Supporting information

for

Selective Protection of Secondary Amines as the *N*-Phenyl Triazenes. Application to Aminoglycoside Antibiotics.

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General Information

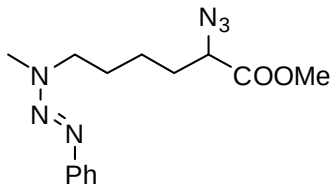
All reagents and solvents were purchased from commercial suppliers and were used without further purification unless otherwise specified. All organic extracts were dried over sodium sulfate and concentrated under vacuum. Chromatographic purifications were carried out over silica gel. Analytical thin-layer chromatography was performed with pre-coated glass backed plates (w/UV 254) and visualized by UV irradiation (254 nm) or by staining with 25% H_2SO_4 in EtOH or ceric ammonium molybdate solution. Specific rotations were obtained using a digital polarimeter in the solvent specified. Infrared spectra were recorded on a FT/IR instrument. High resolution mass spectra were recorded with an electrospray source coupled to a time-of-flight mass analyzer (Waters). ^{1}H, ^{13}C and 2D NMR spectra were recorded on 600 MHz and 400 MHz instruments.

General procedure A: An ice cooled solution of the amine (1 equiv) in a water/methanol mixture (3:7, 0.1 M) was treated with Na_2CO_3 (8 equiv), and then dropwise over 0.5 h with a solution of phenyldiazonium tetrafluoroborate (1.1 equiv) in water (0.1 M). After completion of the addition, Stick's reagent (imidazole-1-sulfonyl azide hydrochloride, 0.3 mmol per primary amine) and a catalytic amount of $CuSO_4$ were added. The reaction mixture was allowed to warm to rt and stirred overnight before it was diluted with ethyl acetate and washed with water and brine. The organic layer was dried and concentrated. The residue was purified by chromatography over silica gel.

General procedure B: The substrate (1 equiv) was dissolved in acetonitrile:H_2O (1:1, 0.1 M). K_2CO_3 (8 equiv) was added and the reaction mixture was cooled to 0 ^oC using an ice bath. A solution of phenyldiazonium tetrafluoroborate (1.1 equiv) in acetonitrile (0.1 M) was added using a syringe pump over 0.5 h. After completion of the addition, 0.22 mmol per amine of imidazole-1-sulfonyl azide hydrochloride and a catalytic amount of $CuSO_4$ were added. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried and concentrated. The residue was purified by chromatography over silica gel.

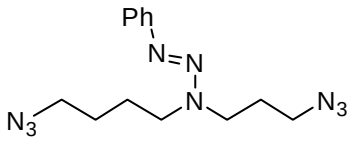
General procedure C: An ice cooled solution of the amine (1 equiv) in a water/methanol mixture (3:7, 0.1 M) was treated with Na_2CO_3 (8 equiv), and then dropwise over 0.5 h with a solution of phenyldiazonium tetrafluoroborate (1.1 equiv) in water (0.1 M). After completion of the addition, 0.24 mmol per amine of benzyl chloroformate was added. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried and concentrated. The residue was purified by chromatography over silica gel.

Methyl 2-azido-6-(1-methyl-3-phenyltriaz-2-en-1-yl)hexanoate (7).



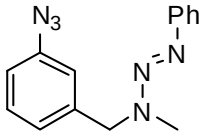
This compound was prepared according to the general procedure A using compound **1** (38 mg, 0.22 mmol) to afford the desired product **7** (38 mg, 58 %) as a yellow oil; *Rf* = 0.8 (40% EtOAc in hexanes); $[\alpha]_D^{25}$= -26.1 (*c* 0.025, MeOH); IR (film) (cm^{-1}): 2105, 1745, 1594 (w); ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.33 – 7.24 (m, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 4.00 (dd, *J* = 8.2, 5.3 Hz, 1H), 3.77 (t, *J* = 7.0 Hz, 2H), 3.71 (s, 3H), 3.19 (s, 3H), 1.91 – 1.81 (m, 1H), 1.79-1.66 (m, 3H), 1.47 – 1.36 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 171.2, 151.0, 128.3, 124.9, 120.0, 61.6, 51.6, 30.5, 27.2, 22.4. ESI-HRMS: *m/z* calcd. for $C_{14}H_{20}N_6NaO_2$ $[M+Na]^+$ 327.1545; found, 327.1561.

3-(4-Azidobutyl)-3-(3-azidopropyl)-1-phenyltriaz-1-ene (8).



This compound was prepared according to the general procedure A using compound **2** (50 mg, 0.20 mmol) to afford the desired product **8** (36 mg, 61 %) as a yellow oil; *Rf* = 0.5 (20% EtOAc in hexanes); IR (film) (cm^{-1}): 2093, 1593 (w); ^{1}H NMR (600 MHz, CD_3OD) δ 7.35 (d, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.9 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.77 (t, *J* = 7.0 Hz, 2H), 3.73 (t, *J* = 7.2 Hz, 2H), 3.35 (t, *J* = 6.6 Hz, 2H), 3.32 (t, *J* = 6.8 Hz, 2H), 1.93 (p, *J* = 6.7 Hz, 2H), 1.74 (p, *J* = 7.3 Hz, 2H), 1.60 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (151 MHz, CD_3OD) δ 150.8, 128.3, 125.0, 120.1, 50.7, 48.7, 27.7, 25.9, 23.8. ESI-HRMS: *m/z* calcd. for $C_{13}H_{20}N_9$ $[M+H]^+$, 302.1842; found, 302.1845.

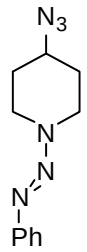
3-(3-Azidobenzyl)-3-methyl-1-phenyltriaz-1-ene (9).



This compound was prepared according to the general procedure A using compound **3** (100 mg, 0.74 mmol) to afford the desired product **9** (135 mg, 69 %) as a yellow oil; *Rf*= 0.7 (20% EtOAc in hexanes); IR (film) (cm^{-1}): 2109, 1590 (w); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.42-7.31 (m, 3H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.05 – 6.92 (m, 2H), 4.97 (s, 2H), 3.21 (br s, 3H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 150.6, 140.5, 139.0, 130.1,

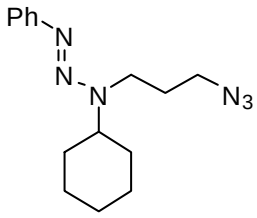
128.9, 125.8, 124.4, 120.8, 118.5, 118.3, 59.0, 34.9. ESI-HRMS: *m/z* calcd. for $C_{14}H_{15}N_6$ $[M+H]^+$, 267.1358; found, 267.1363.

4-Azido-1-(phenyldiazenyl)piperidine (10).



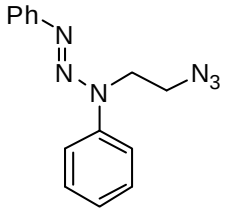
This compound was prepared according to the general procedure A using compound **4** (100 mg, 1 mmol) to afford the desired product **10** (160 mg, 70 %) as a yellow oil; *Rf*= 0.65 (20% EtOAc in hexanes); IR (film) (cm^{-1}): 2092, 1593 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 4.16 (ddd, *J* = 13.6, 6.4, 4.3 Hz, 2H), 3.74 (tt, *J* = 8.3, 3.7 Hz, 1H), 3.56 (ddd, *J* = 13.6, 8.8, 3.9 Hz, 2H), 2.06 – 1.96 (m, 2H), 1.77 (dtd, *J* = 13.1, 8.7, 4.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 128.9, 126.3, 120.7, 57.3, 44.2, 29.9. ESI-HRMS: *m/z* calcd. for $C_{11}H_{15}N_6$ $[M+H]^+$, 231.1358; found, 231.1367.

3-(3-Azidopropyl)-3-cyclohexyl-1-phenyltriaz-1-ene (11).



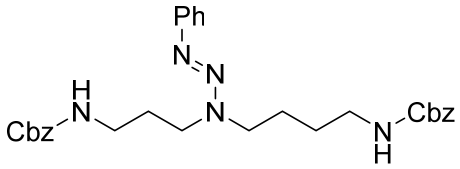
This compound was prepared according to the general procedure A using compound **5** (100 mg, 0.64 mmol) to afford the desired product **11** (110 mg, 60 %) as a yellow oil; *Rf*= 0.75 (20% EtOAc in hexanes); IR (film) (cm^{-1}): 2094, 1594 (w); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.43 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 3.77 – 3.72 (m, 2H), 3.66 (br s, 1H), 3.37 (t, *J* = 6.7 Hz, 2H), 2.05-1.94 (m, 4H), 1.90 (d, *J* = 13.6 Hz, 2H), 1.76 – 1.61 (m, 3H), 1.42 (qt, *J* = 13.1, 3.3 Hz, 2H), 1.24 (qt, *J* = 13.0, 3.7 Hz, 1H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 151.2, 128.7, 125.0, 120.4, 64.4, 49.6, 43.6, 32.4, 26.6, 25.8, 25.5. ESI-HRMS: *m/z* calcd. for $C_{15}H_{23}N_6$ $[M+H]^+$, 287.1984; found, 287.1979.

3-(2-Azidoethyl)-1,3-diphenyltriaz-1-ene (12).



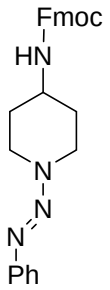
This compound was prepared according to the general procedure A using compound **6** (100 mg, 0.74 mmol) to afford the desired product **12** (81 mg, 41 %) as a red oil; *Rf*= 0.7 (20% EtOAc in hexanes); IR (film) (cm^{-1}): 2098, 1601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.47-7.37 (m, 4H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 4.46 (t, *J* = 6.4 Hz, 2H), 3.69 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 144.6, 129.3, 129.0, 127.2, 123.9, 121.5, 117.4, 47.4, 44.7. ESI-HRMS: *m/z* calcd. for $C_{14}H_{15}N_6$ $[M+H]^+$, 267.1358; found, 267.1350.

Benzyl *N*-(4-(1-(3-(benzyloxycarbonylamino)propyl)-3-phenyltriaz-2-en-1-yl)butyl) carbamate (13).



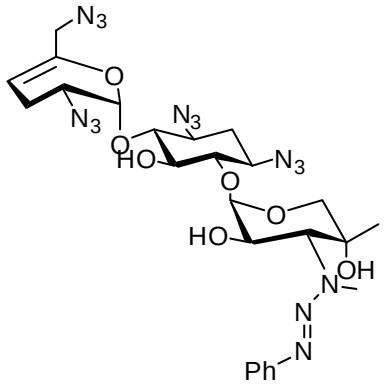
This compound was prepared according to the general procedure C using compound **2** (50 mg, 0.2 mmol) to afford the desired product **13** (55 mg, 54 %) as a yellow oil; *Rf*= 0.5 (60% EtOAc in hexanes); IR (film) (cm^{-1}): 1700, 1591 (w); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.33 (m, 12H), 7.14 (t, *J* = 7.3 Hz, 1H), 5.09 (m, 4H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.74 – 3.68 (m, 2H), 3.25 – 3.20 (m, 2H), 3.19 (br s, 2H), 1.84 (br s, 2H), 1.72 (br s, 2H), 1.59 – 1.47 (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 156.3, 150.7, 137.1, 137.0, 128.8, 127.92, 127.88, 127.85, 127.8, 125.3, 120.3, 66.3, 40.5, 38.4, 27.9, 27.2, 24.7. ESI-HRMS: *m/z* calcd. for $C_{29}H_{36}N_5O_4$ $[M+H]^+$, 518.2767; found, 518.2770.

4-Fluorenylmethyloxycarbonylamino-1-(phenyldiazenyl)piperidine (14)



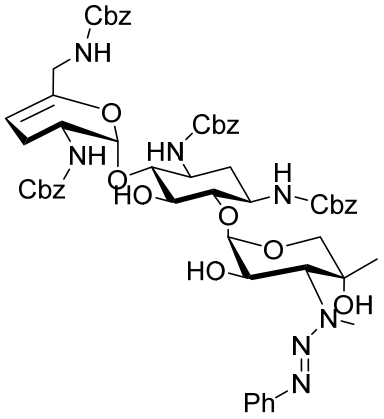
An ice cooled solution of **4** (100 mg, 1 mmol) in a water/methanol mixture (3:7, 4 mL) was treated with Na_2CO_3 (5 mmol), and then dropwise over 0.5 h with a solution of phenyldiazonium tetrafluoroborate (1.1 mmol) in water (4 mL). After completion of the addition, Fmoc-Cl (1.1 mmol) was added. The reaction mixture was allowed to warm to rt and stirred 7 h before it was diluted with brine and extracted with DCM thrice. The organic layer was dried and concentrated. The residue was purified by column chromatography (15% EtOAc in hexanes) over silica gel to give the desired product **14** (329 mg, 77 %) as a yellow solid. *Rf*= 0.25 (20% EtOAc in hexanes); IR (film) (cm^{-1}): 1687, 1538; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.47 – 7.30 (m, 8H), 7.19 (t, *J* = 7.3 Hz, 1H), 4.71 (br d, *J* = 6.1 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 4H), 4.22 (t, *J* = 6.3 Hz, 1H), 3.90 – 3.75 (br s, 1H), 3.32 – 3.14 (m, 2H), 2.16 – 2.04 (m, 2H), 1.59 – 1.34 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 150.3, 143.9, 141.4, 128.9, 127.7, 127.1, 126.2, 124.9, 120.7, 120.0, 66.5, 48.3, 47.3, 45.7, 31.5. ESI-HRMS: *m/z* calcd. for $C_{26}H_{26}N_4NaO_2$ $[M+H]^+$, 449.1953; found, 449.1939.

1,3,2’,6’-Tetra-deamino-1,3,2',6'-tetraazido-3''-*N*-(phenylazo)sisomicin (16).



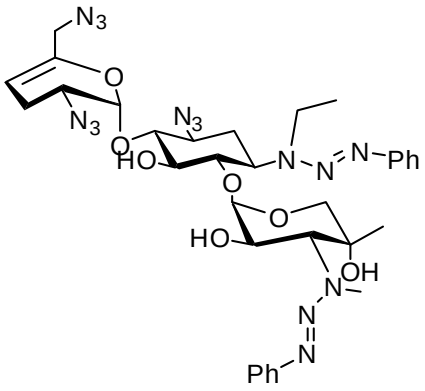
This compound was prepared according to the general procedure A using compound **15** (100 mg, 0.14 mmol) to afford the desired product **16** (83 mg, 88 %) as a yellow solid; *Rf*= 0.4 (5% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$= +143.4 (*c* 0.037, MeOH); IR (film) (cm^{-1}):3442, 2102, 1594 (w); ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 5.89 (d, *J* = 2.3 Hz, 1H), 5.48 (d, *J* = 4.2 Hz, 1H), 4.98 (dd, *J* = 5.2, 2.2 Hz, 1H), 4.40 (dd, *J* = 11.4, 3.8 Hz, 1H), 4.30 (d, *J* = 12.1, 1H), 4.29 (d, *J* = 11.2, 1H) 3.83 – 3.60 (m, 6H), 3.43 (m, 3H), 3.34 (s, 3H), 2.45 (dd, *J* = 15.5, 11.5 Hz, 1H), 2.28 (m, 2H), 1.42 (q, *J* = 12.6 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 151.1, 145.7, 128.4, 125.0, 120.3, 98.9, 98.0, 97.0, 80.1, 79.7, 74.6, 73.2, 68.8, 68.5, 65.3, 60.7, 60.2, 55.1, 54.6, 51.9, 32.6, 21.1, 20.8. ESI-HRMS: *m/z* calcd. for $C_{25}H_{34}N_{15}O_7$ $[M+H]^+$, 656.2766; found, 656.2747.

1,3,2',6'-Tetra-*N*-(benzyloxycarbonyl)-3''-*N*-(phenylazo)sisomicin (17).



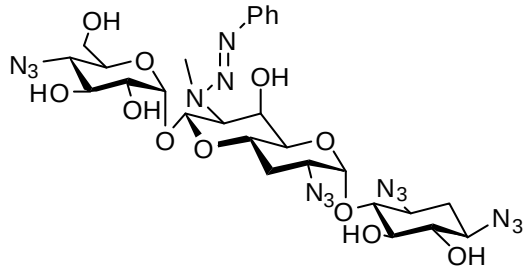
This compound was prepared according to the general procedure C using compound **15** (100 mg, 0.14 mmol) to afford the desired product **17** (125 mg, 79 %) as a yellow solid; *Rf*= 0.33 (5% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$= +9.8 (*c* 0.057, CH_2Cl_2); IR (film) (cm^{-1}): 3416, 1702, 1592 (w); ^{1}H NMR (600 MHz, CD_2Cl_2 + CD_3OD) δ 7.42 – 7.22 (m, 24H), 7.16 (t, *J* = 7.0 Hz, 1H), 5.41 (br s, 1H), 5.18 – 4.94 (m, 9H), 4.56 (br s, 1H), 4.37 – 4.30 (m, 1H), 3.99 – 3.88 (m, 2H), 3.86 – 3.79 (m, 1H), 3.72 – 3.59 (m, 3H), 3.59 – 3.45 (m, 3H), 3.43 – 3.28 (m, 5H), 2.31 (br s, 1H), 2.11 (s, 1H), 2.00 (br s, 1H), 1.30 (br s, 1H), 1.08 (br s, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2 + CD_3OD) δ 156.8, 156.2, 150.7, 146.2, 136.7, 136.5, 128.9, 128.5, 128.4, 128.3, 128.03, 127.95, 127.9, 127.7, 125.7, 120.5, 100.8, 97.3, 96.3, 85.6, 79.7, 75.8, 73.1, 69.1, 68.9, 67.3, 66.7, 66.5, 50.3, 49.6, 47.3, 42.5, 36.4, 33.8, 22.7, 22.2. ESI-HRMS: *m/z* calcd. for $C_{57}H_{65}N_7NaO_{15}$ $[M+Na]^+$ 1110.4436; found, 1110.4463.

3,2',6-Tri-deamino-3,2',6''-triazido-1,3''–di-*N*-(phenylazo)netilmicin (19).



This compound was prepared according to the general procedure A using compound **18** (100 mg, 0.14 mmol) to afford the desired product **19** (37 mg, 35 %) as a yellow solid; *Rf*= 0.5 (50% EtOAc in hexanes); $[\alpha]_D^{25}$= +33.0 (*c* 0.003, CH_2Cl_2); IR (film) (cm^{-1}): 3441, 2104, 1594 (w); ^1H NMR (600 MHz, CD_2Cl_2) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.28 (m, 6H), 7.16 (m, 2H), 5.93 (d, *J* = 2.5 Hz, 1H), 5.08 (d, *J* = 3.9 Hz, 1H), 4.99 (dd, *J* = 5.6, 2.4 Hz, 1H), 4.66 (s, 1H), 4.26 (td, *J* = 10.9, 3.8 Hz, 1H), 3.98 – 3.85 (m, 4H), 3.82 (t, *J* = 9.4 Hz, 1H), 3.78 (d, *J* = 13.9 Hz, 1H), 3.71 (d, *J* = 14.7 Hz, 1H), 3.67 – 3.55 (m, 3H), 3.52 (ddd, *J* = 12.4, 9.7, 4.5 Hz, 1H), 3.46 (ddd, *J* = 11.2, 6.2, 2.5 Hz, 1H), 3.09 (s, 3H), 2.54 – 2.46 (m, 1H), 2.37 – 2.27 (m, 2H), 1.82 (q, *J* = 12.8 Hz, 1H), 1.26 (t, *J* = 7.4 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 150.3, 145.5, 128.8, 126.1, 125.8, 120.6, 120.5, 101.0, 98.3, 96.9, 84.5, 79.9, 76.5, 73.3, 69.2, 67.7, 60.5, 54.9, 52.4, 42.4, 37.0, 32.8, 22.5, 21.3, 12.5. ESI-HRMS: *m/z* calcd. for $C_{33}H_{43}N_{15}NaO_7$ $[M+Na]^+$, 784.3368; found, 784.3348.

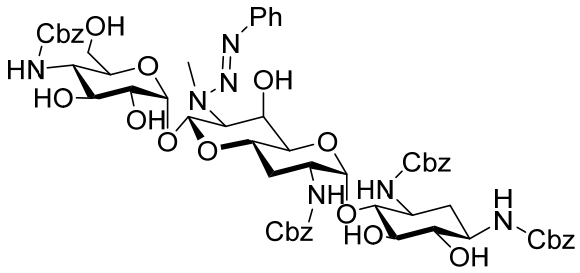
1,3,2',4''-Tetra-deamino-1,3,2',4''-tetraazido-7'-*N*-(phenylazo)apramycin (21).



This compound was prepared according to the general procedure B using compound **20** (free base, 100 mg, 0.19 mmol) to afford the desired product **21** (83 mg, 60 %) as a buff solid; *Rf*= 0.5 (40% EtOAc in hexanes); $[\alpha]_D^{25}$= +52.3 (*c* 0.007, MeOH); IR (film) (cm^{-1}): 3410, 2105, 1595

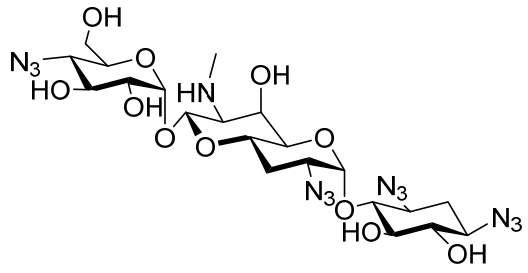
(w); ^{1}H NMR (600 MHz, CD_3OD) δ 7.35 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 5.60 (d, *J* = 3.2 Hz, 1H), 5.53 (d, *J* = 8.4 Hz, 1H), 5.26 (d, *J* = 3.7 Hz, 1H), 4.35 (s, 1H), 4.03 – 3.98 (m, 1H), 3.95 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.92 (t, *J* = 6.3 Hz, 1H), 3.56 (t, *J* = 9.6 Hz, 1H), 3.53 – 3.46 (m, 3H), 3.45 – 3.36 (m, 3H), 3.33 (s, 1H), 3.32 – 3.30 (m, 4H), 3.29 – 3.19 (m, 4H), 3.19 – 3.10 (m, 2H), 2.28 – 2.19 (m, 2H), 2.08 (q, *J* = 11.3 Hz, 1H), 1.47 – 1.36 (m, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 150.8, 128.4, 125.3, 120.6, 97.7, 95.3, 93.9, 79.4, 76.6, 76.5, 72.0, 71.4, 71.0, 70.1, 68.8, 67.8, 66.5, 61.2, 60.3, 60.1, 59.7, 56.4, 35.2, 31.8, 28.0. ESI-HRMS: *m/z* calcd. for $C_{27}H_{37}N_{15}NaO_{11}$ $[M+Na]^+$, 770.2695; found, 770.2660.

1,3,2',4''-Tetra-*N*-(benzyloxycarbonyl)-7'-*N*-(phenylazo)apramycin (22).



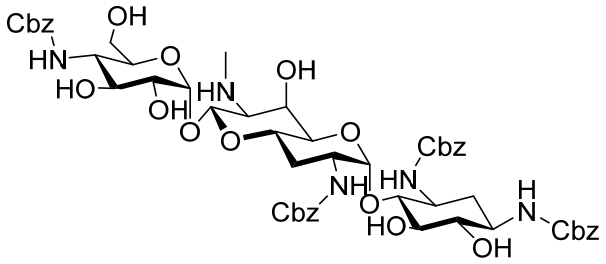
This compound was prepared according to the general procedure C using compound **20** (free base, 100 mg, 0.19 mmol) to afford the desired product **22** (162 mg, 74 %) as a buff solid; *Rf*= 0.6 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$= +19.8 (*c* 0.026, MeOH); IR (film) (cm^{-1}): 3396, 1691, 1532 (w); ^{1}H NMR (600 MHz, CD_3OD) δ 7.35 – 7.16 (m, 24H), 7.04 (t, *J* = 7.3 Hz, 1H), 5.53 (d, *J* = 8.4 Hz, 1H), 5.33 – 5.25 (m, 3H), 5.09 – 5.02 (m, 5H), 4.97 (d, *J* = 12.5 Hz, 1H), 4.87 (d, *J* = 12.9 Hz, 1H), 4.39 (s, 1H), 3.97 (d, *J* = 7.7 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.80 – 3.70 (m, 2H), 3.66 – 3.37 (m, 9H), 3.35 – 3.30 (m, 1H), 3.27 – 3.13 (m, 4H), 2.09 – 1.96 (m, 2H), 1.82 - 1.71 (m, 1H), 1.50 – 1.39 (m, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 157.7, 157.2, 156.9, 156.7, 150.6, 136.8, 128.5, 128.1, 128.0, 127.6, 127.5, 127.4, 125.3, 120.5, 98.2, 95.5, 93.9, 81.4, 77.1, 75.1, 72.2, 72.0, 70.4, 70.2, 69.3, 67.5, 66.5, 66.3, 66.2, 66.1, 60.8, 52.8, 51.4, 50.3, 49.9, 35.0, 34.0, 30.0. ESI-HRMS: *m/z* calcd. for $C_{59}H_{69}N_7NaO_{19}$ $[M+Na]^+$, 1202.4546; found, 1202.4500.

1,3,2’,4’’-Tetra-deamino-1,3,2',4''-tetraazidoapramycin (23).



Compound **21** (10 mg, 0.015 mmol)) was dissolved in a CH_2Cl_2/ethanol mixture (1:1, 0.3 mL) and cooled in an ice bath before trifluoroacteic acid (0.05 mL) was added. The reaction mixture was allowed to warm to rt and was stirred for 0.5 h. After completion the solution was concentrated, toluene (1 mL) was added and the solution concentrated again. The crude product was purified using column chromatography (10% methanol/CH_2Cl_2) to afford **23** (8.5 mg, 98 %) as a buff solid with spectral data identical to the literature.[1]

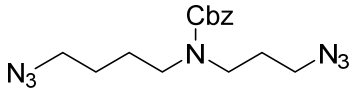
1,3,2',4''-Tetra-*N*-(benzyloxycarbonyl)apramycin (24).



Compound **22** (40 mg, 0.034 mmol)) was dissolved in a CH_2Cl_2/ethanol mixture (1:1, 0.5 mL) and cooled in an ice bath before trifluoroacteic acid (0.1 mL) was added. The reaction mixture was allowed to warm to rt and was stirred for 0.5 h. After completion the solution was concentrated, toluene (1 mL) was added and the solution concentrated again. The crude product was purified using column chromatography (10% methanol/CH_2Cl_2) to afford **24** (35 mg, 96 %) as a buff solid; *Rf*= 0.2 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$= +12.5 (*c* 0.002, MeOH); ^{13}C NMR (101 MHz, CD_3OD) δ 157.3, 156.9, 156.7, 136.8, 128.3, 128.1, 128.1, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3, 97.6, 94.3, 92.1, 80.4, 77.2, 75.1, 71.7, 69.6, 69.1, 66.8, 66.4, 66.3, 66.1, 63.0, 61.5, 60.7, 53.7, 51.5, 50.2, 49.7, 33.9, 29.7, 29.5, 29.3. ESI-HRMS: *m/z* calcd. for $C_{53}H_{66}N_5O_{19}$ $[M+H]^+$, 1076.4352; found, 1076.4324. ^{1}H-NMR spectral data are not listed for

this compound owing to complications owing to the presence of multiple rotamers arising from the presence of the four Cbz groups. See the spectrum on page S-55.

Benzyl (4-azidobutyl)(3-azidopropyl)carbamate (25)

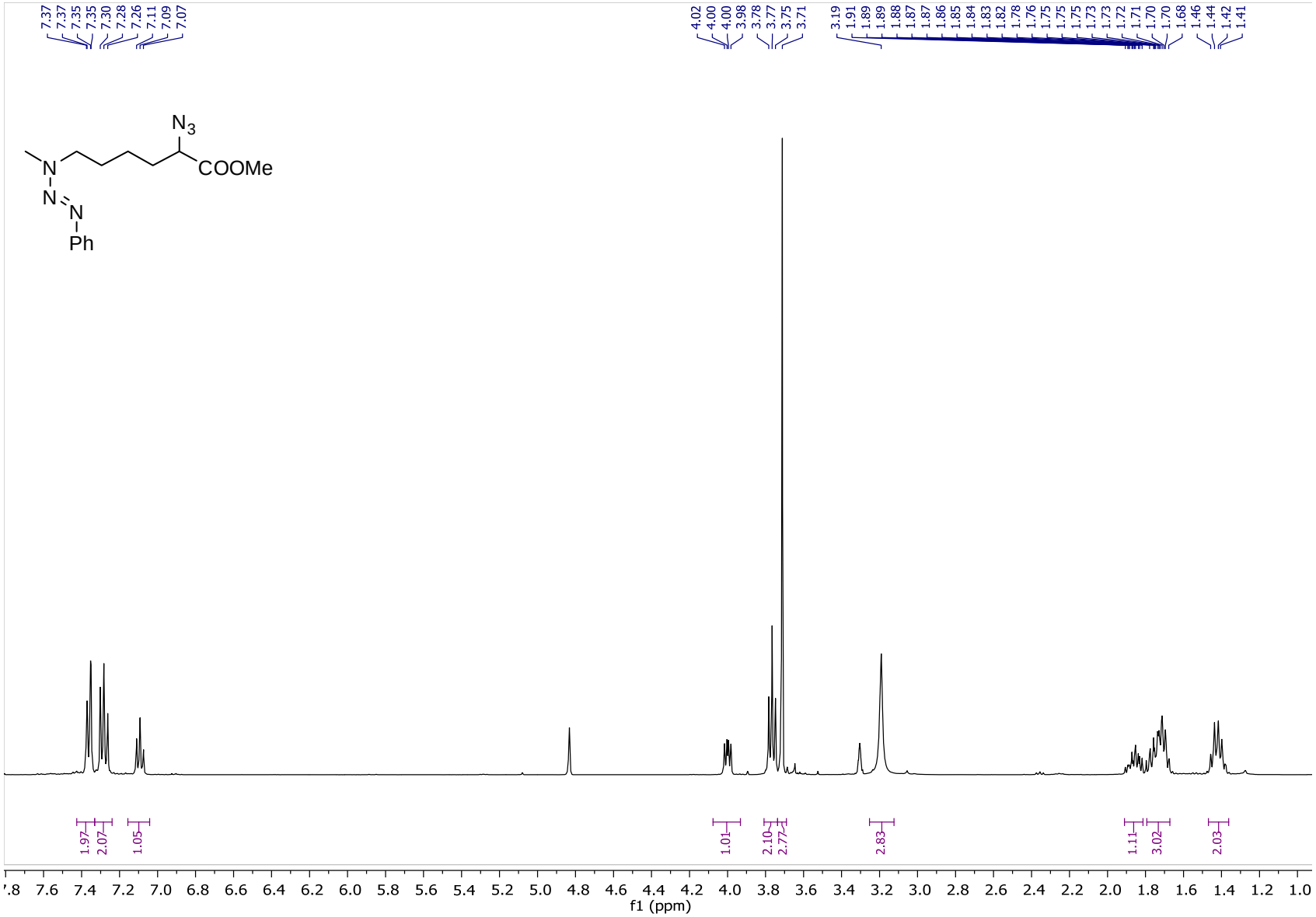


A solution of **2** (100 mg, 0.39 mmol) in a water/methanol mixture (1:1, 4 mL) was treated with Na_2CO_3 (3.9 mmol), imidazole-1-sulfonyl azide hydrochloride (3 equiv) and a catalytic amount of $CuSO_4$. The mixture was stirred for 3 h, after which 5 equiv of benzyl chloroformate was added. The reaction mixture was stirred for another hour before it was diluted with brine and extracted with DCM thrice. The organic layer was dried using Na_2SO_4 and concentrated. The residue was purified by column chromatography to give the desired product **25** (77 mg, 59 %) as a colorless oil; *Rf*= 0.4 (25% EtOAc in hexanes); ^{1}H NMR (600 MHz, CD_3OD) δ 7.43 – 7.20 (m, 5H), 5.11 (s, 2H), 3.40 – 3.17 (m, 11H), 1.87 – 1.71 (m, 2H), 1.66 – 1.57 (m, 2H), 1.57 – 1.45 (m, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 156.5, 136.3, 128.1, 127.7, 127.6, 66.9, 50.7, 48.63, 48.59, 46.7, 46.4, 44.7, 44.2, 27.6, 27.0, 25.7, 25.4, 24.8. (151 MHz, CD_3OD) ESI-HRMS: *m/z* calcd. for $C_{15}H_{21}N_7NaO_2$ $[M+Na]^+$, 354.1654; found, 154.1666

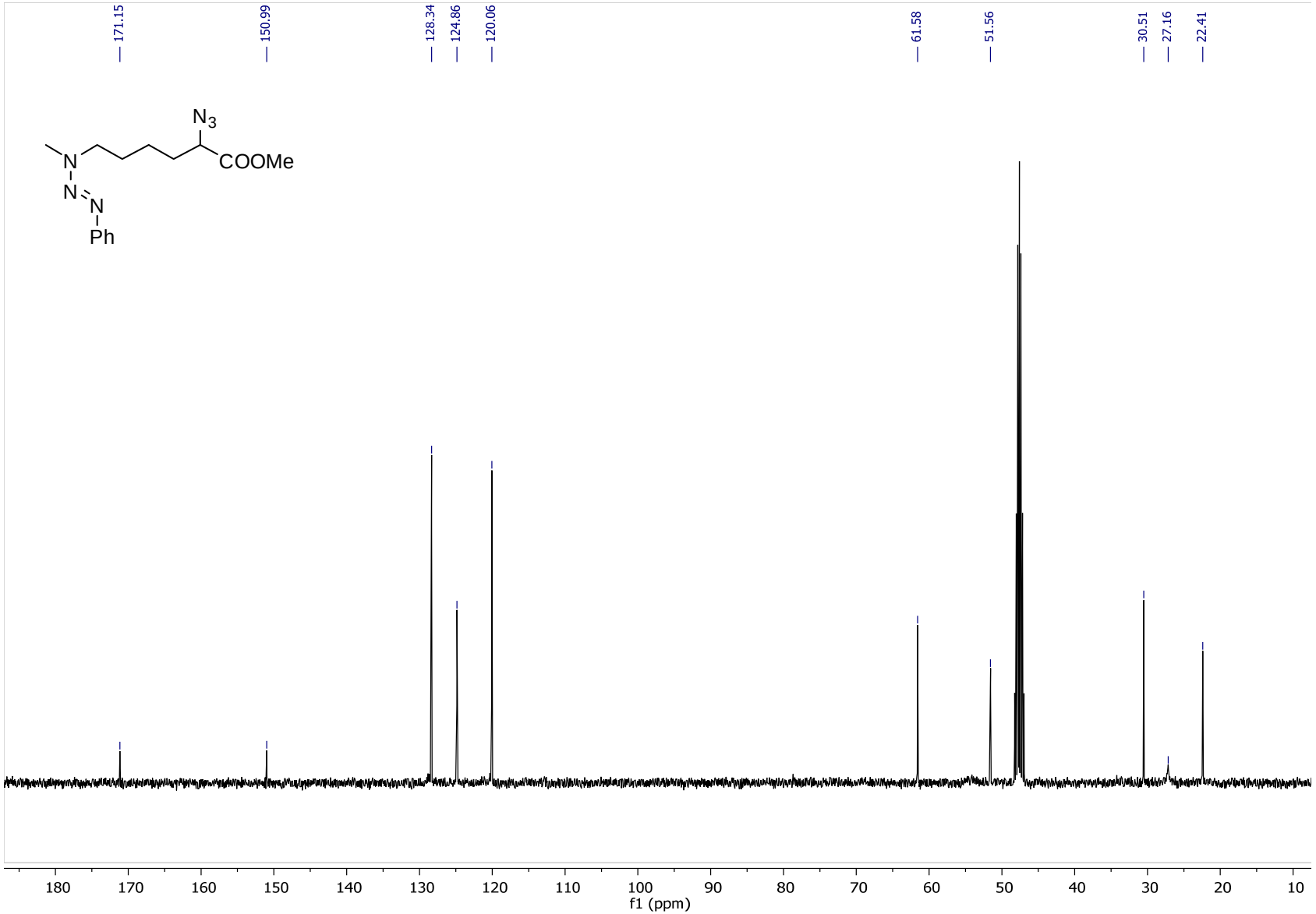
References

1. Mandhapati, A. R.; Shcherbakov, D.; Duscha, S.; Vasella, A.; Böttger, E. C.; Crich, D., *ChemMedChem* **2014,** *9*, 2074-2083.

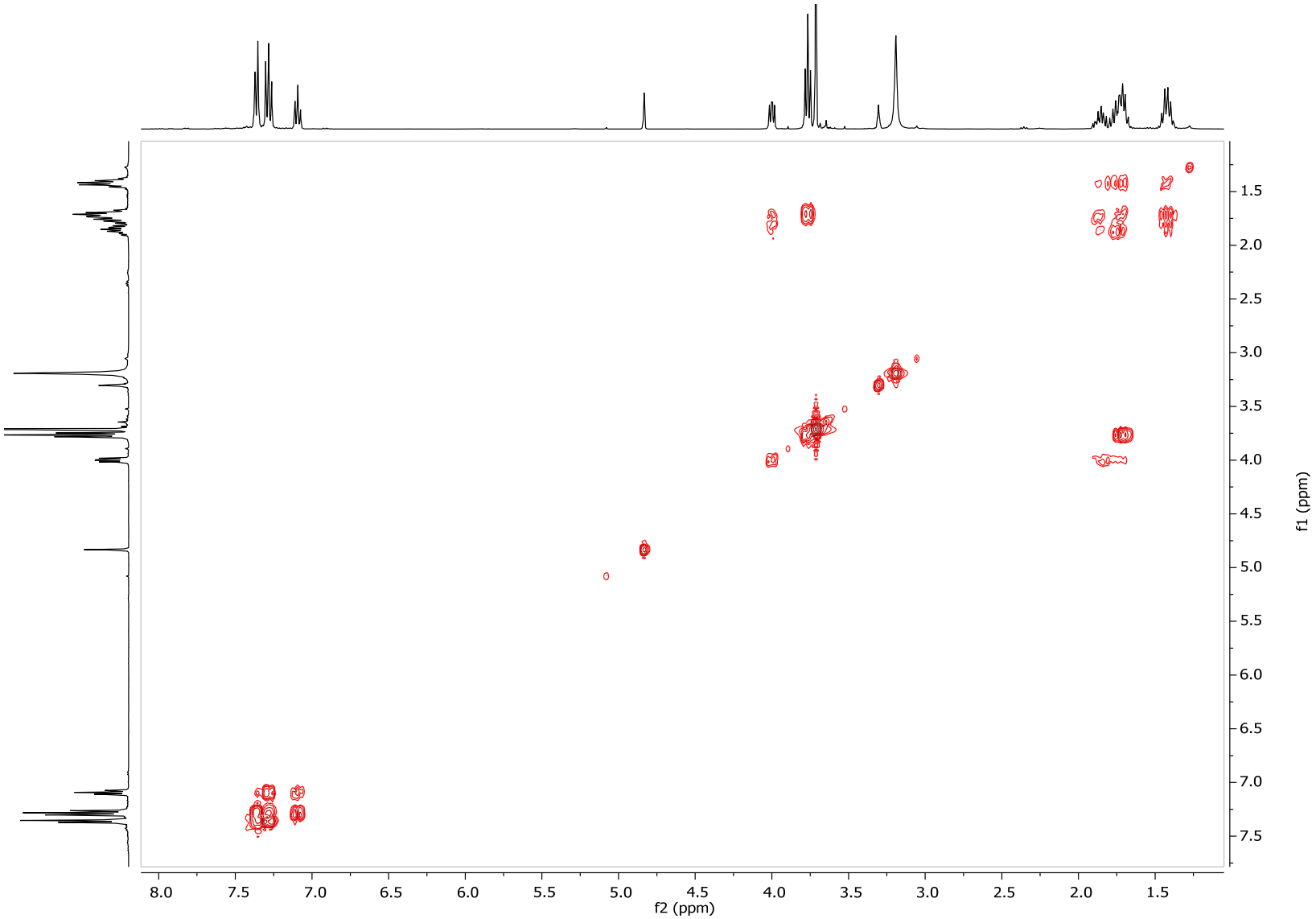
Methyl 2-azido-6-(1-methyl-3-phenyltriaz-2-en-1-yl)hexanoate (7) ^{1}H NMR (400 MHz, CD_3OD)



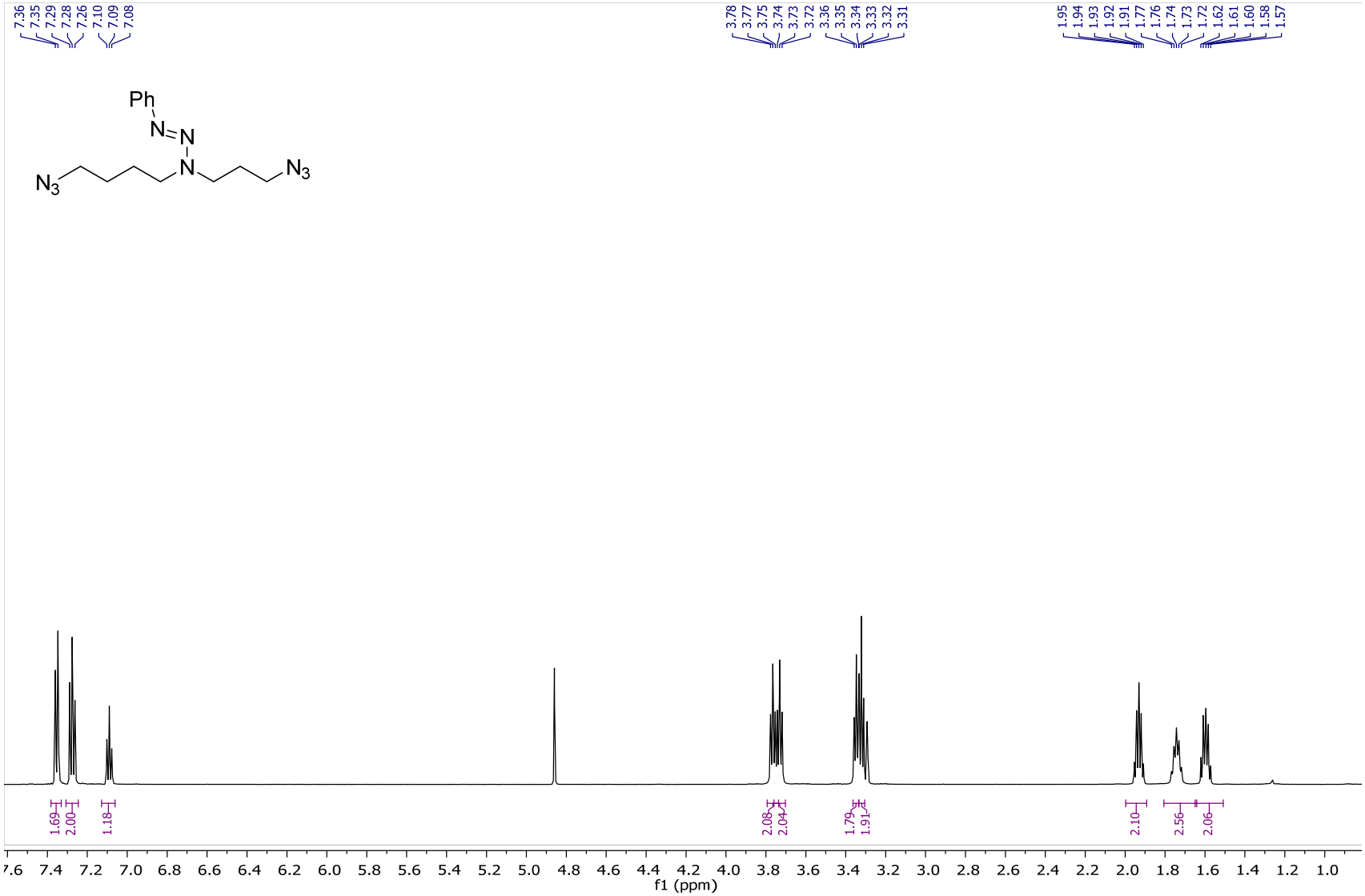
Methyl 2-azido-6-(1-methyl-3-phenyltriaz-2-en-1-yl)hexanoate (7) ^{13}C NMR (400 MHz, CD_3OD)



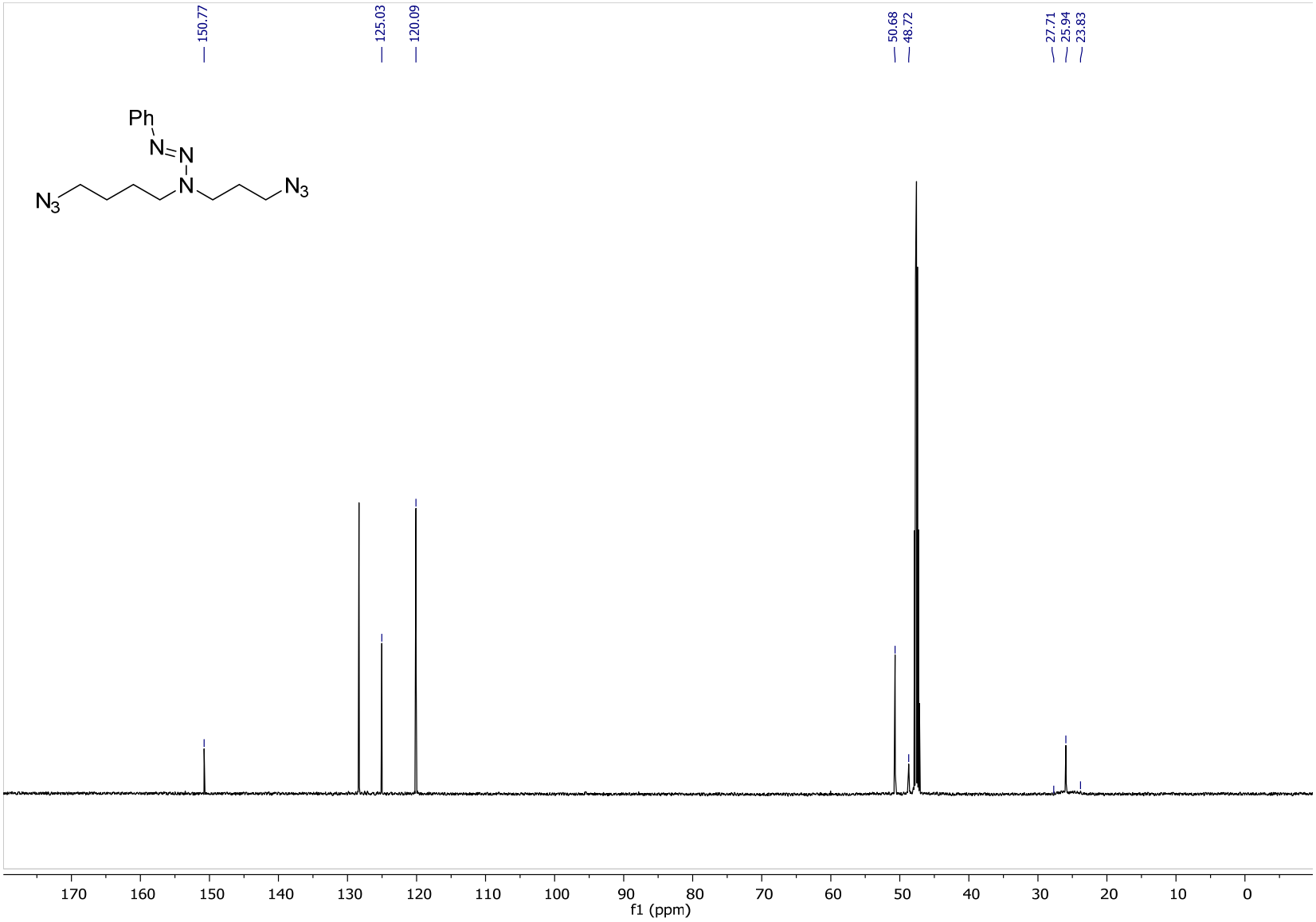
Methyl 2-azido-6-(1-methyl-3-phenyltriaz-2-en-1-yl)hexanoate (7) COSY (400 MHz, CD_3OD)



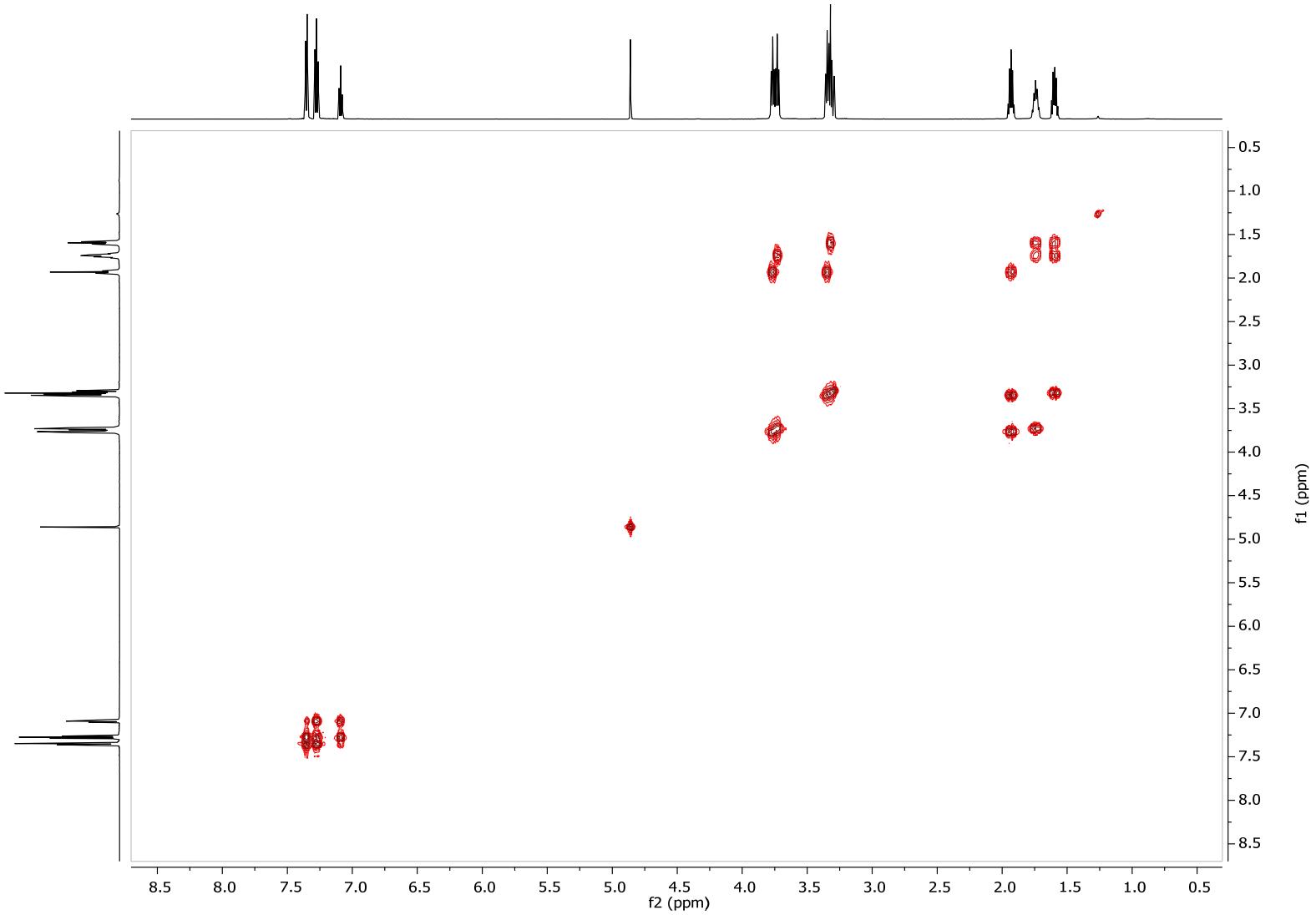
3-(4-Azidobutyl)-3-(3-azidopropyl)-1-phenyltriaz-1-ene (8) ^{1}H NMR (600 MHz, CD_3OD)



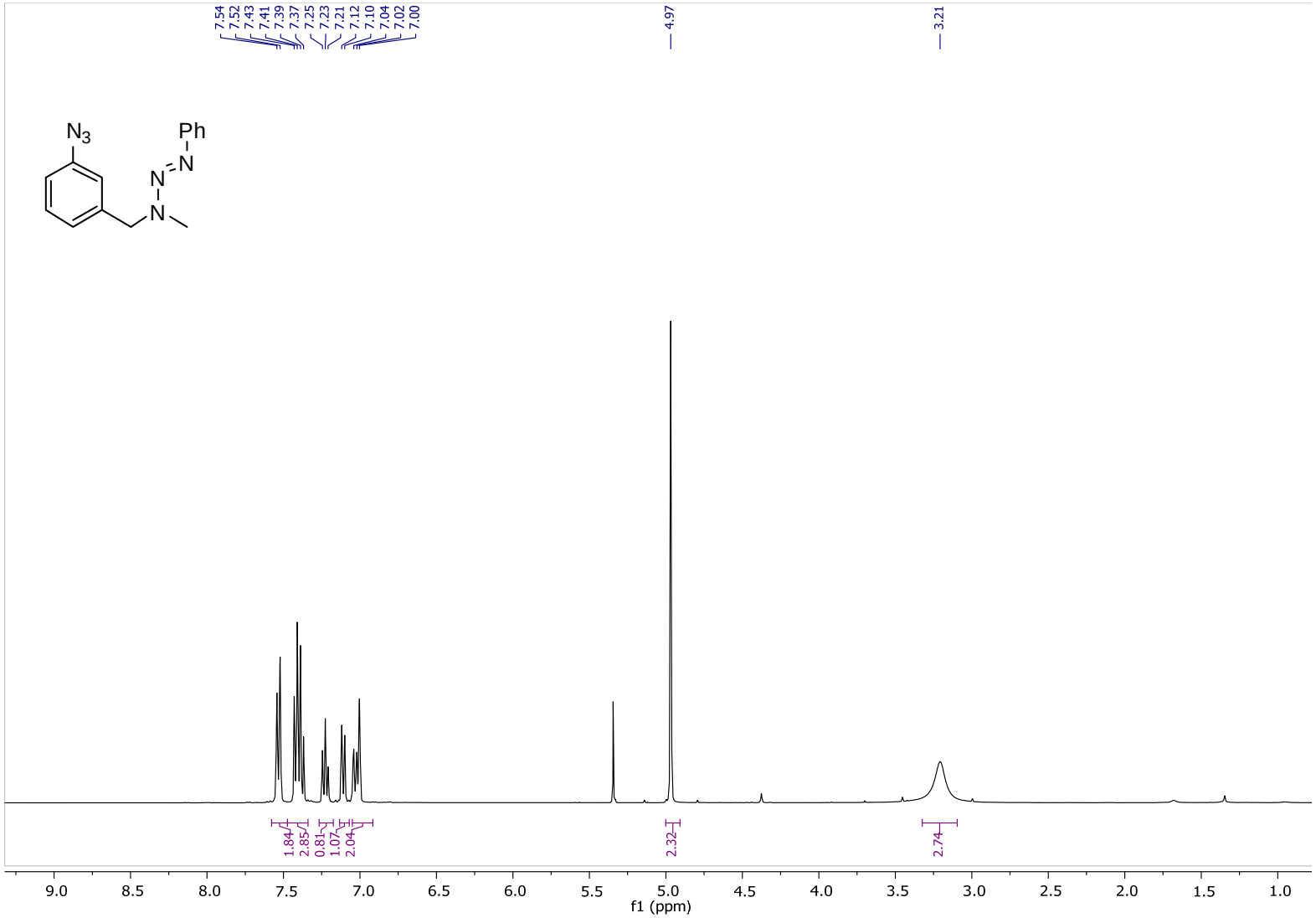
3-(4-azidobutyl)-3-(3-azidopropyl)-1-phenyltriaz-1-ene (8) ^{13}C NMR (151 MHz, CD_3OD)



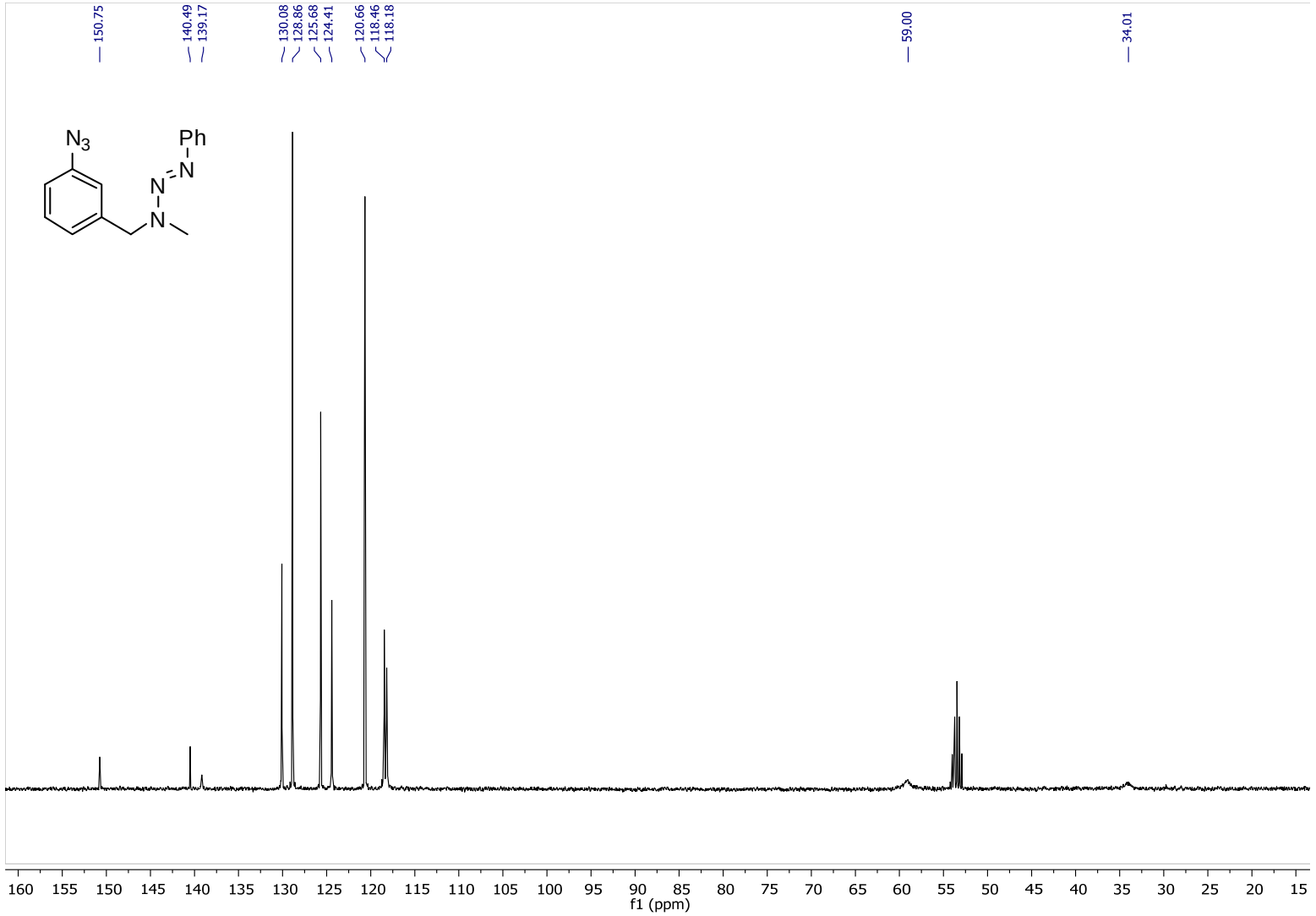
3-(4-azidobutyl)-3-(3-azidopropyl)-1-phenyltriaz-1-ene (8) COSY (600 MHz, CD_3OD)



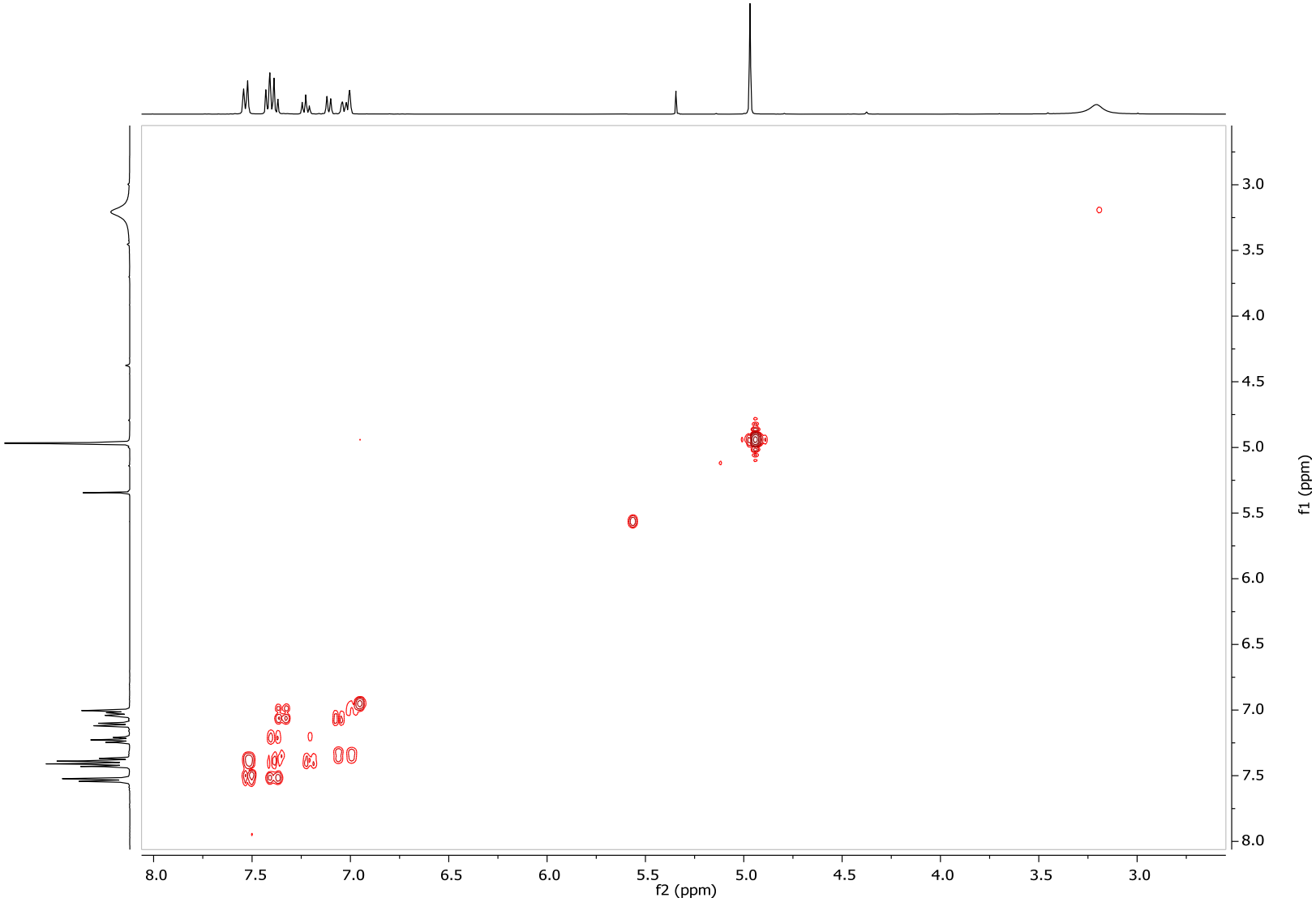
3-(3-Azidobenzyl)-3-methyl-1-phenyltriaz-1-ene (9) ^{1}H NMR (400 MHz, CD_2Cl_2)



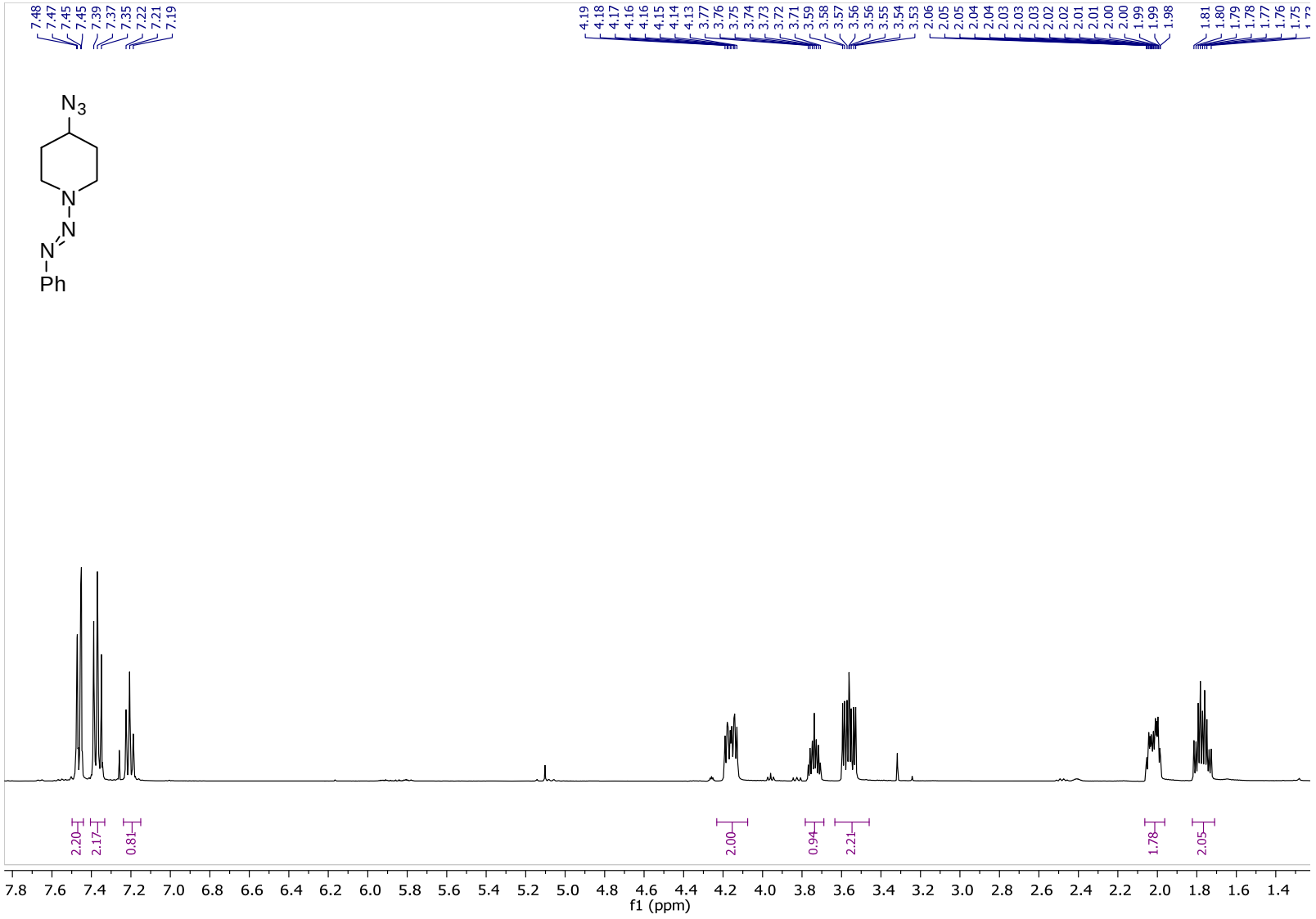
3-(3-Azidobenzyl)-3-methyl-1-phenyltriaz-1-ene (9) ^{13}C NMR (101 MHz, CD_2Cl_2)



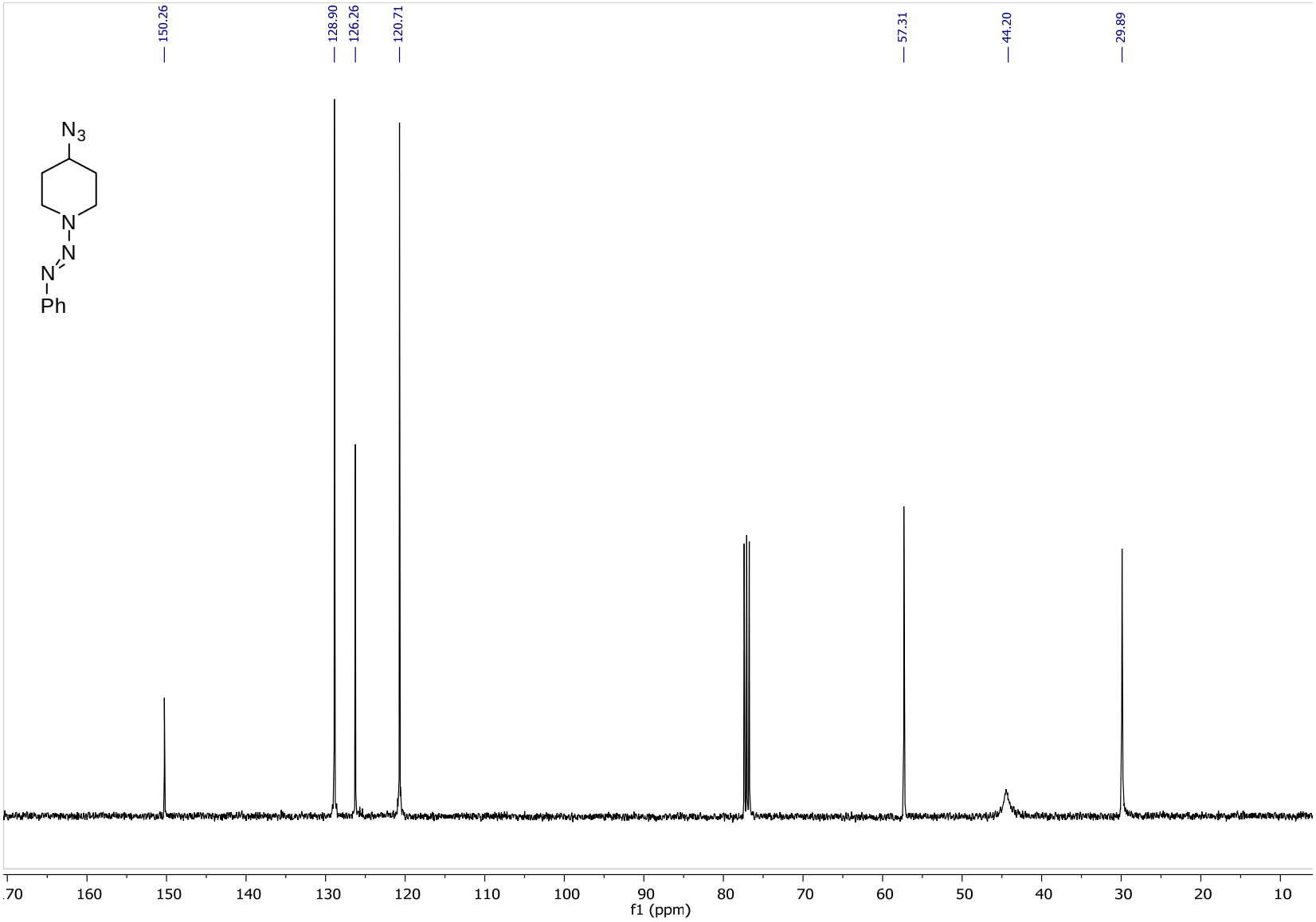
3-(3-Azidobenzyl)-3-methyl-1-phenyltriaz-1-ene (9) COSY (400 MHz, CD_2Cl_2)



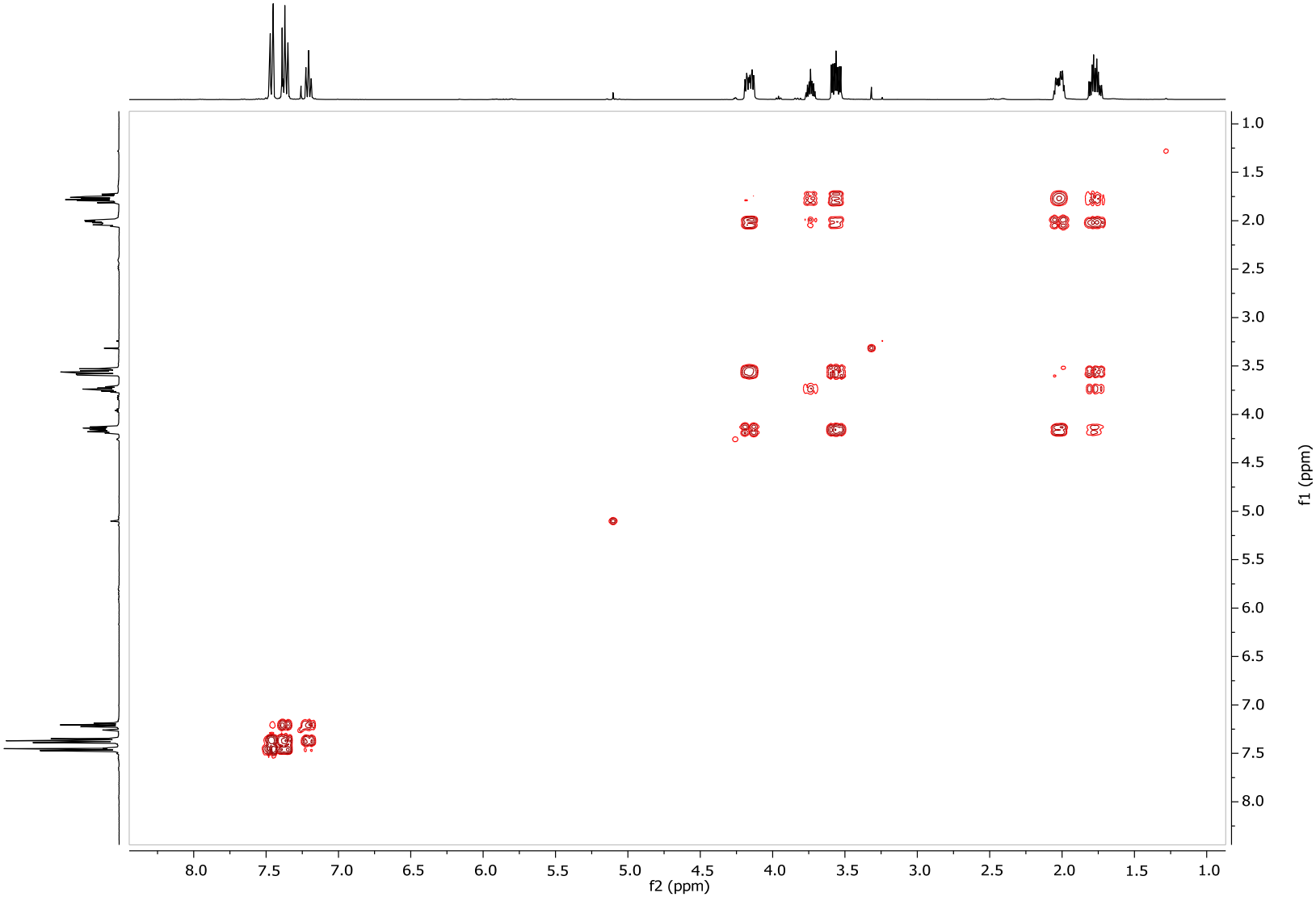
4-Azido-1-(phenyldiazenyl)piperidine (10) ^{1}H NMR (400 MHz, $CDCl_3$)



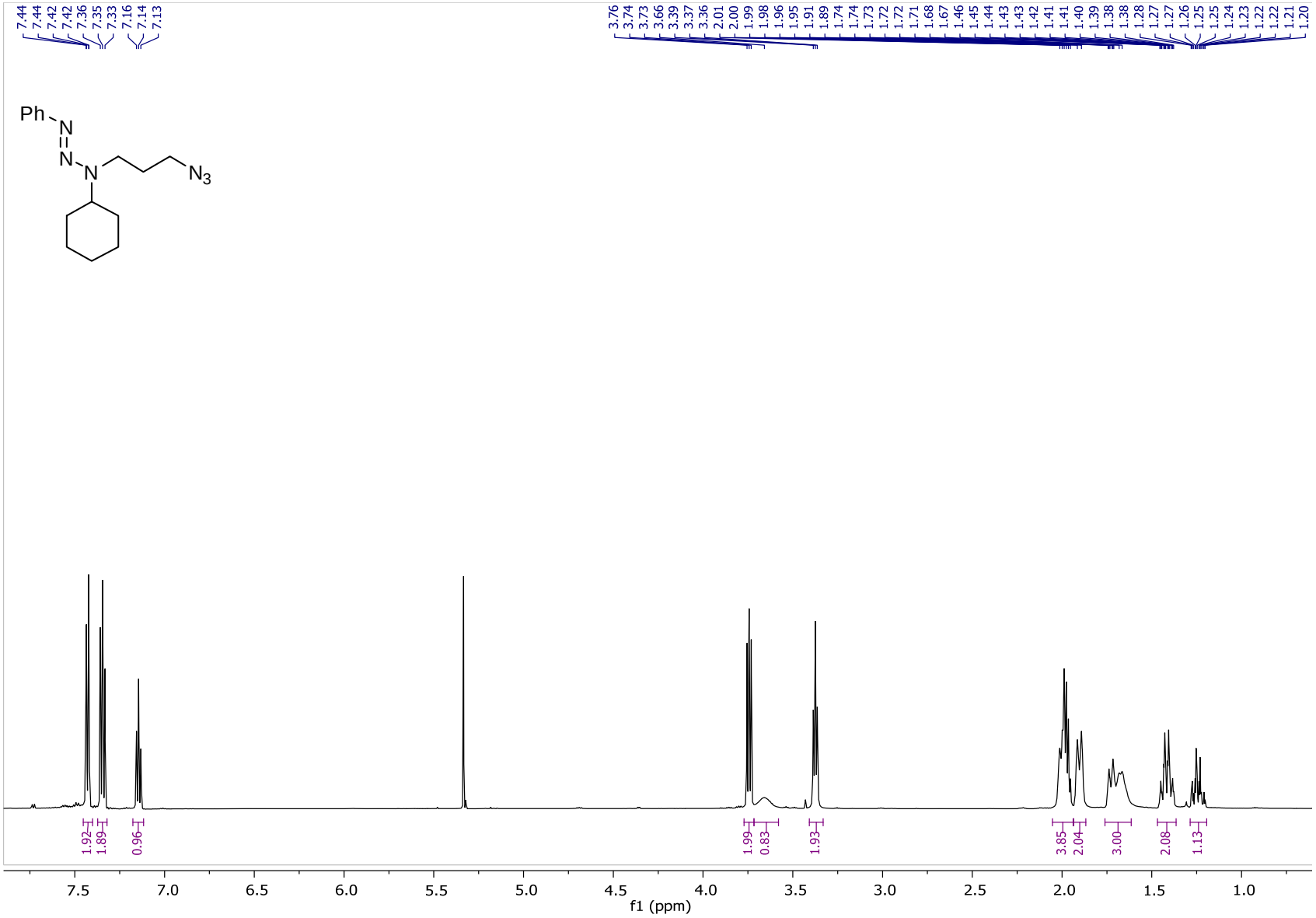
4-Azido-1-(phenyldiazenyl)piperidine (10) ^{13}C NMR (101 MHz, $CDCl_3$)



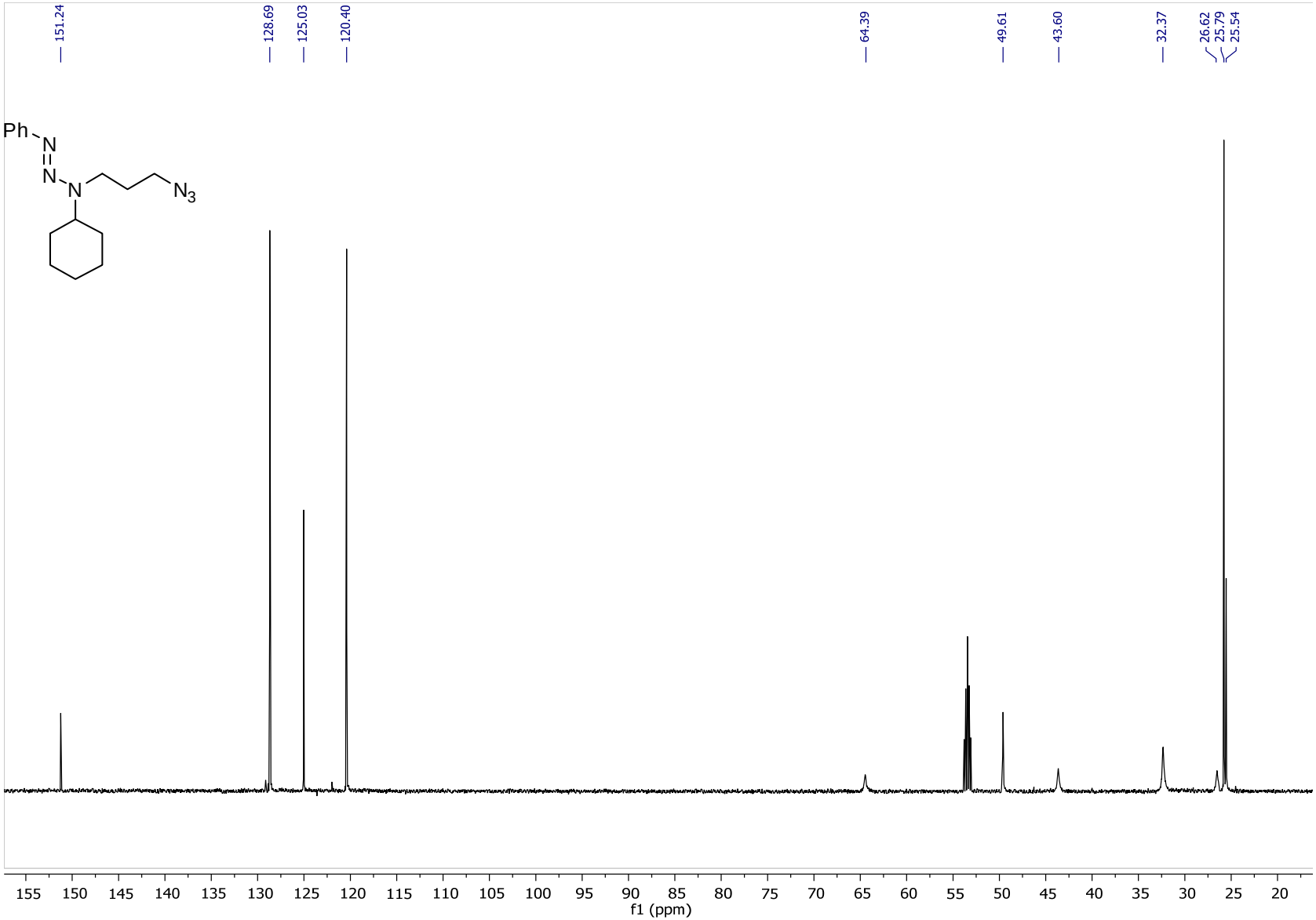
4-Azido-1-(phenyldiazenyl)piperidine (10) COSY (400 MHz, $CDCl_3$)



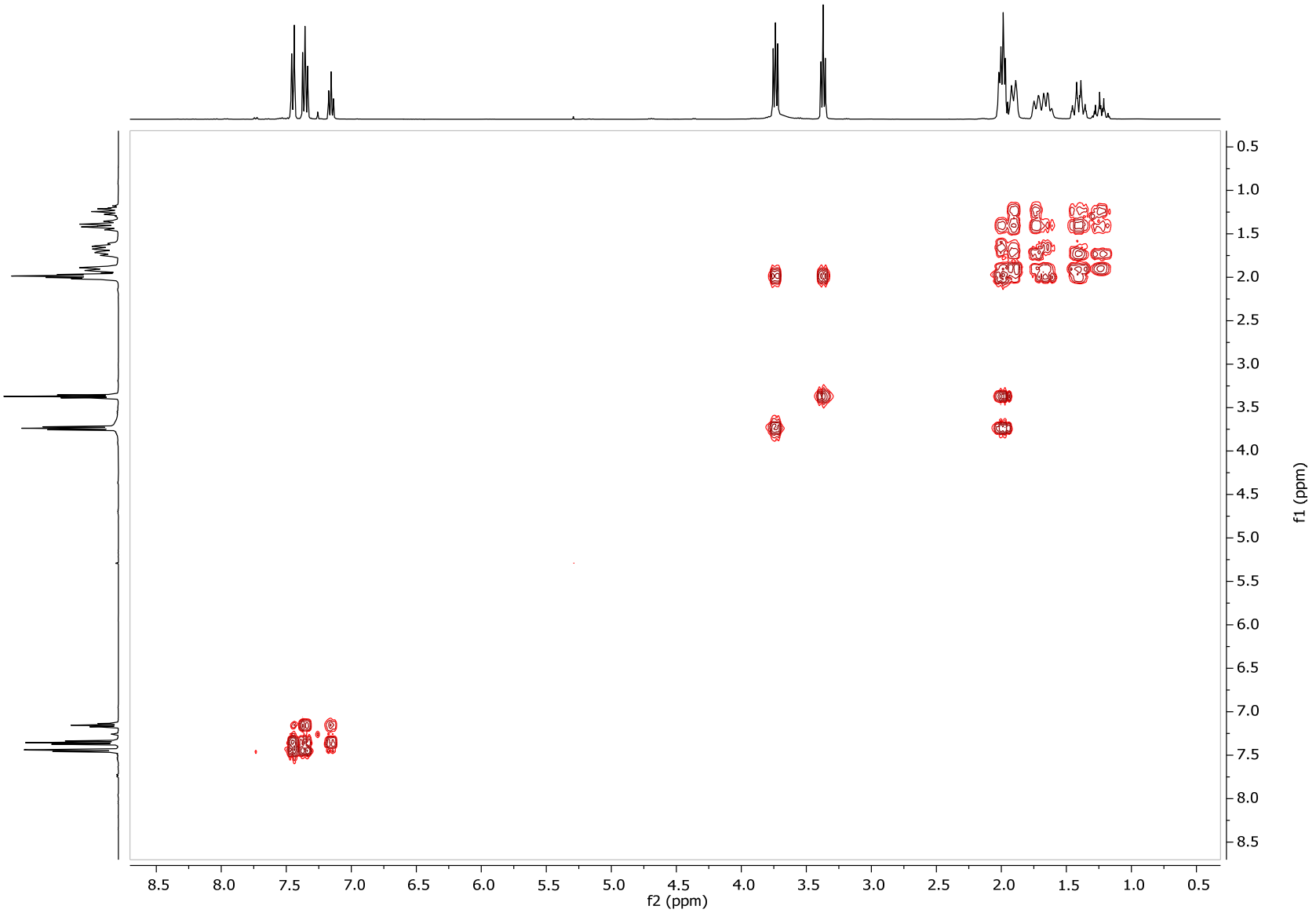
3-(3-Azidopropyl)-3-cyclohexyl-1-phenyltriaz-1-ene (11) ^{1}H NMR (600 MHz, CD_2Cl_2)



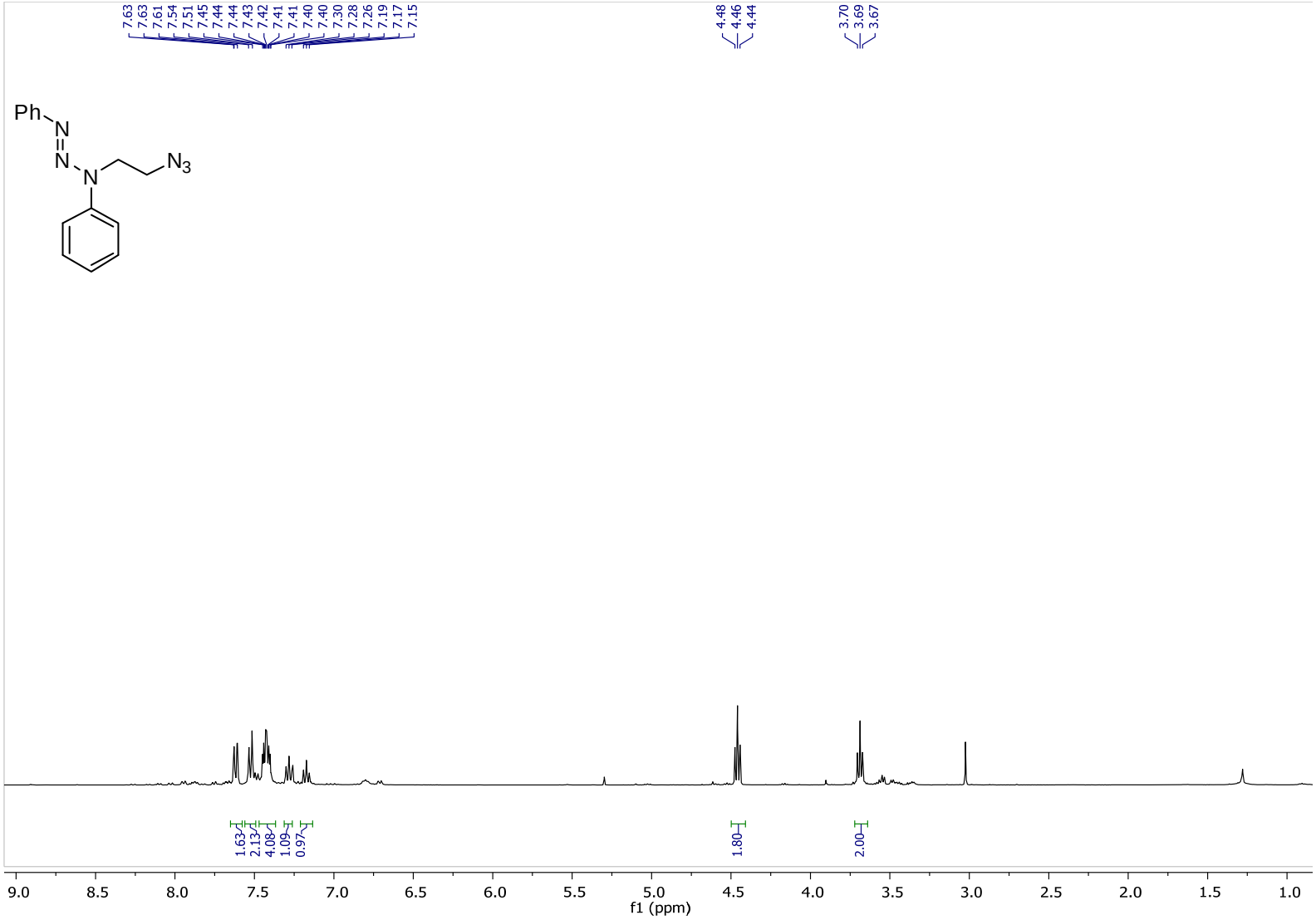
3-(3-Azidopropyl)-3-cyclohexyl-1-phenyltriaz-1-ene (11) ^{13}C NMR (151 MHz, CD_2Cl_2)



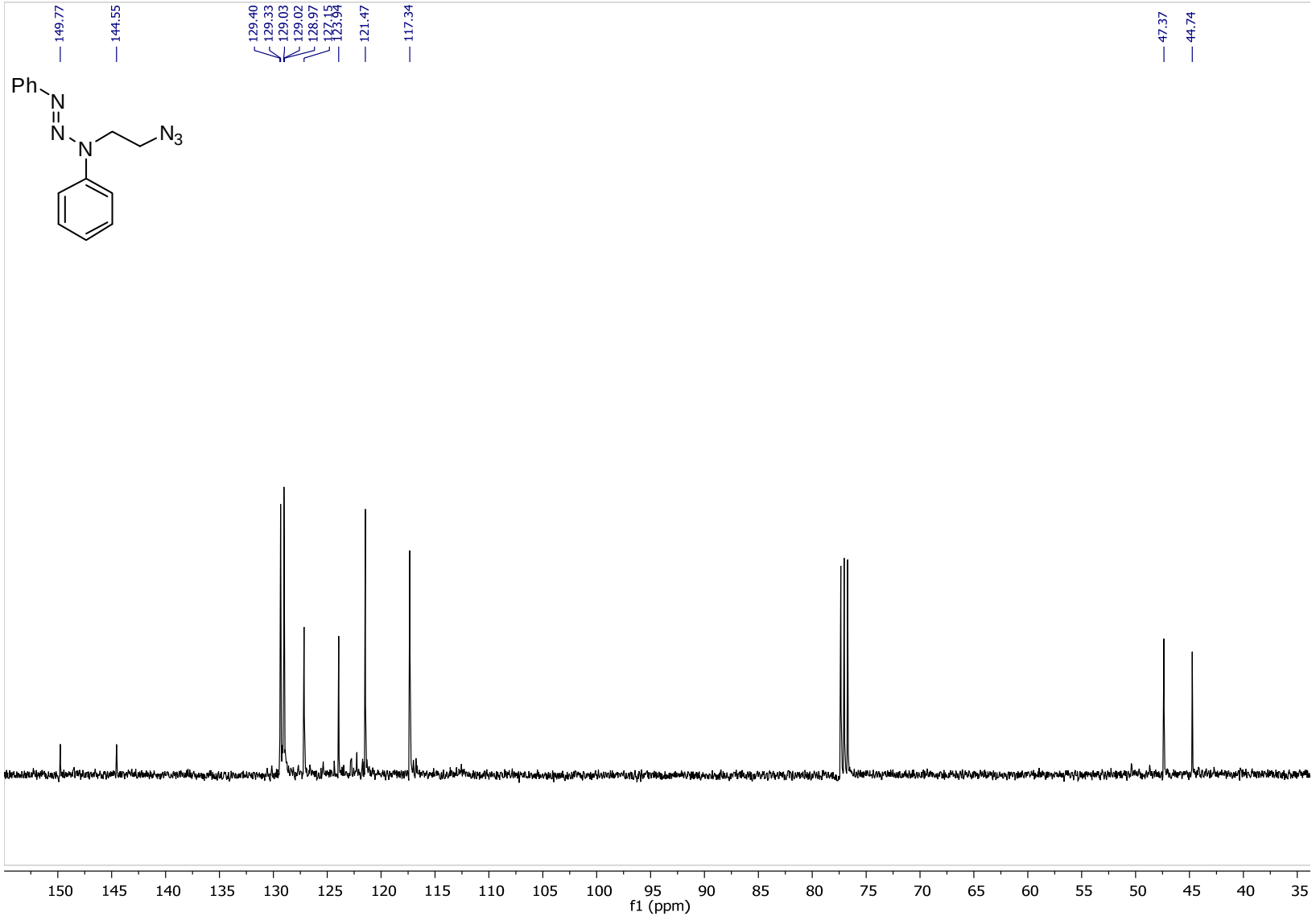
3-(3-Azidopropyl)-3-cyclohexyl-1-phenyltriaz-1-ene (11) COSY (600 MHz, CD_2Cl_2)



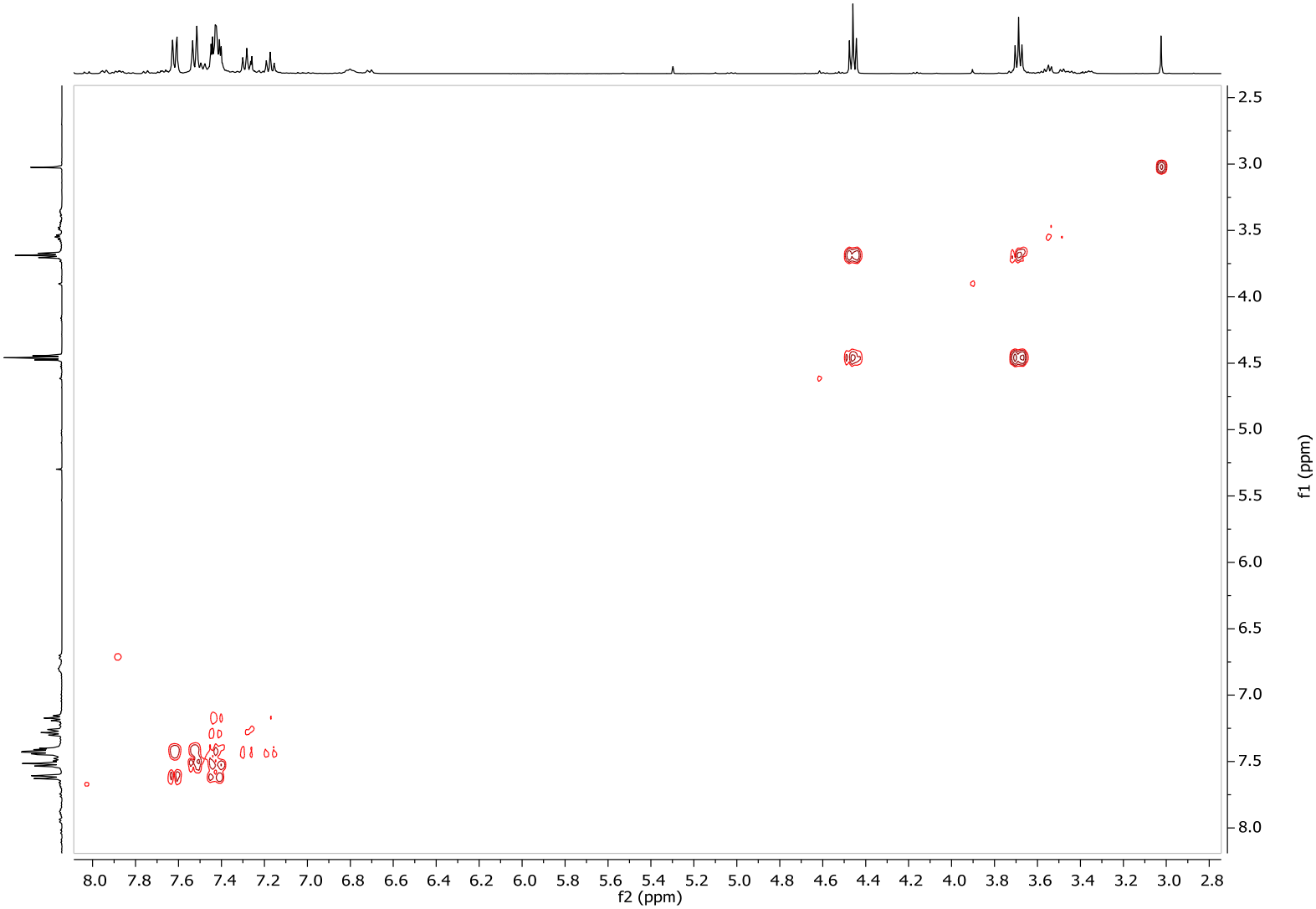
(2-Azidoethyl)-1,3-diphenyltriaz-1-ene (12) ^{1}H NMR (400 MHz, $CDCl_3$)



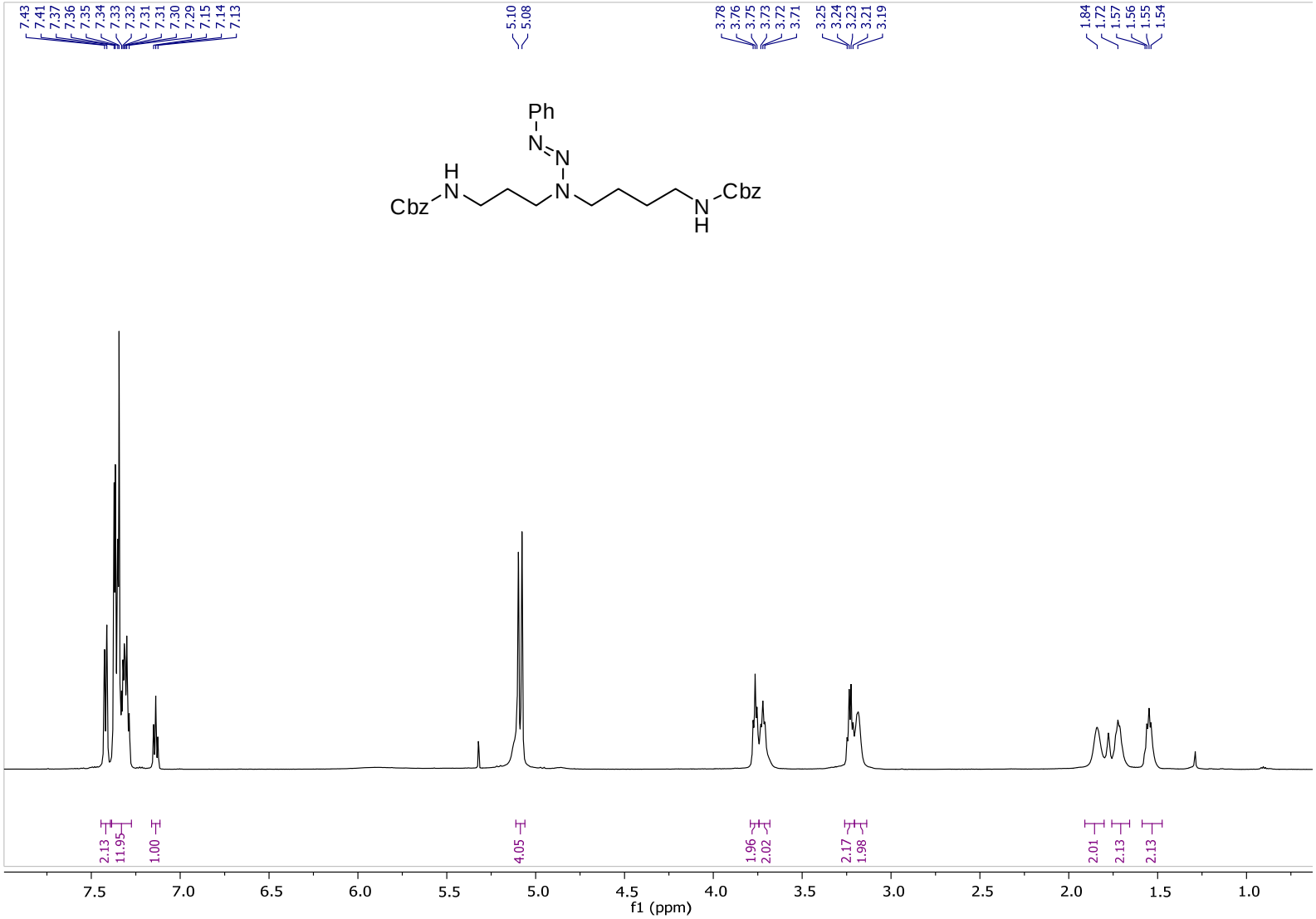
3-(2-Azidoethyl)-1,3-diphenyltriaz-1-ene (12) ^{13}C NMR (101 MHz, $CDCl_3$)



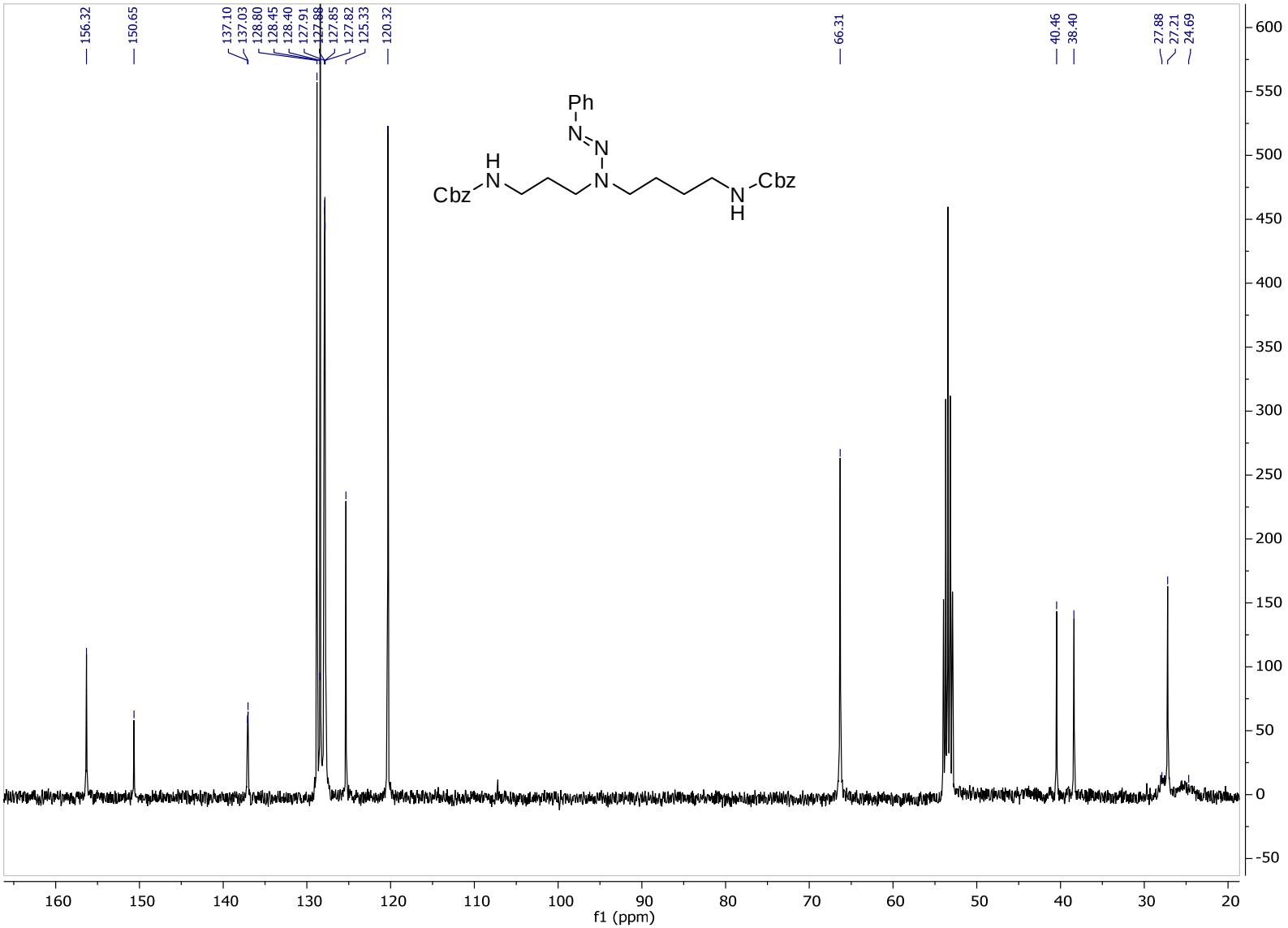
(2-Azidoethyl)-1,3-diphenyltriaz-1-ene (12) COSY (400 MHz, $CDCl_3$)



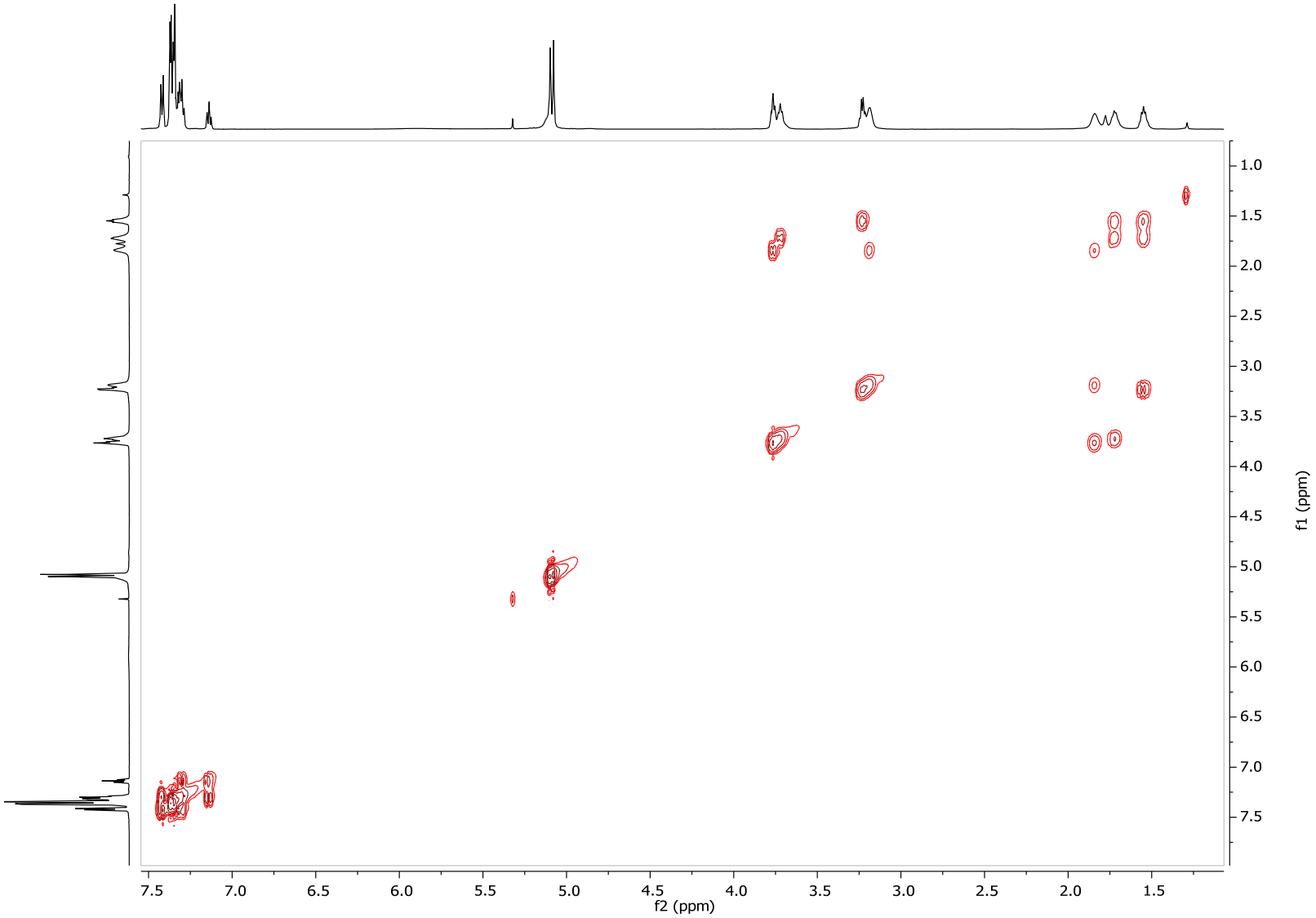
Benzyl(4-(1-(3-(((benzyloxy)carbonyl)amino)propyl)-3-phenyltriaz-2-en-1-yl)butyl)carbamate (13) ^{1}H NMR (600 MHz, CD_2Cl_2)



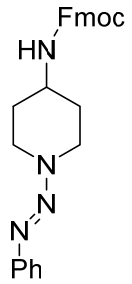
Benzyl(4-(1-(3-(((benzyloxy)carbonyl)amino)propyl)-3-phenyltriaz-2-en-1-yl)butyl)carbamate (13) ^{13}C NMR (101 MHz, CD_2Cl_2):

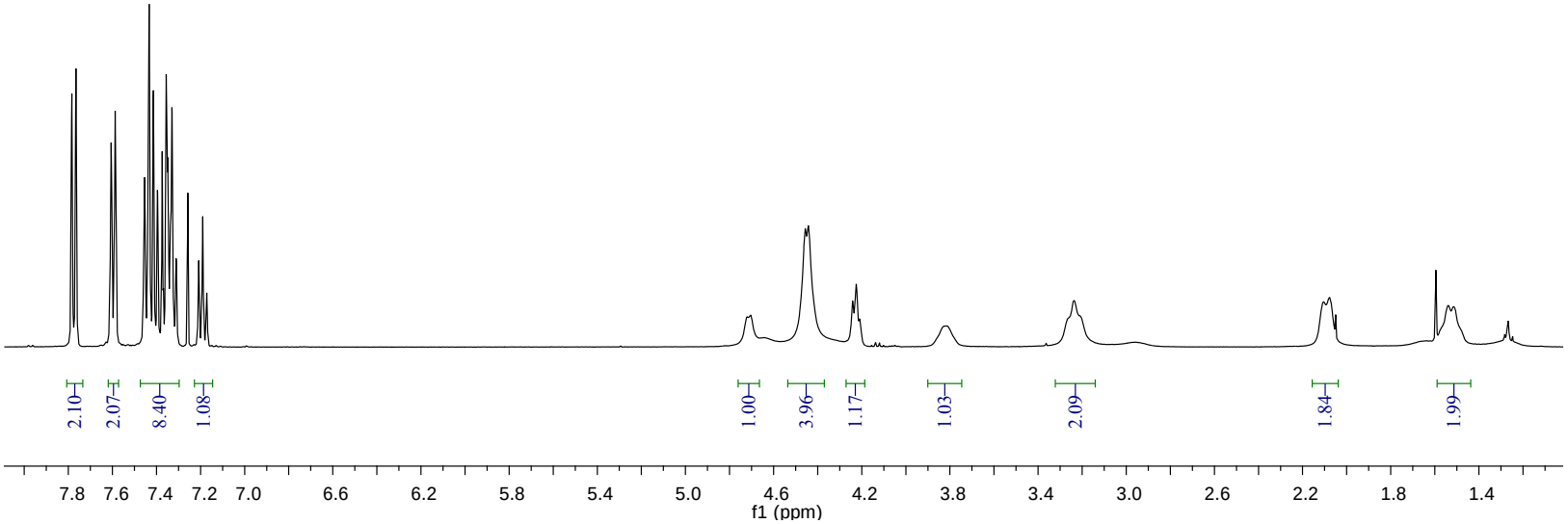


Benzyl(4-(1-(3-(((benzyloxy)carbonyl)amino)propyl)-3-phenyltriaz-2-en-1-yl)butyl)carbamate (13) ^{1}H NMR (600 MHz, CD_2Cl_2)

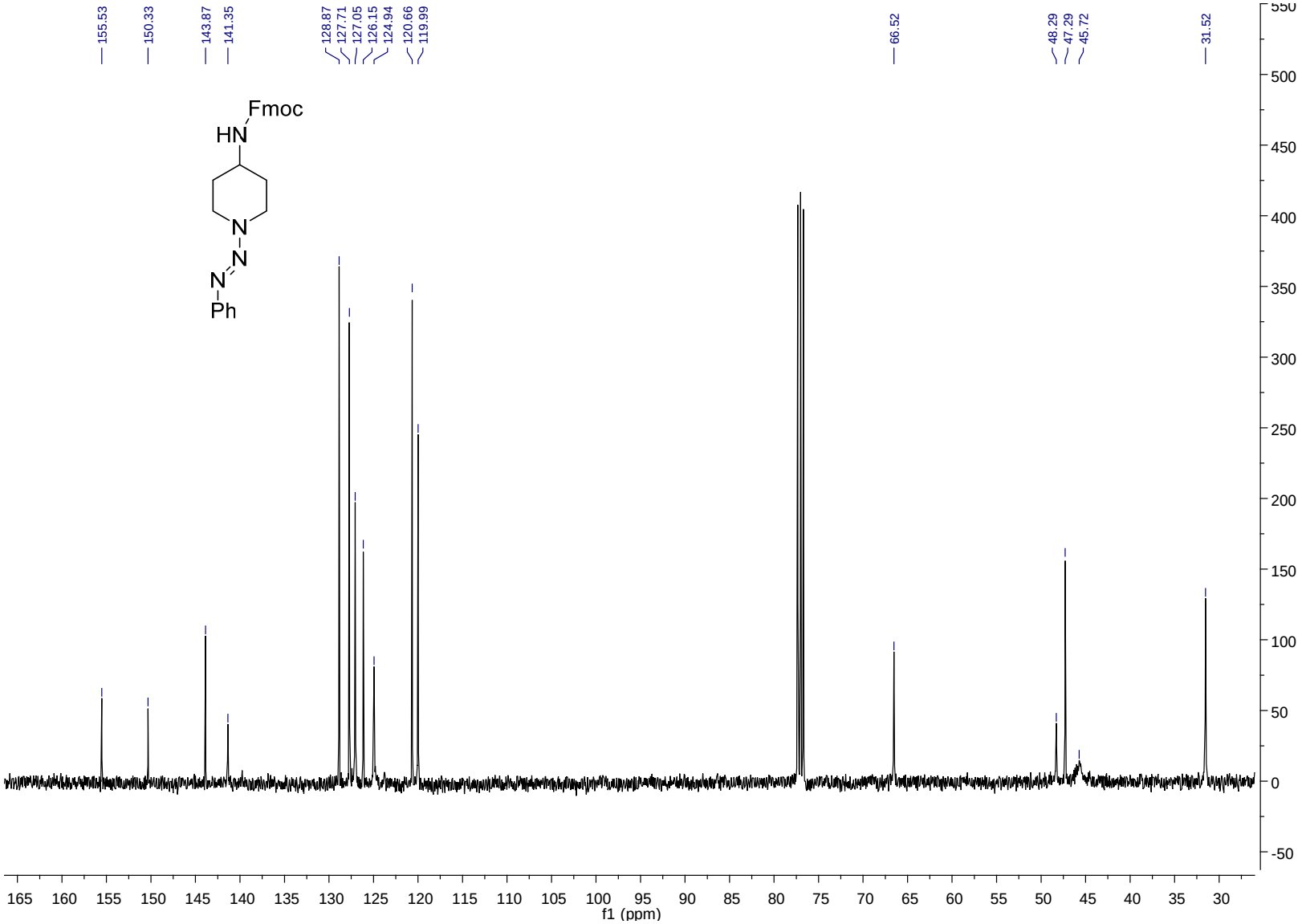


4-Fluorenylmethyloxycarbonylamino-1-(phenyldiazenyl)piperidine (14) ^{1}H NMR (400 MHz, $CDCl_3$)

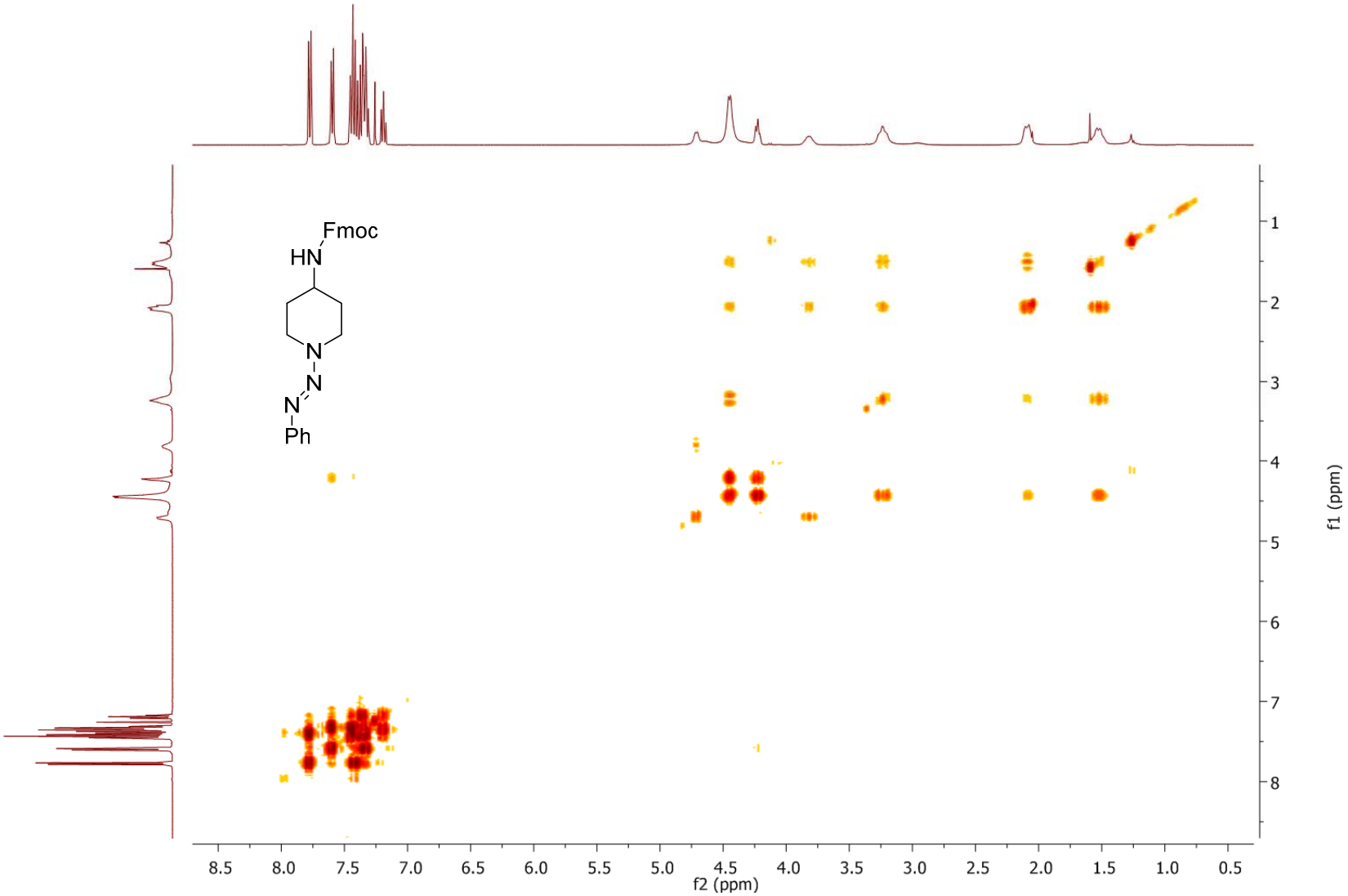




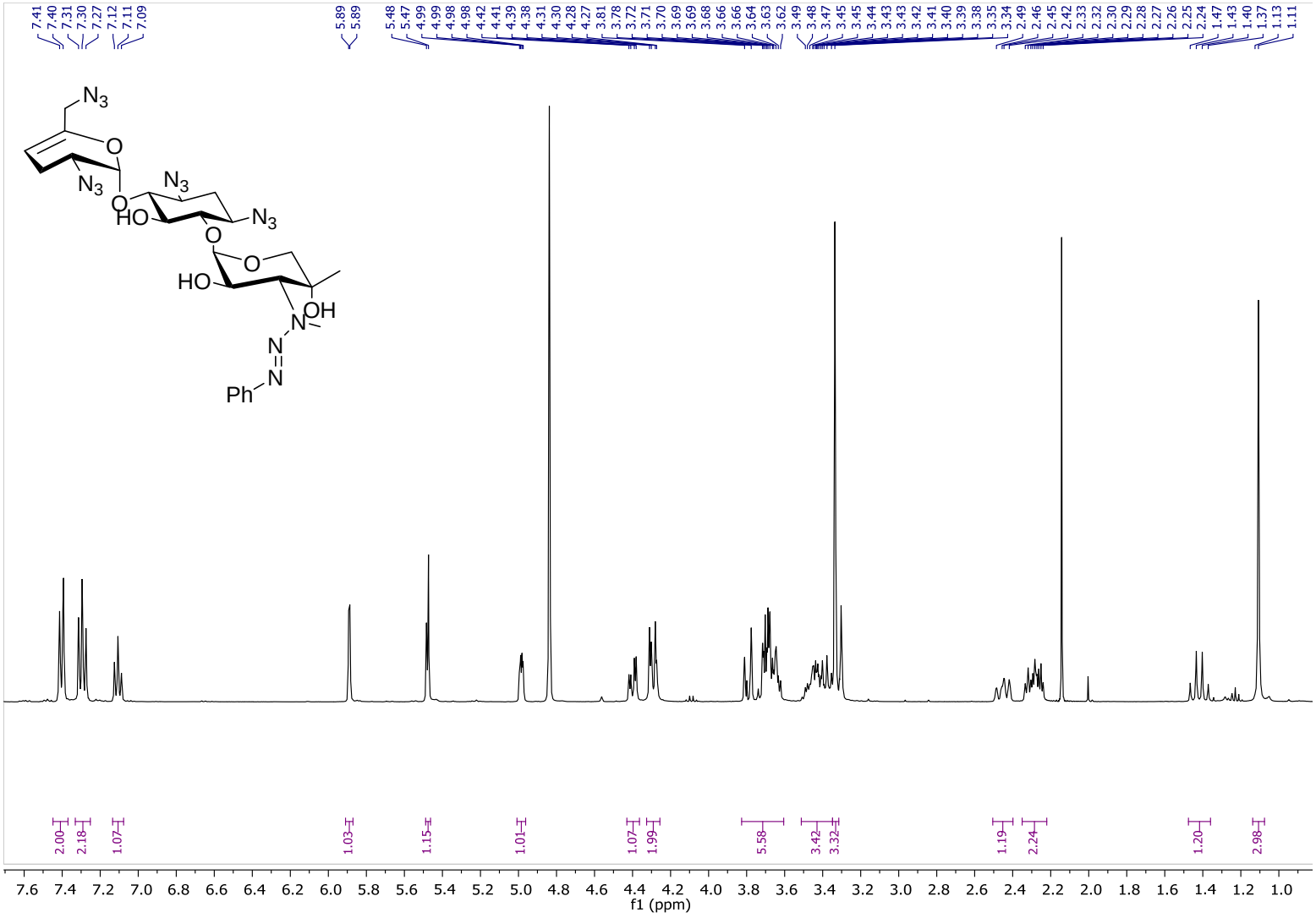
4-Fluorenylmethyloxycarbonylamino-1-(phenyldiazenyl)piperidine (14) ^{13}C NMR (101 MHz, $CDCl_3$)



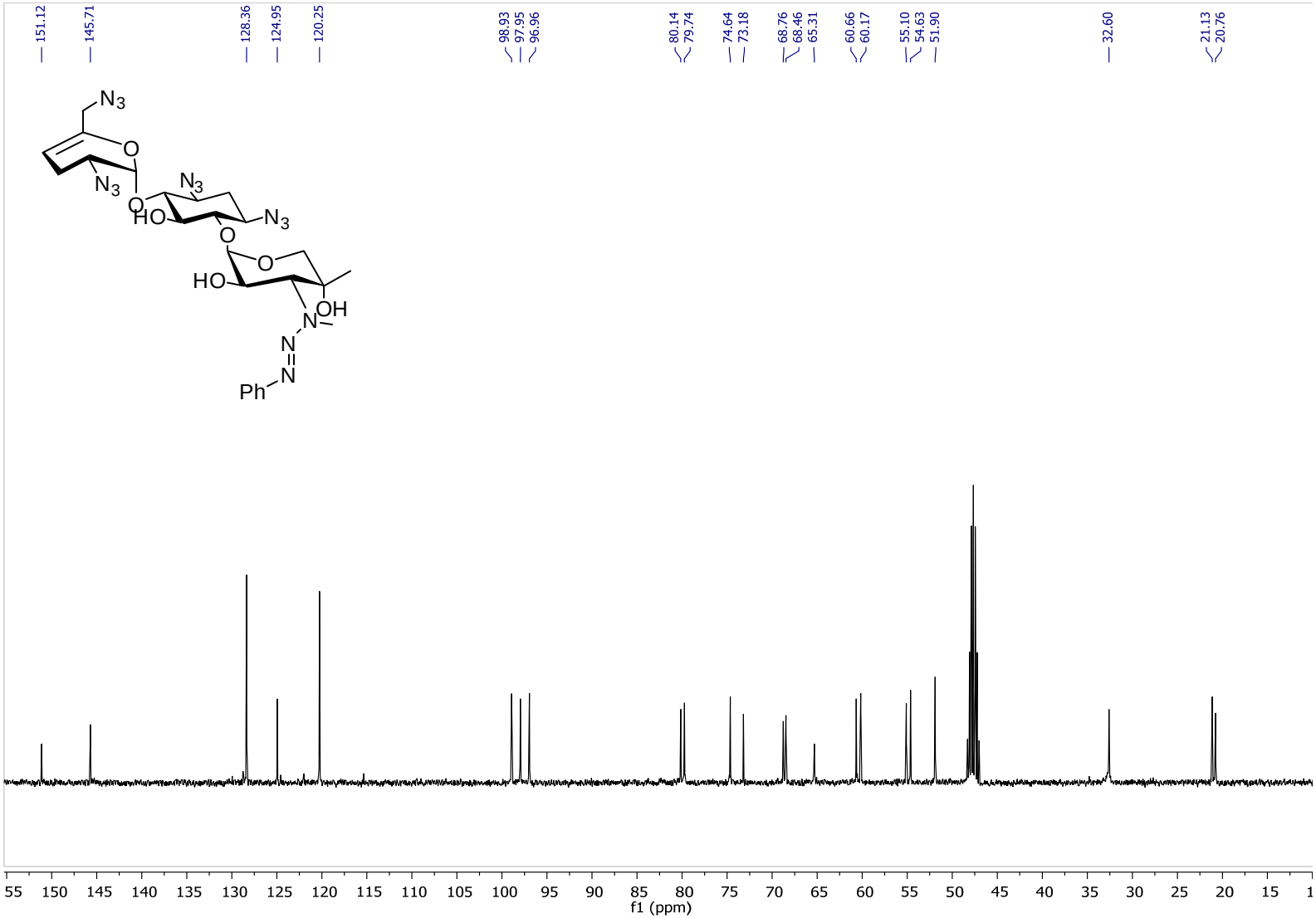
4-Fluorenylmethyloxycarbonylamino-1-(phenyldiazenyl)piperidine (14) COSY NMR (400 MHz, $CDCl_3$)



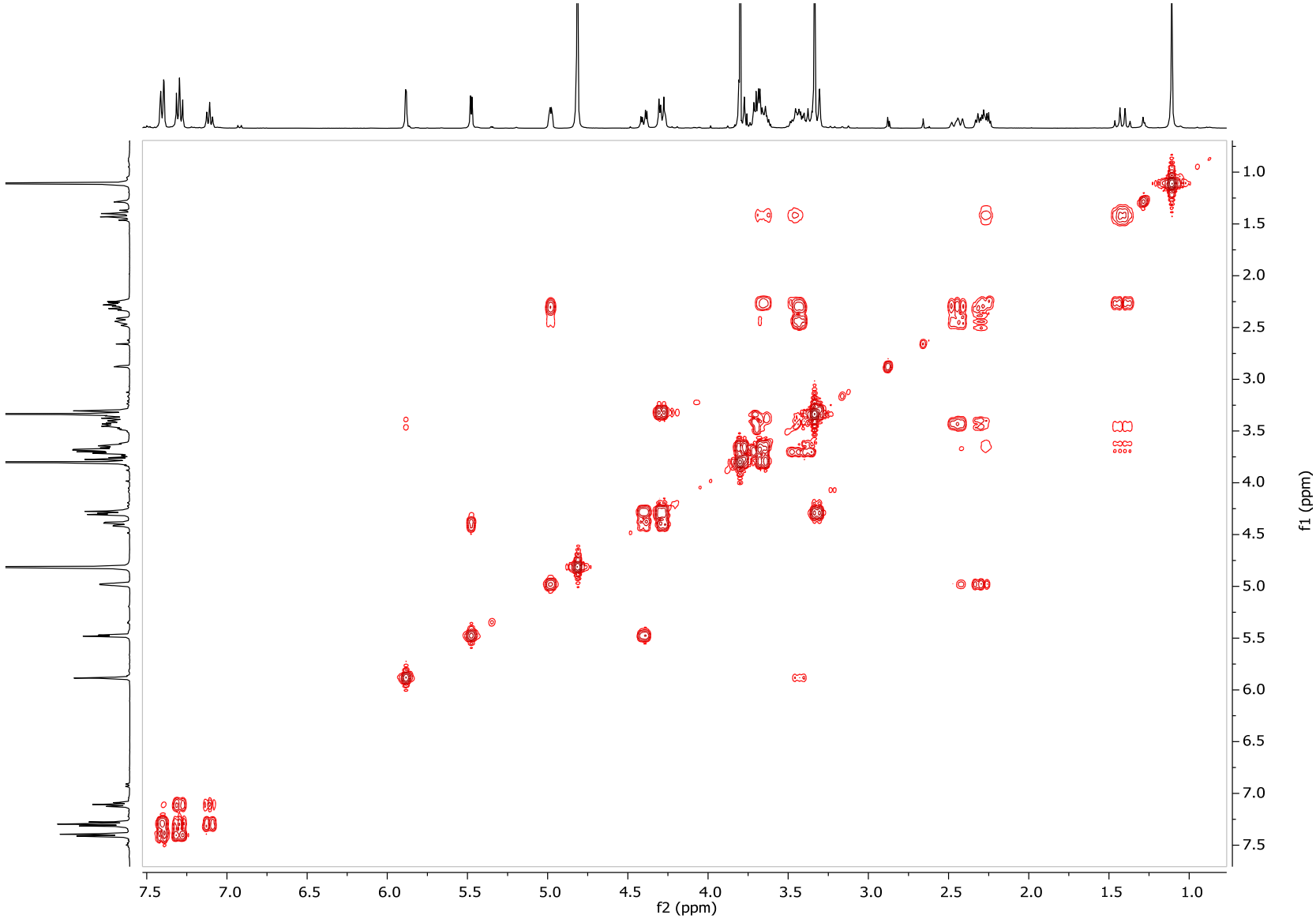
1,3,2',6'-Tetra-deamino-1,3,2',6'-tetraazido-3''-phenylazosisomicin (16) ^{1}H NMR (400 MHz, CD_3OD)



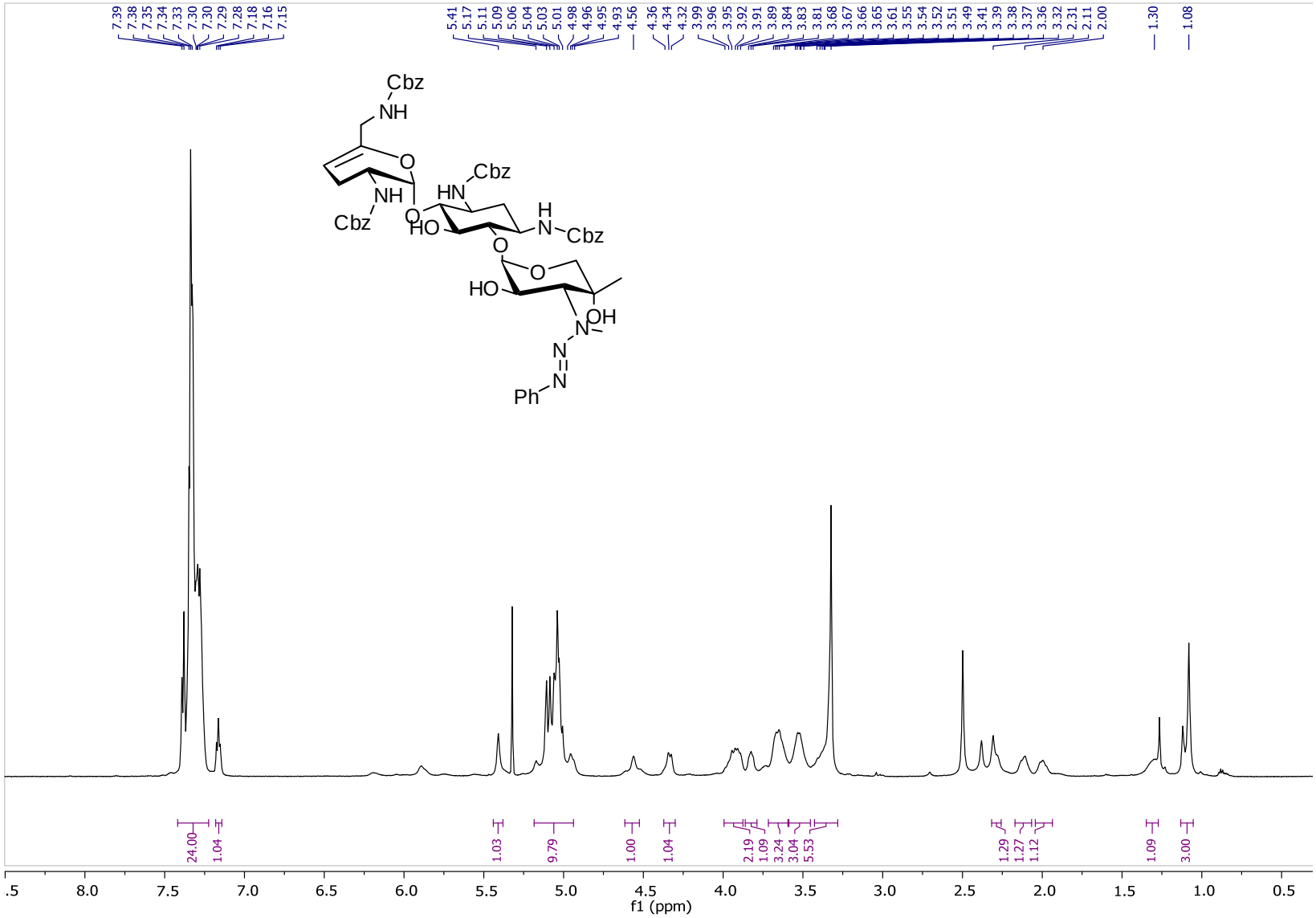
1,3,2',6'-Tetra-deamino-1,3,2',6'-tetraazido-3''-phenylazosisomicin (16) ^{13}C NMR (101 MHz, CD_3OD)



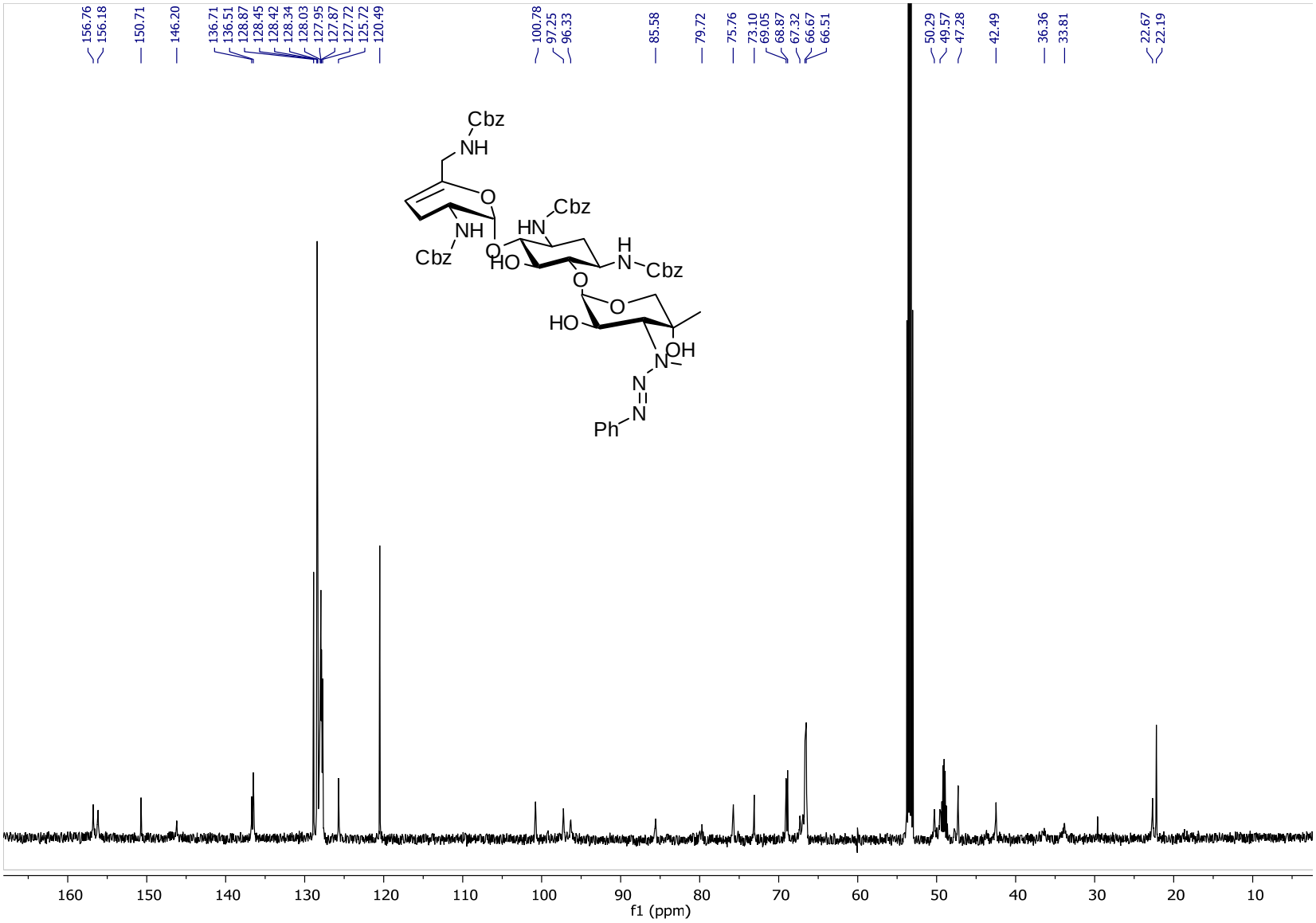
1,3,2',6'-Tetra-deamino-1,3,2',6'-tetraazido-3''-phenylazosisomicin (16) COSY (400 MHz, CD_3OD)



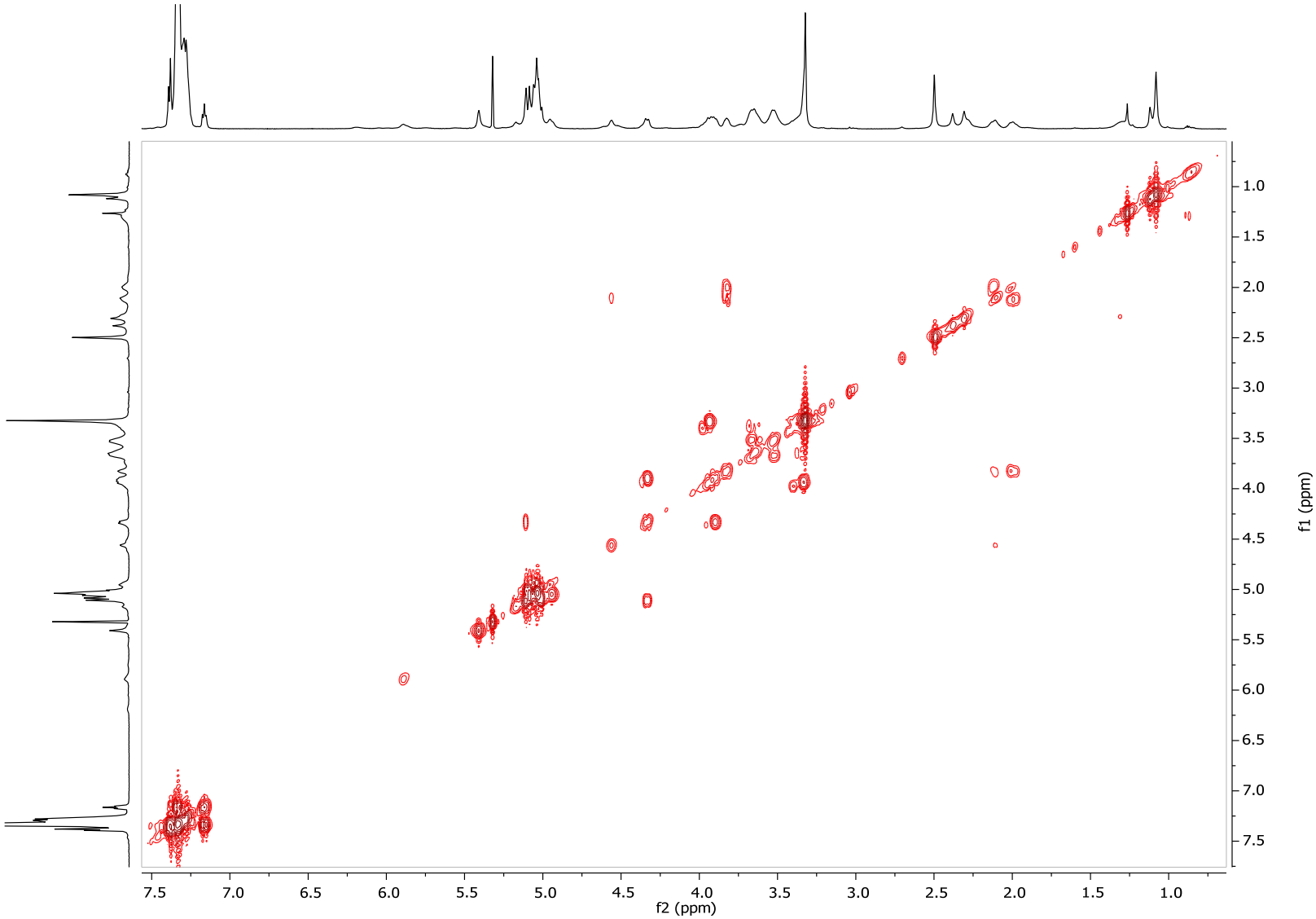
1,3,2',6'-Tetra-*N*-(benzyloxycarbonyl)-3''-*N*-(phenylazo)sisomicin (17) ^{1}H NMR (600 MHz, CD_2Cl_2 + CD_3OD):



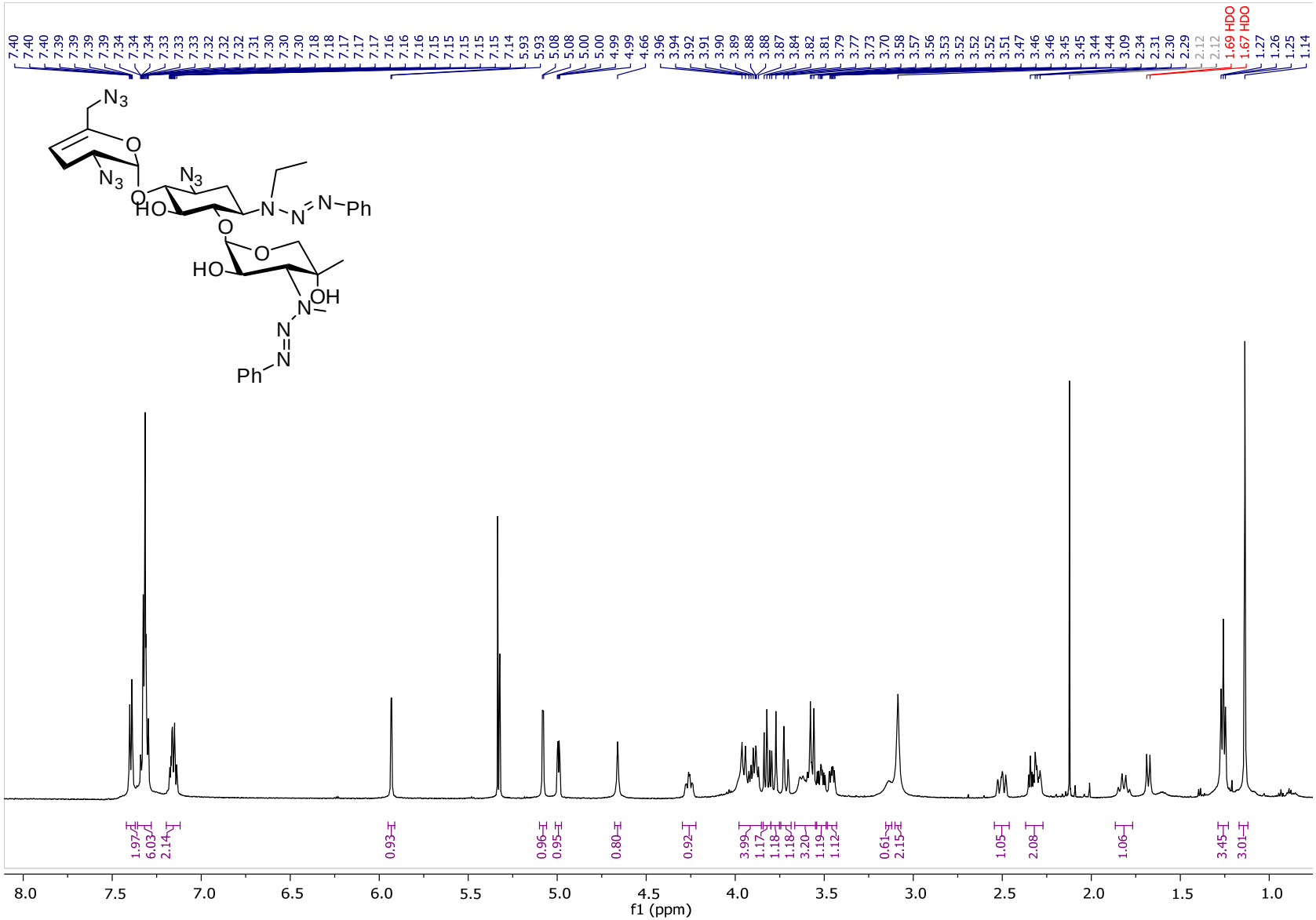
1,3,2',6'-Tetra-*N*-(benzyloxycarbonyl)-3''-*N*-(phenylazo)sisomicin (17) ^{13}C NMR (151 MHz, CD_2Cl_2 + CD_3OD):



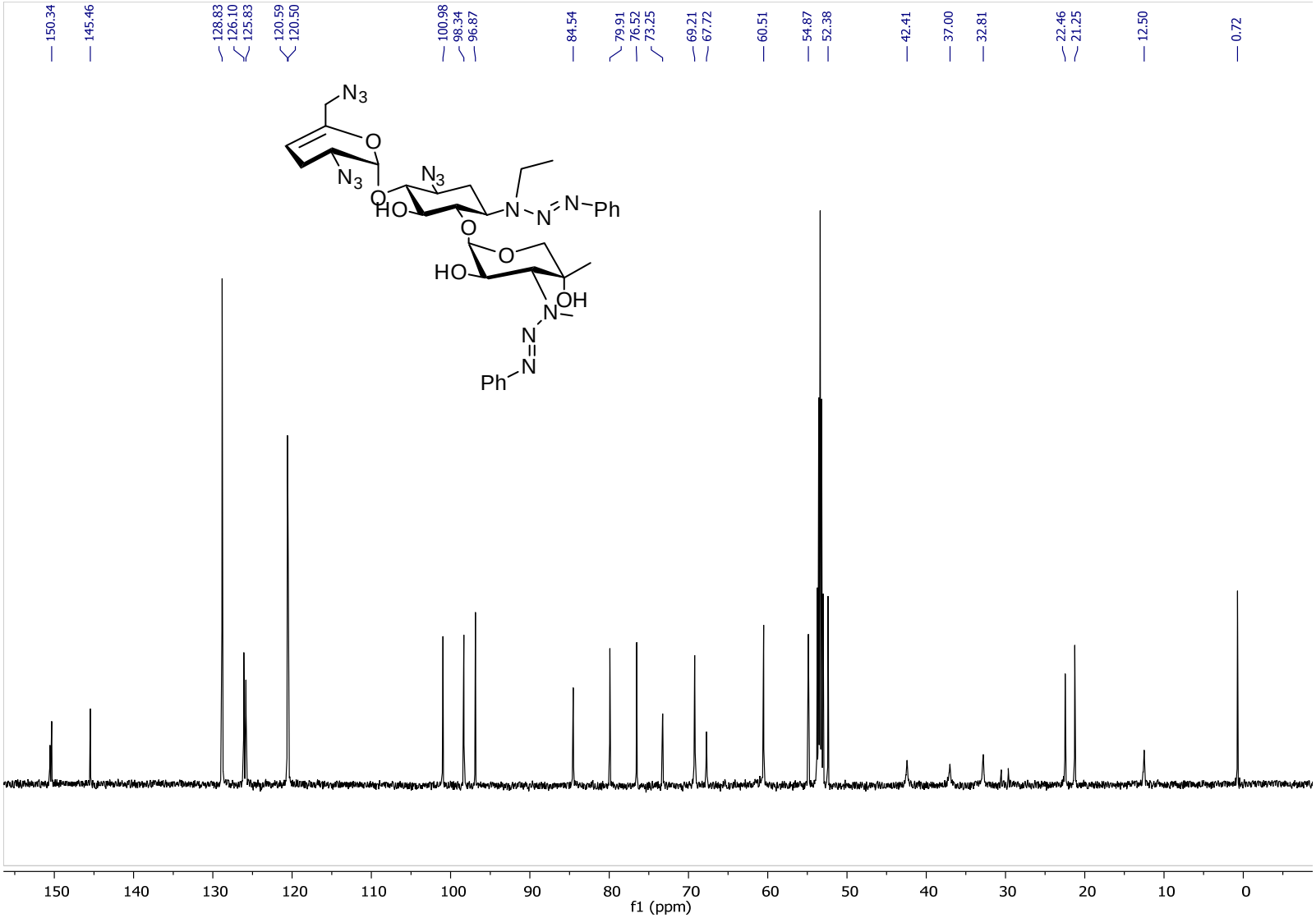
1,3,2',6'-Tetra-*N*-(benzyloxycarbonyl)-3''-*N*-(phenylazo)sisomicin (17) COSY 600 MHz, CD_2Cl_2 + CD_3OD):



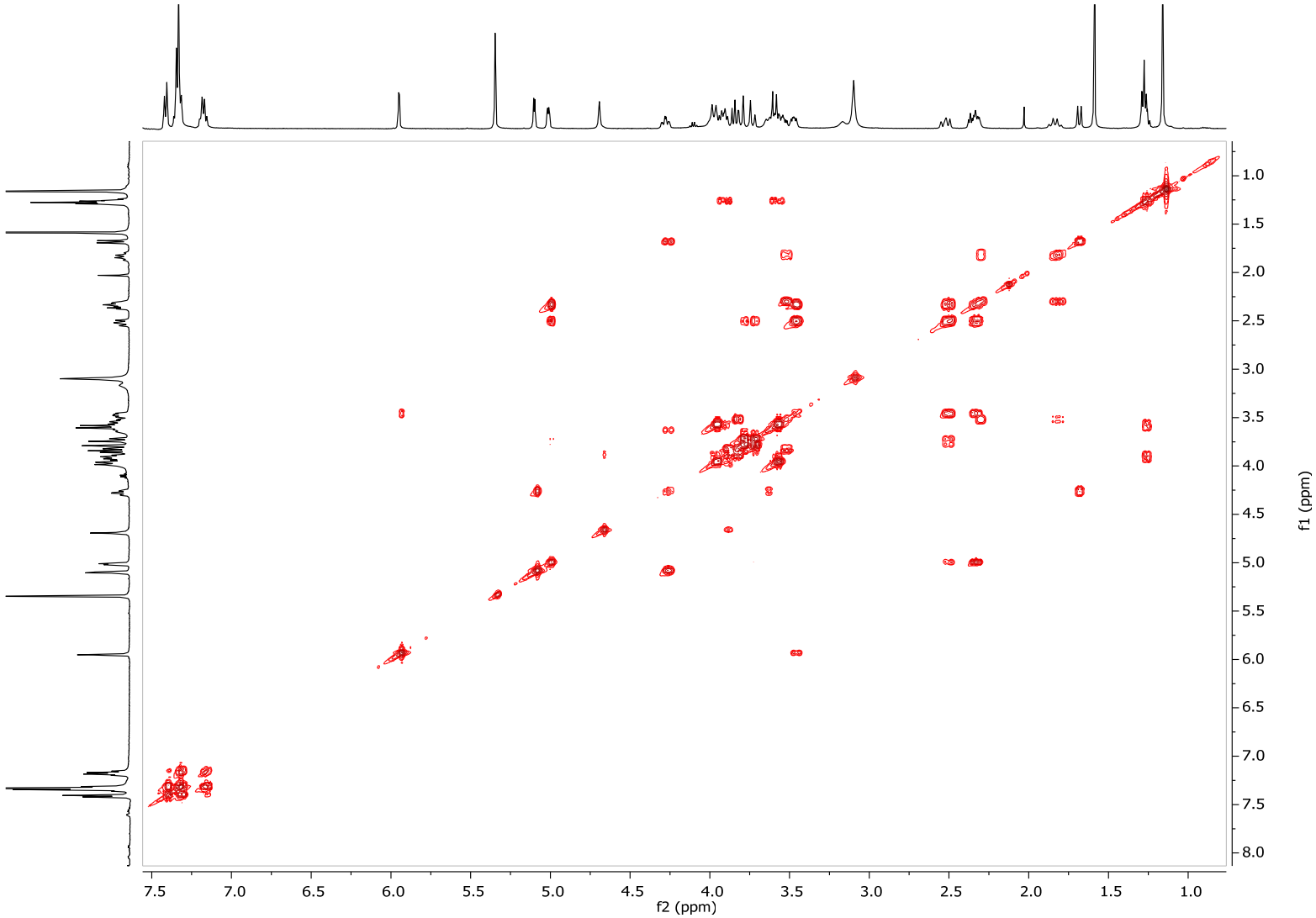
3,2’,6-Tri-deamino-3,2',6'-triazido-1,3''–di-*N*-(phenylazo)netilmicin (19) ^{1}H NMR (600 MHz, CD_2Cl_2)



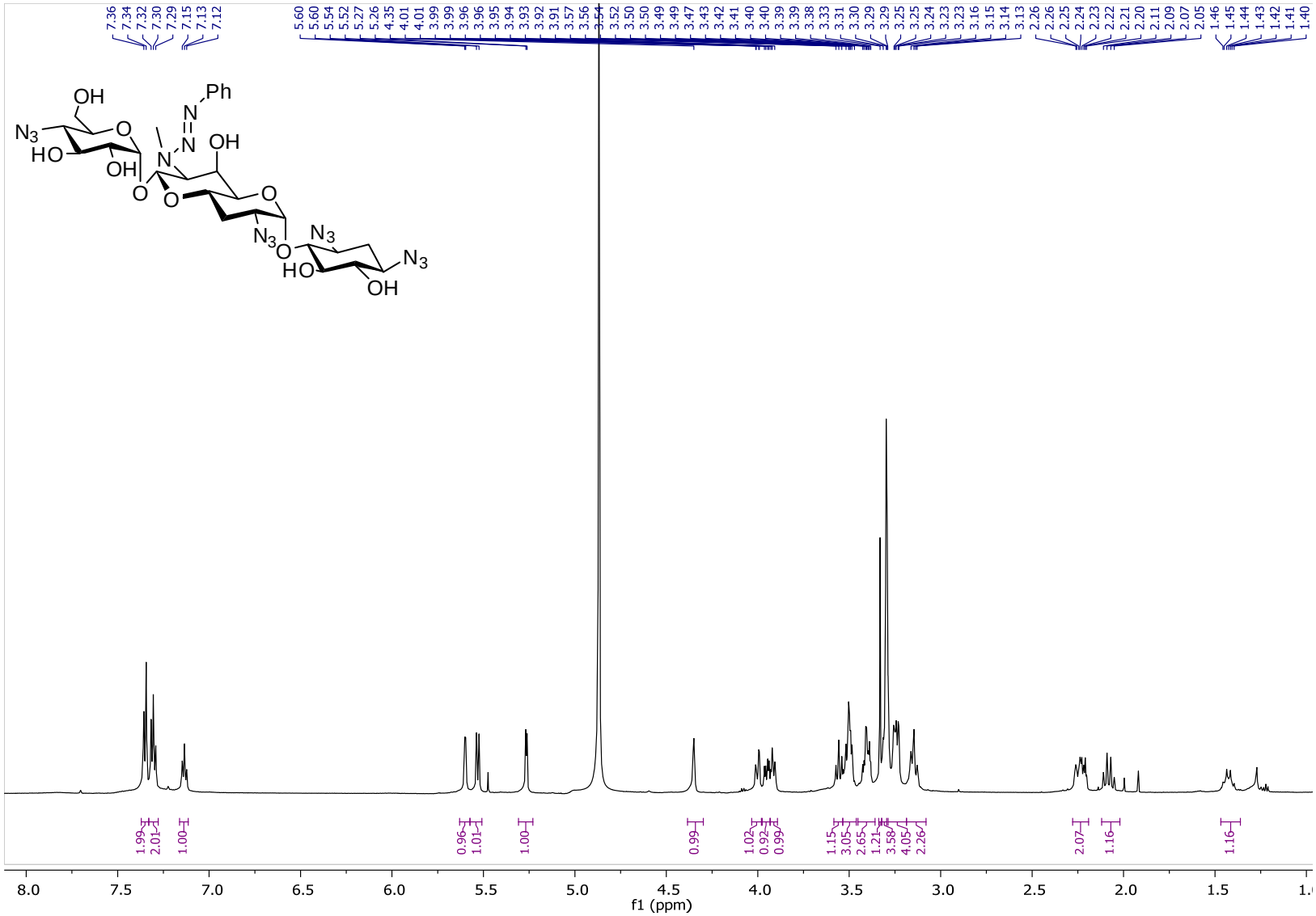
3,2’,6-Tri-deamino-3,2',6'-triazido-1,3''–di-*N*-(phenylazo)netilmicin (19) ^{13}C NMR (151 MHz, CD_2Cl_2)



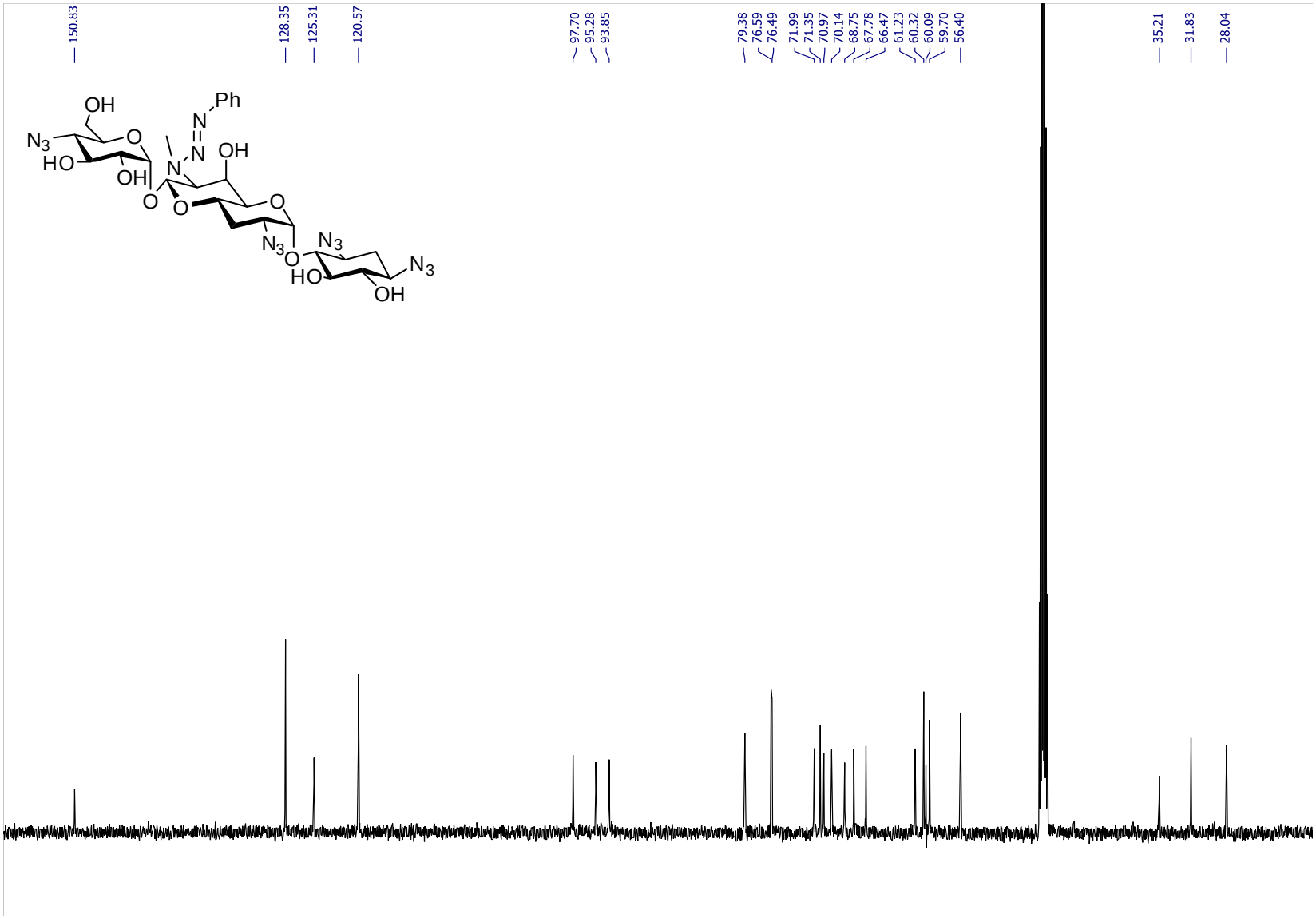
3,2’,6-Tri-deamino-3,2',6'-triazido-1,3''–di-*N*-(phenylazo)netilmicin (19) COSY (600 MHz, CD_2Cl_2)



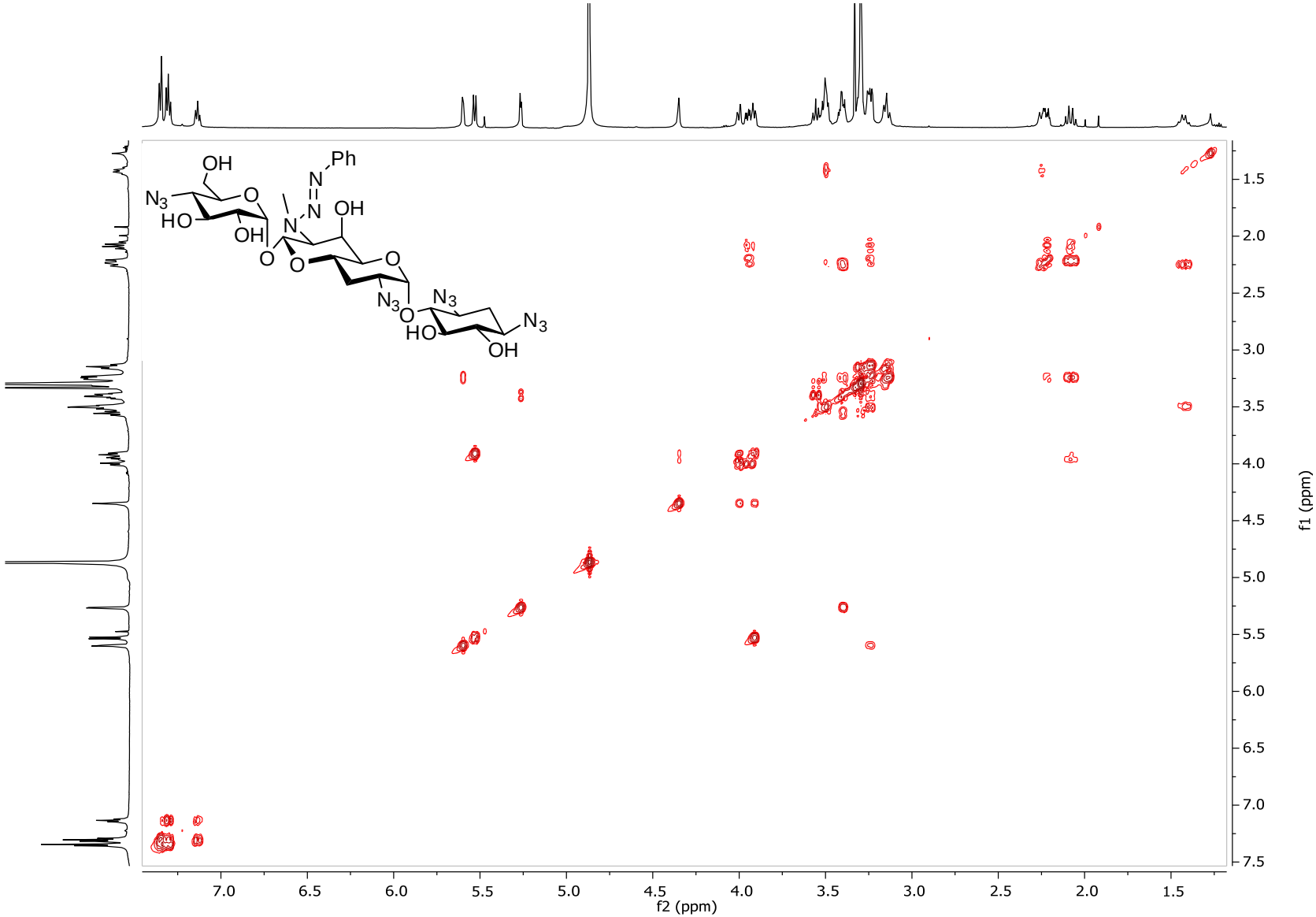
1,3,2’,4’’-Tetra-deamino-1,3,2',4''-tetraazido-7'-*N*-(phenylazo)apramycin (21) ^{1}H NMR (600 MHz, CD_3OD)



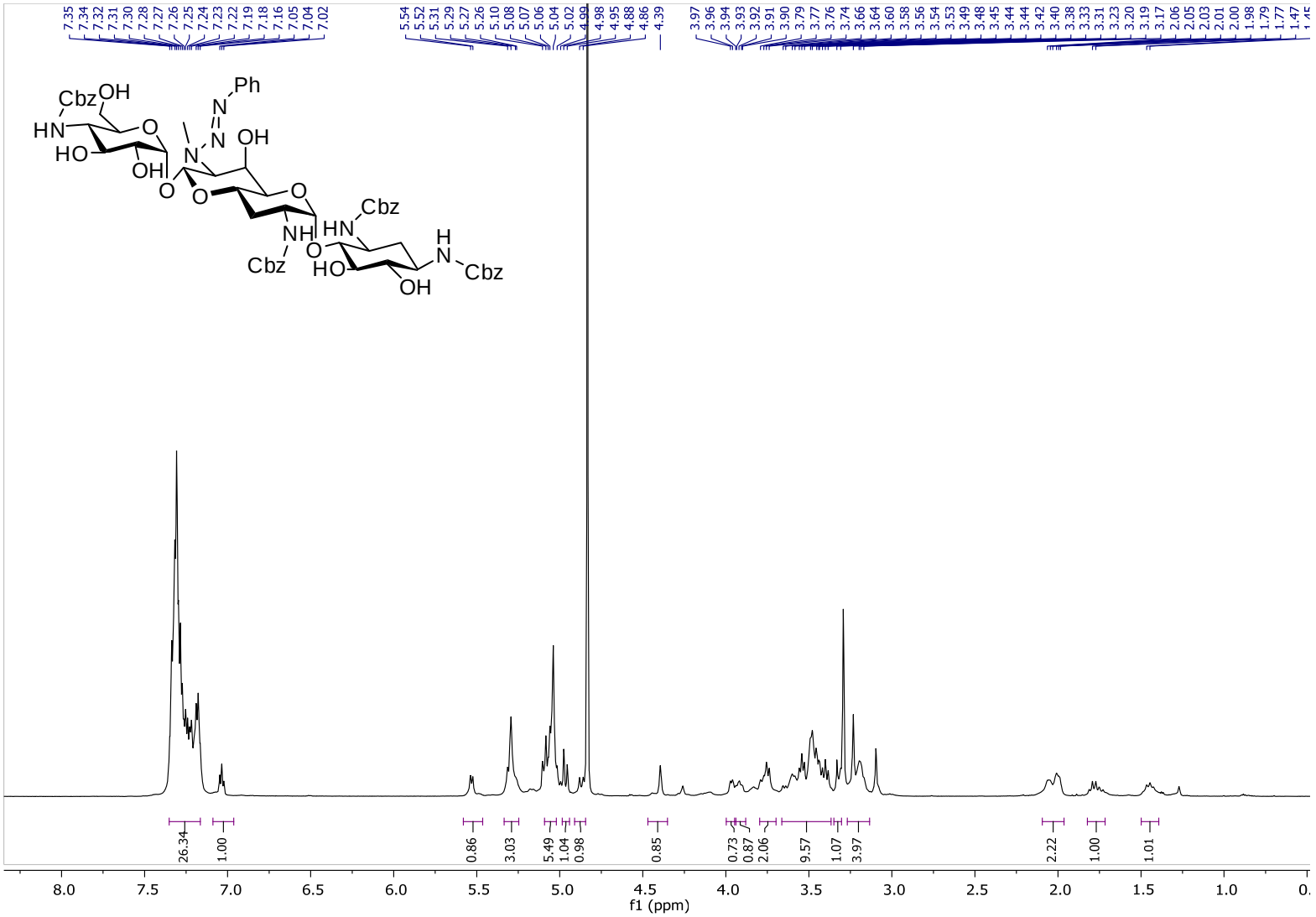
1,3,2’,4’’-Tetra-deamino-1,3,2',4''-tetraazido-7'-*N*-(phenylazo)apramycin (21) ^{13}C NMR (151 MHz, CD_3OD)



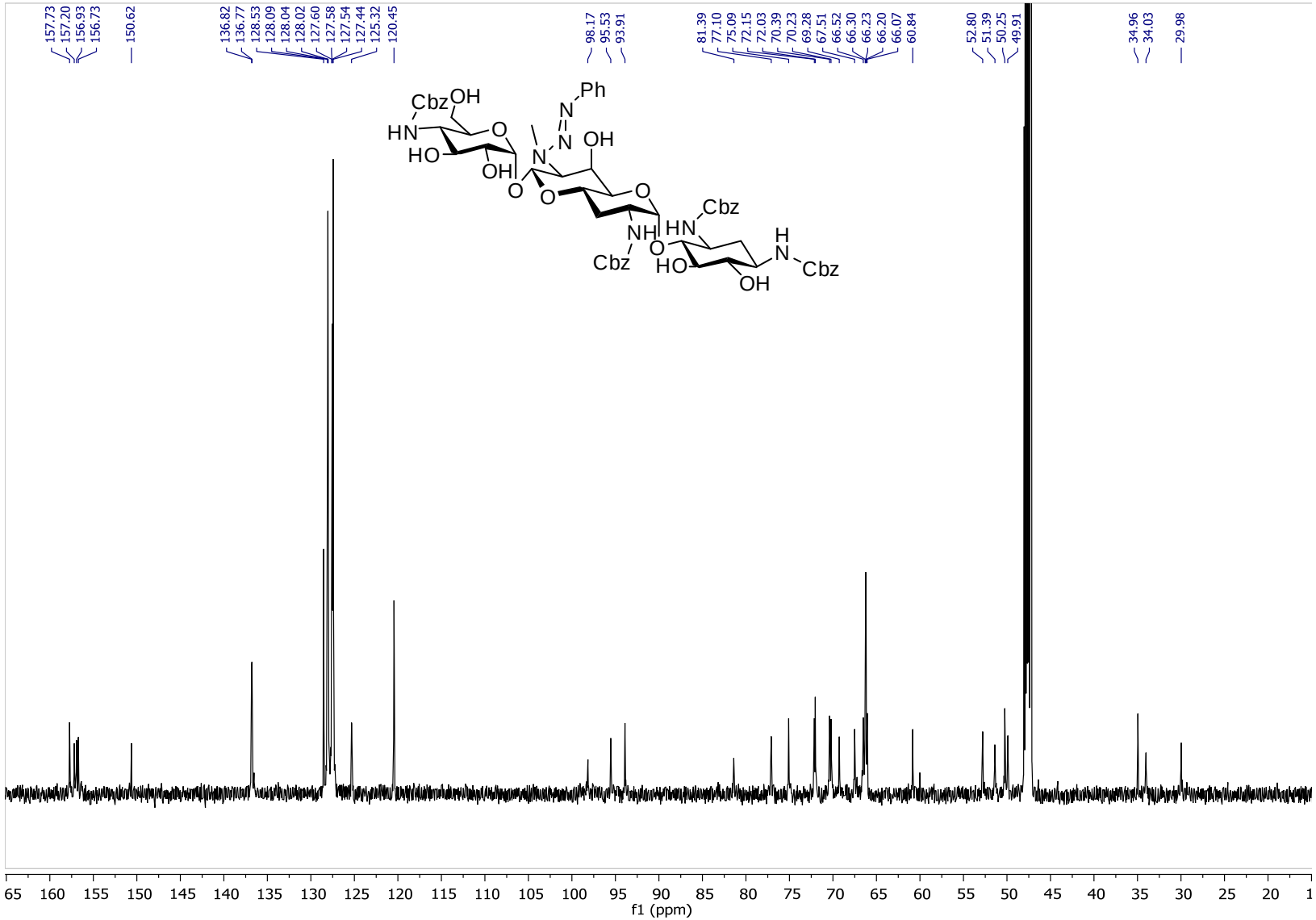
1,3,2’,4’’-Tetra-deamino-1,3,2',4''-tetraazido-7'-*N*-(phenylazo)apramycin (21) COSY (600 MHz, CD_3OD)



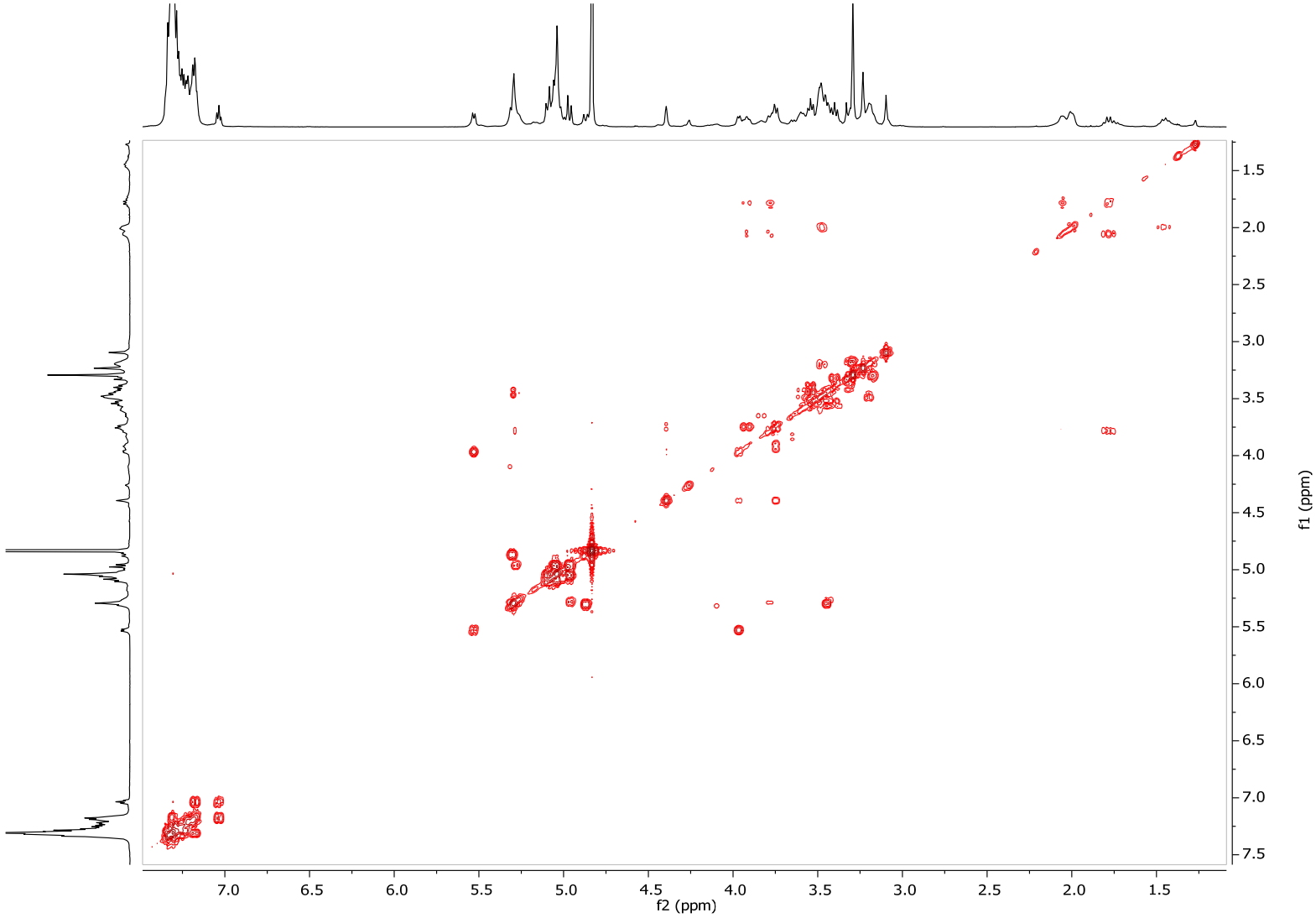
1,3,2',4''-Tetra-*N*-(benzyloxycarbonyl)-7'-*N*-(phenylazo)apramycin (22) ^{1}H NMR (600 MHz, CD_3OD)



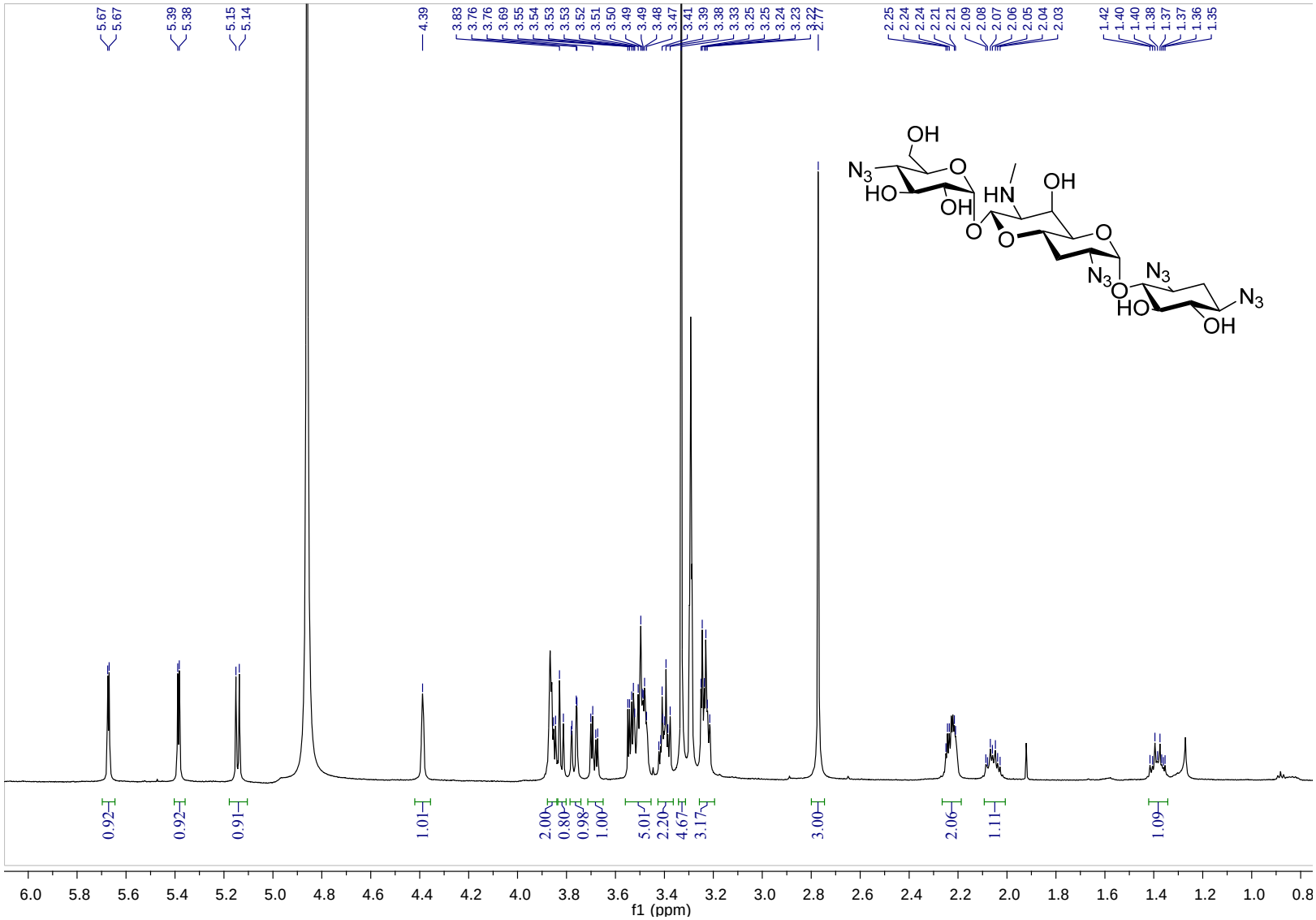
1,3,2',4''-Tetra-*N*-(benzyloxycarbonyl)-7'-*N*-(phenylazo)apramycin (22) ^{13}C NMR (151 MHz, CD_3OD)



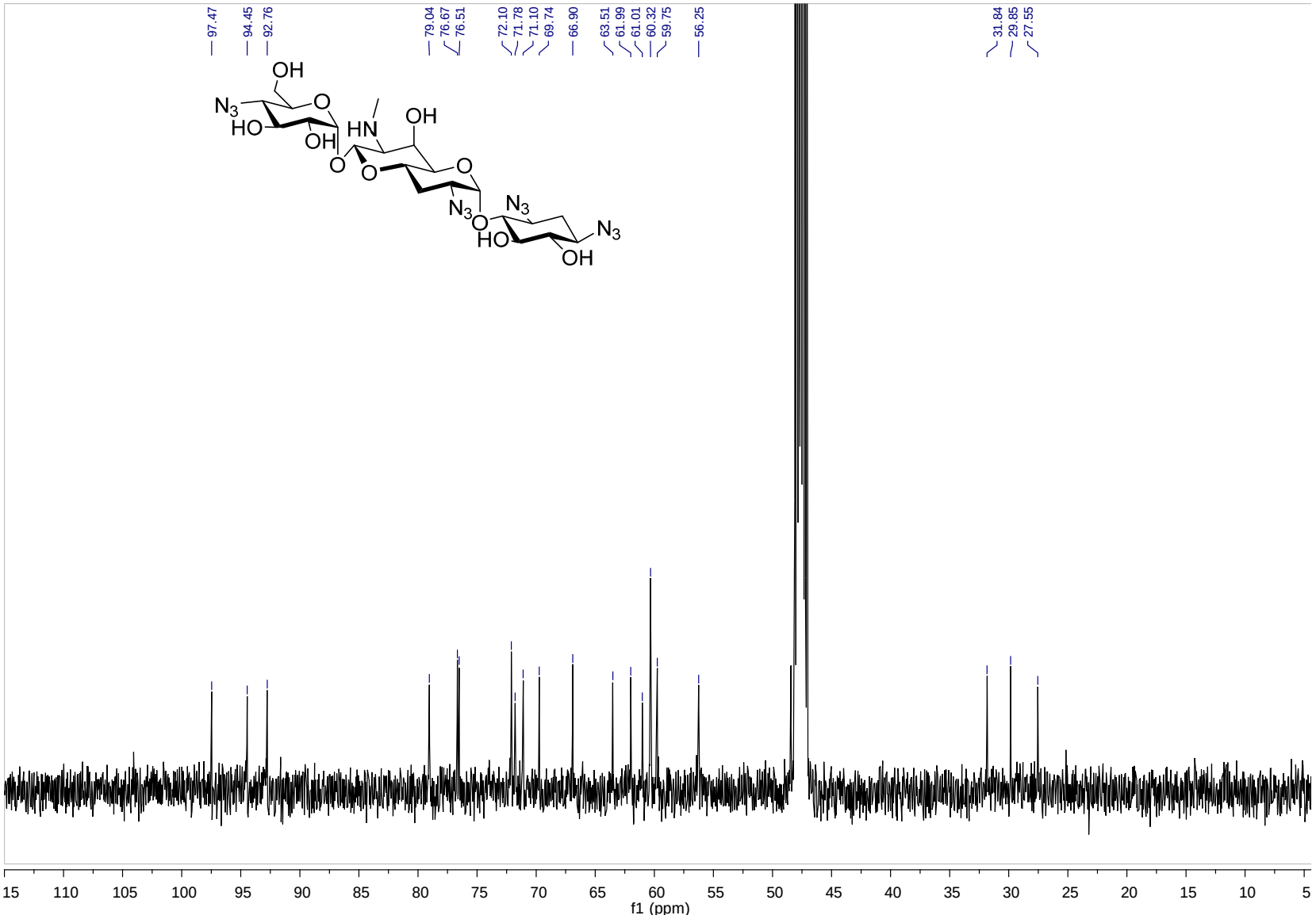
1,3,2',4''-Tetra-*N*-(benzyloxycarbonyl)-7'-*N*-(phenylazo)apramycin (22) COSY (600 MHz, CD_3OD)



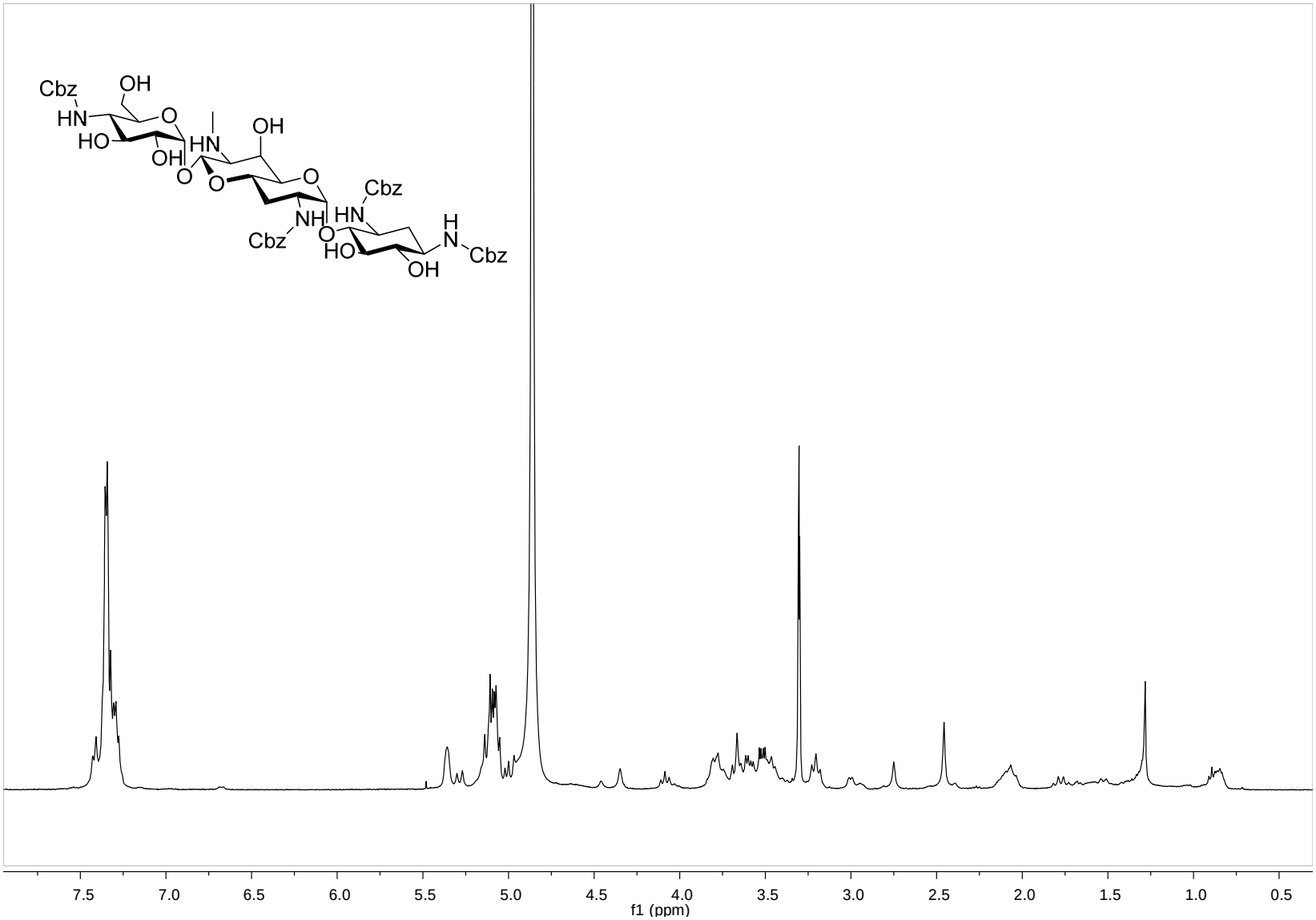
1,3,2’,4’’-Tetra-deamino-1,3,2',4''-tetraazidoapramycin (23) ^{1}H NMR (600 MHz, CD_3OD)



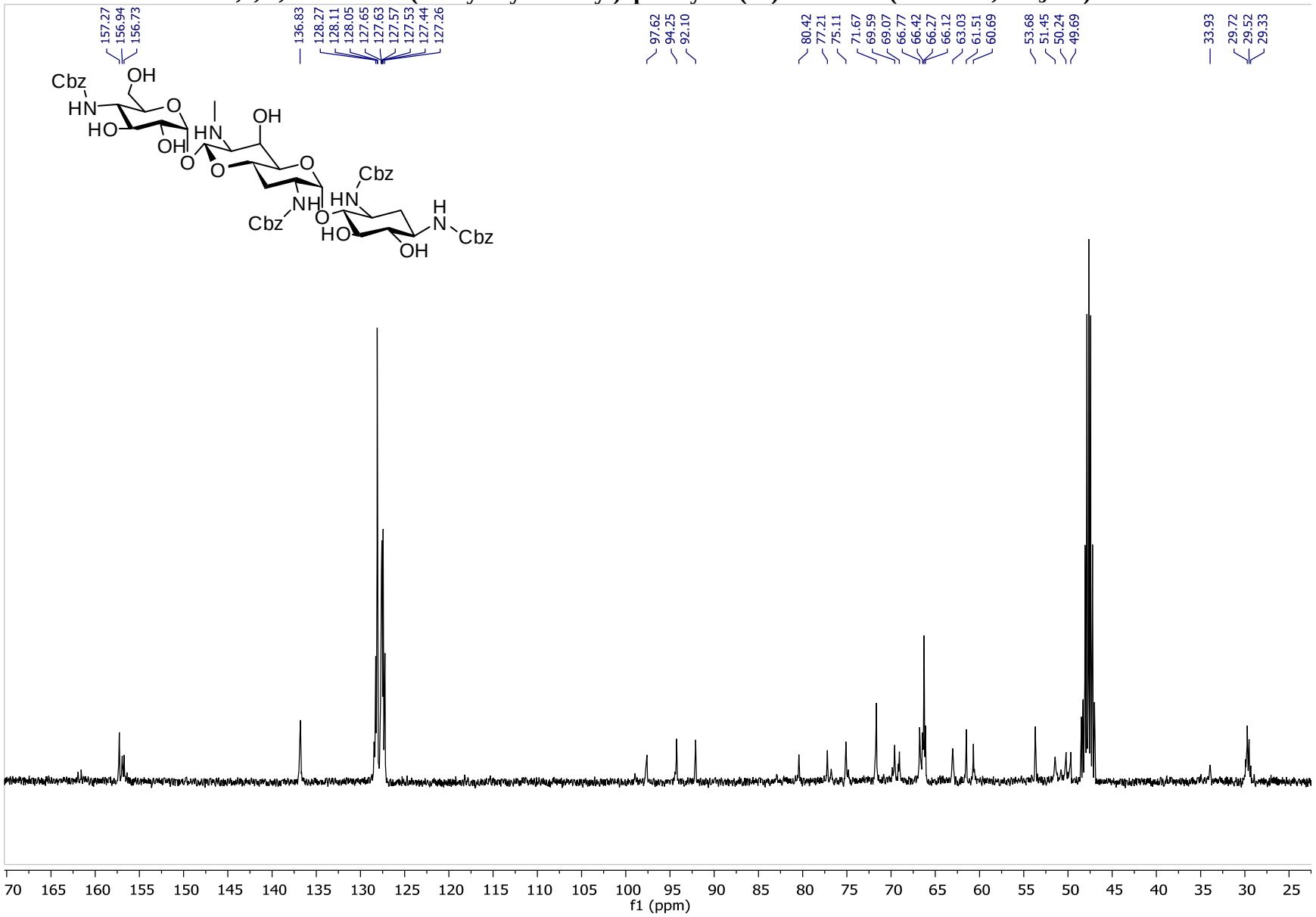
1,3,2’,4’’-Tetra-deamino-1,3,2',4''-tetraazidoapramycin (23) ^{13}C NMR (150 MHz, CD_3OD)



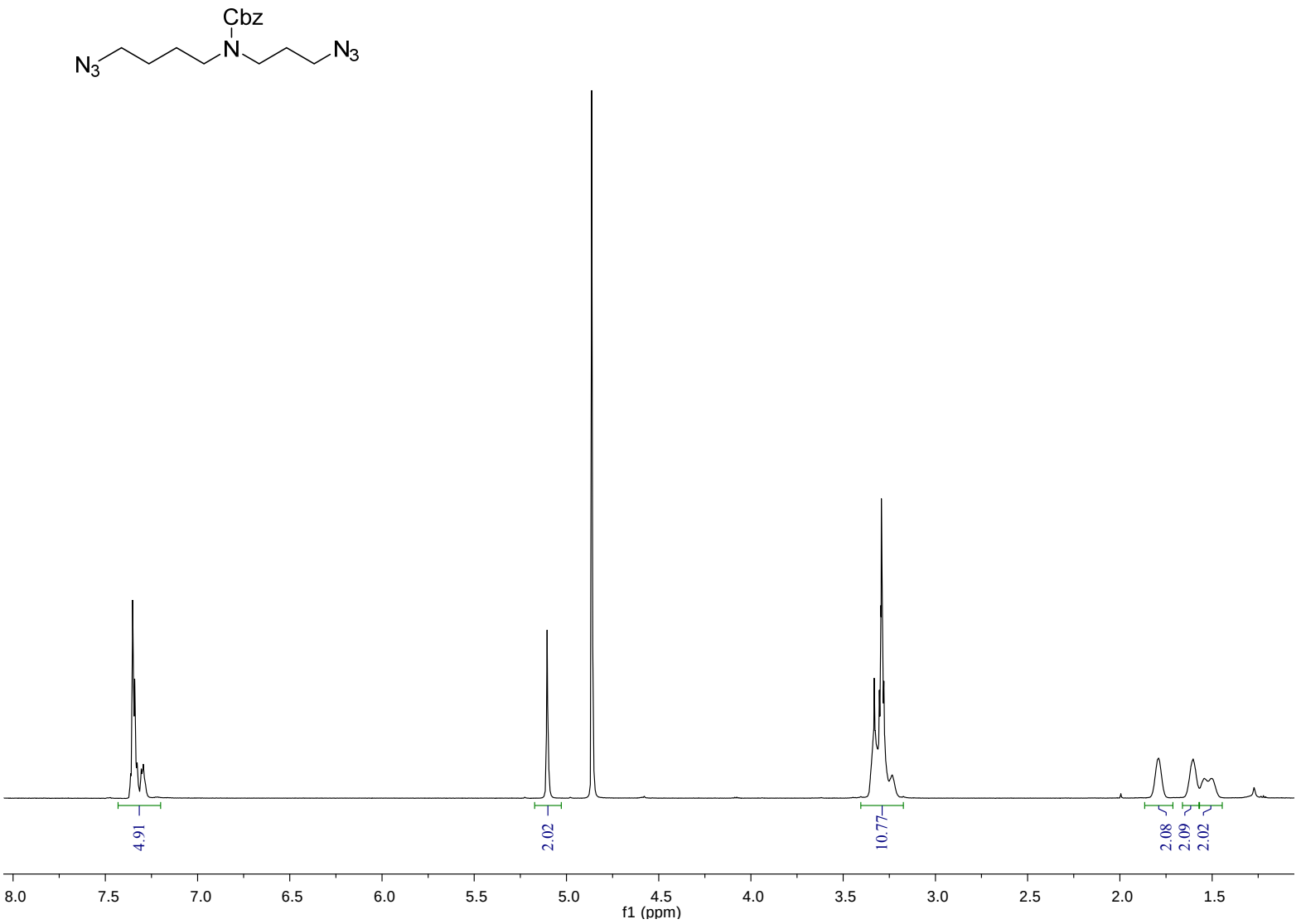
1,3,2',4''-Tetra-*N*-(benzyloxycarbonyl)apramycin (24) ^{1}H NMR (400 MHz, CD_3OD)



1,3,2',4''-Tetra-*N*-(benzyloxycarbonyl)apramycin (24) ^{13}C NMR (101 MHz, CD_3OD)



Benzyl (4-azidobutyl)(3-azidopropyl)carbamate (25) ^{1}H NMR (600 MHz, CD_3OD)



Benzyl (4-azidobutyl)(3-azidopropyl)carbamate (25) ^{13}C NMR (600 MHz, CD_3OD)