Asymmetric Synthesis of Hydrobenzofuranones via Desymmetrization of Cyclohexadienones using the Intramolecular Stetter Reaction

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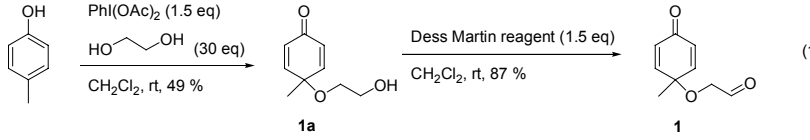
Supporting Information

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Methanol was distilled from CaH_2 prior to use. Methylene chloride was degassed with argon and passed through two column of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate dips followed by heating.

KHMDS (0.5 M solution in toluene), Ethylene glycol (anhydrous, 99.8%) and $PhI(OAc)_2$ (iodobenzene diacetate, 98%) was purchased from Aldrich Chemical Co. and used without purification.

^1H NMR was recorded 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 was recorded at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm or (acetone-D6) taken as 30.8.

General procedure for synthesis of the substrates (parent substrate as example):

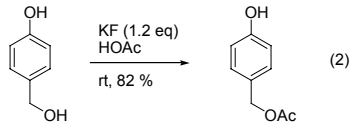


As shown in eq 1 above, a flame-dried 100 ml round bottom flask was charged with cresol (1.08 g, 10 mmol); the flask was purged under vacuum for 5 mins and then refilled with argon and 2 ml CH_2Cl_2. Ethylene glycol (16.7 ml, 300 mmol) and then $PhI(OAc)_2$ (4.83 g, 15 mmol, dissolved in 40 ml CH_2Cl_2) was added dropwise over 2 hours. The solution was then allowed to stir at ambient temperature for further 30 mins. The solution was concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc : Hexane = 1:1) to provide **1a** (823 mg, 49 %) as orange oil.

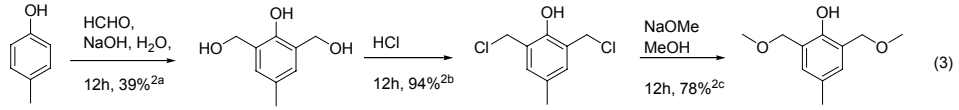
In a flame-dried 50 ml round bottom flask, **1a** (556 mg, 3.86 mmol) was dissolved in 36 ml CH_2Cl_2, Dess Martin periodinane (1.80 g, 4.25 mmol) was added to the solution directly and the solution was then allowed to stir at ambient temperature for 1 hour. The

solution was filtered through Celite 545 and then concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc : Hexane = 1:3) to provide **1** (556 mg, 87 %) as yellow oil.

This is the general procedure for all other substrates (two-step yields are reported respectively in the following sections). All the phenols were purchased from Aldrich and used without further purification except for two phenols: 4-hydroxybenzyl acetate, which is synthesized from 4-(hydroxymethyl)-phenol shown in eq 2[1] and 2,6-bis(methoxymethyl)-4-methylphenol, which is synthesized from cresol shown in eq 3[2]

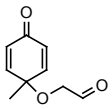


(2)

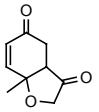


(3)

General procedure for the synthesis of Hydrobenzofuranones: A flame-dried 25 ml round bottom flask was charged with triazolium salt **3** (4.9 mg, 0.012 mmol). The flask was purged under vacuum for 5 mins and then refilled with argon and 12 ml toluene. Argon was bubbled through the solution for 5 mins, and then KHMDS (0.024 ml, 0.012 mmol) was added and the solution was allowed to stir at ambient temperature for 15 minutes. The substrate (around 20 mg, 0.12 mmol) was dissolved in 3 ml toluene and then was added via syringe and the reaction was allowed to stir at ambient temperature. After the reaction was complete (checked by TLC), usually in 5 mins, the reaction mixture was directly purified by flash column chromatography.



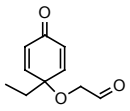
(1-Methyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (1): Rf = 0.30 (2:1 EtOAc/Hex); 43 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 6.75 (d, 2H, *J* = 10.2 Hz), 6.29 (d, 2H, *J* = 10.2 Hz), 3.95 (s, 2H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 184.3, 149.6, 130.7, 73.1, 71.1, 26.0; IR (NaCl, neat) 2976, 1736, 1670, 1624, 1086, 861 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{10}O_3$, 166.0630. Found 166.0630.



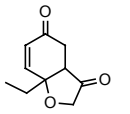
7a-Methyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (2): Rf = 0.48 (2:1 EtOAc/Hex); 90 % yield; $[\alpha]_D^{21}$ = + 69.4 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 160 ºC oven temperature. Major: 5.8 min, Minor: 6.7 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, 1H, *J* = 10.2, 1.7 Hz), 6.01 (d, 1H, *J* = 10.2 Hz), 4.21 (d, 1H, *J* = 17.4 Hz), 3.83 (d, 1H, *J* = 17.4 Hz), 3.02 (d, 1H, *J* = 17.7 Hz), 2.69 (dd, 1H, *J* = 6.9, 1.2 Hz), 2.57 (dd, 1H, *J* = 17.7, 6.9 Hz), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 193.9, 150.6,

[1] John, B. J. W.; Rama, R. B.; Anil K, S. *Synthetic Communications*, **2004**, *34*, 2849-2855.
[2] (a) Barry M, T.; Vince S. C, Y.; Hisanako, I.; Nadine, B. *Organic Letters,* **2002**, *4*, 2621-2623. (b) Paine, R. T.; Tan, Y.; Gan, X. *Inorg. Chem.* **2001**, *40*, 7009-7013. (c) Ledovskikh, V. M.; Shapovalova, Yu. P.; Sumlivenko, N. V. *Ukrainskii Khimicheskii Zhurnal (Russian Edition)*, **1989**, *55*, 858-61.

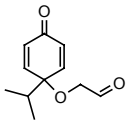
131.1, 78.9, 69.7, 50.8, 33.0, 24.3; IR (NaCl, neat) 2971, 1767, 1680, 1236, 1060, 879 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{10}O_3$, 166.0630. Found 166.0631.



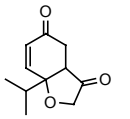
(1-Ethyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (6): Rf = 0.42 (2:1 EtOAc/Hex); 33 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 6.70 (d, 2H, *J* = 10.4 Hz), 6.37 (d, 2H, *J* = 10.0 Hz), 3.98 (s, 2H), 1.89 (q, 2H, *J* = 7.6 Hz), 0.87 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 184.9, 149.0, 132.1, 76.9, 71.0, 32.0, 7.8; IR (NaCl, neat) 2966, 2878, 1733, 1668, 1095, 861 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0792.



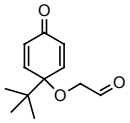
7a-Ethyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (7): Rf = 0.58 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 86.0 (c = 1.7, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 180 ºC oven temperature. Major: 4.1 min, Minor: 4.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, 1H, *J* = 10.5, 1.8 Hz), 6.07 (d, 1H, *J* = 10.2 Hz), 4.20 (dd, 1H, *J* = 17.4, 1.2 Hz), 3.83 (d, 1H, *J* = 17.4 Hz), 3.02 (d, 1H, *J* = 18.0 Hz), 2.71-2.76 (m, 1H), 2.55 (dd, 1H, *J* = 18.0, 7.2 Hz), 1.87-2.11 (m, 2H), 1.09 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 194.2, 150.1, 131.9, 81.4, 69.5, 48.5, 33.4, 30.9, 7.7; IR (NaCl, neat) 2971, 2914, 1766, 1679, 924, 707 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0790.



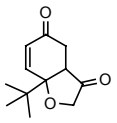
(1-Isopropyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (8): Rf = 0.44 (2:1 EtOAc/Hex); 35 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 6.70 (d, 2H, *J* = 10.5 Hz), 6.38 (d, 2H, *J* = 10.5 Hz), 3.94 (s, 2H), 2.03-2.18 (m, 1H), 0.97 (d, 6H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 184.8, 148.0, 132.5, 78.8, 70.9, 36.5, 17.0; IR (NaCl, neat) 2966, 1736, 1669, 1629, 1079, 856 cm^{-1} ; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0945.



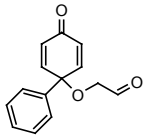
7a-Isopropyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (9): Rf = 0.65 (2:1 EtOAc/Hex); 87 % yield; $[\alpha]_D^{21}$ = + 82.4 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 ºC oven temperature. Major: 7.0 min, Minor: 7.6 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, 1H, *J* = 10.5, 1.5 Hz), 6.14 (d, 1H, *J* = 10.5 Hz), 4.20 (dd, 1H, *J* = 17.4, 1.2 Hz), 3.83 (d, 1H, *J* = 17.4 Hz), 3.04 (d, 1H, *J* = 18.6 Hz), 2.58 (dd, 1H, *J* = 18.3, 7.5 Hz), 2.12-2.28 (m, 1H), 1.10 (dd, 6H, *J* = 7.0, 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.1, 194.4, 149.2, 132.7, 83.6, 69.3, 46.9, 36.1, 34.4, 17.4, 16.7; IR (NaCl, neat) 2966, 2878, 1763, 1684, 1062, 702 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0950.



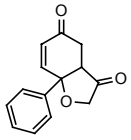
(1-tert-Butyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (10): Rf = 0.48 (2:1 EtOAc/Hex); 24 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 6.87 (d, 2H, *J* = 10.5 Hz), 6.40 (d, 2H, *J* = 10.5 Hz), 3.92 (s, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 184.3, 148.3, 132.6, 80.2, 71.0, 39.5, 25.6; IR (NaCl, neat) 2966, 2873, 1737, 1671, 1079, 861 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{16}O_3$, 208.1099. Found 208.1100.



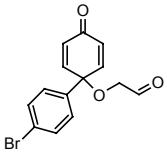
7a-tert-Butyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (11): Rf = 0.69 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 58.0 (c = 2.0, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 ºC oven temperature. Major: 8.4 min, Minor: 9.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, 1H, *J* = 10.6, 1.6 Hz), 6.15 (d, 1H, *J* = 10.5 Hz), 4.20 (d, 1H, *J* = 17.4), 3.83 (d, 1H, *J* = 17.7 Hz), 3.05 (d, 1H, *J* = 18.6 Hz), 2.89 (d, 1H, *J* = 7.5 Hz), 2.61 (dd, 1H, *J* = 18.6, 7.5 Hz), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 194.0, 148.9, 132.8, 85.2, 69.3, 45.6, 37.8, 34.8, 25.2; IR (NaCl, neat) 2959, 2873, 1759, 1676, 939, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{16}O_3$, 208.1099. Found 208.1101.



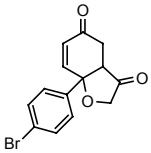
(4-Oxo-1-phenyl-cyclohexa-2,5-dienyloxy)-acetaldehyde (12): Rf = 0.45 (2:1 EtOAc/Hex); 36 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.48-7.53 (m, 2H), 7.30-7.41 (m, 3H), 6.80 (d, 2H, *J* = 10.2 Hz), 6.39 (d, 2H, *J* = 10.2 Hz), 4.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 184.7, 148.4, 137.2, 130.2, 128.8, 128.5, 76.7, 70.6; IR (NaCl, neat) 2821, 1735, 1670, 1629, 1061, 699 cm^{-1} ; HRMS (FAB+) calcd for $C_{14}H_{12}O_3$, 228.0786. Found 228.0779.



7a-Phenyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (13): Rf = 0.70 (2:1 EtOAc/Hex); 87 % yield; $[\alpha]_D^{21}$ = + 230.3 (c = 2.2, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 180 ºC oven temperature. Major: 23.6 min, Minor: 24.6 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.56 (m, 2H), 7.37-7.48 (m, 3H), 6.78 (dd, 1H, *J* = 10.4, 1.8 Hz), 6.28 (d, 1H, *J* = 10.0 Hz), 4.47 (dd, 1H, *J* = 17.6, 1.2 Hz), 3.04 (d, 1H, *J* = 17.6 Hz), 2.86-2.91 (m, 1H), 2.62 (dd, 1H, *J* = 18.0, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 194.1, 148.4, 139.1, 132.4, 129.0, 128.9, 125.0, 82.2, 69.7,52.7, 32.8; IR (NaCl, neat) 2894, 1762, 1685, 1057, 755, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{12}O_3$, 228.0786. Found 228.0784.

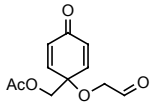


[1-(4-Bromo-phenyl)-4-oxo-cyclohexa-2,5-dienyloxy]-acetaldehyde (14): Rf = 0.38 (2:1 EtOAc/Hex); 20 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.51 (d, 2H, *J* = 8.7 Hz), 7.38 (d, 2H, *J* = 8.7 Hz), 6.76 (d, 2H, *J* = 10.2 Hz), 6.41 (d, 2H, *J* = 10.2 Hz), 4.19 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 184.4, 147.9, 136.4, 130.2, 130.6, 127.3, 122.8, 76.5, 70.6; IR (NaCl, neat) 2822, 1735, 1670, 1074, 1010, 826 cm^{-1} ; HRMS (FAB+) calcd for $C_{14}H_{11}BrO_3$, 305.9892. Found 305.9895.

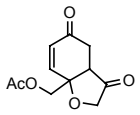


7a-(4-Bromo-phenyl)-3a,7a-dihydro-4H-benzofuran-3,5-dione (15): Rf = 0.68 (2:1 EtOAc/Hex); 78 % yield; $[\alpha]_D^{21}$ = + 212.8 (c = 2.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 95:5 hexanes : isopropanol 1.0 mL / min. Major: 31.8 minutes, Minor: 41.1 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.8 Hz), 6.73 (dd, 1H, *J* = 10.4, 1.6 Hz), 6.29 (d, 1H, *J* = 10.0 Hz), 4.47 (dd, 1H, *J* = 17.6, 1.0 Hz), 3.05 (dd, 1H, *J* = 18.0, 1.0 Hz), 2.83 (dd, 1H, *J* = 7.0, 1.4 Hz), 2.58 (dd, 1H, *J* = 18.0, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 193.7, 147.7, 138.2, 132.7, 132.2, 126.8, 123.1, 81.8, 69.7,52.6, 32.7; IR

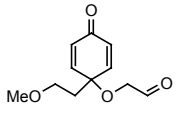
(NaCl, neat) 2884, 1764, 1683, 1055, 1010, 820 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{11}BrO_3$, 305.9892. Found 305.9892.



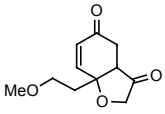
Acetic acid 4-oxo-1-(2-oxo-ethoxy)-cyclohexa-2,5-dienylmethyl ester (16): Rf = 0.23 (2:1 EtOAc/Hex); 9 % yield; ^{1}H NMR (400 MHz, acetone-D6) δ 9.62 (s, 1H), 6.93 (d, 2H, *J* = 10.0 Hz), 6.37 (d, 2H, *J* = 10.0 Hz), 4.30 (s, 2H), 4.10 (s, 2H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, acetone-D6) δ 201.1, 185.9, 171.4, 148.0, 134.4, 76.4, 72.4, 68.2, 21.6; IR (NaCl, neat) 2950, 2827, 1731, 1670, 1230, 856 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_5$, 224.0685. Found 224.0682.



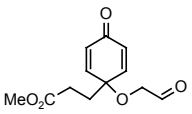
Acetic acid 3,5-dioxo-3,3a,4,5-tetrahydro-2H-benzofuran-7a-ylmethyl ester (17): Rf = 0.5 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 116.1 (c = 1.8, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 ºC oven temperature. Major: 16.2 min, Minor: 16.8 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (dd, 1H, *J* = 10.4, 2.4 Hz), 6.17 (d, 1H, *J* = 10.4 Hz), 4.44 (s, 2H), 4.27 (dd, 1H, *J* = 17.6, 0.8 Hz), 3.89 (d, 1H, *J* = 17.2 Hz), 3.04 (d, 1H, *J* = 18.4 Hz), 2.91 (dd, 1H, *J* = 7.2, 1.2 Hz), 2.62 (dd, 1H, *J* = 18.4, 7.2 Hz), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 193.5, 170.2, 145.8, 133.7, 79.6, 69.4, 65.8, 47.1, 33.0, 20.7; IR (NaCl, neat) 2955, 2899, 1742, 1685, 1229, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_5$, 224.0685. Found 224.0688.



[1-(2-Methoxy-ethyl)-4-oxo-cyclohexa-2,5-dienyloxy]-acetaldehyde (18): Rf = 0.20 (2:1 EtOAc/Hex); 23 % yield; ^{1}H NMR (400 MHz, acetone-D6) δ 9.62 (s, 1H), 6.90 (d, 2H, *J* = 10.0 Hz), 6.26 (d, 2H, *J* = 10.4 Hz), 4.03 (s, 2H), 3.47 (t, 2H, *J* = 6.4 Hz), 3.22 (s, 3H), 2.08 (t, 2H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 201.5, 186.1, 151.2, 132.6, 76.5, 72.4, 68.8, 59.4, 41.0; IR (NaCl, neat) 2925, 2873, 1670, 1624, 1112, 856 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_4$, 210.0892. Found 210.0887.

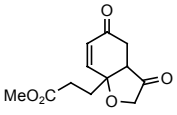


7a-(2-Methoxy-ethyl)-3a,7a-dihydro-4H-benzofuran-3,5-dione (19): Rf = 0.41 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 67.8 (c = 2.0, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 ºC oven temperature. Major: 11.1 min, Minor: 11.5 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (dd, 1H, *J* = 10.6, 1.4 Hz), 6.05 (d, 1H, *J* = 10.4 Hz), 4.20 (d, 1H, *J* = 17.2 Hz), 3.82 (d, 1H, *J* = 17.6 Hz), 3.62-3.69 (m, 1H), 3.49-3.55 (m, 1H), 3.30 (s, 3H), 2.92-3.00 (m, 2H), 2.68 (dd, 1H, *J* = 18.8, 7.6 Hz), 2.11-2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 194.6, 149.8, 131.9, 80.4, 69.2, 67.4, 58.7, 49.3, 37.7, 33.1; IR (NaCl, neat) 2914, 2889, 1757, 1685, 1107, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_4$, 210.0892. Found 210.0889.

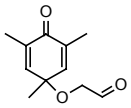


3-[4-Oxo-1-(2-oxo-ethoxy)-cyclohexa-2,5-dienyl]-propionic acid methyl ester (20): Rf = 0.28 (2:1 EtOAc/Hex); 9 % yield; ^{1}H NMR (400 MHz, acetone-D6) δ 9.62 (s, 1H), 6.87 (d, 2H, *J* = 10.4 Hz), 6.32 (d, 2H, *J* = 10.0 Hz), 4.05 (s, 2H), 3.60 (s, 3H), 2.39 (t, 2H, *J* = 7.8 Hz), 2.16 (t, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 201.4, 185.9, 174.3, 150.5, 133.5, 77.1, 72.7, 52.8,

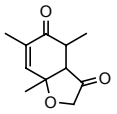
35.7, 29.7; IR (NaCl, neat) 2945, 2838, 1736, 1665, 1070, 856 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_5$, 238.0841. Found 238.0846.



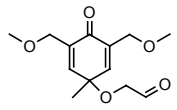
3-(3,5-Dioxo-3,3a,4,5-tetrahydro-2H-benzofuran-7a-yl)-propionic acid methyl ester (21): Rf = 0.50 (2:1 EtOAc/Hex); 94 % yield; $[\alpha]_D^{21}$ = + 88.1 (c = 2.3, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 180 ºC oven temperature. Major: 21.7 min, Minor: 22.7 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (dd, 1H, *J* = 10.5, 1.8 Hz), 6.05 (d, 1H, *J* = 10.2 Hz), 4.19 (dd, 1H, *J* = 17.4 Hz), 3.82 (d, 1H, *J* = 17.4 Hz), 3.69 (s, 3H), 3.01 (d, 1H, *J* = 18.0 Hz), 2.72 (dd, 1H, *J* = 6.9, 1.2 Hz), 2.49-2.65 (m, 3H), 2.20-2.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 193.7, 173.0, 132.1, 80.1, 69.4, 52.0, 48.5, 32.9, 32.2, 27.9; IR (NaCl, neat) 2950, 2843, 1762, 1726, 1685, 1045 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_5$, 238.0841. Found 238.0847.



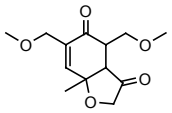
(1,3,5-Trimethyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (22): Rf = 0.55 (2:1 EtOAc/Hex); 52 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 6.46 (s, 2H), 3.88 (s, 2H), 1.87 (s, 6H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 185.8, 144.7, 137.2, 73.1, 70.8, 26.2, 16.0; IR (NaCl, neat) 2924, 1736, 1645, 1372, 1072, 907 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0948.



4,6,7a-Trimethyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (23): Rf = 0.63 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 135.3 (c = 1.4, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 120 ºC oven temperature. Major: 25.9 min, Minor: 27.5 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40-6.44 (m, 1H), 4.15 (d, 1H, *J* = 17.1 Hz), 3.82 (d, 1H, *J* = 17.4 Hz), 3.06 (ddd, 1H, *J* = 15.6, 7.8, 2.1 Hz), 2.45 (s, 1H), 1.77 (d, 3H, *J* = 1.2 Hz), 1.67 (s, 3H), 1.31 (d, 3H, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 198.1, 144.7, 136.3, 78.7, 69.1, 56.5, 39.2, 26.9, 18.0, 16.3; IR (NaCl, neat) 2971, 1763, 1678, 1434, 1052, 861 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0948.

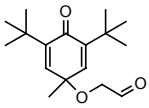


(3,5-Bis-methoxymethyl-1-methyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (24): Rf = 0.28 (2:1 EtOAc/Hex); 52 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 6.76 (s, 2H), 4.18 (s, 4H), 3.90 (s, 2H), 4.18 (s, 4H), 3.90 (s, 2H), 3.42 (s, 6H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 183.4, 144.6, 137.5, 73.3, 71.0, 68.3, 59.0, 26.3; IR (NaCl, neat) 2976, 2821, 1735, 1641, 1190, 1120 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{18}O_5$, 254.1154. Found 254.1150.

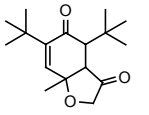


4,6-Bis-methoxymethyl-7a-methyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (25): Rf = 0.53 (2:1 EtOAc/Hex); 71 % yield; $[\alpha]_D^{21}$ = + 98.2 (c = 1.7, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexanes : isopropanol 0.7 mL / min. Major: 26.3 minutes, Minor: 22.4 minutes. ^{1}H NMR (300 MHz, acetone-D6) δ 6.64 (dt, 1H, *J* = 1.8, 1.5 Hz), 4.21 (dd, 1H, *J* = 17.4, 1.2 Hz), 3.96 (d, 2H, *J* = 1.5 Hz), 3.69-3.81 (m, 2H), 3.56 (dd, 1H, *J* = 9.6, 4.6 Hz), 3.31 (d, 6H, *J* = 0.9 Hz), 3.06-3.12 (m, 1H), 2.91-2.94 (m, 11H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 195.6, 147.2, 138.9, 80.4, 74.2, 70.6, 69.8, 59.7, 59.6, 54.4, 47.8, 27.5; IR (NaCl,

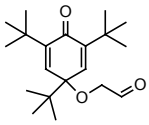
neat) 2981, 2879, 1763, 1118, 1054 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{18}O_5$, 254.1154. Found 254.1166.



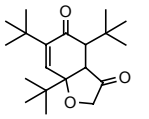
(3,5-Di-tert-butyl-1-methyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (26): Rf = 0.38 (1:3 EtOAc/Hex); 14 % yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 6.40 (s, 2H), 3.85 (s, 2H), 1.47 (s, 3H), 1.22 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 185.5, 149.5, 140.7, 73.0, 70.5, 34.9, 29.5, 26.9; IR (NaCl, neat) 2959, 2869, 1738, 1646, 1364, 879 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{26}O_3$, 278.1882. Found 278.1887.



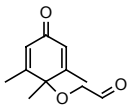
4,6-Di-tert-butyl-7a-methyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (27): Rf = 0.45 (1:3 EtOAc/Hex); 80 % yield; $[\alpha]_D^{21}$ = + 178.8 (c = 1.9, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexanes : isopropanol 0.3 mL / min. Major: 18.8 minutes, Minor: 17.8 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, 1H, *J* = 1.5 Hz), 4.14 (dd, 1H, *J* = 17.4, 1.2 Hz), 3.76 (d, 1H, *J* = 17.4 Hz), 2.68 (d, 1H, *J* = 2.1 Hz), 2.61-2.63 (m, 1H), 1.70 (s, 3H), 1.15 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 197.9, 150.6, 140.1, 78.7, 68.5, 57.2, 52.4, 35.2, 33.6, 29.5, 29.1, 27.4; IR (NaCl, neat) 2960, 2871, 1765, 1672, 1366, 1058 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{26}O_3$, 278.1882. Found 278.1889.



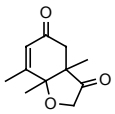
(1,3,5-Tri-tert-butyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (28): Rf = 0.53 (1:3 EtOAc/Hex); 28 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 6.50 (s, 2H), 3.83 (d, 2H, *J* = 0.6 Hz), 1.20 (s, 18H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 185.4, 151.0, 139.2, 80.0, 70.7, 40.1, 35.3, 29.6, 25.8; IR (NaCl, neat) 2959, 2871, 1739, 1666, 1364, 1085 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{32}O_3$, 320.2351. Found 320.2356.



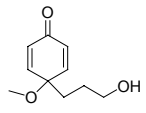
4,6,7a-Tri-tert-butyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (29): Rf = 0.58 (1:3 EtOAc/Hex); 62 % yield; $[\alpha]_D^{21}$ = + 160.7 (c = 2.2, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 120 ºC oven temperature. Major: 244.7 min, Minor: 248.4 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 1H), 4.20 (d, 1H, *J* = 17.1 Hz), 3.99 (d, 1H, *J* = 17.4 Hz), 2.74 (d, 1H, *J* = 4.2 Hz), 2.37 (d, 1H, *J* = 4.2 Hz), 1.14 (d, 18H, *J* = 7.8 Hz), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 200.4, 154.6, 136.1, 85.7, 69.1, 56.5, 45.9, 39.4, 35.5, 33.6, 29.3, 28.7, 25.4; IR (NaCl, neat) 2955, 2868, 1762, 1696, 1358, 1117 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{32}O_3$, 320.2351. Found 320.2351.



(1,2,6-Trimethyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (30): Rf = 0.24 (2:1 EtOAc/Hex); 35 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.08 (s, 2H), 3.59 (s, 2H), 1.92 (s, 6H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 184.3, 158.6, 129.2, 76.8, 70.1, 24.2, 17.6; IR (NaCl, neat) 2991, 1736, 1672, 1634, 1094, 895 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.094.

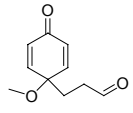


3a,7,7a-Trimethyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (31): Rf = 0.48 (2:1 EtOAc/Hex); 64 % yield; $[\alpha]_D^{21}$ = + 79.6 (c = 1.2, $CHCl_3$); HPLC analysis – Chiracel OD-H column 97:3 hexanes : isopropanol 1.0 mL / min. Major: 27.4 minutes, Minor: 31.4 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.18 (d, 1H, *J* = 17.6 Hz), 3.64 (d, 1H, *J* = 17.6 Hz), 2.90 (d, 1H, *J* = 18.0), 2.26 (d, 1H, *J* = 18.0), 2.01 (s, 3H), 1.49 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 194.2, 162.0, 130.2, 83.1, 68.0, 50.7, 40.5, 19.2, 18.3, 17.9; IR (NaCl, neat) 2971, 1752, 1665, 1265, 1045, 866 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0946.

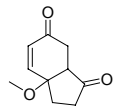


32a

4-(3-hydroxypropyl)-4-methoxycyclohexa-2,5-dienone (32a). A flame-dried 25 ml round bottom flask was charged with 4-(3-hydroxypropyl)-phenol (Aldrich) (152 mg, 1.0 mmol) and 5 ml methanol, then $PhI(OAc)_2$ (386 mg, 1.2 mmol, dissolved in 5 ml methanol) was added dropwise. The solution was then allowed to stir at ambient temperature for further 2 hours. The solution was concentrated in *vacuo* and the residue subjected to column chromatography to provide 32a (116 mg, 64 %); Rf = 0.18 (2:1 EtOAc/Hex).



3-(1-methoxy-4-oxocyclohexa-2,5-dienyl)propanal (32): A flame-dried 10 ml round bottom flask was charged with **32a** (110 mg, 0.6 mmol) and 6 ml methylene chloride, then Dess Martin periodinane (380 mg, 0.9 mmol) was added to the solution directly. The solution was then allowed to stir at ambient temperature for further 1.5 hours. The solution was filtered through Celite 545 and then concentrated in *vacuo*. The residue was subjected to column chromatography to provide **32** (74 mg, 68 %). Rf = 0.45 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, 1H, *J* = 1.2 Hz), 6.73 (d, 2H, *J* = 10.3 Hz), 6.37 (d, 2H, *J* = 10.3 Hz), 3.21 (s, 3H), 2.49 (dt, 2H, *J* = 7.6 Hz, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 185.1, 150.3, 132.0, 74.9, 53.4, 38.4, 31.5; IR (NaCl, neat) 2934, 2827, 1722, 1670, 1634, 1082 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0787.



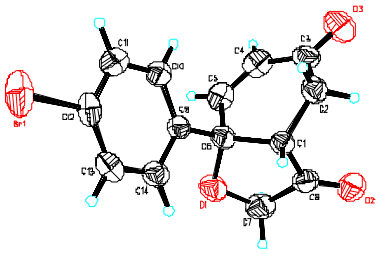
3a-methoxy-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (33): A flame-dried 25 ml round bottom flask was charged with triazolium salt **3** (4.9 mg, 0.1 equiv.). The flask was purged under vacuum for 5 mins and then refilled with argon and 6 ml toluene. Argon was bubbled through the solution for 5 mins, and then 0.1 equiv. KHMDS (0.024 ml) was added and the solution was allowed to stir at ambient temperature for 15 minutes. Toluene and HMDS was removed *in vacuo* by being placed under high vacuum for about 1 hour.[3] 12 ml toluene was then added and argon was bubbled through the solution for 5 mins. **32** (21.6 mg, 1 equiv.) was dissolved in 3 ml toluene and then was added via syringe and the reaction was allowed to stir at ambient temperature for 16 hours. The reaction was quenched by 1ml glacial AcOH and then subjected to column chromatography to provide **33** (13 mg, 60 %). [Pre-elute the column using Hexane (10 % volumn of AcOH in it) and then elute the column with Hexane and ethyl acetate (1 % AcOH in it)][4]; Rf = 0.36 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 200.7 (c = 0.82, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with

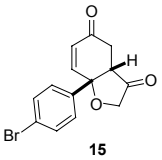
[3] Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284-6289.

[4] We have observed that this product decomposes by methanol elimination and tautomerization to hydroxyindanone on silica gel. These precautions prevent this problem.

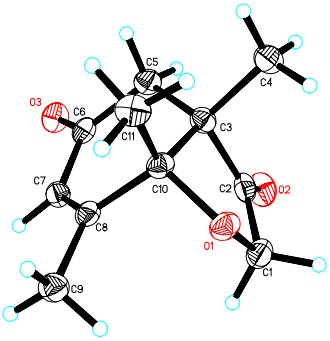
constant 170 ºC oven temperature. Major: 8.3 min, Minor: 8.6 minutes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, 1H, J = 10.3 Hz, J = 1.2 Hz), 6.21 (d, 1H, J = 10.3 Hz), 3.42 (s, 3H), 2.81-2.95 (m, 2H), 2.58-2.77 (m, 2H), 2.13-2.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 195.4, 147.7, 133.3, 78.7, 52.2, 51.4, 36.3, 34.8, 32.8; IR (NaCl, neat) 2917, 2827, 1744, 1683, 1384, 1087 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0787.

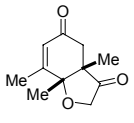
Absolute configurations of 15 and 31[5]:





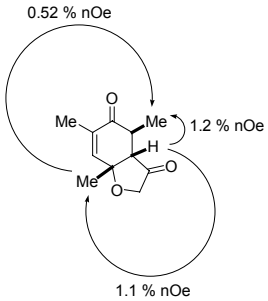
15



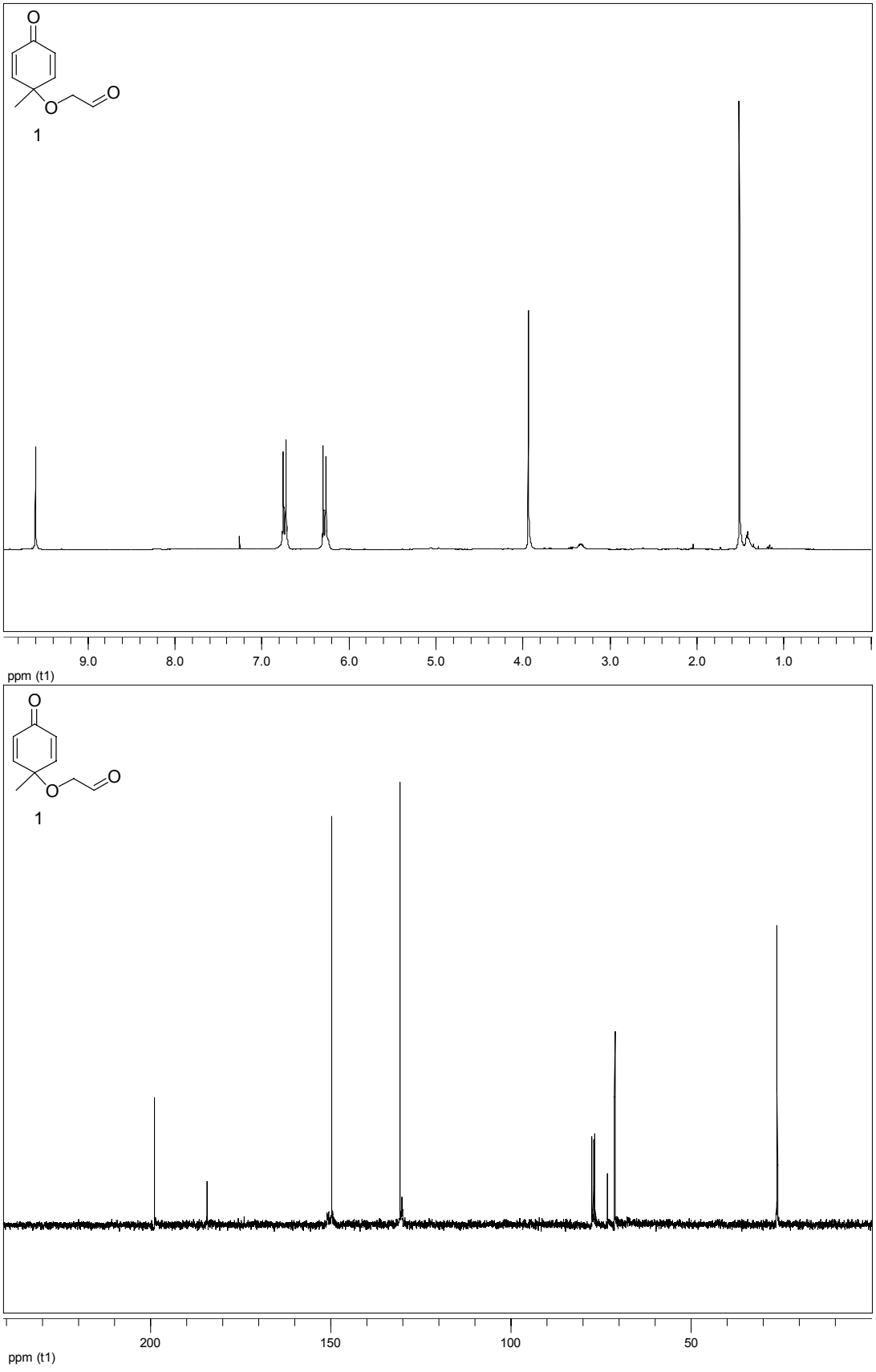


31

NOE experiment of 23:



[5] Determined by anomalous dispersion. See: Thiessen, W.; Hope, H. *Acta Cryst.* **1970**, *B26*, 554-62.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6.0
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2.0
1.0
ppm (t1)
O
O
O
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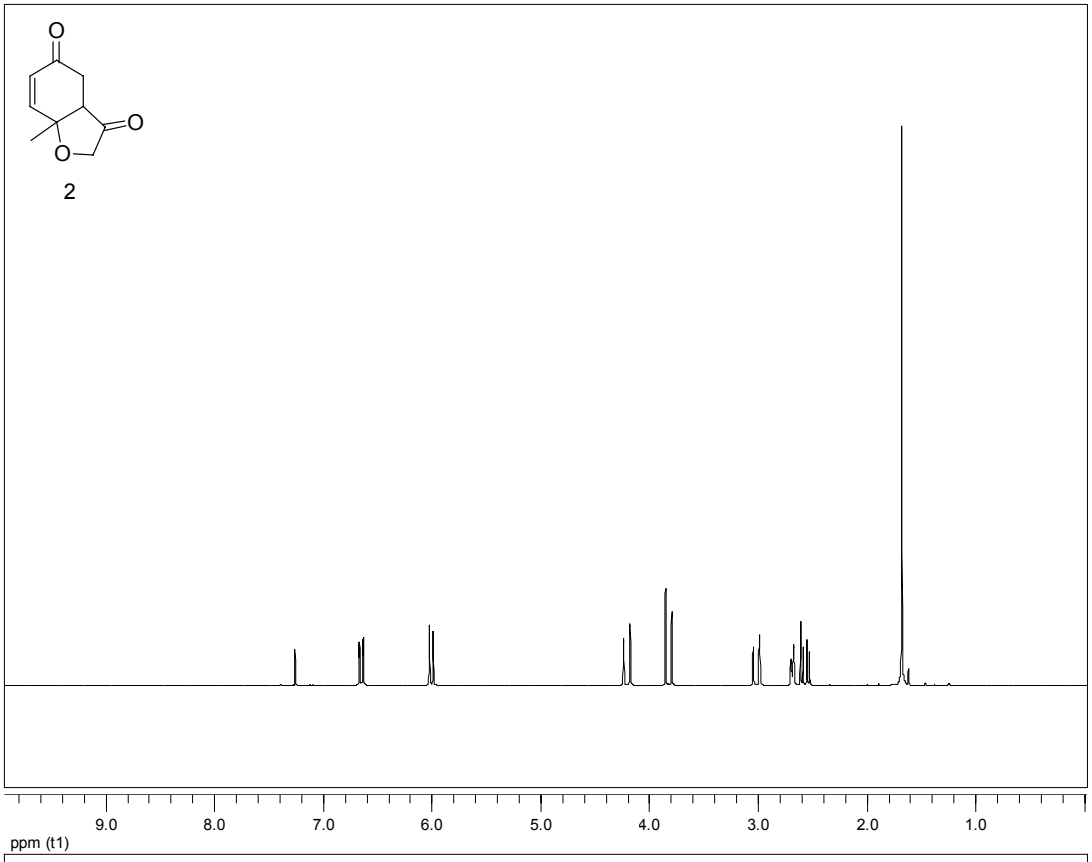
150
100
50
ppm (t1)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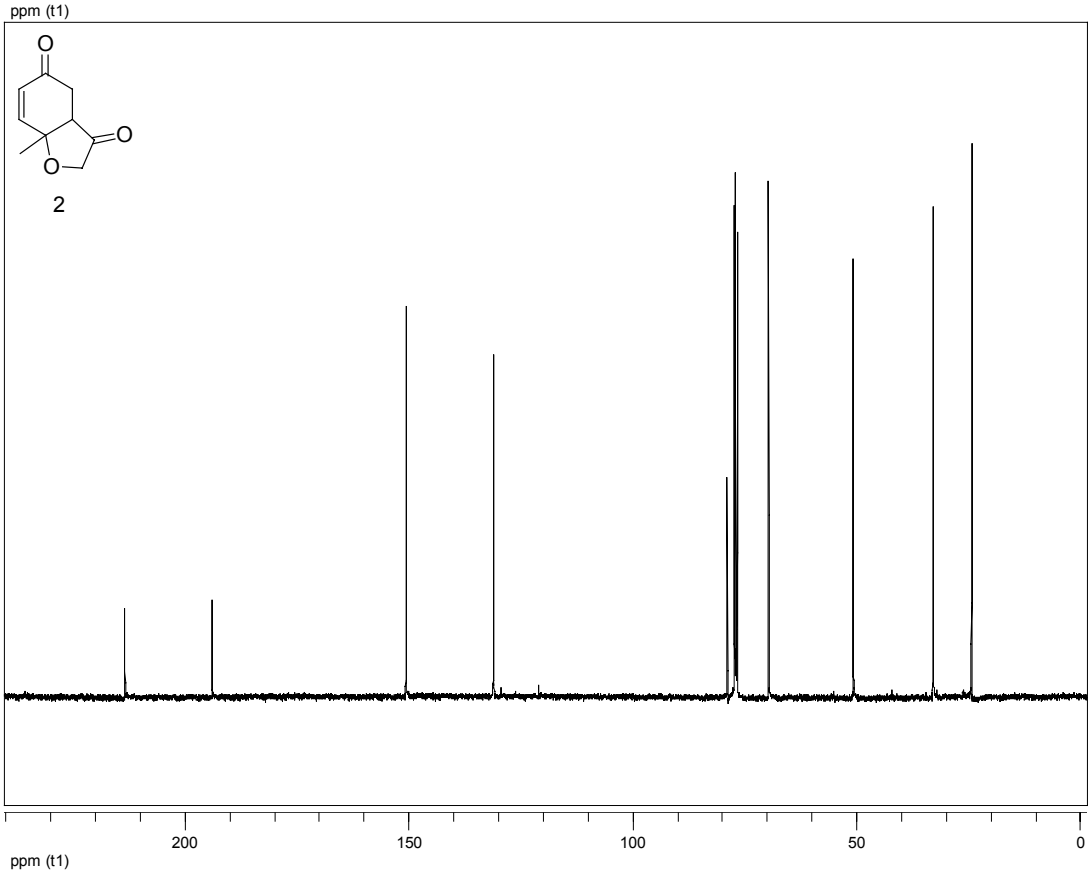
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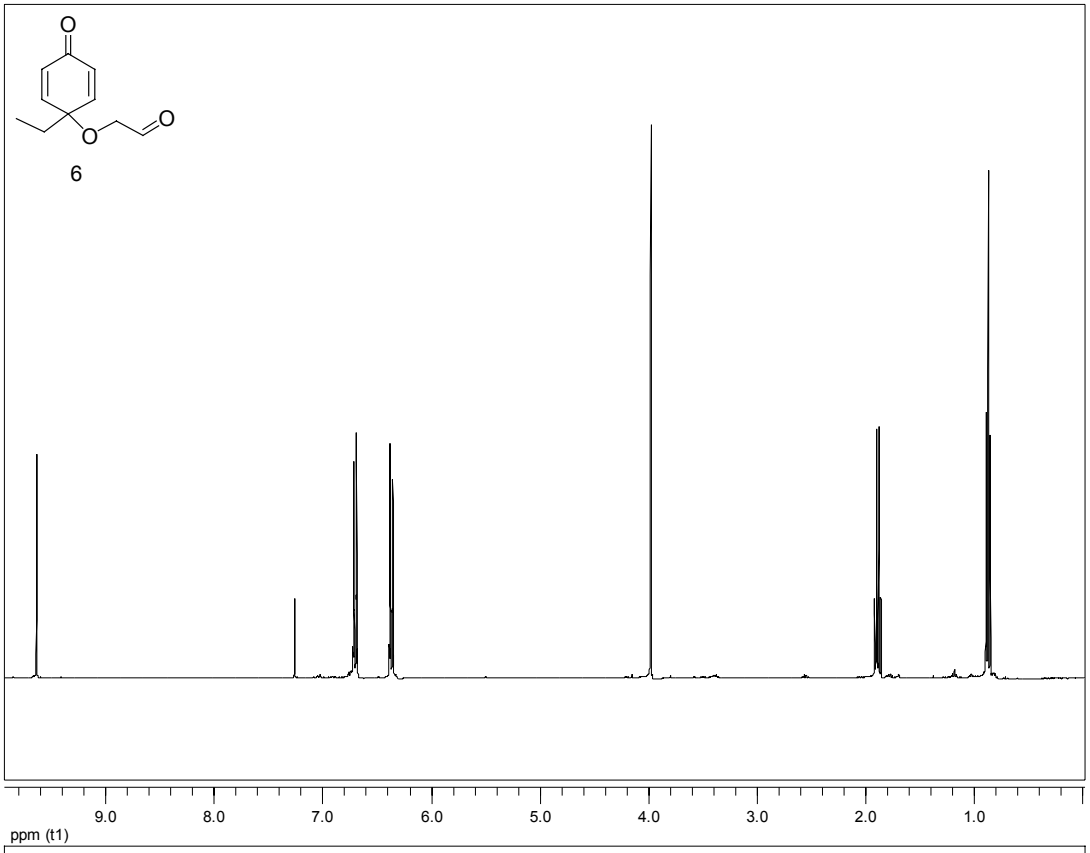
0
ppm (t1)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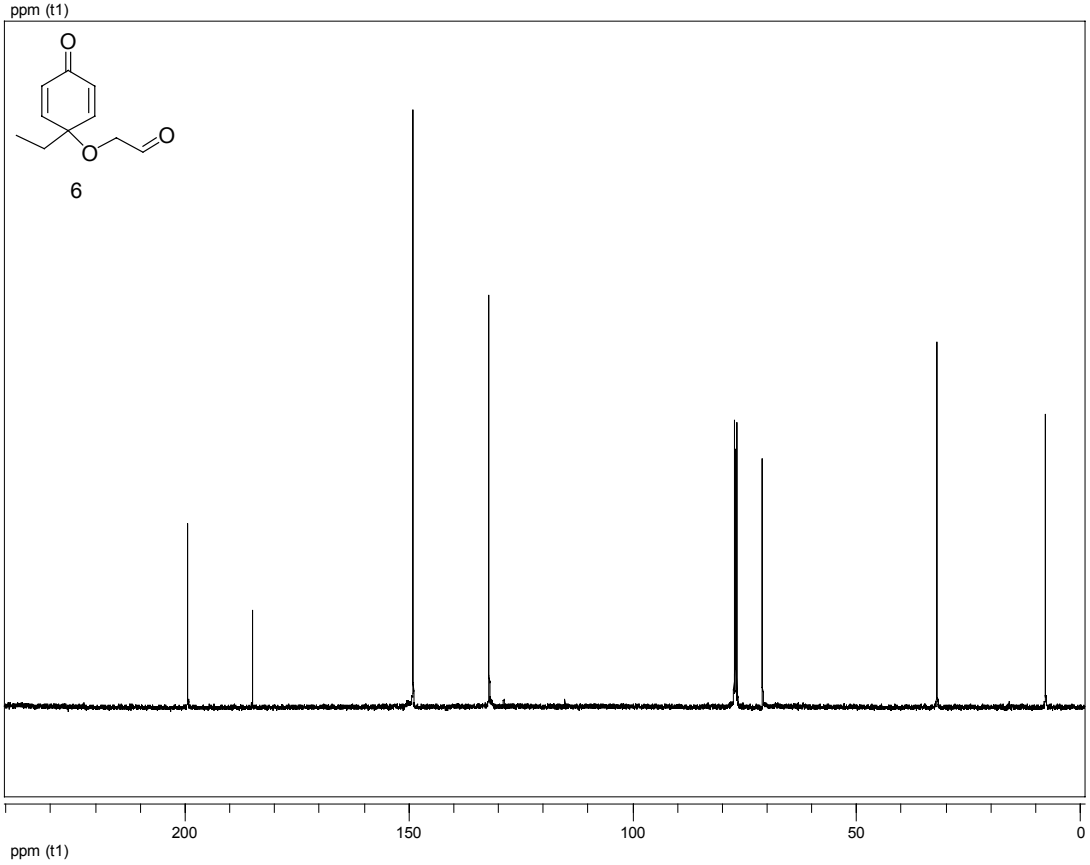
1.0
ppm (t1)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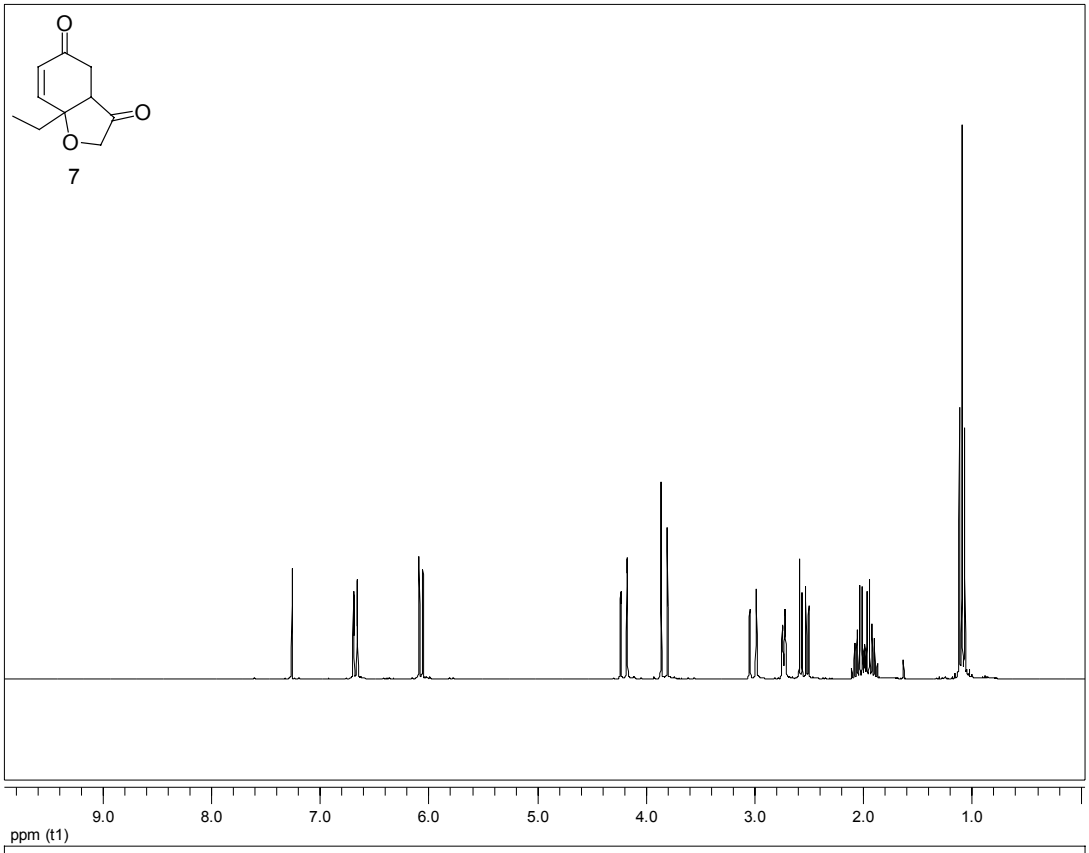
ppm (t1)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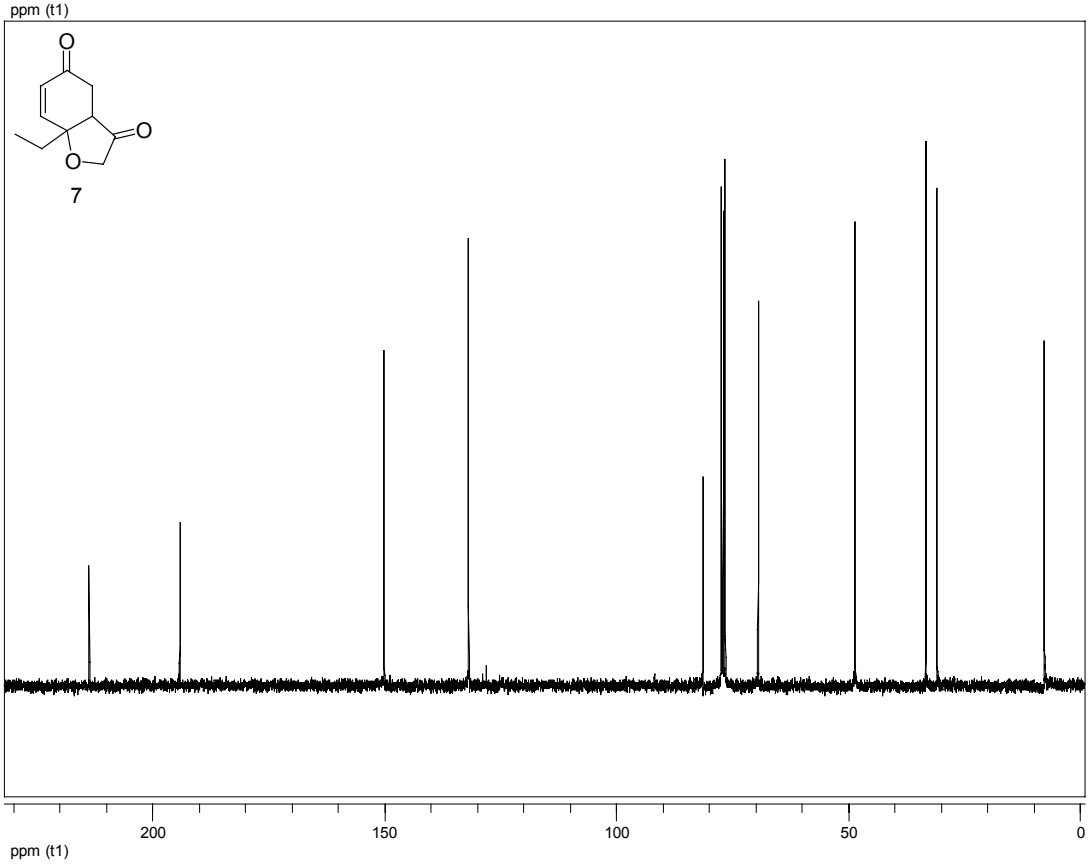
2.0
1.0
ppm (t1)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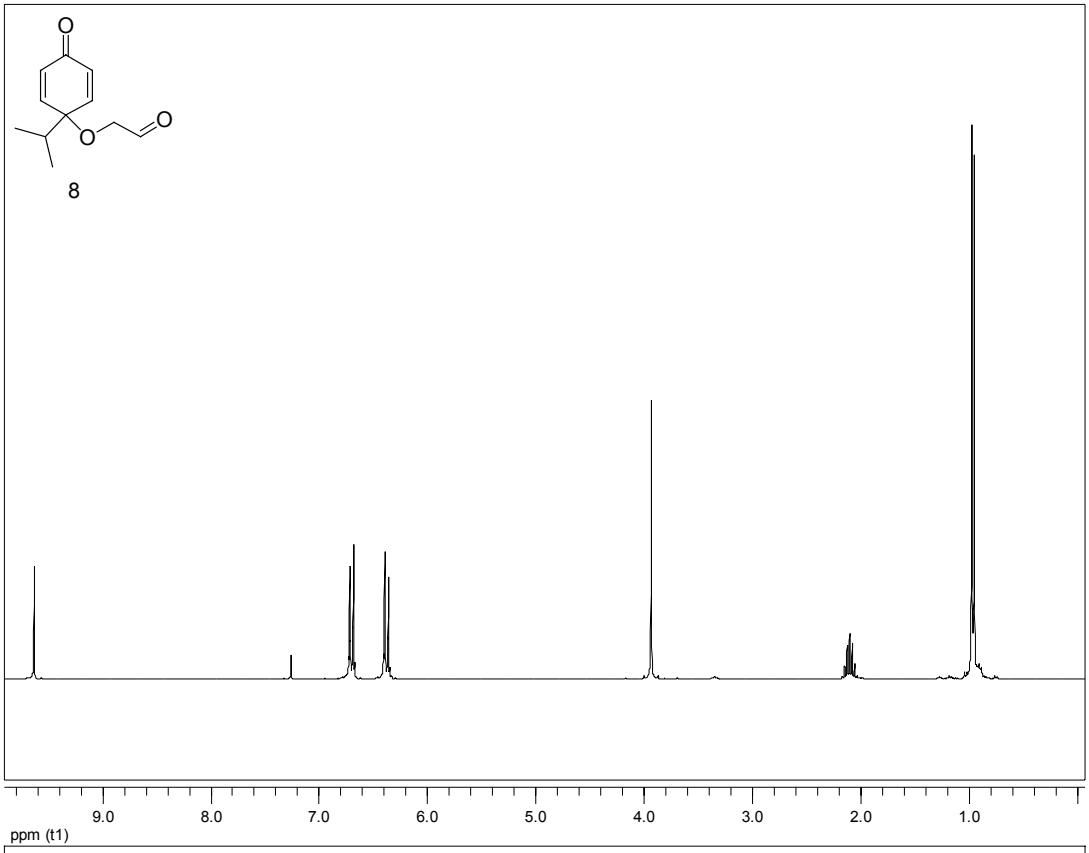
ppm (t1)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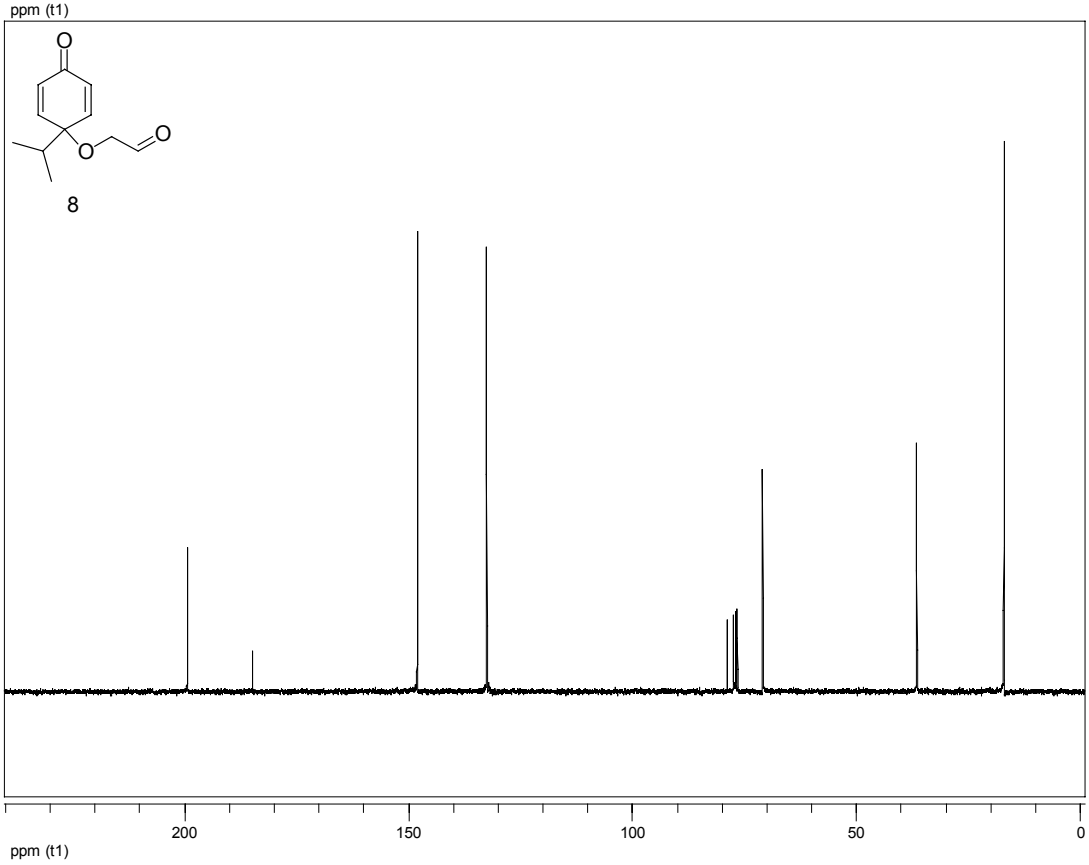
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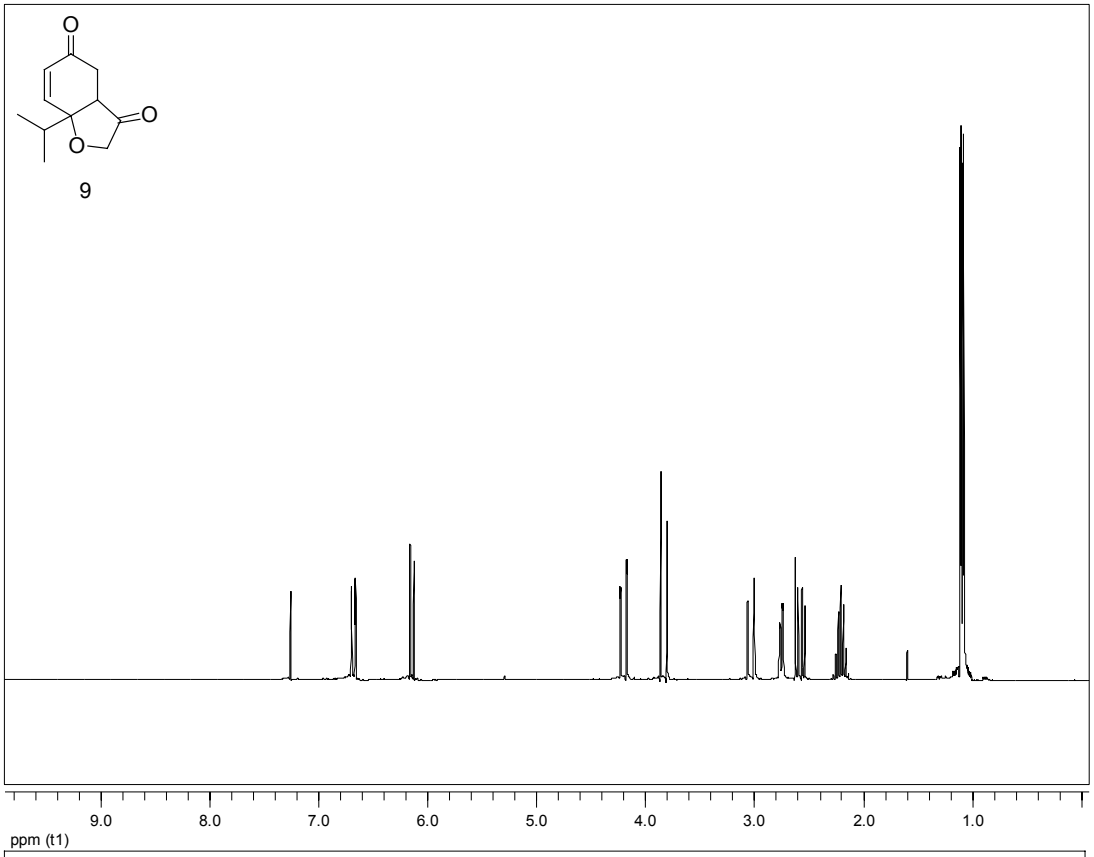
ppm (t1)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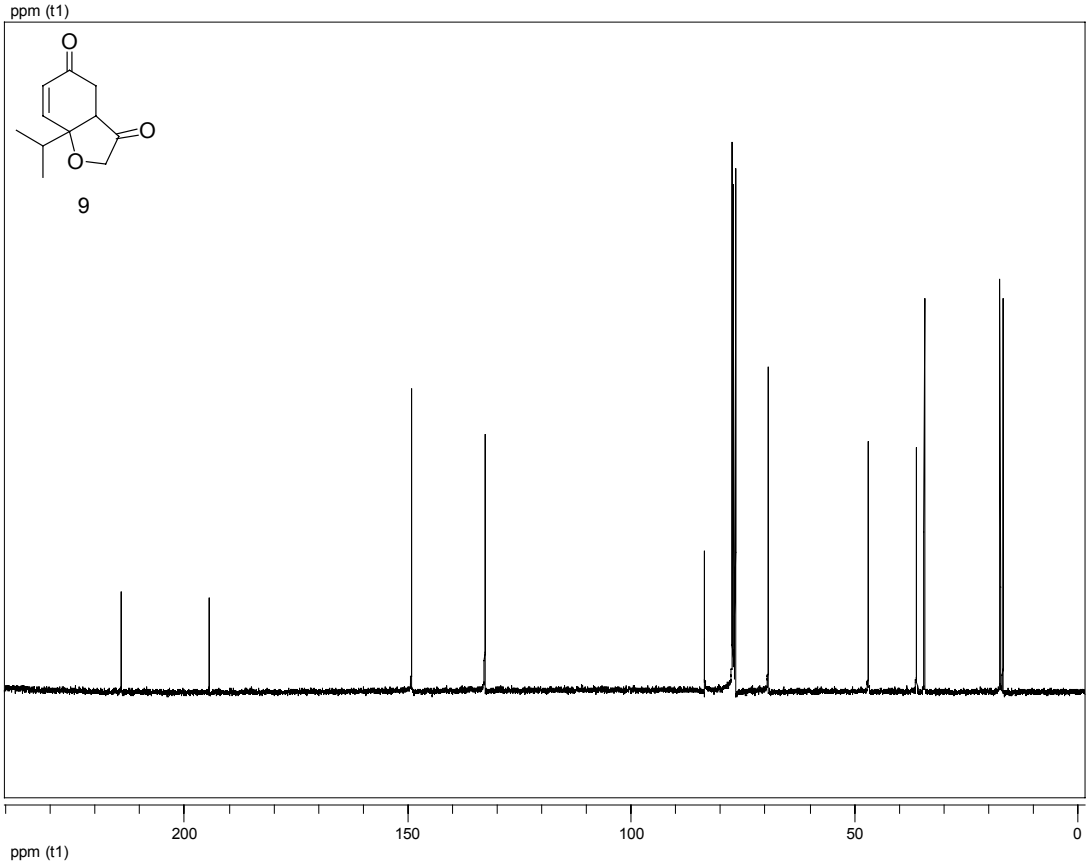
ppm (t1)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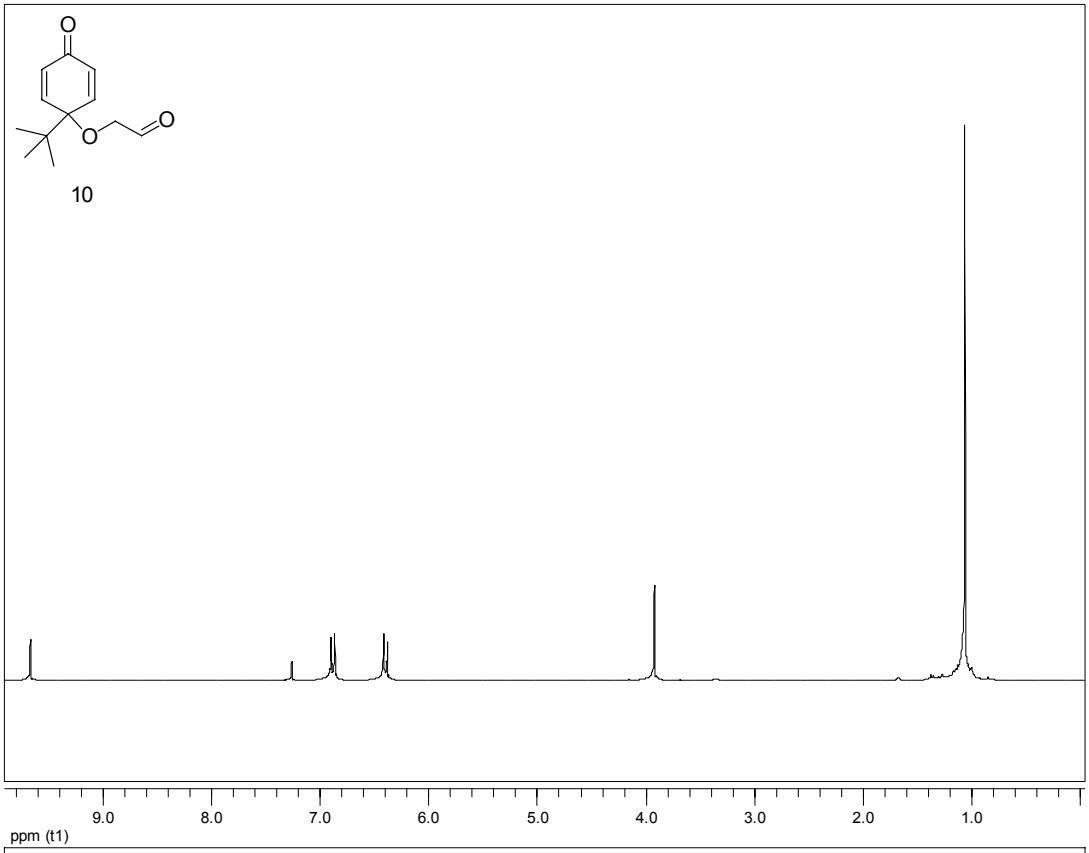
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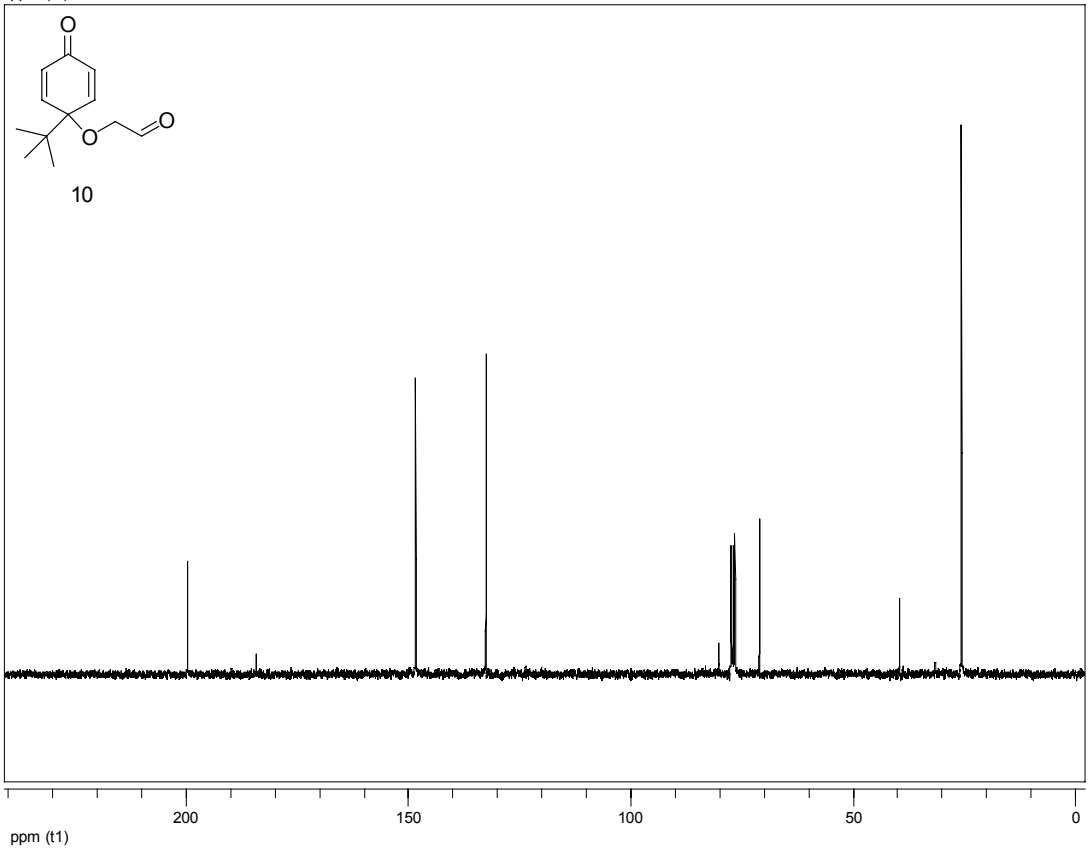
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50
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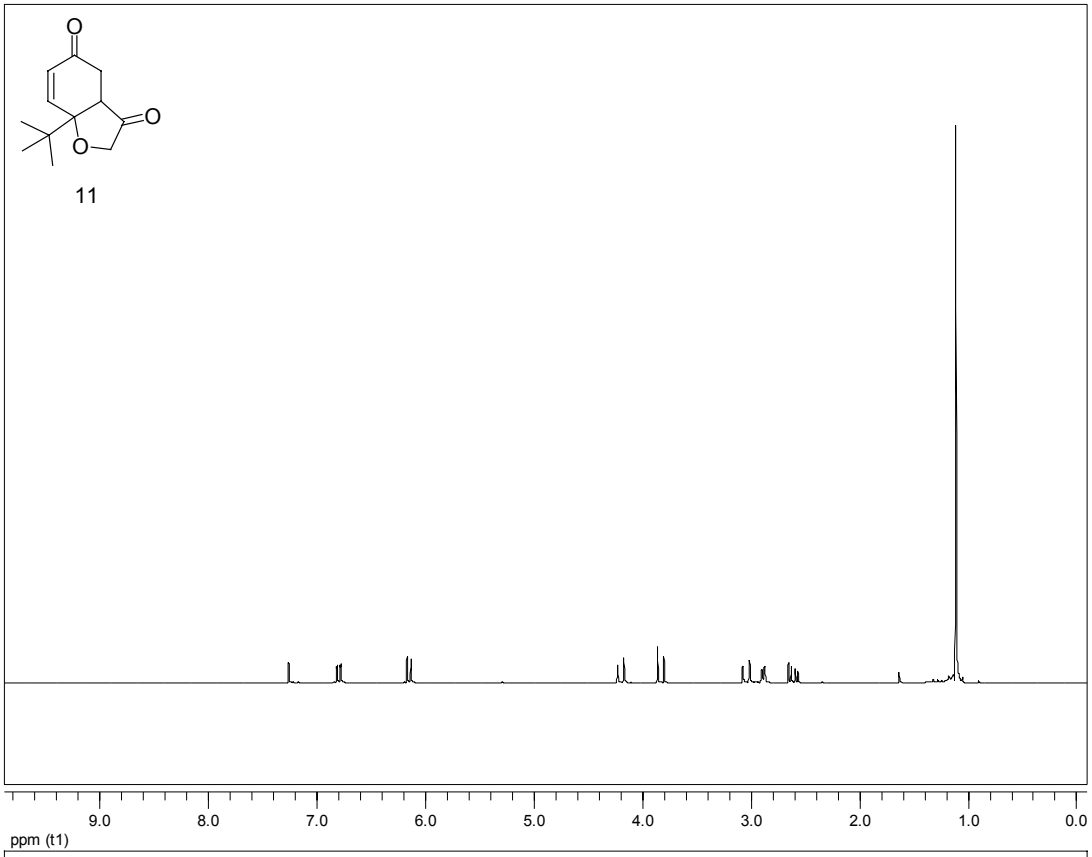
ppm (t1)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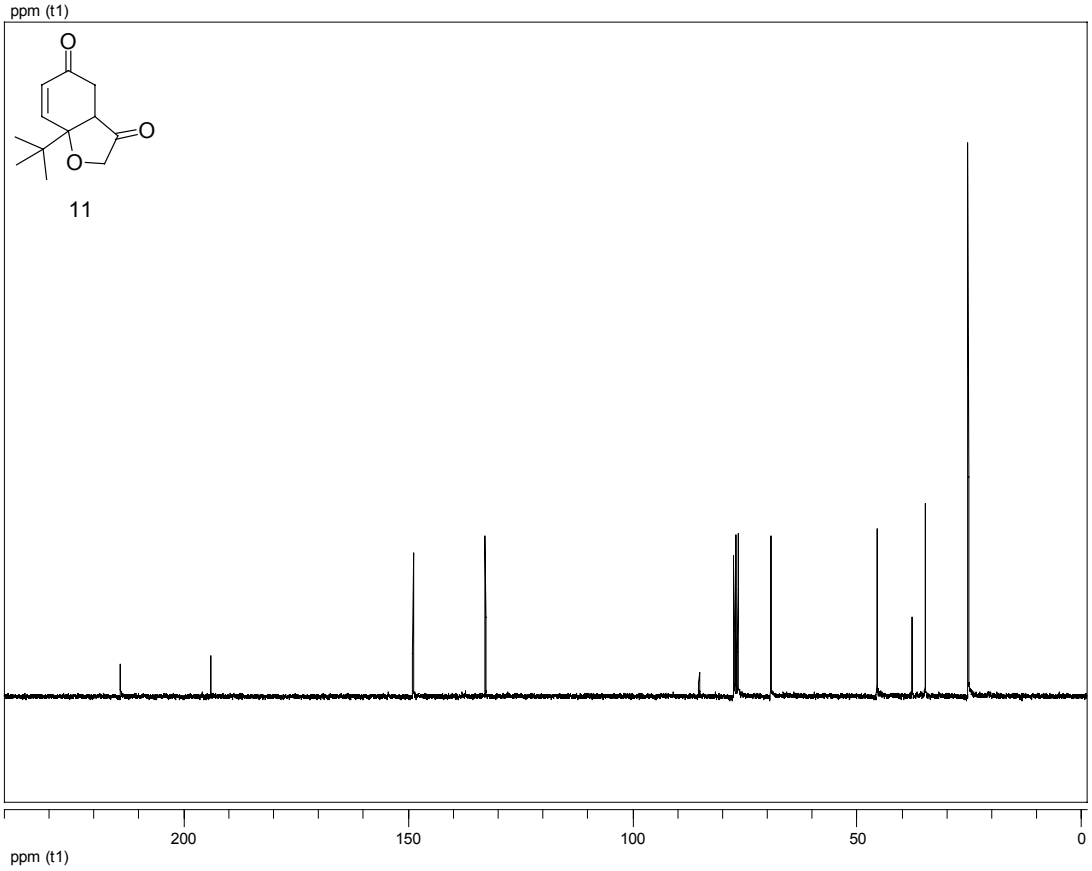
ppm (t1)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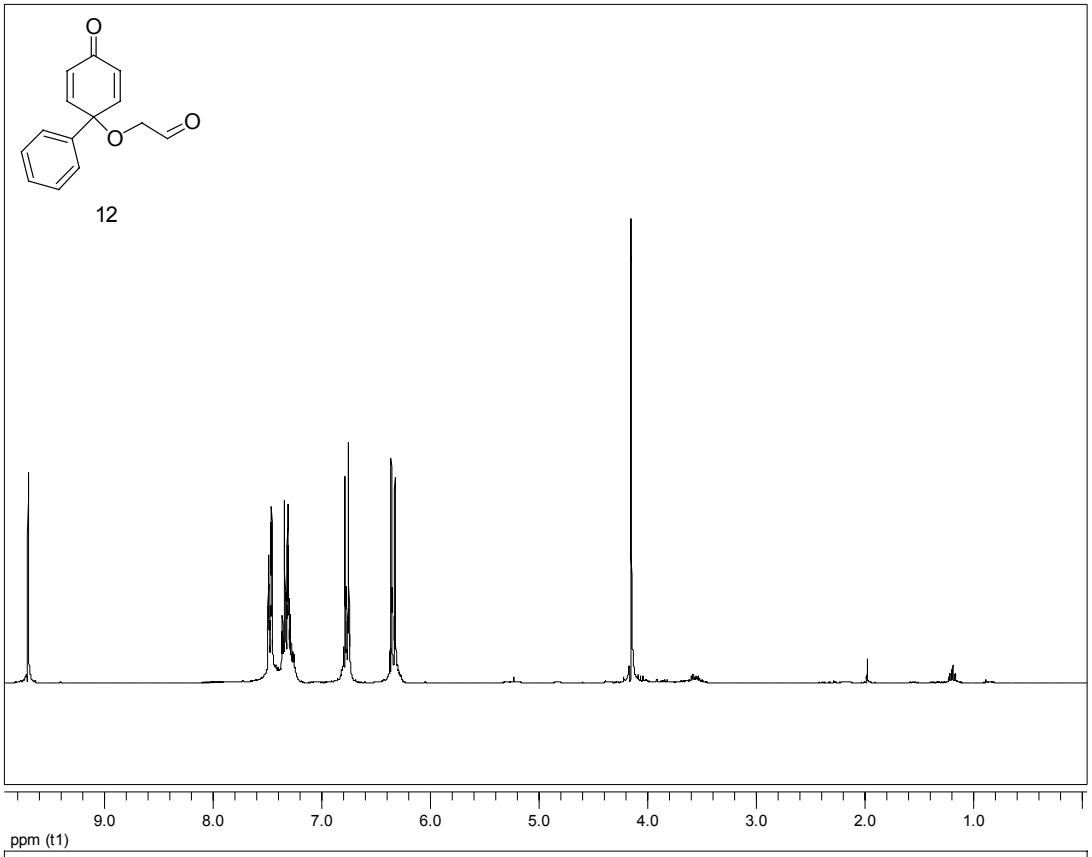
ppm (t1)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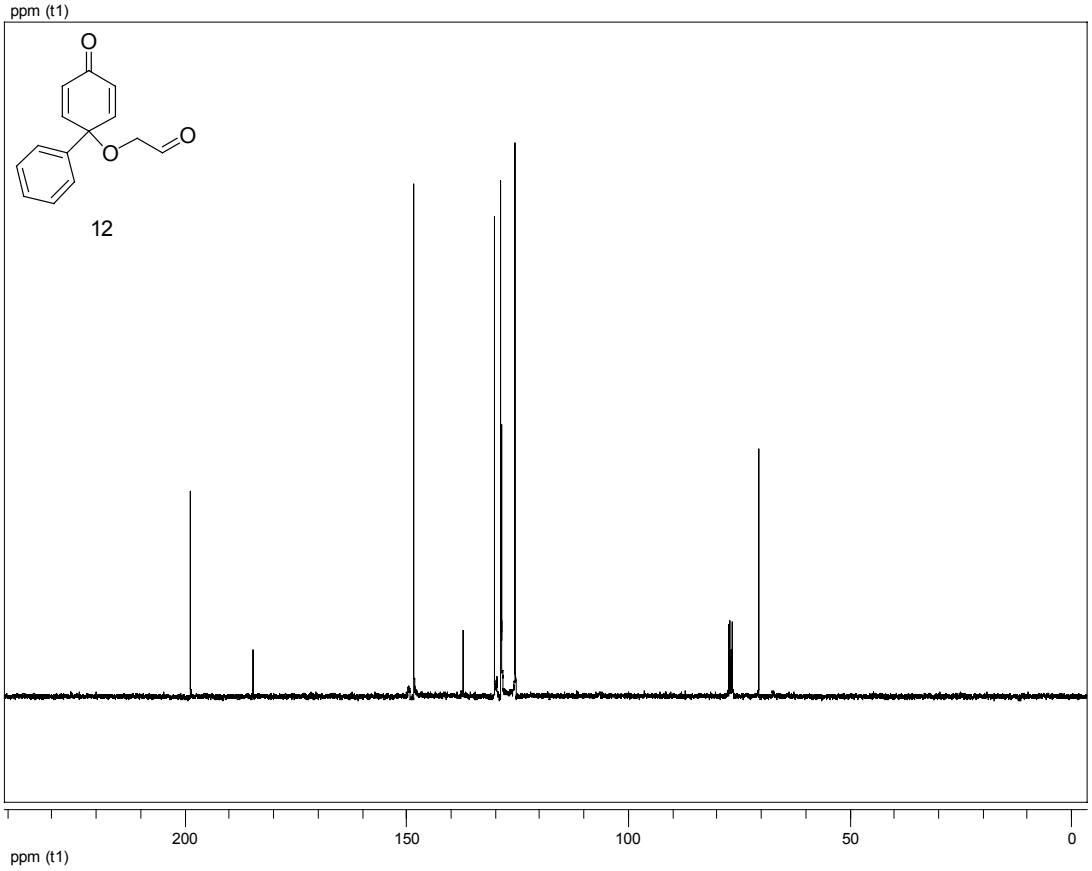
1.0
ppm (t1)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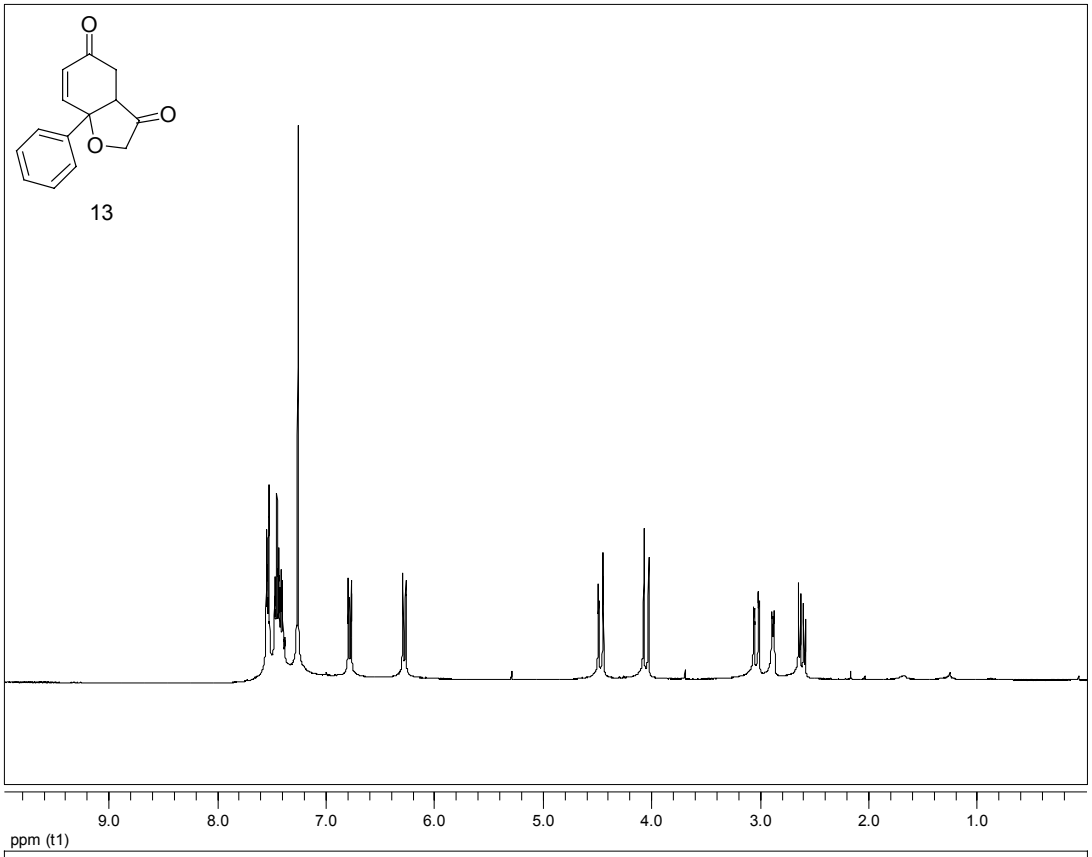
ppm (t1)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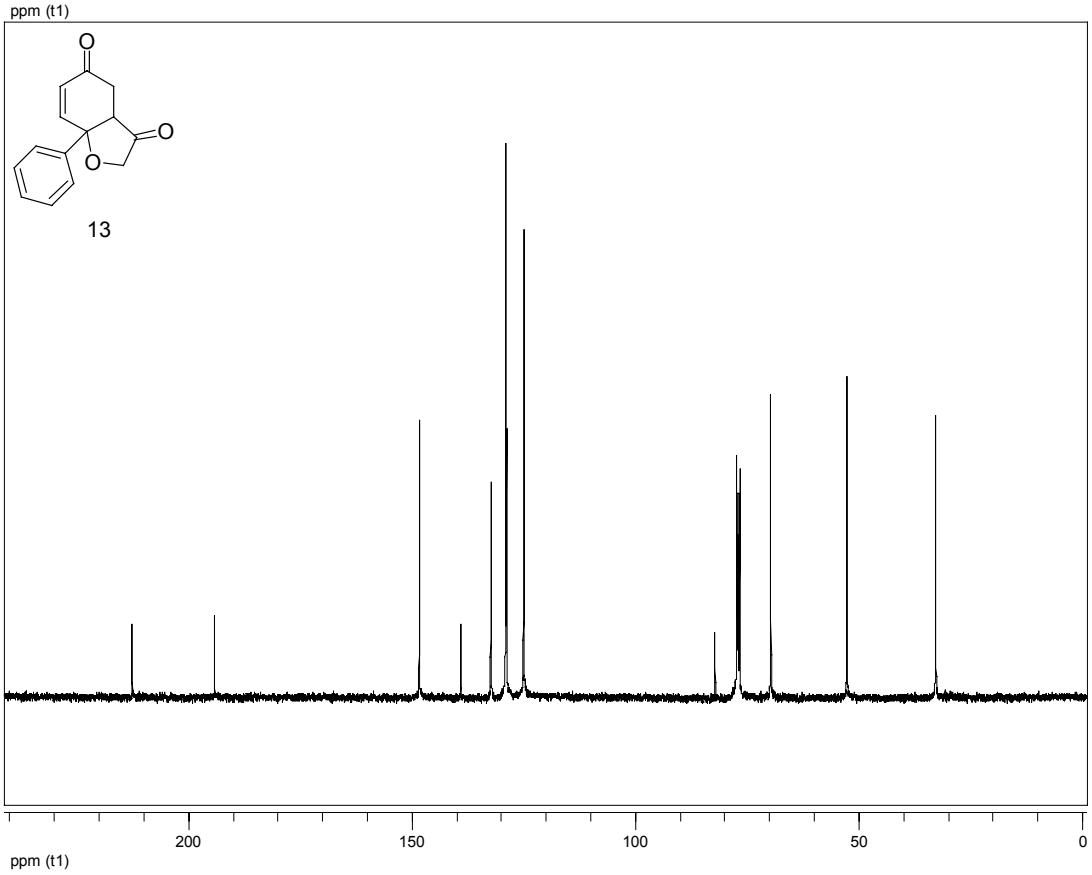
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O
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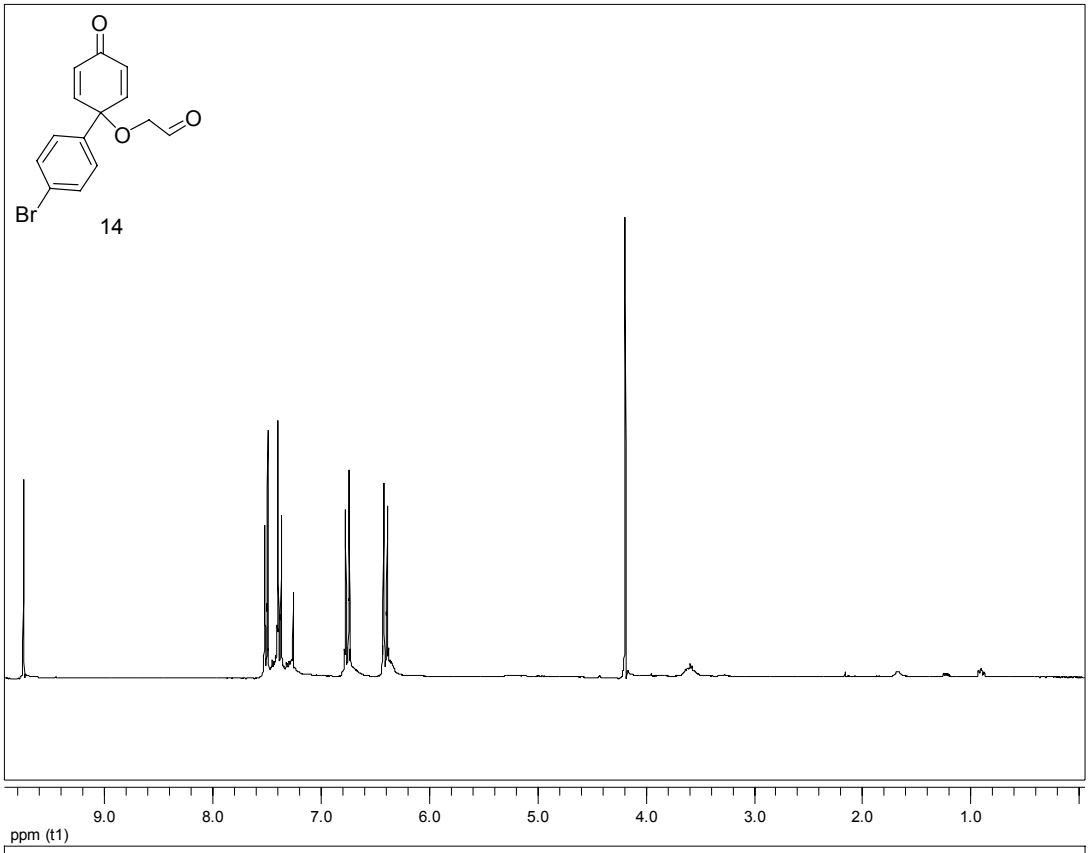
150
100
50
0
ppm (t1)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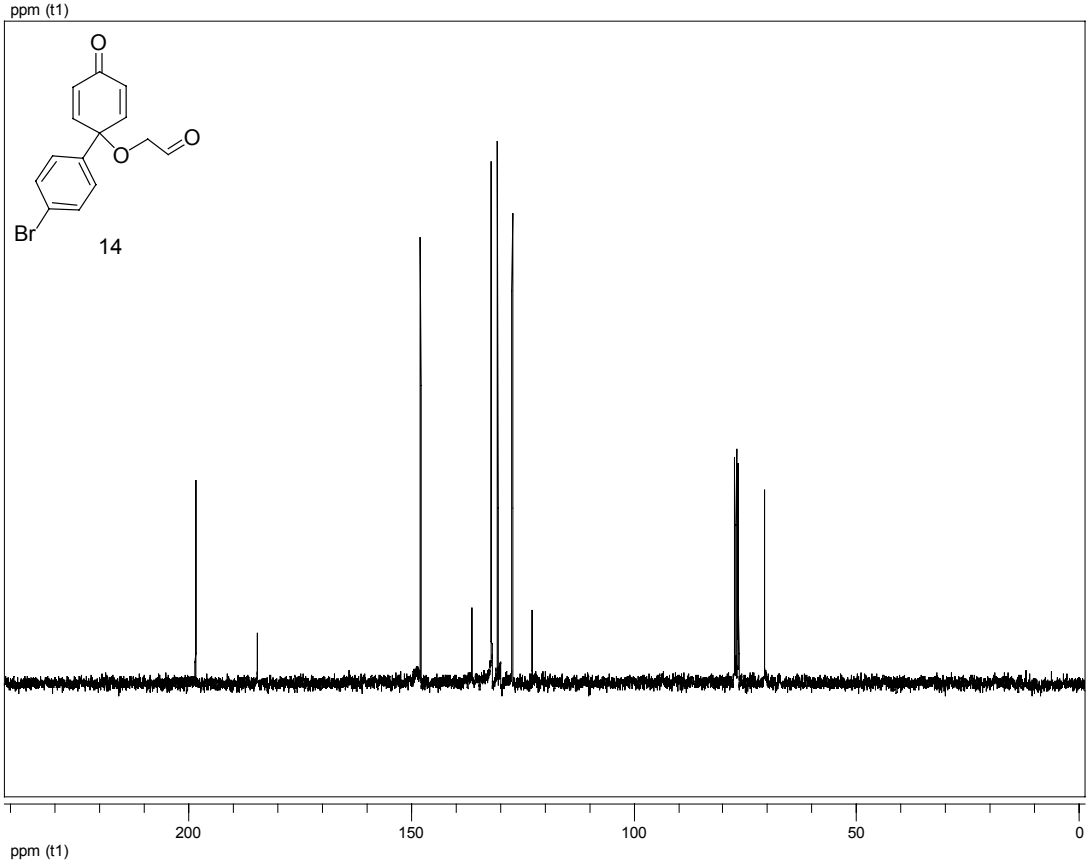
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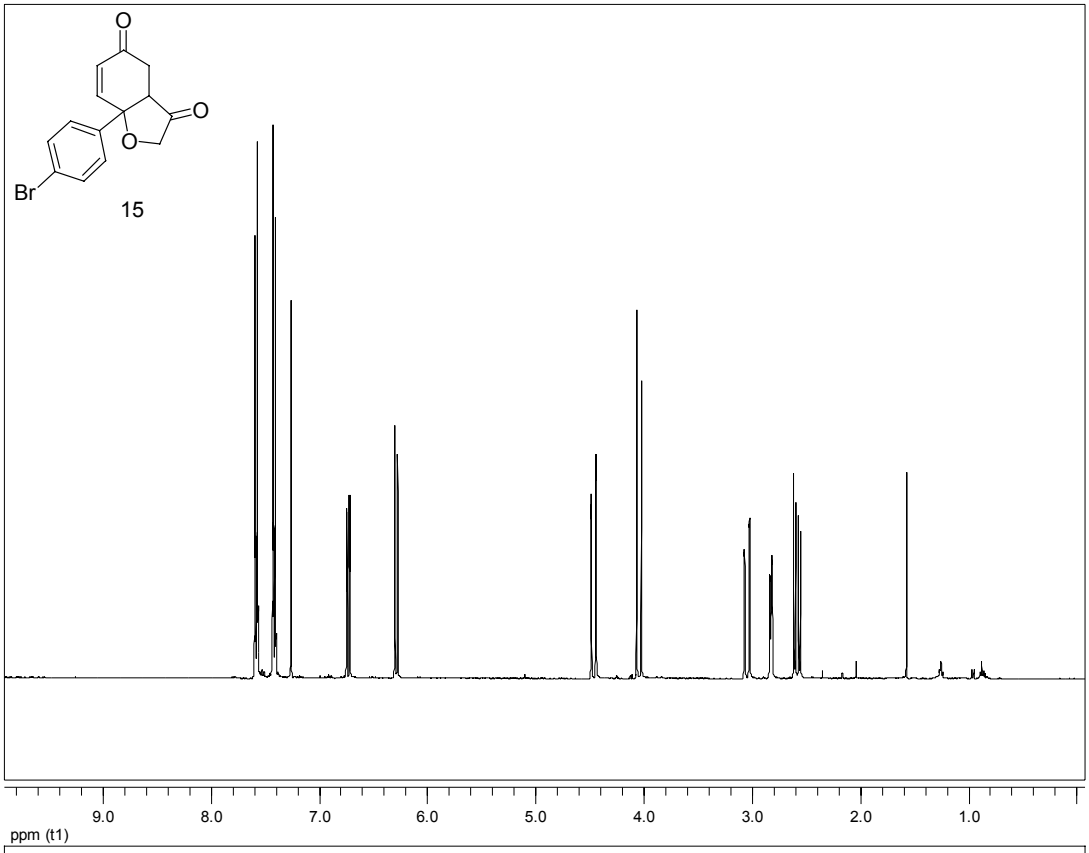
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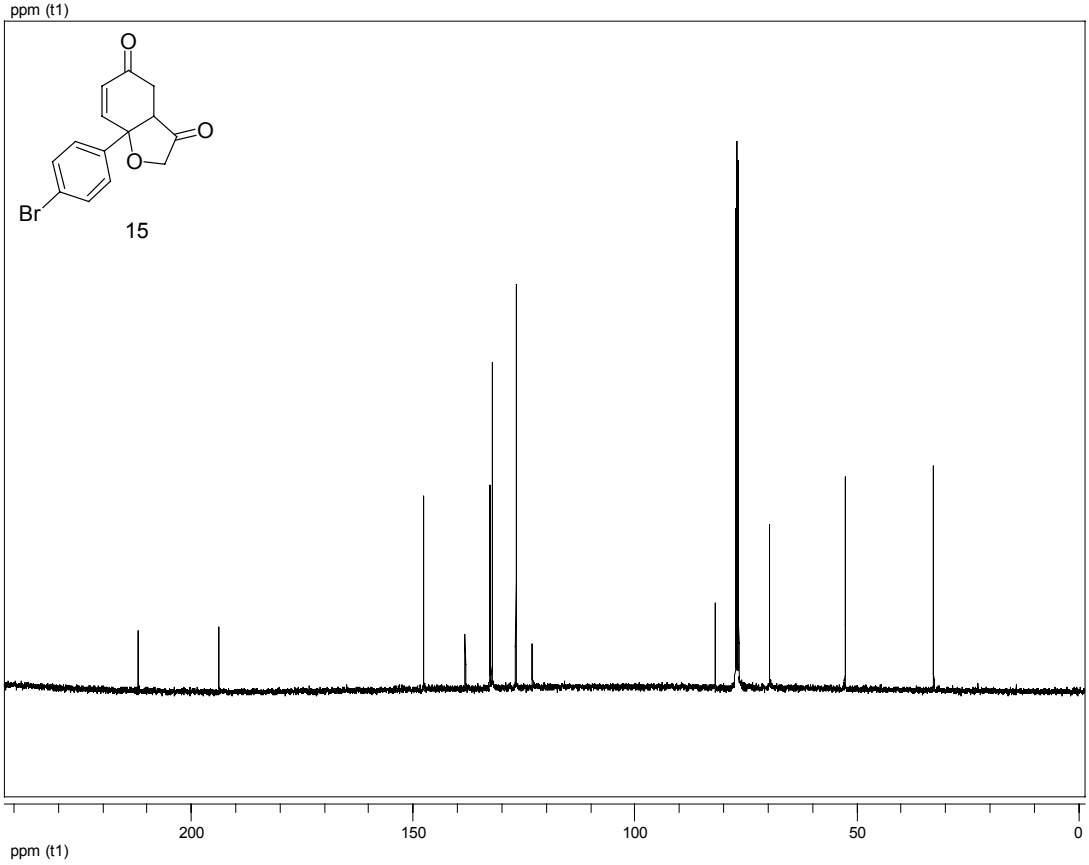
ppm (t1)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Br
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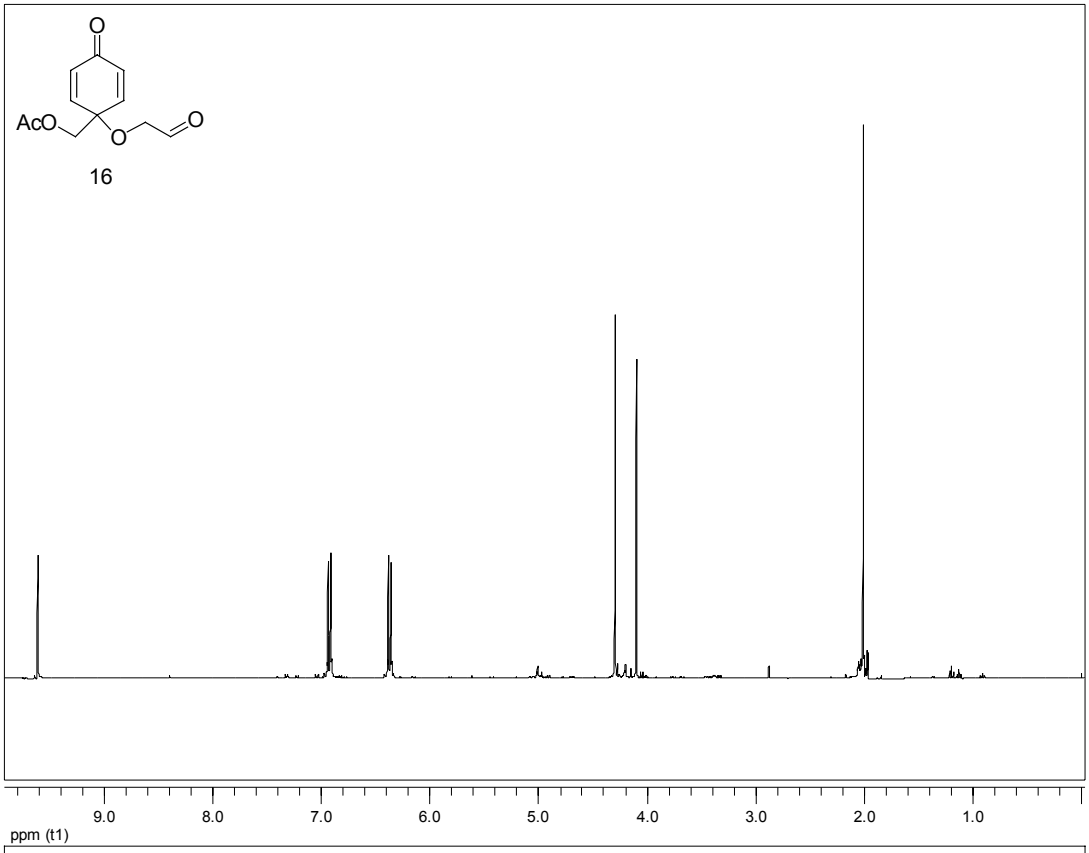
ppm (t1)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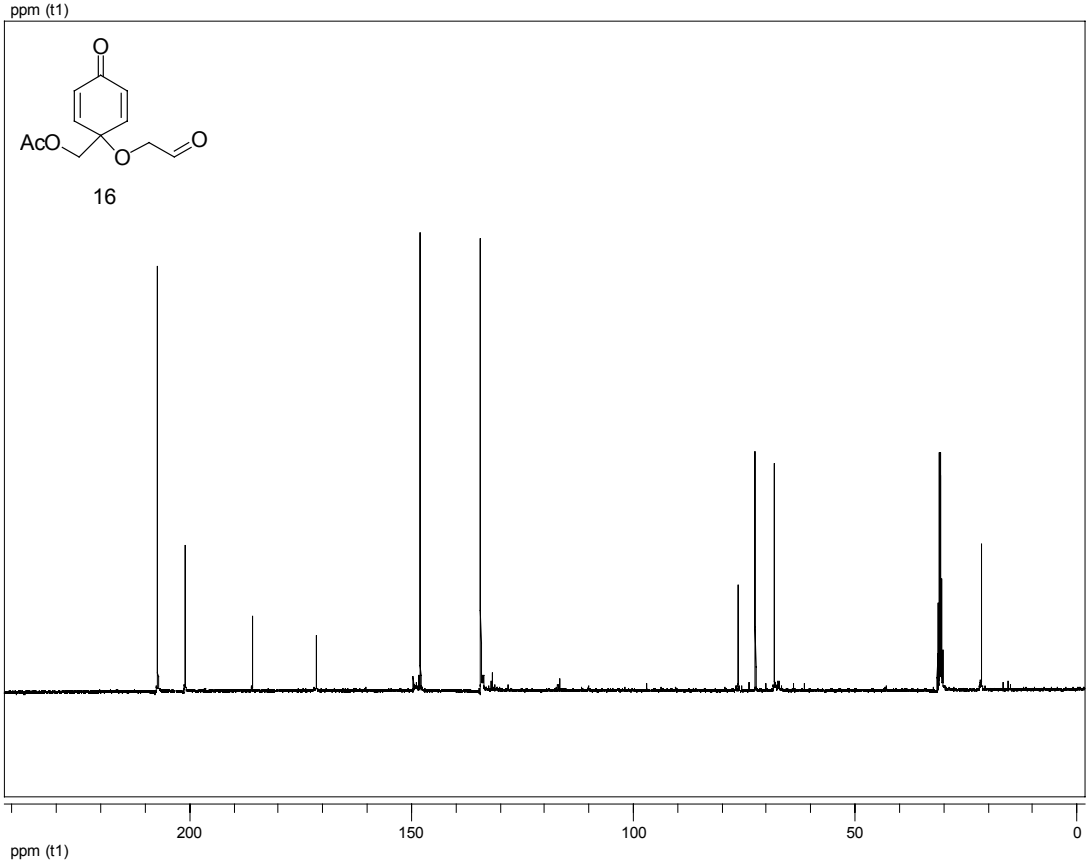
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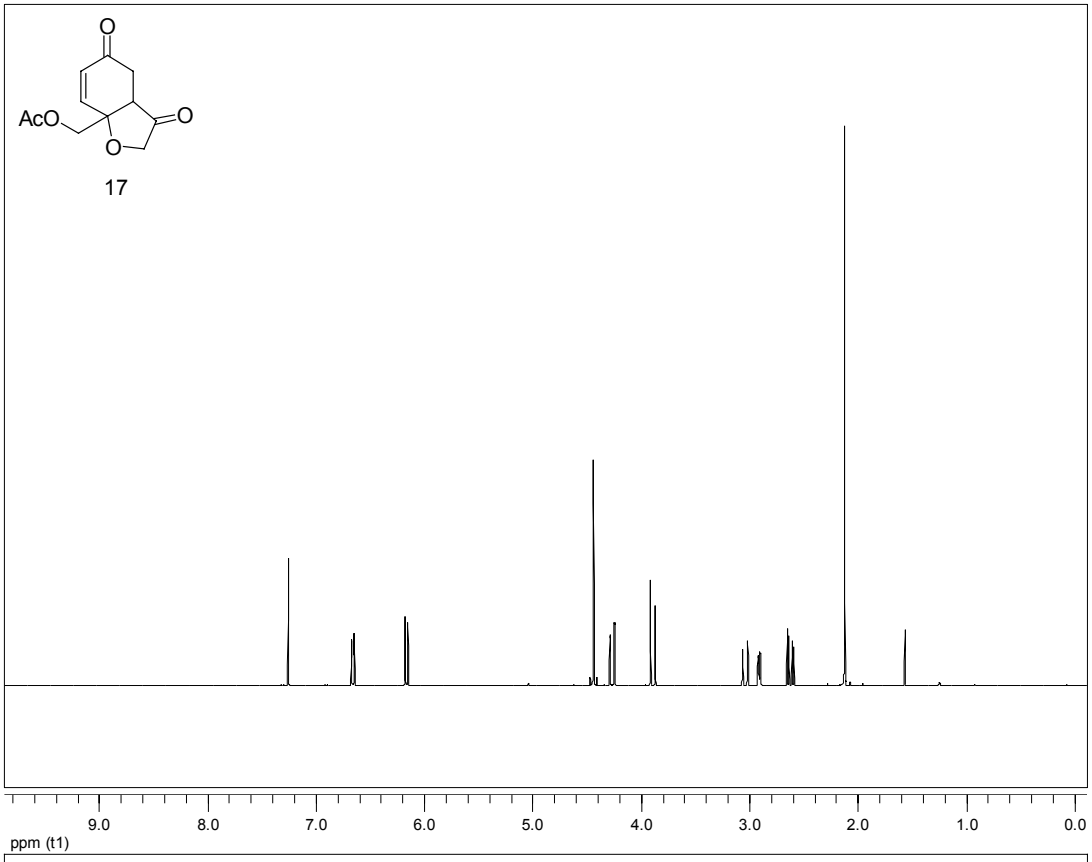
AcO
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5.0
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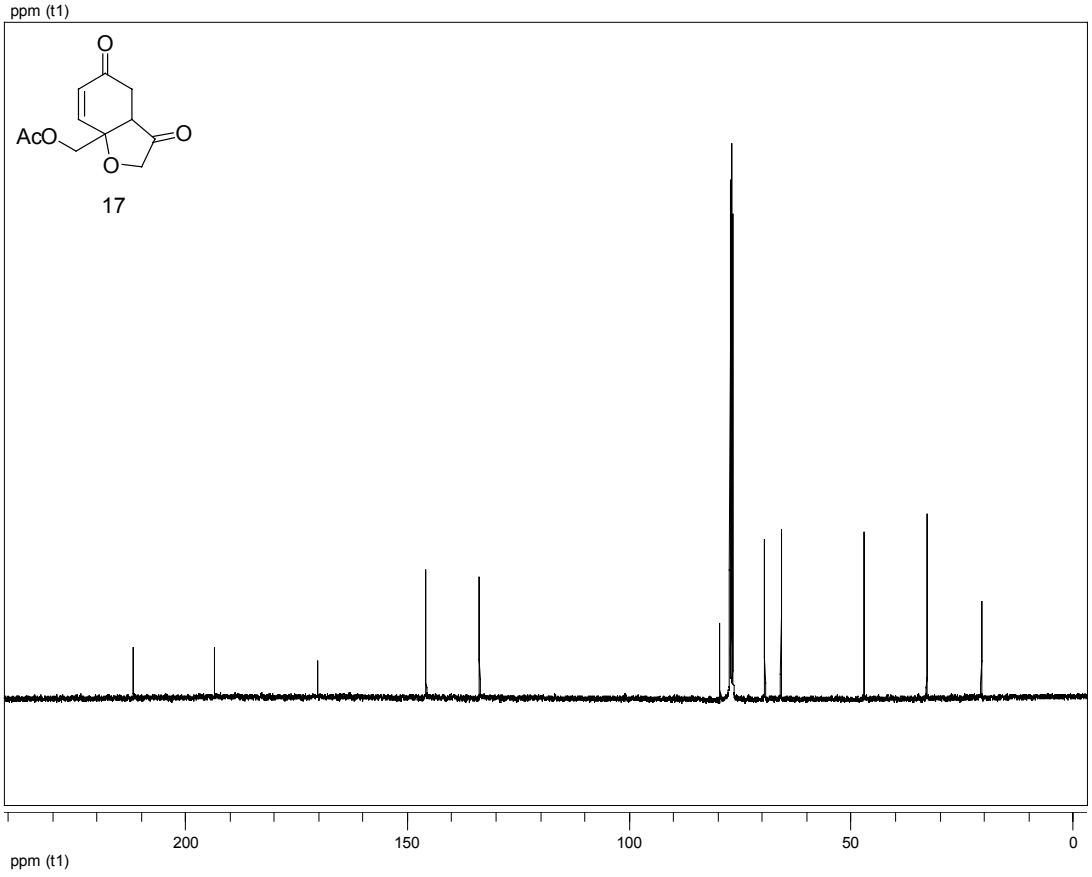
ppm (t1)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17
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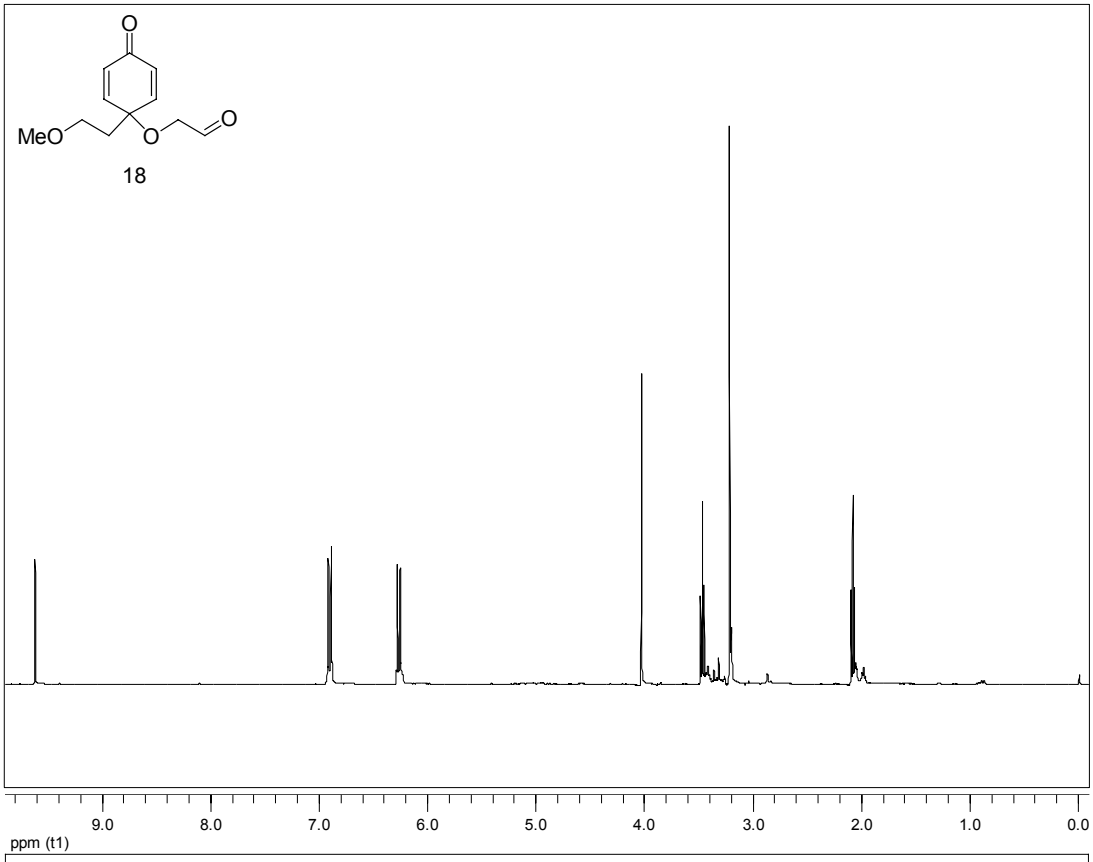
ppm (t1)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3.0
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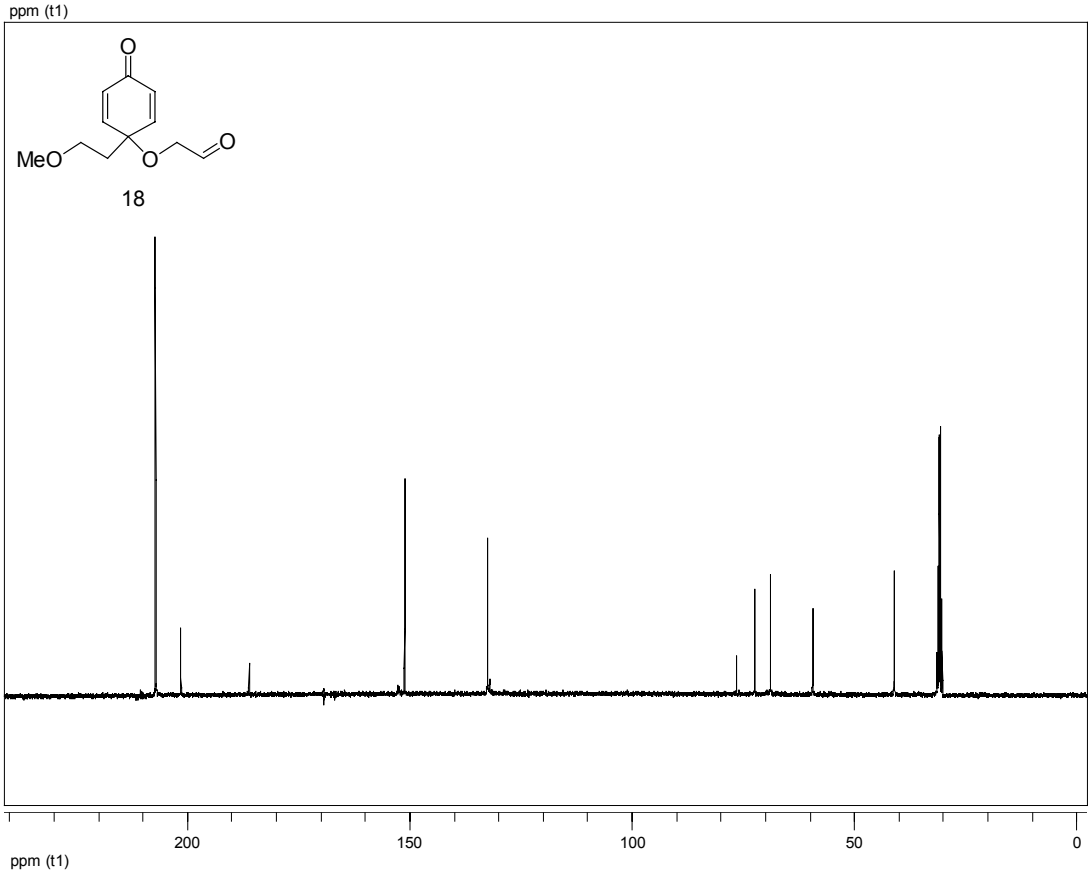
ppm (t1)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O
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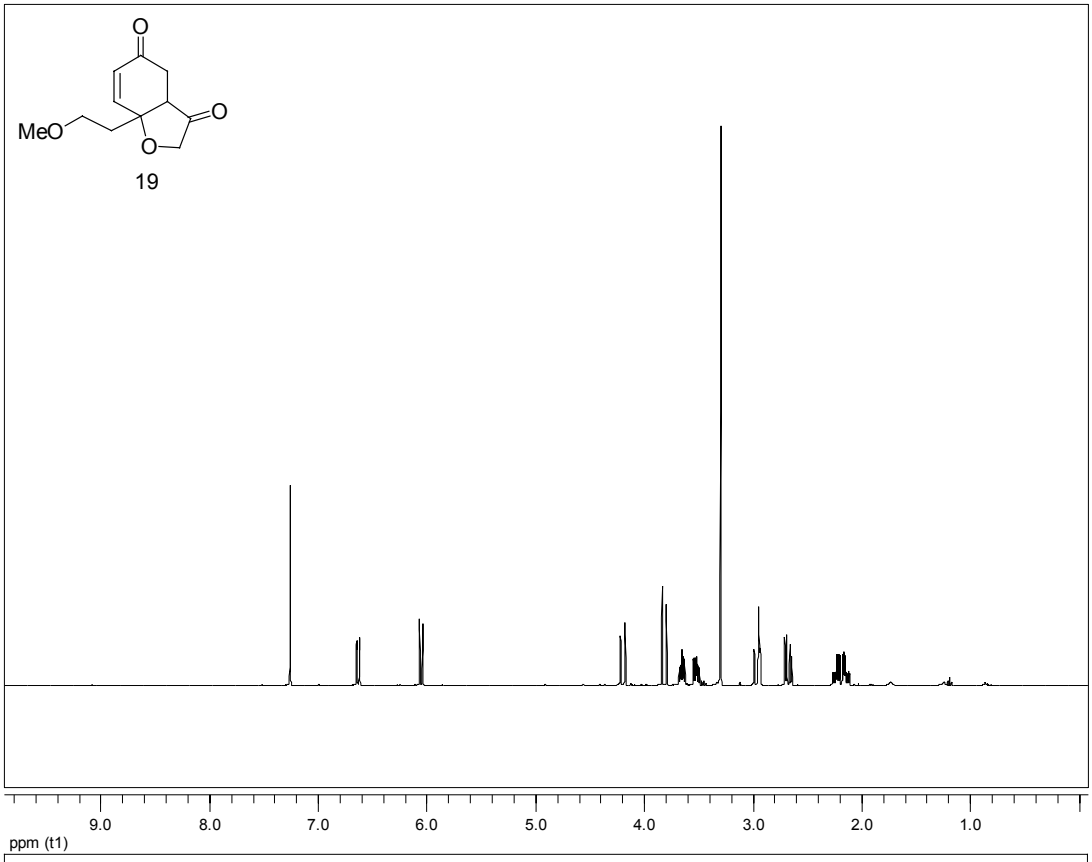
50
0
ppm (t1)


MeO
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O
O
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6.0
5.0
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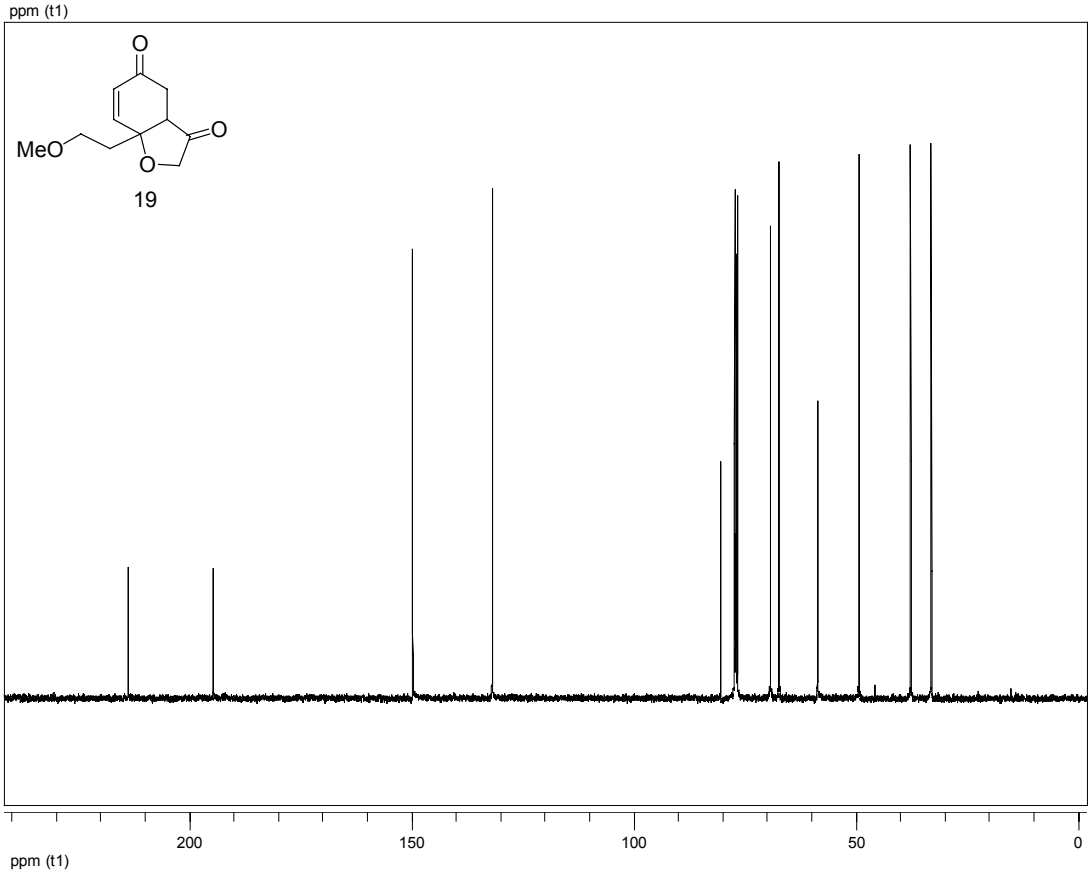
3.0
2.0
1.0
ppm (t1)


MeO
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O
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19
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150
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50
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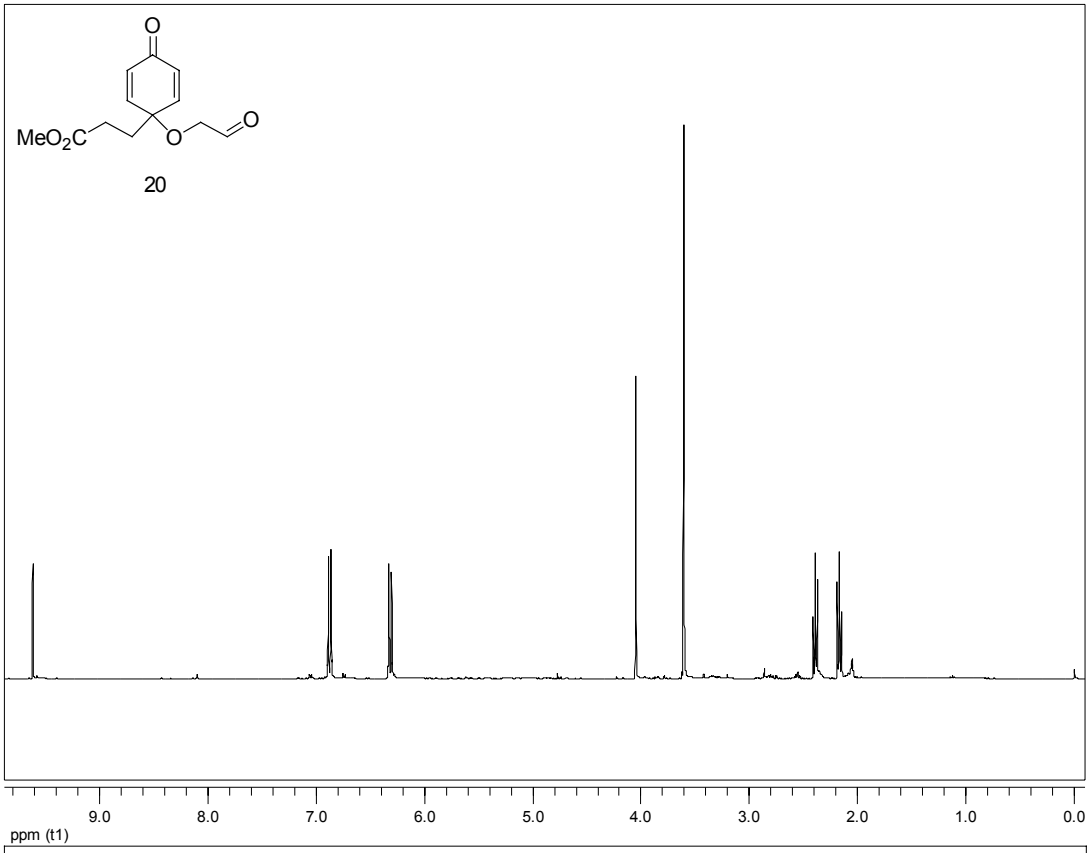
ppm (t1)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7.0
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4.0
3.0
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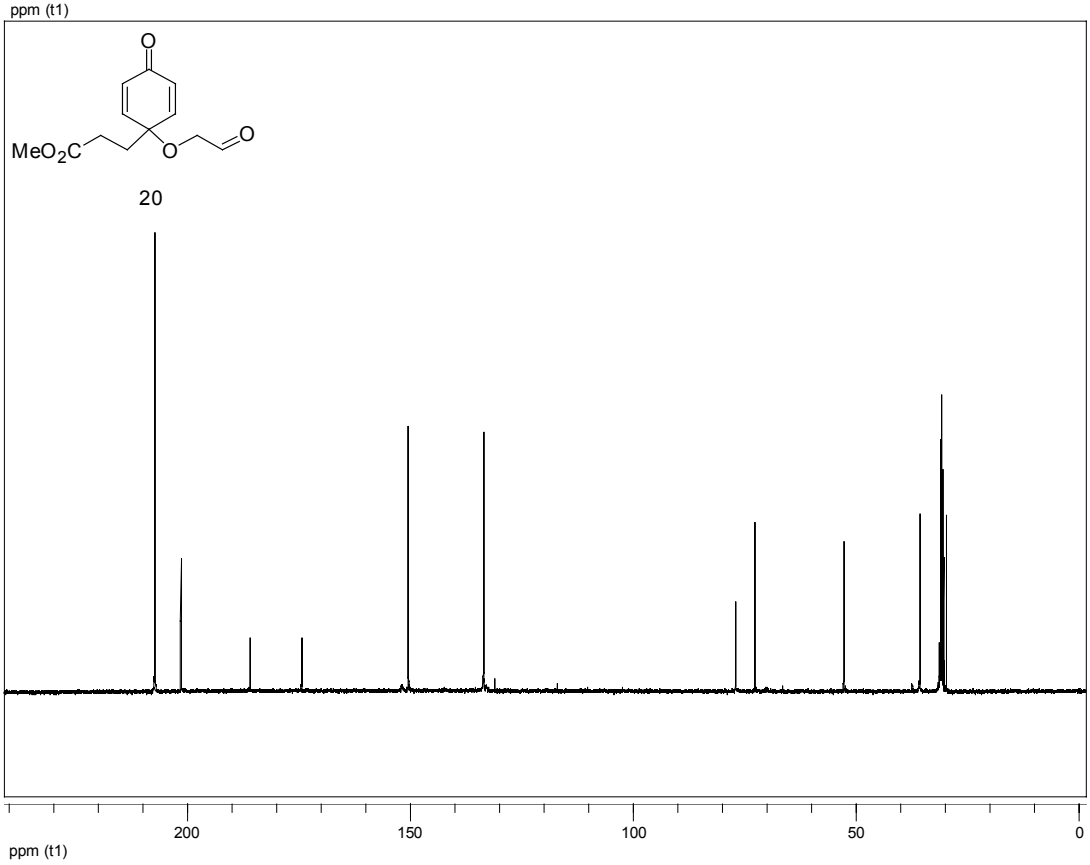
0.0
ppm (t1)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MeO2C
O
O
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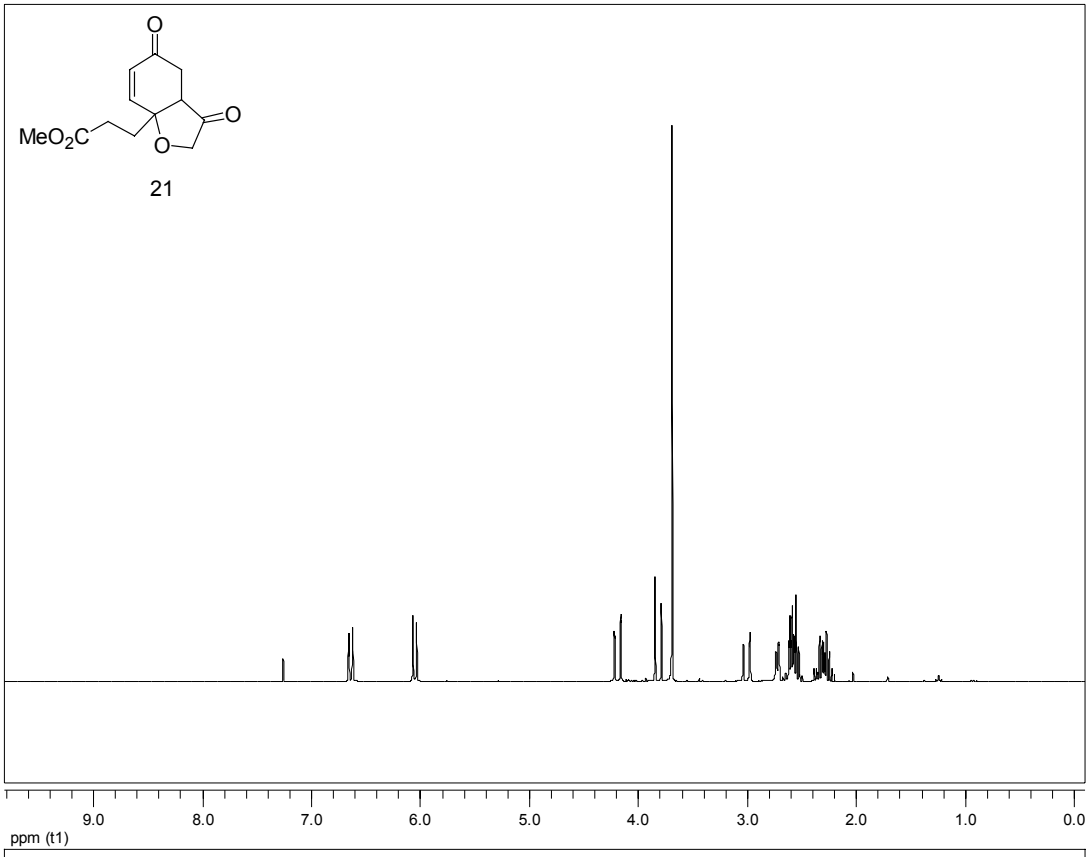
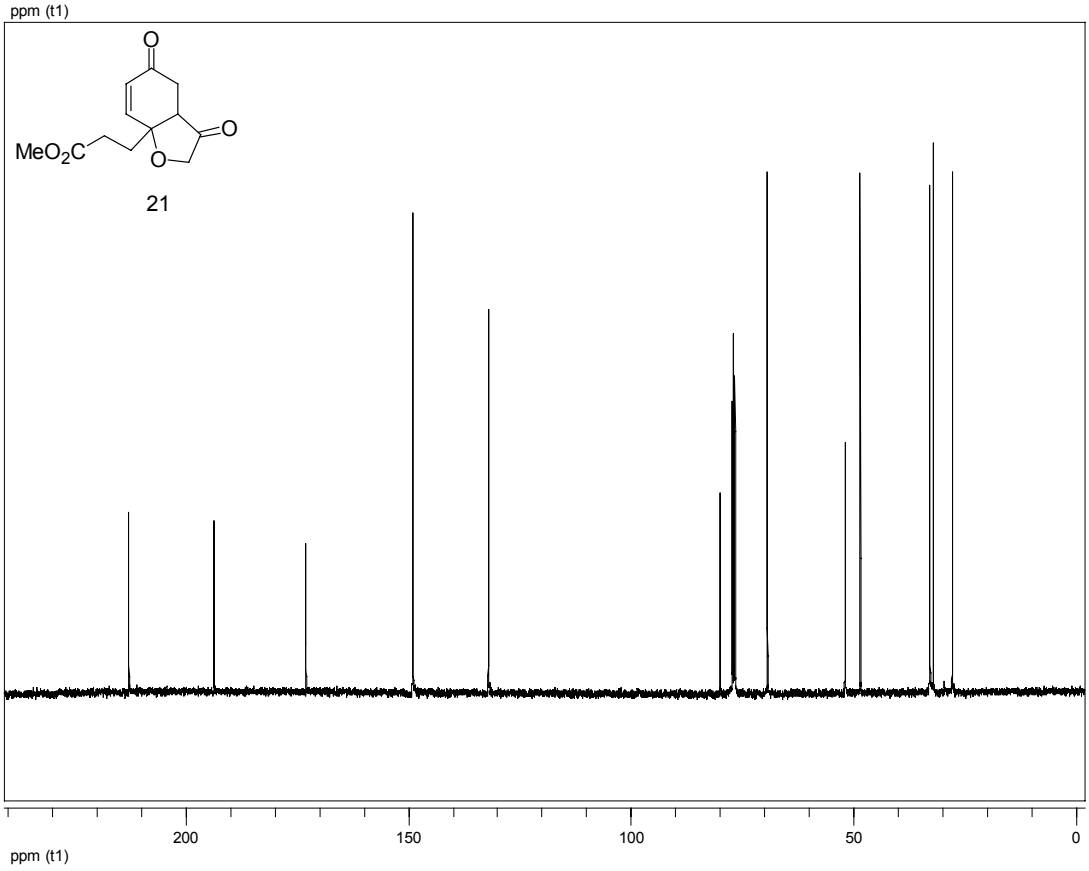
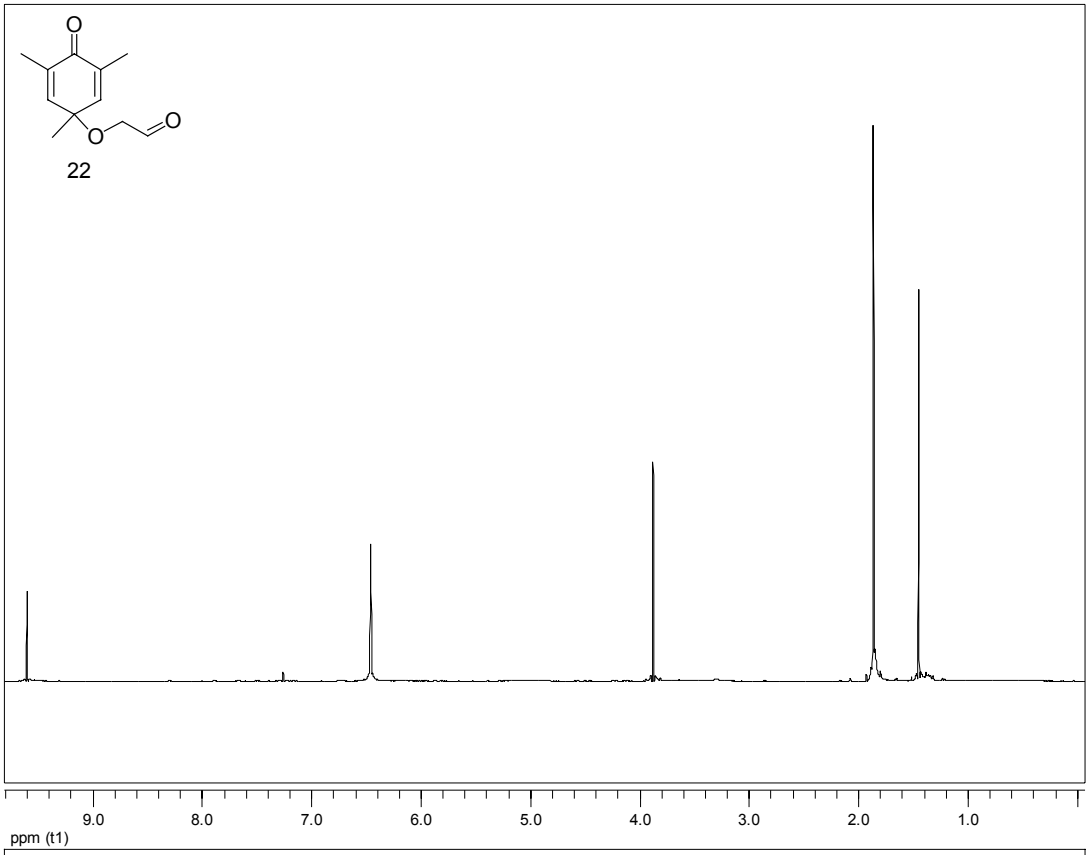
200
150
100
50
0
ppm (t1)


O
O
MeO2C
O
21
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


O
O
MeO2C
O
21
200
150
100
50
0
ppm (t1)


O
O
O
22
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7.0
6.0
5.0
4.0
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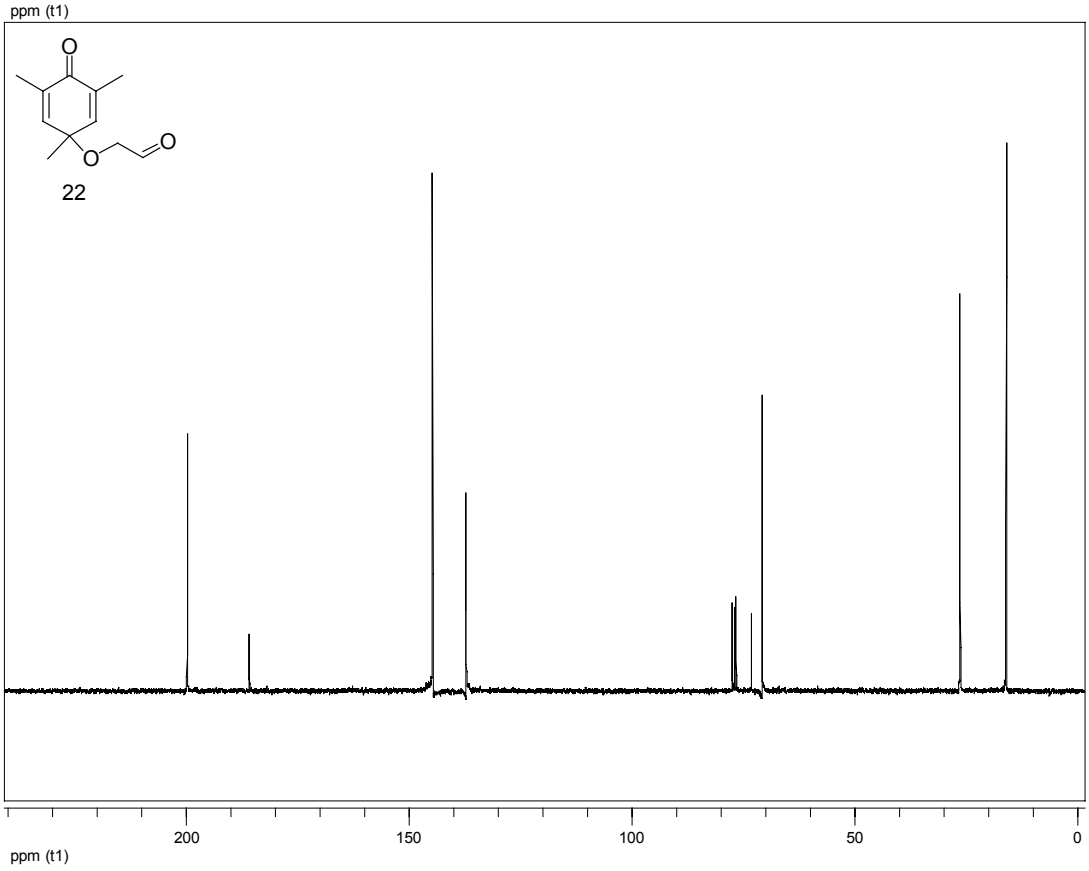
1.0
ppm (t1)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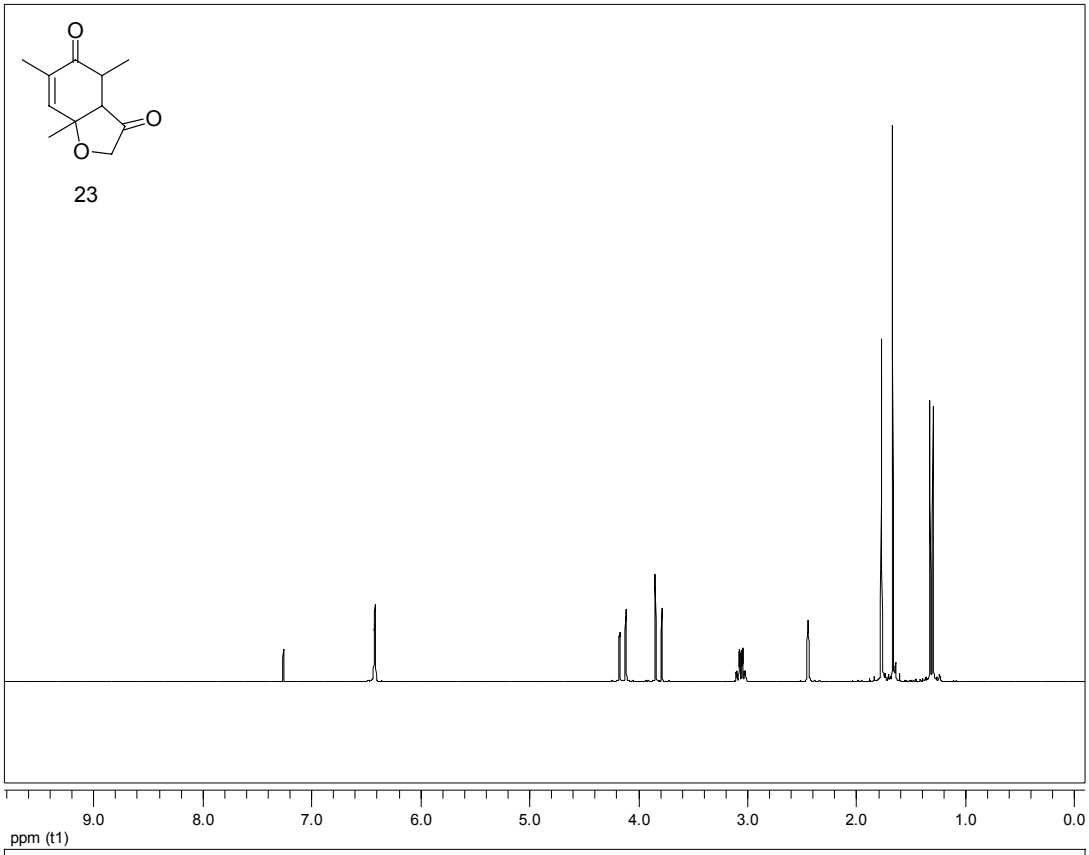
22
200
150
100
50
0
ppm (t1)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O
O
23
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6.0
5.0
4.0
3.0
2.0
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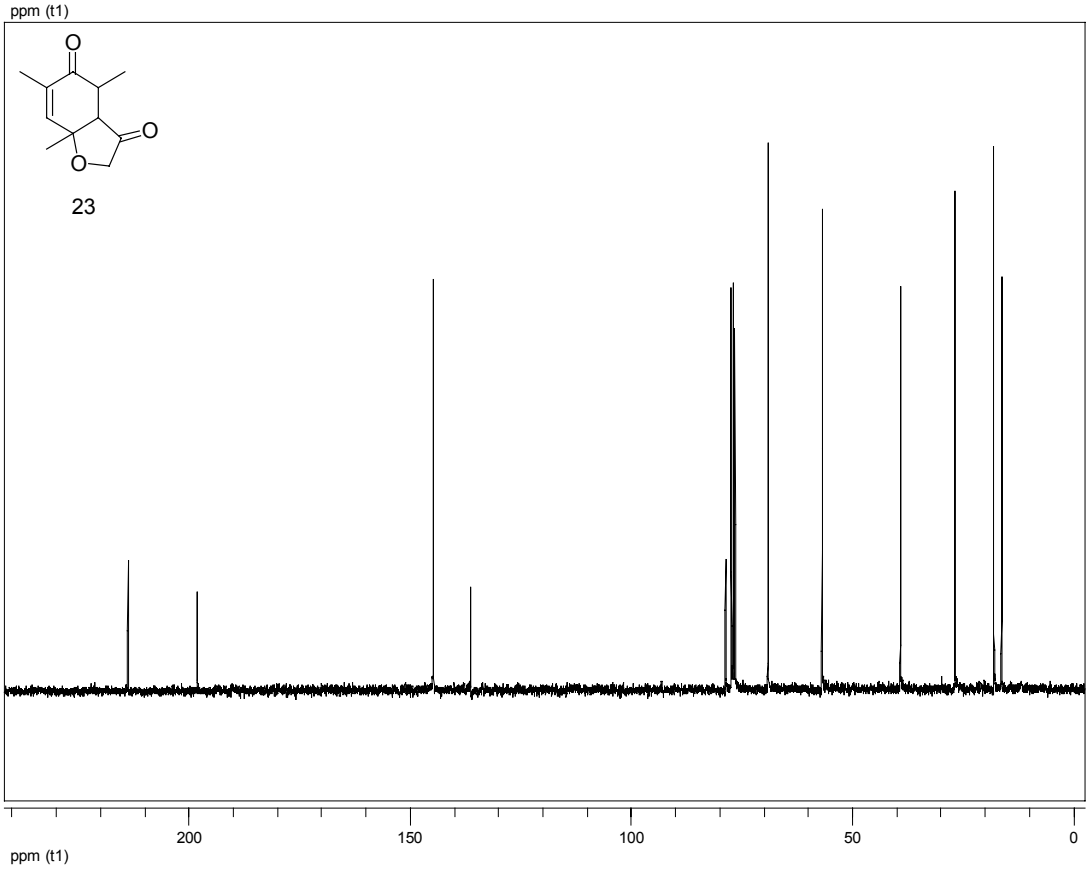
0.0
ppm (t1)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O
23
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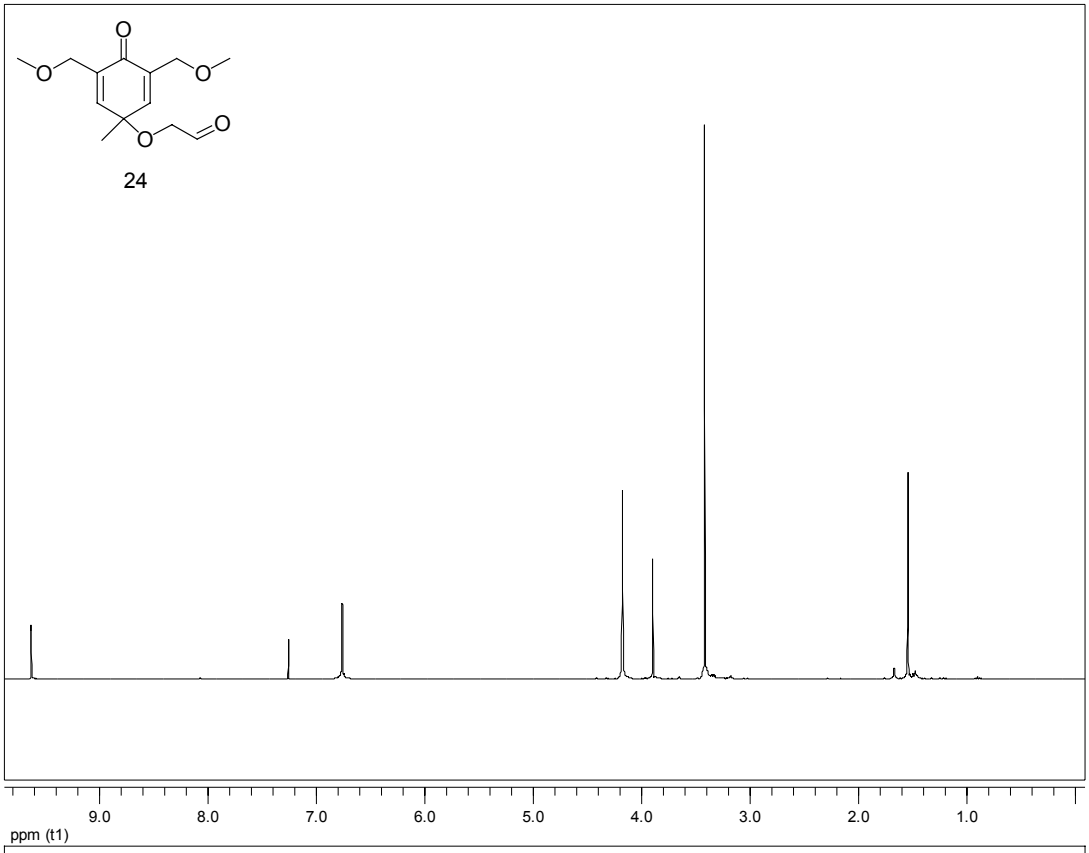
100
50
0
ppm (t1)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O
O
O
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24
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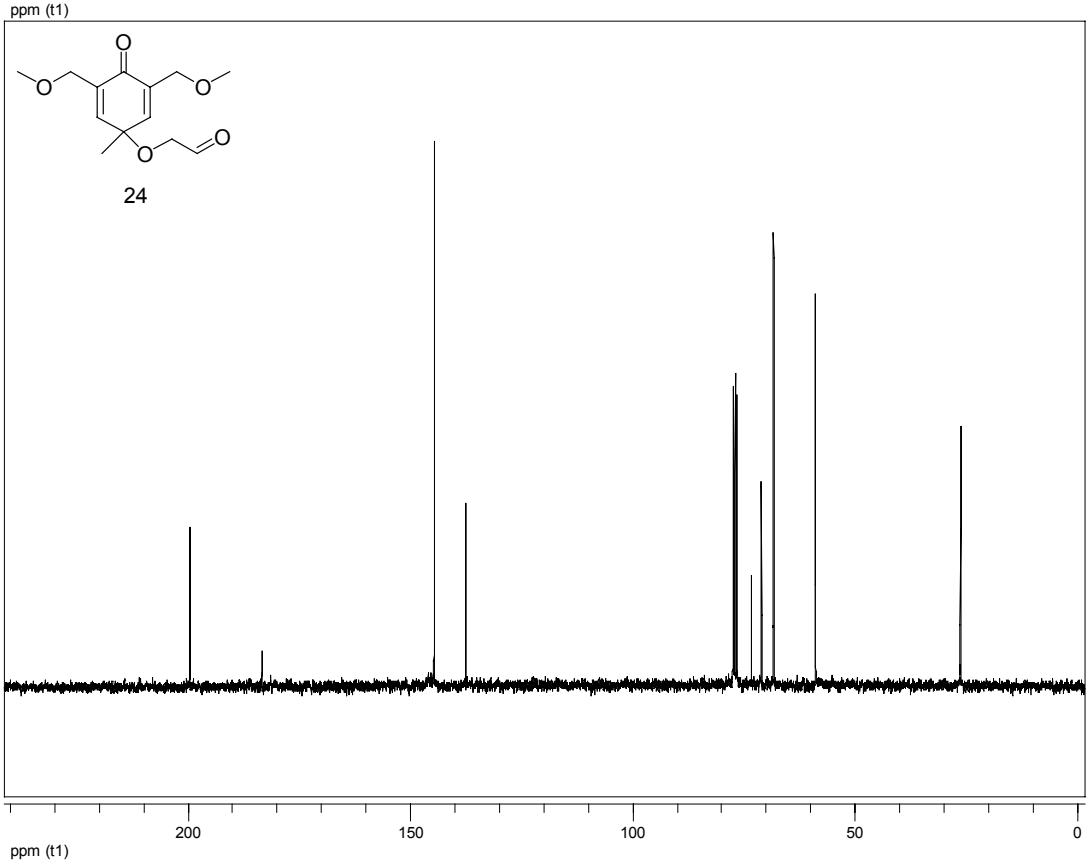
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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24
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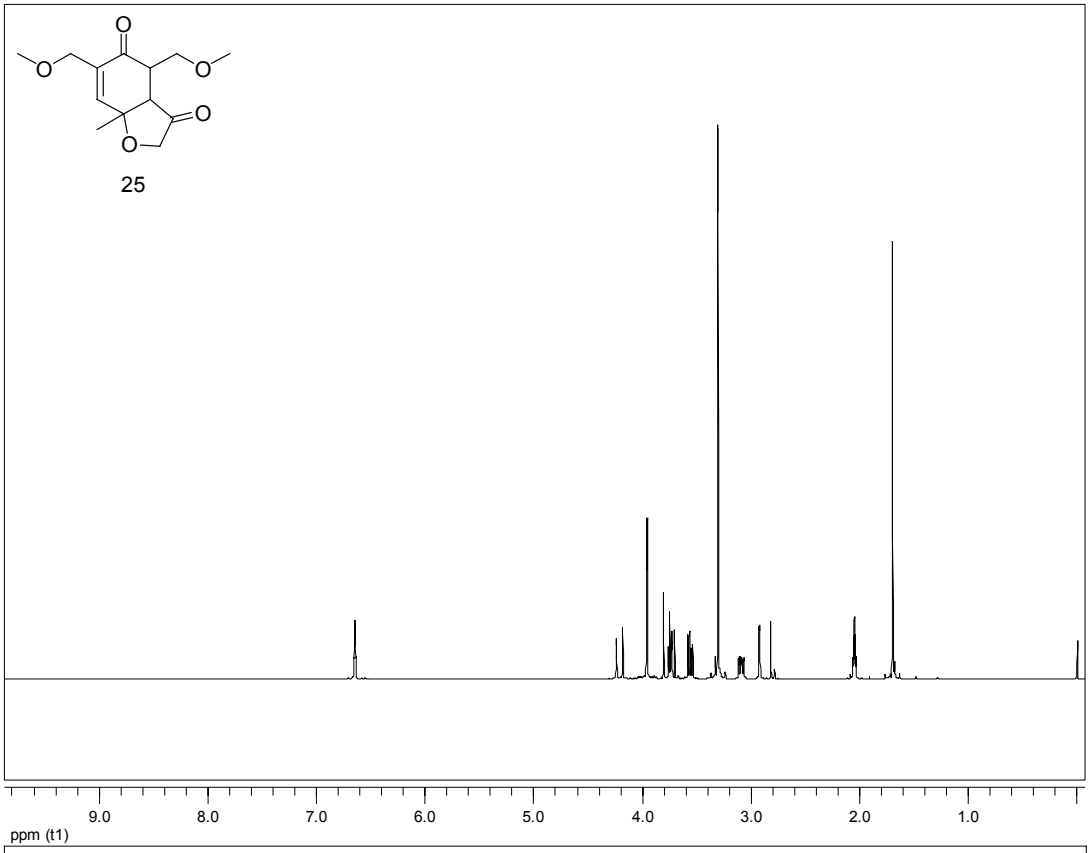
50
0
ppm (t1)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O
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25
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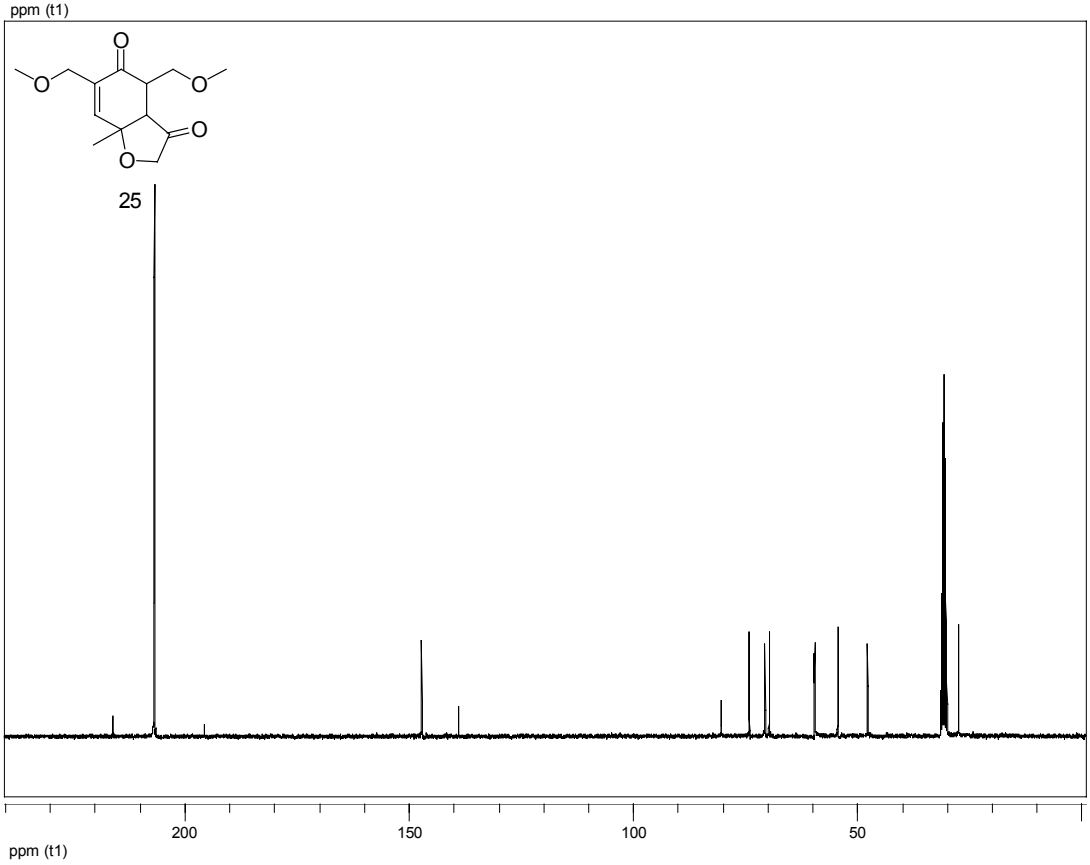
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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200
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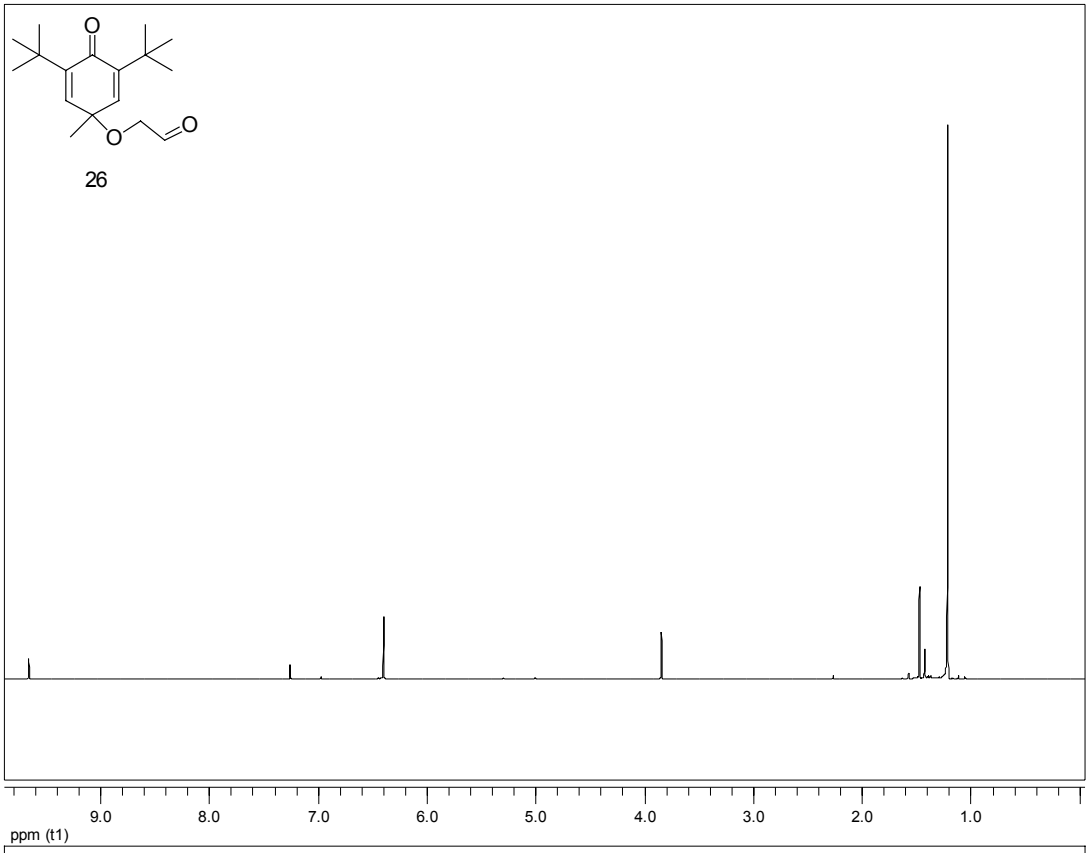
100
50
ppm (t1)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26
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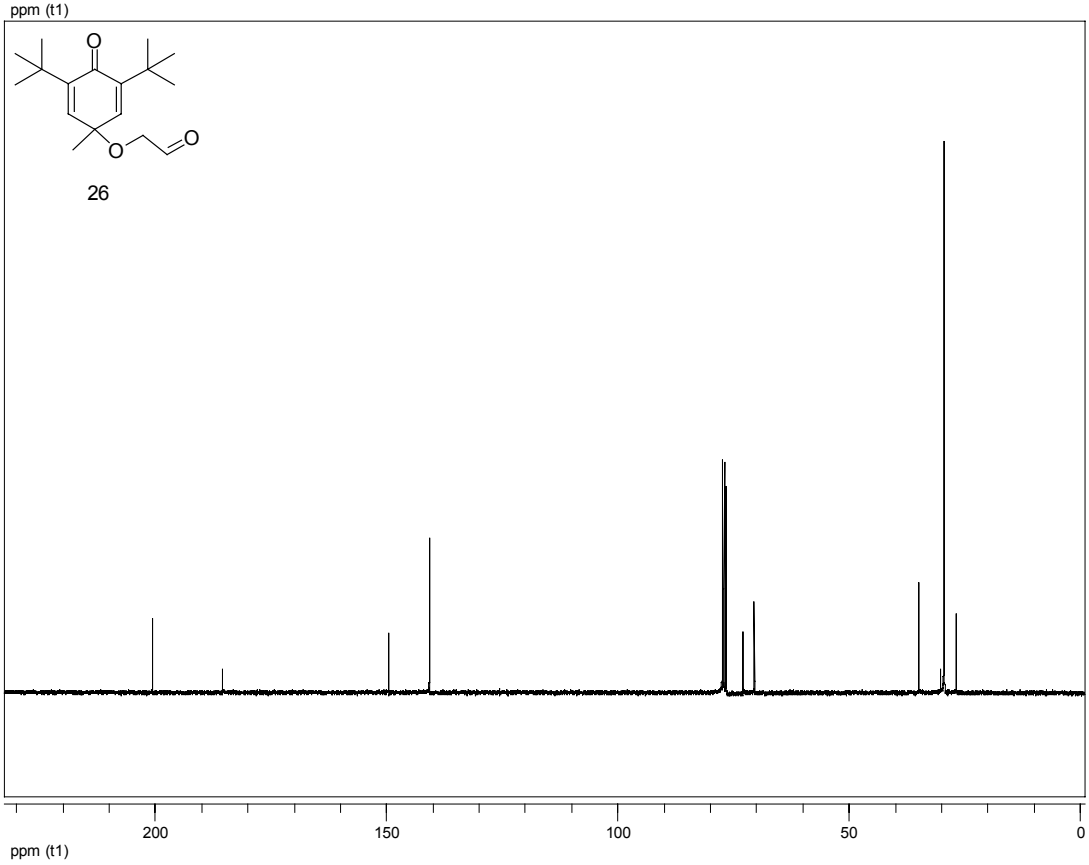
1.0
ppm (t1)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26
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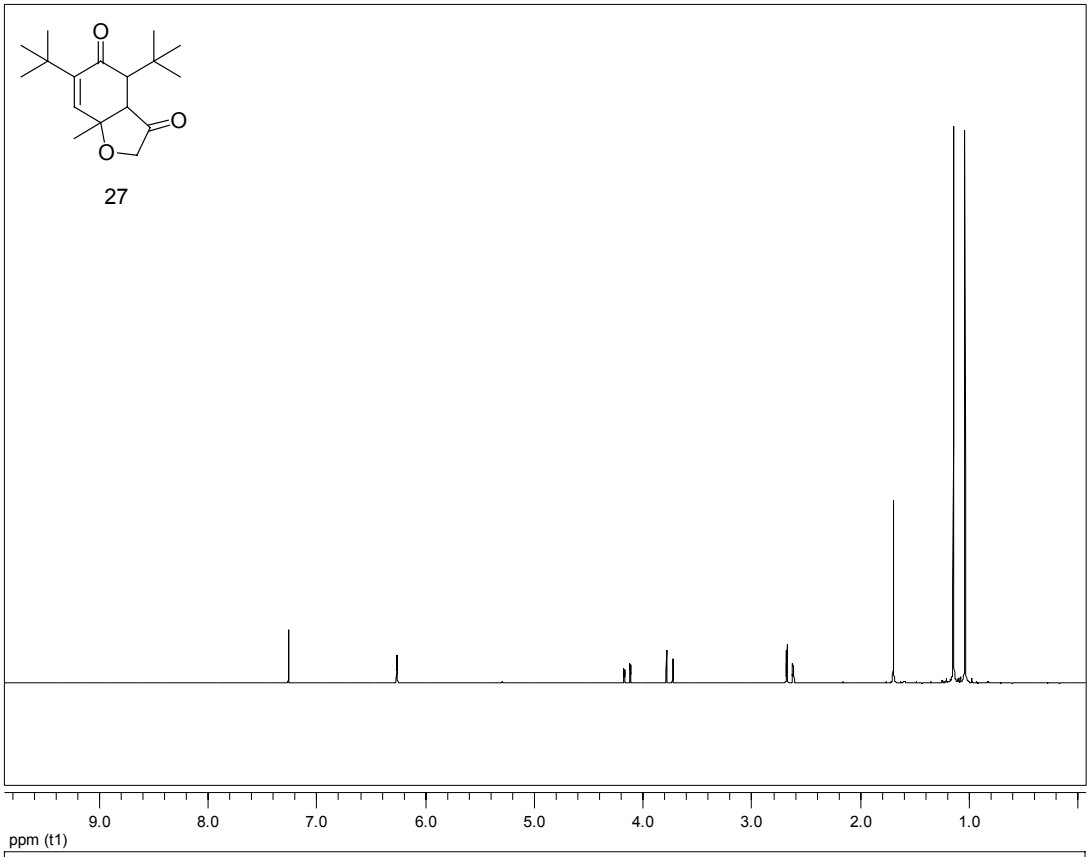
100
50
0
ppm (t1)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O
27
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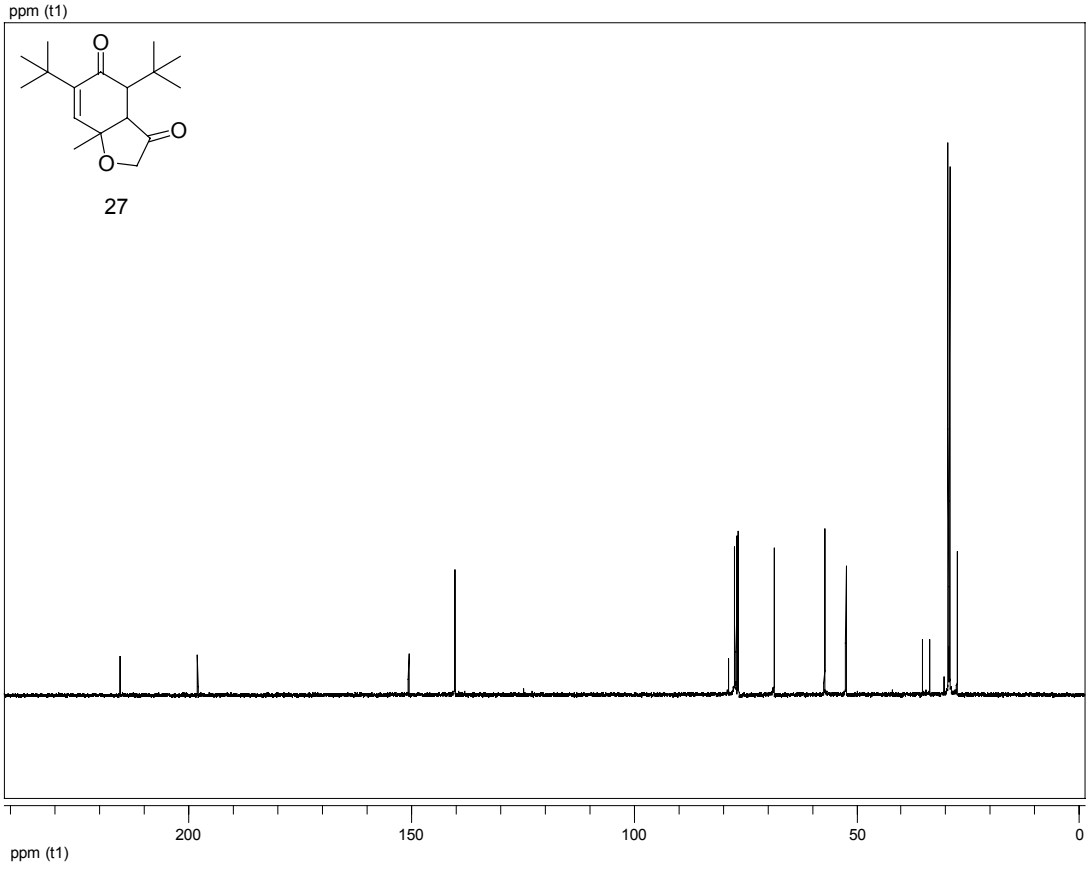
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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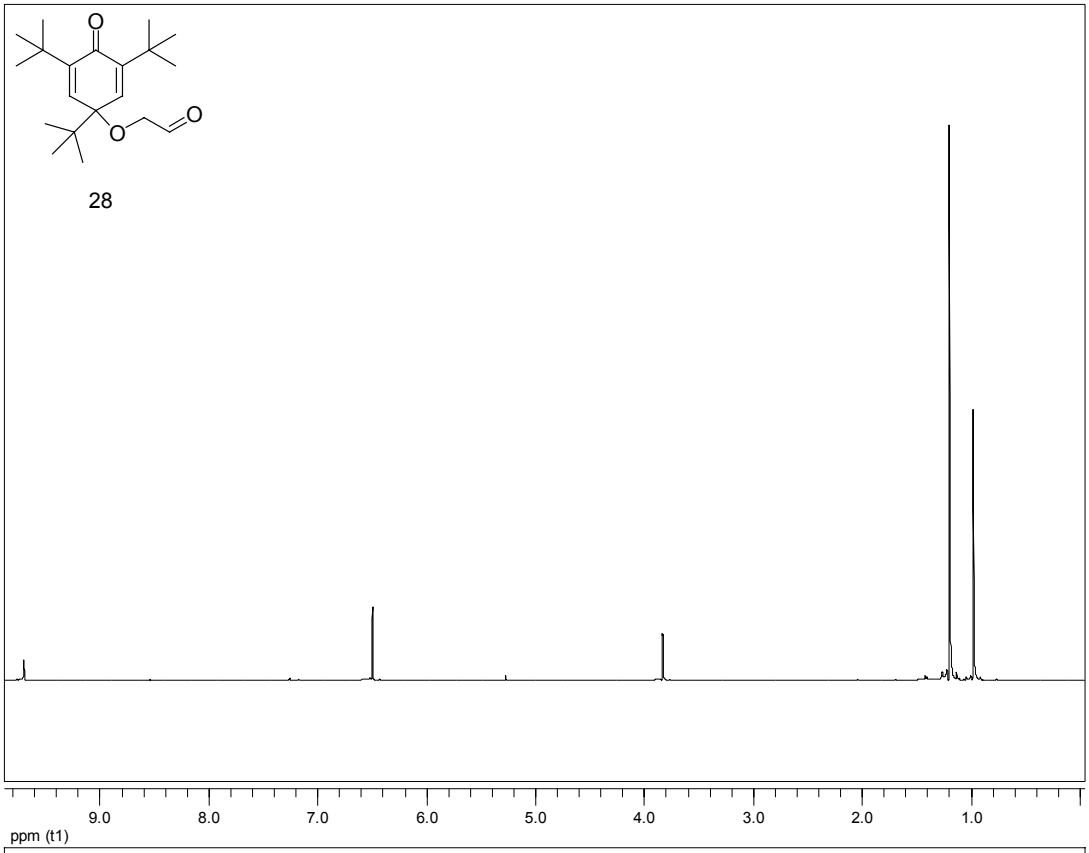
200
150
100
50
0
ppm (t1)


O
O
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28
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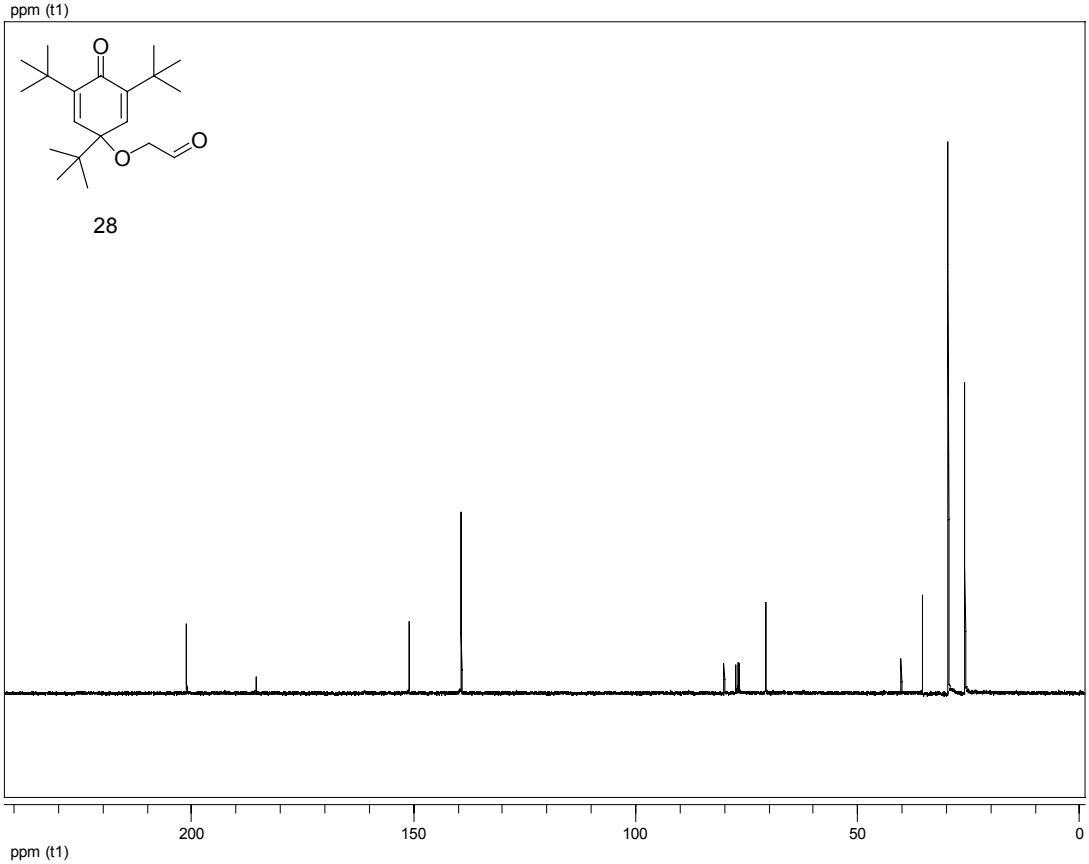
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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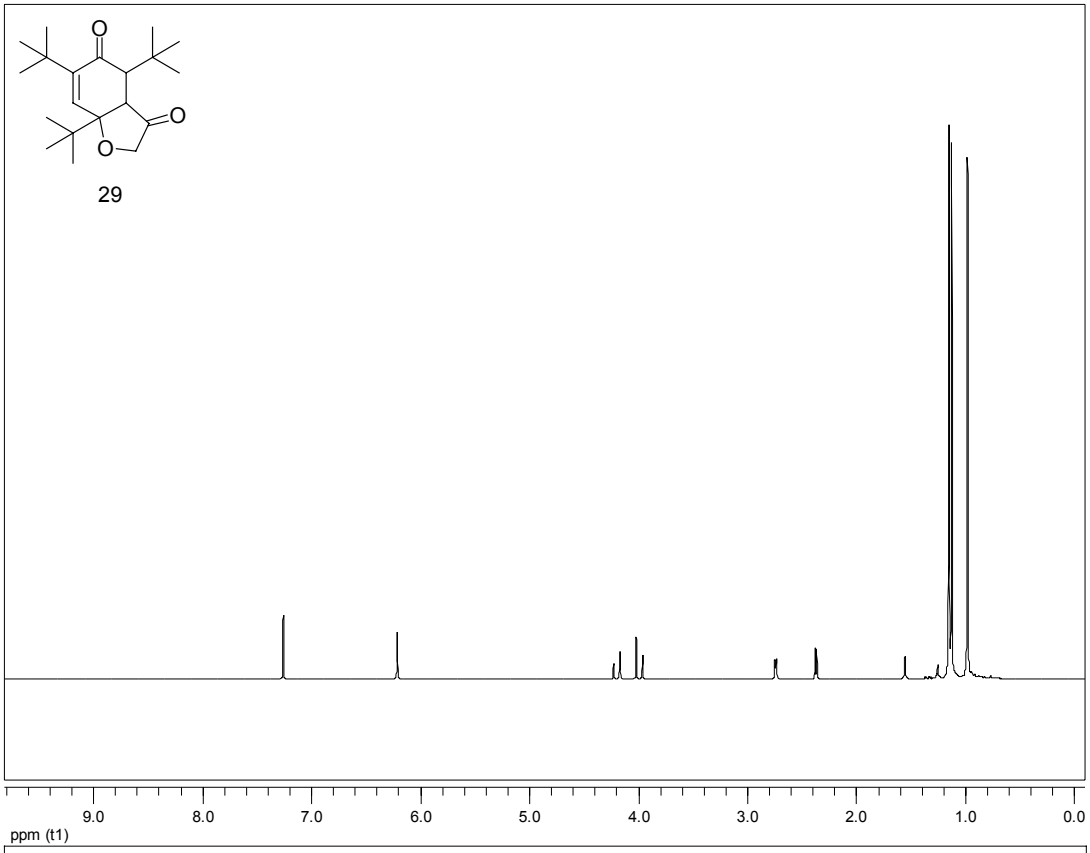
O
28
200
150
100
50
0
ppm (t1)


O
O
O
29
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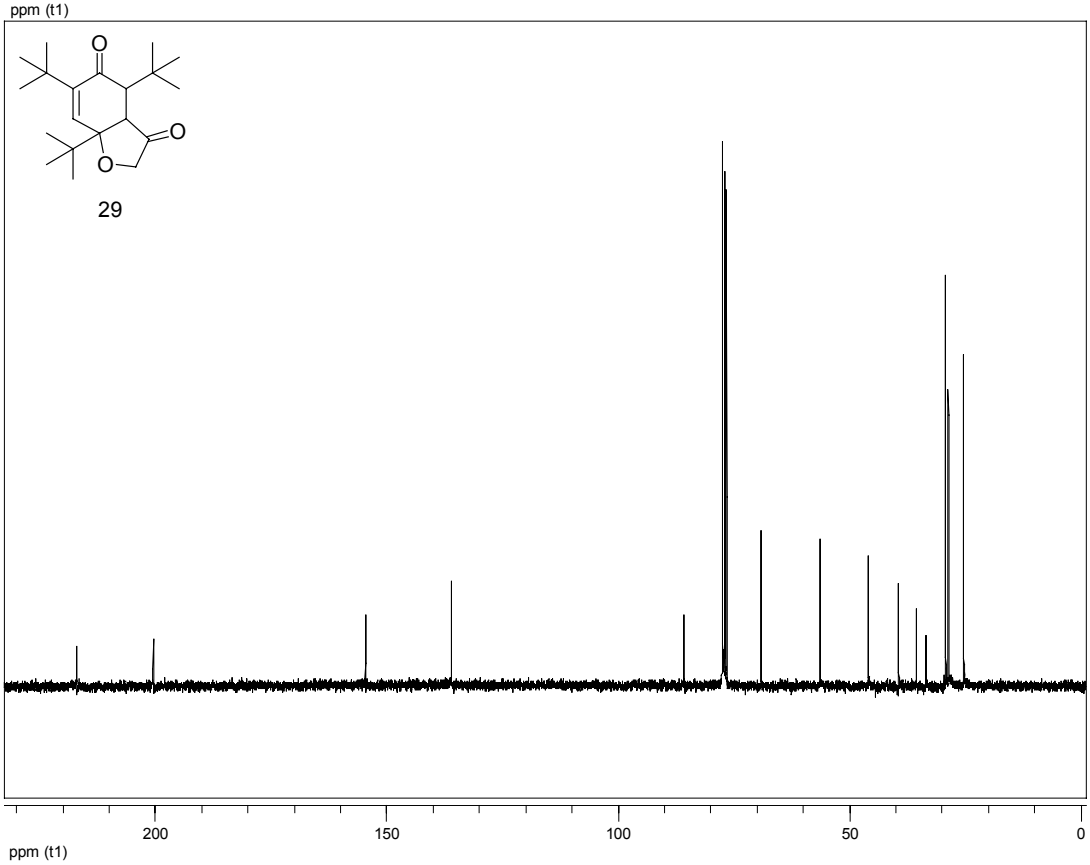
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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O
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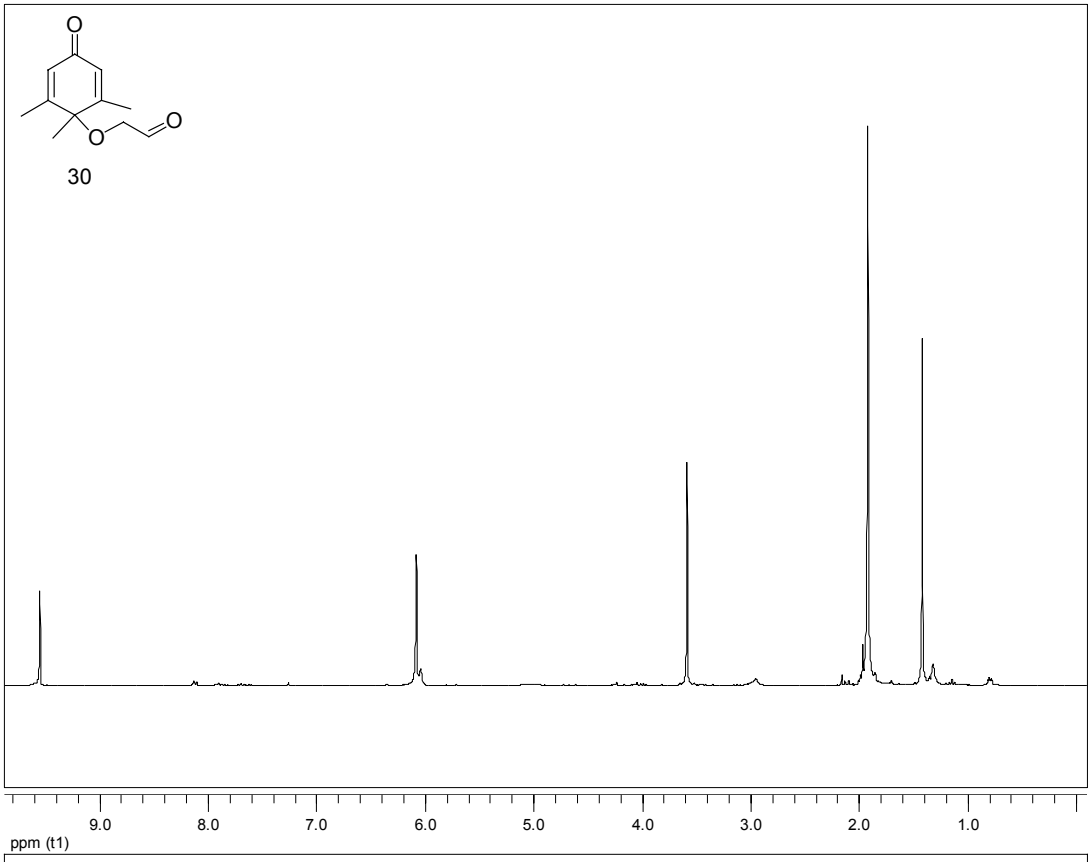
29
200
150
100
50
0
ppm (t1)


O
O
O
30
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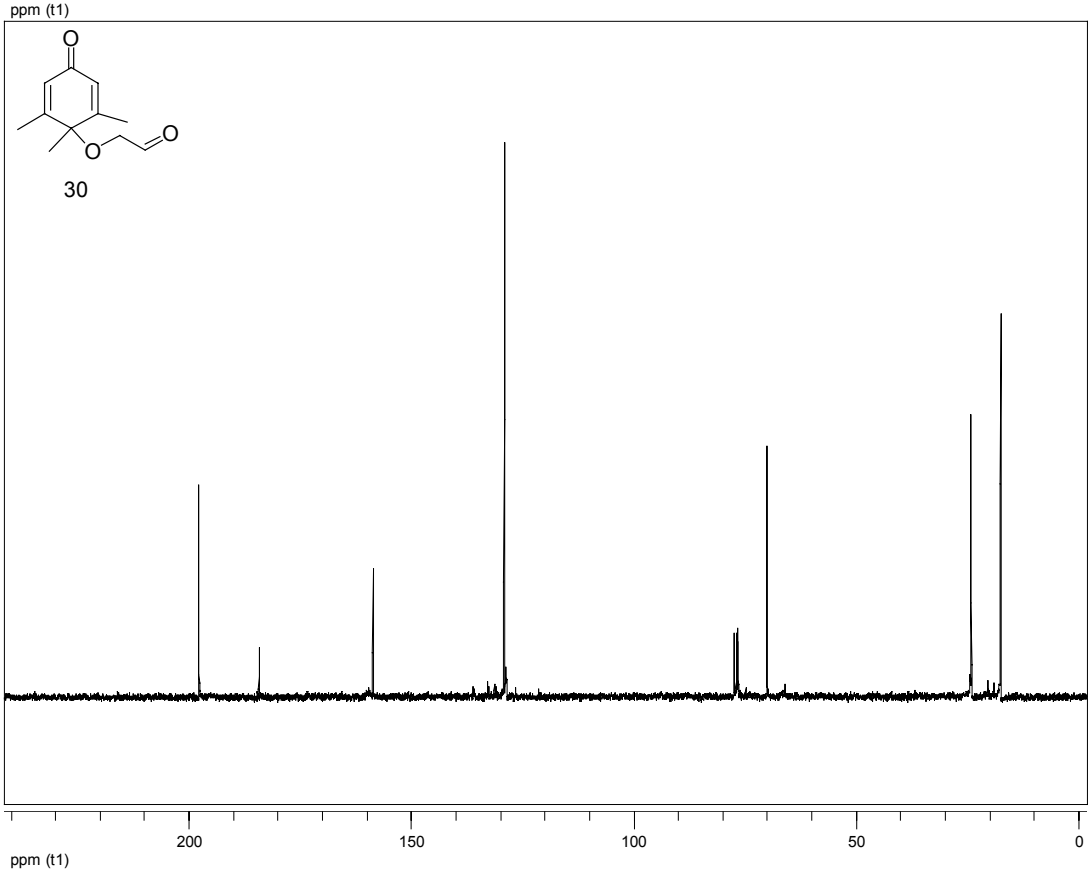
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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O
O
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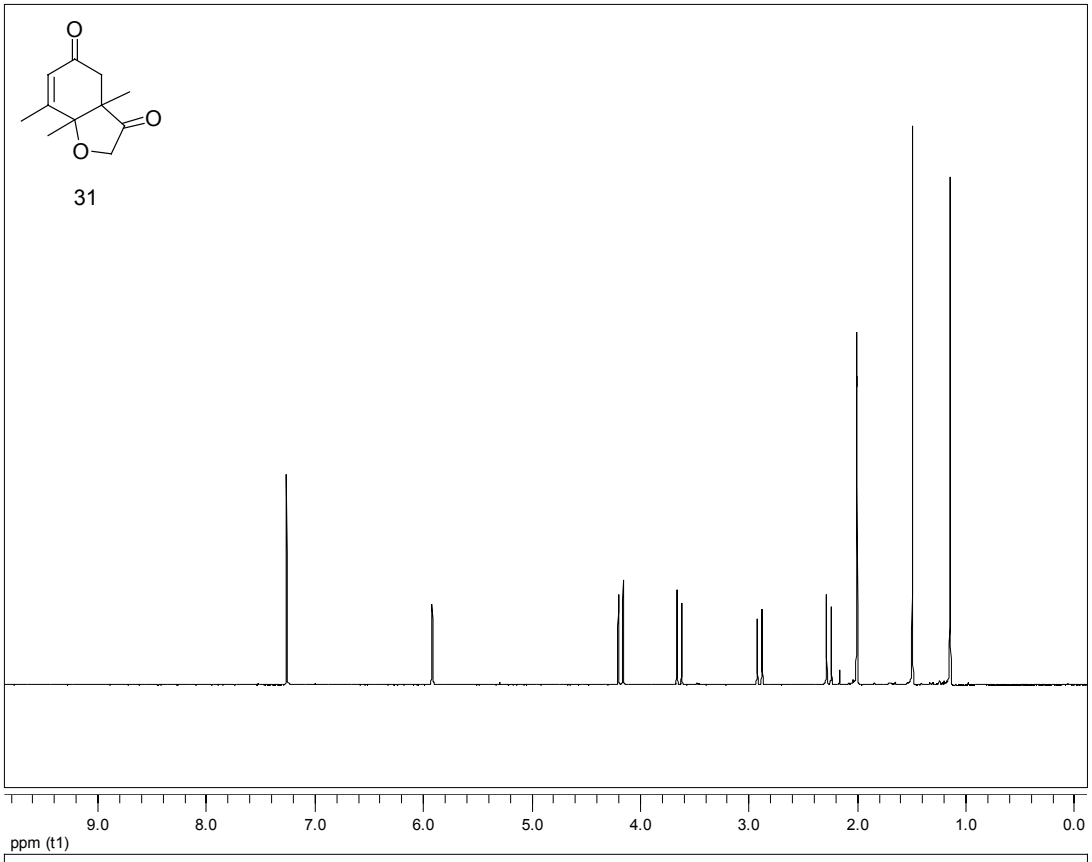
150
100
50
0
ppm (t1)


O
O
O
31
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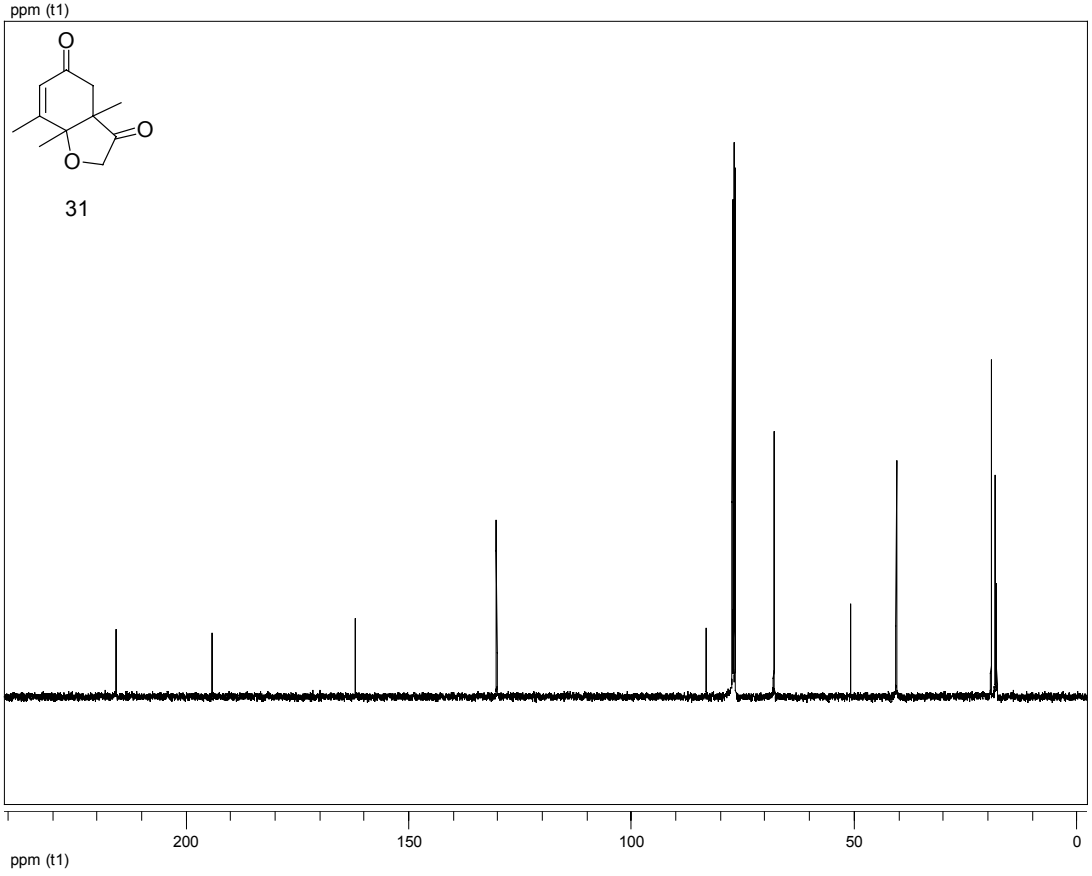
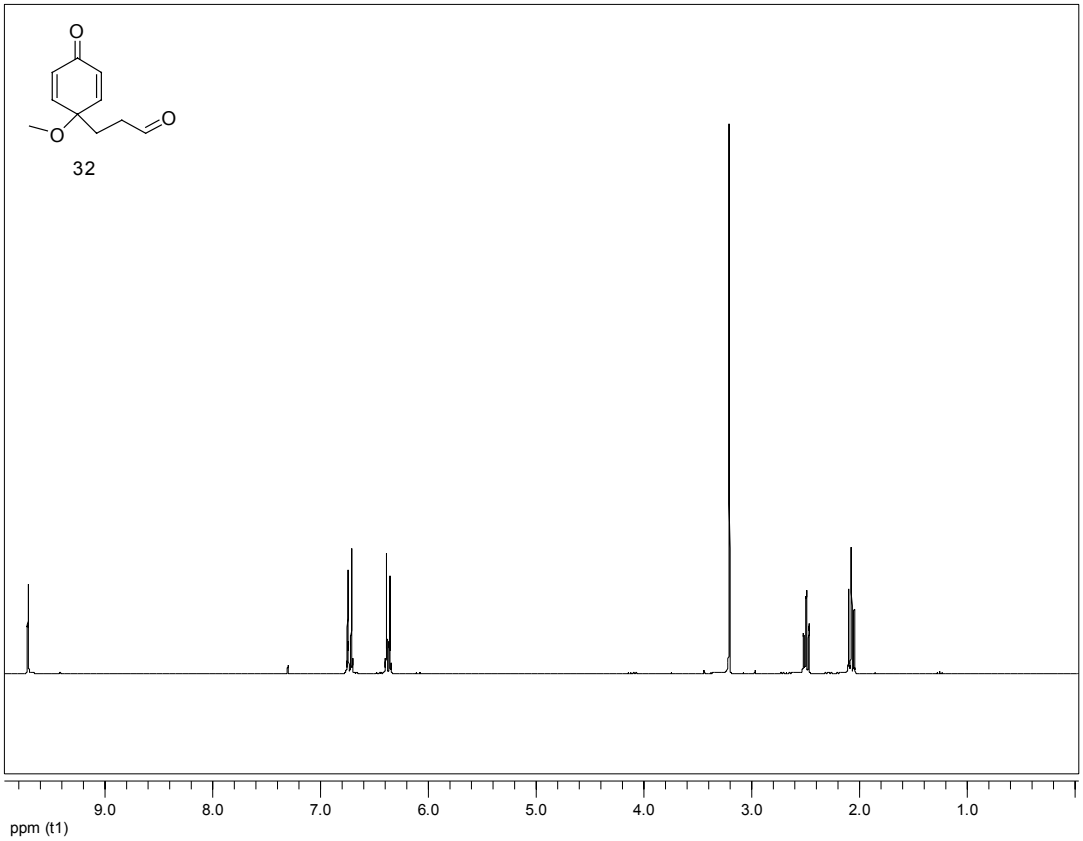
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


O
O
O
31
200
150
100
50
0
ppm (t1)


O
O
O
32
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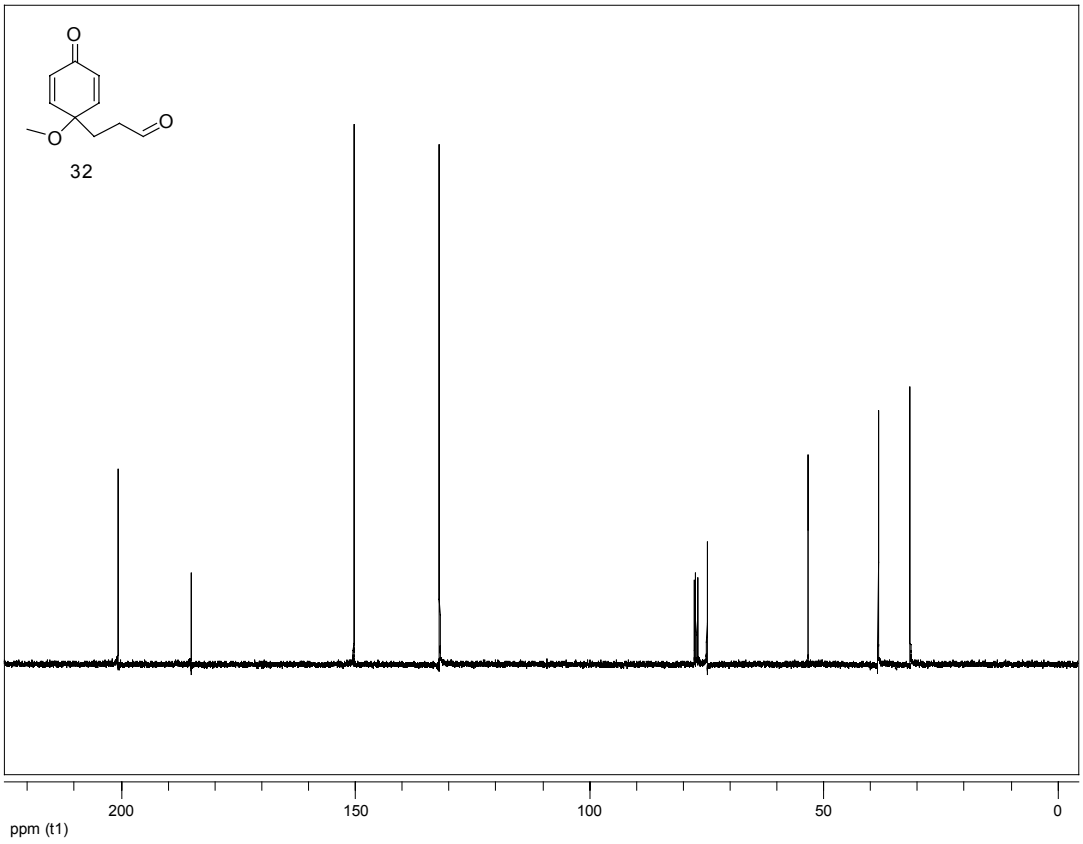
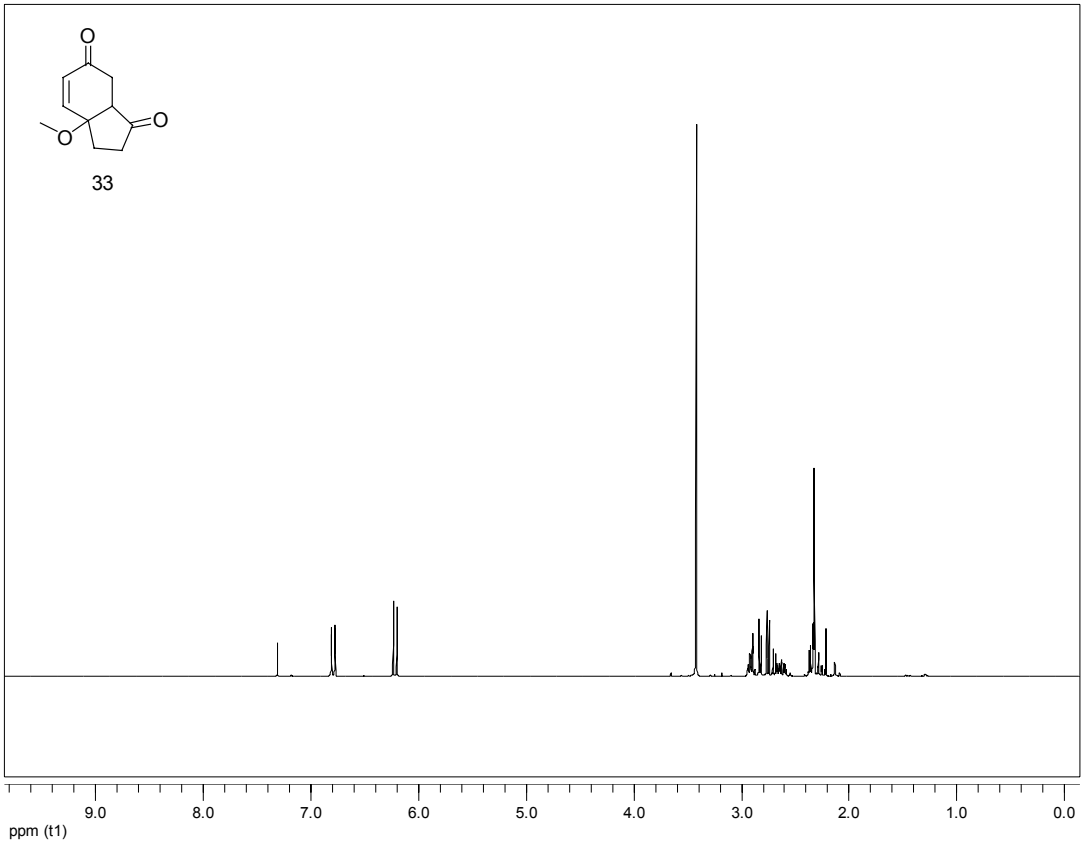
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


O
O
O
32
200
150
100
50
0
ppm (t1)


O
O
O
33
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
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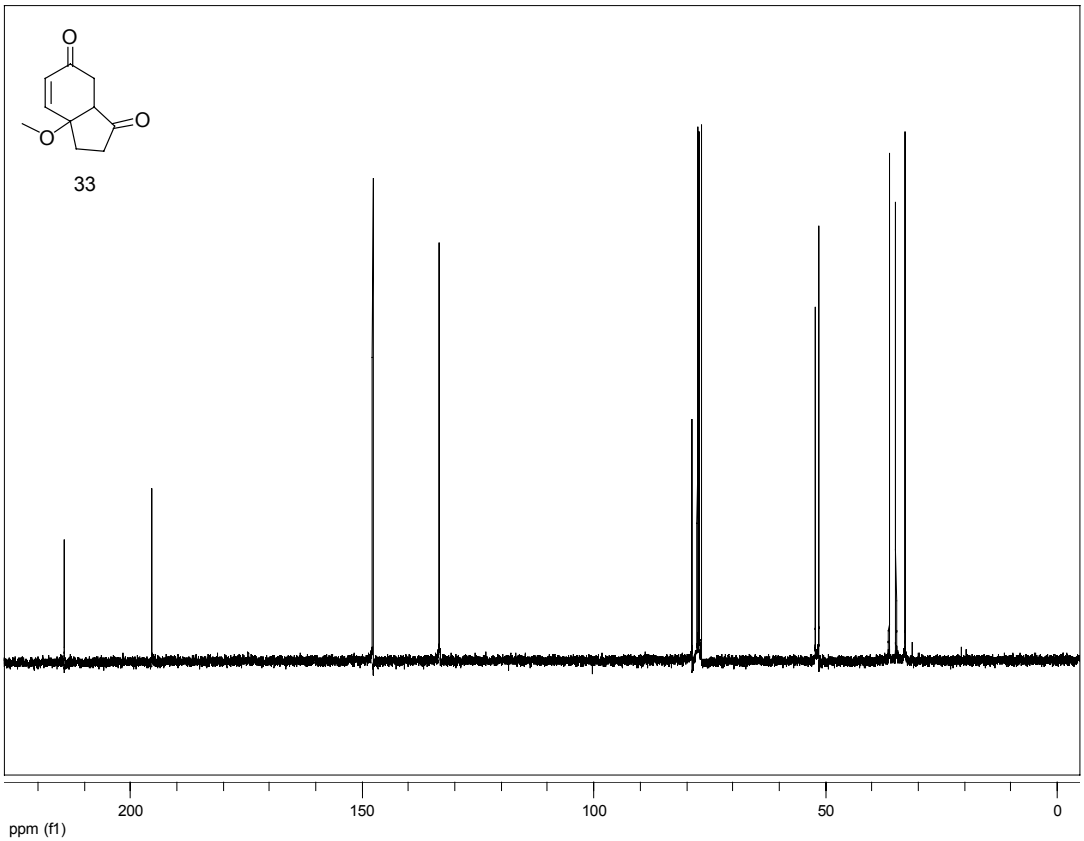
0.0
ppm (t1)


O
O
O
33
200
150
100
50
0
ppm (f1)