Supporting Information

Diversity-oriented synthesis leads to an effective class of bifunctional linchpins uniting anion relay chemistry (ARC) with benzyne reactivity

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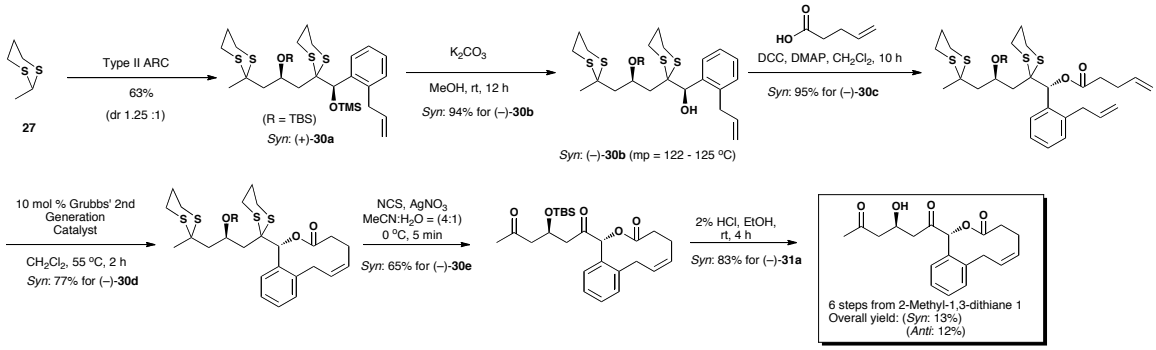
Experimental

I. Materials and Methods

Unless otherwise indicated, all reactions were carried out under an argon atmosphere in flame- or oven-dried glassware equipped with a magnetic stir bar. After aqueous work-up, all organic extracts were dried over sodium or magnesium sulfate, and filtered prior to concentration. Diethyl ether and THF were obtained from a Pure Solv^{TM} PS-400. MeLi (1.6 M in Et_2O), *n*-BuLi (2.5 M in Hexane), KHMDS (0.5 M in toluene) and TBAF (1.0 M in THF) were purchased from Sigma-Aldrich®, and used without purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck pre-coated silica gel plates (Kieselgel $60F_{254}$, Merck). Spots were detected by viewing under a UV light, staining with an anisaldehyde solution composed of acetic acid, sulfuric acid, and MeOH, or staining with a $KMnO_4$ solution composed of potassium carbonate, sodium hydroxide, and water. Silica gel for flash chromatography (particle size 0.040-0.063 mm) was supplied by Silicycle and Sorbent technologies. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^1H and ^{13}C spectra were recorded on a Bruker AM-500 spectrometer. Chemical shifts are reported as δ values relative to internal chloroform (δ7.26 for ^1H and δ 77.0 for ^{13}C). IR spectra were measured as neat oils on a Perkin-Elmer Model 1600 FTIR. Optical rotations were measured on a Jasco polarimeter. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center.

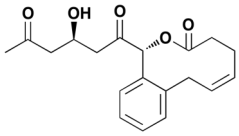
II. Experimental Section

"Natural Product-Like" Libraries Synthesis



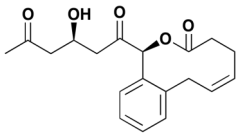
General procedure for 10-membered ring macrolides (31a-31l): To a solution of (+)-**30a** (1.94 g, 3.02 mmol, 1.0 equiv) in MeOH (40 mL) was added K_2CO_3 (4.17, 30.2 mmol, 10.0 equiv) at ambient temperature. After stirring overnight at ambient temperature, H_2O (100 mL) was added. The resulting mixture was then extracted with Et_2O (50 mL X 3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography on silica gel, using diethyl ether/hexane (1/10), provided (–)-**30b** (1.62 g, 2.84 mmol, 94%). To a solution of (–)-**30b** (247.0 mg, 0.43 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) were added DCC (1.0 M in CH_2Cl_2, 4.3 mL, 4.3 mmol, 10.0 equiv), DMAP (26.8 mg, 0.22 mmol, 0.5 equiv) and 4-pentenoic acid (0.44 mL, 4.3 mmol, 10.0 equiv) dropwise at ambient temperature. After stirring for 10 h, CH_2Cl_2 was evaporated, and then filtered through celite with diethyl ether. The filtrates were concentrated *in vacuo* and flash chromatography on silica gel, using diethyl ether/hexane (1/20), provided (–)-**30c** (267.8 mg, 0.41 mmol, 95%) as pale yellow oil. To a solution of (–)-**30c** (60.5 mg, 0.093 mmol, 1.0 equiv) in CH_2Cl_2 (0.003M, 31 mL) at was added 2nd generation Grubbs catalyst (7.89 mg, 0.0093 mmol, 0.1 equiv) at ambient temperature. After stirring for 2 h at 55 ^{o}C, CH_2Cl_2 was evaporated, and then the crude product was purified by flash chromatography on silica gel, using diethyl ether/hexane (1/10) to provide (–)-**30d** (45.1 mg, 0.072 mmol, 77%) as pale yellow oil. To a solution of dithiane (–)-**30d** (39.5 mg, 0.063 mmol, 1.0 equiv) in aqueous CH_3CN (80%, 7.5 mL) at 0 ^{o}C was added NCS (50.5 mg, 0.378 mmol, 6.0 equiv) and $AgNO_3$ (107.0 mg, 0.63 mmol, 10.0 equiv). After being stirred for 5 min at 0 ^{o}C, a saturated aqueous $NaHSO_3$ (3 mL), and $NaHCO_3$ (3 mL) were

added. The resulting mixture was then extracted with Et_2O (10 mL X 3). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography on silica gel, using ethyl acetate/hexane (1/4), provided (–)-**30e** (18.2 mg, 0.041 mmol, 65%) as pale yellow oil. Silyl ether (–)-**30e** (16.1 mg, 0.036 mmol, 1.0 equiv) was treated with 2% HCl in EtOH (3 mL). After stirring for 4 h at ambient temperature, a saturated aqueous NH_4Cl solution (5 mL) was added. The resulting mixture was then extracted with CH_2Cl_2 (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography on silica gel, using ethyl acetate/hexane (1/2), provided (–)-**31a** (9.9 mg, 0.03 mmol, 83%) as pale yellow oil. R_f 0.1 (hexane/ethyl acetate = 3/1)



(–)-31a

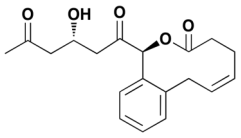
Compounds (–)-31a. $[\alpha]^{20}_D$ –133.9 (c 0.18 $CDCl_3$); IR (film) 3462 (m), 3010 (m), 2920 (m), 2858 (m), 1721 (s), 1359 (m), 1241 (s), 1065 (s), 745 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (m, 4H), 6.10 (s, 1H), 5.49 (td, *J* = 10.5 and 4.5 Hz, 1H), 5.41-5.35 (m, 1H), 4.47-4.41 (m, 1H), 4.10 (t, *J* = 11.5 Hz, 1H), 3.30 (br, 1H), 3.14-3.06 (m, 1H), 2.91 (dd, *J* = 12.5 and 4.5 Hz, 1H), 2.84 (dd, *J* = 17.0 and 7.5 Hz, 1H), 2.72-2.53 (m, 4H), 2.31-2.25 (m, 1H), 2.13 (s, 3H), 2.12-2.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.1, 170.5, 140.0, 132.7, 132.4, 130.9, 130.5, 129.3, 126.5, 125.8, 82.1, 64.2, 48.9, 44.8, 34.0, 32.6, 30.7, 22.9; high resolution mass spectrum (ES^+) m/z 353.1380 [$(M+Na)^+$; calcd for $C_{19}H_{22}O_5Na$: 353.1365].



(+)-31b

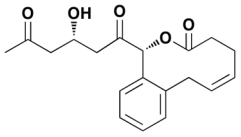
Compounds (+)-31b. $[\alpha]^{20}_D$ +75.2 (c 0.25 $CDCl_3$); IR (film) 3485 (m), 3011 (m), 2922 (m), 2858 (m), 1720 (s), 1359 (m), 1242 (s), 1066 (s), 745 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.21 (m, 4H), 6.10 (s, 1H), 5.49 (td, *J* = 11.0 and 4.5 Hz, 1H), 5.41-5.35 (m, 1H), 4.47-4.42 (m, 1H), 4.10 (t, *J* = 11.8 Hz, 1H), 3.27 (br, 1H), 3.13-3.05 (m, 1H),

2.91 (dd, *J* = 13.0 and 4.5 Hz, 1H), 2.82 (dd, *J* = 17.0 and 5.5 Hz, 1H), 2.72-2.58 (m, 4H), 2.32-2.26 (m, 1H), 2.14 (s, 3H), 2.13-2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 203.2, 170.6, 140.0, 132.8, 132.4, 130.9, 130.4, 129.4, 126.6, 125.8, 82.0, 63.9, 48.8, 44.7, 33.9, 32.7, 30.7, 22.9; high resolution mass spectrum (ES^+) m/z 331.1557 [$(M+H)^+$; calcd for $C_{19}H_{23}O_5$: 331.1557].



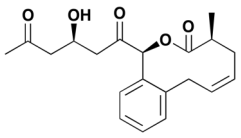
(+)-31c

Compounds (+)-31c. $[\alpha]^{20}_D$ +166.2 (c 0.18 $CDCl_3$); IR (film) 3462 (m), 3010 (m), 2920 (m), 2858 (m), 1721 (s), 1359 (m), 1241 (s), 1065 (s), 745 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (m, 4H), 6.10 (s, 1H), 5.49 (td, *J* = 10.5 and 4.5 Hz, 1H), 5.41-5.35 (m, 1H), 4.47-4.41 (m, 1H), 4.10 (t, *J* = 11.5 Hz, 1H), 3.30 (br, 1H), 3.14-3.06 (m, 1H), 2.91 (dd, *J* = 12.5 and 4.5 Hz, 1H), 2.84 (dd, *J* = 17.0 and 7.5 Hz, 1H), 2.72-2.53 (m, 4H), 2.31-2.25 (m, 1H), 2.13 (s, 3H), 2.12-2.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.1, 170.5, 140.0, 132.7, 132.4, 130.9, 130.5, 129.3, 126.5, 125.8, 82.1, 64.2, 48.9, 44.8, 34.0, 32.6, 30.7, 22.9; high resolution mass spectrum (ES^+) m/z 353.1348 [$(M+Na)^+$; calcd for $C_{19}H_{22}O_5Na$: 353.1365].



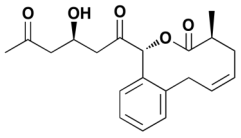
(–)-31d

Compounds (–)-31d. $[\alpha]^{20}_D$ −142.6 (c 1.34 $CDCl_3$); IR (film) 3485 (m), 3011 (m), 2922 (m), 2858 (m), 1720 (s), 1359 (m), 1242 (s), 1066 (s), 745 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.21 (m, 4H), 6.10 (s, 1H), 5.49 (td, *J* = 11.0 and 4.5 Hz, 1H), 5.41-5.35 (m, 1H), 4.47-4.42 (m, 1H), 4.10 (t, *J* = 11.8 Hz, 1H), 3.27 (br, 1H), 3.13-3.05 (m, 1H), 2.91 (dd, *J* = 13.0 and 4.5 Hz, 1H), 2.82 (dd, *J* = 17.0 and 5.5 Hz, 1H), 2.72-2.58 (m, 4H), 2.32-2.26 (m, 1H), 2.14 (s, 3H), 2.13-2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.4, 203.2, 170.6, 140.0, 132.8, 132.4, 130.9, 130.4, 129.4, 126.6, 125.8, 82.0, 63.9, 48.8, 44.7, 33.9, 32.7, 30.7, 22.9; high resolution mass spectrum (ES^-) m/z 329.1394 [$(M–H)^-$; calcd for $C_{19}H_{21}O_5$: 329.1389].



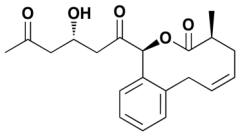
(+)-31e

Compounds (+)-31e. $[\alpha]^{20}_{D}$ +169.5 (c 0.47 $CDCl_3$); IR (film) 3447 (m), 2925 (s), 2857 (m), 1719 (s), 1373 (m), 1242 (s), 1081 (s), 759 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.3 Hz, 1H), 7.30-7.26 (m, 1H), 7.24-7.21 (m, 2H), 6.04 (s, 1H), 5.51-5.44 (m, 1H), 5.40 (td, *J* = 10.7 and 6.1 Hz, 1H), 4.47-4.41 (m, 1H), 4.10 (t, *J* = 11.9 Hz, 1H), 3.28 (d, *J* = 4.0 Hz, 1H), 3.04-2.97 (m, 1H), 2.90-2.86 (m, 1H), 2.82 (dd, *J* = 17.4 and 5.4 Hz, 1H), 2.71 (dd, *J* = 17.4 and 6.8 Hz, 1H), 2.67-2.58 (m, 2H), 2.55-2.43 (m, 1H), 2.14 (s, 3H), 1.99-1.95 (m, 1H), 1.33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.4, 203.2, 173.4, 139.8, 132.5, 132.4, 131.0, 130.4, 129.3, 126.5, 125.4, 82.0, 63.9, 48.8, 44.7, 40.5, 32.7, 31.8, 30.7, 17.9; high resolution mass spectrum (ES^+) m/z 367.1518 [$(M+Na)^+$; calcd for $C_{20}H_{24}O_5Na$: 367.1521].



(–)-31f

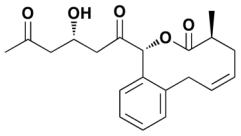
Compounds (–)-31f. $[\alpha]^{20}_{D}$ −95.5 (c 1.18 $CDCl_3$); IR (film) 3439 (m), 2922 (s), 2853 (m), 1715 (s), 1362 (m), 1184 (s), 1094 (m), 741 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.23-7.20 (m, 2H), 6.05 (s, 1H), 5.52-5.47 (m, 1H), 5.45 (td, *J* = 10.1 and 6.3 Hz, 1H), 4.48-4.42 (m, 1H), 4.01 (t, *J* = 11.3 Hz, 1H), 3.36 (br, 1H), 3.24-3.18 (m, 1H), 2.95-2.87 (m, 2H), 2.84 (dd, *J* = 17.1 and 7.6 Hz, 1H), 2.62 (dd, *J* = 17.1 and 4.9 Hz, 1H), 2.55-2.51 (m, 2H), 2.12 (s, 3H), 2.09-2.04 (m, 1H), 1.13 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.5, 173.4, 139.6, 133.5, 132.1, 130.9, 130.4, 129.2, 126.5, 123.2, 82.1, 64.1, 48.9, 45.0, 38.3, 32.4, 30.7, 29.8, 13.9; high resolution mass spectrum (ES^+) m/z 367.1503 [$(M+Na)^+$; calcd for $C_{20}H_{24}O_5Na$: 367.1521].



(+)-31g

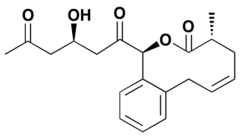
Compounds (+)-31g. $[\alpha]^{20}_{D}$ +141.2 (c 1.35 $CDCl_3$); IR (film) 3420 (m), 2922 (m), 1717 (s), 1375 (m), 1242 (s), 1084 (s), 761 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J*

= 7.4 Hz, 1H), 7.30-7.26 (m, 1H), 7.23-7.20 (m, 2H), 6.04 (s, 1H), 5.47-5.42 (m, 1H), 5.40 (td, *J* = 10.8 and 6.1 Hz, 1H), 4.47-4.42 (m, 1H), 4.10 (t, *J* = 11.9 Hz, 1H), 3.37 (br, 1H), 3.04-2.97 (m, 1H), 2.89-2.83 (m, 2H), 2.61 (dd, *J* = 17.1 and 5.1 Hz, 1H), 2.55-2.52 (m, 2H), 2.51-2.44 (m, 1H), 2.12 (s, 3H), 1.99-1.94 (m, 1H), 1.33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.0, 173.3, 139.8, 132.4, 132.3, 130.9, 130.5, 129.2, 126.4, 125.4, 82.0, 64.1, 48.9, 44.8, 40.6, 32.6, 31.7, 30.6, 17.9; high resolution mass spectrum (ES^+) m/z 345.1695 [$(M+H)^+$; calcd for $C_{20}H_{25}O_5$: 345.1702].



(–)-31h

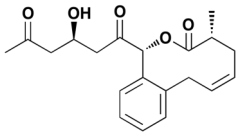
Compounds (–)-31h. $[\alpha]^{20}_D$ −76.3 (c 0.58 $CDCl_3$); IR (film) 3406 (m), 2922 (m), 1720 (s), 1381 (m), 1182 (s), 1095 (s), 762 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.23-7.20 (m, 2H), 6.06 (s, 1H), 5.53-5.48 (m, 1H), 5.46 (td, *J* = 10.2 and 6.4 Hz, 1H), 4.48-4.43 (m, 1H), 4.00 (t, *J* = 11.3 Hz, 1H), 3.29 (br, 1H), 3.21-3.17 (m, 1H), 2.97-2.86 (m, 2H), 2.82 (dd, *J* = 17.3 and 5.3 Hz, 1H), 2.73 (dd, *J* = 17.4 and 6.8 Hz, 1H), 2.67-2.58 (m, 2H), 2.15 (s, 3H), 2.10-2.05 (m, 1H), 1.14 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.4, 203.7, 173.4, 139.5, 133.5, 132.1, 131.0, 130.2, 129.3, 126.5, 123.1, 82.0, 63.8, 48.8, 44.9, 38.3, 32.5, 30.7, 29.8, 14.0; high resolution mass spectrum (ES^+) m/z 367.1518 [$(M+Na)^+$; calcd for $C_{20}H_{24}O_5Na$: 367.1521].



(+)-31i

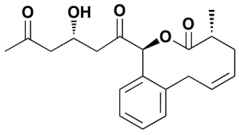
Compounds (+)-31i. $[\alpha]^{20}_D$ +99.6 (c 0.57 $CDCl_3$); IR (film) 3406 (m), 2922 (m), 1720 (s), 1381 (m), 1182 (s), 1095 (s), 762 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.23-7.20 (m, 2H), 6.06 (s, 1H), 5.53-5.48 (m, 1H), 5.46 (td, *J* = 10.2 and 6.4 Hz, 1H), 4.48-4.43 (m, 1H), 4.00 (t, *J* = 11.3 Hz, 1H), 3.29 (br, 1H), 3.21-3.17 (m, 1H), 2.97-2.86 (m, 2H), 2.82 (dd, *J* = 17.3 and 5.3 Hz, 1H), 2.73 (dd, *J* = 17.4 and 6.8 Hz, 1H), 2.67-2.58 (m, 2H), 2.15 (s, 3H), 2.10-2.05 (m, 1H), 1.14 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.4, 203.7, 173.4, 139.5, 133.5, 132.1, 131.0, 130.2, 129.3,

126.5, 123.1, 82.0, 63.8, 48.8, 44.9, 38.3, 32.5, 30.7, 29.8, 14.0; high resolution mass spectrum (ES^+) m/z 367.1518 [$(M+Na)^+$; calcd for $C_{20}H_{24}O_5Na$: 367.1521].



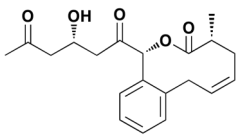
(–)-31j

Compounds (–)-31j. $[\alpha]^{20}_D$ −193.6 (c 0.38 $CDCl_3$); IR (film) 3420 (m), 2922 (m), 1717 (s), 1375 (m), 1242 (s), 1084 (s), 761 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.4 Hz, 1H), 7.30-7.26 (m, 1H), 7.23-7.20 (m, 2H), 6.04 (s, 1H), 5.47-5.42 (m, 1H), 5.40 (td, *J* = 10.8 and 6.1 Hz, 1H), 4.47-4.42 (m, 1H), 4.10 (t, *J* = 11.9 Hz, 1H), 3.37 (br, 1H), 3.04-2.97 (m, 1H), 2.89-2.83 (m, 2H), 2.61 (dd, *J* = 17.1 and 5.1 Hz, 1H), 2.55-2.52 (m, 2H), 2.51-2.44 (m, 1H), 2.12 (s, 3H), 1.99-1.94 (m, 1H), 1.33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.0, 173.3, 139.8, 132.4, 132.3, 130.9, 130.5, 129.2, 126.4, 125.4, 82.0, 64.1, 48.9, 44.8, 40.6, 32.6, 31.7, 30.6, 17.9; high resolution mass spectrum (ES^+) m/z 345.1697 [$(M+H)^+$; calcd for $C_{20}H_{25}O_5$: 345.1702].



(+)-31k

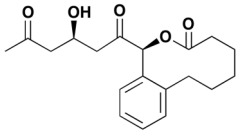
Compounds (+)-31k. $[\alpha]^{20}_D$ +92.7 (c 0.29 $CDCl_3$); IR (film) 3439 (m), 2922 (s), 2853 (m), 1715 (s), 1362 (m), 1184 (s), 1094 (m), 741 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.23-7.20 (m, 2H), 6.05 (s, 1H), 5.52-5.47 (m, 1H), 5.45 (td, *J* = 10.1 and 6.3 Hz, 1H), 4.48-4.42 (m, 1H), 4.01 (t, *J* = 11.3 Hz, 1H), 3.36 (br, 1H), 3.24-3.18 (m, 1H), 2.95-2.87 (m, 2H), 2.84 (dd, *J* = 17.1 and 7.6 Hz, 1H), 2.62 (dd, *J* = 17.1 and 4.9 Hz, 1H), 2.55-2.51 (m, 2H), 2.12 (s, 3H), 2.09-2.04 (m, 1H), 1.13 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.5, 173.4, 139.6, 133.5, 132.1, 130.9, 130.4, 129.2, 126.5, 123.2, 82.1, 64.1, 48.9, 45.0, 38.3, 32.4, 30.7, 29.8, 13.9; high resolution mass spectrum (ES^+) m/z 367.1519 [$(M+Na)^+$; calcd for $C_{20}H_{24}O_5Na$: 367.1521].



(–)-31l

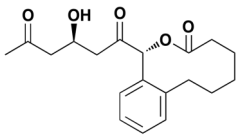
Compounds (–)-31l. $[\alpha]^{20}_{D}$ −131.3 (c 0.51 $CDCl_3$); IR (film) 3447 (m), 2925 (s), 2857 (m), 1719 (s), 1373 (m), 1242 (s), 1081 (s), 759 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.3 Hz, 1H), 7.30-7.26 (m, 1H), 7.24-7.21 (m, 2H), 6.04 (s, 1H), 5.51-5.44 (m, 1H), 5.40 (td, *J* = 10.7 and 6.1 Hz, 1H), 4.47-4.41 (m, 1H), 4.10 (t, *J* = 11.9 Hz, 1H), 3.28 (d, *J* = 4.0 Hz, 1H), 3.04-2.97 (m, 1H), 2.90-2.86 (m, 1H), 2.82 (dd, *J* = 17.4 and 5.4 Hz, 1H), 2.71 (dd, *J* = 17.4 and 6.8 Hz, 1H), 2.67-2.58 (m, 2H), 2.55-2.43 (m, 1H), 2.14 (s, 3H), 1.99-1.95 (m, 1H), 1.33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.4, 203.2, 173.4, 139.8, 132.5, 132.4, 131.0, 130.4, 129.3, 126.5, 125.4, 82.0, 63.9, 48.8, 44.7, 40.5, 32.7, 31.8, 30.7, 17.9; high resolution mass spectrum (ES^+) m/z 345.1718 [$(M+H)^+$; calcd for $C_{20}H_{25}O_5$: 345.1702].

General procedure for catalytic hydrogenation reactions (**31m-31x**): To a solution of **31a** (12.2 mg, 0.037 mmol, 1.0 equiv.) in EtOH (1.85 mL) was added PtO_2 (0.34 mg, 0.001 mmol, 0.04 equiv.). After being stirred under an atmosphere of hydorgen for 1 h at room temperature, the reaction mixture was filtered through celite and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/1) afforded **31m** (11.8 mg, 0.035 mmol, 96%) as a pale yellow oil. R_f 0.1 (hexane/ethyl acetate = 2/1).



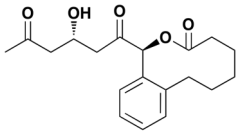
(+)-31m

Compounds (+)-31m. 96% yield. $[\alpha]^{20}_{D}$ +30.0 (c 0.69 $CDCl_3$); IR (film) 3448 (m), 2920 (s), 2864 (m), 1721 (s), 1328 (m), 1238 (s), 1052 (s), 758 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.26 (m, 2H), 7.22-7.17 (m, 2H), 6.16 (s, 1H), 4.46-4.42 (m, 1H), 3.06-3.01 (m, 1H), 2.76 (dd, *J* = 17.4 and 5.1 Hz, 1H), 2.68-2.58 (m, 4H), 2.57-2.51 (m, 1H), 2.44-2.39 (m, 1H), 2.25-2.18 (m, 1H), 2.14 (s, 3H), 2.07-2.00 (m, 1H), 1.77-1.69 (m, 2H), 1.63-1.50 (m, 2H), 0.76-0.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.9, 171.6, 141.7, 132.5, 131.4, 130.9, 129.3, 126.2, 81.8, 63.8, 48.9, 44.9, 35.1, 30.9, 30.7, 28.6, 24.1, 21.8; high resolution mass spectrum (ES^+) m/z 355.1519 [$(M+Na)^+$; calcd for $C_{19}H_{24}O_5Na$: 355.1521].



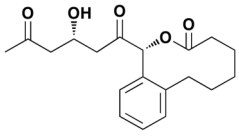
(–)-31n

Compounds (–)-31n. 97% yield. $[\alpha]^{20}_{D}$ –42.5 (c 0.63 $CDCl_3$); IR (film) 3420 (m), 2920 (s), 2853 (m), 1721 (s), 1363 (m), 1239 (s), 1053 (s), 755 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.4 Hz, 1H), 7.30-7.26 (m, 1H), 7.22-7.17 (m, 2H), 6.16 (s, 1H), 4.47-4.42 (m, 1H), 3.08-3.01 (m, 1H), 2.80 (dd, *J* = 17.3 and 7.6 Hz, 1H), 2.68-2.60 (m, 2H), 2.59-2.48 (m, 3H), 2.43-2.38 (m, 1H), 2.25-2.18 (m, 1H), 2.12 (s, 3H), 2.08-2.00 (m, 1H), 1.78-1.69 (m, 2H), 1.63-1.48 (m, 2H), 0.74-0.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.7, 171.6, 141.7, 132.5, 131.4, 131.0, 129.2, 126.2, 82.0, 64.0, 48.9, 45.0, 35.1, 30.9, 30.7, 28.6, 24.0, 21.8; high resolution mass spectrum (ES^+) m/z 355.1522 [$(M+Na)^+$; calcd for $C_{19}H_{24}O_5Na$: 355.1521].



(+)-31o

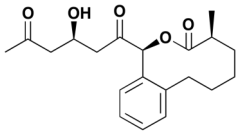
Compounds (+)-31o. 96% yield. $[\alpha]^{20}_{D}$ +99.1 (c 0.60 $CDCl_3$); IR (film) 3420 (m), 2920 (s), 2853 (m), 1721 (s), 1363 (m), 1239 (s), 1053 (s), 755 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.4 Hz, 1H), 7.30-7.26 (m, 1H), 7.22-7.17 (m, 2H), 6.16 (s, 1H), 4.47-4.42 (m, 1H), 3.08-3.01 (m, 1H), 2.80 (dd, *J* = 17.3 and 7.6 Hz, 1H), 2.68-2.60 (m, 2H), 2.59-2.48 (m, 3H), 2.43-2.38 (m, 1H), 2.25-2.18 (m, 1H), 2.12 (s, 3H), 2.08-2.00 (m, 1H), 1.78-1.69 (m, 2H), 1.63-1.48 (m, 2H), 0.74-0.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.7, 171.6, 141.7, 132.5, 131.4, 131.0, 129.2, 126.2, 82.0, 64.0, 48.9, 45.0, 35.1, 30.9, 30.7, 28.6, 24.0, 21.8; high resolution mass spectrum (ES^+) m/z 355.1522 [$(M+Na)^+$; calcd for $C_{19}H_{24}O_5Na$: 355.1521].



(–)-31p

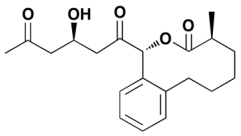
Compounds (–)-31p. 95% yield. $[\alpha]^{20}_{D}$ –83.3 (c 1.30 $CDCl_3$); IR (film) 3448 (m), 2920 (s), 2864 (m), 1721 (s), 1328 (m), 1238 (s), 1052 (s), 758 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.26 (m, 2H), 7.22-7.17 (m, 2H), 6.16 (s, 1H), 4.46-4.42 (m, 1H), 3.06-

3.01 (m, 1H), 2.76 (dd, *J* = 17.4 and 5.1 Hz, 1H), 2.68-2.58 (m, 4H), 2.57-2.51 (m, 1H), 2.44-2.39 (m, 1H), 2.25-2.18 (m, 1H), 2.14 (s, 3H), 2.07-2.00 (m, 1H), 1.77-1.69 (m, 2H), 1.63-1.50 (m, 2H), 0.76-0.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.9, 171.6, 141.7, 132.5, 131.4, 130.9, 129.3, 126.2, 81.8, 63.8, 48.9, 44.9, 35.1, 30.9, 30.7, 28.6, 24.1, 21.8; high resolution mass spectrum (ES^+) m/z 355.1519 [$(M+Na)^+$; calcd for $C_{19}H_{24}O_5Na$: 355.1521].



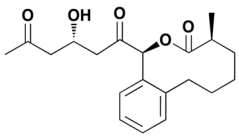
(+)-31q

Compounds (+)-31q. 96% yield. $[\alpha]^{20}_D$ +138.8 (c 1.02 $CDCl_3$); IR (film) 3478 (m), 2927 (s), 2867 (m), 1723 (s), 1366 (m), 1249 (s), 1058 (s), 760 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.6 Hz, 1H), 7.30-7.26 (m, 1H), 7.22-7.17 (m, 2H), 6.05 (s, 1H), 4.45-4.41 (m, 1H), 3.05-2.99 (m, 1H), 2.76 (dd, *J* = 14.3 and 5.3 Hz, 1H), 2.65-2.60 (m, 3H), 2.44-2.38 (m, 2H), 2.14 (s, 3H), 1.86-1.52 (m, 6H), 1.28 (d, *J* = 7.1 Hz, 3H), 0.63-0.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.9, 174.4, 141.4, 132.9, 131.4, 131.2, 129.2, 126.2, 81.7, 63.9, 48.9, 44.8, 42.1, 31.14, 31.12, 30.7, 28.4, 23.0, 18.2; high resolution mass spectrum (ES^+) m/z 369.1692 [$(M+Na)^+$; calcd for $C_{20}H_{26}O_5Na$: 369.1678].



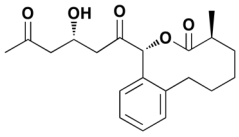
(–)-31r

Compounds (–)-31r. 97% yield. $[\alpha]^{20}_D$ −73.4 (c 0.79 $CDCl_3$); IR (film) 3456 (m), 2924 (s), 2867 (m), 1724 (s), 1362 (m), 1262 (m), 1164 (s), 1066 (m), 758 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.22-7.18 (m, 2H), 6.11 (s, 1H), 4.48-4.44 (m, 1H), 3.29 (d, *J* = 3.7 Hz, 1H), 3.01-2.96 (m, 1H), 2.87-2.82 (m, 1H), 2.79 (dd, *J* = 17.1 and 7.7 Hz, 1H), 2.59-2.49 (m, 3H), 2.43-2.39 (m, 1H), 2.19-2.15 (m, 1H), 2.13 (s, 3H), 1.72-1.48 (m, 4H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.58-0.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 204.0, 174.6, 141.5, 133.0, 131.3, 131.2, 129.3, 126.3, 82.1, 64.1, 48.9, 45.2, 38.7, 31.1, 30.7, 29.7, 28.1, 20.4, 14.4; high resolution mass spectrum (ES^-) m/z 381.1472 [$(M+Cl)^-$; calcd for $C_{20}H_{26}O_5Cl$: 381.1469].



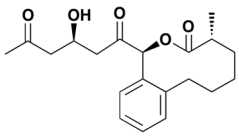
(+)-31s

Compounds (+)-31s. 95% yield. $[\alpha]^{20}_{D}$ +67.8 (c 0.87 $CDCl_3$); IR (film) 3450 (m), 2925 (s), 2856 (m), 1722 (s), 1376 (m), 1251 (s), 1162 (s), 1065 (s), 758 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.3 Hz, 1H), 7.30-7.26 (m, 1H), 7.22-7.18 (m, 2H), 6.09 (s, 1H), 4.48-4.42 (m, 1H), 3.28 (br, 1H), 3.07-3.01 (m, 1H), 2.80 (dd, *J* = 17.3 and 7.4 Hz, 1H), 2.59-2.49 (m, 3H), 2.43-2.40 (m, 2H), 2.13 (s, 3H), 1.86-1.53 (m, 5H), 1.28 (d, *J* = 7.1 Hz, 3H), 0.63-0.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.4, 203.6, 174.4, 141.5, 132.9, 131.4, 131.3, 129.2, 126.2, 81.9, 64.0, 48.9, 45.0, 42.2, 31.2, 30.7, 29.7, 28.3, 22.9, 18.2; high resolution mass spectrum (ES^-) m/z 381.1474 [$(M+Cl)^-$; calcd for $C_{20}H_{26}O_5Cl$: 381.1469].



(–)-31t

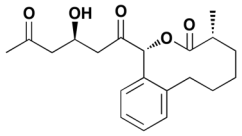
Compounds (–)-31t. 97% yield. $[\alpha]^{20}_{D}$ −57.9 (c 0.83 $CDCl_3$); IR (film) 3441 (m), 3011 (m), 2922 (m), 2858 (m), 1720 (s), 1359 (m), 1242 (s), 1066 (s), 745 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.22-7.18 (m, 2H), 6.11 (s, 1H), 4.47-4.42 (m, 1H), 3.26 (d, *J* = 3.3 Hz, 1H), 2.99-2.94 (m, 1H), 2.87-2.79 (m, 1H), 2.75 (dd, *J* = 17.4 and 5.2 Hz, 1H), 2.66-2.57 (m, 3H), 2.44-2.40 (m, 1H), 2.15 (s, 3H), 1.70-1.43 (m, 5H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.61-0.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 204.2, 174.6, 141.4, 133.0, 131.3, 131.0, 129.3, 126.3, 81.9, 63.9, 48.9, 45.1, 38.7, 31.1, 30.7, 29.8, 28.2, 20.5, 14.4; high resolution mass spectrum (ES^-) m/z 381.1472 [$(M+Cl)^-$; calcd for $C_{20}H_{26}O_5Cl$: 381.1469].



(+)-31u

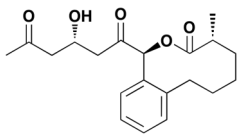
Compounds (+)-31u. 96% yield. $[\alpha]^{20}_{D}$ +82.6 (c 0.56 $CDCl_3$); IR (film) 3441 (m), 3011 (m), 2922 (m), 2858 (m), 1720 (s), 1359 (m), 1242 (s), 1066 (s), 745 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.22-7.18 (m, 2H), 6.11 (s, 1H), 4.47-4.42 (m,

1H), 3.26 (d, *J* = 3.3 Hz, 1H), 2.99-2.94 (m, 1H), 2.87-2.79 (m, 1H), 2.75 (dd, *J* = 17.4 and 5.2 Hz, 1H), 2.66-2.57 (m, 3H), 2.44-2.40 (m, 1H), 2.15 (s, 3H), 1.70-1.43 (m, 5H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.61-0.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 204.2, 174.6, 141.4, 133.0, 131.3, 131.0, 129.3, 126.3, 81.9, 63.9, 48.9, 45.1, 38.7, 31.1, 30.7, 29.8, 28.2, 20.5, 14.4; high resolution mass spectrum (ES^-) m/z 381.1472 [$(M+Cl)^-$; calcd for $C_{20}H_{26}O_5Cl$: 381.1469].



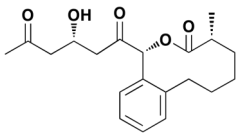
(–)-31v

Compounds (–)-31v. 96% yield. $[\alpha]^{20}_D$ −104.7 (c 0.60 $CDCl_3$); IR (film) 3441 (m), 2925 (s), 2856 (m), 1722 (s), 1367 (m), 1173 (s), 1109 (s), 757 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.3 Hz, 1H), 7.30-7.26 (m, 1H), 7.22-7.18 (m, 2H), 6.09 (s, 1H), 4.48-4.42 (m, 1H), 3.28 (br, 1H), 3.07-3.01 (m, 1H), 2.80 (dd, *J* = 17.3 and 7.4 Hz, 1H), 2.59-2.49 (m, 3H), 2.43-2.40 (m, 2H), 2.13 (s, 3H), 1.86-1.53 (m, 5H), 1.28 (d, *J* = 7.1 Hz, 3H), 0.63-0.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.4, 203.6, 174.4, 141.5, 132.9, 131.4, 131.3, 129.2, 126.2, 81.9, 64.0, 48.9, 45.0, 42.2, 31.2, 30.7, 29.7, 28.3, 22.9, 18.2; high resolution mass spectrum (ES^+) m/z 369.1691 [$(M+Na)^+$; calcd for $C_{20}H_{26}O_5Na$: 369.1678].



(+)-31w

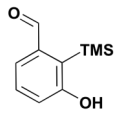
Compounds (+)-31w. 95% yield. $[\alpha]^{20}_D$ +85.1 (c 1.19 $CDCl_3$); IR (film) 3456 (m), 2924 (s), 2867 (m), 1724 (s), 1362 (m), 1262 (m), 1164 (s), 1066 (m), 758 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.22-7.18 (m, 2H), 6.11 (s, 1H), 4.48-4.44 (m, 1H), 3.29 (d, *J* = 3.7 Hz, 1H), 3.01-2.96 (m, 1H), 2.87-2.82 (m, 1H), 2.79 (dd, *J* = 17.1 and 7.7 Hz, 1H), 2.59-2.49 (m, 3H), 2.43-2.39 (m, 1H), 2.19-2.15 (m, 1H), 2.13 (s, 3H), 1.72-1.48 (m, 4H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.58-0.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 204.0, 174.6, 141.5, 133.0, 131.3, 131.2, 129.3, 126.3, 82.1, 64.1, 48.9, 45.2, 38.7, 31.1, 30.7, 29.7, 28.1, 20.4, 14.4; high resolution mass spectrum (ES^-) m/z 381.1472 [$(M+Cl)^-$; calcd for $C_{20}H_{26}O_5Cl$: 381.1469].



(–)-31x

Compounds (–)-31x. 97 % yield. $[\alpha]^{20}_{D}$ –96.8 (c 0.96 $CDCl_3$); IR (film) 3478 (m), 2927 (s), 2867 (m), 1723 (s), 1366 (m), 1249 (s), 1058 (s), 760 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.6 Hz, 1H), 7.30-7.26 (m, 1H), 7.22-7.17 (m, 2H), 6.05 (s, 1H), 4.45-4.41 (m, 1H), 3.05-2.99 (m, 1H), 2.76 (dd, *J* = 14.3 and 5.3 Hz, 1H), 2.65-2.60 (m, 3H), 2.44-2.38 (m, 2H), 2.14 (s, 3H), 1.86-1.52 (m, 6H), 1.28 (d, *J* = 7.1 Hz, 3H), 0.63-0.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ208.3, 203.9, 174.4, 141.4, 132.9, 131.4, 131.2, 129.2, 126.2, 81.7, 63.9, 48.9, 44.8, 42.1, 31.14, 31.12, 30.7, 28.4, 23.0, 18.2; high resolution mass spectrum (ES^+) m/z 369.1692 [$(M+Na)^+$; calcd for $C_{20}H_{26}O_5Na$: 369.1678].

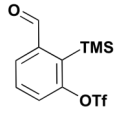
Linchpin Synthesis and Validation for the Type II ARC Protocol



34a'

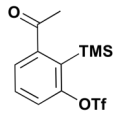
Compound 34a'. To a solution of NaH (547.2 mg, 22.8 mmol, 1.2 equiv.) in THF (85 mL) at 0 ºC was added compound **37** (5.22 g, 19.0 mmol, 1.0 equiv.) in THF (10 mL). After being stirred for 1 h at 0 ºC, *n*-BuLi (2.5 M, 9.12 mL, 22.8 mmol, 1.2 equiv.) was added. After stirring 40 min at 0 ºC, TMSCl (7.43 g, 68.4 mmol, 3 equiv.) was then added. After the addition was complete, the reaction mixture was warmed to room temperature over 2 h. After being stirred for 2 h, 95 mL of 5 % aqueous HCl was added. A saturated aqueous $NaHCO_3$ (50 mL) solution was added after 12 h, and the resulting mixture extracted with Et_2O (50 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/15) afforded **34a'** (3.03 g, 15.6 mmol, 82% yield) as a pale yellow solid. R_f 0.2 (hexane/diethyl ether = 10/1); mp: 151-154 ºC; IR (film) 3202 (s), 2961 (m), 2813 (w), 1924 (w), 1665 (s), 1583 (s), 1287 (s), 841 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.50 (dd, *J* = 7.5 and 1.0 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H),

6.96 (dd, J = 8.0 and 1.0 Hz, 1H), 5.57 (s, 1H), 0.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 161.5, 143.6, 130.7, 126.3, 123.8, 121.0, 2.4; high resolution mass spectrum (CI^+) *m/z* 179.0520 [$(M–CH_3)^+$; calcd for $C_9H_{11}O_2Si$: 179.0528].



34

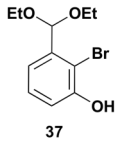
Compound 34. To a solution of the resulting alcohol **34a'** (1.29 g, 6.63 mmol, 1.0 equiv.) in CH_2Cl_2 (67 mL) at 0 ºC were added pyridine (1.57 g, 19.9 mmol, 3.0 equiv.) and Tf_2O (2.81 g, 9.94 mmol, 1.5 equiv.) dropwise. After being stirred for 20 min at room temperature, a saturated aqueous NH_4Cl (5 mL) solution and 1N HCl (5 mL) were added, and the resulting mixture extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/100) afforded **34** (1.88 g, 5.76 mmol, 87% yield) as a pale yellow solid. R_f 0.7 (hexane/ethyl acetate = 10/1); IR (film) 3086 (w), 2959 (m), 2903 (m), 2743 (w), 1959 (w), 1707 (s), 1421 (s), 1216 (s), 1145 (s), 844 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.93 (dd, J = 7.5 and 1.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.52 (dd, J = 7.5 and 1.0 Hz, 1H), 0.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 155.0, 144.4, 135.9, 131.2, 130.0, 125.7, 120.2 (q, J = 318.6 Hz, CF_3), 2.2; high resolution mass spectrum (ES^+) *m/z* 349.0160 [$(M+Na)^+$; calcd for $C_{11}H_{13}F_3O_4SSiNa$: 349.0154].



35

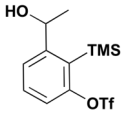
Compound 35. To a solution of **38** (485.6 mg, 1.42 mmol, 1.0 equiv.) in CH_2Cl_2 was added PCC (459.1 mg, 2.13 mmol, 1.5 equiv.). After being stirred for 6 h at room temperature, the reaction mixture was filtered through silica gel and concentrated *in vacuo*. Flash chromatography (diethyl ether/hexane = 1/20) afforded **35** (416.2 mg, 1.22 mmol, 86% yield) as a colorless oil. R_f 0.6 (hexane/ethyl acetate = 10/1); IR (film) 2995 (m), 2955 (m), 2905 (m), 1952 (w), 1696 (s), 1592 (m), 1420 (s), 1214 (s), 901 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 7.0 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 2.62 (s, 3H), 0.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 155.5,

149.6, 133.7, 130.7, 126.7, 123.0, 118.5 (q, J = 318.3 Hz, CF_3), 29.1, 1.6; high resolution mass spectrum (ES^+) *m/z* 363.0295 [$(M+Na)^+$; calcd for $C_{12}H_{15}F_3O_4SSiNa$: 363.0310].



37

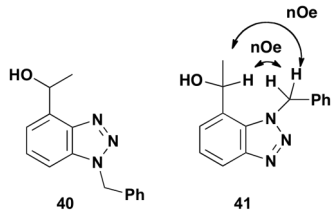
Compound 37. To a solution of 2-bromo-3-hydroxy benzaldehyde **36** (5.74 g, 28.5 mmol, 1.0 equiv.) in EtOH (47 mL) at room temperature were added TABCO (1.17 g, 2.85 mmol, 0.1 equiv.) and $(EtO)_3CH$ (21.1g, 142.5 mmol, 5.0 equiv.). After being stirred for 30 min at 40 ºC, a saturated aqueous $NaHCO_3$ (30 mL) solution was added, and the resulting mixture extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/30) on triethylamine-buffered silica gel (2.5 v/v) afforded **37** (7.22 g, 26.2 mmol, 92% yield) as a pale yellow oil. R_f 0.4 (hexane/diethyl ether = 10/1); IR (film) 3358 (m), 2977 (s), 2928 (s), 2887 (s), 1936 (w), 1462 (s), 1294 (s), 783 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20-7.18 (m, 2H), 6.98 (t, J = 5.0 Hz, 1H), 6.31 (br, 1H), 5.61 (s, 1H), 3.69-3.63 (m, 2H), 3.61-3.55 (m, 2H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 138.6, 128.3, 119.9, 116.3, 111.3, 101.5, 62.5, 15.3; high resolution mass spectrum (CI^+) *m/z* 274.0196 [$(M)^+$; calcd for $C_{11}H_{15}O_3Br$: 274.0205].



38

Compound 38. To a solution of **34** (747.7 mg, 2.29 mmol, 1.0 equiv.) in Et_2O (11.5 mL) at 0 ºC was added MeMgBr (3.0 M in diethyl ether, 0.92 mL, 2.75 mmol, 1.2 equiv.) dropwise. After stirring for 5 min at 0 ºC, a saturated aqueous NH_4Cl (10 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **38** (698.5 mg, 2.04 mmol, 89% yield) as a colorless oil. R_f 0.4 (hexane/ethyl acetate = 4/1); IR (film) 3309 (m), 2983 (m), 2955 (m), 2902 (w), 1713 (w), 1600 (m), 1415 (s), 1140 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.5 Hz, 1H), 7.26 (d, J =

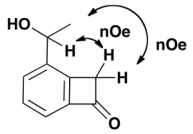
8.5 Hz, 1H), 5.25 (q, *J* = 6.5 Hz, 1H), 2.04 (br, 1H), 1.48 (d, *J* = 6.0 Hz, 3H), 0.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 154.5, 131.3, 129.7, 125.3, 119.2, 118.6 (q, *J* = 318.6 Hz, CF_3), 68.4, 25.7, 2.4; high resolution mass spectrum (ES^+) *m/z* 342.0583 [$(M)^+$; calcd for $C_{12}H_{17}F_3O_4SSi$: 342.0569].



regioisomeric ratio 3.3:1

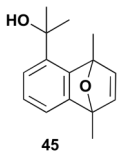
Compound 40 and 41. **Demonstration of Benzyne Reactivity**: To a solution of **38** (19.2 mg, 0.056 mmol, 1.0 equiv.) and benzyl azide (14.6 mg, 0.11 mmol, 2.0 equiv.) in THF (0.6 mL) at –78 ºC was added KHMDS (0.5 M in toluene, 0.12 mL, 0.061 mmol, 1.1 equiv.) dropwise. After being stirred for 10 min at –78 ºC, 3 mL of 1N HCl was added. After 10 min, a saturated aqueous NH_4Cl (3 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/2), and preparative thin layer chromatography (ethyl acetate/hexane = 1/2) afforded a 3.3:1 regioisomeric mixture of **40** and **41** (12.1 mg, 0.048 mmol, 85% yield) as a pale yellow oil. **Intermolecular tri-component [3+2] Benzyne Cycloaddition**: To a solution of linchpin **34** (77.4 mg, 0.24 mmol, 1.0 equiv.) in Et_2O (1.2 mL) at –78 ºC was added MeLi (1.6 M in diethyl ether, 0.18 mL, 0.29 mmol, 1.2 equiv.) dropwise. After stirring for 5 min at –78 ºC, benzyl azide (63.9 mg, 0.48 mmol, 2.0 equiv.) in THF (1.2 mL) was added. After being stirred for 2 min at –78 ºC, 3 mL of 1N HCl was added. A saturated aqueous NH_4Cl (5 mL) solution was then added after 10 min, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/2), and preparative thin layer chromatography (ethyl acetate/hexane = 1/2) afforded a 3.3:1 regioisomeric mixture of **40** and **41** (40.3 mg, 0.16 mmol, 67% yield) as a pale yellow oil. R_f 0.1 (hexane/ethyl acetate = 2/1); For major regioisomer **40**: IR (film) 3388 (s), 2970 (m), 2928 (m), 1951 (w), 1611 (m), 1496 (m), 1267 (s), 1111 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.24 (m, 8H),

5.83 (s, 2H), 5.56 (q, *J* = 6.5 Hz, 1H), 3.59 (br, 1H), 1.75 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 138.0, 134.6, 132.9, 128.9, 128.4, 127.51, 127.49, 119.4, 108.5, 67.8, 52.2, 24.3; high resolution mass spectrum (ES^+) *m/z* 254.1281 [$(M+H)^+$; calcd for $C_{15}H_{16}N_3O$: 254.1293]; For minor regioisomer **41**: IR (film) 3354 (s), 2975 (m), 2927 (m), 2902 (w), 1951 (w), 1600 (m), 1497 (m), 1248 (s), 1092 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.31-7.24 (m, 3H), 7.04 (d, *J* = 7.0 Hz, 2H), 6.26 (d, *J* = 16.5 Hz, 1H), 6.12 (d, *J* = 16.5 Hz, 1H), 5.15 (q, *J* = 6.0 Hz, 1H), 1.99 (br, 1H), 1.50 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 136.8, 131.0, 129.0, 128.7, 128.0, 126.2, 123.98, 123.96, 120.0, 65.6, 53.4, 23.3; high resolution mass spectrum (CI^+) *m/z* 254.1287 [$(M+H)^+$; calcd for $C_{15}H_{16}N_3O$: 254.1293].



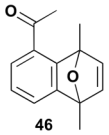
43

Compound 43. To a solution of linchpin **34** (107.1 mg, 0.33 mmol, 1.0 equiv.) and 1,1-diethoxyethylene (190.6 mg, 1.64 mmol, 5.0 equiv.) in THF (3.3 mL) at –78 ºC was added MeLi (1.6 M in diethyl ether, 0.25 mL, 0.40 mmol, 1.2 equiv.) dropwise. After being stirred for 10 min at –78 ºC, the resulting solution was warmed to 0 ºC. After 10 min at 0 ºC, 3 mL of 1N HCl was added and stirred for an additional 2 h at room temperature. A saturated aqueous NH_4Cl (5 mL) solution was then added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/5) afforded **43** (41.6 mg, 0.26 mmol, 78% yield) as a pale yellow oil. R_f 0.2 (hexane/ethyl acetate = 5/1); IR (film) 3422 (m), 2972 (m), 2925 (m), 1765 (s), 1579 (s), 1469 (m), 1281 (m), 1112 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 4.82 (q, *J* = 6.5 Hz, 1H), 4.00 (s, 2H), 2.96 (br, 1H), 1.54 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 151.0, 144.0, 142.8, 135.6, 124.8, 122.1, 68.0, 51.9, 24.6; high resolution mass spectrum (CI^+) *m/z* 145.0658 [$(M–OH)^+$; calcd for $C_{10}H_9O$: 145.0653].



45

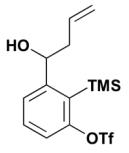
Compound 45. To a solution of linchpin **35** (71.9 mg, 0.21 mmol, 1.0 equiv.) and 2,5-dimethylfuran (100.9 mg, 1.05 mmol, 5.0 equiv.) in THF (2.1 mL) at –78 ºC was added MeLi (1.6 M in diethyl ether, 0.16 mL, 0.25 mmol, 1.2 equiv.) dropwise. After being stirred for 10 min at –78 ºC, TBAF (1.0 M in THF, 0.63 mL, 0.63 mmol, 3.0 equiv.) was added, and the reaction mixture was stirred for 30 min at room temperature. A saturated aqueous NH_4Cl (3 mL) solution was then added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **45** (38.0 mg, 0.164 mmol, 78% yield) as a white solid. R_f 0.3 (hexane/ethyl acetate = 5/1); mp: 160-163 ºC; IR (film) 3420 (s), 2978 (m), 2933 (m), 1452 (m), 1376 (m), 1132 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (dd, J = 5.0 and 2.5 Hz, 1H), 6.94-6.90 (m, 2H), 6.83 (d, J = 5.5 Hz, 1H), 6.71 (d, J = 5.0 Hz, 1H), 2.20 (s, 3H), 1.88 (s, 3H), 1.70 (s, 3H), 1.65 (br, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 150.3, 147.3, 147.0, 143.0, 124.5, 122.1, 117.1, 92.2, 86.8, 73.2, 32.3, 32.2, 20.3, 15.2; high resolution mass spectrum (ES^-) *m/z* 229.1223 [$(M–H)^-$; calcd for $C_{15}H_{17}O_2$: 229.1229].



46

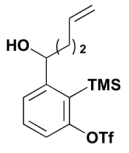
Compound 46. To a solution of **35** (71.4 mg, 0.21 mmol, 1.0 equiv.) and 2,5-dimethylfuran (100.8 mg, 1.05 mmol, 5.0 equiv.) in THF (0.6 mL) at –78 ºC was added KHMDS (0.5 M in toluene, 0.46 mL, 0.23 mmol, 1.1 equiv.) dropwise. After being stirred for 10 min at –78 ºC, TBAF (1.0 M in THF, 0.63 mL, 0.63 mmol, 3.0 equiv.) was added. After 5 min, a saturated aqueous NH_4Cl (3 mL) solution was then added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/6) afforded **46** (23.4 mg, 0.11 mmol, 52% yield) as a pale yellow solid. R_f 0.4 (hexane/ethyl acetate = 5/1); mp: 82-85 ºC; IR (film)

3072 (w), 2976 (m), 2933 (m), 2870 (w), 1689 (s), 1586 (w), 1416 (m), 1381 (s), 1259 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 6.5 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 5.0 Hz, 1H), 6.75 (d, *J* = 5.0 Hz, 1H), 2.57 (s, 3H), 1.89 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 154.6, 153.1, 147.0, 146.6, 133.5, 124.8, 123.8, 120.6, 90.9, 87.3, 28.6, 17.0, 15.2; high resolution mass spectrum (CI^+) *m/z* 215.1075 [$(M+H)^+$; calcd for $C_{14}H_{15}O_2$: 215.1072].



47a

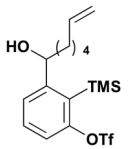
Compound 47a. To a solution of **34** (219.0 mg, 0.67 mmol, 1.0 equiv.) in Et_2O (3.4 mL) at 0 ºC was added allylmagnesium bromide (1.0 M in diethyl ether, 0.80 mL, 0.80 mmol, 1.2 equiv.) dropwise. After stirring for 5 min at 0 ºC, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **47a** (228.4 mg, 0.62 mmol, 92% yield) as a colorless oil. R_f 0.4 (hexane/ethyl acetate = 5/1); IR (film) 3414 (m), 2954 (m), 2906 (m), 1952 (w), 1642 (m), 1599 (m), 1556 (m), 1418 (s), 1211 (s), 1146 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 5.88-8.80 (m, 1H), 5.32-5.19 (m, 2H), 5.09-5.06 (m, 1H), 2.47-2.39 (m, 2H), 2.12 (br, 1H), 0.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 153.0, 134.0, 131.1, 130.0, 125.7, 119.3, 119.0, 118.6 (q, *J* = 318.8 Hz, CF_3), 71.1, 44.4, 2.5; high resolution mass spectrum (ES^+) *m/z* 391.0630 [$(M+Na)^+$; calcd for $C_{14}H_{19}F_3O_4SSiNa$: 391.0630].



47b

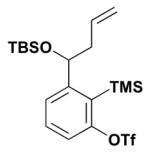
Compound 47b. To a solution of **34** (305.0 mg, 0.93 mmol, 1.0 equiv.) in Et_2O (4.7 mL) at 0 ºC was added 3-butenylmagnesium bromide (0.35 M in diethyl ether, 3.98 mL, 1.39 mmol, 1.5 equiv.) dropwise. After stirring for 5 min at 0 ºC, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3).

The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **47b** (284.8 mg, 0.75 mmol, 80% yield) as a pale yellow oil. R_f 0.4 (hexane/ethyl acetate = 5/1); IR (film) 3406 (m), 3079 (m), 2952 (s), 2853 (m), 1950 (w), 1641 (m), 1599 (m), 1555 (m), 1418 (s), 1252 (s), 1146 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 5.90-5.82 (m, 1H), 5.11-5.02 (m, 3H), 2.37-2.30 (m, 1H), 2.20-2.13 (m, 1H), 2.06 (br, 1H), 1.92-1.84 (m, 1H), 1.75-1.69 (m, 1H), 0.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.9, 137.8, 131.2, 130.1, 125.8, 119.3, 118.5 (q, J = 318.6 Hz, CF_3), 115.4, 71.7, 38.6, 30.4, 2.4; high resolution mass spectrum (ES^+) *m/z* 405.0779 [$(M+Na)^+$; calcd for $C_{15}H_{21}F_3O_4SSiNa$: 405.0780].



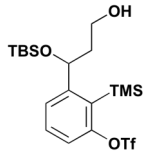
47c

Compound 47c. To a solution of **34** (261.0 mg, 0.80 mmol, 1.0 equiv.) in Et_2O (4.0 mL) at 0 ºC was added 5-hexenylmagnesium bromide (0.58 M in diethyl ether, 2.07 mL, 1.20 mmol, 1.5 equiv.) dropwise. After stirring for 5 min at 0 ºC, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **47c** (257.3 mg, 0.63 mmol, 78% yield) as a pale yellow oil. R_f 0.3 (hexane/ethyl acetate = 5/1); IR (film) 3395 (m), 2935 (s), 2859 (m), 1950 (w), 1641 (w), 1599 (m), 1555 (w), 1419 (s), 1210 (s), 920 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 5.84-5.76 (m, 1H), 5.02-4.94 (m, 3H), 2.09-2.03 (m, 3H), 1.80-1.71 (m, 1H), 1.68-1.56 (m, 2H), 1.46-1.41 (m, 2H), 1.37-1.26 (m, 1H), 0.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 154.2, 138.6, 131.1, 130.0, 125.6, 119.2, 118.6 (q, J = 318.6 Hz, CF_3), 114.5, 72.4, 33.7, 39.6, 28.8, 25.7, 2.4; high resolution mass spectrum (ES^-) *m/z* 409.1117 [$(M–H)^-$; calcd for $C_{17}H_{24}F_3O_4SSi$: 409.1117].



48a'

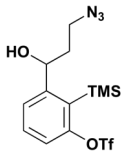
Compound 48a'. To a solution of **47a** (228.4 mg, 0.62 mmol, 1.0 equiv.) in CH_2Cl_2 (3.1 mL) at –78 ºC was added TBDMSOTf (327.8 mg, 1.24 mmol, 2.0 equiv.) dropwise. After being stirred for 20 min at room temperature, a saturated aqueous $CuSO_4$ (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/200) afforded **48a'** (284.8 mg, 0.59 mmol, 95% yield) as a pale yellow oil. R_f 0.9 (hexane/ethyl acetate = 5/1); IR (film) 3078 (m), 2955 (s), 2932 (s), 2859 (s), 1950 (w), 1642 (m), 1599 (m), 1555 (m), 1421 (s), 1253 (s), 1145 (s), 924 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 5.89-5.80 (m, 1H), 5.11-5.04 (m, 3H), 2.32 (t, *J* = 6.5 Hz, 2H), 0.9 (s, 9H), 0.5 (s, 9H), 0.1 (s, 3H), –0.1 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 154.9, 134.6, 130.7, 127.7, 125.7, 118.5 (q, *J* = 318.5 Hz, CF_3), 117.7, 117.5, 71.2, 46.5, 25.8, 18.2, 2.6, –4.5, –4.6; high resolution mass spectrum (ESI^+) *m/z* 505.1484 [$(M+Na)^+$; calcd for $C_{20}H_{33}F_3O_4SSi_2Na$: 505.1488].



48a

Compound 48a. To a solution of **48a'** (219.5 mg, 0.46 mmol, 1.0 equiv.) in CH_2Cl_2:MeOH (22.7 mL, 5:1 v/v) at –78 ºC was bubbled ozone. After being stirred for 10 min, oxygen was bubbled through the resulting solution for 20 min until the bule color disappeared. To the resulting solution was added $NaBH_4$ (34.0 mg, 0.90 mmol, 2.0 equiv.) portionwise at –78 ºC. After being stirred for 1 h at room temperature, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **48a** (164.5 mg, 0.34 mmol, 74% yield) as a pale yellow oil. R_f 0.4 (hexane/ethyl acetate = 5/1); IR (film) 3418 (m), 2955 (s), 2893 (s), 2859 (s), 1687 (w),

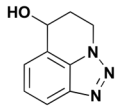
1599 (m), 1555 (m), 1420 (s), 1253 (s), 1144 (s), 933 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 5.32 (dd, *J* = 8.5 and 3.0 Hz, 1H), 3.83-3.74 (m, 2H), 2.49 (br, 1H), 1.96-1.90 (m, 1H), 1.81-1.74 (m, 1H), 0.9 (s, 9H), 0.5 (s, 9H), 0.1 (s, 3H), –0.2 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 154.5, 130.8, 127.7, 125.7, 118.5 (q, *J* = 318.2 Hz, CF_3), 117.9, 71.7, 60.0, 43.2, 25.7, 18.0, 2.5, –4.6, –4.9; high resolution mass spectrum (ESI^+) *m/z* 509.1418 [$(M+Na)^+$; calcd for $C_{19}H_{33}F_3O_5SSi_2Na$: 509.1437].



49a

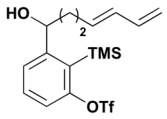
Compound 49a. To a solution of **48a** (160.0 mg, 0.33 mmol, 1.0 equiv.) in CH_2Cl_2 (6.6 mL) at 0 ºC were added triethylamine (100.2 mg, 0.99 mmol, 3.0 equiv.) and methane sulfonyl chloride (75.6 mL, 0.66 mmol, 2.0 equiv.) dropwise. After being stirred for 30 min at 0 ºC, a saturated aqueous $NaHCO_3$ (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of the crude product in DMF (6.6 mL) were added sodium azide (128.7, 1.98 mmol, 6.0 equiv.) and 15-crown-5 (cat.). After stirring for 12 h at 70 ºC, a saturated aqueous $NaHCO_3$ (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of the resulting azide was added 3.2 mL of 3% HCl in MeOH. After 12 h at room temperature, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **49a** (75.0 mg, 0.19 mmol, 57% yield over 3 steps) as a pale yellow oil. R_f 0.3 (hexane/ethyl acetate = 5/1); IR (film) 3436 (w), 2956 (m), 2101 (s), 1599 (m), 1556 (w), 1417 (s), 1214 (s), 1143 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 5.19 (dd, *J* = 10.0 and 3.0 Hz, 1H), 3.66-3.60 (m, 1H), 3.55-3.50 (m, 1H), 2.13 (br, 1H), 2.02-1.94 (m, 1H), 1.89-1.82 (m, 1H), 0.48 (s, 9H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 154.6, 153.1, 131.3, 130.3, 125.8, 119.7, 118.6 (q, J = 318.7 Hz, CF_3), 69.6, 48.6, 38.2, 2.4; high resolution mass spectrum (ESI^+) *m/z* 398.0826 [$(M+H)^+$; calcd for $C_{13}H_{19}F_3N_3O_4SSi$: 398.0818].



50a

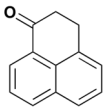
Compound 50a. To a solution of **49a** (53.4 mg, 0.13 mmol, 1.0 equiv.) in THF (26.9 mL) at –78 ºC was added KHMDS (0.5 M in toluene, 0.29 mL, 0.14 mmol, 1.1 equiv.) dropwise. After the addition was complete, the reaction mixture was then warmed to room temperature over 2 h. The resulting solution was concentrated *in vacuo* before 5 mL of 1N HCl was added. After 10 min, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate) afforded **50a** (17.9 mg, 0.10 mmol, 76% yield) as a pale yellow oil. R_f 0.1 (ethyl acetate); IR (film) 3357 (s), 2926 (m), 2854 (m), 1657 (w), 1638 (w), 1516 (w), 1469 (m), 1085 (s), 955 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.0 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 5.25 (br, 1H), 4.80-4.70 (m, 2H), 3.11 (br, 1H), 2.54-2.49 (m, 1H), 2.39-2.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 131.3, 124.9, 124.3, 122.9, 118.7, 63.6, 42.0, 31.9; high resolution mass spectrum (CI^+) *m/z* 176.0830 [$(M+H)^+$; calcd for $C_9H_{10}N_3O$: 176.0824].



51

Compound 51. To a solution of **34** (413.7 mg, 1.26 mmol, 1.0 equiv.) in Et_2O (6.3 mL) at 0 ºC was added (*E*)-hexadienylmagnesium bromide (0.25 M in diethyl ether, 7.56 mL, 1.89 mmol, 1.5 equiv.) dropwise. After stirring for 5 min at 0 ºC, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/20) afforded **51** (392.7 mg, 0.96 mmol, 76% yield) as a pale yellow oil. R_f 0.4 (hexane/ethyl acetate = 5/1); IR (film) 3399 (m), 3087 (w), 2952 (m), 2845 (w), 1653 (w), 1600 (m), 1417 (s),

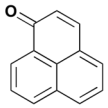
1213 (s), 842 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.34-6.28 (m, 1H), 6.15-6.10 (m, 1H), 5.75-5.71 (m, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 5.05-5.00 (m, 2H), 2.40-2.35 (m, 1H), 2.23-2.19 (m, 1H), 2.00 (br, 1H), 1.91-1.87 (m, 1H), 1.75-1.69 (m, 1H), 0.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.8, 136.9, 133.6, 132.0, 131.2, 130.1, 125.8, 119.3, 118.5 (q, *J* = 318.5 Hz, CF_3), 115.5, 71.6, 38.7, 29.1, 2.4; high resolution mass spectrum (ESI^+) *m/z* 431.0926 [$(M+Na)^+$; calcd for $C_{17}H_{23}F_3O_4SSiNa$: 431.0936].



52

Compound 52. To a solution of **51** (66.4 mg, 0.16 mmol, 1.0 equiv.) in THF (32.5 mL) at –78 ºC was added KHMDS (0.5 M in toluene, 0.36 mL, 0.18 mmol, 1.1 equiv.) dropwise. After the addition was complete, the reaction mixture was then warmed to room temperature over 2 h. The resulting solution was concentrated *in vacuo* before THF (5 mL) and TBAF (1.0 M in THF, 0.48 mL, 0.48 mmol, 3.0 equiv.) were added. After 30 min, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of cycloadduct in CH_2Cl_2 (2.3 mL) was added PCC (103.5 mg, 0.48 mmol, 3.0 equiv.). After being stirred for 1 h at room temperature, the reaction mixture was filtered through silica gel and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **52** (21.0 mg, 0.114 mmol, 71% yield over 2 steps) as a pale yellow solid. R_f 0.5 (hexane/ethyl acetate = 5/1); mp 80-83 ºC; IR (film) 3059 (m), 2927 (m), 2851 (m), 1681 (s), 1619 (m), 1588 (m), 1342 (s), 926 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.0 and 1.0 Hz, 1H), 8.09 (dd, *J* = 8.0 and 1.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.51-7.45 (m, 2H), 3.44 (t, *J* = 7.0 Hz, 2H), 2.98 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 134.0, 133.4, 133.2, 131.6, 129.8, 128.5, 126.2, 125.7, 125.5, 125.0, 38.5, 28.5; high resolution mass spectrum (CI^+) *m/z* 182.0730 [$(M)^+$; calcd for $C_{13}H_{10}O$: 182.0732]. **Alternative**: To a solution of **51** (66.7 mg, 0.17 mmol, 1.0 equiv.) in Et_2O (1.6 mL) at –78 ºC was added MeLi (1.6 M in diethyl ether, 0.12 mL, 0.19 mmol, 1.1 equiv.) dropwise. After being stirred for 5 min, Et_2O (31.0 mL) was

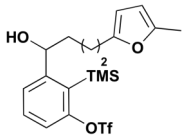
added. To the resulting solution, KO*t*-Bu (1.0 M in THF, 0.19 mL, 0.19 mmol, 1.1 equiv.) was then added at –78 ºC. After the addition was complete, the reaction mixture was then warmed to room temperature over 2 h. The resulting solution was concentrated *in vacuo* before THF (5 mL) and TBAF (1.0 M in THF, 0.48 mL, 0.48 mmol, 3.0 equiv.) were added. After 30 min, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of cycloadduct in CH_2Cl_2 (2.3 mL) was added PCC (109.9 mg, 0.51 mmol, 3.0 equiv.). After being stirred for 1 h at room temperature, the reaction mixture was filtered through silica gel and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **52** (23.2 mg, 0.127 mmol, 75% yield over 2 steps) as a pale yellow solid.



53

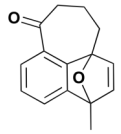
Compound 53. To a solution of **51** (89.6 mg, 0.22 mmol, 1.0 equiv.) in THF (43.9 mL) at –78 ºC was added KHMDS (0.5 M in toluene, 0.48 mL, 0.24 mmol, 1.1 equiv.) dropwise. After the addition was complete, the reaction mixture was then warmed to room temperature over 2 h. The resulting solution was concentrated *in vacuo* before THF (5 mL) and TBAF (1.0 M in THF, 0.66 mL, 0.66 mmol, 3.0 equiv.) were added. After 30 min, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of cycloadduct in Et_2O (2.5 mL) was added MnO_2 (382.5 mg, 4.4 mmol, 20.0 equiv.). After being stirred for 12 h at room temperature, the reaction mixture was filtered through silica gel and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/10) afforded **53** (22.9 mg, 0.127 mmol, 58% yield over 2 steps) as a pale yellow solid. R_f 0.5 (hexane/ethyl acetate = 5/1); mp 150-153 ºC; IR (film) 3041 (m), 2926 (m), 2855 (m), 1640 (s), 1581 (s), 1393 (m), 1358 (m), 1557 (m), 1238 (m), 831 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 7.5 Hz, 1H), 8.20 (dd, *J* = 8.0 and 1.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.80-7.74 (m, 3H), 7.59 (dd, *J* = 8.5 and 7.0 Hz, 1H), 6.73 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 141.7, 134.9, 132.2, 131.9, 131.3, 130.4,

129.5, 129.3, 127.9, 127.6, 127.1, 126.6; high resolution mass spectrum (CI^+) *m/z* 181.0651 [$(M+H)^+$; calcd for $C_{13}H_9O$: 181.0653].



54

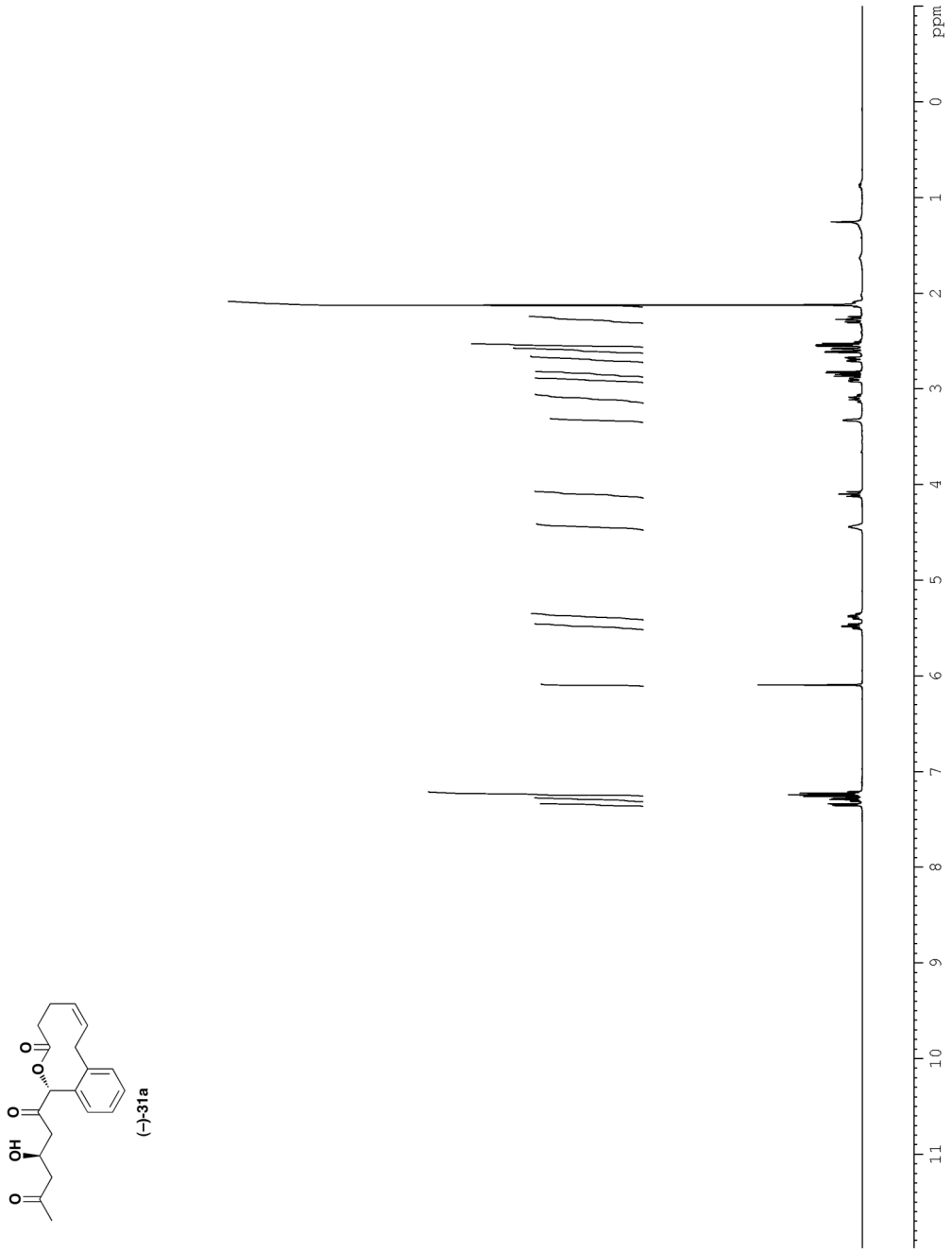
Compound 54. To a solution of **34** (231.2 mg, 0.71 mmol, 1.0 equiv.) in Et_2O (3.5 mL) at 0 ºC was added (3-(5-methylfuran-2-yl)propyl)magnesium bromide (0.7 M in diethyl ether, 1.52 mL, 1.06 mmol, 1.5 equiv.) dropwise. After stirring for 5 min at 0 ºC, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/20) afforded **54** (262.8 mg, 0.58 mmol, 82% yield) as a pale yellow oil. R_f 0.4 (hexane/ethyl acetate = 5/1); IR (film) 3411 (m), 3104 (w), 2951 (s), 2867 (m), 1642 (w), 1600 (m), 1570 (m), 1557 (m), 1418 (s), 1248 (s), 1141 (s), 844 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 5.86-5.84 (m, 2H), 5.03 (dd, *J* = 8.5 and 3.5 Hz, 1H), 2.68-2.57 (m, 2H), 2.25 (s, 3H), 1.98-1.90 (m, 2H), 1.83-1.71 (m, 1H), 1.69-1.64 (m, 2H), 0.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 154.1, 153.6, 150.3, 131.2, 129.9, 125.6, 119.2, 118.6 (q, *J* = 319.1 Hz, CF_3), 105.8, 105.7, 72.3, 39.1, 27.8, 24.8, 13.4, 2.4; high resolution mass spectrum (ESI^+) *m/z* 473.1046 [$(M+Na)^+$; calcd for $C_{19}H_{25}F_3O_5SSiNa$: 473.1042].



55

Compound 55. **Intramolecular [4+2] Benzyne Cycloaddition:** To a solution of **54** (51.0 mg, 0.11 mmol, 1.0 equiv.) in THF (22.6 mL) at –78 ºC was added KHMDS (0.5 M in toluene, 0.24 mL, 0.12 mmol, 1.1 equiv.) dropwise. After the addition was complete, the reaction mixture was then warmed to room temperature over 2 h. The resulting solution was concentrated *in vacuo* before THF (5 mL) and TBAF (1.0 M in THF, 0.33 mL, 0.33 mmol, 3.0 equiv.) were added. After 30 min, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and

concentrated *in vacuo*. To a solution of cycloadduct in CH_2Cl_2 (1.6 mL) was added PCC (36.6 mg, 0.17 mmol, 1.5 equiv.). After being stirred for 1 h at room temperature, the reaction mixture was filtered through silica gel and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/5) afforded **55** (21.0 mg, 0.09 mmol, 82% yield over 2 steps) as a pale yellow oil. R_f 0.4 (hexane/ethyl acetate = 2/1); **One-Pot Intramolecular [4+2] Benzyne Cycloaddition**: To a solution of iodide **56** (125.0 mg, 0.50 mmol, 2.0 equiv.) in Et_2O (0.6 mL) at –78 ºC was added *t*-BuLi (1.7 M in pentane, 0.65 mL, 1.1 mmol, 4.4 equiv.) dropwise. After being stirred for 30 min at –78 ºC, the resulting solution was warmed to room temperature. After 5 min at room temperature, the resulting solution was added to a solution of linchpin **34** (81.4 mg, 0.25 mmol, 1.0 equiv.) in Et_2O (1.4 mL) at –78 ºC. After being stirred for 10 min at –78 ºC, Et_2O (47.9 mL) was added. To the resulting solution, KO*t*-Bu (1.0 M in THF, 0.50 mL, 0.50 mmol, 2.0 equiv.) was then added at –78 ºC. After the addition was complete, the reaction mixture was then warmed to room temperature over 2 h. The resulting solution was concentrated *in vacuo* before THF (5 mL) and TBAF (1.0 M in THF, 0.75 mL, 0.75 mmol, 3.0 equiv.) were added. After 30 min, a saturated aqueous NH_4Cl (5 mL) solution was added, and the resulting mixture extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of cycloadduct in CH_2Cl_2 (3.6 mL) was added PCC (81.9 mg, 0.38 mmol, 1.5 equiv.). After being stirred for 1 h at room temperature, the reaction mixture was filtered through silica gel and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane = 1/5) afforded **55** (18.9 mg, 0.08 mmol, 33% yield over 2 steps) as a pale yellow oil. R_f 0.4 (hexane/ethyl acetate = 2/1); IR (film) 3069 (w), 2933 (s), 2866 (m), 1672 (s), 1605 (m), 1450 (m), 1417 (m), 1294 (s), 1227 (m), 1134 (m), 982 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.91 (d, J = 5.5 Hz, 1H), 6.81 (d, J = 5.5 Hz, 1H), 3.02-2.97 (m, 1H), 2.90-2.85 (m, 1H), 2.63-2.59 (m, 1H), 2.36 (app t, J = 12.5 Hz, 1H), 2.27-2.20 (m, 1H), 2.08-2.01 (m, 1H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 153.4, 151.5, 147.3, 145.6, 130.9, 125.5, 124.4, 122.0, 92.8, 88.5, 46.1, 32.3, 20.6, 15.1; high resolution mass spectrum (CI^+) *m/z* 227.1065 [$(M+H)^+$; calcd for $C_{15}H_{14}F_3O_2$: 227.1072].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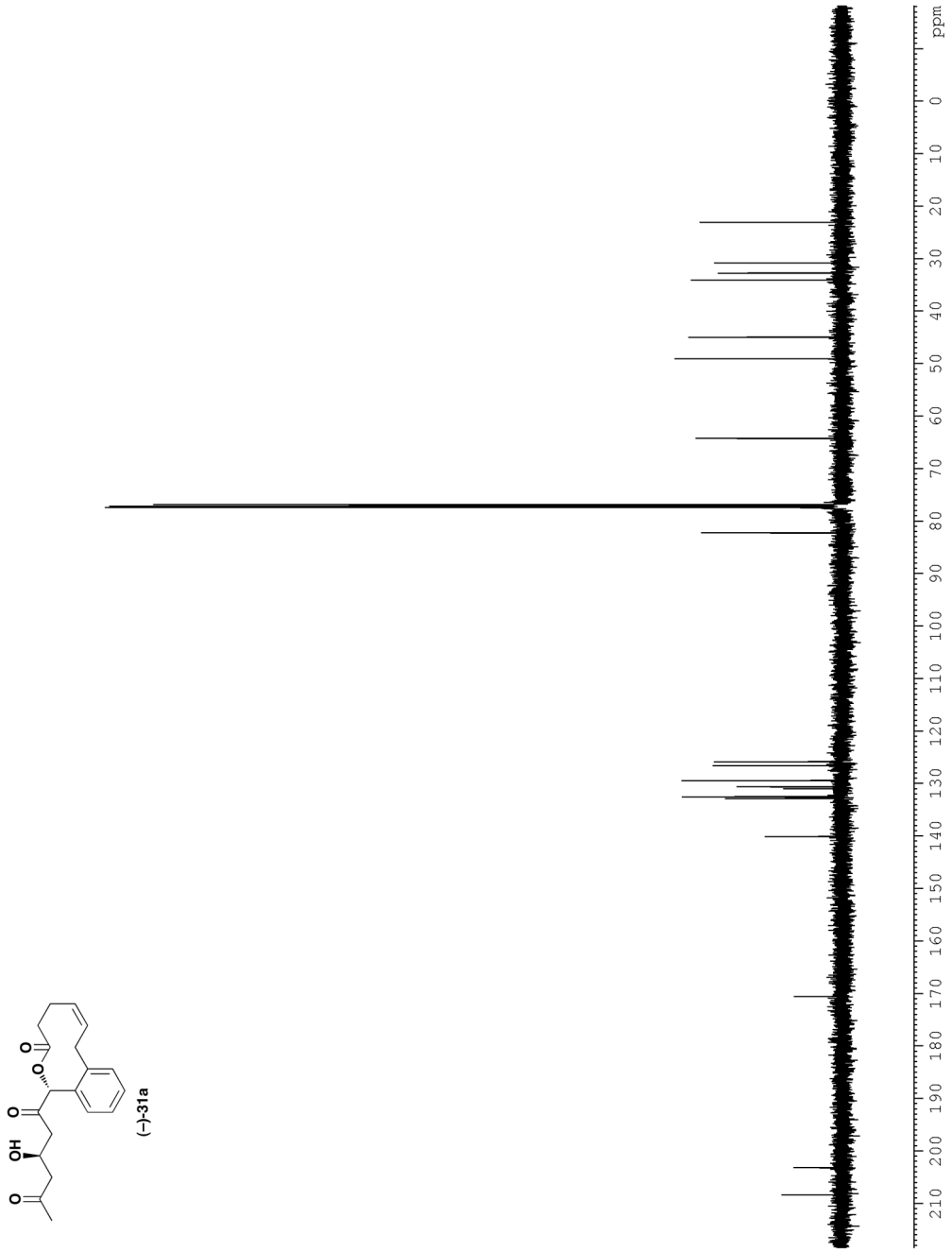
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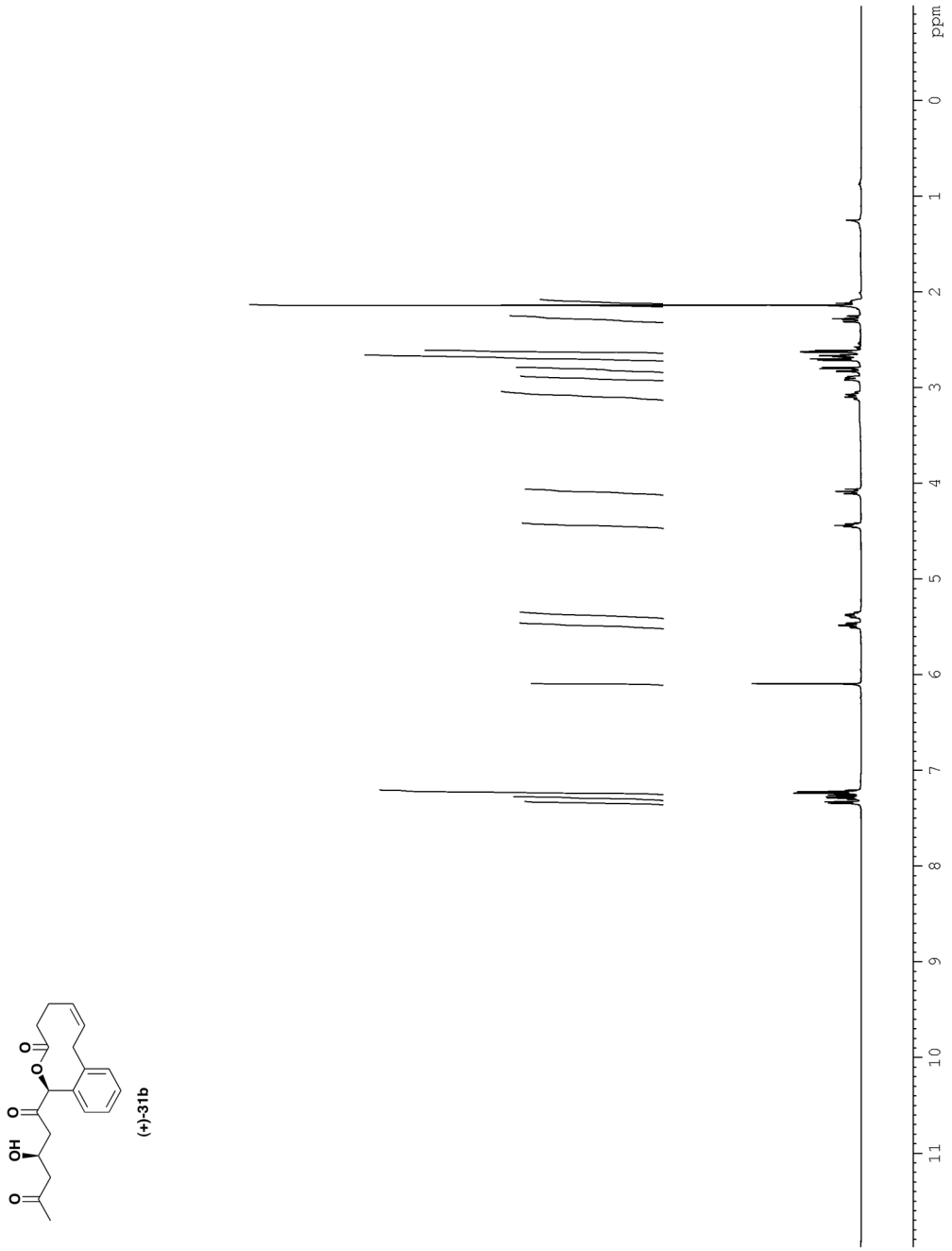
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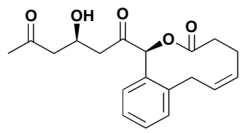
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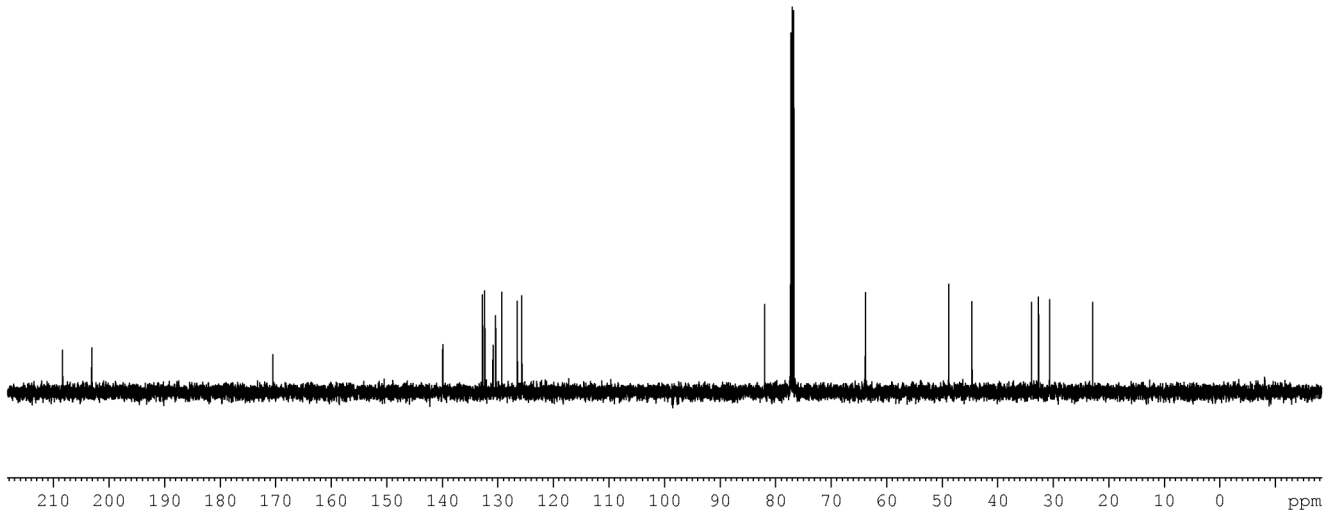
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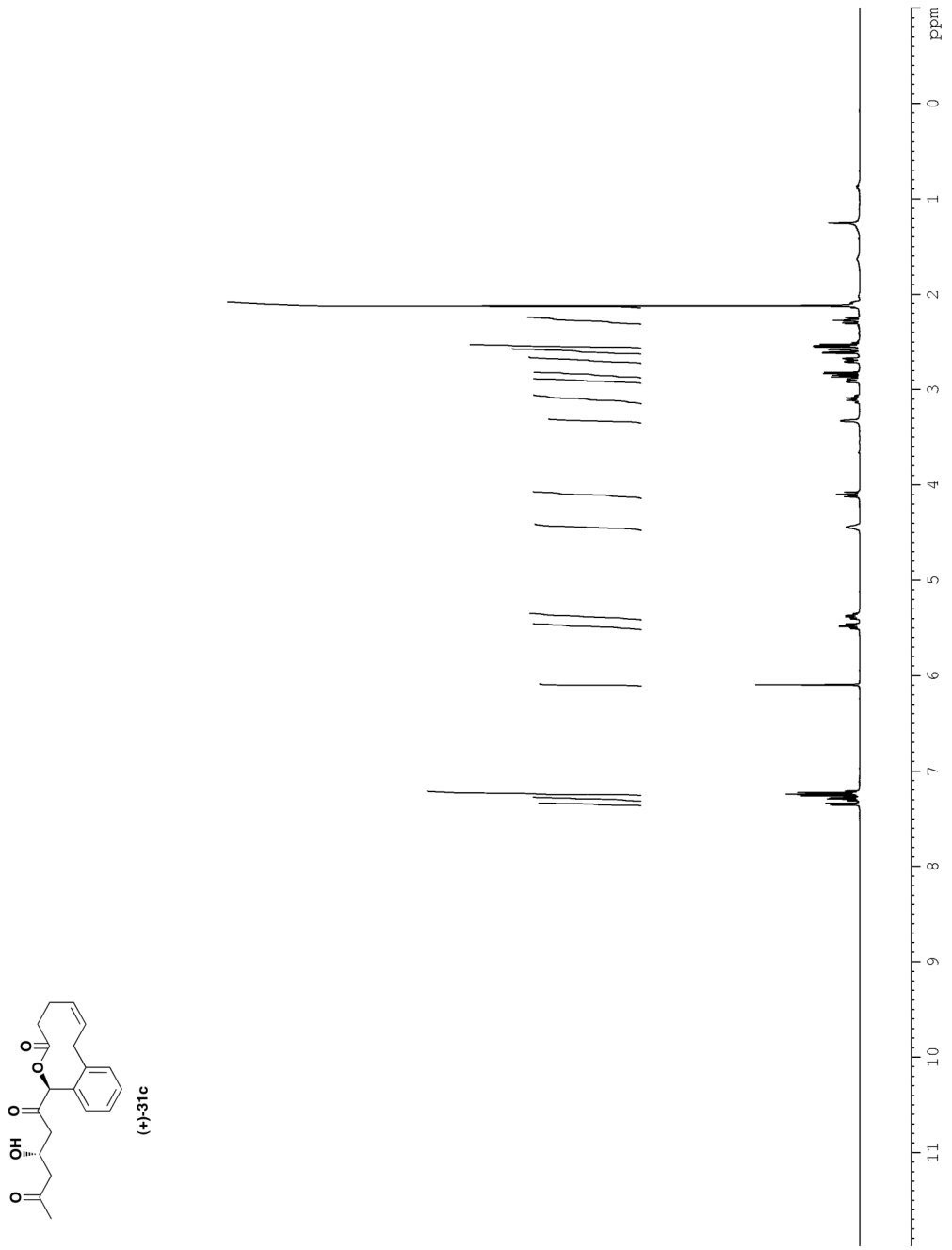
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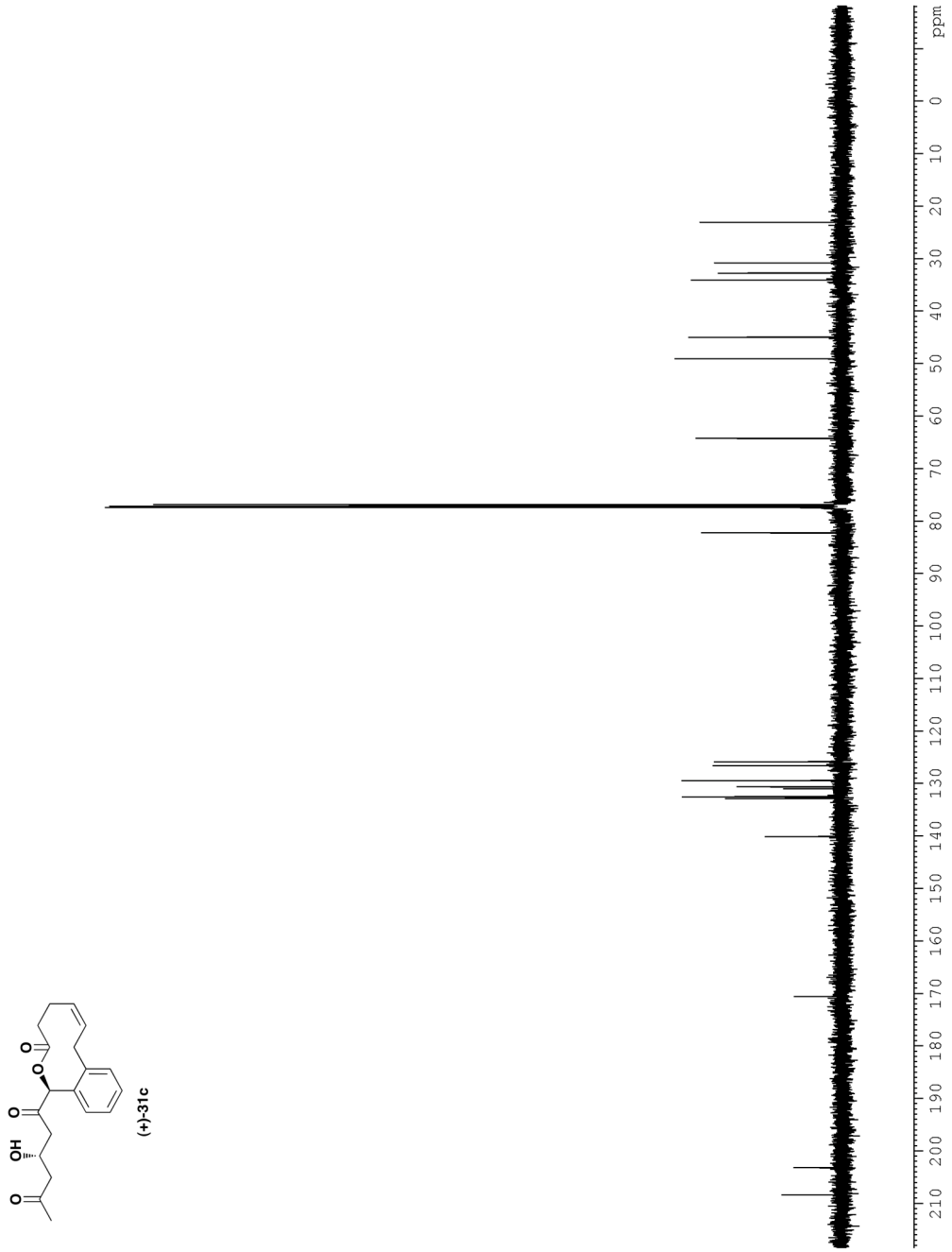
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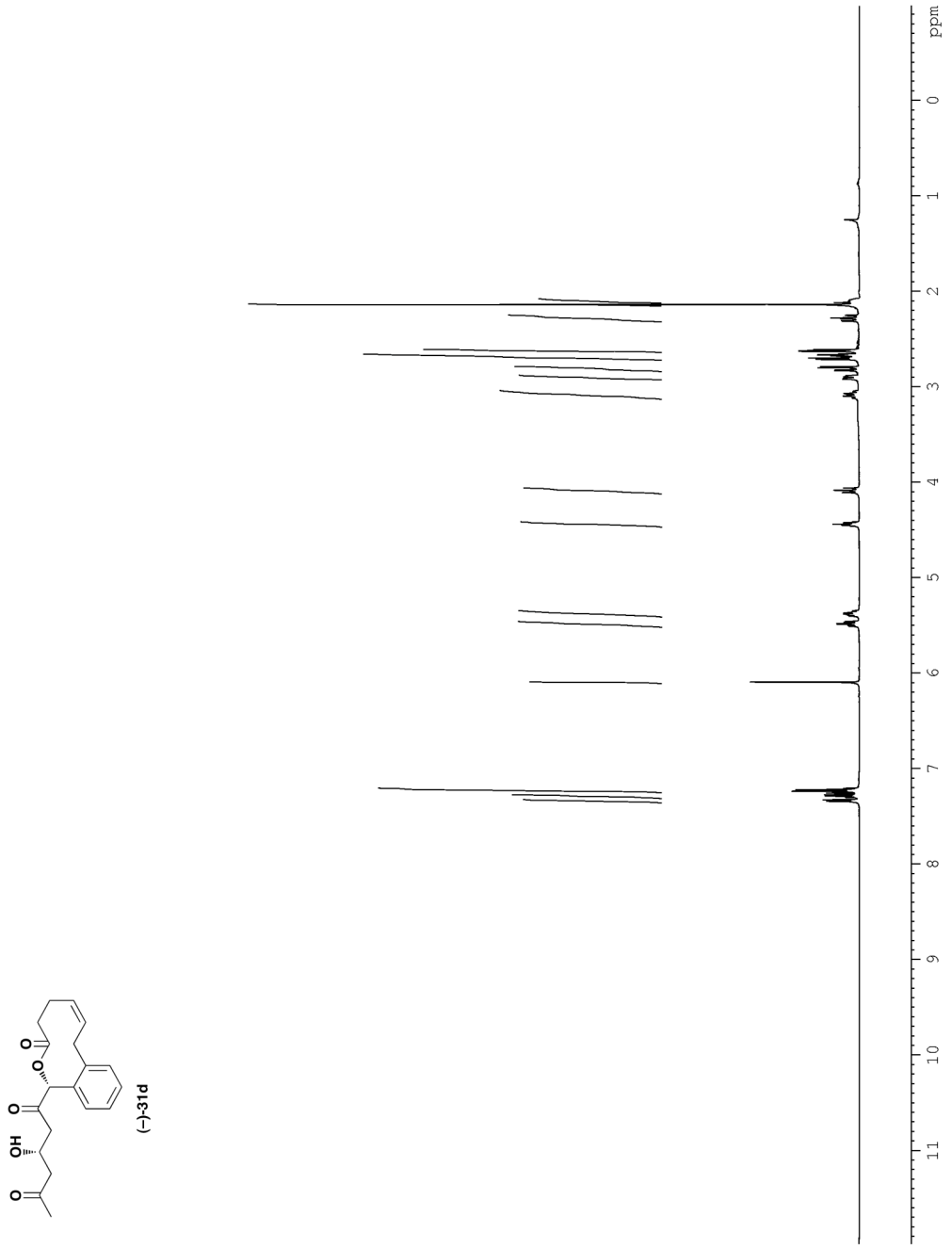
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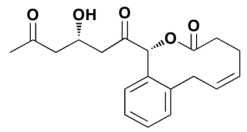
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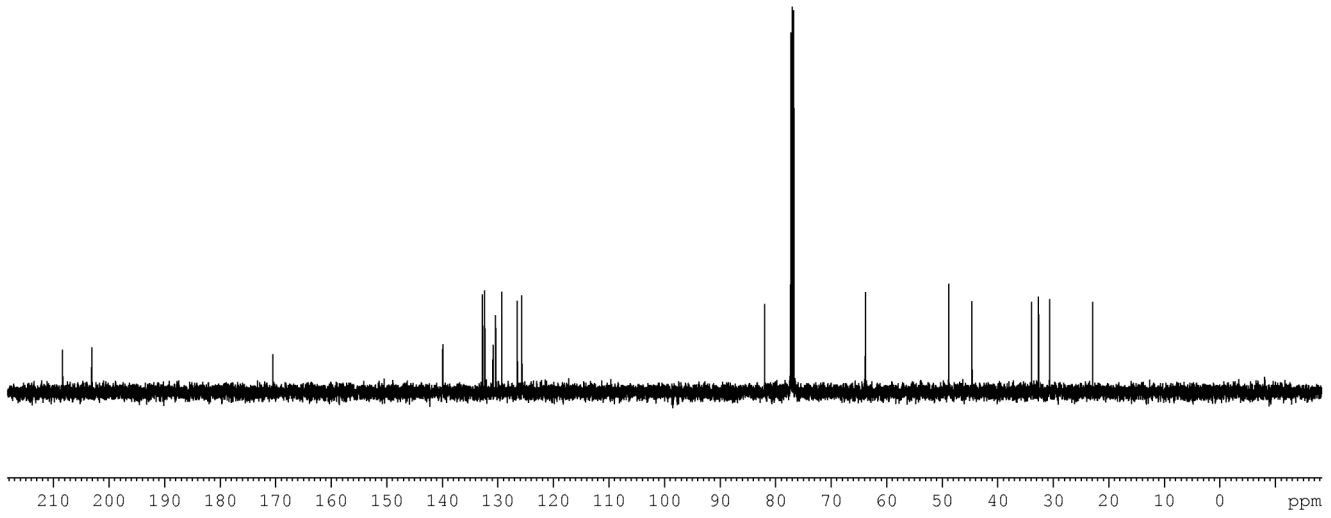
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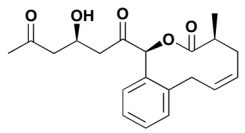

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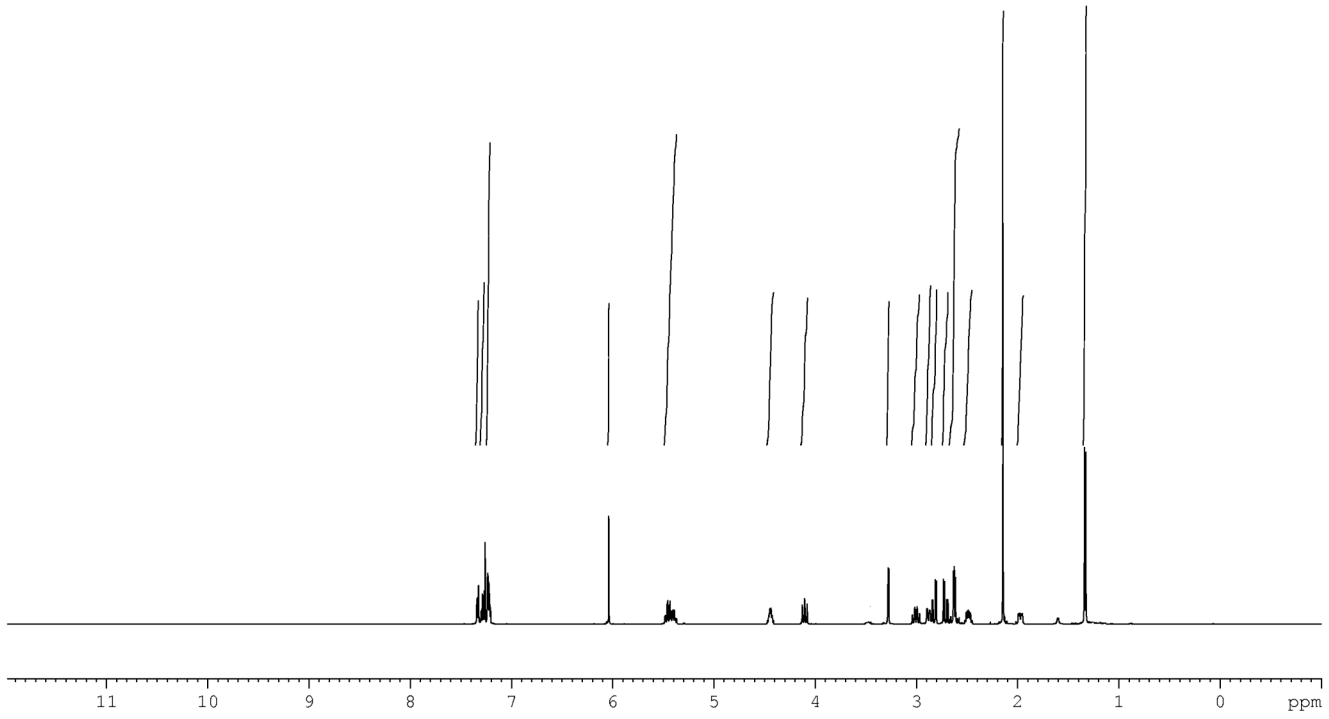

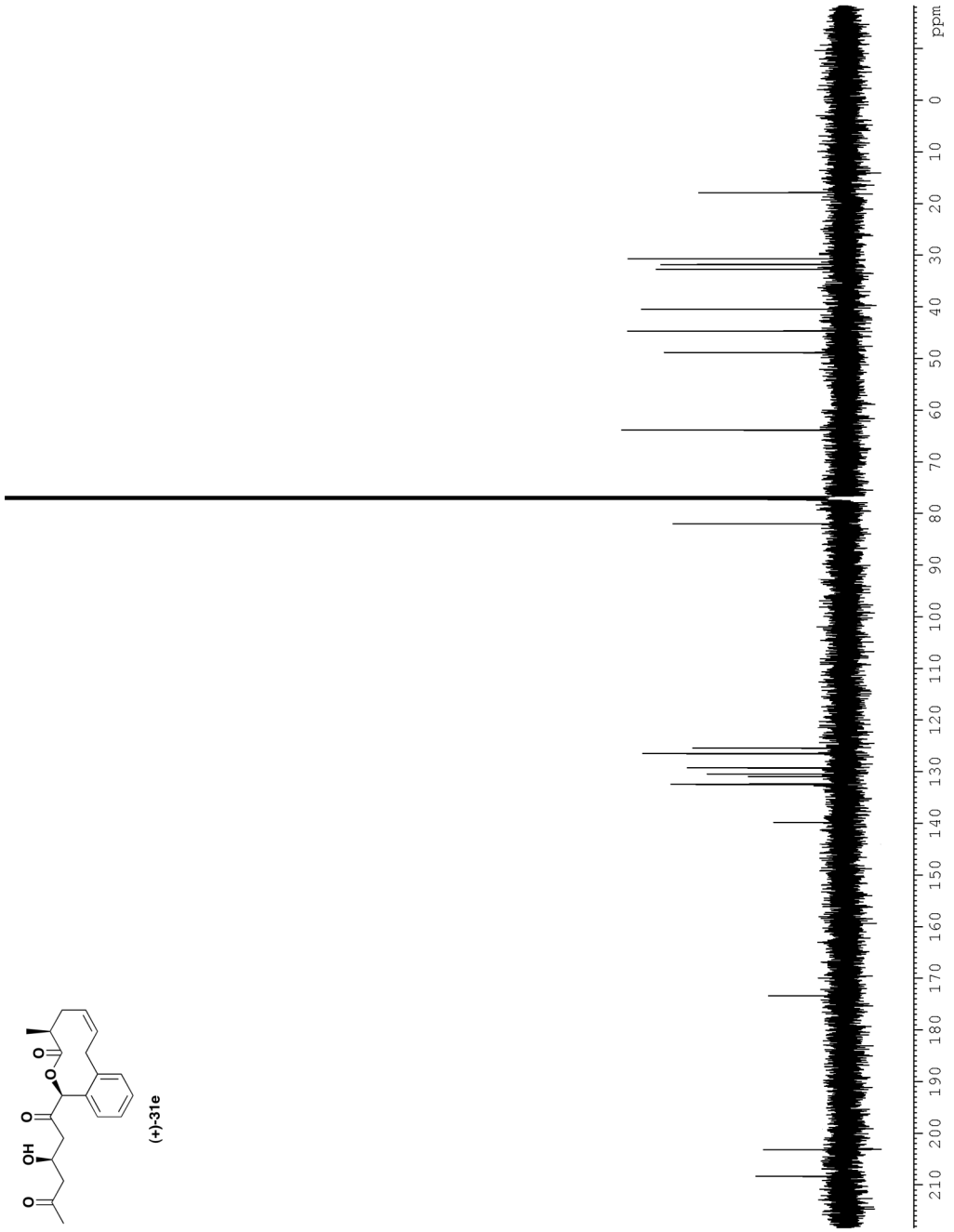
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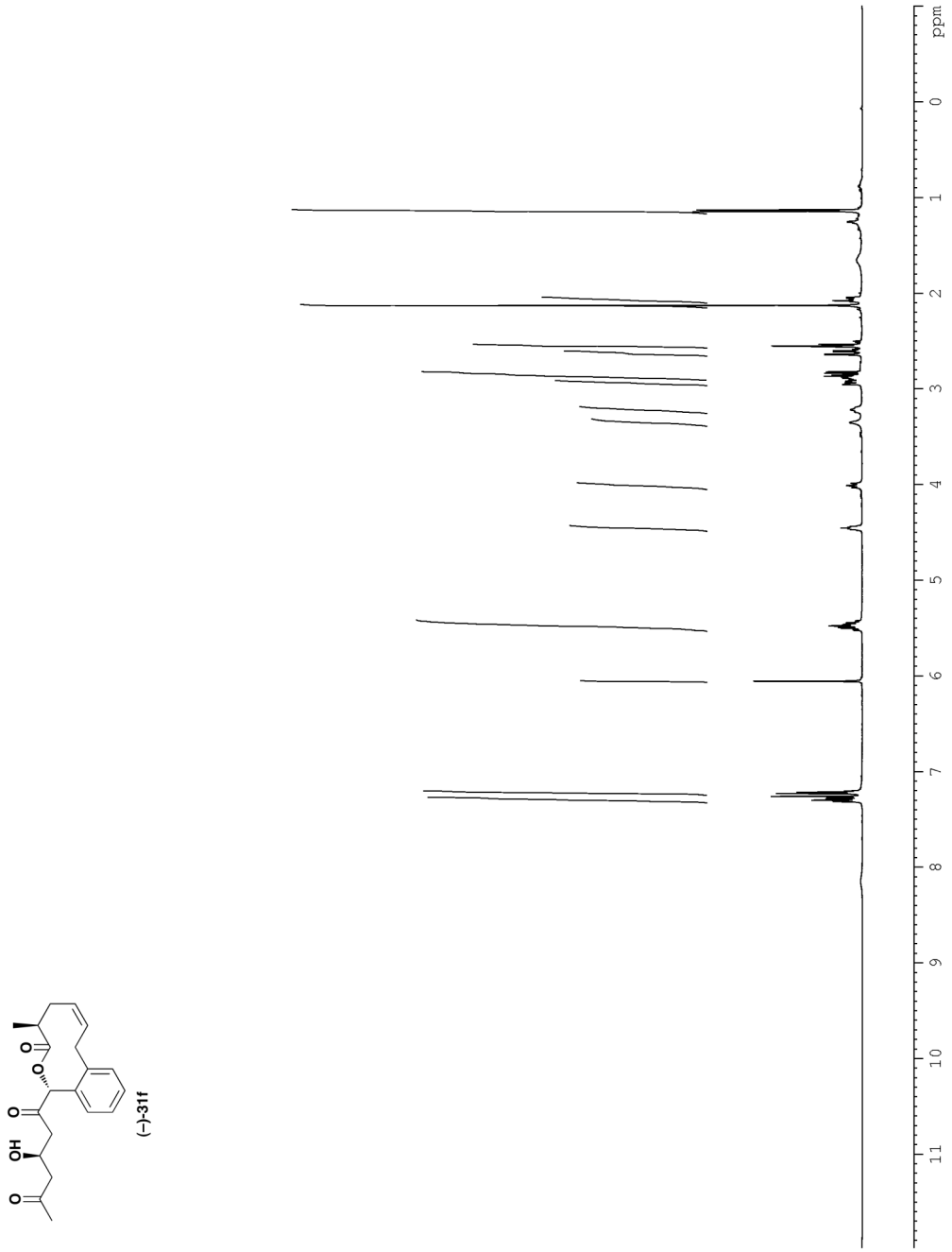
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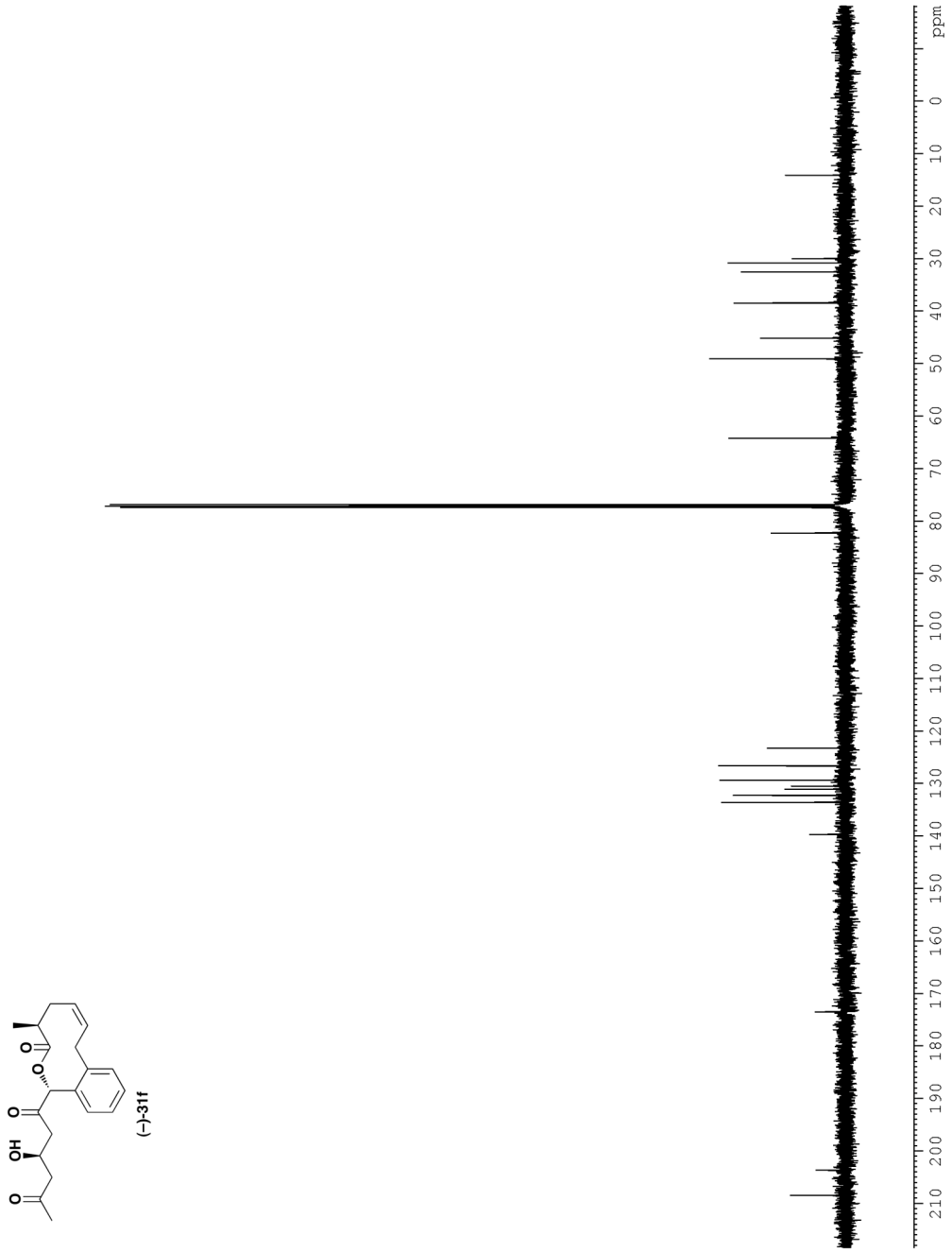
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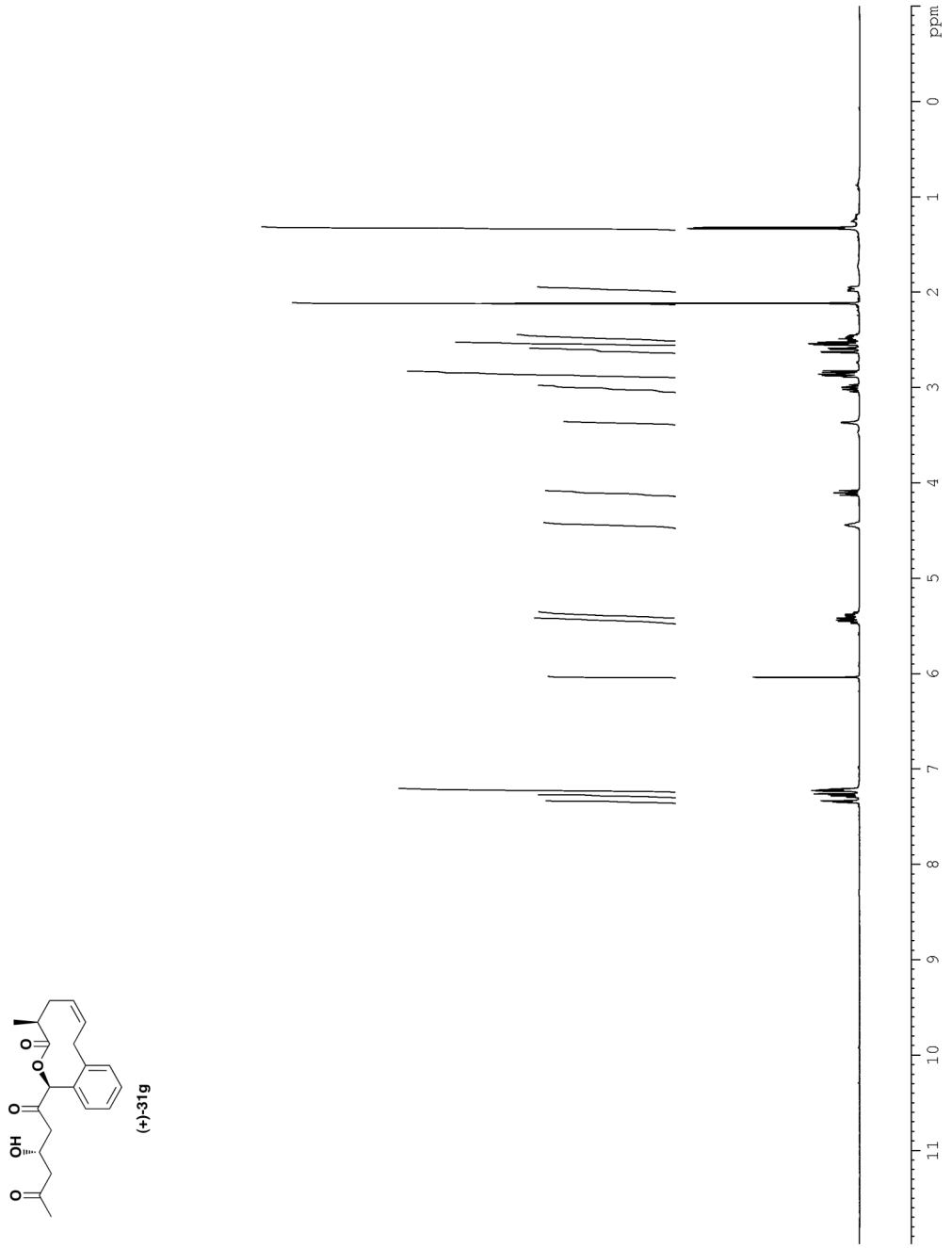
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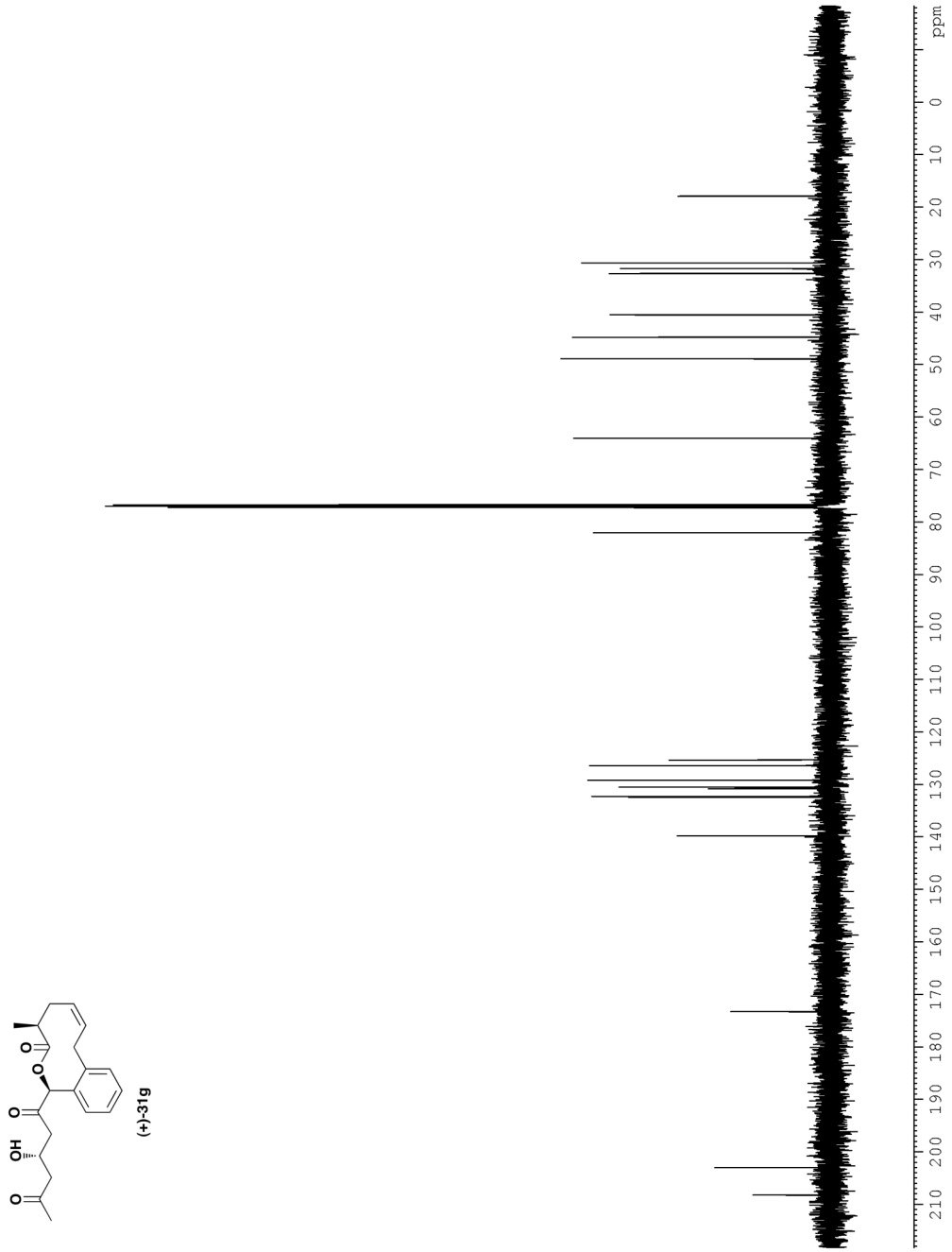
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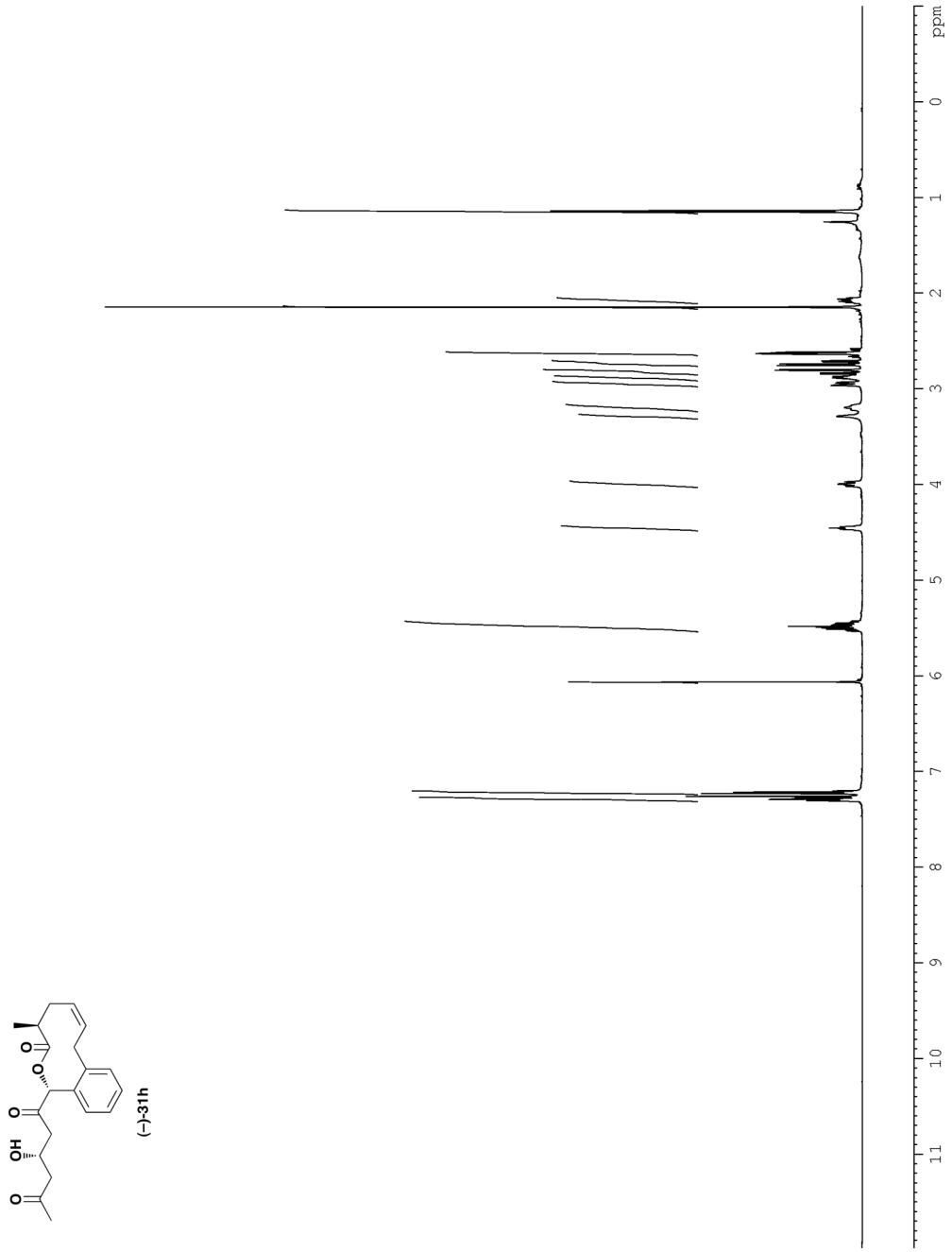
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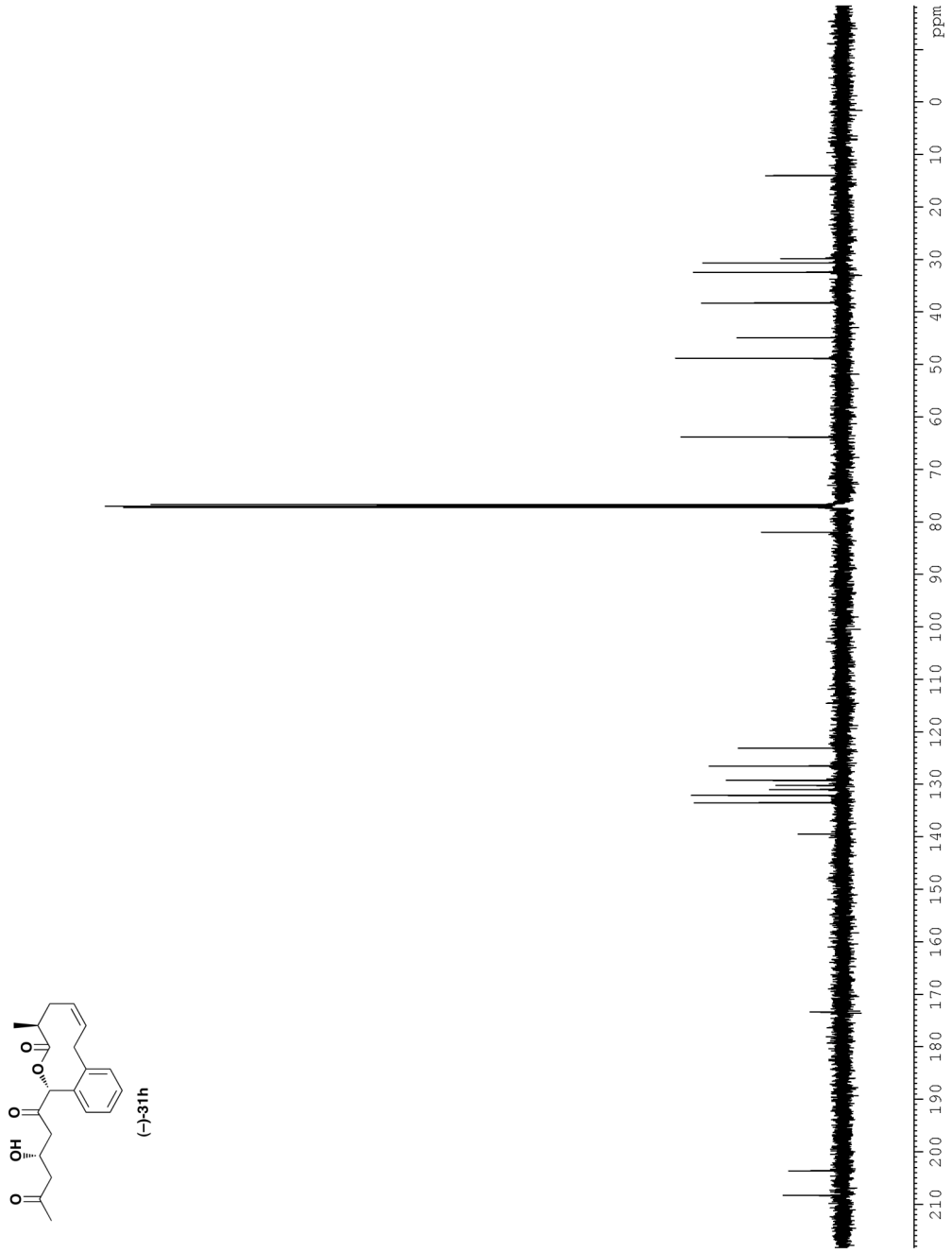
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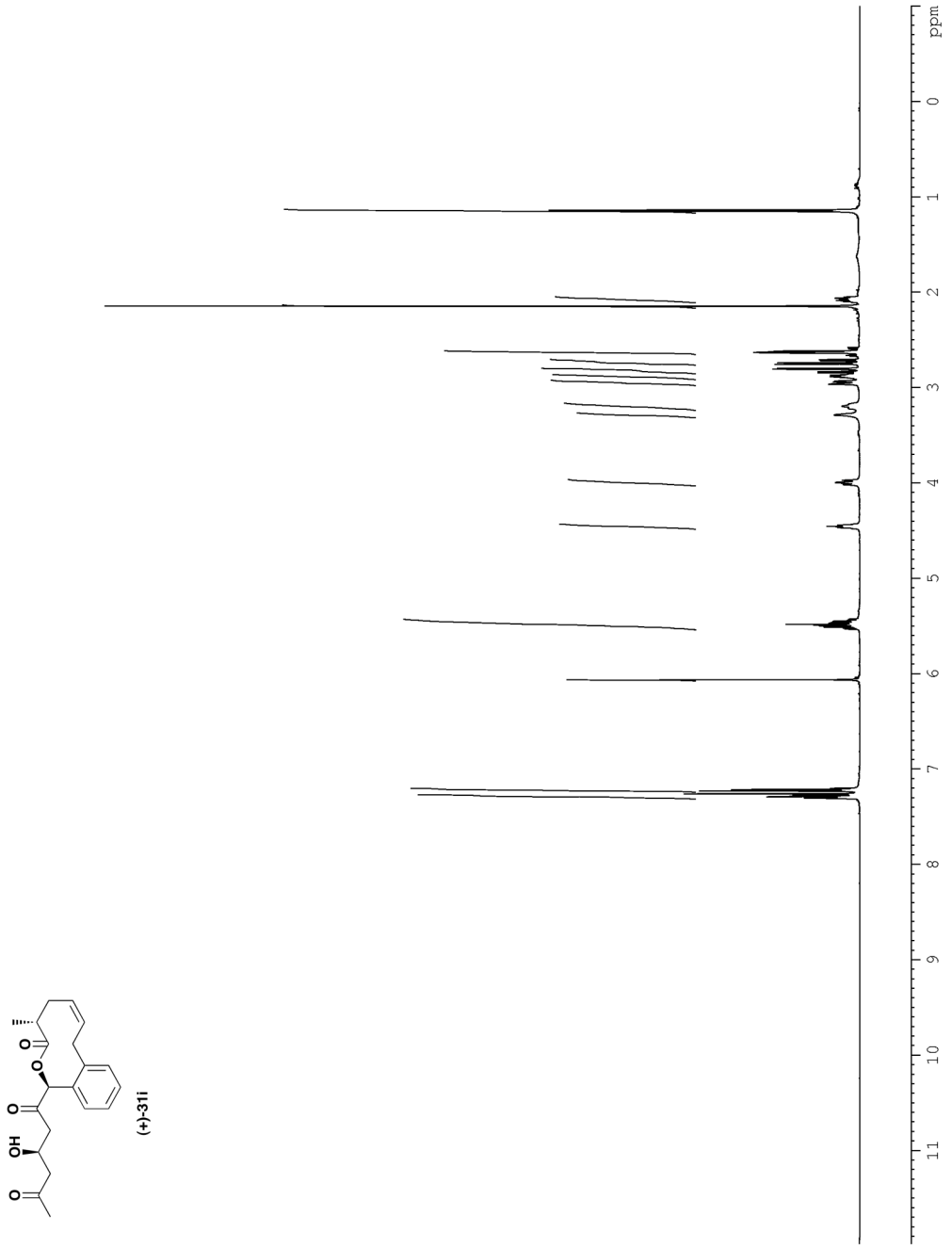
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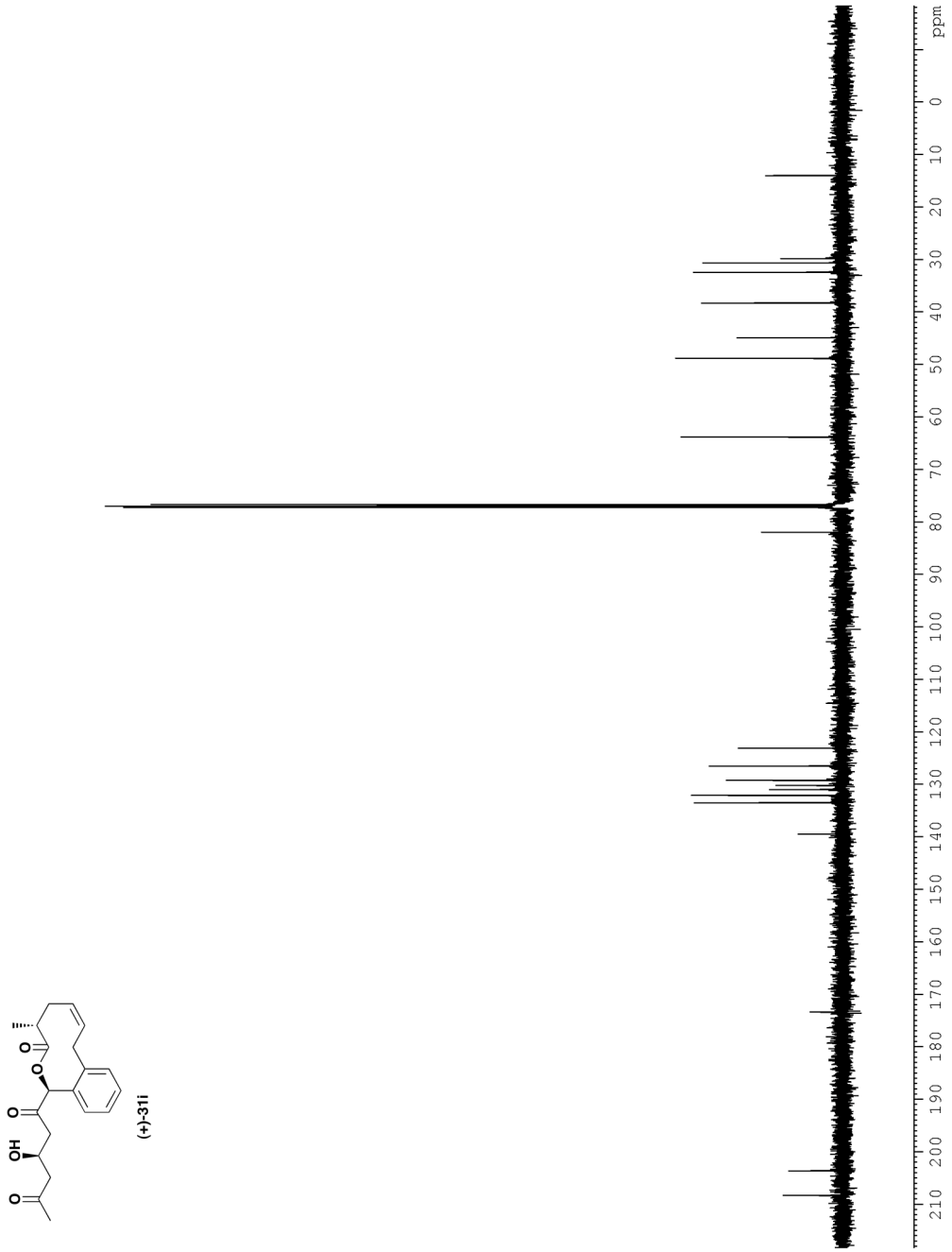
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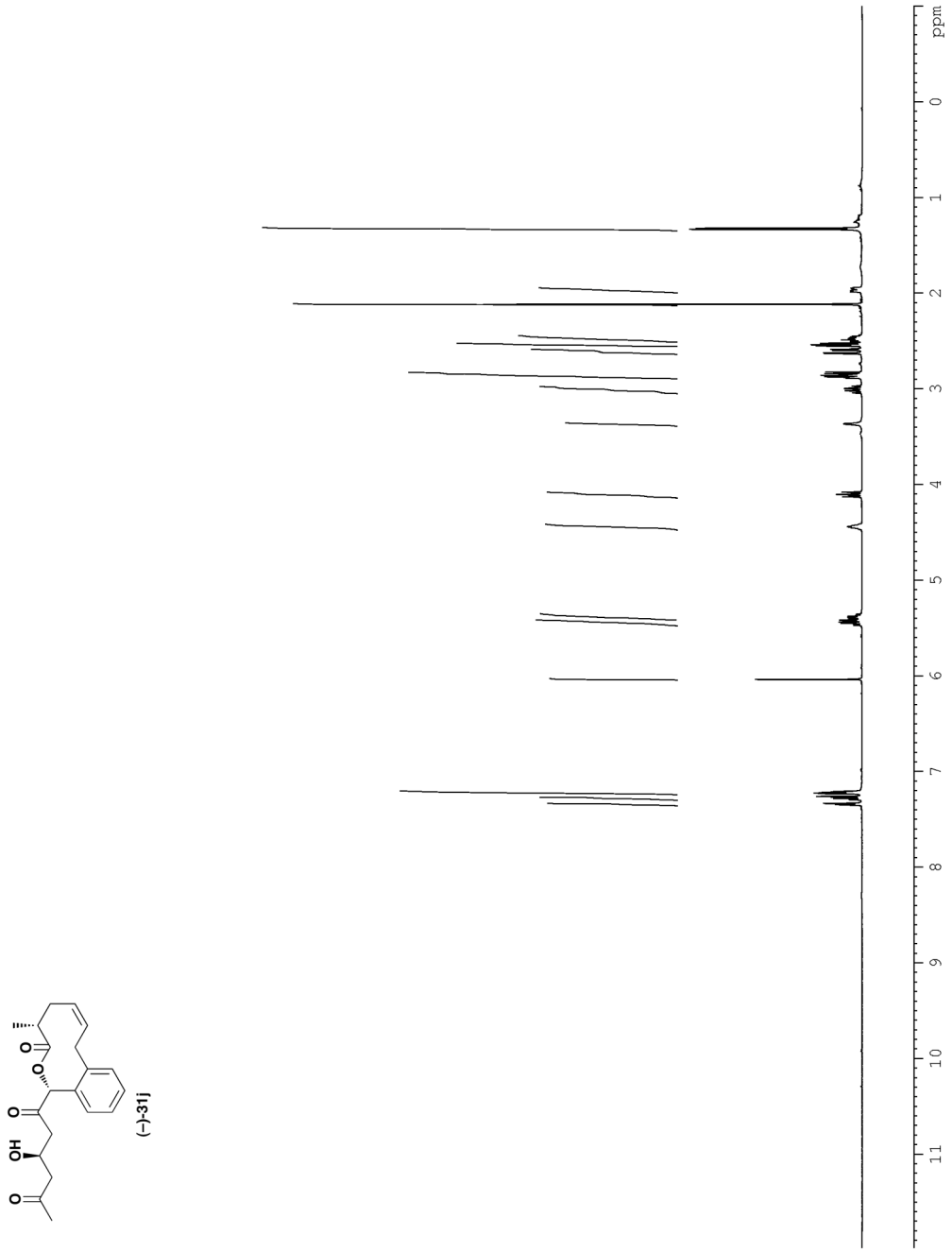
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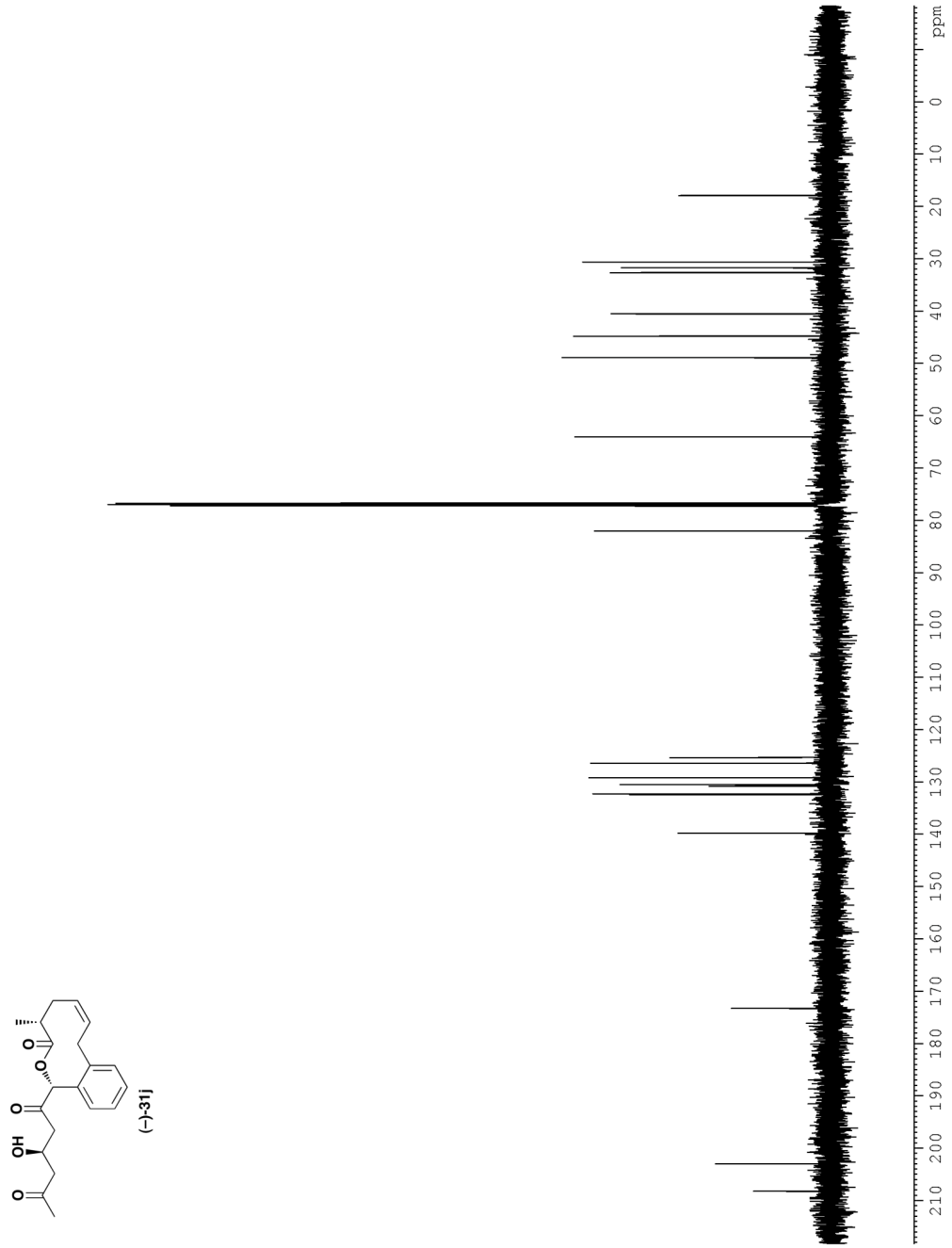
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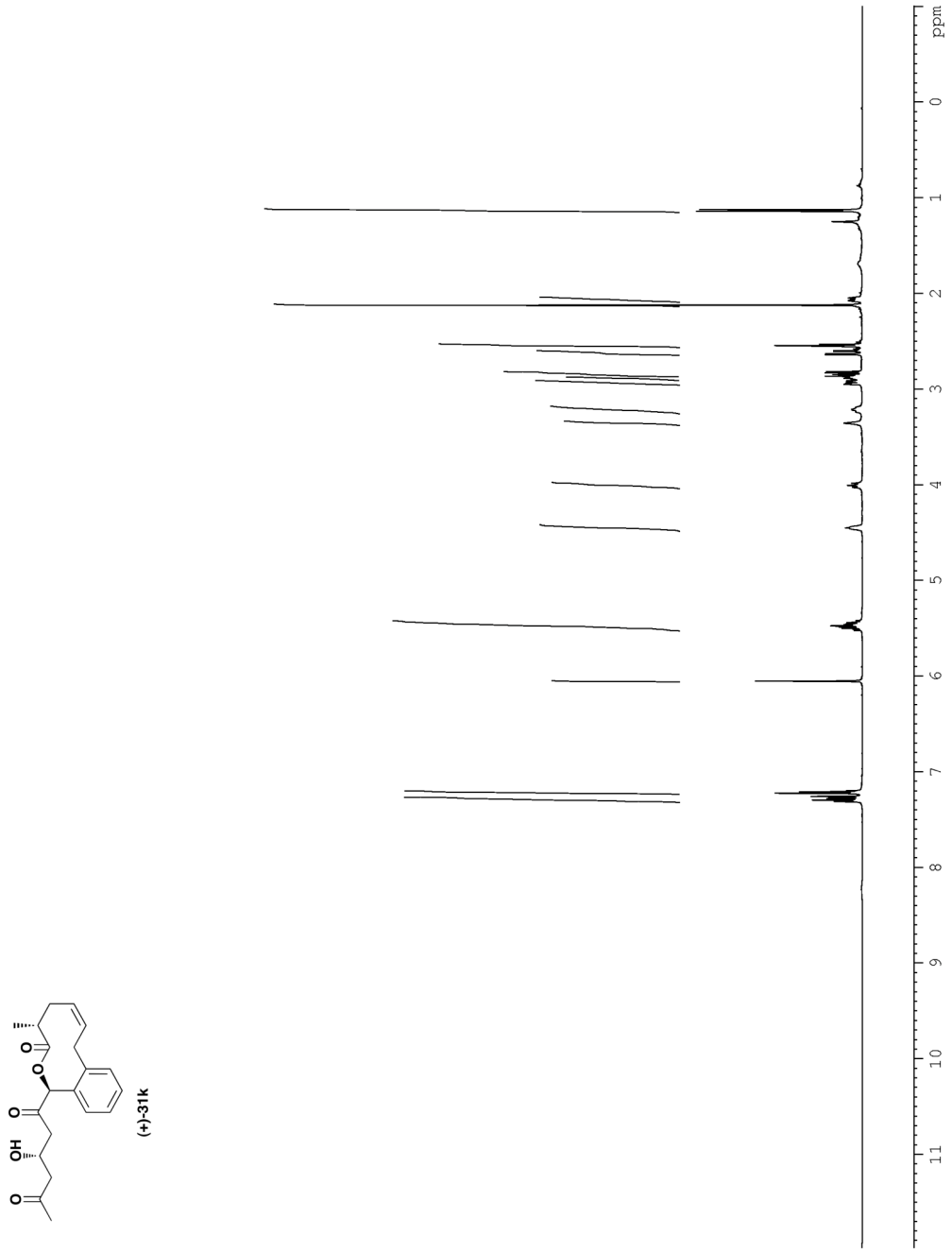
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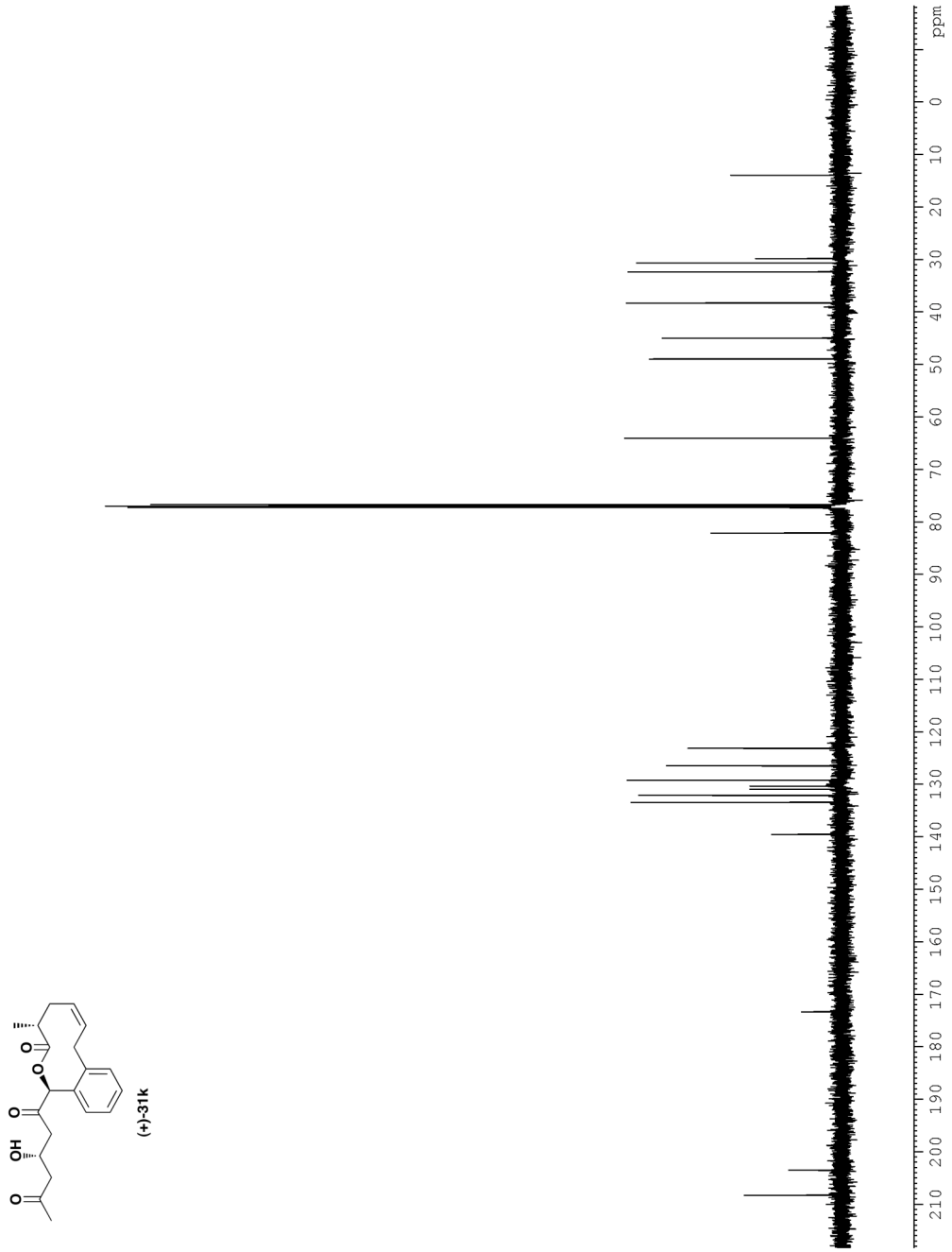
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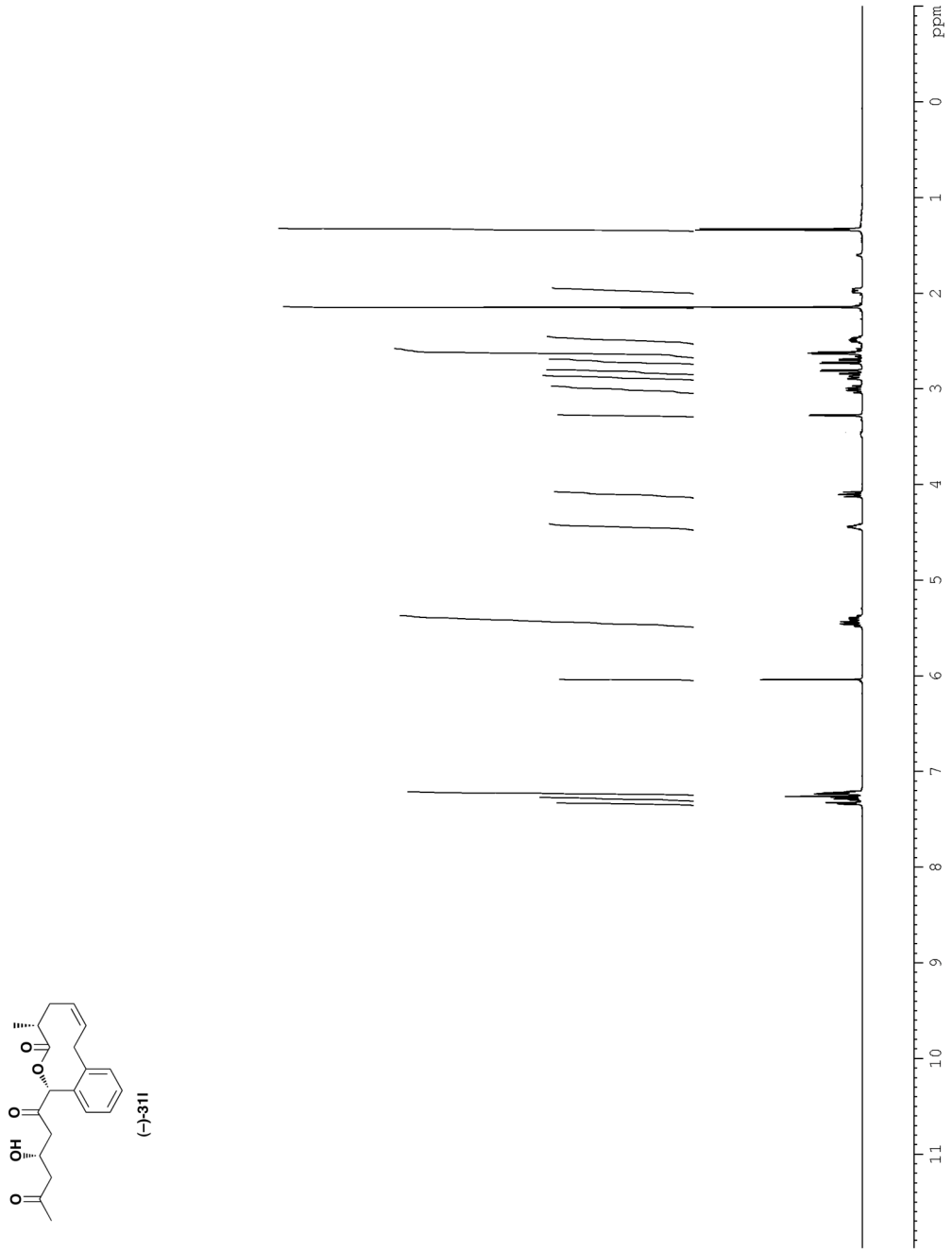
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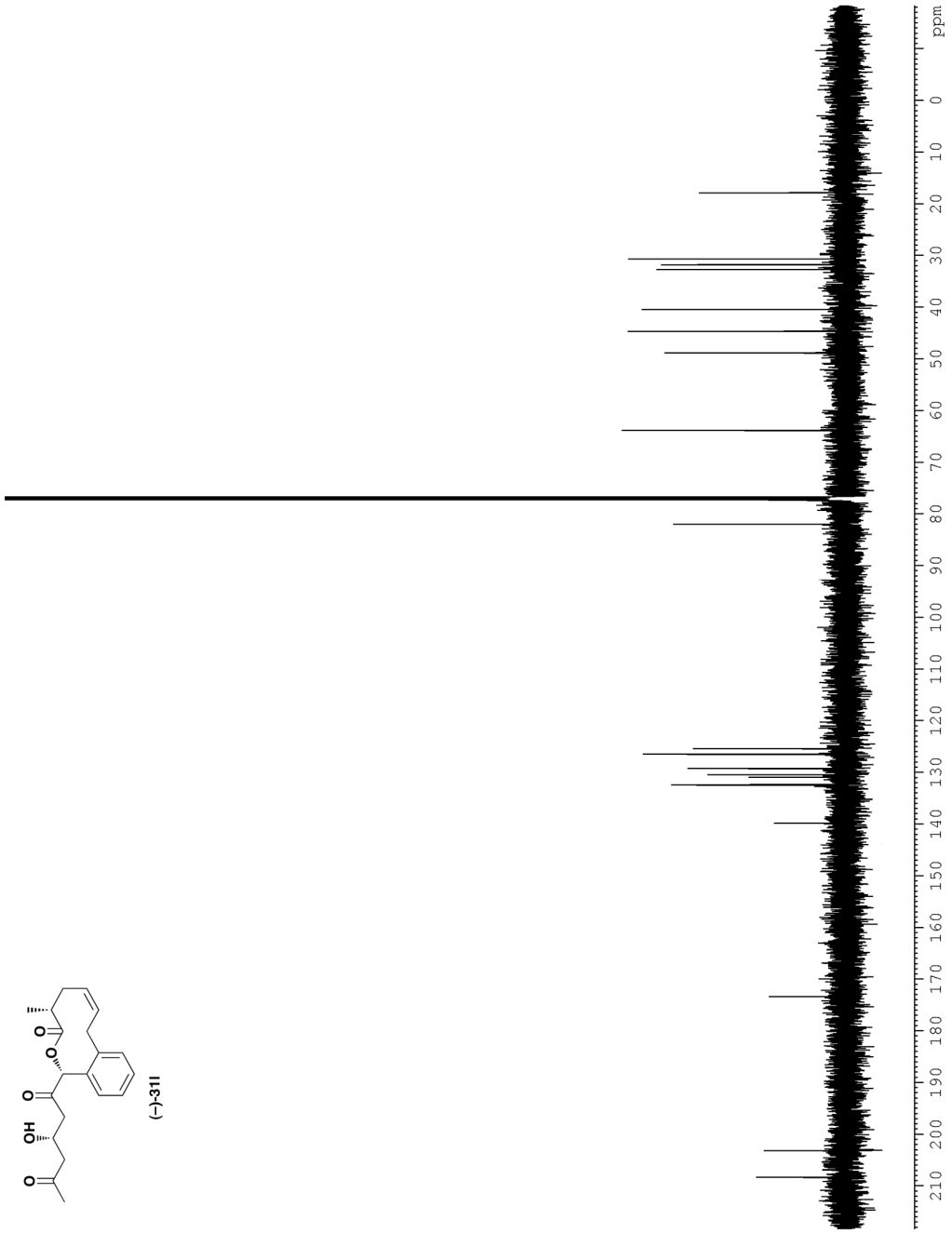
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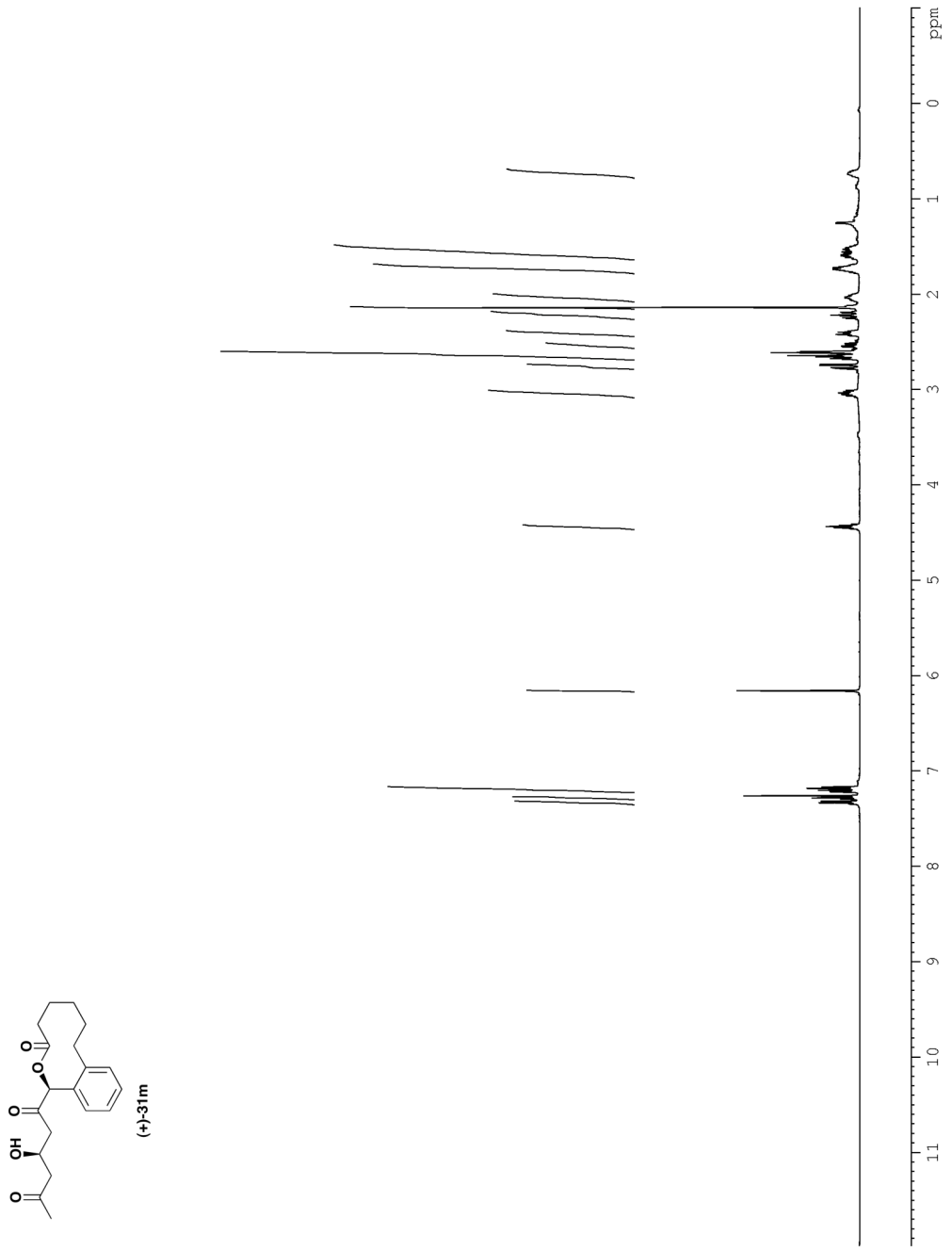
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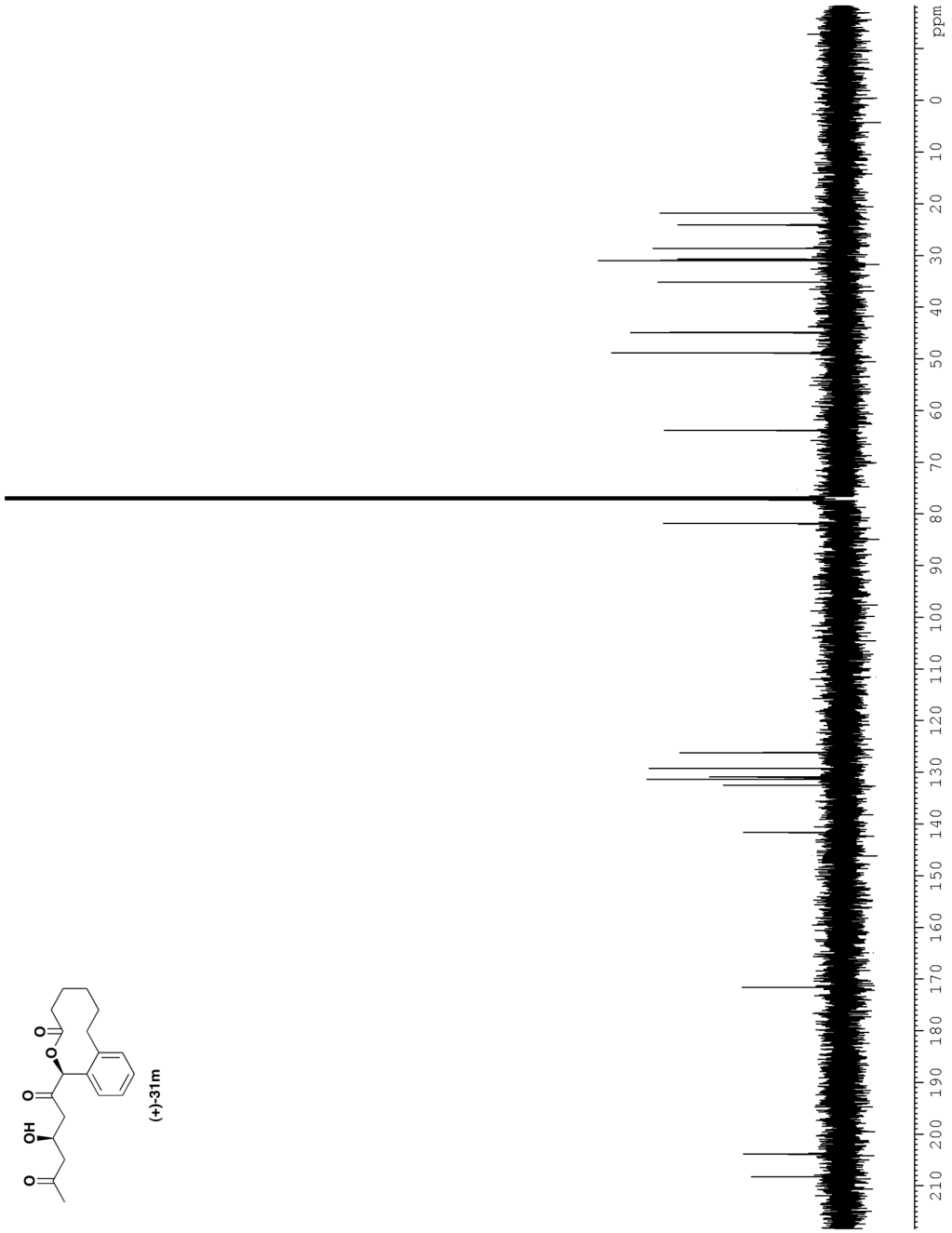
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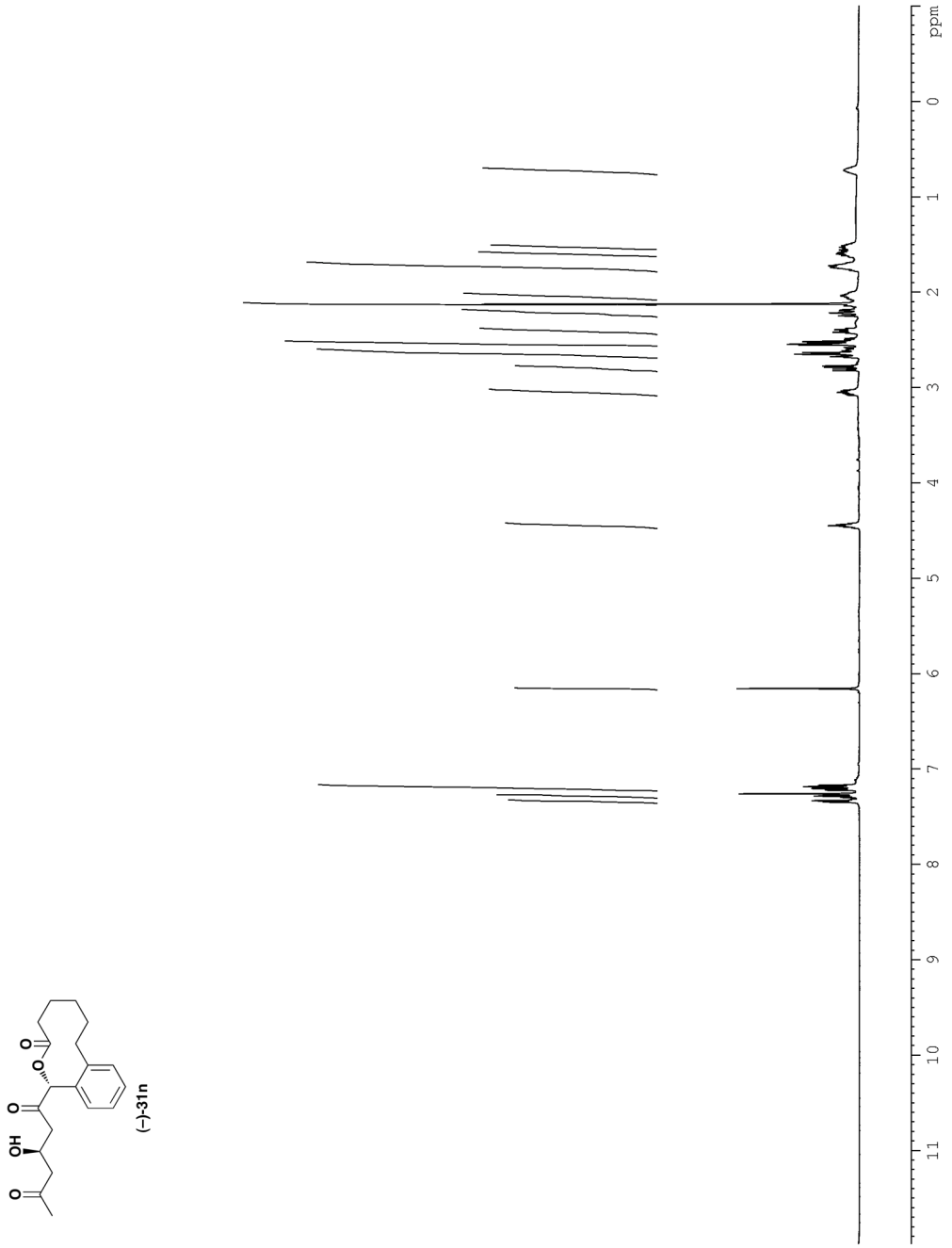
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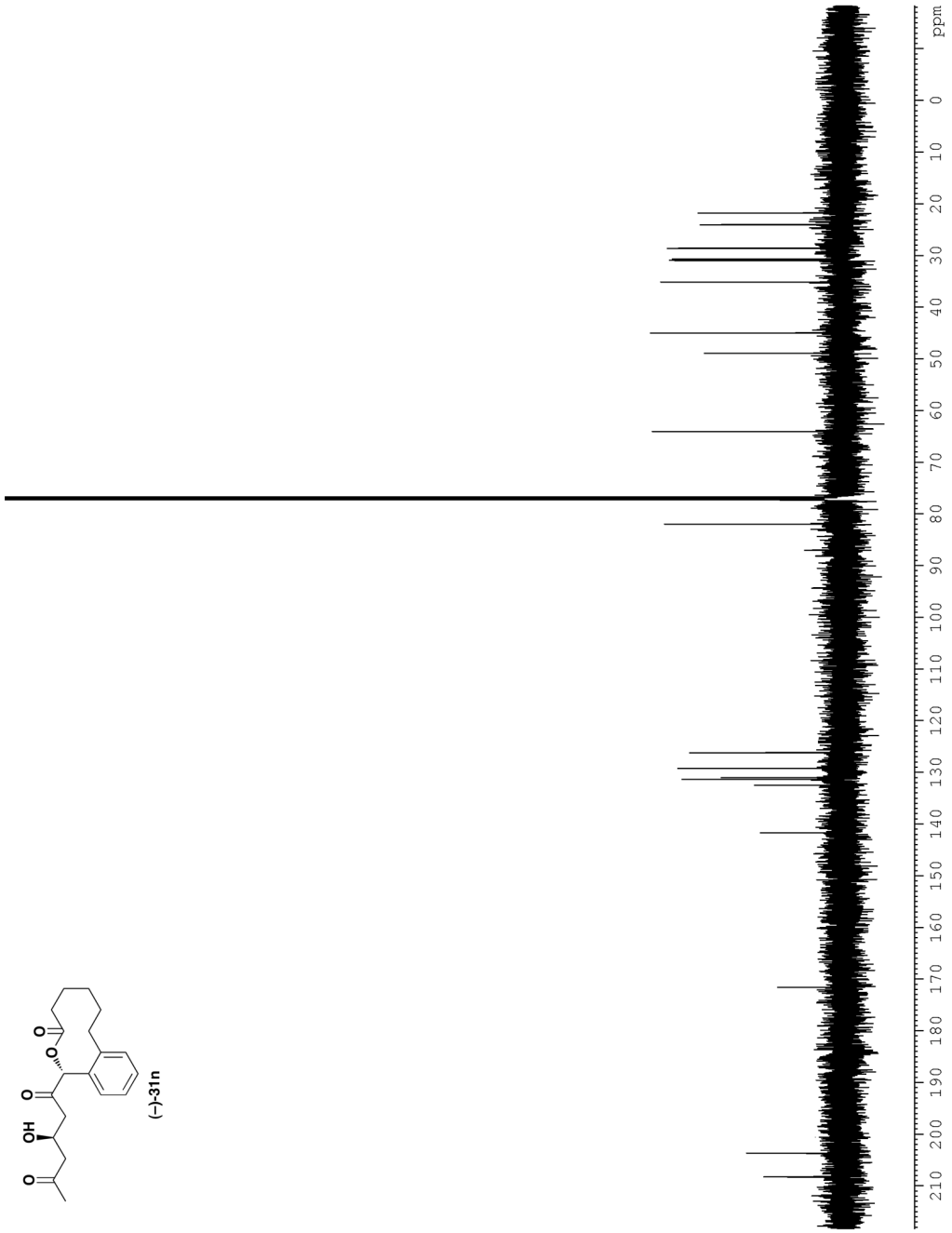
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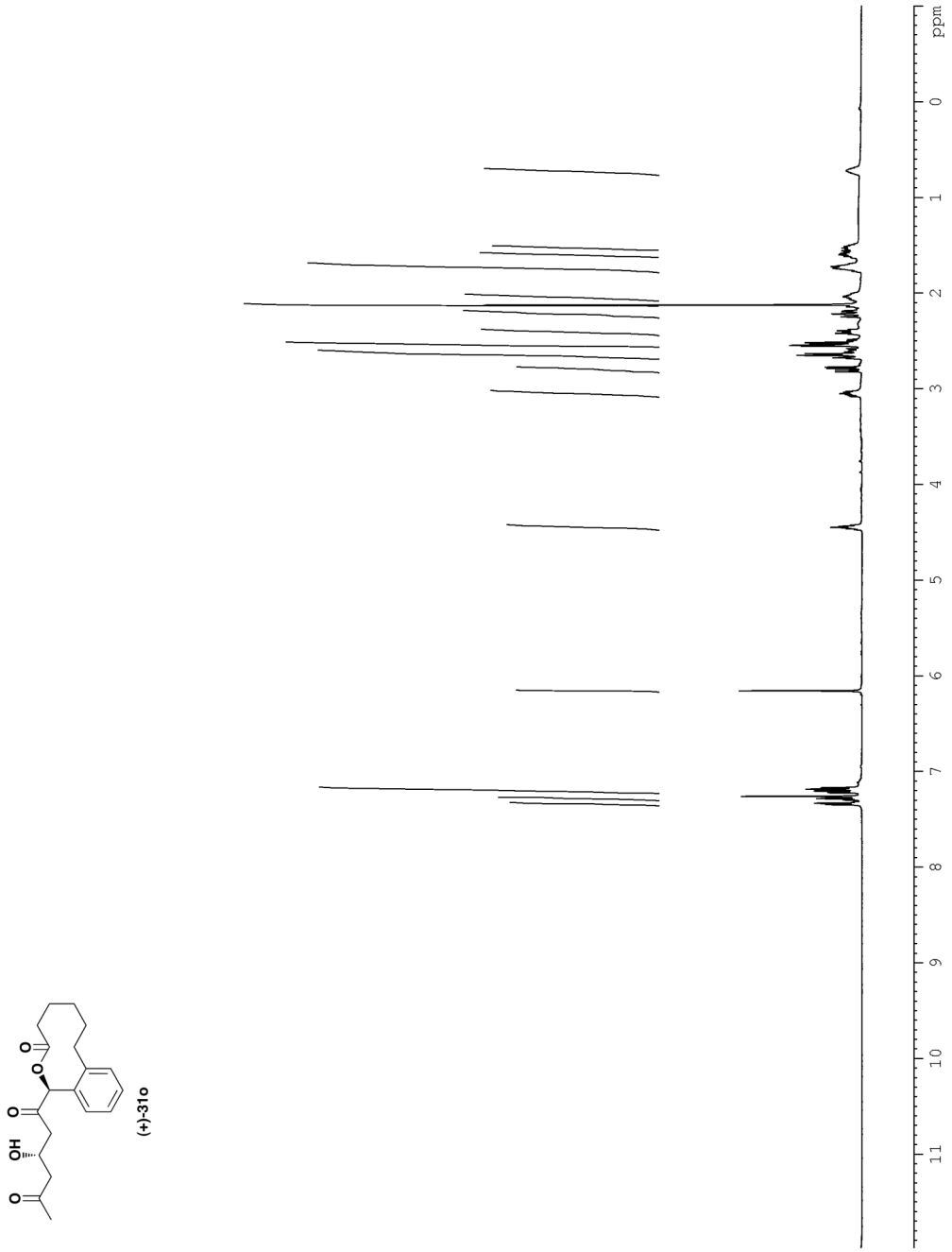
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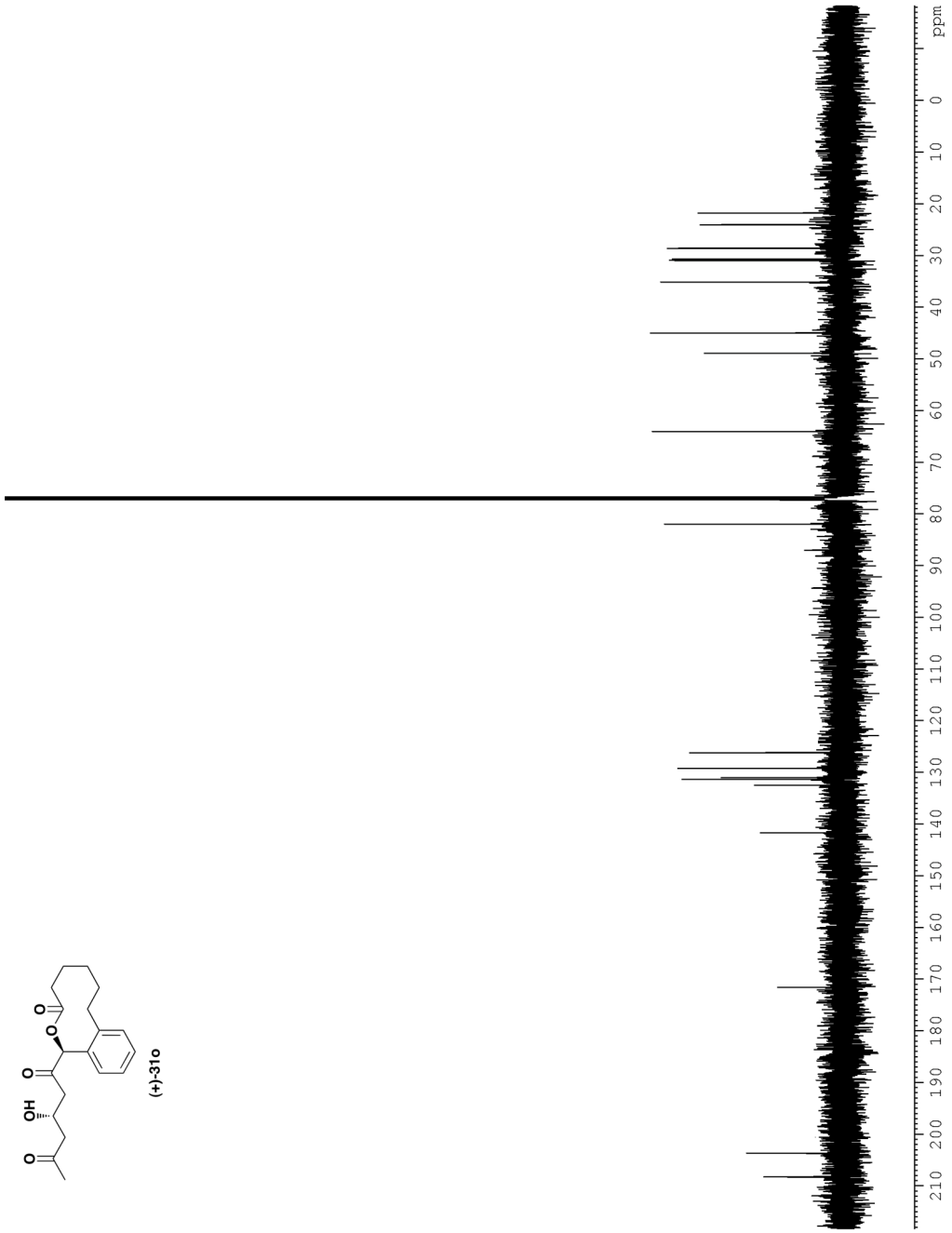
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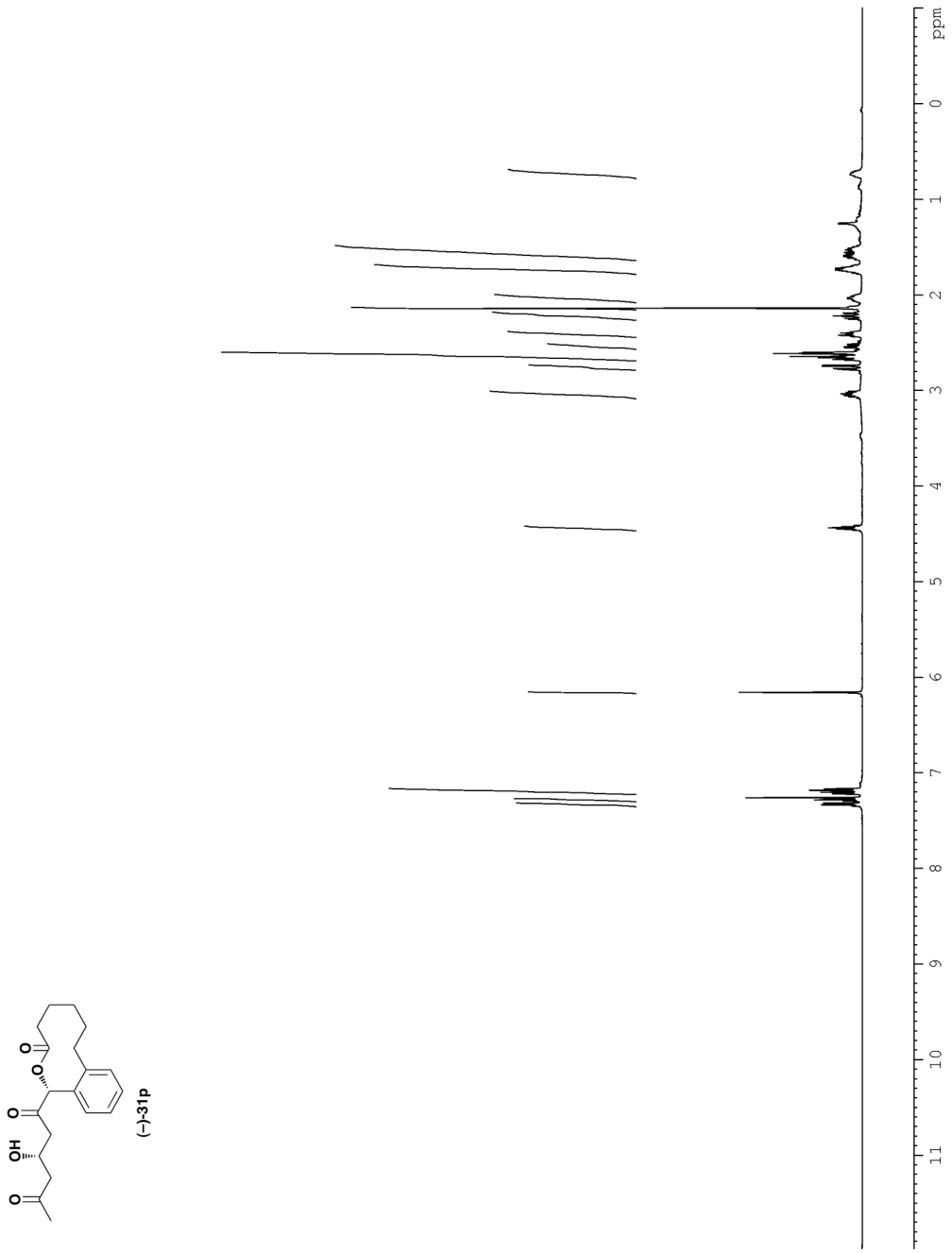
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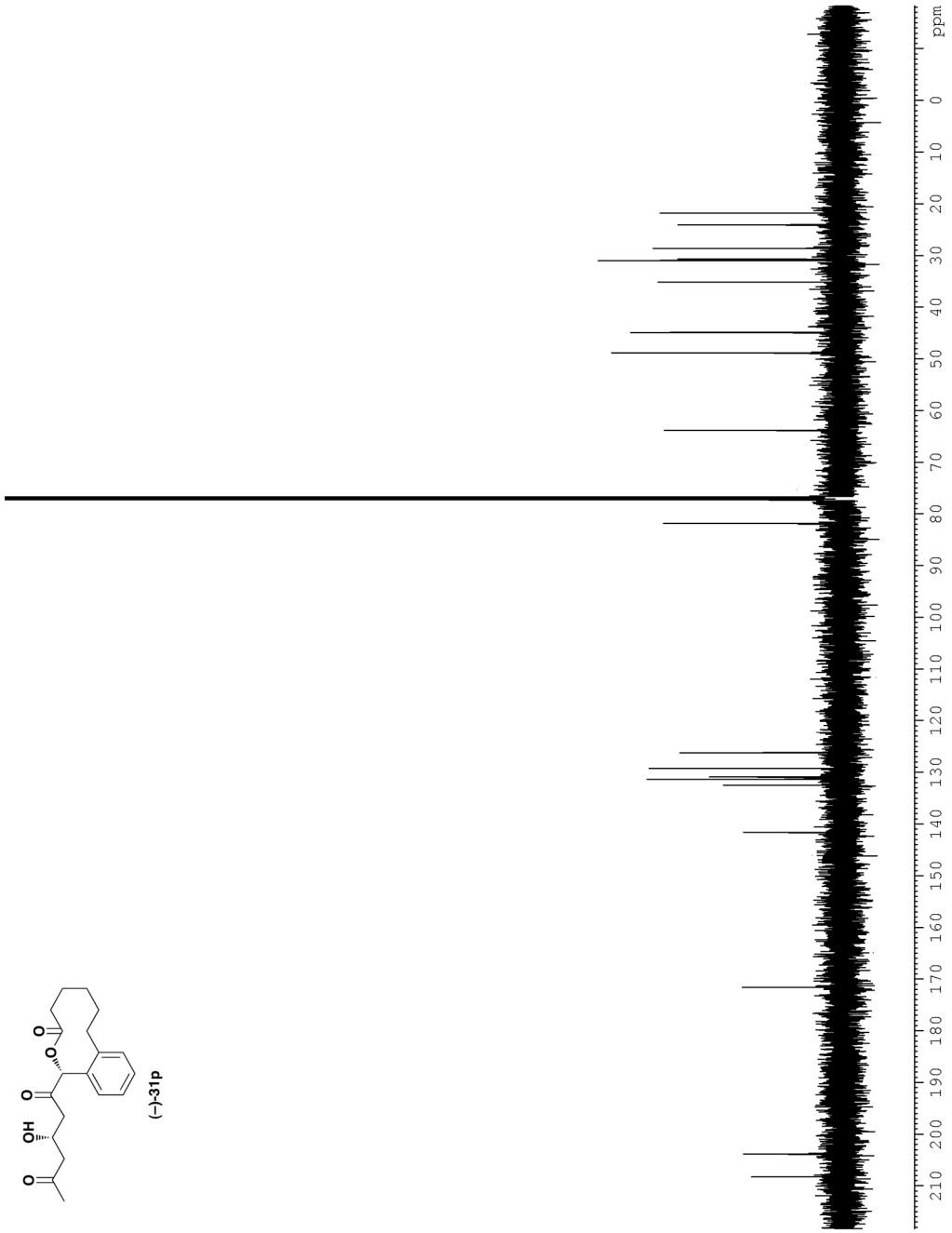
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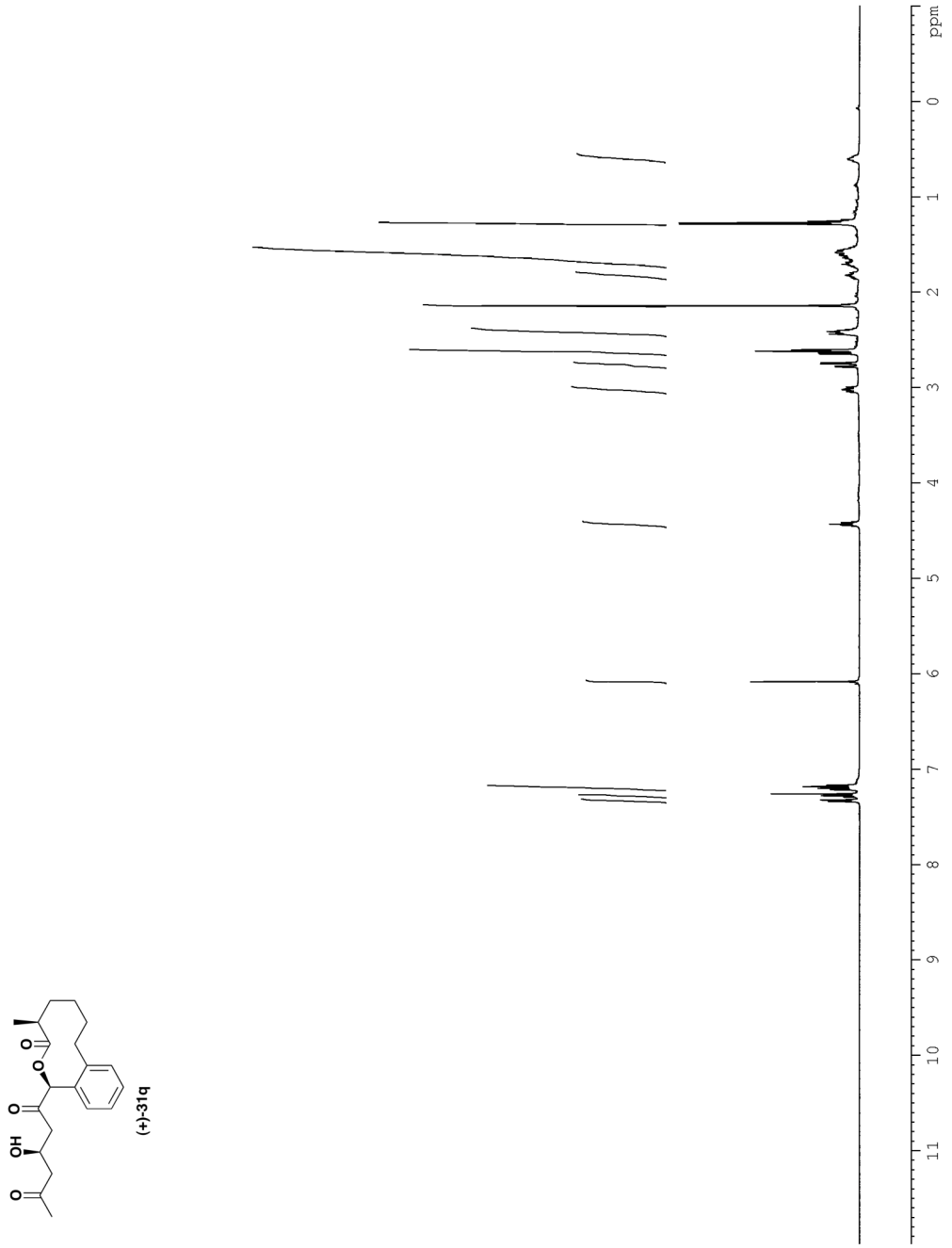
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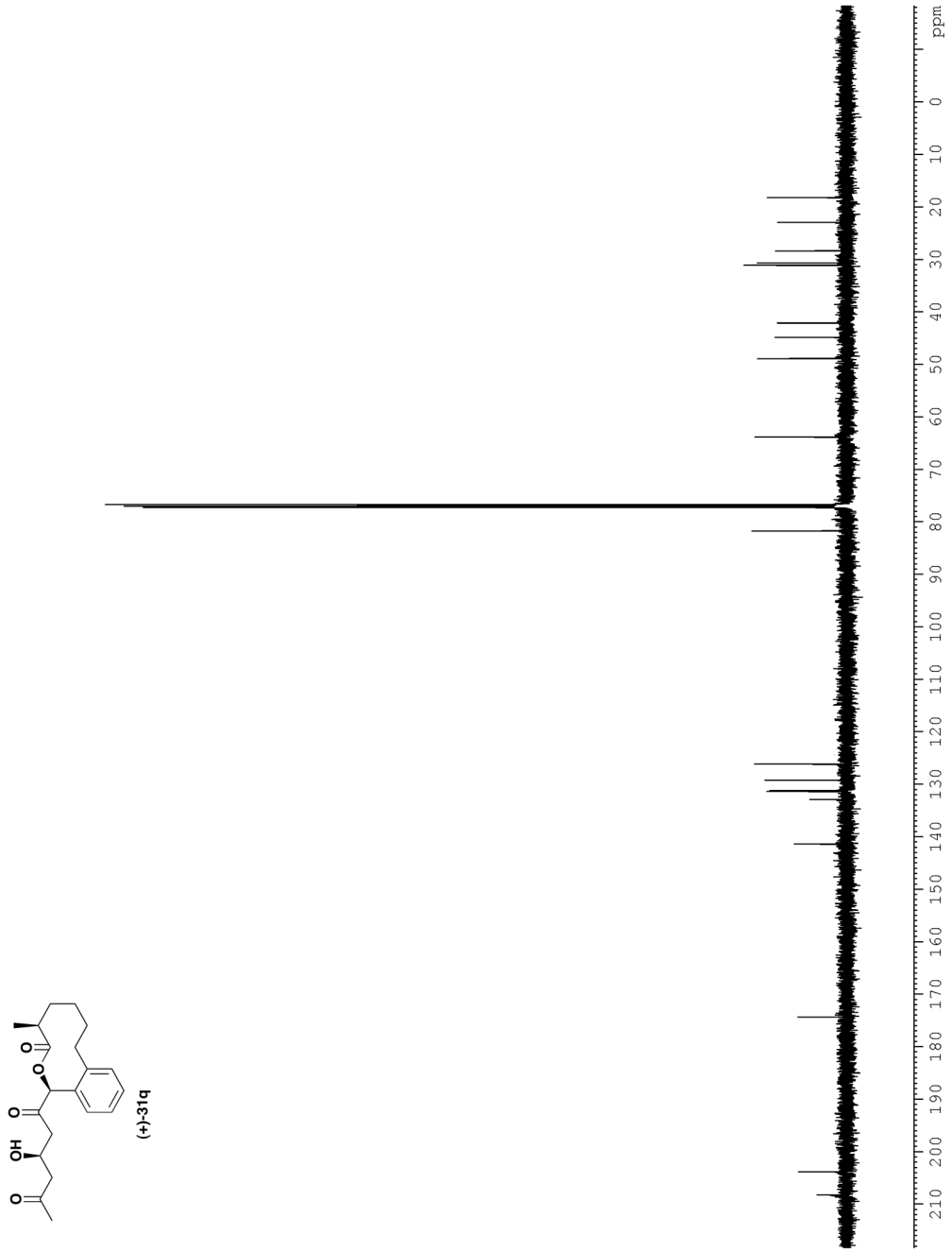
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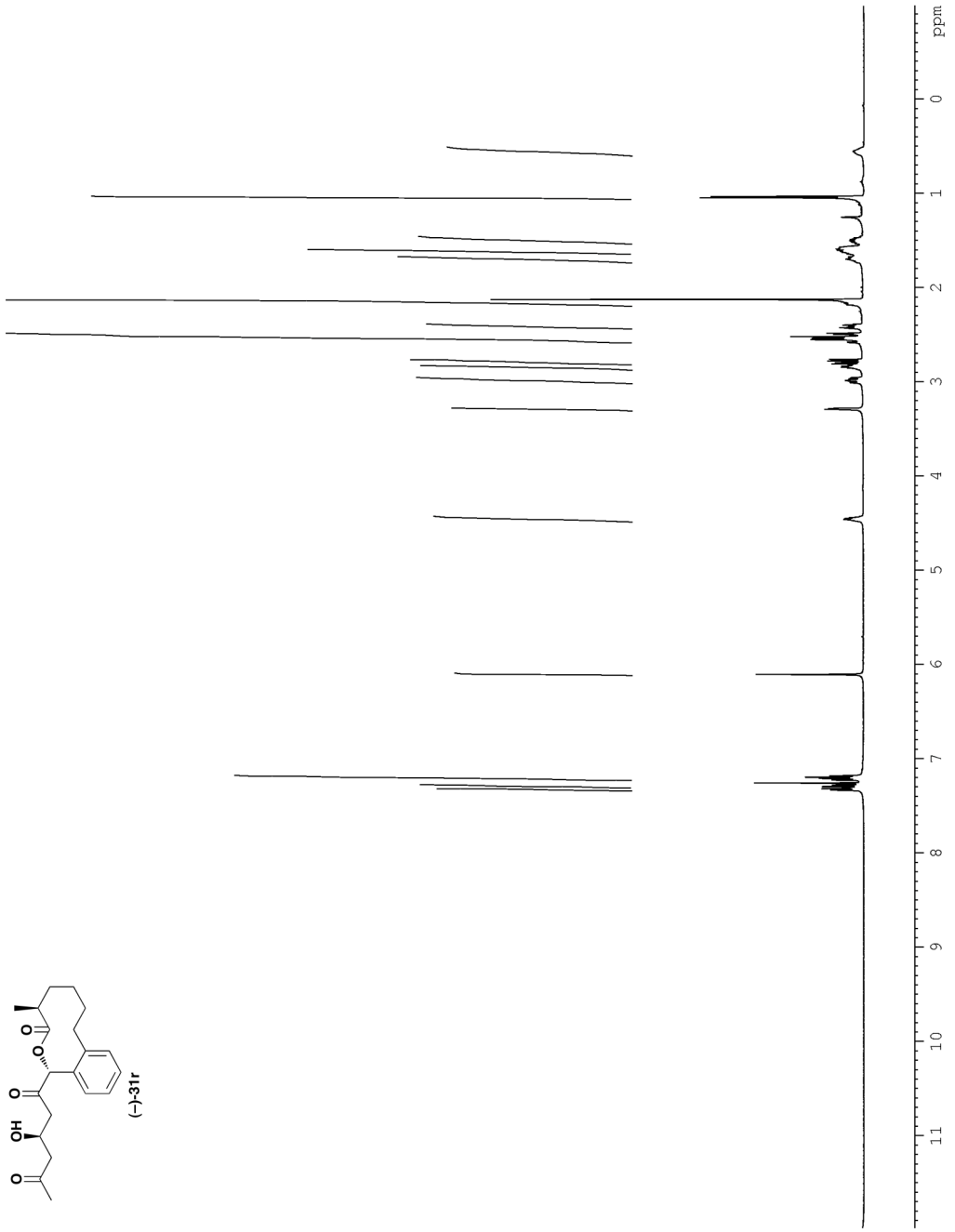
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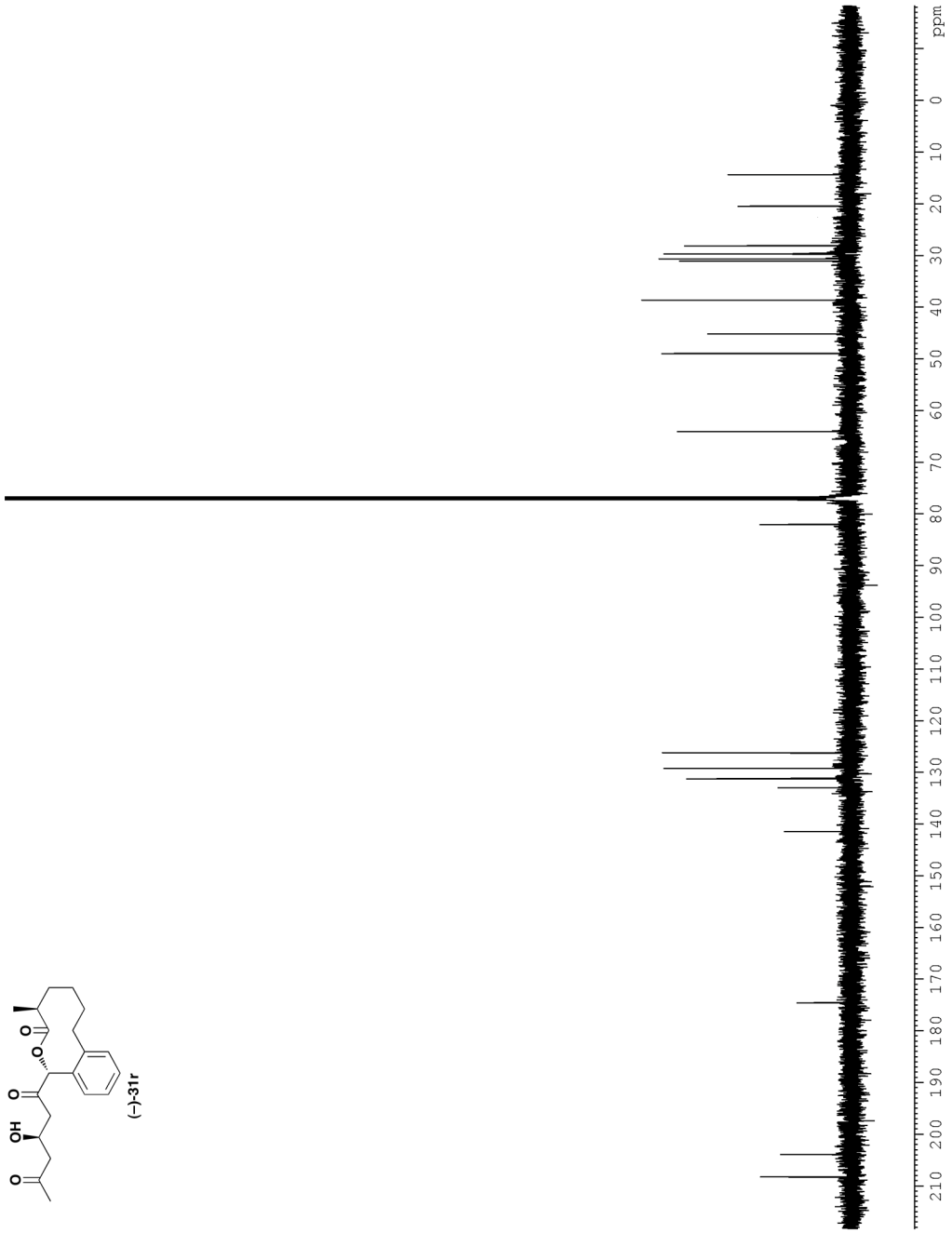
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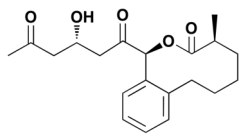

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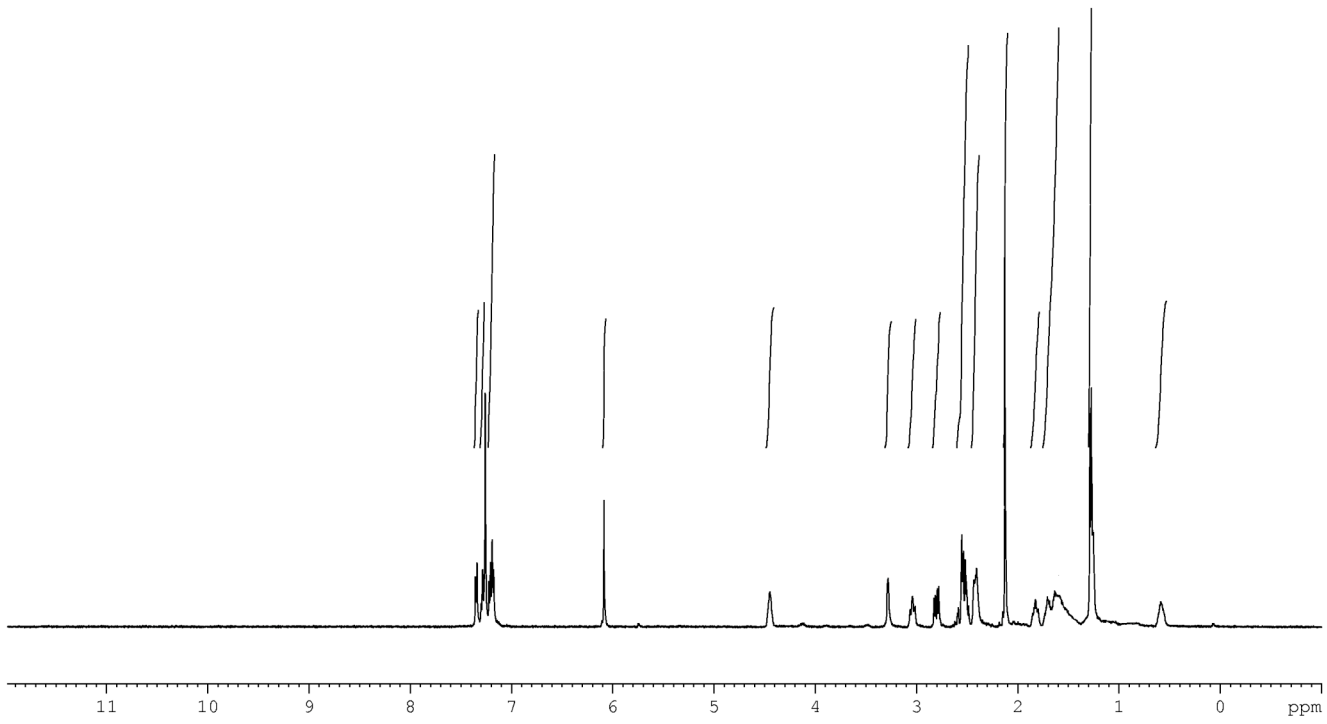

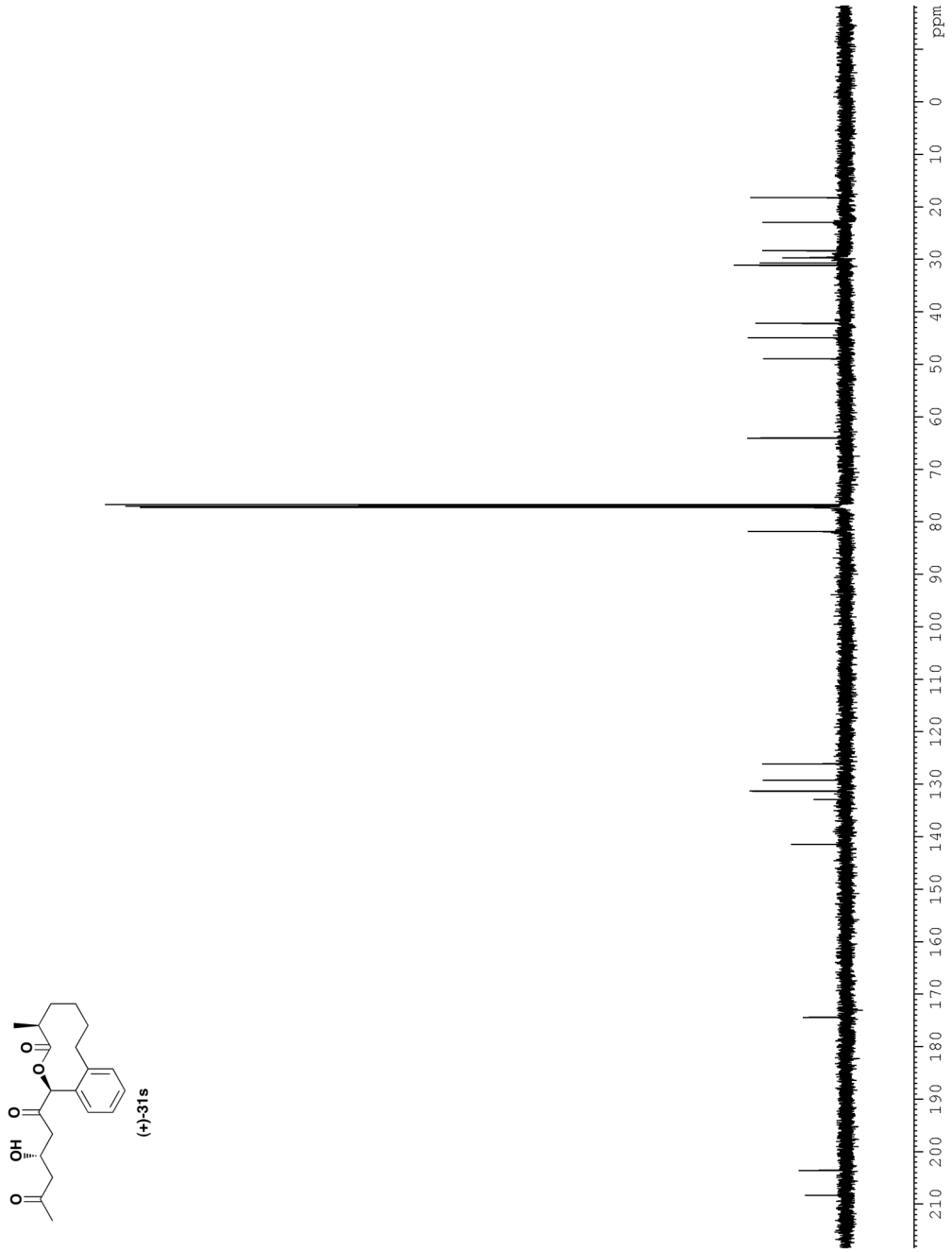
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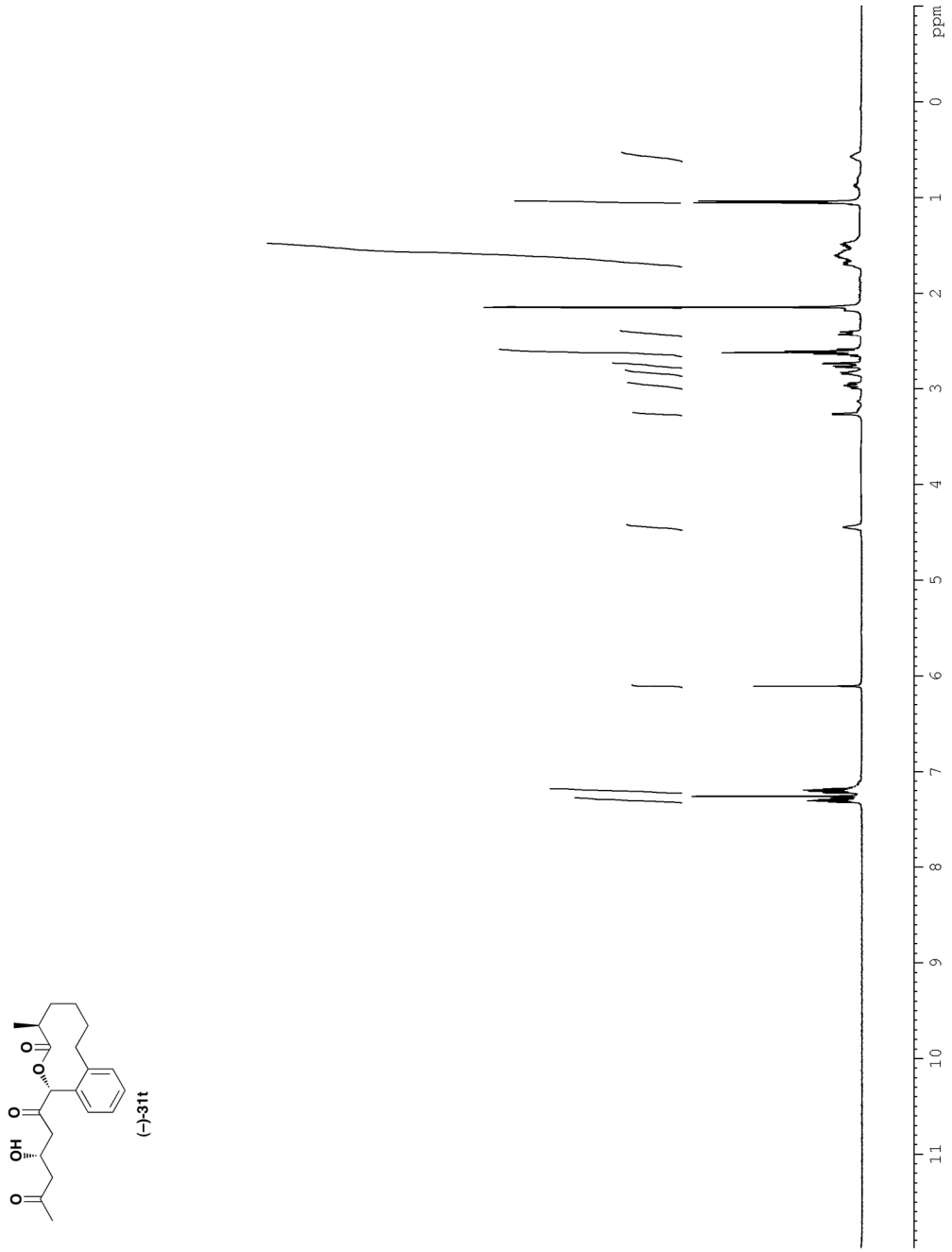
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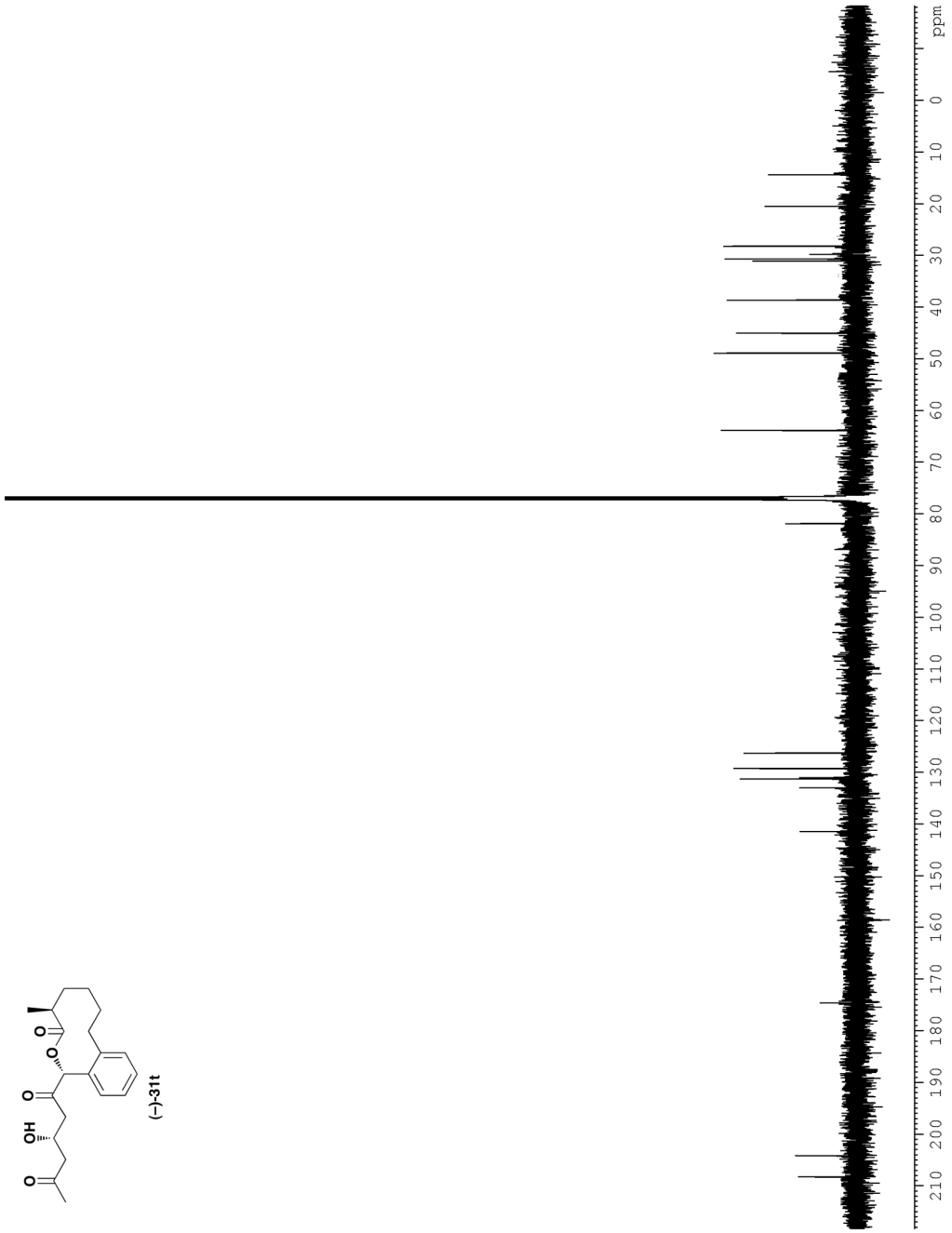
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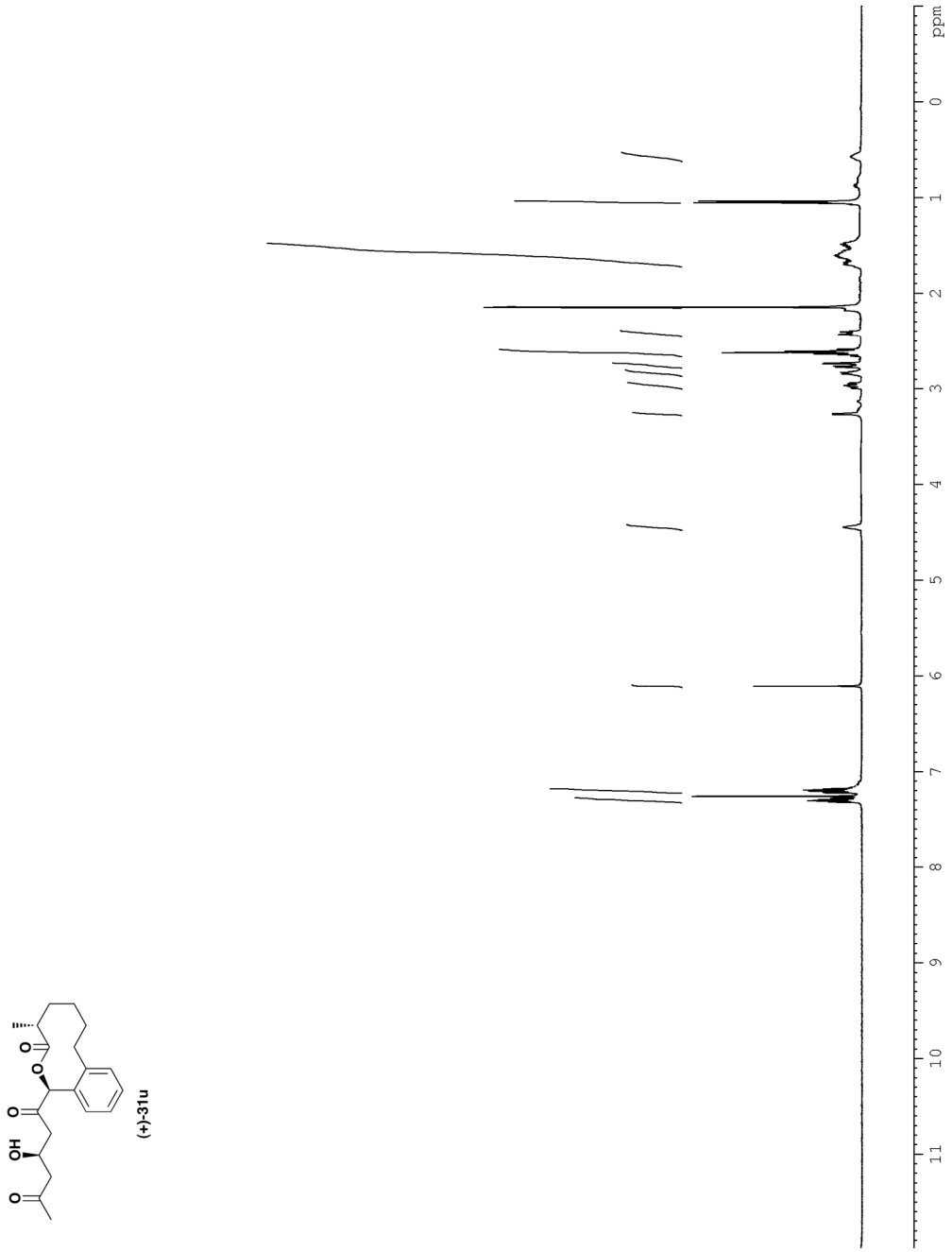
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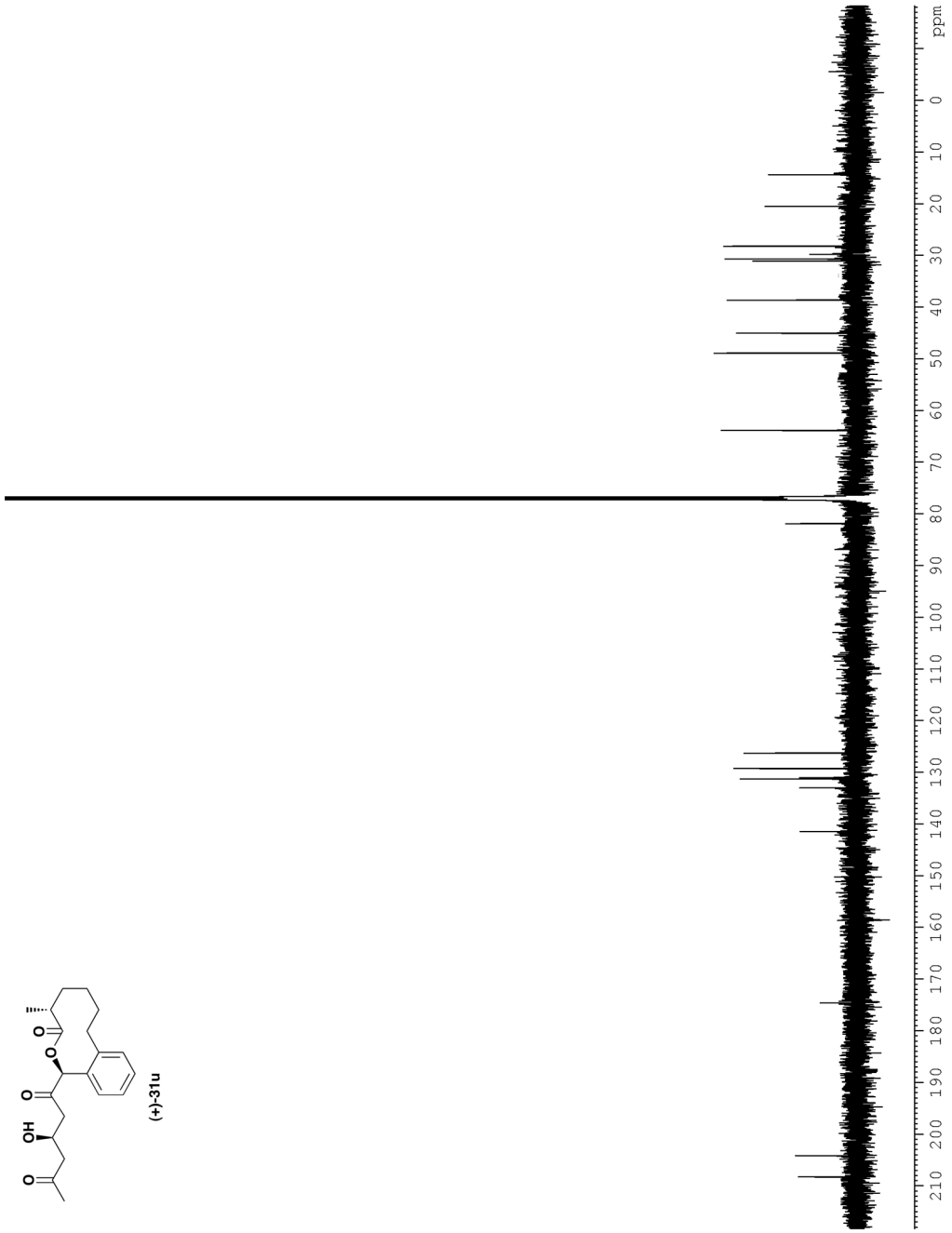
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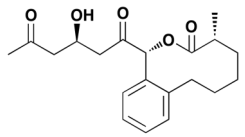

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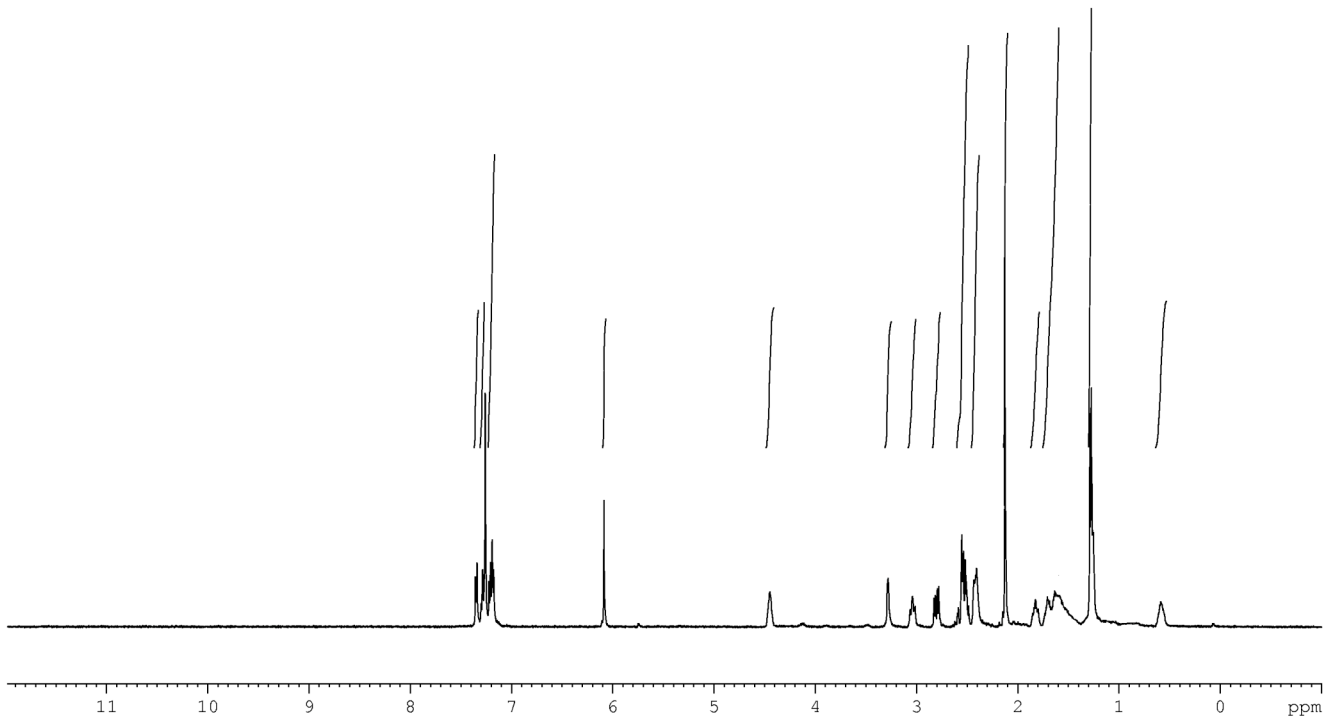

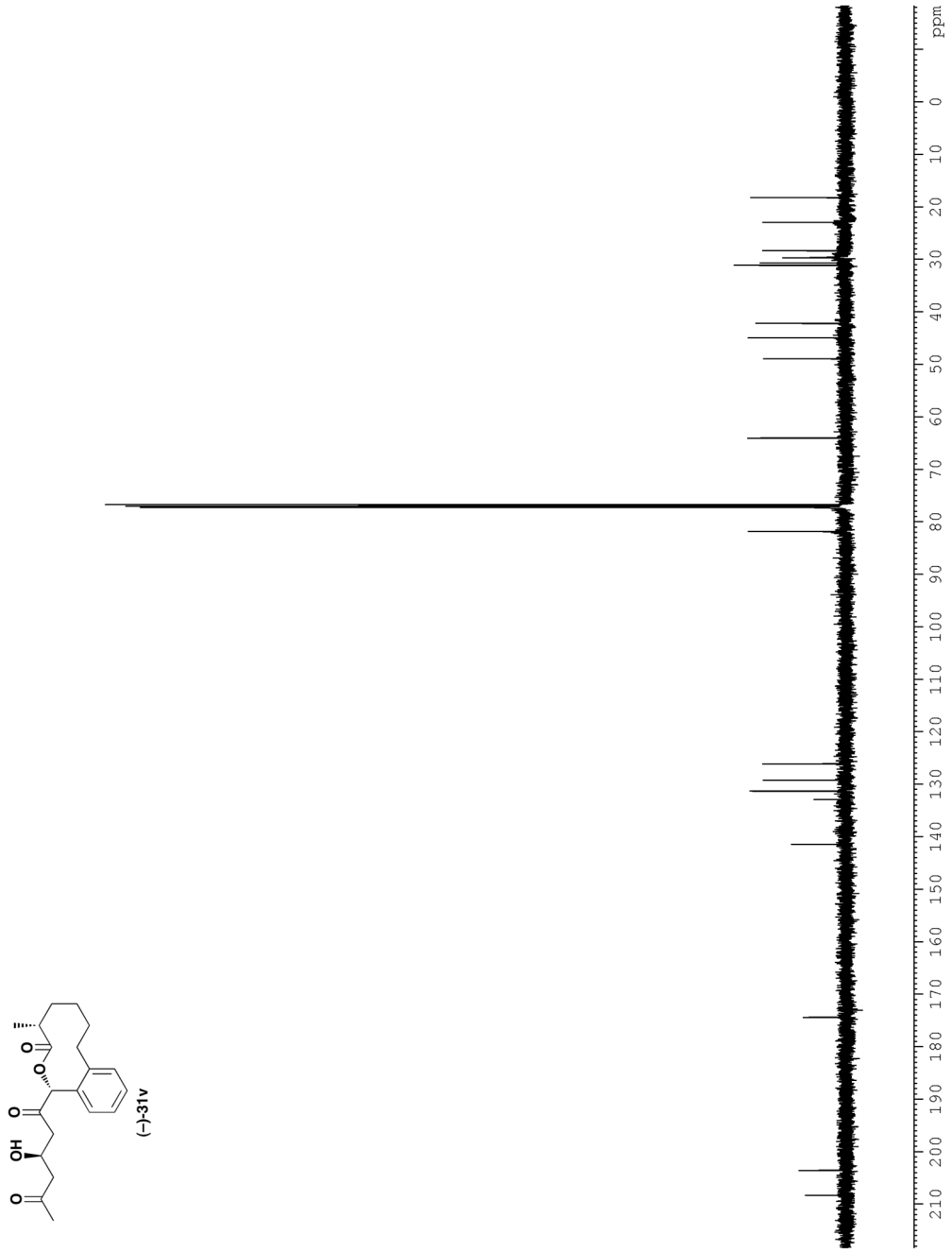
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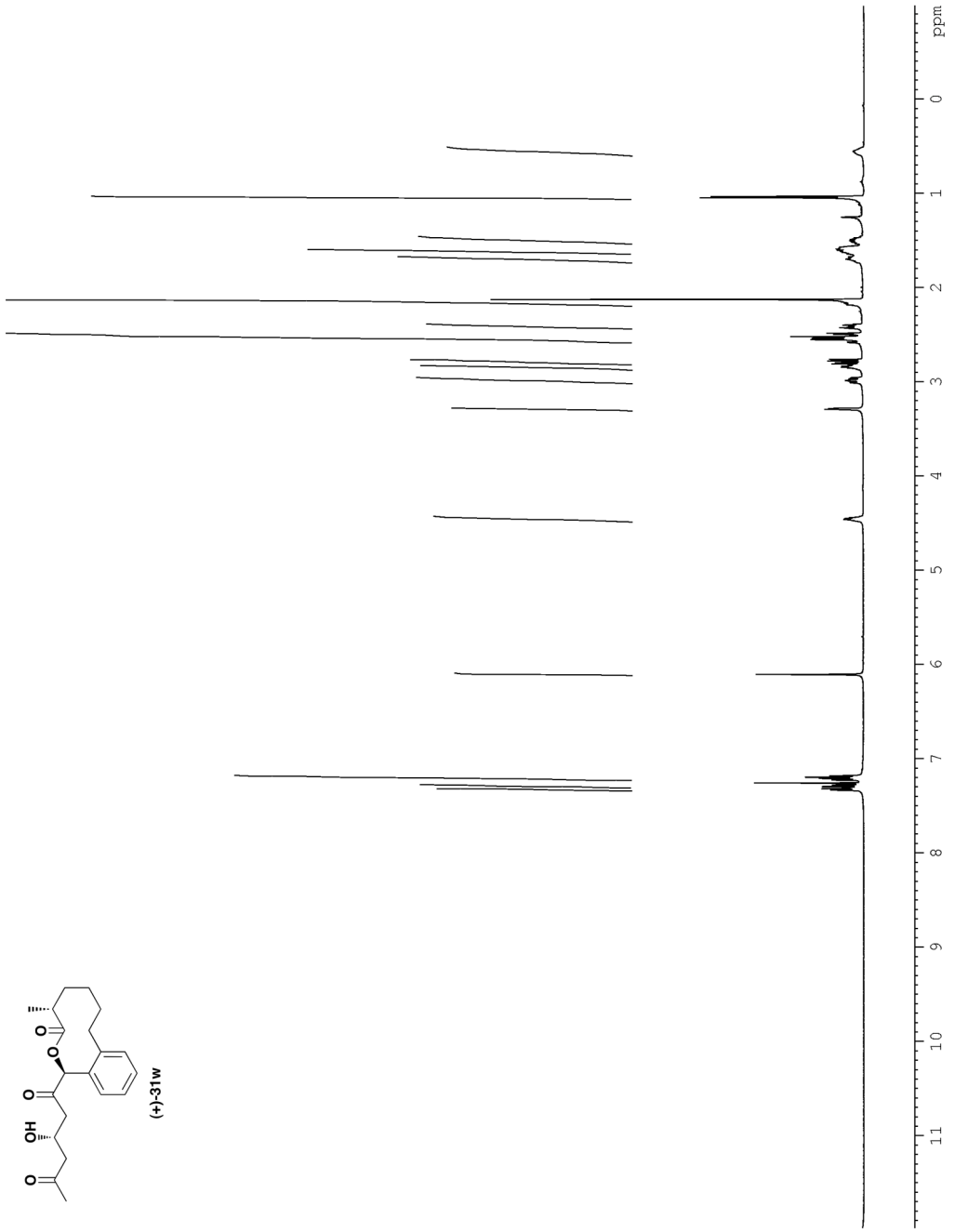
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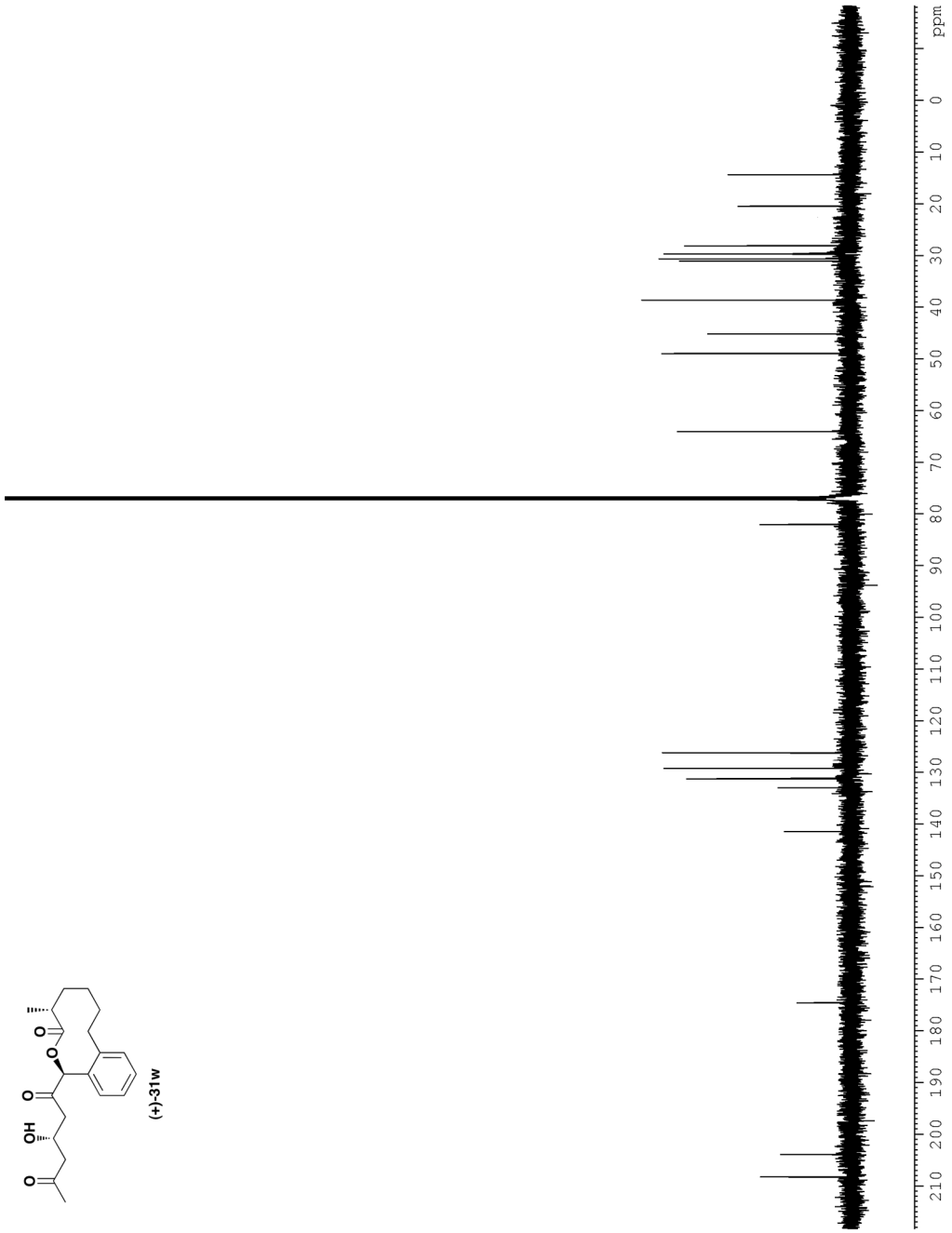
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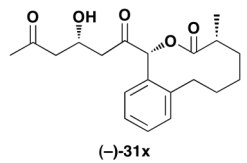

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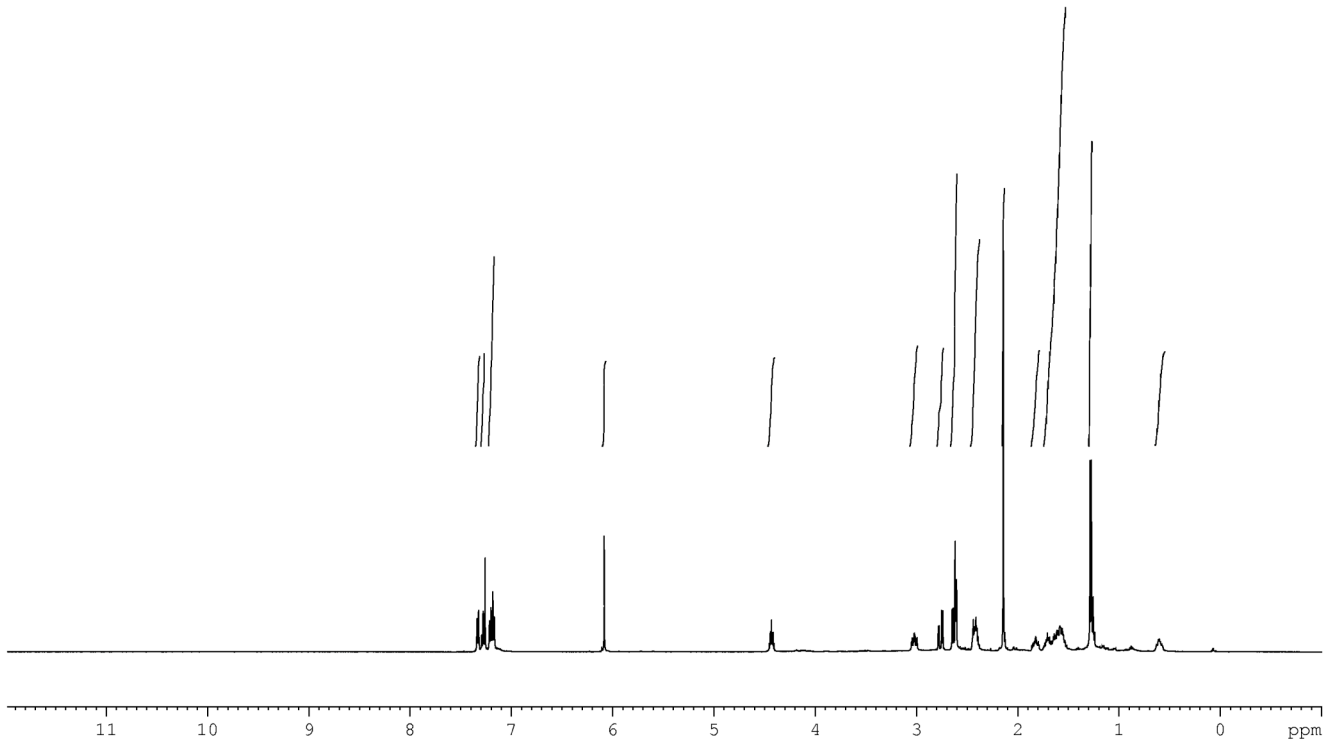

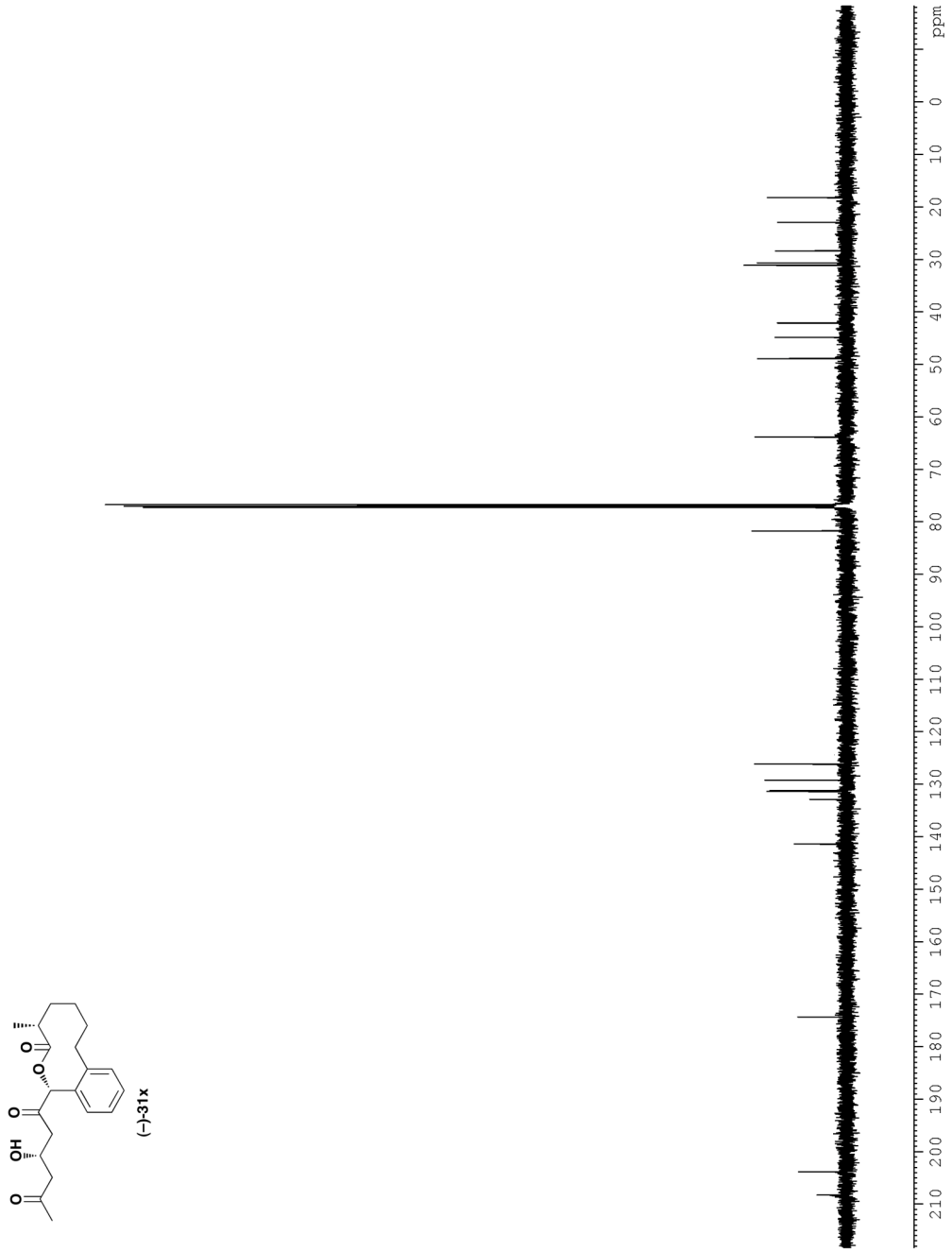
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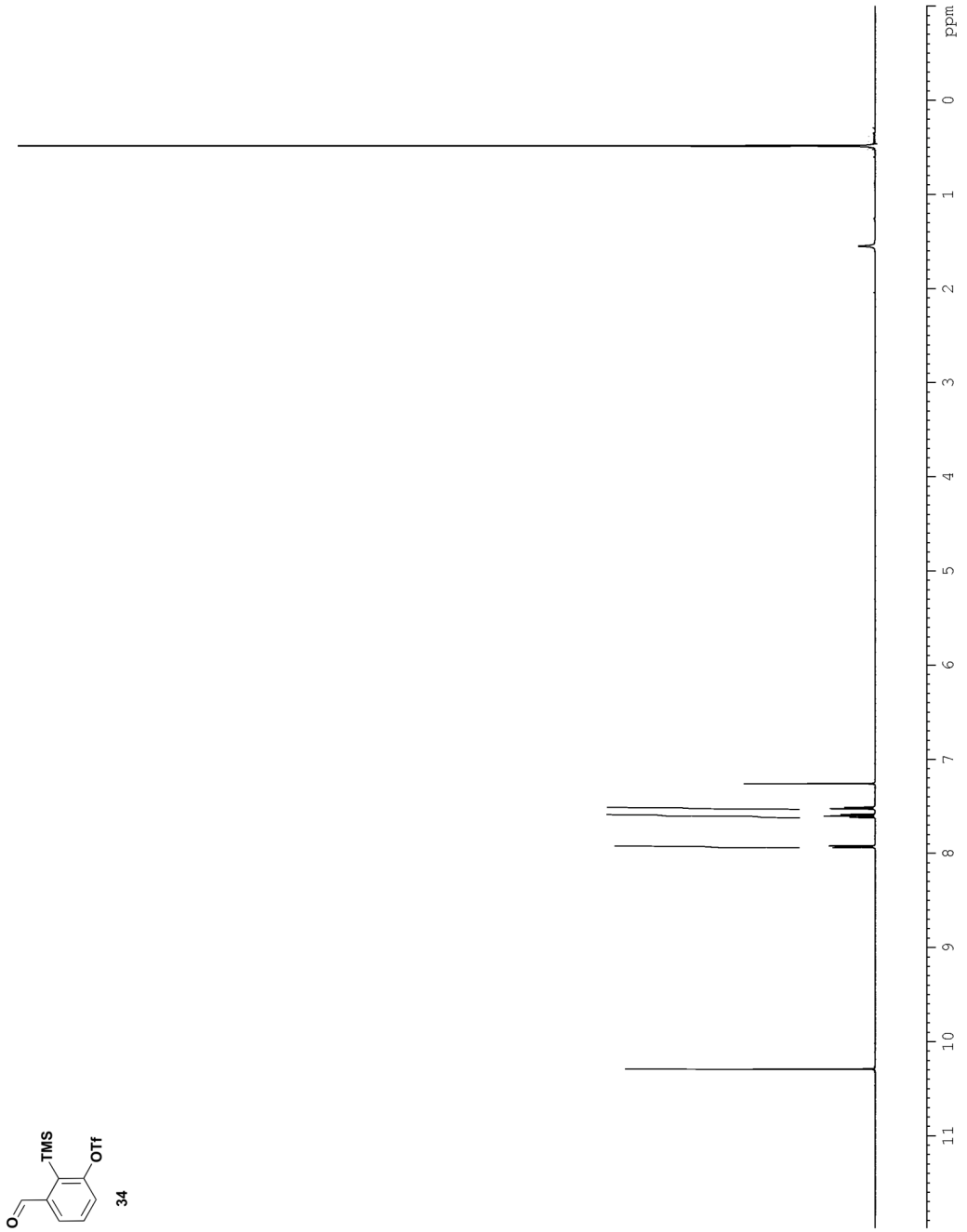
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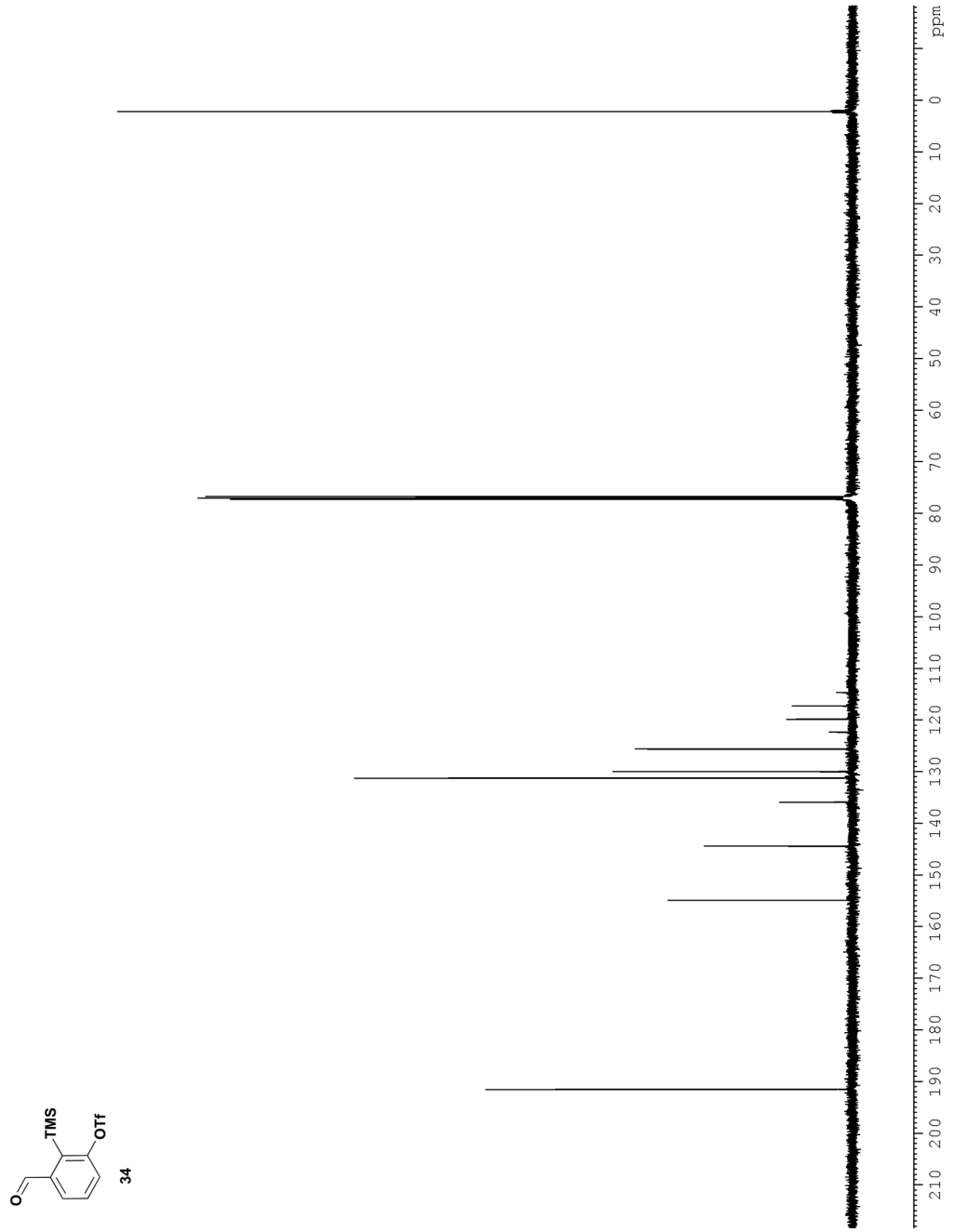
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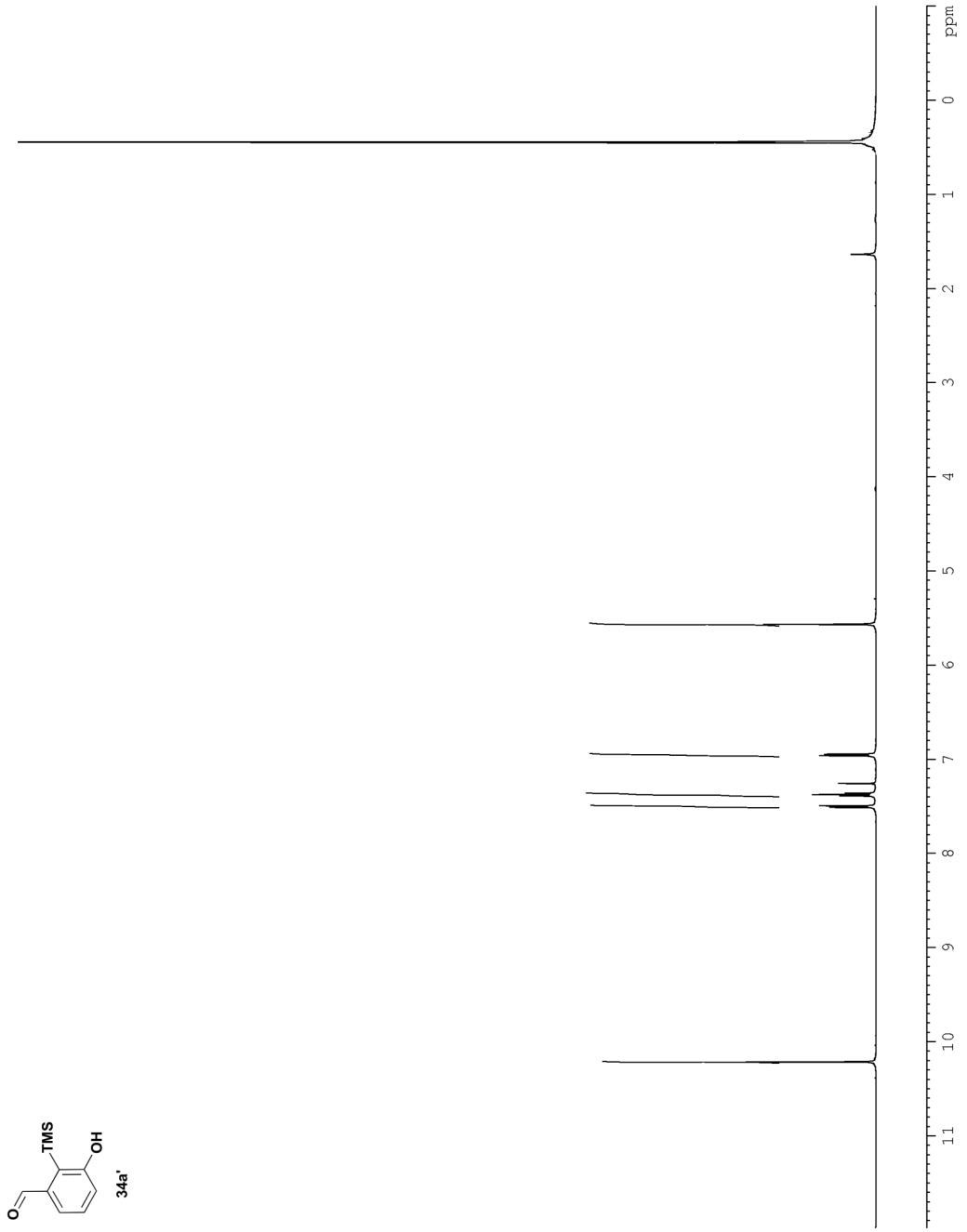
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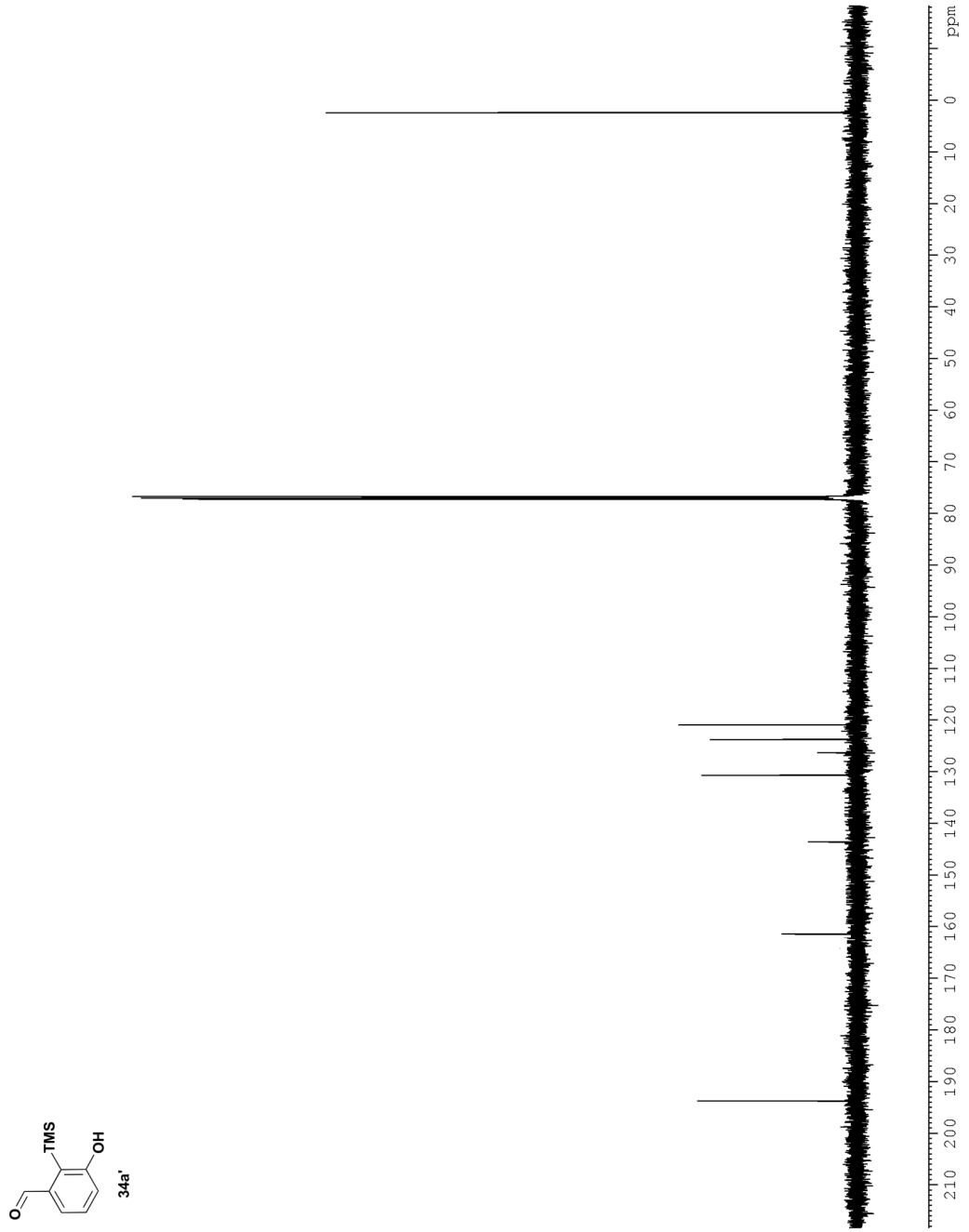
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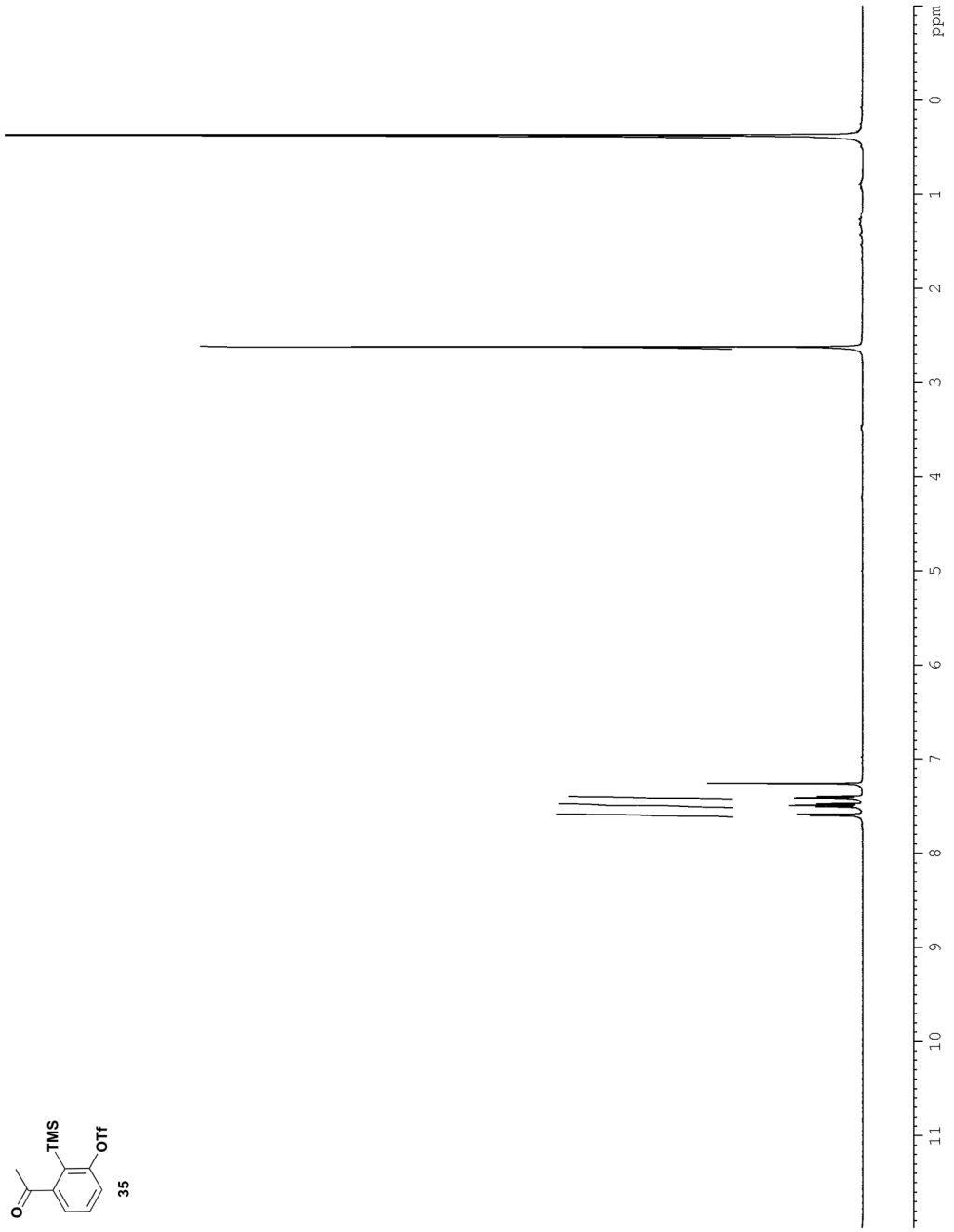
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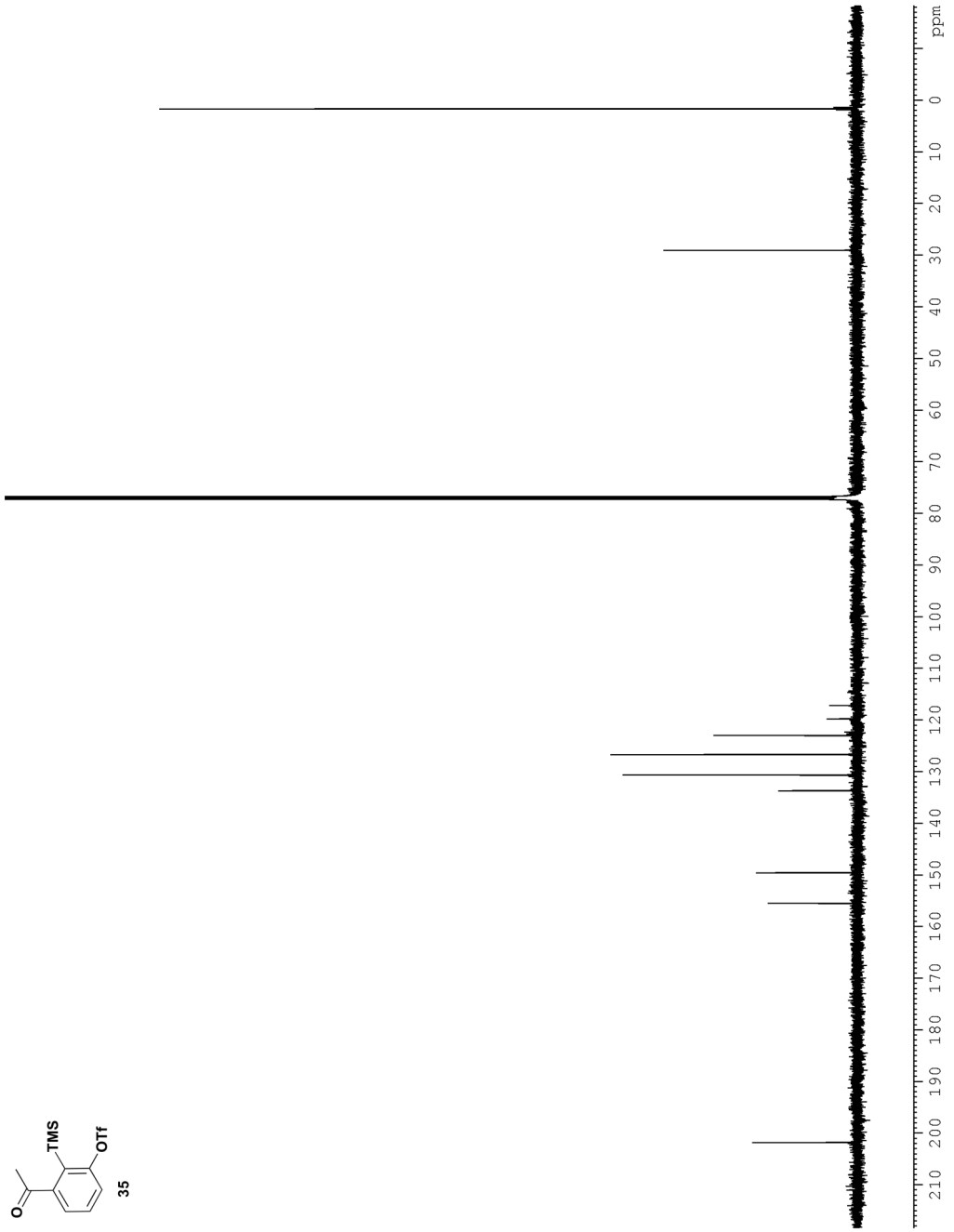
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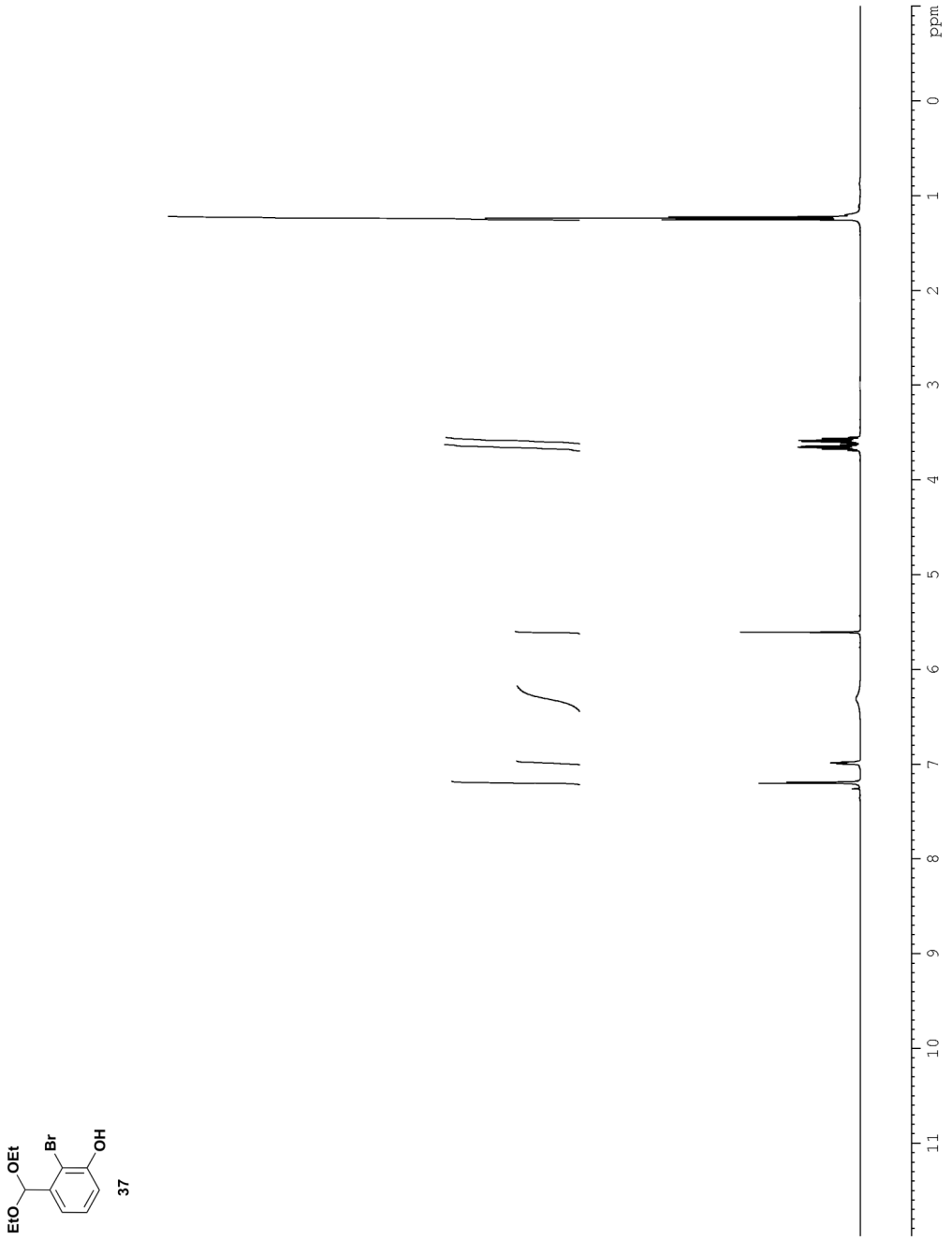
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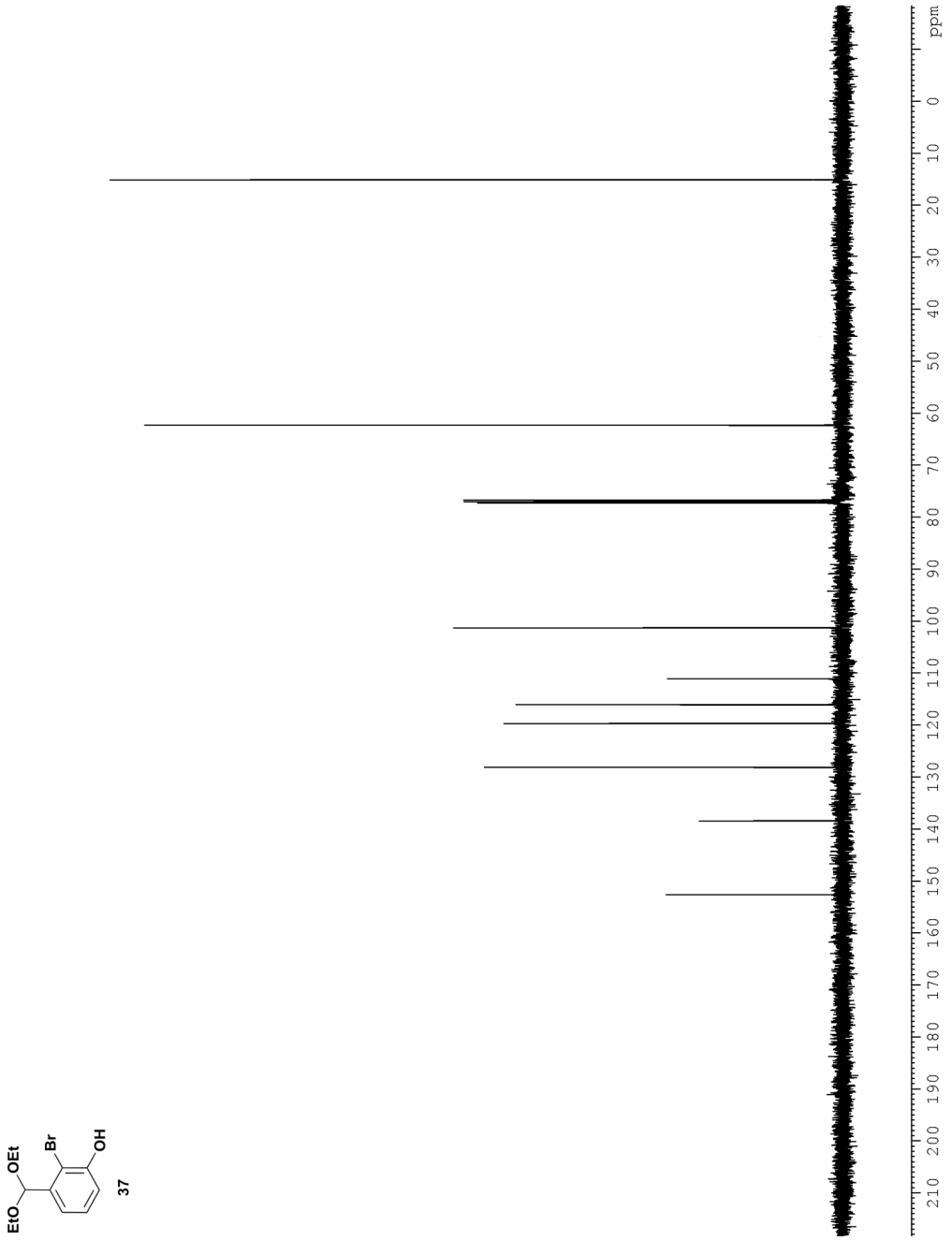
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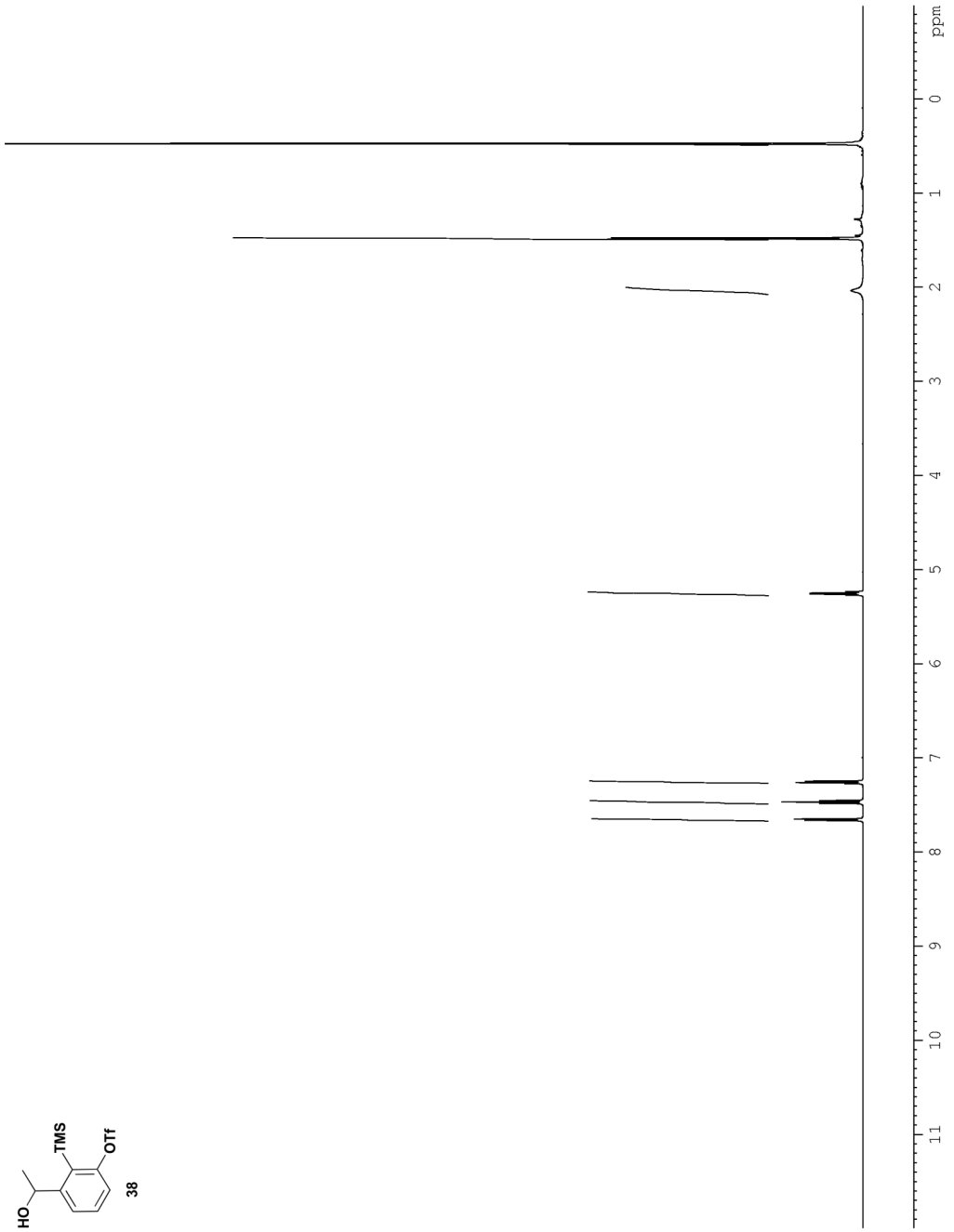
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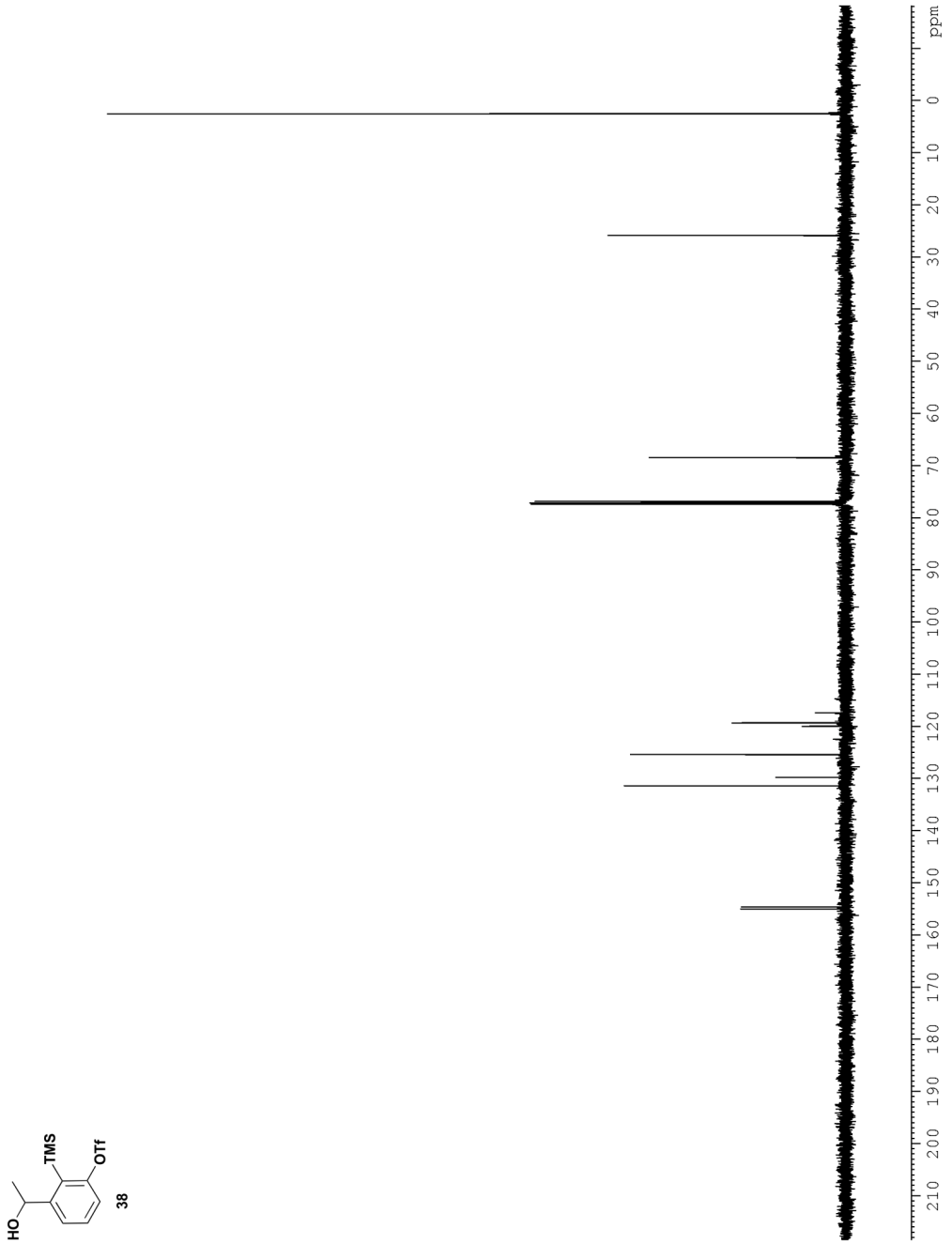
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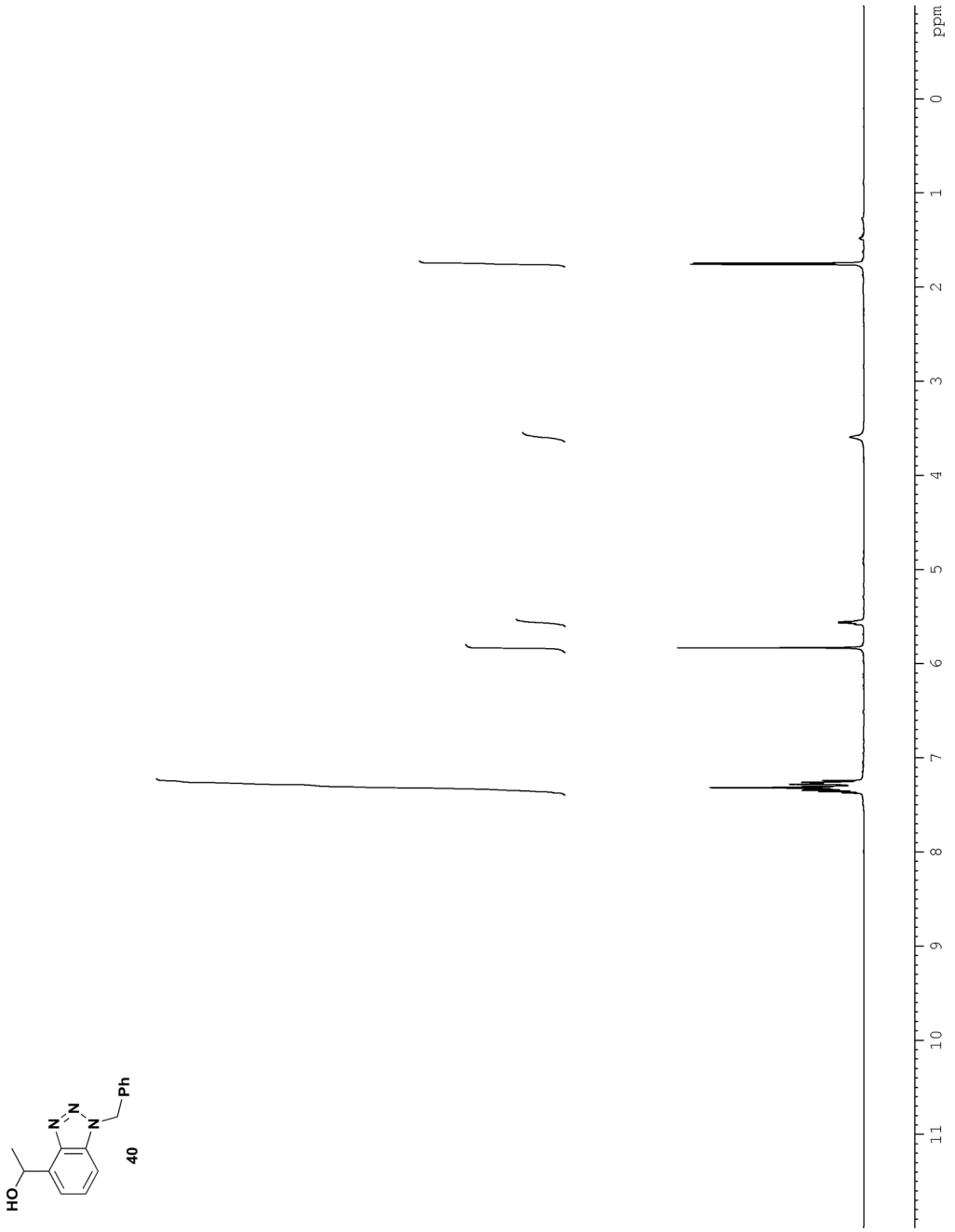
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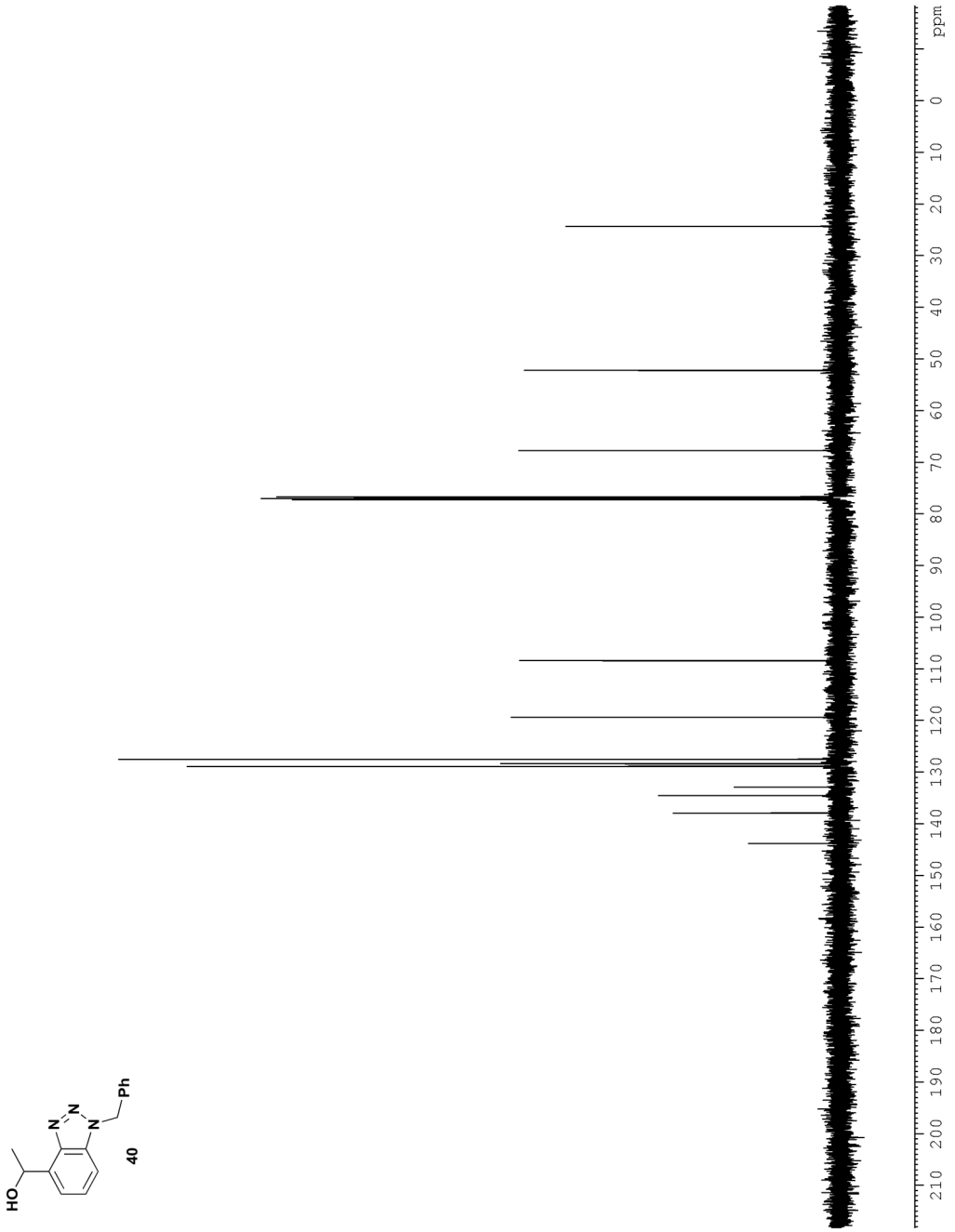
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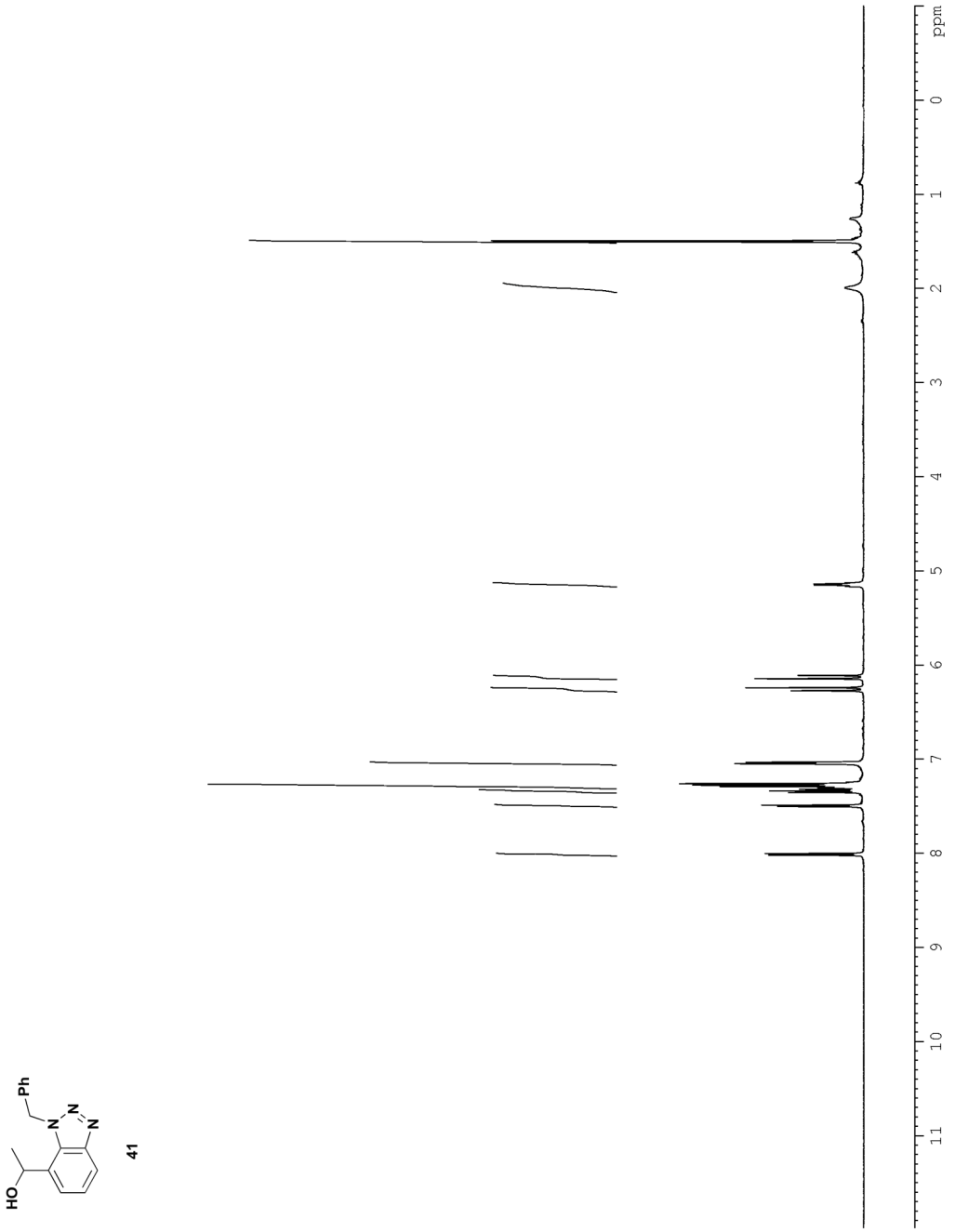
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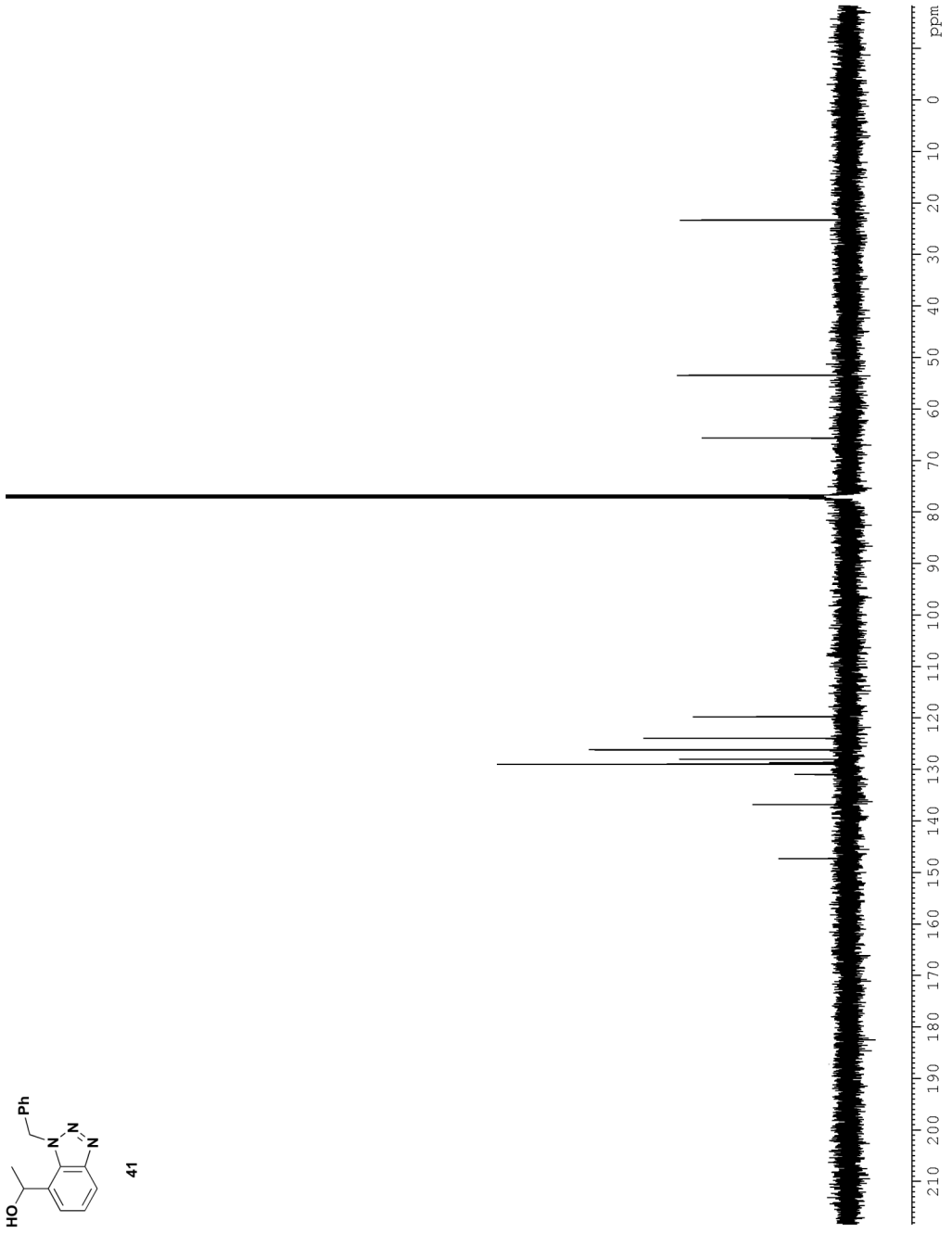
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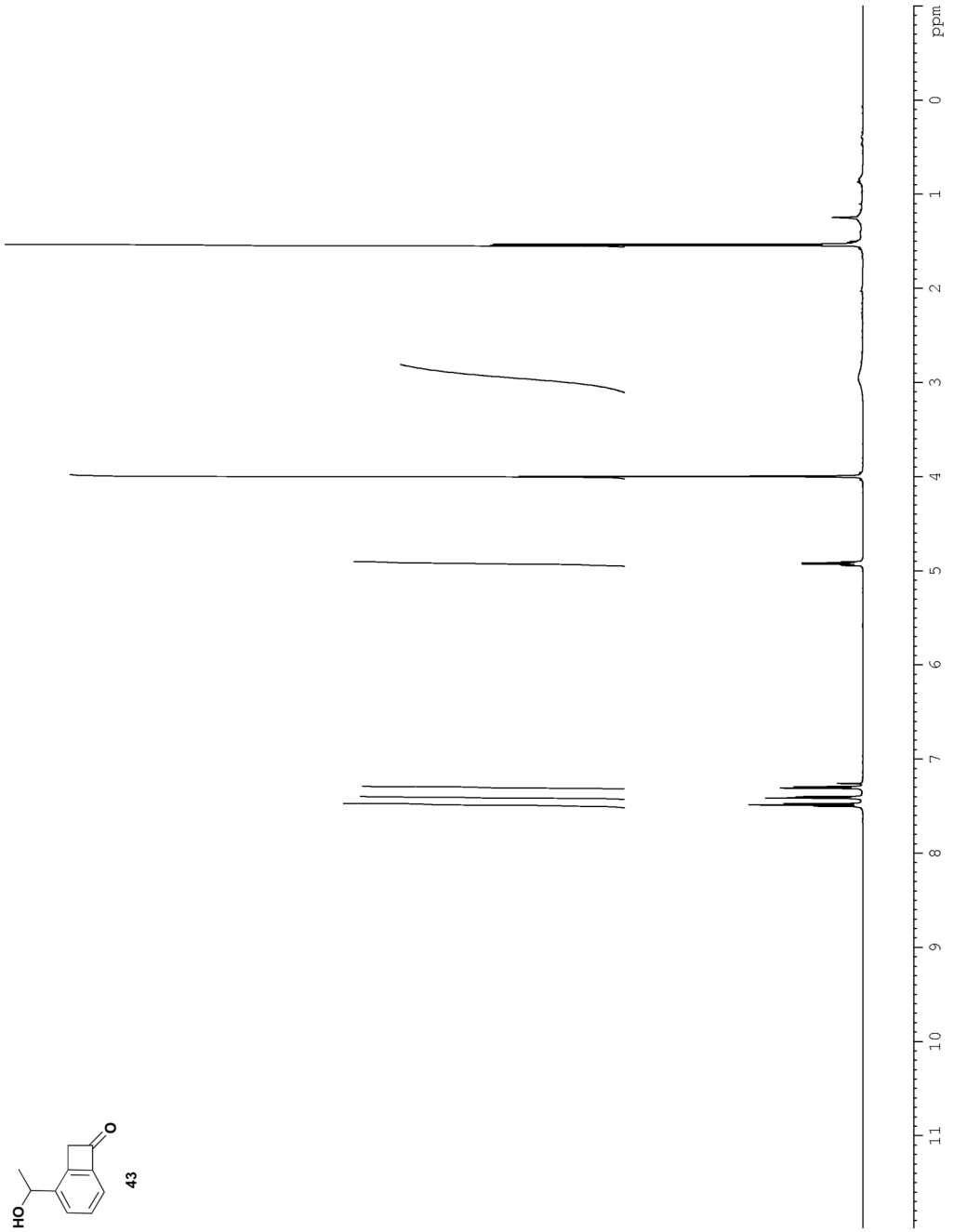
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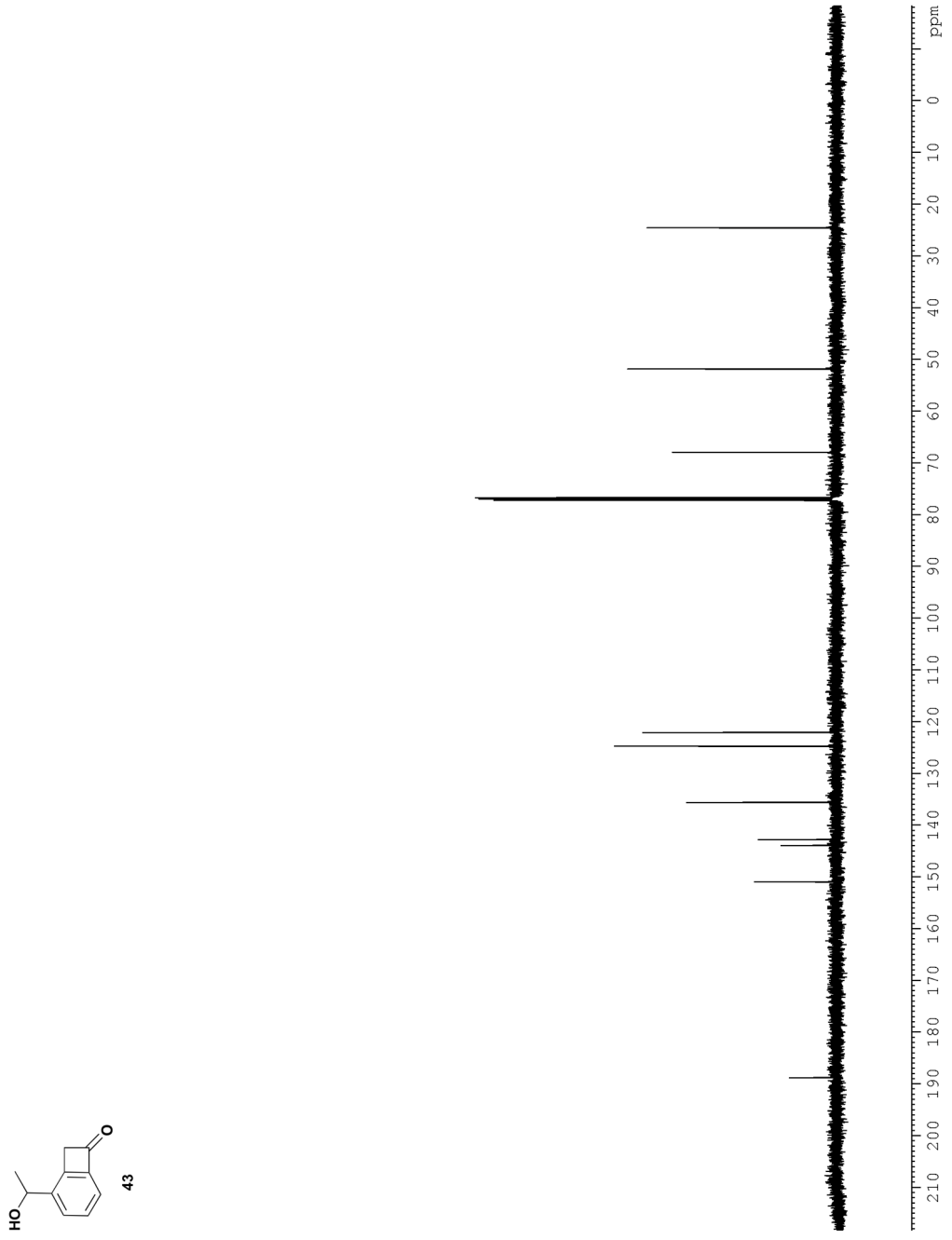
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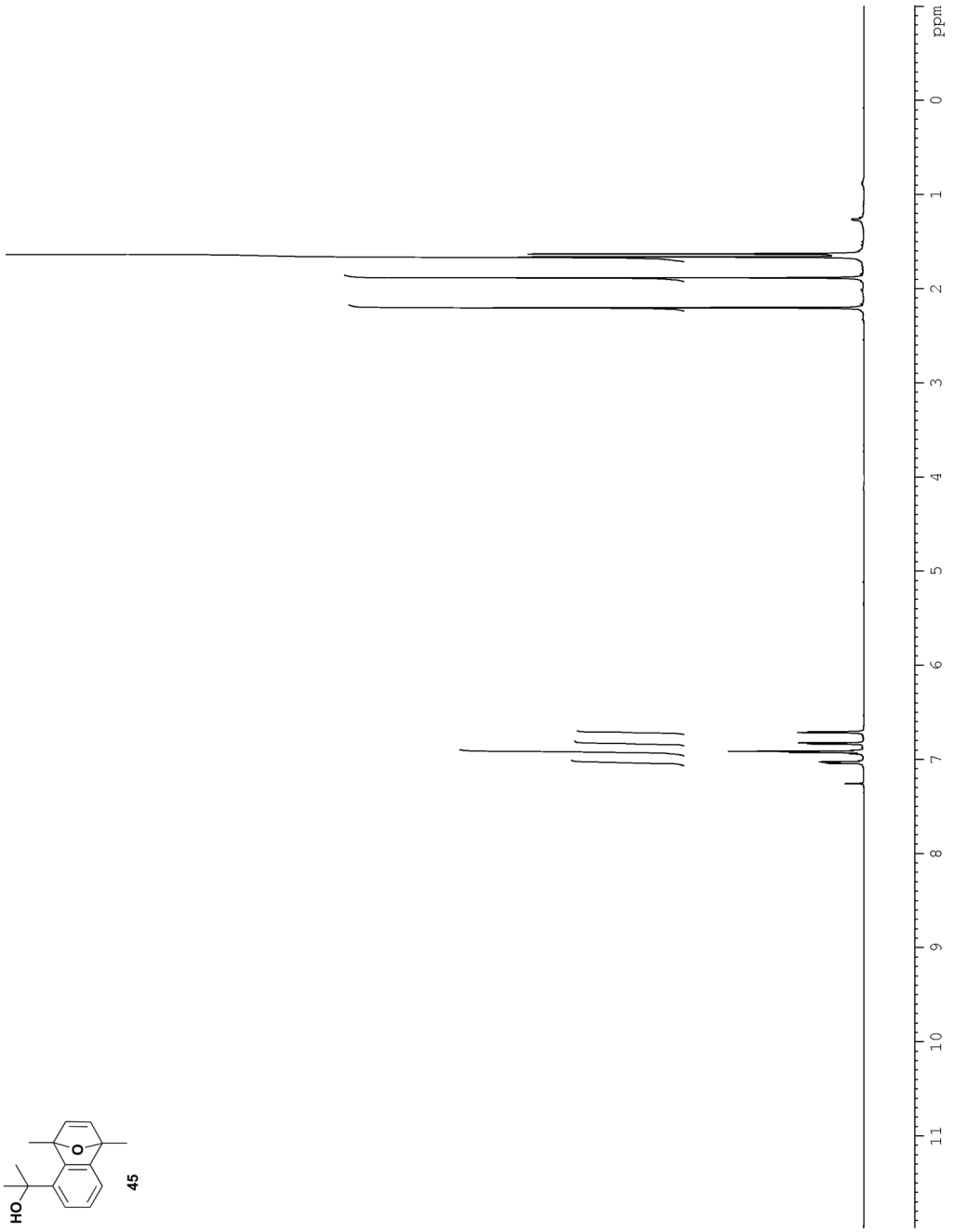
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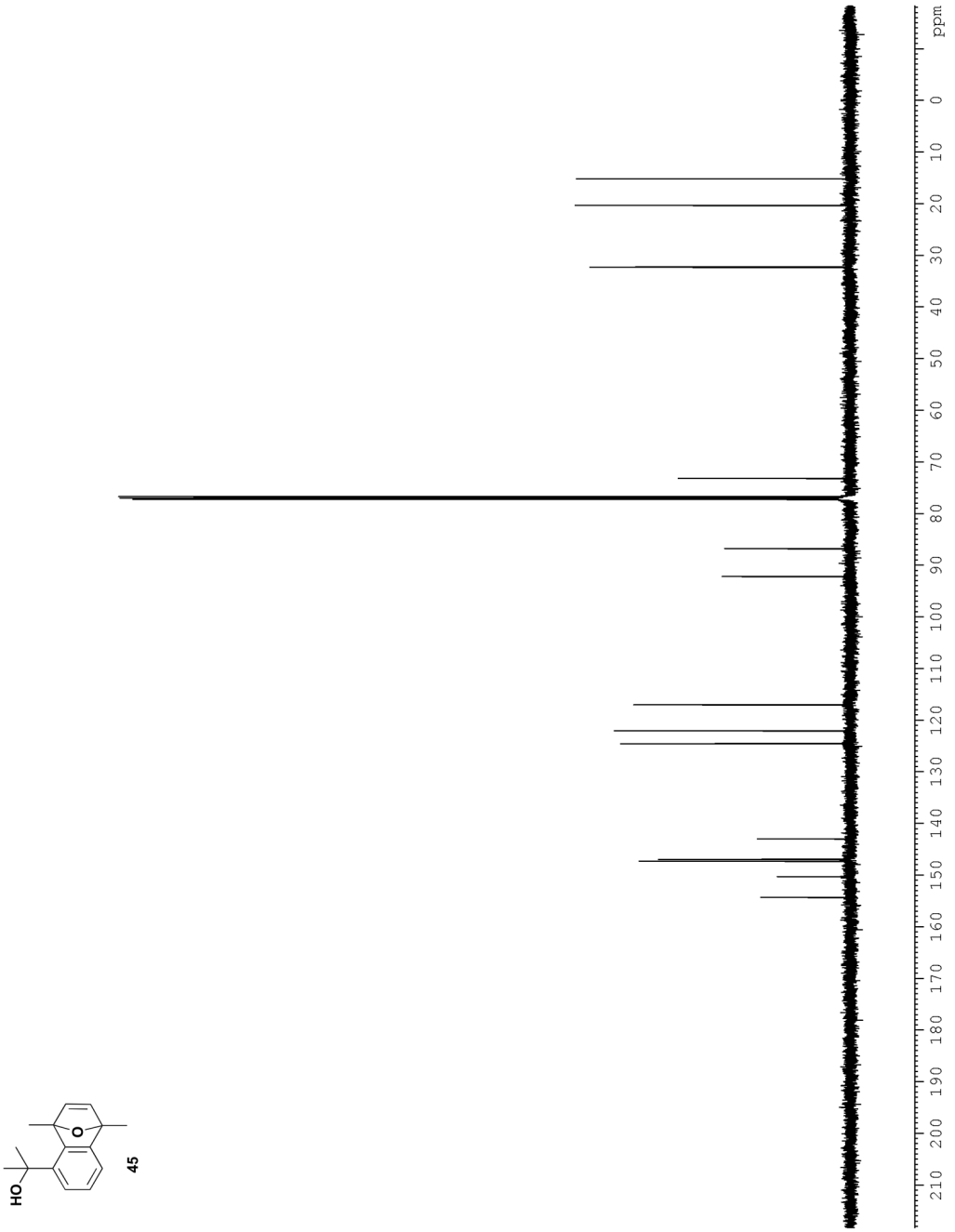
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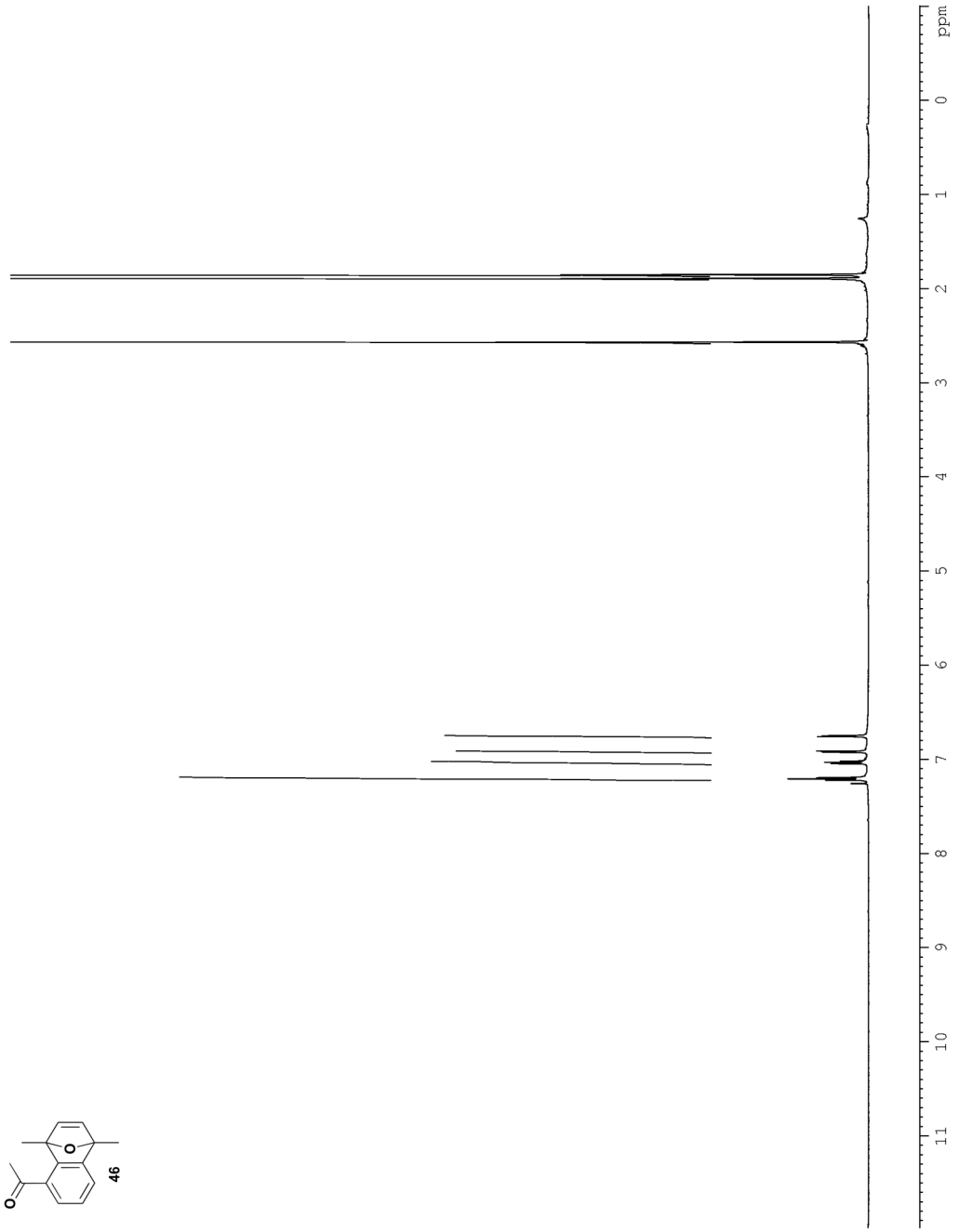
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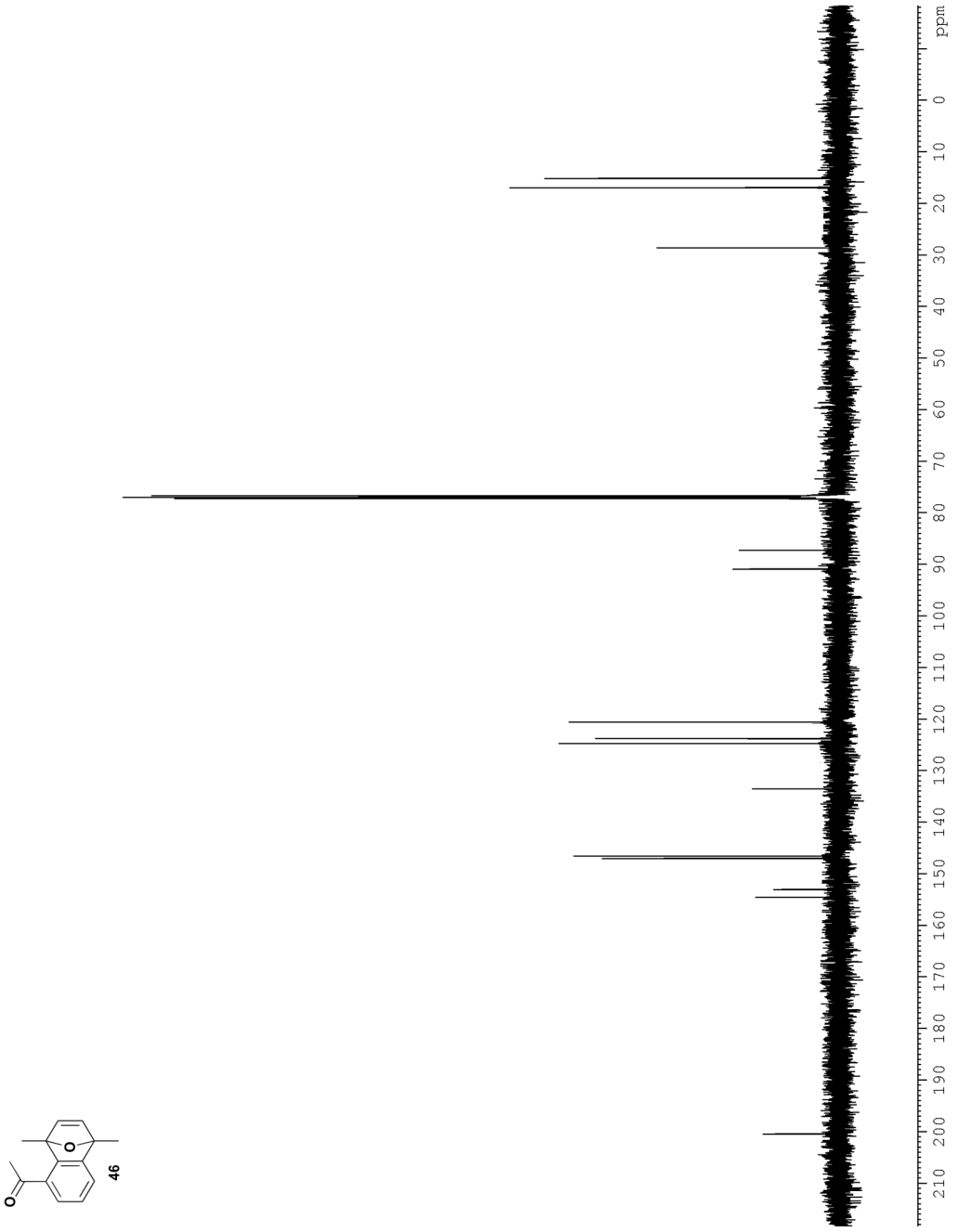
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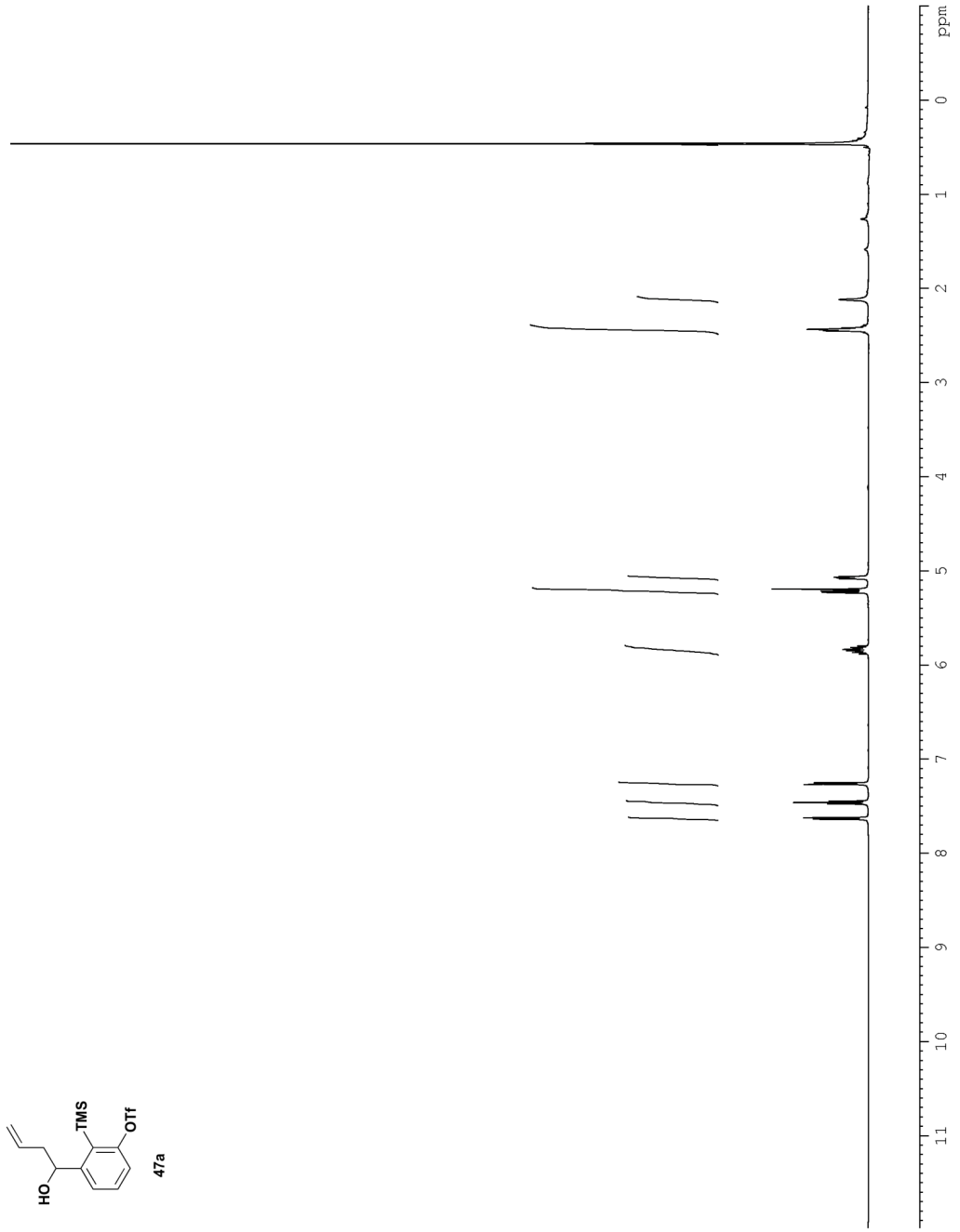
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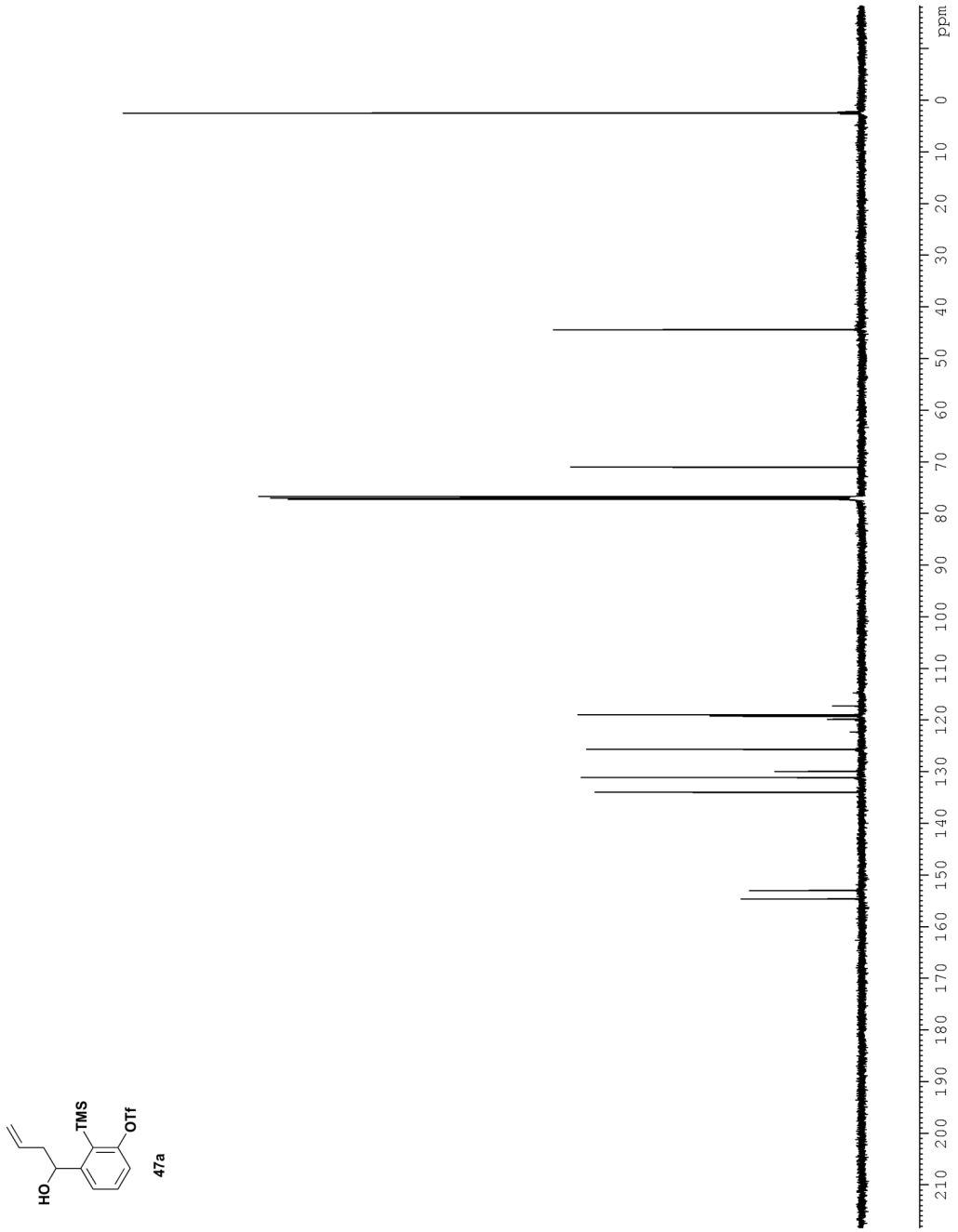
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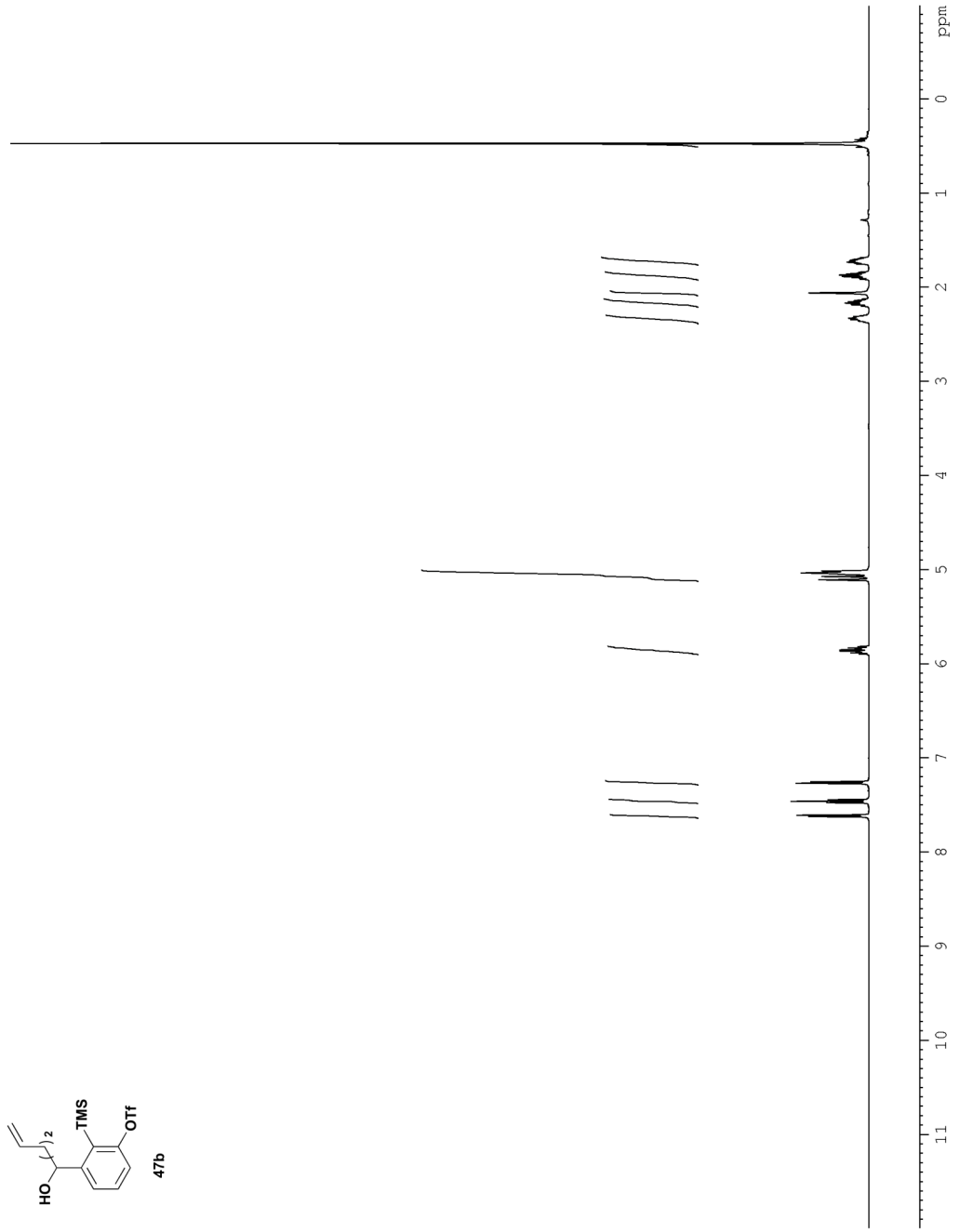
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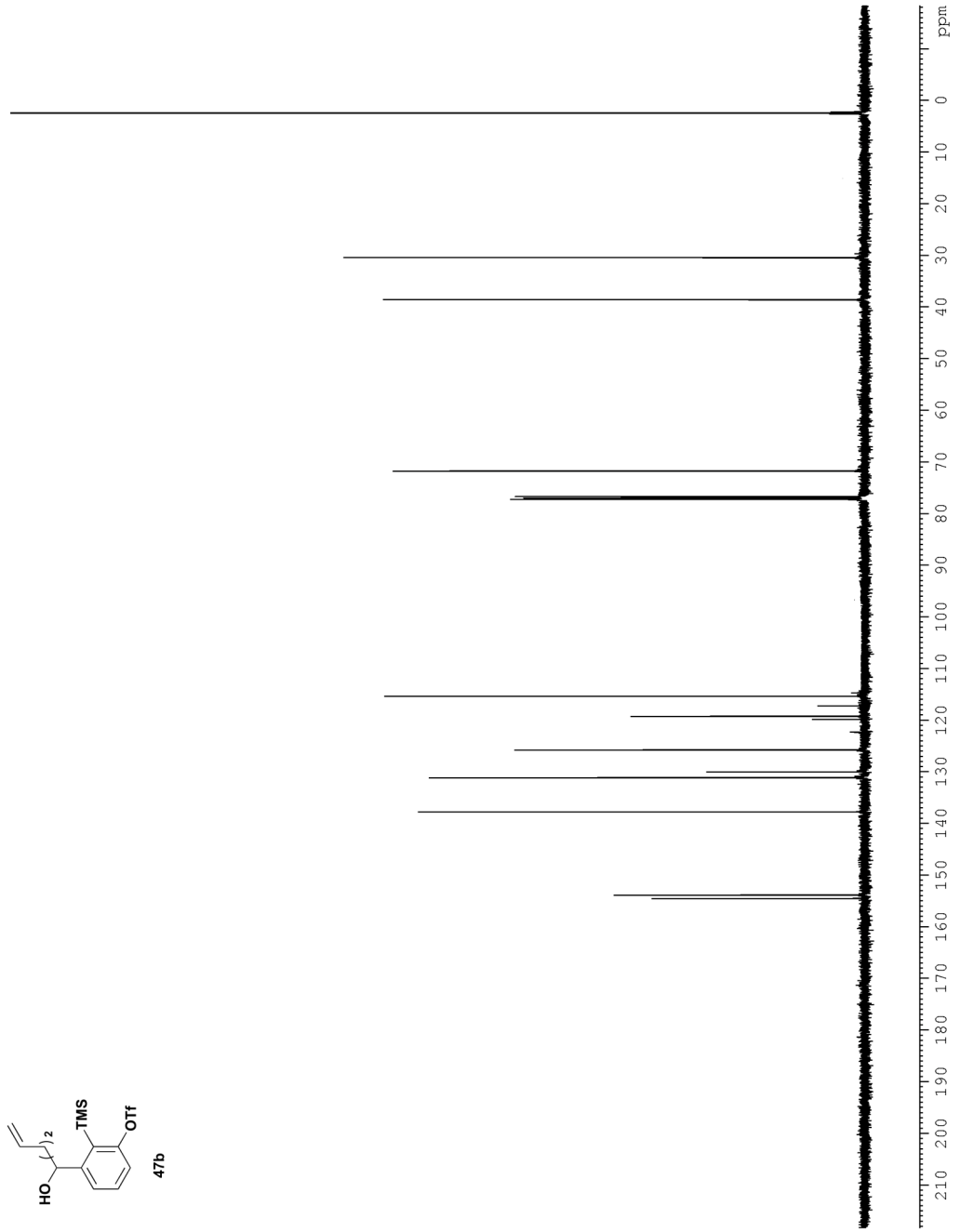
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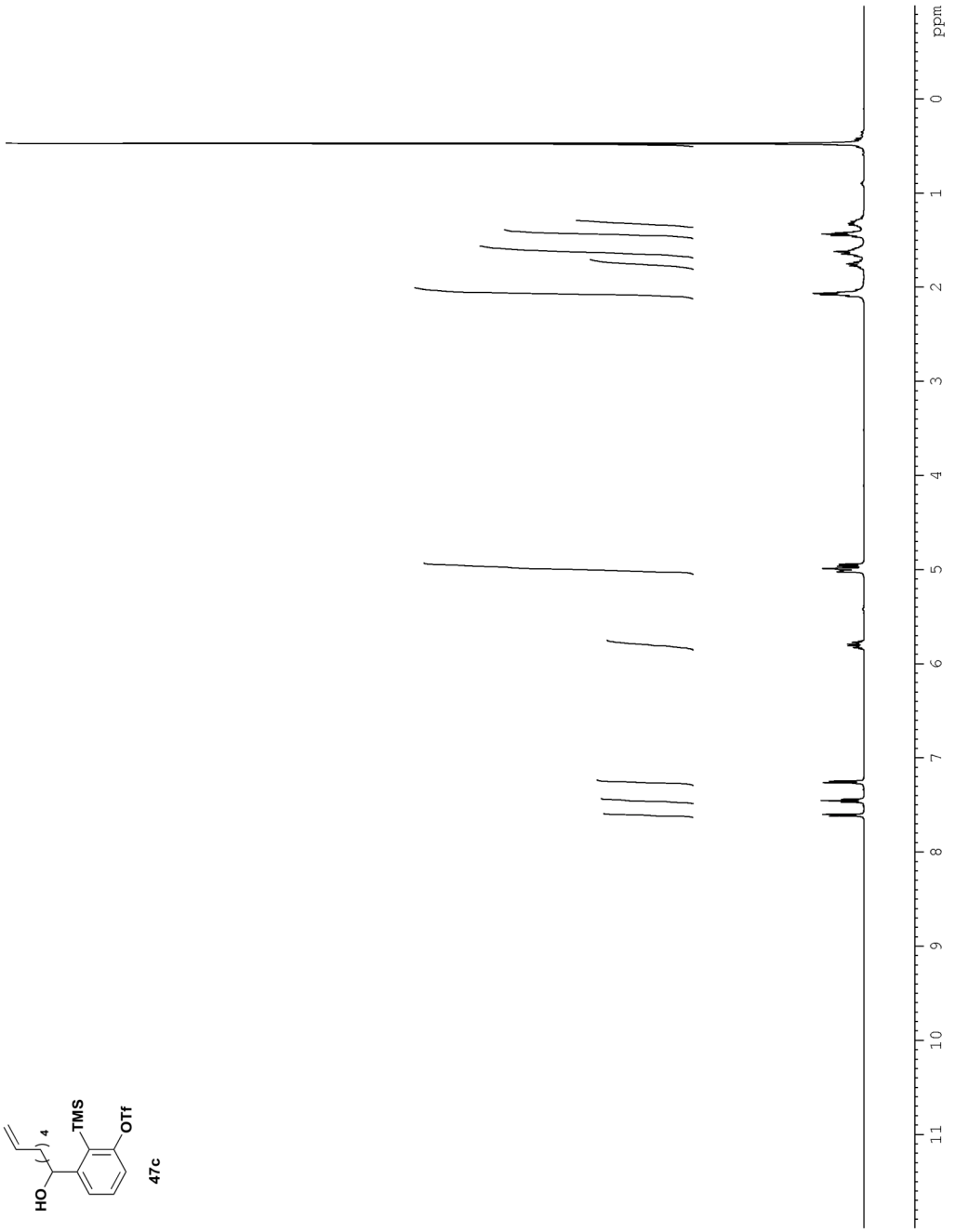
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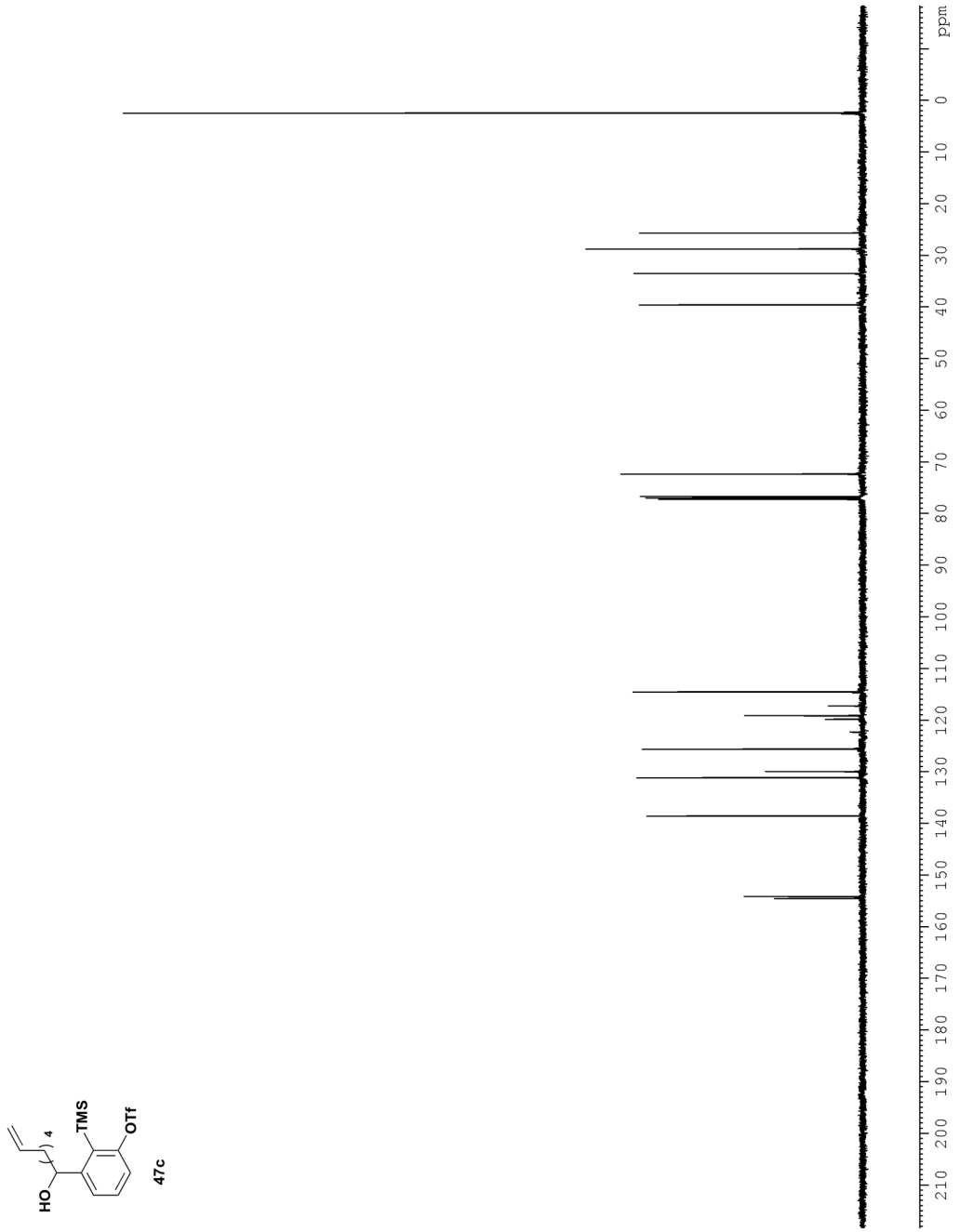
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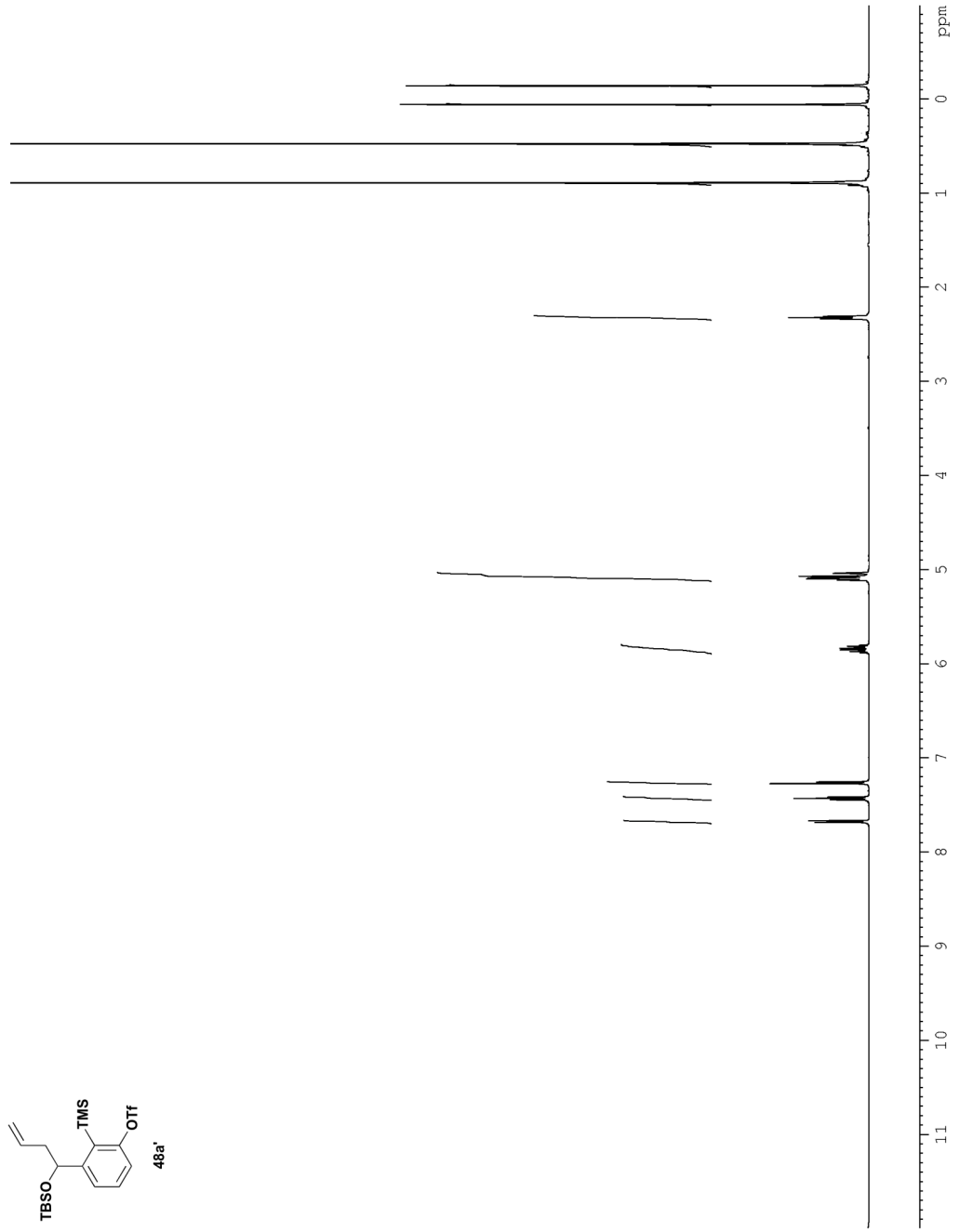
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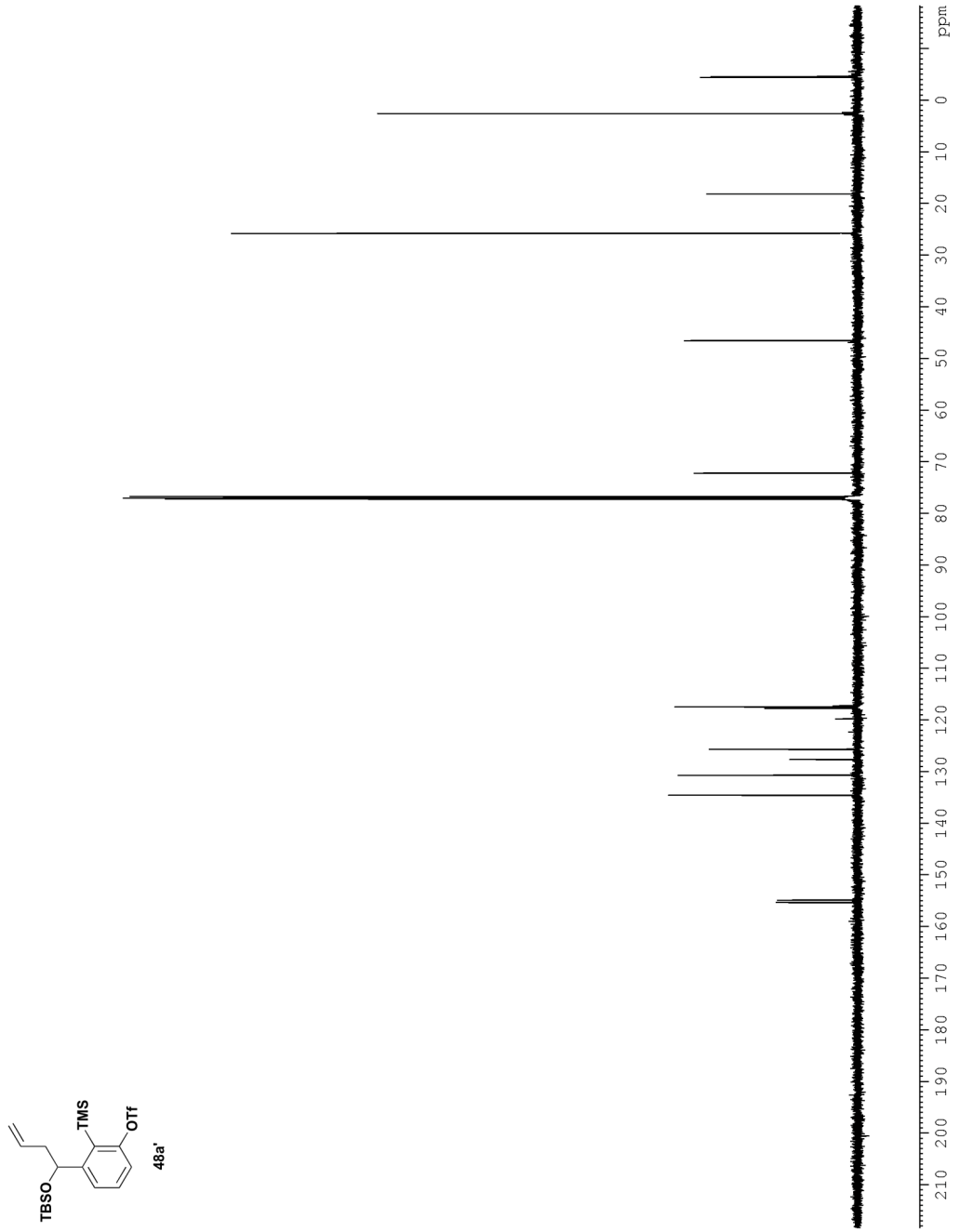
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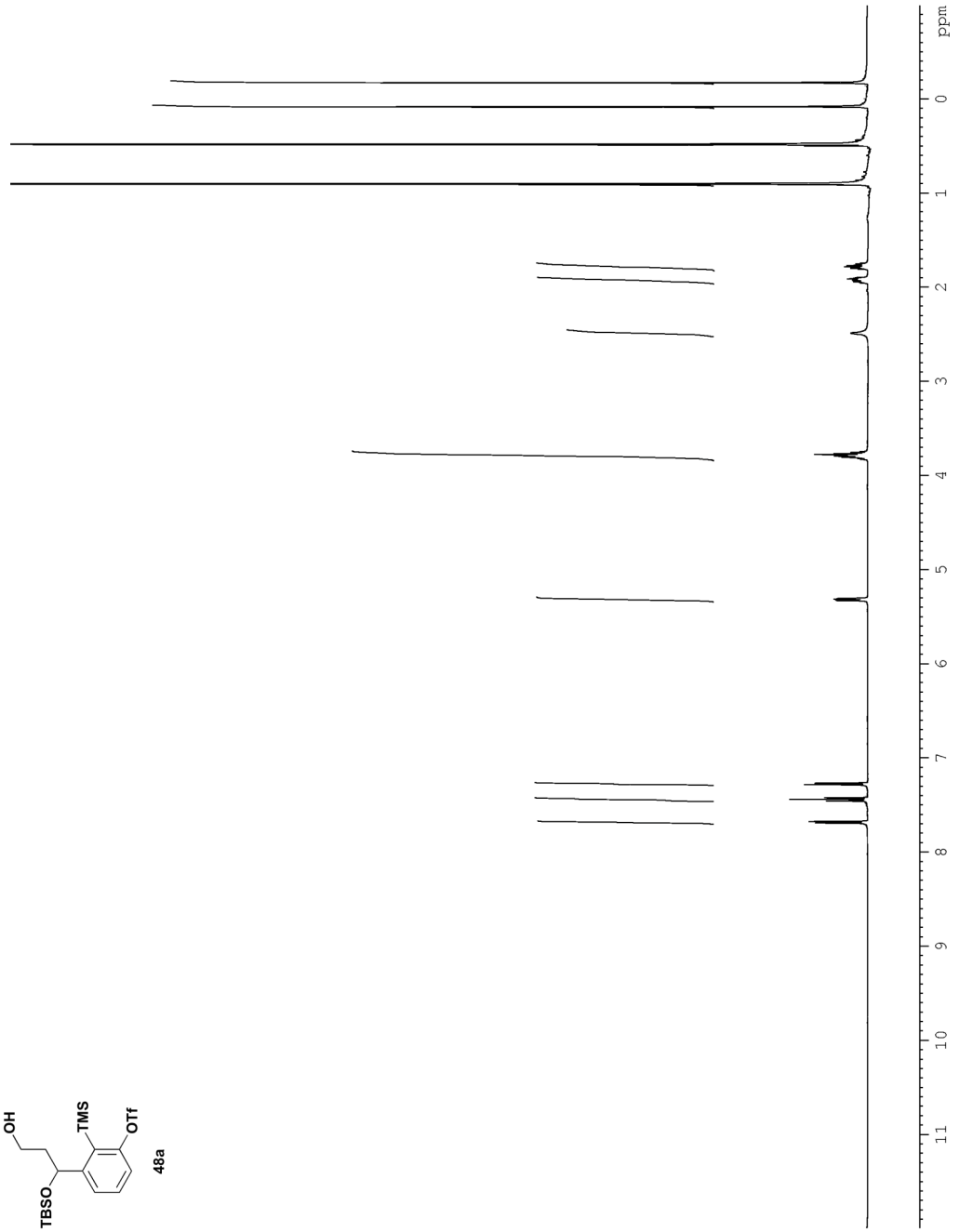
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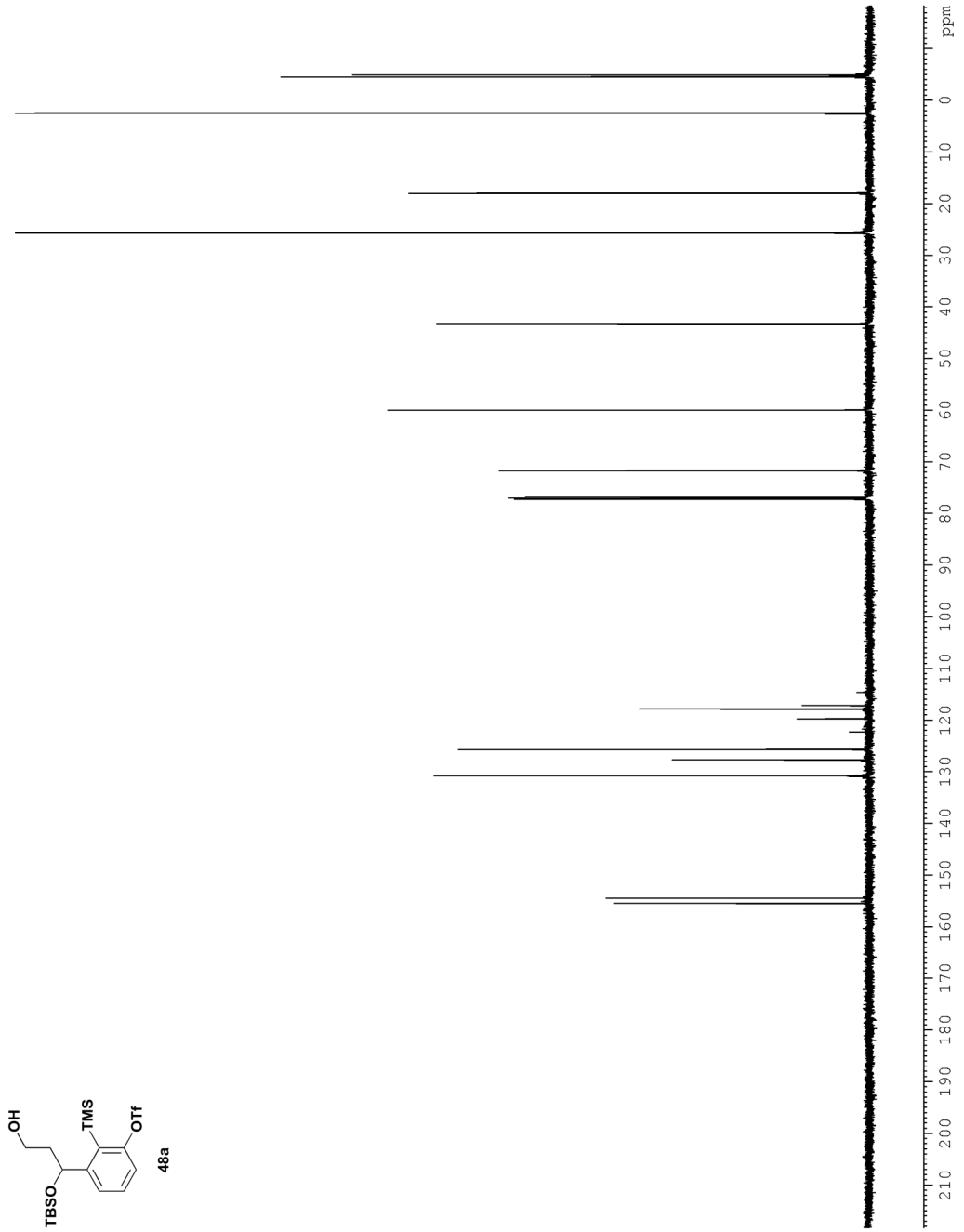
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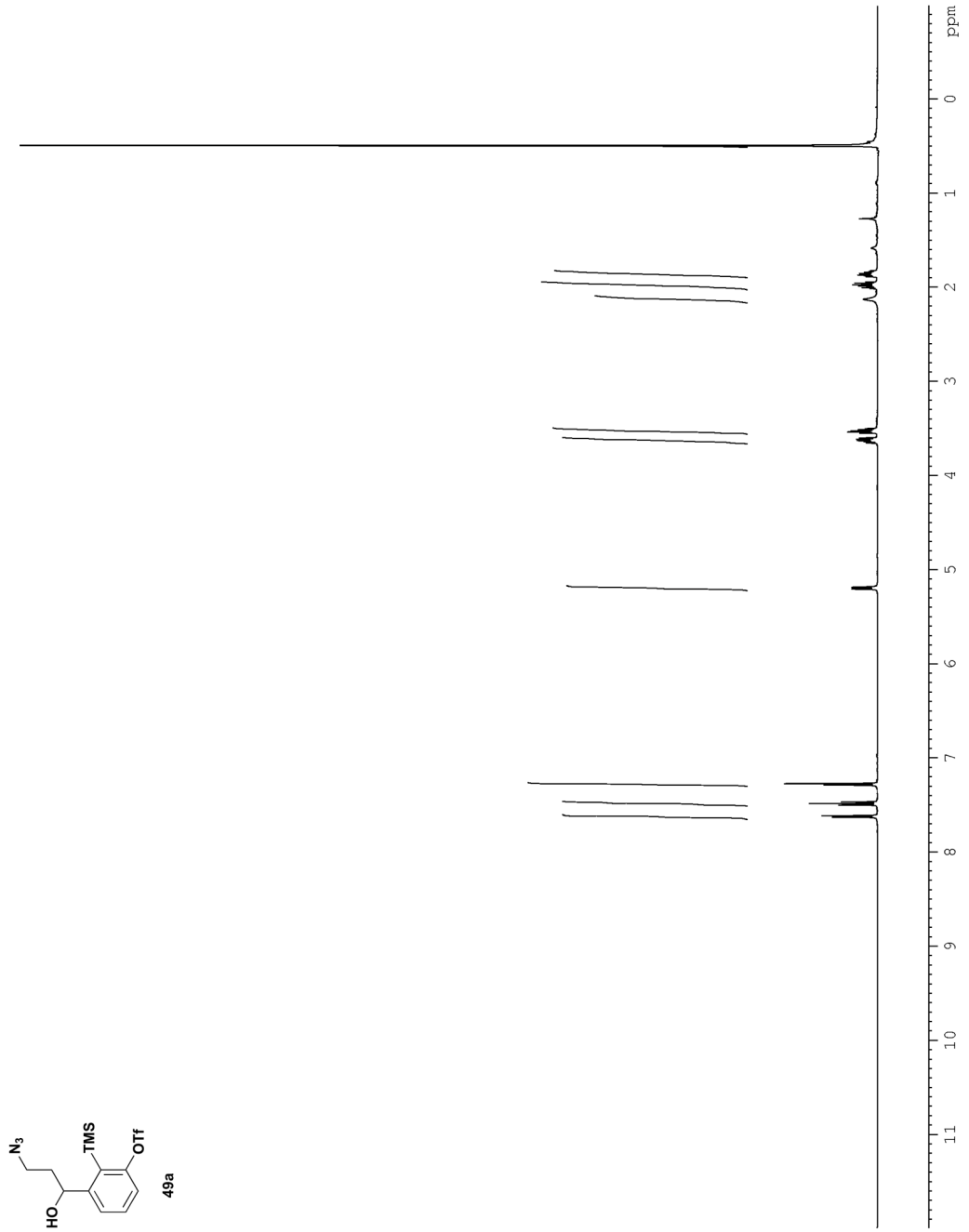
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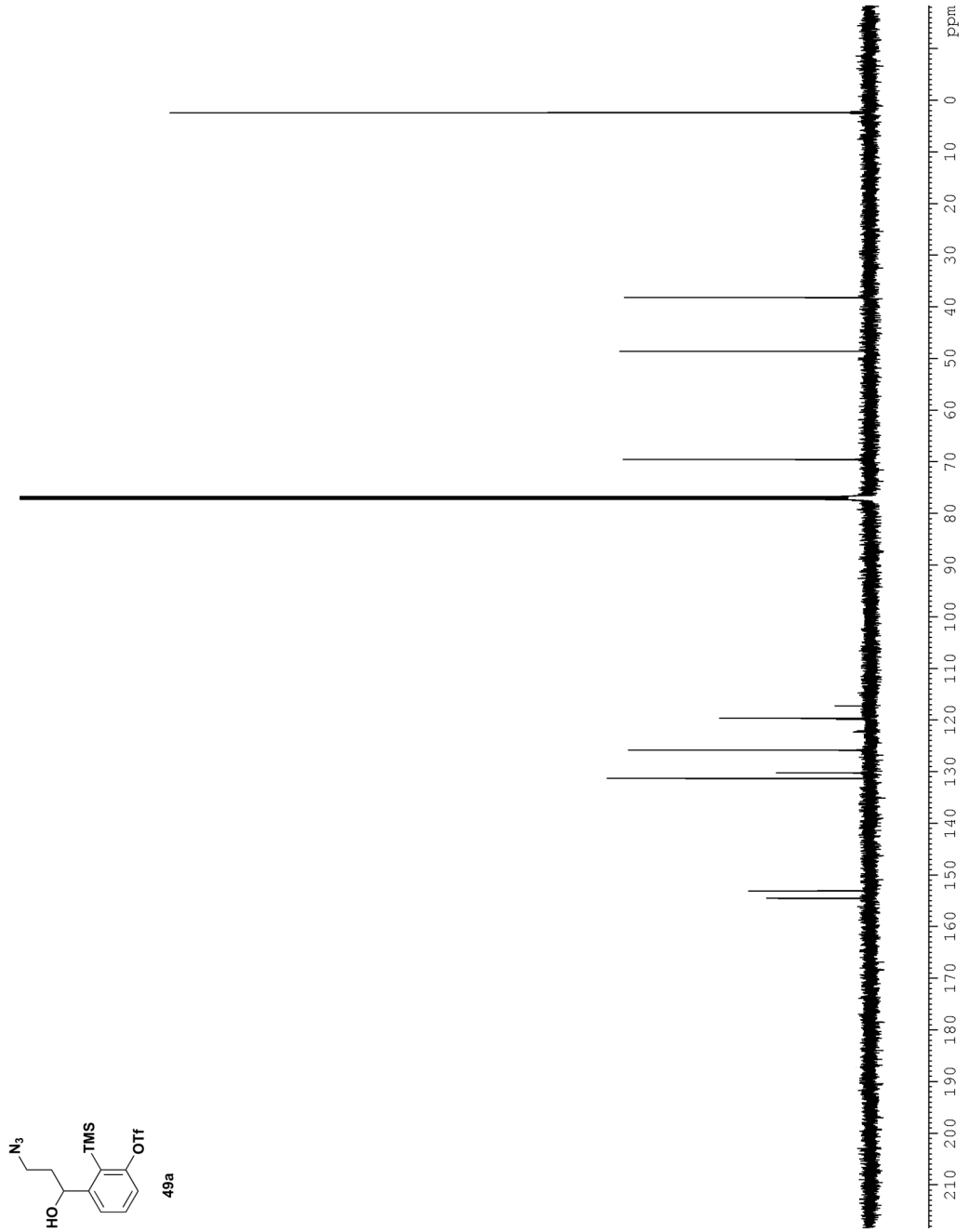
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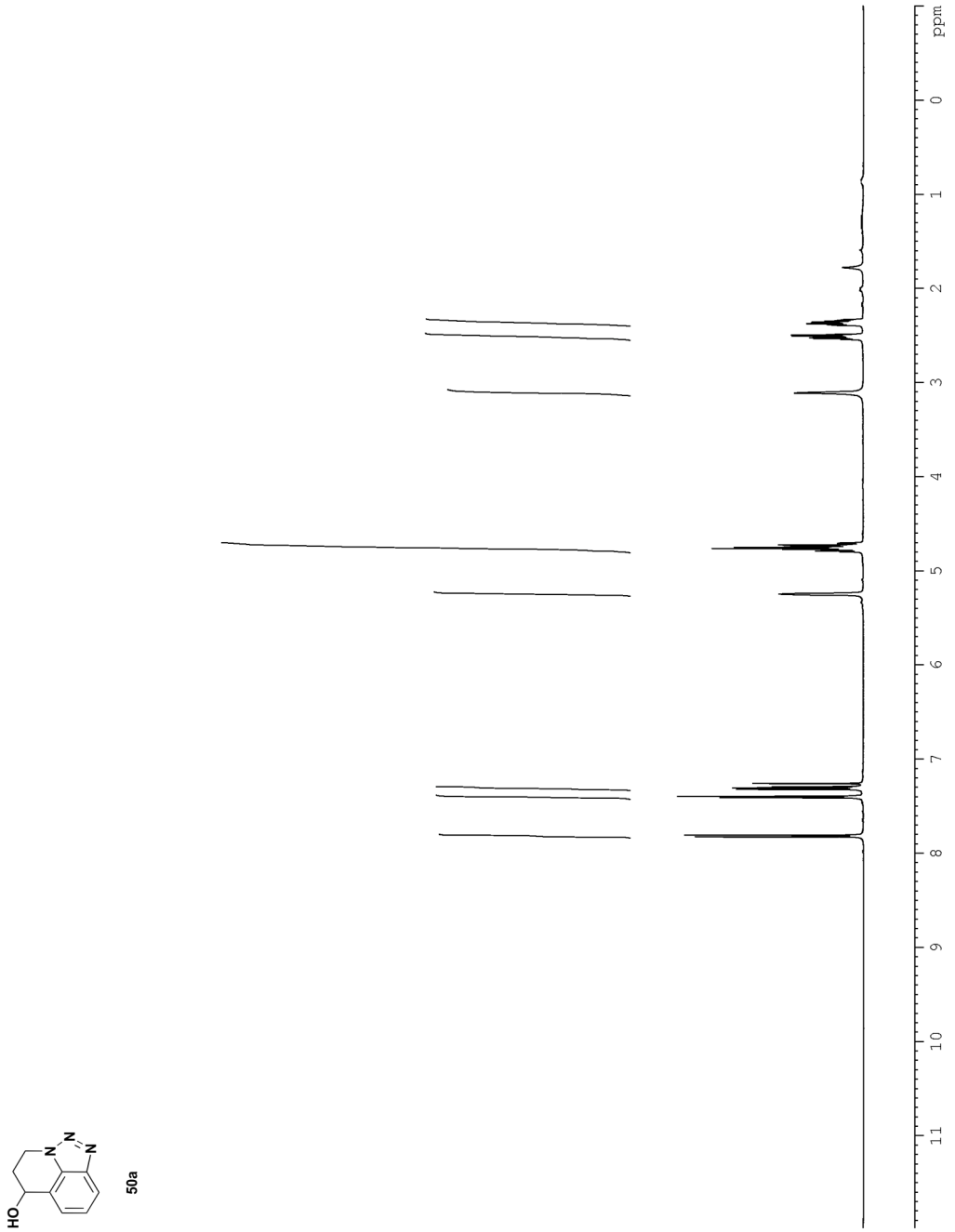
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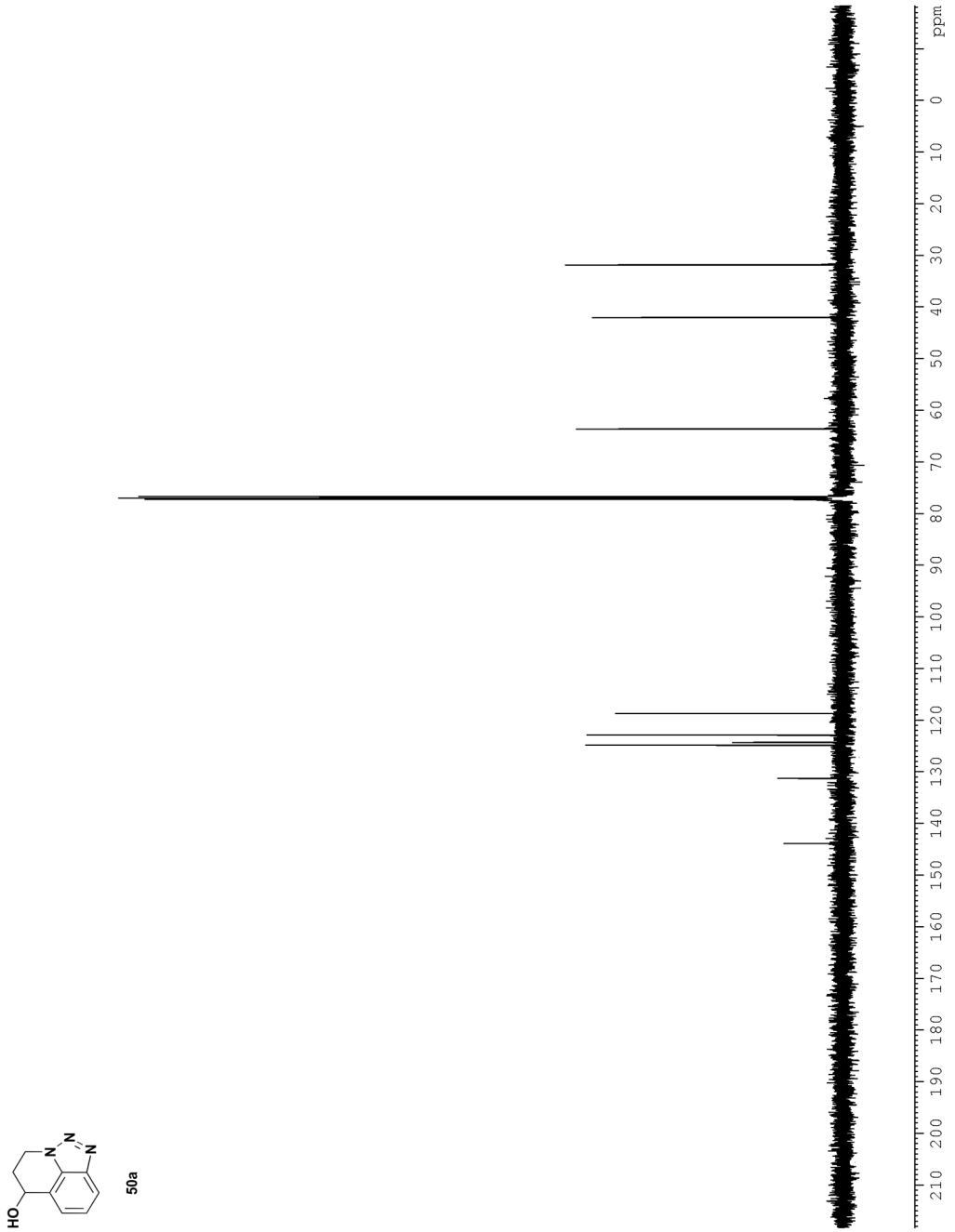
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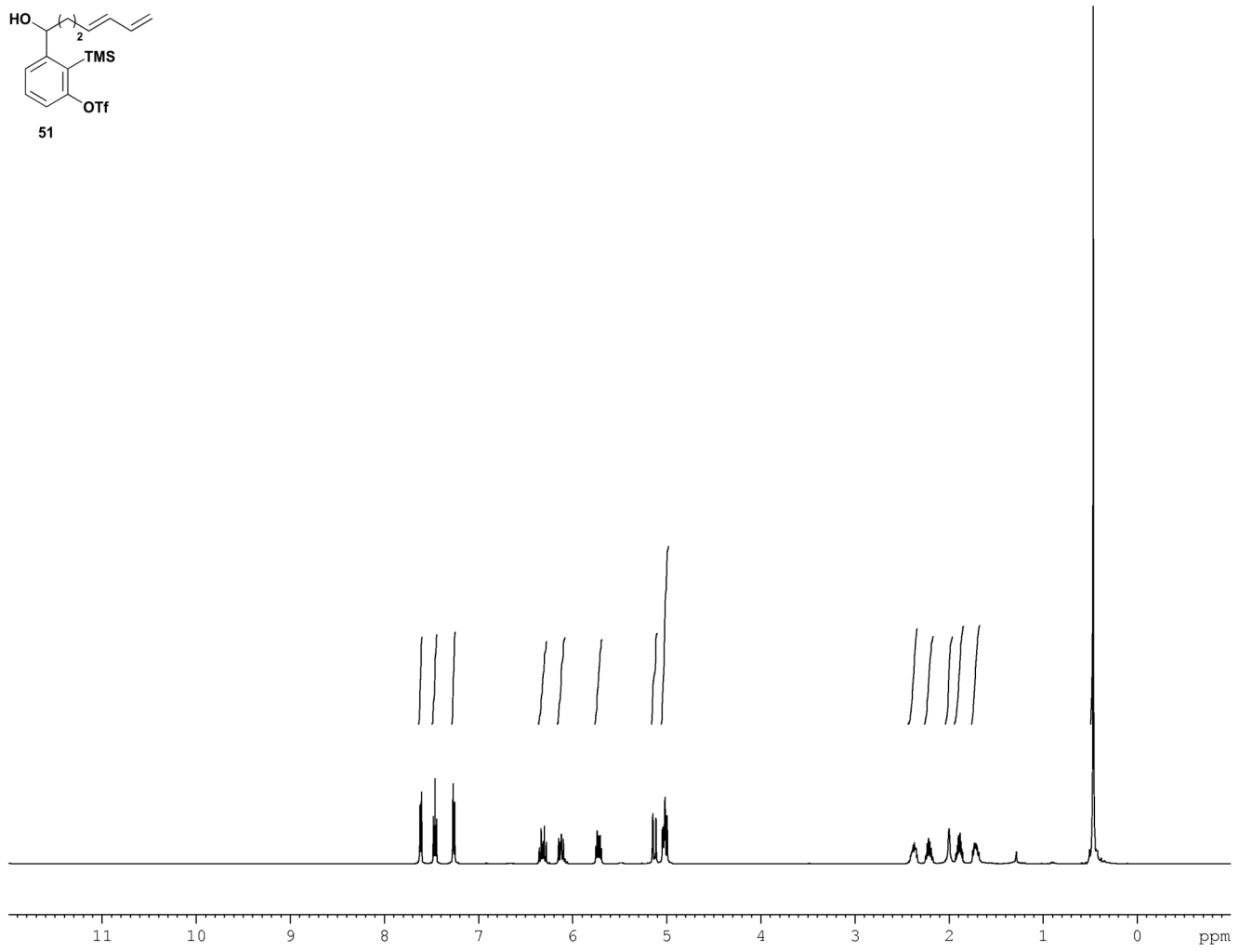
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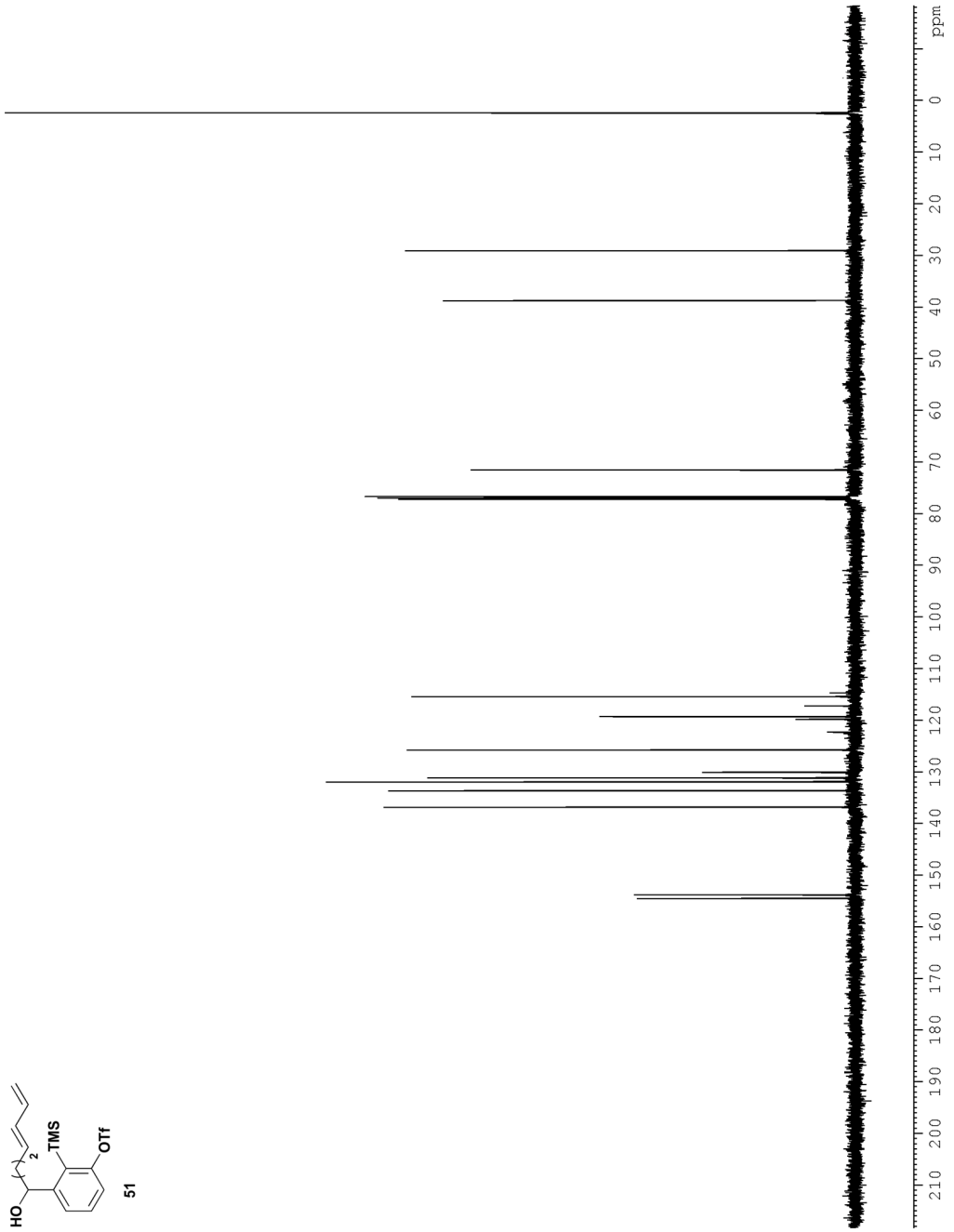
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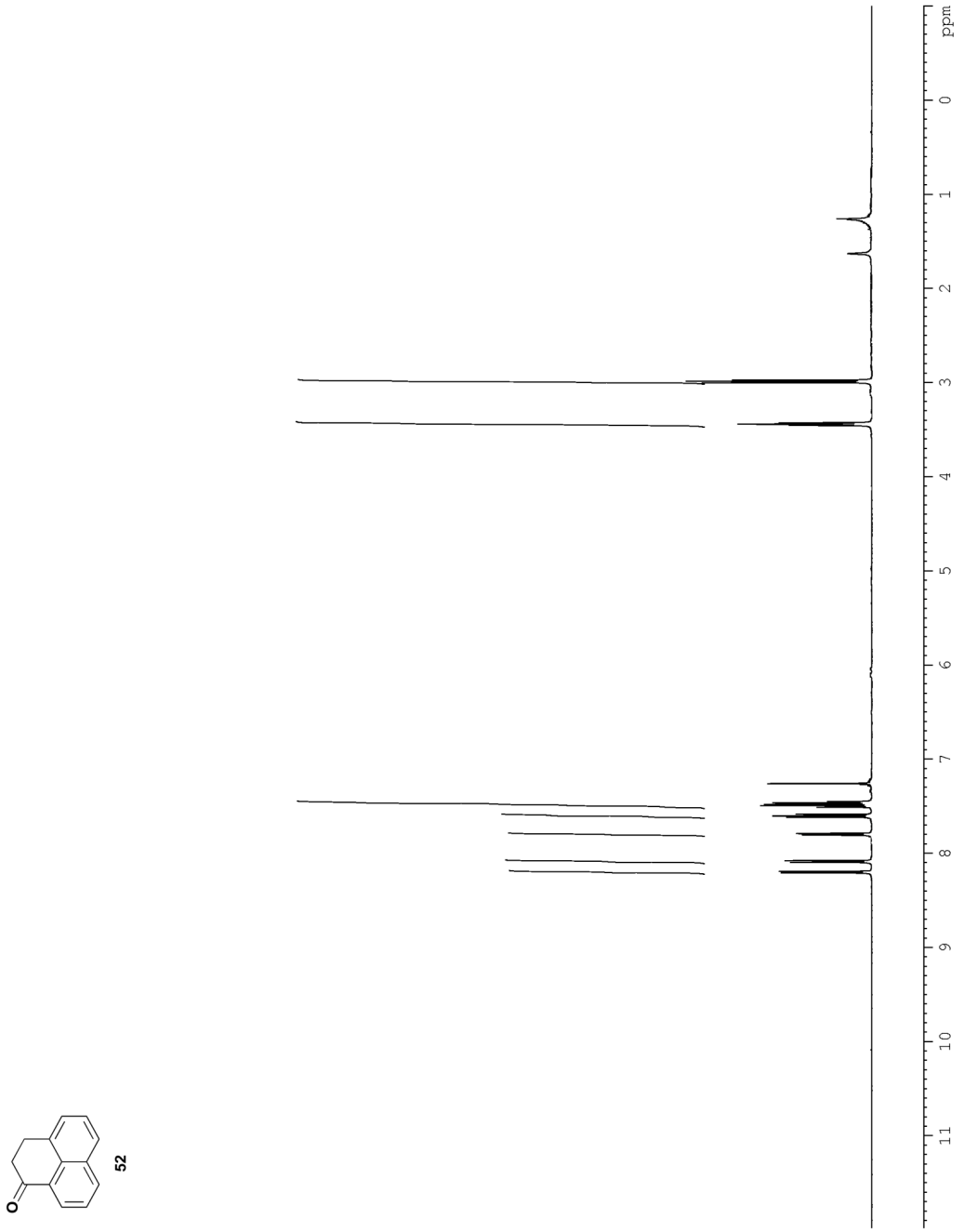
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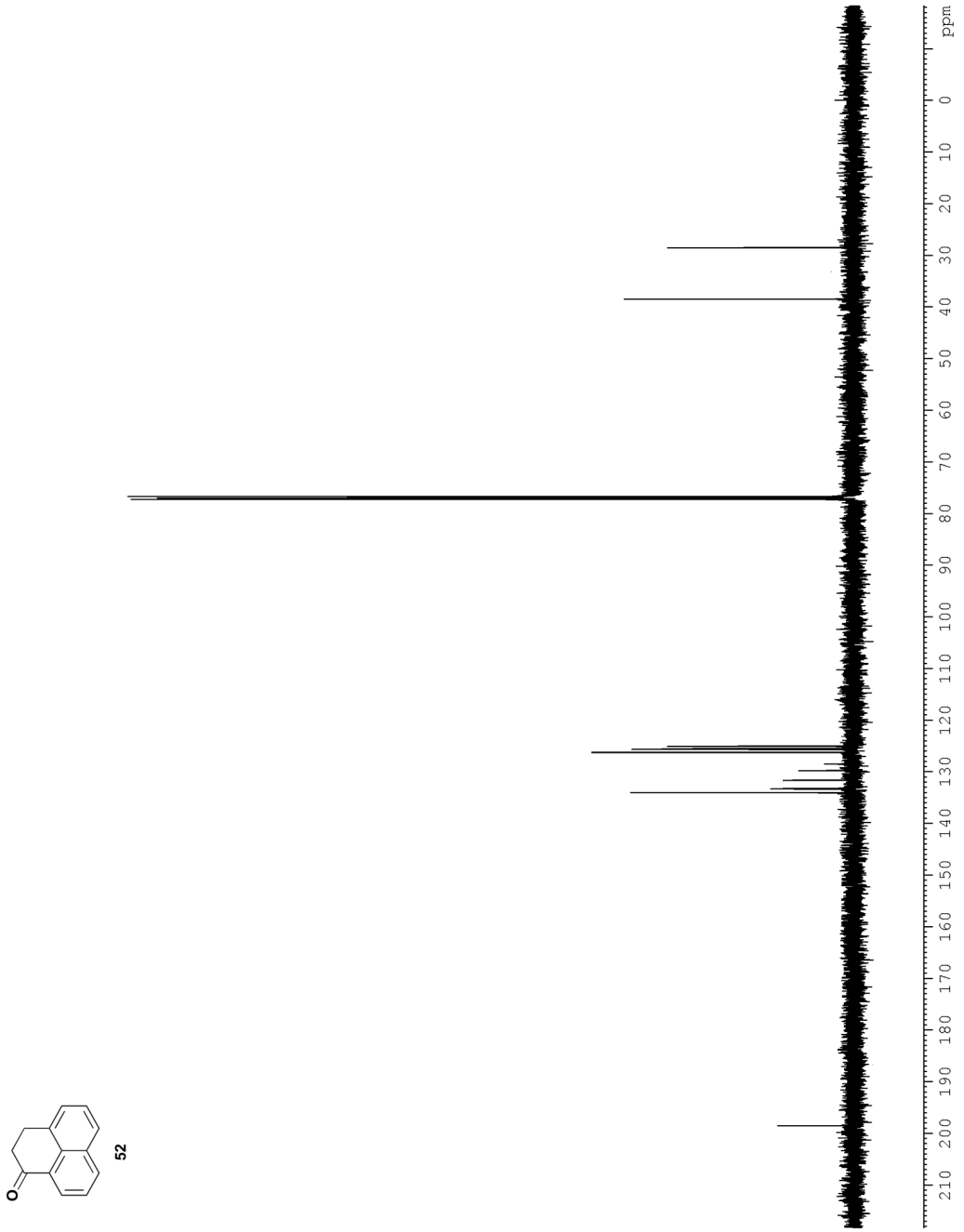
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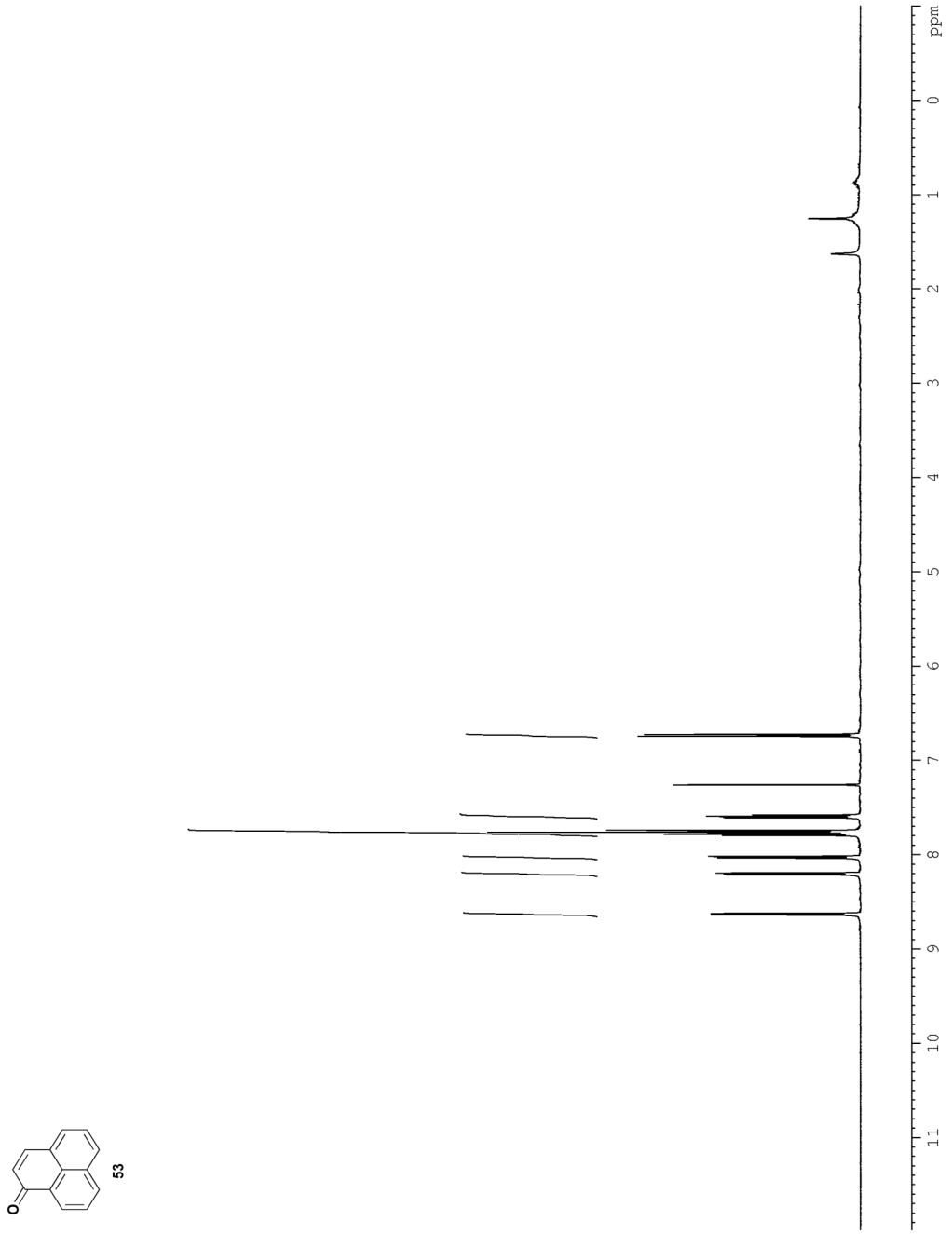
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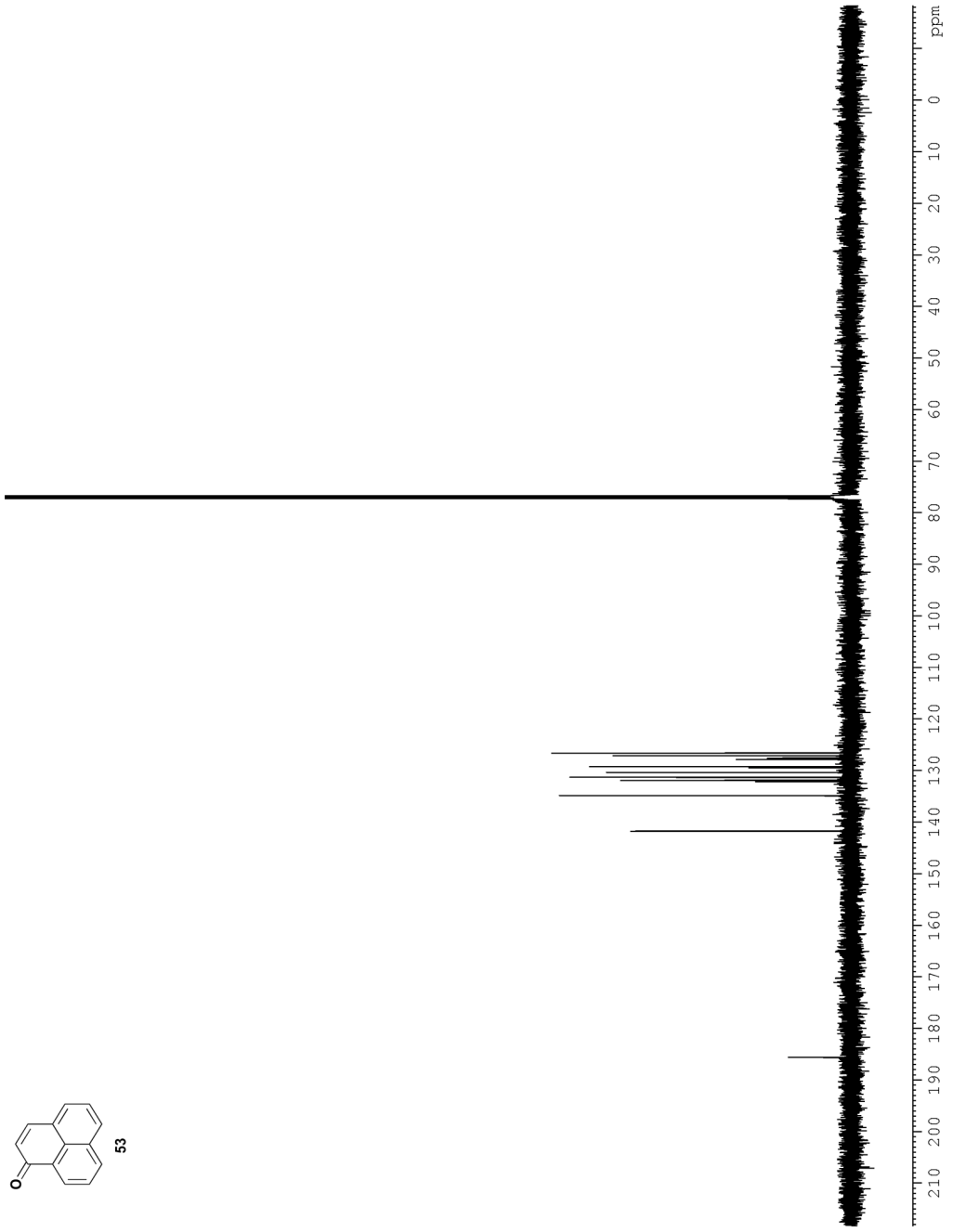
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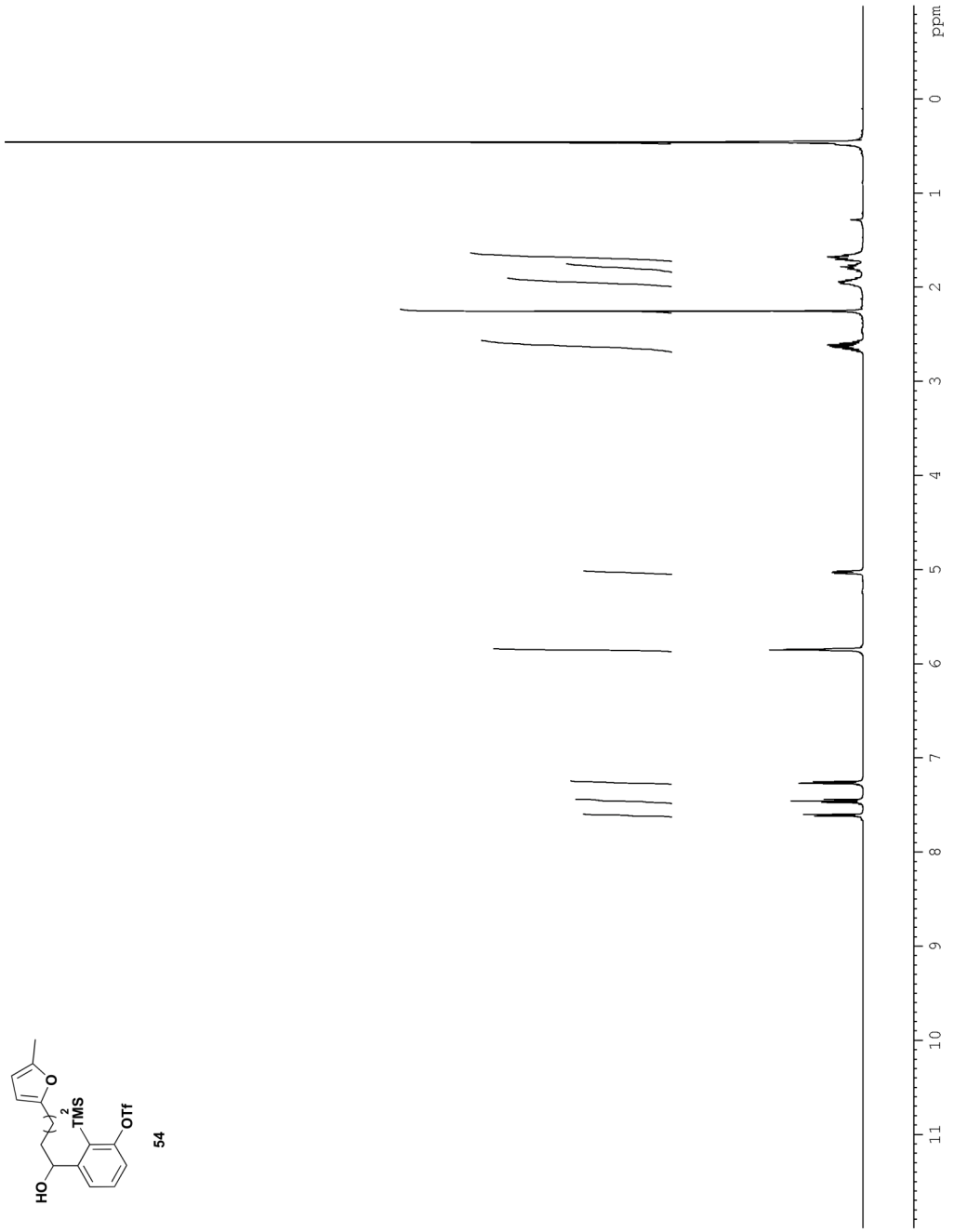
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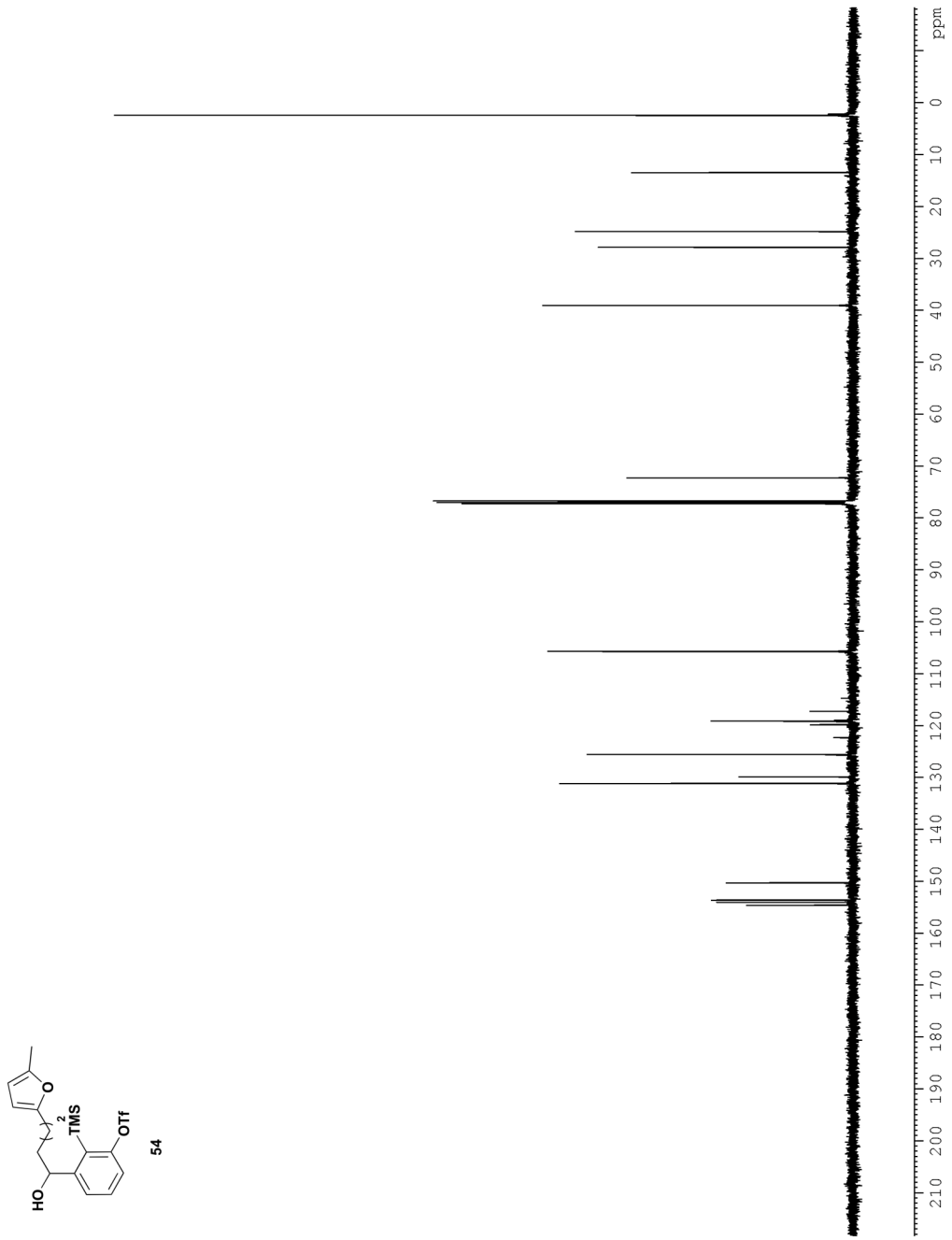
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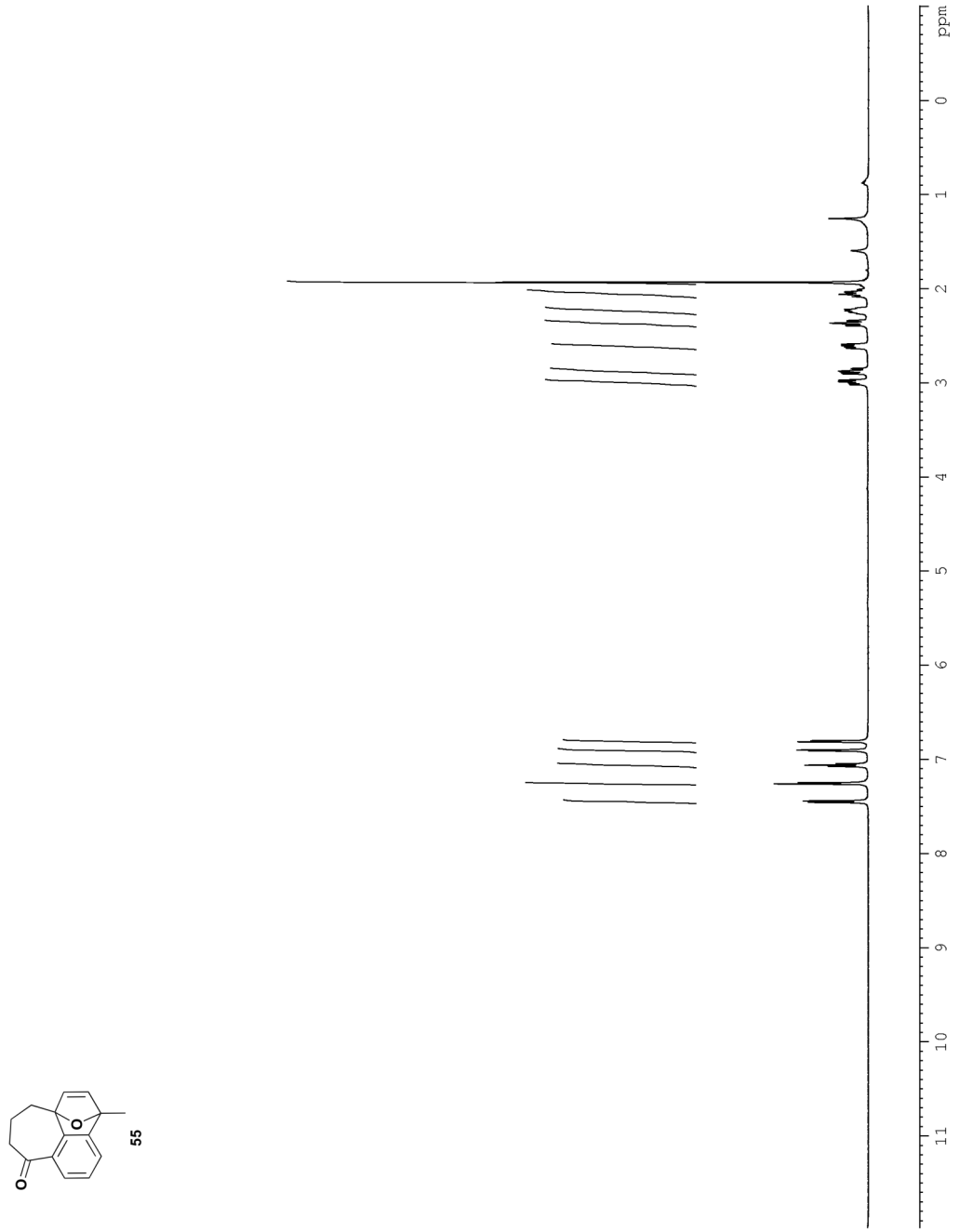
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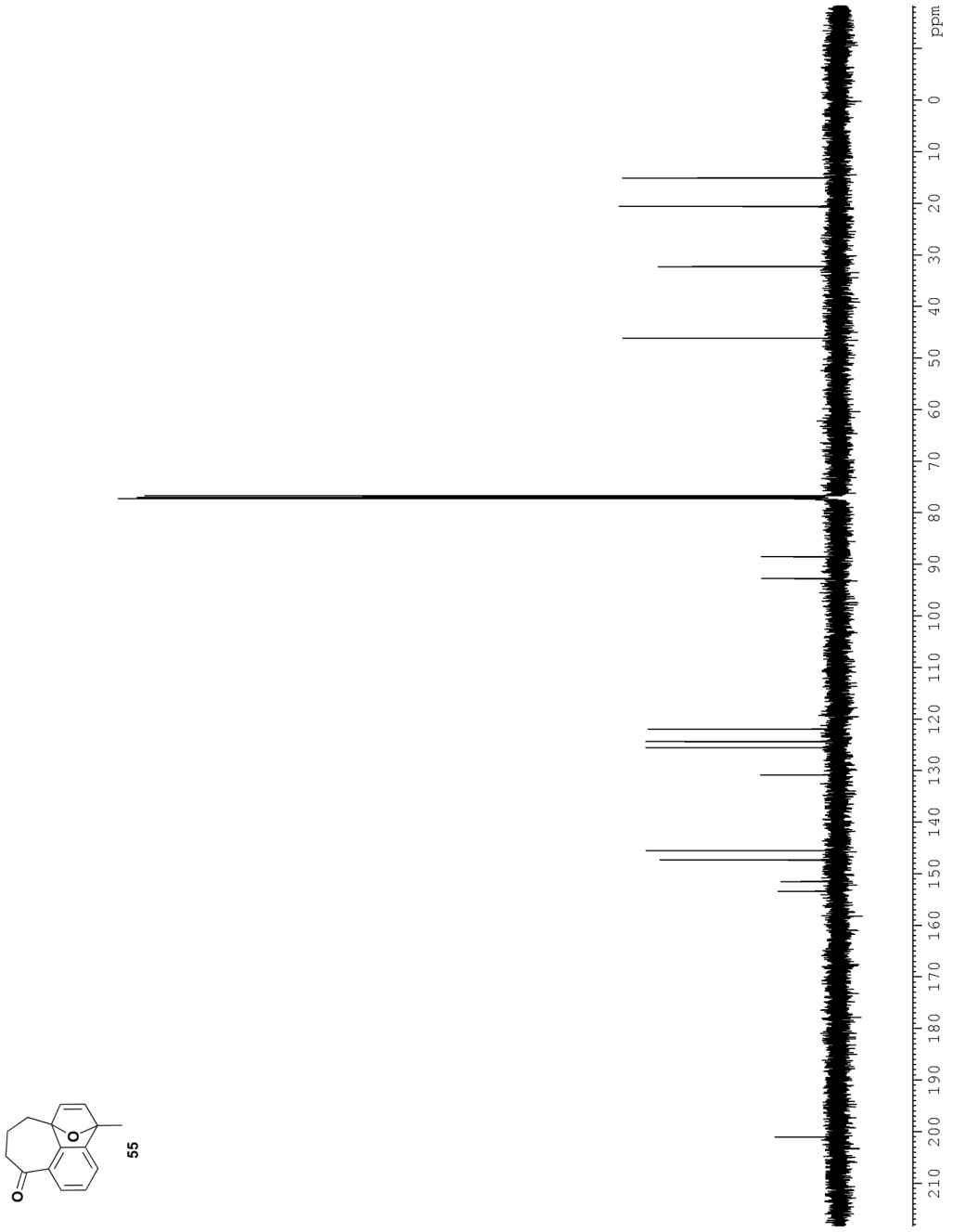
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