

Studies on the Synthesis of 1'-CN-Triazolyl-C-Ribosides

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Supporting Information

1. General information

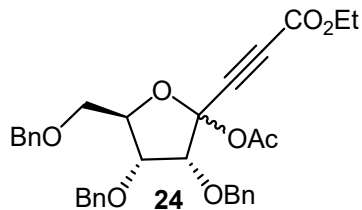
Materials: All reagents, starting materials, and solvents were purchased from commercial suppliers and used without further purification if not otherwise mentioned. Dichloromethane was purified before use by distillation under argon atmosphere. Dry THF was purchased from Aldrich. 2,3,5-Tri-*O*-benzyl-D-ribonolactone (1) was purchased from Biosynth Carbosynth. The 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribo-1,4-lactone was donated by Microbiológica Chemical & Pharmaceutical Company. Benzylazide was prepared according to the literature.¹

Methods: Flash chromatography was performed on silica gel plates (60 Å, 0.035-0.070 mm). Reactions were monitored by thin-layer chromatography on silica gel plates (60 F254 aluminum sheets) which were rendered visible by ultraviolet light and/or spraying with vanillin (15%) + sulfuric acid (2,5%) in EtOH followed by heating.

¹H NMR (400 MHz), ¹³C NMR (100.5 MHz) were recorded on a BRUKER AVANCE NEO 400 MHz spectrometer at 298 K unless otherwise stated. Chemical shifts are given in ppm (δ) and are referenced to the internal solvent signal or to TMS used as an internal standard. Multiplicities are declared as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublets), m (multiplet). Coupling constants *J* are given in Hz. HRMS were determined on a QTOF mass analyzer coupled with electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) with a resolution of 12000.

2. Procedures

Ethyl 3-(1-acetoxy-2,3,5-tri-*O*-benzyl- α/β -D-ribofuranosyl) propiolate (**24**)



An oven-dried round-bottomed flask is charged with 25mL of dry THF and 1.09 mL of ethyl propiolate (10,76 mmol). Then the flask is then cooled to -78°C and then 6.7 mL of *n*-BuLi 1.6M (10,76 mmol) is slowly added. After the addition, the reaction mixture is left stirring for 30 minutes at -78°C . After this time and still at this temperature, a solution of **19**, 3,5-tri-*O*-benzyl-D-ribonolactone (3.00 g, 7.17 mmol), in 25mL of dry THF is slowly added. After the addition, the reaction mixture is left stirring at -78°C for 3h, when 7 mL of acetic anhydride is added. The reaction mixture is slowly warmed up to room temperature and left stirring for additional 30 minutes. Then, 50 mL of a saturated solution of sodium bicarbonate is added and the mixture is vigorously stirred for 1h. The solution is added to a separating funnel and then extracted with ethyl acetate. The organic phase is then washed with brine and dried over anhydrous magnesium sulfate. The organic phase is filtered and the solvent AcOEt/CyH yielding a crude light-yellow oil in 67% yield.

NMR data

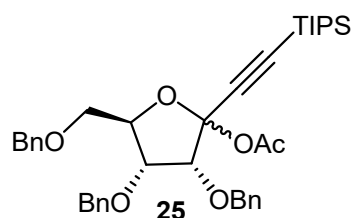
Major anomer:

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.10 (m, 15H), 4.72 (d, $J = 11.9$ Hz, 1H), 4.68 (d, $J = 11.9$ Hz, 1H), 4.62 (d, $J = 12.1$ Hz, 1H), 4.47 (d, $J = 11.9$ Hz, 2H), 4.45 (d, $J = 12.1$ Hz, 2H), 4.35 (d, $J = 11.9$ Hz, 1H), 4.25 (ddd, $J = 3.7$ Hz, 1H), 4.23 (d, $J = 5.7$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.96 (dd, $J = 5.6, 3.9$ Hz, 1H), 3.47 (dd, $J = 11.0, 3.4$ Hz, 1H), 3.39 (dd, $J = 11.0, 3.1$ Hz, 1H), 2.06 (s, 3H), 1.23 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3) δ 168.84, 152.95, 137.94, 137.80, 137.27, 128.53, 128.52, 128.50, 128.27, 128.15, 128.04, 127.99, 127.79, 96.68, 84.12, 83.34, 81.50, 76.90, 76.62, 73.82, 73.72, 72.89, 62.44, 21.72, 14.11.

HRMS (TOF ES⁺) for $(\text{M}+\text{Na})^+ \text{C}_{33}\text{H}_{34}\text{O}_8\text{Na}^+$ (m/z): 581.2144 Da; theoretical 558.2254 Da.

1-(1-acetoxy-2,3,5-tri-*O*-benzyl- α/β -D-ribofuranosyl) triisopropylsilylethyne (25)



An oven-dried round-bottomed flask is charged with 8mL of dry THF and (triisopropylsilyl)acetylene (1.07 mL, 4.78 mmol). Then the flask is then cooled to -78°C and then *n*-BuLi (1.6M, 3.40 mL, 5.02 mmol) is slowly added. After the addition, the reaction mixture is left stirring for 30 minutes at -78°C . After this time and still at this temperature, a solution of 3,5-tri-*O*-benzyl-D-ribonolactone (1.00 g, 2.39 mmol), in 8 mL of dry THF is slowly added. After the addition, the reaction mixture is left stirring at -78°C for 3h, when 2 mL of acetic anhydride is added. The reaction mixture is slowly warmed up to room temperature and left stirring for additional 30 minutes. Then, 20 mL of a saturated solution of sodium bicarbonate is added and the mixture is vigorously stirred for 1h. The solution is added to a separating funnel and then extracted with ethyl acetate. The organic phase is then washed with brine and dried over anhydrous magnesium sulphate. The organic phase is filtered and the solvent removed under reduced pressure product purified by flash column chromatography with 10% Et₂O/CyH. The product was obtained as colorless oil in 55% yield.

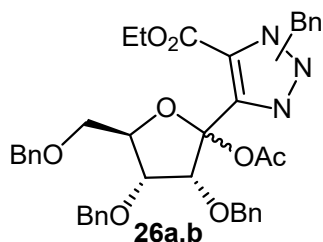
NMR data:

¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.14 (m, 15H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.24 (ddd, *J* = 3.4 Hz, 1H), 4.21 (d, *J* = 5.5 Hz, 1H), 4.01 (dd, *J* = 5.3, 4.7 Hz, 1H), 3.52 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.45 (dd, *J* = 11.2, 3.3 Hz, 1H), 2.01 (s, 3H), 0.99 (s, 24H).

¹³C NMR (101 MHz, CDCl₃) δ 168.46, 138.14, 137.93, 137.83, 128.38, 128.37, 128.35, 127.97, 127.92, 127.89, 127.81, 127.76, 127.59, 102.58, 97.40, 88.25, 84.10, 83.13, 76.83, 73.90, 73.59, 72.73, 69.21, 21.80, 18.59, 11.09.

HRMS (TOF ES⁺) for (M+Na)⁺ C₃₉H₅₀O₆SiNa⁺ (*m/z*): 665.3274 Da; theoretical 665.3274 Da.

Ethyl 1-benzyl-4-(1'-acetoxy-2',3',5'-tri-*O*-benzyl- α/β -D-ribofuranosyl)-1,2,3-triazole-5-carboxylate and Ethyl 1-benzyl-5-(1'-acetoxy-2',3',5'-tri-*O*-benzyl- α/β -D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**26a,b**)



To a round-bottomed flask, containing a solution of 54 mg of the propiolate **24** (0.10 mmol) in 1 mL of toluene was added 51 mg of benzylazide (4eq). The reaction mixture was warmed to 120°C for 4h. Then the solvent was removed and the crude product purified by column chromatography, yielding a yellowish oil as a mixture of regioisomers in 81% yield.

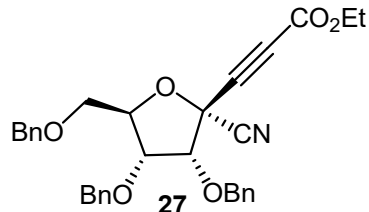
NMR data

Major 26a

¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.10 (m, 16H), 7.02 (dd, $J = 7.3, 1.8$ Hz, 2H), 6.92 (dd, $J = 9.2, 6.0$ Hz, 2H), 5.80 (d, $J = 15.6$ Hz, 1H), 5.64 (d, $J = 15.6$ Hz, 1H), 4.66 (d, $J = 11.3$ Hz, 1H), 4.63 (d, $J = 5.3$ Hz, 1H), 4.60 (d, $J = 12.3$ Hz, 1H), 4.43 (d, $J = 11.4$ Hz, 1H), 4.42 (d, $J = 12.0$ Hz, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.24 (d, $J = 12.0$ Hz, 1H), 4.19 (d, $J = 12.0$ Hz, 1H), 3.91 (t, $J = 5.6$ Hz, 1H), 3.30 (dd, $J = 10.8, 3.3$ Hz, 1H), 3.15 (dd, $J = 10.8, 3.6$ Hz, 1H), 1.60 (s, 3H), 1.35 (t, $J = 7.1$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 169.06, 161.57, 148.29, 137.65, 137.52, 137.30, 136.91, 135.92, 128.56, 128.48, 128.42, 128.38, 128.18, 128.16, 127.99, 127.62, 127.56, 127.25, 126.77, 102.00, 82.71, 81.03, 75.75, 73.99, 73.15, 72.57, 68.27, 61.73, 53.71, 20.99, 14.31.

Ethyl 3-(2,3,5-tri-O-benzyl-1-cyano- α -D-ribofuranosyl) propiolate (**27**)



To a stirring solution of 2.5 g (4,48 mmol) of the propiolate **24** and 2,25 mL (17,92 mmol) of TMSCN in 40 mL of dry dichloromethane at 0°C, 2,44 mL (13,44 mmol) of TMSOTf is slowly added. The reaction mixture is stirred at this temperature for 90 min. Then, 50 mL of a saturated solution of sodium bicarbonate is added and the mixture is vigorously stirred for 1h. The solution is then added to a separating funnel and the aqueous phase is extracted with dichloromethane. The organic phase is washed with brine and dried over anhydrous magnesium sulfate. The organic phase is then filtered and the solvent removed under reduced pressure, The product is purified by flash column chromatography with silica flash with a gradient starting from 5% EtOAc/CyH to 10% EtOAc/CyH. The desired product is obtained as colorless oil in 81% yield with a ratio of 87:13 for the desired α -cyano-riboside.

NMR data

α -Cyano (major):

^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.20 (m, 15H), 4.93 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 11.8 Hz, 2H), 4.55 (d, J = 10.1 Hz, 1H), 4.52 (d, J = 10.1 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 4.7 Hz, 1H), 4.43 – 4.38 (m, 2H), 4.30 (q, J = 7.2 Hz, 2H), 4.06 (dd, J = 4.8, 3.5 Hz, 1H), 3.57 (dd, J = 11.1, 3.1 Hz, 1H), 3.49 (dd, J = 11.1, 3.0 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 152.30, 137.69, 137.50, 136.49, 128.73, 128.59, 128.47, 128.40, 128.05, 127.96, 127.93, 127.77, 114.43, 85.09, 84.83, 79.10, 78.11, 77.36, 73.97, 73.70, 73.03, 71.30, 69.00, 62.83, 14.11.

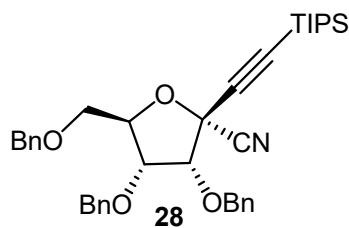
β -Cyano (minor):

NMR data ^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.06 (m, 15H), 4.84 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 4.8 Hz, 1H), 4.26 (dt, J = 5.5, 2.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 1H), 4.04 (t, J = 4.9 Hz, 1H), 3.49 (dd, J = 11.2, 2.8 Hz, 1H), 3.39 (dd, J = 11.2, 3.1 Hz, 1H), 1.21 (t, J = 7.1 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 157.99, 152.32, 137.59, 137.36, 136.42, 128.60, 128.50, 128.48, 128.38, 128.34, 128.31, 127.99, 127.87, 127.77, 115.95, 84.43, 83.80, 79.98, 77.57, 77.37, 74.03, 73.64, 73.03, 70.85, 68.60, 62.64, 14.01.

HRMS (TOF ES⁺) for $(\text{M}+\text{Na})^+$ $\text{C}_{32}\text{H}_{31}\text{NO}_6\text{Na}^+$ (m/z): 548.2046 Da; theoretical 548.2049 Da.

1-(2,3,5-tri-*O*-benzyl-1-cyano-- α -D-ribofuranosyl) triisopropylsilylethyne (**28**)



Following the general procedure for **9**, to a solution of acetate **25** (1.40 g, 2.18 mmol) and trimethylsilyl cyanide (0.82 mL, 6.53 mmol) in dichloromethane at -78°C , Boron trifluoride diethyl etherate (0.81 mL, 6.53 mmol) was slowly added. Then, a saturated solution of sodium bicarbonate is added and the mixture is vigorously stirred for 1h. The solution is then added to a separating funnel and the aqueous phase is extracted with dichloromethane. The organic phase is washed with brine and dried over anhydrous magnesium sulfate. The organic phase is then filtered and the solvent removed under reduced pressure. The product was purified by flash column chromatography with 20% $\text{Et}_2\text{O}/\text{CyH}$ and obtained in 55% yield as a single anomer.

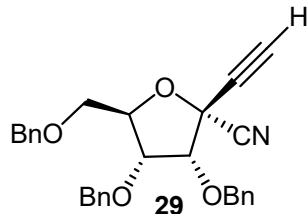
NMR data

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.10 (m, 15H), 4.94 (d, $J = 11.6$ Hz, 1H), 4.66 (d, $J = 11.2$ Hz, 1H), 4.64 (d, $J = 11.6$ Hz, 1H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.42 (d, $J = 12.0$ Hz, 1H), 4.39 (d, $J = 12.4$ Hz, 1H), 4.28 (ddd, $J = 3.4$ Hz, 1H), 4.18 (d, $J = 5.0$ Hz, 1H), 3.97 (t, $J = 4.6$ Hz, 1H), 3.49 (dd, $J = 11.2, 3.2$ Hz, 1H), 3.42 (dd, $J = 11.2, 3.5$ Hz, 1H), 1.05 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, CDCl_3) δ 137.83, 137.55, 136.87, 128.55, 128.45, 128.43, 128.15, 128.06, 127.93, 127.89, 127.73, 127.57, 115.70, 100.47, 91.05, 85.61, 83.75, 77.17, 73.86, 73.54, 72.80, 71.59, 69.08, 18.56, 11.04.

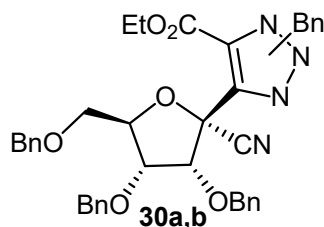
HRMS (TOF ES⁺) for $(\text{M}+\text{NH}_4)^+$ $\text{C}_{38}\text{H}_{51}\text{N}_2\text{O}_4\text{Si}^+$ (m/z): 627.3611Da; theoretical 627.3664 Da.

1-(2,3,5-tri-*O*-benzyl-1-cyano- α -D-ribofuranosyl) ethyne (**29**)



To a degassed solution of **28** (1.0 equiv., 0.05 mmol) in dry THF, triethylamine (1.5 equiv.) and TBAF (3 equiv.) were added and the reaction mixture was stirred under Ar at room temperature. After 5 minutes (consumption of the starting TIPS-protected acetylene indicated by TLC analysis) the mixture was filtered through a pad of silica and the solvent was evaporated. The crude product was used in the following reactions without purification.

Ethyl 1-benzyl-4-(2',3',5'-tri-*O*-benzyl-1'-cyano- α -D-ribofuranosyl)-1,2,3-triazole-5-carboxylate and Ethyl 1-benzyl-5-(2',3',5'-tri-*O*-benzyl-1'-cyano- α -D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**30a,b**)



Following the procedure for **26a,b**, to a round-bottomed flask containing a solution of **27** (800 mg, 1.52 mmol) in 15 mL of toluene was added 810 mg of benzylazide (4eq). The reaction mixture was warmed to 120°C and stirred at this temperature for 4h. Then the solvent was removed and the crude product purified by flash column chromatography, yielding a yellowish oil of a mixture of regioisomers in 84% yield.

NMR data

Major 30a

^1H NMR (400 MHz, CDCl_3) δ 7.36 (t, $J = 6.9$ Hz, 2H), 7.24 – 7.13 (m, 16H), 6.96 (dd, $J = 10.6, 8.7$ Hz, 2H), 6.04 (d, $J = 15.0$ Hz, 1H), 5.51 (d, $J = 15.0$ Hz, 1H), 5.01 (d, $J = 11.3$ Hz, 1H), 4.73 (d, $J = 11.0$ Hz, 1H), 4.62 (d, $J = 3.9$ Hz, 1H), 4.45-4.27 (m, 5H) 4.20 (d, $J = 11.9$ Hz, 1H), 4.17

(d, $J = 4.6$ Hz, 1H), 3.79 (dd, $J = 9.1, 4.4$ Hz, 1H), 3.75 (d, $J = 11.4$ Hz, 1H), 3.46 (d, $J = 11.5$ Hz, 1H) 1.35 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 161.02, 145.61, 137.50, 137.11, 137.03, 135.27, 135.26, 128.80, 128.65, 128.55, 128.52, 128.44, 128.36, 127.93, 127.86, 127.51, 127.40, 114.47, 83.21, 81.26, 78.57, 75.61, 74.47, 73.63, 73.44, 72.92, 62.15, 55.27, 14.35.

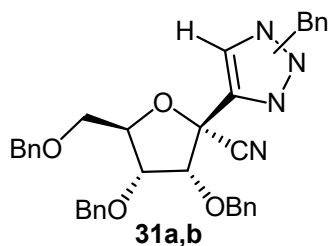
Minor 30b

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.34 (m, 2H), 7.27 – 7.15 (m, 16H), 7.01 – 6.95 (m, 2H), 5.70 (s, 2H), 5.23 (d, $J = 5.1$ Hz, 1H), 4.91 (d, $J = 11.6$ Hz, 1H), 4.77 (d, $J = 11.7$ Hz, 1H), 4.60 (d, $J = 12.0$ Hz, 1H), 4.37-4.29 (m, 4H), 4.22 (d, $J = 12.0$ Hz, 1H), 4.17 (d, $J = 12.3$ Hz, 1H), 3.93 (t, $J = 5.1$ Hz, 1H), 3.35 (dd, $J = 11.0, 3.3$ Hz, 1H), 3.27 (dd, $J = 11.0, 3.5$ Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 157.98, 145.56, 137.82, 137.74, 137.46, 134.34, 128.90, 128.68, 128.49, 128.40, 128.31, 127.97, 127.96, 127.81, 127.61, 127.36, 116.84, 83.42, 81.16, 76.92, 73.76, 73.53, 73.10, 72.73, 68.70, 62.71, 53.95, 13.84.

HRMS (TOF ES⁺) for $(\text{M}+\text{H})^+ \text{C}_{36}\text{H}_{35}\text{N}_4\text{O}_4^+$ (m/z): 659.2879 Da; Theoretical: 659, 2791 Da.

1-Benzyl-4-(2',3',5'-tri-*O*-benzyl-1'-cyano- α -D-ribofuranosyl)-1,2,3-triazole and 1-Benzyl-5-(2',3',5'-tri-*O*-benzyl-1'-cyano- α -D-ribofuranosyl)-1,2,3-triazole (31a,b)



Following the general procedure, for **26a,b** 27 mg (0.05 mmol), to a solution of **29** (0.05 mmol) in 1 mL of toluene, benzylazide was added (0.20 mmol) and stirred at reflux for 6 hours. The product was purified by flash column chromatography with 30% EtOAc/CyH. The product was obtained as viscous colorless oil in quantitative yield, in a 53:47 ratio of regioisomers.

NMR data

31a:

^1H NMR (400 MHz, CDCl_3) δ 7.54 (s, 1H), 7.28 – 6.93 (m, 20H), 5.62 (d, $J = 15.3$ Hz, 1H), 5.45 (d, $J = 15.3$ Hz, 1H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.43 (d, $J = 12.0$ Hz, 1H), 4.39 (dd, $J = 5.3, 2.5$

Hz, 1H), 4.31 (d, $J = 11.8$ Hz, 1H), 4.22 (s, 2H), 4.02 (d, $J = 5.4$ Hz, 1H), 3.99 – 3.94 (m, 1H), 3.36 – 3.27 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 137.19, 137.03, 135.93, 135.19, 133.53, 132.95, 128.68, 128.63, 128.59, 128.56, 128.54, 128.26, 128.15, 128.10, 127.99, 127.81, 127.61, 115.87, 84.93, 82.62, 75.47, 75.08, 73.72, 73.12, 72.62, 68.86, 52.79.

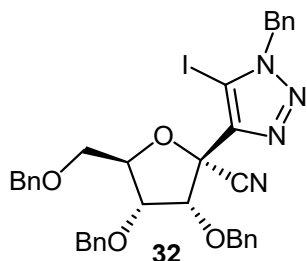
31b

^1H NMR (400 MHz, CDCl_3) δ 7.56 (s, 1H), 7.35 – 7.08 (m, 20H), 5.36 (d, $J = 14.7$ Hz, 1H), 5.26 (d, $J = 14.7$ Hz, 1H), 4.71 (d, $J = 11.8$ Hz, 1H), 4.67 (d, $J = 5.0$ Hz, 1H), 4.59 (d, $J = 12.0$ Hz, 1H), 4.57 (d, $J = 12.0$ Hz, 1H), 4.41 – 4.35 (m, 3H), 4.32 (d, $J = 11.8$ Hz, 1H), 3.98 (t, $J = 5.0$ Hz, 1H), 3.54 (dd, $J = 10.9, 3.6$ Hz, 1H), 3.44 (dd, $J = 10.9, 3.7$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 144.94, 137.80, 137.57, 137.04, 133.84, 129.26, 129.05, 128.45, 128.42, 128.29, 128.25, 128.16, 128.00, 127.86, 127.81, 127.73, 127.61, 123.69, 117.42, 83.20, 82.56, 77.02, 76.46, 73.61, 73.38, 72.51, 68.84, 54.42.

HRMS (TOF ES+) for $(\text{M}+\text{H})^+$ $\text{C}_{36}\text{H}_{35}\text{N}_4\text{O}_4^+$ (m/z): 587.2652 Da; Theoretical: 587.2581 Da.

1-Benzyl-5-iodo-4-(2',3',5'-tri-*O*-benzyl-1'-cyano- α -D-ribofuranosyl)-1,2,3-triazole (32)



To a solution of **29** (1.25 mmol, 0.25 mM) and benzyl azide (0.26 mL, 1.62 mmol, 1.3 equiv.) in dry THF (5 mL), DIPEA (0.30 mL, 1.75 mmol, 1.4 equiv.), NIS (420 mg, 1.87 mmol, 1.5 equiv.) and CuI (333 mg, 1.75 mmol, 1.4 equiv.). The reaction was stirred at room temperature for 24 h. The mixture was filtered through a pad of silica, evaporated, and the residue was purified by flash column chromatography with 10% EtOAc/CyH to give compound **32** in 55% yield.

NMR data

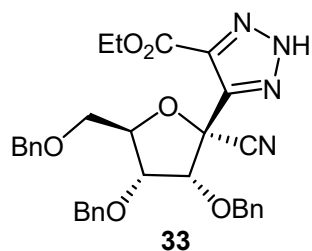
^1H NMR (400 MHz, CDCl_3) δ 7.35 – 6.97 (m, 20H), 5.47 (d, $J = 15.1$ Hz, 1H), 5.39 (d, $J = 15.2$ Hz, 1H), 5.07 (d, $J = 5.3$ Hz, 1H), 4.85 (d, $J = 11.8$ Hz, 1H), 4.72 (d, $J = 11.8$ Hz, 1H), 4.62 (d, J

= 12.0 Hz, 1H), 4.41 – 4.37 (m, 2H), 4.26 (q, $J = 12.1$ Hz, 2H), 3.96 (t, $J = 5.1$ Hz, 1H), 3.42 (dd, $J = 11.0, 3.5$ Hz, 1H), 3.33 (dd, $J = 11.0, 3.7$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 145.88, 137.83, 137.68, 137.27, 133.64, 129.03, 128.75, 128.43, 128.40, 128.35, 128.08, 127.96, 127.80, 127.63, 127.44, 116.10, 83.76, 81.03, 79.93, 77.02, 76.81, 73.60, 73.20, 72.65, 68.69, 54.40.

HRMS (TOF ES⁺) for $(\text{M}+\text{H})^+$ $\text{C}_{36}\text{H}_{34}\text{N}_4\text{O}_4^+$ (m/z): 713.1618 Da; theoretical 713.1546 Da.

Ethyl 4-(1'-cyano-2',3',5'-tri-*O*-benzyl- α -D-ribofuranosyl)-2*H*-1,2,3-triazole-5-carboxylate (**33**)



A solution of TMSN_3 (0,7 mmol) and TBAF (0,7 mmol) in 0,8 mL of toluene was stirred and heated until 110°C , when a solution of **27** (0,25 mmol) in 0,8 mL of toluene was added. After 1 h, the reaction is quenched with 2 mL of HCL 1M and stirred for 10 min. Then, 2 mL of AcOEt was added and the organic phase washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 , filtered and the crude oil obtained after concentration was purified by filtration on silica gel (40% AcOEt – Hex) furnishing the desired product in 76% yield.

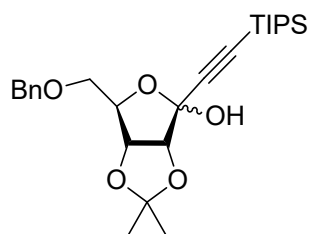
NMR data:

^1H NMR (500 MHz, CDCl_3) δ 7.46 (dd, $J = 6.5, 2.9$ Hz, 2H), 7.36 – 7.26 (m, 10H), 7.23 – 7.20 (m, 2H), 7.11 (dd, $J = 6.6, 2.9$ Hz, 2H), 5.12 (d, $J = 11.8$ Hz, 1H), 4.93 (d, $J = 11.8$ Hz, 1H), 4.58 (d, $J = 11.8$ Hz, 1H), 4.56 (d, $J = 6.3$ Hz, 1H), 4.49 (q, $J = 7.2$ Hz, 2H), 4.47 (d, $J = 10.8$ Hz, 2H), 4.25 (d, $J = 11.8$ Hz, 1H), 4.02 (d, $J = 11.8$ Hz, 1H), 3.95 (dd, $J = 10.9, 2.9$ Hz, 1H), 3.85 (dd, $J = 8.7, 4.5$ Hz, 1H), 3.58 (dd, $J = 11.0, 1.9$ Hz, 1H), 1.44 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 160.72, 140.38, 137.00, 136.30, 135.03, 114.95, 81.43, 81.22, 78.02, 75.22, 73.83, 73.62, 72.67, 67.18, 62.10, 14.39, 13.67.

HRMS (TOF ES⁺) for $(\text{M}+\text{H})^+$ $\text{C}_{32}\text{H}_{33}\text{N}_4\text{O}_6^+$ (m/z): 569.2395 Da; Theoretical $(\text{M}+\text{H})^+$ 569.2396 Da.

1-(5-*O*-Benzyl-2,3 -isopropylidene- α/β -D-ribofuranose) triisopropylsilylethyne or 1-(5-*O*-Benzyl-1-hydroxy-2,3-*O*-isopropylidene- α/β -D-ribofuranosyl) triisopropylsilylethyne (**35**)



35

An oven-dried round-bottomed flask is charged with 12mL of dry THF and (triisopropylsilyl)acetylene (2.09 mL, 9.32 mmol). Then the flask is cooled to -78°C and *n*-BuLi (1.6M, 6.11 mL, 9.78 mmol) is slowly added. After the addition, the reaction mixture is left stirring for 30 minutes at -78°C . 5-benzyloxy-2,3-*O*-isopropylidene-D-ribonolactone **34** (1.11 g, 4.66 mmol), in 12 mL of dry THF is slowly added. After the addition, the reaction mixture is left stirring at -78°C for 3h. Then, 15 mL of a saturated solution of ammonium chloride is added and the mixture is vigorously stirred for 1h. The solution is added to a separating funnel and then extracted with ethyl acetate. The organic phase is then washed with brine and dried over anhydrous magnesium sulfate. The organic phase is filtered and the solvent removed under reduced pressure product purified by flash column chromatography with 10% Et₂O/CyH. The product was obtained as colorless oil in 61% yield.

NMR data:

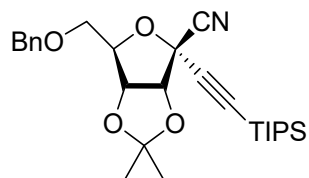
Major anomer:

¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.20 (m, 5H), 4.88 (s, 1H), 4.74 (d, *J* = 5.0 Hz, 1H), 4.59 – 4.43 (m, 3H), 4.35 (t, *J* = 2.7 Hz, 2H), 3.56 (dq, *J* = 10.2, 3.1 Hz, 2H), 1.44 (s, 3H), 1.26 (s, 3H), 0.95 – 1.11 (m, 21H).

¹³C NMR (101 MHz, CDCl₃) δ 136.25, 128.74, 128.41, 128.12, 113.00, 102.15, 101.98, 88.69, 87.37, 84.88, 82.28, 74.00, 71.00, 26.72, 25.69, 18.59, 11.14.

HRMS (TOF ES⁺) for ((M+H)+[-H₂O])⁺ C₂₆H₃₉O₄Si⁺ (*m/z*): 443.2625 Da; theoretical 443.2612 Da.

1-(5-*O*-Benzyl-1-cyano-2,3-*O*-isopropylidene- β -D-ribofuranosyl) triisopropylsilylethyne (**36**)



36

Following the general procedure for **27**, to a solution of hemiacetal **35** (225 mg, 0.488 mmol) and trimethylsilyl cyanide (0.185 mL, 1.46 mmol) in dichloromethane at -78°C, boron trifluoride diethyl etherate (0.30 mL, 0.244 mmol) was slowly added. The reaction mixture is stirred at this temperature for 2h. Then, a saturated solution of sodium bicarbonate is added and the mixture is vigorously stirred for 1h. The solution is then added to a separating funnel and the aqueous phase is extracted with dichloromethane. The organic phase is washed with brine and dried over anhydrous magnesium sulfate. The organic phase is then filtered and the solvent removed under reduced pressure. The product was purified by flash column chromatography with 5% Et₂O/CyH and obtained in 58% yield as a single anomer.

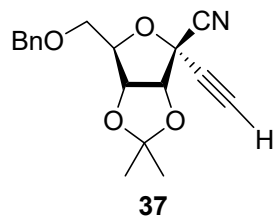
NMR data

¹H NMR (400 MHz, CDCl₃) δ 7.27 – 7.20 (m, 5H), 4.99 (d, J = 5.8 Hz, 1H), 4.81 (dd, J = 5.8, 1.0 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.45 – 4.37 (m, 2H), 3.55 (qd, J = 10.5, 4.1 Hz, 2H), 1.49 (s, 3H), 1.29 (s, 3H), 1.03 (s, 21H).

¹³C NMR (101 MHz, CDCl₃) δ 117.88, 114.74, 97.19, 94.25, 87.25, 84.77, 82.97, 73.51, 69.77, 26.40, 25.40, 18.52, 11.09, 10.99.

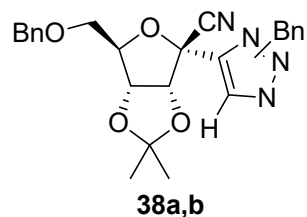
HRMS (TOF ES+) for (M+NH₄)⁺ C₂₇H₄₃N₂O₄Si⁺ (m/z): 487.3003 Da; theoretical 487.2987 Da.

1-(5-*O*-Benzyl-1-cyano-2,3-*O*-isopropylidene- β -D-ribofuranosyl) ethyne (**37**)



To a degassed solution of **36** (1.0 equiv., 0.341 mmol) in dry THF (5 mL), triethylamine (1.5 equiv.) and TBAF (3 equiv.) were added and the reaction mixture was stirred under Ar at room temperature. After 5 minutes (consumption of the starting TIPS-protected acetylene indicated by TLC analysis) the mixture was filtered through a pad of silica and the solvent was evaporated. The crude product was used in the following reactions without purification.

1-Benzyl-4-(5'-O-benzyl-1'-cyano-1'-β-D-ribofuranosyl)-1,2,3-triazole and 1-Benzyl-5-(5'-O-benzyl-1'-cyano-1'-β-D-ribofuranosyl)-1,2,3-triazole (**38a,b**)



Following the procedure for **22a,b**, to a round-bottomed flask containing a solution of **36** (130 mg, 0.415 mmol) in 1.5 mL of toluene was added 221 mg of benzylazide (4eq). The reaction mixture was warmed to 120°C and stirred at this temperature for 48h. Then the solvent was removed and the crude product purified by flash column chromatography with 20% Et₂O/CyH, yielding a yellowish oil of an inseparable mixture of regioisomers in 48% combined yield.

NMR data

Major 38a:

¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1H), 7.34 – 7.15 (m, 10H), 5.54 – 5.40 (m, 2H), 5.15 (d, *J* = 5.7 Hz, 1H), 4.89 (dd, *J* = 5.7, 1.2 Hz, 1H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.52 – 4.43 (m, 2H), 3.65 (qd, *J* = 10.4, 5.1 Hz, 2H), 1.18 (s, 3H), 1.05 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 143.41, 137.36, 134.26, 129.18, 128.92, 128.52, 128.16, 128.11, 127.96, 123.07, 118.95, 114.03, 86.63, 85.43, 83.31, 80.00, 73.58, 69.55, 54.41, 25.69, 24.79

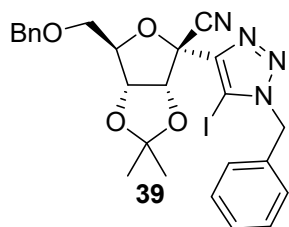
Minor 38b:

^1H NMR (400 MHz, CDCl_3) δ 7.65 (s, 5H), 7.25 – 7.09 (m, 10H), 5.46 (d, $J = 2.7$ Hz, 2H), 4.98 (d, $J = 5.5$ Hz, 1H), 4.78 (d, $J = 5.5$ Hz, 1H), 4.78 (d, $J = 5.5$ Hz, 1H), 4.46 (t, $J = 3.4$ Hz, 1H), 4.35 (d, $J = 12.1$ Hz, 1H), 3.70 – 3.60 (m, 2H), 1.05 (s, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 137.09, 134.33, 134.00, 132.59, 128.62, 128.58, 128.40, 128.36, 128.22, 117.73, 114.33, 87.18, 85.21, 83.26, 79.11, 73.60, 70.15, 53.52, 25.38, 24.63.

HRMS (TOF ES⁺) for $(\text{M}+\text{H})^+$ $\text{C}_{25}\text{H}_{27}\text{N}_4\text{O}_4^+$ (m/z): 447.2036 Da; Theoretical: 447.2027 Da.

1-Benzyl-4-(5'-*O*-benzyl-1'-cyano-1'- β -D-ribofuranosyl)-5-iodo-1,2,3-triazole (**39**)



To a solution of **37** (0.880 mmol, 0.25 mM) and benzyl azide (0.142 mL, 1.14 mmol, 1.3 equiv.) in dry THF (3.5 mL), DIPEA (0.206 mL, 1.23 mmol, 1.4 equiv.), NIS (288 mg, 1.32 mmol, 1.5 equiv.), CuI (227 mg, 1.23 mmol, 1.4 equiv.) and dimethylglycine (45.3 mg, 0.440 mmol, 0.5 equiv.). The reaction was stirred at room temperature for 24 h. The mixture was filtered through a pad of silica, evaporated, and the residue was purified by flash column chromatography with 10% EtOAc/CyH to give compound **38** in 32% yield.

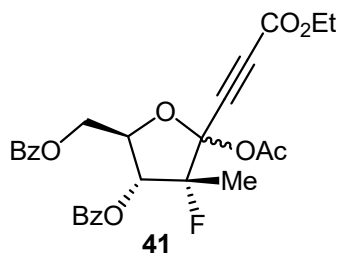
NMR data

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.13 (m, 10H), 5.66 – 5.51 (m, 2H), 5.22 (d, $J = 5.7$ Hz, 1H), 4.92 (dd, $J = 5.7, 1.2$ Hz, 1H), 4.66 (d, $J = 12.2$ Hz, 1H), 4.62 (t, $J = 4.0$ Hz, 1H), 4.48 (d, $J = 12.2$ Hz, 1H), 3.72 – 3.61 (m, 2H), 1.17 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 144.44, 137.42, 134.05, 128.85, 128.52, 128.13, 127.94, 127.70, 118.37, 114.07, 87.33, 85.55, 83.02, 77.87, 73.61, 69.84, 54.25, 25.75, 24.56.

HRMS (TOF ES⁺) for $(\text{M}+\text{H})^+$ $\text{C}_{25}\text{H}_{26}\text{IN}_4\text{O}_4^+$ (m/z): 573.1004 Da; Theoretical: 573.0993 Da.

Ethyl-3-((2*R*)-1-acetoxy-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-methyl- α/β -D-ribofuranosyl) propiolate (**41**)



Following the procedure for **24**, An oven-dried round-bottomed flask is charged with 15mL of dry THF and 1.58 g of ethyl propiolate (16.11 mmol). Then the flask is then cooled to -78°C and then 11.82 mmol of *n*-BuLi 2.5M is slowly added. After the addition, the reaction mixture is left stirring for 30 minutes at -78°C . After this time and still at this temperature, a solution of 2 g (5.37 mmol) of the Lactone **40** in 15mL of dry THF is slowly added. After the addition, the reaction mixture is left stirring at -78°C for 3h, when 10 mL of acetic anhydride is added. The reaction mixture is slowly warmed up to room temperature and left stirring for additional 30 minutes. Then, 50 mL of a saturated solution of sodium bicarbonate is added and the mixture is vigorously stirred for 1h. The solution is added to a separating funnel and then extracted with ethyl acetate. The organic phase is then washed with brine and dried over anhydrous magnesium sulfate. The organic phase is filtered and the solvent removed under reduced pressure. The product could be purified by column chromatography yielding a yellowish oil in 79% yield as a mixture of anomers.

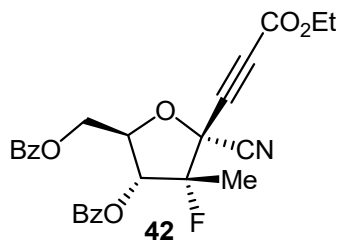
NMR data

^1H NMR (400 MHz, CDCl_3) δ 8.09 – 7.95 (m, 4H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.39 (t, $J = 7.8$ Hz, 2H), 5.52 (dd, $J_{\text{H-F}} = 12.4$, $J_{\text{H-H}} = 7.1$ Hz, 1H), 4.74 – 4.69 (m, 1H), 4.64 (dd, $J = 12.4$, 3.6 Hz, 1H), 4.55 (dd, $J = 12.5$, 4.4 Hz, 1H), 4.24 (q, $J = 7.2$ Hz 2H), 2.20 (s, 3H), 1.82 (d, $J_{\text{H-F}} = 22.5$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.66, 166.13, 165.44, 152.42, 133.95, 133.35, 130.05, 129.85, 128.69, 128.52, 99.35 (d, $J_{\text{C-F}} = 21$ Hz), 98.20 (d, $J = 169$ Hz), 80.14, 79.29, 77.36, 73.78 (d, $J_{\text{C-F}} = 16$ Hz), 62.75, 21.27, 20.40 (d, $J_{\text{C-F}} = 25$ Hz), 14.04.

HRMS (TOF ES+) for $(\text{M}+\text{Na})^+$ $\text{C}_{27}\text{H}_{25}\text{FNaO}_9^+$ (m/z): 535.1374 Da; Theoretical $(\text{M}+\text{Na})^+$ 535.1380 Da.

Ethyl-3-((2*R*)-3,5-di-*O*-benzoyl-1-cyano-2-deoxy-2-fluoro-2-methyl- α -D-ribofuranosyl) propiolate (**42**)



To a solution of compound **41** (90 mg, 0.176 mmol) in dry DCM (1 mL) under argon was added TMSCN (70 mg, 0.702 mmol). After stirring for 10 min, TMSOTf (0.117 g, 0.527 mmol) was added dropwise. The reaction mixture was stirred for 1.5 h at 50 °C. Then, saturate solution of Na_2CO_3 (2mL) was added. The solution is added to a separating funnel and then extracted with ethyl acetate. The organic phase was combined and dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude residue obtained was purified by flash column chromatography on silica gel (hexane/EtOAc 95:5 to 80:20) to afford the product as a yellow oil in 52% yield a mixture of anomers.

NMR data

Major anomer (α -CN):

^1H NMR (400 MHz, CDCl_3) δ 8.11 – 7.98 (m, 4H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.40 (m, 2H), 5.68 (dd, $J_{\text{H-F}} = 16.3$, $J_{\text{H-H}} = 7.8$ Hz, 1H), 4.77 (td, $J = 7.3$, 3.6 Hz, 1H), 4.72 (dd, $J = 12.6$, 3.3 Hz, 1H), 4.49 (dd, $J = 12.6$, 4.1 Hz, 1H), 4.24 (q, $J = 7.1$, 2H), 1.81 (d, $J_{\text{H-F}} = 22.0$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H).

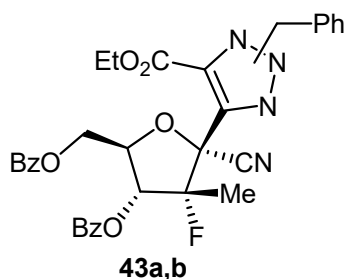
^{13}C NMR (101 MHz, CDCl_3) δ 165.90, 165.21, 151.45, 134.19, 133.36, 130.15, 129.87, 129.76, 129.19, 128.73, 128.50, 111.91 (d, $J_{\text{C-F}} = 5$ Hz), 100.50 (d, $J = 206.3$ Hz), 81.24, 79.82 (d, $J_{\text{C-F}}$

= 1.9 Hz), , 74.75 (d, $J = 5.5$ Hz), δ 74.60 (d, $J_{C-F} = 14.7$ Hz),, 73,19 (d $C-F$, $J = 15.5$ Hz), 63.17, 62.16, 18.53 (d, $J_{C-F} = 24.2$ Hz), 13.89.

^{19}F NMR (376 MHz, CDCl_3) δ -158.79 (s).

HRMS (TOF ES+) for $(\text{M}+\text{Na})^+ \text{C}_{26}\text{H}_{22}\text{FNNO}_7^+$ (m/z): 502.1271 Da; calculated $(\text{M}+\text{Na})^+$ 502.1278 Da.

Ethyl-1-benzyl-4-((2*R*)-3,5-di-*O*-benzoyl-1-cyano-2-deoxy-2-fluoro-2-methyl- α -D-ribofuranosyl)-1,2,3-triazole-5-carboxylate and Ethyl 1-benzyl-5-((2*R*)-3,5-di-*O*-benzoyl-1-cyano-2-deoxy-2-fluoro-2-methyl- α -D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**43 a,b**)



To a solution of compound **42** (0.050g, 0.104 mmol) in toluene (1.5 mL) was added benzyl azide (0.106 g, 0.796 mmol). The mixture was stirred at reflux overnight. After evaporation of the solvent, the crude product was purified by flash column chromatography to give the product 18 as a mixture of regioisomers in quantitative yield.

NMR data:

43a

^1H NMR (500 MHz, CDCl_3) δ 8.13 – 8.10 (m, 2H), 7.97 – 7.92 (m, 2H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.56 – 7.50 (m, 2H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.38 (t, $J = 7.8$ Hz, 2H), 7.34 – 7.29 (m, 2H), 7.21 (dd, $J = 6.5, 2.9$ Hz, 2H), 5.96 (dd, $J_{H-F} = 18.0, J_{H-H} = 8.2$ Hz, 1H), 5.74 (d, $J = 14.5$ Hz, 1H), 5.67 (d, $J = 14.5$ Hz, 1H), 4.86 (dt, $J = 7.9, 4.0$ Hz, 1H), 4.74 (dd, $J = 12.3, 3.6$ Hz, 1H), 4.53 (dd, $J = 12.4, 5.1$ Hz, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 1.65 (d, $J_{H-F} = 22.9$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H).

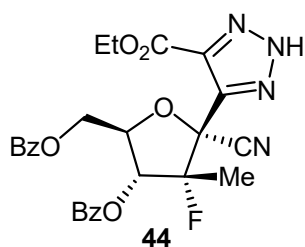
^{13}C NMR (500 MHz, CDCl_3) δ 165.90, 165.35, 157.66, 142.92, 133.91, 133.20, 130.10, 129.77, 128.96, 128.84, 128.77, 127.64, 128.36, 127.93, 114.61 (d, $J_{C-F} = 4\text{Hz}$), 101.13 (d, $J_{C-F} = 200.7$

Hz), 79.08, 74.12 (d, $J_{C-F} = 15.4$ Hz), 64.37, 63.12, 62.74, 54.11, 18.59 (d, $J_{C-F} = 24.5$ Hz), 13.69.

^{19}F NMR (376 MHz, CDCl_3) δ -150.82 (s).

HRMS (TOF ES+) for $(\text{M}+\text{Na})^+$ $\text{C}_{33}\text{H}_{29}\text{FN}_4\text{NaO}_7^+$ (m/z): 635.1913 Da; calculated $(\text{M}+\text{Na})^+$ 635.1912 Da.

Ethyl-5-((2*R*)-3,5-di-*O*-benzoyl-1-cyano-2-deoxy-2-fluoro-2-methyl- α -D-ribofuranosyl)-2*H*-1,2,3-triazole-4-carboxylate (**44**)



A solution of TMSN_3 (0,63 mmol) and TBAF (0,63 mmol) in 0,7 mL of toluene was stirred and heated until 110°C , when a solution of **42** (0,2 mmol) in 0,7 mL of toluene was added. After 1 h, the reaction is quenched with 2 mL of HCL 1M and stirred for 10 min. Then, 2 mL of AcOEt was added and the organic phase washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 , filtered and the crude oil obtained after concentration was purified by filtration on silica gel (40% AcOEt – Hex) furnishing the desired product in 73% yield.

NMR data:

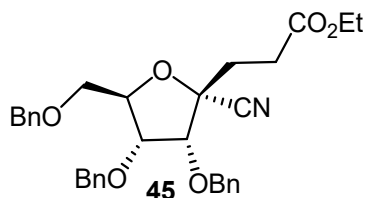
^1H NMR (400 MHz, CDCl_3) δ 8.15 – 7.91 (m, 1H), 7.66 – 7.33 (m, 2H), 5.80 (dd, $J_{H-F} = 15.2$, $J_{H-H} = 8.0$ Hz, 1H), 4.95 – 4.88 (m, 1H), 4.83 – 4.69 (m, 1H), 4.50 – 4.42 (m, 1H), 1.51 (d, $J_{H-F} = 22.8$ Hz, 1H), 1.42 (t, $J = 7.1$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 166.65, 165.70, 159.80, 134.21, 133.60, 130.30, 130.07, 129.89, 129.22, 128.83, 128.57, 128.40, 114.18(d, $J_{C-F} = 6.2$ Hz), 100.22 (d, $J_{C-F} = 204.9$ Hz), 81.13(d, $J_{C-F} = 20.2$ Hz), 79.20, 74.36 (d, $J_{C-F} = 15.8$ Hz), 63.18, 62.82, 19.16 (d, $J_{C-F} = 25$ Hz), 14.18.

^{19}F NMR (376 MHz, CDCl_3) δ -150.75 (s).

HRMS (TOF ES+) for $(\text{M}+\text{H})^+$ $\text{C}_{26}\text{H}_{24}\text{FN}_4\text{O}_7^+$ (m/z): 523.1624 Da; Theoretical $(\text{M}+\text{H})^+$ 523.1625 Da.

Ethyl 3-(2,3,5-tri-*O*-benzyl-1-cyano-- α -D-ribofuranosyl) propanoate (45)



To a solution of the 1'-cyano riboside, **27** (50mg) in ethyl acetate (2mL) was added a small portion of Pd/C 10%, put under a Hydrogen atmosphere (balloon), and left stirring overnight at room temperature. The reaction mixture was then filtered through a small pad of Celite, the solvent removed under pressure, yielding a light-yellow oil in 94% yield.

NMR data:

Major anomer

^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.06 (m, 15H), 4.61 (d, $J = 12.0$ Hz, 1H), 4.54 (d, $J = 12.1$ Hz, 1H), 4.49 (s, $J = 11.9$ Hz, 2H), 4.49 – 4.44 (m, 1H), 4.41 (d, $J = 12.0$ Hz, 1H), 4.34 (d, $J = 12.0$ Hz, 1H), 4.26 (dd, $J = 6.0, 3.2$ Hz, 1H), 4.03 (q, $J = 7.1$ Hz, 2H), 3.86 (dd, $J = 5.3, 2.7$ Hz, 1H), 3.71 (d, $J = 5.3$ Hz, 1H), 3.36 (dd, $J = 10.7, 3.5$ Hz, 1H), 3.32 (dd, $J = 10.7, 3.3$ Hz, 1H), 2.48 (ddd, $J = 13.9, 10.4, 5.8$ Hz, 2H), 2.17 (ddd, $J = 14.2, 10.3, 5.8$ Hz, 1H), 1.93 (ddd, $J = 14.2, 10.4, 5.7$ Hz, 1H), 1.16 (t, $J = 7.1$ Hz, 3H).

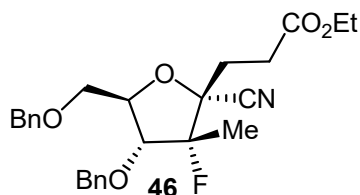
^{13}C NMR (101 MHz, CDCl_3) δ 172.38, 137.66, 137.58, 136.90, 128.59, 128.56, 128.54, 128.52, 128.46, 128.18, 128.09, 128.04, 128.00, 127.94, 127.89, 127.86, 127.77, 127.70, 118.24, 83.76, 82.15, 79.79, 77.42, 77.11, 76.79, 76.52, 69.60, 60.71, 33.04, 29.03, 14.22.

Minor

^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.10 (m, 16H), 7.02 (dd, $J = 7.3, 1.8$ Hz, 2H), 6.92 (dd, $J = 9.2, 6.0$ Hz, 2H), 5.80 (d, $J = 15.6$ Hz, 1H), 5.64 (d, $J = 15.6$ Hz, 1H), 4.66 (d, $J = 11.3$ Hz, 1H), 4.63 (d, $J = 5.3$ Hz, 1H), 4.60 (d, $J = 12.3$ Hz, 1H), 4.43 (d, $J = 11.4$ Hz, 1H), 4.42 (d, $J = 12.0$ Hz, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.33 (m, 1H), 4.24 (d, $J = 12.0$ Hz, 1H), 4.19 (d, $J = 12.0$ Hz, 1H), 3.91 (t, $J = 5.6$ Hz, 1H), 3.30 (dd, $J = 10.8, 3.3$ Hz, 1H), 3.15 (dd, $J = 10.8, 3.6$ Hz, 1H), 1.60 (s, 3H), 1.35 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.52, 137.81, 137.37, 136.94, 128.59, 128.56, 128.54, 128.52, 128.46, 128.18, 128.09, 128.04, 128.00, 127.96, 127.89, 127.86, 127.77, 127.55, 119.79, 82.26, 81.97, 81.81, 79.41, 75.07, 73.58, 72.99, 72.41, 69.52, 29.31, 29.21, 14.33.

Ethyl-3-((2*R*)-3,5-di-*O*-benzyl-1-cyano-2-deoxy-2-fluoro-2-methyl- α -D-ribofuranosyl)propanoate (**46**)



To a solution of the 1'-Cyano riboside **44** (59 mg) in ethyl acetate (2mL) was added a small portion of Pd/C 10%, put under a Hydrogen atmosphere (balloon), and left stirring overnight at room temperature. The reaction mixture was then filtered through a small pad of Celite, the solvent removed under pressure, yielding a light-yellow oil in 36% yield.

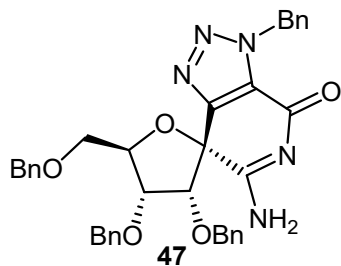
NMR data:

^1H NMR (500 MHz, CDCl_3) δ 8.11 (d, $J = 7.3$ Hz, 2H), 7.99 (d, $J = 7.2$ Hz, 2H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.42 (t, $J = 7.8$ Hz, 2H), 5.47 (dd, $J_{H-F} = 12.2$, $J_{H-H} = 7.1$ Hz, 1H), 4.74 – 4.66 (m, 2H), 4.47 (dd, $J = 12.2$, 3.8 Hz, 1H), 4.11 (tdd, $J = 10.8$, 7.2, 3.7 Hz, 2H), 2.77 – 2.65 (m, 2H), 2.23 – 2.03 (m, 2H), 1.63 (d, $J_{H-F} = 22.6$ Hz, 3H), 1.24 (t, $J = 7.4$ Hz, 3H).

^{19}F NMR (376 MHz, CDCl_3) δ -155.91 (s).

HRMS (TOF ES+) for $(\text{M}+\text{H})^+$ $\text{C}_{26}\text{H}_{27}\text{FNO}_7^+$ (m/z): 484.1766 Da; calculated $(\text{M}+\text{H})^+$ 484.1772 Da.

Spiro[(2',3',5'-tri-*O*-benzyl-1-deoxy- α -D-ribofuranose)-1,7-(6-amino-3-benzyl-3,7-dihydro-4*H*-[1,2,3]triazolo[4,5-*c*]pyridine-4-one)] (**47**)



In a sealed tube 60 mg (0.09mmol) of the regioisomeric mixture of compounds **31a,b** was dissolved in 2mL a saturated solution of ammonia in methanol. The tube was heated to 50°C and left overnight. The solvent was then evaporated and the residue purified by semi-preparative HPLC yielding 38% of a white solid.

NMR data:

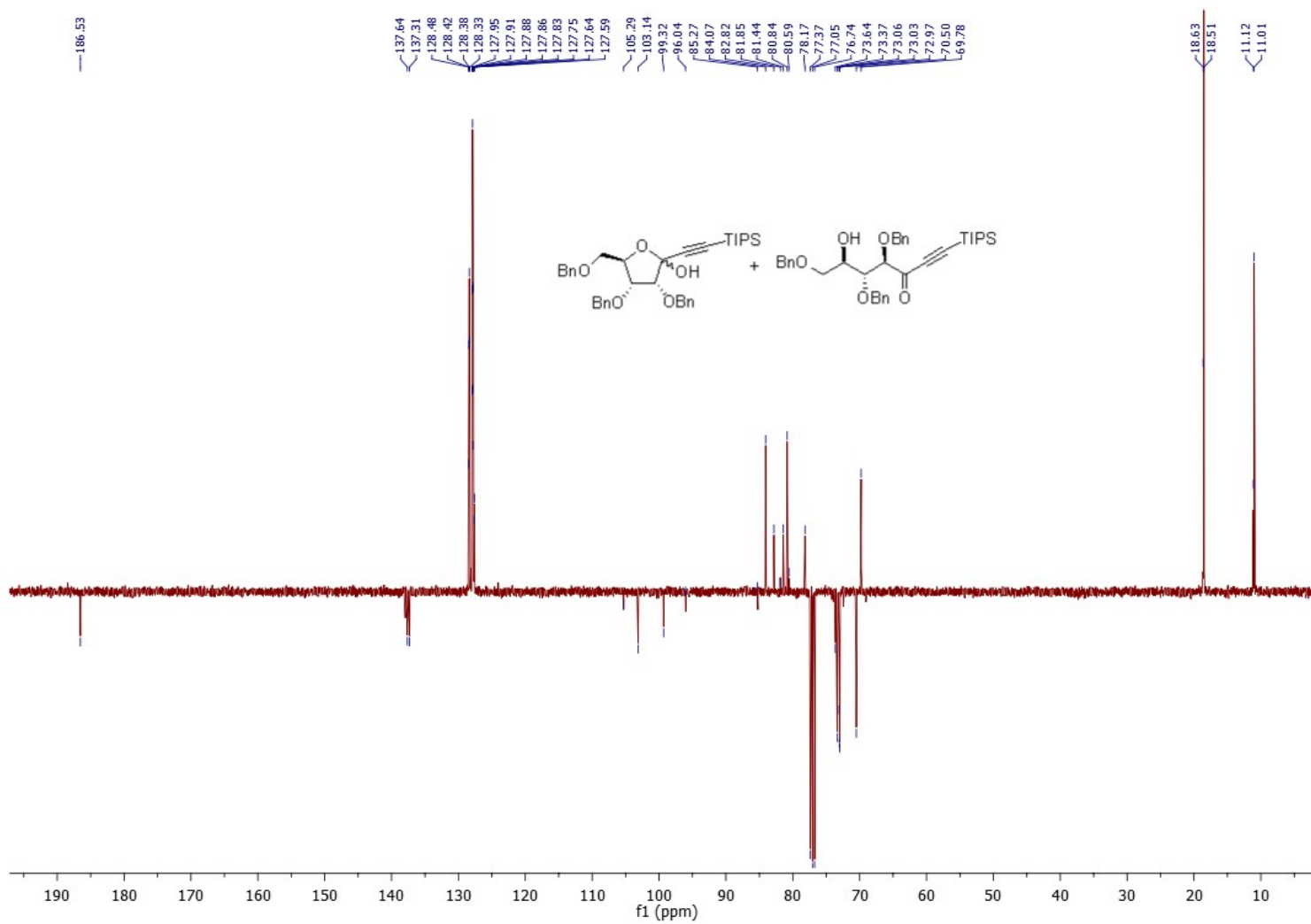
¹H NMR (500 MHz, CDCl₃) δ 8.20 (s, 1H), 7.51 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.42 – 7.10 (m, 27H), 7.07 (d, *J* = 6.6 Hz, 2H), 5.92 (d, *J* = 14.0 Hz, 1H), 5.91 (d, *J* = 14.1 Hz, 1H), 5.81 (d, *J* = 14.1 Hz, 1H), 4.68 (dt, *J* = 6.4, 3.2 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.56 (d, *J* = 4.8 Hz, 1H), 4.45 (dd, *J* = 4.8, 3.2 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.33 (d, *J* = 11.8 Hz, 1H), 3.85 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.81 (dd, *J* = 10.3, 6.6 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 171.57, 161.56, 149.62, 137.87, 136.56, 136.30, 135.24, 134.80, 128.93, 128.81, 128.63, 128.44, 128.34, 128.191, 128.12, 127.86, 127.89, 127.77, 125.03, 124.85, 85.10, 83.63, 79.35, 78.91, 73.67, 73.54, 73.09, 70.31, 52.99.

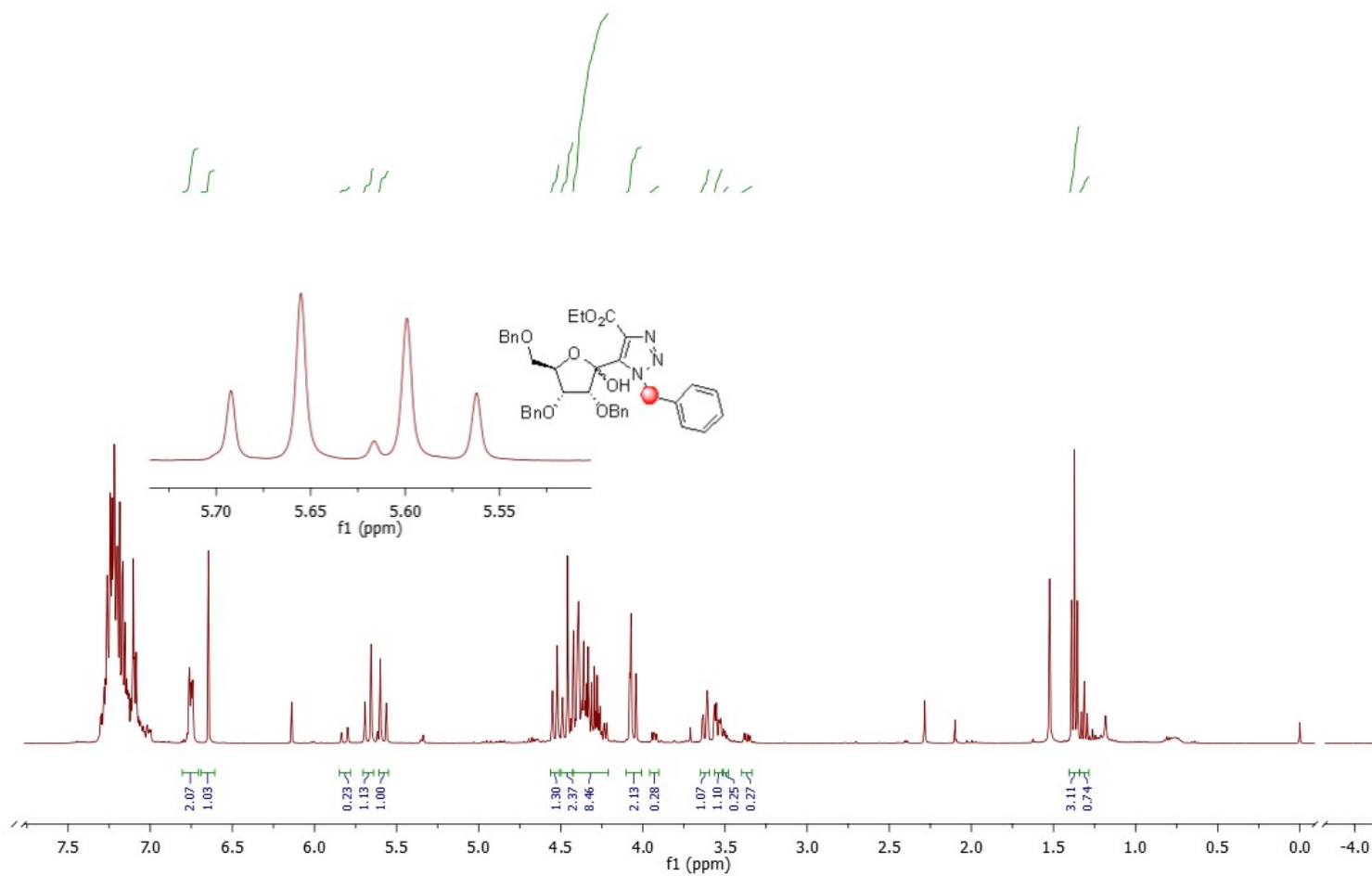
HRMS (TOF ES⁺) for (M+H)⁺ C₃₇H₃₆N₅O₅⁺ (*m/z*): 630.2717 Da; calculated (M+H)⁺ 630.2717 Da.

Spectroscopical data

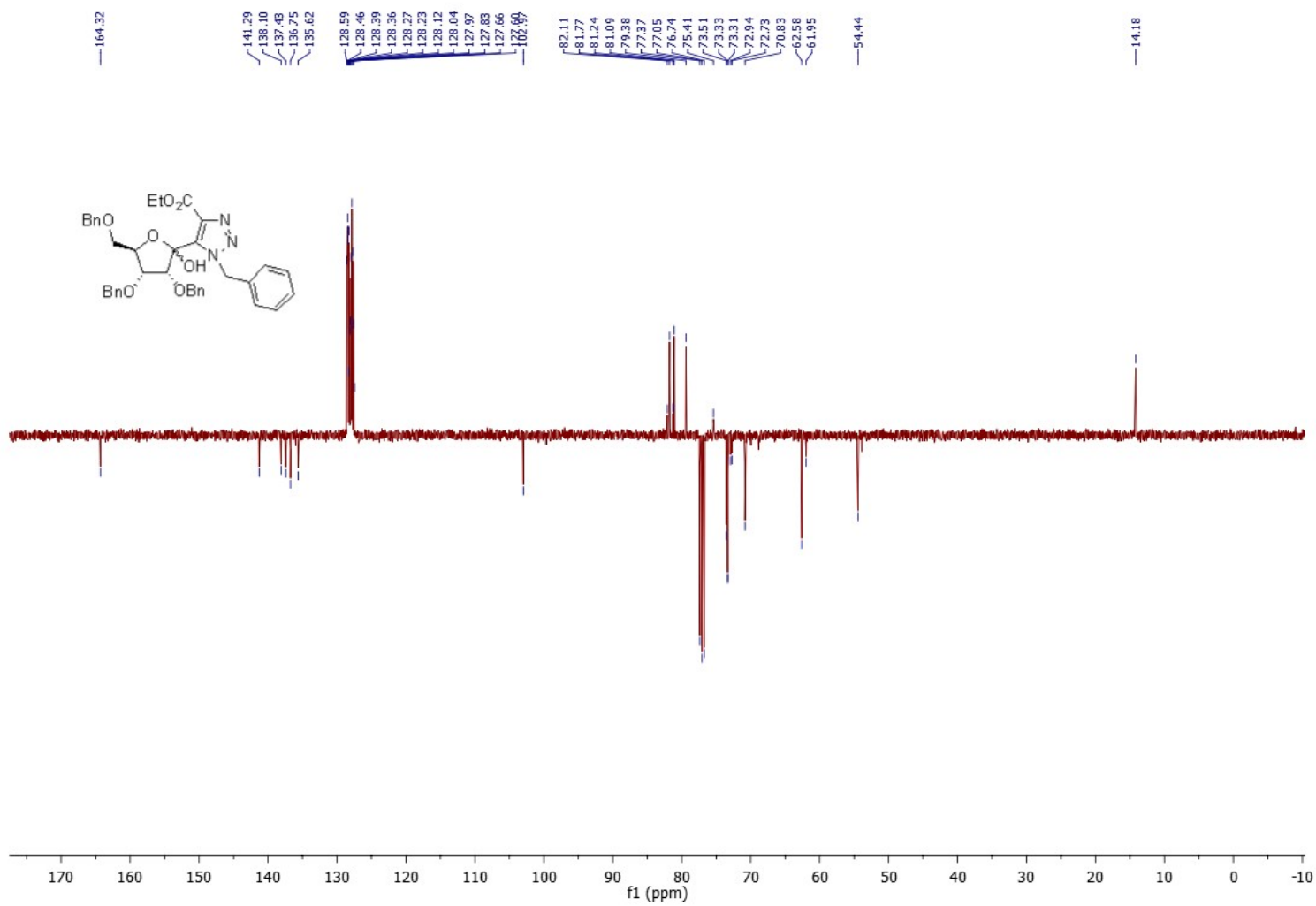
¹³C NMR Spectra for **21**:



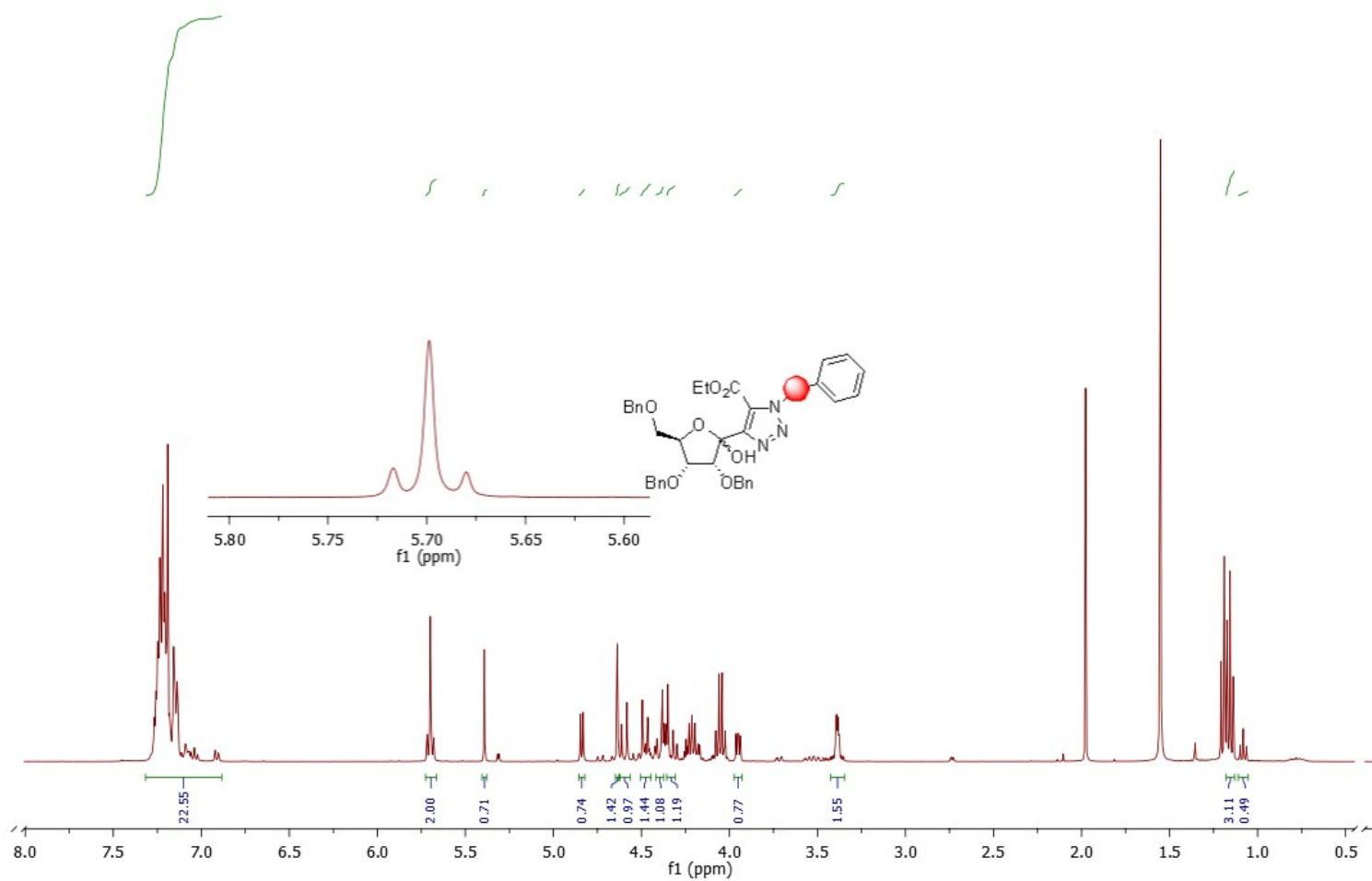
¹H NMR Spectra for **22a**



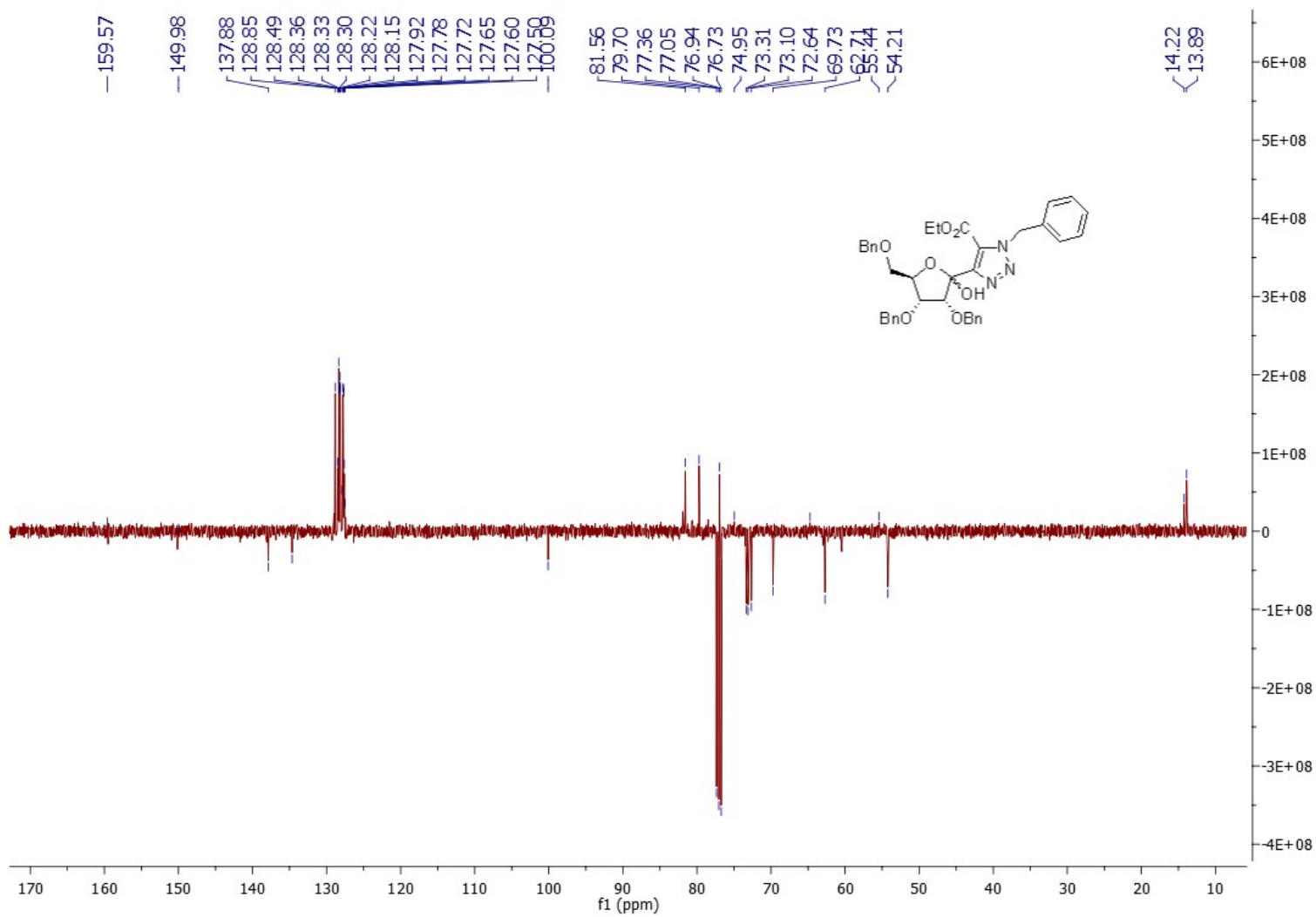
¹³C NMR Spectra for **22a**:



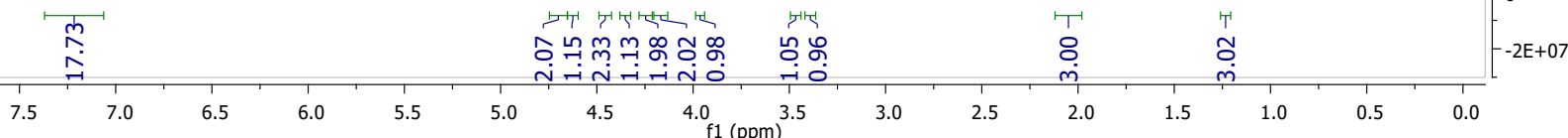
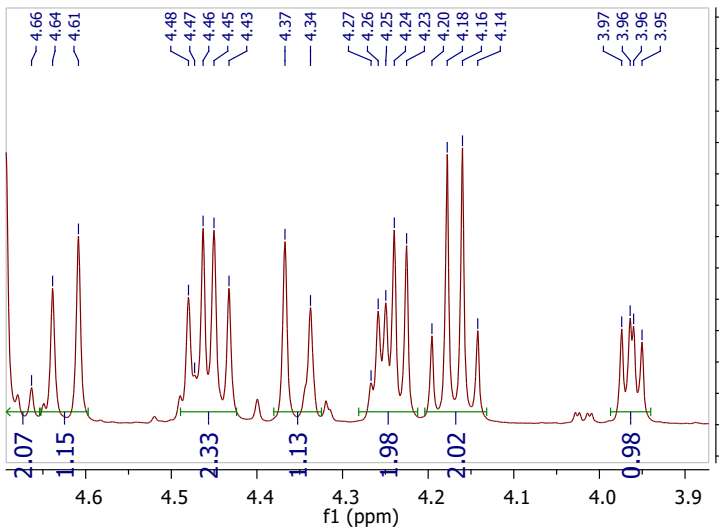
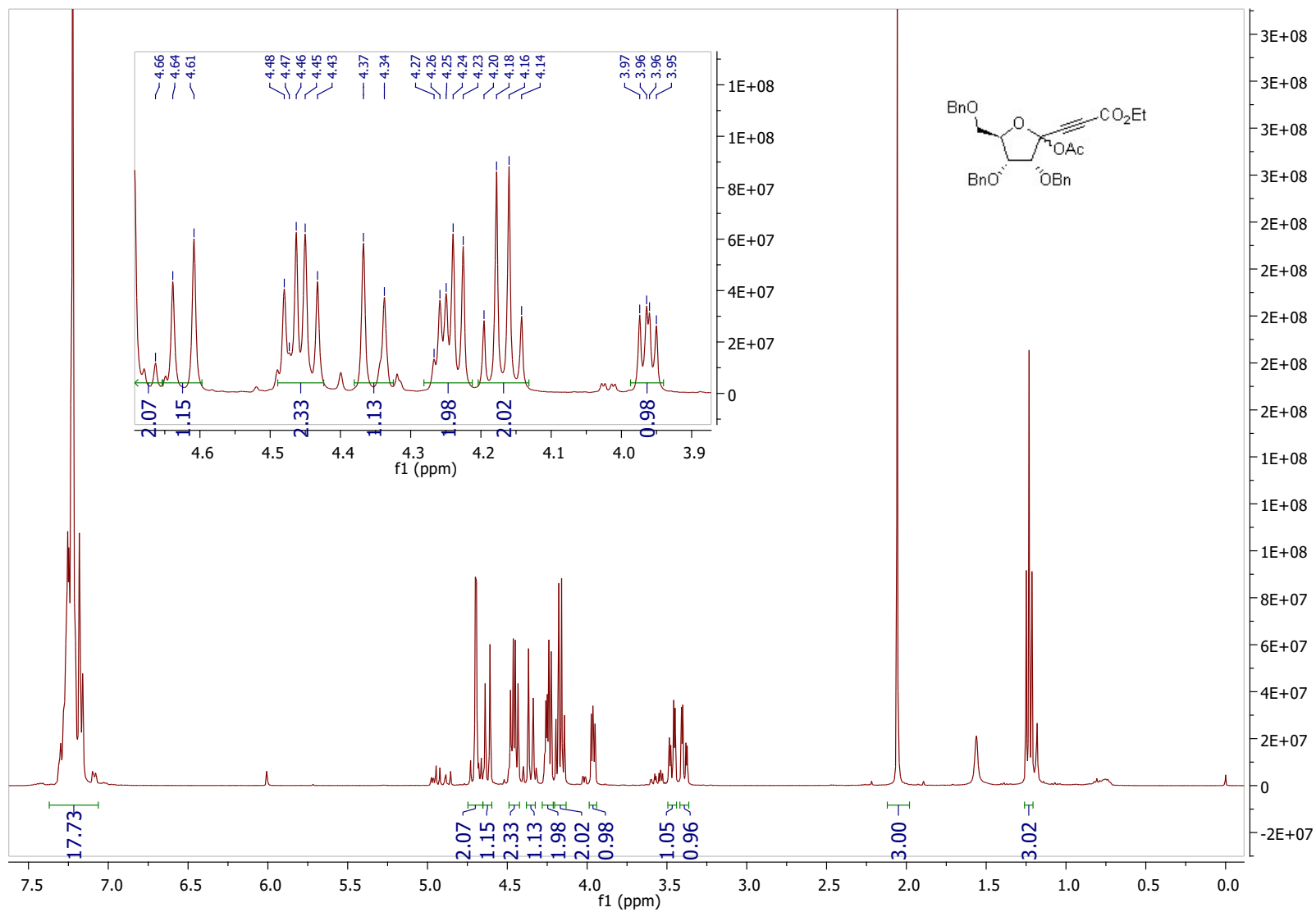
¹H NMR Spectra for **22b**:



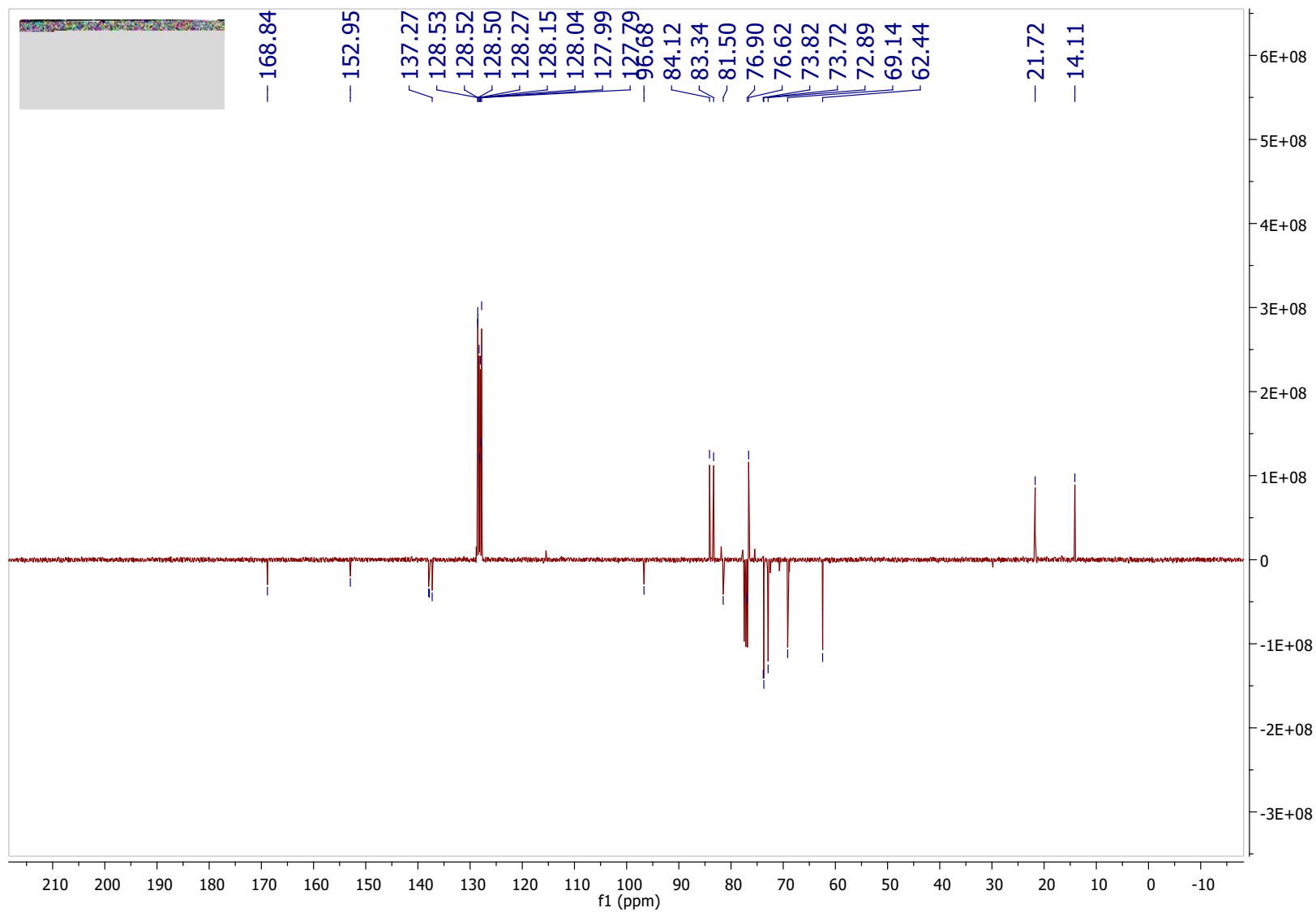
^{13}C NMR Spectra for **22b**:



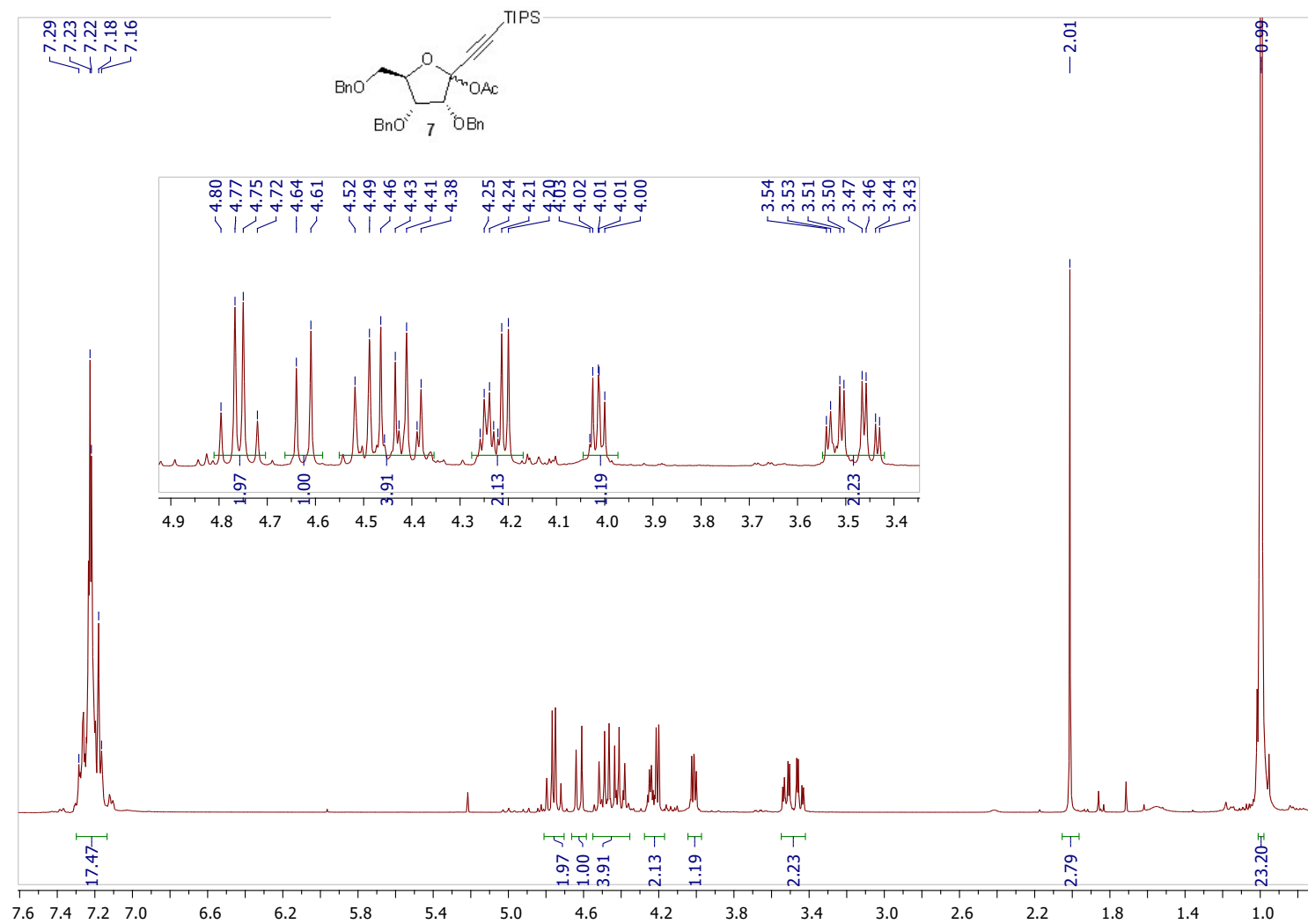
¹H NMR Spectra for **24**:



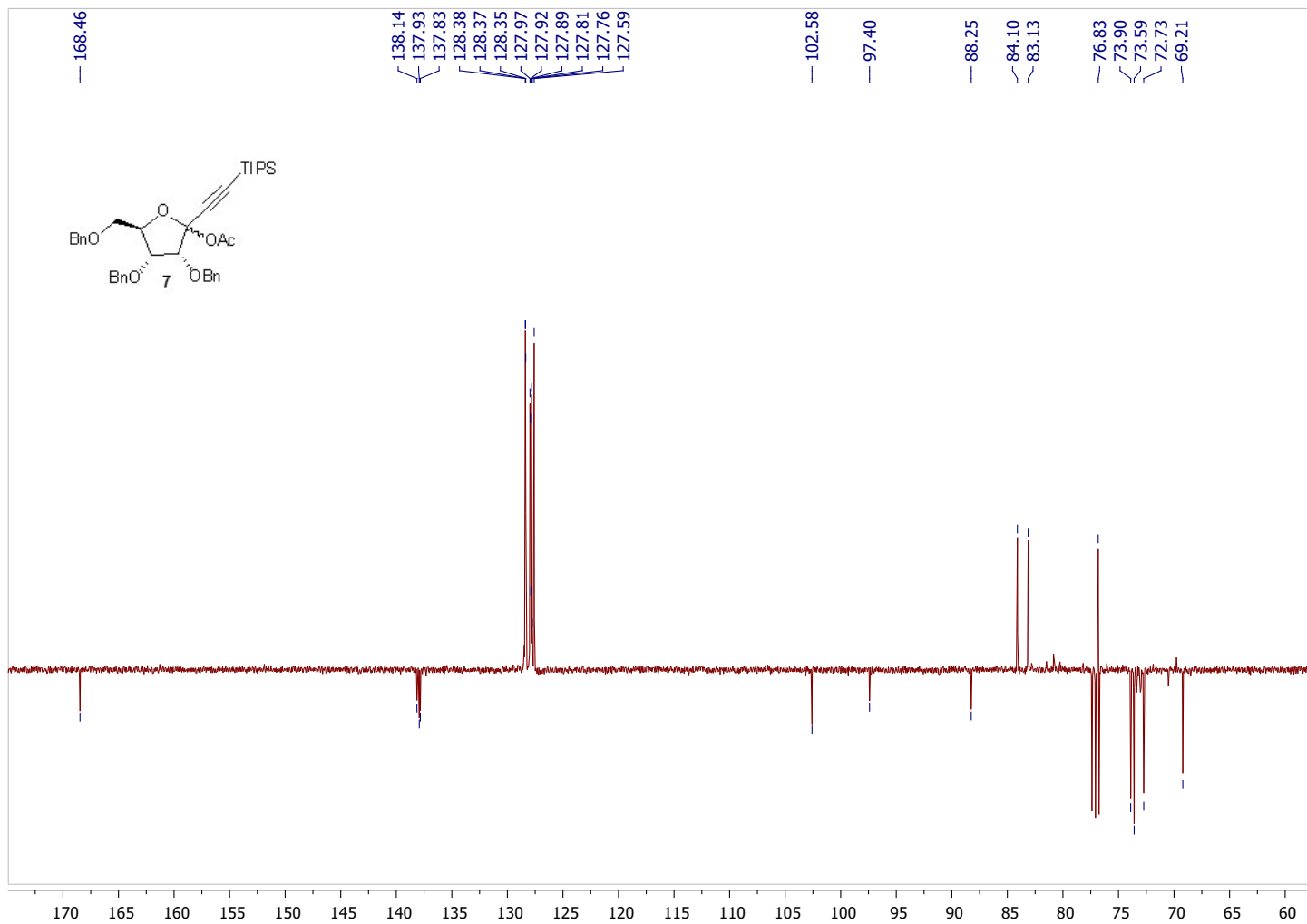
¹³C NMR Spectra for **24**:



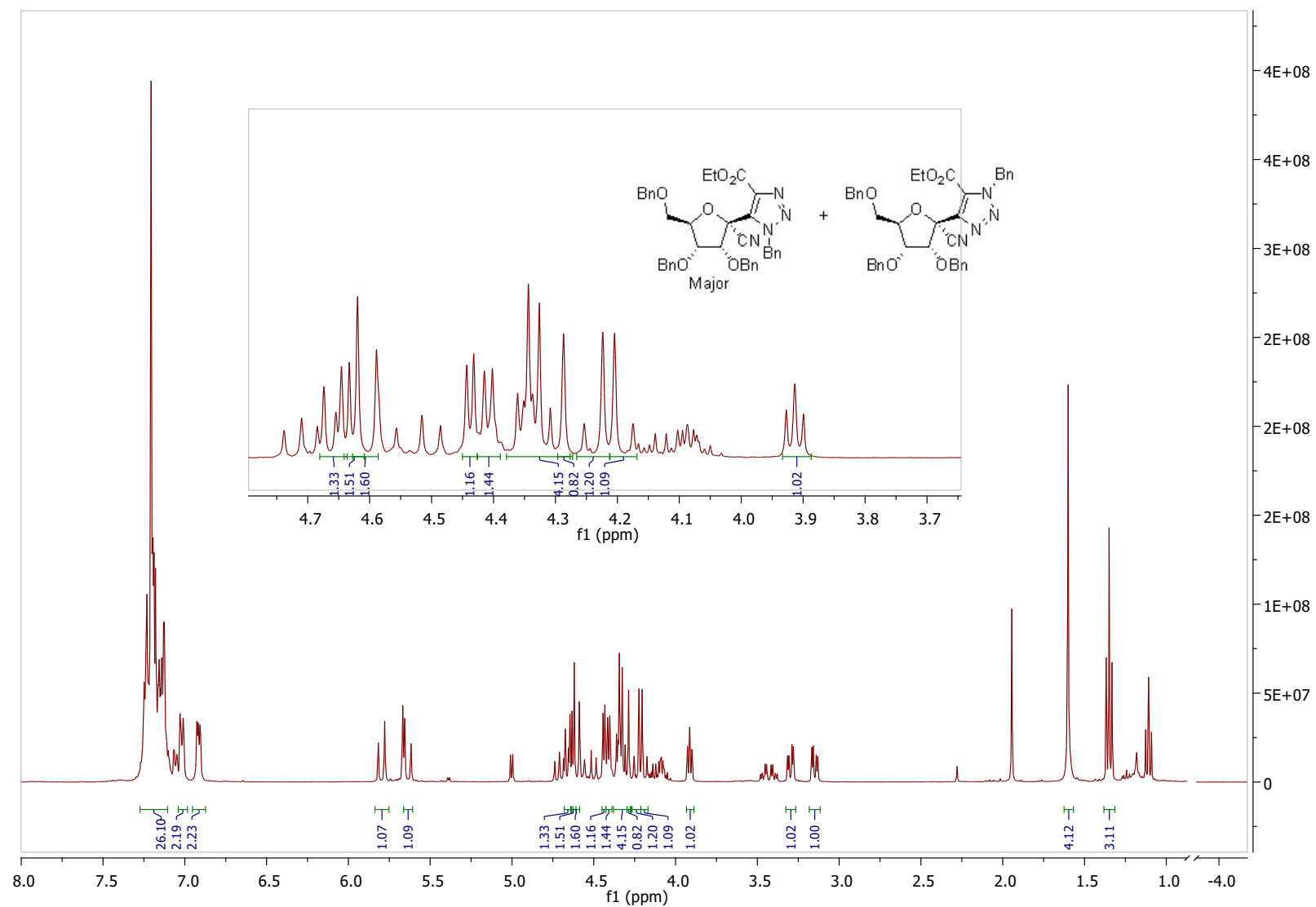
¹H NMR Spectra for **25**:



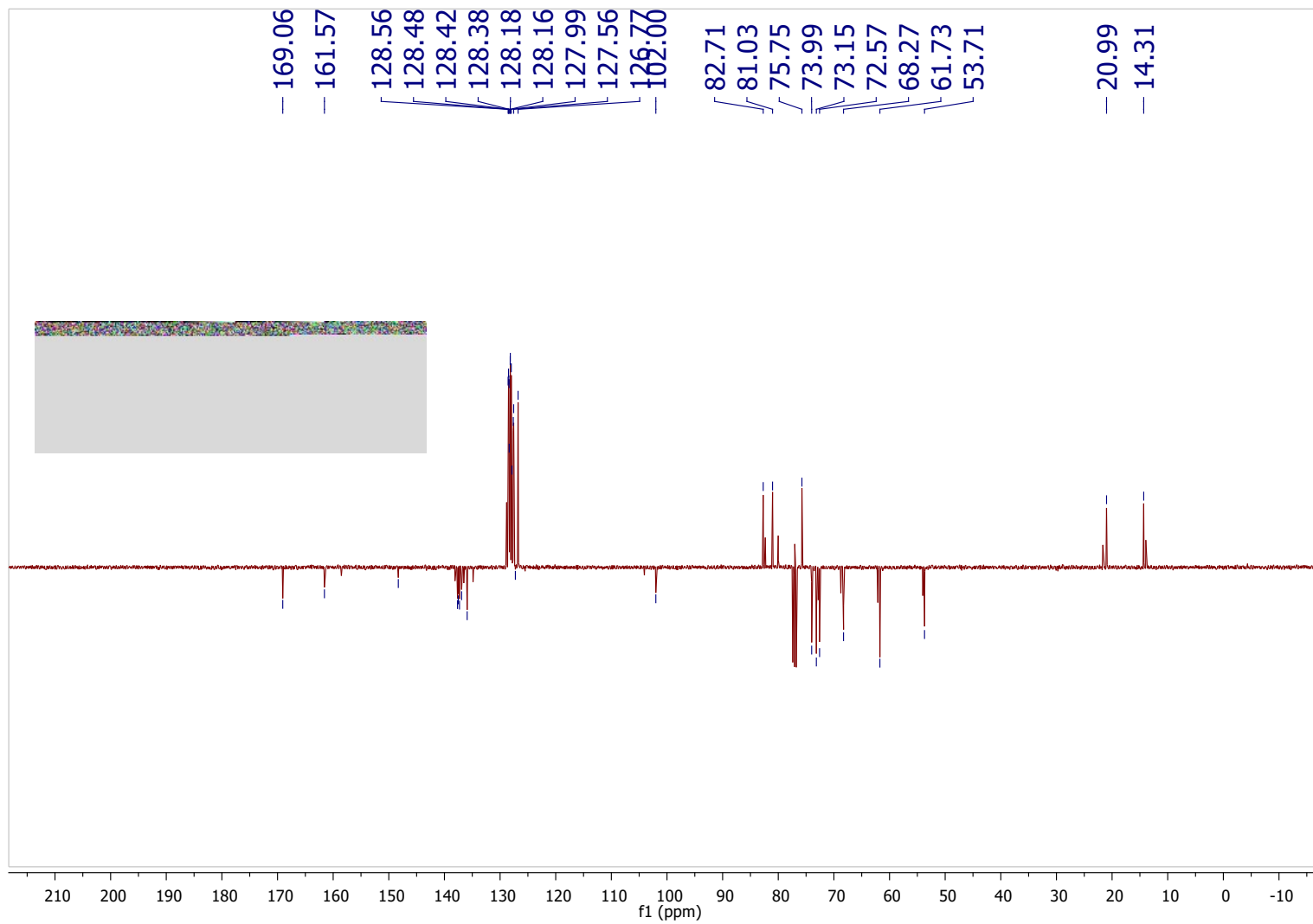
¹³C NMR Spectra for **25**:



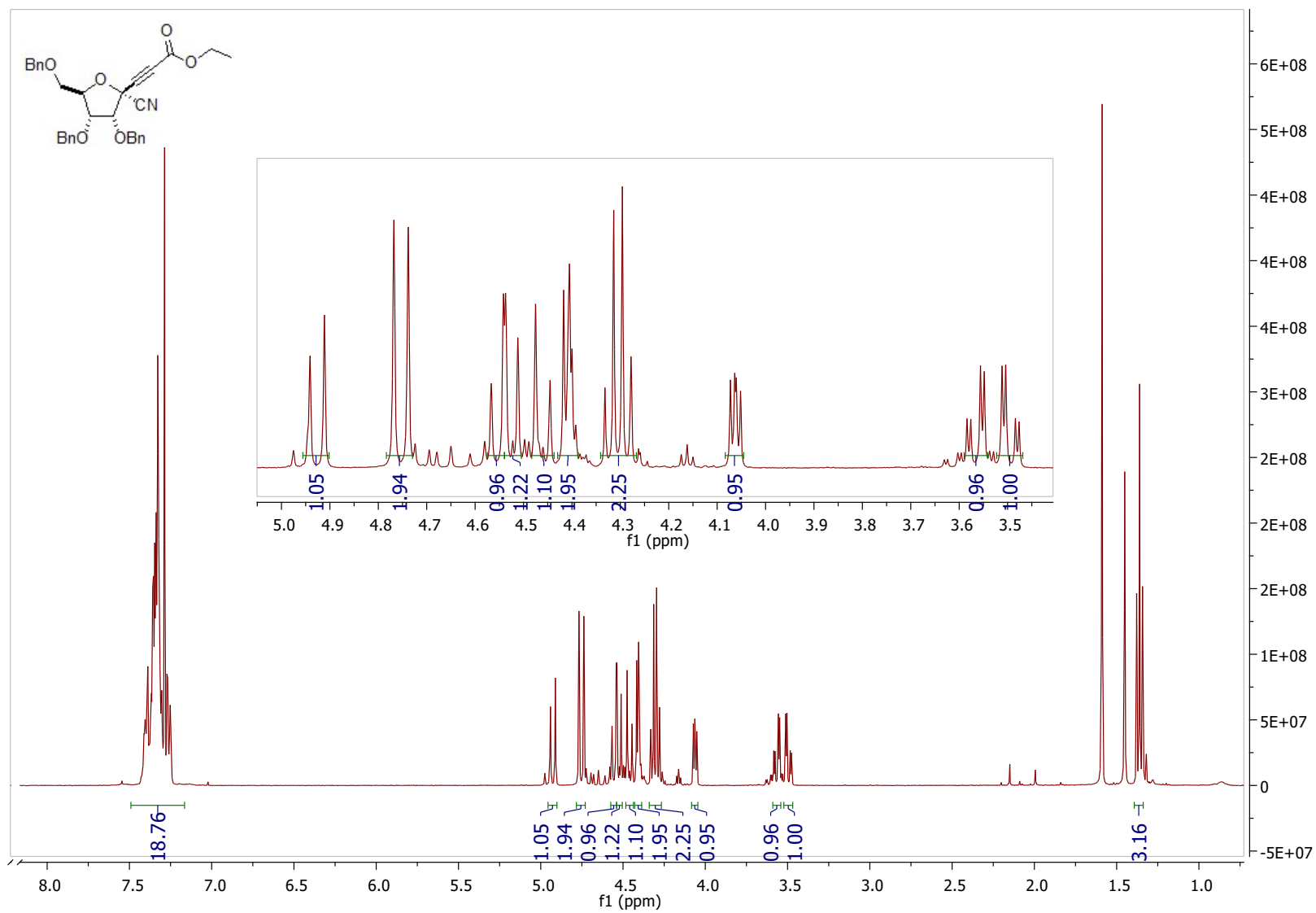
¹H NMR Spectra for **26a** and **26b**:



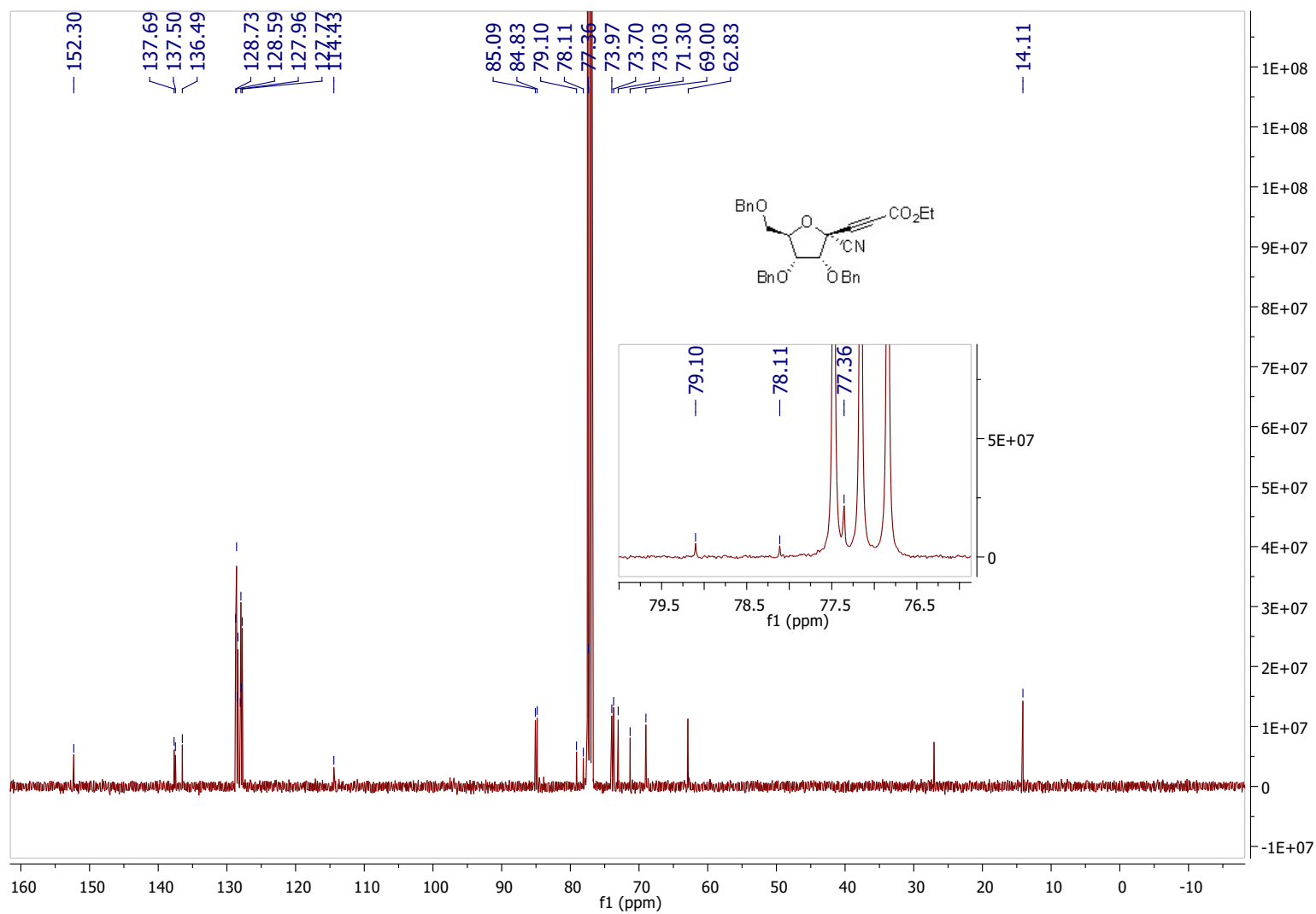
¹³C NMR Spectra for **26a**, **26b**:



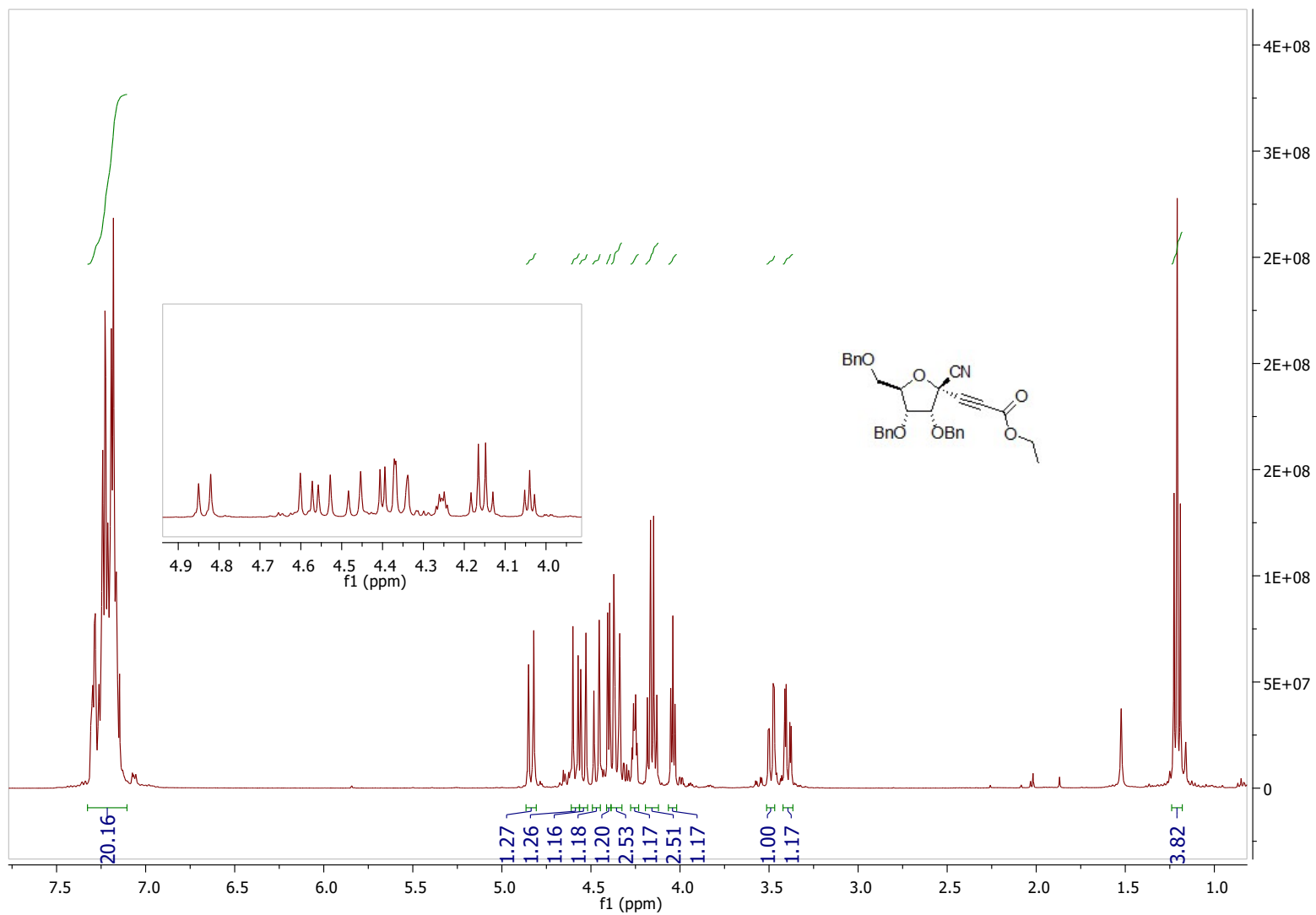
¹H NMR Spectra for **27** (α -cyano) :



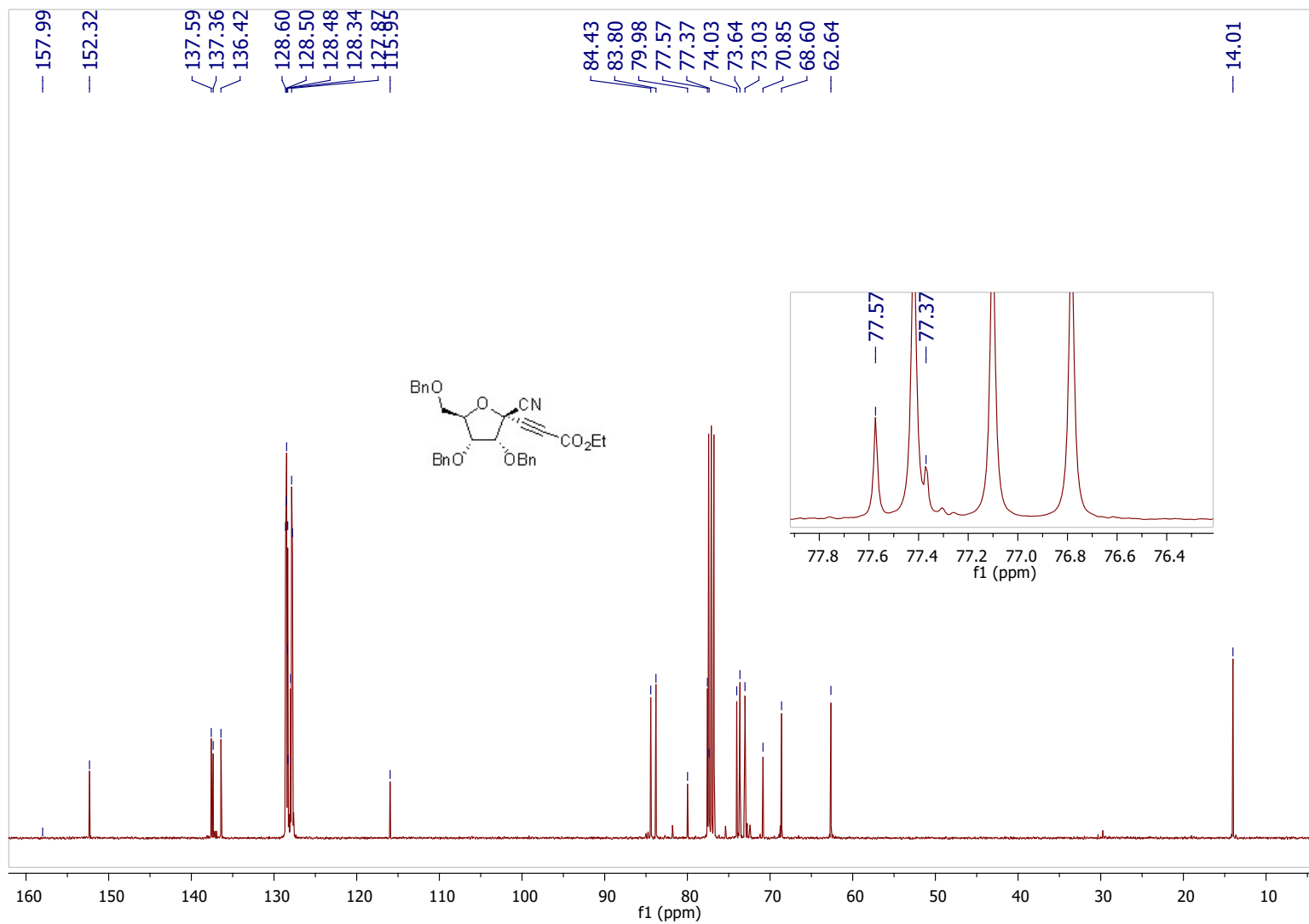
^{13}C NMR Spectra for **27** (α -cyano):



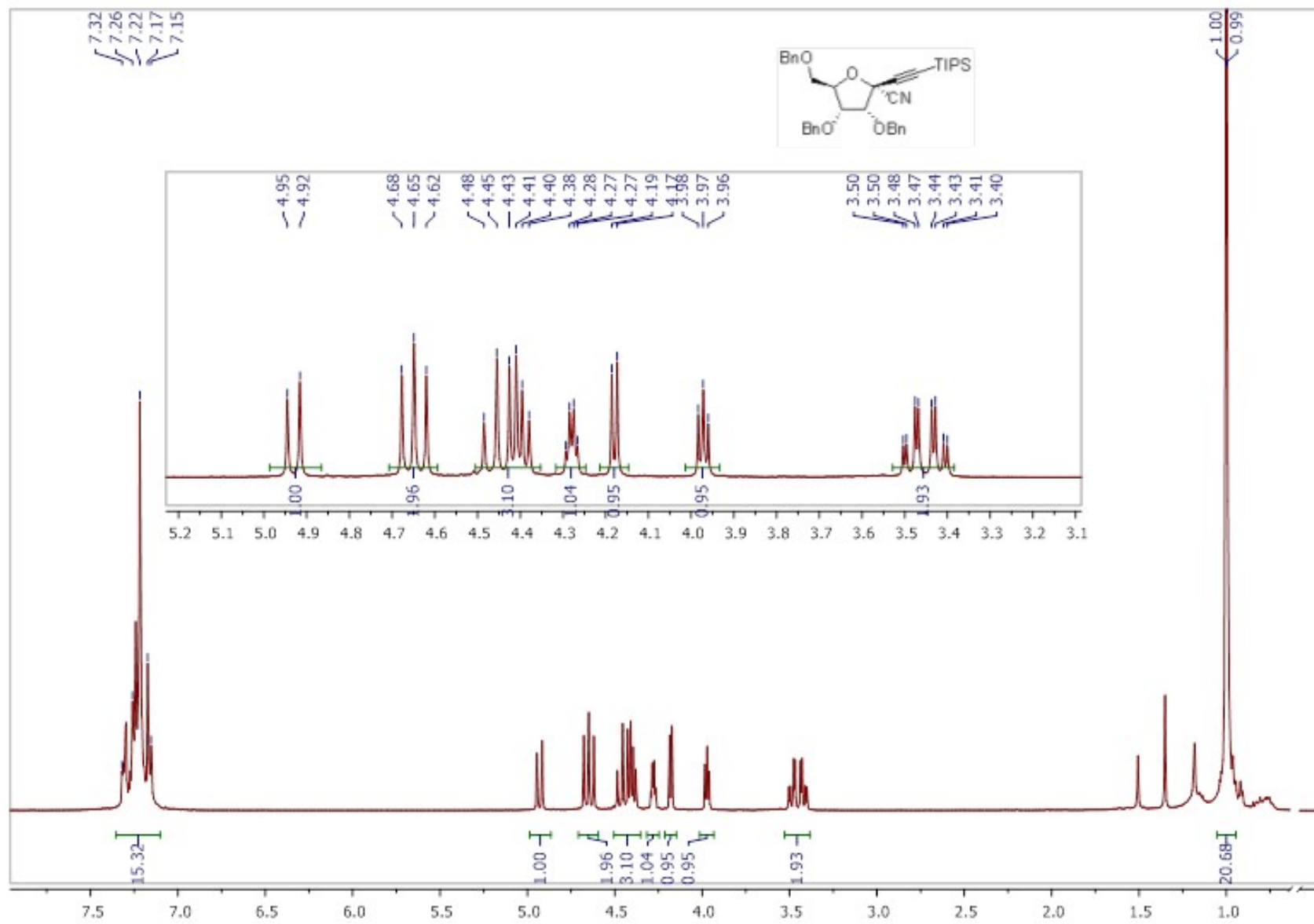
¹H NMR Spectra for **27 (β-cyano)**:



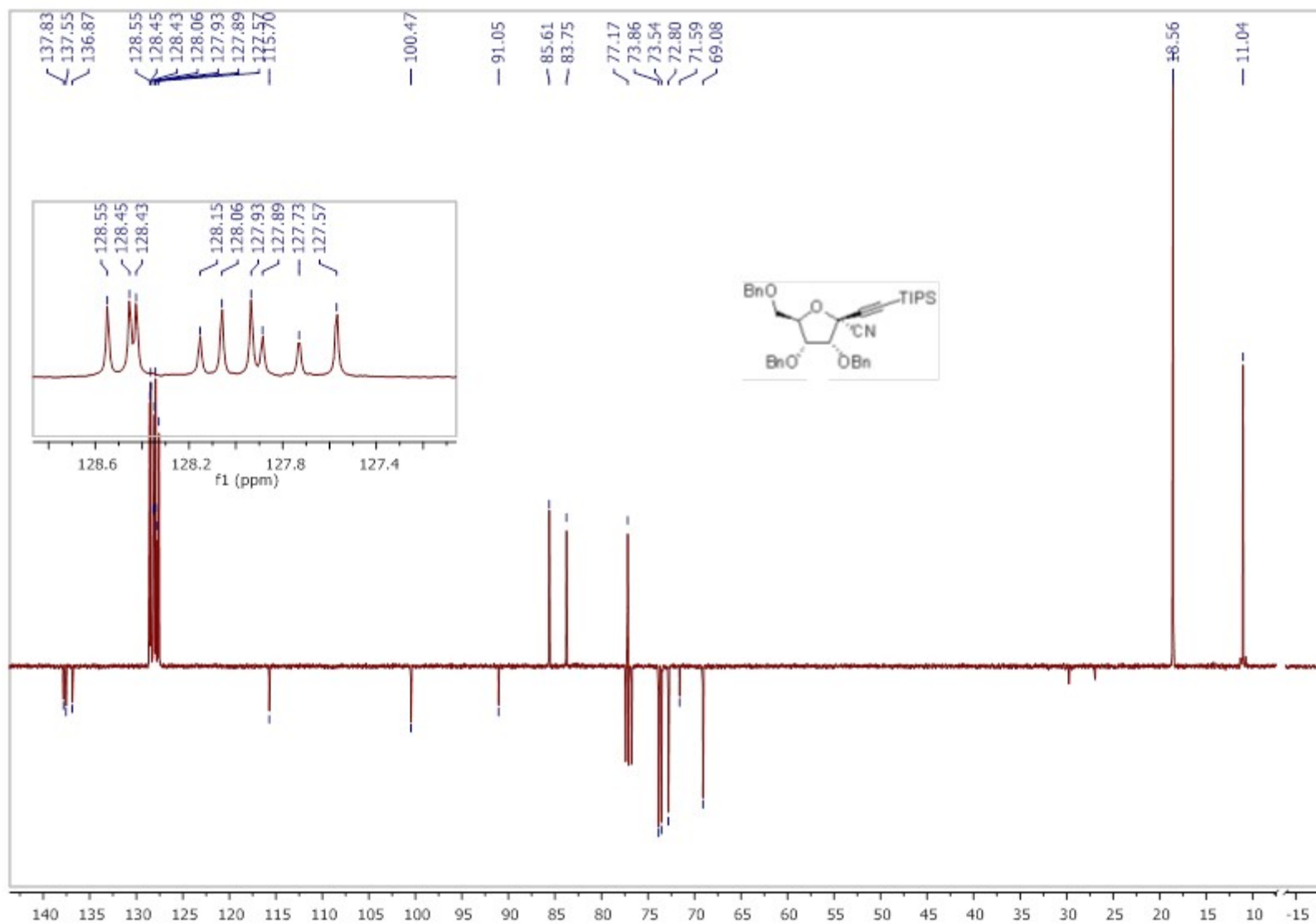
¹³C NMR Spectra for **27** (β-cyano):



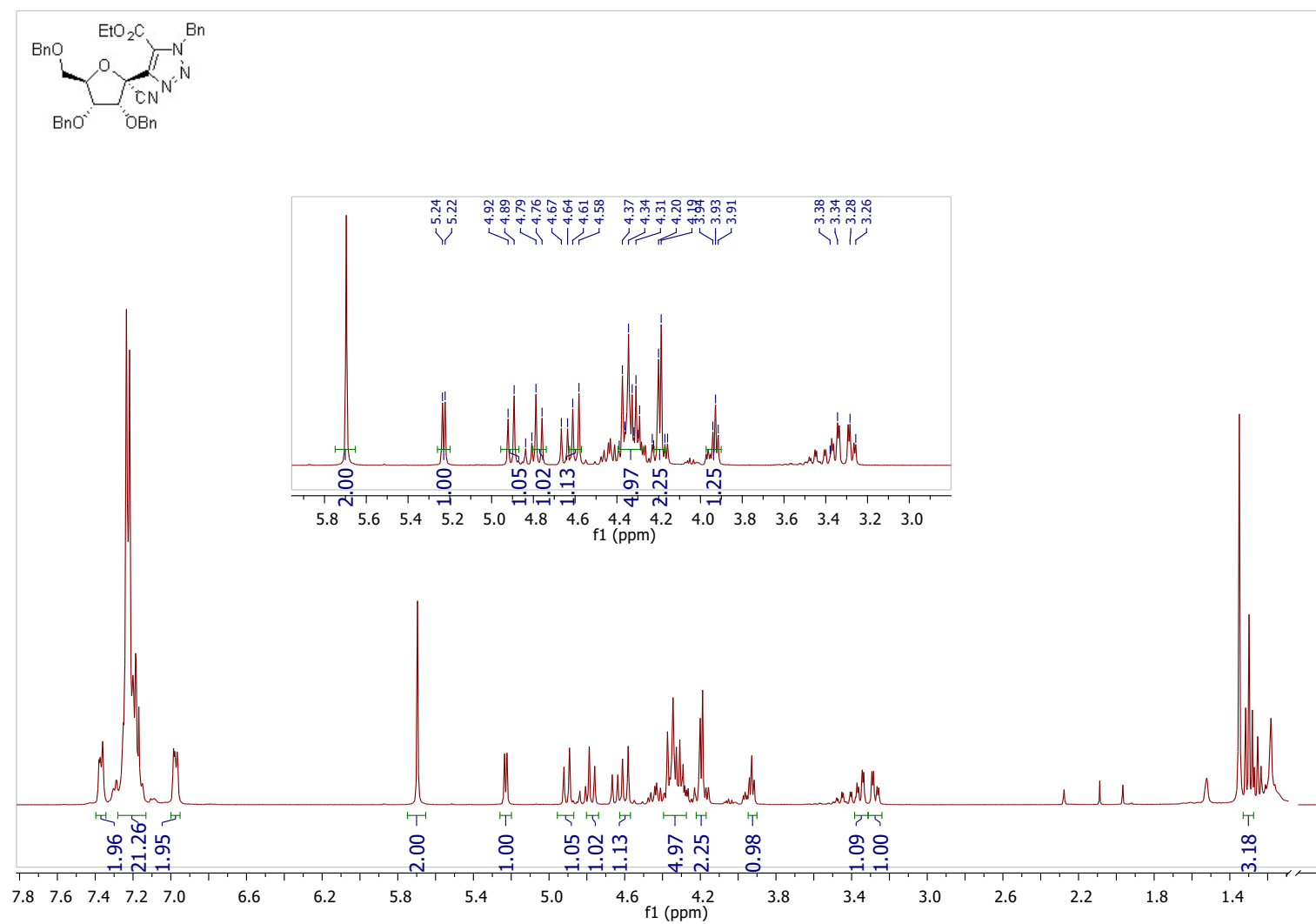
¹H NMR Spectra for **28**:



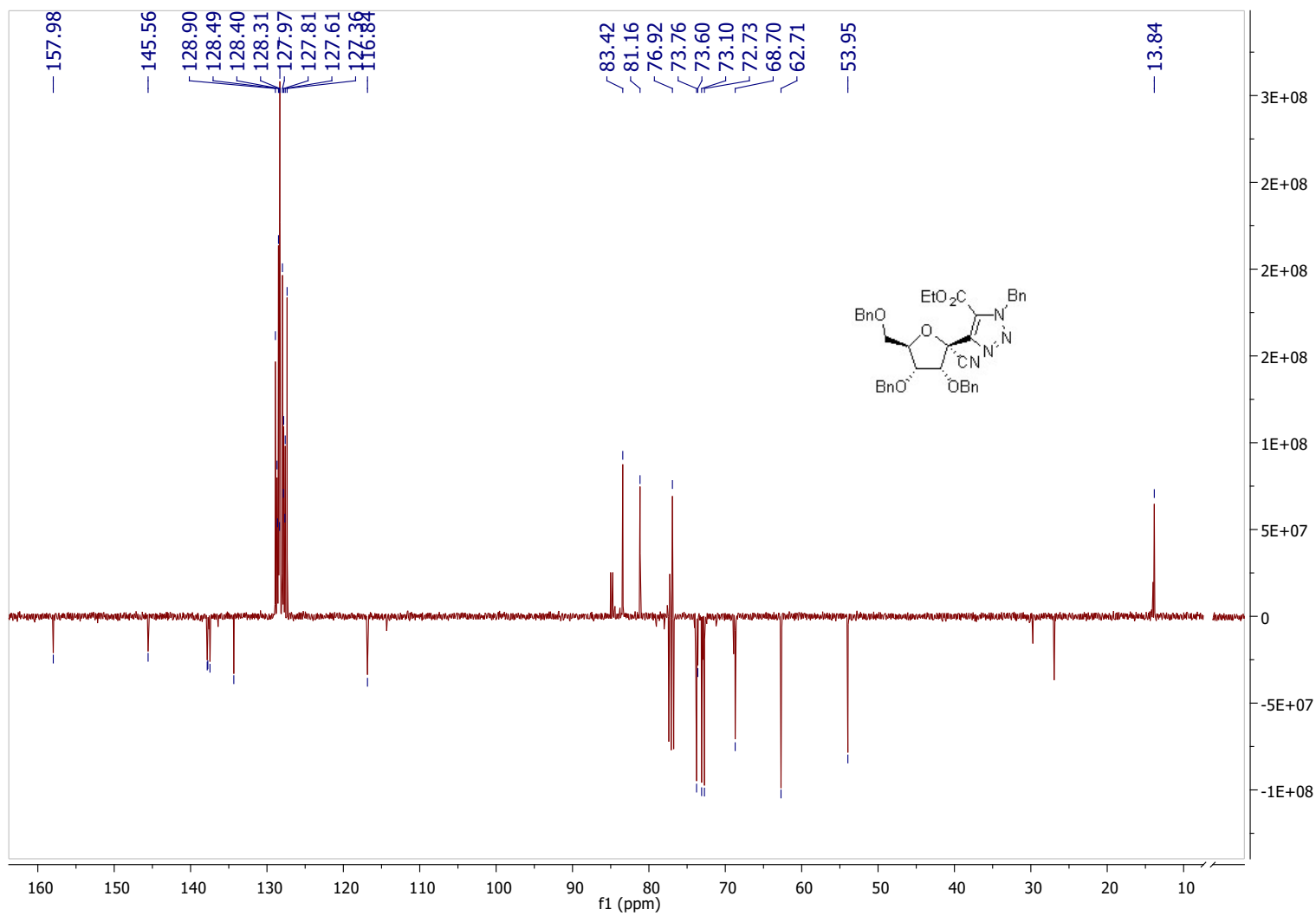
¹³C NMR Spectra for **28**:



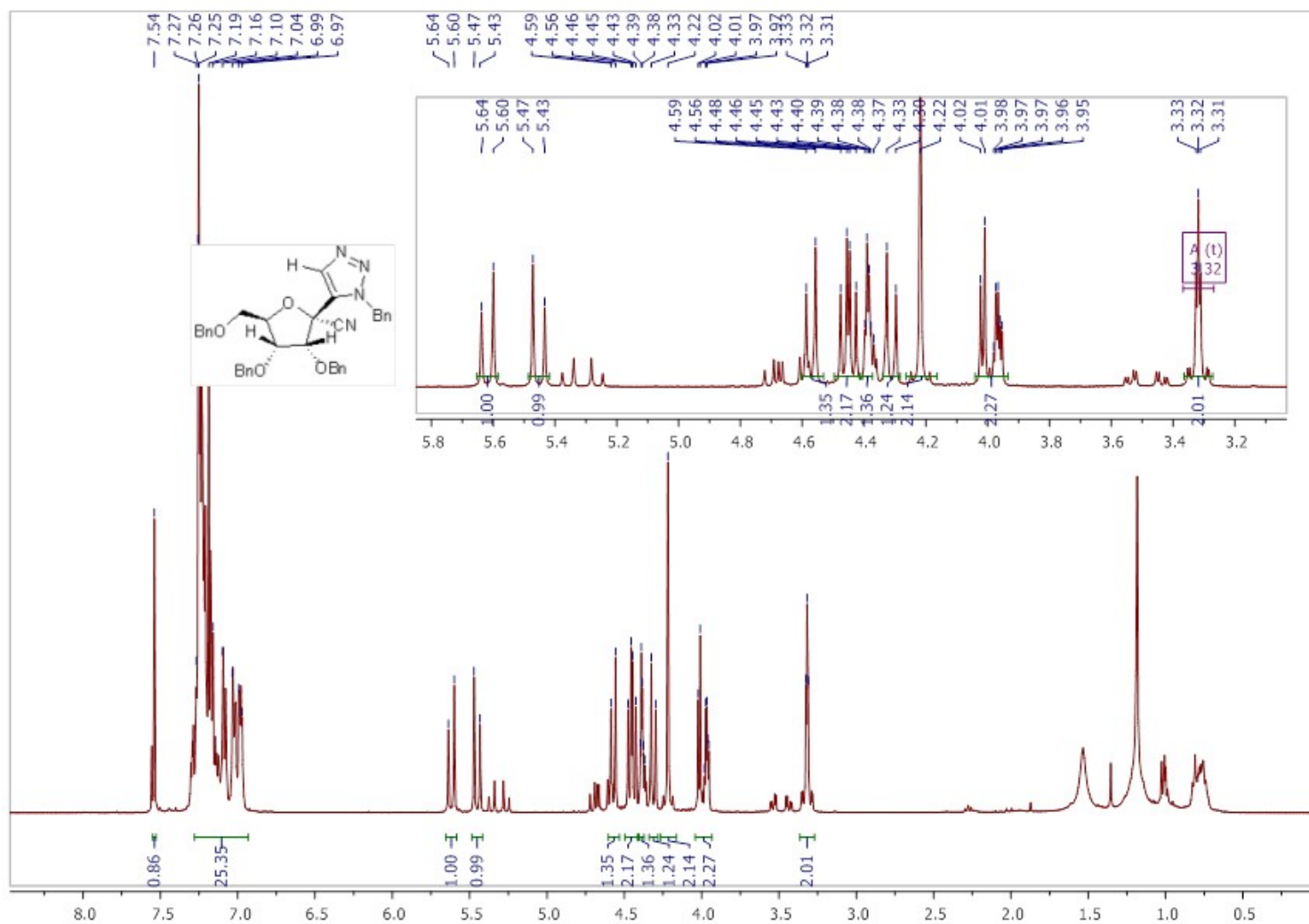
¹H NMR Spectra for **30b**:



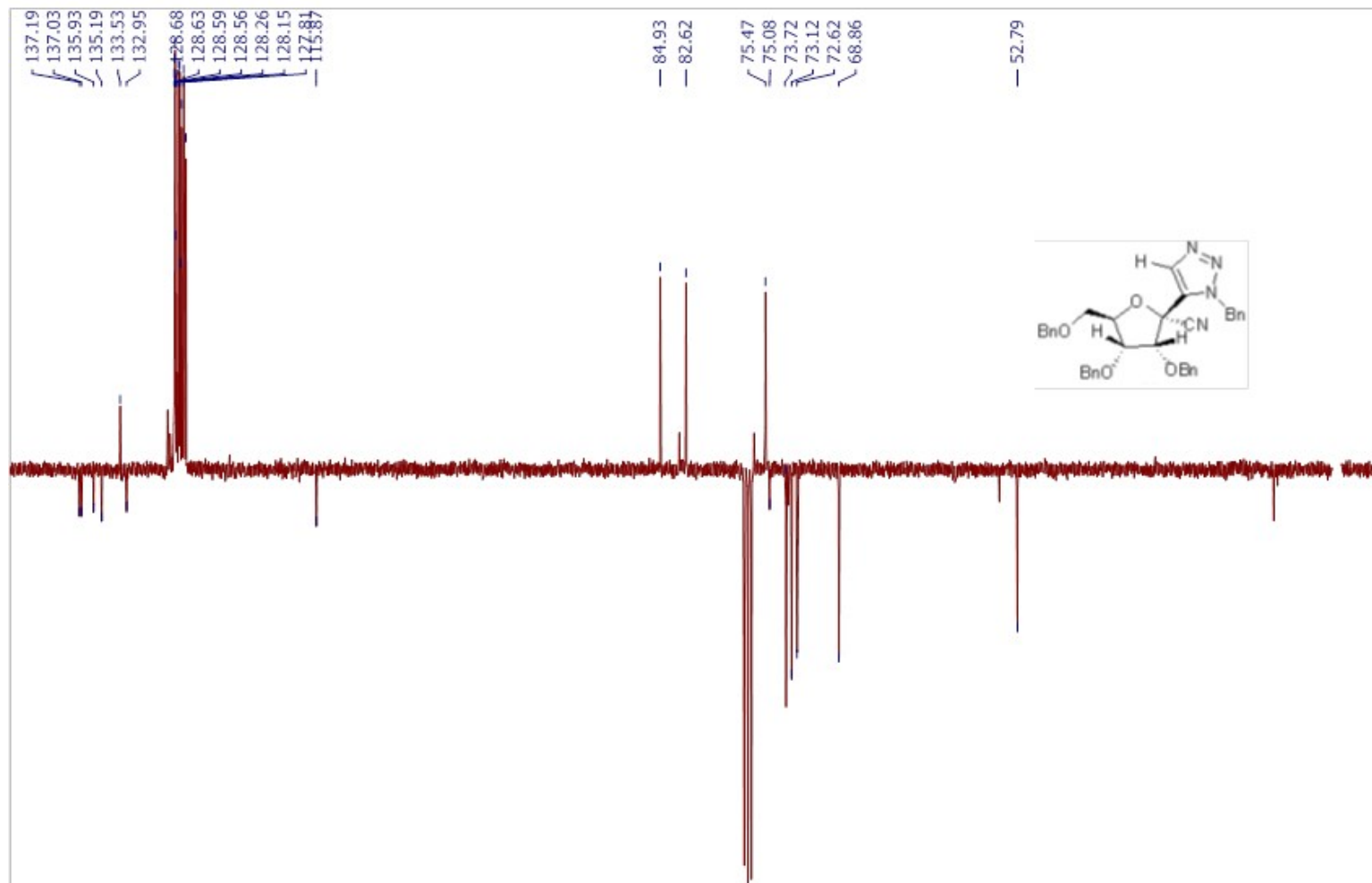
¹³C NMR Spectra for **30b**:



¹H NMR Spectra for **31a**:



^{13}C NMR Spectra for **31a**:



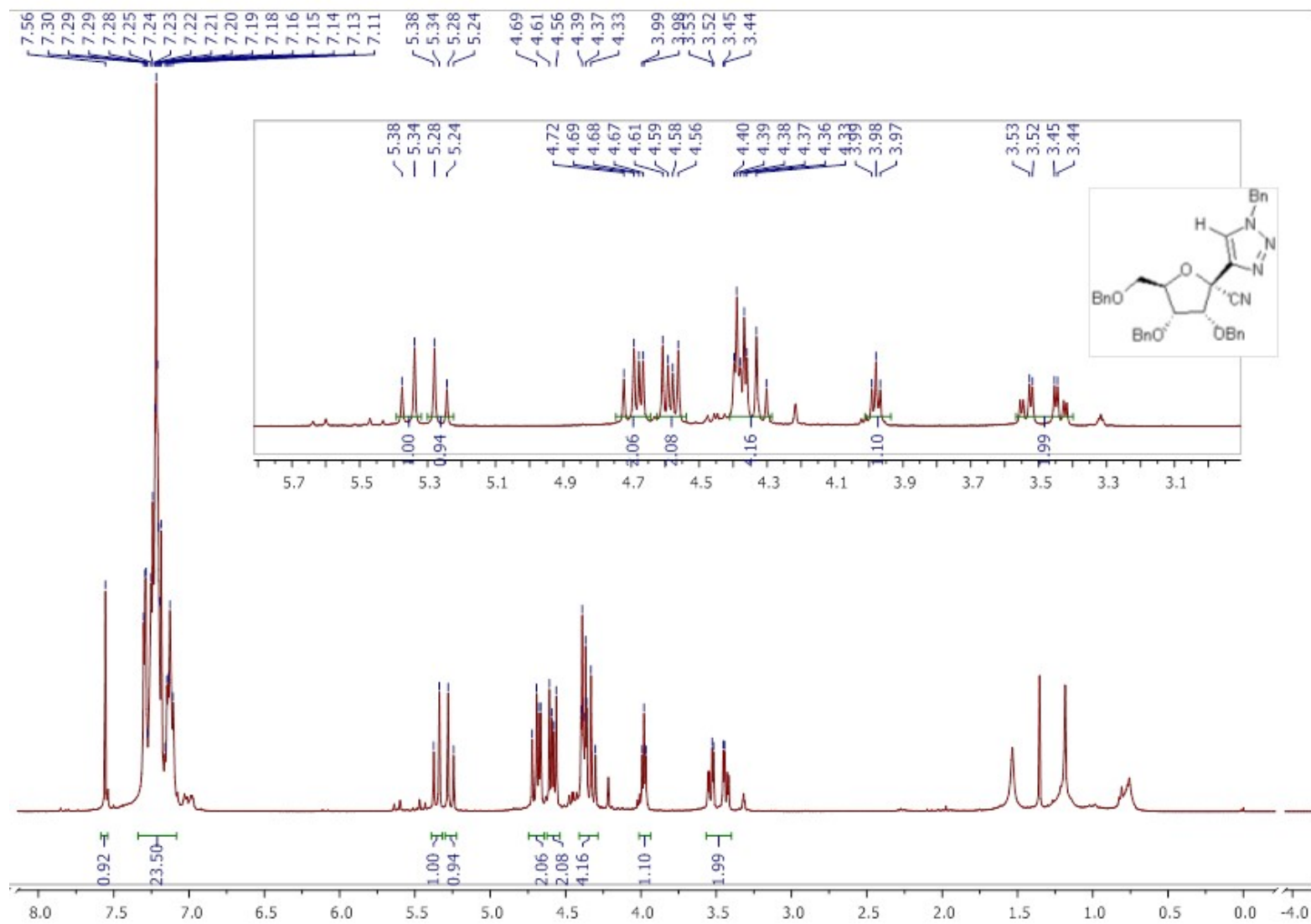
137.19
137.03
135.93
135.19
133.53
132.95

84.93
82.62

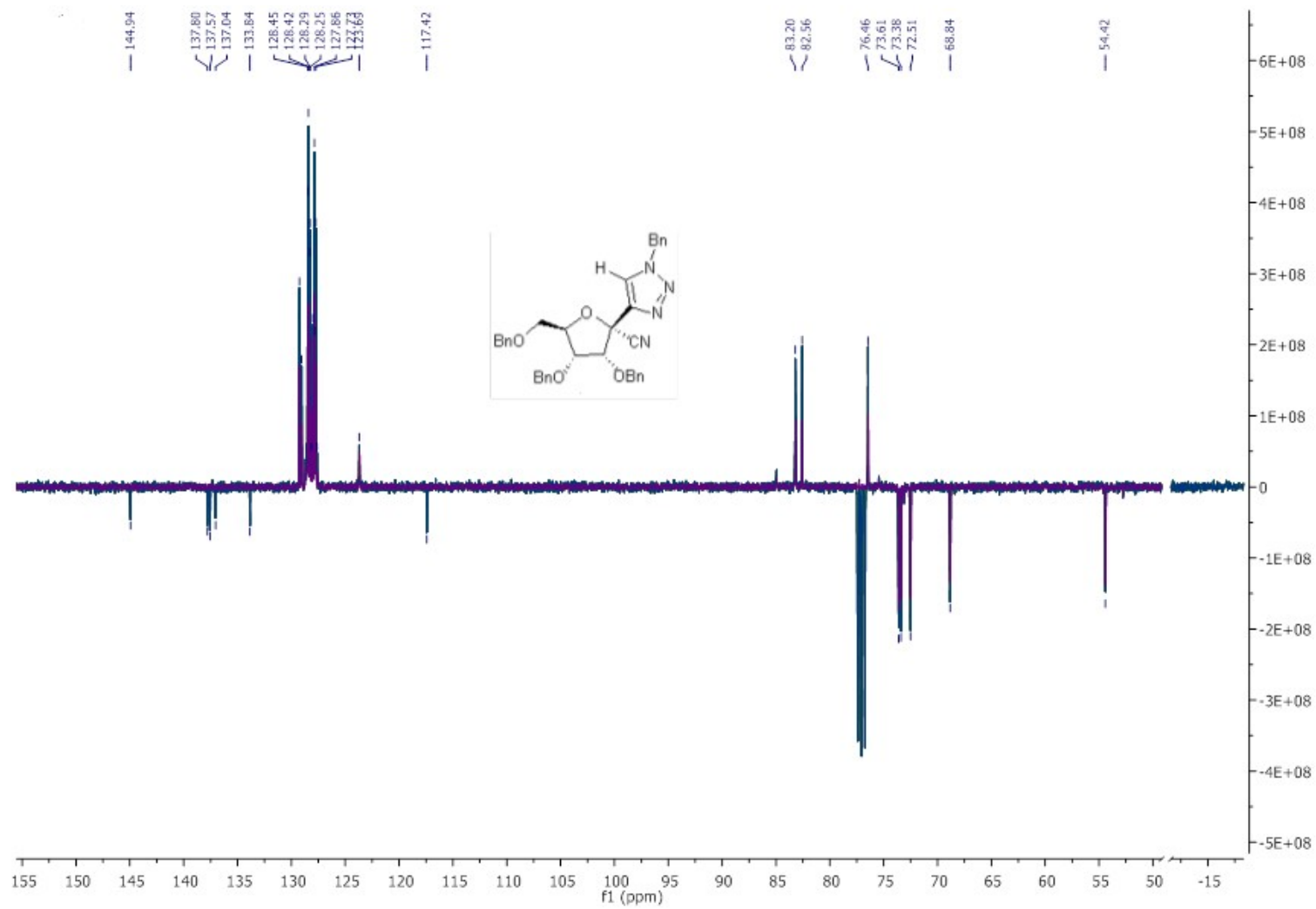
75.47
75.08
73.72
73.12
72.62
68.86

52.79

¹H NMR Spectra for **31b**:



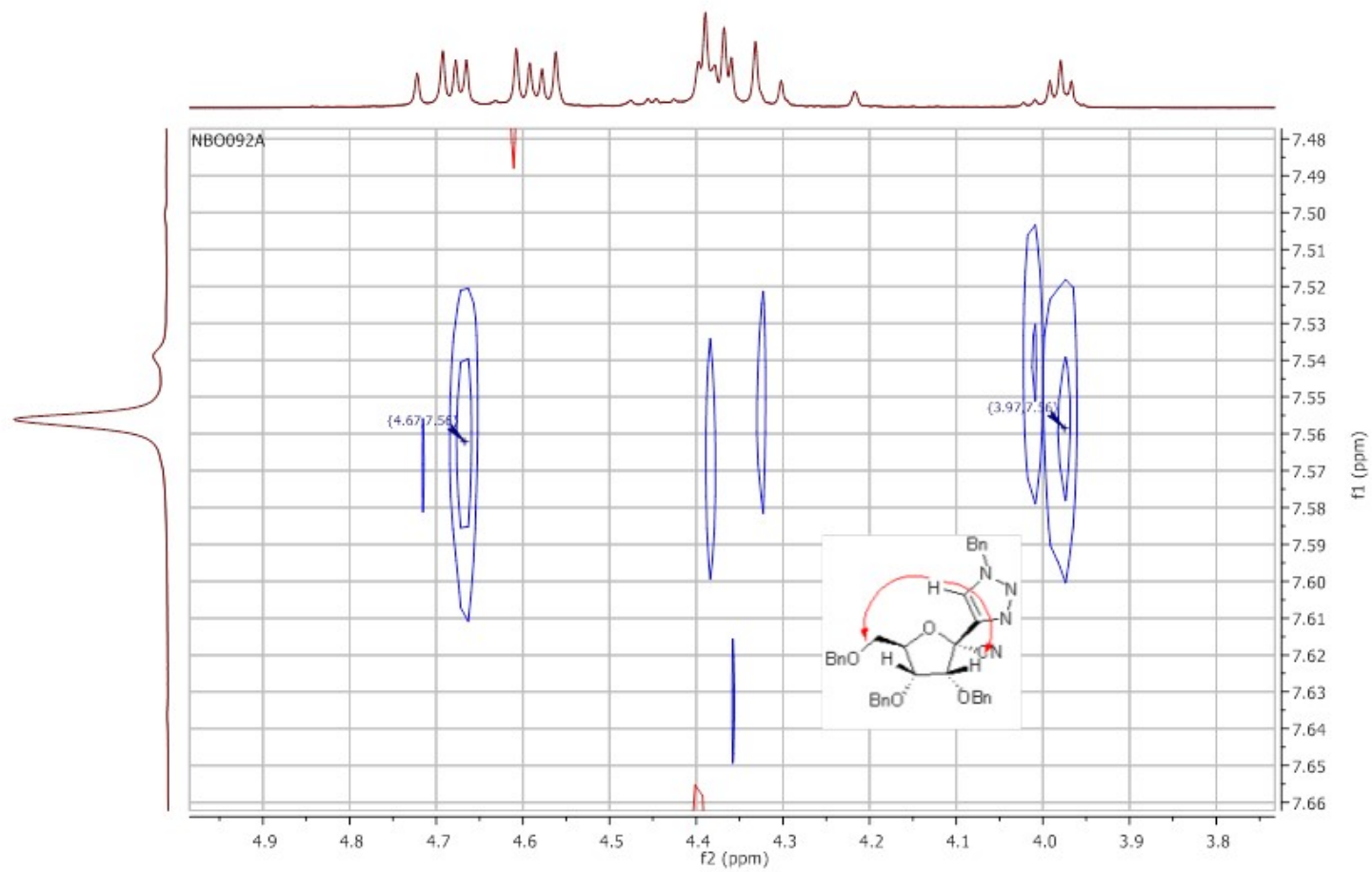
^{13}C NMR Spectra for **31b**:



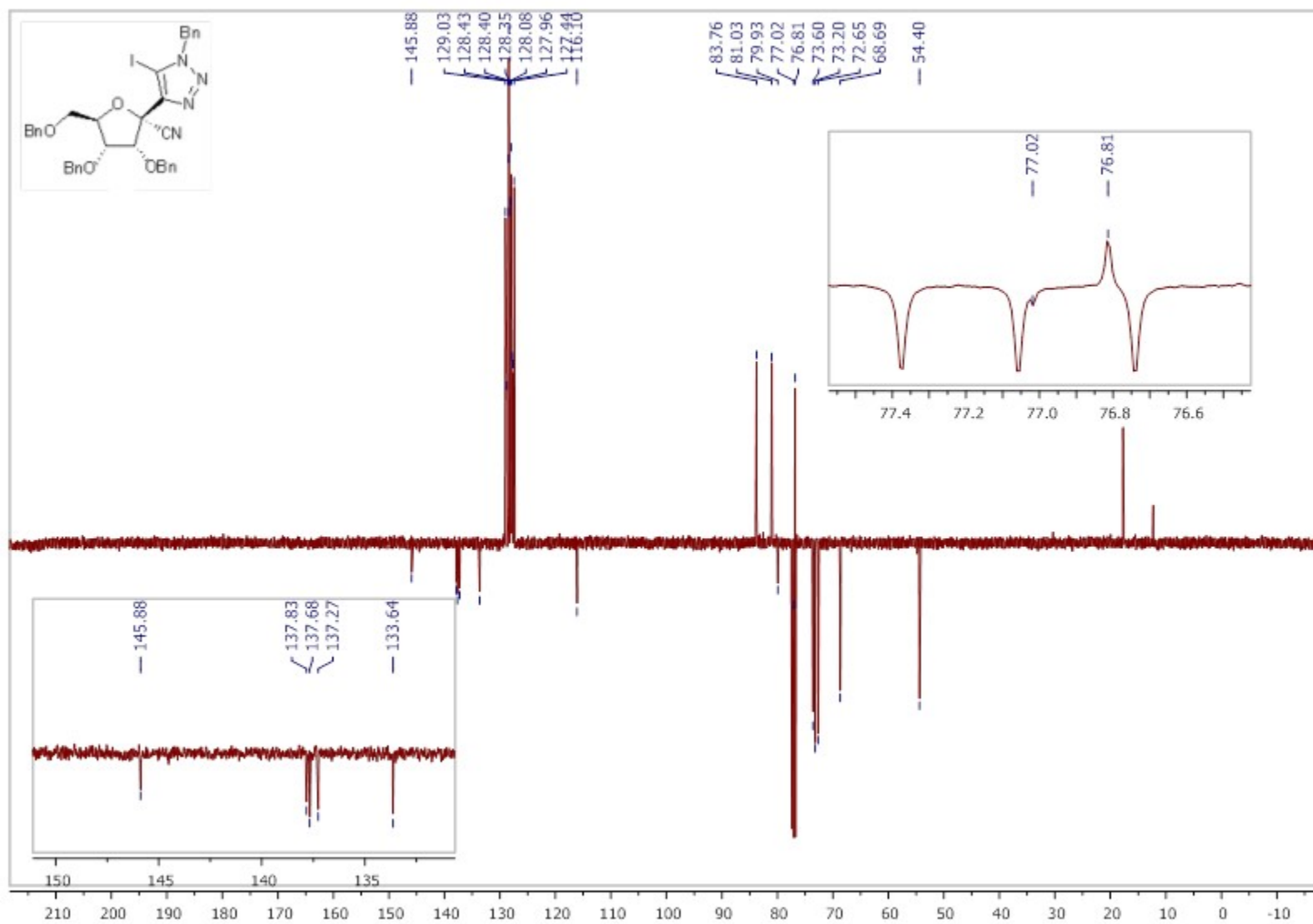
144.94
137.80
137.57
137.04
133.84
128.45
126.42
126.29
126.25
127.86
123.63
117.42

83.20
82.56
76.46
73.61
73.38
72.51
68.84
54.42

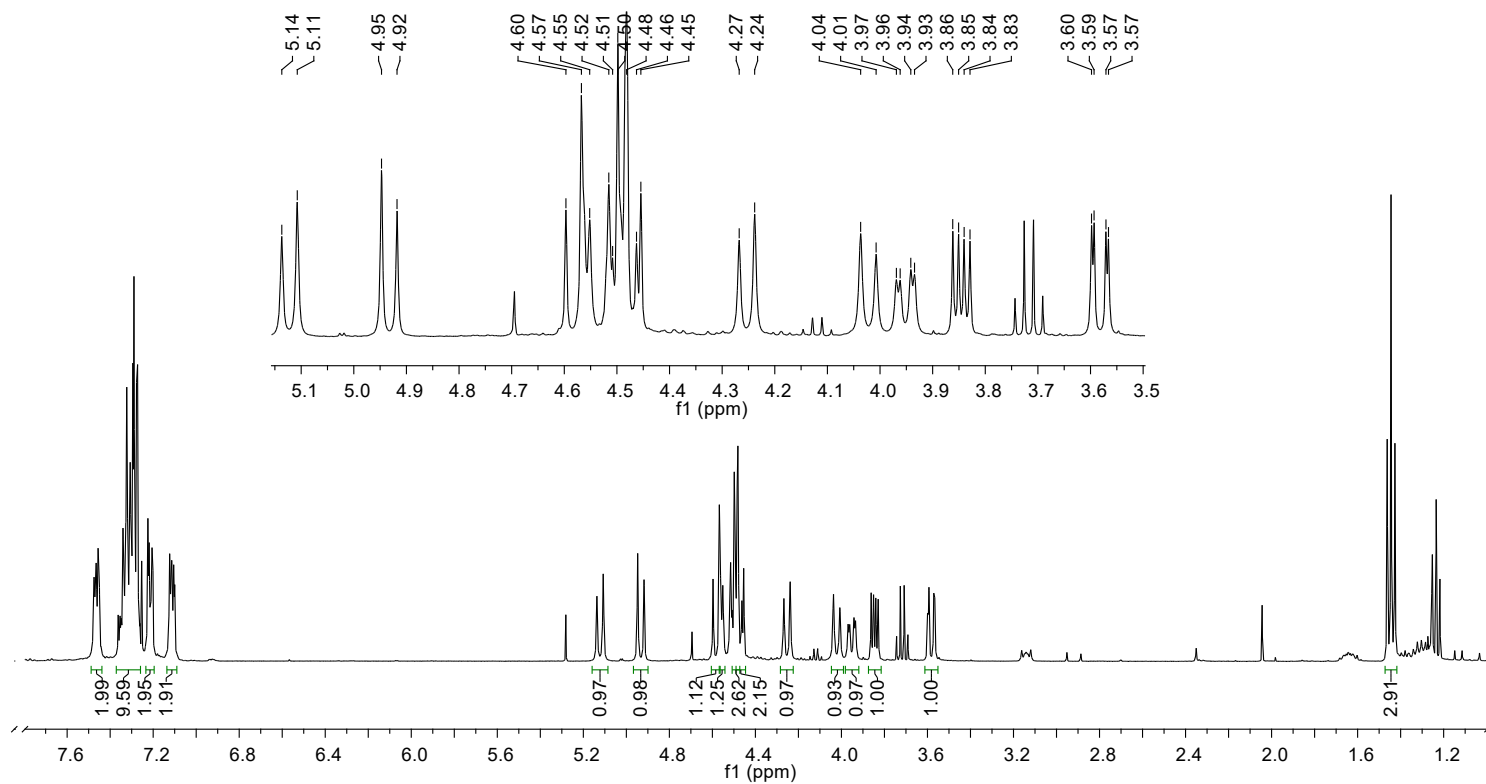
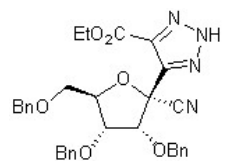
NOESY data for **31b**



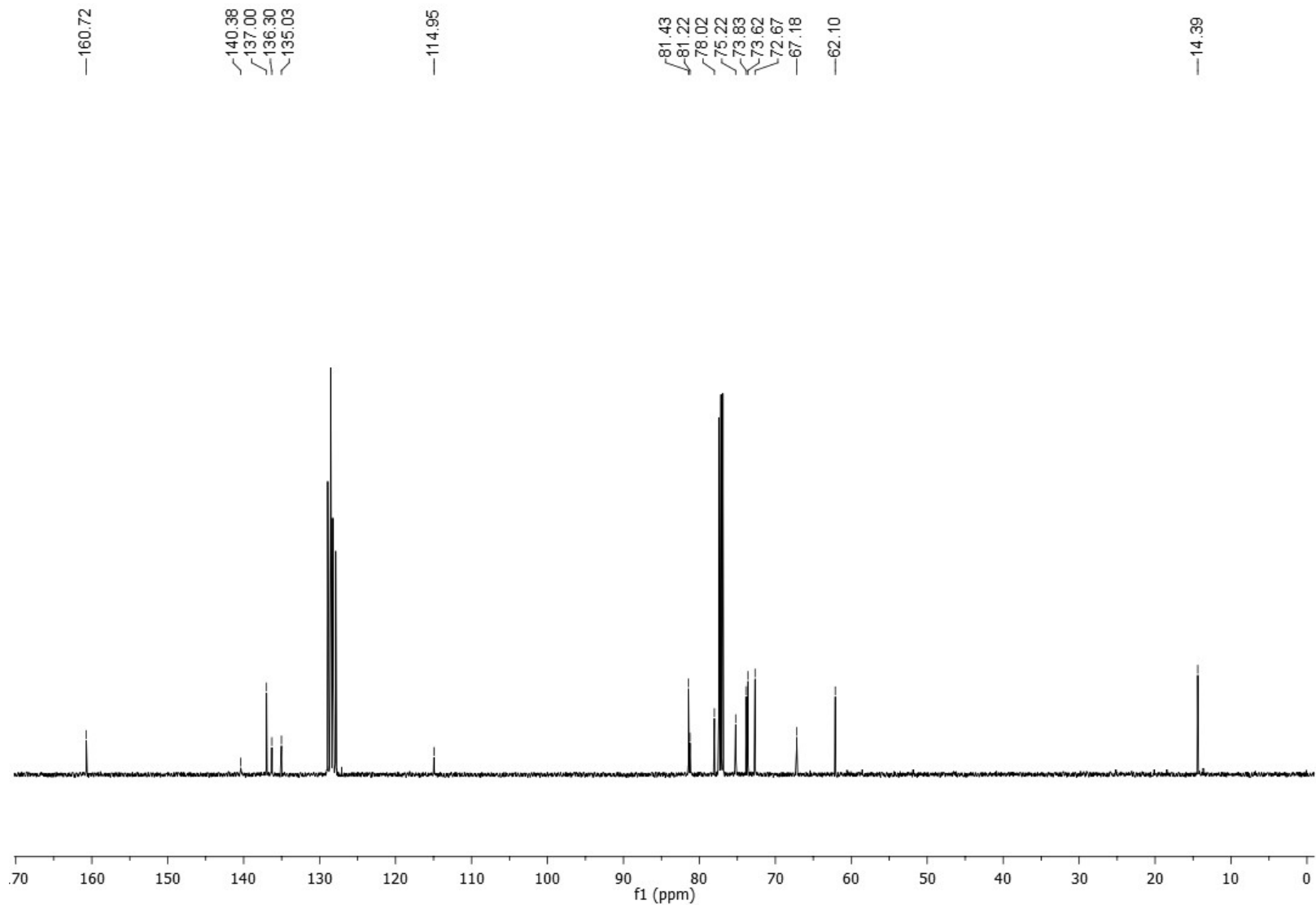
¹³C NMR Spectra for **32**:



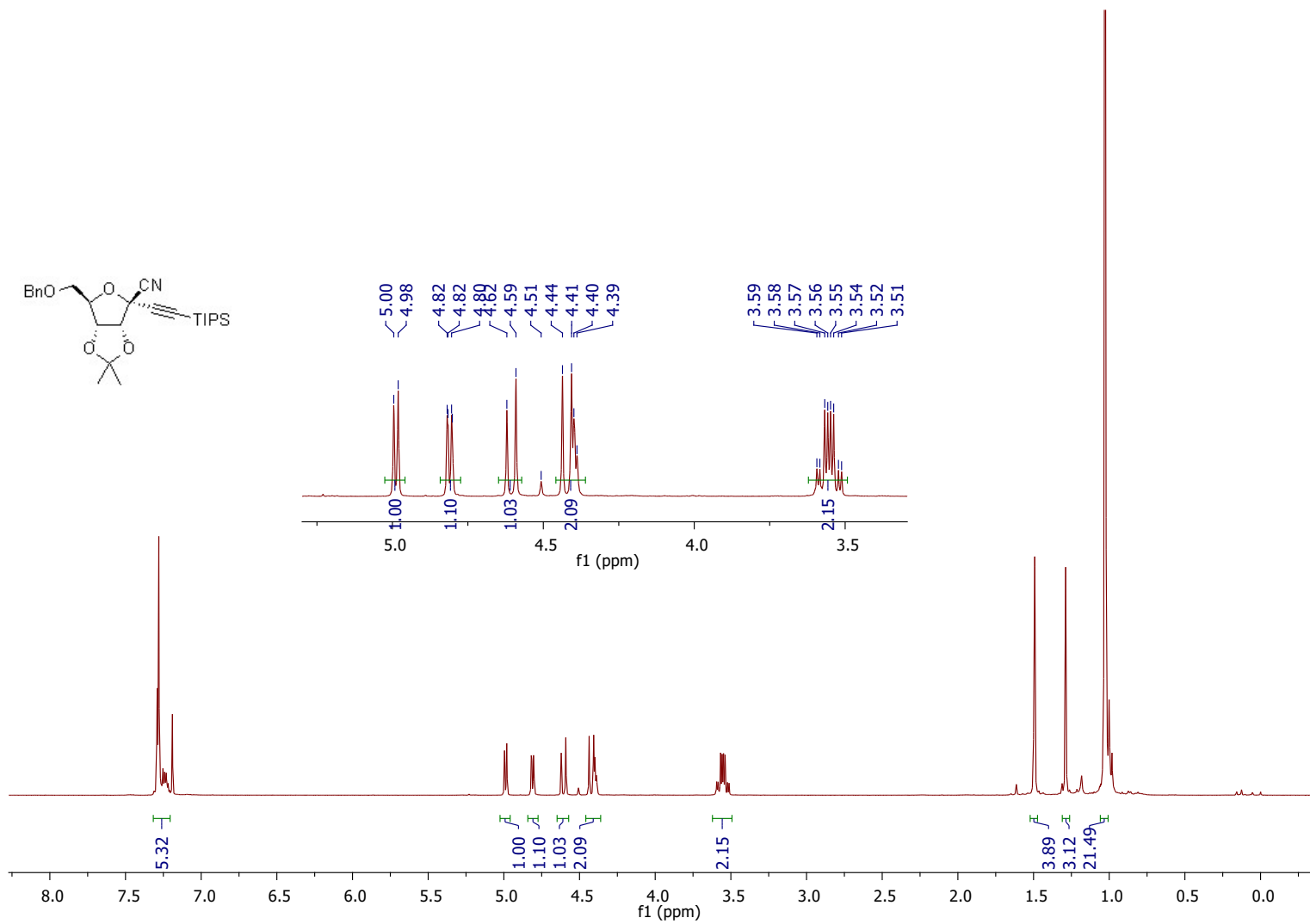
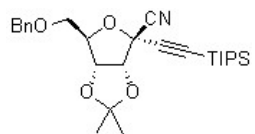
¹H NMR Spectra for 43



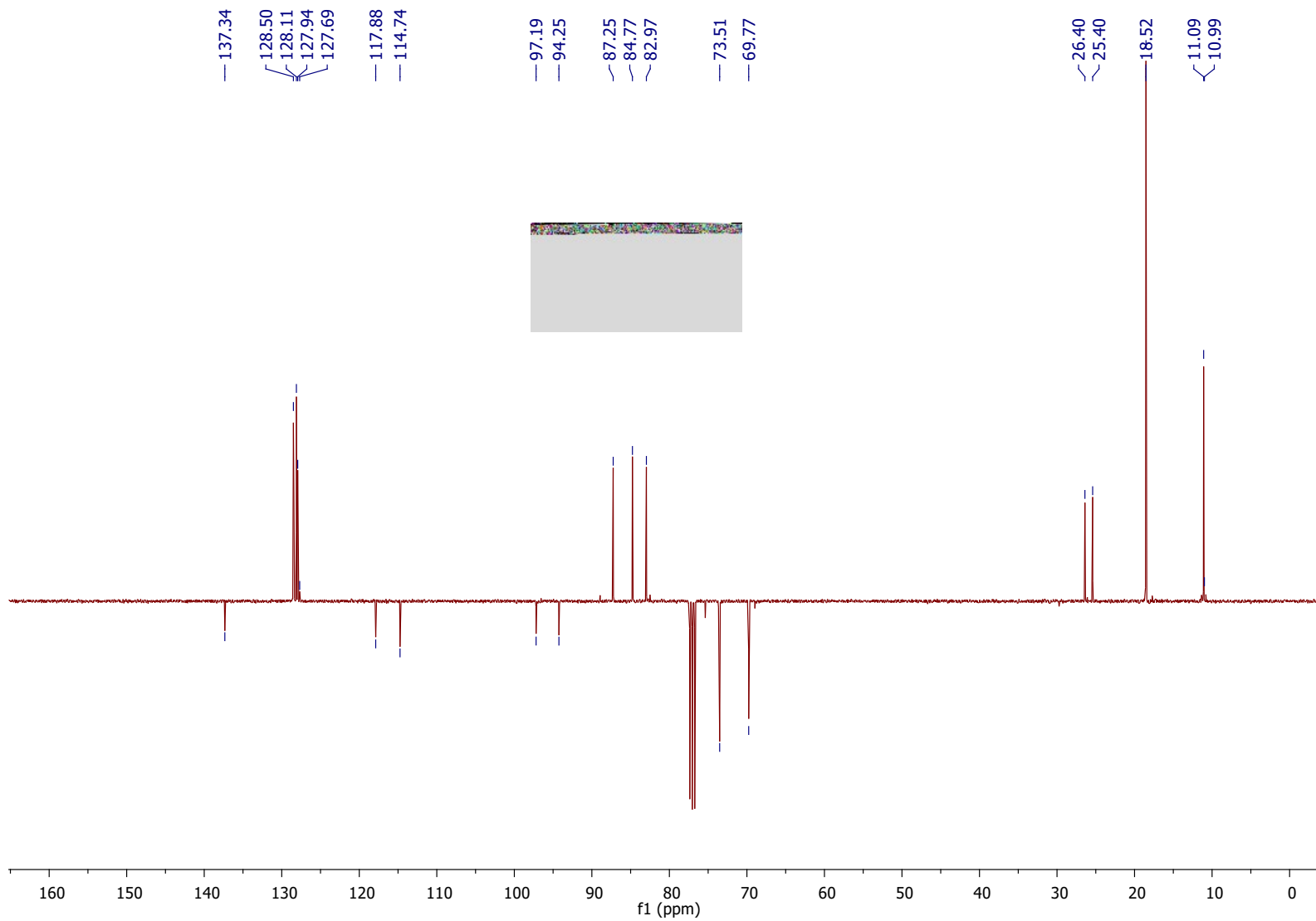
¹³C NMR Spectra for **33**



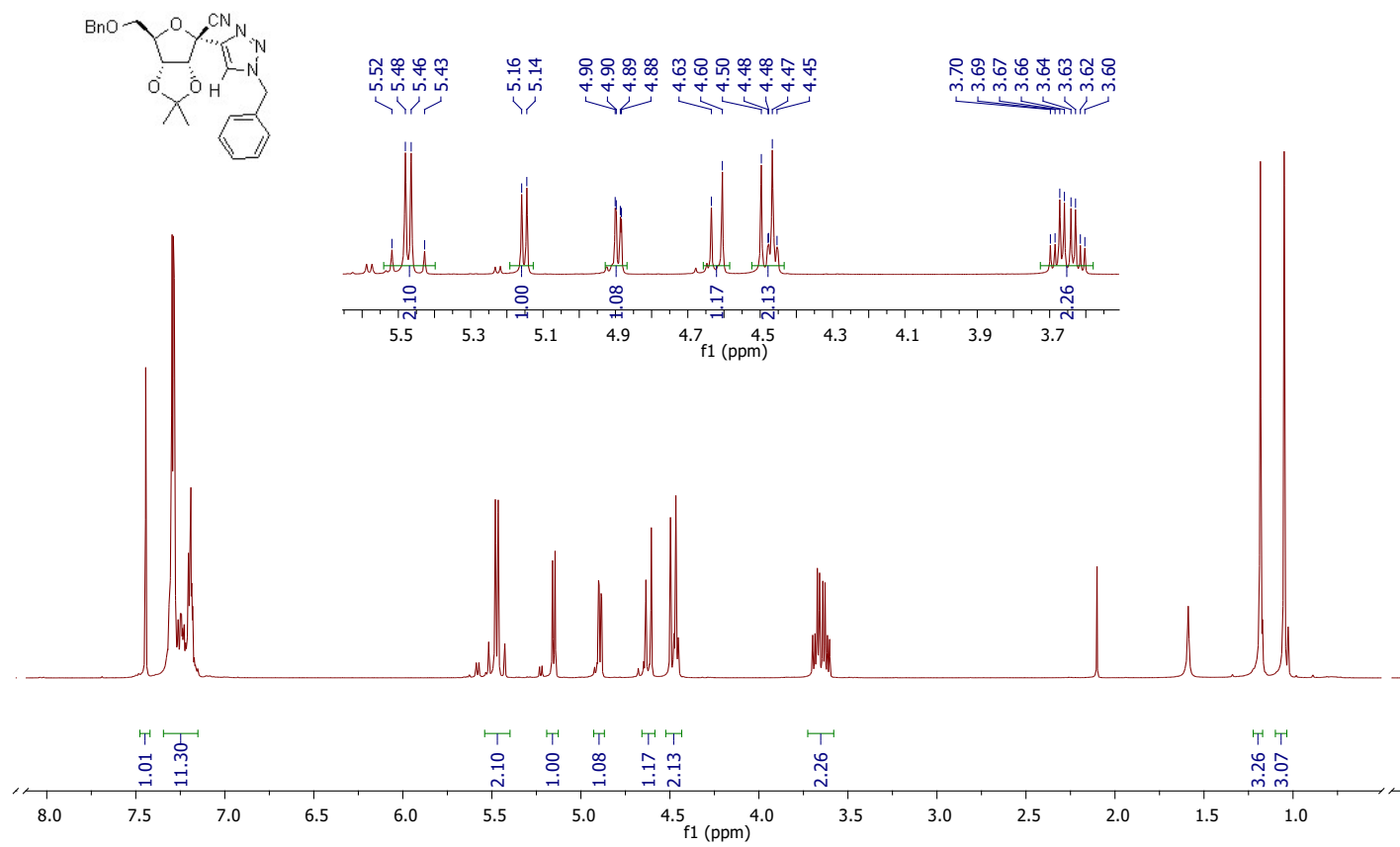
^1H NMR Spectra for **36**:



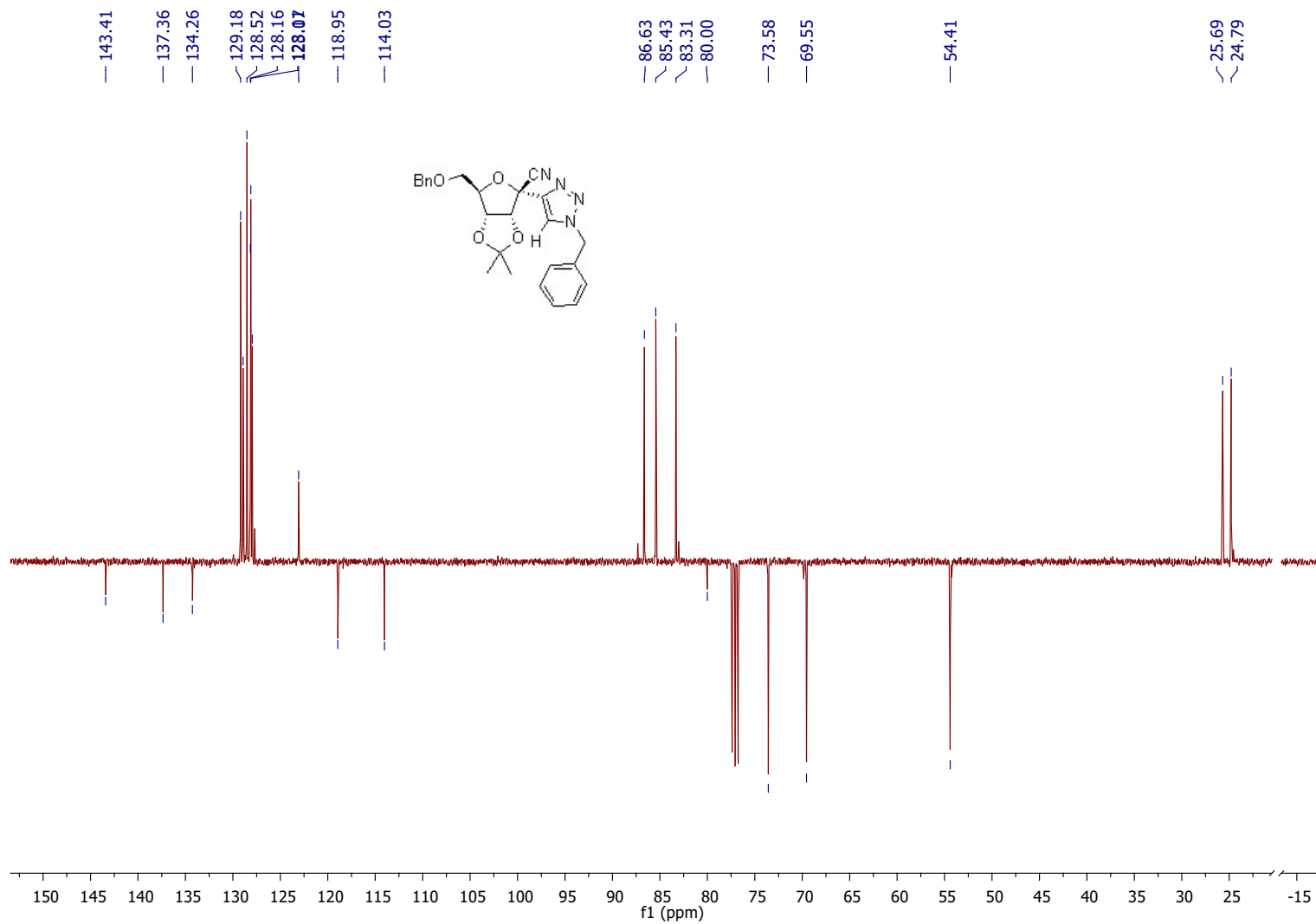
¹³C NMR Spectra for **36**:



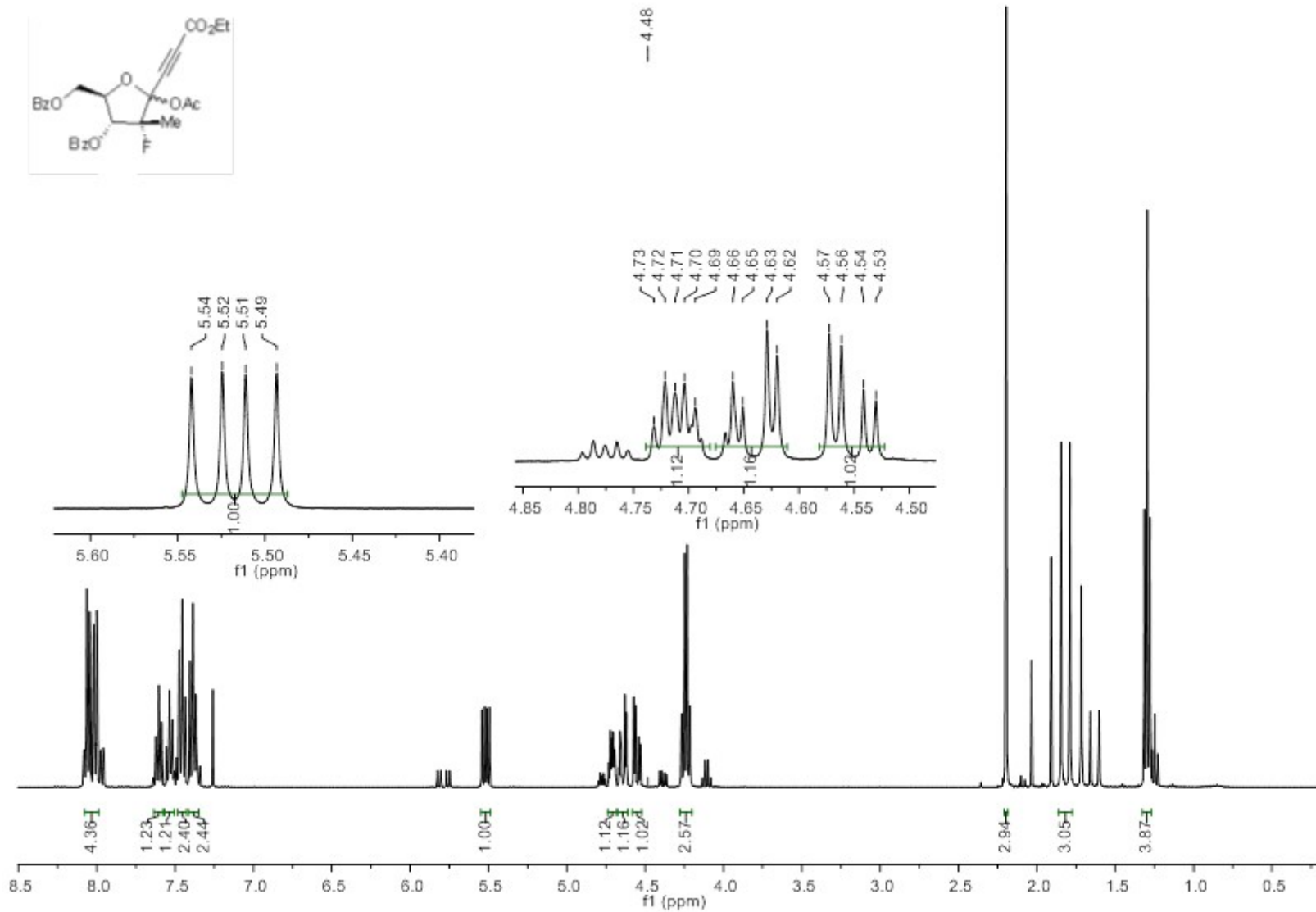
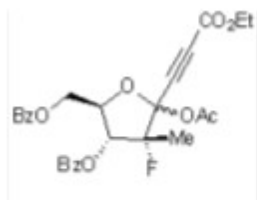
¹H NMR Spectra for **38a**:



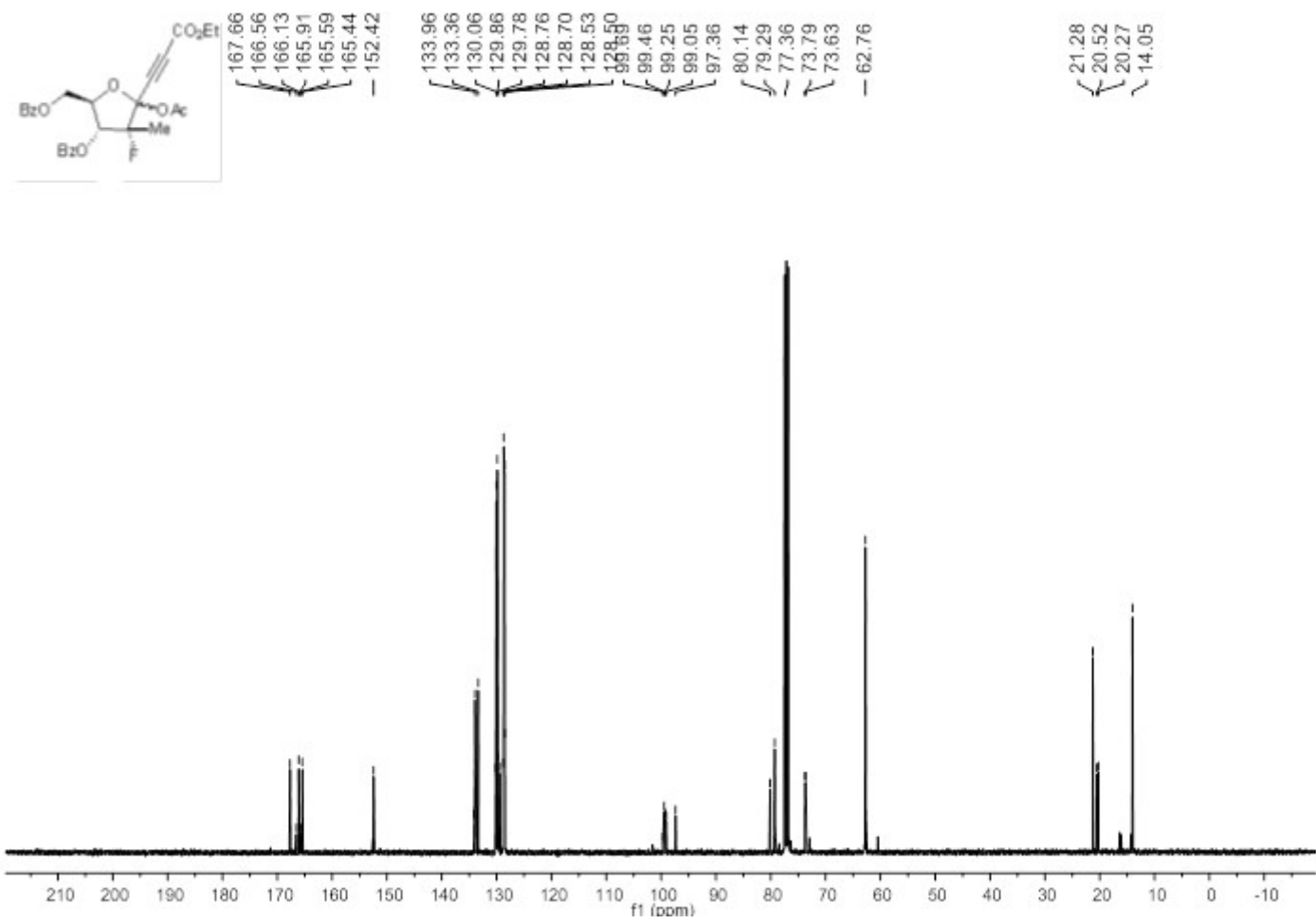
¹³C NMR Spectra for **38a**:



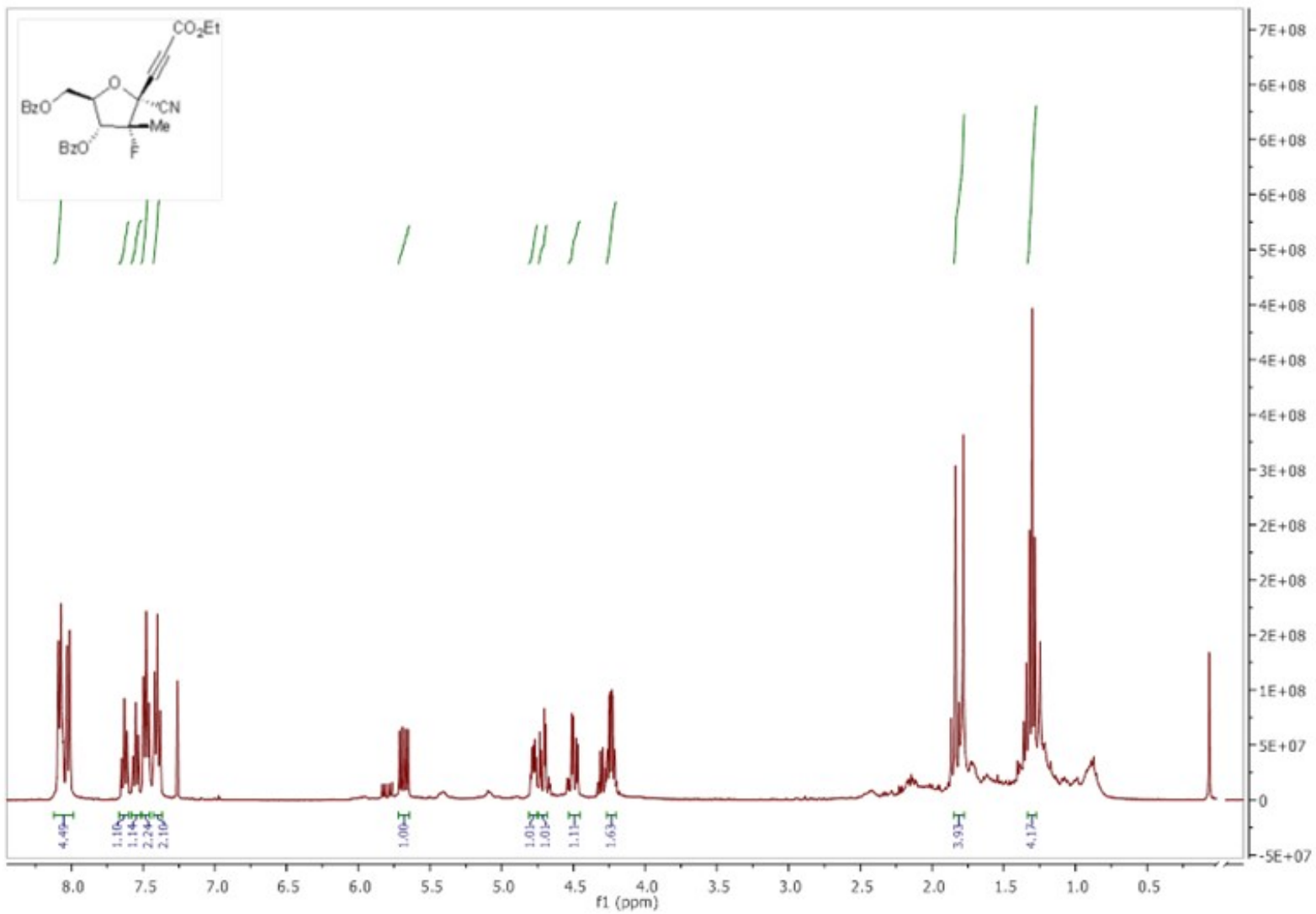
¹H NMR Spectra for **41**:



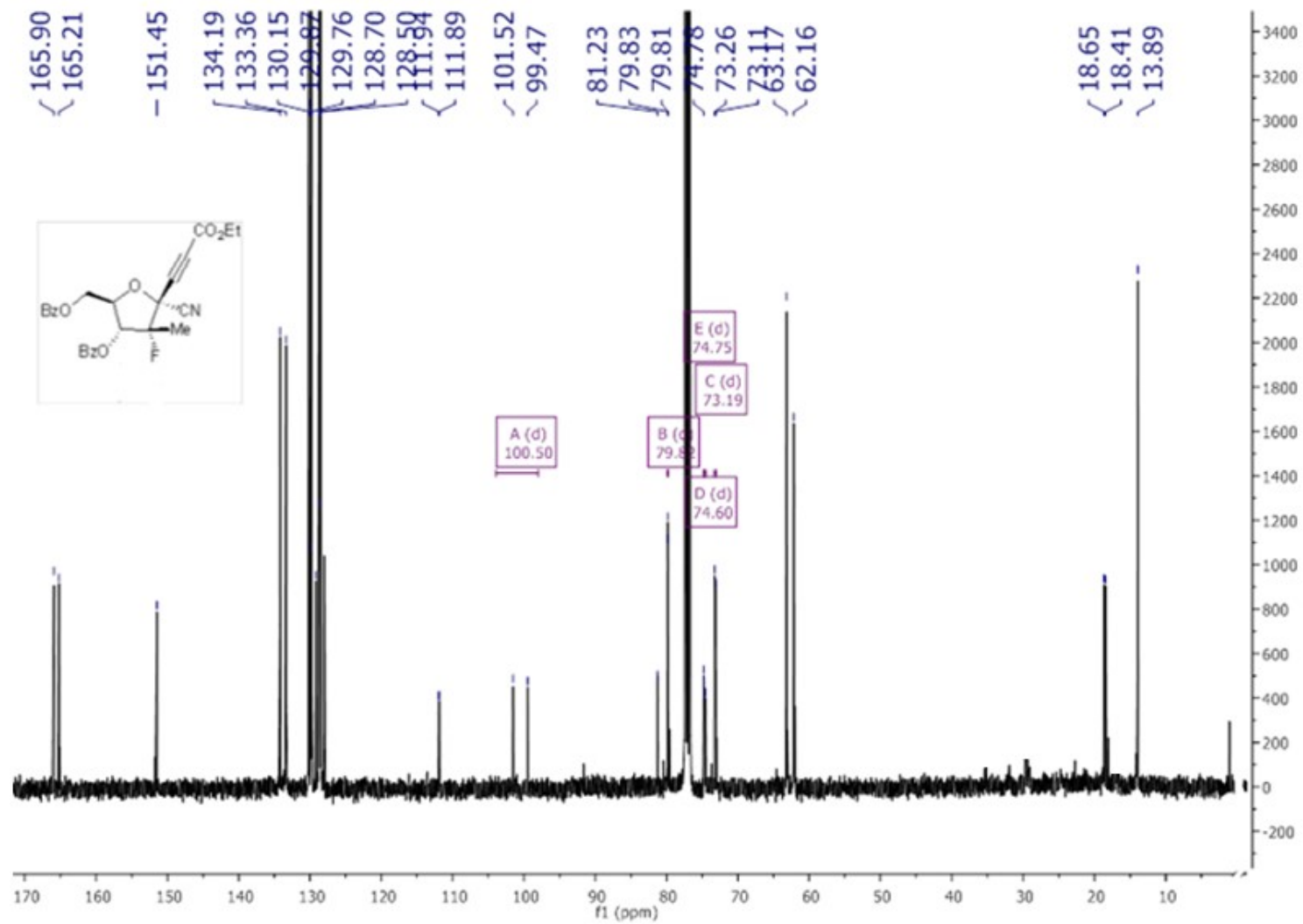
¹³C NMR Spectra for **41**:



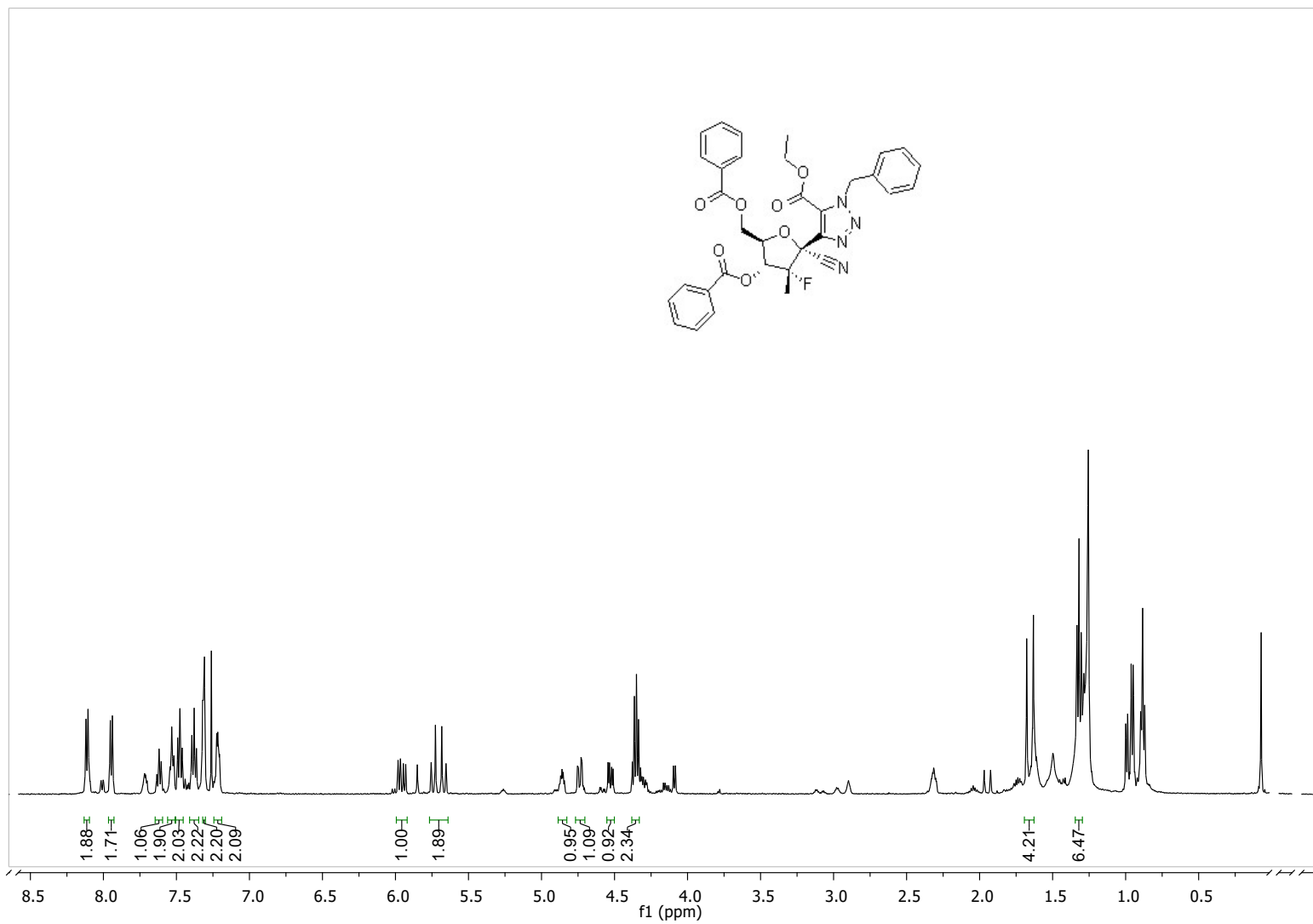
¹H NMR Spectra for **42**:



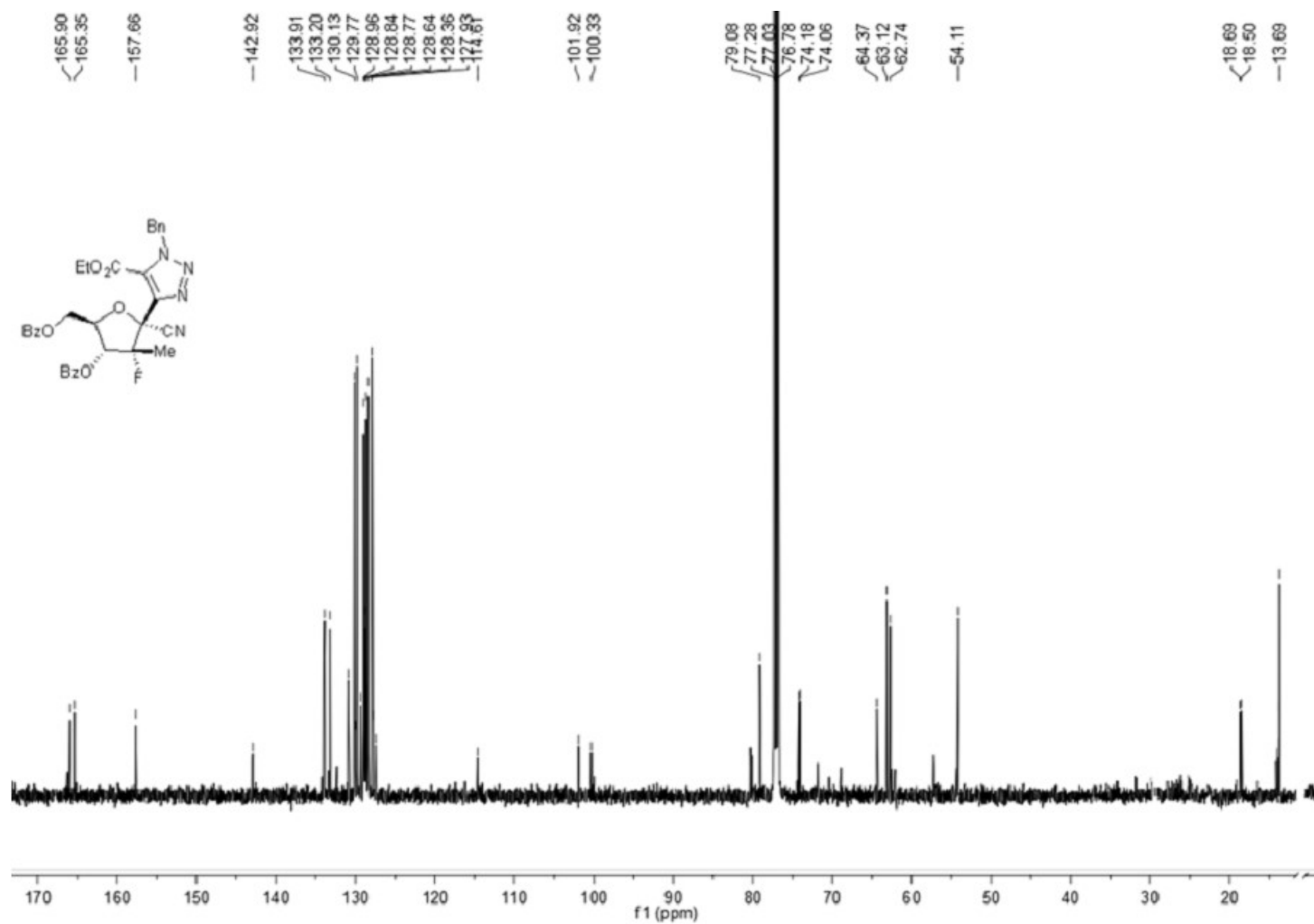
¹³C NMR Spectra for **42**:



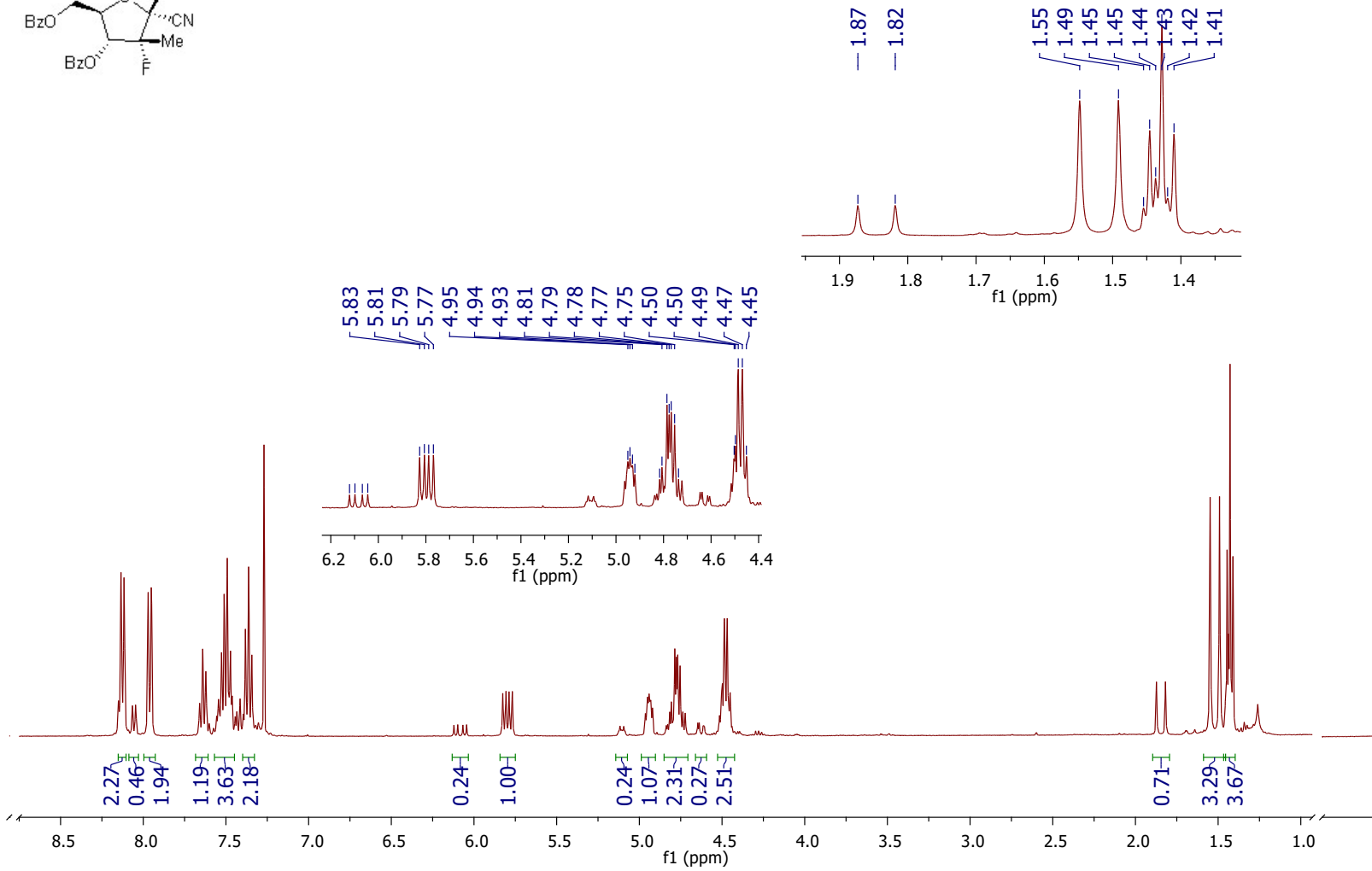
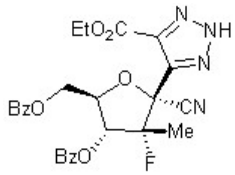
¹H NMR Spectra for **43**:



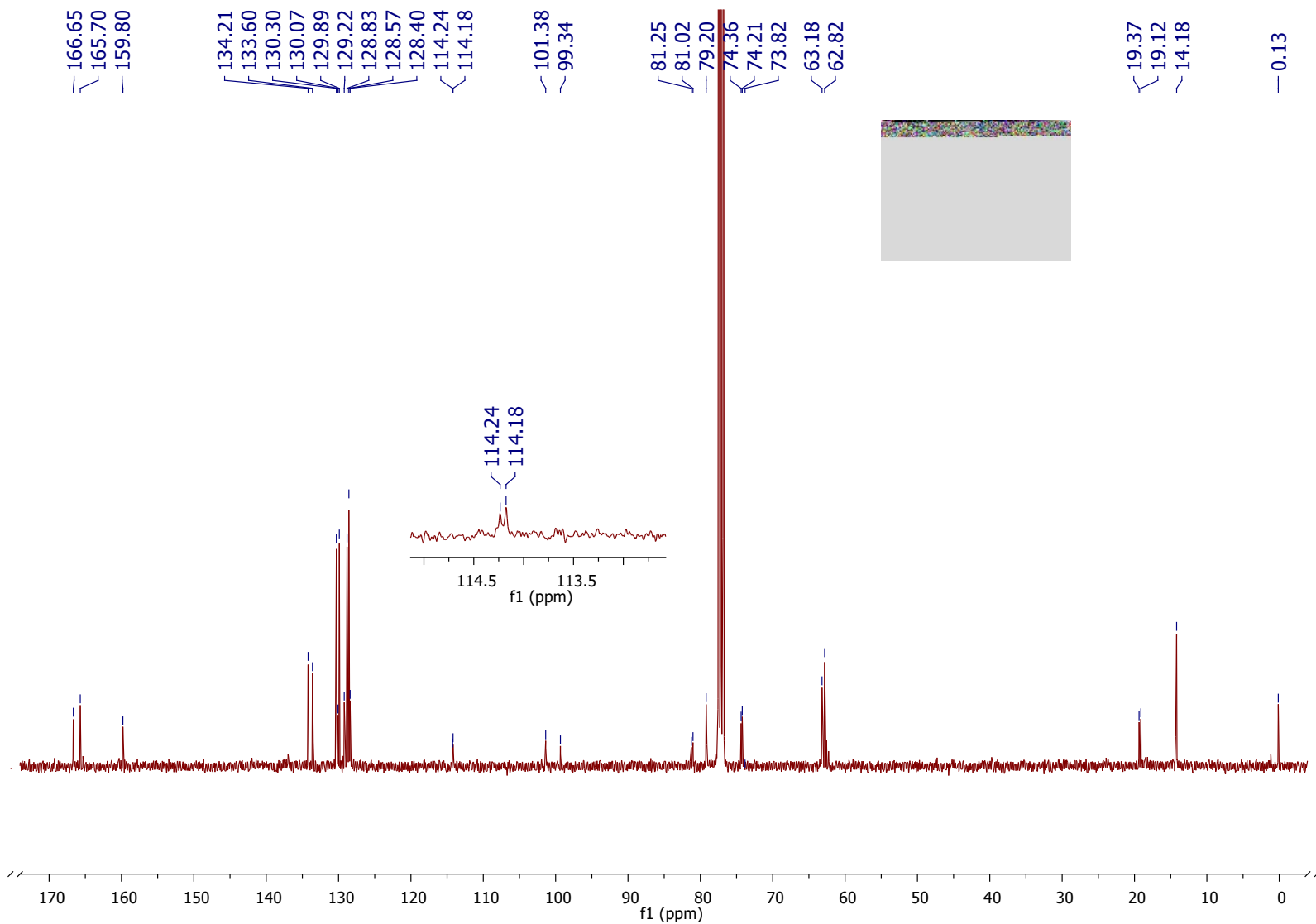
¹³C NMR Spectra for 43:



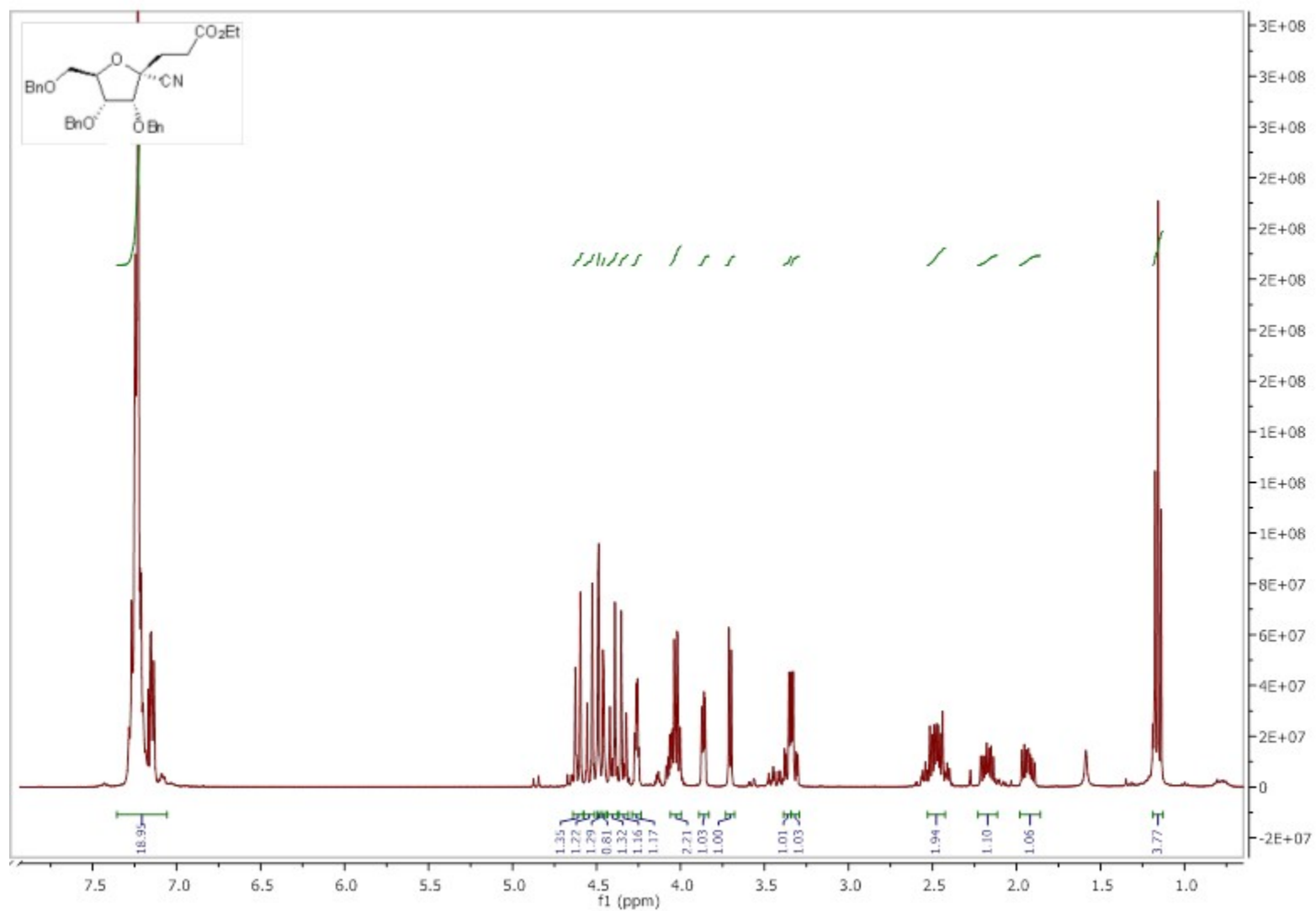
¹H NMR Spectra for 44:



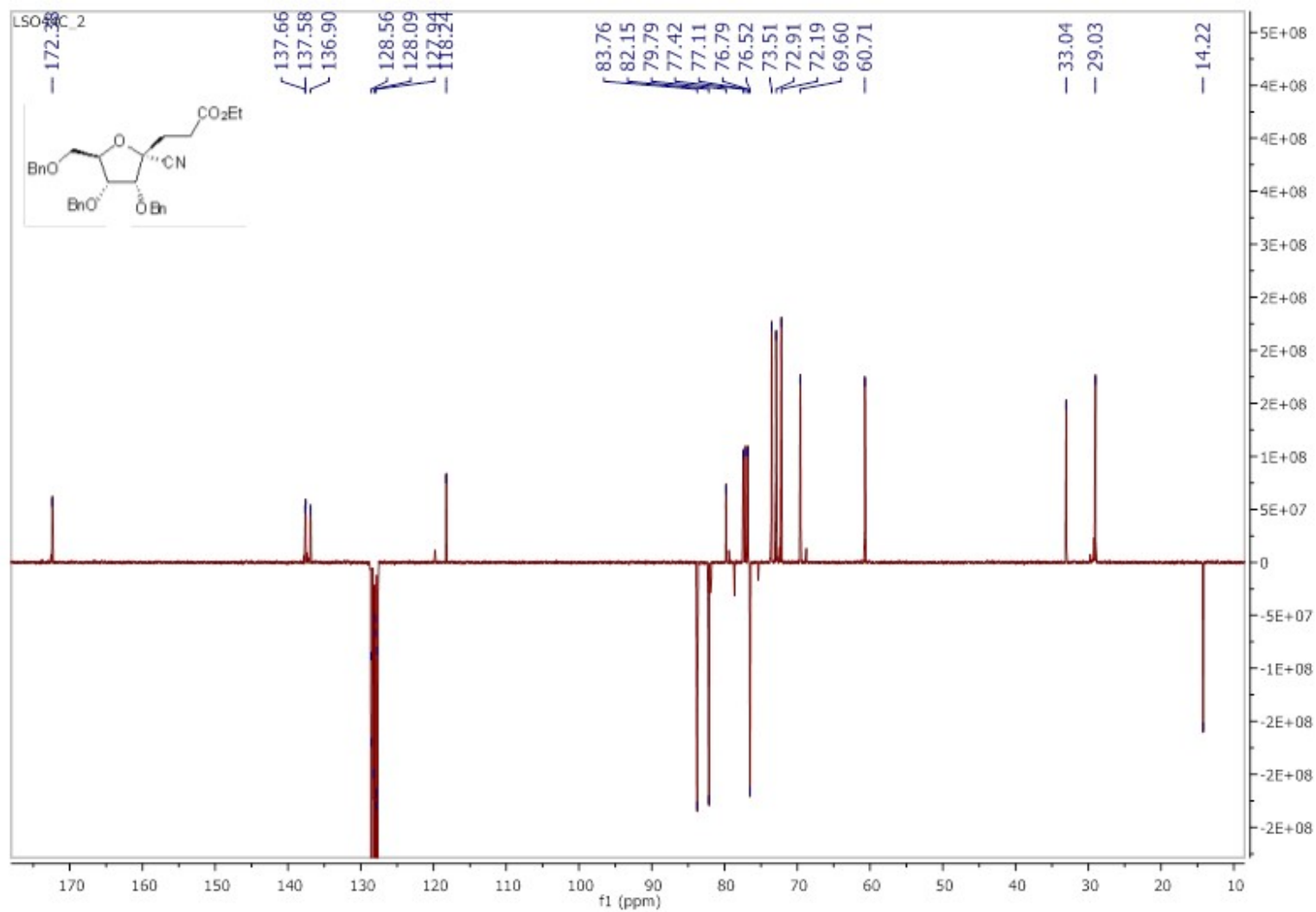
¹³C NMR Spectra for **44**:



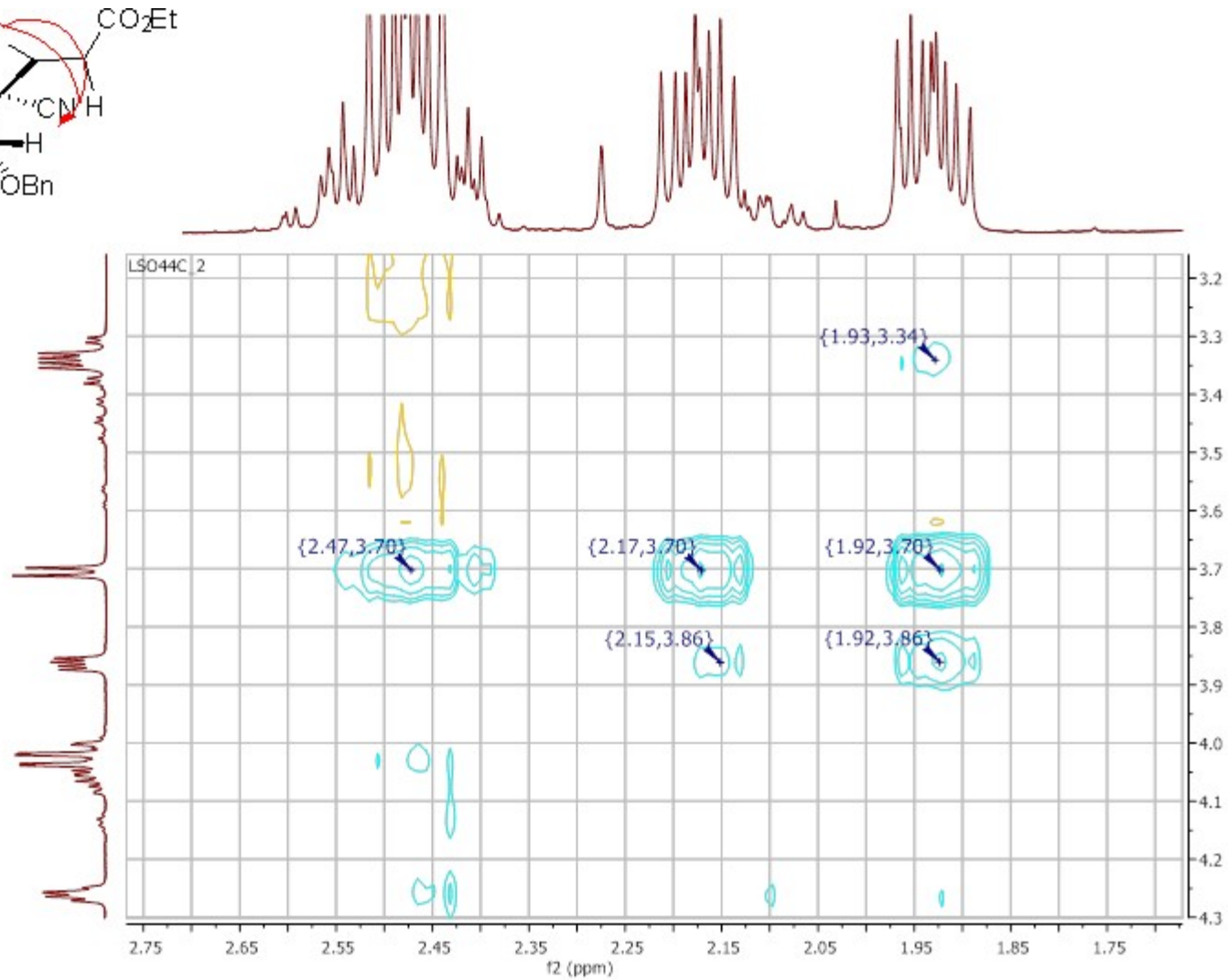
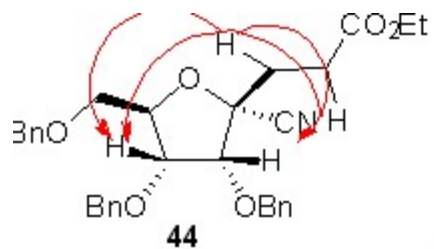
¹H NMR Spectra for **45**:



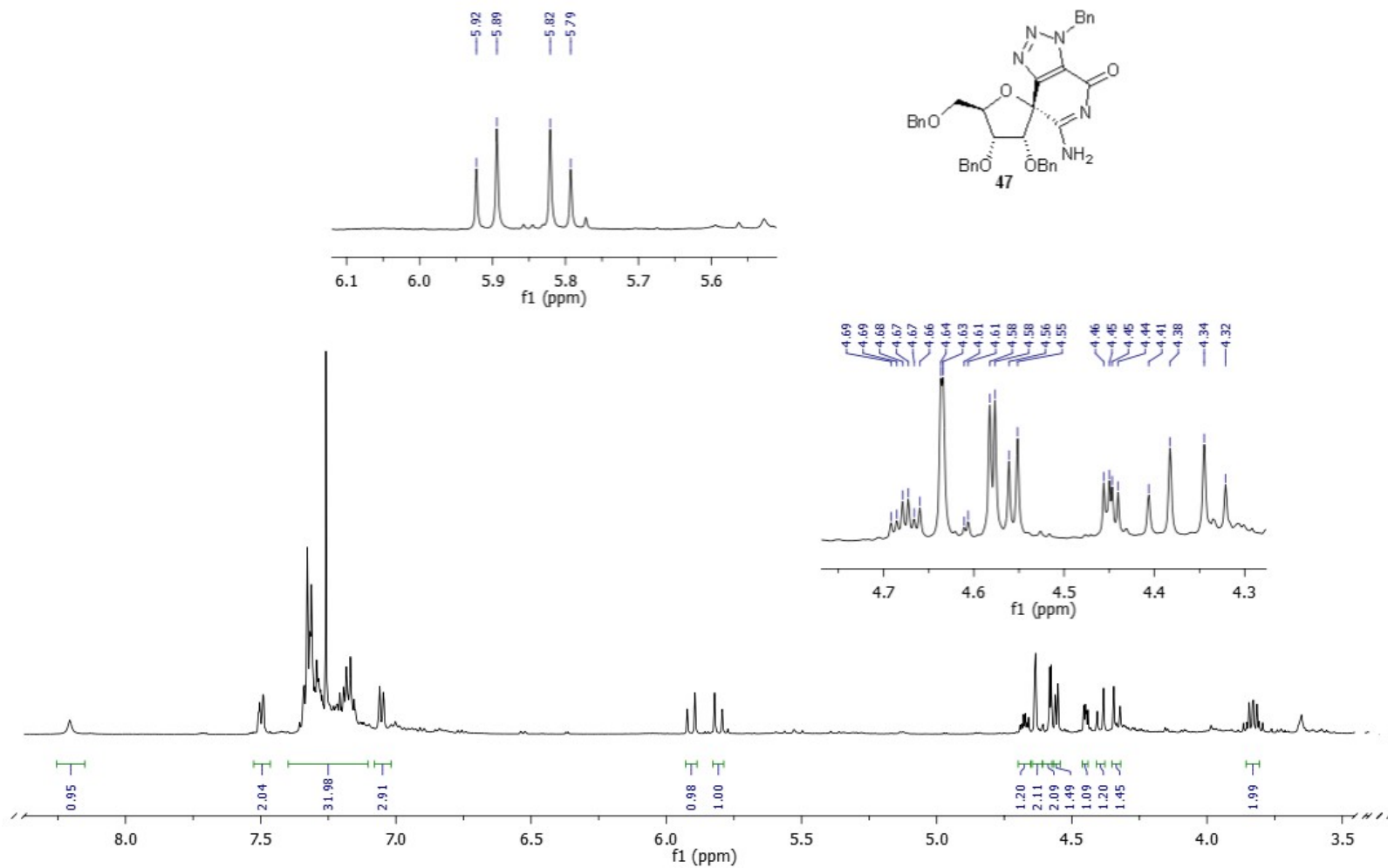
¹³C NMR Spectra for **45**:



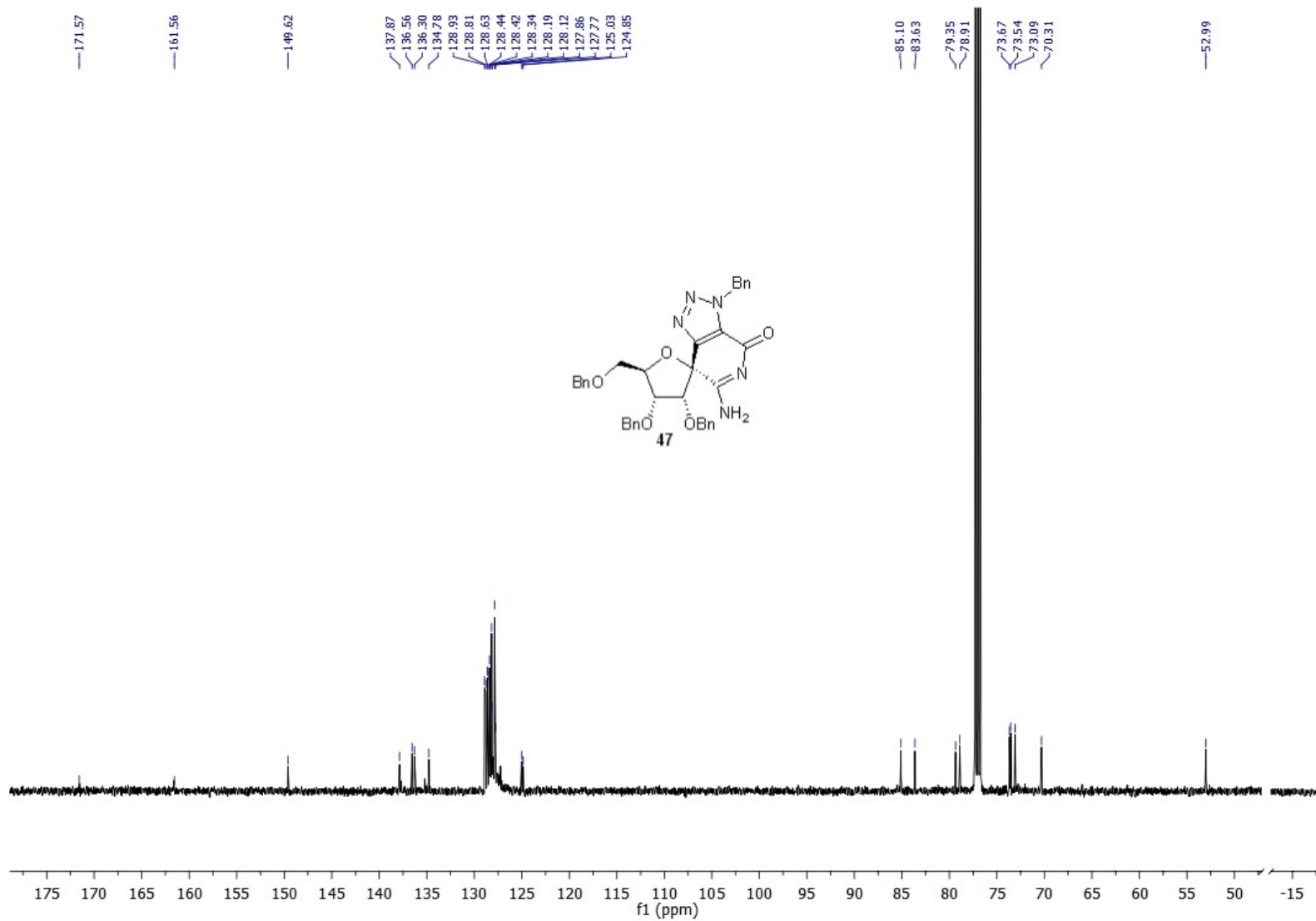
NOESY spectra of **45**:



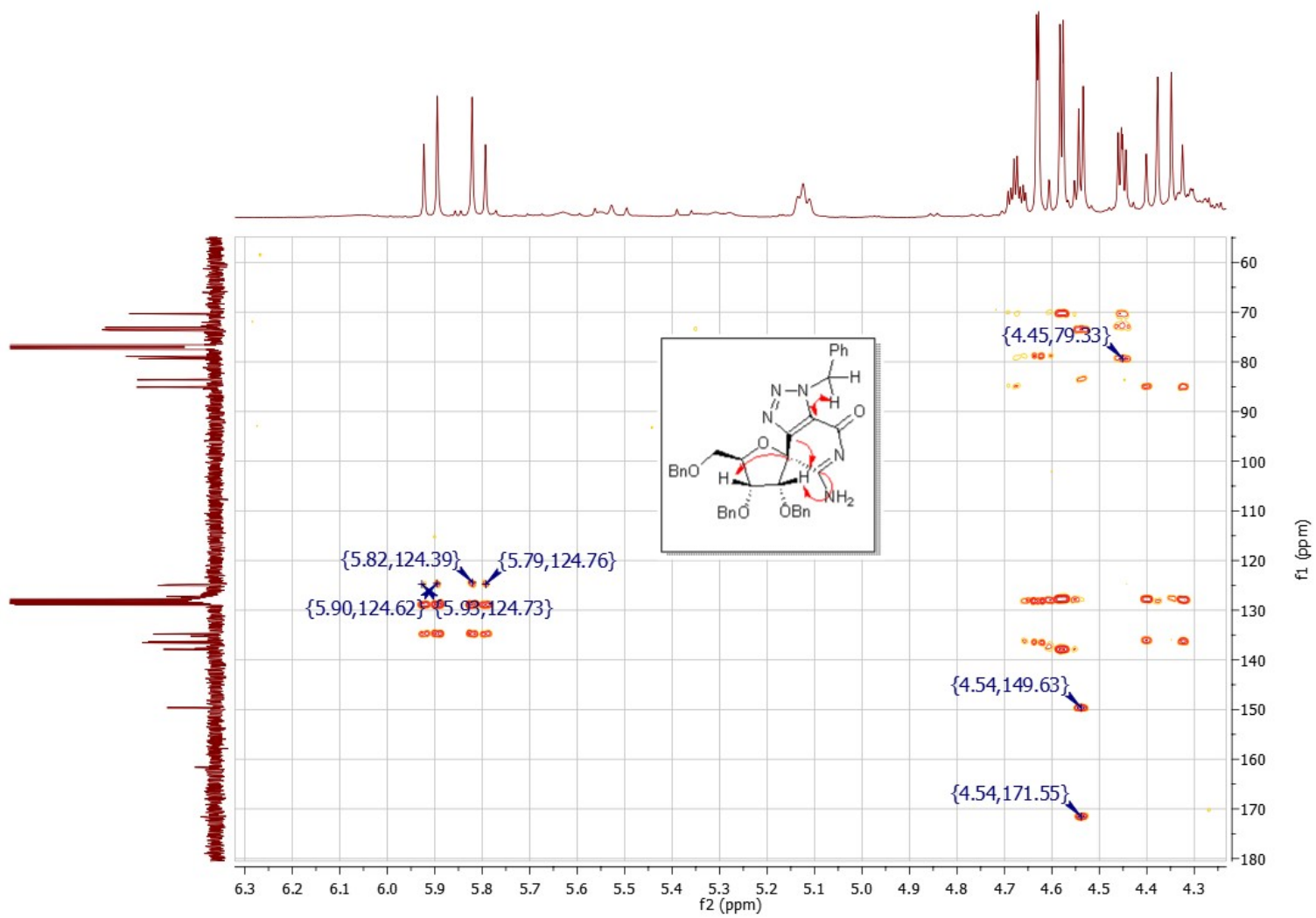
¹H NMR Spectra for **47**:



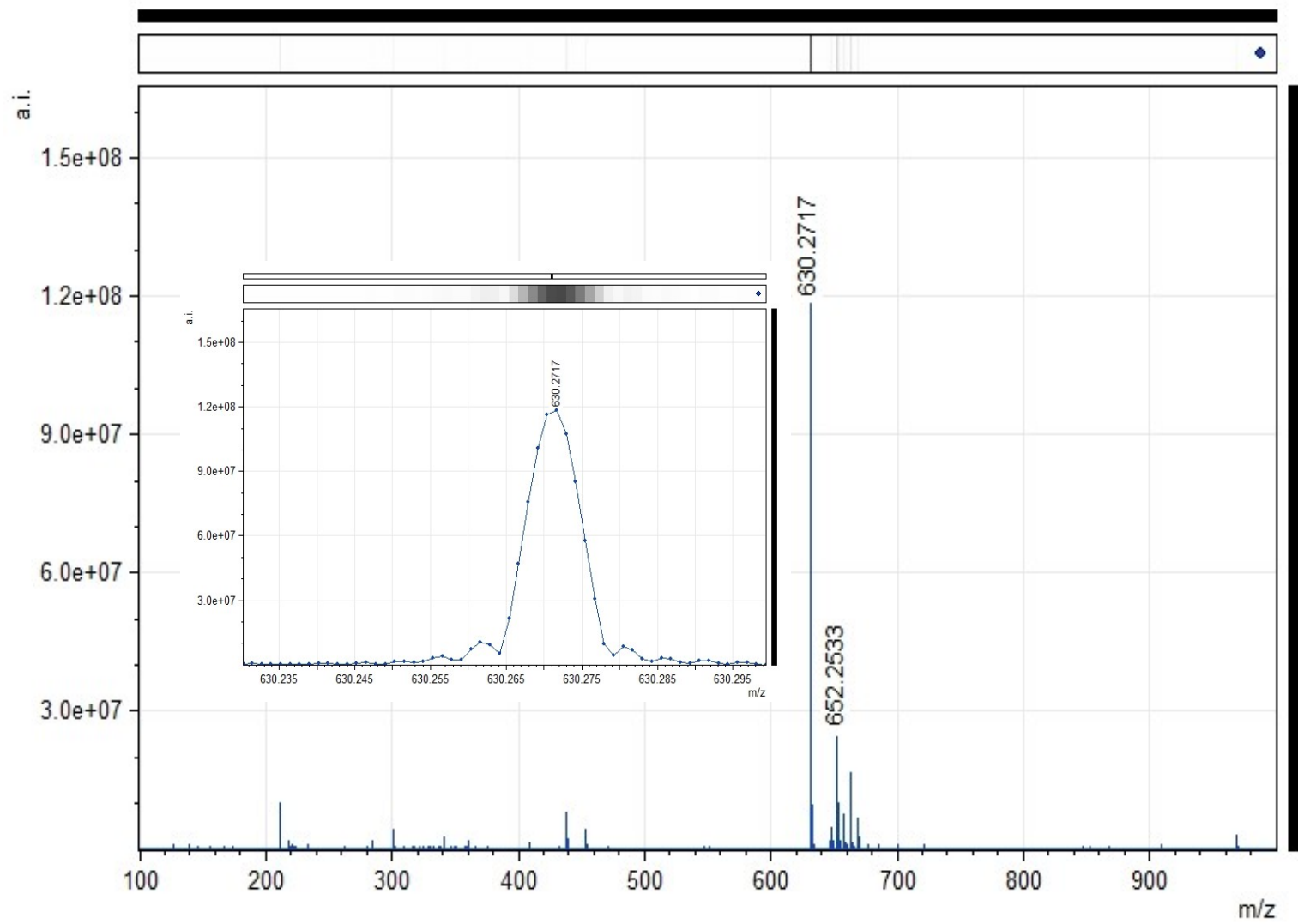
^{13}C NMR Spectra for **47**:



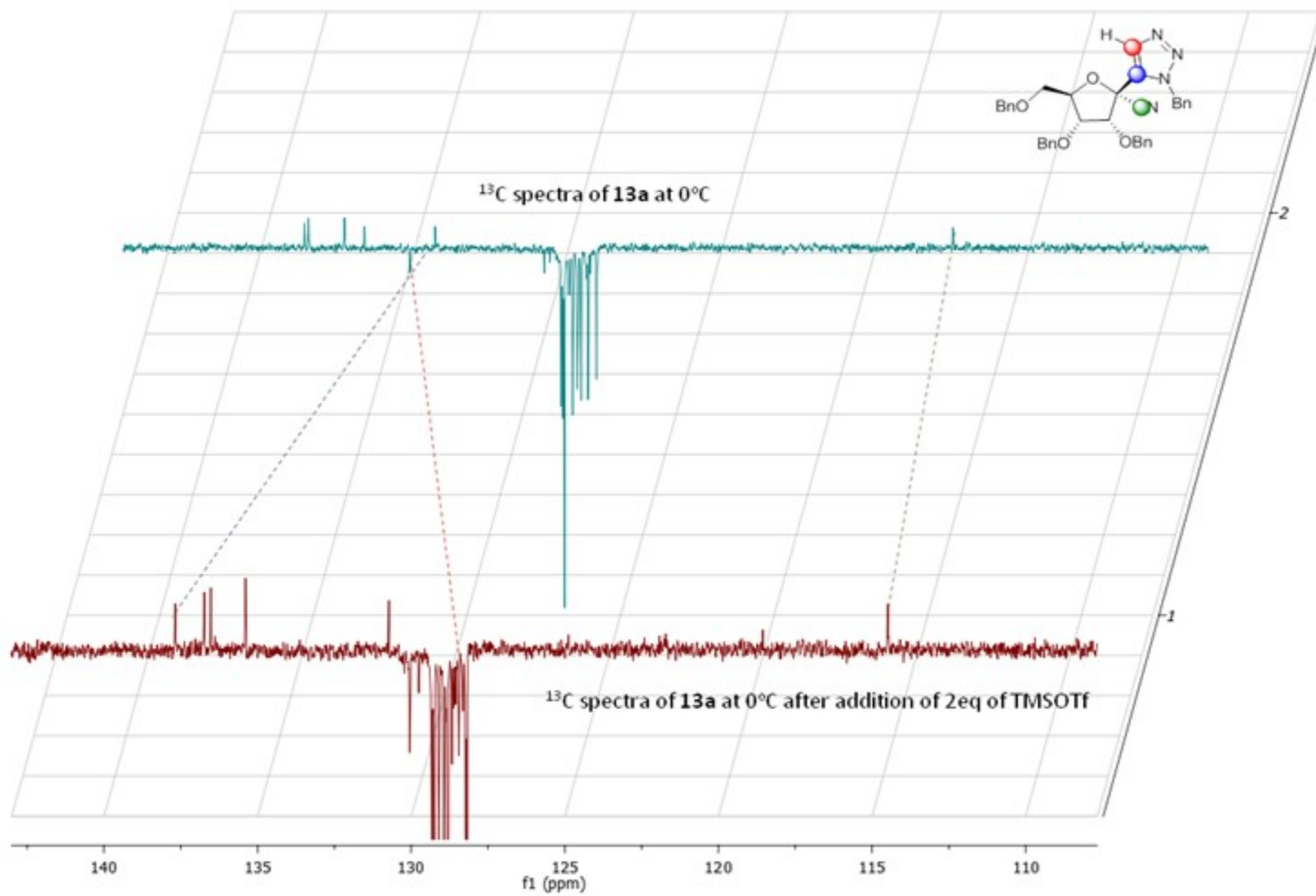
HMBC Correlations of 47:



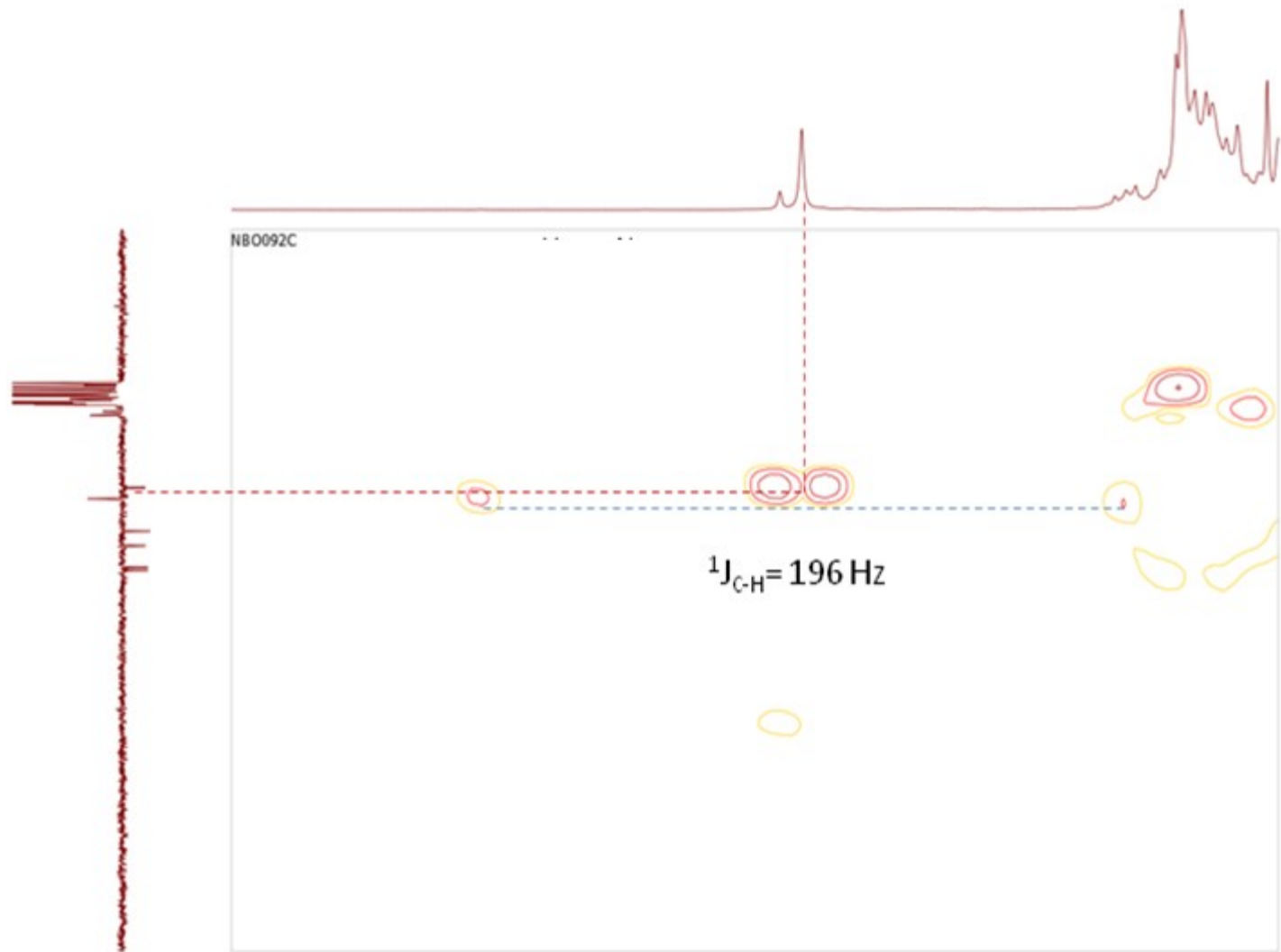
HRMS of compound 47



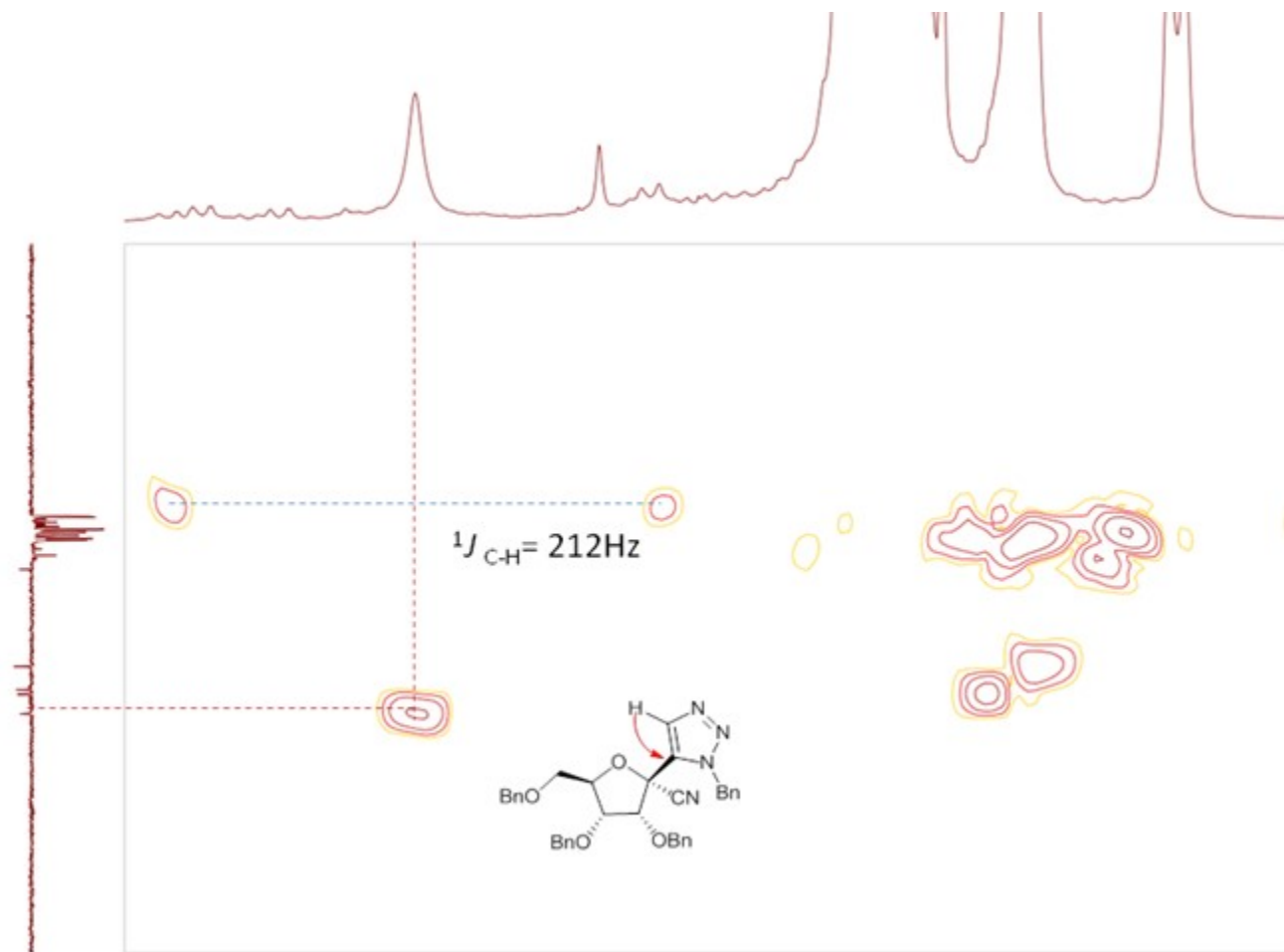
^{13}C NMR experiment for the interaction of **31a** with TMSOTf



HMBC Spectra of **31a** at 0°C



HMBC Spectra of **31a** at 0 °C after addition of 2 eq of TMSOTf



¹ S. G. Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 4, 413.