# Supporting Information

*for*

# The Grob/Eschenmoser Fragmentation of Cycloalkanones Bearing β-Electron Withdrawing Groups: A General Strategy to Acyclic Synthetic Intermediates

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**Index**



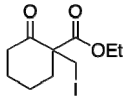
## I. General Procedures

For general experimental information as well as the synthesis and characterization of all new compounds see full paper.

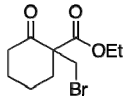
## II. Preparation of fragmentation precursors 1

**a.** Alkylation following the procedure of Beckwith[1] (**1a**, **1b**, **1d**, **1g**, **1j-l**, **1o**, **1p**)

NaH (48 mg of a 60% dispersion in mineral oil, 1.2 mmol) was washed twice with hexane, residual hexane removed under reduced pressure, and then suspended in dry DMSO (5 mL). A solution of β-ketoester (1.0 mmol) in dry DMSO (2.5 mL) was added dropwise and the resulting mixture stirred for 15 min or until gas development ceased. Then a solution of dihalomethane (2 mmol) in dry DMSO (2.5 mL) was added dropwise and the reaction mixture stirred at room temperature for 14 h. $H_2O$ (10 mL) was added and the product extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was purified *via* flash column chromatography.



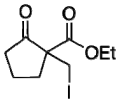

**Ethyl 1-(iodomethyl)-2-oxocyclohexanecarboxylate** (**1a**). $R_f$ 0.5 (1:3, v/v EtOAc:hexane); IR $\nu_{max}$ 2943, 2867, 1713, 1463, 1449, 1282, 1249, 1213, 1158, 1019; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.48-1.56 (m, 1H), 1.59-1.69 (m, 1H), 1.72-1.80 (m, 2H), 1.94-2.01 (m, 1H), 2.41 (dd, *J* = 9.0 Hz, 5.5 Hz, 2H), 2.57-2.63 (m, 1H), 3.29 (d, *J* = 10.5 Hz, 1H), 3.56 (d, *J* = 10.5 Hz, 1H), 4.14-4.25 (m, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 8.60, 14.18, 22.32, 27.43, 37.24, 40.85, 60.72, 62.03, 168.95, 205.32.



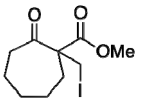

**Ethyl 1-(bromomethyl)-2-oxocyclohexanecarboxylate** (**1b**). $R_f$ 0.6 (3:7, v/v EtOAc:hexane); IR $\nu_{max}$ 2952, 2868, 1714, 1438, 1286, 1267, 1240, 1197, 1175; $^{1}$H-

[1] A. L. J. Beckwith, D. M. O'Shea and S. W. Westwood, *J. Am. Chem. Soc.*, 1988, **110**, 2565.

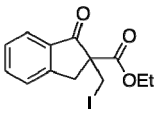
NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.53-1.61 (m, 1H), 1.62-1.80 (m, 1H), 1.87-1.98 (m, 2H), 2.01-2.07 (m, 1H), 2.41-2.45 (m, 2H), 2.67 (dq, *J* = 14.0 Hz, 3.5 Hz, 1H), 3.50 (d, *J* = 11.0 Hz, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 4.15-4.28 (m, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 14.81, 22.22, 27.42, 35.41, 35.60, 41.02, 61.54, 62.08, 168.99, 205.64.



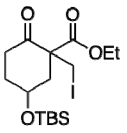
**Ethyl 1-(iodomethyl)-2-oxocyclopentanecarboxylate** (**1g**). $R_f$ 0.5 (1:3, v/v EtOAc:hexane); IR $\nu_{max}$ 2979, 2904, 1754, 1725, 1446, 1277, 1233, 1206, 1183, 1122, 1026; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.93-2.02 (m, 1H), 2.03-2.12 (m, 2H), 2.29-2.38 (m, 1H), 2.42-2.49 (m, 1H), 2.55-2.62 (m, 1H), 3.33 (d, *J* = 10.0 Hz, 1H), 3.57 (d, *J* = 10.0 Hz, 1H), 4.11-4.23 (m, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 7.21, 14.13, 19.18, 34.78, 38.13, 60.95, 62.19, 168.37, 211.00.



**Methyl 1-(iodomethyl)-2-oxocycloheptanecarboxylate** (**1j**). $R_f$ 0.7 (4:1, v/v $CH_2Cl_2$:hexane); IR $\nu_{max}$ 2934, 2859, 1740, 1709, 1454, 1267, 1235, 1192, 1163, 1143; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.29-1.38 (m, 1H), 1.54-1.63 (m, 3H), 1.70-1.78 (m, 2H), 1.98 (ddd, *J* = 15.0 Hz, 9.5 Hz, 1.5 Hz, 1H), 2.25 (ddt, *J* = 15.0 Hz, 9.5 Hz, 1.0 Hz, 1H), 2.43-2.49 (m, 1H), 2.65-2.71 (m, 1H), 3.29 (d, *J* = 10.5 Hz, 1H), 3.72 (s, 3H), 3.75 (dd, *J* = 10.5 Hz, 1.0 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 9.83, 24.58, 25.78, 29.91, 33.31, 42.04, 52.97, 63.92, 170.08, 206.39.



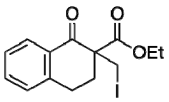
**Ethyl 2-(iodomethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate** (**1l**). $R_f$ 0.7 ($CH_2Cl_2$); IR $\nu_{max}$ 3036, 2980, 2936, 1714, 1607, 1589, 1465, 1417, 1251, 1209; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.0 Hz, 3H), 3.25 (d, *J* = 17.5 Hz, 1H), 3.53 (d, *J* = 10.0 Hz, 1H), 3.80 (d, *J* = 17.5 Hz, 1H), 3.82 (d, *J* = 10.0 Hz, 1H), 4.14-4.22 (m, 2H), 7.40 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.51 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.65 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 7.70, 14.11, 39.11, 61.34, 62.48, 125.32, 126.53, 128.11, 134.70, 135.96, 152.90, 168.34, 198.94; HRMS Found $(M+H)^+$ 344.9982, $C_{13}H_{13}IO_3$ requires $(M+H)^+$ 344.9988.



**Ethyl 5-(*tert*-butyldimethylsilyloxy)-1- (iodomethyl)-2- oxocyclohexanecarb-oxylate** (**1p**). $R_f$ 0.7 ($CH_2Cl_2$); IR $\nu_{max}$ 2954, 2930, 2857, 1737, 1721, 1472, 1464, 1257, 1099; $^1$H-NMR (400 MHz, $CDCl_3$) δ *diastereomer 1*: 0.11 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.66-2.72 (m, 7H), 3.40 (d, *J* = 10.0 Hz, 1H), 3.64 (d, *J* = 10.0 Hz, 1H), 4.18-4.25 (m, 2H) *diastereomer 2*: 0.08 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.66-2.72 (m, 6H), 3.12 (td, *J* = 14.0 Hz, 6.0 Hz, 1H), 3.29 (d, *J* = 10.0 Hz, 1H), 3.49 (d, *J* = 10.0 Hz, 1H), 4.18-4.25 (m, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ *diastereomer 1*: -4.76, -4.52, 8.93, 14.25, 18.22, 25.97, 35.16, 37.30, 44.02, 59.85, 62.40, 66.69, 168.98, 203.94 *diastereomer 2*: -4.98, 7.83, 14.09, 18.42, 25.97, 34.46, 35.52, 44.65, 57.34, 62.04, 65.78, 169.73, 205.56; HRMS Found $(M+H)^+$ 441.0950, $C_{16}H_{29}IO_4Si$ requires $(M+H)^+$ 441.0958; found $(M+Na)^+$ 463.0769, requires $(M+Na)^+$ 463.0777.

**b.** Alkylation following the procedure of Mu[2] (**1f**, **1m**)

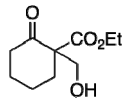
The 1,3-dicarbonyl (1.0 mmol), anhydrous potassium carbonate (276 mg, 2.0 mmol) and tetrabutylammonium bromide (129 mg, 0.4 mmol) were refluxed in dry toluene (5 mL) for 5 h. The reaction mixture was cooled to 40°C, dihaloalkane (1.1 mmol) was added and the mixture stirred for 2 h at 40°C followed by another 2 h at reflux. After cooling to room temperature the reaction mixture was filtered, the filter cake washed with $Et_2O$ (5 mL) and the filtrate concentrated under reduced pressure. The resultant oil was purified *via* flash column chromatography.



**Ethyl 2-(iodomethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate** (**1m**). $R_f$ 0.4 (1:4, v/v EtOAc: hexane); IR $\nu_{max}$ 2980, 2936, 1731, 1682, 1601, 1454, 1293, 1235, 1201, 1016; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.0 Hz, 3H), 2.39 (ddd, *J* = 14.0 Hz, 9.0 Hz, 5.0 Hz, 1H), 2.65 (ddd, *J* = 14.0 Hz, 6.0 Hz, 5.0 Hz, 1H), 2.96 (dt, *J* = 17.0 Hz, 5.0 Hz, 1H), 3.14 (ddd, *J* = 17.0 Hz, 9.0 Hz, 5.0 Hz, 1H), 3.66 (d, *J* = 10.4 Hz, 1H), 3.72 (d, *J* = 10.4 Hz, 1H), 4.16-4.22 (m, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.49 (dt, 7.6 Hz, 1.2 Hz, 1H) 8.03 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 7.49, 14.14, 25.49, 32.65, 57.65, 62.15, 127.10, 128.34, 128.96, 131.32, 134.09, 143.10, 168.95, 192.37.

**c.** Synthesis of Mesylates **1c** and **1e**[3]

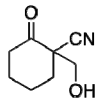
To a solution of $Fe(acac)_3$ (35 mg, 0.1 mmol) and benzaldehyde (20 μL, 0.2 mmol) in dry MeOH (2.5 mL) was slowly added $H_2O_2$ (170 μL of a 30% solution, 1.5 mmol) at 0°C. The resulting red-brown mixture was stirred for 40 min at room temperature, then the respective ketone (1.0 mmol) was added and the solution stirred for 3-15 h. Hydrolysis with $NaHCO_3$ (10 mL of a saturated aqueous solution) was followed by extraction of the product with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The resultant oil was purified immediately *via* flash column chromatography. To a solution of the thus prepared alcohol (1.0 mmol), $NEt_3$ (167 μL, 1.2 mmol) and DMAP (12 mg, 0.1 mmol) in $CH_2Cl_2$ (5 mL) at 0°C was added methanesulfonyl chloride (93 μL, 1.2 mmol). The mixture was stirred for 30 min at 0°C followed by 2 h at room temperature. Evaporation of the solvent and column chromatography (EtOAc:hexane) yielded pure mesylate.



**Ethyl 1-(hydroxymethyl)-2-oxocyclohexanecarboxylate**. $R_f$ 0.1 (1:4, v/v EtOAc:hexane); IR $\nu_{max}$ 3536, 2941, 2870, 1709, 1451, 1205, 1026; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.55-1.66 (m, 2H), 1.76-1.80 (m, 1H), 1.98-2.05 (m, 1H), 2.31-2.35 (m, 1H), 2.40-2.46 (m, 1H), 2.56-2.65 (m, 1H), 2.81-2.85 (m, 1H), 3.69 (dd, *J* = 11.0

[2] X.-J. Mu, J.-P. Zou, Z.-T. Wang and W. Zhang, *Tetrahedron Lett.*, 2005, **46**, 4727.
[3] Alkylation: V. Lecomte and C. Bolm, *Adv. Synth. Catal.*, 2005, **347**, 1666.

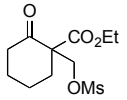
Hz, 9.0 Hz, 1H), 3.80 (dd, *J* = 11.0 Hz, 4.5 Hz, 1H), 4.23 (qd, *J* = 7.0 Hz, 1.0 Hz, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 14.22, 22.08, 27.05, 32.91, 41.08, 61.73, 62.71, 66.52, 171.32, 210.76.

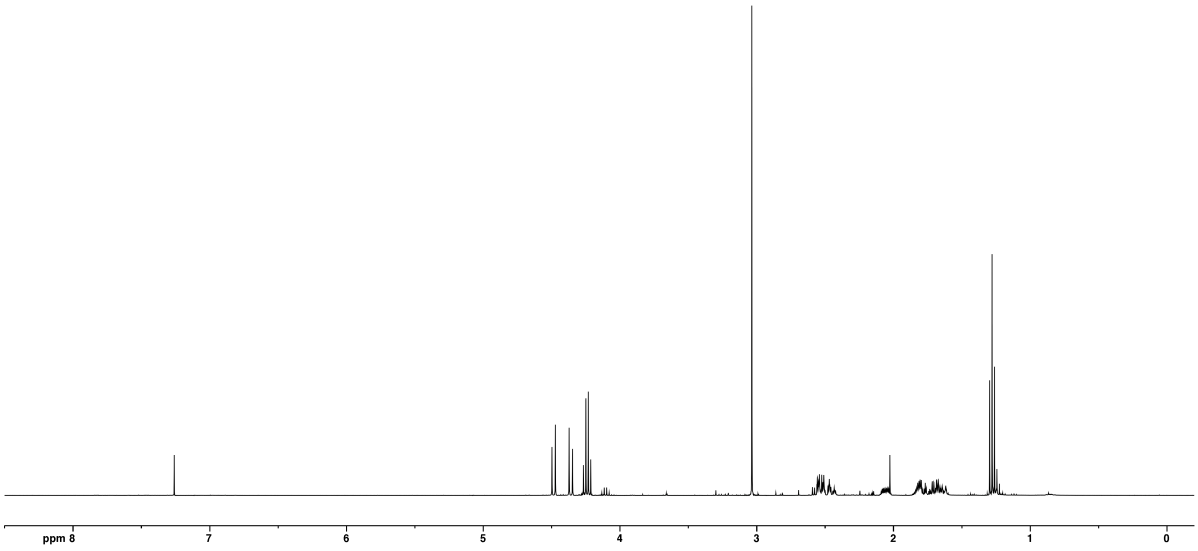


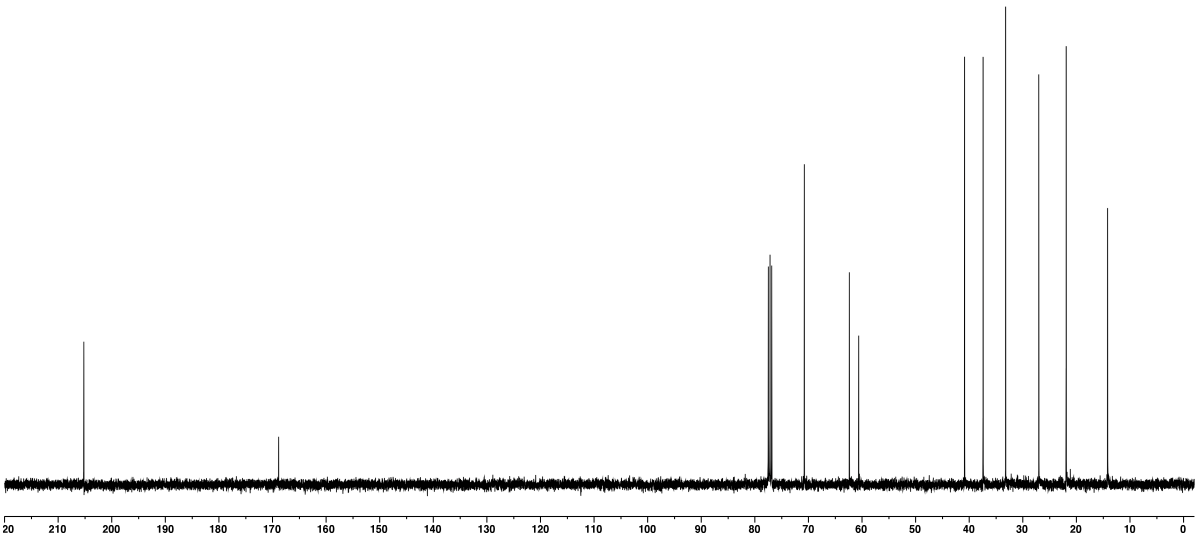

**1-(Hydroxymethyl)-2-oxocyclohexanecarbonitrile**. $R_f$ 0.2 (3:7, v/v EtOAc: hexane); IR $\nu_{max}$ 3444, 2948, 2871, 2247, 1727, 1715, 1061; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.66-1.77 (m, 1H), 1.78-1.86 (m, 1H), 1.88-1.93 (m, 1H), 2.02-2.08 (m, 1H), 2.10-2.17 (m, 1H), 2.24-2.30 (m, 1H), 2.44-2.49 (m, 1H), 2.75-2.83 (m, 1H), 2.86 (br t, *J* = 7.0 Hz 1H), 3.80 (dd, *J* = 11.5 Hz, 7.0 Hz, 1H), 3.87 (dd, *J* = 11.5 Hz, 7.0 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 21.79, 27.61, 34.69, 39.62, 53.00, 64.03, 118.58, 204.42.

## III. $^{1}H$ and $^{13}C$ NMR of new compounds

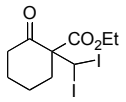
### Ethyl 1-(((methylsulfonyl)oxy)methyl)-2-oxocyclohexanecar-boxylate (1c)

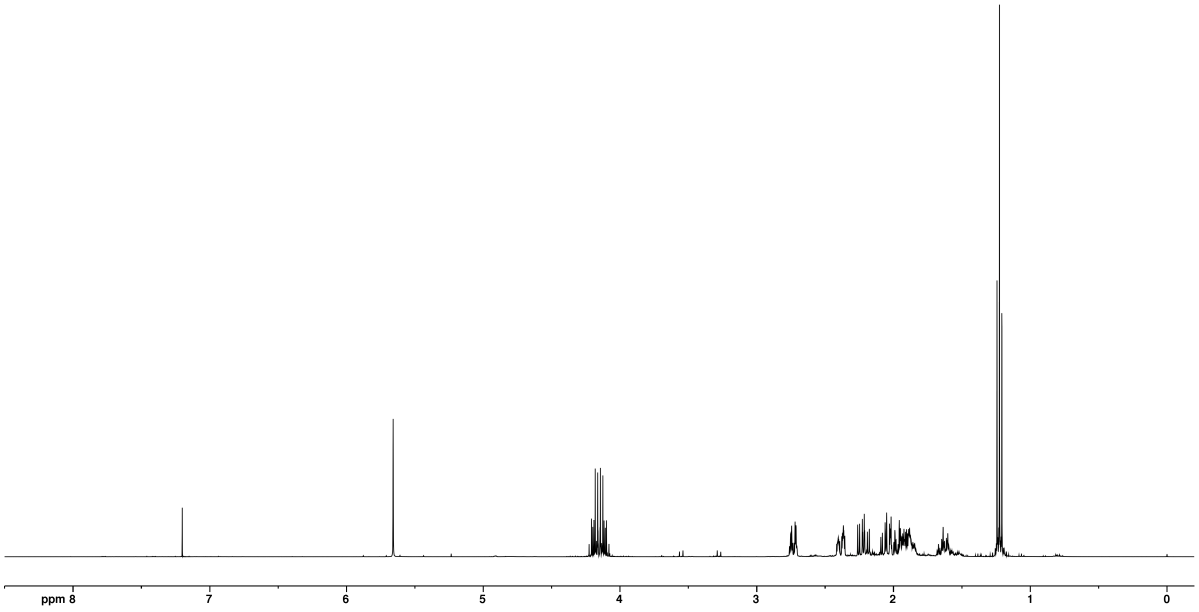


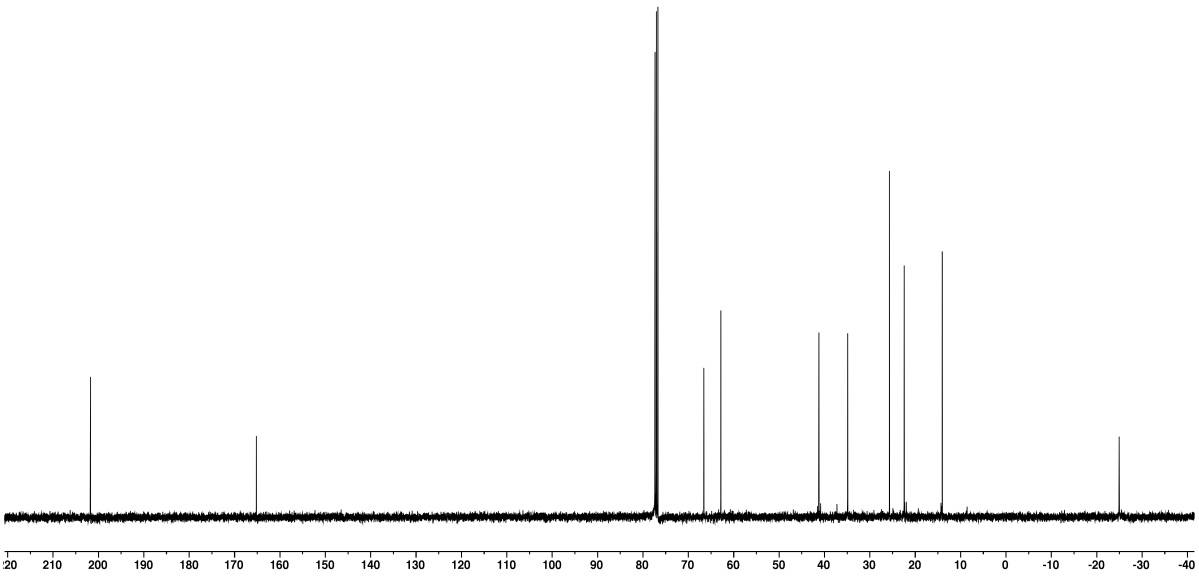



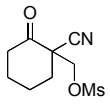
**Ethyl 1-(diiodomethyl)-2-oxocyclohexanecarboxylate** (**1d**)

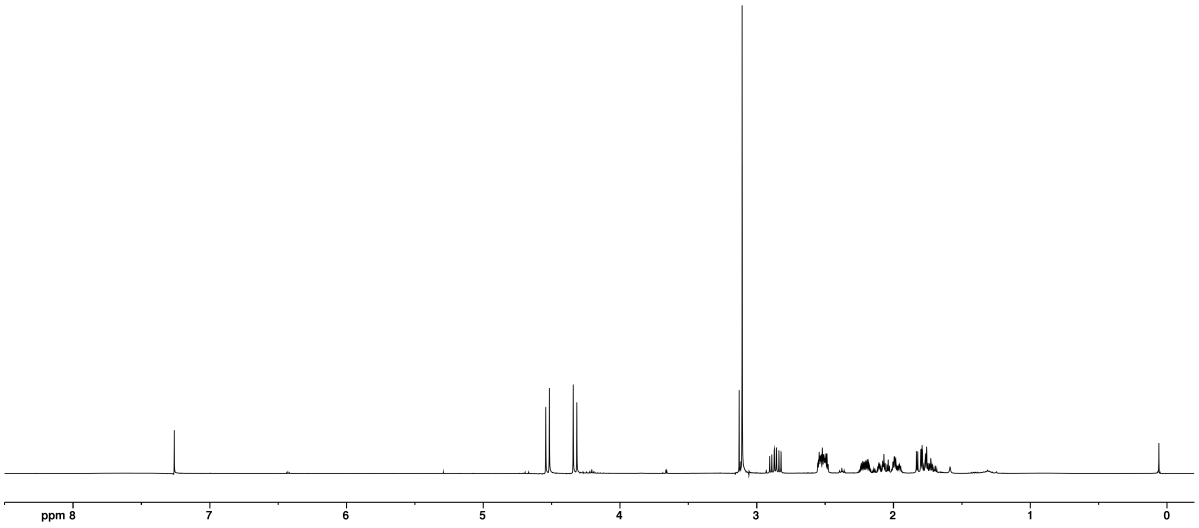


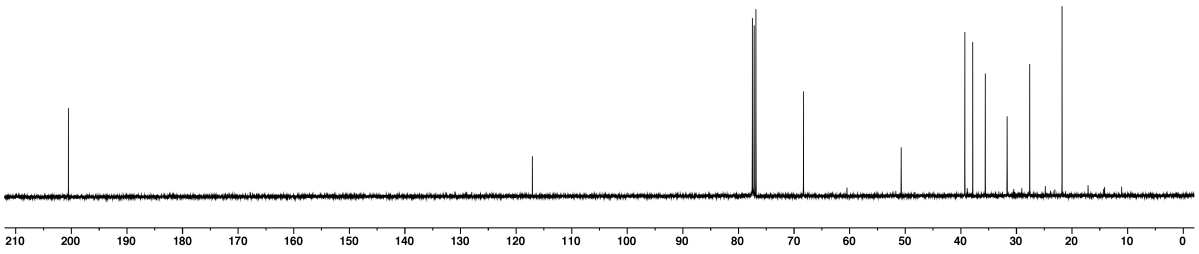



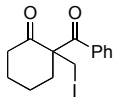
**(1-Cyano-2-oxocyclohexyl)methyl methanesulfonate** (**1e**)

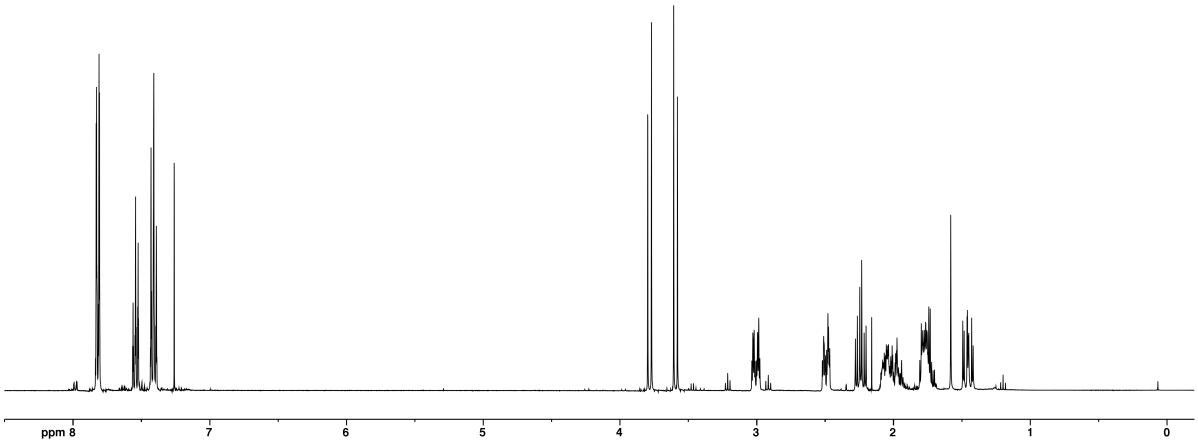


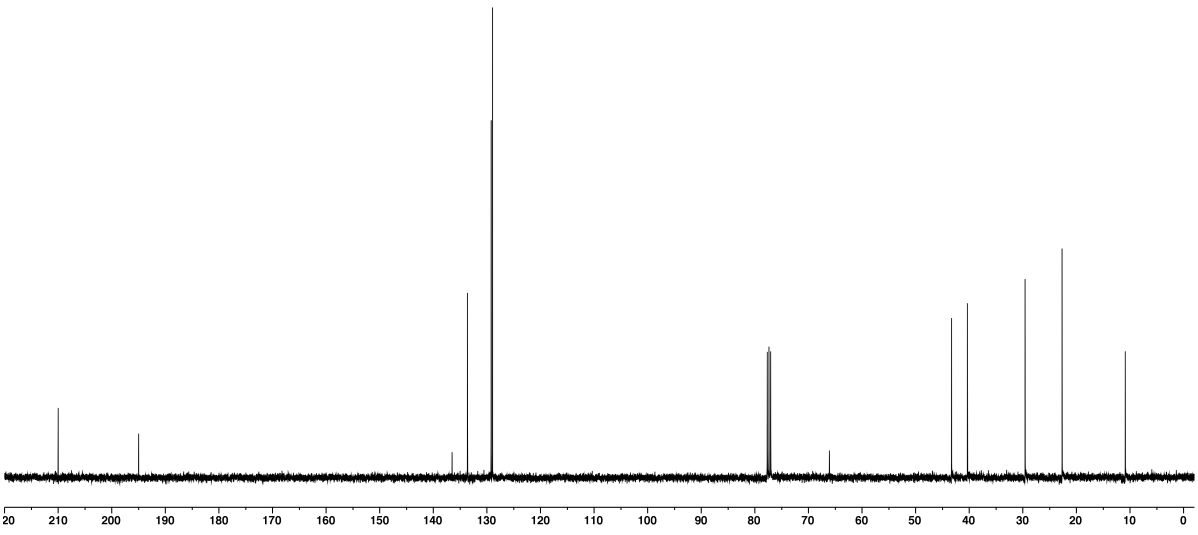



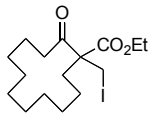
**2-Benzoyl-2-(iodomethyl)cyclohexanone** (**1f**)

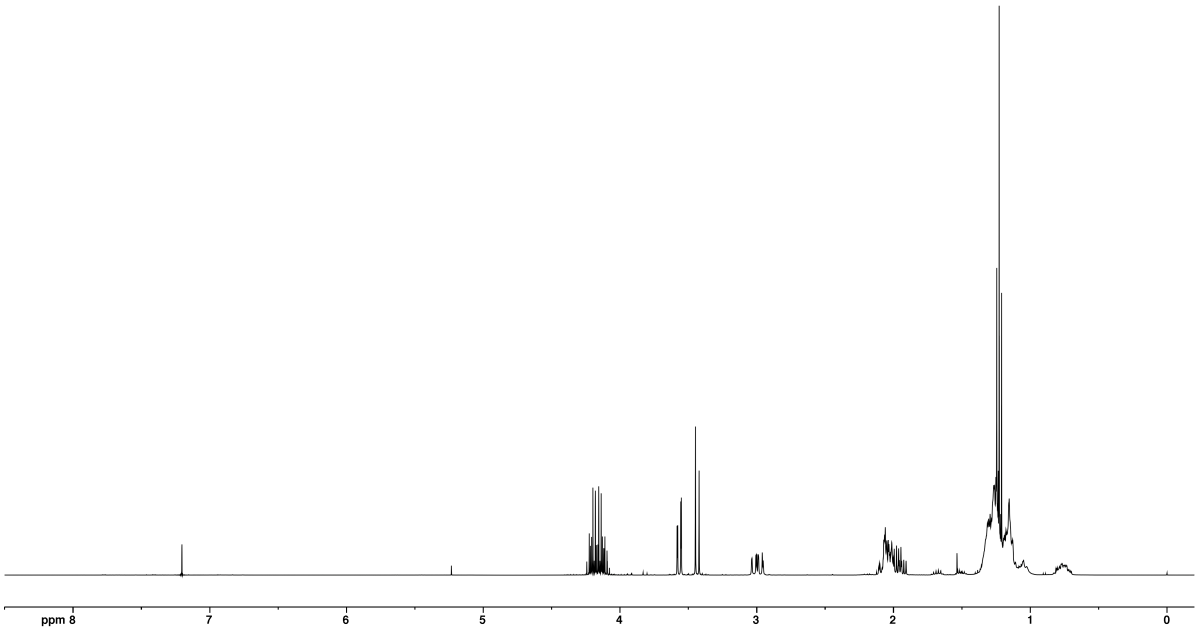


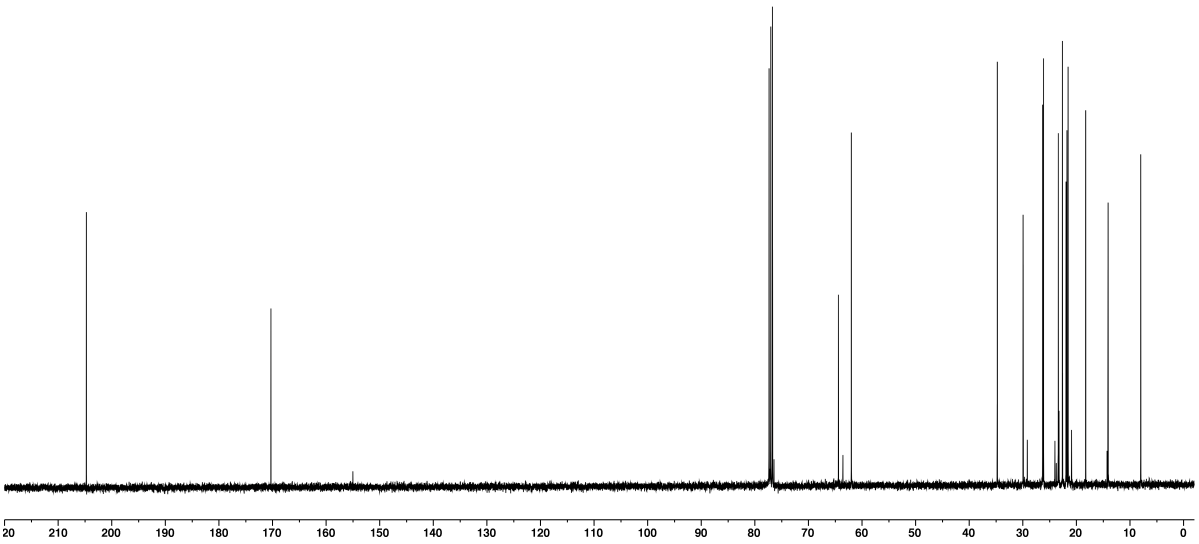



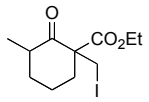
**Ethyl 1-(iodomethyl)-2-oxocyclododecanecarboxylate (1k)**

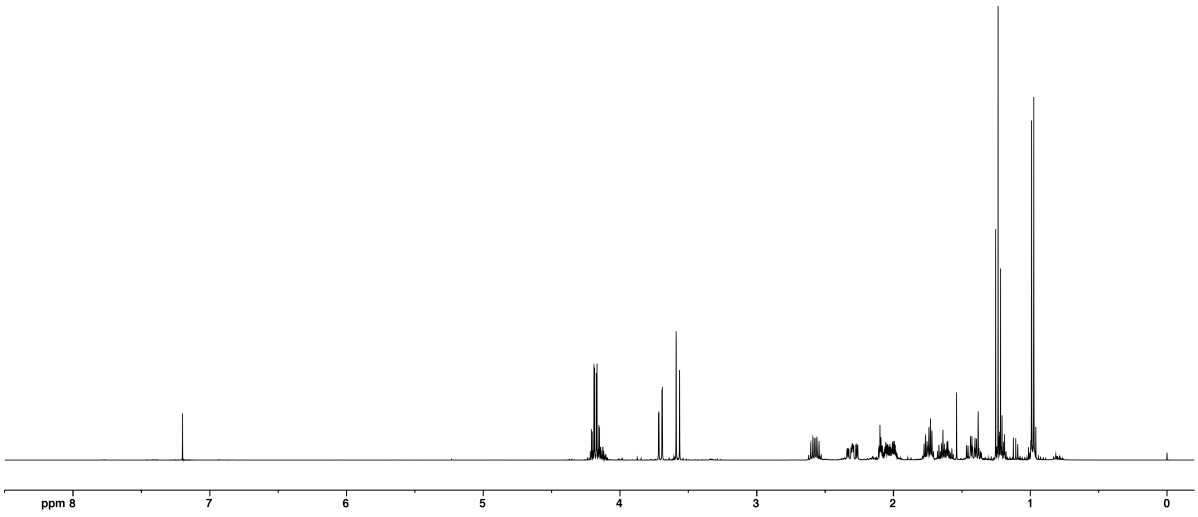


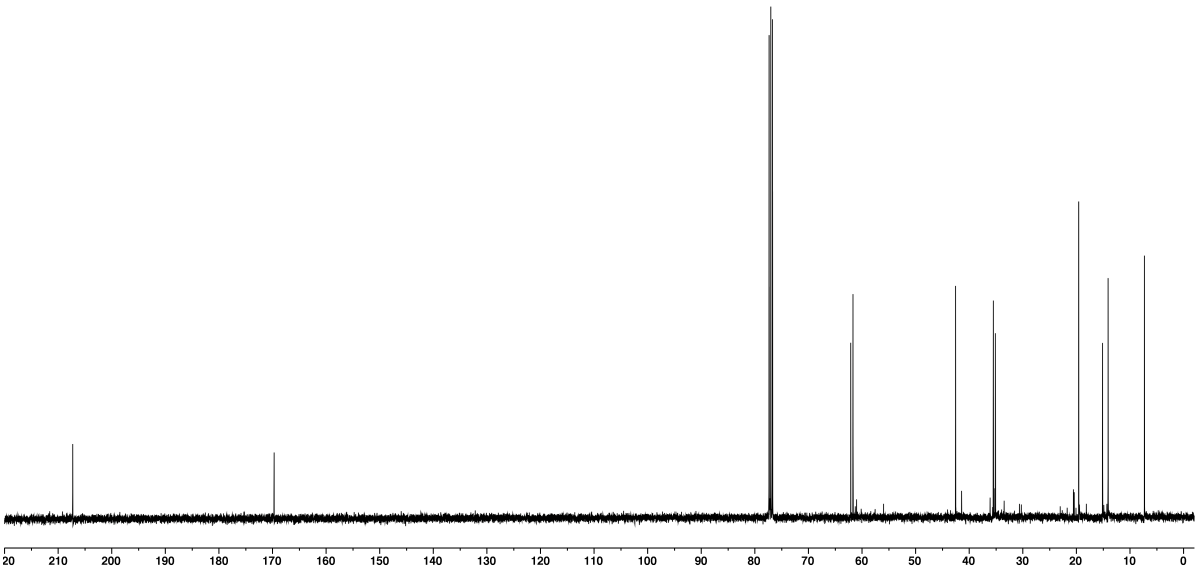



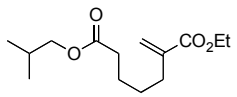
**Ethyl 1-(iodomethyl)-3-methyl-2-oxocyclohexanecarboxylate (1o)**

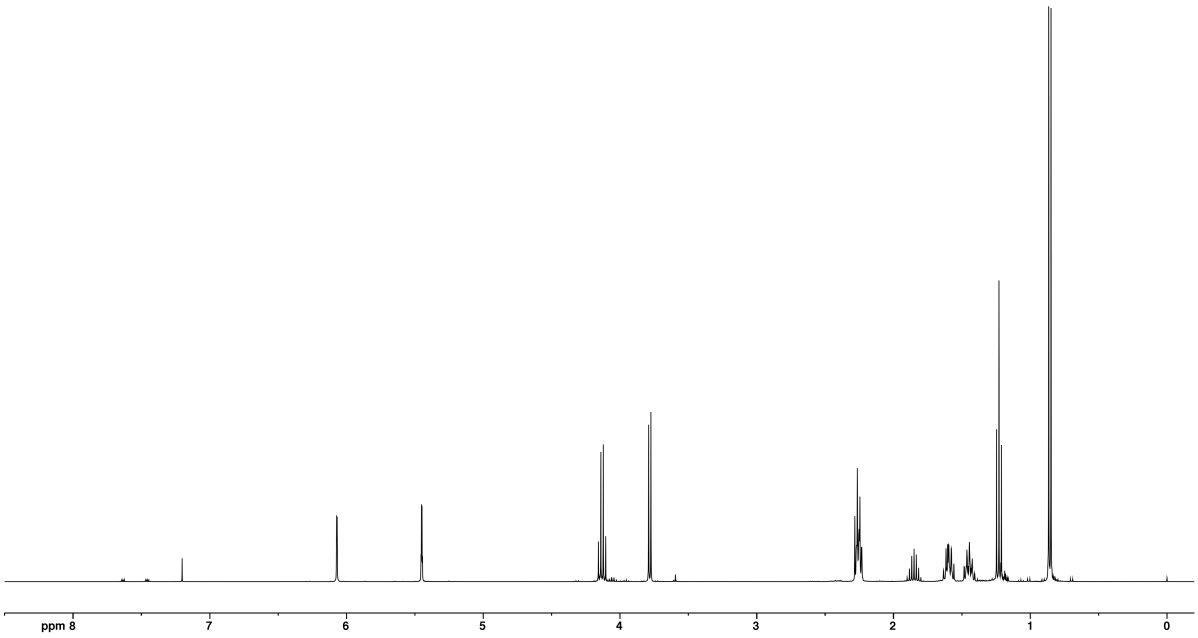


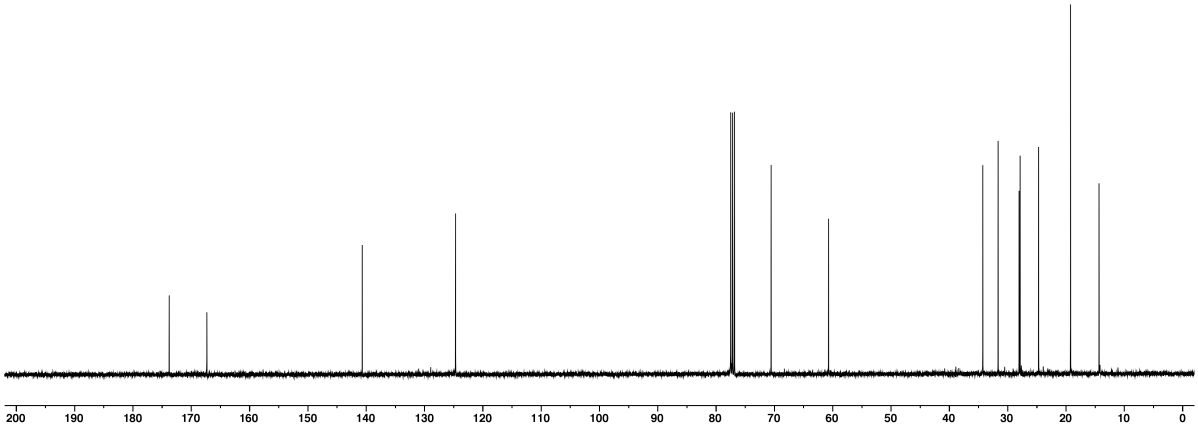



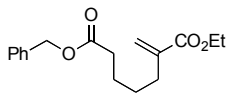
**1-Ethyl 7-isobutyl 2-methyleneheptanedioate** (**5a**, Table 2, entry 1)

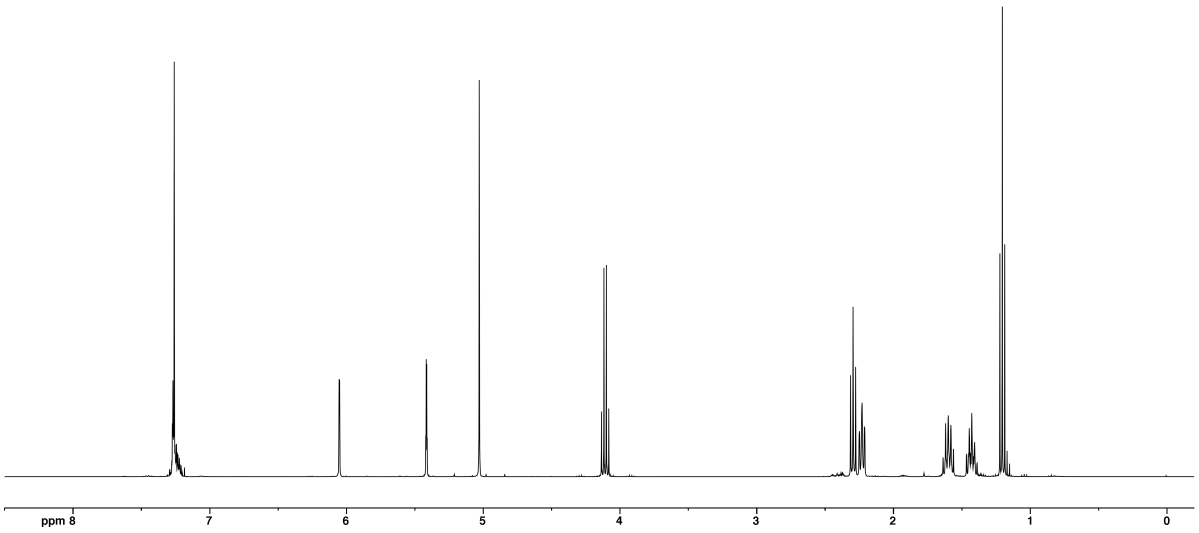


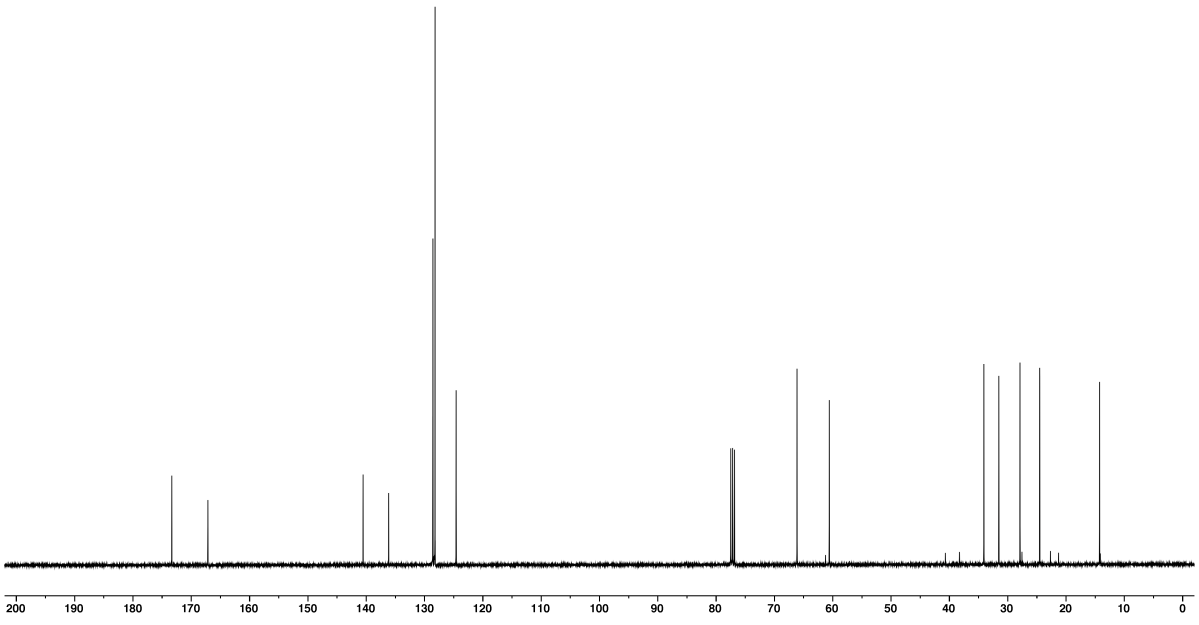



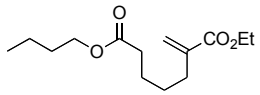
**1-Benzyl 7-ethyl 2-methyleneheptanedioate** (**5a**, Table 2, entry 2)

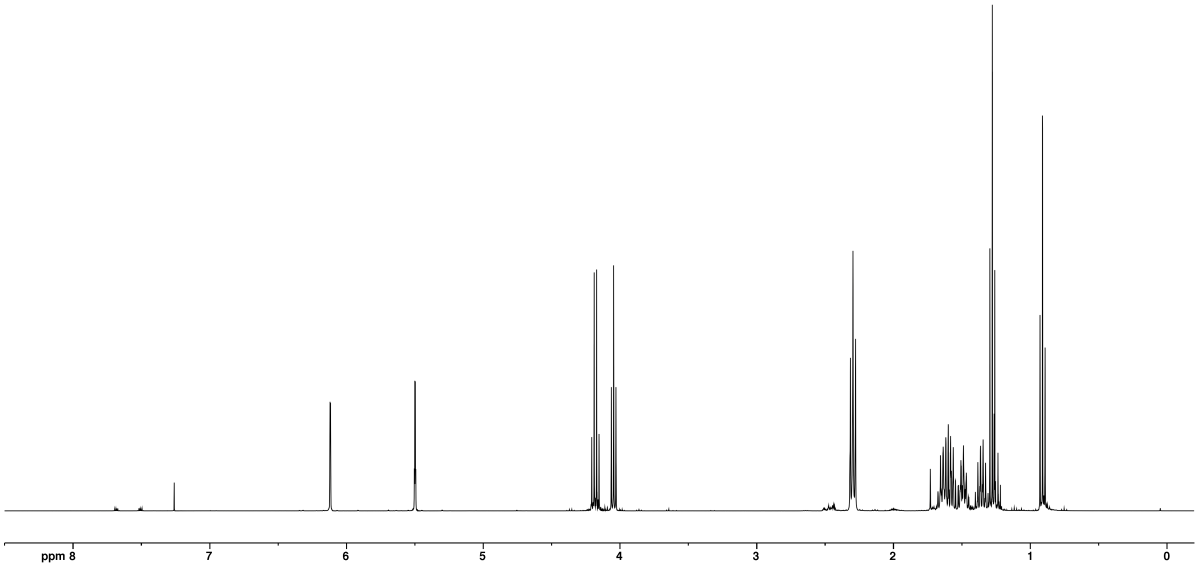


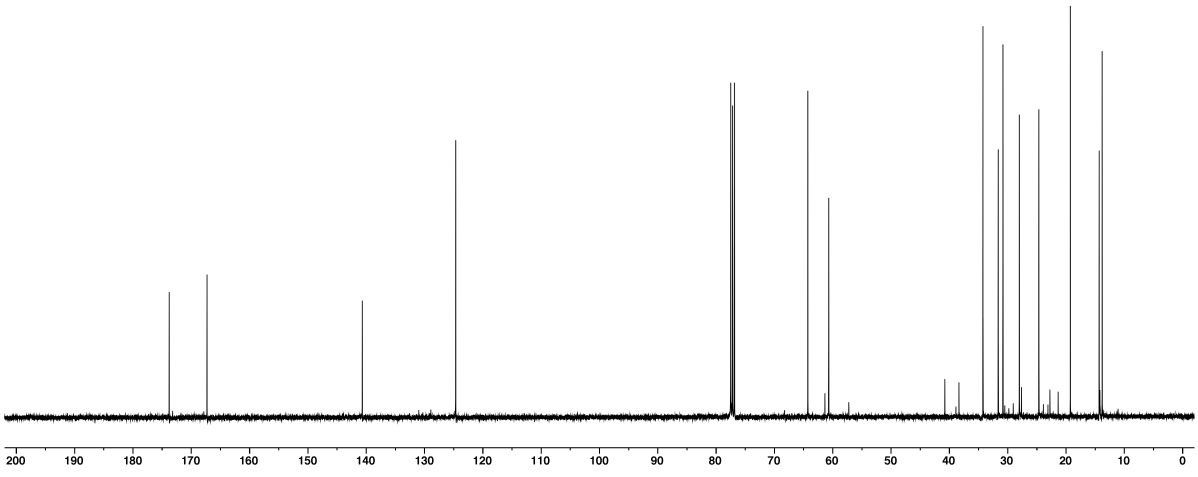



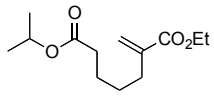
**7-Butyl 1-ethyl 2-methyleneheptanedioate** (**5a**, Table 2, entry 3)

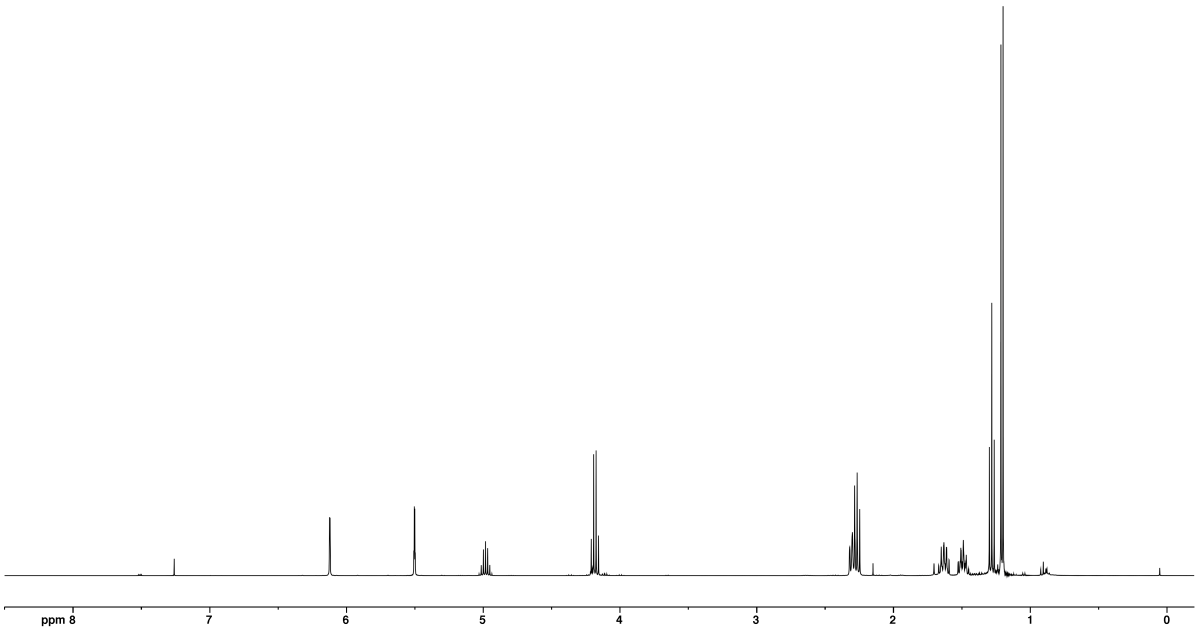


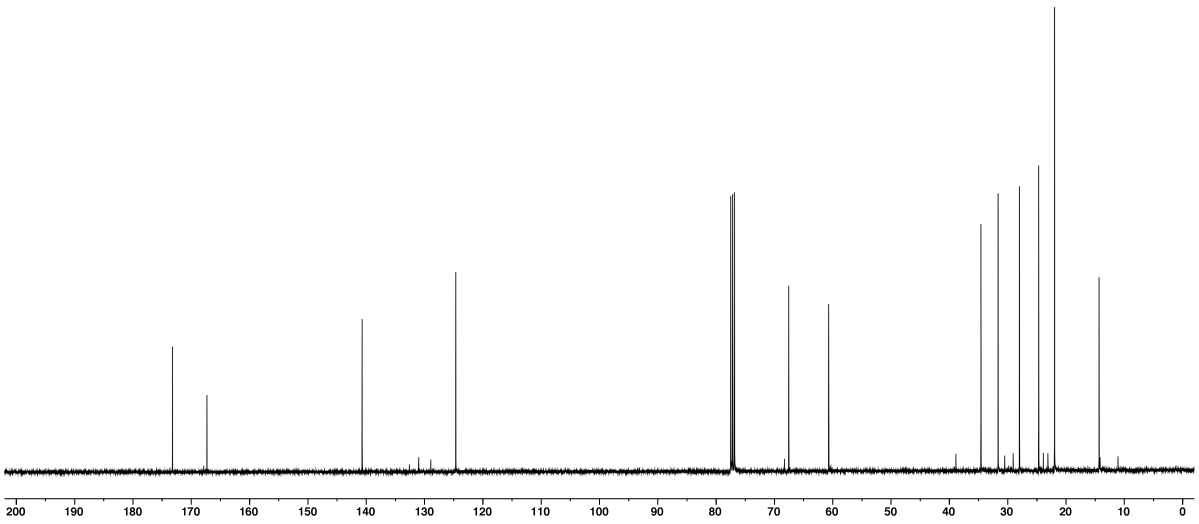



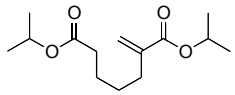
**1-Ethyl 7-isopropyl 2-methyleneheptanedioate** (**5a**, Table 2, entry 5a)

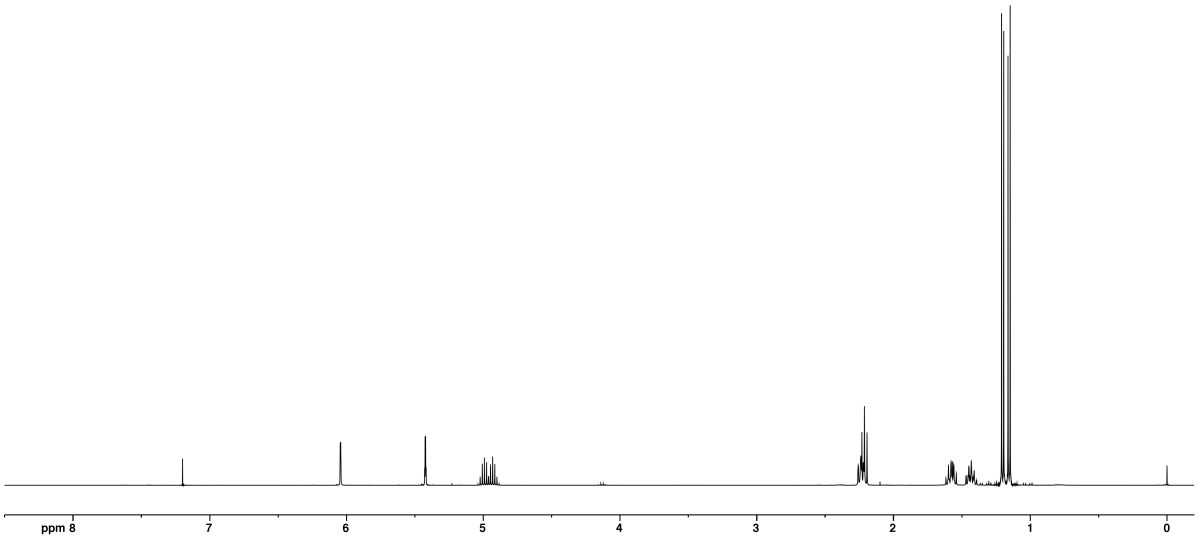


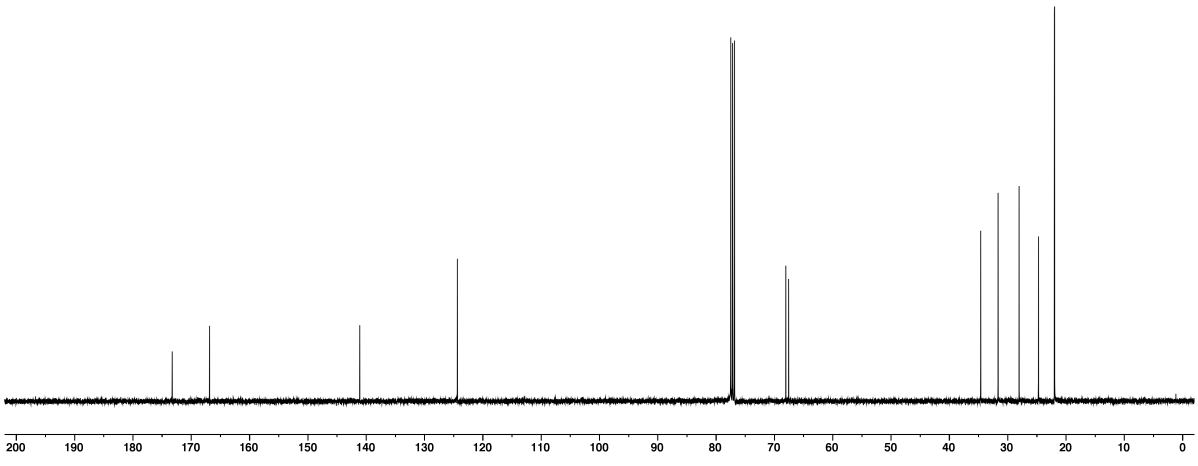



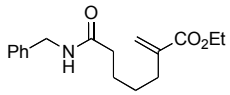
**Diisopropyl 2-methyleneheptanedioate** (**5a**, Table 2, entry 5b)

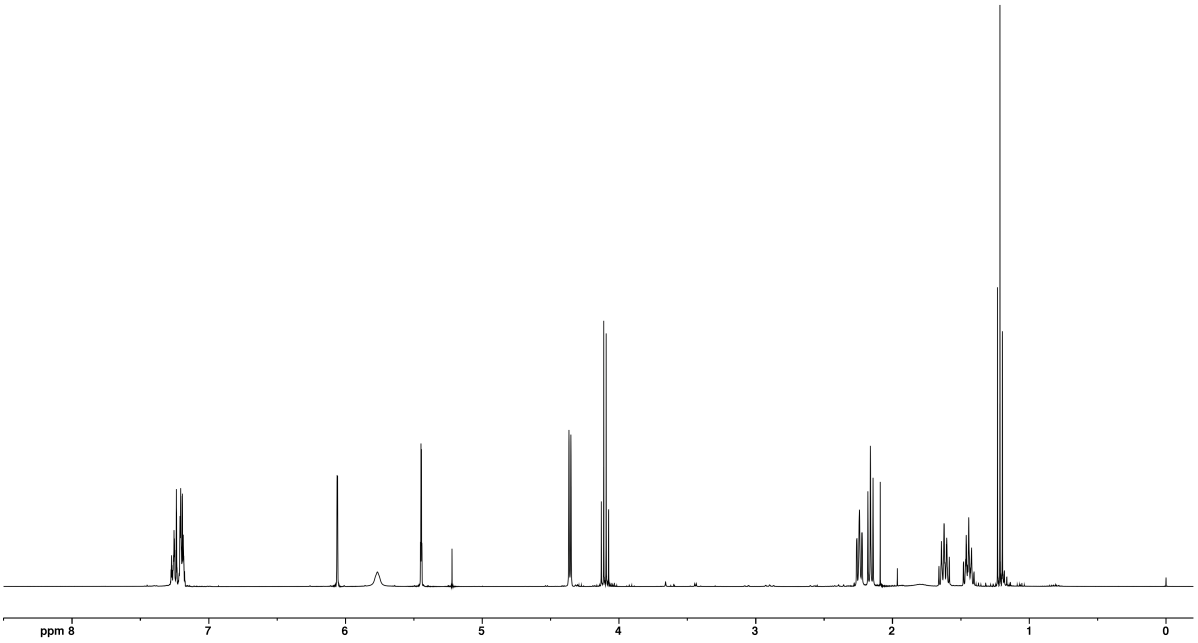


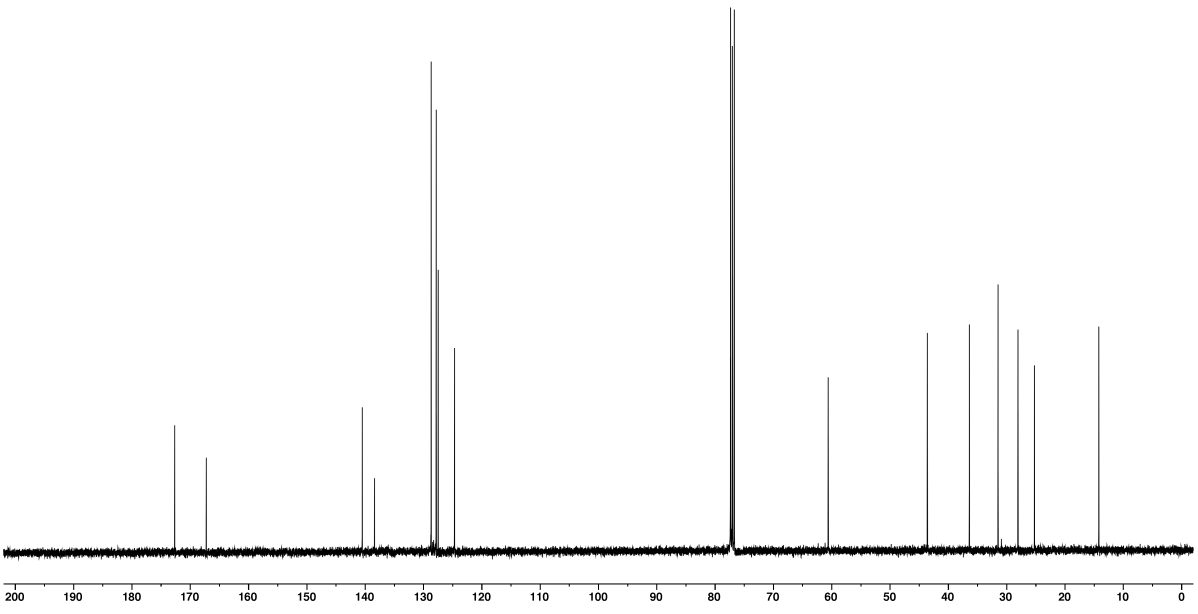


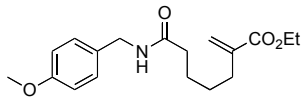
**Ethyl 7-(benzylamino)-2-methylene-7-oxoheptanoate** (**5a**, Table 2, entry 7a)

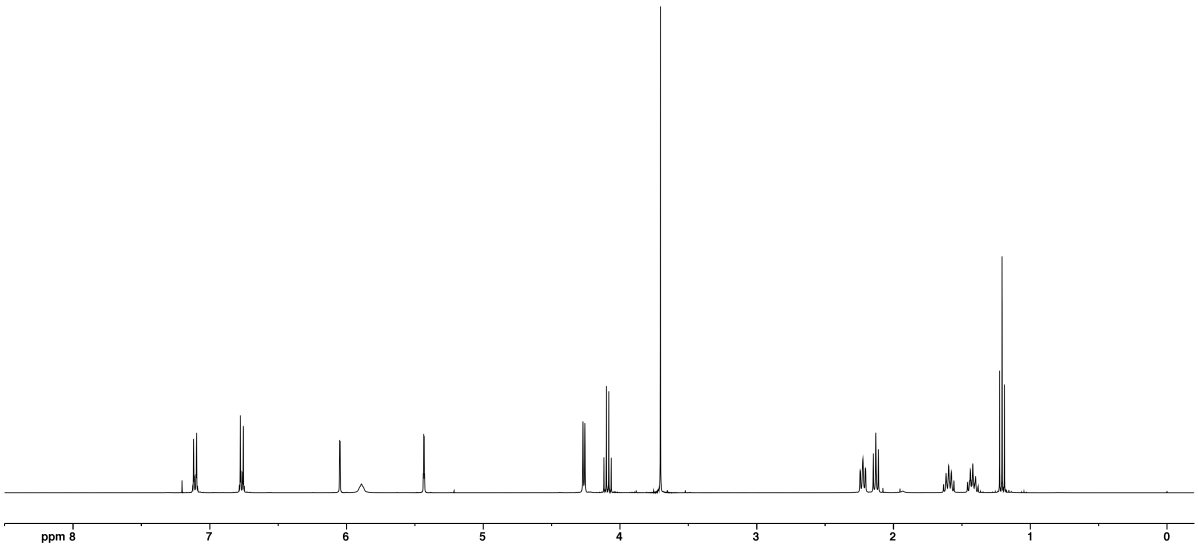


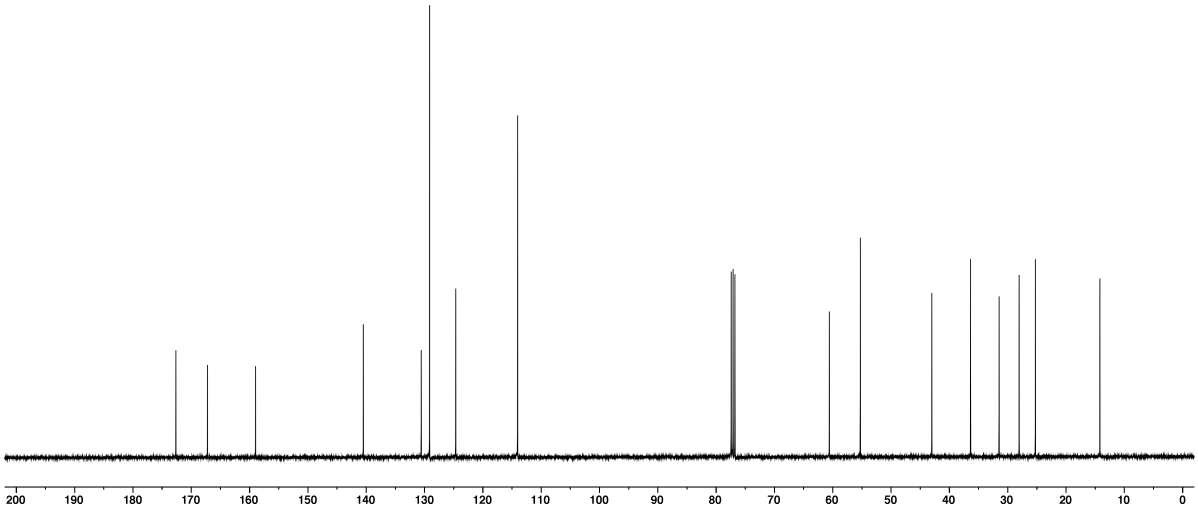



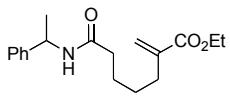
**Ethyl 7-(4-methoxybenzylamino)-2-methylene-7-oxoheptanoate** (**5a**, Table 2, entry 7b)

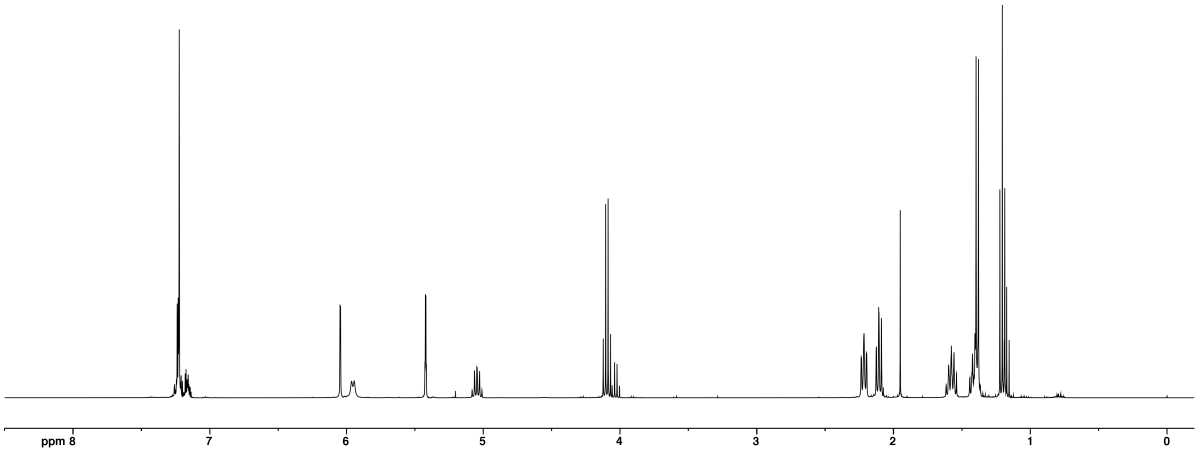


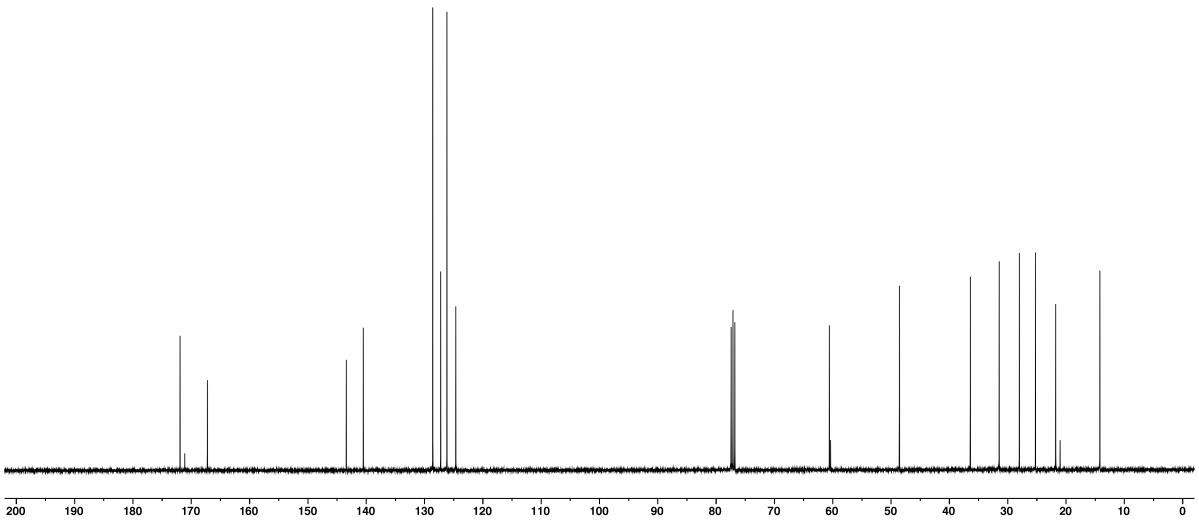



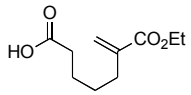
**Ethyl 2-methylene-7-oxo-7-(1-phenylethylamino)heptanoate** (**5a**, Table 2, entry 7c)

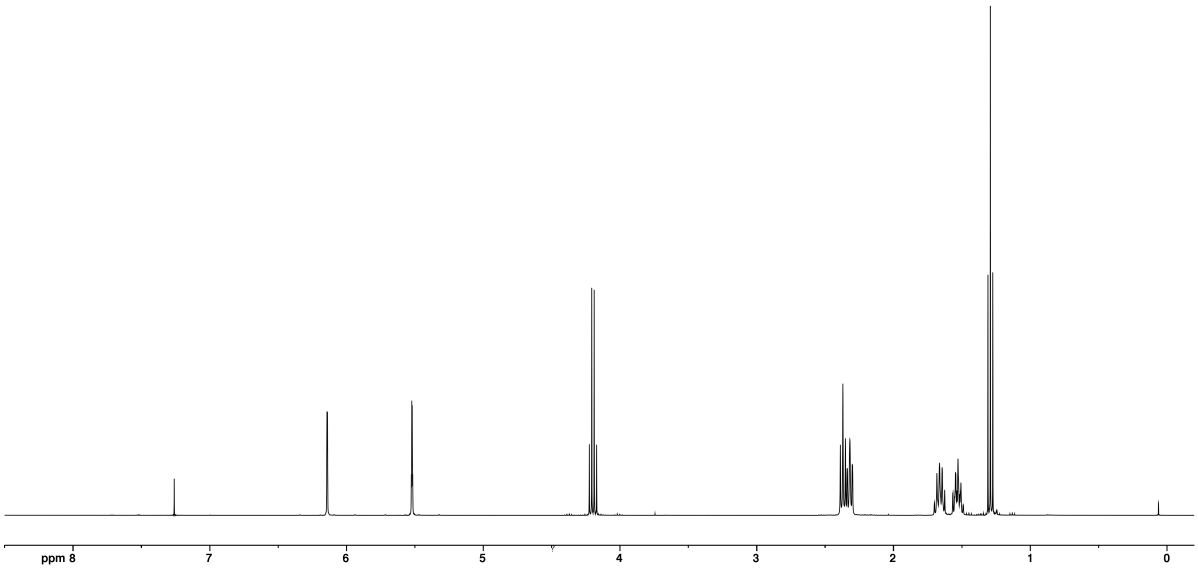


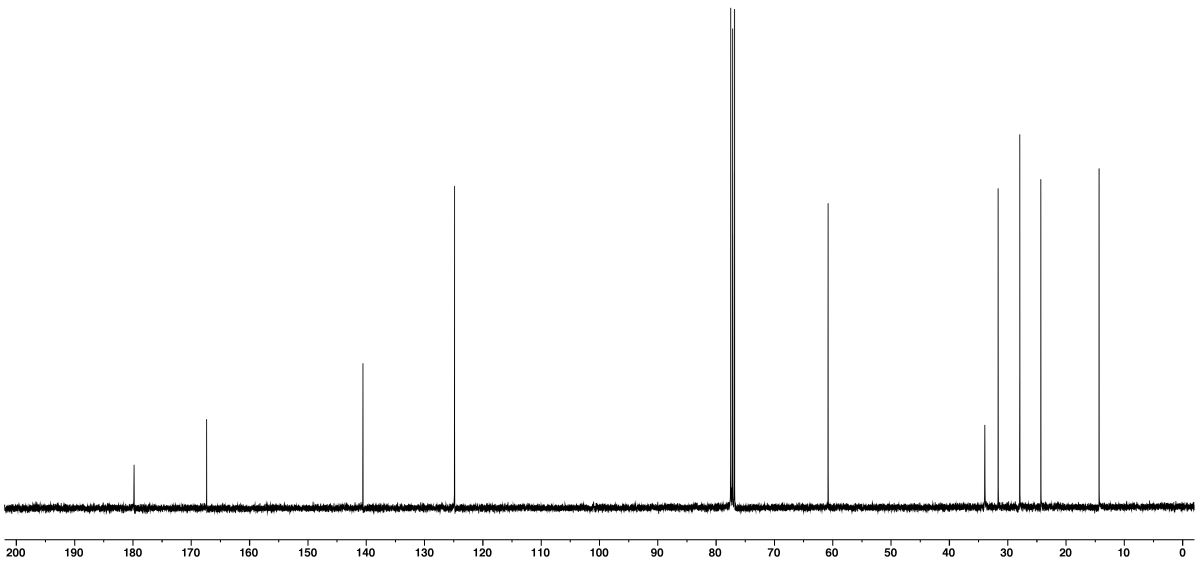



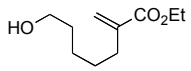
**6-(Ethoxycarbonyl)hept-6-enoic acid** (**5a**, Table 2, entry 8a)

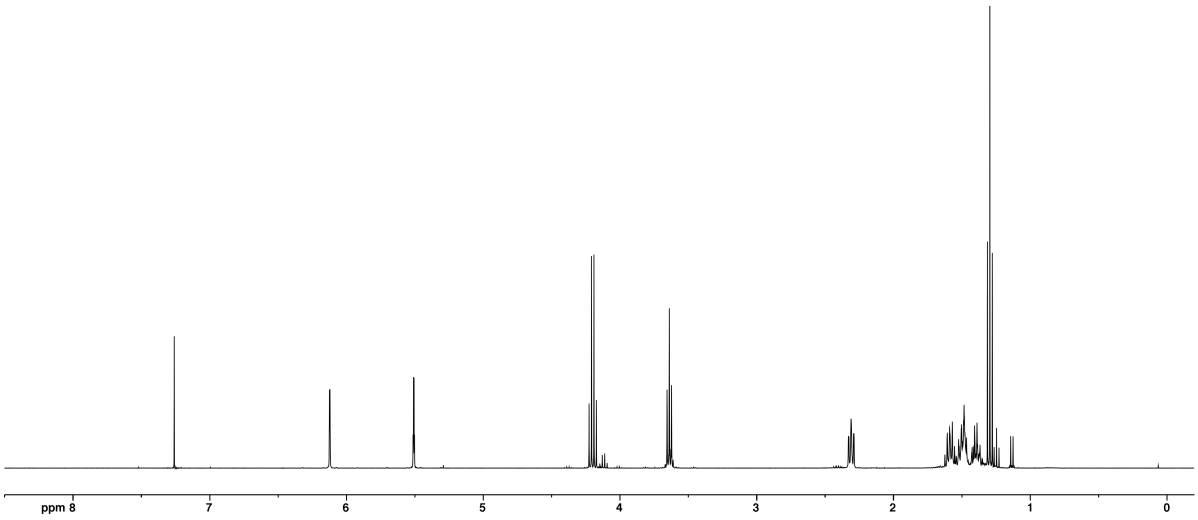


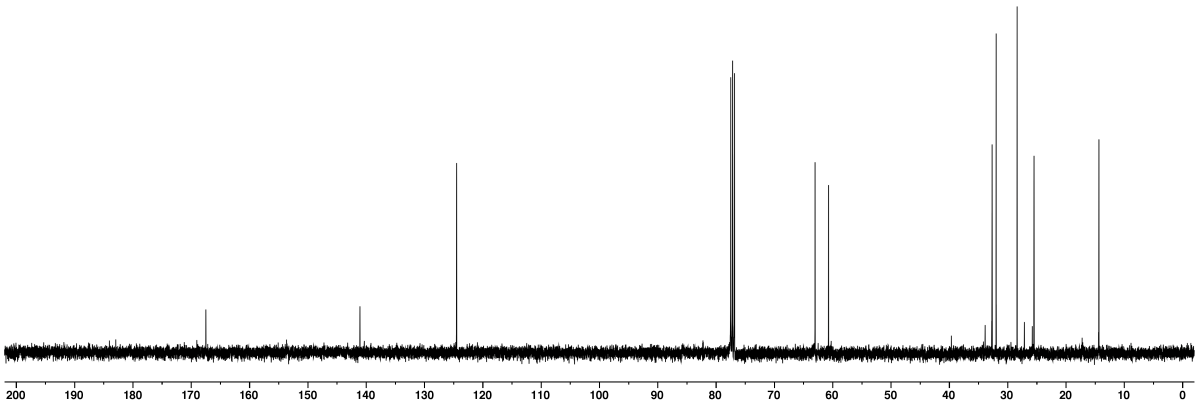



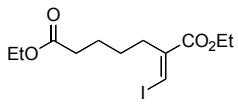
**Ethyl 7-hydroxy-2-methyleneheptanoate** (**5b**)

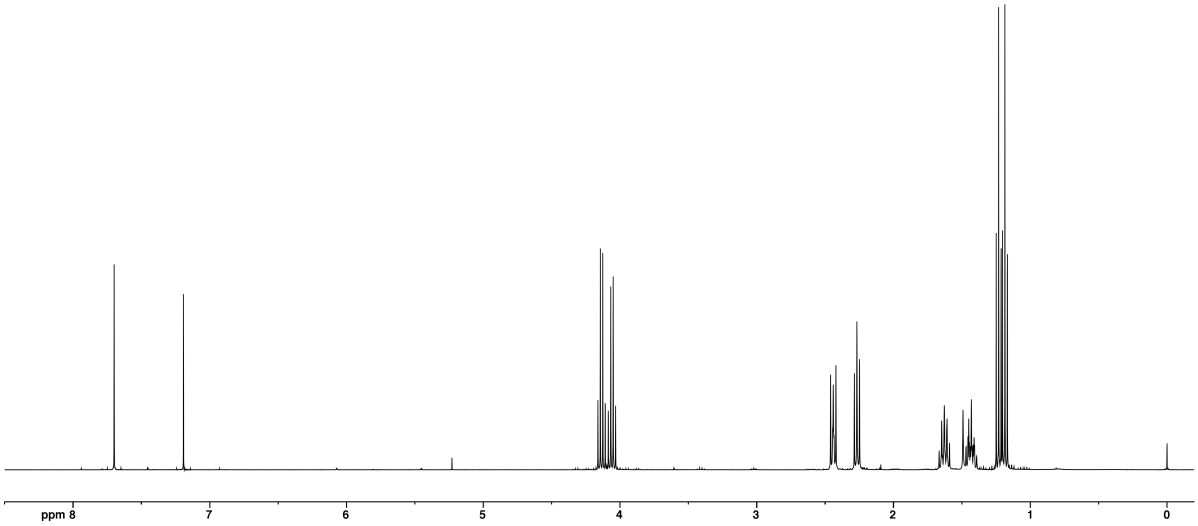


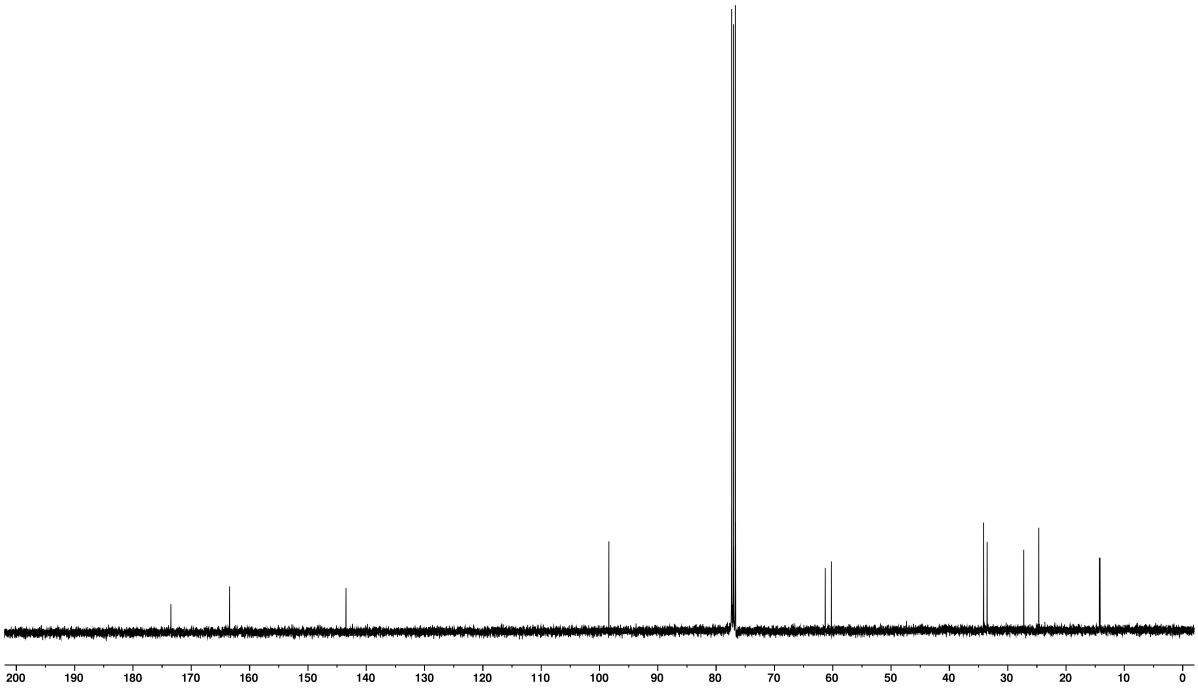



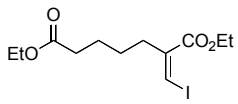
**(*E*)-Diethyl 2-(iodomethylene)heptanedioate** (**5d**)

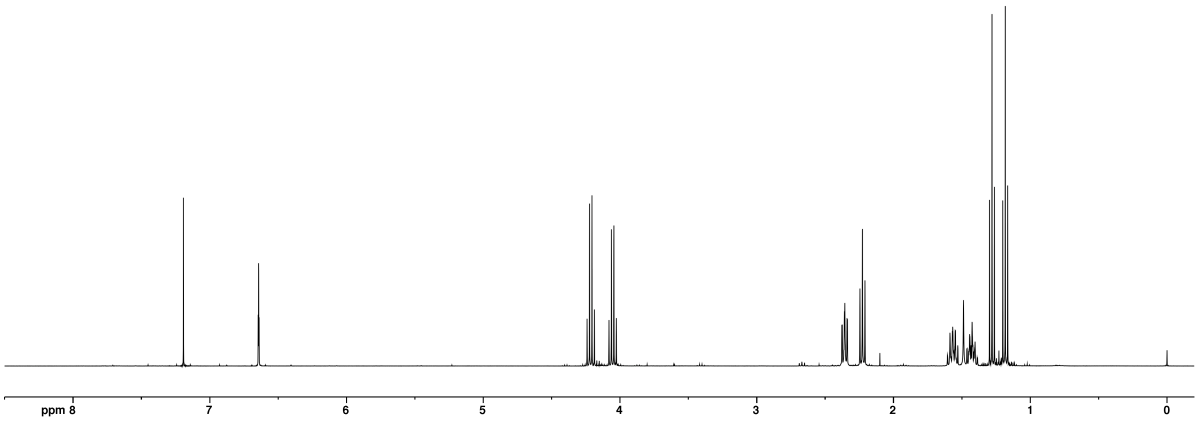


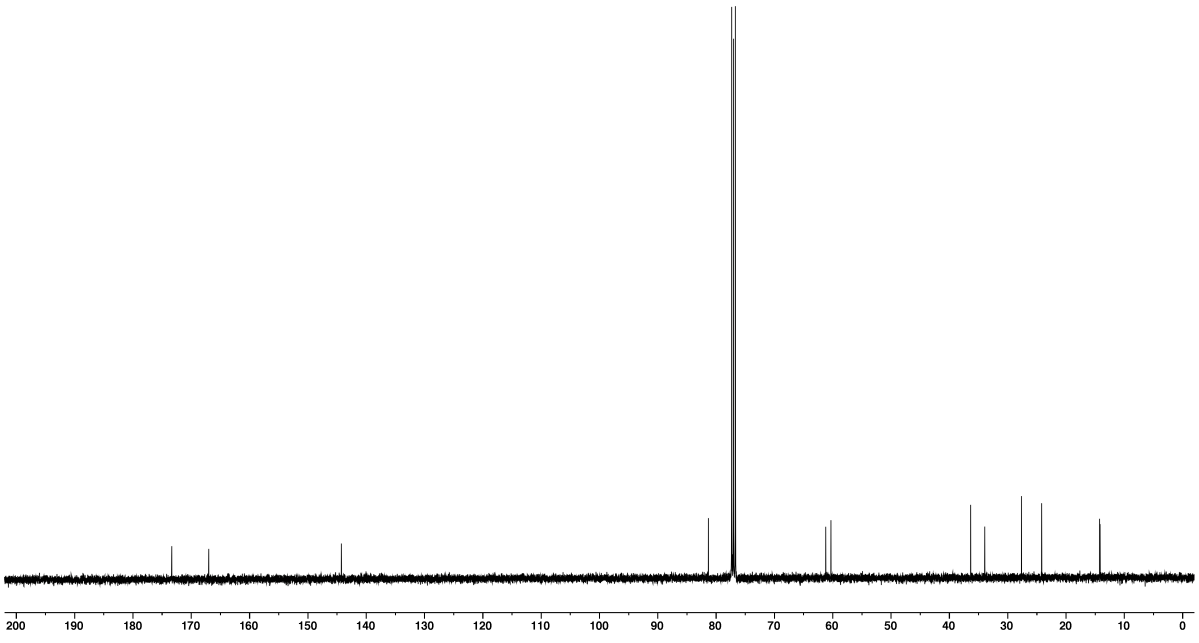



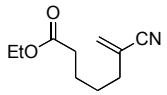
**(*Z*)-Diethyl 2-(iodomethylene)heptanedioate (5d)**

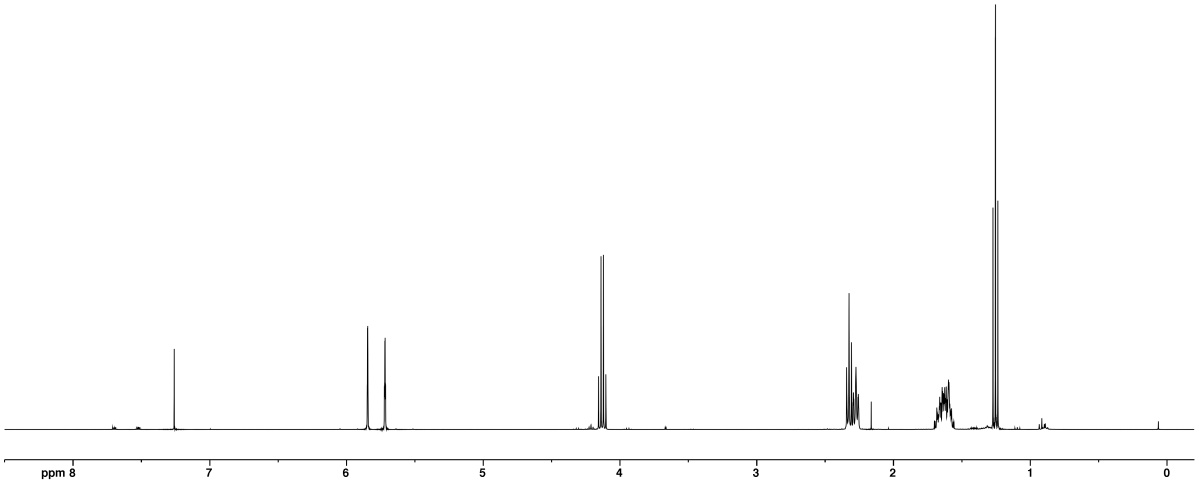


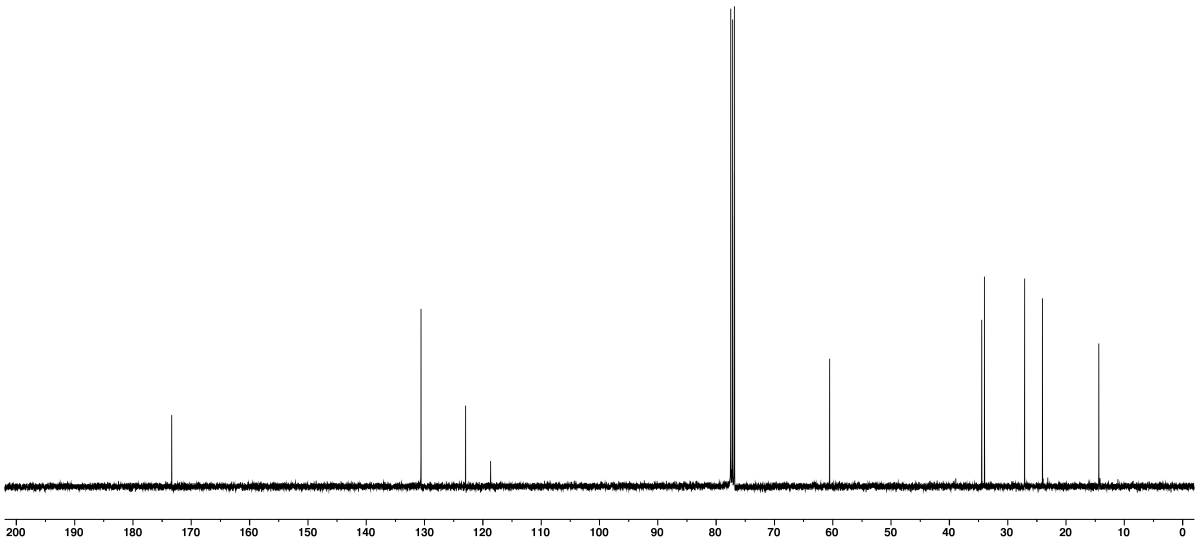



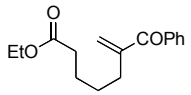
**Ethyl 6-cyanohept-6-enoate** (**5e**)

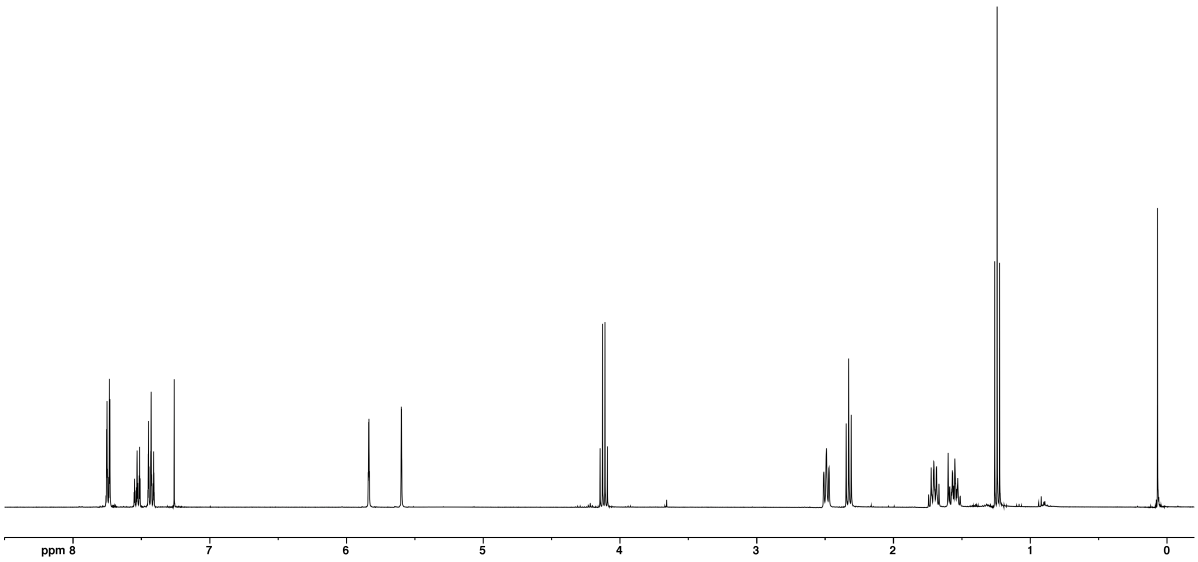


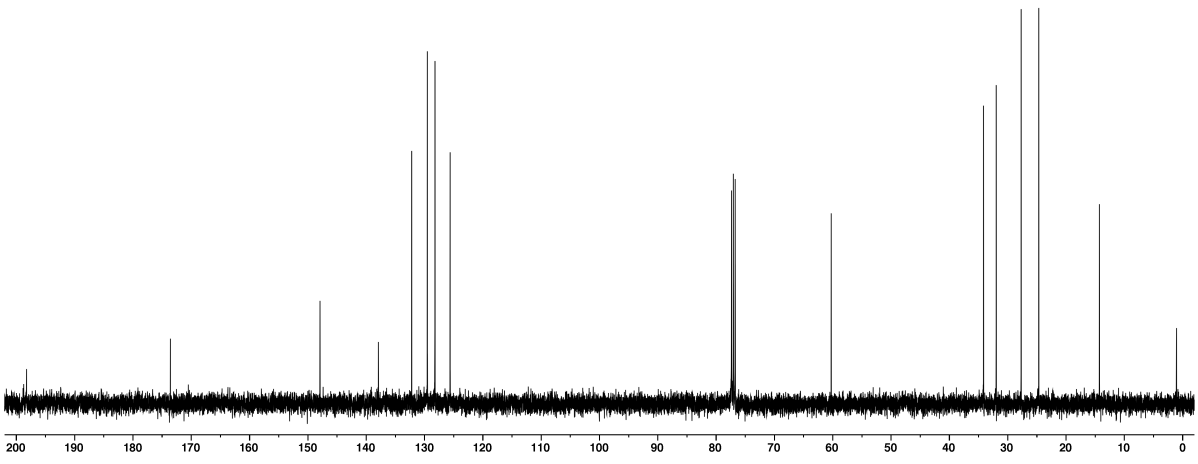



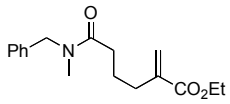
**Ethyl 6-benzoylhept-6-enoate (5f)**

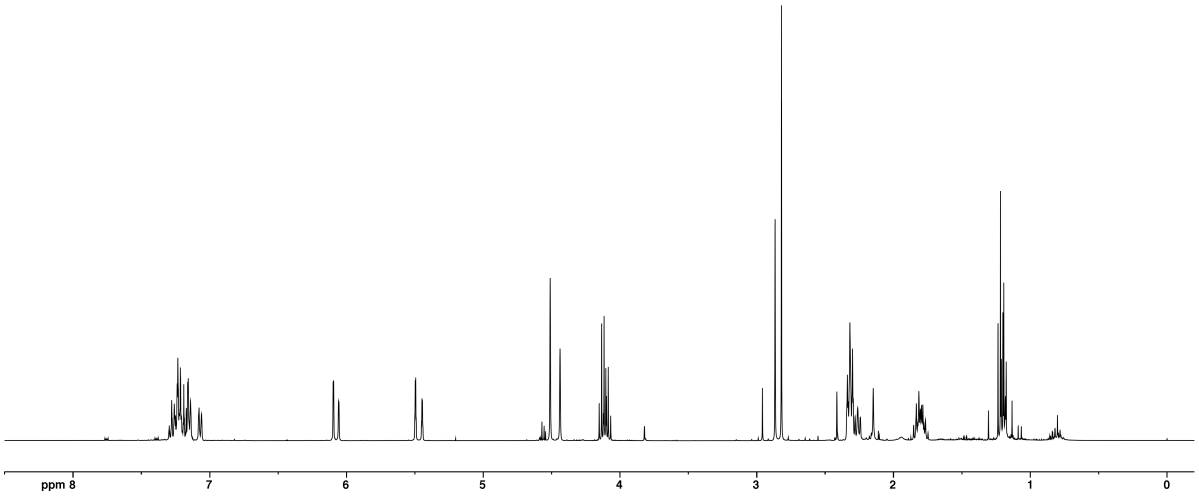


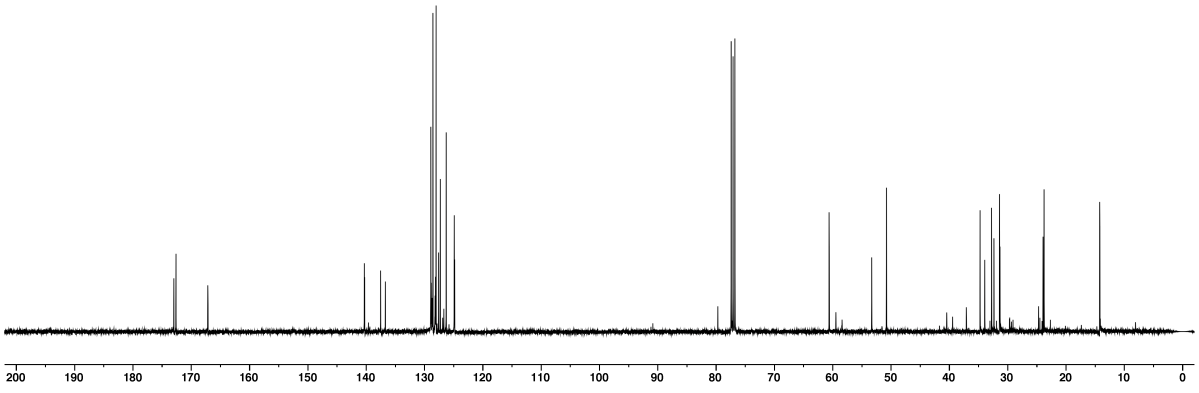



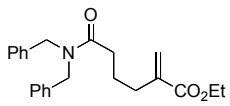
**Ethyl 6-(benzyl(methyl)amino)-2-methylene-6-oxohexanoate** (**5h**)

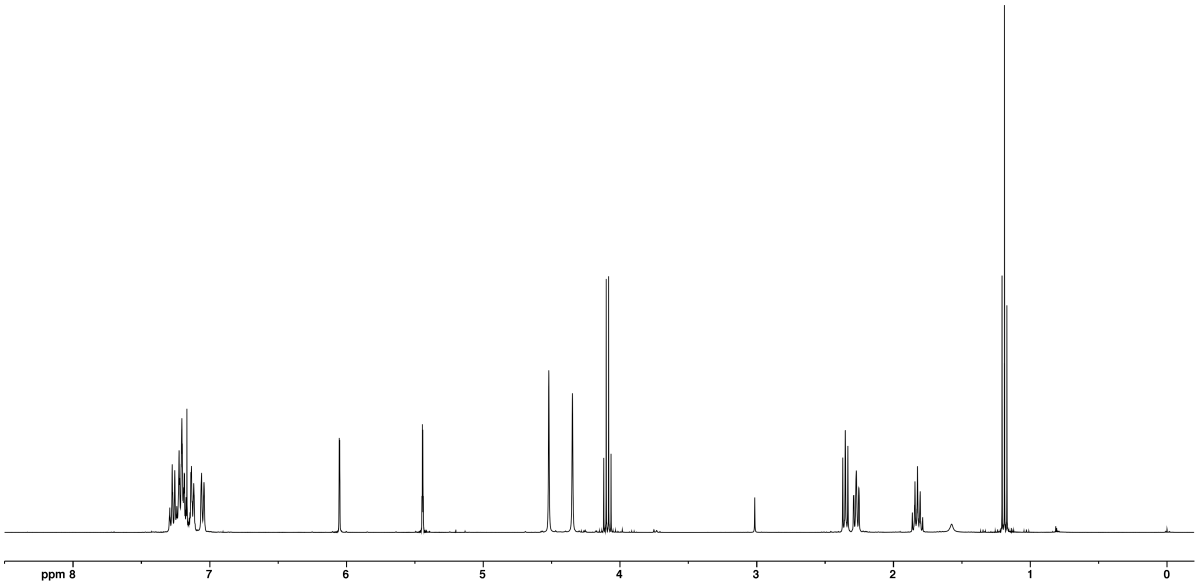


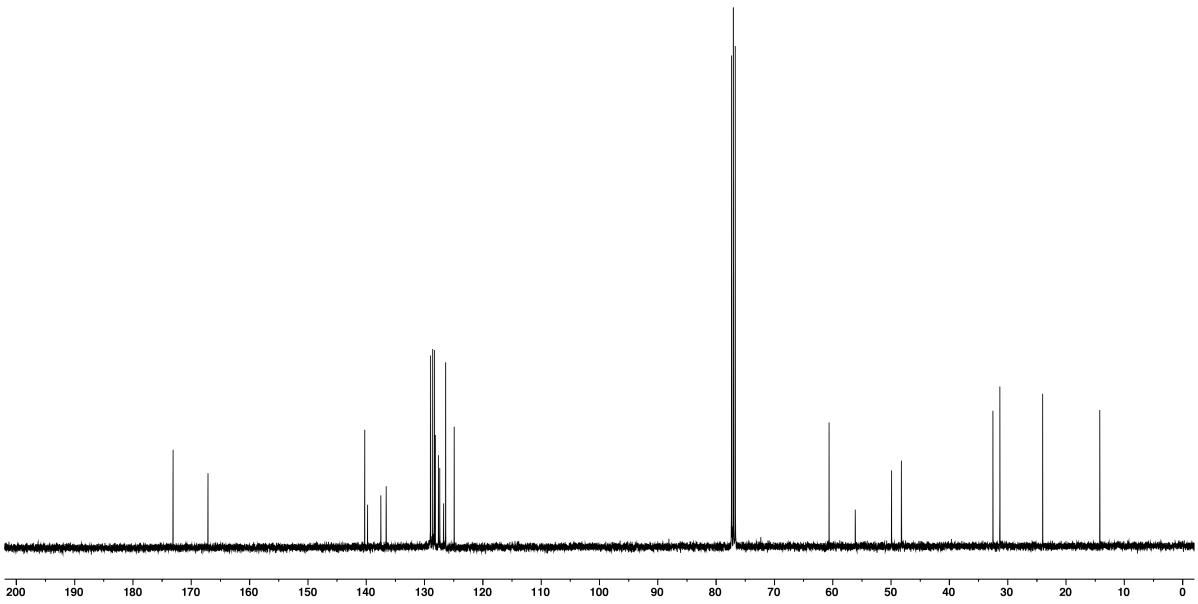



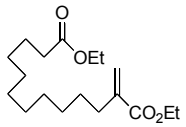
**Ethyl 6-(dibenzylamino)-2-methylene-6-oxohexanoate (5i)**

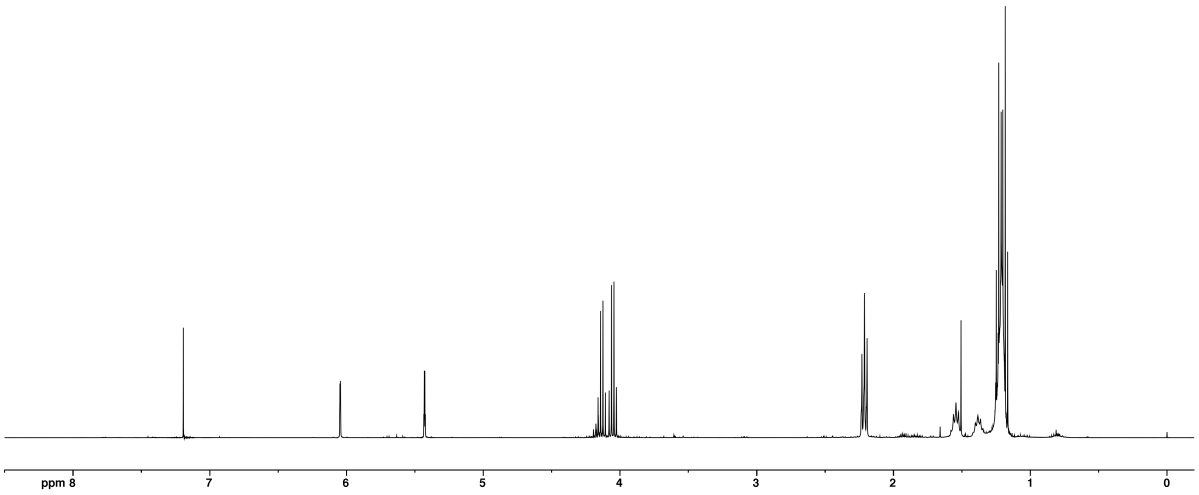


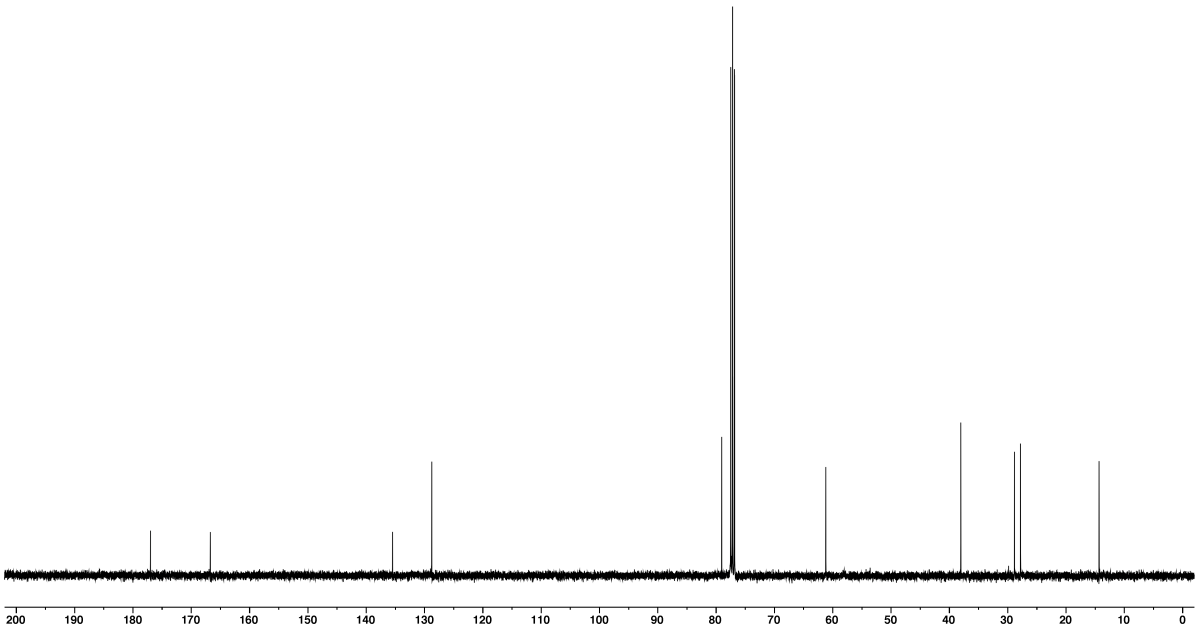



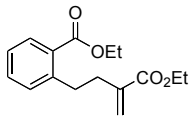
**Diethyl 2-methylenetridecanedioate** (**5k**)

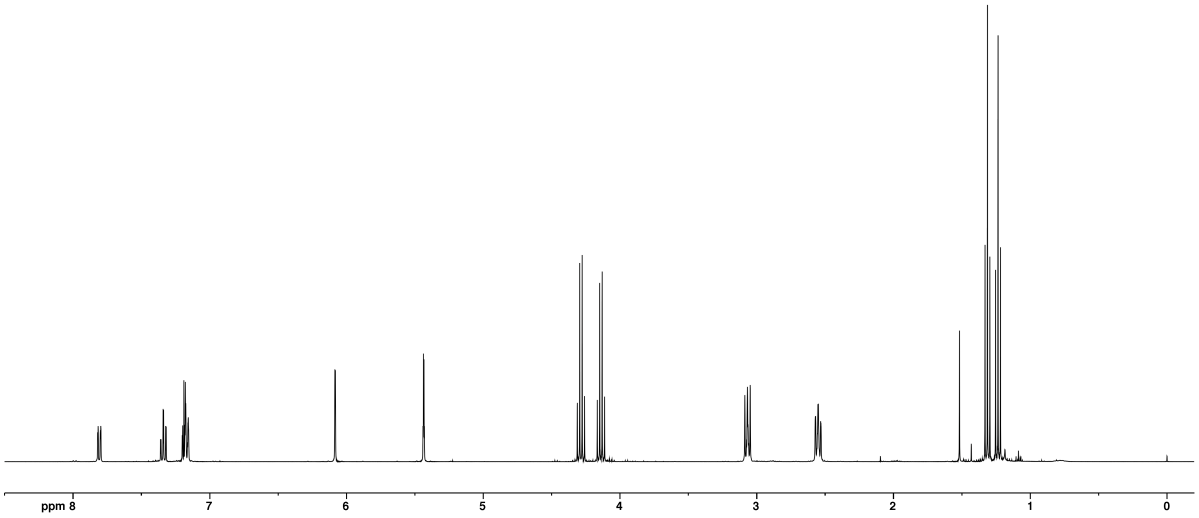


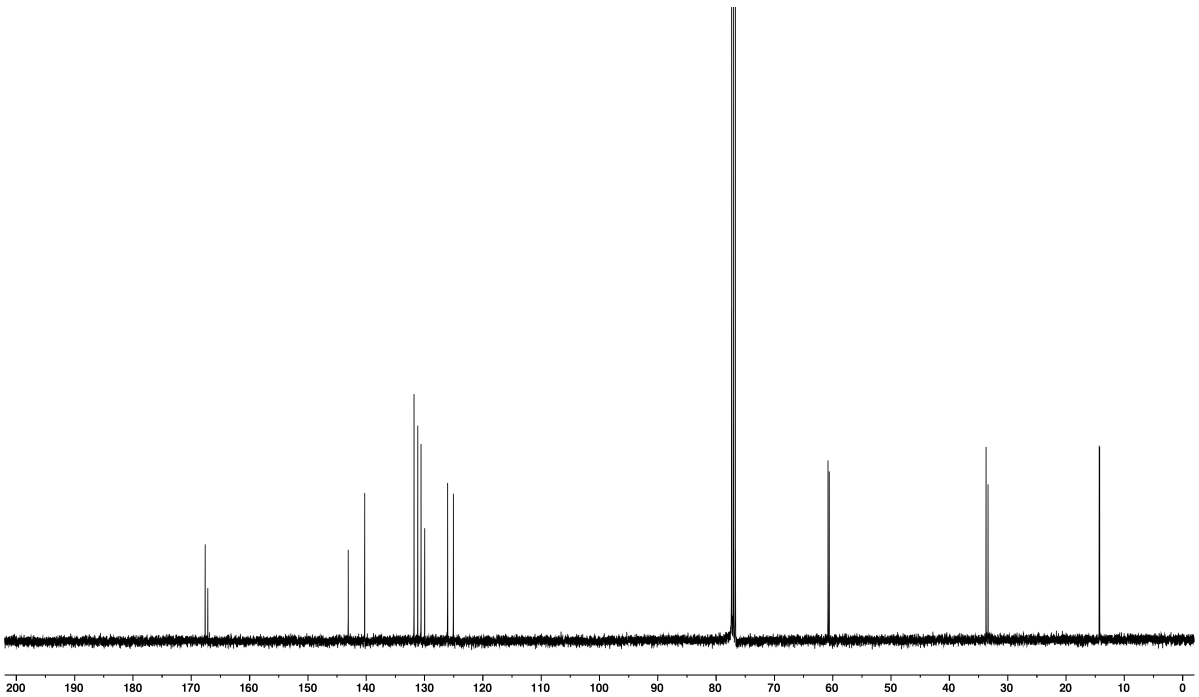



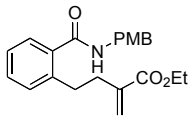
**Ethyl 2-(3-(ethoxycarbonyl)but-3-enyl)benzoate (5m)**

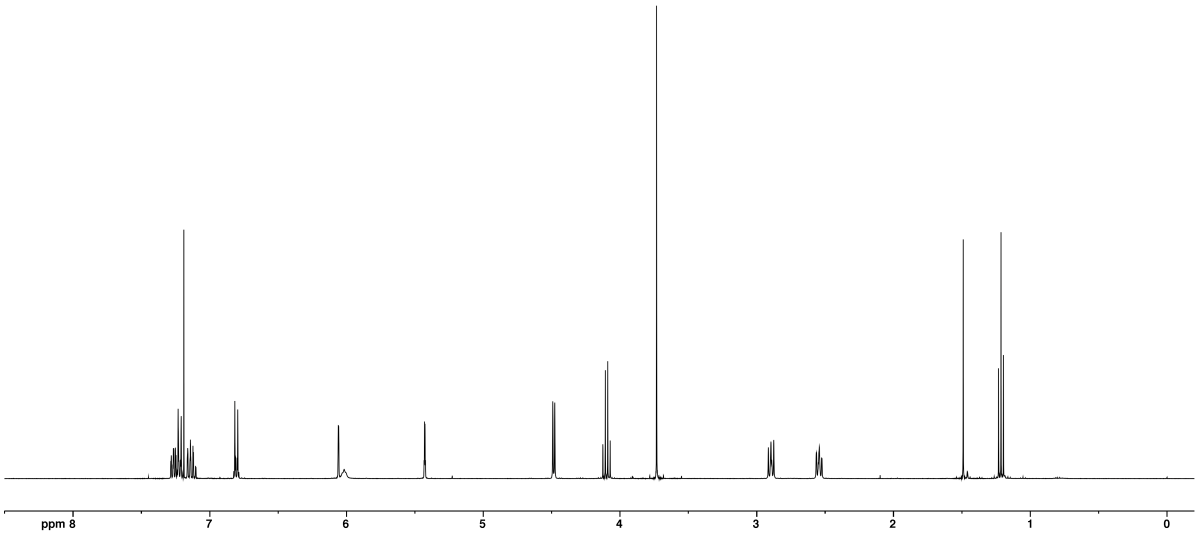


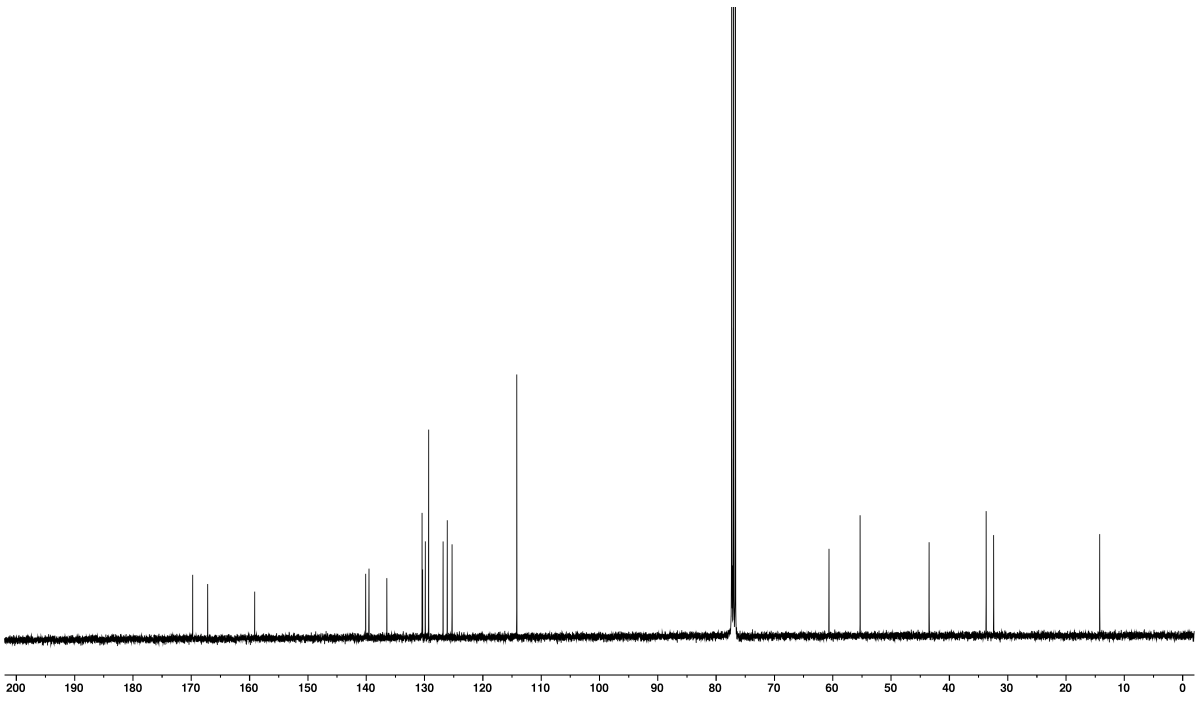



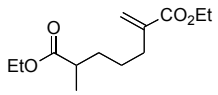
**Ethyl 4-(2-(4-methoxybenzylcarbamoyl)phenyl)-2-methylenebutanoate (5n)**

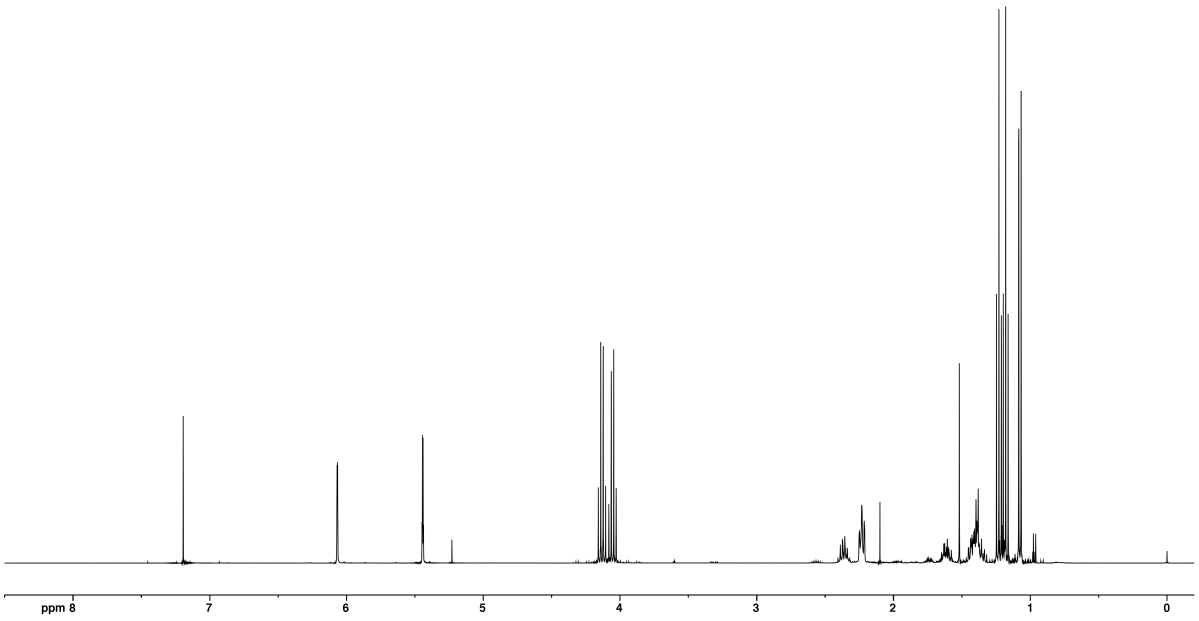


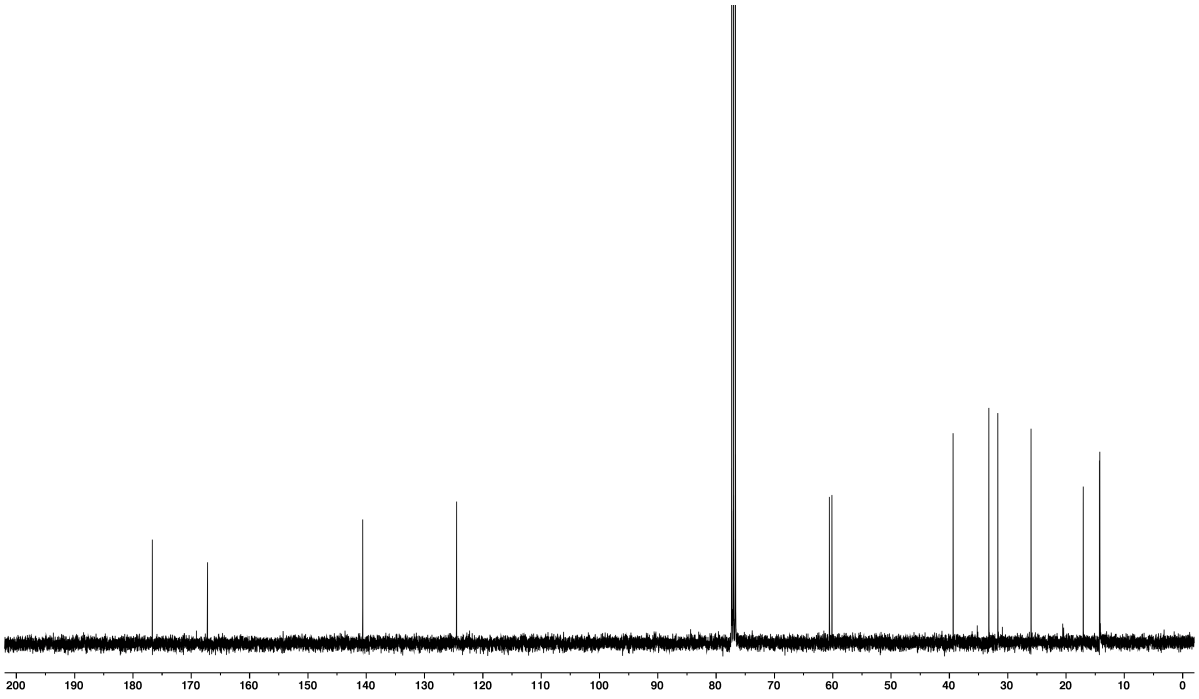



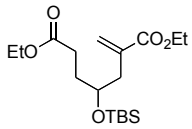
**Diethyl 2-methyl-6-methyleneheptanedioate (5o)**

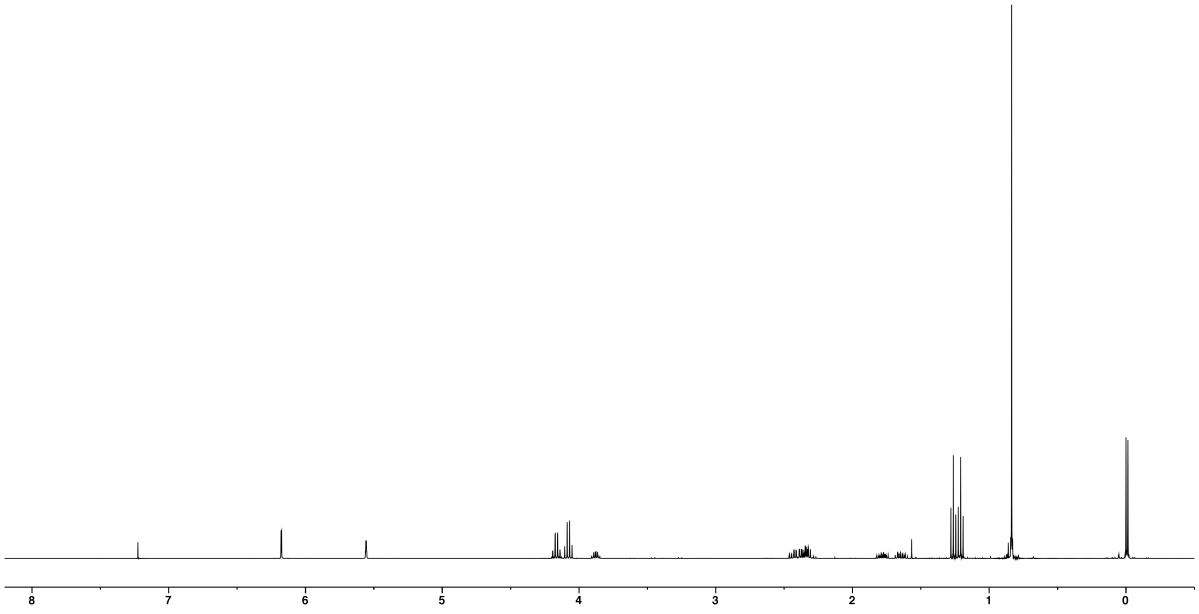


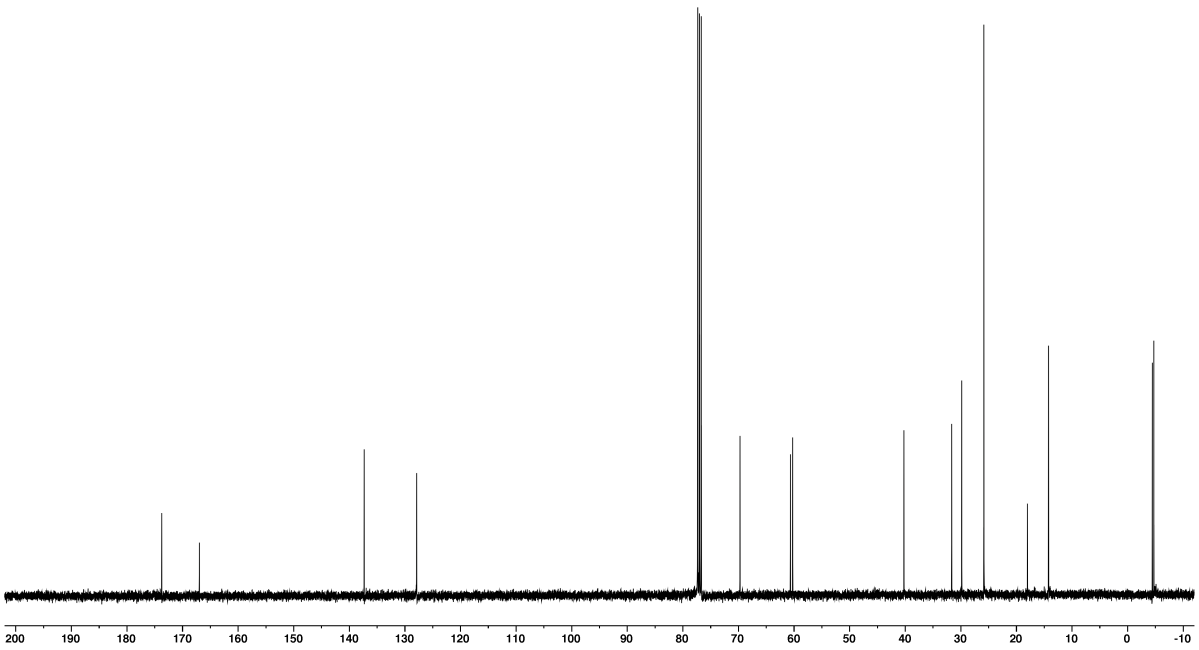



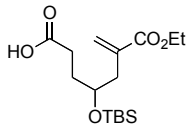
**Diethyl 4-(*tert*-butyldimethylsilyloxy)-2-methyleneheptanedioate (5p)**

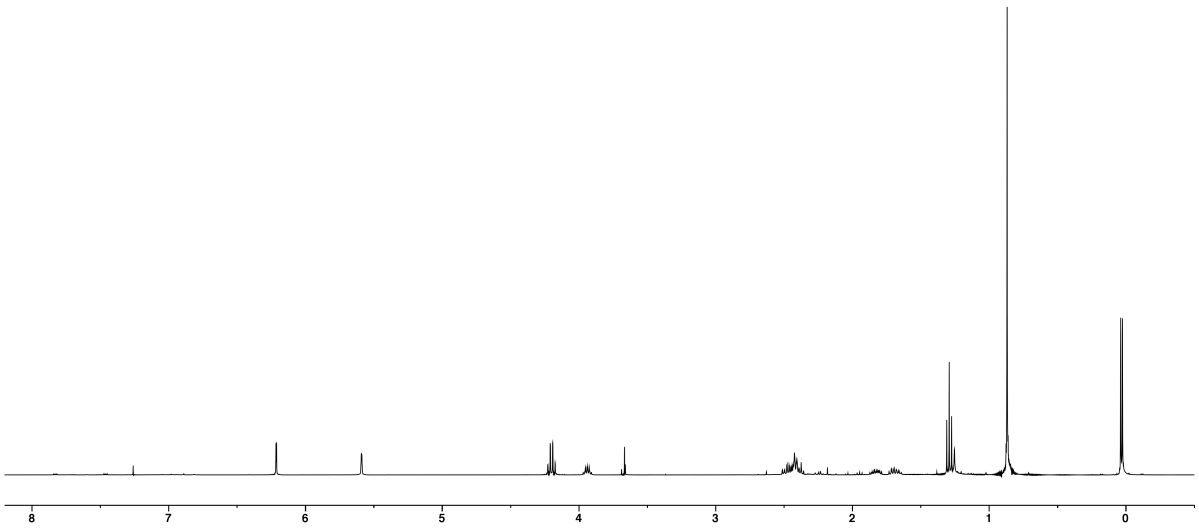


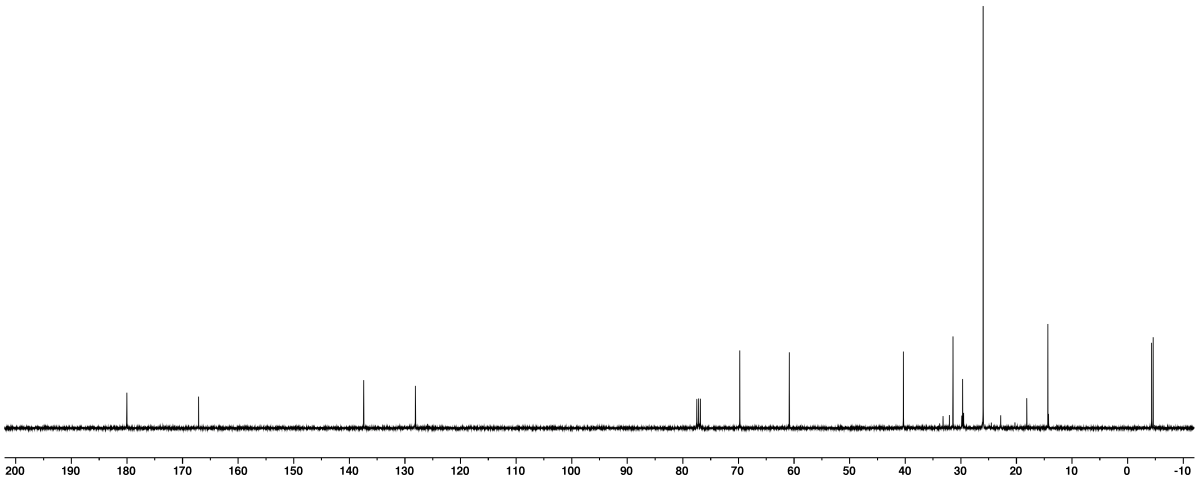



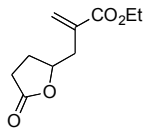
**4-((*tert*-Butyldimethylsilyl)oxy)-6-(ethoxycarbonyl)hept-6-enoic acid (5r)**

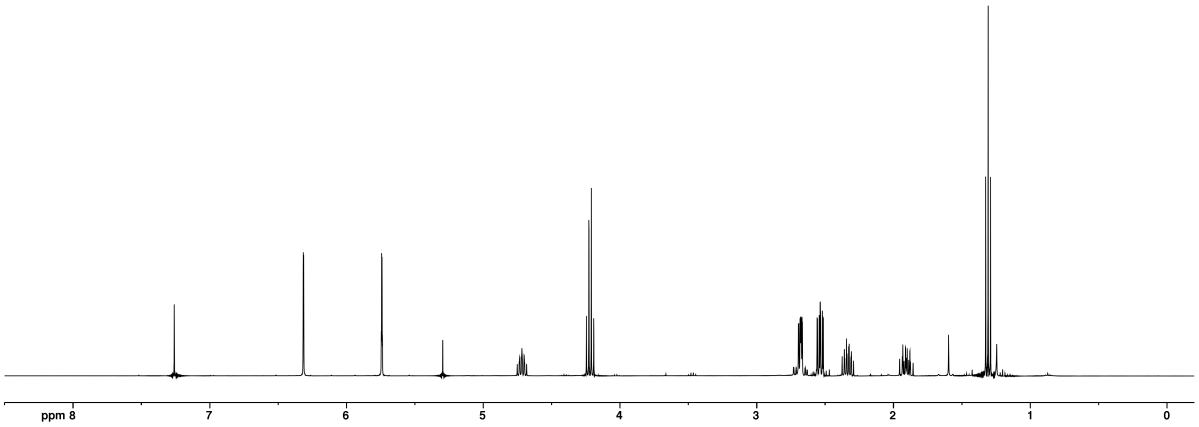


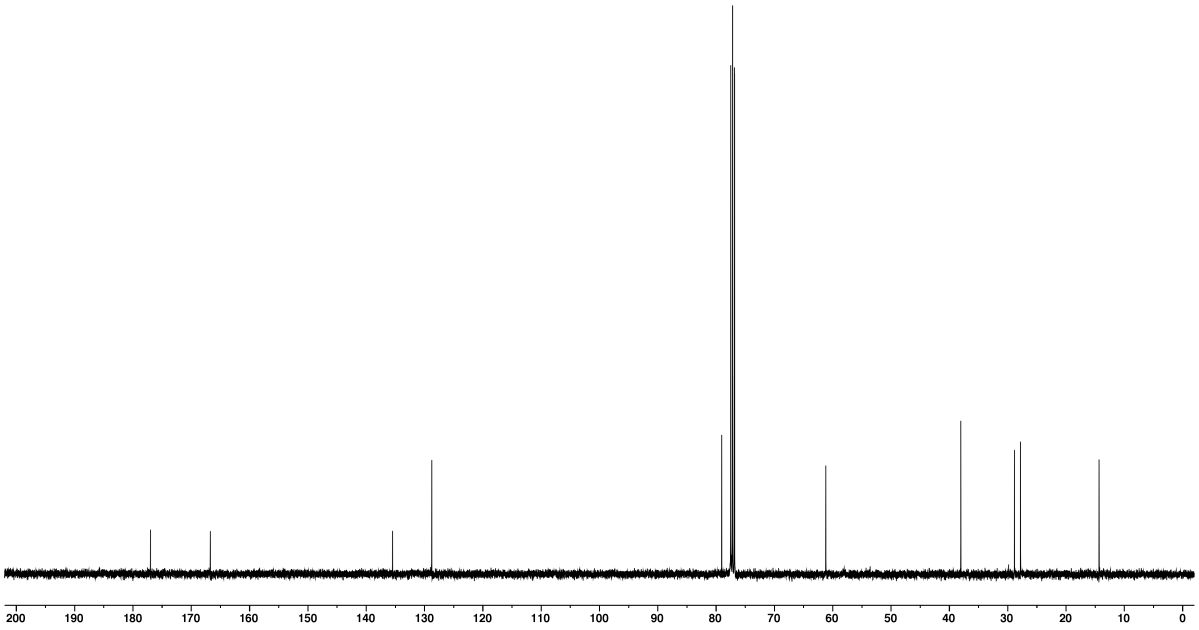



**Ethyl 2-((5-oxotetrahydrofuran-2-yl)methyl)acrylate** (**8**)



**3-(4-Methylene-5-oxotetrahydrofuran-2-yl)propanoic acid** (**9**)