Enantio- and Diastereoselective Intermolecular Stetter Reaction of Glyoxamide with Alkylidene ketoamides

Qin Liu and Tomislav Rovis*

Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

Email: rovis@lamar.colostate.edu

Supporting Information

General Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. CCl_4 was purchased from Aldrich (99.9%) and redistilled before use. Triethylamine, Hünig's base and methanol were distilled from CaH_2. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63µm 60A. Thin layer chromatography was performed on SiliCycle® 250µm 60A plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate dips followed by heating.

^{1}H NMR were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) or deuterated acetone (acetone-D6), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded a Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm.

General procedure for synthesis of the β–keto amides:[1]

A toluene solution (10ml) of methyl 3-oxopentanoate (5 mmol, 0.63 ml), dimethylammonium chloride (10 mmol, 815 mg) and DMAP (2.3 mmol, 1.4 g) was stirred under reflux for 24h. The solution was cooled to room temp and then quenched with water and extract with EtOAc. The organic layer was washed with brine and dried with Na2SO4. Concentration in vacuo followed by column chromatography provided N,N-dimethyl-3-oxopentanamide (**A**) in 94% yield.

Rf = 0.34 (EtOAc); 78 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, 2H), 2.94 (s, 3H), 2.90 (s, 3H), 2.53 (q, 2H, *J* = 7.3 Hz), 1.00 (t, 3H, *J* =7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 167.0, 49.1, 38.1, 36.5, 35.6, 7.8; IR (NaCl, neat) 2939, 1719, 1647, 1398, 1137, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_7H_{13}NO_2$, 143.0946. Found 143.0946.

All other non-commerical available β-keto amides were all synthesized using this general procedure.

[1] Holtz, E.; Albrecht, U.; Langer, P. *Tetrahedron* **2007**, *63*, 3293-3301.

General procedure for synthesis of Michael acceptors:[2]

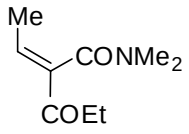
A flame-dried 5 ml round bottom flask with magnetic stir bar was charged with N,N-dimethyl-3-oxopentanamide (4.7 mmol, 670 mg), acetic anhydride (14 mmol, 1.4 ml), and lithium bromide (0.94 mmol, 81mg). The reaction was then heated to 80 ºC and allowed to stir at this temperature for 4 hours. Then, aldehyde (14 mmol) was added and the mixture was further stirred for another 4 hours. Upon cooling, the reaction was quenched with water and extracted with EtOAc. The organic layers were washed with brine and dried with Na2SO4. Concentration in vacuo followed by column chromatography provides the corresponding Michael acceptors.

General procedure for enantio- and diastereoselective intermolecular Stetter reactions:

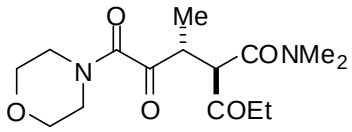
A flame-dried 5 ml test tube was charged with triazolium salt 3 (14.5 mg, 0.032 mmol), Michael acceptor (0.32 mmol) and MgSO4 (20 mg, 0.16 mmol). The test tube was purged under vacuum and then refilled with argon 3 times. Glyoxamide 1 (23 mg, 0.16 mmol) was then added followed by 0.5 ml of distilled CCl4. The test tube was placed in an ice-water bath and Hünig's base (0.028 ml, 0.16 mmol) was added dropwise to the reaction. The mixture was allowed to stir at 0 °C for 12 hours, quenched with 0.1 ml AcOH and directly purified by flash column chromatography to provide Stetter products.

[2] Sylla, M.; Joseph, D.; Chevallier, E.; Camara, C.; Dumas, F. *Synthesis* **2006**, 1045-1049.

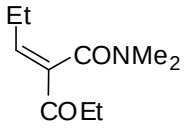
Characterization of Michael acceptors and Stetter products



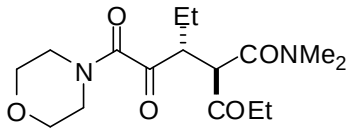
(Z)-2-ethylidene-N,N-dimethyl-3-oxopentanamide (13): Rf = 0.18 (EtOAc); 44 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (q, 1H, *J* = 7.1 Hz), 2.88 (s, 3H), 2.70 (s, 3H), 2.48 (q, 2H, *J* = 7.2 Hz), 1.67 (d, 3H, *J* =7.1 Hz), 0.89 (t, 3H, *J* =7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 167.9, 140.5, 139.0, 37.7, 34.3, 31.4, 15.6, 8.0; IR (NaCl, neat) 2925, 1672, 1638, 1503, 1400, 1144 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{15}NO_2$, 169.1103. Found 169.1103.



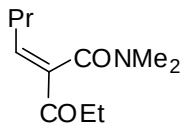
(2R,3R)-N,N,3-trimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (14): Rf = 0.25 (EtOAc); $[\alpha]_D^{21}$ = +24.5 (c = 0.020 g/ml, $CHCl_3$); HPLC analysis – Chiracel ASH column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 20.9 minutes, Minor: 17.5 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (d, 1H, *J* = 9.9 Hz), 3.50-3.84 (m, 9H), 3.22 (s, 3H), 3.06 (s, 3H), 2.32-2.54 (m, 2H), 1.28 (d, 3H, *J* = 7.2 Hz), 1.02 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 201.3, 168.6, 164.9, 67.3, 66.9, 59.0, 46.6, 43.7, 42.0, 38.6, 36.3, 34.2, 15.9, 7.8; IR (NaCl, neat) 2937, 1710, 1638, 1399, 1114, 999 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{24}N_2O_5$, 312.1685, Found 312.1687.



(Z)-N,N-dimethyl-2-propionylpent-2-enamide (12): Rf = 0.34 (EtOAc); 52 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (t, 1H, *J* = 7.6 Hz), 2.96 (s, 3H), 2.78 (s, 3H), 2.56 (q, 2H, *J* = 7.2 Hz), 2.10 (dq, 2H, *J* = 7.5, 7.6 Hz), 1.00 (t, 3H, *J* = 7.5 Hz), 0.99 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 168.0, 145.2, 138.9, 37.9, 34.4, 31.6, 23.5, 12.8, 8.1; IR (NaCl, neat) 2939, 1671, 1637, 1458, 1400, 1143 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}NO_2$, 183.1257, Found 183.1261.

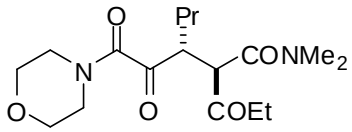


(2R,3R)-3-ethyl-N,N-dimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (11): Rf = 0.26 (EtOAc); $[\alpha]_D^{21}$ = +34.0 (c = 0.047 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 16.4 minutes, Minor: 14.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (d, 1H, *J* = 10.0 Hz), 3.50-3.82 (m, 9H), 3.20 (s, 3H), 3.02 (s, 3H), 2.30-2.52 (m, 2H), 1.68 (dq, 2H, *J* = 7.1, 7.6 Hz), 0.98 (t, 3H, *J* = 7.2 Hz), 0.89 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 200.2, 168.4, 164.8, 67.2, 66.8, 58.6, 49.6, 46.7, 42.2, 38.6, 36.3, 34.2, 23.6, 11.5, 7.8; IR (NaCl, neat) 2971, 1709, 1640, 1461, 1114, 1000 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{26}N_2O_5$, 326.1842, Found 326.1841.

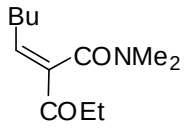


(Z)-N,N-dimethyl-2-propionylhex-2-enamide (15): Rf = 0.44 (EtOAc); 40 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (t, 1H, *J* = 7.6 Hz), 3.05 (s, 3H), 2.86 (s, 3H), 2.64 (q, 2H, *J* = 7.2 Hz), 2.15 (q, 2H, *J* = 7.4 Hz), 1.45-1.57 (m, 2H), 1.08 (t, 3H, *J* = 7.3 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); ^{13}C

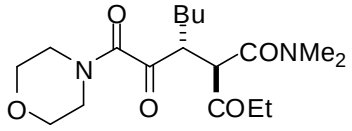
NMR (75 MHz, $CDCl_3$) δ 198.1, 168.0, 143.9, 139.5, 37.9, 34.3, 32.0, 31.5, 21.7, 14.1, 8.0; IR (NaCl, neat) 2936, 2873, 1671, 1638, 1400, 1142 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{19}NO_2$, 197.1416, Found 197.1413.



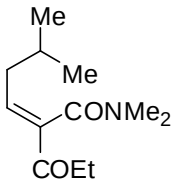
(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhexanamide (16): Rf = 0.32 (EtOAc); $[\alpha]_D^{21}$ = +70.5 (c = 0.044 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 12.3 minutes, Minor: 11.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, 1H, *J* = 9.9 Hz), 3.50-3.82 (m, 9H), 3.20 (s, 3H), 3.02 (s, 3H), 2.28-2.52 (m, 2H), 1.45 -1.72 (m, 2H), 1.20 -1.40 (m, 2H), 0.98 (t, 3H, *J* = 7.2 Hz), 0.86 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 200.2, 168.6, 164.7, 67.1, 66.9, 59.4, 48.2, 46.7, 42.3, 38.5, 36.3, 34.1, 32.8, 20.5, 14.4, 7.8; IR (NaCl, neat) 2960, 1709, 1640, 1461, 1272, 1115 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{28}N_2O_5$, 340.1998, Found 340.2006.



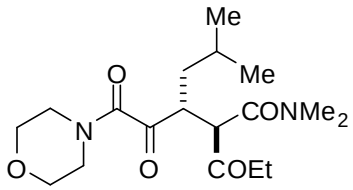
(Z)-N,N-dimethyl-2-propionylhept-2-enamide (17): Rf = 0.49 (EtOAc); 51 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (t, 1H, *J* = 7.6 Hz), 2.86 (s, 3H), 2.69 (s, 3H), 2.58 (q, 2H, *J* = 7.2 Hz), 2.11 (q, 2H, *J* = 7.4 Hz), 1.36-1.44 (m, 2H), 1.23-1.32 (m, 2H), 1.02 (t, 3H, *J* = 7.2 Hz), 0.83 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 168.1, 144.1, 139.4, 37.9, 34.5, 31.7, 30.5, 29.9, 22.7, 14.0, 8.1; IR (NaCl, neat) 2935, 1671, 1640, 1458, 1400, 1142 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{21}NO_2$, 211.1572, Found 211.1571.



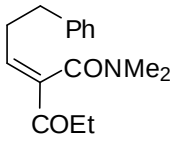
(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylheptanamide (18): Rf = 0.25 (EtOAc); $[\alpha]_D^{21}$ = +72.5 (c = 0.040 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 98:2 hexanes : isopropanol 1.0 mL / min. Major: 45.7 minutes, Minor: 42.3 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (d, 1H, *J* = 9.9 Hz), 3.42-3.72 (m, 9H), 3.12 (s, 3H), 2.94 (s, 3H), 2.86-2.93 (m, 2H), 2.20 -2.43 (m, 2H), 1.44 -1.62 (m, 2H), 1.10 -1.25 (m, 4H), 0.89 (t, 3H, *J* = 7.2 Hz), 0.75 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 200.3, 168.5, 164.7, 67.2, 66.9, 59.2, 48.4, 46.7, 42.3, 38.6, 36.3, 34.2, 30.4, 29.2, 23.0, 14.1, 7.8; IR (NaCl, neat) 2934, 2858, 1709, 1641, 1461, 1115 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{30}N_2O_5$, 354.2155, Found 354.2156.



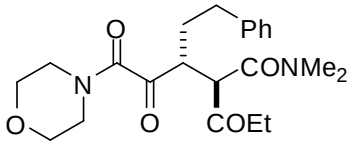
(Z)-N,N,5-trimethyl-2-propionylhex-2-enamide (19): Rf = 0.47 (EtOAc); 28 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (t, 1H, *J* = 7.5 Hz), 3.04 (s, 3H), 2.85 (s, 3H), 2.64 (q, 2H, *J* = 7.1 Hz), 2.06 (dd, 2H, *J* = 7.1, 7.2 Hz), 1.81 (m, 1H), 1.08 (t, 3H, *J* = 7.2 Hz), 0.92 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.9, 143.1, 139.9, 38.9, 37.8, 34.3, 31.5, 28.2, 22.6, 8.0; IR (NaCl, neat) 2956, 2863, 1672, 1637, 1399, 1141 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{21}NO_2$, 211.1572, Found 211.1573.



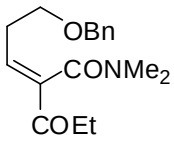
(2R,3R)-N,N,5-trimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhexanamide (20): Rf = 0.26 (EtOAc); $[\alpha]_D^{21}$ = +64.0 (c = 0.025 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 12.5 minutes, Minor: 14.9 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, 1H, *J* = 9.5 Hz), 3.48-3.82 (m, 9H), 3.16 (s, 3H), 3.02 (s, 3H), 2.43-2.57 (m, 1H), 2.24 -2.38 (m, 1H), 1.10 -1.20 (m, 2H), 0.98 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 200.1, 168.6, 164.6, 67.1, 66.8, 60.6, 46.8, 46.2, 42.3, 38.5, 36.3, 34.1, 26.0, 23.7, 22.1, 7.8; IR (NaCl, neat) 2957, 1709, 1640, 1462, 1398, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{30}N_2O_5$, 354.2155, Found 354.2157.



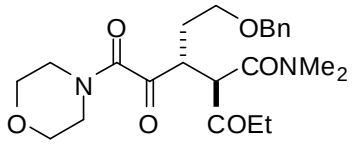
(Z)-N,N-dimethyl-5-phenyl-2-propionylpent-2-enamide (21): Rf = 0.47 (EtOAc); 54 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08-7.24 (m, 5H), 6.68 (t, 1H, *J* = 7.5 Hz), 2.92 (s, 3H), 2.74 (t, 3H, *J* = 7.4 Hz), 2.56 (s, 3H), 2.42-2.58 (m, 4H), 1.00 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 167.8, 142.9, 140.7, 140.0, 128.8, 128.5, 126.5, 37.6, 34.5, 34.4, 32.0, 31.6, 8.2; IR (NaCl, neat) 2935, 1671, 1638, 1400, 1142, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{21}NO_2$, 259.1572, Found 259.1575.



(2R,3R)-N,N-dimethyl-5-morpholino-4,5-dioxo-3-phenethyl-2-propionylpentanamide (22): Rf = 0.41 (EtOAc); $[\alpha]_D^{21}$ = +42.8 (c = 0.042 g/ml, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 19.5 minutes, Minor: 16.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.29 (m, 5H), 4.30 (d, 1H, *J* = 9.6 Hz), 3.54-3.84 (m, 9H), 3.14 (s, 3H), 3.02 (s, 3H), 2.56-2.70 (m, 2H), 2.28 -2.54 (m, 2H), 1.94 -2.10 (m, 1H), 1.76 -1.90 (m, 1H), 1.00 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 199.9, 168.4, 164.7, 141.8, 128.6, 126.2, 67.2, 66.8, 59.6, 47.9, 46.7, 42.3, 38.5, 36.3, 34.2, 33.6, 32.6, 7.8; IR (NaCl, neat) 2935, 1708, 1639, 1454, 1398, 1114 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{30}N_2O_5$, 402.2155, Found 402.2157.

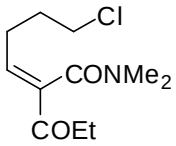


(Z)-5-(benzyloxy)-N,N-dimethyl-2-propionylpent-2-enamide (23): Rf = 0.30 (EtOAc); 35 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.28 (m, 5H), 6.72 (t, 1H, *J* = 7.4 Hz), 4.40 (s, 2H), 3.51 (t, 2H, *J* = 6.1 Hz), 2.93 (s, 3H), 2.71 (s, 3H), 2.36-2.60 (m, 4H), 1.00 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.8, 140.9, 140.7, 138.1, 128.5, 127.8, 73.2, 68.2, 48.9, 37.9, 34.4, 31.5, 30.8, 8.1; IR (NaCl, neat) 2929, 1672, 1641, 1454, 1399, 1100 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{23}NO_3$, 289.1678, Found 289.1680.

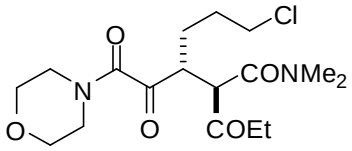


(2R,3R)-3-(2-(benzyloxy)ethyl)-N,N-dimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (24): Rf = 0.35 (EtOAc); $[\alpha]_D^{21}$ = +4.8 (c = 0.060 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 12.4 minutes, Minor: 9.1 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5H), 4.40 (d, 2H, *J* = 4.6 Hz), 4.33 (d, 1H, *J* = 9.4 Hz), 3.44-3.72

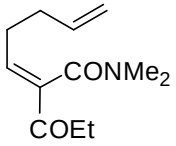
(m, 9H), 3.01 (s, 3H), 2.94 (s, 3H), 2.38-2.66 (m, 4H), 1.92-2.04 (m, 2H), 0.96 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 199.8, 168.1, 164.4, 140.8, 138.2, 128.6, 128.1, 127.9, 73.4, 68.2, 67.1, 66.8, 58.6, 46.6, 45.9, 42.4, 38.2, 36.3, 34.1, 30.8, 29.8, 7.7; IR (NaCl, neat) 2939, 2847, 1711, 1640, 1398, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{32}N_2O_6$, 432.2260, Found 432.2264.



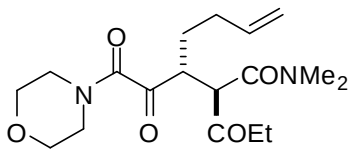
(Z)-6-chloro-N,N-dimethyl-2-propionylhex-2-enamide (25): Rf = 0.26 (EtOAc); 43 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (t, 1H, *J* = 7.6 Hz), 3.55 (t, 2H, *J* = 6.3 Hz), 3.05 (s, 3H), 2.88 (s, 3H), 2.64 (q, 2H, *J* = 7.3 Hz), 2.34 (q, 2H, *J* = 7.4 Hz), 1.92-2.00 (m, 2H), 1.09 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.7, 141.7, 140.4, 44.4, 38.0, 34.6, 31.9, 31.3, 27.4, 8.1; IR (NaCl, neat) 2934, 1673, 1633, 1402, 1229, 1144 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{18}ClNO_2$, 231.1026, Found 231.1028.



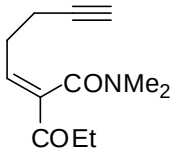
(2R,3R)-6-chloro-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhexanamide (26): Rf = 0.36 (EtOAc); $[\alpha]_D^{21}$ = +33.8 (c = 0.050 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 7.4 minutes, Minor: 9.1 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (d, 1H, *J* = 9.9 Hz), 3.48-3.84 (m, 9H), 3.23 (s, 3H), 3.04 (s, 3H), 2.94-3.00 (m, 2H), 2.30-2.60 (m, 2H), 1.70-1.88 (m, 4H), 0.98 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 199.7, 168.3, 164.7, 67.1, 66.8, 59.5, 47.3, 46.7, 45.0, 42.3, 38.6, 36.3, 34.1, 30.0, 27.9, 7.7; IR (NaCl, neat) 2936, 1708, 1638, 1444, 1271, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{27}ClN_2O_5$, 374.1608, Found 374.1610.



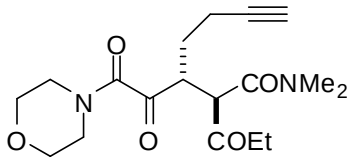
(Z)-N,N-dimethyl-2-propionylhepta-2,6-dienamide (27): Rf = 0.49 (EtOAc); 46 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (t, 1H, *J* = 7.2 Hz), 5.55-5.69 (m, 1H), 4.82-4.94 (m, 2H), 2.88 (s, 3H), 2.71 (s, 3H), 2.49 (q, 2H, *J* = 7.2 Hz), 2.05-2.16 (m, 4H), 0.92 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.8, 143.0, 139.7, 136.9, 116.0, 37.9, 34.4, 32.2, 31.5, 29.2, 8.0; IR (NaCl, neat) 2929, 1671, 1638, 1400, 1142, 906 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}NO_2$, 209.1416, Found 209.1422.



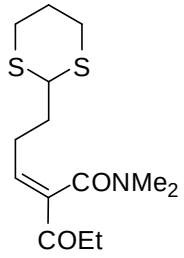
(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhept-6-enamide (28): Rf = 0.36 (EtOAc); $[\alpha]_D^{21}$ = +53.3 (c = 0.045 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 13.7 minutes, Minor: 12.5 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66-5.81 (m, 1H), 4.90-5.02 (m, 2H), 4.27 (d, 1H, *J* = 9.8 Hz), 3.49-3.82 (m, 9H), 3.20 (s, 3H), 3.03 (s, 3H), 2.26-2.56 (m, 2H), 1.96-2.18 (m, 2H), 1.54-1.84 (m, 2H), 0.98 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 199.8, 168.5, 164.7, 137.8, 115.4, 67.1, 66.8, 59.4, 47.7, 46.7, 42.2, 38.5, 36.3, 34.1, 31.3, 29.9, 7.7; IR (NaCl, neat) 2924, 1708, 1639, 1443, 1114, 996 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{28}N_2O_5$, 352.1998, Found 352.2003.



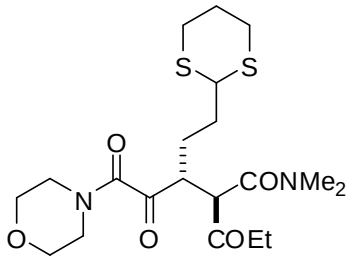
(Z)-N,N-dimethyl-2-propionylhept-2-en-6-ynamide (29): Rf = 0.45 (EtOAc); 53 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (t, 1H, *J* = 7.2 Hz), 3.06 (s, 3H), 2.88 (s, 3H), 2.68 (q, 2H, *J* = 7.2 Hz), 2.38-2.42 (m, 4H), 2.01 (t, 1H, *J* = 2.5 Hz), 1.10 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 167.6, 141.4, 140.5, 82.7, 70.0, 38.1, 34.5, 31.7, 28.9, 17.7, 8.1; IR (NaCl, neat) 2937, 1672, 1633, 1503, 1400, 1143 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}NO_2$, 207.1259, Found 207.1258.



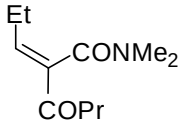
(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhept-6-ynamide (30): Rf = 0.33 (EtOAc); $[\alpha]_D^{21}$ = +54.5 (c = 0.044 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 22.3 minutes, Minor: 20.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (d, 1H, *J* = 9.2 Hz), 3.48-3.82 (m, 9H), 3.18 (s, 3H), 3.02 (s, 3H), 2.22-2.58 (m, 4H), 1.90-2.04 (m, 2H), 1.66-1.78 (m, 1H), 0.98 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 199.0, 168.3, 164.6, 69.1, 67.1, 66.8, 59.6, 47.1, 46.7, 42.3, 38.5, 36.3, 34.3, 29.5, 16.8, 7.7; IR (NaCl, neat) 2924, 2847, 1707, 1637, 1444, 1113, cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{26}N_2O_5$, 350.1842, Found 350.1845.



(Z)-5-(1,3-dithian-2-yl)-N,N-dimethyl-2-propionylpent-2-enamide (31): Rf = 0.42 (EtOAc); 52 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (t, 1H, *J* = 7.6 Hz), 4.01 (t, 1H, *J* = 6.9 Hz), 3.05 (s, 3H), 2.82-2.88 (m, 5H), 2.64 (q, 2H), 2.40 (q, 2H, *J* = 7.6 Hz), 1.79-2.15 (m, 4H), 1.08 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.6, 141.9, 140.2, 46.7, 38.0, 34.5, 34.0, 31.7, 30.3, 27.2, 25.9, 8.1; IR (NaCl, neat) 2933, 1671, 1634, 1511, 1399, 1143 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{23}NO_2S_2$, 301.1170, Found 301.1174.

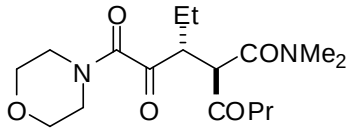


(2R,3R)-3-(2-(1,3-dithian-2-yl)ethyl)-N,N-dimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (32): Rf = 0.35 (EtOAc); $[\alpha]_D^{21}$ = +46.7 (c = 0.030 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 30:70 hexanes : isopropanol 1.0 mL / min. Major: 15.1 minutes, Minor: 27.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (d, 1H, *J* = 9.6 Hz), 3.50-3.80 (m, 9H), 3.22 (s, 3H), 2.76-2.84 (m, 4H), 2.30-2.54 (m, 2H), 1.70-1.90 (m, 6H), 0.98 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 199.7, 168.2, 164.6, 67.2, 66.8, 58.8, 47.7, 47.3, 46.7, 42.3, 38.7, 36.4, 34.2, 32.8, 30.5, 30.4, 27.6, 26.1, 7.8; IR (NaCl, neat) 2924, 1709, 1638, 1444, 1114, 996 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{32}N_2O_5S_2$, 444.1753, Found 444.1756.

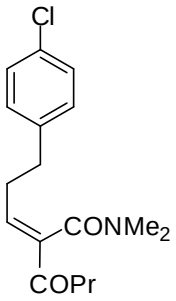


(Z)-N,N-dimethyl-3-oxo-2-propylidenehexanamide (33): Rf = 0.47 (EtOAc); 61 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (t, 1H, *J* = 7.6 Hz), 2.90 (s, 3H), 2.46 (t, 2H, *J* = 7.2 Hz), 2.00-2.10 (m, 2H), 1.42-1.55 (m, 2H), 0.94 (t, 3H, *J* = 7.6 Hz), 0.77 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 167.9, 145.2, 139.2, 40.0, 37.8, 34.3, 23.5, 17.5, 13.8, 12.8; IR

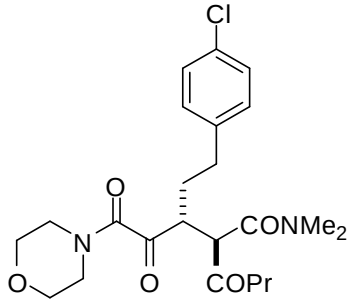
(NaCl, neat) 2964, 2875, 1638, 1458, 1399, 1130 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{19}NO_2$, 197.1416, Found 197.1417.



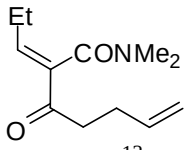
(R)-N,N-dimethyl-2-((R)-1-morpholino-1,2-dioxopentan-3-yl)-3-oxohexanamide (34): Rf = 0.34 (EtOAc); $[\alpha]_D^{21}$ = +82.0 (c = 0.050 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 6.9 minutes, Minor: 6.1 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (d, 1H, *J* = 10.1 Hz), 3.50-3.82 (m, 9H), 3.22 (s, 3H), 3.04 (s, 3H), 2.25-2.48 (m, 2H), 1.64-1.75 (m, 2H), 1.48-1.58 (m, 2H), 0.90 (t, 3H, *J* = 7.4 Hz), 0.85 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 200.1, 168.4, 164.7, 67.1, 66.8, 59.1, 49.5, 46.6, 42.7, 42.2, 38.6, 36.3, 23.6, 17.1, 13.7, 11.5; IR (NaCl, neat) 2965, 2933, 1708, 1640, 1397, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{28}N_2O_5$, 340.1998, Found 340.1998.



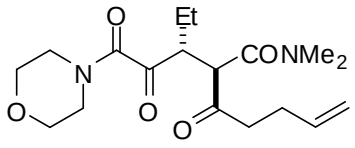
(Z)-2-(3-(4-chlorophenyl)propylidene)-N,N-dimethyl-3-oxohexanamide (35): Rf = 0.39 (EtOAc); 45 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.27 (m, 2H), 7.07-7.12 (m, 2H), 6.68 (t, 1H, *J* = 7.5 Hz), 3.00 (s, 3H), 2.77 (t, 3H, *J* = 7.5 Hz), 2.66 (s, 3H), 2.44-2.57 (m, 4H), 1.54-1.67 (m, 2H), 0.90 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 167.7, 142.4, 140.6, 139.2, 132.3, 130.0, 128.9, 40.4, 37.8, 34.5, 34.0, 31.8, 17.7, 14.0; IR (NaCl, neat) 2933, 1670, 1637, 1491, 1400, 1090 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{22}ClNO_2$, 307.1339, Found 307.1337.



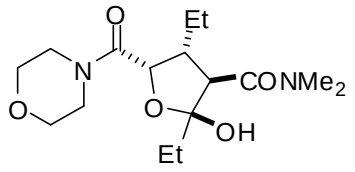
(R)-2-((R)-5-(4-chlorophenyl)-1-morpholino-1,2-dioxopentan-3-yl)-N,N-dimethyl-3-oxohexanamide (36): Rf = 0.37 (EtOAc); $[\alpha]_D^{21}$ = +49.6 (c = 0.046 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 10.8 minutes, Minor: 12.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.23 (m, 2H), 7.04-7.08 (m, 2H), 4.27 (d, 1H, *J* = 9.8 Hz), 3.50-3.82 (m, 9H), 3.14 (s, 3H), 3.02 (s, 3H), 2.52-2.68 (m, 2H), 2.22 - 2.46 (m, 2H), 1.70-2.00 (m, 2H), 1.48 -1.57 (m, 2H), 0.85 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 199.6, 168.2, 164.7, 140.2, 131.8, 129.9, 128.6, 67.1, 66.8, 60.2, 47.7, 46.7, 42.6, 42.3, 38.5, 36.3, 32.9, 32.6, 17.1, 13.7; IR (NaCl, neat) 2963, 2931, 1708, 1640, 1492, 1114 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{31}ClN_2O_5$, 450.1921, Found 450.1922.



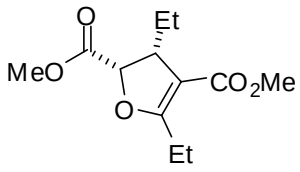
(Z)-N,N-dimethyl-3-oxo-2-propylidenehept-6-enamide (37): Rf = 0.41 (EtOAc); 43 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (t, 1H, *J* = 7.6 Hz), 5.72-5.84 (m, 1H), 4.92-5.40 (m, 2H), 3.20 (s, 3H), 2.84 (s, 3H), 2.62-2.72 (m, 2H), 2.28-2.37 (m, 2H), 2.12-2.22 (m, 2H), 1.07 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 167.9, 145.5, 139.2, 137.3, 115.6, 38.0, 37.6, 34.5, 28.0, 23.6, 12.9; IR (NaCl, neat) 2933, 1639, 1399, 1265, 1137, 912 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}NO_2$, 209.1416, Found 209.1419.



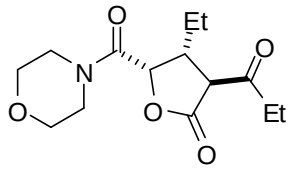
(R)-N,N-dimethyl-2-(R)-1-morpholino-1,2-dioxopentan-3-yl)-3-oxohept-6-enamide (38): Rf = 0.33 (EtOAc); $[\alpha]_D^{21}$ = +68.1 (c = 0.053 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 7.5 minutes, Minor: 6.6 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65-5.79 (m, 1H), 4.93-5.02 (m, 2H), 4.30 (d, 1H, *J* = 10.1 Hz), 3.48-3.82 (m, 9H), 3.22 (s, 3H), 3.04 (s, 3H), 2.38-2.62 (m, 2H), 2.22-2.30 (m, 2H), 1.64-1.76 (m, 2H), 0.91 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 200.1, 168.3, 164.7, 136.7, 115.8, 67.2, 66.8, 59.0, 49.5, 46.6, 42.2, 39.9, 38.6, 36.3, 27.5, 23.6, 11.5; IR (NaCl, neat) 2924, 2858, 1709, 1639, 1442, 1114 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{28}N_2O_5$, 352.1998, Found 352.2007.



2,4-diethyl-2-hydroxy-N,N-dimethyl-5-(morpholine-4-carbonyl)tetrahydrofuran-3-carboxamide (39): A flame-dried 5 ml round bottom flask was charged with **11** (50 mg, 0.15 mmol) in 2 mL THF. Upon cooling to -78 °C, Et_3BHLi (1.0 M in THF, 0.46 mL, 0.46 mmol) was added dropwise via syringe. After stirring for 2 h at -78 °C, 4.0 mL of saturated aq. NH_4Cl was added at -78 °C via syringe and the mixture was allowed to warm up to ambient temperature slowly. The reaction mixture was then diluted with EtOAc and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product (7:1 dr) was purified by column chromatography to give pure hemiketal **40** (48 mg, 85%). Rf = 0.14 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.20 (d, 1H, *J* = 7.2 Hz), 3.45-3.80 (m, 8H), 3.34-3.42 (m, 1H), 3.10 (s, 3H), 2.97 (s, 3H), 1.66 (q, 2H, *J* = 7.5 Hz), 1.44-1.55 (m, 2H), 0.89 (t, 3H, *J* = 7.5 Hz), 0.84 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 169.3, 106.8, 80.4, 67.0, 51.9, 47.4, 46.4, 43.0, 38.0, 36.3, 33.0, 26.1, 12.2, 8.3; IR (NaCl, neat) 3262, 2964, 2857, 1651, 1459, 1114 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{28}N_2O_5$, 328.1998, Found 328.1998.

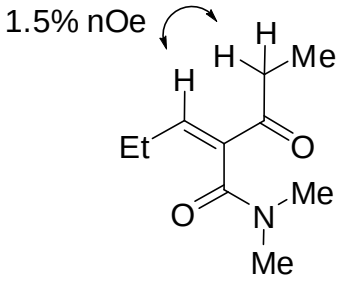


dimethyl 3,5-diethyl-2,3-dihydrofuran-2,4-dicarboxylate (40): A flame-dried 5 ml round bottom flask was charged with **39** (20 mg, 0.06 mmol) in 2 mL dry HCl/MeOH (1M). The reaction was allowed to reflux for 24 hours. After cooling down to ambient temperauture, the reaction mixture was then diluted with EtOAc/water and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product (10:1 dr) was purified by column chromatography to give **40** (11 mg, 75%). Rf = 0.76 (EtOAc); $[\alpha]_D^{21}$ = -4.5 (c = 0.011 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 8.3 min, minor: 7.6 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (d, 1H, *J* = 3.9 Hz), 3.76 (s, 3H), 3.69 (s, 3H), 3.16-3.27 (m, 1H), 2.60-2.80 (m, 2H), 1.75-1.84 (m, 1H), 1.46-1.55 (m, 1H), 1.16 (t, 3H, *J* = 7.6 Hz), 0.92 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 171.5, 165.7, 104.2, 82.1, 52.5, 51.0, 48.7, 26.4, 21.5, 11.3, 10.1; IR (NaCl, neat) 2960, 2868, 1760, 1704, 1434, 1204 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{18}O_5$, 242.1154, Found 242.1153.

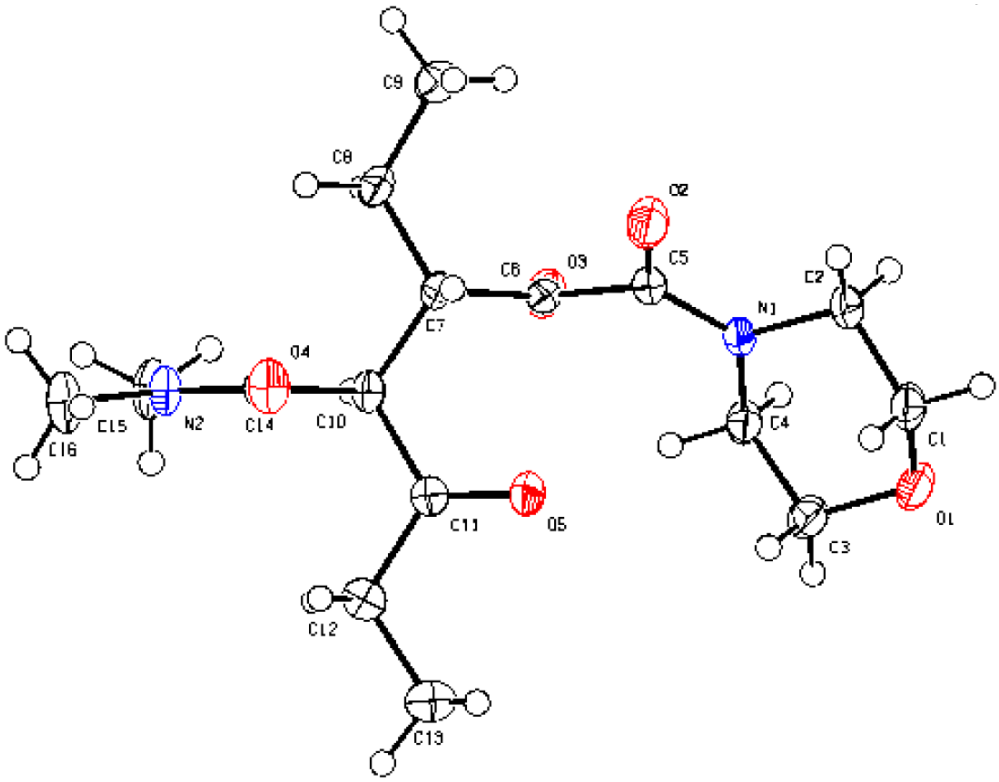


4-ethyl-5-(morpholine-4-carbonyl)-3-propionyldihydro-furan-2(3H)-one (41): A flame-dried 5 ml sealed tube was charged with **39** (8 mg, 0.024 mmol) and 0.006 ml TFA in 1 mL toluene. The reaction was allowed to stir at 120 °C for 48 hours. After cooling down to ambient temperauture, the reaction mixture was then diluted with EtOAc/water and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product (8:1 dr) was purified by column chromatography to give **41** (5 mg, 72%). Rf = 0.45 (EtOAc); $[\alpha]_D^{21}$ = -24.0 (c = 0.005 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column, 70:30 hexanes/*iso*-propanol, 1.0 mL/min. Major: 8.8 min, minor: 12.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (d, 1H, *J* = 5.3 Hz), 3.45-3.76 (m, 8H), 3.34-3.44 (m, 1H), 3.29 (d, 1H, *J* = 6.6 Hz), 2.86-3.01 (m, 1H), 2.60-2.73 (m, 1H), 1.62-1.73 (m, 1H), 1.46-1.56 (m, 1H), 1.10 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 172.1, 165.8, 78.3, 66.9, 66.7, 58.3, 46.0, 43.0, 41.3, 35.0, 26.1, 11.6, 7.7; IR (NaCl, neat) 2965, 2853, 1774, 1657, 1465, 1115 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{21}NO_5$, 283.1421, Found 283.1421.

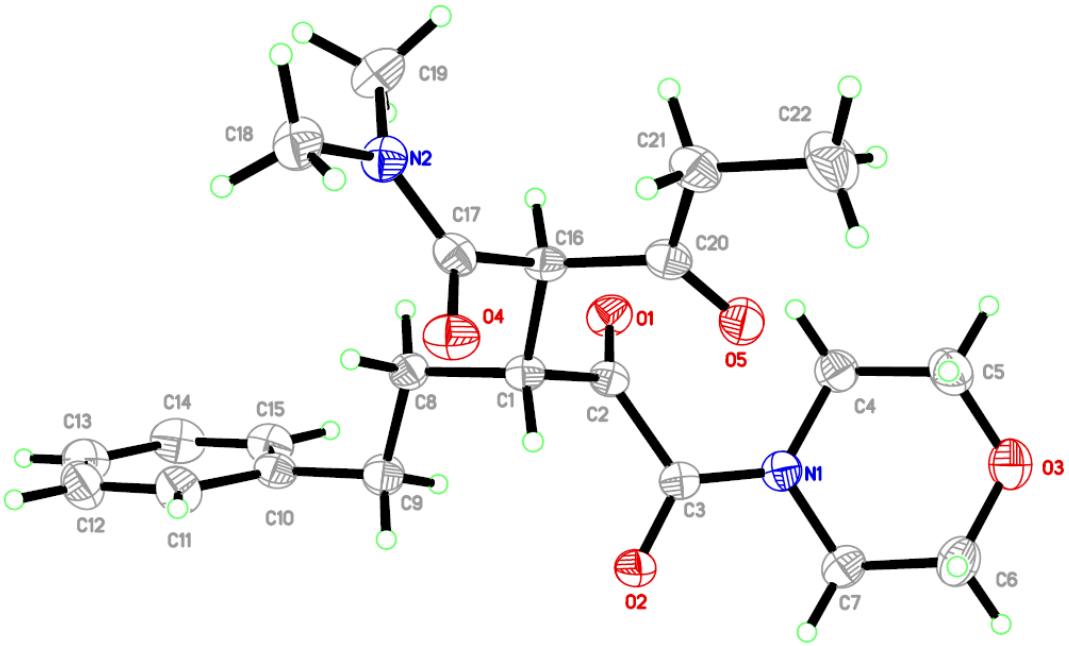
nOe experiment of **12**:



Relative configuration of **11**:

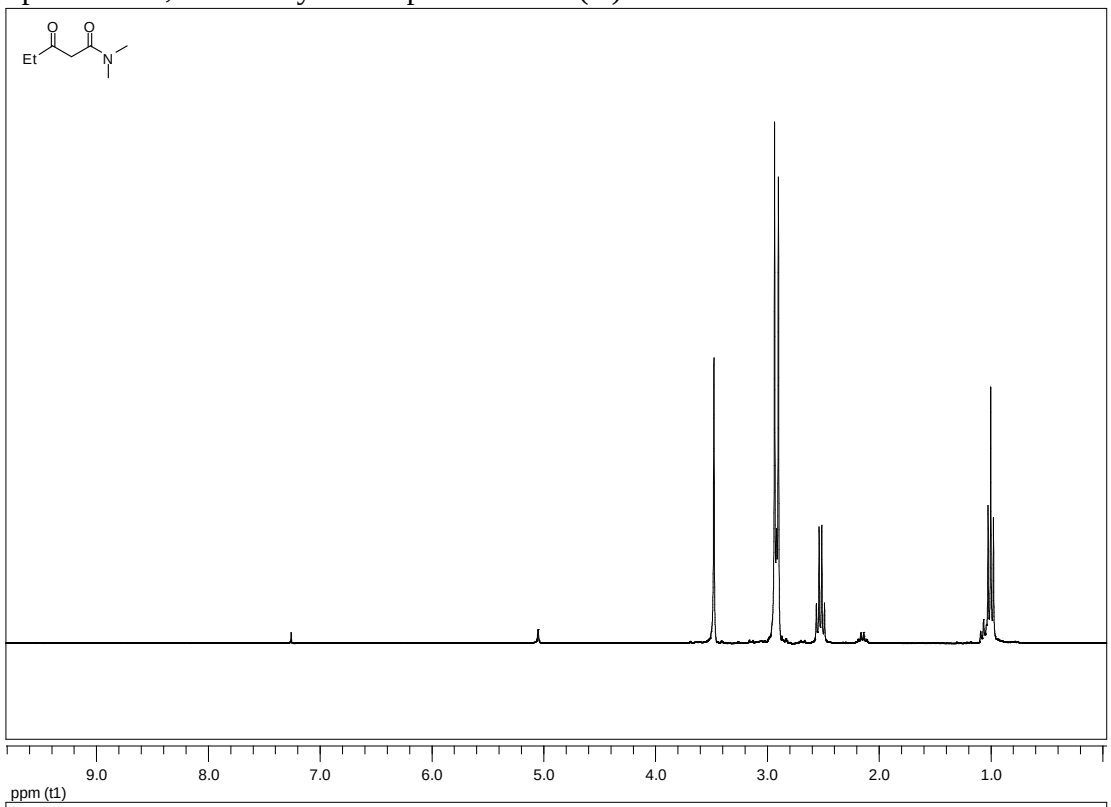


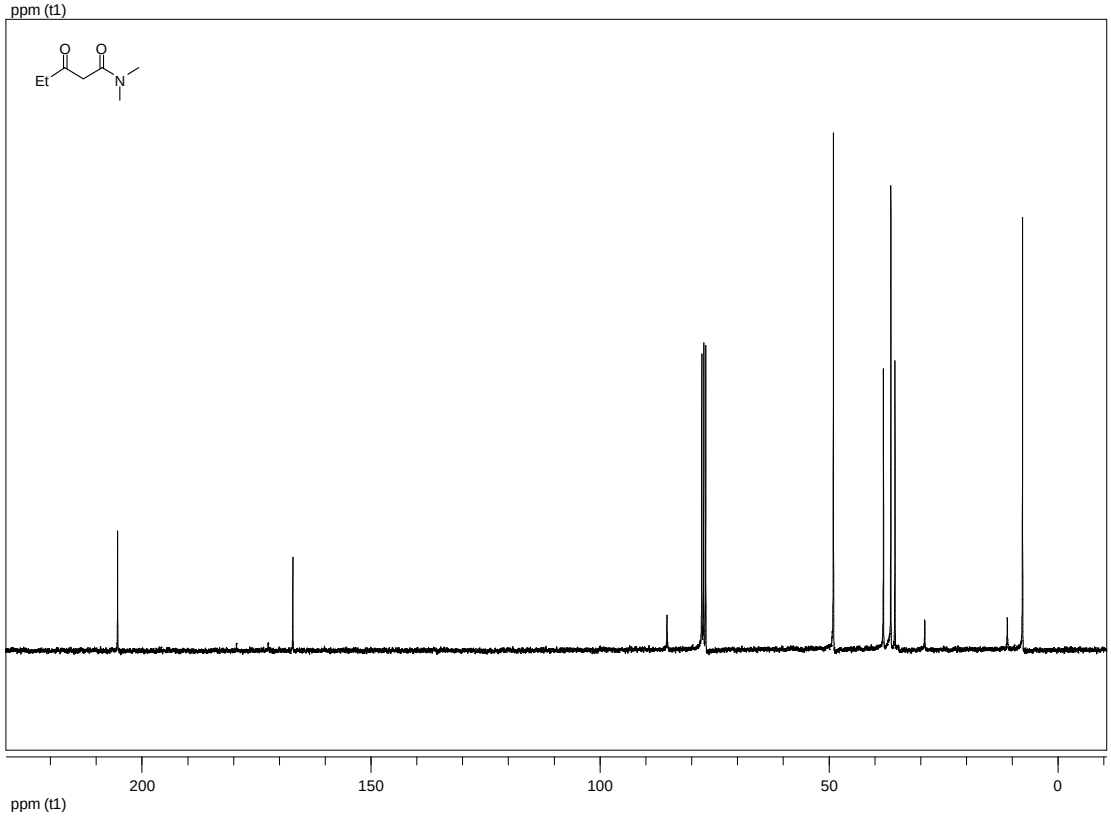
Absolute configuration of **22**:



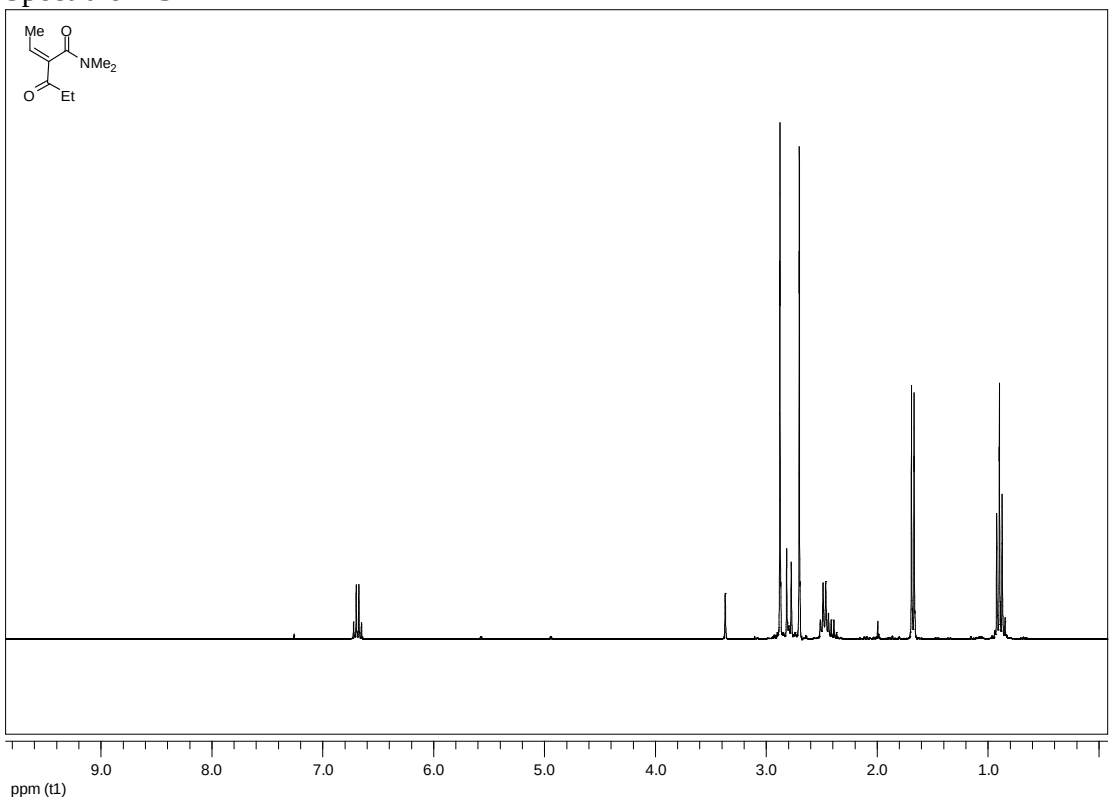
Copies of ^{1}H and ^{13}C NMR Spectra

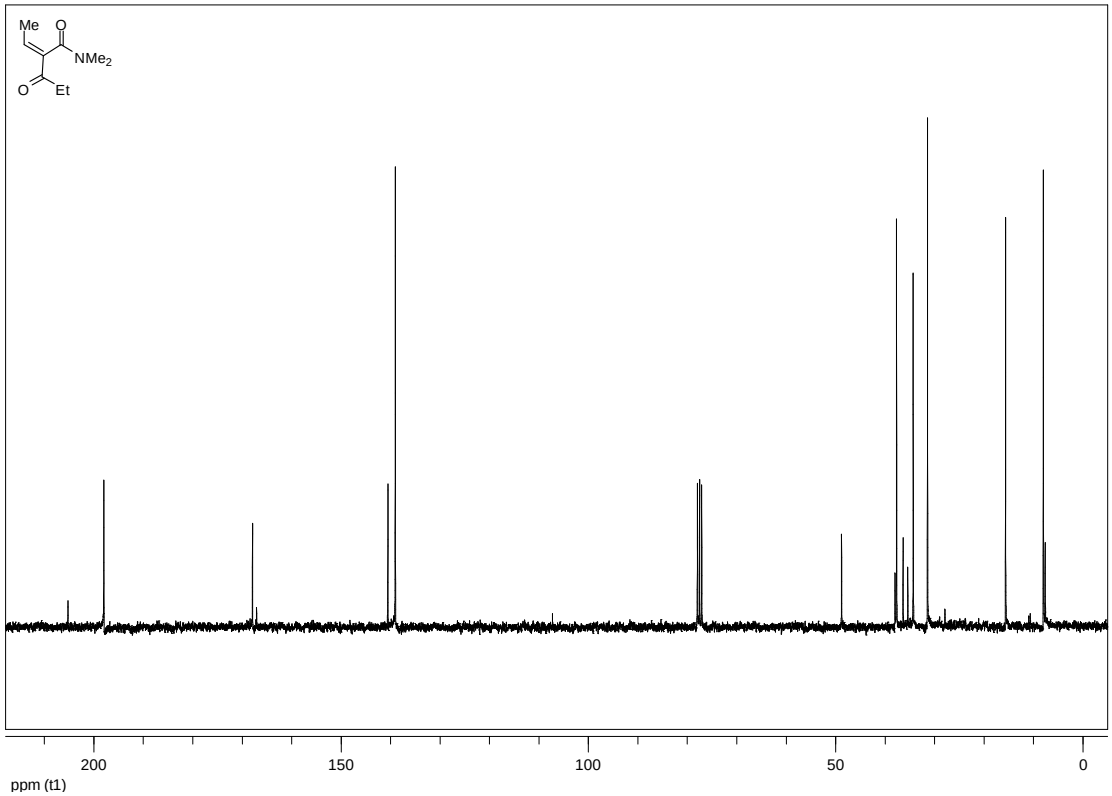
Spectra of N,N-dimethyl-3-oxopentanamide (A)



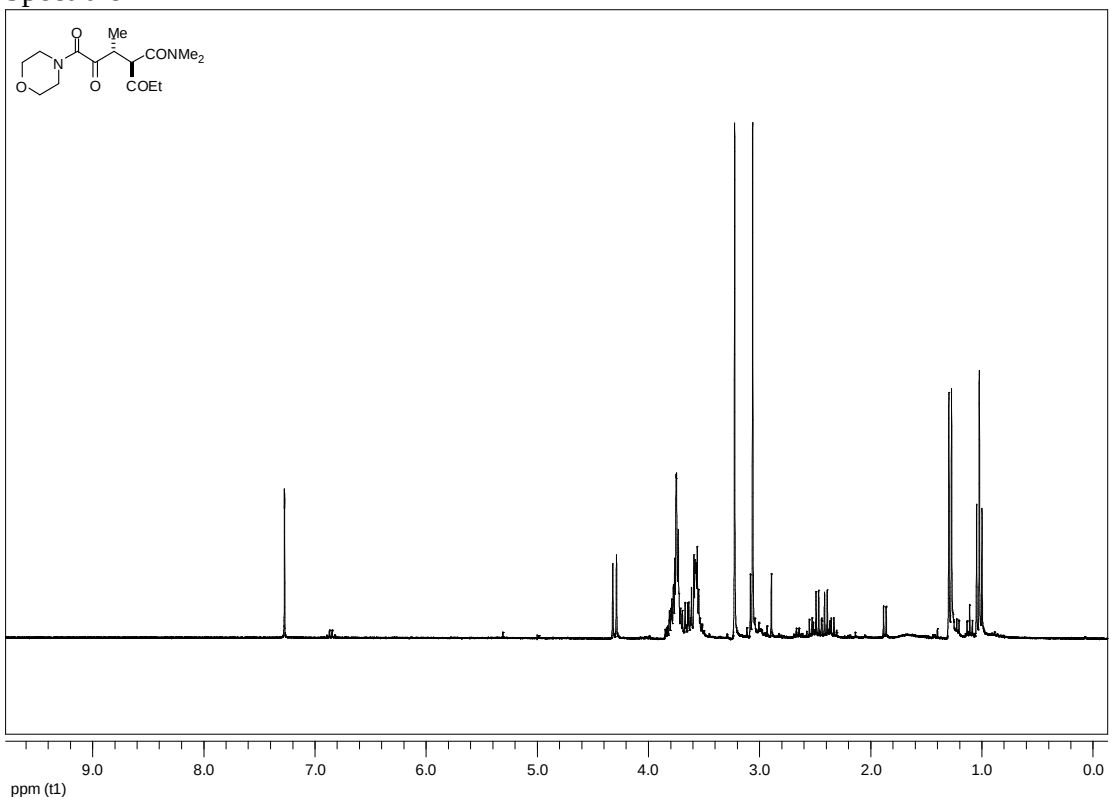


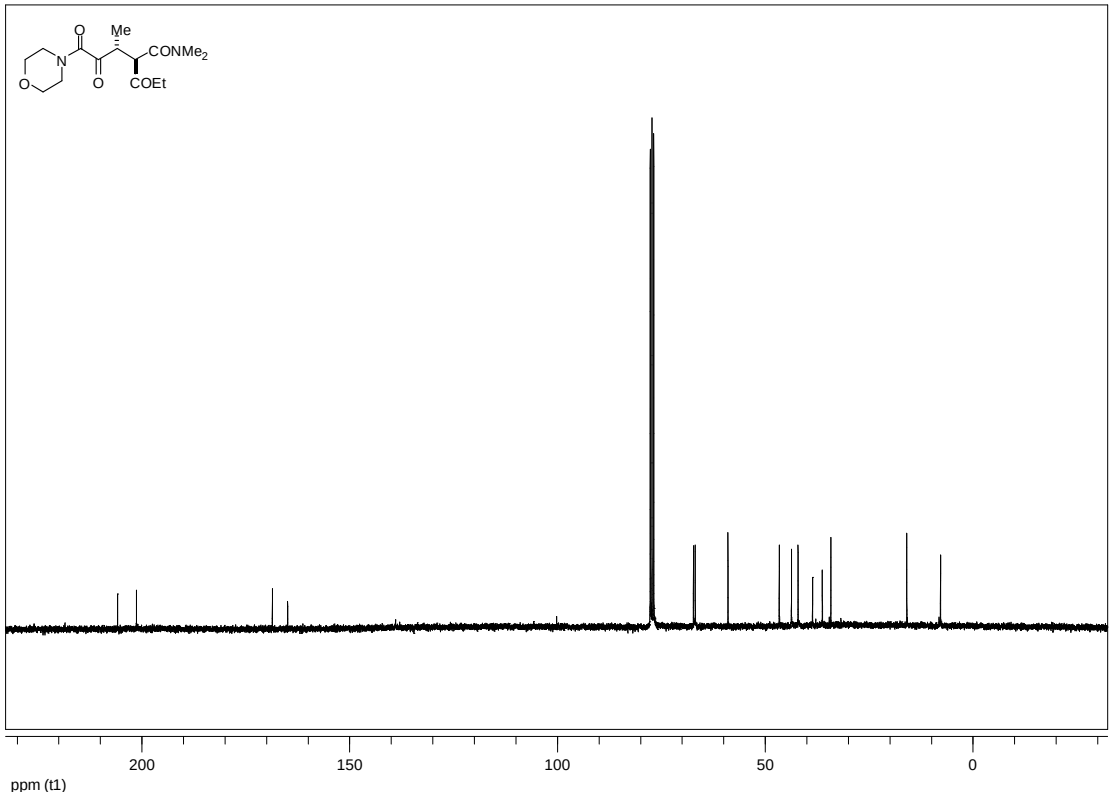
Spectra of **13**





Spectra of **14**





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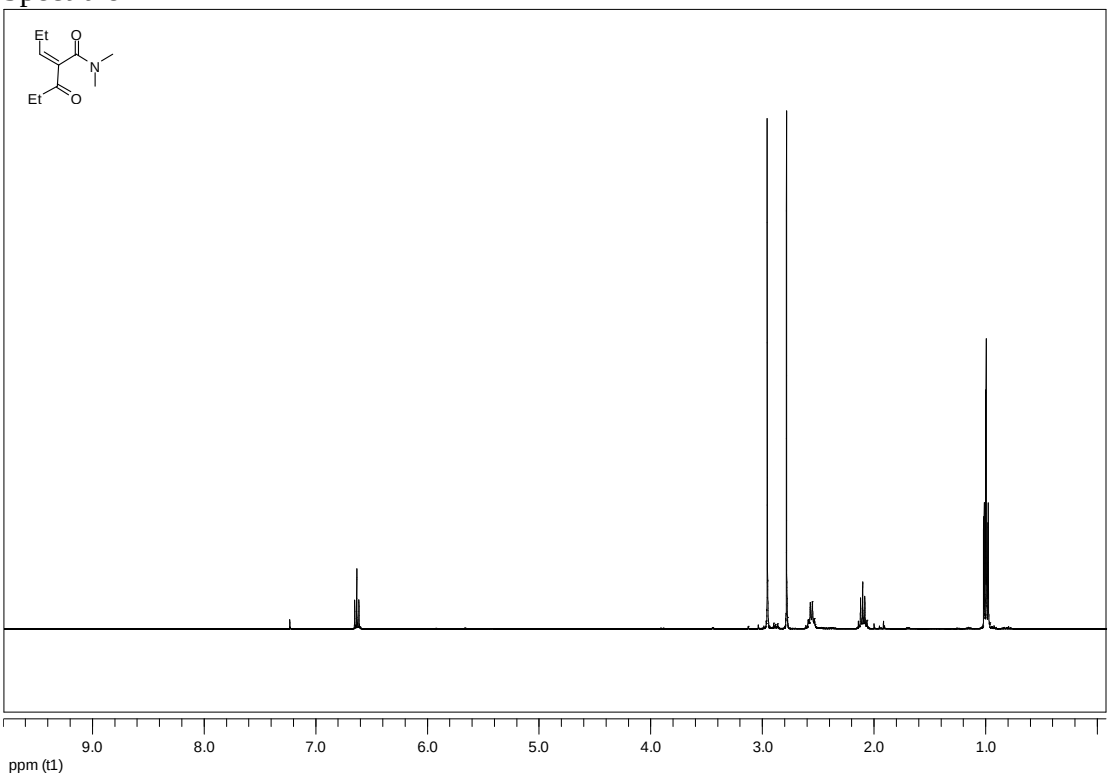
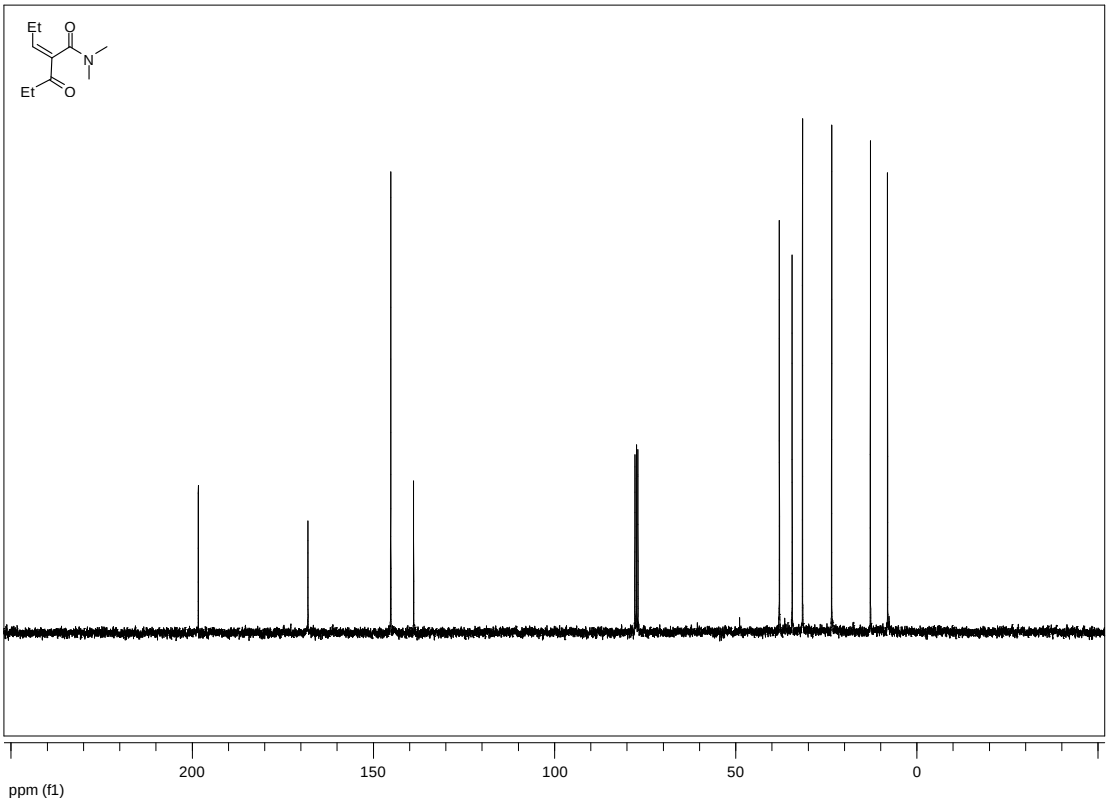
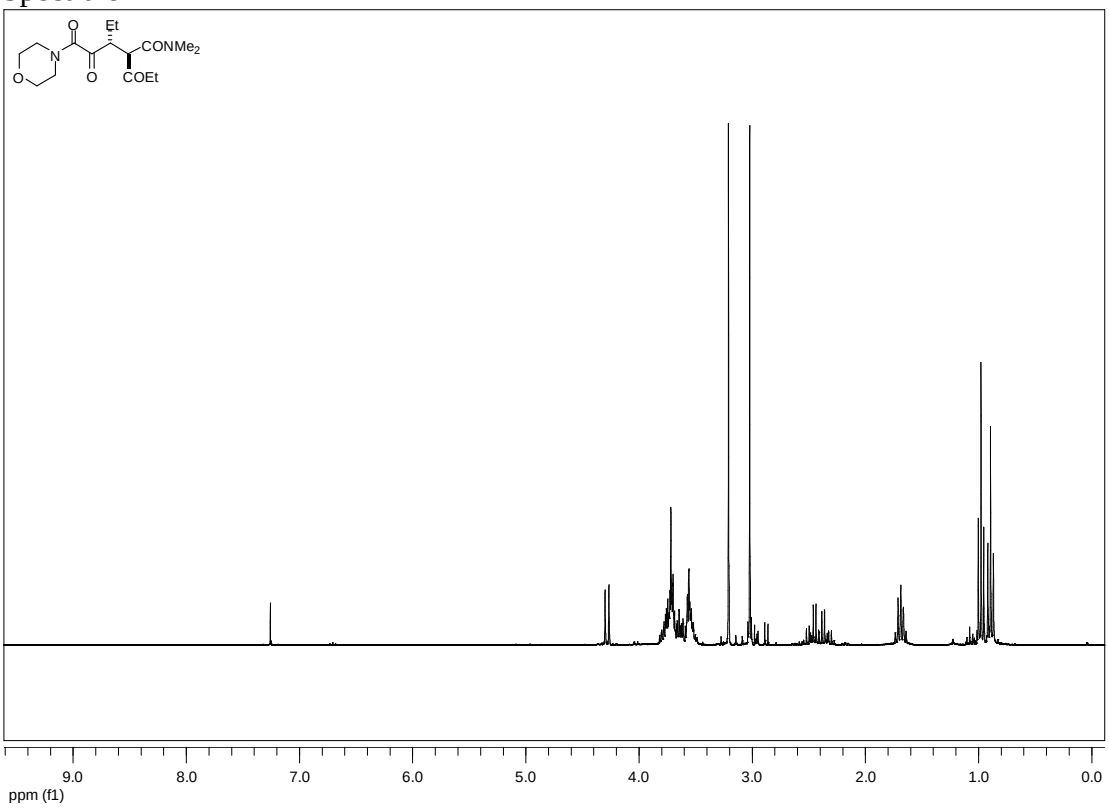
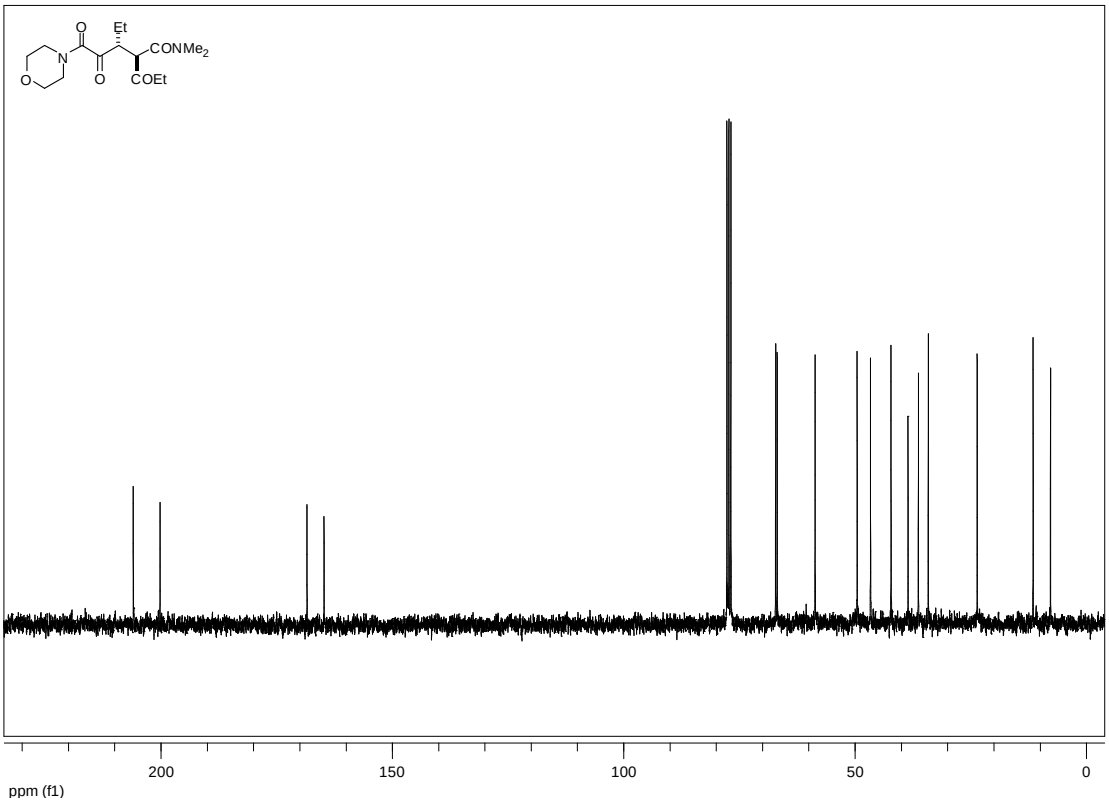




Spectra of **11**





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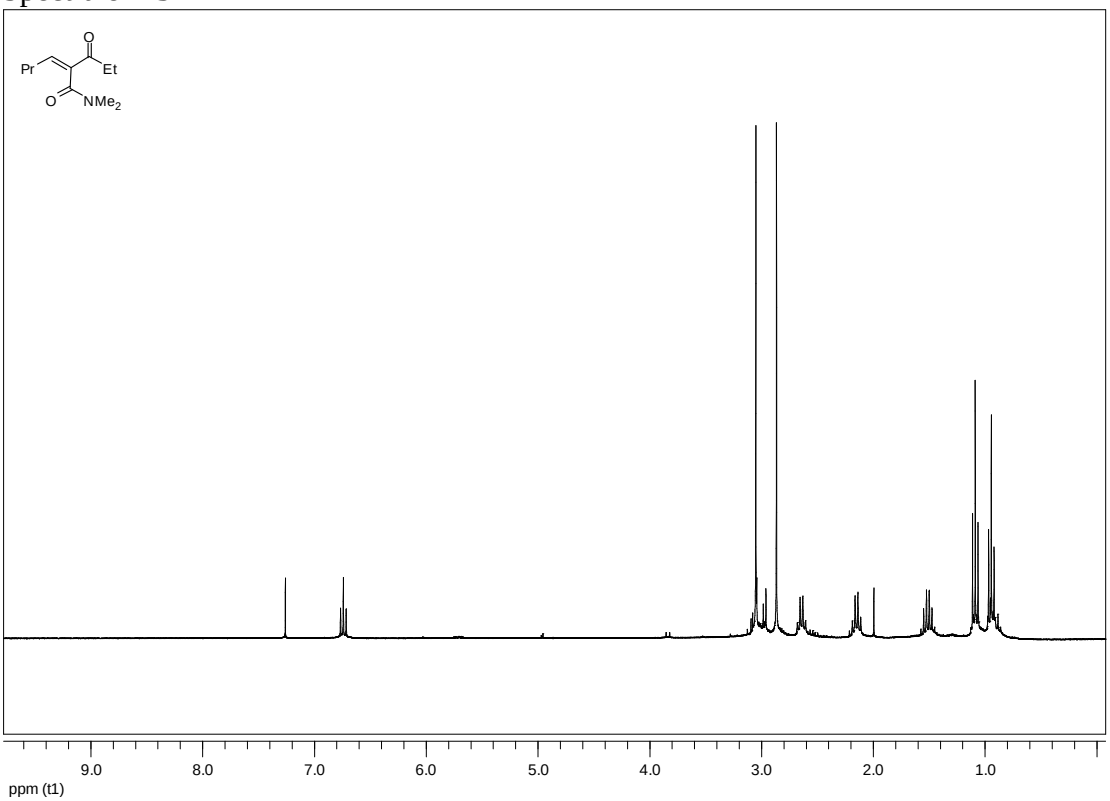

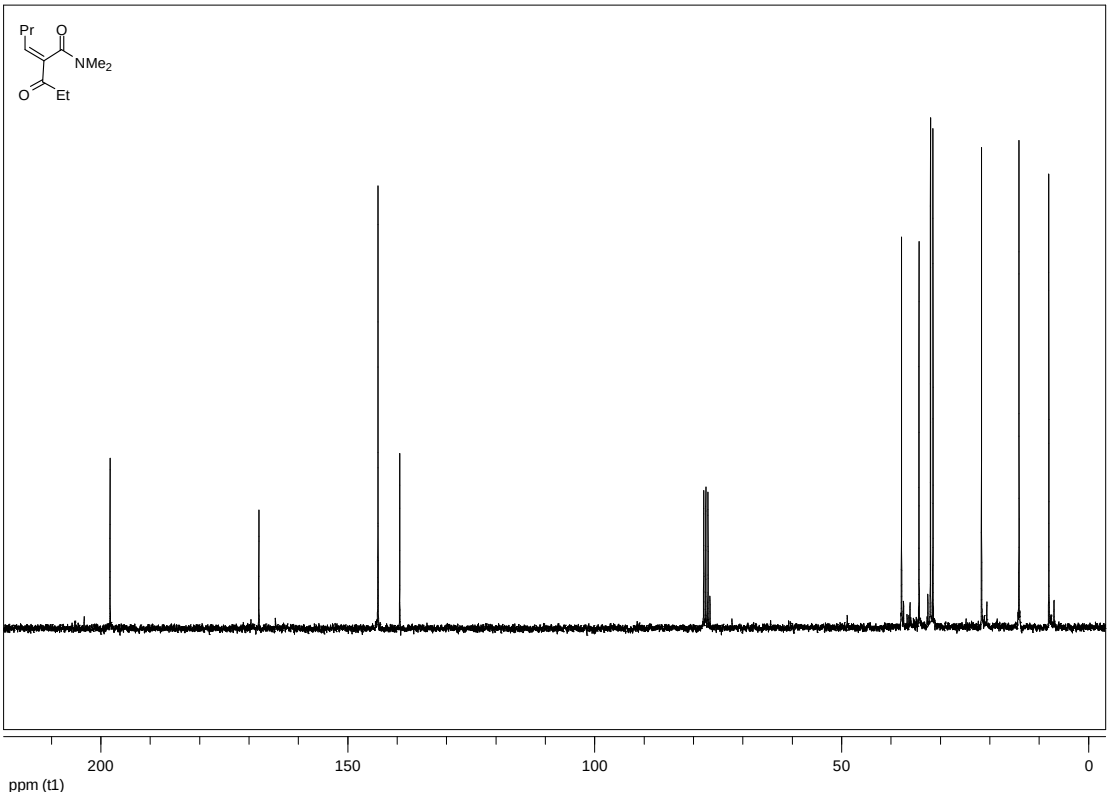

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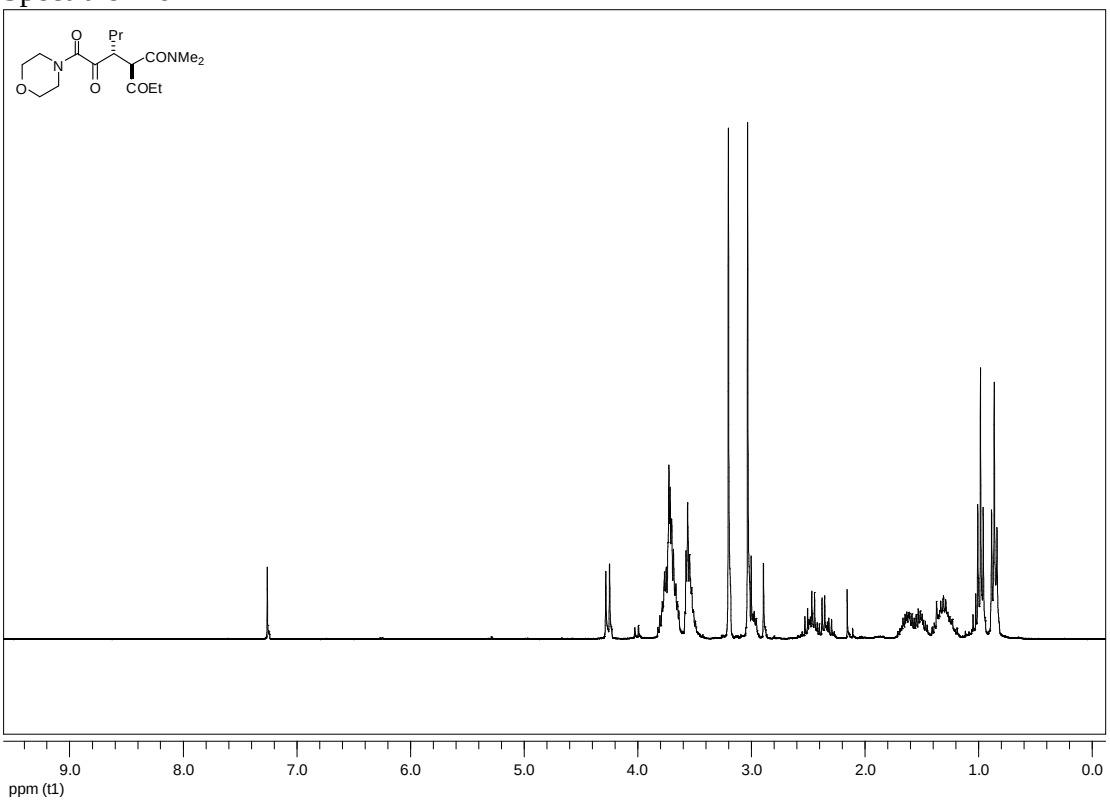
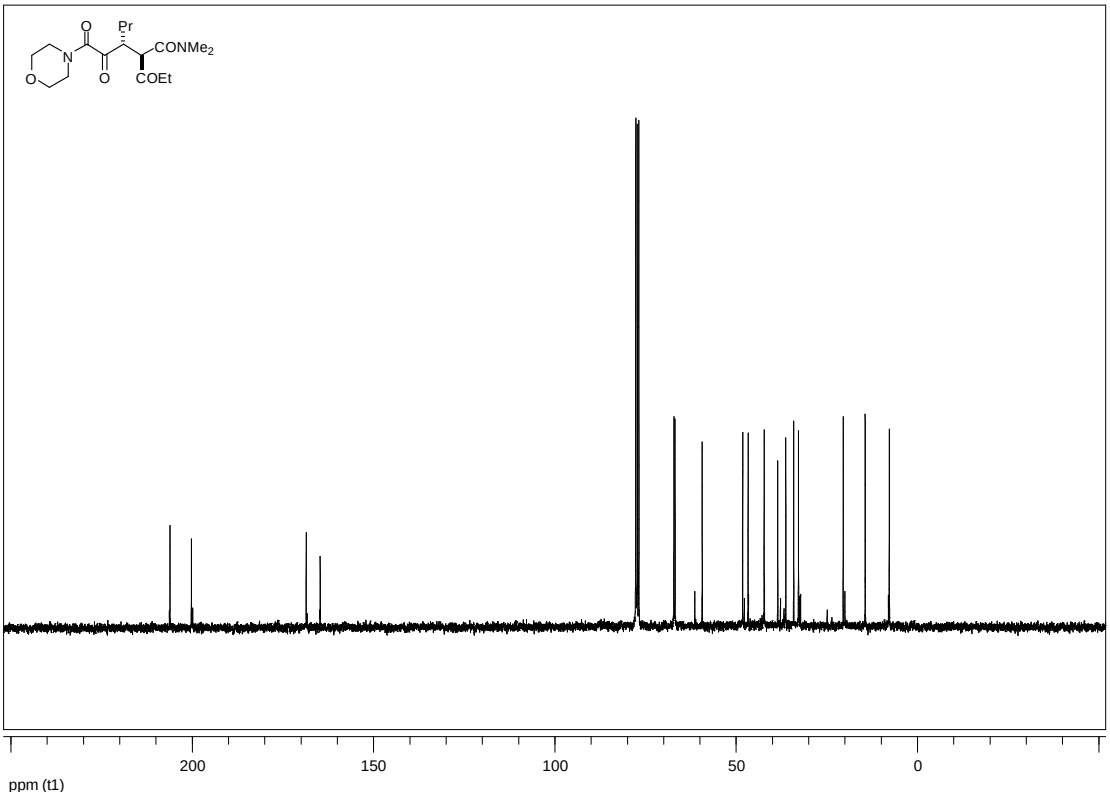
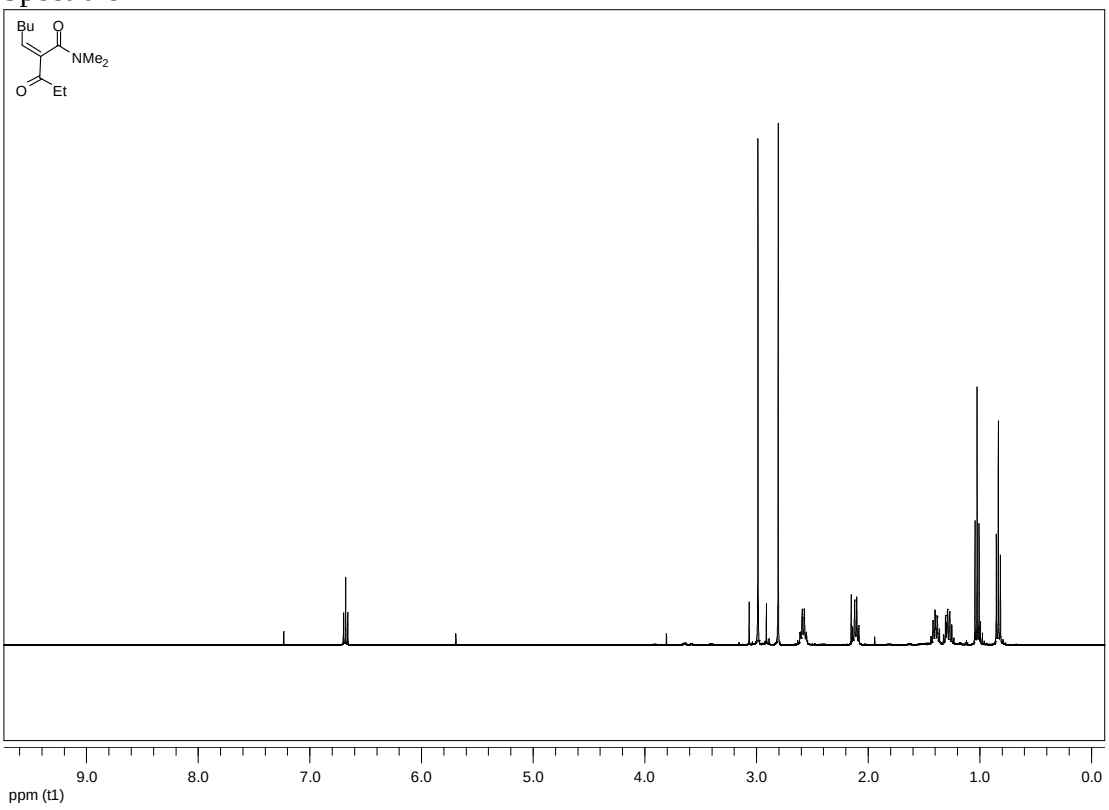
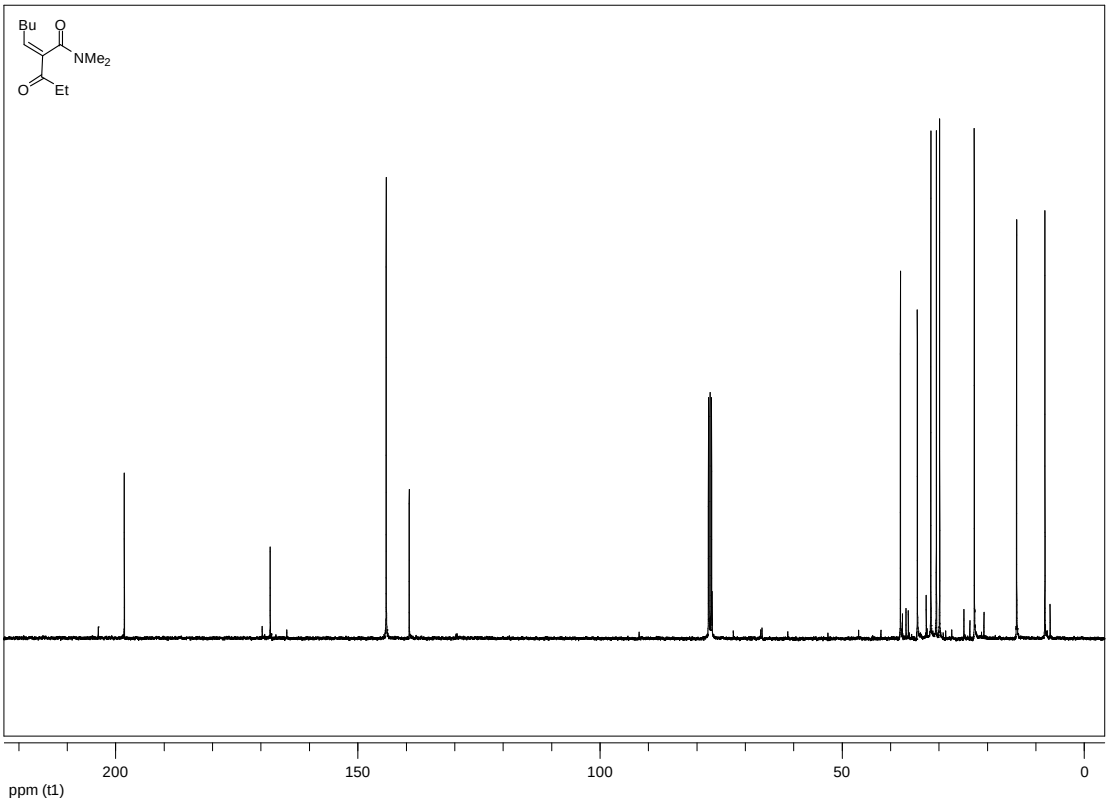


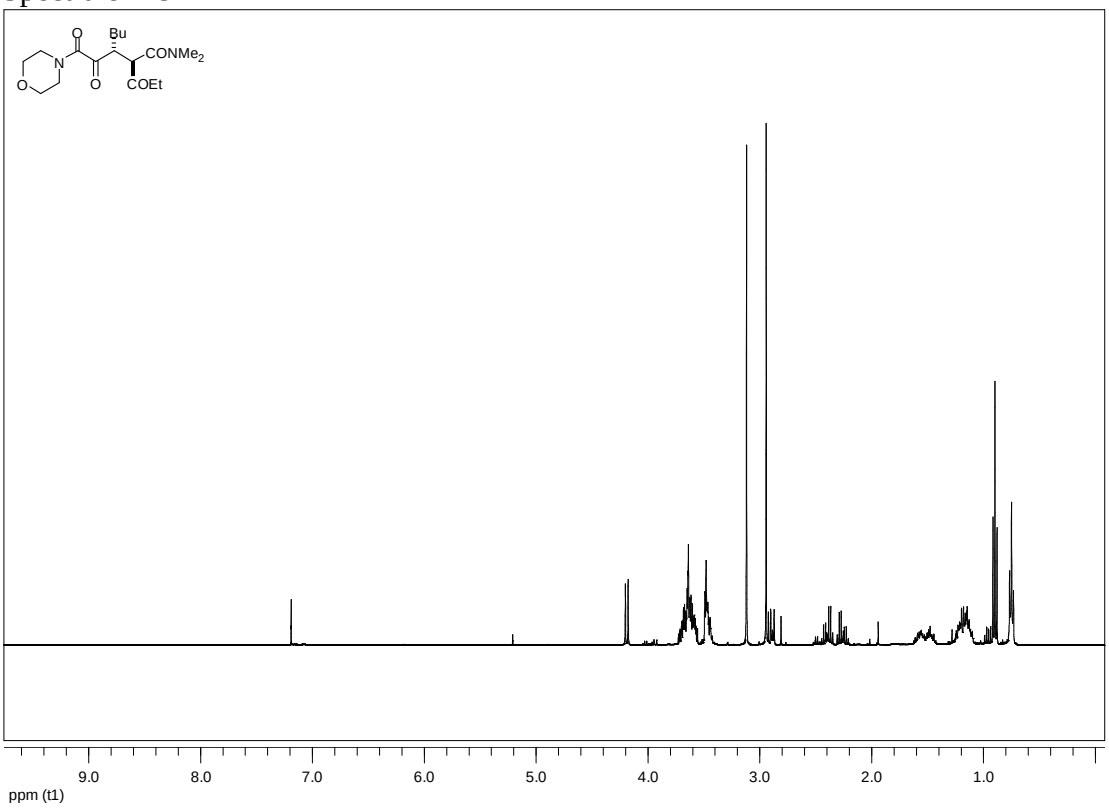


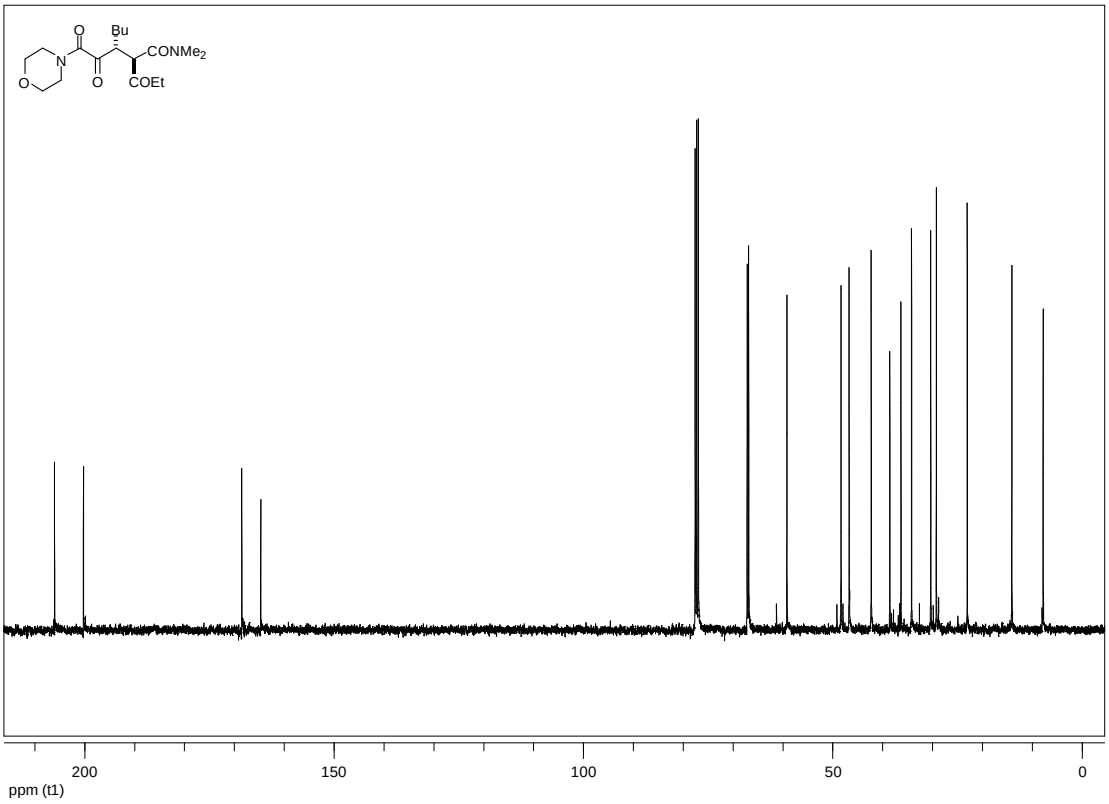
Spectra of **17**



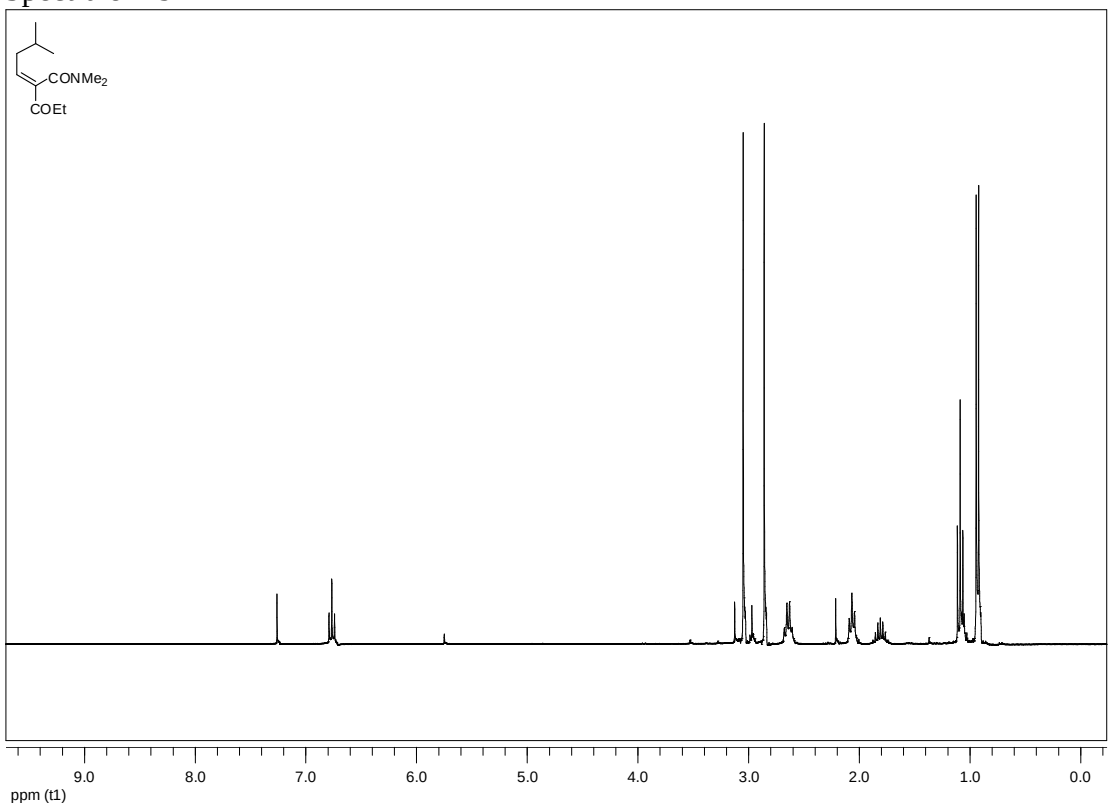


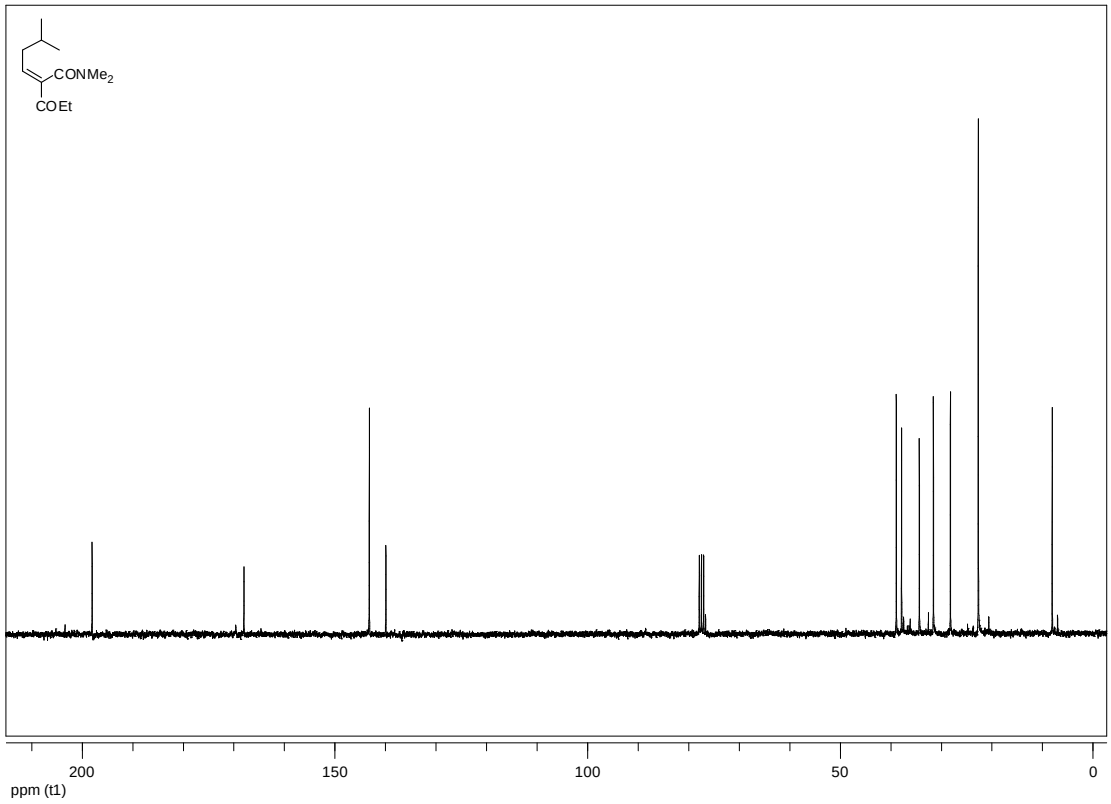
Spectra of **18**





Spectra of **19**





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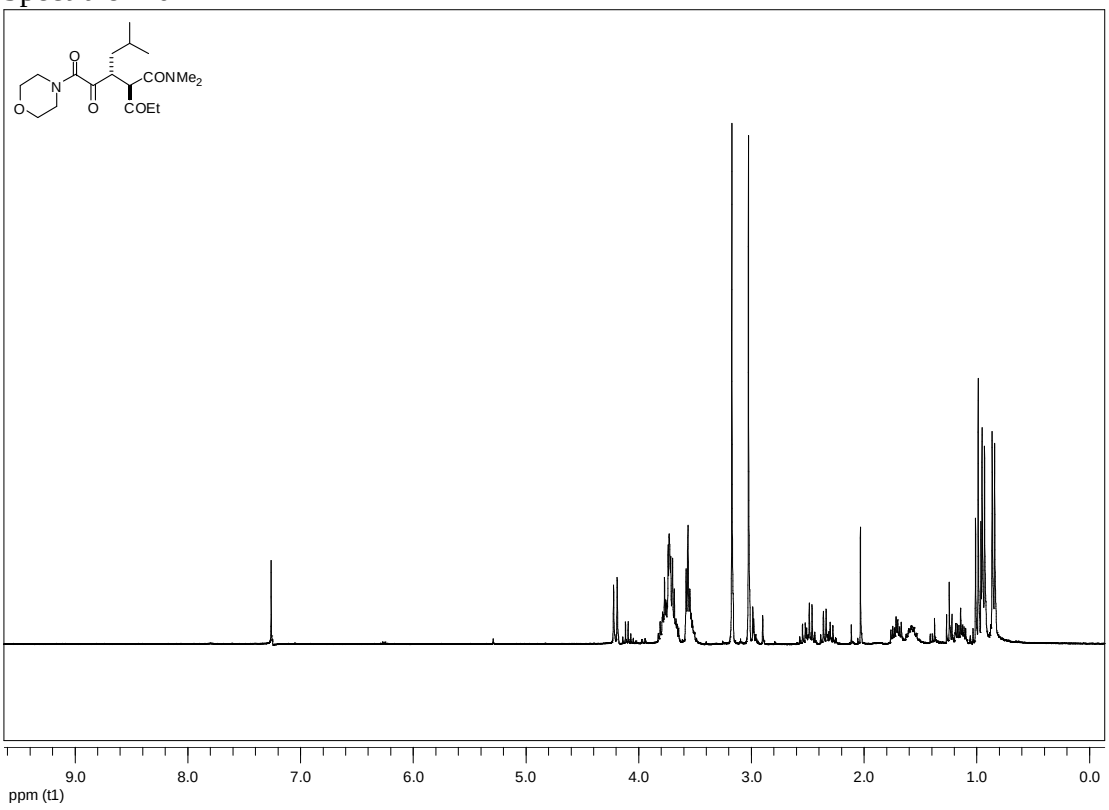
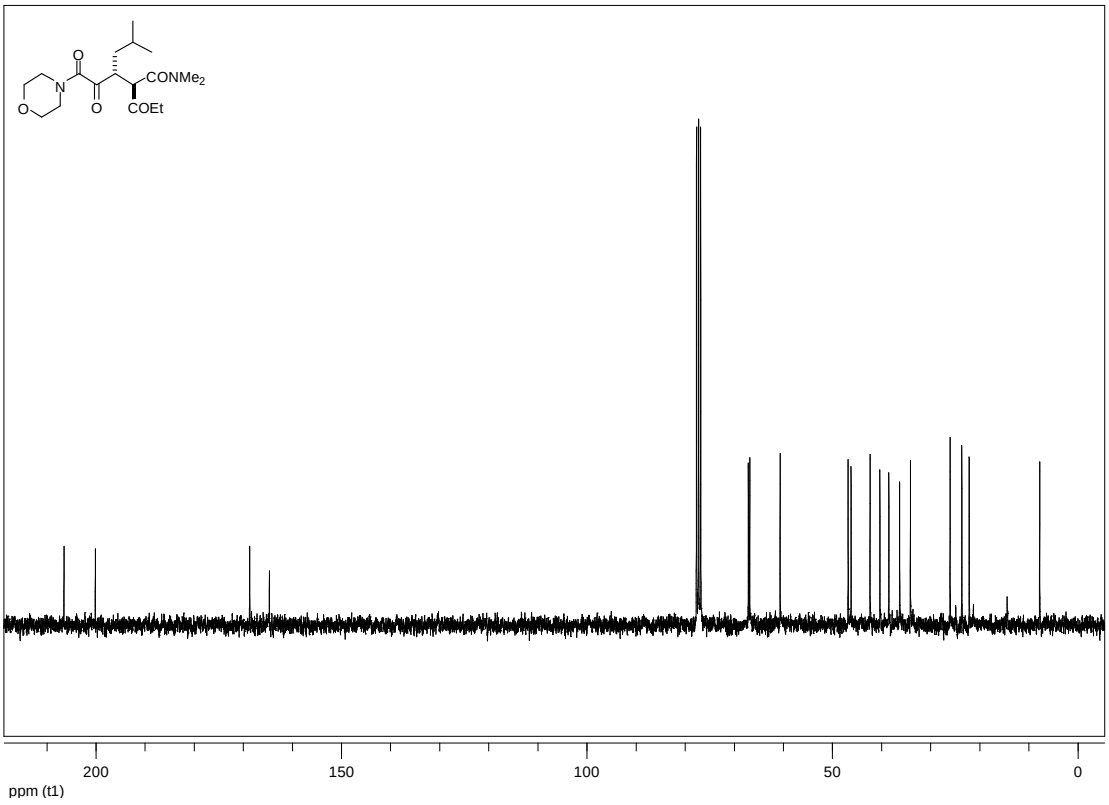
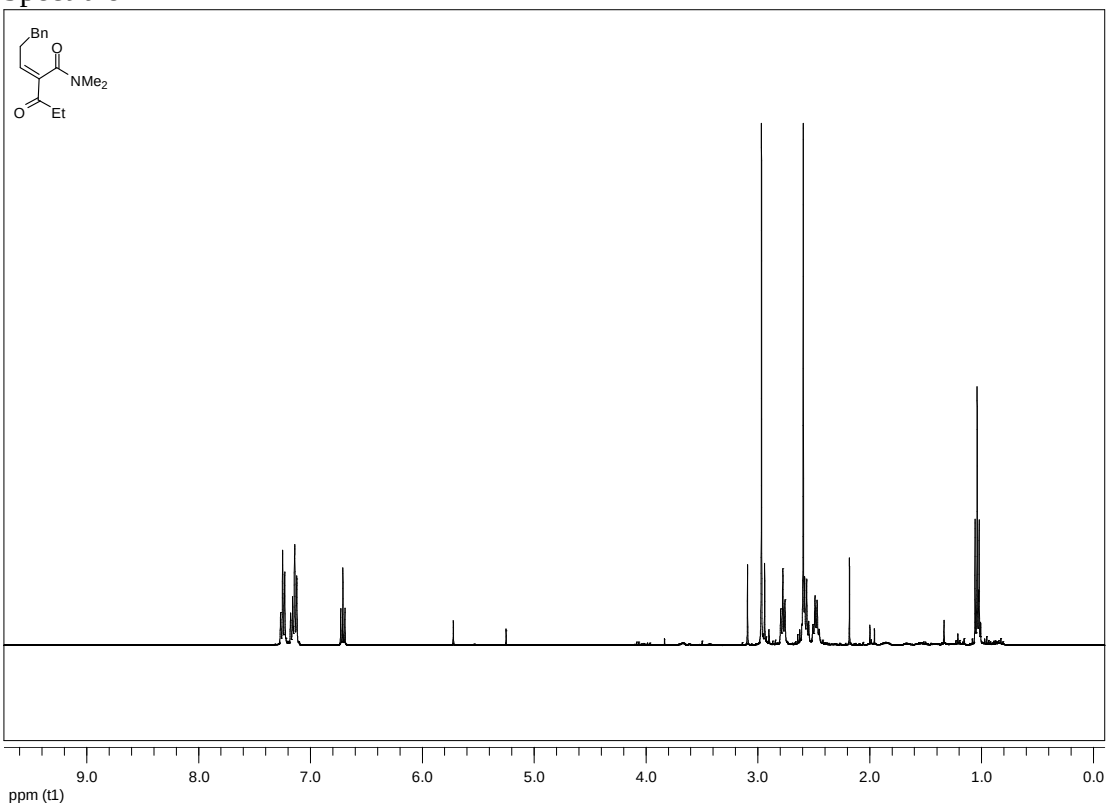
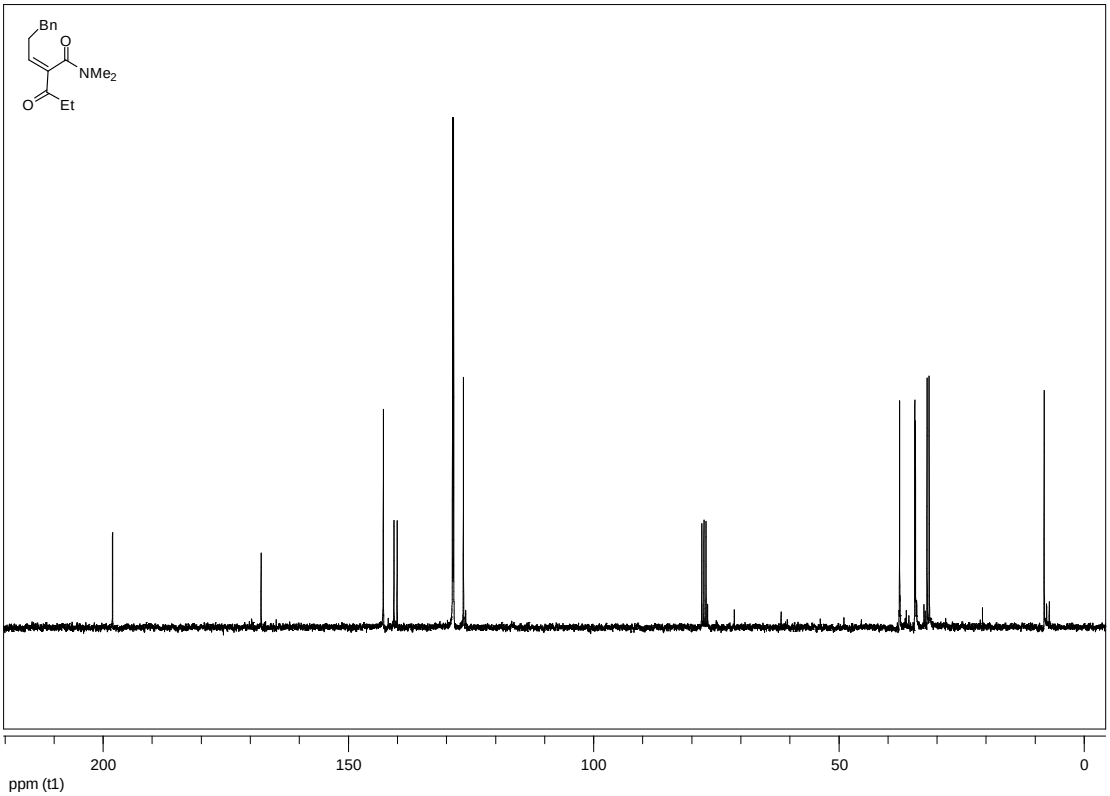




Spectra of **21**





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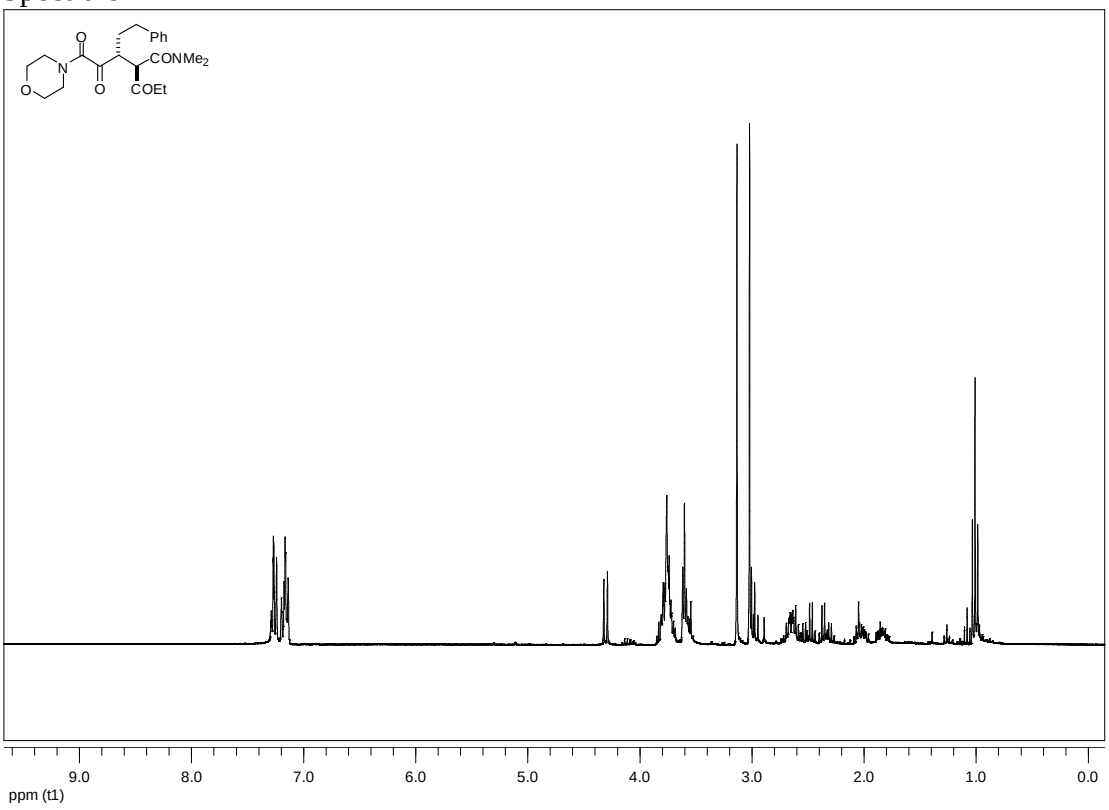

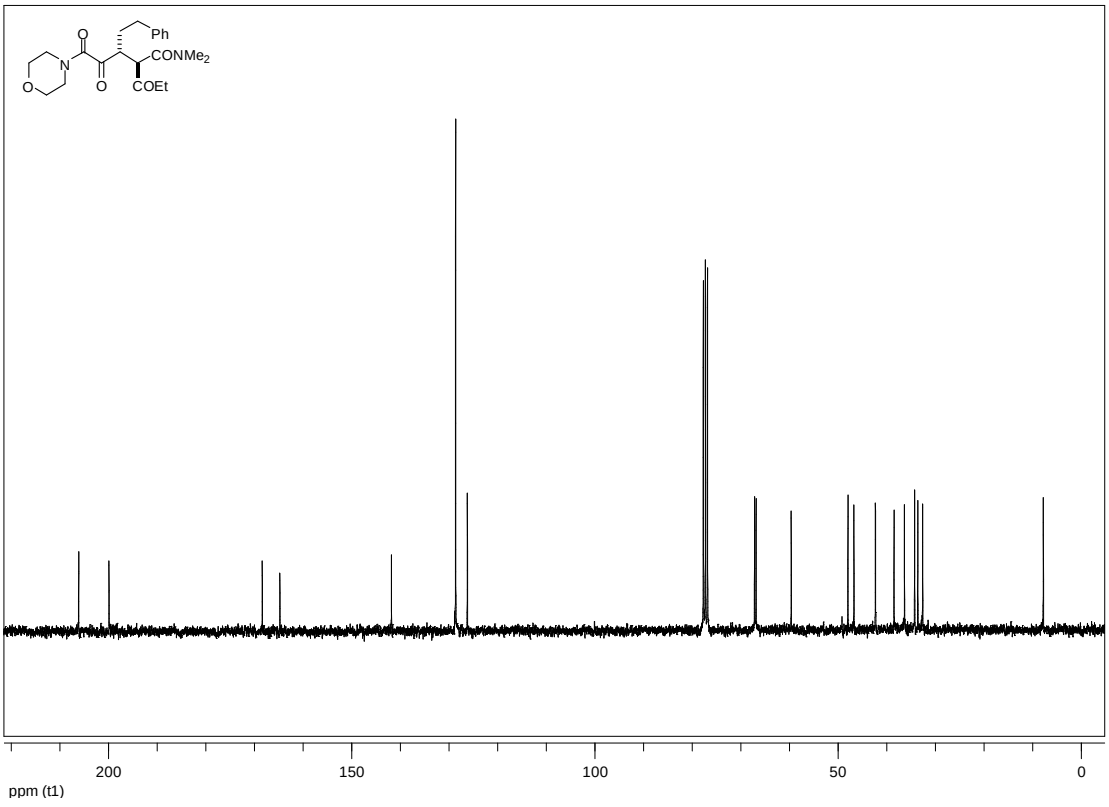

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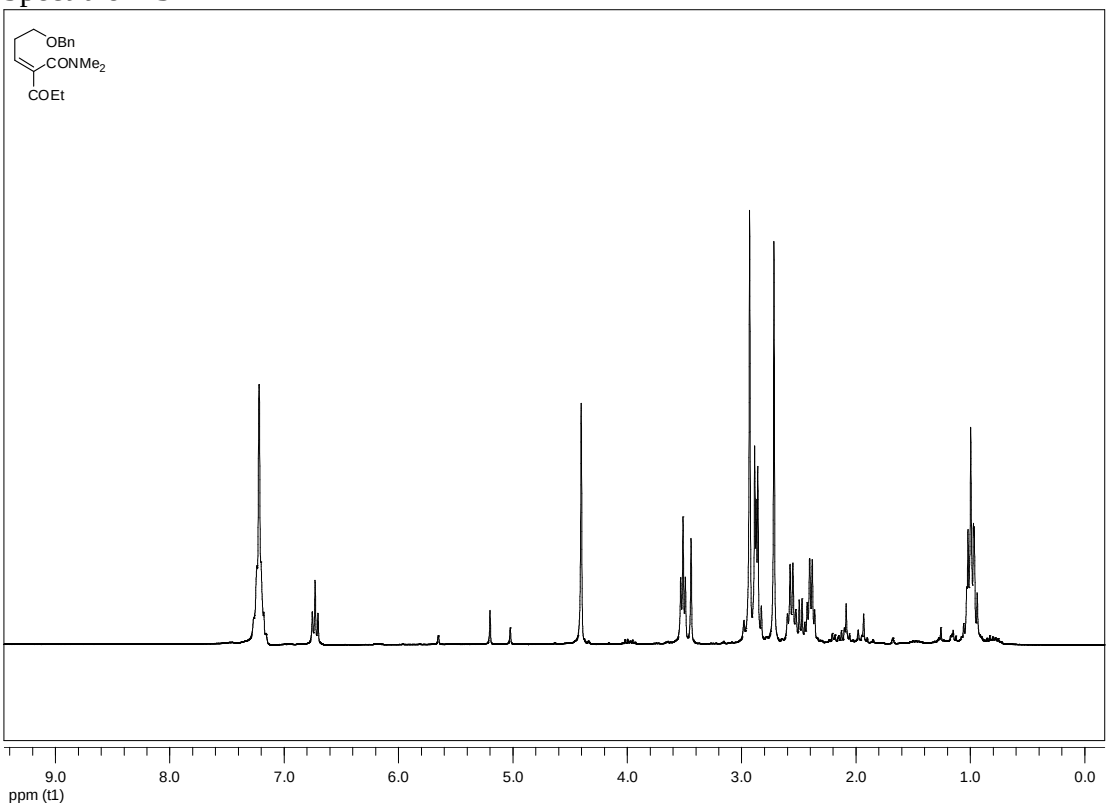
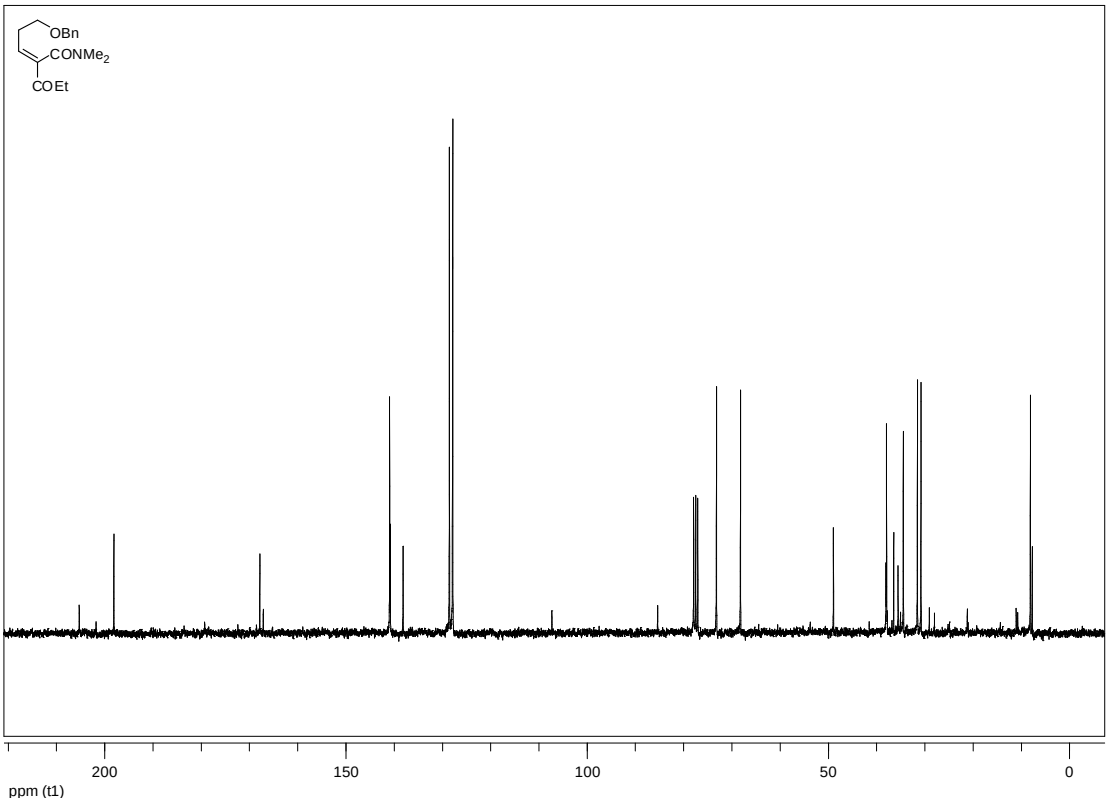
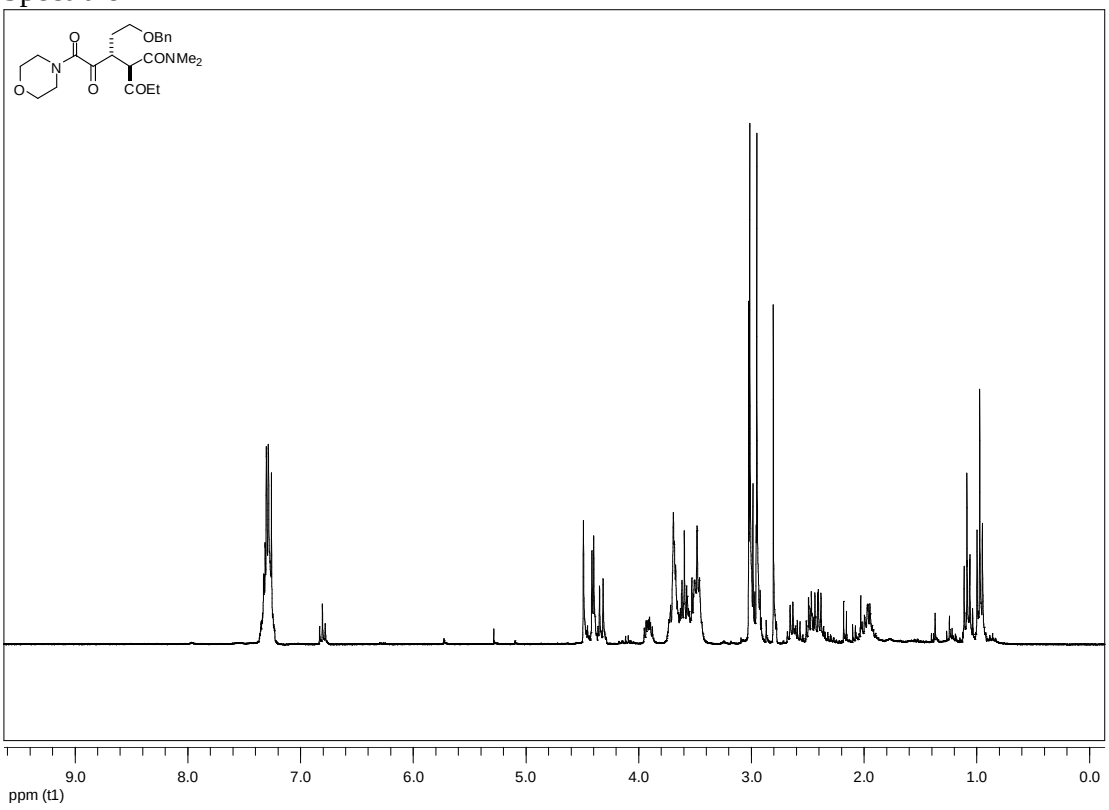
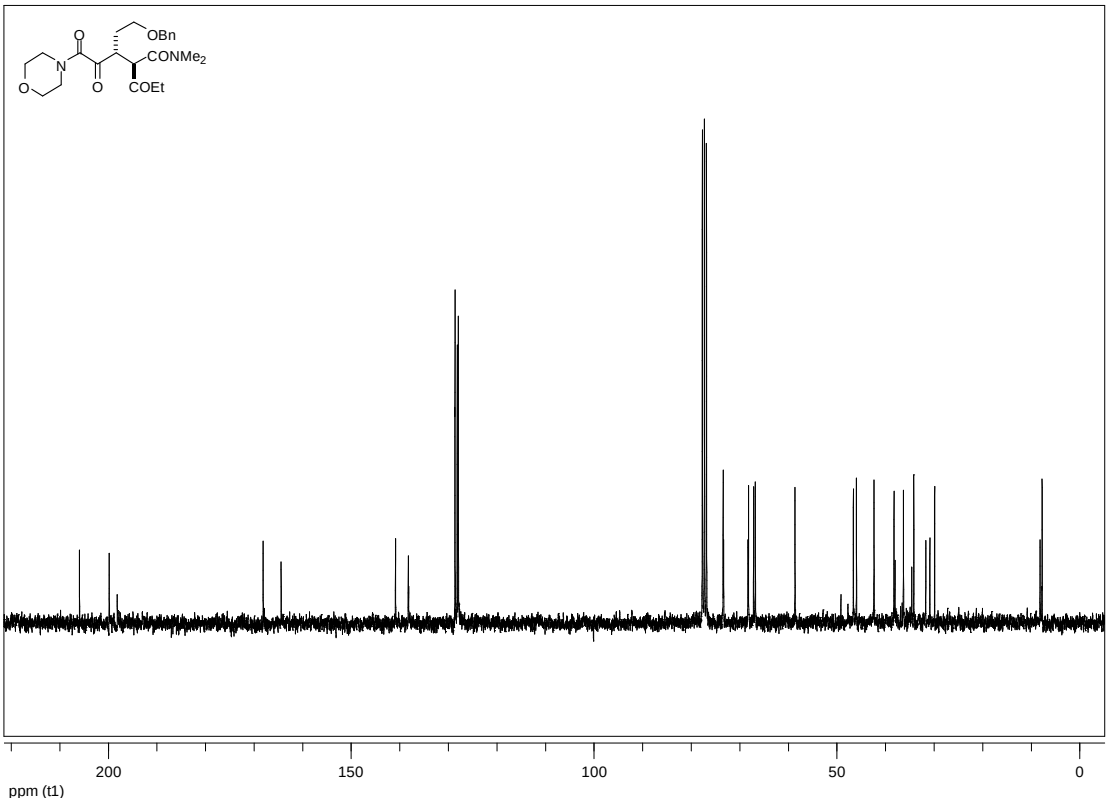


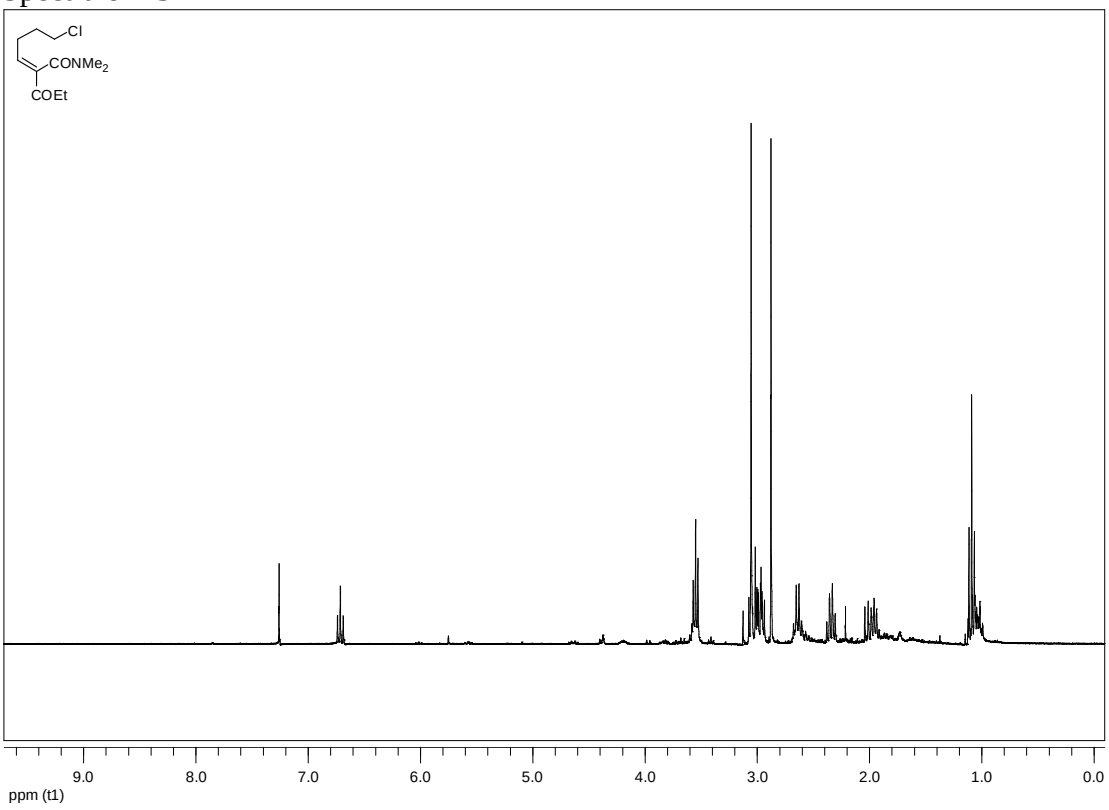


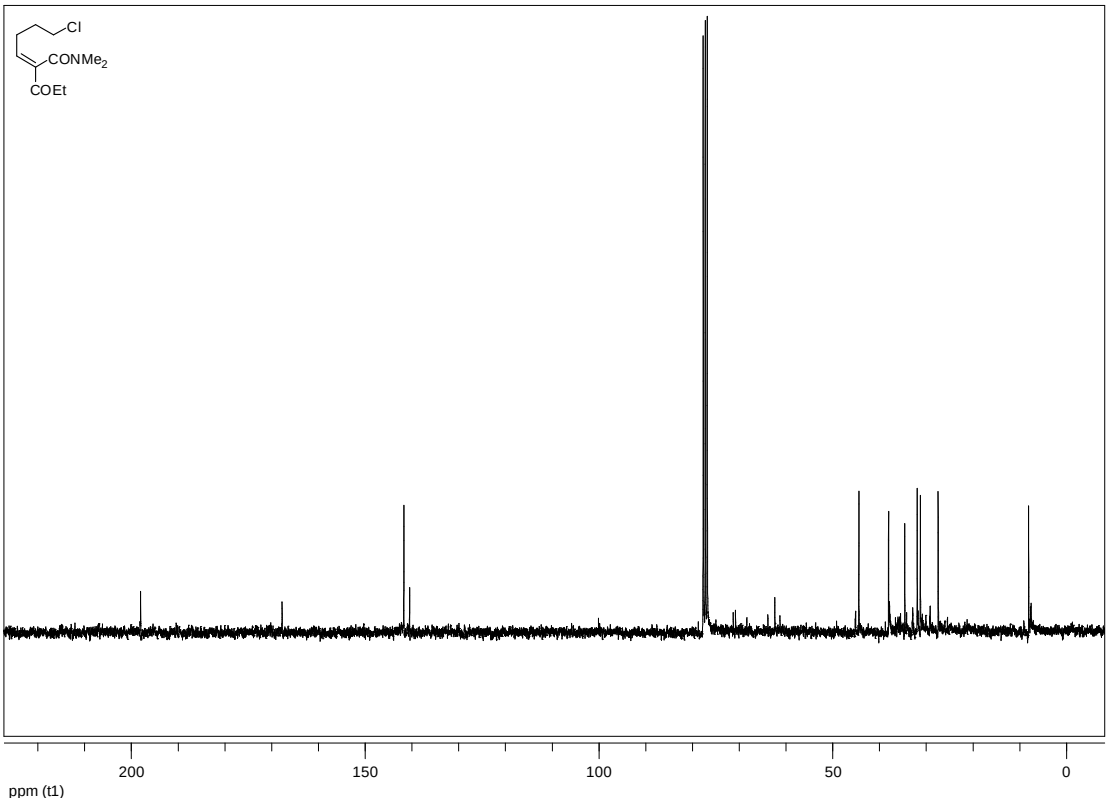
Spectra of **24**



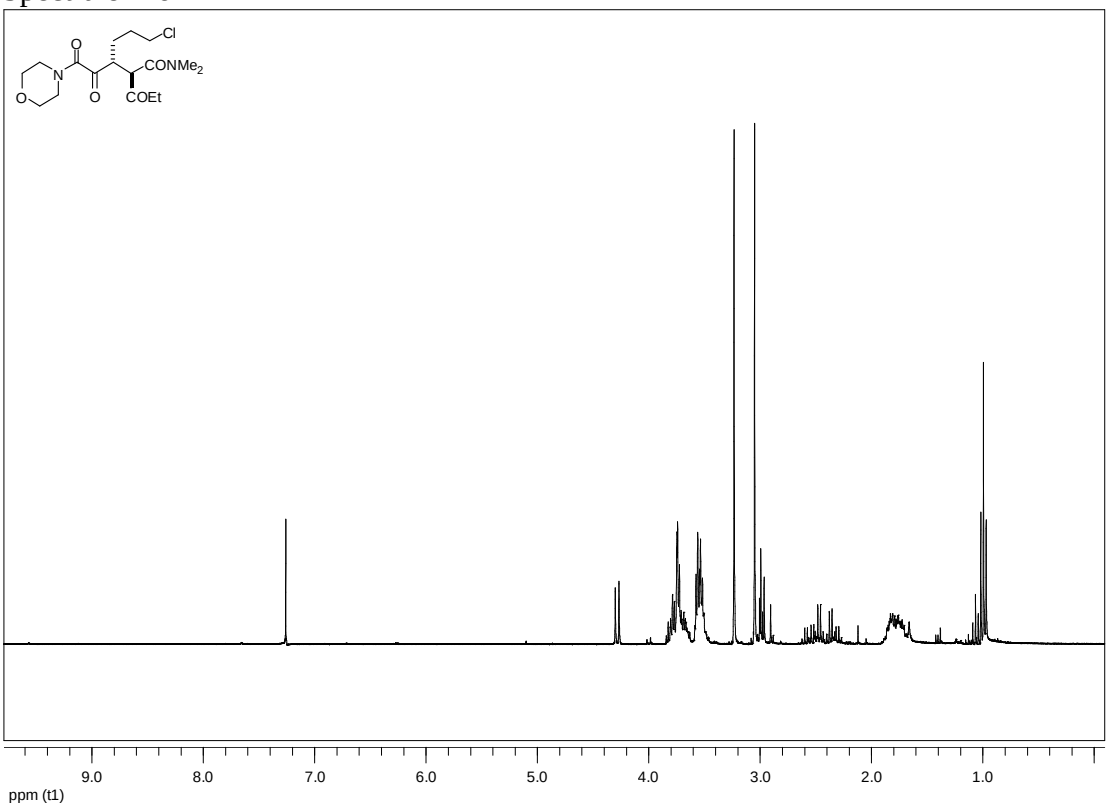


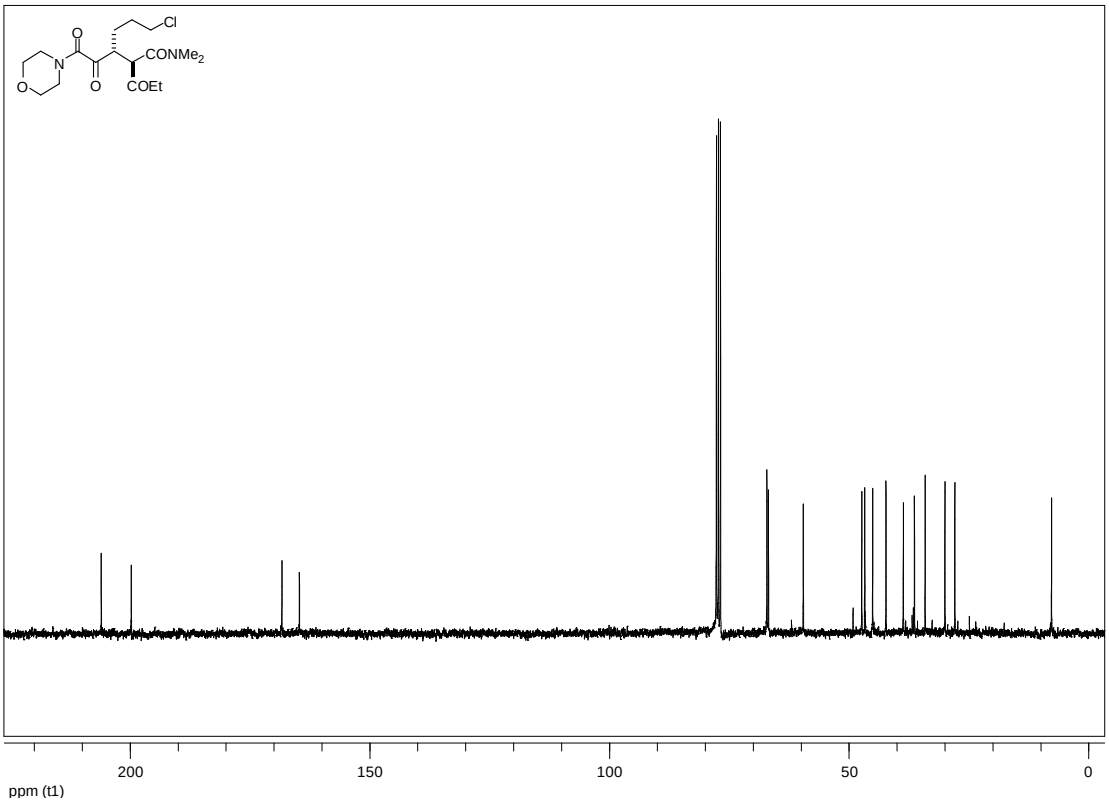
Spectra of **25**



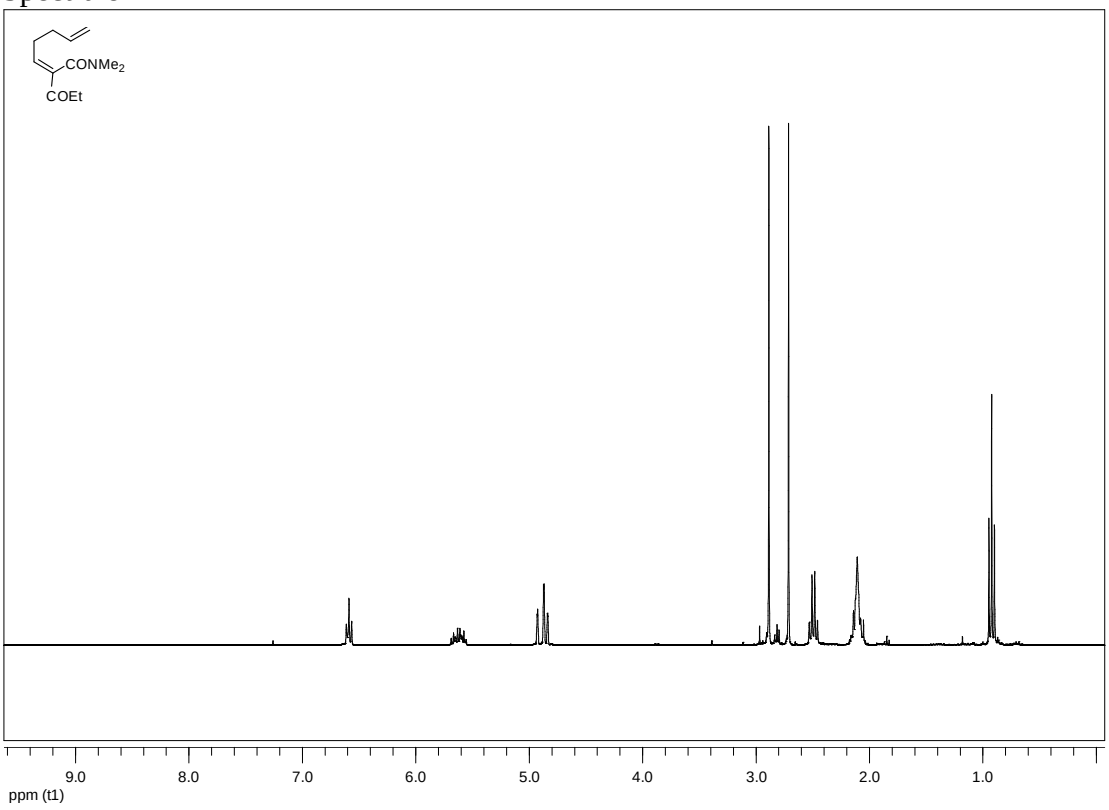


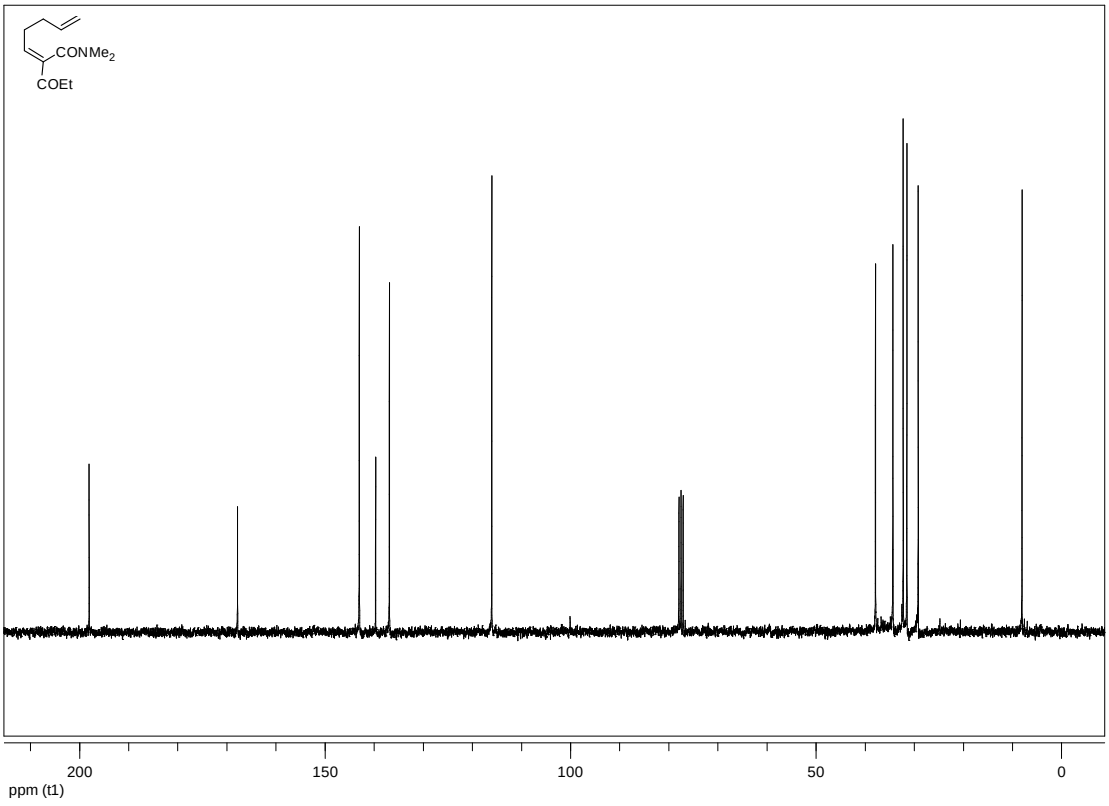
Spectra of **26**





Spectra of **27**





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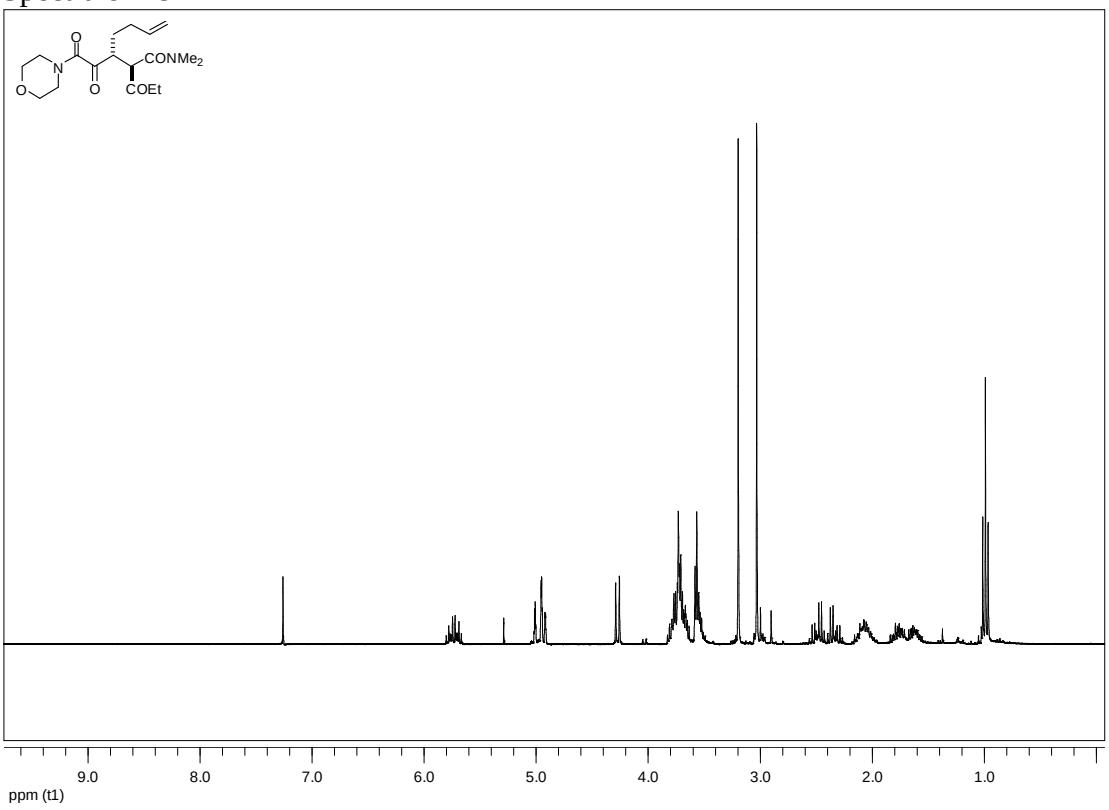

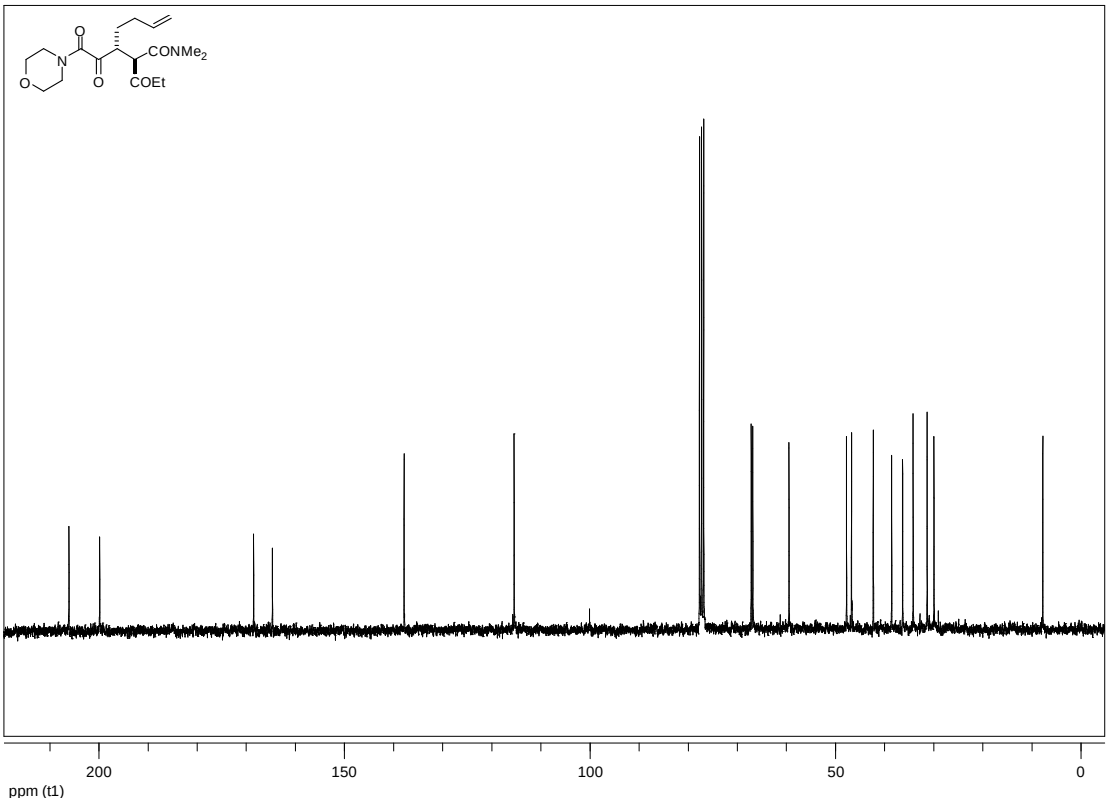

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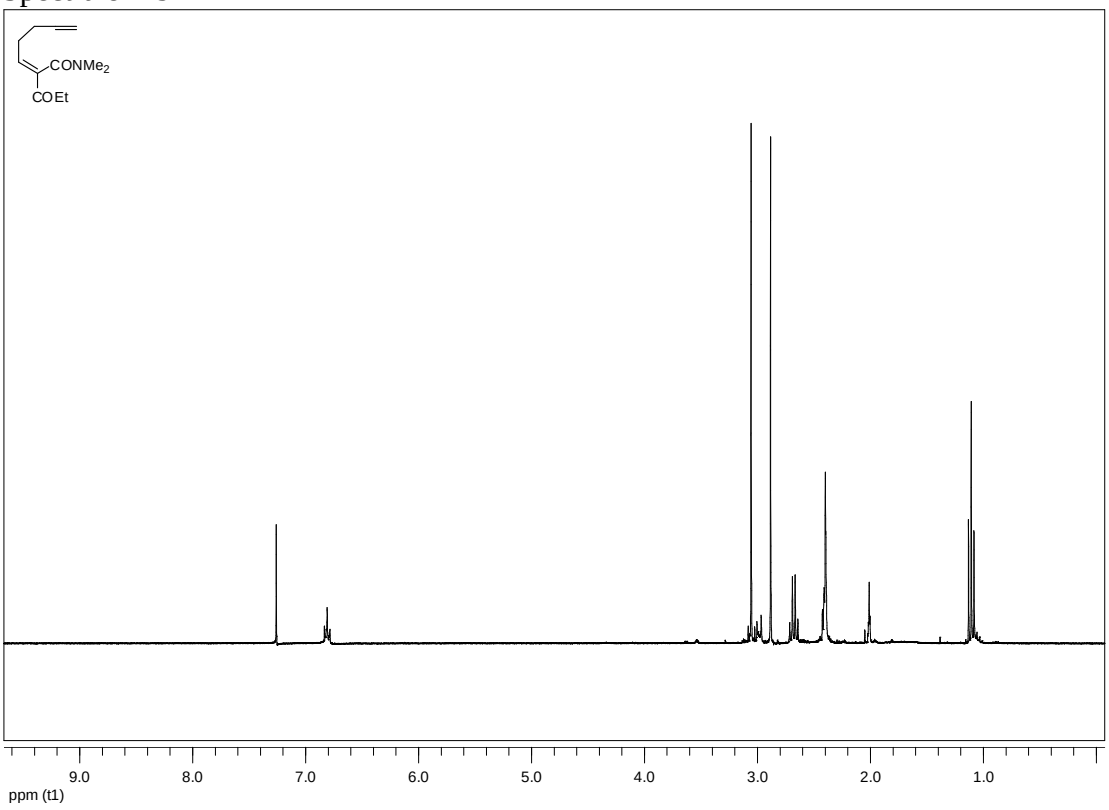

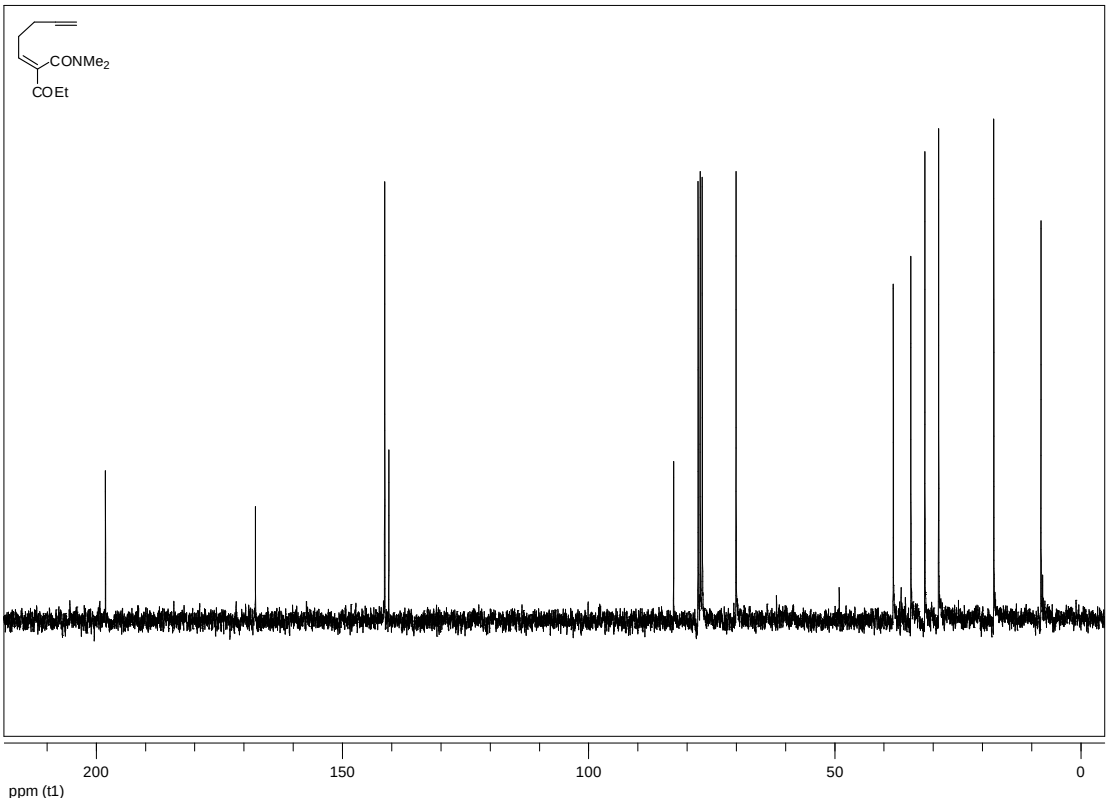

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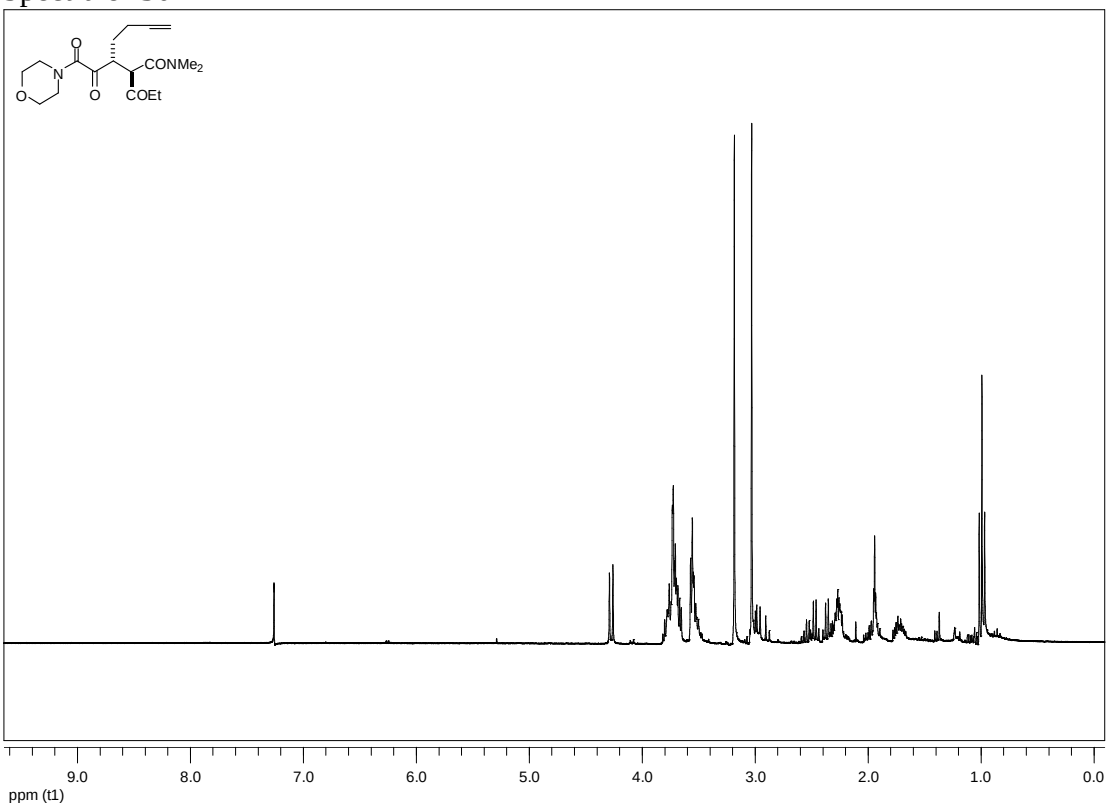

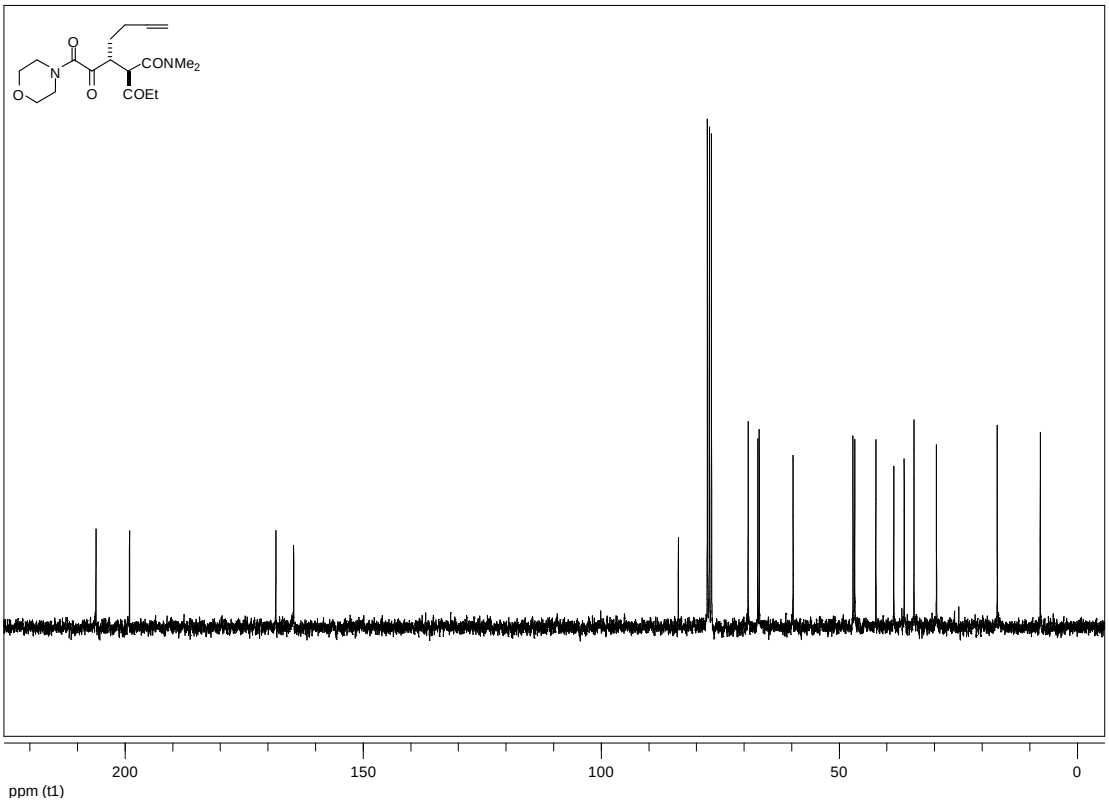

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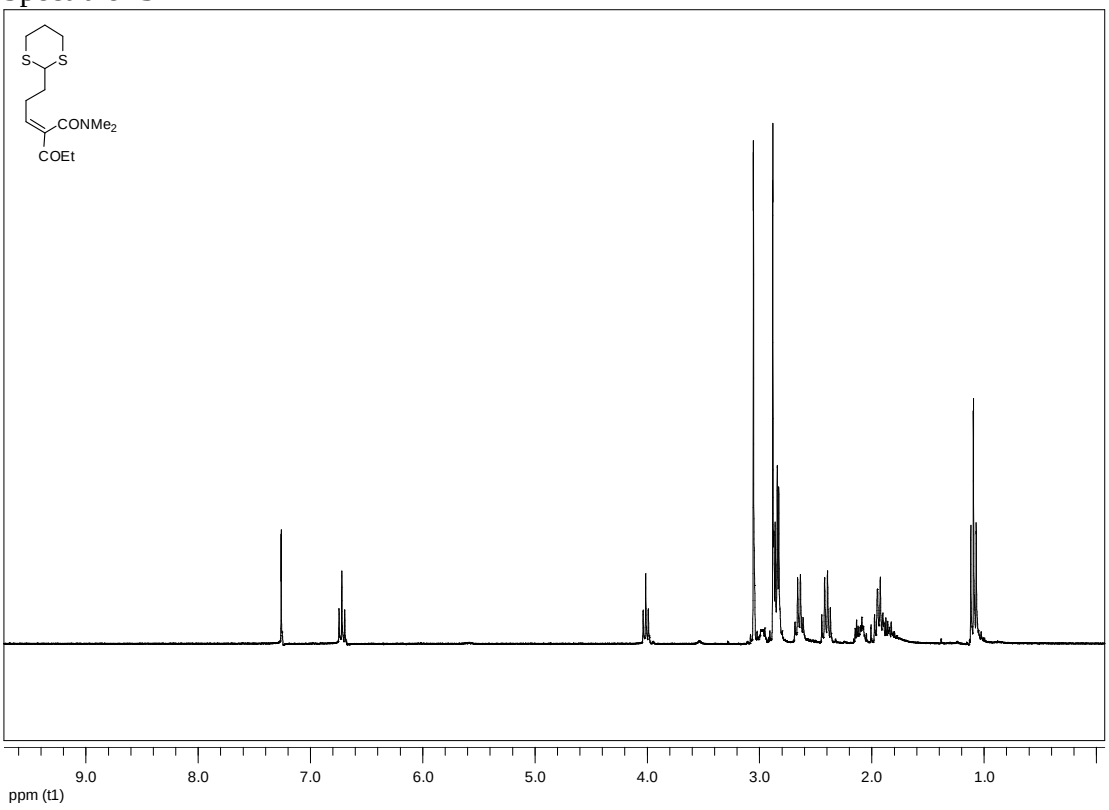

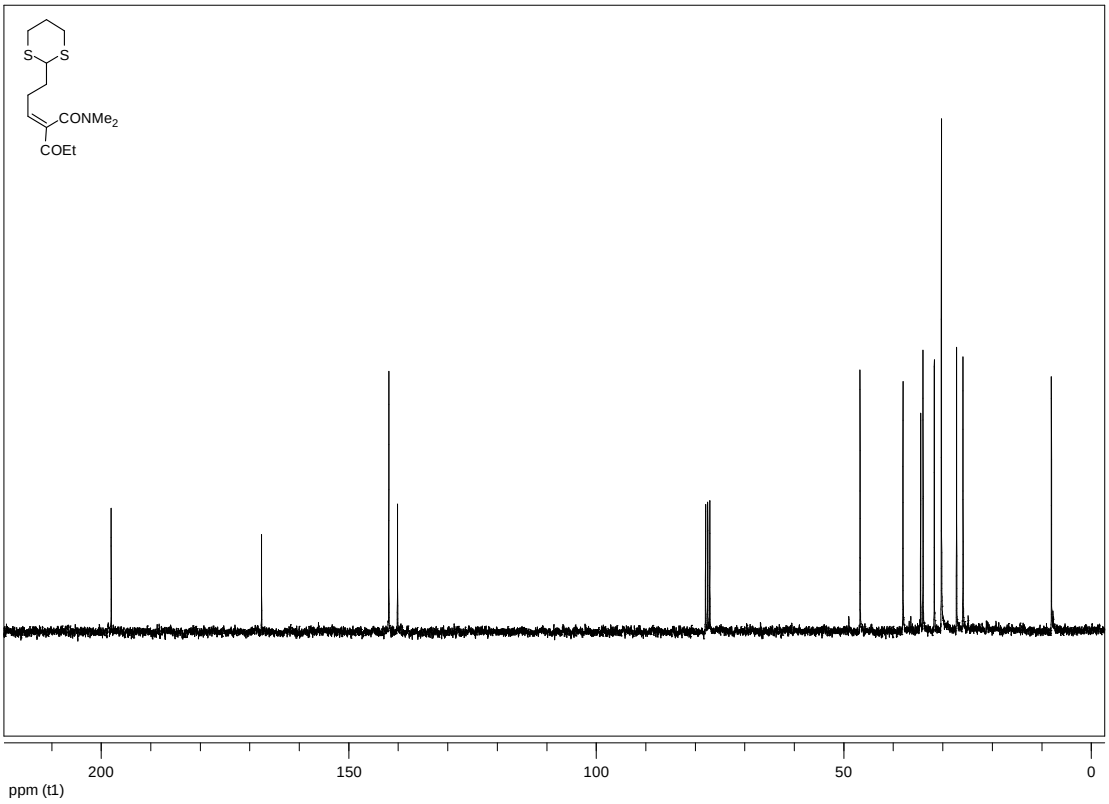

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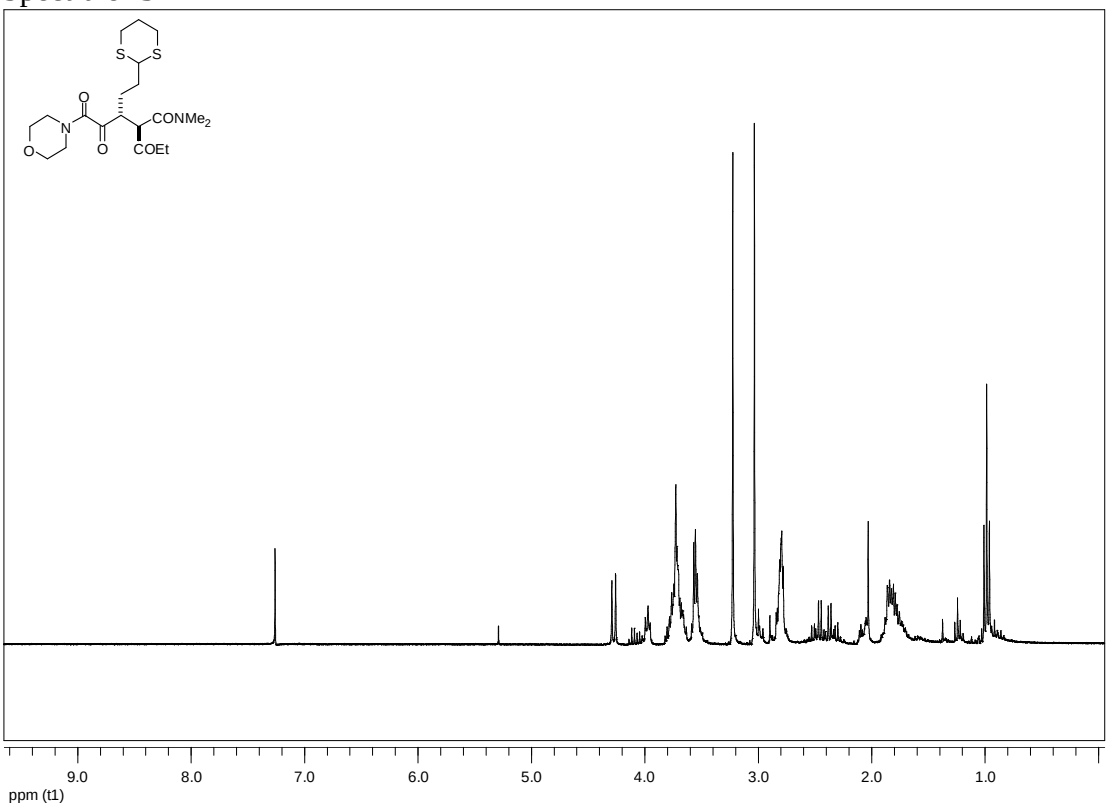

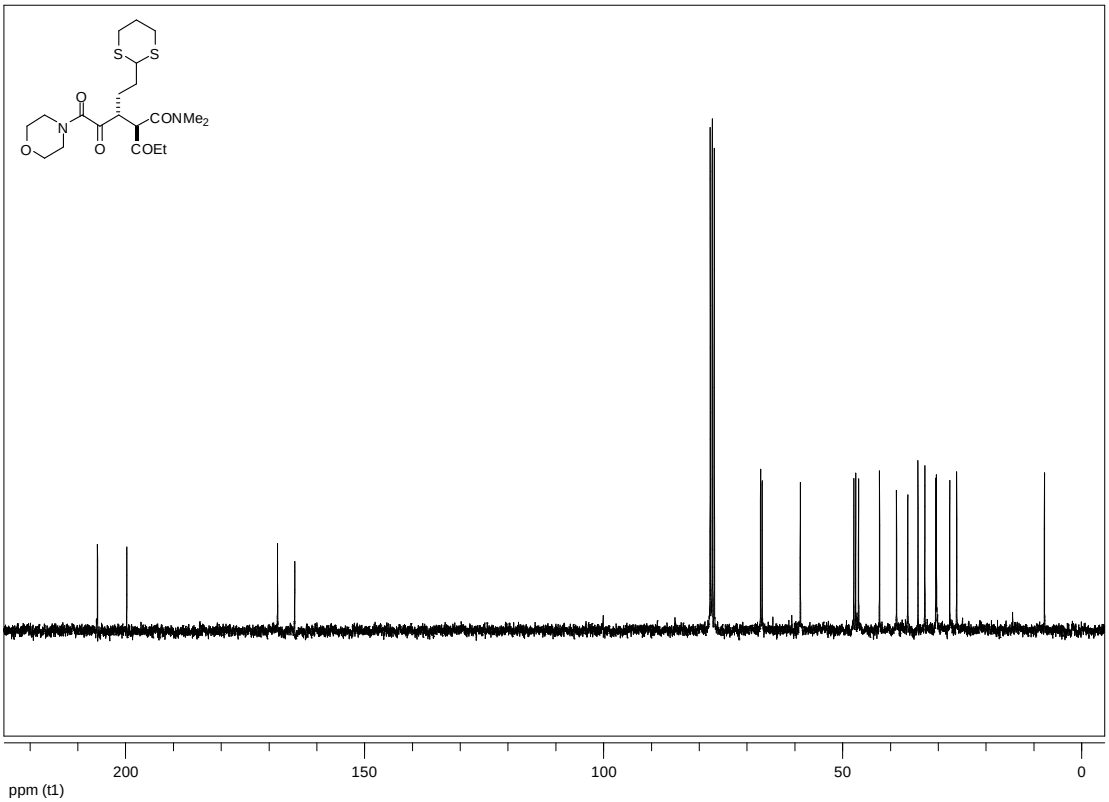

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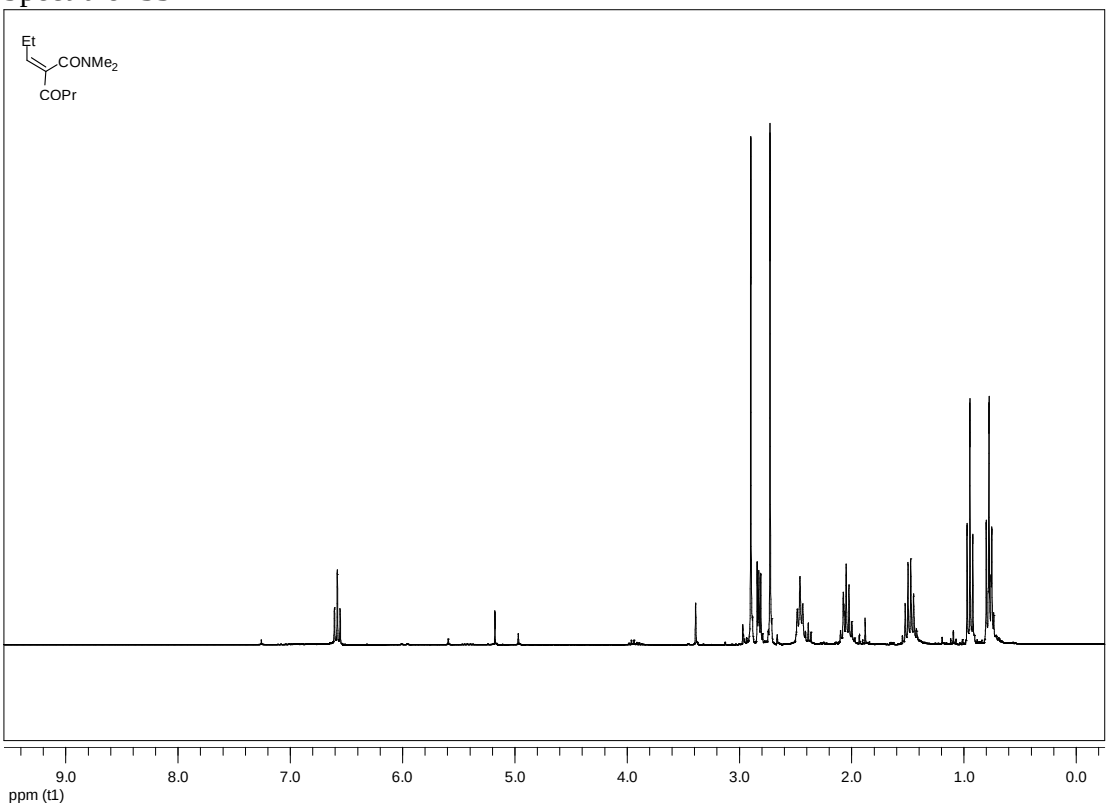

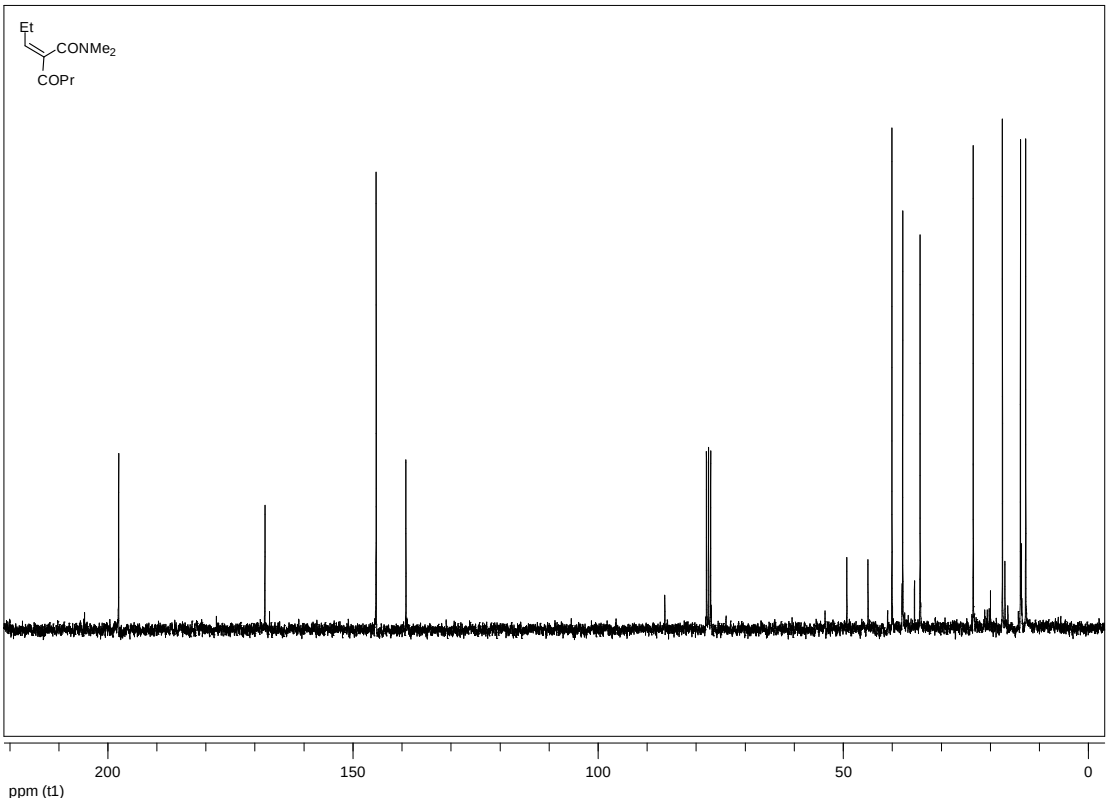

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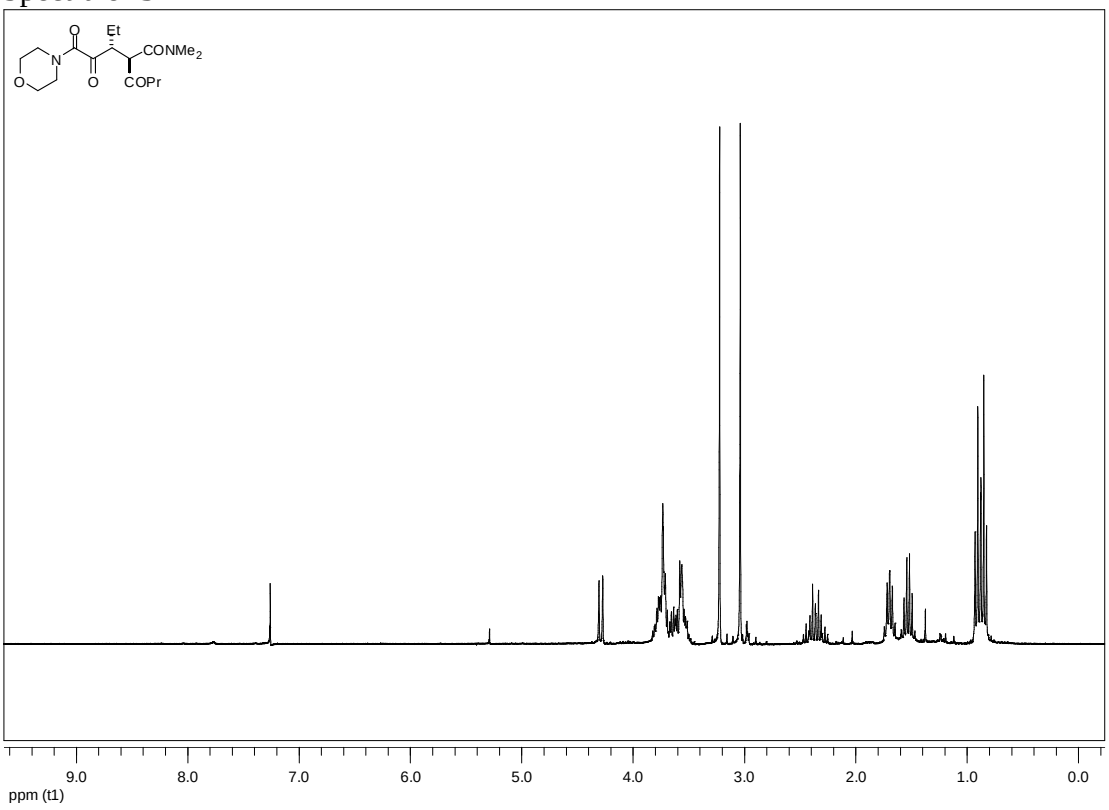

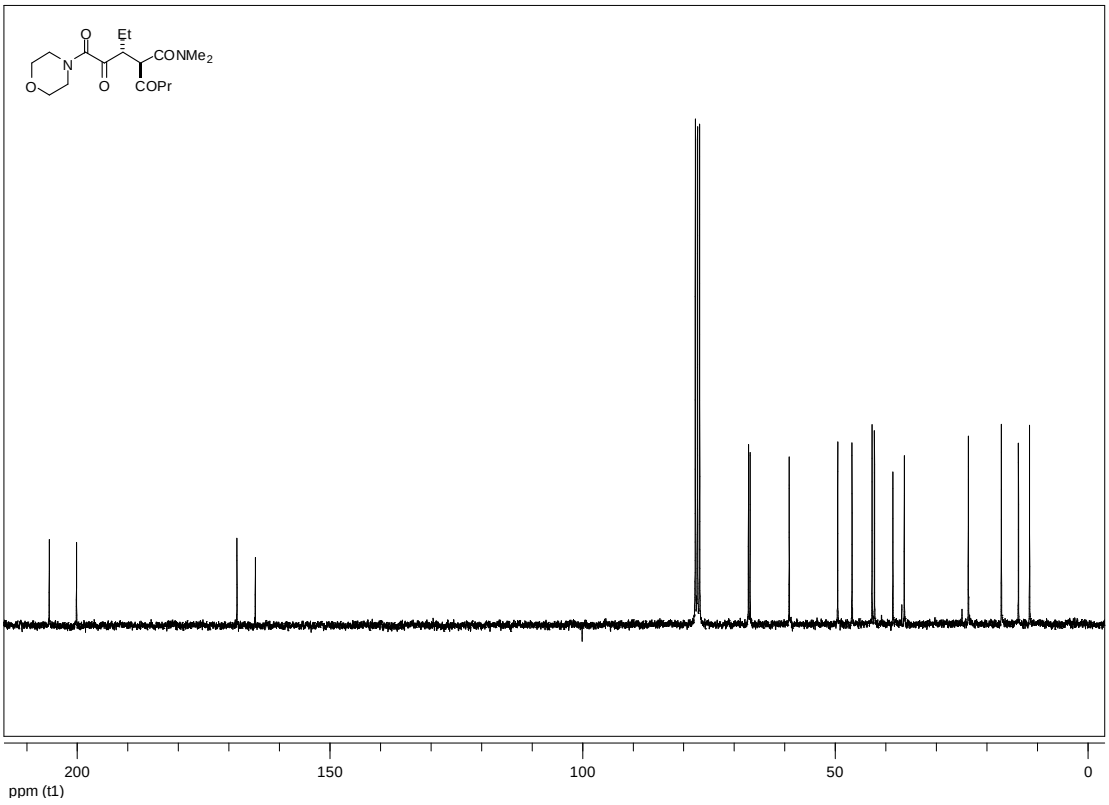

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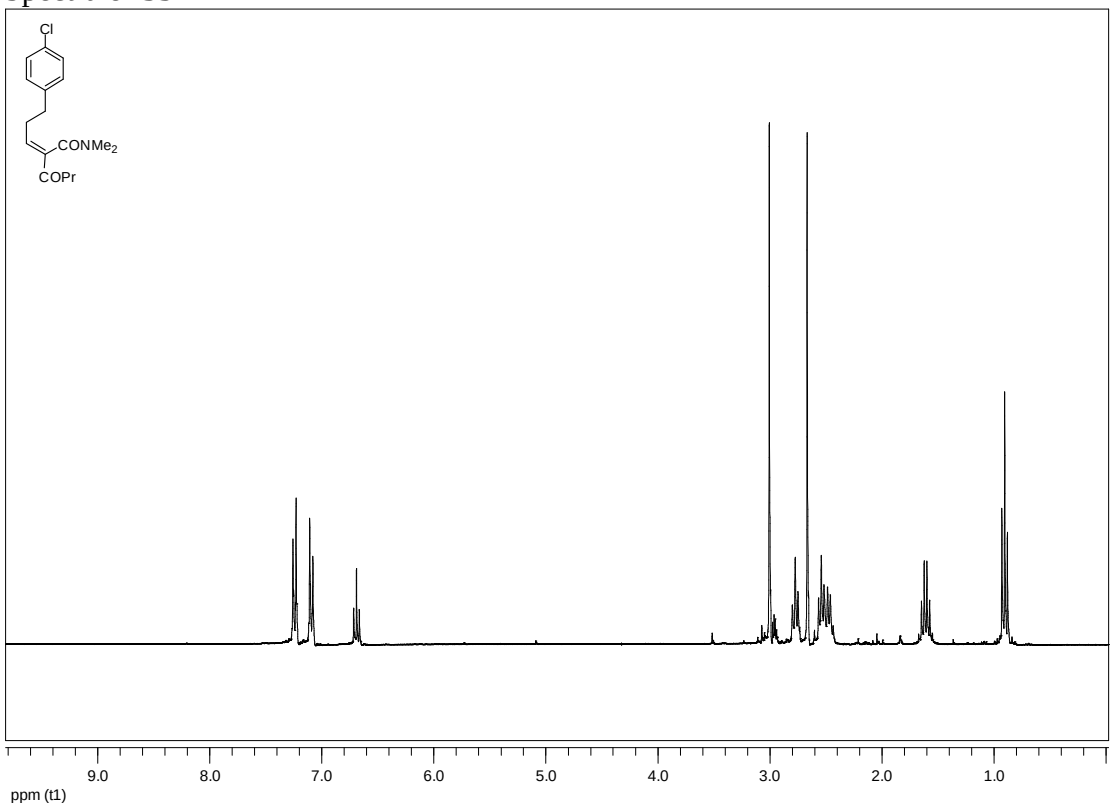

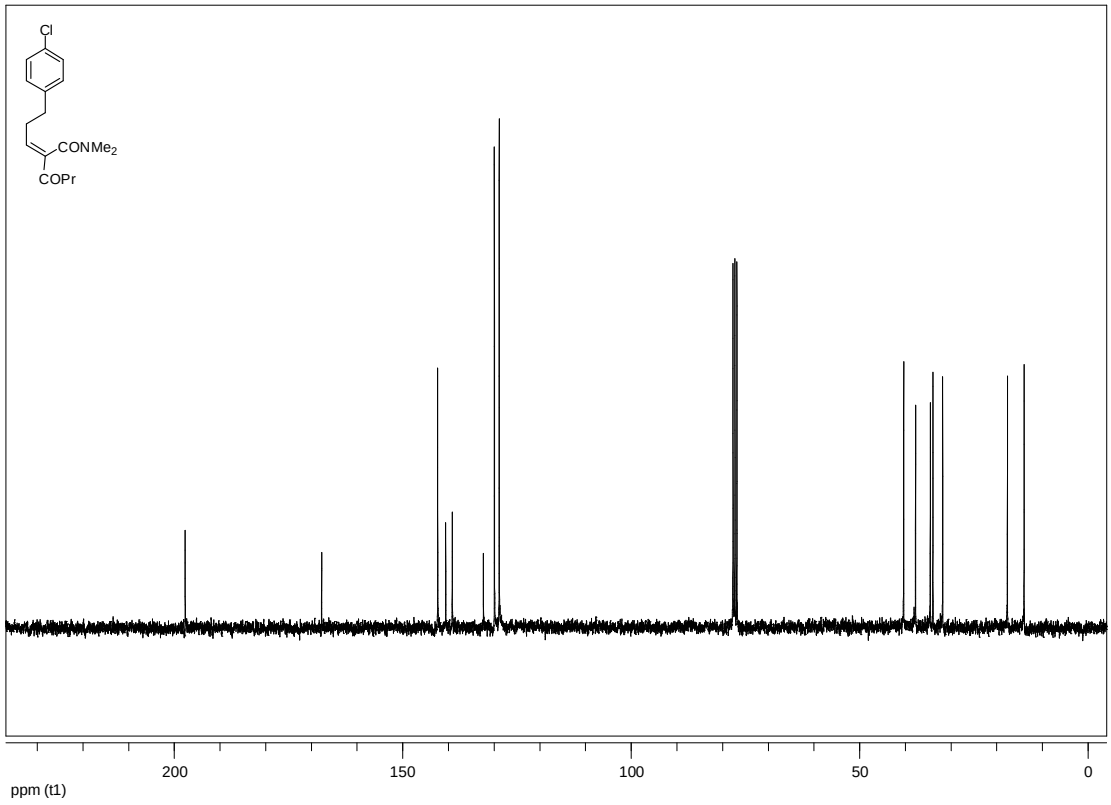

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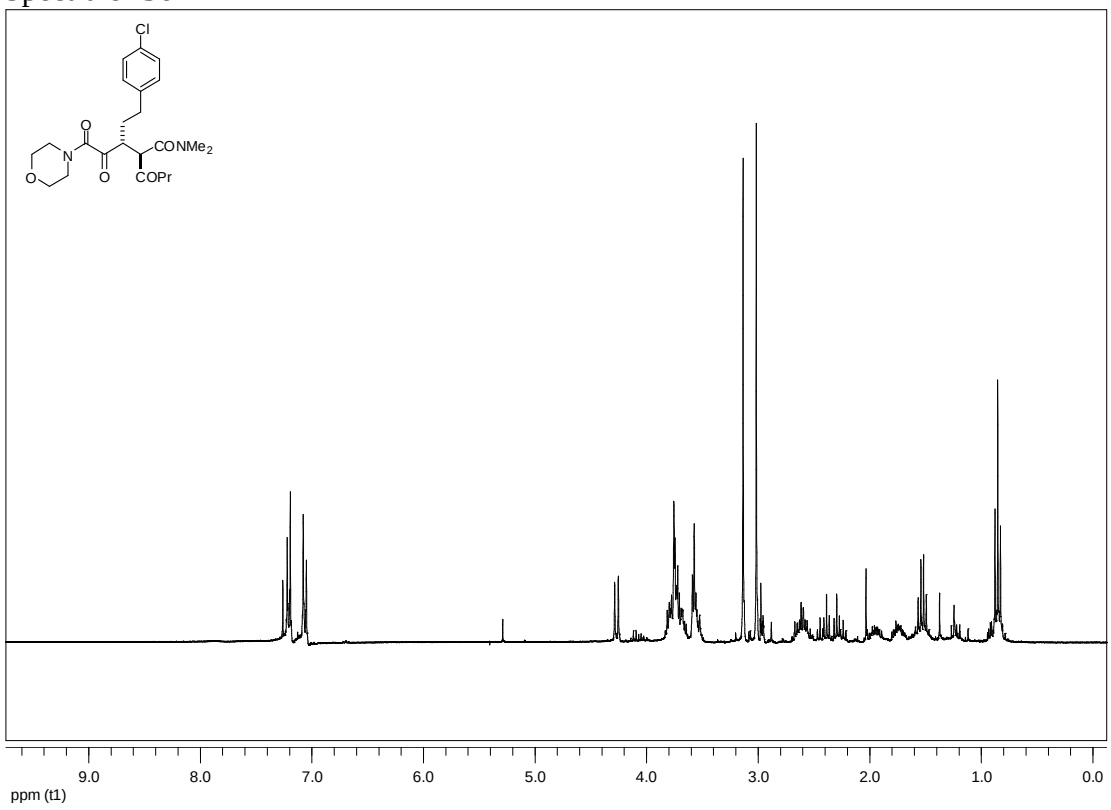

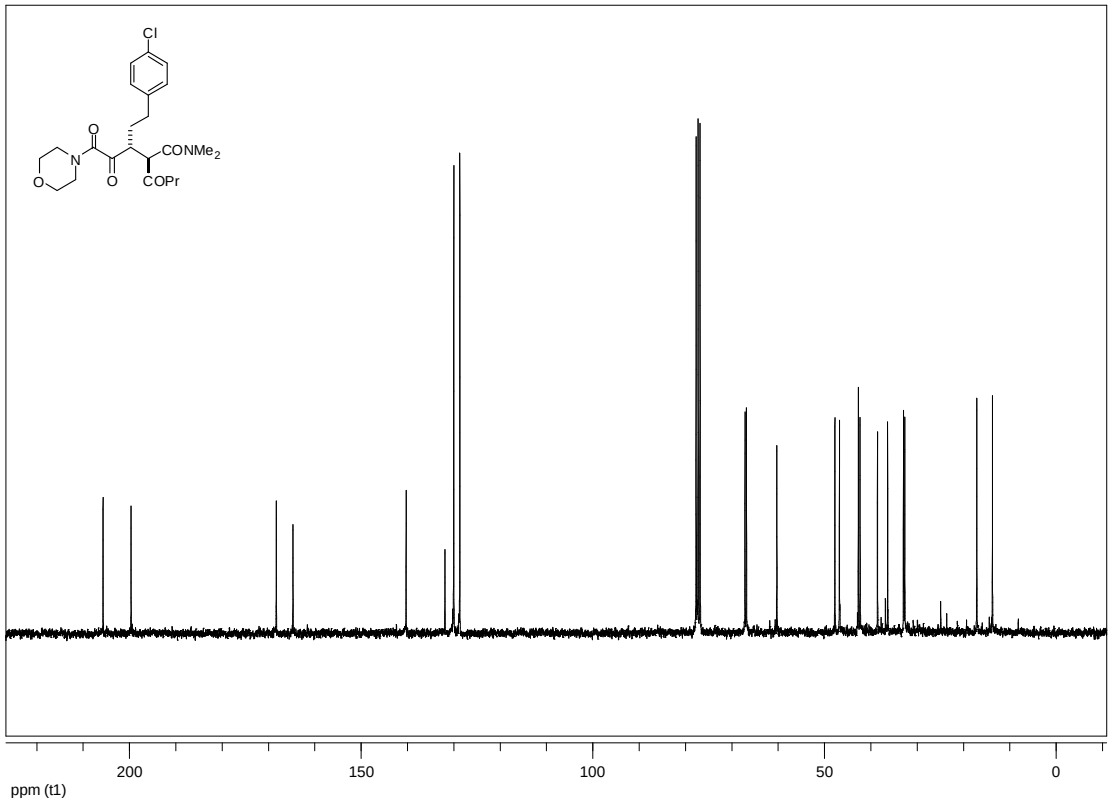

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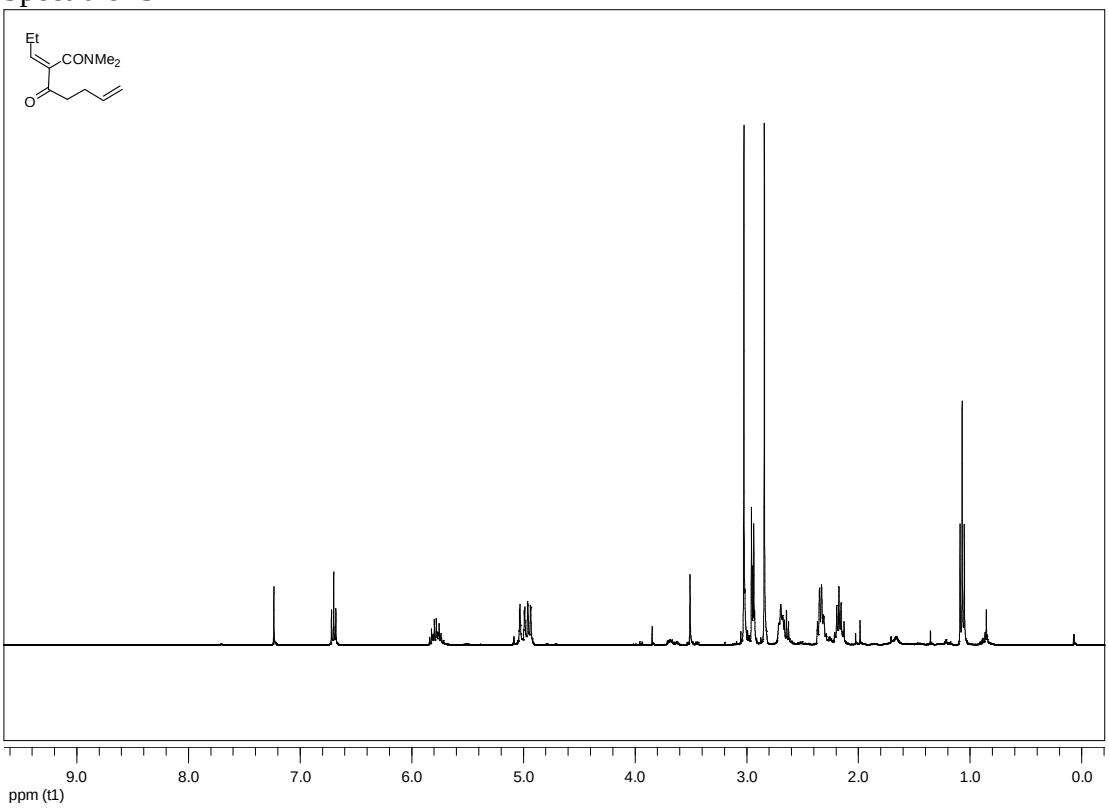

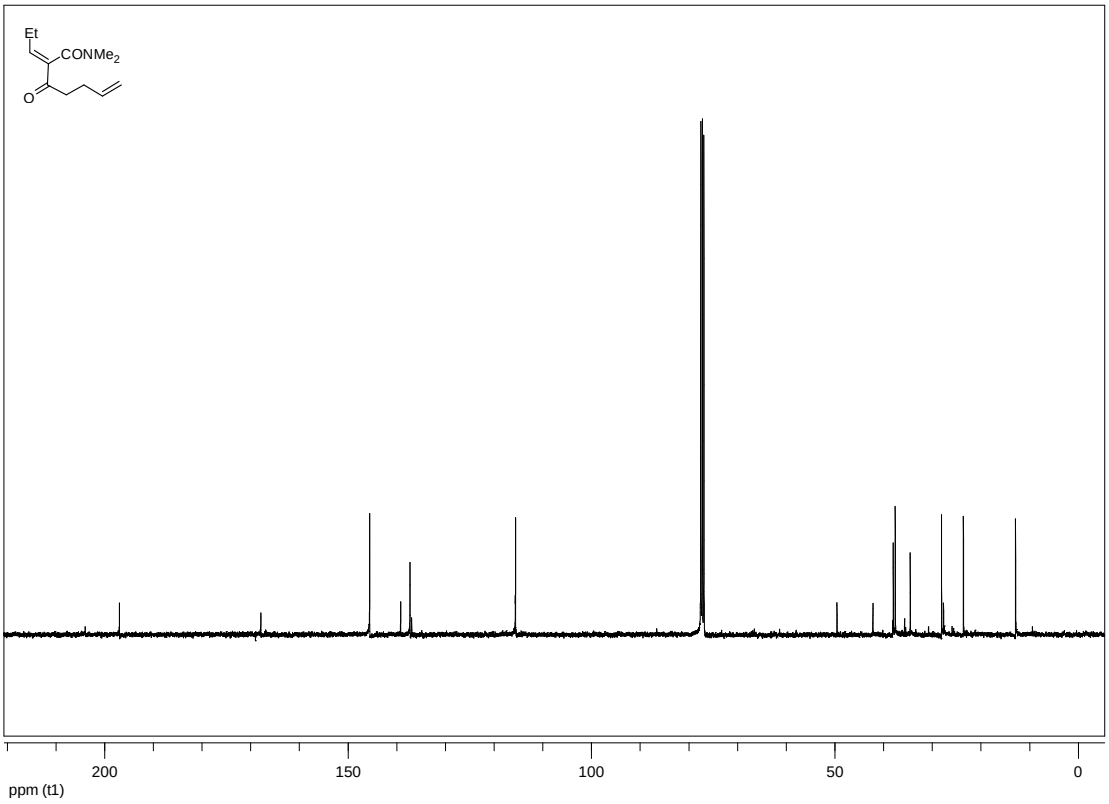

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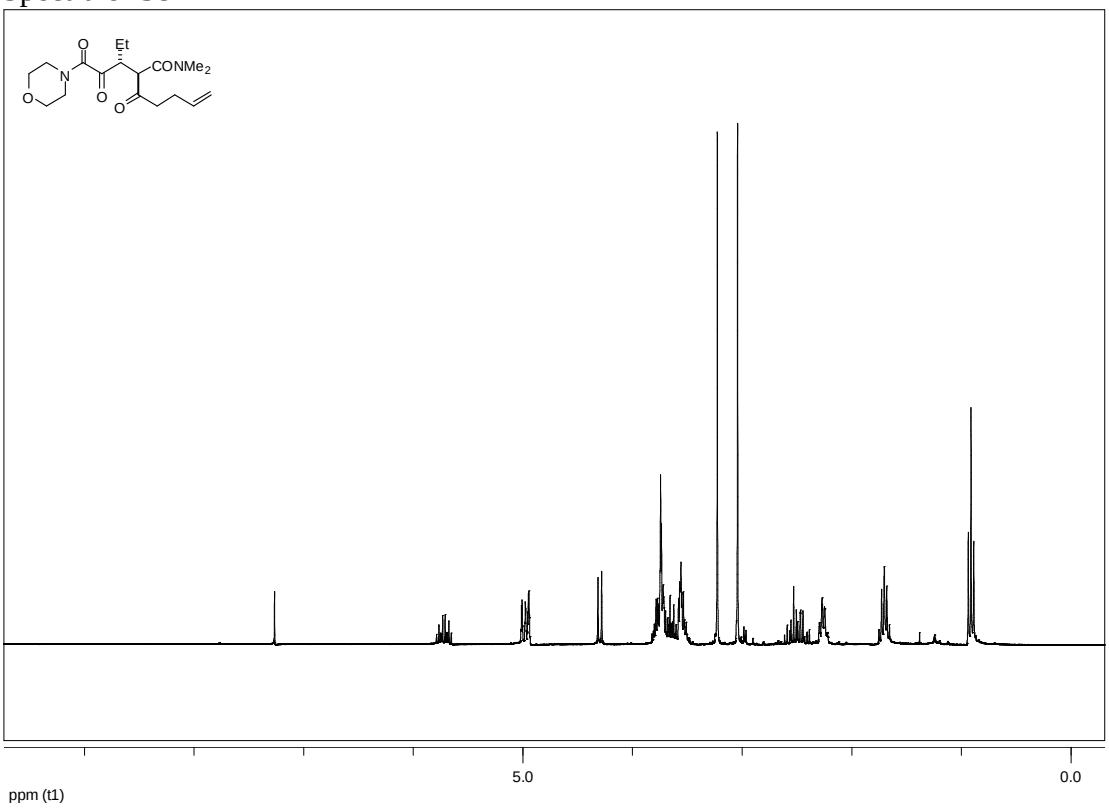

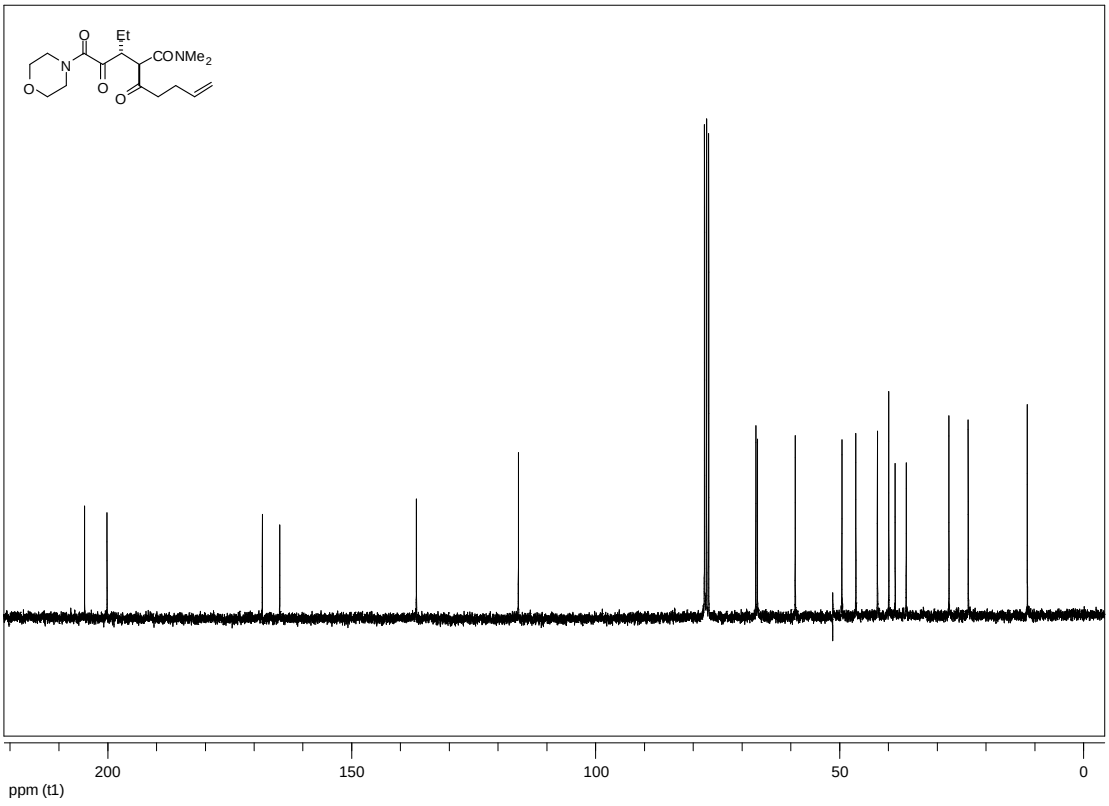

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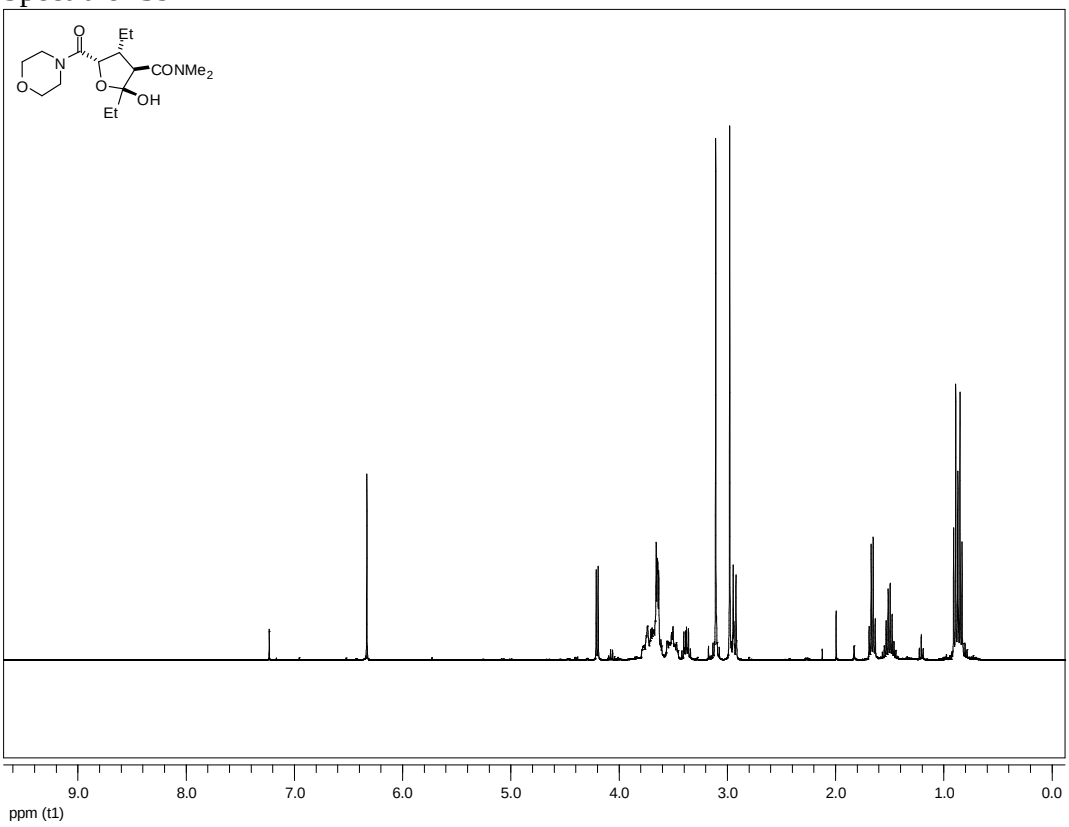

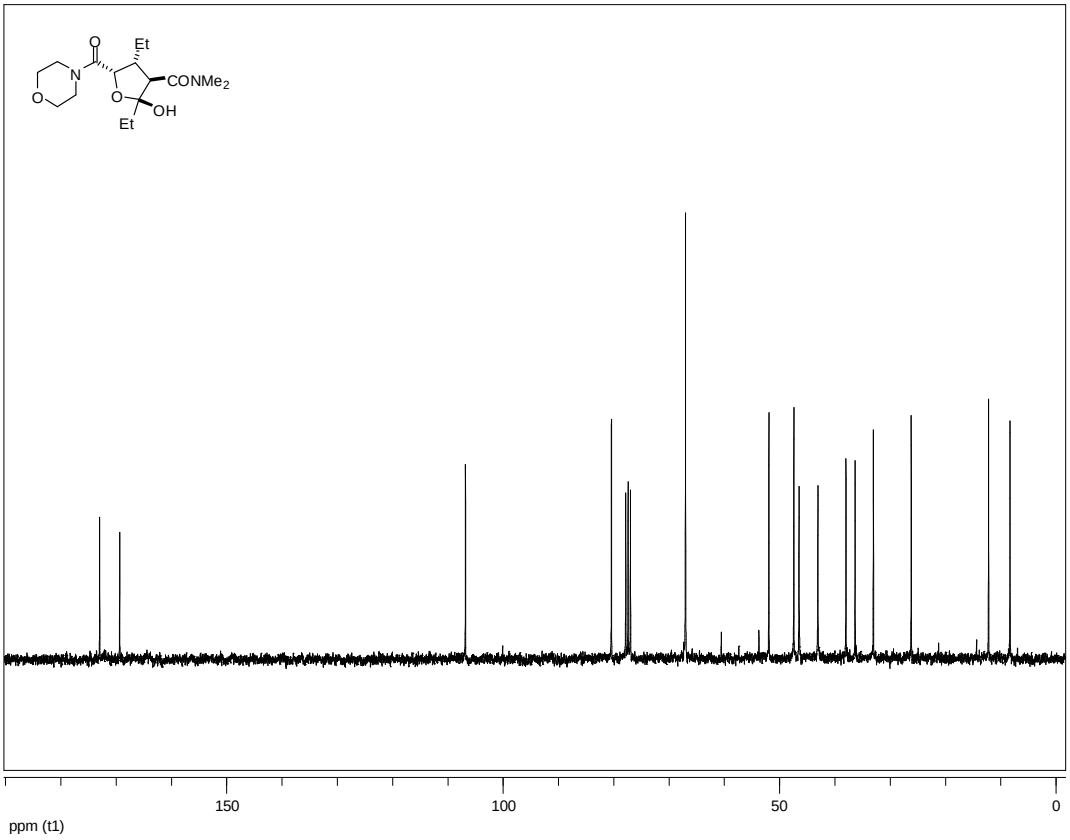

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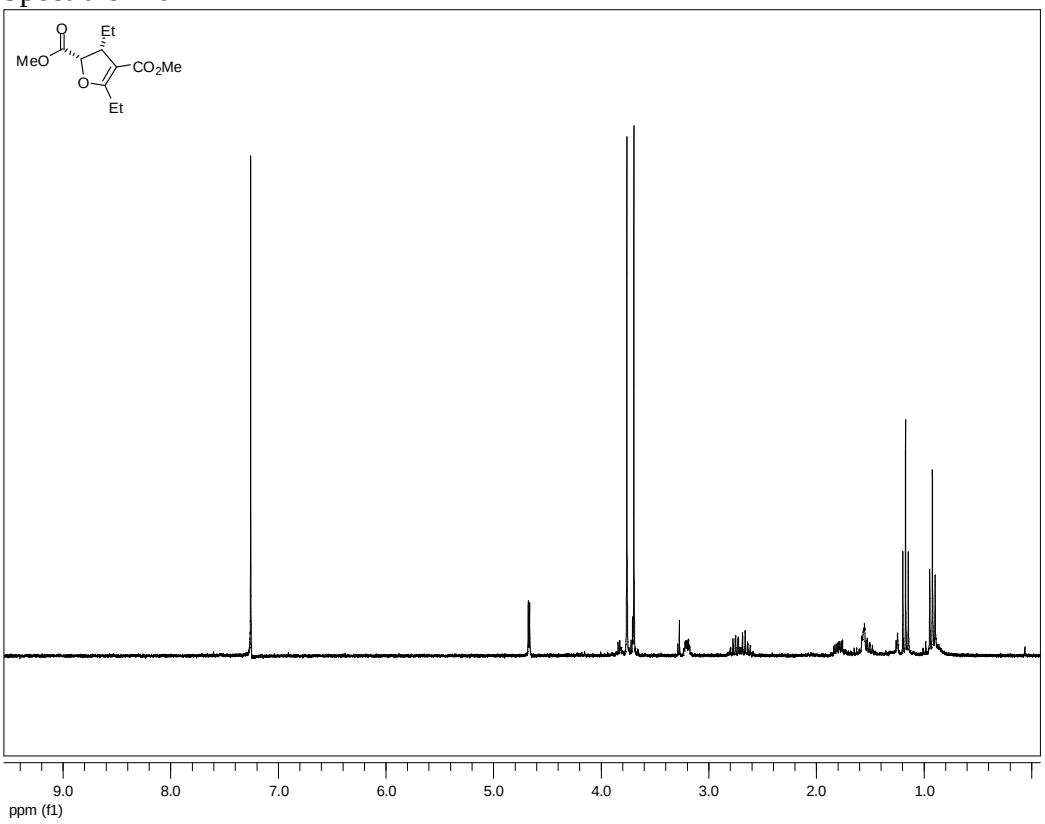

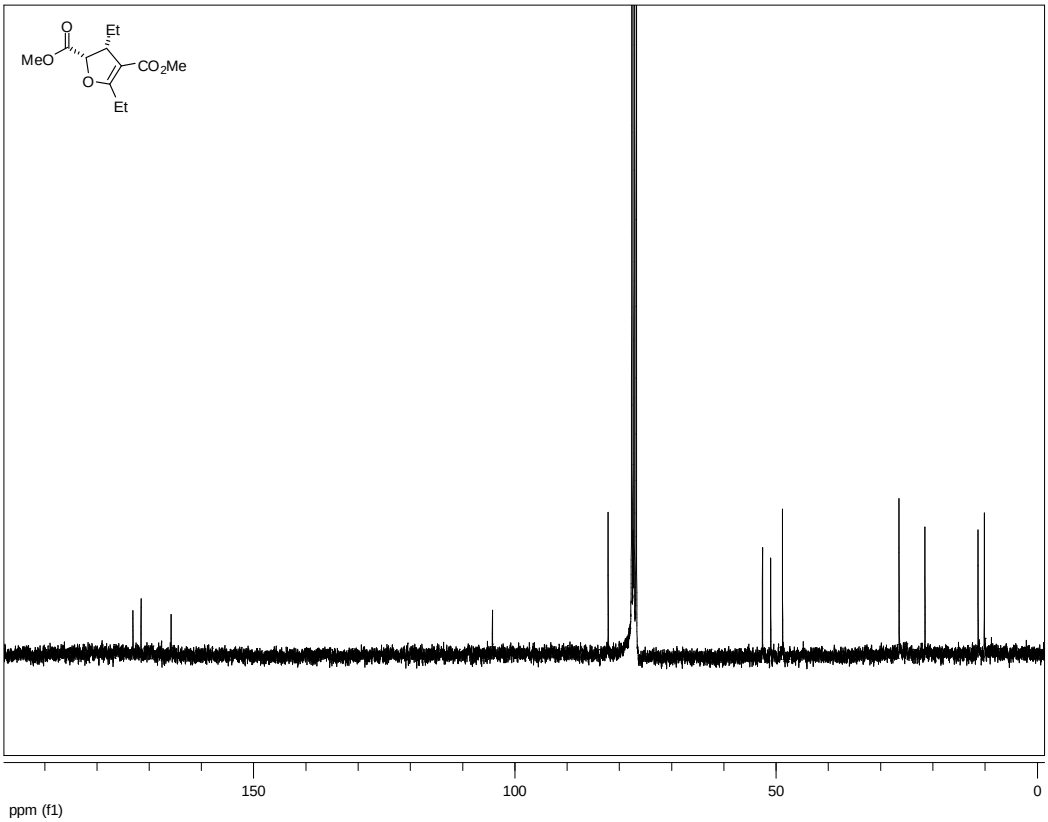

Spectra of **41**