Enantioselective Synthesis of Hydrobenzofuranones Using an Asymmetric Desymmetrizing Intramolecular Stetter Reaction of Cyclohexadienones

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Supporting Information

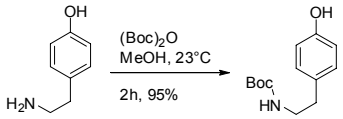
General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Methanol was distilled from CaH_2 prior to use. Methylene chloride was degassed with argon and passed through two column of neutral alumina. Toluene was degassed with argon and 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.

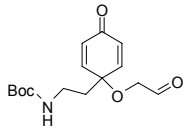
KHMDS (0.5 M solution in toluene), Ethylene glycol (anhydrous, 99.8%) and $PhI(OAc)_2$ (iodobenzene diacetate, 98%) was purchased from Aldrich Chemical Co. and used without purification.

^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.

Full characterizations of **1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 20, 27, 28, 29, 30, 31, 32, 33, 34, 36, 37, 38, 39, 40, 41, 42** have been reported in preliminary communication.[1]

Synthesis of ***tert*-butyl 4-hydroxyphenethylcarbamate** (starting material of substrate **10**):

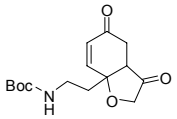




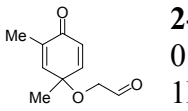
tert-butyl 2-(4-oxo-1-(2-oxoethoxy)cyclohexa-2,5-dienyl)ethylcarbamate (10): This substrate is somewhat sensitive and could not be satisfactorily purified without extensive decomposition. Rf = 0.23 (2:1 EtOAc/Hex); ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 6.79 (d, 1H, *J* = 10.2 Hz), 6.37 (d, 1H, *J* = 10.2 Hz), 4.84 (s, 1H), 3.99 (s, 2H), 3.26 (dd, 2H, *J* = 6.6, 6.5

[1] Q. Liu, T. Rovis, *Journal of the American Chemical Society* **2006**, *128*, 2552.

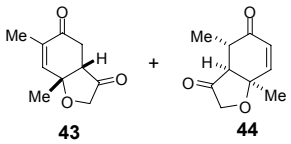
Hz), 2.05 (t, 2H, *J* = 7.1 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 185.1, 148.4, 132.1, 94.6, 71.0, 53.7, 39.8, 36.1, 28.6; IR (NaCl, neat) 3355, 2971, 2925, 1693, 1669, 1167 cm^{-1}; HRMS (EI+) calcd for $C_{15}H_{21}NO_5$, 295.1420. Found 295.1419.



tert-butyl 2-(3,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-7a-yl)ethyl carbamate (35): Rf = 0.49 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 39.6 (c = 0.9, $CHCl_3$); HPLC analysis – Chiracel AD-H column 93:7 hexanes : isopropanol 1.0 mL / min. Major: 35.8 minutes, Minor: 29.8 minutes.; IR (NaCl, neat) 3360, 2971, 2925, 1766, 1788, 1168 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{21}O_5$, 295.1420. Found 295.1419.

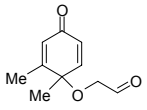


2-(1,3-dimethyl-4-oxocyclohexa-2,5-dienyloxy)acetaldehyde (16): Rf = 0.46 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 6.70 (dd, 1H, *J* = 10.0, 3.0 Hz), 6.48-6.51 (m, 1H), 6.27 (d, 1H, *J* = 10.0 Hz), 3.91 (s, 2H), 1.88 (d, 3H, *J* = 1.4 Hz), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 185.5, 149.8, 145.2, 137.9, 130.8, 73.8, 71.3, 26.5, 16.1; IR (NaCl, neat) 2966, 2919, 1735, 1673, 1644, 1098 cm^{-1}; HRMS (EI+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.

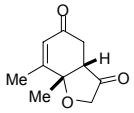


43 **44**

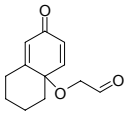
(3aS,7aR)-6,7a-dimethyl-3a,4-dihydrobenzofuran-3,5(2H, 7aH)-dione (43) and **(3aS,4S,7aR)-4,7a-dimethyl-3a,4-dihydrobenzofuran-3,5(2H,7aH)-dione (44)**: 43 and 44 cannot be separated. Rf = 0.54 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 61.2 (c = 0.9, $CHCl_3$, mixture of **43** and **44** with 2:1 ratio); Gas chromatography analysis – Chiraldex GTA column, gas flow 3ml/min with constant 130 ºC oven temperature. **43**: Major: 9.6 min, Minor: 10.7 minutes; **44**: Major: 10.3 min, Minor: 13.4 minutes; IR (NaCl, neat) 2966, 2919, 2883, 1764, 1682, 1055 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.



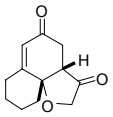
2-(1,2-dimethyl-4-oxocyclohexa-2,5-dienyloxy)acetaldehyde (17): Rf = 0.35 (2:1 EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 6.74 (d, 1H, *J* = 10.0 Hz), 6.28 (dd, 1H, *J* = 10.0, 1.9 Hz), 6.19 (s, 1H), 3.80 (dd, 2H, *J* = 34.4, 17.7 Hz), 1.98 (d, 3H, *J* = 1.0 Hz), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 185.2, 158.9, 150.5, 130.7, 129.8, 75.2, 70.9, 25.3, 18.0; IR (NaCl, neat) 2981, 1735, 1670, 1635, 1294, 1093 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.



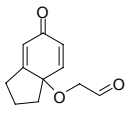
7,7a-dimethyl-3a,4-dihydrobenzofuran-3,5(2H,7aH)-dione (45): Rf = 0.44 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 6.6 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex GTA column, gas flow 3ml/min with constant 150 ºC oven temperature. Major: 8.5 min, Minor: 8.9 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.17 (dd, 1H, *J* = 17.2, 1.1 Hz), 3.64 (d, 1H, *J* = 17.2 Hz), 3.01 (ddd, 1H, *J* = 17.9, 1.4, 1.0 Hz), 2.69 (d, 1H, *J* = 7.1 Hz), 2.56 (dd, 1H, *J* = 17.9, 7.0 Hz), 1.98 (d, 3H, *J* = 1.3 Hz), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 193.7, 160.9, 130.1, 81.0, 69.5, 52.2, 33.2, 23.8, 18.2; IR (NaCl, neat) 2981, 2914, 1760, 1683, 1270, 1052 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.



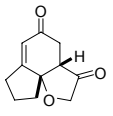
2-(7-oxo-1,2,3,4,4a,7-hexahydronaphthalen-4a-yloxy)acetaldehyde (18): Rf = 0.38 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 6.68 (d, 1H, *J* = 10.0 Hz), 6.31 (dd, 1H, *J* = 10.0, 1.9 Hz), 6.22 (s, 1H), 3.79 (dd, 2H, *J* = 17.8, 2.5 Hz), 2.23-2.44 (m, 3H), 1.92-2.10 (m, 2H), 1.60-1.72 (m, 1H), 1.28-1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 185.9, 161.6, 149.8, 131.4, 127.3, 74.4, 70.2, 39.2, 32.7, 28.1, 20.5; IR (NaCl, neat) 2939, 2855, 1734, 1664, 1092, 883 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_3$, 206.0943. Found 206.0942.



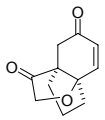
3a,4,7,8,9,10-hexahydro-2H-naphtho[1-b]furan-3,5-dione (46): Rf = 0.56 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 2.3 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 ºC oven temperature. Major: 22.0 min, Minor: 21.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.15 (dd, 1H, *J* = 17.2, 0.7 Hz), 3.69 (d, 1H, *J* = 17.2 Hz), 2.97 (d, 1H, *J* = 16.5 Hz), 2.62-2.75 (m, 1H), 2.46-2.60 (m, 2H), 1.90-2.26 (m, 5H), 1.70-1.80 (m, 1H), 1.32-1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 194.6, 163.7, 126.6, 80.9, 68.9, 50.6, 37.9, 34.2, 32.5, 28.1, 21.3; IR (NaCl, neat) 2940, 2858, 1762, 1675, 1245, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_3$, 206.0943. Found 206.0942.



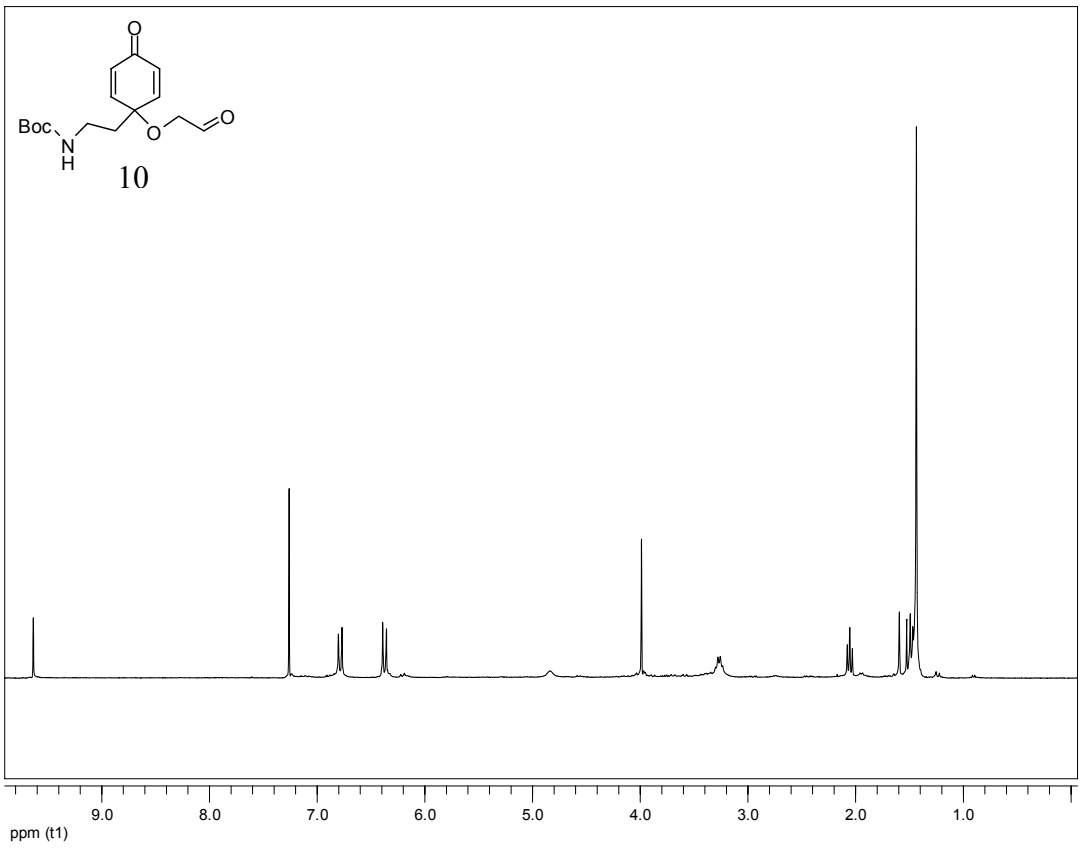
2-(6-oxo-2,3,3a,6-tetrahydro-1H-inden-3a-yloxy)acetaldehyde (19): Rf = 0.4 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 6.80 (d, 1H, *J* = 10.0 Hz), 6.28 (dd, 1H, *J* = 9.9, 1.7 Hz), 6.17-6.20 (m, 1H), 3.81 (dd, 2H, *J* = 24.7, 17.9 Hz), 2.61-2.78 (m, 1H), 2.40-2.54 (m, 1H), 2.18-2.34 (m, 2H), 1.88-2.22 (m, 1H), 1.60-1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 185.9, 165.5, 144.0, 132.2, 125.9, 79.4, 69.9, 35.6, 28.8, 21.8; IR (NaCl, neat) 2955, 2838, 1733, 1668, 1645, 1046 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_3$, 192.0786. Found 192.0786.



3a,4,8,9-tetrahydroindeno[4-b]furan-3,5(2H,7H)-dione (49): Rf = 0.42 (4:1 Et_2O/Hex); $[\alpha]_D^{21}$ = + 13.2 (c = 0.1, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 150 ºC oven temperature. Major: 29.7 min, Minor: 27.0 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (dd, 1H, *J* = 2.0, 1.9 Hz), 4.20 (dd, 1H, *J* = 17.5, 0.8 Hz), 4.07 (d, 1H, *J* = 17.5), 2.76-2.94 (m, 2H), 2.46-2.64 (m, 3H), 2.06-2.24 (m, 2H), 1.84-1.96 (m, 1H), 1.52-1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 195.2, 164.8, 125.3, 85.4, 69.4, 48.4, 35.0, 34.4, 29.6, 20.8; IR (NaCl, neat) 2955, 2843, 1757, 1675, 1035, 912 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_3$, 192.0786. Found 192.0786.



[4.3.3]oxo-propellenedione (50): Rf = 0.48 (4:1 Et_2O/Hex); $[\alpha]_D^{21}$ = - 112.7 (c = 0.36, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 150 ºC oven temperature. Major: 11.6 min, Minor: 13.0 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, 1H, *J* = 10.3 Hz), 6.02 (d, 1H, *J* = 10.3 Hz), 4.30 (d, 1H, *J* = 17.3 Hz), 3.88 (d, 1H, *J* = 17.3 Hz), 3.06 (d, 1H, *J* = 17.4 Hz), 2.36 (d, 1H, *J* = 17.4 Hz), 2.30-2.40 (m, 1H), 1.94-2.18 (m, 4H), 1.68-1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 195.4, 147.4, 130.3, 90.7, 69.9, 57.9, 41.2, 37.8, 36.9, 24.4; IR (NaCl, neat) 2955, 2873, 1757, 1670, 1050, 917 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_3$, 192.0786. Found 192.0786.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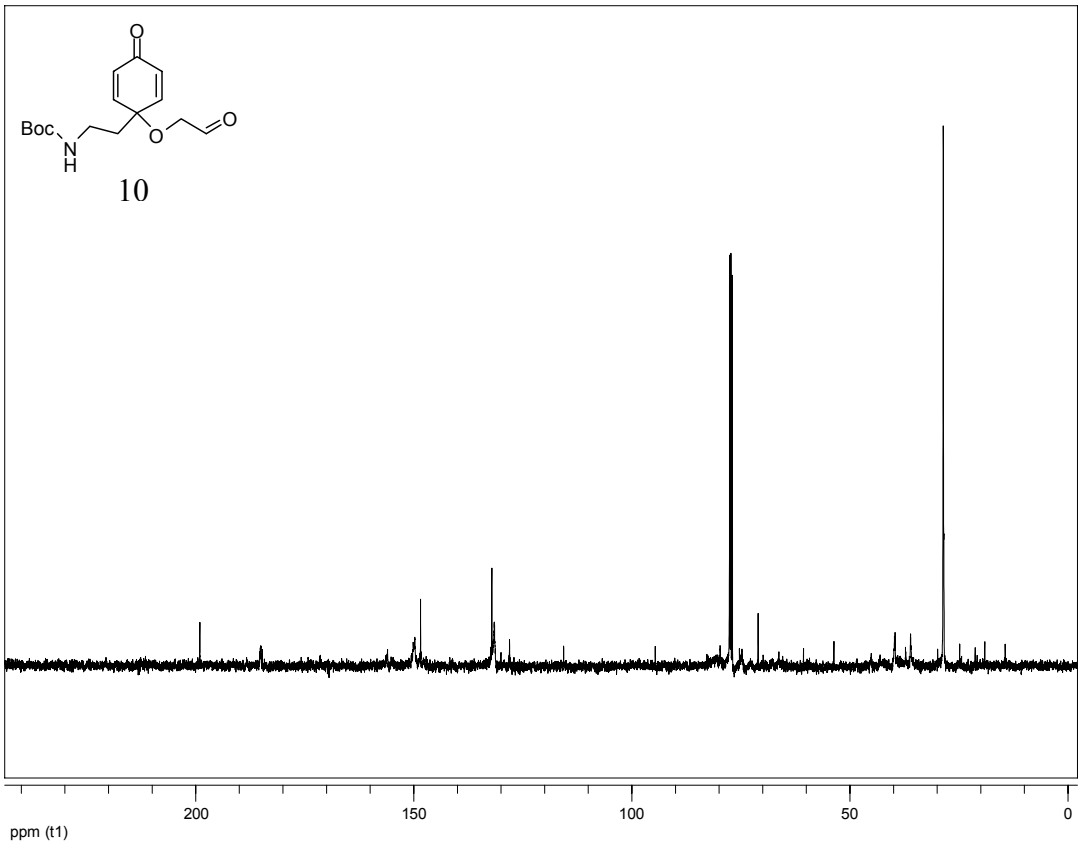
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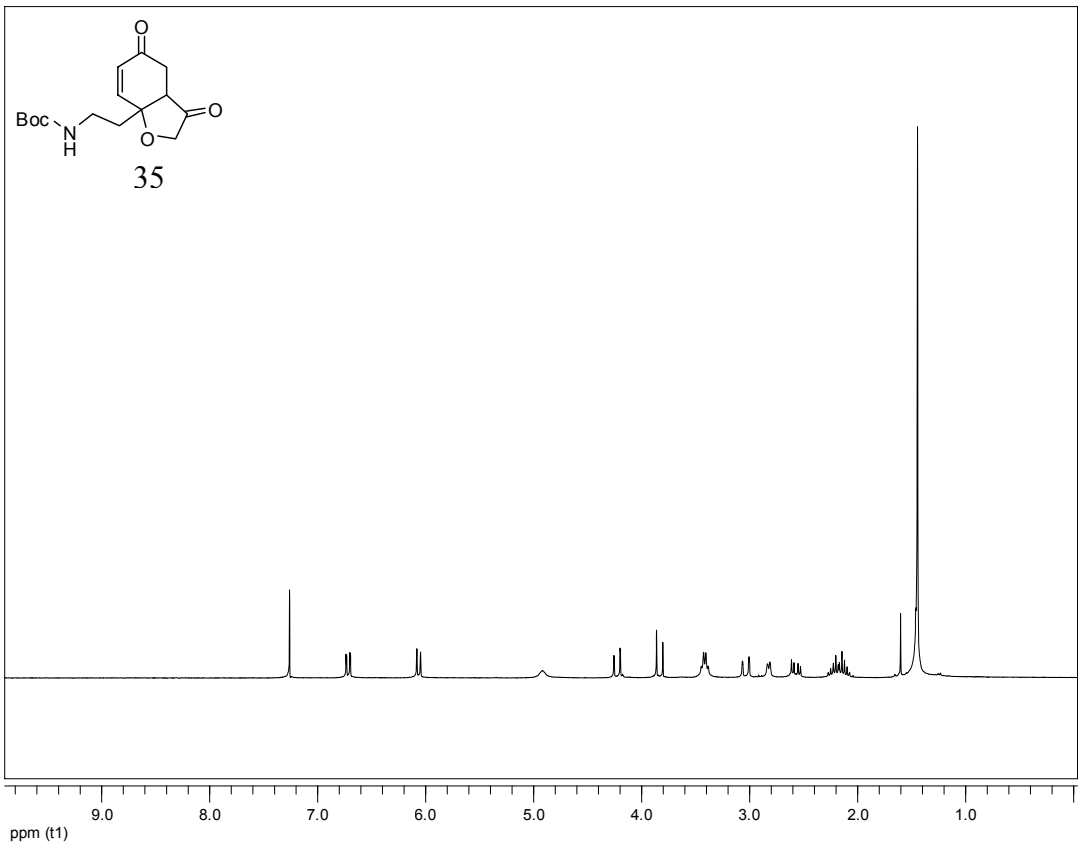
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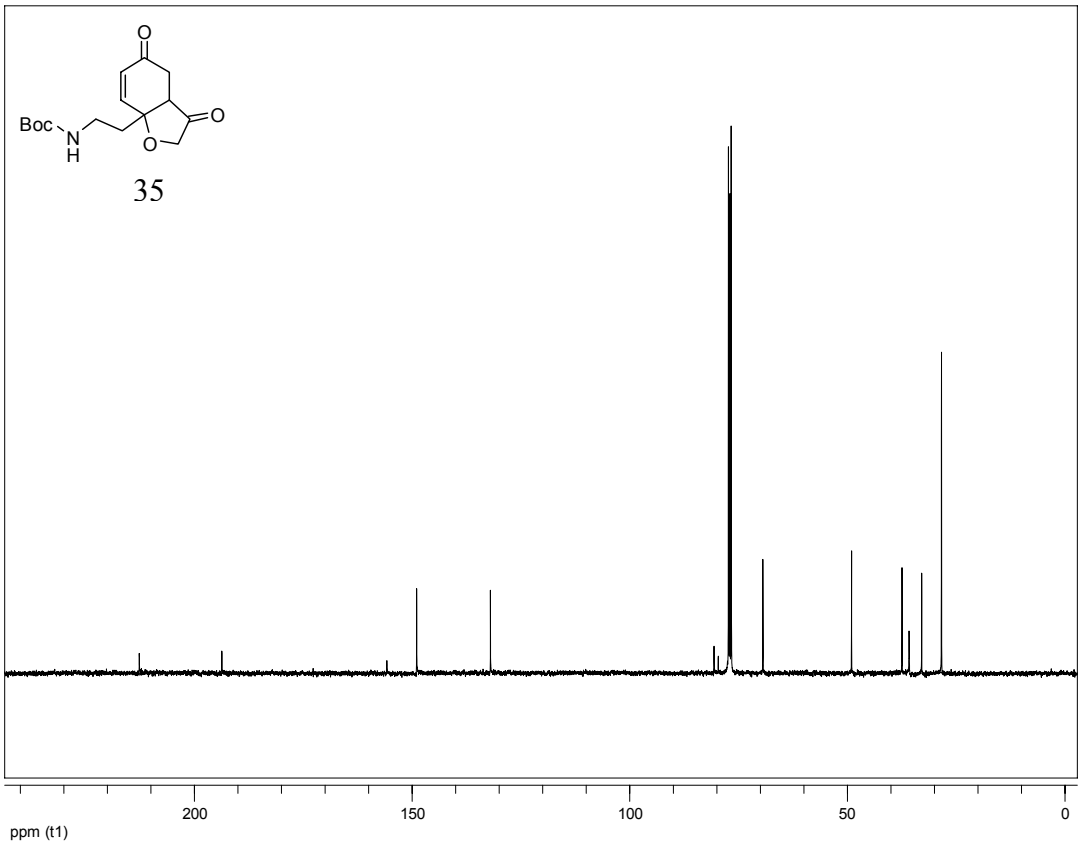
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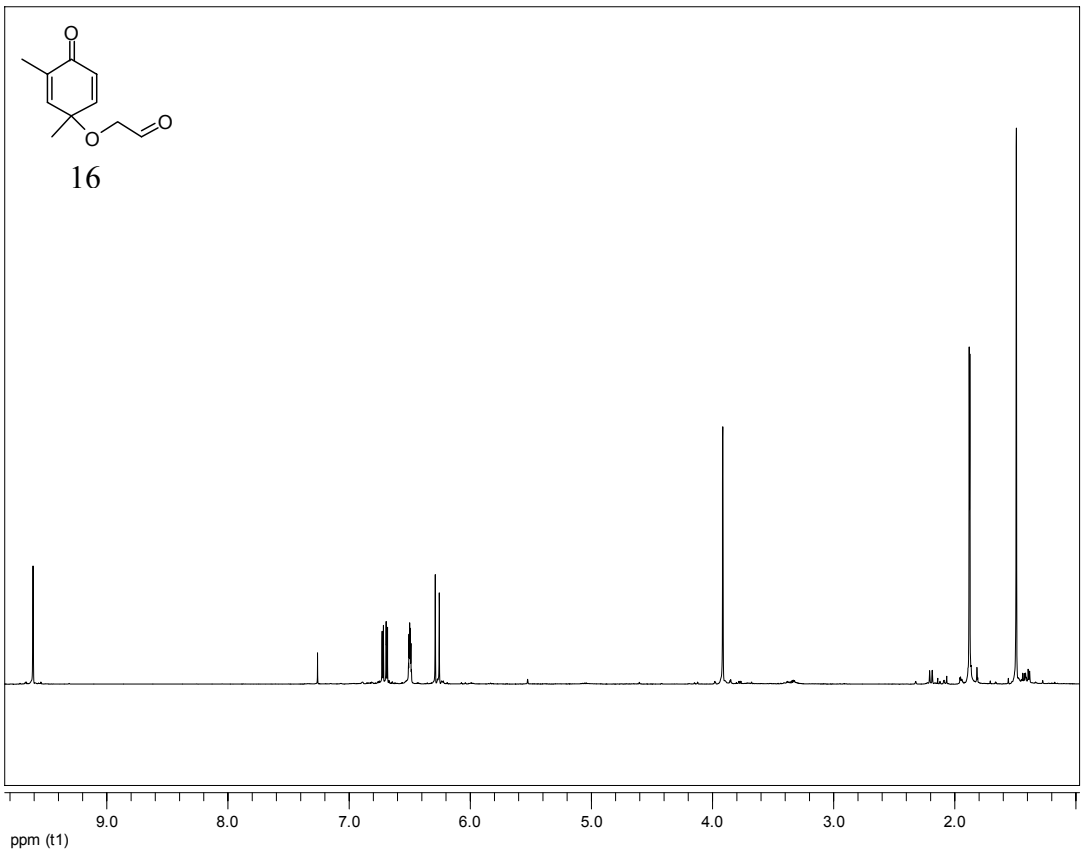
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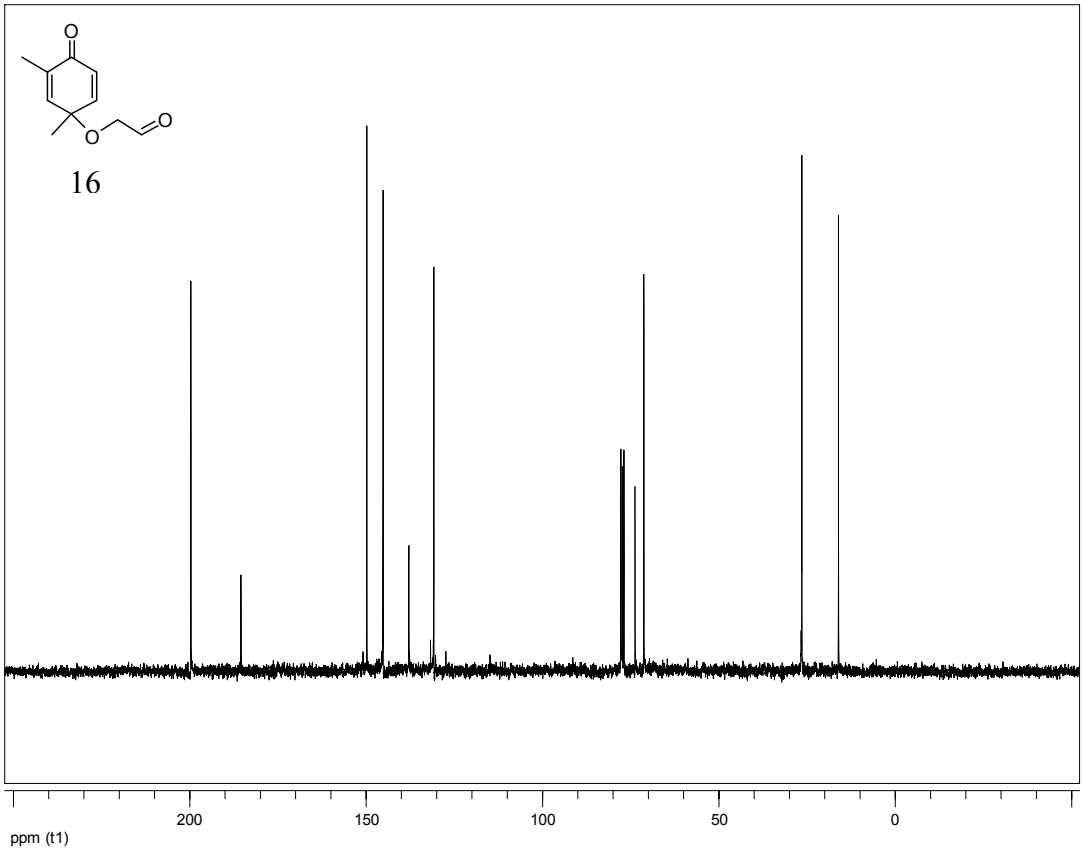
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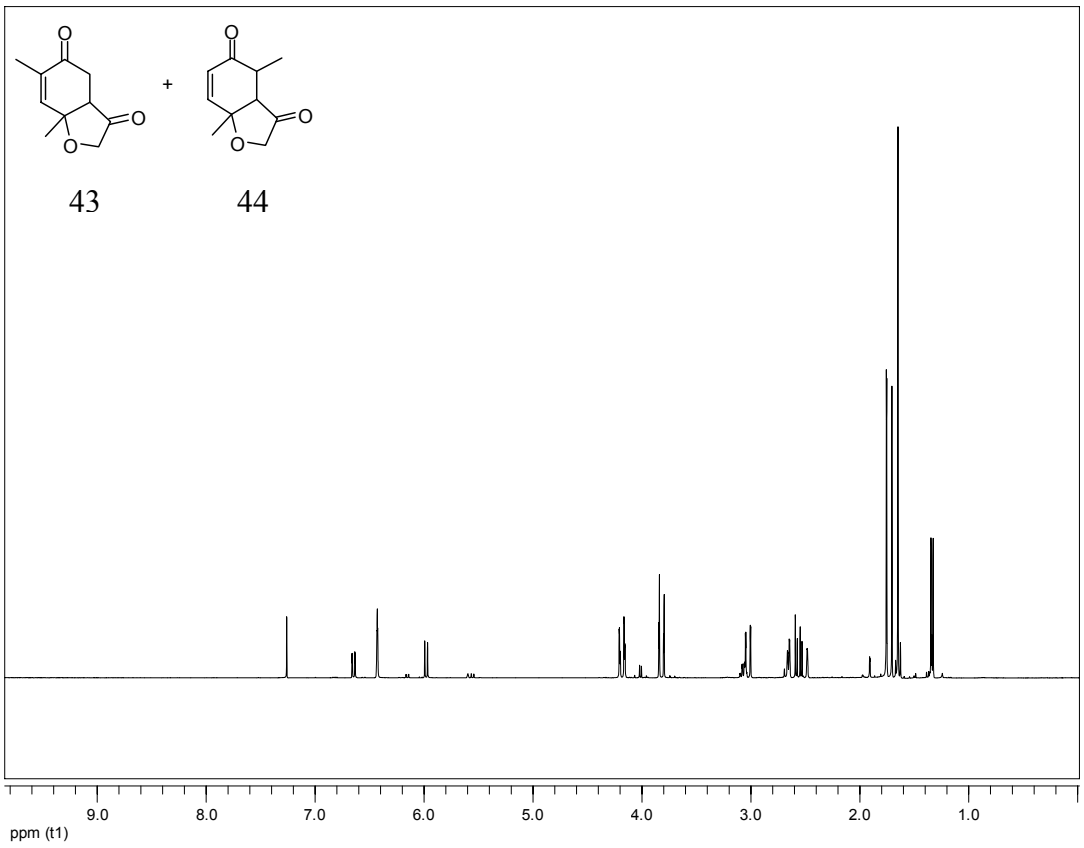
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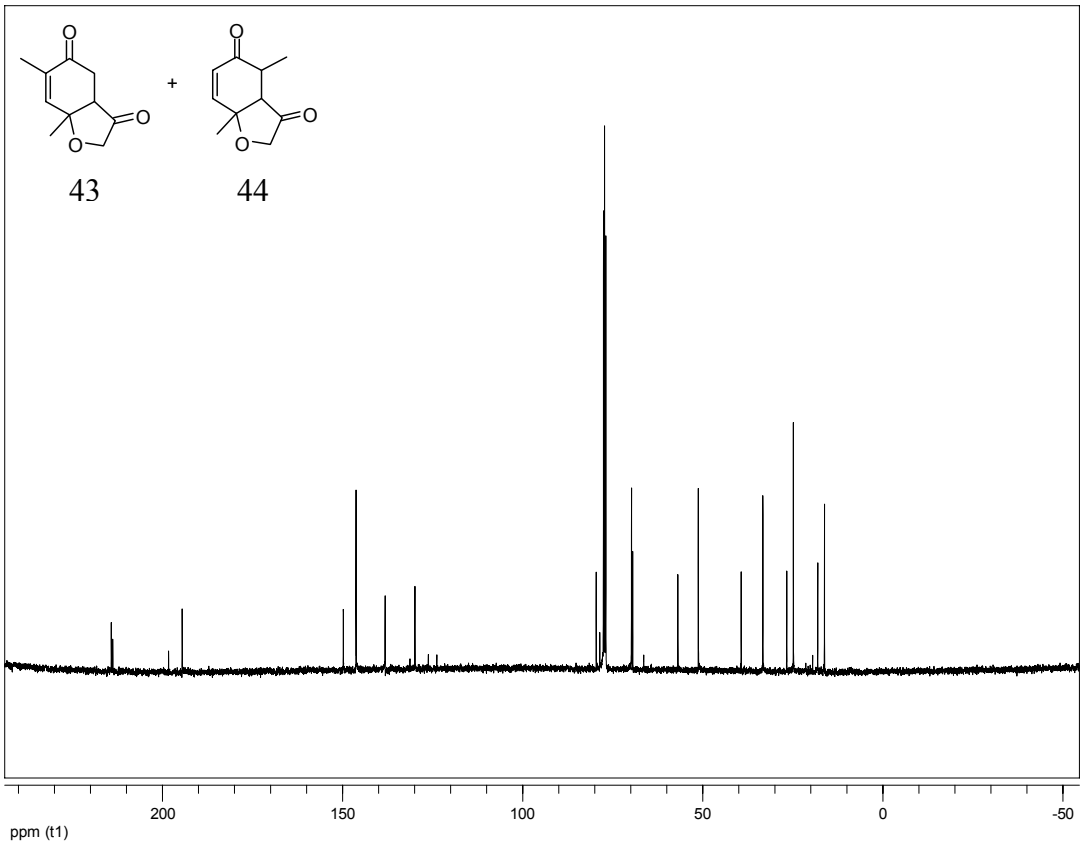
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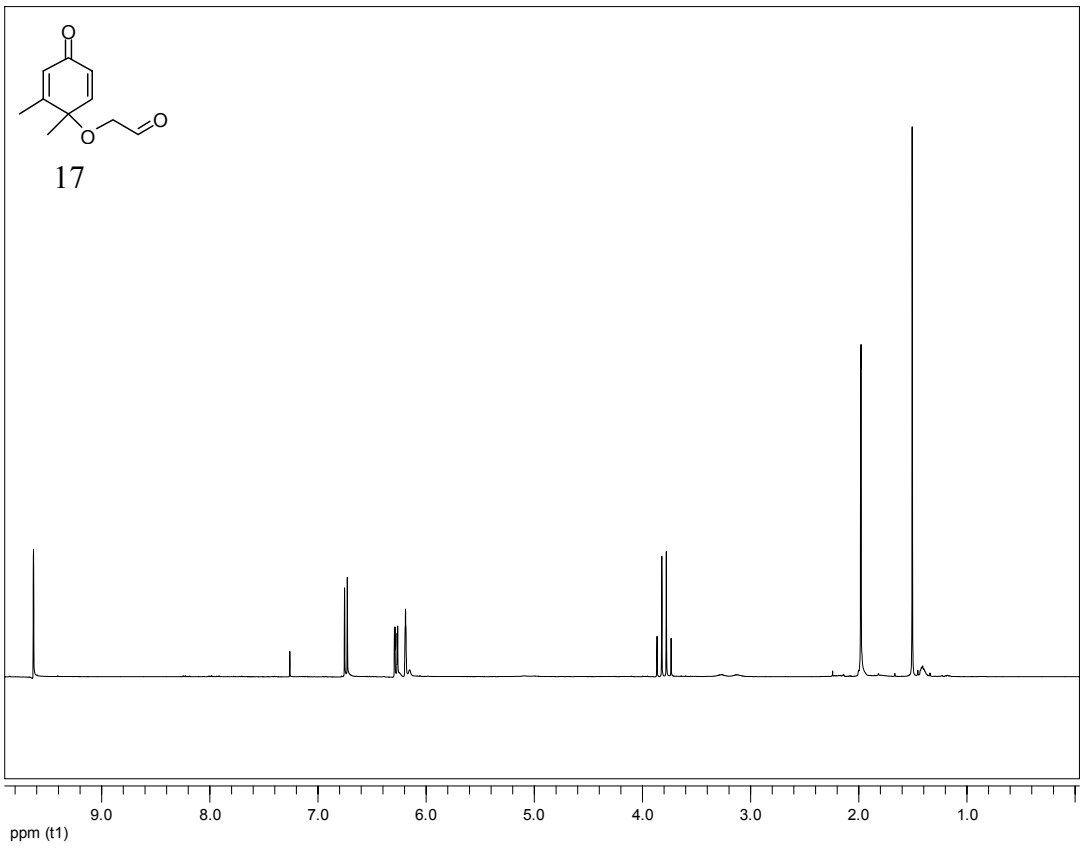
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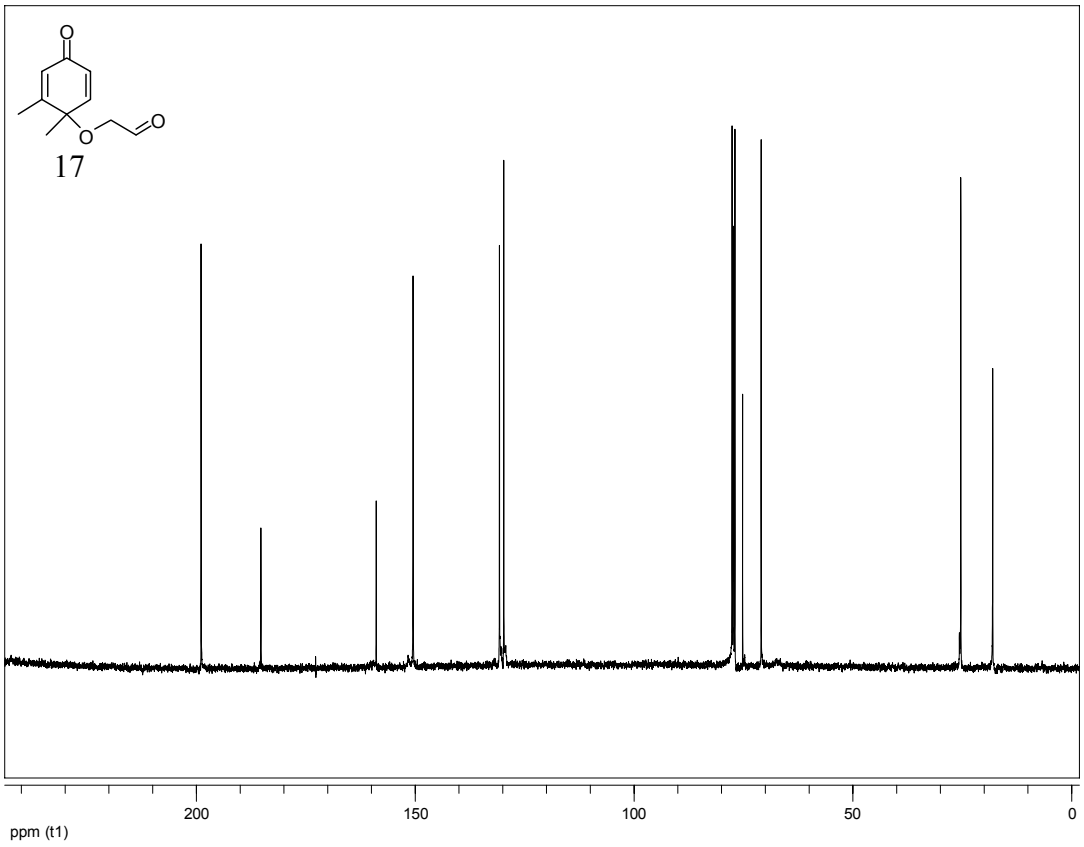
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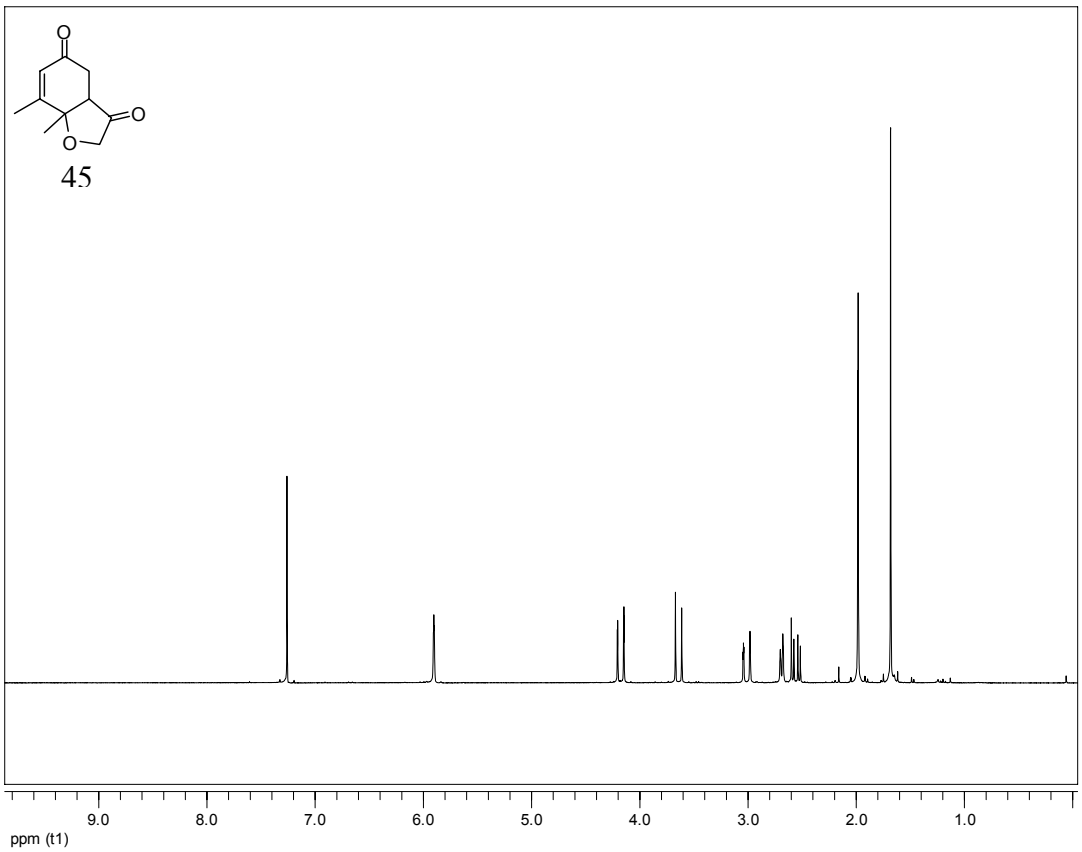
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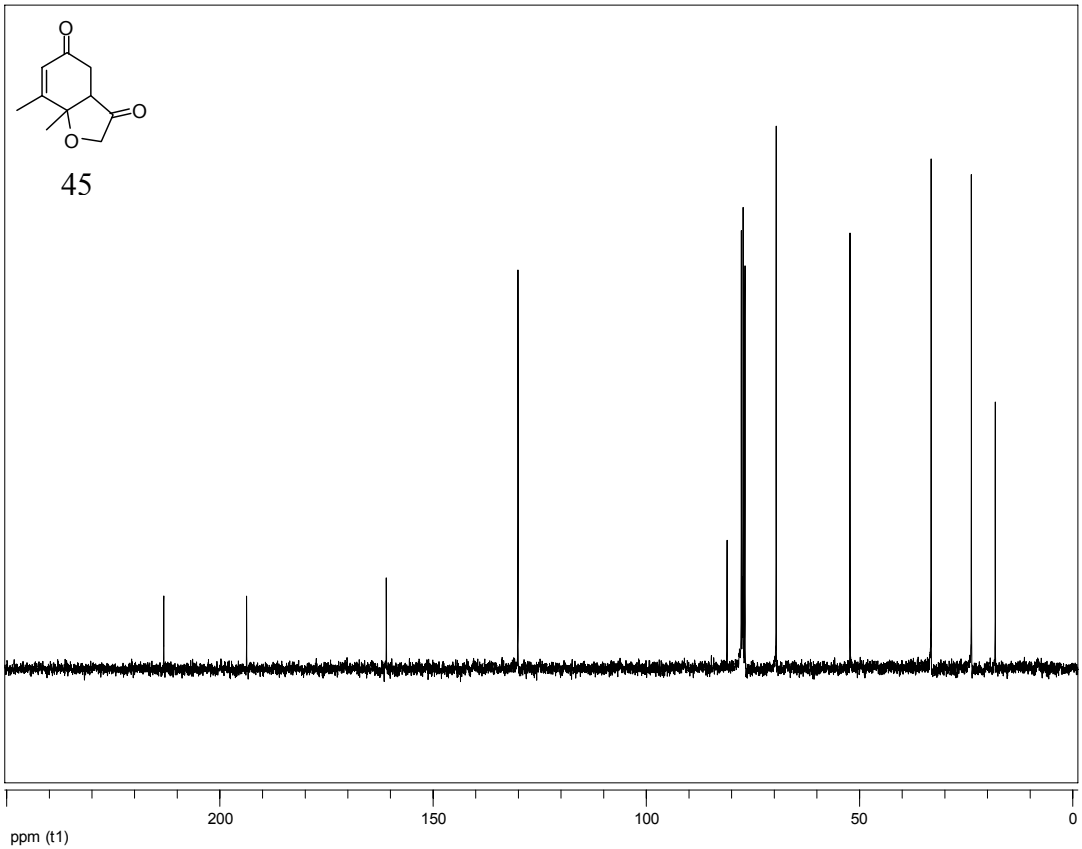
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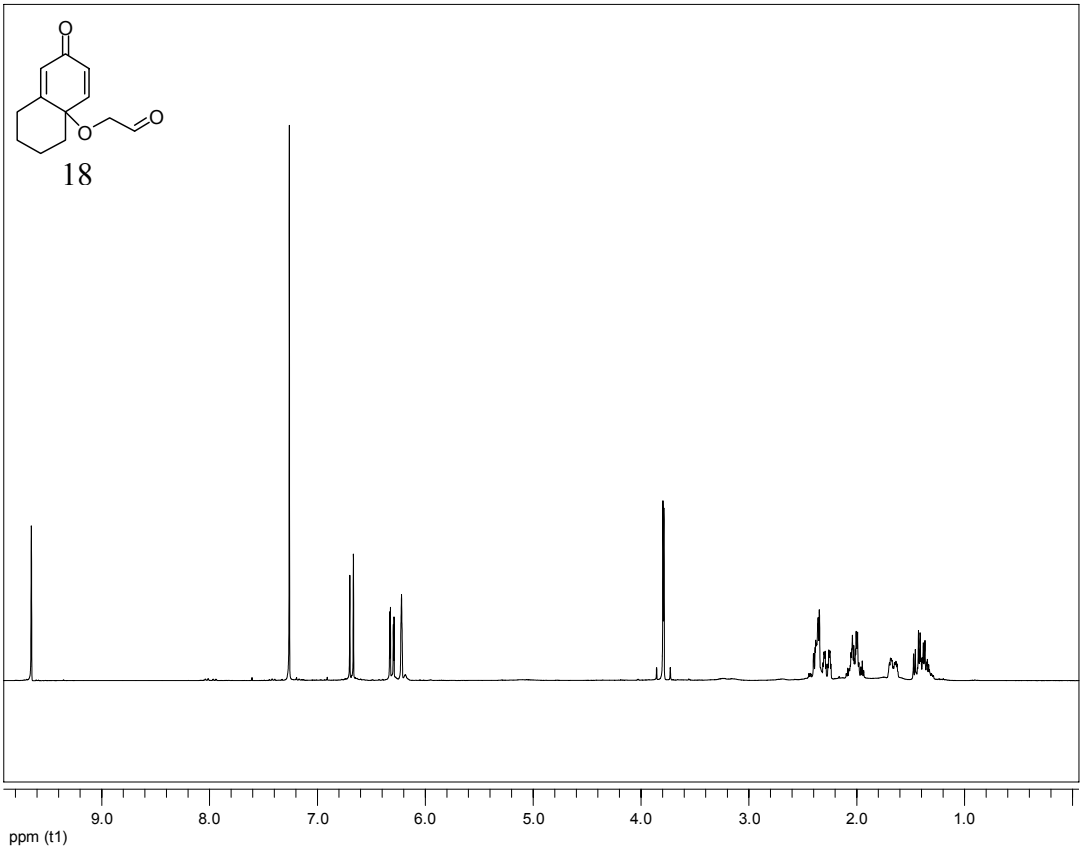
ppm (t1)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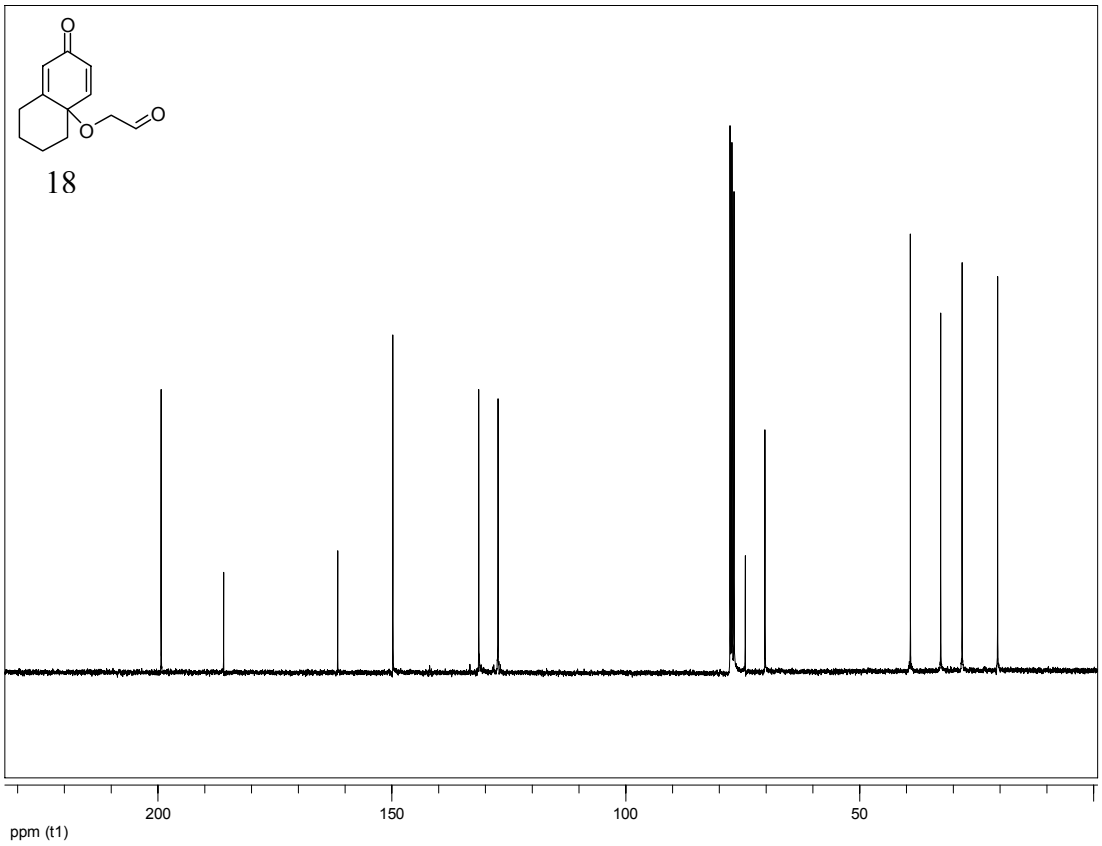
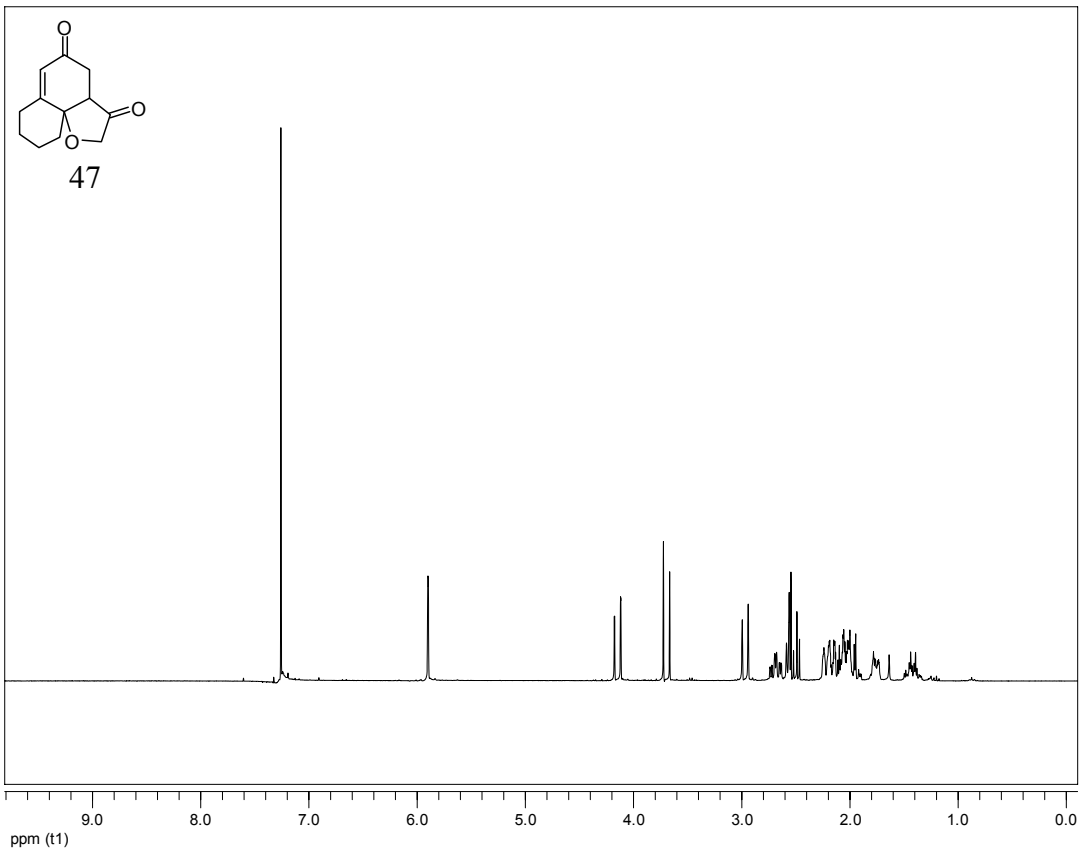
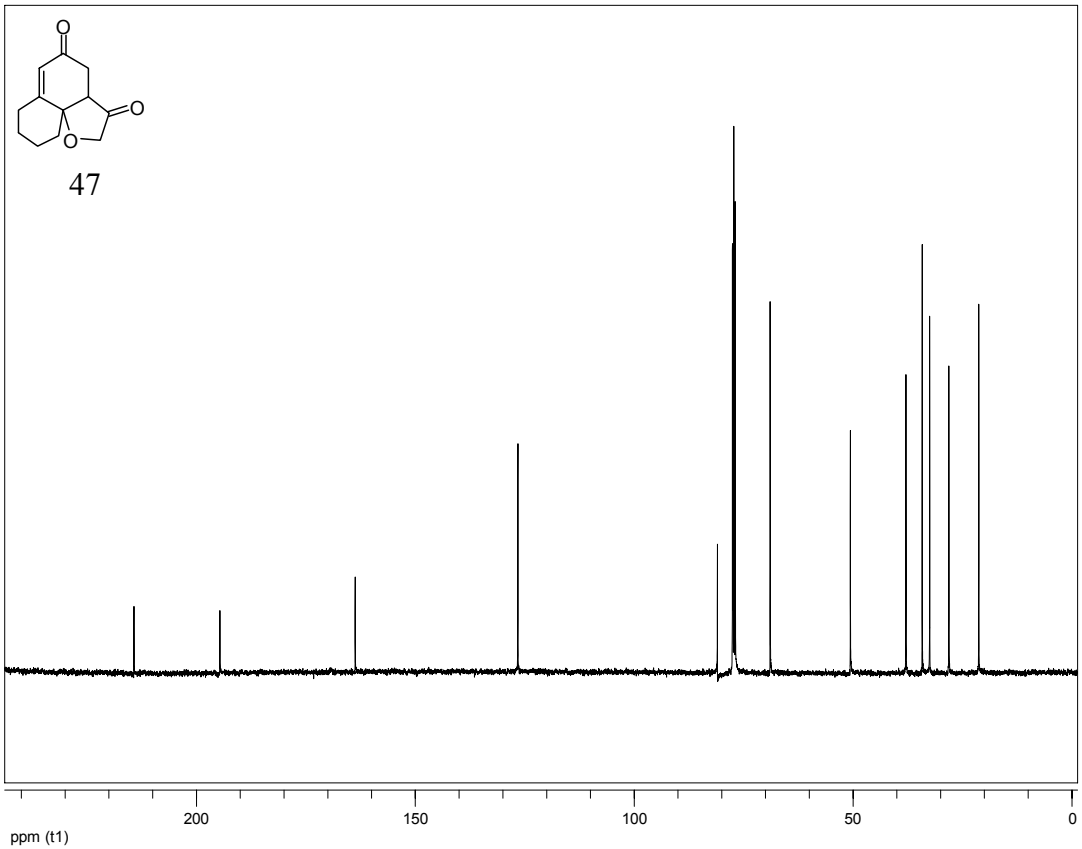
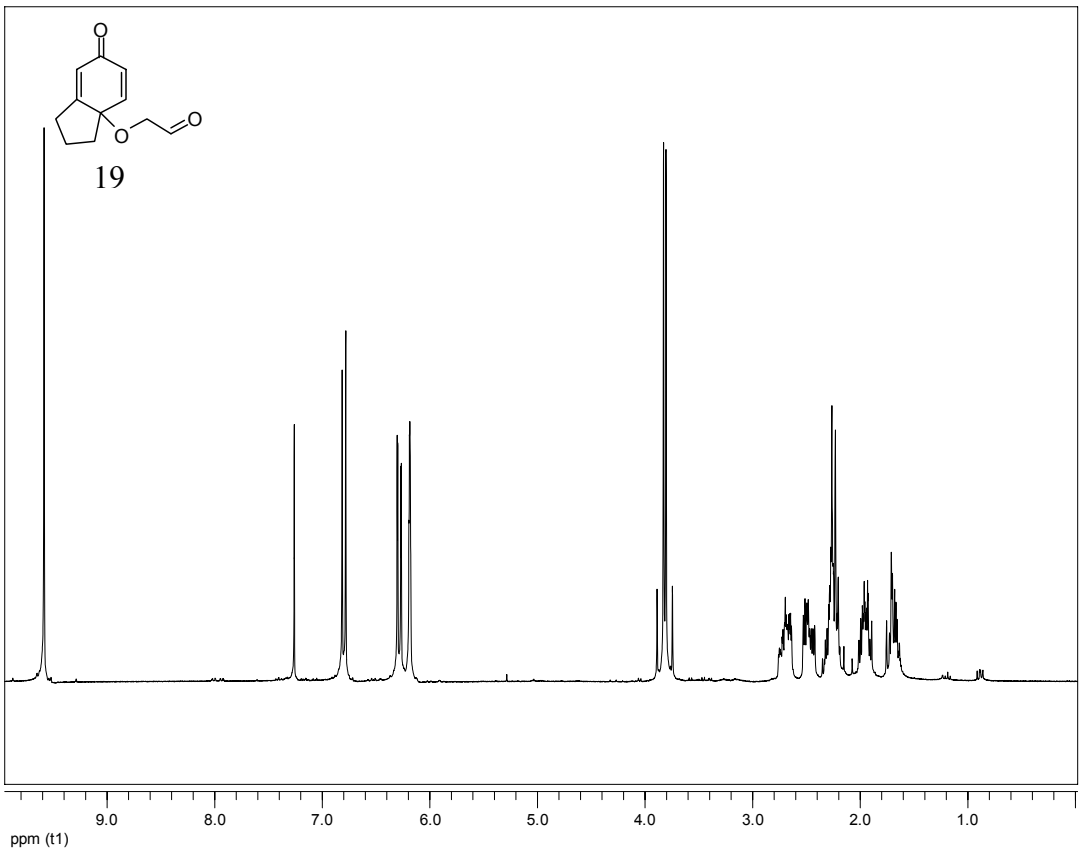
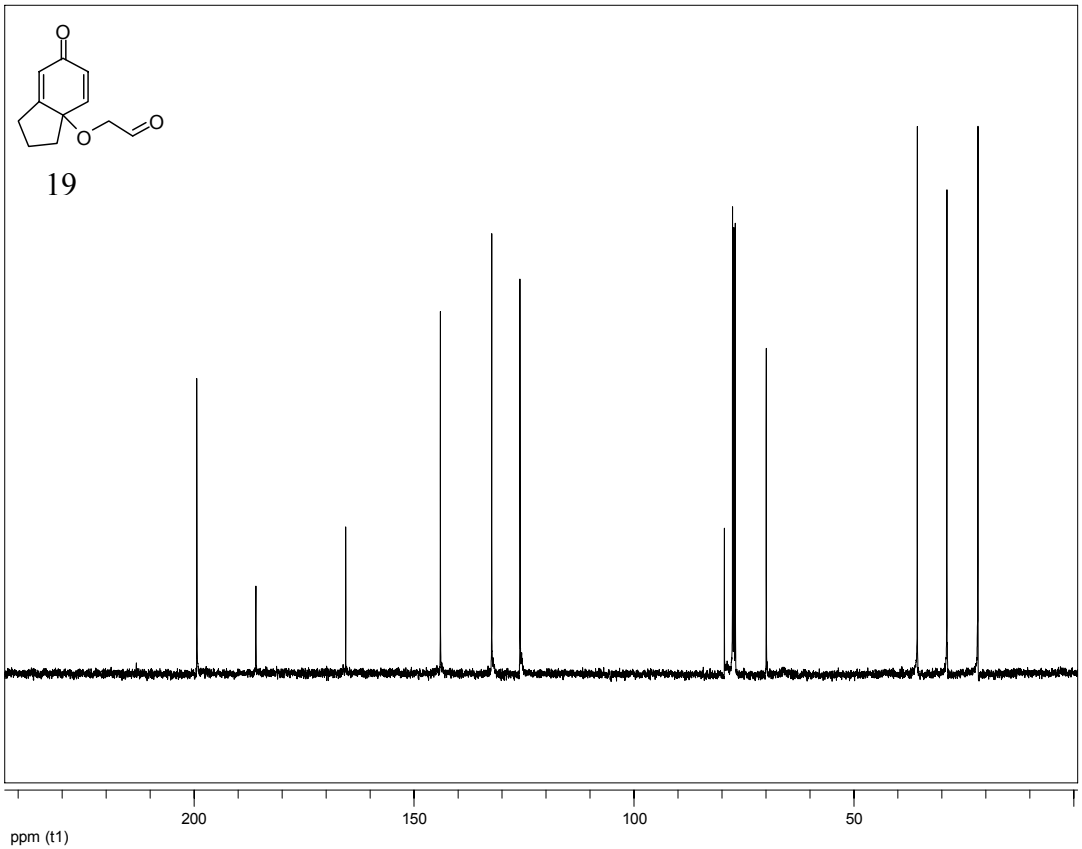
2.0
1.0
ppm (t1)

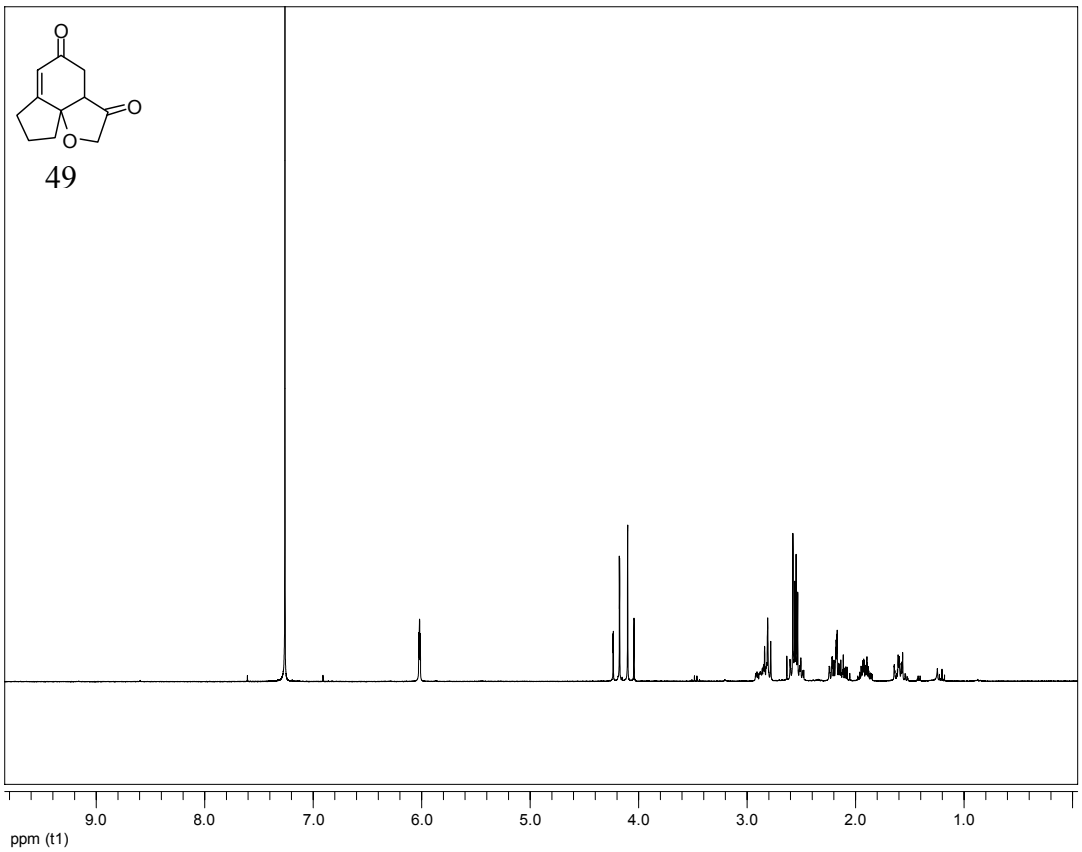

O
O
O
18
200
150
100
50
ppm (t1)

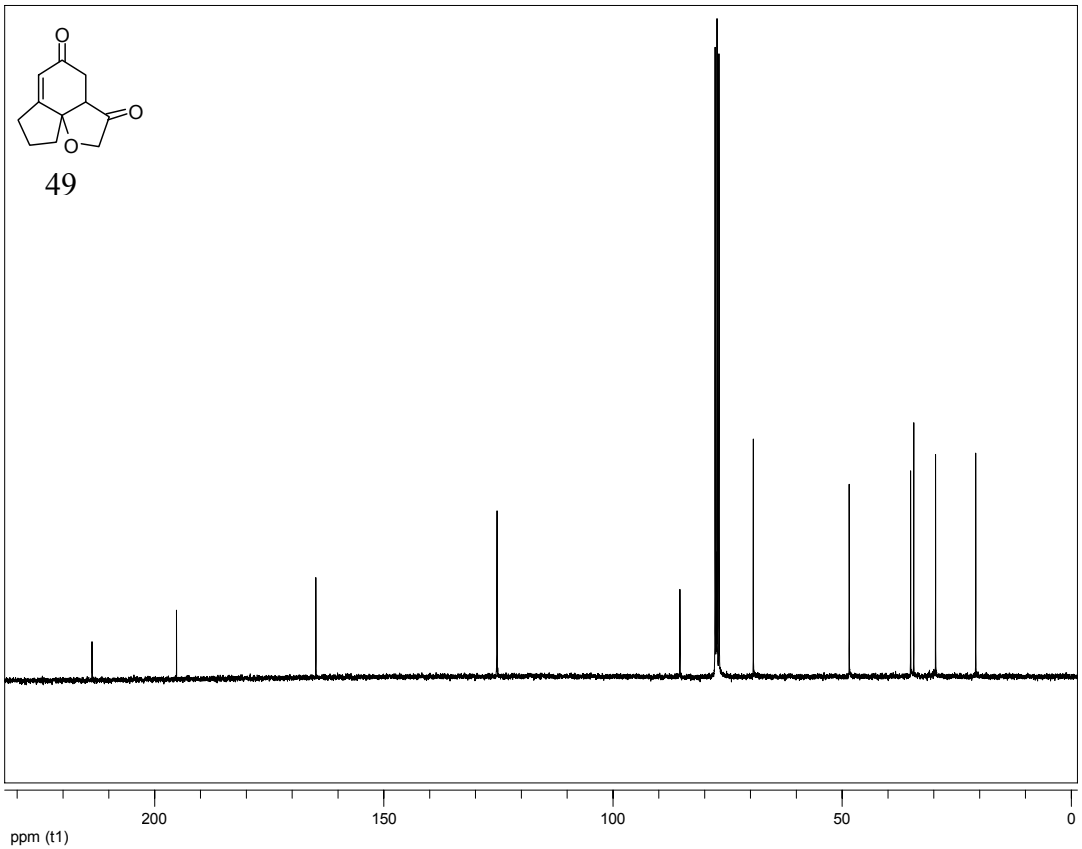

O
O
O
47
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

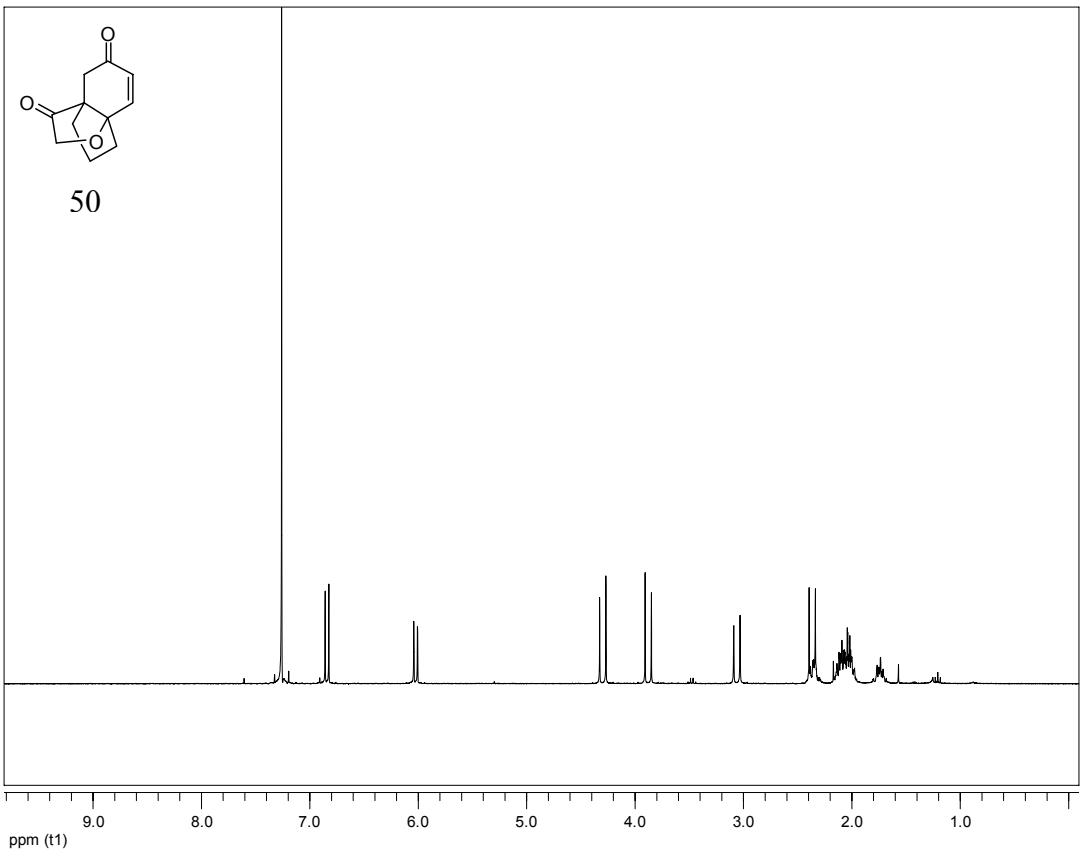

O
O
O
47
200
150
100
50
0
ppm (t1)


O
O
O
19
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


O
O
O
19
200
150
100
50
ppm (t1)


O
O
O
49
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


O
O
O
49
200
150
100
50
0
ppm (t1)



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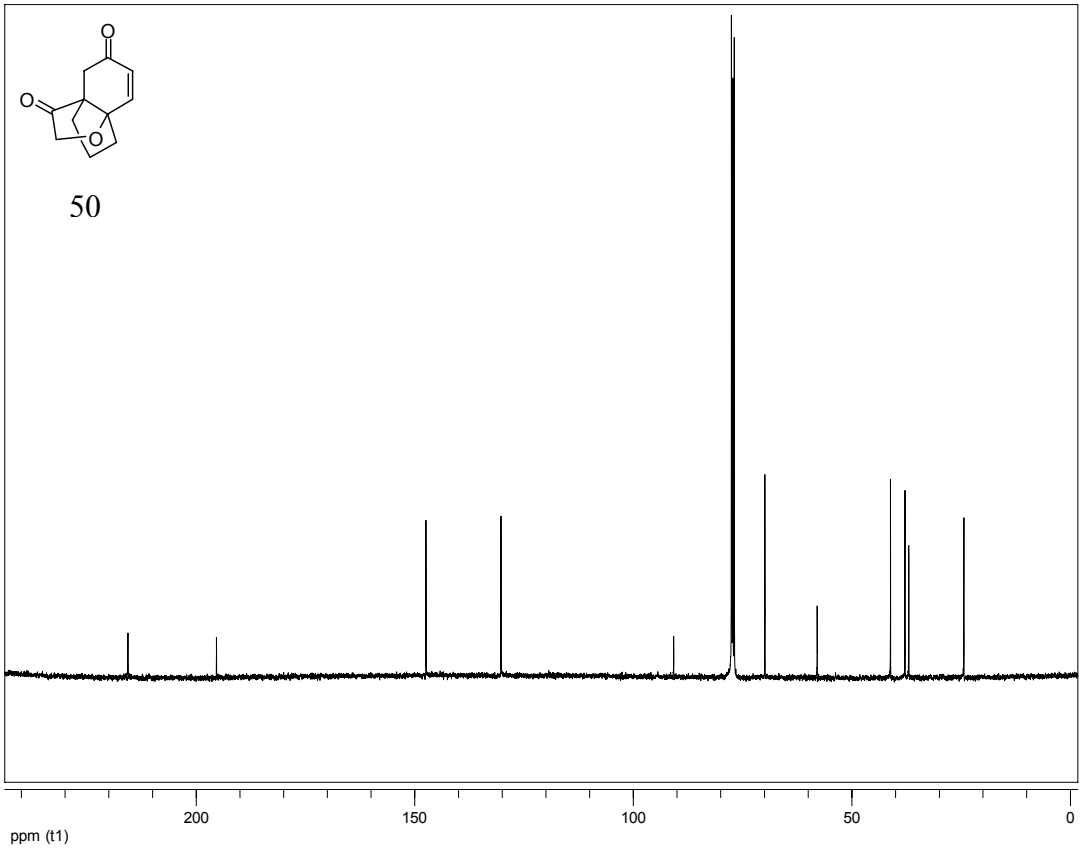

50