Flexible Total Synthesis of Biphenomycin B

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Supporting Information: 8 pages

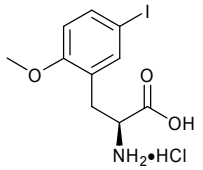
General Information

All reactions were carried out under an inert atmosphere of argon. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 400 or a Bruker DRX 400 (400.13 MHz and 100.61 MHz respectively; 500.13 MHz and 125.61 MHz respectively), with chemical shifts (δ) reported in ppm relative to the solvent residual signals and coupling constants reported in Hz. High resolution mass spectra (HR-MS) were measured on a Thermo Orbitrap coupled to a Thermo Accela HPLC system using electrospray ionization (ESI). Analytical HPLC-MS data were recorded on an Agilent HPLC (1100 series) with a C18 column (CC125/4 NUCLEODUR C18 Gravity 5μ) coupled to a Finnigan LCQ ESI spectrometer, detection: 280 nm; flow rate: 1.0 ml/min; time: 15 min; solvents A: 0.1% HCOOH in H_2O, B: 0.1% HCOOH in ACN, 1 min 10% B, in 10 min to 100% B. Analytical GC-MS data were recorded on a HP 6890 GC-MS system based on electron impact detection (EI) using an High Resolution Gas Chromatography Column (length: 25 m, I.D.: 0.2 mm, Film: 0.33 μm) and a heating profile of ambient to 100°C in 1 min, then in 5 min to 300°C, and constant at 300°C for 5 min. Preparative HPLC was performed on an Agilent HPLC (1100 series) and Waters HPLC 2767 using a 125/21 NUCLEODUR C18 Gravity 5 μ column(Macherey-Nagel).

For IR spectroscopy a Bruker Tensor 27 FT equipped with an ATR and the OPUS software was used. Chromatographic purification refers to flash chromatography using the indicated solvents and Merck silica gel 60. Thin layer chromatography (TLC) was performed using silica (Merck silica gel 60 F254 on aluminum foil). Compounds on TLC were visualized by UV detection or staining with $KMnO_4$ solution. Melting points were determined using a Büchi B-540 device and are uncorrected.

Anhydrous solvents were purchased from Fluka or Acros except dichloromethane, which was distilled from calcium hydride. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Reagents were purchased from Aldrich or Acros and used as supplied.

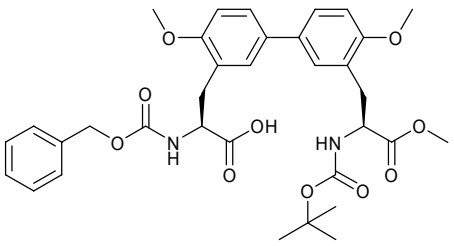
(*S*)-2-Amino-3-(5'-iodo-2'-methoxyphenyl)propanoic acid hydrochloride (6)



Colourless solid. ^{1}H-NMR (400 MHz, CD_3OD): δ = 3.07 (dd, *J* = 7.12 Hz, 3.8 Hz, 1H), 3.35 (dd, *J* = 6.54 Hz, 2,74 Hz, 1H), 3.89 (s, 3H), 4.25 (dd, , *J* = 7.64 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 2.32 Hz, 1H), 7.65 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H). ^{13}C-NMR (100 MHz, CD_3OD): δ = 32.9, 54.5, 56.7, 83.9, 115.0, 127.1, 140.1, 141.5, 159.6, 171.7. e.e. 96 %.[1] HPLC-ESI: R_t = 6.26 min, *M*/*Z* = 322.0, $[\alpha]_D^{20}$ = + 8.9 (*c* = 0.5, MeOH). IR: *v* = 806, 1252, 1485, 1736, 2901, 3601 cm^{-1}. Mp 213.4-215.1 °C. HRMS: for $C_{10}H_{13}NO_3I$ $[M+H]^+$ calcd. 321.9935; found 321.9927.

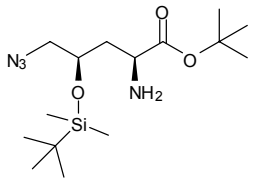
[1] Enantiomeric excess was determined by two independent derivatizations with (*R*)- and (*S*)-phenylethylamine isocyanate (Aldrich) followed by HPLC analysis.

Biaryl 9



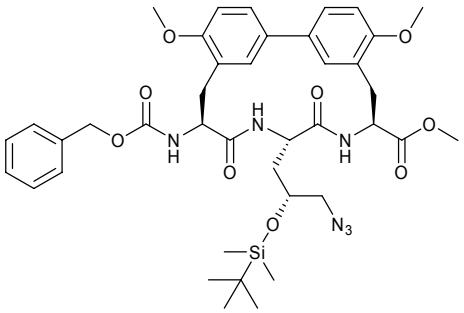
Colourless solid. ^{1}H-NMR (400 MHz, CD_3OD): δ = 1.34 (s, 9H), 2.87-3.39 (m, 4H), 3.67 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.48 (m, 2H), 4.96 (q, *J* = 9.84 Hz, 2H), 6.93-7.42 (m, 11H). ^{13}C-NMR (100 MHz, CD_3OD): δ = 25.8, 29.5, 56.8, 56.8, 68.2, 76.6, 112.6, 129.4, 129.5, 129.6, 130.2, 131.3, 138.9, 159.1, 168.9, 172.3. R_f = 0.52 (CH_2Cl_2/MeOH 9:1). HPLC-ESI: R_t = 10.19 min, *M*/*Z* = 636.7, $[\alpha]_D^{20}$ = + 20.1 (*c* = 1.2, MeOH). IR: *v* = 1024, 1244, 1493, 1710, 2939, 3338 cm^{-1}. Mp 113.6-115.9 °C. HRMS: for $C_{34}H_{40}N_2O_{10}Na$ [M+Na^+] calcd. 659.2575, found 659.2550.

(3*S*,5*R*)-3-Amino-6-azido-5-(*tert*butyl-dimethylsilyloxy)hexanoicacid *tert*butylester (14)



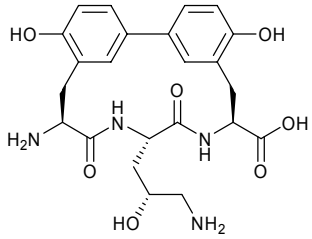
Colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 6H), 0.90 (m, 9H), 1.39-1.45 (m, 12H), 1.62 (s, 2H), 1.78 (m, 1H), 3.46 (q, *J* = 4.69 Hz, 1H), 3.62-3.77 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = -5.1, 18.5, 26.1, 28.3, 35.7, 42.3, 52.5, 60.1, 67.1, 81.6, 175.5. R_f = 0.42 (cyclohexane/EtOAc 2:1). GC-MS: R_t = 5.30 min, *M*/*Z* = 345. $[\alpha]_D^{20}$ = -73 (*c* = 1.0, $CHCl_3$). IR: *v* = 1158, 1254, 1741, 2121, 2859, 2931 cm^{-1}. HRMS: for $C_{15}H_{33}N_4O_3{}^{28}Si$ [M+H]$^+$ calcd. 345.2316, found 345.2316.

Cyclopeptide 17



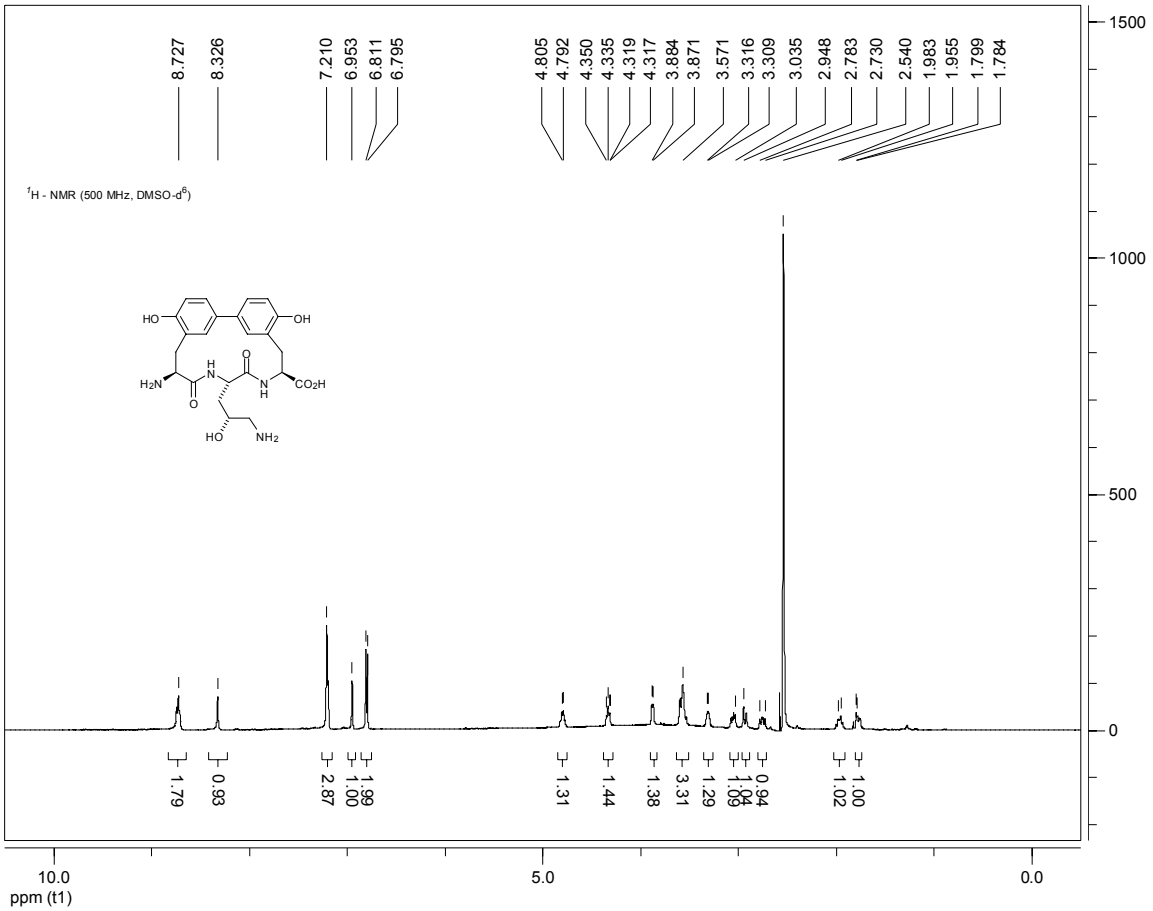
Colourless solid. ^{1}H-NMR (400 MHz, DMSO-d^{6}): δ = 0.11 (s, 6H), 0.91 (s, 9H), 1.27 (m, 2H), 1.65-1.72 (m, 2H), 2.81-2.88 (m, 2H), 3.55-3.66 (m, 2H), 3.73 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 4.51 (t, *J* = 5.96 Hz, 1H), 4.76-4.85 (m, 2H), 5.04-5.11 (q, *J* = 10.08 Hz, 2H), 6.47 (d, *J* = 7.24 Hz, 1H), 6.98-7.08 (m, 3H), 7.35-7.38 (m, 5H), 7.45-7.48 (m, 3H), 8.68 (d, *J* = 9.04 Hz, 1H), 9.19 (d, *J* = 8.4 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d^{6}): δ = -4.7, 18.7, 26.5, 34.3, 50.1, 51.8, 53.2, 55.0, 56.4, 61.1, 66.3, 67.1, 111.5, 122.4, 125.3, 127.0, 128.5, 128.6, 129.2, 130.5, 132.4, 132.6, 137.8, 156.5, 157.4, 170.8, 172.2, 172.7. R_f = 0.58 (CH_2Cl_2/MeOH 13:1). HPLC-ESI: R_t = 11.46 min, *M*/*Z* = 789.2. $[\alpha]_D^{20}$ = -0.74 (*c* = 0.8, DMSO). IR: ν = 837, 1026, 1244, 1495, 1643, 2121, 2857, 2929, 3266 cm^{-1}. Mp >215 °C (dec.). HRMS: for $C_{40}H_{53}N_6O_9{}^{28}Si$ $[M+H]^+$ calcd. 789.3638, found 789.3640.

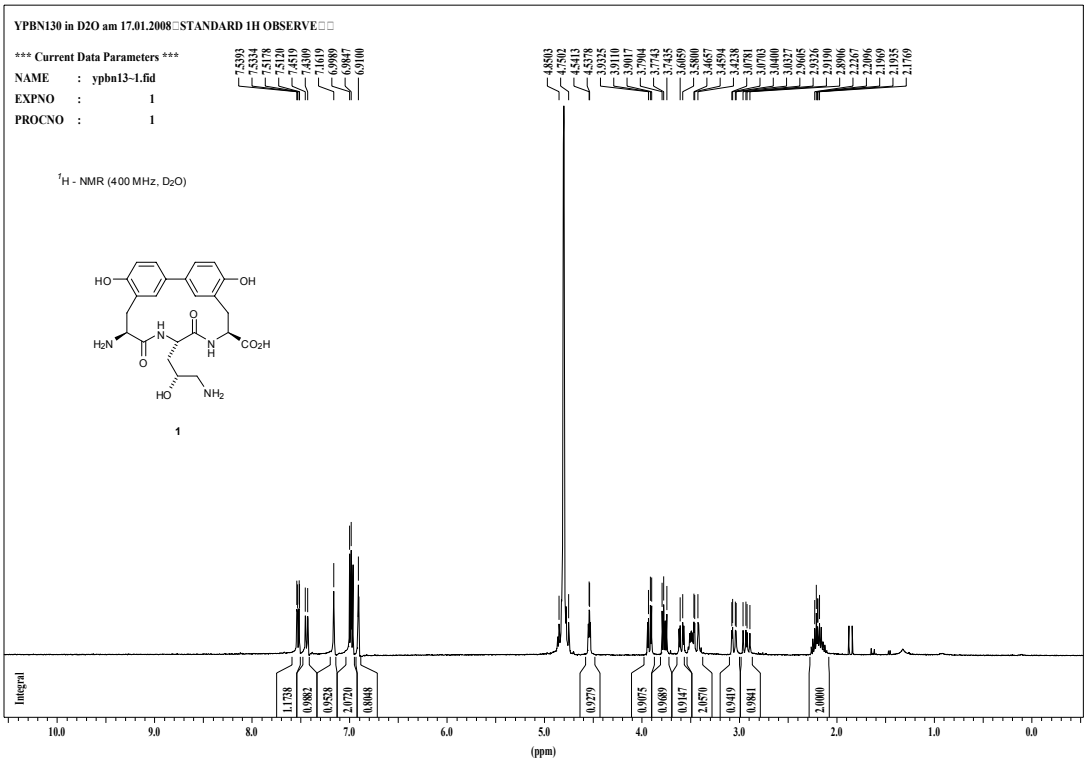
Biphenomycin B (1)



Colourless powder. ^{1}H-NMR (500 MHz, DMSO-d^{6}): δ = 1.78-1.79 (m, 1H), 1.95-1.98 (m, 1H), 2.73-2.78 (m, 1H), 2.94 (m, 1H), 3.03 (m, 1H), 3.31 (m, 1H), 3.57 (m, 3H), 3.88 (d, *J* = 6.5 Hz, 1H), 4.31-4.35 (m, 2H), 4.79-4.80 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 1H), 7.21 (s, 3H), 8.32 (s, 1H), 8.72 (s, 2H). ^{13}C-NMR (125 MHz, DMSO-d^{6}): δ = 29.5, 35.3, 51.3, 51.6, 54.5, 55.0, 63.2, 116.2, 116.4, 124.4, 125.0, 125.1, 127.2, 128.0, 128.7, 131.7, 132.0, 154.8, 155.3, 170.6, 172.3, 176.7. HPLC-ESI: R_t = 2.25 min, *M*/*Z* = 473.1. $[\alpha]_D^{20}$ = + 4.45 (*c* = 0.375, 1 M HCl). IR: *v* = 848, 1242, 1390, 1637, 2928, 3078, 3270 cm^{-1}. Mp >215 °C (dec.). HRMS: for $C_{23}H_{29}N_4O_7$ $[M+H]^+$ calcd. 473.2031, found: 473.2026.

Copies of Biphenomycin (1) NMR Spectra

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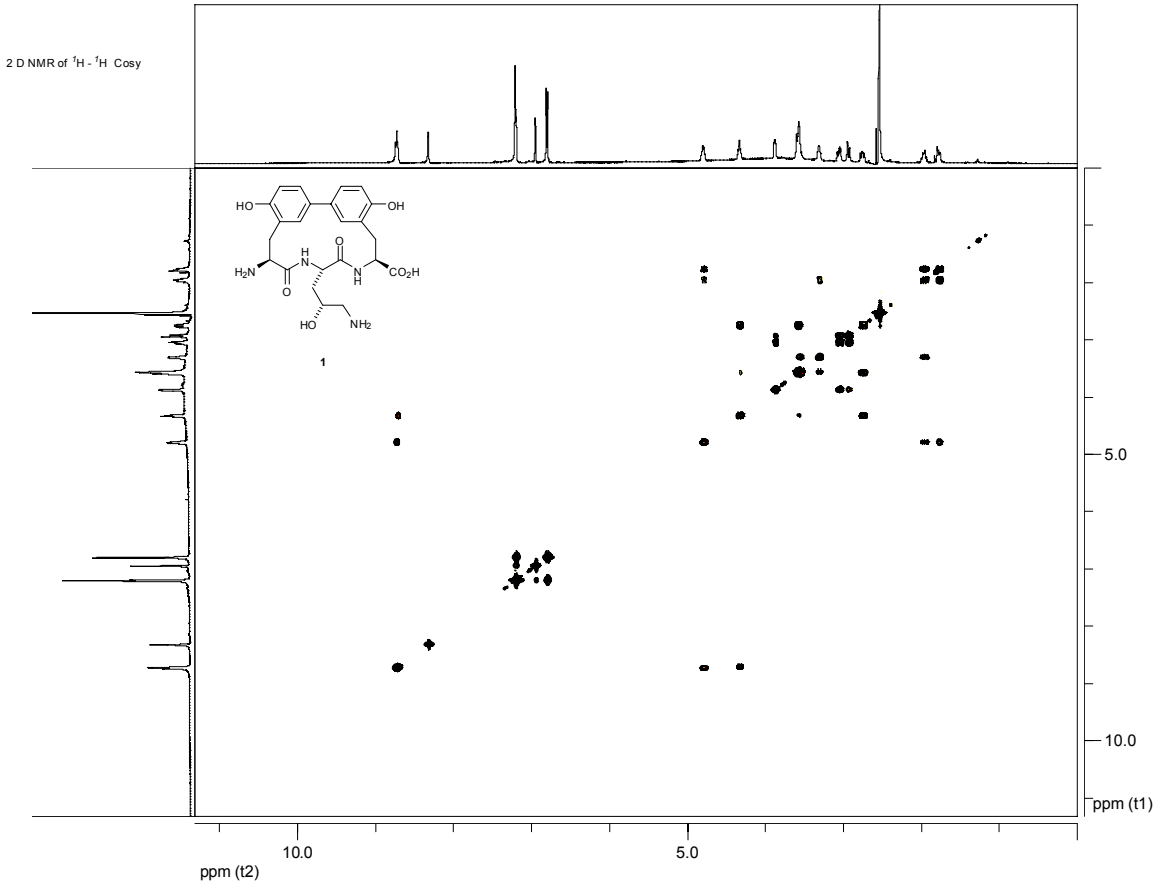
Integral
(ppm)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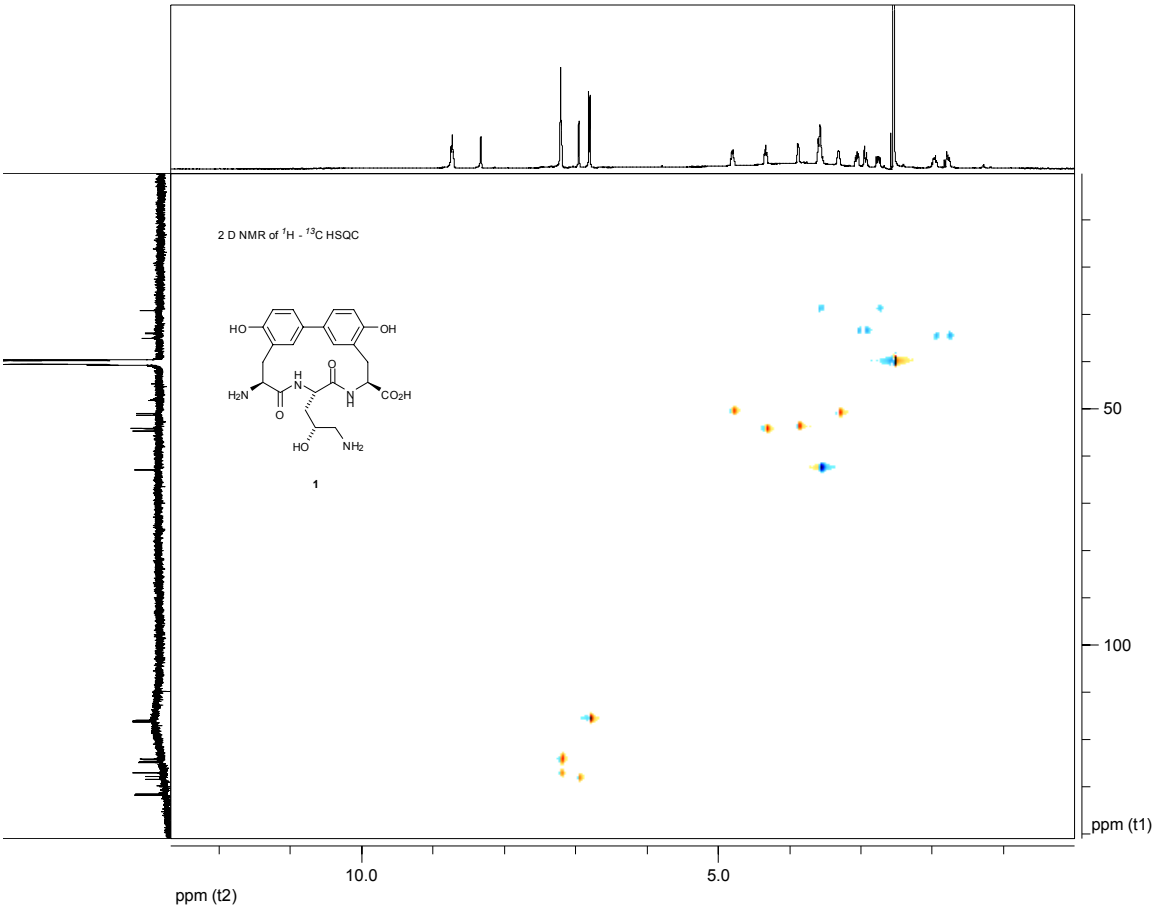
ppm (t1)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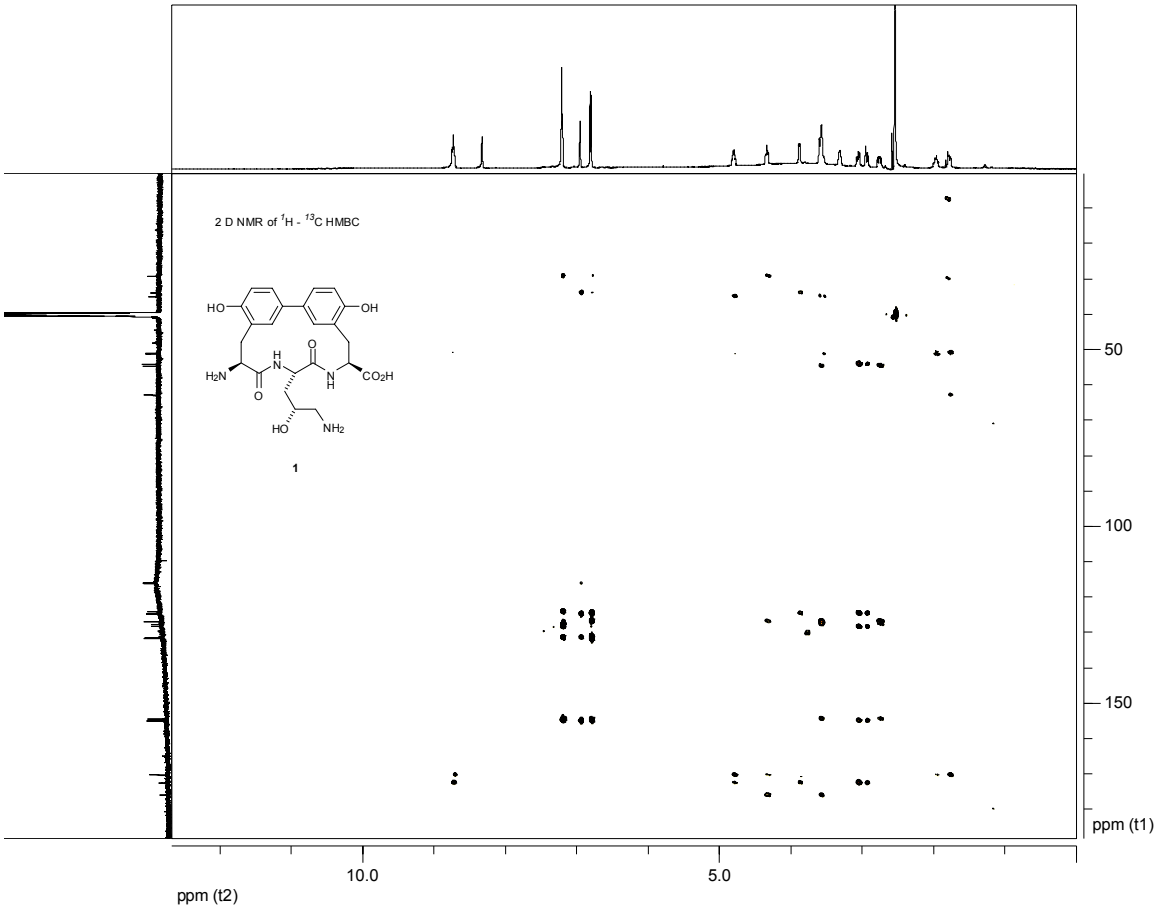
ppm (t2)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NH2
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100
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ppm (t1)
10.0
5.0
ppm (t2)