Spirocycles as Rigidified sp^3-Rich Scaffolds for a Fragment Collection

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Supporting Information

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General Remarks

All reactions were carried out under argon or nitrogen atmosphere using oven-dried glassware at room temperature unless otherwise stated. Temperatures of -78 °C were maintained using a dry ice acetone

bath. Temperatures of 0 °C were maintained using an ice-water bath. Room temperature (rt) refers to ambient temperatures. All reagents were used as received from commercial sources or prepared as described in the literature unless otherwise stated. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2), methanol (MeOH) and toluene were distilled from calcium hydride. Tetrahydrofuran (THF) was dried using sodium wire and distilled from a mixture of calcium hydride and lithium aluminium hydride with triphenylmethane as indicator. Diethyl ether (Et_2O) was distilled from a mixture of calcium hydride and lithium aluminium hydride. Ethyl acetate (EtOAc) was distilled before use; petroleum ether (PE) was distilled before use and refers to the fraction between 40-60 °C. Anhydrous dimethylformamide (DMF), 1,2-dichloroethane (DCE), *tert*-butyl alcohol (*t*BuOH) and pentane were purchased from commercial sources and used without further purification. Reactions were monitored by thin layer chromatography (TLC) using pre-coated Merck glass backed silica gel 60 F_{254} plates and visualised by quenching of UV fluorescence (λ_{Max} = 254 nm) or by staining with potassium permanganate. Retention factors (R_f) are quoted to 0.01. Flash column chromatography was carried out using Merck 9385 Kieselgel 60 SiO_2 (230-400 mesh) under a positive pressure of dry nitrogen. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Melting points (mp) were obtained using a Büchi Melting Point B-545 or Gallenkamp MPD350. BM2. 5 melting point apparatus and are uncorrected. Optical rotations were measured on an Anton Paar MCP 100 Modular Compact Polarimeter. Infrared (IR) spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer using an ATR sampling accessory either as solids or liquid films. Selected absorptions (ν_{Max}) are reported in wavenumbers (cm^{-1}) with the following abbreviations: w, weak; m, medium; s, strong; br, broad. Proton magnetic resonance spectra were recorded using an internal deuterium lock at ambient temperatures on Bruker Avance III HD (400 MHz; Smart probe), Bruker Avance III (400 MHz; QNP Cryoprobe) or Bruker Avance III (500 MHz, DUL Cryoprobe) spectrometers. Chemical shifts (δ) are quoted in ppm to the nearest 0.01 ppm and are referenced to the residual non-deuterated solvent peak ($CDCl_3$: 7.26, DMSO-d_6: 2.50). Discernable coupling constants (*J*) are reported as measured values in Hertz, rounded to the nearest 0.1 Hz. Carbon magnetic resonance spectra were recorded using an internal deuterium lock at ambient temperatures on Bruker Avance III HD (101 MHz), Bruker Avance III (101 MHz) or Bruker Avance 500 (126 MHz) spectrometers with broadband proton decoupling. Chemical shifts (δ) are quoted in ppm to the nearest 0.1 ppm and are referenced to the deuterated solvent peak ($CDCl_3$: 77.16, DMSO-d_6: 39.52). Multiplicity is only reported when coupling to ^{19}F nuclei is observed with the appropriate coupling constant in Hz. Fluorine magnetic resonance spectra were recorded using an internal deuterium lock at ambient temperatures on Bruker Avance Neo Prodigy (376 MHz, Cryoprobe) spectrometer. Chemical shifts (δ) are quoted in ppm to the nearest 0.1 ppm. Data are reported as: chemical shift, number of nuclei, multiplicity and coupling constants. High resolution mass spectrometry (HRMS) measurements

were recorded with a Micromass Q-TOF, Waters Vion IMS Qtof or a Waters LCT Premier TOF mass spectrometer using Electrospray ionisation (ESI) techniques. Mass values are reported within the ±5 ppm error limit.

(*R*)-3-(but-3-en-1-yl)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (**(*R*)-15**) was prepared as described in the literature; analytical data were in agreement with those reported.[1]

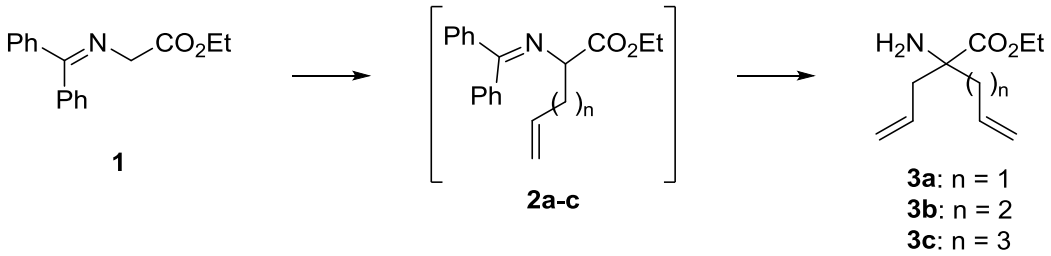
Ethyl benzimidate hydrochloride was prepared as described in the literature; analytical data were in agreement with those reported.[2]

(1) Fustero, S.; Mateu, N.; Albert, L.; Aceña, J. L. *J. Org. Chem.* **2009**, *74*, 4429–4433.

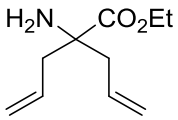
(2) Berger, O.; Wein, S.; Duckert, J.-F.; Maynadier, M.; Fangour, S. El; Escale, R.; Durand, T.; Vial, H.; Vo-Hoang, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5815–5817.

Procedures and Analytical Data

Building block synthesis

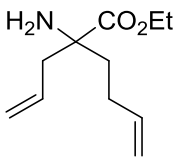


Ethyl 2-allyl-2-aminopent-4-enoate (3a)



To a solution of **1** (500 mg, 1.87 mmol) in THF (20 mL) at 0 °C was added *t*BuOK (629 mg, 5.61 mmol) and the reaction stirred for 10 min, followed by the dropwise addition of allyl bromide (970 µL, 11.2 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. Upon completion, HCl (3 M aq, 10 mL) was added and the reaction stirred for 10 min before diluting with H_2O (20 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL). The aqueous phase was basified with Na_2CO_3 (pH ≈ 12). The basic aqueous layer was then extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product **3a** (229 mg, 67%) as a colourless oil. The crude product **3a** was taken on to the next step without further purification. R_f = 0.41 (EtOAc). IR (ATR) $\nu_{Max.}$ 3379 (w), 3078 (w), 2980 (w), 1729 (s), 1640 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 – 5.64 (2H, m), 5.16 – 5.10 (4H, m), 4.17 (2H, q, *J* = 7.1 Hz), 2.55 (2H, br dd, *J* = 13.5, 6.5 Hz), 2.26 (2H, br dd, *J* = 13.5, 8.3 Hz), 1.67 (2H, br s), 1.27 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 132.7, 119.6, 61.2, 60.4, 44.2, 14.5. HRMS (ESI) calcd for $[C_{10}H_{17}NO_2Na]^+$: 206.1151, found 206.1147.

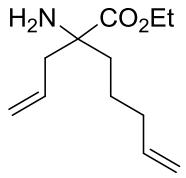
Ethyl 2-allyl-2-aminohex-5-enoate (3b)



To a solution of **1** (10.35 g, 38.7 mmol) in THF (250 mL) was added *t*BuOK (10.9 g, 96.7 mmol) and 4-bromo-1-butene (11.8 mL, 116 mmol) in three batches over a period of 64 h. Upon completion, the reaction was cooled to 0 °C, *t*BuOK (6.52 g, 58.1 mmol) was added and stirred for 10 min, followed by the dropwise addition of allyl bromide (5.03 mL, 58.1 mmol). The reaction mixture was warmed to rt and stirred for 5 h.

A further amount of *t*BuOK (2.17 g, 19.3 mmol) and allyl bromide (1.68 mL, 19.3 mmol) were added and the mixture stirred for 1 h. Upon completion HCl (3 M aq, 50 mL) was added and the reaction stirred for 10 min before removing the organic solvent *in vacuo*. The aqueous residue was washed with Et_2O (3 x 50 mL). The aqueous phase was basified with Na_2CO_3 (pH ≈ 12). The basic aqueous layer was then extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product **3b** (4.67 g, 61%) as a pale orange oil. The crude product **3b** was taken on to the following steps without further purification. R_f = 0.10 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3374 (w), 3077 (w), 2979 (w), 2925 (w), 1726 (s), 1640 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.61 (2H, m), 5.15 – 5.09 (2H, m), 5.00 (1H, dq, *J* = 17.0, 1.6 Hz), 4.93 (1H, dq, *J* = 10.1, 1.6 Hz), 4.16 (2H, q, *J* = 7.1 Hz), 2.55 (1H, br dd, *J* = 13.5, 6.4 Hz), 2.24 (1H, br dd, *J* = 13.5, 8.5 Hz), 2.17 – 2.06 (1H, m), 1.99 – 1.88 (1H, m), 1.88 – 1.80 (1H, m), 1.67 – 1.58 (3H, m), 1.27 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 138.0, 132.8, 119.6, 115.0, 61.1, 60.5, 44.5, 39.2, 28.5, 14.4. HRMS (ESI) calcd for $[C_{11}H_{19}NO_2Na]^+$: 220.1313, found 220.1309.

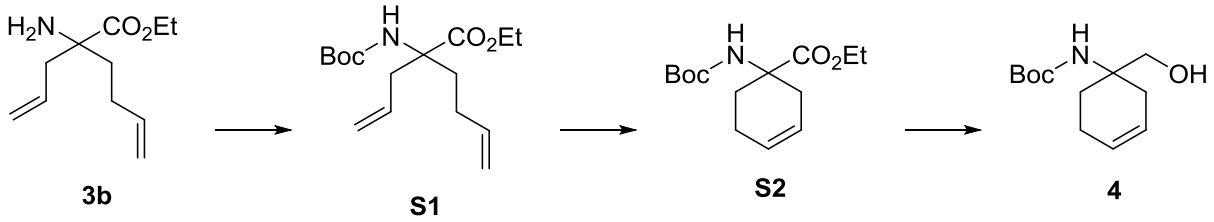
Ethyl 2-allyl-2-aminohept-6-enoate (3c)



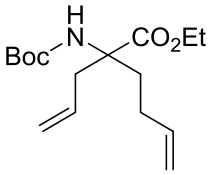
To a solution of **1** (1.00 g, 3.74 mmol) in THF (40 mL) at 0 °C was added *t*BuOK (629 mg, 5.61 mmol) and the reaction stirred for 10 min, followed by the dropwise addition of 5-bromo-1-pentene (1.33 mL, 11.2 mmol). The reaction mixture was warmed to rt and stirred overnight. Upon completion, the reaction was diluted with NH_4Cl (sat. aq, 50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/EtOAc, 9:1) to give crude **2c** (825 mg) as a colourless oil. To a solution of crude **2c** (550 mg) in THF (20 mL) at 0 °C was added *t*BuOK (276 mg, 2.46 mmol) and the reaction stirred for 10 min, followed by the dropwise addition of allyl bromide (426 µL, 4.92 mmol). The reaction mixture was warmed to rt and stirred overnight. Upon completion, the reaction was diluted with NH_4Cl (sat. aq, 25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/Et_2O, 9:1) to give a crude intermediate (343 mg) as a colourless oil. To a solution of the crude intermediate (300 mg) in THF (8.0 mL) was added HCl (3 M aq, 1.0 mL) and the reaction stirred for 10 min before diluting with H_2O (25 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL). The aqueous phase was basified with Na_2CO_3 (pH ≈ 12). The basic aqueous layer was then extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried over $MgSO_4$, filtered

and concentrated *in vacuo* to yield the crude product **3c** (144 mg, 31%) as a colourless oil. The crude product **3c** was taken on to the next step without further purification. R_f = 0.10 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3376 (w), 2981 (w), 2932 (w), 1728 (s), 1640 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 – 5.60 (2H, m), 5.14 – 5.07 (2H, m), 5.00 – 4.90 (2H, m), 4.15 (2H, q, *J* = 7.2 Hz), 2.53 (1H, br dd, *J* = 13.5, 6.5 Hz), 2.21 (1H, br dd, *J* = 13.5, 8.4 Hz), 2.01 (1H, brq, *J* = 7.2 Hz), 1.78 – 1.38 (5H, m), 1.28 – 1.15 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 138.3, 132.9, 119.5, 114.9, 61.1, 60.6, 44.4, 39.6, 33.9, 23.3, 14.4. HRMS (ESI) calcd for $[C_{12}H_{22}NO_2]^+$: 212.1644, found 212.1642.

Synthesis of the cyclohexene intermediate 4

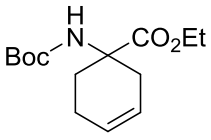


Ethyl 2-allyl-2-((*tert*-butoxycarbonyl)amino)hex-5-enoate (S1)



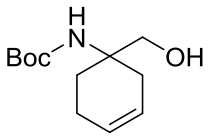
To a solution of **3b** (1.00 g, 5.07 mmol) in THF (35 mL) was added Boc_2O (1.66 g, 7.60 mmol) and the reaction heated to 50 °C in a sealed tube overnight. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, CH_2Cl_2) to yield **S1** (1.28 g, 85%) as a transparent viscous oil. R_f = 0.37 (PE/EtOAc, 9:1). IR (ATR) $\nu_{Max.}$ 3426 (w, br), 3080 (w), 2979 (w), 1714 (s), 1641 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 – 5.67 (1H, m), 5.67 – 5.53 (1H, m), 5.49 (1H, br s), 5.08 – 5.01 (2H, m), 4.96 (1H, dq, *J* = 17.1, 1.5 Hz), 4.91 (1H, d, *J* = 10.1 Hz), 4.18 (2H, q, *J* = 7.1 Hz), 3.04 (1H, br s), 2.46 (1H, dd, *J* = 13.9, 7.4 Hz), 2.42 – 2.28 (1H, m), 2.11 – 1.96 (1H, m), 1.90 – 1.72 (2H, m), 1.41 (9H, s), 1.26 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 153.9, 137.7, 132.6, 118.9, 115.1, 79.2, 63.3, 61.8, 40.0, 34.6, 28.6, 28.5, 14.4. HRMS (ESI) calcd for $[C_{16}H_{27}NO_4Na]^+$: 320.1832, found 320.1822.

Ethyl 1-((*tert*-butoxycarbonyl)amino)cyclohex-3-ene-1-carboxylate (S2)



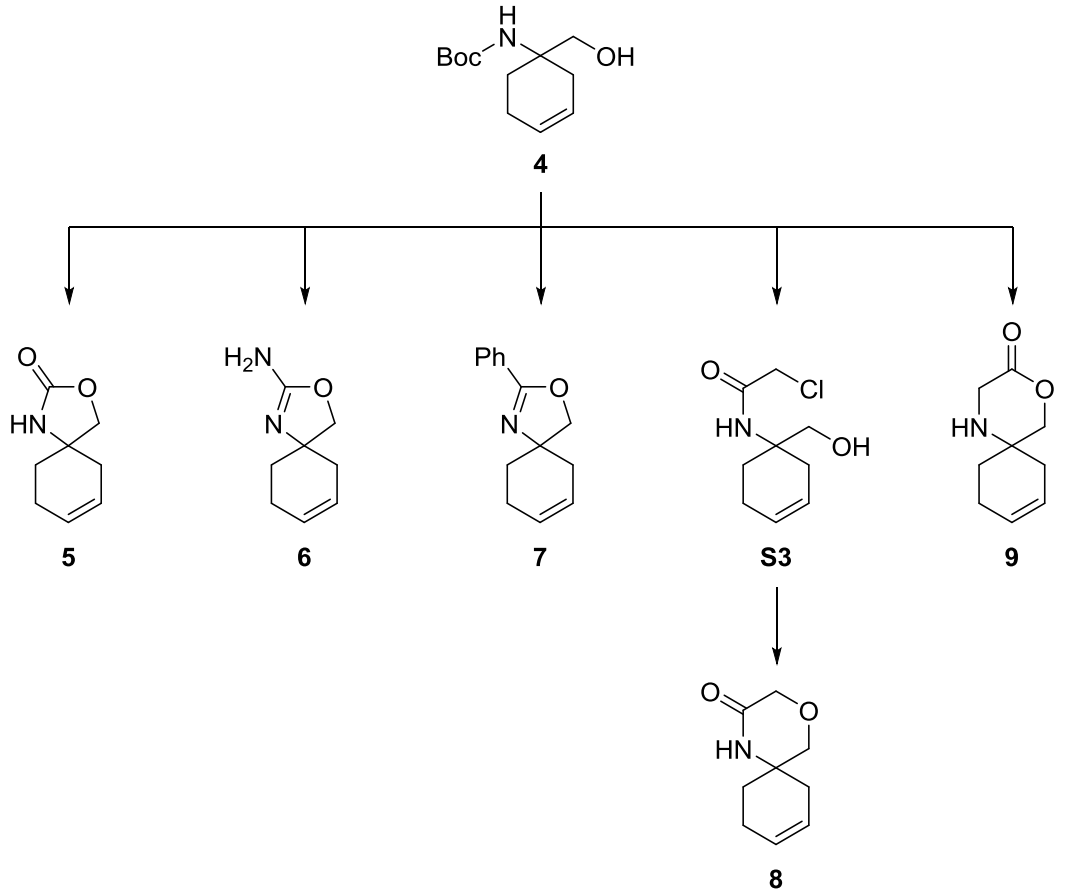
A solution of crude **S1** (6.25 g, 21.0 mmol) in CH_2Cl_2 (300 mL) was degassed with argon, followed by the addition of Grubbs II catalyst (18 mg, 21 µmol). The reaction was heated under reflux for 1 h followed by the addition of another portion of Grubbs II catalyst (18 mg, 21 µmol) and the reaction was heated under reflux for further 1 h before being concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/EtOAc, 9:1) to yield **S2** (3.86 g, 69%) as a transparent viscous oil. R_f = 0.12 (PE/EtOAc, 9:1). IR (ATR) $\nu_{Max.}$ 3368 (m, br), 2977 (w), 1706 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 – 5.70 (1H, m), 5.61 – 5.55 (1H, m), 4.78 (1H, br s), 4.26 – 4.13 (2H, m), 2.62 – 2.53 (1H, m), 2.29 – 2.01 (4H, m), 1.95 – 1.86 (1H, m), 1.43 (9H, s), 1.26 (3H, t, J = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 155.0, 127.2, 122.6, 79.9, 61.2, 57.0, 34.2, 28.4, 27.7, 21.9, 14.3. HRMS (ESI) calcd for $[C_{14}H_{24}NO_4]^+$: 270.1705, found 270.1718.

***tert*-Butyl (1-(hydroxymethyl)cyclohex-3-en-1-yl)carbamate (4)**

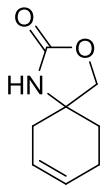


To a solution of **S2** (3.86 g, 14.4 mmol) in THF (150 mL) was added $LiBH_4$ (2 M in THF, 14.4 mL, 28.8 mmol), and the reaction stirred overnight. The reaction mixture was diluted with NH_4Cl (sat. aq, 150 mL), stirred for 10 min and then extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq, 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product **4** (3.28 g, 100%) as a white amorphous solid. The crude product **4** was taken on to the following steps without further purification. R_f = 0.26 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3265 (m, br), 3076 (w), 3020 (w), 2968 (w), 2933 (w), 1676 (s). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.59 (1H, br d, J = 10.0 Hz), 5.50 (1H, br d, J = 10.0 Hz), 4.62 (1H, t, J = 5.6 Hz), 4.41 (1H, br s), 3.45 – 3.36 (2H, m), 2.27 – 1.86 (5H, m), 1.57 – 1.47 (1H, m), 1.36 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 127.6, 123.3, 80.1, 69.3, 55.1, 34.1, 28.5, 27.4, 22.2. HRMS (ESI) calcd for $[C_{12}H_{22}NO_3]^+$: 228.1600, found 228.1595.

Synthesis of different core heterocycles

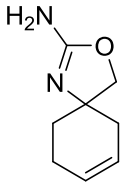


3-Oxa-1-azaspiro[4.5]dec-7-ene-2-one (5)



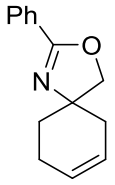
To a solution of crude **4** (3.28 g, 14.4 mmol) in THF (150 mL) was added *t*BuOK (1.62g, 14.4 mmol) and the reaction stirred for 1 h. The reaction mixture was diluted with $NaHCO_3$ (sat. aq, 150 mL), stirred for 10 min and then extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude **5** (2.05 g, 93% yield) as a white amorphous solid. The crude product was further purified by recrystallization from Et_2O/pentane 1:1 to yield pure **5** (718 mg, 33%) as a white crystalline solid. R_f = 0.21 (PE/EtOAc, 1:1). Mp 84 – 85 °C (Et_2O/Pentane). IR (ATR) $\nu_{Max.}$ 3235 (m, br), 3039 (w), 2922 (w), 2904 (w), 2845 (w), 1731 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 – 5.70 (1H, m), 5.66 – 5.59 (1H, m), 5.46 (1H, br s), 4.14 (1H, d, *J* = 8.5 Hz), 4.11 (1H, d, *J* = 8.5 Hz), 2.34 – 2.15 (4H, m), 1.90 – 1.82 (1H, m), 1.80 – 1.72 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 127.1, 123.6, 75.6, 56.2, 36.9, 32.3, 22.7. HRMS (ESI) calcd for $[C_8H_{11}NO_2Na]^+$: 176.0682, found 176.0676.

3-Oxa-1-azaspiro[4.5]deca-1,7-dien-2-amine (6)



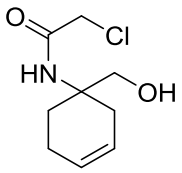
Compound **4** (313 mg, 1.38 mmol) was dissolved in HCl (4 M in dioxane, 10 mL) and stirred at rt for 1 h, then concentrated *in vacuo*. The residue was dissolved in H_2O (10 mL) and basified with Na_2CO_3 (pH ≈ 12). The basic aqueous was then extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of the residue in EtOH (5 mL) was added BrCN (175 mg, 1.65 mmol) and heated under reflux overnight. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), washed with NaOH (1 M aq, 10 mL) and the aqueous extracted with CH_2Cl_2 (10 mL). The combined organic layers were concentrated *in vacuo* to yield the crude product **6** (122 mg, 58%) as an off-white amorphous solid. The crude product was crystallised from CH_2Cl_2 for the single crystal X-ray crystallography analysis. Mp 198 – 199 °C (CH_2Cl_2). IR (ATR) $\nu_{Max.}$ 3437 (m, br), 2903 (w), 1666 (s), 1650 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 – 5.66 (1H, m), 5.66 – 5.59 (1H, m), 4.17 (2H, br s), 4.01 (1H, d, *J* = 7.9 Hz), 3.97 (1H, d, *J* = 7.9 Hz), 2.34 – 2.19 (2H, m), 2.14 – 2.02 (2H, m), 1.85 – 1.76 (1H, m), 1.69 – 1.61 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 127.1, 124.8, 78.8, 66.7, 38.0, 33.6, 23.3. HRMS (ESI) calcd for $[C_8H_{13}N_2O]^+$: 153.1028, found 153.1025.

2-Phenyl-3-oxa-1-azaspiro[4.5]deca-1,7-diene (7)



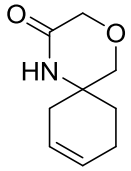
Compound **4** (70.3 mg, 0.31 mmol) was dissolved in HCl (4 M in dioxane, 10 mL) and stirred at rt for 1 h, then concentrated *in vacuo*. A solution of the residue and ethyl benzimidate hydrochloride (41.4 mg, 0.28 mmol) in DCE (1.0 mL) was heated under reflux overnight. The reaction was cooled to rt, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/EtOAc, 7:3) to yield **7** (34.0 mg, 57%) as a white amorphous solid. R_f = 0.44 (PE/EtOAc, 7:3). IR (ATR) $\nu_{Max.}$ 2905 (w), 1648 (s), 1581 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.92 (2H, m), 7.48 – 7.44 (1H, m), 7.41 – 7.37 (2H, m), 5.77 – 5.73 (1H, m), 5.69 – 5.63 (1H, m), 4.16 (1H, d, *J* = 8.5 Hz), 4.11 (1H, d, *J* = 8.5 Hz), 2.48 – 2.43 (1H, m), 2.36 – 2.29 (1H, m), 2.17 – 2.08 (2H, m), 2.05 – 1.98 (1H, m), 1.75 – 1.69 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 131.4, 128.4, 128.4, 128.2, 127.3, 124.5, 77.8, 69.5, 37.4, 33.1, 23.0. HRMS (ESI) calcd for $[C_{14}H_{16}NO]^+$: 214.1226, found 214.1222.

2-Chloro-N-(1-(hydroxymethyl)cyclohex-3-en-1-yl)acetamide (S3)



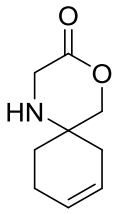
To a solution of **4** (1.19 g, 5.24 mmol) in THF (50 mL) was added HCl (3 M aq, 17.5 mL) and heated under reflux for 3 h, then concentrated *in vauco*. To a solution of the residue in CH_2Cl_2 (50 mL) was added Et_3N (2.2 mL, 15.7 mmol) followed by the dropwise addition of chloroacetyl chloride (0.42 mL, 5.24 mmol) at 0 °C. The reaction mixture was stirred for 90 min, then diluted with NH_4Cl (sat. aq, 25 mL) and stirred for further 10 min. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/Et_2O, 9:1) to yield **S3** (261 mg, 24%) as a white amorphous solid. R_f = 0.14 (CH_2Cl_2/Et_2O, 9:1). IR (ATR) $\nu_{Max.}$ 3352 (m, br), 3271 (m), 3070 (w), 2938 (w), 1654 (s), 1549 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (1H, br s), 5.81 – 5.76 (1H, m), 5.64 – 5.59 (1H, m), 4.30 (1H, t, *J* = 6.5 Hz), 4.04 (2H, s), 3.75 (2H, d, *J* = 6.5 Hz), 2.25 – 2.16 (3H, m), 2.11 – 2.02 (2H, m), 1.80 – 1.72 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 127.6, 123.0, 68.5, 57.6, 43.1, 33.6, 27.4, 22.0. HRMS (ESI) calcd for $[C_9H_{15}NO_2{}^{35}Cl]^+$: 204.0786, found 204.0776.

4-Oxa-1-azaspiro[5.5]undec-8-en-2-one (8)



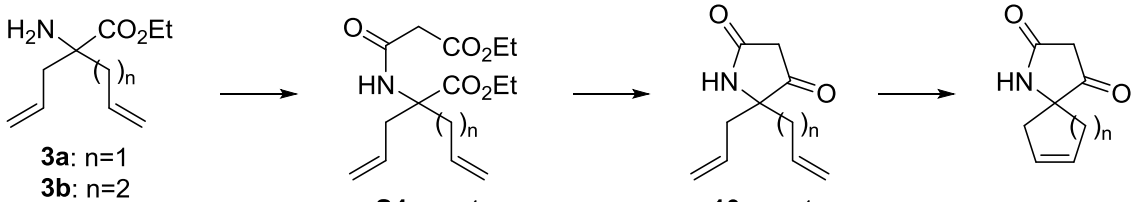
To a solution of **S3** (260 mg, 1.28 mmol) in *t*BuOH (25 mL) at 30 °C was added *t*BuOK (158 mg, 1.40 mmol) and stirred for 5 h. The reaction mixture was diluted with NH_4Cl (sat. aq, 20 mL) and stirred for 10 min, then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product **8** (212 mg, 99%) as an off-white amorphous solid. R_f = 0.12 (PE/EtOAc, 1:1). IR (ATR) $\nu_{Max.}$ 3165 (m, br), 3072 (w), 2920 (w), 1664 (s), 1641 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 – 5.70 (1H, m), 5.64 – 5.57 (1H, m), 4.20 (1H, d, *J* = 11.1 Hz), 4.14 (1H, d, *J* = 11.1 Hz), 3.69 (2H, s), 2.21 – 1.95 (4H, m), 1.82 – 1.74 (1H, m), 1.69 – 1.61 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 126.8, 123.4, 76.3, 48.3, 44.1, 33.3, 28.6, 22.1. HRMS (ESI) calcd for $[C_9H_{13}NO_2Na]^+$: 190.0839, found 190.0833.

4-Oxa-1-azaspiro[5.5]undec-8-en-3-one (9)

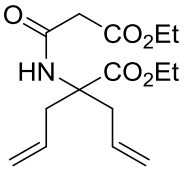


Compound **4** (891 mg, 3.93 mmol) was dissolved in HCl (4 M in dioxane, 10 mL) and stirred at rt for 1 h, then concentrated *in vacuo*. The residue was dissolved in H_2O (10 mL) and basified with Na_2CO_3 (pH ≈ 12). The basic aqueous was then extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of the residue in MeCN (26 mL) was added phenyl bromoacetate (930 mg, 4.32 mmol) and DIPEA (1.70 mL, 9.83 mmol) and stirred at rt for 4 h, then concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to yield **9** (282 mg, 43%) as a white amorphous solid. R_f = 0.21 (EtOAc).IR (ATR) $\nu_{Max.}$ 3317 (w), 2921 (w), 1730 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 – 5.70 (1H, m), 5.62 – 5.57 (1H, m), 4.20 (1H, d, *J* = 11.0 Hz), 4.13 (1H, d, *J* = 11.0 Hz), 3.68 (2H, s), 2.17 – 1.97 (5H, m), 1.80 – 1.74 (1H, m), 1.67 – 1.61 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 126.7, 123.3, 76.2, 48.2, 44.0, 33.2, 28.6, 22.0. HRMS (ESI) calcd for $[C_9H_{14}NO_2]^+$: 168.1019, found 168.1017.

Synthesis of different carbocycles



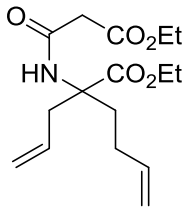
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)pent-4-enoate (S4a)



To a solution of **3a** (200 mg, 1.09 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (304 µL, 2.18 mmol) followed by ethyl malonyl chloride (210 µL, 1.64 mmol) at 0 °C and stirred for 20 min. The reaction mixture was diluted with NH_4Cl (sat. aq, 10 mL) and H_2O (5 mL) and stirred for 10 min then extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude

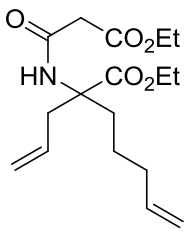
product was purified by flash column chromatography (silica gel, PE/EtOAc, 4:1) to yield **S4a** (264 mg, 81%) as a transparent viscous oil. R_f = 0.17 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3310 (w, br), 3074 (w), 2981 (w), 1733 (s), 1656 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, br s), 5.65 – 5.53 (2H, m), 5.09 – 5.02 (4H, m), 4.24 – 4.15 (4H, m), 3.26 (2H, s), 3.15 (2H, br dd, *J* = 13.9, 7.2 Hz), 2.52 (2H, br dd, *J* = 13.9, 7.4 Hz), 1.29 – 1.24 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 168.8, 164.0, 132.2, 119.1, 64.4, 62.0, 61.6, 42.6, 39.1, 14.3, 14.1. HRMS (ESI) calcd for $[C_{15}H_{24}NO_5]^+$: 298.1654, found 298.1644.

Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)hex-5-enoate (S4b)



To a solution of **3b** (1.0 g, 5.07 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (1.52 mL, 10.9 mmol), followed by the dropwise addition of ethyl malonyl chloride (1.04 mL, 8.11 mmol) and the reaction stirred for 30 min. The reaction mixture was diluted with NH_4Cl (sat. aq, 25 mL) and stirred for 10 min then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, PE/EtOAc, 4:1) to yield **S4b** (1.27 g, 81%) as a pale yellow viscous oil. R_f = 0.23 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3337 (w, br), 2980 (w), 1732 (s), 1681 (m), 1650 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, br s), 5.79 – 5.67 (1H, m), 5.65 – 5.51 (1H, m), 5.10 – 5.02 (2H, m), 5.02 – 4.94 (2H, m), 4.27 – 4.18 (4H, m), 3.29 (2H, s), 3.26 – 3.18 (1H, m), 2.61 – 2.47 (2H, m), 2.10 – 1.97 (1H, m), 1.92 – 1.74 (2H, m), 1.32 – 1.26 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 168.9, 163.9, 137.5, 132.3, 119.0, 115.3, 64.7, 62.1, 61.7, 42.8, 39.5, 34.1, 28.7, 14.3, 14.2. HRMS (ESI) calcd for $[C_{16}H_{26}NO_5]^+$: 312.1811, found 312.1820.

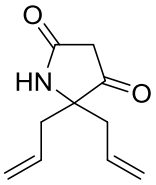
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)hept-6-enoate (S4c)



To a solution of **3c** (100 mg, 0.473 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added Et_3N (132 µL, 0.946 mmol) followed by ethyl malonyl chloride (91 µL, 0.710 mmol) and the reaction stirred for 20 min. The reaction mixture was diluted with NH_4Cl (sat. aq, 10 mL) and H_2O (5 mL) and stirred for 10 min then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in*

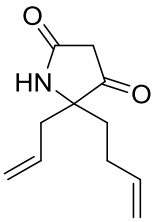
vacuo. The crude product was purified by flash column chromatography (silica gel, PE/EtOAc, 4:1) to yield **S4c** (113 mg, 73%) as a transparent viscous oil. R_f = 0.19 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3326 (w, br), 3081 (w), 2982 (w), 2939 (w), 1734 (s), 1682 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, br s), 5.78 – 5.66 (1H, m), 5.63 – 5.52 (1H, m), 5.07 – 5.00 (2H, m), 5.00 – 4.90 (2H, m), 4.26 – 4.16 (4H, m), 3.27 (2H, s), 3.18 (1H, br dd, *J* = 14.0, 7.2 Hz), 2.50 (1H, br dd, *J* = 14.0, 7.5 Hz), 2.41 (1H, br td, *J* = 13.0, 4.6 Hz), 2.08 – 1.92 (2H, m), 1.82 – 1.71 (1H, m), 1.44 – 1.32 (1H, m), 1.32 – 1.24 (6H, m), 1.14 – 1.01 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 169.0, 163.9, 138.3, 132.4, 119.0, 115.0, 64.9, 62.0, 61.7, 42.8, 39.4, 34.5, 33.5, 23.5, 14.4, 14.2. HRMS (ESI) calcd for $[C_{17}H_{27}NO_5Na]^+$: 348.1781, found 348.1770.

5,5-Diallylpyrrolidine-2,4-dione (10a)



To a solution of **S4a** (200 mg, 0.673 mmol) in THF (10 mL) was added *t*BuOK (113 mg, 1.01 mmol) and the reaction heated under reflux for 2 h. The reaction mixture was diluted with EtOAc (20 mL), HCl (3 M aq, 10 mL) and brine (20 mL) and stirred for 10 min. The organic layer was then separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in MeCN/H_2O (9:1, 10 mL) and heated under reflux for 1 h, then concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, PE/EtOAc, 1:1) to yield **10a** (104 mg, 86%) as a white amorphous solid. R_f = 0.13 (PE/EtOAc, 1:1). IR (ATR) $\nu_{Max.}$ 3212 (w, br), 2981 (w), 1768 (m), 1698 (s), 1640 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (H, br s), 5.77 – 5.64 (2H, m), 5.23 – 5.12 (4H, m), 2.89 (2H, s), 2.50 – 2.35 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 170.5, 130.5, 121.5, 71.5, 41.7, 41.3. HRMS (ESI) calcd for $[C_{10}H_{14}NO_2]^+$: 180.1025, found 180.1021.

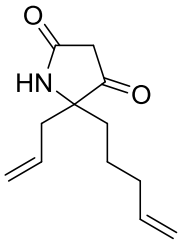
5-Allyl-5-(but-3-en-1-yl)pyrrolidine-2,4-dione (10b)



To a solution of **S4b** (2.03 g, 6.81 mmol) in THF (70 mL) was added *t*BuOK (1.15 g, 10.2 mmol) and the reaction heated under reflux for 1 h. Upon completion, the reaction was diluted with HCl (3 M aq, 50 mL) and heated under reflux for 30 min. The organic solvent was removed in vacuo and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and

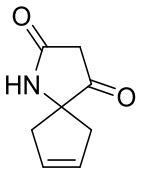
concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, PE/EtOAc, 1:1) to yield **10b** (1.24 g, 94%) as a white amorphous solid. R_f = 0.10 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3282 (w, br), 3081 (w), 2921 (w), 2848 (w), 1639 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.62 (1H, m), 5.74 – 5.62 (2H, m), 5.17 (1H, d, *J* = 10.4 Hz), 5.13 (1H, d, *J* = 17.4 Hz), 5.00 (1H, d, *J* = 17.4 Hz), 4.95 (1H, d, *J* = 10.4 Hz), 2.91 (1H, d *J* = 22.3 Hz), 2.88 (1H, d *J* = 22.3 Hz), 2.46 – 2.31 (2H, m), 2.22 – 2.11 (1H, m), 2.03 – 1.87 (2H, m), 1.77 – 1.67 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 171.6, 137.0, 130.5, 121.3, 116.1, 71.6, 42.8, 41.8, 35.8, 28.4. HRMS (ESI) calcd for $[C_{11}H_{16}NO_2]^+$: 194.1181, found 194.1184.

5-Allyl-5-(pent-4-en-1-yl)pyrrolidine-2,4-dione (10c)



To a solution of **S4c** (72 mg, 0.221 mmol) in THF (4.0 mL) was added *t*BuOK (37 mg, 0.332 mmol) and the reaction heated under reflux for 2 h. The reaction mixture was diluted with HCl (3 M aq, 4.0 mL) and brine (10 mL) and stirred for 10 min. The organic layer was then removed and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in MeCN/H_2O (9:1, 4.0 mL) and heated under reflux for 1 h, then concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, PE/EtOAc, 1:1) to yield **10c** (40 mg, 87%) as a transparent viscous oil. R_f = 0.22 (PE/EtOAc, 1:1). IR (ATR) $\nu_{Max.}$ 3196 (w, br), 2943 (w), 1641 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.58 (1H, m), 5.77 – 5.62 (2H, m), 5.19 – 5.09 (2H, m), 5.01 – 4.93 (2H, m), 2.91 (1H, d, *J* = 22.4 Hz), 2.89 (1H, d, *J* = 22.4 Hz), 2.46 – 2.31 (2H, m), 2.06 – 1.98 (2H, m), 1.82 – 1.72 (1H, m), 1.65 – 1.55 (1H, m), 1.55 – 1.43 (1H, m), 1.27 – 1.14 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 171.4, 137.6, 130.7, 121.2, 115.6, 71.9, 41.8, 41.7, 36.4, 33.6, 23.0. HRMS (ESI) calcd for $[C_{12}H_{17}NO_2Na]^+$: 230.1152, found 230.1146.

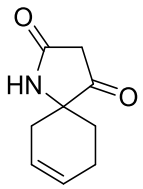
1-Azaspiro[4.4]non-7-ene-2,4-dione (11)



A solution of **10a** (95 mg, 0.530 mmol) in toluene (25 mL) was degassed with argon and heated to 70 °C, followed by the addition of Grubbs II catalyst (17 mg, 0.020 mmol) and the reaction stirred for 90 min, then concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2 then

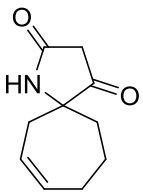
EtOAc) to yield **11** (55.0 mg, 69%) as a brown amorphous solid. R_f = 0.23 (EtOAc). Mp 154 – 155 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 3180 (w, br), 3083 (w), 2949 (w), 2846 (w), 1764, (s), 1702 (s), 1673 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, br s), 5.69 (2H, s), 3.08 (2H, s), 2.97 (2H, d, *J* = 15.9 Hz), 2.53 (2H, d, *J* = 15.9 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.1, 169.9, 127.6, 73.4, 45.5, 40.5. HRMS (ESI) calcd for $[C_8H_{10}NO_2]^+$: 152.0712, found 152.0710.

1-Azaspiro[4.5]dec-7-ene-2,4-dione (12)



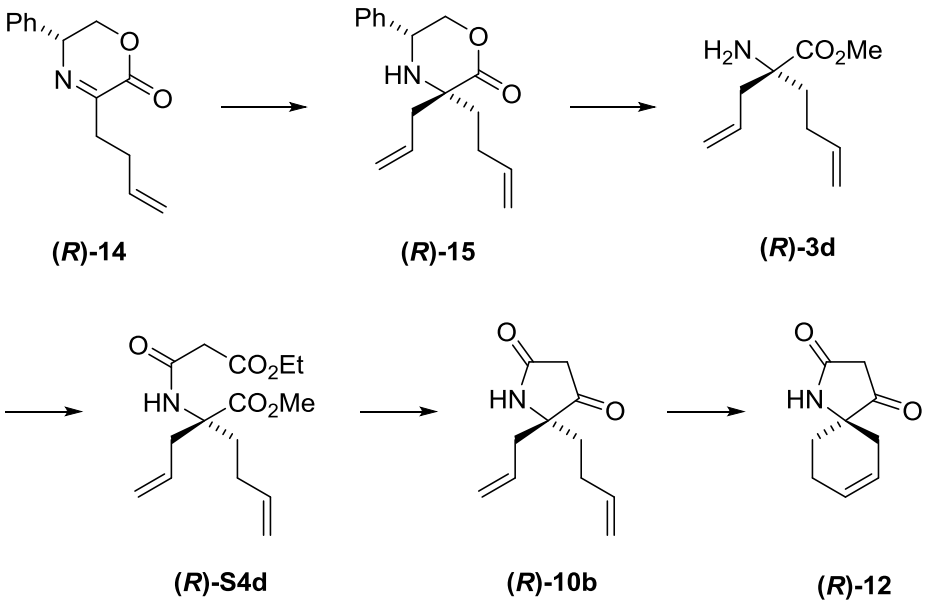
A solution of **10b** (1.12 g, 5.78 mmol) in CH_2Cl_2 (250 mL) was degassed with argon, followed by the addition of Grubbs II catalyst (49.1 mg, 0.058 mmol) and the reaction heated under reflux for 1 h, then concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2 then EtOAc) to yield **12** (950 mg, 99%) as a pale brown amorphous solid. R_f = 0.23 (EtOAc). IR (ATR) $\nu_{Max.}$ 3177 (w, br), 3033 (w), 2921 (w), 2845 (w), 1650 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, br s), 5.85 – 5.79 (1H, m), 5.72 – 5.66 (1H, m), 3.12 (1H, d, *J* = 22.1 Hz), 3.06 (1H, d, *J* = 22.1 Hz), 2.46 – 2.31 (2H, m), 2.22 – 2.11 (1H, m), 2.03 – 1.87 (2H, m), 1.77 – 1.67 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 170.7, 126.8, 123.1, 66.3, 40.3, 33.5, 29.4, 21.4. HRMS (ESI) calcd for $[C_9H_{12}NO_2]^+$: 166.0868, found 166.0869.

1-Azaspiro[4.6]undec-7-ene-2,4-dione (13)

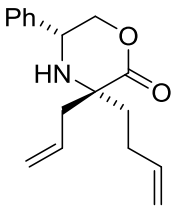


A solution of **10c** (38 mg, 0.183 mmol) in CH_2Cl_2 (10 mL) was degassed with argon, followed by the addition of Grubbs II catalyst (15 mg, 0.018 mmol) and the reaction heated under reflux for 30 min, then concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2 then PE/EtOAc, 1:1) to yield **13** (25.5 mg, 78%) as a pale brown amorphous solid. R_f = 0.15 (PE/EtOAc, 1:1). IR (ATR) $\nu_{Max.}$ 3199 (w, br), 2929 (w), 2836 (w), 1630 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, br s), 6.11 – 6.03 (1H, m), 5.67 – 5.58 (1H, m), 3.08 (2H, s), 2.66 – 2.59 (1H, m), 2.35 – 2.25 (1H, m), 2.22 – 2.11 (2H, m), 2.06 – 1.95 (1H, m), 1.95 – 1.85 (1H, m), 1.85 – 1.74 (1H, m), 1.41 – 1.29 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 169.5, 136.2, 125.2, 67.4, 39.7, 39.0, 34.5, 28.1, 20.7. HRMS (ESI) calcd for $[C_{10}H_{13}NO_2Na]^+$: 202.0839, found 202.0832.

Enantioselective synthesis of 12

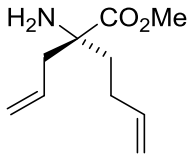


(3*R*,5*R*)-3-Allyl-3-(but-3-en-1-yl)-5-phenylmorpholine-2-one ((*R*)-15)



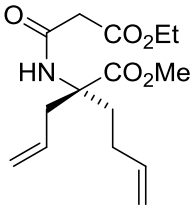
To a solution of **(*R*)-14** (1.45 g, 6.32 mmol) in DMF (50 mL) at 0 °C was added activated zinc powder (620 mg, 9.48 mmol), followed by the dropwise addition of allyl bromide (820 µL, 9.48 mmol). The reaction was stirred at 0 °C for further 1 h. Upon completion, the reaction was diluted with NH_4Cl (sat. aq, 100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were concentrated *in vacuo*, the residue was redissolved in EtOAc (10 mL) and washed with LiCl (10% aq, 3 x 10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, PE/EtOAc, 9:1) to yield **(*R*)-15** (1.20 g, 70%) as a transparent viscous oil. R_f = 0.24 (PE/EtOAc, 9:1). IR (ATR) $\nu_{Max.}$ 3326 (w), 3076 (w), 2978 (w), 2927 (w), 2849 (w), 1731 (s), 1639 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.31 (5H, m), 5.91 – 5.77 (2H, m), 5.21 (1H, dd, *J* = 10.2, 1.8 Hz), 5.15 (1H, ddt, *J* = 17.1, 1.8, 1.2 Hz), 5.09 (1H, ddt, *J* = 17.1, 1.8, 1.2 Hz), 5.00 (1H, ddt, *J* = 10.2, 1.8, 1.2 Hz), 4.36 (1H, dd, *J* = 8.4, 5.5 Hz), 4.28 – 4.20 (2H, m), 2.85 (1H, br dd, *J* = 13.7, 8.1 Hz), 2.61 – 2.45 (2H, m), 2.21 – 2.01 (2H, m), 1.83 (1H, br s), 1.57 (1H, ddd, *J* = 13.3, 11.3, 4.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 138.3, 138.1, 132.1, 129.0, 128.8, 127.3, 120.9, 115.1, 75.0, 63.3, 53.2, 43.5, 39.5 (12), 29.0. HRMS (ESI) calcd for $[C_{17}H_{22}NO_2]^+$: 272.1645, found 272.1643. $[\alpha]_D^{20}$ +12.5° (c = 0.600, $CHCl_3$).

Methyl (*R*)-2-allyl-2-aminohex-5-enoate ((*R*)-3d)



To a solution of **(*R*)-15** (1.10 g, 4.05 mmol) in MeOH (40 mL) was added thionyl chloride (588 µL, 9.60 mmol) and the reaction stirred for 2 h at rt, then concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and $NaHCO_3$ (sat. aq, 50 mL) and stirred for 20 min. The layers were separated and the aqueous extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude intermediate. To a solution of the crude intermediate in CH_2Cl_2/MeOH (2:1, 45 mL) at 0 °C was added $Pb(OAc)_4$ (2.51 g, 5.67 mmol) and the reaction stirred for 1 h. The reaction was diluted with HCl (2 M aq, 80 mL), warmed to rt and stirred for 2 h. The reaction mixture was filtered through a pad of Celite before separating the layers, the aqueous was further extracted with EtOAc (3 x 50 mL) and the organic layers were discarded. The aqueous phase was basified with Na_2CO_3 (until pH ≈ 12 obtained). The basic aqueous layer was then extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product **(*R*)-3d** (680 mg, 92%) as a transparent oil. The crude product **(*R*)-3d** was taken on to the next step without further purification. R_f = 0.09 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 3336 (w), 2928 (w), 2855 (w), 1731 (s), 1639 (m), 1589 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.62 (2H, m), 5.18 – 5.11 (2H, m), 5.04 – 4.98 (1H, m), 4.96 – 4.91 (1H, m), 3.71 (3H, s), 2.57 (1H, br dd, *J* = 13.6, 6.6 Hz), 2.35 (1H, br dd, *J* = 13.6, 8.3 Hz), 2.27 – 1.67 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 137.6, 132.1, 120.2, 115.3, 61.3, 52.4, 43.7, 38.4, 28.3. HRMS (ESI) calcd for $[C_{10}H_{18}NO_2]^+$: 184.1338, found 184.1335. $[\alpha]_D^{20}$ +27.0° (c = 0.300, $CHCl_3$).

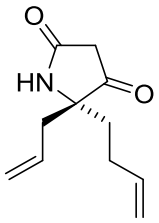
Methyl (*R*)-2-allyl-2-(3-ethoxy-3-oxopropanamido)hex-5-enoate ((*R*)-S4d)



To a solution of **(*R*)-3d** (140 mg, 0.764 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C was added a solution of Et_3N (213 µL, 1.53 mmol) in CH_2Cl_2 (1.0 mL), followed by the dropwise addition of a solution of ethyl malonyl chloride (147 µL, 1.15 mmol) in CH_2Cl_2 (1.0 mL) and the reaction stirred for 30 min. The reaction mixture was diluted with NH_4Cl (sat. aq, 10 mL) and stirred for 10 min then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product

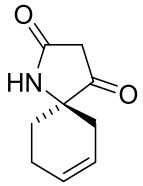
was purified by flash column chromatography (silica gel, PE/EtOAc, 4:1) to yield **(*R*)-S4d** (105 mg, 46%) as a transparent viscous oil.R_f = 0.33 (PE/EtOAc, 2:1). IR (ATR) $\nu_{Max.}$ 3327 (w, br), 3080 (w), 2980 (w), 1735 (s), 1656 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, br s), 5.78 – 5.67 (1H, m), 5.65 – 5.53 (1H, m), 5.10 – 5.03 (2H, m), 4.98 (1H, dq, *J* = 17.2, 1.5 Hz), 4.93 (1H, br d, *J* = 10.1 Hz), 4.22 (2H, q, *J* = 7.2 Hz), 3.77 (3H, s), 3.29 (2H, s), 3.20 (1H, br dd, *J* = 13.9, 7.3 Hz), 2.59 – 2.48 (2H, m), 2.09 – 1.99 (1H, m), 1.93 – 1.75 (2H, m), 1.29 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 169.0, 164.0, 137.4, 132.3, 119.1, 115.3, 64.8, 61.8, 52.9, 42.7, 39.5, 34.1, 28.7, 14.2. HRMS (ESI) calcd for $[C_{15}H_{23}NO_5Na]^+$: 320.1474, found 320.1473. $[\alpha]_D^{20}$ +13.3° (c = 0.120, MeOH).

(*R*)-5-Allyl-5-(but-3-en-1-yl)pyrrolidine-2,4-dione ((*R*)-10b)



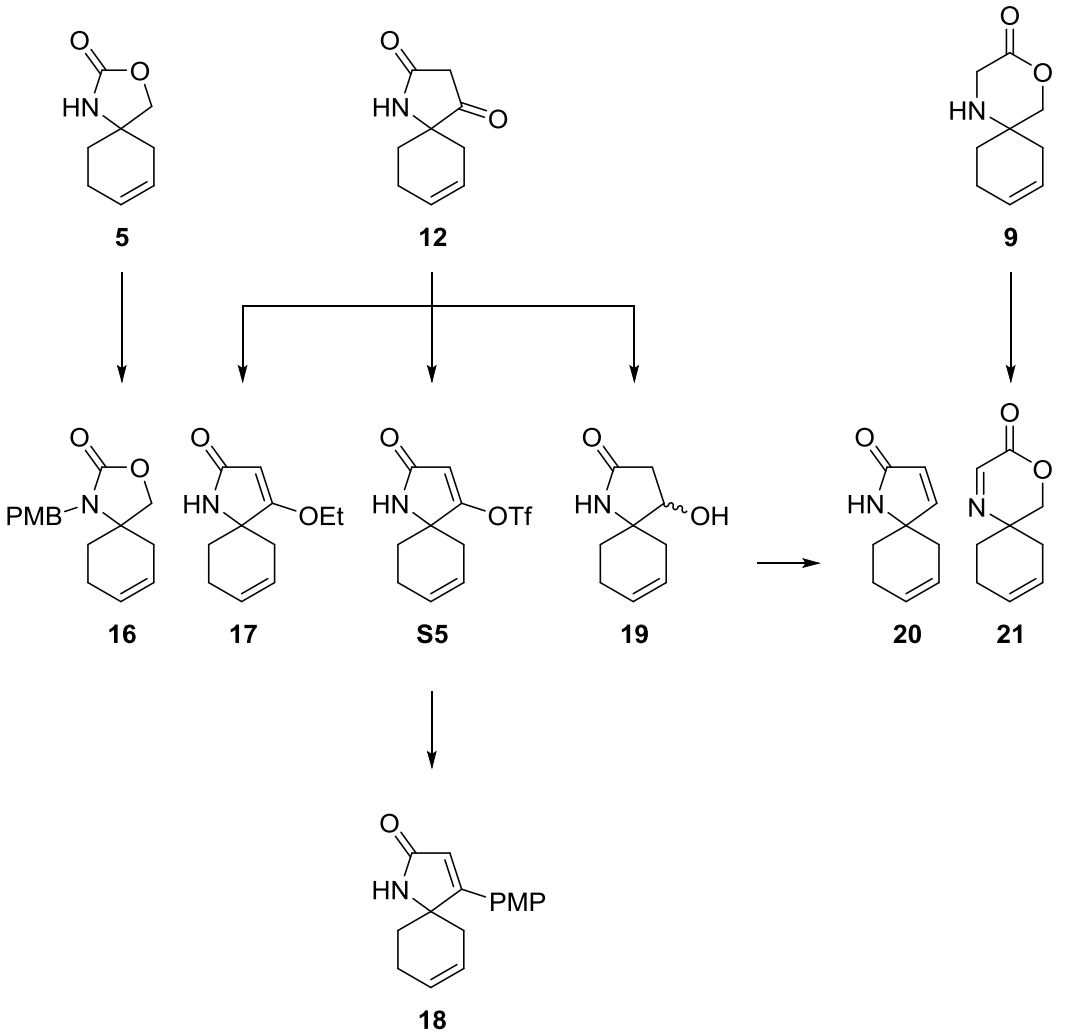
To a solution of **(*R*)-S4d** (95 mg, 0.319 mmol) in THF (2.5 mL) was added a solution of *t*BuOK (54 mg, 0.479 mmol) in THF (1.0 mL), and the reaction heated under reflux for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and HCl (1 M aq, 10 mL) and stirred for 10 min. The organic layer was then separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil (78 mg). A solution of the oil (70 mg) in MeCN/H_2O (9:1, 3.5 mL) was heated under reflux for 1 h, then concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, PE/EtOAc, 1:1) to yield **(*R*)-10b** (51 mg, 92%) as a transparent viscous oil. Analytical data matched that of **10b**. $[\alpha]_D^{20}$ +111.9° (c = 0.176, MeOH).

(*R*)-1-Azaspiro[4.5]dec-7-ene-2,4-dione ((*R*)-12)

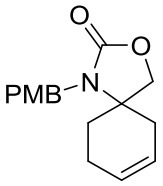


A solution of **(*R*)-10b** (39 mg, 0.202 mmol) in CH_2Cl_2 (10 mL) was degassed with argon, followed by the addition of Grubbs II catalyst (17 mg, 0.020 mmol) and the reaction heated under reflux for 1 h, then concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2 then EtOAc) to yield **(*R*)-12** (32.5 mg, 97%) as a brown amorphous solid. Analytical data matched that of **12**. $[\alpha]_D^{20}$ +45.4° (c = 0.410, MeOH).

Heterocycle modification



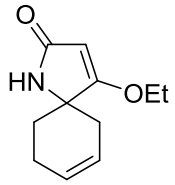
1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]dec-7-ene-2-one (16)



To a solution of pure **5** (718 mg, 4.69 mmol) in DMF (50 mL) was added NaH (60 w/w % dispersion in mineral oil, 281 mg, 7.03 mmol) and the reaction stirred for 1.5 h at 50 °C, followed by the addition of 4-methoxybenzyl chloride (953 µL, 7.03 mmol) and stirred overnight at 50 °C. The reaction mixture was quenched by $NaHCO_3$ (sat. aq, 50 mL), stirred for 10 min, and then diluted with H_2O (50 mL), brine (100 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were concentrated *in vacuo*, the residue dissolved in Et_2O (20 mL), washed with LiCl (10% aq, 3 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/Et_2O, 1:1 to 0:1) to yield **16** (1.23 g, 96%) as a white amorphous solid. R_f = 0.43 (Et_2O). IR (ATR) $\nu_{Max.}$ 3033 (w), 2926 (w), 2902 (w), 2835 (w), 1736 (s), 1613 (w), 1514 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (2H, m), 6.86 –

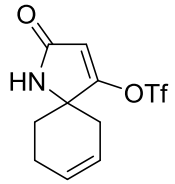
6.81 (2H, m), 5.68 – 5.58 (1H, m), 5.58 – 5.48 (1H, m), 4.40 (1H, d, *J* = 15.5 Hz), 4.30 (1H, d, *J* = 15.5 Hz), 4.04 (1H, d, *J* = 8.4 Hz), 4.01 (1H, dd, *J* = 8.4, 0.8 Hz), 3.79 (3H, s), 2.32 – 2.14 (2H, m), 2.14 – 2.00 (1H, m), 2.00 – 1.90 (1H, m), 1.86 – 1.75 (1H, m), 1.58 – 1.50 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 158.5, 130.6, 129.1, 126.8, 123.8, 114.0, 73.0, 60.0, 55.4, 43.8, 33.4, 30.6, 23.1. HRMS (ESI) calcd for $[C_{16}H_{19}NO_3Na]^+$: 296.1257, found 296.1247.

4-Ethoxy-1-azaspiro[4.5]deca-3,7-dien-2-one (17)



To a solution of **12** (100 mg, 0.61 mmol) in THF (10 mL) at 0 °C was added KHMDS (0.5 M in toluene, 1.22 mL, 0.61 mmol) and stirred for 10 min, then EtBr (90 µL, 0.73 mmol) and 18-crown-6 (176 mg, 0.66 mmol) were added. The reaction was warmed to rt and stirred overnight, then concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to yield **17** (64.1 mg, 54%) as a yellow-white amorphous solid. R_f = 0.24 (EtOAc). IR (ATR) $\nu_{Max.}$ 3188 (w), 3060 (w), 2933 (w), 1672 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.69 (2H, m), 4.91 (1H, d, *J* = 1.7 Hz), 4.01 (2H, q, *J* = 7.1 Hz), 2.61 (1H, dsex, *J* = 17.3, 2.3 Hz), 2.33 – 2.11 (2H, m), 1.98 – 1.83 (2H, m), 1.62 – 1.54 (1H, m), 1.39 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 173.3, 126.6, 124.3, 92.2, 67.3, 60.0, 33.7, 29.3, 22.7, 14.2. HRMS (ESI) calcd for $[C_{11}H_{16}NO_2]^+$: 194.1176, found 194.1181.

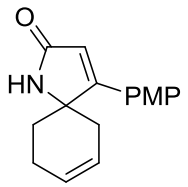
2-Oxo-1-azaspiro[4.5]deca-3,7-dien-4-yl trifluoromethanesulfonate (S5)



To a solution of **12** (100mg, 0.61 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added Et_3N (0.25 mL, 1.82 mmol) and Tf_2O (300 µL, 1.82 mmol) dropwise, and stirred for 1 h, then concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/Et_2O, 3:7 to 1:9) to yield **S5** (107 mg, 59%) as a white amorphous solid. R_f = 0.18 (PE/Et_2O, 3:7). IR (ATR) $\nu_{Max.}$ 3164 (w), 2926 (w), 1698 (s), 1634 (s), 1332 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (1H, br s), 5.94 (1H, d, *J* = 1.8 Hz), 5.88 – 5.82 (1H, m), 5.79 – 5.72 (1H, m), 2.64 (1H, dsex, *J* = 17.2, 2.3 Hz), 2.43 – 2.33 (1H, m), 2.29 – 2.17 (1H, m), 2.03 – 1.93 (2H, m), 1.73 – 1.66 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 168.1, 126.8, 123.2, 118.6 (q, *J* = 321.5 Hz), 107.5, 60.9,

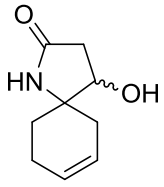
32.8, 28.8, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.5 (3F, s). HRMS (ESI) calcd for $[C_{10}H_{11}NO_4F_3S]^+$: 298.0355, found 298.0361.

4-(4-Methoxyphenyl)-1-azaspiro[4.5]deca-3,7-dien-2-one (18)



To a solution of **S5** (50.0 mg, 0.170 mmol) and (4-methoxyphenyl)boronic acid (38.3 mg, 0.250 mmol) in THF (1.7 mL) was added $Pd(PPh_3)_4$ (9.7 mg, 8.0 µmol) and a solution of Na_2CO_3 (39.2 mg, 0.37 mmol) in H_2O (0.2 mL). The reaction was stirred at rt for 40 min then heated under reflux for 3 h. The reaction mixture was cooled to rt and filtered through Celite, washed with EtOAc, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, Et_2O to EtOAc) to yield **18** (31.5 mg, 73%) as a yellow-white amorphous solid. The product was crystallised from CH_2Cl_2 for the single crystal X-ray crystallography analysis. R_f = 0.11 (Et_2O). Mp 196 – 197 °C (CH_2Cl_2). IR (ATR) $\nu_{Max.}$ 3160 (w), 3035 (w), 2924 (w), 1680 (s), 1607 (m), 1511 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.9 Hz), 6.93 (2H, d, *J* = 8.9 Hz), 6.35 (1H, br s), 6.18 (1H, d, *J* = 1.9 Hz), 5.89 – 5.82 (1H, m), 5.82 – 5.75 (1H, m), 3.84 (3H, s), 2.80 (1H, dqui, *J* = 17.6, 2.7 Hz), 2.39 – 2.17 (3H, m), 2.02 – 1.92 (1H, m), 1.77 – 1.68 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 165.5, 160.7, 129.1, 126.8, 124.8, 124.8, 120.5, 114.3, 63.6, 55.5, 34.9, 30.5, 23.3. HRMS (ESI) calcd for $[C_{16}H_{18}NO_2]^+$: 256.1338, found 256.1331.

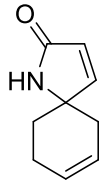
4-Hydroxy-1-azaspiro[4.5]dec-7-en-2-one (19)



To a suspension of $NaBH_4$ (38.9 mg, 1.03 mmol) in MeOH (2.0 mL) at 0 °C was added **12** (100 mg, 0.61 mmol), then warmed to rt and stirred for 1 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to yield an inseparable mixture of diastereomers **19** (23 mg, 23%; dr = 3.1:1) as a white amorphous solid. R_f = 0.06 (EtOAc). IR (ATR) $\nu_{Max.}$ 3368 (m), 3194 (m, br), 2950 (w), 1698 (s), 1662 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 – 5.69 (2H, m), 5.65 – 5.59 (1H, m), 4.19 (1H, m), 2.75 (1H, dd, *J* = 17.2, 6.9 Hz), 2.39 (1H, dd, *J* = 17.1, 5.2 Hz), 2.35 – 2.27 (2H, m), 2.23 – 2.08 (1H, m), 2.02 (1H, m), 2.02 – 1.95 (1H, m), 1.89 – 1.81 (1H, m), 1.79 –

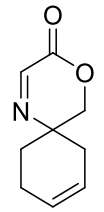
1.72 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 127.7, 124.1, 73.8, 60.9, 39.4, 36.4, 26.6, 22.6. HRMS (ESI) calcd for $[C_9H_{13}NO_2Na]^+$: 190.0844, found 190.0841.

1-Azaspiro[4.5]deca-3,7-dien-2-one (20)



A solution of **19** (23.0 mg, 0.14 mmol) in TFAA (67 µL, 0.48 mmol) and heated under reflux for 12 h, then concentrated *in vacuo*. To a solution of the residue in CH_2Cl_2 (0.25 mL) was added Et_3N (24 µL, 0.17 mmol) and stirred at rt for 12 h, followed by the addition of a solution of $KHCO_3$ (36 mg, 0.36 mmol) in MeOH (0.25 mL) and stirred for a further 2 h. The reaction mixture was diluted with $CHCl_3$ (5 mL) and washed with HCl (1 M aq, 5 mL) H_2O (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to yield **20** (6.3 mg, 30%) as an off-white amorphous solid. R_f = 0.18 (EtOAc). The product was crystallised from CH_2Cl_2 for the single crystal X-ray crystallography analysis. Mp 75 – 76 °C (CH_2Cl_2). IR (ATR) $\nu_{Max.}$ 3170 (m), 3030 (w), 2926 (w), 1682 (s), 1655 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, br d, *J* = 5.6 Hz), 6.15 (1H, br s), 6.03 (1H, br d, *J* = 5.6 Hz), 5.84 – 5.78 (1H, m), 5.76 – 5.70 (1H, m), 2.39 – 2.31 (1H, m), 2.31 – 2.15 (2H, m), 2.11 – 2.02 (1H, m), 1.85 – 1.75 (1H, m), 1.75 – 1.67 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8*, 154.8, 126.8, 125.8*, 124.4, 62.4, 34.5, 31.0, 23.7 ppm; *only observed in HSQC and HMBC. HRMS (ESI) calcd for $[C_9H_{12}NO]^+$: 150.0919, found 150.0918.

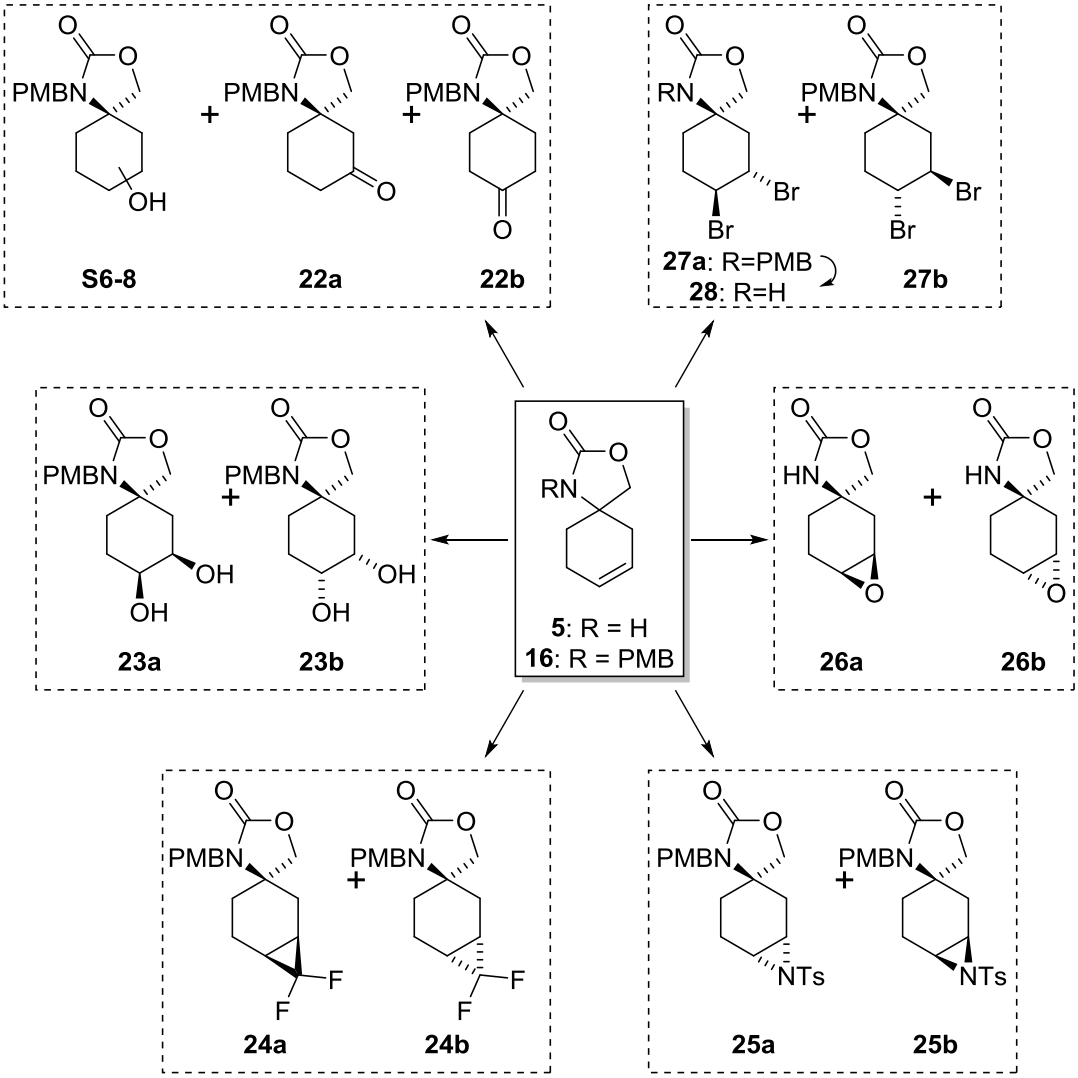
4-Oxa-1-azaspiro[5.5]undeca-1,8-dien-3-one (21)



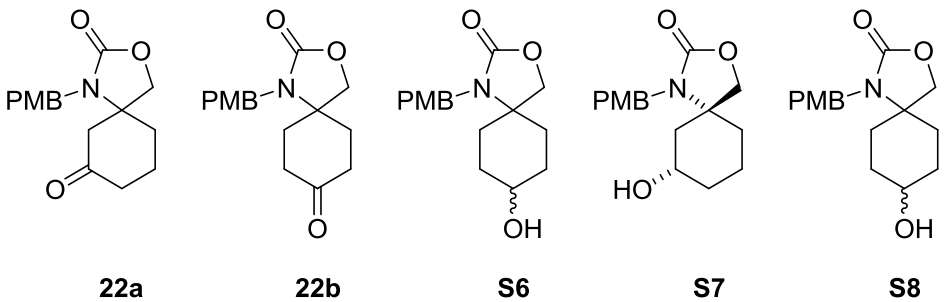
To a solution of **9** (100 mg, 0.60 mmol) in MeCN (6 mL) was added $Pb(OAc)_4$ (345 mg, 0.78 mmol) and stirred at rt for 30 min, then diluted with EtOAc (10 mL) and filtered through Celite. The filtrate was washed with $NaHCO_3$ (sat. aq, 20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/EtOAc, 4:1) to yield **21** (60 mg, 60%) as a yellow oil. R_f = 0.25 (PE/EtOAc, 4:1). IR (ATR) $\nu_{Max.}$ 2923 (w), 1737 (s), 1622 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 5.84 – 5.75 (1H, m), 5.72 – 5.63 (1H, m), 4.29 (1H, d, *J* = 11.6 Hz), 4.25 (1H, d, *J* = 11.6 Hz), 2.32 – 2.20 (2H, m), 2.16 – 2.03 (2H, m), 2.03 – 1.94 (1H, m), 1.71 – 1.63 (1H, m). ^{13}C NMR (101

MHz, $CDCl_3$) δ 154.8, 151.2, 126.7, 123.1, 72.1, 56.0, 32.8, 30.3, 22.2. HRMS (ESI) calcd for $[C_9H_{11}NO_2Na]^+$: 188.0682, found 188.0681.

Double bond modification



1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]decane-2,7-dione (22a), 1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]decane-2,8-dione (22b), 8-hydroxy-1-(4-methoxy-benzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S6), (5*R,7*S**)-7-Hydroxy-1-(4-methoxy-benzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S7) and 8-hydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S8)**



16 (109 mg, 0.400 mmol) was added to a solution of iron(II) acetylacetonate (20.4 mg, 0.08 mmol) and poly(methylhydrosiloxane) (272 µL) in *t*BuOH (4.0 mL) and the reaction stirred for 24 h at 50 °C. The reaction mixture was then quenched by silica gel, stirred for 10 min, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/EtOAc, 9:1 to 0:1) to yield unreacted **16** (8.8 mg, 8%), ketones **22a** (32.5 mg, 28%) and **22b** (17.0 mg, 15%) as white solids, and a mixture of alcohols **S6**, **S7** and **S8** (38.5 mg, 33% combined) as a transparent viscous oil. The individual alcohol isomers were separated by preparative TLC (silica gel, eluting with either 5% MeOH in CH_2Cl_2 or EtOAc). **S6** appeared as a transparent viscous oil, **S7** and **S8** as white amorphous solids. **S7** was crystallised from Et_2O for the single crystal X-ray crystallography analysis. **S6** and **S8** gave viscous oils or fibrous materials after each attempted crystallisation, that were not suitable for single crystal X-ray crystallography analysis, therefore their geometry could not be assigned.

Analytical data for **22a**: R_f = 0.49 (EtOAc). Mp 100 – 101 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 2962 (w), 2930 (w), 1717 (s), 1615 (w), 1514 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (2H, m), 6.89 – 6.82 (2H, m), 4.43 (1H, d, *J* = 16.2 Hz), 4.42 (1H, d, *J* = 16.2 Hz), 3.98 (1H, d, *J* = 8.9 Hz), 3.96 (1H, d, *J* = 8.9 Hz), 3.80 (3H, s), 2.49 (1H, d, *J* = 13.6 Hz), 2.39 – 2.29 (2H, m), 2.20 (1H, td, *J* = 14.0, 6.1 Hz), 2.08 – 1.91 (2H, m), 1.81 – 1.72 (1H, m), 1.44 (1H, qt, *J* = 13.5, 4.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 159.4, 157.7, 129.7, 129.1, 114.3, 71.7, 63.7, 55.4, 50.3, 44.0, 40.2, 33.6, 20.0. HRMS (ESI) calcd for $[C_{16}H_{20}NO_4]^+$: 290.1392, found 290.1399.

Analytical data for **22b**: R_f = 0.44 (EtOAc). Mp 121 – 122 °C (crystal decomposition), 136 – 137 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 2906 (w), 1732 (s), 1706 (s), 1616 (w), 1513 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (2H, m), 6.86 – 6.82 (2H, m), 4.37 (2H, s), 4.36 (2H, s), 3.79 (3H, s), 2.43 – 2.29 (4H, m), 2.04 (2H, td, *J* = 13.4, 5.5 Hz), 1.86 (2H, dqui, *J* = 13.8, 3.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.3, 159.4, 157.9, 130.1, 129.0, 114.3, 71.2, 60.4, 55.4, 44.0, 37.2, 33.0. HRMS (ESI) calcd for $[C_{16}H_{20}NO_4]^+$: 290.1392, found 290.1402.

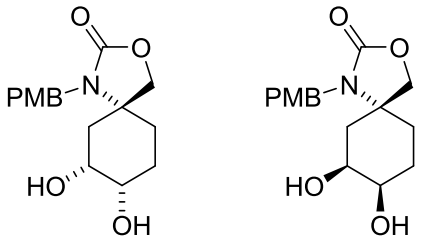
Analytical data for **S6**: R_f = 0.29 (5% MeOH in CH_2Cl_2). IR (ATR) $\nu_{Max.}$ 3358 (w, br), 2921 (w), 2852 (w), 1728 (s), 1660 (w), 1513 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (2H, dt, *J* = 8.7, 2.5 Hz), 6.84 (2H, dt, *J* = 8.7, 2.5 Hz), 4.37 (2H, s), 4.10 (2H, s), 4.02 (1H, sex, *J* = 2.5 Hz), 3.79 (3H, s), 2.07 (2H, td, *J* = 13.5, 4.0 Hz), 1.81 (2H, br d, *J* = 16.4 Hz), 1.47 (2H, tdd, *J* = 14.3, 3.7, 2.6 Hz), 1.34 (2H, dqui, *J* = 13.1, 2.0 Hz), 1.17 (1H, d, *J* = 2.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 158.3, 130.8, 129.1, 114.0, 71.6, 63.7, 61.4, 55.4, 43.6, 29.5, 27.7. HRMS (ESI) calcd for $[C_{16}H_{22}NO_4]^+$: 292.1549, found 292.1544.

Analytical data for **S7**: R_f = 0.23 (5% MeOH in CH_2Cl_2). Mp 134 – 135 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 3472 (w, br), 2921 (w), 2851 (w), 1728 (s), 1613 (w), 1510 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, dt, *J* = 9.6, 2.5 Hz), 6.84 (2H, dt, *J* = 9.6, 2.5 Hz), 4.37 (1H, d, *J* = 15.9 Hz), 4.33 (1H, d, *J* = 15.9 Hz), 4.05 (1H, d, *J* = 8.8 Hz), 4.04 (1H, d, *J* = 8.8 Hz), 3.79 (3H, s), 3.58 – 3.48 (1H, m), 1.97 – 1.92 (1H, m), 1.92 – 1.87 (1H, m), 1.79 – 1.73 (1H,

m), 1.55 – 1.47 (3H, m), 1.45 – 1.37 (1H, m), 1.27 – 1.16 (1H, m), 1.14 – 1.04 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 158.1, 130.4, 129.0, 114.2, 72.1, 67.7, 62.1, 55.4, 43.7, 43.5, 34.2, 33.0, 19.6. HRMS (ESI) calcd for $[C_{16}H_{22}NO_4]^+$: 292.1549, found 292.1553.

Analytical data for **S8**: R_f = 0.23 (EtOAc). IR (ATR) $\nu_{Max.}$ 3441 (w, br), 2940 (w), 2861 (w), 1720 (s), 1612 (w), 1511 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, br d, *J* = 8.6 Hz), 6.84 (2H, br d, *J* = 8.6 Hz), 4.32 (2H, s), 4.13 (2H, s), 3.79 (3H, s), 3.59 – 3.48 (1H, m), 1.99 – 1.90 (2H, m), 1.68 – 1.51 (5H, m), 1.32 – 1.19 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 158.3, 130.5, 128.9, 114.1, 71.9, 69.0, 60.9, 55.4, 43.7, 32.1, 31.8. HRMS (ESI) calcd for $[C_{16}H_{22}NO_4]^+$: 292.1549, found 292.1545.

(5*R,7*R**,8*S**)-7,8-Dihydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (23a) and (5*R**,7*S**,8*R**)-7,8-dihydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]-decan-2-one (23b)**



23a **23b**

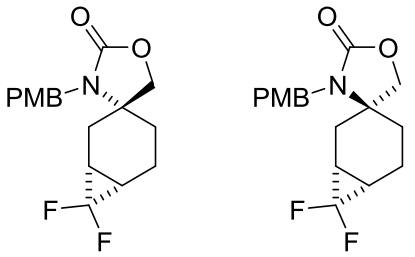
To a solution of **16** (55 mg, 0.20 mmol) in THF (1.0 mL) was added 4-methylmorpholine *N*-oxide (47 mg, 0.40 mmol), citric acid (77 mg, 0.40 mmol), H_2O (1.0 mL) and OsO_4 (2.5 w/w % solution in *t*BuOH, 20 µL, 2.0 µmol) and the reaction stirred for 2 h at rt. The reaction mixture was quenched by Na_2SO_3 (sat. aq, 1.0 mL), stirred for 10 min, and then diluted with brine (1.0 mL) and extracted with EtOAc (3 x 3.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude mixture of **23b** and **23a** (63 mg, **23b**/**23a** = 1:2.5) as a transparent oil. The crude product was purified by flash column chromatography (silica gel, EtOAc to 5% MeOH in Et_2O) to yield **23b** (12.6 mg), **23a** (33.2 mg) and a mixture of **23b** and **23a** (15 mg) all as white solids. Overall yield: **23b** + **23a** (60.8 mg, 99%). **23b** spontaneously crystallised from C_6D_6 and the co-crystals formed were used for the single crystal X-ray crystallography analysis.

Analytical data for **23a**: R_f = 0.13 (EtOAc). Mp 120 – 121 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 3422 (w, br), 3305 (w, br), 2956 (w), 2898 (w), 1717 (s), 1613 (w), 1511 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, dt, *J* = 8.6, 2.5 Hz), 6.83 (2H, dt, *J* = 8.6, 2.5 Hz), 4.33 (2H, s), 4.07 (1H, d, *J* = 8.6 Hz), 4.05 (1H, d, *J* = 8.6 Hz), 3.92 – 3.88 (1H, m), 3.78 (3H, s), 3.56 (1H, br d, *J* = 10.7 Hz), 2.39 (1H, br s), 2.31 (1H, br s), 2.02 – 1.89 (3H, m), 1.57 (1H, ddd, *J* = 12.2, 4.4, 1.9 Hz), 1.43 – 1.23 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 158.2, 130.3, 129.1, 114.1,

72.0, 68.8, 67.1, 61.8, 55.4, 43.6, 36.2, 26.3, 26.0. HRMS (ESI) calcd for $[C_{16}H_{22}NO_5]^+$: 308.1498, found 308.1484.

Analytical data for **23b**: R_f = 0.20 (EtOAc). Mp 122 – 123 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 3434 (w, br), 3356 (w, br), 2917 (w), 2851 (w), 1704 (s), 1611 (w), 1511 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (2H, dt, *J* = 8.7, 2.5 Hz), 6.84 (2H, dt, *J* = 8.7, 2.5 Hz), 4.41 (1H, d, *J* = 15.9 Hz), 4.33 (1H, dd, *J* = 9.4, 1.2 Hz), 4.26 (1H, d, *J* = 9.4 Hz), 4.21 (1H, d, *J* = 15.9 Hz), 3.99 (1H, br s), 3.79 (3H, s), 3.61 – 3.54 (1H, m), 2.30 (1H, br s), 1.91 – 1.82 (2H, m), 1.79 – 1.66 (3H, m), 1.66 – 1.52 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 158.6, 130.5, 128.8, 114.2, 73.4, 70.5, 69.5, 60.4, 55.4, 43.5, 37.9, 30.9, 25.1. HRMS (ESI) calcd for $[C_{16}H_{22}NO_5]^+$: 308.1498, found 308.1513.

(1*R,3*R**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24a) and (1*R**,3*S**,6*S**)-7,7-difluoro-3'-(4-methoxybenzyl)spiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24b)**



24a **24b**

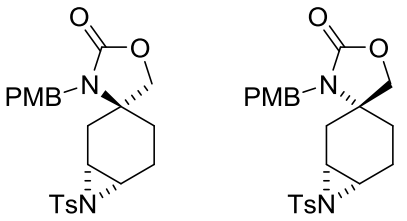
To a solution of **16** (55 mg, 0.20 mmol) in THF (0.30 mL) was added anhydrous NaI (6.0 mg, 0.040 mmol) and $TMSCF_3$ (74 µL, 0.50 mmol) and the reaction stirred at 65 °C in a sealed tube. After 6 h, the reaction was cooled to rt and opened to air, then more $TMSCF_3$ (74 µL, 0.50 mmol) was added, the tube sealed and heated to 65 °C overnight. The reaction was then cooled to rt again and opened to air followed by the removal of solvent *in vacuo*. The residue was dissolved in Et_2O (10 mL) and washed with H_2O (10 mL), Na_2SO_3 (sat. aq, 10 mL), $NaHCO_3$ (sat. aq, 10 mL) and H_2O (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, PE/Et_2O 1:1 to 1:4) to yield unreacted **16** (31.4 mg, 58%) as a white solid, **24b** (0.8 mg, 1%) as a transparent viscous oil and **25a** (16.2 mg, 25%) as a white solid. Overall yield based on recovered starting material: **24b** + **24a** (17.0 mg, 62%). **24a** was crystallised from Et_2O for the single crystal X-ray crystallography analysis.

Analytical data for **24a**: R_f = 0.04 (PE/Et_2O 1:1). Mp 90 – 91 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 2931 (w), 1736 (s), 1614 (w), 1514 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, dt, *J* = 8.9, 2.5 Hz), 6.85 (2H, dt, *J* = 8.9, 2.5 Hz), 4.34 (1H, d, *J* = 15.6 Hz), 4.23 (1H, d, *J* = 15.6 Hz), 4.16 (1H, d, *J* = 8.5 Hz), 3.95 (1H, dd, *J* = 8.5, 1.7 Hz), 3.79 (3H, s), 2.10 – 2.03 (1H, m), 1.87 – 1.72 (2H, m), 1.68 – 1.55 (3H, m), 1.53 – 1.44 (1H, m), 1.33 – 1.26 (1H, m). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 159.3, 158.1, 130.2, 129.4, 114.1, 113.9 (dd, *J* = 287.3, 284.0 Hz), 71.5 (d, *J* = 1.5 Hz), 59.0 (d, *J* = 3.6 Hz), 55.4, 43.8, 29.0 (dd, *J* = 4.6, 1.0 Hz), 23.2 (d, *J* = 3.1 Hz), 16.2 (t, *J* = 11.3 Hz), 16.1 (t, *J* = 11.3 Hz), 15.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -127.2 (1F, dtd, *J* = 157.7, 14.1, 1.2 Hz), -150.4 (1F, d, *J* = 157.7 Hz). HRMS (ESI) calcd for $[C_{17}H_{20}NO_3F_2]^+$: 324.1411, found 324.1418.

Analytical data for **24b**: R_f = 0.06 (PE/Et_2O 1:1). IR (ATR) $\nu_{Max.}$ 2933 (w), 1738 (s), 1612 (w), 1512 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, br d, *J* = 8.7 Hz), 6.85 (2H, br d, *J* = 8.7 Hz), 4.49 (1H, d, *J* = 15.9 Hz), 4.32 (1H, d, *J* = 15.9 Hz), 4.03 (1H, dd, *J* = 8.9, 1.3 Hz), 3.94 (1H, d, *J* = 8.9 Hz), 3.80 (3H, s), 2.06 – 1.97 (1H, m), 1.96 (1H, dd, *J* = 15.3, 8.3 Hz), 1.73 (1H, d, *J* = 15.3 Hz), 1.68 – 1.50 (4H, m), 1.44 – 1.36 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 158.4, 130.3, 128.6, 114.3, 114.1 (dd, *J* = 287.3, 284.2 Hz), 73.8 (d, *J* = 11.5 Hz), 59.1 (d, *J* = 2.1 Hz), 55.4, 44.2, 29.8 (dd, *J* = 2.6, 0.6 Hz), 24.9 (dd, *J* = 2.0, 0.6 Hz), 18.0 (t, *J* = 11.7 Hz), 16.9 (t, *J* = 11.5 Hz), 13.8 (d, *J* = 3.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -127.3 (1F, dt, *J* = 157.4, 13.8 Hz), -149.4 (1F, d, *J* = 157.4 Hz). HRMS (ESI) calcd for $[C_{17}H_{20}NO_3F_2]^+$: 324.1411, found 324.1419.

(1*R,3*S**,6*S**)-3'-(4-Methoxybenzyl)-7-tosyl-7-azaspiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (25a) and (1*R**,3*R**,6*S**)-3'-(4-methoxybenzyl)-7-tosyl-7-azaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (25b)**



25a **25b**

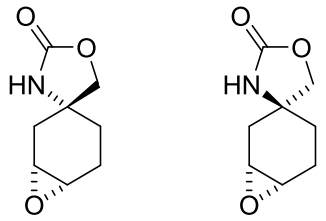
To a solution of **16** (55 mg, 0.20 mmol) in MeCN (1.0 mL) was added chloramine T trihydrate (62 mg, 0.22 mmol) and trimethylphenylammonium tribromide (7.5 mg, 0.020 mmol) and the reaction stirred at rt over 4 Å molecular sieves overnight. The reaction mixture was filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography (silica gel, Et_2O) to yield **25a** (34.5 mg, 39%) and **25b** (25.1 mg, 28%) both as white amorphous solids. **25b** was crystallised from Et_2O for the single crystal X-ray crystallography analysis.

Analytical data for **25a**: R_f = 0.19 (Et_2O). Mp 177 – 178 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 2952 (w), 2936 (w), 2921 (w), 1729 (s), 1615 (w), 1513 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (2H, dt, *J* = 8.3, 1.7 Hz), 7.34 (2H, br d, *J* = 8.3 Hz), 7.19 (2H, dt, *J* = 8.7, 2.5 Hz), 6.83 (2H, dt, *J* = 8.7, 2.5 Hz), 4.37 (1H, d, *J* = 15.8 Hz), 4.19 (1H, d, *J* = 15.8 Hz), 4.06 (1H, d, *J* = 9.4 Hz), 3.96 (1H, dd, *J* = 9.4, 0.7 Hz), 3.79 (3H, s), 3.02 (1H, ddd, *J* = 6.9, 3.2, 1.7 Hz), 2.95 (1H, t, *J* = 6.7 Hz), 2.46 (3H, s), 2.14 (1H, dtd, *J* = 15.9, 7.1, 1.8 Hz), 1.93 – 1.77 (3H, m), 1.50 (1H, td, *J* = 12.7, 7.7 Hz), 1.39 (1H, ddd, *J* = 13.4, 7.0, 1.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 158.1, 145.0, 135.2,

130.2, 130.1, 128.9, 127.7, 114.2, 72.3, 60.0, 55.4, 43.7, 40.9, 36.7, 32.3, 28.2, 21.8, 20.2. HRMS (ESI) calcd for $[C_{23}H_{27}N_2O_5S]^+$: 443.1641, found 443.1622.

Analytical data for **25b**: R_f = 0.12 (Et_2O). Mp 122 – 123 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 2962 (w), 2934 (w), 1733 (s), 1615 (w), 1514 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, br d, *J* = 8.2 Hz), 7.35 (2H, br d, *J* = 8.2 Hz), 7.18 (2H, dt, *J* = 8.6, 2.4 Hz), 6.78 (2H, dt, *J* = 8.6, 2.4 Hz), 4.34 (1H, d, *J* = 15.5 Hz), 4.10 (1H, d, *J* = 15.5 Hz), 4.00 (1H, d, *J* = 8.4 Hz), 3.87 (1H, dd, *J* = 8.4, 1.4 Hz), 3.78 (3H, s), 2.97 (1H, br d, *J* = 6.7 Hz), 2.88 (1H, t, *J* = 6.7 Hz), 2.47 (3H, s), 2.10 – 2.02 (1H, m), 1.92 (1H, ddd, *J* = 15.2, 6.8, 2.0 Hz), 1.81 – 1.71 (2H, m), 1.67 (1H, ddd, *J* = 14.5, 4.2, 2.9 Hz), 1.24 – 1.17 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 157.9, 144.9, 135.1, 130.0, 129.9, 129.3, 127.8, 114.1, 73.0, 58.8, 55.4, 43.7, 38.4, 37.4, 29.5, 27.2, 21.8, 20.4. HRMS (ESI) calcd for $[C_{23}H_{27}N_2O_5S]^+$: 443.1641, found 443.1629.

(1*R,3*R**,6*S**)-7-Oxaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (26a) and (1*R**,3*S**,6*S**)-7-oxaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (26b)**



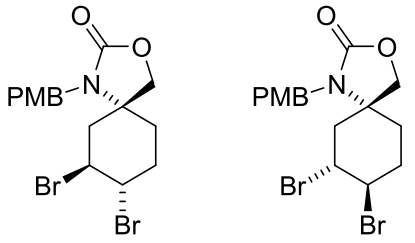
26a **26b**

To a solution of **5** (30.6 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) was added mCPBA (69.0 mg, 0.400 mmol) and $NaHCO_3$ (50.4 mg, 0.600 mmol) and the reaction stirred at rt overnight. The reaction mixture was quenched by a mixture of $NaHCO_3$ (sat. aq, 8.0 mL) and Na_2SO_3 (sat. aq, 2.0 mL), stirred for 10 min then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with the same aqueous mixture as above (2 x 10 mL), NaCl (sat. aq, 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 1 to 2% MeOH in CH_2Cl_2) to yield **26b** (1.9 mg, 6%) and crude **26a**, both as a white amorphous solids. Crude **26a** was purified by flash column chromatography (silica gel, PE/EtOAc, 1:1 to 0:1) to yield **26a** (15.5 mg, 46%) as a white solid. **26a** was crystallised from Et_2O for the single crystal X-ray crystallography analysis.

Analytical data for **26a**: R_f = 0.25 (5% MeOH in CH_2Cl_2). Mp 110 – 111 °C (crystal decomposition), 116 – 117 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 3299 (m), 3008 (w), 2910 (w), 1734 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (1H, br s), 4.03 (1H, d, *J* = 9.3 Hz), 4.02 (1H, d, *J* = 9.3 Hz), 3.29 (1H, br s), 3.23 – 3.20 (1H, m), 2.29 (1H, br d, *J* = 15.0 Hz), 2.14 – 2.09 (2H, m), 1.94 (1H, br d, *J* = 15.0 Hz), 1.78 – 1.72 (1H, m), 1.45 – 1.37 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 75.9, 55.6, 53.1, 51.0, 35.5, 30.7, 20.7. HRMS (ESI) calcd for $[C_8H_{12}NO_3]^+$: 170.0812, found 170.0810.

Analytical data for **26b**: R_f = 0.27 (5% MeOH in CH_2Cl_2). IR (ATR) $\nu_{Max.}$ 3289 (m), 3000 (w), 2919 (w), 2851 (w), 1737 (s), 1708 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (1H, br s), 4.14 (1H, d, *J* = 9.1 Hz), 4.09 (1H, d, *J* = 9.1 Hz), 3.26 – 3.23 (1H, m), 3.20 – 3.17 (1H, m), 2.22 (1H, br d, *J* = 15.3 Hz), 2.18 – 2.02 (3H, m) 1.69 (1H, dtd, *J* = 13.1, 6.6, 0.9 Hz), 1.53 (1H, br dt, *J* = 13.8, 6.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 75.1, 55.6, 51.8, 50.7, 36.6, 30.1, 21.1. HRMS (ESI) calcd for $[C_8H_{12}NO_3]^+$: 170.0812, found 170.0808.

(5*R,7*S**,8*S**)-7,8-Dibromo-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (27a) and (5*R**,7*R**,8*R**)-7,8-dibromo-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]-decan-2-one (27b)**



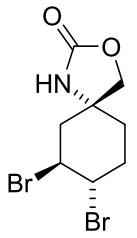
27a **27b**

To a solution of **16** (54.7 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added trimethyl-phenylammonium tribromide (75.2 mg, 0.200 mmol) and the reaction stirred at 0 °C for 2 h, then warmed to rt and stirred overnight. The reaction mixture was filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography (silica gel, PE/Et_2O 1:1 to 0:1) to yield **27a** (76.0 mg), a mixture of **27a** and **27b** (3.7 mg, **27a**/**27b** = 4.9:1) and **27b** (3.4 mg) all as white amorphous solids. Overall yield: **27a** + **27b** (83.1 mg, 96%). **27a** was crystallised from Et_2O for the single crystal X-ray crystallography analysis.

Analytical data for **27a**: R_f = 0.49 (Et_2O). Mp 108 – 109 °C (Et_2O).IR (ATR) $\nu_{Max.}$ 2998 (w), 2960 (w), 2927 (w), 2838 (w), 1737 (s), 1610 (w), 1509 (s).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, br d, *J* = 8.7 Hz),6.85 (2H, br d, *J* = 8.7 Hz),4.62 – 4.54 (3H, m),4.38 (1H, d, *J* = 9.1 Hz),4.33 (1H, dd, *J* = 9.1, 1.4 Hz),4.20 (1H, d, *J* = 15.8 Hz),3.80 (3H, s),2.91 (1H, dd, *J* = 15.4, 3.9 Hz),2.45 (1H, dddd, *J* = 15.4, 13.2, 3.4, 3.0 Hz),2.18 (1H, tdd, *J* = 13.6, 3.9, 1.2 Hz),2.04 – 1.96 (1H, m),1.89 – 1.82 (1H, m),1.64 – 1.57 (1H, m).^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 158.0, 130.4, 129.0, 114.3, 73.5, 60.7, 55.4, 51.2, 49.6, 43.8, 35.5, 26.2, 25.4. HRMS (ESI) calcd for $[C_{16}H_{20}NO_3{}^{79}Br_2]^+$: 431.9804, found 431.9800.

Analytical data for **27b**: R_f = 0.40 (Et_2O). Mp 68 – 69 °C (Et_2O). IR (ATR) $\nu_{Max.}$ 2932 (w), 1737 (s), 1611 (w), 1512 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.7 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 4.48 (1H, d, *J* = 15.8 Hz), 4.23 (1H, d, *J* = 15.8 Hz), 4.17 (1H, d, *J* = 8.7 Hz), 4.10 (1H, d, *J* = 8.7 Hz), 3.95 – 3.77 (5H, m), 2.47 – 2.33 (2H, m), 2.29 – 2.13 (1H, m), 1.86 – 1.72 (1H, m), 1.64 (1H, td, *J* = 13.6, 3.5 Hz), 1.60 – 1.52 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 157.6, 129.7, 129.0, 114.4, 71.0, 61.7, 55.5, 53.6, 51.4, 45.0, 44.0, 34.5, 33.5.HRMS (ESI) calcd for $[C_{16}H_{20}NO_3{}^{79}Br_2{}^{23}Na]^+$: 453.9624, found 453.9623.

(5*R,7*S**,8*S**)-7,8-Dibromo-3-oxa-1-azaspiro[4.5]decan-2-one (28)**



To a solution of **27a** (10.8 mg, 25 µmol) in MeCN (400 µL) and H_2O (100 µL) was added CAN (41.1 mg, 75 µmol) and stirred for 1 h at rt. Upon completion, the reaction mixture was quenched with $NaHCO_3$ (sat. aq, 3 mL), diluted with H_2O (6 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$, then filtered through a silica gel, washed with CH_2Cl_2 to remove the *p*-anisaldehyde by-product, then eluted with Et_2O and concentrated *in vacuo* to yield **28** (7.5 mg, 96%) as a white amorphous solid. The product was crystallised from Et_2O for the single crystal X-ray crystallography analysis. R_f = 0.27 (CH_2Cl_2/Et_2O 4:1). Mp 173 – 174 °C (decomposition, Et_2O). IR (ATR) $\nu_{Max.}$ 3197 (w), 3122 (w), 2954 (w), 1741 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (1H, br s), 4.55 – 4.46 (1H, m), 4.41 (1H, br s), 4.35 (1H, d, *J* = 9.0 Hz), 4.31 (1H, d, *J* = 9.0 Hz), 2.78 (1H, dd, *J* = 14.8, 3.8 Hz), 2.55 – 2.44 (1H, m), 2.22 (1H, dd, *J* = 14.8, 5.7 Hz), 2.12 – 1.95 (2H, m), 1.92 – 1.81 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 75.1, 57.5, 51.8, 50.4, 41.0, 32.8, 28.4. HRMS (ESI) calcd for $[C_8H_{12}NO_2{}^{79}Br_2]^+$: 311.9229, found 311.9219.

Computational Analysis

Calculation of the energy minimised conformations for both libraries were performed with Molecular Operating Environment (MOE) software package version 2012.10 using the following parameters:

Conformational Search Settings	
Force field	MMFF94x
Solvation	Born
Method	LowModeMD
Rejection Limit	100
RMS Gradient	0.005
Iteration Limit	10000
MM Iteration Limit	500
RMSD Limit	0.15
Energy Window	3
Conformation Limit	100

The following structural and physicochemical properties were also calculated using MOE 2018.0602:

Parameter	**Description**	**Property***
npr1	Normalised PMI ratio (1) (pmi1 / pmi3)	-
npr2	Normalised PMI ratio (2) (pmi2 / pmi3)	-
a_acc	Number of hydrogen-bond acceptor atoms	HBA
a_aro	Number of aromatic atoms	-
a_don	Number of hydrogen-bond donor atoms	HBD
a_heavy	Number of non-hydrogen heavy atoms	-
b_rotN	Number of rotatable bonds	RBC
chiral	Number of chiral centres	chiral
SlogP	Log octanol/water partition coefficient	SlogP
TPSA	Topological polar surface area ($Å^2$)	TPSA
weight	Molecular weight (Da)	MW

* as appears in Table 1 of the main article

The number of sp^3 atoms (sp3-Atom) was calculated using Osiris Datawarrior version 4.7.3.

The following properties were calculated using Microsoft Excel 2010:

Parameter*	Description
Fsp^3	Fraction of sp^3 atoms (sp3-Atom / a_heavy)
Far	Fraction of aromatic atoms (a_aro / a_heavy)
npr1 + npr2	Sum of the normalised PMI ratios
Fflat	Fraction of molecules below the 'flat land' line (defined as: npr1 + npr2 ≤ 1.1)

* as appears in Table 1 of the main article

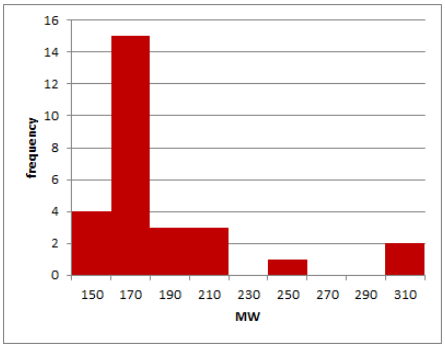
Spirocyclic library

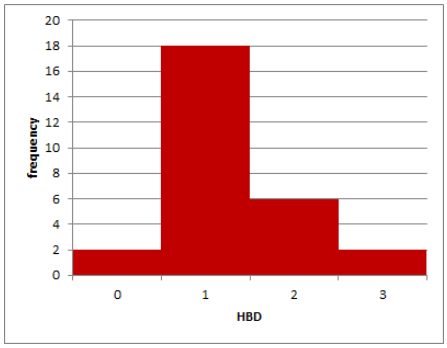
The spirocyclic library is based on the reported spirocyclic fragments. When applicable, protecting groups were removed yielding compounds numbered in general as X'.

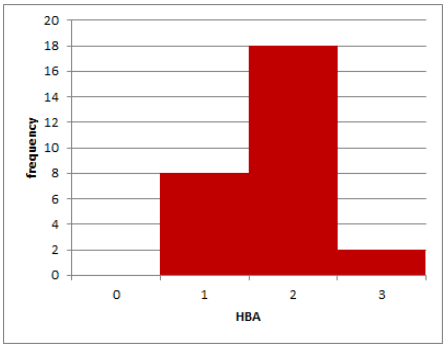
Normalised PMI ratios and molecular formulae of the library:

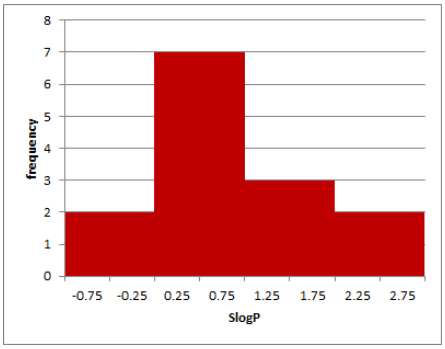
Compound	SMILES	npr1	npr2	Molecular Formula
12	O=C1[C@]2(NC(=O)C1)CC=CCC2	0.5336	0.9195	C9H11NO2
5	O=C1OC[C@]2(N1)CC=CCC2	0.3346	0.9505	C8H11NO2
9	O=C1OC[C@]2(NC1)CC=CCC2	0.2861	0.9367	C9H13NO2
7	c1(C=2OC[C@]3(N=2)CC=CCC3)ccccc1	0.2010	0.9075	C14H15NO
8	O=C1N[C@@]2(COC1)CC=CCC2	0.3961	0.8850	C9H13NO2
6	NC=1OC[C@]2(N=1)CC=CCC2	0.3275	0.9491	C8H12N2O
11	O=C1C2(NC(=O)C1)CC=CC2	0.3879	0.8086	C8H9NO2
13	O=C1[C@]2(NC(=O)C1)CC=CCCC2	0.5826	0.9781	C10H13NO2
18	O(C)c1ccc(C=2[C@]3(NC(=O)C=2)CC=CCC3)cc1	0.2737	0.8730	C16H17NO2
19	O=C1N[C@@]2(C(O)C1)CC=CCC2	0.4161	0.8470	C9H13NO2
21	O=C1OC[C@]2(N=C1)CC=CCC2	0.2499	0.8763	C9H11NO2
17	O(CC)C=1[C@]2(NC(=O)C=1)CC=CCC2	0.4464	0.7134	C11H15NO2
20	O=C1N[C@@]2(C=C1)CC=CCC2	0.3282	0.9689	C9H11NO
22b'	O=C1OCC2(N1)CCC(=O)CC2	0.2504	0.9771	C8H11NO3
22a'	O=C1OC[C@]2(N1)CC(=O)CCC2	0.2870	0.8968	C8H11NO3
S7'	O=C1OC[C@]2(N1)C[C@@H](O)CCC2	0.3619	0.9290	C8H13NO3
S6'	O=C1OCC2(N1)CCC(O)CC2	0.2614	0.9788	C8H13NO3
S8'	O=C1OCC2(N1)CCC(O)CC2	0.2614	0.9789	C8H13NO3
23a'	O=C1OC[C@]2(N1)C[C@@H](O)[C@@H](O)CC2	0.2965	0.9561	C8H13NO4
23b'	O=C1OC[C@]2(N1)C[C@H](O)[C@H](O)CC2	0.3059	0.9261	C8H13NO4
28	Br[C@@H]1[C@@H](Br)CC[C@@]2(NC(=O)OC2)C1	0.3131	0.7957	C8H11NO2Br2
27b'	Br[C@H]1[C@H](Br)CC[C@@]2(NC(=O)OC2)C1	0.3871	0.7196	C8H11NO2Br2
26a	O=C1OC[C@]2(N1)C[C@H]1O[C@H]1CC2	0.3455	0.9534	C8H11NO3
24a'	FC1(F)[C@H]2[C@@H]1CC[C@@]1(NC(=O)OC1)C2	0.3173	0.8961	C9H11NO2F2
26b	O=C1OC[C@]2(N1)C[C@@H]1O[C@@H]1CC2	0.4577	0.9443	C8H11NO3
24b'	FC1(F)[C@@H]2[C@H]1CC[C@@]1(NC(=O)OC1)C2	0.3725	0.9335	C9H11NO2F2
25a'	O=C1OC[C@]2(N1)C[C@H]1N[C@H]1CC2	0.2416	0.9675	C8H12N2O2
25b'	O=C1OC[C@]2(N1)C[C@@H]1N[C@@H]1CC2	0.4516	0.9439	C8H12N2O2

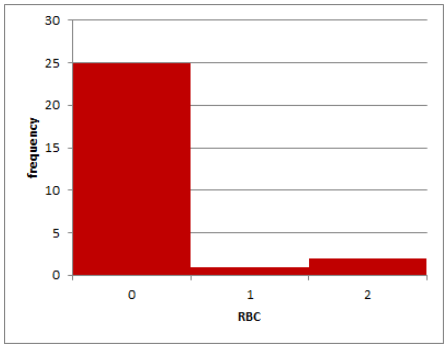
The distributions of the physicochemical properties of the library are displayed as histograms:

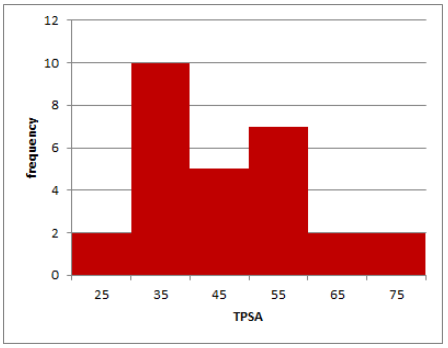


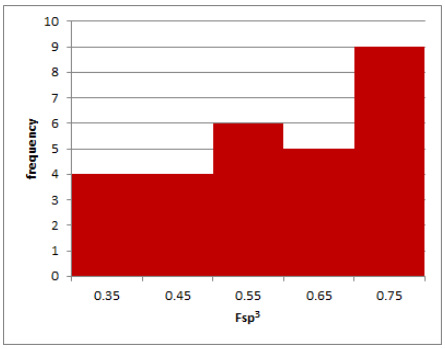


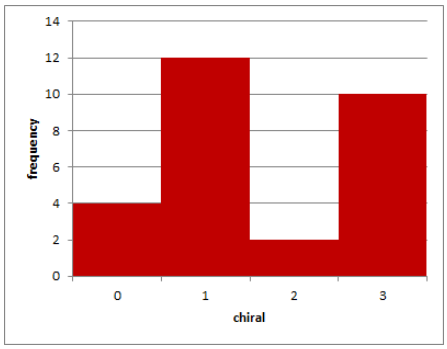


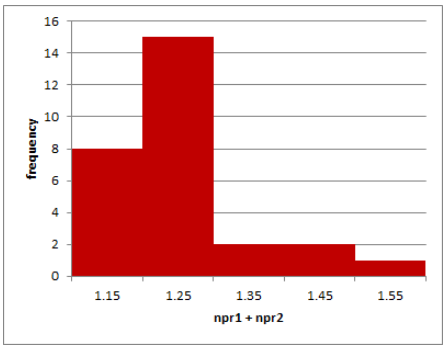












Maybridge core fragment collection

This library is based on the core 1000-member collection within the Maybridge Fragment library. Details of the library (including SMILES and SDF) are available from 'http://www.maybridge.com/' under the 'Ro3 Fragment library section. More details can be found at:

'http://www.maybridge.com/images/pdfs/MB_Ro3_fragment_flyer_2011_EUR_v7.pdf'

The best-matched fragments were chosen based on heavy atom and hetero atom counts compared to the spirocycle library. For heteroatom counts of 2 and 3, only exact heavy atom matches (i.e. same number of N and O atoms) were used, whereas for heteroatom counts of 4 and 5 no exact matches were found and therefore only the total heteroatom counts were used.

Normalised PMI ratios and molecular formulae of the Maybridge best-matched fragments:

SMILES	npr1	npr2	Molecular Formula
OCCNCc1ccccc1	0.1566	0.9438	C9H13NO
Oc1c2c(nccc2)ccc1	0.3618	0.6382	C9H7NO
O=C(C)c1cc(C#N)ccc1	0.2475	0.7561	C9H7NO
O=C1Nc2c(cccc2)CC1	0.2480	0.7704	C9H9NO
OC[C@H](N)Cc1ccccc1	0.2401	0.9471	C9H13NO
Oc1cc2ncccc2cc1	0.2253	0.7747	C9H7NO
O(C)c1cc(CC#N)ccc1	0.2339	0.8611	C9H9NO
O(C)c1cc2c([nH]cc2)cc1	0.2076	0.7963	C9H9NO
NCc1cc2c(OCC2)cc1	0.2047	0.8484	C9H11NO
N#Cc1cc2c(occ2)cc1	0.1741	0.8259	C9H5NO
Oc1c(C)cc(C#N)cc1C	0.3298	0.6775	C9H9NO
c1(-c2ccccc2)ocnc1	0.1600	0.8400	C9H7NO
OCCc1ccc(C#N)cc1	0.1608	0.9466	C9H9NO
O=C(N)c1c(C)c(C)ccc1	0.3472	0.7208	C9H11NO
O=C(N)c1cc(C)c(C)cc1	0.2338	0.7872	C9H11NO
OC[C@H]1[C@@H](NCc2ccccc2)CCCC1	0.1717	0.9024	C14H21NO
O[C@@H]([C@@H](N)c1ccccc1)c1ccccc1	0.4721	0.7911	C14H15NO
O(c1c(CNC)cccc1)c1ccccc1	0.3960	0.7590	C14H15NO
O(c1ccc(CNC)cc1)c1ccccc1	0.1063	0.9808	C14H15NO
O(Cc1cc(CN)ccc1)c1ccccc1	0.1368	0.9586	C14H15NO
O=C1CC2N(Cc3ccccc3)C(C1)CC2	0.2342	0.9468	C14H17NO
O=C(OCc1ccccc1)N	0.1520	0.9775	C8H9NO2
O=C(N)c1ccc(OC)cc1	0.1434	0.8704	C8H9NO2
O=C1NC(=O)[C@@H]2[C@H]1CC=CC2	0.3972	0.8514	C8H9NO2
O=C(OCC)[C@H]1[C@@H](N)CCC1	0.2814	0.8759	C8H15NO2
O=C(C)c1c(O)cc(N)cc1	0.2658	0.7756	C8H9NO2
O=C1OCc2c1cc(N)cc2	0.2879	0.7163	C8H7NO2
O=C(N(C)C)C1CCOCC1	0.3110	0.9079	C8H15NO2
O=C(N)Cc1ccc(O)cc1	0.1807	0.9326	C8H9NO2

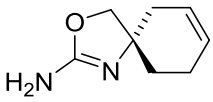
Nc1cc2c(OCOC2)cc1	0.2340	0.7841	C8H9NO2
N#Cc1cc2OCOc2cc1	0.1844	0.8194	C8H5NO2
O=C(OC)c1c(C)[nH]c(C)c1	0.2785	0.7317	C8H11NO2
O=C(N)COc1ccccc1	0.1227	0.8802	C8H9NO2
O=C(OC)c1cc(N)ccc1	0.2016	0.8018	C8H9NO2
O=C(O)c1c(N)cc(C)cc1	0.2578	0.7459	C8H9NO2
O(C)c1cc2nc[nH]c2cc1	0.2120	0.7920	C8H8N2O
O=C1N(C)N=C(C(C)(C)C)C1	0.2896	0.8515	C8H14N2O
Oc1nc(C(C)C)nc(C)c1	0.4024	0.7353	C8H12N2O
OCC1=Cn2c(ncc2)C=C1	0.1881	0.8499	C8H8N2O
OCc1cc2nc[nH]c2cc1	0.2025	0.8439	C8H8N2O
O=C1NN=Cc2c1cccc2	0.3495	0.6505	C8H6N2O
N#CCCNCC1OCCC1	0.0719	0.9648	C8H14N2O
OC1(C#N)C2CCN(C1)CC2	0.5090	0.8849	C8H12N2O
Oc1c(C#N)c(C)cc(C)n1	0.3510	0.6569	C8H8N2O
OCc1nc(CCCC)[nH]c1	0.1723	0.8988	C8H14N2O
O=C(CC#N)N1CCCCC1	0.1898	0.8750	C8H12N2O
O=C(NCc1cnccc1)C	0.2305	0.9262	C8H10N2O
O=C(O)c1cc2c([nH]cc2)cc1	0.1798	0.8202	C9H7NO2
O=C(OCC)c1ccc(N)cc1	0.1503	0.8545	C9H11NO2
O=C(Nc1ccc(OC)cc1)C	0.1073	0.8974	C9H11NO2
O=C(OCC)[C@H]1[C@H](N)CC=CC1	0.3119	0.8862	C9H15NO2
O=C(OCC)c1c(C)cc(C)[nH]1	0.2959	0.7147	C9H13NO2
O(C(C)(C)C)C(=O)N1CC=CC1	0.2214	0.8897	C9H15NO2
O=C(OCc1ccccc1)CN	0.1301	0.9955	C9H11NO2
O=C(OC)c1cc(N)c(C)cc1	0.1827	0.8227	C9H11NO2
O=C1C(CCC#N)C(=O)CCC1	0.3067	0.7990	C9H11NO2
O=C(C)N1CCC(C(=O)C)CC1	0.2330	0.8951	C9H15NO2
O=C(OC)c1cc(CN)ccc1	0.2111	0.8248	C9H11NO2
O=C(OC)c1cc(C#N)ccc1	0.2563	0.7466	C9H7NO2
O=C(OCC)c1c(C)[nH]c(C)c1	0.2602	0.7501	C9H13NO2
O=C(OC)c1c(C#N)cccc1	0.3960	0.6518	C9H7NO2
O=Nc1c(O)ccc2c1cccc2	0.3216	0.6978	C10H7NO2
O=C(Oc1c2c([nH]c1)cccc2)C	0.2915	0.7757	C10H9NO2
O=C1O[C@H]([C@@H](C)N1)c1ccccc1	0.2327	0.9131	C10H11NO2
O=C(OC)c1cc2c([nH]cc2)cc1	0.1679	0.8345	C10H9NO2
O=C1Oc2c(C(C)=C1)ccc(N)c2	0.2982	0.7046	C10H9NO2
NCc1c2OCCCOc2ccc1	0.4024	0.6688	C10H13NO2
NCc1cc2OCCCOc2cc1	0.2122	0.8505	C10H13NO2
OCc1noc(-c2ccccc2)c1	0.1157	0.9080	C10H9NO2
OCc1onc(-c2ccccc2)c1	0.1294	0.9000	C10H9NO2
OCC1N(Cc2occc2)CCC1	0.2605	0.8751	C10H15NO2
O=C1OC[C@H](Cc2ccccc2)N1	0.1333	0.9562	C10H11NO2
OCCN(CCO)c1ccccc1	0.4901	0.7449	C10H15NO2
O(C)c1c(OC)cc2c(c1)CNCC2	0.3130	0.7029	C11H15NO2
O=C1OC(C)(C)[C@@H](c2ccccc2)N1	0.2965	0.8657	C11H13NO2
O=C(NCC(=O)C)Cc1ccccc1	0.2460	0.8973	C11H13NO2

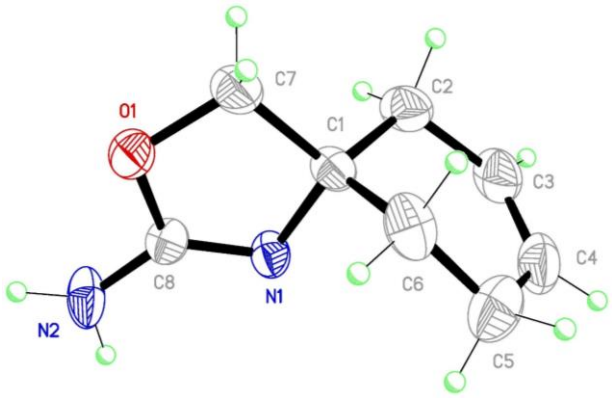
O=C(OC)c1ncc2c(c1)cccc2	0.1409	0.8612	C11H9NO2
O=C(C)c1c(N)c(CCC)c(O)cc1	0.3040	0.7637	C11H15NO2
O=C(O)CC1(CN(C)C)CCCCC1	0.4960	0.7257	C11H21NO2
OCc1c(C)onc1-c1ccccc1	0.2664	0.7941	C11H11NO2
O(CCN(C)C)c1c(CO)cccc1	0.1946	0.8300	C11H17NO2
O(C(C)(C)C)C(=O)c1cc(N)ccc1	0.1824	0.8858	C11H15NO2
O=C(Nc1ccc(OCC=C)cc1)C	0.0702	0.9422	C11H13NO2
O=C(Nc1cc2c(C(=O)CC2)cc1)C	0.1551	0.8506	C11H11NO2
O=C(N(C)C)c1c-2c(C(=O)c3c-2cccc3)ccc1	0.4483	0.6742	C16H13NO2
O(C)c1ccc(CNCc2ccc(OC)cc2)cc1	0.1178	0.9595	C16H19NO2
O=C(CC12CC3CC(C1)CC(C2)C3)N1CCOCC1	0.1592	0.9586	C16H25NO2
FC(F)(F)c1ccc(CO)cc1	0.1638	0.9439	C8H7OF3
Clc1cc(OCC(=O)O)ccc1	0.1310	0.8709	C8H7O3Cl
Fc1cc2C(=O)C(=O)Nc2cc1	0.2277	0.7723	C8H4NO2F
Fc1c(NC(=O)C)ccc(F)c1	0.2136	0.7891	C8H7NOF2
Clc1c(NC(=O)C)c(F)ccc1	0.4058	0.6018	C8H7NOClF
Fc1c(OC(=O)C)ccc(F)c1	0.2273	0.8861	C8H6O2F2
S(CC)c1c(C(=O)O)cccn1	0.3754	0.6717	C8H9NO2S
ClC1=NNC(=O)c2c1cccc2	0.4180	0.5820	C8H5N2OCl
O=C(O)c1sc2ncccc2c1	0.1817	0.8183	C8H5NO2S
NCc1nc(-c2sccc2)sc1	0.2239	0.7930	C8H8N2S2
OCc1noc(-c2sccc2)c1	0.1229	0.9019	C8H7NO2S
O=C(O)c1n(C)c2c(scc2)c1	0.2212	0.7815	C8H7NO2S
OCc1n[nH]c(-c2sccc2)c1	0.1134	0.8956	C8H8N2OS
N(Cc1scc2OCCOc12)C	0.3228	0.7224	C8H11NO2S
S(=O)(=O)(C)c1ccc(C#N)cc1	0.1549	0.9370	C8H7NO2S
S(C)c1sc2c(n1)ccc(N)c2	0.1548	0.8474	C8H8N2S2
S=C1NCN(C2CCCC2)CN1	0.1229	0.9184	C8H15N3S
Clc1nc(-c2occc2)ccn1	0.1873	0.8127	C8H5N2OCl
Clc1sc(C2=NN(C)CC2)cc1	0.1058	0.9037	C8H9N2ClS
Clc1c(Cl)ccc(NC(=O)C)c1	0.1982	0.8037	C8H7NOCl2
Clc1ccc(SCC(=O)O)cc1	0.0971	0.9480	C8H7O2ClS
Clc1c(C)c(C#N)c(O)nc1C	0.3474	0.6582	C8H7N2OCl
Clc1cc(C(=O)OC)c(O)cc1	0.2323	0.7701	C8H7O3Cl
Fc1ccc(CNC(=O)N)cc1	0.1160	0.9905	C8H9N2OF
FC(F)(F)c1c(CO)cccc1	0.4573	0.6836	C8H7OF3
Clc1c(CO)nc(CCCC)[nH]1	0.2479	0.8232	C8H13N2OCl
S=C(NN)NC1C2C=CC(C1)C2	0.3102	0.8552	C8H13N3S
Clc1cc(Cl)cc(OCC#N)c1	0.3151	0.6866	C8H5NOCl2
S(CC#N)c1c(F)cc(F)cc1	0.1607	0.9087	C8H5NF2S
S=C(Nc1c(OC)cccc1)N	0.2920	0.7332	C8H10N2OS
Clc1c(C(=O)OC)ccc(F)c1	0.3007	0.7813	C8H6O2ClF
O=C1NN=C(c2sccc2)CC1	0.1465	0.8724	C8H8N2OS
FC(F)(F)c1cc(N)c(OC)cc1	0.2119	0.8552	C8H8NOF3
Fc1cc(F)cc(C(O)C(=O)O)c1	0.3356	0.8586	C8H6O3F2
FC(F)(F)c1nc(C)c(C#N)cc1	0.1955	0.8740	C8H5N2F3
Clc1ccc(CNS(=O)(=O)C)cc1	0.0957	0.9716	C8H10NO2ClS

O=C(O)c1nc(-c2sccc2)sc1	0.1809	0.8191	C8H5NO2S2
S(=O)(=O)(N)c1cc2c(cc1)COC2	0.1890	0.8939	C8H9NO3S
Clc1sc(C(OC(C)(C)C)=O)cn1	0.1276	0.9275	C8H10NO2ClS
ClC=1C(=O)C(Cl)=CN(CCC#N)C=1	0.3168	0.7079	C8H6N2OCl2
Clc1cc(NC(=S)N)c(OC)cc1	0.3658	0.6540	C8H9N2OClS
FC(F)(F)c1cnc(N(C)C)cc1	0.1554	0.9094	C8H9N2F3
FC(F)(F)Oc1ccc(CO)cc1	0.1400	0.9484	C8H7O2F3
FC(F)(F)Oc1ccc(CC#N)cc1	0.1403	0.9705	C9H6NOF3
Fc1c(NC(=O)C)c(C#N)cc(F)c1	0.3497	0.6673	C9H6N2OF2
Fc1c(F)ccc(-c2nc(N)sc2)c1	0.1461	0.8637	C9H6N2F2S
O=C(O)c1sc(-c2nc(C)sc2)cc1	0.1087	0.8927	C9H7NO2S2
Fc1c(N(C)C)c(F)cc(C(=O)N)c1	0.2561	0.7567	C9H10N2OF2
Clc1c(F)ccc(NC(=O)CSC)c1	0.1720	0.8946	C9H9NOClFS
O=S1(=O)CCN(Cc2sccc2)CC1	0.1538	0.9913	C9H13NO2S2
S(C)c1c(C(=O)C)c(C)c(C(=O)O)s1	0.3663	0.7309	C9H10O3S2
Clc1c(F)ccc(N2C(=O)C=CS2)c1	0.2071	0.7929	C9H5NOClFS
Clc1c(F)c(N2C(=O)C=CS2)ccc1	0.2380	0.7645	C9H5NOClFS
Clc1sc([SH0](=O)C)c2C(=O)CCCc12	0.4492	0.6241	C9H9O2ClS2
Clc1c(Cl)cccc1NC(=O)N(C)C	0.2101	0.8023	C9H10N2OCl2
Clc1ccc(CCNC(=S)NN)cc1	0.1770	0.9074	C9H12N3ClS
Clc1cc2C(=O)CCS(=O)(=O)c2cc1	0.2936	0.7708	C9H7O3ClS
Clc1ccc(S(=O)(=O)CCC#N)cc1	0.1325	0.9591	C9H8NO2ClS
Fc1cc2C(=O)CCS(=O)(=O)c2cc1	0.3716	0.7099	C9H7O3FS
FC(F)(F)c1cc(OCC#N)ccc1	0.1718	0.8767	C9H6NOF3

Crystallographic Data

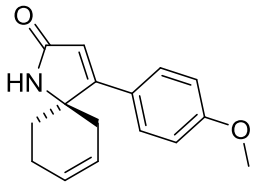
3-Oxa-1-azaspiro[4.5]deca-1,7-dien-2-amine (6)

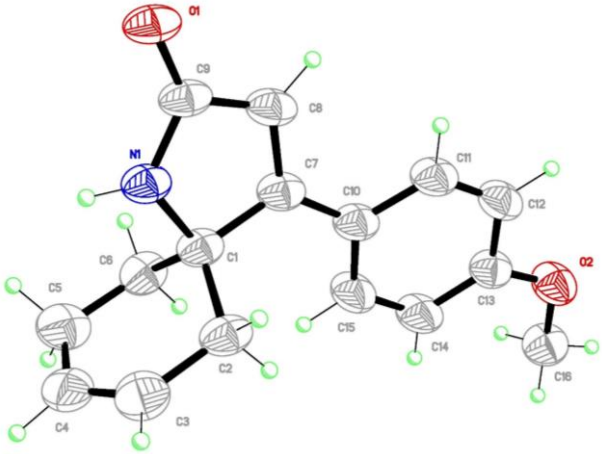




Identification code	DS_B1_0020	CCDC	1912267
Empirical formula	$C_8H_{12}N_2O$	Formula weight (Da)	152.20
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Monoclinic	Space group	P $2_1/c$
Unit cell lengths (Å)	a = 10.3028(8) b = 7.6579(5) c = 10.3040(8)	Unit cell angles (°)	α = 90 β = 91.728(5) γ = 90
Volume ($Å^3$)	812.593	Z	4
Density calculated (gcm^{-3})	1.244	Absorption coefficient (mm^{-1})	0.678
F(000)	328	Crystal size (mm^3)	0.250 × 0.060 × 0.020
θ range for data coll. (°)	4.293 – 66.966	Completeness to θ = 66.966°	99.9%
Reflections collected	9075	Independent reflections	1443
Index ranges	–12 ≤ h ≤ 12 –9 ≤ k ≤ 9 –12 ≤ l ≤ 12	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.987/0.849
Data/restraints/parameters	1443/0/108		
Goodness of fit F^2	1.094	Largest diff. peak/hole ($eÅ^{-3}$)	0.189/-0.184
Final R indices [I > 2σ(I)]	R1 = 0.0465 wR2 = 0.1122	R indices (all data)	R1 = 0.0583 wR2 = 0.1185

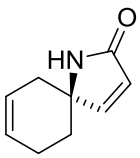
4-(4-Methoxyphenyl)-1-azaspiro[4.5]deca-3,7-dien-2-one (18)

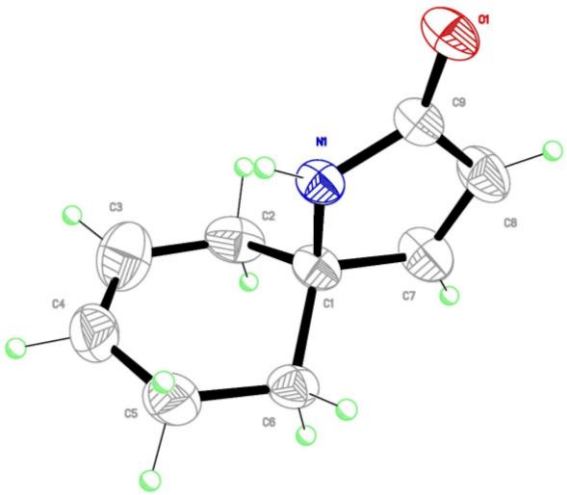




Identification code	DS_B1_0023	CCDC	1912268
Empirical formula	$C_{16}H_{17}NO_2$	Formula weight (Da)	255.31
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Triclinic	Space group	P $\bar{1}$
Unit cell lengths (Å)	a = 5.9870(3) b = 9.9585(5) c = 11.5405(6)	Unit cell angles (°)	α = 71.715(3) β = 83.642(3) γ = 89.345(3)
Volume (Å^3)	649.10(6)	Z	2
Density calculated (gcm^{-3})	1.306	Absorption coefficient (mm^{-1})	0.687
F(000)	272	Crystal size (mm^3)	0.200 × 0.200 × 0.100
θ range for data coll. (°)	4.060 – 67.188	Completeness to θ = 67.188°	98.6%
Reflections collected	6875	Independent reflections	2283
Index ranges	–7 ≤ h ≤ 7 –11 ≤ k ≤ 11 –13 ≤ l ≤ 13	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.934/0.875
Data/restraints/parameters	2283/0/177		
Goodness of fit F^2	1.048	Largest diff. peak/hole (eÅ^{-3})	0.314/-0.261
Final R indices [I > 2σ(I)]	R1 = 0.0558 wR2 = 0.1488	R indices (all data)	R1 = 0.0737 wR2 = 0.1626

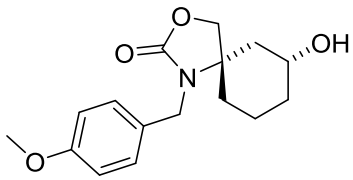
1-Azaspiro[4.5]deca-3,7-dien-2-one (20)

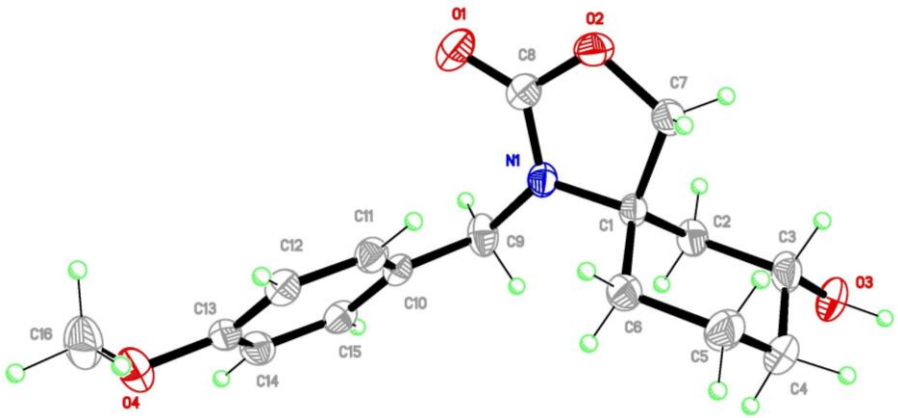




Identification code	DS_B1_0024	CCDC	1912266
Empirical formula	$C_9H_{11}NO$	Formula weight (Da)	149.19
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Orthorhombic	Space group	P n a 2_1
Unit cell lengths (Å)	a = 10.2930(5) b = 9.8937(5) c = 7.6125(4)	Unit cell angles (°)	α = 90 β = 90 γ = 90
Volume ($Å^3$)	775.23(7)	Z	4
Density calculated (gcm^{-3})	1.278	Absorption coefficient (mm^{-1})	0.667
F(000)	320	Crystal size (mm^3)	0.180 × 0.080 × 0.040
θ range for data coll. (°)	6.204 – 66.745	Completeness to θ = 66.745°	99.9%
Reflections collected	2582	Independent reflections	1285
Index ranges	–12 ≤ h ≤ 12 –10 ≤ k ≤ 11 –8 ≤ l ≤ 9	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.974/0.889
Data/restraints/parameters	1285/1/104		
Goodness of fit F^2	1.075	Largest diff. peak/hole ($eÅ^{-3}$)	0.213/-0.198
Final R indices [I > 2σ(I)]	R1 = 0.0446 wR2 = 0.1130	R indices (all data)	R1 = 0.0510 wR2 = 0.1194

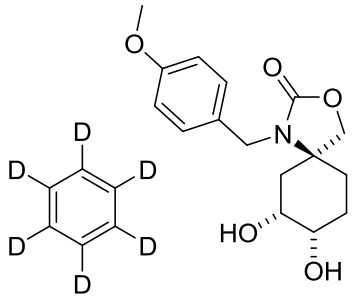
(5*R,7*S**)-7-Hydroxy-1-(4-methoxy-benzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S7)**

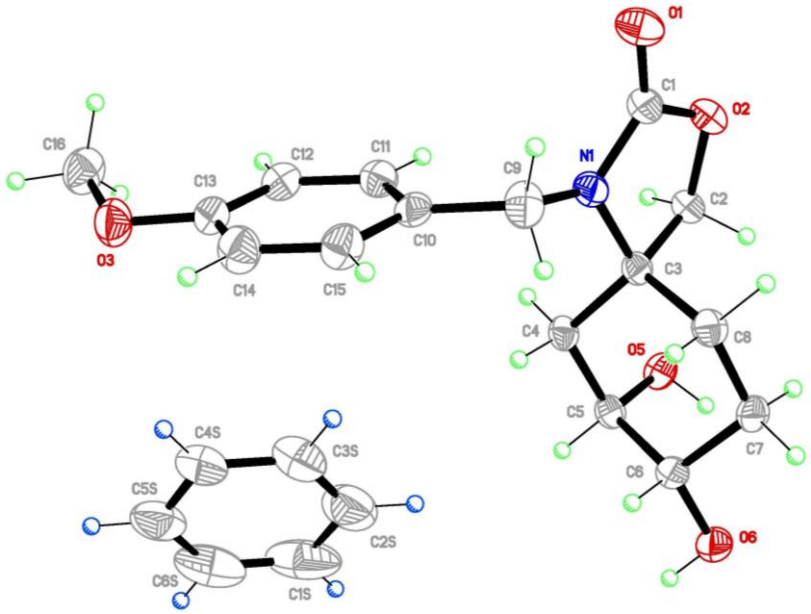




Identification code	DS_B1_0022	CCDC	1912287
Empirical formula	$C_{16}H_{21}NO_4$	Formula weight (Da)	291.34
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Monoclinic	Space group	P 2_1/c
Unit cell lengths (Å)	a = 9.1715(2) b = 6.6200(2) c = 23.5770(6)	Unit cell angles (°)	α = 90 β = 92.5461(12) γ = 90
Volume (Å^3)	1430.07	Z	4
Density calculated (gcm^{-3})	1.353	Absorption coefficient (mm^{-1})	0.795
F(000)	624	Crystal size (mm^3)	0.220 × 0.100 × 0.040
θ range for data coll. (°)	3.753 – 67.040	Completeness to θ = 67.040°	99.7%
Reflections collected	15488	Independent reflections	2545
Index ranges	–10 ≤ h ≤ 10 –7 ≤ k ≤ 7 –28 ≤ l ≤ 28	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.969/0.845
Data/restraints/parameters	2545/2/204		
Goodness of fit F^2	1.306	Largest diff. peak/hole (eÅ^{-3})	0.245/-0.286
Final R indices [I > 2σ(I)]	R1 = 0.0654 wR2 = 0.1474	R indices (all data)	R1 = 0.0692 wR2 = 0.1490

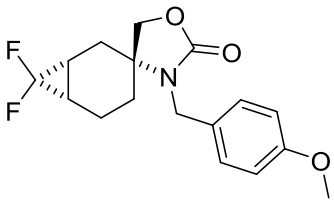
(5*R,7*S**,8*R**)-7,8-Dihydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]-decan-2-one (23b)**

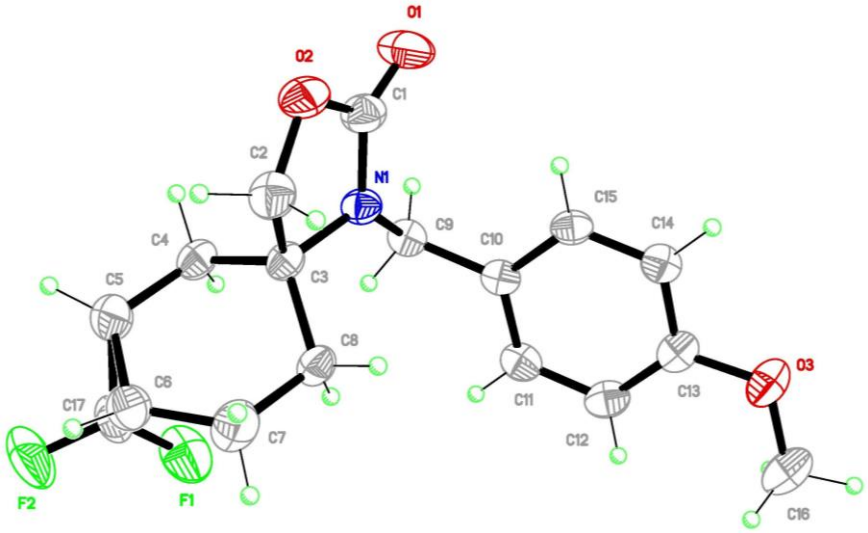




Identification code	DS_B1_0015	CCDC	1912286
Empirical formula	$C_{22}H_{21}D_6NO_5$	Formula weight (Da)	391.48
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Triclinic	Space group	P $\bar{1}$
Unit cell lengths (Å)	a = 6.2880(2) b = 7.9649(3) c = 20.1941(8)	Unit cell angles (°)	α = 82.118(3) β = 87.204(2) γ = 82.302(2)
Volume ($Å^3$)	992.33(6)	Z	2
Density calculated (gcm^{-3})	1.310	Absorption coefficient (mm^{-1})	0.743
F(000)	412	Crystal size (mm^3)	0.120 × 0.120 × 0.020
θ range for data coll. (°)	2.210 – 66.855	Completeness to θ = 66.855°	99.5%
Reflections collected	13031	Independent reflections	3530
Index ranges	–7 ≤ h ≤ 7 –9 ≤ k ≤ 9 –23 ≤ l ≤ 24	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.985/0.916
Data/restraints/parameters	3530/0/261		
Goodness of fit F^2	1.037	Largest diff. peak/hole ($eÅ^{-3}$)	0.234/-0.181
Final R indices [I > 2σ(I)]	R1 = 0.0434 wR2 = 0.0890	R indices (all data)	R1 = 0.0681 wR2 = 0.0988

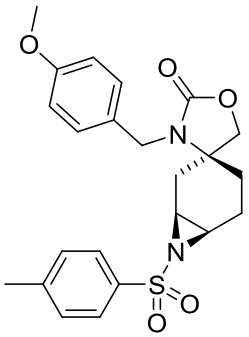
(1*R,3*R**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24a)**

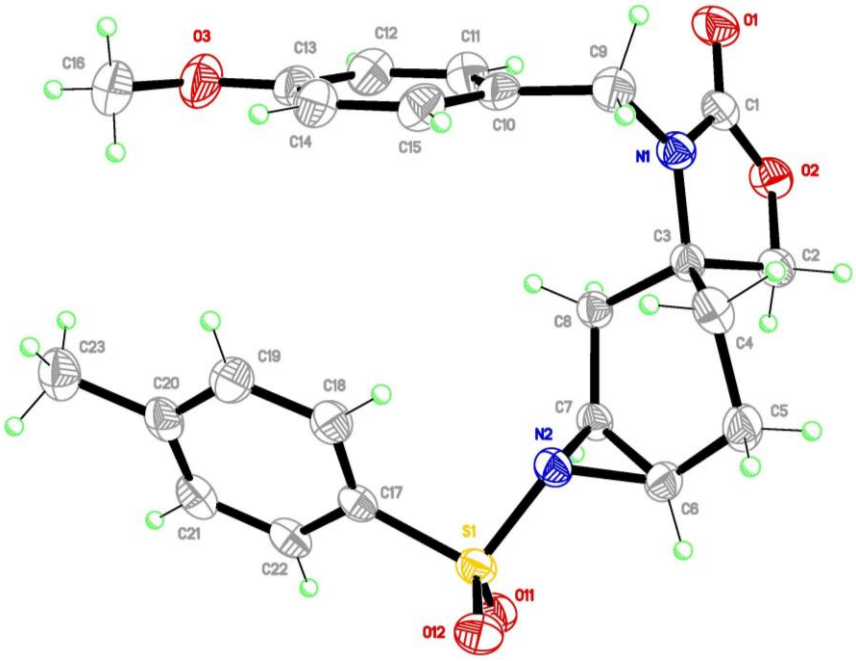




Identification code	DS_B1_0018	CCDC	1912284
Empirical formula	$C_{17}H_{19}F_2NO_3$	Formula weight (Da)	323.33
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Monoclinic	Space group	P 2_1/c
Unit cell lengths (Å)	a = 13.5002(5) b = 12.3831(5) c = 9.9272(4)	Unit cell angles (°)	α = 90 β = 110.910(2) γ = 90
Volume (Å^3)	1550.28(11)	Z	4
Density calculated (gcm^{-3})	1.385	Absorption coefficient (mm^{-1})	0.934
F(000)	680	Crystal size (mm^3)	0.300 × 0.180 × 0.120
θ range for data coll. (°)	3.505 – 66.845	Completeness to θ = 66.845°	99.6%
Reflections collected	11811	Independent reflections	2739
Index ranges	–16 ≤ h ≤ 16 –14 ≤ k ≤ 10 –11 ≤ l ≤ 11	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.896/0.767
Data/restraints/parameters	2739/0/228		
Goodness of fit F^2	1.112	Largest diff. peak/hole (eÅ^{-3})	0.239/-0.193
Final R indices [I > 2σ(I)]	R1 = 0.0416 wR2 = 0.0990	R indices (all data)	R1 = 0.0453 wR2 = 0.1012

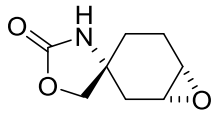
(1*R,3*R**,6*S**)-3'-(4-Methoxybenzyl)-7-tosyl-7-azaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (25b)**

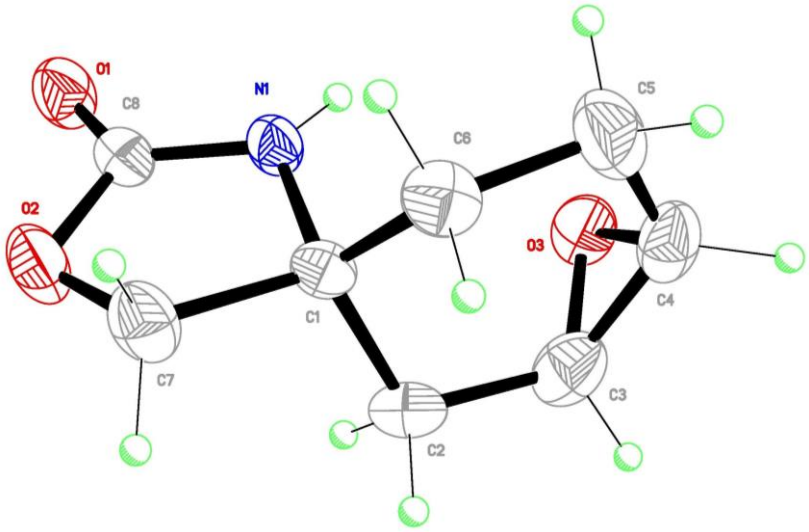




Identification code	DS_B1_0014	CCDC	1912283
Empirical formula	$C_{23}H_{26}N_2O_5S$	Formula weight (Da)	442.52
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Triclinic	Space group	P $\bar{1}$
Unit cell lengths (Å)	a = 7.0012(2) b = 12.6065(4) c = 12.9625(4)	Unit cell angles (°)	α = 80.1740(10) β = 75.6130(10) γ = 76.4970(10)
Volume (Å^3)	1069.83(6)	Z	2
Density calculated (gcm^{-3})	1.374	Absorption coefficient (mm^{-1})	1.668
F(000)	468	Crystal size (mm^3)	0.250 × 0.200 × 0.150
θ range for data coll. (°)	3.545 – 66.774	Completeness to θ = 66.774°	98.7%
Reflections collected	8306	Independent reflections	3741
Index ranges	–7 ≤ h ≤ 8 –15 ≤ k ≤ 13 –14 ≤ l ≤ 15	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.7886/0.681
Data/restraints/parameters	3741/0/282		
Goodness of fit F^2	1.038	Largest diff. peak/hole (eÅ^{-3})	0.308/-0.418
Final R indices [I > 2σ(I)]	R1 = 0.0353 wR2 = 0.0894	R indices (all data)	R1 = 0.0403 wR2 = 0.0931

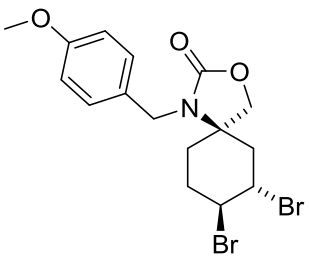
(1*R,3*R**,6*S**)-7-Oxaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (26a)**

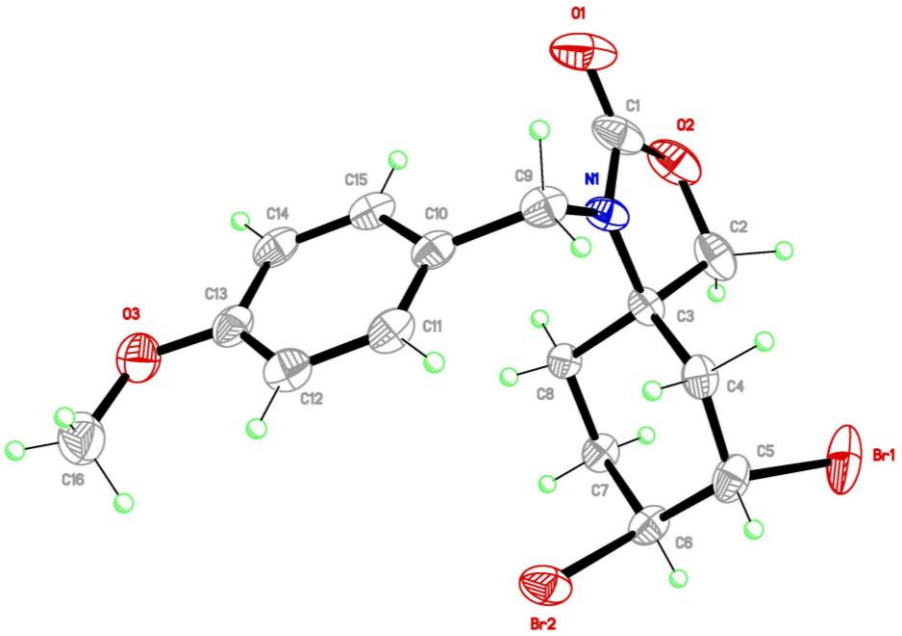




Identification code	DS_B1_0021	CCDC	1912289
Empirical formula	$C_8H_{11}NO_3$	Formula weight (Da)	169.18
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Monoclinic	Space group	P 2_1/n
Unit cell lengths (Å)	a = 5.7530(2) b = 12.8809(4) c = 10.6497(3)	Unit cell angles (°)	α = 90 β = 92.918(2) γ = 90
Volume (Å^3)	788.16(4)	Z	4
Density calculated (gcm^{-3})	1.426	Absorption coefficient (mm^{-1})	0.919
F(000)	360	Crystal size (mm^3)	0.250 × 0.080 × 0.070
θ range for data coll. (°)	5.393 – 66.842	Completeness to θ = 66.842°	99.6%
Reflections collected	5783	Independent reflections	1394
Index ranges	–7 ≤ h ≤ 8 –15 ≤ k ≤ 13 –14 ≤ l ≤ 15	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.7886/0.681
Data/restraints/parameters	1394/18/132		
Goodness of fit F^2	1.137	Largest diff. peak/hole (eÅ^{-3})	0.187/-0.199
Final R indices [I > 2σ(I)]	R1 = 0.0415 wR2 = 0.1001	R indices (all data)	R1 = 0.0477 wR2 = 0.1035

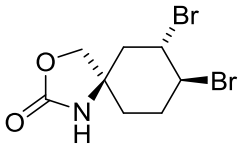
(5*R,7*S**,8*S**)-7,8-Dibromo-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (27a)**

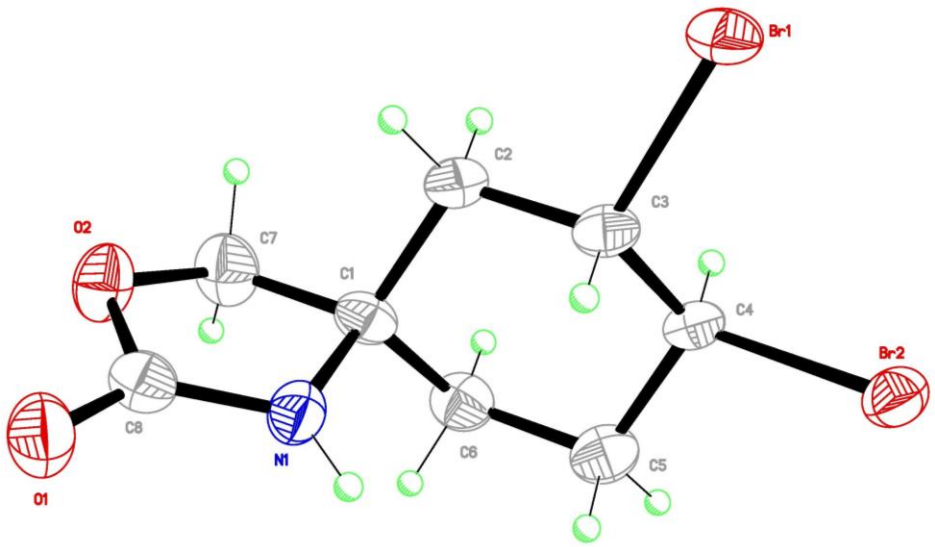




Identification code	DS_B1_0019	CCDC	1912285
Empirical formula	$C_{16}H_{19}Br_2NO_3$	Formula weight (Da)	433.14
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Monoclinic	Space group	P 2_1/n
Unit cell lengths (Å)	a = 6.4606(2) b = 12.5480(3) c = 20.3610(6)	Unit cell angles (°)	α = 90 β = 98.4700(10) γ = 90
Volume (Å^3)	1632.61(8)	Z	4
Density calculated (gcm^{-3})	1.762	Absorption coefficient (mm^{-1})	6.403
F(000)	864	Crystal size (mm^3)	0.140 × 0.140 × 0.140
θ range for data coll. (°)	4.151 – 66.735	Completeness to θ = 66.735°	99.5%
Reflections collected	17954	Independent reflections	2886
Index ranges	–7 ≤ h ≤ 6 –14 ≤ k ≤ 13 –21 ≤ l ≤ 24	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.468/0.468
Data/restraints/parameters	2886/0/201		
Goodness of fit F^2	1.092	Largest diff. peak/hole (eÅ^{-3})	0.546/-0.461
Final R indices [I > 2σ(I)]	R1 = 0.0243 wR2 = 0.0573	R indices (all data)	R1 = 0.0264 wR2 = 0.0581

(5*R,7*S**,8*S**)-7,8-Dibromo-3-oxa-1-azaspiro[4.5]decan-2-one (28)**



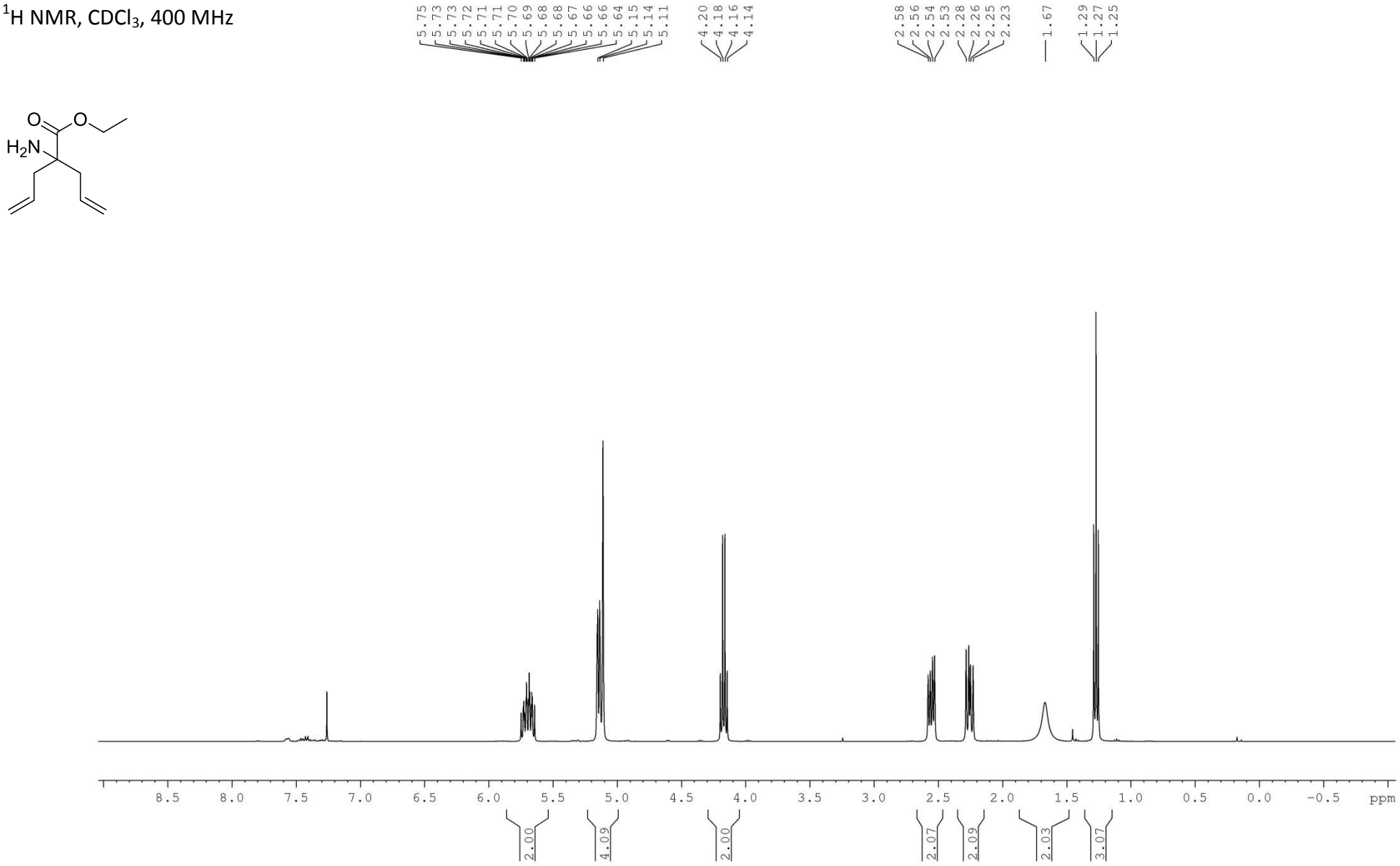


Identification code	DS_B1_0026	CCDC	1912288
Empirical formula	$C_8H_{11}Br_2NO_2$	Formula weight (Da)	313.00
Temperature (K)	180(2)	Wavelength (Å)	1.54178
Crystal system	Monoclinic	Space group	P 2_1/c
Unit cell lengths (Å)	a = 13.0067(12) b = 6.2766(6) c = 12.8006(10)	Unit cell angles (°)	α = 90 β = 103.002(6) γ = 90
Volume (Å^3)	1018.22(16)	Z	4
Density calculated (gcm^{-3})	2.042	Absorption coefficient (mm^{-1})	9.863
F(000)	608	Crystal size (mm^3)	0.300 × 0.040 × 0.010
θ range for data coll. (°)	3.486 – 66.672	Completeness to θ = 66.672°	99.7%
Reflections collected	13072	Independent reflections	1806
Index ranges	–15 ≤ h ≤ 15 –7 ≤ k ≤ 6 –14 ≤ l ≤ 15	Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan	Max./min. transmission	0.908/0.156
Data/restraints/parameters	1806/0/118		
Goodness of fit F^2	1.046	Largest diff. peak/hole (eÅ^{-3})	0.945/-0.788
Final R indices [I > 2σ(I)]	R1 = 0.0528 wR2 = 0.1174	R indices (all data)	R1 = 0.0884 wR2 = 0.1336

NMR Spectra

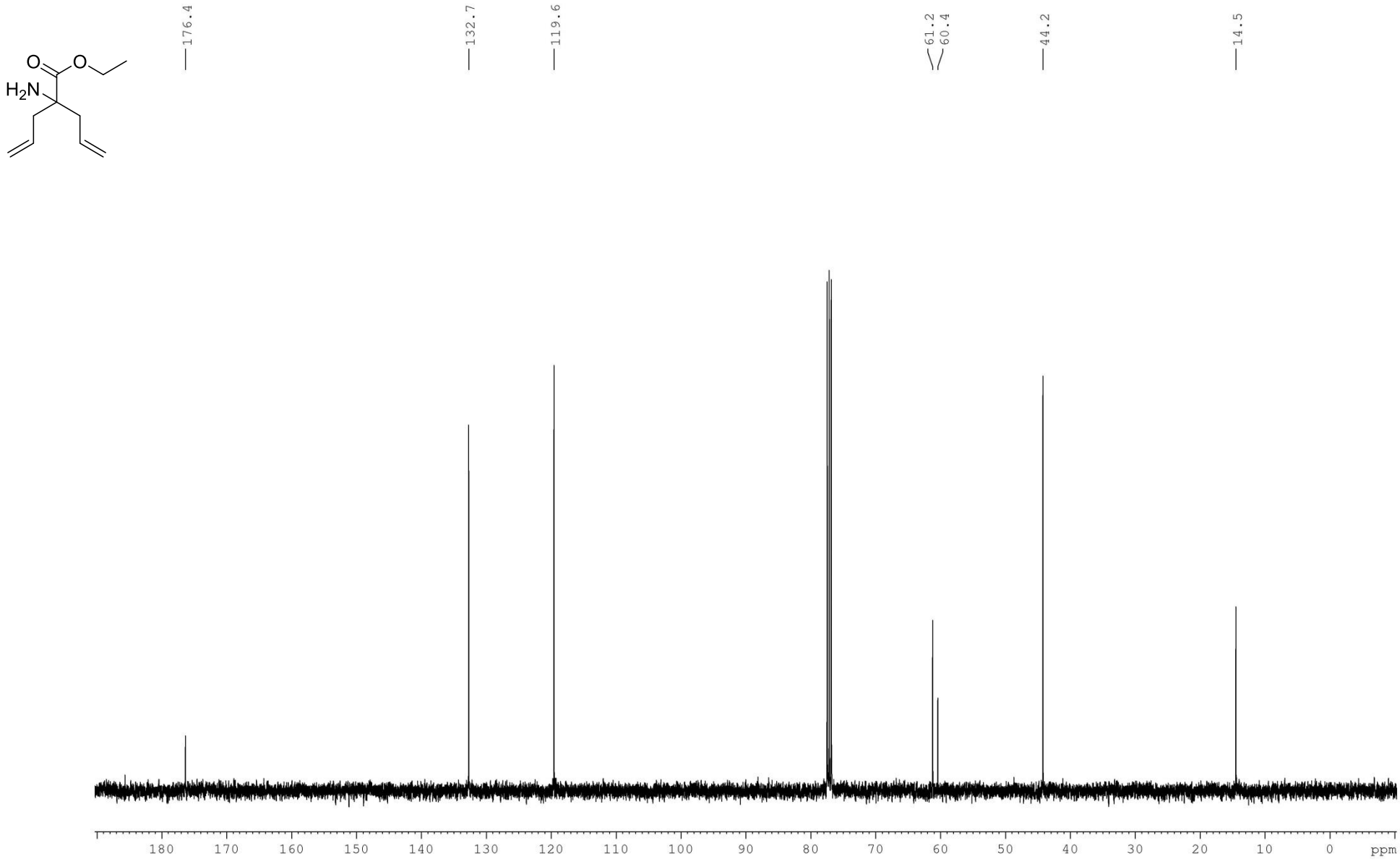
Ethyl 2-allyl-2-aminopent-4-enoate (3a)

^{1}H NMR, $CDCl_3$, 400 MHz



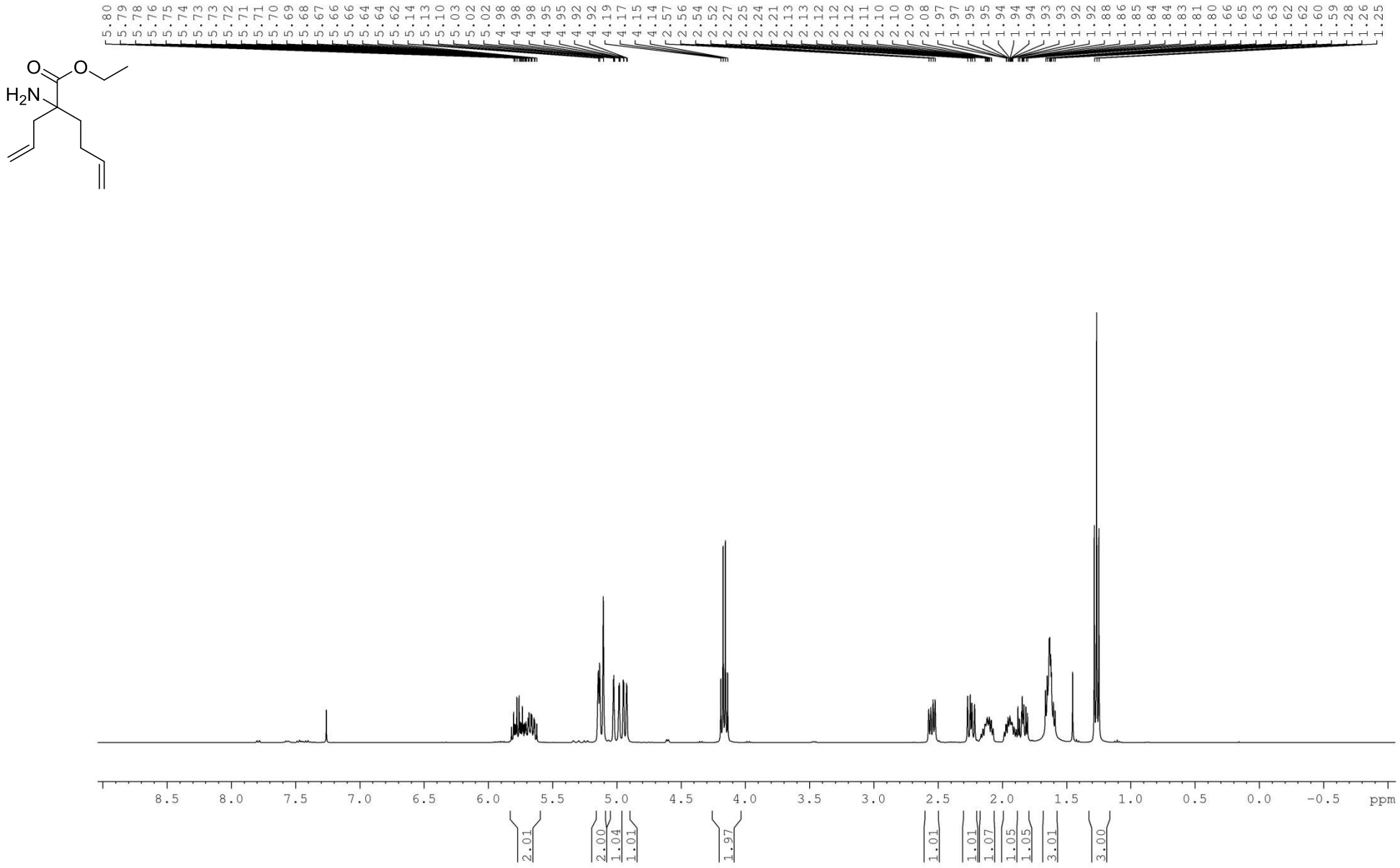
Ethyl 2-allyl-2-aminopent-4-enoate (3a)

^{13}C NMR, $CDCl_3$, 101 MHz



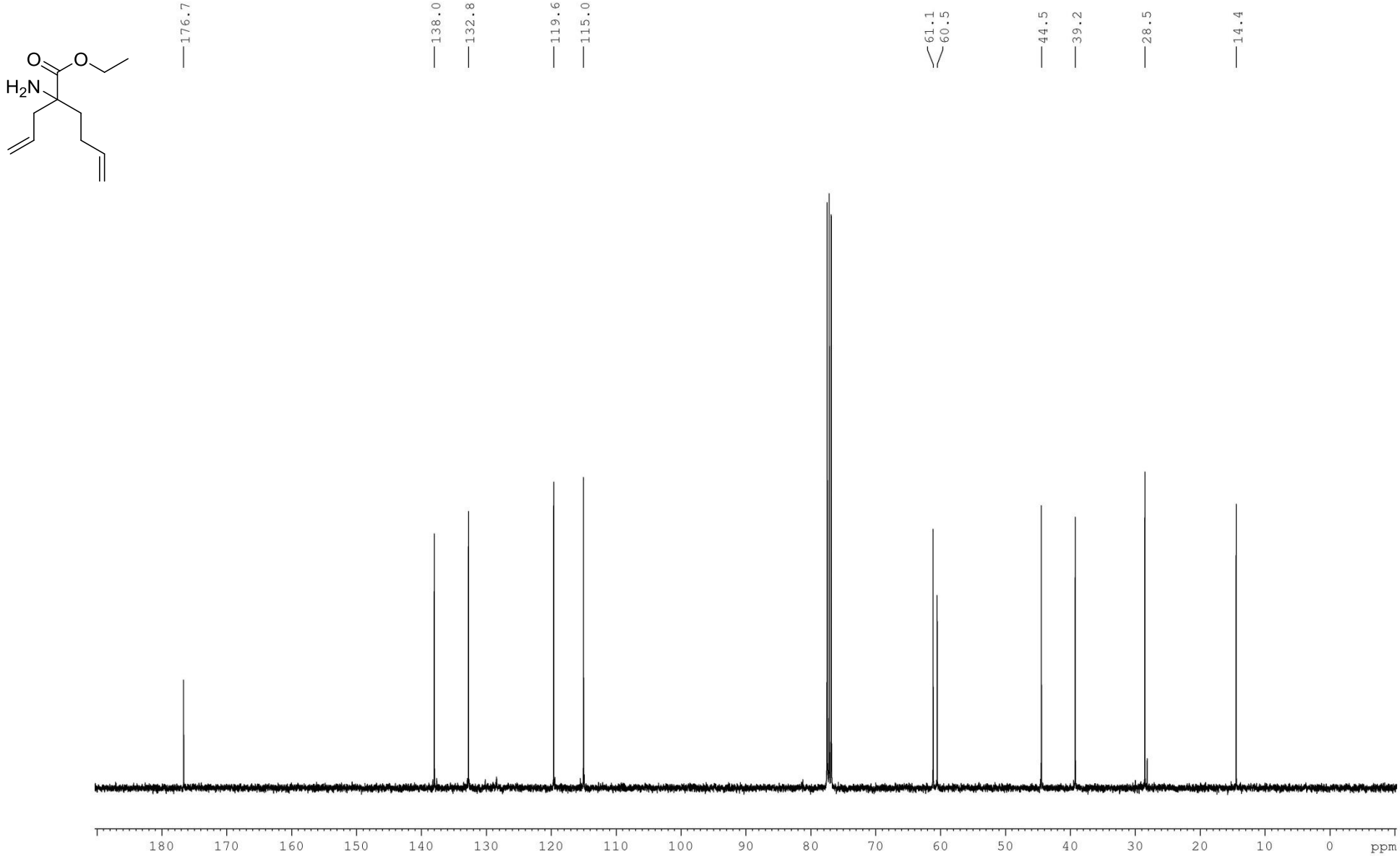
Ethyl 2-allyl-2-aminohex-5-enoate (3b)

^{1}H NMR, $CDCl_3$, 400 MHz



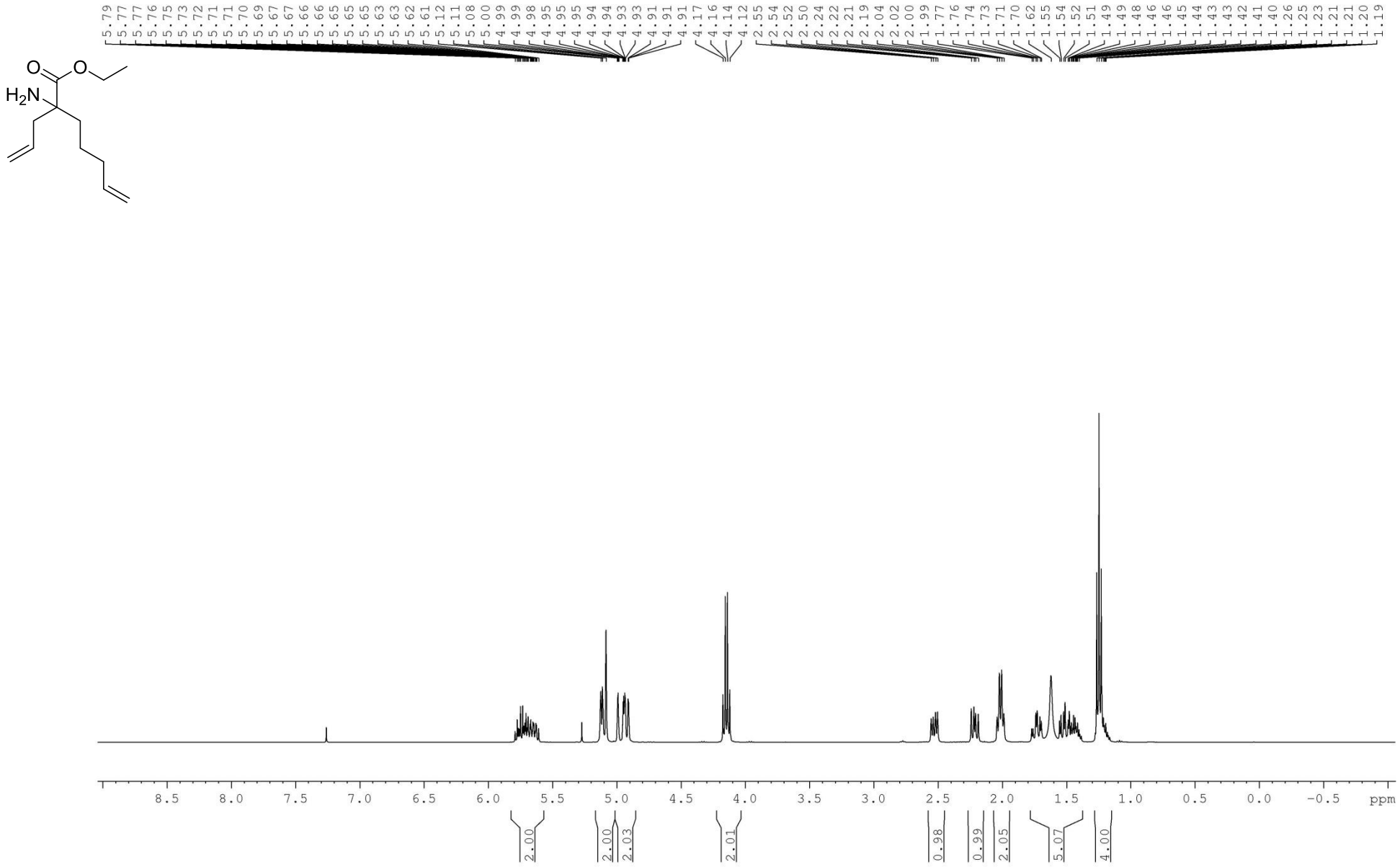
Ethyl 2-allyl-2-aminohex-5-enoate (3b)

^{13}C NMR, $CDCl_3$, 101 MHz



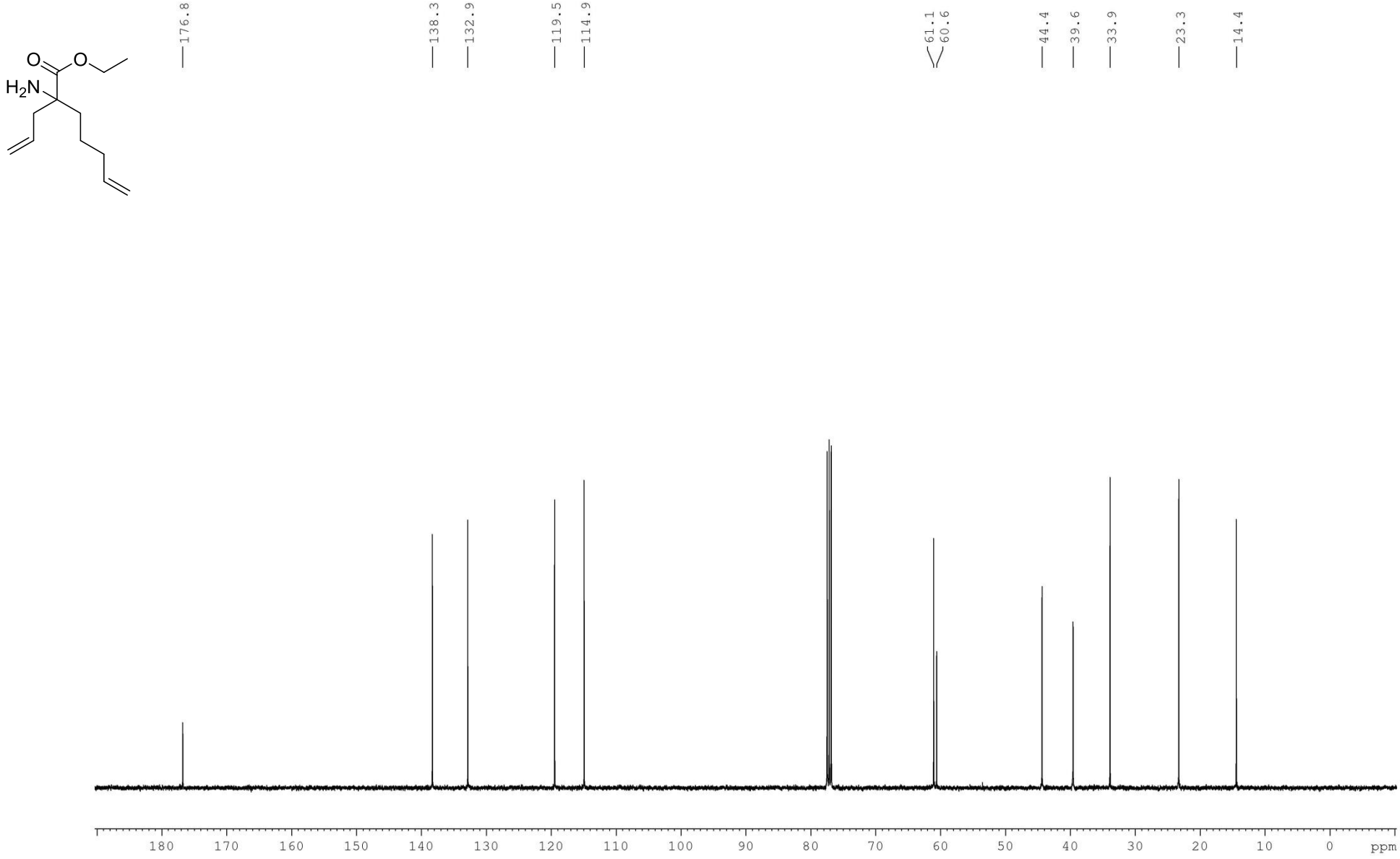
Ethyl 2-allyl-2-aminohept-6-enoate (3c)

^{1}H NMR, $CDCl_3$, 400 MHz



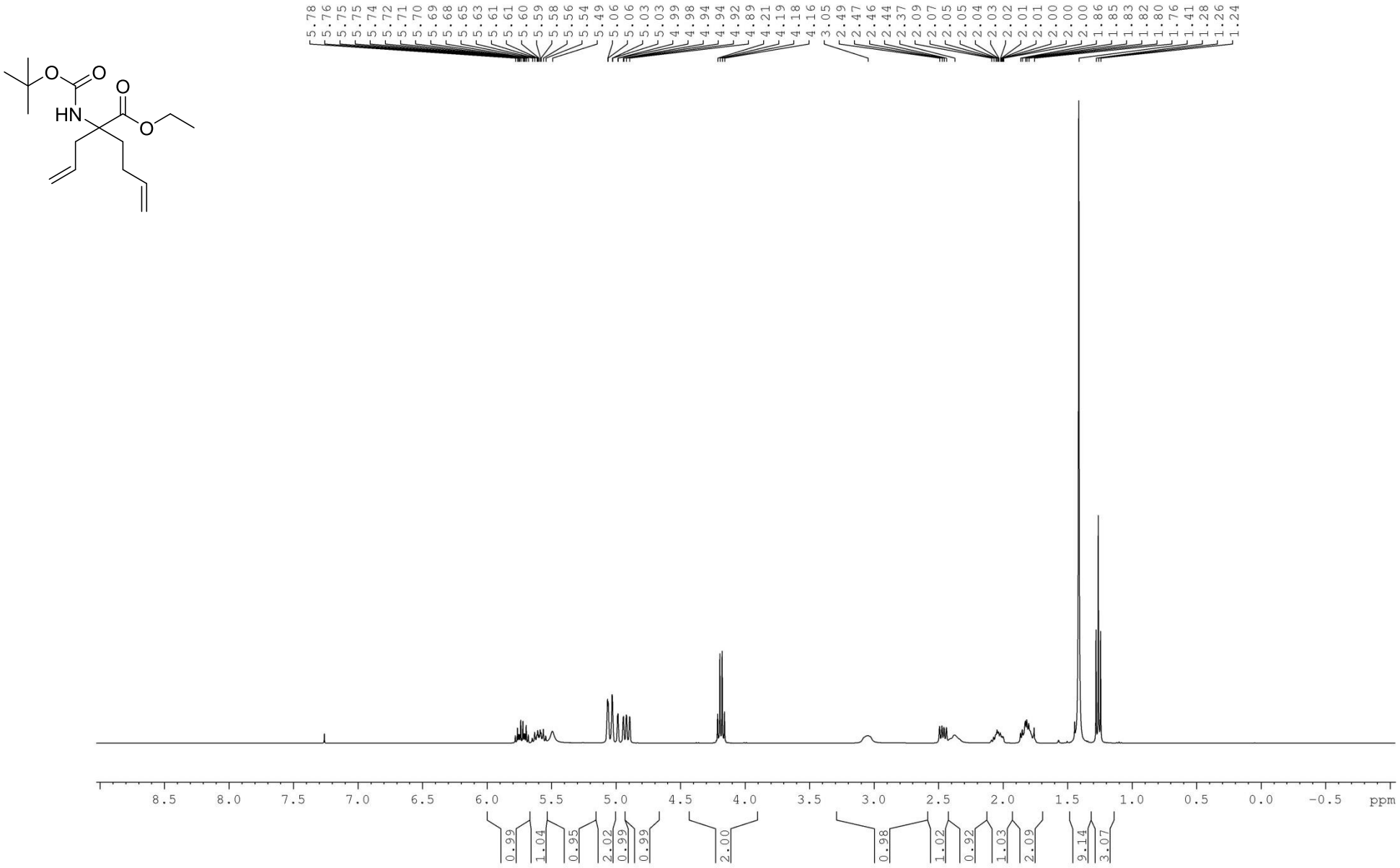
Ethyl 2-allyl-2-aminohept-6-enoate (3c)

^{13}C NMR, $CDCl_3$, 101 MHz



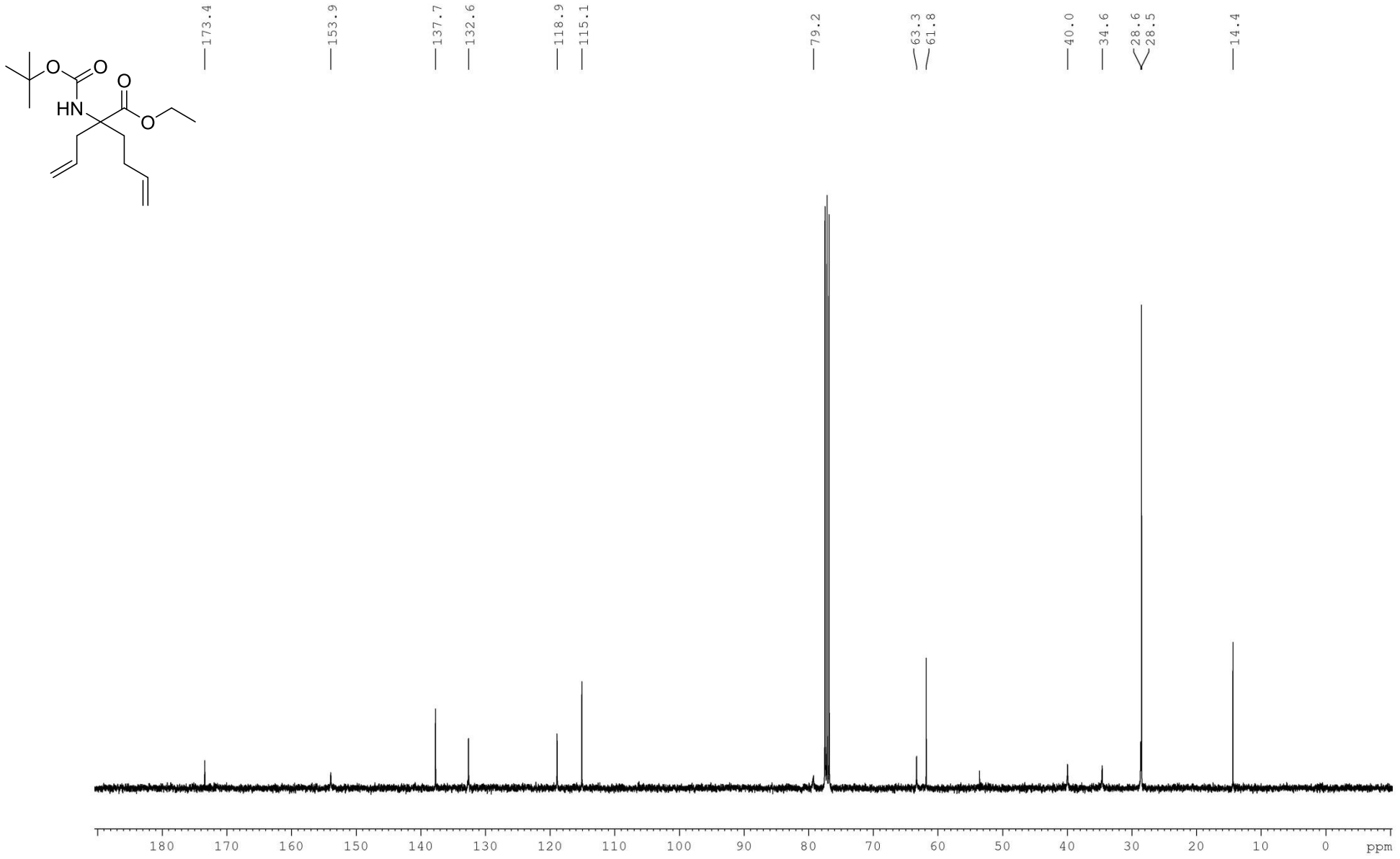
Ethyl 2-allyl-2-((*tert*-butoxycarbonyl)amino)hex-5-enoate (S1)

^{1}H NMR, $CDCl_3$, 400 MHz



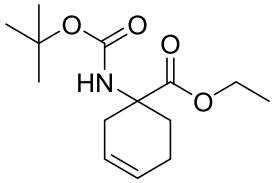
Ethyl 2-allyl-2-((*tert*-butoxycarbonyl)amino)hex-5-enoate (S1)

^{13}C NMR, $CDCl_3$, 101 MHz



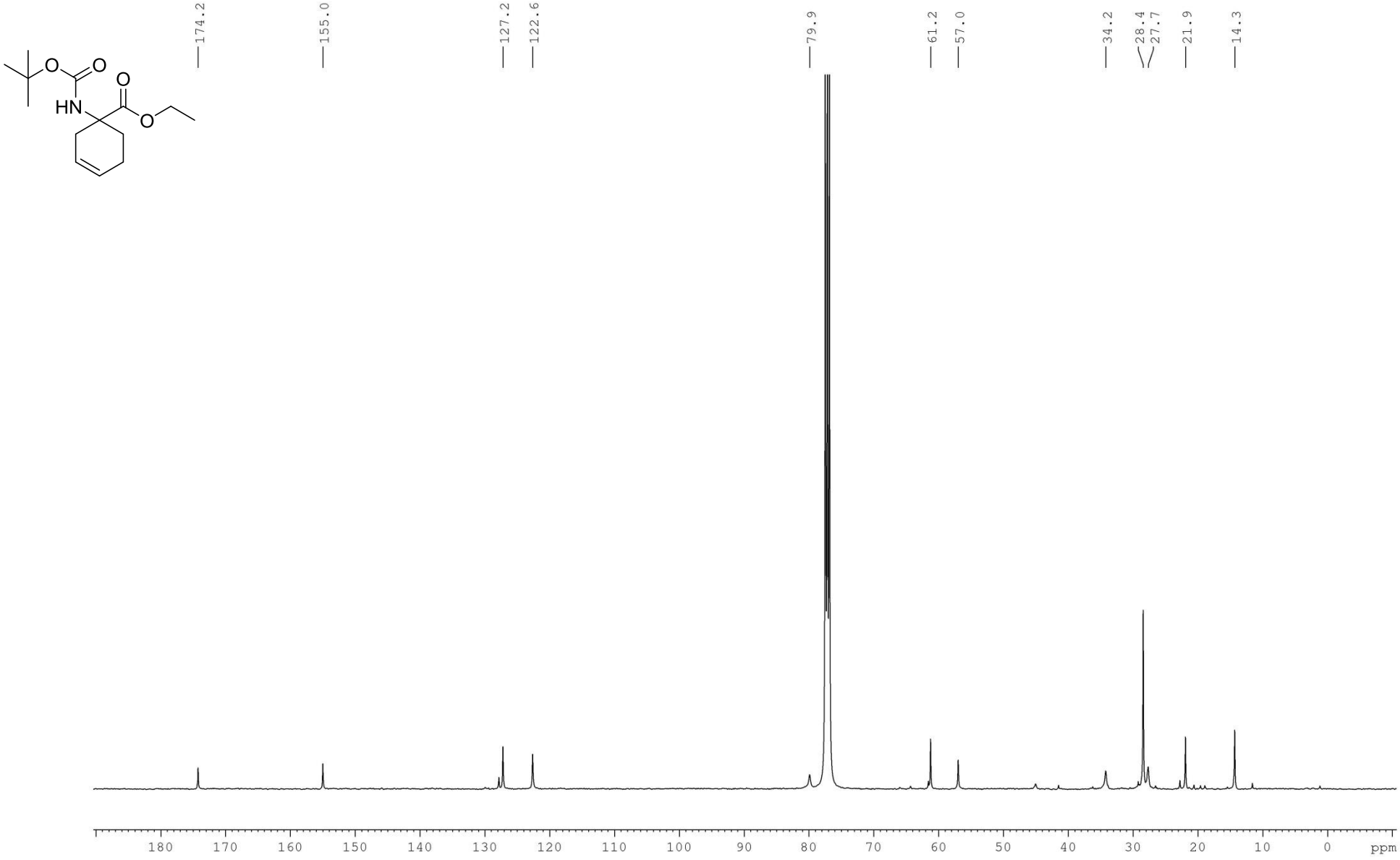
Ethyl 1-((*tert*-butoxycarbonyl)amino)cyclohex-3-ene-1-carboxylate (S2)

^{1}H NMR, $CDCl_3$, 400 MHz



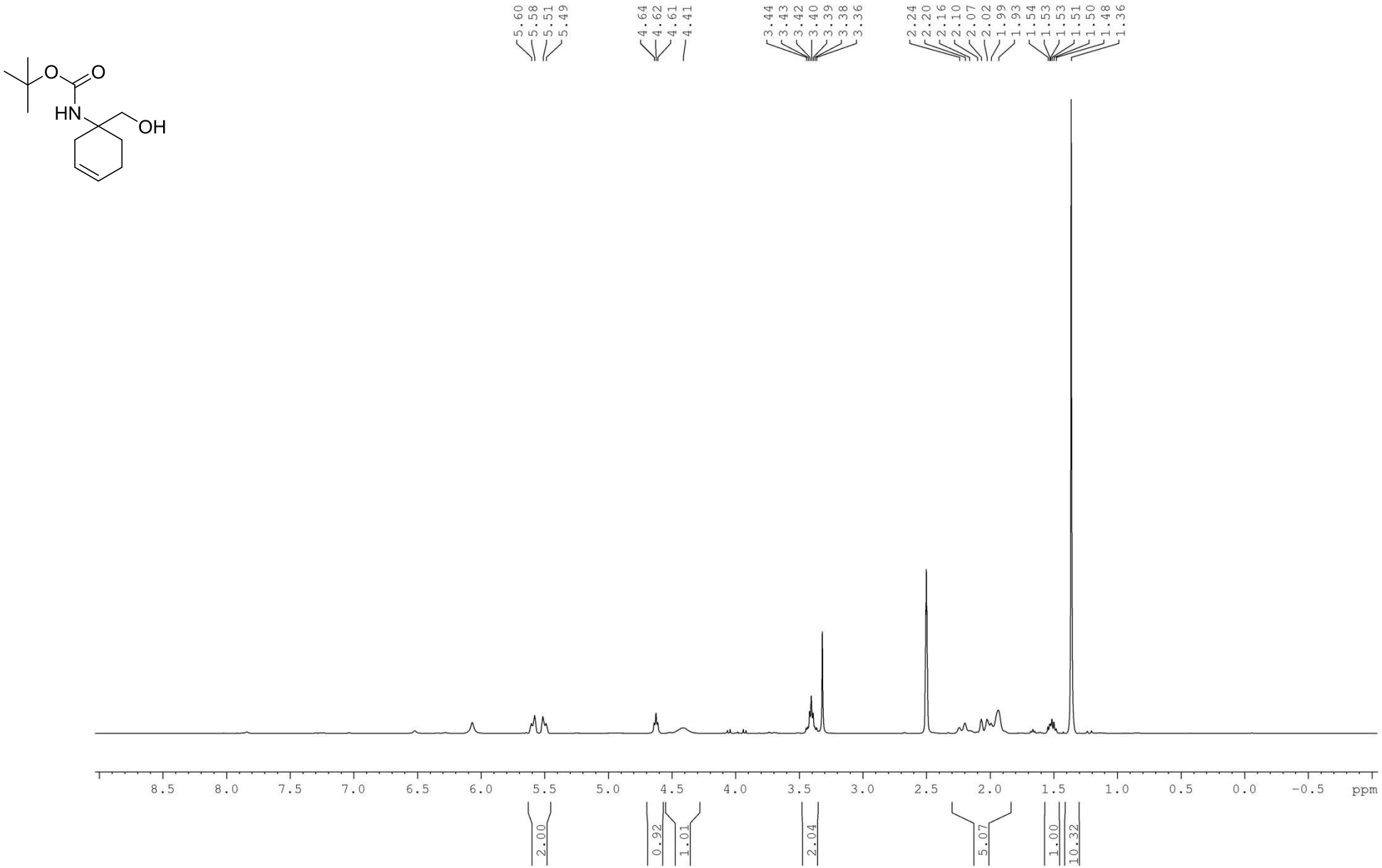
Ethyl 1-((*tert*-butoxycarbonyl)amino)cyclohex-3-ene-1-carboxylate (S2)

^{13}C NMR, $CDCl_3$, 101 MHz, LB = 10 Hz



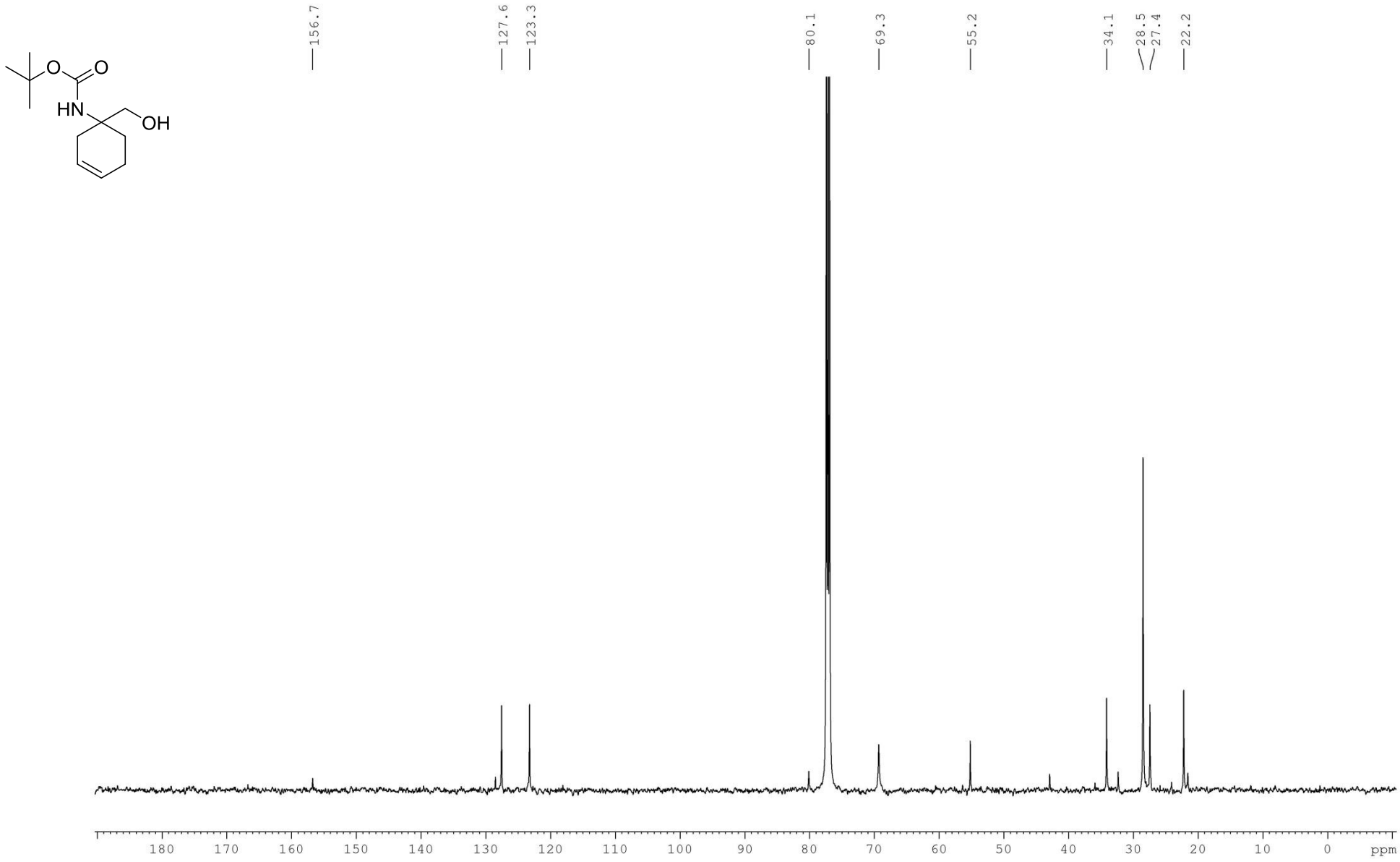
tert-Butyl (1-(hydroxymethyl)cyclohex-3-en-1-yl)carbamate (4)

^{1}H NMR, DMSO-d_6, 400 MHz



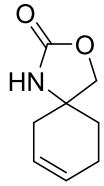
tert-Butyl (1-(hydroxymethyl)cyclohex-3-en-1-yl)carbamate (4)

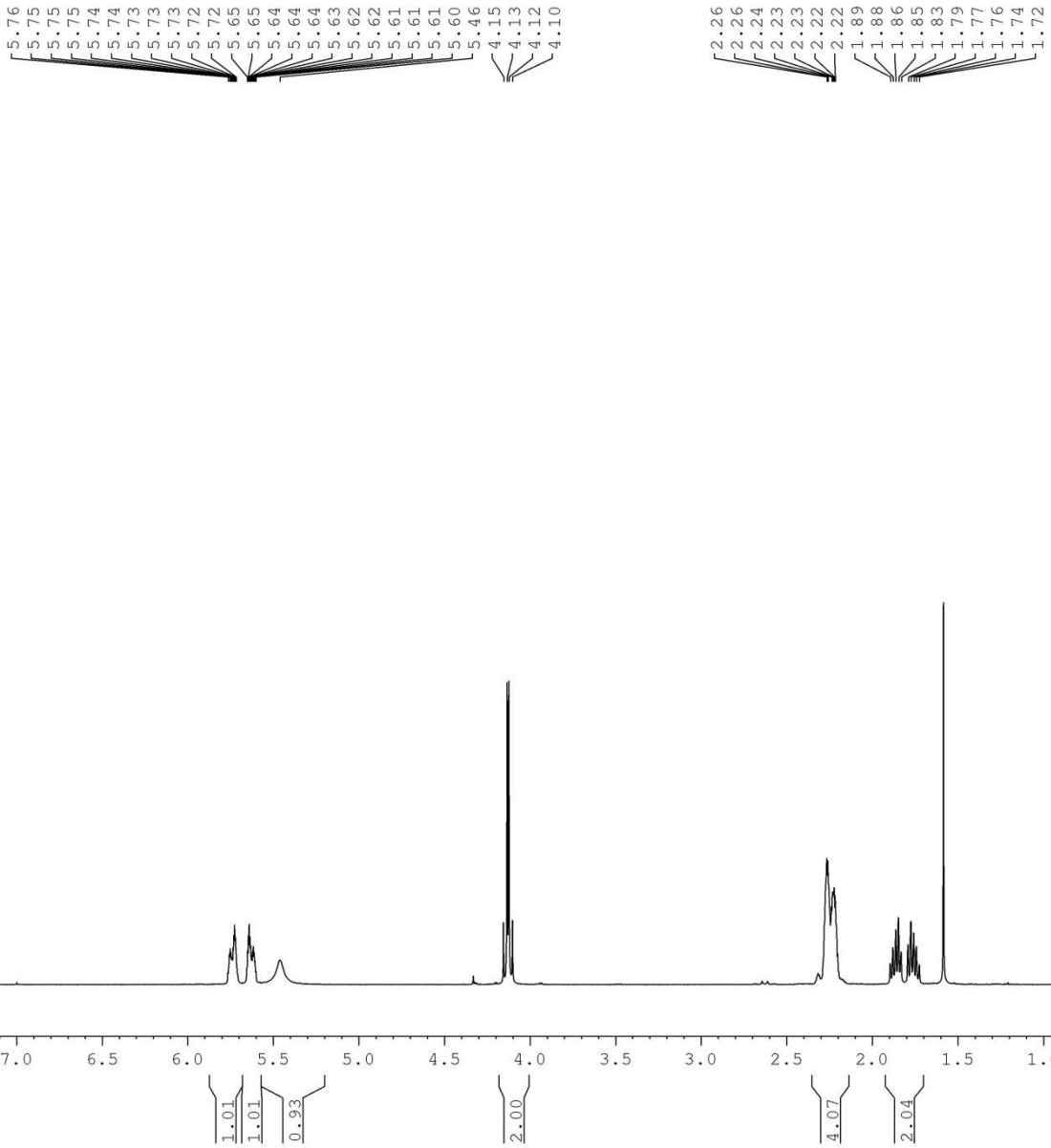
^{13}C NMR, $CDCl_3$, 101 MHz



3-Oxa-1-azaspiro[4.5]dec-7-ene-2-one (5)

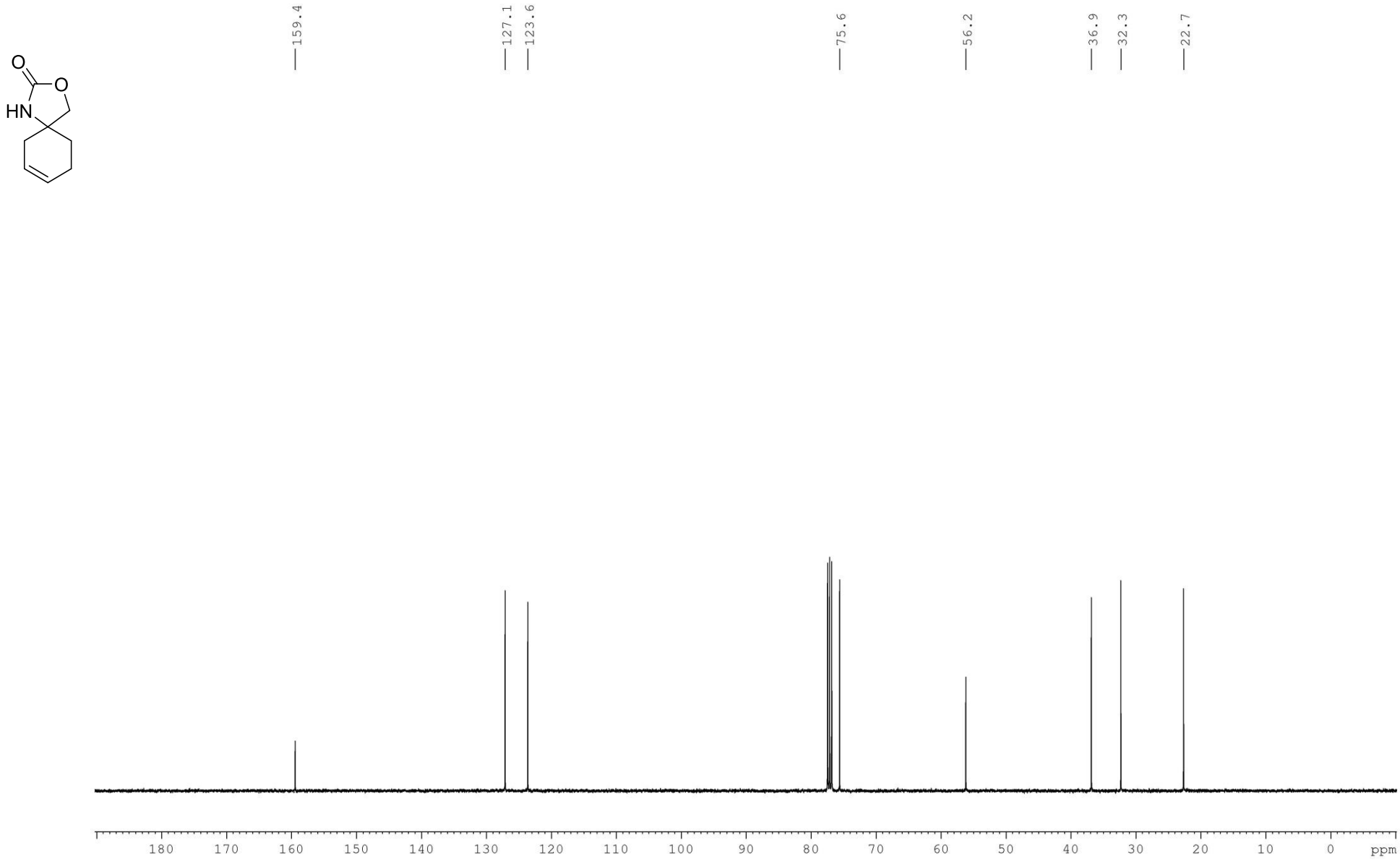
^{1}H NMR, $CDCl_3$, 400 MHz





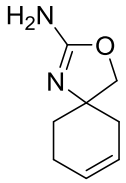
3-Oxa-1-azaspiro[4.5]dec-7-ene-2-one (5)

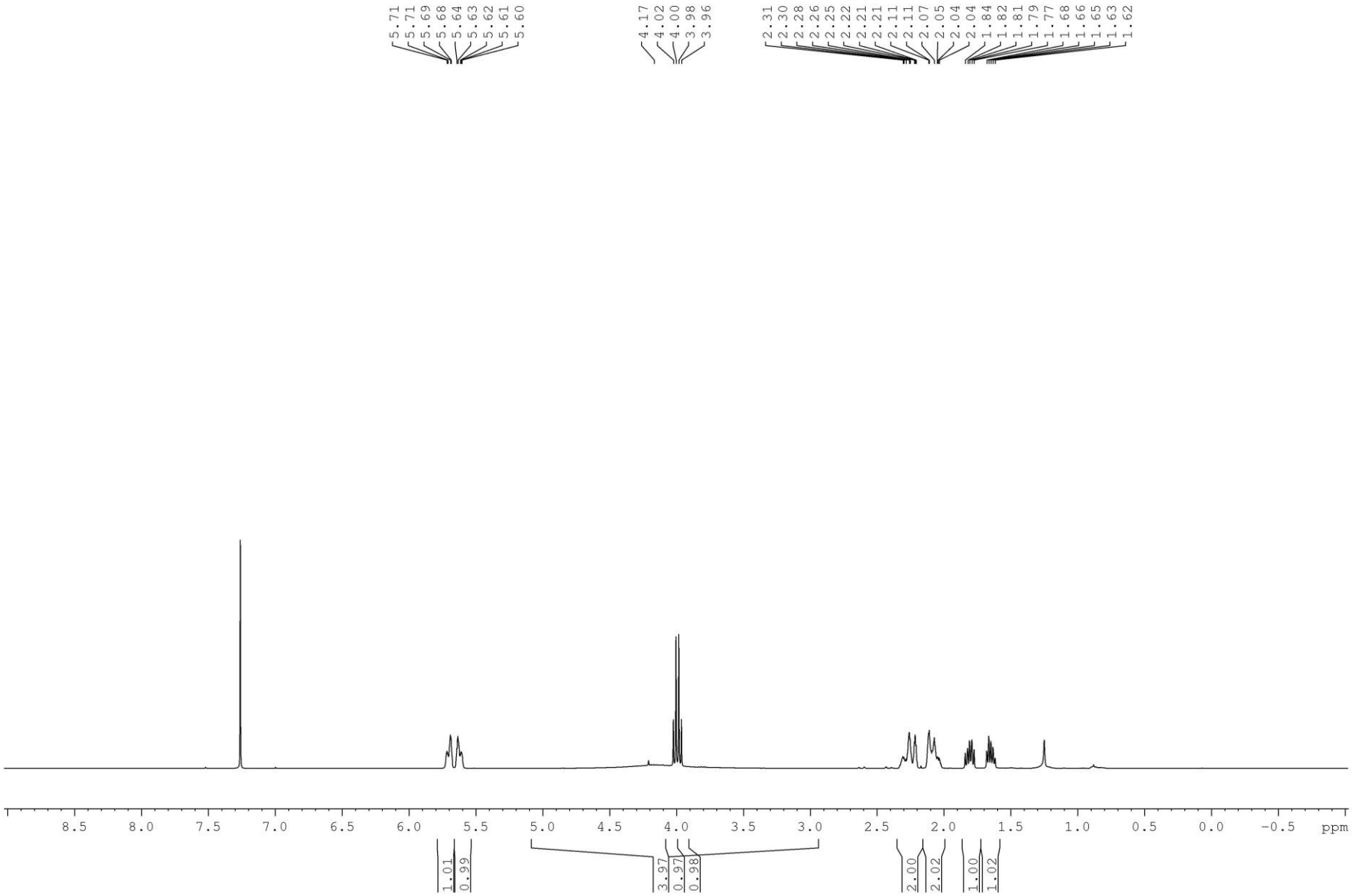
^{13}C NMR, $CDCl_3$, 101 MHz



3-Oxa-1-azaspiro[4.5]deca-1,7-dien-2-amine (6)

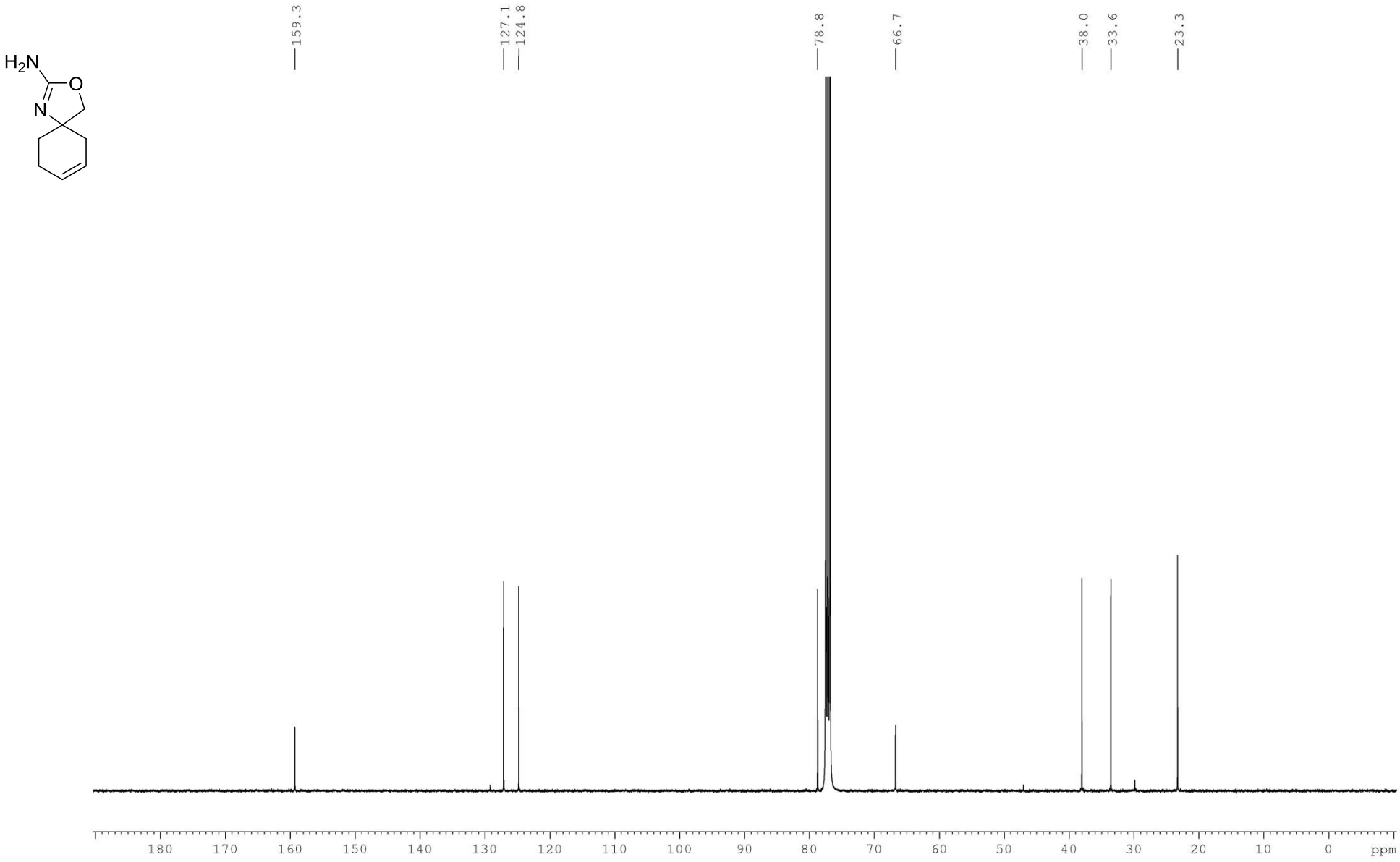
^{1}H NMR, $CDCl_3$, 400 MHz





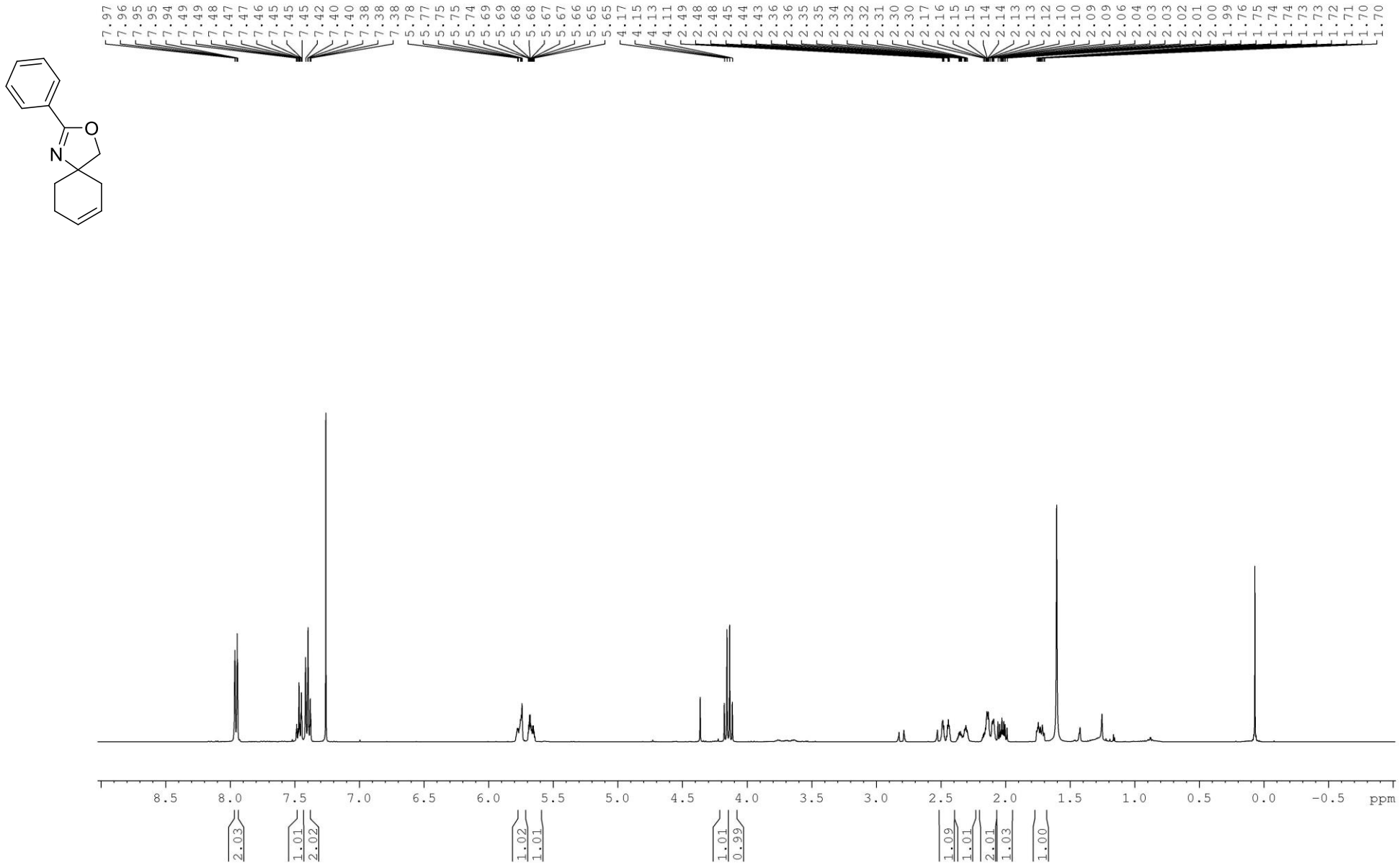
3-Oxa-1-azaspiro[4.5]deca-1,7-dien-2-amine (6)

^{13}C NMR, $CDCl_3$, 101 MHz



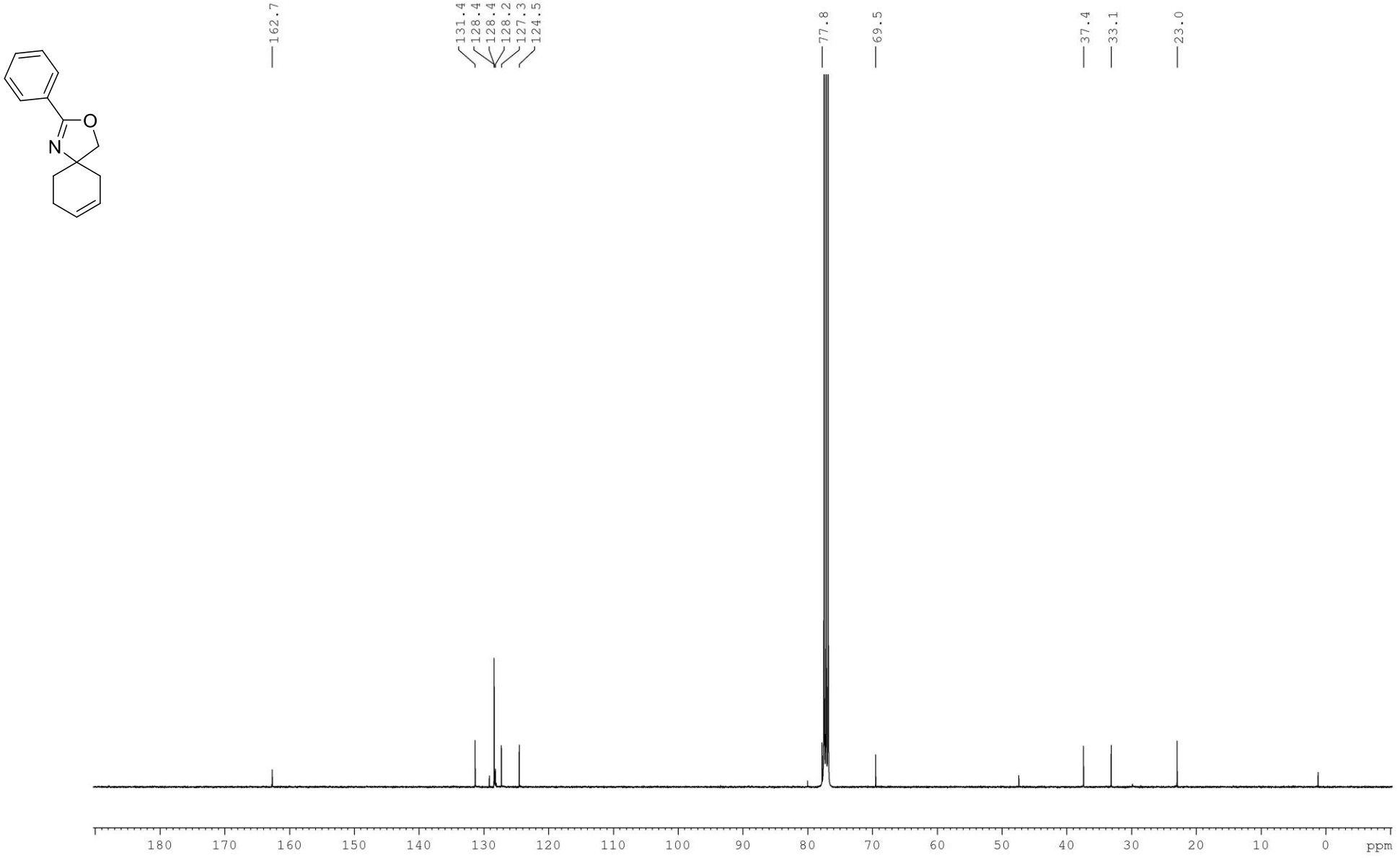
2-Phenyl-3-oxa-1-azaspiro[4.5]deca-1,7-diene (7)

^{1}H NMR, $CDCl_3$, 400 MHz



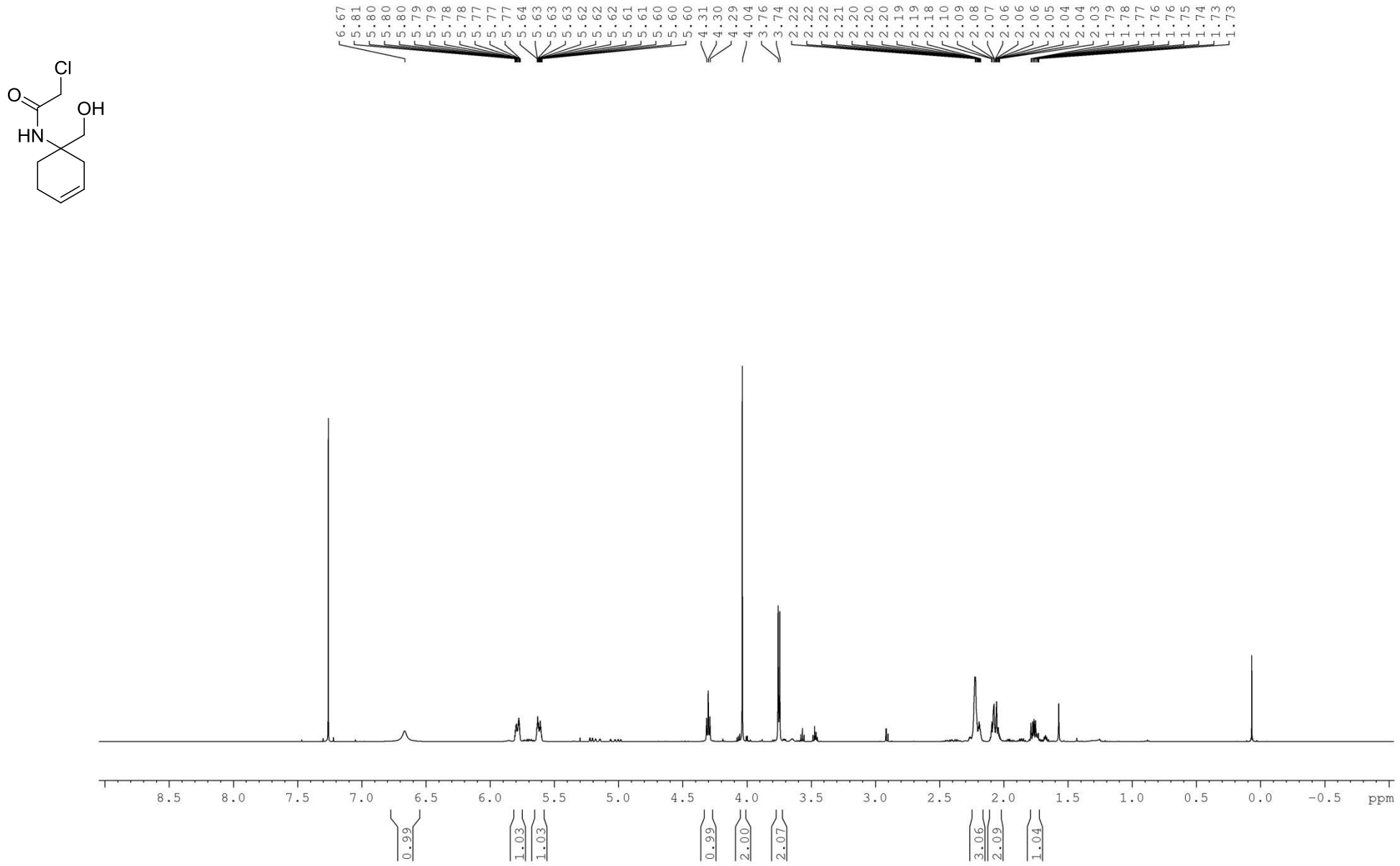
2-Phenyl-3-oxa-1-azaspiro[4.5]deca-1,7-diene (7)

^{13}C NMR, $CDCl_3$, 101 MHz



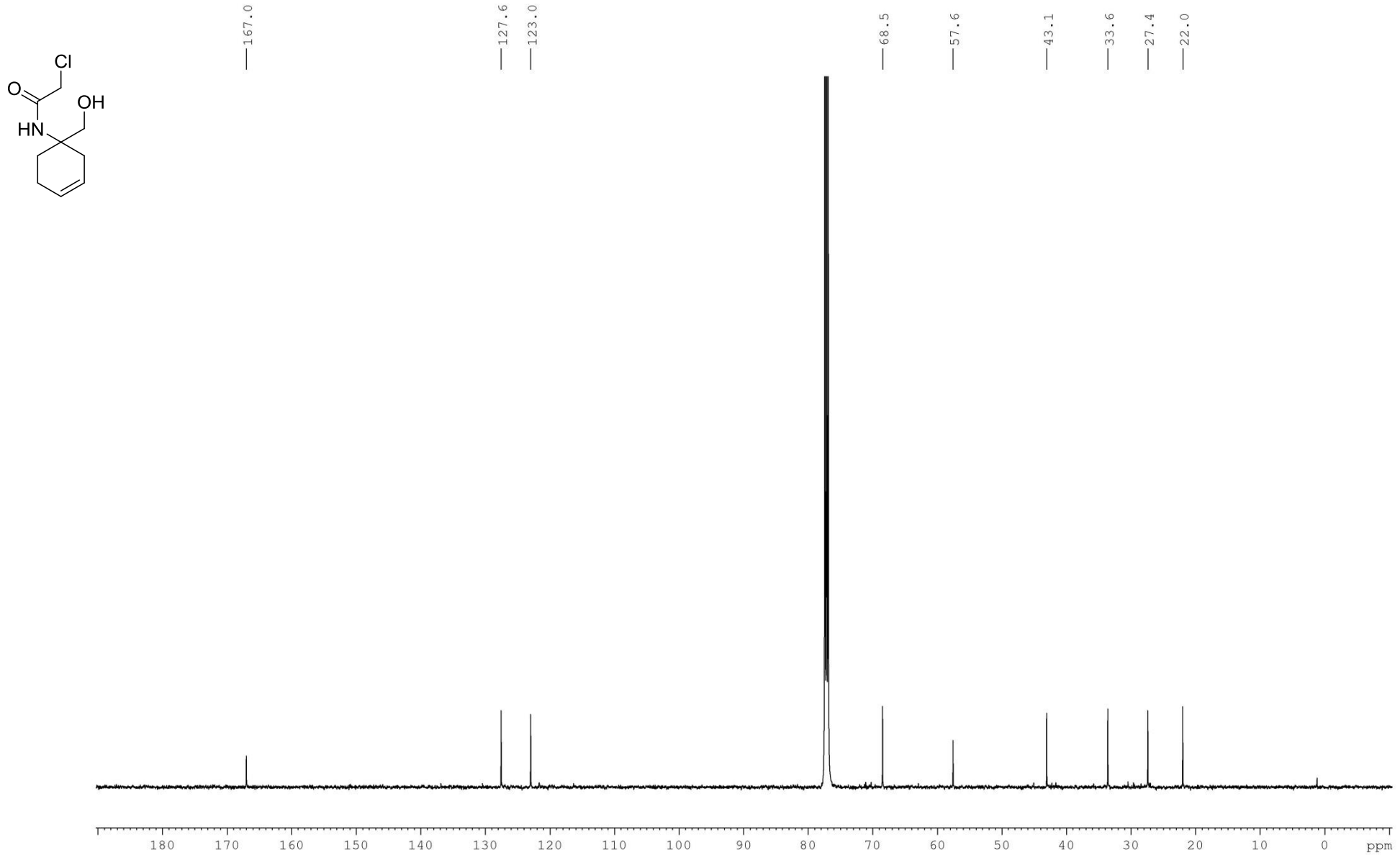
2-Chloro-N-(1-(hydroxymethyl)cyclohex-3-en-1-yl)acetamide (S3)

^{1}H NMR, $CDCl_3$, 500 MHz



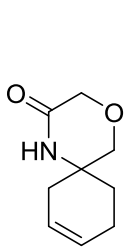
2-Chloro-N-(1-(hydroxymethyl)cyclohex-3-en-1-yl)acetamide (S3)

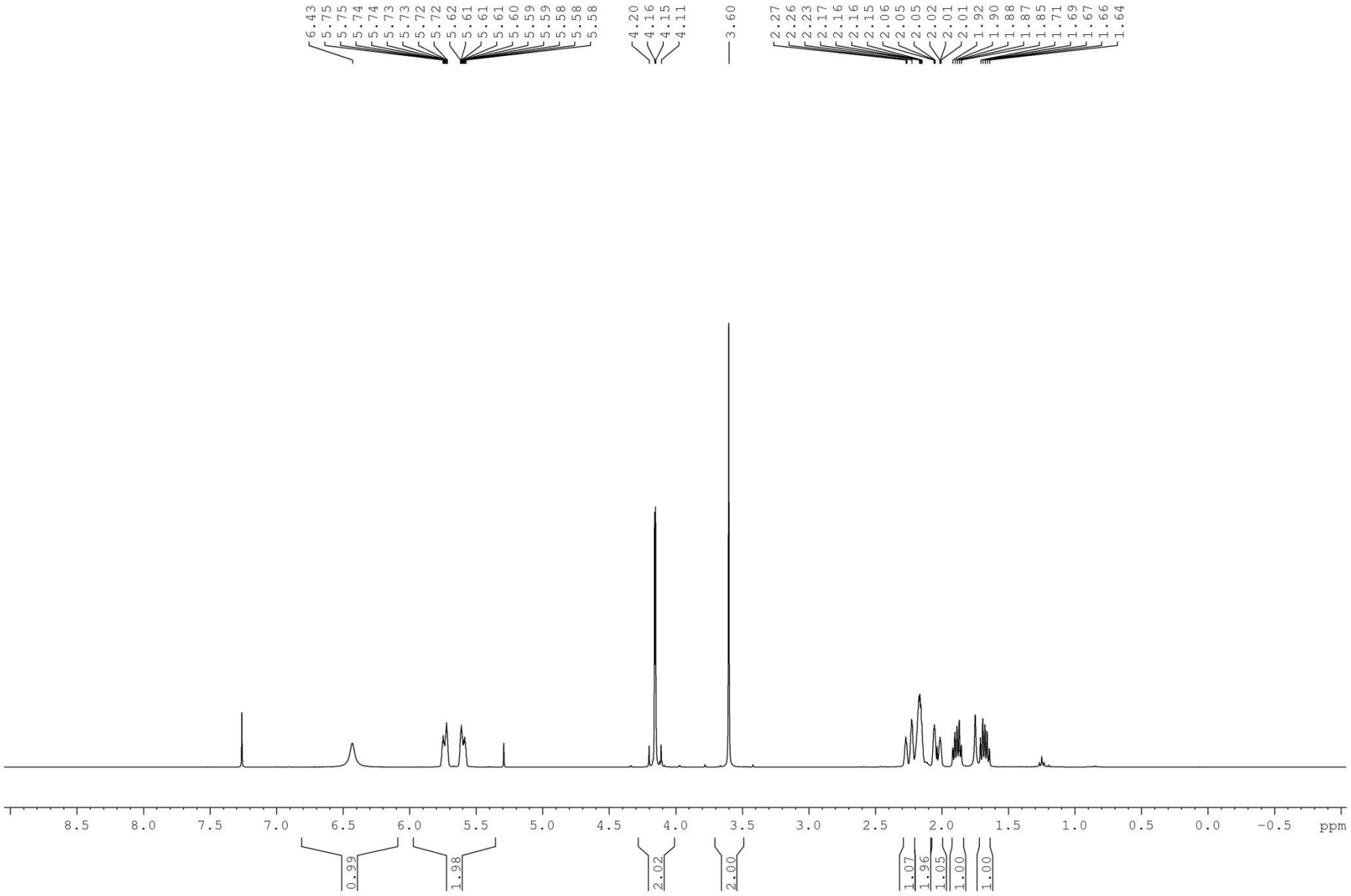
^{13}C NMR, $CDCl_3$, 126 MHz



4-Oxa-1-azaspiro[5.5]undec-8-en-2-one (8)

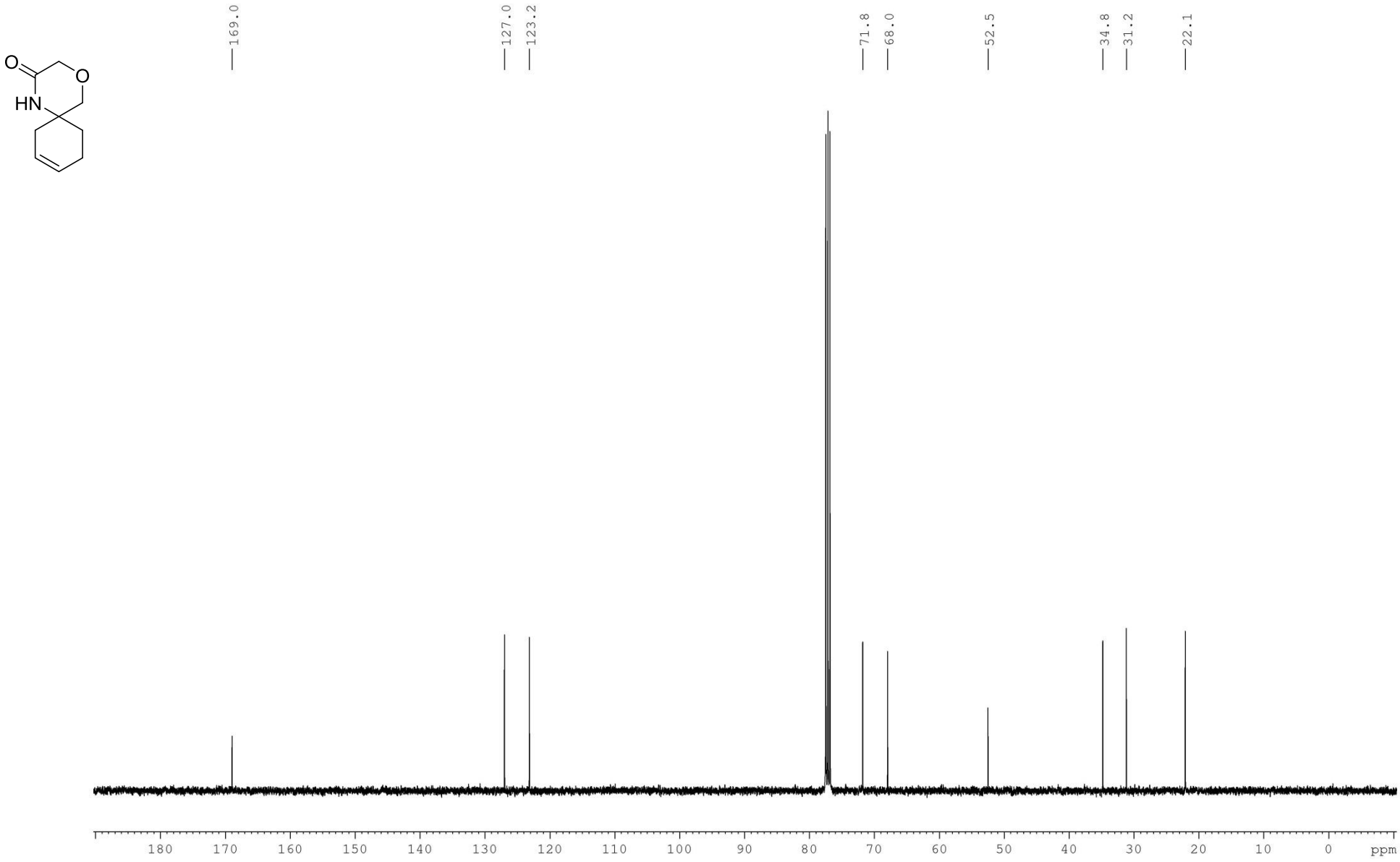
^{1}H NMR, $CDCl_3$, 400 MHz





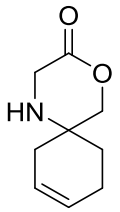
4-Oxa-1-azaspiro[5.5]undec-8-en-2-one (8)

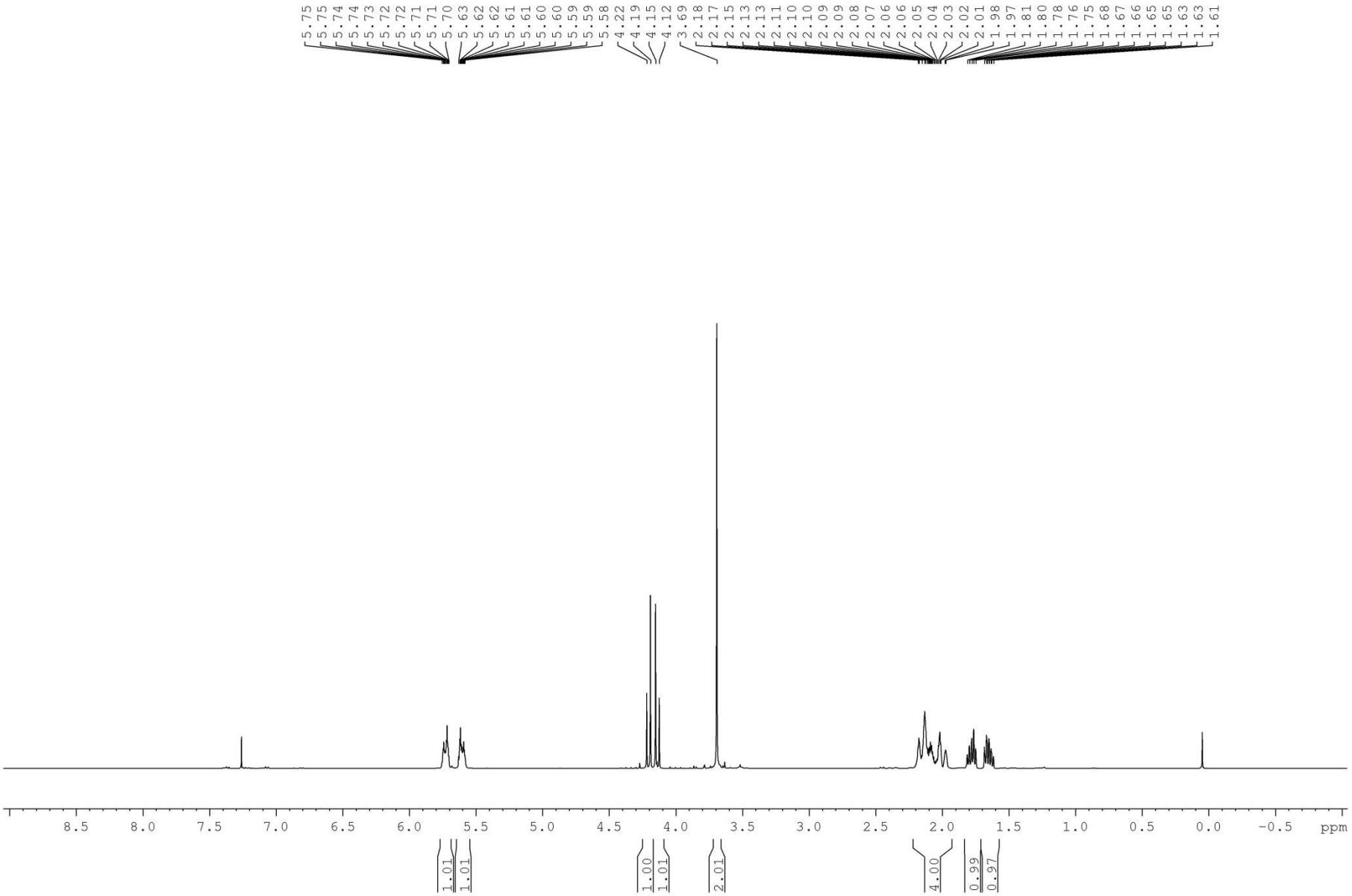
^{13}C NMR, $CDCl_3$, 101 MHz



4-Oxa-1-azaspiro[5.5]undec-8-en-3-one (9)

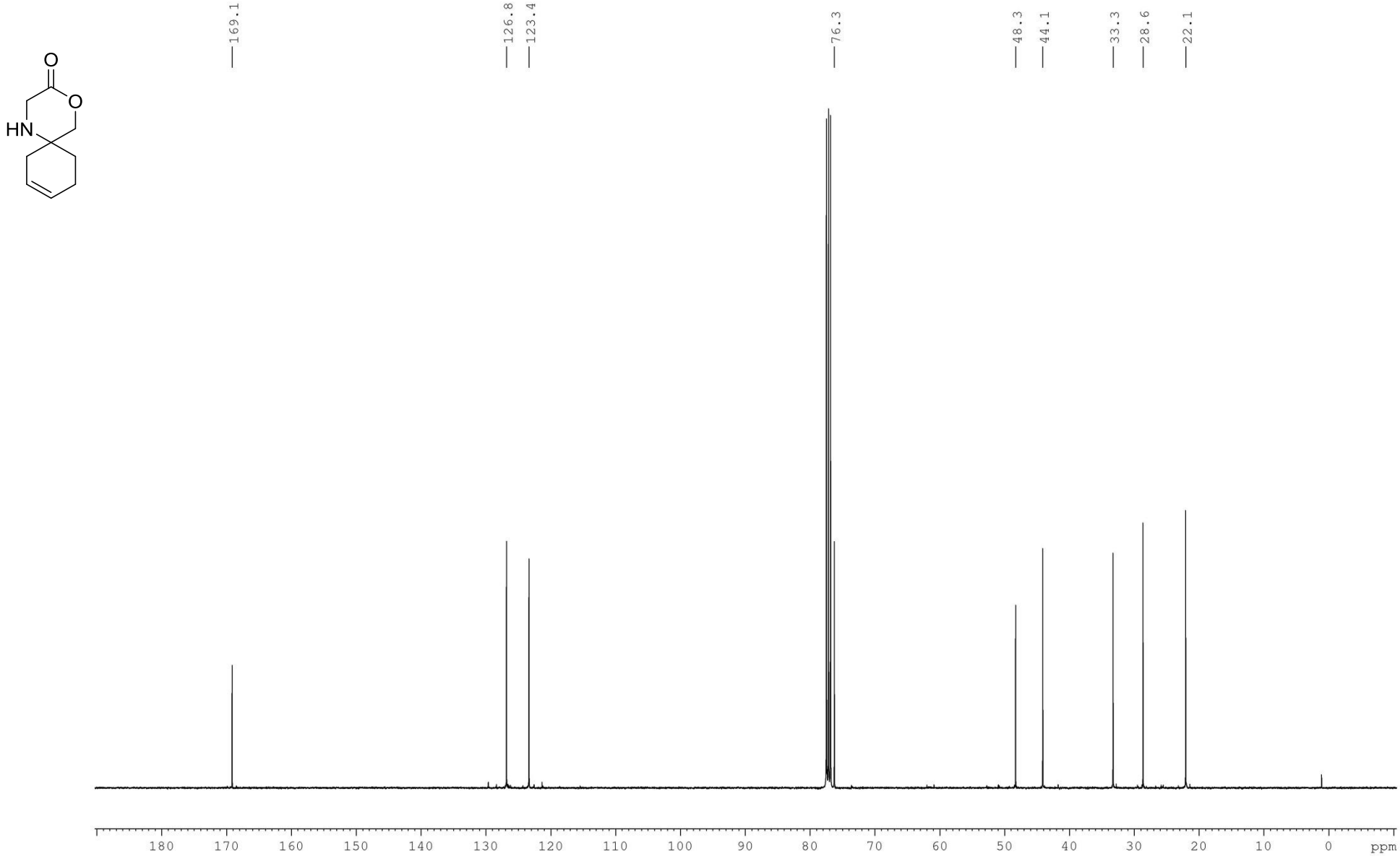
^{1}H NMR, $CDCl_3$, 400 MHz





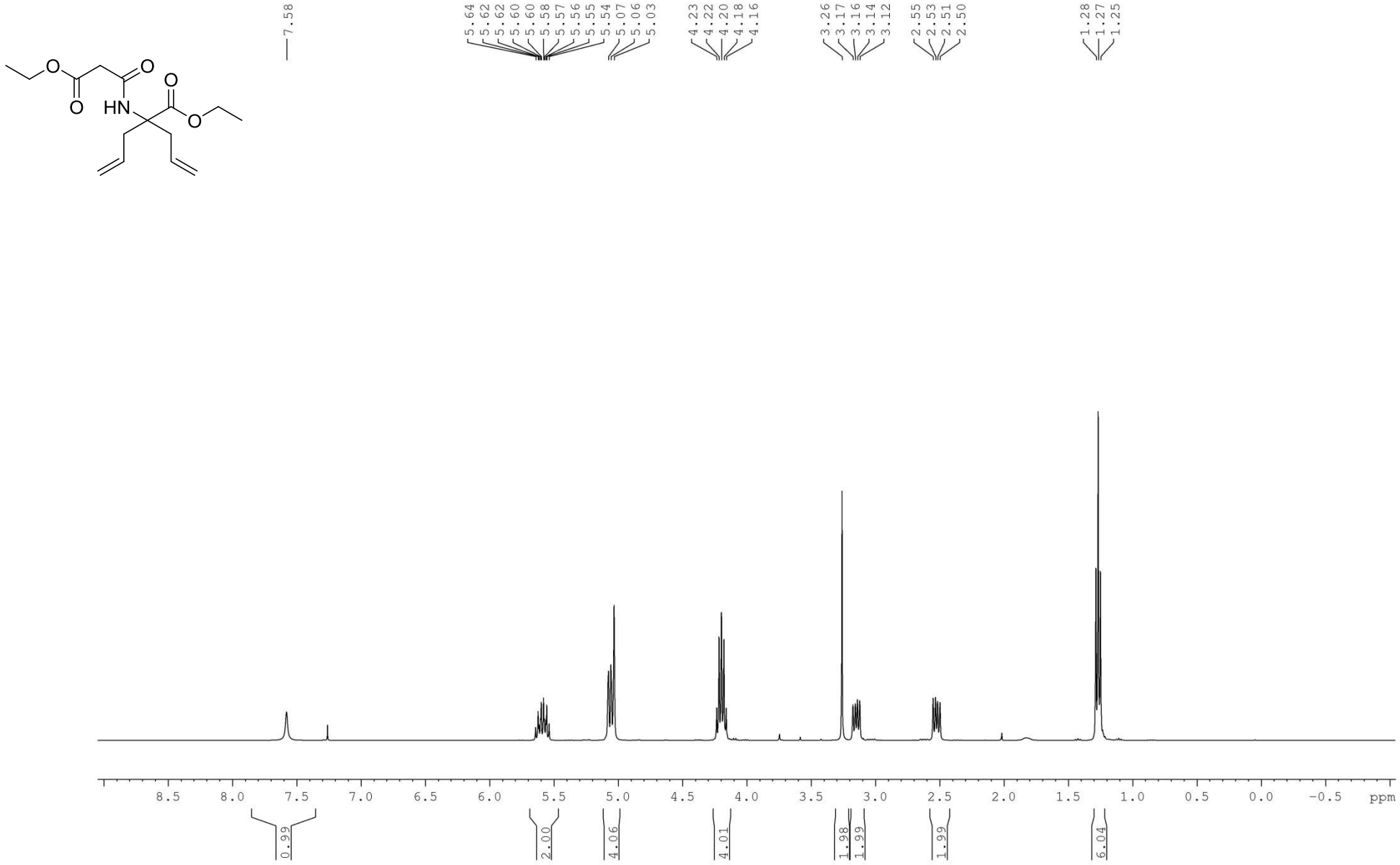
4-Oxa-1-azaspiro[5.5]undec-8-en-3-one (9)

^{13}C NMR, $CDCl_3$, 101 MHz



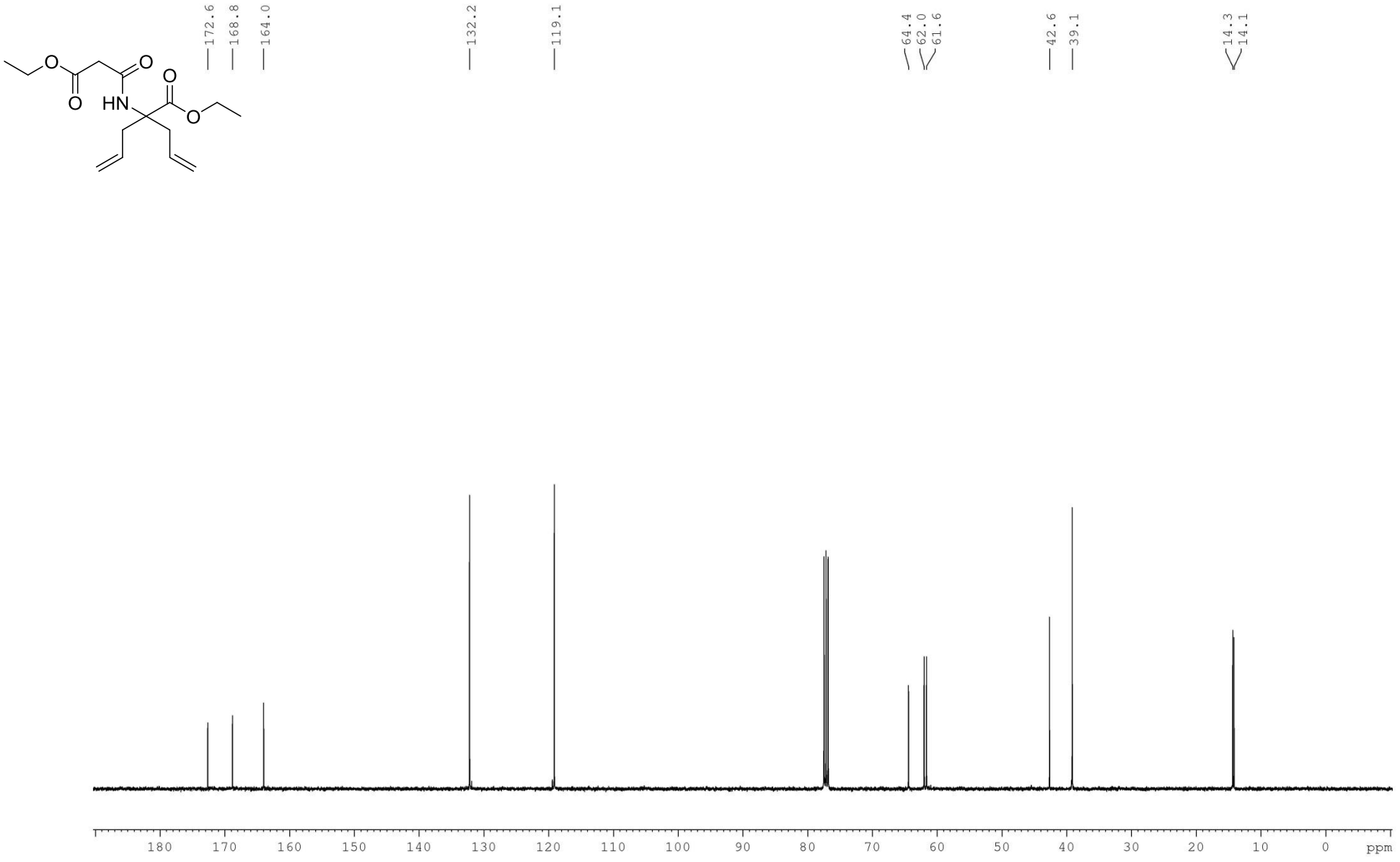
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)pent-4-enoate (S4a)

^{1}H NMR, $CDCl_3$, 400 MHz



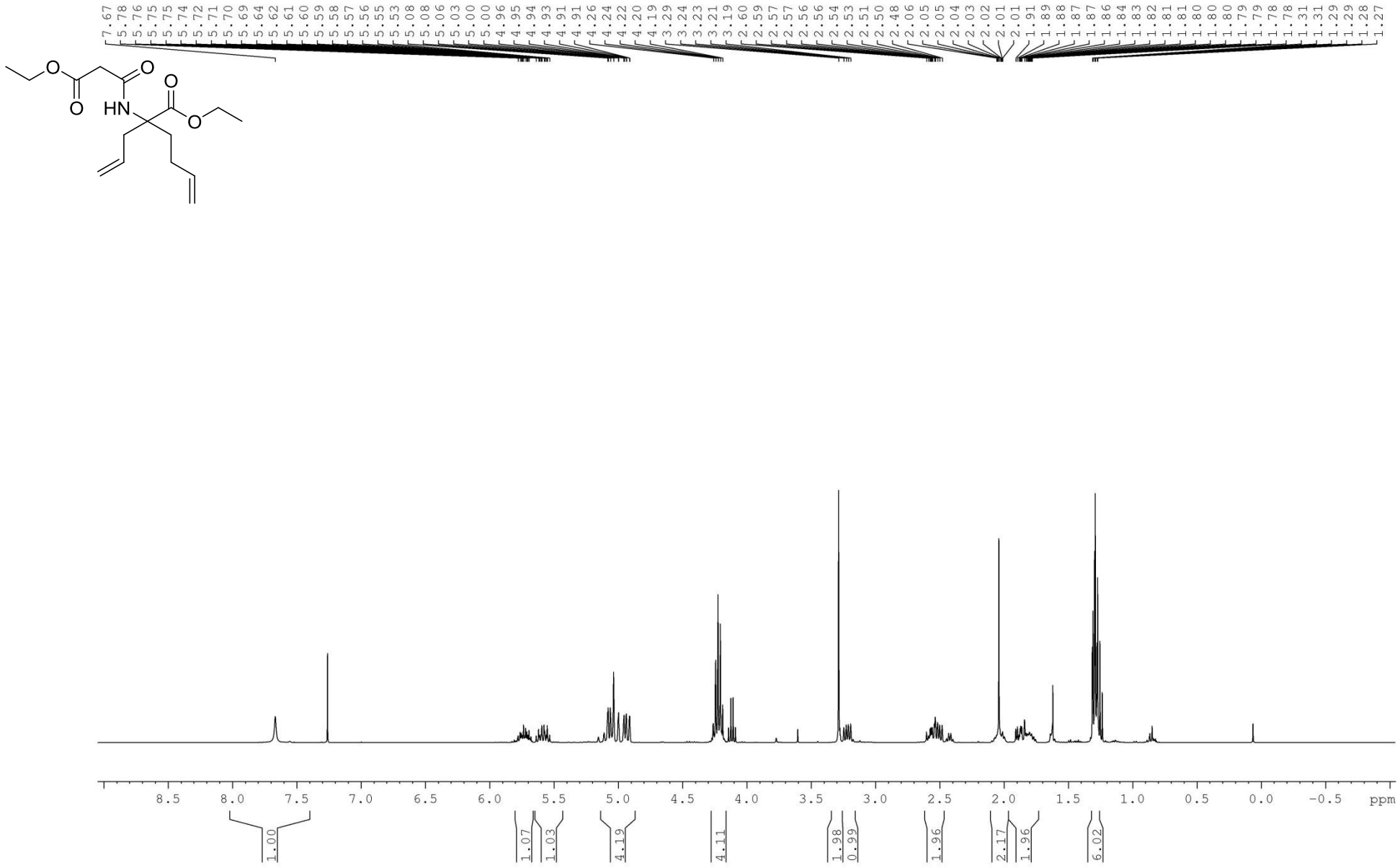
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)pent-4-enoate (S4a)

^{13}C NMR, $CDCl_3$, 101 MHz



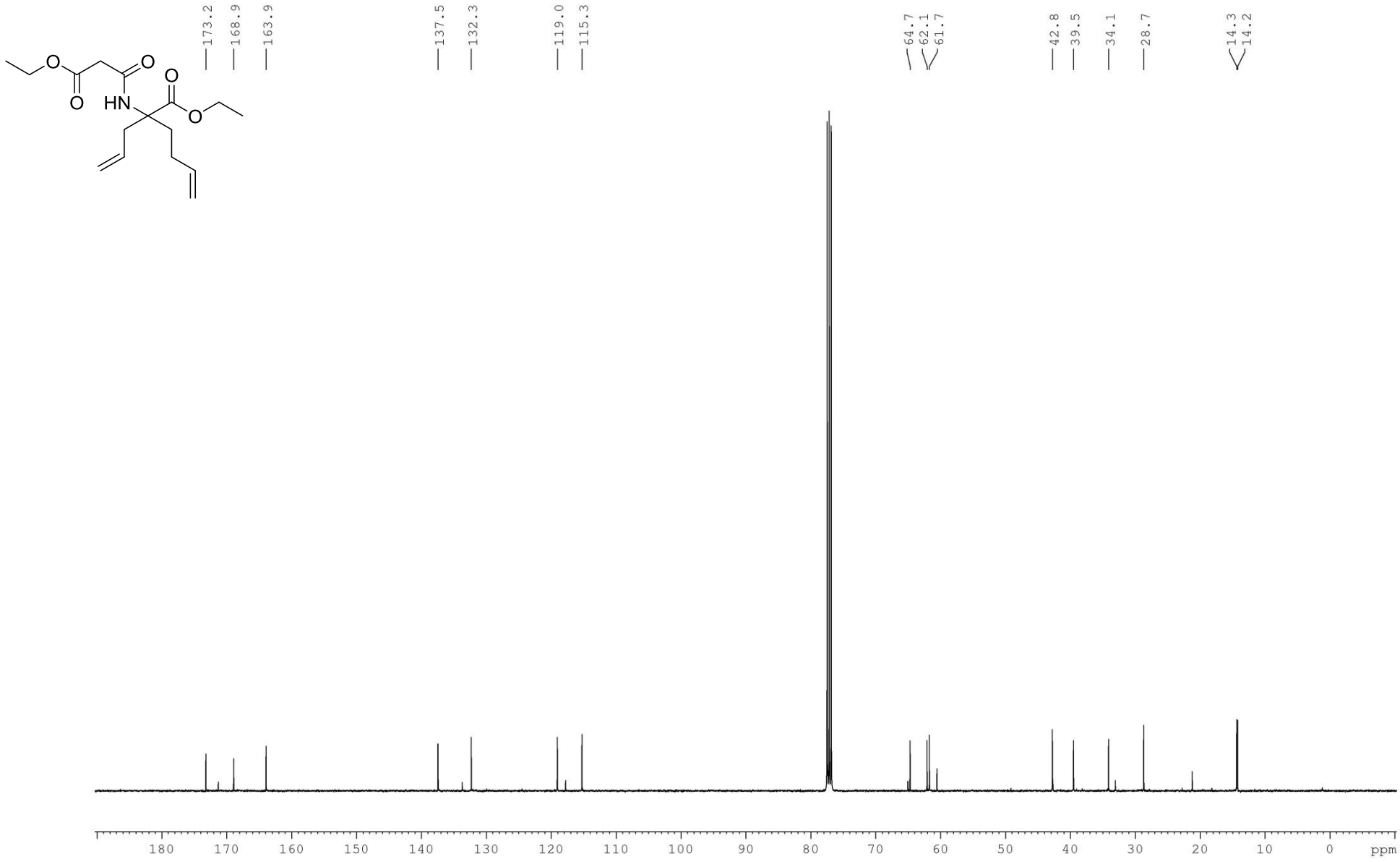
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)hex-5-enoate (S4b)

^{1}H NMR, $CDCl_3$, 400 MHz



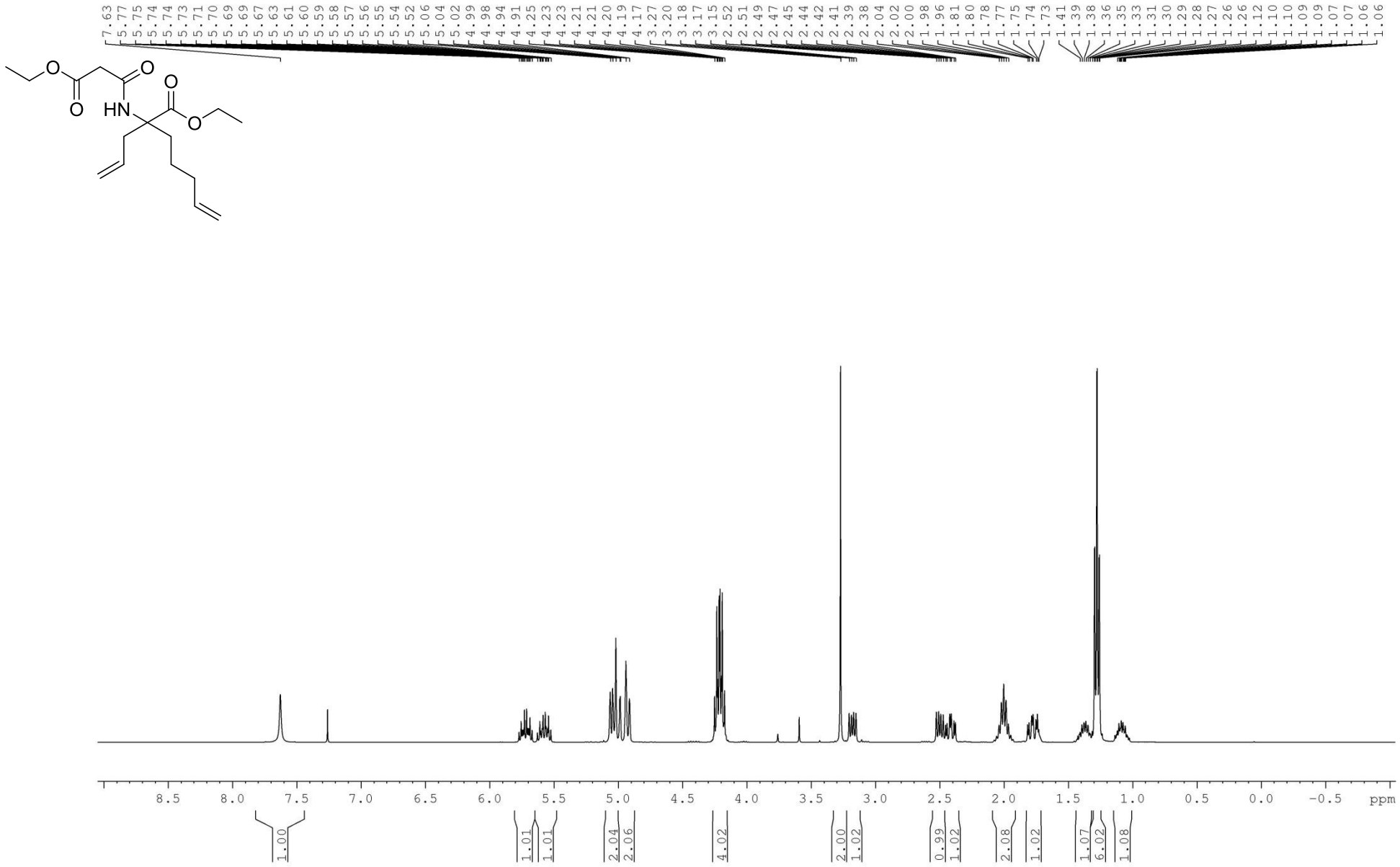
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)hex-5-enoate (S4b)

^{13}C NMR, $CDCl_3$, 101 MHz



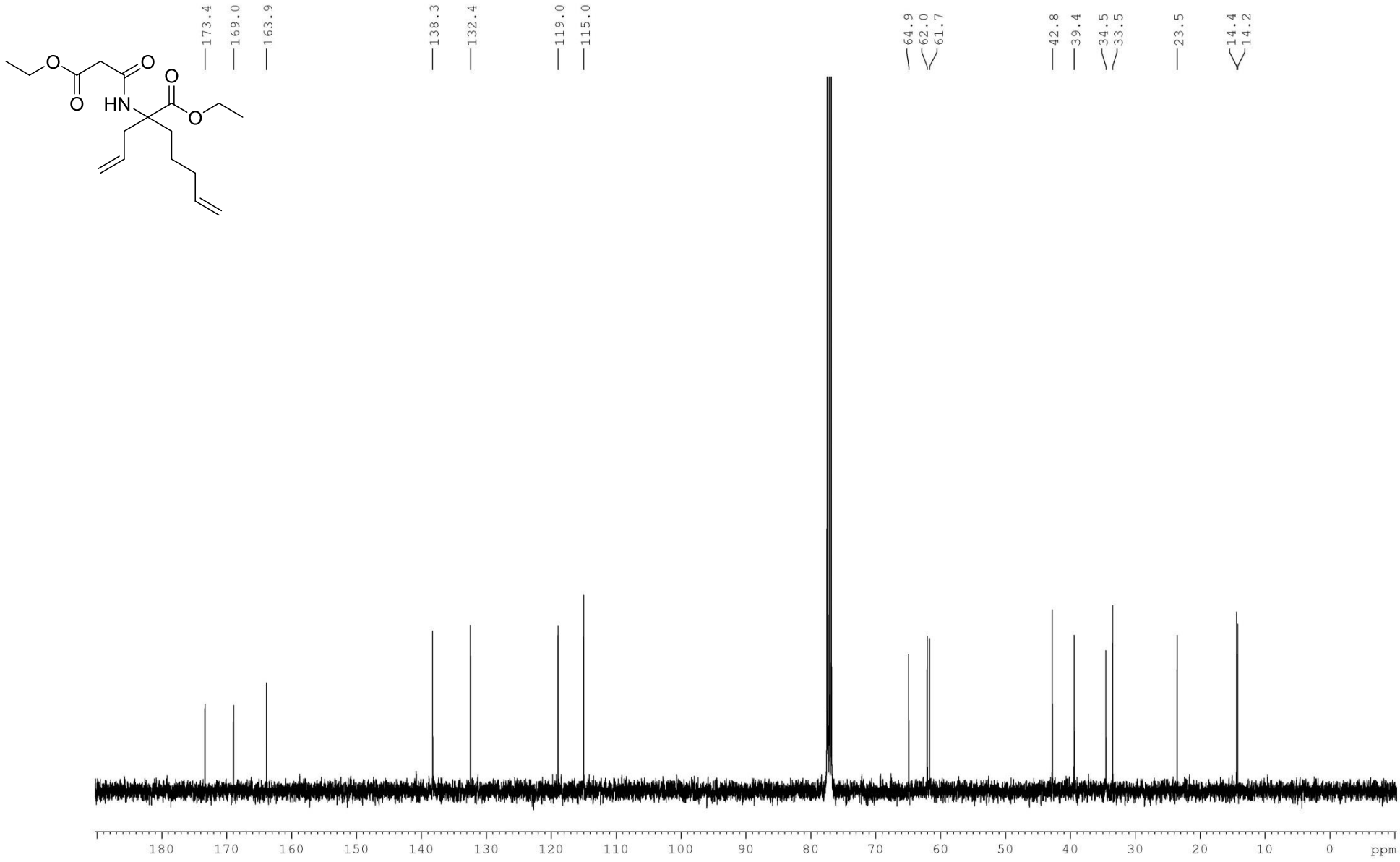
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)hept-6-enoate (S4c)

^{1}H NMR, $CDCl_3$, 400 MHz



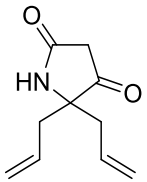
Ethyl 2-allyl-2-(3-ethoxy-3-oxopropanamido)hept-6-enoate (S4c)

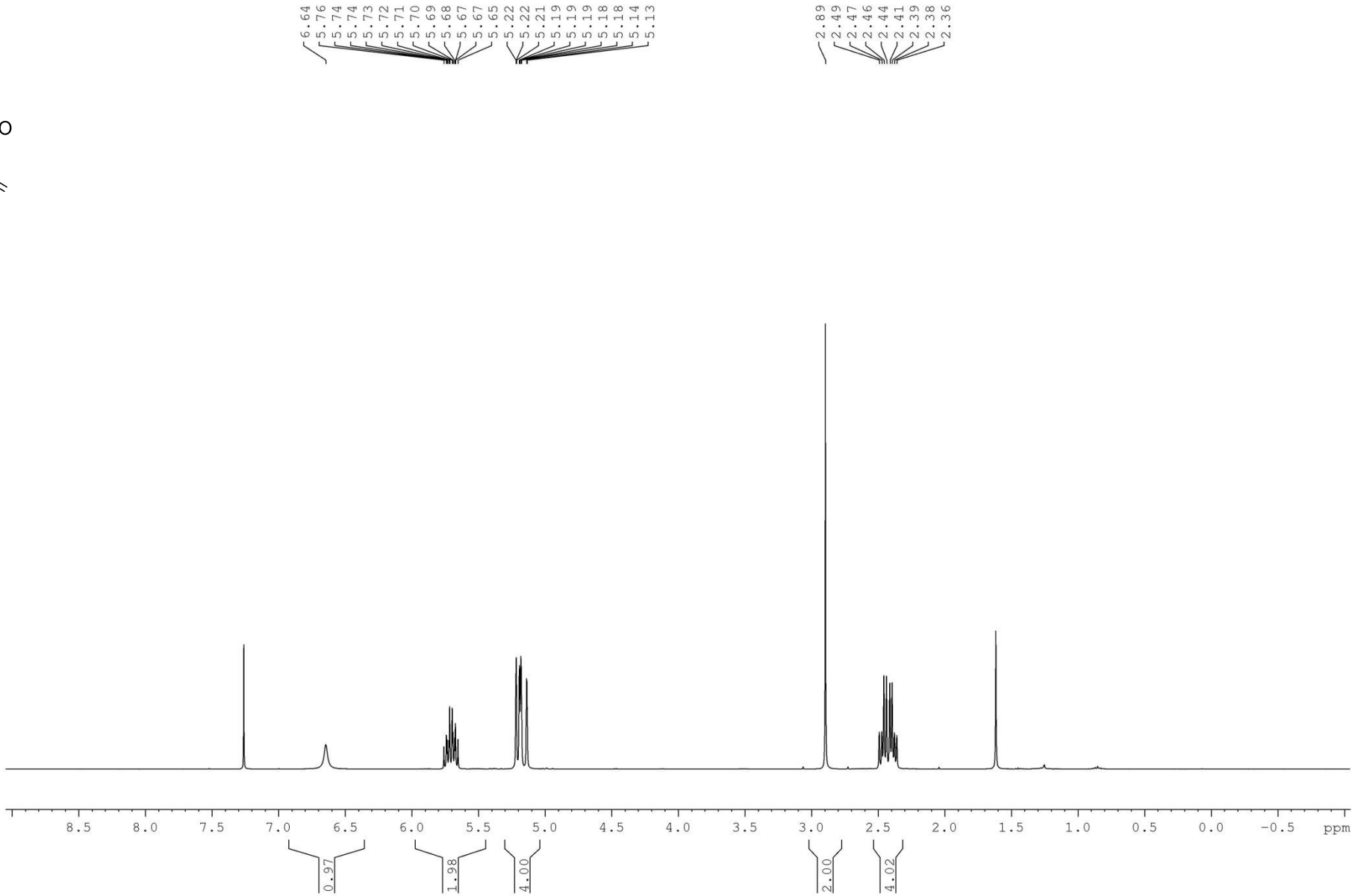
^{13}C NMR, $CDCl_3$, 101 MHz



5,5-Diallylpyrrolidine-2,4-dione (10a)

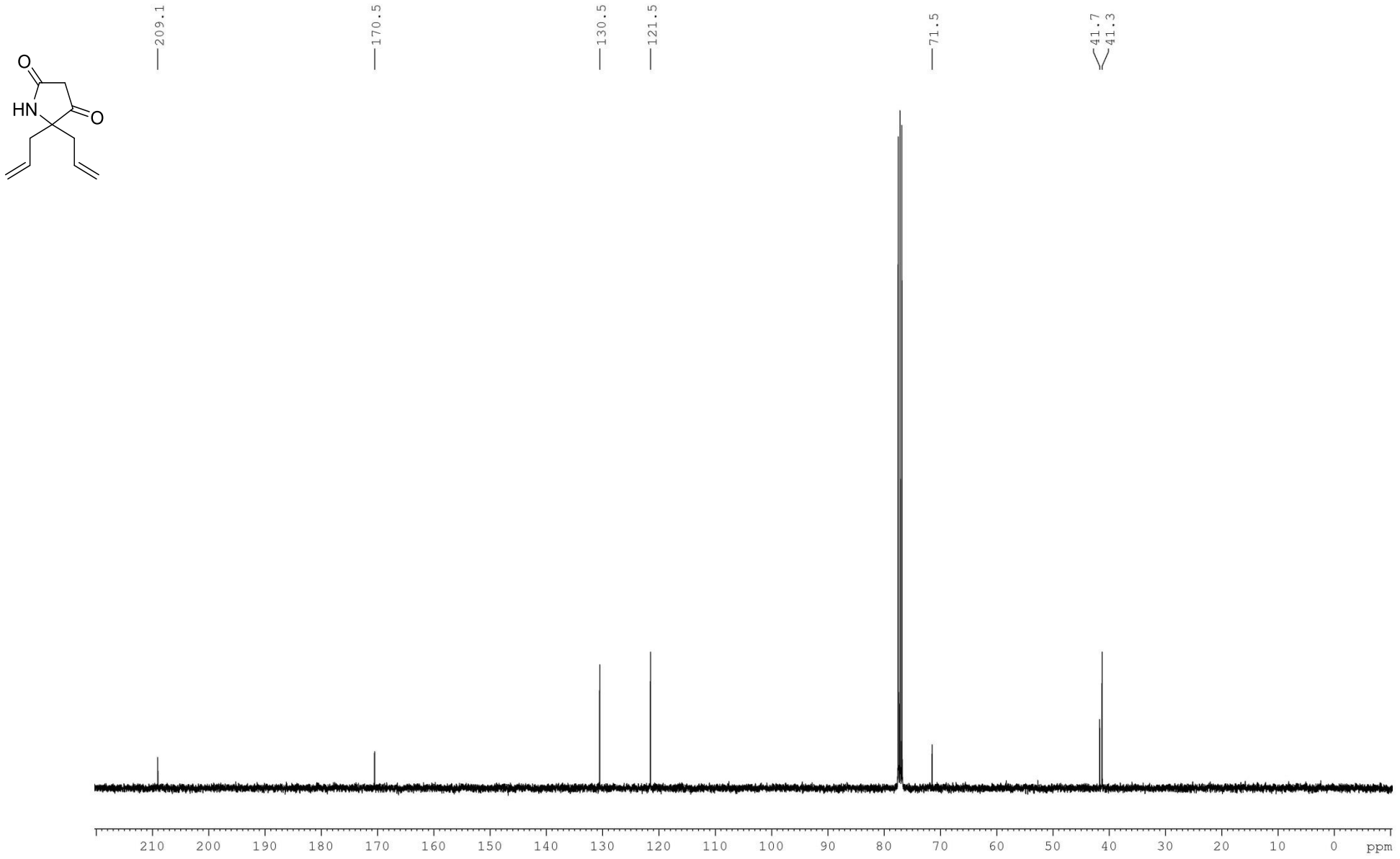
^{1}H NMR, $CDCl_3$, 400 MHz





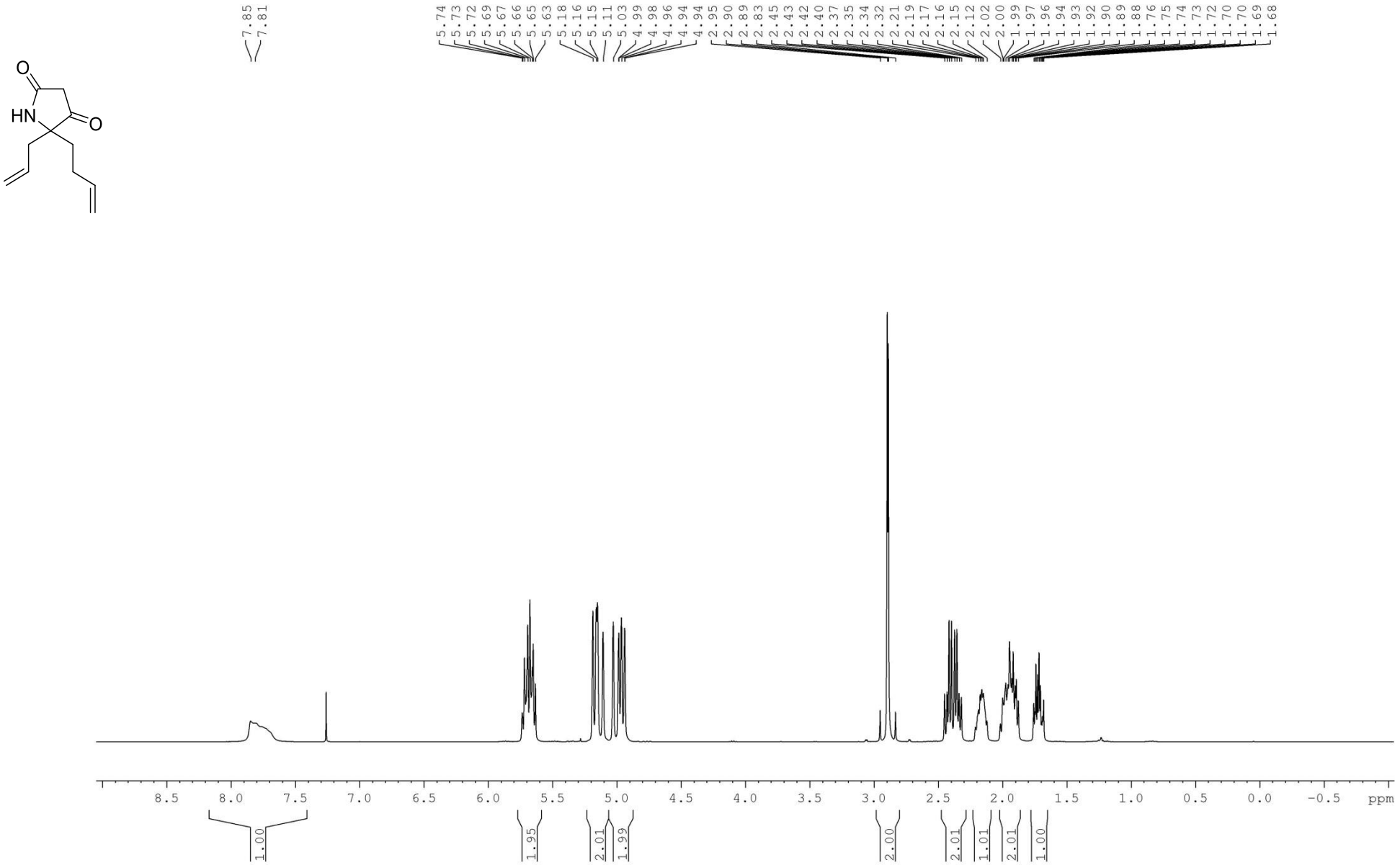
5,5-Diallylpyrrolidine-2,4-dione (10a)

^{13}C NMR, $CDCl_3$, 101 MHz



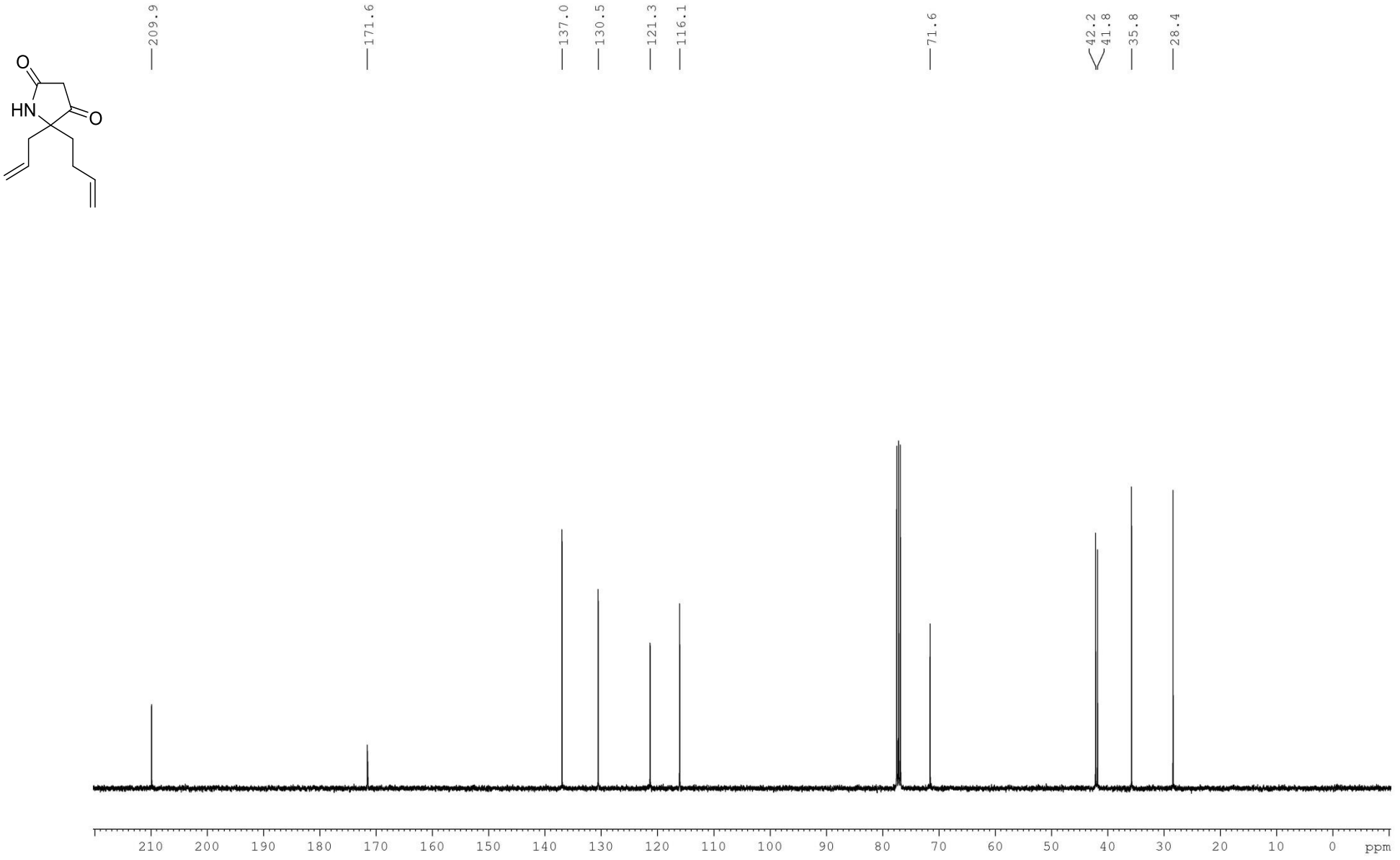
5-Allyl-5-(but-3-en-1-yl)pyrrolidine-2,4-dione (10b)

^{1}H NMR, $CDCl_3$, 400 MHz



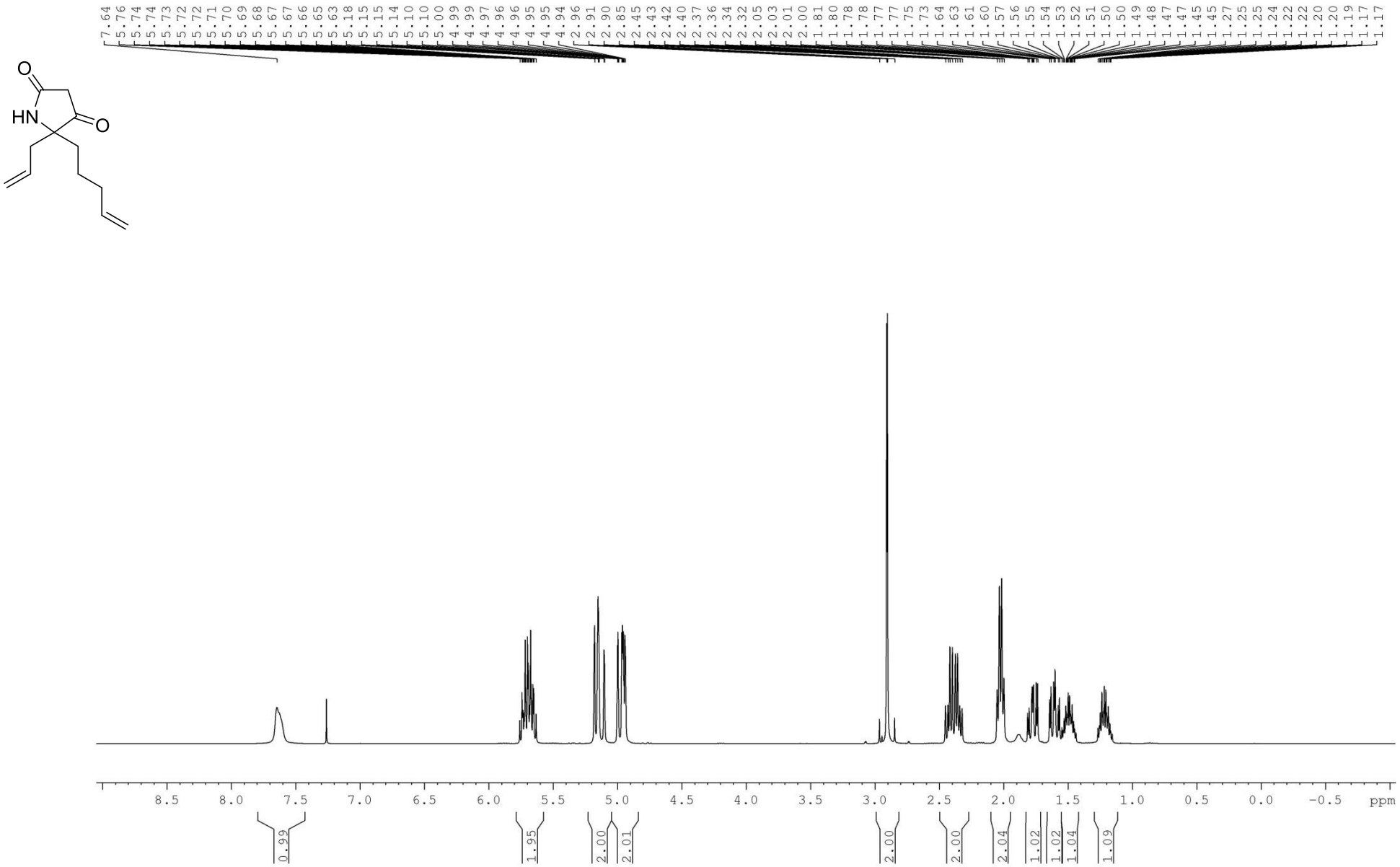
5-Allyl-5-(but-3-en-1-yl)pyrrolidine-2,4-dione (10b)

^{13}C NMR, $CDCl_3$, 101 MHz



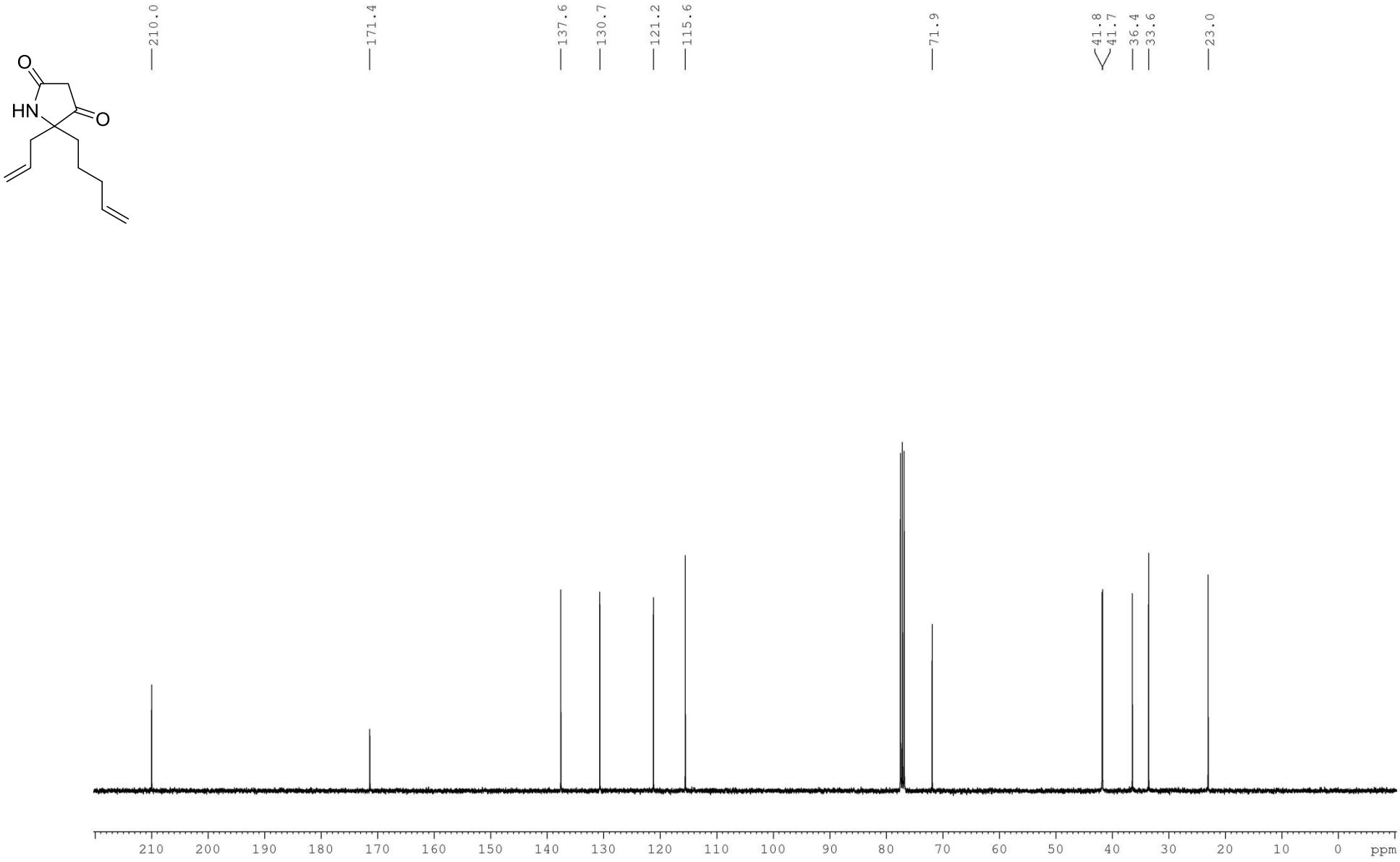
5-Allyl-5-(pent-4-en-1-yl)pyrrolidine-2,4-dione (10c)

^{1}H NMR, $CDCl_3$, 400 MHz



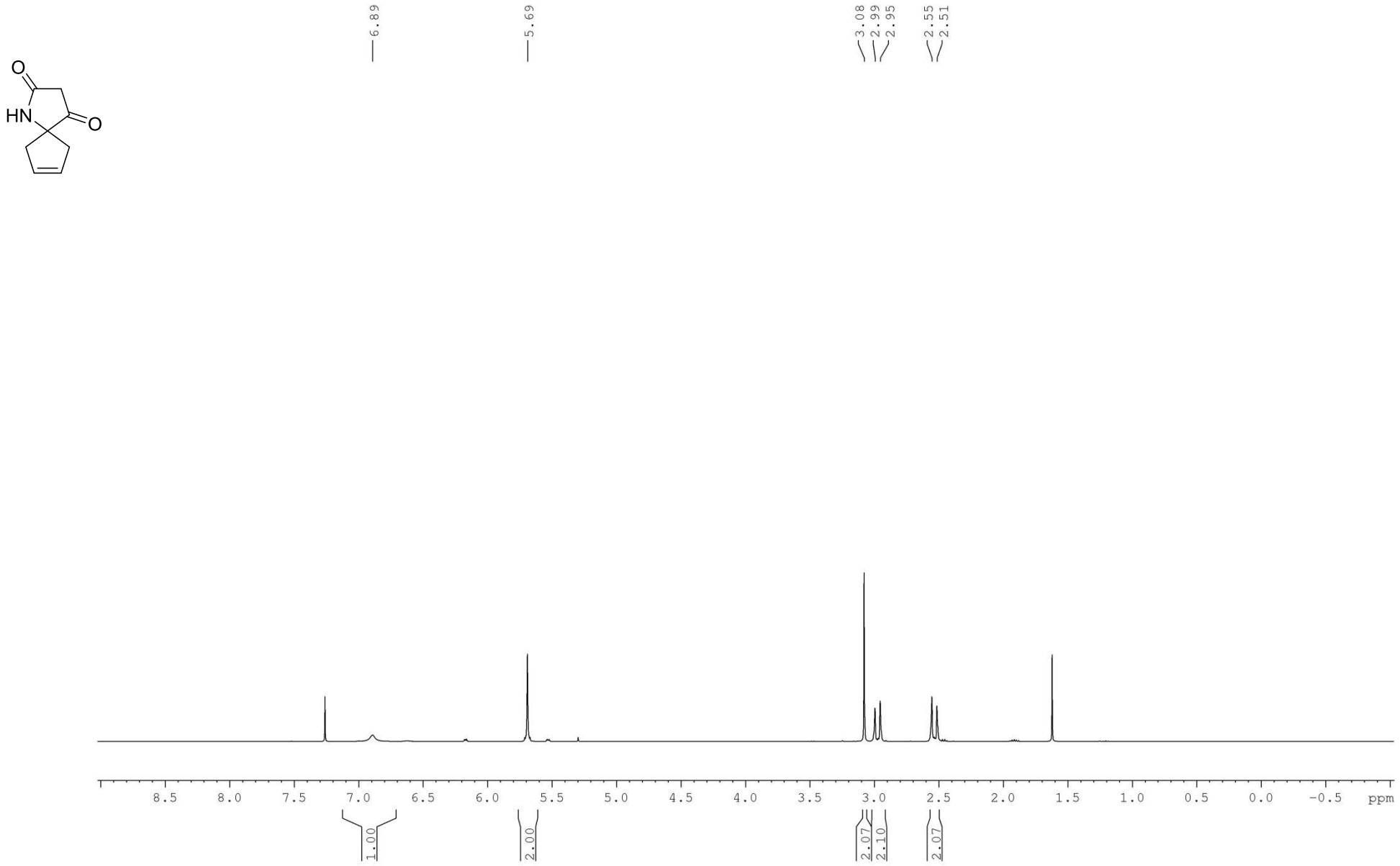
5-Allyl-5-(pent-4-en-1-yl)pyrrolidine-2,4-dione (10c)

^{13}C NMR, $CDCl_3$, 101 MHz



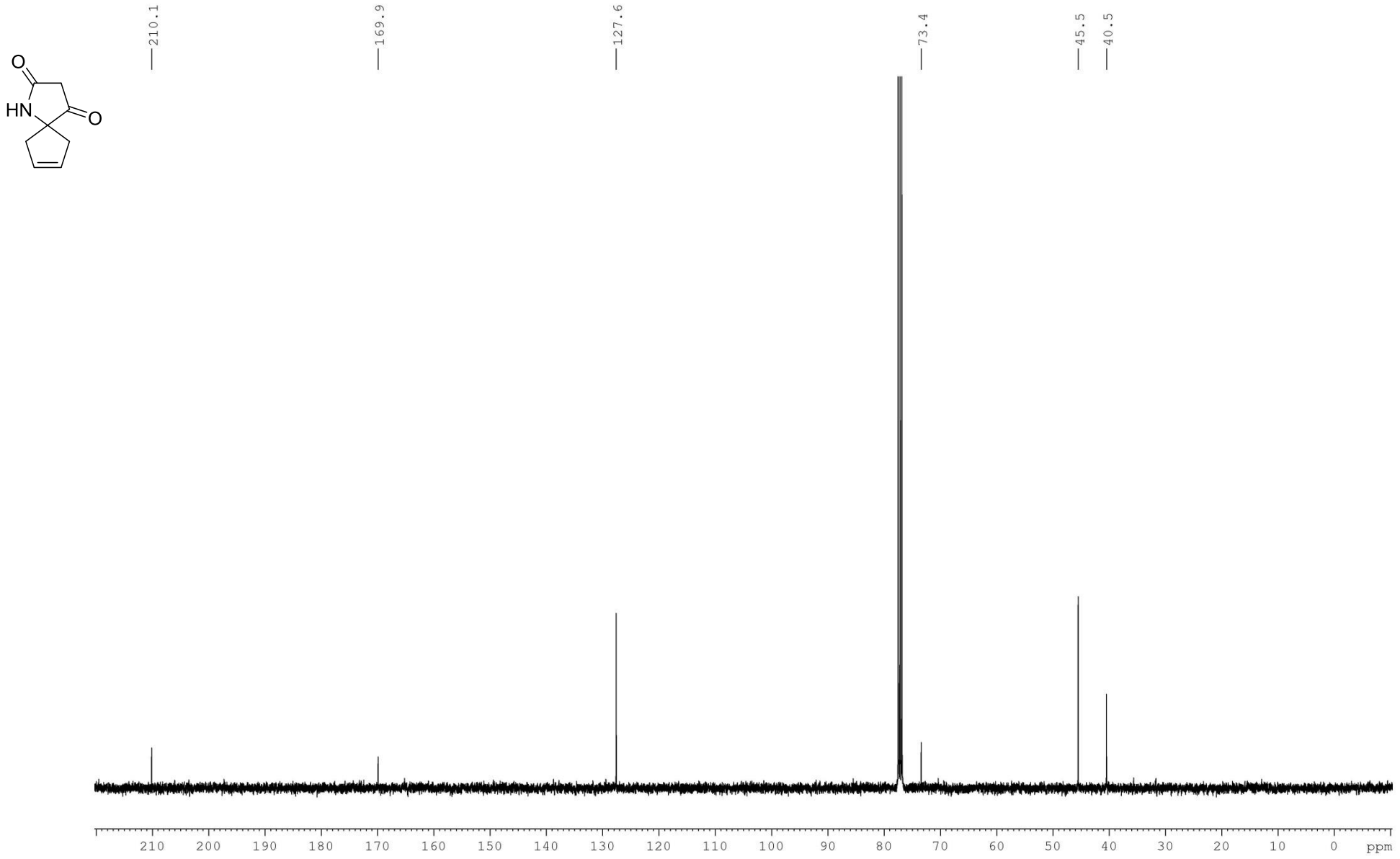
1-Azaspiro[4.4]non-7-ene-2,4-dione (11)

^{1}H NMR, $CDCl_3$, 400 MHz



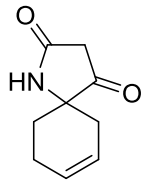
1-Azaspiro[4.4]non-7-ene-2,4-dione (11)

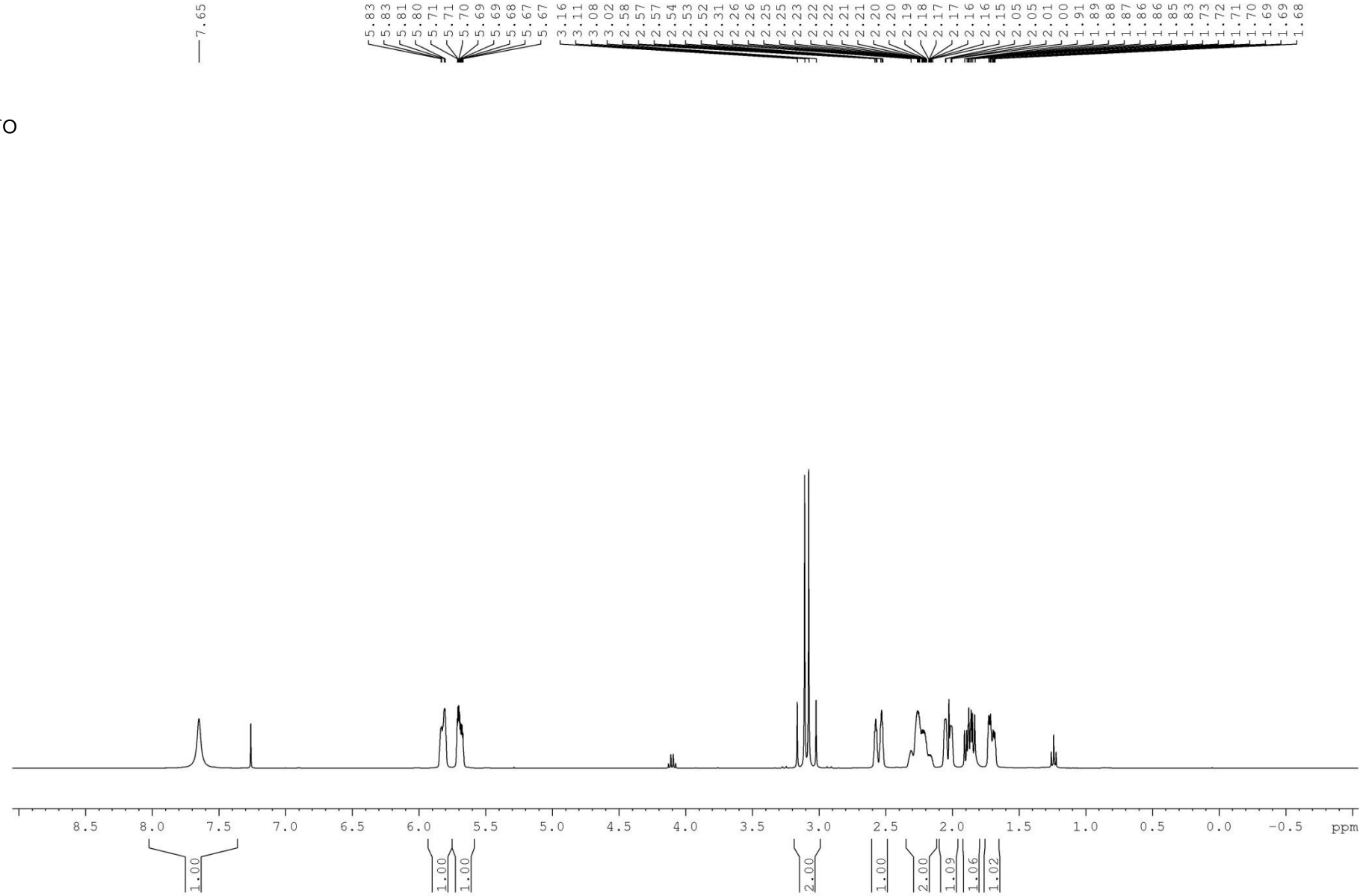
^{13}C NMR, $CDCl_3$, 101 MHz



1-Azaspiro[4.5]dec-7-ene-2,4-dione (12)

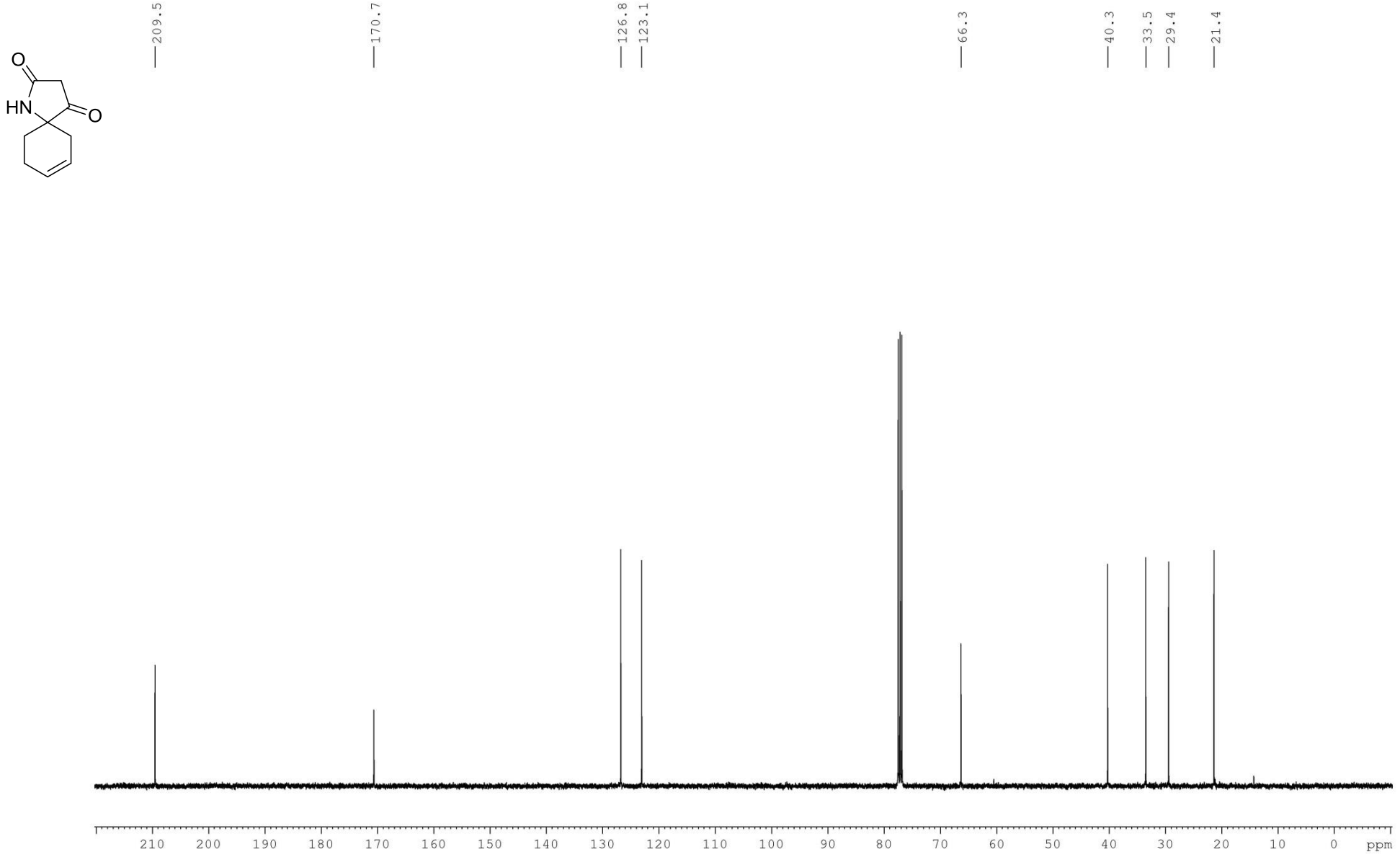
^{1}H NMR, $CDCl_3$, 400 MHz





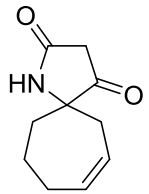
1-Azaspiro[4.5]dec-7-ene-2,4-dione (12)

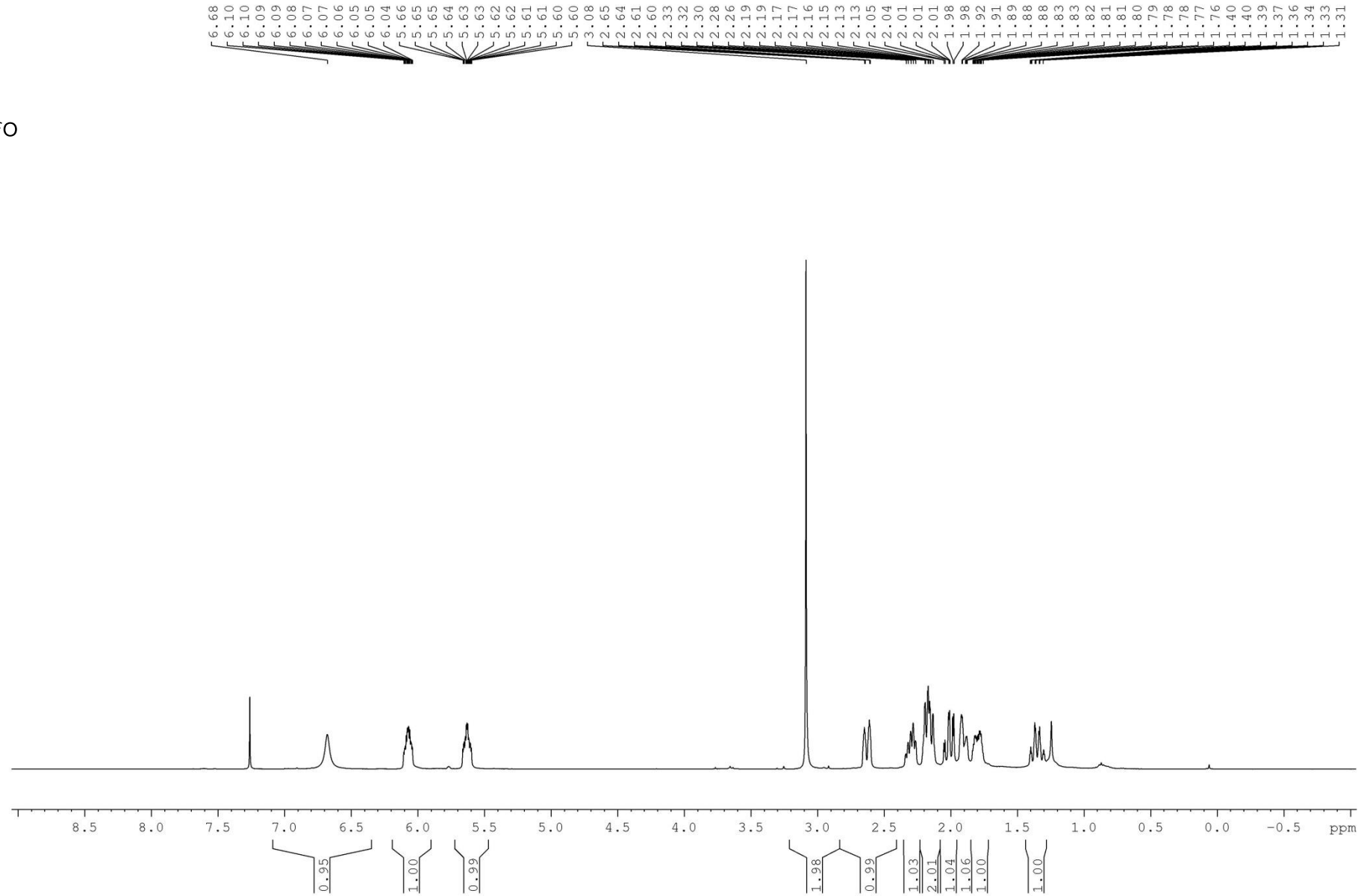
^{13}C NMR, $CDCl_3$, 101 MHz



1-Azaspiro[4.6]undec-7-ene-2,4-dione (13)

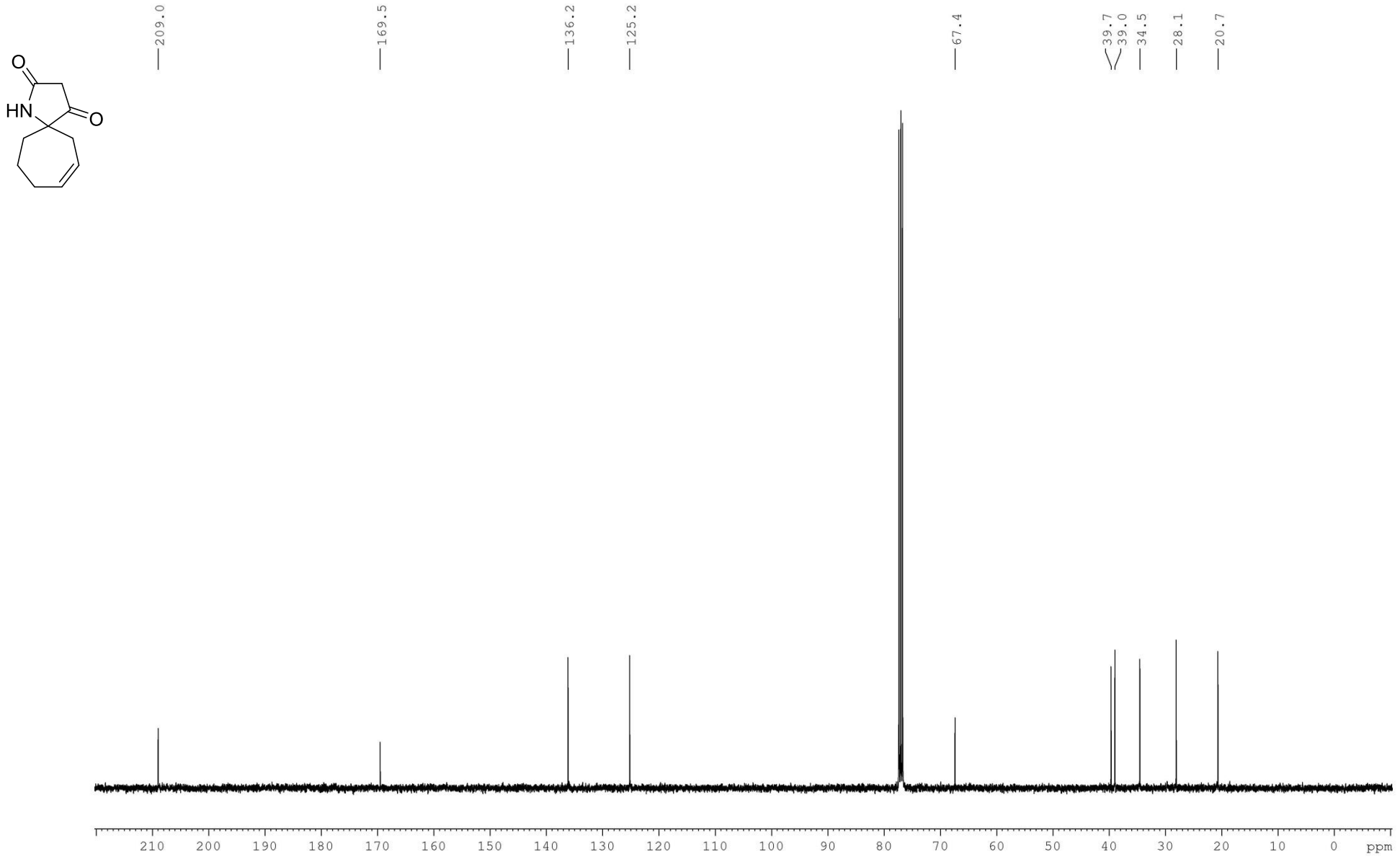
^{1}H NMR, $CDCl_3$, 400 MHz





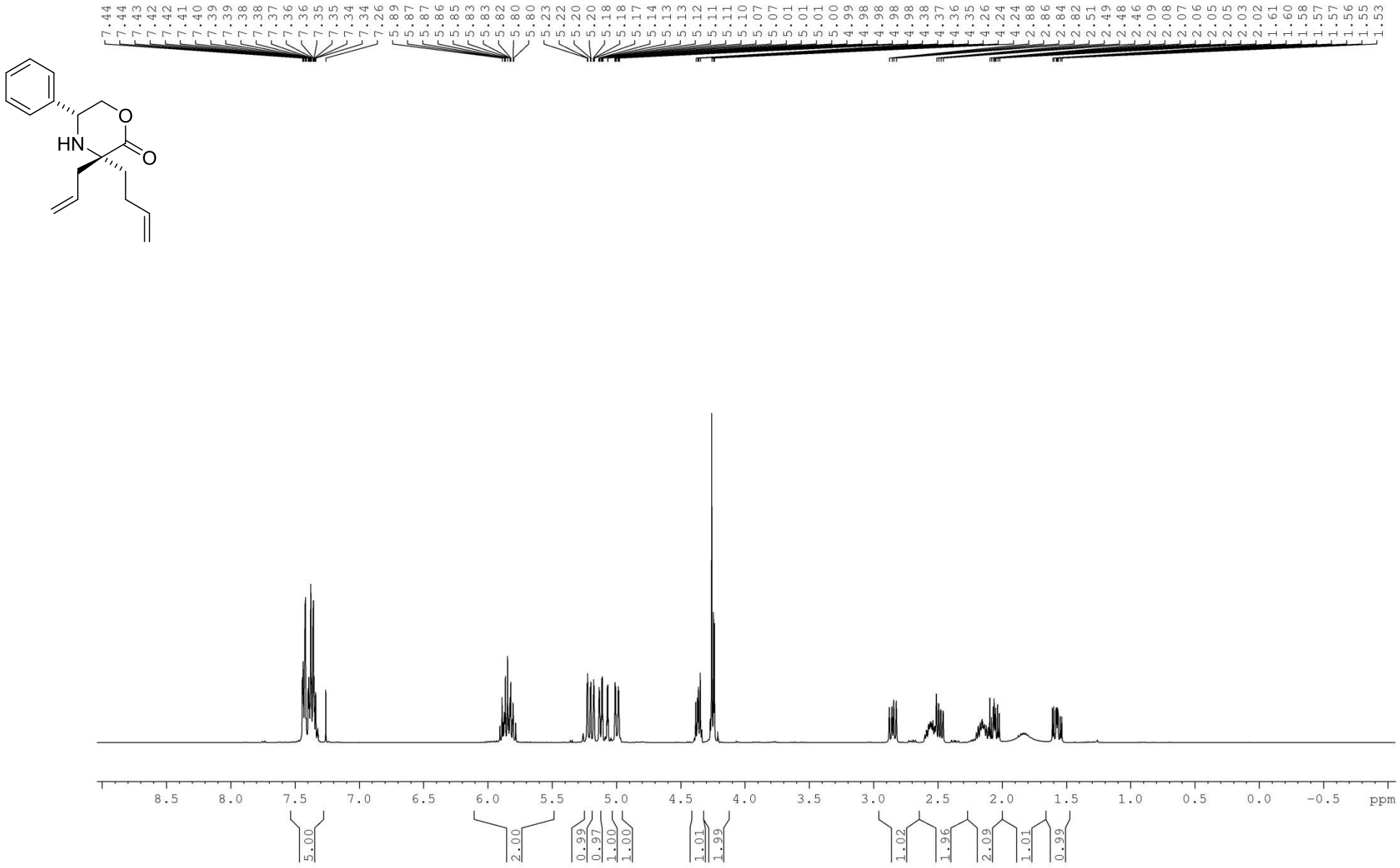
1-Azaspiro[4.6]undec-7-ene-2,4-dione (13)

^{13}C NMR, $CDCl_3$, 101 MHz



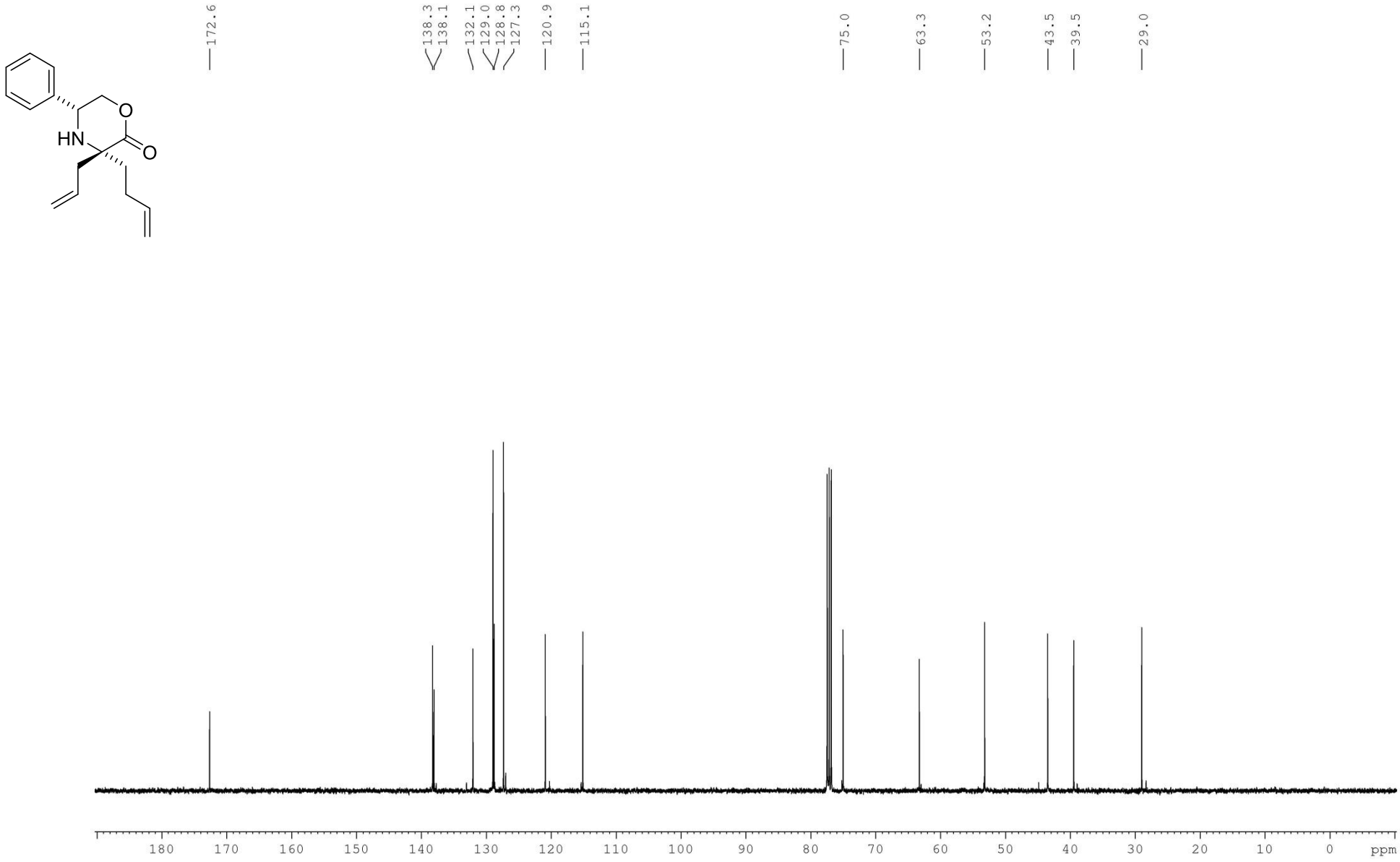
(3*R*,5*R*)-3-Allyl-3-(but-3-en-1-yl)-5-phenylmorpholine-2-one ((*R*)-15)

^{1}H NMR, $CDCl_3$, 400 MHz



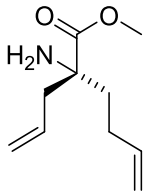
(3*R*,5*R*)-3-Allyl-3-(but-3-en-1-yl)-5-phenylmorpholine-2-one ((*R*)-15)

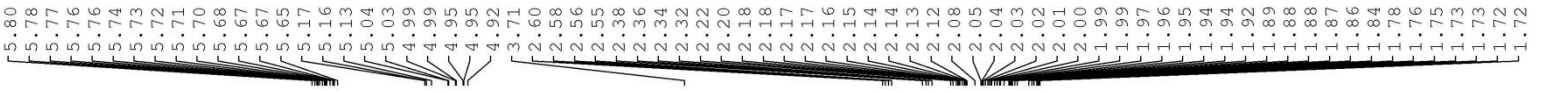
^{13}C NMR, $CDCl_3$, 101 MHz

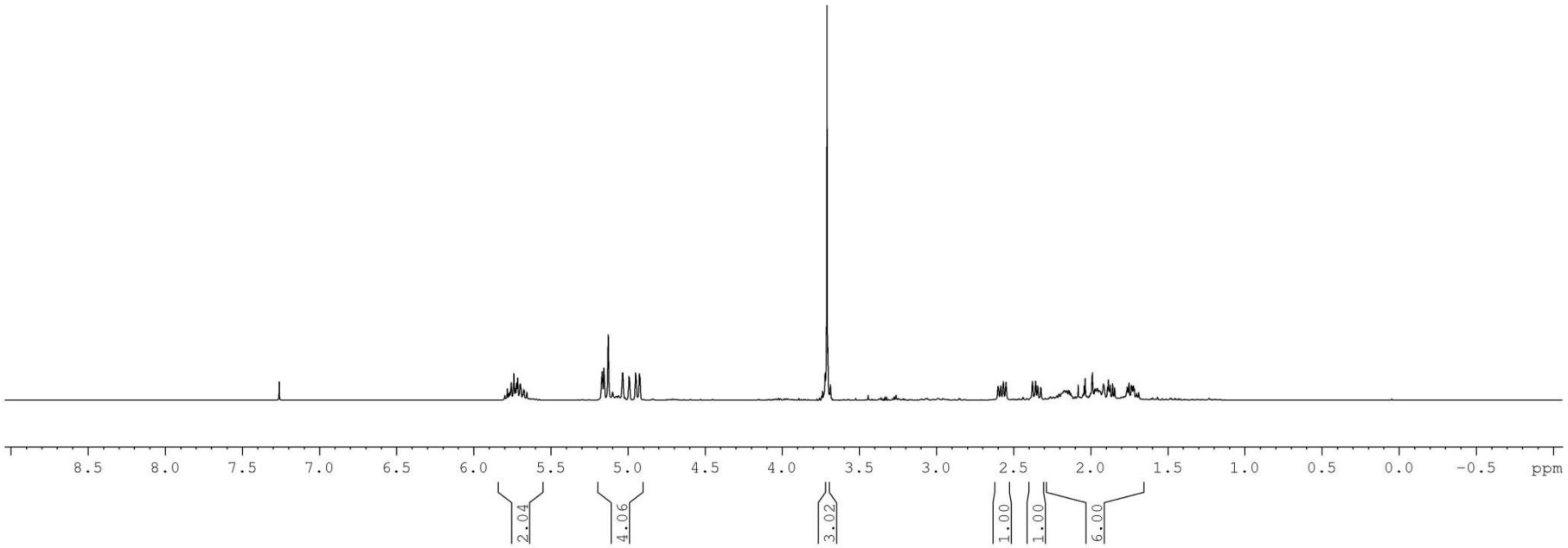


Methyl (*R*)-2-allyl-2-aminohex-5-enoate ((*R*)-3d)

^{1}H NMR, $CDCl_3$, 400 MHz

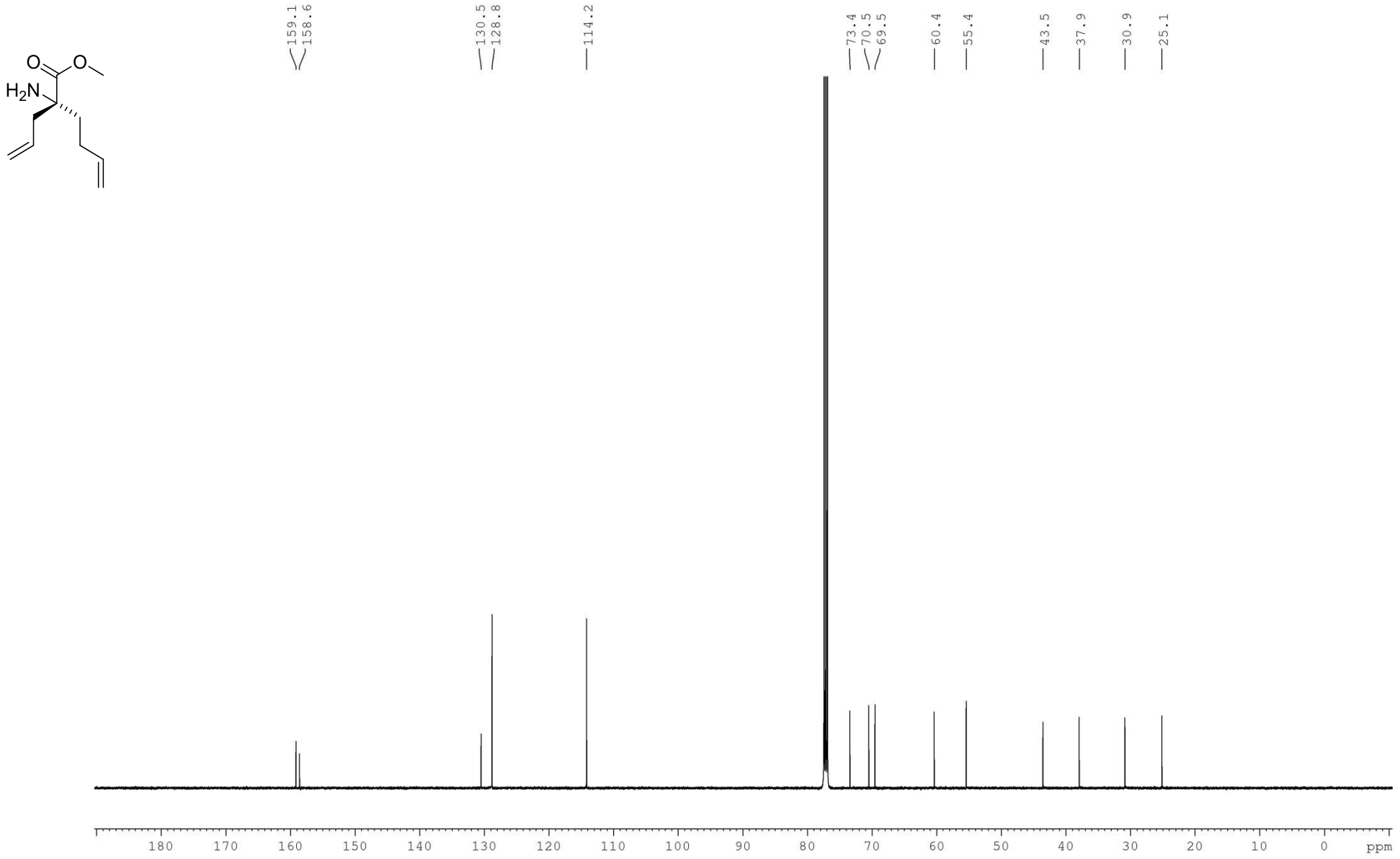






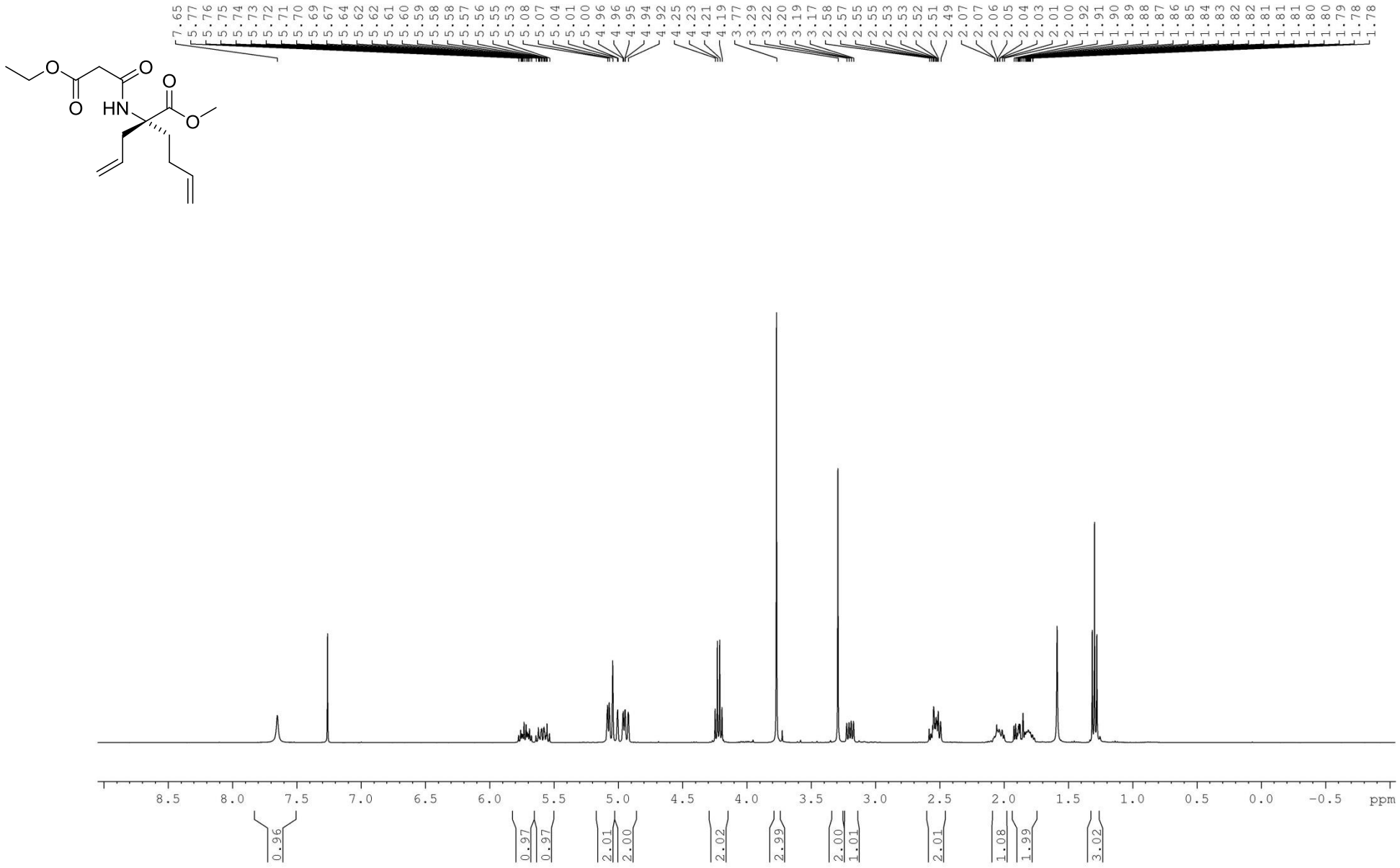
Methyl (*R*)-2-allyl-2-aminohex-5-enoate ((*R*)-3d)

^{13}C NMR, $CDCl_3$, 101 MHz



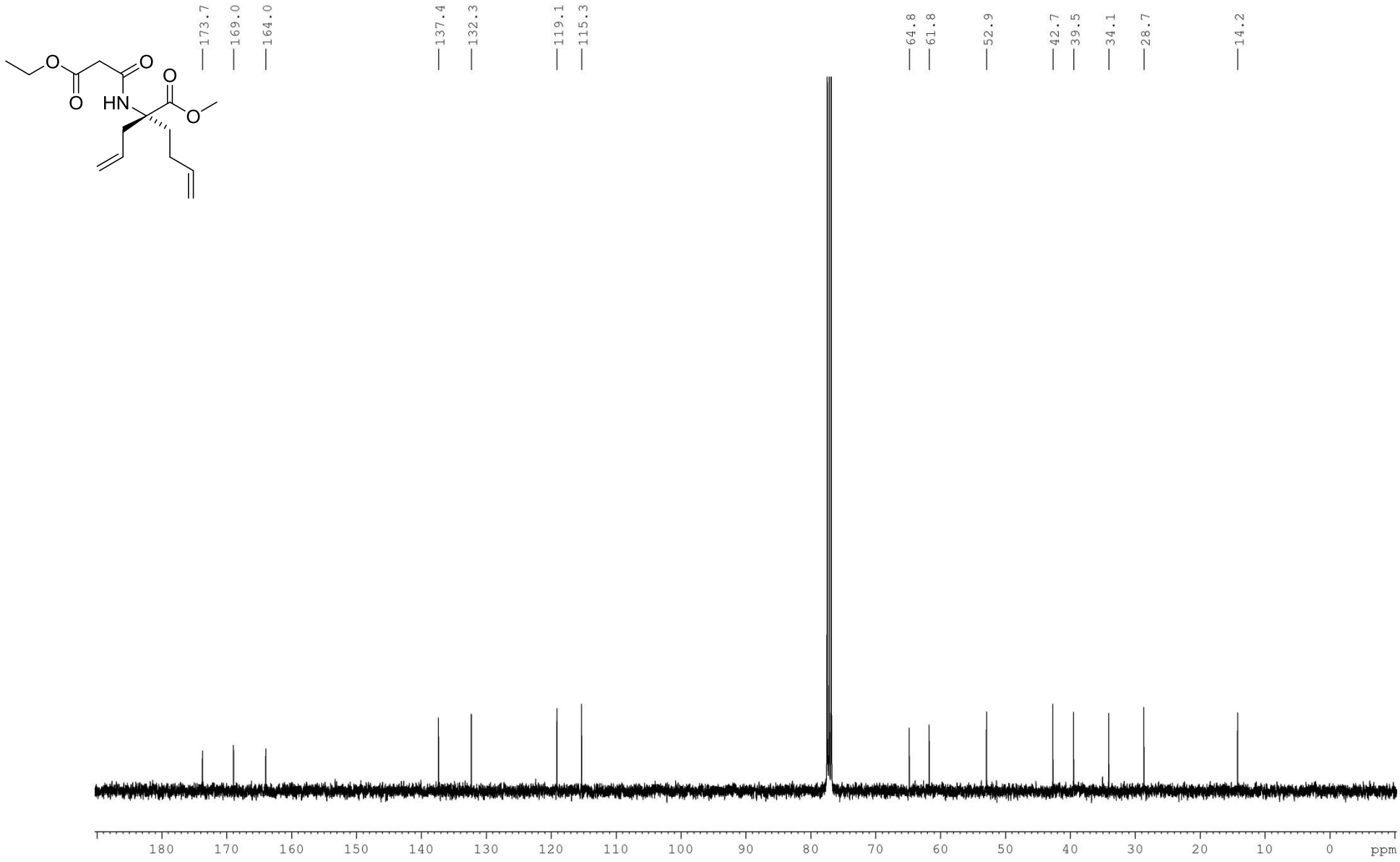
Methyl (*R*)-2-allyl-2-(3-ethoxy-3-oxopropanamido)hex-5-enoate ((*R*)-S4d)

^{1}H NMR, $CDCl_3$, 400 MHz



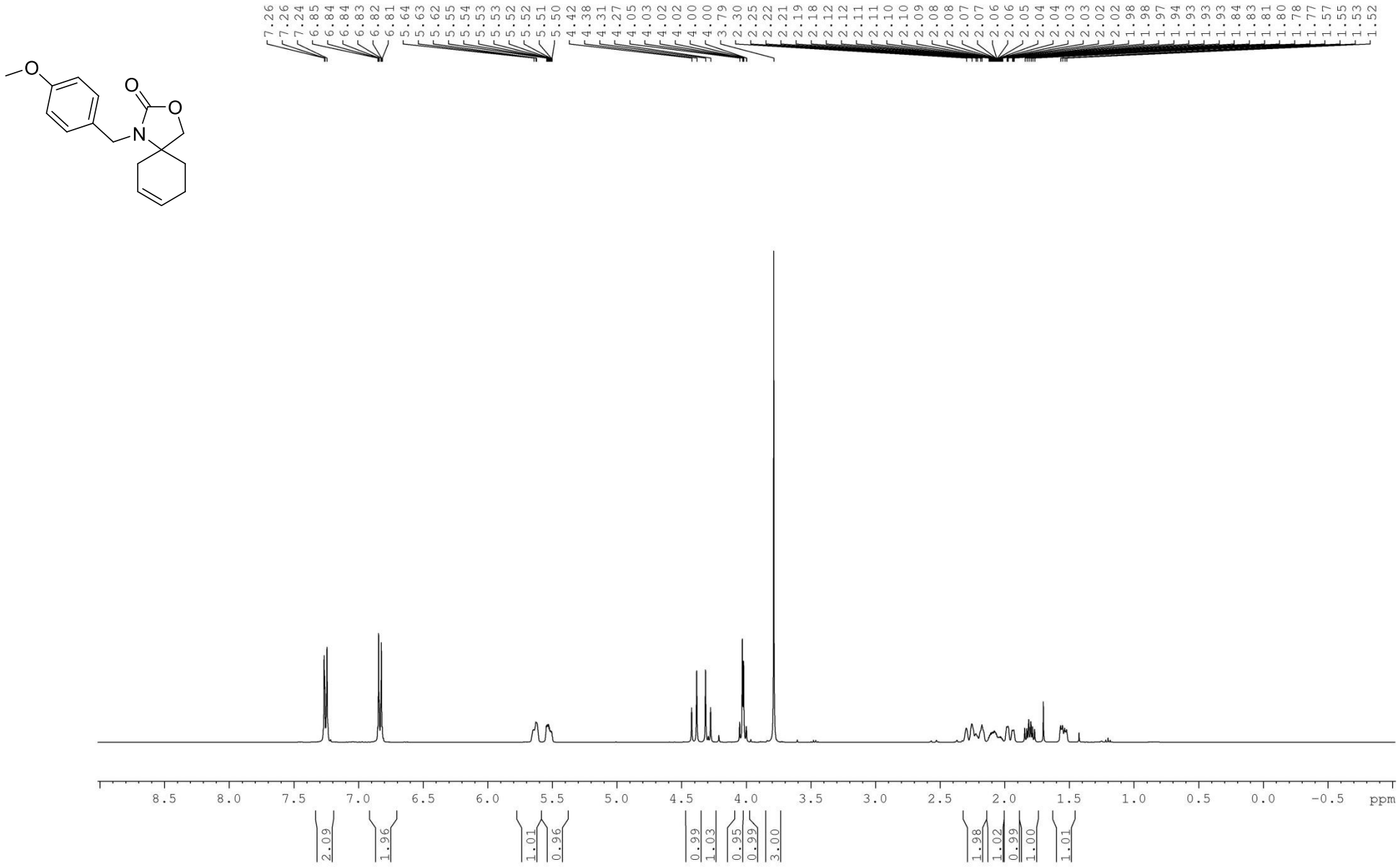
Methyl (*R*)-2-allyl-2-(3-ethoxy-3-oxopropanamido)hex-5-enoate ((*R*)-S4d)

^{13}C NMR, $CDCl_3$, 101 MHz



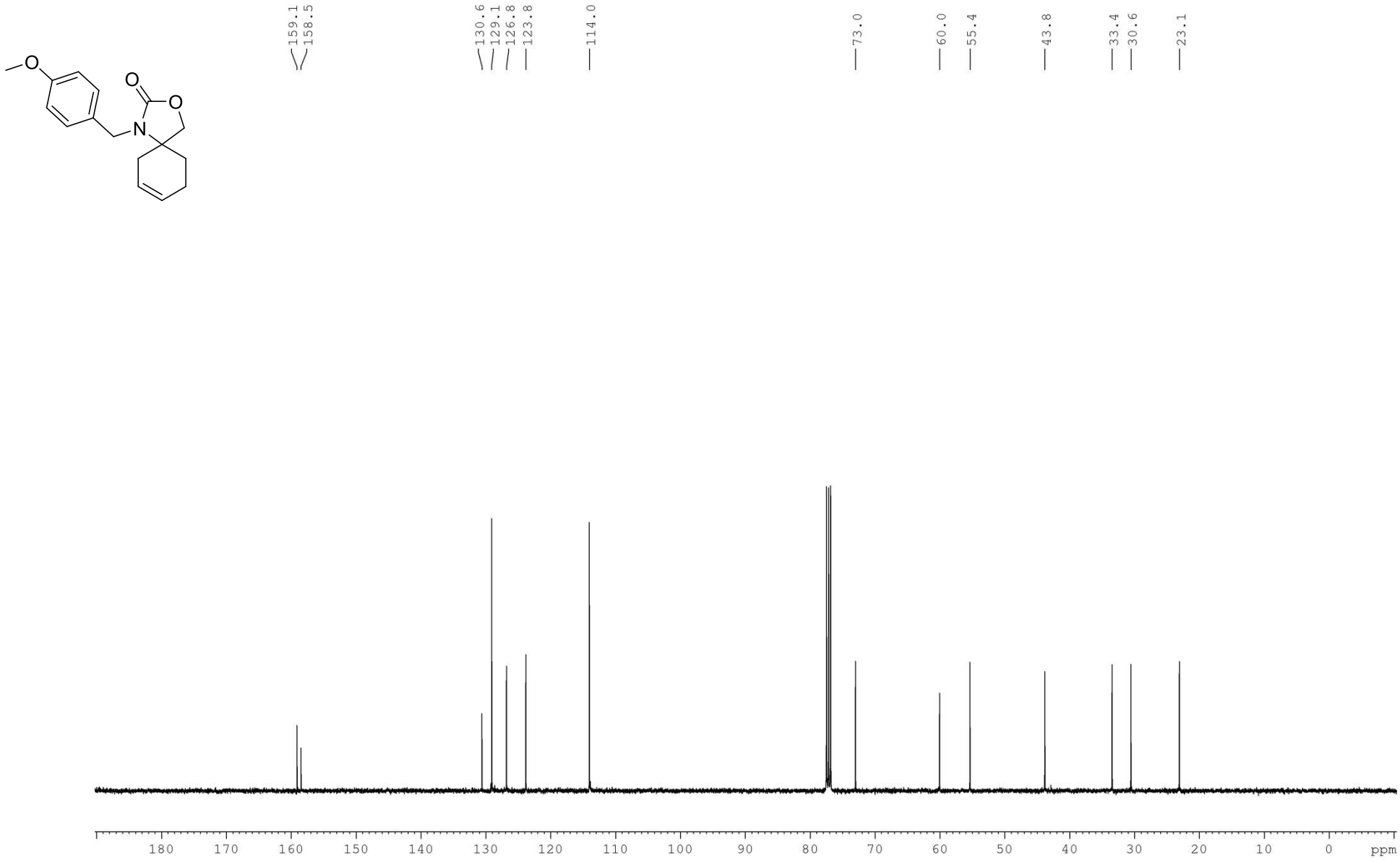
1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]dec-7-ene-2-one (16)

^{1}H NMR, $CDCl_3$, 400 MHz



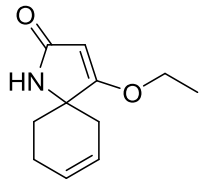
1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]dec-7-ene-2-one (16)

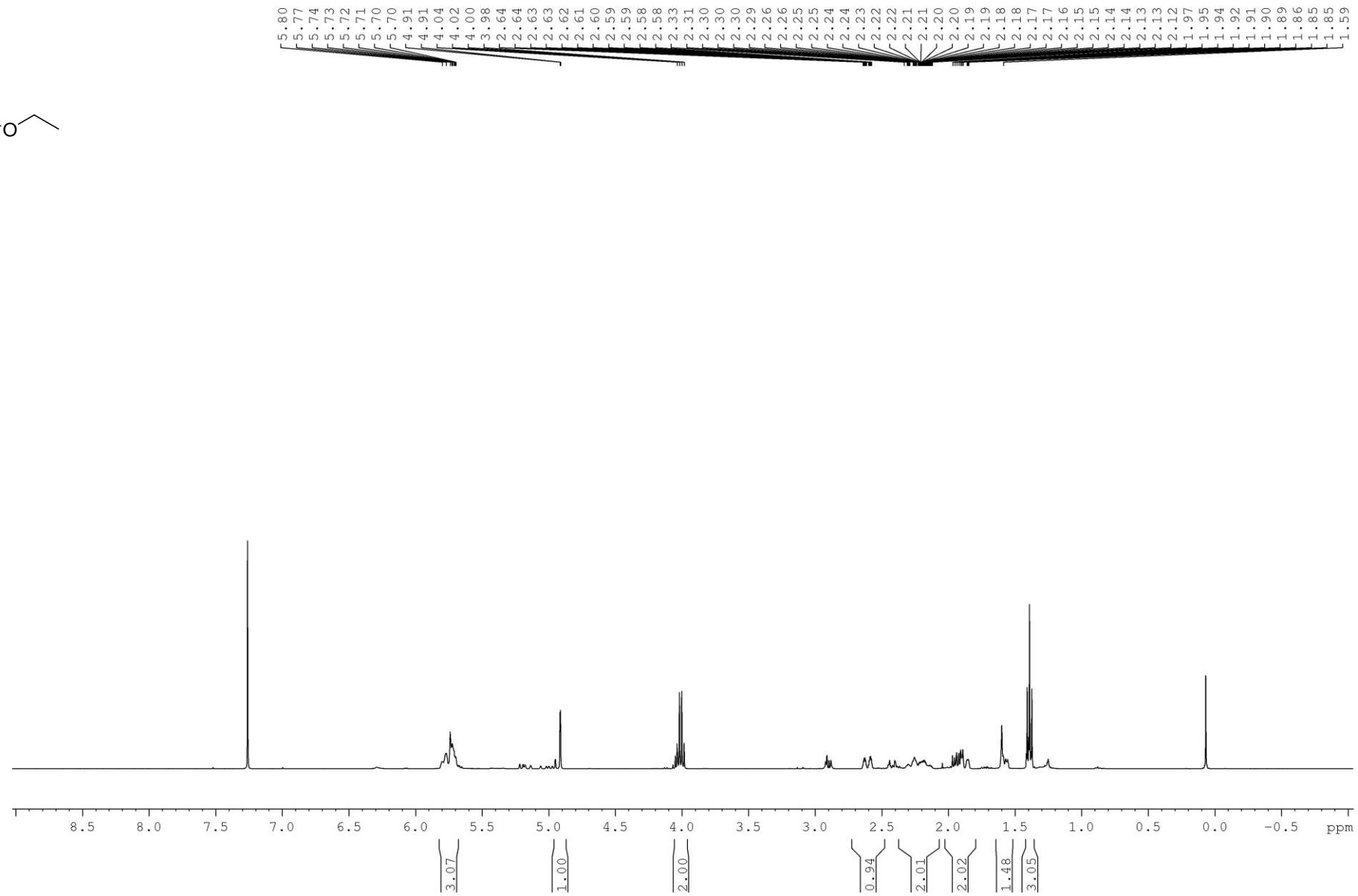
^{13}C NMR, $CDCl_3$, 101 MHz



4-Ethoxy-1-azaspiro[4.5]deca-3,7-dien-2-one (17)

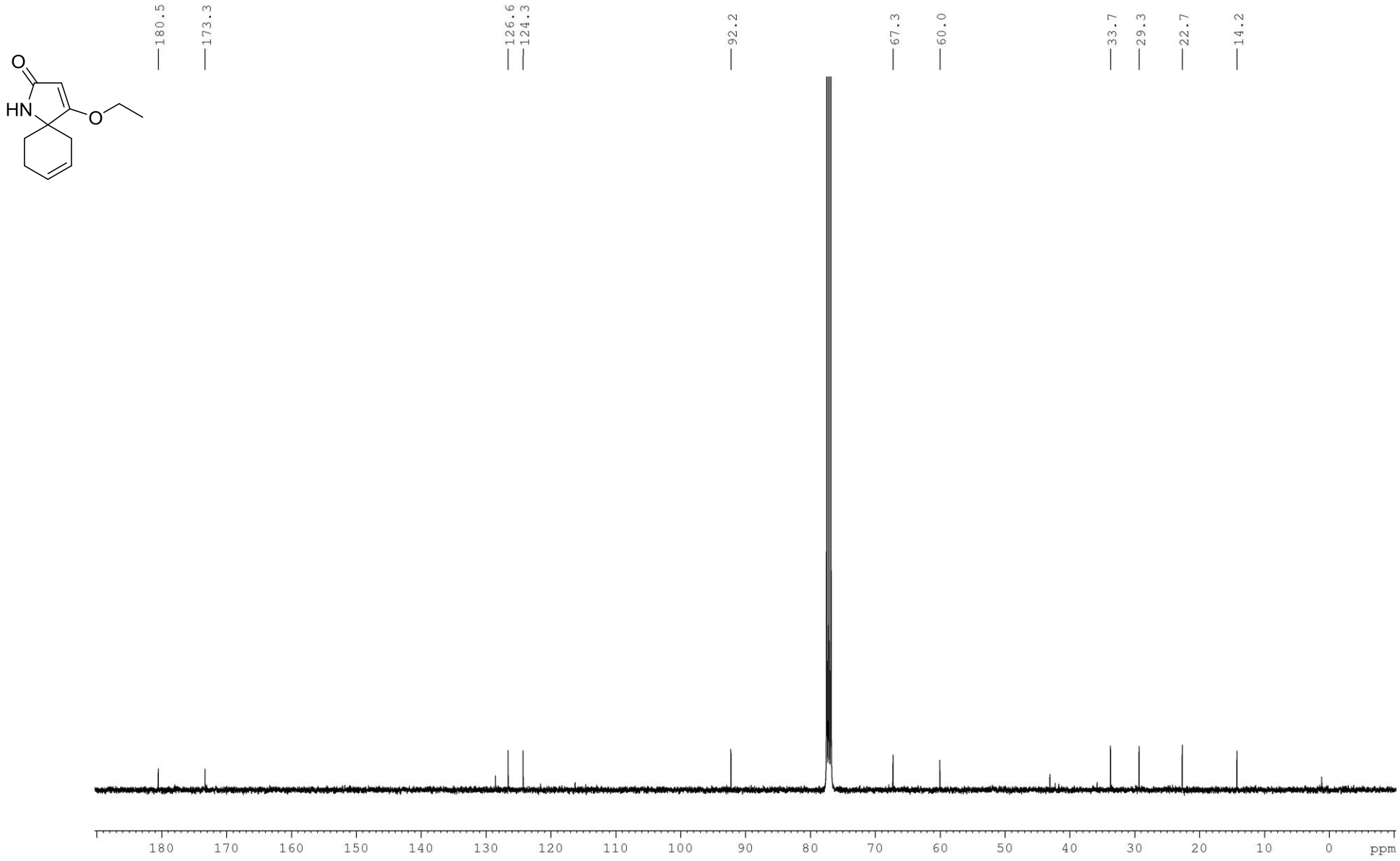
^{1}H NMR, $CDCl_3$, 400 MHz





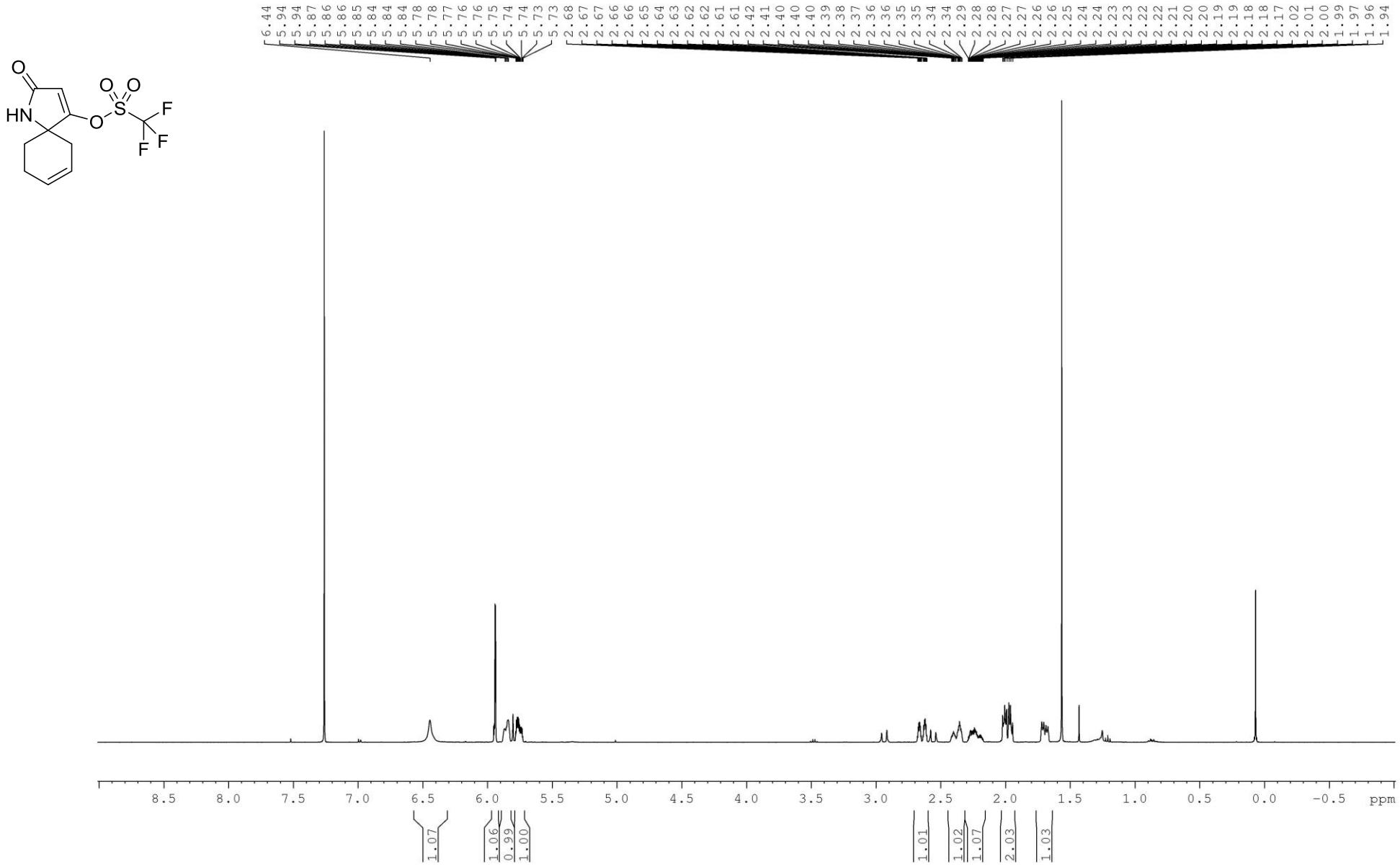
4-Ethoxy-1-azaspiro[4.5]deca-3,7-dien-2-one (17)

^{13}C NMR, $CDCl_3$, 101 MHz



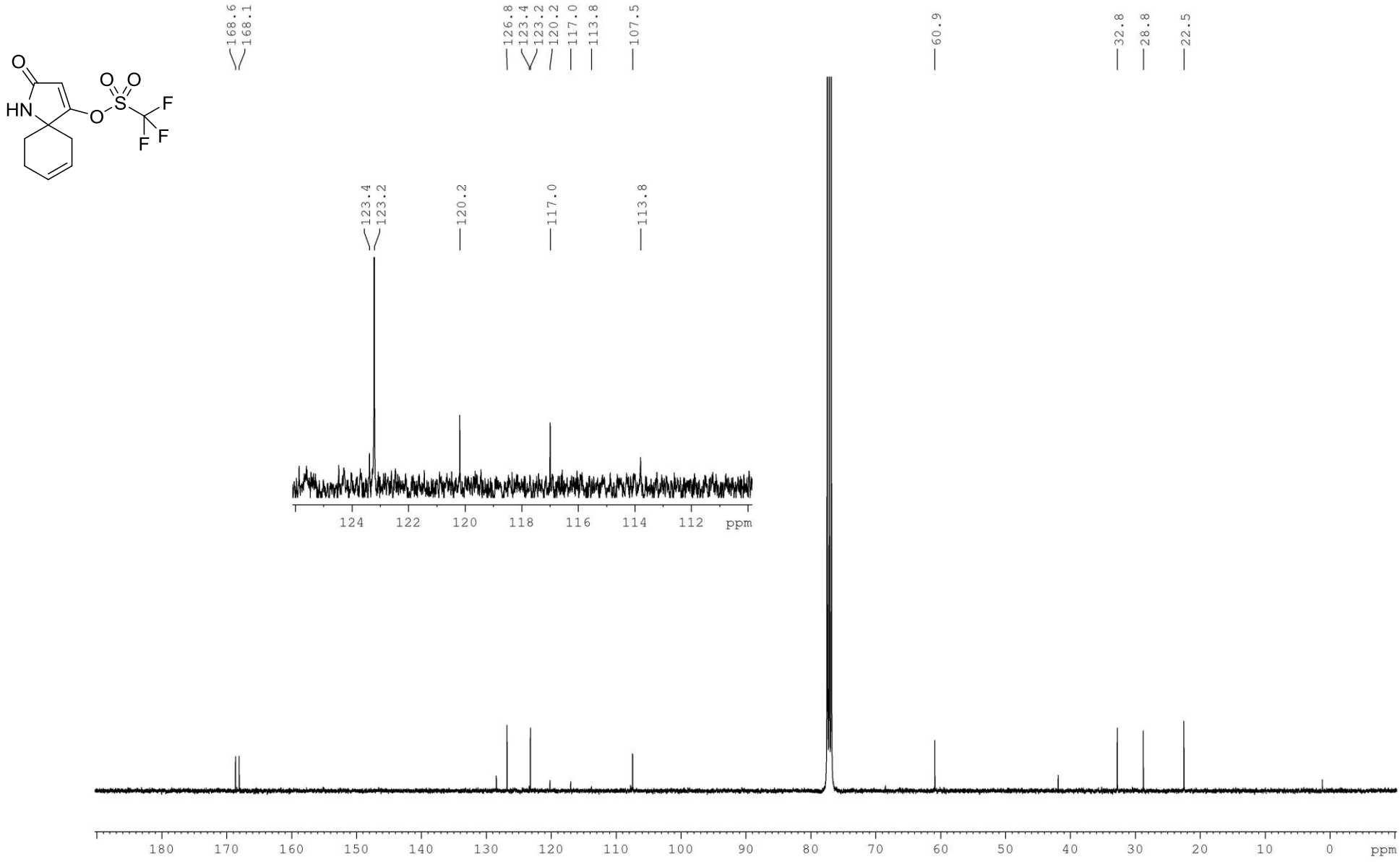
2-Oxo-1-azaspiro[4.5]deca-3,7-dien-4-yl trifluoromethanesulfonate (S5)

^{1}H NMR, $CDCl_3$, 400 MHz



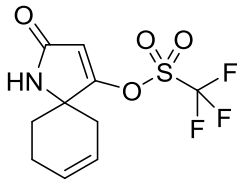
2-Oxo-1-azaspiro[4.5]deca-3,7-dien-4-yl trifluoromethanesulfonate (S5)

^{13}C NMR, $CDCl_3$, 101 MHz



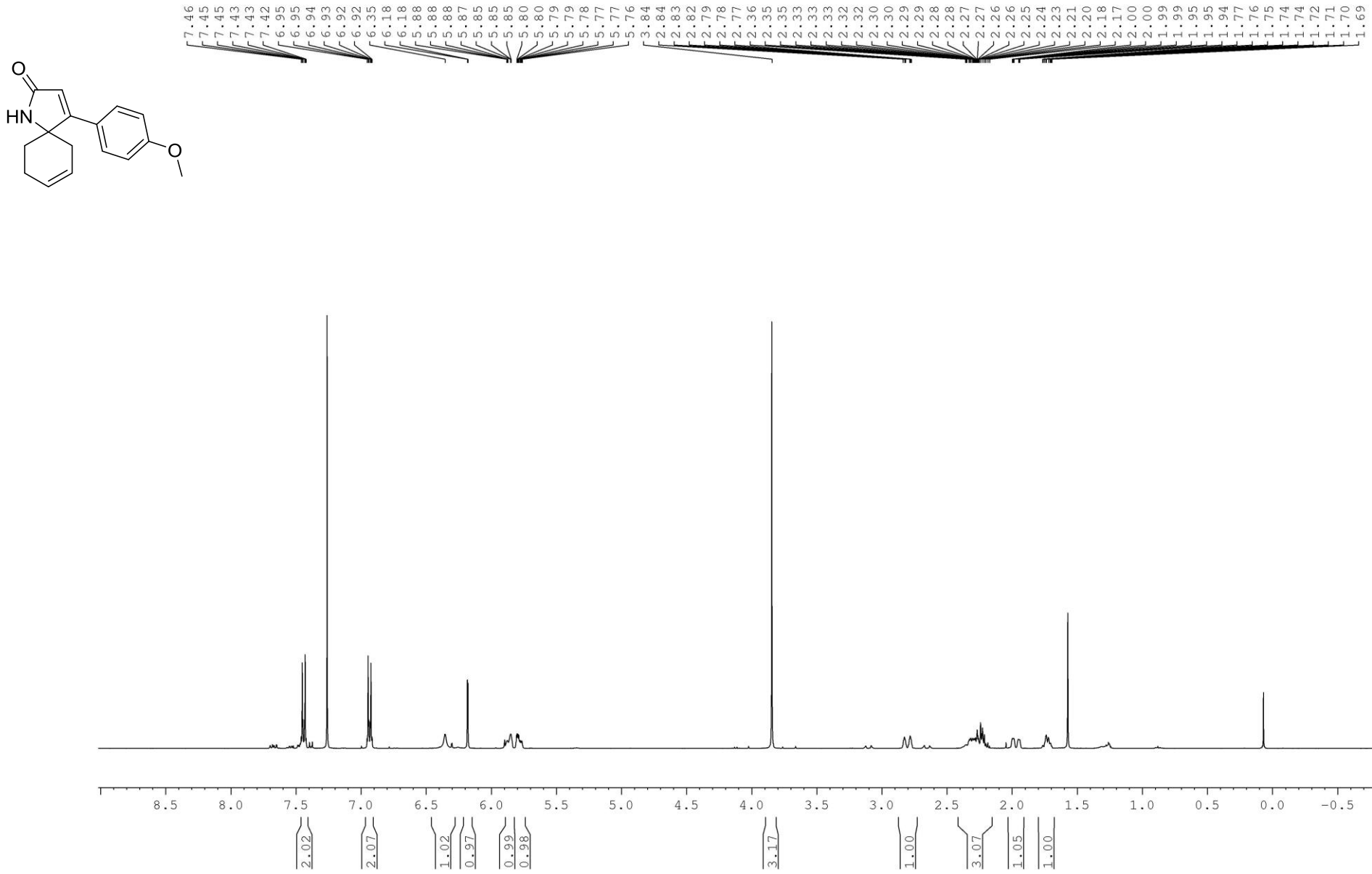
2-Oxo-1-azaspiro[4.5]deca-3,7-dien-4-yl trifluoromethanesulfonate (S5)

^{19}F NMR, $CDCl_3$, 376 MHz



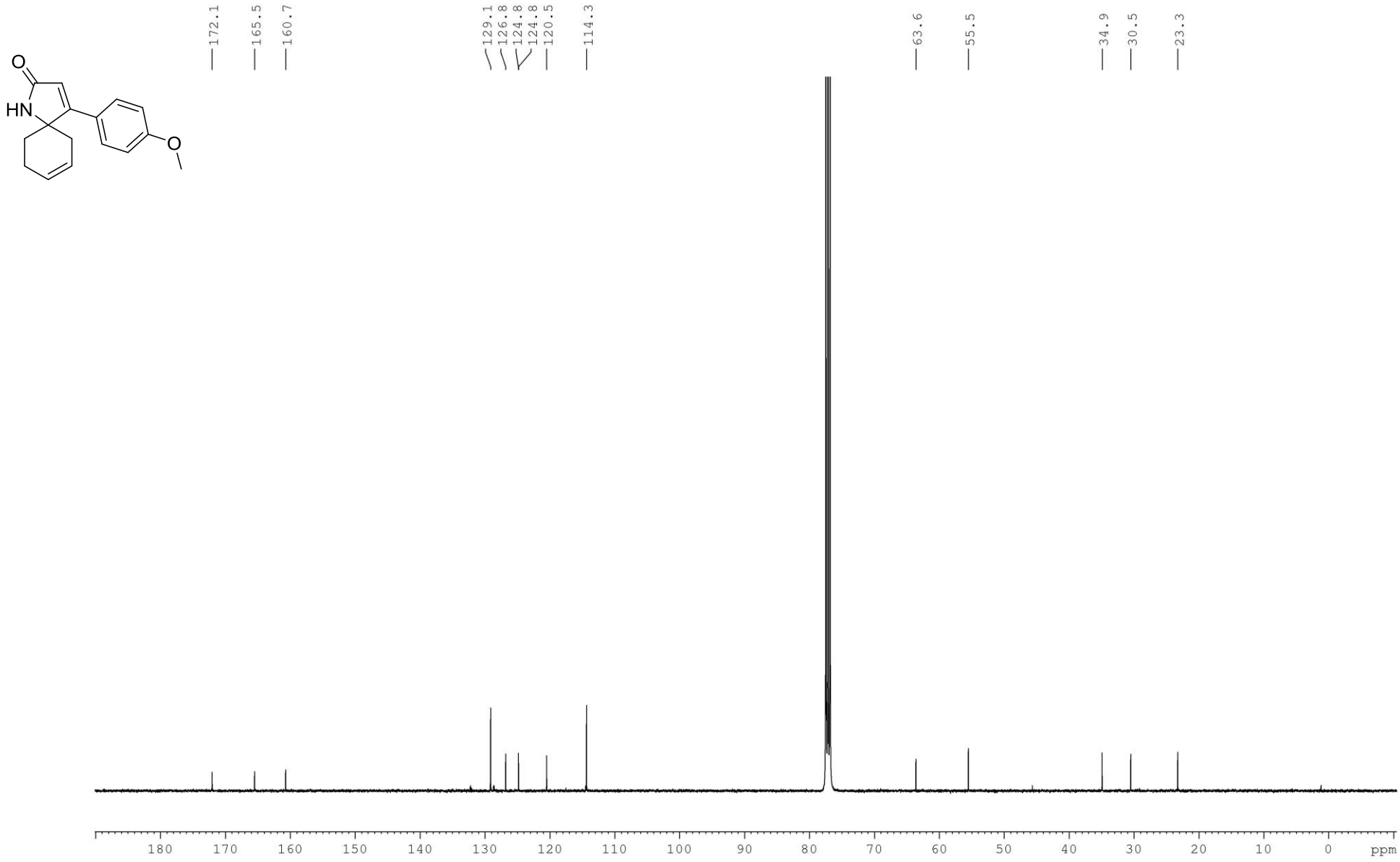
4-(4-Methoxyphenyl)-1-azaspiro[4.5]deca-3,7-dien-2-one (18)

^{1}H NMR, $CDCl_3$, 400 MHz



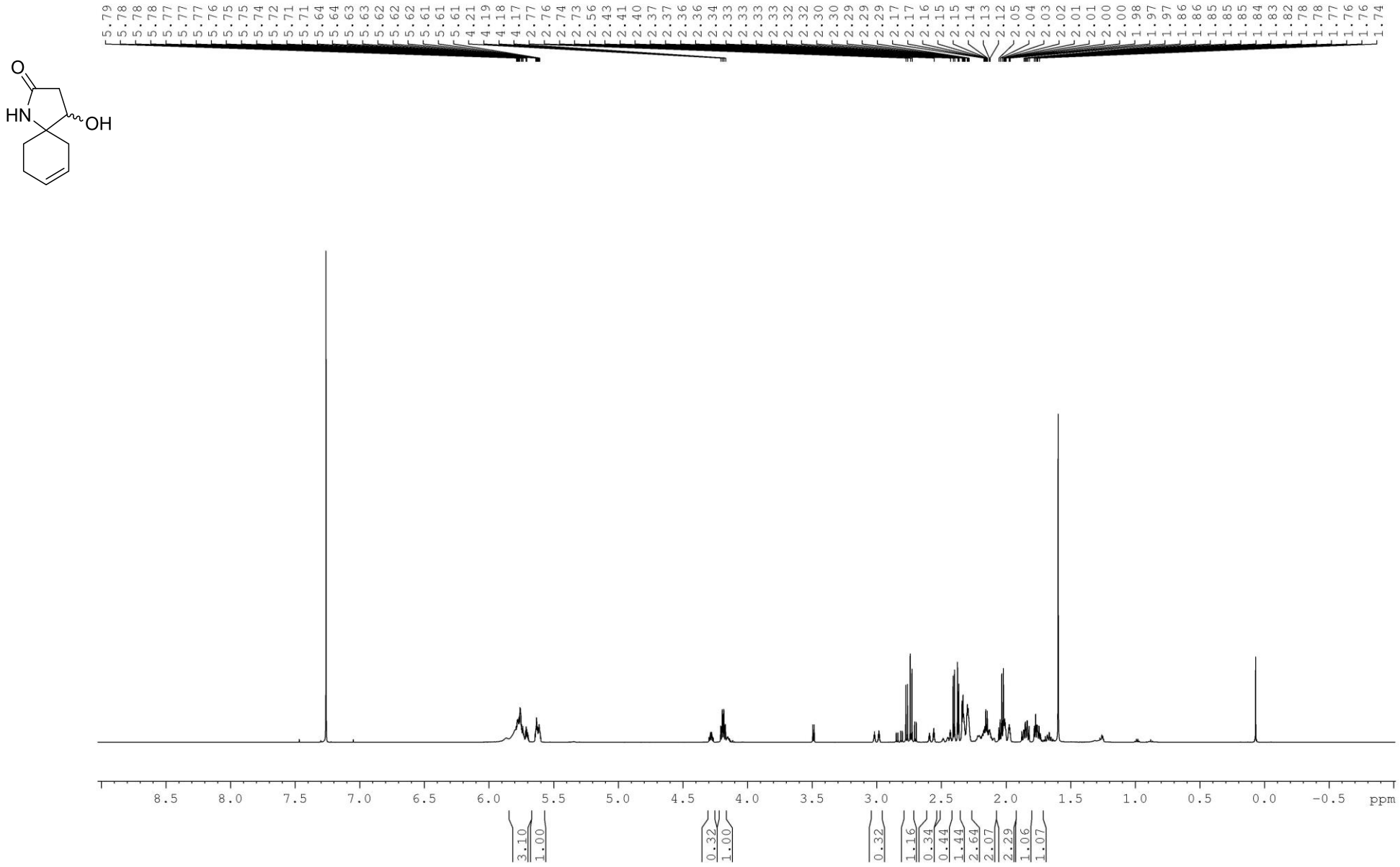
4-(4-Methoxyphenyl)-1-azaspiro[4.5]deca-3,7-dien-2-one (18)

^{13}C NMR, $CDCl_3$, 101 MHz



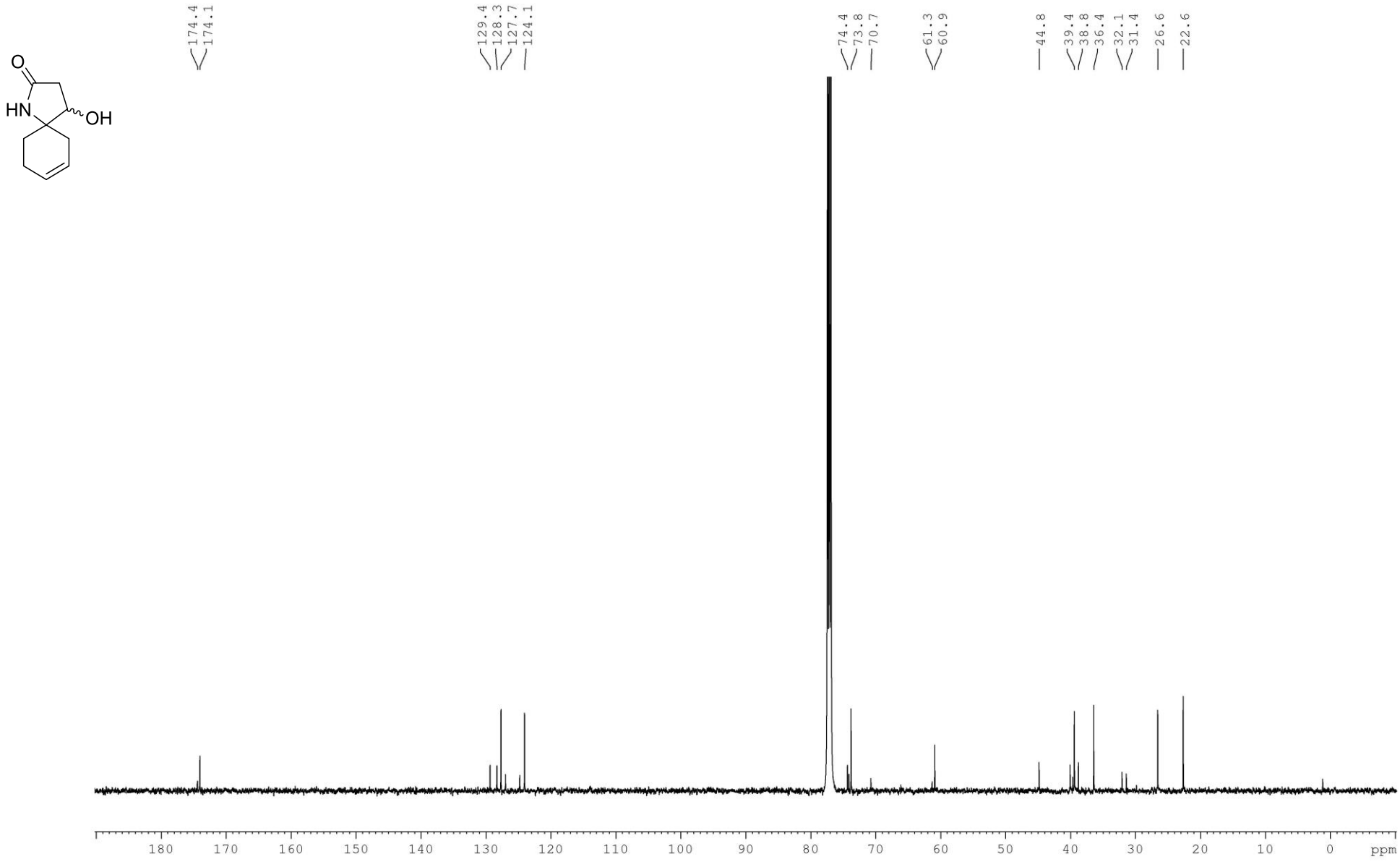
4-Hydroxy-1-azaspiro[4.5]dec-7-en-2-one (19)

^{1}H NMR, $CDCl_3$, 500 MHz



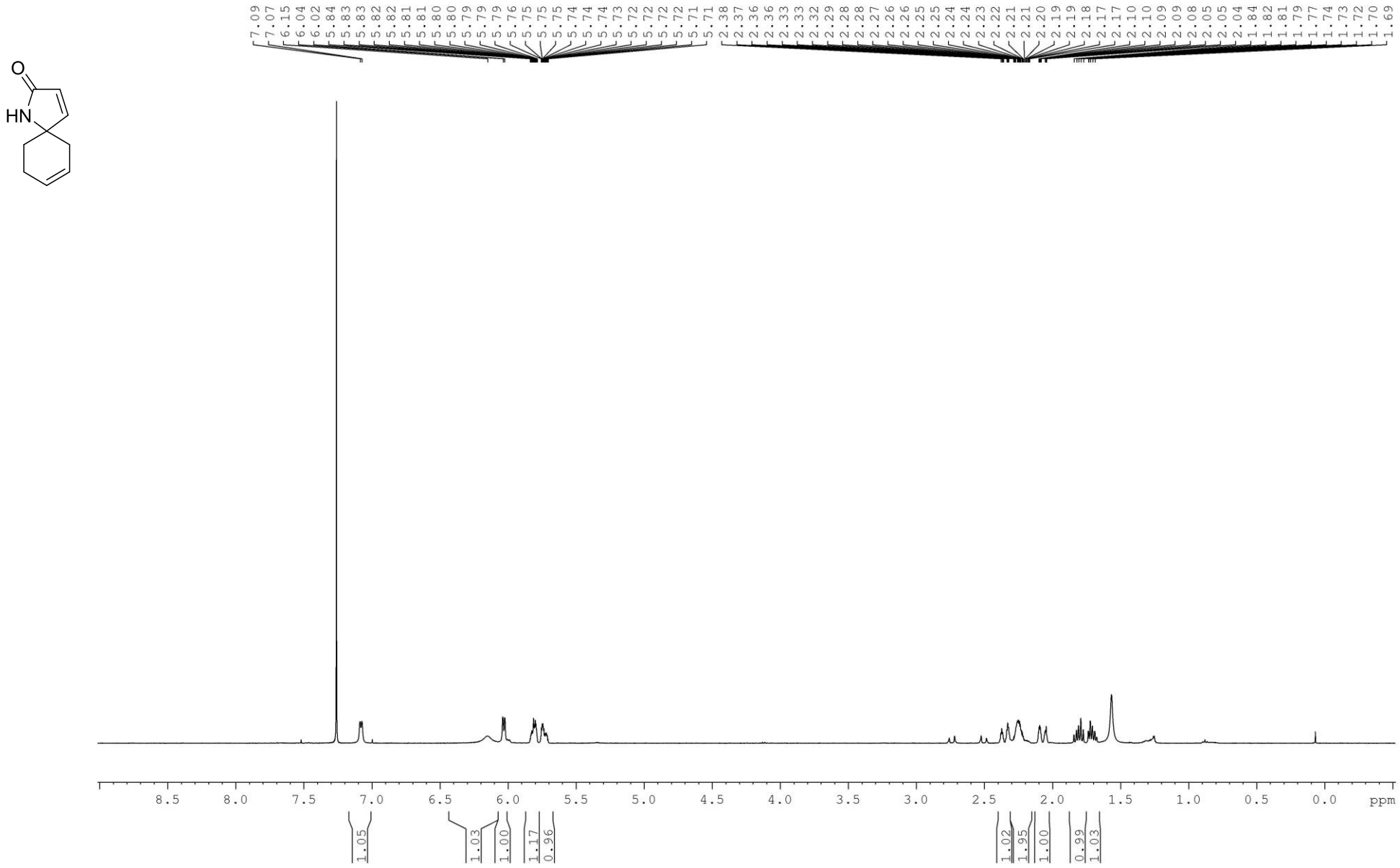
4-Hydroxy-1-azaspiro[4.5]dec-7-en-2-one (19)

^{13}C NMR, $CDCl_3$, 126 MHz



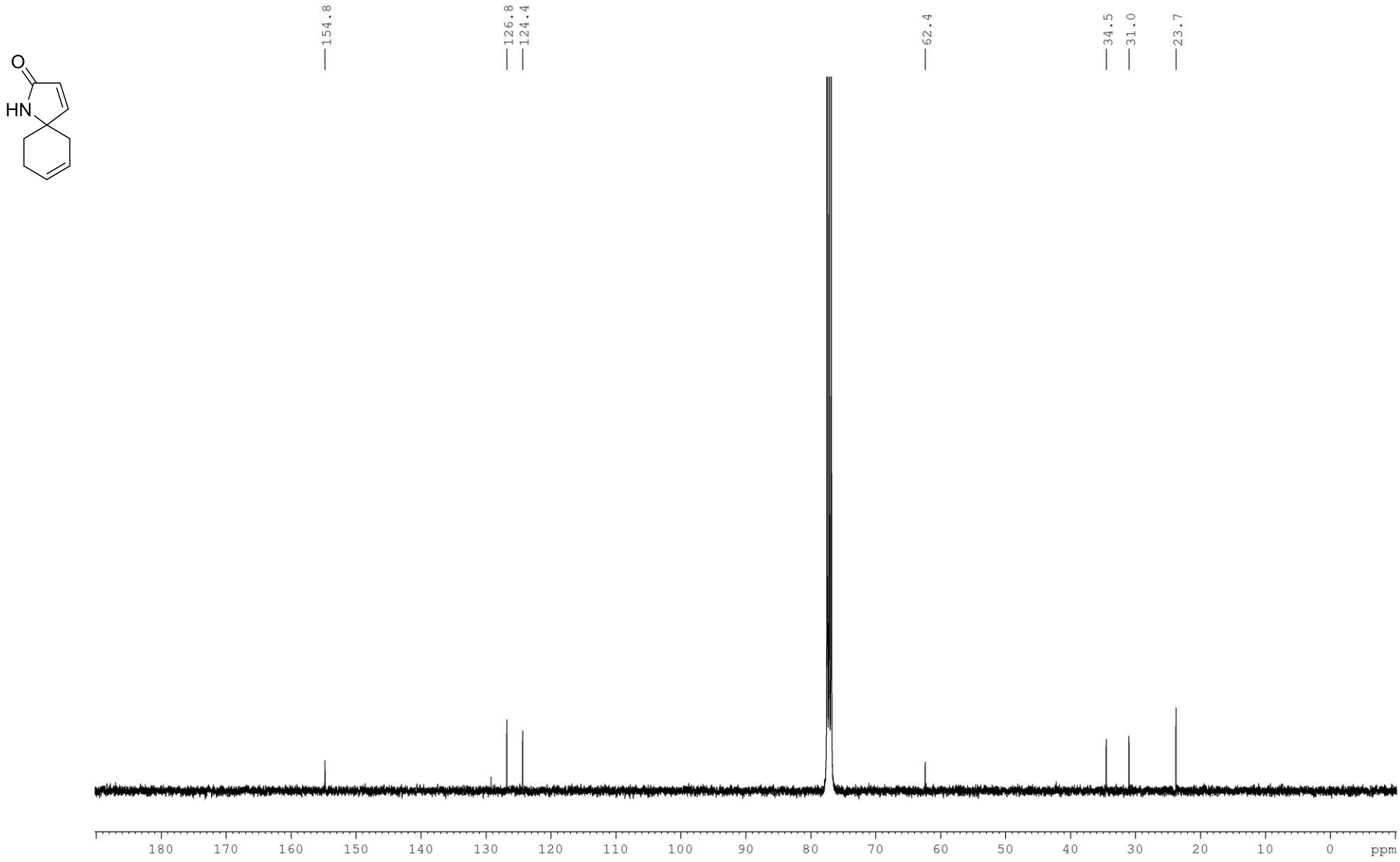
1-Azaspiro[4.5]deca-3,7-dien-2-one (20)

^{1}H NMR, $CDCl_3$, 400 MHz



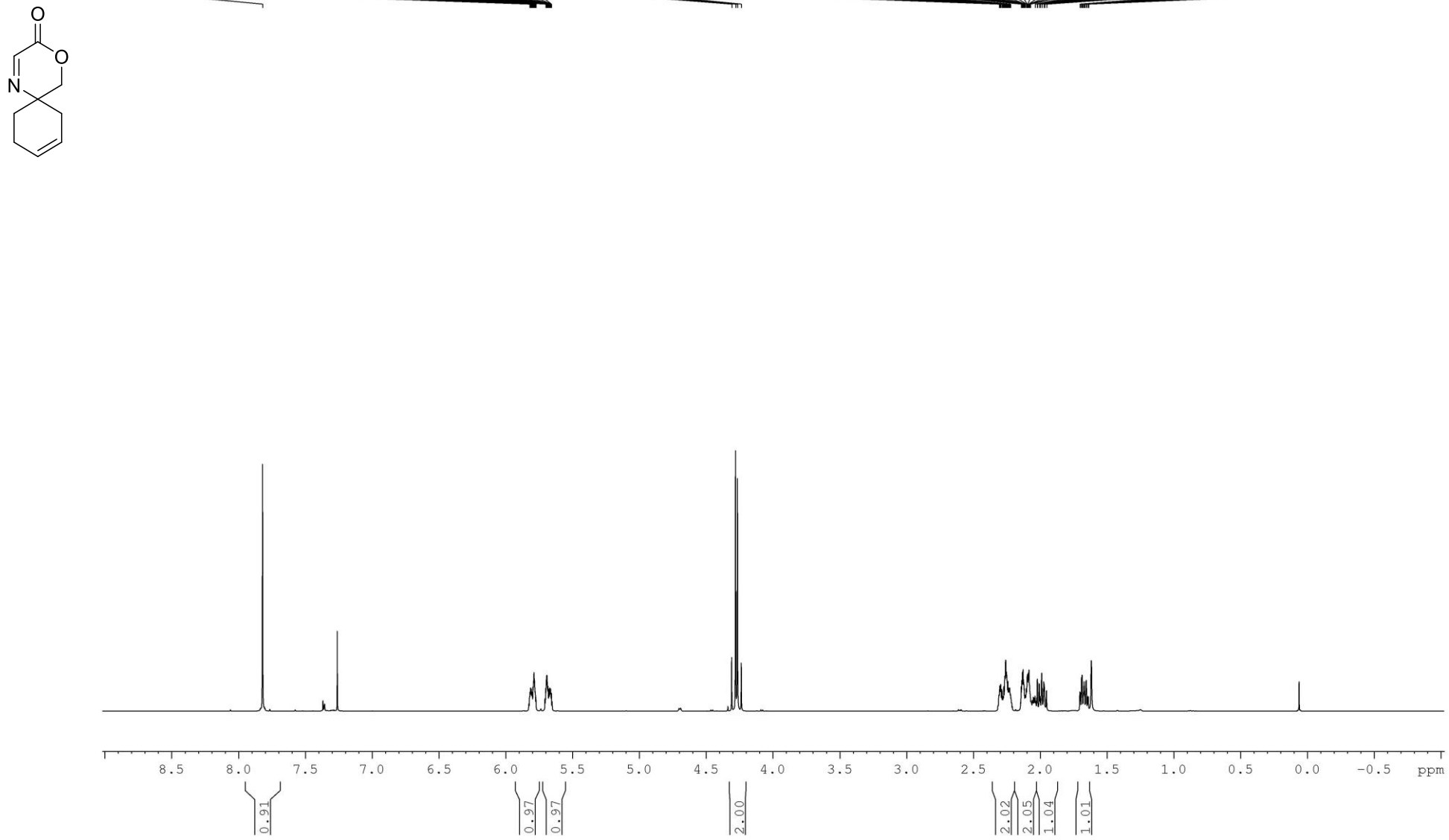
1-Azaspiro[4.5]deca-3,7-dien-2-one (20)

^{13}C NMR, $CDCl_3$, 101 MHz



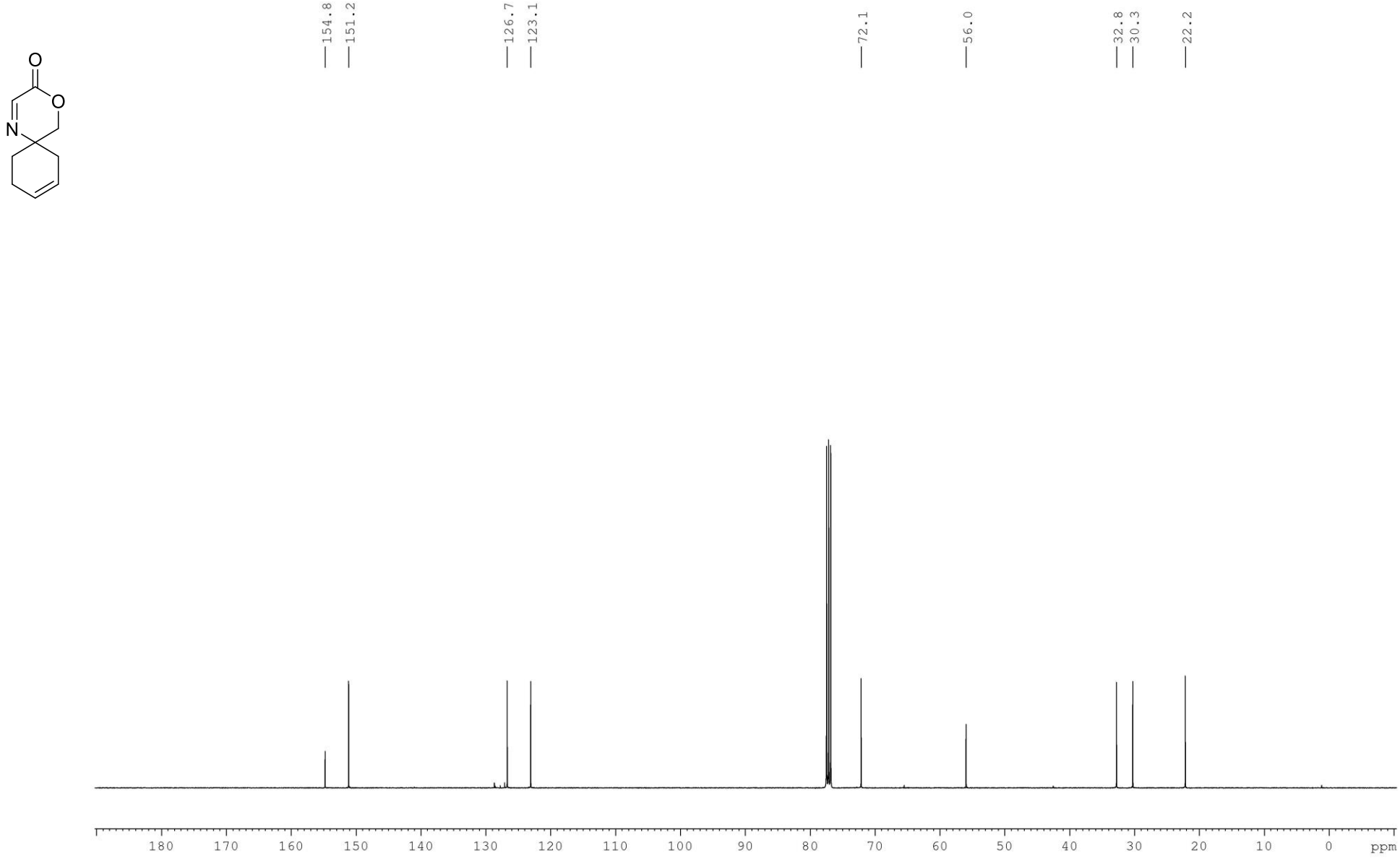
4-Oxa-1-azaspiro[5.5]undeca-1,8-dien-3-one (21)

^{1}H NMR, $CDCl_3$, 400 MHz



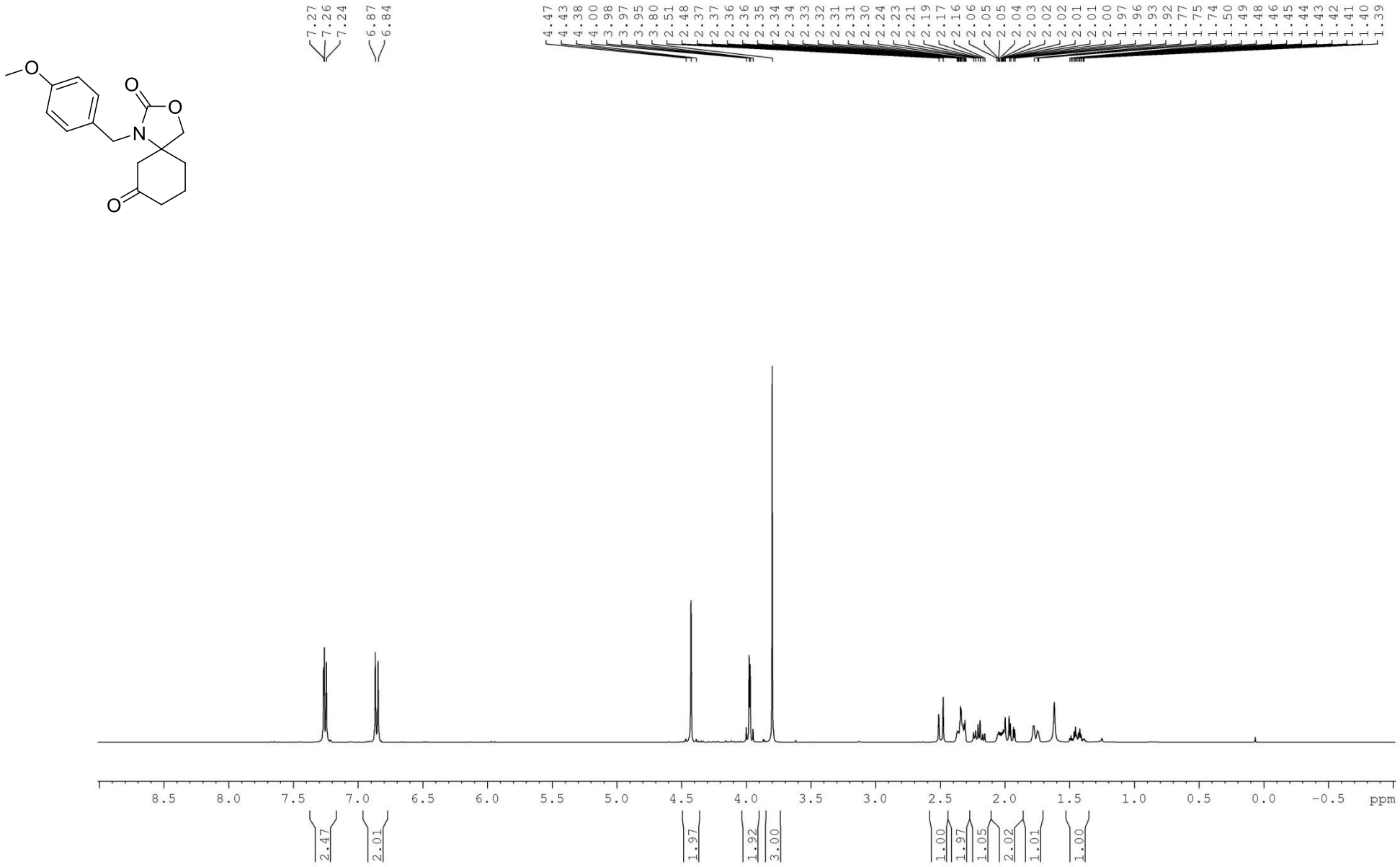
4-Oxa-1-azaspiro[5.5]undeca-1,8-dien-3-one (21)

^{13}C NMR, $CDCl_3$, 101 MHz



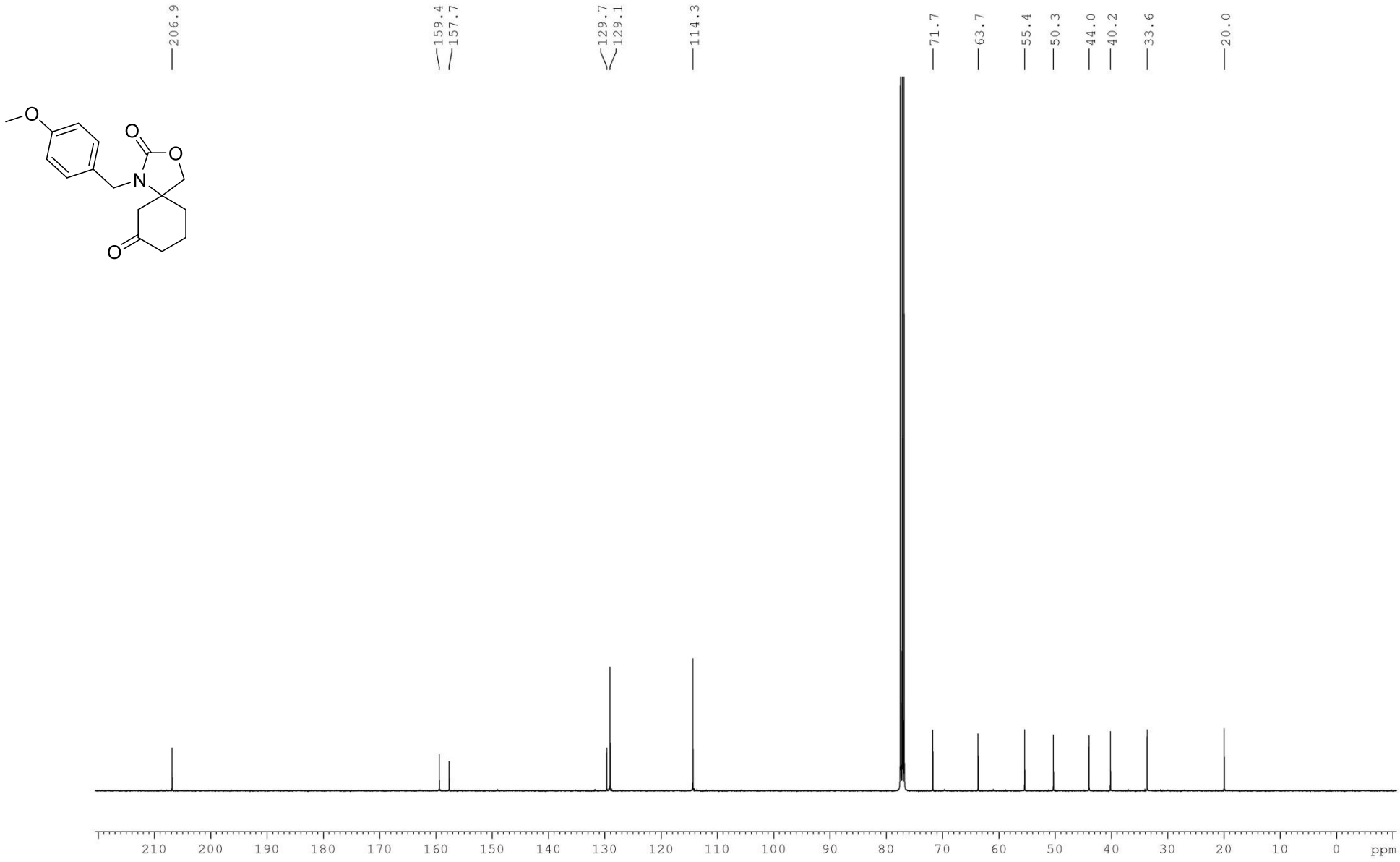
1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]decane-2,7-dione (22a)

^{1}H NMR, $CDCl_3$, 400 MHz



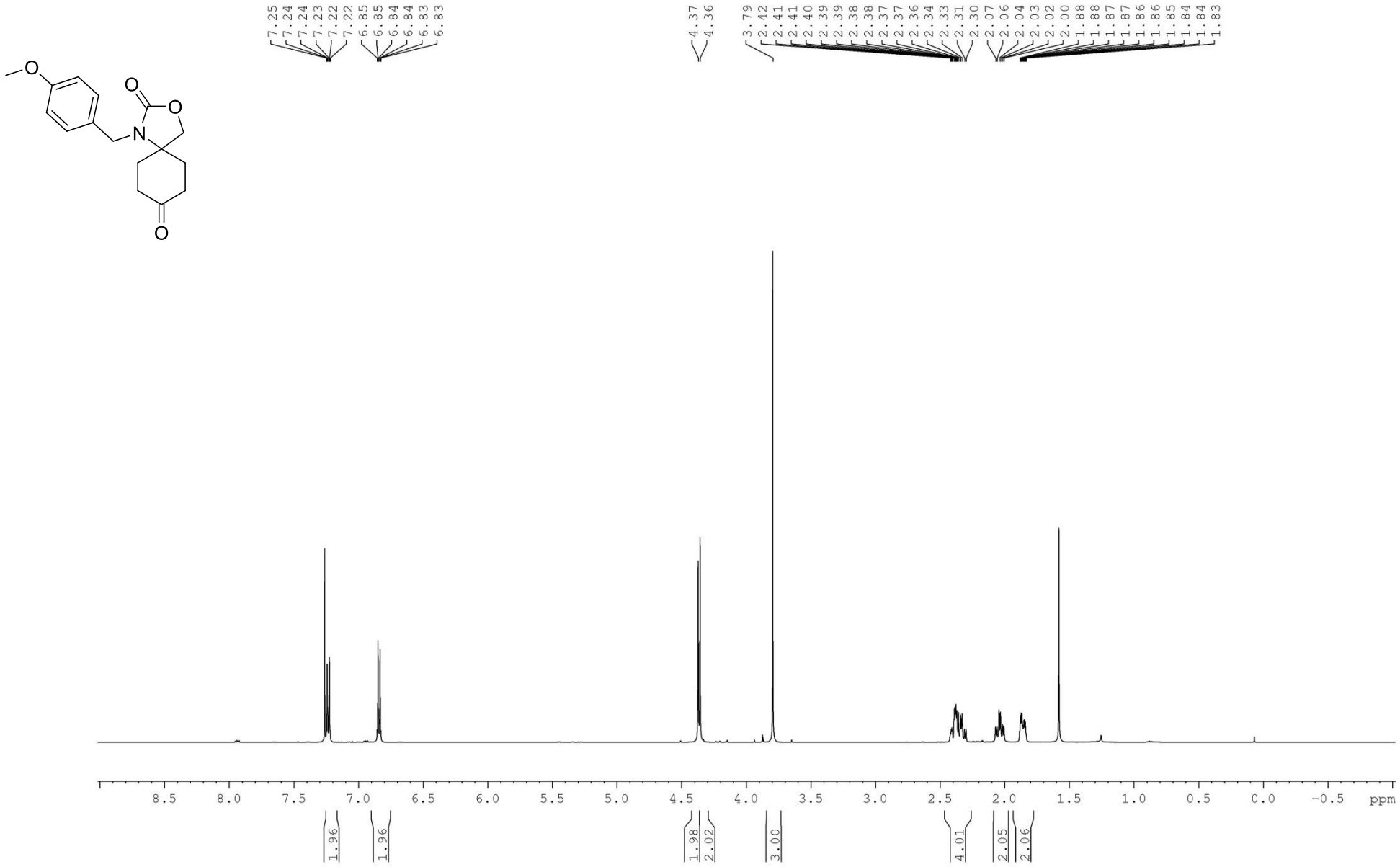
1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]decane-2,7-dione (22a)

^{13}C NMR, $CDCl_3$, 101 MHz



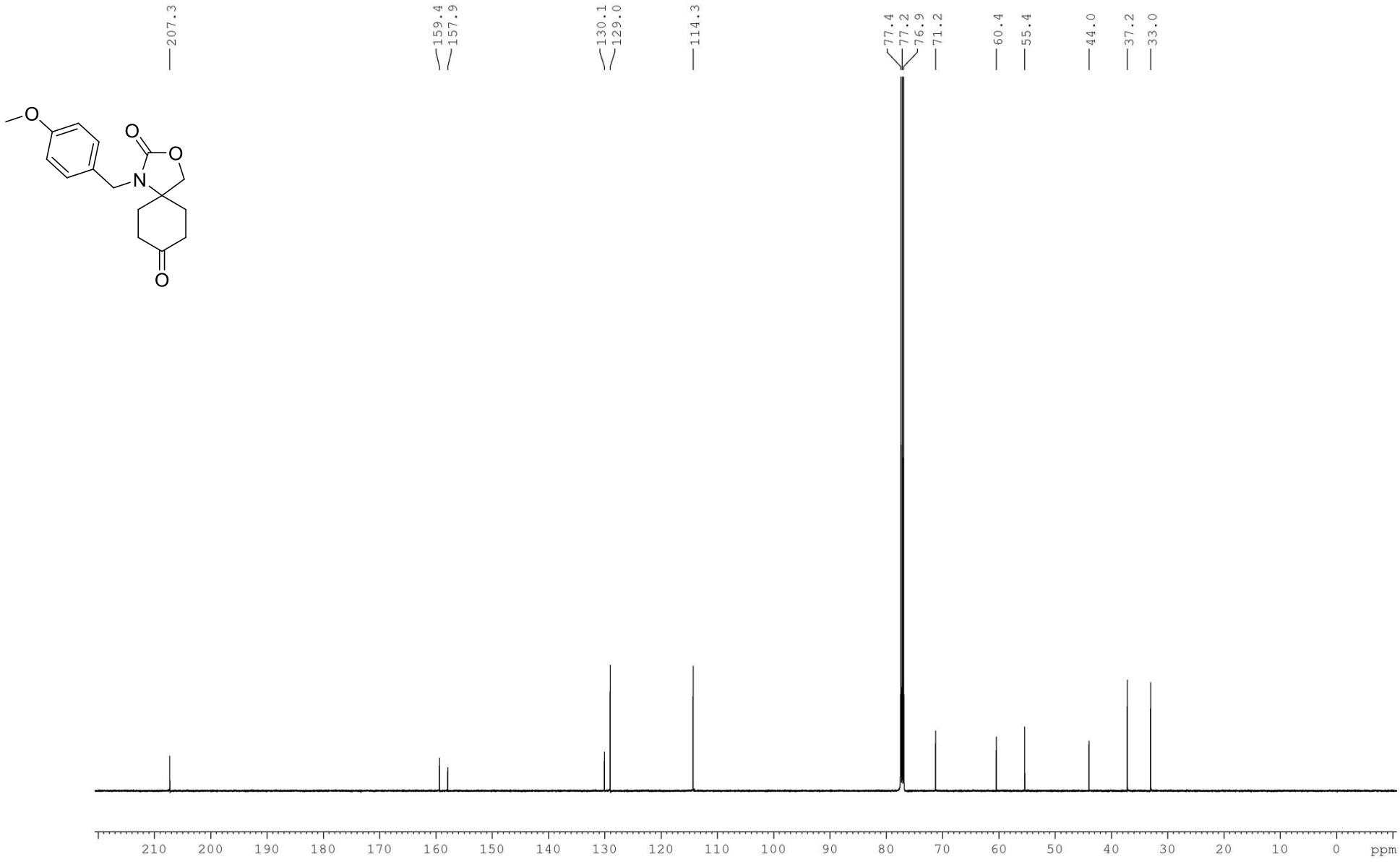
1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]decane-2,8-dione (22b)

^{1}H NMR, $CDCl_3$, 500 MHz



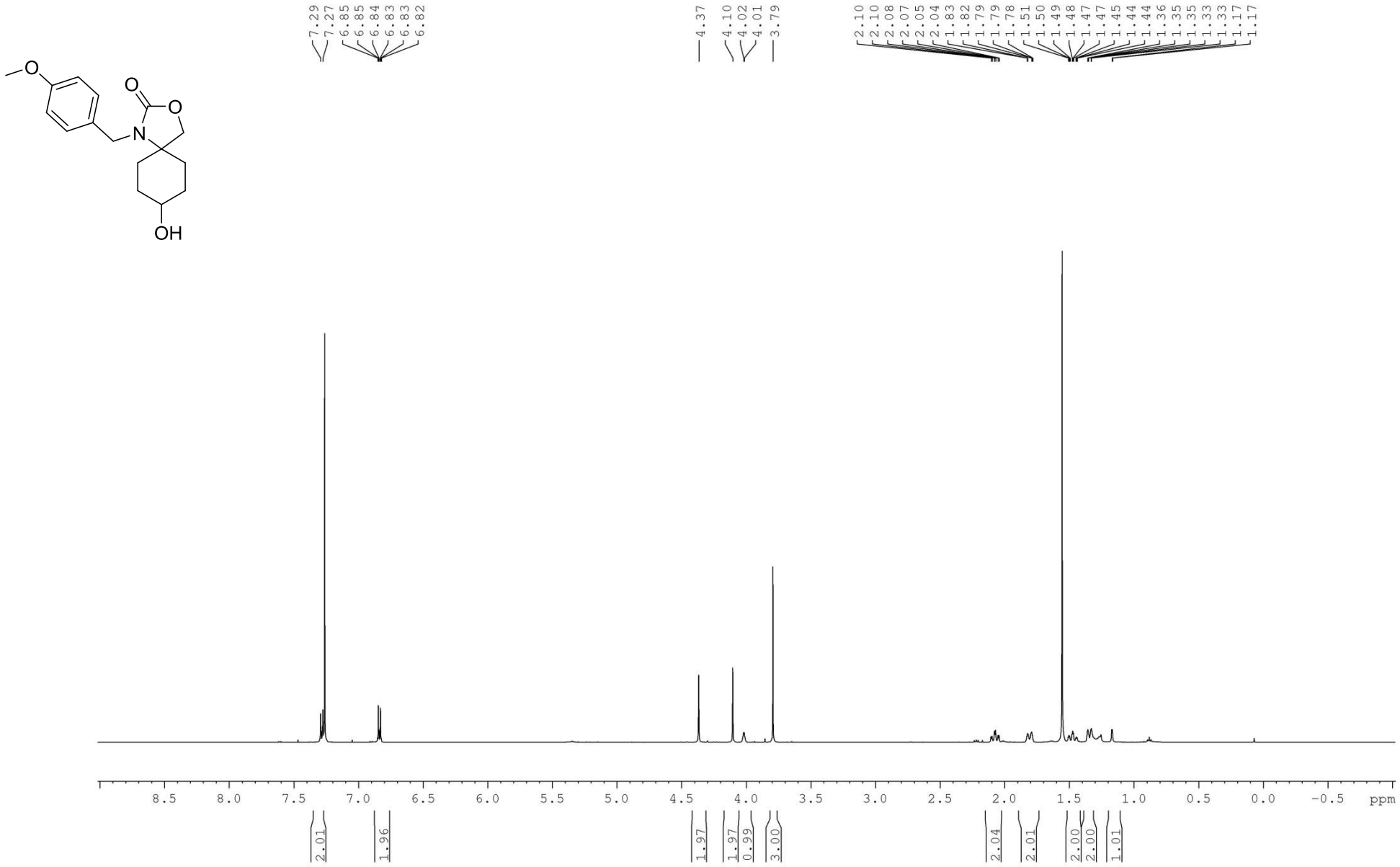
1-(4-Methoxybenzyl)-3-oxa-1-azaspiro[4.5]decane-2,8-dione (22b)

^{13}C NMR, $CDCl_3$, 126 MHz



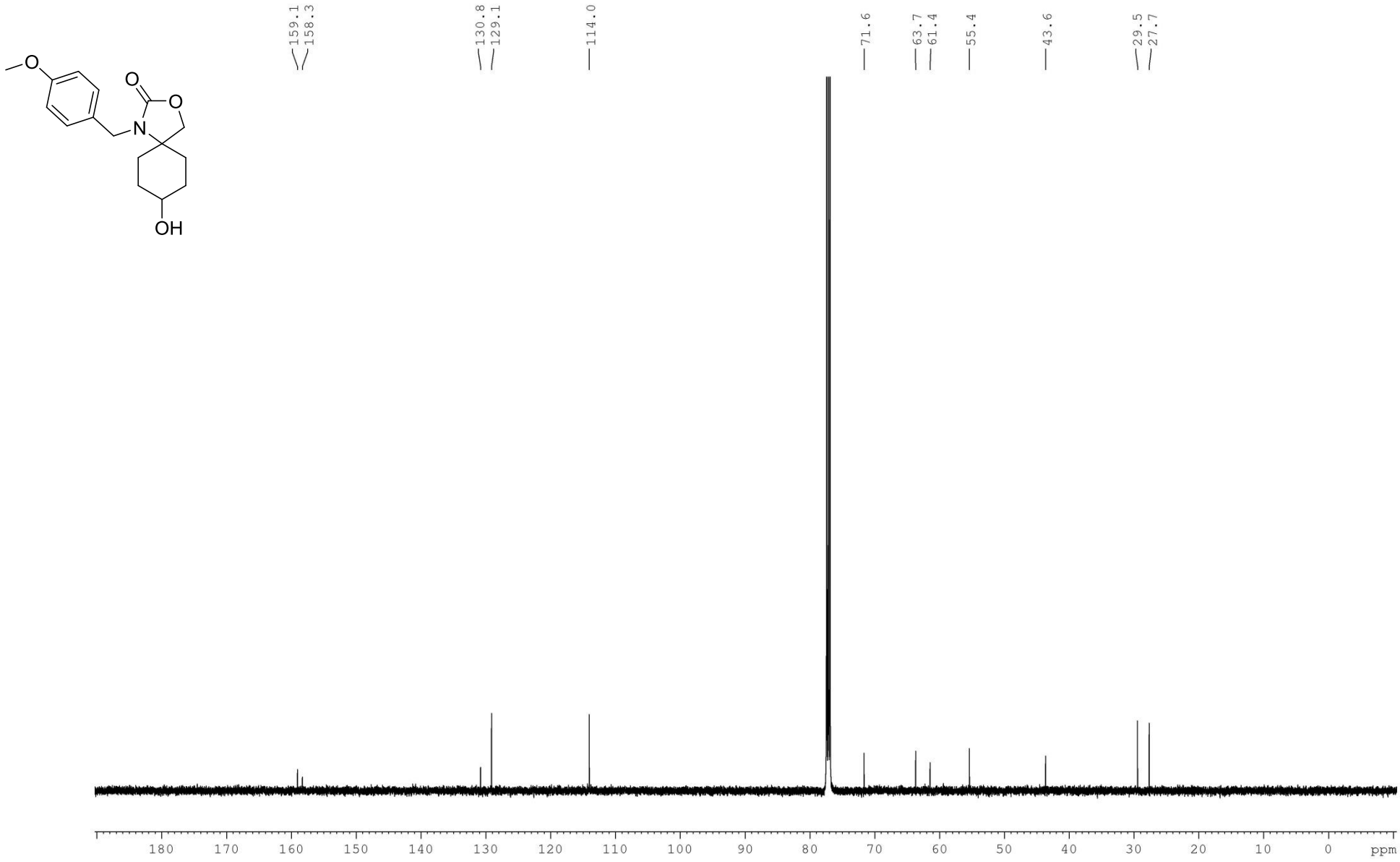
8-Hydroxy-1-(4-methoxy-benzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S6)

^{1}H NMR, $CDCl_3$, 500 MHz



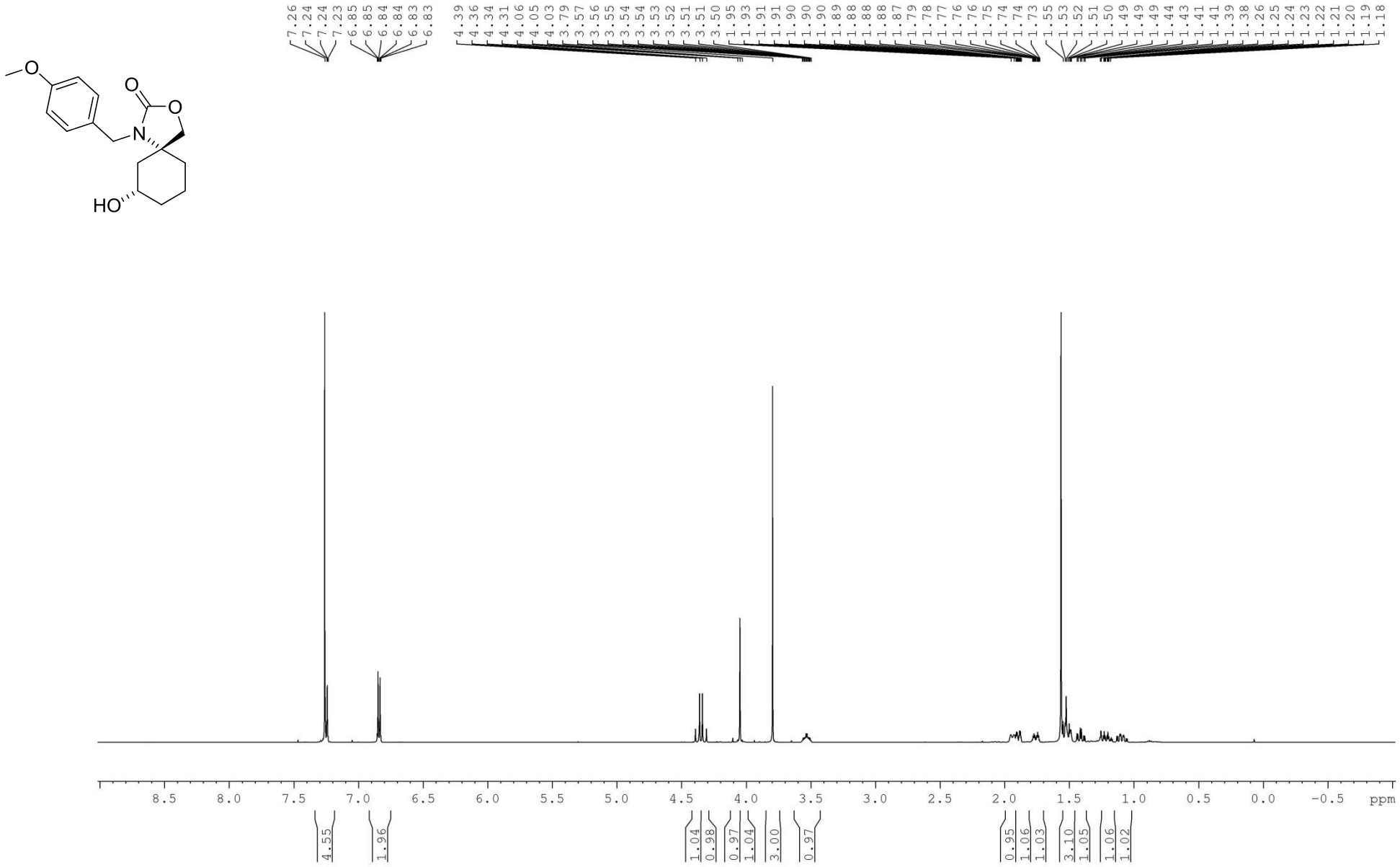
8-Hydroxy-1-(4-methoxy-benzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S6)

^{13}C NMR, $CDCl_3$, 126 MHz



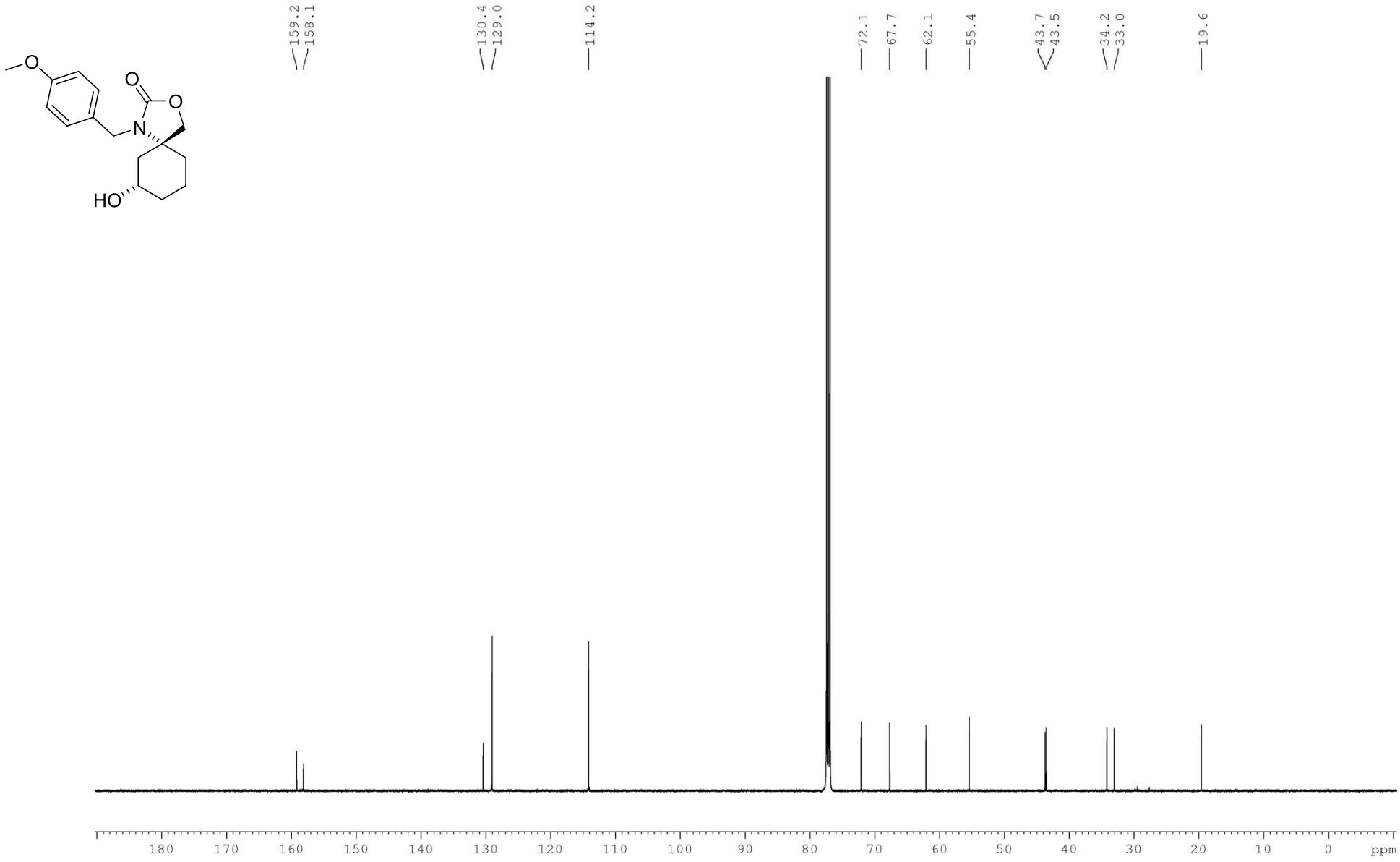
(5*R,7*S**)-7-Hydroxy-1-(4-methoxy-benzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S7)**

^{1}H NMR, $CDCl_3$, 500 MHz



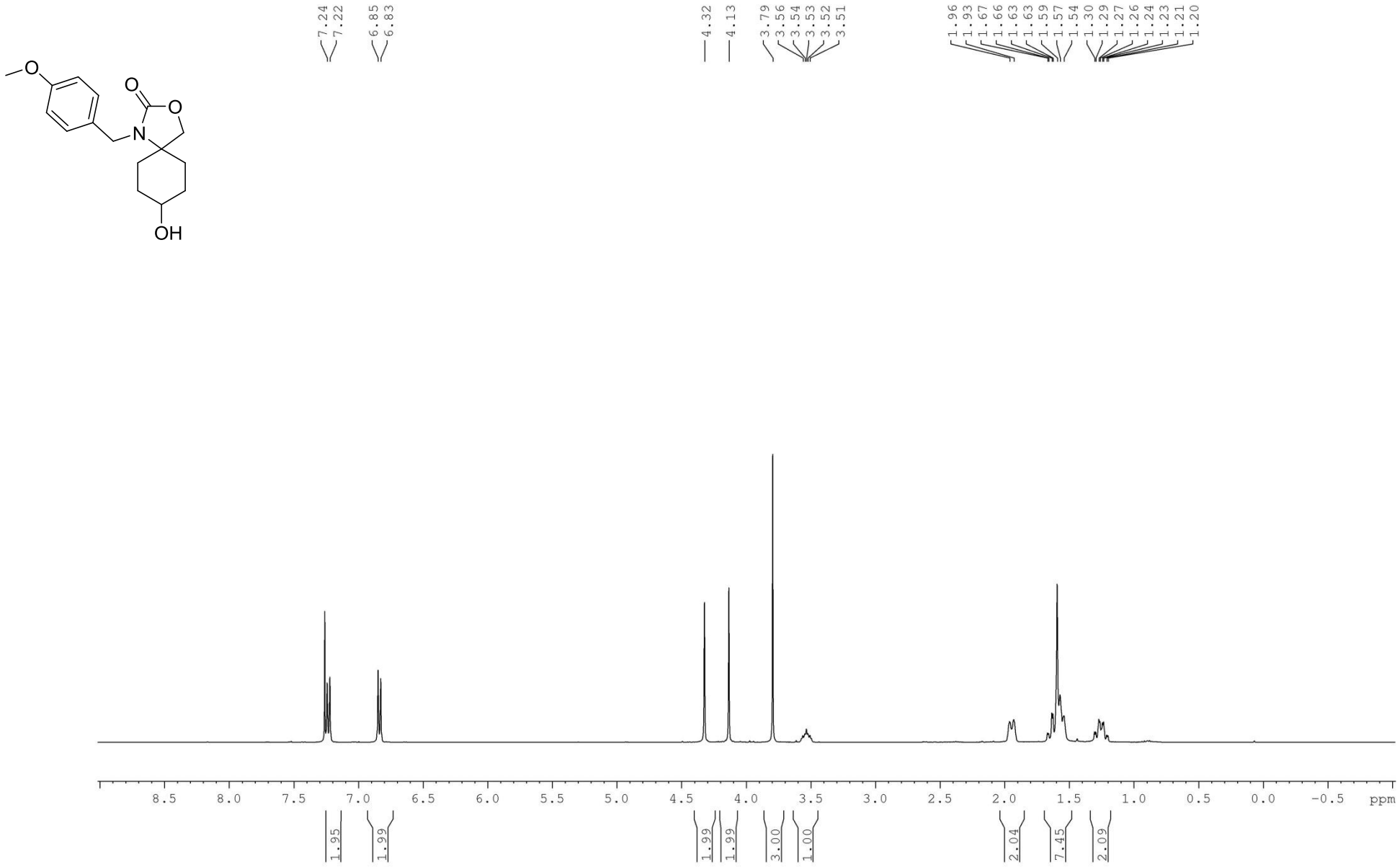
(5*R,7*S**)-7-Hydroxy-1-(4-methoxy-benzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S7)**

^{13}C NMR, $CDCl_3$, 126 MHz



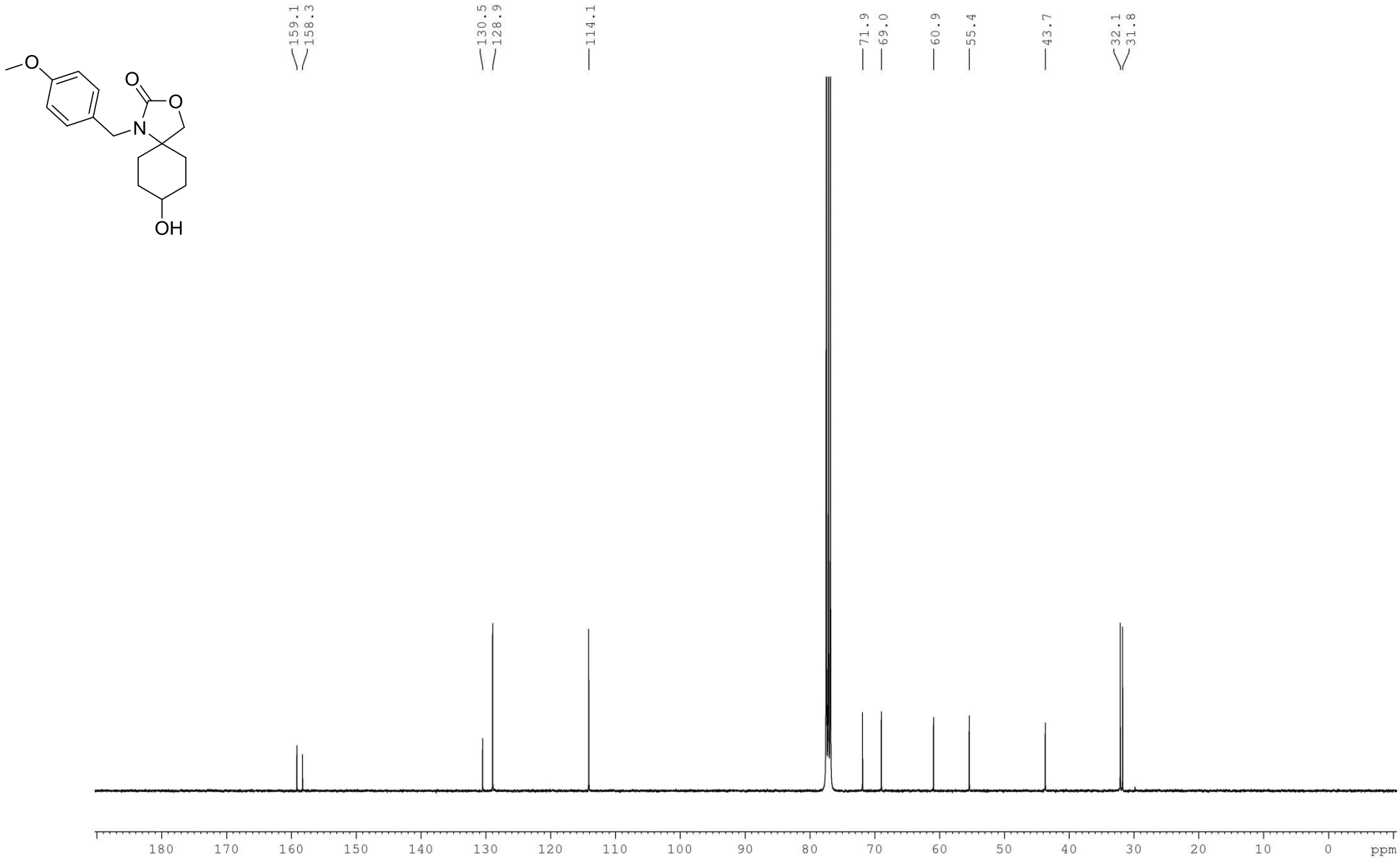
8-Hydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S8)

^{1}H NMR, $CDCl_3$, 400 MHz



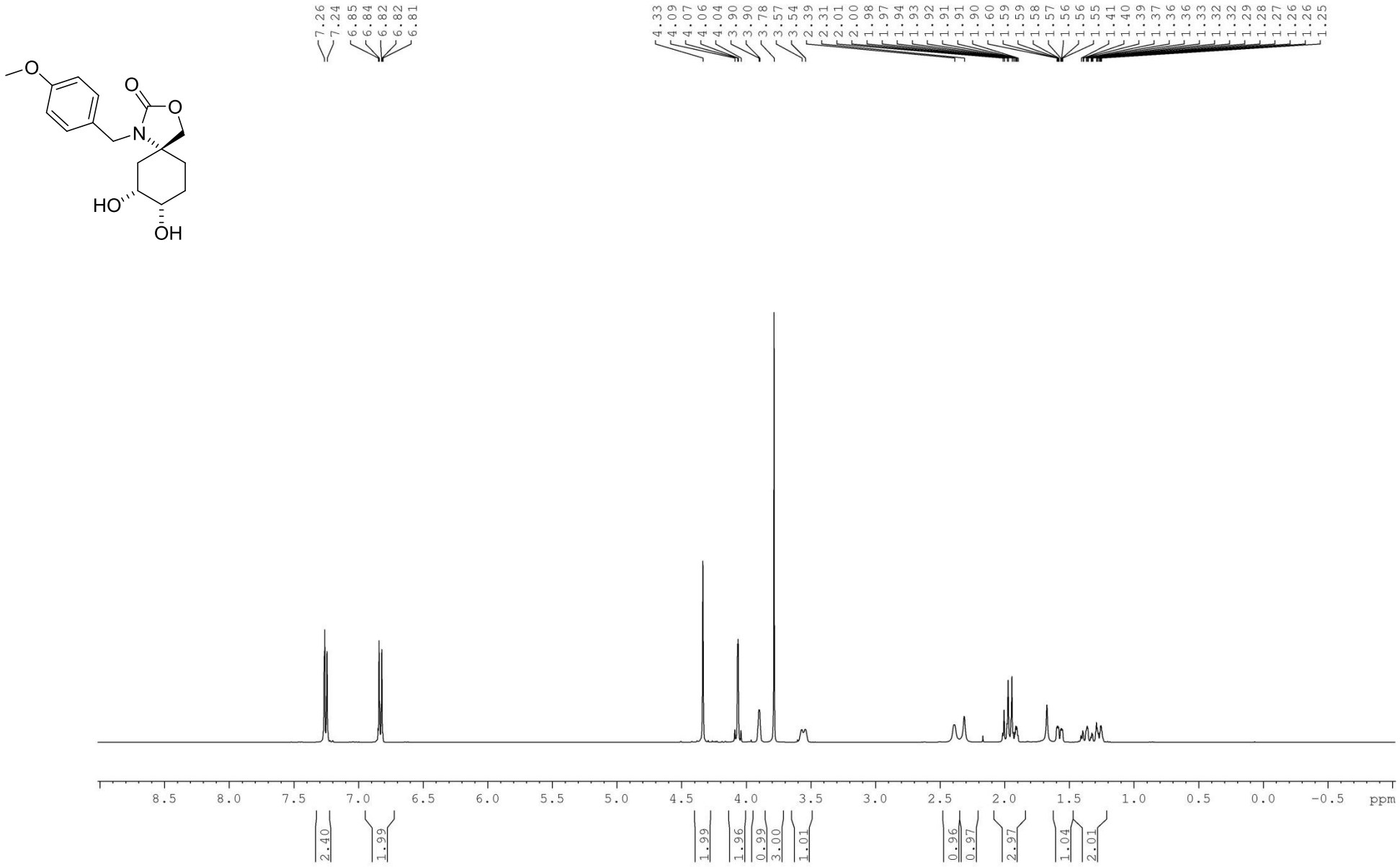
8-Hydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (S8)

^{13}C NMR, $CDCl_3$, 101 MHz



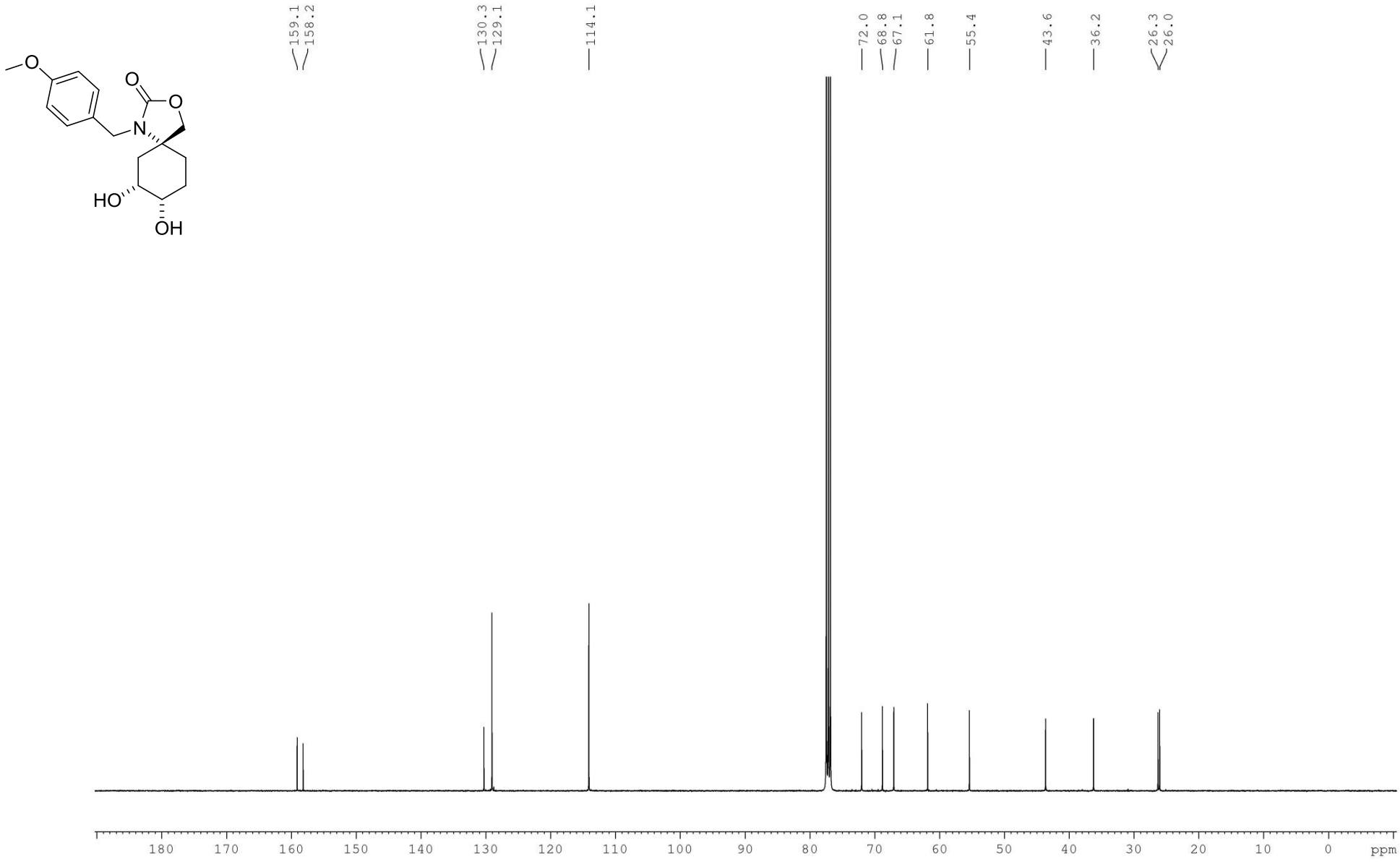
(5*R,7*R**,8*S**)-7,8-Dihydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (23a)**

^{1}H NMR, $CDCl_3$, 400 MHz



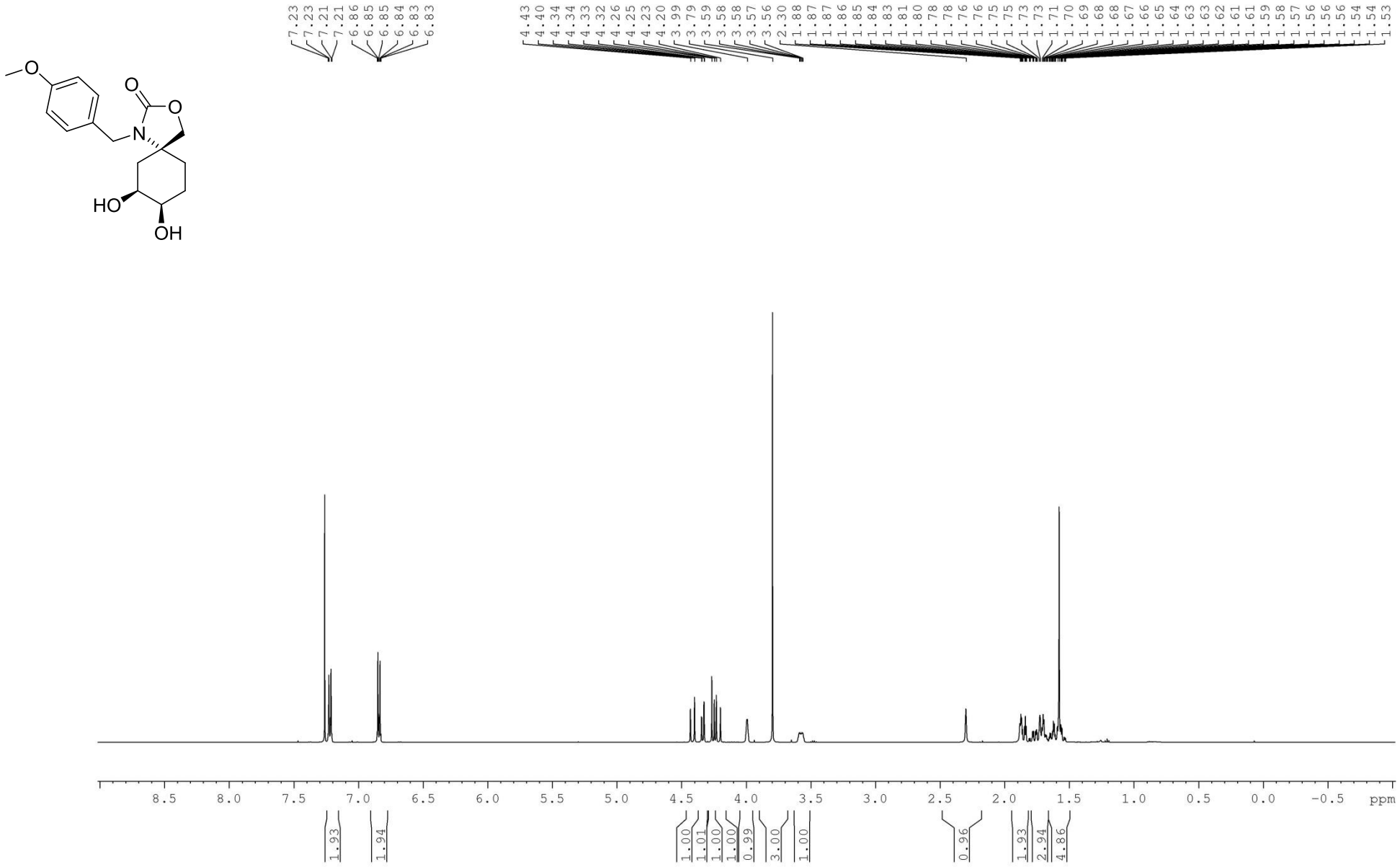
(5*R,7*R**,8*S**)-7,8-Dihydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (23a)**

^{13}C NMR, $CDCl_3$, 101 MHz



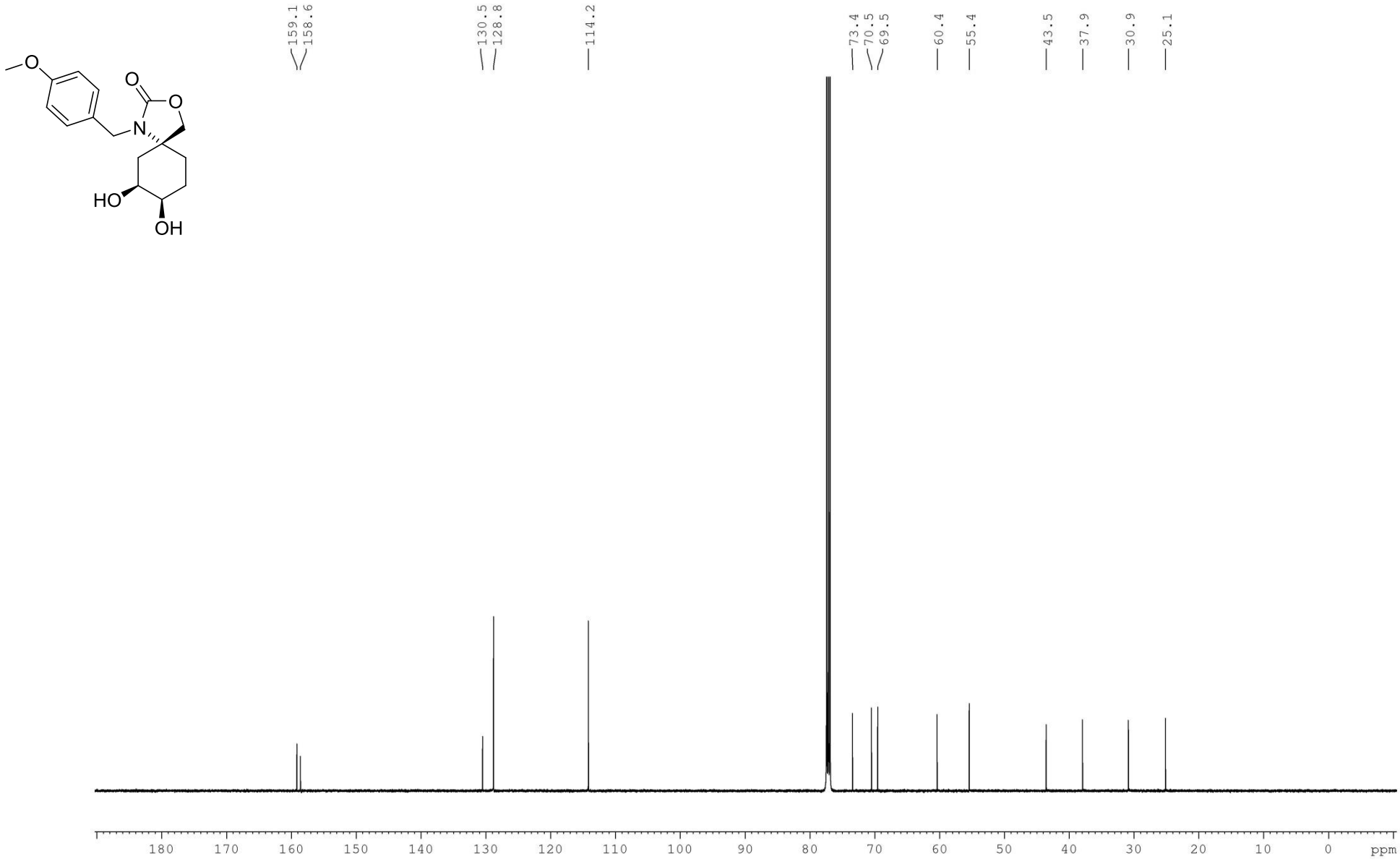
(5*R,7*S**,8*R**)-7,8-Dihydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]-decan-2-one (23b)**

^{1}H NMR, $CDCl_3$, 500 MHz



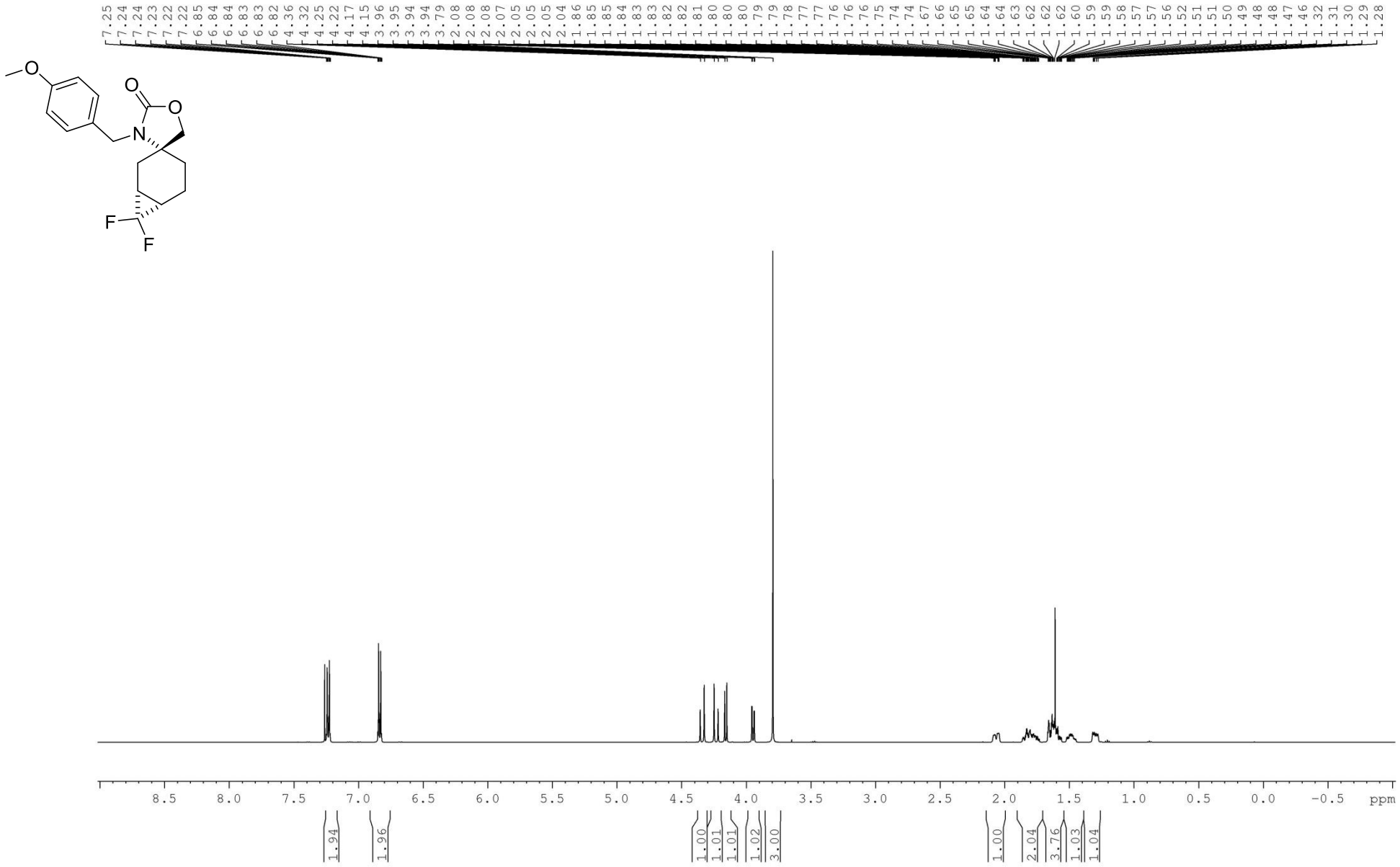
(5*R,7*S**,8*R**)-7,8-Dihydroxy-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]-decan-2-one (23b)**

^{13}C NMR, $CDCl_3$, 126 MHz



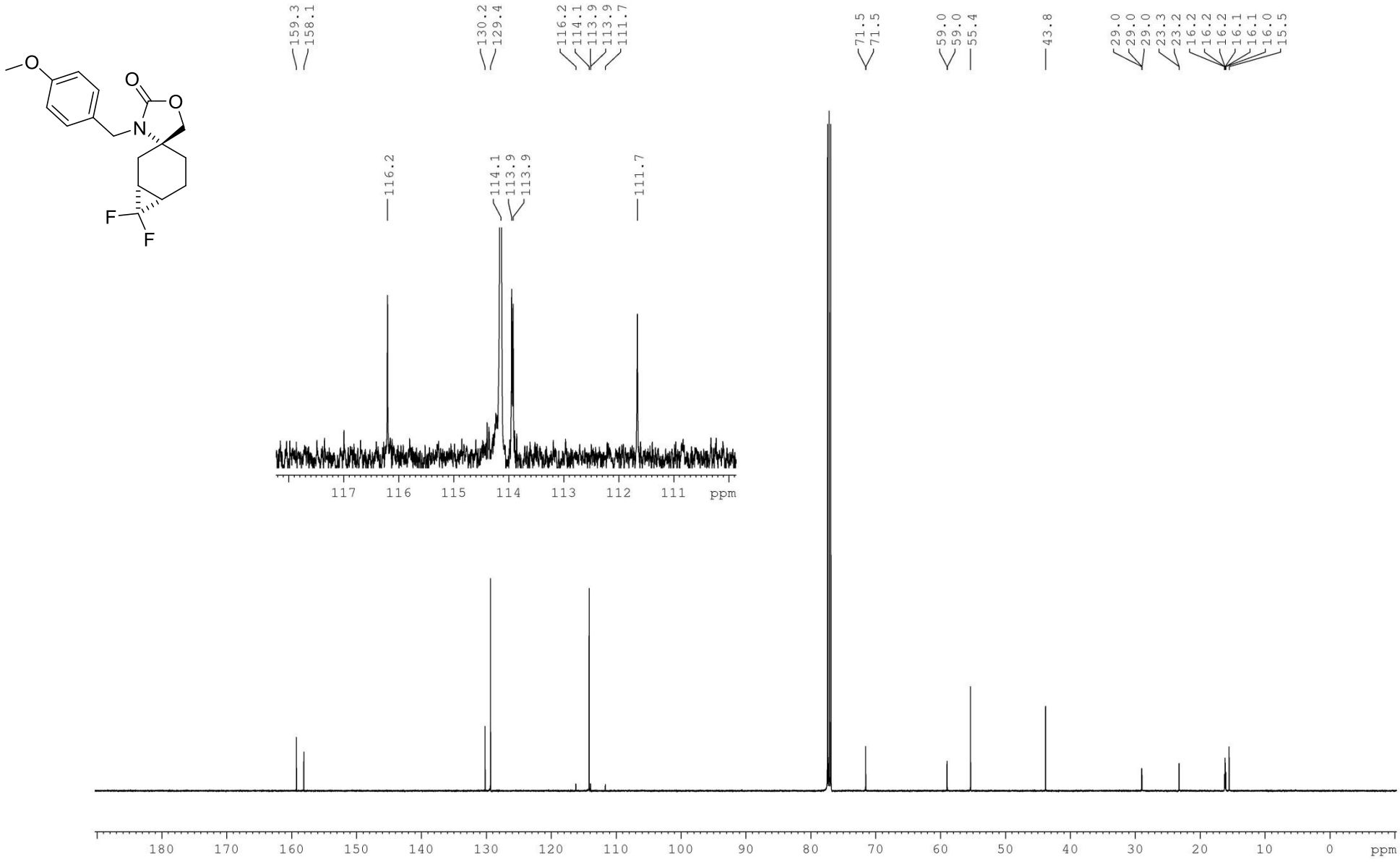
(1*R,3*R**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24a)**

^{1}H NMR, $CDCl_3$, 500 MHz



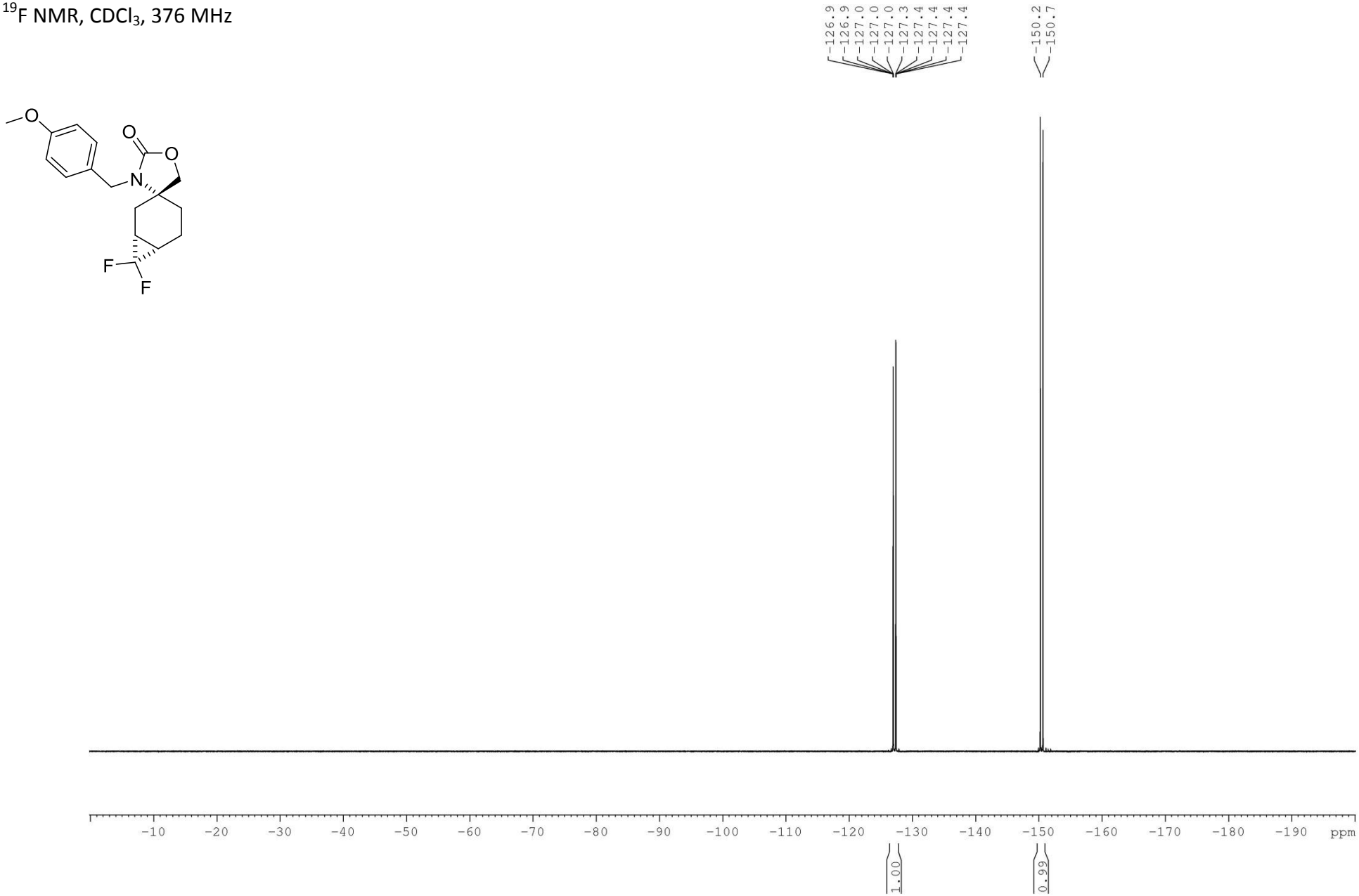
(1*R,3*R**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24a)**

^{13}C NMR, $CDCl_3$, 126 MHz



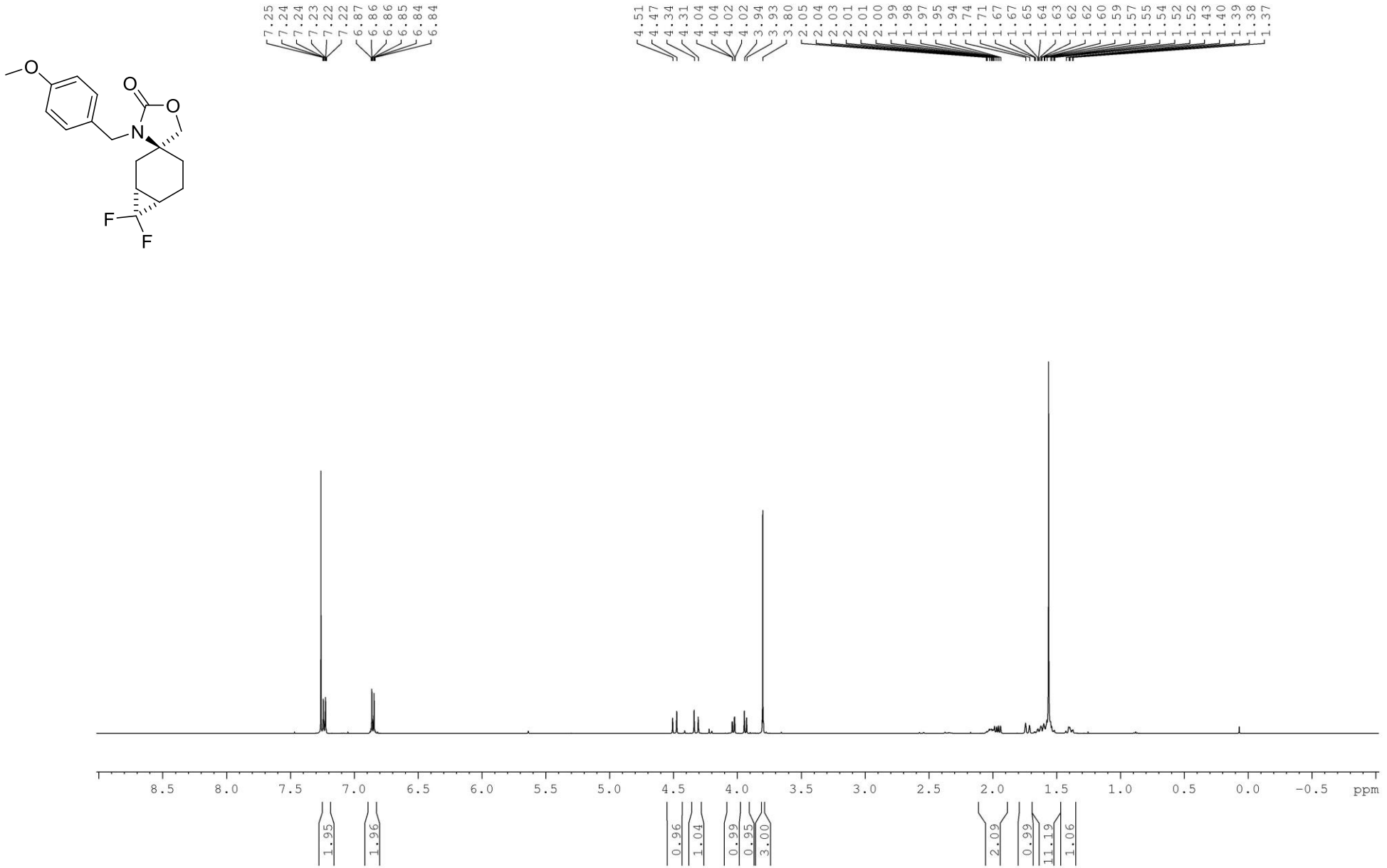
(1*R,3*R**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24a)**

^{19}F NMR, $CDCl_3$, 376 MHz



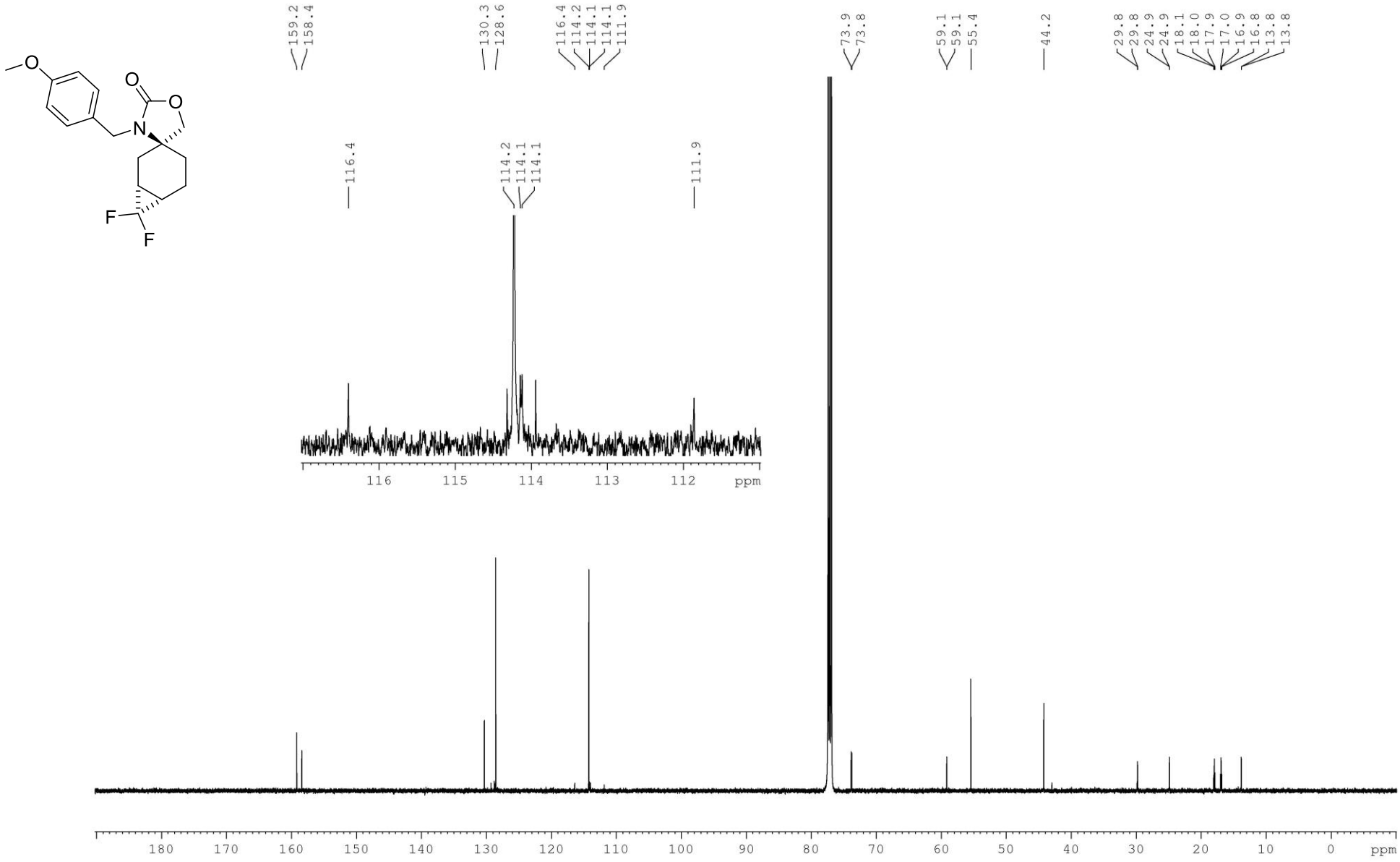
(1*R,3*S**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24b)**

^{1}H NMR, $CDCl_3$, 500 MHz



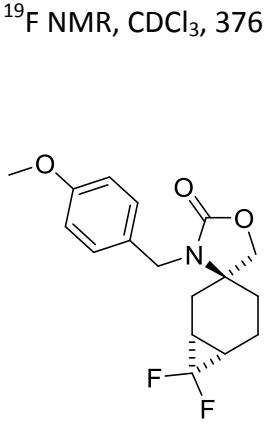
(1*R,3*S**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24b)**

^{13}C NMR, $CDCl_3$, 126 MHz



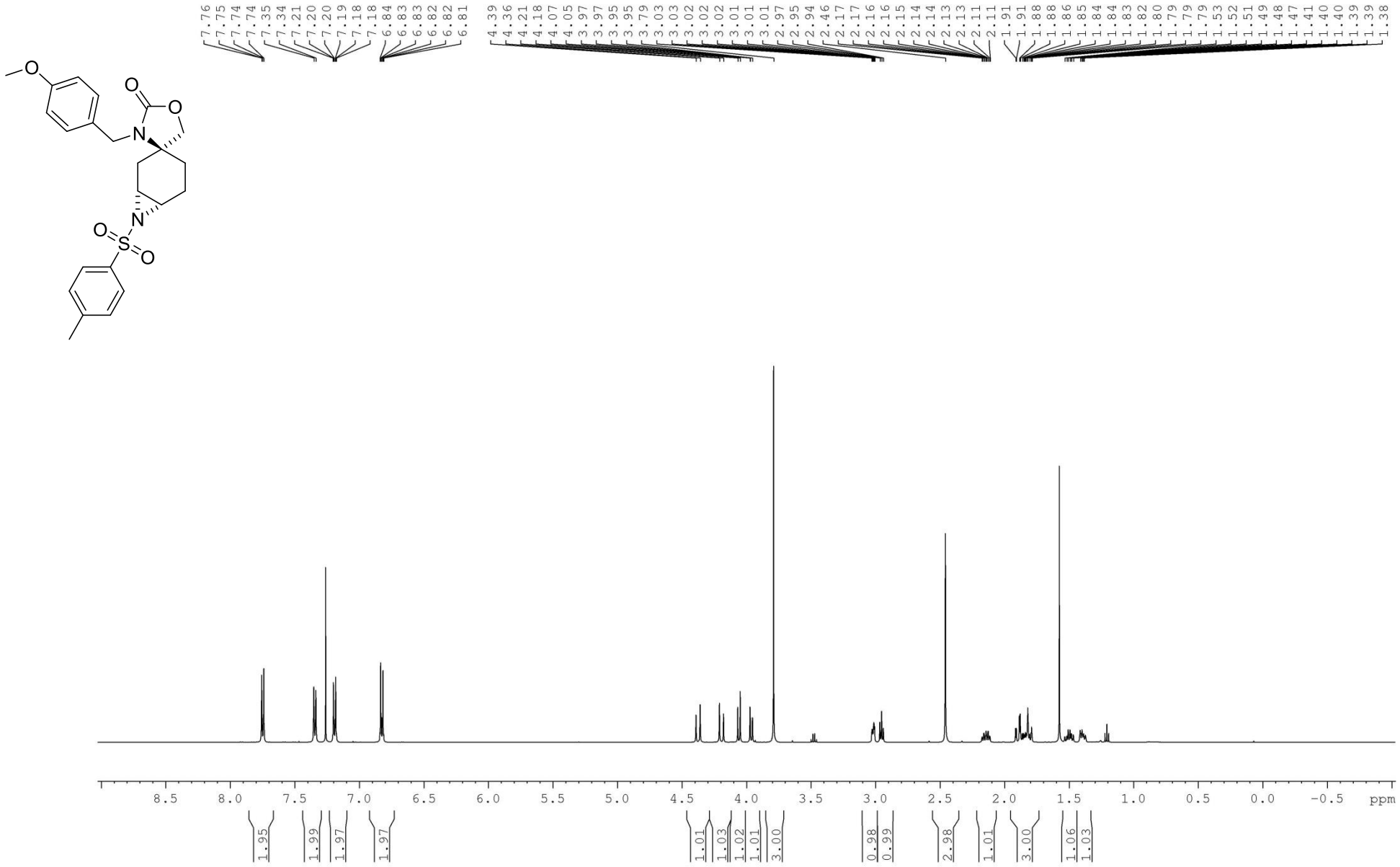
(1*R,3*S**,6*S**)-7,7-Difluoro-3'-(4-methoxybenzyl)spiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (24b)**

^{19}F NMR, $CDCl_3$, 376 MHz



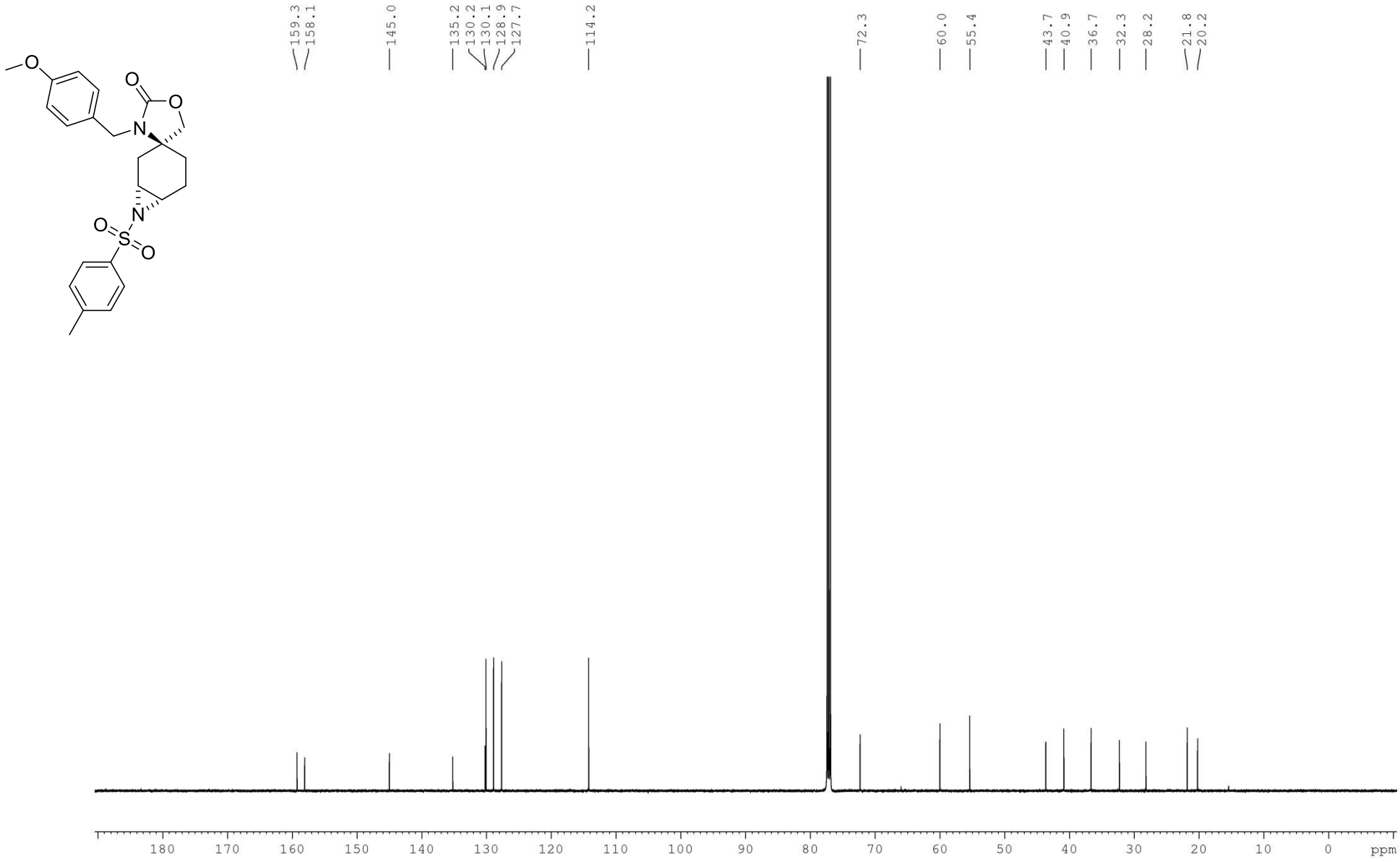
(1*R,3*R**,6*S**)-3'-(4-Methoxybenzyl)-7-tosyl-7-azaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (25a)**

^{1}H NMR, $CDCl_3$, 500 MHz



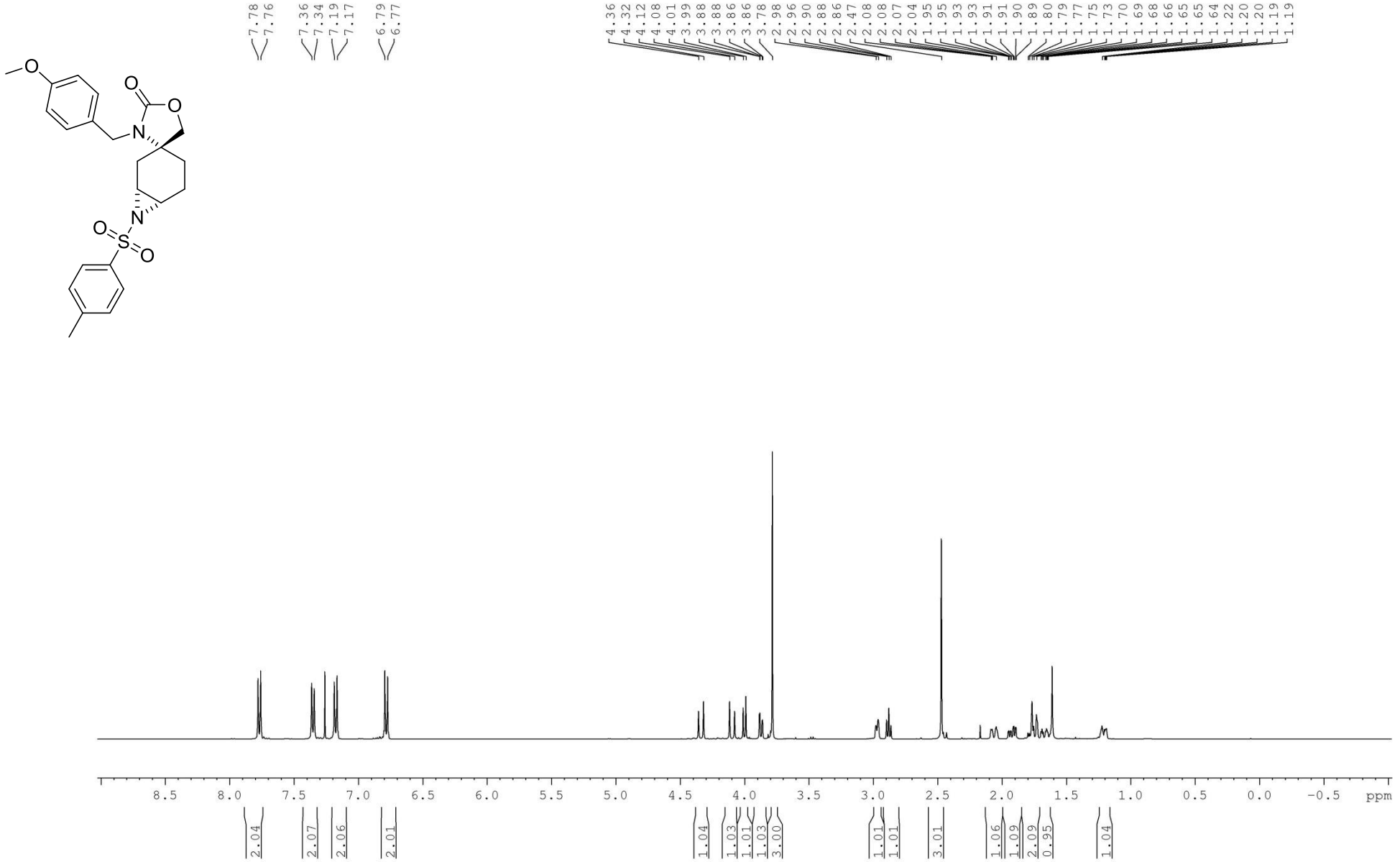
(1*R,3*R**,6*S**)-3'-(4-Methoxybenzyl)-7-tosyl-7-azaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (25a)**

^{13}C NMR, $CDCl_3$, 126 MHz



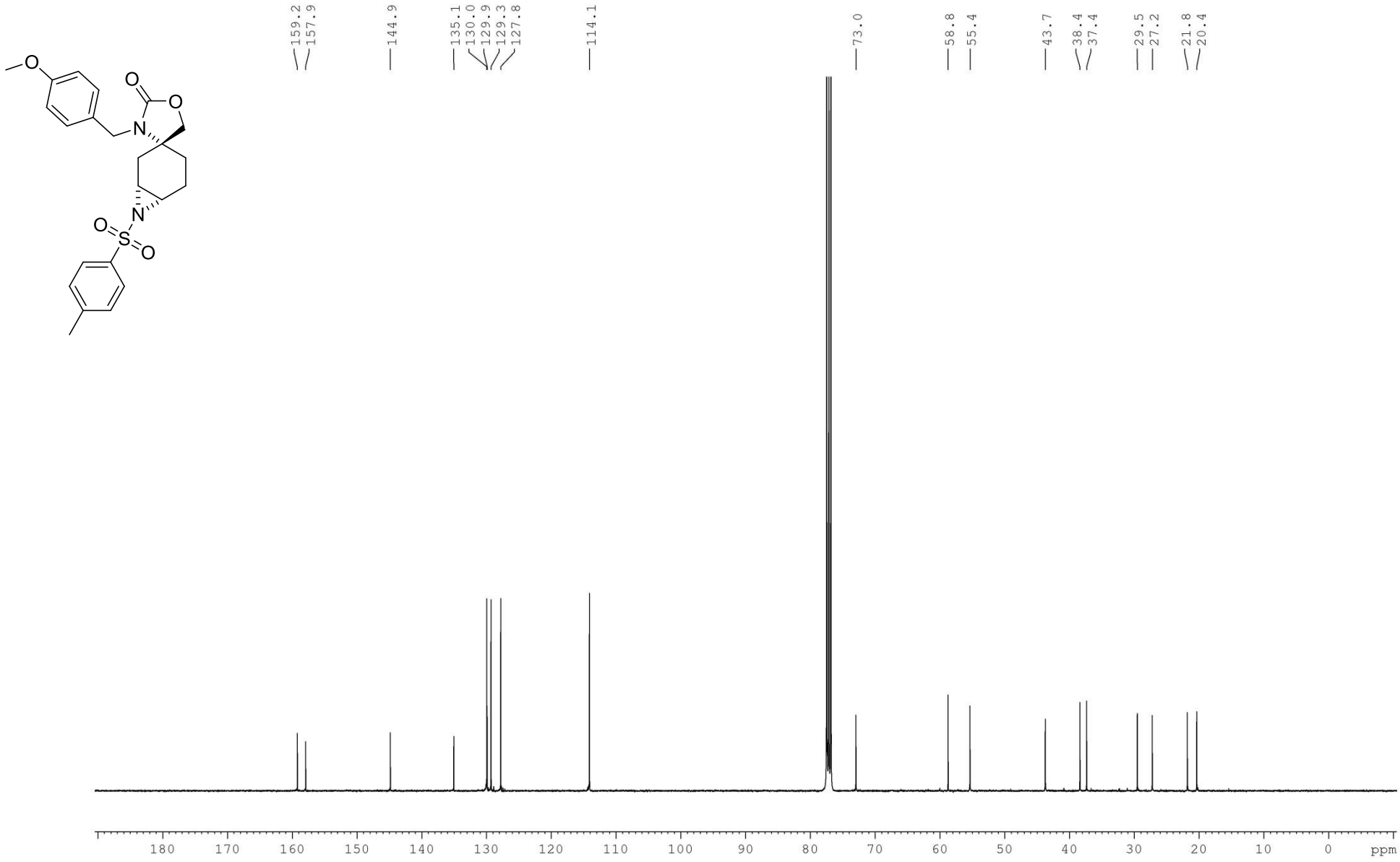
(1*R,3*S**,6*S**)-3'-(4-Methoxybenzyl)-7-tosyl-7-azaspiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (25b)**

^{1}H NMR, $CDCl_3$, 400 MHz



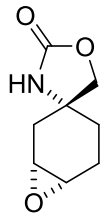
(1*R,3*S**,6*S**)-3'-(4-Methoxybenzyl)-7-tosyl-7-azaspiro-[bicycle[4.1.0]heptane-3,4'-oxazolidin]-2'-one (25b)**

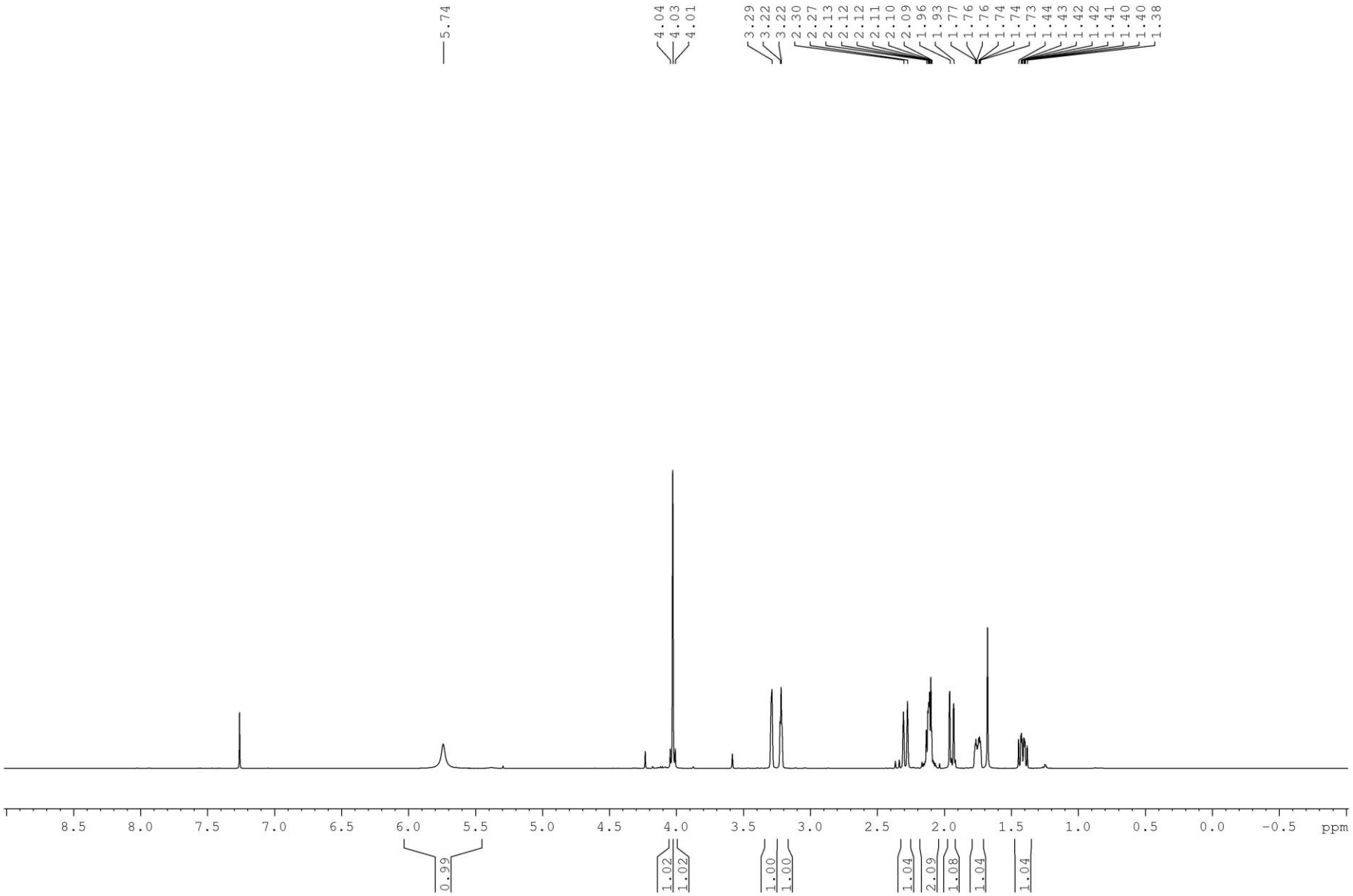
^{13}C NMR, $CDCl_3$, 101 MHz



(1*R,3*R**,6*S**)-7-Oxaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (26a)**

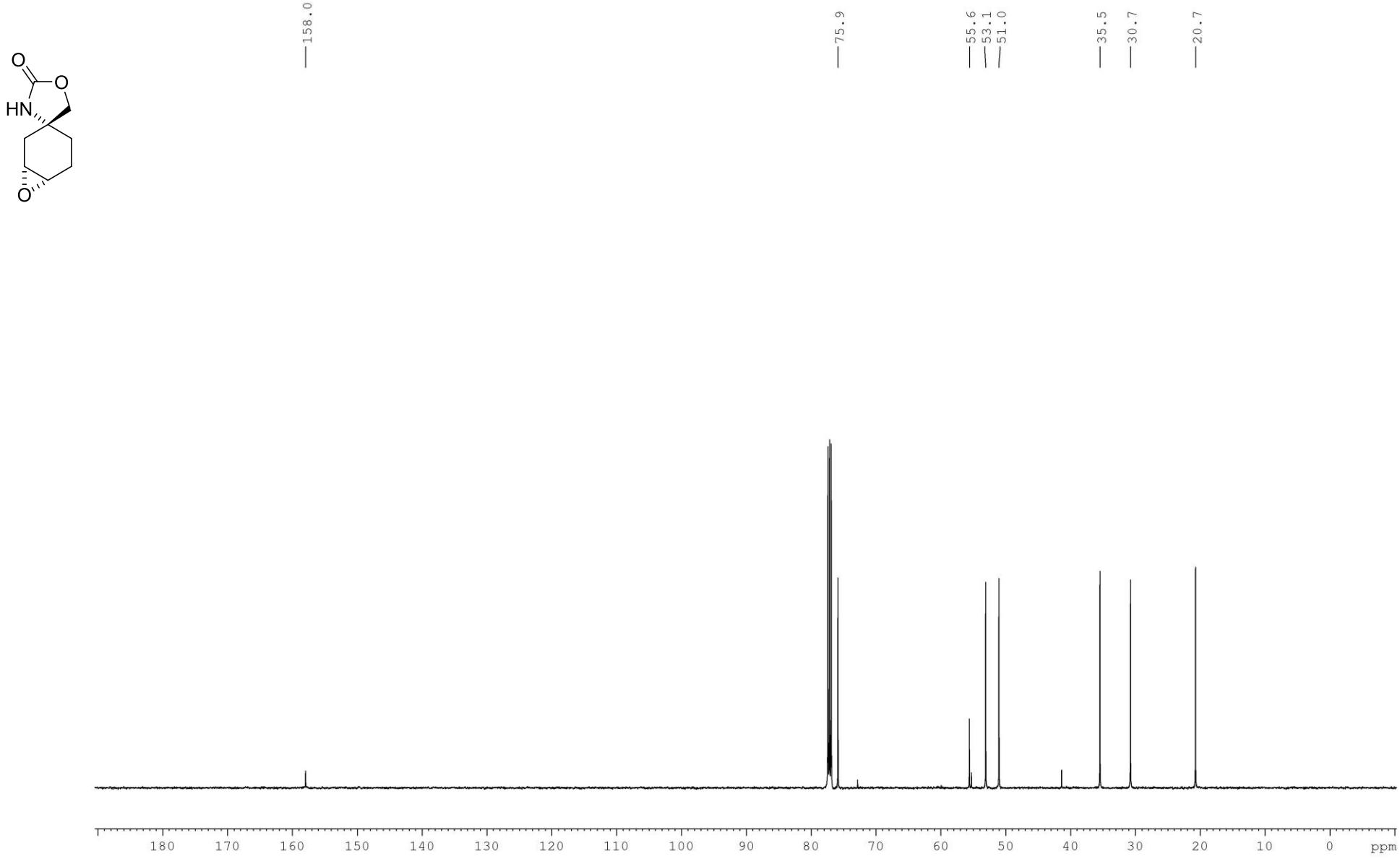
^{1}H NMR, $CDCl_3$, 500 MHz





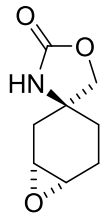
(1*R,3*R**,6*S**)-7-Oxaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (26a)**

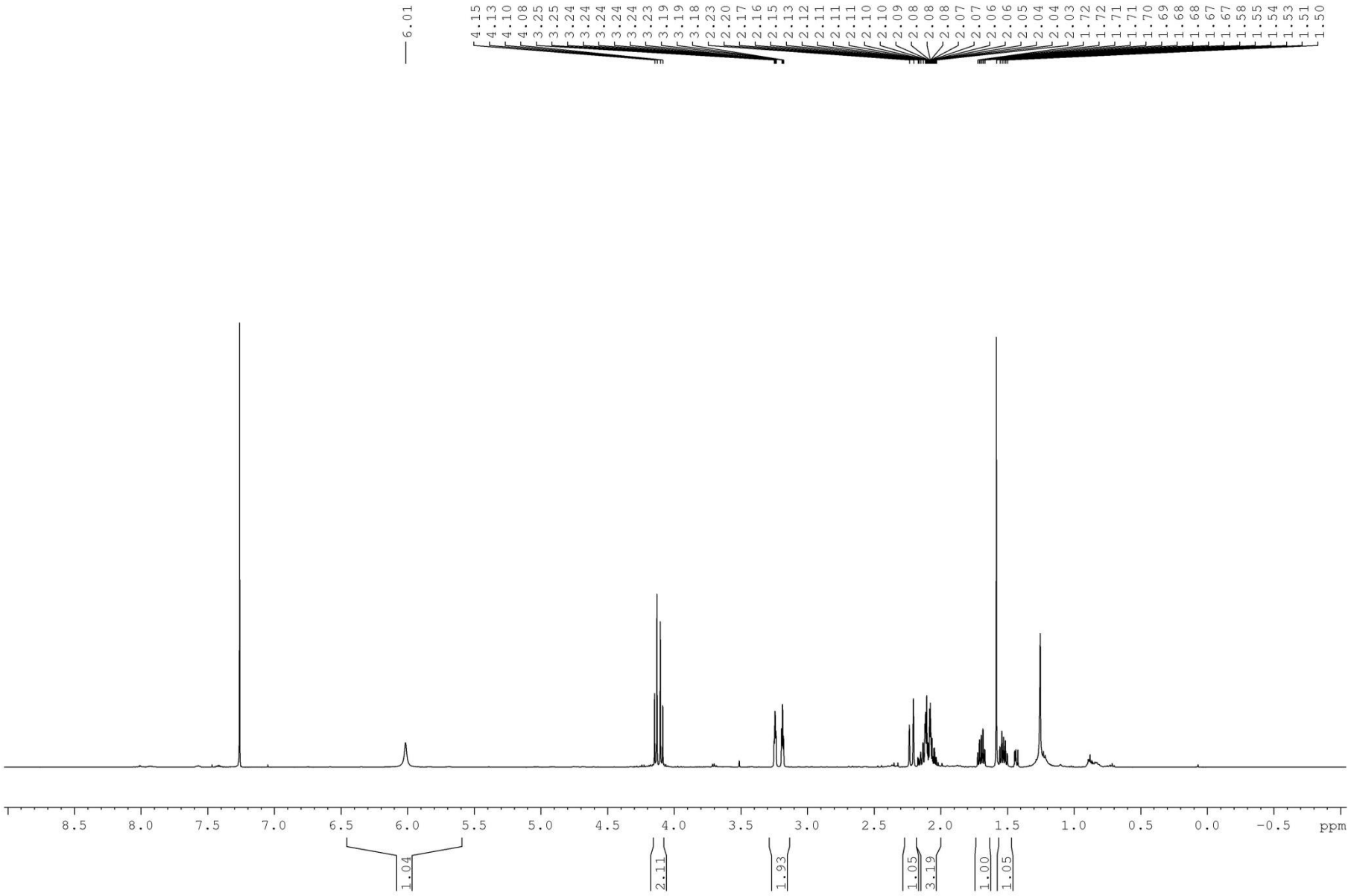
^{13}C NMR, $CDCl_3$, 126 MHz



(1*R,3*S**,6*S**)-7-Oxaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (26b)**

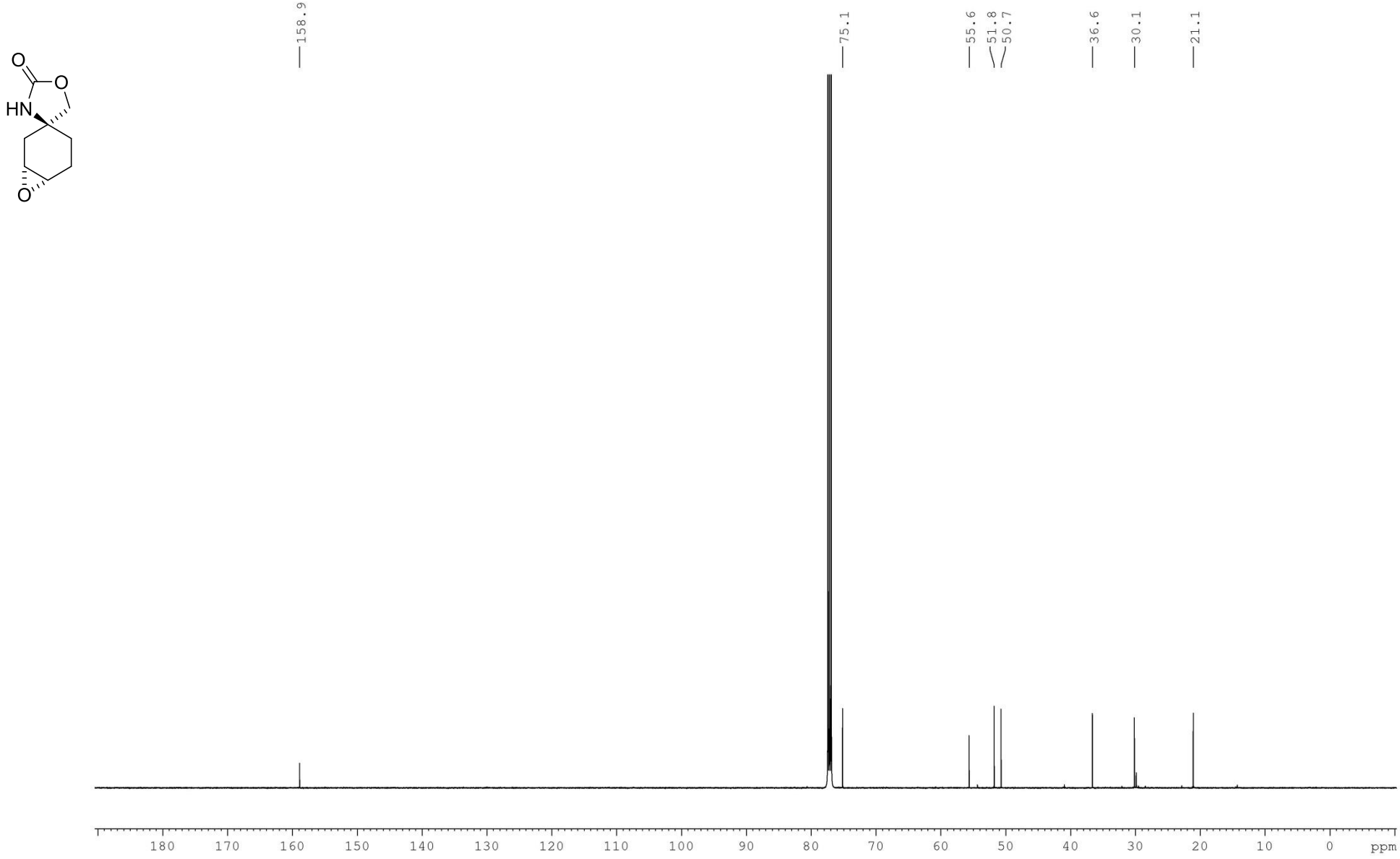
^{1}H NMR, $CDCl_3$, 500 MHz





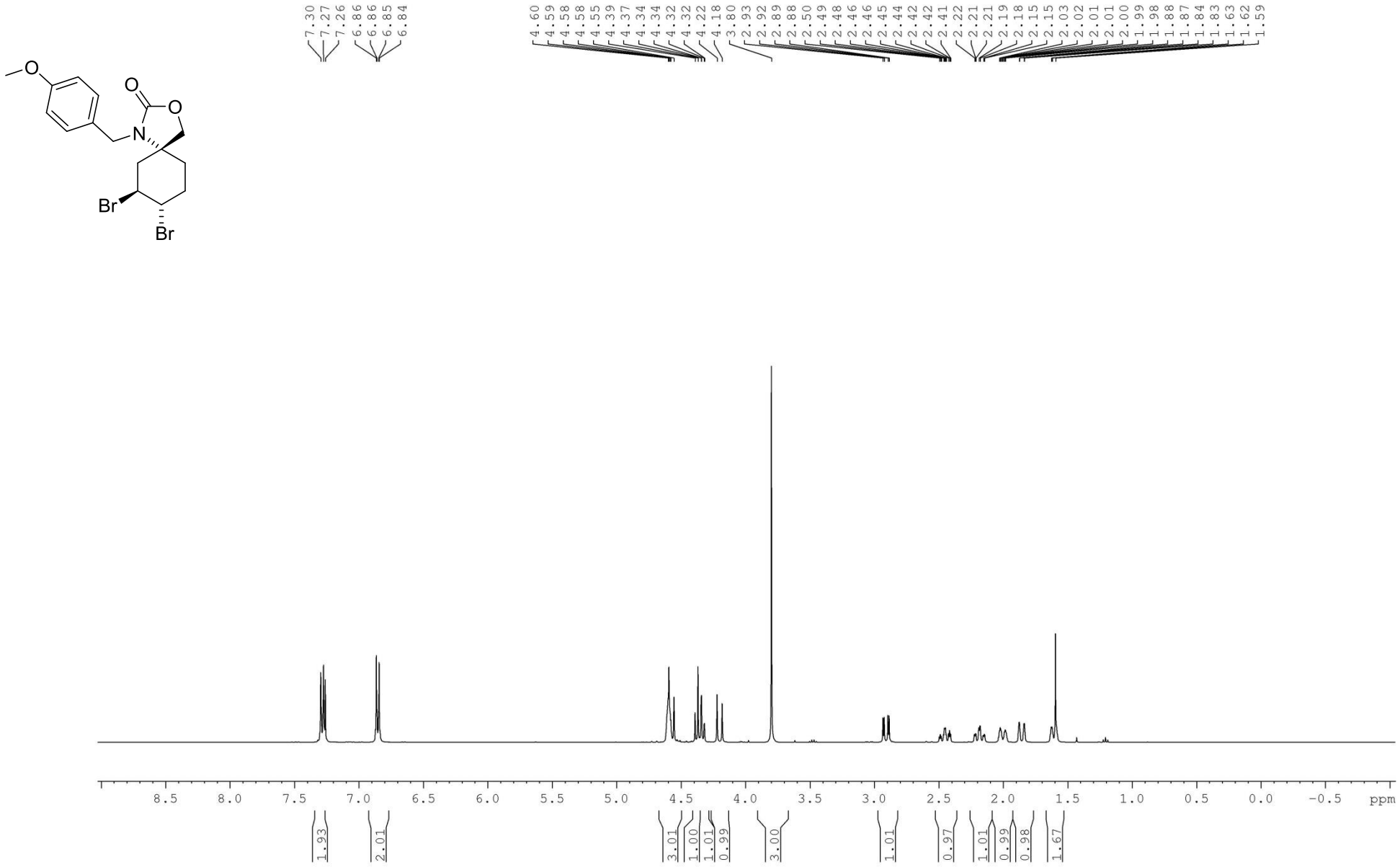
(1*R,3*S**,6*S**)-7-Oxaspiro[bicyclo[4.1.0]heptane-3,4'-oxazolidin]-2'-one (26b)**

^{13}C NMR, $CDCl_3$, 126 MHz



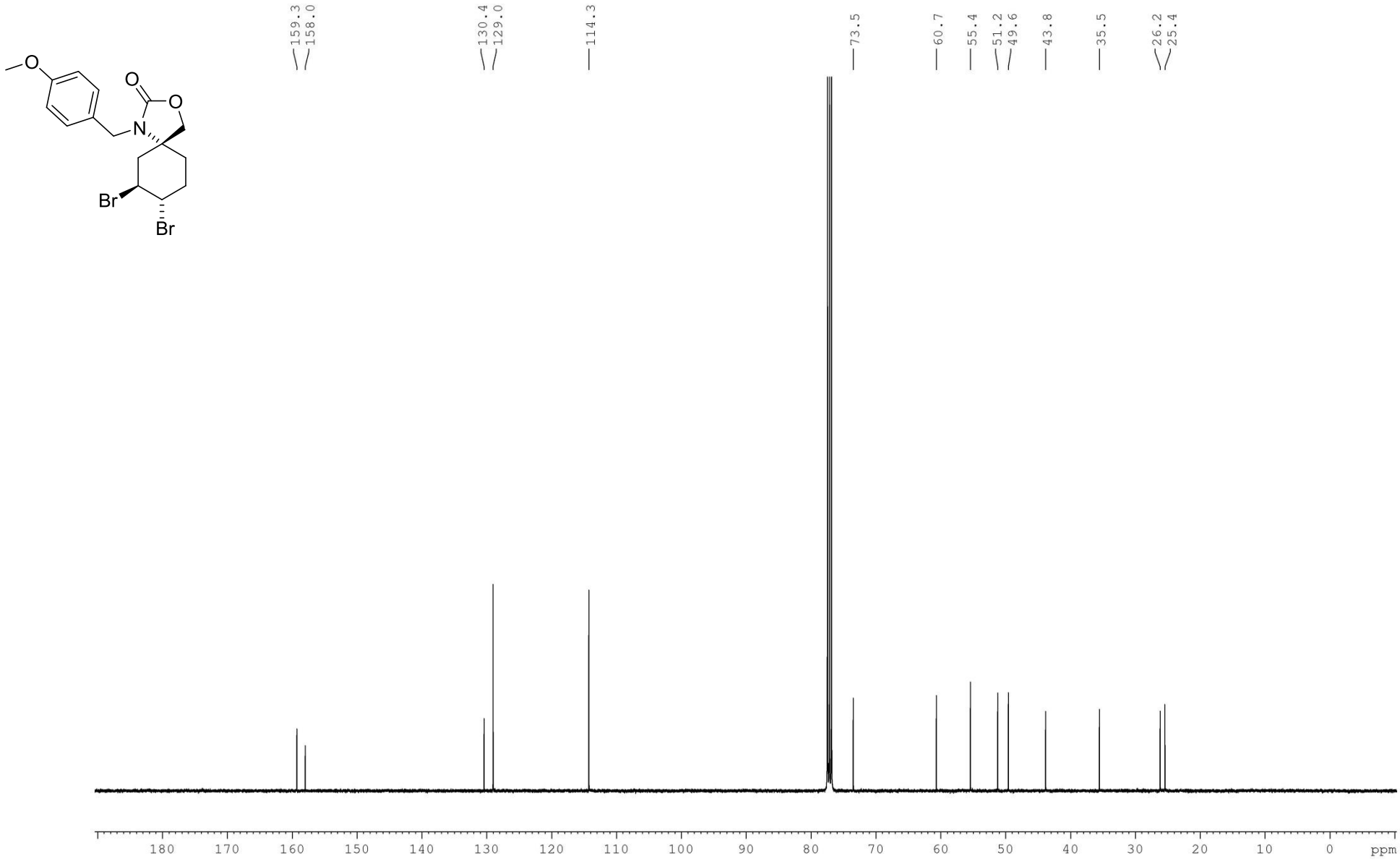
(5*R,7*S**,8*S**)-7,8-Dibromo-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (27a)**

^{1}H NMR, $CDCl_3$, 400 MHz



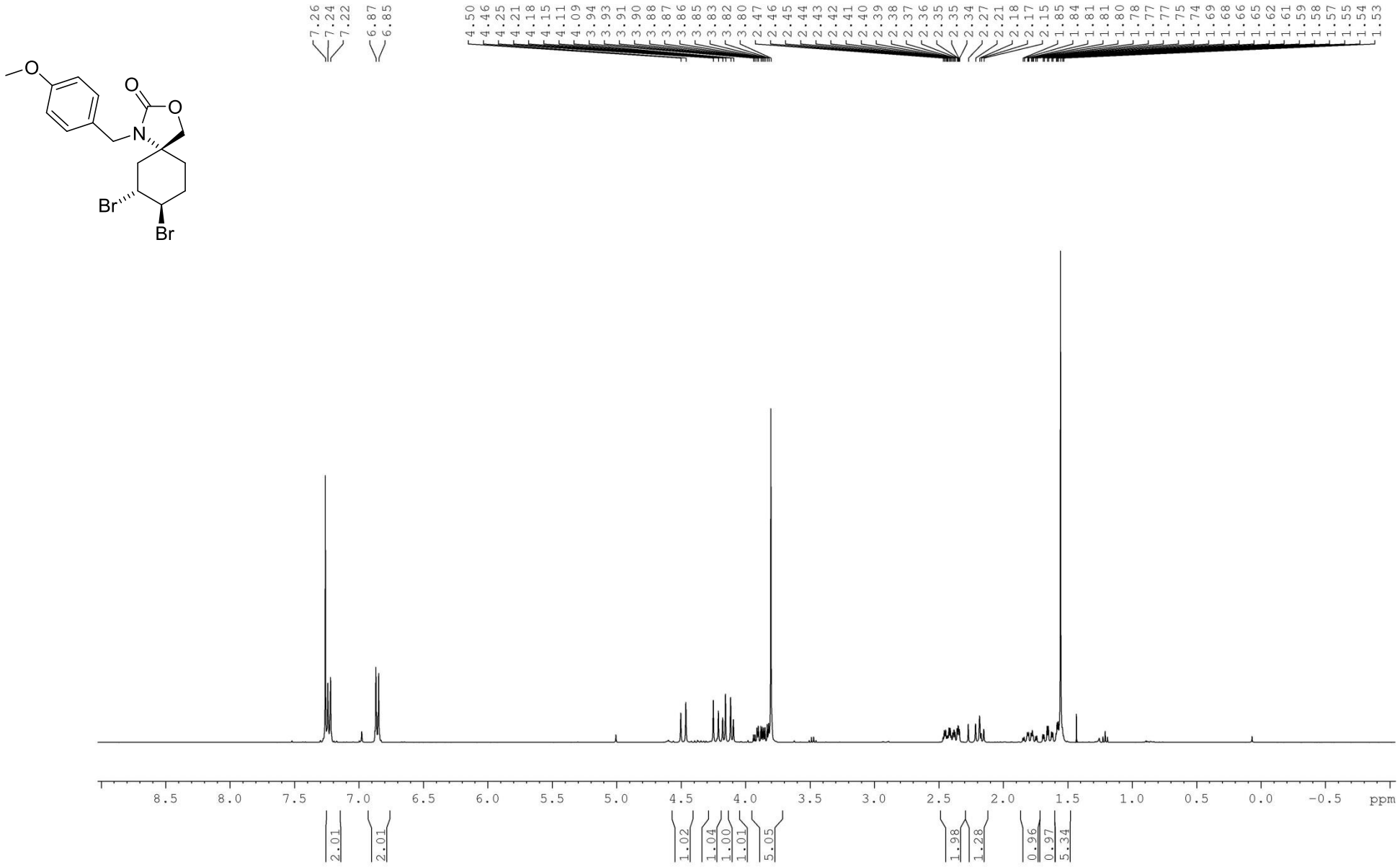
(5*R,7*S**,8*S**)-7,8-Dibromo-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]decan-2-one (27a)**

^{13}C NMR, $CDCl_3$, 126 MHz



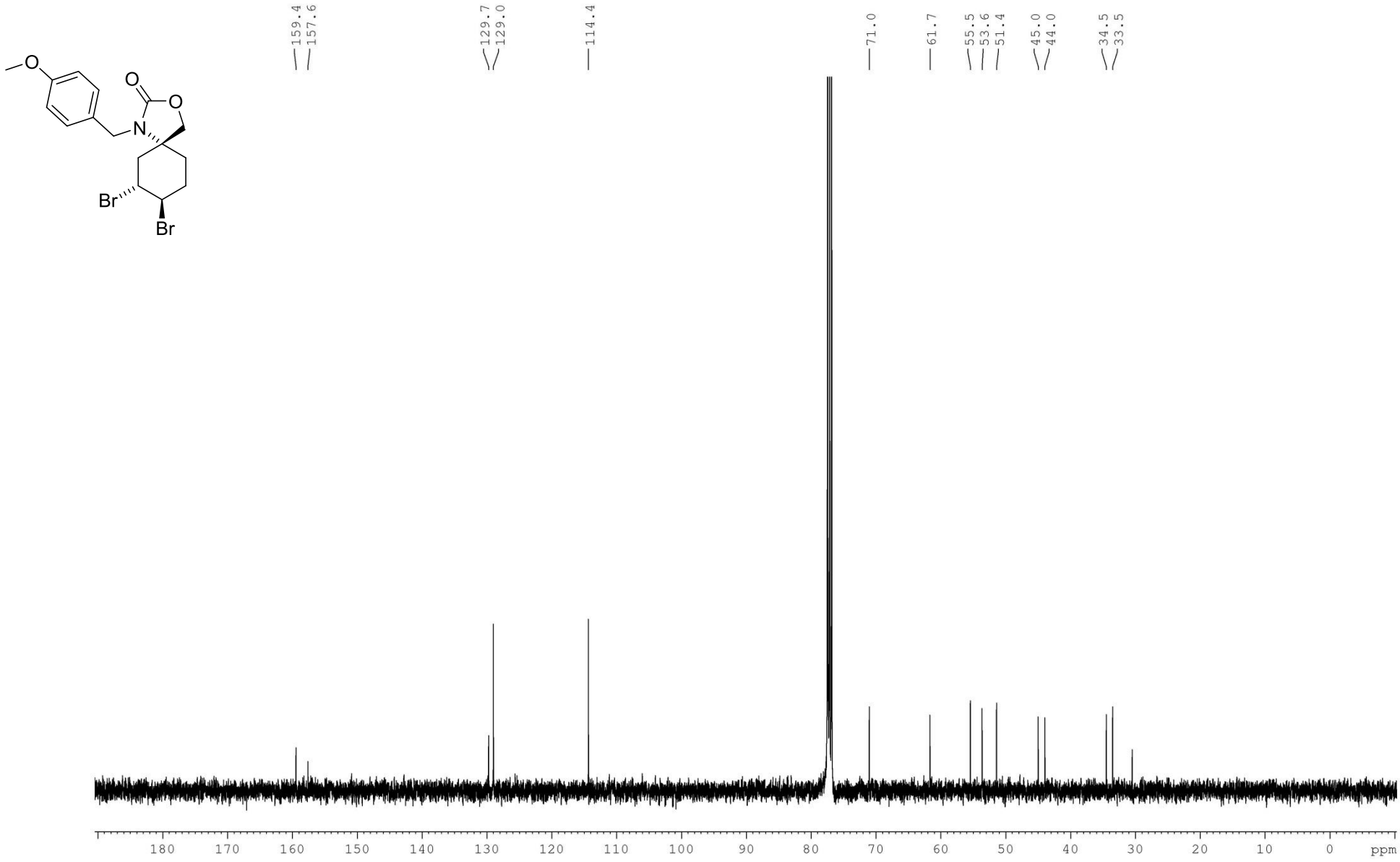
(5*R,7*R**,8*R**)-7,8-Dibromo-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]-decan-2-one (27b)**

^{1}H NMR, $CDCl_3$, 400 MHz



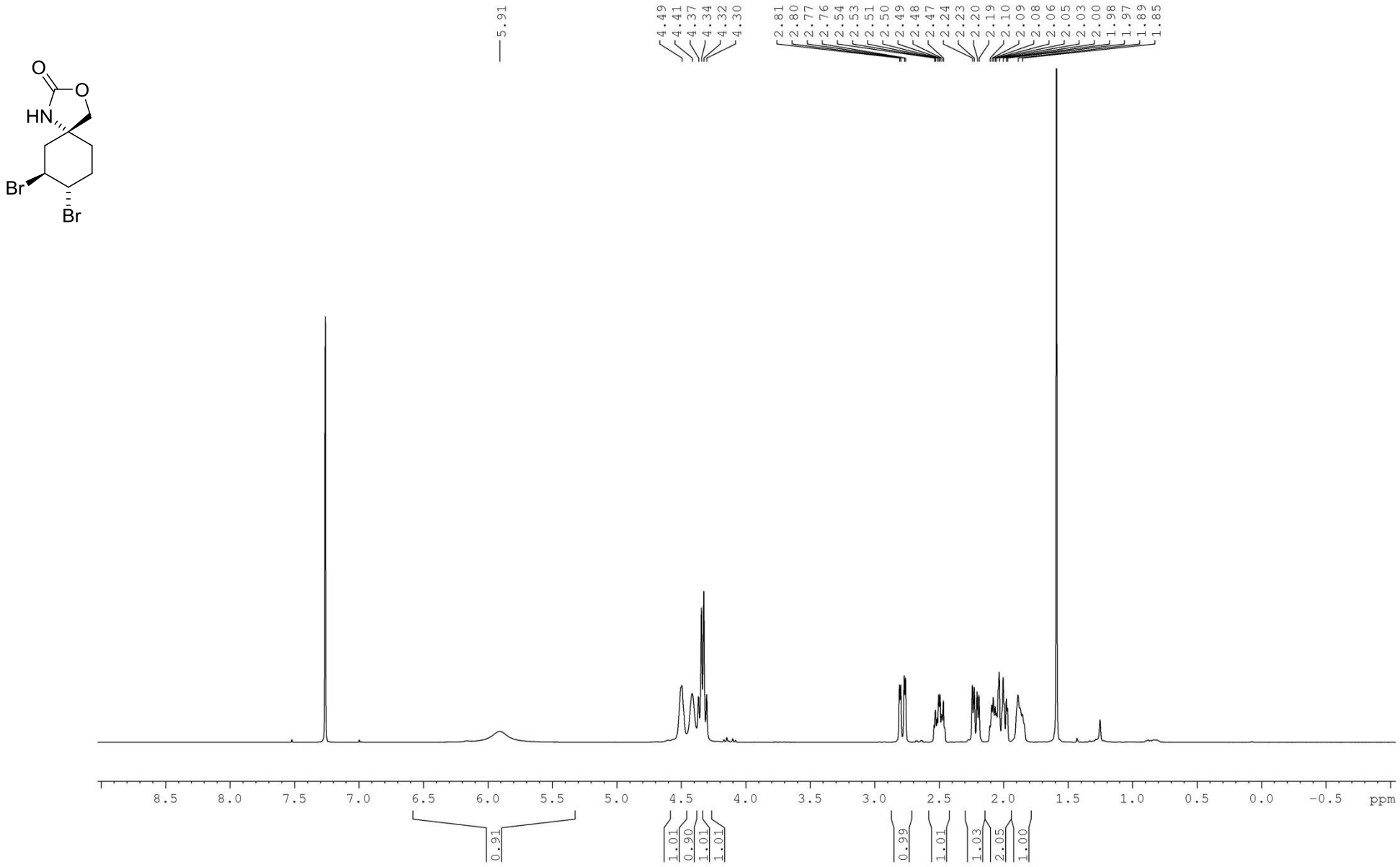
(5*R,7*R**,8*R**)-7,8-Dibromo-1-(4-methoxybenzyl)-3-oxa-1-azaspiro[4.5]-decan-2-one (27b)**

^{13}C NMR, $CDCl_3$, 101 MHz



(5*R,7*S**,8*S**)-7,8-Dibromo-3-oxa-1-azaspiro[4.5]decan-2-one (28)**

^{1}H NMR, $CDCl_3$, 400 MHz



(5*R,7*S**,8*S**)-7,8-Dibromo-3-oxa-1-azaspiro[4.5]decan-2-one (28)**

^{13}C NMR, $CDCl_3$, 101 MHz