Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information for

Preparation of novel bicyclo[2.1.1]hexanes: an opening towards new chemical space

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1) General information

All reactions were performed with oven-dried glassware and under an inert atmosphere (nitrogen) unless otherwise stated. All solvents were used as purchased unless otherwise stated. Commercial reagents were used as purchased without further purification. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230–400 mesh) fluorescent treated silica and were visualized under UV light (250 and 354 nm) and/or by staining with aqueous potassium permanganate solution. Medium pressure liquid chromatography (MPLC) was performed on a Biotage Isolera Four with built-in UV-detector and fraction collector with Agela technologies silica gel columns.

^{1}H NMR spectra were recorded in deuterated solvents on Bruker spectrometer at 400 MHz or 300 MHz Nanalysis NMReady-60PRO spectrometer at 60 MHz, with residual protic solvent as the internal standard. ^{13}C NMR spectra were recorded in deuterated solvents on Bruker spectrometer at 100 MHz or 75 MHz, with the central peak of the deuterated solvent as the internal standard. The ^{1}H NMR spectra are reported as δ/ppm downfield from tetramethylsilane (multiplicity, number of protons, coupling constant J/Hz). The ^{13}C NMR spectra are reported as δ/ppm. Data are reported as follows : s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, coupling constants *J* in Hz.

Mass spectra by ESI-MS were recorded on *Shimadzu LCMS-2020*, coupled with *Shimadzu LC-2040C.* TLC–MS data was obtained on Advion Expression CMS coupled with Plate Express TLC-plate Reader (APCI method).

High Intensity Photoreactors were custom designed and built in coordination with the mechanical workshop in the Department of Chemistry and Biosciences at ETH Zürich having blue LEDs, equally spaced in a circle design, powered by a 10.3 A power supply, emitting 350 W of light. The LEDs were water cooled and further cooled by built-in fans to maintain an ambient temperature.

Photochemistry reactions using 365 nm LEDs were performed in a EvoluChem PhotoRedOx Box.

2) General procedures

2.1) General procedure A: Methylenation of phenylacetaldehydes derivatives

To a solution of phenylacetaldehydes **4a-f** (1 equiv) and Et_3N (10 equiv.) and CH_2Cl_2 (0.15 molar), Eschenmoser's salt (2.05 equiv.) was added in one portion. The resulting orange slurry, which turned into a yellowish solution after 10 minutes, was stirred at room temperature for 90 minutes. The reaction mixture was transferred to a separating funnel and was washed with saturated aqueous $NaHCO_3$ (twice) and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure (note: the temperature of the rotary evaporator bath should not exceed 20 °C to avoid polymerization) to afford 2-phenylacrylaldehyde **5a-d** yellow oils.

2.2) General procedure B: Allyl Grignard addition

To a solution of 2-phenylacrylaldehyde **5a-d** (1.0 equiv.) in dry THF (0.30 molar) at 0°C was added allyl magnesium chloride (2.0 equiv.2.0 M in THF) and the reaction was stirred 1h in an ice bath. The reaction was quenched with a sat. aq. sol. of NH_4Cl and the aqueous phase was extracted with Ethyl Acetate thrice. The combined organics layers were washed with brine, dried on Na_2SO_4 , filtered, and evaporated under reduced. The crude was purified by flash chromatography (Cyclohexane: ethyl acetate 90:10) to yield alcohols **6a-d** as white solids.

2.3) General procedure C: DMP Oxidation of secondary alcohols

To a solution of alcohols **6a-d** (1.0 equiv.) in dry CH_2Cl_2 (0.10 molar), DMP (1.5 equiv.) was added in one portion and it was stirred for 1 hour at room temperature. The reaction mixture was quenched with a 1:1 mixture of sat. aq. solutions of. $NaHCO_3$ $Na_2S_2O_3$ and the resulting biphasic mixture was left stirring for 15 min before it was transferred into a separating funnel. The aqueous layer was extracted with CH_2Cl_2 (thrice) and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield ketones **7a-d.** The crude products were taken to the next step without further purification.

2.4) General procedure D: [2+2] cycloaddition with Iridium / Blue LEDs

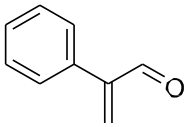
Ketones **7a-d** (1.0 equiv.)were dissolved in dry CH_3CN (0.075 molar) and to the solution was added $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (2 mol %) and the mixture was degassed with nitrogen for 5 minutes before being irradiated with blue LEDs in a photoreactor (400W). After 4 hours of stirring, the volatiles were evaporated under reduced pressure and the crude was was purified by flash chromatography (Cyclohexane : ethyl acetate 90:10) to yield white solids for bicyclo[2.1.1]hexanes **8a-d**.

2.5) General procedure E: Ketone reduction to secondary alcohols

Ketone **8a-d** (1.0 equiv.) were dissolved in anhydrous Methanol (0.10 molar) under nitrogen. The mixture was cooled to 0 °C with an ice bath and $NaBH_4$ (2.0 equiv.) was added in portions to the stirring solution. The mixture was allowed to warm to room temperature overnight and upon completion of the reaction, the volatiles were evaporated under reduced pressure. To the residue was added water

and ethyl acetate and the two layers were separated. The aqueous was washed with ethyl acetate (thrice). The combined organics were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The pure alcohols **9a-d** were isolated without further purification.

3) Procedures and characterization

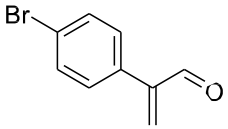


5a

2-phenylacrylaldehyde (5a): according to general procedure A with phenylacetaldehyde **4a** (10 g, 85 mmol), Et_3N (xx mL, 850 mmol), Eschenmoser's salt (32 g, 180 mmol) and dry CH_2Cl_2 (570 mL), 2-phenylacrylaldehyde **5a** (13.0g, quant., 90 % purity) was obtained as an oil. Analytical data matched the literature. [1]

Link for ^{1H} NMR Spectra of **5a**

LRMS (APCI) m/z (C_9H_8O): theor. for $[M+H]^+$ 133.06, exp. 133.2



5b

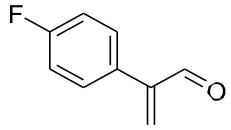
2-(4-bromophenyl)acrylaldehyde (5b): according to general procedure A with 2-(4-bromophenyl)acetaldehyde **4b** (1.20 g, 6 mmol), Et_3N (8.4 mL, 60 mmol), Eschenmoser's salt (2.3 g, 12.0 mmol) and dry CH_2Cl_2 (40 mL), 2-(4-bromophenyl)acrylaldehyde **5b** (1.2 g, 94 %., 92% purity) was obtained as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.56 – 7.49 (m, 2H), 7.39 – 7.30 (m, 2H), 6.65 (s, 1H), 6.21 (s, 1H).

Link for ^{1H} NMR Spectra of **5b**

LRMS (APCI) m/z (C_9H_7BrO): theor. for $[M+H]^+$ 210.97, exp.211.1

[1] J. Choi, H. Park, H. J. Yoo, S. Kim, E. J. Sorensen and C. Lee, *Journal of the American Chemical Society*, 2014, **136**, 9918-9921.



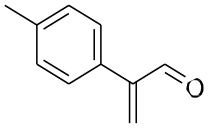
5c

2-(4-fluorophenyl)acrylaldehyde (5c): according to general procedure A with 2-(4-fluorophenyl)acetaldehyde **4c** (1.20 g, 8.7 mmol), Et_3N (12 mL, 87 mmol), Eschenmoser's salt (3.3 g, 18.0 mmol) and dry CH_2Cl_2 (60 mL), 2-(4-fluorophenyl)acrylaldehyde **5c** (1.3 g, 93 %., 90% purity) was obtained as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.49 – 7.42 (m, 2H), 7.11 – 7.05 (m, 2H), 6.63 (s, 1H), 6.18 (s, 1H).

Link for ^{1H} NMR Spectra of **5c**

LRMS (APCI) m/z (C_9H_7FO): theor. for $[M+H]^+$ 151.15, exp.151.2



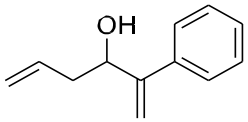
5d

2-(*p*-tolyl)acrylaldehyde (5d): according to general procedure A with 2-(p-tolyl)acetaldehyde **4d** (0.5 g, 3.7 mmol), Et_3N (5.2 mL, 37.3 mmol), Eschenmoser's salt (1.4 g, 7.6 mmol) and dry CH_2Cl_2 (30 mL), 2-(*p*-tolyl)acrylaldehyde **5d** (0.5 g, 95 %., 90% purity) was obtained as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.42 – 7.32 (m, 2H), 7.21 (dt, *J* = 7.9, 0.7 Hz, 2H), 6.61 (d, *J* = 0.7 Hz, 1H), 6.14 (d, *J* = 0.7 Hz, 1H), 2.37 (s, 3H).

Link for ^{1H} NMR Spectra of **5d**

LRMS (APCI) m/z ($C_{10}H_{10}O$): theor. for $[M+H]^+$ 147.19, exp.147.3



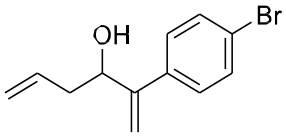
6a

2-phenylhexa-1,5-dien-3-ol (6a): Following general procedure B with 2-phenylacrylaldehyde **5a** (13.0 g, 89 mmol, 90 %), AllylMgCl (93 mL, 190 mmol) in THF (350 mL), 2-phenylhexa-1,5-dien-3-ol **6a** (8.2 g, 53 %) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 5.89 – 5.74 (m, 1H), 5.39 (t, *J* = 1.4 Hz, 1H), 5.33 (t, *J* = 1.0 Hz, 1H), 5.17 – 5.09 (m, 2H), 4.71 (dd, *J* = 7.8, 4.2 Hz, 1H), 2.41 (dddt, *J* = 14.3, 6.8, 4.2, 1.3 Hz, 1H), 2.23 (dtt, *J* = 14.2, 7.5, 1.2 Hz, 1H), 1.99 (s, 1H).

Link for ^{1H} NMR Spectra of **6a**

LRMS (ESI) m/z ($C_{12}H_{14}O$): theor. for $[M+H]^+$ 175.24, exp.175.3



6b

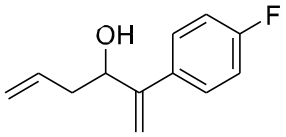
2-(4-bromophenyl)hexa-1,5-dien-3-ol (6b): Following general procedure B with 2-(4-bromophenyl)acrylaldehyde **5b** (1.2 g, 5.6 mmol), AllylMgCl (5.9 mL, 11.8 mmol) in THF (35 mL), 2-(4-bromophenyl)hexa-1,5-dien-3-ol **6b** (0.8 g, 56 %) was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.28 – 7.25 (m, 2H), 5.83 – 5.72 (m, 1H), 5.39 (t, *J* = 1.3 Hz, 1H), 5.32 (t, *J* = 1.0 Hz, 1H), 5.17 – 5.06 (m, 2H), 4.64 (dddd, *J* = 6.3, 4.2, 2.7, 1.1 Hz, 1H), 2.38 (dddt, *J* = 13.8, 6.8, 4.3, 1.4 Hz, 1H), 2.21 (dtt, *J* = 14.3, 7.7, 1.2 Hz, 1H), 1.94 (d, *J* = 4.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.91, 138.80, 133.97, 131.52, 128.65, 121.73, 118.61, 113.66, 72.35, 40.44.

Link for NMR Spectra of **6b**

LRMS (ESI) m/z ($C_{12}H_{13}BrO$): theor. for $[M+H]^+$ 254.14, exp.254.1



6c

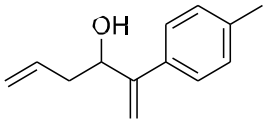
2-(4-fluorophenyl)hexa-1,5-dien-3-ol (6c): Following general procedure B with 2-(4-fluorophenyl)acrylaldehyde **5c** (1.2 g, 7.2 mmol), AllylMgCl (7.6 mL, 15 mmol) in THF (30 mL), 2-(4-fluorophenyl)hexa-1,5-dien-3-ol **6c** (0.68 g, 50 %) was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.05 – 6.99 (m, 2H), 5.84-5.73 (m 1H), 5.36 (t, J = 1.3 Hz, 1H), 5.28 (t, J = 1.0 Hz, 1H), 5.17 – 5.11 (m, 2H), 4.64 (dt, J = 7.6, 4.2 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.26 – 2.18 (m, 1H), 1.95 (d, J = 4.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.99, 134.08, 128.67, 128.56, 118.48, 115.38, 115.10, 113.15, 72.57, 40.42.

Link for NMR Spectra of **6c**

LRMS (ESI) m/z ($C_{12}H_{13}FO$): theor. for $[M+H]^+$ 193.23, exp.193.2



6d

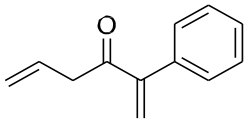
2-(p-tolyl)hexa-1,5-dien-3-ol (6d): Following general procedure B with 2-(*p*-tolyl)acrylaldehyde **5d** (0.57 g, 3.5 mmol), AllylMgCl (3.7 mL, 7.3 mmol) in THF (18 mL), 2-(p-tolyl)hexa-1,5-dien-3-ol **6d** (0.39 g, 59 %) was obtained.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.19 – 7.10 (m, 2H), 5.92 – 5.72 (m, 1H), 5.35 (t, *J* = 1.4 Hz, 1H), 5.31 (t, *J* = 1.1 Hz, 1H), 5.17 – 5.07 (m, 2H), 4.69 (dt, *J* = 7.6, 3.7 Hz, 1H), 2.36 (s, 3H), 2.35 – 2.17 (m, 2H), 1.98 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.01, 137.58, 137.13, 134.49, 129.22, 126.88, 118.38, 112.23, 72.47, 40.64, 21.24.

Link for NMR Spectra of **6d**

LRMS (ESI) m/z ($C_1H_{16}O$): theor. for $[M+H]^+$ 189.27, exp.189.4



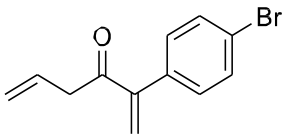
7a

2-phenylhexa-1,5-dien-3-one (7a): Following general procedure C with 2-phenylhexa-1,5-dien-3-ol **6a** (6.0g, 30 mmol), DMP (20 g.,47 mmol) and CH_2Cl_2 (300 mL)., 2-phenylhexa-1,5-dien-3-one **7a** (6 g, 80 %, 82% purity) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 6.14 (d, *J* = 0.6 Hz, 1H), 6.00 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.93 (d, *J* = 0.6 Hz, 1H), 5.23 – 5.10 (m, 2H), 3.53 (dt, *J* = 6.8, 1.4 Hz, 2H).

Link for ^{1H} NMR Spectra of **7a**

LRMS (ESI) m/z ($C_{12}H_{12}O$): theor. for $[M+H]^+$ 173.23, exp. 173.05



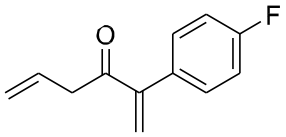
7b

2-(4-bromophenyl)hexa-1,5-dien-3-one (7b): Following general procedure C with 2-(4-bromophenyl)hexa-1,5-dien-3-ol **6b** (0.7 g, 3.0 mmol), DMP (1.3 g, 3 mmol) and CH_2Cl_2 (30 mL)., 2-(4-bromophenyl)hexa-1,5-dien-3-one **7b** (0.9 g, 90 %, 80% purity) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.22 – 7.16 (m, 2H), 6.18 (s, 1H), 6.05 – 5.99 (m, 1H), 5.98 (s, 1H), 5.24 – 5.13 (m, 2H), 3.54 (dt, *J* = 6.8, 1.5 Hz, 2H).

Link for ^{1H} NMR Spectra of **7b**

LRMS (ESI) m/z ($C_{12}H_{11}OBr$): theor. for $[M+H]^+$ 252.12, exp. 252.95



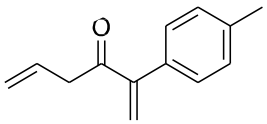
7c

2-(4-fluorophenyl)hexa-1,5-dien-3-one (7c): Following general procedure C with 2-(4-fluorophenyl)hexa-1,5-dien-3-ol **6c** (0.65 g, 3.4 mmol), DMP (1.4 g, 3.4 mmol) and CH_2Cl_2 (35 mL)., 2-(4-fluorophenyl)hexa-1,5-dien-3-one **7c** (0.7 g, 98 %, 90% purity) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.26 – 7.21 (m, 2H), 6.36 (s, 1H), 6.23 – 6.10 (m, 1H), 6.15 (s, 1H), 5.42 – 5.33 (m, 2H), 3.74 (dt, *J* = 6.7, 1.4 Hz, 2H)

Link for ^{1H} NMR Spectra of **7c**

LRMS (ESI) m/z ($C_{12}H_{11}OF$): theor. for $[M+H]^+$ 191.22, exp. 191.25



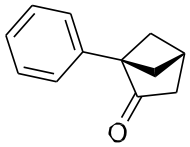
7d

2-(*p*-tolyl)hexa-1,5-dien-3-one (7d): Following general procedure C with 22-(p-tolyl)hexa-1,5-dien-3-ol **6d** (0.34 g, 1.9 mmol), DMP (0.7 g, 1.9 mmol) and CH_2Cl_2 (20 mL)., 2-(p-tolyl)hexa-1,5-dien-3-one **7d** (0.43 g, 90 %, 70% purity) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.07 (m, 4H), 6.08 (s, 1H), 6.05 – 5. (m, 1H), 5.89 (s, 1H), 5.19 (dt, *J* = 10.2, 1.4 Hz, 1H), 5.14 (dq, *J* = 17.1, 1.5 Hz, 1H), 3.51 (d, *J* = 6.8 Hz, 1H), 2.36 (s, 4H).

Link for ^{1H} NMR Spectra of **7d**

LRMS (ESI) m/z ($C_{13}H_{14}O$): theor. for $[M+H]^+$ 187.2, exp. 187.1



8a

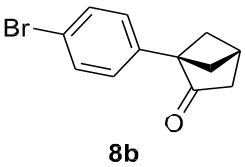
1-phenylbicyclo[2.1.1]hexan-2-one (8a): Following general procedure D with 2-phenylhexa-1,5-dien-3-one **7a** (6 g, 28.6 mmol) and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (540 mg) in CH_3CN (380 mL), 1-phenylbicyclo[2.1.1]hexan-2-one **8a** (4.50 g, 89 %) was obtained as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.31 – 7.23 (m, 1H), 7.14 (dt, 2H), 2.86 (h, *J* = 1.6 Hz, 1H), 2.42 (dtt, *J* = 5.4, 3.1, 1.2 Hz, 4H), 2.11 (dd, *J* = 4.5, 2.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 211.68, 136.83, 128.33, 127.10, 126.66, 68.06, 44.84, 42.45, 30.94.

Link for NMR Spectra of **8a**

LRMS (ESI) m/z ($C_{12}H_{12}O$): theor. for $[M+H]^+$ 173.23, exp. 173.20



8b

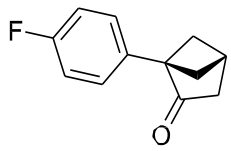
1-(4-bromophenyl)bicyclo[2.1.1]hexan-2-one (8b): Following general procedure D with 2-(4-bromophenyl)hexa-1,5-dien-3-one **7b** (380 mg, 1.2 mmol) and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (100 mg) in CH_3CN (16 mL), 1-(4-bromophenyl)bicyclo[2.1.1]hexan-2-one **8b** (168 mg, 55 %) was obtained as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.05 – 6.97 (m, 2H), 2.86 (tt, *J* = 3.5, 1.7 Hz, 1H), 2.41 (td, *J* = 2.8, 1.4 Hz, 4H), 2.08 (dd, *J* = 4.7, 2.2 Hz, 2H).

^{13}C NMR (75 MHz, CDCl3) δ 211.25, 135.92, 131.57, 128.60, 121.29, 67.58, 44.94, 42.42, 31.07.

Link for NMR Spectra of **8b**

LRMS (ESI) m/z ($C_{12}H_{11}OBr$): theor. for $[M+H]^+$ 252.12, exp. 252.9



8c

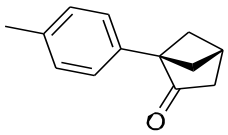
1-(4-fluorophenyl)bicyclo[2.1.1]hexan-2-one (8c): Following general procedure D with 2-(4-fluorophenyl)hexa-1,5-dien-3-one **7c** (600 mg, 28.6 mmol) and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (62 mg) in CH_3CN (37 mL), 1-(4-fluorophenyl)bicyclo[2.1.1]hexan-2-one **8c** (275 mg, 52 %) was obtained as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.17 – 6.96 (m, 4H), 2.85 (tt, *J* = 3.4, 1.7 Hz, 1H), 2.41 (pd, *J* = 3.9, 1.6 Hz, 4H), 2.08 (dd, *J* = 4.7, 2.2 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 211.68, 163.74, 160.49, 132.70, 132.66, 128.51, 128.41, 115.49, 115.20, 67.45, 45.05, 42.44, 30.96.

Link for NMR Spectra of **8c**

LRMS (ESI) m/z ($C_{12}H_{11}OF$): theor. for $[M+H]^+$ 191.22, exp. 191.09



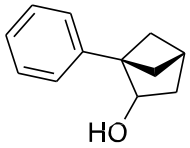
1-(p-tolyl)bicyclo[2.1.1]hexan-2-one (8d): Following general procedure D with 2-(p-tolyl)hexa-1,5-dien-3-one **7d** (430 mg, 2.31 mmol) and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (52 mg) in CH3CN (31 mL), 1-(p-tolyl)bicyclo[2.1.1]hexan-2-one **8d** (178 mg, 58 %) was obtained as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H), 7.09 – 7.00 (m, 2H), 2.85 (tt, *J* = 3.4, 1.7 Hz, 1H), 2.46 – 2.37 (m, 4H), 2.35 (s, 3H), 2.09 (dd, *J* = 4.7, 2.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.05, 136.83, 133.89, 129.14, 126.62, 67.96, 44.94, 42.52, 31.01, 21.26.

Link for NMR Spectra of **8d**

LRMS (ESI) m/z ($C_{13}H_{14}O$): theor. for $[M+H]^+$ 187.25, exp. 187.3



9a

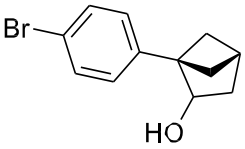
1-phenylbicyclo[2.1.1]hexan-2-ol (9a): Following general procedure E with 1-phenylbicyclo[2.1.1]hexan-2-one **8a** (1.0 g, 5,8 mmol) and $NaBH_4$ (440 mg, 11.6 mmol) in MeOH (29 mL), 1-phenylbicyclo[2.1.1]hexan-2-ol **9a** (1.0 g, quant.) was obtained as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 7.25 – 7.16 (m, 3H), 4.28 (dt, J = 7.3, 1.9 Hz, 1H), 2.48 (tt, J = 3.1, 1.5 Hz, 1H), 2.27 (dddd, J = 11.5, 7.3, 2.6, 1.5 Hz, 1H), 1.98 (dd, J = 9.5, 6.7 Hz, 1H), 1.87 – 1.69 (m, 3H), 1.65 – 1.50 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.92, 128.40, 126.48, 126.29, 76.05, 59.18, 43.80, 39.28, 37.51, 35.03.

Link for NMR Spectra of **9a**

LRMS (ESI) m/z ($C_{12}H_{14}O$): theor. for $[M+H]^+$ 175.24, exp. 175.50



9b

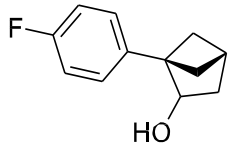
1-(4-bromophenyl)bicyclo[2.1.1]hexan-2-ol (9b): Following general procedure E with 1-(4-bromophenyl)bicyclo[2.1.1]hexan-2-one **8b** (40 mg, 0.16 mmol) and $NaBH_4$ (12 mg, 0.32 mmol) in MeOH (1 mL), 1-(4-bromophenyl)bicyclo[2.1.1]hexan-2-ol **9b** (37 mg, 90 %) was obtained as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.43 (m, 2H), 7.07 (m, 2H), 4.27 (dt, J = 7.3, 1.8 Hz, 1H), 2.47 (tt, J = 3.0, 1.5 Hz, 1H), 2.27 (dddd, J = 11.5, 7.3, 2.6, 1.5 Hz, 1H), 1.96 (dd, J = 9.5, 6.7 Hz, 2H), 1.83 – 1.71 (m, 2H), 1.59 – 1.47 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.98, 131.50, 128.17, 120.40, 75.98, 58.71, 43.76, 39.55, 37.70, 35.06.

Link for NMR Spectra of **9b**

LRMS (ESI) m/z ($C_{12}H_{13}OBr$): theor. for $[M+H]^+$ 254.14, exp. 254.9



9c

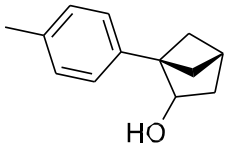
1-(4-fluorophenyl)bicyclo[2.1.1]hexan-2-ol (9c): Following general procedure E with 2-(4-fluorophenyl)hexa-1,5-dien-3-one **8c** (40 mg, 0.21 mmol) and $NaBH_4$ (16 mg, 0.42 mmol) in MeOH (1 mL), 1-(4-fluorophenyl)bicyclo[2.1.1]hexan-2-ol **9c** (37 mg, 92 %) was obtained as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.09 (m, 2H), 7.07 – 6.93 (m, 2H), 4.27 (dt, *J* = 7.3, 1.8 Hz, 1H), 2.46 (tt, *J* = 3.0, 1.5 Hz, 1H), 2.27 (dddd, *J* = 11.5, 7.3, 2.6, 1.5 Hz, 1H), 1.95 (dd, *J* = 9.5, 6.7 Hz, 1H), 1.78 (m, ii2H), 1.60 – 1.50 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 127.90, 127.79, 115.37, 115.09, 75.98, 58.57, 43.86, 39.51, 37.76, 34.98.

Link for NMR Spectra of **9c**

LRMS (ESI) m/z ($C_{12}H_{13}OF$): theor. for $[M+H]^+$ 193.23, exp. 193.1



9d

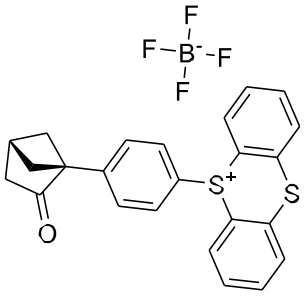
1-(p-tolyl)bicyclo[2.1.1]hexan-2-ol (9d): Following general procedure E with -(p-tolyl)bicyclo[2.1.1]hexan-2-one **8d** (40 mg, 0.21 mmol) and $NaBH_4$ (16 mg, 0.43 mmol) in MeOH (1 mL), 1-(p-tolyl)bicyclo[2.1.1]hexan-2-ol **9d** (39 mg, 93%.) was obtained as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 6.99 (m, 4H), 4.28 (dt, *J* = 7.3, 1.8 Hz, 1H), 2.46 (tt, *J* = 3.0, 1.5 Hz, 1H), 2.34 (s, 4H), 2.26 (dddd, *J* = 11.5, 7.3, 2.6, 1.5 Hz, 1H), 1.96 (dd, *J* = 9.5, 6.7 Hz, 1H), 1.82 – 1.74 (m, 2H), 1.68 (s, 2H), 1.60 – 1.51 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.79, 136.10, 129.16, 126.22, 76.03, 58.97, 43.90, 39.30, 37.56, 35.06, 21.20.

Link for NMR Spectra of **9d**

LRMS (ESI) m/z ($C_{13}H_{16}O$): theor. for $[M+H]^+$ 189.27, exp. 189.4



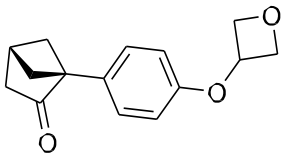
10

5-(4-(2-oxobicyclo[2.1.1]hexan-1-yl)phenyl)-5H-thianthren-5-ium tetrafluoroborate (10): Under an ambient atmosphere, a 20 ml microwave-vial was charged with 1-phenylbicyclo[2.1.1]hexan-2-one (100 mg, 1.0 equiv, 0.581 mmol.), and dry CH_3CN (5.8 mL, 0.10 molar). Trifluoroacetic anhydride (0.24 mL, 3.0 equiv., 1.74 mmol.) was added while stirring the reaction mixture. After cooling to 0 °C, thianthrene oxide (135 mg, 1.0 equiv., 0.581 mmol) was added in one portion, followed by the addition of $HBF_4{\cdot}OEt_2$ (95 µL, 1.20 equiv., 0.697 mmol) in one portion at 0 °C, leading to a purple suspension. The vial was sealed with a screw-cap, and the mixture was stirred at 0 °C for 1 hour, followed by stirring at 25 °C for 1 hour, until a slight purple solution was obtained. The reaction mixture was concentrated under reduced pressure, and diluted with CH_2Cl_2 (10 mL). The organic phase was poured onto a sat. aqueous $NaHCO_3$ solution (10 mL). The layers were separated. The organic layer was washed with a 10 % aqueous solution of $NaBF_4$ (2 × 5 mL), and with water (2 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with DCM / MeOH (95 / 5) and the desired product 5-(4-(2-oxobicyclo[2.1.1]hexan-1-yl)phenyl)-5H-thianthren-5-ium tetrafluoroborate (85 mg, 31 %) was obtained as colorless foam.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (dd, J = 7.8, 1.4 Hz, 2H), 8.07 (dd, J = 7.8, 1.3 Hz, 2H), 7.89 (dtd, J = 21.3, 7.5, 1.5 Hz, 4H), 7.28-7.17 (m, 4 H), 2.80 – 2.73 (m, 1H), 2.33 (s, 4H), 2.08 – 2.01 (m, 2H).

Link for ^{1H} Spectra for **10**

LRMS (ESI) m/z ($C_{24}H_{19}OS_2BF_4$): theor. for $[M\text{-}BF4]^-$ 387.53, exp. 387.0



11

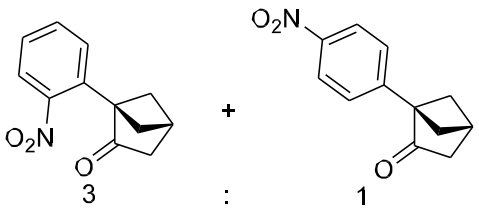
1-(4-(oxetane-3-yloxy)phenyl)bicyclo[2.1.1]hexan-2-one (11): in a small vial were added copper (I) thiophene-2-carboxylate (29 mg, 1.0 equiv., 0.15 mmol), oxetan-3-ol (28 mg, 2.5 equiv., 0.38 mmol), Na_2CO_3 (16 mg, 1.0 equiv., 0.15 mmol) and 4° molecular sieves (100 mg). Dry CH_3CN (0.8 mL, 0.2 molar) was added to the vial, which was sealed. The resulting solution was stirred for 2 hours before it was opened and thianthrenium salt **10** (90 mg, 1.0 equiv., 0.15 mmol, 80 %) and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (8.5 mg, 0.05 equiv., 7.6 µmol) were added. The vial was sealed again and irradiated with Blue LEDs in a 400 W photoreactor. After completion of the reaction, the volatiles were evaporated and the crude was purified by flash chromatography (Cyclohexane : ethyl acetate 70:30) to yield an oil for 1-(4-(oxetan-3-yloxy)phenyl)bicyclo[2.1.1]hexan-2-one **11** (10 mg, 27 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 – 7.02 (m, 2H), 6.71 – 6.65 (m, 2H), 5.19 (tt, *J* = 6.2, 5.2 Hz, 1H), 4.96 (ddd, *J* = 7.1, 6.1, 1.0 Hz, 2H), 4.80 – 4.72 (m, 2H), 2.84 (ddt, *J* = 5.1, 3.4, 1.5 Hz, 1H), 2.39 (qt, *J* = 3.3, 1.8 Hz, 4H), 2.13 – 2.01 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.14, 155.87, 128.85, 128.24, 114.57, 78.22, 77.58, 77.16, 76.74, 70.26, 67.54, 45.08, 42.52, 30.98.

Link for NMR Spectra for **11**

LRMS (ESI) m/z ($C_{15}H_{16}O_3$): theor. for $[M+H]^+$ 245.29, exp. 245.6



12a **12b**

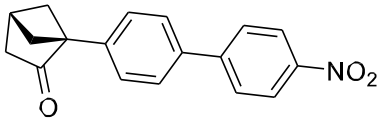
1-(2-nitrophenyl)bicyclo[2.1.1]hexan-2-one (12a) & 1-(4-nitrophenyl)bicyclo[2.1.1]hexan-2-one (12b): 1-phenylbicyclo[2.1.1]hexan-2-one **8** (500 mg, 1.0 equiv., 2.82 mmol) was dissolved in a 2:1 mixture of acetic acid (8.2 mL) and acetic anhydride (4.1 mL). The resulting mixture was cooled down to 0°C. A cold mixture of sulfuric acid (1.72 mL, 96% Wt, 11.0 equiv., 31.0 mmol) and nitric acid (130 µL, 90% Wt, 0.9 equiv., 2.53 mmol) was added dropwise at 0°C under vigorous stirring. The reaction mixture was stirred at the same temperature for 15 minutes and poured into iced water and extracted once with Ethyl Acetate (20 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography on silica (Hexanes : Ethyl Acetate 70 : 30) to yield a yellow oil for the mixture of **12a** and **12b** (552 mg, 90%)**,** which were not separable at this point.

^{1}H NMR of **12a**(400 MHz, $CDCl_3$): δ =7.92 (dd, J = 8.2, 1.3 Hz, 1H), 7.50 (td, J = 7.6, 1.4 Hz, 1H), 7.37 (ddd, J = 8.1, 7.4, 1.5 Hz, 1H), 7.14 (dd, J = 7.7, 1.4 Hz, 1H), 2.80 (tt, J = 3.7, 1.5 Hz, 1H), 2.45 – 2.37 (m, 4H), 2.26 (dd, J = 4.6, 2.1 Hz, 2H).

^{1}H NMR of **12b**(400 MHz, $CDCl_3$,): δ 8.19 – 8.08 (m, 2H), 7.27 – 7.19 (m, 2H), 2.86 (tt, J = 3.0, 1.5 Hz, 1H), 2.38 – 2.31 (m, 4H), 2.09 (dd, J = 4.6, 2.2 Hz, 2H).

Link for NMR Spectra for **12a & 12b**

LRMS (ESI) m/z ($C_{12}H_{11}NO_3$): theor. for $[M+H]^+$ 218.22, exp. 218.2



13

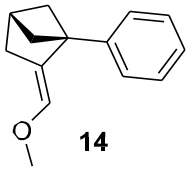
1-(4'-nitro-[1,1'-biphenyl]-4-yl)bicyclo[2.1.1]hexan-2-one (13): 1-In a microwave tube, (4-bromophenyl)bicyclo[2.1.1]hexan-2-one **8a** (100 mg, 1.0 equiv., 0.398 mmol) was dissolved in a 1:1 mixture of Dioxane:Water (0.10 molar) and (4-nitrophenyl)boronic acid (100mg, 1.50 equiv., 0.597 mmol) was added alongside Cs_2CO_3 (390 mg, 3.00 equiv., 1.19 mmol). The mixture was degassed with nitrogen before addition of $Pd(PPh_3)_4$ (9.2 mg, 0.02 equiv., 0.076 mmol). The mixture was purged with nitrogen for 5 minutes before being sealed and stirred overnight at 100 °C. Upon completion of the reaction, the layers were separated and the aqueous was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography on silica (Hexanes : Ethyl Acetate 80 : 20) to yield a colorless solid for 1-(4'-nitro-[1,01'-biphenyl]-4-yl)bicyclo[2.1.1]hexan-2-one **13** (58 mg, 50 %).

^{1}H NMR (400 MHz, $CDCl_3$) d 8.41 – 8.24 (m, 2H), 7.84 – 7.66 (m, 2H), 7.65 – 7.57 (m, 2H), 7.32 – 7.22 (m, 2H), 2.99 – 2.76 (m, 1H), 2.56 – 2.38 (m, 4H), 2.16 (dd, *J* = 4.5, 2.1 Hz, 2H).

^{13}C NMR (75 MHz,$CDCl_3$) d 211.59, 147.50, 147.19, 137.98, 137.71, 128.47, 127.84, 127.67, 127.52, 124.52, 124.26, 67.93, 45.06, 42.51, 31.22.

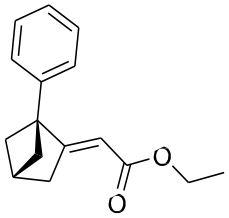
Link for NMR Spectra for **13**

LRMS (ESI) m/z ($C_{18}H_{15}NO_3$): theor. for $[M+H]^+$ 294.32, exp. 294.6



14

2-(methoxymethylene)-1-phenylbicyclo[2.1.1]hexane (14): In a dry flask under nitrogen, (Methoxymethyl)triphenylphosphonium chloride (880 mg, 2.20 equiv., 2.55 mmol) was suspended in dry THF (6.0 mL). The suspension was cooled to -78 °C and a 1M solution of KOtBu (3.50 mL, 3.0 equiv., 3.48 mmol) in THF was added dropwise. The reaction turned to bright orange. Upon stirring for 30 minutes at -78 °C, 1-phenylbicyclo[2.1.1]hexan-2-one **8** (200 mg, 1.0 equiv., 1.16 mmol) dissolved in dry THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight. It was then quenched with sat. aqueous NH_4Cl solution (10 mL) and the layers were separated. The aqueous layer was washed with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Upon concentration, a white solid precipitated and was filtered off. The crude filtrate was filtered through a pad of silica (Hexanes : Ethyl Acetate 8:2). The filtrate was then concentrated under reduced pressure and used directly in the next step without further purification.



15

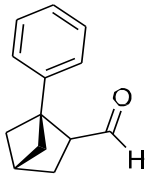
ethyl-2-(1-phenylbicyclo[2.1.1]hexan-2-ylidene)acetate (15): NaH (60 % in mineral oil, 15 mg, 1.50 equiv., 0.37 mmol) was suspended in dry THF (1.50 mL, 0.1 molar) and the suspension was cooled to 0 °C. Triethyl phosphonoacetate (60 µL, 1.20 equiv., 0.29 mmol) was added and the reaction was stirred for 15 minutes at this temperature. 1-phenylbicyclo[2.1.1]hexan-2-one **8** (42 mg, 1.0 equiv., 0.24 mmol) was added as a solution in THF (0.9 mL) and the reaction mixture was allowed to warm to room temperature overnight. Upon completion of the reaction, ethyl acetate (10 mL) and water (10 mL) were added. The layers were separated and the aqueous was washed with ethyl acetate twice (2 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash column chromatography (Hexanes : Ethyl Acetate 80 : 20) to yield an oil for ethyl 2-(1-phenylbicyclo[2.1.1]hexan-2-ylidene)acetate **15** (20mg, 34 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.29 – 7.22 (m, 1H), 7.14 – 7.04 (m, 2H), 5.27 (td, *J* = 2.1, 0.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.91 (p, *J* = 2.1 Hz, 2H), 2.69 (dq, *J* = 2.9, 1.5 Hz, 1H), 2.16 – 2.05 (m, 2H), 1.84 (dd, *J* = 4.1, 2.0 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.92, 167.44, 140.02, 128.55, 126.91, 126.64, 109.28, 63.73, 59.70, 45.81, 38.71, 33.01, 14.49.

Link for NMR Spectra for **15**

LRMS (APCI) m/z ($C_{16}H_{18}O_2$): theor. for $[M+H]^+$ 243.32, exp. 243.0



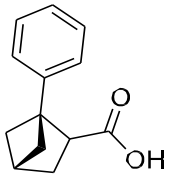
16

1-phenylbicyclo[2.1.1]hexane-2-carbaldehyde (16): The residue **14** obtained was re-dissolved in dry CH_3CN (3.5 mL, 0.10 molar) and a 2M aqueous solution of HCl (0.52 mL, 3.0 equiv., 1.0 mmol) was added. The resulting mixture was stirred for 2 hours at room temperature. Then, the layers were separated and the aqueous was washed with Ethyl Acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-phenylbicyclo[2.1.1]hexane-2-carbaldehyde **16** (45 mg, 21 % over two steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, J = 2.8 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.25 – 7.18 (m, 3H), 3.06 (dddd, J = 8.6, 4.2, 2.7, 1.7 Hz, 1H), 2.58 (tt, J = 2.8, 1.4 Hz, 1H), 2.19 (dddd, J = 11.4, 4.0, 2.6, 1.4 Hz, 1H), 2.03 (dddd, J = 11.4, 8.8, 2.6, 1.5 Hz, 1H), 1.90 (dtd, J = 7.0, 2.7, 1.7 Hz, 1H), 1.85 (dt, J = 5.5, 2.7 Hz, 1H), 1.73 (qd, J = 9.7, 6.6 Hz, 2H).

Link for ^{1H} NMR Spectra for **16**

LRMS (APCI) m/z ($C_{13}H_{14}O$): theor. for $[M+H]^+$ 187.25, exp. 187.7



17

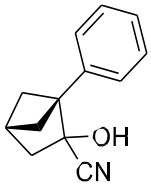
1-phenylbicyclo[2.1.1]hexane-2-carboxylic acid (17): 1-phenylbicyclo[2.1.1]hexane-2-carbaldehyde **16** (45 mg, 1.0 equiv.,0.24 mmol) was dissolved in CH_3CN (1.6 mL, 0.15 molar) and NaH_2PO_4 (9 mg, 0.30 equiv., 0.072 mmol) was added as a solution in water (1.60 mL, 0.15 molar). Then, 30 % hydrogen peroxide in water (27 µL, 1.1 equiv., 0.27 mmol) was added to the reaction mixture before addition of $NaClO_2$ (38 mg, 1.40 equiv., 0.34 mmol, 80 %) as an aqueous solution (0.35 mL, 0.70 molar). The resulting mixture was stirred at room temperature for 3 hours. Then, the pH was lowered to 1 with a 2M aqueous solution of $KHSO_4$. Next, the organics were extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-phenylbicyclo[2.1.1]hexane-2-carboxylic acid **17** (50 mg, quant.) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1H), 7.31 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 2.97 (ddd, J = 9.0, 4.3, 1.5 Hz, 1H), 2.46 (tt, J = 2.8, 1.4 Hz, 1H), 2.18 – 2.04 (m, 2H), 1.90 (dddd, J = 11.1, 4.1, 2.6, 1.4 Hz, 1H), 1.77 (dtd, J = 6.7, 2.6, 1.5 Hz, 1H), 1.70 – 1.56 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 176.04, 142.08, 127.87, 126.05, 125.91, 57.47, 47.20, 46.31, 37.55, 34.48, 33.91.

Link for NMR Spectra for **17**

LRMS (ESI) m/z ($C_{13}H_{14}O_2$): theor. for $[M-H]^-$ 201.25, exp. 201.2



18a

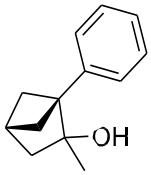
2-hydroxy-1-phenylbicyclo[2.1.1]hexane-2-carbonitrile (18a): 1-phenylbicyclo[2.1.1]hexan-2-one **8** (205 mg, 1.0 equiv., 1.19 mmol) and Zinc Iodide (7.5 mg, 0.02 equiv., 0.023 mmol) were dissolved in anhydrous CH_2Cl_2 (11.6 mL, 0.15 molar) under nitrogen and the resulting solution was cooled to 0 °C. Then, TMS-CN (180 µL, 1.20 equiv., 1.43 mmol) was added dropwise. The mixture was stirred at room temperature for 4 hours before the volatiles were evaporated under reduced pressure. The residue was filtered through a pad of silica eluting with a 9 : 1 mixture of Cyclohexane : Ethyl Acetate and the filtrate was concentrated under reduced pressure. The oil obtained was dissolved in THF (5 mL) and Water (3 mL). To the biphasic solution was added 2.0 molar HCl (3 mL, 5.00 equiv., 5.9 mmol) at room temperature and it was stirred for 3 hours. 10 mL of saturated $NaHCO_3$ was added carefully and the mixture was extracted with ether three times (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-hydroxy-1-phenylbicyclo[2.1.1]hexane-2-carbonitrile **18a** (220 mg, 93 % over two steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 3H), 7.23 – 7.16 (m, 2H), 2.63 – 2.51 (m, 2H), 2.36 (s, 1H), 2.11 – 1.96 (m, 4H), 1.89 (dt, J = 6.8, 2.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.23, 128.79, 128.03, 126.78, 121.26, 75.31, 62.87, 45.76, 43.32, 38.94, 34.63.

Link for NMR Spectra for **18a**

LRMS (APCI) m/z ($C_{13}H_{13}NO$): theor. for $[M+H]^+$ 200.25, exp. 200.1



18b

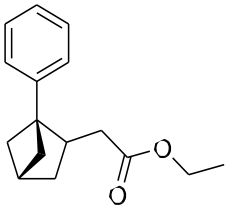
2-methyl-1-phenylbicyclo[2.1.1]hexan-2-ol (18b): 1-phenylbicyclo[2.1.1]hexan-2-one **8** (35 mg, 1.0 equiv., 0.20 mmol) was dissolved in anhydrous THF (2 mL, 0.10 molar) and the solution was cooled to 0 °C. A 3.0 molar solution of MeMgBr (400 µL, 6.0 equiv., 1.2 mmol) was added dropwise and the mixture was stirred at room temperature for 1 hour, upon which the reaction was quenched with saturated aqueous NH_4Cl (5 mL). It was extracted with Ethyl acetate thrice (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-methyl-1-phenylbicyclo[2.1.1]hexan-2-ol (32 mg, 84%) as an oily pure crude product.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 5H), 2.46 (tt, *J* = 3.1, 1.5 Hz, 1H), 2.26 (dd, *J* = 9.6, 6.5 Hz, 1H), 1.94 (ddt, *J* = 2.8, 1.9, 1.1 Hz, 2H), 1.88 (dt, *J* = 6.2, 2.7 Hz, 1H), 1.84 – 1.73 (m, 2H), 1.24 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.17, 128.03, 126.97, 126.40, 78.37, 62.35, 45.17, 43.07, 41.43, 33.95, 24.83

Link for NMR Spectra for **18b**

LRMS (APCI) m/z ($C_{13}H_{16}O$): theor. for $[M+H]^+$ 189.27, exp. 189.8



19

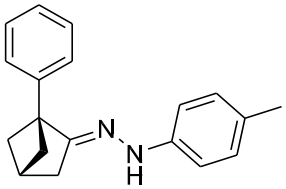
ethyl 2-(1-phenylbicyclo[2.1.1]hexan-2-yl)acetate (19): ethyl-2-(1-phenylbicyclo[2.1.1]hexan-2-ylidene)acetate **15** (18 mg, 1.0 equiv., 0.074 mmol) was dissolved in Methanol (1.5 mL, 0.05 molar). Three cycles of nitrogen and vacuum were performed and Pd/C (8 mg, 0.10 equiv., 10 mol%) was added. Three more cycles were performed and three cycles of hydrogen/vacuum (1 bar in a balloon) were achieved before stirring the reaction mixture for 3 hours at room temperature under the hydrogen atmosphere. Once completed, the reaction mixture was filtered over a short pad of celite and the pad was washed with methanol. The filtrate was concentrated under reduced pressure to yield ethyl 2-(1-phenylbicyclo[2.1.1]hexan-2-yl)acetate **19** (16 mg, 89 %) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 2H), 7.22 – 7.08 (m, 3H), 3.99 (q, *J* = 7.1 Hz, 2H), 2.65 – 2.54 (m, 1H), 2.50 (tt, *J* = 2.9, 1.5 Hz, 1H), 2.33 – 2.03 (m, 3H), 1.75 (ddd, *J* = 5.7, 3.3, 1.8 Hz, 2H), 1.71 – 1.58 (m, 2H), 1.43 (dddd, *J* = 11.1, 4.0, 2.6, 1.4 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.55, 128.26, 126.21, 126.15, 60.26, 45.94, 40.71, 37.43, 37.34, 36.14, 35.87, 14.32.

Link for NMR Spectra for **19**

LRMS (APCI) m/z ($C_{16}H_{20}O_2$): theor. for $[M+H]^+$ 245.33, exp. 245.4



20

4-methyl-N'-(1-phenylbicyclo[2.1.1]hexan-2-ylidene)benzenesulfonohydrazide (20): A solution of p-toluenesulfonhydrazide (216 mg, 1.0 equiv., 1.16 mmol) in anhydrous Methanol (2.32 mL, 0.5 molar) was stirred and heated to 60 °C until $TsNHNH_2$ was completely dissolved. Then,1-phenylbicyclo[2.1.1]hexan-2-one **8** (200 mg, 1.0 equiv., 1.16 mmol) was added to the stirring mixture. After 1 hour, the desired product precipitated. The slurry was filtered and the precipitate was washed with cold cyclohexane to afford 4-methyl-N'-(1-phenylbicyclo[2.1.1]hexan-2 ylidene)benzenesulfonohydrazide **20** (270 mg, 68 %) as a white solid.

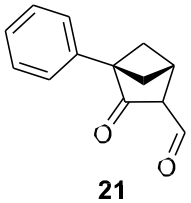
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.62 – 7.52 (m, 2H), 7.40 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 7.06 – 6.99 (m, 2H), 2.60 (dq, J = 3.2, 1.6 Hz, 1H), 2.43 (q, J = 1.9 Hz, 2H), 2.40 (s, 3H), 2.14 (q, J = 3.3 Hz, 2H), 1.69 (dd, J = 4.3, 2.1 Hz, 2H).

^{13}C NMR (300 MHz, DMSO-d_6) δ 166.54, 143.03, 138.18, 136.16, 129.05, 127.65, 127.54, 127.00, 126.50, 61.31, 45.39, 34.90, 31.12, 21.00.

Link for NMR Spectra for **20**

LRMS (ESI) m/z ($C_{19}H_{20}N_2$): theor. for $[M+H]^+$ 277.38, exp. 277.0

Note: **20** decomposed if dissolved in $CDCl_3$ for analysis.



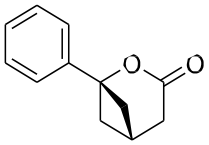
21

3-oxo-4-phenylbicyclo[2.1.1]hexane-2-carbaldehyde (21): an oven-dried round-bottom flask under nitrogen was loaded with dry THF (2.0 mL) and *N*-(Propan-2-yl)cyclohexanamine (0.12 mL, 2.60 equiv., 0.75 mmol) before being cooled to 0 °C. To the mixture was added *n*-BuLi (0.5 mL, 2.70 equiv., 1.6 molar, 0.78 mmol) dropwise. After 30 minutes of stirring, the reaction mixture was cooled to -78 °C and a solution of 1-phenylbicyclo[2.1.1]hexan-2-one **8** (50 mg, 1.0 equiv., 0.29 mmol) in THF (1.0 mL) was added dropwise and further stirred for 1 hour. Then, ethyl formate (0.11 mL, 4.50 equiv., 1.3 mmol) in THF (0.5 mL) was added and stirring was continued for 1 hour at -78 °C before quenching the reaction with sat. aq. NH_4Cl (5 mL). After warming to room temperature, the organic layer was separated, the aqueous was extracted with ether thrice (3 x 5 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Hexanes : Ethyl Acetate 80 : 20) to yield an oil for 3-oxo-4-phenylbicyclo[2.1.1]hexane-2-carbaldehyde **21** (10 mg, 17 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (t, *J* = 0.7 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 7.15 – 7.10 (m, 2H), 3.62 – 3.59 (m, 1H), 3.16 (td, *J* = 3.6, 1.1 Hz, 1H), 2.53 – 2.47 (m, 2H), 2.36 – 2.21 (m, 1H), 2.10 (dd, *J* = 9.7, 7.4 Hz, 1H).

Link for ^{1H} NMR Spectra for **21**

LRMS (APCI) m/z ($C_{13}H_{12}O_2$): theor. for $[M+H]^+$ 201.24, exp. 201.1



22

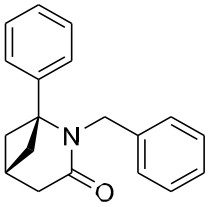
1-phenyl-2-oxabicyclo[3.1.1]heptan-3-one (22): 1-phenylbicyclo[2.1.1]hexan-2-one **8** (300 mg, 1.0 equiv., 1.742 mmol) was dissolved in dry CH_2Cl_2 (11.6 mL, 0.15 molar) under nitrogen and mCPBA (1.2 g, 3.0 equiv., 77 %, 5.226 mmol) was added and the resulting solution was put at reflux for 72 hours. It was then quenched with an aqueous solution of sat. Na_2SO_3 (10 mL) and it was stirred for 30 minutes. The layers were separated and the aqueous was washed with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Hexanes : Ethyl Acetate 60 : 40) to yield a yellow solid for 1-phenyl-2-oxabicyclo[3.1.1]heptan-3-one **22** (260 mg, 80 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 2.99 (dt, *J* = 2.8, 1.0 Hz, 2H), 2.75 (tt, *J* = 5.7, 2.7 Hz, 1H), 2.68 – 2.54 (m, 2H), 2.16 – 2.01 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.68, 139.26, 128.55, 128.54, 128.53, 128.52, 128.51, 125.35, 125.34, 125.33, 125.31, 39.73, 39.32, 26.70.

Link for NMR Spectra for **22**

LRMS (APCI) m/z ($C_{12}H_{12}O_2$): theor. for $[M+H]^+$ 189.23, exp. 189.5



23

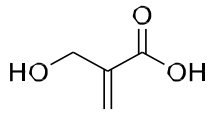
2-benzyl-1-phenyl-2-azabicyclo[3.1.1]heptan-3-one (23): A solution of 1-phenylbicyclo[2.1.1]hexan-2-one **8** (300 mg, 1.0 equiv., 1.742 mmol) and freshly prepared Benzyl Azide (465mg, 2.0 equiv., 3.48 mmol) in anhydrous CH_2Cl_2 (11.5 mL, 0.15 molar) was cooled to 0 °C. Then, a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (4.35 mL, 2.50 equiv., 4.35 mmol) was added dropwise. The resulting suspension was stirred overnight while allowing to warm to room temperature. Then, it was diluted with 20 mL of ethyl acetate and partitioned between 50 mL of ethyl acetate and 30 mL of saturated $NaHCO_3$. The organic layer was extracted with 30 mL of brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Hexanes : Ethyl Acetate 1 : 1) to yield 2-benzyl-1-phenyl-2-azabicyclo[3.1.1]heptan-3-one **23** (240 mg, 50 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.04 (m, 6H), 6.94 – 6.86 (m, 2H), 6.74 – 6.68 (m, 2H), 4.39 (s, 2H), 2.95 (d, *J* = 2.8 Hz, 2H), 2.74 (tt, *J* = 5.8, 2.8 Hz, 1H), 2.55 – 2.46 (m, 2H), 2.23 (dd, *J* = 7.0, 2.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.01, 139.90, 138.88, 128.00, 127.98, 127.78, 127.25, 126.56, 66.71, 46.63, 42.00, 40.39, 28.31.

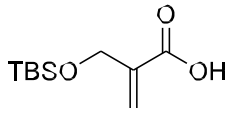
Link for NMR Spectra for **23**

LRMS (APCI) m/z ($C_{19}H_{19}NO$): theor. for $[M+H]^+$ 278.37, exp. 278.7



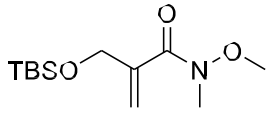
S1

2-(Hydroxymethyl)-2-propenoic acid (S1): methyl 2-(hydroxymethyl)acrylate **24** (10.0 g, 1.00 equiv., 86 mmol), $LiOH.H_2O$ (9.10 g, 2.50 equiv.,215 mmol) were stirred in mixture of THF (140 mL), MeOH (48 mL) and water (48 mL) for 2 hours at room temperature. The volatiles were evaporated under reduced pressure. The aqueous was extracted twice with diethyl ether (100 mL) before being acidified to pH = 2 with 6M HCl. The resulting acidic aqueous layer was extracted five times with diethyl ether (50 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-(hydroxymethyl)acrylic acid **S1** (7.0 g, 80 %) as an oil. Analytical data matched the literature.[2]



S2

2-(((TBS)oxy)methyl)acrylic acid (S2): following a literature precedent, **S1** (1.25 g, 1.0 equiv., 12.2 mmol) was converted to 2-(((TBS)oxy)methyl)acrylic acid **S2** and used crude without further purification. Analytical data matched the literature.[3]



25

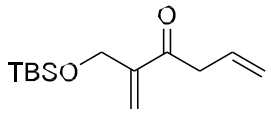
2-(((TBS)oxy)methyl)-*N*-methoxy-*N*-methylacrylamide (25): the crude residue of **S2** (1.30 g, 1.0 equiv., 6.01 mmol) was dissolved in dry CH2Cl2 (30 mL, 0.20 molar) and DIPEA (3.1 mL, 3.0 equiv., 18 mmol) was added. It was cooled to 0 °C, treated with EDC.HCl (1.27 g, 1.10 equiv., 6.61 mmol) and after 10 minutes of stirring, *O,N*-dimethyl-hydroxylamine hydrochloride (650 mg, 1.10 equiv., 6.61 mmol) was added in one portion. he reaction was allowed to warm to room temperature overnight. It was quenched with a sat. aqueous solution of $NaHCO_3$ (20 mL) and addition of CH_2Cl_2 (30 mL). The layers were separated and the aqueous was back extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Hexanes : Ethyl Acetate 70 : 30) to yield a colorless oil for 2-(((TBS)oxy)methyl)-*N*-methoxy-*N*-methylacrylamide **25** (1.05 g, 67 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 – 5.54 (m, 1H), 5.47 (q, J = 1.5 Hz, 1H), 4.37 (t, J = 1.7 Hz, 2H), 3.66 (s, 3H), 3.25 (s, 3H), 0.90 (d, J = 0.7 Hz, 9H), 0.08 (d, J = 0.7 Hz, 6H).

Link for ^{1H} NMR Spectra for **25**

LRMS (APCI) m/z ($C_{12}H_{25}NO_3Si$): theor. for $[M+H]^+$ 260.42, exp. 260.1

[2] T. Mendgen, T. Scholz and C. D. Klein, *Bioorganic & Medicinal Chemistry Letters*, 2010, **20**, 5757-5762.
[3] S. Jaegli, J.-P. Vors, L. Neuville and J. Zhu, *Synlett*, 2009, **2009**, 2997-2999.



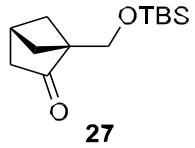
26

2-(((TBS)oxy)methyl)-*N*-methoxy-*N*-methylacrylamide (26): A solution of 2-(((TBS)oxy)methyl)-*N*-methoxy-*N*-methylacrylamide (520 mg, 1.0 equiv., 2.0 mmol) in dry THF (20 mL, 0.10 molar) under nitrogen was cooled to -78 °C-. Then, a 2M solution of allylmagnesium chloride in THF (2.0 mL, 2.0 equiv., 4.0 mmol) was adzded dropwise to the reaction mixture and stirring was continued at -78 °C for 30 more minutes before warming it to room temperature. It was further stirred for 1 hour and quenched by addition of a sat. aqueous solution of NH4Cl (20 mL). The aqueous layer was separated and extracted with Ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Hexanes : Ethyl Acetate 95 : 5) to yield a colorless oil for 2-(((TBS)oxy)methyl)hexa-1,5-dien-3-one **26**(385 mg, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (td, J = 1.9, 0.8 Hz, 1H), 6.12 (td, J = 2.1, 0.8 Hz, 1H), 5.96 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.21 – 5.11 (m, 2H), 4.37 (t, J = 2.0 Hz, 2H), 3.50 (t, J = 1.4 Hz, 1H), 3.49 (t, J = 1.5 Hz, 1H), 0.92 (s, 9H), 0.08 (s, 6H).

Link for ^{1H} NMR Spectra for **26**

LRMS (APCI) m/z ($C_{12}H_{24}O_2Si$): theor. for $[M+H]^+$ 241.42, exp. 241.2



27

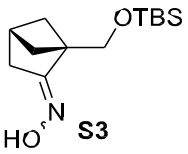
1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-one (27): 2-(((tert-butyldimethylsilyl)oxy)methyl)hexa-1,5-dien-3-one (1.50 g, 1.0 equiv., 6.24 mmol) was dissolved in dry CH_3CN (83 mL, 0.075 molar) under nitrogen and 2-Isopropyithioxanthone (160 mg, 0.10 equiv., 0.624 mmol) was added. The mixture was degassed with nitrogen for 5 minutes before being transferred to a Quartz tube that was previously dried and sparged with nitrogen. Once in the Quartz tube, it was degassed with nitrogen again for 5 more minutes and stirred overnight under irradiation of a 365 nm lamp. Upon completion of the reaction, the volatiles were evaporated under reduced pressure and the residue was purified by Flash column chromatography (Hexanes : Ethyl Acetate 90:10) to yield 1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-one **27** (1.17 g, 72 %) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 2H), 2.73 (tt, J = 3.3, 1.6 Hz, 1H), 2.29 – 2.20 (m, 4H), 1.53 (dd, J = 4.6, 2.0 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.86, 77.58, 77.16, 76.74, 67.07, 59.89, 43.24, 41.48, 31.38, 26.04, 18.46, -5.29.

Link for NMR Spectra for **27**

LRMS (APCI) m/z ($C_{12}H_{24}O_2Si$): theor. for $[M+H]^+$ 241.42, exp. 241.5



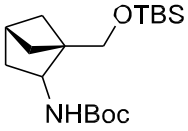
S3

1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-one oxime (S3):1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-one (300 mg, 1.0 equiv., 1.25 mmol) was dissolved in a 2 : 1 mixture of Water (8.3 mL, 0.15 molar) and MeOH (5 mL, 0.25 molar). To the mixture were successively added Sodium acetate (410 mg, 4.00 equiv., 4.9 mmol) and Hydroxylamine hydrochloride (105 mg, 1.20 equiv.,1.5 mmol). The reaction was stirred at reflux for 3 hours. The mixture was cooled to room temperature and water (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a white solid for 1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-one oxime **S3** (318 mg, quant.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 2H), 2.57 (tt, J = 3.0, 1.4 Hz, 1H), 2.51 (td, J = 2.2, 1.4 Hz, 2H), 2.11 (qd, J = 3.8, 1.5 Hz, 2H), 1.33 (dd, J = 4.3, 2.0 Hz, 2H), 0.90 (s, 8H), 0.04 (s, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.78, 60.72, 60.30, 42.23, 34.60, 31.83, 26.08, 18.50, -5.24.

Link for NMR Spectra for **S3**



28

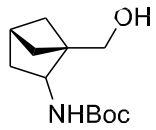
tert-butyl (1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-yl)carbamate (28): 1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-one oxime **S1** (318 mg, 1.0 equiv., 1.25 mmol) was dissolved in dry MeOH (4.0 mL, 0.05 molar) under nitrogen and it was treated with Boc anhydride (580 µL, 2.00 equiv., 2.51 mmol), and $NiCl_2.6H_2O$ (120 mg, 0.40 equiv., 0.50 mmol). It was cooled to 0 °C and $NaBH_4$ (570 mg, 12.0 equiv., 15.0 mmol) was added in small portions. The mixture immediately turned black. The reaction was to room temperature overnight. Upon completion of the reaction, diethylenetriamine (270 µL, 2.00 equiv., 2.50 mmol) was added at once and the volatiles were evaporated under reduced pressure. The residue was dissolved in Ethyl Acetate (20 mL) and a 10 % aqueous citric acid solution (20 mL). The layers were separated and the organic layer was washed with a sat. aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Hexanes : Ethyl Acetate 80 : 20) to yield tert-butyl (1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-yl)carbamate **28** (320 mg, 75 %) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.79 (s, 1H), 3.72 (s, 2H), 2.44 – 2.37 (m, 1H), 2.25 (t, J = 9.7 Hz, 1H), 1.53 – 1.37 (m, 13H), 1.03 (dd, J = 9.5, 6.7 Hz, 1H), 0.90 (s, 9H), 0.04 (d, J = 0.6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.30, 77.58, 77.16, 76.74, 53.13, 40.26, 35.73, 28.57, 27.96, 27.06, 26.05, 18.36, -5.24, -5.45.

Link for NMR Spectra for **28**

LRMS (APCI) m/z ($C_{18}H_{35}NO_3Si$): theor. for $[M+H]^+$ 342.57, exp. 342.6



S4

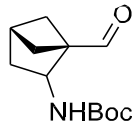
tert-butyl (1-(hydroxymethyl)bicyclo[2.1.1]hexan-2-yl)carbamate (S4): A solution of tert-butyl (1-(((TBS)oxy)methyl)bicyclo[2.1.1]hexan-2-yl)carbamate **28** (100 mg, 1.0 equiv., 0.293 mmol) in THF (1.95 mL, 0.15 molar) was cooled to 0 °C. Then, a 1M solution of TBAF (0.90 mL, 3.0 equiv., 0.44 mmol) in THF was added dropwise. The resulting mixture was stirred for 30 minutes at room temperature before being quenched with a sat. aqueous solution of NH_4Cl (5 mL). The aqueous layer was then extracted with ethyl acetate (3 x 5 mL) and the organic layers were combined. They were then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Hexanes : Ethyl Acetate 70 : 30) to yield tert-butyl (1-(hydroxymethyl)bicyclo[2.1.1]hexan-2-yl)carbamate **S4** (62 mg, 93 %) as a colorless solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 6.90 (d, J = 7.9 Hz, 1H), 4.20 (dd, J = 6.9, 4.8 Hz, 1H), 3.73 (d, J = 8.9 Hz, 1H), 3.44 – 3.33 (m, 2H), 2.26 (m, 1H), 2.00 (m, 1H), 1.53 – 1.46 (m, 1H), 1.22 (dd, J = 9.2, 6.4 Hz, 1H), 0.96 (dd, J = 9.5, 6.5 Hz, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 156.02, 77.72, 60.60, 57.28, 50.40, 36.00, 34.71, 34.05, 28.21, 26.32.

Link for NMR Spectra for **S4**

LRMS (APCI) m/z ($C_{12}H_{21}NO_3$): theor. for $[M+H]^+$ 228.3, exp. 228.0



S5

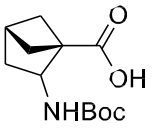
tert-butyl (1-formylbicyclo[2.1.1]hexan-2-yl)carbamate (S5): A solution of tert-butyl (1-(hydroxymethyl)bicyclo[2.1.1]hexan-2-yl)carbamate **S5** (62 mg, 1.0 equiv., 0,272 mmol) in anhydrous CH_2Cl_2 (5,5 mL, 0.05 molar) was treated with DMP (290 mg, 2.5 equiv., 0,681 mmol) and the mixture was stirred for 2 hours at room temperature. It was quenched with a 1:1 mixture of sat. aq. $NaHCO_3$:$Na_2S_2O_3$ and the layers were separated. The aqueous layer was extracted thrice with CH_2Cl_2 (3 x 5 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was filtered through a short column of silica eluting with a mixture of 80 : 20 of Hexanes : Ethyl Acetate to afford tert-butyl (1-formylbicyclo[2.1.1]hexan-2-yl)carbamate **S5** (32 mg, 52 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.57 (s, 1H), 4.15 (dq, *J* = 8.3, 3.0 Hz, 1H), 2.37 – 2.28 (m, *J* = 1.0 Hz, 1H), 2.08 (ddt, *J* = 10.7, 8.9, 1.6 Hz, 1H), 1.68 (dt, *J* = 6.5, 3.2 Hz, 1H), 1.63 – 1.48 (m, 3H), 1.36 (m, 10H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 200.92, 168.10, 94.03, 77.96, 63.70, 51.60, 40.75, 34.27, 28.13, 26.33.

Link for NMR Spectra for **S5**

LRMS (APCI) m/z ($C_{12}H_{19}NO_3$): theor. for $[M+H]^+$ 226.29, exp. 226.4



29

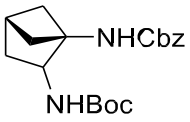
2-((tert-butoxycarbonyl)amino)bicyclo[2.1.1]hexane-1-carboxylic acid (29): tert-butyl (1-formylbicyclo[2.1.1]hexan-2-yl)carbamate **S5** (32 mg, 1.0 equiv.,0.014 mmol) was dissolved in CH_3CN (2.8 mL, 0.05 molar) and NaH_2PO_4 (5 mg, 0.30 equiv., 0.004 mmol) was added a solution in water (2.8 mL, 0.05 molar). Then, 30 % hydrogen peroxide in water (18 µL, 1.2 equiv., 0.017 mmol) was added to the reaction mixture before addition of $NaClO_2$ (25 mg, 1.60 equiv., 0.022 mmol, 80 %) as an aqueous solution (300 µL, 0.50 molar). The resulting mixture was stirred at room temperature for 3 hours. Then, the pH was lowered to 1 with a 2M aqueous solution of $KHSO_4$. Then, the organics were extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-((tert-butoxycarbonyl)amino)bicyclo[2.1.1]hexane-1-carboxylic acid **29** (50 mg, quant.) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.99 (s, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 4.20 – 4.10 (m, 1H), 2.20 (s, 1H), 2.07 (t, *J* = 8.7 Hz, 1H), 1.76 – 1.66 (m, 1H), 1.66 – 1.60 (m, 2H), 1.37 (s, 9H), 1.35 – 1.25 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 173.65, 155.16, 77.51, 55.53, 52.28, 42.33, 36.82, 35.70, 33.32, 28.27.

Link for NMR Spectra for **29**

LRMS (APCI) m/z ($C_{12}H_{19}NO_4$): theor. for $[M+H]^+$ 242.29, exp. 242.0



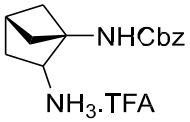
30

benzyl tert-butyl bicyclo[2.1.1]hexane-1,2-diyldicarbamate (30): 2-((tert-butoxycarbonyl)amino)bicyclo[2.1.1]hexane-1-carboxylic acid **29** (20 mg, 1.0 equiv., 83 µmol) was dissolved in dry Toluene (1.7 mL, 0.05 molar) under nitrogen and Et_3N (29 µL, 2.50 equiv., 0.21 mmol) was added. Diphenylphosphoryl azide (45 µL, 2.5 equiv., 0.21 mmol) was then added before heating the mixture at 110 °C for 2 hours. It was cooled to room temperature and Benzyl alcohol (34 µL, 4.0 equiv., 0.33 mmol) was added before being refluxed overnight. Upon completion of the reaction, the volatiles were evaporated under reduced pressure and the crude was purified by flash column chromatography (Hexanes : Ethyl Acetate 75 : 25) to afford benzyl tert-butyl bicyclo[2.1.1]hexane-1,2-diyldicarbamate **30** (14 mg, 50 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34 – 7.29 (m, 5H), 5.16 (td, *J* = 5.8, 0.8 Hz, 1H), 4.98 (q, *J* = 12.3 Hz, 2H), 4.49 (d, *J* = 5.7 Hz, 2H), 3.92 (s, 1H), 2.16 (s, 1H), 1.94 (t, *J* = 10.0 Hz, 1H), 1.85 (s, 1H), 1.56 (t, *J* = 8.2 Hz, 1H), 1.39 (m, *J* = 3.9 Hz, 11H).

Link for ^{1H} NMR Spectra for **30**

LRMS (APCI) m/z ($C_{12}H_{26}N_2O_4$): theor. for $[M+H]^+$ 347.43, exp. 347.3



31

benzyl (2-aminobicyclo[2.1.1]hexan-1-yl)carbamate.TFA (31): benzyl tert-butyl bicyclo[2.1.1]hexane-1,2-diyldicarbamate **30** (14 mg, 1.0 equiv., 43 µmol) was dissolved in dry CH_2Cl_2 (1.7 mL, 0.05 molar) and it was cooled to 0 °C. It was then treated with TFA (67 µL, 20 equiv., 0.87 mmol) and the solution was allowed to warm to room temperature and stirred for 5 hours. The volatiles were evaporated under reduced pressure and the residue was triturated with diethyl ether (3 mL). The TFA salt precipitated and was collected by filtration. The solid was further dried under vacuum to yield benzyl (2-aminobicyclo[2.1.1]hexan-1-yl)carbamate.TFA **31** (7.0 mg, 50 %).

^{1}H NMR (400 MHz, MeOD-d_4) δ 7.40 – 7.28 (m, 5H), 5.09 (d, *J* = 3.4 Hz, 2H), 3.82 (d, *J* = 8.3 Hz, 1H), 2.43 (dt, *J* = 3.6, 1.7 Hz, 1H), 2.27 (t, *J* = 10.3 Hz, 1H), 1.91 (t, *J* = 8.7 Hz, 1H), 1.83 (dtd, *J* = 7.7, 2.9, 1.4 Hz, 1H), 1.75 (dt, *J* = 6.9, 3.3 Hz, 1H), 1.70 – 1.57 (m, 2H).

Link for ^{1H} NMR Spectra for **31**

LRMS (APCI) m/z ($C_{14}H_{18}N_2O_2$): theor. for $[M\text{-}TFAH]^+$ 247.31, exp. 247.5

4) NMR Spectra

*Figure 1: ^{1}H NMR Spectra of **5a***

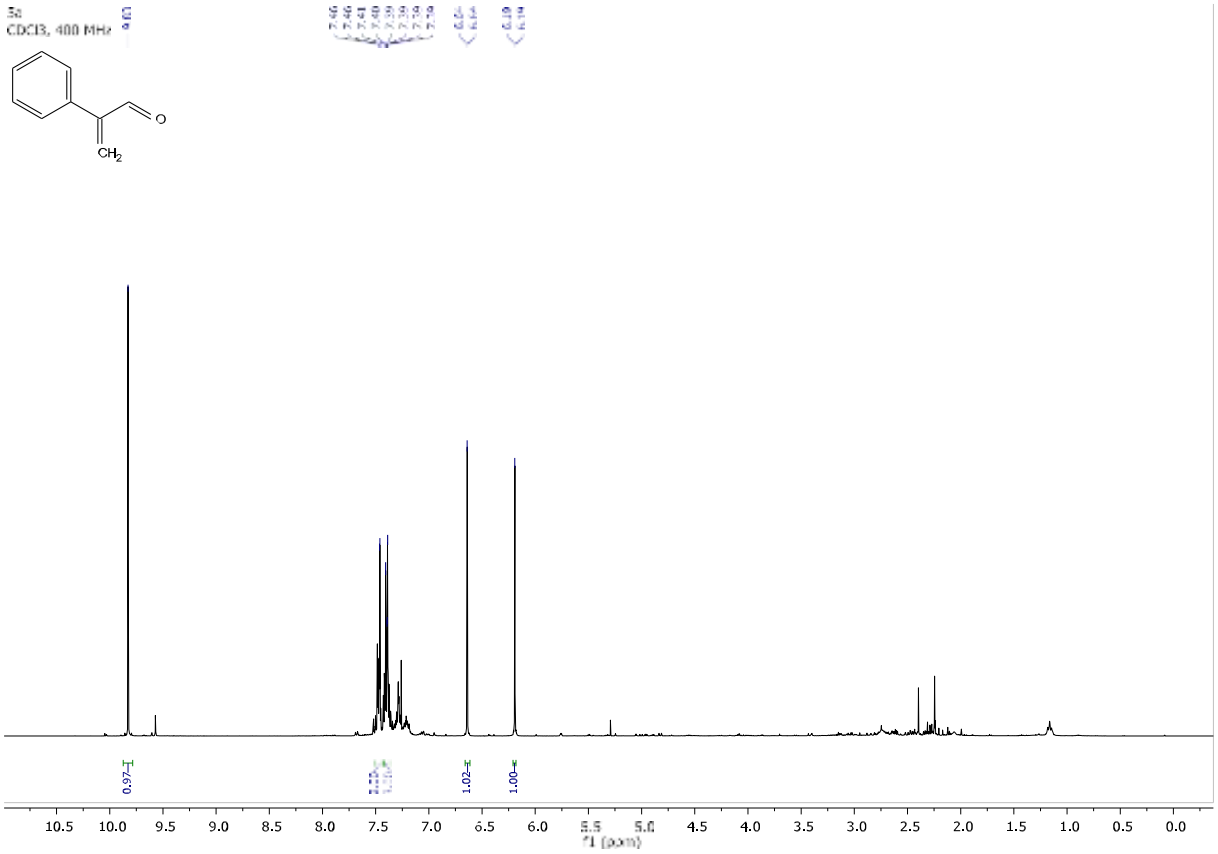


*Figure 2: [1]H NMR Spectra of **5b***

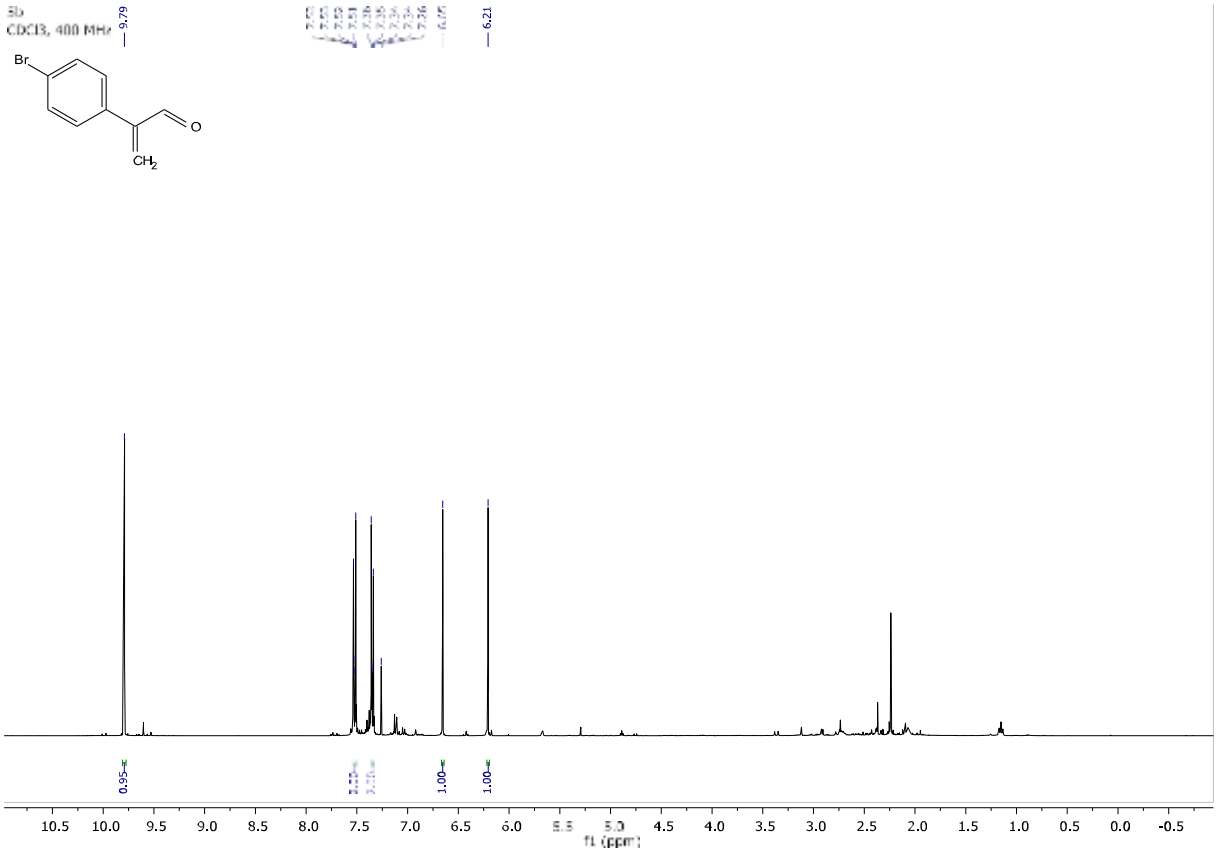


*Figure 3: ^{1}H NMR Spectra of **5c***

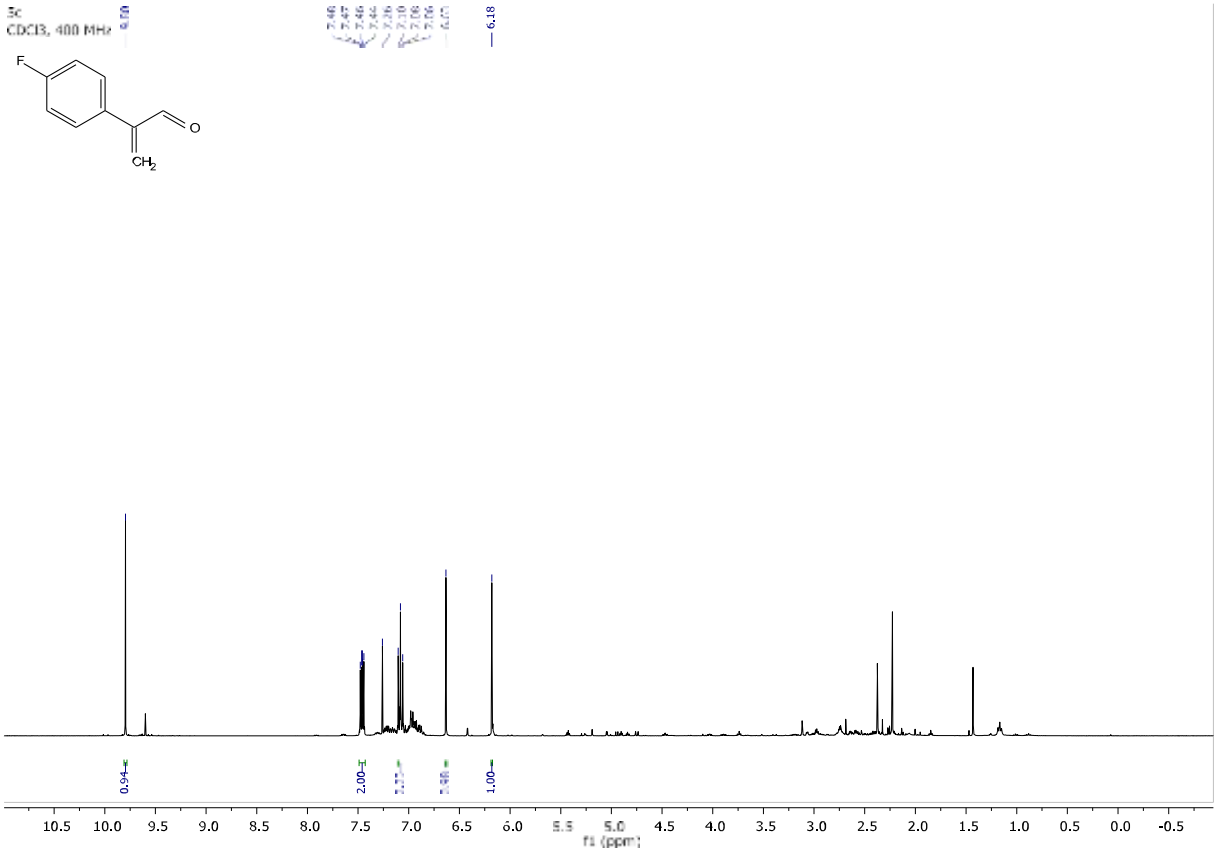


*Figure 4: [1]H NMR Spectra of **5d***

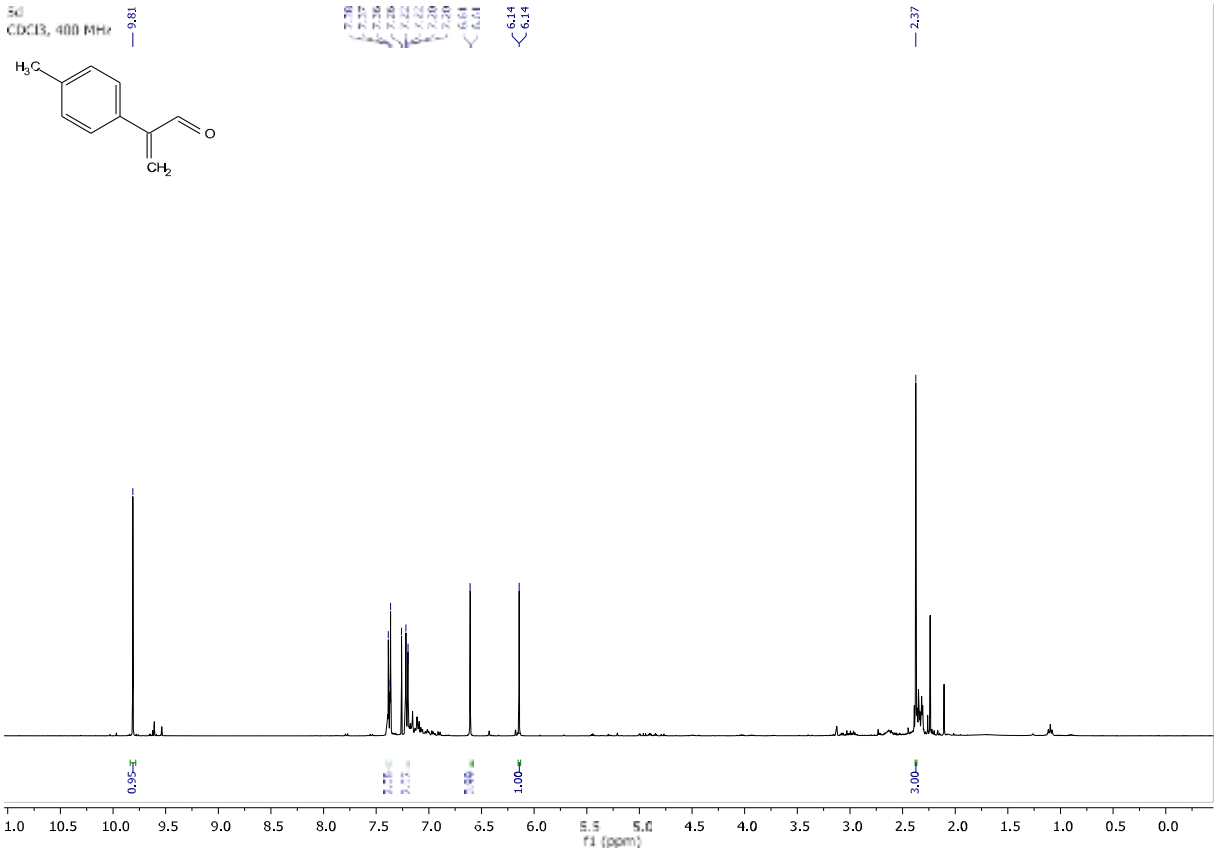


*Figure 5: ^{1}H NMR Spectra of **6a***

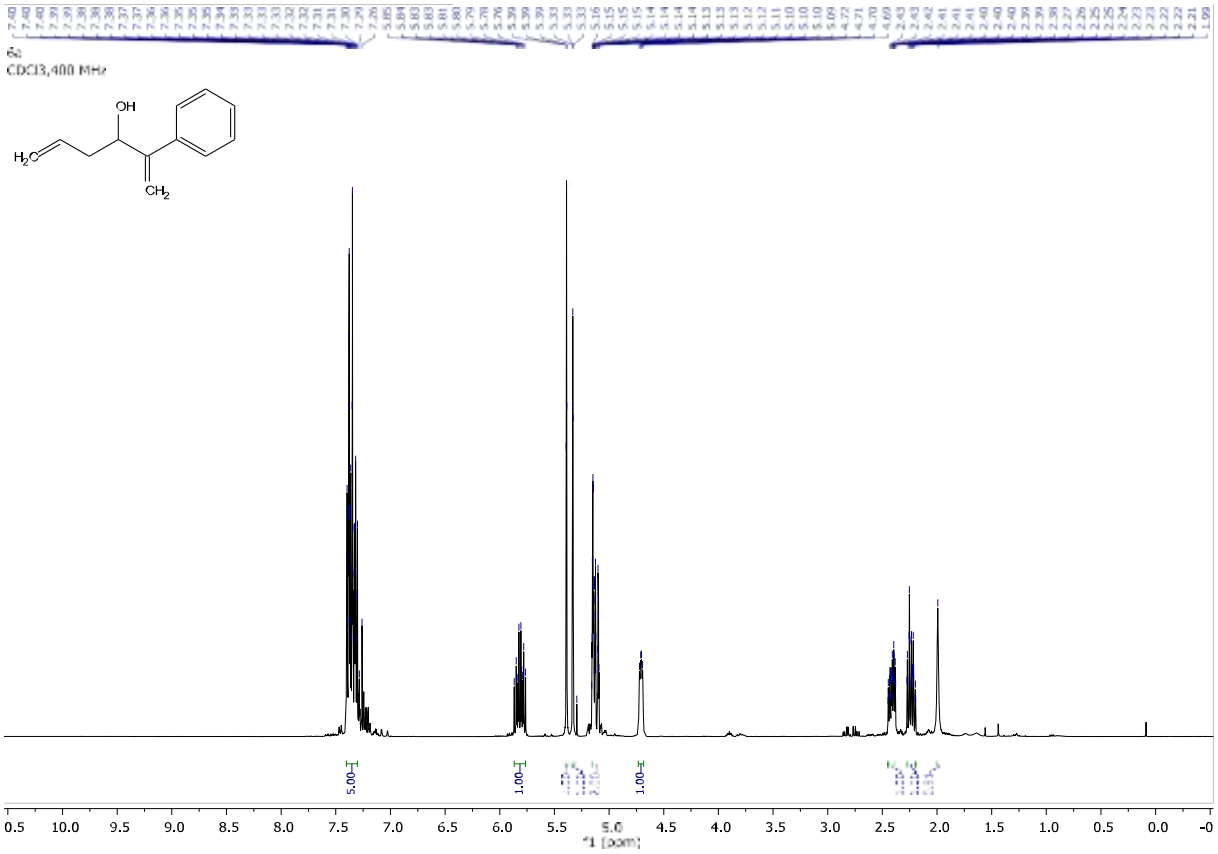
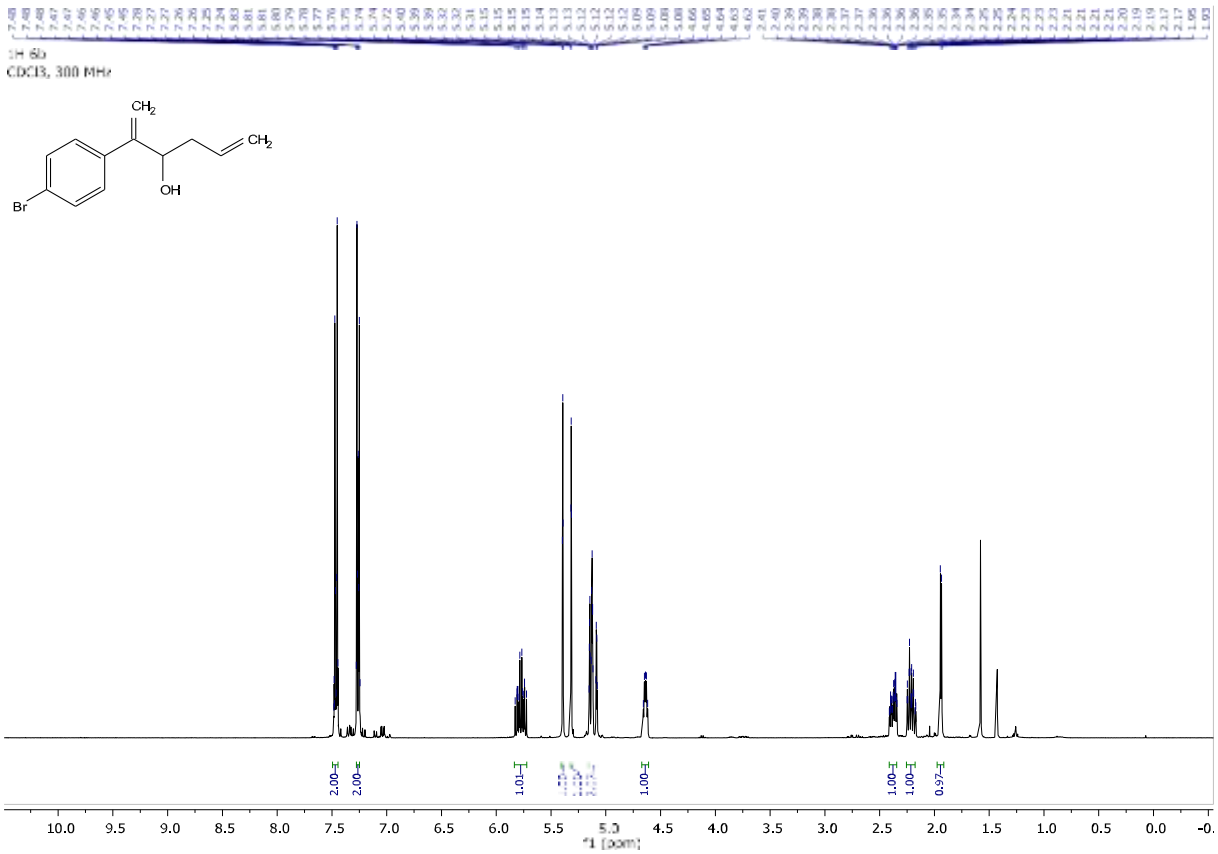


*Figure 6: NMR Spectra of **6b***



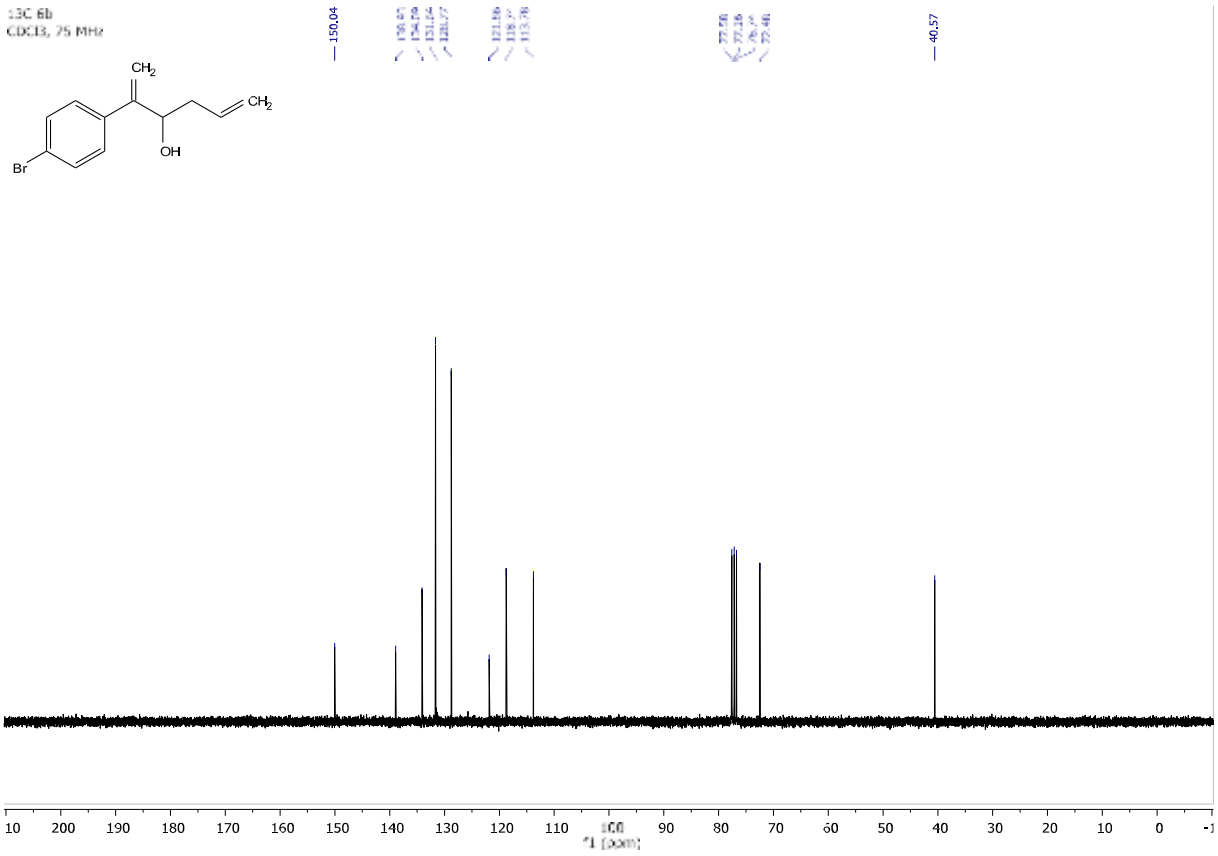


*Figure 7: NMR Spectra of **6c***

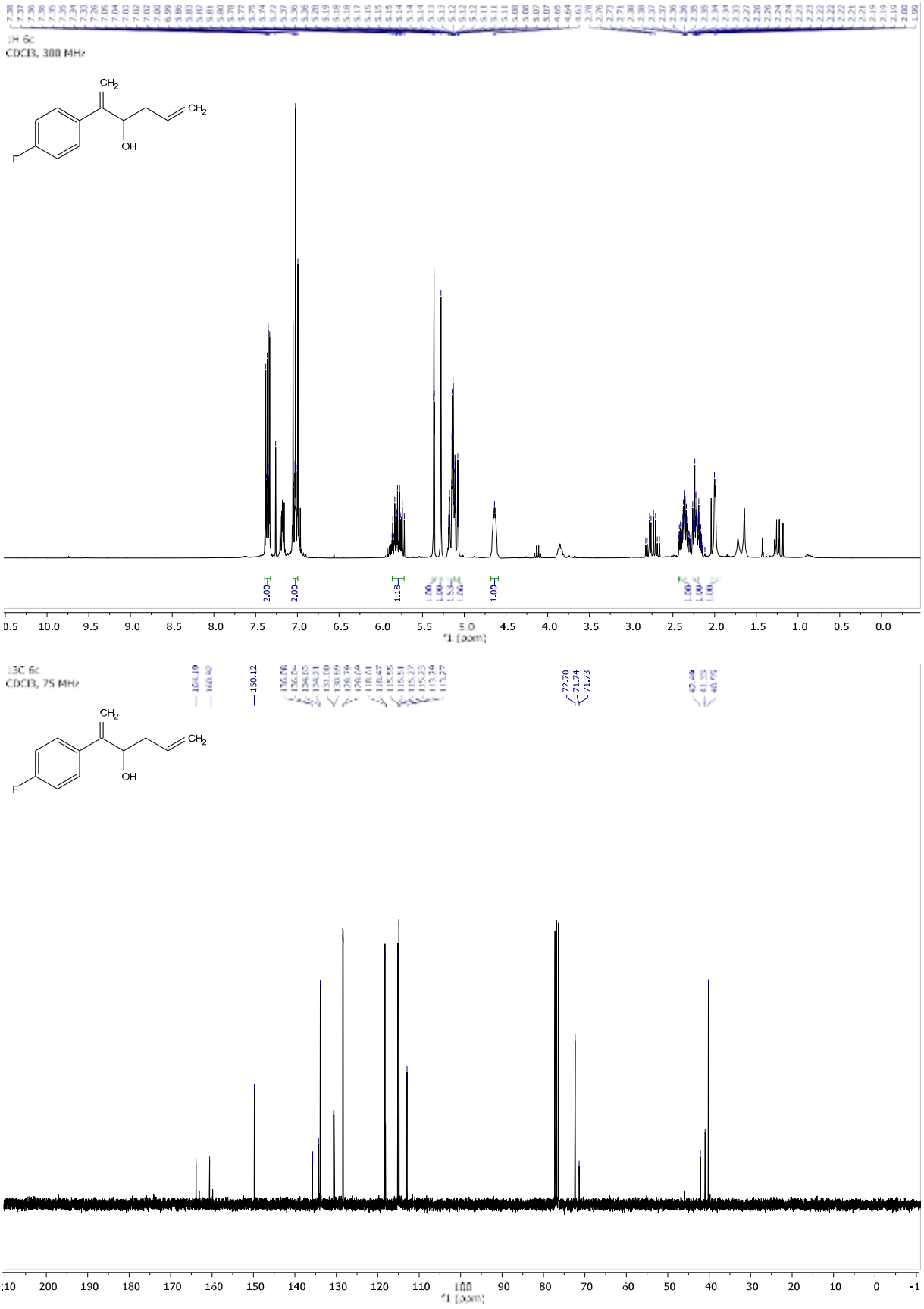


*Figure 8: NMR Spectra of **6d***

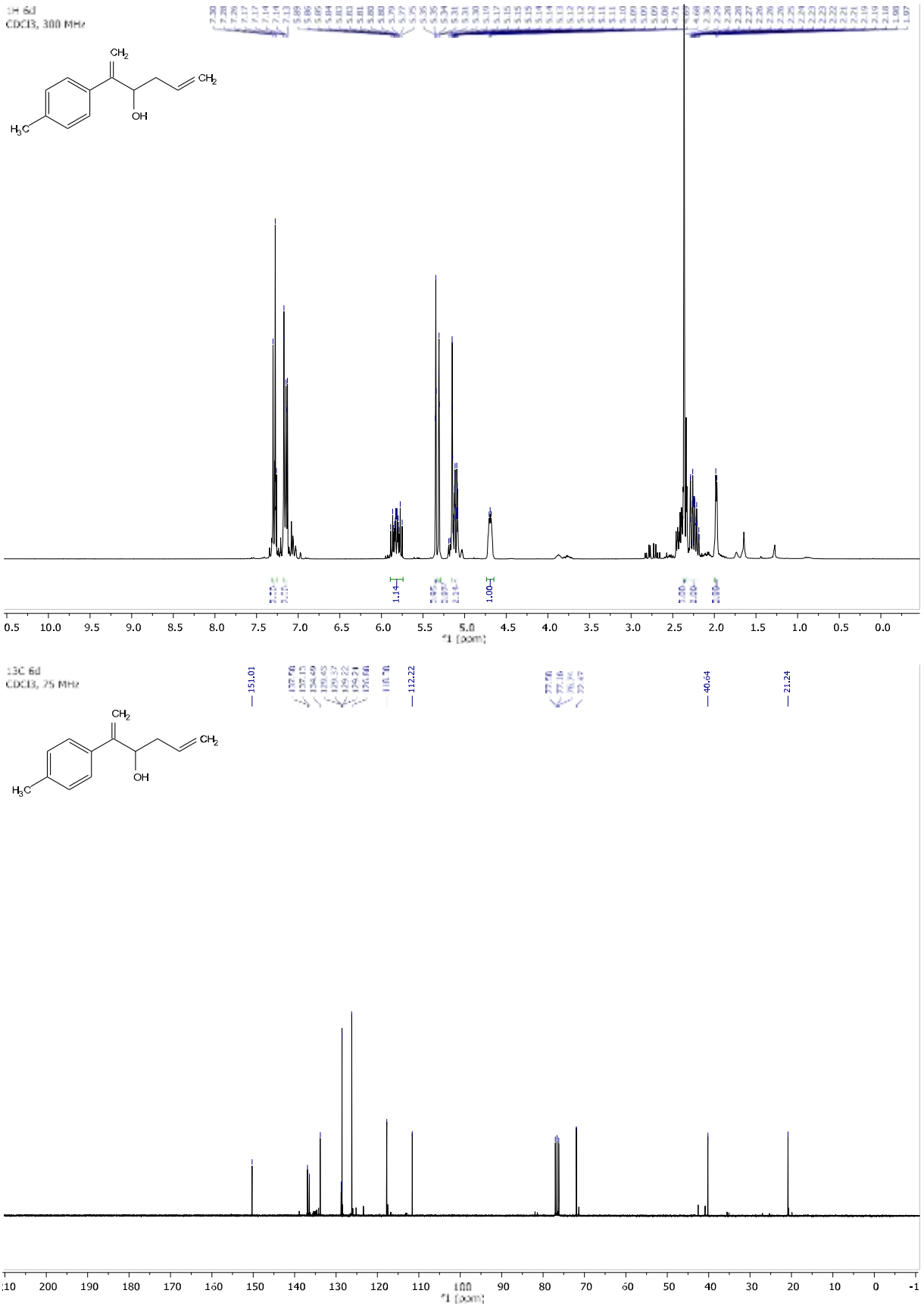


*Figure 9: ^{1}H NMR Spectra of **7a***

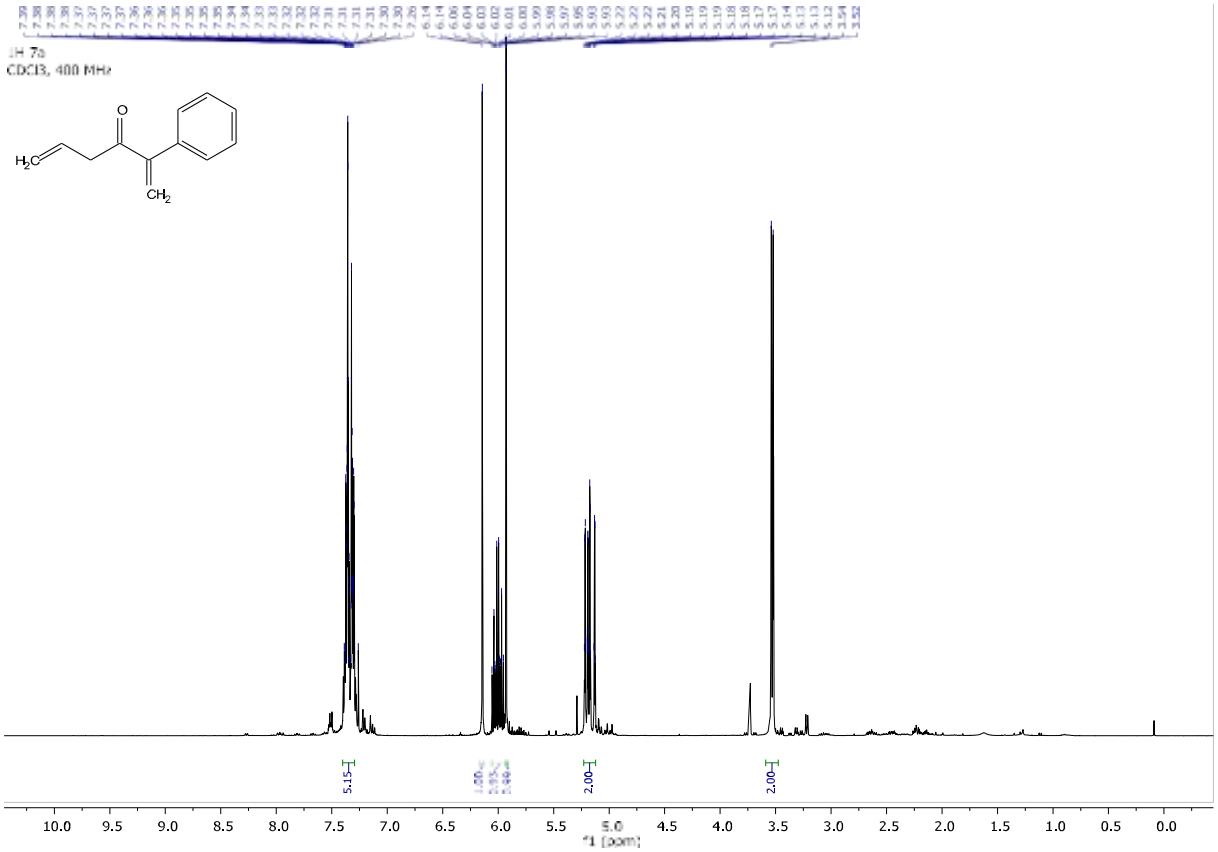


*Figure 10: ^{1}H NMR Spectra of **7b***

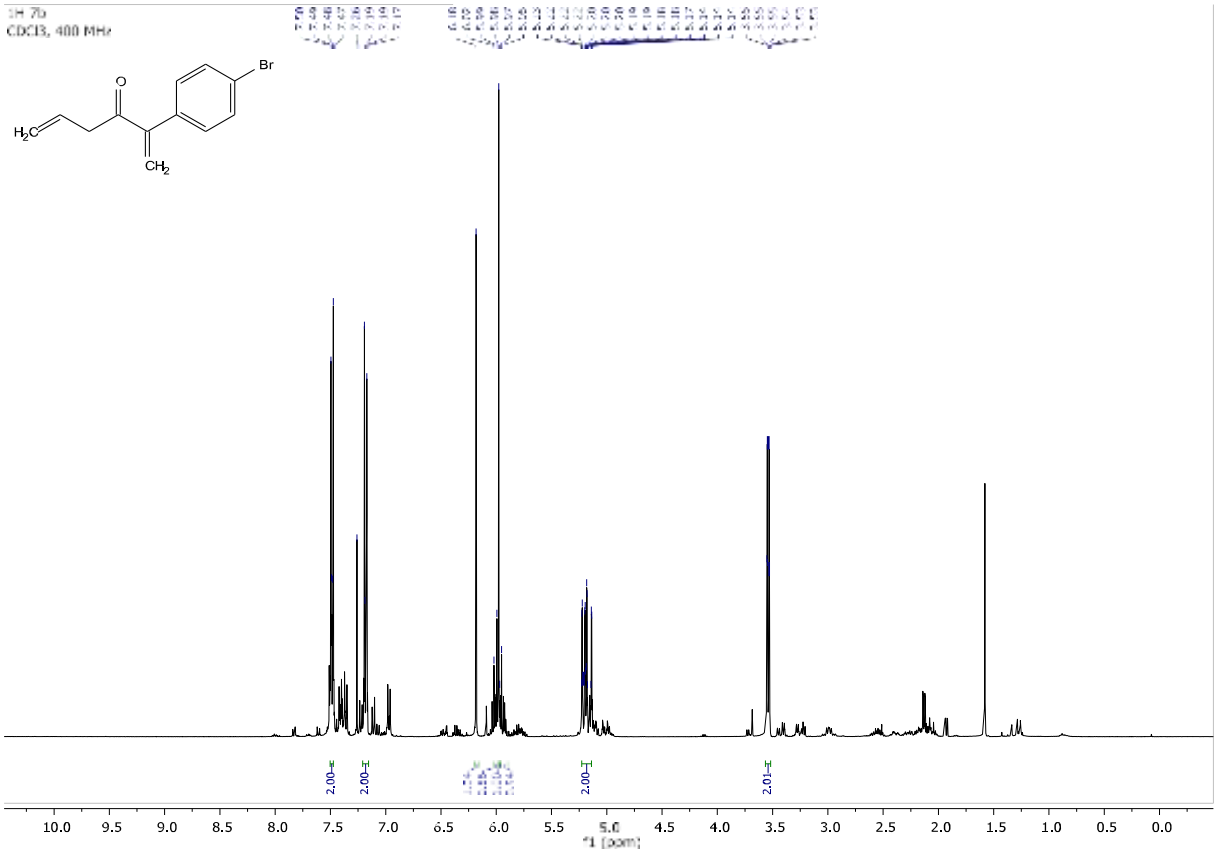


*Figure 11: ^{1}H NMR Spectra of **7c***

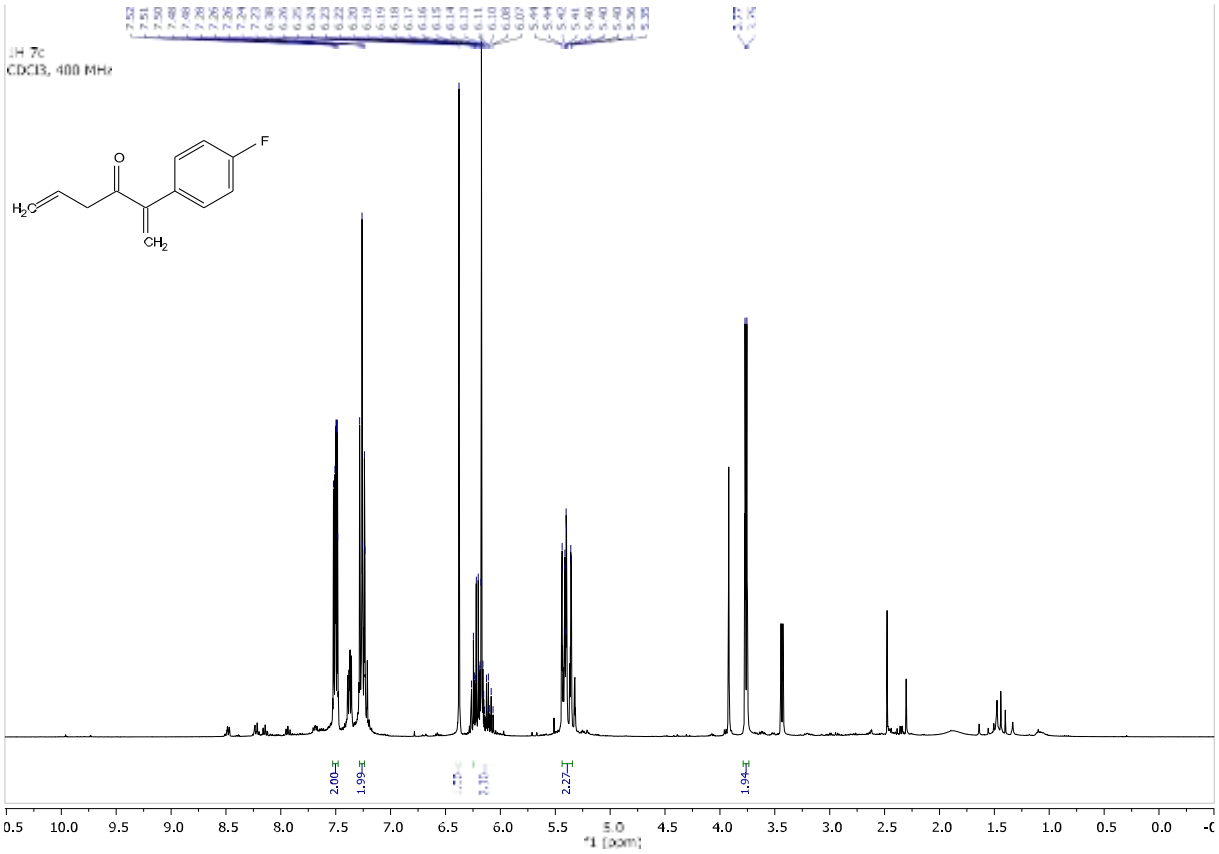


*Figure 12:[1]H NMR Spectra of **7d***

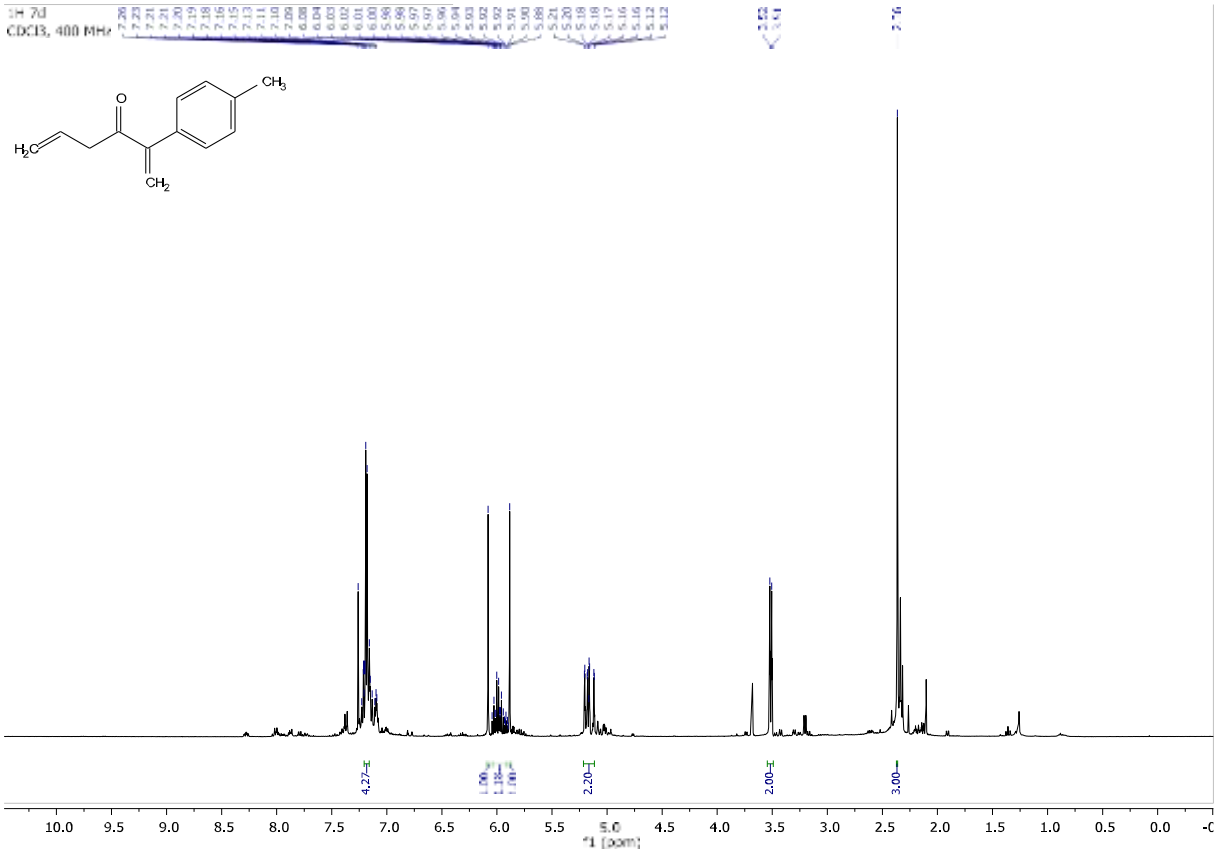
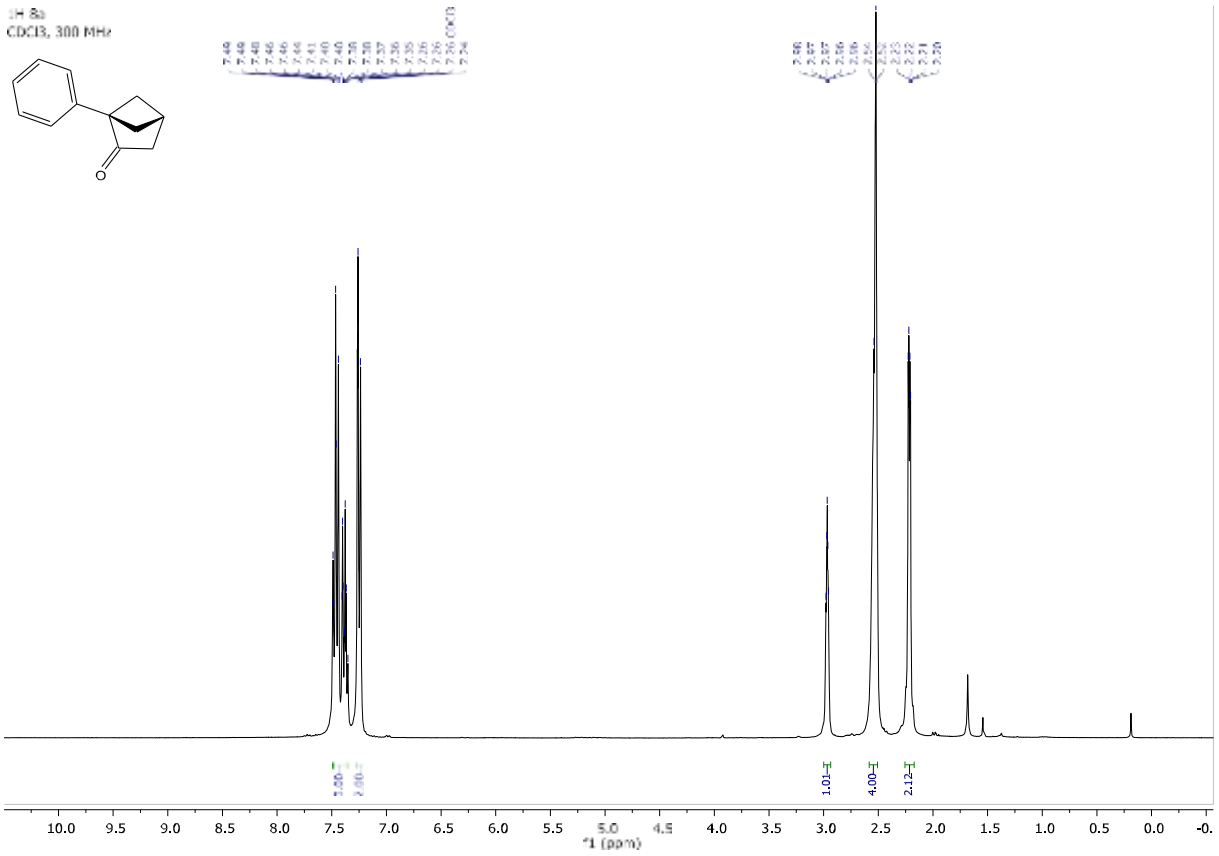


*Figure 13: NMR Spectra of **8a***



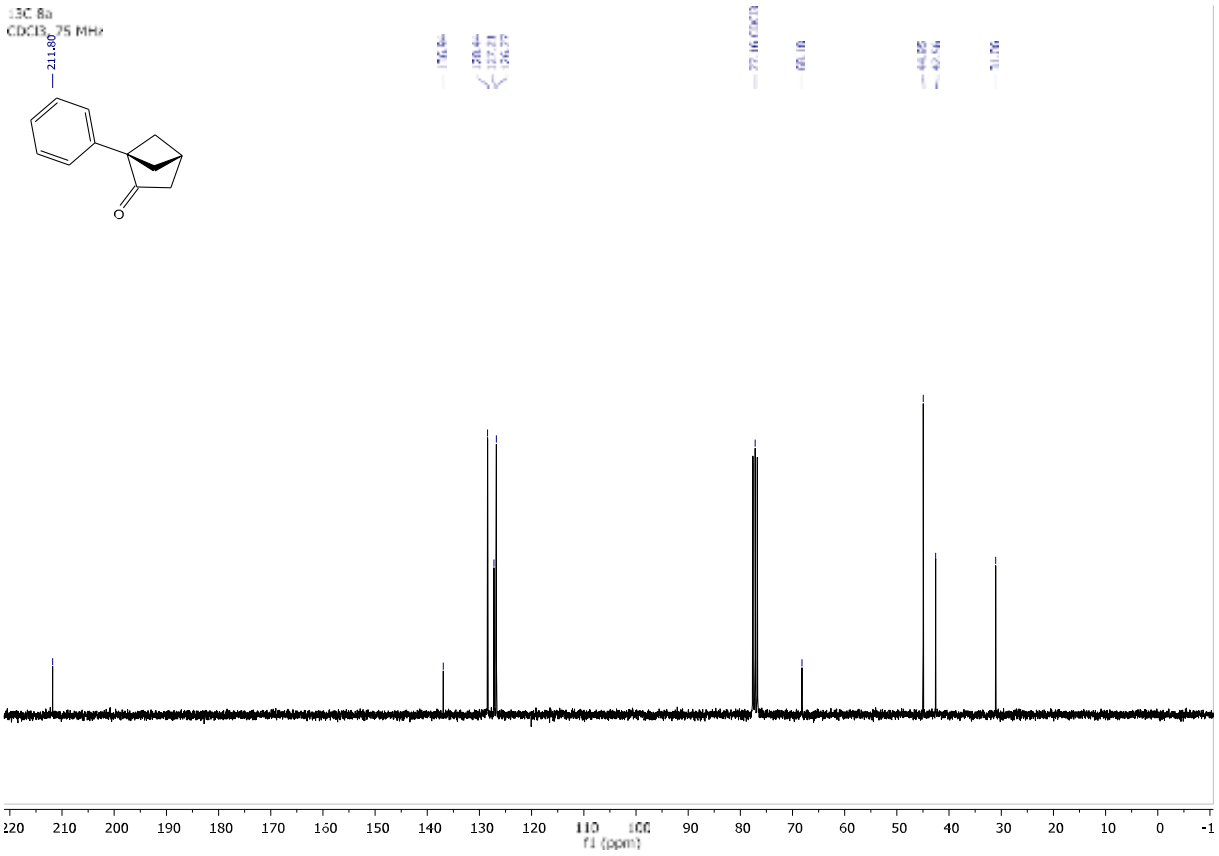
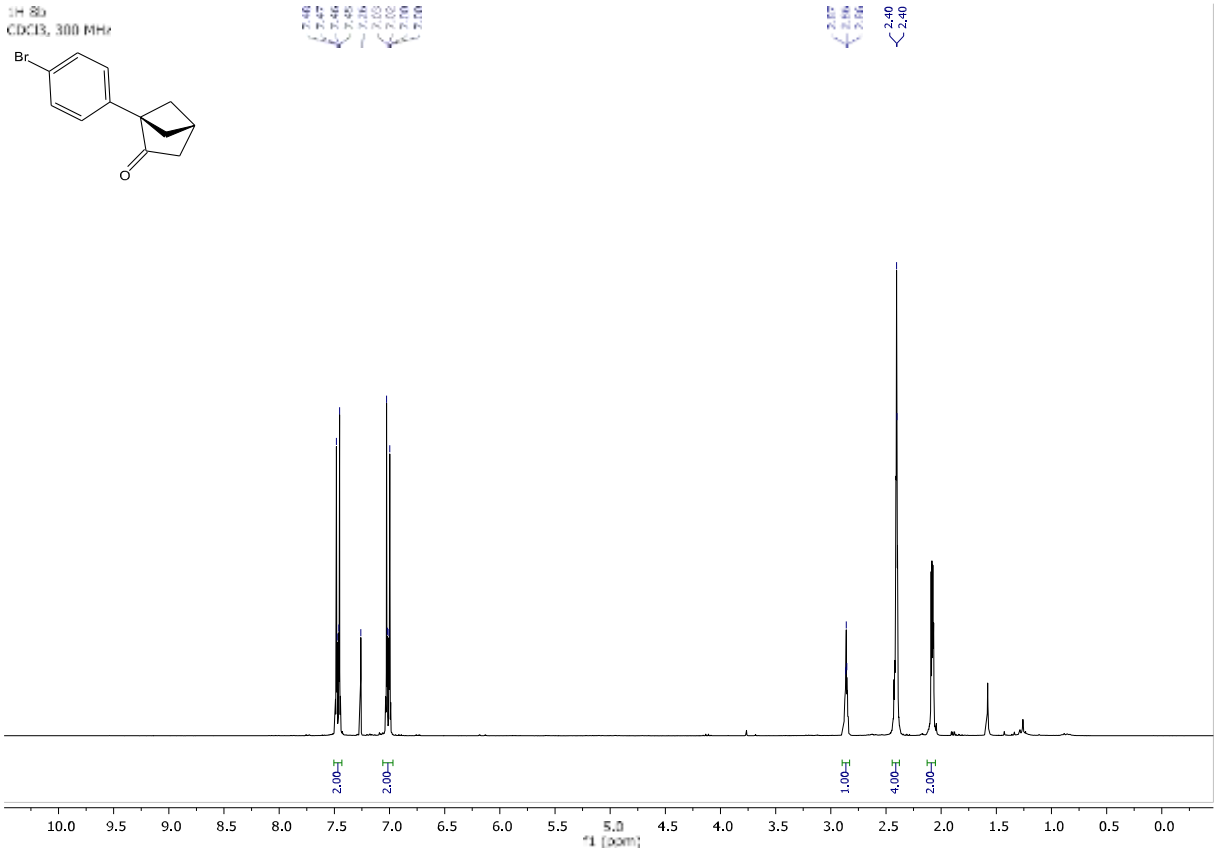


*Figure 14: NMR Spectra of **8b***



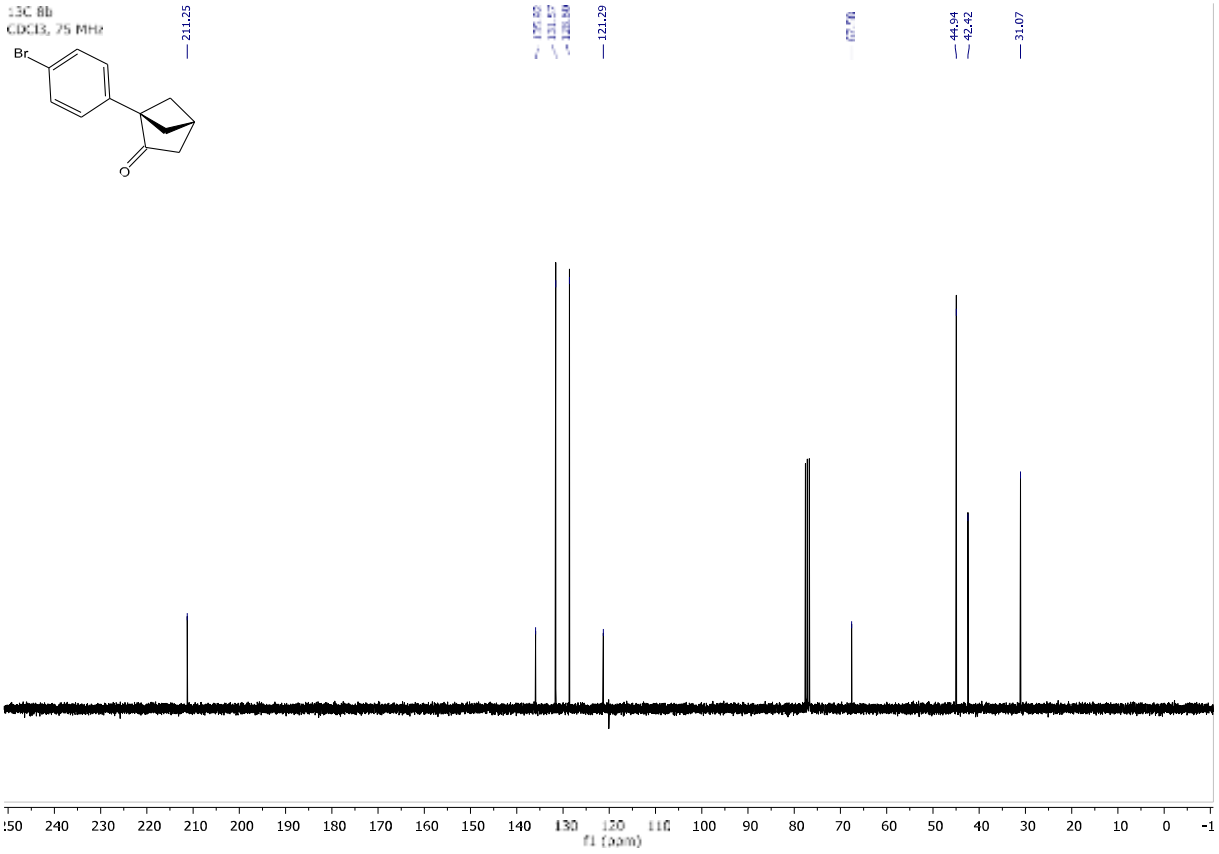


*Figure 15: NMR Spectra of **8c***

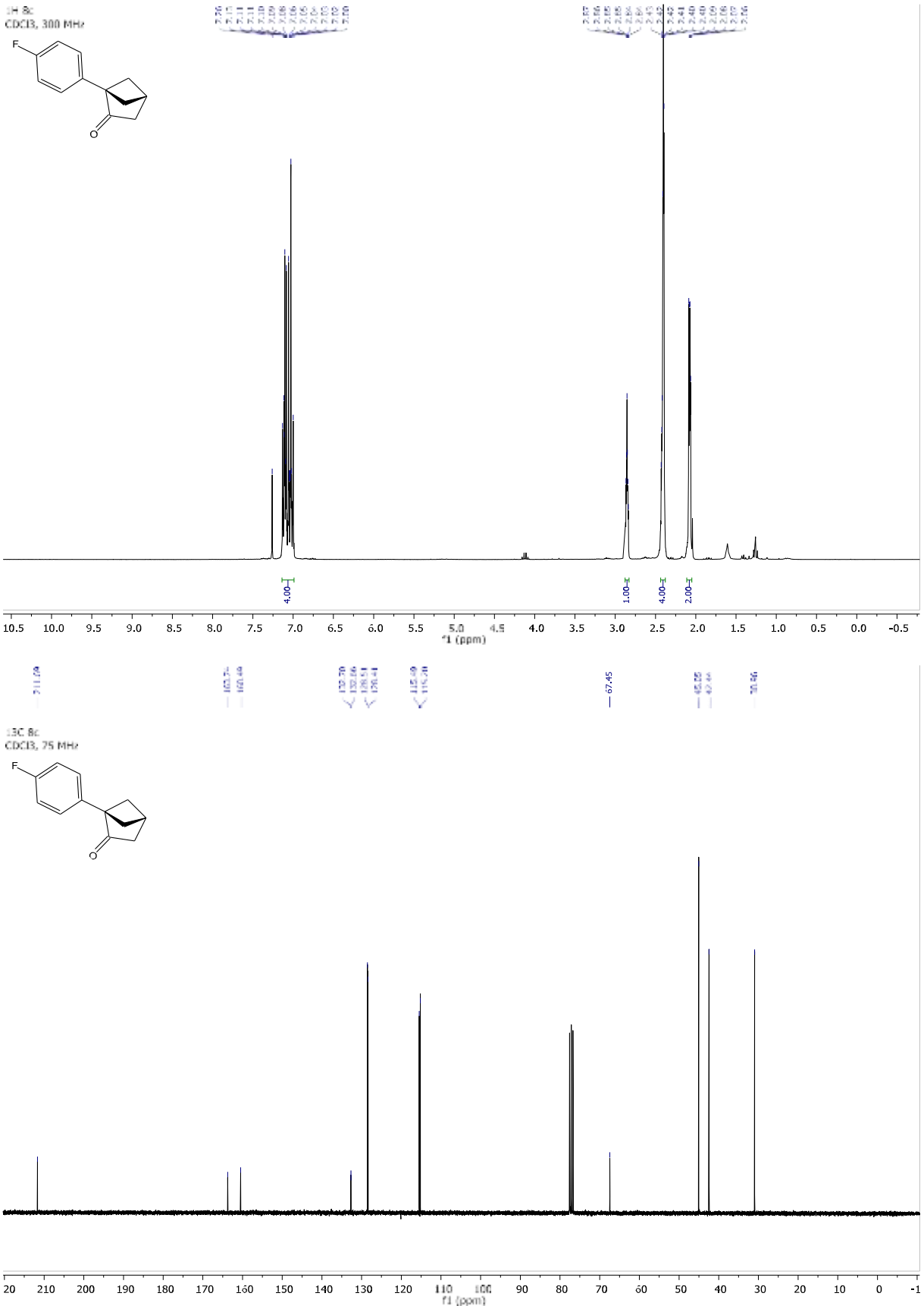


*Figure 16: NMR Spectra of **8d***

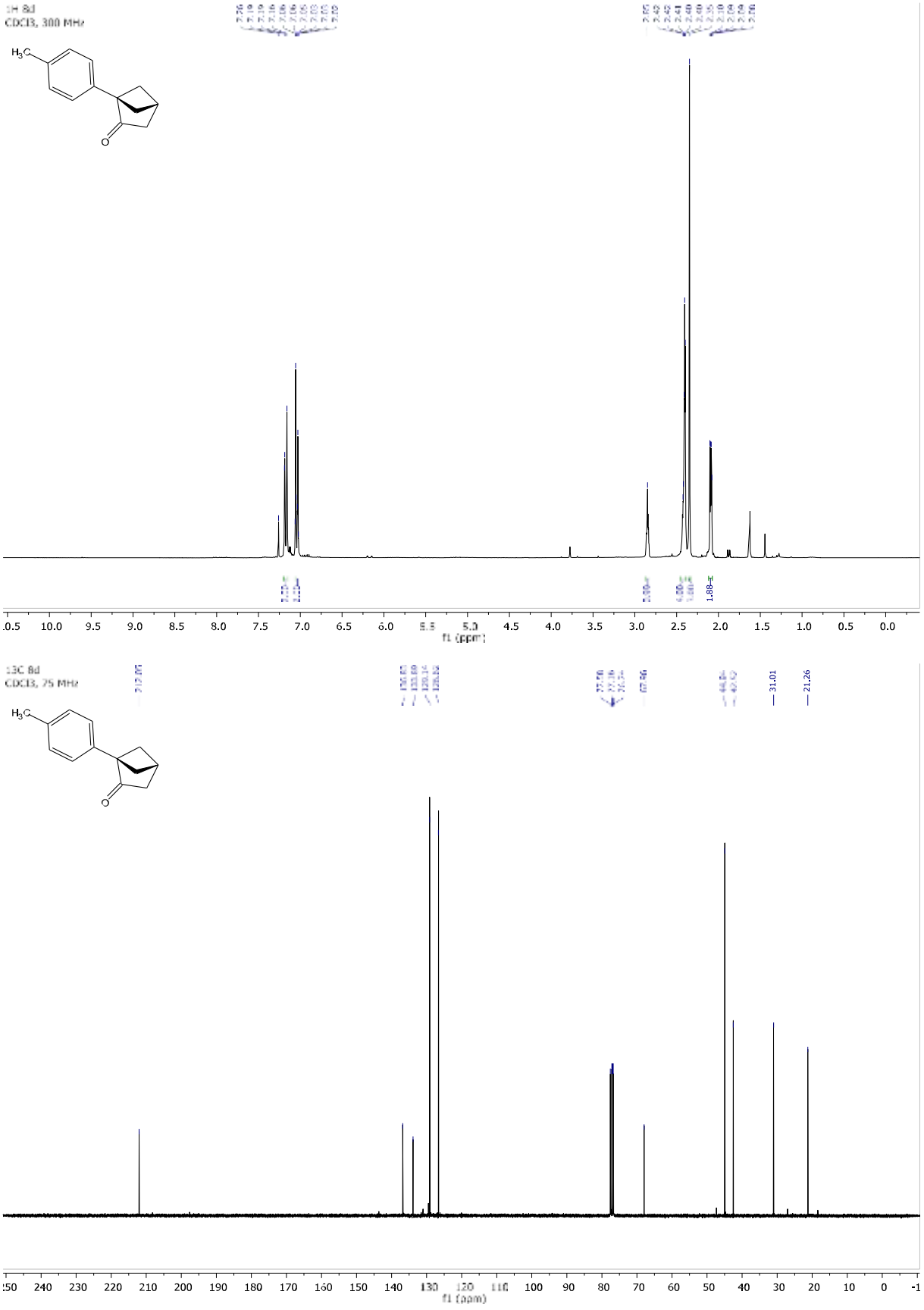
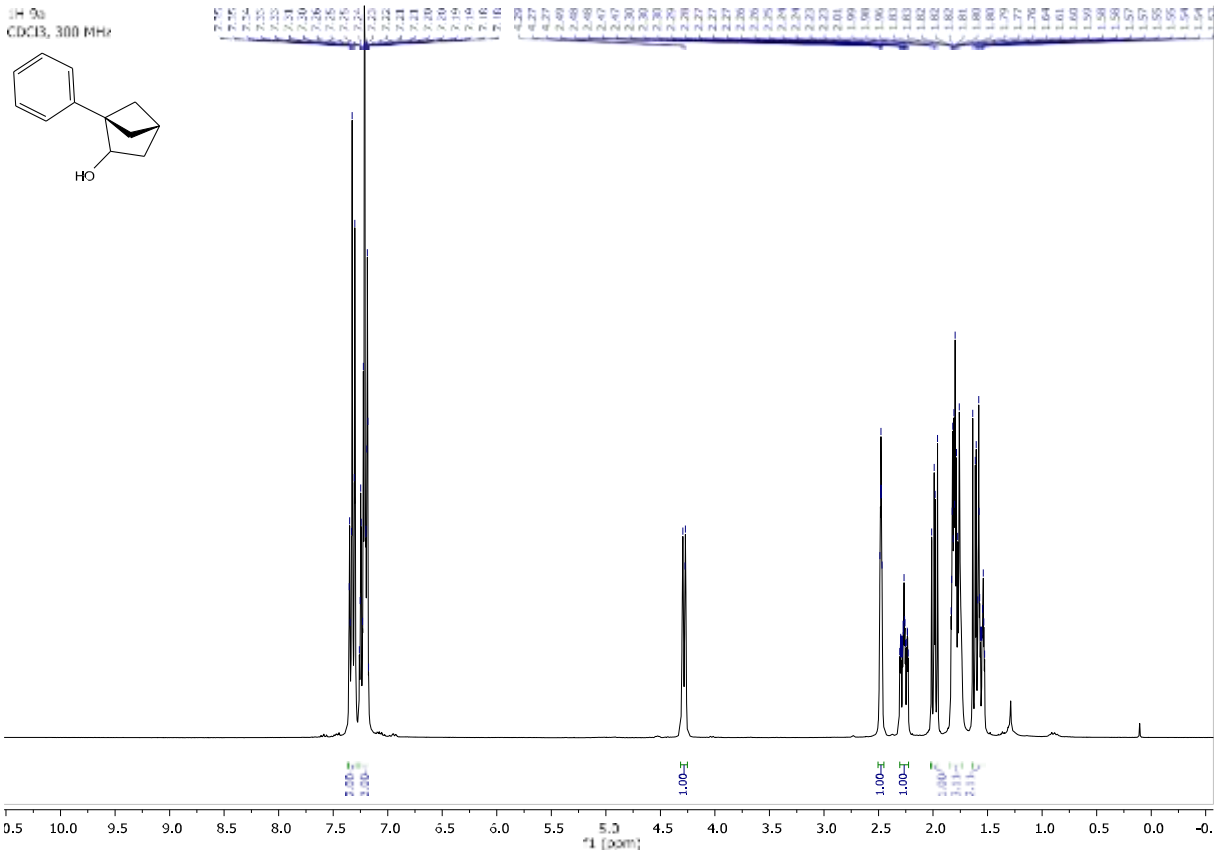


*Figure 17: NMR Spectra of **9a***



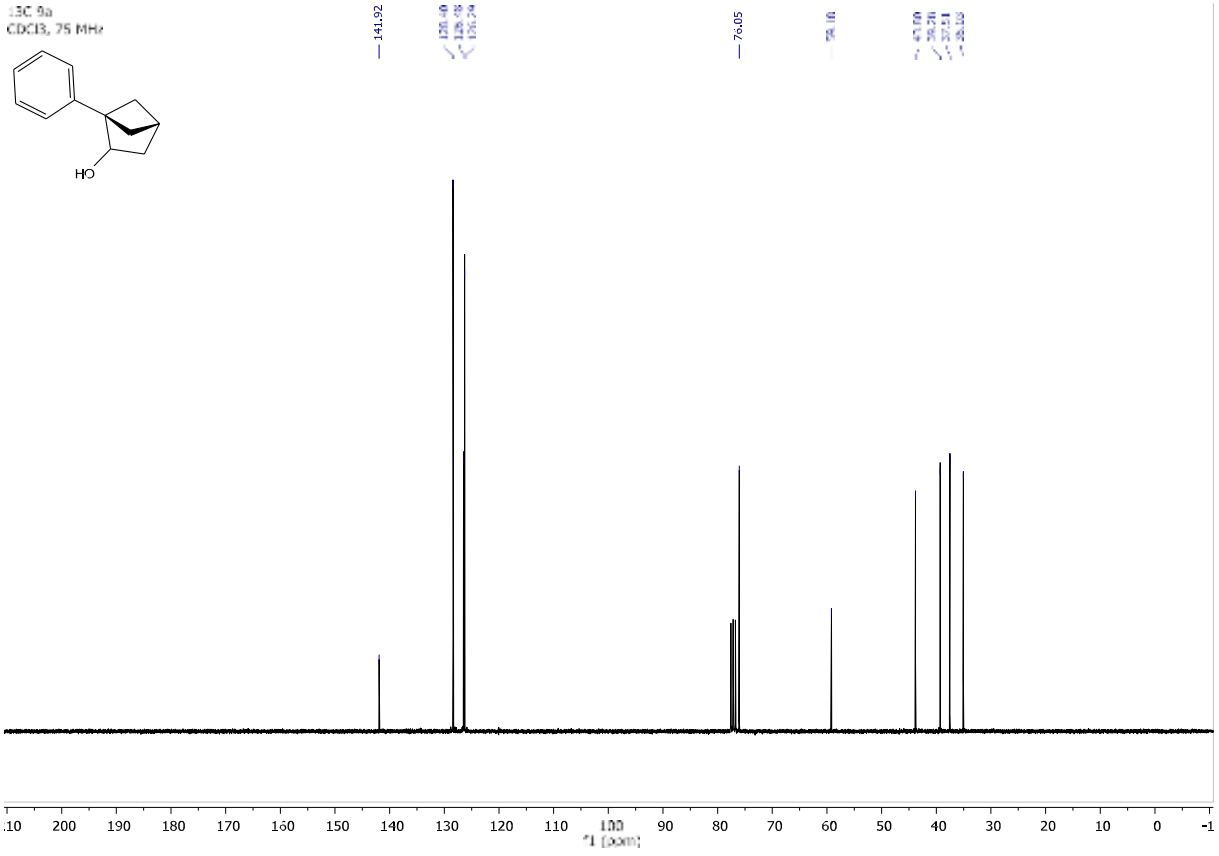
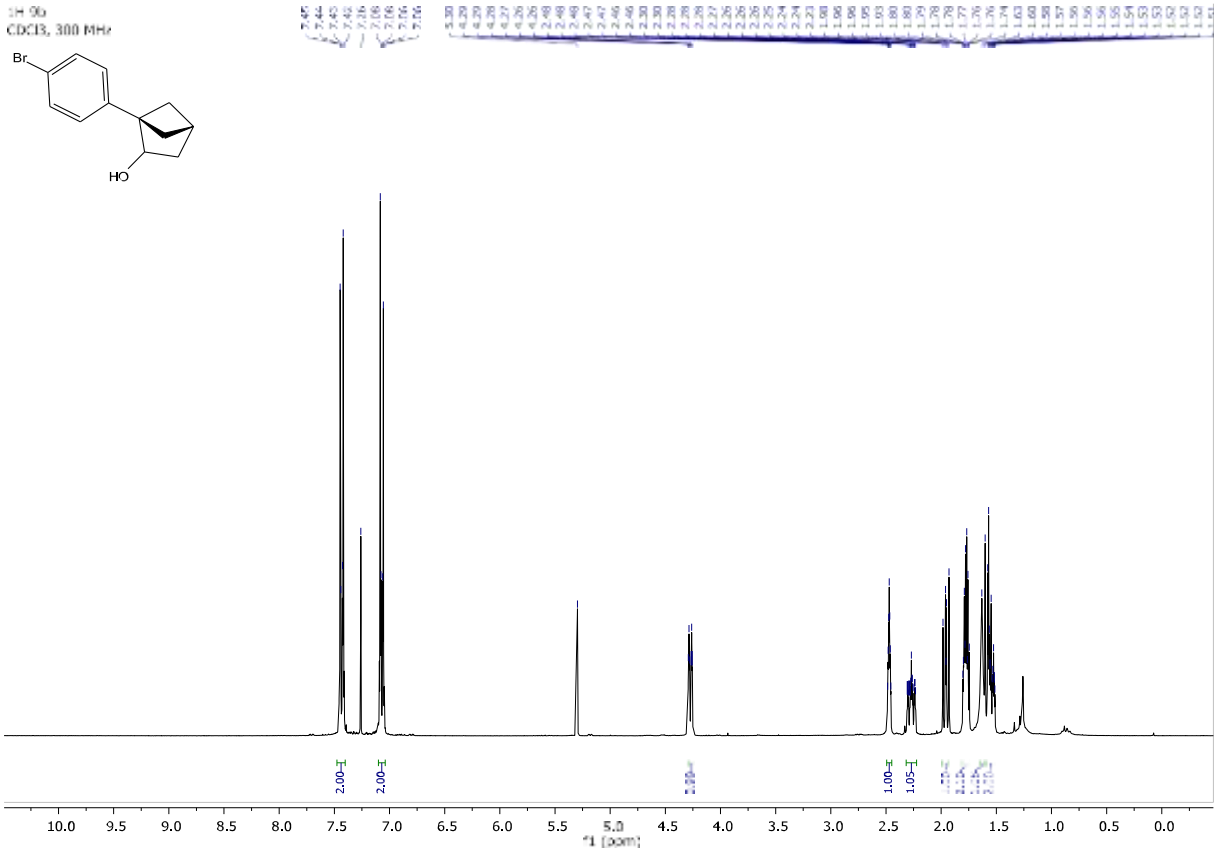


*Figure 18: NMR Spectra of **9b***



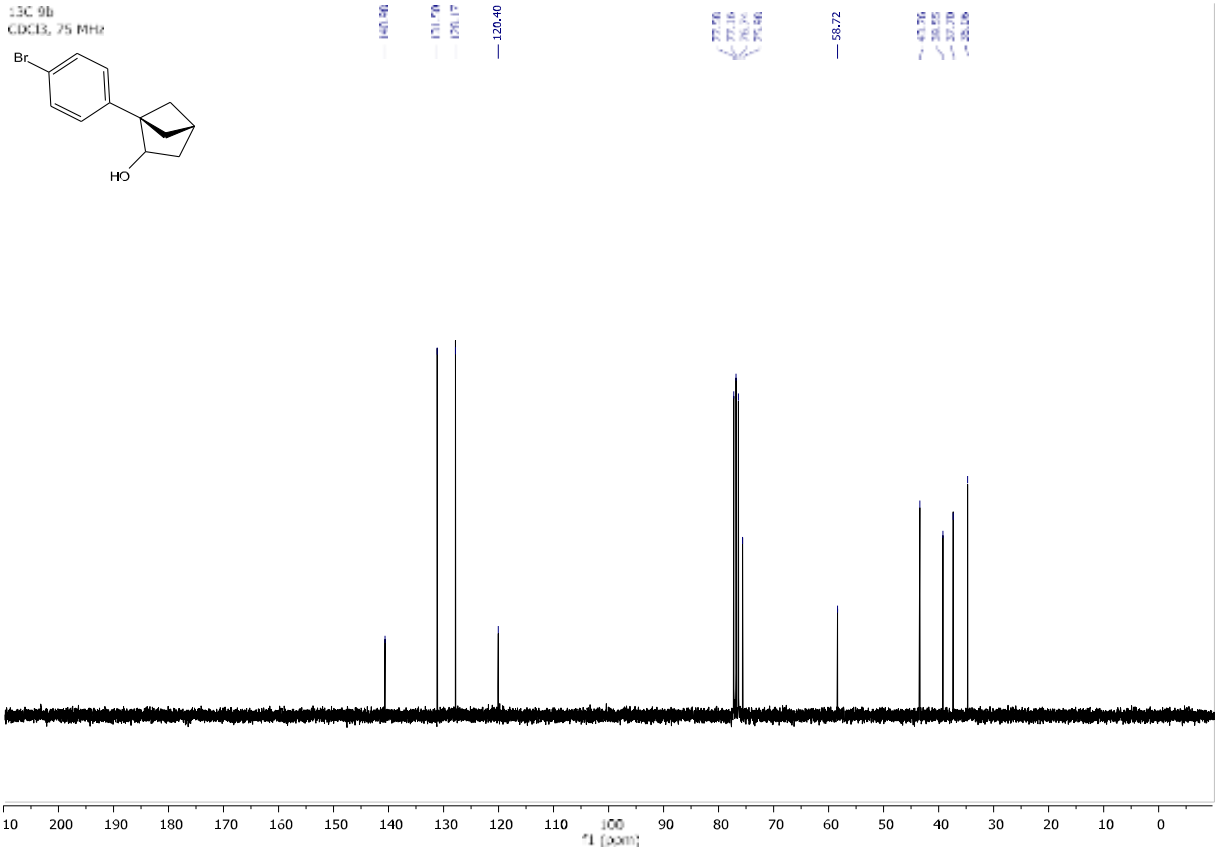
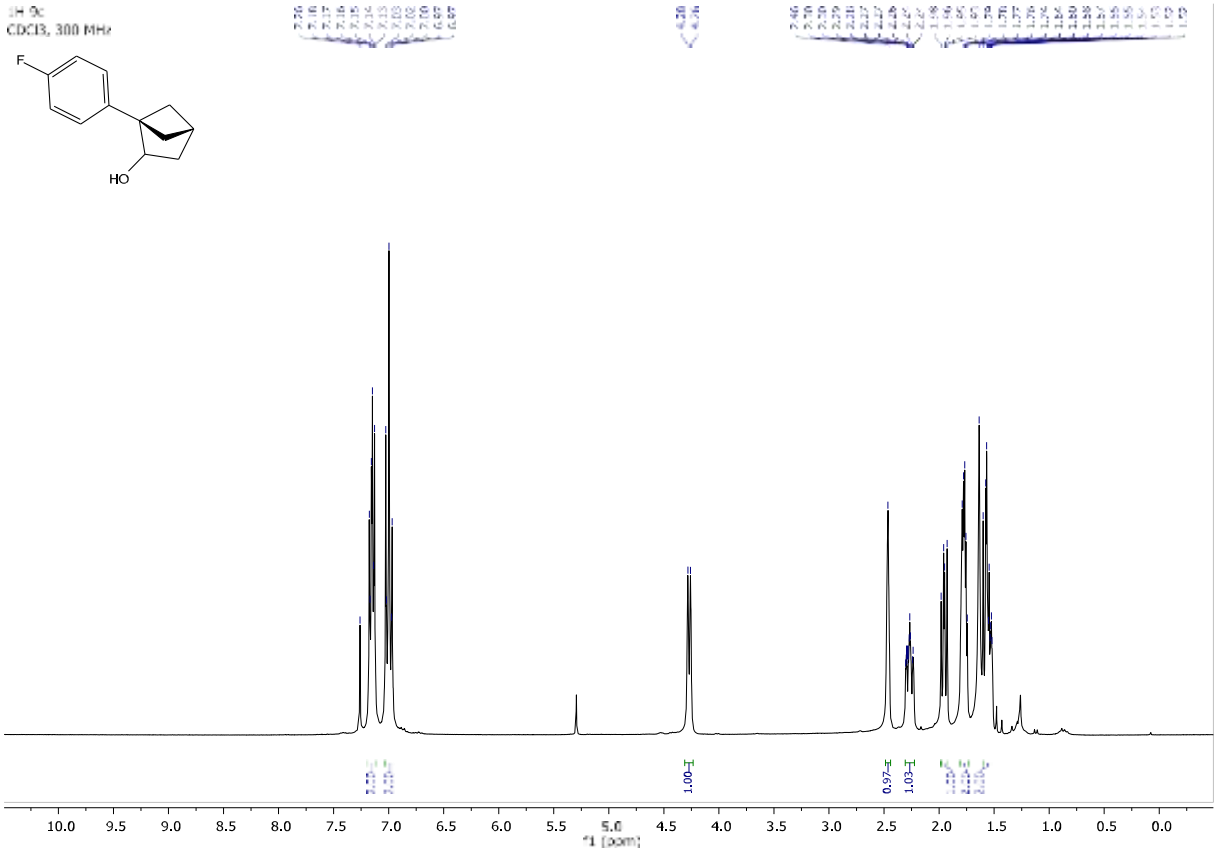


*Figure 19: NMR Spectra of **9c***



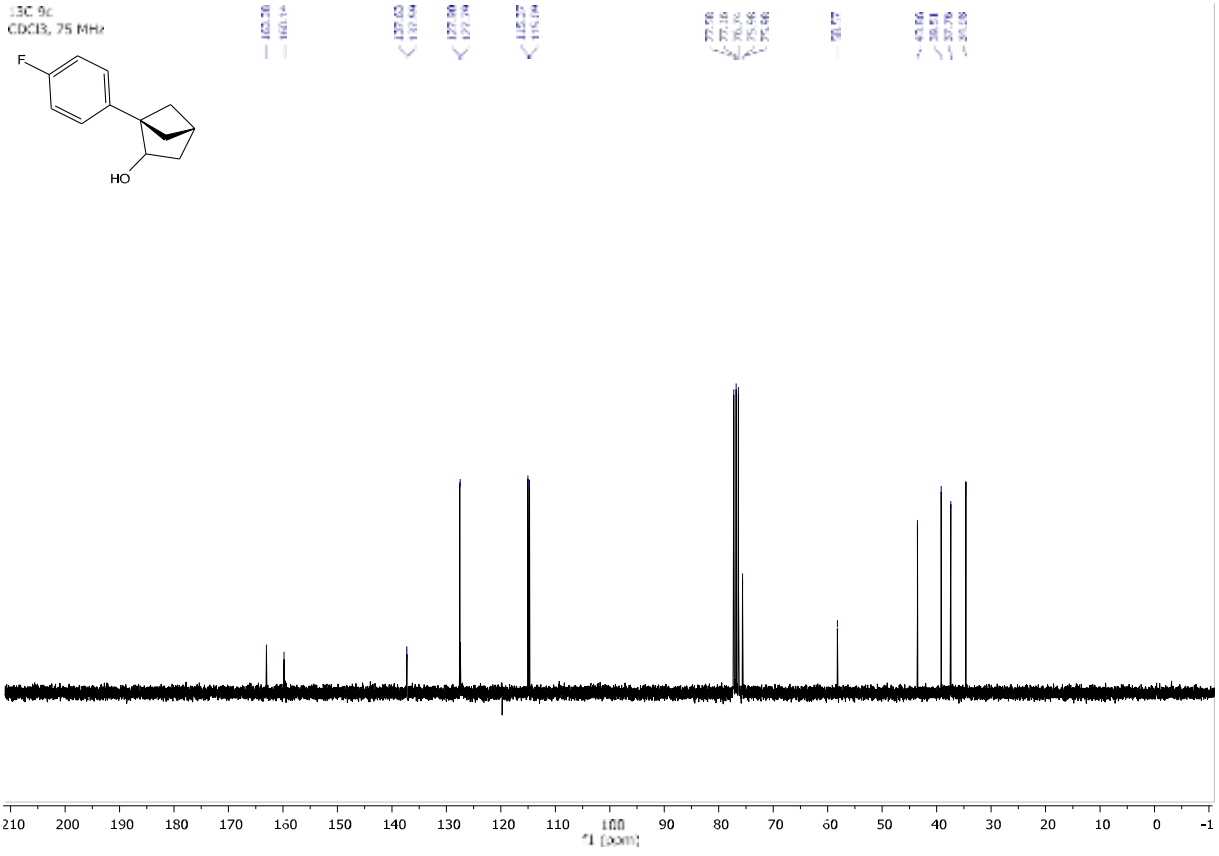
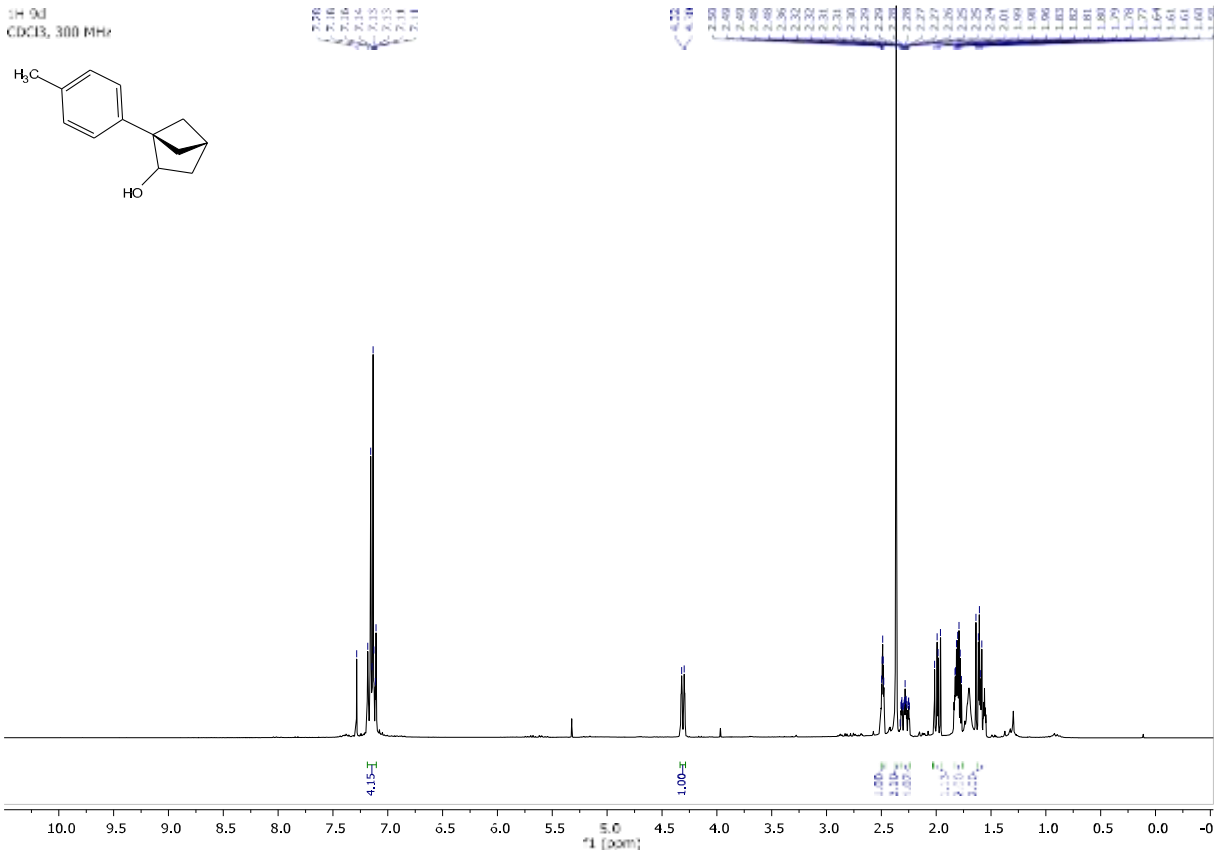


*Figure 20 NMR Spectra of **9d***



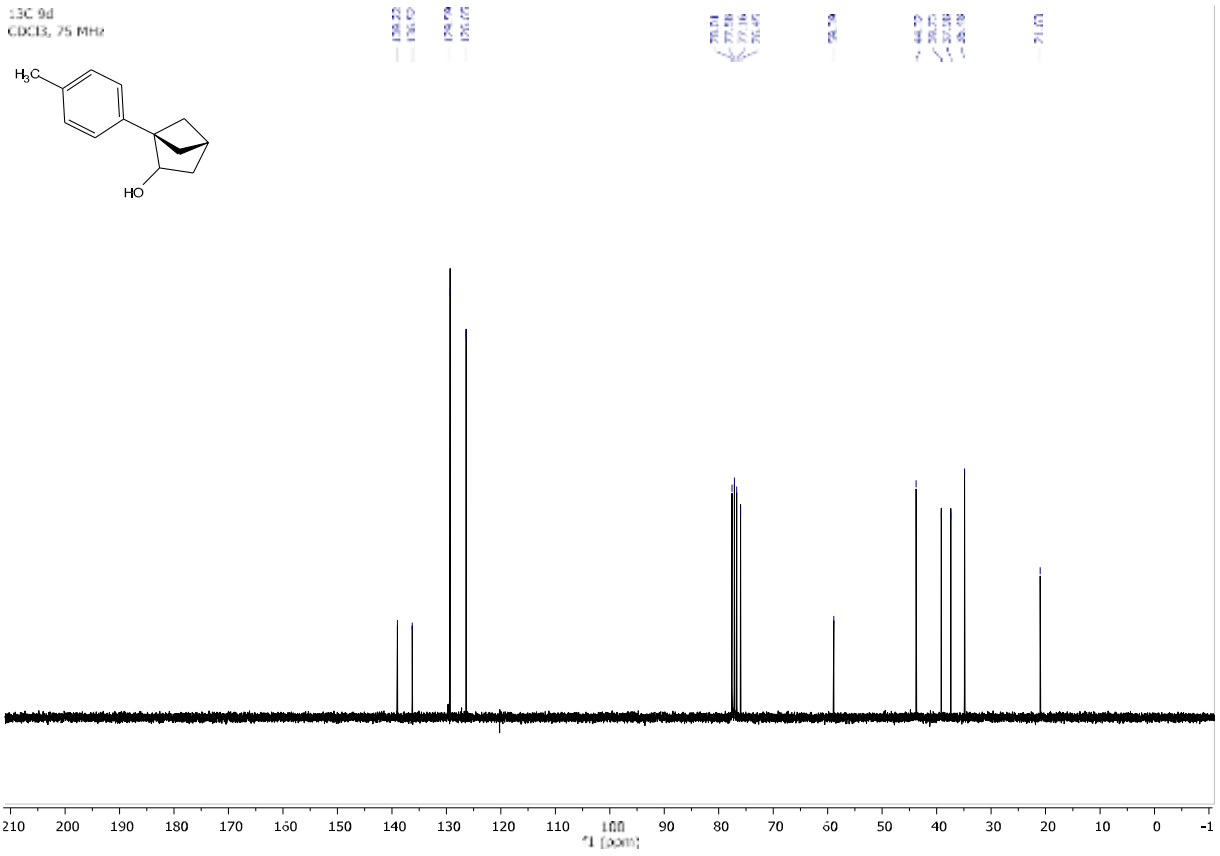


*Figure 21: ^{1}H Spectra for **10***

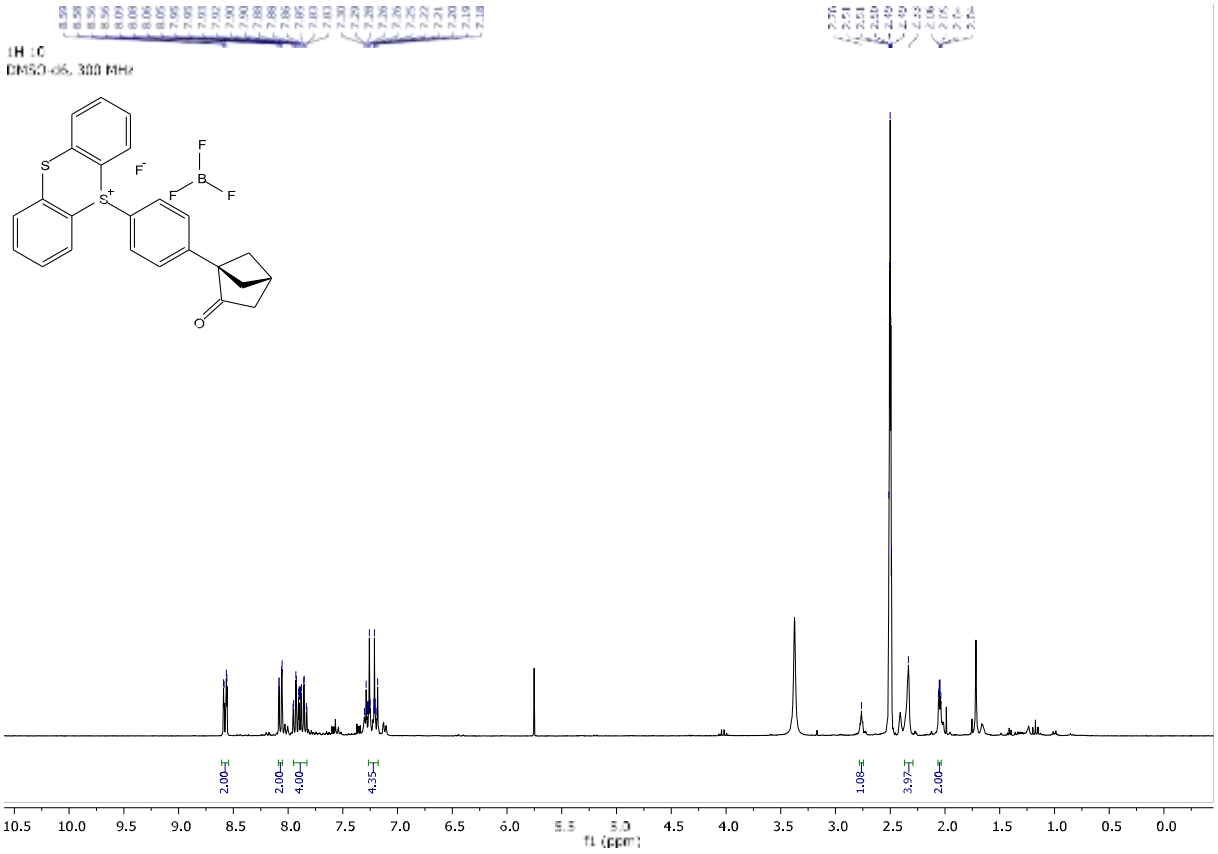


*Figure 22: NMR Spectra for **11***

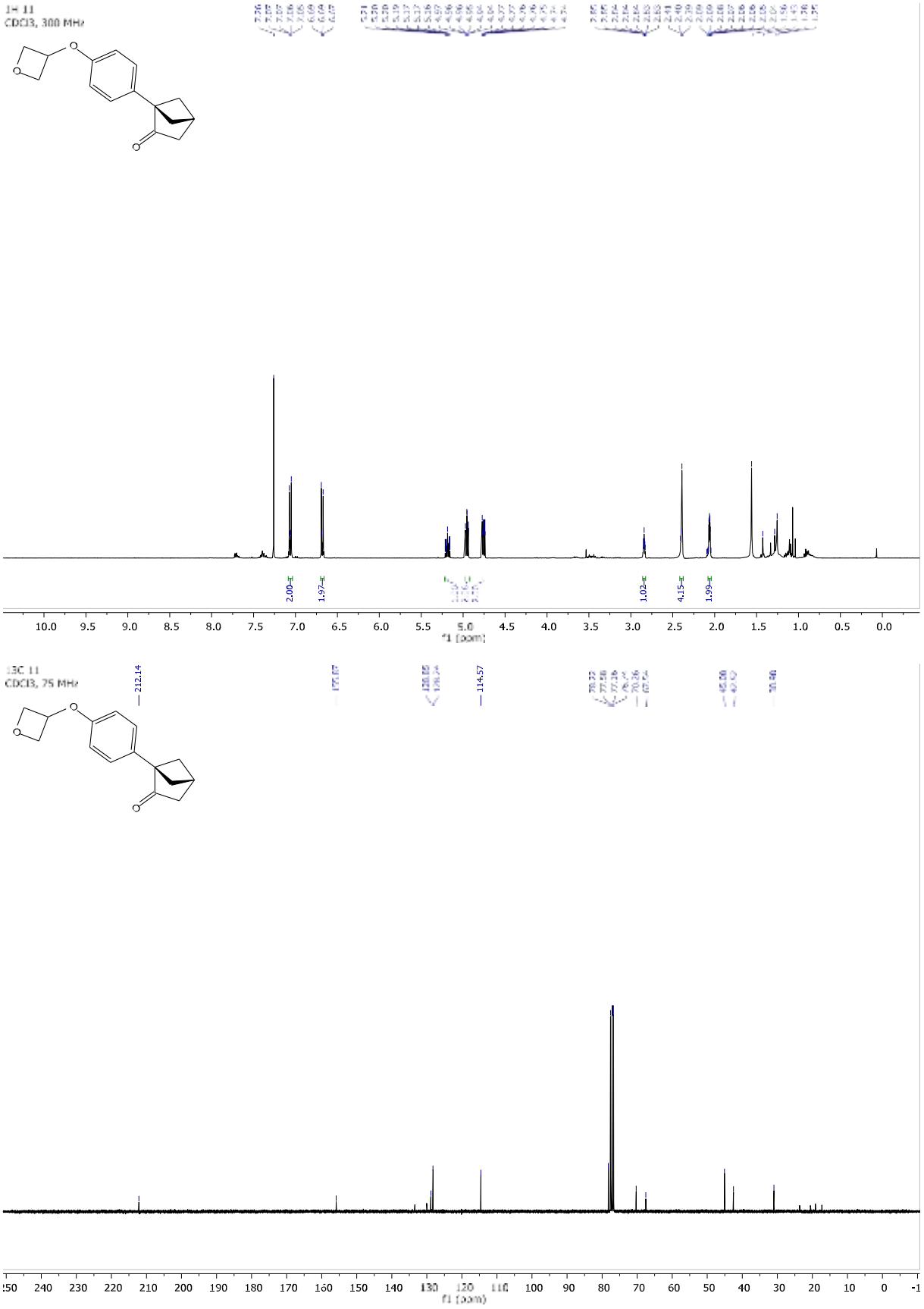


*Figure 23: NMR Spectra for **12a & 12b***

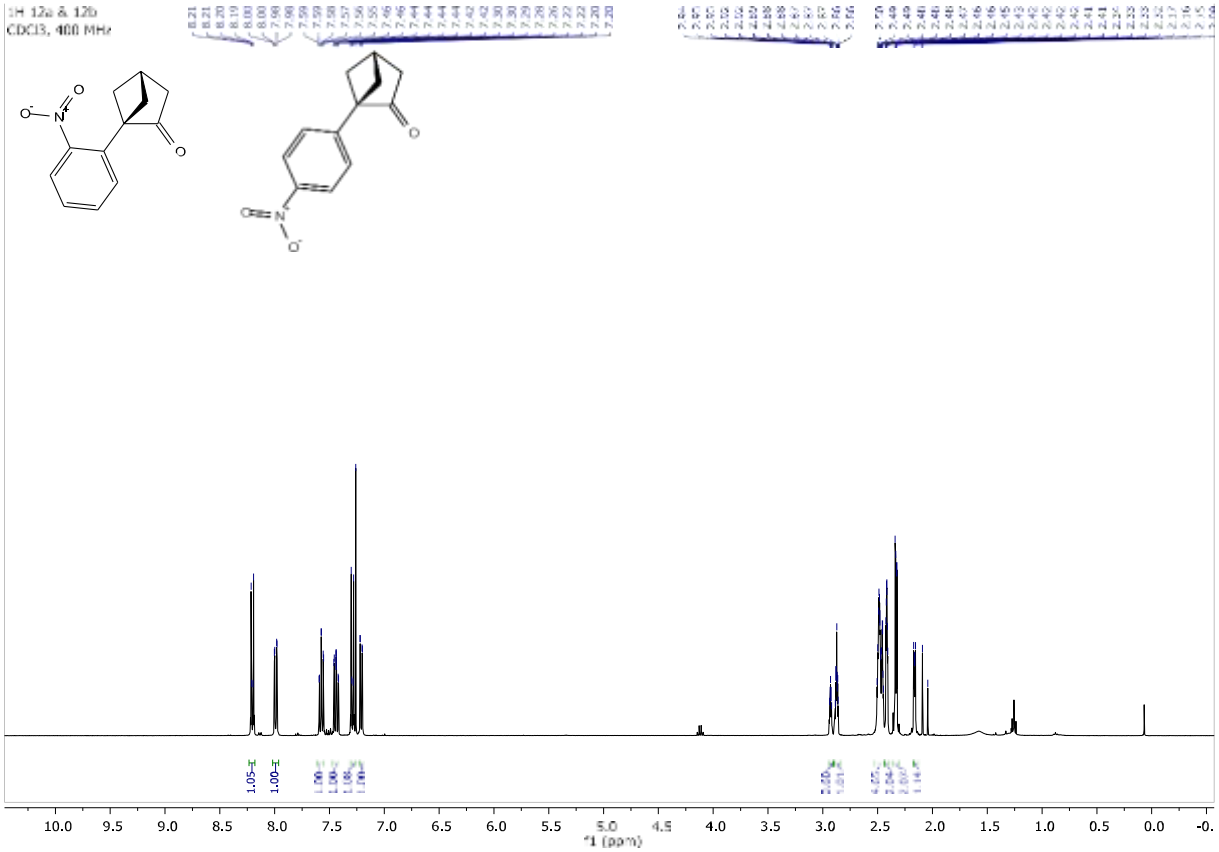


*Figure 24: NMR Spectra for **13***

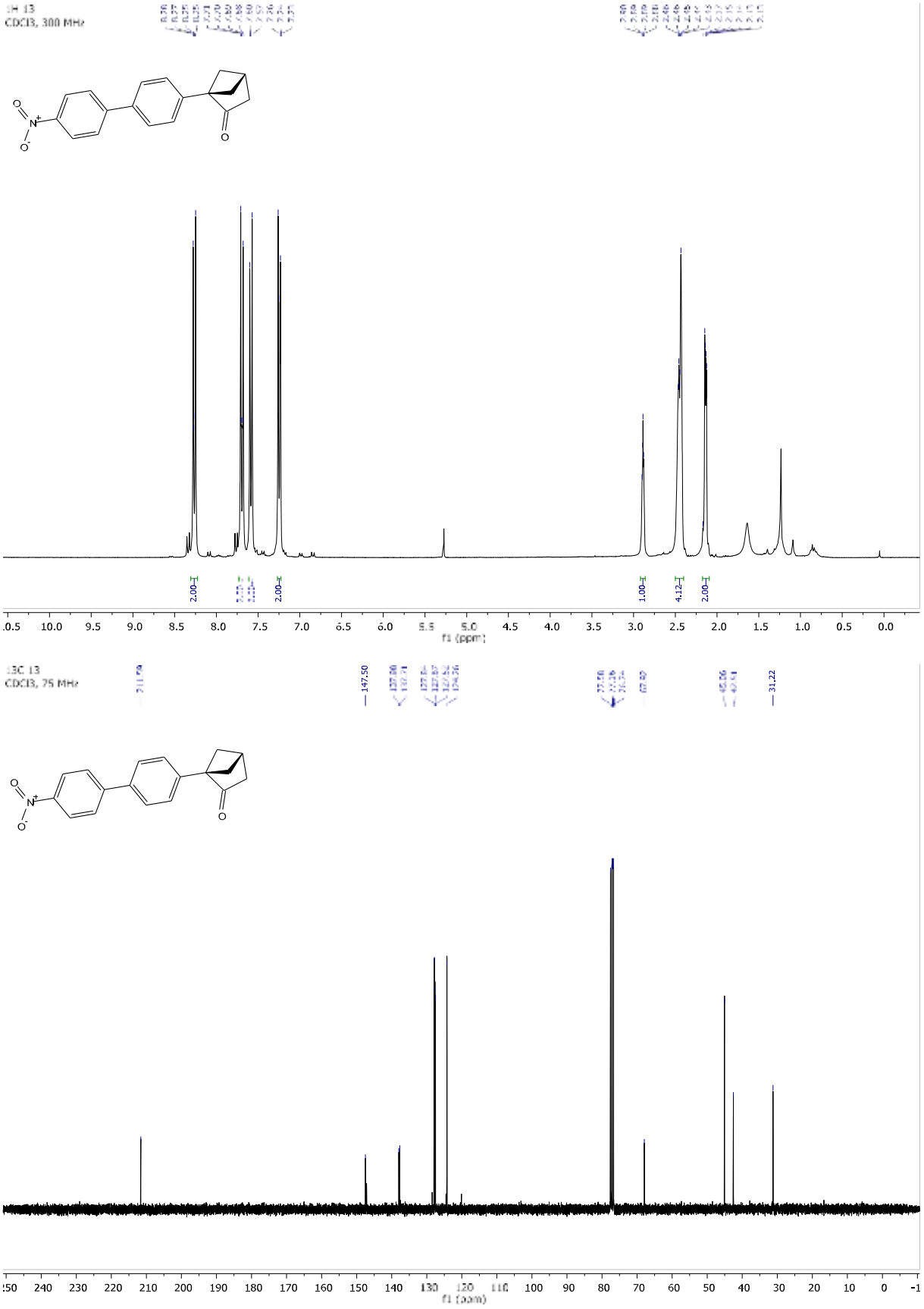
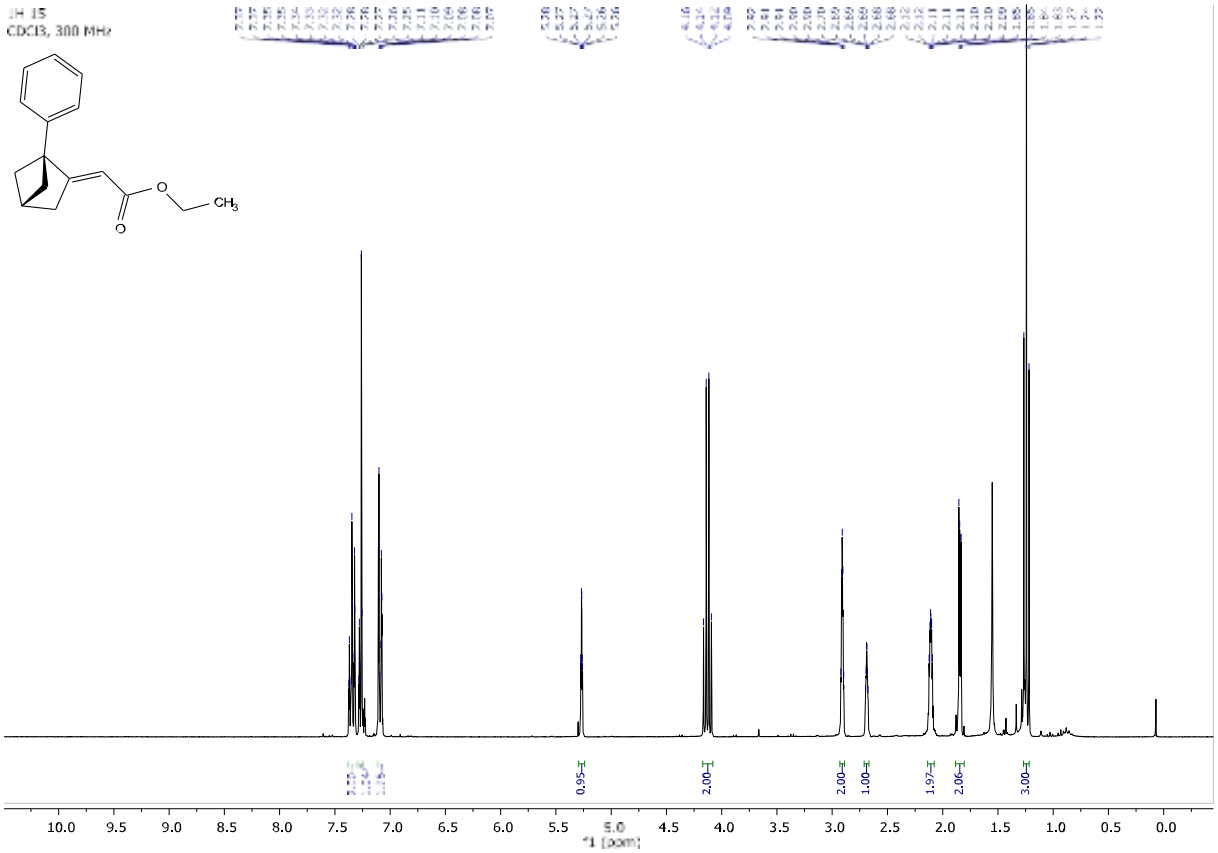


*Figure 25: NMR Spectra for **15***



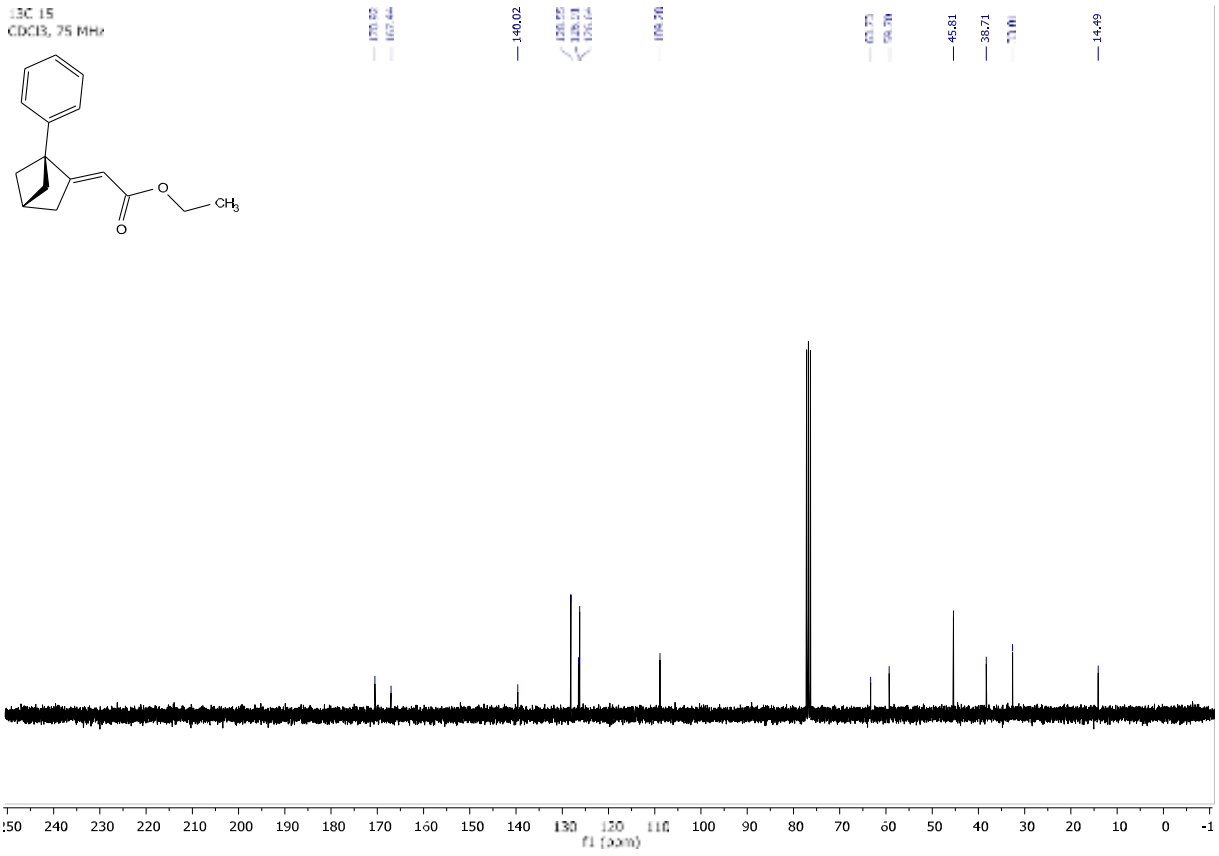


*Figure 26: ^{1}H NMR Spectra for **16***

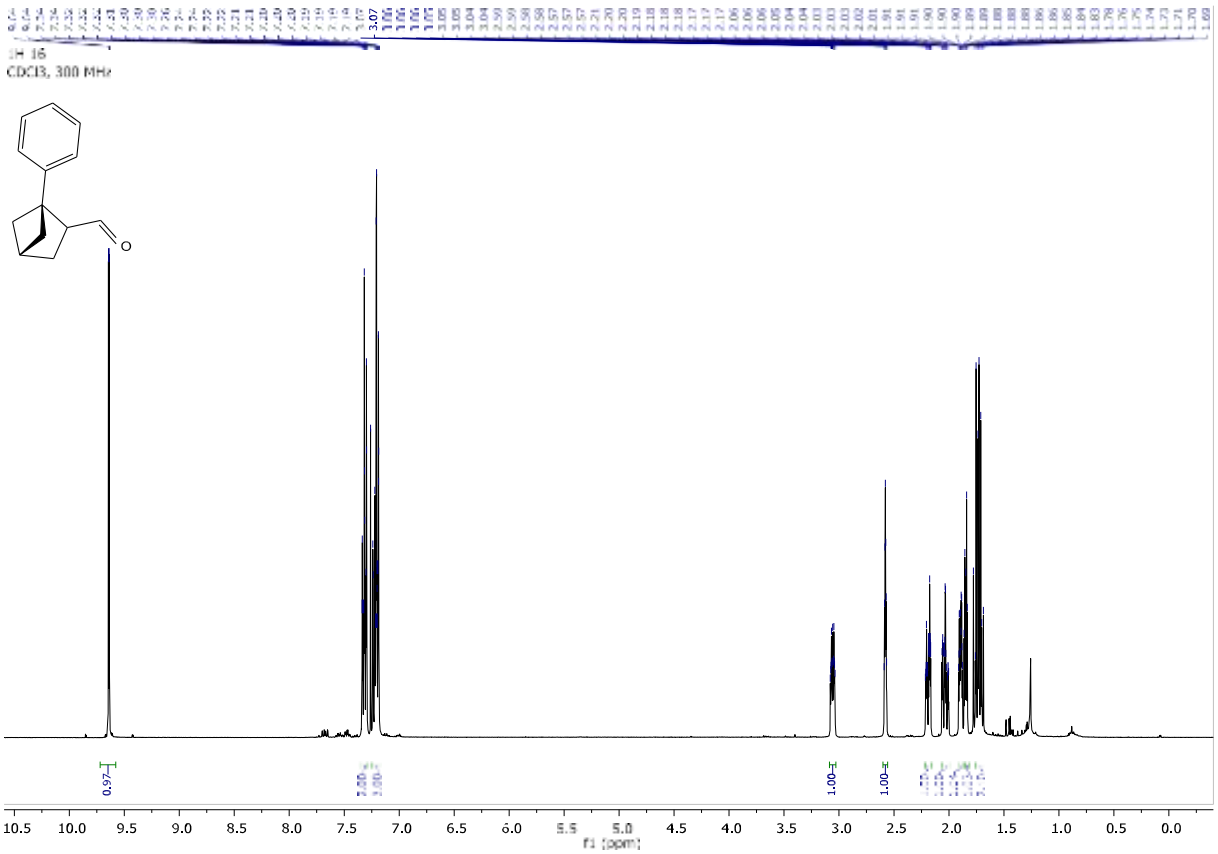
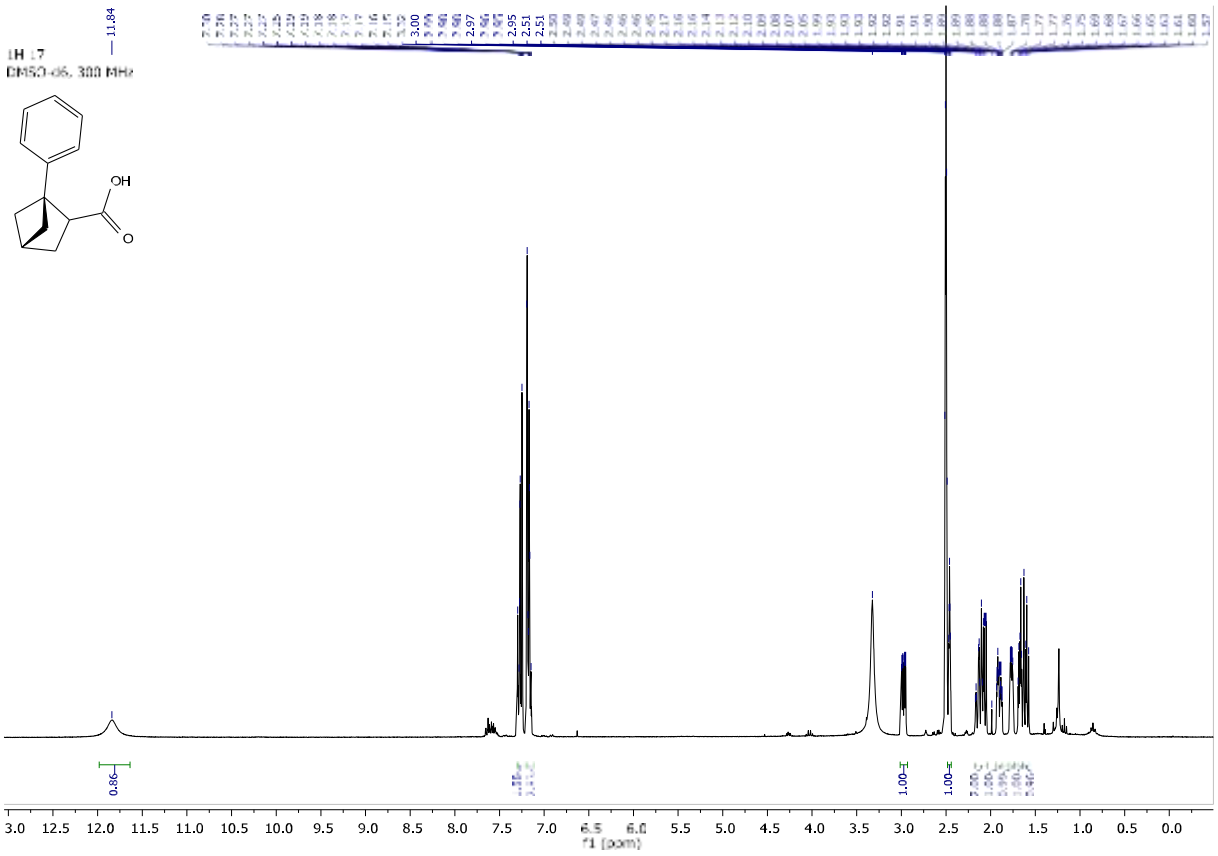


*Figure 27: NMR Spectra for **17***



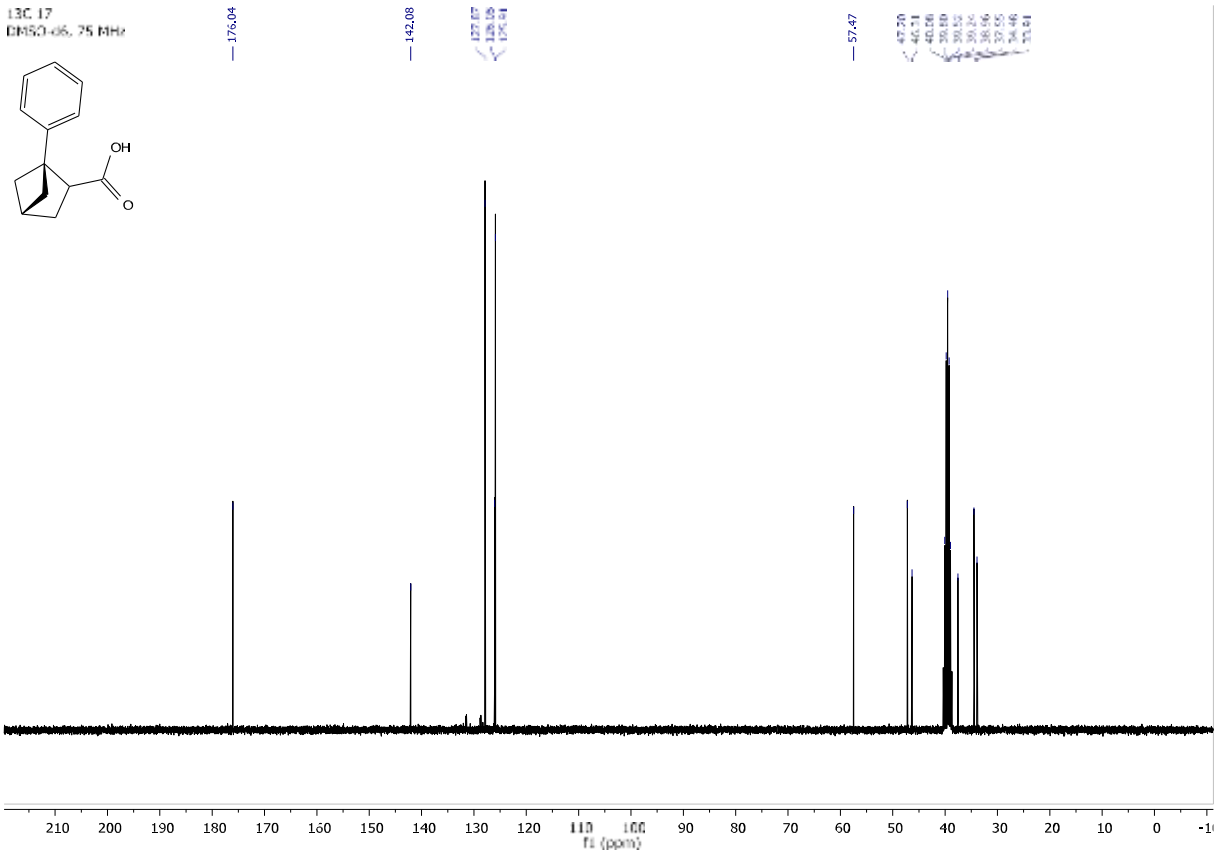


*Figure 28: NMR Spectra for **18a***

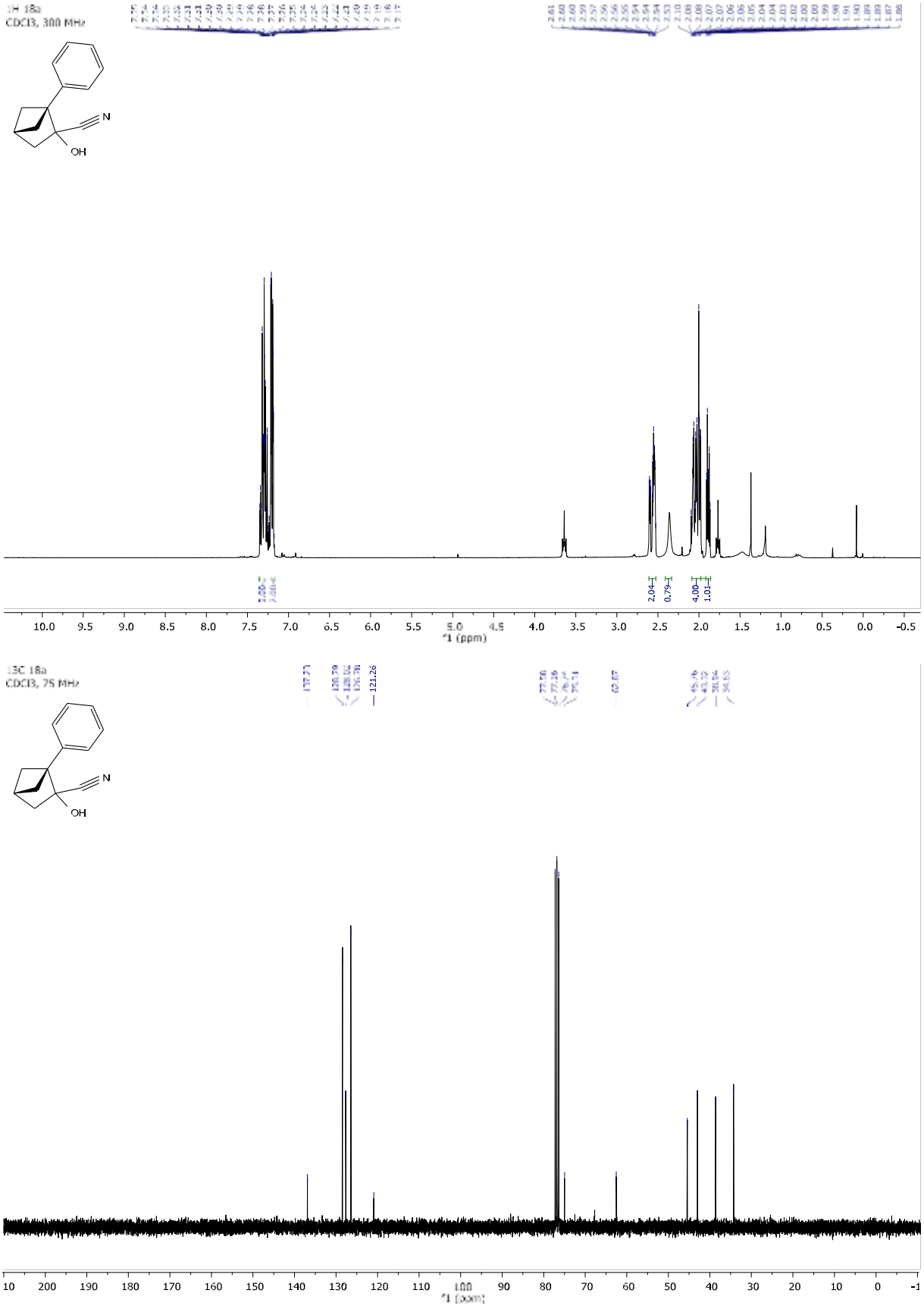
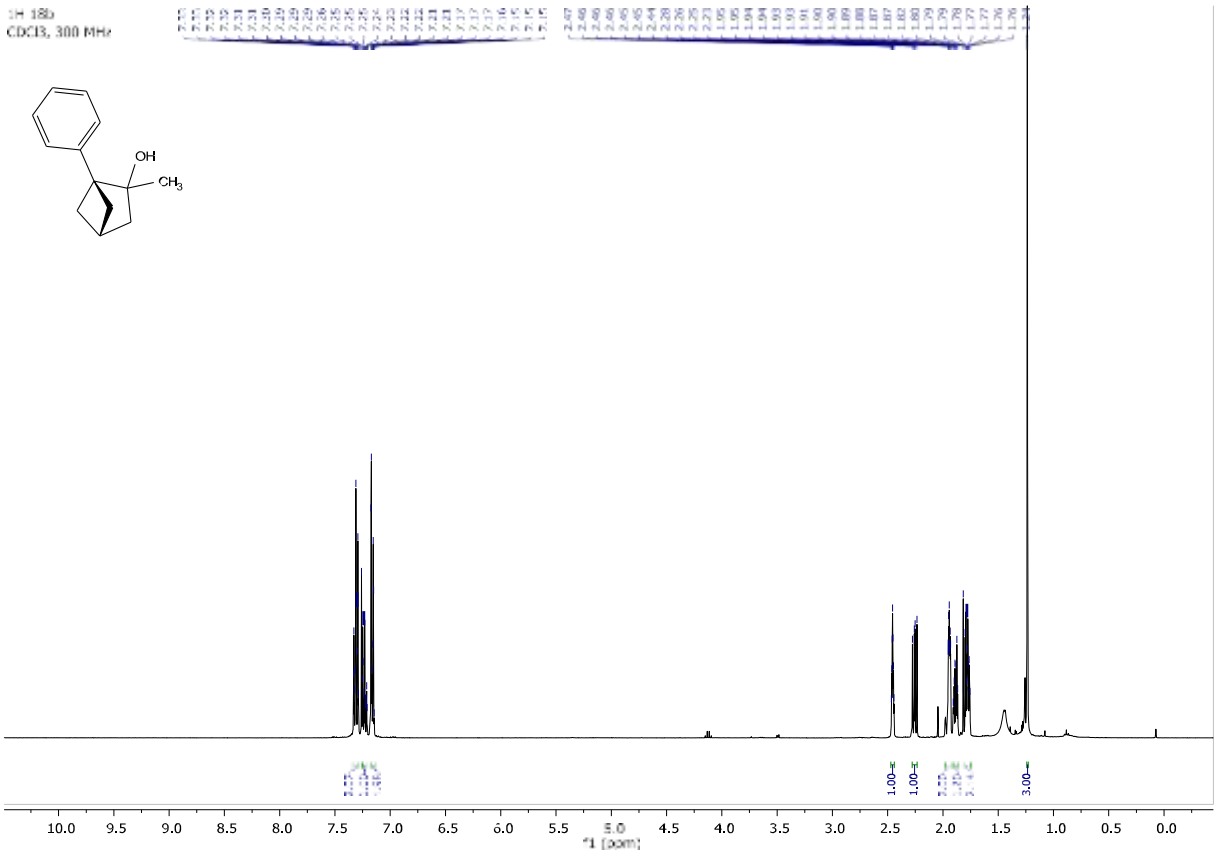


*Figure 29: NMR Spectra for **18b***



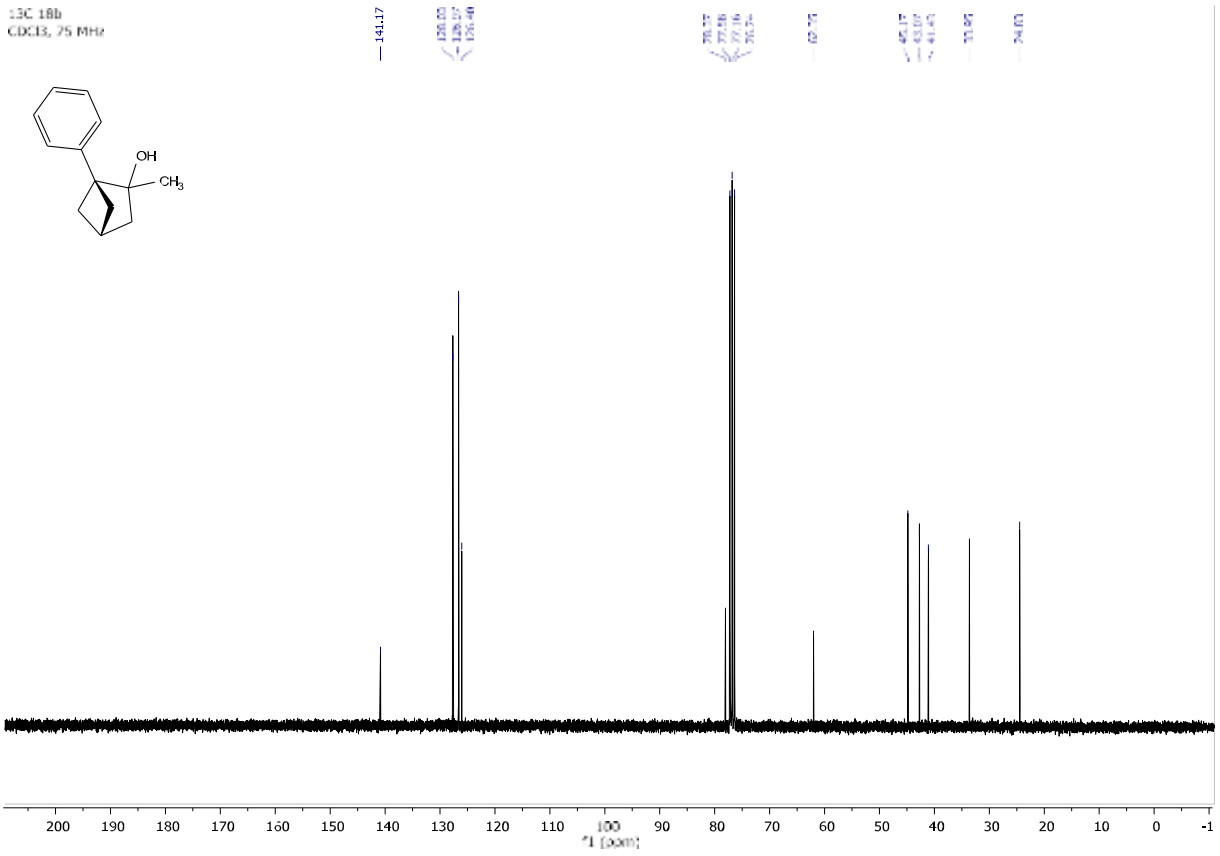
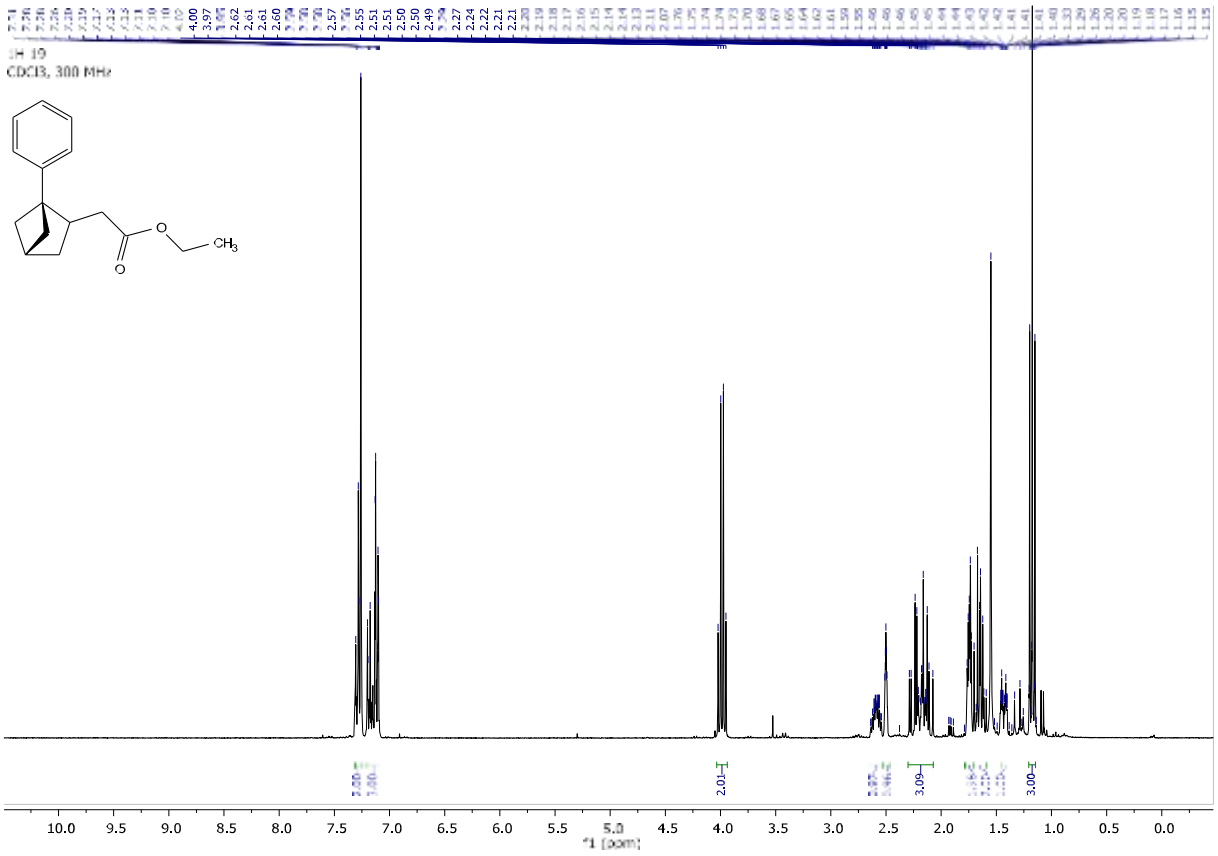


*Figure 30: NMR Spectra for **19***



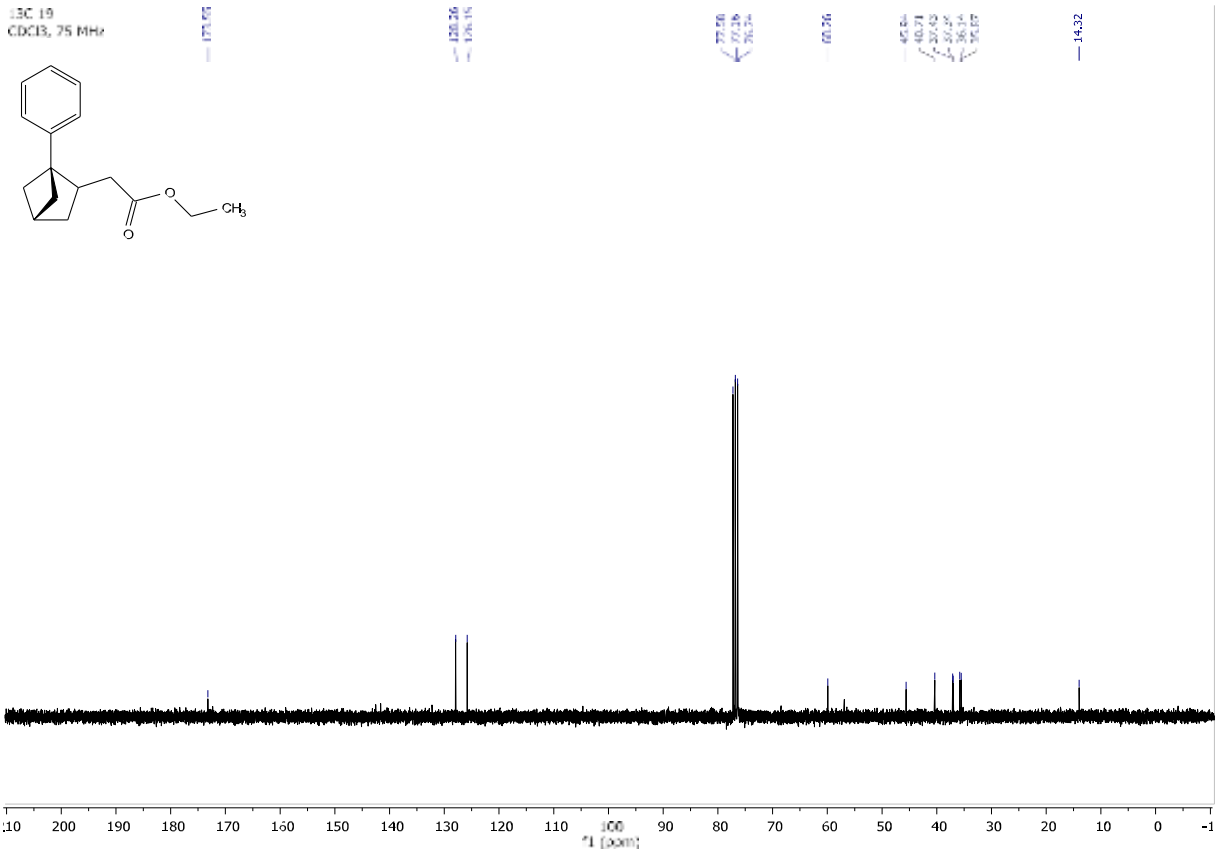
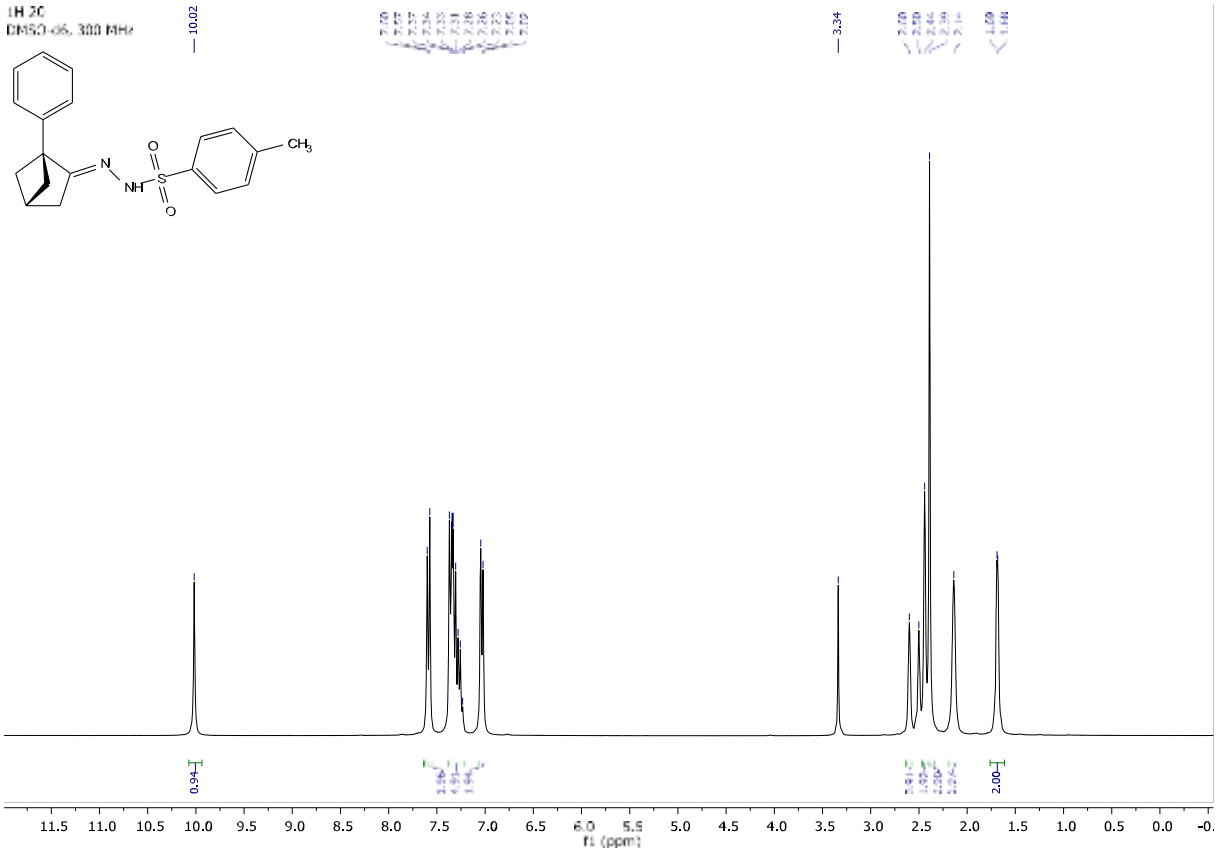


*Figure 31: NMR Spectra for **20***



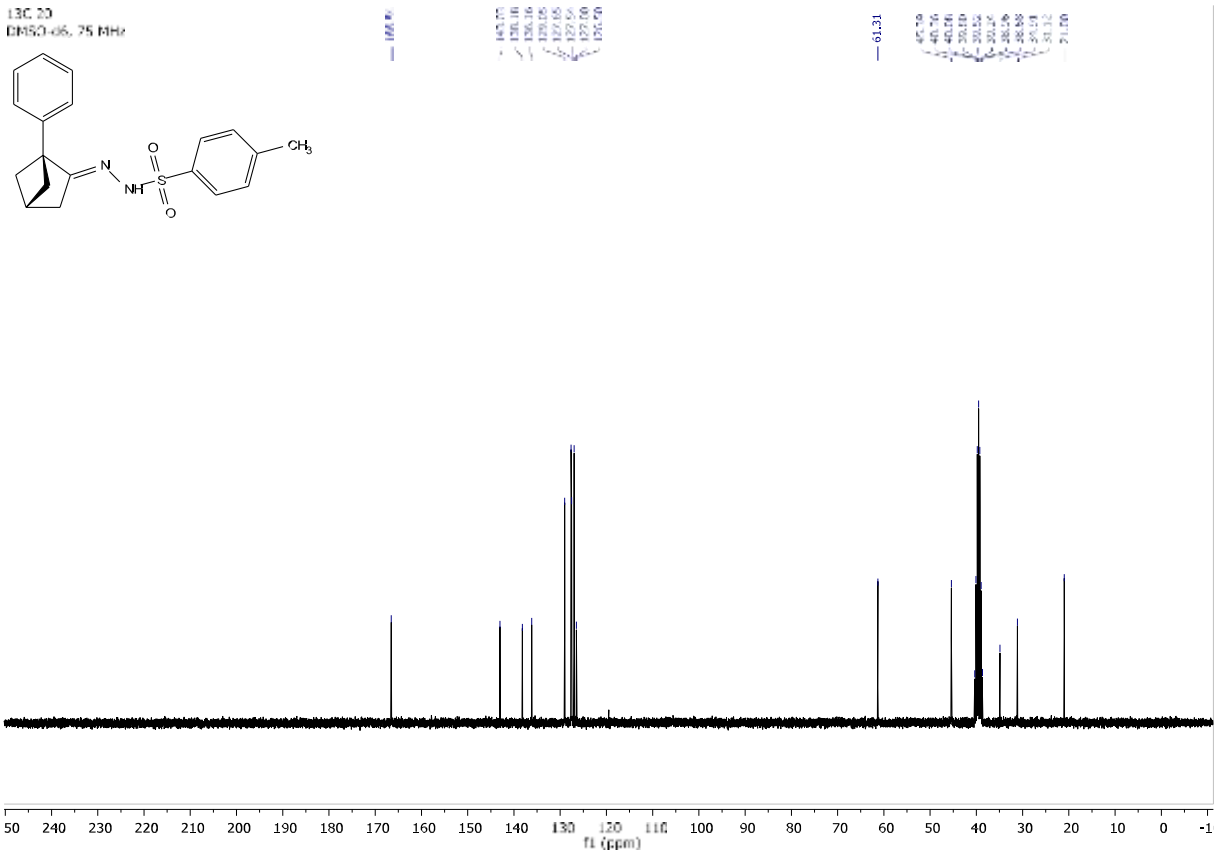


*Figure 32: ^{1}H NMR Spectra for **21***

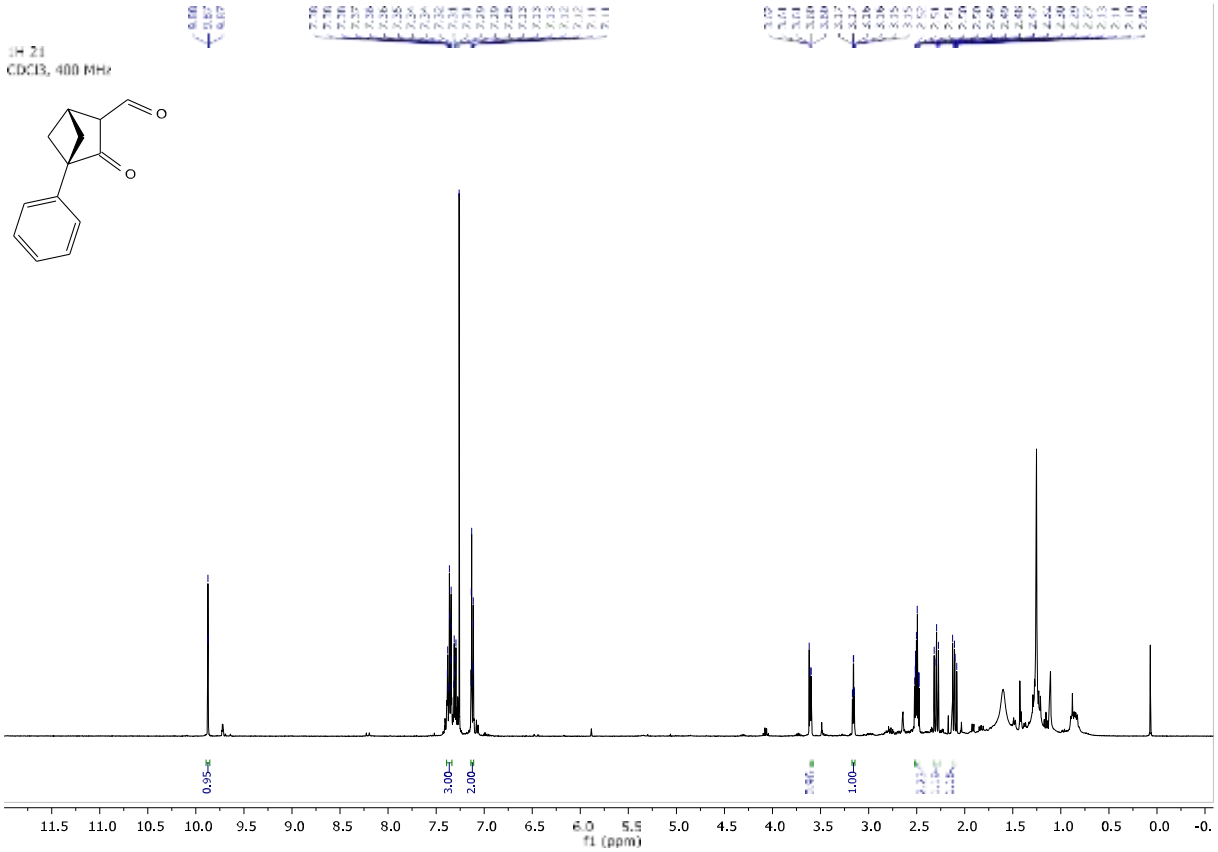


*Figure 33: NMR Spectra for **22***

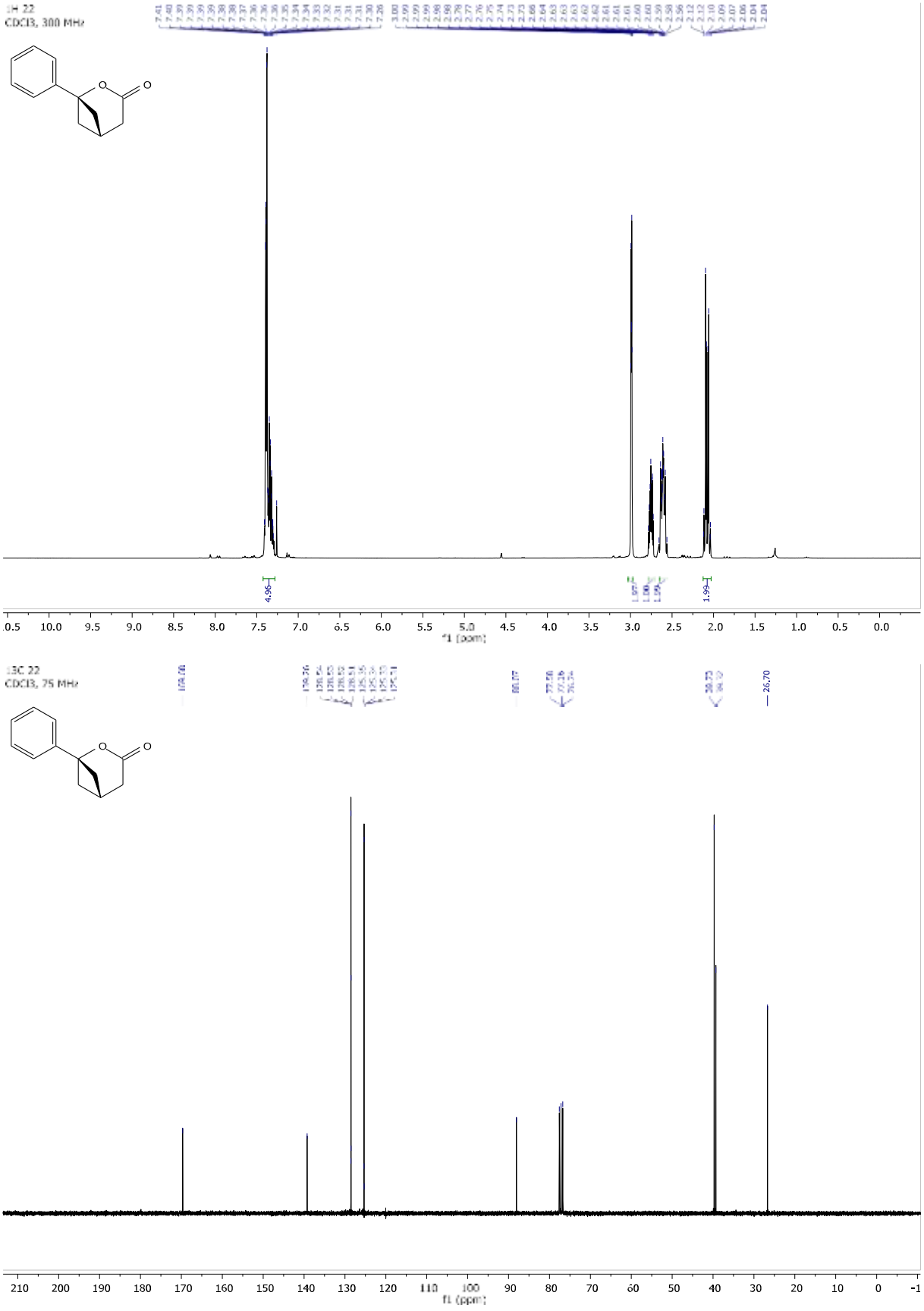
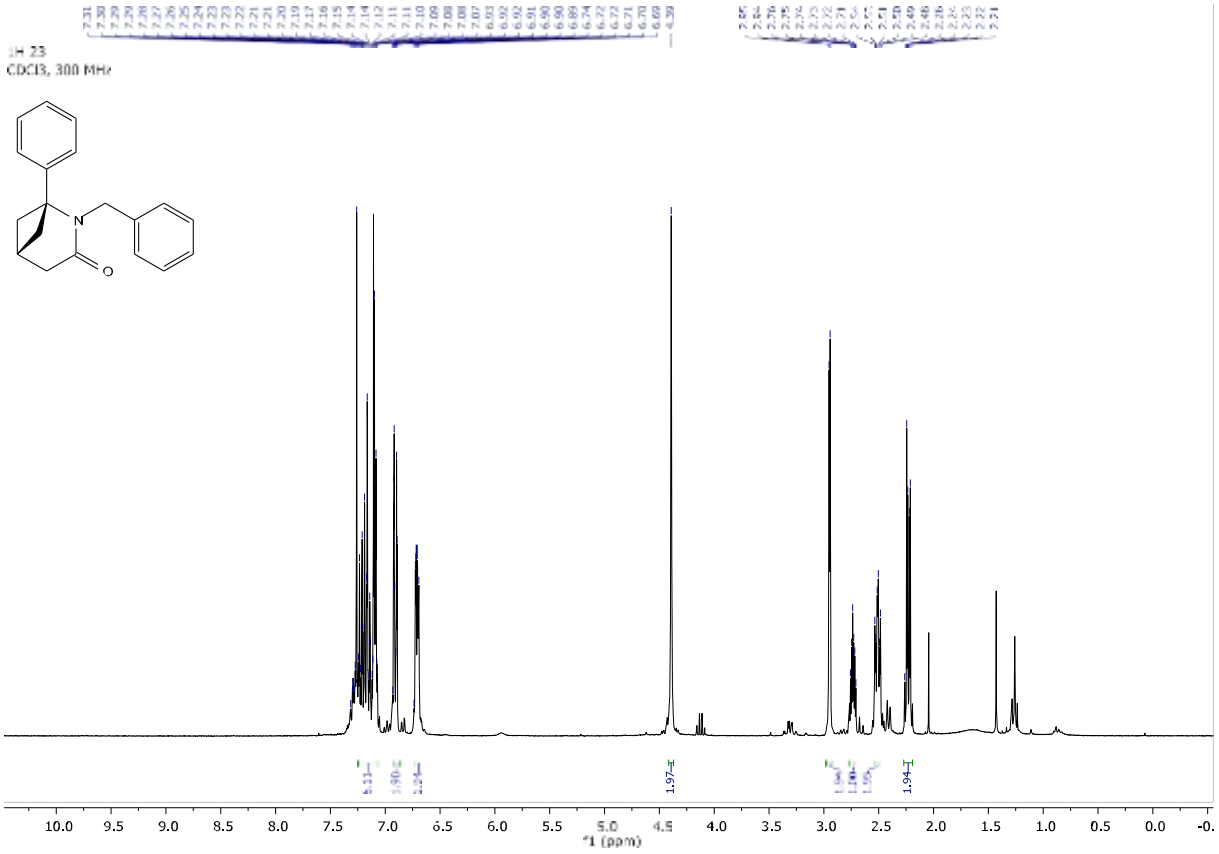


*Figure 34: NMR Spectra for **23***



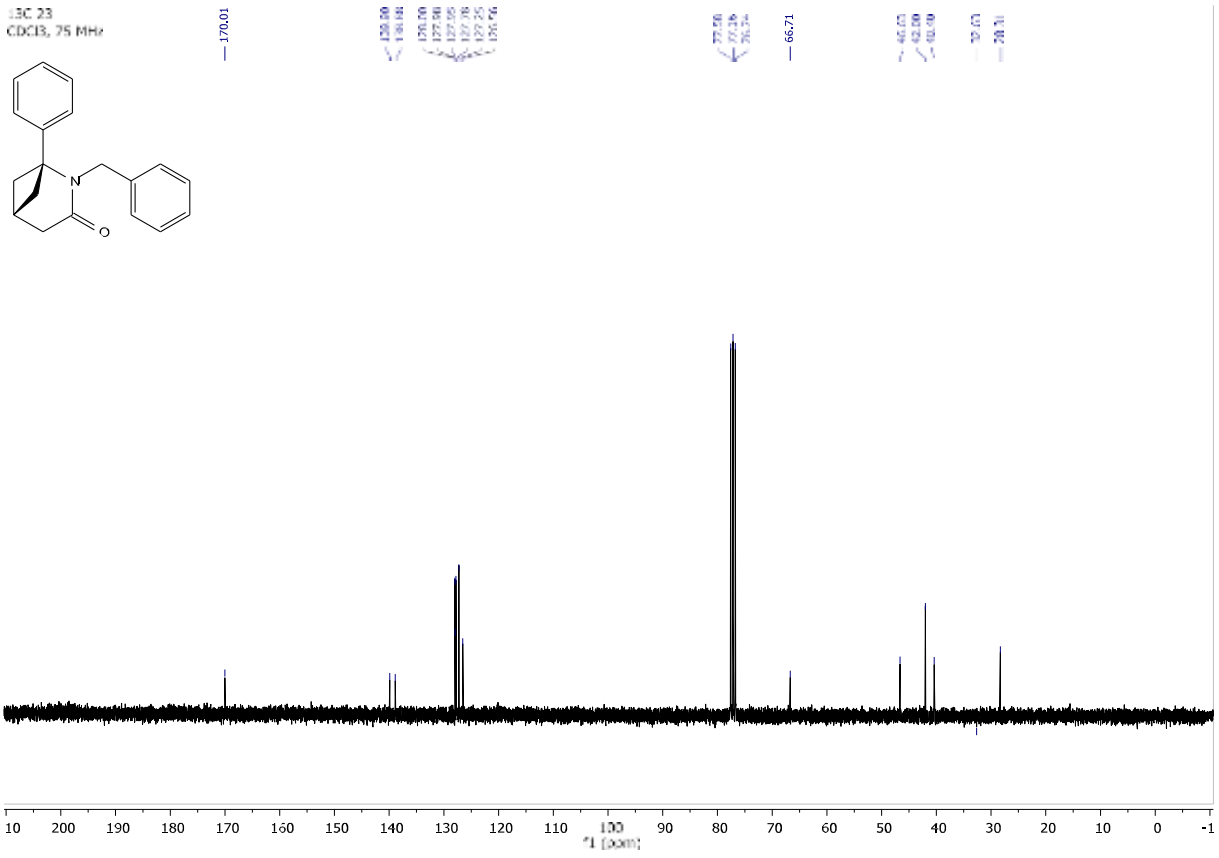


*Figure 35: ^{1}H NMR Spectra for **25***

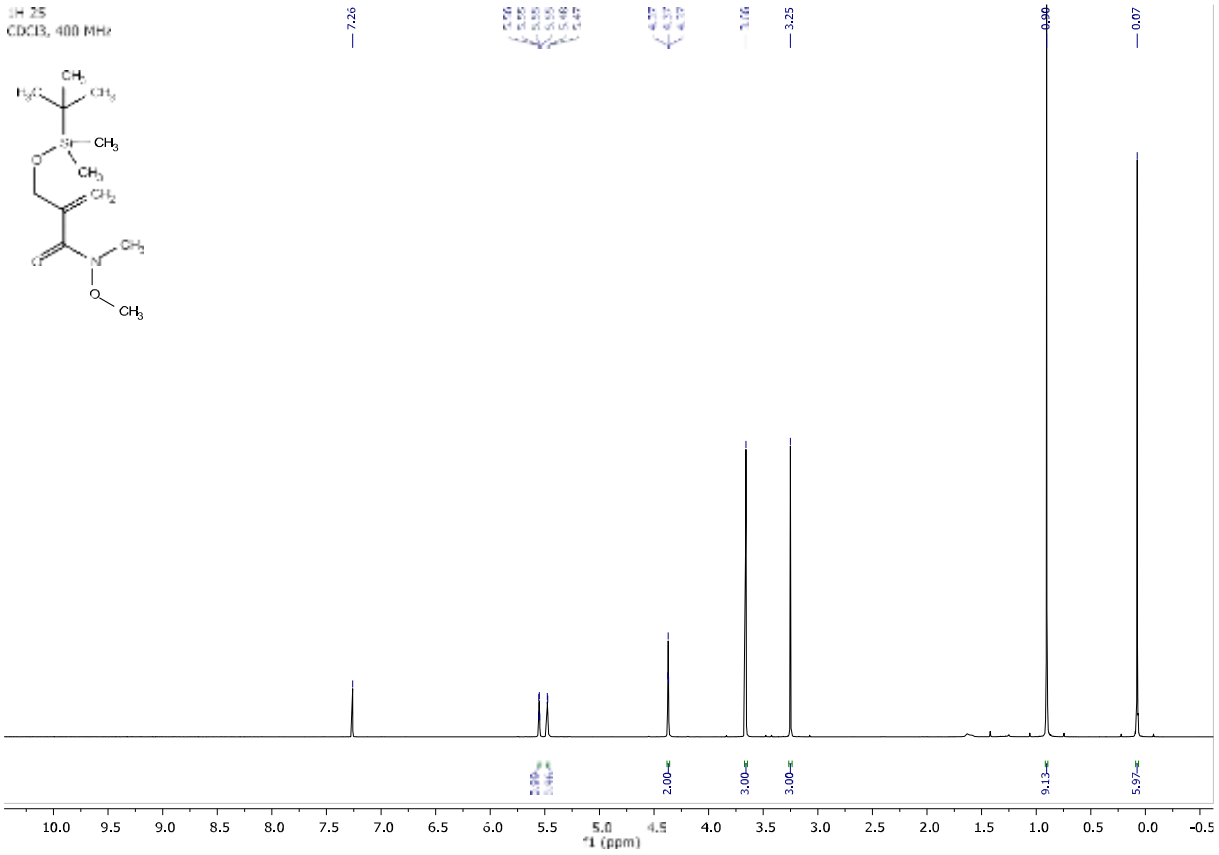


*Figure 36: ^{1}H NMR Spectra for **26***

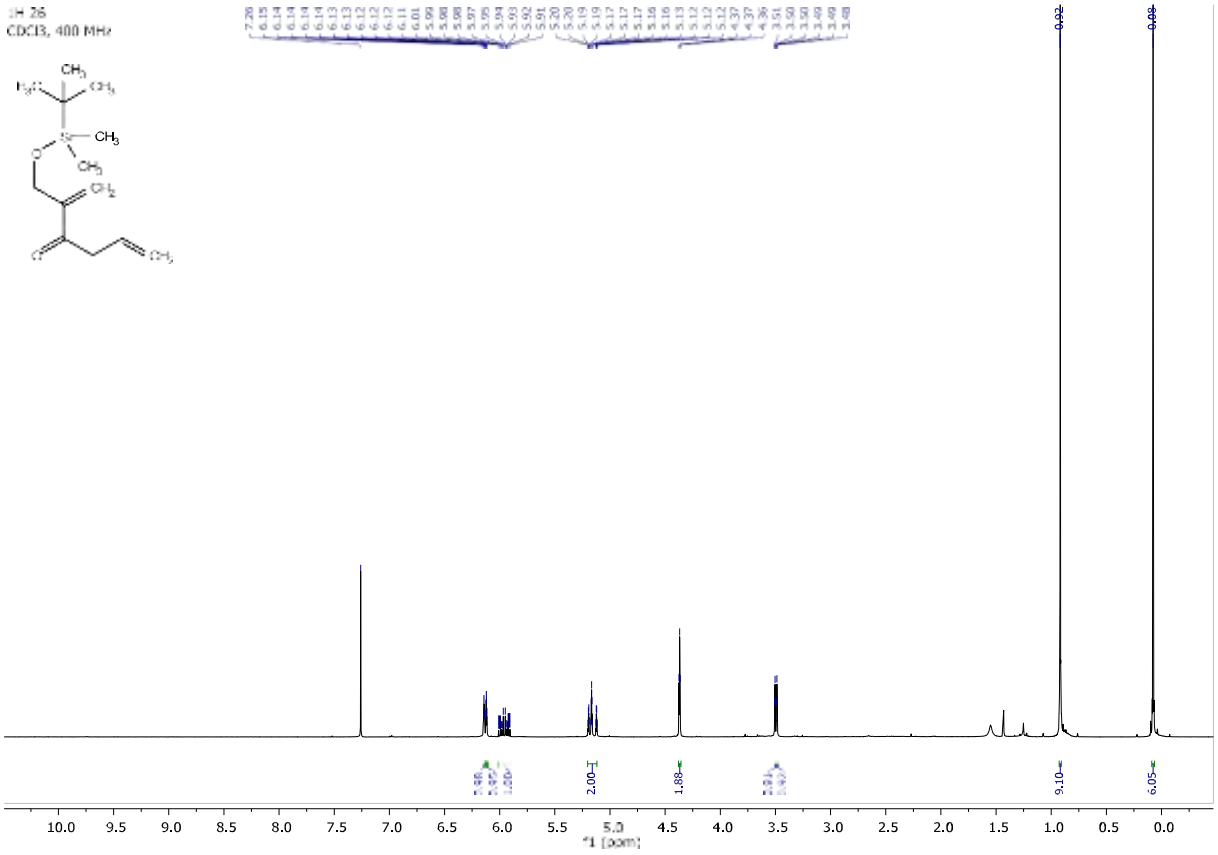
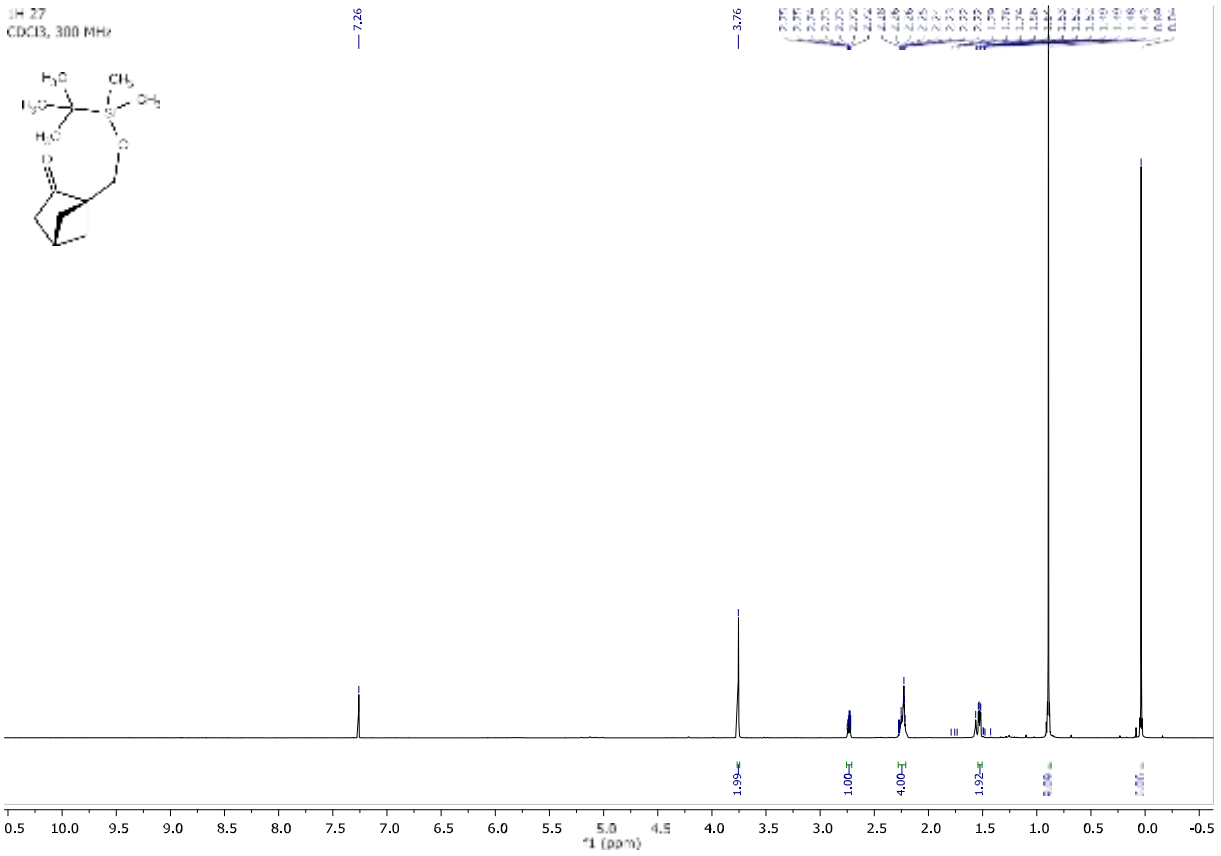


*Figure 37: NMR Spectra for **27***



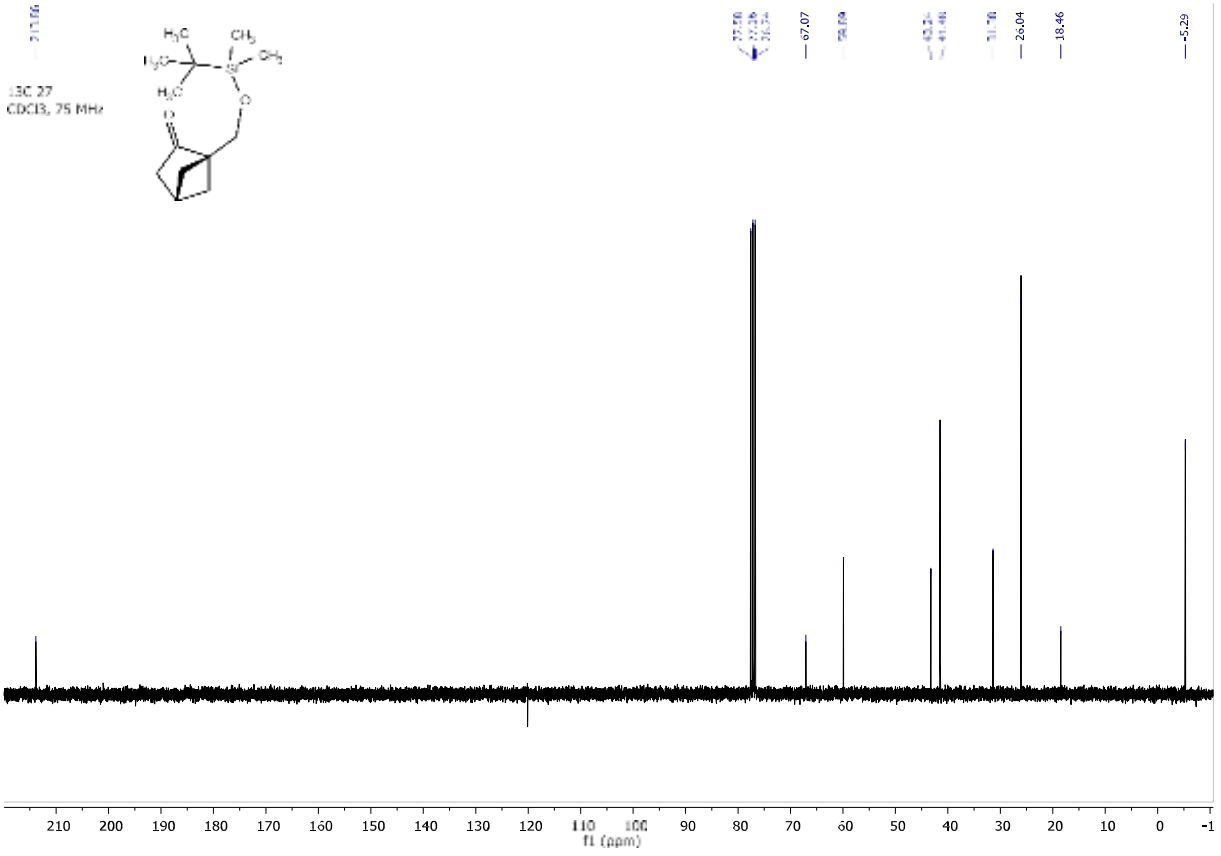
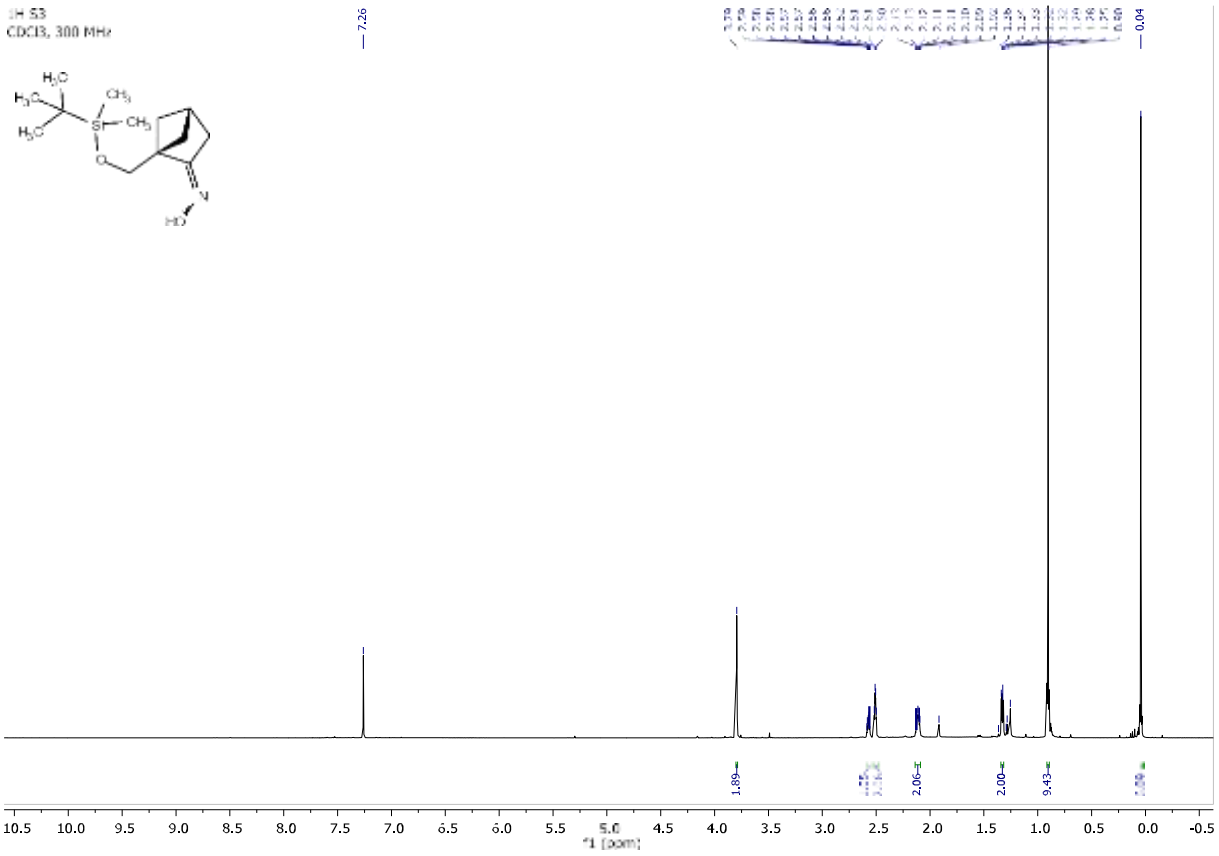


*Figure 38: NMR Spectra for **S3***



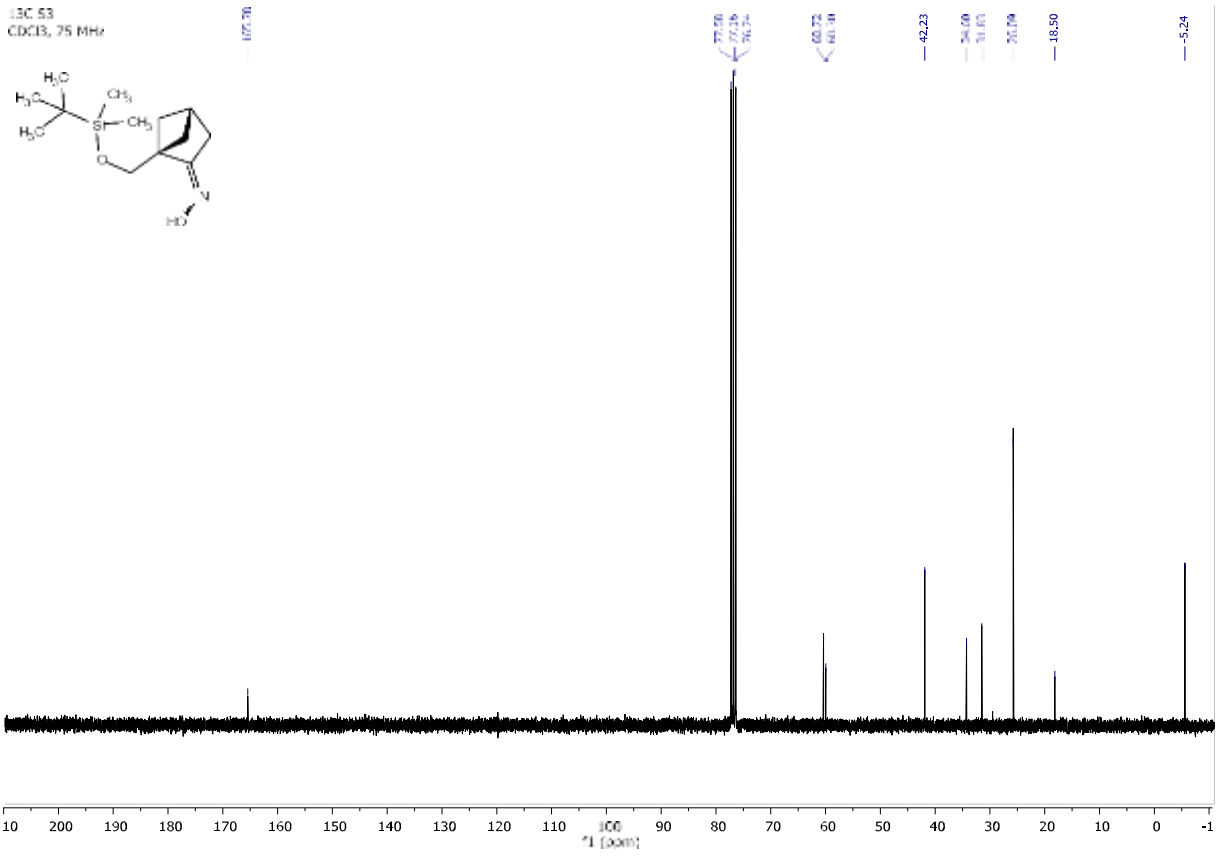


*Figure 39: NMR Spectra for **28***

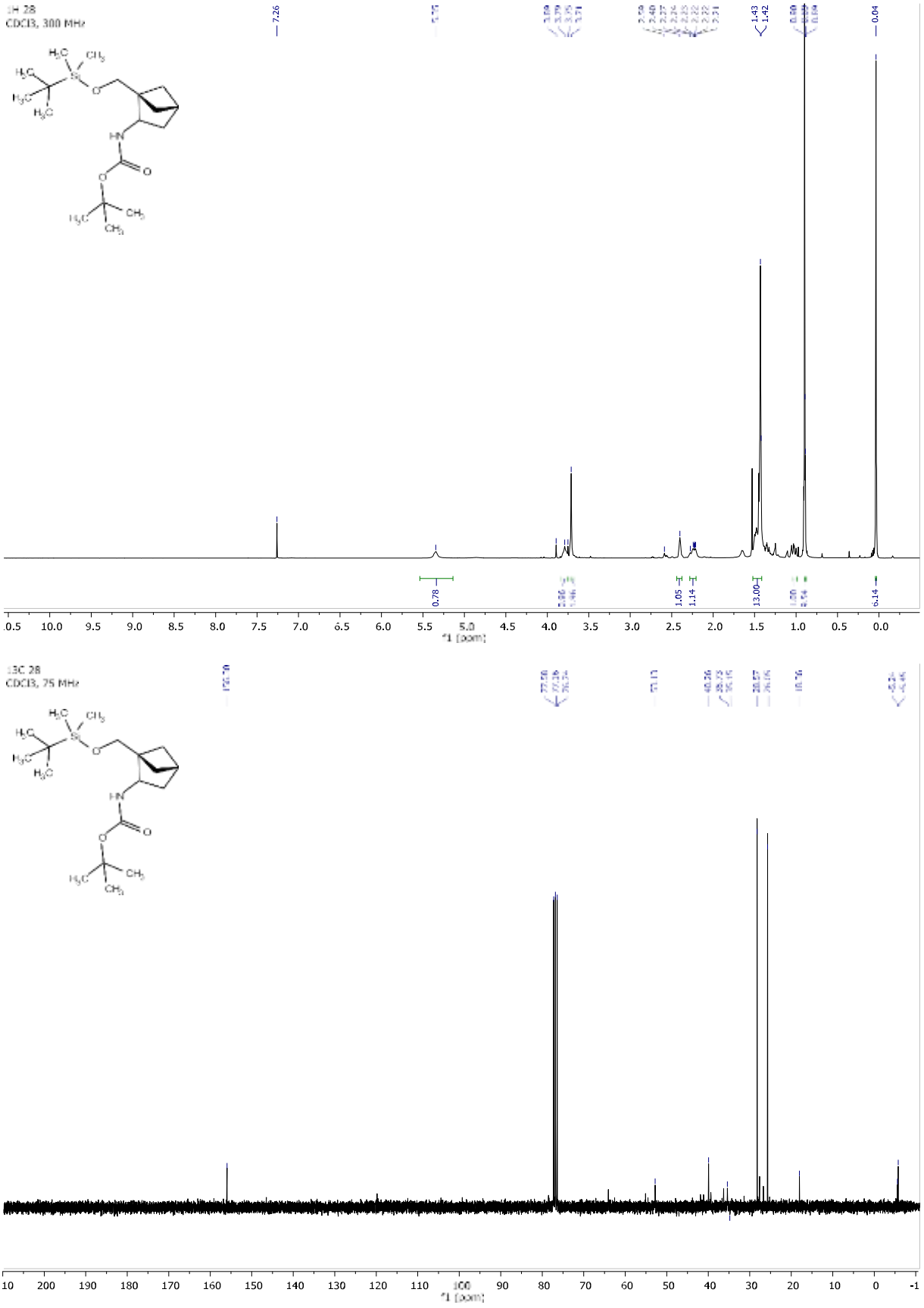


*Figure 40: NMR Spectra for **S4***

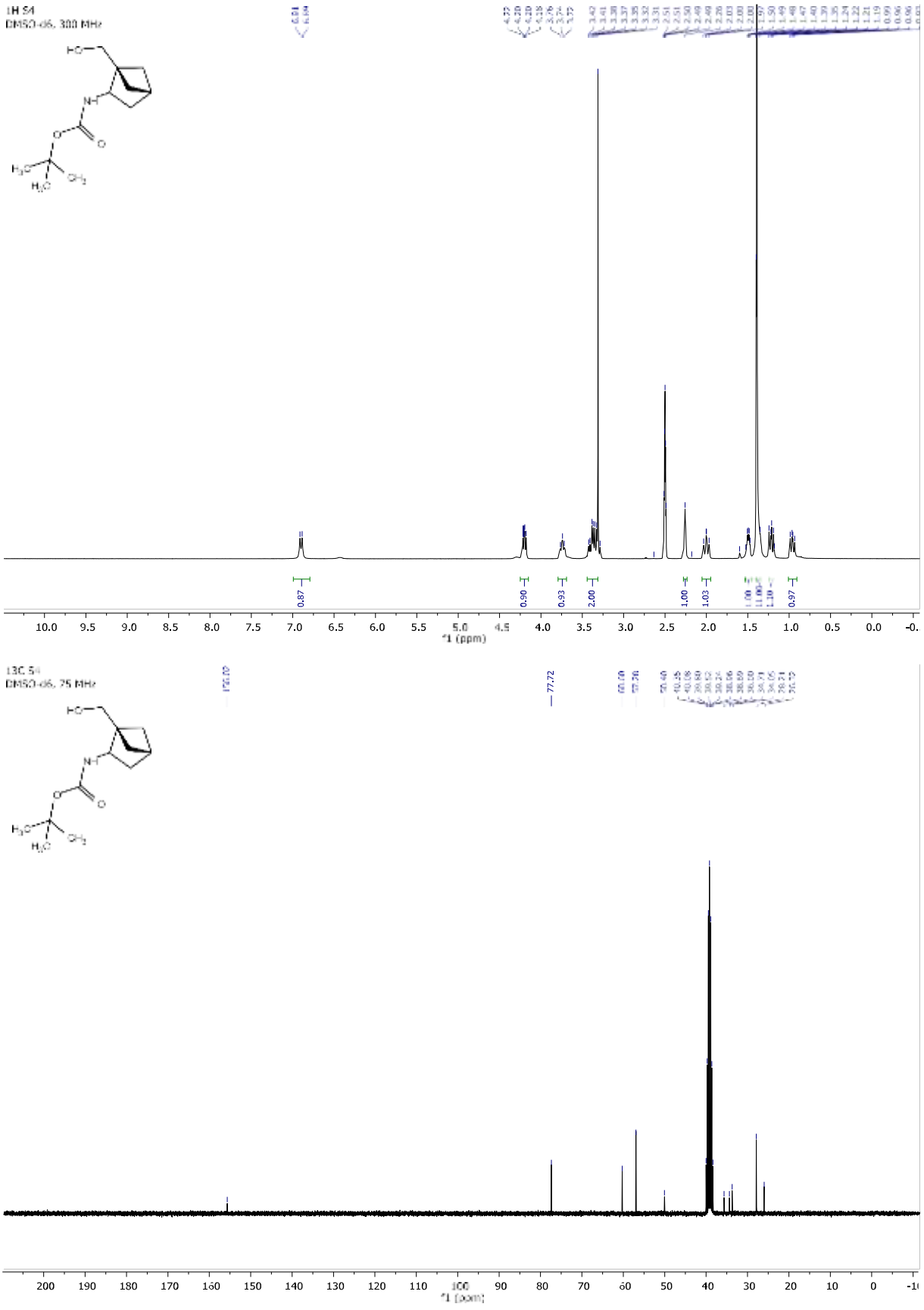


*Figure 41: NMR Spectra for **S5***

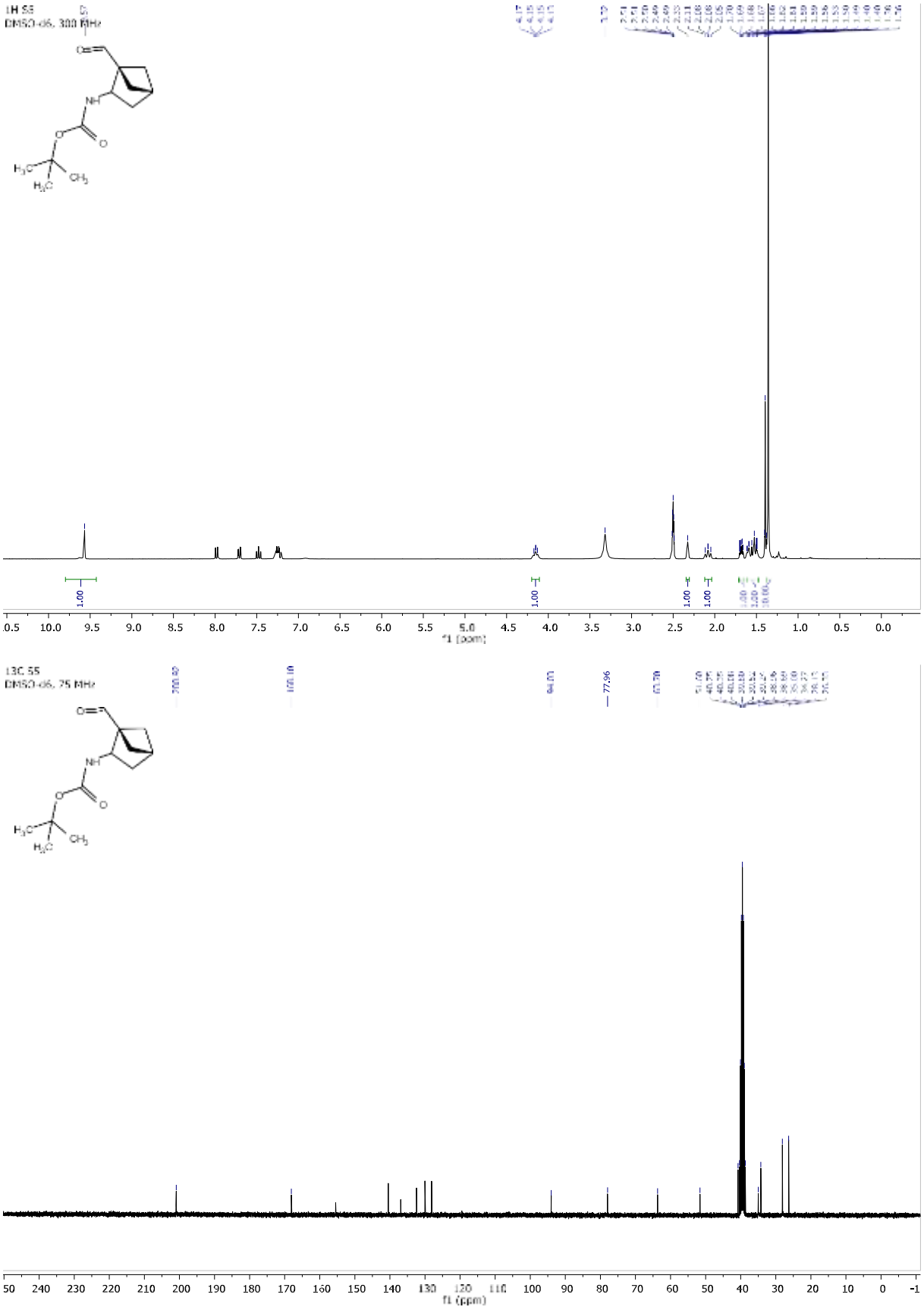


*Figure 42: NMR Spectra for **29***

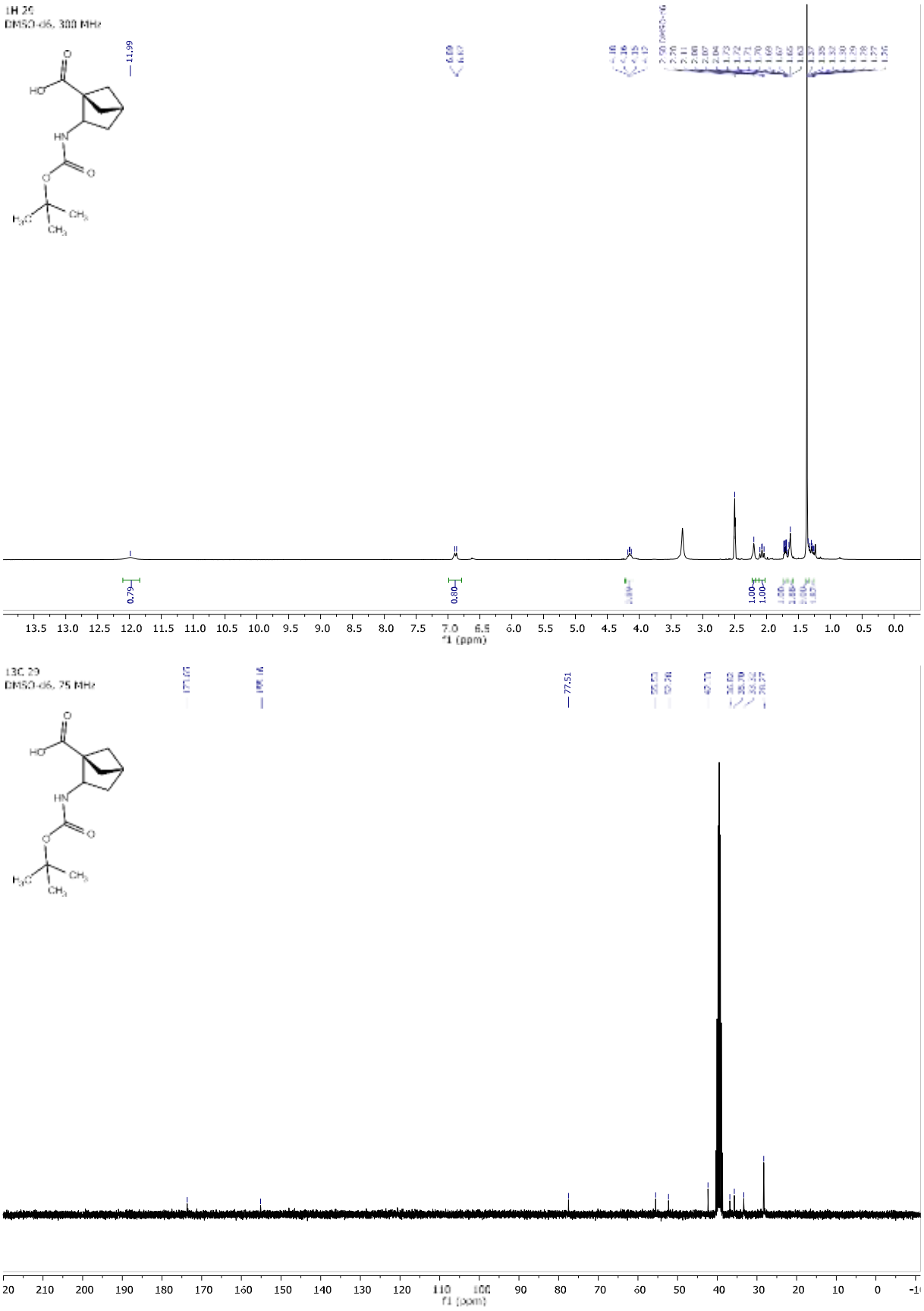


*Figure 43: ^{1}H NMR Spectra for **30***

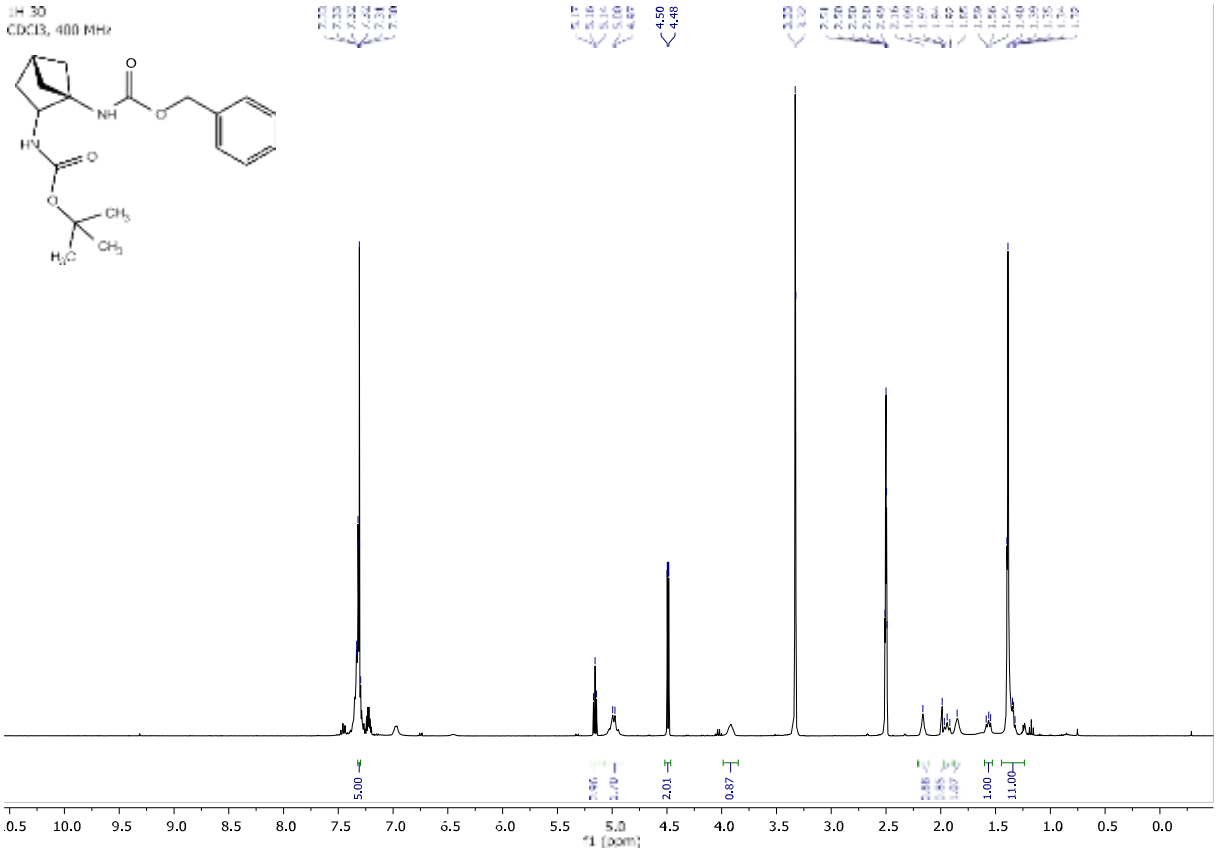


*Figure 44: ^{1}H NMR Spectra for **31***