Supporting Information

Nine-Step Stereoselective Synthesis of Islatravir From Deoxyribose

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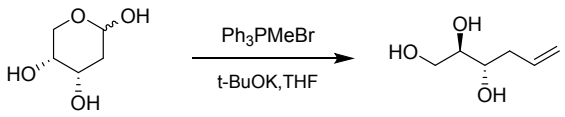
General Information

All reagents and reagent grade solvents were used as received from commercial suppliers unless otherwise noted. All reactions were carried out under N_2 atmosphere unless otherwise noted. Where reactions in round-bottom flasks were run above room temperature, aluminum heating blocks were used in conjunction with various models of IKA stirrer hotplates. Reactions at –78 ºC were run using isopropanol-dry ice cooling baths.Ozonolysis was performed using compressed air and an Ozonia OZAT CFS-1/3 2G Ozone Generator for reactions >10 g of substrate or a Triogen LAB2B laboratory ozone generator for ≤10 g of substrate. The ozone output and consumption was monitored with a BMT-964 Messtechnik GMBH ozone monitor. NMR spectra were primarily obtained on a 500 MHz Bruker AVANCE III spectrometer and chemical shifts are reported in ppm and referenced to residual solvent peaks while coupling constants are reported in hertz. High resolution mass spectra (HRMS) were obtained on an Accurate-Mass Time-of-Flight (TOF) mass spectrometer and reported as m/z (relative intensity). Optical rotation measurements were taken on a Perkin Elmer polarimeter equipped with PCB 1500 water Peltier system. Measurements were recorded at 25°C at 589 nm in a jacketed 5 cm cell at a concentration of 10 mg/mL (c=1.0) unless otherwise noted.

Experimental Procedures and Characterization Data

(2*R*,3*S*)-Hex-5-ene-1,2,3-triol SI-1



SI-1

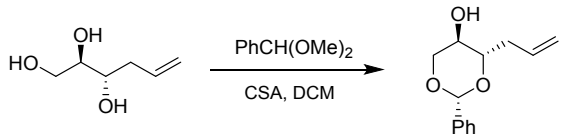
A 10 L three-necked round bottom flask equipped with mechanical stirrer was charged with Ph_3PMeBr (2.28 kg, 6.37 mol, 1.8 eq) and THF (3.3 L). The vessel was placed under nitrogen (3 x vacuum/fill cycles) and the cooled to 0 ºC. *t*-BuOK (715 g, 6.37mol, 1.8 eq) was added in portions at 0 ºC over 30 mins, causing the white suspension turned to turn bright yellow. The yellow suspension was stirred at 0 ºC for 60 mins and then 2-Deoxy-D-ribose (475 g, 3.54 mol, 1 eq) was added in portions over 30 mins at 0 ºC, and the reaction mixture was warmed to 15 ºC slowly, resulting in an exothermic reaction. The resulting yellow suspension at was stirred at 15 ºC for 16 hours, fading in color to gray over this time. The reaction mixture was again cooled to 0 ºC, NH_4Cl (475 g) was added in portions and the gray suspension was stirred at 15 ºC for 1 hour. The solids were removed by filtration, the cake was washed with THF (1.25 L) and the filtrate was concentrated under reduced pressure. The residue was redissolved in EtOAc (1.25 L) and stirred at 15 ºC for 30 minutes, causing a large amount of solid to precipitate. The solid was removed by filtration, washed with EtOAc (0.25 L) and discarded. The aqueous phase was extraced with water (1.25 L, 1 L, 5 x 600 mL) to give an aqueous solution of the desired product. The organic phase was discarded and the aqueous phase was washed with 1:1 EtOAc/petroleum ether (600 mL) and then concentrated under reduced pressure to give a brown oil. The brown oil was repeatedly concentrated from acetonitrile (3 x 300 mL) to remove traces of water, giving (2*R*,3*S*)-hex-5-ene-1,2,3-triol **SI-1** as a brown oil (558.8 g) that was used in the subsequent step without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.87 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H), 5.05 (ddt, J = 17.2, 2.8, 1.5 Hz, 1H), 4.97 (ddt, J = 10.2, 2.3, 1.1 Hz, 1H), 4.45 (d, J = 2.7 Hz, 1H), 4.43 (d, J = 3.3 Hz, 1H), 4.32 (t, J = 5.7 Hz, 1H), 3.53 (ddd, J = 10.8, 5.8, 4.0 Hz, 1H), 3.40–3.31 (m, 2H), 3.30–3.20 (m, 1H), 2.33 (m, 1H), 2.13–2.00 (m, 1H).

^{13}C NMR (126 MHz, DMSO) δ 136.6, 116.0, 74.4, 71.3, 63.3, 37.5.

Data match those previously reported.[1]

(2*R*,4*S*,5*R*)-4-Allyl-2-phenyl-1,3-dioxan-5-ol SI-2



SI-1 **SI-2**

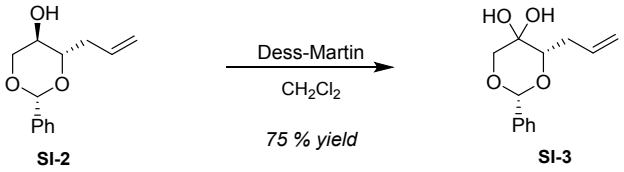
A 5 L three-necked round flask equipped with magnetic stirrer was charged with compound **SI-1** (400 g, 3.03 mol, 1.0 eq) and MTBE (2.8 L) at 15 ºC resulting in a brown suspension. Benzaldehyde dimethyl acetal (599 g, 3.93 mol, 593 mL, 1.3 eq) was added, followed by camphor-10-sulfonic acid (211 g, 908 mmol, 0.3 eq.) and the reaction mixture was stirred at 15 ºC for 16 hours, forming a brown solution. The solution was cooled to 0 ºC, quenched by addition of triethylamine (400 mL) and concentrated under reduced presure. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (20:1–5:1) to give (2*R*,4*S*,5*R*)-4-allyl-2-phenyl-1,3-dioxan-5-ol **SI-2** as a colorless, crystalline solid (330 g, 49% yield over 2 steps).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44–7.31 (m, 5H), 5.90 (td, J = 17.1, 6.9 Hz, 1H), 5.49 (s, 1H), 5.24 (d, J = 5.2 Hz, 1H), 5.12 (d, J = 17.1 Hz, 1H), 5.05 (d, J = 10.4 Hz, 1H), 4.09 (dd, J = 10.4, 5.2 Hz, 1H), 3.60–3.53 (m, 1H), 3.49 (t, J = 10.4 Hz, 1H), 3.37 (dt, J = 14.4, 7.5 Hz, 2H), 2.61 (dd, J = 14.4, 5.8 Hz, 1H), 2.25 (dt, J = 14.9, 7.5 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 138.3, 134.8, 128.5, 127.9, 126.1, 116.9, 99.9, 81.1, 70.9, 64.2, 35.5.

Data match those previously reported.[1]

(2*R*,4*S*)-4-Allyl-2-phenyl-1,3-dioxane-5,5-diol SI-3



Note: A literature synthesis of the keto-form of SI-3 has been reported,[1] but the compound was not isolated or characterized. The reported procedure was optimized to reduce the amount of oxidant used and remove the need for column chromatography through isolation of the low-melting ketone as its crystalline solid hydrate.

A 3 L three-necked round bottom flask was charged with compound **SI-2** (295 g, 1.34 mol, 1 eq.) and DCM (890 mL) and the reaction mixture was cooled to 0 ºC. Dess-Martin periodinane (625 g, 1.47mol, 1.1 eq) was added in portions at this temperature and after the addition had completed the resulting white suspension was stirred at 15ºC for 16 hours, turning into a yellow solution. The reaction was quenched by addition of 4.4 L of a 1:1 mixture of 10% aqueous $NaHCO_3$ and 10 % aqueous $Na_2S_2O_3$. The aqueous phase was extracted with ethyl acetate (1 x 700 mL, 1 x 500 mL) and the combined organic phases were washed with saturated aqueous NaCl solution (500 mL), dried (Na_2SO_4) and concentrated. The residue was suspended in MTBE (1 L), stirred at 15ºC for 30 min, filtered to remove insoluble solids and concentrated to give crude product (350 g) as yellow oil.

The crude product was redissolved in acetonitrile (350 mL) at 15 ºC and H_2O (280 mL) was added dropwise into the solution, causing a white solid to form. Petroleum ether (70 mL) was added to the suspension, the mixture was stirred for 30 minutes at 15 ºC and the solids were collected by filtration. The filter cake was washed with H_2O (100 mL) and petroleum ether (50 mL) to give pure (2*R*,4*S*)-4-allyl-2-phenyl-1,3-dioxane-5,5-diol **SI-3** (237.5 g, 75% yield, 98.1% purity by GC) as a white crystalline solid.

This aqueous recrystallization gives the product as a stable hydrate:

$[\alpha]_D^{20}$ = –44.83 (c 1.00, MeCN);

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49–7.20 (m, 5H), 5.93–5.83 (m, 1H), 5.83 (s, 1H), 5.75 (s, 1H), 5.52 (s, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 3.83 (d, *J* = 11.1 Hz, 1H), 3.71–3.60 (m, 2H), 2.52 (m, 1H), 2.26 (dt, *J* = 15.9, 9.0 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 138.5, 136.2, 128.6, 128.0, 126.3, 116.4, 100.3, 87.3, 82.4, 74.7, 31.3.

HRMS (ESI) m/z: $[M + H]^+$ Calc'd for $C_{13}H_{15}O_3^+$ 219.1016; Found 219.1013

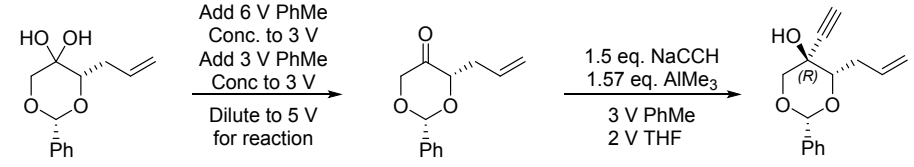
The hydrate could be converted to the ketone form by azeotropic drying with toluene or acetonitrile and is typically obtained as a yellow oil. NMR data for the ketone form are given below:

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, J = 7.5, 2.3 Hz, 2H), 7.45–7.39 (m, 3H), 6.12 (s, 1H), 5.84 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.16 (dd, J = 17.2, 1.8 Hz, 1H), 5.09 (ddd, J = 10.3, 2.2, 1.1 Hz, 1H), 4.75 (ddd, J = 6.8, 4.3, 1.1 Hz, 1H), 4.63 (dd, J = 17.3, 1.2 Hz, 1H), 4.41 (d, J = 17.3 Hz, 1H), 2.68–2.58 (m, 1H), 2.49–2.40 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 205.2, 137.5, 133.5, 129.0, 128.2, 126.1, 117.8, 98.4, 81.9, 72.7, 33.7.

Note: a small amount of ketone is often visible in the NMR spectra of the hydrate and vice versa, depending on the amount of water present in the NMR solvents and the delay between dissolving the sample and collecting the data.

(2*R*,4*S*,5*R*)-4-Allyl-5-ethynyl-2-phenyl-1,3-dioxan-5-ol 4a (100 g scale)



SI-3
6.67 wt% H_2O
(= 0.9 eq. H_2O)

5
0.015 wt% H_2O
(= 0.02 eq. H_2O)

4a
66% yield
14:1 d.r.

*Dehydration of **SI-3**:* (2*R*,4*S*)-4-allyl-2-phenyl-1,3-dioxane-5,5-diol **SI-3** (100 g, 423 mmol) was suspended in toluene (600 mL). The resulting mixture was concentrated to ~300 mL under reduced pressure. Toluene (300 mL) was added and the resulting suspension was again concentrated to ~300 mL to give a dry solution of (2*R*,4*S*)-4-allyl-2-phenyl-1,3-dioxan-5-one **5** (Karl Fischer titration gives 0.015 wt% H_2O).

Preparation of sodium trimethylethynylaluminate (STEA) solution: trimethylaluminum (2 M in PhMe; 317 mL, 635 mmol) was slowly added to a 0 °C suspension of ethynylsodium (18 wt% in xylenes; 169 g, 635 mmol) in toluene (300 ml) and THF (200 ml) over 1 hour, keeping the internal temperature below 6 °C. After addition had completed, the resulting solution was stirred at 0 °C for 15 minutes. Note: All reactions utilizing $AlMe_3$ in this paper relied on the more stable solution in toluene as opposed to the hazzardous and pyrophoric neat $AlMe_3$. Despite this precaution, the addition of $AlMe_3$ is highly exothermic and should be performed with care.

The dry solution of (2*R*,4*S*)-4-allyl-2-phenyl-1,3-dioxan-5-one **5** was cooled to 0 °C and the cold STEA solution was then added dropwise over 1.5 hours. The resulting orange-brown reaction mixture was stirred at 0 °C for 1 hour then warmed to room temperature and stirred overnight. After 16 hours, the reaction mixture was re-cooled to 0 °C and 5 M hydrochloric acid (500 mL) was slowly added over 3 hours, keeping the internal temperature below 5 °C. *Note: initial reaction is vigorously exothermic and generates a large volume of gas.* After addition had completed, the biphasic mixture was stirred vigorously for 15 minutes and then stood until the layers separated (ca. 5 minutes). The layers were separated and the aqueous phase was back extracted with toluene (2 x 200 mL). At this point no remaining product can be detected in the aqueous phase. The combined organic phases washed with water (300 mL), saturated aqueous sodium hydrogen carbonate solution (300 mL) and brine (300 mL), dried ($MgSO_4$) and concentrated to give the crude (2*R*,4*S*,5*R*)-4-allyl-5-ethynyl-2-phenyl-1,3-dioxan-5-ol **4a** (90.56 g, 278 mmol, 65.7 % yield based on 75 wt% purity determined by ^1H NMR) as a turbid orange oil

that was not purified further. Diastereomeric ratio by HPLC and ^{1}H NMR shown to be 14:1 in favor of the desired compound **4a**. For comparison, data for undesired diastereomer **4b** are given below on page SI-17

For characterization purposes, a small sample was purified by flash column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4):

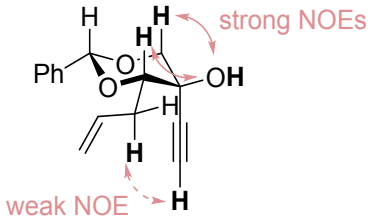
$[\alpha]_D^{20}$ = –52.52 (c 1.31, MeOH);

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43–7.33 (m, 5H), 6.07 (s, 1H), 5.88 (ddt, J = 17.3, 10.4, 6.6 Hz, 1H), 5.56 (s, 1H), 5.12 (d, J = 17.2 Hz, 1H), 5.04 (d, J = 11.0 Hz, 1H), 4.06 (d, J = 10.4 Hz, 1H), 3.67–3.59 (m, 2H), 3.35 (s, 1H), 2.62 (dd, J = 14.8, 6.6 Hz, 1H), 2.33 (dt, J = 15.8, 8.3 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 138.0, 135.1, 128.7, 128.0, 126.2, 116.8, 100.4, 84.4, 82.3, 75.5, 74.8, 64.0, 33.7.

HRMS (ESI) m/z: $[M + H]^+$ Calc'd for $C_{15}H_{17}O_3^+$ 245.1172; Found 245.1173

The stereochemistry of the product was assigned based on the following NOE observations (and confirmed later in the synthesis through interception of known intermediates):

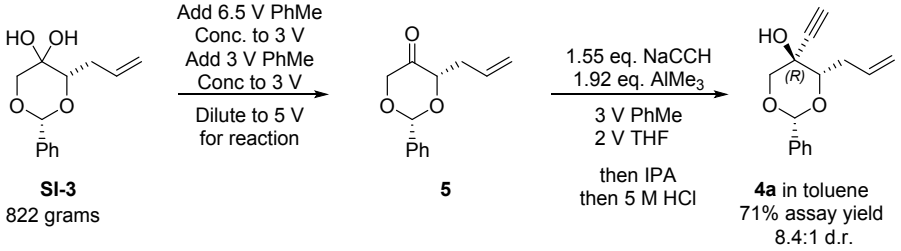


Note: use of DMSO-d6 as NMR solvent is important to observe NOEs to the hydroxyl proton. The NOESY spectrum (pulse program noesygpphpp) was acquired on a Bruker 600 MHz Avance III HD spectrometer equipped with a He-cooled 1.7 mm triple resonance microcryoprobe at 2k x 256 points with 16 scans and a 300 ms mixing time. Spectra were processed in MestReNova, ver. 12.0.3 with sine squared 90° apodizations and 3rd order polynomial baseline corrections in both dimensions.

For comparison, data for undesired isomer **4b** are given below (see page SI-17).

A larger scale version of this procedure is provided on the following page.

(2*R*,4*S*,5*R*)-4-Allyl-5-ethynyl-2-phenyl-1,3-dioxan-5-ol 4a (822 g scale)



*Conversion of the ketone hydrate **SI-3** to the ketone **5**:* A 30 liter jacketed cylindrical vessel equipped with thermocouple, distillation head and mechanical stirrer was charged with toluene (5.4 L, 6.5 V) and (2*R*,4*S*)-4-allyl-2-phenyl-1,3-dioxane-5,5-diol (822 g, 3.1 mol) **SI-3**. The jacket temperature was set to 55 ºC and the stirred suspension was allowed to warm to this temperature. Vacuum was then applied to begin distillation of the toluene; the vacuum was adjusted to keep the internal temperature at 50 ºC during the distillation. After the volume had been reduced by half to ca. 2.5 L, additional toluene (2.5 L, 3 V) was charged and the volume was again reduced by distillation to an approximate final value of 2.5 L. At this point, all solids have dissolved and the solution is diluted with additional toluene (1.6 L, 2 V) to give a pale yellow toluene solution of the starting ketone (4.1 L, 5 V). Conversion of the hydrate to the ketone was confirmed by ^{1}H NMR analysis of an aliquot of this solution diluted with DMSO-d6 (data for both hydrate and ketone are provided on page SI-7 for comparison); if conversion is not complete then addition concentration from toluene can be performed by repeating the previous operations. Karl-Fisher analysis showed 270 ppm of water in solution at this point. The solution was placed under nitrogen and the jacket was set to –5 ºC to cool the solution in preparation for aluminate addition.

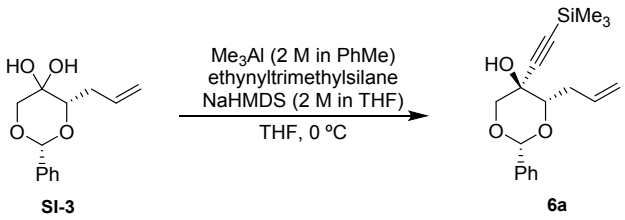
Preparation of sodium trimethylethynylaluminate (STEA) solution: A separate 20 L reactor equipped with nitrogen bubbler, mechanical stirrer and thermocouple was charged with toluene (2.5 L, 3V) and tetrahydrofuran (1.6 L, 2 V). The vessel was inerted with nitrogen and the jacket was set to –5 ºC. Ethynylsodium suspension (18 wt% in xylene, 1352 g, 4.81 mol, 1.55 eq.) was carefully charged and the resulting suspension was allowed to cool to 0 ºC. Trimethylaluminum solution (2 M in toluene, 2409 g, 5.95 mol, 1.92 eq.) was carefully charged at a rate that kept the internal temperature of the suspension below 5 ºC. *Note: this addition is significantly exothermic and must be performed slowly and with care!* After addition had completely, all of the solid ethynylsodium had dissolved and the resulting sodium trimethylethynylaluminate (STEA) solution was stirred for 30 minutes.

Alkynylation: The STEA solution was transferred slowly to the 30 L vessel containing the toluene solution of the ketone at a rate that kept the temperature in the receiving vessel below 5 ºC. *Note: this reaction is exothermic and addition takes several hours*. After addition had completed, the reaction was assayed by ^{1}H NMR on an aliquot diluted with DMSO-d6. Typically, the reaction was complete by the time the addition had finished.

The reaction mixture was quenched by slow addition of charging isopropyl alcohol (826 g) while keeping the temperature below 5 °C. *Note: Initial addition is extremely exothermic and a large volume of methane is also evolved.* In a separate 20 L reactor, 5 M hydrochloric acid solution was prepared by charging concentrated hydrochloric acid (2022 g, 20.52 mol, 6.2 eq.) to water (2422 g) and the solution was chilled to 0 °C. This 5 M hydrochloric acid solution was then transferred to the main reaction vessel, again keeping the temperature below 5 ºC. After addition had completed, the resulting biphasic solution was vigorously agitated for 15 minutes then stirring was ceased and the layers were allowed to separate. The aqueous was separated and extracted with toluene (2 x 1.5 L). These extracts were recombined with the organic phase from the first phase cut and the combined organics were washed with water (2.5 L), sodium bicarbonate solution (8.75 wt%, 2.5 L) and sodium bicarbonate solution (25 wt%, 3.0 L). The vessel was equipped with a distillation head and the jacket temperature was increased to 55 ºC. The toluene solution was concentrated to 1.2 L in volume and was then removed for analysis. Quantitative ^{1}H NMR versus 1,3,5-trimethoxybenzene was used to measure the wt% of the product in solution. The *title compound* was obtained as a solution in toluene (36.7 wt%, 1239 g of solution containing 453 g of product, 72.1 % assay yield).

On this larger scale, the diastereomeric ratio as determined by ^{1}H NMR was 8.4:1 in favor of the desired compound **4a**. For comparison, data for undesired diastereomer **4b** are on page SI-17

(2*R*,4*S*,5*R*)-4-allyl-2-phenyl-5-((trimethylsilyl)ethynyl)-1,3-dioxan-5-ol 6a



Note: **SI-3** (0.5 g, 2.12 mmol) was dried by concentration from toluene (2 x 10 mL) immediately before use.

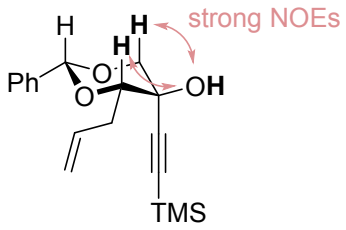
Ethynyltrimethylsilane (0.601 mL, 4.34 mmol, 2.05 eq.) was slowly added to commercial NaHMDS solution (2 M in THF, 2.12 mL, 4.23 mmol, 2.0 eq.) at room temperature, causing no visible reaction or exotherm, and the pale yellow solution was stirred at room temperature for three hours. After this time a fine, pale yellow suspension of insoluble sodiated ethynyltrimethylsilane had formed and this was cooled to 0 ºC. Trimethylaluminum (2 M in PhMe, 2.22 mL, 4.44 mmol, 2.1 eq.) was slowly added causing the solids to dissolve and a clear brown solution to form (care: exothermic!). The aluminate solution was stirred at 0 °C for 15 minutes and (2*R*,4*S*)-4-allyl-2-phenyl-1,3-dioxane-5,5-diol (0.5 g, 2.12 mmol, 1.0 eq.) in PhMe (2.5 mL) was added over 5 minutes. After addition had completed, the resulting brown solution was warmed to room temperature and stirred for 16 hours. The reaction mixture was carefully quenched with saturated aqueous ammonium chloride solution (10 mL) and transferred to a separating funnel containing MTBE (10 mL) and water (10 mL). The layers were separated and the aqueous phase was extracted with MTBE (2 x 10 mL). The combined ethereal layers were washed with brine, dried (MgSO4) and concentrated to give the crude product as an orange oil. Purified by flash column chromatography on silica gel (4:1 hexanes:EtOAc) to give (2*R*,4*S*,5*R*)-4-allyl-2-phenyl-5-((trimethylsilyl)ethynyl)-1,3-dioxan-5-ol **6a** as a colorless oil (1.14 g, 85% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.45–7.41 (m, 2H), 7.38–7.35 (m, 3H), 6.04 (s, 1H), 5.87 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H), 5.54 (s, 1H), 5.10 (dd, J = 17.3, 1.9 Hz, 1H), 5.02 (ddd, J = 10.2, 2.3, 1.2 Hz, 1H), 4.03 (d, J = 10.5 Hz, 1H), 3.61 (d, J = 10.5 Hz, 1H), 3.60 (dd, J = 9.9, 2.4 Hz, 1H), 2.60 (m, 1H), 2.37–2.25 (m, 1H), 0.18 (s, 9H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 138.1, 135.2, 128.8, 128.0, 126.4, 116.7, 107.1, 100.6, 88.7, 82.4, 74.6, 64.4, 33.7, 0.0.

HRMS (ESI) m/z: $[M + H]^+$ Calc'd for $C_{18}H_{25}O_3Si^+$ 317.1567; Found 317.1570.

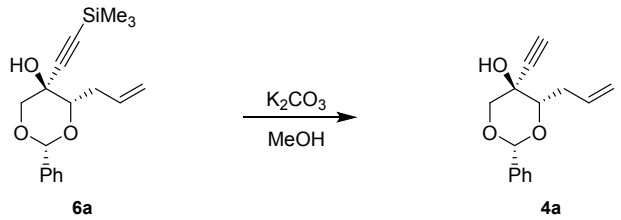
The stereochemistry of the product was assigned on the basis of the following NOE observations and supported by interception of **4a** by desilylation with K_2CO_3/MeOH (see below):



Note: use of DMSO-d6 as NMR solvent is important in order to observe NOEs to the hydroxyl proton. The structure was confirmed by HSQC, HMBC, and ROESY spectra (pulse programs gHSQCAD, gHMBCAD, and ROESYAD, repsectively) that were acquired on a Varian 600 MHz DDR spectrometer equipped with a room temperature inverse probe. Acquisition details were as follows: multiplicy-edited HSQC data, 2k x 200 points with 8 scans and a 145 Hz J-optimization; HMBC data with one-bond suppression, 2k x 256 points, with 32 scans and a 8 Hz J-optimization; ROESY data, 2k x 256 points with 16 scans and a 250 ms mixing time. All spectra were processed in MestReNova, ver. 12.0.3 with sine squared 90° apodizations and 3rd order polynomial baseline corrections in both dimensions.

Diastereomeric ratio as determined by ^{1}H NMR on the crude material is ca. 14:1 in favor of **6a**.

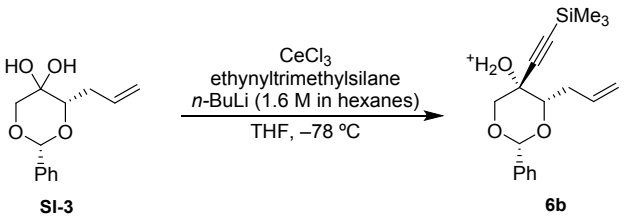
(2*R*,4*S*,5*R*)-4-allyl-5-ethynyl-2-phenyl-1,3-dioxan-5-ol 4a



Solid potassium carbonate (218 mg, 1.58 mmol, 5 eq.) was added to (2*R*,4*S*,5*R*)-4-allyl-2-phenyl-5-((trimethylsilyl)ethynyl)-1,3-dioxan-5-ol (100 mg, 0.32 mmol, 1 eq.) **6a** in a mixture of methanol (2.0 mL) and THF (2.0 mL) and the resulting brown suspension was stirred at room temperature. After 4 hours, the mixture was poured into a separating funnel containing 1 M hydrochloric acid (10 mL) and MTBE (10 mL). The layers separated and the aqueous phase was extracted with one portion of MTBE (10 mL). The combined ethereal extracts were concentrated to give crude (2*R*,4*S*,5*R*)-4-allyl-5-ethynyl-2-phenyl-1,3-dioxan-5-ol **4a** (74 mg, 0.30 mmol, 96 % yield) as a light brown oil that did not require further purification.

Data matched those given for **4a** above, confirming the stereochemistry of **6a**.

(2*R*,4*S*,5*S*)-4-allyl-2-phenyl-5-((trimethylsilyl)ethynyl)-1,3-dioxan-5-ol 6b



*Note: **SI-3** (0.5 g, 2.12 mmol) was dried by concentration from PhMe (2 x 10 mL) immediately before use.*

n-Butyllithium (2.5 M in hexanes, 1.61 mL, 4.02 mmol) was added dropwise to ethynyltrimethylsilane (0.59 mL, 4.23 mmol) in THF (2.5 ml) in a 5 mL scintillation vial at 0 °C and the solution was stirred at this temperature for 15 minutes. Meanwhile, a separate 20 mL scintillation vial was charged with anhydrous cerium(iii) chloride (1.04 g, 4.23 mmol) and THF (2.5 mL) to give an off-white suspension that was cooled to –78 °C in a dry ice-acetone bath. The lithium trimethylsilylacetylide solution was transferred to the vial containing the cerium chloride suspension via syringe, resulting in a taupe-colored suspension that was stirred at –78 °C for 1 hour. After this time, (2*R*,4*S*)-4-allyl-2-phenyl-1,3-dioxane-5,5-diol **SI-3** (0.5 g, 2.116 mmol) in THF (2.5 mL) was added slowly by syringe and stirring was continued at –78 °C. The reaction mixture was stirred at –78 °C for 3 hours, and then carefully quenched at this temperature with saturated aqueous ammonium chloride solution (10 mL). The biphasic mixture was transferred to a separating funnel containing water (30 mL) and MTBE (10 mL). The layers separated and the aqueous phase was extracted with MTBE (3 x 10 mL). The organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude product as a brown oil that was purified by flash column chromatography on silica gel (4 :1 hexanes : EtOAc). Obtained (2*R*,4*S*,5*S*)-4-allyl-2-phenyl-5-((trimethylsilyl)ethynyl)-1,3-dioxan-5-ol **6b** as a colorless oil (2.50 g, 93% yield).

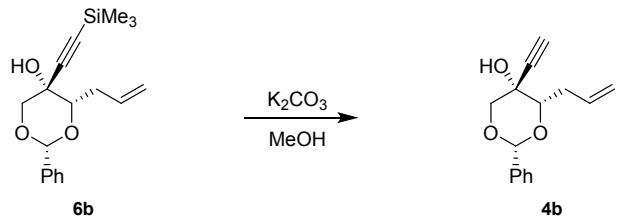
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46–7.42 (m, 2H), 7.41–7.32 (m, 3H), 5.91 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.66 (s, 1H), 5.63 (s, 1H), 5.11 (dd, J = 17.2, 1.9 Hz, 1H), 5.07–5.00 (m, 1H), 4.02 (d, J = 11.6 Hz, 1H), 3.97 (d, J = 11.5 Hz, 1H), 3.90 (dd, J = 9.5, 3.1 Hz, 1H), 2.50–2.46 (m, 1H), 2.44–2.35 (m, 1H), 0.17 (s, 9H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 138.2, 135.5, 128.7, 127.9, 126.2, 116.6, 105.2, 100.3, 90.5, 81.8, 74.6, 64.6, 33.8, –0.2.

LCMS (ESI) m/z: $[M + H]^+$ Calc'd for $C_{18}H_{25}O_3Si^+$ 317.2; Found 317.2.

Note: Connectivity and stereochemistry of ***6b*** *were determined by HSQC, HMBC, and ROESY spectra (pulse programs gHSQCAD, gHMBCAD, and ROESYAD, repsectively) were acquired on a Varian 600 MHz DDR spectrometer equipped with a He-cooled triple resonance (HCN) cryoprobe. Acquisition details were as follows: multiplicy-edited HSQC data, 2k x 256 points with 8 scans and a 145 Hz J-optimization; HMBC data with one-bond suppression, 2k x 256 points, with 16 scans and a 8 Hz J-optimization; ROESY data, 2k x 256 points with 16 scans and a 250 ms mixing time. All spectra were processed in MestReNova, ver. 12.0.3 with sine squared 90° apodizations and 3rd order polynomial baseline corrections in both dimensions.*

(2*R*,4*S*,5*S*)-4-allyl-5-ethynyl-2-phenyl-1,3-dioxan-5-ol 4b



Potassium carbonate (2.18 g, 15.80 mmol) was added to (2*R*,4*S*,5*S*)-4-allyl-2-phenyl-5-((trimethylsilyl)ethynyl)-1,3-dioxan-5-ol **6b** (1.00 g, 3.16 mmol) in methanol (20.00 mL) and THF (20.00 mL) and the resulting colorless suspension was stirred at room temperature. After 4 hours, the reaction mixture was poured into a separating funnel containing 1 M HCl (40 mL) and MTBE (20 mL). Layers separated and the aqueous phase was extracted with MTBE (2 x 20 mL). The combined ethereal extracts were concentrated and the residue was purified by flash column chromatography on silica gel (4:1 hexanes:EtOAc) to give crude (2*R*,4*S*,5*S*)-4-allyl-5-ethynyl-2-phenyl-1,3-dioxan-5-ol **4b** as a colorless oil (539 mg, 70% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46–7.42 (m, 2H), 7.40–7.33 (m, 3H), 5.90 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.66 (d, J = 0.9 Hz, 1H), 5.63 (s, 1H), 5.12 (dd, J = 17.2, 1.9 Hz, 1H), 5.06–5.01 (m, 1H), 4.04 (dd, J = 11.5, 1.0 Hz, 1H), 3.99 (d, J = 11.6 Hz, 1H), 3.90 (dd, J = 9.6, 3.0 Hz, 1H), 3.57 (s, 1H), 2.49–2.35 (m, 2H).

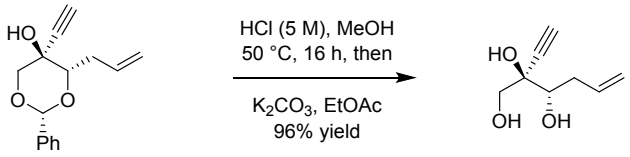
^{13}C NMR (126 MHz, DMSO-d_6) δ 138.2, 135.3, 128.6, 127.9, 126.2, 116.77, 100.3, 82.9, 81.6, 77.1, 74.8, 64.0, 33.5.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.43–7.32 (m, 3H), 5.97 (dddd, *J* = 17.1, 10.2, 8.0, 5.9 Hz, 1H), 5.50 (s, 1H), 5.19 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.11 (dq, *J* = 10.1, 1.0 Hz, 1H), 3.89 (d, *J* = 10.7 Hz, 1H), 3.68 (dd, *J* = 8.9, 4.2 Hz, 1H), 3.65 (dd, *J* = 10.7, 1.1 Hz, 1H), 3.49 (s, 1H), 2.50 (dddt, *J* = 14.5, 8.0, 4.2, 1.2 Hz, 1H), 2.34 (dddt, *J* = 14.6, 8.9, 5.8, 1.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 135.3, 129.0, 128.4, 126.3, 117.2, 101.8, 83.8, 77.5, 77.2, 67.1, 33.7, 20.0.

HRMS (ESI) m/z: $[M - H]^-$ Calc'd for $C_{15}H_{15}O_3^-$ 243.1027; Found 243.1009.

(2*R*,3*S*)-2-Ethynylhex-5-ene-1,2,3-triol 7



4a **7**

Benzylidene acetal **4a** (88.0 g, 295 mmol) was concentrated from 200 mL of MeOH to remove any residual toluene from the previous step. MeOH was added (880 mL, 10 vol) followed by HCl (295 mL of 5 M, 1.47 mol) at a rate to maintaining the exotherm between 35–40 °C. The mixture was heated to 50 °C and the disappearance of the acetal was monitored by HPLC. After 16 h, the reaction was washed with heptane (100 mL x 2) then 10% MTBE in heptane (100 mL x 2). The aqueous layer was then neutralized with K_2CO_3 (180 g, 4.5 equiv) added slow enough to minimize effervescence. Upon neutralization, the MeOH and aqueous layers seperated, and the desired product was further extracted with MeOH (100 mL x 2). The MeOH layer was concentrated to dryness and the salty oil left over was slurried in EtOAc then filtered through a 1 cm plug of solka flock and concentrated again giving an orange oil (44.0 g, 98 wt%, 96% yield).

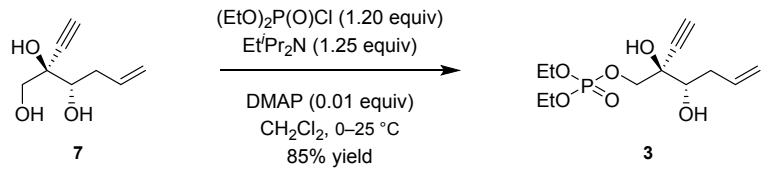
$[\alpha]_D^{20}$ = –42.7 (c 0.96, MeOH);

^{1}H NMR (500 MHz, DMSO-d_6) δ 5.89 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.11 (s, 1H), 5.04 (dd, *J* = 17.2, 1.5 Hz, 1H), 4.98 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.67 (d, *J* = 6.2 Hz, 1H), 4.63 (t, *J* = 6.3 Hz, 1H), 3.57 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.46 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.45–3.42 (m, 1H), 3.15 (s, 1H), 2.46 (dd, *J* = 7.1, 1.8 Hz, 1H), 2.20 – 2.10 (m, 1H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 137.2, 115.9, 85.1, 75.4, 73.4, 72.3, 66.2, 36.0.

HRMS (ESI) m/z: $[M + H]^+$ Calc'd for $C_8H_{12}O_3^+$ 157.0859; Found 157.0865.

Diethyl ((2*R*,3*S*)-2-ethynyl-2,3-dihydroxyhex-5-en-1-yl) phosphate 3



Triol **7** (820 mg, 5.25 mmol) was added to a 50 mL round bottom flask and diluted with CH_2Cl_2 (25 mL). The mixture was cooled to 0 °C, and Hünig's base (1.14 mL, 848 mg, 6.56 mmol, 1.25 equiv) was added followed by DMAP (6.4 mg, 0.053 mmol). Finally, diethylchlorophosphate (910 μL, 1087 mg, 6.30 mmol, 1.20 equiv) was added dropwise over 10 min, and the reaction was allowed to warm to RT over 1 h. After stiring an for additional 18 h, the reaction was diluted with HCl solution (0.1 M in brine; 10 mL) and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product (2.12 g, 63.4 wt%, 4.62 mmol, 88%) was purified by column chromatography (30–70% EtOAc in hexanes) providing **3** as a yellow oil (1.31 g, 4.46 mmol, 85% yield).

$[\alpha]_D^{20}$ = –43.9 (c 0.85, MeOH);

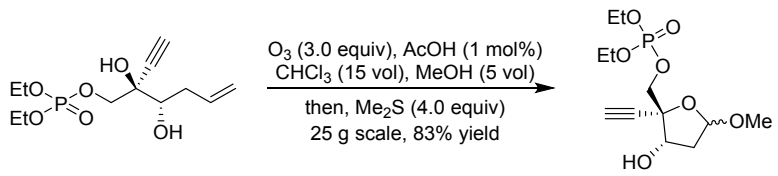
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H), 5.19 (dd, *J* = 17.2, 1.9 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.7 Hz, 1H), 4.33 (dd, *J* = 11.0, 9.1 Hz, 1H), 4.26 (dd, *J* = 15.1, 7.8 Hz, 2H), 4.22–4.08 (m, 4H), 3.71 (dd, *J* = 10.1, 2.7 Hz, 1H), 2.69 (ddq, *J* = 14.3, 6.6, 1.4 Hz, 1H), 2.53 (s, 1H), 2.36–2.26 (m, 1H), 1.41–1.31 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 118.1, 81.3, 75.5, 73.5 (d, *J* = 4.8 Hz), 72.8, 70.8 (d, *J* = 5.6 Hz), 64.7 (d, *J* = 4.5 Hz), 64.7 (d, *J* = 4.5 Hz), 36.2, 16.2 (d, *J* = 6.6 Hz)

^{31}P NMR (202 MHz, $CDCl_3$) δ 0.71.

HRMS (ESI) m/z: $[M + H]^+$ Calc'd for $C_{12}H_{22}O_6P^+$ 293.1149; Found 293.1158

Diethyl (((2*R*,3*S*)-2-ethynyl-3-hydroxy-5-methoxytetrahydrofuran-2-yl)methyl) phosphate 8



3 **8**

Phosphate ester **3** (25.0 g, 74.4 mmol) was added to a cylindrical vessel followed by MeOH (125 mL), $CHCl_3$ (375 mL), and acetic acid (42.9 μL, 0.744 mmol, 0.01 equiv). The reaction was cooled to –20 °C and O_3 was bubbled through the solution for 67 min at a rate of 9.60 g/h (10.7 g, 223.2 mmol, 3.00 equiv). *Note: O_3 was generated from air at a flow rate of 8.0 L/min and concentration was determined using a BMT 964 analyzer.* During this time the reaction was monitored by ^{1}H NMR spectroscopy on reaction aliquots, which showed complete conversion around 50 min. The ozone generator was turned off and the reaction was purged with N_2 at 8.0 L/min for 2 h before adding neat dimethyl sulfide (21.8 mL, 298 mmol, 4.00 equiv) at –20 °C. The reaction was then allowed to warm to 25 °C and stir overnight. At this time, a ^{1}H NMR spectrum of the crude material indicated 98% conversion to a mixture of lactol and methyl glycoside that converted to only the methyl glycoside **8** upon concentration (25.9 g at 78 wt%, 65.5 mmol, 88% yield). The product could be used without purification or could be purified by column chromatography (5–20% MeOH in DCM) to separate the 2:1 mixture of anomers of anomers (19.1 g, 61.8 mmol, 83% yield).

$[\alpha]_D^{20}$ = –8.6 (c 0.51, MeOH);

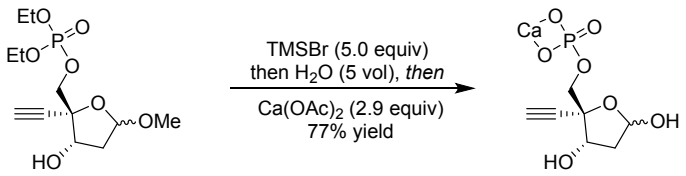
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11–5.06 (m, 1H, major + minor), 4.49 (dd, *J* = 8.0, 6.8 Hz, 1H, major), 4.26 (dd, *J* = 6.5, 2.5 Hz, 1H, minor), 4.19–4.07 (m, 7H), 3.42 (s, 3H, minor), 3.34 (s, 3H, major), 2.70 (s, 1H, major + minor), 2.33–2.19 (m, 3H, major + minor), 2.15–2.09 (m, 1H, major + minor), 1.39–1.31 (m, 6H, major + minor)

^{13}C NMR (126 MHz, $CDCl_3$) δ 105.8, 104.1, 83.6 (d, *J* = 8.5 Hz), 82.4 (d, *J* = 8.0 Hz), 79.6, 79.4, 77.8, 77.8, 73.7, 73.0, 69.6 (d, *J* = 5.6 Hz), 69.6 (d, *J* = 5.6 Hz), 64.4 (d, *J* = 6.0 Hz), 64.3 (d, *J* = 5.9 Hz), 55.5, 55.4, 41.2, 40.1, 16.2 (d, *J* = 6.6 Hz).

^{31}P NMR (203 MHz, $CDCl_3$) δ –1.43, –1.48.

HRMS (ESI) m/z: $[M + H]^+$ Calc'd for $C_{12}H_{22}O7P^+$ 309.1098; Found 309.1114

Calcium ((2*R*,3*S*)-2-ethynyl-3,5-dihydroxytetrahydrofuran-2-yl)methyl phosphate 9



8 **9**

Lactol phosphate ester **8** (1.00 g, 3.24 mmol) was disolved in CH_2Cl_2 (20 mL). Bromotrimethylsilane (2.14 mL, 16.22 mmol, 5.0 equiv) was added dropwise at 25 °C and the mixture was stirred for 4 h while monitoring conversion by TLC. Upon complete conversion, water (5 mL) was added and the biphasic mixture was vigorously stirred for 15 min before separating the layers. The aqueous phase was analyzed by ^{1}H NMR spectroscopy using DMF as internal standard, showing an 88% assay yield of the phosphoric acid. Solid calcium acetate (1.486 g, 9.39 mmol, 2.9 equiv) was added until the pH was > 3.2. The reaction mixture was stirred for 20 min before adding acetone (30 mL), which caused a white precipitate to form. The solids were collected by filtration to give the desired calcium salt **9** as an off-white powder (1.67 g, 44 wt%, 2.65 mmol, 82% yield). The major impurity in the crude product was found to be excess calcium acetate that could be largely removed by washing the solid with ^{i}PrOH (2 x 10 mL) to give **9** (846 mg, 81 wt%, 2.48 mmol, 77% yield), which was used without further purification.

Compound exists as a ~1:1 mixture of anomers in aqueous solution:

^{1}H NMR (500 MHz, D_2O) δ 5.62 (br s, 1H), 5.56 (br s, 1H) 4.59 (t, J = 7.1 Hz, 1H), 4.43 (t, J = 7.3 Hz, 1H), 3.99–3.85 (m, 6H), 3.10 (s, 1H), 3.08 (s, 1H), 2.71–2.60 (m, 1H), 2.40–2.31 (m, 1H), 2.31–2.24 (m, 1H), 2.12–2.03 (m, 1H).

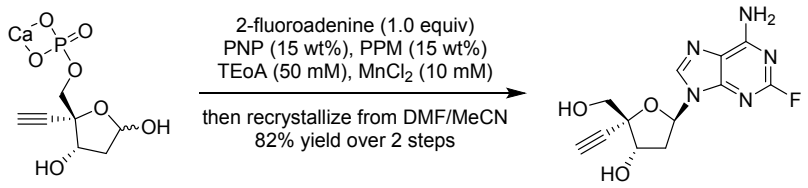
^{13}C NMR (126 MHz, D_2O) δ 97.5, 97.3, 82.9 (d, J = 6.8 Hz), 81.8 (d, J = 7.5 Hz), 80.4, 79.8, 78.3, 78.1, 71.3, 71.0, 67.2, 66.5, 39.7, 39.5.

^{31}P NMR (202 MHz, D_2O) δ 2.06.

Collection of HRMS and optical rotation data were hampered by the extremely low solubility of **9** in all solvents (including water).

Fully assigned ^{1}H and ^{13}C NMR data for the corresponding phosphoric acid have also been reported.[3]

4'-Ethynyl-2-fluoro-2'-deoxyadenosine 1



2-Fluoroadenine (1.0 g, 6.53 mmol, pin-milled) and calcium phosphate **9** (3.76 g, 9.80 mmol, 1.5 equiv) were added to a cylindrical vessel equipped with an overhead stirrer, a pH probe and an automatic dosing unit to control the pH (EZ-max-102 by Mettler Toledo). Buffer (30 mL of 50 mM triethanolamine and 10 mM $MnCl_2$ in water) was added and the pH was adjusted from 6.94 to 7.50 using 2 M KOH added with the automatic dosing unit. The stirring was slowed to 50 RPM and evolved purine nucleoside phosphorylase (150 mg, 15 wt% vs. 2-fluoroadenine) and evolved phosphopentamutase (150 mg, 15 wt% vs. 2-fluoroadenine) were added to the reaction. *Note: for details on the evolution of these enzymes see Enzymes section below and Reference 3. Extremely low yields were obtained using the wild-type enzymes*. Once the enzymes were dissolved, the stirring was increased to 300 rpm and the temperature of the reaction was raised to 40 °C. The pH was automatically controled with 2 M KOH and the reaction was periodically monitored by UPLC analysis. After 24 h, the reaction was filtered on to a frit, the solids were washed with water (2 x 10 mL), and dried with a nitrogen stream for 1 h to provide desired product **1** (3.631 g, 52.3 wt%, 6.10 mmol, 93% yield). The crude solid was slurried in DMF (7.6 mL) and water (1.9 mL), and filtered through a frit. The solids were washed with a 4:1 mixture of DMF:water (1.9 mL), and the combined filtrate was heated to 40 °C. Water (28 mL) was added to the warmed filtrate over 2 h with seed crystals added after 15 min. Upon completion of the addition of water the mixture was cooled to 0 °C, the solids were collected by filtration and washed with 2 x 2 mL of cold water to provide pure **1** (1.67 g, 98.8 wt%, 82% yield).

Data match those previously reported.[2]

Enzyme Preparation and Sequences

Screening and evolution

Wild-type Purine Nucleoside Phosphorylase (PNP) from *E. coli* was purchased from Millipore Sigma. Screening libraries of diverse PNPs and phosphopentomutases (PPMs) were obtained from Codexis, USA. Subsequent improvements in activity were enabled through directed evolution.

For further details on the optimization and production of these enzymes see Reference 3.

Enzyme Sequences

Evolved PPM amino acid sequence

MKRAFIMVLDSFGIGATEDAERFGDVGADTLGHIAEACAKGEADNGRKGPLNLPNLTRLGLAK
AHEGSTGFIPAGMDGNAEVIGAYAWAHEMSSGKDSVSGHWEIAGVPVLFEWGYFSDHENSFPQ
ELLDKLVERANLPGYLGNCRSSGTVILDQLGEEHMKTGKPIFYTSAASVFQIACHEETFGLDKLY
ELCEIAREELTNGGYNIGRVIARPFIGDKAGNFQRTGNRRDLAVEPPAPTVLQKLVDEKHGQVVS
VGKIADIYANCGITKKVKATGLDALFDATIKEMKEAGDNTIVFTNFVDFDSSWGHRRDVAGYAA
GLELFDRRLPELMSLLRDDDILILTADHGCDPTWTGTDHTREHIPVLVYGPKVKPGSLGHRETFA
DIGQTLAKYFGTSDMEYGKAMF

Evolved PNP amino acid sequence

MTTPHINAEMGDFADVVLMPGDPLRAKYIAETFLEDAREVNNVRGMLGFTGTYKGRKISVMGH
GAGIPSCSIYTKELITDFGVKKIIRVGTCGAVLPHVKLRDVVIGMGACTDSKVNRIRFKDHDFAAI
ADFDMVRNAVDAAKALGIDPRVGNLHSADLFYSPDGEMFDVMEKYGIVGVEMEAAGIYGVAA
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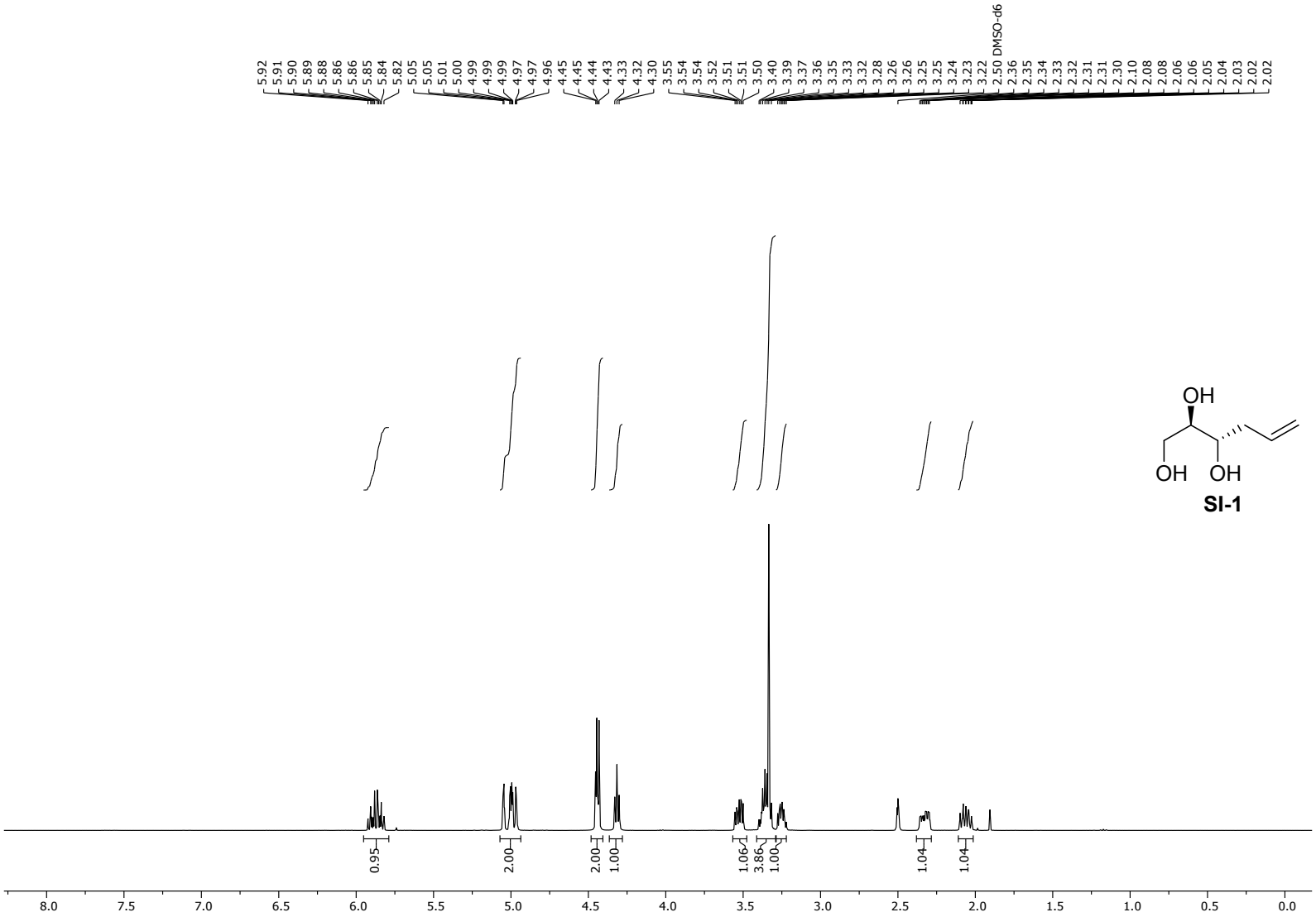
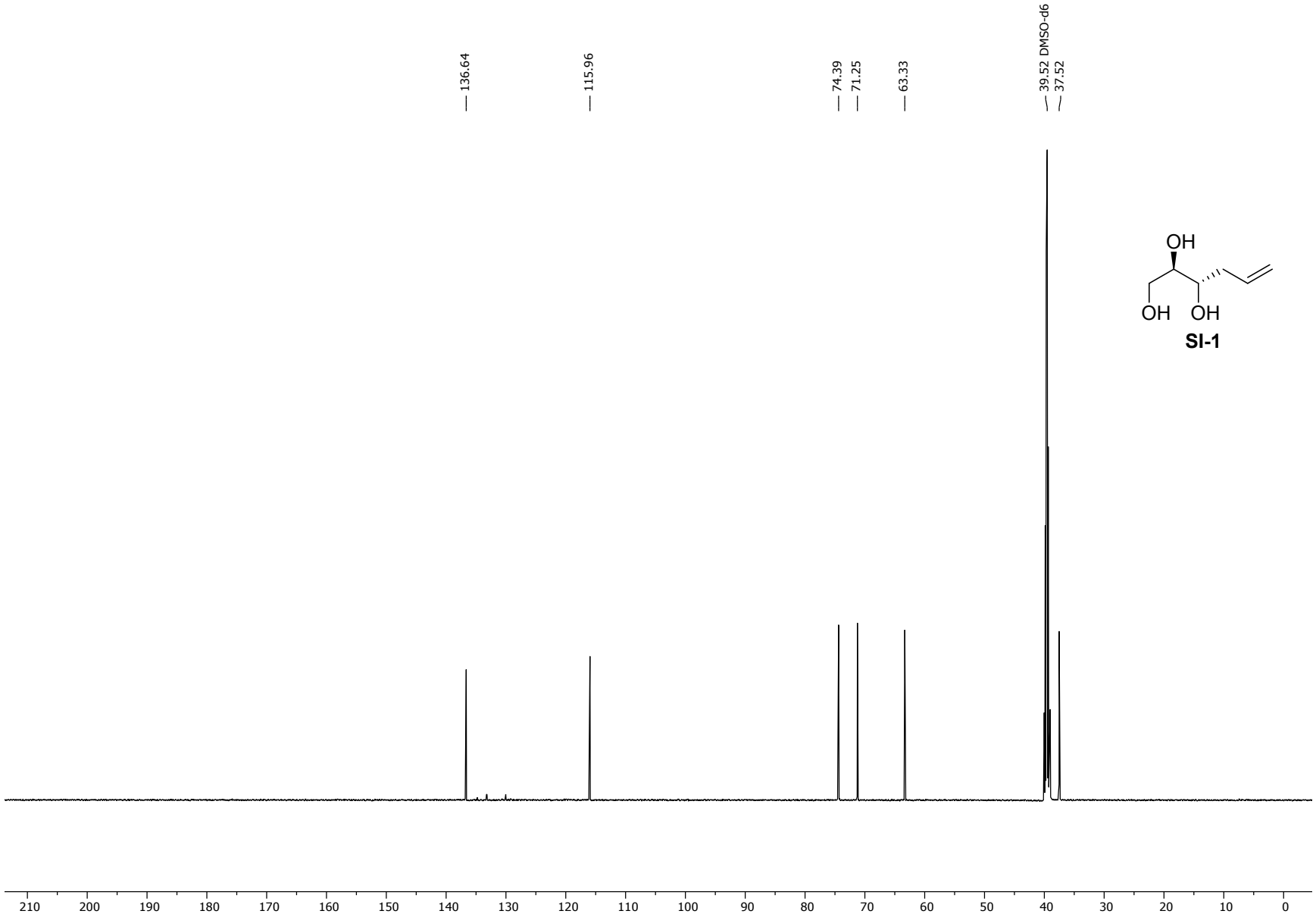
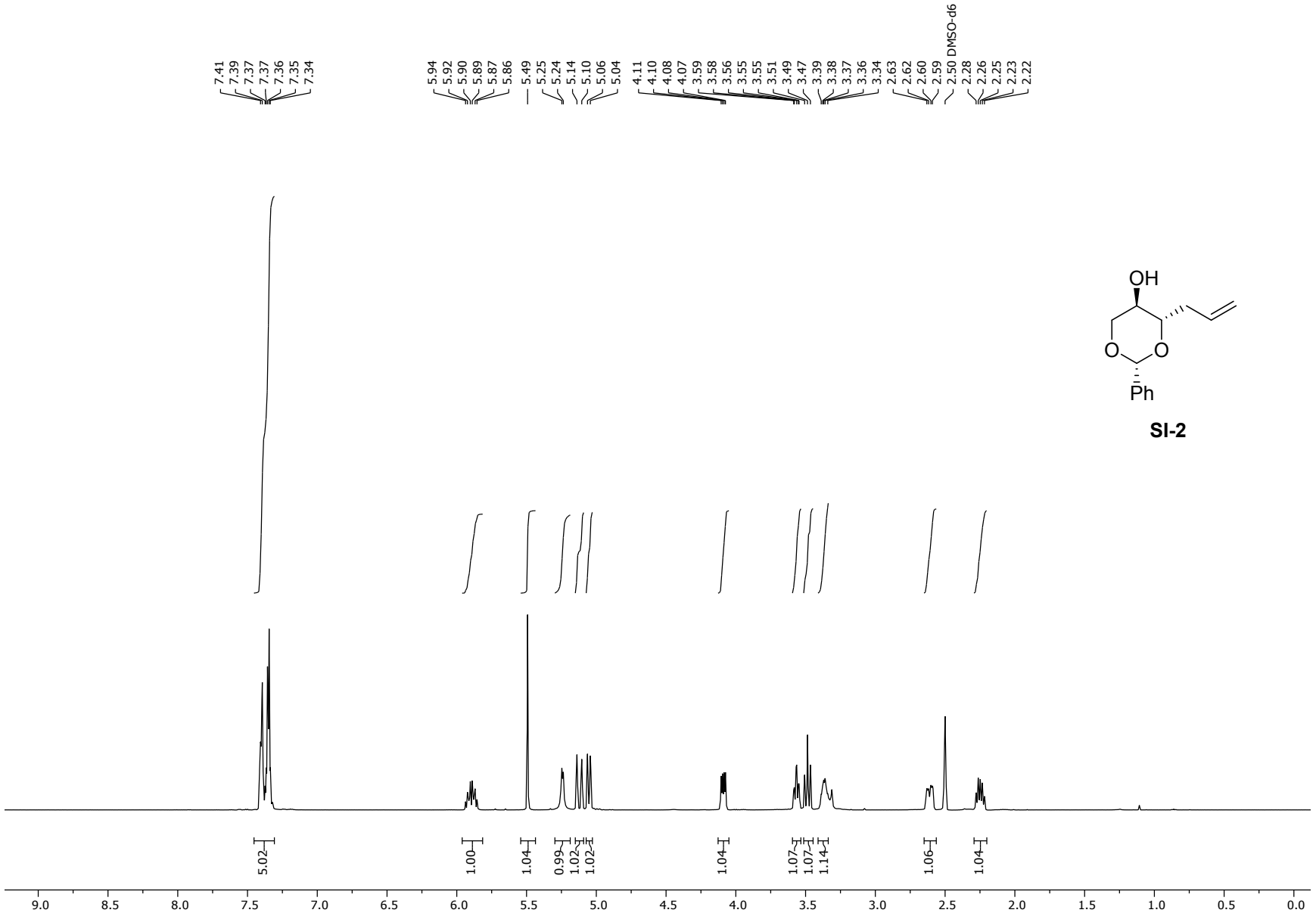
Copies of NMR Spectra



^{1}H NMR spectrum at 500 MHz in DMSO-d6

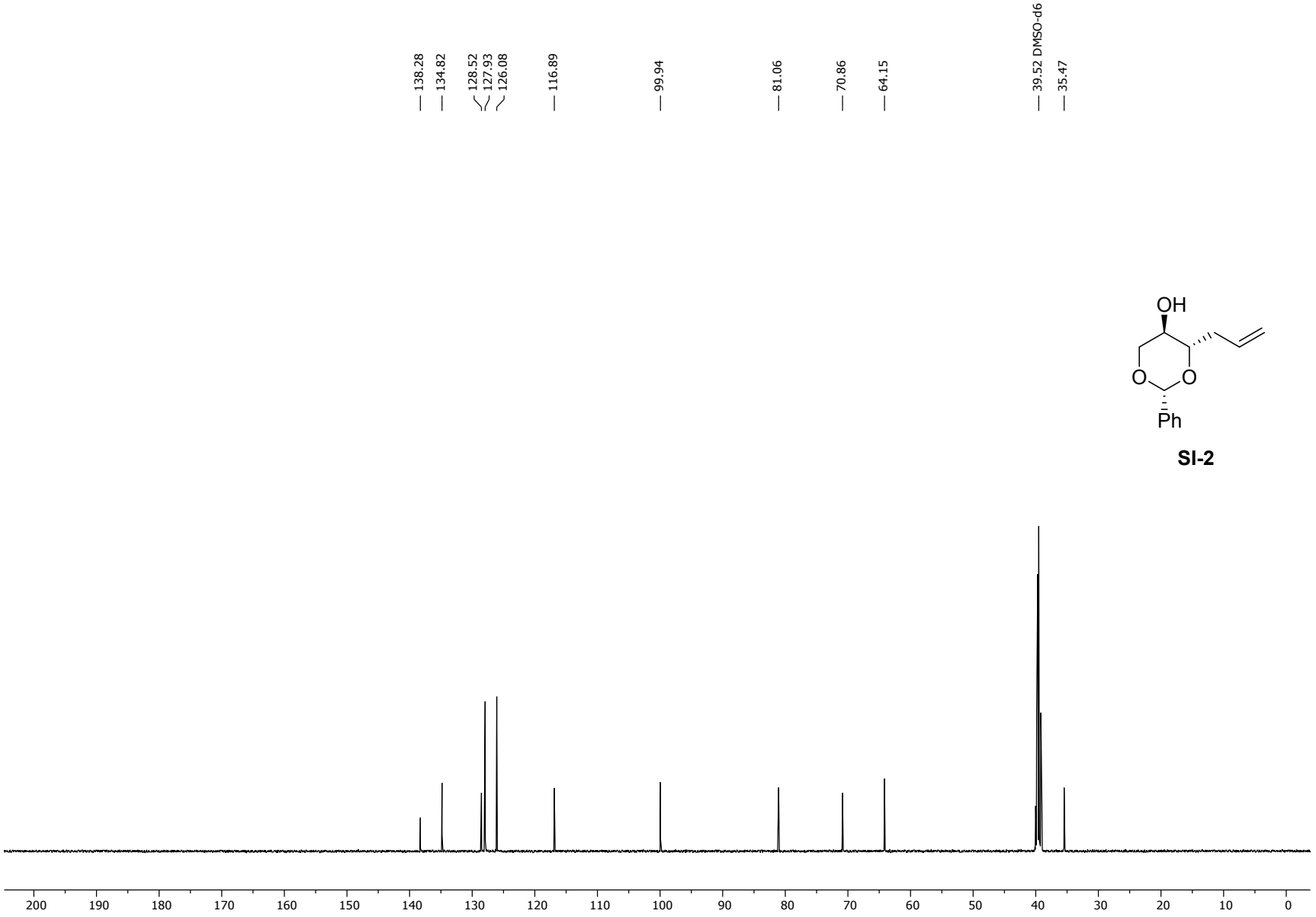


^{13}C NMR spectrum at 126 MHz in DMSO-d6



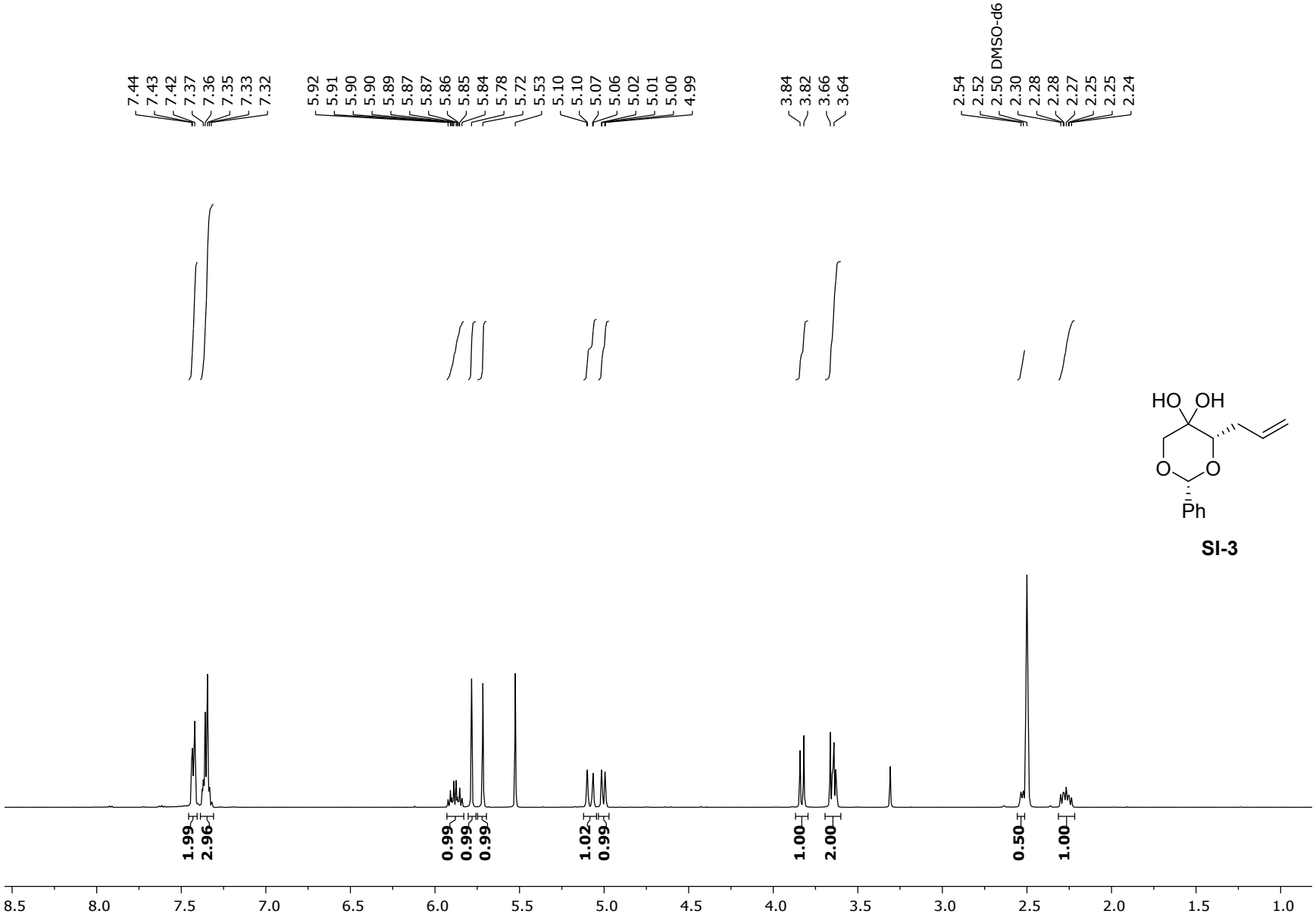
SI-2

^{1}H NMR spectrum at 500 MHz in DMSO-d6



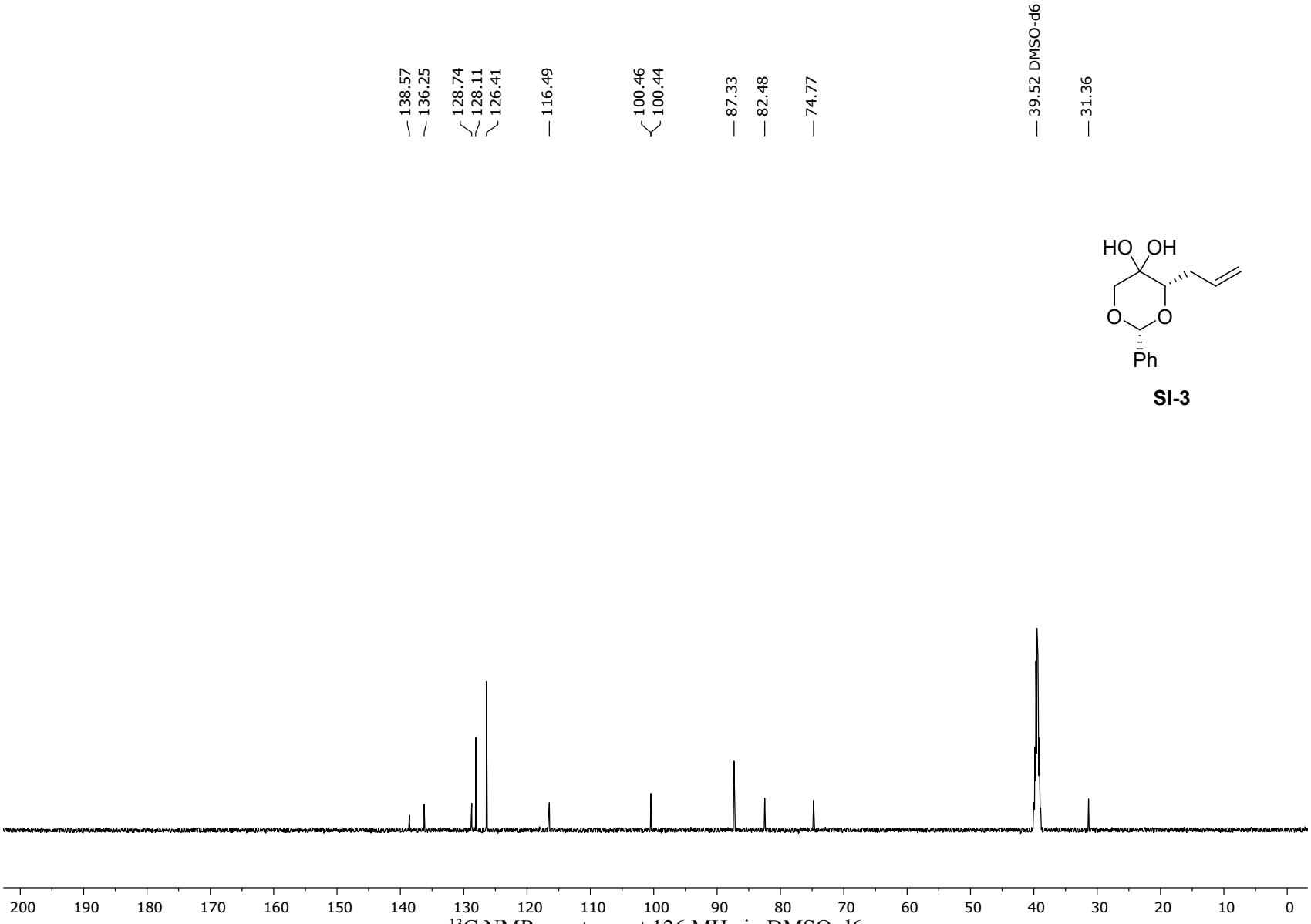
SI-2

^{13}C NMR spectrum at 126 MHz in DMSO-d6



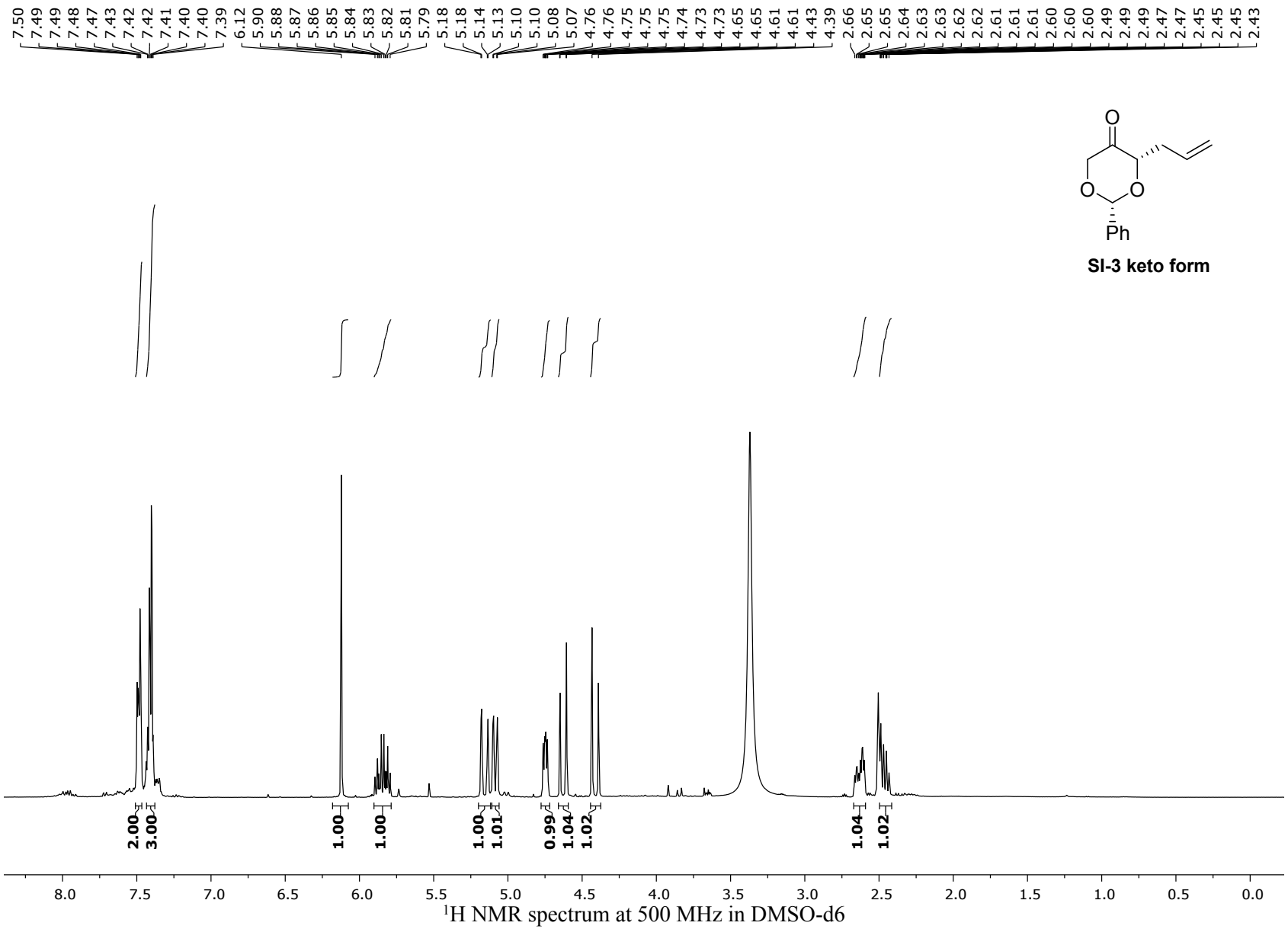
SI-3

^{1}H NMR spectrum at 500 MHz in DMSO-d6



SI-3

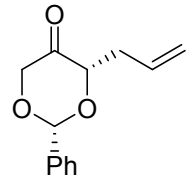
^{13}C NMR spectrum at 126 MHz in DMSO-d6



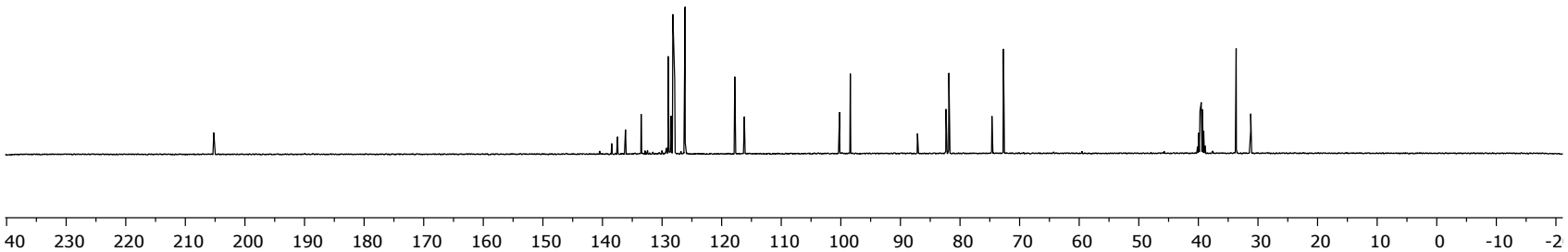
^{1}H NMR spectrum at 500 MHz in DMSO-d6

205.22
137.47
133.51
128.98
128.19
126.14
117.80
98.41
81.87
72.71
39.52 DMSO-d6
33.66

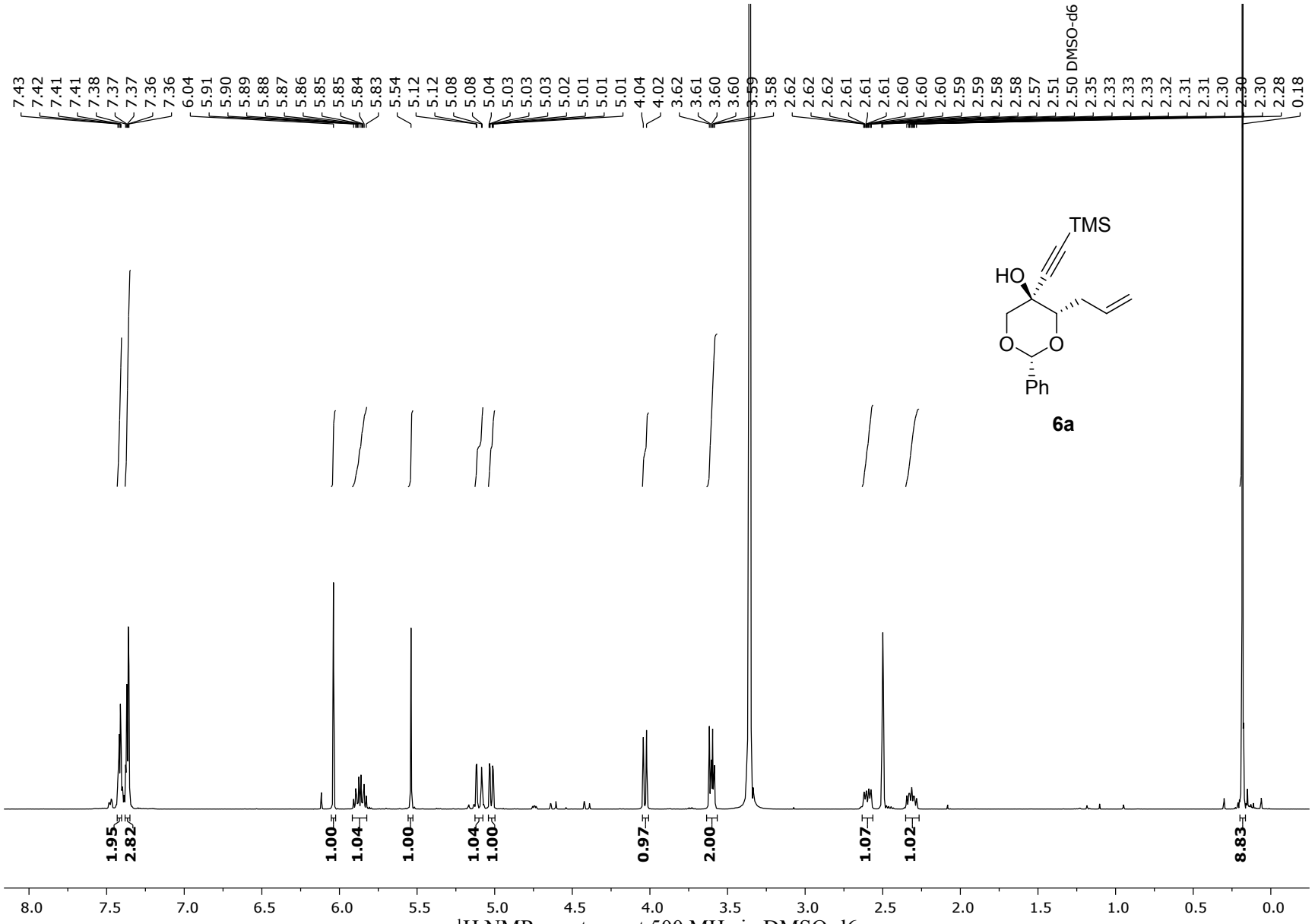
Note: contains some of the ketone hydrate (compare with above) due to picking up water from the solvent and air. Only ketone peaks are picked.



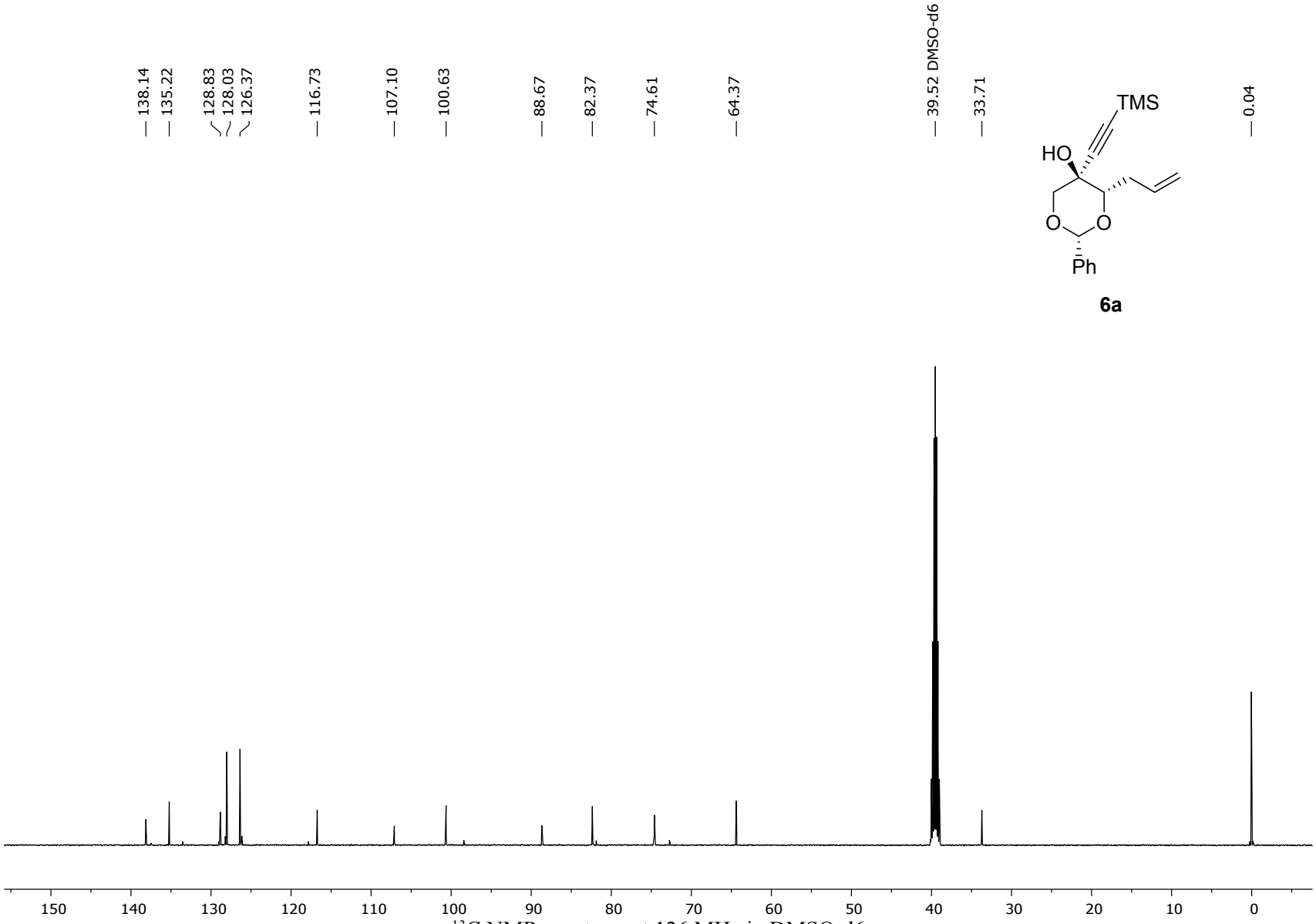
SI-3 keto form



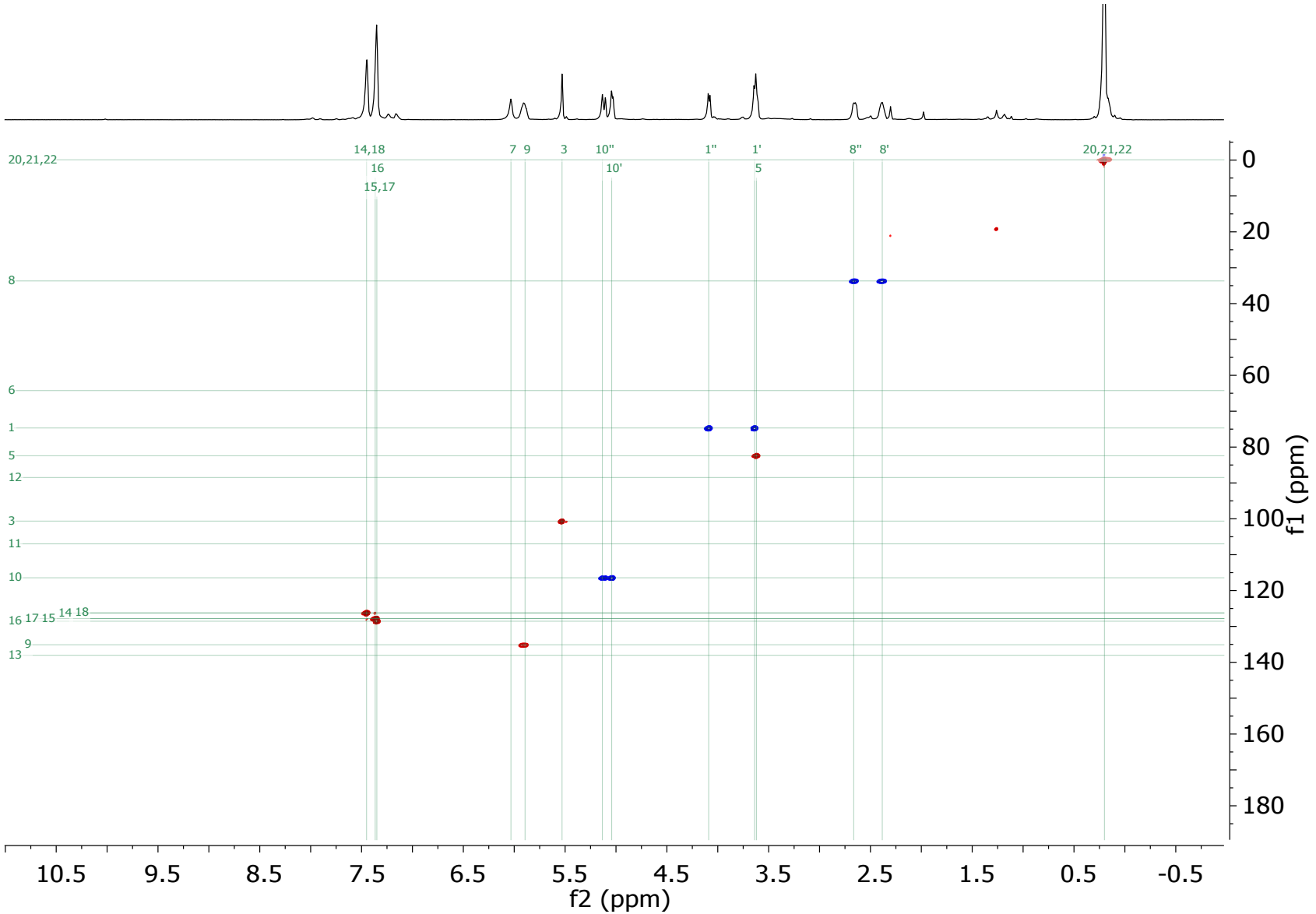
^{13}C NMR spectrum at 126 MHz in DMSO-d6



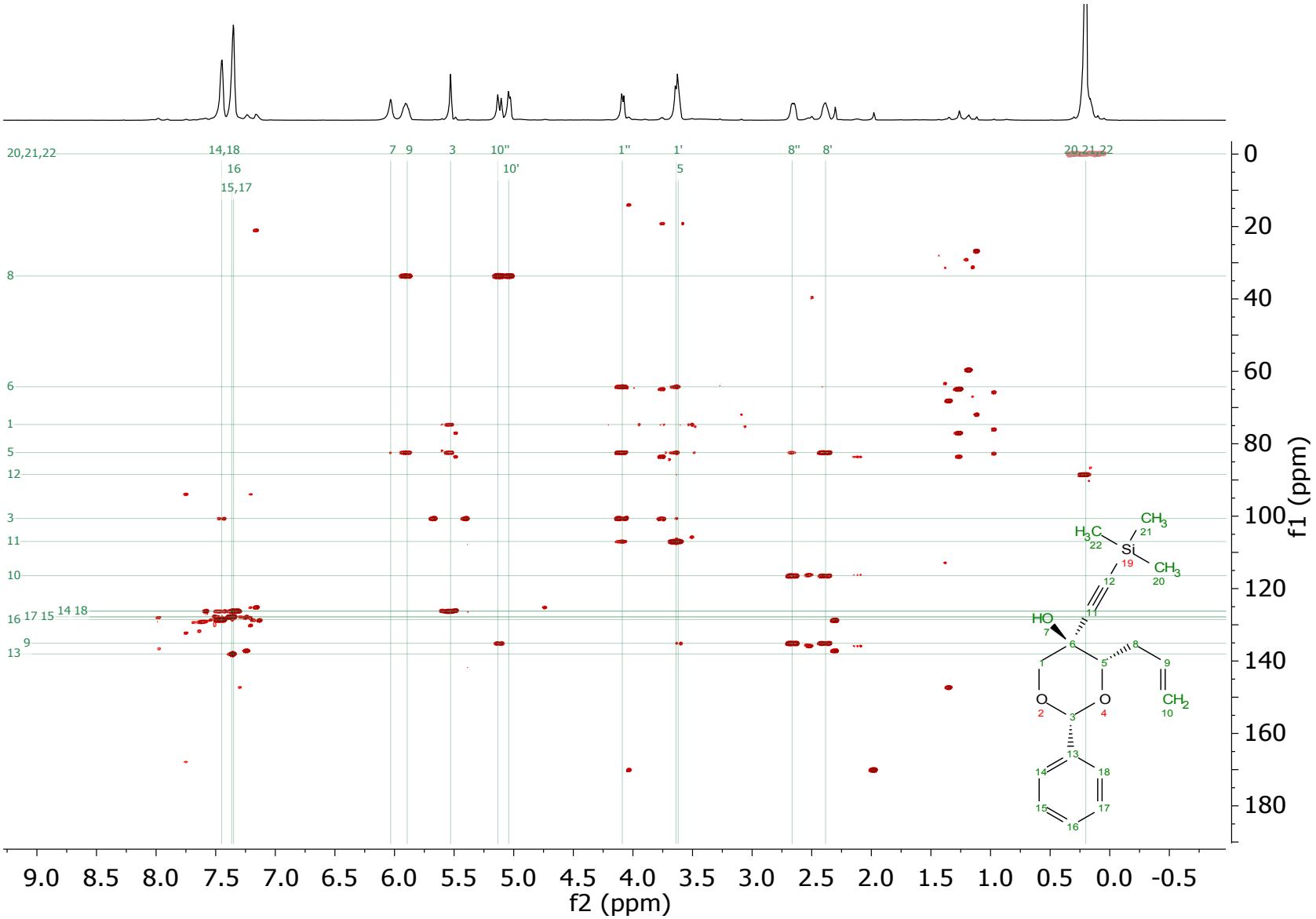
^{1}H NMR spectrum at 500 MHz in DMSO-d6



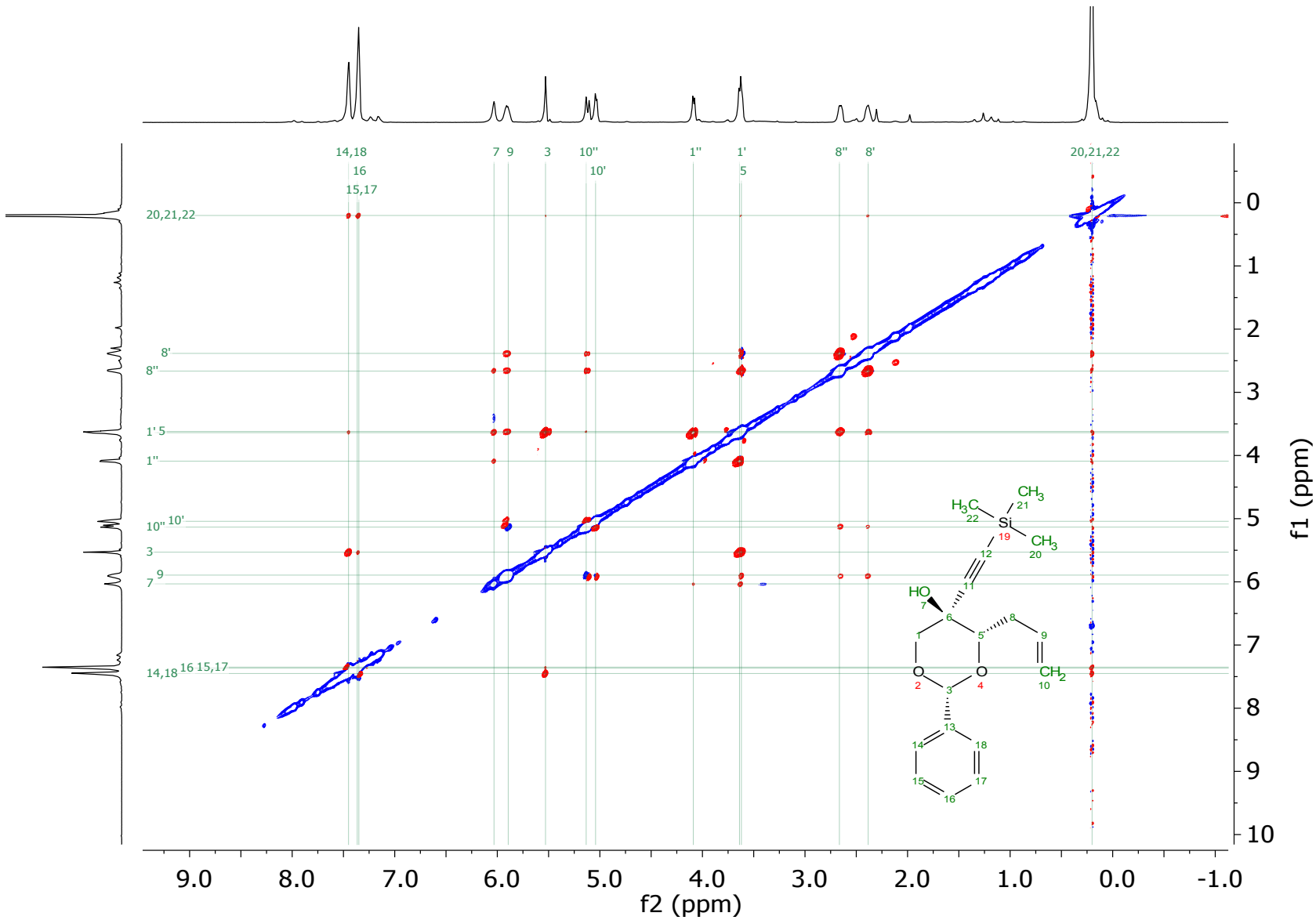
^{13}C NMR spectrum at 126 MHz in DMSO-d6



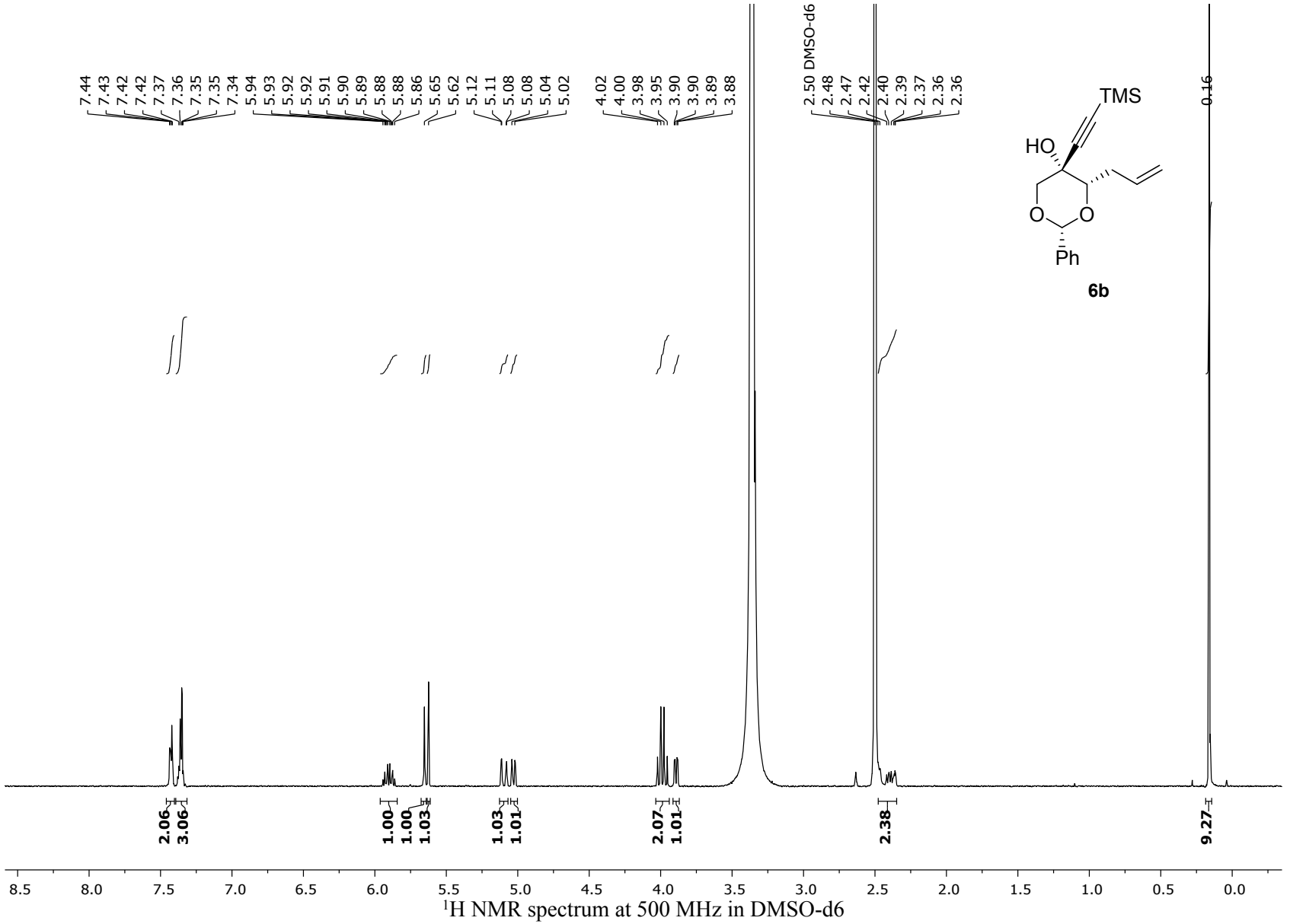
HSCQ spectrum at 500 MHz in DMSO-d6



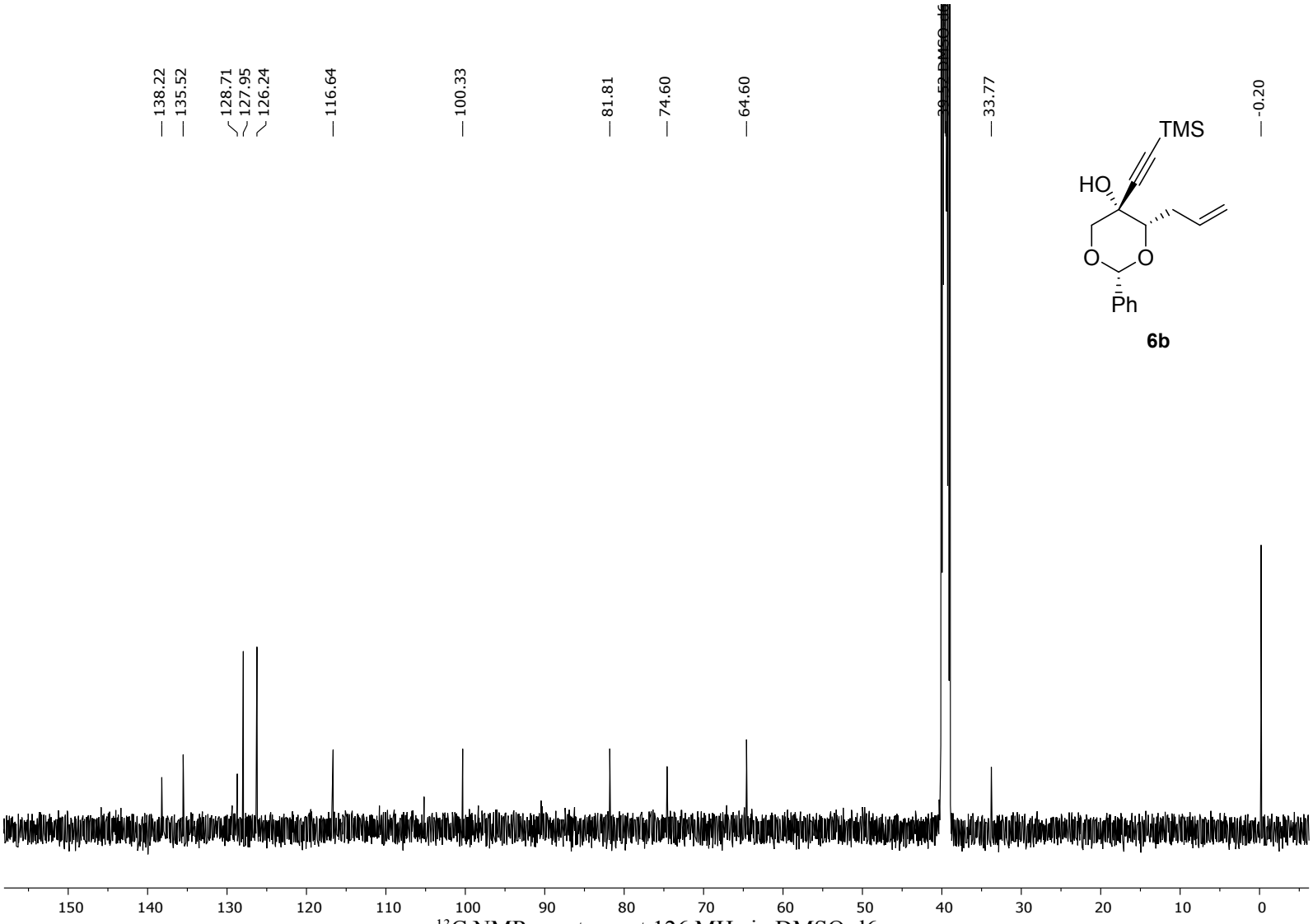
HMBC spectrum at 600 MHz in DMSO-d6



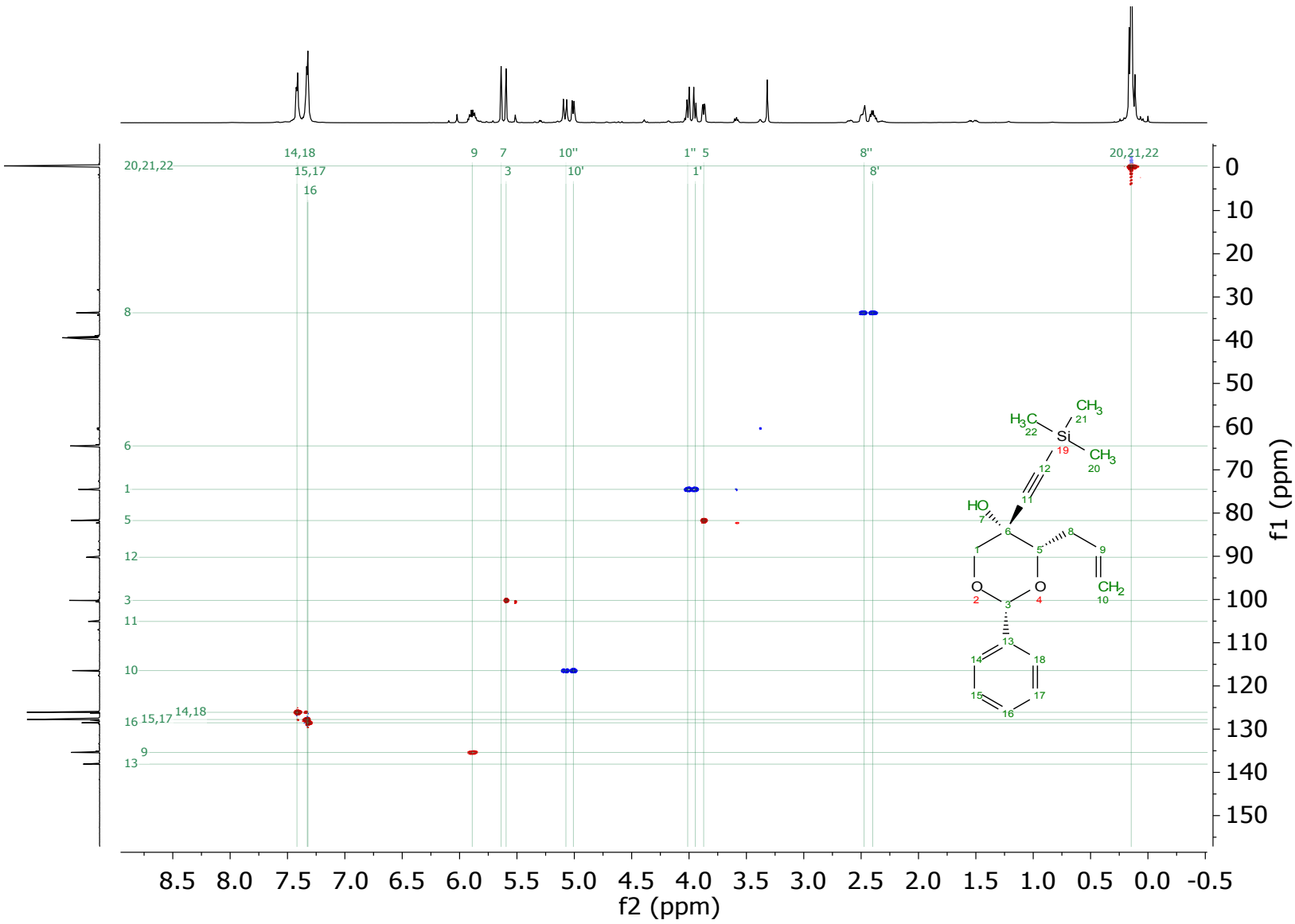
ROESY spectrum at 600 MHz in DMSO-d6



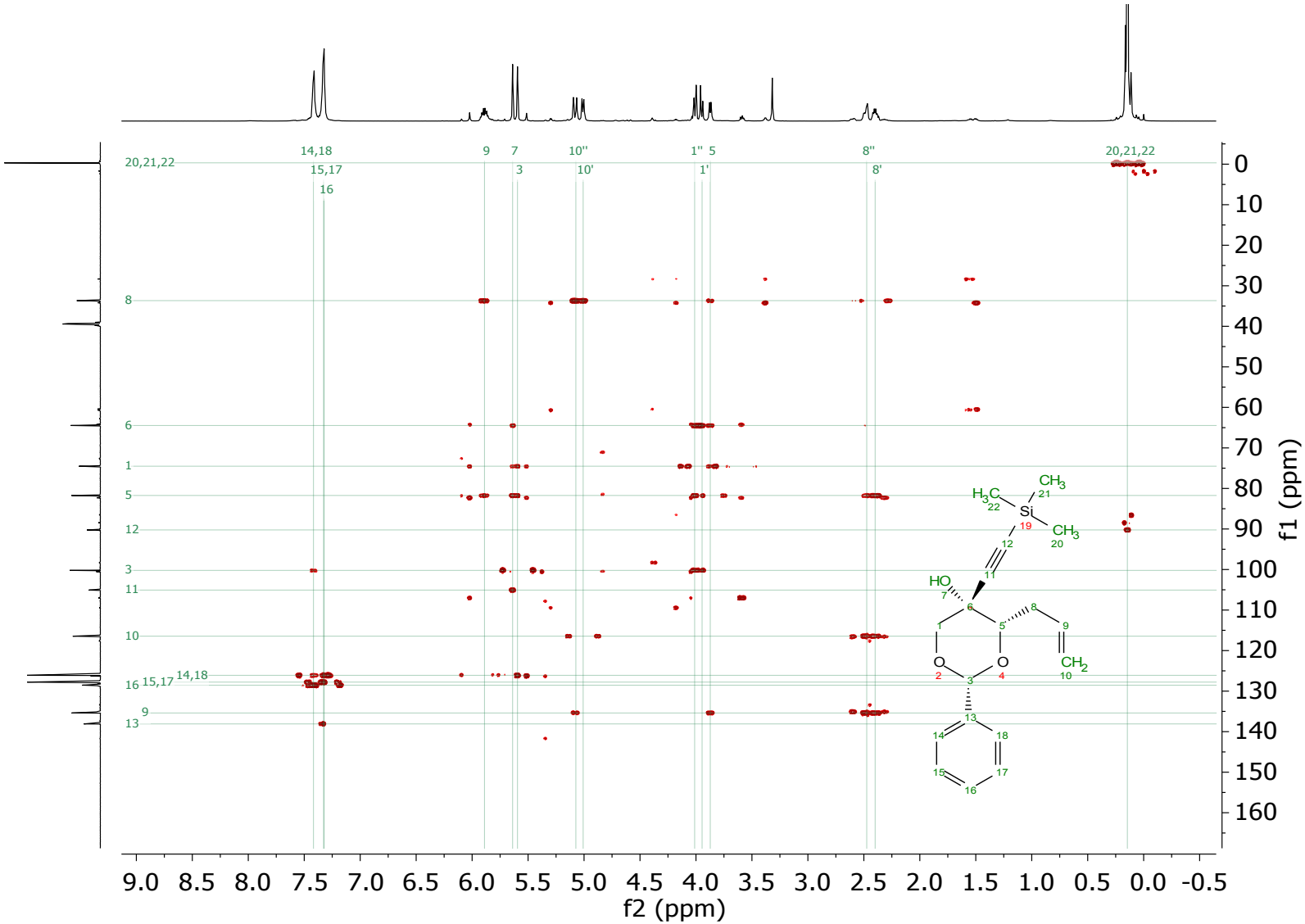
^{1}H NMR spectrum at 500 MHz in DMSO-d6



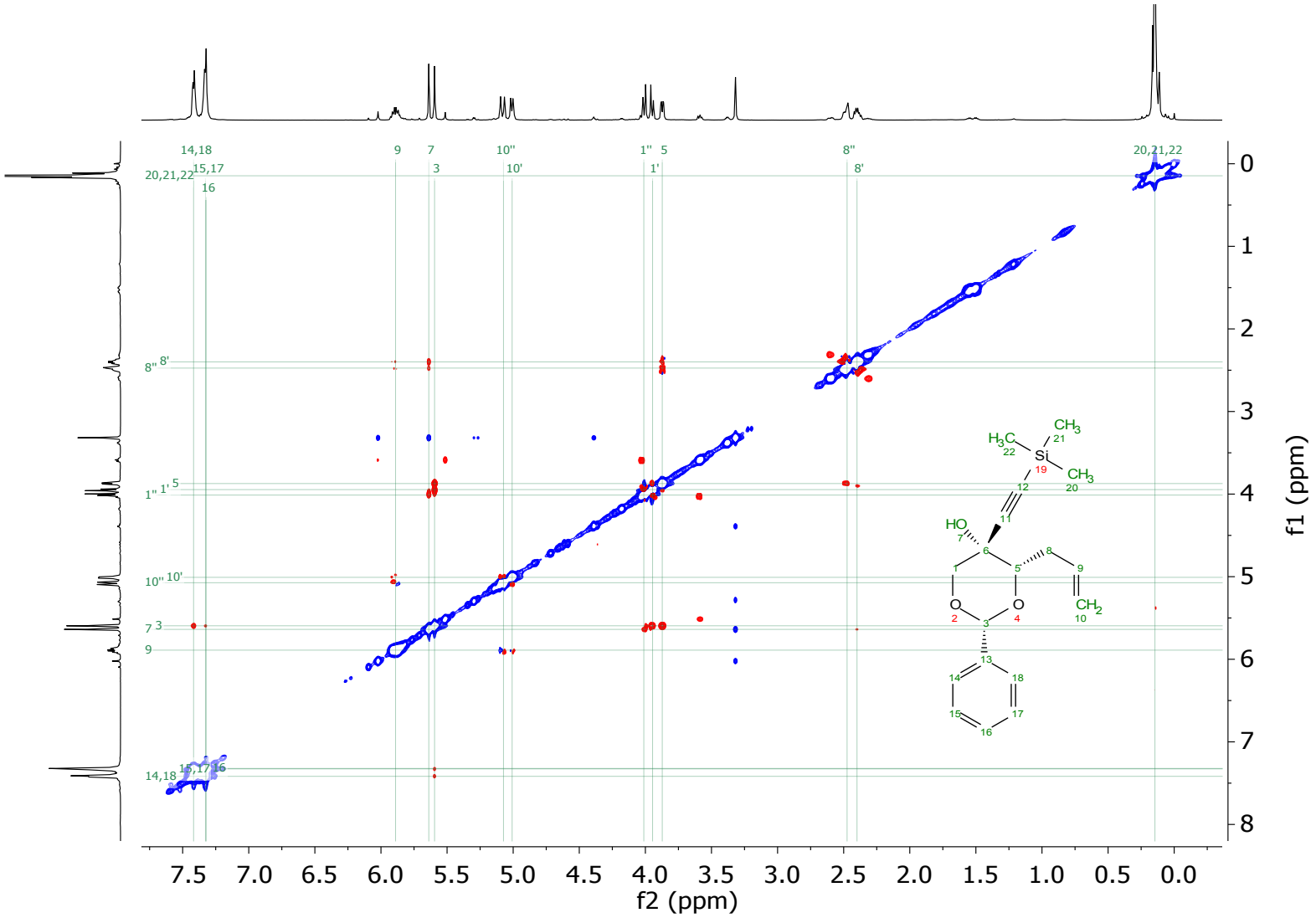
^{13}C NMR spectrum at 126 MHz in DMSO-d6



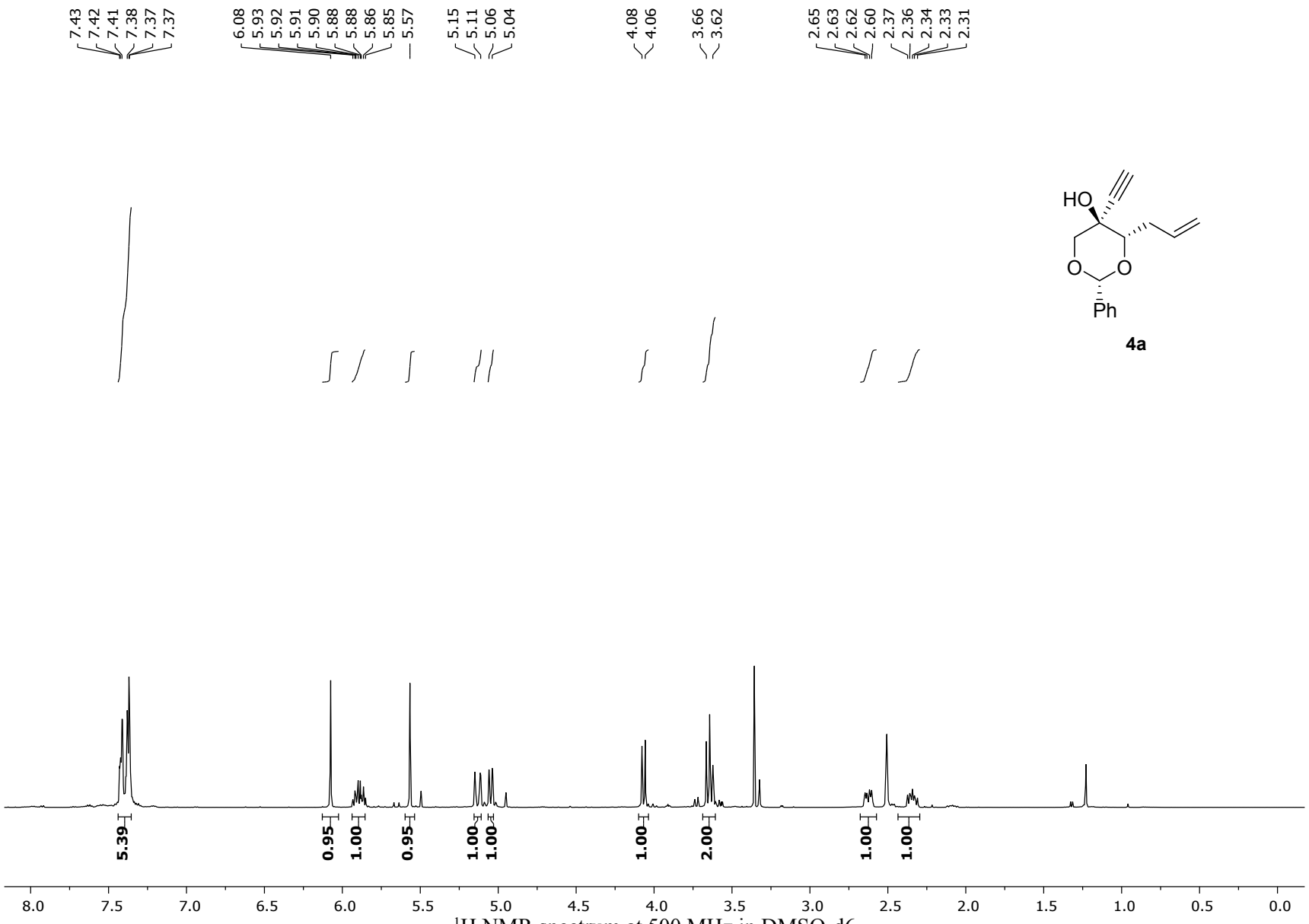
HSQC spectrum of **6b** at 600 MHz in DMSO-d6



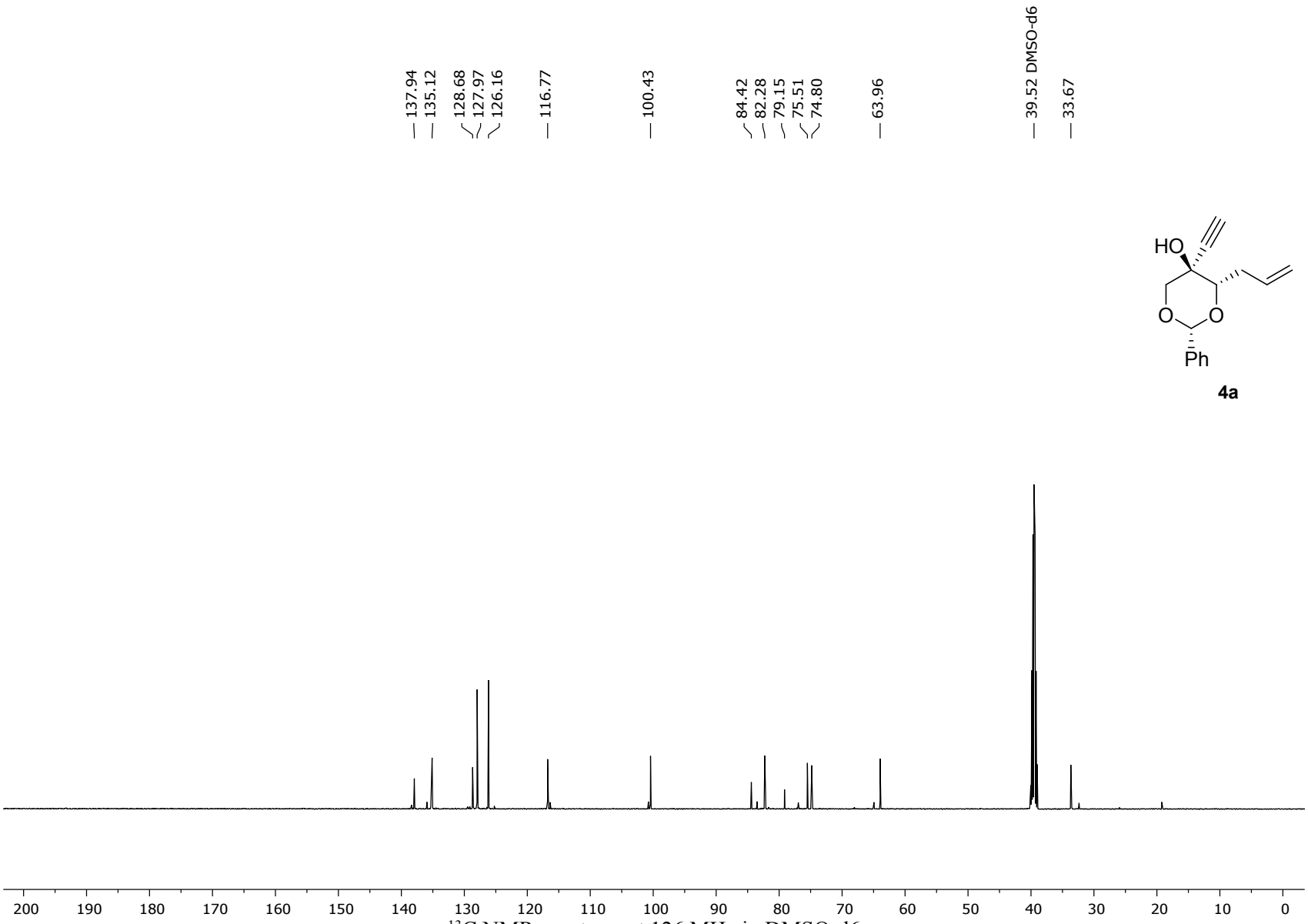
HMBC spectrum of **6b** at 600 MHz in DMSO-d6



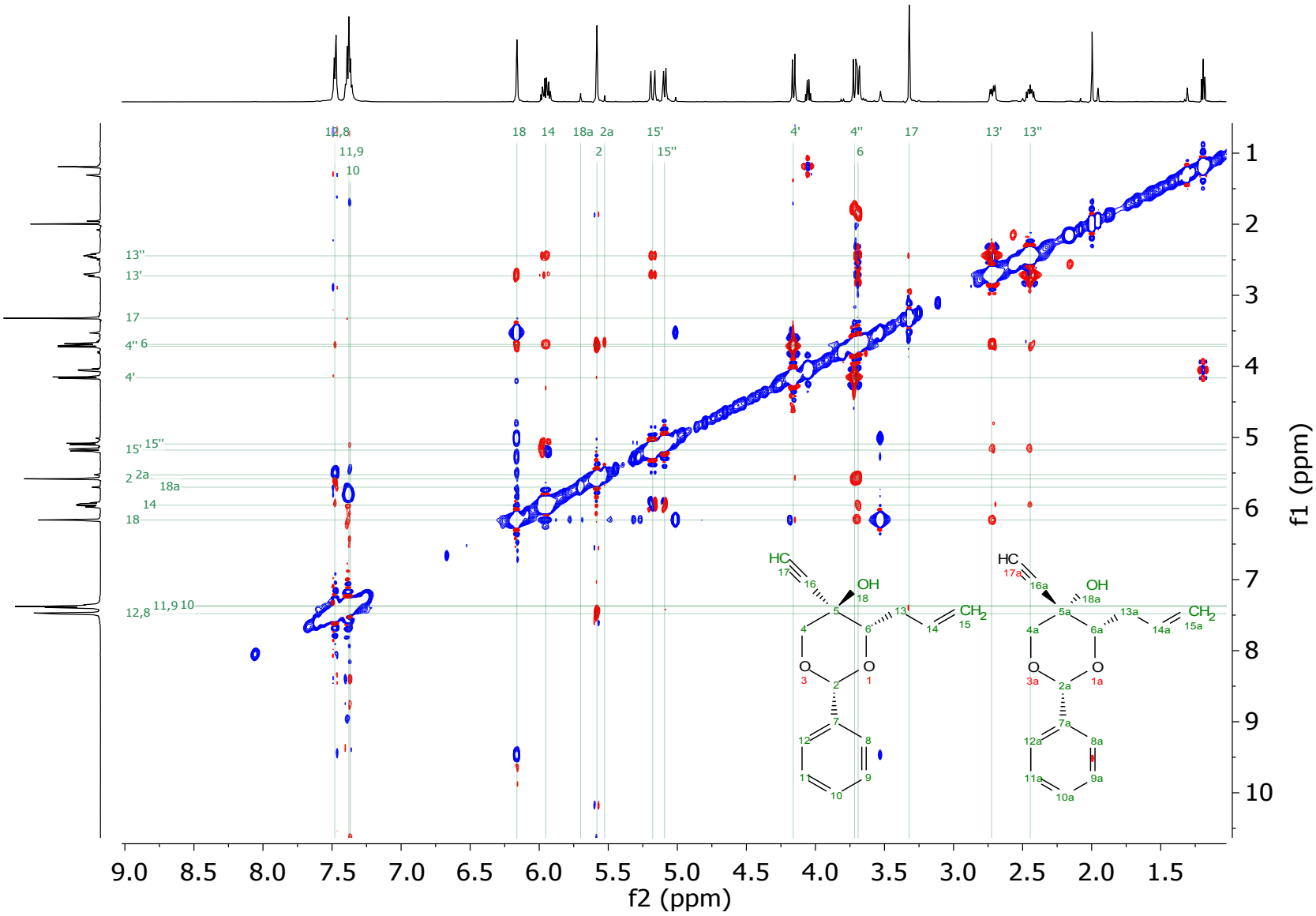
ROESY spectrum of **6b** at 600 MHz in DMSO-d6



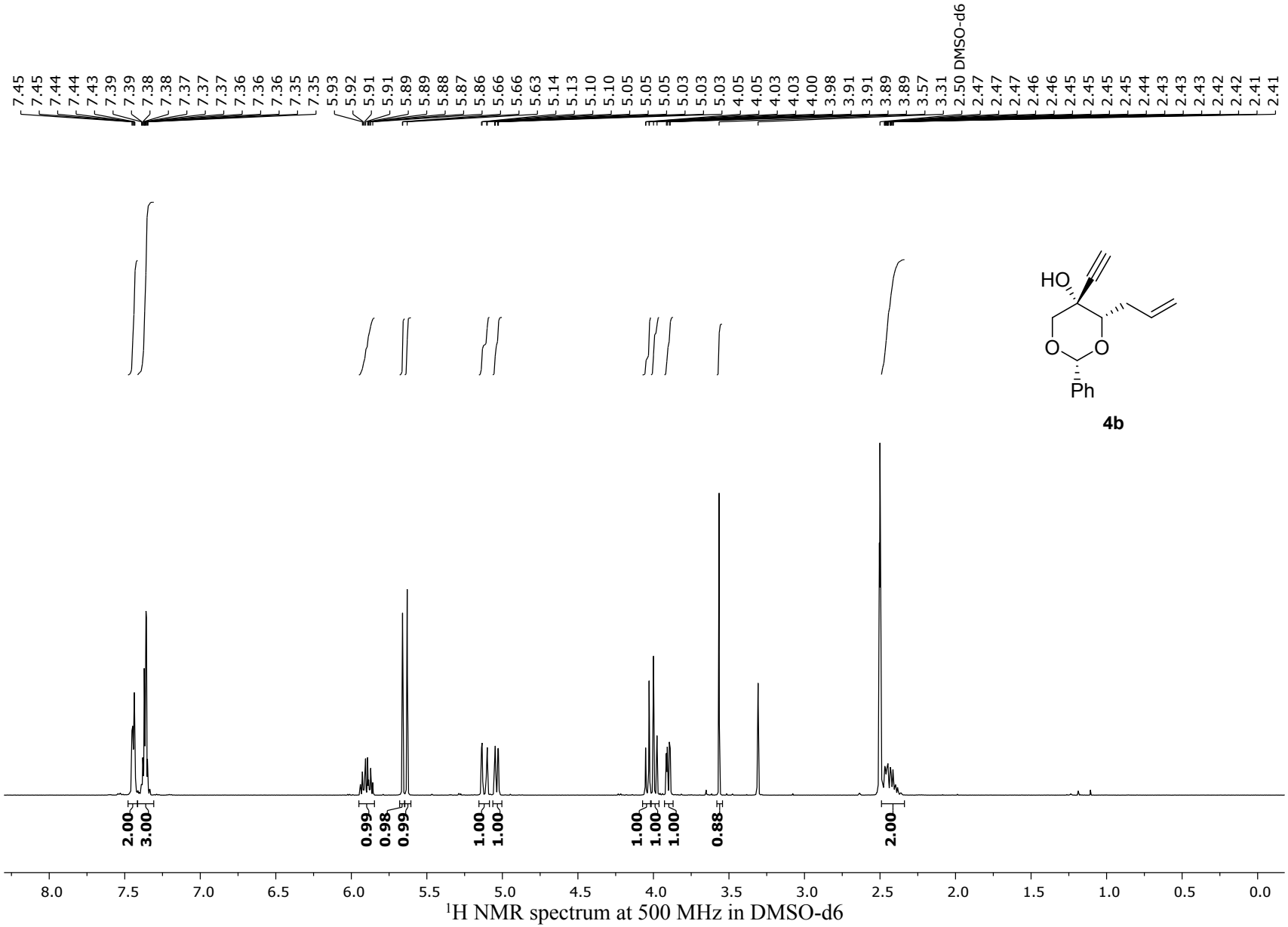
^{1}H NMR spectrum at 500 MHz in DMSO-d6



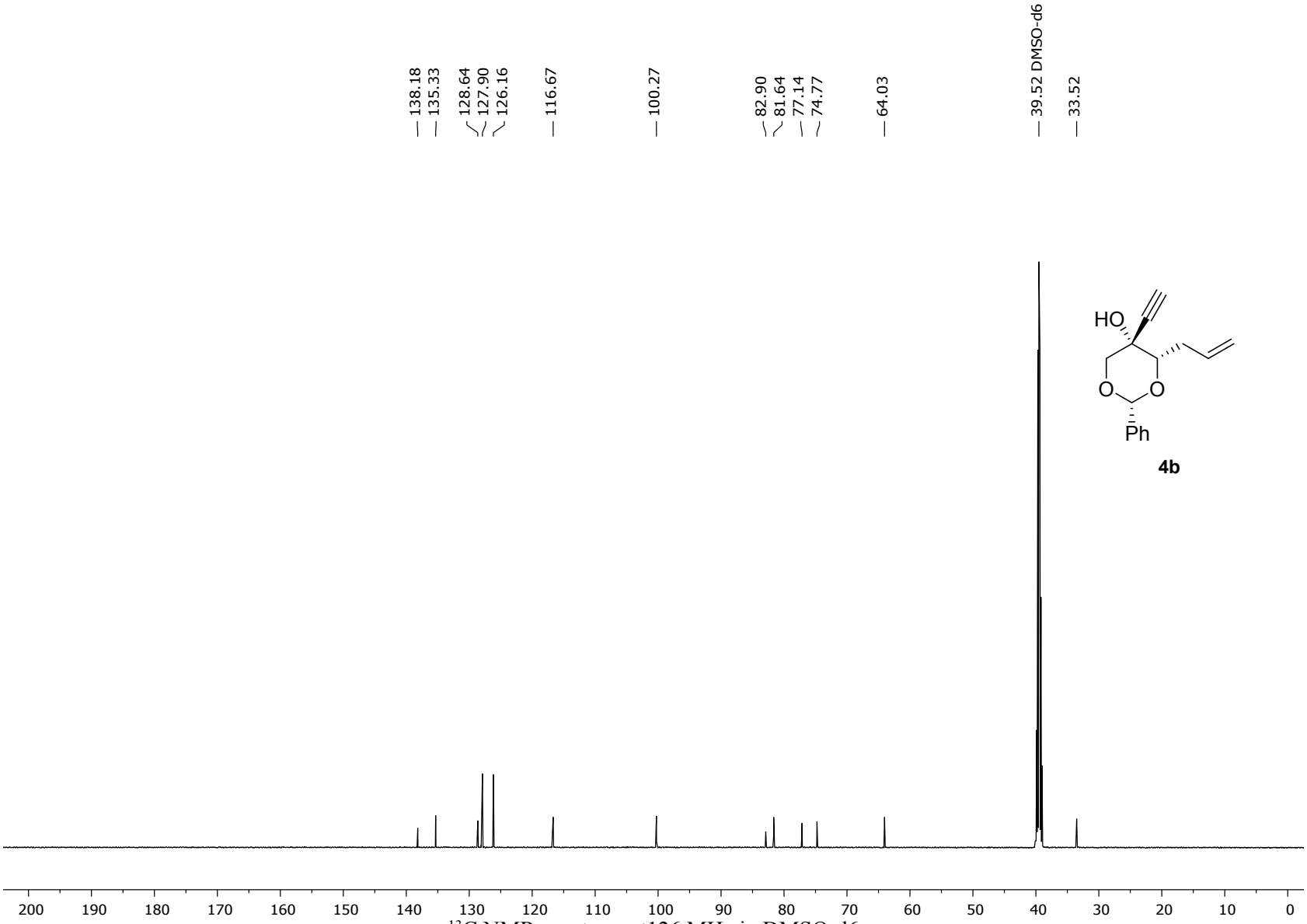
^{13}C NMR spectrum at 126 MHz in DMSO-d6



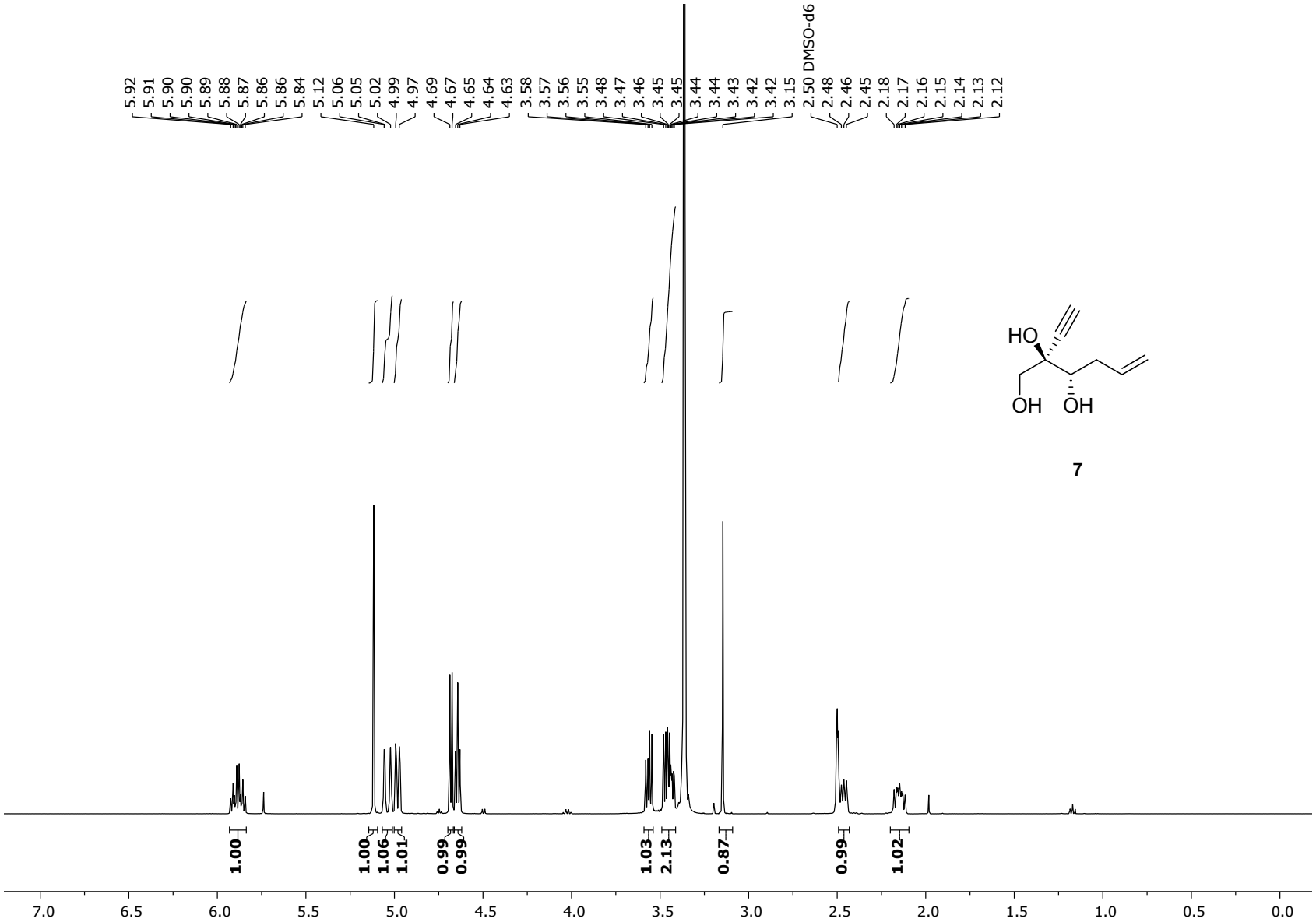
NOESY spectrum of **4a** (with a trace amount of **4b**) at 600 MHz in DMSO-d6



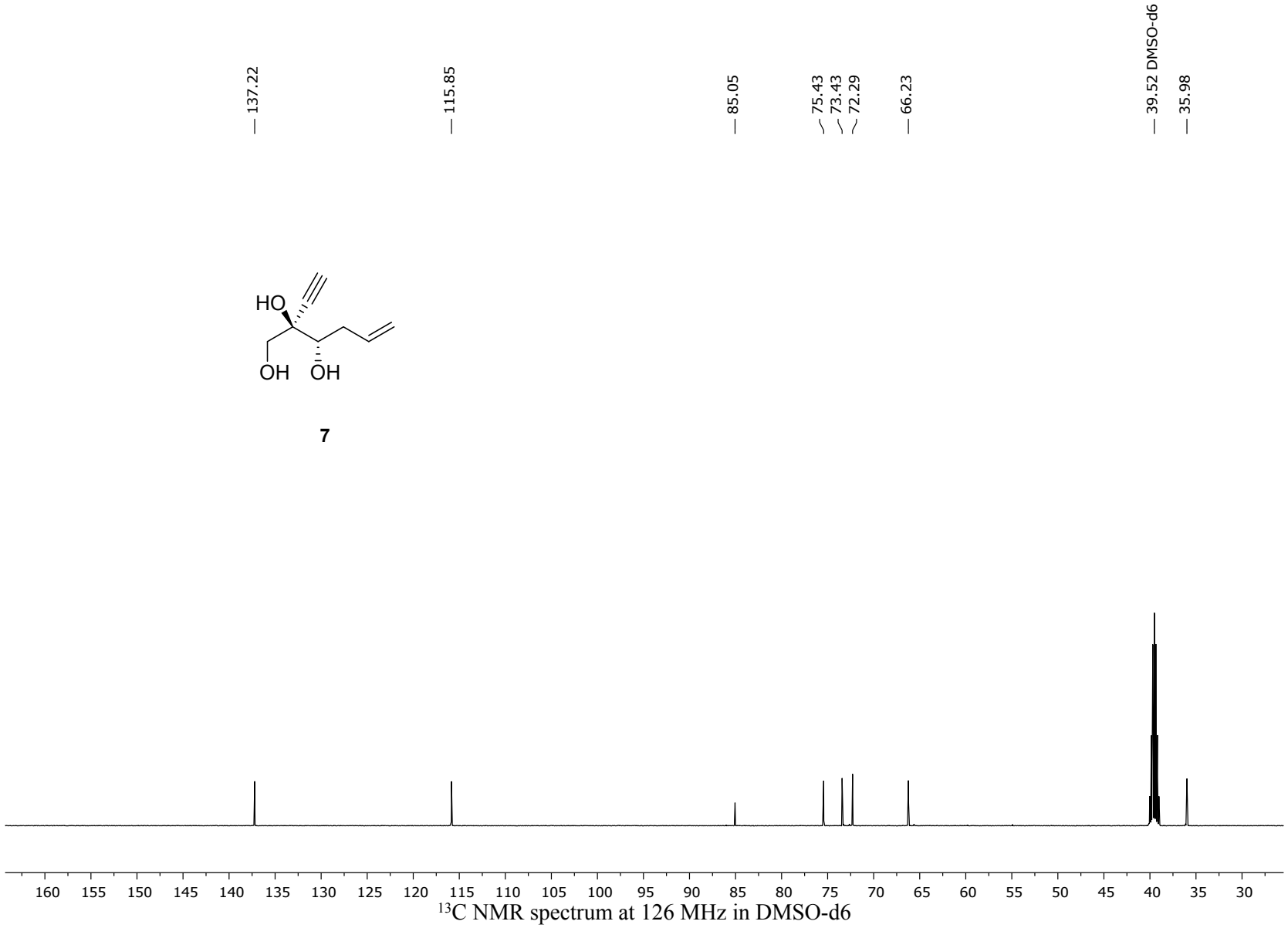
^{1}H NMR spectrum at 500 MHz in DMSO-d6



^{13}C NMR spectrum at126 MHz in DMSO-d6

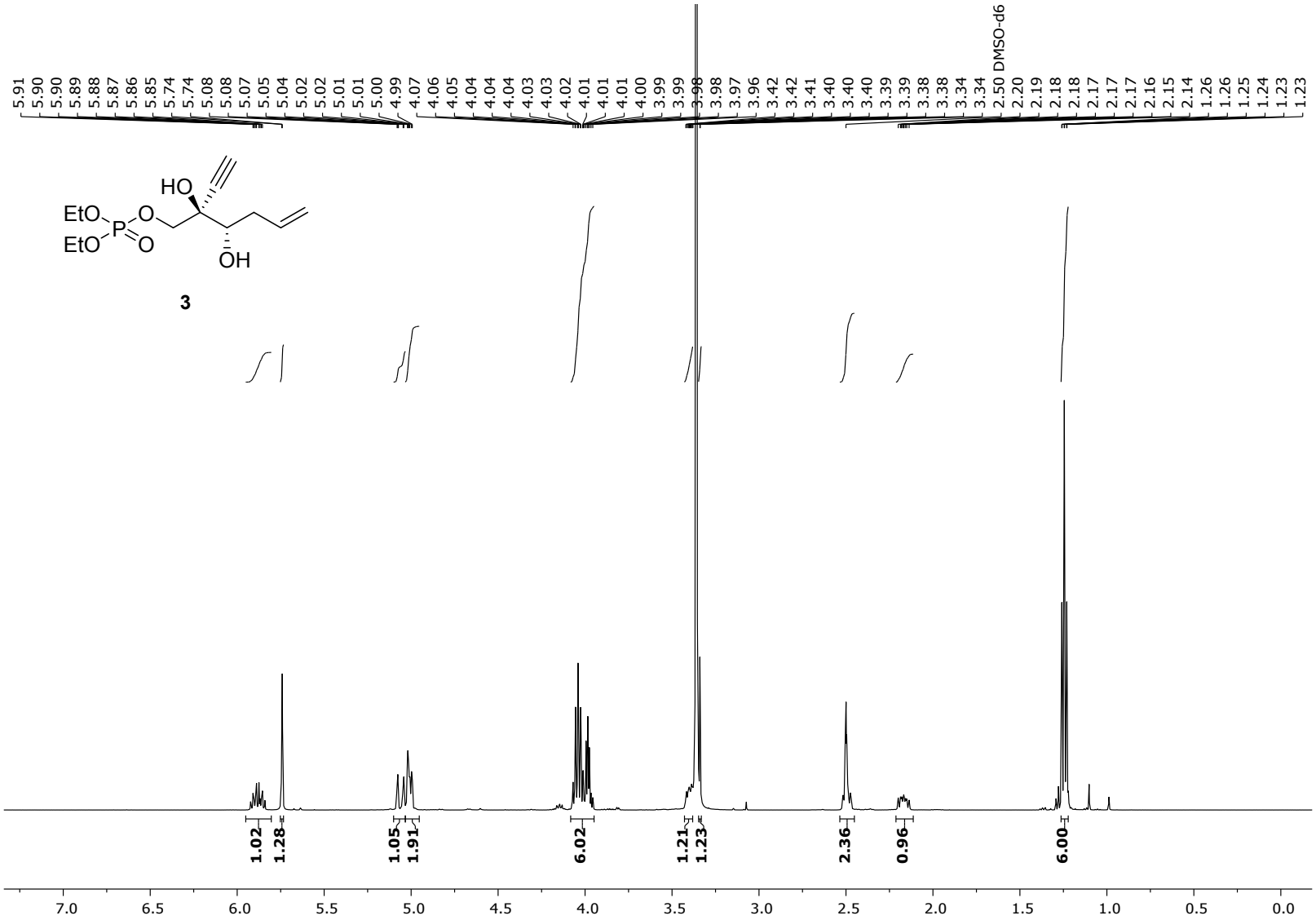


^{1}H NMR spectrum at 500 MHz in DMSO-d6

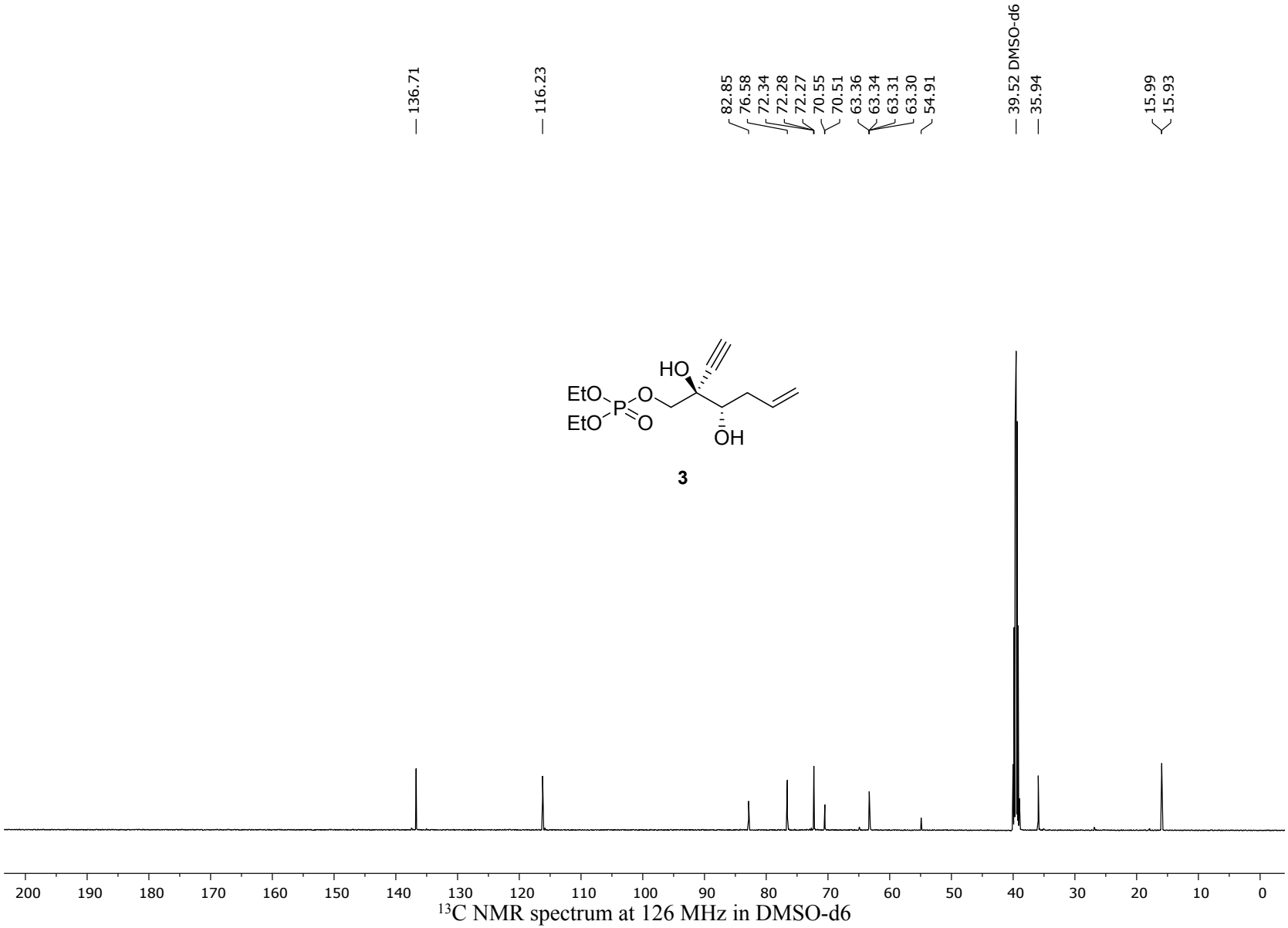


7

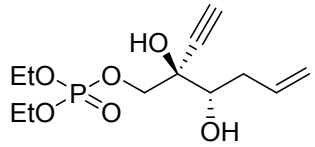
^{13}C NMR spectrum at 126 MHz in DMSO-d6



^{1}H NMR spectrum at 500 MHz in DMSO-d6



^{13}C NMR spectrum at 126 MHz in DMSO-d6



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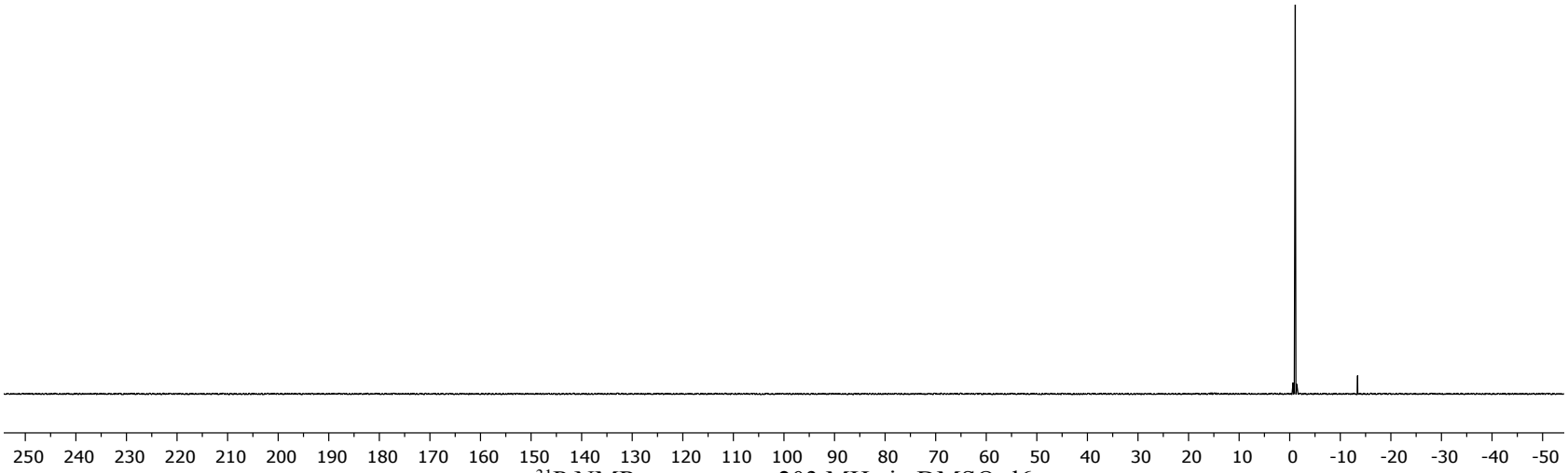
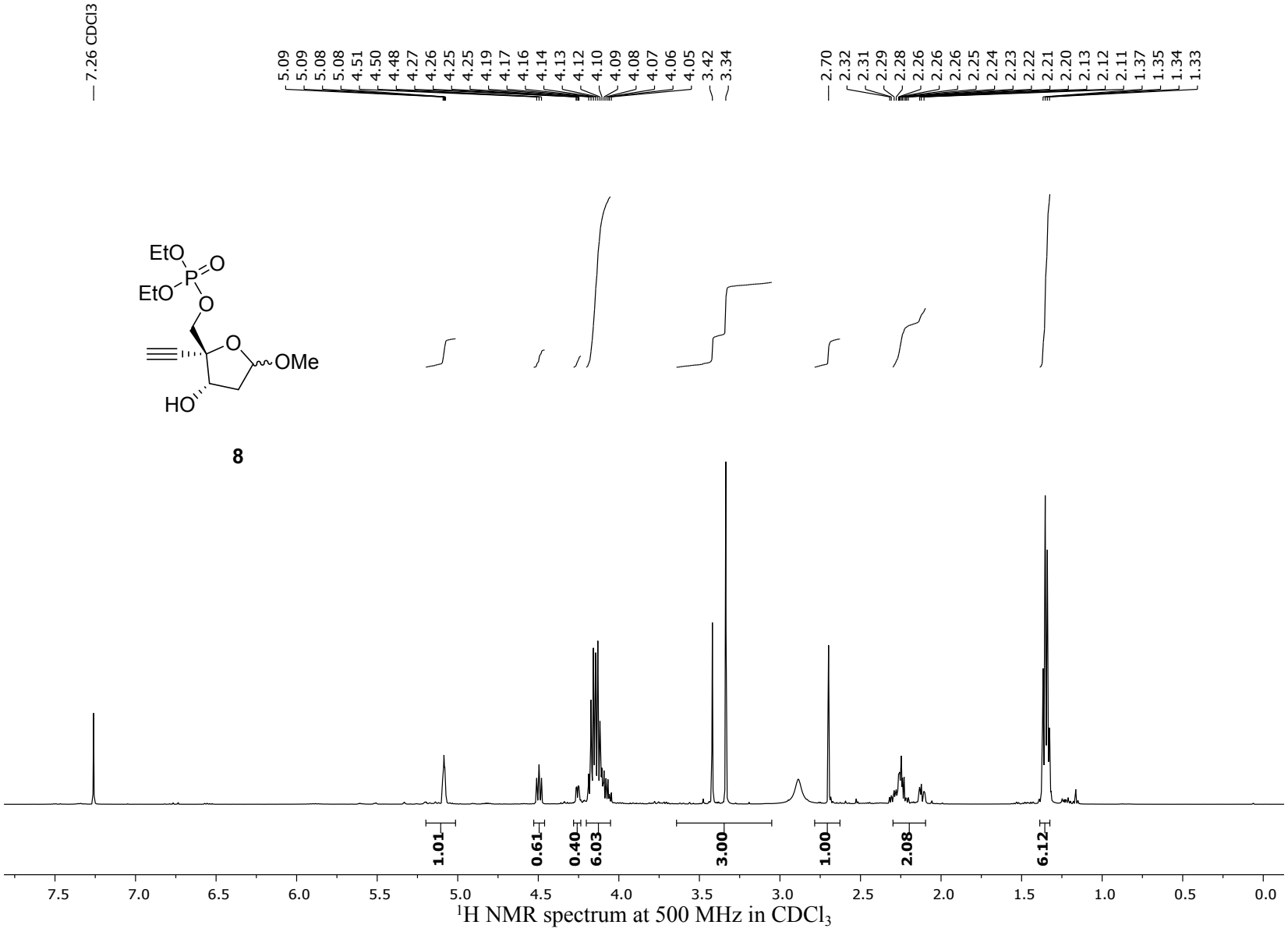
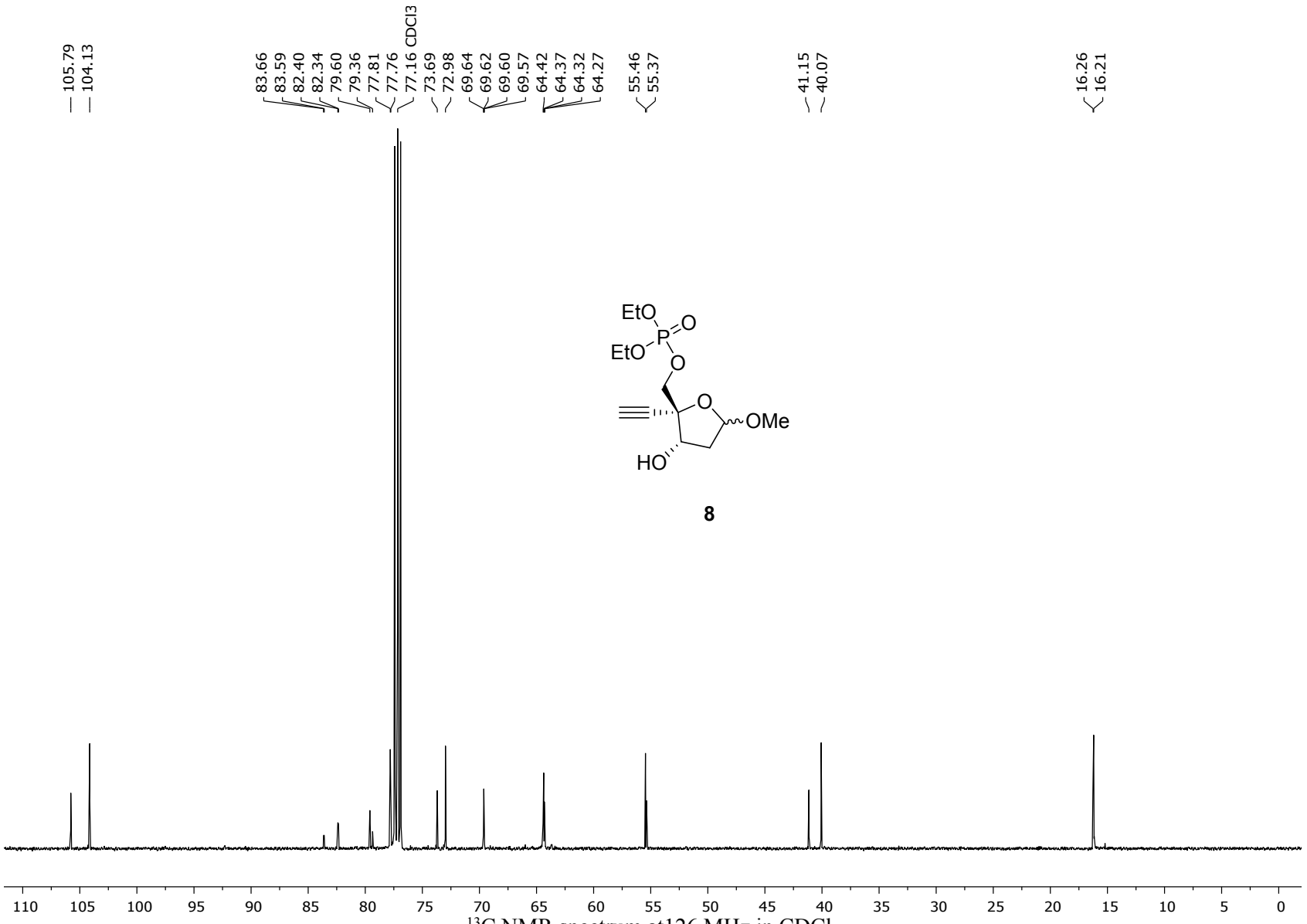


^{31}P NMR spectrum at 203 MHz in DMSO-d6

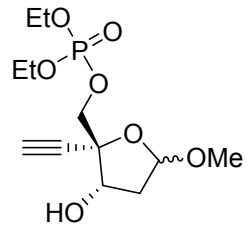


^{1}H NMR spectrum at 500 MHz in $CDCl_3$



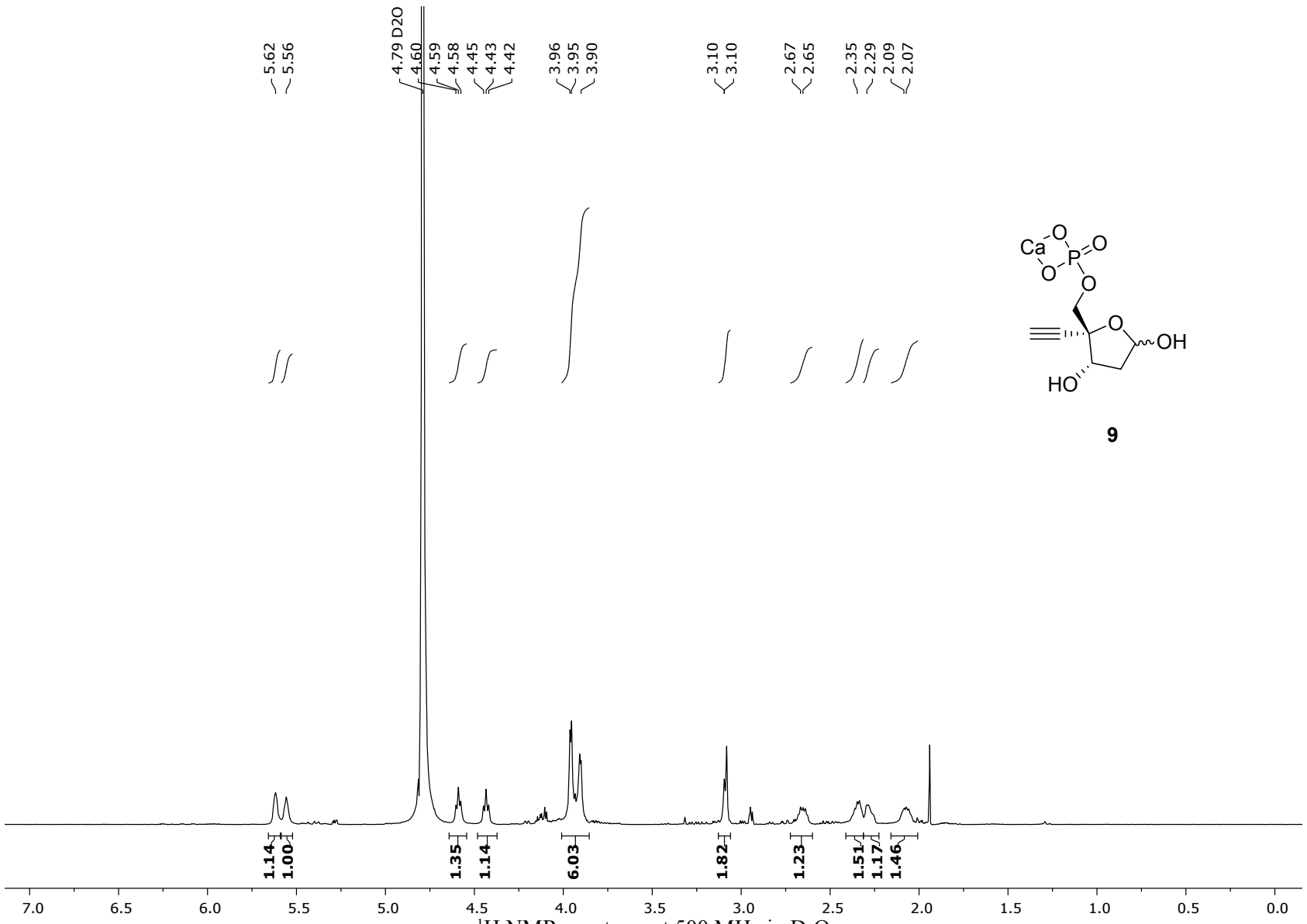
8

^{13}C NMR spectrum at126 MHz in $CDCl_3$



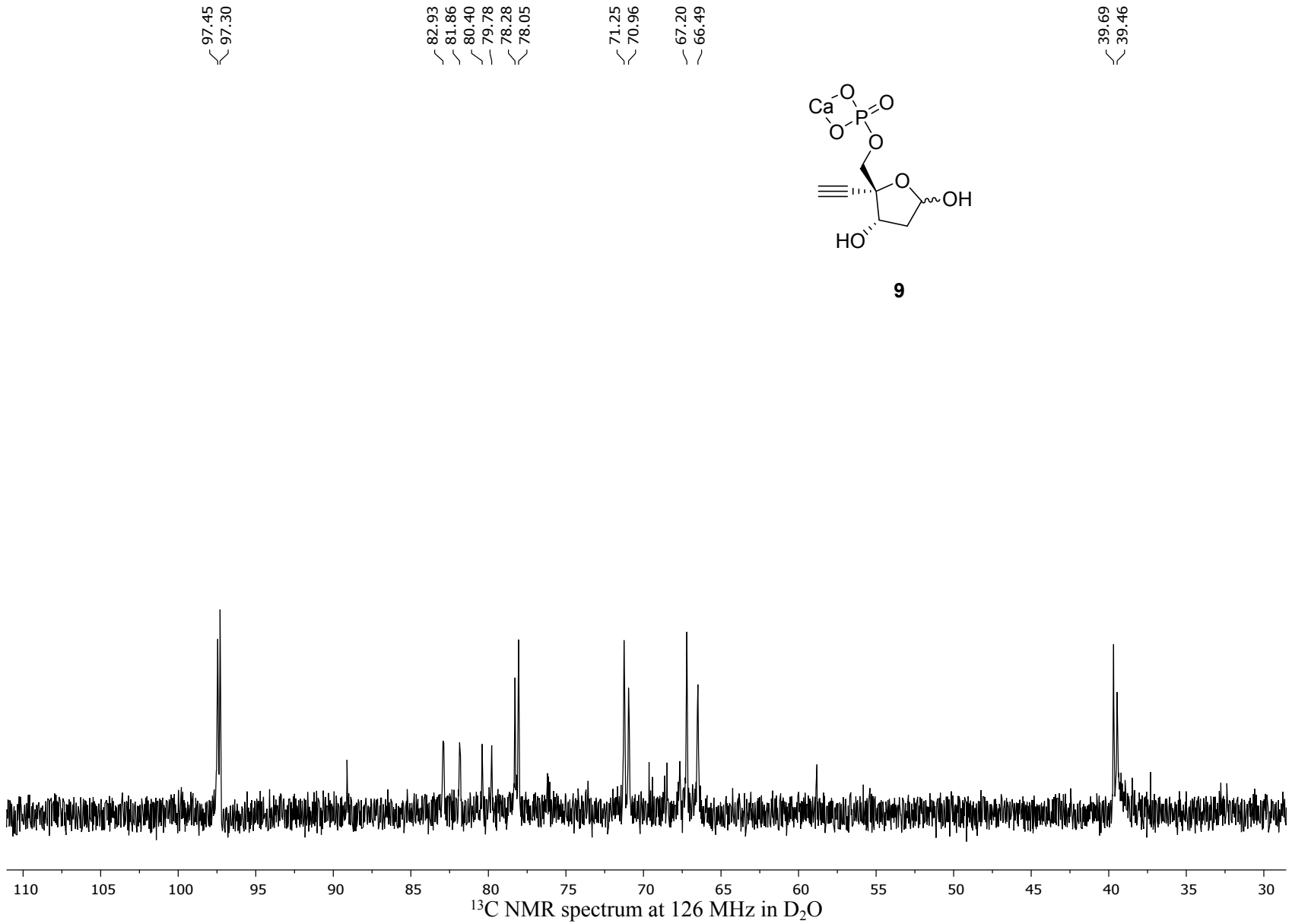
8

^{31}P NMR spectrum at 203 MHz in $CDCl_3$



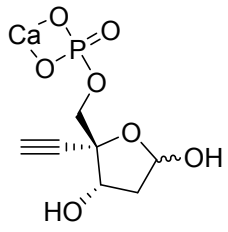
9

^{1}H NMR spectrum at 500 MHz in D_2O



9

^{13}C NMR spectrum at 126 MHz in D_2O



9

^{31}P NMR spectrum at 203 MHz in D_2O

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2. McLaughlin, M.; Kong, J.; Belyk, K. M.; Chen, B.; Gibson, A. W.; Keen, S. P.; Lieberman, D. R.; Milczek, E. M.; Moore, J. C.; Murray, D.; Peng, F.; Qi, J.; Reamer, R. A.; Song, Z. J.; Tan, L.; Wang, L.; Williams, M. J. *Org. Lett.* **2017**, *19*, 926−929.
3. Huffman, M. A.; Fryszkowska, A.; Alvizo, O; Borra-Garske, M.; Campos, K. R.; Canada, K. A.; Devine, P. N.; Duan, Da.; Forstater, J. H.; Grosser, S. T.; Halsey, H. M.; Hughes, G. J.; Jo, J.; Joyce, L. A.; Kolev, J. N.; Liang, J.; Maloney, K. M.; Mann, B. F.; Marshall, N. M.; McLaughlin, M.; Moore, J. C.; Murphy, G. S.; Nawrat, C. C.; Nazor, J.; Novick, S.; Patel, N. R.; Rodriguez-Granillo, A.; Robaire, S. A.; Sherer, E.; Truppo, M. D.; Whittaker, A. M.; Verma, D.; Xiao, L.; Xu, Y.; Yang, H. *Science* **2019**, *366*, 1255–1259.