Diastereoselective Intramolecular Additions of Allyl- and Propargylsilanes to Iminium Ions: Synthesis of Cyclic and Bicyclic Quaternary Amino Acids

Santos Fustero,*[,†,‡] Natalia Mateu,[†,‡] Antonio Simón-Fuentes[†] and José Luis Aceña*[,‡]

[†]*Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain*

[‡]*Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain.*

SUPPORTING INFORMATION

Table of contents:

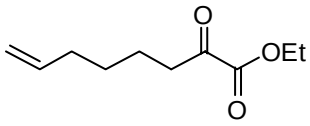
GENERAL METHODS.

All reactions were carried out under argon or nitrogen atmosphere. The following solvents were purified prior to use: THF was distilled from sodium/benzophenone; CH_2Cl_2 was distilled from calcium hydride. All other solvents and reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm E. Merck precoated silica gel plates. Visualization was carried out with UV light and vainillin or potassium permanganate stains. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm). Melting points were measured on a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1020 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AC300 spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad. High-resolution mass spectra were carried out by the Universidad de Valencia Mass Spectrometry Service.

Microwave experiments were carried out on sealed vials using an Initiator™ 2.0, by Biotage. The equipment contains an IR probe in order to control the internal temperature of the reaction mixture. The solutions were pre-stirred before the irradiation was started. The absorbance of the solvent was set as "normal" and the reaction time was initiated as soon the system reached the input temperature. At the end of the irradiation, the mixture was cooled to room temperature with an air flow, and the pressure was liberated with a needle before removing the vial cap.

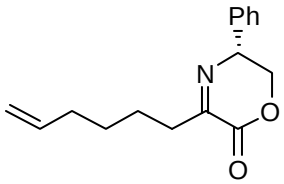
SYNTHESIS AND CHARACTERIZATION OF NEW COMPOUNDS

Synthesis of ethyl 2-oxooct-7-enoate (S1).



A solution of 6-bromo-1-hexene (3.00 g, 18.18 mmol) in THF (30 mL) was added dropwise to a dry flask containing magnesium (1.47 g, 60.60 mmol) and iodine (3 mg). After 2 h stirring vigorously, the resulting Grignard reagent was added dropwise to a cold (–78 ºC) solution of diethyl oxalate (1.64 mL, 12.12 mmol) in THF (12 mL). After 1 h, the reaction was quenched with sat. aq NH_4Cl, the aqueous layer was extracted with Et_2O (3 x 30 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 2.21 g of **S1** (>99% yield) as a colorless oil. R_f: 0.30 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 1.36-1.45 (m, 2H), 1.55-1.68 (m, 2H), 1.97-2.09 (m, 2H), 2.80 (t, J = 7.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 4.88-5.02 (m, 2H), 5.67-5.83 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.2, 28.0, 33.2, 38.9, 62.2, 114.7, 138.0, 161.1, 194.4. HRMS (EI) calcd for $C_{10}H_{16}O_3$ $[M]^+$: 184.1099; found: 184.1102.

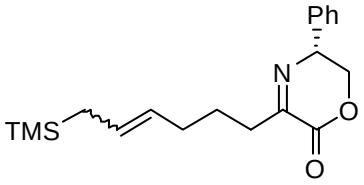
Synthesis of (*R*)-3-(hex-5-enyl)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (4b).



A solution of (*R*)-phenylglycinol (825 mg, 6.0 mmol) and **S1** (1.11 g, 6.0 mmol) in CF_3CH_2OH (18 mL) in the presence of powdered, activated 3Å molecular sieves (3 g) was heated under microwave irradiation at 100 ºC for 50 min. The crude product was filtered through Celite, concentrated at reduced pressure and purified by column chromatography on silica to afford 1.10 g of **4b** (71% yield) as a colorless oil. R_f: 0.35 (hexane/EtOAc, 5:1). $[\alpha]^{25}_D$ –156.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-

1.57 (m, 2H), 1.65-1.79 (m, 2H), 2.07-2.17 (m, 2H), 2.71-2.81 (m, 2H), 4.18 (dd, *J* = 11.5, 10.9 Hz, 1H), 4.54 (dd, *J* = 11.5, 4.5 Hz, 1H), 4.80-4.89 (m, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 5.03 (d, *J* = 17.0 Hz, 1H), 5.73-5.90 (m, 1H), 7.30-7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 28.4, 33.4, 34.2, 59.5, 71.4, 114.6, 127.0, 128.2, 128.8, 136.9, 138.5, 155.3, 163.1. HRMS (EI) calcd for $C_{16}H_{19}NO_2$ $[M]^+$: 257.1416; found: 257.1407.

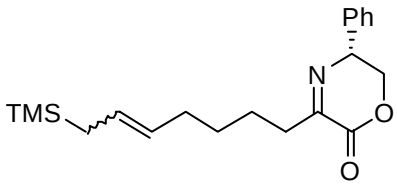
Synthesis of (*R*)-5-phenyl-3-(6-(trimethylsilyl)hex-4-enyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one (5a).



Grubbs 2nd generation catalyst (506 mg, 10 mol %) and allyltrimethylsilane (1.89 mL, 11.92 mmol) were added to a solution of **4a**[1] (1.45 g, 5.96 mmol) in CH_2Cl_2 (29.8 mL). The mixture was heated at reflux for 12 h and then it was allowed to cool down to room temperature and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 1.49 g of **5a** as a mixture of *trans* and *cis* isomers (*ca.* 90:10 ratio as determined by ^{1}H NMR) as a colorless oil (76% yield). R_f: 0.30 (hexane/EtOAc, 6:1). Data of the *trans* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 1.42 (dq, *J* = 7.8, 1.0 Hz, 2H), 1.70-1.83 (m, 2H), 2.02-2.18 (m, 2H), 2.70-2.81 (m, 2H), 4.19 (dd, *J* = 11.5, 10.9 Hz, 1H), 4.55 (dd, *J* = 11.5, 4.5 Hz, 1H), 4.81-4.89 (m, 1H), 5.20-5.35 (m, 1H), 5.37-5.50 (m, 1H), 7.31-7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –2.0, 22.6, 26.4, 32.3, 33.9, 59.5, 71.3, 127.0, 127.2, 127.7, 128.2, 128.8, 137.0, 155.3, 163.3. HRMS (EI) calcd for $C_{19}H_{27}NO_2Si$ $[M]^+$: 329.1811; found: 329.1819.

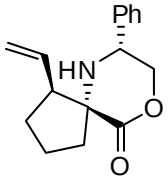
[1] Fustero, S.; Albert, L.; Aceña, J. L.; Sanz-Cervera, J. F.; Asensio, A. *Org. Lett.* **2008**, *10*, 605–608.

Synthesis of (*R*)-5-phenyl-3-(7-(trimethylsilyl)hept-5-enyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one (5b).



Following the same procedure as for **5a**, starting from 2.20 g (8.55 mmol) of **4b**, 2.02 g of **5b** were obtained as a mixture of *trans* and *cis* isomers (*ca.* 90:10 ratio as determined by ^{1}H NMR) as a colorless oil (69% yield). R_f: 0.25 (hexane/EtOAc, 5:1). Data of the *trans* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.02 (s, 9H), 1.34-1.52 (m, 4H), 1.63-1.80 (m, 2H), 1.97-2.12 (m, 2H), 2.65-2.83 (m, 2H), 4.19 (dd, *J* = 11.5, 10.9 Hz, 1H), 4.55 (dd, *J* = 11.5, 4.5 Hz, 1H), 4.80-4.90 (m, 1H), 5.16-5.33 (m, 1H), 5.33-5.47 (m, 1H), 7.30-7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –2.0, 22.6, 25.6, 29.6, 32.4, 34.4, 59.6, 71.4, 126.5, 127.1, 128.2, 128.3, 128.9, 137.0, 155.4, 163.3. HRMS (EI) calcd for $C_{20}H_{29}NO_2Si$ $[M]^+$: 343.1968; found: 343.1964.

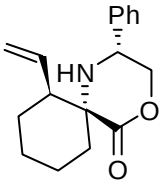
Synthesis of (1*S*,5*R*,7*R*)-7-phenyl-1-vinyl-6-aza-9-oxaspiro[4.5]decan-10-one (6a).



TFA (1.31 mL, 17.60 mmol) was added to a solution of **5a** (1.16 g, 3.52 mmol) in CH_2Cl_2 (35 mL) and the mixture was stirred overnight at room temperature. Then, the solvents were evaporated at reduced pressure and the residue was redissolved in EtOAc (50 mL) and washed with sat. aq. $NaHCO_3$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 600 mg of the major isomer **6a** as a white solid (66% yield) together with 212 mg (23% yield) of an inseparable mixture of two diastereoisomers. R_f: 0.30 (hexane/EtOAc, 5:1). Mp: 63-65 ºC. $[\alpha]^{25}_D$ –56.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64-1.93 (m, 5H), 2.00 (br, 1H), 2.34-2.50 (m, 1H), 2.62 (dt, *J* = 9.3, 7.6 Hz, 1H), 4.15 (t, *J* = 10.7 Hz, 1H), 4.26 (dd, *J* = 10.7, 3.9 Hz, 1H), 4.52 (dd, *J* = 10.7, 3.9

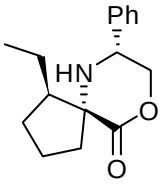
Hz, 1H), 5.03 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.16 (ddd, *J* = 17.0, 1.9, 0.7 Hz, 1H), 5.86 (ddd, *J* = 17.0, 10.0, 9.5 Hz, 1H), 7.18-7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 33.1, 40.9, 52.6, 59.6, 69.8, 74.2, 116.2, 126.6, 128.0, 128.5, 138.1, 139.6, 171.3. HRMS (EI) calcd for $C_{16}H_{19}NO_2$ $[M]^+$: 257.1416; found: 257.1413.

Synthesis of (2*R*,6*R*,7*S*)-2-phenyl-7-vinyl-1-aza-4-oxaspiro[5.5]undecan-5-one (6b).



Following the same procedure as for **6a**, starting from 2.02 g (5.90 mmol) of **5b**, 960 mg of the major isomer **6b** were obtained as a colorless oil (60% yield) together with 176 mg (11% yield) of an inseparable mixture of two diastereoisomers. R_f: 0.29 (hexane/EtOAc, 5:1). $[\alpha]^{25}_D$ +7.7 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34-1.52 (m, 2H), 1.57-1.83 (m, 4H), 1.83-2.02 (m, 2H), 2.89-3.01 (m, 1H), 4.32-4.43 (m, 3H), 5.18 (br, 1H), 5.19 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.21 (dt, *J* = 10.8, 1.4 Hz, 1H), 5.95 (ddd, *J* = 17.2, 10.8, 6.4 Hz, 1H), 7.32-7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 24.4, 24.4, 39.2, 46.6, 56.1, 62.6, 72.6, 117.5, 127.3, 128.9, 128.9, 136.9, 137.8, 172.9. HRMS (EI) calcd for $C_{17}H_{21}NO_2$ $[M]^+$: 271.1572; found: 271.1571.

Synthesis of (1*R*,5*R*,7*R*)-1-ethyl-7-phenyl-6-aza-9-oxaspiro[4.5]decan-10-one (7).

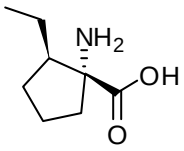


Pd-C (10% wt, 1.3 mg, 10 mol %) was added to a solution of **6a** (30 mg, 0.12 mmol) in MeOH (2.3 mL). The mixture was stirred under H_2 atmosphere (1 atm) for 4 h and then filtered and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 29 mg of **7** (95% yield) as a white solid. R_f: 0.25 (hexane/EtOAc, 5:1). Mp: 92-93 ºC. $[\alpha]^{25}_D$ –82.4 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.30-1.55 (m, 2H), 1.56-2.11 (m, 7H), 2.41-2.56 (m, 1H), 4.27 (t, *J* = 11.3 Hz, 1H), 4.40 (dd, *J* =

11.3, 3.7 Hz, 1H), 4.41 (dd, J = 11.3, 3.7 Hz, 1H), 7.29-7.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 23.6, 26.3, 32.0, 41.3, 53.1, 55.8, 69.8, 74.5, 127.0, 128.4, 128.8, 138.4, 171.7. HRMS (EI) calcd for $C_{16}H_{21}NO_2$ $[M]^+$: 259.1572; found: 259.1564.

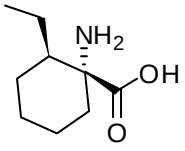
X-Ray data of 7: Orthorombic crystal system, space group *P*2(1)2(1)2(1). Unit cell dimensions a = 6.30590(10) Å, α = 90°, b = 9.8235(2) Å, β = 90°, c = 23.4873(4) Å, γ = 90°, V = 1454.94(4) Å^3, Z = 4, d_{calcd} = 1.184 mg/m^3. Absorption coefficient = 0.61 mm^{-1}. F(000) = 560. Crystal size 0.25 × 0.15 × 0.10 mm^3. Reflections collected 11005, independent reflections 2758 [R_{int} = 0.026].

Synthesis of (1*R*,2*R*)-1-amino-2-ethylcyclopentanecarboxylic acid (8a).



Pd-C (10% wt, 78 mg, 0.73 mmol) was added to a solution of **6a** (75 mg, 0.29 mmol) in MeOH (5.8 mL). The mixture was stirred under H_2 atmosphere (1 atm) for 16 h and then filtered and concentrated at reduced pressure. The product was purified on DOWEX 50WX8-100 to afford 40 mg of **8a** (88% yield) as a white solid. Its NMR data matched those previously reported.[2] Mp: 270-271 ºC. $[\alpha]^{25}_D$ –27.3 (*c* 1.0, MeOH). (lit. data: Mp: 267 ºC (decomp.); $[\alpha]^{25}_D$ –20.9 (*c* 1.0, MeOH)). HRMS (FAB) calcd for $C_8H_{16}NO_2$ $[M+H]^+$: 158.1181; found: 158.1180.

Synthesis of (1*R*,2*R*)-1-amino-2-ethylcyclohexanecarboxylic acid (8b).

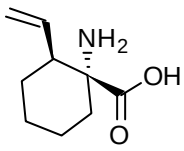


Following the same procedure as for **8a**, starting from 75 mg (0.28 mmol) of **6b**, 44 mg of **8b** were obtained as a white solid (92% yield). Mp: 250-252 ºC. $[\alpha]^{25}_D$ –14.6 (*c* 0.8, MeOH). ^{1}H NMR (300 MHz,

[2] Wede, J.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **2000**, *11*, 3231–3252.

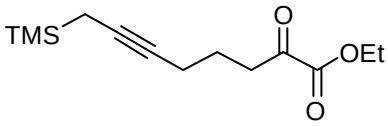
D_2O) δ 0.93 (t, *J* = 7.2 Hz, 3H), 0.99-1.20 (m, 2H), 1.21-1.45 (m, 3H), 1.45-1.69 (m, 1H), 1.71-2.06 (m, 5H). ^{13}C NMR (75 MHz, D_2O) δ 11.3, 20.1, 23.5, 24.5, 24.9, 33.3, 42.1, 65.9, 177.6. HRMS (FAB) calcd for $C_9H_{18}NO_2$ $[M+H]^+$: 172.1338; found: 172.1338.

Synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclohexanecarboxylic acid (9).



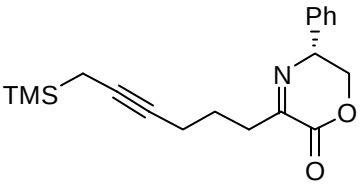
$LiOH·H_2O$ (23 mg, 0.54 mmol) was added to a solution of **6b** (74 mg, 0.27 mmol) in a 5:1 mixture of THF:H_2O (2.7 mL). The reaction was stirred for 3 h and then diluted with H_2O (5 mL) and the organic solvents were removed at reduced pressure. The aqueous phase was washed with Et_2O (3 x 5 mL) and then it was concentrated at reduced pressure. The residue was redissolved in a 1:1 mixture of CH_2Cl_2:MeOH (2.6 mL) and $Pb(OAc)_4$ (164 mg, 0.37 mmol) was added at 0 ºC. The reaction mixture was vigorously stirred for 1 h at 0 ºC, and then 2.7 mL of 0.5 M HCl was added. The temperature was allowed to warm to room temperature and after 4 h of additional stirring the reaction mixture was filtered through celite eluting with CH_2Cl_2 and H_2O. The organic solvents were removed at reduced pressure and the aqueous residue was washed again with CH_2Cl_2 and then concentrated at reduced pressure. The product was purified on DOWEX 50WX8-100 to afford 24 mg of **9** (54% yield) as a white solid. Mp: 269-271 ºC. $[\alpha]^{25}_D$ −19.6 (*c* 0.7, MeOH). ^1H NMR (300 MHz, D_2O) δ 1.10-1.36 (m, 3H), 1.57-1.77 (m, 3H), 1.77-1.96 (m, 2H), 2.54-2.67 (m, 1H), 5.06 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.09 (dt, *J* = 10.8, 1.3 Hz, 1H), 5.50-5.65 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ 19.8, 23.9, 24.4, 32.4, 43.4, 65.0, 118.5, 135.6, 179.5. HRMS (FAB) calcd for $C_9H_{16}NO_2$ $[M+H]^+$: 170.1181; found: 170.1181.

Synthesis of ethyl 2-oxo-8-(trimethylsilyl)oct-6-ynoate (11).



Following the same procedure as for **S1**, from 666 mg (2.86 mmol) of (6-bromohex-2-ynyl)trimethylsilane,[3] 276 mg of **11** were obtained as a colorless oil (38% yield). R_f: 0.30 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.37 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 2.6 Hz, 2H), 1.80 (quint, J = 6.9 Hz, 2H), 2.19-2.27 (m, 2H), 2.97 (t, J = 7.1 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –2.1, 6.9, 14.0, 18.2, 22.7, 38.2, 62.4, 77.3, 78.9, 161.0, 194.3. HRMS (EI) calcd for $C_{13}H_{22}O_3Si$ $[M]^+$: 254.1338; found: 254.1337.

Synthesis of (*R*)-5-phenyl-3-(6-(trimethylsilyl)hex-4-ynyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one (12).

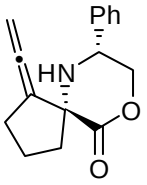


Following the same procedure as for **4b**, from 240 mg (0.94 mmol) of **11**, 154 mg of **12** were obtained as a colorless oil (50% yield). R_f: 0.29 (hexane/EtOAc, 5:1). $[\alpha]^{25}_D$ −128.6 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.42 (t, J = 2.6 Hz, 2H), 1.89 (quint, J = 7.0 Hz, 2H), 2.29 (tt, J = 6.9, 2.7 Hz, 2H), 2.86 (td, J = 7.3, 2.4 Hz, 2H), 4.19 (t, J = 11.3 Hz, 1H), 4.54 (dd, J = 11.5, 4.5 Hz, 1H), 4.80-4.89 (m, 1H), 7.28-7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –2.1, 6.9, 18.4, 25.5, 33.4, 59.5, 71.3, 77.8, 78.5, 127.0, 128.2, 128.8, 136.9. 155.2, 162.7. HRMS (EI) calcd for $C_{19}H_{25}NO_2Si$ $[M]^+$: 327.1655; found: 327.1652.

[3] Schinzer, D.; Dettmer, G.; Ruppelt, M.; Sólyom, S.; Steffen, J. *J. Org. Chem.* **1988**, *53*, 3823–3828.

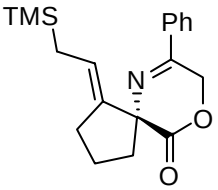
Synthesis of (5*R*,7*R*)-7-phenyl-1-vinylidene-6-aza-9-oxaspiro[4.5]decan-10-one (13) and (*R*,*E*)-7-phenyl-1-(2-(trimethylsilyl)ethylidene)-6-aza-9-oxaspiro[4.5]dec-6-en-10-one (14).

A solution of **12** (131 mg, 0.40 mmol) in HCO_2H (4 mL) was stirred for 4 h at room temperature and then the reaction mixture was quenched with sat. aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 58 mg of **13** (57% yield) and 16 mg of **14** (5% yield) both as colorless oils.



Data for **13**:

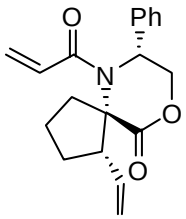
R$_f$: 0.20 (hexane/EtOAc, 5:1). $[\alpha]^{25}_D$ –182.9 (*c* 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69-1.88 (m, 2H), 1.88-2.08 (m, 2H), 2.55-2.69 (m, 3H), 4.29 (t, *J* = 10.7 Hz, 1H), 4.36 (dd, *J* = 10.7, 4.1 Hz, 1H), 4.77 (dd, *J* = 10.6, 4.1 Hz, 1H), 4.94 (dt, *J* = 10.6, 4.4 Hz, 1H), 5.05 (dt, *J* = 10.6, 4.4 Hz, 1H), 7.30-7.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 30.2, 41.4, 52.8, 69.3, 74.7, 79.2, 108.4, 127.3, 128.6, 128.8, 137.9, 170.8, 203.2. HRMS (EI) calcd for $C_{16}H_{17}NO_2$ $[M]^+$: 255.1259; found: 255.1250.



Data for **14**:

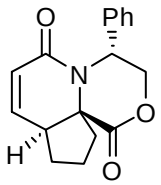
R$_f$: 0.28 (hexane/EtOAc, 5:1). $[\alpha]^{25}_D$ –54.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.03 (s, 9H), 1.42-1.50 (m, 2H), 2.04-2.18 (m, 3H), 2.38-2.61 (m, 3H), 5.27 (tt, *J* = 8.8, 2.5 Hz, 1H), 5.36 (d, *J* = 17.0 Hz, 1H), 5.49 (d, *J* = 17.0 Hz, 1H). 7.39-7.52 (m, 3H), 7.71-7.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –1.6, 20.9, 23.1, 28.4, 40.1, 68.4, 69.3, 121.9, 126.0, 128.8, 131.1, 134.7, 142.1, 158.4, 170.1. HRMS (EI) calcd for $C_{19}H_{25}NO_2Si$ $[M]^+$: 327.1655; found: 327.1640.

Synthesis of (1*S*,5*S*,7*R*)-6-acryloyl-7-phenyl-1-vinyl-6-aza-9-oxaspiro[4.5]decan-10-one (15).



Et_3N (0.49 mL, 3.50 mmol) and acryloyl chloride (0.28 mL, 3.50 mmol) were added to a solution of **6a** (450 mg, 1.75 mmol) in CH_2Cl_2 (14 mL) at 0 ºC. The mixture was stirred at room temperature for 2 h, and then sat. aq NH_4Cl was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 468 mg of **15** (86% yield) as a white solid. R_f: 0.37 (hexane/EtOAc, 3:1). Mp: 135-137 ºC. $[\alpha]^{25}_D$ −193.7 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69-1.83 (m, 1H), 1.84-2.03 (m, 2H), 2.21-2.40 (m, 1H), 2.65 (ddd, *J* = 12.8, 10.0, 2.6 Hz, 1H), 2.76 (dt, *J* = 12.9, 8.4 Hz, 1H), 4.00 (dt, *J* = 10.6, 6.6 Hz, 1H), 4.52 (dd, *J* = 11.6, 1.9 Hz, 1H), 4.85 (dd, *J* = 11.6, 2.7 Hz, 1H), 5.12 (br, 1H), 5.15 (dd, *J* = 9.9, 2.1 Hz, 1H), 5.24 (ddd, *J* = 16.9, 2.1, 0.6 Hz, 1H), 5.62 (dd, *J* = 9.4, 2.9 Hz, 1H), 5.68 (dt, *J* = 16.9, 10.0 Hz, 1H), 6.25 (dd, *J* = 16.7, 9.4 Hz, 1H), 6.33 (dd, *J* = 16.7, 2.9 Hz, 1H), 7.19-7.25 (m, 2H), 7.27-7.42 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 33.3, 37.5, 52.5, 55.8, 69.4, 74.8, 119.1, 125.9, 128.3, 129.1, 129.3, 129.3, 136.9, 137.6, 166.0, 170.8. HRMS (EI) calcd for $C_{19}H_{21}NO_3$ $[M]^+$: 311.1521; found: 311.1528.

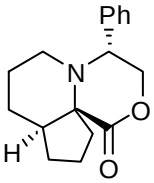
Synthesis of (1*R*,5*R*,10*S*)-2,7-dioxo-5-phenyl-6-aza-3-oxatricyclo[8.3.0.0^{1,6}]tridec-8-ene (16).



Grubbs 2nd generation catalyst (127 mg, 10 mol %) was added to a solution of **15** (468 mg, 1.50 mmol) in CH_2Cl_2 (15 mL). The mixture was heated at reflux for 6 h and then it was allowed to cool down to room temperature and concentrated at reduced pressure. The product was purified by column

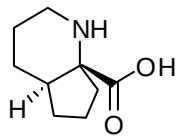
chromatography on silica to afford 267 mg of **16** (63% yield) as a white solid. R_f: 0.37 (hexane/EtOAc, 3:1). Mp: 164-166 ºC. $[\alpha]^{25}_D$ +84.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75-2.10 (m, 5H), 2.19-2.32 (m, 1H), 3.08-3.21 (m, 1H), 4.57 (dd, *J* = 12.0, 11.0 Hz, 1H), 4.95 (dd, *J* = 12.0, 9.8 Hz, 1H), 5.97 (dd, *J* = 9.5, 3.2 Hz, 1H), 6.03 (dd, *J* = 10.8, 9.4 Hz, 1H), 6.90 (ddd, *J* = 9.5, 2.4, 0.5 Hz, 1H), 7.26-7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 23.5, 33.1, 46.0, 53.5, 68.2, 69.4, 123.7, 125.4, 127.8, 128.9, 138.8, 144.0, 169.1, 169.6. HRMS (EI) calcd for $C_{17}H_{17}NO_3$ $[M]^+$: 283.1208; found: 283.1210.

Synthesis of (1*R*,5*R*,10*S*)-2-oxo-5-phenyl-6-aza-3-oxatricyclo[8.3.0.0^{1,6}]tridecane (17).



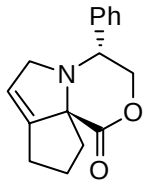
BH_3·THF (1 M in THF, 1.75 mL, 1.75 mmol) was added to a solution of **16** (100 mg, 0.35 mmol) in THF (7 mL) at 0 ºC. The mixture was stirred at room temperature for 12 h and then it was treated with 1M NaOH solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 30 mg of **17** (33% yield) as a white solid. R_f: 0.35 (hexane/EtOAc, 3:1). Mp: 111-112 ºC. $[\alpha]^{25}_D$ +118.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-1.80 (m, 7H), 1.80-1.97 (m, 3H), 1.97-2.07 (m, 1H), 2.64 (td, *J* = 11.0, 3.2 Hz, 1H), 2.98 (dt, *J* = 12.2, 3.7 Hz, 1H), 4.01 (dd, *J* = 11.2, 8.0 Hz, 1H), 4.37 (t, *J* = 11.5 Hz, 1H), 4.70 (dd, *J* = 12.0, 7.9 Hz, 1H), 7.27-7.47 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 23.2, 26.1, 26.6, 36.8, 48.9, 56.0, 63.5, 67.4, 69.2, 126.4, 127.4, 128.6, 140.5, 172.2. HRMS (EI) calcd for $C_{17}H_{21}NO_2$ $[M]^+$: 271.1572; found: 271.1568.

Synthesis of (4a*S*,7a*R*)-octahydro-1*H*-cyclopenta[b]pyridine-7a-carboxylic acid (18).



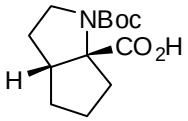
Following the same procedure as for **8a**, from 30 mg (0.11 mmol) of **17**, 17 mg of **18** were obtained as a white solid (94% yield). Mp: 280-281 ºC. $[\alpha]^{25}_{D}$ +12.8 (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 1.37-1.56 (m, 2H), 1.56-1.81 (m, 8H), 1.81-1.95 (m, 1H), 2.91 (td, *J* = 13.4, 3.9 Hz, 1H), 3.15-3.24 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ 19.4, 22.8, 23.6, 26.4, 34.6, 43.5, 45.8, 70.1, 175.0. HRMS (EI) calcd for $C_9H_{15}NO_2$ $[M]^+$: 169.1103; found: 169.1101.

Synthesis of (1*R*,5*R*)-2-oxo-5-phenyl-6-aza-3-oxatricyclo[7.3.0.0^{1,6}]dodec-8-ene (19).



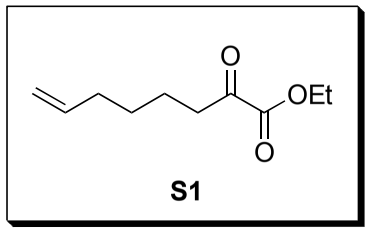
AuCl (1.2 mg, 5 mol %) was added to a solution of **13** (30 mg, 0.118 mmol) in CH_2Cl_2 (1.8 mL). The mixture was stirred at room temperature for 6 h and then it was concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 24 mg of **19** (80% yield) as a white solid. R_f: 0.30 (hexane/EtOAc, 10:1). Mp: 139-140 ºC. $[\alpha]^{25}_{D}$ – 8.6 (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90-2.24 (m, 4H), 2.31-2.45 (m, 1H), 2.52-2.68 (m, 1H), 3.64 (ddt, *J* = 13.3, 4.5, 1.6 Hz, 1H), 3.95-4.03 (m, 2H), 4.14 (t, *J* = 11.4 Hz, 1H), 4.26 (dd, *J* = 11.5, 3.9 Hz, 1H), 5.46-5.51 (m, 1H), 7.29-7.41 (m, 3H), 7.42-7.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.7, 39.5, 65.1, 66.1, 71.1, 78.7, 118.7, 127.2, 128.2, 128.7, 138.1, 147.6, 173.0. HRMS (EI) calcd for $C_{16}H_{17}NO_2$ $[M]^+$: 255.1259; found: 255.1255.

Synthesis of (3a*S*,6a*S*)-1-(*tert*-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-6a-carboxylic acid (20).



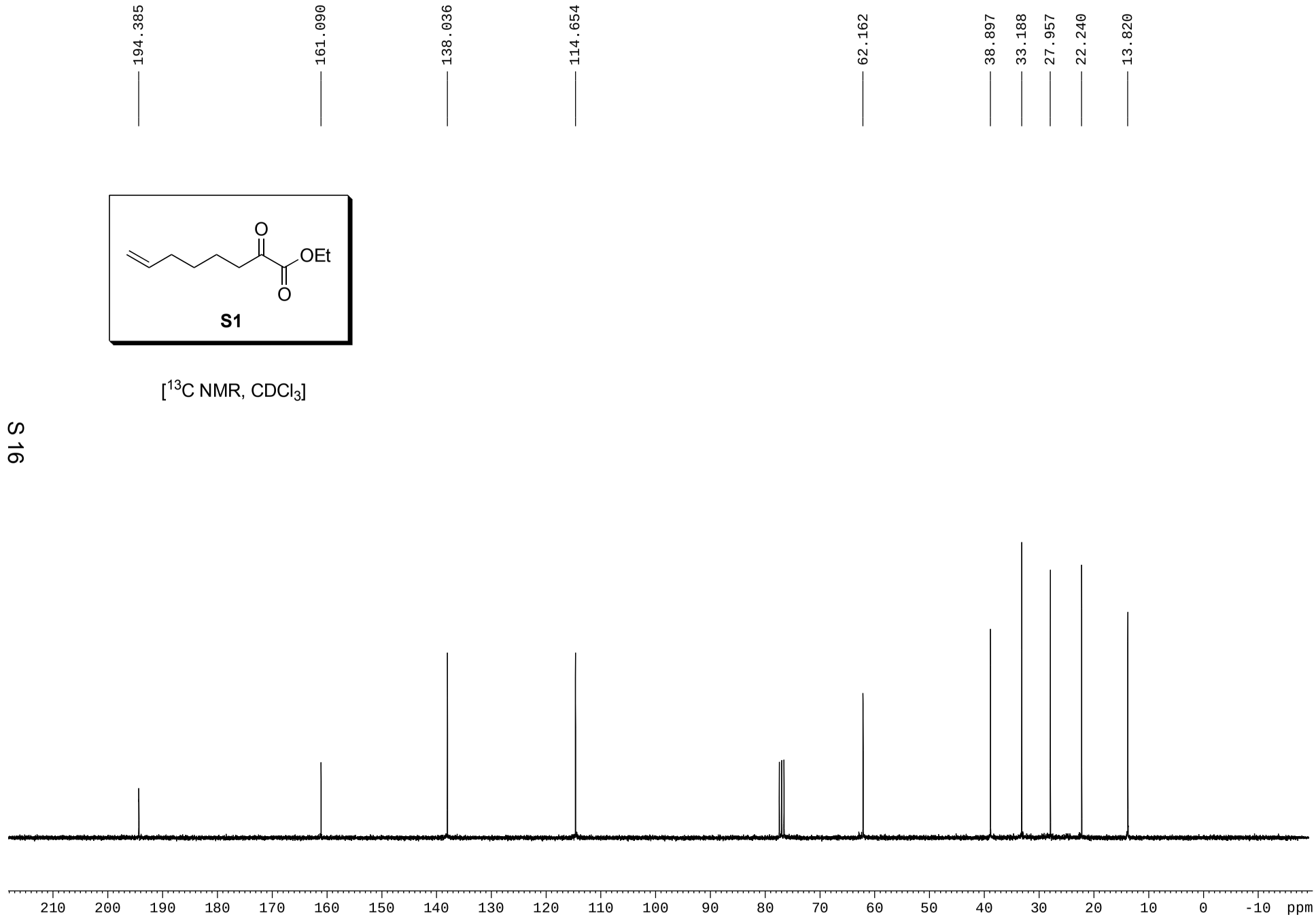
Pd-C (10% wt, 2.2 mg, 50 mol %) and Boc_2O (16 mg, 0.086 mmol) were added to a solution of **19** (11 mg, 0.043 mmol) in MeOH (1 mL). The mixture was stirred under H_2 atmosphere (1 atm) for 4 h and then filtered and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 10 mg of **20** (95% yield) as a white solid. Its NMR data matched those previously reported for its enantiomer.[4] R_f: 0.25 (hexane/EtOAc, 2:1). Mp: 158-160 ºC. $[\alpha]^{25}_D$ −10.9 (*c* 0.5, $CHCl_3$) (literature data for its enantiomer: Mp: 145 ºC. $[\alpha]^{25}_D$ + 6.9 (*c* 0.75, $CHCl_3$)). HRMS (EI) calcd for $C_{13}H_{21}NO_4$ $[M]^+$: 255.1471; found: 255.1479.

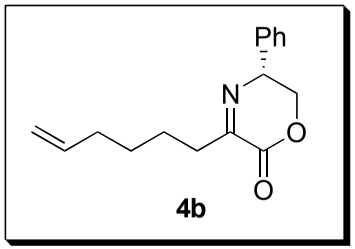
[4] Ranatunga, S.; Del Valle, J. R. *Tetrahedron Lett.* **2009**, *50*, 2464–2466.



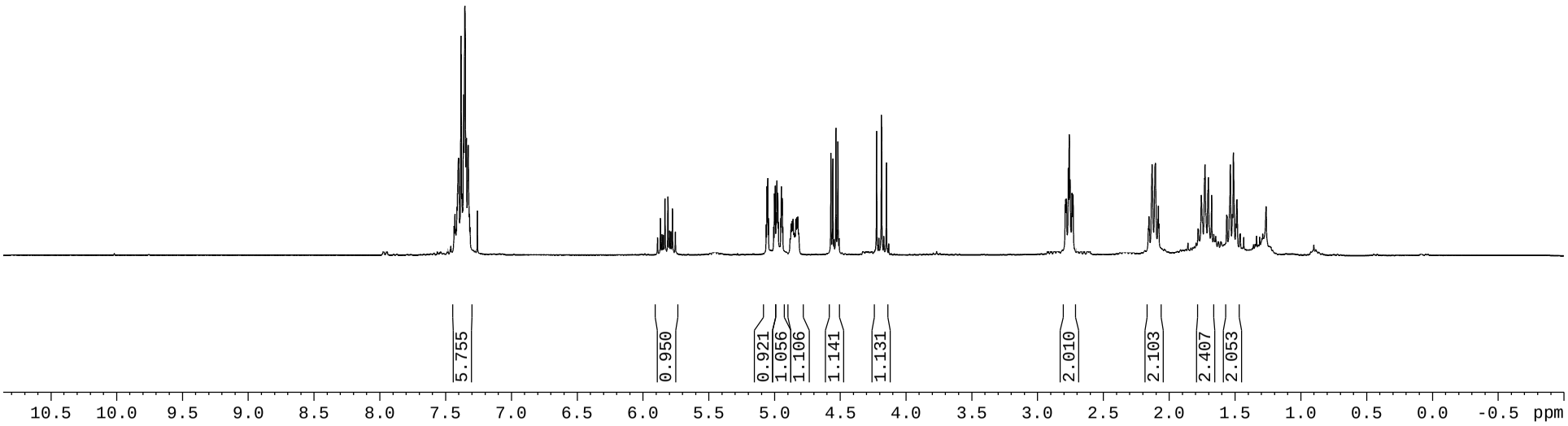
S1

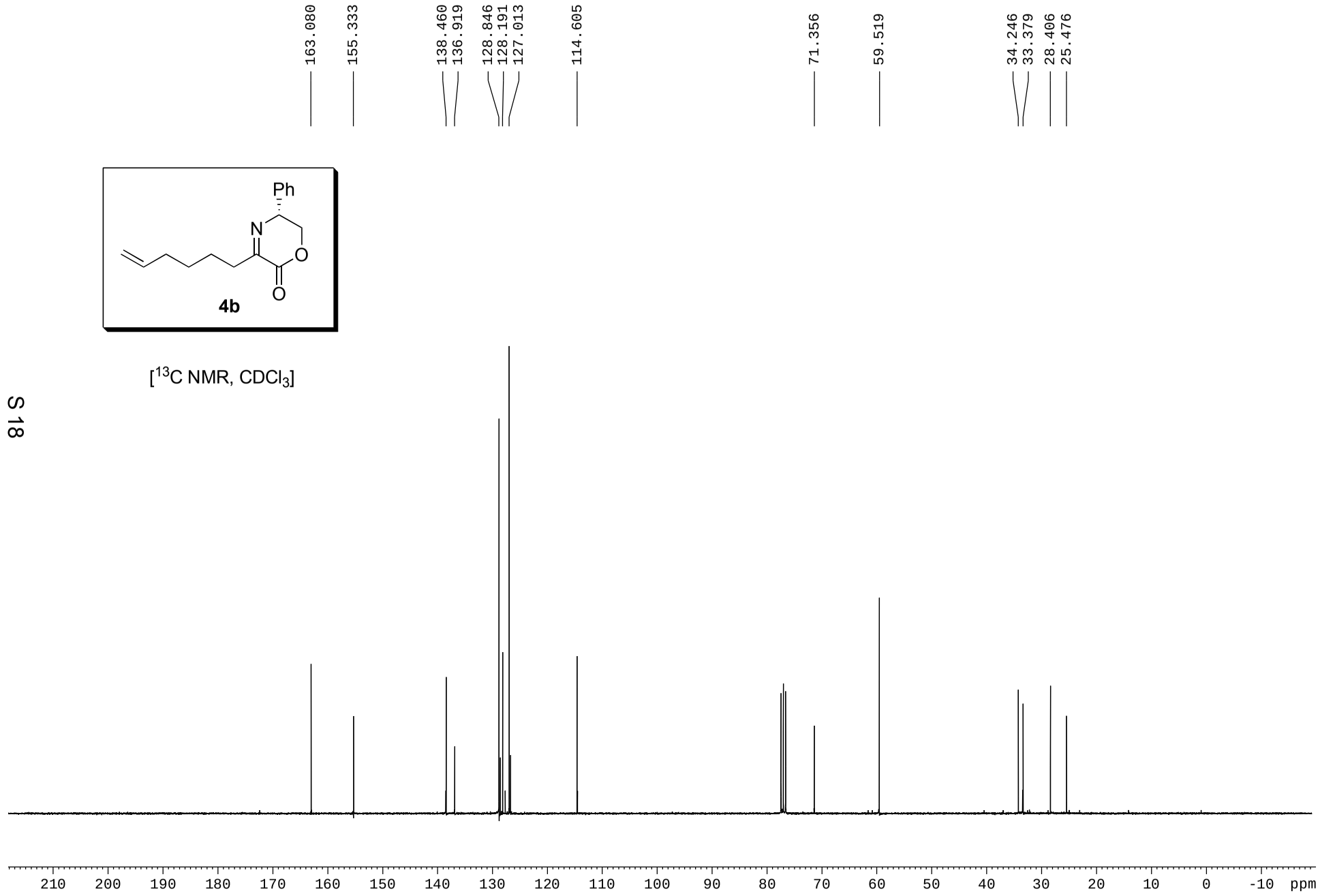
[^{1}H NMR, $CDCl_3$]

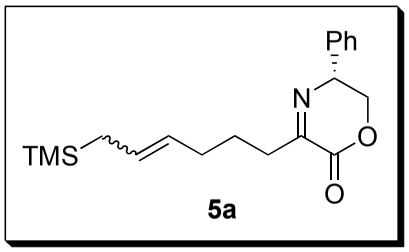

194.385
161.090
138.036
114.654
62.162
38.897
33.188
27.957
22.240
13.820
O
OEt
O
S1
[13C NMR, CDCl3]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


Ph
N
O
O
4b

[^{1}H NMR, $CDCl_3$]

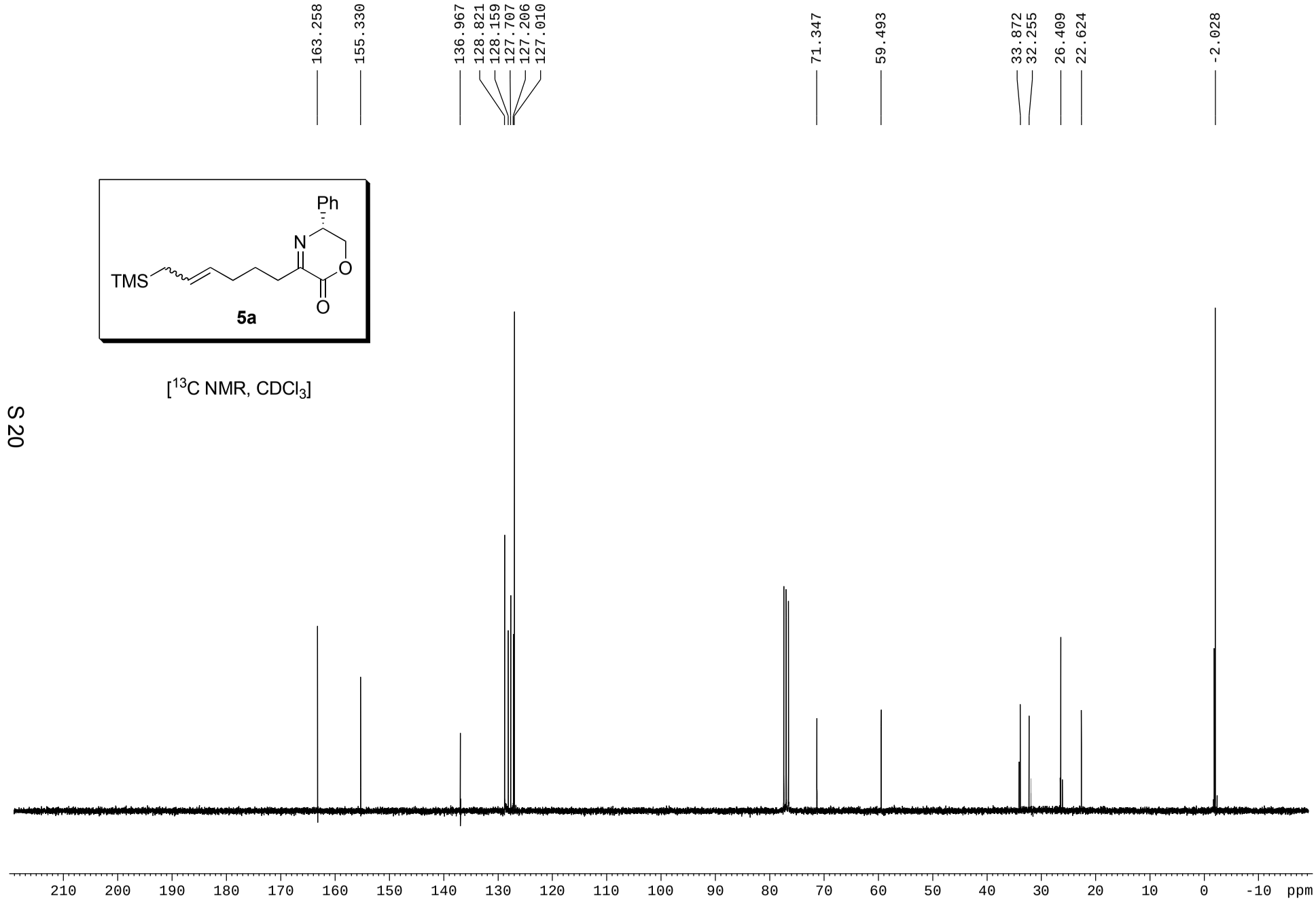

5.755
0.950
0.921
1.056
1.106
1.141
1.131
2.010
2.103
2.407
2.053
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

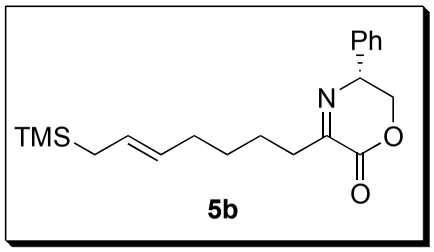

163.080
155.333
138.460
136.919
128.846
128.191
127.013
114.605
71.356
59.519
34.246
33.379
28.406
25.476
Ph
N
O
O
4b
[13C NMR, CDCl3]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm


Ph
N
O
TMS
O
5a

[^{1}H NMR, $CDCl_3$]

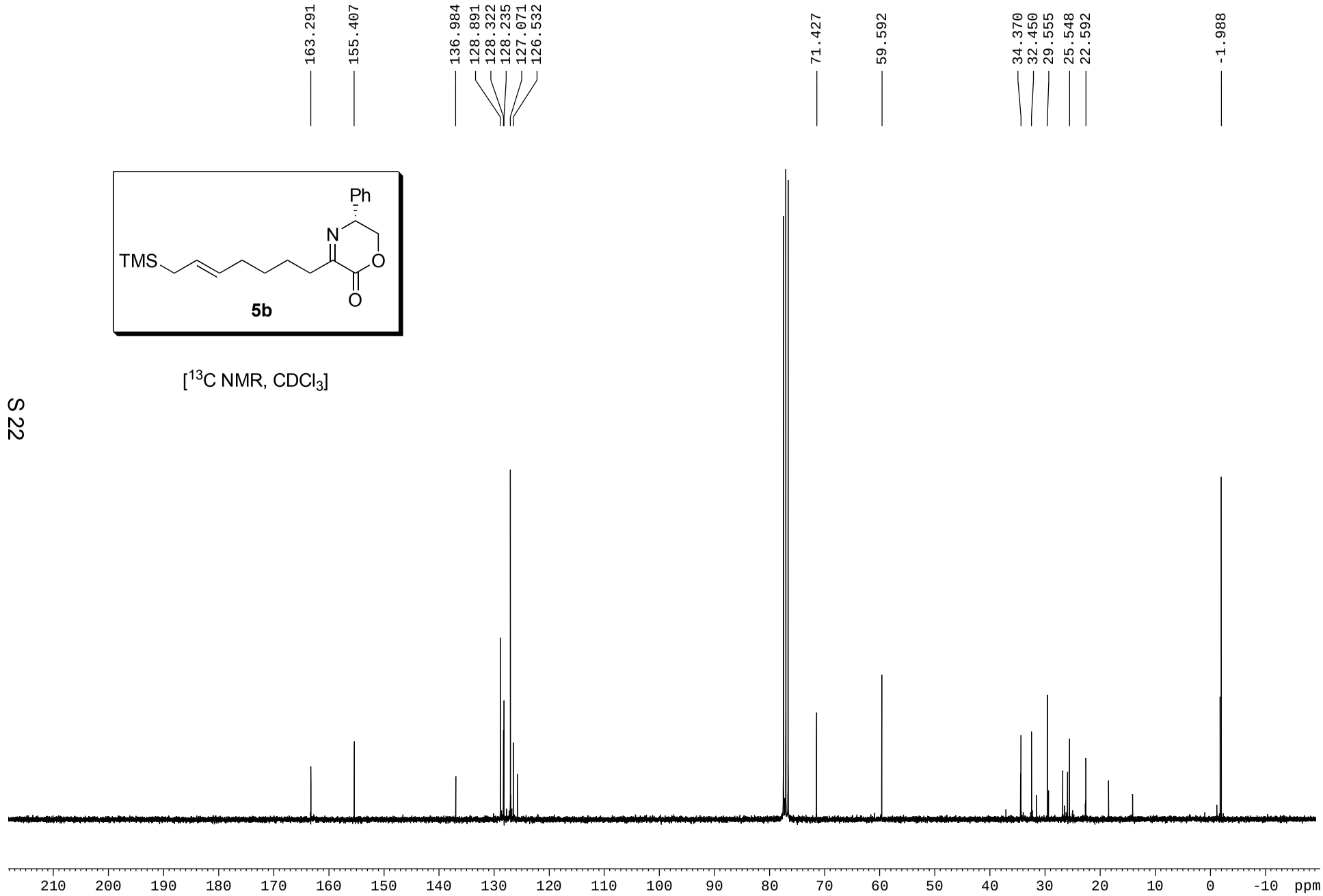
5.237
1.110
1.072
1.000
1.048
1.044
2.036
2.267
2.117
2.498
9.092
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

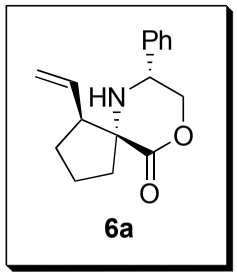

163.258
155.330
136.967
128.821
128.159
127.707
127.206
127.010
71.347
59.493
33.872
32.255
26.409
22.624
-2.028
Ph
N
O
TMS
O
5a
[13C NMR, CDCl3]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm



5b

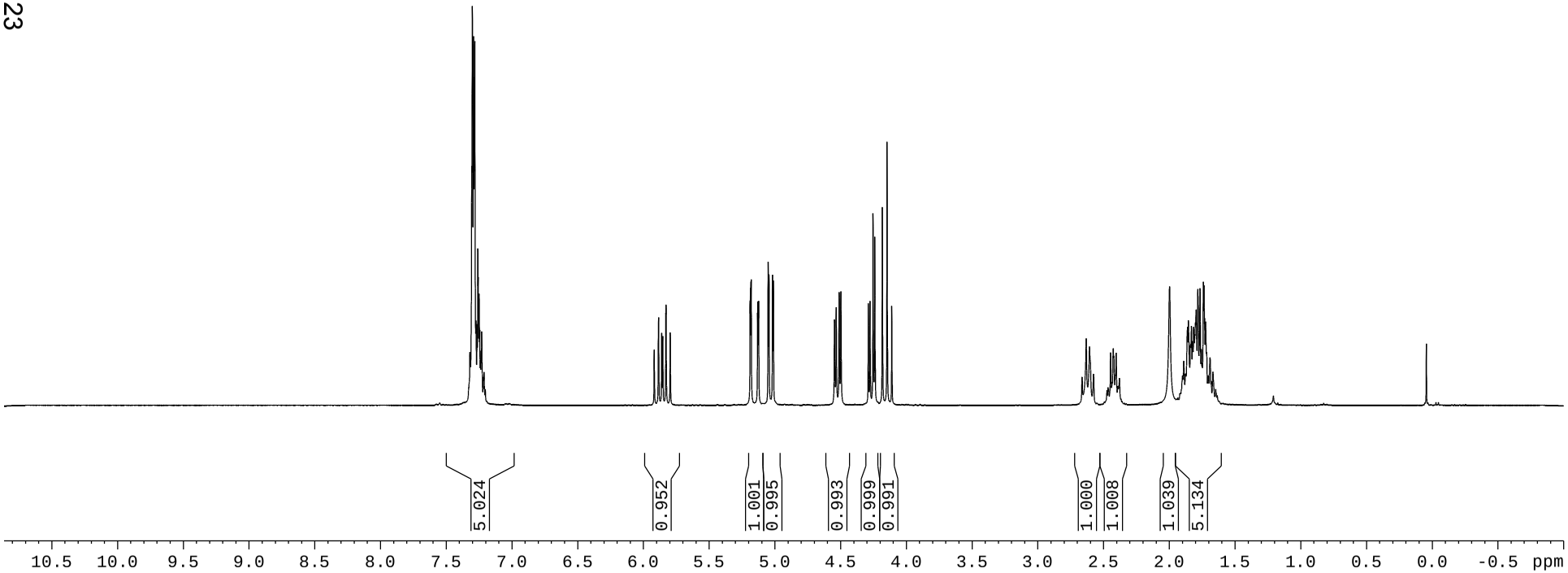
[^{1}H NMR, $CDCl_3$]

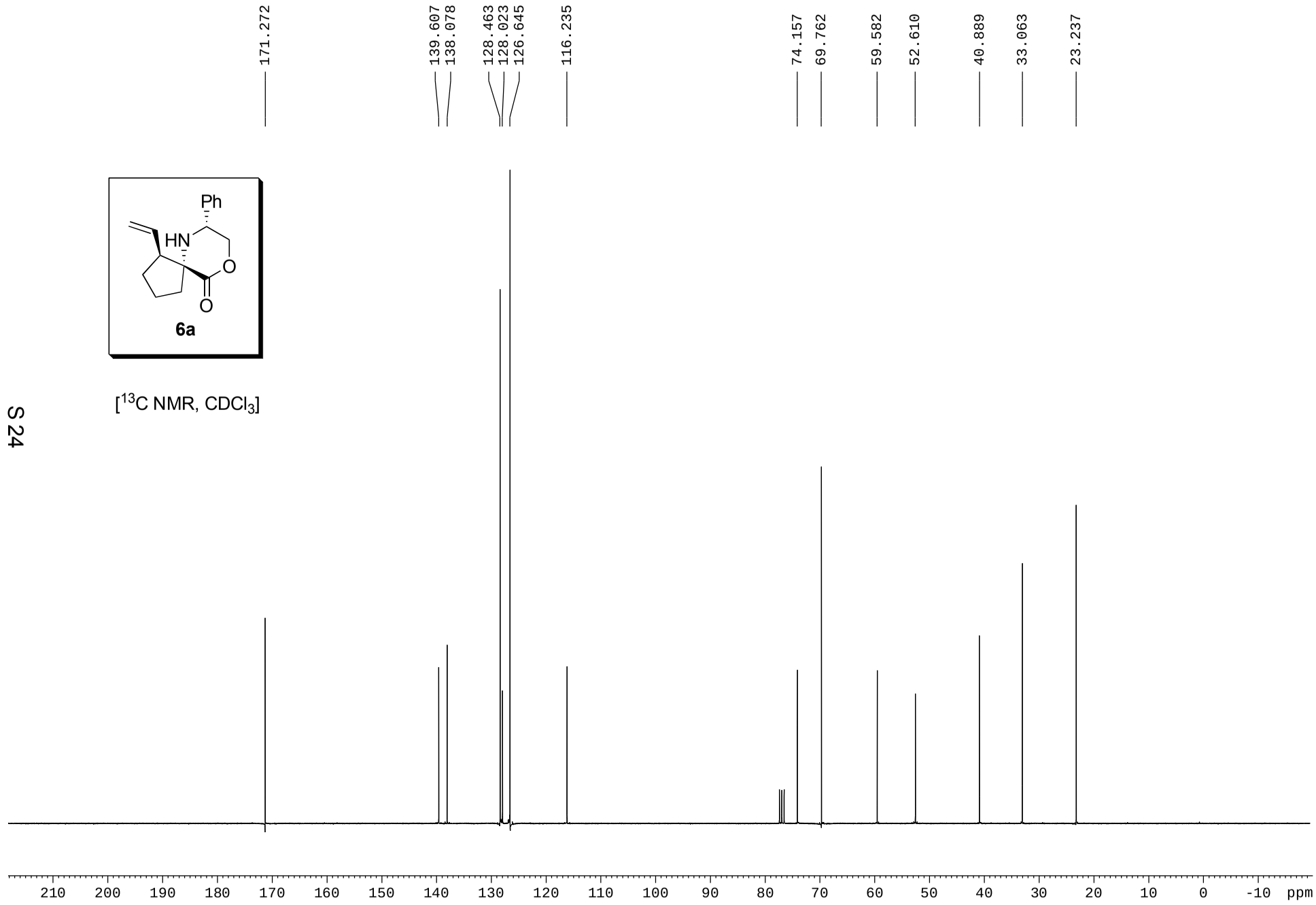

163.291
155.407
136.984
128.891
128.322
128.235
127.071
126.532
71.427
59.592
34.370
32.450
29.555
25.548
22.592
-1.988
Ph
N
O
TMS
O
5b
[13C NMR, CDCl3]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

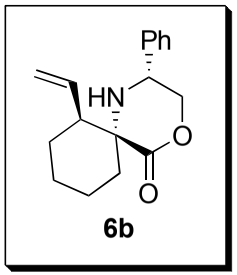


6a

[^{1}H NMR, $CDCl_3$]

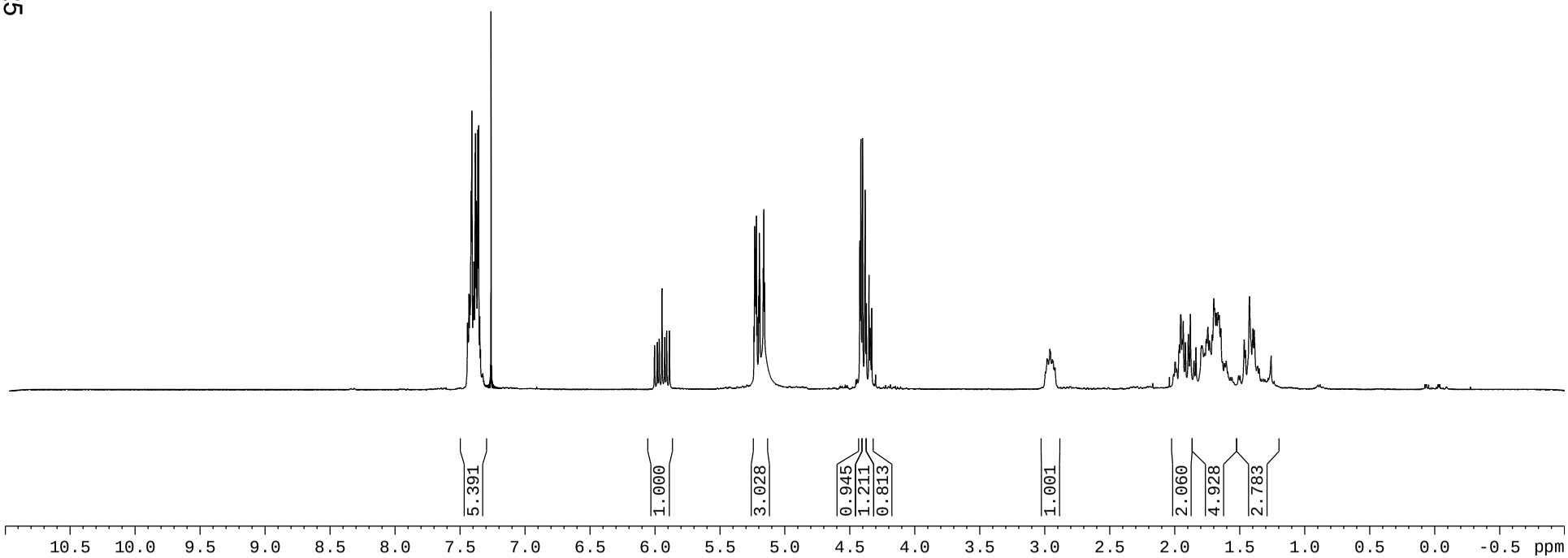


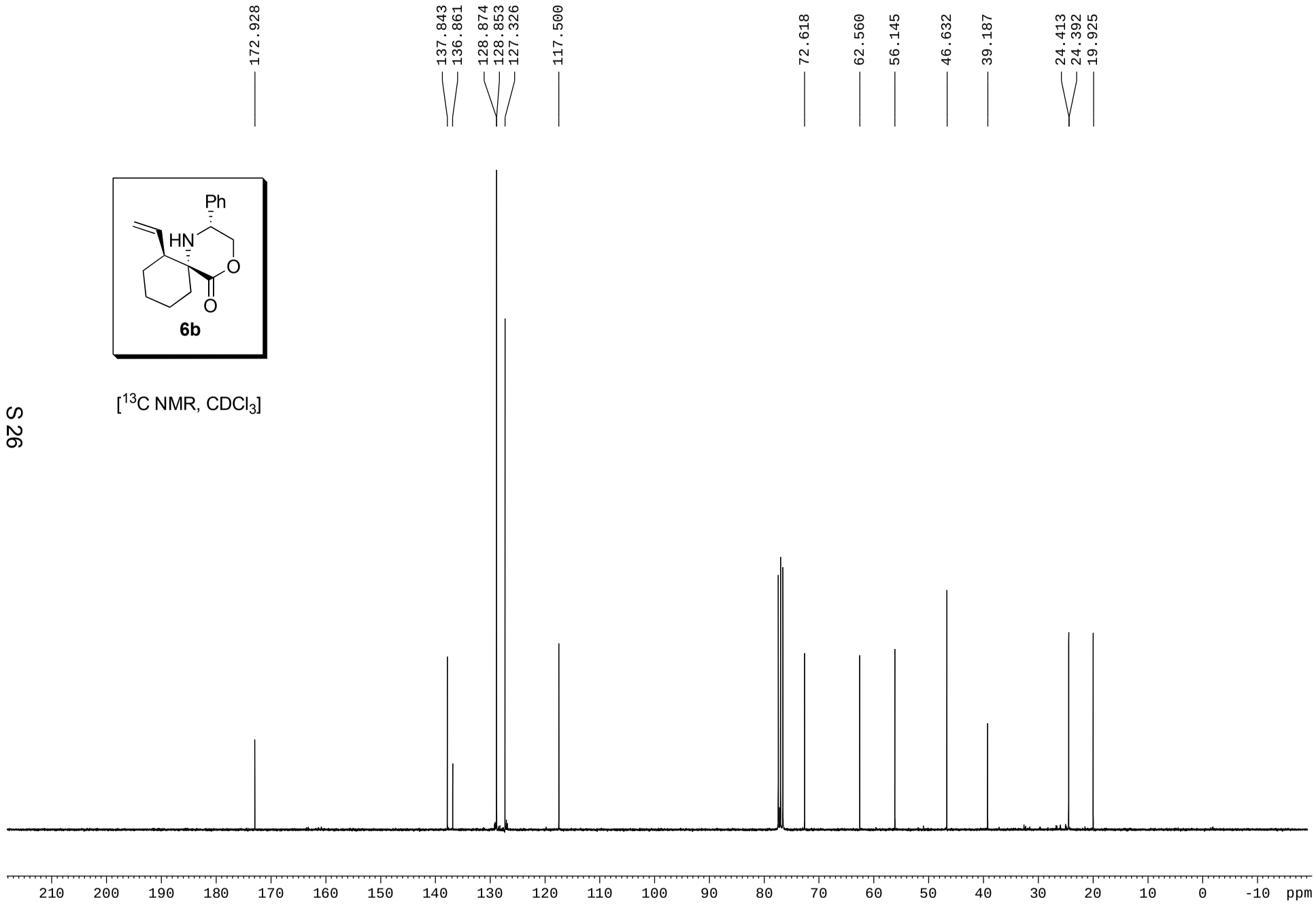

171.272
139.607
138.078
128.463
128.023
126.645
116.235
74.157
69.762
59.582
52.610
40.889
33.063
23.237
Ph
HN
O
O
6a
[13C NMR, CDCl3]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

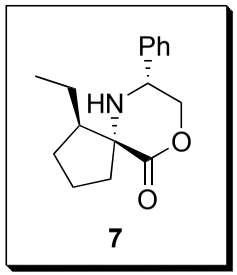


6b

[^{1}H NMR, $CDCl_3$]

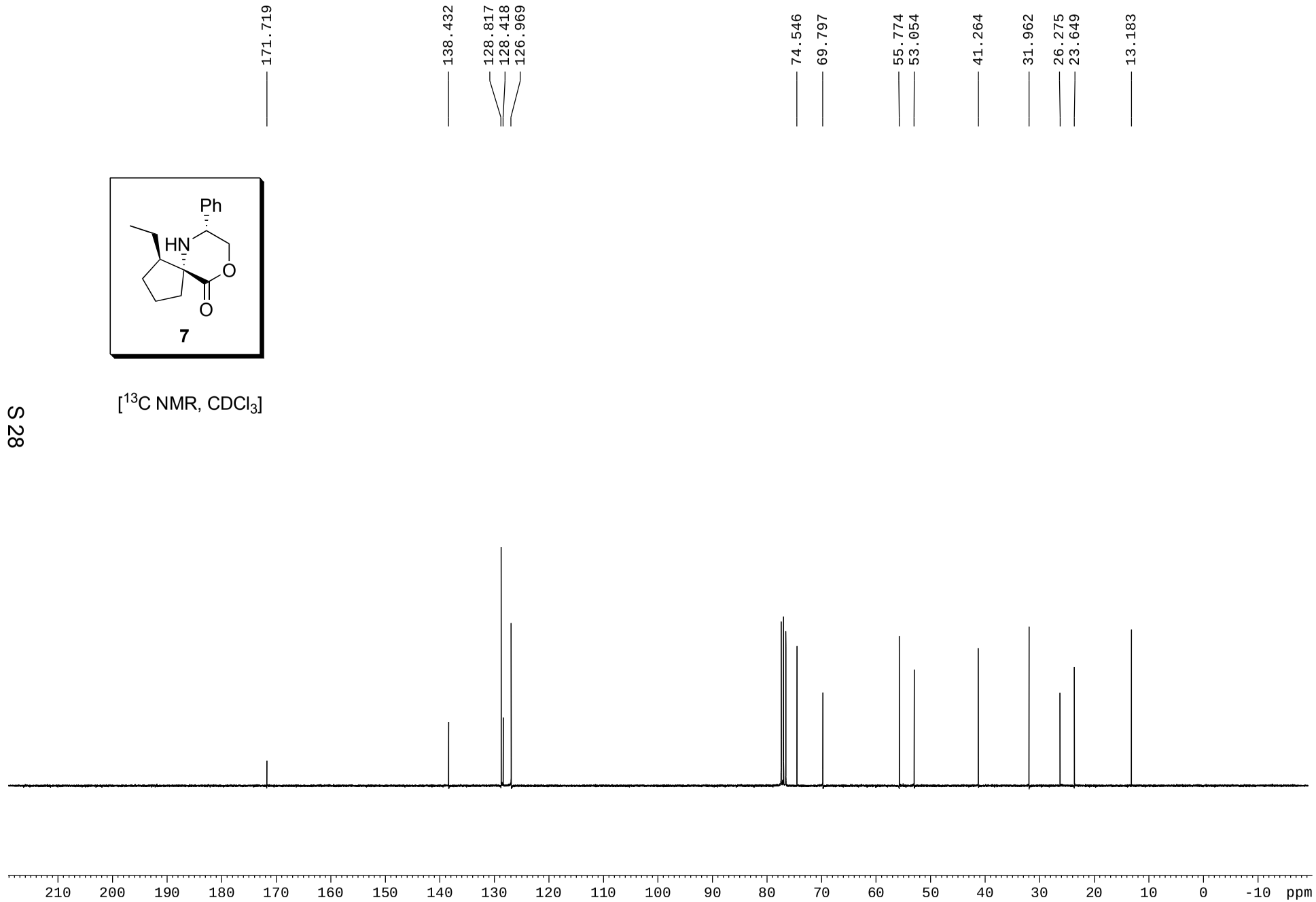


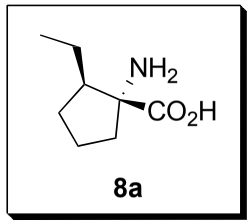

172.928
137.843
136.861
128.874
128.853
127.326
117.500
72.618
62.560
56.145
46.632
39.187
24.413
24.392
19.925
Ph
HN
O
O
6b
[13C NMR, CDCl3]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm



7

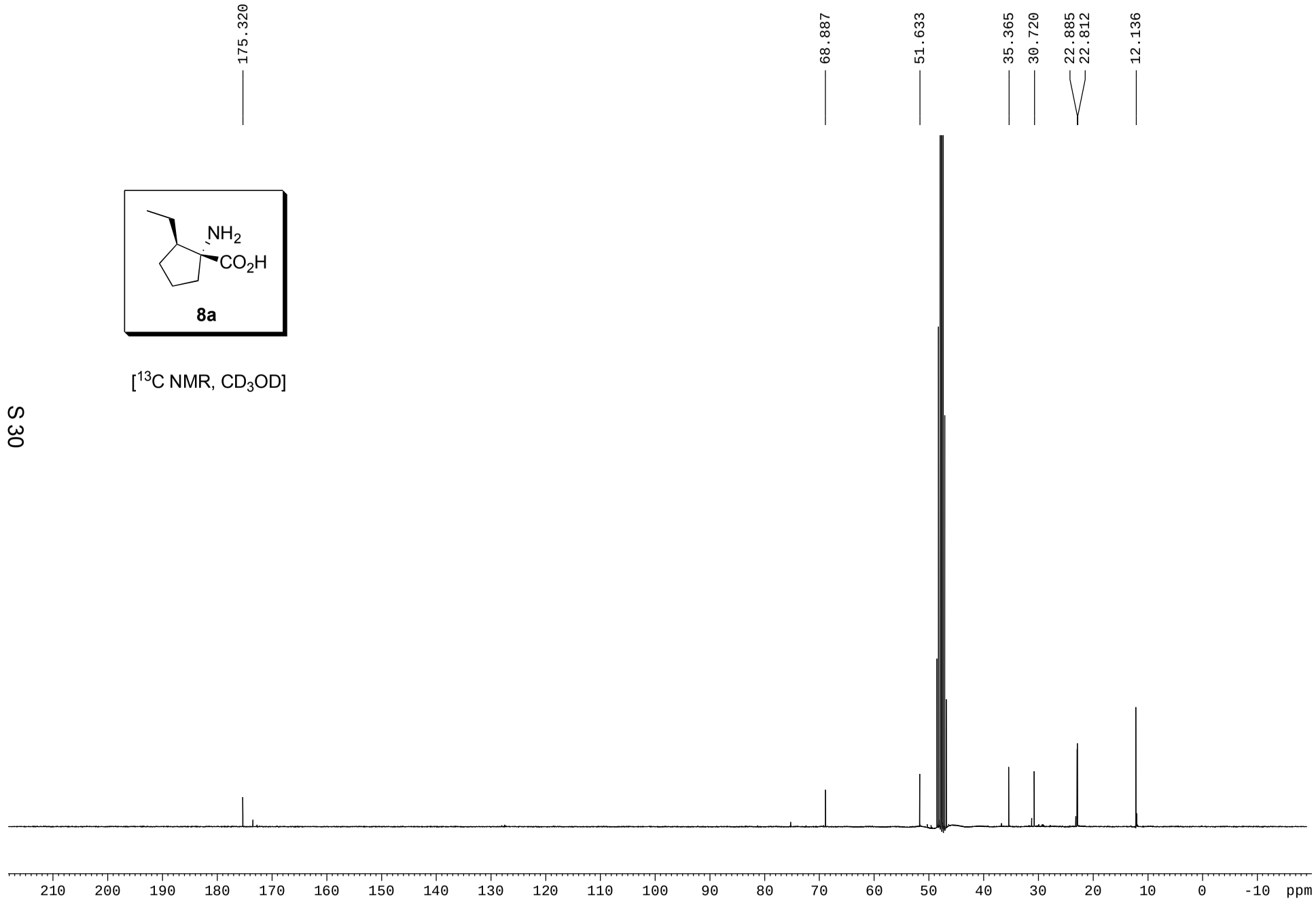
[^{1}H NMR, $CDCl_3$]

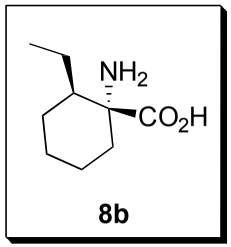

171.719
138.432
128.817
128.418
126.969
74.546
69.797
55.774
53.054
41.264
31.962
26.275
23.649
13.183
Ph
HN
O
O
7
[13C NMR, CDCl3]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm



8a

[^{1}H NMR, CD_3OD]

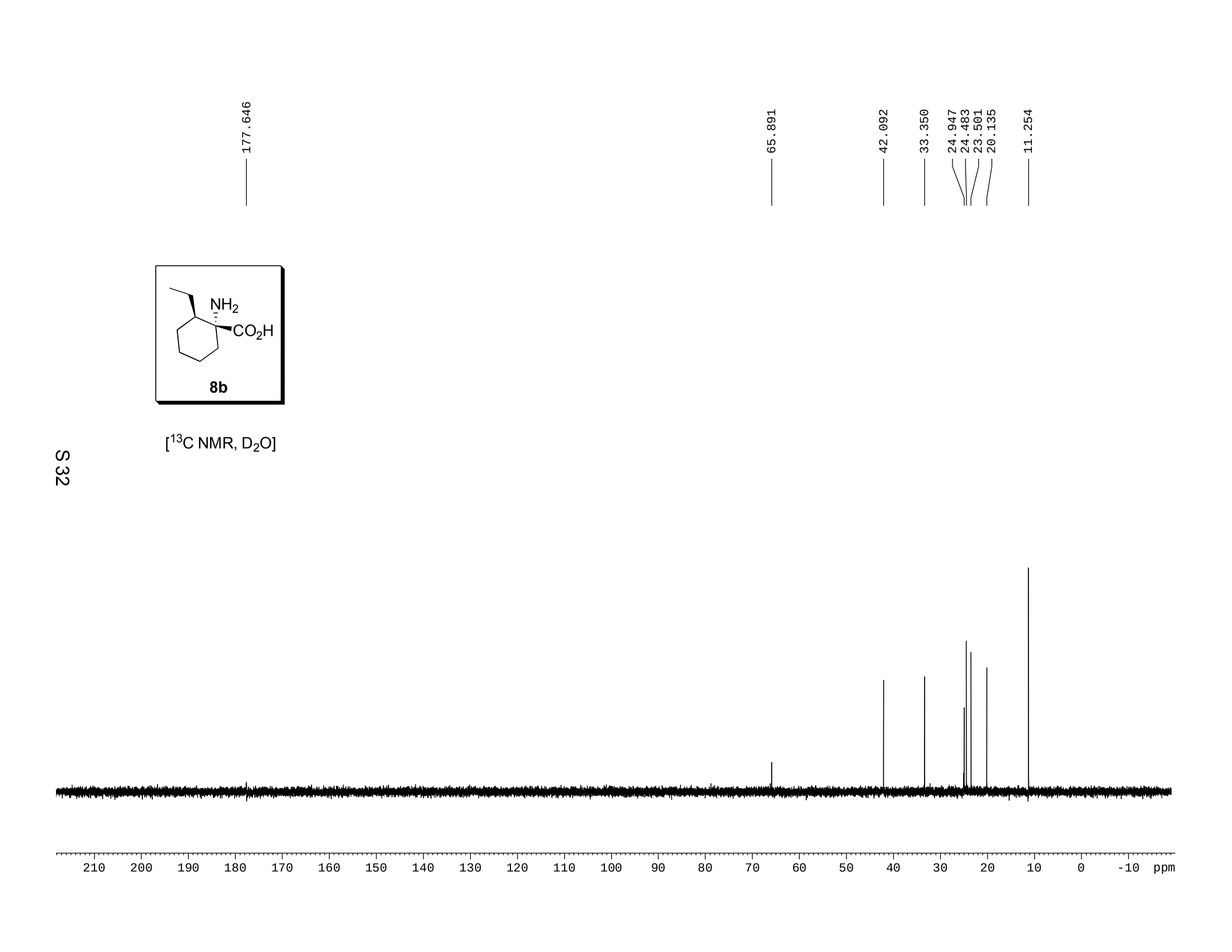

175.320
68.887
51.633
35.365
30.720
22.885
22.812
12.136
NH2
CO2H
8a
[13C NMR, CD3OD]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

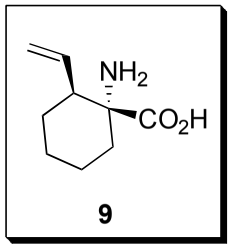

NH2
CO2H

8b

[^{1}H NMR, D_2O]

5.713
1.322
3.067
2.001
3.000
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

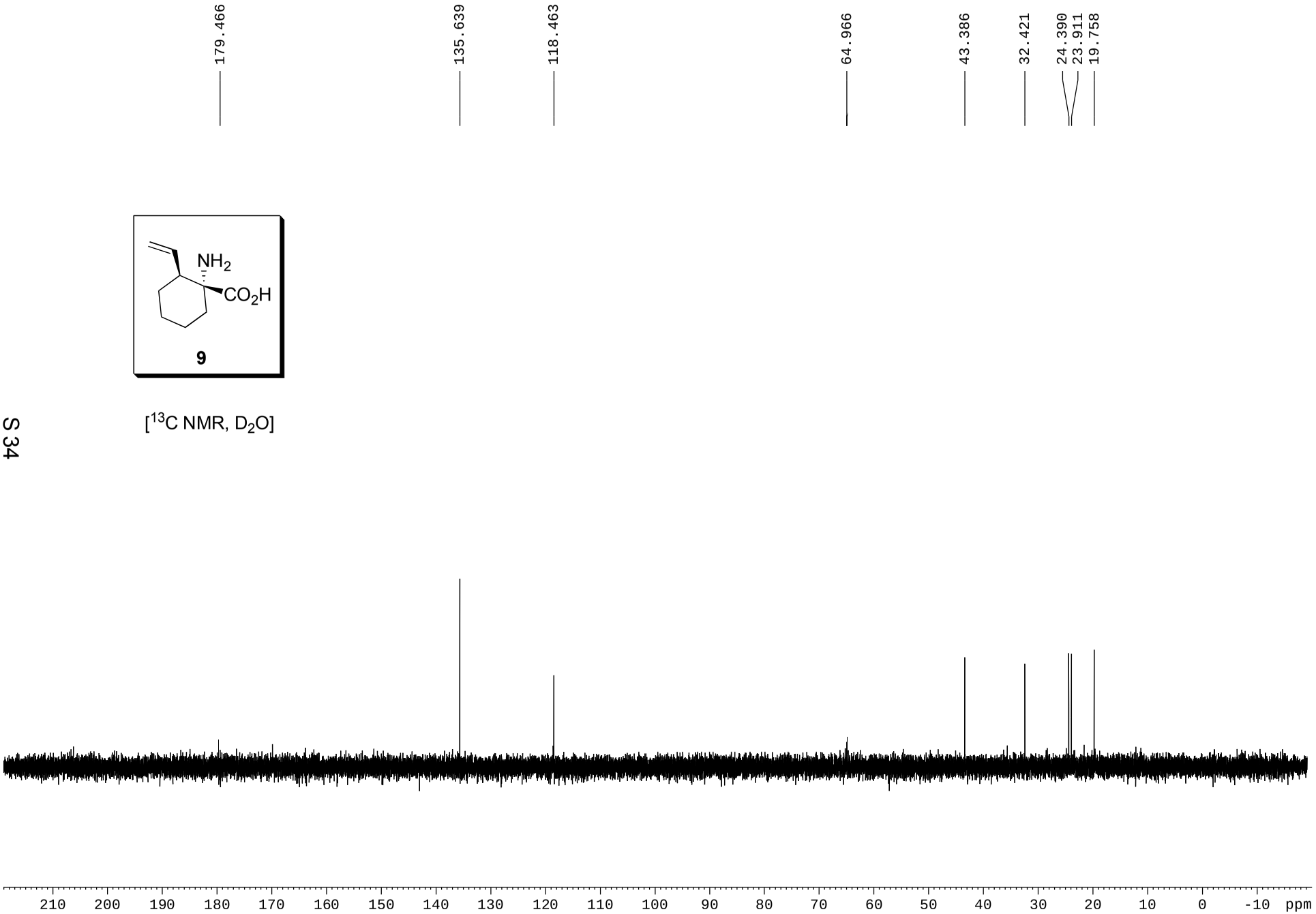

177.646
65.891
42.092
33.350
24.947
24.483
23.501
20.135
11.254
NH2
CO2H
8b
[13C NMR, D2O]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

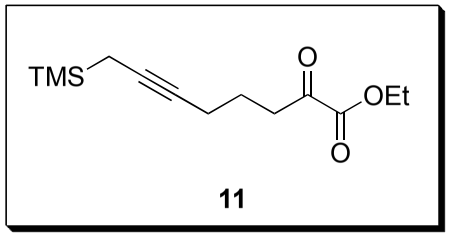

NH2
CO2H

9

[^{1}H NMR, D_2O]

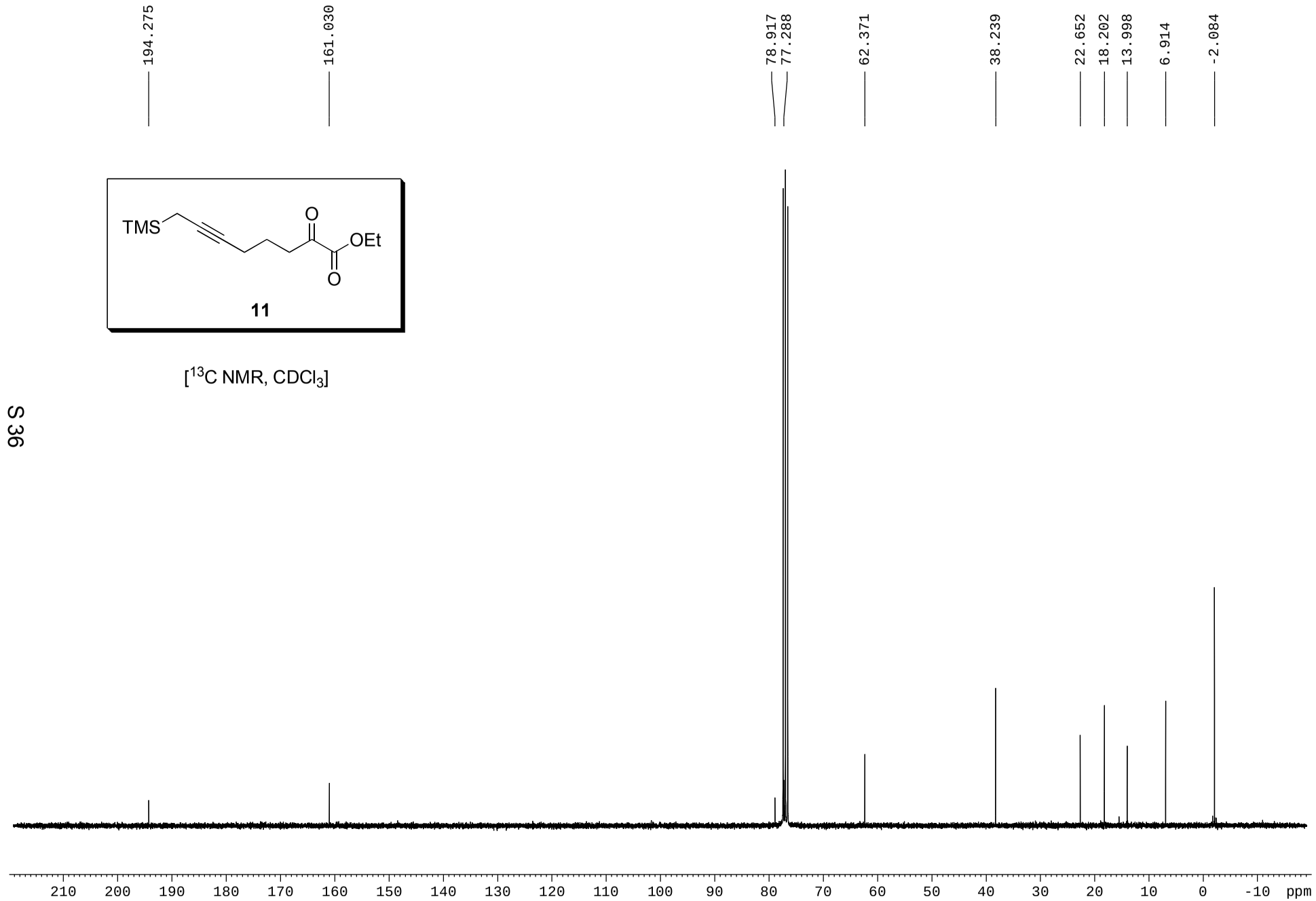
1.000
2.063
0.900
2.023
3.605
3.007
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

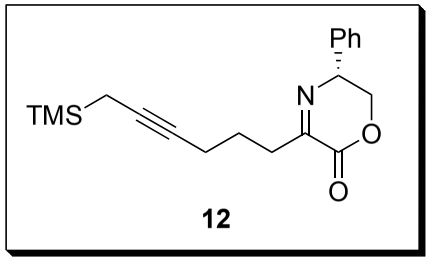

179.466
135.639
118.463
64.966
43.386
32.421
24.390
23.911
19.758
NH2
CO2H
9
[13C NMR, D2O]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm



11

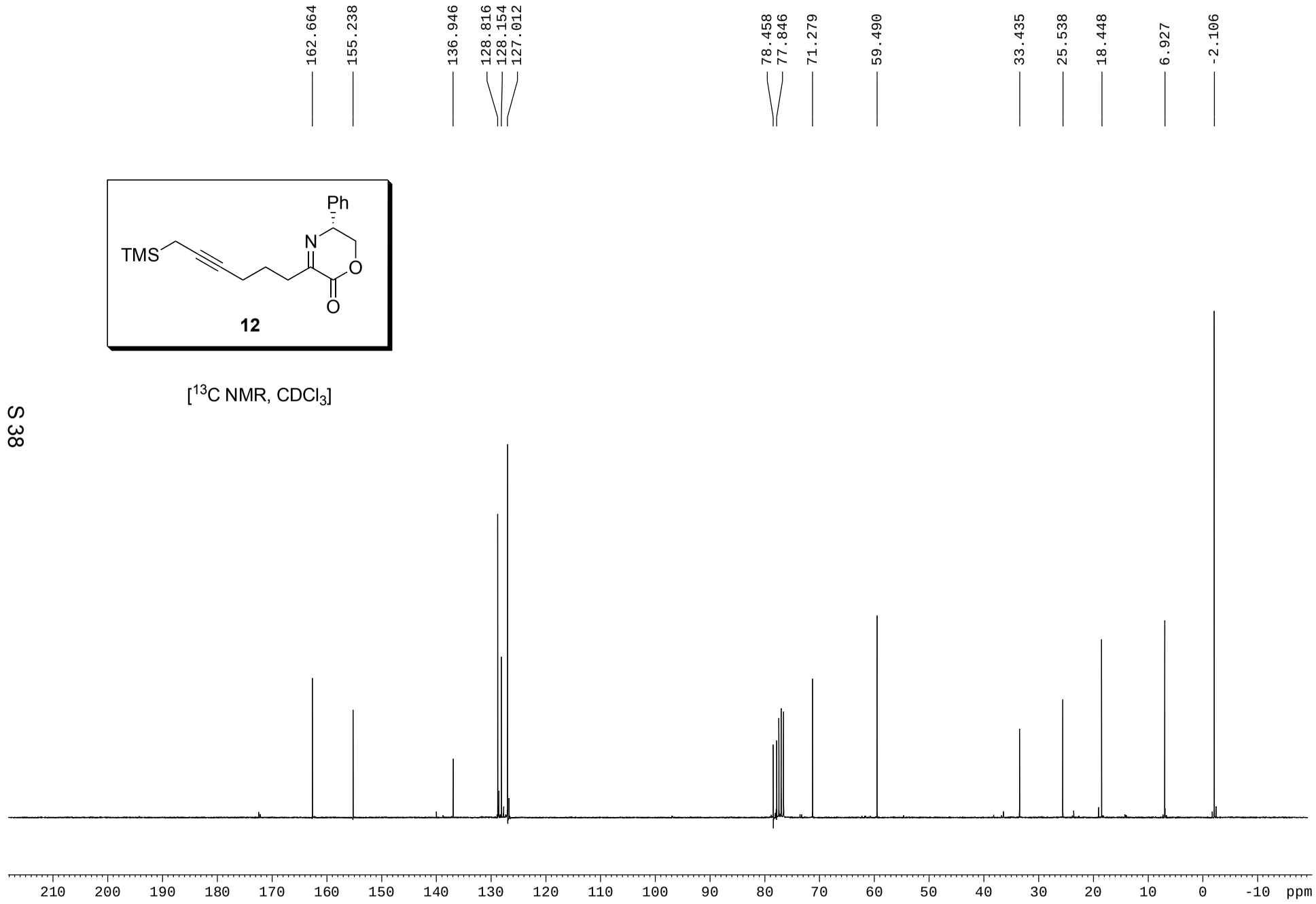
[^{1}H NMR, $CDCl_3$]

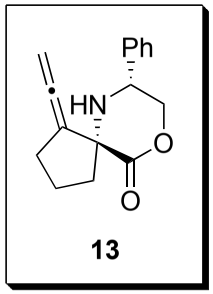

194.275
161.030
78.917
77.288
62.371
38.239
22.652
18.202
13.998
6.914
-2.084
TMS
O
OEt
O
11
[13C NMR, CDCl3]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm



12

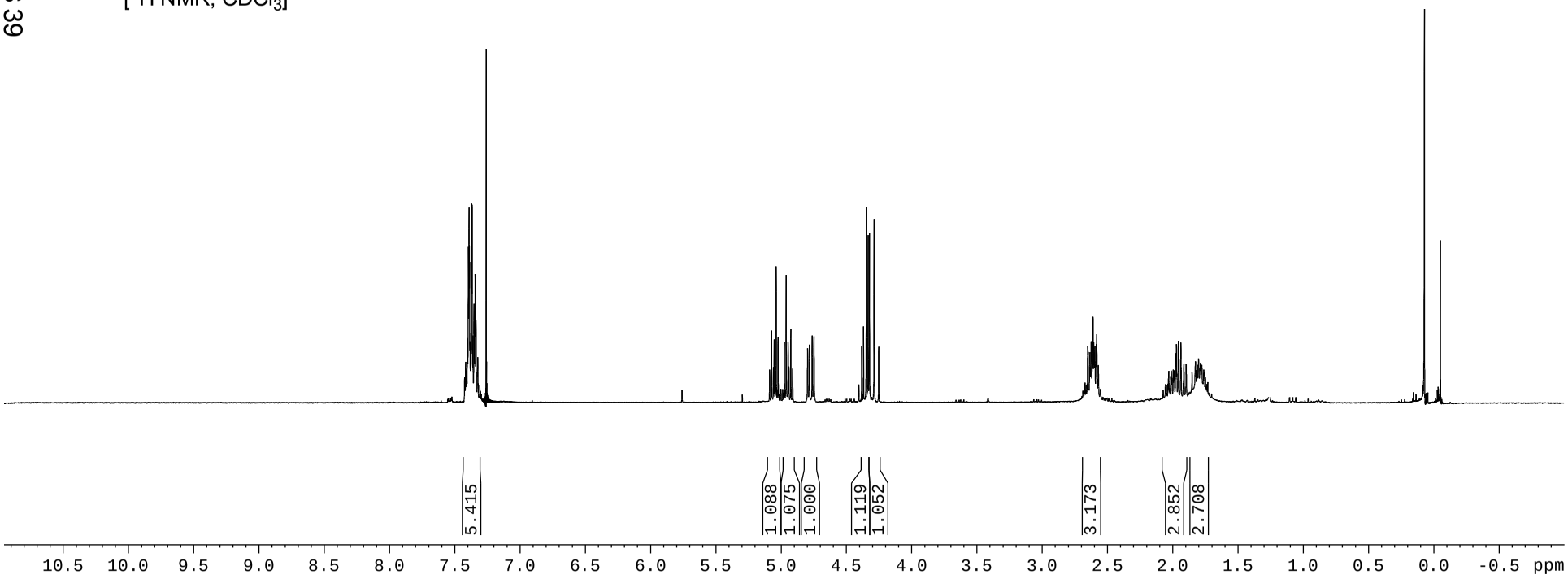
[^{1}H NMR, $CDCl_3$]

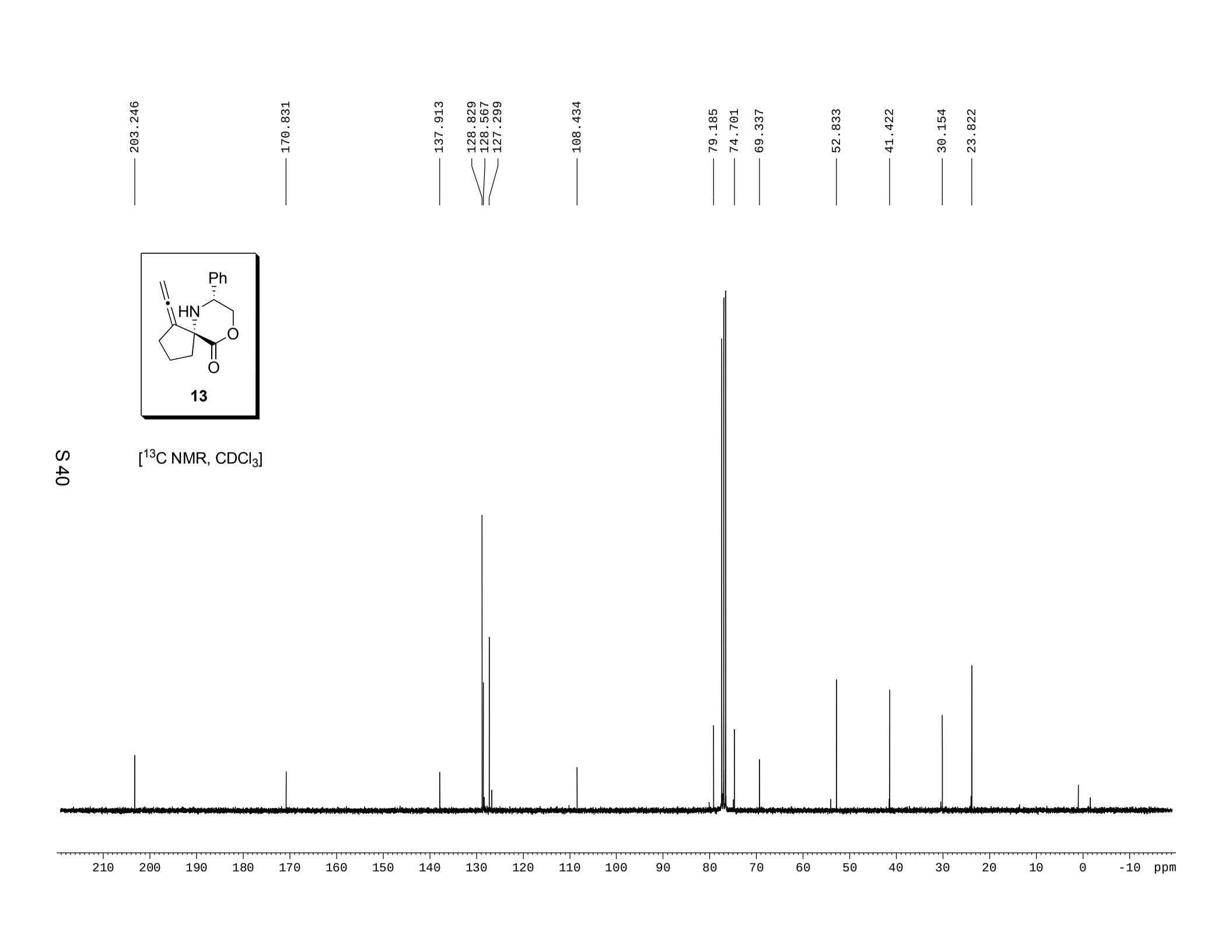

162.664
155.238
136.946
128.816
128.154
127.012
78.458
77.846
71.279
59.490
33.435
25.538
18.448
6.927
-2.106
Ph
N
O
O
TMS
12
[13C NMR, CDCl3]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

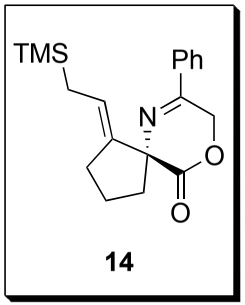


13

[^{1}H NMR, $CDCl_3$]

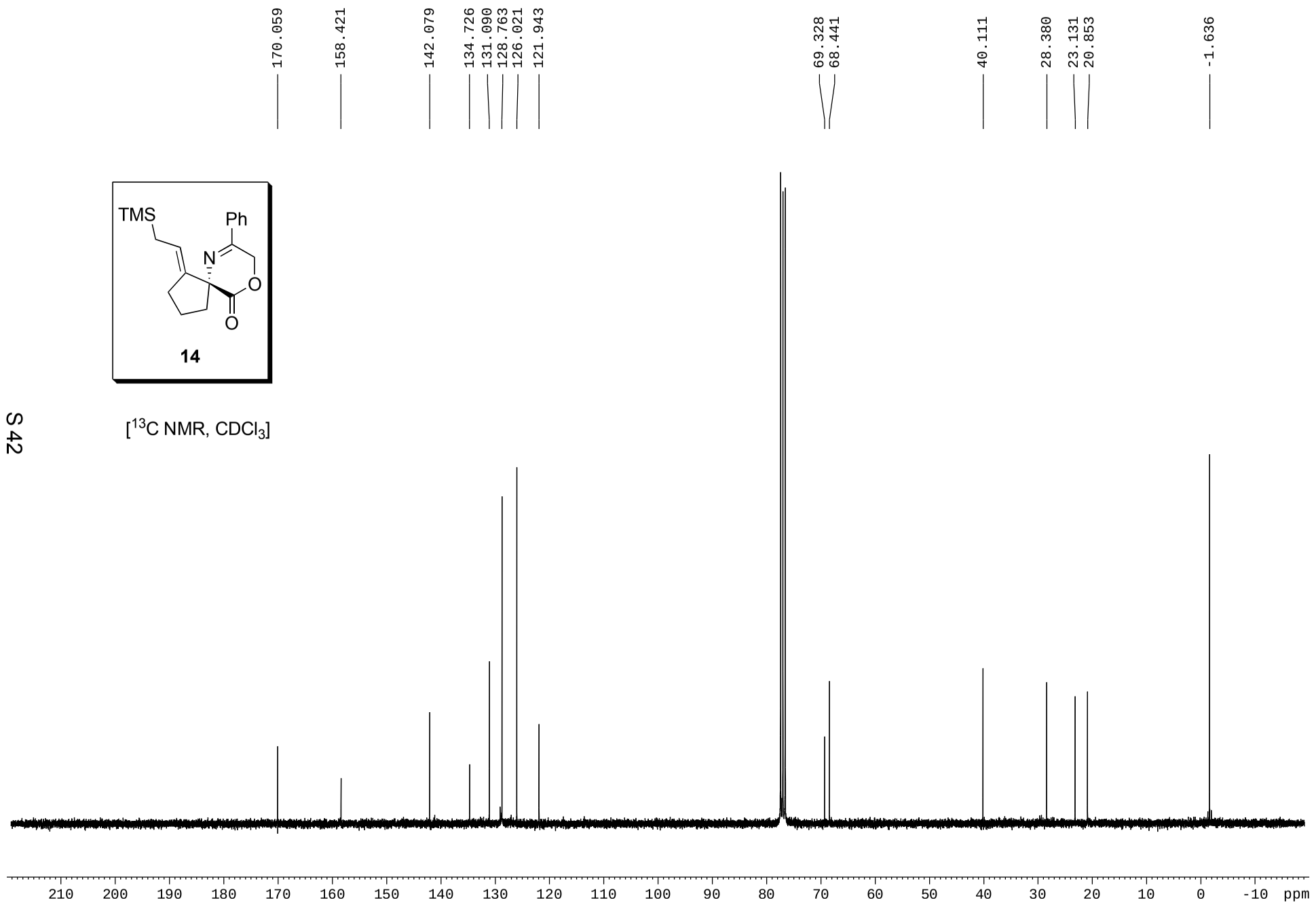


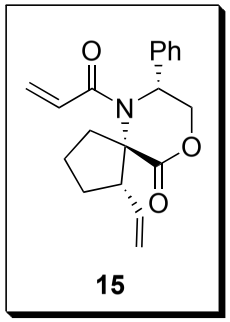

203.246
170.831
137.913
128.829
128.567
127.299
108.434
79.185
74.701
69.337
52.833
41.422
30.154
23.822
Ph
HN
O
O
13
[13C NMR, CDCl3]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm



14

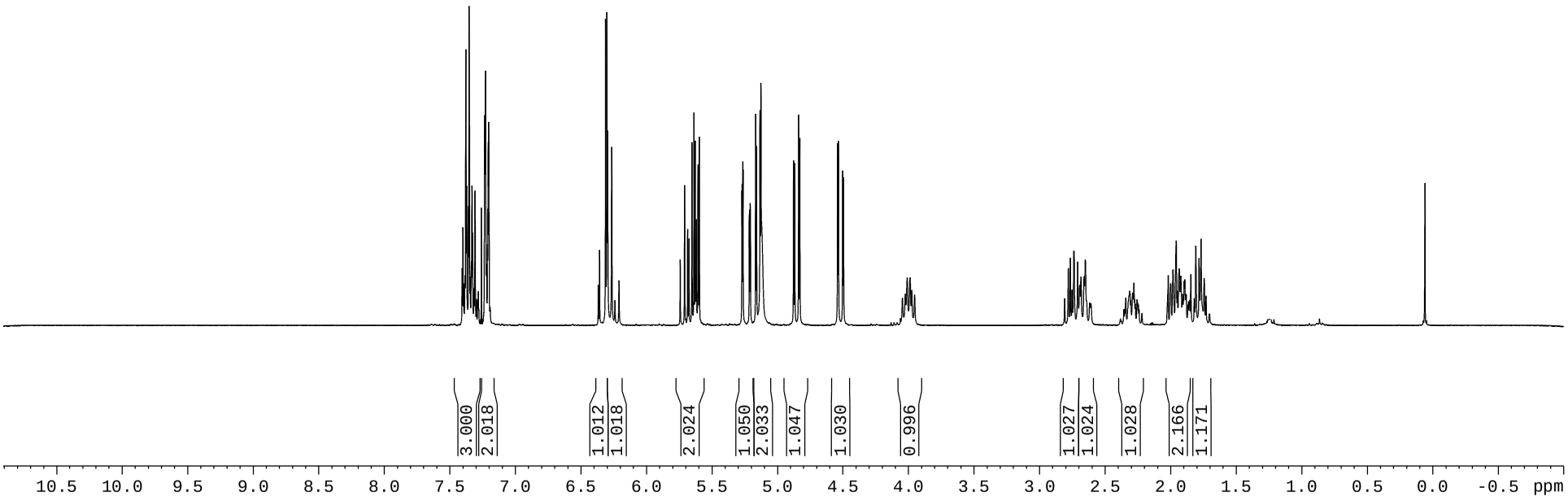
[^{1}H NMR, $CDCl_3$]

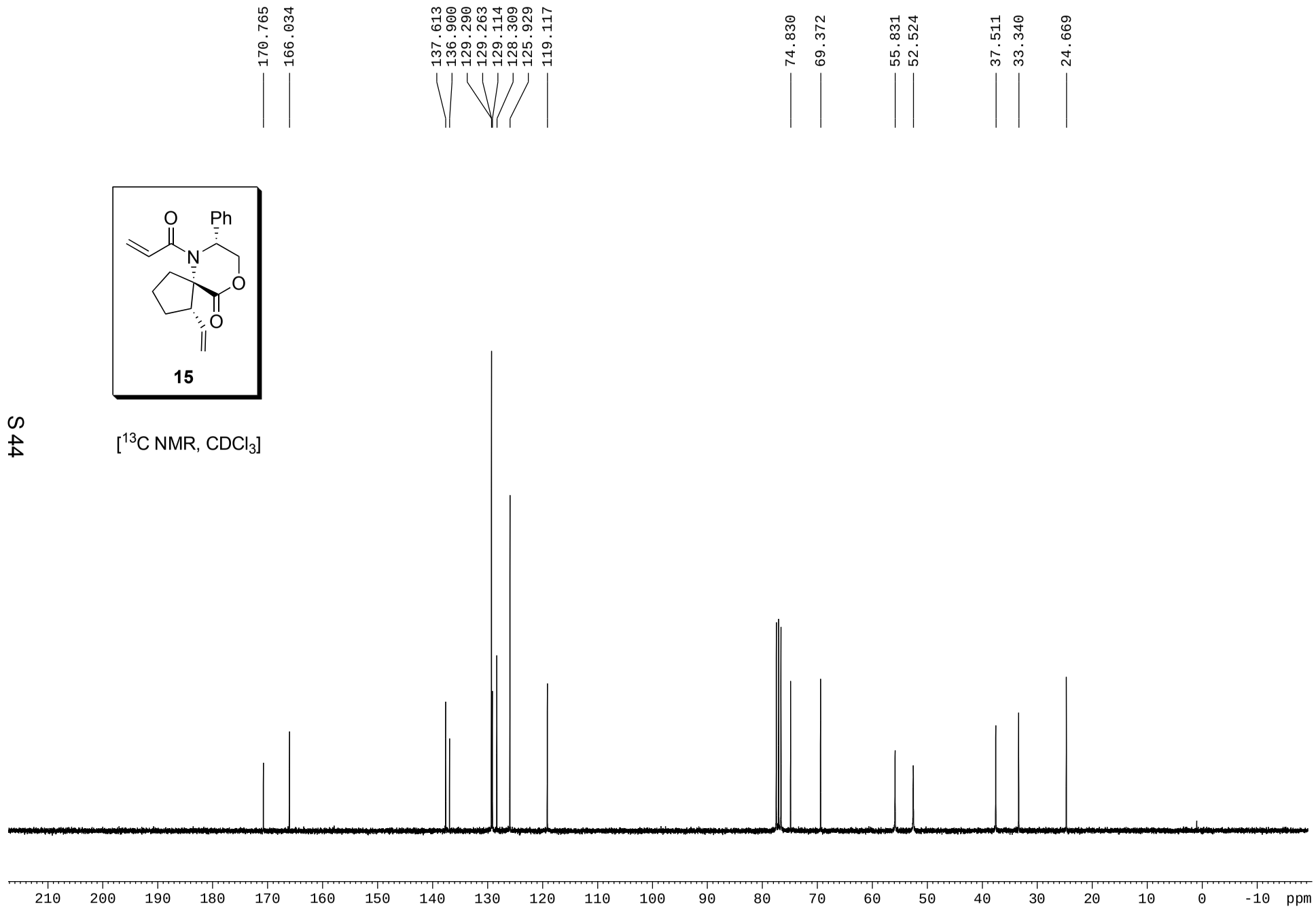

170.059
158.421
142.079
134.726
131.090
128.763
126.021
121.943
69.328
68.441
40.111
28.380
23.131
20.853
-1.636
TMS
Ph
N
O
O
14
[13C NMR, CDCl3]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

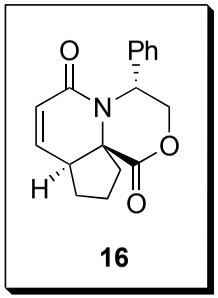


15

[^{1}H NMR, $CDCl_3$]

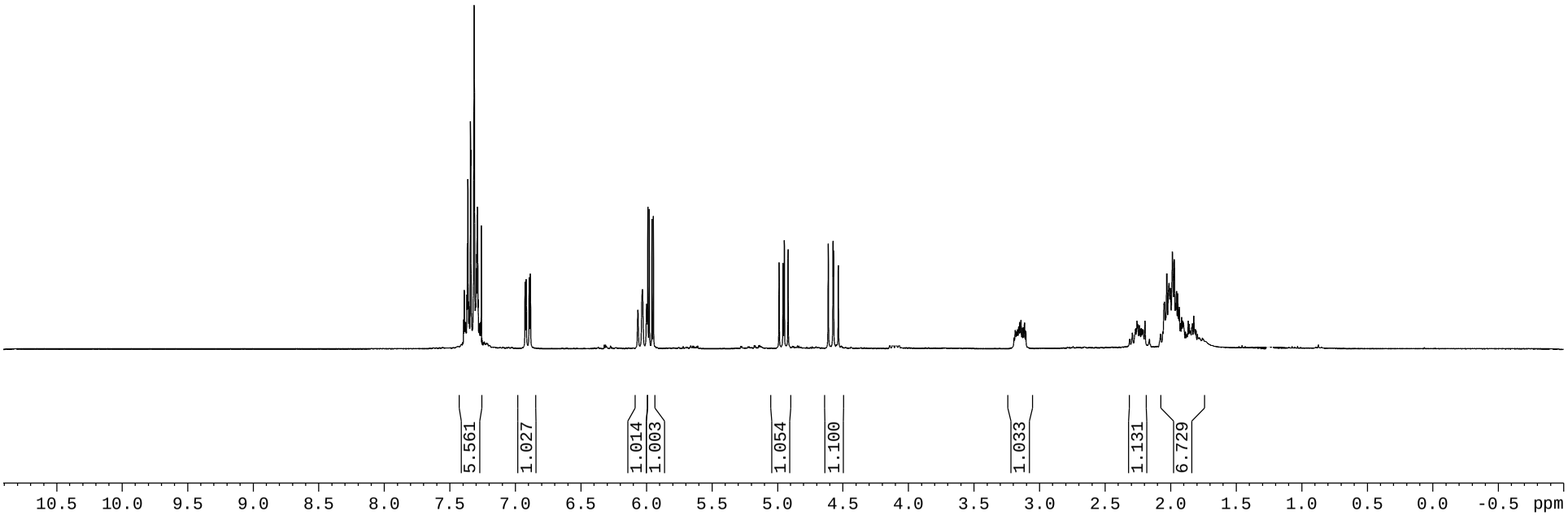



170.765
166.034
137.613
136.900
129.290
129.263
129.114
128.309
125.929
119.117
74.830
69.372
55.831
52.524
37.511
33.340
24.669
O
Ph
N
O
O
15
[13C NMR, CDCl3]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

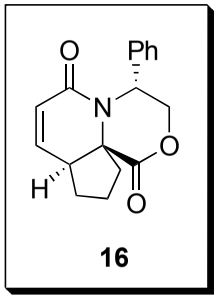


16

[^{1}H NMR, $CDCl_3$]

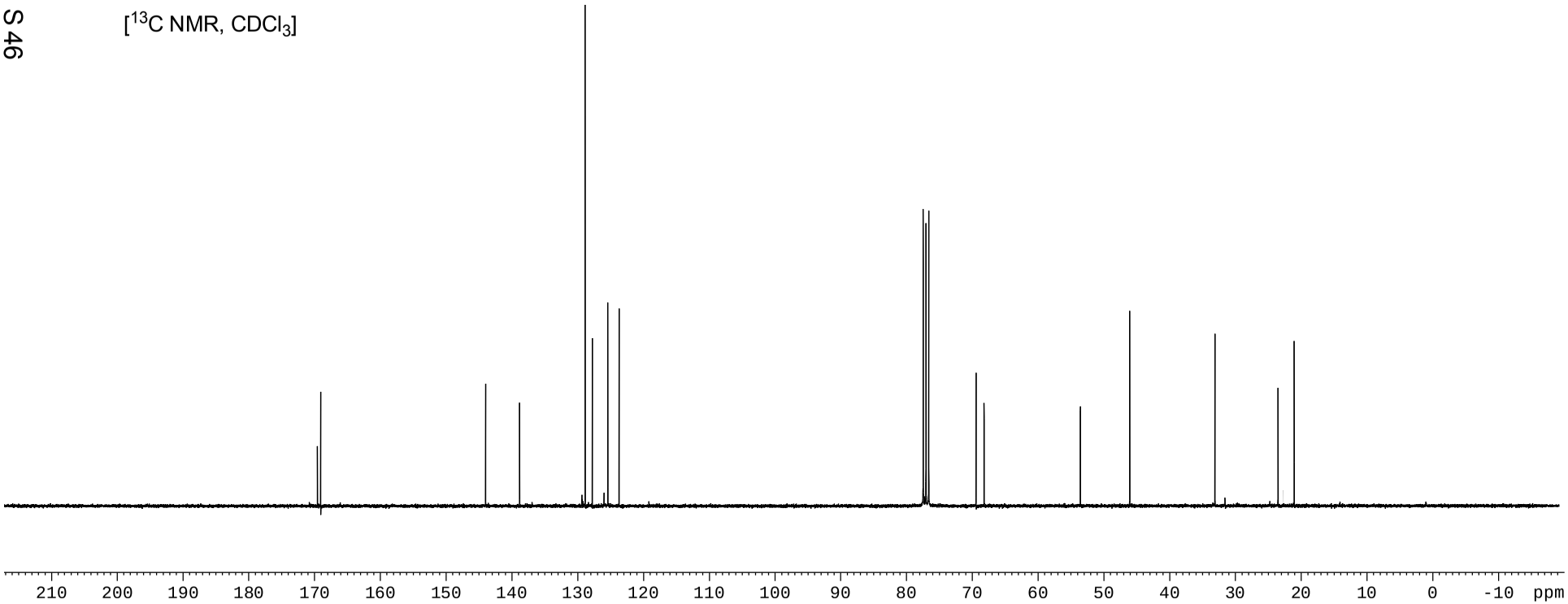


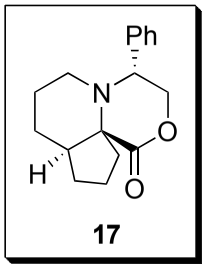
169.577
169.054
143.985
138.820
128.856
127.765
125.411
123.707
69.385
68.167
53.532
46.038
33.063
23.486
21.019



16

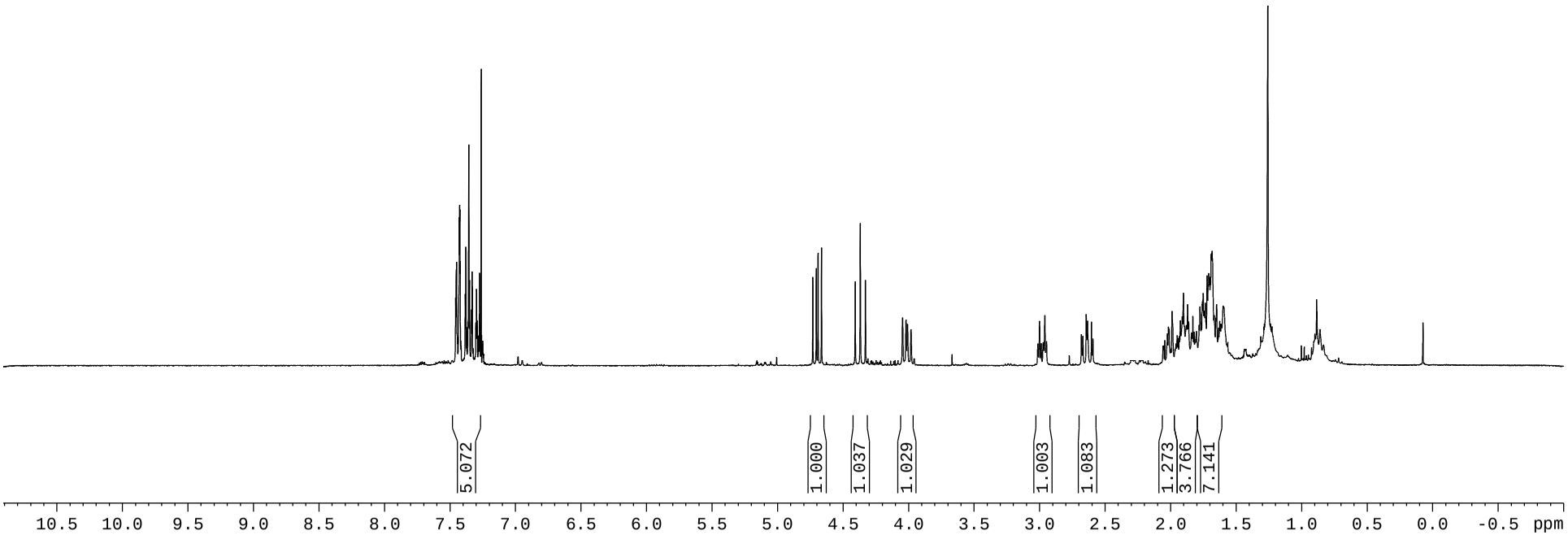
[^{13}C NMR, $CDCl_3$]

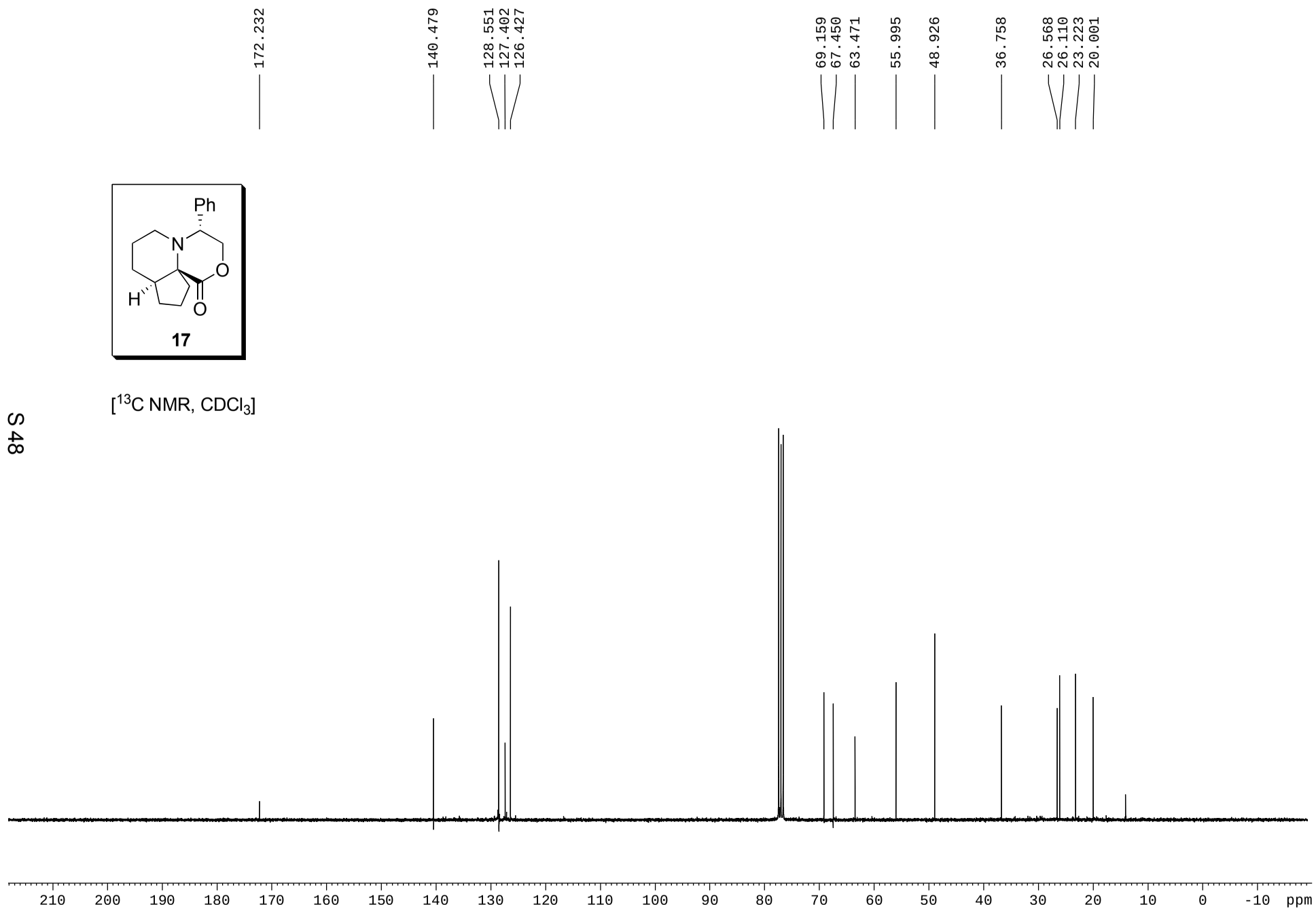


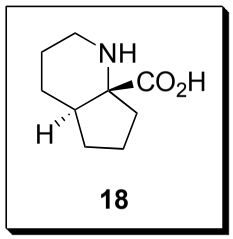


17

[^{1}H NMR, $CDCl_3$]



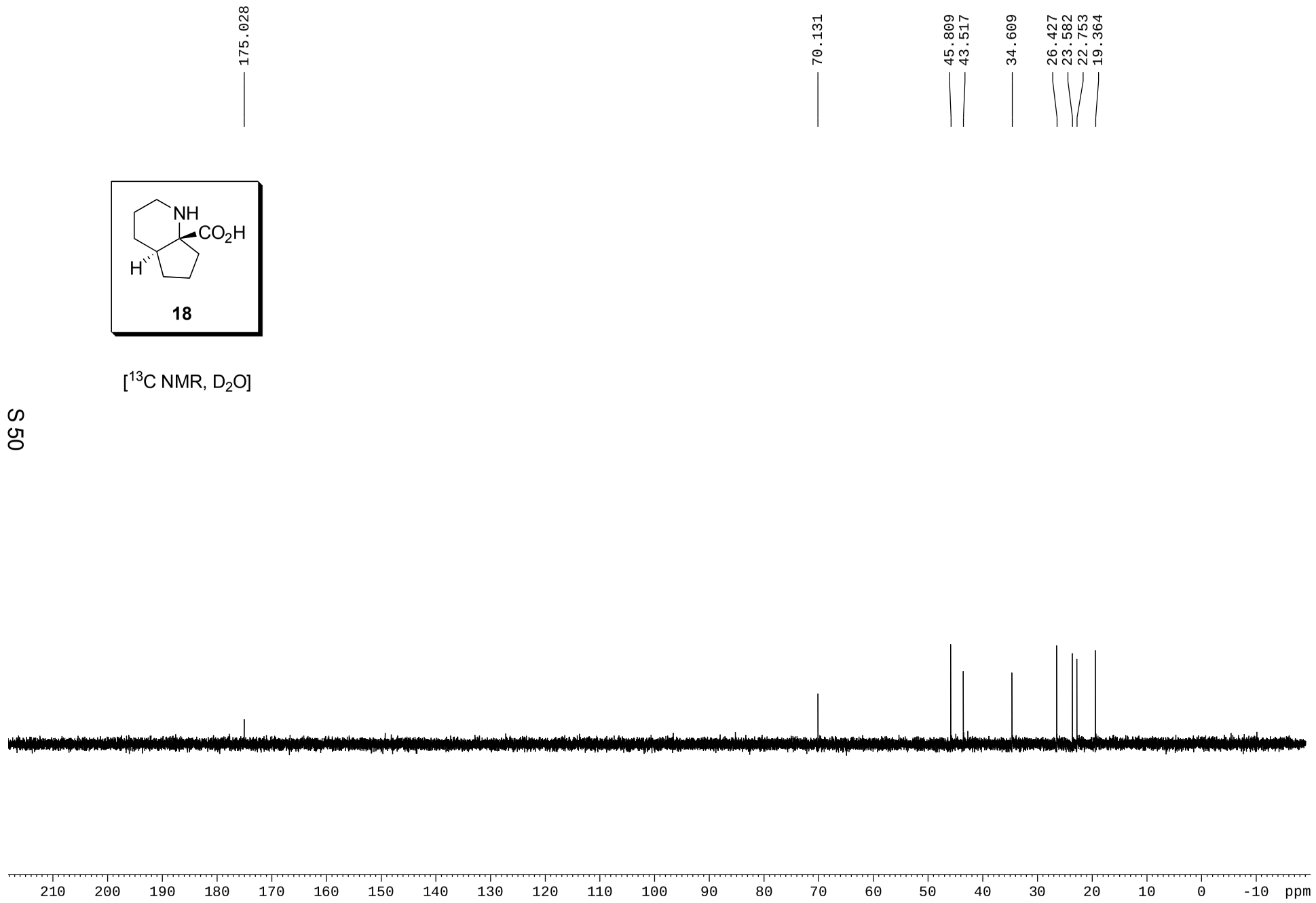

172.232
140.479
128.551
127.402
126.427
69.159
67.450
63.471
55.995
48.926
36.758
26.568
26.110
23.223
20.001
Ph
N
O
H
O
17
[13C NMR, CDCl3]
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

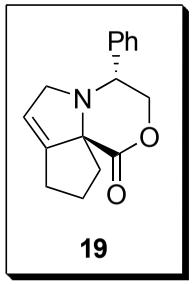

NH
CO2H
H

18

[^{1}H NMR, D_2O]

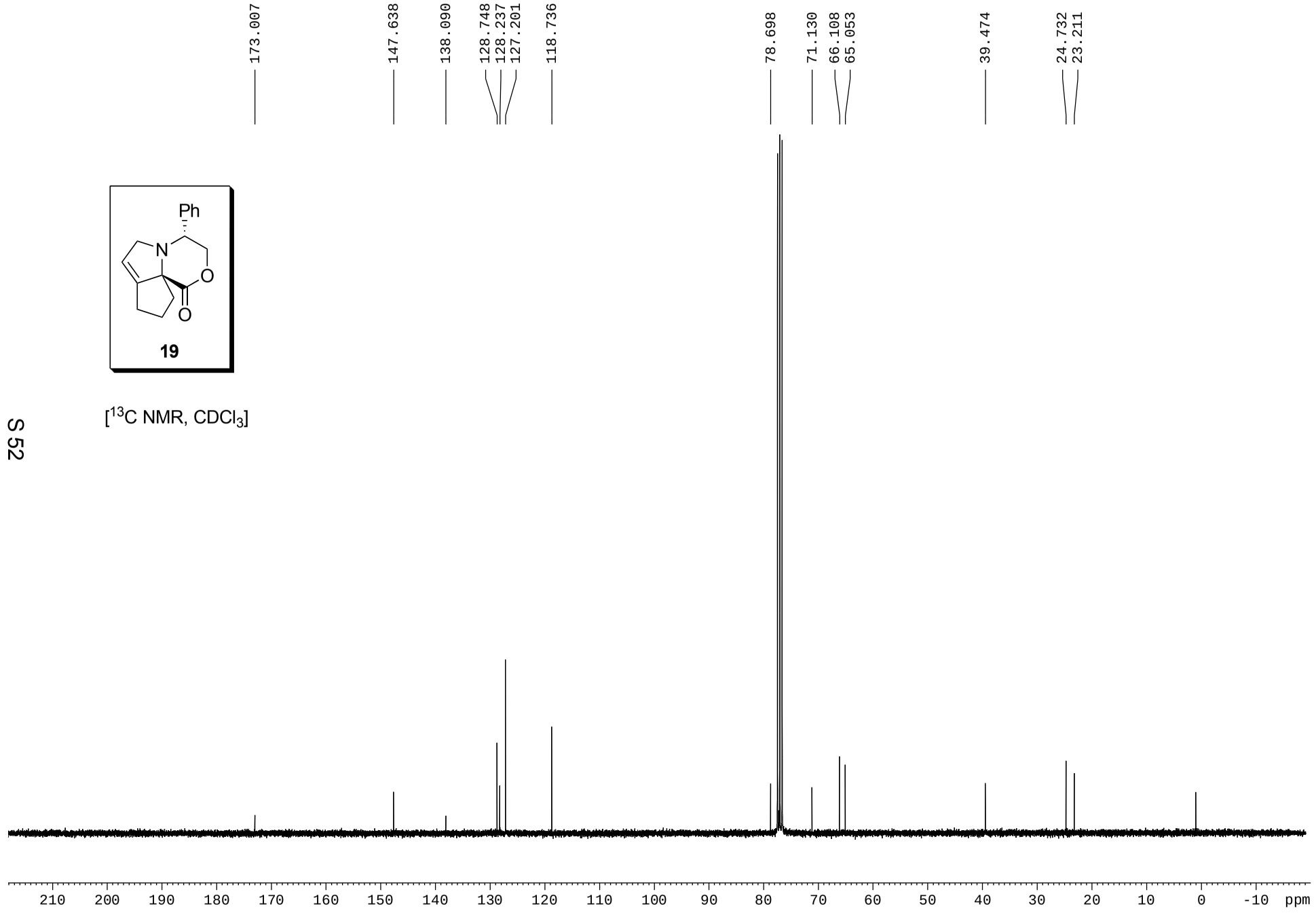
0.994
1.000
1.046
8.481
2.216
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

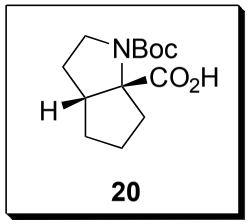

175.028
70.131
45.809
43.517
34.609
26.427
23.582
22.753
19.364
NH
CO2H
H
18
[13C NMR, D2O]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm



19

[^{1}H NMR, $CDCl_3$]

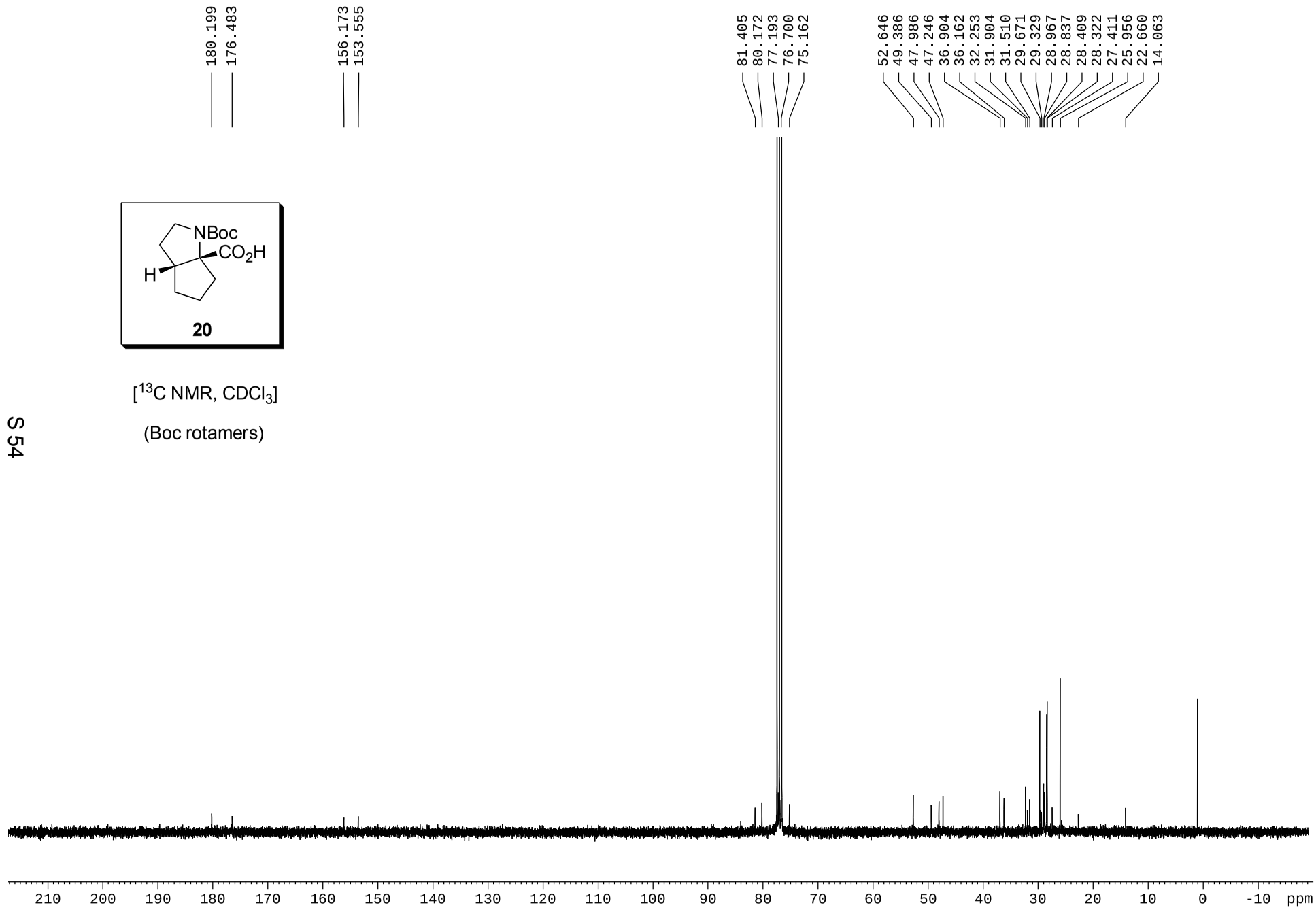

173.007
147.638
138.090
128.748
128.237
127.201
118.736
78.698
71.130
66.108
65.053
39.474
24.732
23.211
Ph
N
O
O
19
[13C NMR, CDCl3]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm



20

[^{1}H NMR, $CDCl_3$]

(Boc rotamers)


180.199
176.483
156.173
153.555
81.405
80.172
77.193
76.700
75.162
52.646
49.386
47.986
47.246
36.904
36.162
32.253
31.904
31.510
29.671
29.329
28.967
28.837
28.409
28.322
27.411
25.956
22.660
14.063
NBoc
CO2H
H
20
[13C NMR, CDCl3]
(Boc rotamers)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm