Electronic Supplementary Information

Synthesis of cyclic peptide hemicryptophanes: enantioselective recognition of a chiral zwitterionic guest

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General Information

^{1}H NMR spectra were recorded using a Varian Unity Inova 500 (500 MHz) a Varian Unity Inova 400 (400 MHz) or a Bruker AVANCE2 500 MHz spectrometer with TXI cryoprobe. Spectra were recorded at 298 K. Spectra were obtained in deuterated DMSO, unless otherwise stated, utilising the residual solvent peak as the internal reference. The spectra are reported as: parts per million (ppm) downfield shift, relative to the residual solvent peak; relative integral, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq doublet of quartets, m = multiplet) and coupling constant (*J* in Hz). ^{13}C NMR spectra were recorded using a Varian Unity Inova 500 (125 MHz) or a Varian Unity Inova 400 (100 MHz) and spectra were obtained at 298 K unless stated otherwise. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard of the solvent peak; DMSO (39.5). IR spectra were recorded on a Perkin Elmer FT-IR spectrometer and were obtained from a thin film of the neat product. Absorption maxima are expressed in wavenumbers (cm^{-1}). All mass spectra were recorded on an Agilent 6220 ESI-TOF Mass Spectrometer coupled to an Agillent 1100 LC System (Agilent, Palo Alto, CA). All data were acquired and reference mass corrected via a dual spray electrospray ionisation (ESI) source. Acquisition was performed using the Agilent Mass Hunter software version B.02.01 and analysis was performed using the Agilent Mass Hunter software version B.04.00. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-1000 polarimeter at 589 nm with a cell path length of 10 cm; solution concentrations are reported in grams per 100 ml using the indicated spectroscopic grade solvents.

Most reagents were commercially available reagent grade chemicals and were used without further purification. Toluene was distilled over sodium. Anhydrous THF, Et_2O and CH_2Cl_2 were obtained from solvent drying and dispensing system where the solvent was dried by passage through two packed columns of neutral alumina. Methanol and triethylamine were distilled from calcium hydride. Powdered molecular sieves were activated with a microwave and allowed to cool under vacuum. DMSO and DMF were dried over activated sieves (4 Å) for 16 h before use. DMSO was degassed using the freeze-thaw method (3 repetitions) followed by bubbling with argon for 30 min.

Analytical thin layer chromatography was performed with aluminium backed plates precoated with silica gel 60 F254 (0.2 mm), and visualisation was achieved by inspection under short-wave UV light followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250mL)]. Flash chromatography was performed using silica gel (230-400 mesh); eluting solvents reported as % v/v mixtures Analytical, preparative and semi-preparative reverse phase

HPLC (RP-HPLC) were performed using an Agilent 1200 series LC System. Analytical HPLC employed a SGE Protecol-P C18 HPH 125 column (4.6 × 150 mm column, 5 µm particle size, flow rate of 1 mL min^{-1}). Preparative RP-HPLC employed a Phenomenex C18 column (21.2 × 150 mm, 5 µm particle size, flow rate 8 mL min^{-1}). Semi-preparative RP-HPLC employed a Phenomenex Synergy Hydro-RP column (50 × 21.2 mm, 4 µm particle size, flow rate 5 mL min^{-1}). The mobile phase consisted of eluents A (0.1% TFA in water) and B (0.1% TFA in acetonitrile). The results were analysed on Agilent ChemStation version B.01.03 software.

(*R*)-Carnitine was obtained from Sigma Aldrich. (*S*)-Carnitine was synthesised from (*R*)-carnitine according to the procedure of Giannessi et al.[1]

General methods

General methods for Manual Peptide Synthesis:

Resin loading: 2-Chlorotrityl resin (1.0 g, 1.7 mmol/g) was swollen with CH_2Cl_2 (5 mL) for 30 min. To this was added a solution of Fmoc-Gly-OH (1.0 g, 3.4 mmol) in 4:1 CH_2Cl_2:DMF (5 mL). The mixture was treated with diisopropylethylamine (1.4 mL, 8.5 mmol) and agitated for 16 h. MeOH (20 mL) was added and the solution stirred for a further 20 min. The resin was then filtered and washed with CH_2Cl_2 (3 × 20 mL), DMF (3 × 20 mL) and CH_2Cl_2 (5 × 20 mL). The resin was then dried under reduced pressure. The loading was tested by deprotecting the resin with 20% piperidine in DMF (2 × 10 mL for 5 min) and then measuring the absorbance of the piperidine-fulvene adduct at $\lambda = 301$ nm.

Iterative peptide assembly: The hexapeptide (**3**/**4**) was synthesized by coupling amino acids manually in polypropylene syringes with sintered discs (Torviq) on a 0.25 mmol scale. The following sequence of steps was used; deprotection, washing, coupling, and washing.

Deprotection: The resin was treated with 20% piperidine in DMF (2 × 10 mL for 5 min) A TNBSA test for the detection of primary amines was then carried out. If the test was negative, the deprotection step was done again. Otherwise, the next coupling was carried out.

TNBSA test: A small sample of resin was treated with DIPEA (20µL) and 2,4,6-trinitrobenzene sulfonic acid (20µL). The resin turns orange in less than ten minutes if the test is positive.

Washing: The resin was sequentially washed with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL) and DMF (5 × 5 mL).

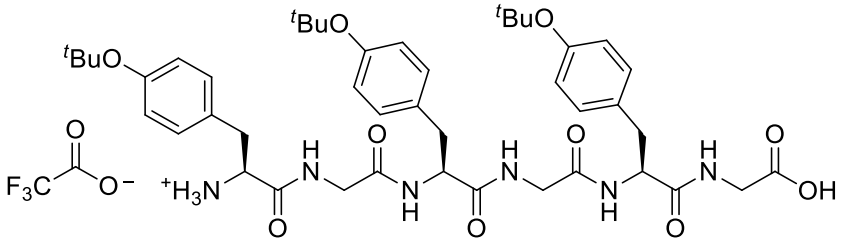
Coupling: A solution of the Fmoc-amino acid (4 eq), PyBOP (4 eq) and diisopropylethylamine (8 eq) was dissolved in DMF (5 mL) and added to the resin. The resin was then shaken on an orbital shaker (175 rpm) for 2 h. A TNBSA test was then carried out. If the test was positive, the coupling step was repeated.

General methods for Microwave Peptide Synthesis

All linear peptides were synthesised using a CEM microwave peptide synthesiser. Solid phase synthesis was carried out on a 0.25 mmol scale using Fmoc/*t*Bu chemistry on the previously synthesised Fmoc-Gly loaded 2-chlorotritylchloride resin (0.66 mmol/g) and using commercially available appropriately protected amino acid subunits. All amino acid subunits were coupled using HATU (0.5 M) as the activating agent. Couplings were performed at 70 °C for 300 sec.

Deprotection: Fmoc deprotection was performed with a 35% solution of pieridine in DMF (3 × 5 mL) for 5 min.

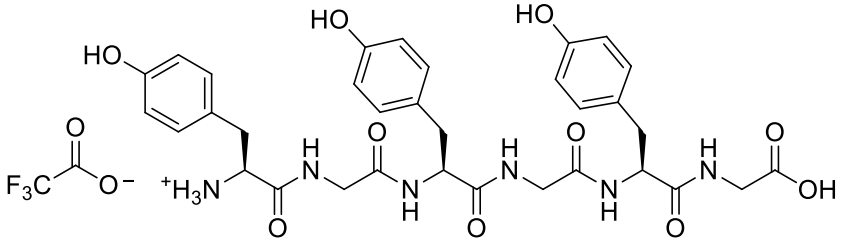
Protected linear peptide 3



Method A: The hexapeptide **3** was synthesised following the general method for *manual solid phase peptide synthesis.* The peptide was cleaved from the resin by agitating with 1% TFA in 4:1 MeCN:H_2O (3 × 10 mL) for 20 min. The solvent was removed under reduced pressure and the residue azeotropically distilled with toluene (3 × 30 mL). The residue was then triturated with Et_2O (3 × 40 mL) to afford **3** as an amorphous colourless solid (0.16 g, 65%, based on 0.25 mmol scale, 0.65 mmol/g loading), which was used without further purification. Mp: 220–225 °C (dec), MS (ESI) *m/z* 847 [$(M+H)^+$, 100%]; HRMS (ESI, $[M+H]^+$) calcd. for $C_{45}H_{63}O_{10}N_6$ 847.4606, found 847.4610. Analytical HPLC: retention time: 13.1 min (gradient of acetonitrile: 0% to 100% in 25 min). Peptide **3** was extremely insoluble so further characterisation was performed on the deprotected peptide **4**. This was obtained by treating a sample of **3** with 5% TFA in 4:1 MeCN:H_2O for 1 h, followed by evaporation of the solvent and ether trituration.

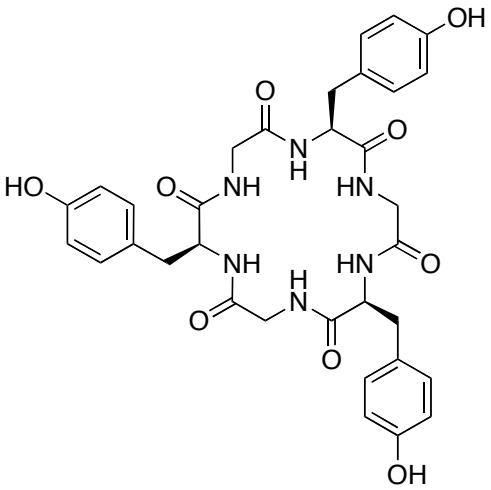
Method B: Peptide **3** was synthesised according to the general method for *microwave peptide synthesis*. The peptide was cleaved from the resin by agitating with 1% TFA in 4:1 MeCN:H_2O (3 × 10 mL) for 20 min. The solvent was removed under reduced pressure and the residue azeotropically distilled with toluene (3 × 30 mL). The residue was then triturated with Et_2O (3 × 40 mL). This afforded **3** as an amorphous colourless solid that was used without further purification (0.22 g, 91%, based on 0.25 mmol scale, 0.65 mmol/g loading). Characterisation identical to that described above.

Deprotected linear peptide 4



Peptide **4** was synthesised according to the general method for microwave peptide synthesis. The peptide was cleaved from the resin by agitating with 5% TFA in 4:1 MeCN:H_2O (3 × 10 mL) for 20 min. The solvent was removed under reduced pressure and the residue azeotropically distilled with toluene (3 × 30 mL). The residue was then triturated with Et_2O (3 × 40 mL) to afford **4** as an amorphous colourless solid (0.17 g, 85%, based on 0.25 mmol scale, 0.65 mmol/g loading), which was used without further purification. Mp: 200–205 °C; $[\alpha]^{24}_D$ +72 (*c* 0.30, DMSO); MS (ESI) *m/z* 679 [$(M+H)^+$, 100%]; HRMS (ESI, $[M+H]^+$) calcd. for $C_{33}H_{39}N_6O_{10}$ 679.2728 found 679.2726; IR (Thin film): 3285, 1628, 1513, 1442, 1408, 1209 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.34 (1 H, br s), 9.21 (2 H, br s), 8.58 (1 H, t, *J* = 5.31 Hz), 8.27-8.20 (3 H, m), 8.03 (1 H, d, *J* = 8.6 Hz), 7.03-6.99 (6 H, m), 6.68 (2 H, d, *J* = 8 4 Hz), 6.62 (4 H, d, *J* = 8.4 Hz), 4.43 (3 H, m), 3.89-3.57 (4 H, m), 2.97-2.87 (3 H, m), 2.75-2.72 (2 H, m), 2.67-2.59 (3 H, m) (4 exchangeable protons obscured or not observed); ^{13}C NMR (100 MHz, DMSO) δ 171.5, 171.5, 171.2, 171.2, 169.0, 168.5, 168.1, 156.5, 155.8 (2 C), 130.5, 130.1 (2 C), 127.9(3), 127.9(0), 125.2, 115.4, 115.0 (2 C), 54.4, 54.3, 54.0, 41.9, 41.8, 41.0, 36.9, 36.9, 36.7.

Cyclic hexapeptide c(YGYGYG) 6

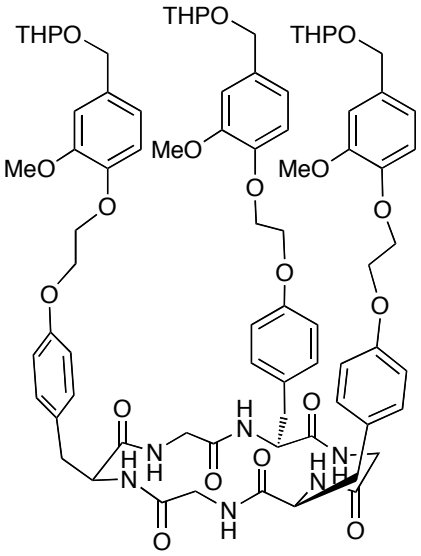


Method A: Under an atmosphere of nitrogen, diisopropylethylamine (25 µL, 0.96 mmol) was added to a solution of peptide **3** (0.18 g, 0.19 mmol) and PyBop (0.30 g, 0.58 mmol) in DMF (40 mL). The mixture was stirred for 16 h at room temperature. The solvent was removed under vacuum and the residue was dissolved in chloroform (50 mL) and water (50 mL). The organic layer was separated and the aqueous phase was extracted with chloroform (2 × 50 mL). The combined organic layers were washed with water (3 × 100 mL). The organic solvent was removed under vacuum and the residue was triturated with ether (3 × 20 mL) to give the crude protected cyclic peptide **5** (98 mg, 62%). MS (ESI) *m/z* 829; HRMS (ESI, $[M+H]^+$) calcd. for $C_{45}H_{61}O_9N_6$ 829.4500, found 829.4495; HPLC: retention time: 15.3 min (gradient of acetonitrile: 0% to 100% in 25 min).
A solution of 9:0.5:0.5 TFA:H_2O:CH_2Cl_2 was added to **5** (98 mg) and the solution was stirred for 1 h. The TFA was evaporated and the residue dissolved in a 1:1 solution of acetonitrile and water, filtered and lyophilised. The lyophilised solid was dissolved in minimal DMSO and purified by RP-HPLC with a gradient of acetonitrile (0 min: 15% MeCN, 60 min: 40% MeCN, Hydro-80 column) to give **6** (30 mg, 24% for the cyclisation and deprotection); Mp: 210–214 °C (dec); $[\alpha]^{24}_D$ –30 (*c* 0.26, DMSO); MS (ESI) m/z 661 [$(M+H)^+$, 100%]; HRMS (ESI, $[M+H]^+$) calcd. for $C_{33}H_{37}N_6O_9$ 661.2622, found. 661.2616; IR (Thin film): 3286, 1662, 1638, 1539, 1513, 1239 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 9.16 (3 H, br s), 8.18 (3 H, t, *J* = 5.7 Hz), 7.99 (3 H, d, *J* = 7.6 Hz), 6.96 (6 H, d, *J* = 8.5 Hz), 6.63 (6 H, d, *J* = 8.5 Hz), 4.27 – 4.19 (3 H, m), 3.71 (3 H, dd, *J* = 15.9, 5.3), 3.48 (3 H, dd, *J* = 15.9, 6.0 Hz), 2.95 (3 H, dd, *J* = 13.8, 5.6 Hz), 2.75 (3 H, dd, *J* = 13.8, 8.8 Hz); ^{13}C NMR (126 MHz, DMSO) δ 171.1, 168.8, 155.8, 129.9, 127.8, 115.0, 54.8, 42.6, 35.7. HPLC: retention time: 15.3 min (gradient of acetonitrile: 0% to 100% in 25 min).

Method B: Under an atmosphere of nitrogen, diisopropylethylamine (475 µL, 2.85 mmol) was added to a solution of the deprotected peptide **4** (450 mg, 0.57 mmol) and PyBop (887 mg, 1.71

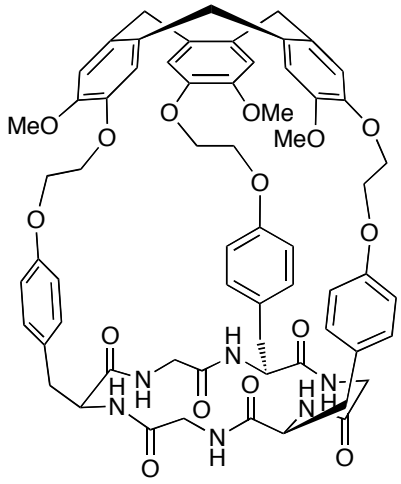
mmol) in DMF (114 mL). The solution was stirred for 1 h. The solvent was then evaporated and the residue was redissolved in 3:1 chlorofom:isopropanol and absorbed onto silica. Purification by flash chromatography (SiO_2) eluting with 10–100% MeOH in CH_2Cl_2 afforded **6** (376 mg, quantitative). Characterisation identical to that described above.

Tris-vanillyl cyclic peptide 8

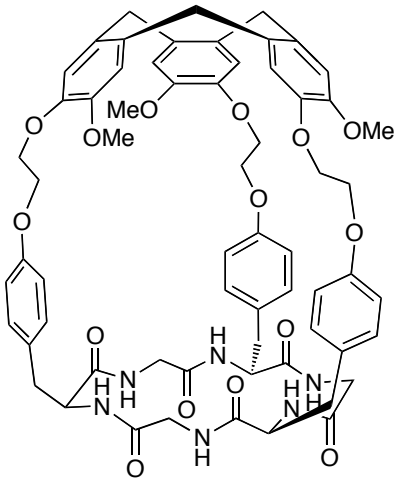


The cyclic peptide **6** (60 mg, 90 μmol), vanillyl ethylbromide **7**[2,3] (0.16 g, 0.45 mmol) and cesium carbonate (0.15 g, 0.45 mmol) were dissolved in DMSO (3 mL). The solution was stirred for 16 h at 60 °C. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2) eluting with 5–10% MeOH in CH_2Cl_2 to afford **8** as a colourless solid (60 mg, 55%). Mp. 240–243 °C; $[\alpha]^{24}_D$ –15 (*c* 0.67, $CHCl_3$); MS (ESI) *m/z* 1475 [$(M+Na)^+$, 100%]; HRMS (ESI, $[M+Na]^+$) calcd. for $C_{78}H_{96}N_6O_{21}Na$ 1475.6526, found 1475.6521; IR (Thin film): 3284, 2941, 1656, 1632, 1509, 1252, 1233, 1036 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.21 (3 H, t, *J* = 5.3 Hz), 8.09 (3 H, br s,), 7.12 (6 H, d, *J* = 8.7 Hz), 6.97 (3 H, d, *J* = 8.2), 6.93 (3 H, d, *J* = 1.9 Hz), 6.87 (6 H, d, *J* = 8.7 Hz), 6.85, (3 H, dd, *J* = 8.2, 1.9 Hz), 4.64 (3 H, m), 4.59 (3 H, d, *J* = 12.0 Hz), 4.37 (3 H, d, *J* = 12.0 Hz), 4.30 (3 H, m), 4.25 (12 H, s), 3.8 (3 H, dd, *J* = 8.0, 3.3 Hz), 3.78 (3 H, dd, *J* = 8.0, 3.3 Hz), 3.74 (9 H, s), 3.51–3.44 (6 H, m), 3.04 (3 H, dd, *J* = 14.0, 5.3 Hz), 2.86 (3 H, m), 1.76–1.60 (6 H, m), 1.53-1.45 (12 H, m); ^{13}C NMR (126 MHz, DMSO) 171.1, 168.9, 156.9, 148.9, 147.2, 131.2, 130.2, 130.0, 120.2, 114.2, 113.2, 112.0, 97.1, 68.0, 67.2, 66.3, 61.4, 55.5, 54.7,42.6, 35.6, 30.2, 25.1, 19.1; IR (Thin film): 3284, 2941, 1656, 1632, 1509, 1252, 1233, 1036 cm^{-1}.

Hemicryptophanes *ML*-2 and *PL*-2



***ML*-2**



***PL*-2**

The tris-vanillyl cyclic peptide **8** (66 mg, 0.045 mmol) was dissolved in formic acid (10 mL) and the solution was stirred for 3 h at room temperature. The solvent was then evaporated and the residue was partitioned between chloroform (20 mL) and aqueous potassium carbonate (10%, 20 mL). The aqueous phase was extracted with chloroform (2 × 10 mL). The combined organic layers were washed with distilled water (2 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (SiO_2) eluting with (5–10% MeOH in CH_2Cl_2) to give *ML*-**2** as a colourless amorphous solid (11 mg, 21%). Further elution gave *PL*-**2** as a colourless amorphous solid (22 mg, 43%).

ML-**2**; R_f = 0.2 (10% MeOH in CH_2Cl_2); Mp. 240–243 °C; $[\alpha]^{24}_D$ +25 (*c* 0.25, MeOH); MS (ESI) *m/z* 1147 [$(M+H)^+$, 100%]; HRMS (ESI, $[M+H]^+$) calcd. for $C_{63}H_{67}N_6O_{15}$ 1147.4659, found 1147.4655; IR (Thin film): 3331, 1656, 1605, 1511, 1252 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.26 (3 H, br s, 1–NH), 7.17 (3 H, s, H18), 7.13 (3 H, s, H15), 7.09 (6 H, d, *J* = 8.4 Hz, H6, H10), 6.95 (3 H, d, *J* = 6.7 Hz, 3–NH), 6.77 (6 H, d, *J* = 8.4 Hz, H7, H9), 4.81 (3 H, d, *J* = 13.6 Hz, H19a), 4.49 (3 H, dt, *J* = 7.7, 5.3 Hz, H3), 4.38-4.31 (6 H, m, H11), 4.25-4.20 (6 H, m, H12), 3.93 (3 H, d, *J* = 16.4 Hz, H1a), 3.72 (9 H, s, 14-OMe), 3.58 (3 H, d, *J* = 13.6 Hz, H19b), 3.36 (3 H, d, *J* = 16.4 Hz, H1b), 3.11 (3 H, dd, *J* = 14.5, 7.0 Hz, H4a), 2.95 (3 H, dd, *J* = 14.5, 6.6 Hz, H4b). ^{13}C NMR (125 MHz, acetone-d_6) δ 171.7 (C=O, C20), 170.3 (C=O, C2), 158.4 (Cq, C8), 149.8 (Cq, C14), 147.5 (Cq, C13), 134.3 (Cq, C17), 133.1 (Cq, C16), 131.2 (2 C, CH, C6, C10), 130.2 (Cq, C5), 118.0 (CH, C18), 115.6 (2 C, CH, C7, C9), 115.0 (CH, C15), 69.1 (CH_2, C11), 67.2 (CH_2, C12), 56.4 (CH_3, 14–OMe), 55.2 (CH, C3), 43.6 (CH_2, C1), 36.4 (CH_2, C19), 35.8 (CH_2, C4). CD ($6.5.10^{-4}$ M in CH_2Cl_2) 237 (-34.0), 253.3 (16.4), 276.5 (12.9). HPLC: retention time: 26.8(4) min (gradient of acetonitrile: 0 min: 30%; 3min: 30%; 83min: 60%).

PL-**2**: R_f = 0.1 (10% MeOH in CH_2Cl_2); Mpt. 240–243 °C; $[\alpha]^{24}_D$ –48 (*c* 0.25, MeOH),; MS (ESI) *m/z* 1147 [$(M+H)^+$, 100%]; HRMS (ESI, $[M+H]^+$) calcd. $C_{63}H_{67}N_6O_{15}$ 1147.4659 found 1147.4643; IR (Thin film): 3309, 2931, 1662, 1509, 1251 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6) δ 7.92 (3 H, br s, 1–NH), 7.27 (3 H, s, H15), 7.12 (3 H, s, H18), 7.08 (6 H, d, *J* = 8.5 Hz, H6, H10), 7.00 (3 H, d, *J* = 7.2 Hz, 3–NH), 6.74 (6 H, d, *J* = 8.5 Hz, H7, H9), 4.77 (3 H, d, *J* = 13.5 Hz, H19a), 4.48 (3 H, dt, *J* = 7.2, 6.7 Hz, H3), 4.23 (6 H, m, H11), 4.34 (6 H, m, H12), 4.02 (3 H, dd, *J* = 16.4, 3.1 Hz, H1a), 3.68 (9 H, s, 14–OMe), 3.55 (3 H, d, *J* = 13.5 Hz, H19b), 3.44 (3 H, d, *J* = 16.4 Hz H1b), 3.09 (3 H, dd, *J* = 14.2, 7.7 Hz, H4a), 3.00 (3 H, dd, *J* = 14.2, 4.2 Hz, H4b). ^{13}C NMR (125 MHz, acetone-d_6) δ 171.7 (C=O, C20), 170.6 (C=O, C2), 157.9 (Cq, C8), 149.4 (Cq, C14), 147.8 (Cq, C13), 133.8 (Cq, C16), 133.3 (Cq, C17), 131.4 (2 C, CH, C6, C10), 130.4 (Cq, C5), 116.7 (CH, C15), 115.9 (2 C, CH, C7, C9), 115.7 (CH, C18), 67.8 (CH_2, C12), 67.3 (CH_2, C11), 56.8 (CH_3, 14–OMe), 54.8 (CH, C3), 43.5 (CH_2, C1), 36.3 (CH_2, C19), 35.8 (CH_2, C4). CD (9.10^{-5} M in CH_2Cl_2) 235.1 (23.2), 253.8 (-12.5), 278.7 (-19.9). HPLC: retention time: 26.8(0) min (gradient of acetonitrile: 0 min: 30%; 3 min: 30%; 83 min: 60%).

ESI Mass Spectrometry Experiments

All high resolution MS experiments were conducted according to the following example. A solution of host hemicryptophane (0.785 mM in 20% CH_3CN in H_2O, 1000 µL) and guest (3.93 mM, 5 equiv.) was prepared and the mass spectrum recorded on an Agilent 6220 ESI-TOF mass spectrometer (Agilent, Palo Alto, CA). All data were acquired and reference mass corrected via a dual spray electrospray ionisation (ESI) source. Acquisition was performed using the Agilent Mass Hunter software version B.02.01 and analysis was performed using the Agilent Mass Hunter software version B.04.00.

References

1. I. Bernabei, R. Castagnani, A. F. De, W. S. P. De, F. Giannessi, D. Misiti, S. Muck, N. Scafetta and M. O. Tinti, *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 2076-2078.
2. T. Brotin, T. Devic, A. Lesage, L. Emsley and A. Collet, *Chem. - Eur. J.*, 2001, **7**, 1561-1573.
3. P. D. Raytchev, O. Perraud, C. Aronica, A. Martinez and J.-P. Dutasta, *J. Org. Chem.*, 2010, **75**, 2099-2102.

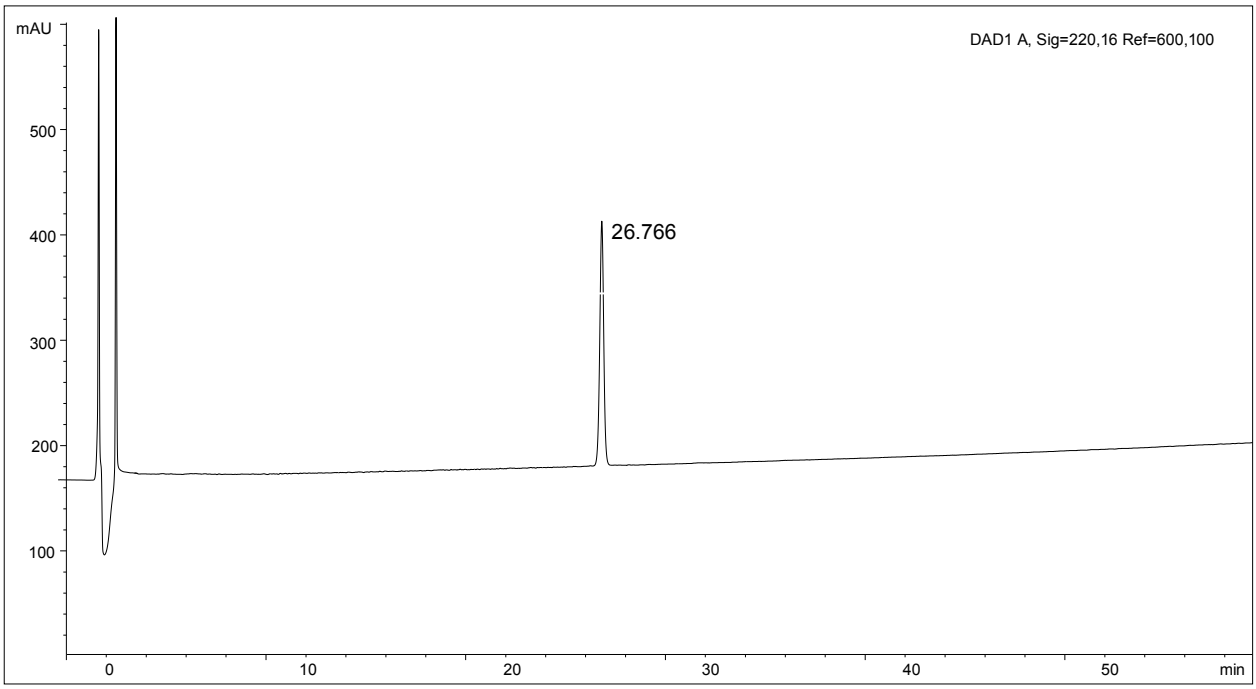


Fig. ESI-1 HPLC Trace of hemicryptophane *PL*-**2**

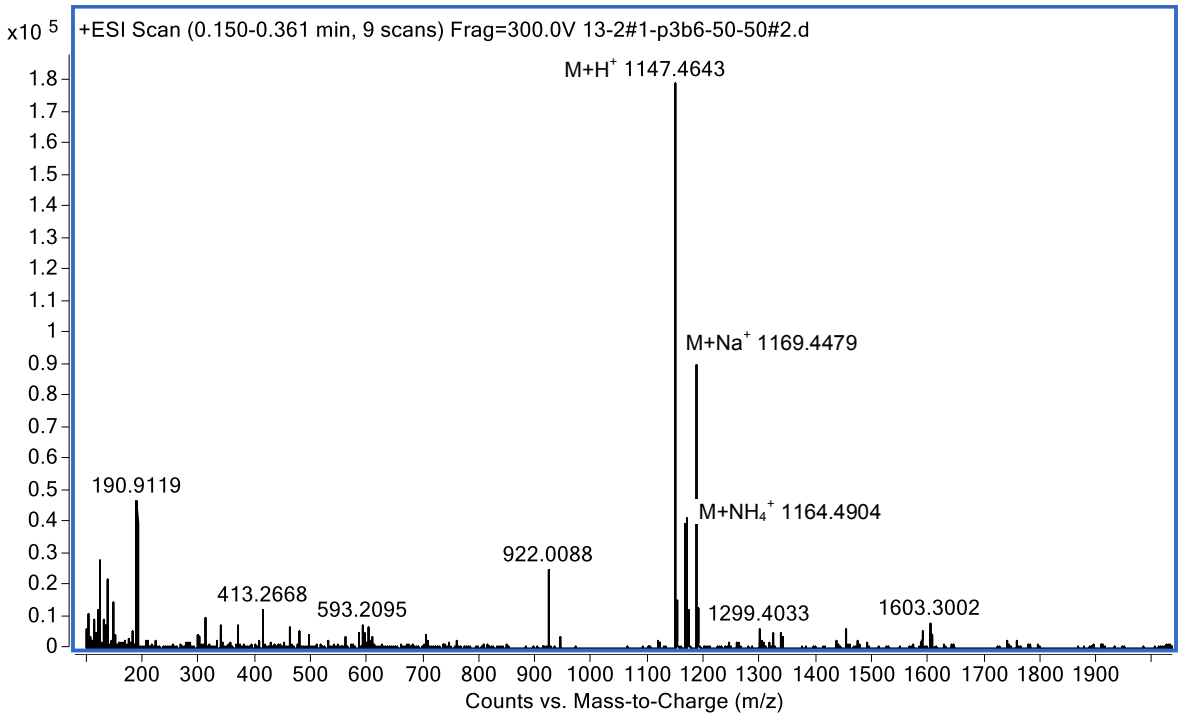


Fig. ESI-2 ESI MS of hemicryptophane *PL*-**2**

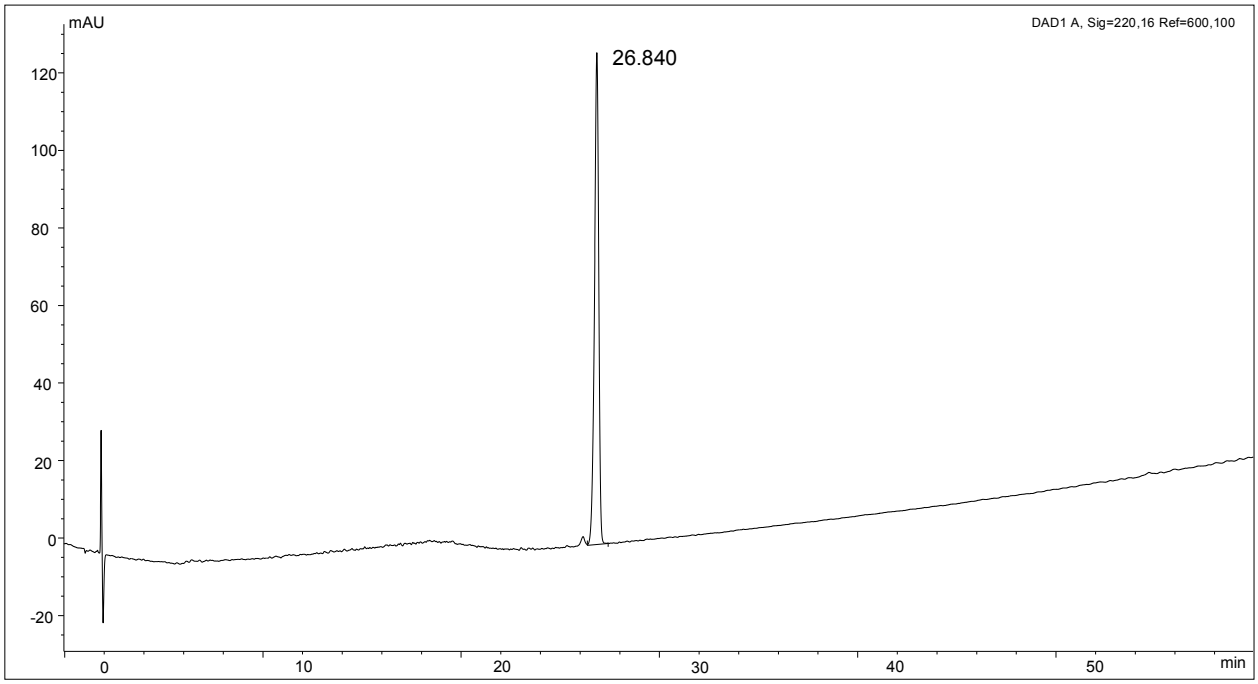


Fig. ESI-3 HPLC Trace of hemicryptophane *ML*-**2**

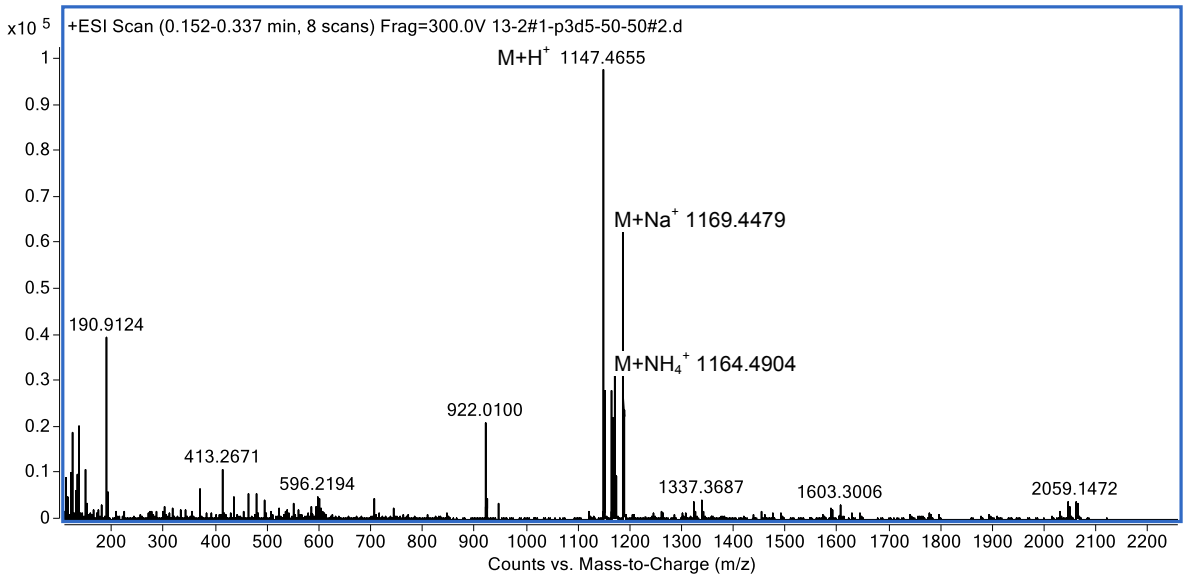
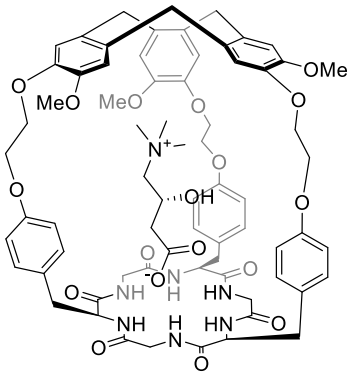


Fig. ESI-4 ESI MS of hemicryptophane *ML*-**2**



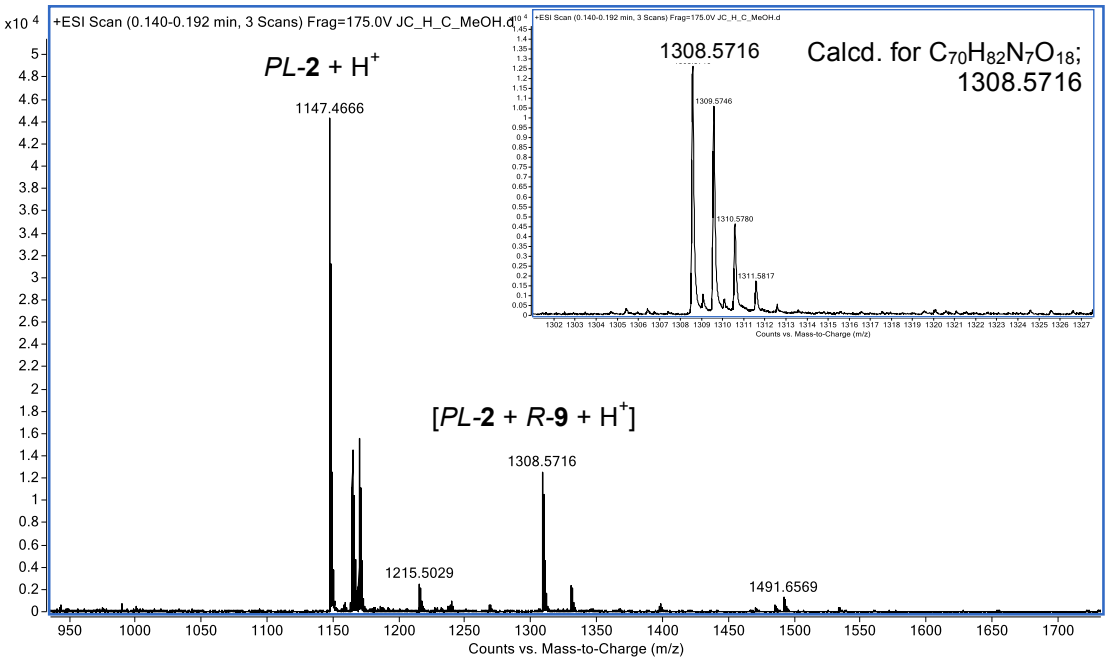


Fig. ESI-5 ESI MS of host:guest complex of hemicryptophane + carnitine; *PL*-**2** + *R*-**9**

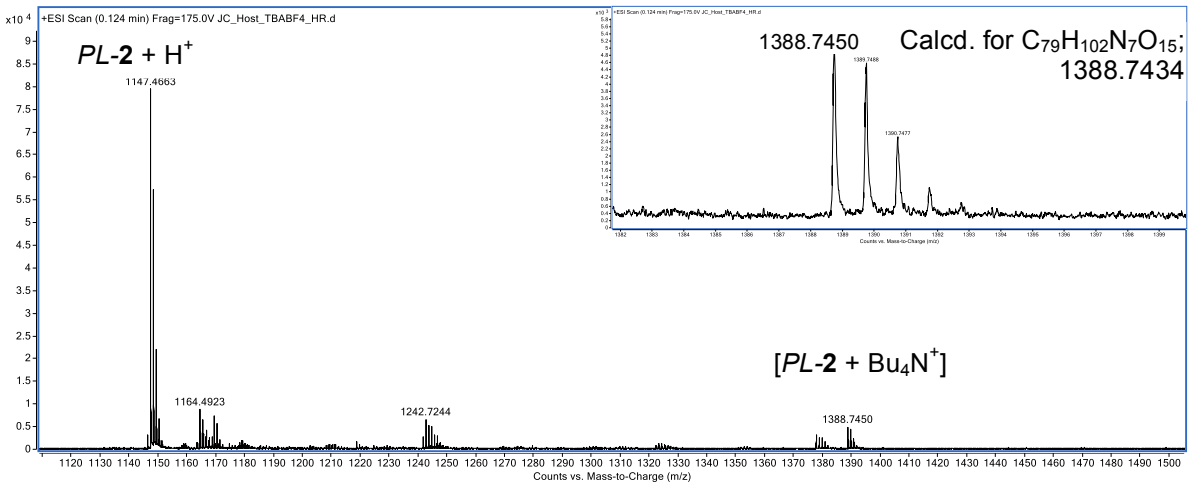


Fig. ESI-6 ESI MS of hemicryptophane *PL*-**2** + $Bu_4N^+BF_4^-$

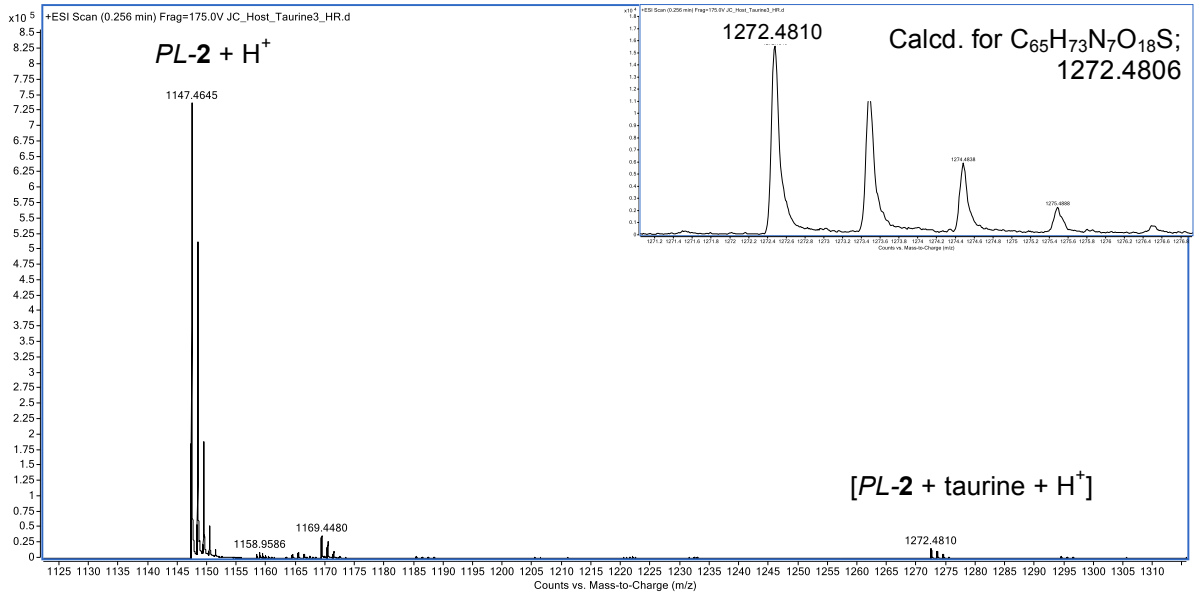


Fig. ESI-7 ESI MS of hemicryptophane *PL*-**2** + taurine

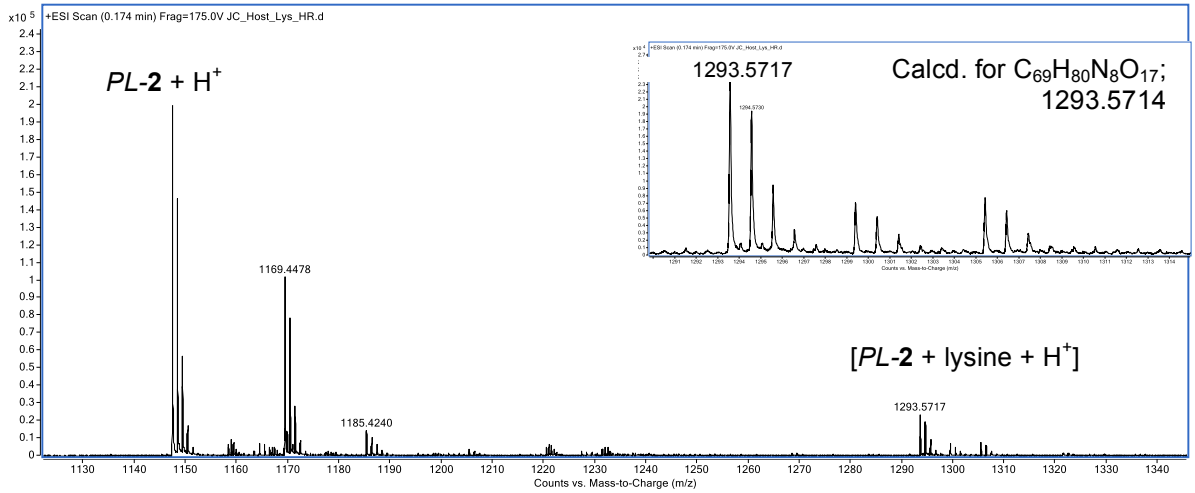


Fig. ESI-8 ESI MS of hemicryptophane *PL*-**2** + lysine

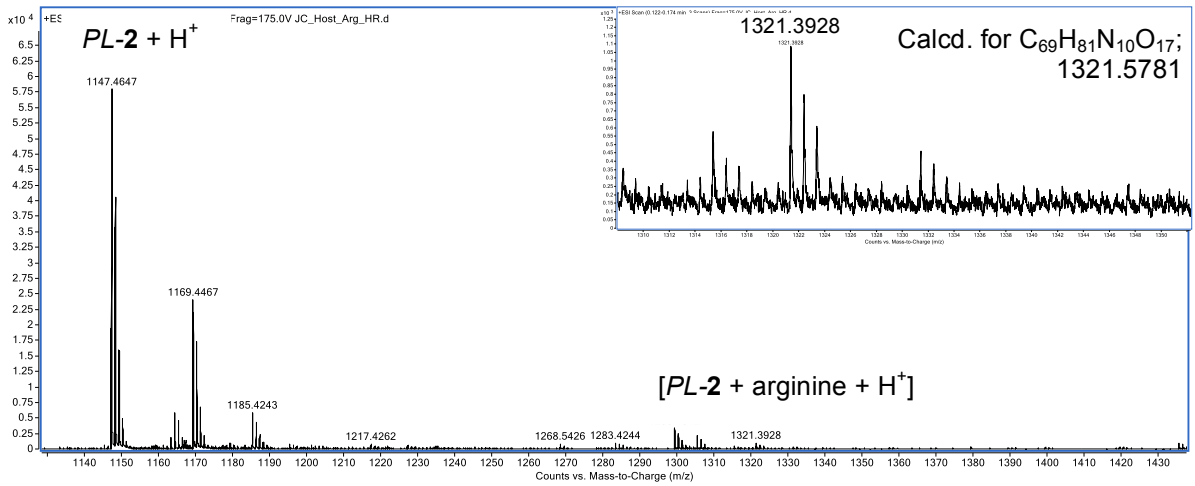


Fig. ESI-9 ESI MS of hemicryptophane *PL*-**2** + arginine

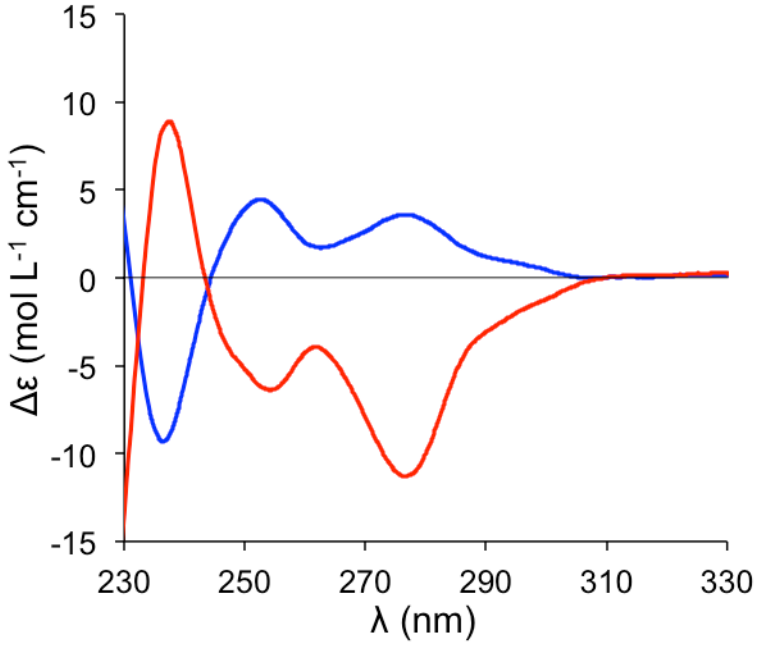


Fig. ESI-10 CD spectra of *PL*-**2** (blue) and *ML*-**2** (red) in CH_2Cl_2

Job Plot

Stock solutions (2.0 mM in CD_3CN) of *PL*-**2** and *R*-**9** were prepared. The required concentration of (*R*)-carnitine in CD_3CN was obtained by addition of a 10 µL aliquot from a 2.0 M stock solution of carnitine dissolved in H_2O. The two stock solutions were mixed in NMR spectroscopy tubes in different ratios. In this way, relative concentrations (molar fraction, α) were varied continuously but their sum was kept constant (2.0 mM). ^{1}H NMR spectra were recorded for each sample and values of the chemical shifts of the host (δ_{obs}) were measured. The Job plot was obtained by plotting $(\delta_{obs}-\delta_{free})\alpha$ vs α, for which δ_{free} is the chemical shift of the proton in the uncomplexed host. The stoichiometry of the complex was obtained from the value of the molar fraction, α, at which a maximum is observed (i.e., $\alpha_{max} = 0.5$ observed for 1:1 complexation).

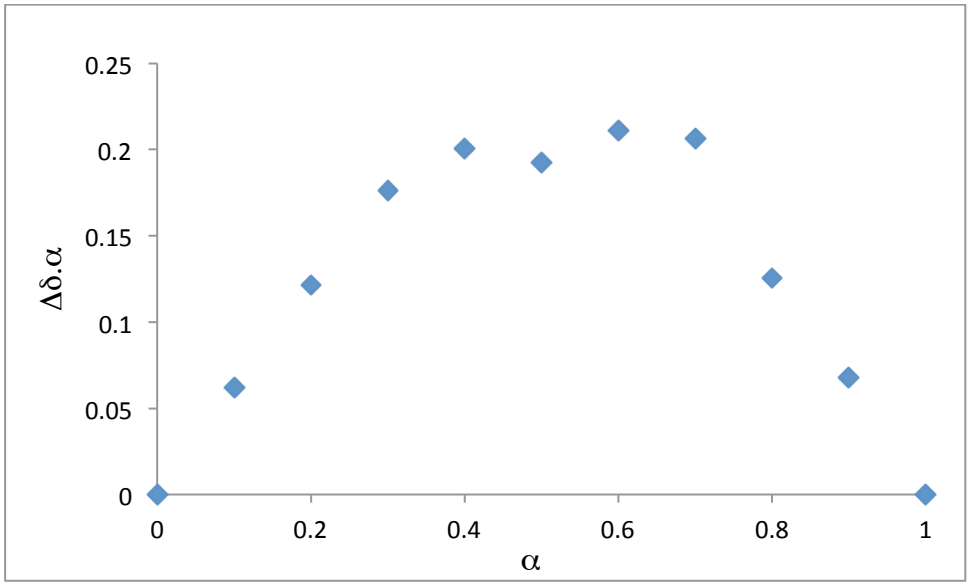


Fig. ESI-11 Job plot of (*R*)-carnitine *R*-**9** with host *PL*-**2**; α is the host's mole fraction.

NMR Titrations

All ^{1}H NMR titration experiments were performed in CD_3CN (unless otherwise noted) and were conducted according to the following example. Into a solution of hemicryptophane (0.785 mM in CD_3CN, 1000 µL) in an NMR spectroscopy tube was added sequentially 5 µL aliquots of a solution of carnitine (15.7 mM) and hemicryptophane (0.785 mM) in CD_3CN. In this way the concentration of carnitine increased while keeping the concentration of the hemicryptophane constant. The carnitine/hemicryptophane solution was prepared by addition of a 10 µL aliquot from a 1.57 M stock solution of carnitine in H_2O to a solution of hemicryptophane (0.785 mM) in CD_3CN (1000 µL). The change in chemical shift (Δδ) of the proton signals of the host were measured after each addition and plotted as a function of the guest/host ratio. Association constants K_a were obtained by nonlinear least-squares fitting of this plot using the WinEQNMR2 program.

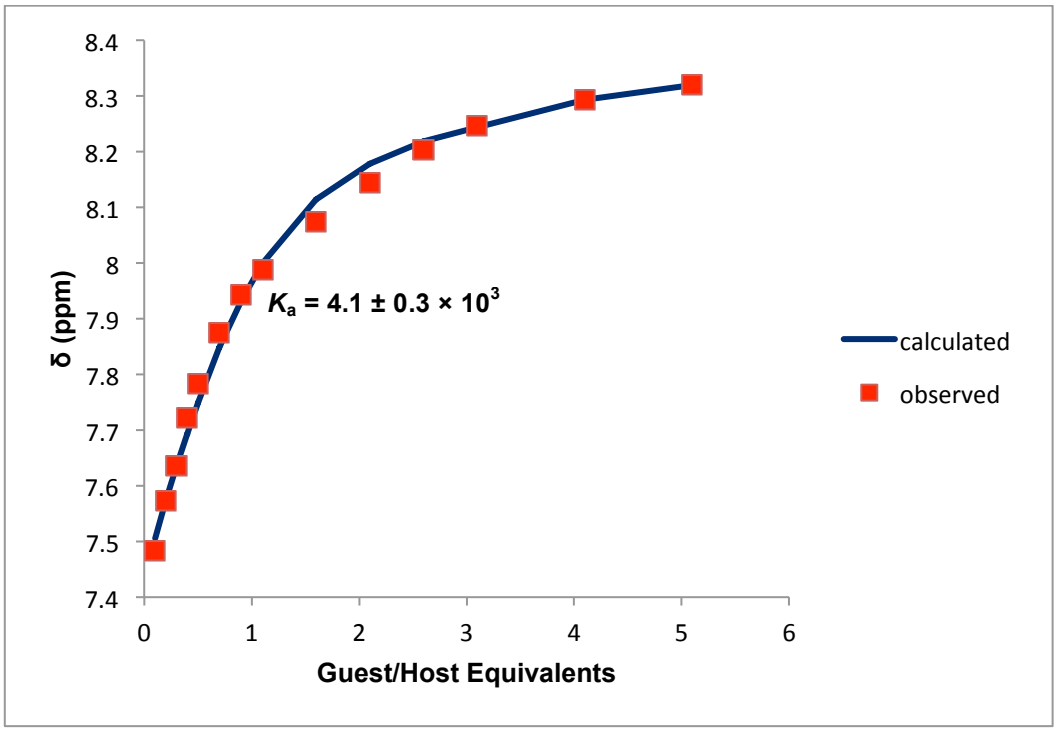


Fig. ESI-12 ^{1}H NMR titration of hemicryptophane *PL*-2 with (*R*)-carnitine *R*-9; $\delta_{NH(Gly)}$ of *PL*-**2** as a function of [*R*-**9**]/[*PL*-**2**] ratio.

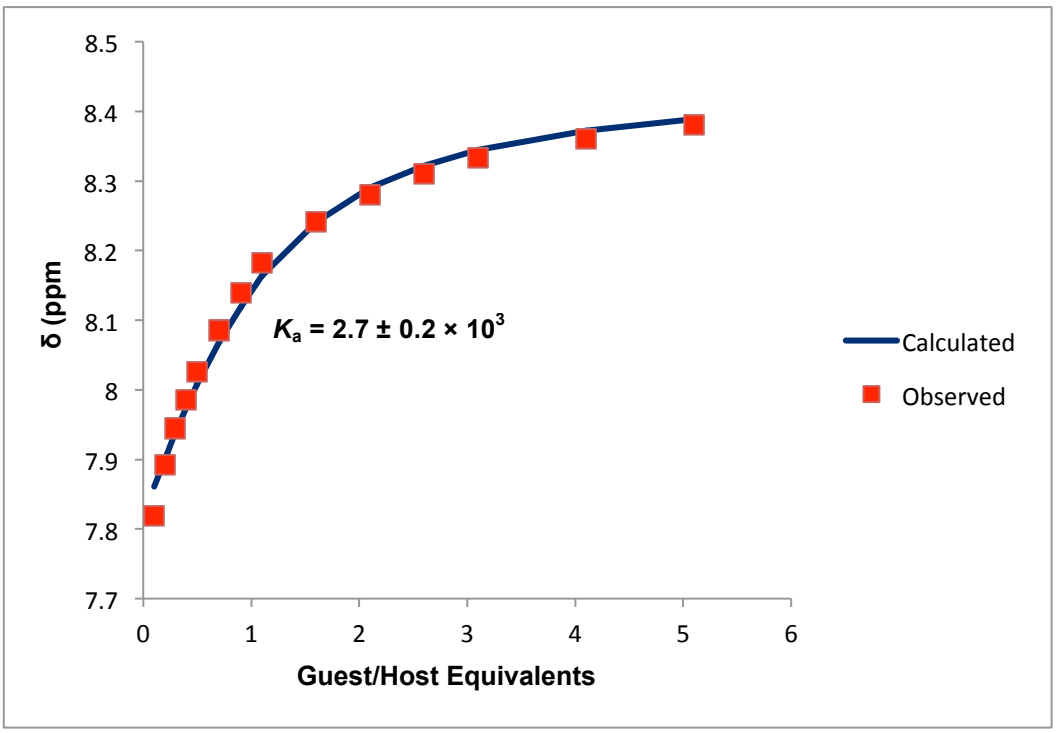


Fig. ESI-13 ^{1}**H NMR titration of hemicryptophane *PL*-2 with (*S*)-carnitine *S*-9;** $\delta_{NH(Gly)}$ of *PL*-**2** as a function of [*S*-**9**]/[*PL*-**2**] ratio.

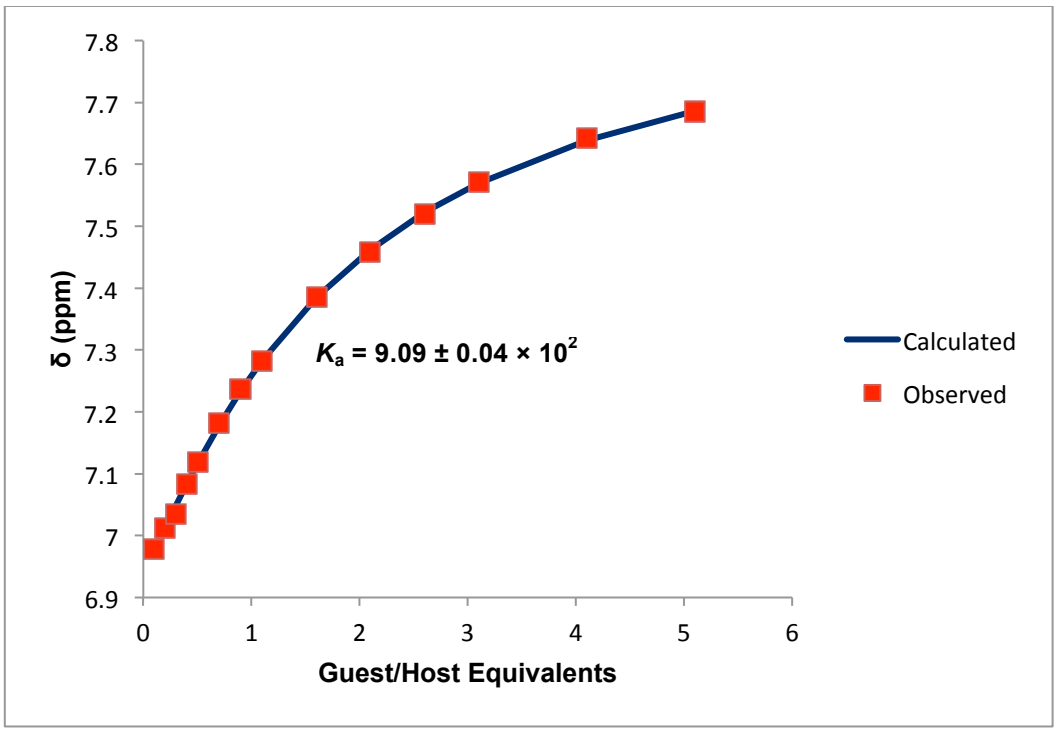


Fig. ESI-14 ^{1}**H NMR titration of hemicryptophane *ML*-2 with (*R*)-carnitine *R*-9;** $\delta_{NH(Gly)}$ of *ML*-**2** as a function of [*R*-**9**]/[*ML*-**2**] ratio.

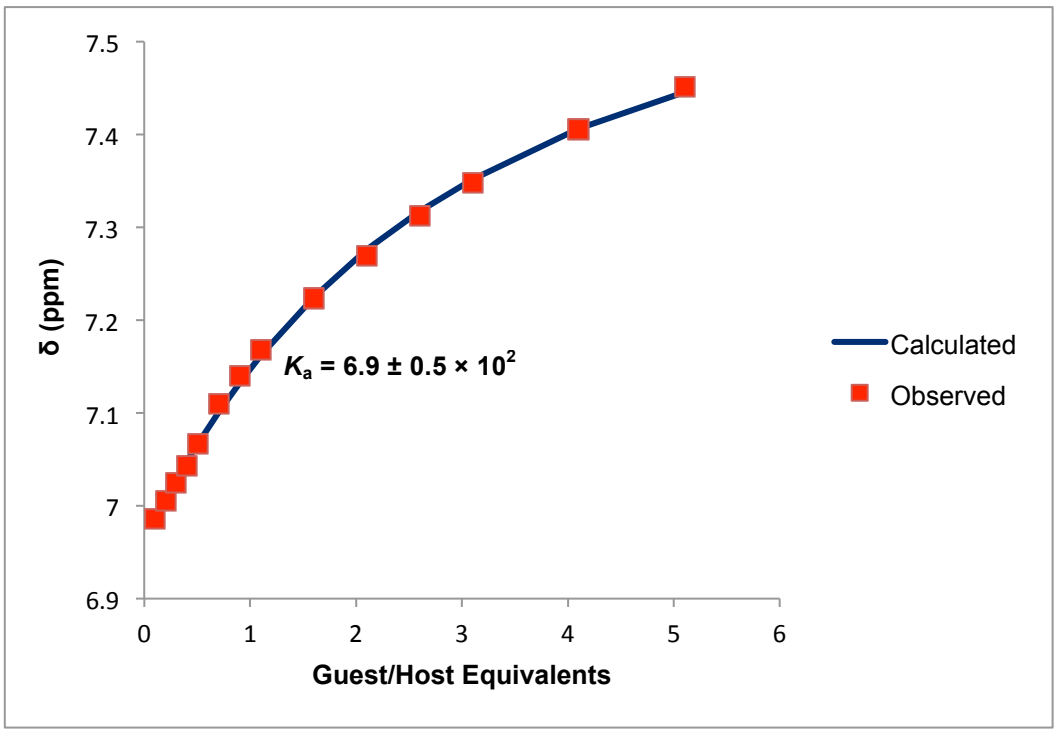


Fig. ESI-15 ^{1}**H NMR titration of hemicryptophane *ML*-2 with (*S*)-carnitine *S*-9;** $\delta_{NH(Gly)}$ of ***ML*-2** as a function of [*S*-**9**]/[*ML*-**2**] ratio.

Table ESI-1: K_a values determined from ^{1}H NMR titrations calculated from shifts of glycyl NH and CTV OMe protons (Δδ plots for OMe peaks; data not shown).

Host	Guest	$\Delta\delta_{max}$(Gly-NH)	K_a	$\Delta\delta_{max}$ (OMe)	K_a
PL-**2**	*R*-**9**	-0.8945	4.1 ± 0.3 × 10^3	0.0265	4.04 ± 0.04 × 10^3
PL-**2**	*S*-**9**	-0.5937	2.7 ± 0.2 × 10^3	0.0172	2.61 ± 0.02 × 10^3
ML-**2**	*R*-**9**	-0.7194	9.1 ± 0.1 × 10^2	-0.0101	1.02 ± 0.01 × 10^3
ML-**2**	*S*-**9**	-0.4791	6.9 ± 0.5 × 10^2	-0.0034	6.37 ± 0.04 × 10^2

Control binding experiments were conducted with cyclic peptide c(GYGYGY) **6** to confirm the ditopic binding of **9** with hemicryptophane *PL*-**2**. ^{1}H NMR titrations were conducted in d_6-DMSO as **6** was insoluble in CD_3CN. Binding of hemicryptophane *PL*-**2** with (*R*)-carnitine **9** was also determined in d_6-DMSO. The solutions were prepared in the same manner as described above.

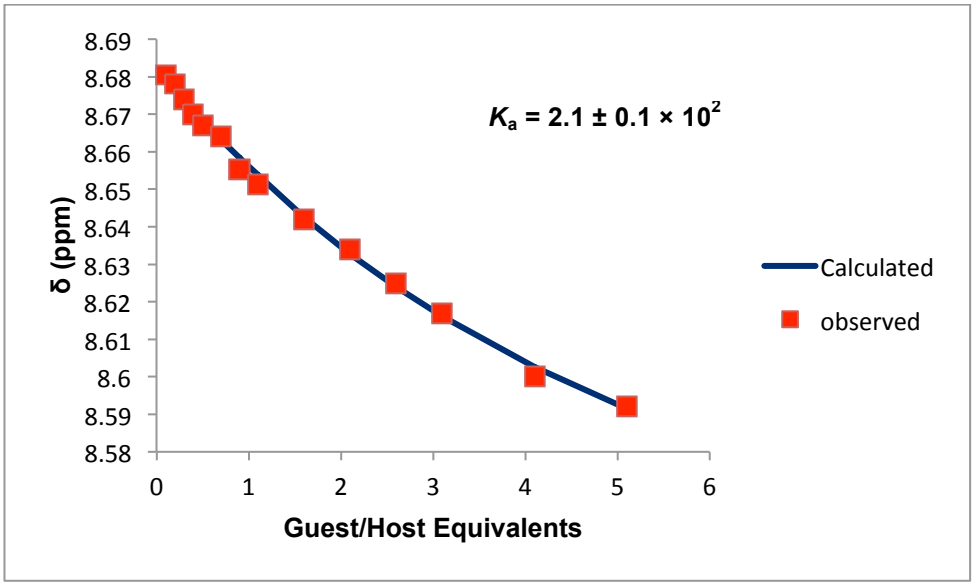


Fig. ESI-16 ^{1}H NMR titration of cyclic peptide 6 with carnitine *R*-9 in d_6-DMSO; $\delta_{NH(Gly)}$ of **6** as a function of [*R*-**9**]/[**6**] ratio. $K_a = 2.1 \pm 0.1 \times 10^2$

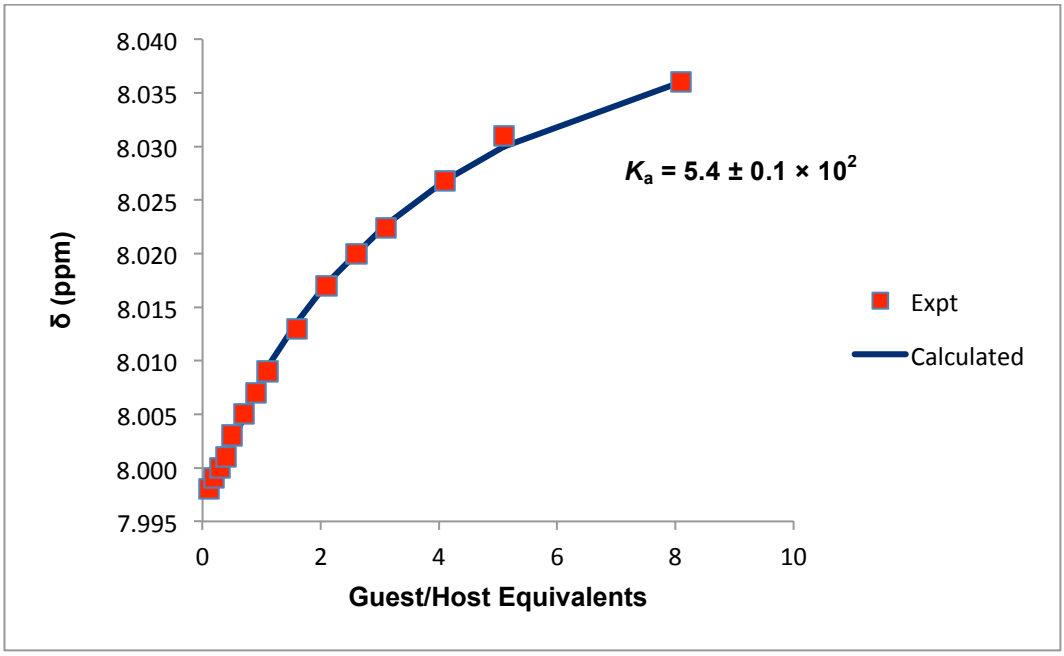
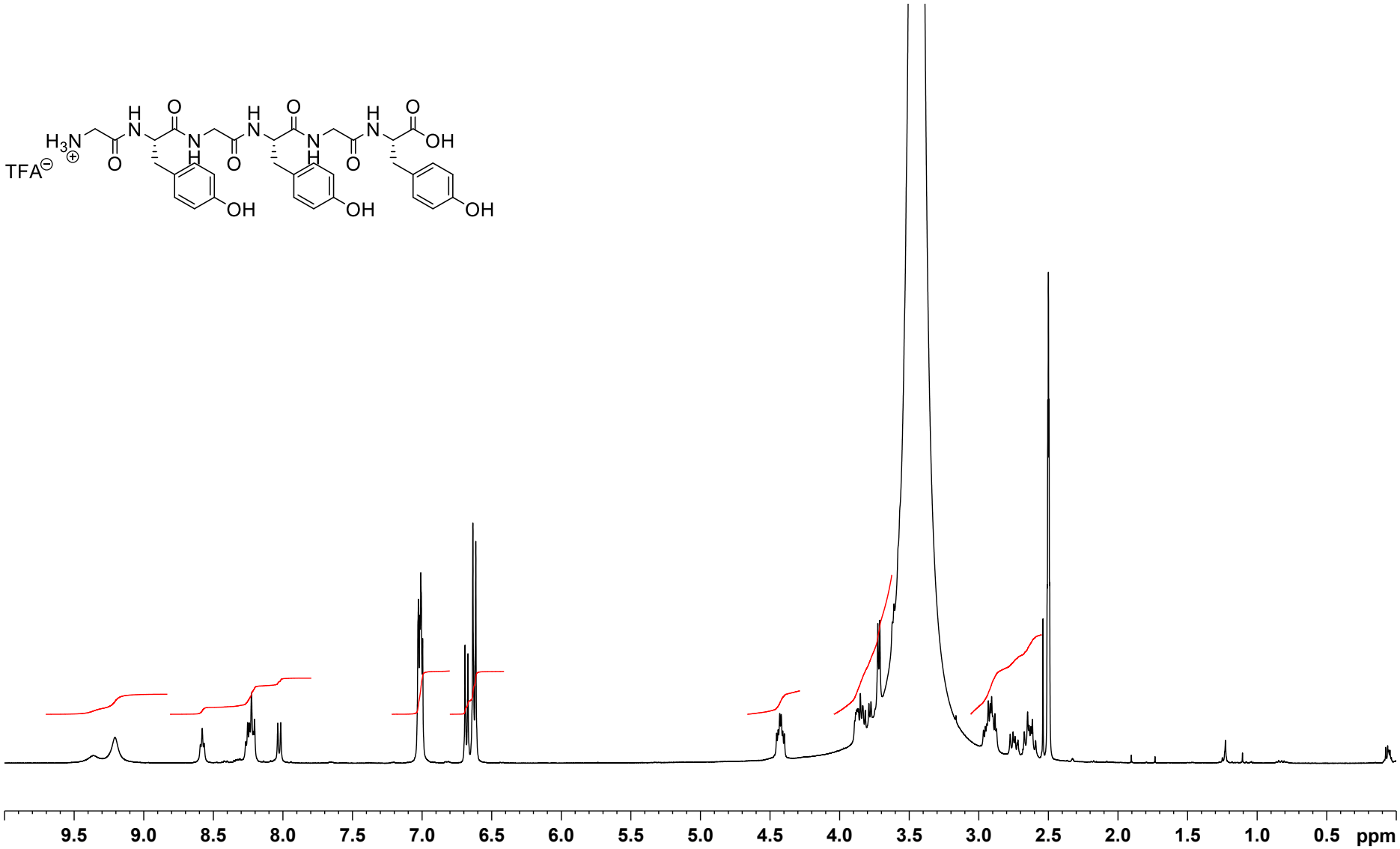
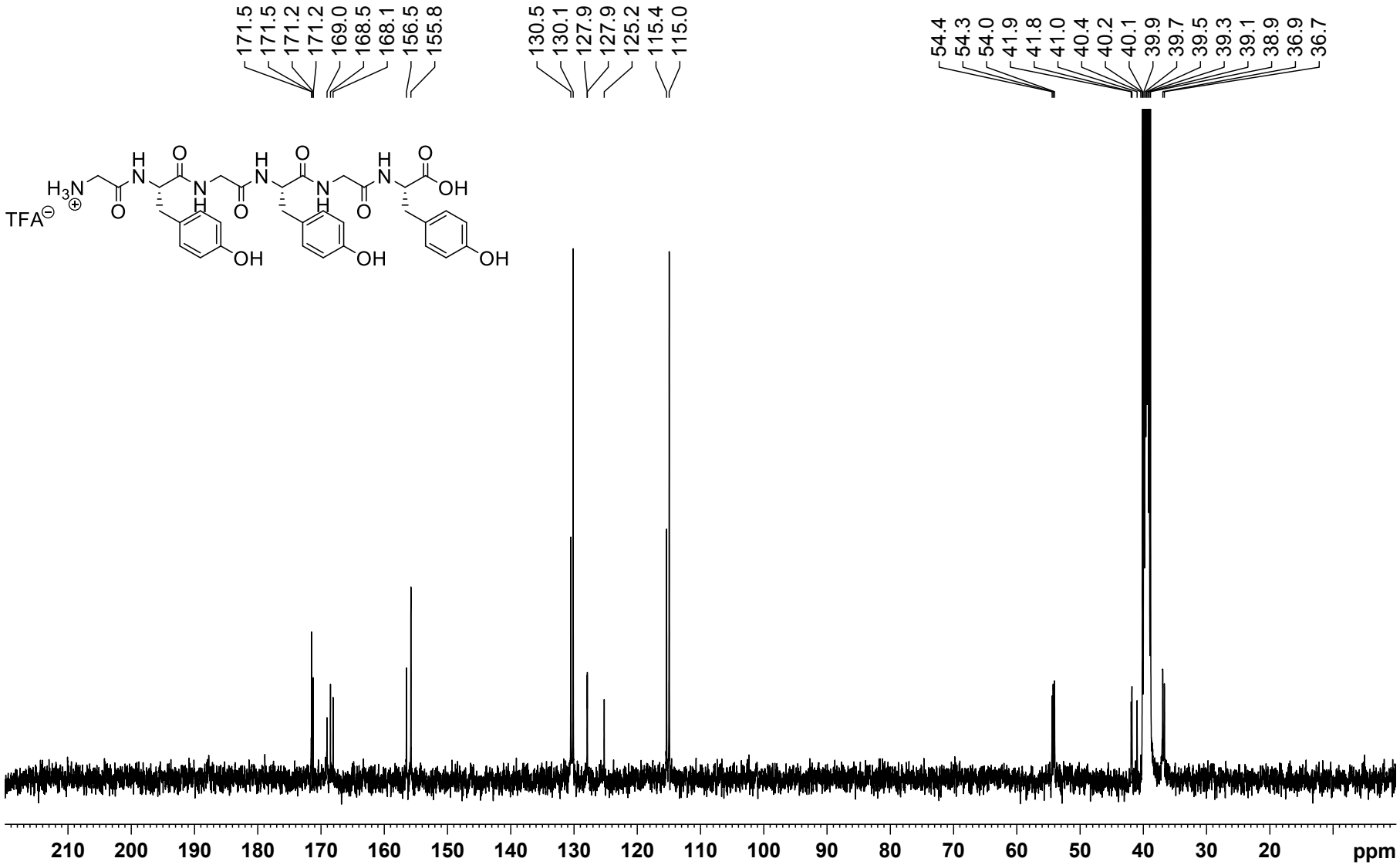


Fig. ESI-17 ^{1}H NMR titration of hemicryptophane *PL*-2 with (*R*)-carnitine *R*-9 d_6-DMSO; $\delta_{NH(Gly)}$ of *PL*-**2** as a function of [*R*-**9**]/[*PL*-**2**] ratio. $K_a = 5.4 \pm 0.1 \times 10^2$

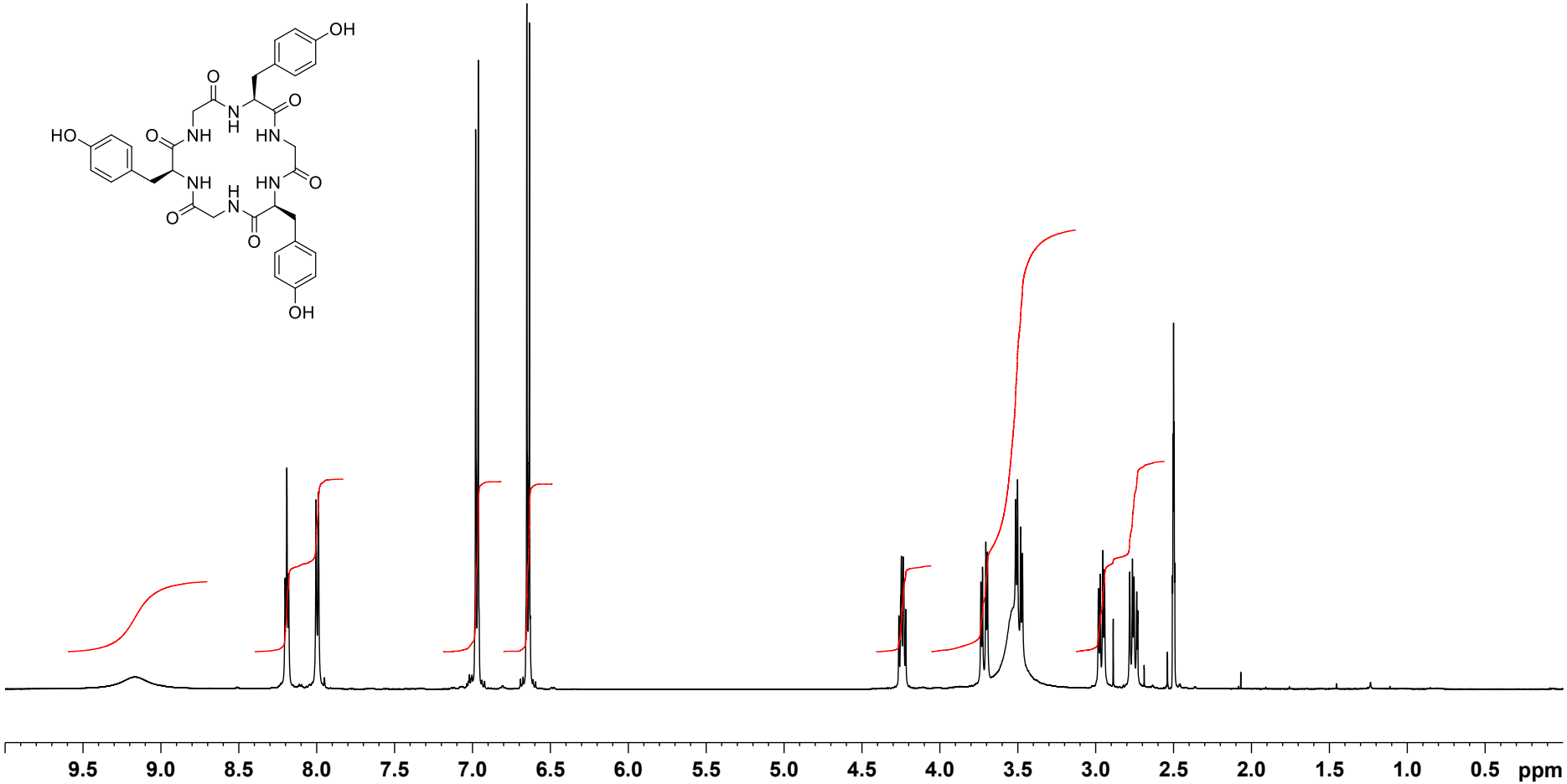
Linear deprotected peptide 4 (400 MHz, DMSO-d_6). Method B



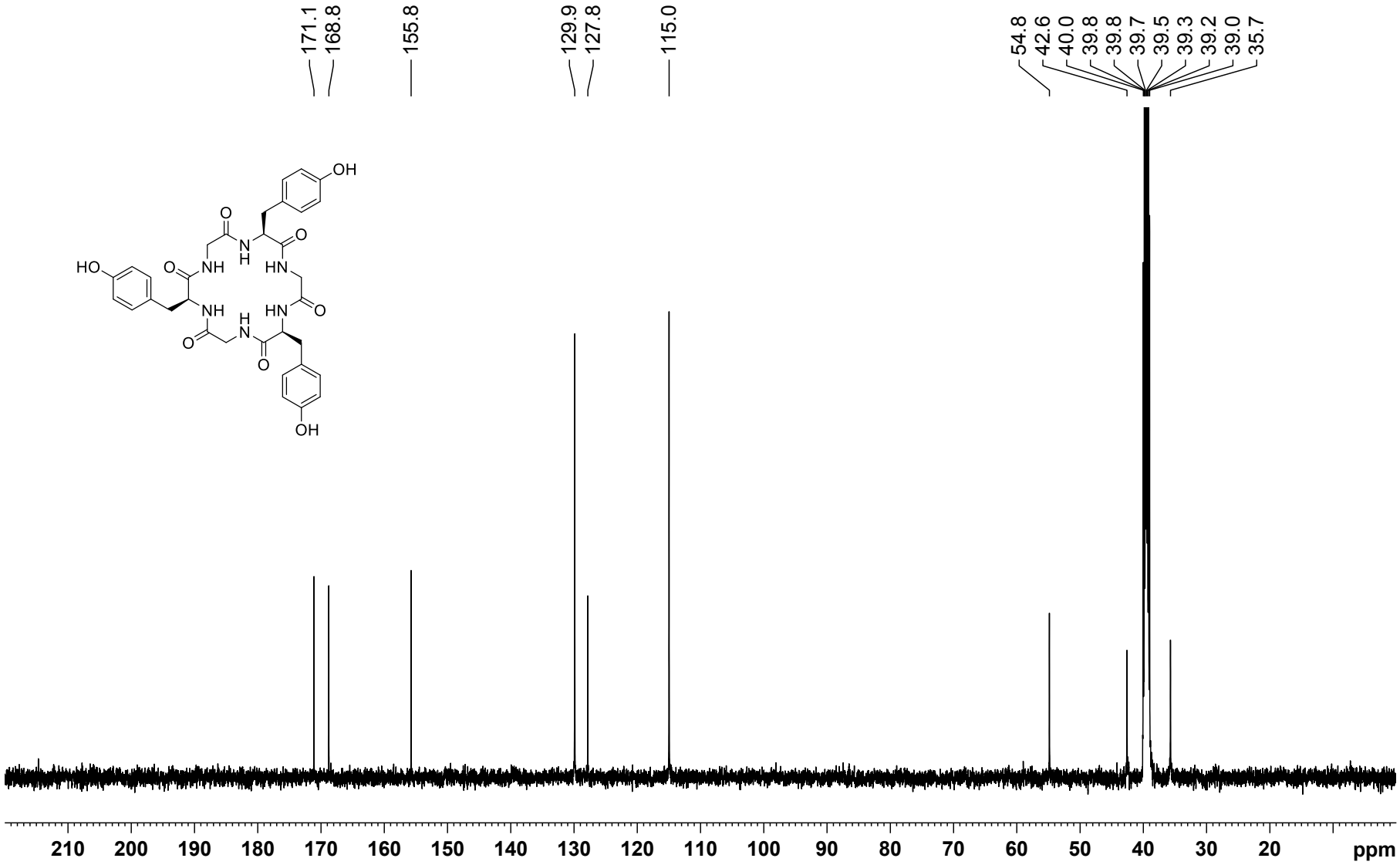
Linear deprotected peptide4 (100 MHz, DMSO-d_6). Method B



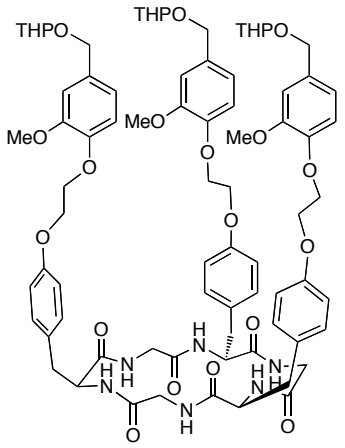
Cyclic hexapeptide c(YGYGYG) 6 (500 MHz, DMSO-d_6). Method A



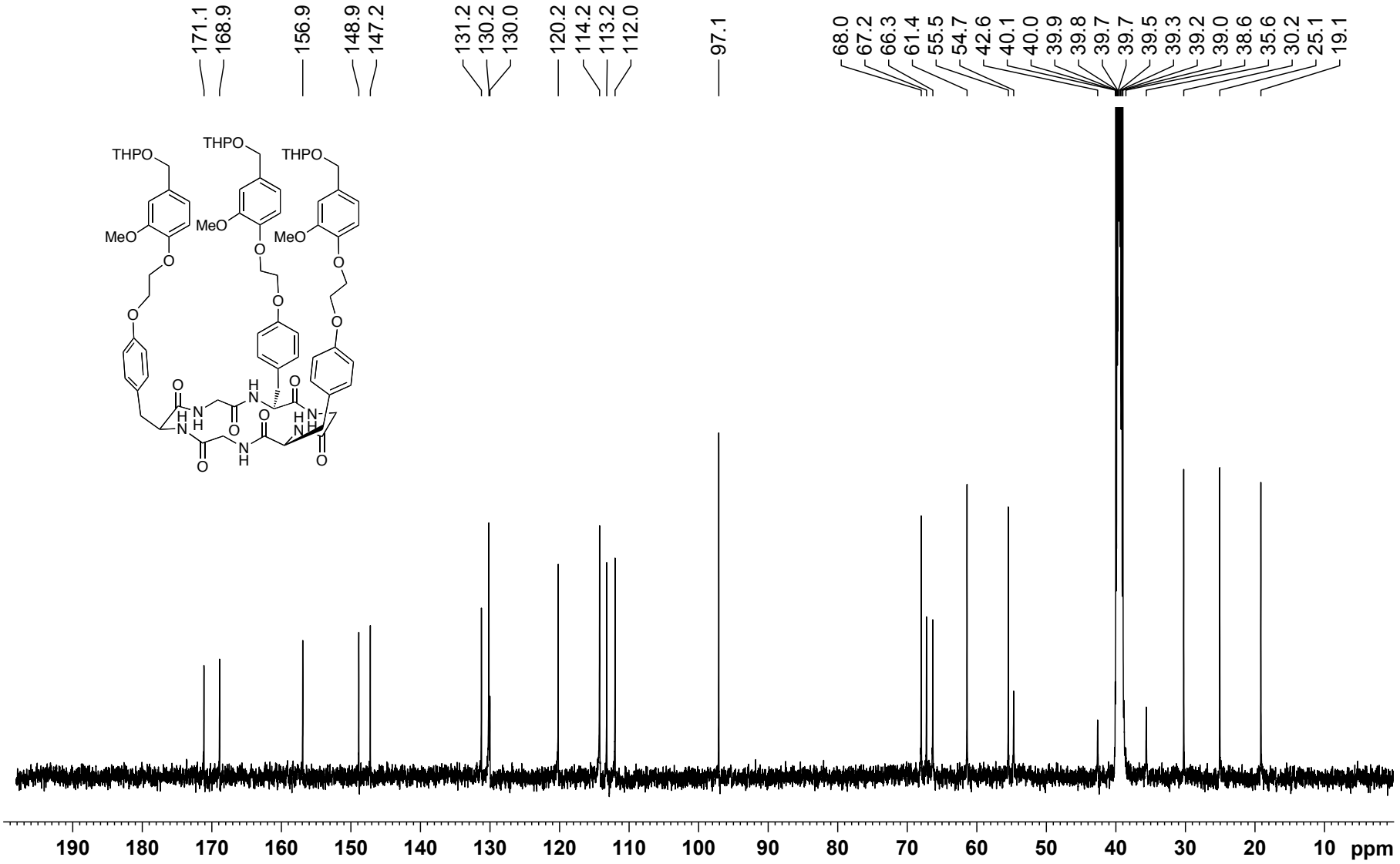
Cyclic hexapeptide c(YGYGYG) 6 (125 MHz, DMSO-d_6). Method A



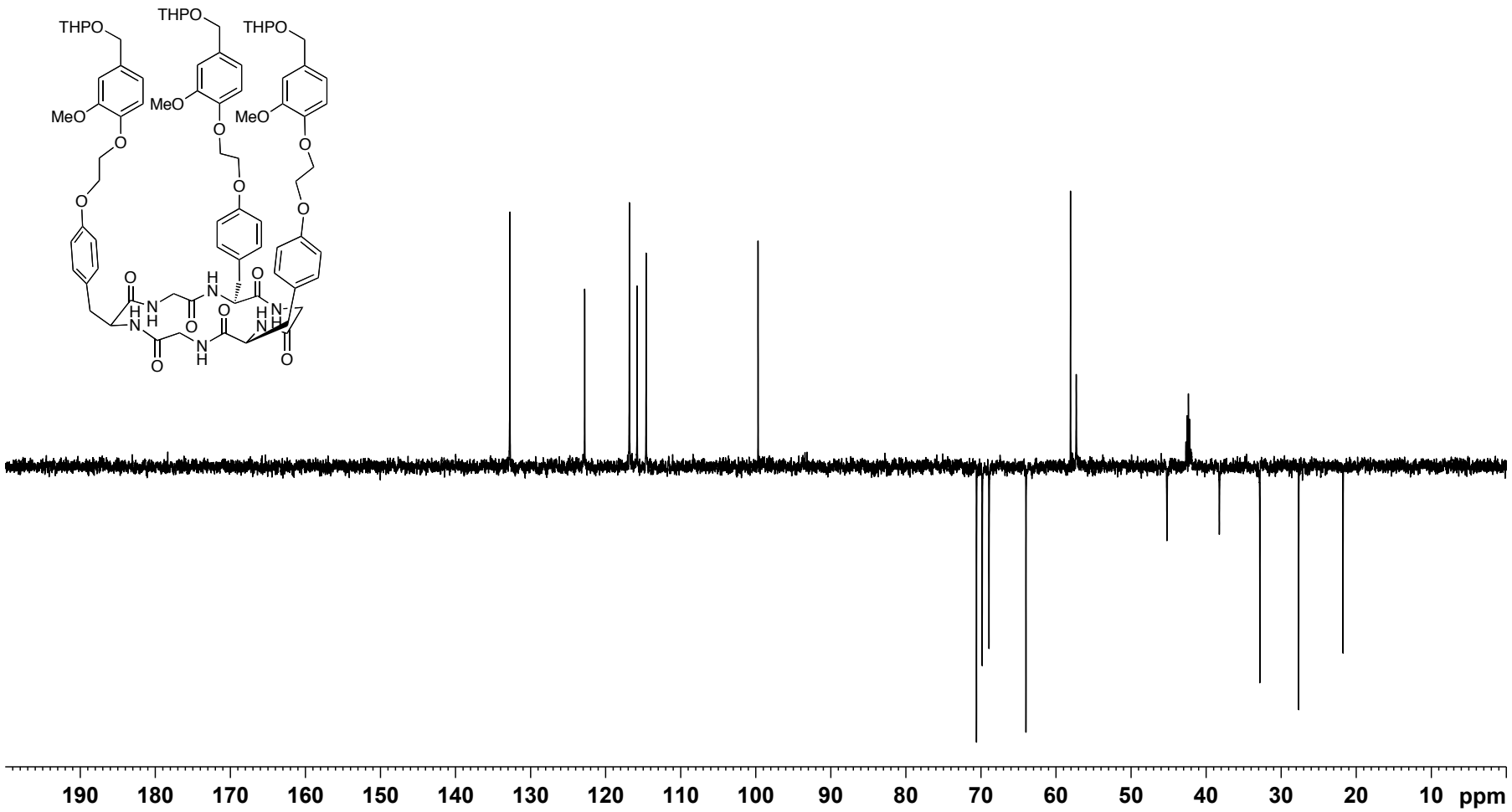
Tris-vanillyl cyclic peptide 8 (500 MHz, DMSO-d_6)



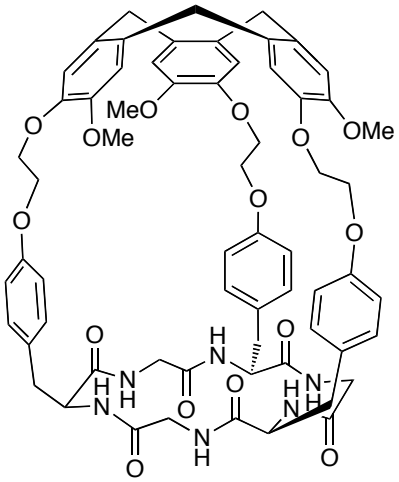
Tris-vanillyl cyclic peptide 8 (500 MHz, DMSO-d_6)



Tris-vanillyl cyclic peptide 8 (500 MHz, DMSO-d_6)



Hemicrytophane *PL-2* (500 MHz, acetone-d_6)



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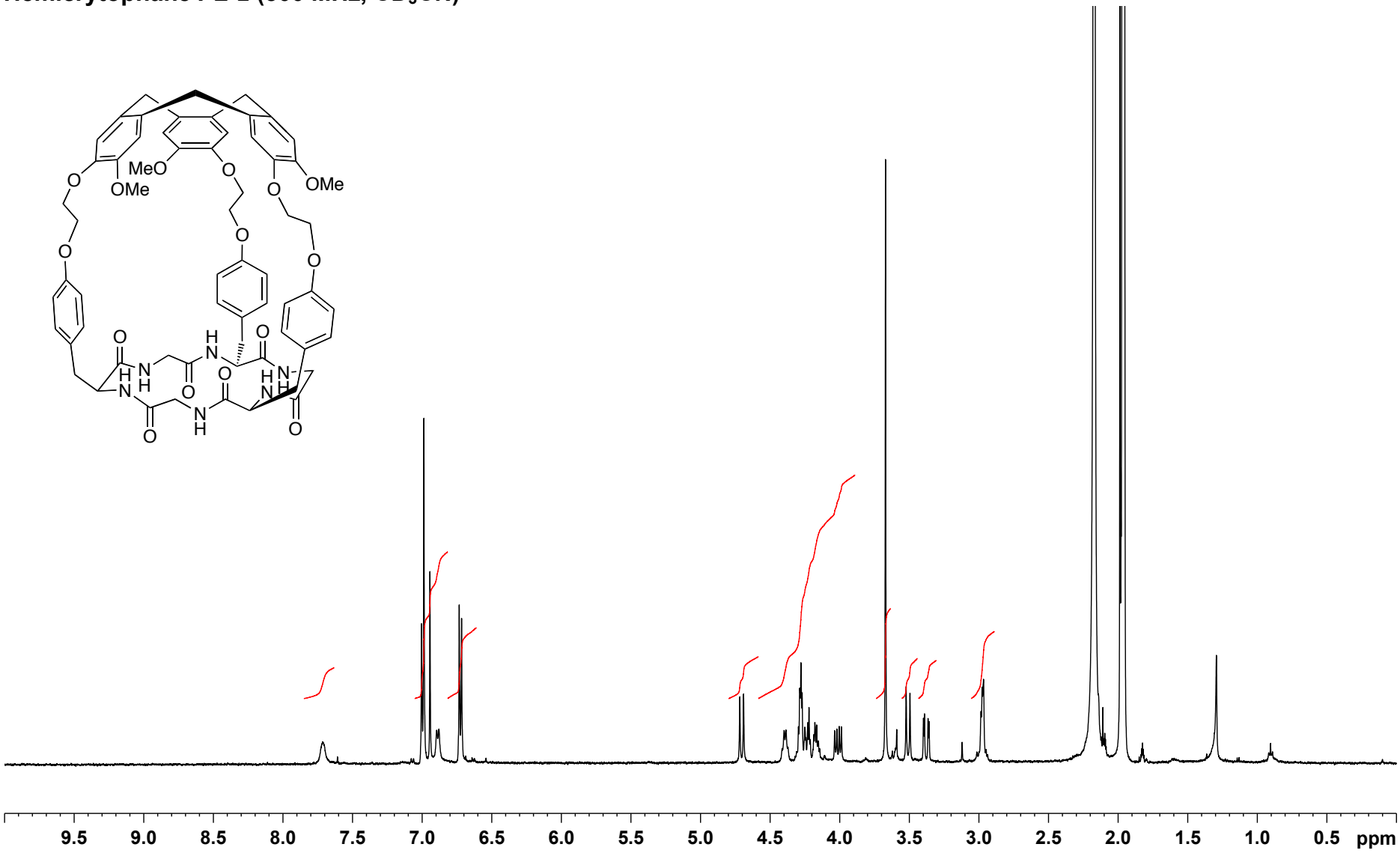

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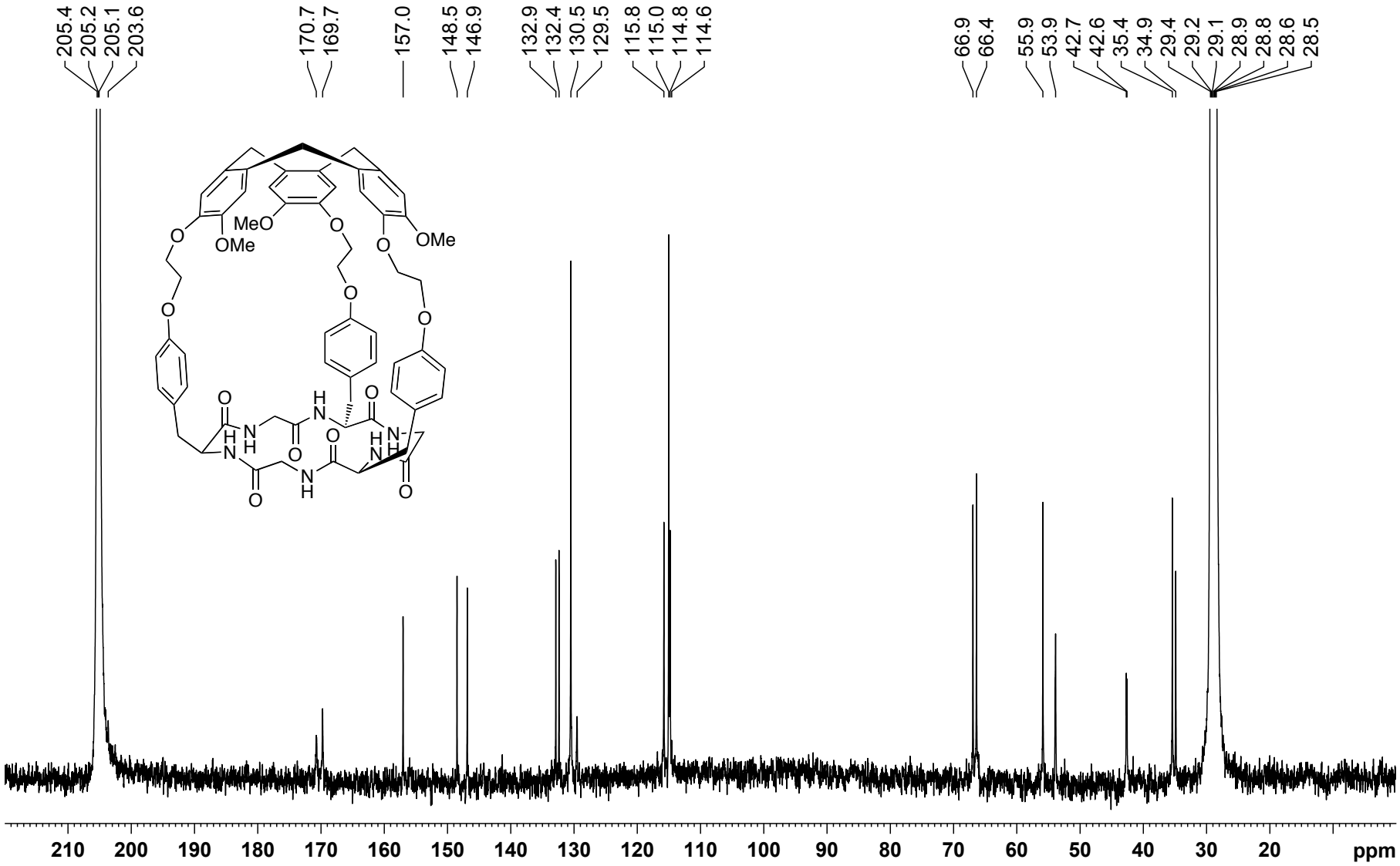

Hemicrytophane *PL*-2 (125 MHz, acetone-d_6) COSY

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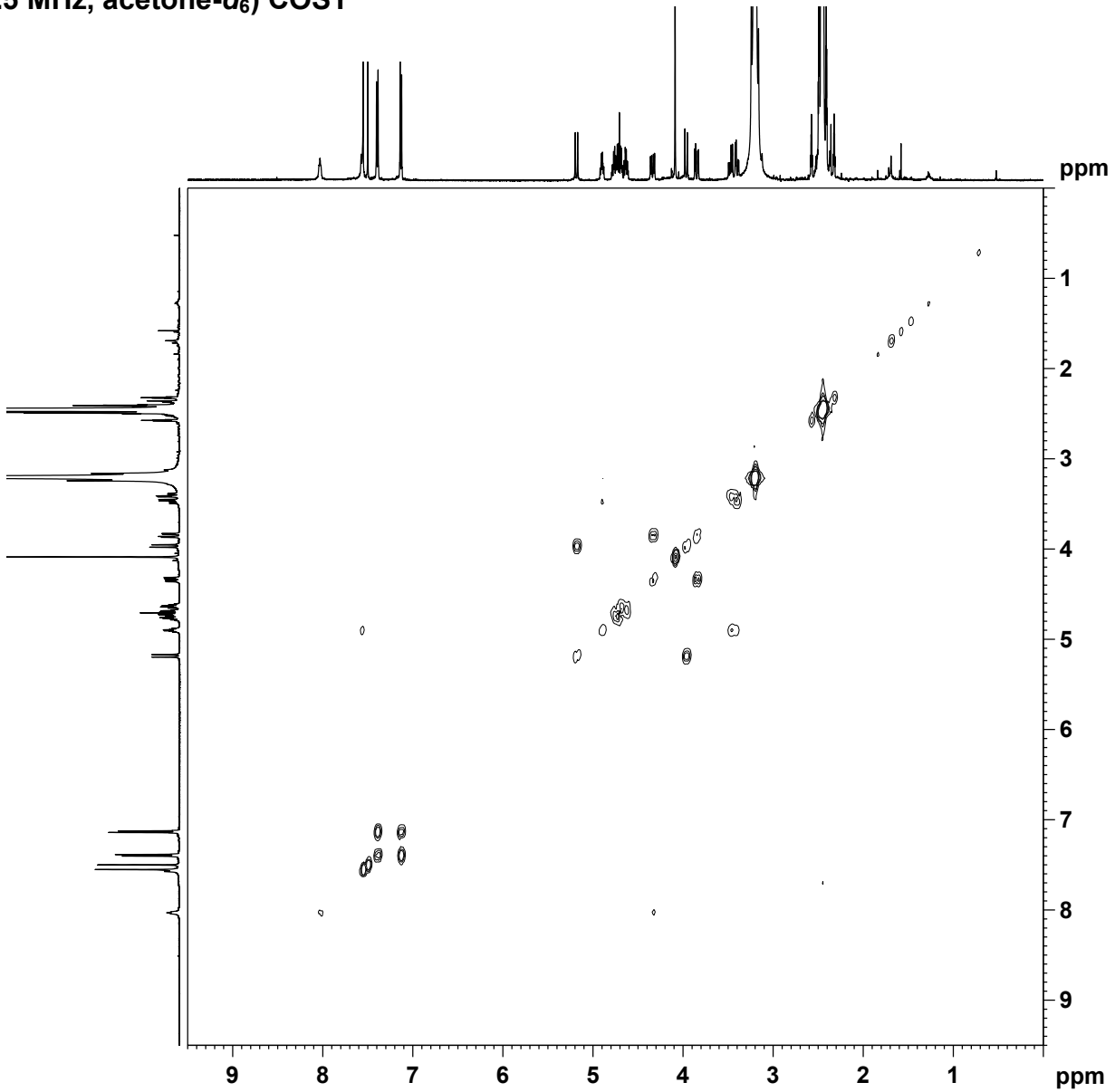

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P4                   30.00 usec
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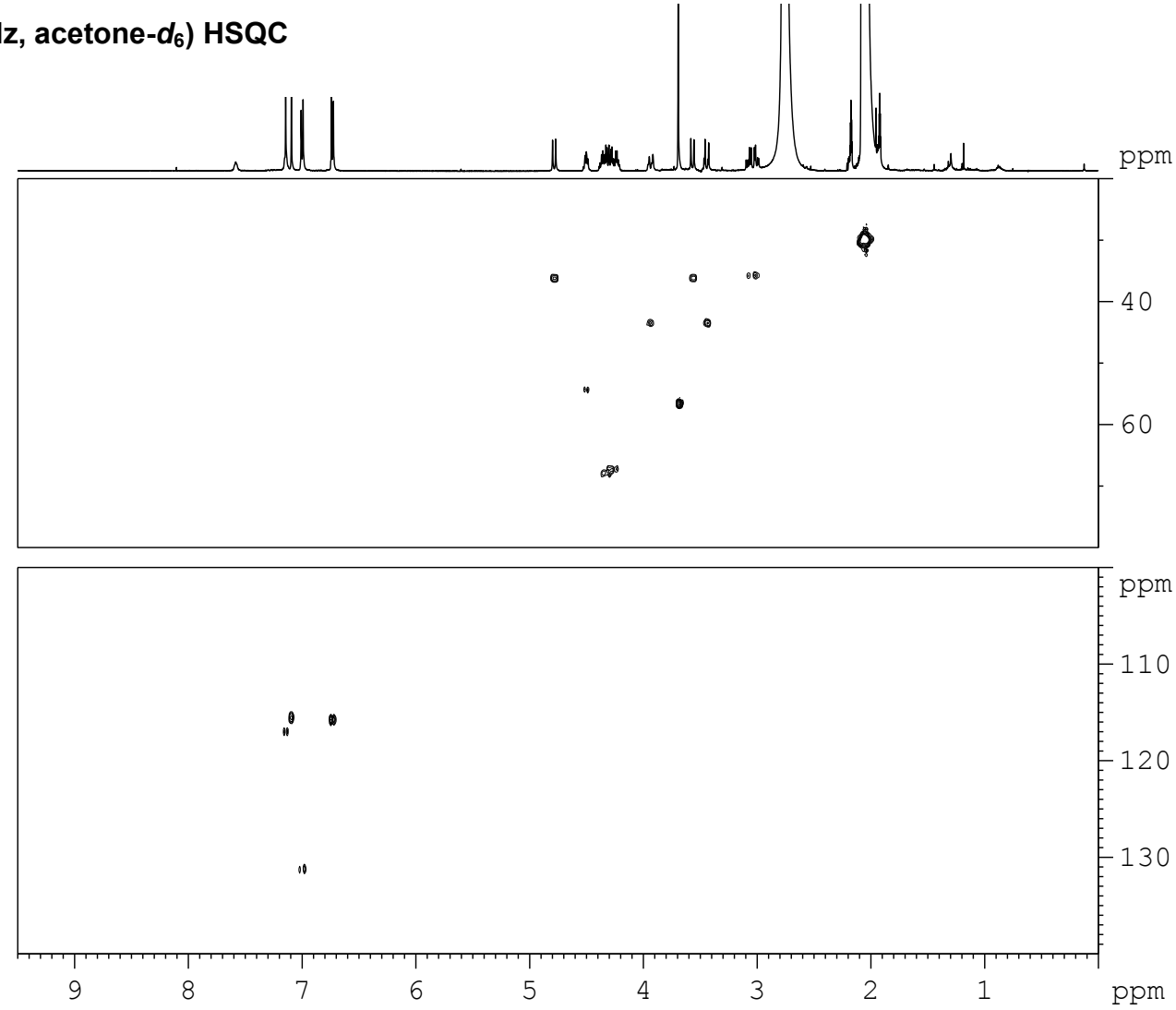

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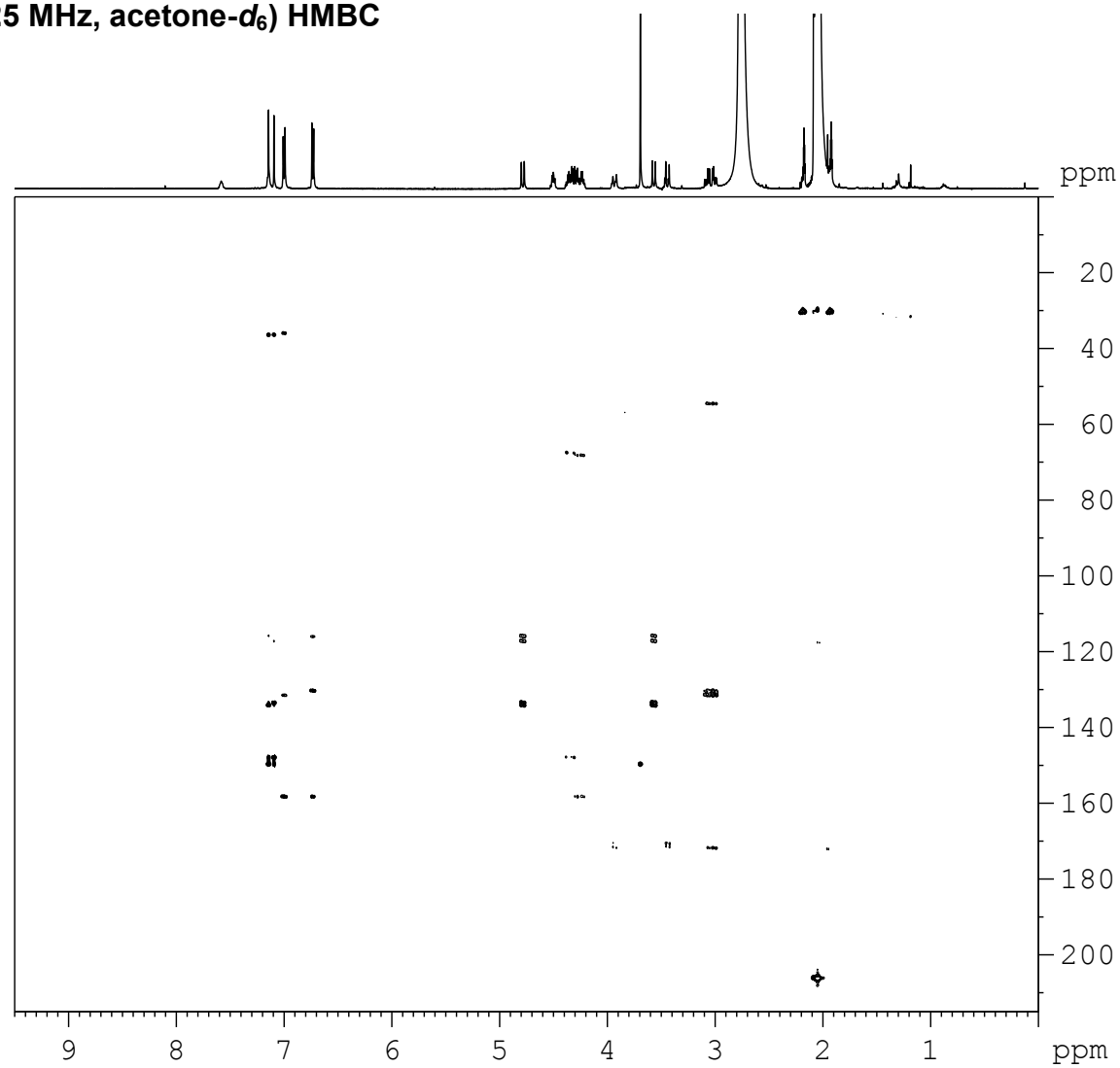
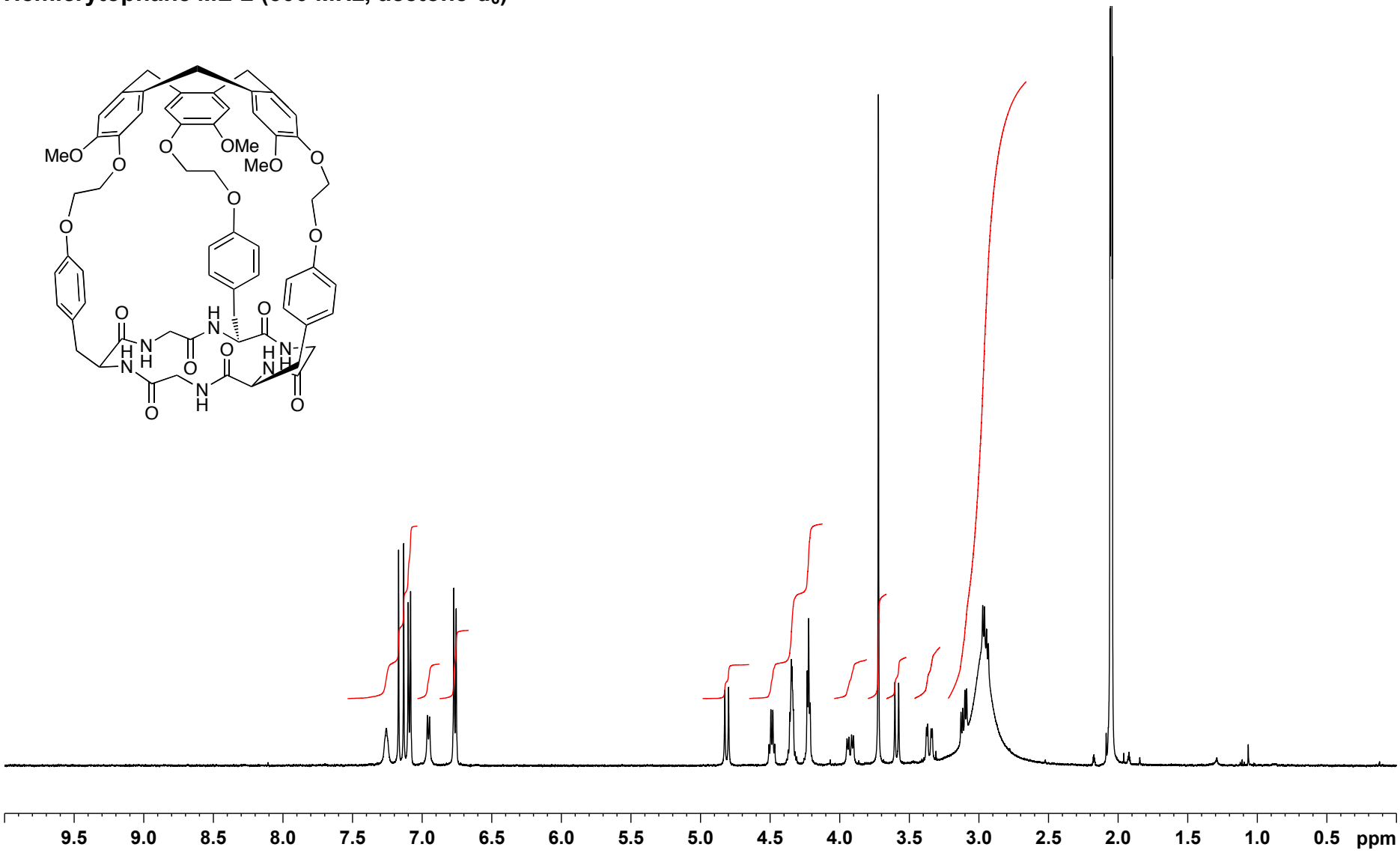
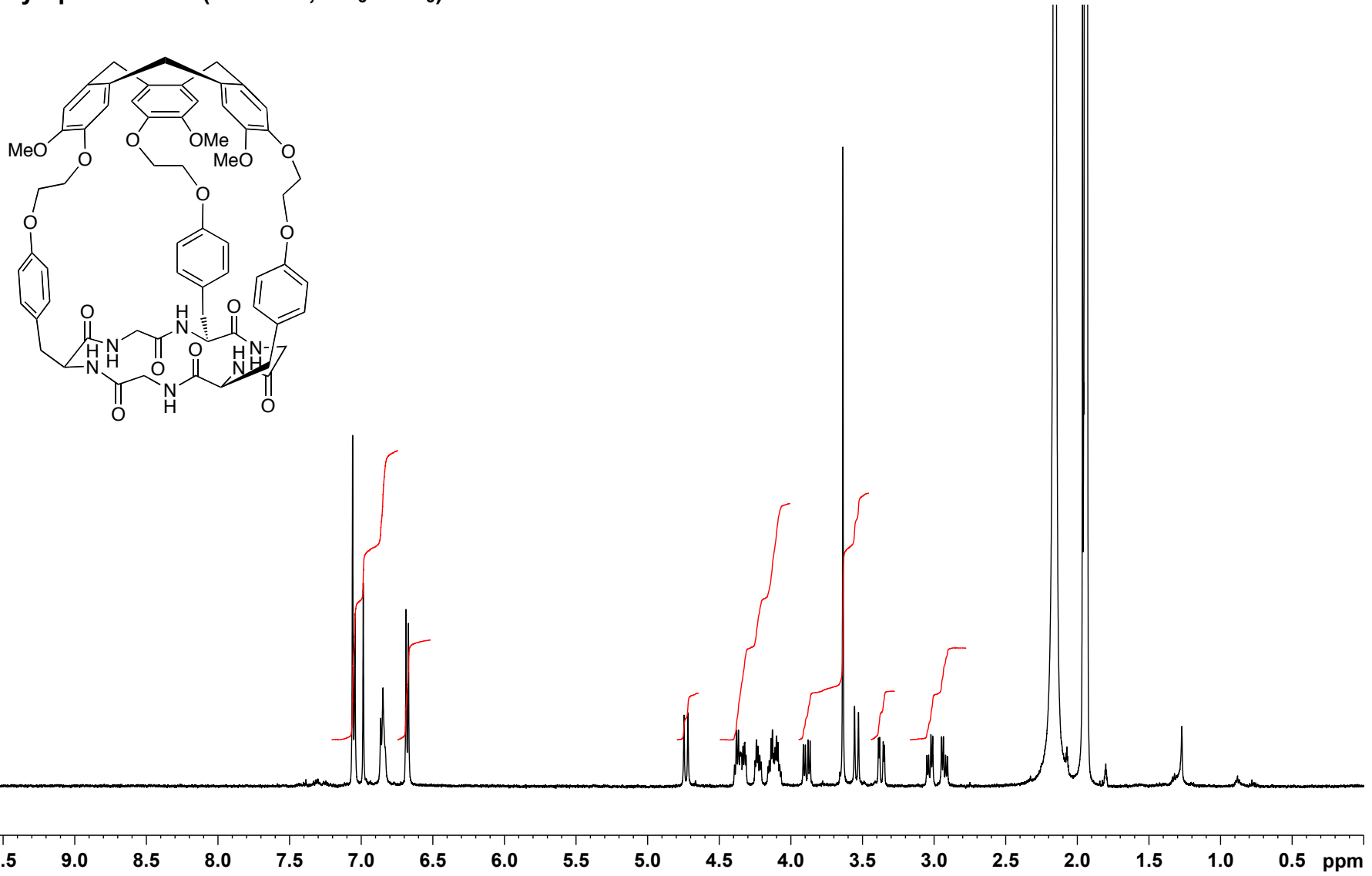


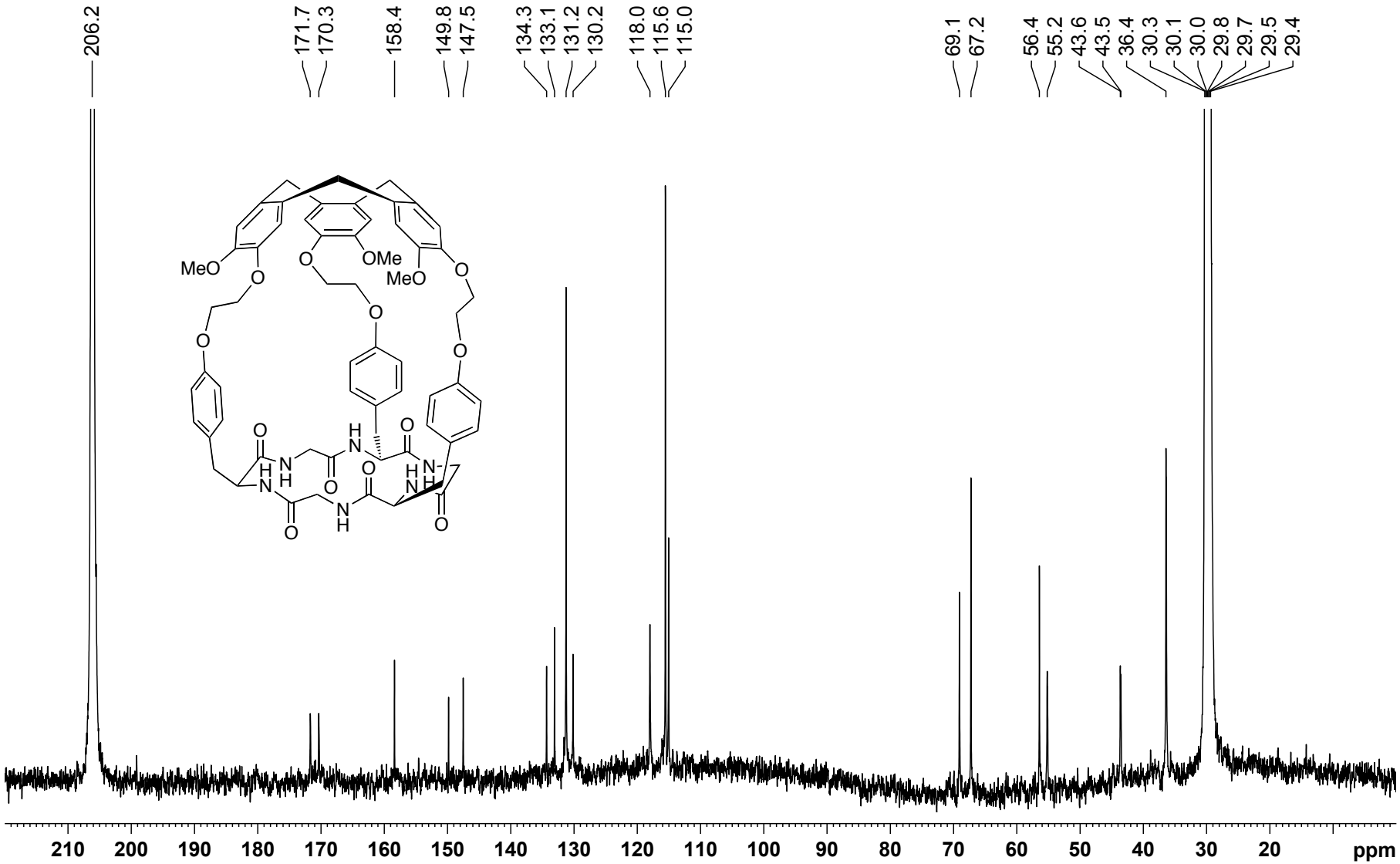
Hemicrytophane *ML*-2 (500 MHz, acetone-d_6)



Hemicrytophane *ML*-2 (500 MHz, CD_3CN-d_3)



Hemicrytophane *ML*-2 (125 MHz, acetone-d_6)



Hemicrytophane *ML*-2 (125 MHz, acetone-d_6) COSY

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D16            0.00020000 sec
IN0            0.00014295 sec

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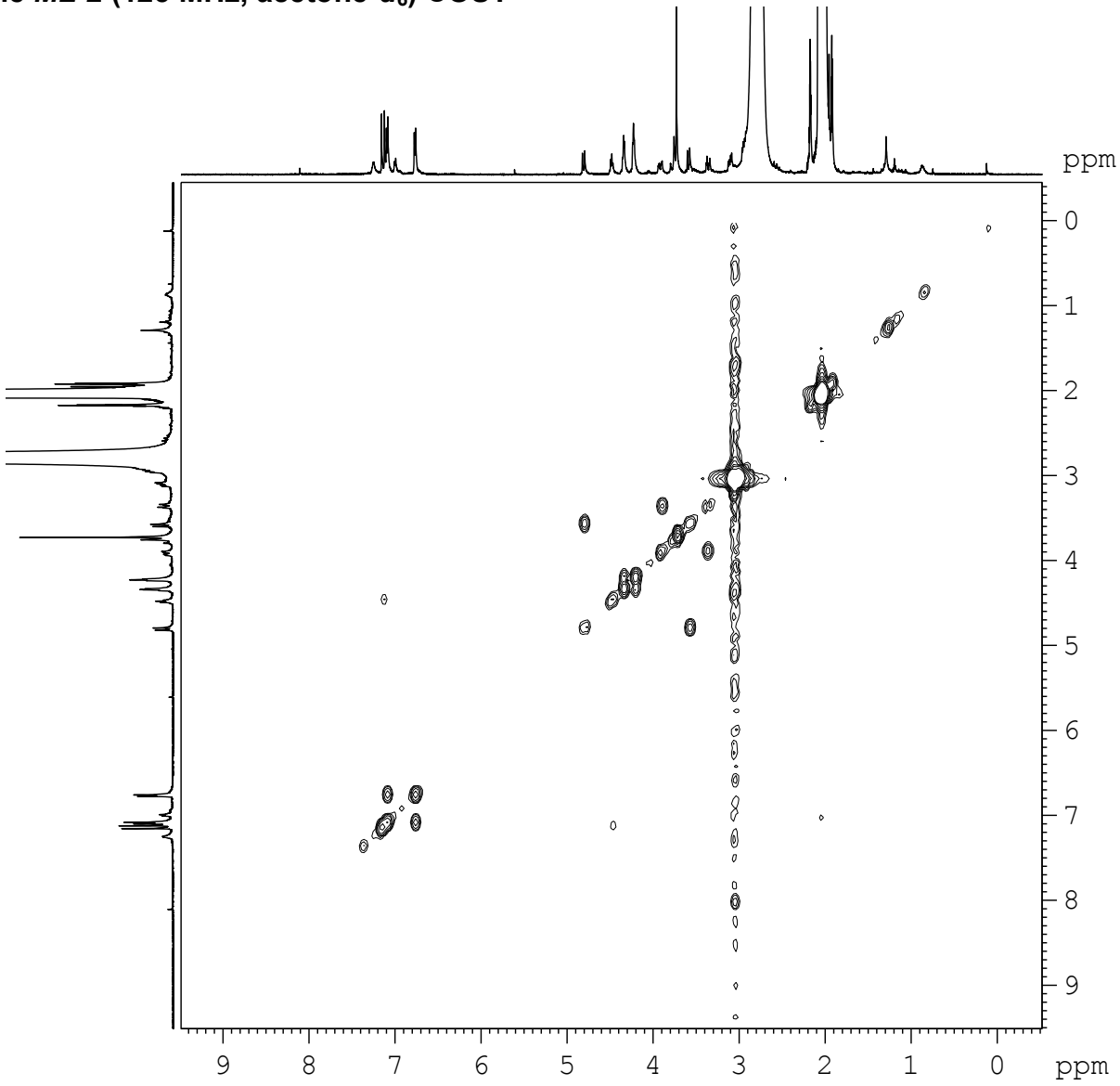
P1                   8.80 usec
PL1                  5.50 dB
PL1W         -1.#IND0000 W
SFO1         499.6834978 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPZ1                10.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                     256
SFO1             499.6835 MHz
FIDRES          27.326441 Hz
SW                 14.000 ppm
FnMODE                 QF

F2 - Processing parameters
SI                    1024
SF            499.6800043 MHz
WDW                 QSINE
SSB       0
LB        0 Hz
GB        0
PC                   1.40

F1 - Processing parameters
SI                     512
MC2                     QF
SF            499.6799996 MHz
WDW           States-TPPI
SSB       0
LB        0 Hz
GB        0
```



Hemicrytophane *ML*-2 (125 MHz, acetone-d_6) HSQC

```
Current Data Parameters
NAME      13-2-3-2_29072011
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20110729
Time                 12.02
INSTRUM              spect
PROBHD   5 mm CPTXI 1H-
PULPROG          hsqcetgp
TD                   4096
SOLVENT           Acetone
NS                     64
DS                     16
SWH               7002.801 Hz
FIDRES            1.709668 Hz
AQ               0.2925044 sec
RG                 11585.2
DW                  71.400 usec
DE                  10.00 usec
TE                  305.1 K
CNST2         145.0000000
D0             0.00000300 sec
D1             1.50000000 sec
D4             0.00172414 sec
D11            0.03000000 sec
D13            0.00000400 sec
D16            0.00020000 sec
IN0            0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.80 usec
P2                  17.60 usec
P28       0 usec
PL1                  5.50 dB
PL1W          -1.#IND0000 W
SFO1          499.6830042 MHz

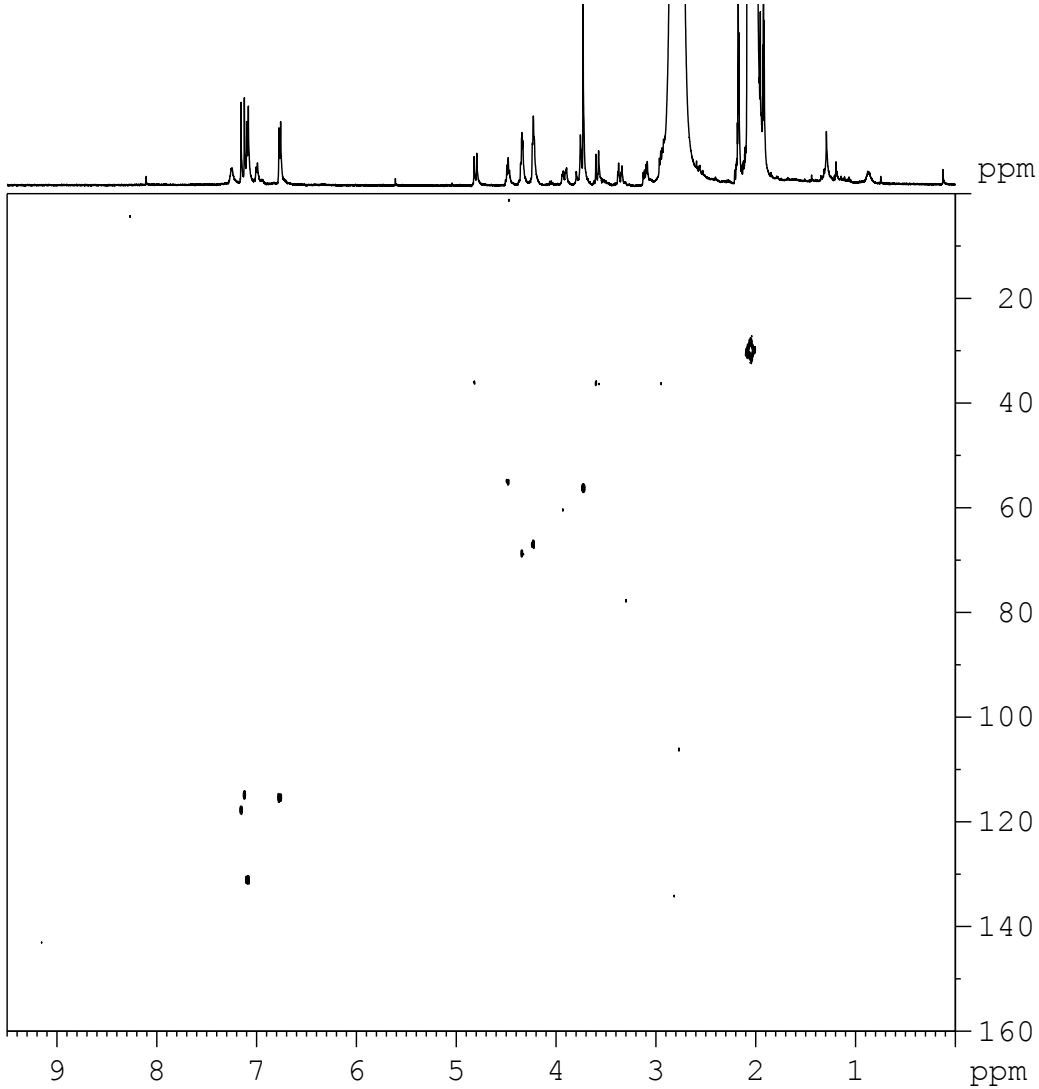
======== CHANNEL f2 ========
CPDPRG2               garp
NUC2                   13C
P3                  15.00 usec
P4                  30.00 usec
PCPD2               65.00 usec
PL2                 -0.30 dB
PL12                12.44 dB
PL2W          -1.#IND0000 W
PL12W         -1.#IND0000 W
SFO2          125.6572005 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPZ1                80.00 %
GPZ2                20.10 %
P16               1000.00 usec

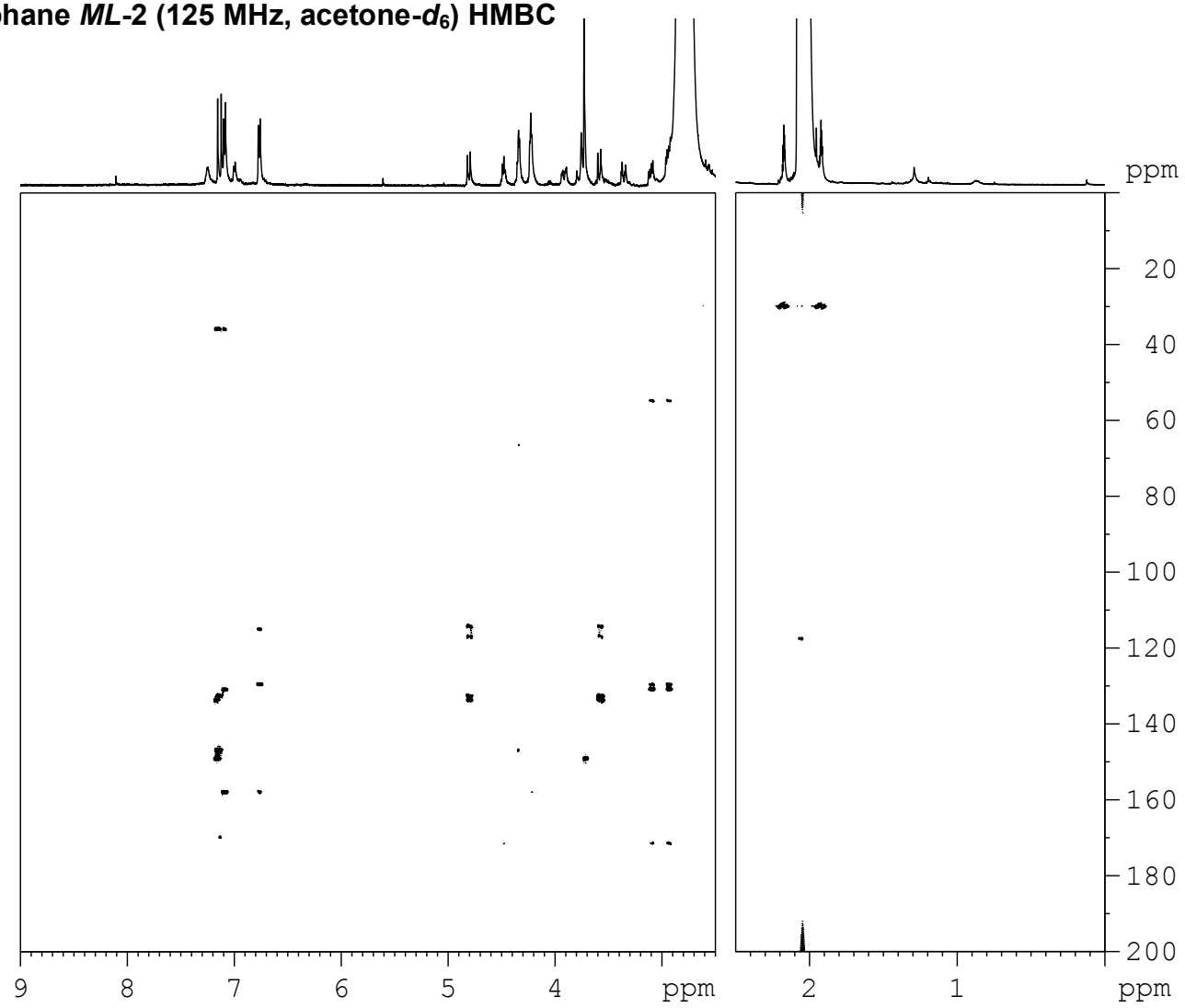
F1 - Acquisition parameters
TD                     512
SFO1             125.6572 MHz
FIDRES          49.084843 Hz
SW                200.000 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                    4096
SF           499.6800076 MHz
WDW                  QSINE
SSB       0
LB        0 Hz
GB        0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2        echo-antiecho
SF             125.6445383 MHz
WDW                  SINE
SSB       0
LB        0 Hz
GB        0
```



Hemicrytophane *ML*-2 (125 MHz, acetone-d_6) HMBC




```
Current Data Parameters
NAME      13-2-3-2_29072011
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_              20110730
Time                  4.34
INSTRUM              spect
PROBHD   5 mm CPTXI 1H-
PULPROG    hmbcgplpndqf
TD                   4096
SOLVENT           Acetone
NS                    128
DS                     16
SWH             7002.801 Hz
FIDRES          1.709668 Hz
AQ             0.2925044 sec
RG               11585.2
DW                71.400 usec
DE                10.00 usec
TE                305.1 K
CNST2         145.0000000
CNST13         10.0000000
D0             0.00000300 sec
D1             1.50000000 sec
D2             0.00344828 sec
D6             0.05000000 sec
D16            0.00020000 sec
IN0            0.00001810 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.80 usec
P2                17.60 usec
PL1                5.50 dB
PL1W         -1.#IND0000 W
SFO1         499.6834978 MHz

======== CHANNEL f2 ========
NUC2                 13C
P3                15.00 usec
PL2               -0.30 dB
PL2W         -1.#IND0000 W
SFO2         125.6572005 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPNAM3          SINE.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                    512
SFO1           125.6572 MHz
FIDRES         53.993328 Hz
SW               220.000 ppm
FnMODE                QF

F2 - Processing parameters
SI                   4096
SF           499.6800000 MHz
WDW                 QSINE
SSB                     2
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                   2048
MC2                    QF
SF           125.6446360 MHz
WDW                  ê•»└
SSB       0
LB        0 Hz
GB        0
```

Gaussian archive file for *PL*-2:*R*-9 complex

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