Electronic Supplementary Material (ESI) for ChemComm.

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

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Supporting Information

Table of Contents

General Experimental and Materials

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen using standard anhydrous techniques. All reagents were obtained from commercially available sources and used without further purification, or where indicated prepared internally. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or stainless steel cannula. Reactions performed at 0 °C were done so using an ice bath; those performed at -78 °C were done so using an acetone/dry ice bath. Anhydrous dichloromethane was obtained by distillation from calcium hydride. Other anhydrous reaction solvents were obtained from standard anhydrous solvent engineering system. Triethylamine was stored over potassium hydroxide. All products were dried on a rotary evaporator followed by connection to a high vacuum system to remove any residual solvent. Flash chromatography was performed on silica gel (Merck 60H, 40-60 nm, 230 – 300 mesh). Analytical thin layer chromatography was performed on aluminium backed silica (60 F_{254}) plates.

Instrumentation

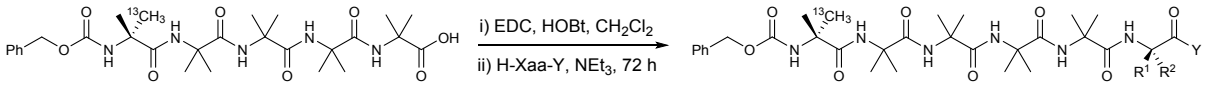
All ^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained using Bruker Ultrashield 300, 400 or 500 MHz spectrometers. Chemical shifts are quoted in parts per million (ppm) and coupling constants (*J*) are quoted in Hz, given to the nearest 0.5 Hz. ^{1}H-NMR were referenced to the residual deuterated solvent peak ($CDCl_3$ 7.27; CD_3OD 3.31 ppm) and ^{13}C-NMR were referenced to the carbon resonance of the solvent ($CDCl_3$ 77.0; CD_3OD 49.05 ppm. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet), spt (septet) and m (multiplet) or denoted as br (broad), or some combination of these, where appropriate. Where ^{1}H-NMR spectra were run in CD_3OD, D_2O 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) werenrecorded 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.

Methods for the synthesis of H-Aib_4O^tBu,[1] HBr.H-(*R*)-Aib*OH,[2] Z-αMvOH,[3] Z-αMvO^{t}Bu,[4] Z-AlaN$(CH_2)_4$[5] and H-TleO^{t}Bu[6] have been reported previously.

Synthetic Procedures

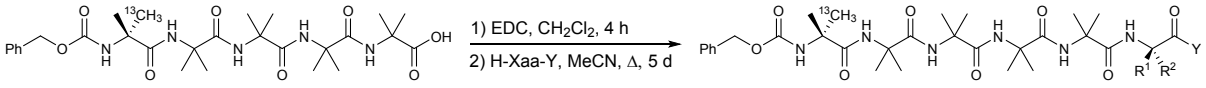
General Procedure A: Coupling of Cbz-Aib*-Aib$_4$-OH and H-Xaa-Y



(where R^1 = H, Y = O^{t}Bu or NH^{t}Bu)

Z-(*R*)-Aib*-Aib$_4$-OH (1 eq.) and 1-Hydroxybenzotriazole hydrate (1.3 eq.) were dissolved in CH_2Cl_2 (60 mL/mmol) and the suspension cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide (1.1 eq.) was added and the reaction was allowed to warm to room temperature and stirred until it was homogenous. The amino acid derivative "H-Xaa-Y" (prepared by the quantitative hydrogenolysis of Z-Xaa-Y)(2.5 eq.) and triethylamine (2 eq. if using the free amine, 3 eq. if using the HCl salt) were added and the reaction mixture stirred for 72 h. The solvent was removed *in vacuo* and EtOAc (400 mL/mmol) was added. The organic phase was washed with $KHSO_4$ (5%, 2 x 100 mL/mmol), $NaHCO_3$ (2 x 100 mL/mmol), brine (100 mL/mmol), dried ($MgSO_4$), filtered and concentrated. The pure peptide was isolated by column chromatography.

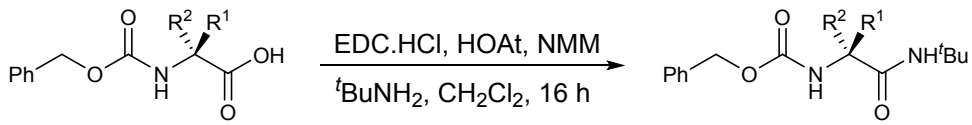
General Procedure B: Coupling of Cbz-Aib*-Aib$_4$-OH and H-Xaa-Y



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

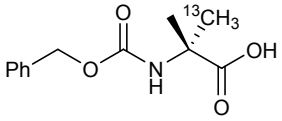
Z-(*R*)-Aib*-Aib$_4$-OH (1 eq.) was dissolved in CH_2Cl_2 (60 mL/mmol) and the suspension cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide (1.5 eq.) was added and the reaction was allowed to warm to room temperature and stirred for 4 h. The solvent was removed *in vacuo* and EtOAc (200 mL/mmol) was added. The organic phase was washed with $KHSO_4$ (2 x 75 mL/mmol), brine (75 mL/mmol), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude azlactone was then placed under high vacuum (<0.1 mbar) before being dissolved in MeCN (60 mL/mmol). The amino acid derivative "H-Xaa-Y" (1.5 eq.) was added and the reaction stirred at reflux for 5 d. After removing the solvent *in vacuo*, the pure peptide was isolated by column chromatography.

General Procedure C: Synthesis of Cbz-Xaa-NH^{t}Bu



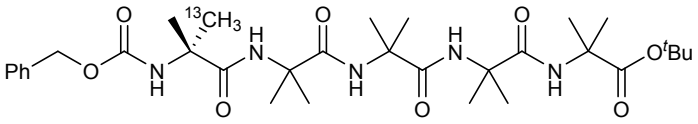
Z-Xaa-OH (1 eq.), ^{t}BuNH$_2$ (1.1 eq.) and 1-hydroxy-7-azabenzotriazole (1 eq.) were dissolved in CH_2Cl_2 (3 mL/mmol). 4-Methylmorpholine (3 eq.) and then *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1 eq.) were added and the reaction stirred for 16 h. EtOAC (7 mL/mmol) was then added and the organic phase washed with H_2O (2 x 3 mL/mmol), $NaHCO_3$ (sat., 2 x 3 mL/mmol), NH_4Cl (sat., 2 x 3 mL/mmol), dried (Na_2SO_4), filtered and concentrated. In all cases, the product was isolated as pure without further purification.

Z-(*R*)-Aib*-OH (*R*)-1



Benzyl chloroformate (0.64 mL, 4.47 mmol) was added to H-(*R*)-Aib*-OH (719 mg, 3.89 mmol) over 30 min in acetone/NaOH (2 M) (3.75 mL of each) at 0 °C. The pH was adjusted to 13 by the addition of NaOH (2 M) and the reaction stirred for 16 h at room temperature. A second portion of benzyl chloroformate (0.64 mL, 4.47 mmol) was added at 0 °C over 30 min and the reaction basified so that pH=13. After stirring for 6 h at room temperature, the acetone was removed *in vacuo* and the resulting mixture diluted with NaOH (2 M, 20 mL) then washed with Et_2O (2 x 20 mL). The aqueous phase was acidified so that pH=1 with HCl (conc.) and was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude reaction product was purified by column chromatography (1:1 PE:EtOAc) to give Cbz-(*R*)-Aib*-OH (751 mg, 81%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.30-7.40 (5H, m, ArCH x5), 5.35 (1H, br s, NH), 5.12 (2H, s, $PhCH_2$), 1.59 (3H, d, $^3J_{CH}$=4.5 Hz, CH_3), 1.59 (3H, d, $^1J_{CH}$=130.0 Hz, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 179.5 (CO), 155.3 (CO), 136.1 (ArC), 128.5 (ArCH), 128.1 (ArCH), 66.9 (CH_2), 56.3 (d, *J*=36.5, $^{\alpha}C$-*CH_3), 25.1 (*CH_3). IR (neat) ν_{max}/cm^{-1} = 3328, 3036, 2989, 2932, 1716, 1683. HRMS (ES$^-$, CH_2Cl_2) Calc. for $C_{11}{}^{13}CH_{14}NO_4$ ([M-H]$^+$) = 237.0961, found 237.0968. Mp 69-71 °C. The *e.r.* of the product was determined by integration of the ^{13}C-NMR spectrum of the crude mixture of Z-(*R*)-Aib*-PheOtBu diastereoisomers following coupling to H-PheO^{t}Bu.

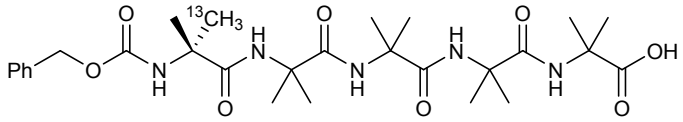
Z-(*R*)-Aib*-Aib$_4$-O^{t}Bu 2



Cbz-(*R*)-Aib*-OH (72 mg, 0.30 mmol) and pyridine (24 μL, 0.30 mmol) were dissolved in CH_2Cl_2 (3 mL) and fluoro-*N,N,N′,N′*-tetramethylformamidinium hexafluorophosphate (119 mg, 0.45 mmol) was added. The solution was stirred for 3 h, then diluted with CH_2Cl_2 (7 mL) and washed with ice-cold water (4 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of H-Aib$_4$-O^{t}Bu (149 mg, 0.36 mmol) and *N*,*N*-diisopropylethylamine (63 μL, 0.36 mmol) in CH_2Cl_2 (8 mL), a solution of the crude acid fluoride in CH_2Cl_2 (2 mL) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 6 d. The mixture was diluted with EtOAc (40 mL), washed with $KHSO_4$ (5%, 2 x 10 mL), $NaHCO_3$ (sat., 2 x 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give Cbz-(*R*)-Aib*-Aib$_4$-O^{t}Bu (139 mg, 73%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.39 (1H, br s, NH), 7.38 (1H, br s, NH), 7.36 (5H, m, ArCH x5), 7.32 (1H, br s, NH), 7.21 (1H, br s, NH), 6.33 (1H, br s, NH), 5.48 (1H, br s, NH), 5.12 (2H, s, CH_2O), 1.52 (6H, s, CH_3 x2), 1.47 (6H, s, CH_3 x2), 1.46 (3H, d, ^1J=129.0, *CH_3), 1.46 (3H, d, ^3J=4.5, *CH_3-C-CH_3), 1.44 (6H, s, CH_3 x2), 1.43 (9H, s, C(CH_3)$_3$), 1.32 (6H, s, CH_3 x2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 174.0 (CO), 173.8 (CO), 173.6 (CO), 173.50 (CO), 173.5 (CO), 155.7 (CO), 136.0 (ArC), 128.7 (ArCH), 128.7 (ArCH), 128.2 (ArCH), 79.7 (CMe_3), 67.5 (*C*H_2O), 57.5 ($^{\alpha}$C), 57.0 ($^{\alpha}$C), 56.9 ($^{\alpha}$C), 56.7 ($^{\alpha}$C), 56.3 (d, J_C = 40.0 Hz, $^{\alpha}C$-*CH_3), 27.9 (C(*C*H_3)$_3$), 25.5 (CH_3), 25.2 (CH_3), 25.1 (*CH_3), 24.8 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3338,

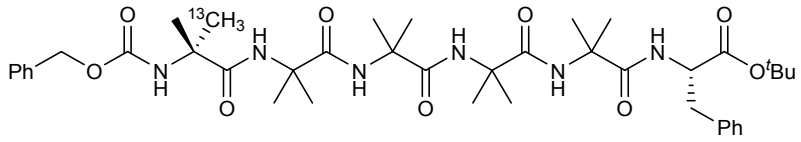
2982, 2925, 1731, 1702, 1699, 1682, 1649, 1530. HRMS (ES$^+$, CH_2Cl_2) Calc. for $C_{31}{}^{13}CH_{52}N_5O_8$ ([M+H]$^+$) = 635.3844, found 635.3846. Mp 246-248 °C.

Z-(*R*)-Aib*-Aib$_4$-OH



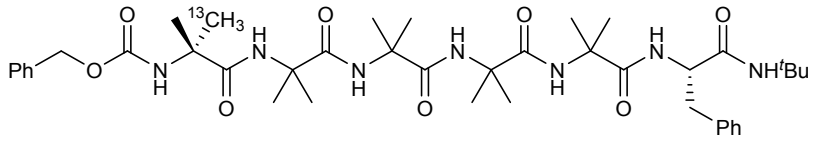
Z-(*R*)-Aib*-Aib$_4$-O^{t}Bu (870 mg, 1.37 mmol) was dissolved in CH_2Cl_2 (8 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (5 mL) was added dropwise and the resulting solution was allowed to warm to room temperature and stirred for 16 h. The solvents were removed *in vacuo* and Et_2O (3 x 10 mL) was added to help co-evaporate any traces of trifluoroacetic acid. The crude reaction product was purified by recrystallisation in MeCN to give Z-(*R*)-Aib*-Aib$_4$-OH (595 mg, 75%) as a white solid. ^{1}H-NMR (400 MHz, CD_3OD) δ_H 8.02 (1H, br s, NH), 7.75 (1H, br s, NH), 7.72 (1H, br s, NH), 7.65 (1H, br s, NH), 7.29-7.41 (5H, m, ArCH x5), 5.13 (2H, s, CH_2O), 4.62 (1H, br s, NH), 1.50 (6H, s, CH_3 x2), 1.46 (6H, s, CH_3 x2), 1.40 (3H, d, ^1J=128.5, CH_3*), 1.40 (3H, d, ^3J=4.5, *CH_3-C-*C*H_3), 1.35 (6H, s, CH_3 x2), 1.32 (6H, s, CH_3 x2). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 178.5 (CO), 177.2 (CO), 177.0 (CO), 177.0 (CO), 176.9 (CO), 158.1 (CO), 138.9 (ArC), 129.7 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 67.8 (CH_2), 58.0 ($^\alpha$C), 57.9 ($^\alpha$C), 57.8 (d, J_C=37.5, $^\alpha$*C*-*CH_3), 57.7 ($^\alpha$C), 57.2 ($^\alpha$C), 25.8 (CH_3), 25.7 (CH_3), 25.5 (CH_3), 25.3 (*CH_3). IR (neat) ν_{max}/cm^{-1} = 3299, 2983. 2467, 1745, 1695, 1647, 1531. HRMS (ES$^+$, MeOH) Calc. for $C_{27}{}^{13}CH_{44}N_5O_8$ ([M+H]$^+$) = 279.3218, found 579.3215. Mp 264-268 °C.

Z-(*R*)-Aib*-Aib$_4$-PheO^{t}Bu 3-PheO^{t}Bu



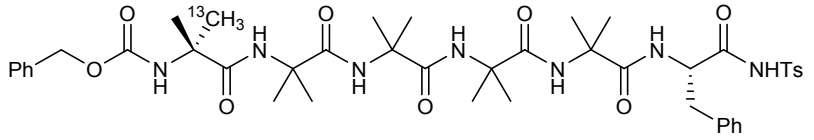
Z-(*R*)-Aib*-Aib$_4$-PheO^{t}Bu was prepared according to general procedure A (0.17 mmol scale). The pure peptide (126 mg, 93%) was isolated as a white solid by column chromatography (2-5% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, CD_3OD) δ_H 7.91 (1H, br s, NH), 7.85 (1H, br s, NH), 7.83 (1H, br s, NH), 7.73 (1H, br s, NH), 7.30 (10H, m, ArCH x10), 5.17 (1H, d, *J*=12.5, H^A of AB system, CH_2OCO), 5.10 (1H, d, *J*=12.5, H^B of AB system, CH_2OCO), 4.44 (1H, q, *J*=7.5, $^\alpha$CH), 3.15 (1H, dd, *J*=14.0, 7.5, CH_2, H^A of ABX system, CH_2Ph), 3.09 (1H, dd, *J*=14.0, 7.5, H^B of ABX system, CH_2Ph), 1.49 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.42 (2.3H, d, ^3J=4.0, CH_3 major), 1.42 (0.7H, d, ^1J=129.0, *CH_3 minor), 1.40 (0.7H, d, ^3J=4.0, CH_3 minor), 1.40 (2.3H, d, ^1J=129.0, *CH_3 major), 1.38 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.35 (9H, s, C(CH_3)$_3$) 1.30 (3H, s, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 177.6 (CO), 177.6 (CO), 177.3 (CO), 176.9 (CO), 176.9 (CO), 172.4 (CO), 158.1 (CO), 139.0 (ArC), 138.9 (ArC), 130.7 (ArCH), 129.8 (ArCH), 129.4 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 127.7 (ArCH), 82.6 (CMe_3), 67.8 (*C*H_2OCO), 58.2 ($^\alpha$C), 58.1 ($^\alpha$C), 57.9 ($^\alpha$C), 57.8 (d, J_C = 39.0, $^\alpha$*C*-*CH_3), 57.7 ($^\alpha$C), 56.9 ($^\alpha$CH), 38.6 (CH_2Ph), 28.3 (C(*C*H_3)$_3$), 26.1 (CH_3), 25.9 (CH_3), 25.8 (*CH_3 major and CH_3 x2), 25.6 (CH_3), 25.6 (CH_3), 25.0 (CH_3), 25.0 (*CH_3 minor and CH_3). IR (neat) ν_{max}/cm^{-1} = 3310, 2983, 2934, 1703, 1660, 1530. HRMS (ES$^+$, MeOH) Calc. for $C_{40}{}^{13}CH_{6o}N_6NaO_9$ ([M+Na]$^+$) = 804.4348, found 804.4340. Mp 96-100 °C. $[\alpha]_D^{20}$ = −6.8 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-PheNH^{t}Bu 3-PheNH^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-PheNH^{t}Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (33 mg, 82%) was isolated as a white solid by column chromatography (1-2% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.06 (1H, br s, NH), 7.91 (1H, br s, NH), 7.75 (1H, br s, NH), 7.73 (1H, br s, NH), 7.71 (1H, br d, *J*=8.0, NH), 7.36 (7H, m, ArCH x7), 7.27 (1H, br s, NH), 7.18 (3H, m, ArCH x3), 5.21 (1H, d, *J*=12.5, CH_2-OCO, H^A of AB system), 5.06 (1H, d, *J*=12.5, CH_2-OCO, H^B of AB system), 4.38 (1H, ddd, *J*=11.5, 8.5, 3.0, $^\alpha$CH), 3.41 (1H, dd, *J*=14.5, 3.0, CH_2-Ph, H^A of ABX system), 2.92 (1H, dd, *J*=14.0, 11.5, CH_2-Ph, H^B of ABX system), 1.46 (6H, s, CH_3 x2), 1.44 (0.7H, d, *J*=4.5, CH_3 minor), 1.44 (2.3H, d, *J*=128.5, *CH_3 major), 1.40 (12H, m, CH_3 and C(CH_3)$_3$), 1.39 (0.7H, d, *J*=129.0, *CH_3 minor), 1.39 (2.3H, m, CH_3 major), 1.39 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.17 (3H, s, CH_3). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 177.9 (CO), 177.7 (CO), 177.3 (CO), 177.3 (CO), 176.9 (CO), 173.2 (CO), 158.0 (CO), 139.8 (ArC), 138.8 (ArC), 130.2 (ArCH), 129.6 (ArCH), 129.3 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 127.5 (ArCH), 67.7 (*C*H_2OCO), 58.0 ($^\alpha$C), 57.9 ($^\alpha$C), 57.9 ($^\alpha$C), 57.6 ($^\alpha$C), 57.6 (d, J_C=39.0, $^\alpha$*C*-*CH_3), 57.5 ($^\alpha$C), 52.6 (CMe_3), 38.1 (CH_2Ph), 29.0 (C(*C*H_3)$_3$), 27.4 (CH_3), 27.2 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 26.6 (CH_3), 26.1 (*CH_3 minor), 24.4 (*CH_3 major and CH_3), 24.2 (CH_3), 23.7 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3308, 2925, 1656, 1533, 1454. HRMS (ES$^+$, MeOH) Calc. for $C_{40}{}^{13}CH_{62}N_7O_8$ ([M+H]$^+$) 781.4688, found 781.4673. Mp 120-122 °C. $[\alpha]_D^{20}$ = 7.2 (*c* 0.5, CH_2Cl_2).

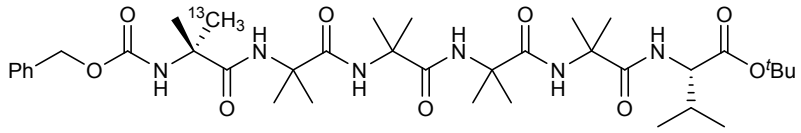
Z-(*R*)-Aib*-Aib$_4$-PheNHTs 3-PheNHTs



Z-(*R*)-Aib*-Aib$_4$-PheNHTs was prepared according to general procedure A (0.052 mmol scale), except DMF (1 mL) was added to solubilise the amine. The pure peptide (35 mg, 77%) was isolated as a white solid by column chromatography (0.25-5% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.56 (1H, br s, NHTs), 8.01 (2H, d, *J*=8.5, ArCH x2), 7.78 (2H, br m, NH x2), 7.72 (1H, br s, NH), 7.49 (1H, br s, NH), 7.35 (5H, m, ArCH x5), 7.30 (2H, d, *J*=8.5, ArCH x2), 7.09 – 7.24 (5H, m, ArCH x5), 6.64 (1H, br s, NH), 5.82 (1H, br s, NH), 5.20 (1H, d, *J*=12.5, CH_2O, H^A of AB system), 5.03 (1H, d, *J*=12.5, CH_2O, H^B of AB system), 4.56 (1H, m, $^\alpha$CH), 3.44 (1H, d, *J*=14.0, CH_2), 2.97 (1H, dd, *J*=13.5, 13.5, CH_2), 2.42 (3H, s, CH_3-Ar), 1.63 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.49 (0.8H, d, *J*= 3.5, CH_3 minor), 1.49 (2.2H, d, *J*=129.0, *CH_3 major), 1.46 (3H, s, CH_3), 1.43 (2.2H, d, *J*=4.0, CH_3 major), 1.43 (0.8H, d, *J*=130.0, *CH_3 minor), 1.41 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.19 (3H, s, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 176.5 (CO), 175.6 (CO), 175.3 (CO), 174.4 (CO), 174.1 (CO), 171.6 (CO), 156.0 (CO), 144.2 (ArC), 137.9 (ArC), 136.5 (ArC), 129.3 (ArCH), 129.1 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.5 (ArC), 128.1 (ArCH), 127.9 (ArCH), 127.9 (ArCH), 126.3 (ArCH), 67.3 (CH_2O), 56.9 ($^\alpha$C), 56.9 ($^\alpha$C), 56.7 ($^\alpha$C), 56.5 (d, J_C=38.0, $^\alpha$*C*-*CH_3), 56.4 ($^\alpha$C), 55.6 ($^\alpha$CH), 36.4 (CH_2), 26.4 (*CH_3 minor), 25.9 – 26.9 (CH_3 x4), 23.6 (*CH_3 major), 22.8 – 24.3 (CH_3 x4), 21.6 (CH_3-Ar). IR (neat) ν_{max}/cm^{-1} = 3299,

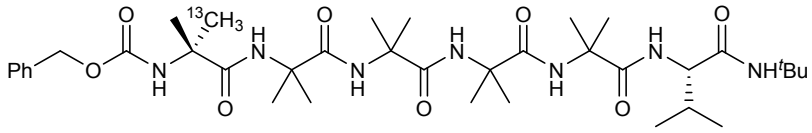
2985, 1701, 1651, 1526. HRMS (ES$^+$, MeOH) Calc. for $C_{43}{}^{13}CH_{59}N_7O_{10}SNa$ ([M+Na]$^+$) 901.3975, found 901.3981. Mp 135-137 $[\alpha]_D^{20}$ = 20.0 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-ValO^{t}Bu 3-ValO^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-ValO^{t}Bu was prepared according to general procedure A (0.104 mmol scale). The pure peptide (69 mg, 91%) was isolated as a white solid by column chromatography (2-5% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 7.85 (1H, br s, NH), 7.79 (1H, b s, NH), 7.58 (1H, br s, NH), 7.34 (5H, m, ArCH x5), 5.18 (1H, d, *J*=12.5, CH_2, H^A of AB system), 5.09 (1H, d, *J*=13.0, CH_2, H^B of AB system), 4.03 (1H, d, *J*=7.0, $^\alpha$CH), 2.23 (1H, dq, *J*=7.0, 7.0, C*H*$(CH_3)_2$), 1.50 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.45 (12H, s, CH_3 and $C(CH_3)_3$), 1.45 (3H, s, CH_3), 1.42 (2.3H, d, *J*=4.5, CH_3 major), 1.42 (0.7H, d, *J*=129.0, *CH_3 minor), 1.40 (3H, s, CH_3), 1.40 (0.7H, m, CH_3 minor), 1.40 (2.3H, d, *J*=129.0, *CH_3 major), 1.36 (6H, s, CH_3 x2), 1.28 (3H, s, CH_3), 1.04 (3H, d, *J*=7.0, C*H*$_3$-CH), 1.00 (3H, d, *J*=6.5, C*H*$_3$-CH). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 177.7 (CO), 177.3 (CO), 177.2 (CO), 176.9 (CO), 176.7 (CO), 172.4 (CO), 158.1 (CO), 138.9 (ArC), 129.7 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 82.4 (CMe_3), 67.8 (CH_2), 61.3 ($^\alpha$CH), 58.1 ($^\alpha$C), 58.0 ($^\alpha$C), 57.9 ($^\alpha$C), 57.8 (d, J_C=36.5, $^\alpha$*C*-*CH_3), 57.7 ($^\alpha$C), 31.4 (CH), 28.5 ($C(CH_3)_3$), 27.4 (CH_3), 26.9 (CH_3), 26.4 (CH_3), 26.2 (CH_3), 25.9 (*CH_3 major and CH_3), 25.4 (*CH_3 minor and CH_3), 24.8 (CH_3), 24.4 (CH_3), 19.8 (*C*H$_3$-CH), 19.5 (*C*H$_3$-CH). IR (neat) ν_{max}/cm^{-1} = 3309, 2982, 2935, 2476, 1702, 1650, 1527, 1469, 1455, 1417. HRMS (ES$^+$, MeOH) Calc. for $C_{36}{}^{13}CH_{60}N_6O_9Na$ ([M+Na]$^+$) 756.4353, found 756.4327. Mp 200-204 °C. $[\alpha]_D^{20}$ = −22.4 (*c* 1, CH_2Cl_2).

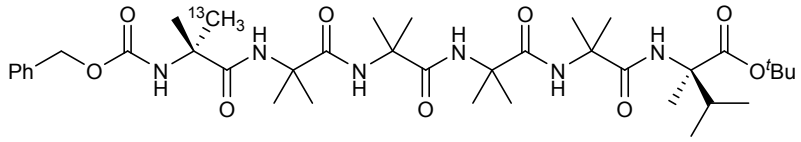
Z-(*R*)-Aib*-Aib$_4$-ValNH^{t}Bu 3-ValNH^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-ValNH^{t}Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (31 mg, 81%) was isolated as a white solid by column chromatography (2-5% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.07 (1H, br s, NH), 7.9 (1H, br s, NH), 7.82 (1H, br s, NH), 7.75 (1H, br s, NH), 7.55 (1H, br s, NH), 7.28 – 7.42 (5H, m, ArCH x5), 7.09 (1H, br s, NH), 5.21 (1H, d, *J*=13.0, CH_2, H^A of AB system), 5.06 (1H, d, *J*=13.0, CH_2, H^B of AB system), 3.99 (1H, d, *J*=6.0, $^\alpha$CH), 2.33(1H, dq, *J*=6.5, 6.5 C*H*$(CH_3)_2$), 1.49 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.43 (2.2H, d, *J*=128.5, *CH_3 major), 1.43 (0. 8H, m, CH_3 minor), 1.40 (2.2H, m, CH_3 major), 1.40 (0.8H, d, *J*=128.5, *CH_3 minor), 1.39 (3H, s, CH_3), 1.37 (12H, s, CH_3 and $(C(CH_3)_3$), 1.36 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.04 (3H, d, *J*=7.0, C*H*$_3$-CH), 0.98 (3H, d, *J*=7.0, C*H*$_3$-CH). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 178.1 (CO), 177.4 (CO), 177.3 (CO), 177.2 (CO), 177.0 (CO), 173.5 (CO), 158.1 (CO), 138.9 (ArC), 129.8 (ArCH), 129.2 (ArCH), 128.7 (ArCH), 67.8 (CH_2), 62.0 ($^\alpha$CH), 58.1 ($^\alpha$C), 57.9 ($^\alpha$C), 57.9 ($^\alpha$C), 57.8 ($^\alpha$C), 57.7 (d, *J*=36.5, $^\alpha$*C*-*CH_3), 52.6 (CMe_3), 31.0 (CH), 29.2 ($C(CH_3)_3$), 28.0 (CH_3), 27.2 (CH_3), 27.0 (CH_3), 26.7 (CH_3), 26.2 (*CH_3 minor), 24.8 (CH_3), 24.5 (*CH_3 major), 24.3 (CH_3), 24.2 (CH_3), 23.8 (CH_3), 19.9 (*C*H$_3$-CH), 18.5 (*C*H$_3$-CH). IR (neat) ν_{max}/cm^{-1} = 3309, 2981, 2474, 1699, 1646, 1526, 1471, 1417.

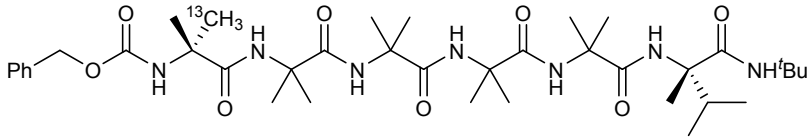
HRMS (ES$^+$, MeOH) Calc. for $C_{36}{}^{13}CH_{62}N_7O_8$ ([M+H]$^+$) 733.4688, found 733.4680. Mp 96-98 °C. $[\alpha]_D^{20}$ = 18.8 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-αMvO^{t}Bu 3-αMvO^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-αMvO^{t}Bu was prepared according to general procedure B (0.052 mmol scale). The pure peptide (13 mg, 33%) was isolated as a white solid by column chromatography (0.5-5% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.44 (1H, br s, NH), 7.35 (6H, m, ArCH x5 and NH), 7.18 (1H, br s, NH), 6.37 (1H, br s, NH), 5.76 (1H, br s, NH), 5.73 (1H, br s, NH), 5.15 (1H, d, *J*=12.0, CH_2, H^A of AB system), 5.08 (1H, d, *J*=12.0, CH_2, H^B of AB system), 2.24 (1H, dq, *J*=6.5, 6.5, CH), 1.51 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.48 (0.7H, d, *J*=129.0, *CH_3 minor), 1.48 (2.3H, m, CH_3 major), 1.46 (3H, s, CH_3), 1.46 (2.3H, d, *J*=129.5, *CH_3 major), 1.46 (0.7H, m, CH_3 minor), 1.45 (12H, m, $C(CH_3)_3$ and CH_3), 1.43 (6H, s, CH_3 x2), 1.35 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.01 (3H, d, *J*=7.0, C*H*$_3$-CH), 0.98 (3H, d, *J*=7.0, C*H*$_3$-CH). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 174.5 (CO), 174.1 (CO), 174.0 (CO), 173.8 (CO), 173.7 (CO), 172.3 (CO), 155.9 (CO), 136.1 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.2 (ArCH), 79.9 (CMe_3), 67.4 (CH_2), 62.3 ($^\alpha$C), 57.2 (d, *J* = 37.0, $^\alpha$C-*CH_3), 56.7 ($^\alpha$C), 56.6 ($^\alpha$C), 56.6 ($^\alpha$C), 56.4 ($^\alpha$C), 34.8 (CH), 28.0 ($C(CH_3)_3$), 25.6 (*CH_3 major), 24.5 (*CH_3 minor), 24.2 – 25.9 (all other CH_3), 18.5 (CH_3), 17.9 (*C*H_3-CH), 17.6 (*C*H_3-CH). IR (neat) ν_{max}/cm^{-1} = 3319, 2981, 2934, 2481, 1703, 1651, 1523. HRMS (ES$^+$, MeOH) Calc. for $C_{37}{}^{13}CH_{63}N_6O_9$ ([M+H]$^+$) = 748.4690, found 748.4701. Mp 125-127. $[\alpha]_D^{20}$ = −16.8 (*c* 0.5, CH_2Cl_2).

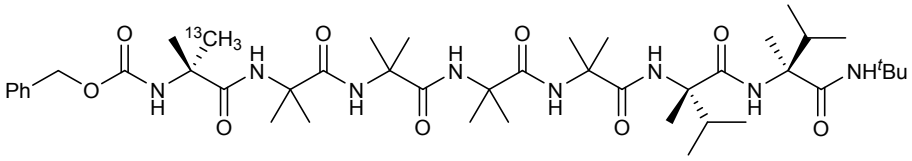
Z-(*R*)-Aib*-Aib$_4$-αMvNH^{t}Bu 3-αMvNH^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-αMvNH^{t}Bu was prepared according to general procedure B (0.052 mmol scale). The pure peptide (21 mg, 54%) was isolated as a white solid by column chromatography (1% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 7.82 (1H, br s, NH), 7.82 (1H, br s, NH), 7.30-7.41 (5H, m, ArCH x5), 7.28 (1H, br s, NH), 7.03 (1H, br s, NH), 5.20 (1H, d *J*=13.0, CH_2, H^A of AB system), 5.06 (1H, d *J*=13.0, CH_2, H^B of AB system), 2.09 (1H, dq, *J*=6.5, 6.5, CH), 1.45 (3H, s, CH_3), 1.43 (2.3H, d, ^{1}*J*=129.0, *CH_3 major), 1.43 (0.7H, m, CH_3 minor), 1.39 (0.7H, d, ^{1}*J*=128.5, *CH_3 minor), 1.39 (2.3H, m, CH_3 major), 1.42 (3H, s, CH_3), 1.38 (9H, m, CH_3 x3), 1.38 (9H, s, $C(CH_3)_3$), 1.35 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.03 (3H, d, *J*=6.5, CH_3-CH), 0.94 (3H, d, *J*=6.5, CH_3-CH). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 177.3 (CO), 177.1 (CO), 177.0 (CO), 176.8 (CO), 175.9 (CO), 158.1 (CO), 138.9 (ArC), 129.8 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 67.8 (CH_2), 64.6 (CMe_3), 58.1 ($^\alpha$C), 58.0 ($^\alpha$C), 57.9 ($^\alpha$C), 57.8 ($^\alpha$C -*CH_3), 57.7 ($^\alpha$C), 52.4 ($^\alpha$C), 37.2 (CH), 29.2 ($C(CH_3)_3$), 27.8 (CH_3), 27.3 (CH_3), 27.0 (CH_3), 26.7 (CH_3), 26.2 (*CH_3 minor), 24.8 (CH_3), 24.5 (*CH_3 major), 24.2 (CH_3), 24.0 (CH_3), 23.8 (CH_3), 18.6 (CH_3), 17.8 (*C*H_3-CH), 17.2 (*C*H_3-CH). IR (neat) ν_{max}/cm^{-1} = 3319, 2982, 2479, 1651, 1525, 1471, 1454, 1414, 1380, 1361.

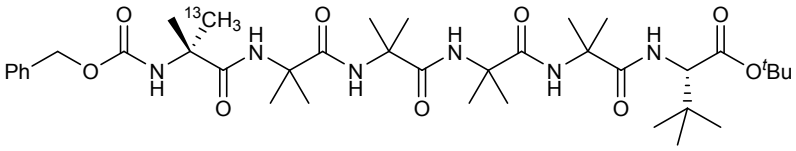
HRMS (ES$^+$, MeOH) Calc. for $C_{37}{}^{13}CH_{64}N_7O_8$ ([M+H]$^+$) = 747.4850, found 747.4814. Mp 215-217 °C. $[\alpha]_D^{20}$ = 16.0 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-(αMv)$_2$NH^{t}Bu 3-(αMv)$_2$NH^{t}Bu



Z-(*R*)-Aib*-Aib4-(αMv)$_2$NH*t*Bu was prepared according to general procedure B (0.052 mmol scale). The crude reaction product was dissolved in CH_2Cl_2 (20 mL) and washed with HCl (1 M, 2 x 5 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The pure peptide (26 mg, 58%) was isolated as a white solid by column chromatography (1% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.58 (1H, br s, NH), 7.50 (1H, br s, NH), 7.48 (1H, br s, NH), 7.36 (5H, m, ArCH x5), 7.20 (1H, br s, NH), 7.03 (1H, br s, NH), 6.85 (1H, br s, NH), 6.40 (1H, br s, NH), 5.59 (1H, br s, NH), 5.22 (1H, d, *J*=12.0, CH_2, H^A of AB system), 5.04 (1H, d, *J*=12.5, CH_2, H^B of AB system), 2.12 (1H, dq, *J*=7.0, 7.0, CH), 2.03 (1H, dq, *J*=7.0, 7.0, CH), 1.52 (0.7H, d, *J*=4.5, CH_3 minor), 1.52 (2.3H, d, *J*=129.0, *CH_3 major), 1.49 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.47 (6H, s, CH_3 x2), 1.46 (3H, s, CH_3), 1.45 (0.7H, d, *J*=129.5, * CH_3 minor), 1.45 (2.3H, m, CH_3 major), 1.45 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.40 (9H, s, C(CH_3)$_3$), 1.38 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.06 (3H, d, *J*=7.0, C*H*$_3$-CH), 1.02 (3H, d, *J*=7.0, C*H*$_3$-CH), 0.95 (3H, d, *J*=7.0, C*H*$_3$-CH), 0.93 (3H, d, *J*=7.0, C*H*$_3$-CH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 175.1 (CO), 175.0 (CO), 174.8 (CO), 174.2 (CO), 174.1 (CO), 173.9 (CO), 172.7 (CO), 156.0 (CO), 136.1 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.1 (ArCH), 67.4 (CH_2) 63.2 (αC), 62.8 (αC), 57.2 (d, J_C=39.0, α*C*-*CH_3), 56.8 (αC), 56.6 (αC), 56.5 (αC), 56.3 (αC), 50.7 (CMe_3), 35.8 (CH), 35.6 (CH), 29.7 (CH_3), 28.6 (C(*C*H$_3$)$_3$), 27.4 (CH_3), 27.3 (CH_3), 26.9 (CH_3), 26.8 (*CH_3 minor), 26.7 (CH_3), 23.2 (*CH_3 major), 23.1 (CH_3), 22.9 (CH_3), 22.8 (CH_3), 18.0 (CH_3), 17.9 (CH_3), 17.3 (CH_3), 17.2 (CH_3), 16.6 (CH_3), 15.4 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3314, 2983, 1699, 1660, 1531, 1456, 1411. HRMS (ES$^+$, MeOH) Calc. for $C_{44}{}^{13}CH_{75}N_8O_9$ ([M+H]$^+$) 860.5685, found 860.5687. Mp 241-243 °C. $[\alpha]_D^{20}$ = 15.2 (*c* 0.5, CH_2Cl_2).

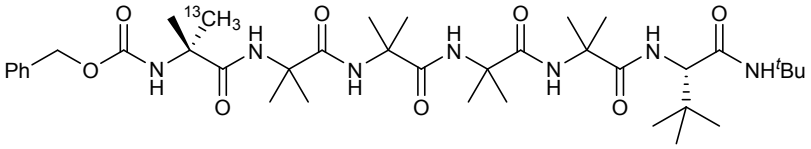
Z-(*R*)-Aib*-Aib$_4$-TleO^{t}Bu 3-TleO^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-TleO^{t}Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (33 mg, 85%) was isolated as a white solid by column chromatography (2% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, CD_3OD) δ_H 7.82 (1H, br s, NH), 7.80 (1H, br s, NH), 7.29-7.43 (6H, m, ArCH x5 and NH), 5.17 (1H, d, *J*=13.0, CH_2OCO, H^A of AB system), 5.10 (1H, d, *J*=13.0, CH_2OCO, H^B of AB system), 4.11 (1H, d, *J*=8.0, CH), 1.49 (6H, s, CH_3 x2), 1.46 (3H, s, CH_3), 1.46 (9H, s, C(CH_3)$_3$) 1.45 (0.7H, d, ^1J=128.5, *CH_3 minor), 1.45 (2.3H, d, ^3J=4.5, CH_3 major), 1.45 (3H, s, CH_3), 1.42 (2.3H, d, ^1J=128.5, *CH_3 major), 1.42 (0.7H, d, ^3J=4.5, CH_3 minor), 1.39 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.07 (9H, s, C(CH_3)$_3$). ^{13}C-NMR (101 MHz, CD_3OD) δ_C 177.6 (CO), 177.2 (CO), 177.0 (CO), 176.9 (CO), 176.8 (CO), 171.8 (CO), 158.0 (CO), 138.9 (ArC), 129.7 (ArCH), 129.2 (ArCH), 128.8

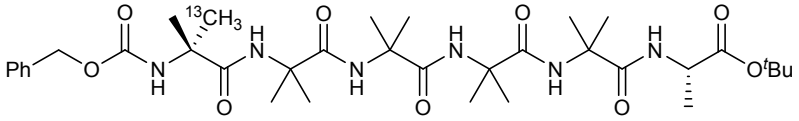
(ArCH), 82.5 (CMe_3), 67.8 (CH_2), 64.0 ($^{\alpha}$CH), 58.2 ($^{\alpha}$C), 58.1 ($^{\alpha}$C), 58.0 ($^{\alpha}$C), 57.8 (d, *J*=44.0, $^{\alpha}$*C*- *CH_3), 57.7 ($^{\alpha}$C), 35.1 (CMe_3), 28.6 (C(*C*H_3)$_3$), 27.6 (C(*C*H_3)$_3$), 27.1 (CH_3), 26.8 (CH_3), 26.2 (CH_3), 25.8 (*CH_3 major and CH_3 x2), 25.2 (CH_3), 24.9 (*CH_3 minor and CH_3), 24.6 (CH_3). IR (neat) ν_{max}/cm^{-1} =3305, 2981, 2477, 2360, 1700, 1650, 1522, 1472, 1415. HRMS (ES$^+$, MeOH) Calc. for $C_{37}{}^{13}CH_{62}N_6O_9Na$ ([M+Na]$^+$) 770.4510, found 770.4541. Mp 126-128 °C. $[\alpha]_D^{20}$ = −18.4 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-TleNH*t*Bu 3-TleNH*t*Bu



Z-(*R*)-Aib*-Aib$_4$-TleNH*t*Bu was prepared according to general procedure A (0.055 mmol scale). The pure peptide (28 mg, 68%) was isolated as a white solid by column chromatography (2-5% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.05 (1H, br s, NH), 7.88 (1H, br s, NH), 7.82 (1H, br s, NH), 7.75 (1H, br s, NH), 7.46 (1H, d, *J*=8.0, N*H*-CH), 7.34 (5H, m, ArCH x5), 7.09 (1H, br s, NH), 5.20 (1H, d, *J*=12.5, CH_2, H^A of AB system), 5.06 (1H, d, *J*=12.5, CH_2, H^B of AB system), 3.93 (1H, d, *J*=8.0, CH), 1.48 (6H, s, CH_3 x2), 1.45 (6H, s, CH_3 x2), 1.43 (0.7H, d, *J*=4.5, CH_3 minor), 1.43 (2.3H, d, *J*=128.5, *CH_3 major), 1.39 (2.3H, d, *J*=4.0, CH_3 major), 1.39 (0.7H, d, *J*=129.0, *CH_3 minor), 1.38 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.36 (12H, s, CH_3 and C(CH_3)$_3$), 1.10 (9H, s, C(CH_3)$_3$). ^{13}C-NMR (101 MHz, CD_3OD) δ_C 177.5 (CO), 177.4 (CO), 177.1 (CO), 177.0 (CO), 176.9 (CO), 172.5 (CO), 158.0 (CO), 138.7 (ArC), 129.6 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 67.7 (CH_2), 65.1 ($^{\alpha}$CH), 58.1 ($^{\alpha}$C), 57.9 ($^{\alpha}$C), 57.8 ($^{\alpha}$C), 57.6 (d, *J*=40.5, $^{\alpha}$*C*-*CH_3), 57.5 ($^{\alpha}$C), 52.5 (CMe_3), 34.8 (CMe_3), 29.0 (C(*C*H_3)$_3$), 27.8 (C(*C*H_3)$_3$), 27.7 (CH_3), 27.0 (CH_3), 26.7 (CH_3), 26.4 (CH_3), 26.0 (*CH_3 minor), 25.2 (CH_3), 24.5 (*CH_3 major and CH_3), 24.2 (CH_3), 23.8 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3305, 2983, 2477, 1703, 1644, 1528, 1454. HRMS (ES$^+$, MeOH) Calc. for $C_{37}{}^{13}CH_{63}N_7O_8Na$ ([M+Na]$^+$) 769.4664, found 769.4669. Mp 211-213. $[\alpha]_D^{20}$ = 16.8 (*c* 1, CH_2Cl_2).

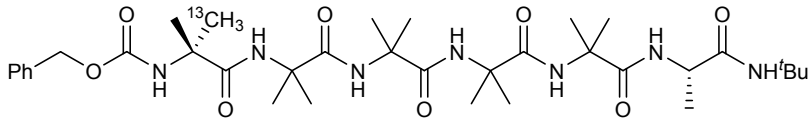
Z-(*R*)-Aib*-Aib$_4$-AlaO*t*Bu 3-AlaO*t*Bu



Z-(*R*)-Aib*-Aib$_4$-AlaO*t*Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (32 mg, 87%) was isolated as a white solid by column chromatography (2% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 7.92 (1H, br s, NH), 7.76 (1H, br s, NH), 7.74 (1H, br s, NH), 7.71 (1H, br s, NH), 7.29-7.41 (5H, m, ArCH x5), 5.18 (1H, d, *J*=13.0, CH_2, H^A of AB system), 5.08 (1H, d, *J*=13.0, CH_2, H^B of AB system), 4.21 (1H, dt, *J*=7.0, 7.0, CH), 1.52 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.45 (3H, m, C*H*$_3$-CH), 1.44 (9H, s, C(CH_3)$_3$), 1.43 (H, s, CH_3 x2), 1.41 (0.66H, d, ^{1}*J*=128.5, *CH_3 minor), 1.41 (2.34H, d, ^{3}*J*=4.5, CH_3 major), 1.40 (3H, s, CH_3), 1.39 (2.34H, d, ^{1}*J*=128.5, *CH_3 major), 1.39 (0.66H, d, ^{3}*J*=4.5, CH_3 minor), 1.37 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.27 (3H, s, CH_3). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 177.6 (CO), 177.3 (CO), 177.3 (CO), 177.0 (CO), 176.9 (CO), 173.8 (CO), 158.1 (CO), 138.9 (ArC), 129.7 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 82.3 (CMe_3), 58.1 ($^{\alpha}$C), 58.1 ($^{\alpha}$C), 57.9 ($^{\alpha}$C), 57.8 (d, *J*=36.5, $^{\alpha}$C-*CH_3), 57.7 ($^{\alpha}$C), 50.9 ($^{\alpha}$CH), 28.4 (C(*C*H_3)$_3$), 27.7 (CH_3), 27.0 (CH_3), 26.5 (CH_3), 26.3 (CH_3), 26.0 (*CH_3 major and CH_3), 24.7 (*CH_3 minor and CH_3), 24.4 (CH_3), 24.1 (CH_3, 17.3 (*C*H_3CH). IR (neat)

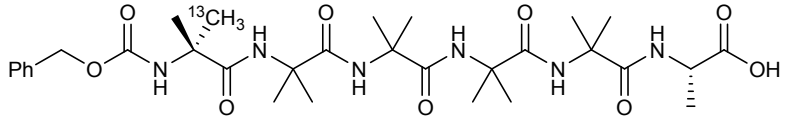
ν_{max}/cm^{-1} = 3340, 3288, 2987, 2931, 1726, 1702, 1652, 1530. HRMS (ES$^+$, MeOH) Calc. for $C_{34}{}^{13}CH_{56}N_6O_9Na$ ([M+Na]$^+$) 728.4040, found 728.4013. Mp 225-229 °C. $[\alpha]_D^{20}$ = −36.4 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-AlaNH^{t}Bu 3-AlaNH^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-AlaNH^{t}Bu was prepared according to general procedure A (0.052 mmol scale). The pure peptide (33 mg, 90%) was isolated as a white solid by column chromatography (2% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.04 (1H, br s, NH), 7.98 (1H, br s, NH), 7.88 (1H, d, *J*=7.0, NH), 7.74 (2H, br s, NH x2), 7.29-7.40 (5H, m, ArCH x5), 7.09 (1H, br s, NH), 5.20 (1H, d, *J*=13.0, CH_2, H^A of AB system), 5.06 (1H, d, *J*=13.0, CH_2, H^B of AB system), 4.11 (1H, dt, *J*=7.0, 7.0, CH), 1.56 (3H, s, CH_3), 1.46 (6H, s, CH_3 x2), 1.42 (3H, d, *J*=7.0, CH_3), 1.42 (2.36H, d, ^{1}*J*=128.5, *CH_3 major), 1.42 (0.42H, m, CH_3 minor), 1.39 (0.64H, d, ^{1}*J*=128.5, *CH_3 minor), 1.39 (2.36H, m, CH_3 major), 1.37 (9H, s, C(CH_3)$_3$), 1.35-1.39 (9H, m, CH_3 x3), 1.26 3H, s, CH_3). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 177.7 (CO), 177.6 (CO), 177.3 (CO), 177.0 (CO), 175.0 (CO), 159.1 (CO), 138.9 (ArC), 129.8 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 67.8 (CH_2), 58.1 ($^\alpha$C), 58.1 ($^\alpha$C), 57.8 ($^\alpha$C), 57.8 (d, *J*=40.0, $^\alpha$*C*-*CH_3), 57.7 ($^\alpha$C), 52.6 (CMe_3), 52.2 ($^\alpha$CH), 29.2 (C(*C*H_3)$_3$), 27.8 (CH_3), 27.2 (CH_3), 27.0 (CH_3), 26.7 (CH_3), 26.3 (*CH_3 minor), 24.8 (CH_3), 24.5 (*CH_3 major), 24.0 (CH_3), 23.9 (CH_3), 23.8 (CH_3), 17.9 (*C*H_3-$^\alpha$CH). IR (neat) ν_{max}/cm^{-1} = 3305, 2982, 2475, 1650, 1526, 1454, 1416, 1382, 1361. HRMS (ES$^+$, MeOH) Calc. for $C_{34}{}^{13}CH_{55}N_6O_9Na$ ([M+Na]$^+$) 727.3994, found 727.3962. Mp 204-206 °C. $[\alpha]_D^{20}$ = 28.4 (*c* 1, CH_2Cl_2).

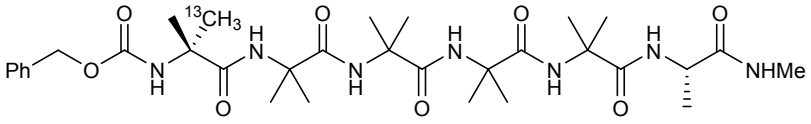
Z-(*R*)-Aib*-Aib$_4$-AlaOH 3-AlaOH



3-AlaO^{t}Bu (17 mg) was dissolved in CH_2Cl_2 (1 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (200 μL) was added dropwise and the resulting solution was allowed to warm to room temperature and stirred for 45 min. The solvents were removed *in vacuo* and the crude reaction product was purified by column chromatography (2-10% MeOH in CH_2Cl_2) to give 3-AlaOH (15 mg, >99%) as a white solid. ^{1}H-NMR (500 MHz, CD_3OD) δ_H 8.02 (1H, br s, NH), 7.91 (1H, br s,NH), 7.77 (1H, br s, NH), 7.70 (1H, br s, NH), 7.34 (5H, m, ArCH x5), 5.18 (1H, d, *J*=13.0, CH_2, H^A of AB system), 5.08 (1H, d, *J*=13.0, CH_2, H^B of AB system), 4.34 (1H, q, *J*=7.5, $^\alpha$CH), 1.50 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.47 (3H, d, *J*=7.5, C*H*$_3$-CH), 1.45 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.43 (2.4H, d, *J*=4.5, CH_3 major), 1.43 (0.6H, d, *J*=129.0, *CH_3 minor), 1.39 (0.6H, m, CH_3 minor), 1.39 (2.4H, d, J=129.0, *CH_3 major), 1.39 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.28 (3H, s, CH_3). ^{13}C-NMR (126 MHz, CD_3OD) δ_C 177.6 (CO), 177.4 (CO), 177.2 (CO), 177.1 (CO), 176.9 (CO), 176.3 (CO), 158.0 (CO), 138.7 (ArC), 129.6 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 67.6 (CH2), 58.1 ($^\alpha$C), 58.0 ($^\alpha$C), 57.9 ($^\alpha$C), 57.8 (d, *J*=37.0, $^\alpha$*C*-*CH_3), 57.7 ($^\alpha$C), 50.0 ($^\alpha$CH), 27.2 (CH_3), 26.3 (CH_3), 25.9 (*CH_3 major and CH_3 x2), 25.3 (CH_3), 24.7 (*CH_3 minor and CH_3), 24.4 (CH_3), 24.2 (CH_3), 17.5 (*C*H_3-CH). IR (neat) ν_{max}/cm^{-1} = 3304, 2985, 2939, 1751, 1653,

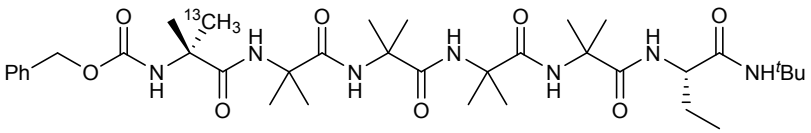
1524, 1455. HRMS (ES$^+$, MeOH) Calc. for $C_{38}{}^{13}CH_{53}N_7O_7Na$ ([M+Na]$^+$) =, 635.3916 found 635.3932. Mp 227-229 °C. = $[\alpha]_D^{20}$ –44.0 (*c* 0.5, MeOH).

Z-(*R*)-Aib*-Aib$_4$-AlaNHMe 3-AlaNHMe



3-AlaOH (13 mg, 0.02 mmol) and 1-Hydroxybenzotriazole hydrate (5 mg, 0.026 mmol) were dissolved in CH_2Cl_2 (2 mL) and *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide (4 mg, 0.022 mmol) was added and the reaction was stirred until it was homogenous. $MeNH_2$ (4 mg, 0.05 mmol) and N,N-diisopropylethylamine (16 μl, 0.09 mmol) were added and the reaction mixture stirred for 24 h. The reaction was diluted with CH_2Cl_2 (10 mL) and the organic phase was washed with $KHSO_4$ (5%, 2 x 3 mL), $NaHCO_3$ (2 3 mL), brine (3 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude reaction product was purified by column chromatography (1-5% MeOH in CH_2Cl_2) to give 3-AlaNHMe (10 mg, 75%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.68 (1H, br s, NH), 7.61 (1H, br d, *J*=8.0, N*H*-CH), 7.57 (1H, br s, NH), 7.46 (1H, br s, NH), 7.42 (1H, q, *J*=4.5, N*H*-CH_3), 7.27 (5H, m, ArCH x5), 6.75 (1H, br s, NH), 6.15 (1H, br s, NH), 5.14 (1H, d, *J*=12.5, CH_2O, H^A of AB system), 4.96 (1H, d, *J*=12.5, CH_2O, H^B of AB system), 4.38 (1H, dq, *J*=7.5, 7.5, $^\alpha$CH), 2.69 (3H, d, *J*=4.5, C*H*$_3$-NH), 1.49 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.42 (2.4H, d, *J*=129.0, *CH_3 major), 1.42 (0.6H, m, CH_3 minor), 1.42 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.40 (3H, d, *J*=4.5, C*H*$_3$-NH), 1.37 (3H, s, CH_3), 1.36 (0.6H, d, *J*=129.5, *CH_3 minor), 1.36 (2.4H, m, CH_3 major), 1.34 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.14 (3H, s, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 176.4 (CO), 175.8 (CO), 175.2 (CO), 174.6 (CO), 174.5 (CO), 174.1 (CO), 156.1 (CO), 136.3 (ArC), 128.6 (ArCH), 128.4 (ArCH), 127.9 (ArCH), 67.2 ($^\alpha$C), 57.0 (d, *J*=39.5, $^\alpha$*C*-*CH_3), 57.0 ($^\alpha$C), 56.7 ($^\alpha$C), 56.6 ($^\alpha$C), 56.4 ($^\alpha$C), 49.6 ($^\alpha$CH), 27.5 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 26.6 (*CH_3 minor), 26.5 (CH_3), 26.2 (CH_3-NH), 25.9 (CH_3), 25.1 (CH_3), 23.2 (*CH_3 major), 22.7 (CH_3), 22.7 (CH_3), 17.3 (*C*H$_3$-CH). IR (neat) ν_{max}/cm^{-1} = 3298, 2984, 2936, 2472, 1698, 1647, 1528, 1414. HRMS (ES$^+$, MeOH) Calc. for $C_{31}{}^{13}CH_{51}N_7O_8Na$ ([M+Na]$^+$) 685.3730, found 685.3713. Mp 230-232°C. $[\alpha]_D^{20}$ = 38.4 (*c* 0.5, CH_2Cl_2).

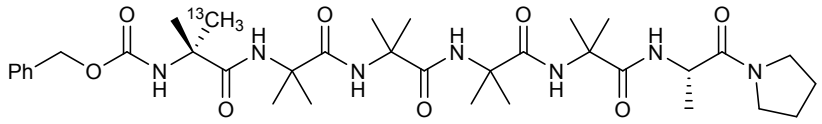
Z-(*R*)-Aib*-Aib$_4$-AbuNH^{t}Bu 3-AbuNH^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-AbuNH^{t}Bu was prepared according to general procedure A (0.026 mmol scale). The pure peptide (17 mg, 91%) was isolated as a white solid by column chromatography (1-5% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.67 (1H, br s, NH), 7.59 (1H, d, *J*=7.5, N*H*-CH), 7.53 (1H, br s, NH), 7.49 (1H, br s, NH), 7.33 (5H, m, ArCH x5), 6.89 (1H, br s, NH), 6.74 (1H, br s, NH), 6.29 (1H, br s, NH), 5.21 (1H, d, *J*=12.5, CH_2O, H^A of AB system), 5.04 (1H, d, *J*=12.5, CH_2O, H^B of AB system), 4.13 (1H, ddd, *J*= 11.0, 8.0, 3.5, CH), 2.13 (1H, m, CH_2), 1.79 (1H, m, CH_2), 1.58 (3H, s, CH_3), 1.51 (3H, s,

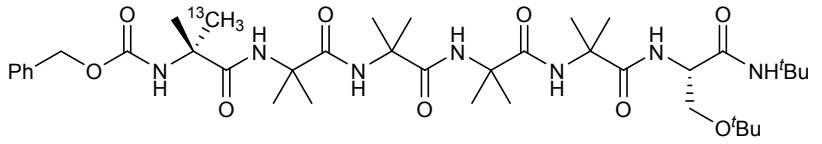
CH_3), 1.51 (2.3H, d, *J*=129.0, *CH_3 major), 1.51 (0.7H, m, CH_3 minor), 1.49 (6H, s, CH_3 x2), 1.44 (0.7H, d, *J*=129.0, *CH_3 minor), 1.44 (2.3H, m, CH_3 major), 1.44 (3H, s, CH_3), 1.39 (12H, s, CH_3 and $C(CH_3)_3$), 1.38 (3H, s, CH_3), 1.21 (3H, s, CH_3), 0.94 (3H, t, *J*=7.5, C*H*$_3$-CH). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 175.7 (CO), 175.5 (CO), 175.4 (CO), 174.6 (CO), 174.2 (CO), 172.5 (CO), 156.1 (CO), 136.4 (ArC), 128.6 (ArCH), 128.4 (ArCH), 127.9 (ArCH), 67.1 (CH_2O), 57.1 (d, *J*=39.4, $^{\alpha}$C-*CH_3), 57.0 ($^{\alpha}$C), 56.7 ($^{\alpha}$C), 56.6 ($^{\alpha}$C), 56.6 ($^{\alpha}$C), 56.4 ($^{\alpha}$CH), 51.0 (CMe_3), 28.8 (CH_3), 27.8 (CH_3), 27.0 (CH_3), 26.9 (CH_3), 26.6 (*CH_3 minor and CH_3 x2), 24.6 (CH_2), 23.3 (*CH_3 major and CH_3 x2), 22.8 (CH_3), 11.28 (*C*H$_3$-CH). IR (neat) ν_{max}/cm^{-1} = 3315, 2980, 2935, 2473, 1703, 1644, 1525. HRMS (ES$^+$, MeOH) Calc. for $C_{35}{}^{13}CH_{60}N_7O_8$ ([M+H]$^+$) 719.4537, found 719.4538. Mp 164-167. $[\alpha]_D^{20}$ = 20.0 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-AlaN(CH$_2$)$_4$ 3-AlaN(CH$_2$)$_4$



Z-(*R*)-Aib*-Aib$_4$-AlaN(CH$_2$)$_4$ was prepared according to general procedure A (0.026 mmol scale). The pure peptide (14 mg, 77%) was isolated as a white solid by column chromatography (1-5% MeOH in CH_2Cl_2). ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.55 (1H, br s, NH), 7.52 (1H, br s, NH), 7.43 (1H, br s, NH), 7.41 (1H, br s, NH), 7.33 (5H, m, ArCH x5), 6.70 (1H, br m, NH), 5.99 (1H, br m, NH), 5.13 (1H, d, *J*=12.5, H^A of AB system, CH_2O), 5.08 (1H, d, *J*=12.5, H^B of AB system, CH_2O), 4.61 (1H, m, $^{\alpha}$CH), 3.74 (1H, m, CH_2N), 3.43 (3H, m, CH_2N), 1.91 (2H, m, CH_2), 1.79 (2H, m, CH_2), 1.54 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.37 (3H, d, *J*=7.0, C*H*$_3$-CH), 1.32 (3H, s, CH_3), 1.29 (3H, s, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 175.1 (CO), 174.9 (CO), 174.6 (CO), 174.31 (CO), 173.9 (CO), 170.90 (CO), 156.0 (CO), 136.3 (ArC), 128.7 (ArCH), 128.5 (ArCH), 128.0 (ArCH), 67.2 (CH_2OBn), 57.1 (d, *J* 37.0, $^{\alpha}$*C*-*CH_3), 56.8 ($^{\alpha}$C x2), 56.7 ($^{\alpha}$C), 56.4 ($^{\alpha}$C), 47.6 ($^{\alpha}$CH), 46.1 (CH_2N), 29.7 (CH_3), 26.2 (CH_2), 25.2 (*CH_3 major), 24.8 (*CH_3 minor), 24.3-25.9 (CH_3 x7), 24.0 (CH_2), 17.0 (*C*H$_3$-$^{\alpha}$CH). IR (neat) ν_{max}/cm^{-1} = 3506, 2983, 2936, 1703, 1652, 1528. HRMS (ES$^+$, MeOH) Calc. for $C_{34}{}^{13}CH_{55}N_7O_8Na$ ([M+Na]$^+$) 725.4043, found 725.4030. Mp 197-199. $[\alpha]_D^{20}$ = −21.6 (*c* 0.5, CH_2Cl_2).

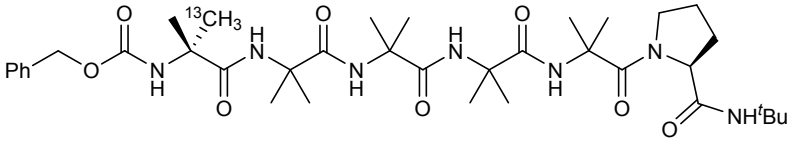
Z-(*R*)-Aib*-Aib$_4$-Ser(O^{t}Bu)NH^{t}Bu 3-Ser(O^{t}Bu)NH^{t}Bu



Z-(*R*)-Aib*-Aib$_4$-Ser(O^{t}Bu)NH^{t}Bu was prepared according to general procedure A (0.026 mmol scale). The pure peptide (20 mg, 99%) was isolated as a white solid by column chromatography (1-5% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.61 (1H, br s, NH), 7.58 (1H, br s, NH), 7.46 (1H, br s, NH), 7.34 (6H, m, ArCH x5 and NH), 7.01 (1H, br s, NH), 6.75 (1H, br s, NH), 6.27 (1H, br s, NH), 5.17 (1H, d, *J*=12.5, CH_2OCO, H^A of AB system), 5.07 (1H, d, *J*=12.5, CH_2OCO, H^B of AB system), 4.45 (1H, m, CH), 3.70 (2H, m, CH_2OCMe_3), 1.55 (3H, s, CH_3), 1.50 (6H, s, CH_3), 1.49 (3H, s, CH_3), 1.48 (2.3H, d, *J*=129.0, *CH_3 major), 1.48 (0.7H, m, CH_3 minor), 1.45 (2.3H, d, *J*=4.0, CH_3 major), 1.45 (0.7H, d, *J*=129.5, *CH_3 minor), 1.42 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.38 (12H, s, CH_3 and $C(CH_3)_3$), 1.25 (3H, s, CH_3), 1.13 (9H, s, $C(CH_3)_3$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 175.5 (CO), 175.4 (CO), 174.8 (CO), 174.5

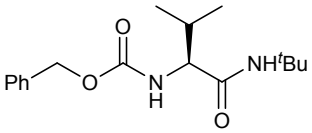
(CO), 174.2 (CO), 170.2 (CO), 156.1 (CO), 136.4 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.0 (ArCH), 72.8 ($OCMe_3$), 67.1 (CH_2OCO), 61.8 (CH_2OCMe_3), 57.0 (d, *J*=38.5, $^{\alpha}$C-*CH_3), 56.8 ($^{\alpha}$C), 56.7 ($^{\alpha}$C), 56.7 ($^{\alpha}$C), 56.4 ($^{\alpha}$C), 55.5 ($^{\alpha}$CH), 51.2 ($NHCMe_3$), 28.7 ($C(CH_3)_3$), 27.5 ($C(CH_3)_3$), 27.4 (CH_3), 25.9 (*CH_3 minor and CH_3 x3), 24.0 (*CH_3 major and CH_3 x3), 23.3 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3308, 2976, 2934, 1478, 1703, 1648, 1527. HRMS (ES$^+$, MeOH) Calc. for $C_{38}{}^{13}CH_{66}N_7O_9$ ([M+H]$^+$) 777.4956, found 777.4957. Mp 121-123. $[\alpha]_D^{20}$ = 21.2 (*c* 1, CH_2Cl_2).

Z-(*R*)-Aib*-Aib$_4$-ProNH^{t}Bu 3-ProNH^{t}Bu



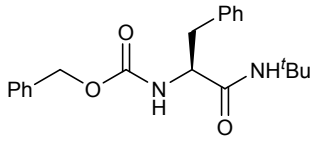
Z-(*R*)-Aib*-Aib$_4$-ProNH^{t}Bu was prepared according to general procedure A (0.031 mmol scale). The pure peptide (18 mg, 79%) was isolated as a white solid by column chromatography (1-5% MeOH in CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.59 (1H, br s, NH), 7.53 (1H, br s, NH), 7.34 (6H, m, ArCH x5 and NH), 7.13 (1H, br s, NH), 6.85 (1H, br s, NH), 6.66 (1H, br s, NH), 5.14 (1H, d, *J* 12.5, CH_2O, H^A of AB system), 5.08 (1H, d, *J*=12.5, CH_2O, H^B of AB system), 4.50 (1H, m, CH), 3.69 (2H, m, CH_2N), 1.82 – 2.05 (2H, m , CH_2), 1.63 – 1.92 (2H, m, CH_2), 1.56 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.49 (6H, s, CH_3 x2), 1.47 (2.3H, d, *J*=129.0, *CH_3 major), 1.46 (0.7H, m, CH_3 minor), 1.46 (2.3H, d, *J*=4.0, CH_3 major), 1.46 (0.7H, m, *CH_3 minor), 1.41 (9H, m, CH_3 x3), 1.37 (9H, s, $C(CH_3)_3$), 1.29 (3H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 175.2 (CO), 174.8 (CO), 174.7 (CO), 174.2 (CO), 172.9 (CO), 172.4 (CO), 156.1 (CO), 136.5 (ArC), 128.6 (ArCH), 128.3 (ArCH), 127.8 (ArCH), 67.0 (CH_2O), 62.8 ($^{\alpha}$CH), 57.0 (d, *J*=39.0, $^{\alpha}$*C*-*CH_3), 57.0 ($^{\alpha}$C), 56.8 ($^{\alpha}$C), 56.6 ($^{\alpha}$C), 56.4 ($^{\alpha}$C), 51.0 (CMe_3), 48.1 (CH_2N), 29.1 (CH_2), 28.8 ($C(CH_3)_3$), 26.8 (CH_2), 25.9 (CH_3), 25.6 (*CH_3 minor and CH_3 x3), 24.2 (*CH_3 major and CH_3 x4). IR (neat) ν_{max}/cm^{-1} = 3305, 2983, 2936, 1703, 1645, 1529. HRMS (ES$^+$, MeOH) Calc. for $C_{36}{}^{13}CH_{59}N_7O_8Na$ ([M+Na]$^+$) = 753.4356, found 753.4344. Mp 87-89. $[\alpha]_D^{20}$ = −11.2 (*c* 1, CH_2Cl_2).

Z-ValNH^{t}Bu



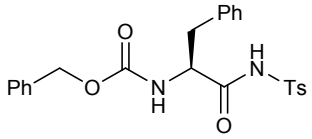
Z-ValNH^{t}Bu was prepared according to general procedure C (1 mmol scale). The pure product (251 mg, 82%) was isolated as a white solid.^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.34 (5H, m, ArCH x5), 5.57 (1H, br s, NH), 5.37 (1H, br d, *J*=8.0, N*H*-CH), 5.11 (2H, s, CH_2O), 3.81 (1H, dd, *J*=8.5, 7.0, CH), 2.06 (1H, ddq, *J*=7.0, 7.0, 7.0), 1.35 (9H, s, $C(CH_3)_3$), 0.96 (3H, d, *J*=7.0, CH_3), 0.92 (3H, d, *J*=7.0, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 170.2 (CO), 156.4 (CO), 136.3 (ArC), 128.5 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 66.9 (CH_2O), 60.9 (CH-NH), 51.5 (CMe_3), 31.4 (CH), 28.7 ($C(CH_3)_3$), 19.2 (CH_3), 17.9 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3333, 3231, 2963, 1698, 1651. HRMS (ES$^+$, MeOH) Calc. for $C_{15}H_{27}N_2O_3$ ([M+H]$^+$) = 307.2022, found 307.2009. Mp 108-111 °C. $[\alpha]_D^{20}$ −8.8 (*c* 0.5, $CHCl_3$).

Z-PheNH^{t}Bu



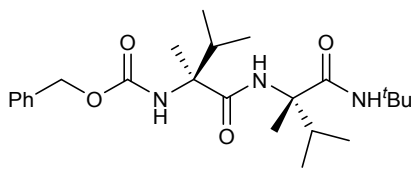
Z-PheNH^{t}Bu was prepared according to general procedure C (2 mmol scale). The pure product (517 mg, 71%) was isolated as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.31 (10H, m, ArCH x 10) 5.47 (1H, br s, NH) 5.11 (2H, m, CH_2O) 4.21 (1H, br s, NH) 3.17 (1H, m, CH_2CH) 2.90 (1H, m, CH_2CH) 1.18 (9H, s, $C(CH_3)_3$). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 169.4 (CO) 155.8 (CO) 136.8 (ArC) 136.3 (ArC) 129.4 (ArCH) 128.7 (ArCH) 128.5 (ArCH) 128.2 (ArCH) 128.0 (ArCH) 127.0 (ArCH) 66.9 (CH_2O) 56.9 (CMe_3) 51.3 (CH) 39.4 (CH_2CH) 28.4 ($C(CH_3)_3$). IR (neat) ν_{max}/cm^{-1} = 3341, 3274, 3062, 2966, 1703, 1688, 1651. HRMS (ES$^+$, $CHCl_3$) Calc. for $C_{21}H_{27}N_2O_3$ ([M+H]$^+$) = 355.2010, found 355.2010. Mp 96-98 °C. $[\alpha]_D^{20}$ –11.3 (*c* 1, $CHCl_3$).

Z-Phe-NHTs



p-Toluenesulfonyl isocyanate (0.17 mL, 1.1 mmol) was added dropwise to Z-Phe-OH (299 mg, 1 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h, then diluted with $CHCl_3$ (20 mL) and washed with HCl (1 M, 10 mL). The aqueous phase was extracted with $CHCl_3$ (2 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude reaction product was purified by column chromatography (1:1 PE:EtOAc) to give Z-Phe-NHTs (201 mg, 44%) as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.89 (2H, d, *J*=7.5, ArCH x2), 7.36 (7H, m, ArCH x7), 7.30 (1H, br s, NH) 7.20 (3H, m, ArCH x3), 6.98 (2H, d, *J*=7.5, ArCH x2), 5.20 (1H, d, *J*=7.5, NH), 5.08 (2H, m, CH_2OCO), 4.47 (1H, m, $^\alpha$CH), 3.02 (1H, dd, *J*=14.0, 6.0, CH_2Ph, H^A of ABX system), 2.97 (1H, dd, *J*=14.0, 7.0, CH_2Ph, H^B of ABX system), 2.46 (3H, s, CH_3). ^{13}C-NMR (126MHz, $CDCl_3$) δ_C 169.1 (CO), 156.3 (CO), 145.2 (ArC), 135.6 (ArC), 135.3 (ArC), 134.9 (ArC), 129.5 (ArCH), 129.2 (ArCH), 128.8 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.4 (ArCH), 67.7 (CH_2), 56.1 ($^\alpha$CH), 37.5 (CH_2), 21.7 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3148, 1685, 1518, 1453, 1345, 1289, 1172. HRMS (ES$^+$, CH_2Cl_2) Calc. for $C_{24}H_{24}N_2O_5S$ ([M+Na]$^+$) = 475.1298, found 475.1302. Mp 53-57 °C. $[\alpha]_D^{20}$ = –29.0 (*c* 1, CH_2Cl_2).

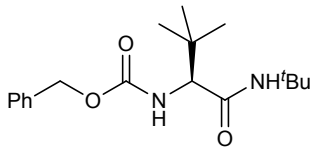
Z-(αMv)$_2$NH^{t}Bu



Z-αMvOH (105 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (5 mL) and the solution cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide (85 μL, 0.48 mmol) was added and the reaction was

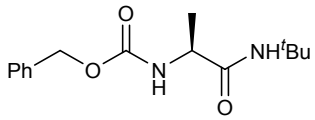
allowed to warm to room temperature and stirred for 4 h. The solvent was removed *in vacuo* and EtOAc (20 mL) was added. The organic phase was washed with $KHSO_4$ (2 x 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude azlactone was then place under high vacuum (<0.1 mbar) before being dissolved in MeCN (8 mL). H-αMvNH^{t}Bu (prepared by the quantitative hydrogenolysis of Z-αMvNH^{t}Bu) (62 mg, 0.33 mmol) was added and the reaction stirred at reflux for 5 d. After removing the solvent *in vacuo*, the crude reaction product was purified by column chromatography (1% MeOH in CH_2Cl_2) to give Z-(αMv)$_2$NH^{t}Bu (82 mg, 57%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.34 (5H, m, ArCH x5), 6.84 (1H, br s, NH), 6.34 (1H, br s, NH), 5.20 (1H, d, *J*=12.0, CH_2, H^A of AB system), 5.07 (1H, br s, NH), 5.01 (1H, d, *J*=12.0, CH_2, H^B of AB system), 1.97 (1H, spt, *J*=7.0, CH), 1.95 (1H, spt, *J*=7.0, CH), 1.48 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.38 (9H, s, C(CH_3)$_3$), 0.97 (3H, d, *J*=7.0, C*H*$_3$-CH), 0.96 (3H, d, *J*=7.0, C*H*$_3$-CH), 0.83 (3H, d, *J*=7.0, C*H*$_3$-CH), 0.77 (3H, d, *J*=7.0, C*H*$_3$-CH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 171.8 (CO), 171.1 (CO), 155.5 (CO), 135.9 (ArC), 128.6 (ArCH), 128.5 (ArCH), 128.5 (ArCH), 67.2 (CH_2), 63.6 ($^\alpha$CH), 63.1 ($^\alpha$CH), 51.0 (CMe_3), 35.8 (CH), 35.4 (CH), 28.6 (C(*C*H$_3$)$_3$), 18.6 (CH_3), 18.5 (CH_3), 17.2 (*C*H$_3$-CH), 17.1 (*C*H$_3$-CH), 17.1 (*C*H$_3$-CH), 16.8 (*C*H$_3$-CH). IR (neat) ν_{max}/cm^{-1} =3440, 3359, 3283, 2967, 1711, 1665, 1526, 1499, 1455. HRMS (ES$^+$, CH_2Cl_2) Calc. for $C_{24}H_{39}N_3O_4Na$ ([M+Na]$^+$), 456.2833, 456.2818. Mp 95-99 °C. $[\alpha]_D^{20}$ = −5.2 (*c* 0.5, CH_2Cl_2).

Z-TleNH^{t}Bu



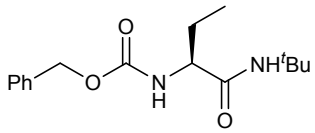
Z-TleNH^{t}Bu was prepared according to general procedure C (0.61 mmol scale). The pure product (181 mg, 93%) was isolated as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.34 (5H, m, ArCH), 5.54 (1H, d, *J*=9.0, NH), 5.38 (1H, br s, NH), 5.13 (1H, d, *J*=12.5, CH_2, H^A of AB system), 5.09 (1H, d, *J*=12.5, CH_2, H^B of AB system), 3.74 (1H, d, *J*=9.5, $^\alpha$CH), 1.35 (9H, s, C(CH_3)$_3$), 0.99 (9H, s, C(CH_3)$_3$). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 169.5 (CO), 156.4 (CO), 136.3 (ArC), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 66.9 (*C*H$_2$OCO), 63.3 ($^\alpha$C), 51.7 (CMe_3), 34.8 (CMe_3), 28.7 (C(*C*H$_3$)), 26.6 (C(*C*H$_3$)). IR (neat) ν_{max}/cm^{-1} = 3341, 3276, 3065, 2961, 1702, 1653, 1537. HRMS (ES$^+$, CH_2Cl_2) Calc. for $C_{18}H_{29}N_2O_3$ ([M+H]$^+$) = 321.2173, found 321.2186. Mp 96-98 °C. $[\alpha]_D^{20}$ = 12.8 (*c* 1, CH_2Cl_2).

Z-AlaNH^{t}Bu



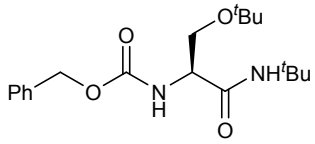
Z-AlaNH^{t}Bu was prepared according to general procedure C (10 mmol scale). The pure product (2.61 g, 94%) was isolated as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.33 (5H, m, ArCH), 5.80 (1H, br s, NH), 5.36 (1H, br s, NH), 5.12 (2H, s, CH_2), 4.11 (1H, m, $^\alpha$CH), 1.35 (3H, d, *J*=7.0, CH_3), 1.33 (9H, s, C(CH_3)$_3$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 171.3 (CO), 155.9 (CO), 136.3 (ArC), 128.5 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 66.9 (CH_2), 51.3 (CMe_3), 50.9 ($^\alpha$CH), 28.6 (C(*C*H$_3$)$_3$), 18.7 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3354, 3293, 2971, 1707, 1656, 1523, 1498, 1454. HRMS (ES$^+$, CH_2Cl_2) Calc. for $C_{15}H_{22}N_2O_3Na$ ([M+Na]$^+$) = 301.1523, found 301.1514. Mp 48-50 °C. $[\alpha]_D^{20}$ = −16 (*c* 1, CH_2Cl_2).

Z-AbuNH^{t}Bu



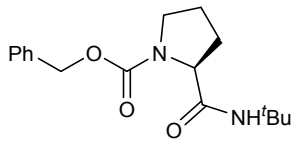
Z-AbuNH^{t}Bu was prepared according to general procedure C (2 mmol scale). The pure product (536 mg, 92%) was isolated as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.33 (5H, m, ArCH x5), 5.80 (1H, br s, NH), 5.46 (1H, br d, *J*=6.5, N*H*-CH), 5.10 (2H, s, CH_2O), 3.98 (1H, ddd, *J*=6.5, 6.5, 6.5, CH), 1.83 (1H, m, CH_2), 1.63 (1H, m, CH_2), 1.34 (9H, s, $C(CH_3)_3$), 0.93 (3H, t, *J*=7.5, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 170.6 (CO), 156.1 (CO), 136.3 (ArC), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 66.8 (CH_2O), 56.5 (CH), 51.4 (CMe_3), 28.7 ($C(CH_3)_3$), 26.1 (CH_2), 9.7 (CH_3). IR (neat) ν_{max}/cm^{-1} = 3292, 2968, 1695, 1654, 1543. HRMS (ES$^+$, MeOH) Calc. for $C_{16}H_{25}N_2O_3$ ([M+H]$^+$) = 293.1865, found 293.1863. Mp 81-83 °C. $[\alpha]_D^{20}$ = 6.0 (*c* 1, CH_2Cl_2).

Z-Ser(O^{t}Bu)NH^{t}Bu



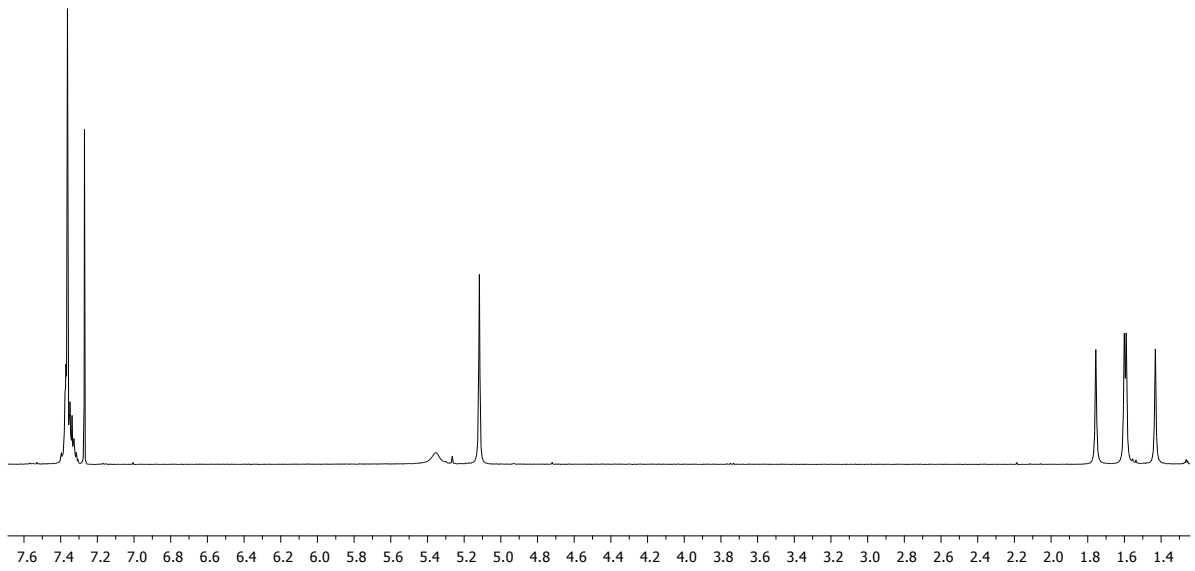
Z-Ser(O^{t}Bu)NH^{t}Bu was prepared according to general procedure C (1 mmol scale). The pure product (318 mg, 91%) was isolated as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.34 (5H, m, ArCH x5), 6.52 (1H, br s, NH), 5.75 (1H, br s, NH), 5.15 (1H, d, *J*=12.0, CH_2OBn), 5.09 (1H, d, *J*=12.5, CH_2OBn), 4.08 (1H, br s, CH), 3.77 (1H, br s, CH_2), 3.30 (1H, br dd, *J*=8.5, 8.5, CH_2), 1.34 (9H, s, $C(CH_3)_3$), 1.20 (9H, s, $C(CH_3)_3$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 169.1 (CO), 156.0 (CO), 136.3 (ArC), 128.5 (ArCH), 128.1 (ArCH), 128.1 (ArCH), 74.1 ($OCMe_3$), 66.9 (CH_2OBn), 62.0 (CH_2), 54.4 (CH), 51.2 ($NCMe_3$), 28.7 ($C(CH_3)_3$), 27.4 ($C(CH_3)_3$). IR (neat) ν_{max}/cm^{-1} = 3325, 2971, 1720, 1661, 1498, 1454. HRMS (ES$^+$, MeOH) Calc. for $C_{19}H_{30}N_2O_4Na$ ([M+Na]$^+$) = 373.2103, found 373.2094. $[\alpha]_D^{20}$ = 16.4 (*c* 1, CH_2Cl_2).

Z-ProNH^{t}Bu

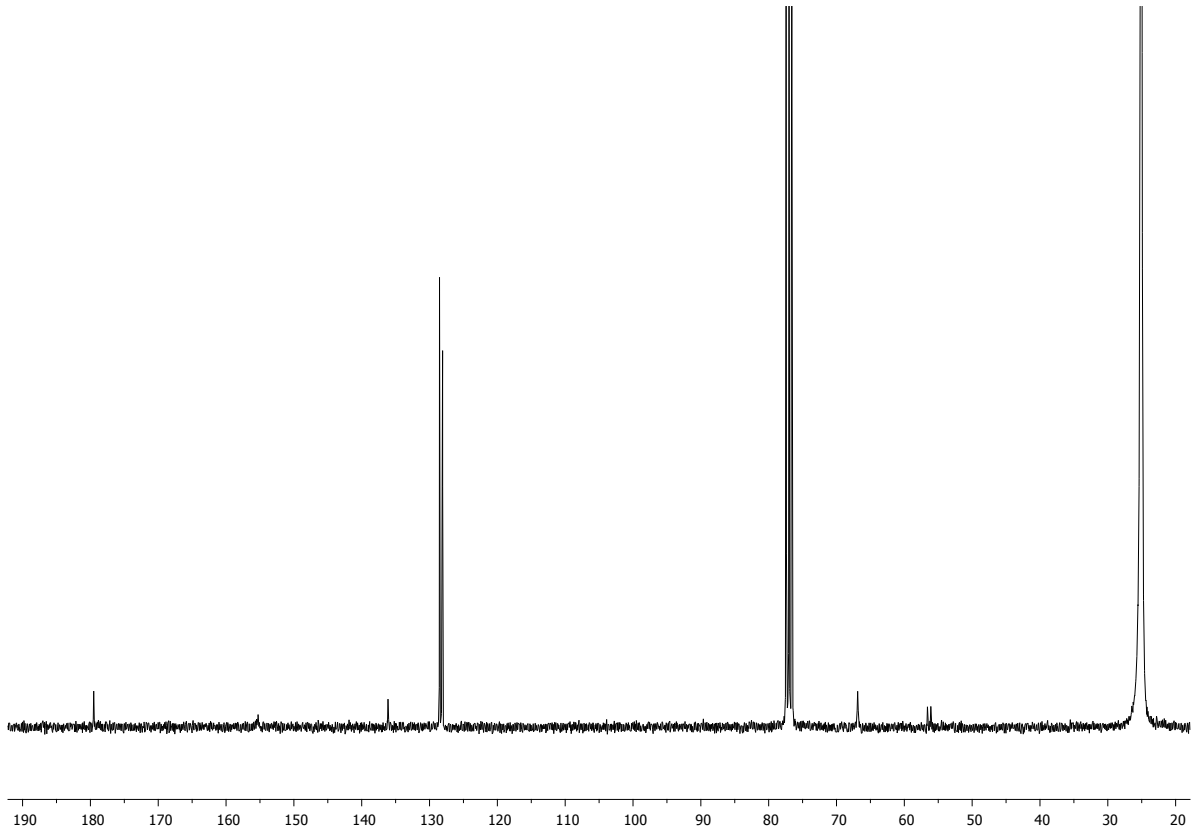


Z-ProNH^{t}Bu was prepared according to general procedure C (1 mmol scale). The pure product (289 mg, 95%) was isolated as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.26 (5H, m, ArCH x5), 6.48 (1H, br s, NH), 5.57 (1H, br s, NH), 5.05 (2H, br m, CH_2O), 4.14 (1H, br s, CH), 3.39 (2H, br m, CH_2N), 1.75 – 2.30 (4H, br m, CH_2 x2), 1.19 (9H, br m, $C(CH_3)_3$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 128.5 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 67.2 (CH_2O), 61.3 (CH), 51.0 (CMe_3), 47.1 (CH_2N), 31.0 (CH_2), 28.6 ($C(CH_3)_3$), 24.5 (CH_2). ArC and CO (x2) signals not observed due to exchange broadening resulting from amide *cis/trans* isomerisation. IR (neat) ν_{max}/cm^{-1} = 3306, 2974, 2866, 1701, 1656, 1556. HRMS (ES$^+$, MeOH) Calc. for $C_{17}H_{24}N_2O_3Na$ ([M+Na]$^+$) = 327.1685, found 327.1688. Mp 95-98 °C. $[\alpha]_D^{20}$ = –68.4 (*c* 1, CH_2Cl_2).

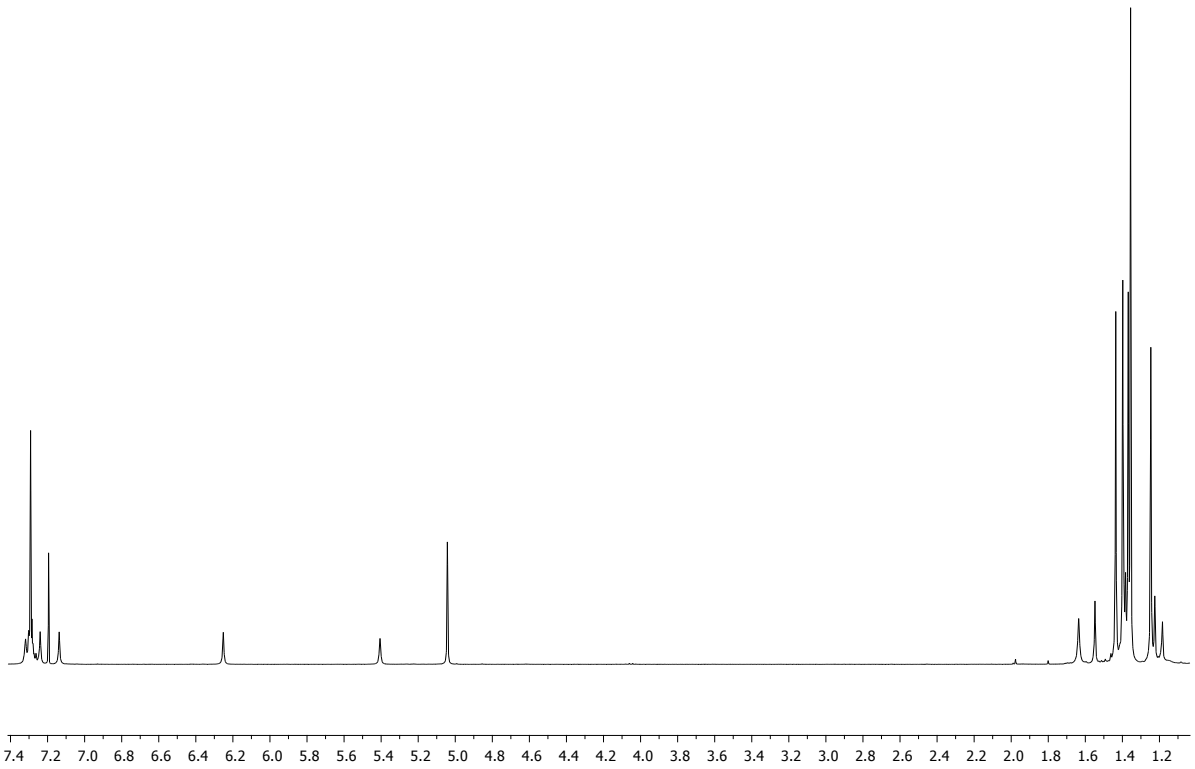
^{1}H-NMR of Cbz-(*R*)-Aib*-OH



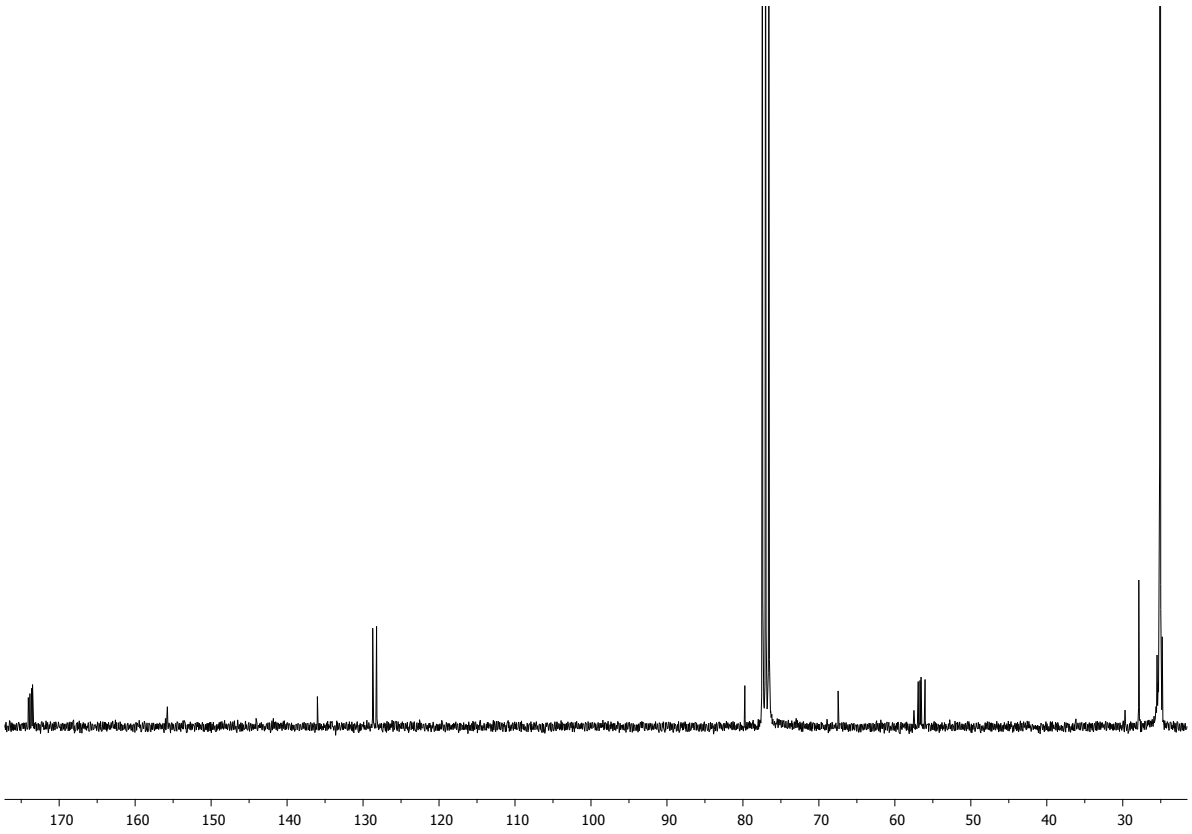
^{13}C-NMR of Cbz-(*R*)-Aib*-OH



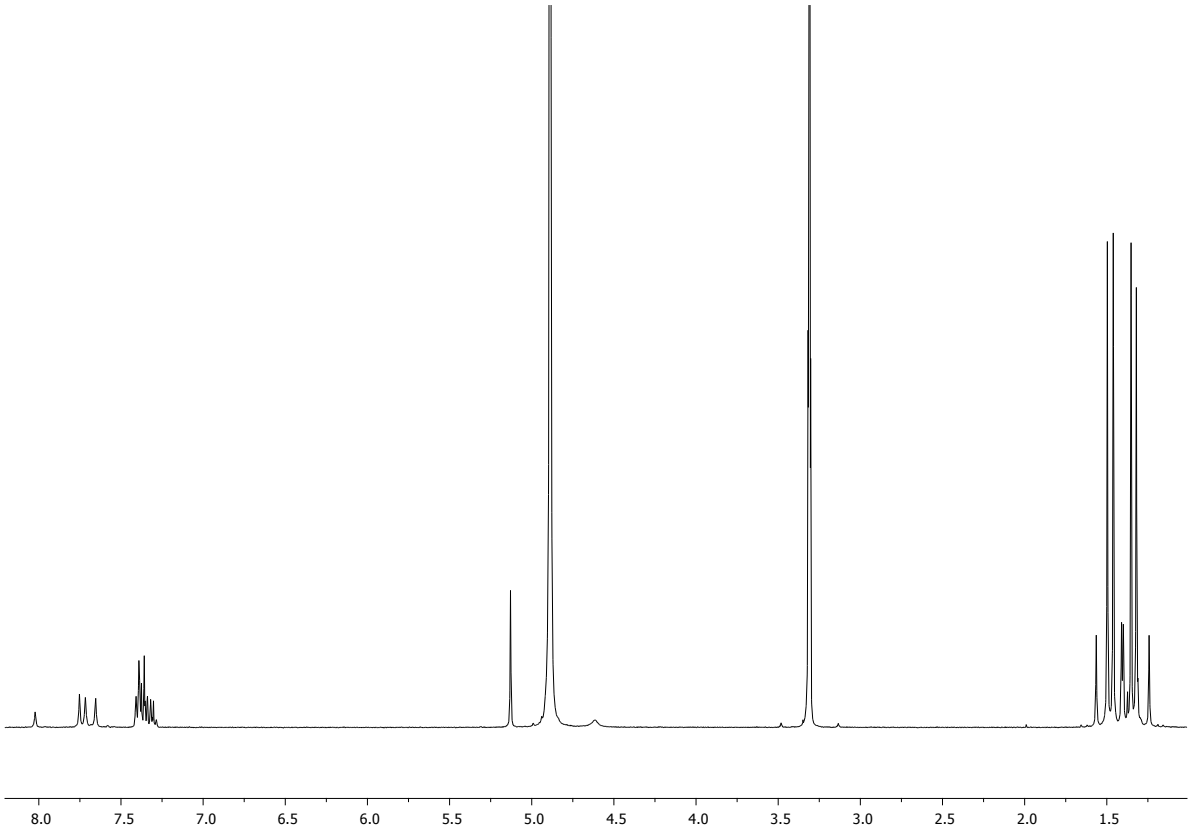
^{1}H-NMR of Cbz-(*R*)-Aib*-Aib$_4$-O^{t}Bu



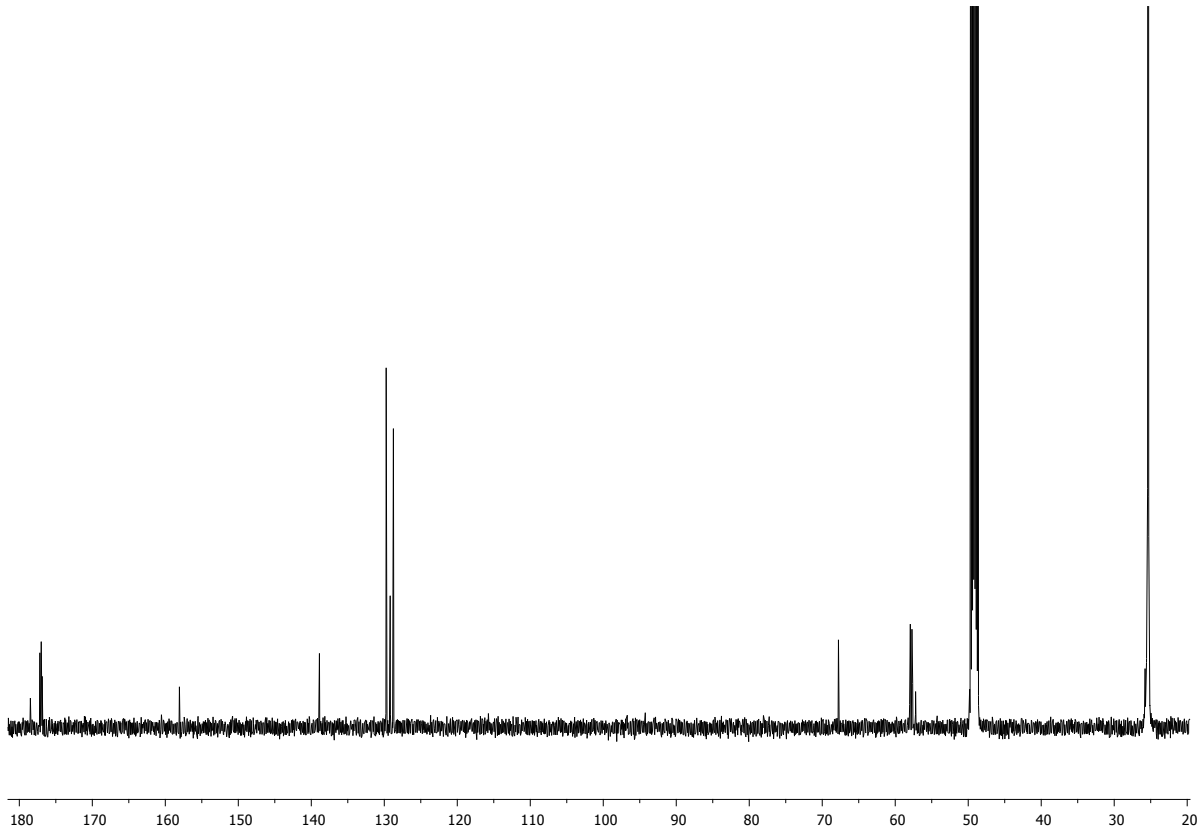
^{13}C-NMR of Cbz-(*R*)-Aib*-Aib$_4$-O^{t}Bu



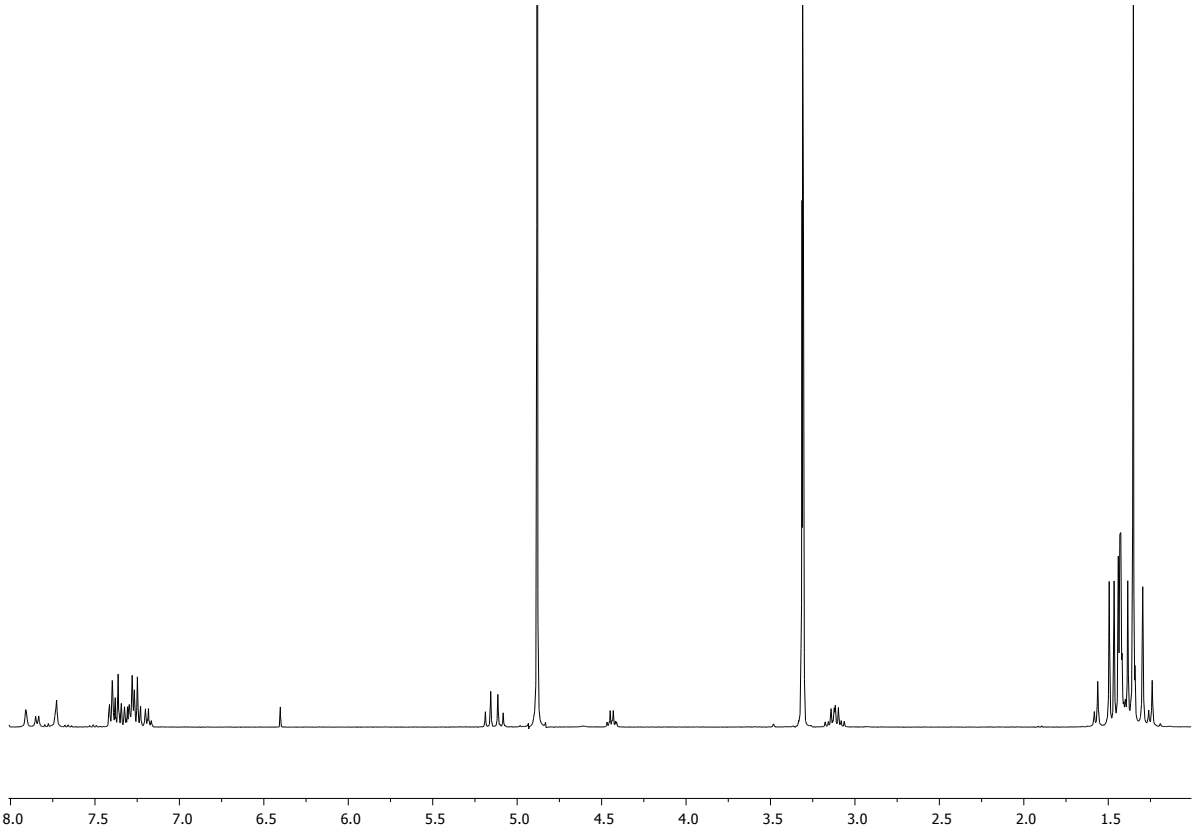
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-OH



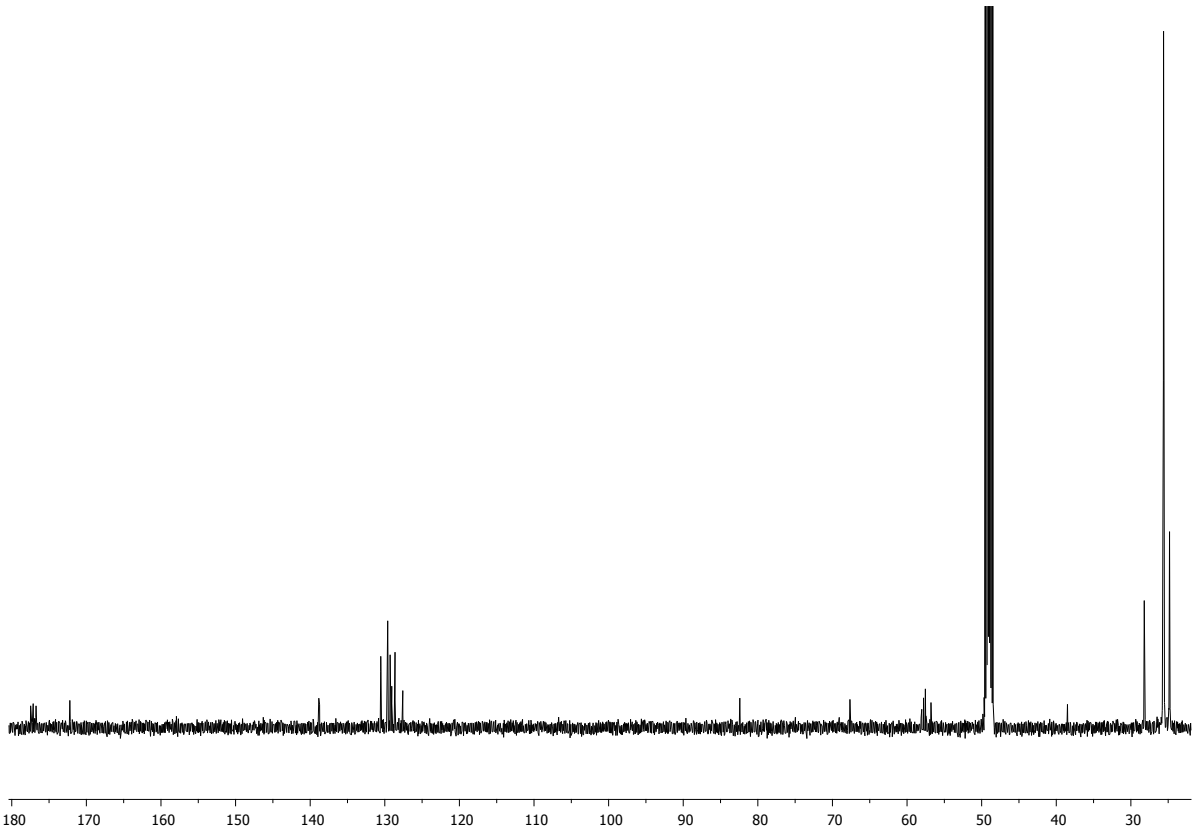
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-OH



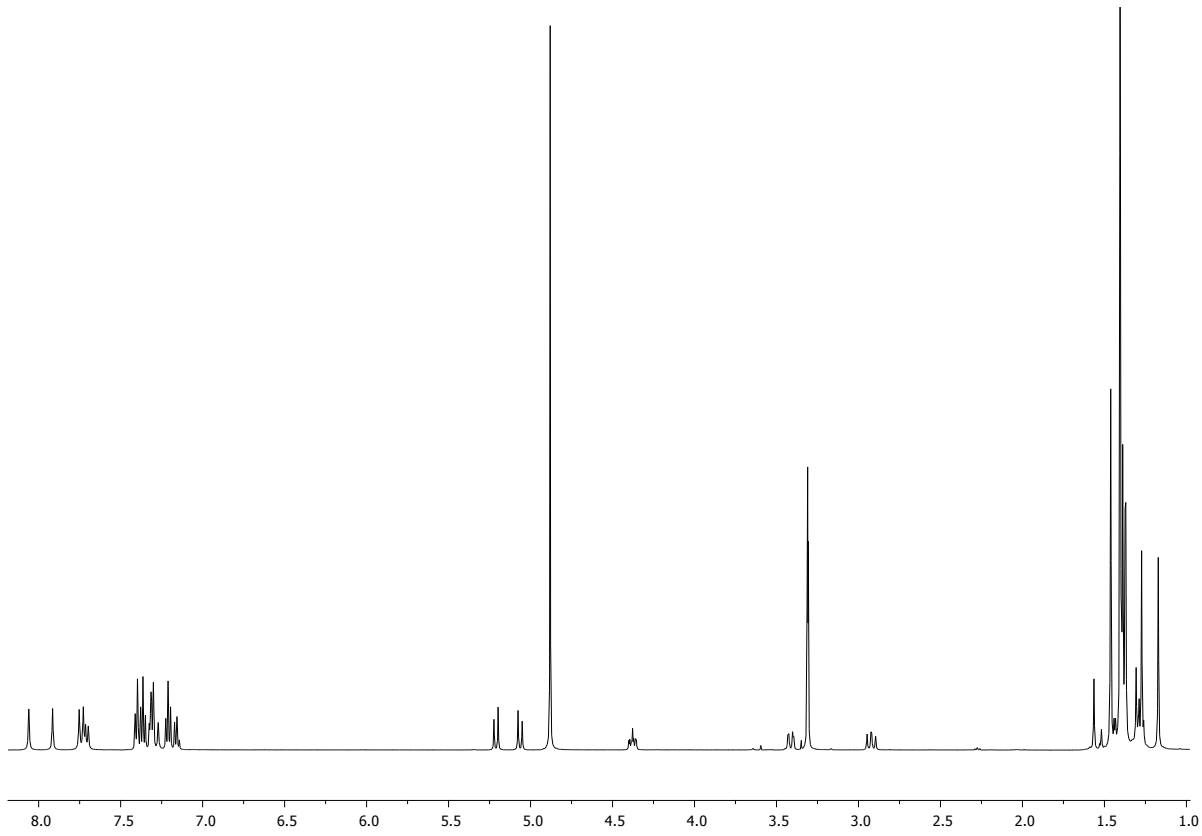
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-PheO^{t}Bu



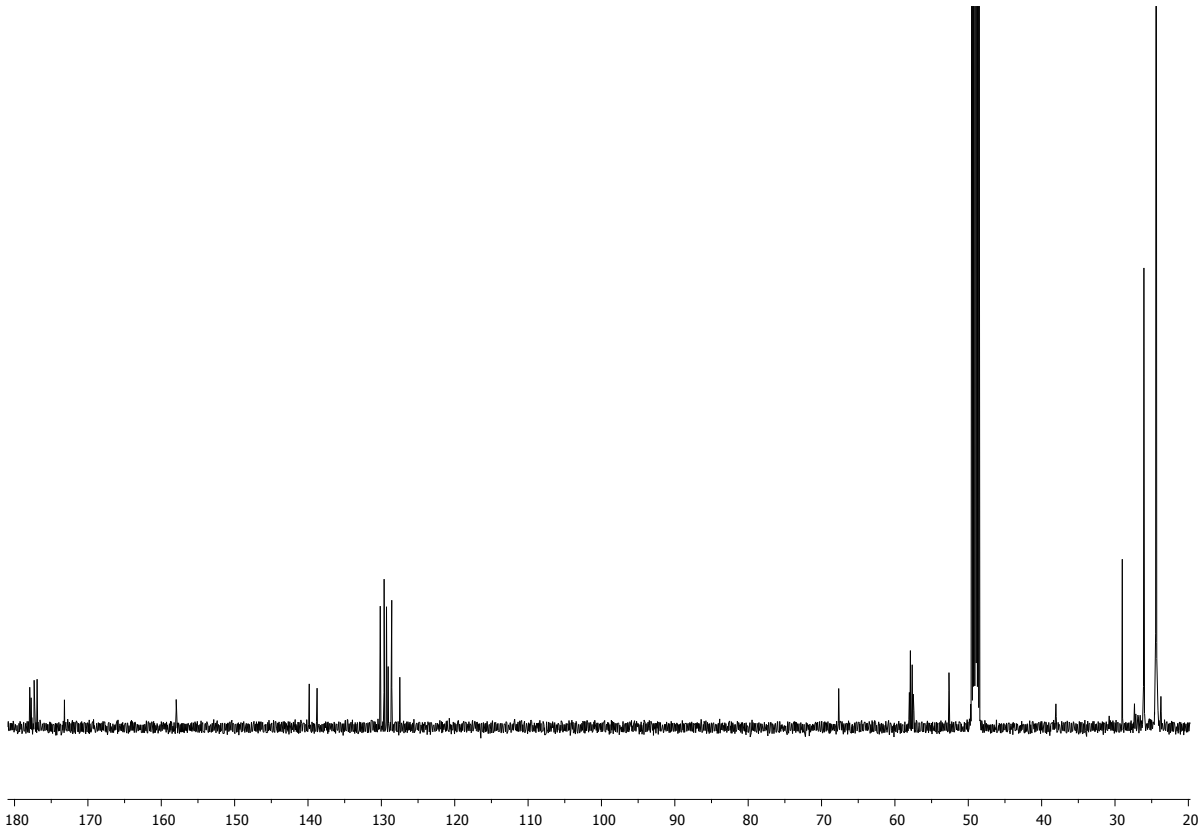
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-PheO^{t}Bu



^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-PheNH^{t}Bu



^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-PheNH^{t}Bu



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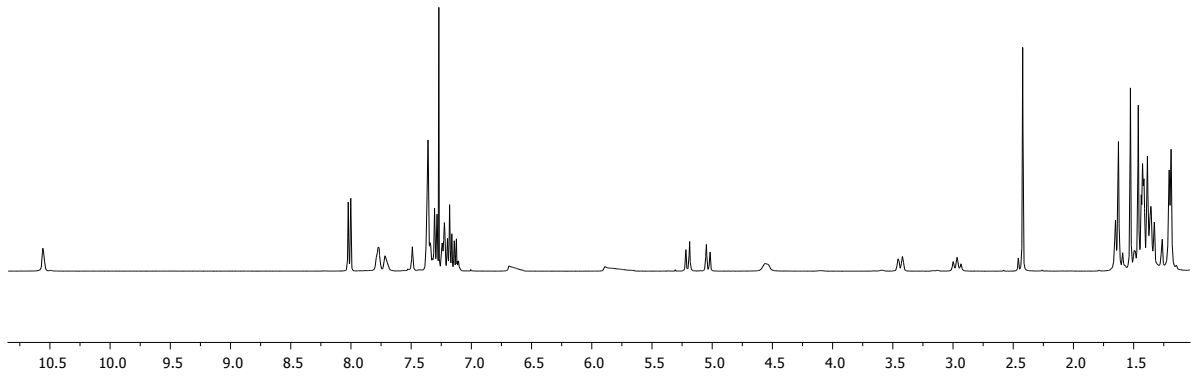
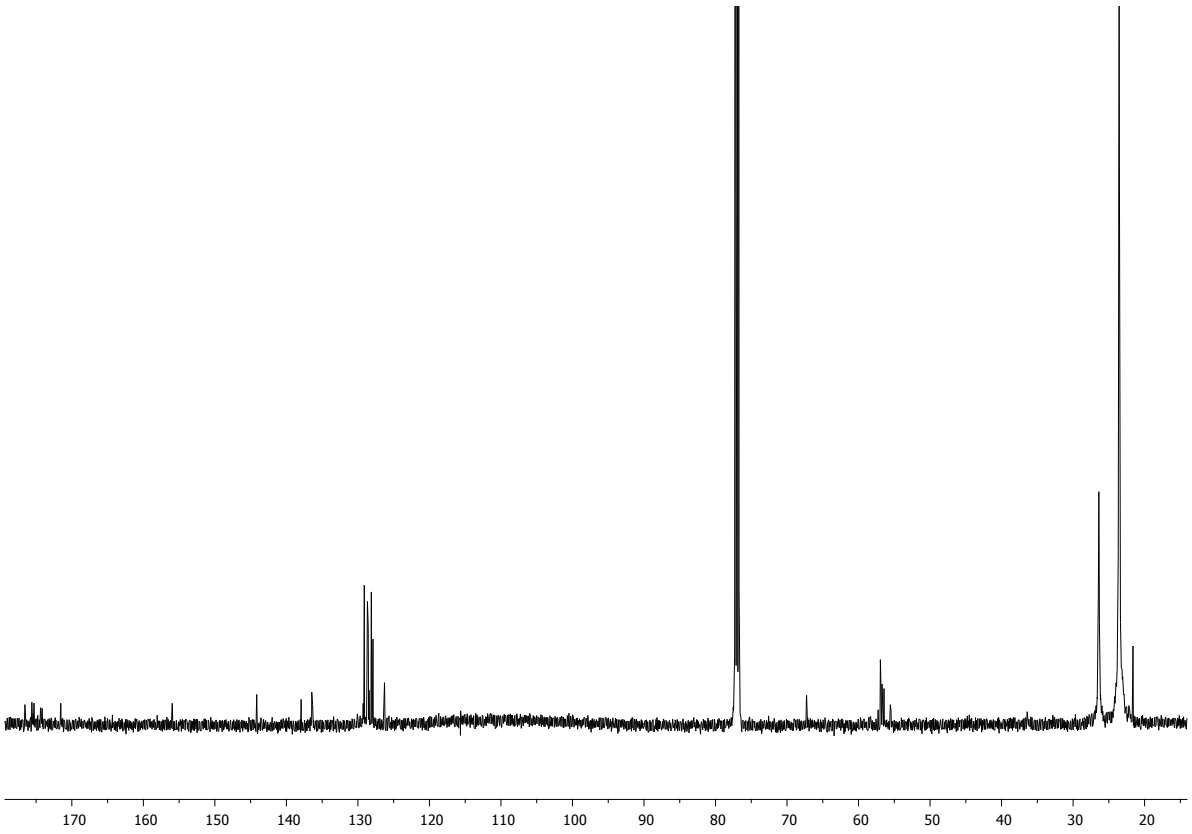


^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-PheNHTs



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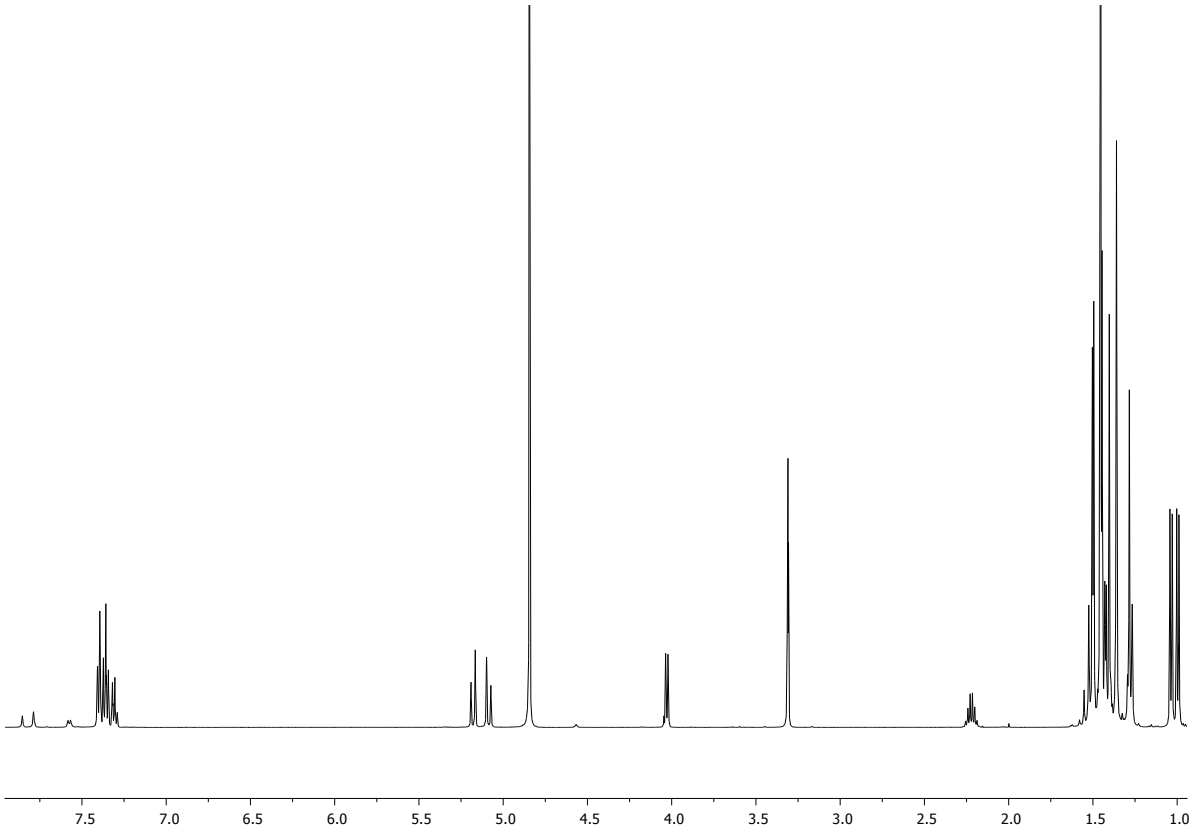

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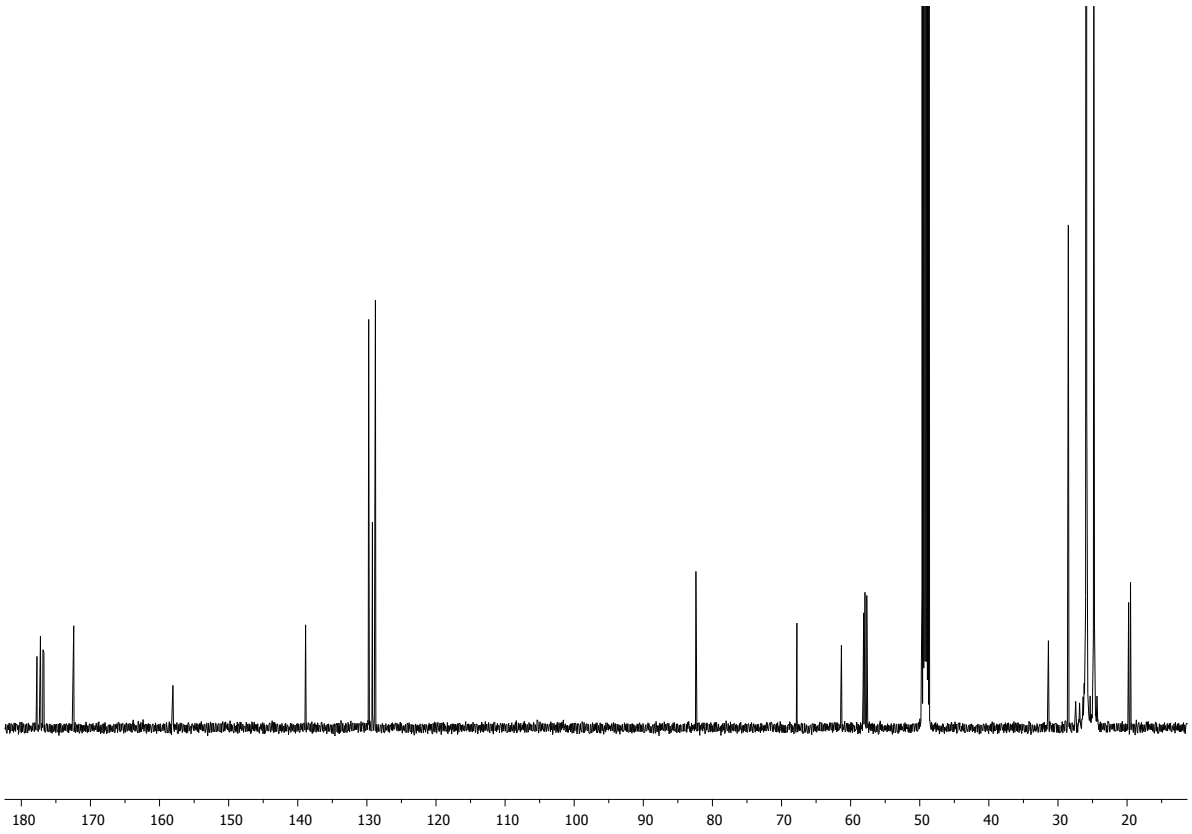

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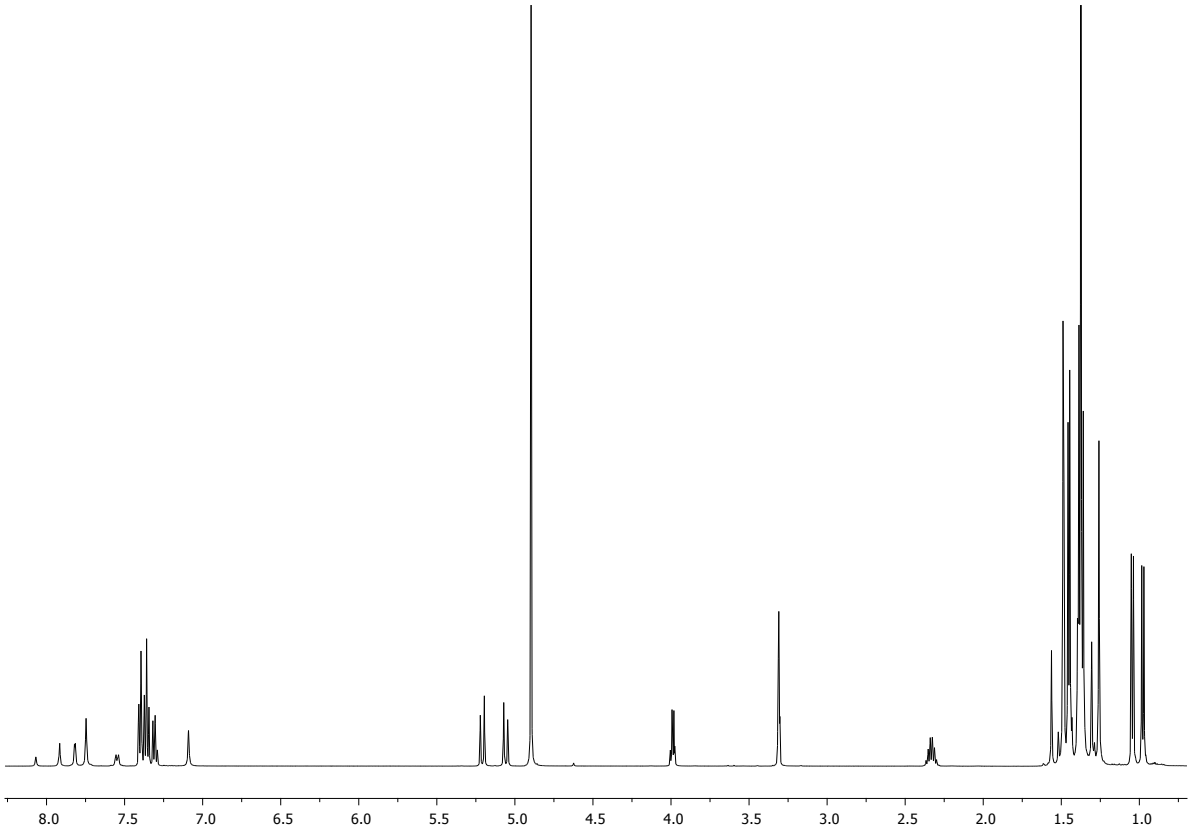
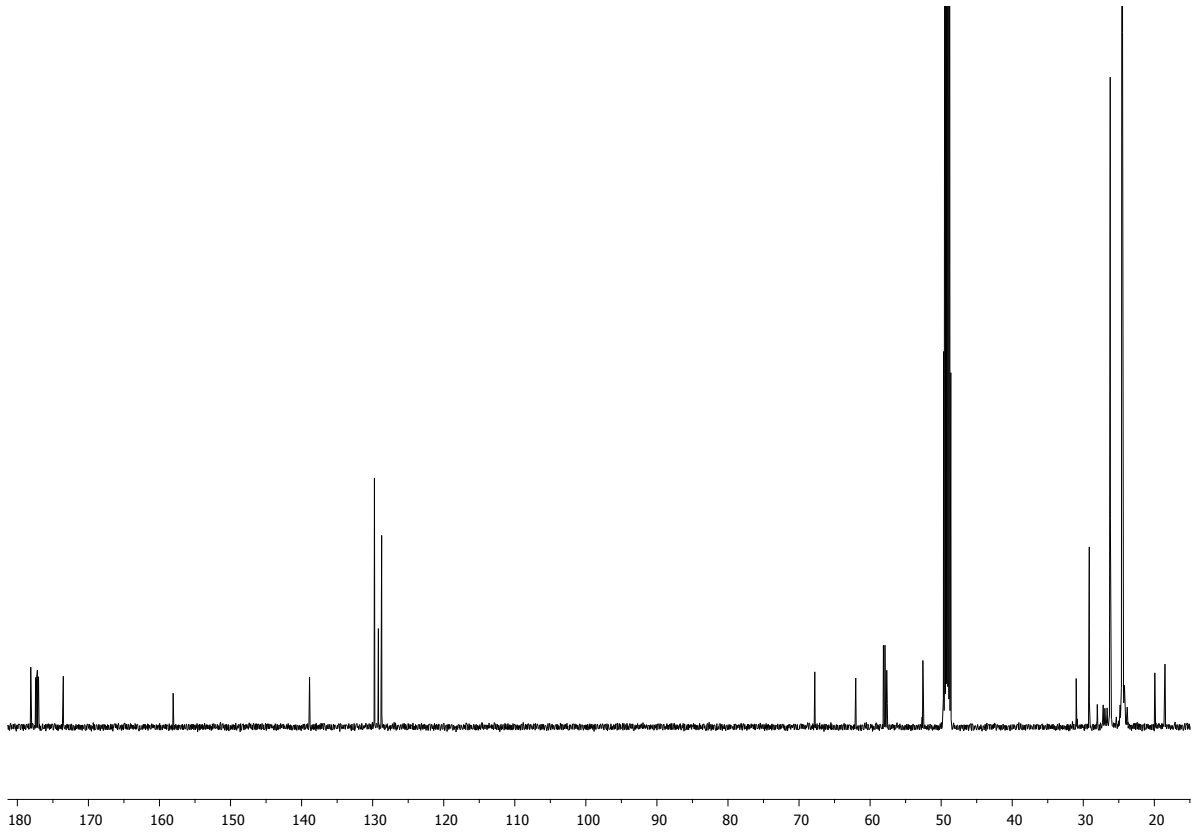
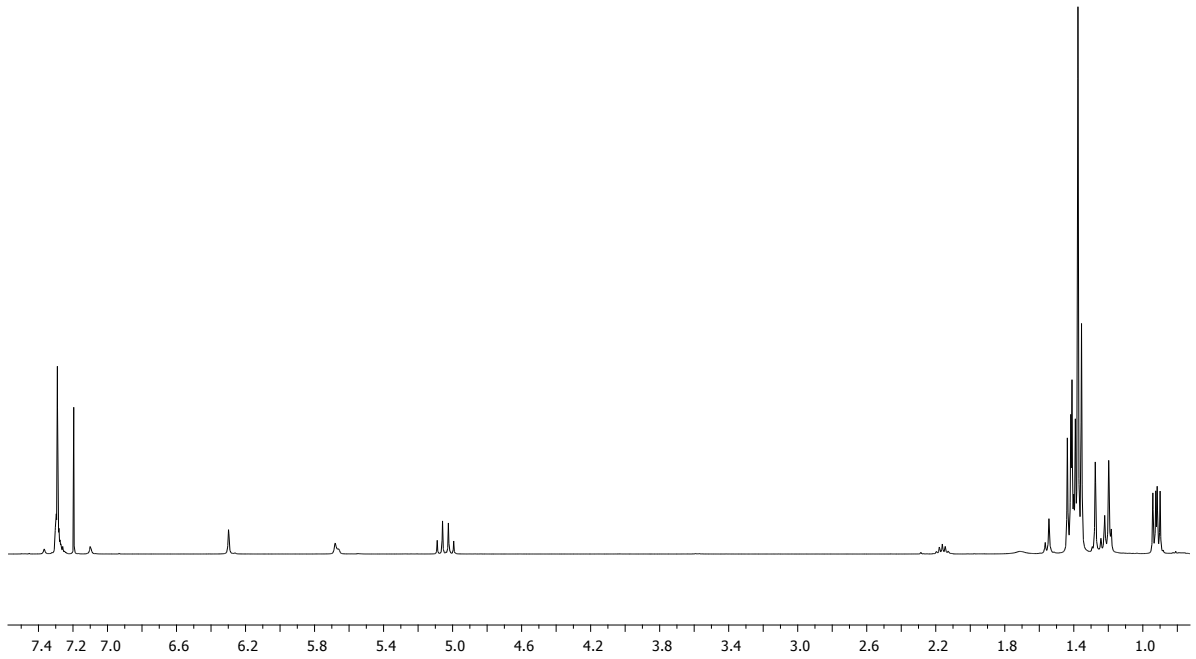


^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-ValNH^{t}Bu



^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-αMvO^{t}Bu



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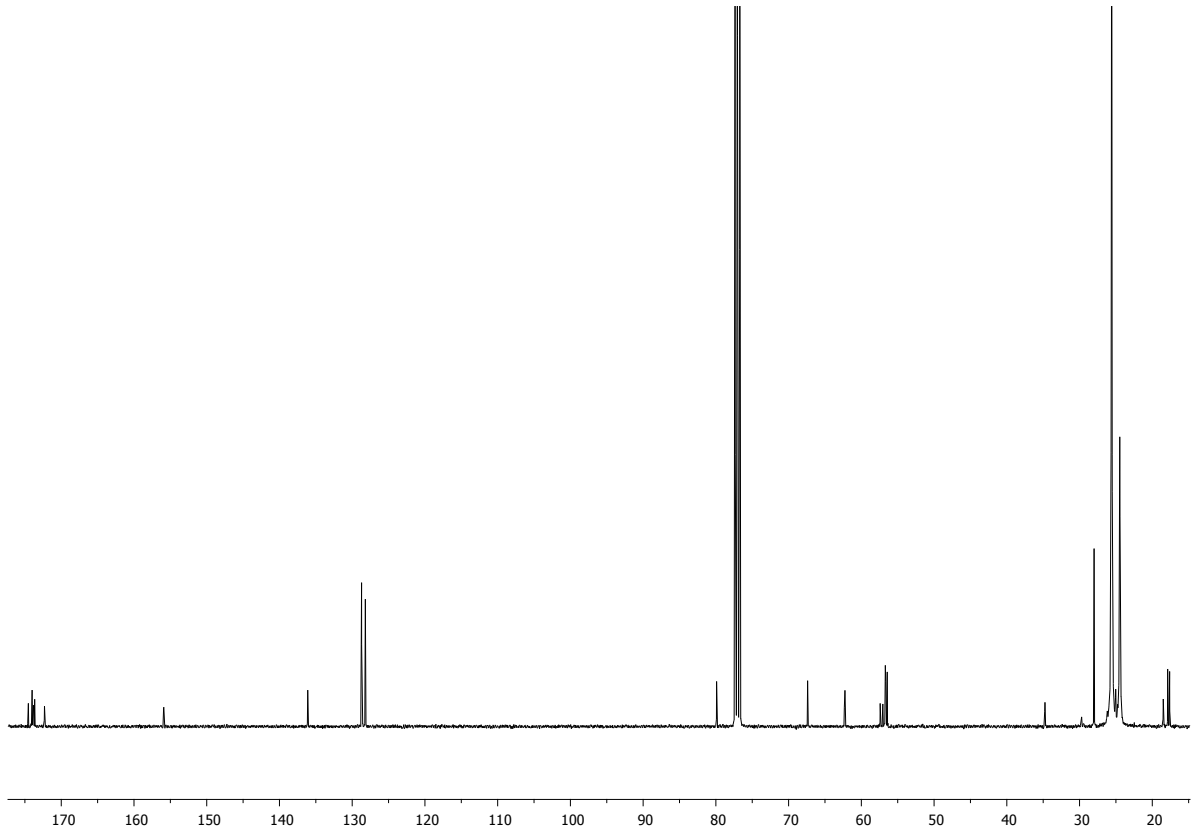

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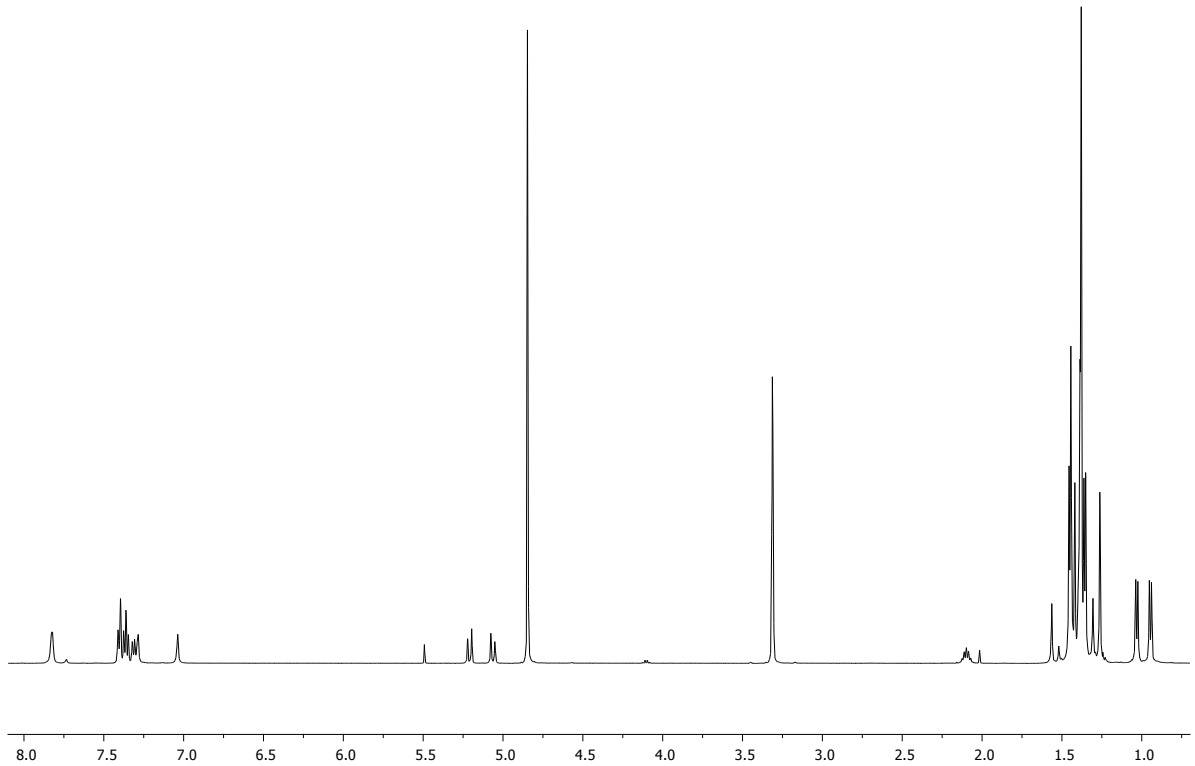

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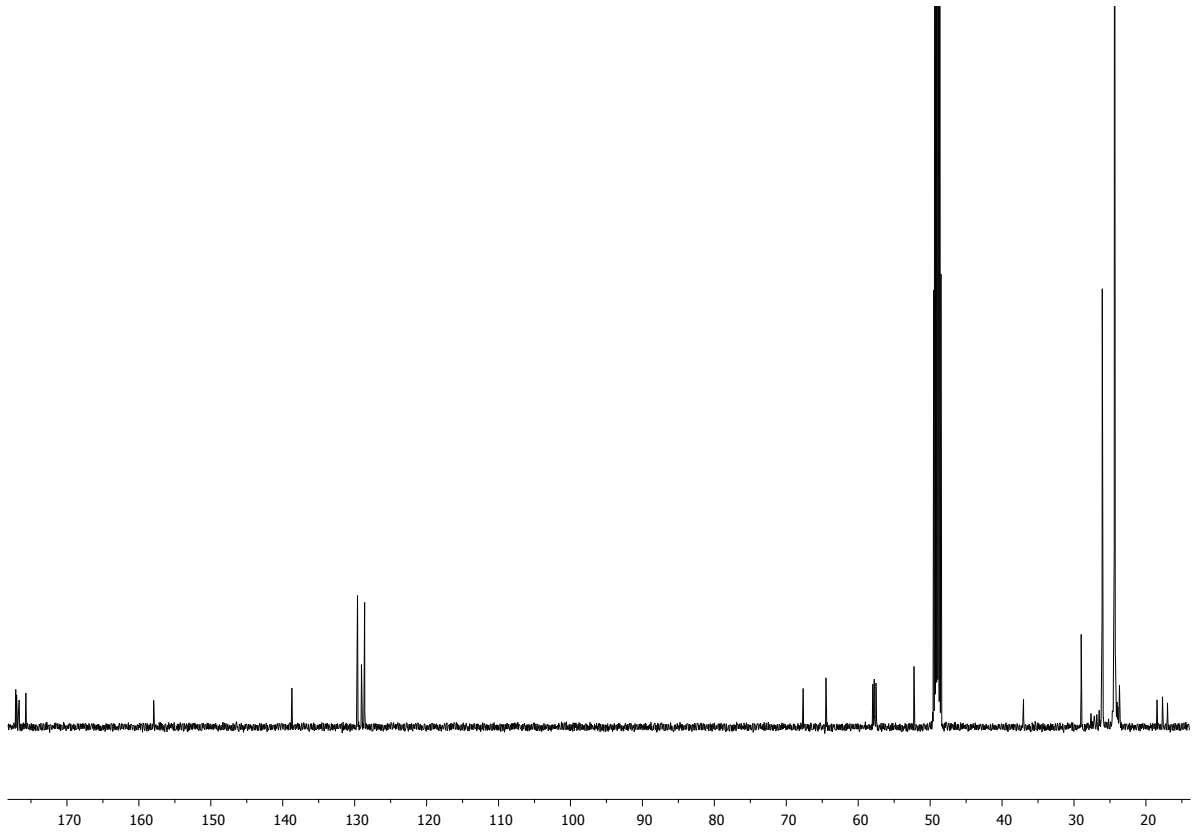
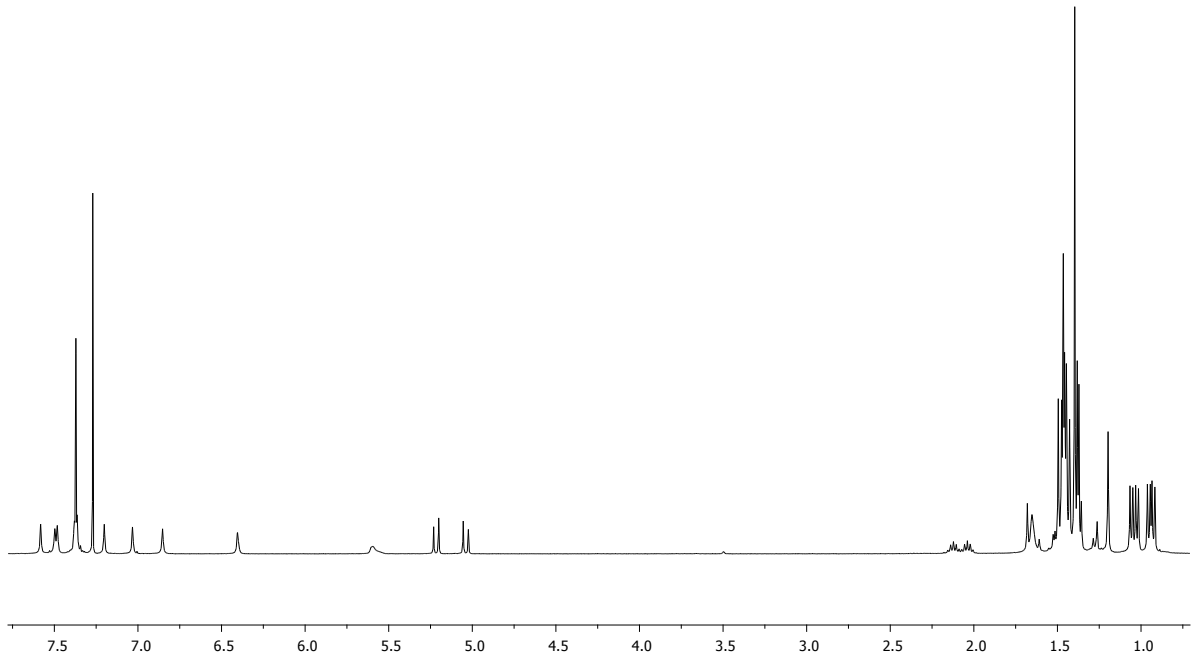


^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-(αMv)$_2$NH^{t}Bu



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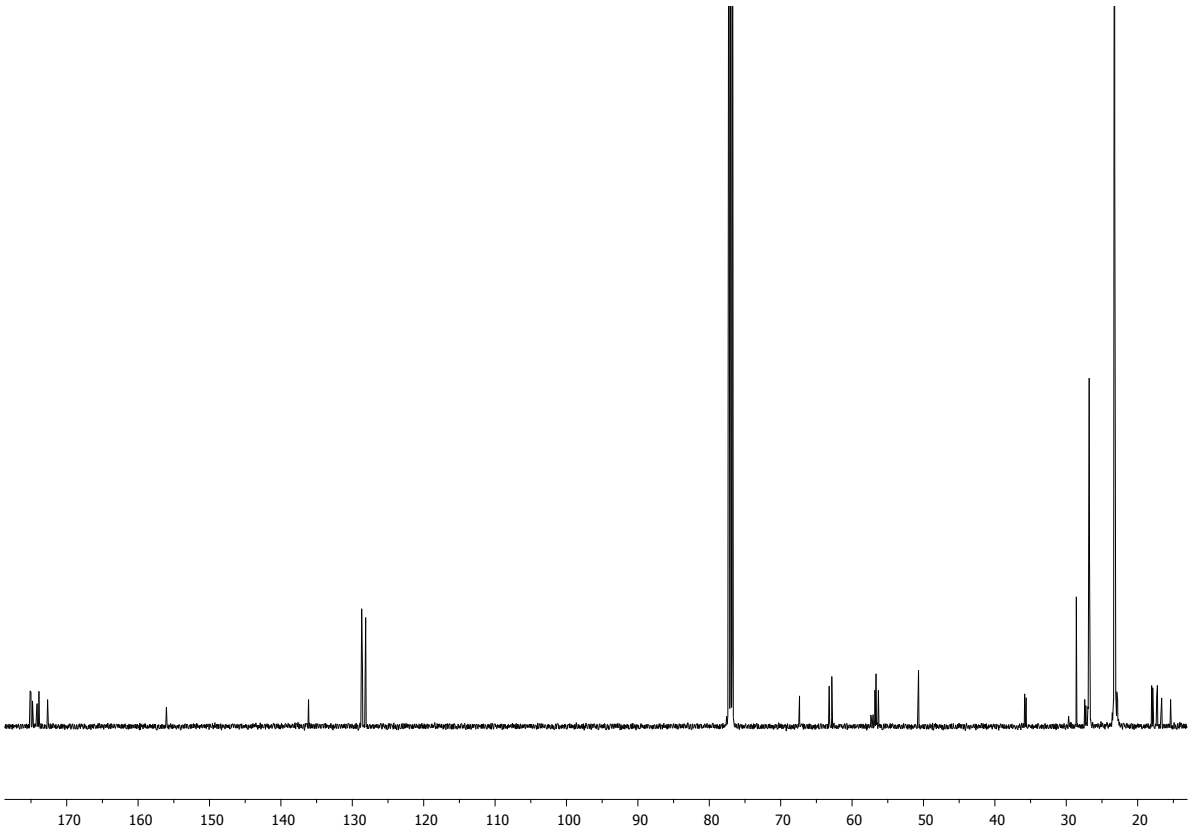
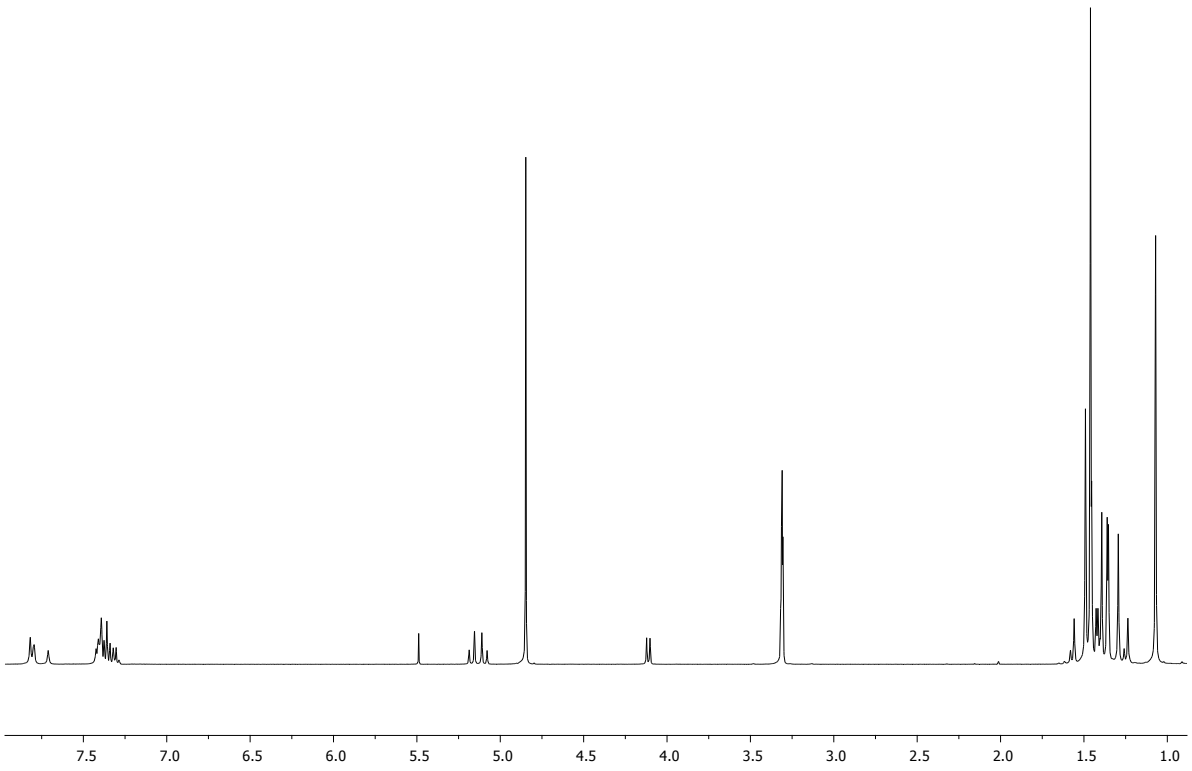


^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-TleO^{t}Bu



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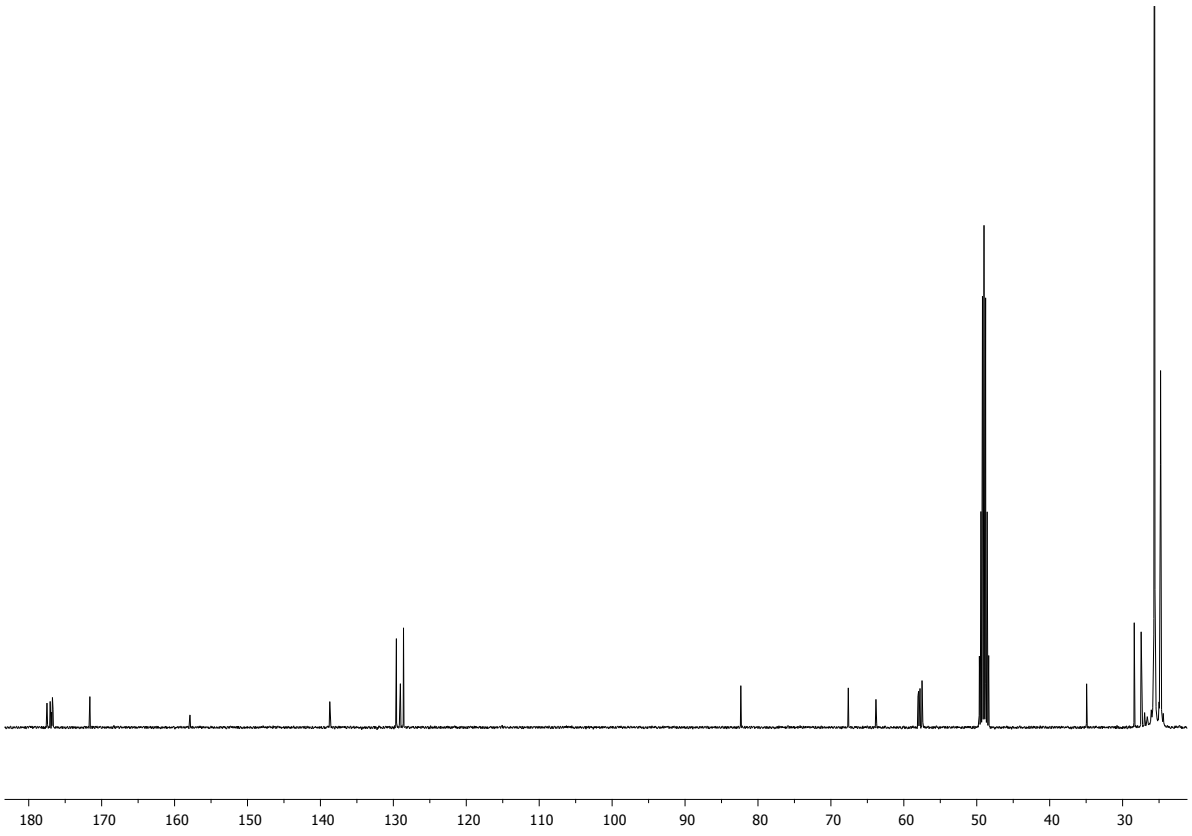

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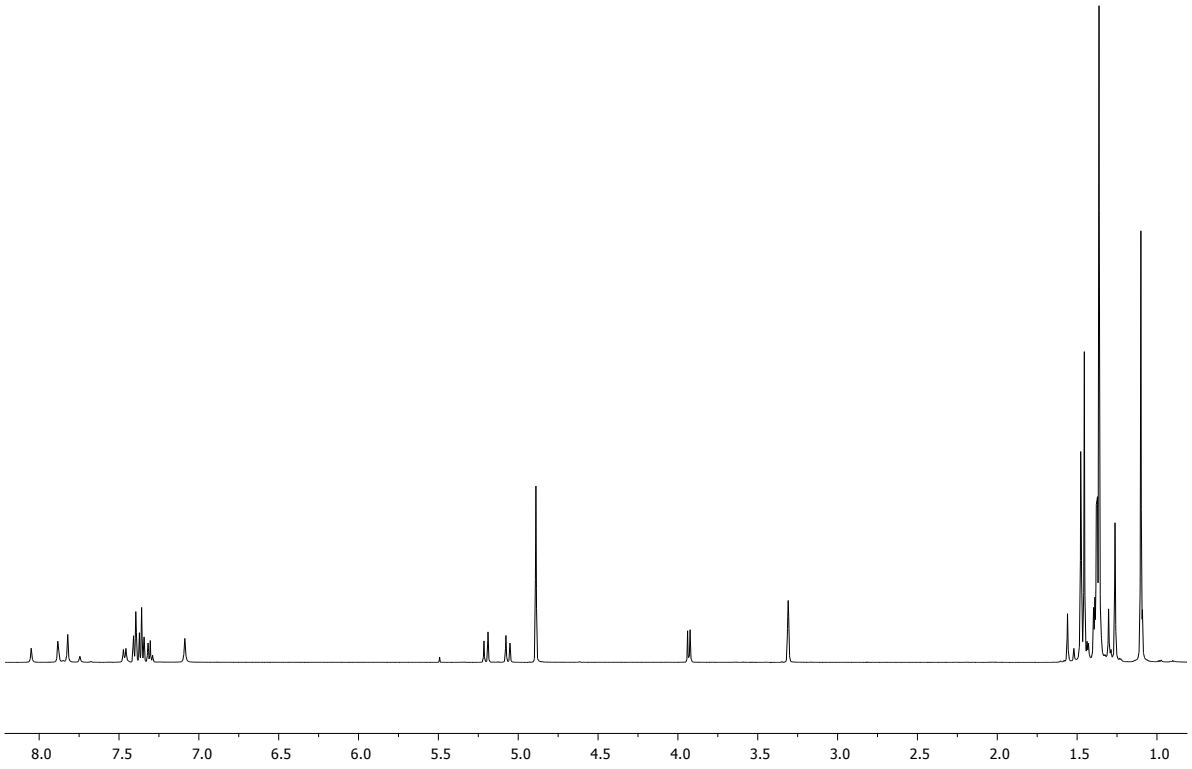

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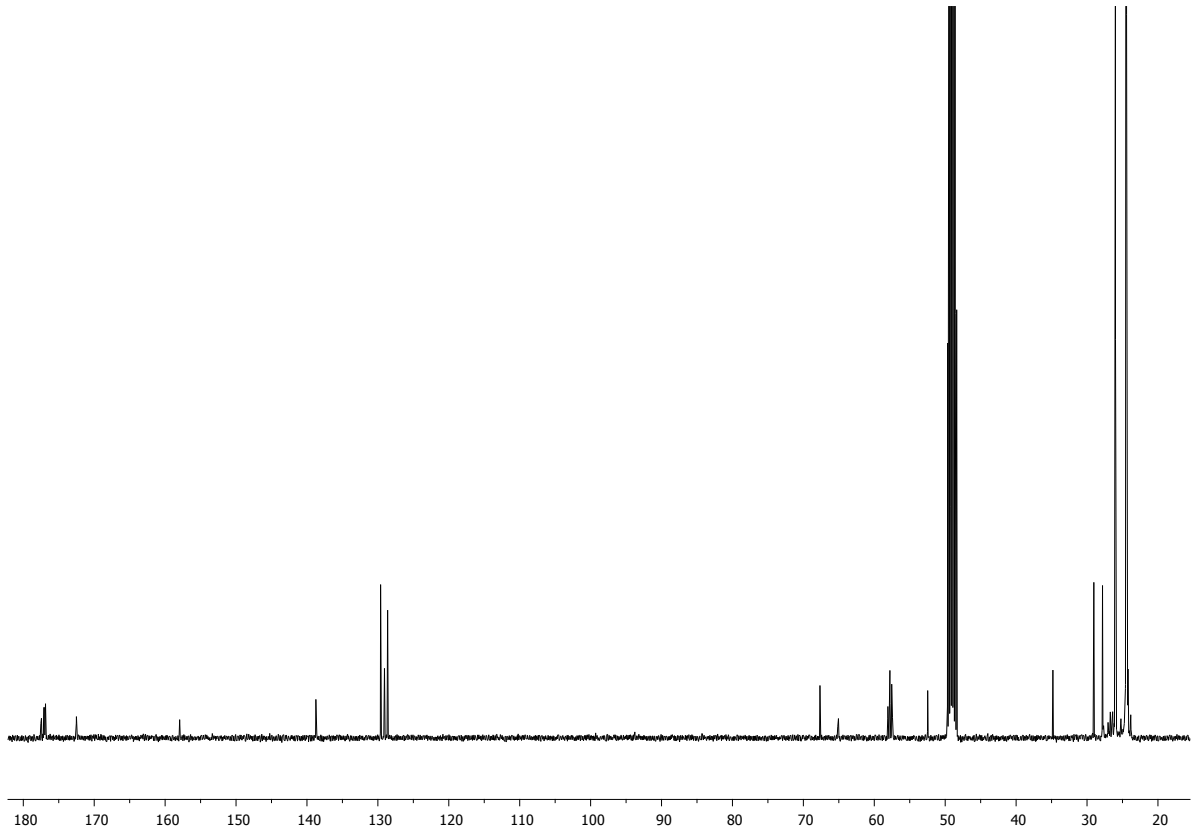
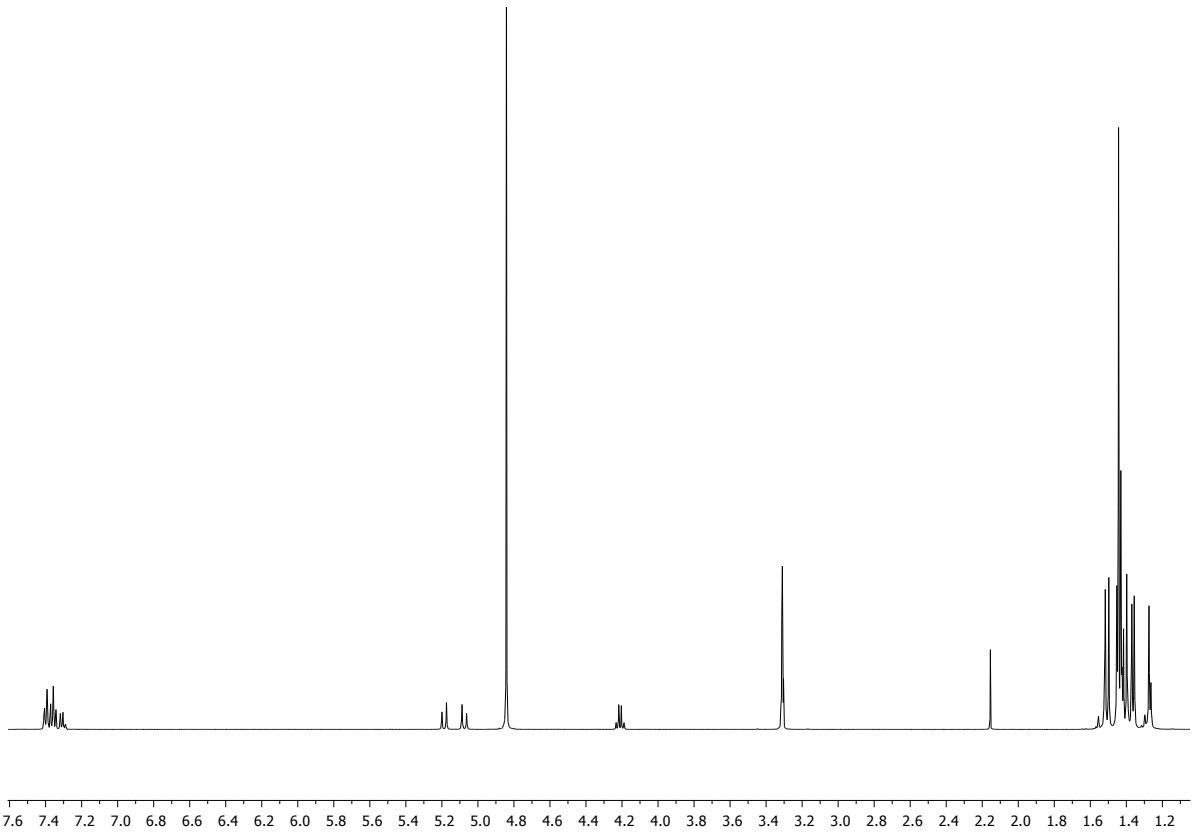


^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaO^{t}Bu



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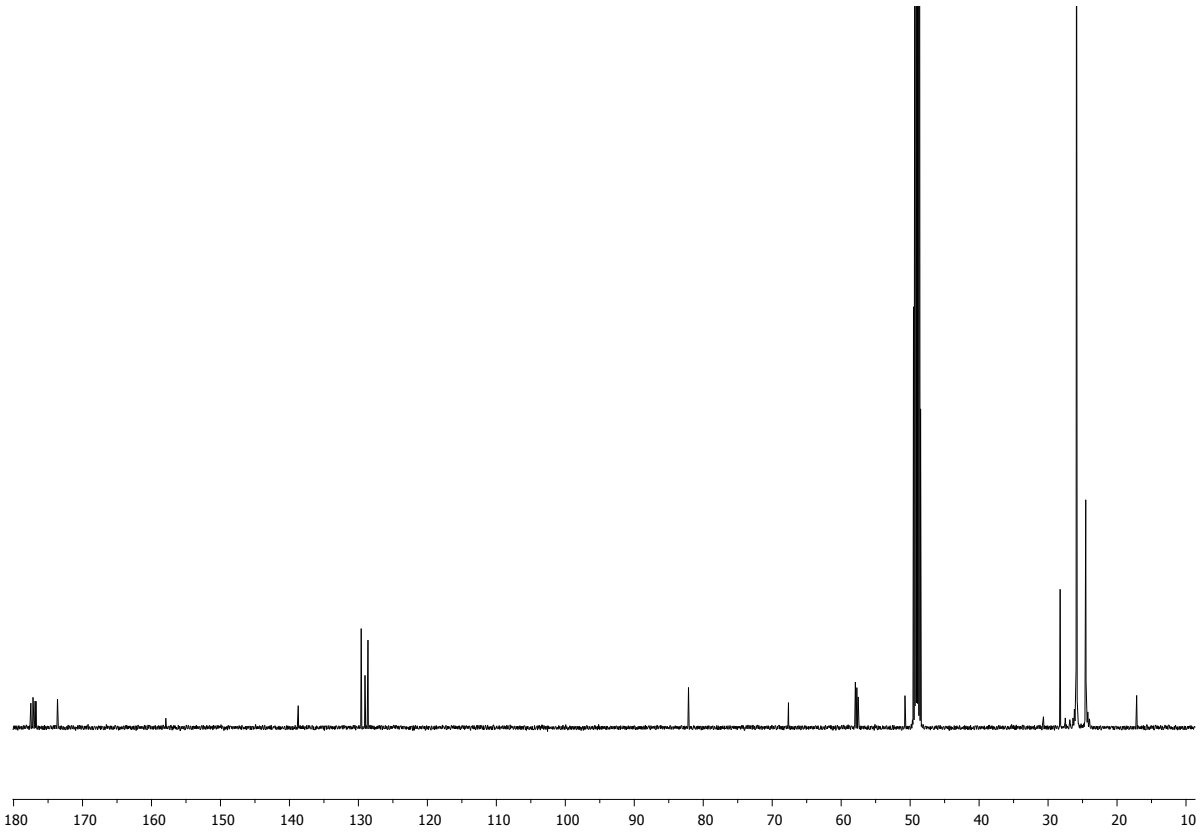
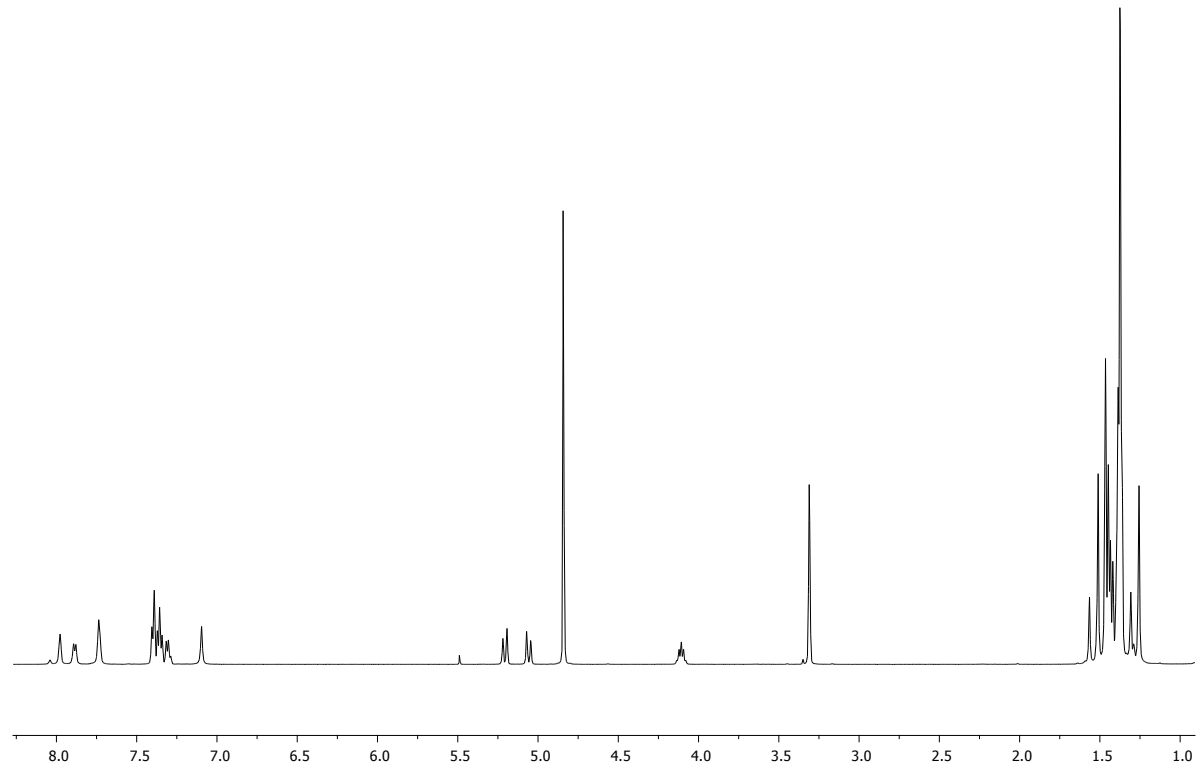
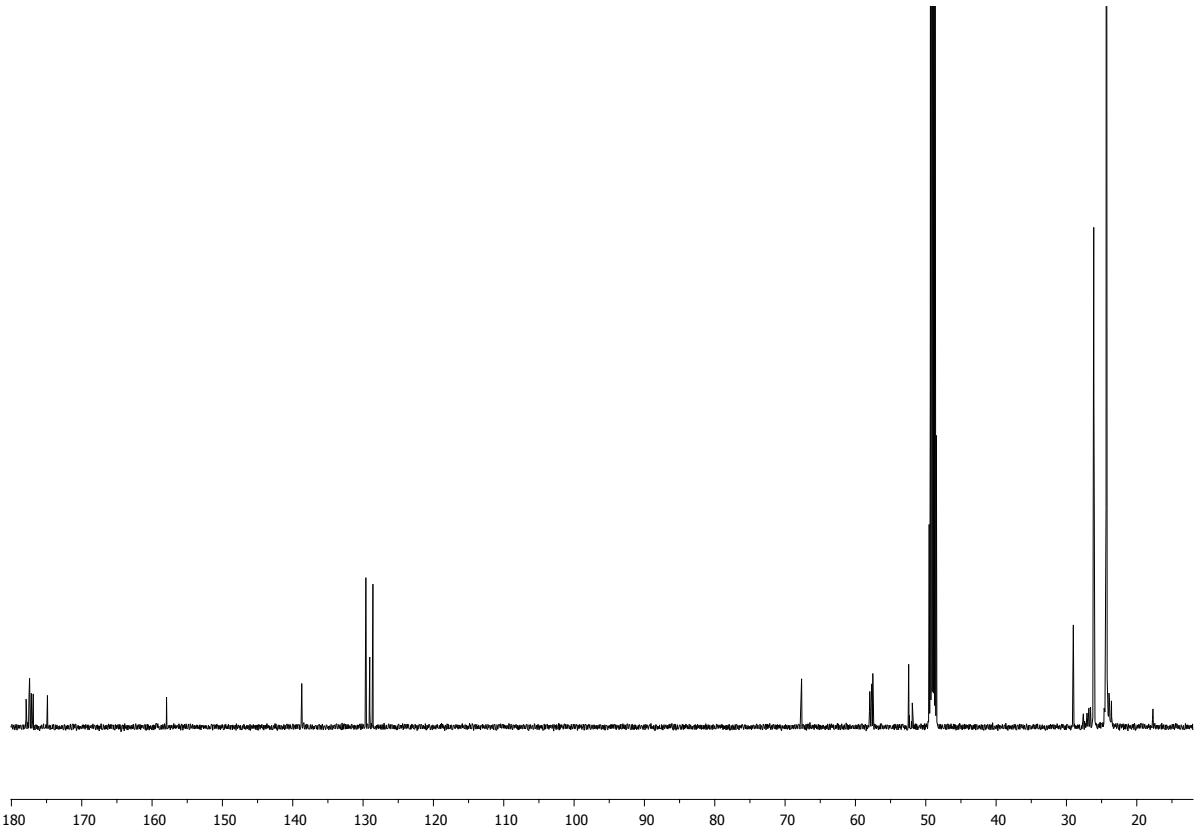


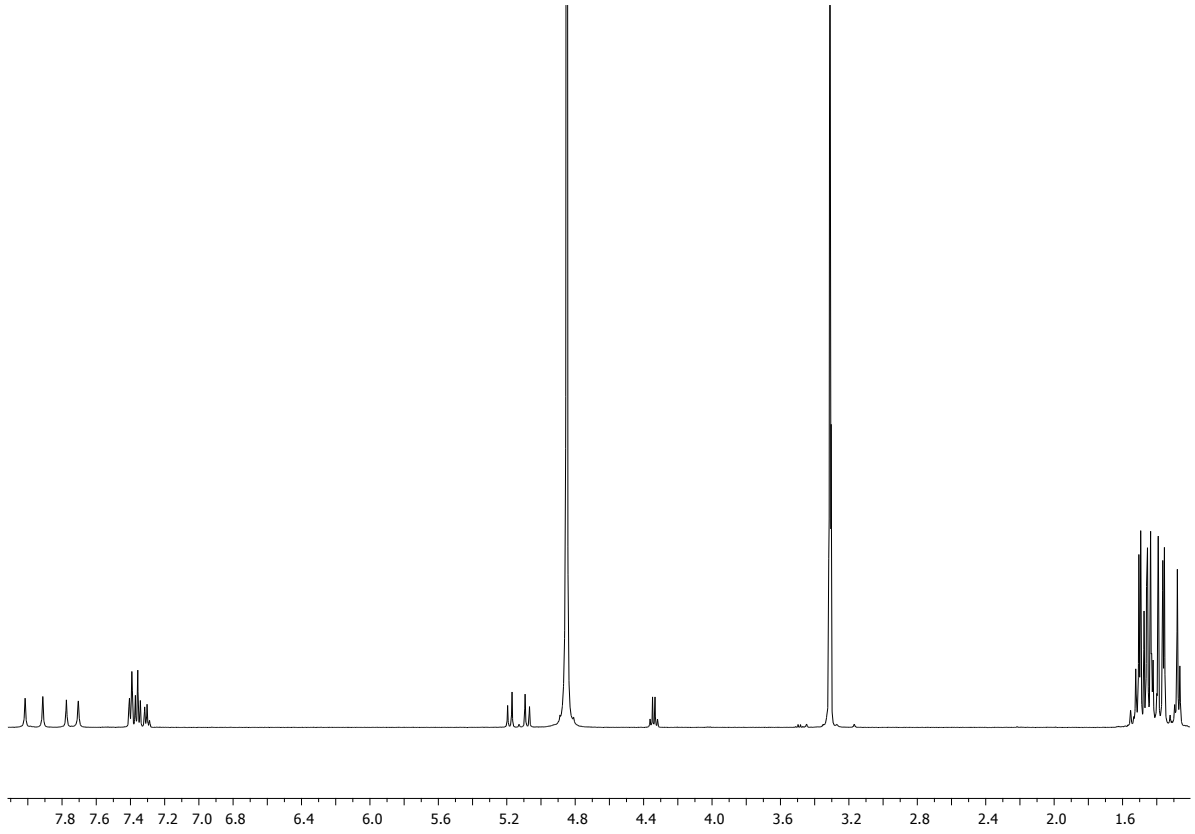
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaNH^{t}Bu



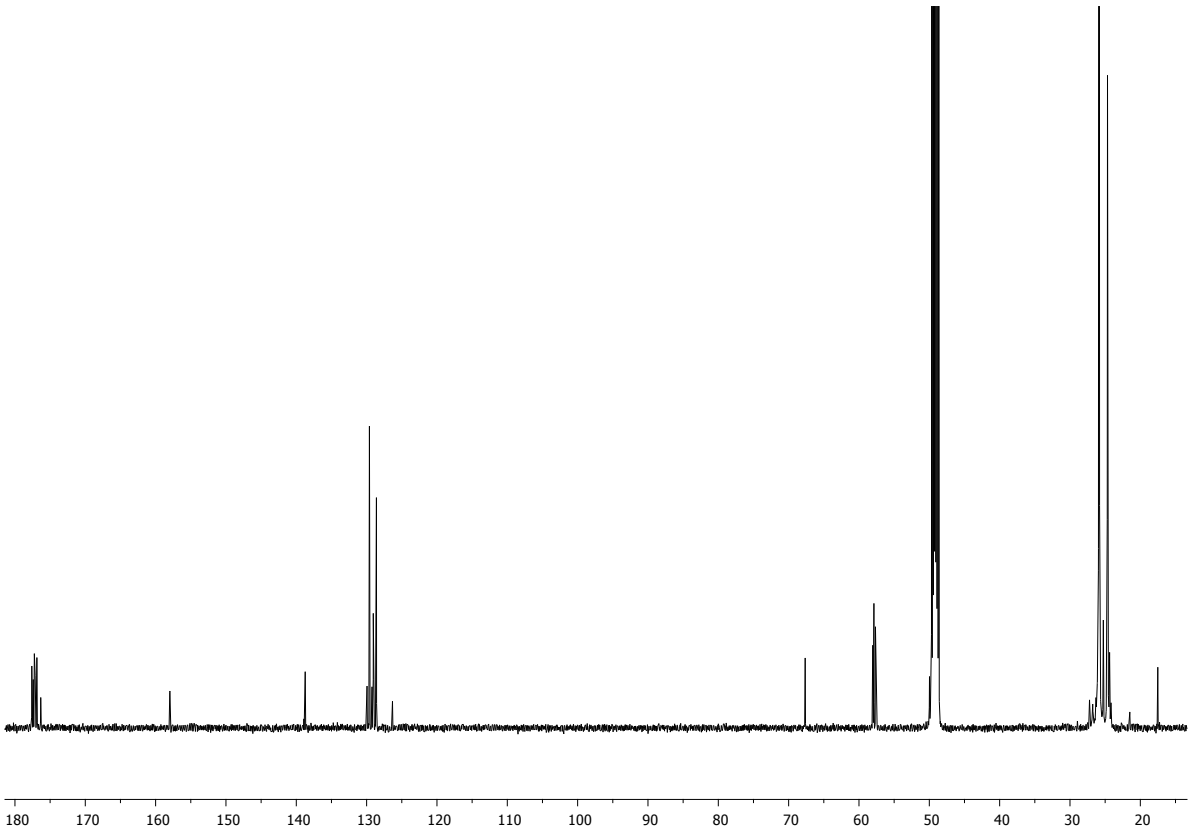
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaNH^{t}Bu



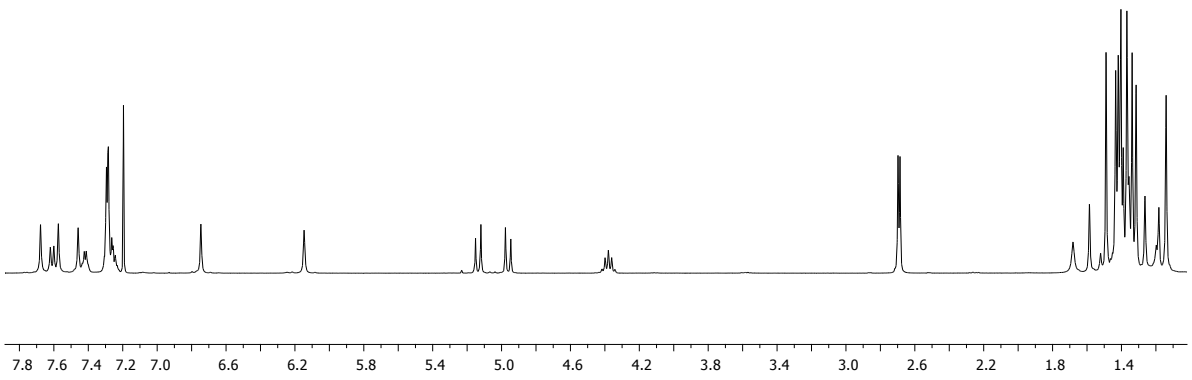
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaOH



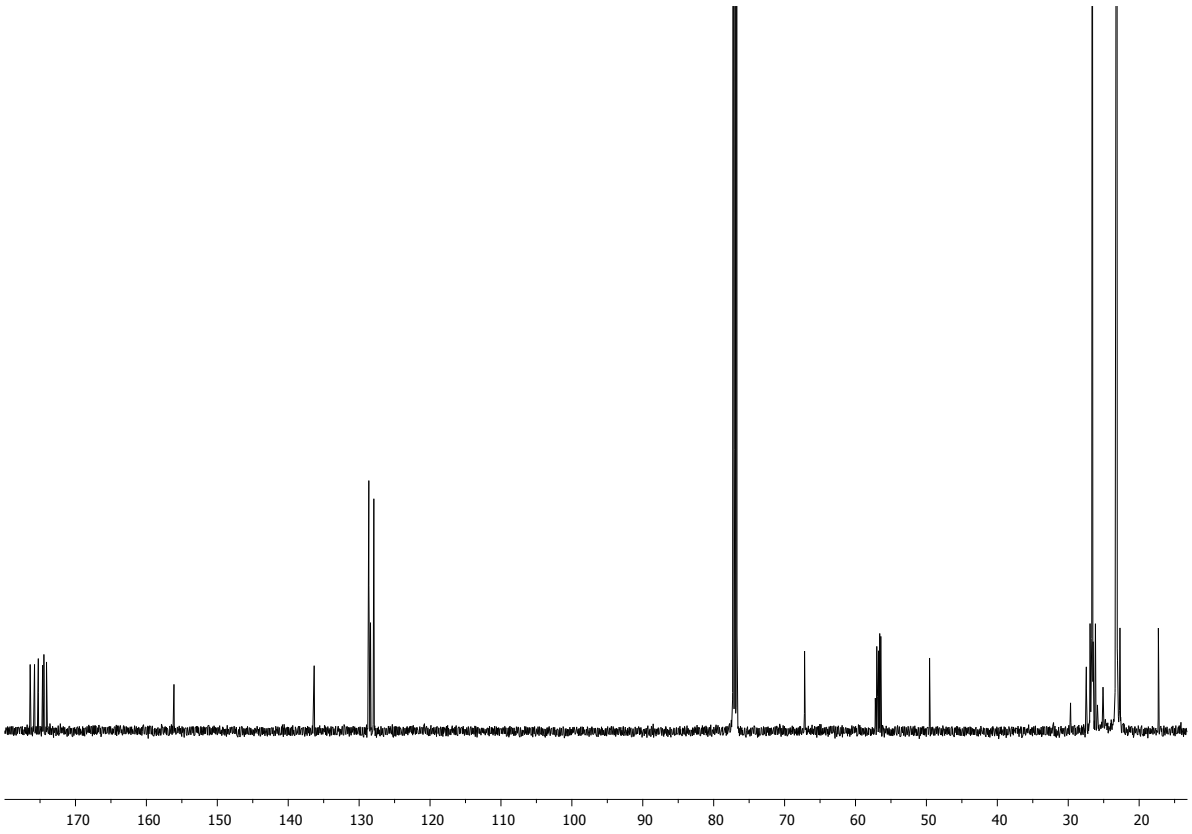
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaOH



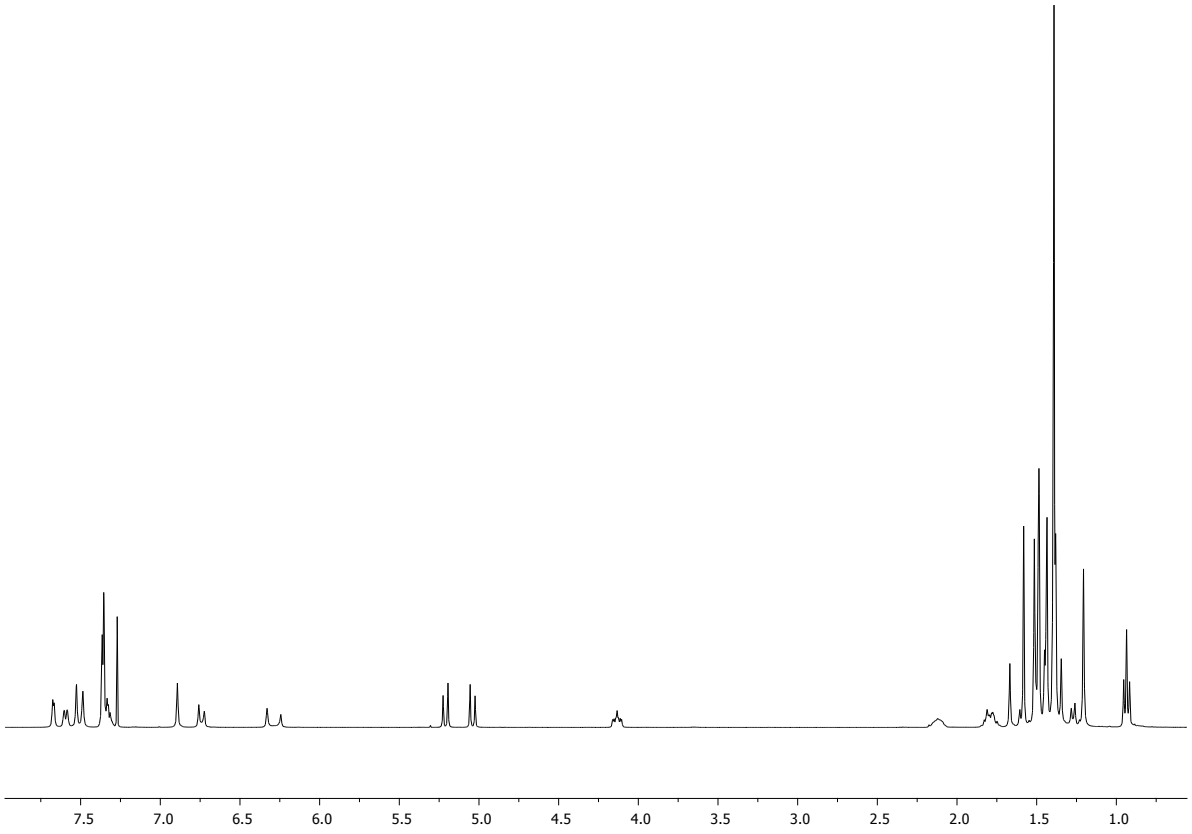
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaNHMe



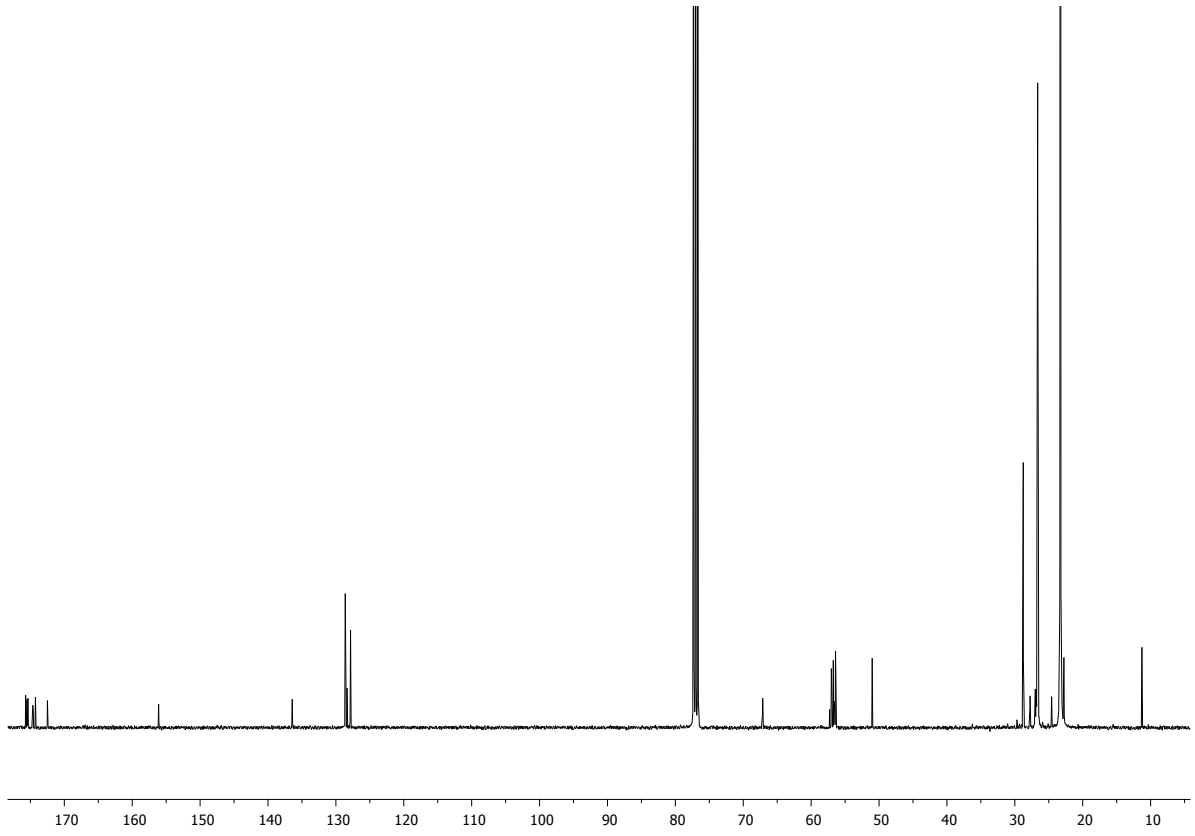
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaNHMe



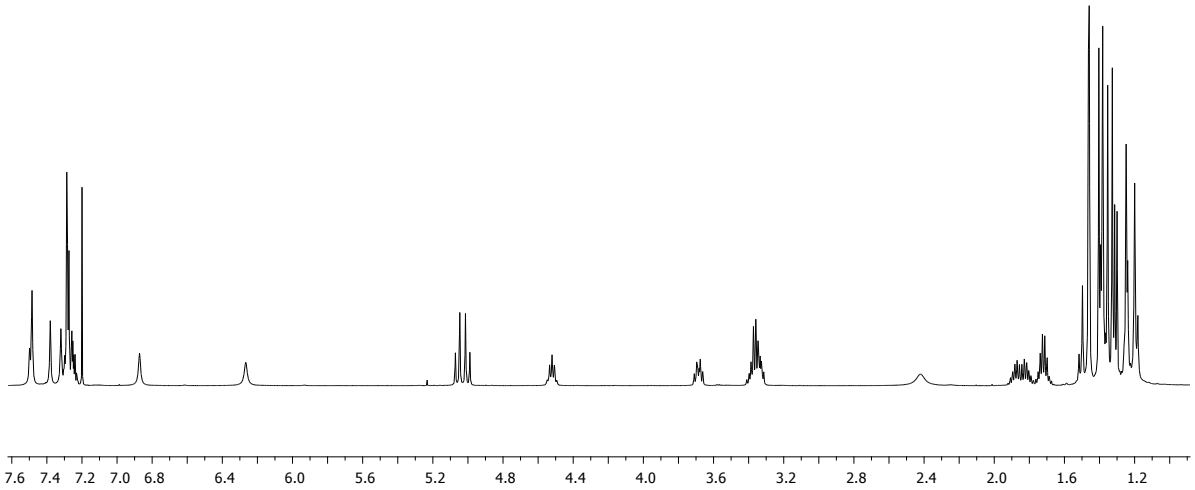
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-AbuNH^{t}Bu



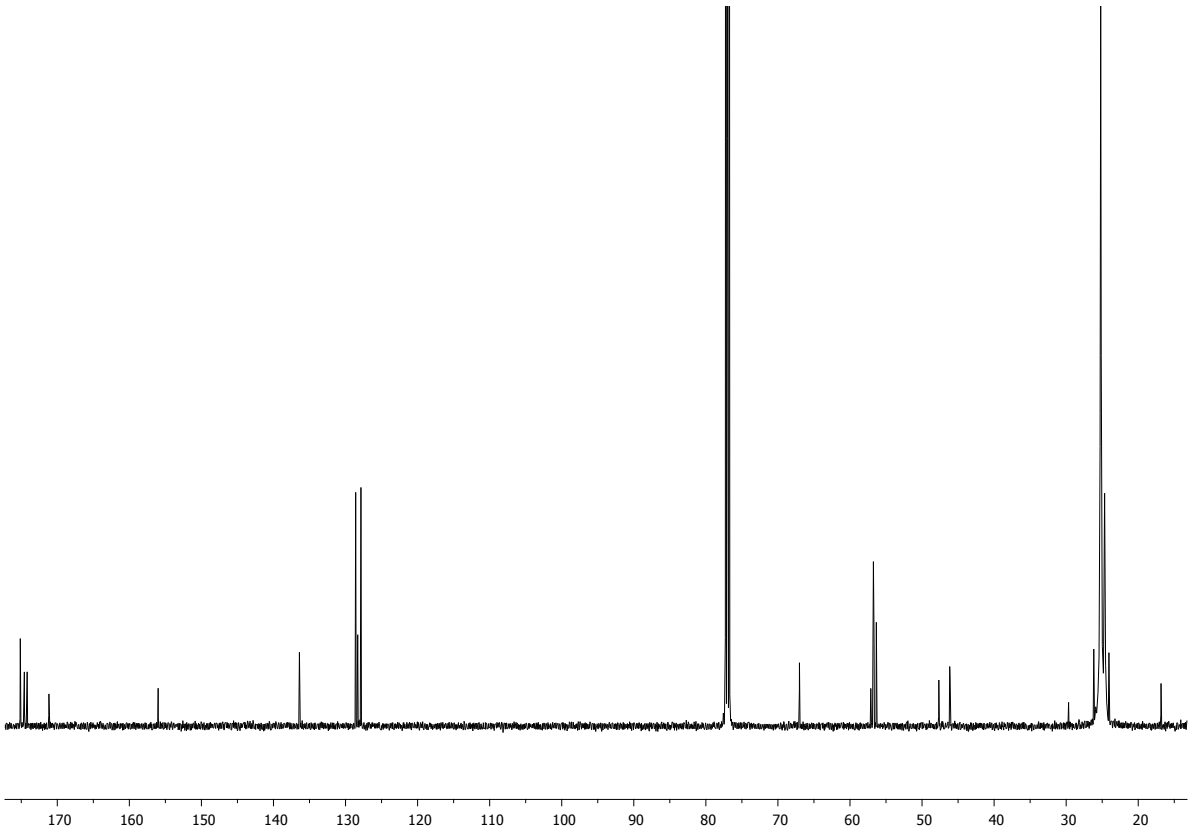
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-AbuNH^{t}Bu



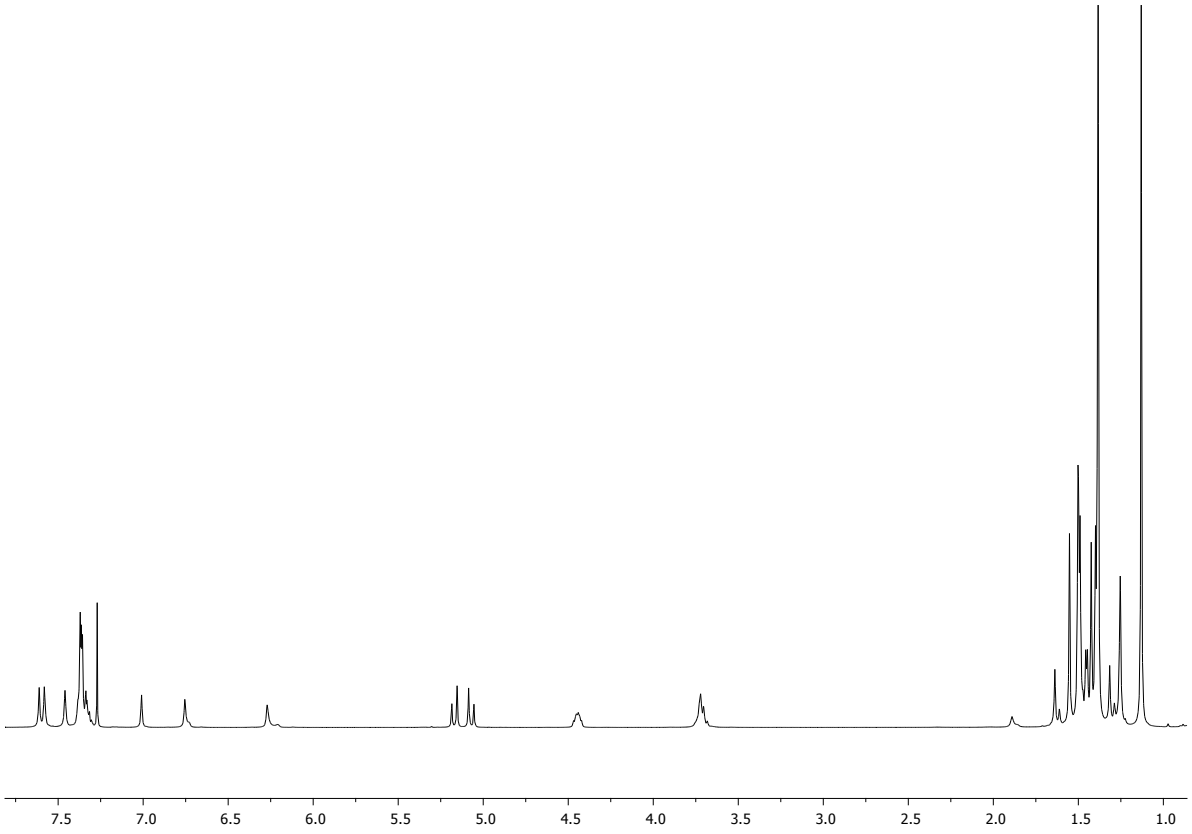
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaN(CH$_2$)$_4$



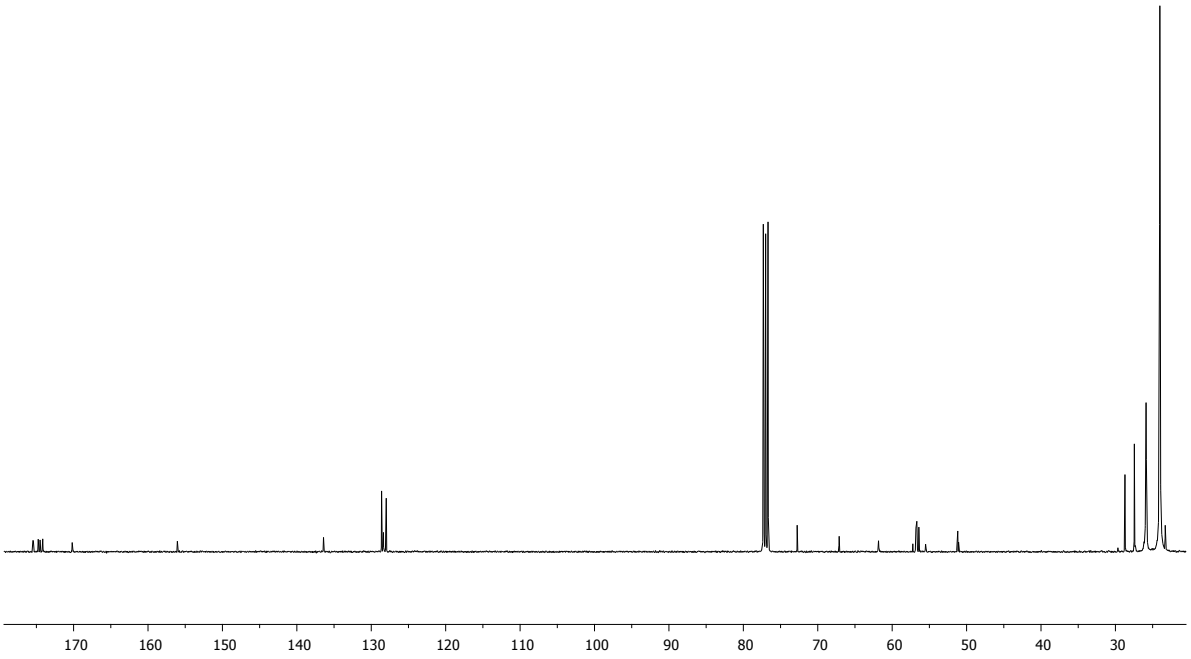
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-AlaN(CH$_2$)$_4$



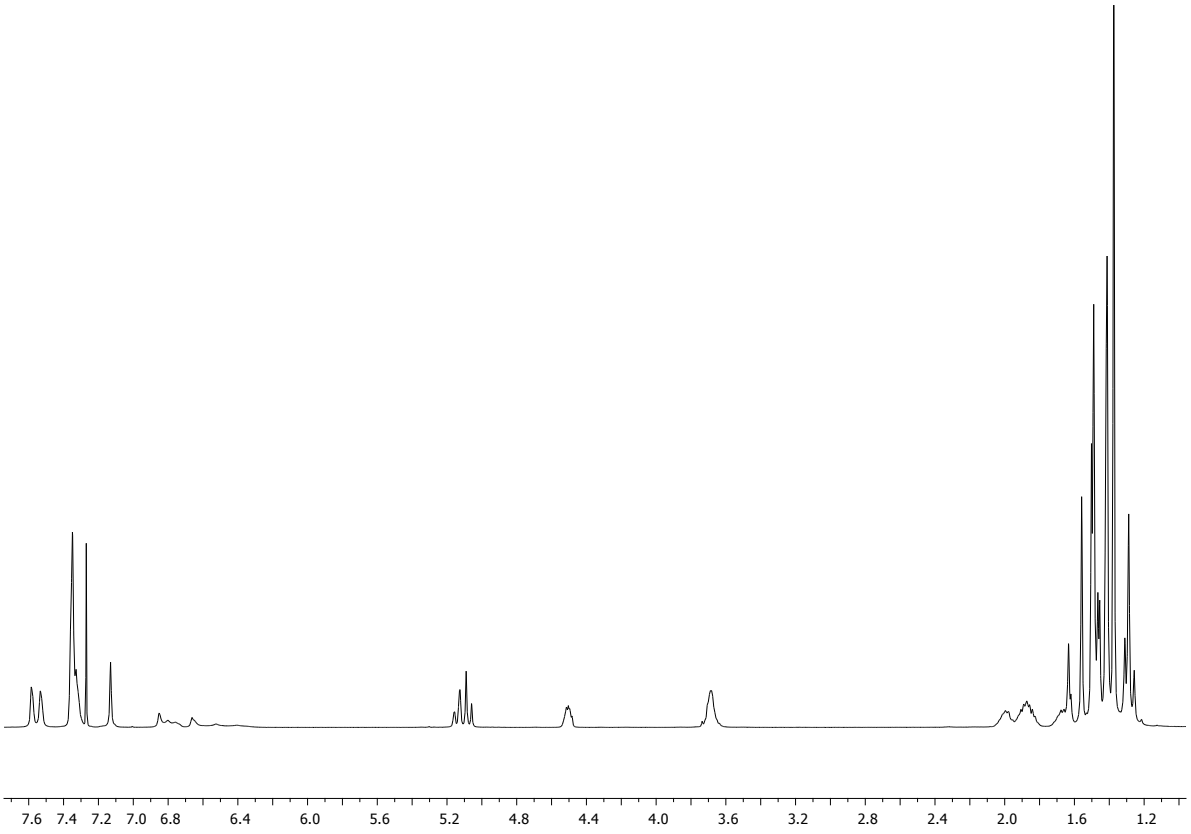
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-Ser(O^{t}Bu)NH^{t}Bu



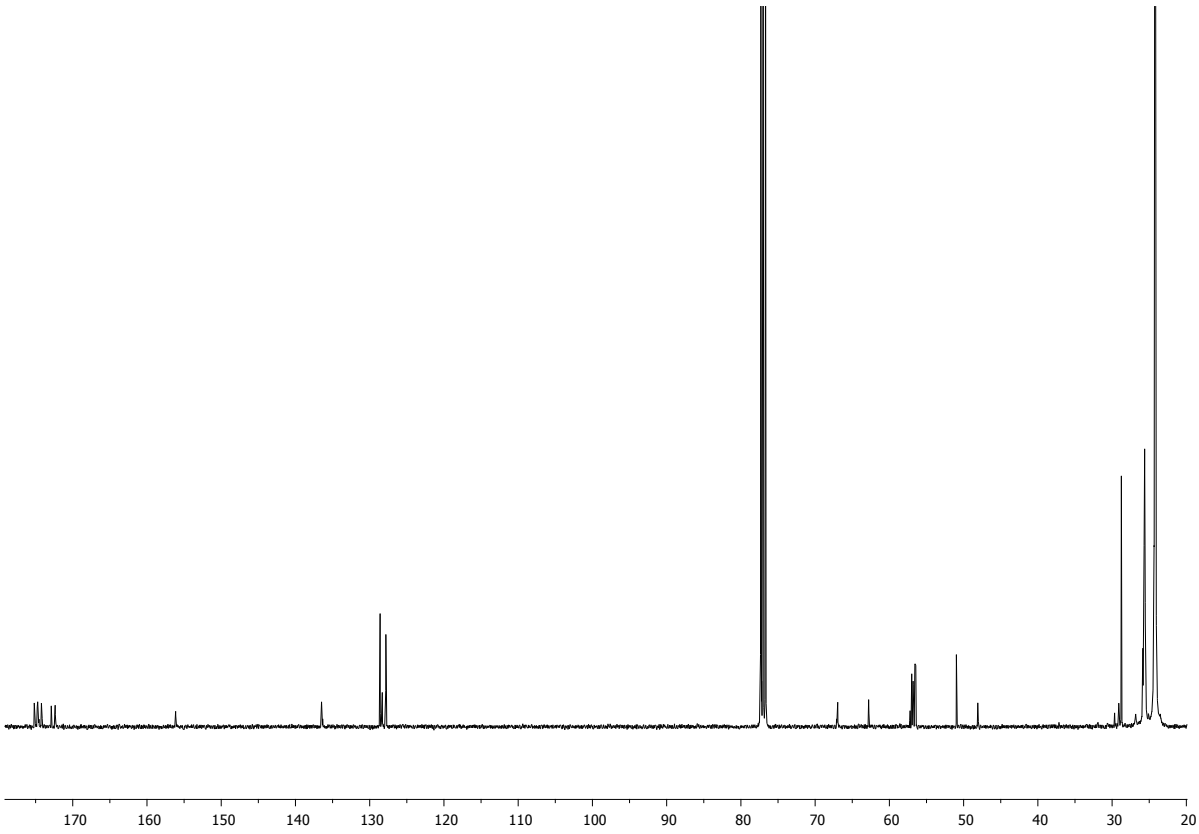
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-Ser(O^{t}Bu)NH^{t}Bu



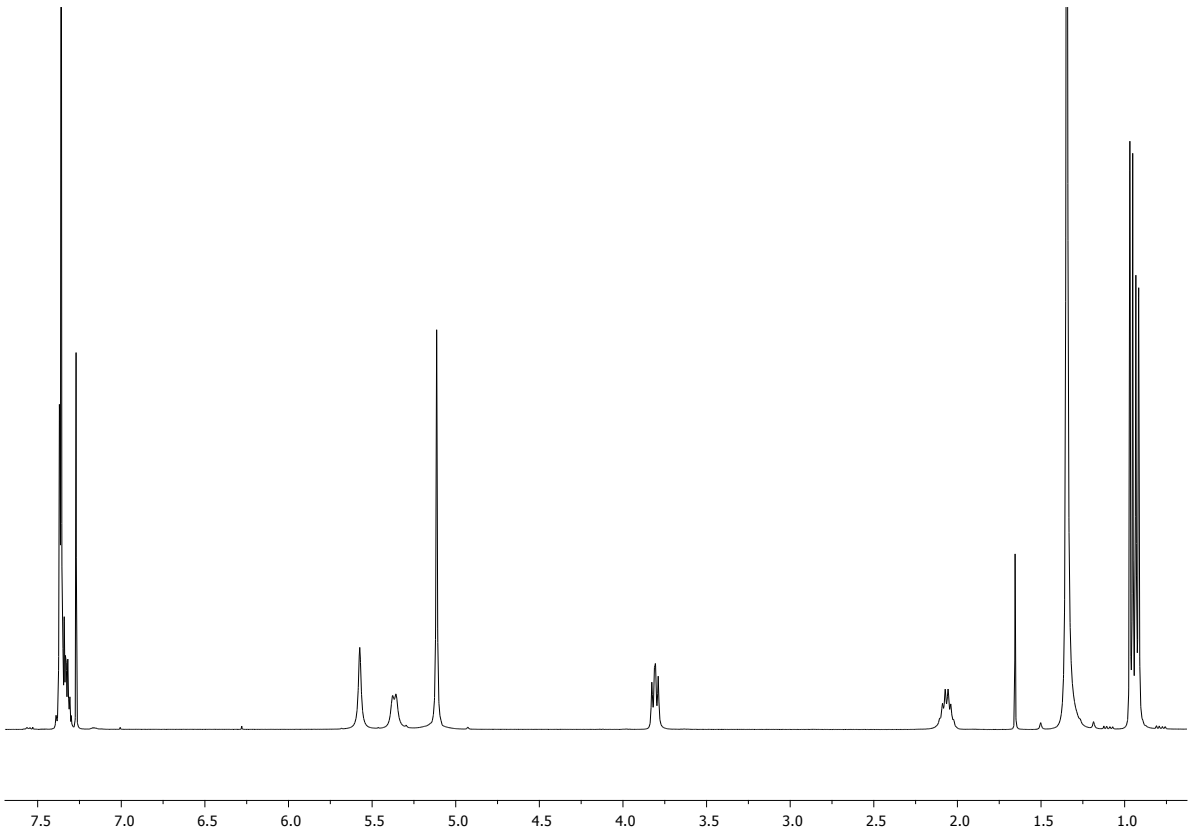
^{1}H-NMR of Z-(*R*)-Aib*-Aib$_4$-ProNH^{t}Bu



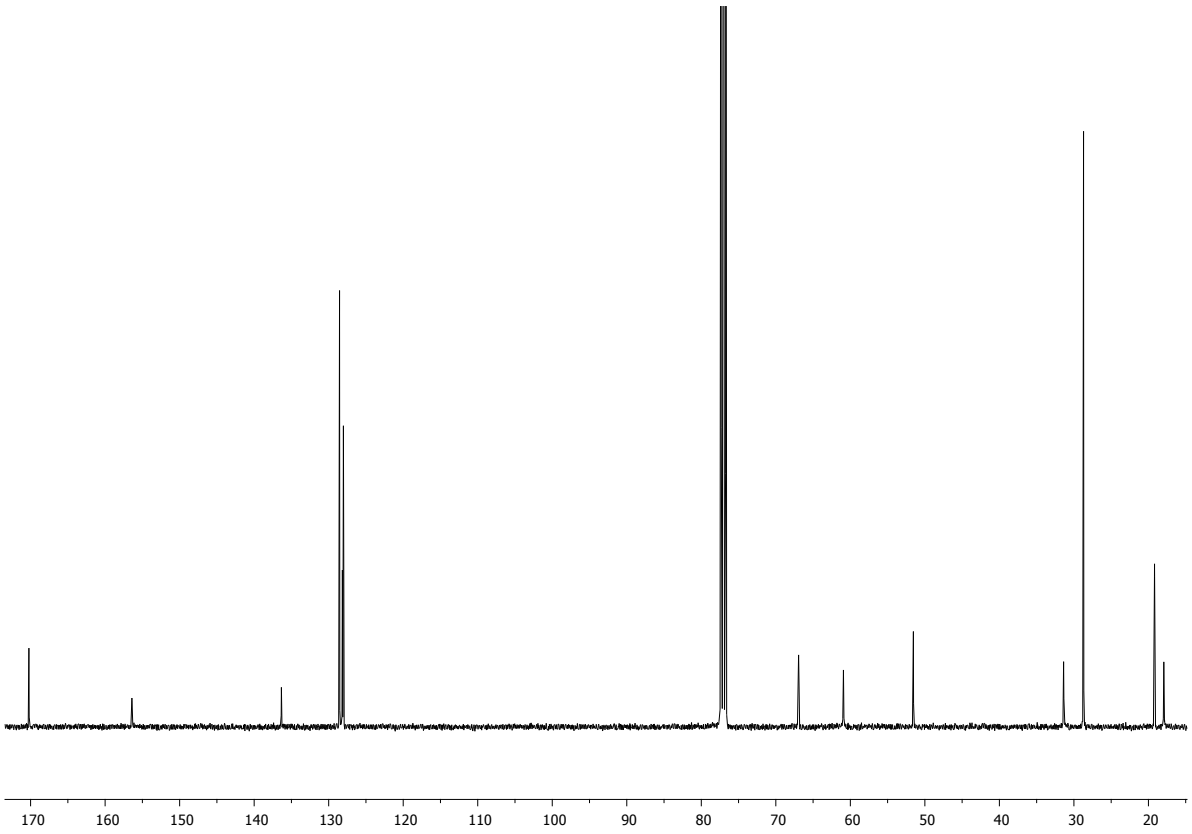
^{13}C-NMR of Z-(*R*)-Aib*-Aib$_4$-ProNH^{t}Bu



^{1}H-NMR of Z-ValNH^{t}Bu



^{13}C-NMR of Z-ValNH^{t}Bu



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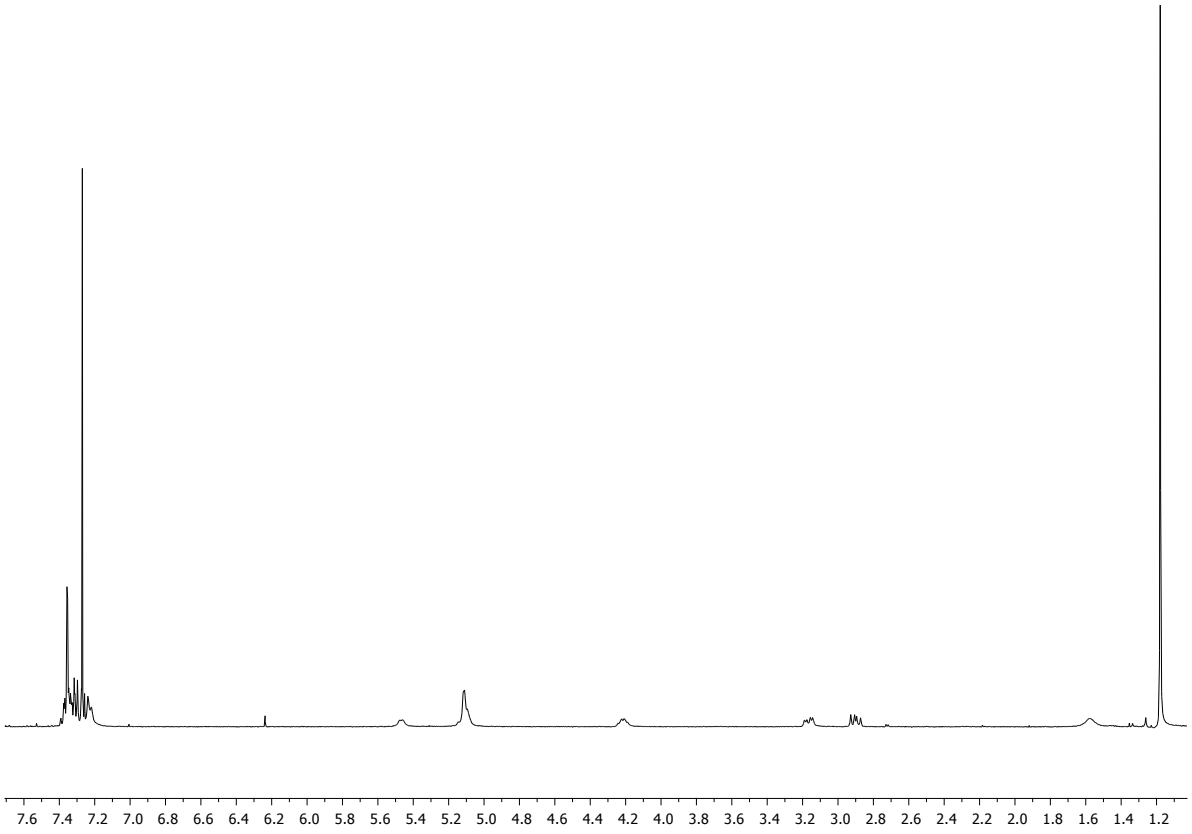
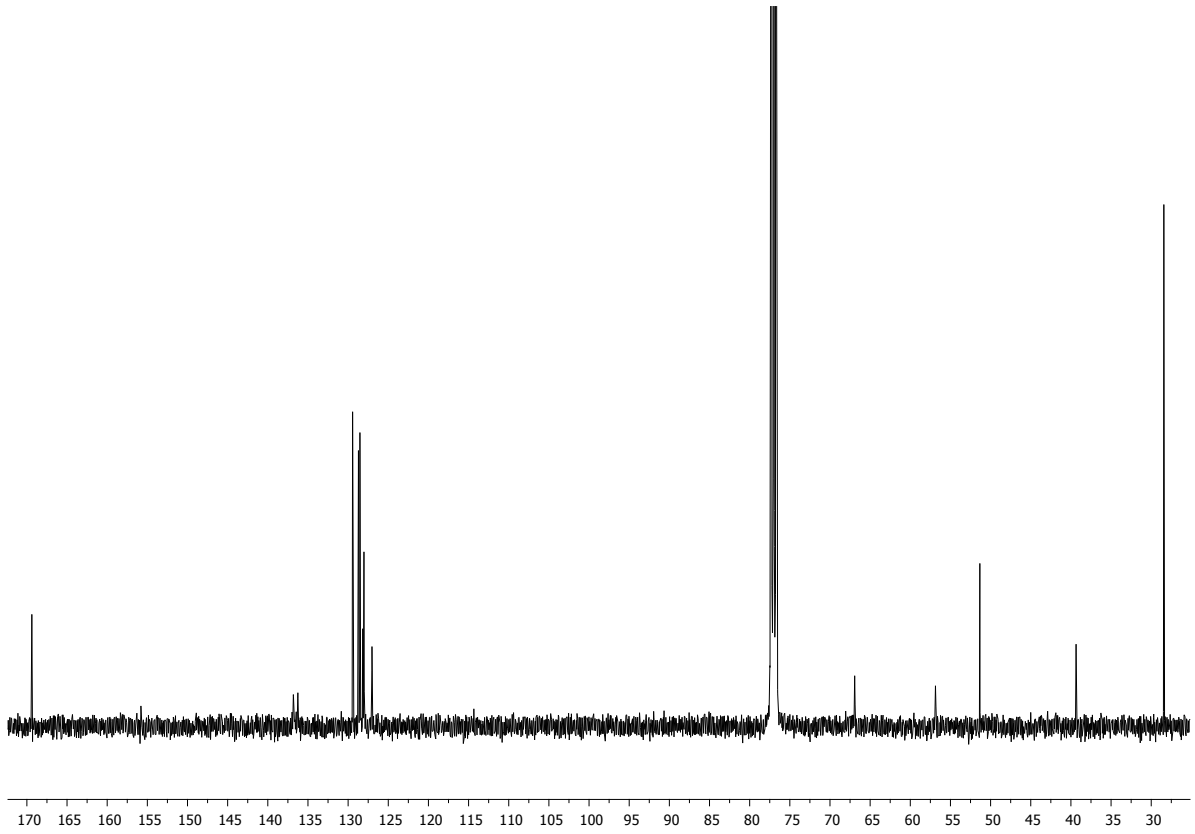
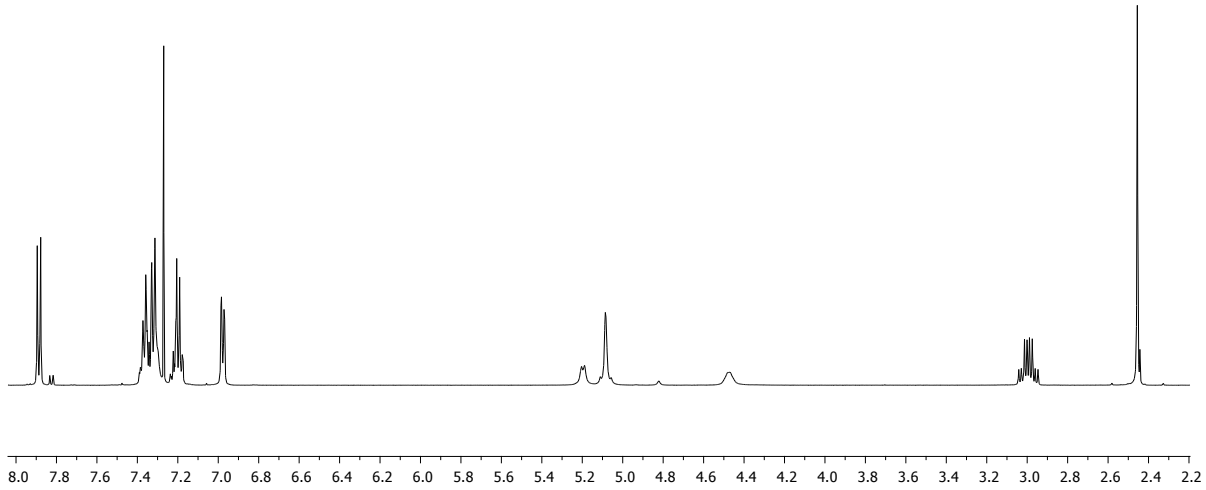


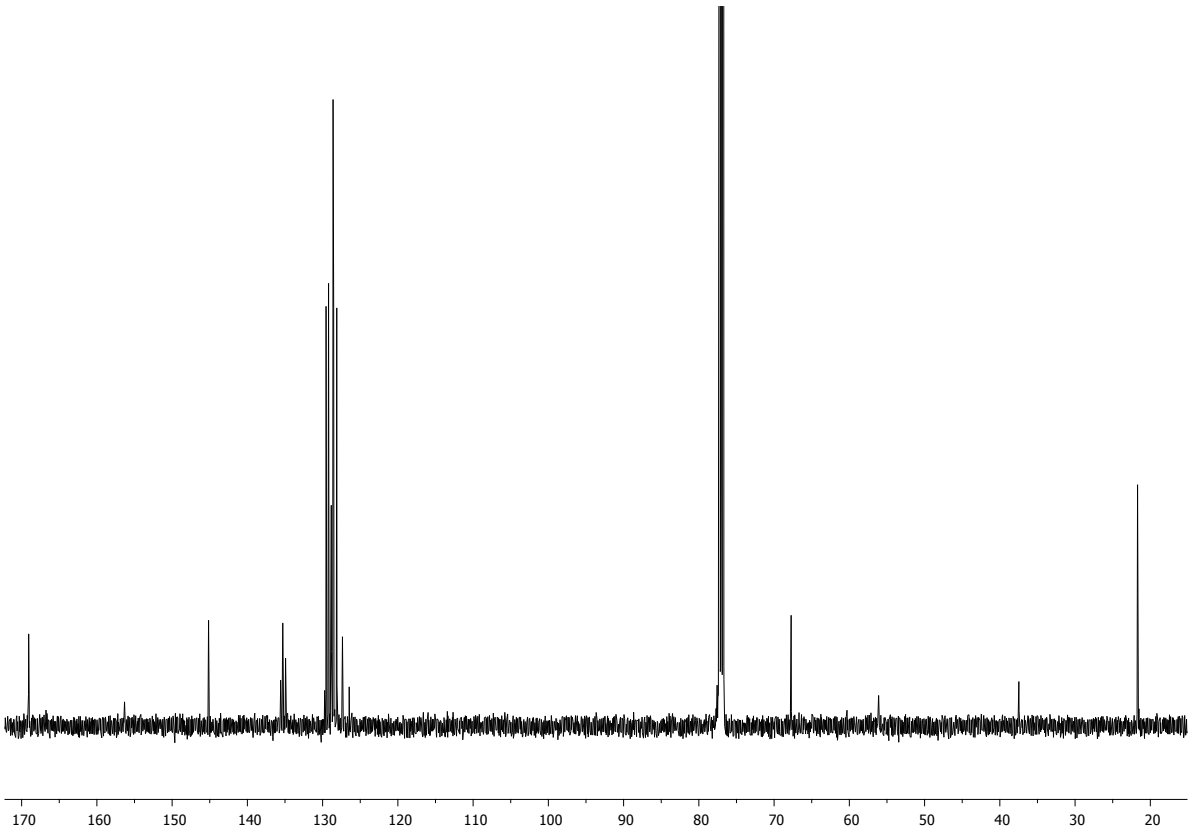
^{13}C-NMR of Z-PheNH^{t}Bu



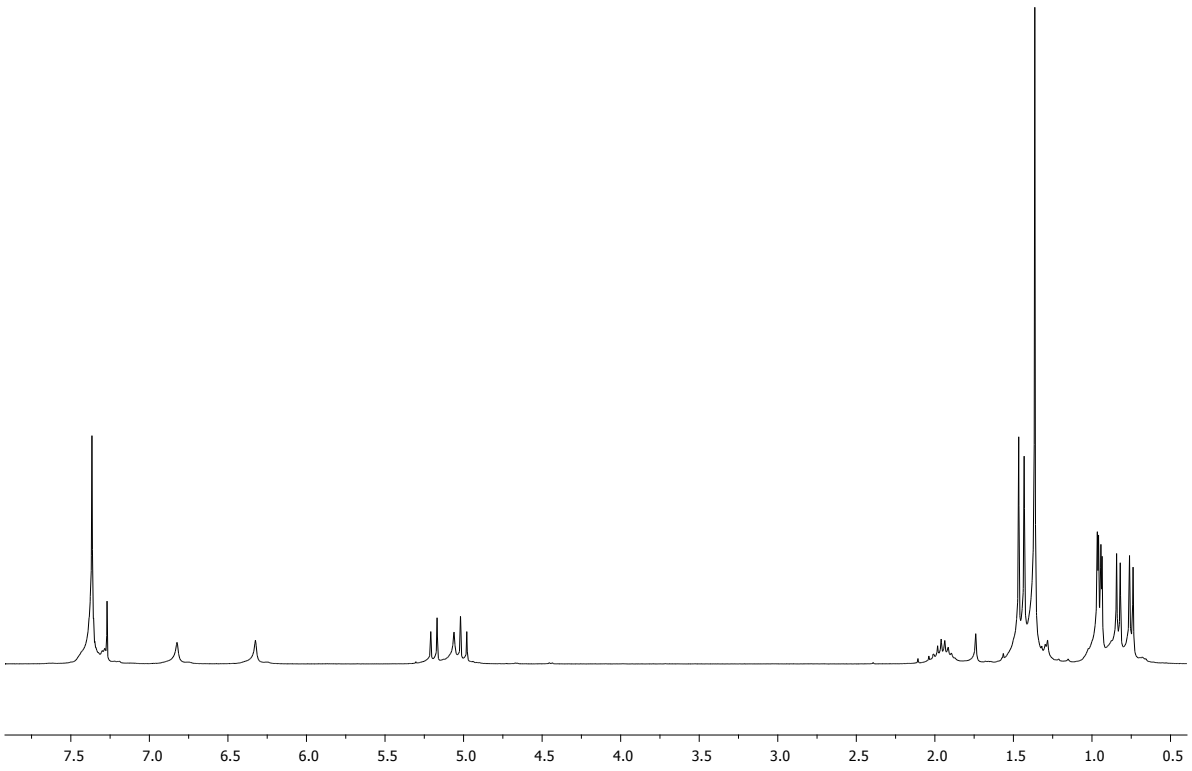
^{1}H-NMR of Z-Phe-NHTs



^{13}C-NMR of Z-Phe-NHTs



^{1}H-NMR of Z-(αMv)$_2$NH^{t}Bu



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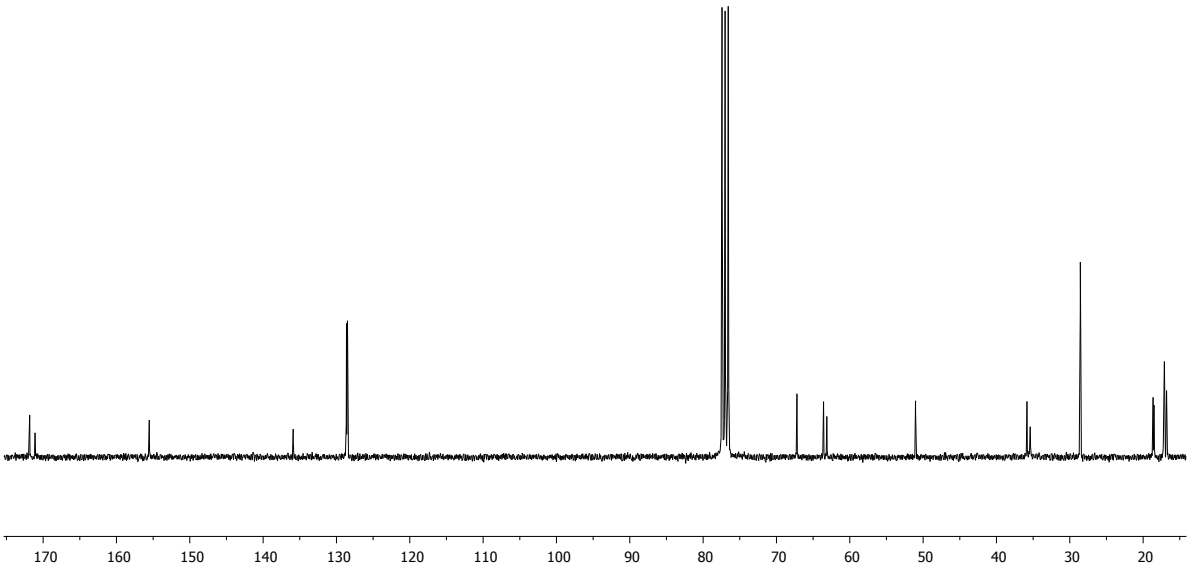

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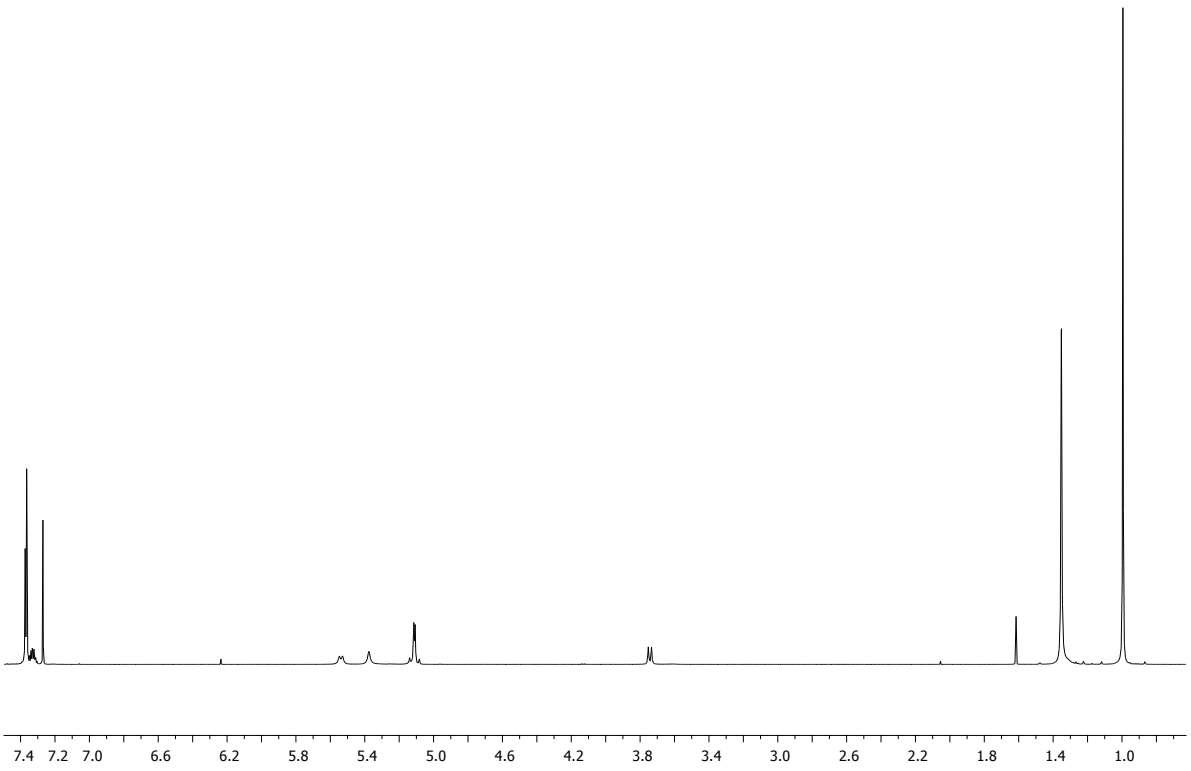
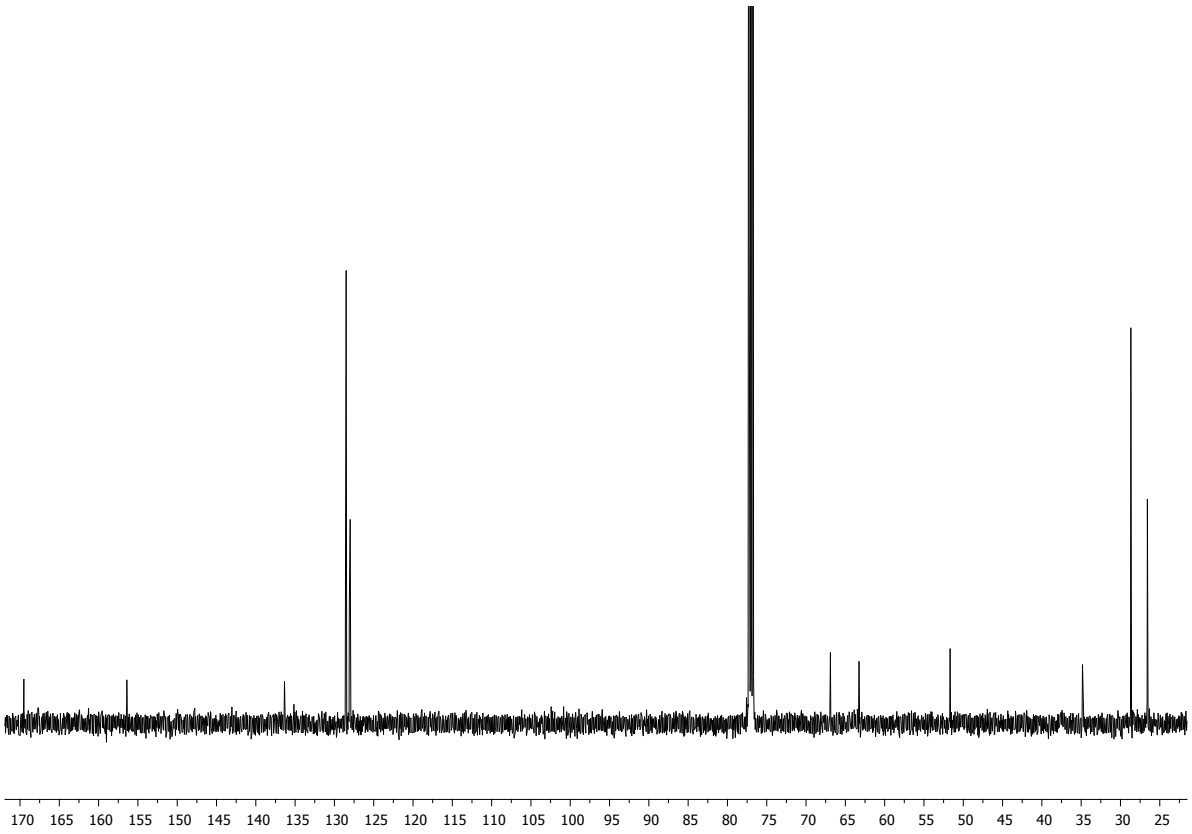
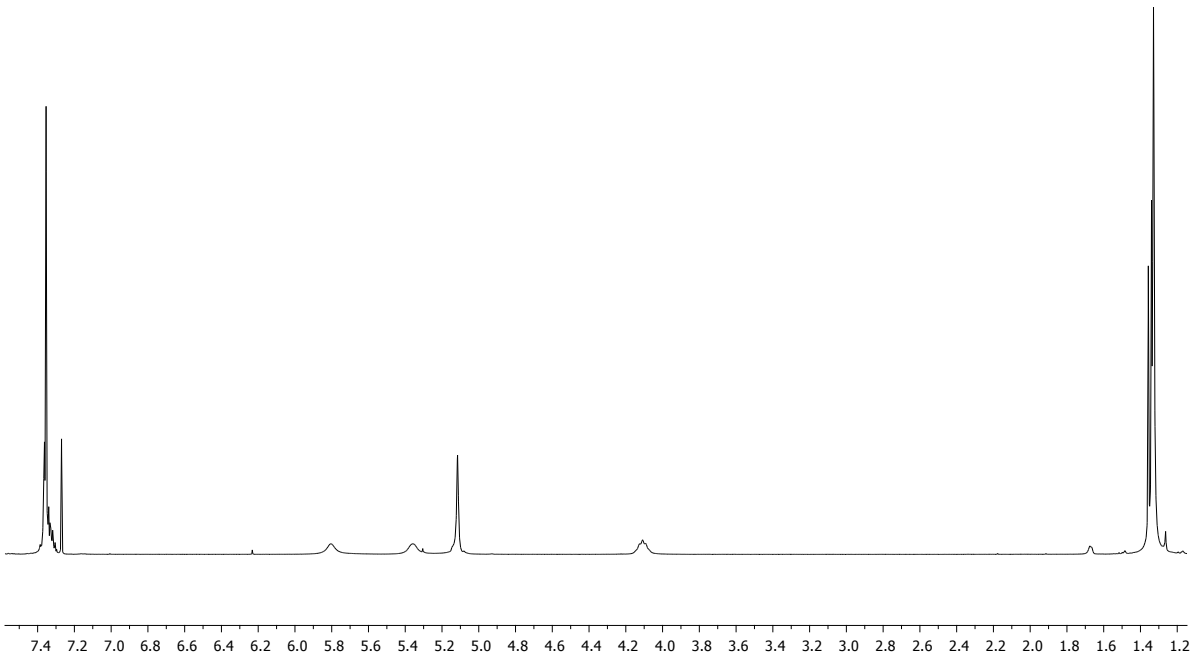


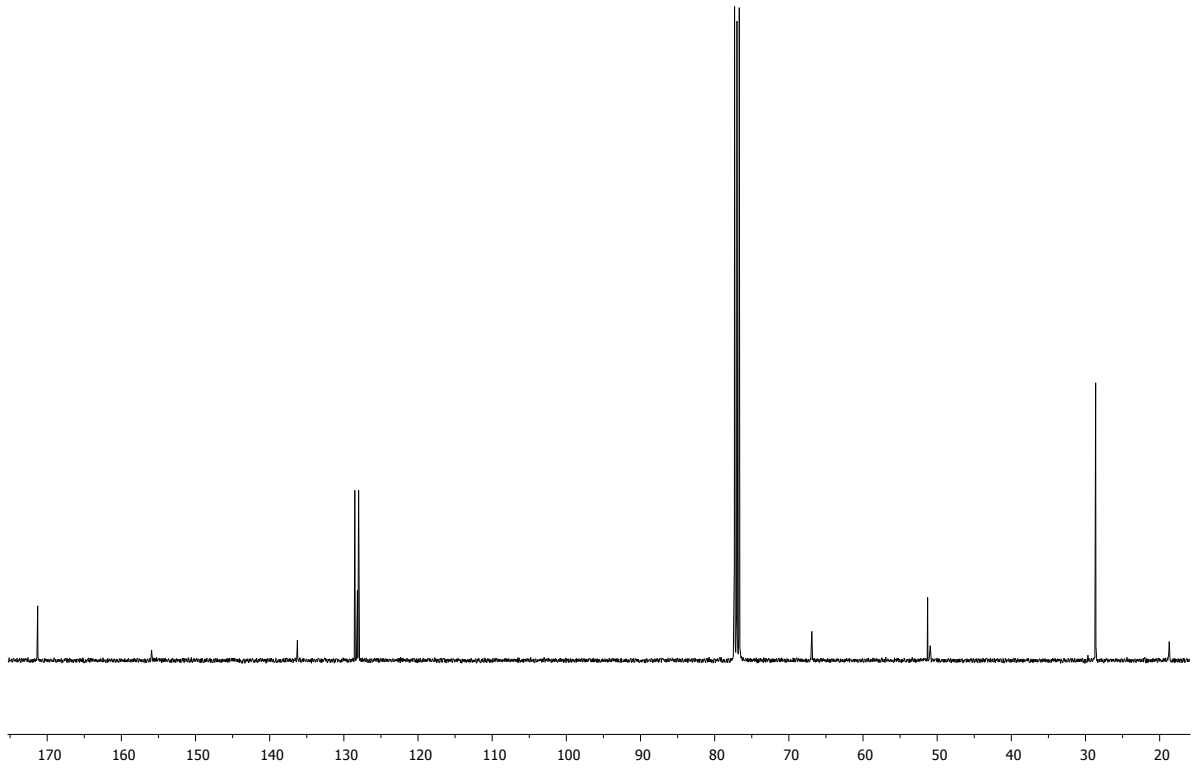
^{13}C-NMR of Z-TleNH^{t}Bu



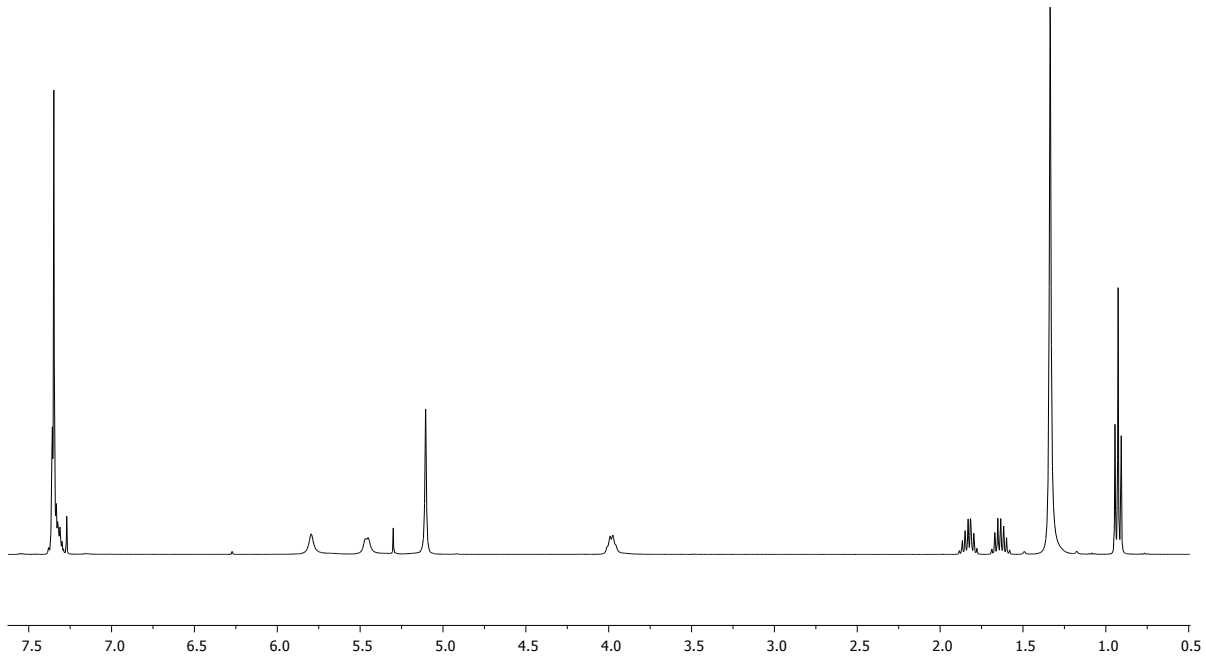
^{1}H-NMR of Z-AlaNH^{t}Bu



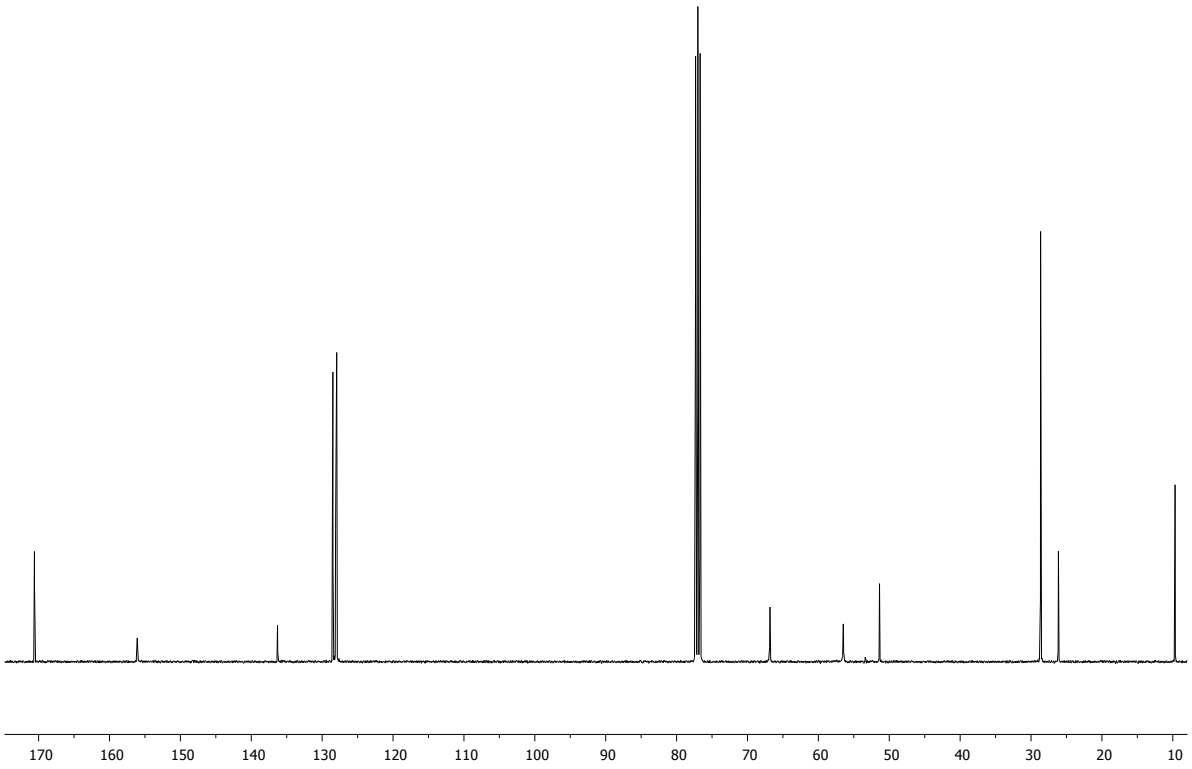
^{13}C-NMR of Z-AlaNH^{t}Bu



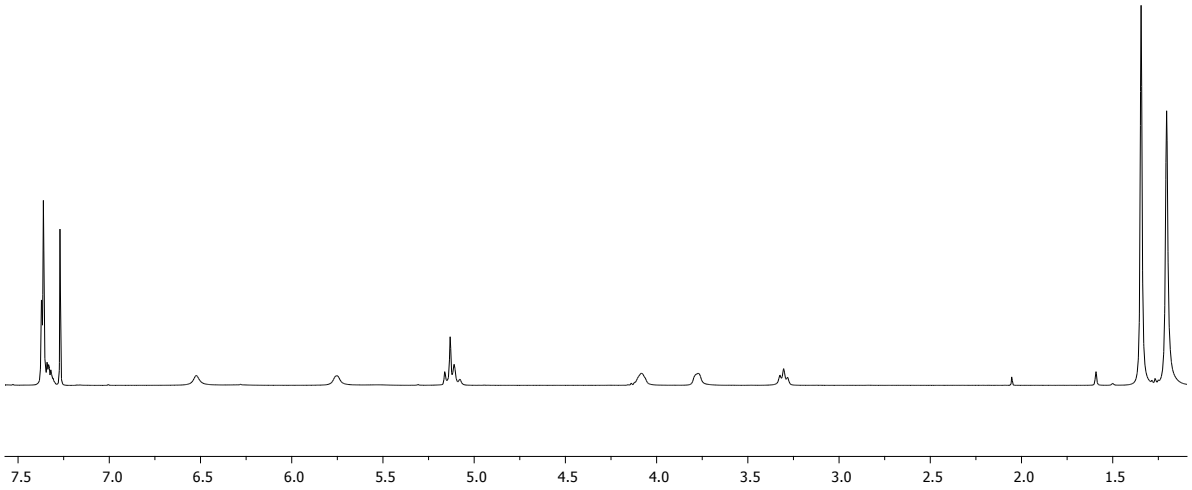
^{1}H-NMR of Z-AbuNH^{t}Bu



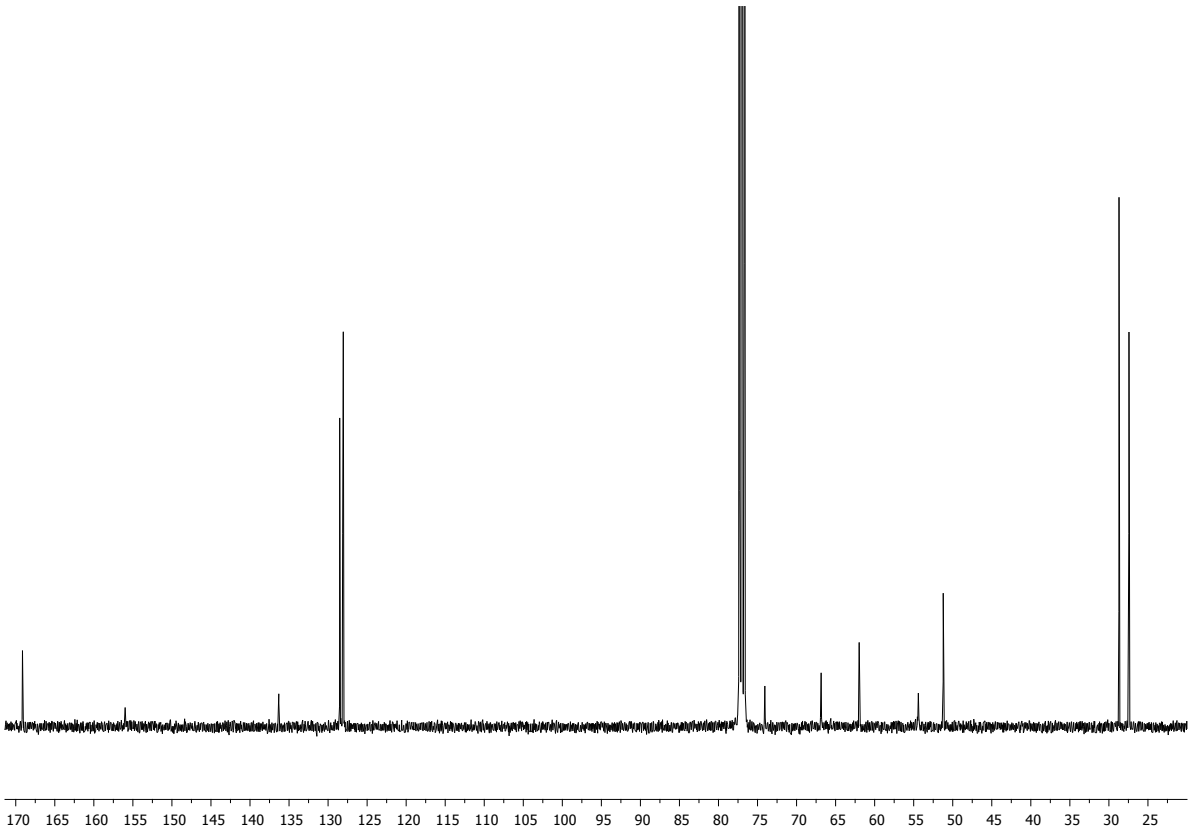
^{13}C-NMR of Z-AbuNH^{t}Bu



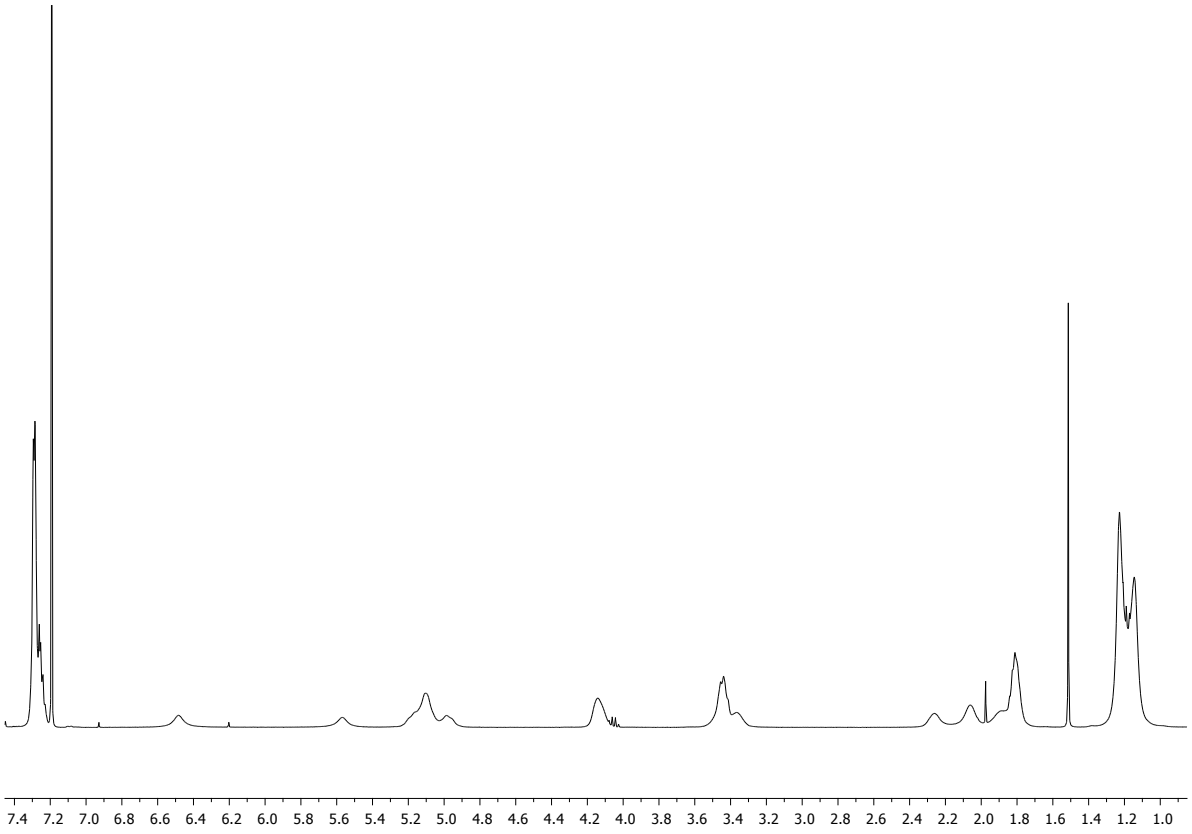
^{1}H-NMR of Z-Ser(O^{t}Bu)NH^{t}Bu



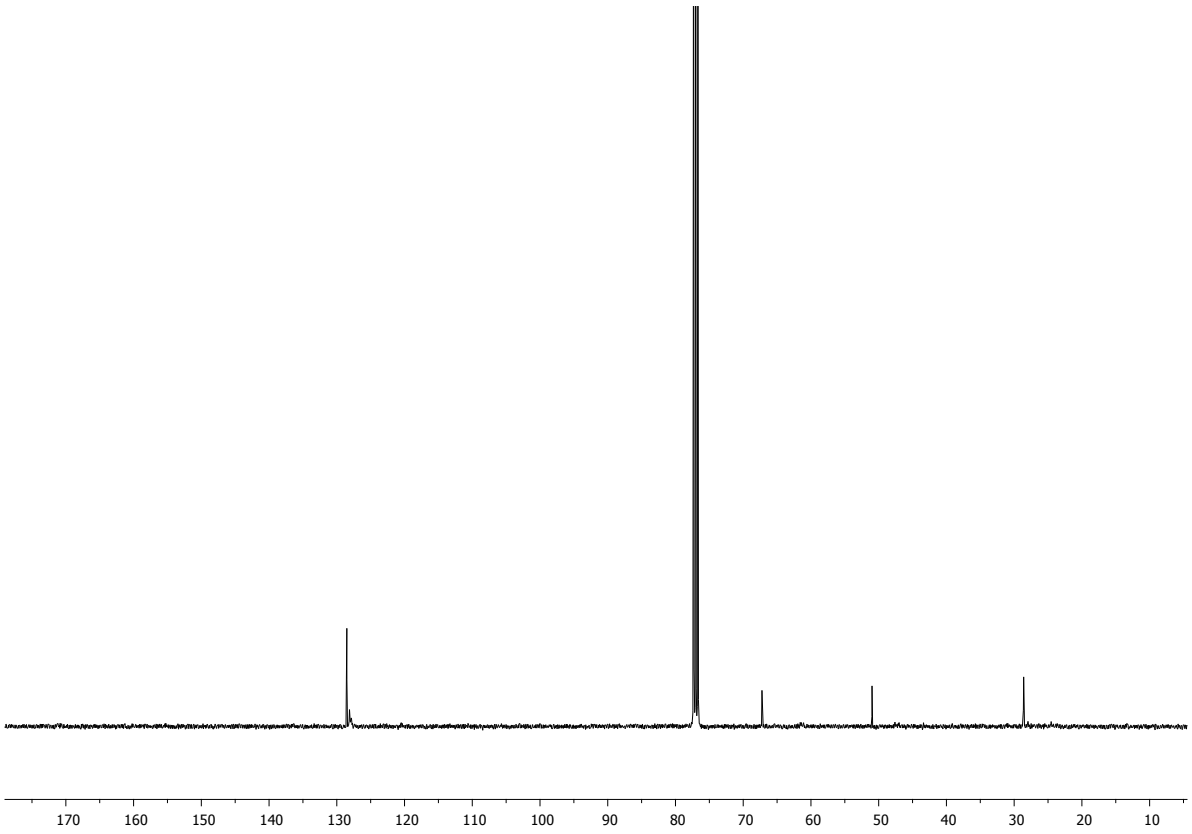
^{13}C-NMR of Z-Ser(O^{t}Bu)NH^{t}Bu



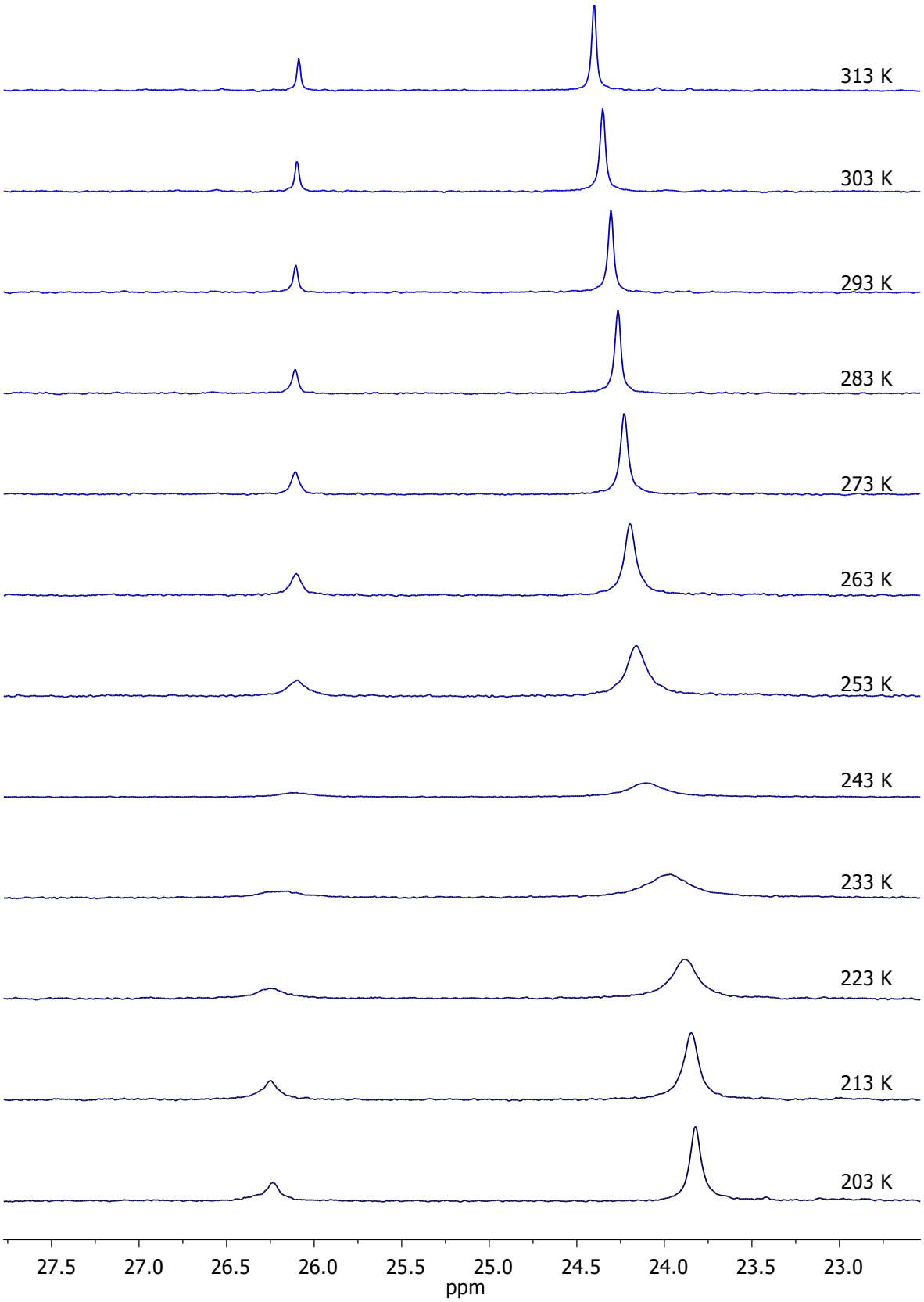
^{1}H-NMR of Z-ProNH^{t}Bu



^{13}C-NMR of Z-ProNH^{t}Bu

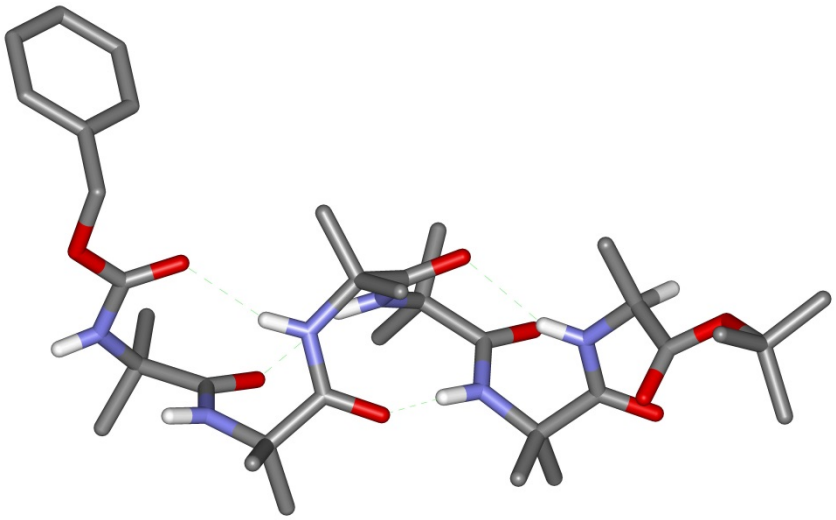


Variable Temperature NMR Example (-70 to 40 °C) of Z-Aib*-Aib$_4$-AlaNH^{t}Bu in MeOD (zoomed in to CH_3 region)



X-ray Crystallographic Analysis of 3-AlaO^{t}Bu

Metrical parameters for the structure of **3**-AlaO^{t}Bu are available free of charge from the Cambridge Crystallographic Data Centre (reference number CCDC 994389).



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