Electronic Supplementary Material (ESI) for RSC Advances

Expedient synthesis of bicyclo[3.2.1]octanes and bicyclo[3.3.1]nonanes *via* the Double Michael Addition to cyclic dienones

Aurélie Moulia, Joycelyn Teo, Charles W. Johannes, and Jean-Alexandre Richard[*a]*

[a]Organic Chemistry, Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology and Research (A*STAR), 11 Biopolis Way, The Helios Block, #03-08, Singapore 138667

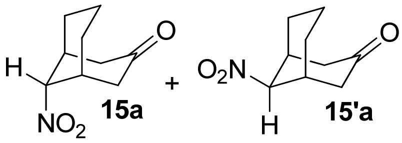
E-mail: jean_alexandre@ices.a-star.edu.sg

Supplementary Information

I) Experimental Section

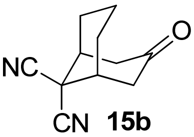
Experimental Data for Compounds

General Procedures. All reactions were carried out under a nitrogen or argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), hexane, diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Methanol (MeOH), benzene, and *N*,*N*'-dimethylformamide (DMF) were purchased in anhydrous form and used without further purification. Water, ethyl acetate (EtOAc), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), and hexanes were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, anisaldehyde, potassium permanganate and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a Bruker AV-600 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, pent = pentet, hex = hexet, br = broad. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer with diamond ATR accessory. Optical rotation ($[\alpha]_D^{25}$) were recorded on a Perkin-Elmer Model 341 polarimeter at 25 °C using thermostable optical glass cell (100 mm path length). Melting points (m.p.) are uncorrected, and recorded on a Buchi B-540 melting point apparatus. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage.



Ketones 15a/15'a: To a stirred solution of 2,7-cyclooctadien-1-one (**8**) (1 g, 8.19 mmol) in DMSO (80 mL) at room temperature were added nitromethane (**10a**) (500 µL, 9.3 mmol) and DBU (120 µL, 0.80 mmol). The resulting mixture was stirred for 3 h before H_2O (100 mL) and AcOEt (100 mL) were added. The layers were separated and the aqueous layer was extracted with AcOEt (100 mL). The combined organic layers were washed with HCl (1.0 N aq., 100 mL), dried (Na_2SO_4) and concentrated in *vacuo* to afford a 2/1 mixture of bicycles **15a** and **15'a** (940 mg, 63%) as a white solid. For analytical purposes, a fraction of the crude mixture was purified by silica gel chromatography and the structure of the major diastereoisomer was assigned to ketone **15a** by 2D NMR experiments (Note: **15a** is the most stable isomer, **15'a** isomerizes to **15a** when treated with silica gel and/or upon prolonged storage).

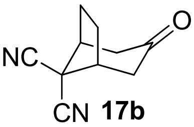
15a: R_f = 0.5 (silica gel, hexanes/EtOAc 80:20); IR (film) ν_{max} 2938, 1703, 1536, 1465, 1453, 1408, 1385, 1362, 1317, 1255, 1230, 1190, 1134, 1106, 1071, 992, 952, 931, 892, 869, 834, 753 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.46 (s, 1H), 3.13 (s, 2H), 2.69 (dd, *J* = 17.8, 6.0 Hz, 2H), 2.37 (dq, *J* = 17.0, 1,4 Hz, 2H), 1.91 (ddq, *J* = 15.3, 4.5, 2.1 Hz, 2H), 1.78–1.68 (m, 2H), 1.59–1.49 (m, 1H), 1.43–1.20 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.9, 85.3, 42.0 (2C), 33.8 (2C), 32.2 (2C), 16.7 ppm; HRMS (ESI): calcd for $C_9H_{14}NO_3^+$ $[M + H]^+$ 184.0974, found 184.0972.



15b

Ketone 15b: To a stirred solution of 2,7-cyclooctadien-1-one (**8**) (200 mg, 1.64 mmol) in CH_3CN (10 mL) at room temperature were added malononitrile (**10b**) (135 mg, 2.04 mmol) and DBU (49 µL, 0.33 mmol). The resulting mixture was stirred at room temperature for 16 h before the medium was concentrated under reduced pressure. The crude residue was dissolved in EtOAc (20 mL) and washed with HCl (1.0 N aq., 10 mL) and H_2O (10 mL). The organic layer was then dried (Na_2SO_4) and concentrated in *vacuo* to afford pure bicycle **15b** (269 mg, 87%) as a light yellow solid.

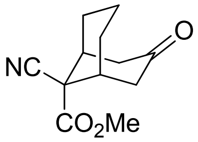
15b: R_f = 0.5 (silica gel, hexanes/EtOAc 70:30); IR (film) ν_{max} 3423, 2950, 2882, 2214, 1717, 1567, 1455, 1413, 1361, 1344, 1268, 1183, 1122, 1099, 973, 954, 893, 822, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 2.96 (ddd, *J* = 18.3, 6.1, 1.4 Hz, 2H), 2.87 (d, *J* = 4.6 Hz, 2H), 2.66–2.49 (m, 2H), 2.14 (m, 2H), 1.90–1.82 (m, 2H), 1.67 (ddt, *J* = 15.5, 5.1, 2.7 Hz, 1H), 1.48–1.38 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.9, 115.5, 115.1, 43.2 (2C), 37.9, 37.2 (2C), 26.0 (2C), 15.8 ppm; HRMS (ESI): calcd for $C_{11}H_{13}N_2O^+$ $[M + H]^+$ 189.1028, found 189.1022.



17b

Ketone 17b: To a stirred solution of 2,6-cycloheptadien-1-one (**9**) (66 mg, 0.61 mmol) in CH_3CN (30 mL) at room temperature were added malononitrile (**10b**) (40 mg, 0.61 mmol) and DBU (18 µL, 0.120 mmol). The resulting mixture was stirred at room temperature for 3 days under argon atmosphere. After concentration under reduce pressure, the mixture was dissolved in EtOAc (15 mL) and washed with HCl (1.0 N aq., 10 mL). The layers were separated and the organic layer was washed with H_2O (2 x 10 mL), dried (Na_2SO_4) and concentrated in *vacuo* to afford pure bicycle **27** (90 mg, 84%) as a light yellow solid.

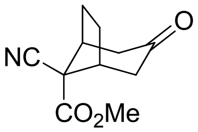
17b: R_f = 0.6 (silica gel, hexanes/EtOAc 70:30); IR (film) ν_{max} 2967, 2909, 2243, 1725, 1567, 1473, 1456, 1426, 1410, 1345, 1317, 1261, 1227, 1201, 1137, 998, 982, 943, 890, 864, 796, 734 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 3.13 (dd, *J* = 4.3, 2.5 Hz, 2H), 2.92–2.86 (m, 2H), 2.54–2.49 (m, 2H), 2.36–2.31 (m, 2H), 1.90–1.85 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.3, 114.9, 114.0, 46.1 (2C), 44.7, 41.6, 27.4 (2C) ppm; HRMS (ESI): calcd for $C_{10}H_{11}N_2O^+$ $[M + H]^+$ 175.0871, found 175.0876.



15c

Ketone 15c: To a stirred solution of 2,7-cyclooctadien-1-one (**8**) (260 mg, 2.13 mmol) in CH_3CN (19 mL) at room temperature were added methylcyanoacetate (**10c**) (211 µL, 2.40 mmol) and DBU (60 µL, 0.40 mmol). The resulting mixture was stirred for 48 h before DBU (160 µL, 1.07 mmol) was added to the mixture in order to get the reaction to completion. After 24 h, the medium was concentrated under reduced pressure and the residue was dissolved in EtOAc (20 mL) and washed with HCl (1.0 N aq., 20 mL) and H_2O (2 x 20 mL). The organic layer was then dried (Na_2SO_4) and concentrated in *vacuo* to afford pure bicycle **15c** (409 mg, 87%) as a yellow oil.

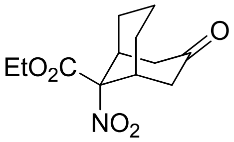
15c: R_f = 0.4 (silica gel, hexanes/EtOAc 70:30); IR (film) ν_{max} 2945, 2880, 2241, 2006, 1741, 1708, 1447, 1436, 1410, 1363, 1338, 1260, 1241, 1186, 1113, 1057, 1038, 962, 892, 781 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 3.90 (s, 3H), 2.92 (s, 2H), 2.72 (dd, *J* = 18.1, 5.8 Hz, 2H), 2.43 (d, *J* = 17.9 Hz, 2H), 2.23–2.13 (m, 2H), 1.79 (d, *J* = 13.8 Hz, 2H), 1.64 (d, *J* = 15.2 Hz, 1H), 1.39 (tdd, *J* = 18.7, 9.6, 4.7 Hz, 1H; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.2, 167.9, 118.8, 54.3, 48.1, 43.3 (2C), 35.6 (2C), 29.6 (2C), 16.6 ppm; HRMS (ESI): calcd for $C_{12}H_{15}NNaO_3^+$ $[M + Na]^+$ 244.0950, found 244.0948.



17c

Ketone 17c: To a stirred solution of 2,6-cycloheptadien-1-one (**9**) (244 mg, 2.26 mmol) in CH$_3$CN (18 mL) at room temperature were added methylcyanoacetate (**10c**) (219 μL, 2.49 mmol) and DBU (61 μL, 0.41 mmol). The resulting mixture was stirred for 48 h before DBU (34 μL, 2.273 mmol) was added to the mixture in order to get the reaction to completion. After 24 h, the medium was concentrated under reduced pressure and the residue was dissolved in EtOAc (20 mL) and washed with HCl (1.0 N aq., 20 mL) and H$_2$O (2 x 20 mL). The organic layer was then dried (Na$_2$SO$_4$) and concentrated in *vacuo* to afford pure bicycle **17c** (361 mg, 77%) as a yellow oil.

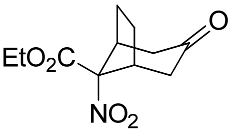
17c: R$_f$ = 0.4 (silica gel, hexanes/EtOAc 70:30); IR (film) ν_{max} 2956, 2887, 1745, 1718, 1449, 1435, 1341, 1251, 1236, 1195, 1114, 1037, 966, 915, 746 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ = 3.87 (s, 3H), 3.09 (dd, *J* = 4.0, 2.6 Hz, 2H), 2.94 (d, *J* = 17.6 Hz, 2H), 2.47–2.42 (m, 2H), 2.03–1.98 (m, 2H), 1.71–1.66 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$): δ = 207.9, 167.2, 117.7, 54.3, 53.4, 47.2 (2C), 42.2 (2C), 27.7 (2C) ppm; HRMS (ESI): calcd for $C_{11}H_{13}NNaO_3^+$ $[M + Na]^+$ 230.0793, found 230.0782.



16d

Ketone 16d: To a stirred solution of 2,7-cyclooctadien-1-one (**8**) (112 mg, 0.918 mmol) in CH$_3$CN (30 mL) at room temperature were added ethylnitroacetate (**10d**) (122 μL, 1.10 mmol) and DBU (137 μL, 0.92 mmol). The resulting mixture was stirred at 80 °C for 26 h before it was concentrated under reduced pressure. The residue was then dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H$_2$O (2 x 10 mL). The layers were separated and the organic layer was dried (Na$_2$SO$_4$) and concentrated in *vacuo* to afford pure bicycle **16d** (225 mg, 96%) as a light yellow oil.

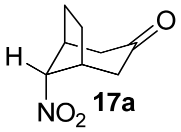
16d: R_f = 0.6 (silica gel, hexanes/EtOAc 70:30); IR (film) ν_{max} 2942, 2882, 1746, 1712, 1547, 1471, 1454, 1411, 1372, 1338, 1266, 1232, 1208, 1124, 1109, 1095, 1080, 1062, 1039, 979, 926, 906, 856, 781, 767, 729 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.30 (q, *J* = 7.1 Hz, 2H), 3.40 (dd, *J* = 5.8, 2.9 Hz, 2H), 2.70 (dd, *J* = 18.4, 5.7 Hz, 2H), 2.43 (d, *J* = 18.3 Hz, 2H), 1.98–1.86 (m, 2H), 1.86–1.77 (m, 2H), 1.53–1.46 (m, 1H), 1.37–1.27 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.7, 164.8, 96.0, 63.7, 43.4 (2C), 35.5 (2C), 30.2 (2C), 16.1, 14.1 ppm; HRMS (ESI): calcd for $C_{12}H_{17}NNaO_5^+$ $[M + Na]^+$ 278.1004, found 278.0993.



18d

Ketone 18d: To a stirred solution of 2,6-cycloheptadien-1-one (**9**) (59 mg, 0.55 mmol) in CH_3CN (15 mL) at room temperature were added ethylnitroacetate (**10d**) (73 µL, 0.65 mmol) and DBU (81 µL, 0.543 mmol). The resulting mixture was stirred at 50 °C for 24 h before it was concentrated under reduced pressure. The residue was then dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H_2O (2 x 10 mL). The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated in *vacuo* to afford pure bicycle **18d** (97 mg, 74%) as a light yellow oil.

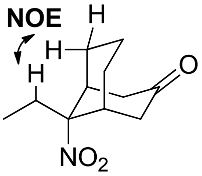
18d: R_f = 0.5 (silica gel, hexanes/EtOAc 70:30); IR (film) ν_{max} 2968, 2926, 2896, 1746, 1720, 1544, 1469, 1455, 1414, 1369, 1357, 1342, 1298, 1248, 1227, 1190, 1085, 1045, 1026, 855, 799, 770, 744 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.32 (q, *J* = 7.2 Hz, 2H), 3.25 (dd, *J* = 4.4, 2.4 Hz, 2H), 2.84 (ddd, *J* = 18.2, 2.3, 1.5 Hz, 2H), 2.44–2.39 (m, 2H), 2.09–2.04 (m, 2H), 1.73–1.69 (m, 2H), 1.31 (dd, *J* = 9.2, 5.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.0, 165.2, 99.6, 63.9, 45.9 (2C), 40.0 (2C), 26.8 (2C), 14.1 ppm; HRMS (ESI): calcd for $C_{11}H_{15}NNaO_5^+$ $[M + Na]^+$ 264.0848, found 264.0851.



17a

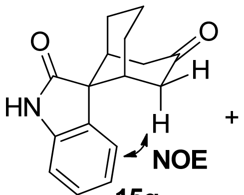
Ketone 17a: To a stirred solution of 2,6-cycloheptadien-1-one (**9**) (103 mg, 0.952 mmol) in CH_3CN (30 mL) at room temperature were added nitromethane (**10a**) (62 µL, 1.15 mmol) and KF/basic Al_2O_3 (102 mg).[1] The resulting mixture was stirred at 80 °C for 18 h before the solids were removed by filtration over silica. The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H_2O (2 x 10 mL). The organic layer was then dried (Na_2SO_4) and concentrated in *vacuo* to afford pure bicycle **17a** (67 mg, 42%) as an orange oil.

17a: $R_f = 0.8$ (silica gel, hexanes/EtOAc 60:40); IR (film) ν_{max} 2959, 2926, 2887, 1712, 1668, 1538, 1470, 1455, 1412, 1377, 1341, 1312, 1271, 1259, 1192, 1153, 1081, 1016, 929, 850, 796, 771, 719 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.88 (s, 1H), 3.19 (d, *J* = 1.8 Hz, 2H), 2.62 (d, *J* = 17.2 Hz, 2H), 2.48 (d, *J* = 17.5 Hz, 2H), 2.15–2.08 (m, 2H), 1.74–1.68 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.9, 93.0, 48.6 (2C), 39.8 (2C), 27.5 (2C) ppm; HRMS (ESI): calcd for $C_8H_{11}NNaO_3^+$ $[M + Na]^+$ 192.0637, found 192.0636.



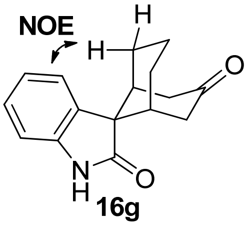
16f

16f: $R_f = 0.4$ (silica gel, hexanes/EtOAc 70:30); IR (film) ν_{max} 2945, 2880, 1706, 1531, 1461, 1437, 1414, 1374, 1353, 1328, 1260, 1178, 1128, 967, 897, 839, 804, 714 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.94 (dd, *J* = 4.9, 2.7 Hz, 2H), 2.71–2.57 (m, 2H), 2.37 (dd, *J* = 17.8, 1.7 Hz, 2H), 2.14 (q, *J* = 7.4 Hz, 2H), 2.00–1.85 (m, 2H), 1.78–1.70 (m, 2H), 1.54 (ddd, *J* = 15.3, 6.4, 4.0 Hz, 1H), 1.41–1.29 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 210.1, 94.7, 44.1 (2C), 35.6 (2C), 29.8, 29.4 (2C), 16.3, 7.1 ppm; HRMS (ESI): calcd for $C_{11}H_{17}NNaO_3^+$ $[M + Na]^+$ 234.1106, found 234.1106.



15g

+



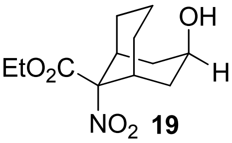
16g

Ketone 15g/16g: To a stirred solution of 2,7-cyclooctadien-1-one (**8**) (36 mg, 0.294 mmol) in CH_3CN (9 mL) at room temperature were added oxindole (46 mg, 1.17 mmol) and KF/basic Al_2O_3 (41 mg). The resulting mixture was stirred at 80 °C for 4 days before the solids were removed by filtration over silica. The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H_2O (2 x 10 mL). The organic layer was then dried (Na_2SO_4), concentrated in *vacuo* and purified by flash column chromatography (silica gel, hexanes:EtOAc 80/20) to afford bicycles **15g** (25 mg, 33%) and **16g** (14 mg, 19%) as pink and yellow solids respectively.

15g: R_f = 0.6 (silica gel, hexanes/EtOAc 60:40); IR (film) ν_{max} 3174, 3077, 3036, 2961, 2916, 2893, 1695, 1621, 1591, 1475, 1467, 1447, 1407, 1328, 1299, 1259, 1240, 1213, 1175, 1104, 1073, 1019, 977, 917, 888, 844, 801, 758, 745, 715 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.28–7.25 (m, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.00 (td, *J* = 7.7, 1.1 Hz, 1H), 6.93 (dd, *J* = 7.8, 0.6 Hz, 1H), 3.17 (dd, *J* = 19.3, 6.5 Hz, 2H), 2.92–2.83 (m, 2H), 2.51 (d, *J* = 19.4 Hz, 2H), 2.27 (s, 2H), 1.75–1.66 (m, 1H), 1.52–1.41 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.0, 180.1, 140.7, 133.1, 128.7, 127.2, 122.1, 110.1, 50.9, 45.5 (2C), 35.6 (2C), 26.9 (2C), 16.1 ppm; HRMS (ESI): calcd for $C_{16}H_{17}NNaO_2^+$ $[M + Na]^+$ 278.1157, found 278.1156.

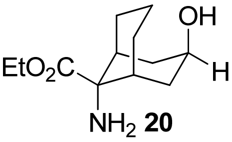
16g: R_f = 0.6 (silica gel, hexanes/EtOAc 60:40); IR (film) ν_{max} 3256, 2952, 2924, 2879, 1695, 1618, 1589, 1473, 1401, 1332, 1262, 1235, 1192, 1102, 1928, 906, 802, 757, 744, 727 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.68 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.28 (td, *J* = 7.6, 0.7 Hz, 1H), 7.06 (td, *J* = 7.7, 1.0 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 3.62 (dd, *J* = 18.0, 6.4 Hz, 2H), 2.50–2.41 (m, 2H), 2.31 (d, *J* =

18.0 Hz, 2H), 2.21 (s, 2H), 1.82–1.76 (m, 1H), 1.72 (ddd, *J* = 20.3, 13.0, 5.4 Hz, 1H), 1.65–1.59 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.7, 181.2, 141.0, 132.6, 128.7, 128.6, 121.9, 110.3, 51.0, 43.7 (2C), 35.2 (2C), 28.1 (2C), 16.0 ppm; HRMS (ESI): calcd for $C_{16}H_{17}NNaO_2^+$ $[M + Na]^+$ 278.1157, found 278.1156.


19

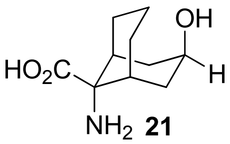
Alcohol 19: To a stirred solution of ketone **16d** (1.43 g, 5.6 mmol) in CH_3OH (50 mL) at room temperature was added $NaBH_4$ (2.8 g, 74.1 mmol). The resulting mixture was stirred for 2 h before acetone (30 mL) was added and the medium was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with H_2O (2 x 70 mL). The organic layer was then dried (Na_2SO_4) and concentrated in *vacuo* to afford pure bicycle **19** (1.13 g, 79%) as a light yellow solid.

19: R_f = 0.5 (silica gel, hexanes/EtOAc 60:40); IR (film) ν_{max} 3415, 2936, 2871, 1745, 1546, 1453, 1371, 1340, 1296, 1226, 1122, 1097, 1046, 1025, 957, 894, 859, 847, 707 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.24 (q, *J* = 7.1 Hz, 2H), 3.89 (ddd, *J* = 7.7, 5.0, 2.6 Hz, 1H), 3.14 (ddd, *J* = 5.8, 3.6, 1.7 Hz, 2H), 2.40 (dt, *J* = 15.5, 7.8 Hz, 2H), 2.23 (qt, *J* = 13.7, 5.9 Hz, 1H), 1.82–1.75 (m, 2H), 1.73–1.66 (m, 2H), 1.53 (ddd, *J* = 15.7, 5.1, 1.7 Hz, 2H), 1.39–1.30 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.7, 97.5, 63.1, 61.4, 35.5 (2C), 32.7 (2C), 30.1 (2C), 14.6, 14.1 ppm; HRMS (ESI): calcd for $C_{12}H_{19}NNaO_5^+$ $[M + Na]^+$ 280.1161, found 280.1158.


20

Amino-alcohol 20: A suspension of Ra/Ni in water was washed three times with CH_3OH before alcohol **19** (115 mg, 0.47 mmol) was added in solution in CH_3OH (8 mL). The resulting mixture was stirred under a hydrogen atmosphere for 2 h before the solution was filtered over a short pad of silica. The filtrate was concentrated in *vacuo* to afford pure bicycle **20** (80 mg, 75%) as a light yellow solid.

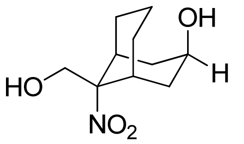
20: R_f = 0.2 (silica gel, hexanes/EtOAc 50:50); IR (film) ν_{max} 3368, 2919, 1713, 1590, 1452, 1366, 1296, 1263, 1224, 1196, 1164, 1127, 1112, 1080, 1036, 956, 921, 902, 858, 836, 770, 718 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ = 4.28 (ddd, *J* = 7.7, 4.8, 2.9 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.51 (dt, *J* = 15.3, 7.6 Hz, 2H), 2.46–2.39 (m, 1H), 2.24–2.13 (m, 2H), 1.76–1.64 (m, 2H), 1.60–1.52 (m, 2H), 1.48–1.43 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.21 (dddd, *J* = 13.3, 7.5, 3.6, 1.7 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD): δ = 178.3, 63.7, 62.4, 61.6, 36.3 (2C), 35.5 (2C), 31.2 (2C), 16.8, 15.3 ppm; HRMS (ESI): calcd for $C_{12}H_{22}NO_3^+$ $[M + H]^+$ 228.1600, found 228.1592.



21

Amino-acid 21: To a stirred solution of amino-ester **20** (9 mg, 0.04 mmol) in THF/CH_3OH/H_2O (3:1:1, 2.5 mL) at room temperature was added LiOH (10 mg, 0.42 mmol). The resulting mixture was stirred for 16 h before HCl (1.0 N aq., 2 mL) was added. The medium was concentrated under reduced pressure and the residue was dissolved in H_2O and purified on Dowex 50 WX8-100 to afford amino-acid **21** (9 mg, quant.) as a white solid.

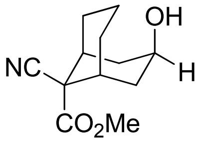
21: R_f = 0.4 (silica gel, CH_2Cl_2/CH_3OH 90:10); IR (film) ν_{max} 3368, 1652, 1452, 1143, 1046, 1023, 989, 826, 763 cm^{-1}; ^1H NMR (600 MHz, D_2O) δ = 4.14 (t, *J* = 6.7 Hz, 1H), 2.51–2.21 (m, 5H), 1.90 (dq, *J* = 13.0, 6.5, 4.9 Hz, 2H), 1.76 (d, *J* = 15.4 Hz, 2H), 1.61 (dd, *J* = 14.2, 6.1 Hz, 2H), 1.37–1.21 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 174.4, 64.7, 60.4, 35.7 (2C), 33.0 (2C), 29.7 (2C), 15.9 ppm; HRMS (ESI): calcd for $C_{10}H_{18}NO_3^+$ $[M + H]^+$ 200.1287, found 200.1278.



23

Diol 23: To a stirred solution of ester **19** (87 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added Dibal-H (1.0 M in CH_2Cl_2, 1.7 mL, 1.7 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 16 h before it was quenched with sodium potassium tartrate (10 mL, sat. aq.) The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo*. Flash column chromatography (silica gel, hexanes:EtOAc 7:3) afforded alcohol **23** (37 mg, 50%) as a white solid.

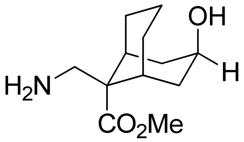
23: R_f = 0.4 (silica gel, hexanes/EtOAc 50:50); IR (film) ν_{max} 3147, 2931, 2871, 1709, 1534, 1471, 1450, 1343, 1311, 1260, 1218, 1122, 1052, 1004, 957, 933, 844, 799, 752, 708 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 4.77 (s, 1H), 4.02 (s, 2H), 3.86 (tt, *J* = 7.6, 5.7 Hz, 1H), 2.82 (dt, *J* = 5.3, 2.4 Hz, 2H), 2.37 (dt, *J* = 15.5, 7.8 Hz, 2H), 2.31–2.14 (m, 1H), 1.88–1.75 (m, 2H), 1.70–1.61 (m, 2H), 1.52–1.40 (m, 3H), 1.26 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 96.1, 66.4, 62.0, 35.8 (2C), 30.7 (2C), 29.5 (2C), 14.4 ppm; HRMS (ESI): calcd for $C_{10}H_{17}NNaO_4^+$ $[M + Na]^+$ 238.1055, found 238.1049.



24

Alcohol 24: To a stirred solution of ketone **15c** (220 mg, 1.0 mmol) in CH_3OH (12 mL) at room temperature was added $NaBH_4$ (378 g, 10.0 mmol). The resulting mixture was stirred for 2 h before acetone (10 mL) was added and the medium was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (2 x 20 mL). The organic layer was then dried (Na_2SO_4) and concentrated in *vacuo* to afford pure bicycle **24** (165 g, 75%) as a light yellow solid.

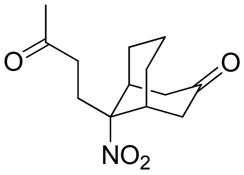
24: R_f = 0.5 (silica gel, hexanes/EtOAc 50:50); IR (film) ν_{max} 3416, 2935, 2869, 1743, 1435, 1265, 1239, 1123, 1061, 891, 786 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 3.81–3.72 (m, 1H), 2.83–2.59 (m, 2H), 2.29 (ddd, *J* = 15.4, 8.5, 7.2 Hz, 2H), 2.17 (tt, *J* = 13.7, 5.4 Hz, 1H), 2.02 (tdd, *J* = 13.8, 5.4, 3.9 Hz, 2H), 1.80–1.74 (s, 1H), 1.62 (ddt, *J* = 14.4, 3.4, 1.6 Hz, 2H), 1.53–1.45 (m, 1H), 1.42 (ddd, *J* = 15.0, 6.3, 2.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9, 119.6, 61.7, 54.0, 48.0, 34.4 (2C), 32.2 (2C), 29.5 (2C), 14.9 ppm; HRMS (ESI): calcd for $C_{12}H_{17}NNaO_3^+$ $[M + Na]^+$ 246.1106, found 246.1108.



25

Amino-alcohol 25: A suspension of Ra/Ni in water was washed three times with CH_3OH before alcohol **24** (20 mg, 0.09 mmol) was added in solution in CH_3OH (3 mL). The resulting mixture was stirred under a hydrogen atmosphere for 16 h before the solution was filtered over a short pad of silica. The filtrate was concentrated in *vacuo* to afford pure bicycle **25** (17 mg, 85%) as a light yellow solid.

25: R_f = 0.2 (silica gel, hexanes/EtOAc 50:50); IR (film) ν_{max} 3368, 2921, 2870, 1717, 1595, 1448, 1379, 1268, 1237, 1167, 1121, 1057, 954, 919, 814, 712 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ = 3.75 (s, 3H), 3.75–3.70 (m, 1H), 2.92 (s, 2H), 2.47–2.29 (m, 4H), 2.09 (qt, *J* = 13.3, 5.6 Hz, 1H), 1.87–1.75 (m, 2H), 1.47–1.28 (m, 5H); ^{13}C NMR (150 MHz, CD_3OD): δ = 179.4, 64.8, 53.3, 51.6, 47.1, 37.8 (2C), 31.5 (2C), 28.9 (2C), 16.4 ppm; HRMS (ESI): calcd for $C_{12}H_{22}NO_3^+$ $[M + H]^+$ 228.1600, found 228.1586.



29

Diketone 28: To a stirred solution of bicycles **15a/15'a** (**15a/15'a** = 2:1, 50 mg, 0.27 mmol) in CH_3CN (4 mL) at room temperature were added methyl vinyl ketone (**28**) (45 µL, 0.55

mmol) and DBU (40 µL, 0.27 mmol). The resulting mixture was stirred for 2.5 h before the medium was concentrated under reduced pressure. The residue was dissolved in AcOEt (20 mL) and washed with HCl (1.0 N aq., 10 mL) and H_2O (10 mL), dried (Na_2SO_4) and concentrated in *vacuo* to afford diketone **29** (69 mg, quant.) as an orange oil.

29: R_f = 0.5 (silica gel, hexanes/EtOAc 50:50); IR (film) ν_{max} 3483, 2947, 2878, 1708, 1531, 1459, 1438, 1412, 1376, 1346, 1301, 1258, 1222, 1176, 1121, 1102, 1068, 975, 940, 862, 836, 792, 714 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 2.91 (s, 2H), 2.64 (dd, *J* = 18.4, 5.8 Hz, 2H), 2.50–2.33 (m, 6H), 2.17 (s, 3H), 1.99–1.90 (m, 2H), 1.75 (dtd, *J* = 13.7, 3.3, 1.6 Hz, 2H), 1.60–1.51 (m, 1H), 1.43–1.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.4, 206.3, 93.6, 44.0 (2C), 37.5, 36.0 (2C), 30.5, 30.2, 29.4 (2C), 16.2 ppm; HRMS (ESI): calcd for $C_{13}H_{19}NNaO_4^+$ $[M + Na]^+$ 276.1211, found 276.1219.

II) Abbreviations

DMSO = dimethyl sulfoxide

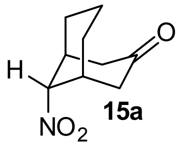
DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

Dibal-H = diisobutylaluminium hydride

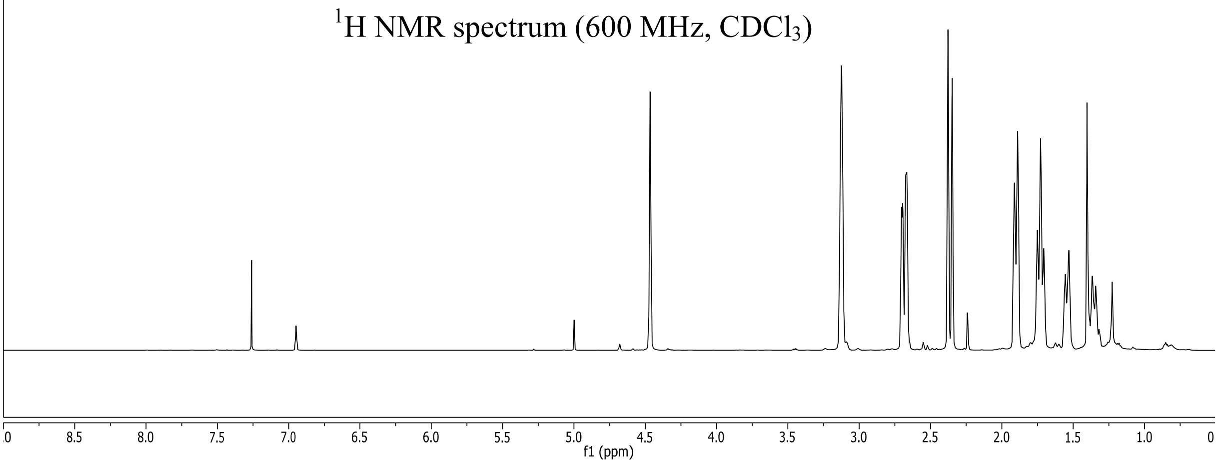
III) References

[1] J.-T. Li, W.-Z. Xu, G.-F. Chen, T.-S. Li, *Ultrason. Sonochem*. **2005**, *12*, 473–476.

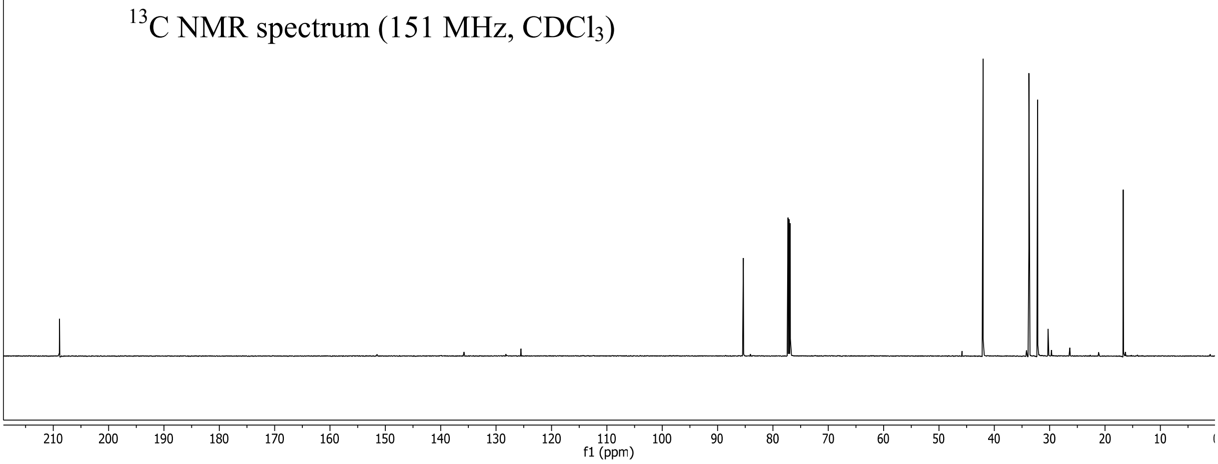
IV) ^{1}H and ^{13}C NMR Spectra of Compounds



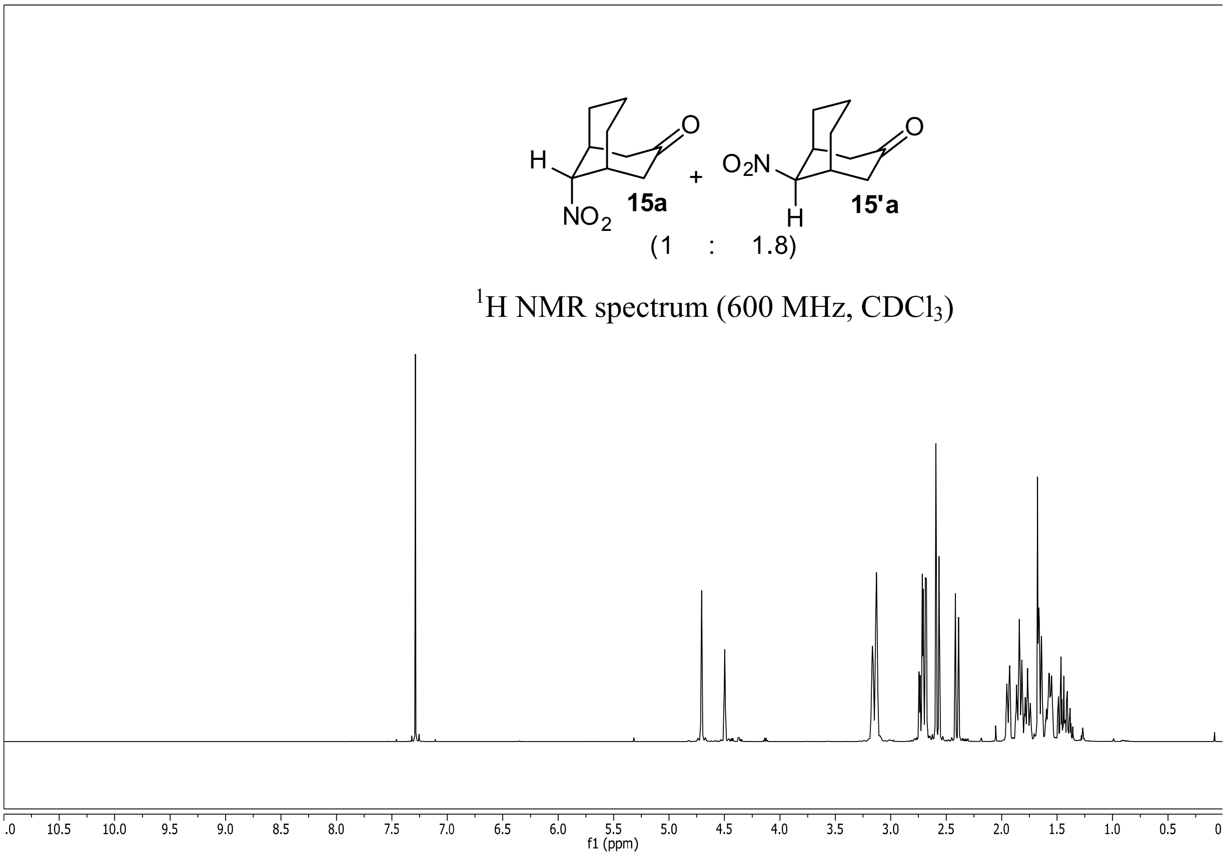
15a



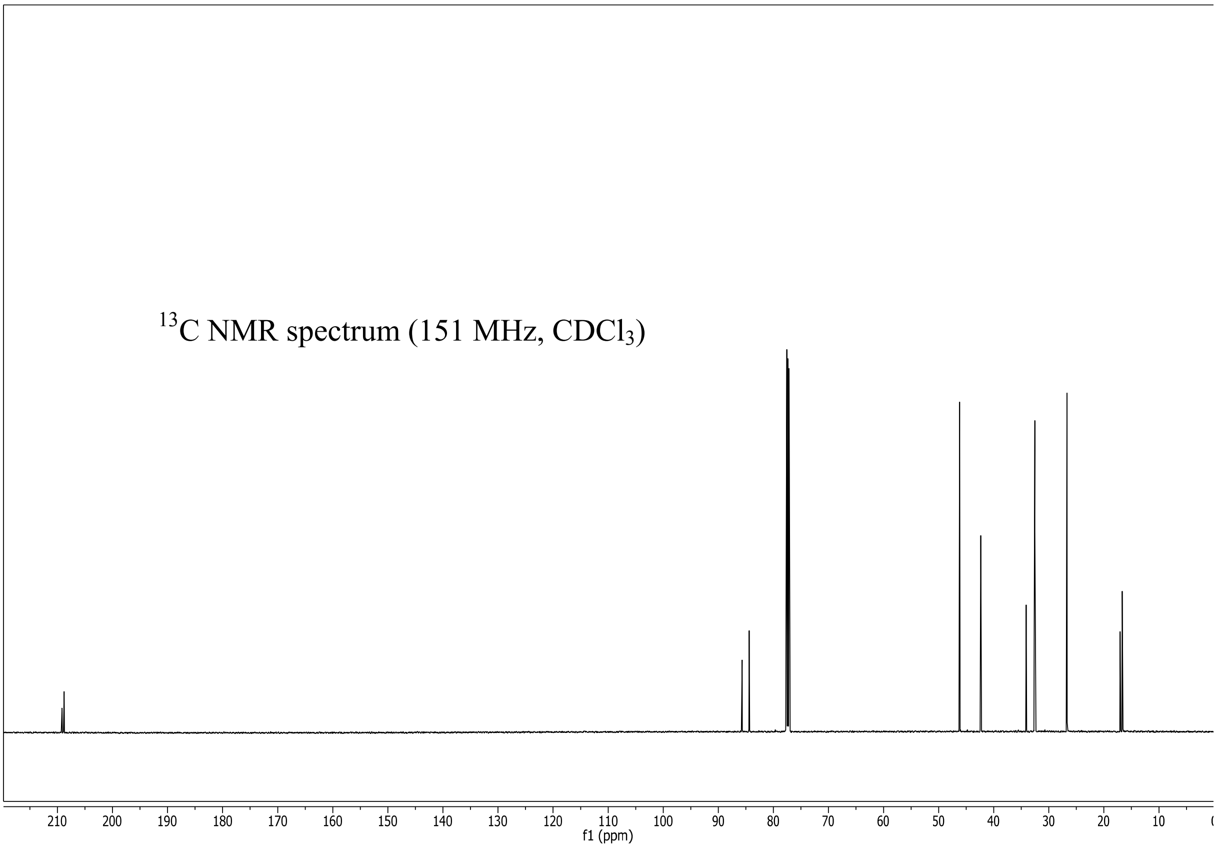
^{1}H NMR spectrum (600 MHz, $CDCl_3$)



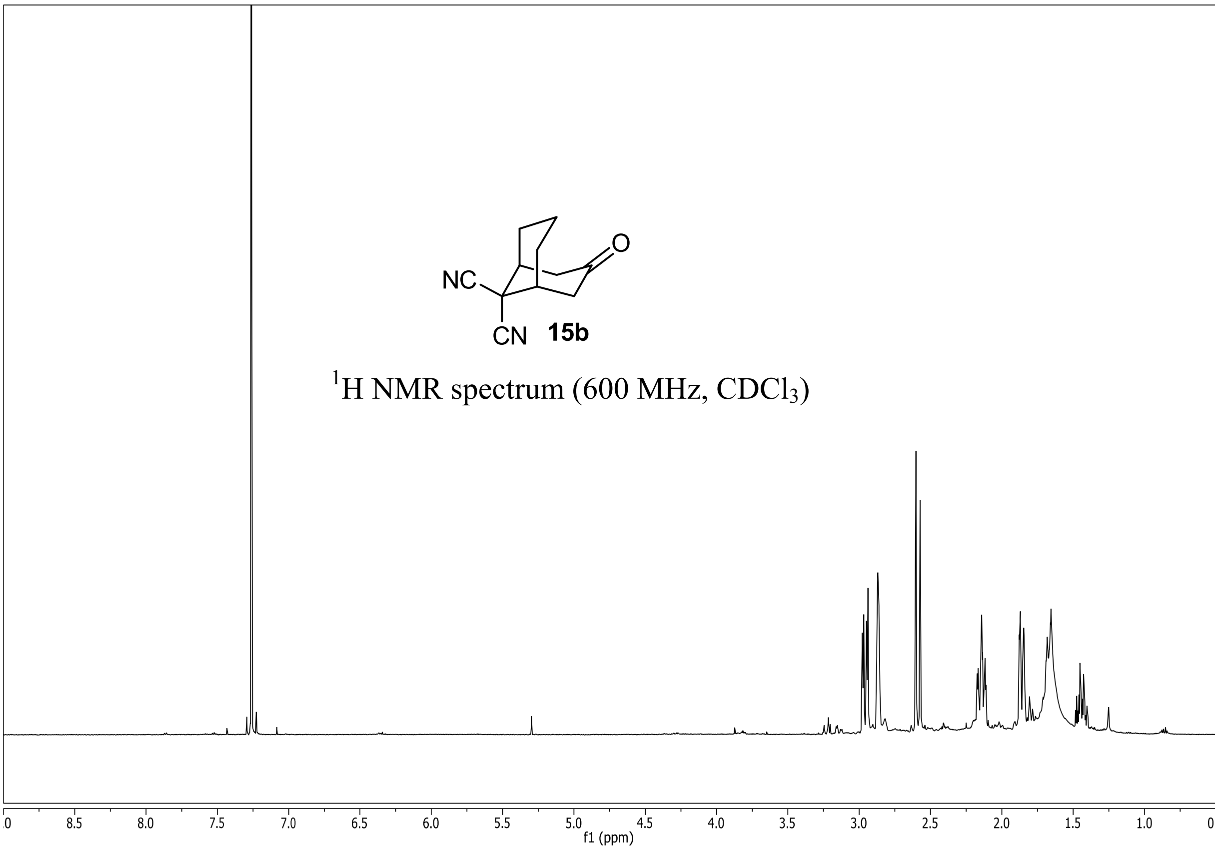
^{13}C NMR spectrum (151 MHz, $CDCl_3$)



^{1}H NMR spectrum (600 MHz, $CDCl_3$)

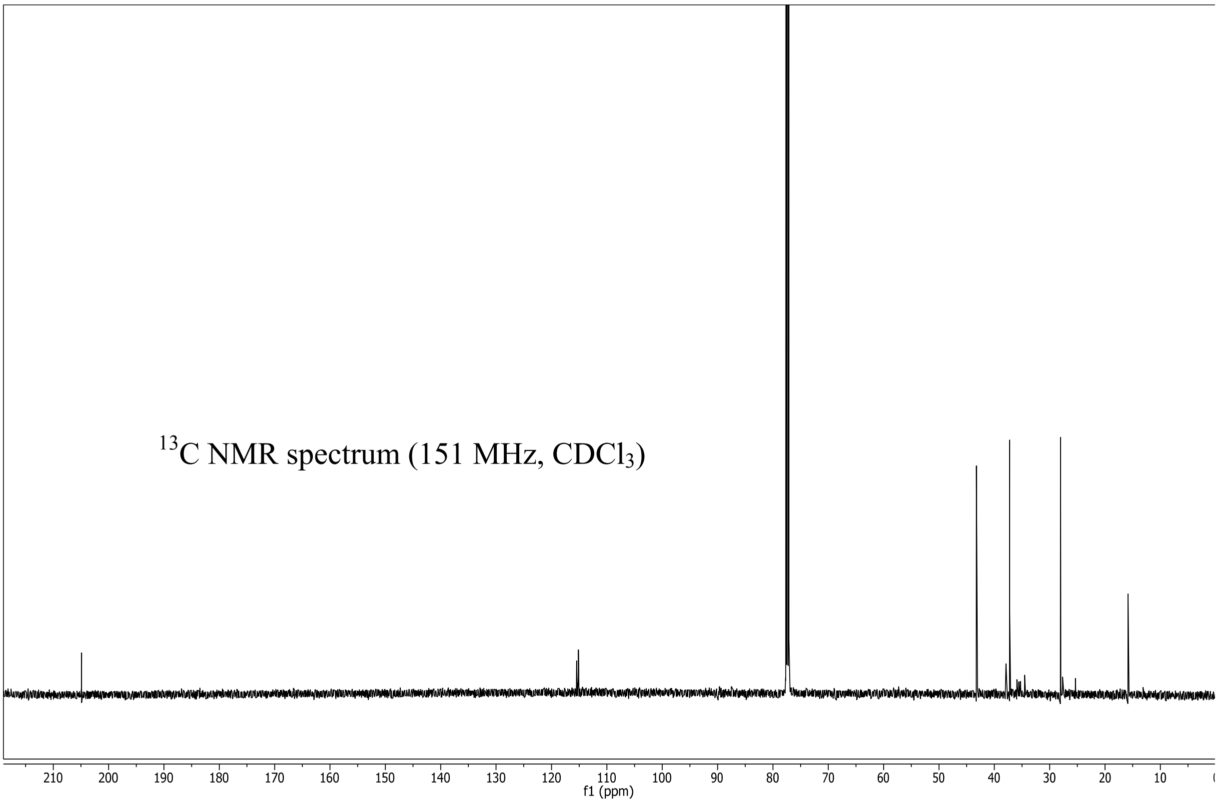


^{13}C NMR spectrum (151 MHz, $CDCl_3$)

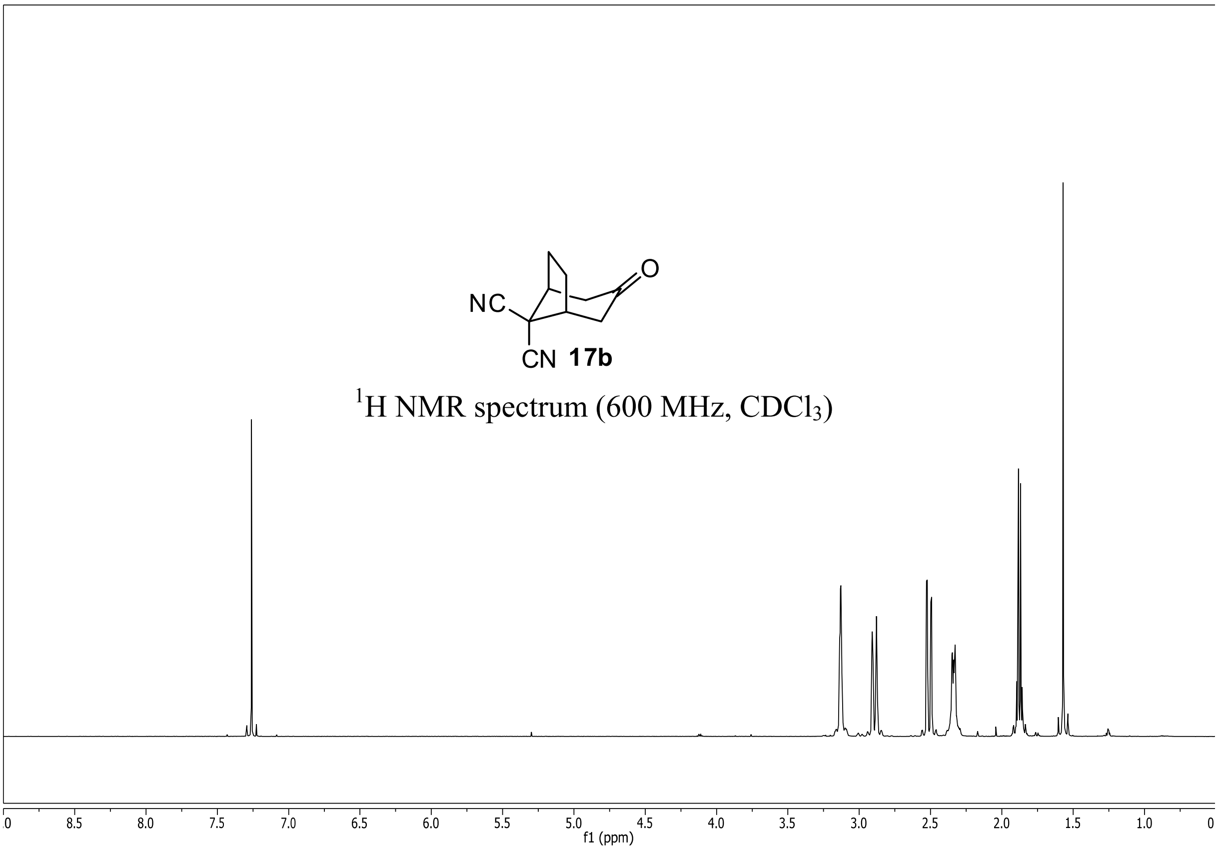


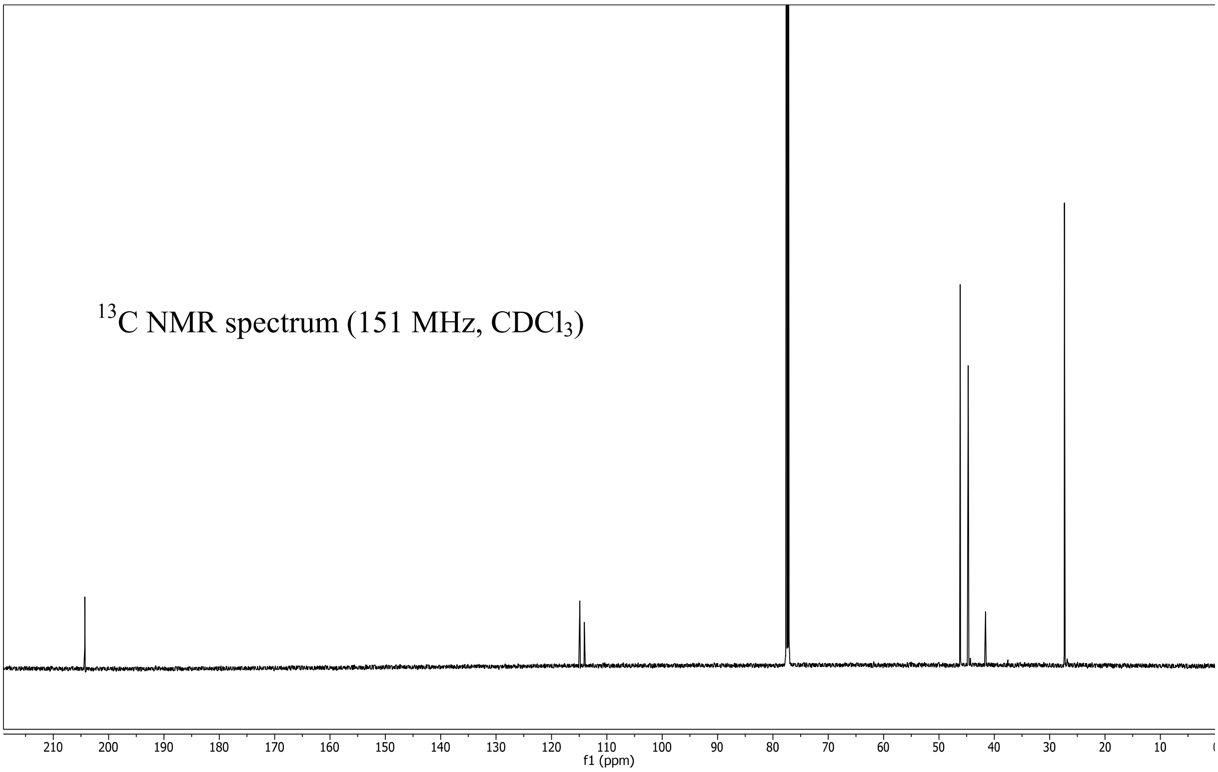
15b

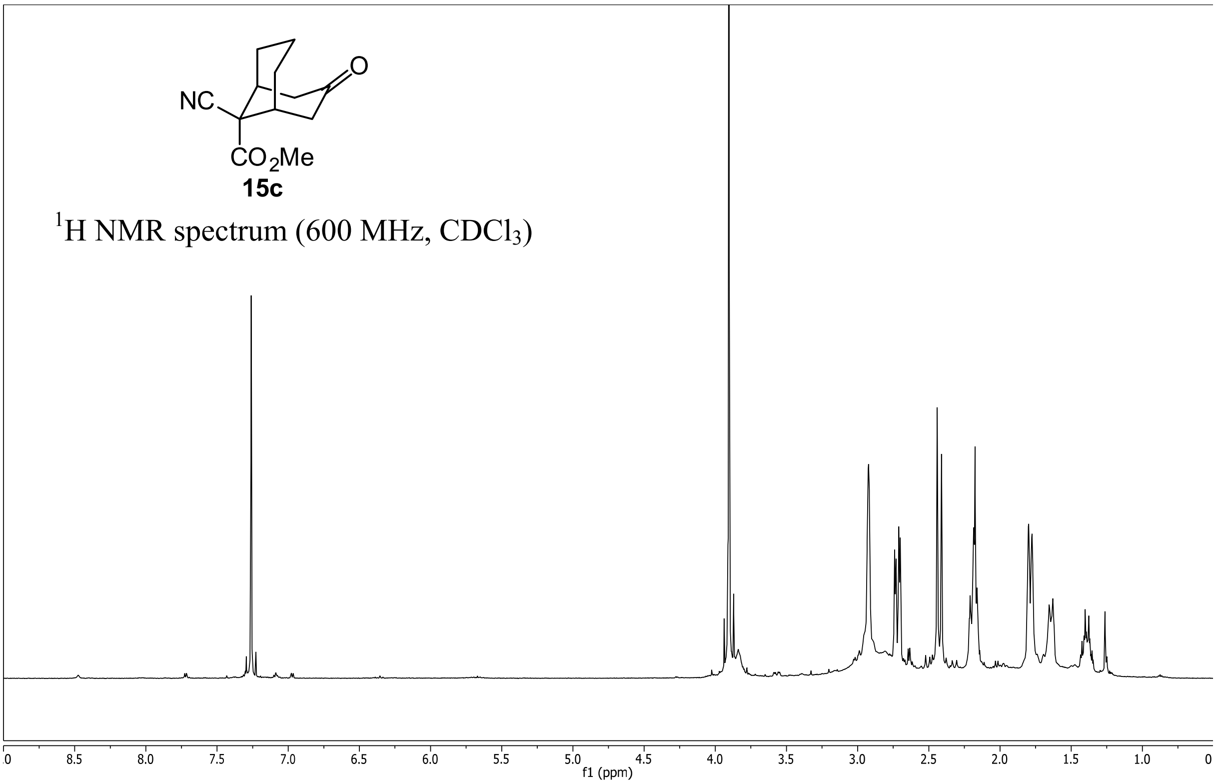
^{1}H NMR spectrum (600 MHz, $CDCl_3$)



^{13}C NMR spectrum (151 MHz, $CDCl_3$)

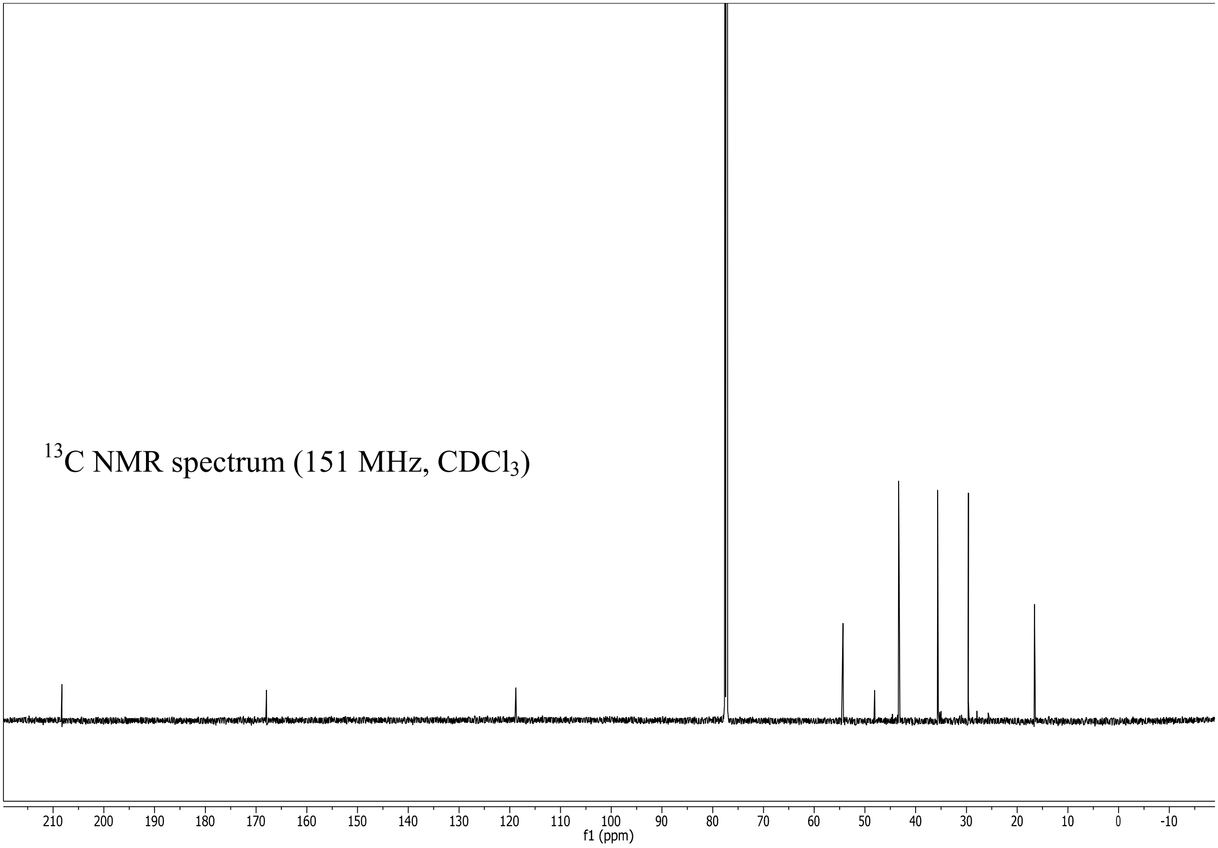

NC
O
CN
17b
^{1}H NMR spectrum (600 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


^{13}C NMR spectrum (151 MHz, $CDCl_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

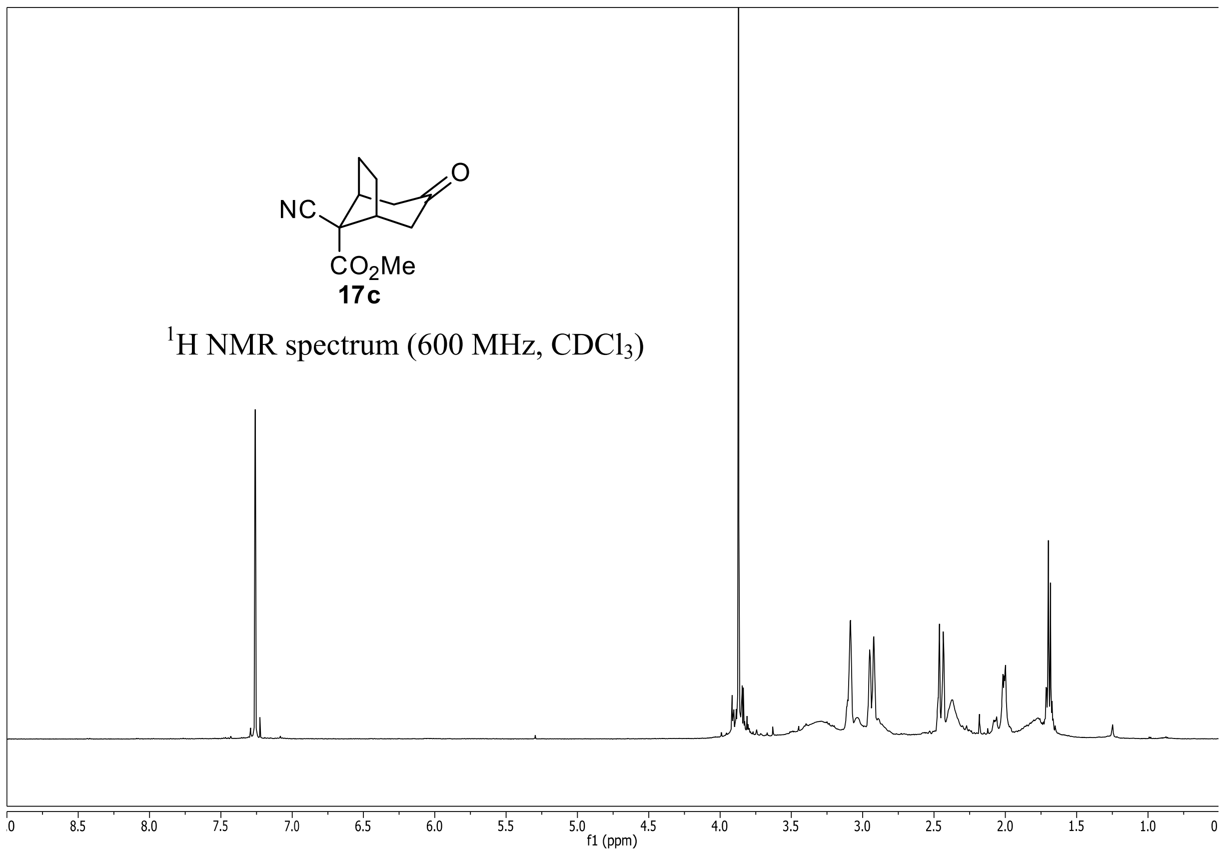


15c

^{1}H NMR spectrum (600 MHz, $CDCl_3$)

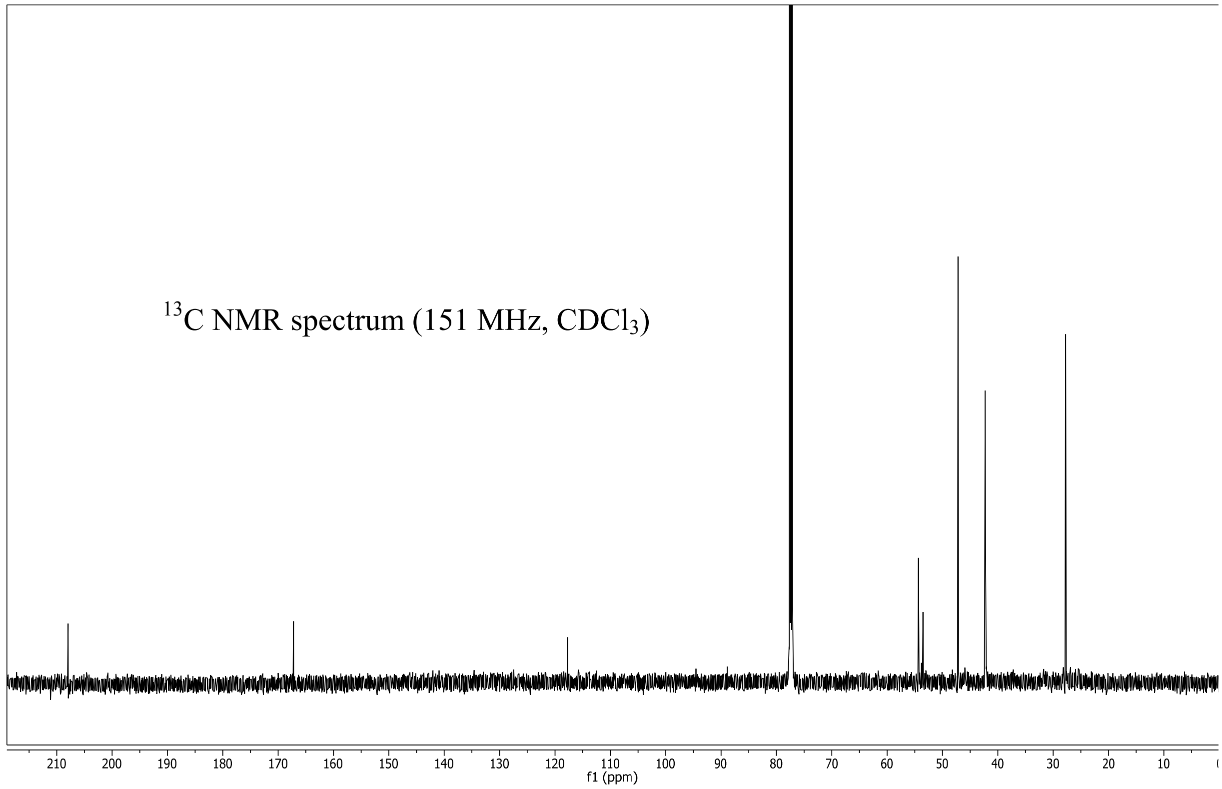


^{13}C NMR spectrum (151 MHz, $CDCl_3$)

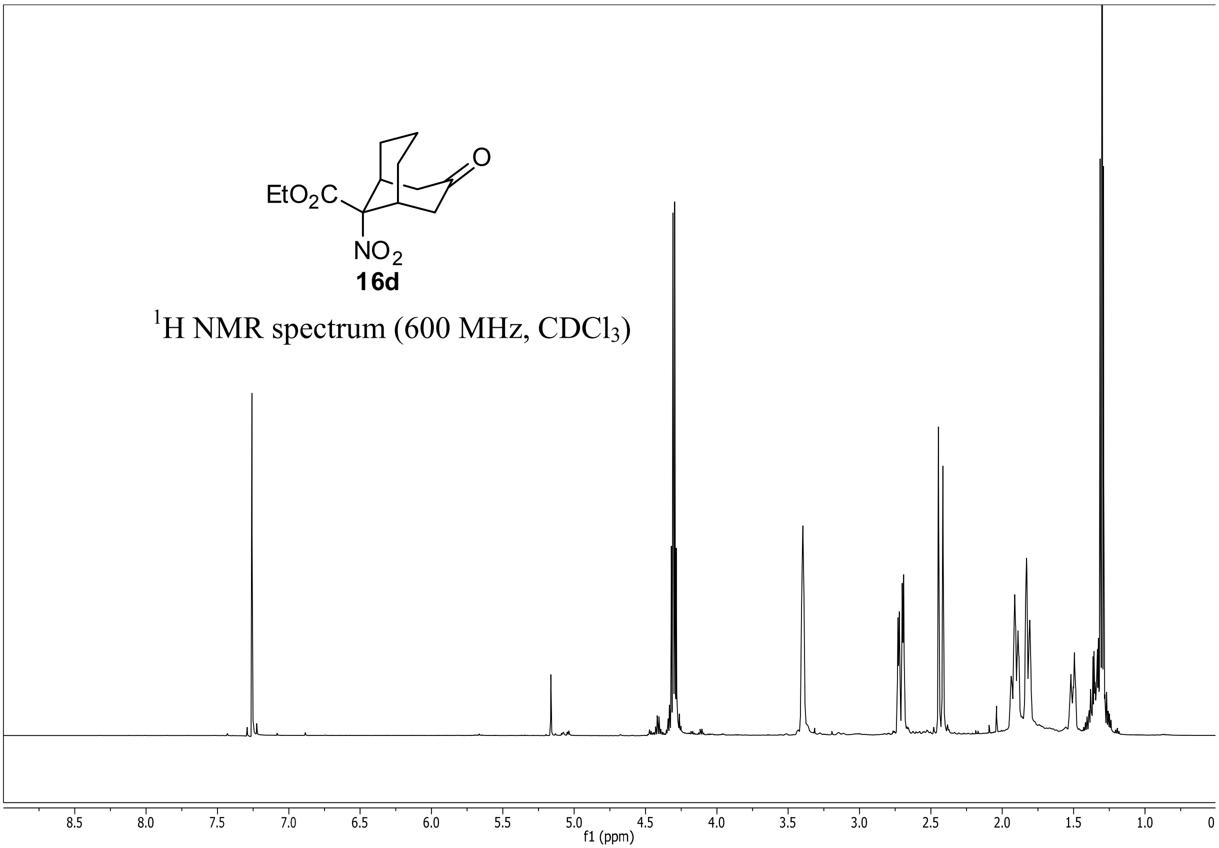


17c

^{1}H NMR spectrum (600 MHz, CDCl$_3$)

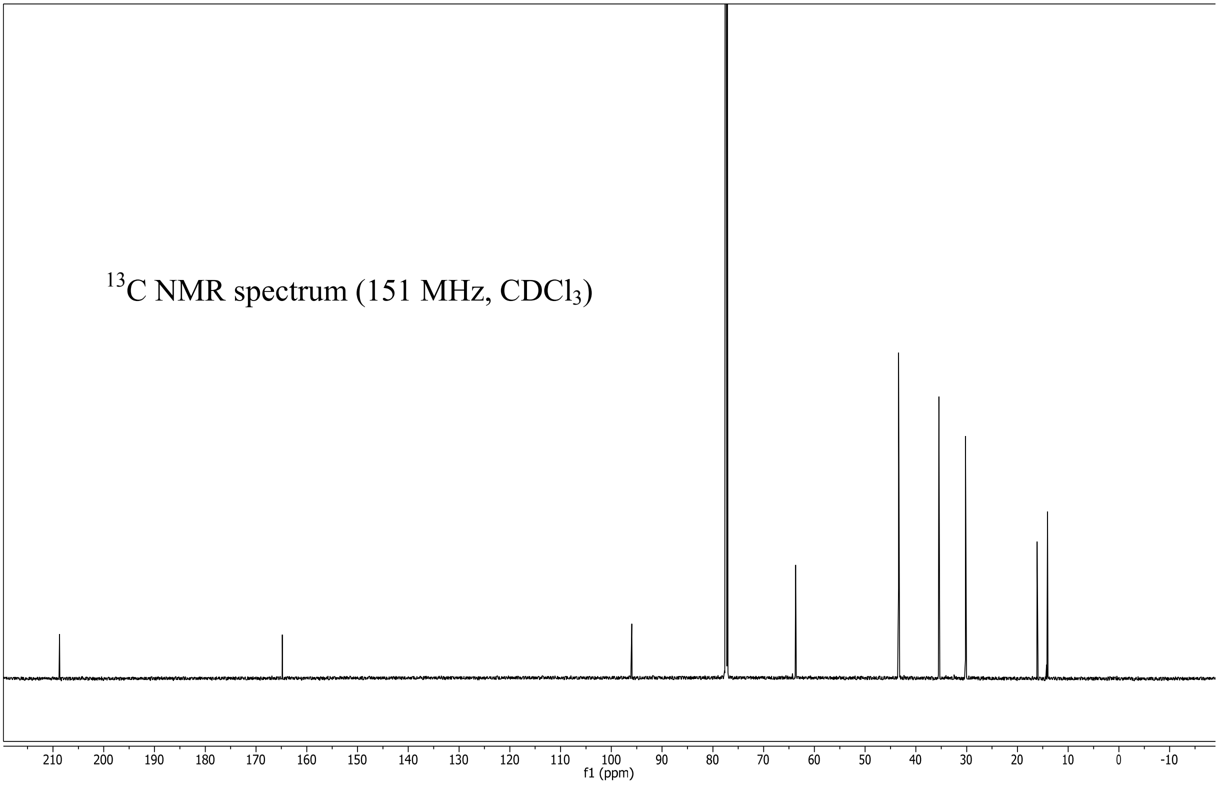


^{13}C NMR spectrum (151 MHz, CDCl$_3$)

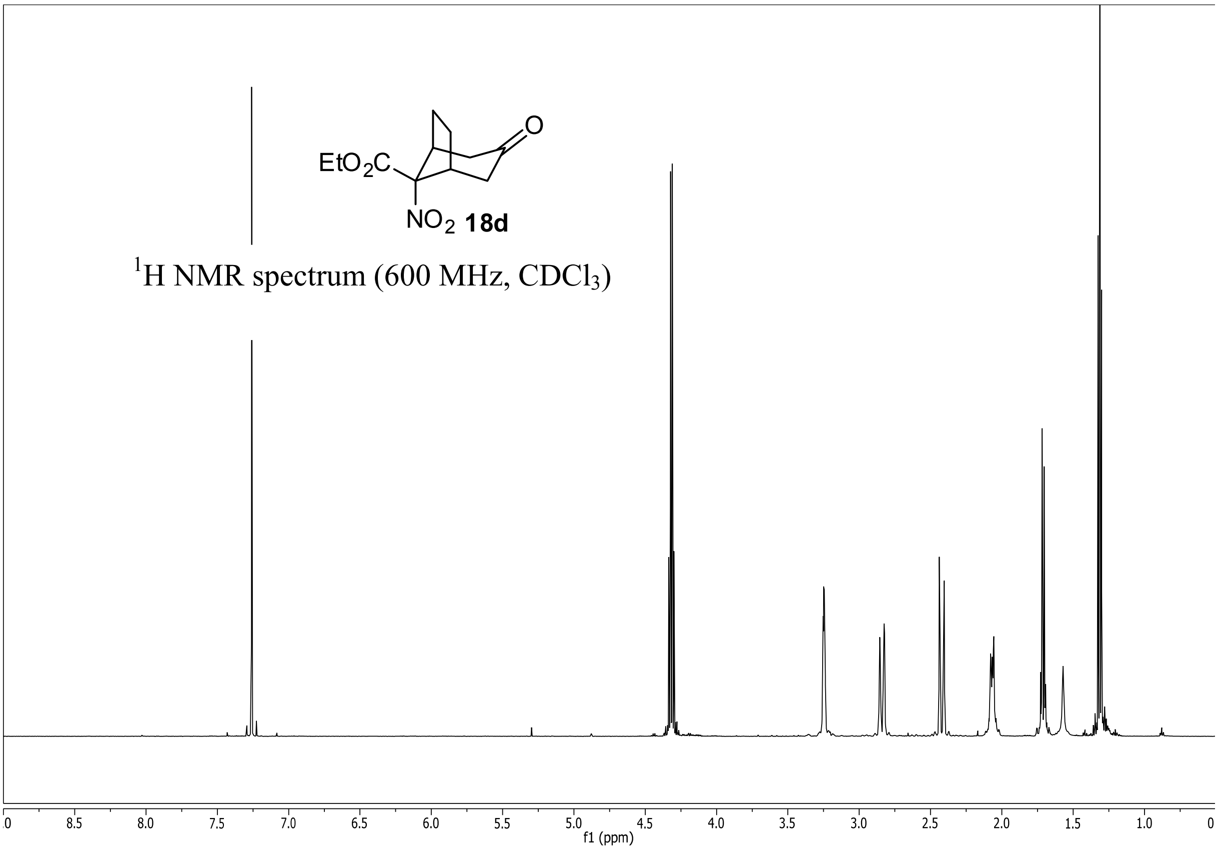


16d

^{1}H NMR spectrum (600 MHz, $CDCl_3$)

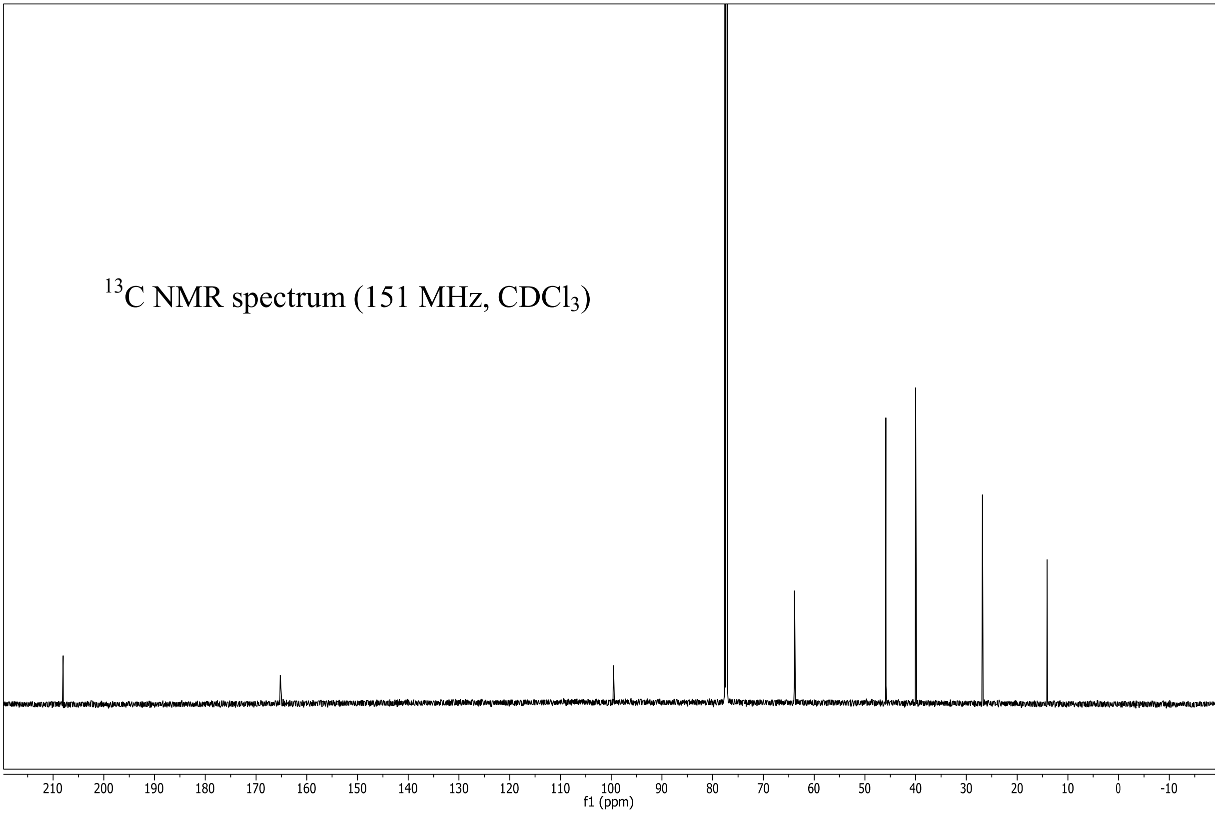


^{13}C NMR spectrum (151 MHz, $CDCl_3$)

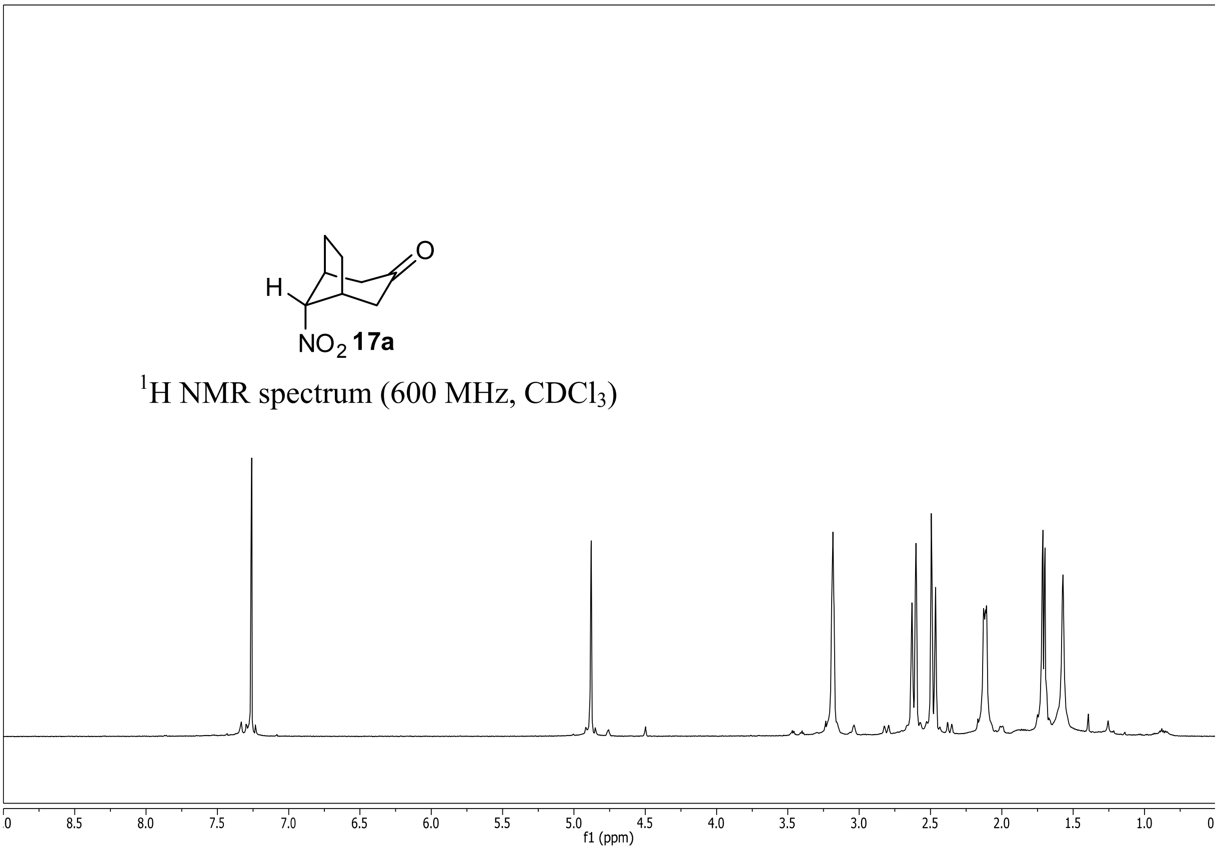


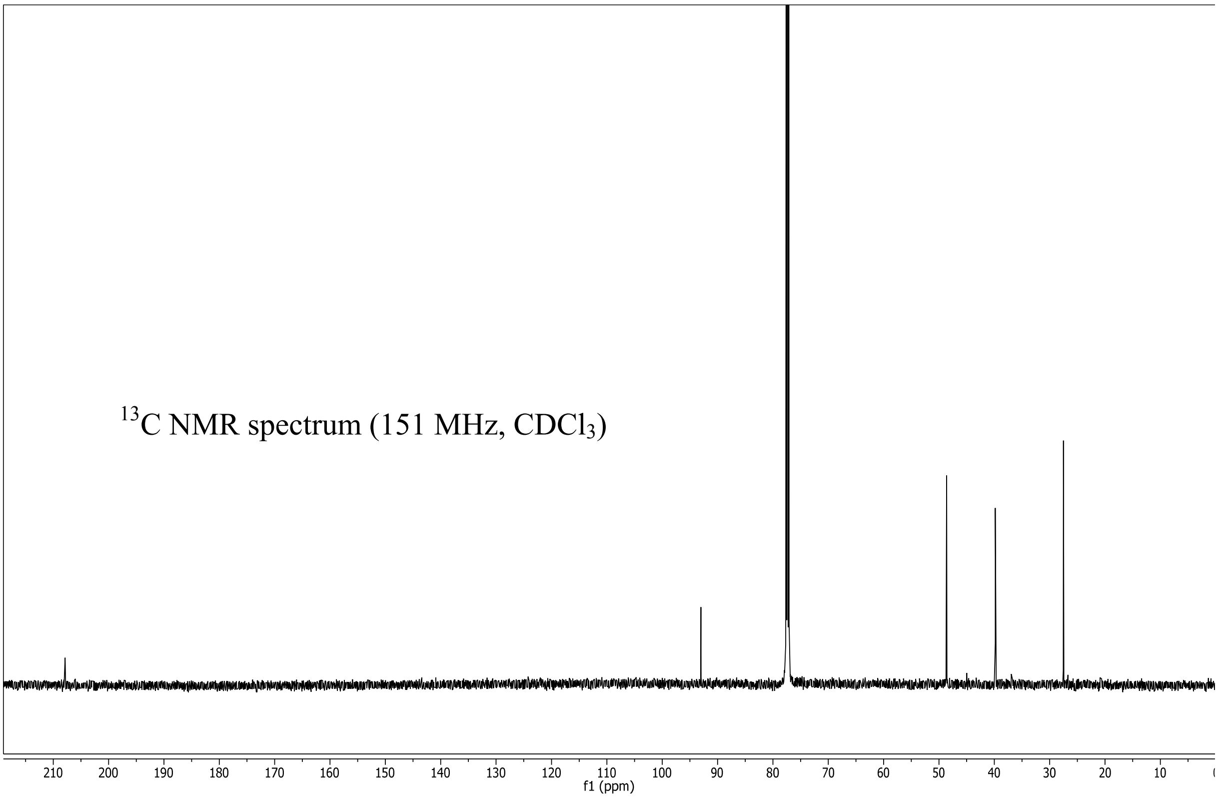
18d

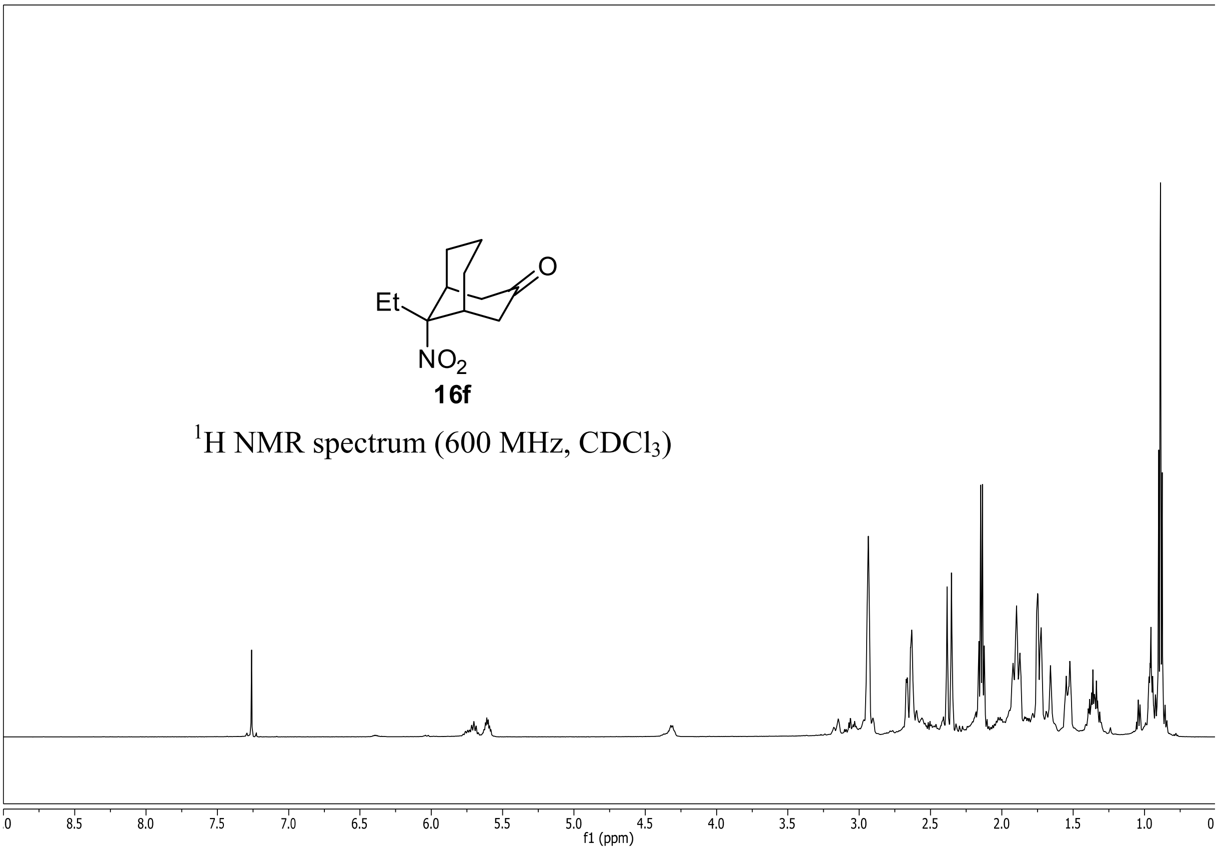
^{1}H NMR spectrum (600 MHz, CDCl$_3$)

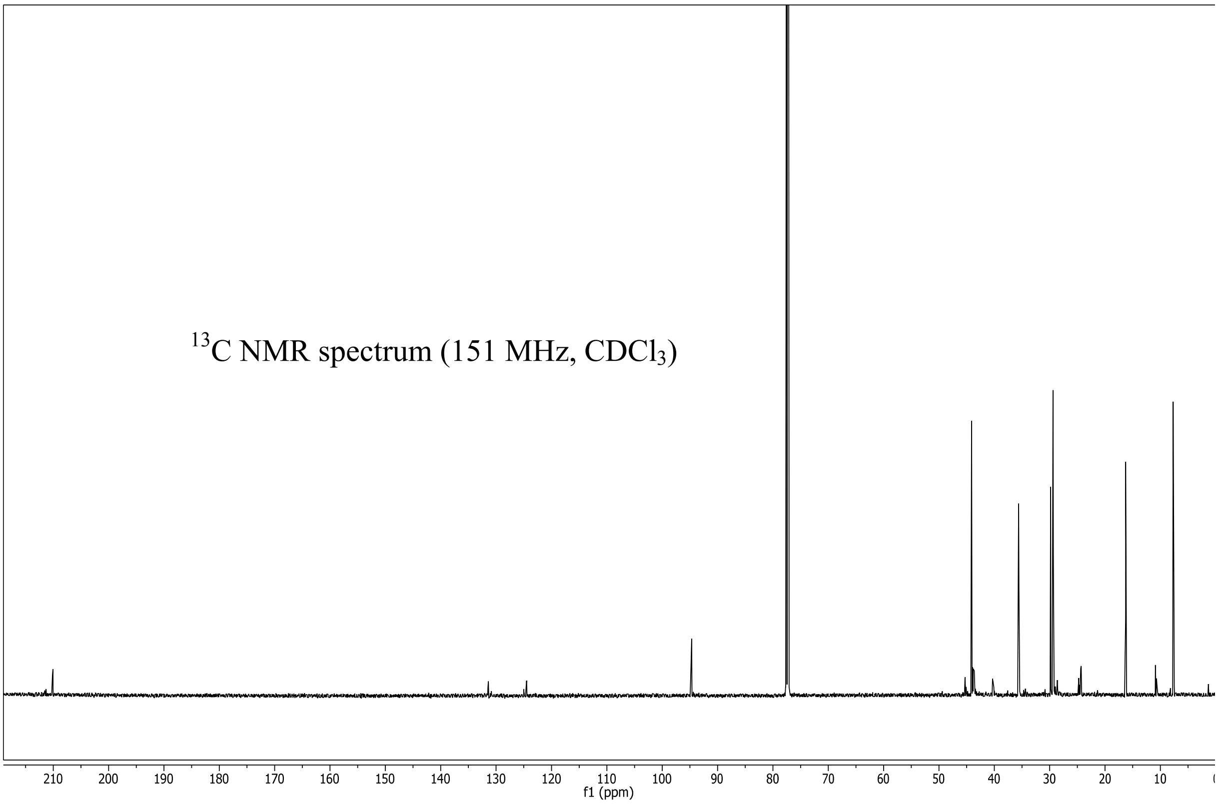


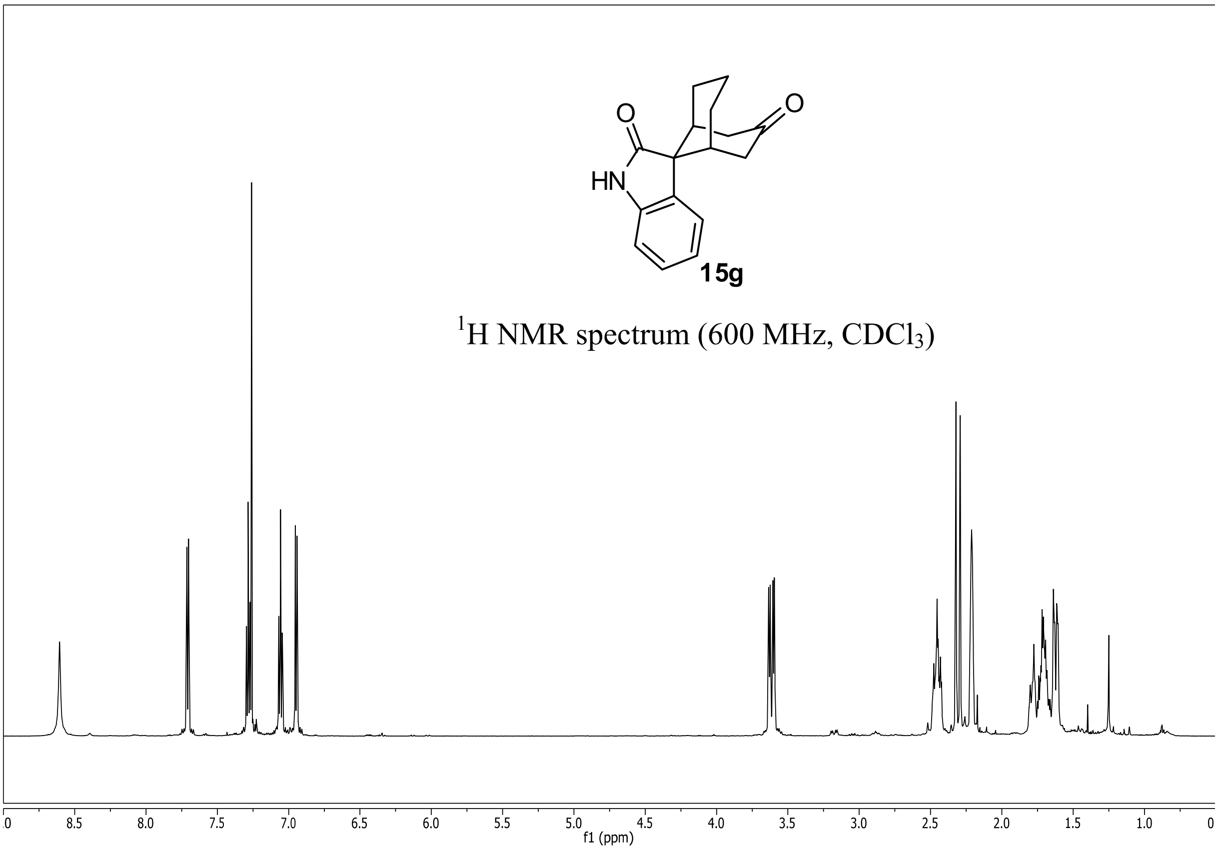
^{13}C NMR spectrum (151 MHz, CDCl$_3$)


O
H
NO2
17a
1H NMR spectrum (600 MHz, CDCl3)
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
f1 (ppm)


13C NMR spectrum (151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

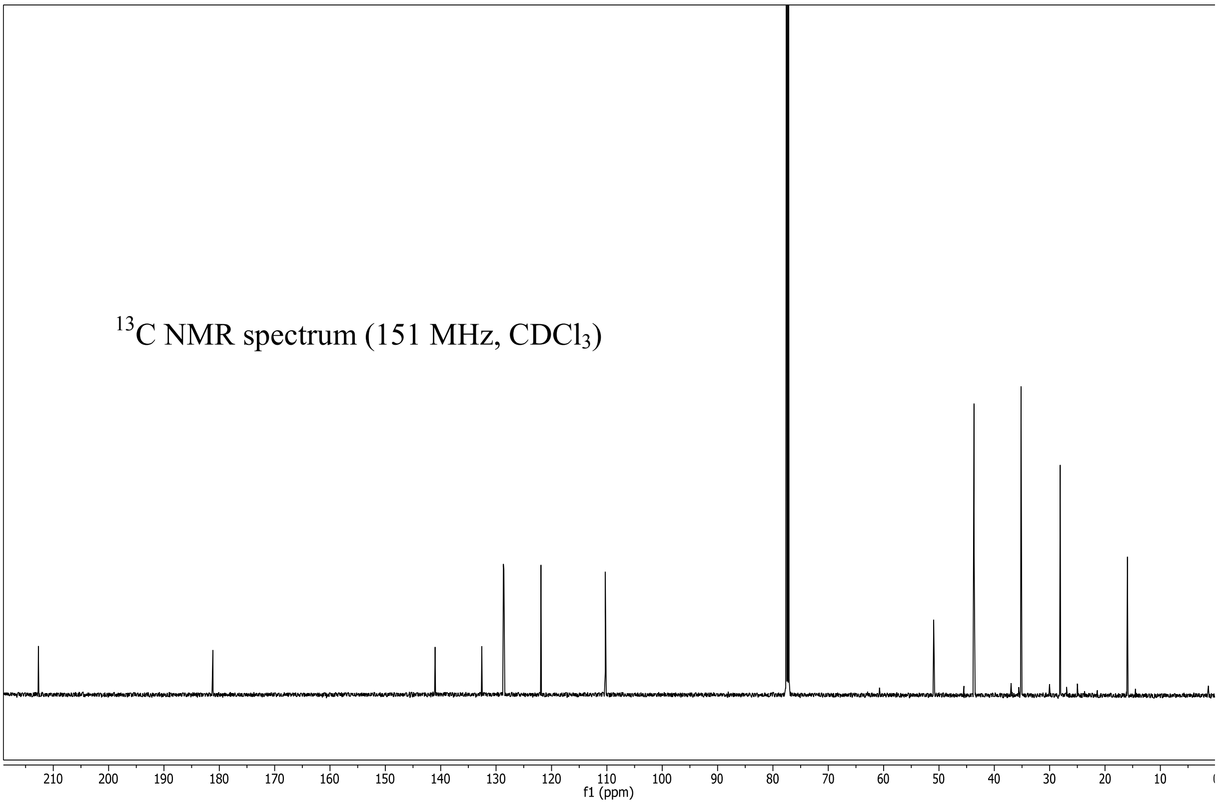

O
Et
NO_2
16f
^{1}H NMR spectrum (600 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


^{13}C NMR spectrum (151 MHz, $CDCl_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

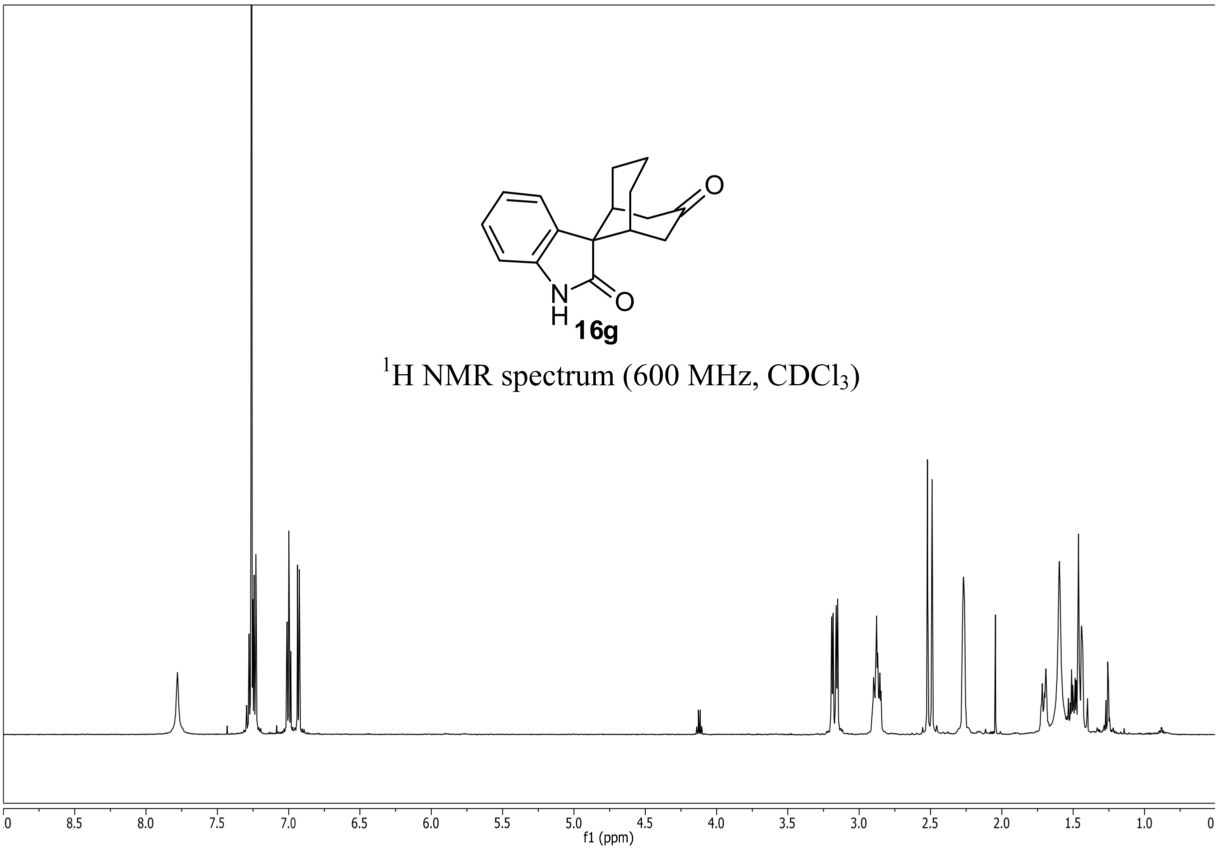


15g

^{1}H NMR spectrum (600 MHz, CDCl$_3$)

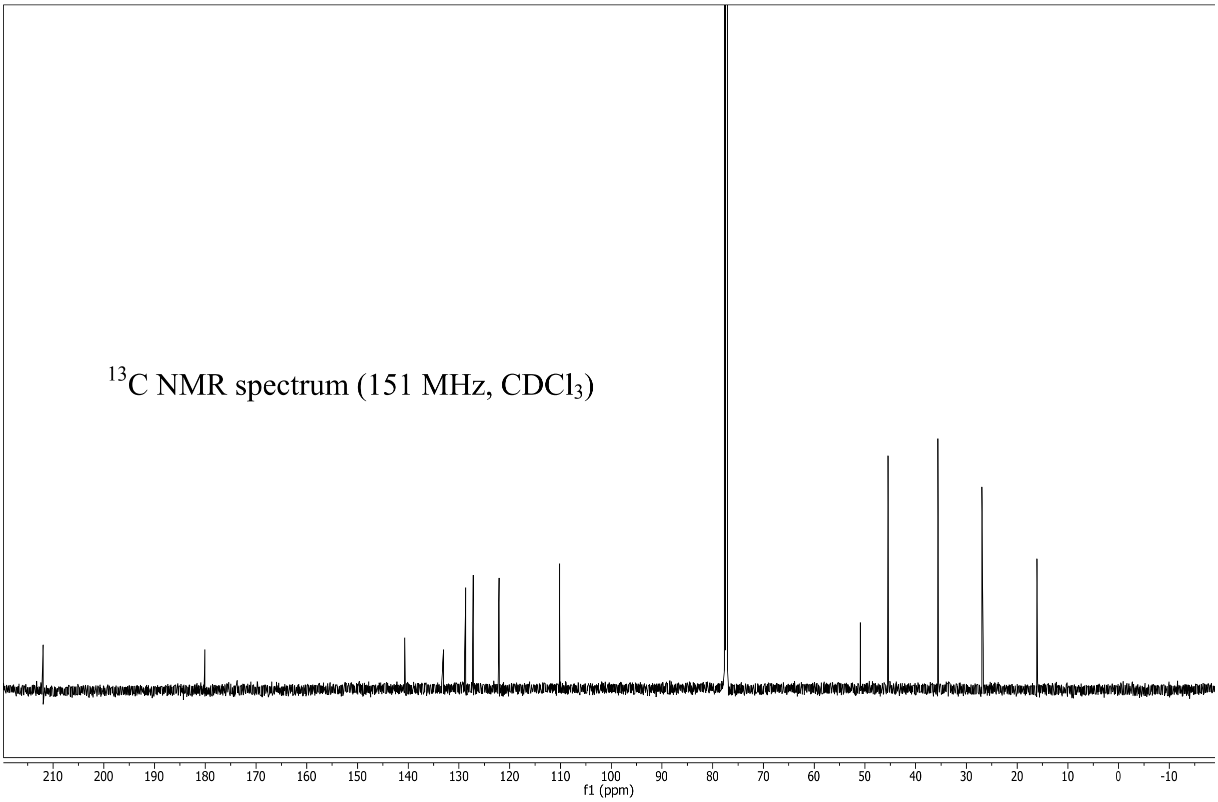


^{13}C NMR spectrum (151 MHz, CDCl$_3$)

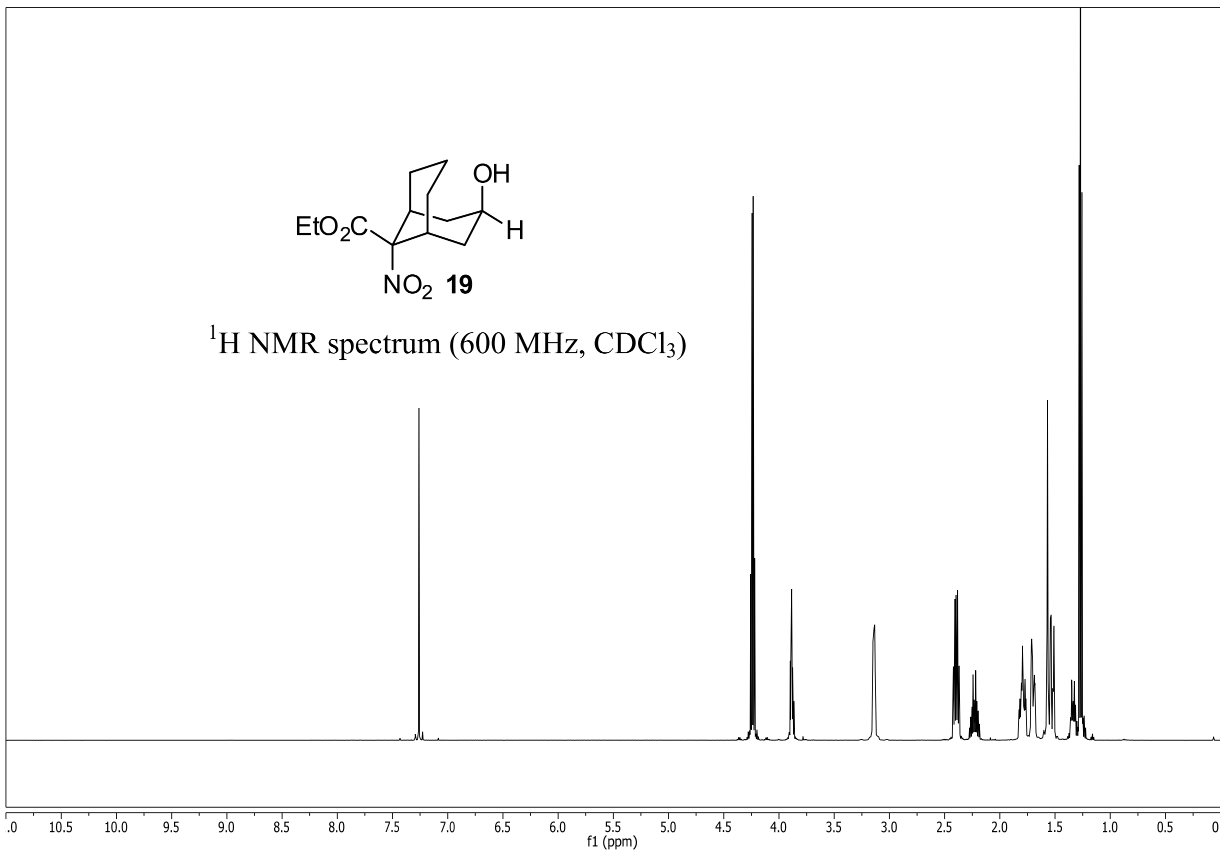


16g

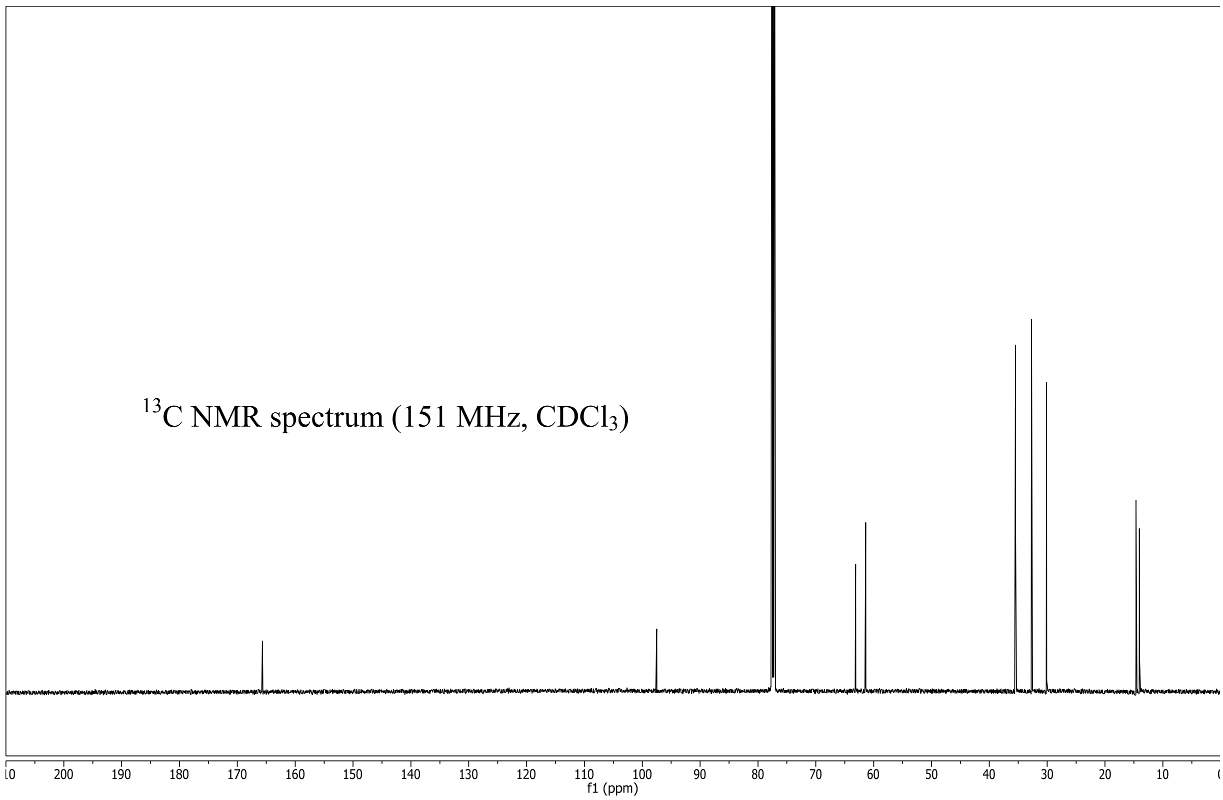
^{1}H NMR spectrum (600 MHz, $CDCl_3$)



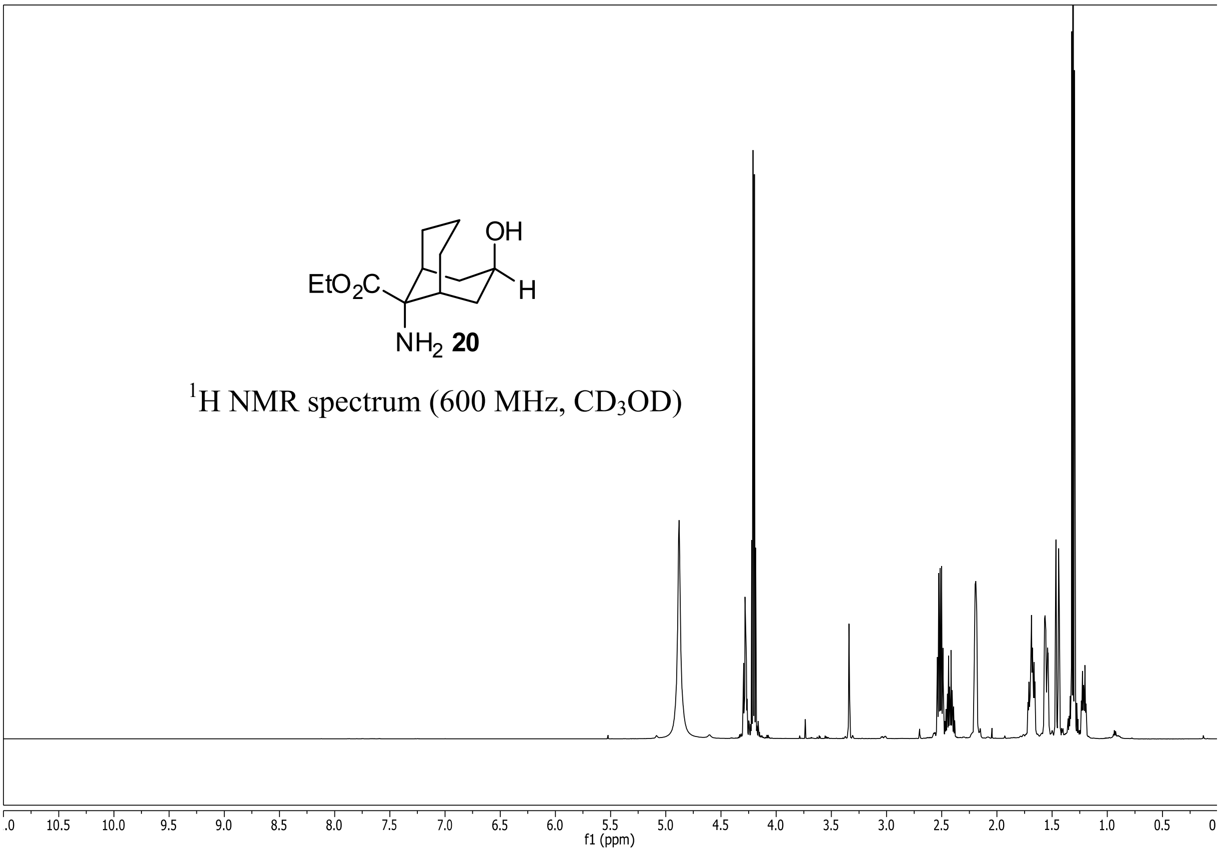
^{13}C NMR spectrum (151 MHz, $CDCl_3$)



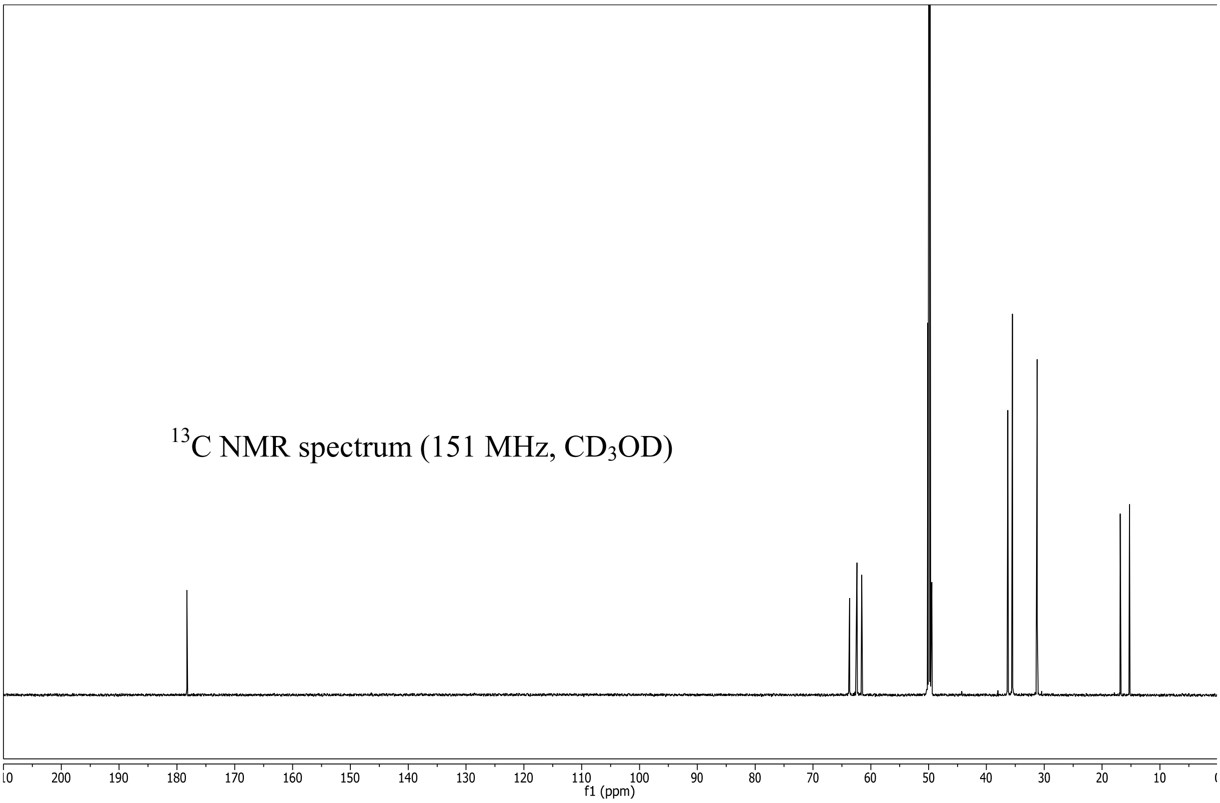
^{1}H NMR spectrum (600 MHz, $CDCl_3$)



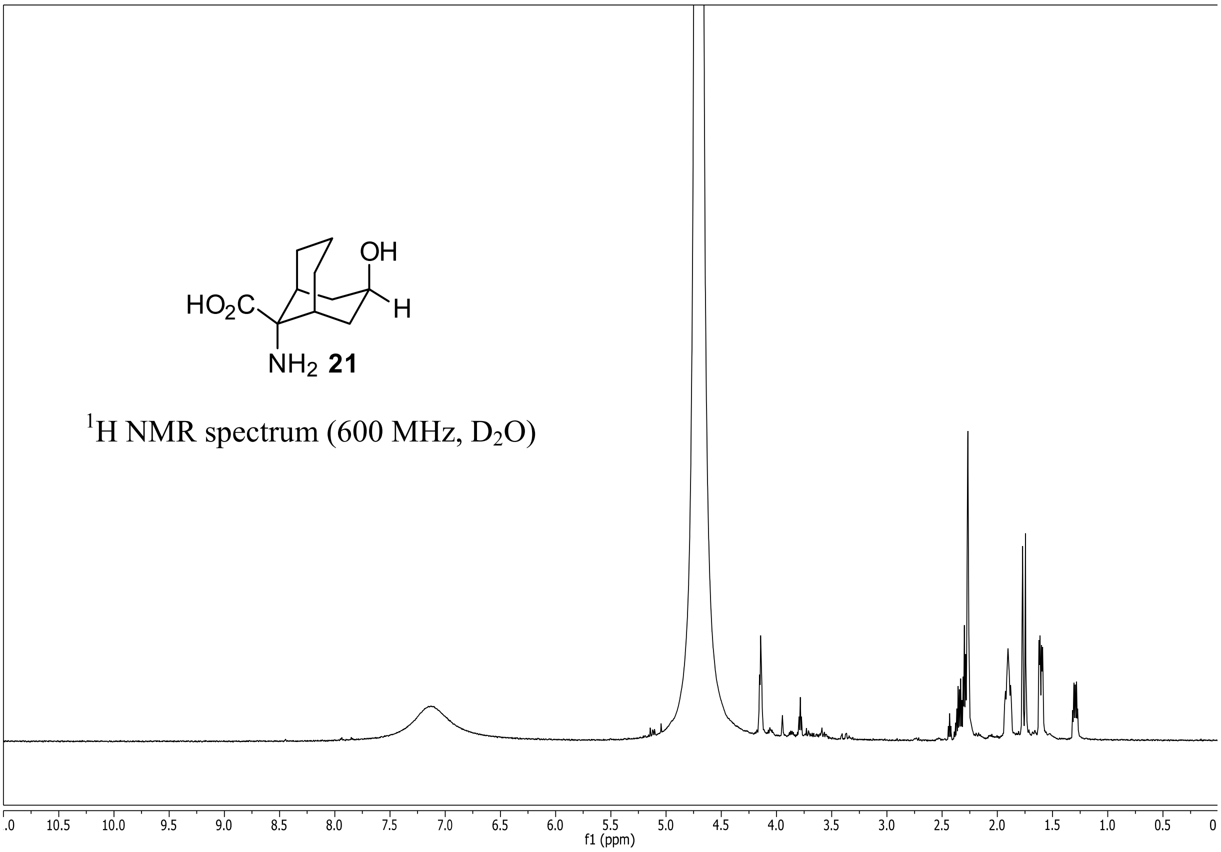
^{13}C NMR spectrum (151 MHz, $CDCl_3$)

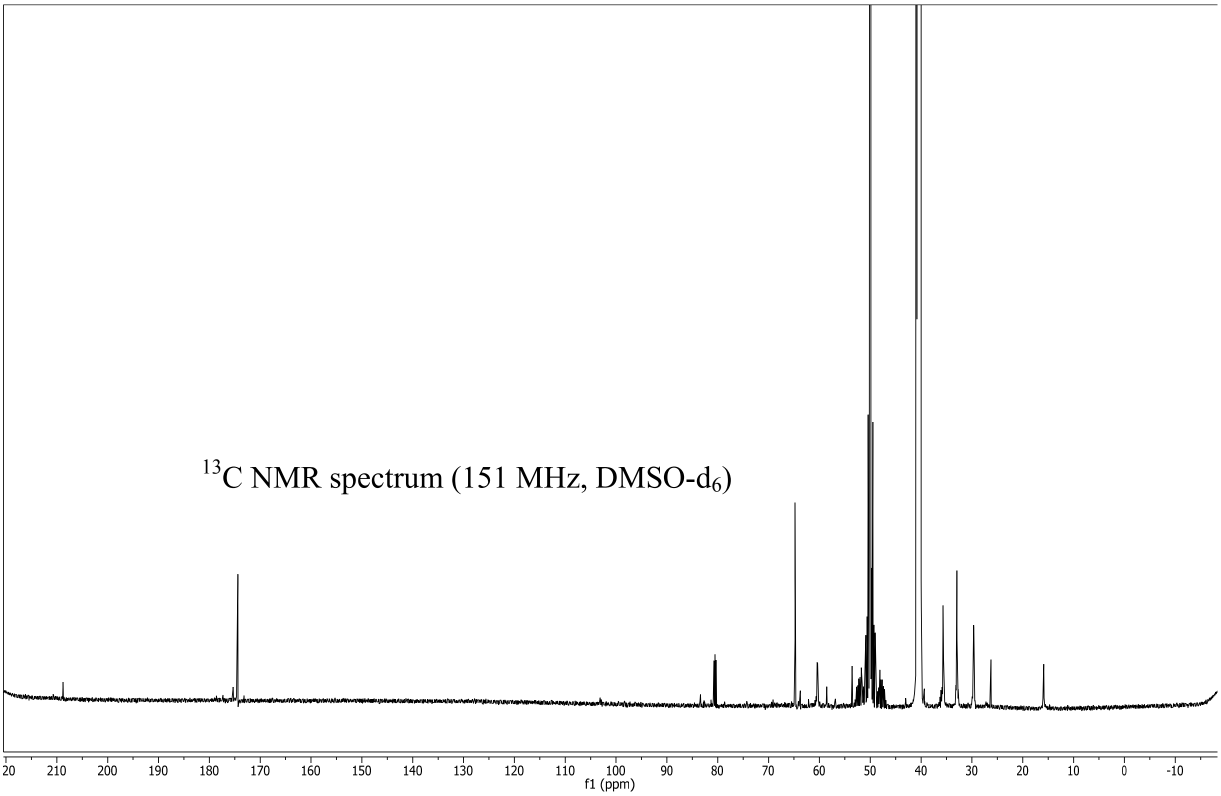


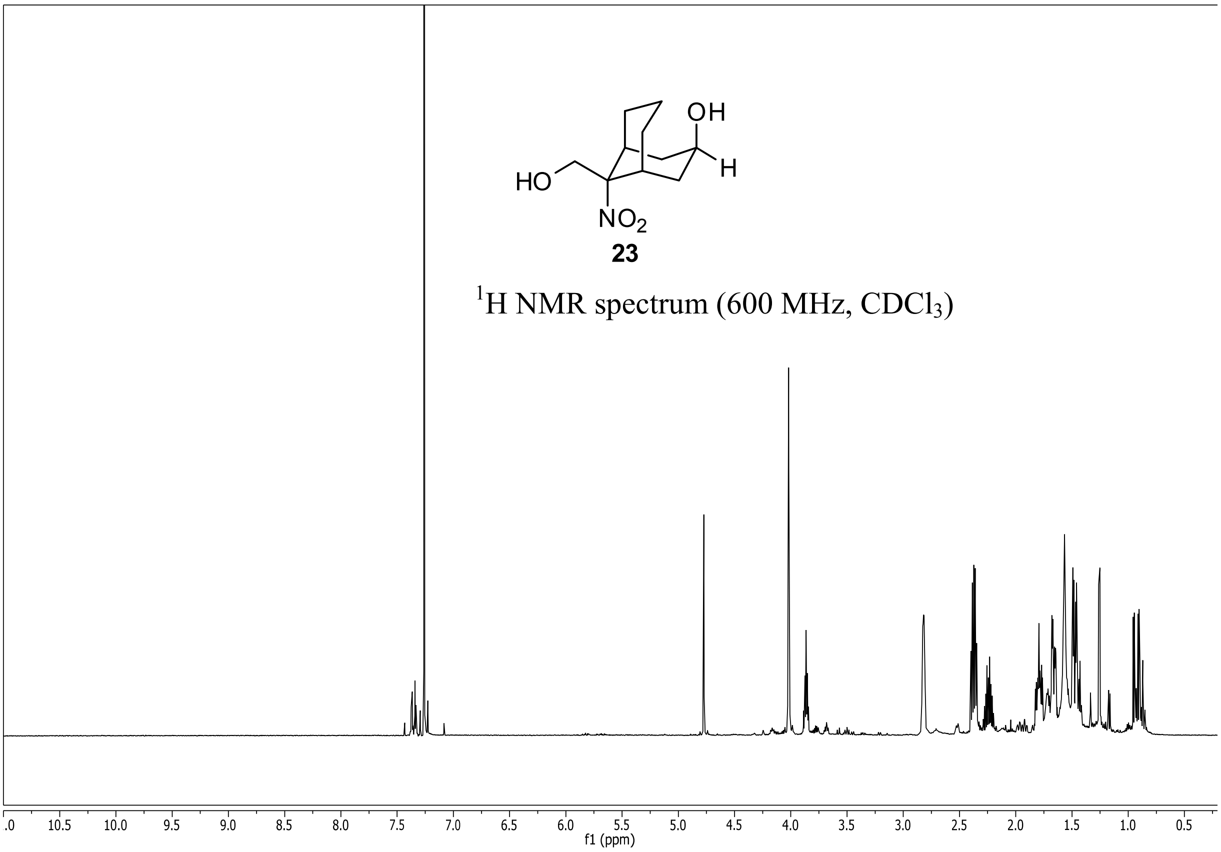
^{1}H NMR spectrum (600 MHz, CD$_3$OD)



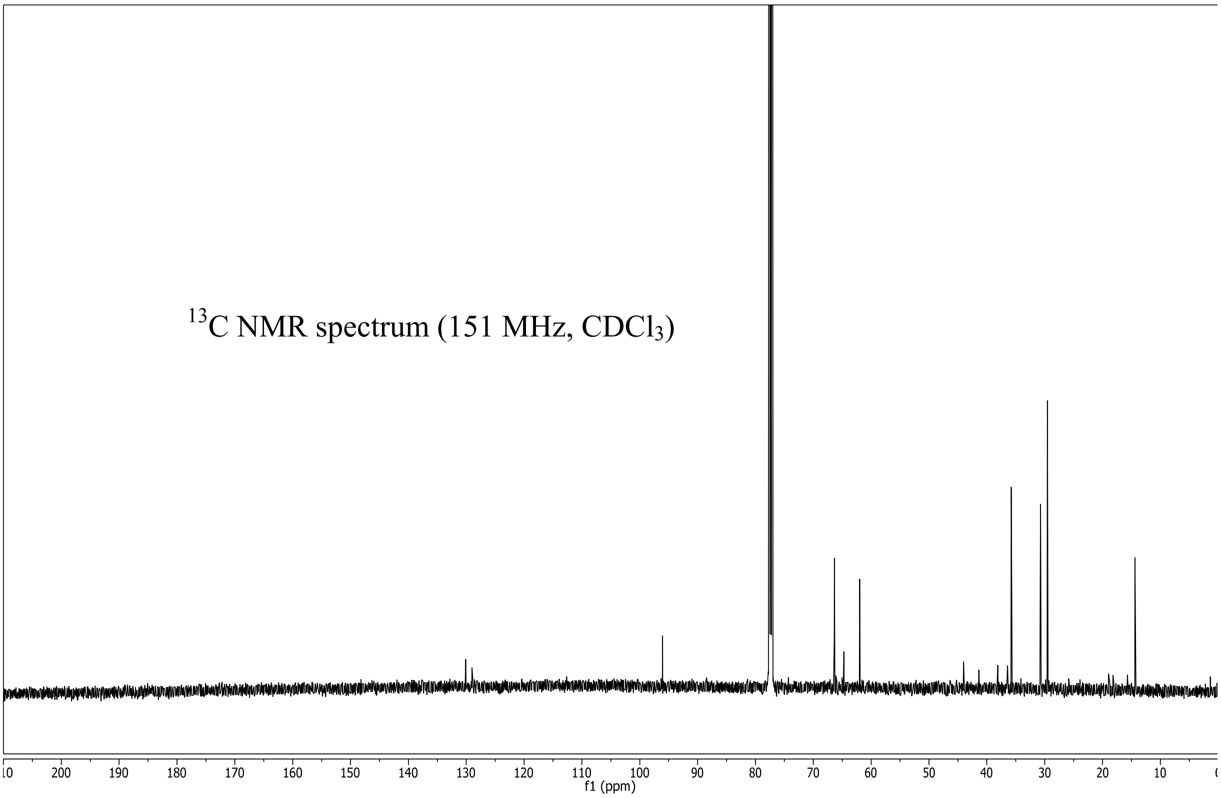
^{13}C NMR spectrum (151 MHz, CD$_3$OD)


OH
HO2C
H
NH2 21
1H NMR spectrum (600 MHz, D2O)
.0
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
f1 (ppm)

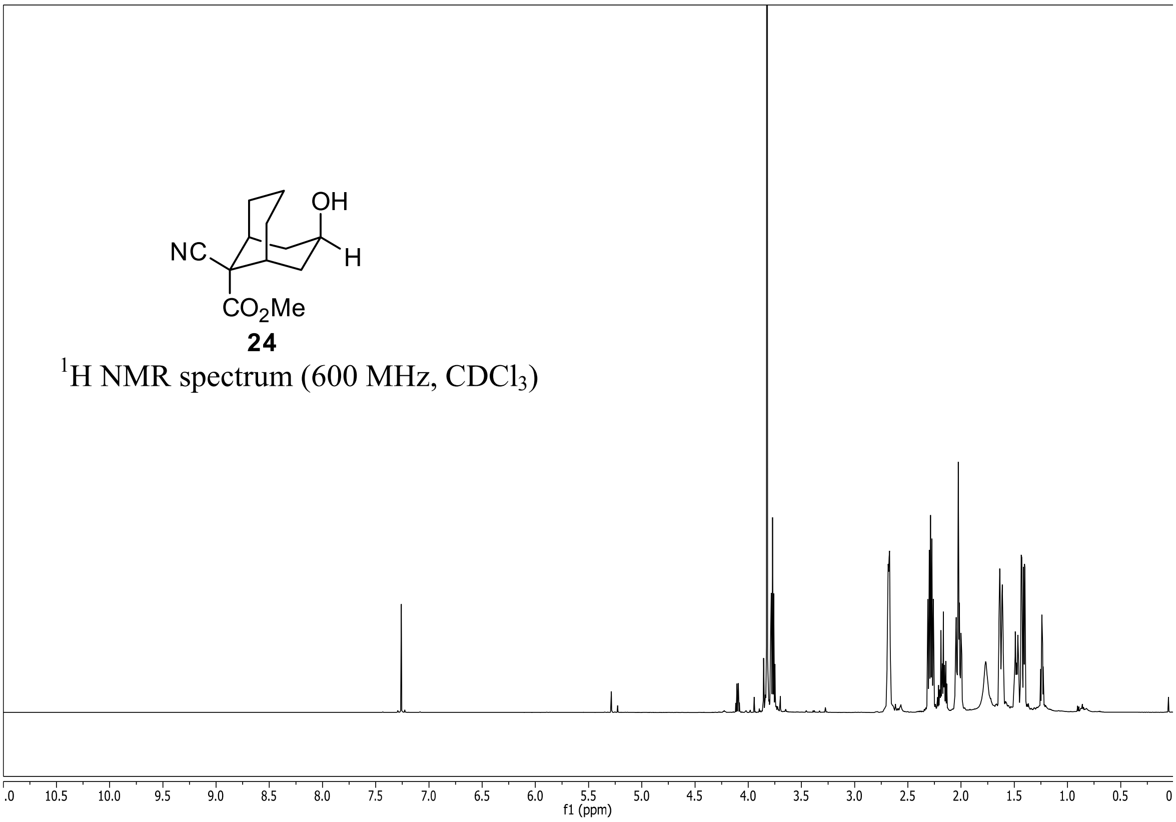

13C NMR spectrum (151 MHz, DMSO-d6)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



^{1}H NMR spectrum (600 MHz, $CDCl_3$)

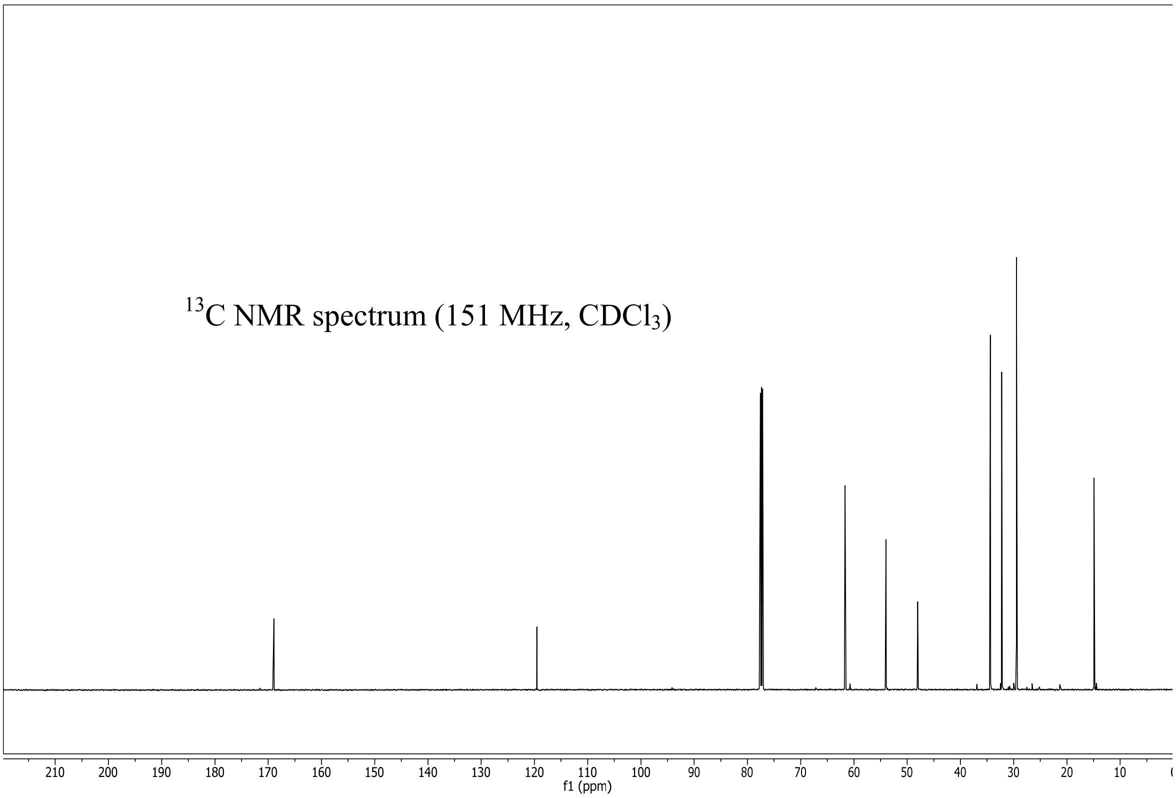


^{13}C NMR spectrum (151 MHz, $CDCl_3$)

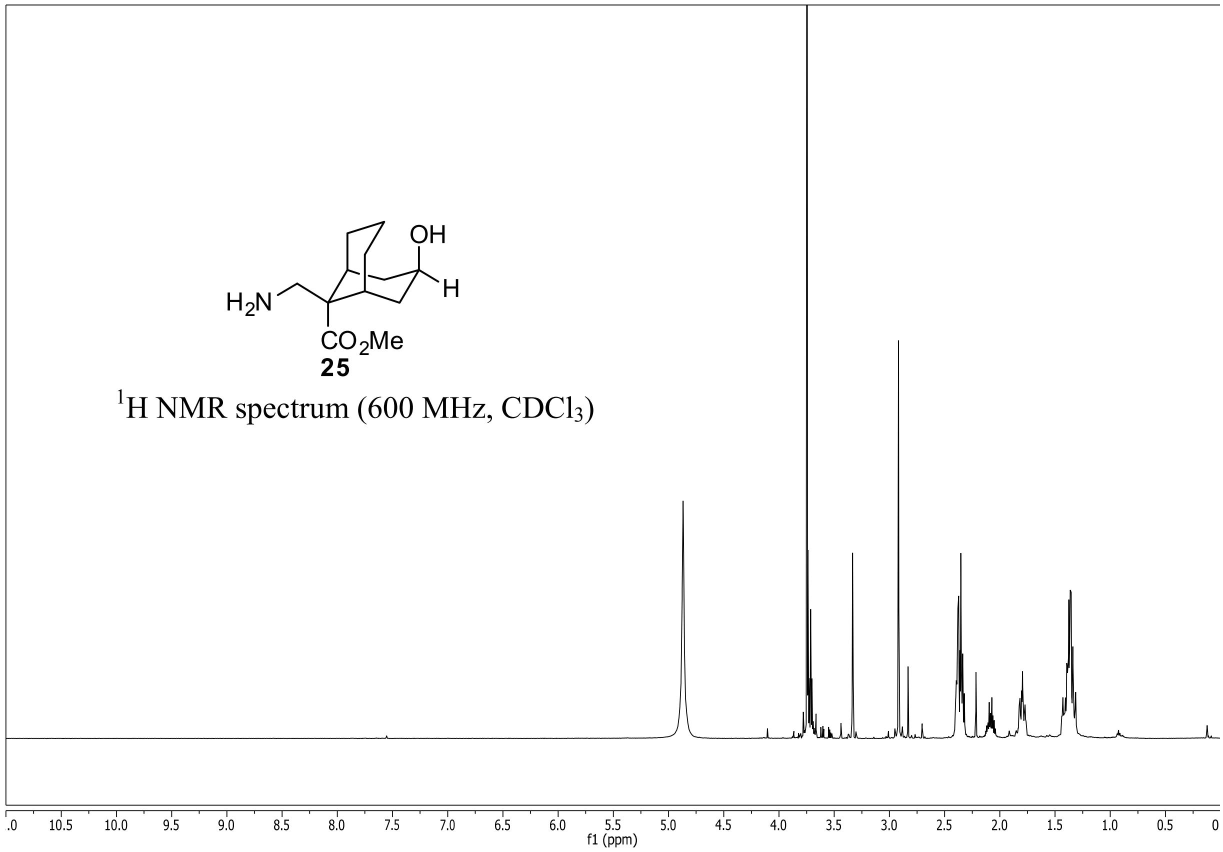


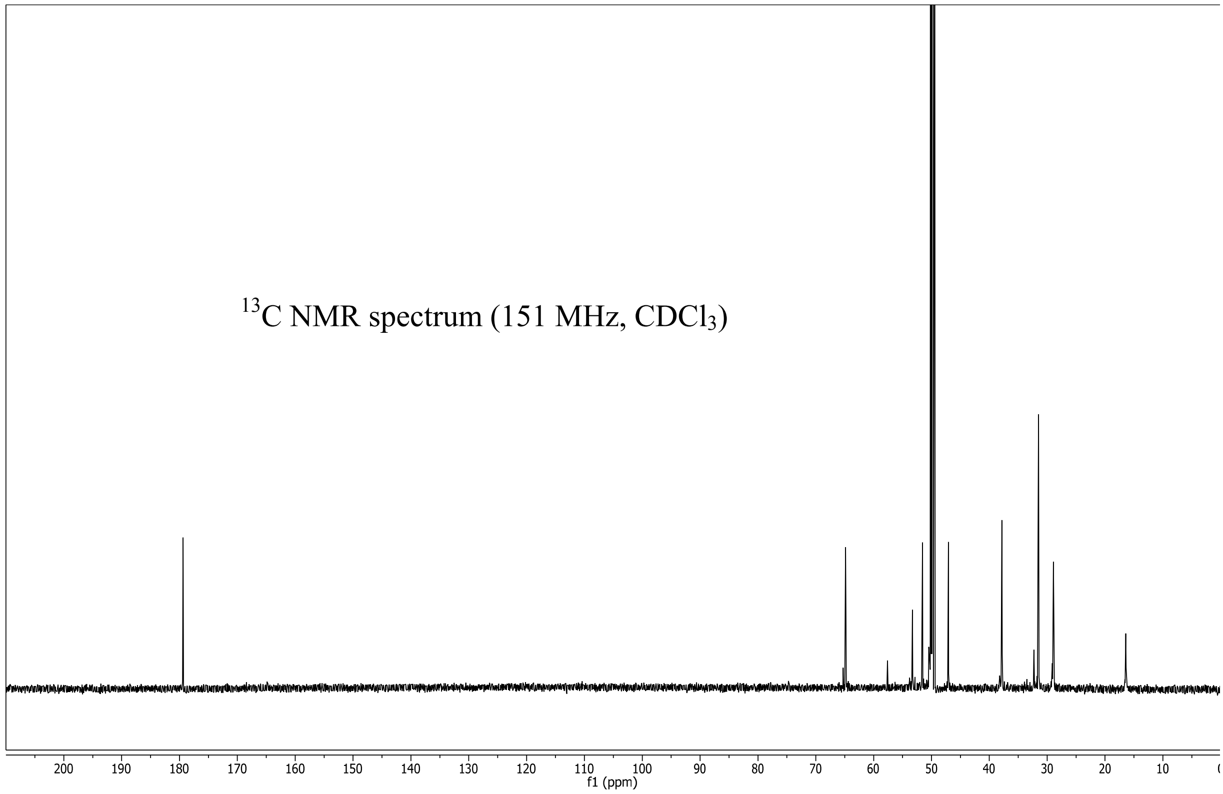
24

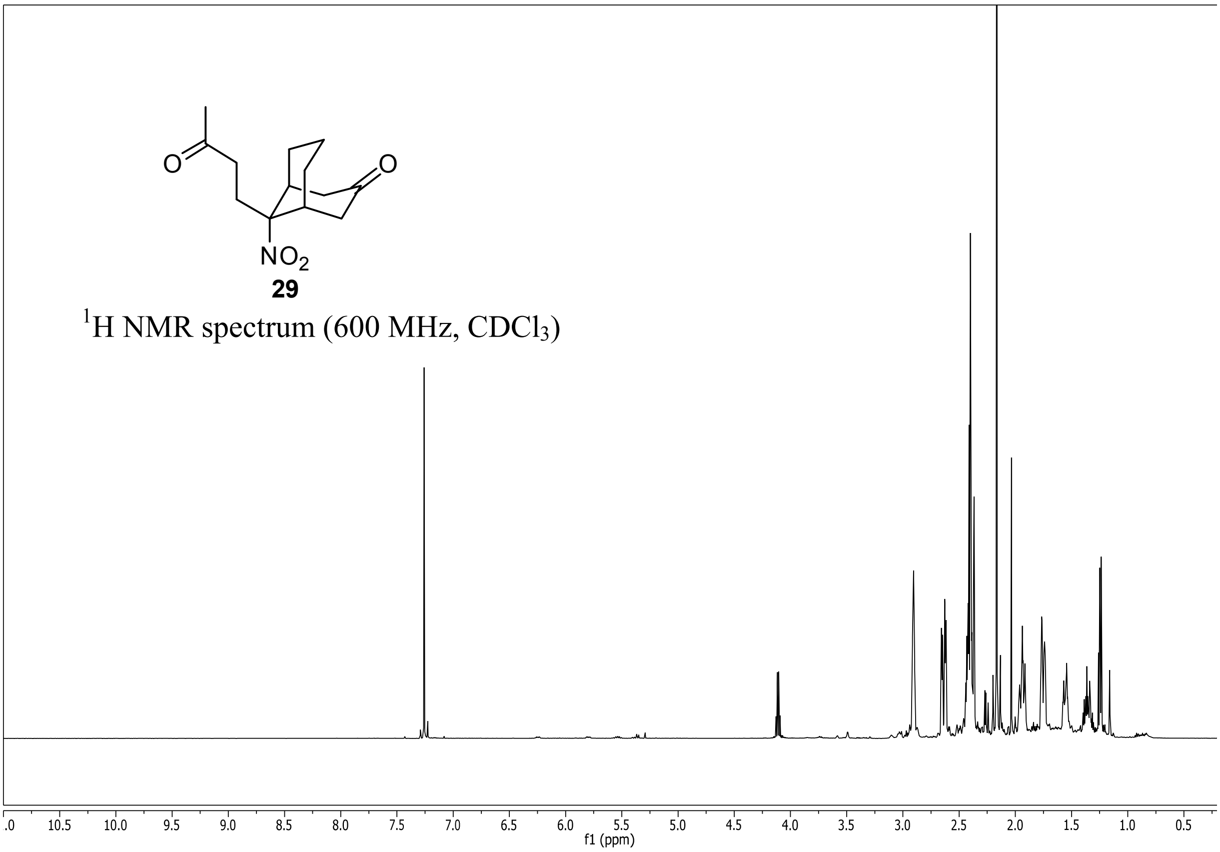
^{1}H NMR spectrum (600 MHz, $CDCl_3$)



^{13}C NMR spectrum (151 MHz, $CDCl_3$)

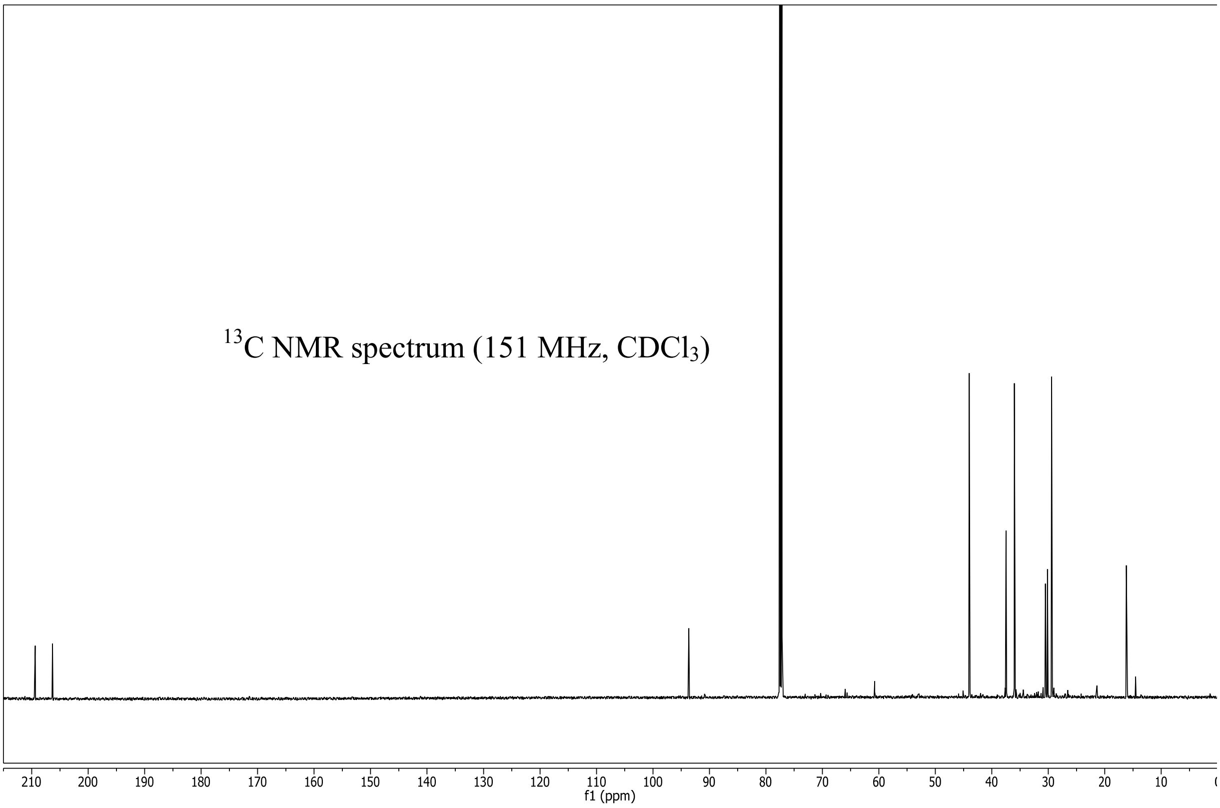

OH
H
H_2N
CO_2Me
25
^{1}H NMR spectrum (600 MHz, $CDCl_3$)
.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


^{13}C NMR spectrum (151 MHz, $CDCl_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



29

^{1}H NMR spectrum (600 MHz, CDCl$_3$)



^{13}C NMR spectrum (151 MHz, CDCl$_3$)