Supporting Information

Efficient Convergent Synthesis of 1,3-Diazepinone Nucleosides by Ring-Closing Metathesis and Direct Glycosylation

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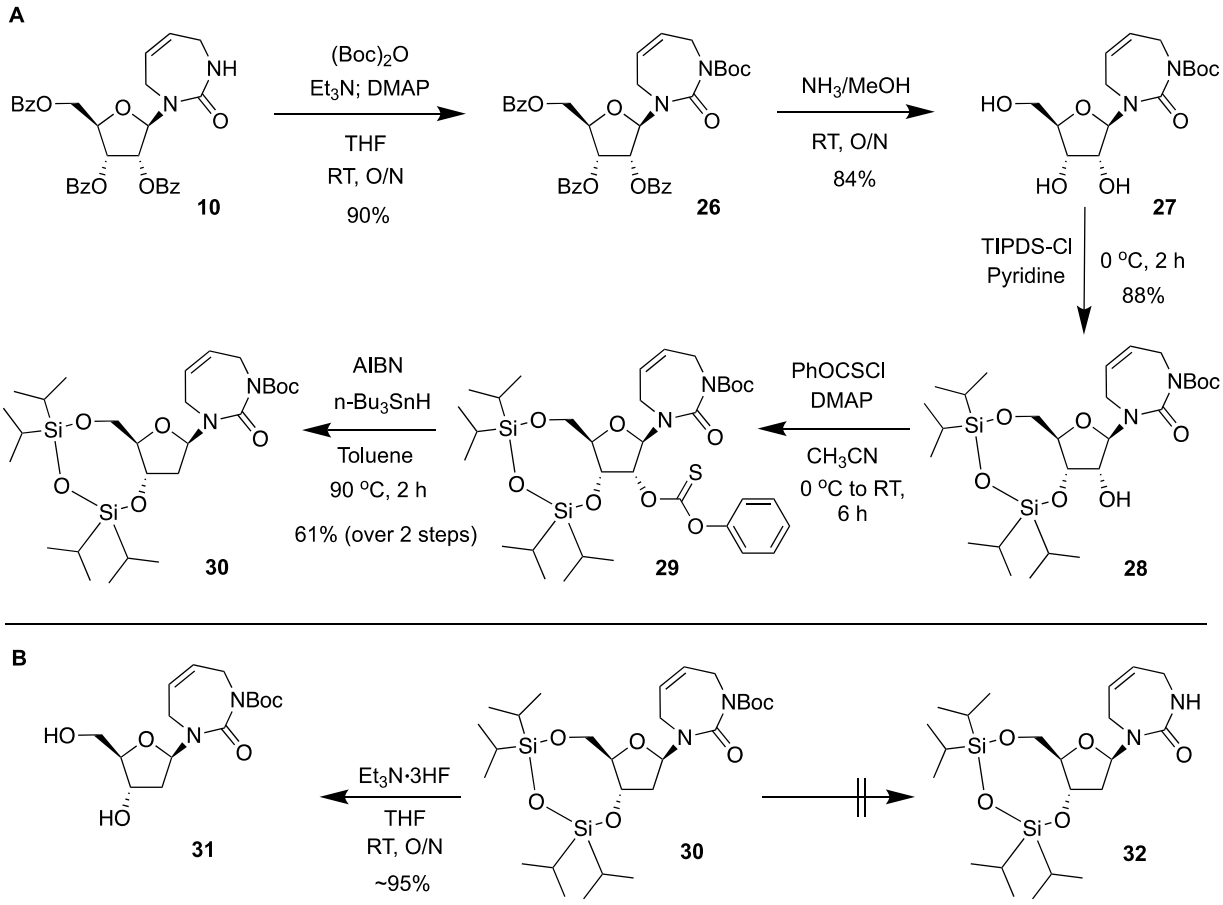


Scheme S1. Attempted synthesis of 2′-deoxyribo-diazepinone nucleoside by 2′-deoxygenation.

To attempt 2′-deoxygenation, the urea NH in tribenzoyl-protected riboside **10** was first orthogonally blocked with Boc to give fully protected **26** in high yield. We had observed that protection of this diazepinone NH was critical as it otherwise interfered with the 2′-thioacylation (**28** to **29**). From **26**, methanolic ammonia was used to remove the benzoyl protection to furnish *N*-Boc-protected diazepinone riboside **27**, which was selectively 5′- and 3′-TIPDS-protected to provide silyl derivative **28**. This was then reacted with phenyl chlorothionoformate to give the deoxygenation precursor **29**, which was subjected to Barton-McCombie deoxygenation to yield the protected 2′-deoxy-diazepinone nucleoside **30** in 40% yield over two steps. Finally, with the protected nucleoside **30** in hand, we tried to remove the *N*- and *O*- protecting groups. While the

silyl group could be removed in quantitative yield to give **31** with ease, subsequent attempts to remove the *N*-Boc group with mild acidic conditions including Lewis acids gave a mixture of products. The same *N*-Boc deprotection issue occurred when first attempting to remove this group from nucleoside **30** before the TIPDS removal. These problems, along with the long synthetic scheme prompted us to explore an alternative strategy.

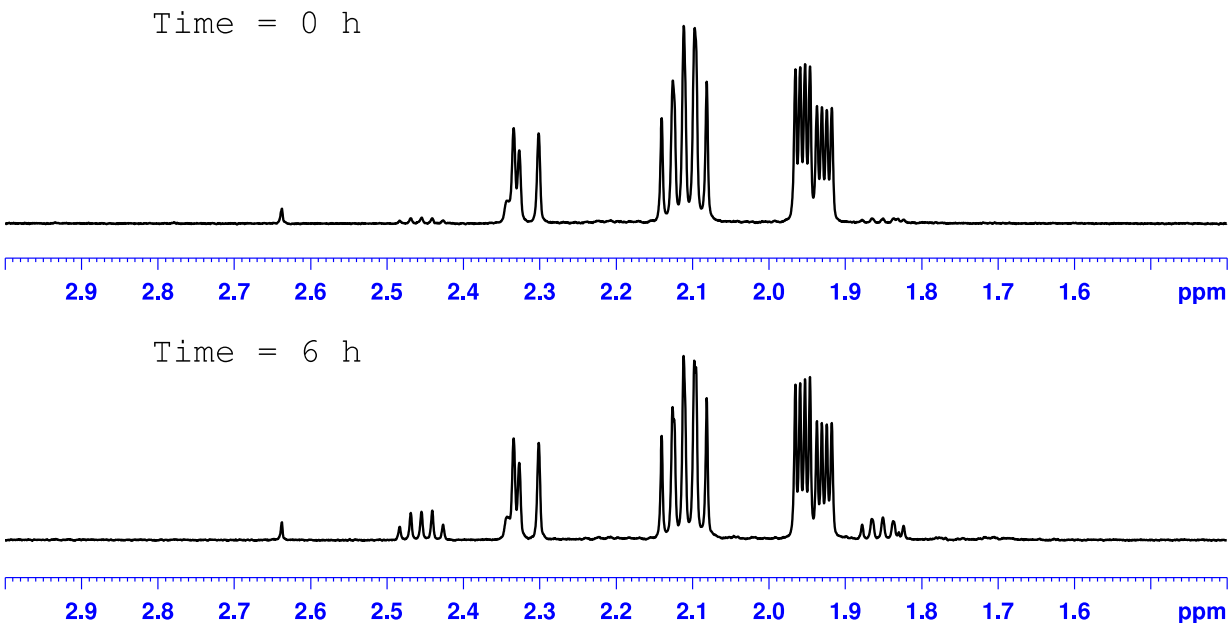


Figure S1. Comparison of ^{1}H NMR spectra of 2′-deoxyribo-diazepinone nucleoside **16** in D_2O. Top) Fully deprotected nucleoside **16** showing 2′-CH_2 multiplets at 2.15–2.08 and 1.97–1.91 ppm at time zero. Bottom) Same sample after 6 h in D_2O at room temperature showing additional 2′-CH_2 multiplets forming at 2.49–2.42 and 1.88–1.82 ppm.

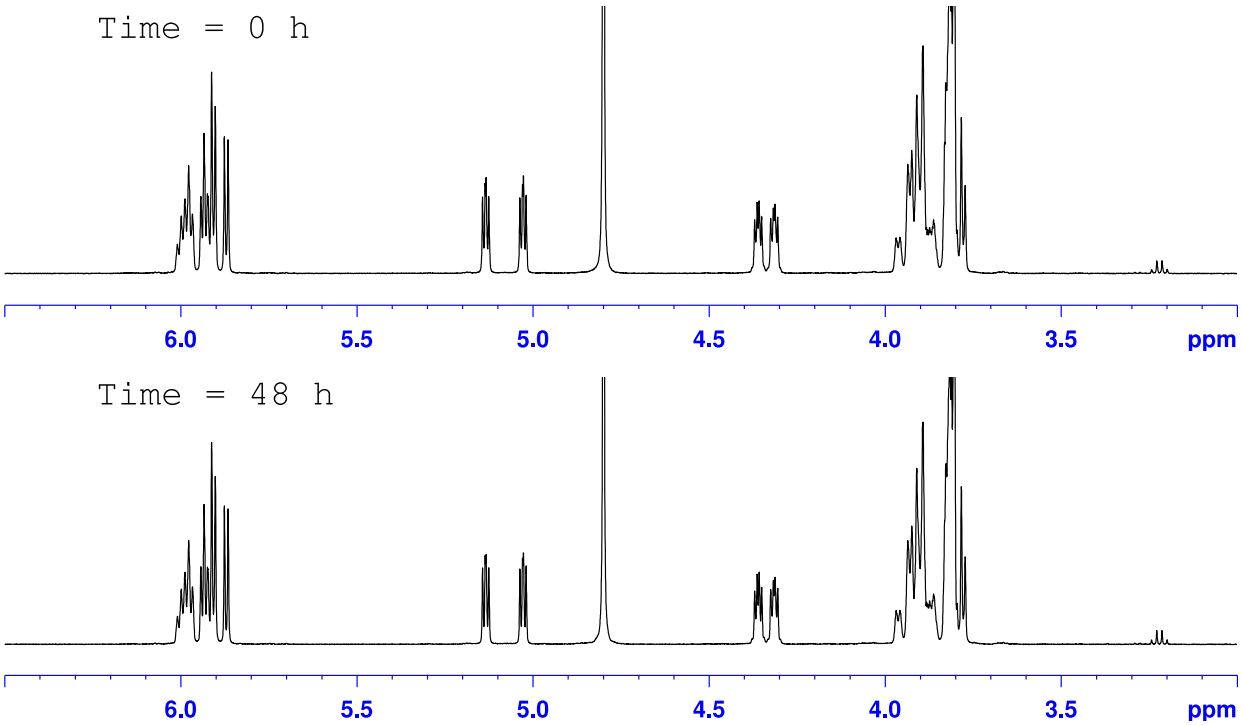


Figure S2. Comparison of ^{1}H NMR spectra of 2′-fluoroarabino-diazepinone nucleoside **21** in D_2O: Top) Fully deprotected nucleoside **21** at time zero. Bottom) Same sample after 48 h in D_2O at room temperature showing no change in spectra.

Figure S3. Comparison of ^{1}H NMR spectra of 2′-deoxy-2′,2′-difluoro-diazepinone nucleoside **23** in D_2O: Top) Fully deprotected nucleoside **23** at time zero. Bottom) Same sample after 48 h in D_2O at room temperature showing no change in spectra.

2D NOESY NMR crosspeaks were used to confirm β and α anomer assignment after glycosylation:

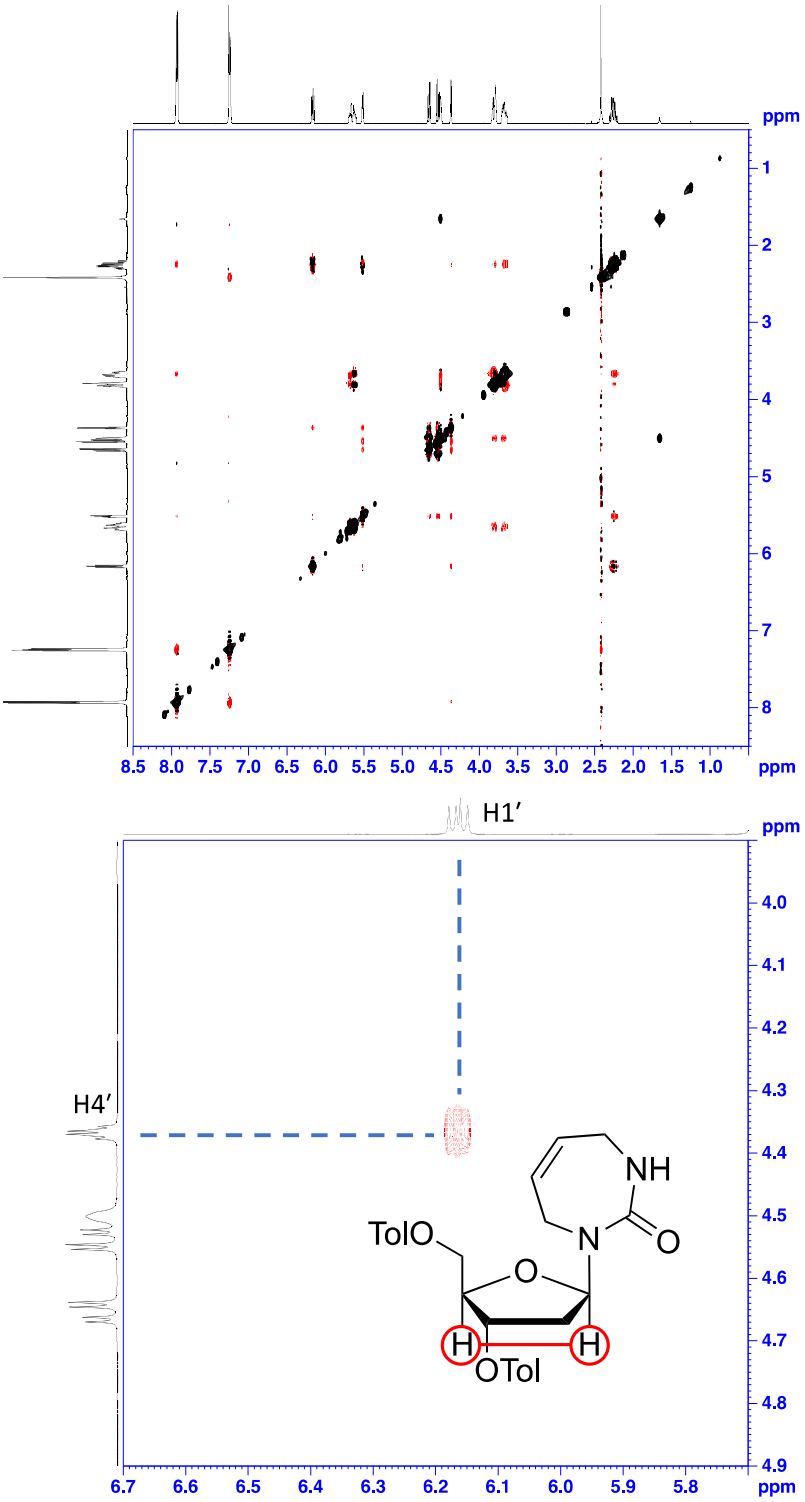


Figure S4. 2D NOESY NMR spectra for nucleoside 14 (β-anomer). Top: Whole spectrum, Bottom: Zoomed region showing through space interaction of anomeric proton with H4′.

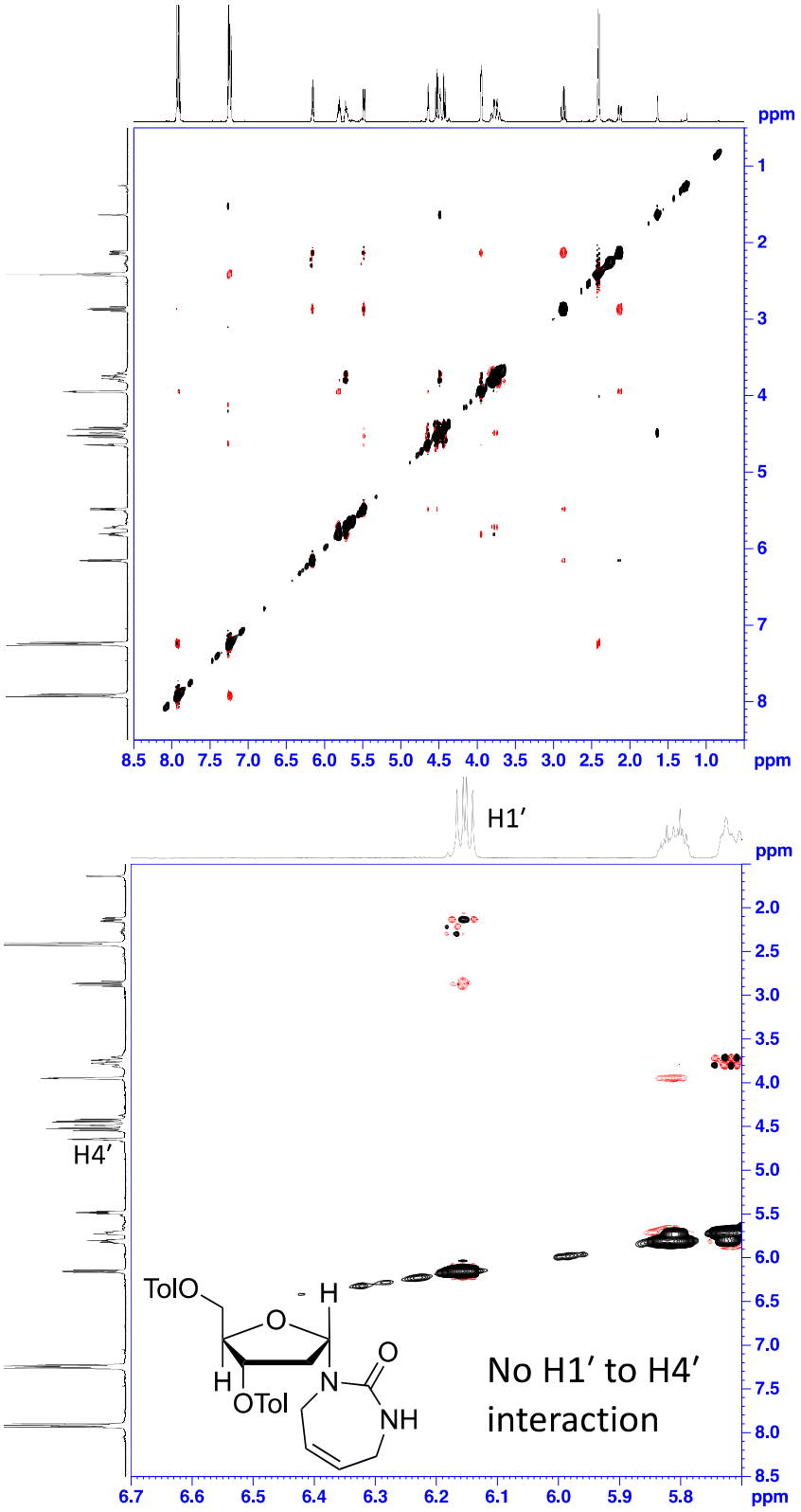


Figure S5. 2D NOESY NMR spectra for nucleoside 15 (α-anomer). Top: Whole spectrum, Bottom: Zoomed region showing no through space interaction between anomeric proton and H4′.

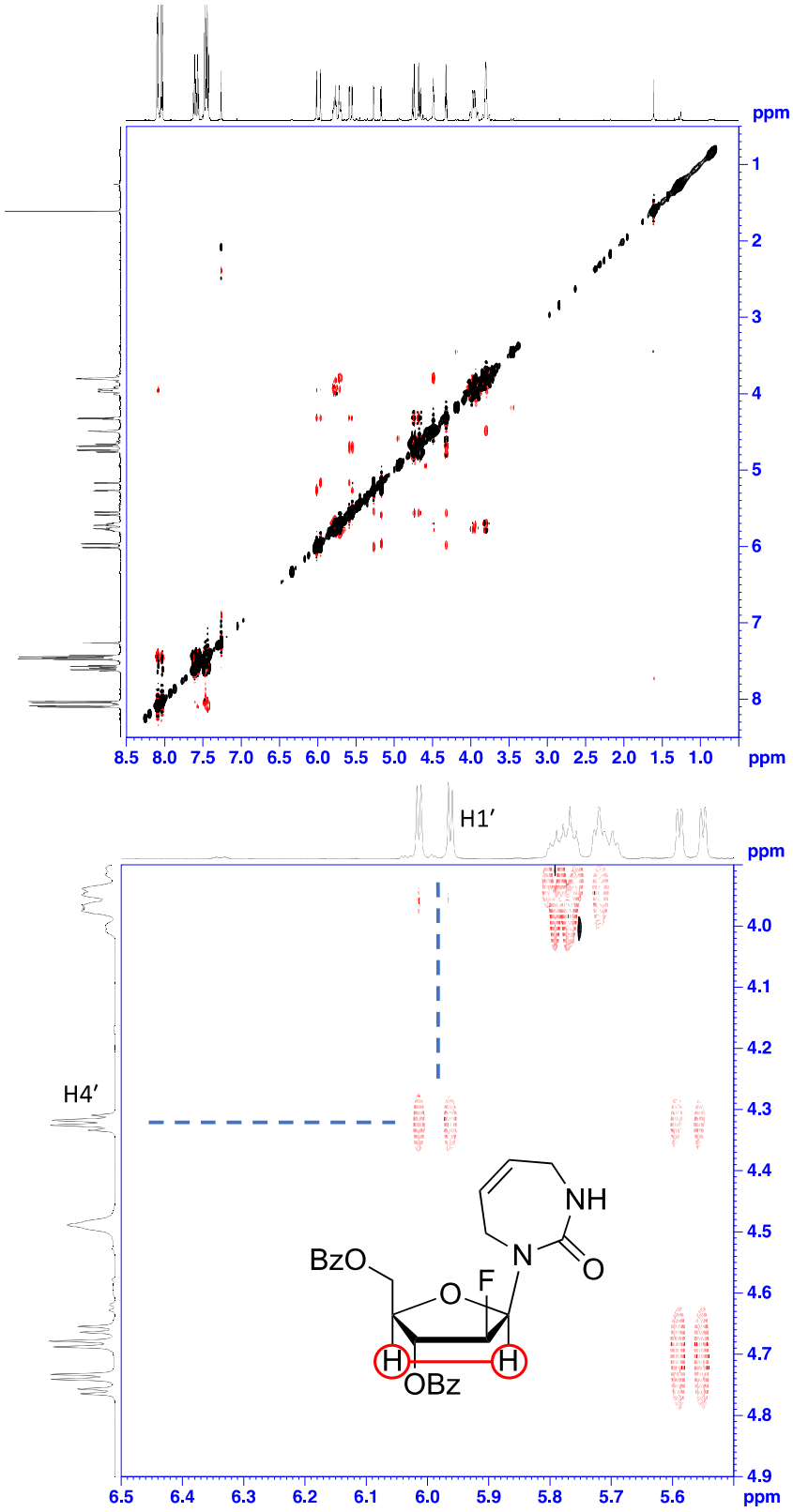


Figure S6. 2D NOESY NMR spectra for nucleoside 20 (β-anomer). Top: Whole spectrum, Bottom: Zoomed region showing through space interaction of anomeric proton with H4′.

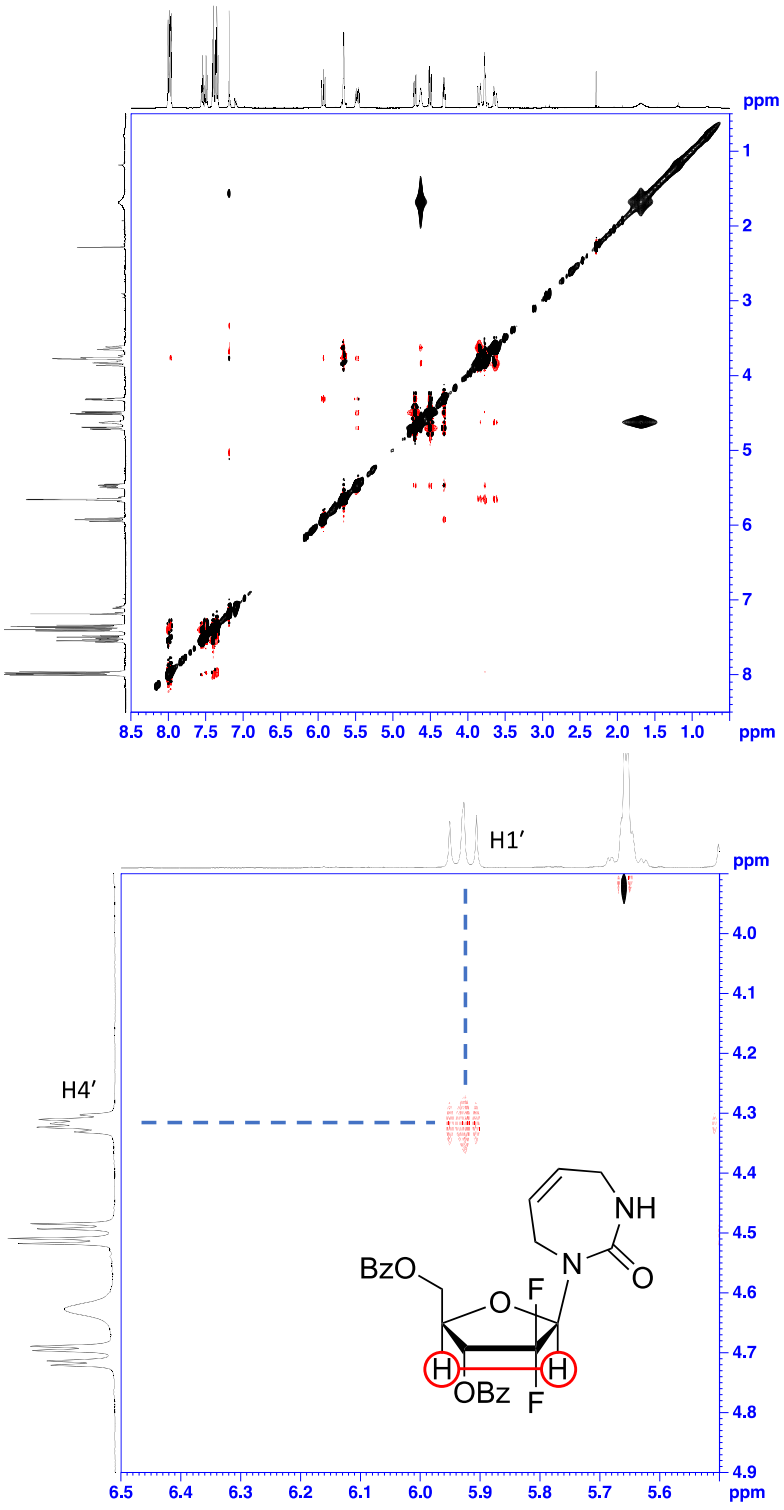
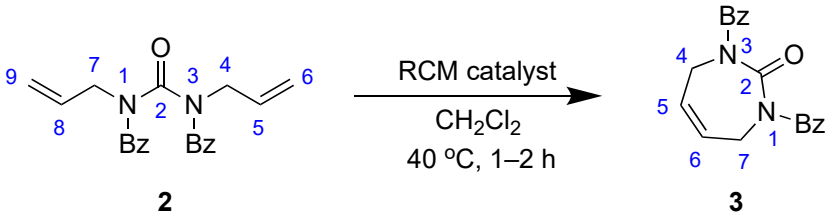


Figure S7. 2D NOESY NMR spectra for nucleoside 23 (β-anomer). Top: Whole spectrum, Bottom: Zoomed region showing through space interaction of anomeric proton with H4′.

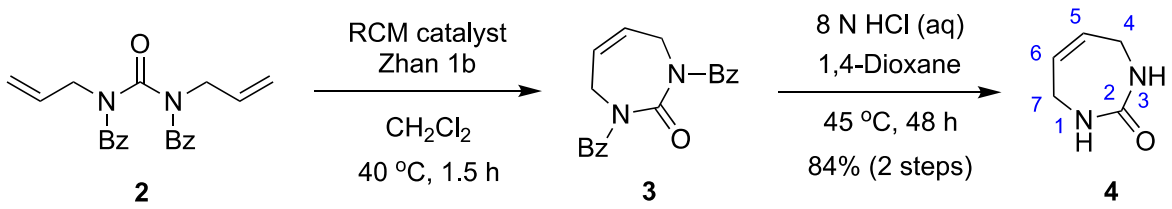
General procedure for RCM reactions with different catalysts



2 **3**

Compound **2** (0.42 g, 1.2 mmol) was dissolved in anhydrous CH_2Cl_2 (200 mL) and this solution degassed using 10 × fill cycles of vacuum and argon. The solution was then heated to 40 °C under an argon atmosphere. After 15 min, RCM catalyst (0.12 mmol, 0.10 eq) was then added to the solution. The solution was stirred for 1 h or until TLC indicated reaction had reached completion (the reaction with the Grubbs first-generation catalyst was slower and took 2 h to complete) (R_f starting material = 0.67, R_f product = 0.51, 25% EtOAc/hexanes, visualized by UV). Solvents were evaporated under reduced pressure, the residue redissolved in a minimum volume of CH_2Cl_2, and purified by flash chromatography using a silica gel column (SiliaSep, 40 g, gradient elution with CH_2Cl_2). Product containing fractions were pooled and evaporated in *vacuo* to give the diazepinone derivative as a white solid. TLC: R_f = 0.50 (25% EtOAc/hexanes).

RCM and Bz deprotection without intermediate purification



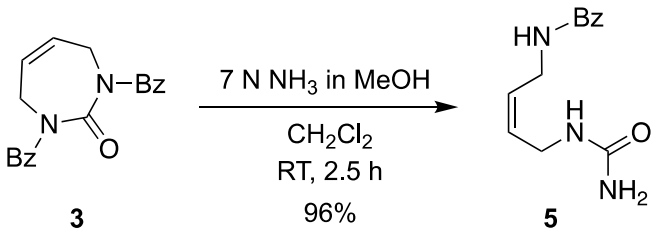
2 **3** **4**

Compound **2** (2.50 g, 7.18 mmol) was dissolved in anhydrous CH_2Cl_2 (1.3 L) and solution degassed. The solution was heated to 40 °C, and Zhan 1b catalyst (0.053 g, 0.072 mmol, 0.01 eq) was then added to the solution and stirred for 1 h. Upon completion (monitored by TLC), another three additions of compound **2** (2.50 g each) and Zhan 1b catalyst (0.053 g each) were performed

in the same vessel, as described previously. The solvent was evaporated to provide 9.67 g of brown solid.

Without purification, crude compound **3** (9.67 g) was dissolved in 1,4-dioxane (60 mL) and cooled in an ice bath. Aqueous 8 N HCl (30 mL) was slowly added whilst stirring. The mixture was warmed to room temperature before heating at 45 °C for 48 h. The reaction mixture was cooled to 0 °C and neutralised to pH 7 with aqueous 4 N NaOH (~80 mL). The solvents were evaporated *in vacuo* and the residue was dried under high vacuum overnight. The dried product was ground using a pestle and mortar and triturated with 10% MeOH/CH_2Cl_2, filtering and repeating until TLC (R_f = 0.60, 10% MeOH/CH_2Cl_2, visualised by ninhydrin stain) showed no more product eluting. The solution was passed through a short silica gel bed, eluting with 10% MeOH/CH_2Cl_2 until TLC (same conditions and visualisation) showed no further product coming out. The combined fractions were evaporated in *vacuo* to give a pale-yellow solid. Recrystallization from MeOH gave compound **4** as a white crystalline solid. First crop: 2.01 g. Second crop: 0.54 g. The filtrate was concentrated in *vacuo*, and the residue was purified by flash column chromatography, using elution gradient of 10–20% MeOH/CH_2Cl_2. Fractions were pooled based on TLC and evaporated. The residue was recrystallised from MeOH to give a third crop: 0.15 g. Total yield over two steps: 2.70 g, 84%.

(*Z*)-*N*-(4-Ureidobut-2-en-1-yl)benzamide (5).



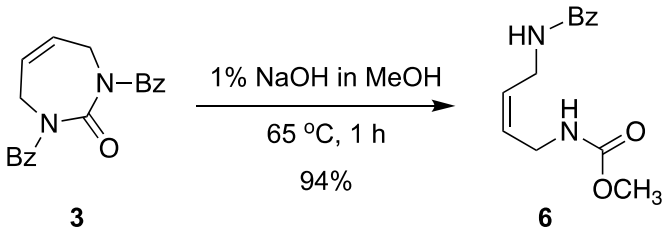
3 **5**

Benzoyl-protected diazepinone **3** (0.50 g, 1.56 mmol) was dissolved in a small amount of anhydrous dichloromethane (2 mL), this solution was then charged with 7 N methanolic ammonia (50 mL) in a sealed glass vessel and stirred at room temperature. TLC indicated the reaction was complete within 2.5 h by consumption of starting material, and formation of a new lower spot (stained by ninhydrin stain). Solvents were evaporated under reduced pressure, the residue redissolved in a minimum volume of CH_2Cl_2, and purified by flash chromatography using a silica gel column (SiliaSep, 12 g, gradient elution with 0–10 % MeOH/CH_2Cl_2). Product containing fractions were pooled and evaporated in *vacuo* to give the product (0.35 g, 96%) as a white solid, which was identified as the ring-opened urea compound **5**. TLC: R_f = 0.42 (10% MeOH/CH_2Cl_2).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65 (t, J = 5.4 Hz, 1H), 7.86–7.84 (m, 2H), 7.53–7.50 (m, 1H), 7.47–7.44 (m, 2H), 6.04 (t, J = 5.6 Hz, 1H), 5.52–5.42 (m, 4H), 3.94 (t, J = 5.8 Hz, 2H), 3.72 (t, J = 5.8 Hz, 2H) ppm.

^{13}C NMR (126 MHz, DMSO-d_6): δ 165.92 (C=O), 158.64 (C=O), 134.40 (C), 131.11 (CH), 130.01 (CH), 128.26 (2 × CH), 127.57 (CH), 127.15 (2 × CH), 36.45 (CH_2), 36.25 (CH_2) ppm.

Methyl (*Z*)-(4-benzamidobut-2-en-1-yl)carbamate (6).



3 **6**

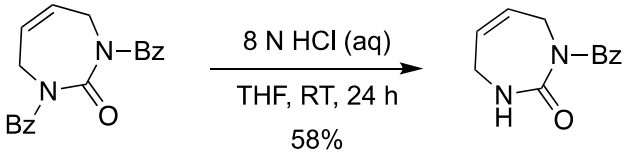
Benzoyl-protected diazepinone **4** (3.42 g, 10.7 mmol) was dissolved in a solution of 1 % NaOH in methanol and refluxed at 65 °C for 1 h. The reaction mixture was cooled to room temperature, neutralized with aqueous 2 N HCl solution, and concentrated under reduced pressure. The solid

residue was triturated with 10 % MeOH/CH_2Cl_2 and filtered. This was repeated, and combined organic fractions evaporated to dryness. The solid was redissolved in CH_2Cl_2 and purified by flash column chromatography using a silica gel column (SiliaSep, 40 g, elution with 50–100% EtOAc/CH_2Cl_2/. Product containing fractions were pooled, dried, and recrystallized from EtOAc to give the product (2.50 g, 94%) as a white solid, which was identified as the ring-opened carbamate compound **6**. TLC: R_f = 0.45 (50% EtOAc/CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 7.4 Hz, 2H), 7.49–7.46 (m, 1H), 7.42-7.39 (m, 2H), 7.12 (br s, 1H), 5.70 (q, J = 8.4 Hz, 1H), 5.62–5.57 (m, 1H), 5.30 (br s, 1H), 4.13 (t, J = 6.5 Hz, 2H), 3.88 (t, J = 6.2 Hz, 2H), 3.67 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.42 (C=O), 157.40 (C=O), 134.49 (C), 131.52 (CH), 129.35 (CH), 128.55 (2 × CH), 128.36 (CH), 127.23 (2 × CH), 52.30 (OCH_3), 37.73 (CH_2), 36.18 (CH_2) ppm.

1-Benzoyl-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (7).



3 **7**

When the *bis*-Bz protected compound **3** (2.0, 6.24 mmol) was treated with 8 N HCl in THF at room temperature for 24 h, compound **7** was isolated as the major product (0.78 g, 58%).

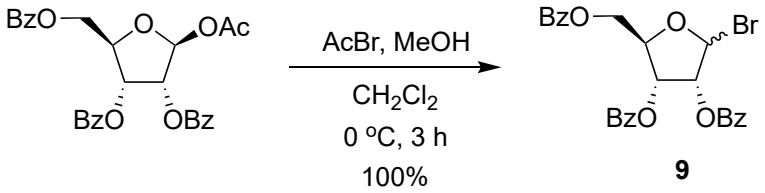
^{1}H NMR (500 MHz, DMSO-d_6): δ 8.07 (t, J = 4.0 Hz, 1H), 7.53–7.49 (m, 3H), 7.45–7.41 (m, 2H), 5.87–5.83 (m, 1H), 5.81–5.77 (m, 1H), 4.32–4.30 (m, 2H), 3.87–3.85 (m, 2H) ppm.

^{13}C NMR (126 MHz, DMSO-d_6): δ 170.28, 159.47, 135.70, 131.68, 128.34, 127.26, 126.27, 125.30, 41.63 ppm.

HRMS (ESI) *m/z*: Calcd. for $C_{12}H_{12}N_2O_2Na$ $[M + Na]^+$ 239.0791; found 239.0790.

Synthesis of Diazepinone Riboside

2,3,5-Tri-*O*-benzoyl-*α*,*β*-D-ribofuranosyl bromide (9).



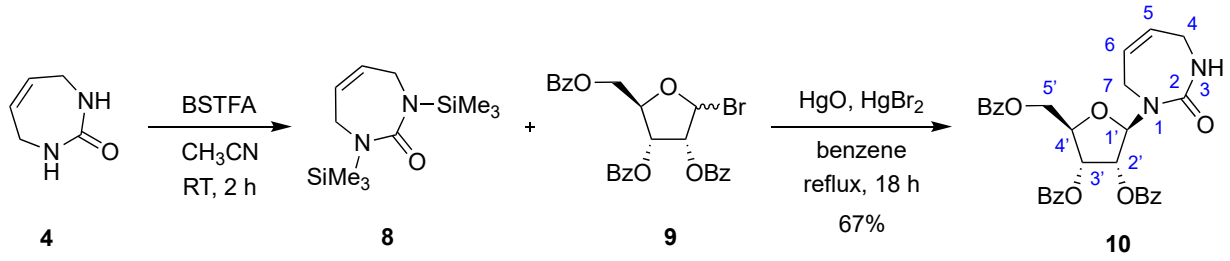
Anhydrous CH_2Cl_2 (140 mL) was added to a round-bottom flask, tightly sealed, and degassed using 10 × cycles of vacuum and argon fill. Three argon balloons were used for increased pressure. The CH_2Cl_2 was cooled to 0 °C and acetyl bromide (3.30 mL, 44.4 mmol) was added followed by the slow addition of MeOH (1.89 mL, 46.6 mmol). After stirring for 15 min at 0 °C, a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (5.60 g, 11.1 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise over 20 min. After stirring at 0 °C for 3 h, the reaction mixture was concentrated *in vacuo*, keeping the bath temperature below 10 °C, to yield a pale-yellow syrup. Dry CH_2Cl_2 (25 mL) and toluene (25 mL) were sequentially distilled *in vacuo* from the syrup, keeping the bath temperature below 15 °C, providing the 2,3,5-tri-*O*-benzoyl-*α*,*β*-D-ribofuranosyl bromide **7** (5.84 g, 100%) as a pale-yellow syrup; TLC (2 % MeOH-CH_2Cl_2) indicated complete conversion to the bromo sugar **9**. ^{1}H NMR indicated the product was a 1:1 mixture of a/b-anomers.

^{1}H NMR (500 MHz, $CDCl_3$) (~1:1 mixture of a/b -anomers) δ 8.18–8.15 (m, 1H), 8.11–8.07 (m, 3H), 8.02–8.00 (m, 2H), 7.97–7.95 (m, 1H), 7.92–7.90 (m, 2H), 7.63–7.58 (m, 2H), 7.56–7.51 (m, 3H), 7.51–7.32 (m, 10H), 7.27–7.24 (m, 1H), 7.19–7.14 (m, 2H), 6.97 (d, J = 4.6 Hz, 0.5H), 6.27 (dd, J = 8.0, 4.6 Hz, 1H), 6.12 (d, J = 4.6, 1H), 5.86 (dd, J = 7.0, 3.1 Hz, 0.5H), 5.46 (dd, J = 7.0, 4.5 Hz, 0.5H), 4.95–4.91 (m, 1.5H), 4.85–4.80 (m, 1.5H), 4.73–4.69 (m, 1.5H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) (~1:1 mixture of a/b -anomers) δ 166.26, 166.09, 165.93, 165.33, 165.08, 165.01, 133.95, 133.86, 133.81, 133.79, 133.61, 133.38, 130.20, 130.08, 130.00, 129.91, 129.85, 129.56, 129.42, 129.17, 128.83, 128.77, 128.74, 128.73, 128.64, 128.62, 128.60, 128.50, 128.35, 125.43, 89.15, 87.05, 83.61, 81.69, 79.16, 72.85, 71.13, 69.83, 63.67, 63.17 ppm.

HRMS (ESI): *m/z* Calcd. for $C_{26}H_{21}O_7$ $[M - Br + H]^+$ 445.1282; found 445.1268.

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (10).



To a suspension of the 1,3-diazepinone **4** (0.75 g, 6.69 mmol) in anhydrous CH_3CN (25 mL) was added excess BSTFA (8 mL) and the mixture was stirred at room temperature for 2 h. Solvent and excess reagent were removed by evaporation under reduced pressure and the residue was dried under high vacuum for 30 min to provide the persilylated cyclic urea **8** as a clear oil, which was used immediately in the glycosylation reaction.

A solution of the persilylated cyclic urea **8** in dry benzene (15 mL) was rapidly added to a refluxing mixture of HgO (2.70 g) and $HgBr_2$ (2.70 g) in dry benzene (150 mL) under dry N_2 atmosphere. After 10 min, a solution of 2,3,5-tri-*O*-benzoyl-α,β-D-ribofuranosyl bromide **9** (4.70 g, 8.92 mmol) in dry benzene (25 mL) was rapidly added and refluxing continued for 18 h. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, and the filter cake was washed with EtOAc. The combined filtrates were washed with saturated aqueous $NaHCO_3$ (200

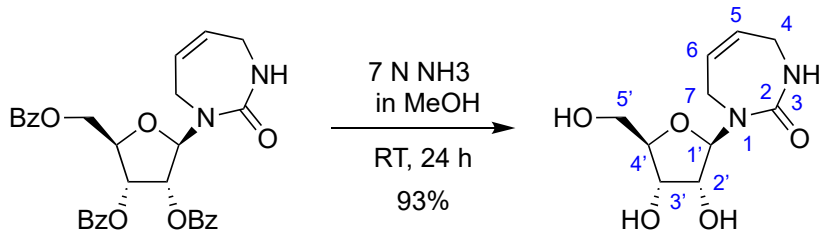
mL) and water (200 mL). The organic portion was dried (Na_2SO_4), filtered and evaporated under reduced pressure to about 5 mL and applied to a silica gel column, eluting with EtOAc-hexanes (1:1), to provide the protected nucleoside **10** (2.51 g, 67%) as a white foamy solid. TLC: R_f = 0.45 (55% EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.13 (m, 2H, Ph), 7.96–7.93 (m, 4H, H-Ph), 7.62–7.58 (m, 1H, H-Ph), 7.56–7.48 (m, 4H, H-Ph), 7.38–7.33 (m ,4H, H-Ph), 6.13 (d, J = 7.5 Hz, 1H, H-1′), 5.78 (dd, J = 6.0, 3.0 Hz, 1H, H-3′), 5.64 (dd, J = 7.0, 6.5 Hz, 1H, H-2′), 5.65–5.61 (m, 1H, H-5), 5.59–5.54 (m, 1H, H-6), 4.79 (dd, J = 13.0, 4.0 Hz, 1H, H-5′), 4.58–4.54 (m, 3H, 3-H, H-4′, H-5′), 3.90–3.83 (m, 1H, H-7), 3.80–3.76 (m, 1H, H-4), 3.71 (dd, J = 17.5, 6.0 Hz, 1H, H-7), 3.60–3.55 (m, 1H, H-4) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.22 (C-2), 165.63 (C=O-Bz), 165.53 (C=O-Bz), 165.47 (C=O-Bz), 133.66 (CH-Ph), 133.57 (CH-Ph), 133.54 (CH-Ph), 129.94 (2 × CH-Ph), 129.81 (2 × CH-Ph), 129.67 (C-Ph), 129.08 (C-Ph), 129.05 (C-Ph), 128.82 (2 × CH-Ph), 128.58 (2 × CH-Ph), 128.54 (2 × CH-Ph), 127.07 (CH-5), 125.72 (CH-6), 88.40 (C-1′), 79.03 (CH-4′), 71.67 (CH-3′), 71.00 (CH-2′), 64.52 (CH_2-5′), 43.35 (CH_2-4), 41.30 (CH_2-7) ppm.

HRMS (ESI): m/z Calcd. for $C_{31}H_{29}N_2O_8$ $[M + H]^+$ 557.1918; found 557.1912.

1-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (11).



10 **11**

To a solution of the protected nucleoside **10** (0.28 g, 0.50 mmol) in $CHCl_3$ (2 mL) placed in a pressure bottle was added a cold solution of 7 N NH_3 in MeOH (35 mL) and the resulting mixture was kept at room temperature for 24 h, occasionally shaking the reaction vessel. The reaction mixture was concentrated *in vacuo* and the residue was extracted with H_2O (35 mL) and the aqueous solution was repeatedly extracted with $CHCl_3$ (5 × 25 mL). The aqueous layer was filtered through a syringe filter and lyophilized to provide the de-protected nucleoside **11** (0.113 g, 93%) as an off-white powder.

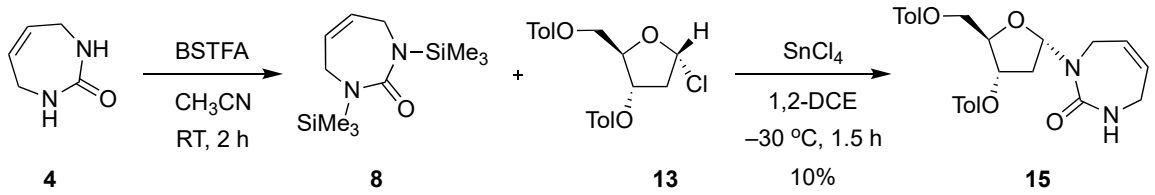
^{1}H NMR (500 MHz, D_2O) δ 6.00–5.95 (m, 1H, H-5), 5.95–5.90 (m, 1H, H-6), 5.53 (d, J = 7.0, 1H, H-1′), 4.14 (t, J = 6.5 Hz, 1H, H-2′/3′), 4.10 (dd, J = 6.0, 1H, H-2′/3′), 3.94 (dd, J = 8.1, 4.0 Hz, 1H, H-4′), 3.91–3.85 (m, 2H, H-5′), 3.80–3.70 (m, 4H, H-4, H-7) ppm.

^{1}H NMR (500 MHz, DMSO-d_6) δ 6.08 (d, J = 3.2 Hz, 1H, H-3), 5.82–5.70 (m, 2H, H-5, H-6), 5.32 (d, J = 5.8 Hz, 1H, H-1′), 4.81 (dd, J = 12.4, 5.8 Hz, 2H, H-2′/3′), 4.75 (t, J = 5.5 Hz, 1H, H-2′/3′), 3.81–3.74 (m, 2H, H-5′), 3.70–3.57 (m, 4H, H-4, H-7), 3.54–3.40 (m, 3H, H-4′, H-2′/3′ ppm.

^{13}C NMR (126 MHz, D_2O) δ 166.37 (C-2), 128.19 (CH-5), 126.58 (CH-6), 89.72 (CH-1′), 82.87 (CH-4′), 70.61 (CH-2′), 69.97 (CH-3′), 61.53 (CH_2-5′), 41.81 (CH_2-4), 40.49 (CH_2-7).

HRMS (ESI): m/z Calcd. for $C_{10}H_{17}N_2O_5$ $[M + H]^+$ 245.1132; found 245.1129.

((2*R*,3*S*,5*S*)-3-((4-Methylbenzoyl)oxy)-5-(2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate (15).



4 **8** **13** **15**

A mixture of diazepinone **4** (0.25 g, 2.23 mmol) in CH_3CN (10 mL) was treated with BSTFA (2.0 mL, excess) at room temperature under argon. After stirring the reaction mixture at room temperature for 2 h, solvents were evaporated under reduced pressure. The residue was dried under high vacuum to provide the *bis*-silylated product as a clear oil, which was used as such in the glycosylation reaction.

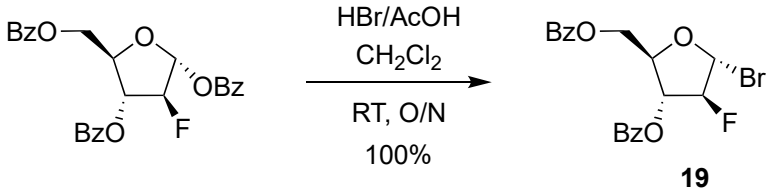
The *bis*-silylated diazepinone **8** was dissolved in 1,2-DCE (15 mL) to give a colorless solution and cooled to −30 °C using a bath of dry ice in CH_3CN. Freshly distilled $SnCl_4$ (0.81 mL, 6.95 mmol) was added, followed by Hoffer's chlorosugar **13** (0.85 g, 2.19 mmol). This gave a clear yellow solution which was stirred at −30 °C for 1.5 h, at which point the mixture had turned dark brown. Pyridine (2.5 mL) and water (12 mL) were added, and the reaction mixture was stirred at room temperature 1 h. After diluting with water (25 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were filtered through a bed of celite, washed with saturated aqueous NaCl (50 mL), dried (Na_2SO_4), and evaporated to dryness. The resulting dark yellow residue was dissolved in CH_2Cl_2 and purified by flash column chromatography using a silica gel column (SiliaSep, 25 g, gradient elution with 0–20% Acetone/CH_2Cl_2) to give the pure α-anomer compound **15** (0.10 g, 10%) as a white foamy solid. TLC: 8% acetone in CH_2Cl_2; R_f = 0.35).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.89 (m, 4H, H-Ph), 7.27–7.22 (m, 4H, H-Ph), 6.15 (dd, J = 7.7, 5.1 Hz, 1H, NH), 5.84–5.79 (m ,1H, H-5/6), 5.74–5.69 (m, 1H, H-5/6), 5.48 (dt, J = 7.5, 5.5, 2.8 Hz, 1H, H-1′), 4.64 (dd, J = 6.6, 4.2 Hz, 1H, H-4′), 4.53 (dd, J = 11.8, 4.2 Hz, 1H, H-5′), 4.48 (br s, 1H, H-3′), 4.43 (dd, J = 11.8, 4.4 Hz, 1H, H-5′), 3.96–3.93 (m, 2H, H-4, H-7), 3.82–3.69 (m, 2H, H-4, H-7), 2.87 (dt, J = 15.3, 7.7 Hz, 1H, H-2′), 2.42 (s, 3H, CH_3-Tol), 2.40 (s, 3H, CH_3-Tol), 2.13 (ddd, J = 15.1, 8.0, 3.1 Hz, 1H, H-2′) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.46 (C=O-Tol), 166.11 (C=O-Tol), 165.46 (C-2), 144.41 (C-Ph), 144.06 (C-Ph), 129.86 (2 × CH-Ph), 129.71 (2 × CH-Ph), 129.42 (2 × CH-Ph), 129.35 (2 × CH-Ph), 127.24 (CH-Ph), 127.02 (CH-Ph), 126.92 (CH-5/6), 126.08 (CH-5/6), 87.82 (CH-1′), 81.77 (CH-4′), 75.60 (CH-3′), 65.13 (CH_2-5′), 43.48 (CH_2-7), 40.77 (CH_2-4), 36.56 (CH_2-2′), 21.84 (CH_3-Tol), 21.82 (CH_3-Tol) ppm.

HRMS (ESI): m/z Calcd. for $C_{26}H_{28}N_2O_6Na$ $[M + Na]^+$ 487.1840; found 487.1839.

2-Deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl bromide (19).



19

A solution of 2-deoxy-2-fluoro-1,3,5-tri-*O*-benzoyl-*a*-D-arabinofuranose (1.40 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was treated with a 30% HBr solution in AcOH (1.80 mL). After stirring at room temperature overnight, the reaction mixture was washed with H_2O (2 ×10 mL) and saturated $NaHCO_3$ solution (2 × 10 mL). The organic portion was dried (Na_2SO_4) and concentrated under reduced pressure to provide the product **19** as a pale-yellow syrup (1.27 g, 100%). TLC: R_f = 0.50 (100% CH_2Cl_2).

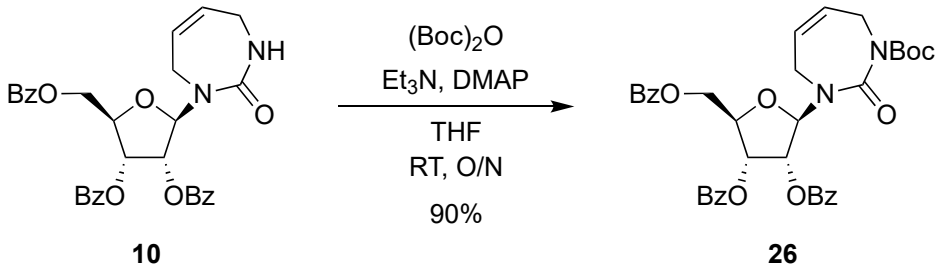
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.2, 1.2 Hz, 2H), 8.07 (dd, J = 8.4, 1.2 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 6.64 (d, J = 12.1 Hz, 1H), 5.60 (d, J = 50.0 Hz, 1H), 5.55 (dd, J = 21.9, 3.6 Hz, 1H, overlapping), 4.84–4.78 (m, 2H), 4.72 (dd, J = 11.5, 3.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.19, 165.71, 134.08, 133.42, 130.17 (2C), 129.97 (2C), 128.82 (2C), 128.57 (2C), 100.77 (d, J = 191.7), 87.70 (d, J = 31.3), 84.87, 76.36 (d, J = 31.8), 62.64 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ −165.92 ppm.

Attempted Synthesis of 2′-Deoxyribo-Diazepinone Nucleoside by 2′-Deoxygenation

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(3-(*tert*-butoxycarbonyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (26).

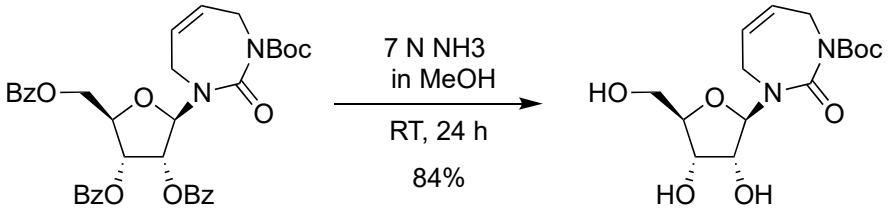


To a stirred solution of diazepinone riboside **10** (3.40 g, 6.10 mmol) in anhydrous THF (60 mL) at room temperature under argon was slowly added Et_3N (1.05 mL, 7.50 mmol) followed by the addition of DMAP (0.37 g, 3.0 mmol) in one portion. After 15 min, a solution of $(Boc)_2O$ (1.64 g, 7.5 mmol) in anhydrous THF (10 mL) was added dropwise. The resulting reaction mixture stirred at room temperature overnight (TLC indicated complete conversion of the starting material), quenched with H_2O (100 mL), and extracted with EtOAc (100 mL). The organic portion was washed with saturated aqueous NaCl solution (100 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting orange-brown residue was purified by flash column chromatography using a silica gel column (Biotage, 50 g, gradient elution with 0–70% EtOAc/hexanes) to provide the *N*-Boc protected nucleoside **26** (3.60 g, 90%) as a white foamy solid. TLC: R_f = 0.40 (30% EtOAc-hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18–8.15 (m, 2H), 7.97–7.93 (m, 4H), 7.64–7.61 (m, 1H), 7.58–7.50 (m, 4H), 7.42–7.33 (m, 4H), 6.32 (d, J = 7.7 Hz, 1H), 5.81 (dd, J = 6.0, 2.6 Hz, 1H), 5.58–5.47 (m, 2H), 4.88 (dd, J = 12.9, 3.6 Hz, 1H), 4.59–4.55 (m, 2H), 4.25 (d, J = 18.5 Hz, 1H), 3.98 (d, J = 18.9 Hz, 1H), 3.83 (dd, J = 17.0, 2.3 Hz, 1H), 3.74 (dd, J = 16.9, 5.0 Hz, 1H), 1.38 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$,): δ 166.18 (C), 165.65 (C), 165.41(C), 158.41(C), 153.09 (C), 133.79 (CH), 133.73 (CH), 129.96 (2 × CH), 129.93 (2 × CH)), 129.82 (2C, CH), 129.53 (C), 128.97 (C), 128.93 (2 × CH), 128.66 (2 × CH), 128.60 (2 × CH), 128.41 (CH), 123.95, 86.84 (CH), 82.16 (C), 79.97 (CH), 71.66 (CH), 71.31 (CH), 64.31 (CH_2), 43.98 (CH_2), 39.67 (CH_2), 28.20 ((CH_3)$_3$) ppm.

***tert*-Butyl 3-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (27).**



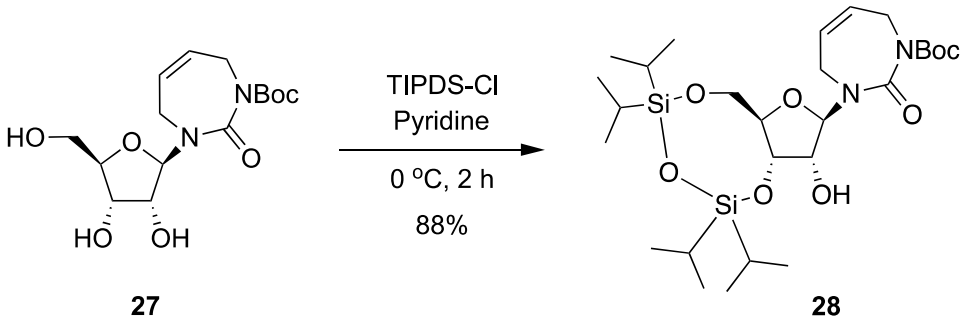
26 **27**

To a solution of the protected nucleoside **26** (0.60 g, 0.91 mmol) in $CHCl_3$ (2 mL) placed in a pressure bottle was added a cold solution of 7 N NH_3 in MeOH (70 mL) and the resulting mixture was kept at room temperature for 24 h, occasionally shaking the reaction vessel. The reaction mixture was concentrated *in vacuo* and the residue was extracted with H_2O (50 mL) and the aqueous solution was repeatedly extracted with $CHCl_3$ (5 × 25 mL). The aqueous layer was filtered through a syringe filter and lyophilized to provide the de-protected nucleoside **27** (0.26 g, 84%) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91–5.87 (m, 1H), 5.80–5.77 (m, 1H), 5.70 (d, J = 5.7 Hz, 1H, H-1′), 4.33 (d, J = 18.9 Hz, 1H), 4.16–4.11 (m, 3H), 4.03 (q, J = 3.5 Hz, 1H), 4.0–3.95 (m, 1H), 3.90 (dd, J = 17.3, 5.6 Hz, 1H), 3.80 (dd, J = 12.6, 3.4 Hz, 1H), 3.74 (dd, J = 12.6, 4.6 Hz, 1H), 1.49 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$,): δ 159.85, 153.70, 127.79, 123.50, 88.83, 84.30, 83.96, 71.53, 70.11, 61.35, 43.70, 39.67, 27.33 ppm.

***tert*-Butyl 3-((6a*R*,8*R*,9*R*,9a*S*)-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (28).**



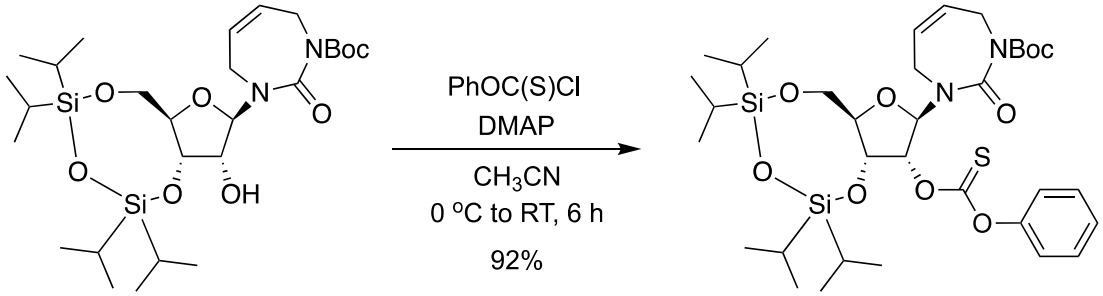
27 **28**

The *N*-Boc protected diazepinone riboside **27** (0.26 g, 0.74 mmol) was dissolved in anhydrous pyridine (15 mL) and the solution was cooled to 0 °C using ice bath. TIPDS-Cl (0.31 mL, 0.96 mmol) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 2 h, and then quenched with ice. The solvents were evaporated under reduced pressure to give a yellow oil. The residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution. The organic portion was dried (Na_2SO_4), filtered, and concentrated in *vacuo* to give a yellow oil. This material was dissolved in a minimum volume of 10% EtOAc/hexanes and purified by flash column chromatography using a silica gel column (Biotage, 25 g, gradient elution with 0–30% EtOAc/hexanes) to provide 3,5-TIPDS-protected nucleoside **28** (0.38 g, 88%) as a white foamy solid. TLC: R_f = 0.25 (20% EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77–5.73 (m, 1H), 5.72–5.68 (m, 1H), 5.55 (d, J = 2.7 Hz, 1H, H-1′), 4.39 (t, J = 13.5 Hz, 1H), 4.26 (br d, J = 18.8 Hz, 1H), 4.15 (br d, J = 19.7 Hz, 1H), 4.03–3.98 (m, 3H), 3.91–3.86 (m, 2H), 3.73 (q, J = 7.2 Hz, 1H), 1.47 (s, 9H), 1.11–1.02 (m, 28H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$,): δ 157.39 (C), 153.05 (C), 128.74 (CH), 124.17 (CH), 91.87 (CH), 82.00 (C), 81.58 (CH), 73.57 (CH), 70.95 (CH), 62.10 (CH_2), 43.75 (CH_2), 41.37 (CH_2), 28.34 ((CH_3)$_3$), 17.58, 17.49, 17.45, 17.43, 17.25, 17.11, 17.01, 13.50, 13.25, 12.94, 12.71 ppm.

***tert*-butyl 2-oxo-3-((6a*R*,8*R*,9*R*,9a*R*)-2,2,4,4-tetraisopropyl-9-((phenoxycarbonothioyl)-oxy)tetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (29).**



28 **29**

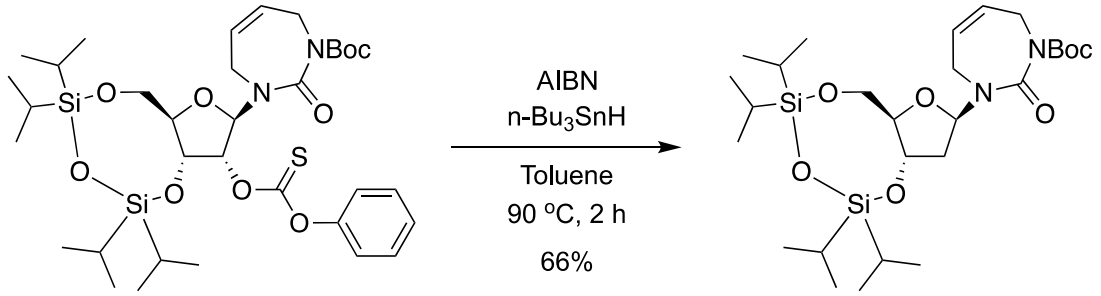
To a stirring solution of 3,5-TIPDS-protected riboside **28** (1.02 g, 1.74 mmol) in anhydrous CH_3CN (30 mL) at 0 °C was added DMAP (0.62 g, 5.10 mmol). After stirring the mixture under argon for 5 min, phenylthiochloroformate (0.45 g, 2.6 mmol) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 15 min, warmed to room temperature and stirred for 6 h. After the reaction was complete, solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous NaCl solution (50 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography using a silica gel column (Biotage, 25 g, gradient elution with 0–50% EtOAc/hexanes) to provide intermediate **29** (1.16 g, 92%) as a yellow gum. TLC: R_f = 0.40 (20% EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (t, J = 7.9 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.10 (d, J = 7.7 Hz, 2H), 5.86 (d, J = 1.7 Hz, 1H), 5.78 (dd, J = 5.9, 1.5 Hz, 1H), 5.80–5.71 (m, 2H, overlapping),

4.52 (dd, J = 8.7, 5.9 Hz, 1H), 4.31 (br d, J = 19.1 Hz, 1H), 4.15–4.11 (m, 2H), 4.01 (dd, J = 13.1, 2.7 Hz, 1H), 4.00–3.96 (m, 1H, overlapping), 3.88 (dt, J = 8.7, 2.5 Hz, 1H), 3.78 (dd, J = 16.9, 5.2 Hz, 1H), 1.47 (s, 9H), 1.12–1.05 (m, 28H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$,): δ 194.17 (C), 157.19 (C), 153.55 (C), 153.09 (C), 129.65 (2 × CH-Ph), 128.98 (CH-Ph), 126.74 (CH-Ph), 123.74 (CH-Ph), 121.93 (2 × CH-Ph), 89.21 (CH-1′), 83.61 CH-2′), 82.20 (C-*t*Bu), 81.10 (CH-4′), 69.42 (CH-3′), 60.28 (CH_2-5′), 43.77 (CH_2-7), 40.91 (CH_2-4), 28.36 (3 × CH_3-*t*Bu), 17.55, 17.48, 17.45, 17.41, 17.23, 17.19, 17.14, 17.02 (CH_3-TIPDS), 13.48, 13.15, 12.97, 12.90 (CH-TIPDS) ppm.

***tert*-Butyl 2-oxo-3-((6a*R*,8*R*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (30).**



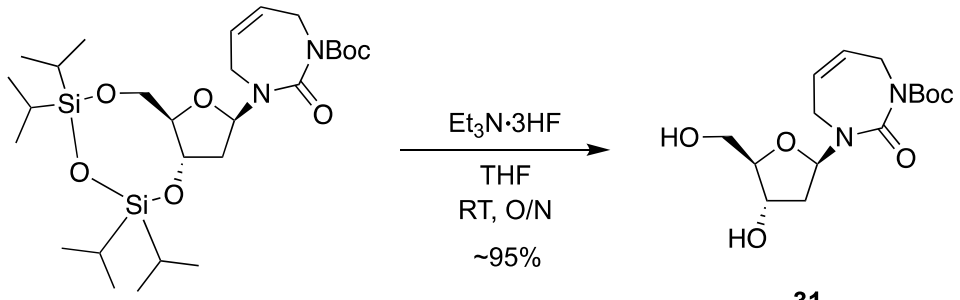
29 **30**

To a solution of compound **29** (0.44 g, 0.68 mmol) in toluene (12 mL) were added AIBN (0.033 g, 0.20 mmol) and tributyltin hydride (0.32 mL, 1.19 mmol) at room temperature. The mixture was degassed using vacuum-argon fill cycles (5 ×) and then heated to 90 °C for 2 h. After cooling the reaction mixture to room temperature, solvent was removed under reduced pressure. The residue was purified by flash column chromatography using a silica gel column (Biotage, 25 g, gradient elution with 0–50% EtOAc/hexanes) to provide deoxygenated intermediate **30** (0.26 g, 66%) as a white foamy solid. TLC: R_f = 0.66 (20% EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (dd, J = 7.8, 4.6 Hz, 1H, H-1′), 5.80–5.75 (m, 1H, H-5/6), 5.70–5.66 (m, 1H, H-5/6), 4.47 (q, J = 7.6 Hz, 1H, H-3′), 4.27–4.23 (m, 1H, H-4/7), 4.14–4.10 (m, 1H, H-4/7), 4.02 (dd, J = 12.4, 3.4 Hz, 1H, H-5′), 3.93 (dd, J = 12.4, 4.8 Hz, 1H, H-5′), 3.87–3.83 (m, 1H, H-4/7), 3.73 (dd, J = 16.8, 4.3 Hz, 1H, H4/7), 3.66 (ddd, J = 8.0, 4.7, 3.6 Hz, 1H, H-4′), 2.27 (ddd, J = 15.5, 13.6, 7.7 Hz, 1H, H-2′), 2.04 (ddd, J = 13.0, 8.0, 4.5 Hz, 1H, H-2′), 1.47 (s, 9H, *t*Bu), 1.10–1.01 (m, 28H, TIPDS) ppm.

^{13}C NMR (126 MHz, $CDCl_3$,): δ 157.22 (C), 153.09 (C), 128.57 (CH-5/6), 124.47 (CH5/6), 84.13 (CH-4′), 83.96 (CH-1′), 81.95 (C-*t*Bu), 70.26 (CH-3′), 61.82 (CH_2-5′), 43.79 (CH_2-7), 39.35 (CH_2-4), 38.17 (CH_2-2′), 28.36 (3 × CH_3-*t*Bu), 17.62, 17.52, 17.49, 17.48, 17.21, 17.11, 17.01 (CH_3-TIPDS), 13.60, 13.31, 13.01, 12.65 (CH-TIPDS) ppm.

***tert*-Butyl 3-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (31).**



30 **31**

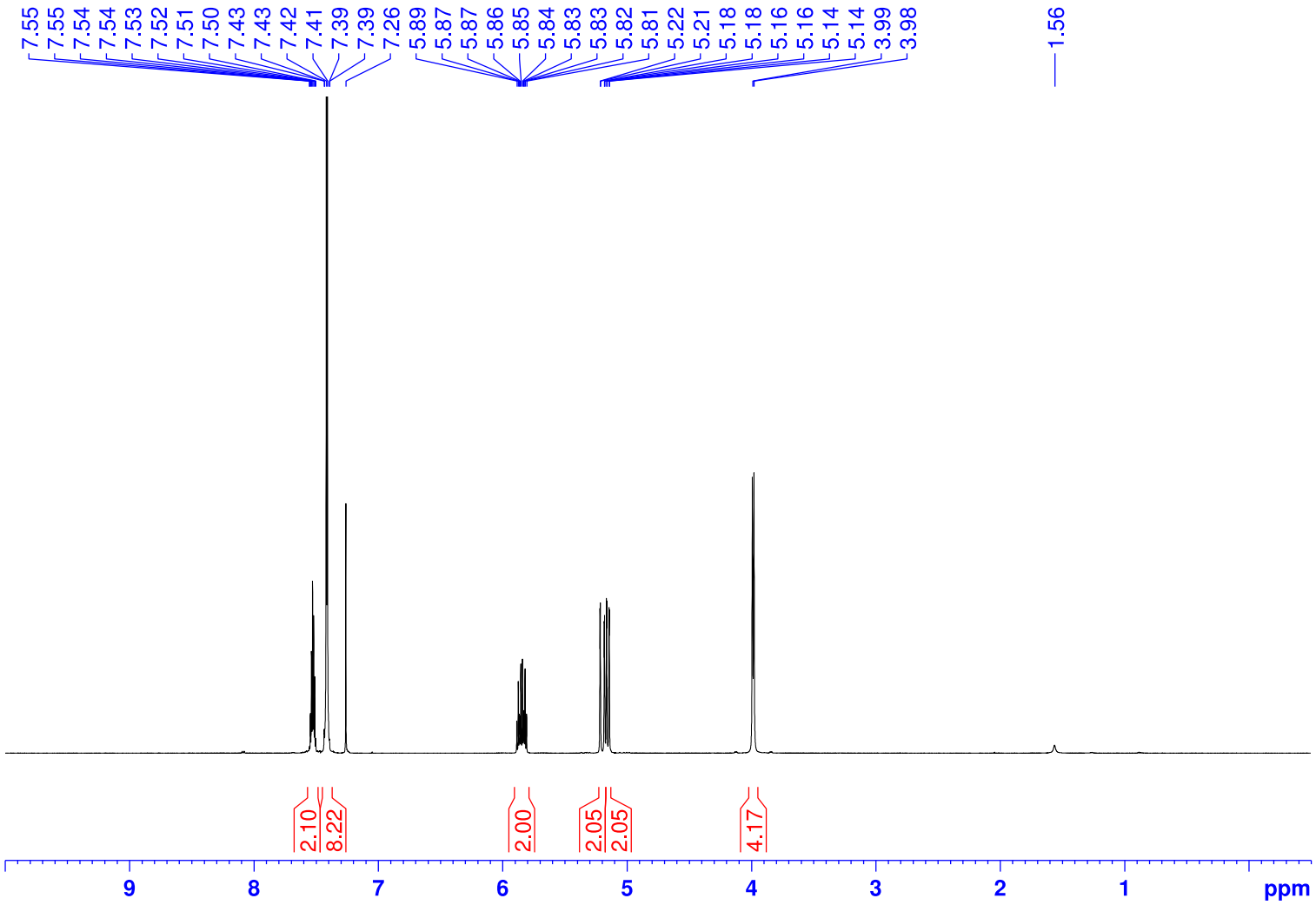
To a solution of the protected 2-deoxy nucleoside **30** (0.22 g, 0.38 mmol) in anhydrous THF (4 mL) was added $Et_3N{\bullet}3HF$ (0.32 mL, 1.9 mmol) and Et_3N (0.13 mL, 0.77 mmol). The resulting reaction mixture was stirred at room temperature overnight. The solvents were evaporated under reduced pressure and coevaporated with toluene and then chloroform. The residue was dissolved in a minimum volume of CH_2Cl_2 and purified by flash column chromatography using a silica gel

column (Biotage, 10 g, gradient elution with 0–10% MeOH/CH_2Cl_2) to provide the TIPDS deprotected nucleoside **31** (0.13 g, ~95%) as a viscid solid (contains trace amounts of Et_3N-3HF). TLC: R_f = 0.30 (100% EtOAc).

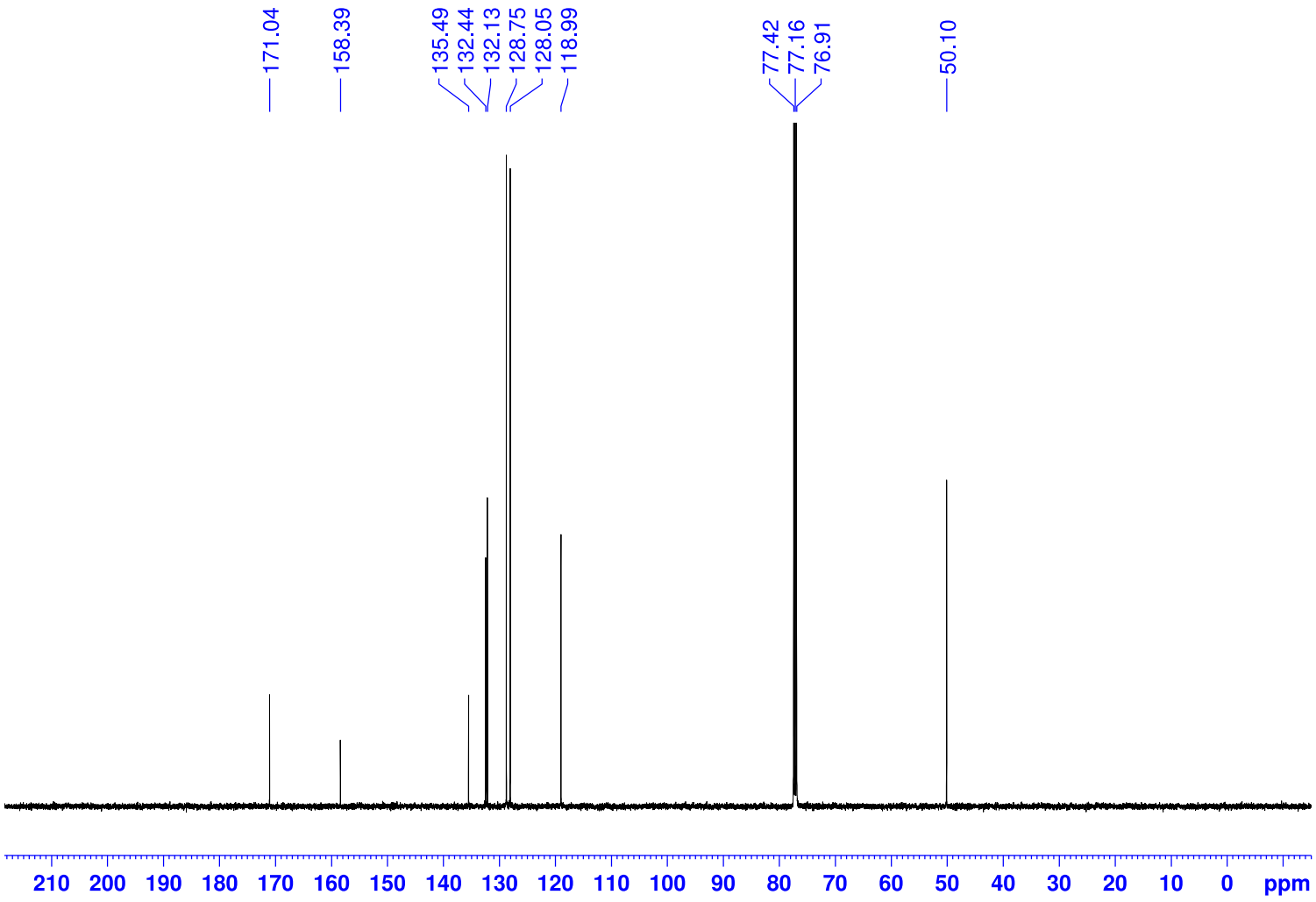
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.03 (t, J = 7.0 Hz, 1H), 5.83–5.78 (m, 1H), 5.70–5.66 (m, 1H), 4.45 (q, J = 5.0 Hz, 1H), 4.23 (br d, J = 18.8 Hz, 1H), 4.14 (br d, J = 19.0 Hz, 1H), 3.86 (q, J = 4.0 Hz, 1H, overlapping), 3.85–3.75 (m, 4H), 2.15–2.09 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$,): δ 157.59 (C), 153.04 (C), 128.50 (CH), 124.51 (CH), 86.33 (CH), 85.77 (CH), 82.07 (C), 71.54, 62.72 (CH_2), 43.88 (CH_2), 40.52 (CH_2), 38.15 (CH_2), 28.34 $(CH_3)_3$ ppm.

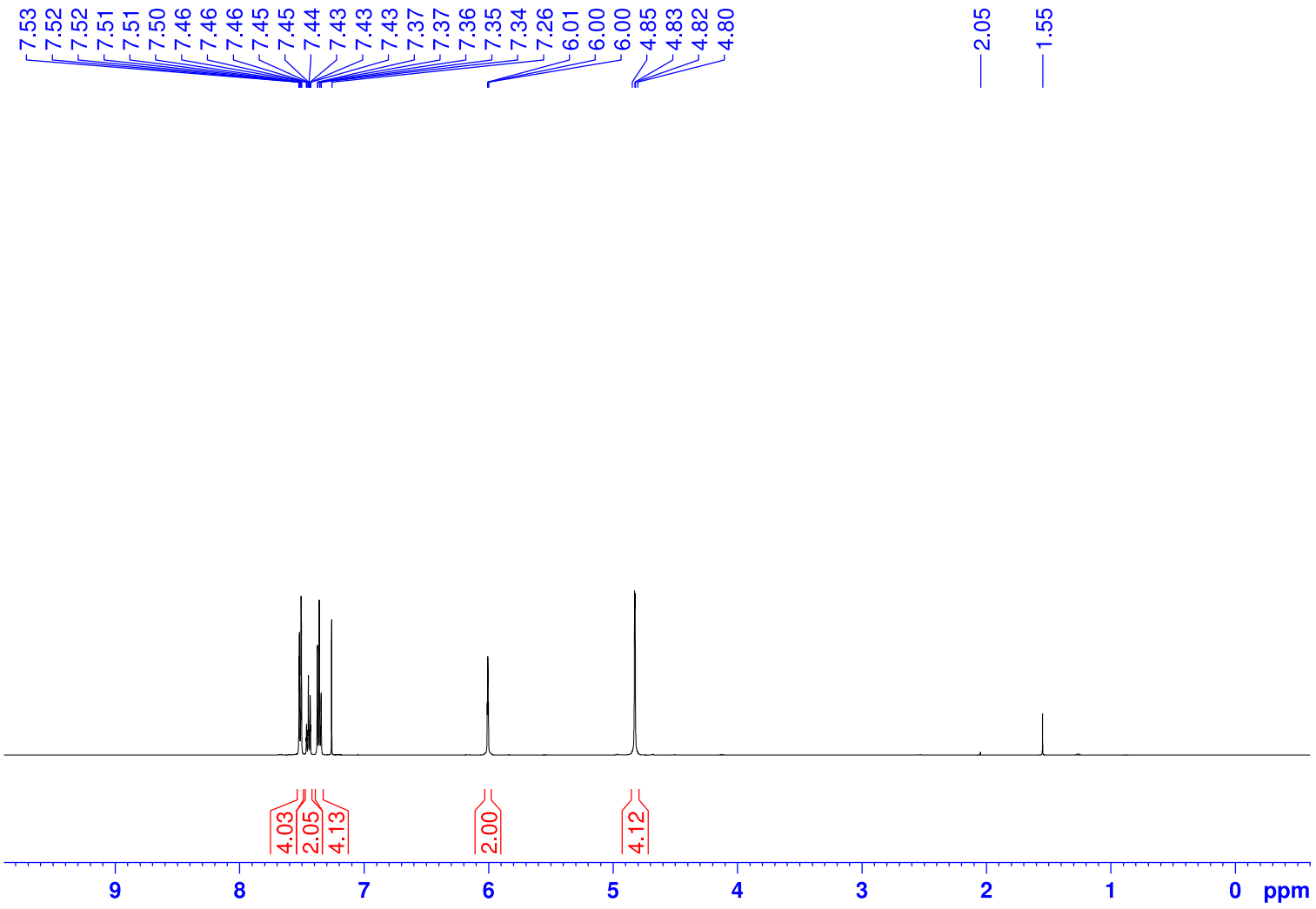
Copies of ^{1}H, ^{13}C, DEPT-135, and ^{19}F NMR spectra:



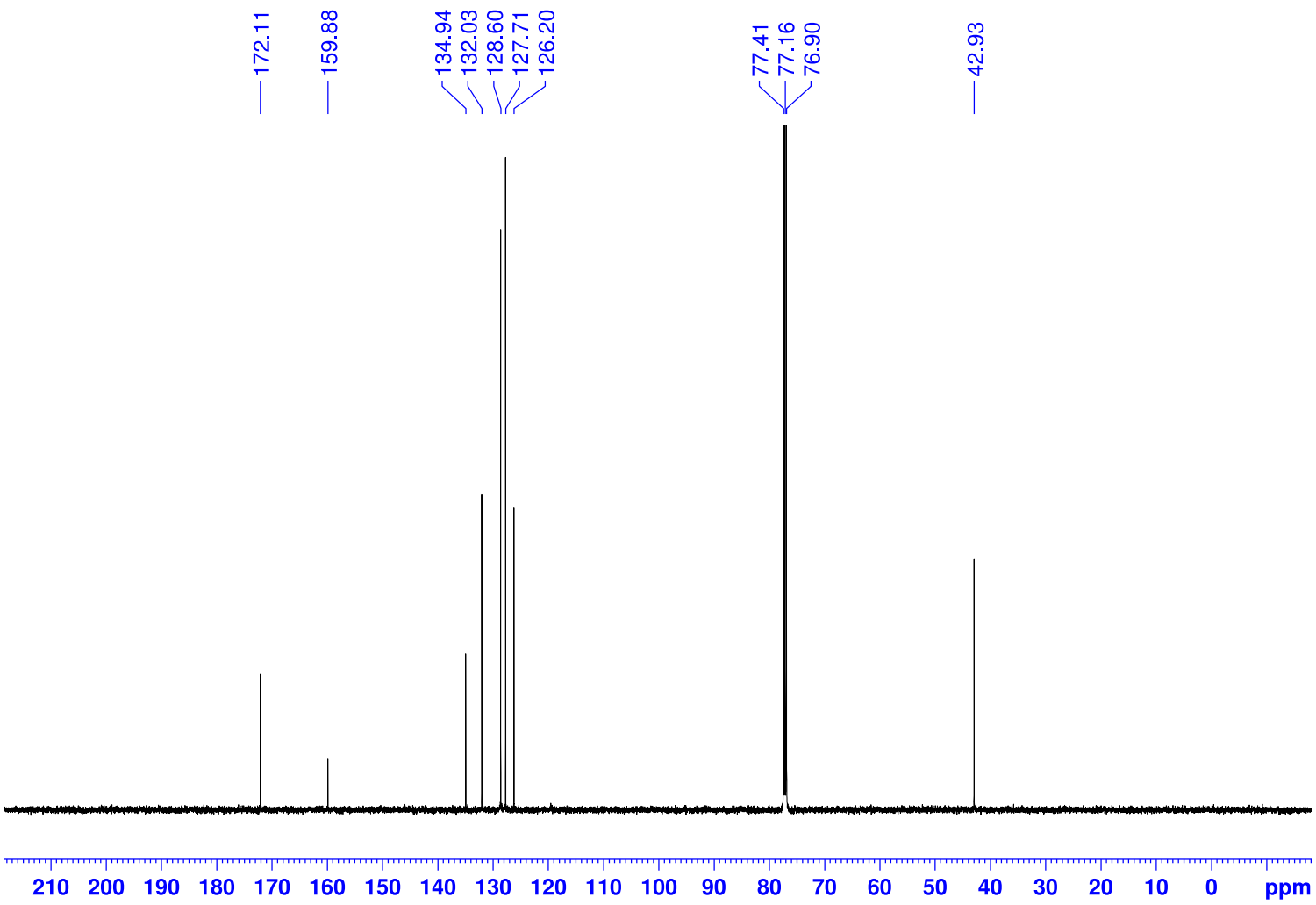
^{1}H NMR spectrum of compound 2 (500 MHz, $CDCl_3$)



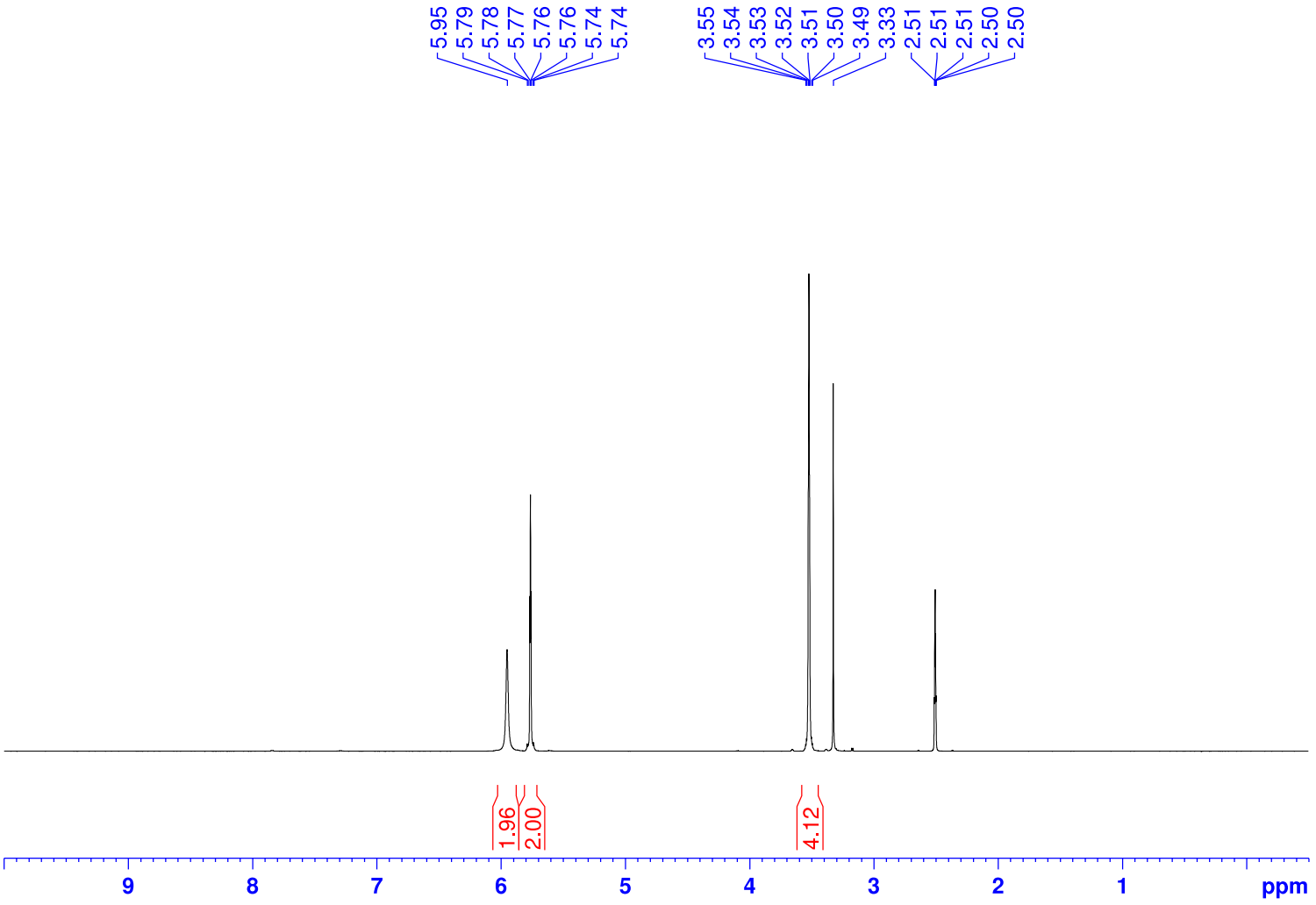
^{13}C NMR spectrum of compound 2 (126 MHz, $CDCl_3$)



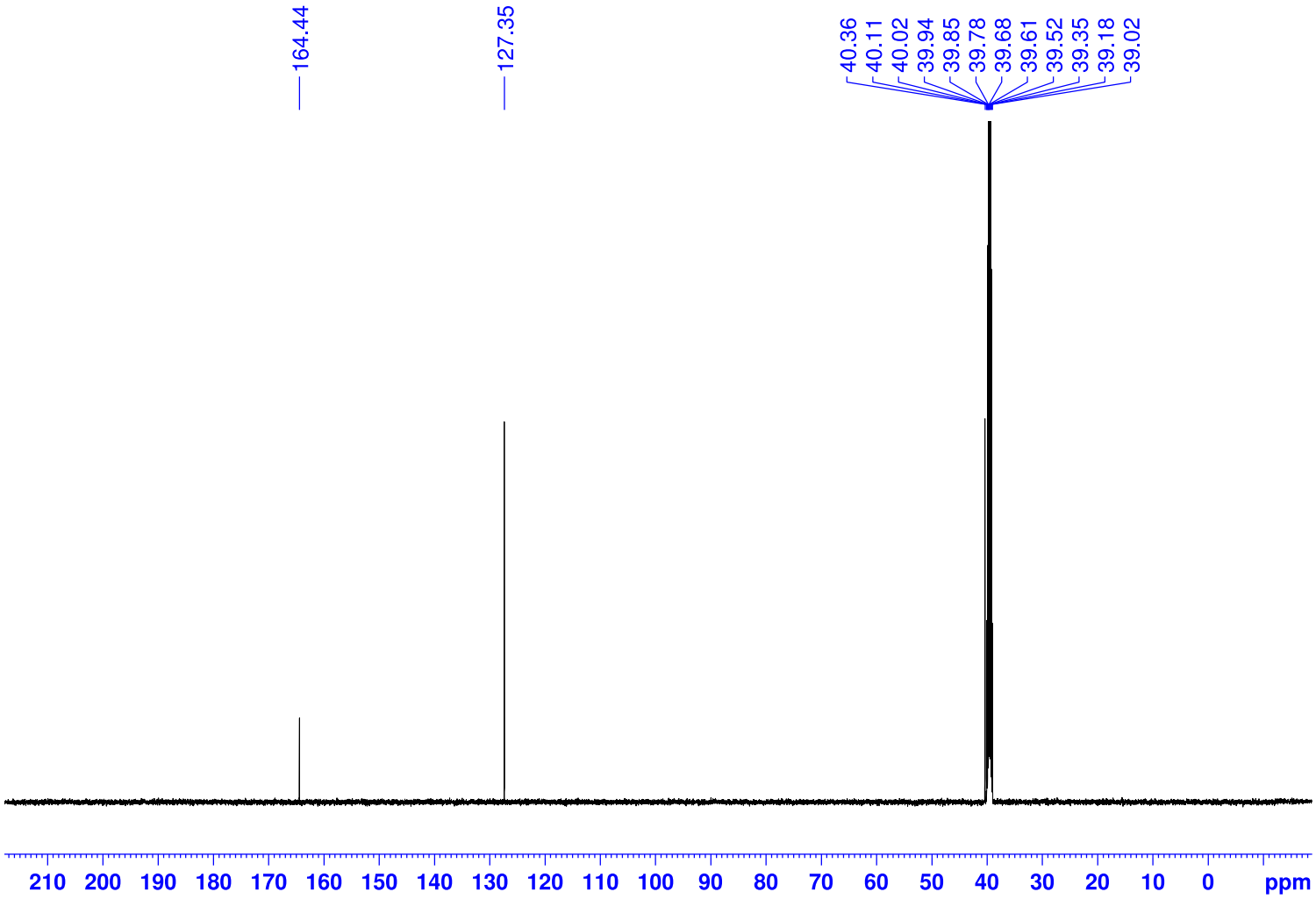
^{1}H NMR spectrum of compound 3 (500 MHz, $CDCl_3$)



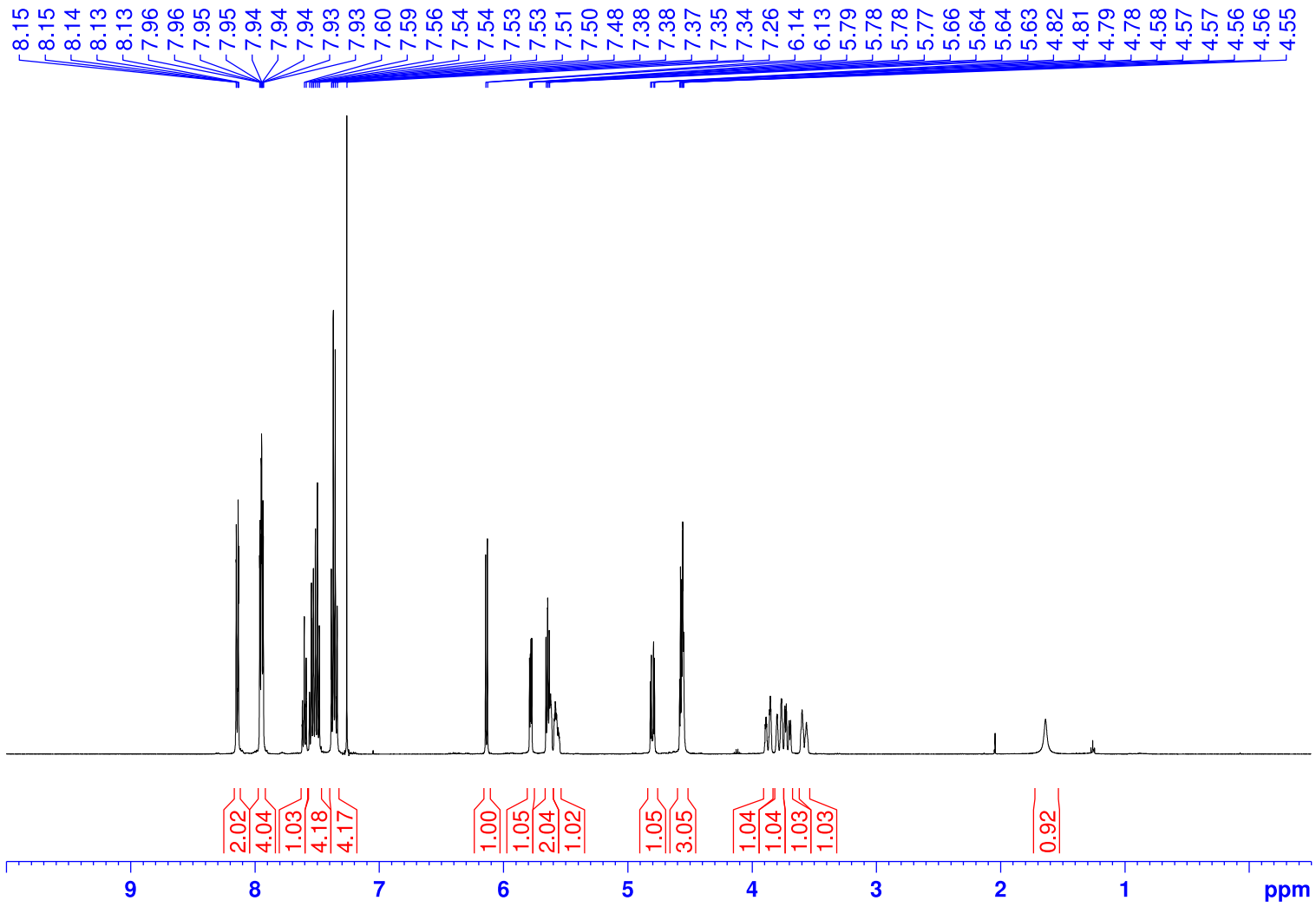
^{13}C NMR spectrum of compound 3 (126 MHz, $CDCl_3$)



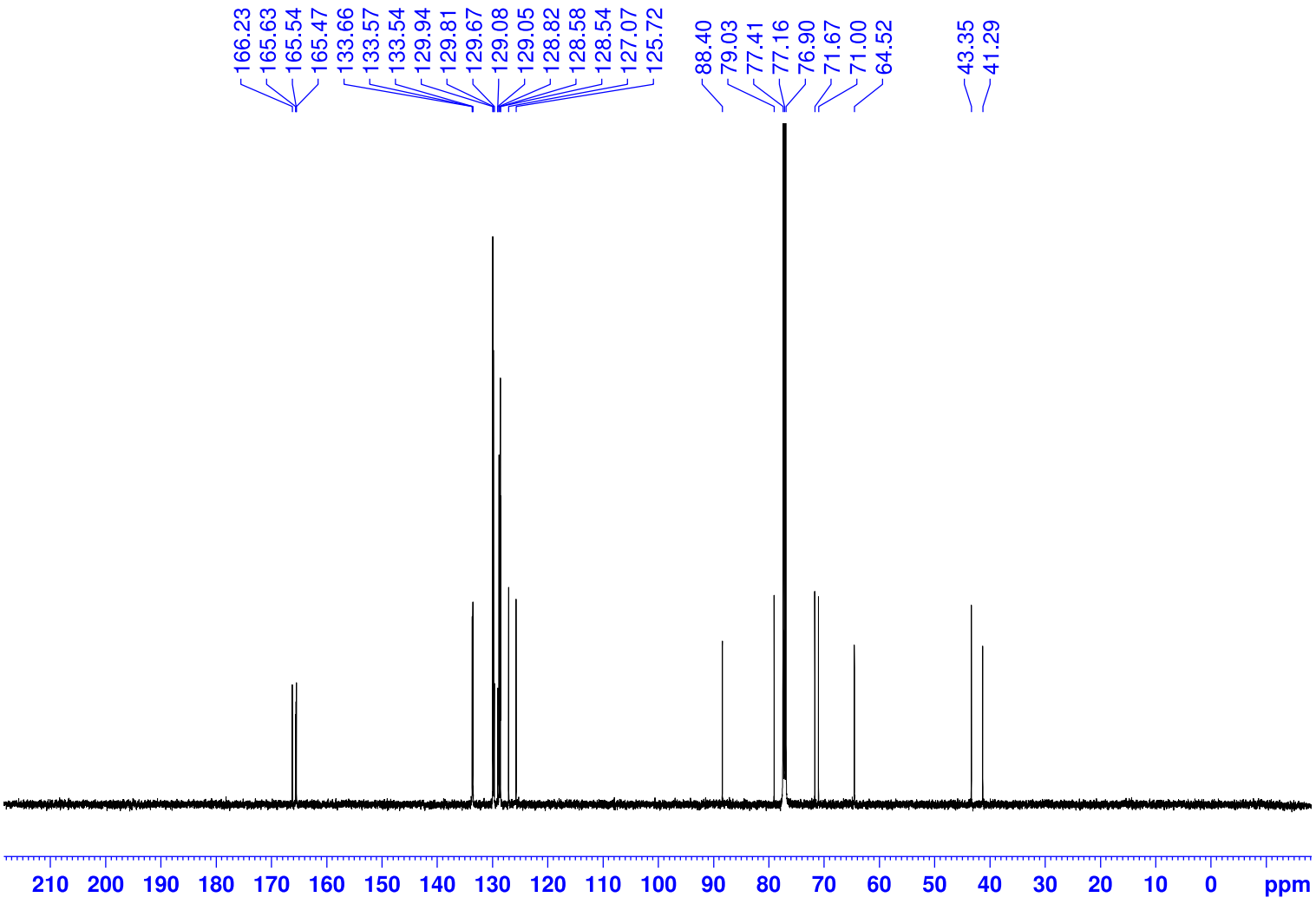
^{1}H NMR spectrum of compound 4 (500 MHz, DMSO-d_6)



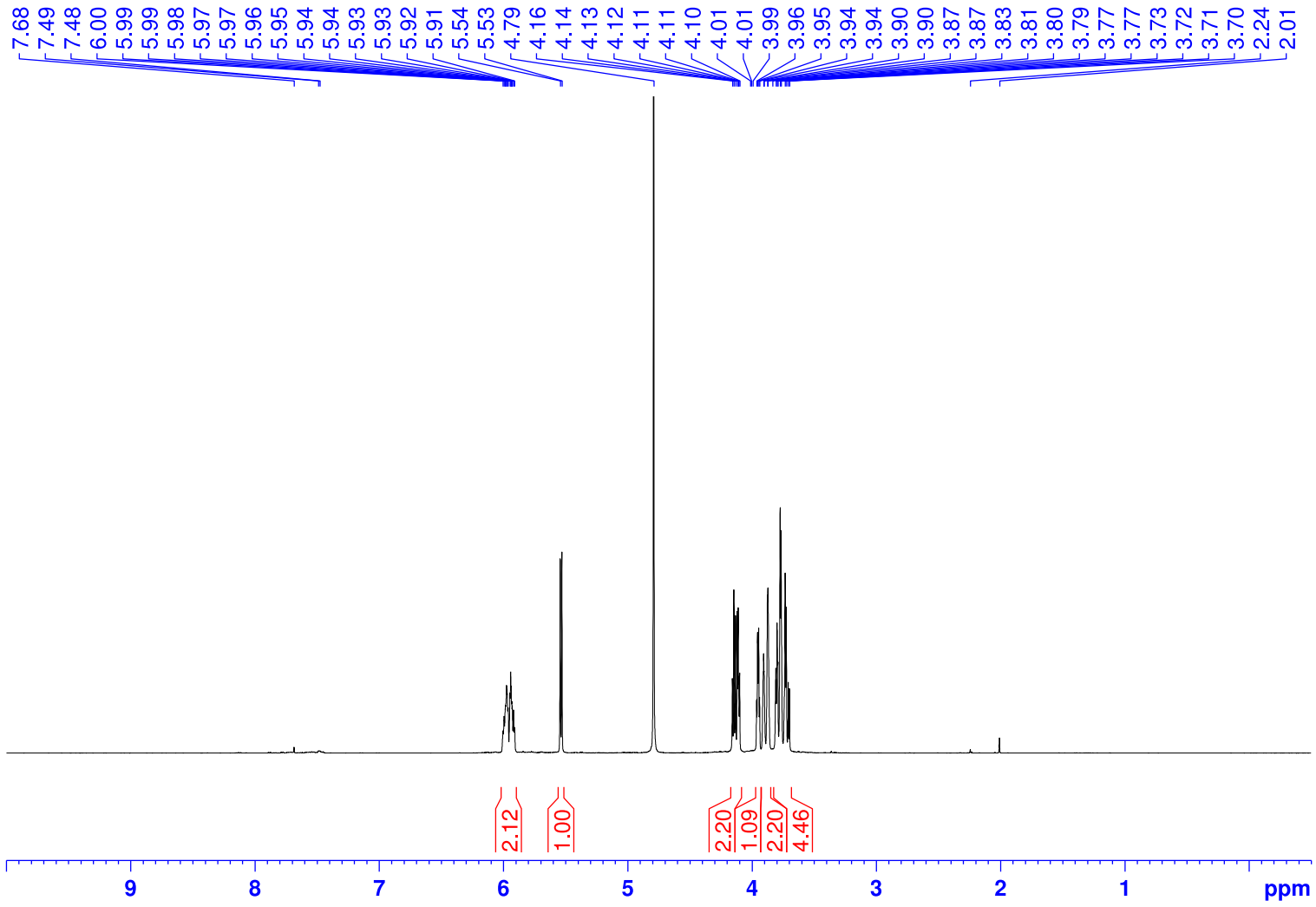
^{13}C NMR spectrum of compound 4 (126 MHz, DMSO-d_6)



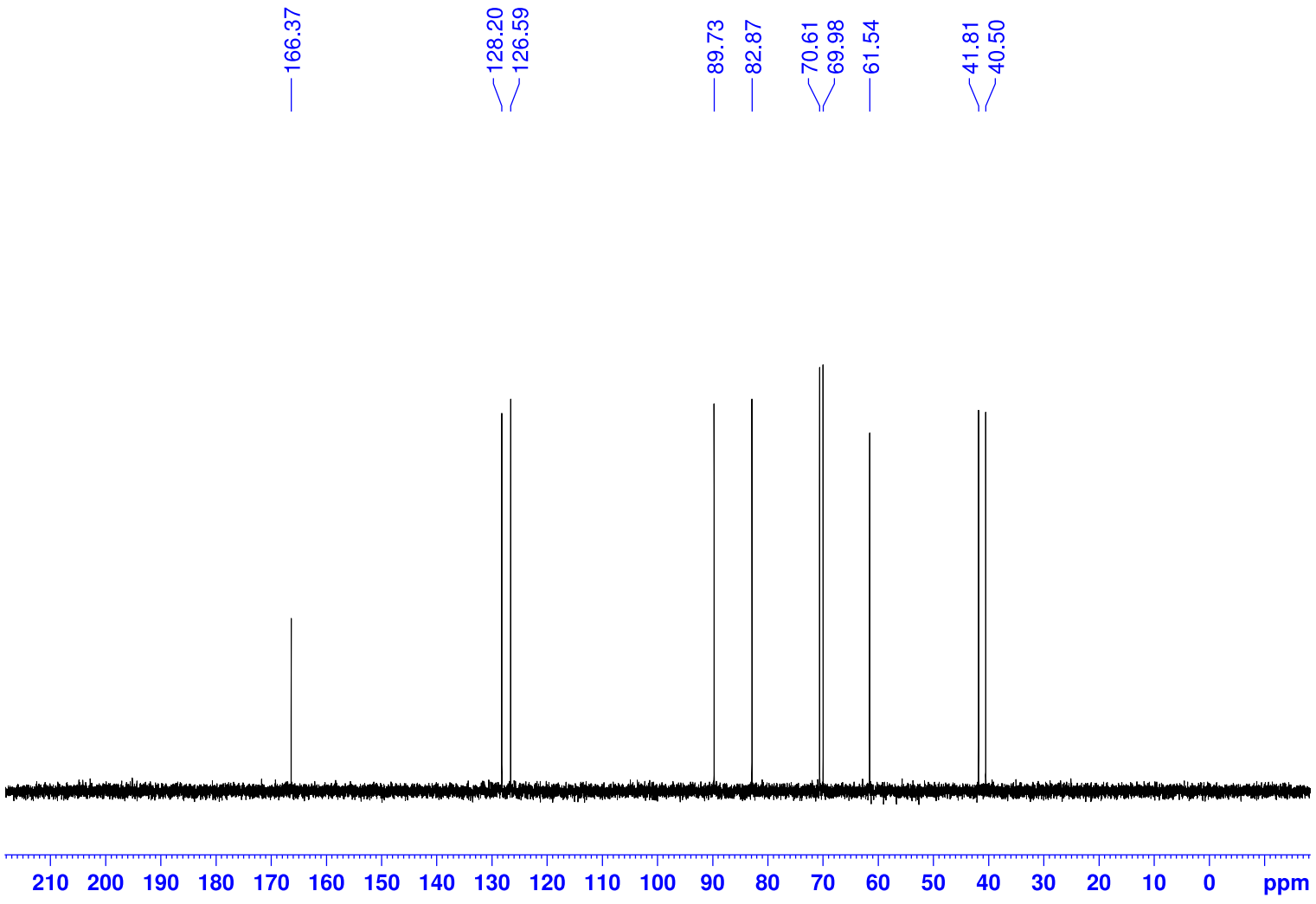
^{1}H NMR spectrum of compound 10 (500 MHz, $CDCl_3$)



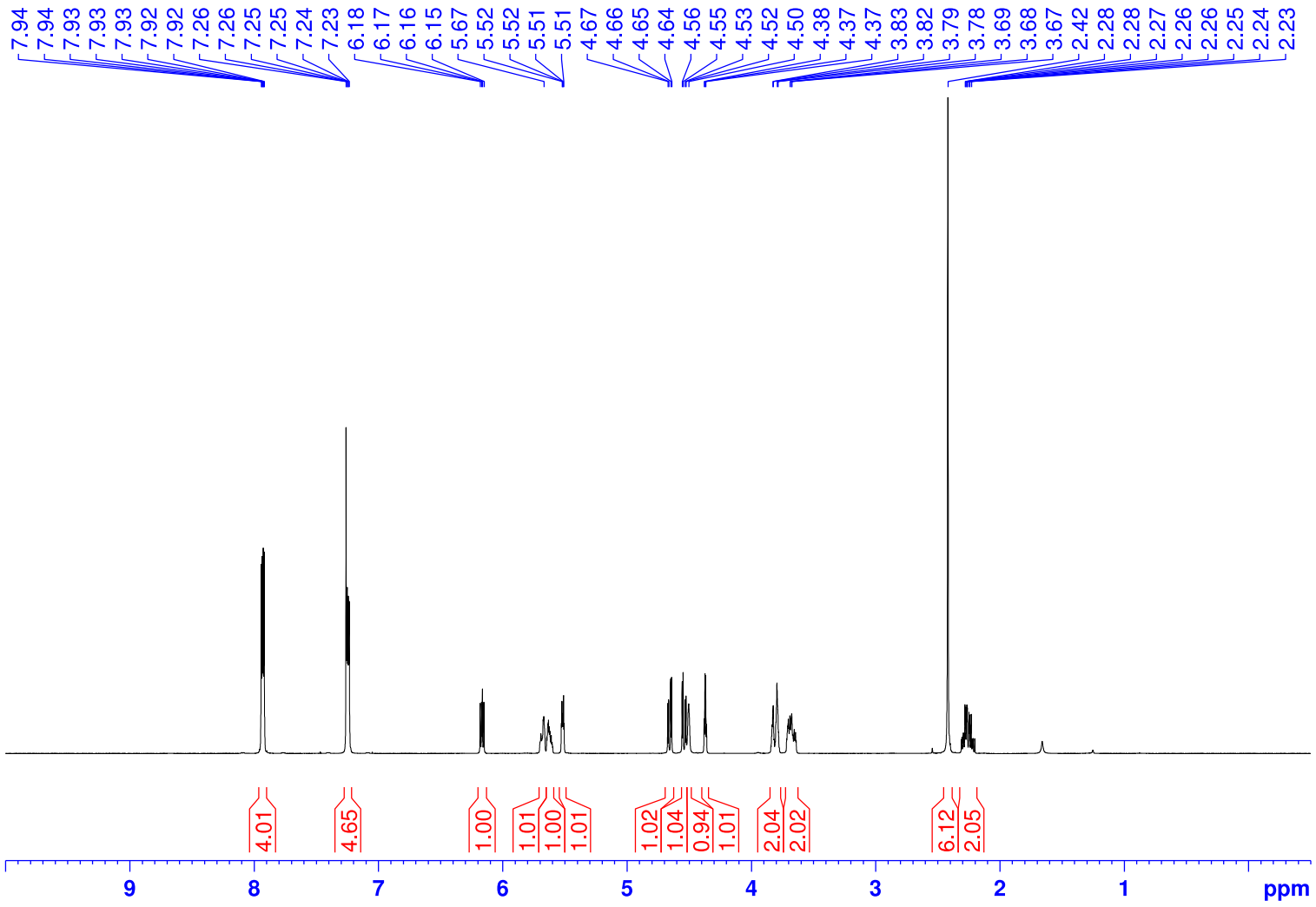
^{13}C NMR spectrum of compound 10 (126 MHz, $CDCl_3$)



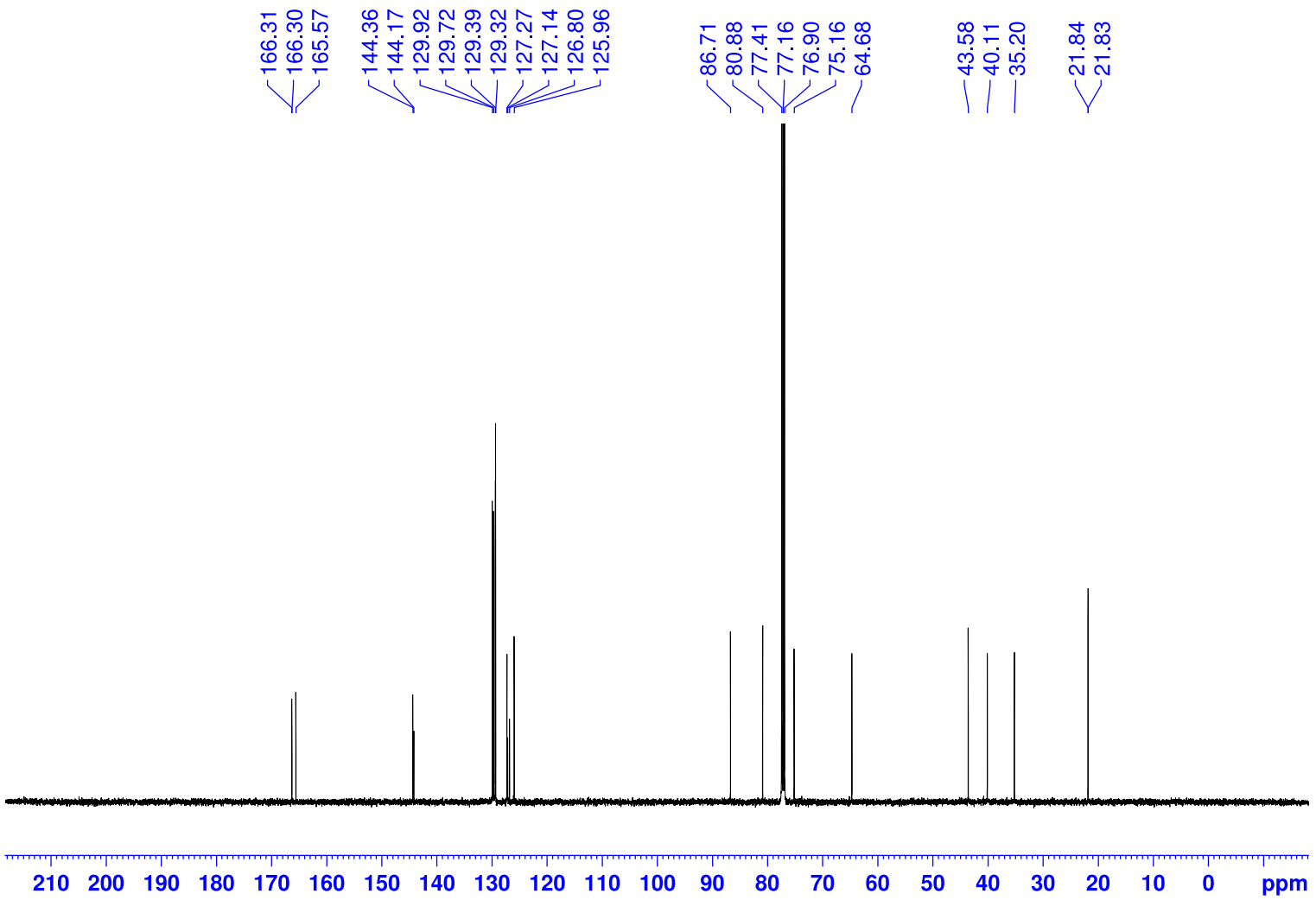
^{1}H NMR spectrum of compound 11 (500 MHz, D_2O)



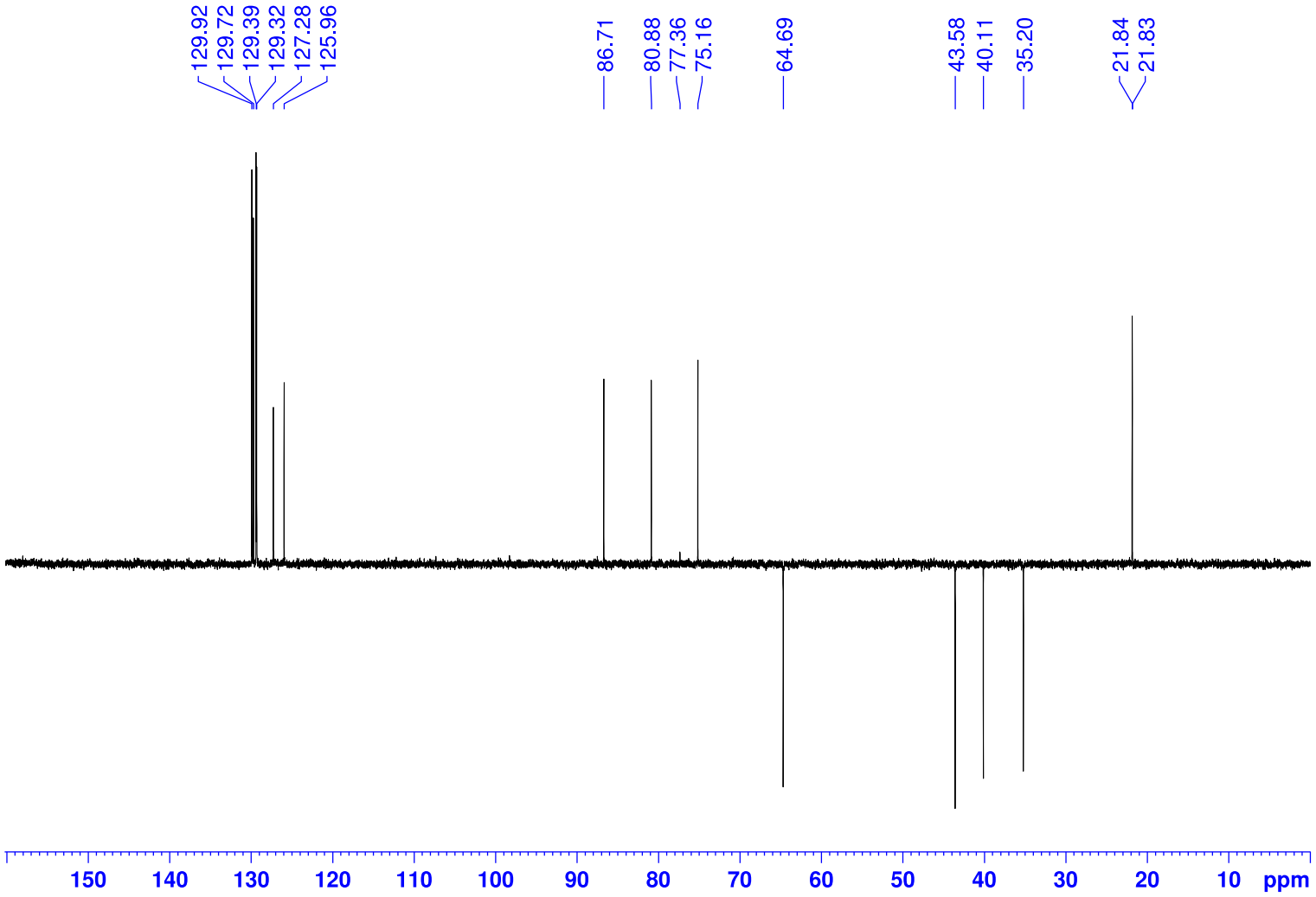
^{13}C NMR spectrum of compound 11 (126 MHz, D_2O)



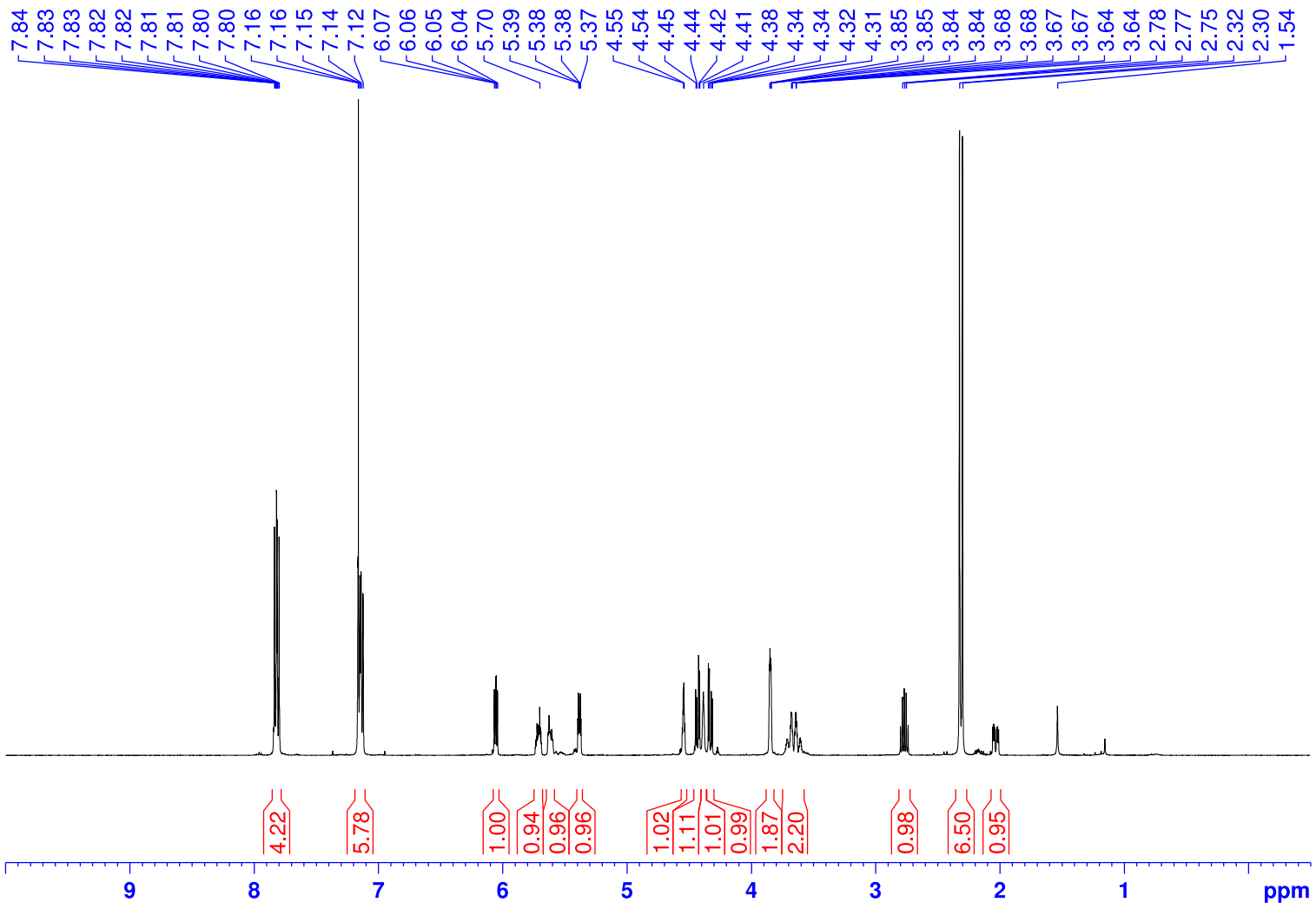
^{1}H NMR spectrum of compound 14 (500 MHz, $CDCl_3$)



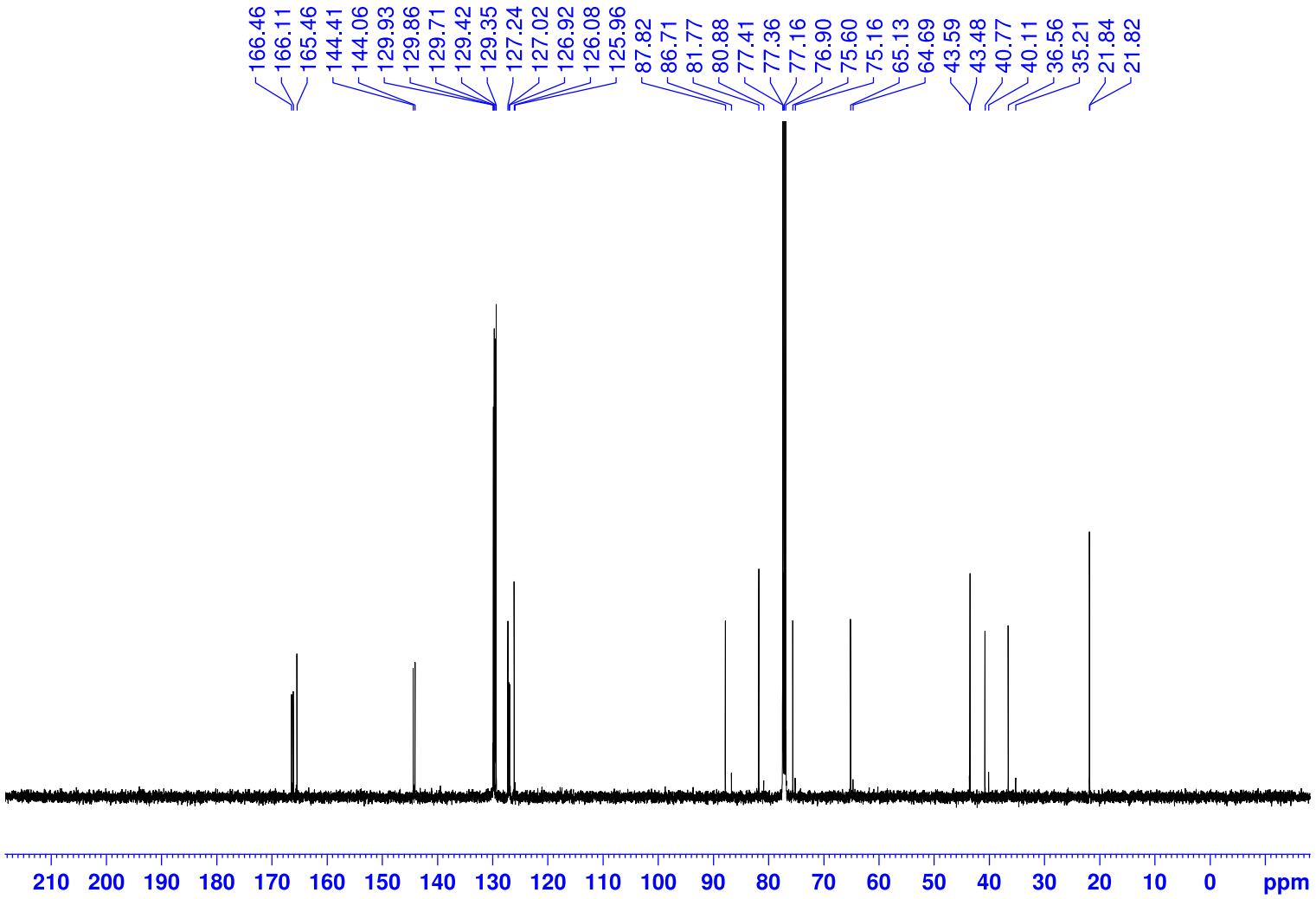
^{13}C NMR spectrum of compound 14 (126 MHz, $CDCl_3$)



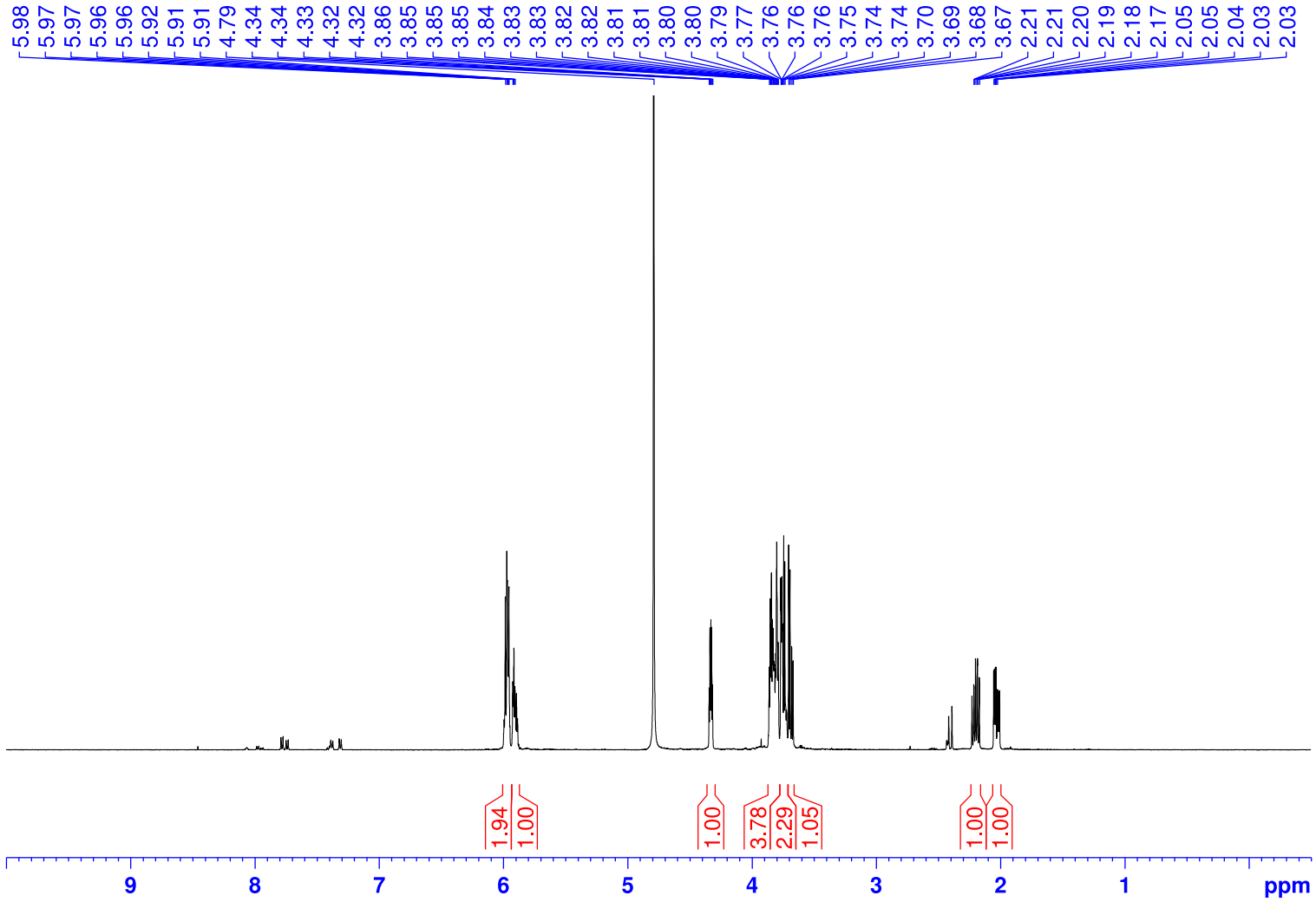
^{13}C DEPT-135 NMR spectrum of compound 14 (126 MHz, $CDCl_3$)



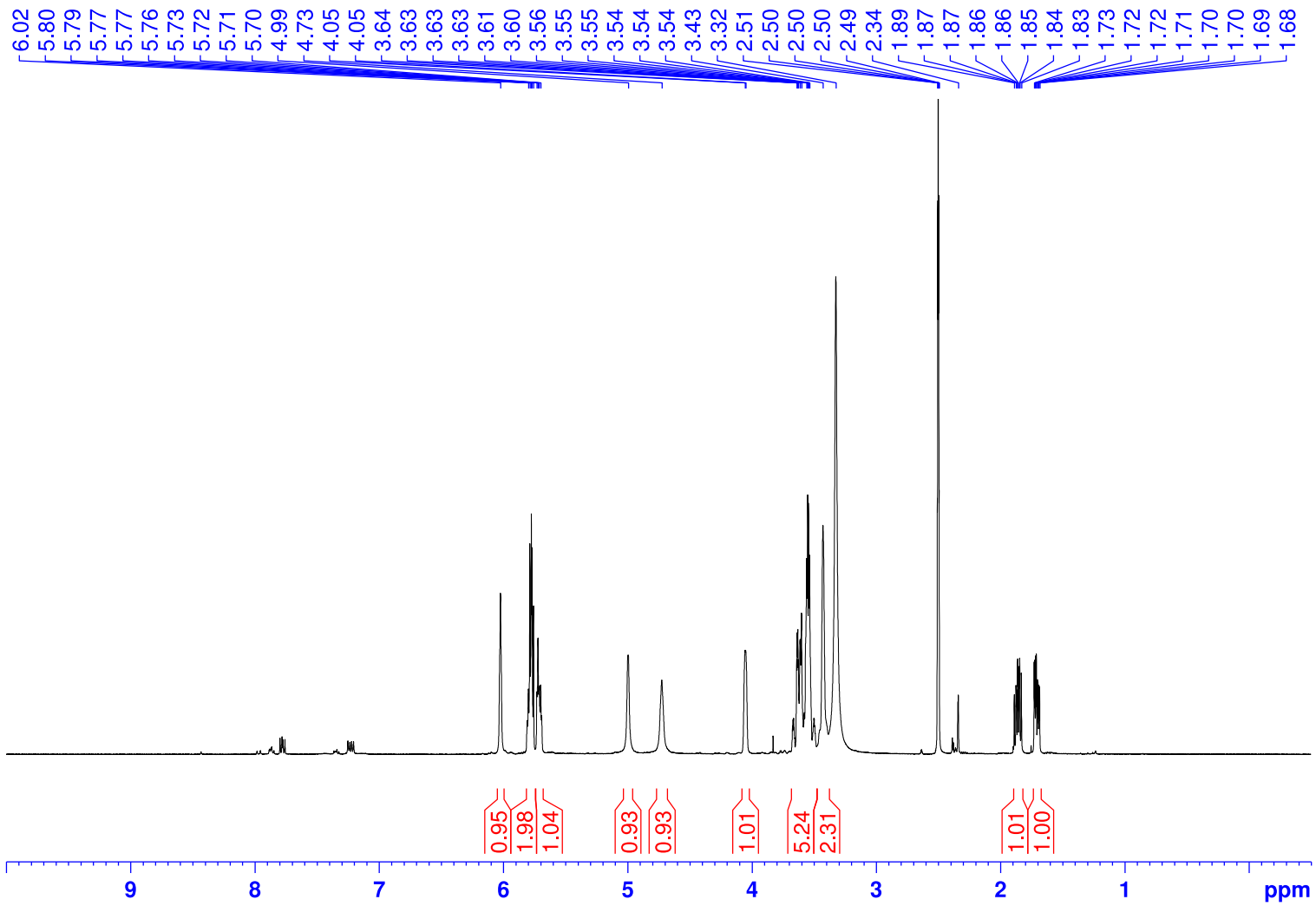
^{1}H NMR spectrum of compound 15 (500 MHz, $CDCl_3$)



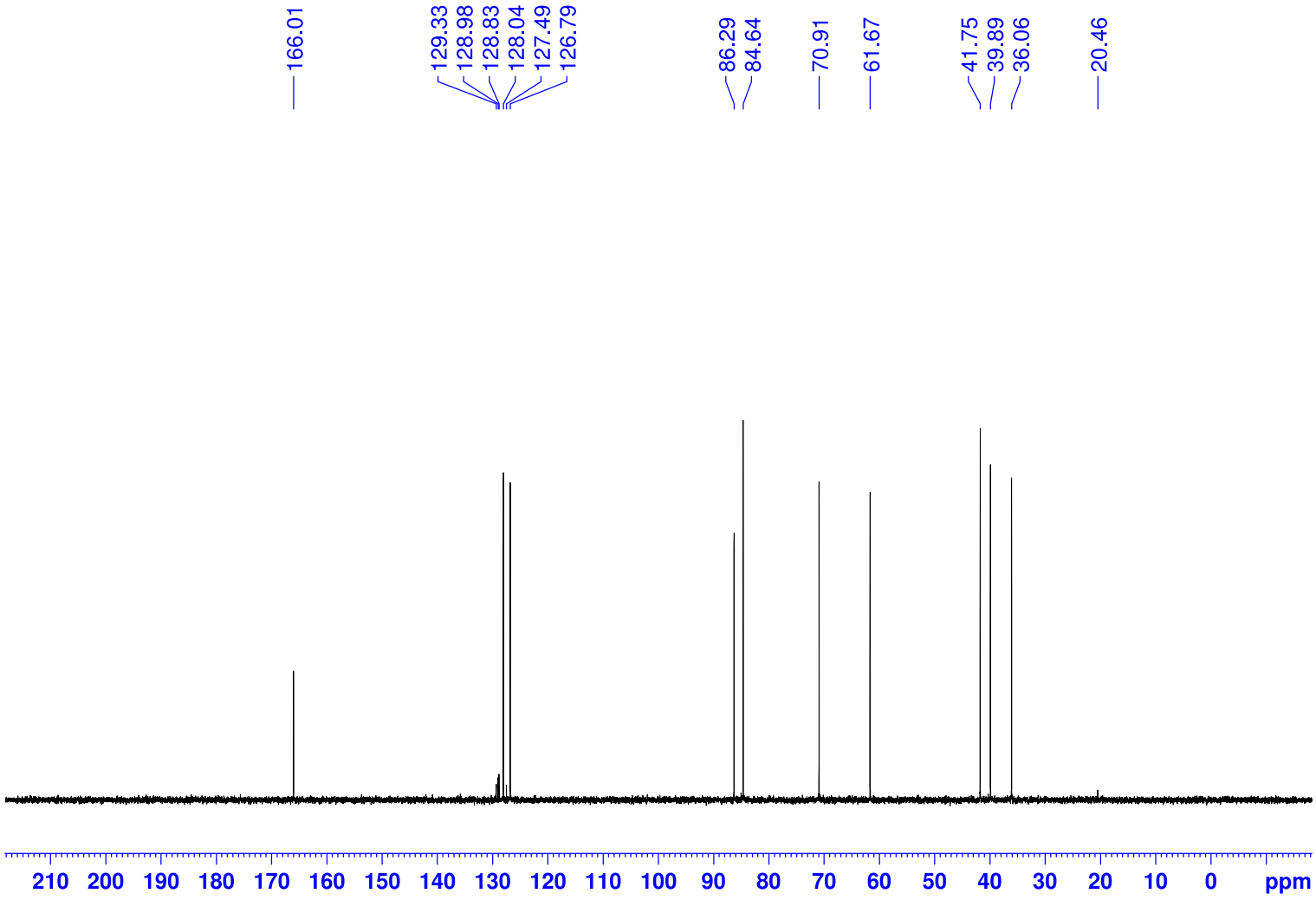
^{13}C NMR spectrum of compound 15 (126 MHz, $CDCl_3$)



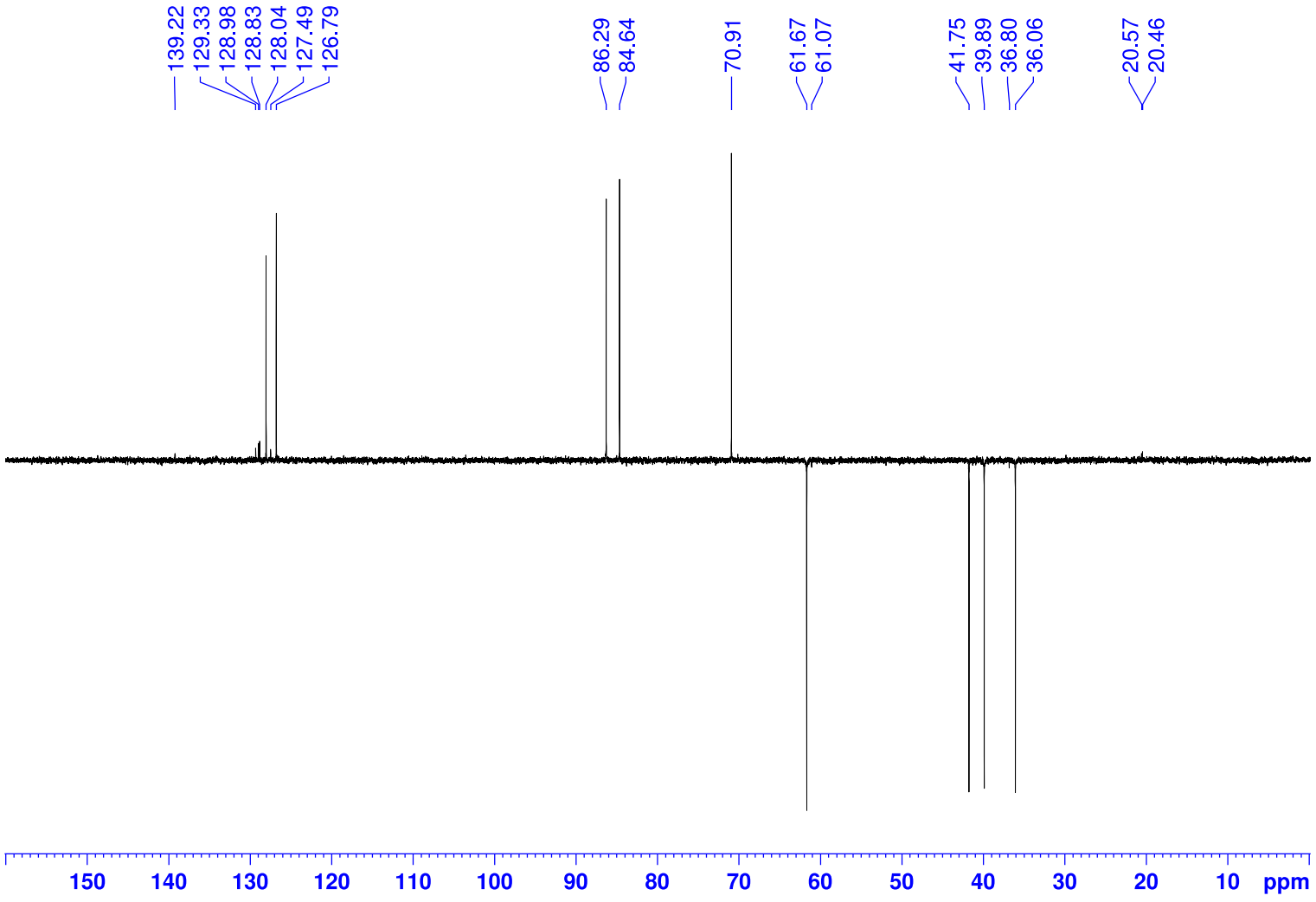
^{1}H NMR spectrum of compound 16 (500 MHz, D_2O)



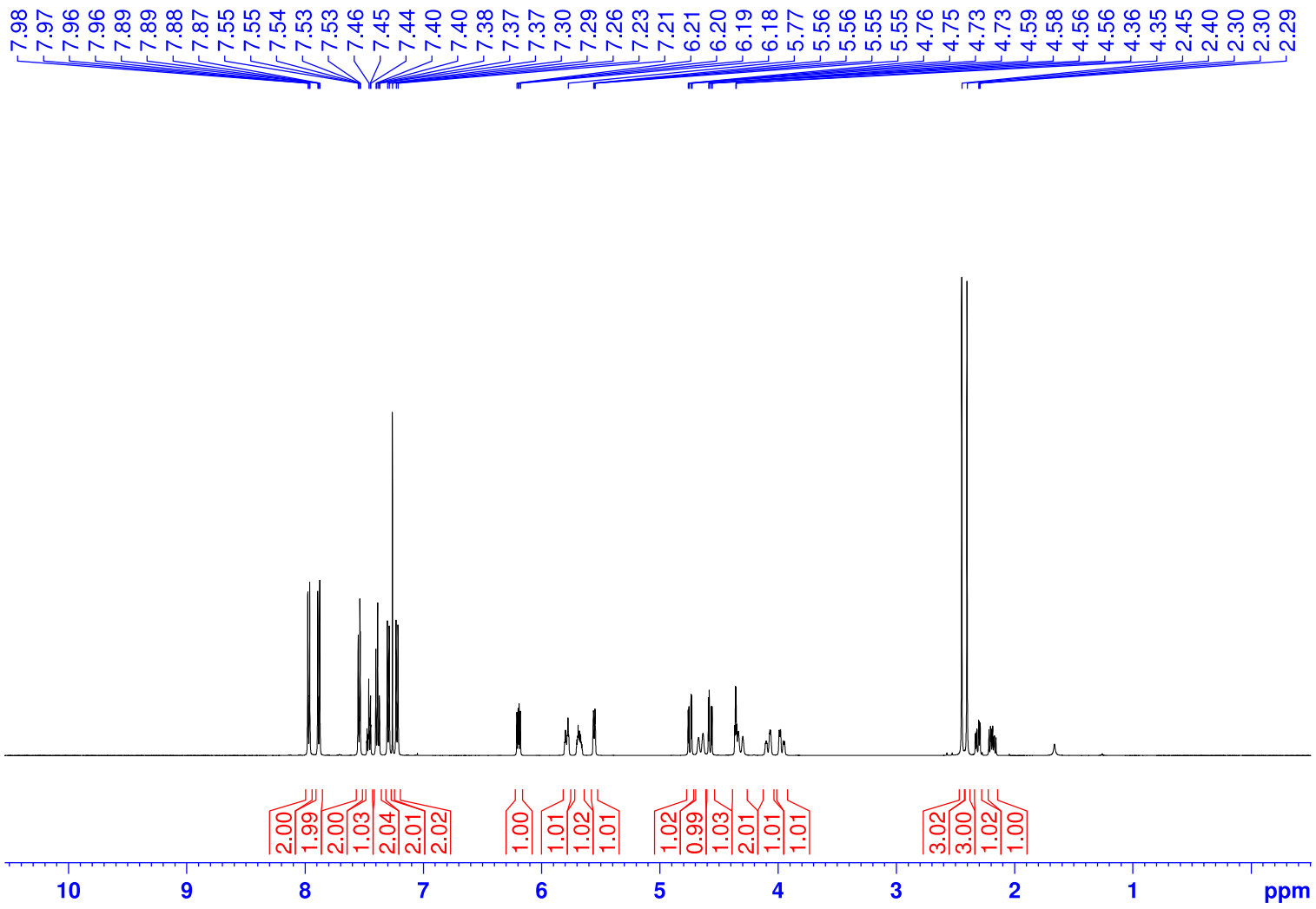
^{1}H NMR spectrum of compound 16 (500 MHz, DMSO-d_6)



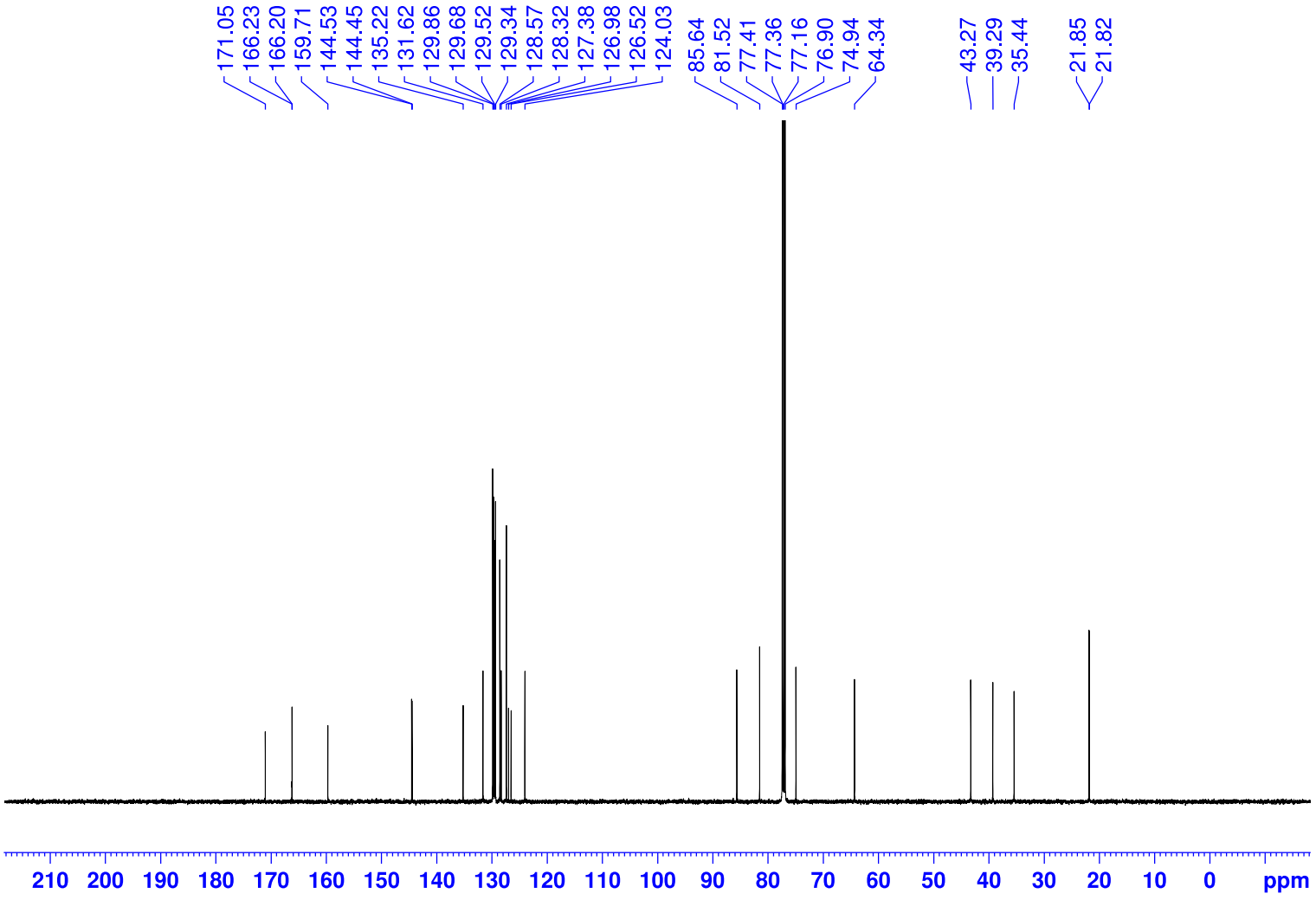
^{13}C NMR spectrum of compound 16 (126 MHz, D_2O)



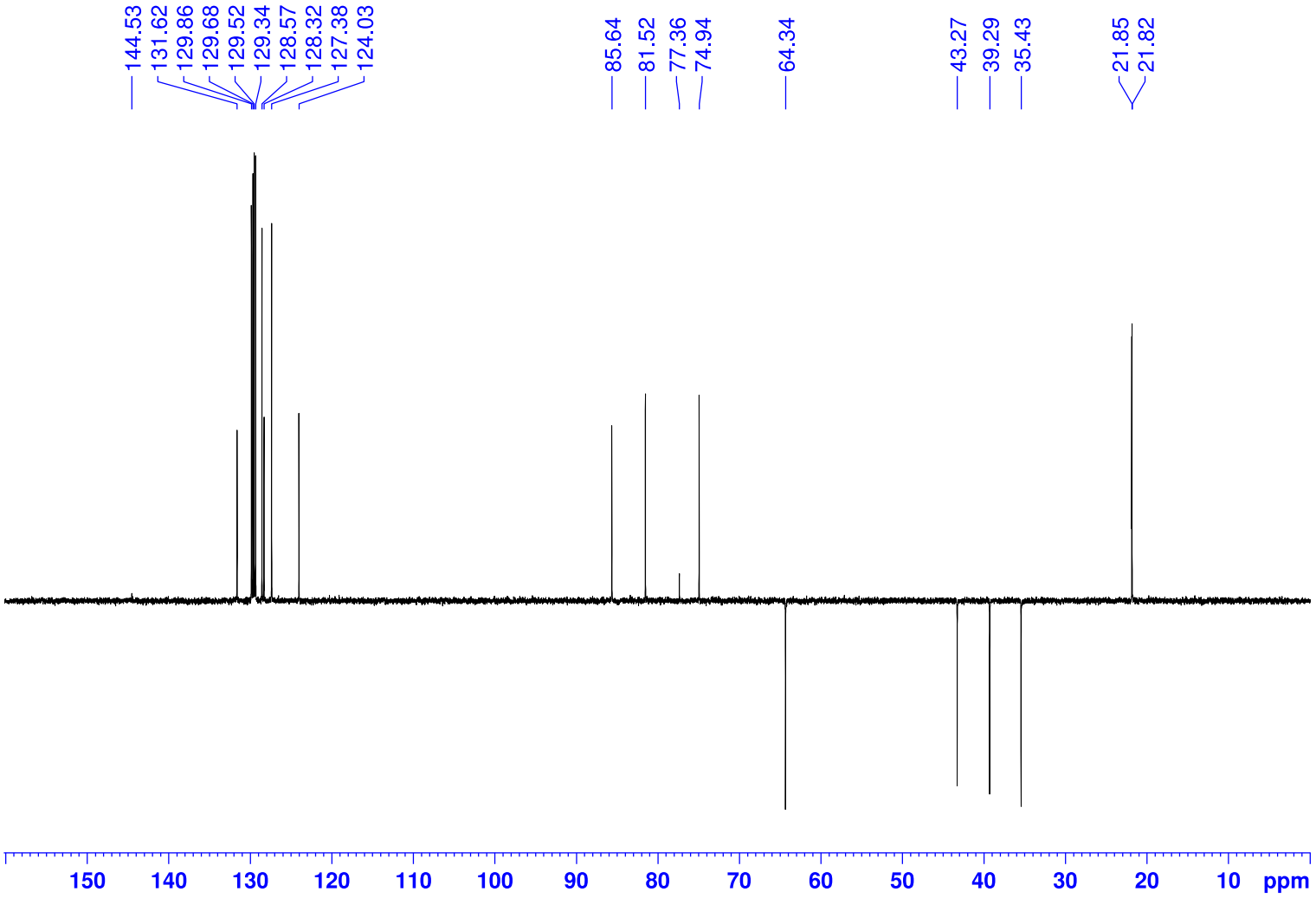
^{13}C DEPT-135 NMR spectrum of compound 16 (126 MHz, D_2O)



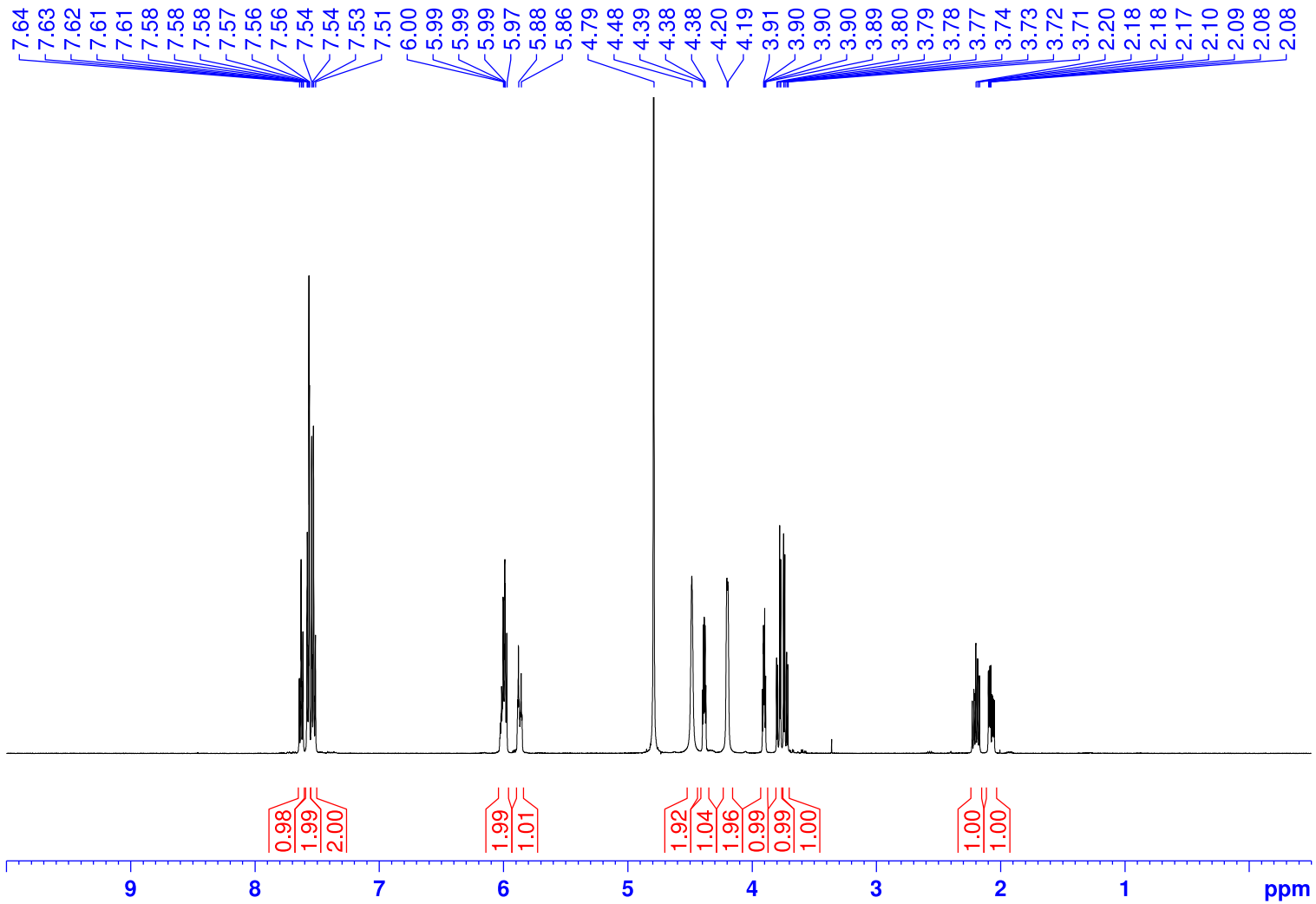
^{1}H NMR spectrum of compound 17 (500 MHz, $CDCl_3$)



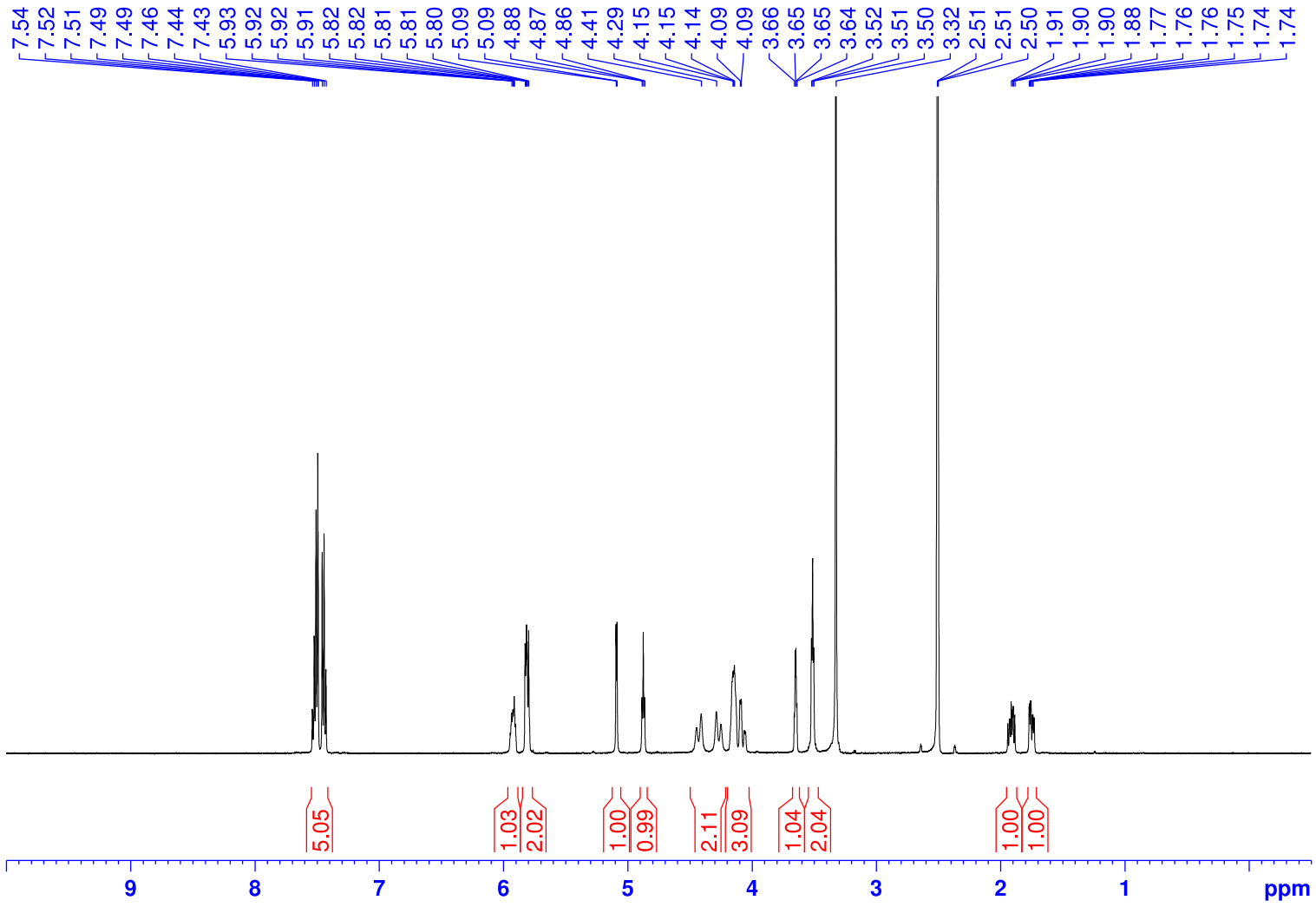
^{13}C NMR spectrum of compound 17 (126 MHz, $CDCl_3$)



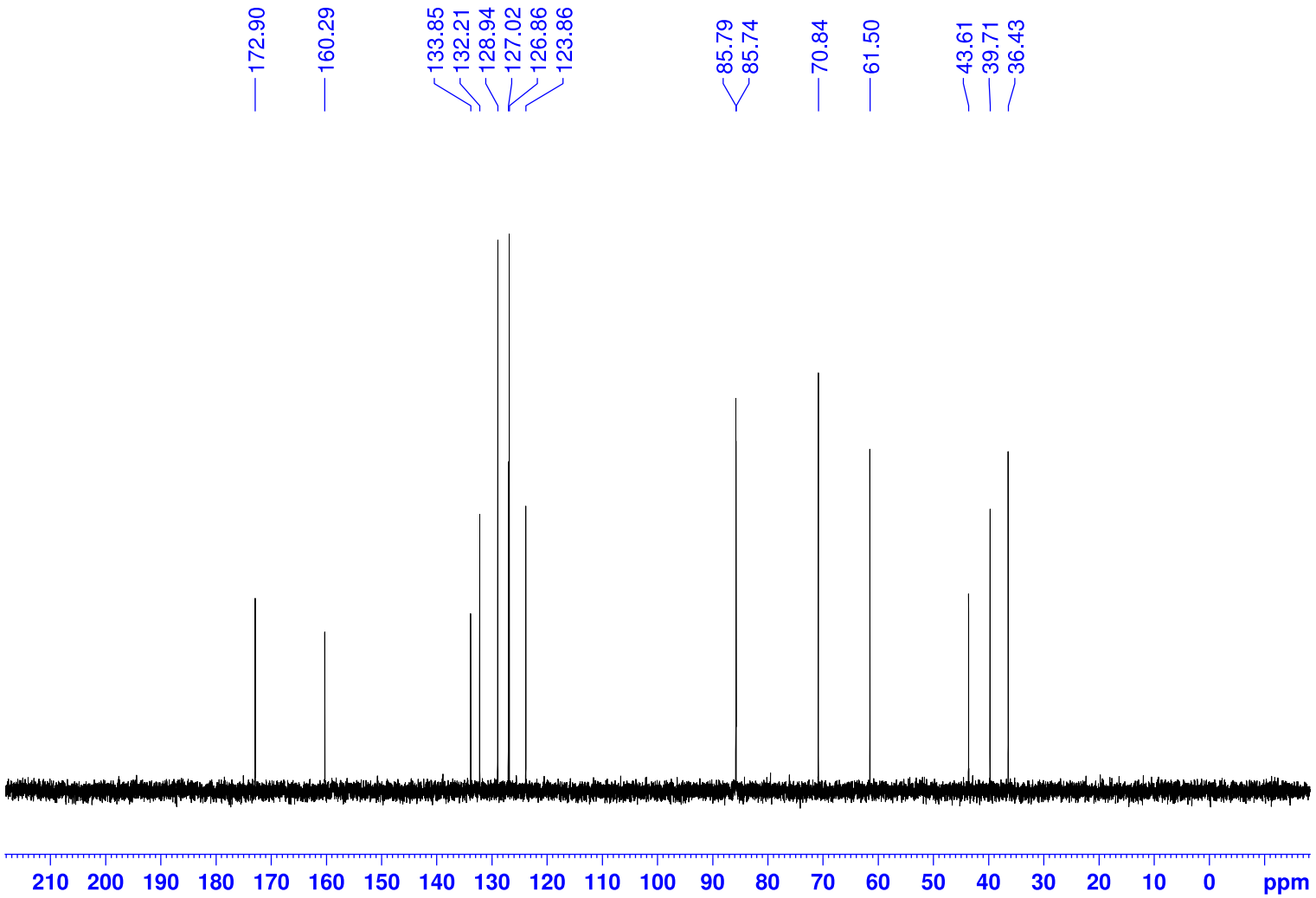
^{13}C DEPT-135 NMR spectrum of compound 17 (126 MHz, $CDCl_3$)



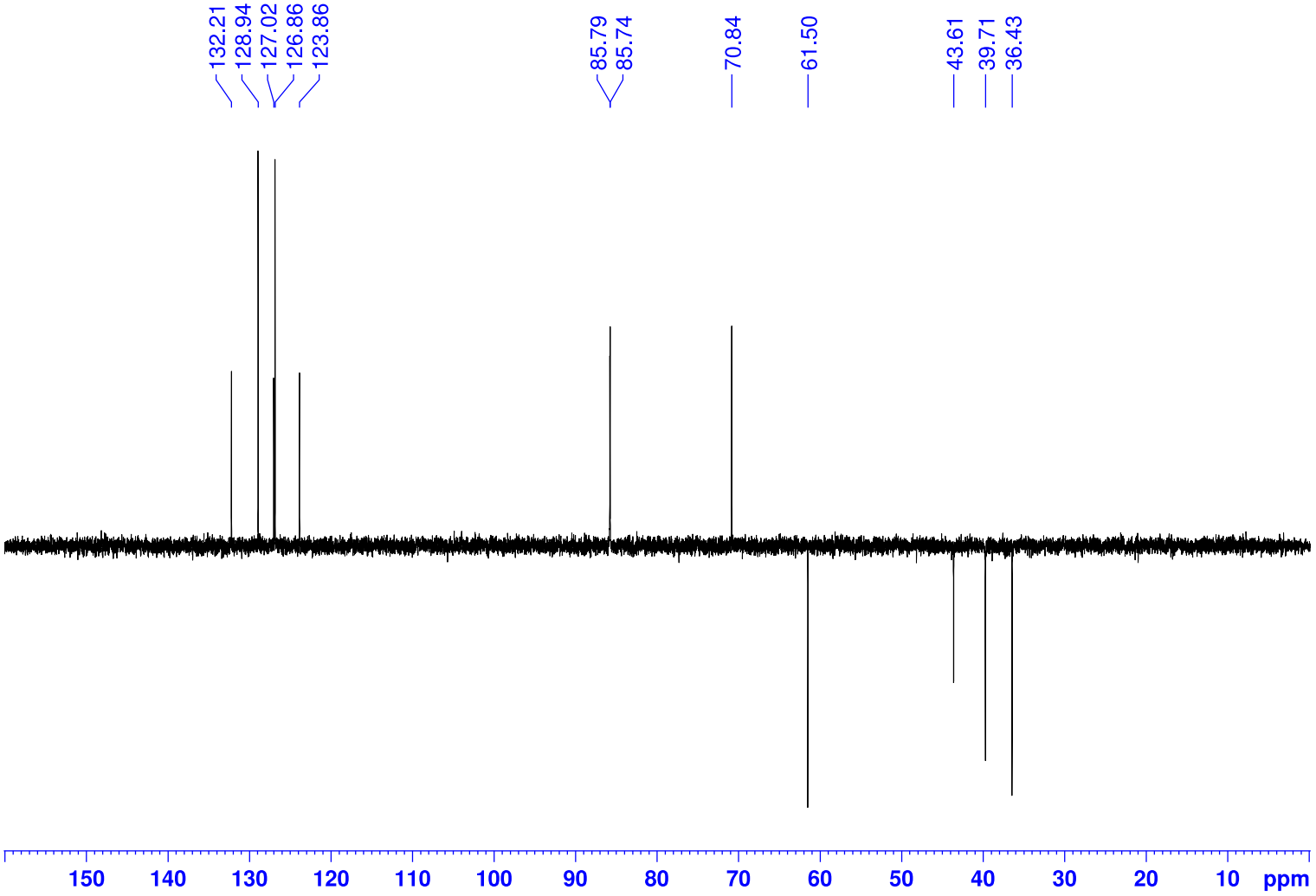
^{1}H NMR spectrum of compound 18 (500 MHz, D_2O)



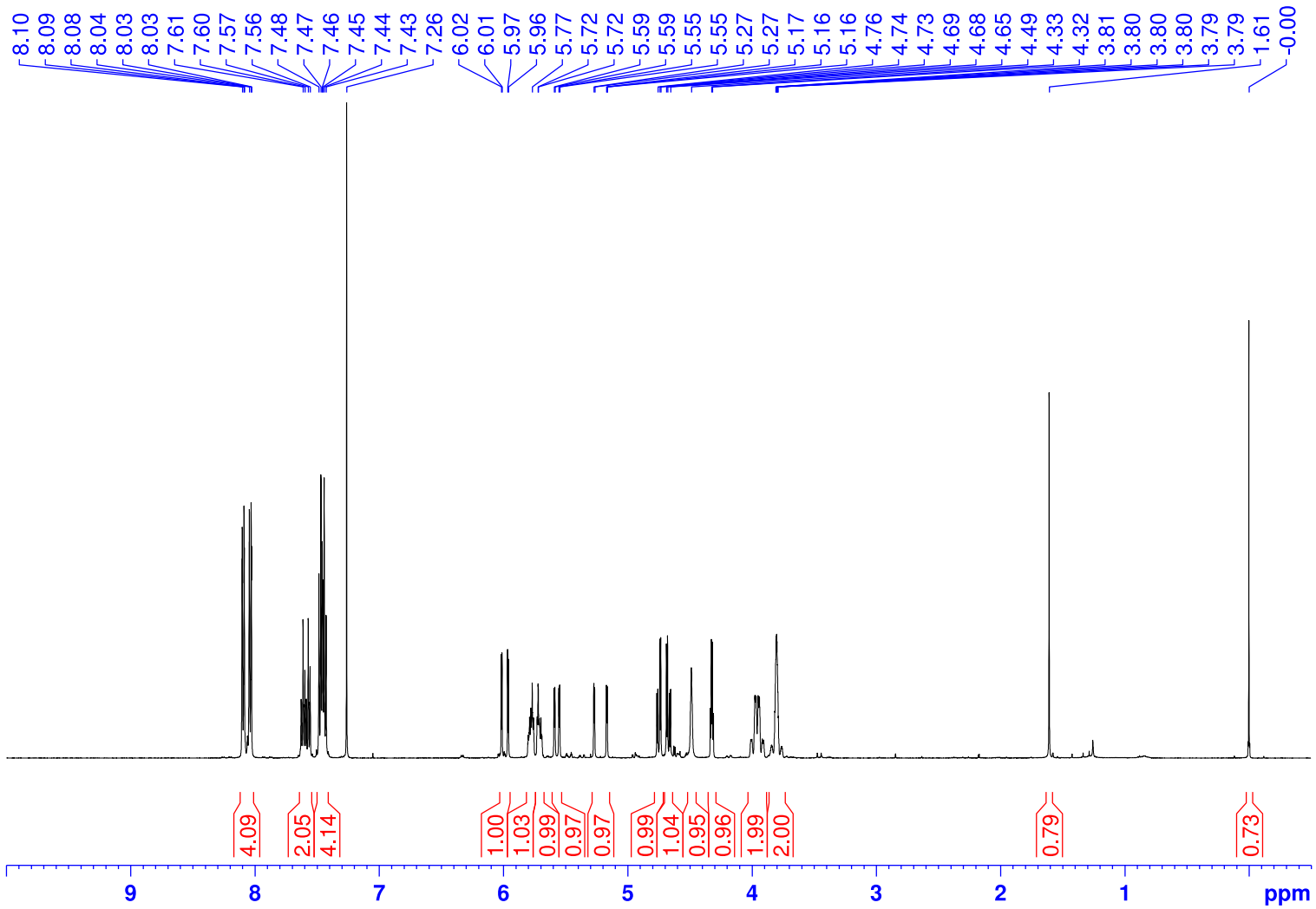
^{1}H NMR spectrum of compound 18 (500 MHz, DMSO-d_6)



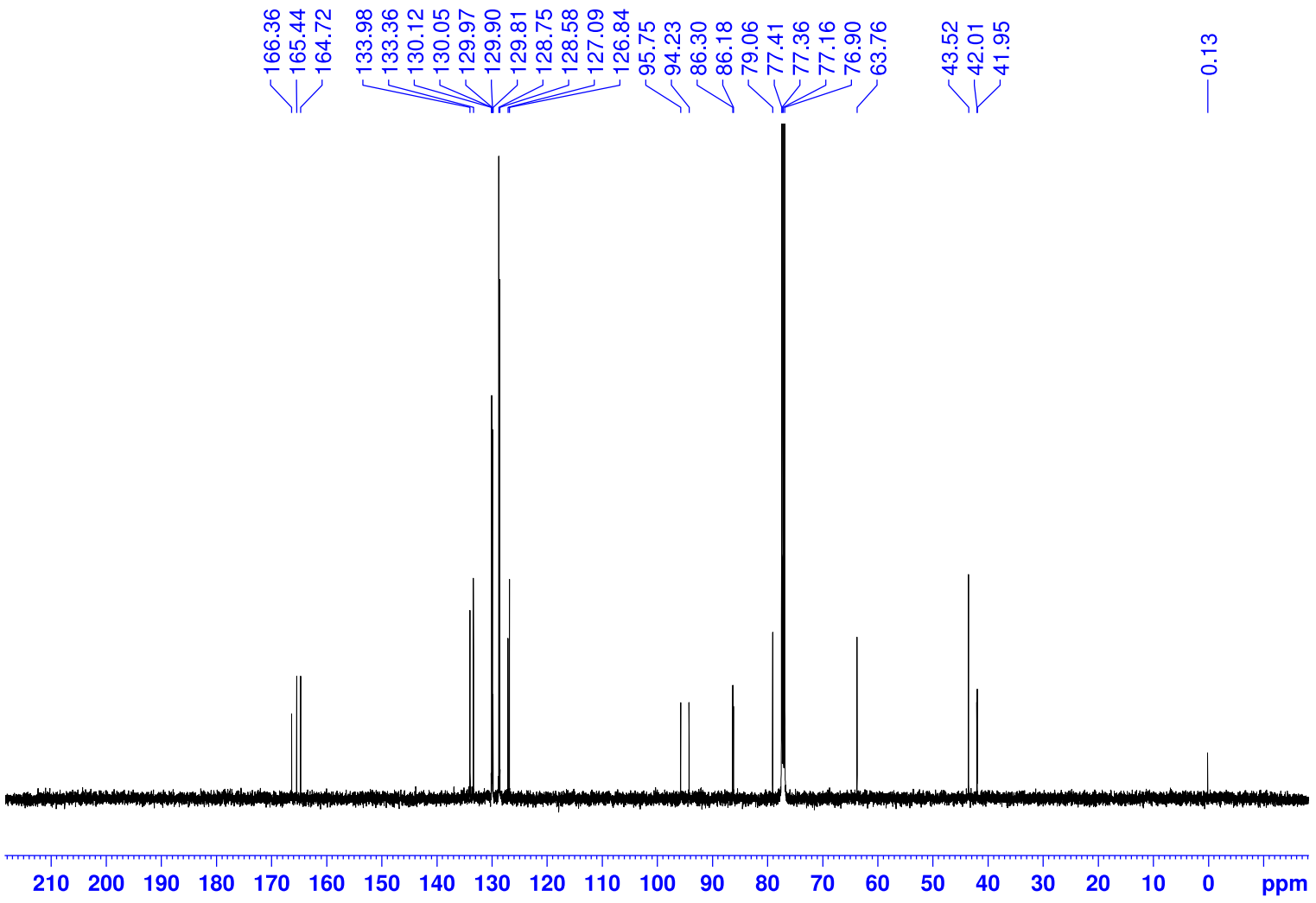
^{13}C NMR spectrum of compound 18 (126 MHz, D_2O)



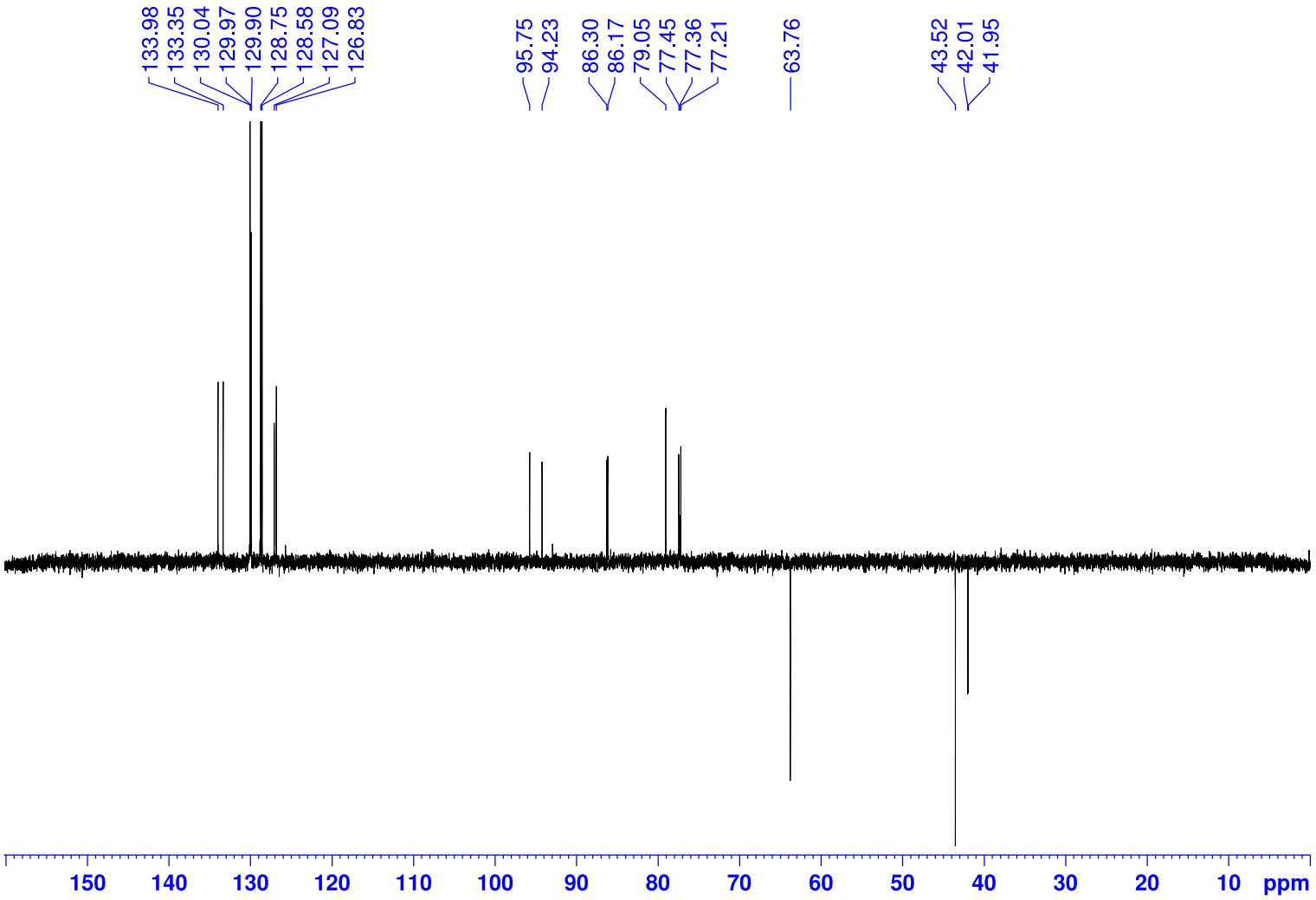
^{13}C DEPT-135 NMR spectrum of compound 18 (126 MHz, D_2O)



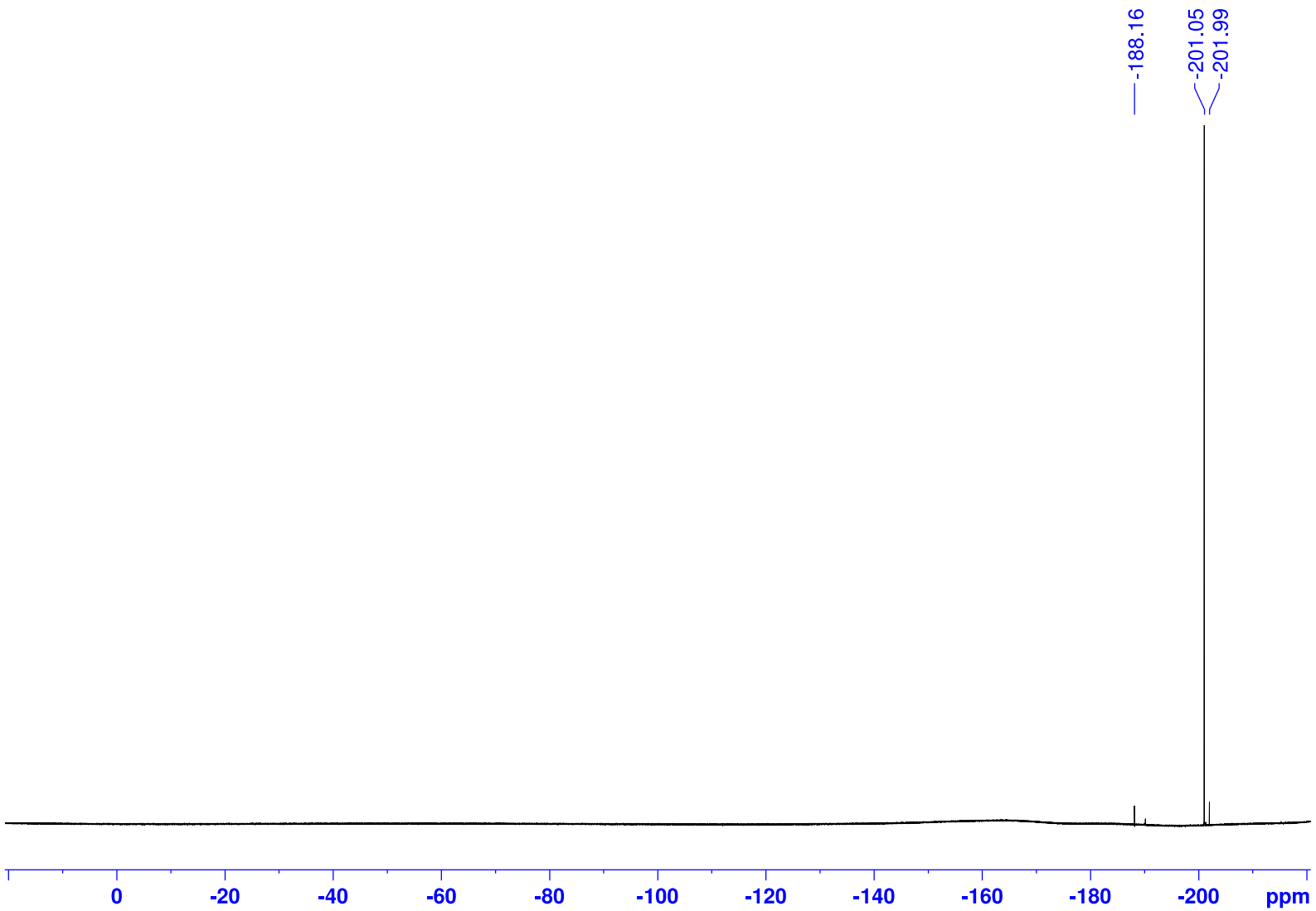
^{1}H NMR spectrum of compound 20 (500 MHz, $CDCl_3$)



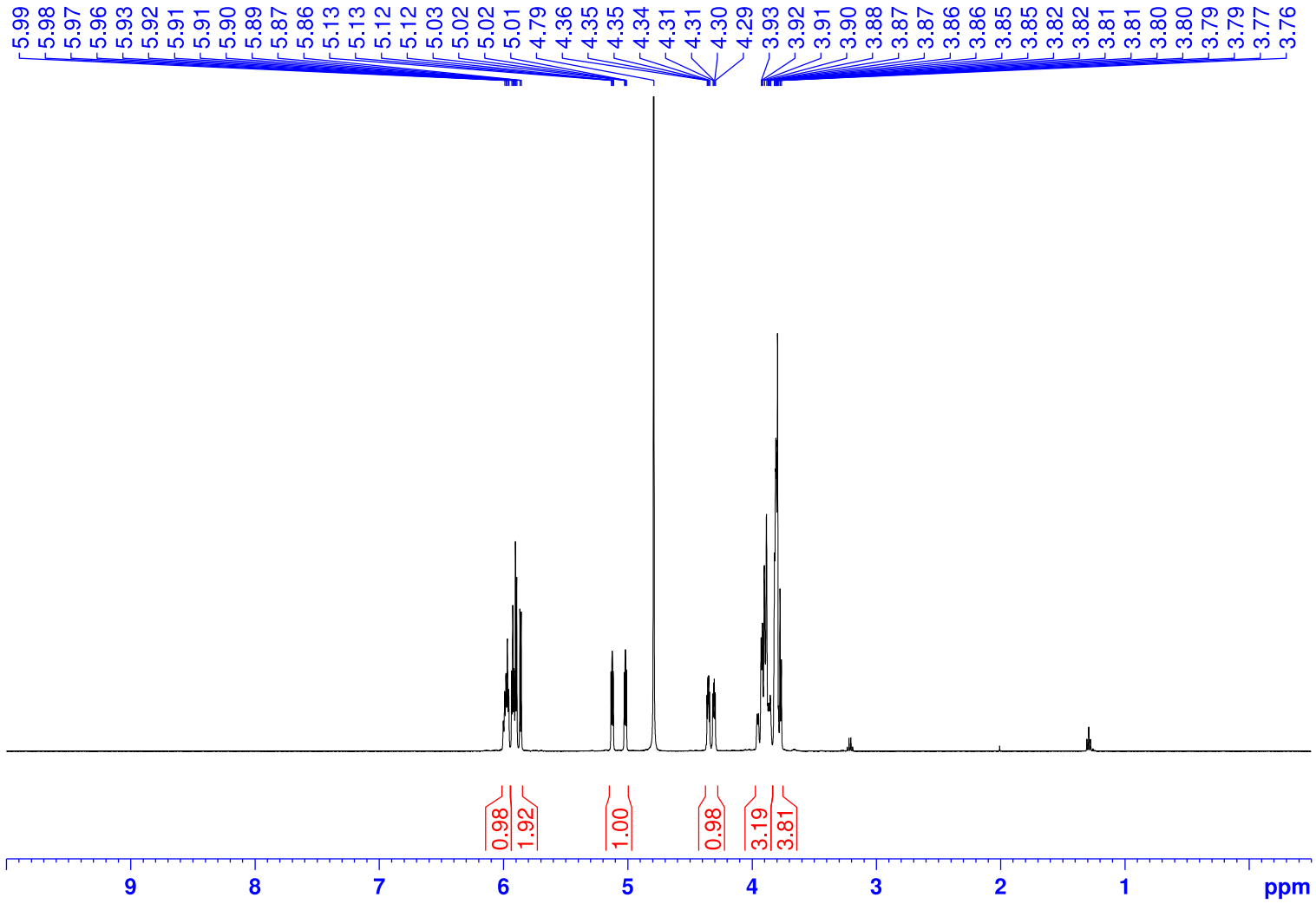
^{13}C NMR spectrum of compound 20 (126 MHz, $CDCl_3$)



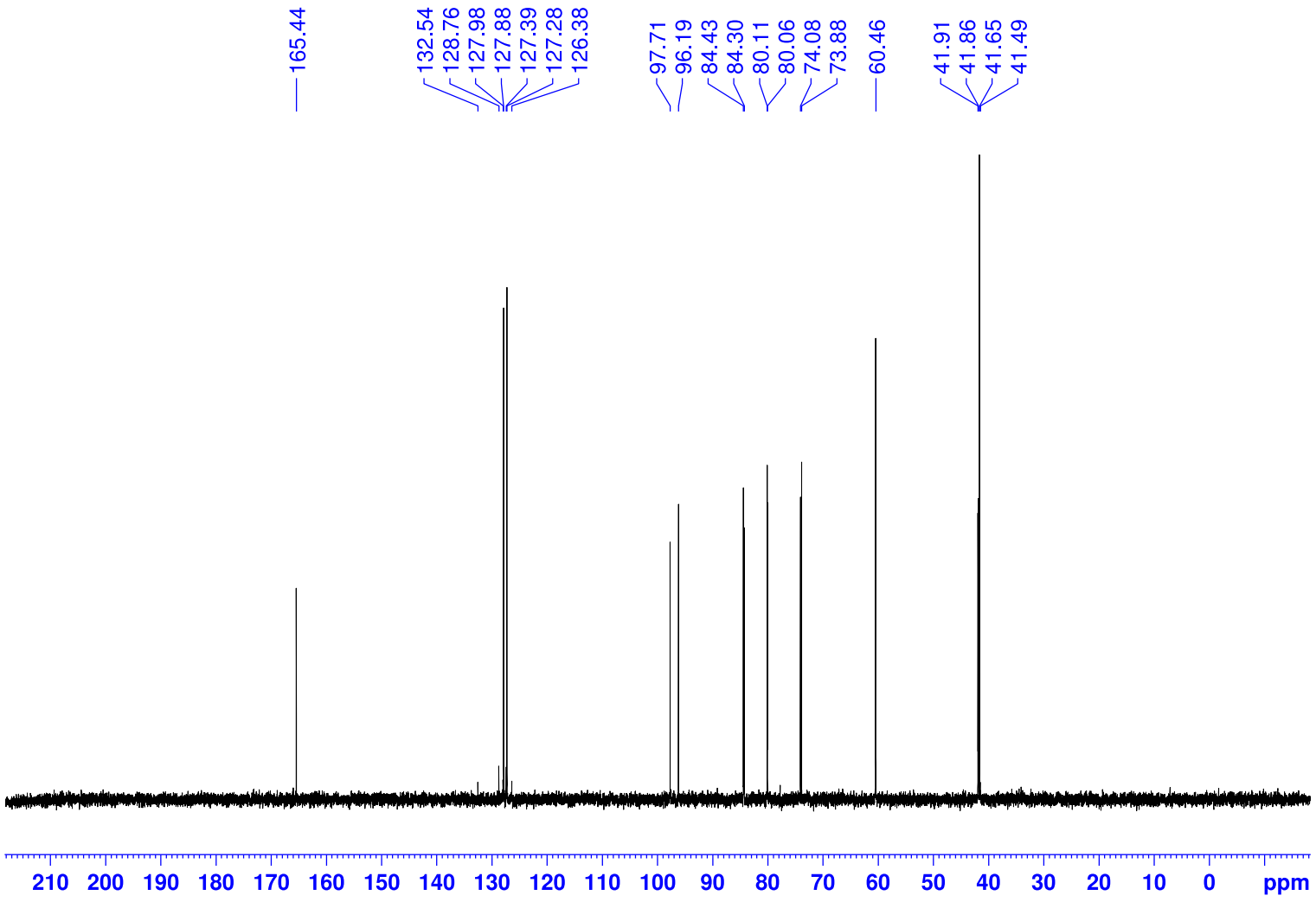
^{13}C DEPT-135 NMR spectrum of compound 20 (126 MHz, $CDCl_3$)



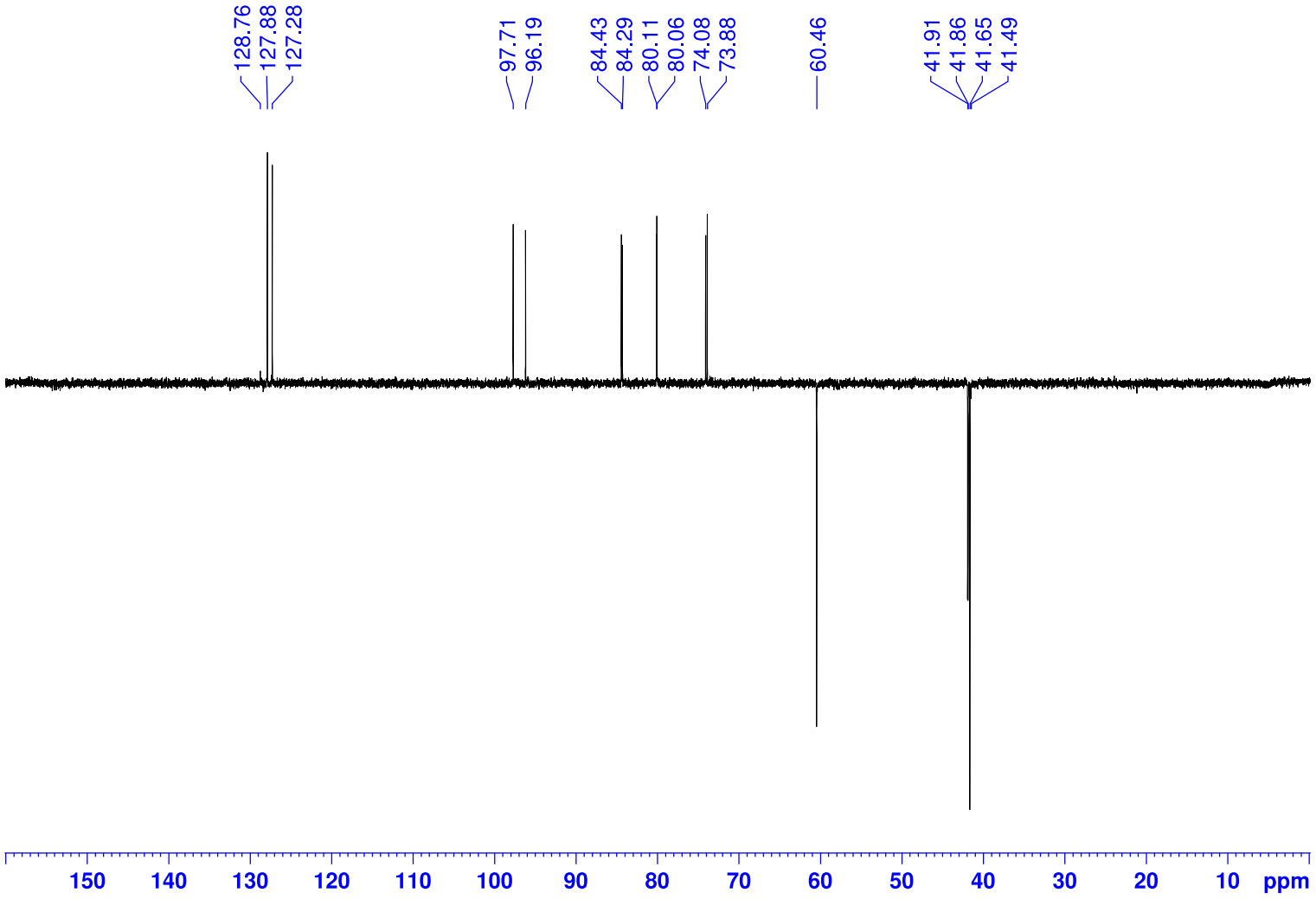
^{19}F NMR spectrum of compound 20 (470 MHz, $CDCl_3$)



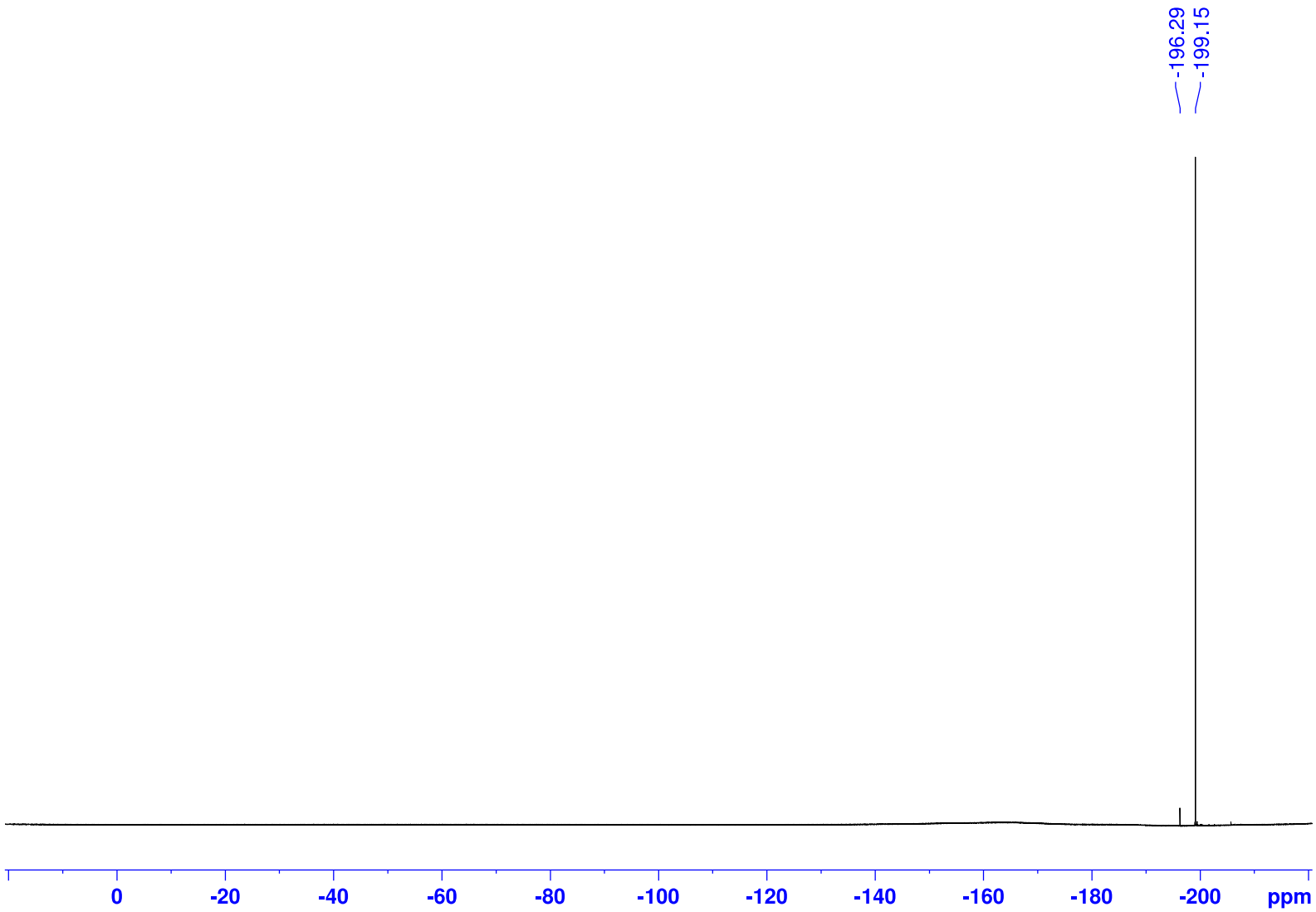
^{1}H NMR spectrum of compound 21 (500 MHz, D_2O)



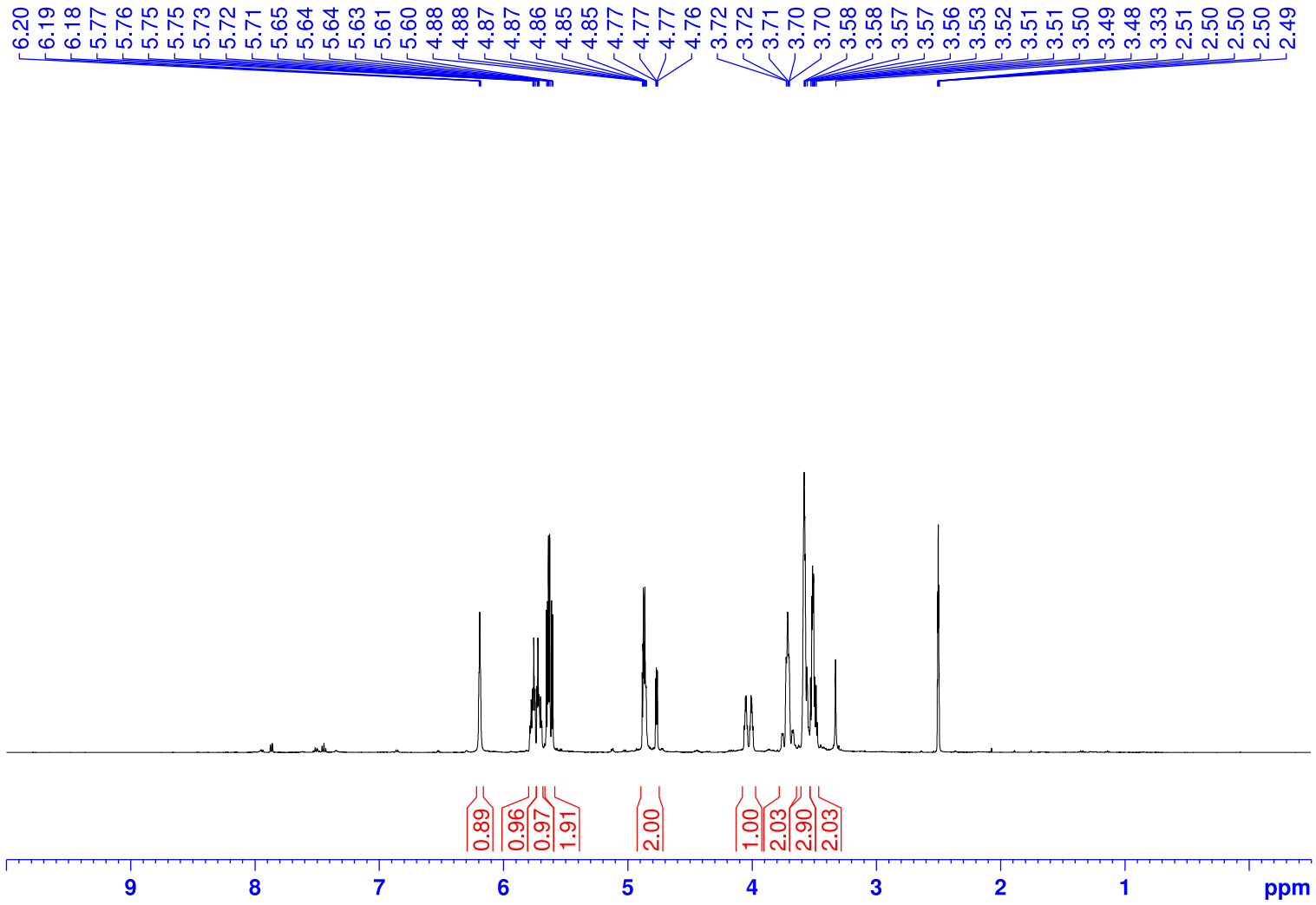
^{13}C NMR spectrum of compound 21 (126 MHz, D_2O)



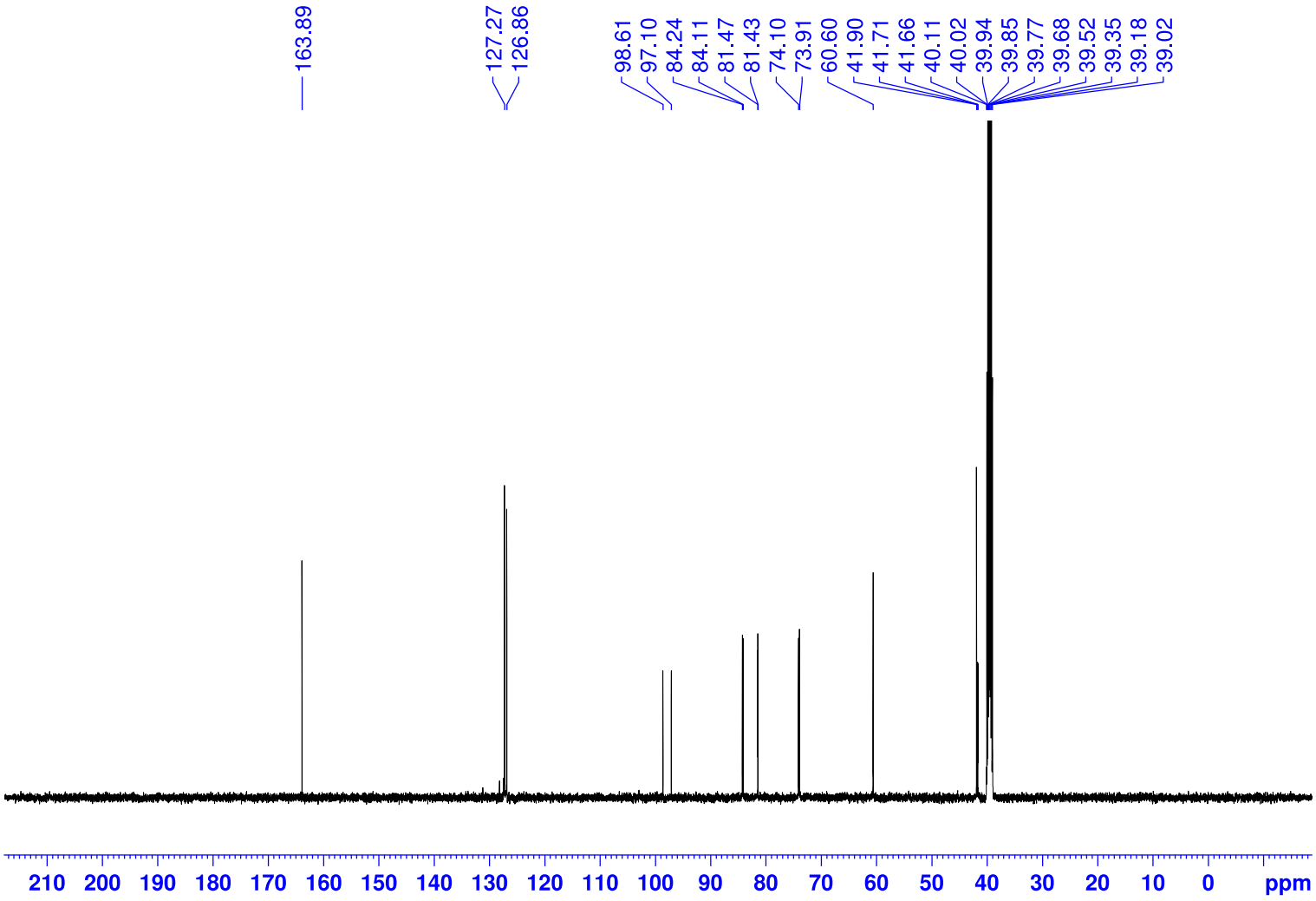
^{13}C DEPT-135 NMR spectrum of compound 21 (126 MHz, D_2O)



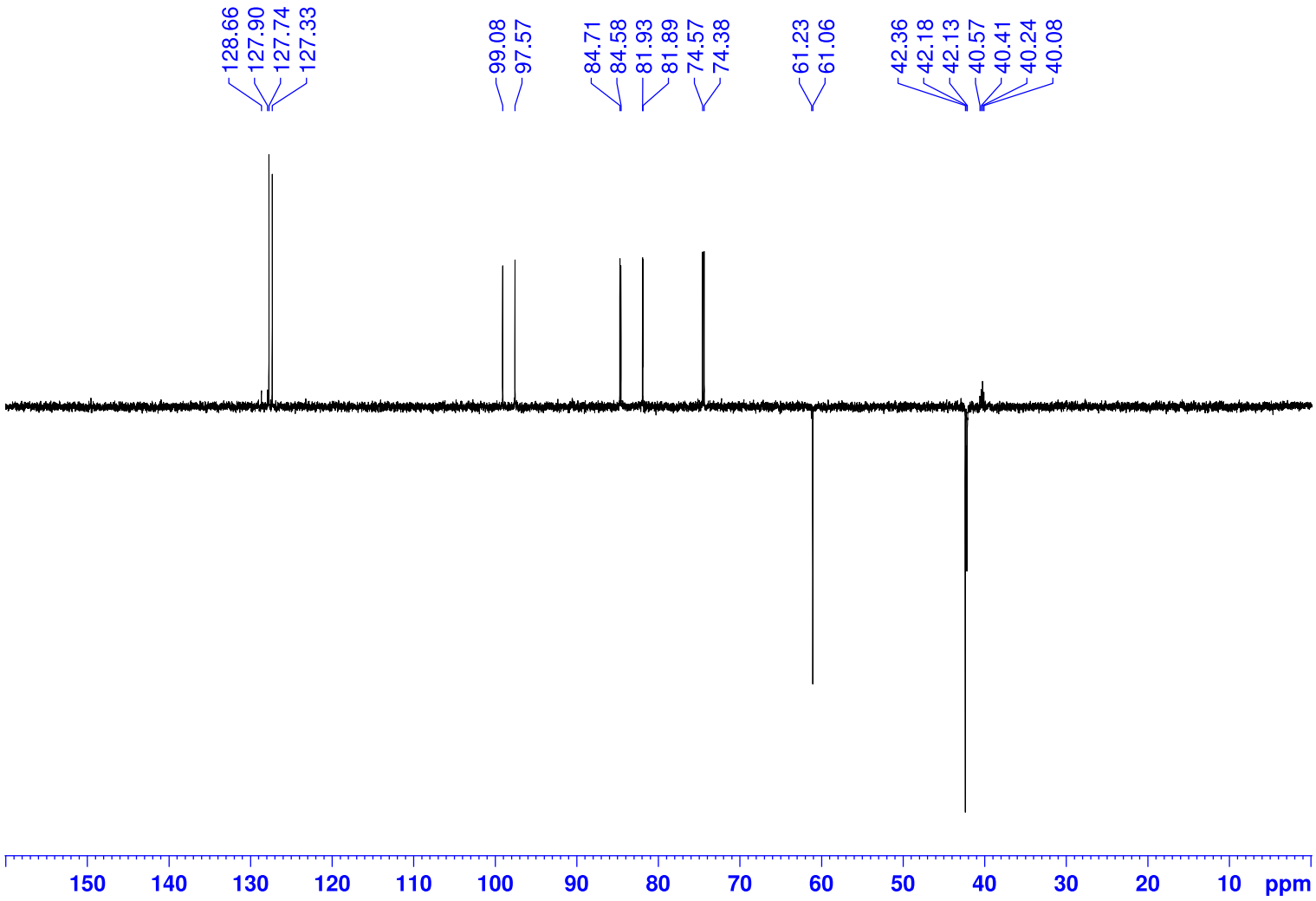
^{19}F NMR spectrum of compound 21 (470 MHz, D_2O)



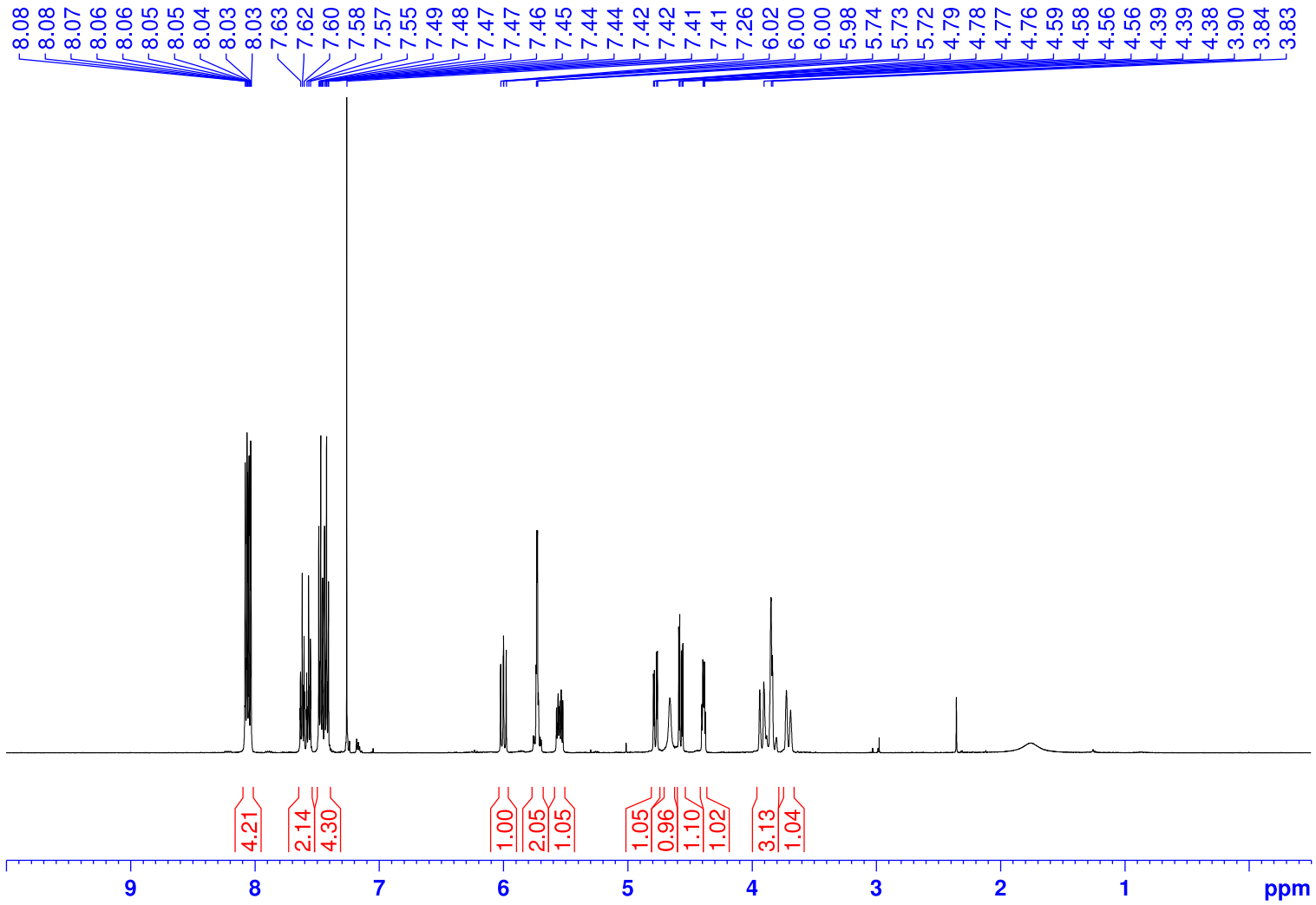
^{1}H NMR spectrum of compound 21 (500 MHz, DMSO-d_6)



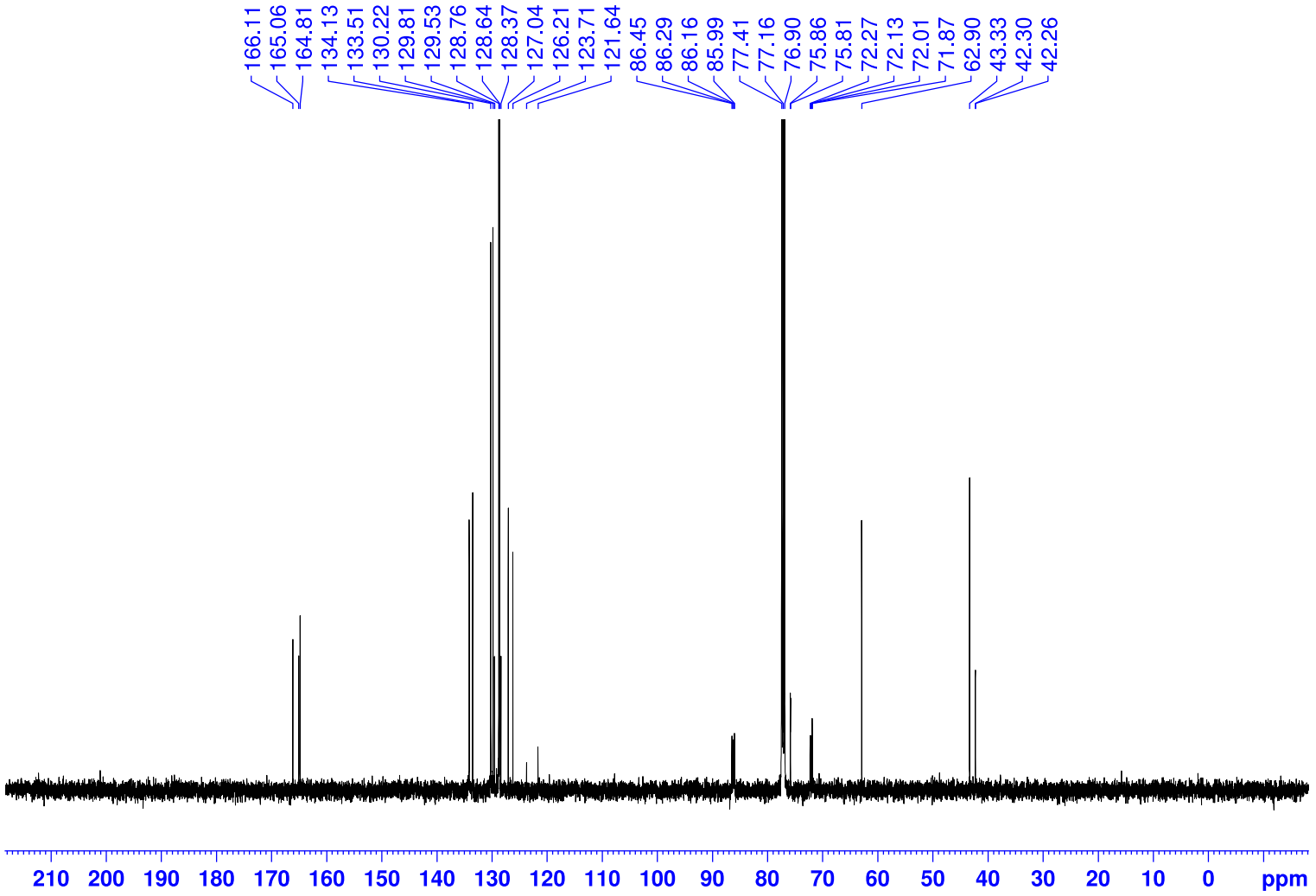
^{13}C NMR spectrum of compound 21 (126 MHz, DMSO-d_6)



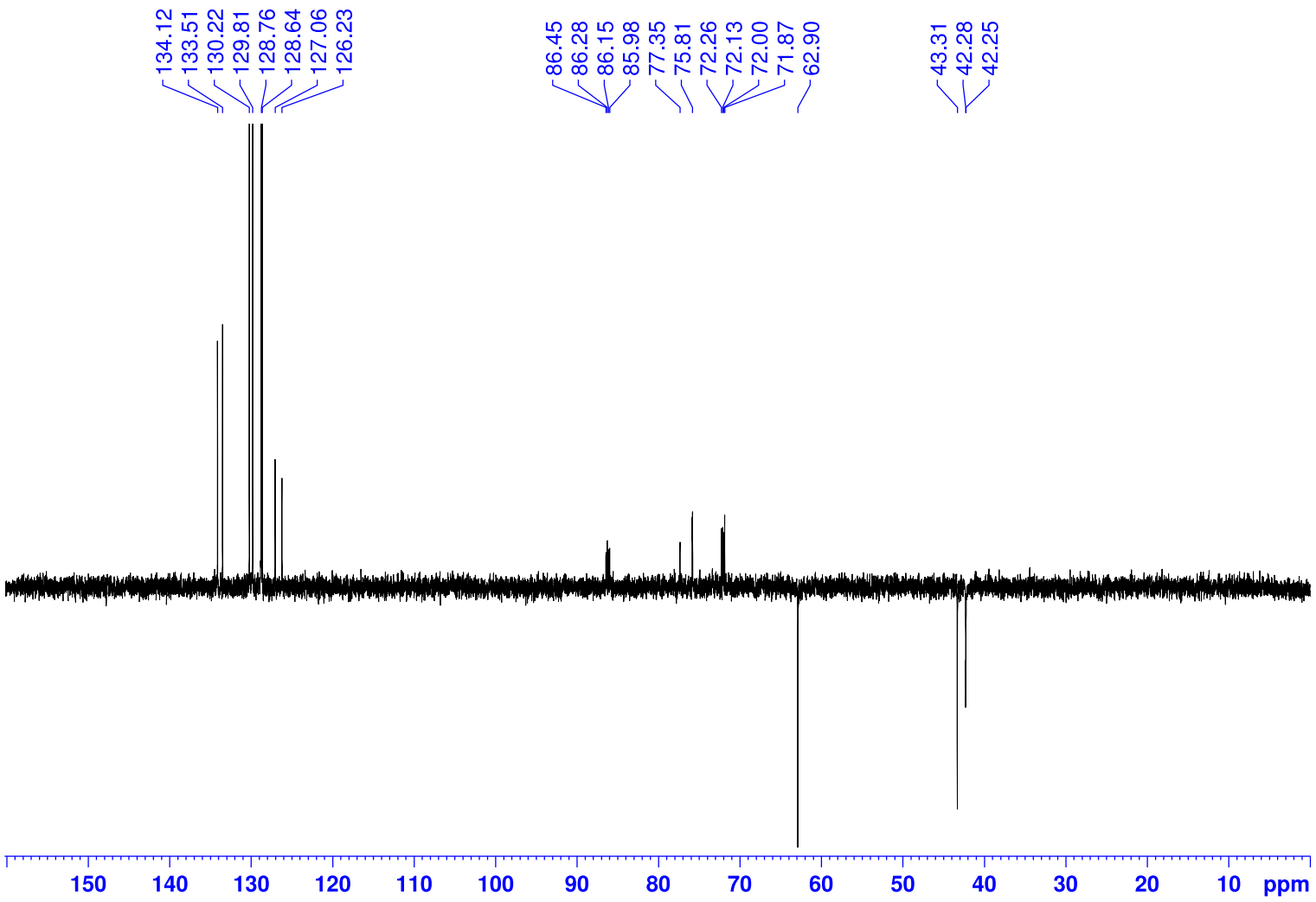
^{13}C DEPT-135 NMR spectrum of compound 21 (126 MHz, DMSO-d_6)



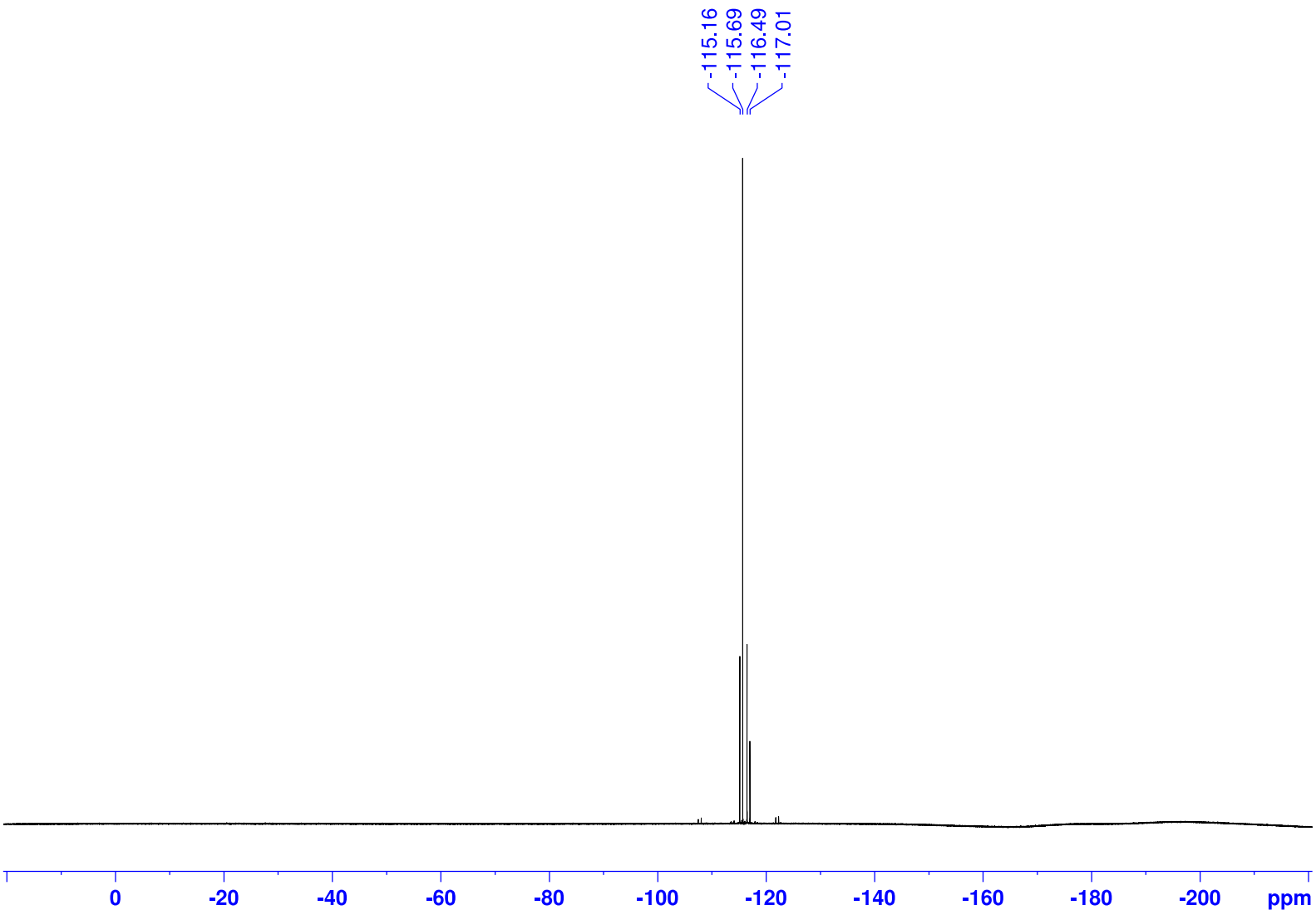
^{1}H NMR spectrum of compound 23 (500 MHz, $CDCl_3$)



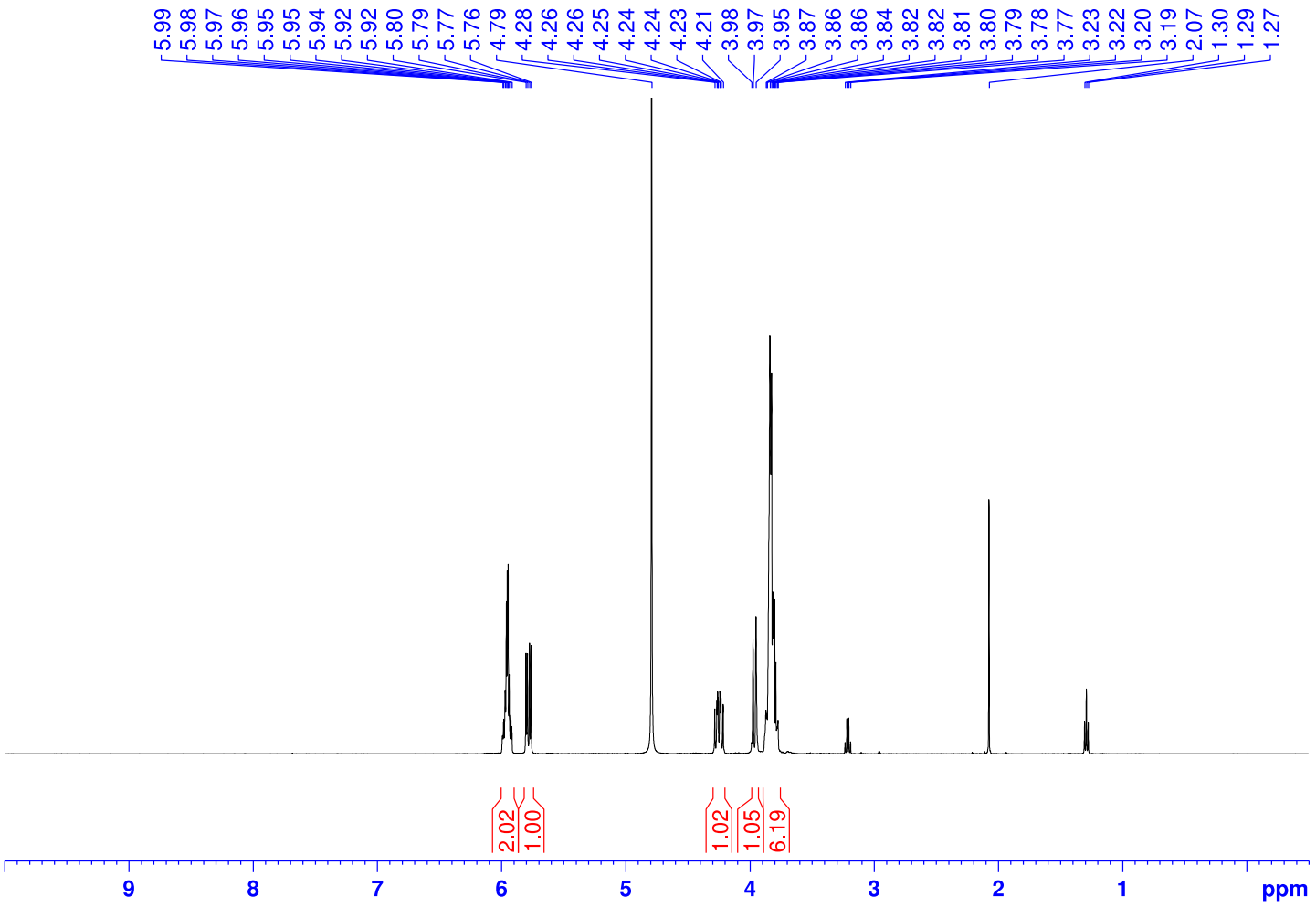
^{13}C NMR spectrum of compound 23 (126 MHz, $CDCl_3$)



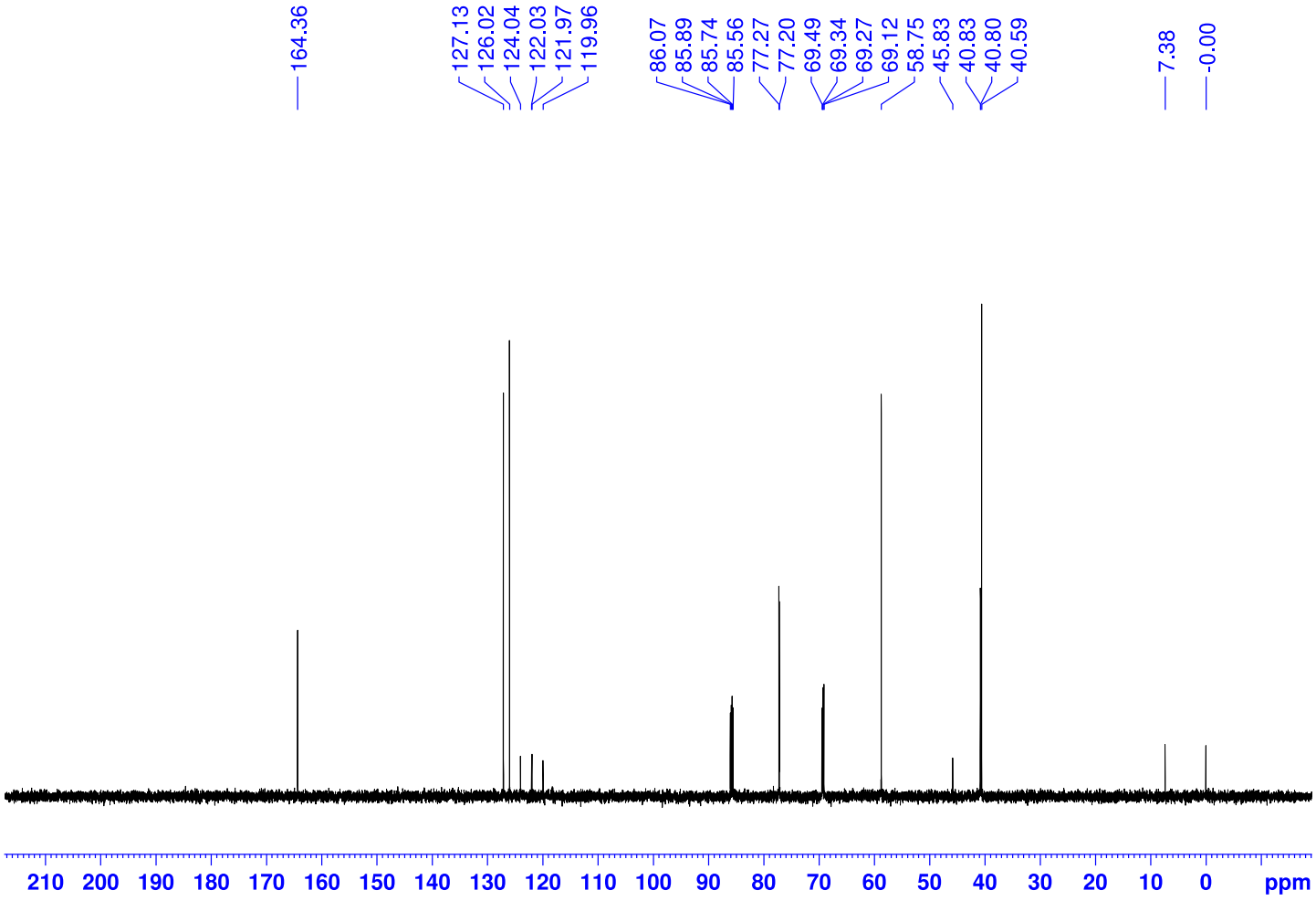
^{13}C DEPT-135 NMR spectrum of compound 23 (126 MHz, $CDCl_3$)



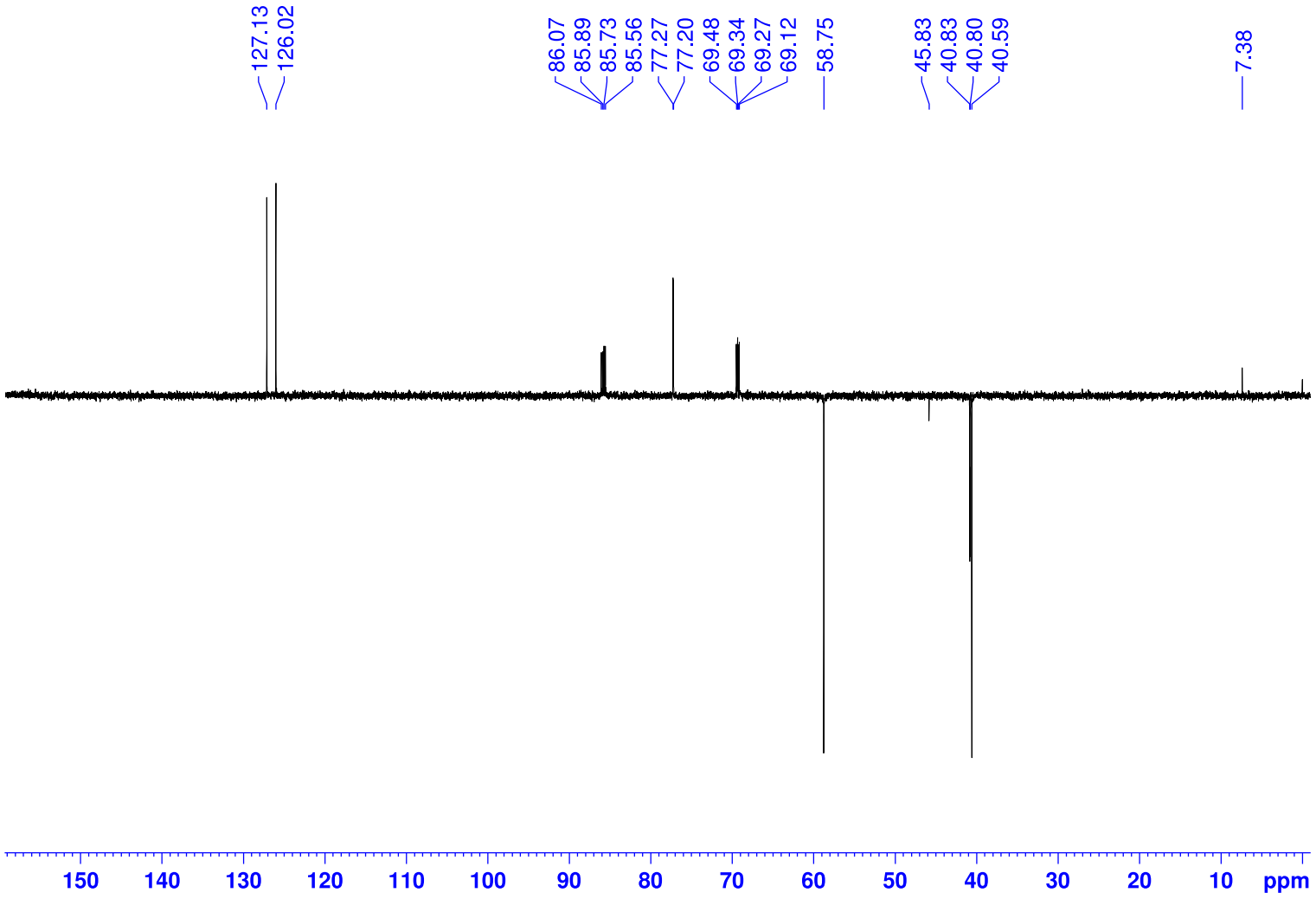
^{19}F NMR spectrum of compound 23 (470 MHz, $CDCl_3$)



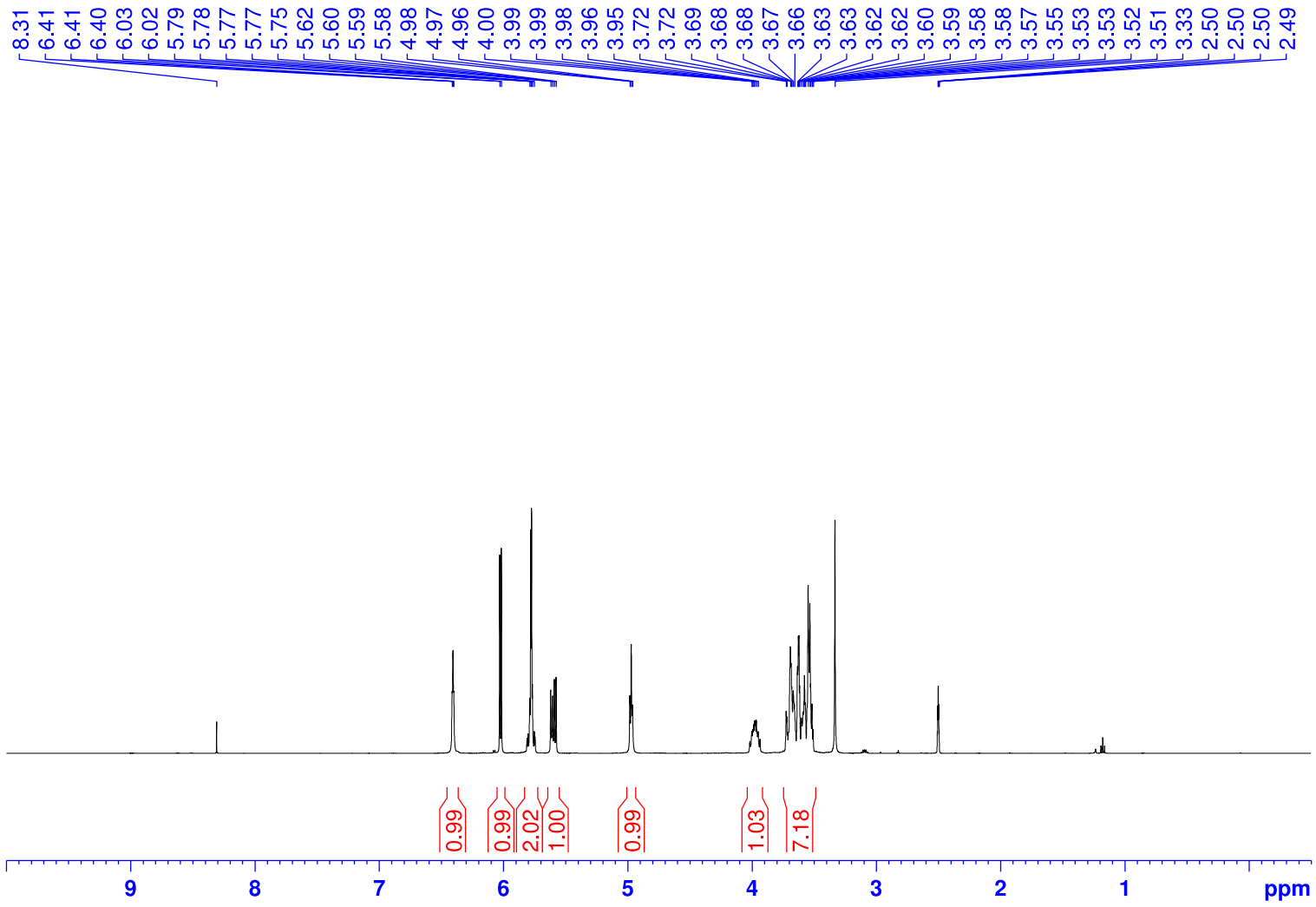
^{1}H NMR spectrum of compound 25 (500 MHz, D_2O)



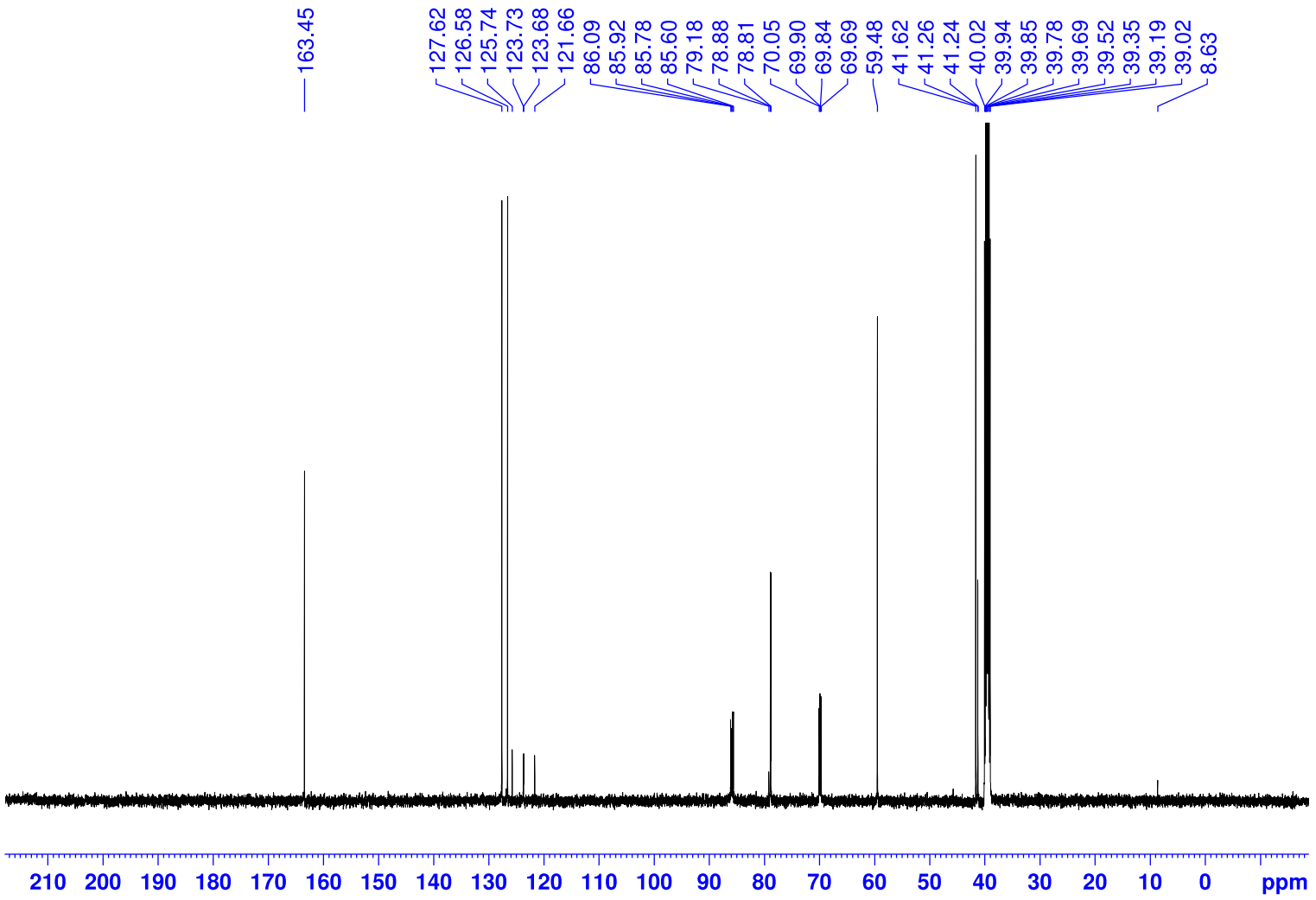
^{13}C NMR spectrum of compound 25 (126 MHz, D_2O)



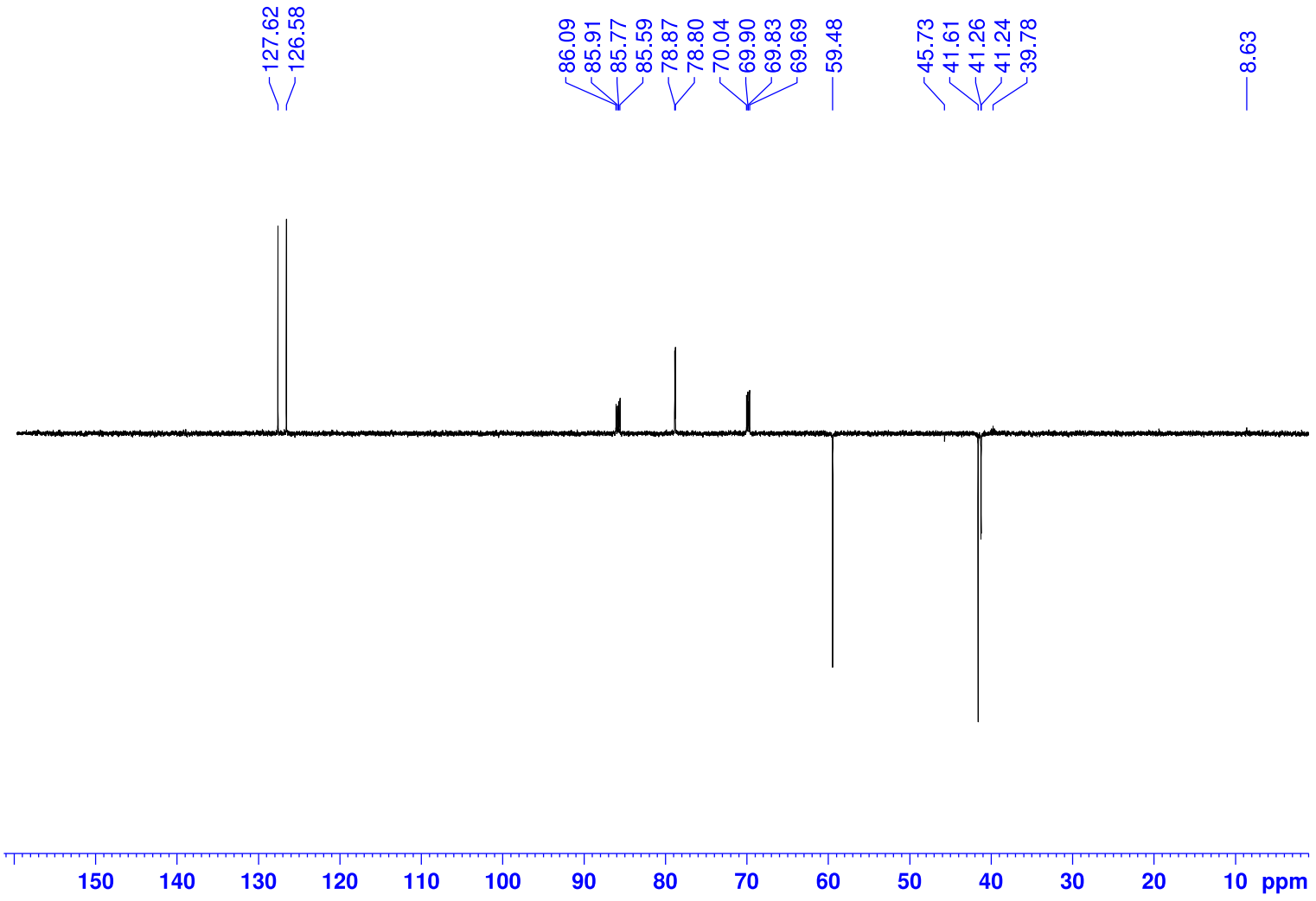
^{13}C DEPT-135 NMR spectrum of compound 25 (126 MHz, D_2O)



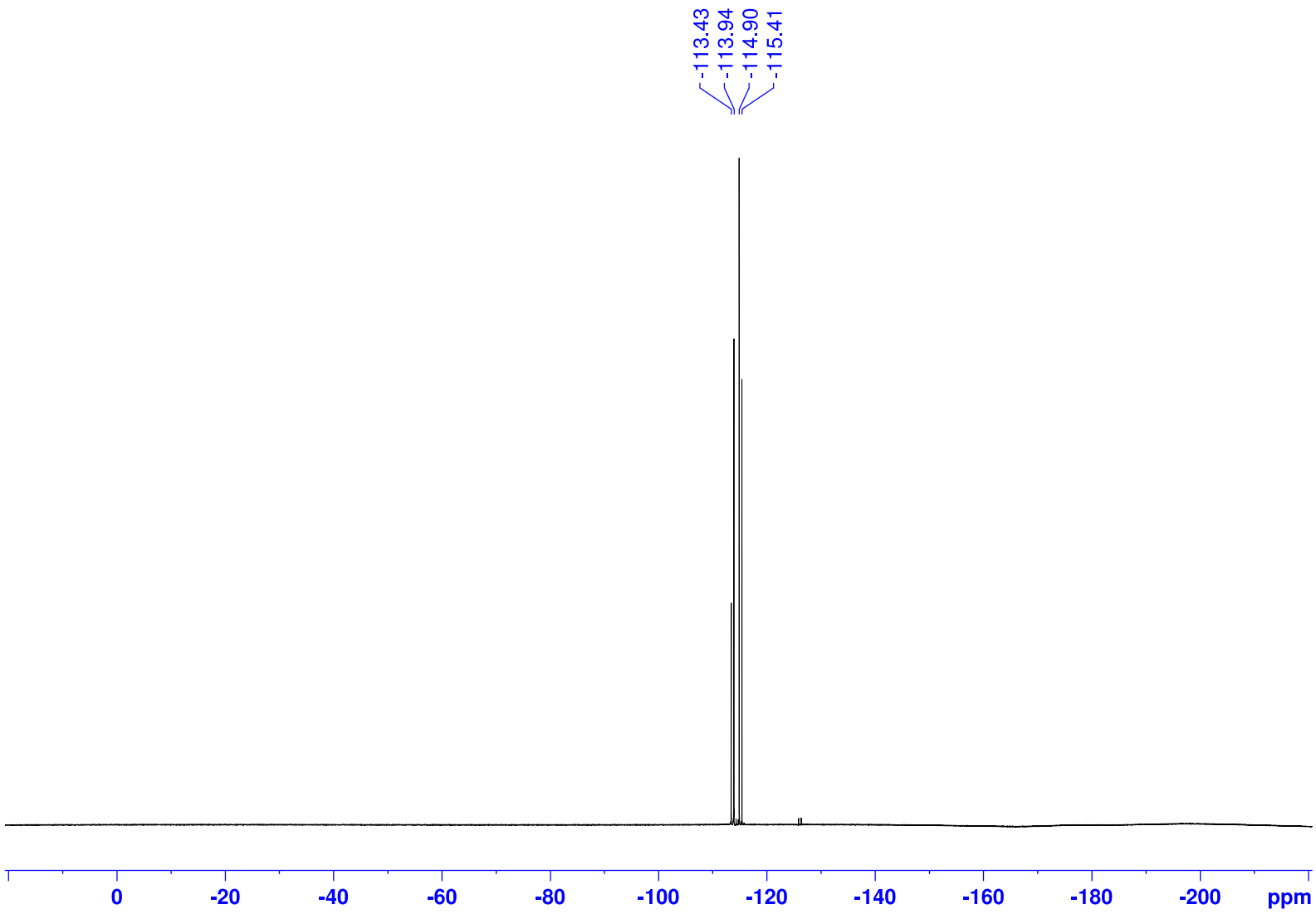
^{1}H NMR spectrum of compound 25 (500 MHz, DMSO-d_6)



^{13}C NMR spectrum of compound 25 (126 MHz, DMSO-d_6)



^{13}C DEPT-135 NMR spectrum of compound 25 (126 MHz, DMSO-d_6)



^{19}F NMR spectrum of compound 25 (470 MHz, DMSO-d_6)