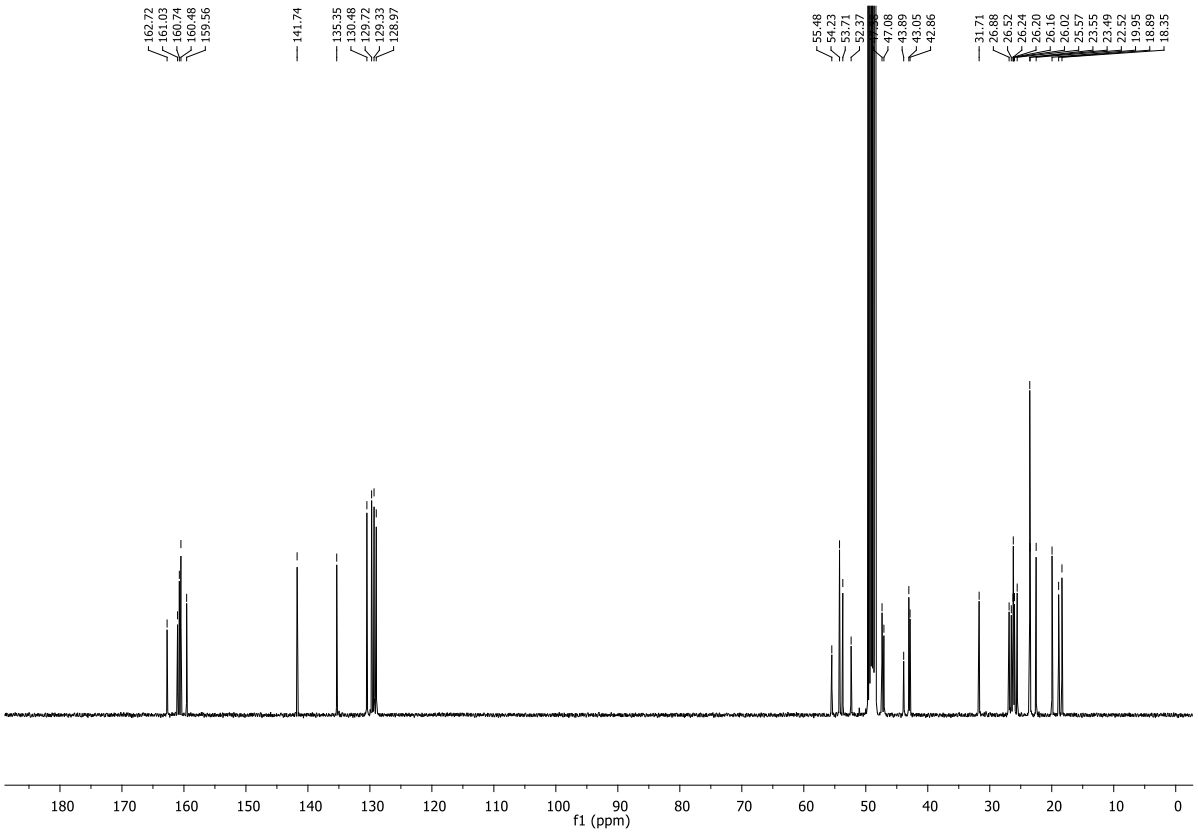
HSQC spectrum of **Aze-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (CD_3OH):



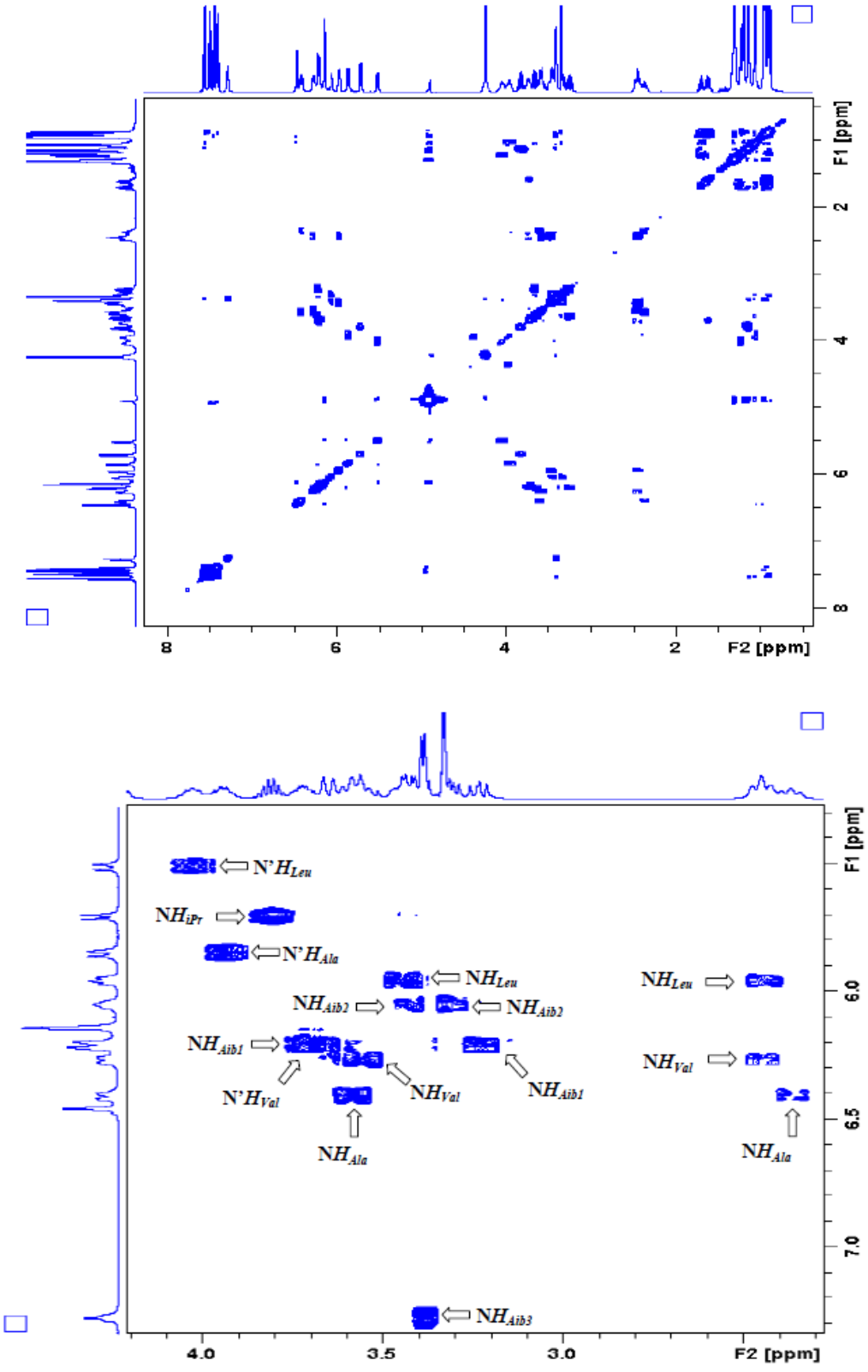
^{1}H NMR spectrum of **Aze-Aib^{u}-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (500 MHz, CD_3OH) :



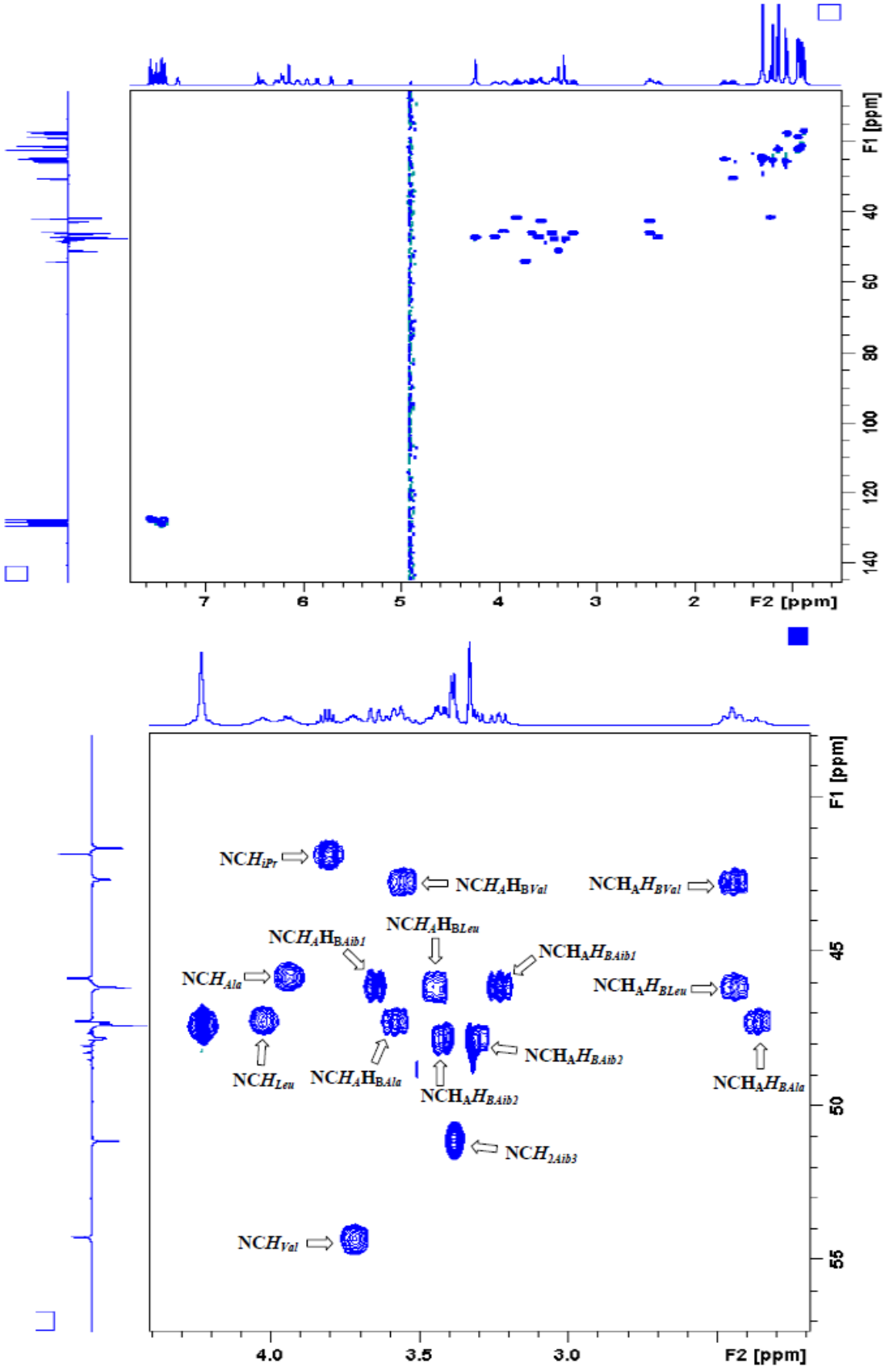
^{13}C NMR spectrum of **Aze-Aib^{u}-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (125 MHz, CD_3OH) :



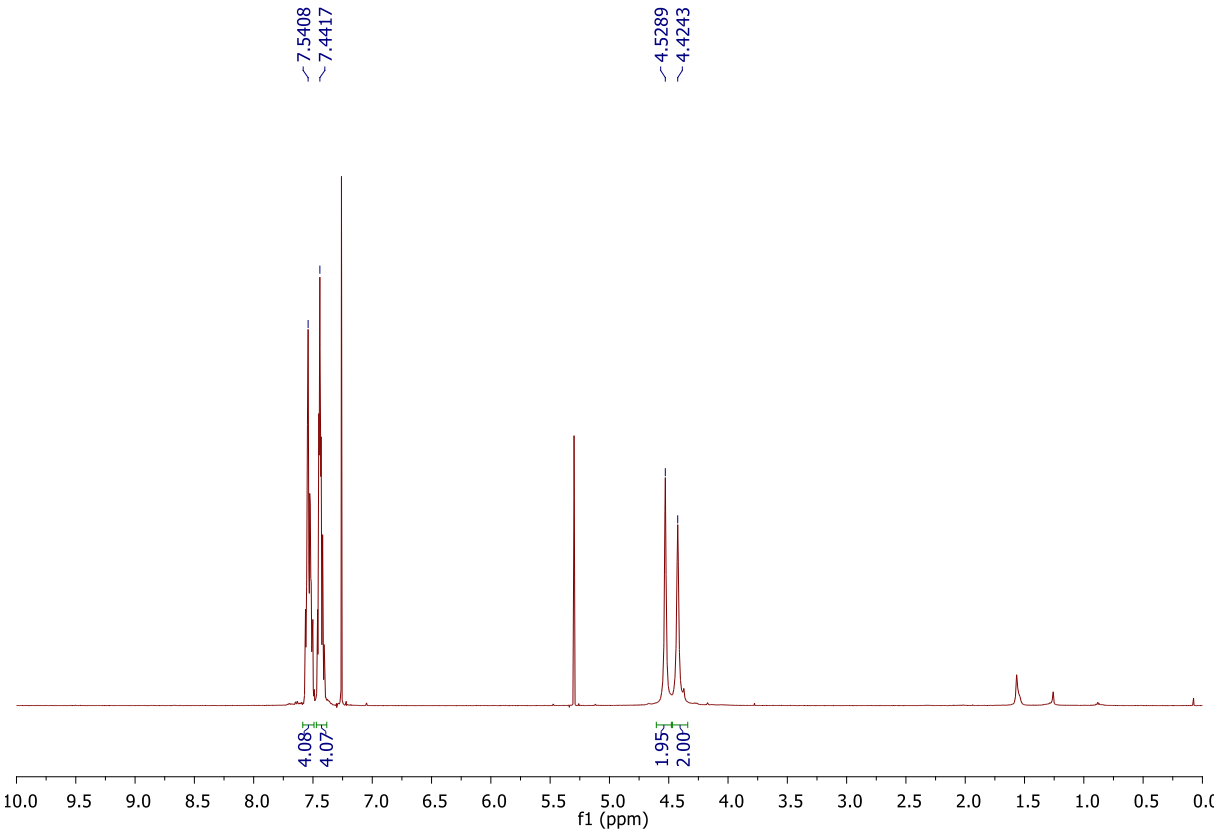
COSY spectrum of **Aze-Aib^{u}-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (500 MHz, CD_3OH):



HSQC spectrum of **Aze-Aib^{u}-Aib^{u}-Aib^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH*i*Pr** (CD_3OH):

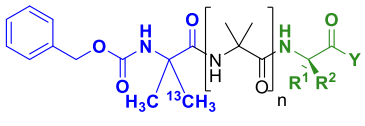


^{1}H NMR spectrum of **AzeCl** (500 MHz, $CDCl_3$):



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]



8a-j: CbzAib*-Aib$_4$-X$_{aa}$Y
X$_{aa}$ = Ala, Phe, tLeu, Val
Y = NH*t*Bu, O*t*Bu

a : n = 4 X$_{aa}$ = (L)-Ala Y = NH*t*Bu
b : n = 4 X$_{aa}$ = (L)-Phe Y = NH*t*Bu
c : n = 4 X$_{aa}$ = (L)-*t*Leu Y = NH*t*Bu
d : n = 4 X$_{aa}$ = (L)-Ala Y = O*t*Bu
e : n = 4 X$_{aa}$ = (D)-Ala Y = O*t*Bu
f : n = 4, X$_{aa}$ = (L)-Val Y = O*t*Bu
g : n = 4 X$_{aa}$ = (L)-Phe Y = O*t*Bu
h : n = 8 X$_{aa}$ = (L)-Ala Y = O*t*Bu
i : n = 11 X$_{aa}$ = (L)-Ala Y = O*t*Bu
j : n = 12 X$_{aa}$ = (L)-Ala Y = O*t*Bu

Figure S1: Peptides **8a-j**.

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:

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

where $\Delta\delta_{slow}$ and $\Delta\delta_{fast}$ 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:

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

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).

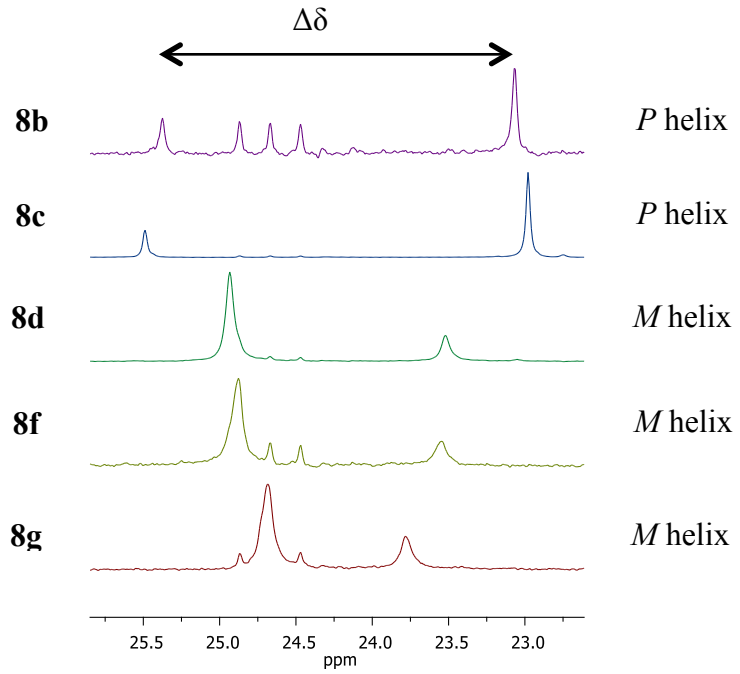


Figure S2: DEPT-135 spectra of peptides **8b-d** and **8f-g** in THF-8d, showing the anisochronicity Δδ of the ^{13}C-labelled probe.

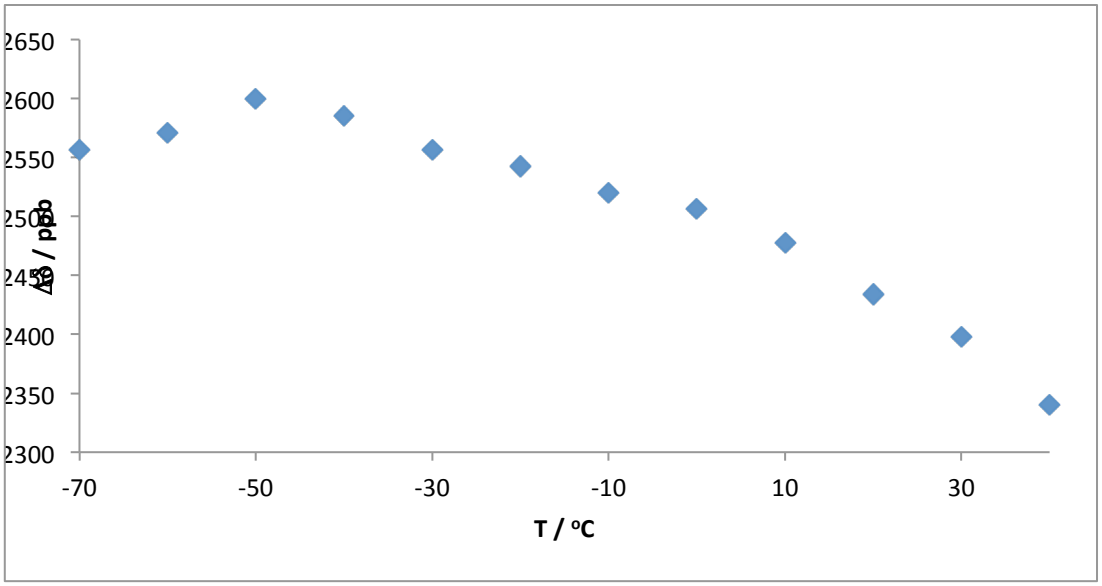


Figure S2: Variation of the ^{13}C-labelled probe anisochronicity Δδ measured in THF-8d with the temperature in the case of peptide **8a**.

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

						MeOH	**THF**		
Entry	peptide	R^1	R^2	Y	n	h.e. (%)	$\Delta\delta_{fast}$ (ppb)	$\Delta\delta_{slow}$ (ppb)	h.e. (%)
1	**8a**	Me	H	NH*t*Bu	4	75 (P)	2434	2557[a]	95 (P)
2	**8b**	CH_2Ph	H	NH*t*Bu	4	70 (P)	2308	/	90 (P)
3	**8c**	*t*Bu	H	NH*t*Bu	4	65 (P)	2510	/	98 (P)
4	**8d**	Me	H	O*t*Bu	4	55 (M)	1413	/	55 (M)
5	**8e**	H	Me	O*t*Bu	4	55 (P)	/	/	55 (P)
6	**8f**	*i*Pr	H	O*t*Bu	4	46 (M)	1332	/	52 (M)
7	**8g**	CH_2Ph	H	O*t*Bu	4	34 (M)	902	/	35 (M)
8	**8h**	Me	H	O*t*Bu	8	40 (M)	/	/	52 (M)
9	**8i**	Me	H	O*t*Bu	11	31 (M)	/	/	50 (M)
10	**8j**	Me	H	O*t*Bu	12	29 (M)	/	/	49 (M)

[a] $\Delta\delta_{slow}$ 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 Δδ of the methylene groups of the dibenzazepine probe and molar ellipticity $\theta_{250\,nm}$ measured in MeOH for peptides **2a-j** and **2x**.

Entry	Peptide	R^1	R^2	Y	n	Δδ (ppm)	θ at 250 nm ($deg.cm^2.dm^{-1}$)
1	**2a**	Me	H	NH*t*Bu	4	369	32400
2	**2b**	CH_2Ph	H	NH*t*Bu	4	323	27300
3	**2c**	*t*Bu	H	NH*t*Bu	4	326	28300
4	**2e**	H	Me	O*t*Bu	4	264	23500
5	**2d**	Me	H	O*t*Bu	4	264	-24500
6	**2f**	*i*Pr	H	O*t*Bu	4	229	-19400
7	**2g**	CH_2Ph	H	O*t*Bu	4	182	-16200
8	**2h**	Me	H	O*t*Bu	8	195	-17200
9	**2i**	Me	H	O*t*Bu	11	/	/
10	**2j**	Me	H	O*t*Bu	12	139	-12800
11	**2x**	/	/	O*t*Bu	4	0	300

[a] Data not available due to the low solubility of peptide **2i** in MeOH.

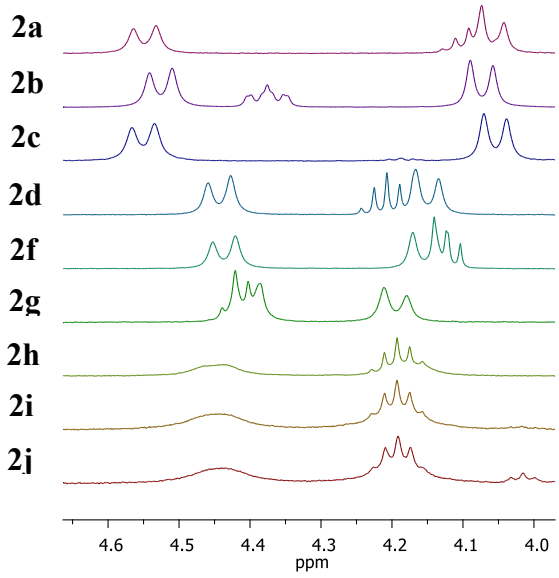


Figure S4: Portion of the ^1H NMR in THF-8d of **2a-d** and **2f-j**, showing the anisochronicity Δδ of the methylene proton of the dibenzazepine probe.

Table S3: Anisochronicity Δδ of the methylene groups of the dibenzazepine probe measured in THF for peptides **2a-d** and **2f-j**.

Entry	Peptide	R^1	R^2	Y	n	Δδ (ppm)
1	**2a**	Me	H	NH*t*Bu	4	491
2	**2b**	CH_2Ph	H	NH*t*Bu	4	451
3	**2c**	*t*Bu	H	NH*t*Bu	4	495
4	**2d**	Me	H	O*t*Bu	4	291
5	**2f**	*i*Pr	H	O*t*Bu	4	279
6	**2g**	CH_2Ph	H	O*t*Bu	4	206
7	**2h**	Me	H	O*t*Bu	8	270
8	**2i**	Me	H	O*t*Bu	11	264
9	**2j**	Me	H	O*t*Bu	12	261

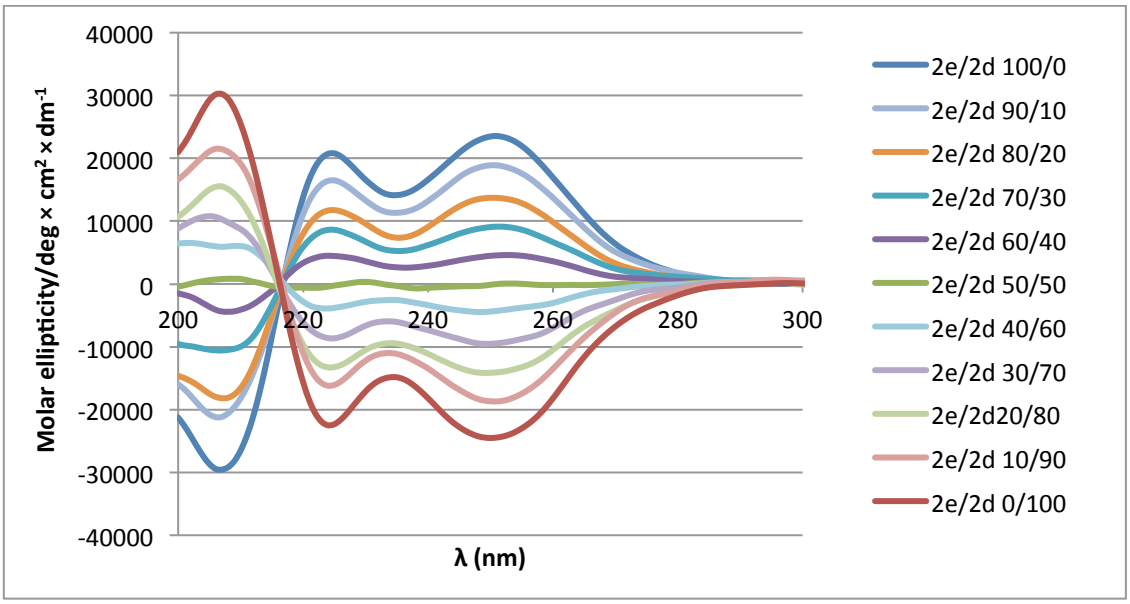


Figure S2: CD spectra obtained by mixing peptides **2d** and **2e** in various proportions in methanol.

Table S3: Anisochronicity Δδ of the methylene groups of the dibenzazepine probe and molar ellipticity $\theta_{250\ nm}$ measured in MeOH when peptides **2d** and **2e** are mixed in various proportions.

2e/**2d**	Δδ (ppm)	θ at 250 nm ($degcm^2dm^{-1}$)
100/0	264	23500
90/10	265	18900
80/20	265	13700
70/30	265	9100
60/40	265	4500
50/50	265	-100
40/60	/	-4400
30/70	/	-9500
20/80	265	-14100
10/90	/	-18700
0/100	264	-24500

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