Supporting Information

Synthesis of Spiromamakone A Benzo Analogues via Double Oxa-Michael Addition of 1,8-Dihydroxynaphthalene

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Contents

General Techniques. All commercially available reagents and anhydrous solvents including tetrahydrofuran (THF) and dichloromethane (DCM) were purchased and used without further purification. Anhydrous *N*, *N*-dimethylformamide (DMF) and acetonitrile were obtained by distillation from calcium hydride. All reactions were monitored by thin layer chromatography (TLC) performed on 0.25 mm silica gel glassplates (60 F_{254}) using UV light and ethanolic *p*-anisaldehyde-sulfuric acid, ethanolic molybdatophosphoric acid, aqueous cerium sulfate-hexaammonium heptamolybdate-sulfuric acid, or aqueous potassium permanganate-potassium carbonate-sodium hydroxide solutions as visualizing agents. Flash column chromatography was carried out with silica gel (spherical, neutral, 63-210 μm grade). Preparative thin layer chromatography were performed on 0.75 mm Wakogel® B-5F PLC plates. Further purification was performed on gel permeation chromatography (GPC) on a Japan Analytical Industry Model LC-918 (recycling preparative HPLC) using UV detector 3702 and refractive index detector RI-50. Yields refer to chromatographically and spectroscopically homogenous materials. Melting points were measured on a melting point apparatus and were uncorrected. Only the strongest and/or structurally important absorptions of infrared (IR) spectra are reported in reciprocal centimeters (cm^{-1}). ^{1}H NMR spectra (400 MHz and 600 MHz) and ^{13}C{^{1}H}NMR spectra (100 MHz and 151 MHz) were recorded in the indicated solvent. Chemical shifts (δ) are reported in delta (δ) units, parts per million (ppm). Chemical shifts for ^{1}H NMR spectra are given relative to signals for internal tetramethylsilane (0 ppm) or residual nondeuterated solvents, i.e., chloroform (7.26 ppm). Chemical shifts for ^{13}C NMR spectra are given relative to the signal for chloroform-*d* (77.0 ppm). Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), dt (double triplet), br–s (broad singlet). Coupling constants (*J*) are represented in hertz (Hz). ^{1}H and ^{13}C NMR chemical shifts were assigned using a combination of COSY, NOESY, HMQC, and HMBC. Low and high-resolution mass spectra were measured on TOF-MS with EI, FAB, or ESI probe.

2-((2-(1,3-Dioxolan-2-yl)phenyl)(methylthio)methylene)-1*H*-indene-1,3(2*H*)-dione (6)

To a solution of α, α'-dioxoketene dithioacetal **8**[1] (250 mg, 1.00 mmol) in anhydrous THF (4 mL) was added arylmagnesium bromide **7**[2] [freshly prepared as follows: To a suspension of magnesium turnings (48.6 mg, 2.00 mmol) in anhydrous THF (2 mL) were successively added 1,2-dibromoethane (8.6 μL. 0.10 mmol) and a solution of aryl bromide (458 mg, 2.00 mmol) in anhydrous THF (2 mL) with stirring under reflux conditions. After the addition was complete, the resulting mixture was refluxed for further 1.5 h and cooled to rt.] with stirring at –78 °C. After being stirred at the same temperature for 2 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to give **6** (320 mg, 91%) as a yellow solid.

mp: 175–177 °C. IR ν (neat, cm^{-1}): 3063, 3019, 2890, 1717, 1674, 1598, 1538, 1486, 1353, 1332, 1251, 1217, 1136, 1116, 1074, 977, 938, 741, 667. ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, 1H, J = 7.2 Hz), 7.74–7.65 (m, 4H), 7.52–7.50 (m, 2H), 7.06–7.04 (m, 1H), 5.72 (s, 1H), 4.08–3.89 (m, 4H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 186.0, 171.6, 140.7, 140.6, 134.4, 134.2, 133.9, 133.8, 129.6, 129.1, 127.1, 126.5, 124.5, 123.0, 122.3, 101.4, 65.4, 65.3, 15.0. LRMS (EI) *m/z* (relative intensity) 352 $[M]^+$ (34), 305 (58), 279 (100), 149 (52). HRMS (EI) calcd for $C_{20}H_{16}O_4S$: 352.0769; found: 352.0754 $[M]^+$.

2-((2-(1,3-Dioxolan-2-yl)phenyl)(methylsulfonyl)methylene)-1*H*-indene-1,3(2*H*)-dione (9)

To a suspension of vinylogous thioester **6** (35.2 mg, 0.100 mmol) and activated MS 4Å (200 mg) in anhydrous DCM (1.0 mL) was added *m*CPBA (containing *ca.* 25% water, purity estimated at 60%, 86.3 mg, 0.300 mmol) with stirring at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was filtered. Then, the filtrate was treated with saturated aqueous $Na_2S_2O_3$. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 2:1) to give **9** (31.9 mg, 84%) as a pale yellow amorphous mass.

IR ν (neat, cm^{-1}): 3026, 2898, 1739, 1699, 1623, 1593, 1378, 1183, 963, 880, 749. ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, 1H, J = 7.2 Hz), 7.87 (d, 1H, J = 7.2 Hz), 7.80 (m, 2H), 7.73 (d, 1H, J = 7.2 Hz), 7.61 (dd, 1H, J = 7.2, 7.2 Hz), 7.49 (m, 2H), 6.01 (s, 1H), 3.91–4.08 (m, 4H), 3.17 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.9, 189.5, 160.1, 141.4, 141.3, 138.2, 135.7, 135.5, 131.9, 131.5, 129.9, 128.7, 127.3, 123.5, 123.4, 122.1, 101.5, 65.2, 40.6. HRMS (ESI) calcd for $C_{20}H_{16}O_6SNa$: 407.0560; found: 407.0555 [M+Na].

2-((2-(1,3-Dioxolan-2-yl)phenyl)(methoxythio)methylene)-1*H*-indene-1,3(2*H*)-dione (S1)

To a solution of vinylogous thioester **6** (35.2 mg, 0.100 mmol) and $NaHCO_3$ (84.0 mg, 1.00

mmol) in MeCN-H_2O (10:1, 1.0 mL) was added a solution of Selectfluor (53.1 mg, 0.150 mmol) in MeCN-H_2O (10:1, 1.0 mL) with stirring at 0 °C. After being stirred at the same temperature for 2 h, the reaction mixture was evaporated. The resulting mixture was diluted with $CHCl_3$, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1) to give an inseparable 5:1 diastereomeric mixture of sulfoxide **S1** (33.6 mg, 91%) as a pale yellow amorphous mass.

IR ν (neat, cm^{-1}): 2921, 2890, 1689, 1587, 1420, 1202, 1136, 1068, 943, 755. ^1H NMR (400 MHz, $CDCl_3$) (dr = ca. 5:1) δ 8.00 (m, 1H), 7.89–7.80 (m, 3H), 7.76 (d, 0.17H, J = 7.2 Hz), 7.65 (d, 0.83H, J = 7.2 Hz), 7.57 (m, 1H), 7.49 (m, 1H), 7.14 (d, 0.17H, J = 8.0 Hz), 7.11 (d, 0.83H, J = 7.6 Hz), 6.03 (s, 0.83H), 5.90 (s, 0.17H), 4.05-3.65 (m, 4H), 3.07 (s, 0.5H), 2.92 (s, 2.5H). ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 189.6, 185.4, 179.4, 142.2, 140.5, 138.9, 135.9, 135.7, 130.1, 128.3, 127.7, 127.1, 126.9, 126.2, 123.7, 123.4, 102.8, 64.5, 64.4, 41.3 HRMS (ESI) calcd for $C_{20}H_{17}O_5S$: 369.0791; found: 369.0783 [M+H].

2-(2-(2-(1,3-Dioxolan-2-yl)phenyl)naphtho[1,8-*de*][1,3]dioxin-2-yl)-1*H*-indene-1,3(2*H*)-dione (4)

From sulfone **9**: To a solution of **9** (11.5 mg, 0.0300 mmol) and 1,8-dihydroxynaphthalene (**5**) (4.8 mg, 0.030 mmol) in anhydrous THF (0.5 mL) was added K_2CO_3 (8.3 mg, 0.060 mmol) with stirring at room temperature. After being stirred at the same temperature for 30 min, the reaction mixture was treated with saturated aqueous NH_4Cl. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (hexane: ethyl acetate = 2:1) to give **4** (10.8 mg, 78%) as a pale brown amorphous mass.

From sulfoxide **S1**: To a solution of **S1** (36.8 mg, 0.100 mmol) and 1,8-dihydroxynaphthalene (**5**) (16.0 mg, 0.100 mmol) in anhydrous THF (1.0 mL) was added K_2CO_3 (27.8 mg, 0.200 mmol) with stirring at room temperature. After being stirred at the same temperature for 6 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (hexane: ethyl acetate = 2:1) to give **4** (12.1 mg, 26%) as a pale brown amorphous mass.

IR ν (neat, cm^{-1}): 3020, 2954, 2929, 2894, 1713, 1608, 1413, 1380, 1265, 1143, 819, 755.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (dd, 2H, *J* = 5.8, 3.1 Hz), 7.85 (dd, 2H, *J* = 5.8, 3.1 Hz), 7.70 (d, 1H, *J* = 7.6 Hz), 7.36 (d, 1H, *J* = 7.9 Hz), 7.32 (d, 2H, *J* = 8.3 Hz), 7.29 (dd, 2H, *J* = 8.3, 7.2 Hz), 7.27–7.25 (m, 1H), 7.11 (dd, 1H, *J* = 7.6, 7.9 Hz), 6.91 (d, 2H, *J* = 7.2 Hz), 6.90 (s, 1H), 4.59 (s, 1H), 4.18–4.13 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.7, 146.8, 143.5, 136.5, 135.4, 135.1, 134.0, 129.5, 129.4, 128.0, 127.5, 127.1, 123.4, 120.8, 113.7, 109.1, 103.6, 100.1, 65.3, 60.5. LRMS (EI) *m/z* (relative intensity) 464 $[M]^+$ (76), 403 (21), 305 (100), 149 (19). HRMS (EI) calcd for $C_{29}H_{20}O_6$: 464.1260; found: 464.1227 $[M]^+$

3'-Hydroxy-3'*H*-dispiro[indene-2,2'-indene-1',2''-naphtho[1,8-*de*][1,3]dioxine]-1,3-dione (Dibenzo-spiromamakone A, 2)

To a solution of naphthalene acetal **4** (11.9 mg, 0.0256 mmol) in THF (0.3 mL) was added 1 M HCl (0.3 mL) with stirring at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was basified with saturated aqueous $NaHCO_3$. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (hexane: ethyl acetate = 3:1) to give spiromamakone A dibenzo analogue **2** (7.9 mg, 73%) as a white solid.

mp: 218 °C. IR ν (neat, cm^{-1}): 3432, 3057, 2923, 2853, 1742, 1706, 1607, 1412, 1378, 1273, 1055, 757, 667. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (d, 1H, *J* = 7.8 Hz), 7.64 (d, 1H, *J* = 7.8 Hz), 7.58 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.58 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.51 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.40 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.38 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 7.33 (d, 1H, *J* = 7.8 Hz), 7.26 (d, 1H, *J* = 7.8 Hz), 7.23 (d, 1H, *J* = 7.8 Hz), 7.09 (dd, 1H, *J*= 7.8, 7.8 Hz), 6.87 (d, 1H, *J* = 7.8 Hz), 6.60 (d, 1H, *J* = 7.8 Hz), 6.02 (d, 1H, *J* = 11.4 Hz), 2.77 (d, 1H, *J* = 11.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.1, 195.0, 147.5, 147.3, 143.5, 143.2, 142.7, 137.9, 135.4, 135.1, 133.7, 131.7, 129.7, 127.7, 127.0, 124.0, 123.7, 122.7, 122.3, 120.9, 120.5, 113.2, 110.4, 109.4, 107.9, 77.0, 73.4. HRMS (ESI) calcd for $C_{27}H_{16}O_5Na$: 443.0895; found: 443.0900 [M+Na].

2-(Bis(methylthio)methylene)cyclopentane-1,3-dione (11)

To a solution of 1,3-cyclopentandione (**10**) (4.91 g, 50.0 mmol) in anhydrous DMF (150 mL) was added K_2CO_3 (20.7 g, 150 mmol) with stirring at room temperature. After being stirred at the same temperature for 30 min, the reaction mixture was cooled to 0 °C, and treated carbon disulfide (4.5 mL, 75 mmol). The mixture was warmed to room temperature and then stirred for 1.5 h. To the mixture was slowly added iodomethane (9.3 mL, 150 mmol) at 0 °C. After being stirred for further 2 h, the reaction mixture was evaporated. The residue was diluted with acetone and filtered through a Celite pad. The filtrate was recrystallized from acetone to give compound **11** (6.92 g, 69%) as a yellow solid. Mother liquid was concentrated and purified by silica gel column chromatography (hexane: ethyl acetate = 2:1 to 1:2) to give **11** (2.37 g, 23%).

mp: 118–119 °C. IR ν (neat, cm^{-1}): 3007, 2938, 1641, 1441, 1413, 1317, 1201. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 6H), 2.60 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 189.1, 122.2, 33.6, 20.9. HRMS (ESI) calcd for $C_8H_{11}O_2S_2$: 203.0200; found: 203.0193 $[M+H]^+$.

2-((2-(1,3-Dioxolan-2-yl)phenyl)(methylthio)methylene)cyclopentane-1,3-dione (12)

To a solution of α, α'-dioxoketene dithioacetal **11** (1.01 g, 5.00 mmol) in anhydrous THF (20 mL) was added arylmagnesium bromide **7**^{2} (2.0 equiv, prepared as above) with stirring at –78 °C. After being stirred at the same temperature for 1 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1) to give **12** (1.49 g, 98%) as a yellow solid.

mp: 148–149 °C. IR ν (neat, cm^{-1}): 2890, 1661, 1511, 1478, 1424, 1258, 1075, 901, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (m, 1H), 7.48 (m, 2H), 6.94 (m, 1H), 5.62 (s, 1H), 4.07–3.92 (m 4H), 2.68 (t, 2H, J = 8.4 Hz), 2.57 (t, 2H, J = 8.4 Hz), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1, 197.6, 178.1, 133.6, 166.4, 129.7, 129.0, 127.1, 125.8, 125.6, 101.4, 65.3, 65.2, 34.9, 33.8, 15.3. HRMS (ESI) calcd for $C_{16}H_{16}O_4SNa$: 327.0667; found: 327.0654 $[M+Na]^+$.

2-((2-(1,3-Dioxolan-2-yl)phenyl)(methoxythio)methylene)cyclopentane-1,3-dione (13)

To a solution of **12** (30.4 mg, 0.100 mmol) and $NaHCO_3$ (84.0 mg, 1.00 mmol) in MeCN-H_2O (10:1, 1.0 mL) was added a solution of Selectfluor (53.1 mg, 0.150 mmol) in MeCN-H_2O (10:1, 1.0 mL) with stirring at room temperature. After being stirred for 1 h, the reaction mixture was evaporated. The resulting mixture was diluted with $CHCl_3$, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:4) to give an inseparable 5:1 diastereomeric mixture of **13** (29.2 mg, 91%) as a pale yellow amorphous mass.

IR ν (neat, cm^{-1}): 2890, 1731, 1689, 1611, 1590, 1353, 1249, 1209, 1070, 1032, 944, 745. ^{1}H NMR (400 MHz, $CDCl_3$) (dr = ca. 5:1) δ 7.72 (d, 0.17H, J = 7.6 Hz), 7.62 (d, 0.83H, J = 8.0 Hz), 7.54 (m, 1H), 7.46 (m, 1H), 7.03 (d, 0.17H, J = 7.8 Hz), 6.98 (d, 0.83H, J = 6.8 Hz), 6.03 (s, 0.83H), 5.84 (s, 0.17H), 4.05–3.62 (m, 4H), 3.05 (s, 0.50H), 2.85–2.81 (m, 6.5H). ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 202.7, 197.3, 185.7, 139.2, 130.3, 130.1, 128.3, 127.1, 126.8, 125.8, 102.7, 64.5, 64.3, 40.9, 36.4, 34.4 HRMS (ESI) calcd for $C_{16}H_{16}O_5NaS$: 343.0616; found: 343.0617

$[M+Na]^+$.

3'-Hydroxy-3'*H*-dispiro[cyclopentane-1,2'-indene-1',2''-naphtho[1,8-*de*][1,3]dioxine]-2,5-dione (Dihydro-monobenzo-spiromamakone A, 15)

To a solution of **13** (9.6 mg, 0.030 mmol) and 1,8-dihydroxynaphthalene (**5**) (4.8 mg, 0.030 mmol) in anhydrous THF (0.30 mL) was added K_2CO_3 (8.3 mg, 0.060 mmol) with stirring at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was acidified with aqueous 1 M HCl (0.30 mL) and stirred for further 1 h. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (hexane: ethyl acetate = 1:1) to give **15** (5.4 mg, 48%) as a pale brown amorphous mass.

IR ν (neat, cm^{-1}): 3466, 3056, 3019, 2928, 1723, 1608, 1413, 1379, 1273, 1192, 1065, 1057, 1042, 818, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60–7.52 (m, 3H), 7.50–7.41 (m, 3H), 7.19 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.98 (d, 1H, *J* = 7.6 Hz), 6.86 (d, 1H, *J* = 7.6 Hz), 6.77 (d, 1H, *J* = 7.6 Hz), 5.87 (d, 1H, *J* = 12.0 Hz), 2.92 (d, 1H, *J* = 12.0 Hz), 2.75–2.66 (m, 1H), 2.62–2.49 (m, 2H), 2.29–2.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.4, 206.9, 147.0, 146.5, 143.4, 136.8, 133.8, 131.4, 129.4, 128.0, 127.3, 123.9, 123.2, 121.7, 121.0, 113.4, 110.7, 109.6, 107.7, 76.4, 74.7, 37.7, 36.3. HRMS (ESI) calcd for $C_{23}H_{16}O_5Na$: 395.0895; found: 395.0884 $[M+Na]^+$.

2,5-Dioxo-3'*H*-dispiro[cyclopentane-1,2'-indene-1',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-yl acetate (Dihydro-monobenzo-spiromamakone A acetate, 16)

To a solution of **15** (37.2 mg, 0.100 mmol) and Et_3N (18 μL, 0.13 mmol) in anhydrous DCM (1 mL) were added acetic anhydride (11 μL, 0.12 mmol) and DMAP (1.2 mg, 10 μmol) with stirring at room temperature. After being stirred for 1 h, the reaction mixture was acidified with aqueous 0.5 M HCl. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (hexane: ethyl acetate = 1:1) to give **16** (31.0 mg, 75%) as a colorless amorphous mass.

IR ν (neat, cm^{-1}): 3063, 3022, 2928, 1729, 1612, 1608, 1413, 1376, 1276, 1262, 1237, 1048, 822, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.52 (m, 4H), 7.48–7.43 (m, 2H), 7.36 (m, 1H), 7.16 (d, 1H, *J* = 7.6 Hz), 6.94 (d, 1H, *J* = 7.6 Hz), 6.88 (d, 1H, *J* = 7.6 Hz), 6.06 (s, 1H), 2.51 (dd, 1H, *J* = 8.8, 4.8 Hz), 2.33 (dd, 1H, *J* = 8.8, 4.8 Hz), 2.04 (s, 3H), 1.75 (dd, 1H, *J* = 8.8, 4.8 Hz), 1.61 (dd, 1H, *J* = 8.8, 4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 205.7, 172.4, 146.9, 146.8, 138.8, 138.5, 133.6, 131.6, 130.3, 127.9, 127.6, 124.9, 124.0, 121.4, 121.1, 113.6, 110.9, 110.3, 109.4, 79.8, 70.6, 36.5, 35.6, 20.9. HRMS (ESI) calcd for $C_{25}H_{18}O_6Na$: 437.1001; found: 437.0988 $[M+Na]^+$.

2,5-Dioxo-3'*H*-dispiro[cyclopentane-1,2'-indene-1',2''-naphtho[1,8-*de*][1,3]dioxin]-3-en-3'-yl acetate (monobenzo-spiromamakone A acetate, 17)

To a solution of **16** (41.4 mg, 0.100 mmol) in anhydrous THF (0.5 mL) was added a solution of trimethylphenylammonium tribromide (37.6 mg, 0.100 mmol) in anhydrous THF (0.5 mL) with stirring at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$. The immiscible mixture was extracted with ethyl acetate twice. The combined organic layer was washed with saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (toluene: ethyl acetate = 10:1) to give **17** (31.8 mg, 76%) as a colorless solid.

mp: 198–199 °C. IR ν (neat, cm^{-1}): 3063, 3026, 1737, 1709, 1609, 1413, 1378, 1274, 1257, 1223, 1051, 819, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55–7.33 (m, 7H), 7.09 (d, 1H, *J* = 8.0 Hz), 6.88 (m, 4H), 6.53 (s, 1H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 195.8, 171.0, 148.8, 148.7, 147.2, 147.1, 139.0, 138.8, 133.9, 131.5, 130.1, 127.8, 127.4, 124.7, 123.5, 121.2, 120.9, 113.1, 110.3, 109.8, 107.7, 76.6, 66.5, 20.7. HRMS (ESI) calcd for $C_{25}H_{16}O_6Na$: 435.0845; found: 435.0832 $[M+Na]^+$.

3'-Hydroxy-3'*H*-dispiro[cyclopentane-1,2'-indene-1',2''-naphtho[1,8-*de*][1,3]dioxin]-3-ene-2,5-dione (monobenzo-spiromamakone A) (3)

To a solution of **17** (41.2 mg, 0.100 mmol) in EtOH (0.15 mL) was added 30 wt% aqueous H_2SO_4 (0.15 mL) with stirring at room temperature. After being stirred at 50 °C for 4 h, the reaction mixture was diluted with ethyl acetate and washed with H_2O twice and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was pure enough for analysis (37.0 mg, quant.) as a colorless solid.

mp: 200–201 °C. IR ν (neat, cm^{-1}): 3496, 3067, 3019, 2925, 1703, 1608, 1412, 1379, 1272, 1194, 1120, 1065, 1043, 818, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57–7.31 (m, 7H), 7.09–7.05 (m, 2H), 6.91–6.83 (m, 3H), 5.84 (d, 1H, *J* = 11.6 Hz), 2.53 (d, 1H, *J* = 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 197.7, 150.3, 149.6, 147.5, 147.3, 143.0, 137.7, 134.0, 131.6, 129.7, 128.0, 127.3, 123.9, 123.5, 121.4, 120.9, 113.1, 110.4, 109.3, 107.0, 76.3, 69.7. HRMS (ESI) calcd for $C_{23}H_{14}O_5Na$: 393.0739; found: 393.0728 $[M+Na]^+$.

References

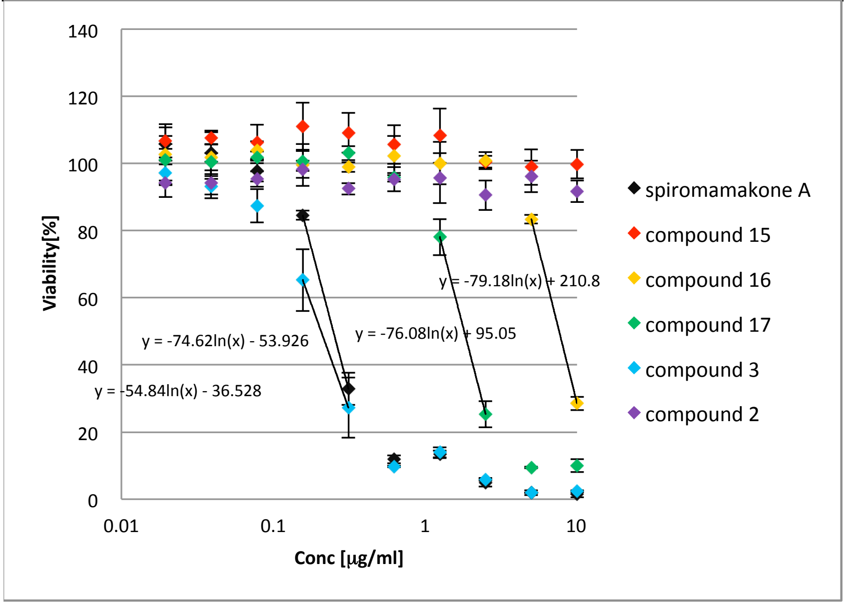
1) Verma, R. K.; Ila, H.; Singh, M. S. *Tetrahedron* **2010**, *66*, 7389–7398.

2) Tomcufcik, A. S.; Wright, W. B., Jr.; Meyer, W. E. U.S. Patent 4,892,885, Jan 9, 1990.

Cytotoxicity Assay

HeLa cells were maintained in DMEM medium (WAKO, Japan) with 10% FBS (Gibco, USA) and penicillin (50 U/mL)-streptomycin (50 µg/mL) (Gibco, USA) at 37 °C in a humidified incubator with 5% CO_2. Cells were seeded in 384-well plate at a density of 1,000 cells/20 µL/well. After 4h, cells were treated with different concentrations of compounds for 48 h. The vehicle solvent (DMSO) was used as a control. Cell viabilities were measured using Cell Counting Kit-8 (Dojindo, Japan) and Envision Multilabel Plate Reader (Perkin Elmer, USA).

conc (µg/ml)	10	5	2.5	1.25	0.625	0.3125	0.15625	0.078125	0.0390625	0.01953125
spiromamakone A	1.5	2.0	4.8	13.3	11.9	32.9	84.6	97.8	103.0	105.8
stdev	1.0	0.7	1.1	1.2	1.2	4.8	1.3	3.1	6.8	5.0
compound **15**	99.8	98.9	100.6	108.3	105.7	109.1	111.1	106.3	107.5	106.7
stdev	4.2	5.3	1.8	8.1	5.8	5.9	7.0	5.2	1.8	4.9
compound **16**	28.5	83.4	100.9	100.1	102.3	98.9	99.5	104.0	101.8	102.7
stdev	1.9	1.3	2.6	6.3	5.9	1.4	6.2	2.6	1.3	3.1
compound **17**	10.0	9.4	25.3	78.1	95.9	103.1	100.8	101.8	100.5	101.0
stdev	1.9	0.2	3.9	5.4	1.3	2.1	3.0	1.7	5.1	7.2
compound **3**	2.3	1.9	5.9	14.0	9.8	27.3	65.3	87.4	93.2	97.2
stdev	0.3	0.1	0.4	1.5	0.2	8.9	9.2	4.9	3.6	7.2
compound **2**	91.7	96.2	90.6	95.7	95.3	92.5	98.3	95.4	94.3	94.3
stdev	3.2	4.7	4.4	7.5	3.6	1.7	2.6	2.3	3.6	0.7



IC_{50}(spiromamakone A) = Exp(-(50+53.926)/74.62) = 0.248 µg/ml

IC_{50}(HND-001) = not available

IC_{50}(HND-002) = Exp(-(50-210.8)/79.18) = 7.62 µg/ml

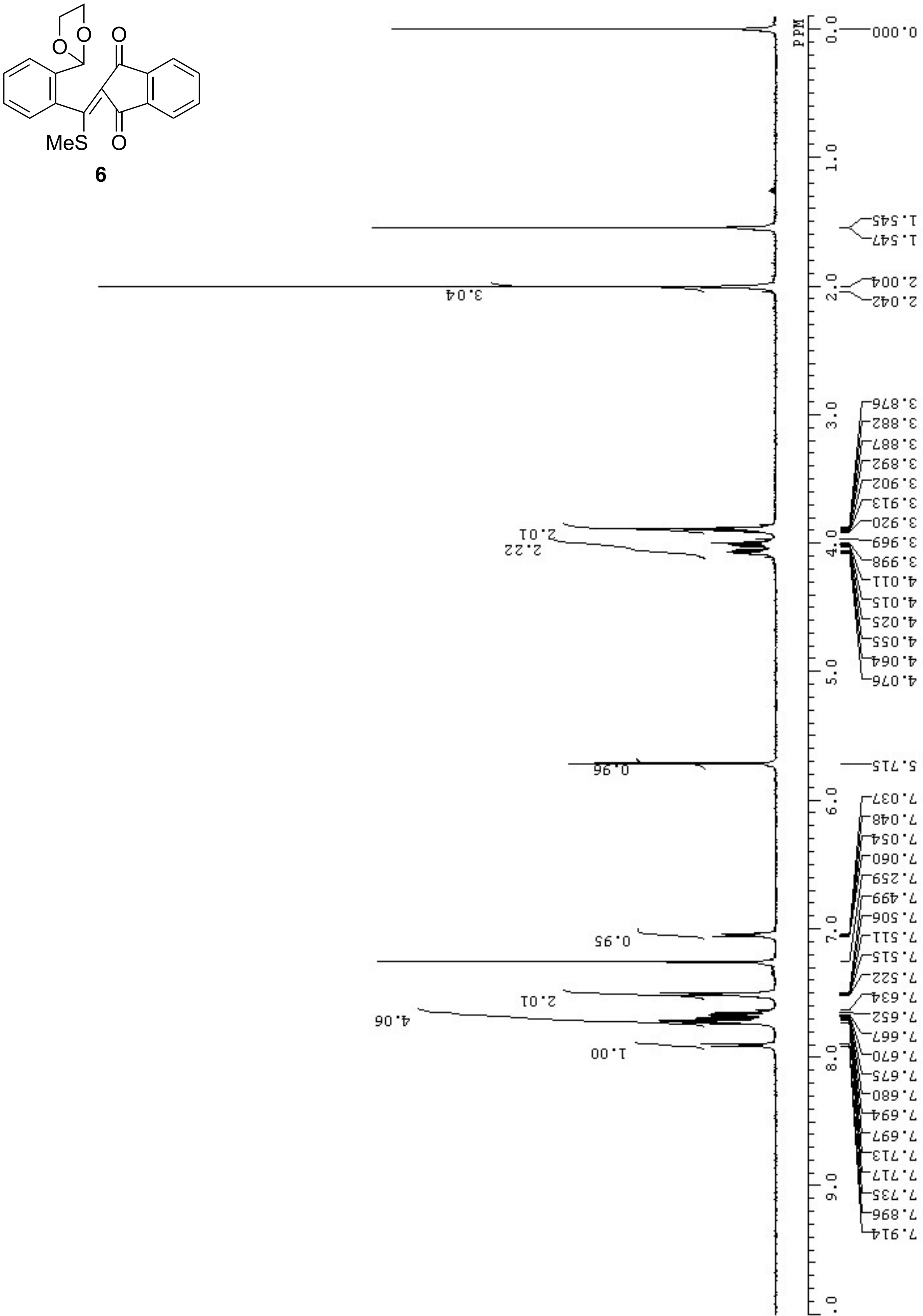
IC_{50}(HND-003) = Exp(-(50-95.05)/76.08) = 1.81 µg/ml

IC_{50}(HND-004) = Exp(-(50+36.528)/54.84) = 0.206 µg/ml

IC_{50}(HND-005) = not available

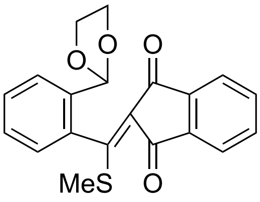
	MW	µM
1	320.0685	0.7748341
15	372.0998	26.874511
16	414.1103	18.400895
17	412.0947	4.3921943
3	370.0841	0.5566302
2	420.0998	23.803868

^{1}H NMR spectrum of **6**



6

^{13}C NMR spectrum of **6**



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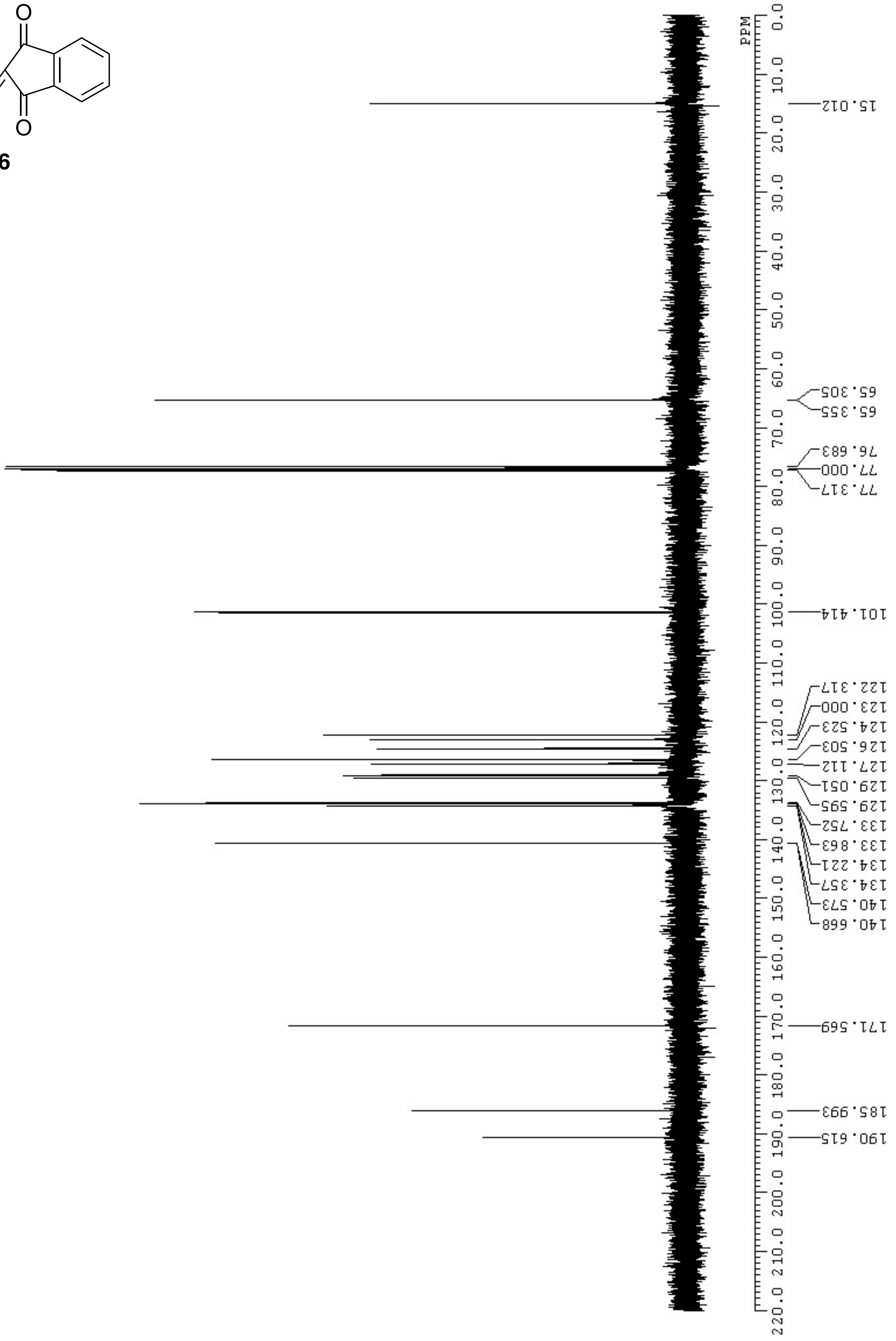

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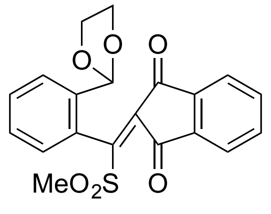

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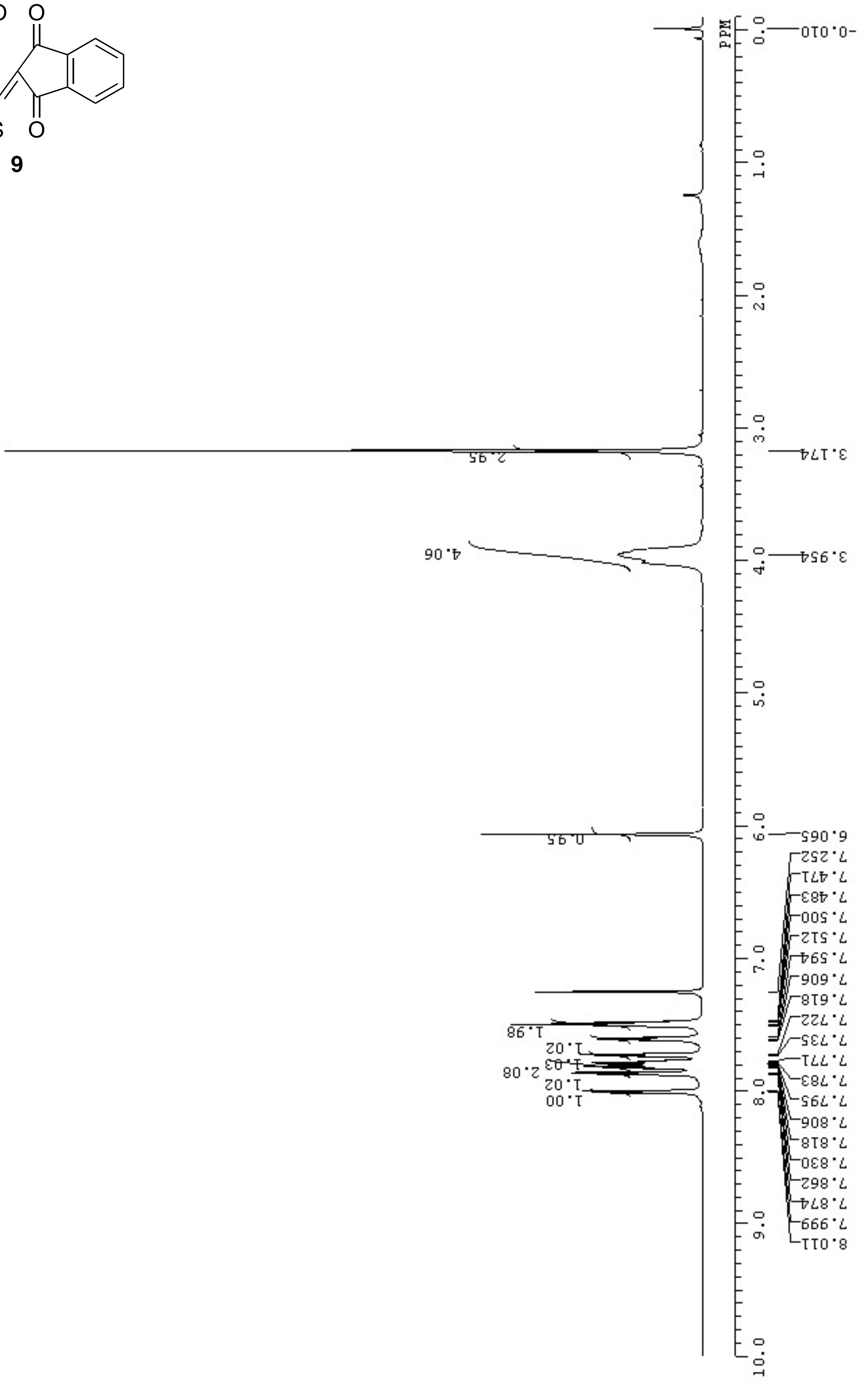
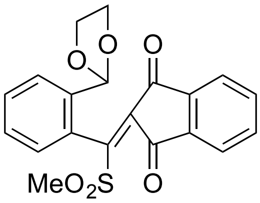


^{13}C NMR spectrum of **9**



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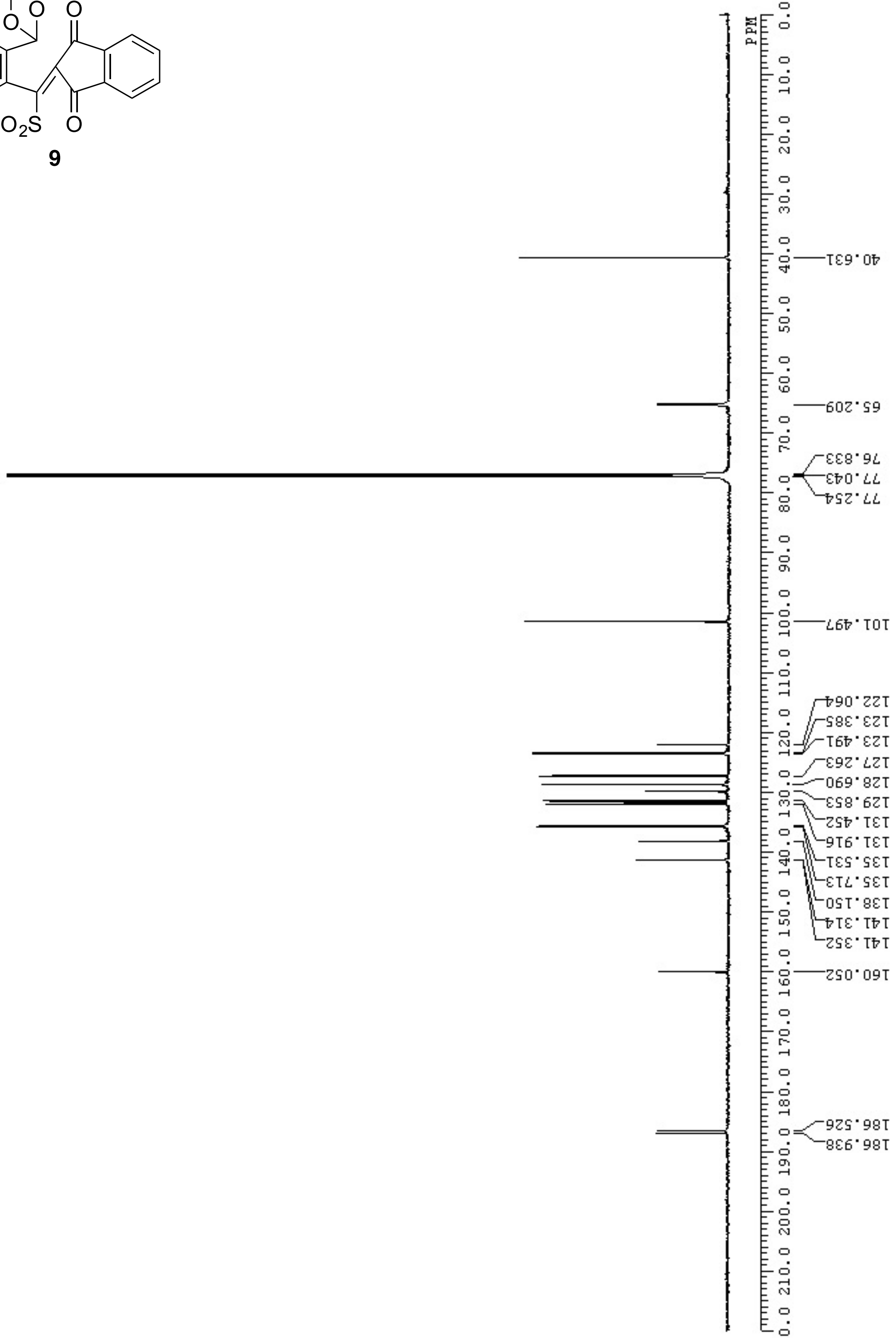
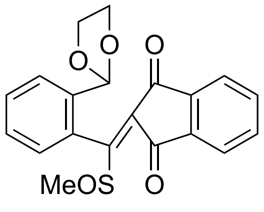
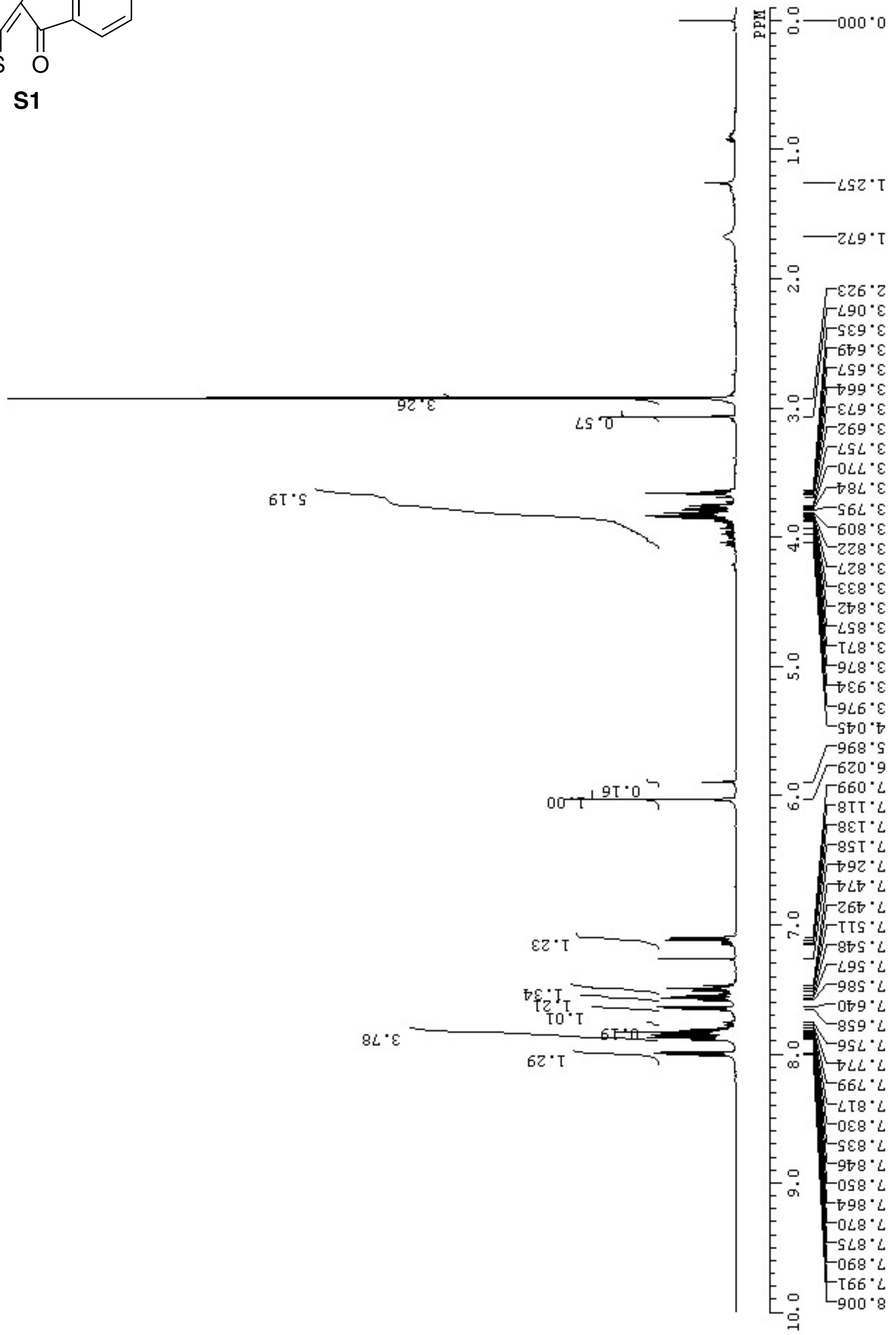


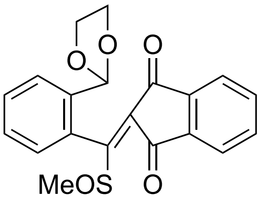
^{1}H NMR spectrum of **S1**



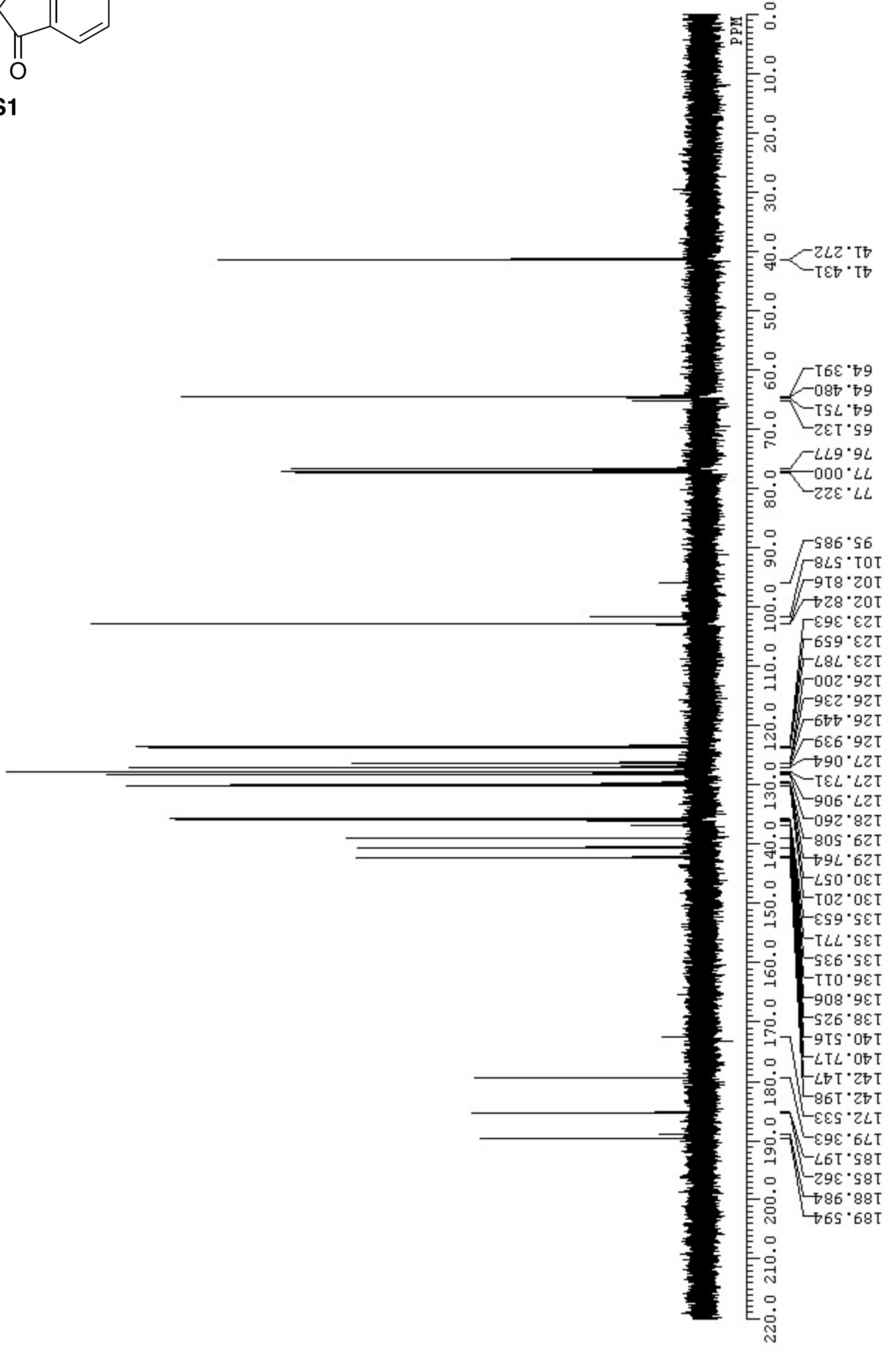
S1



^{13}C NMR spectrum of **S1**

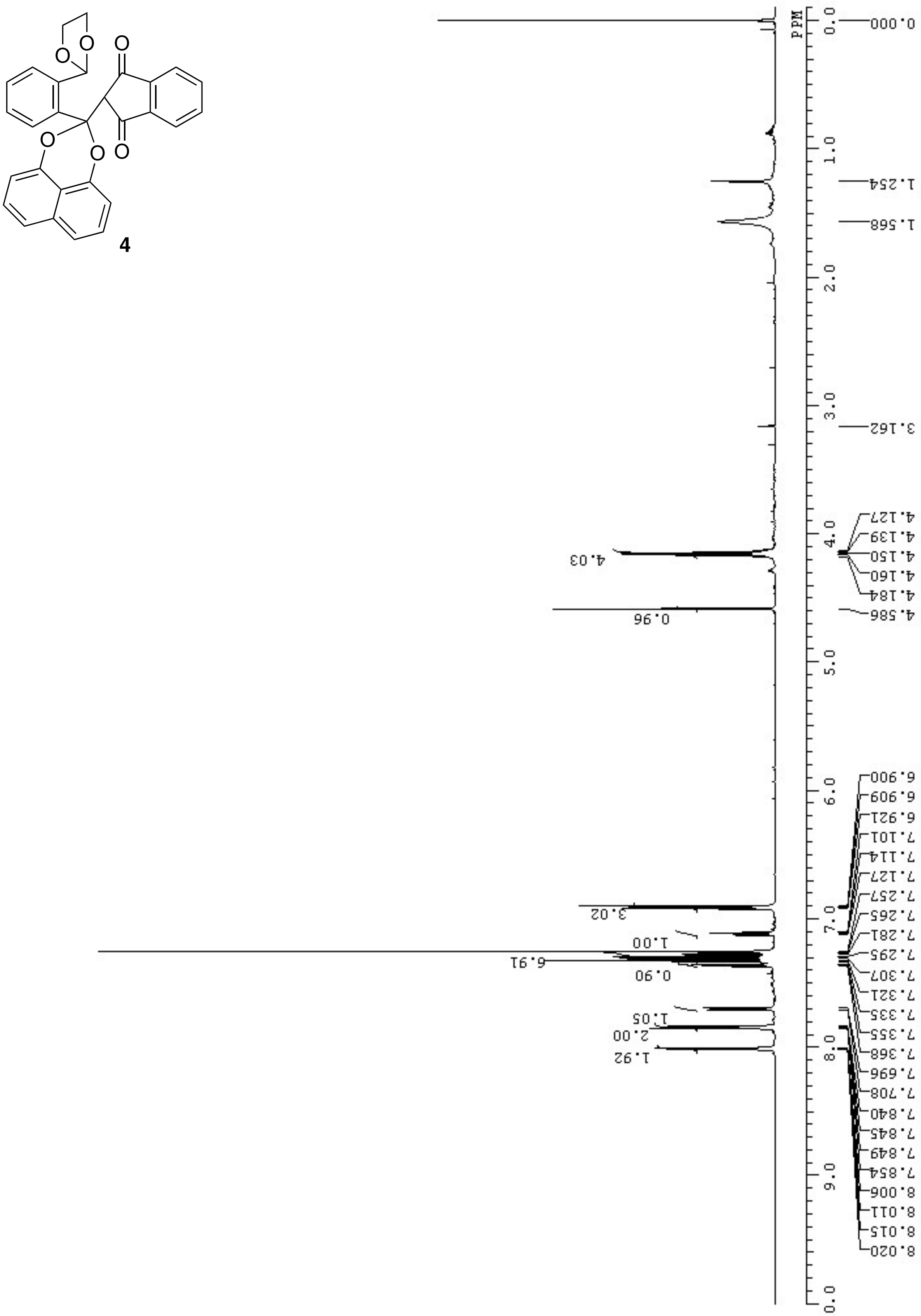


S1

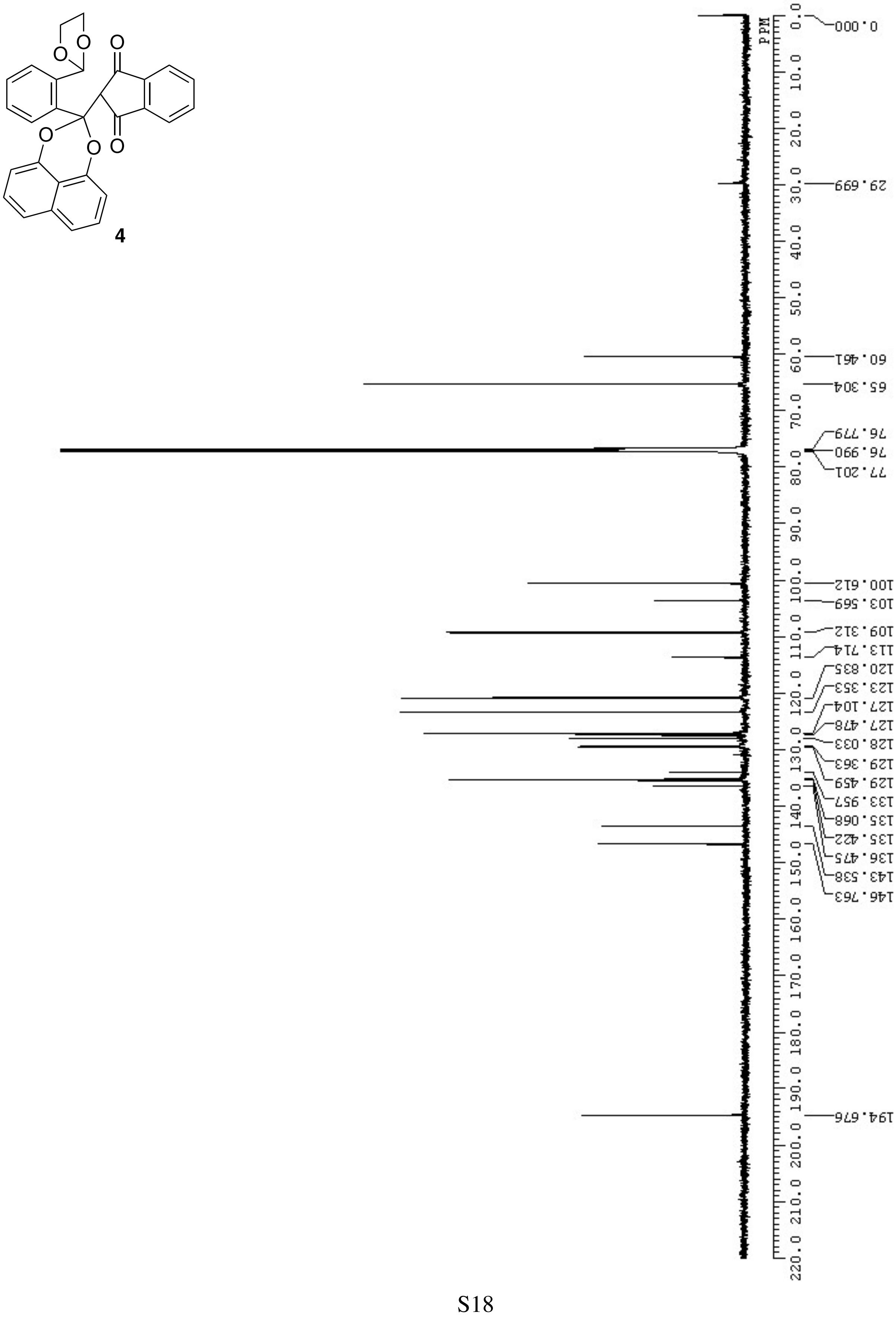


^{1}H NMR spectrum of **4**

4

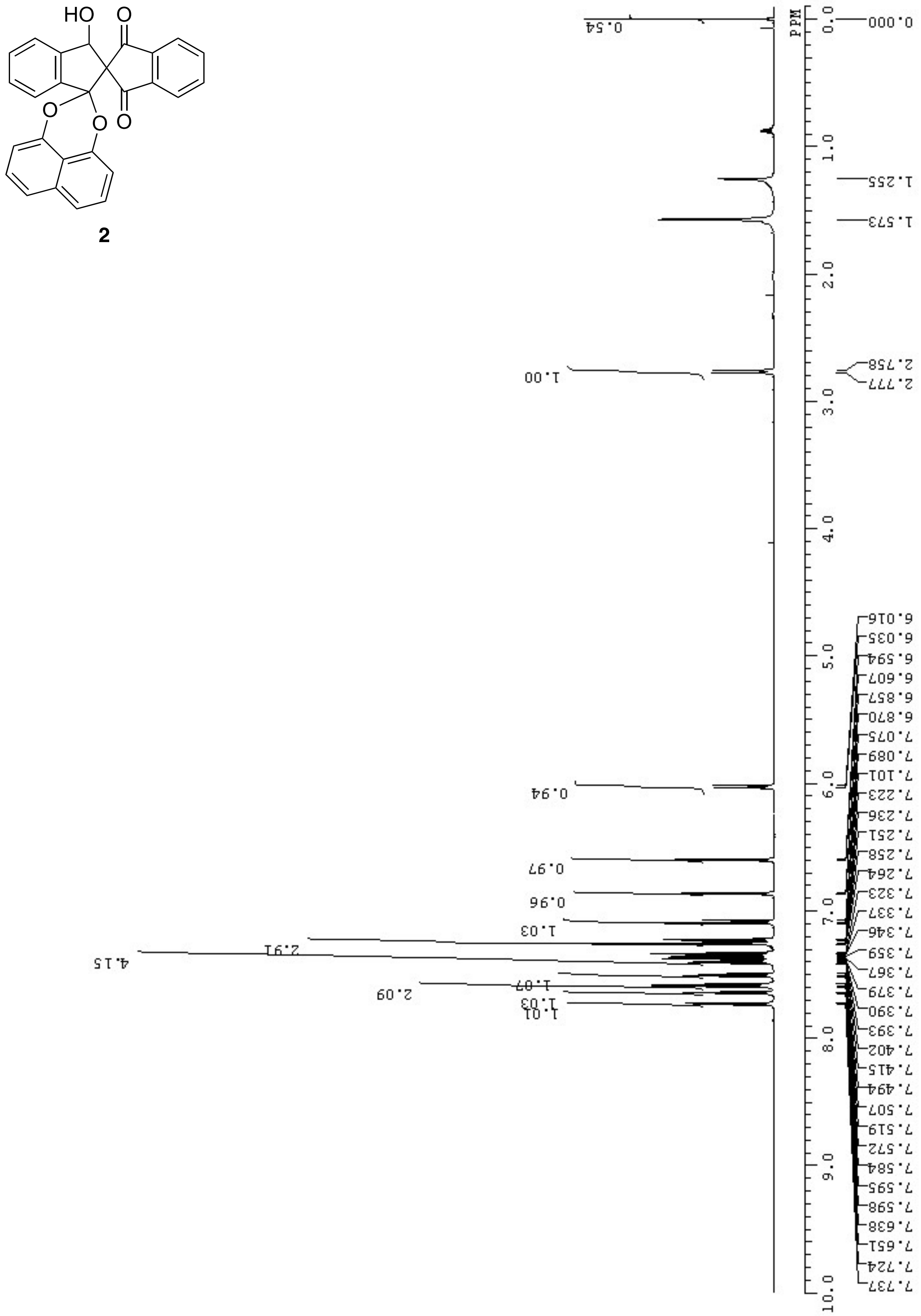


^{13}C NMR spectrum of **4**

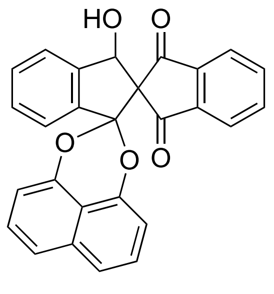


4

^{1}H NMR spectrum of **2**



^{13}C NMR spectrum of **2**



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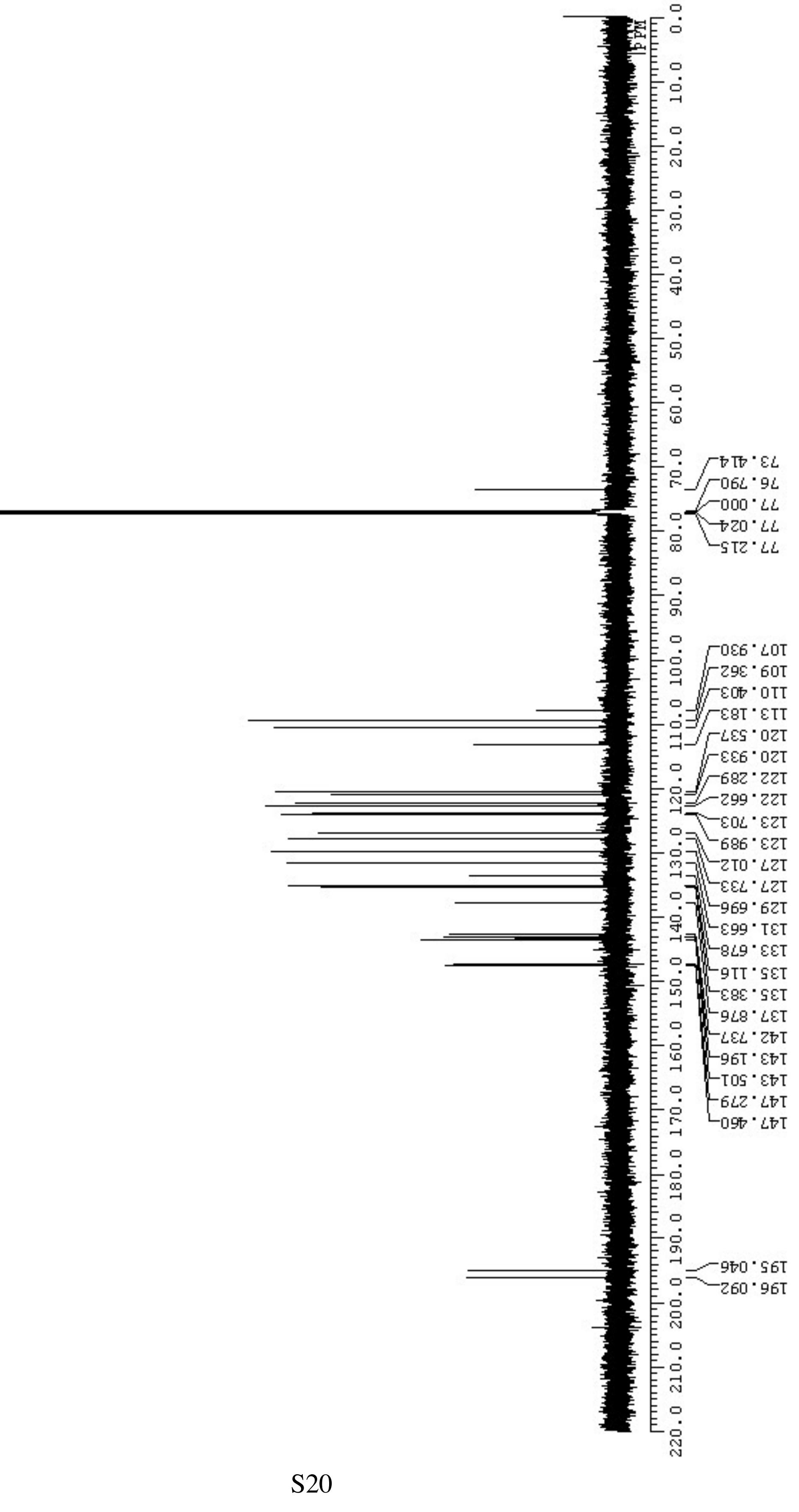
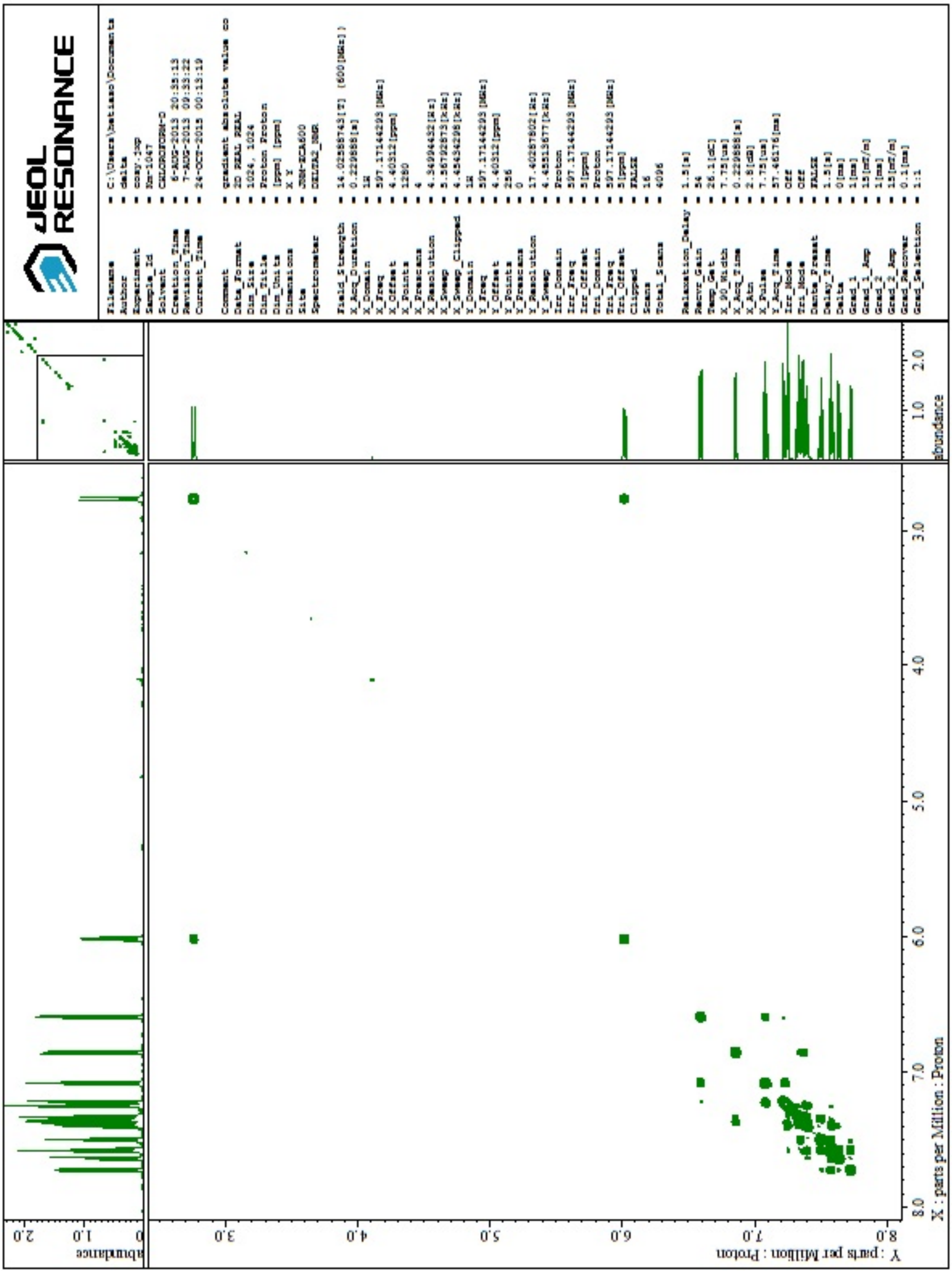
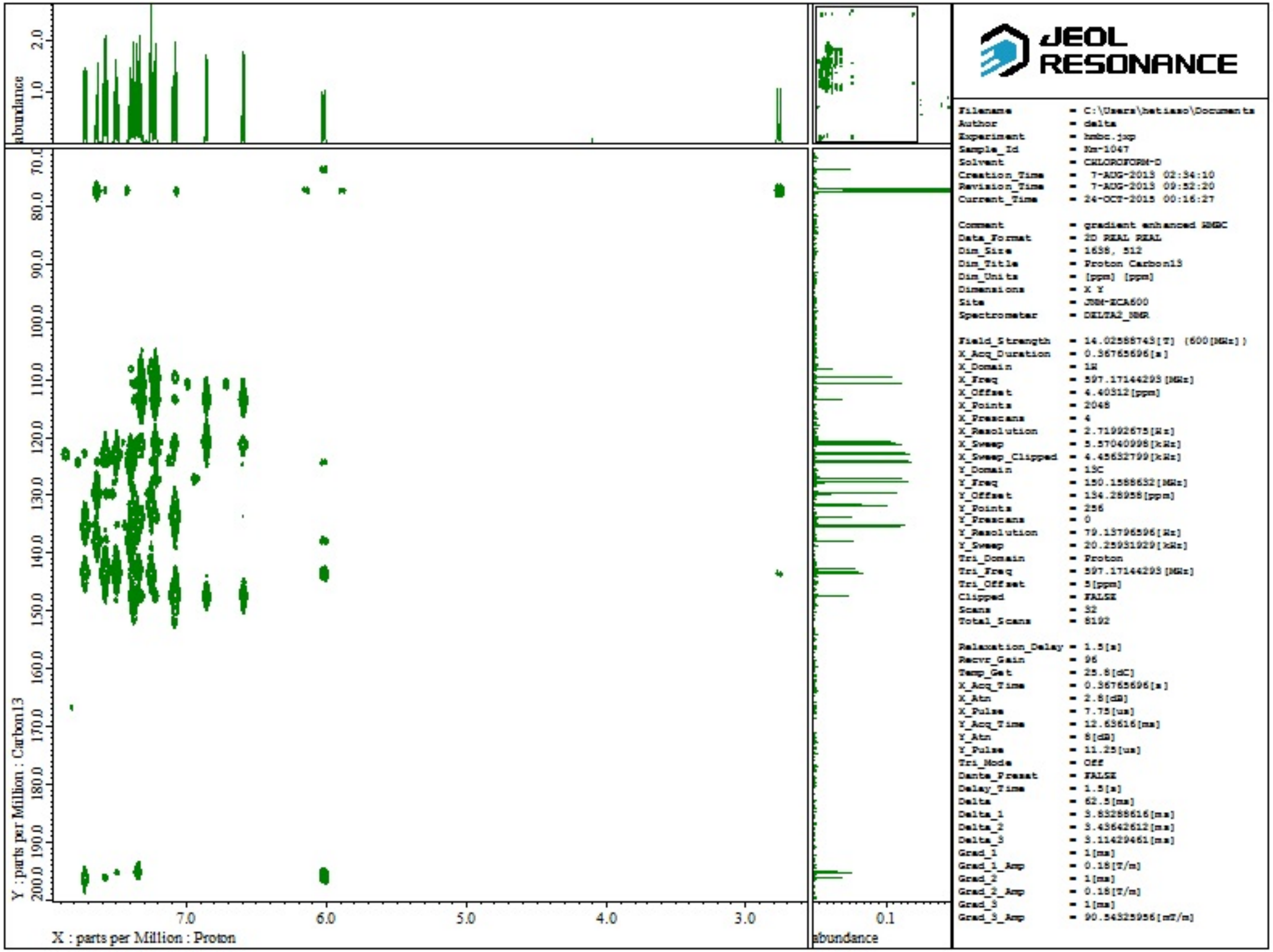


COSY spectrum of **2**



HMQC spectrum of **2**



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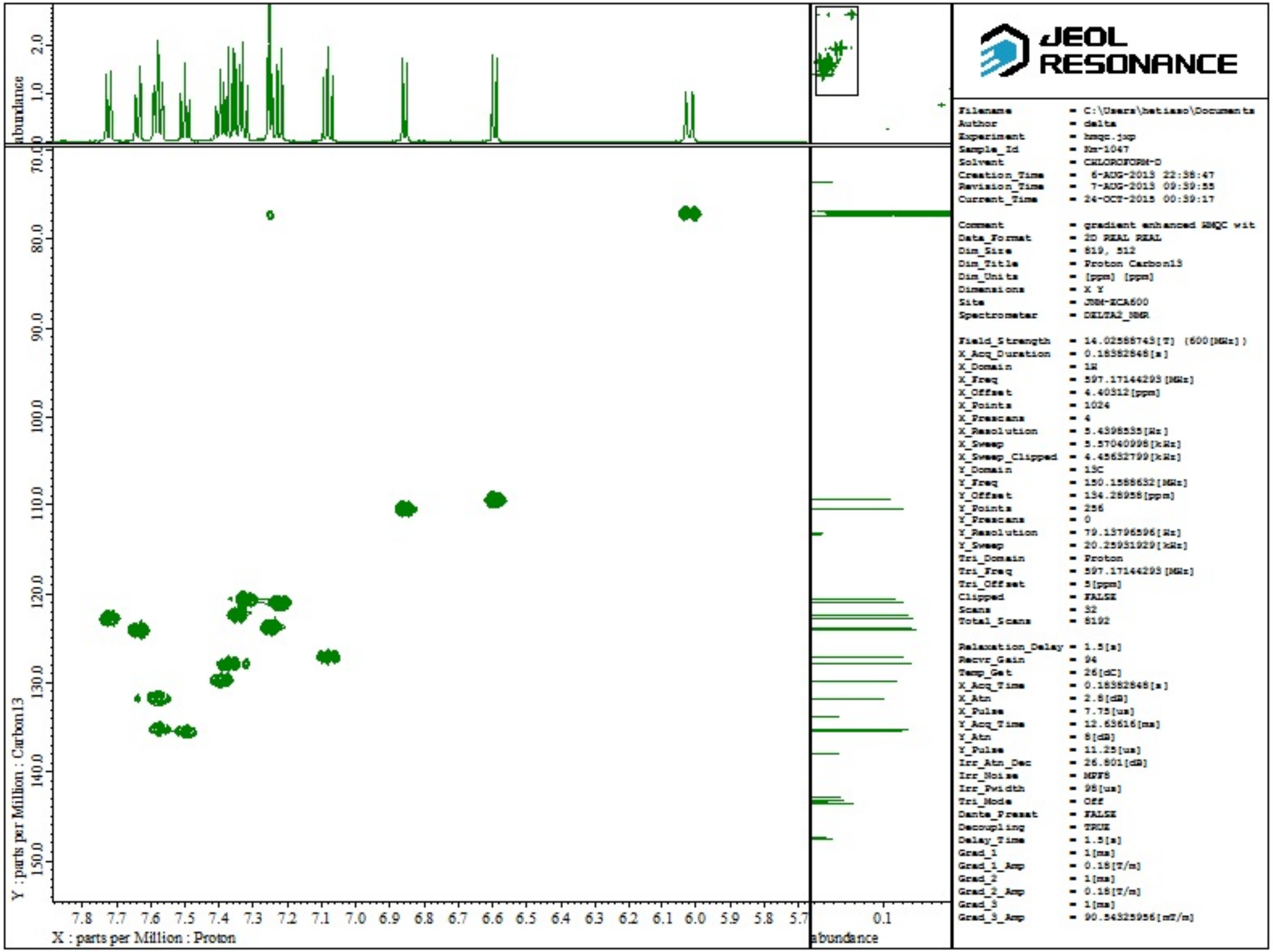
HMBC spectrum of **2**



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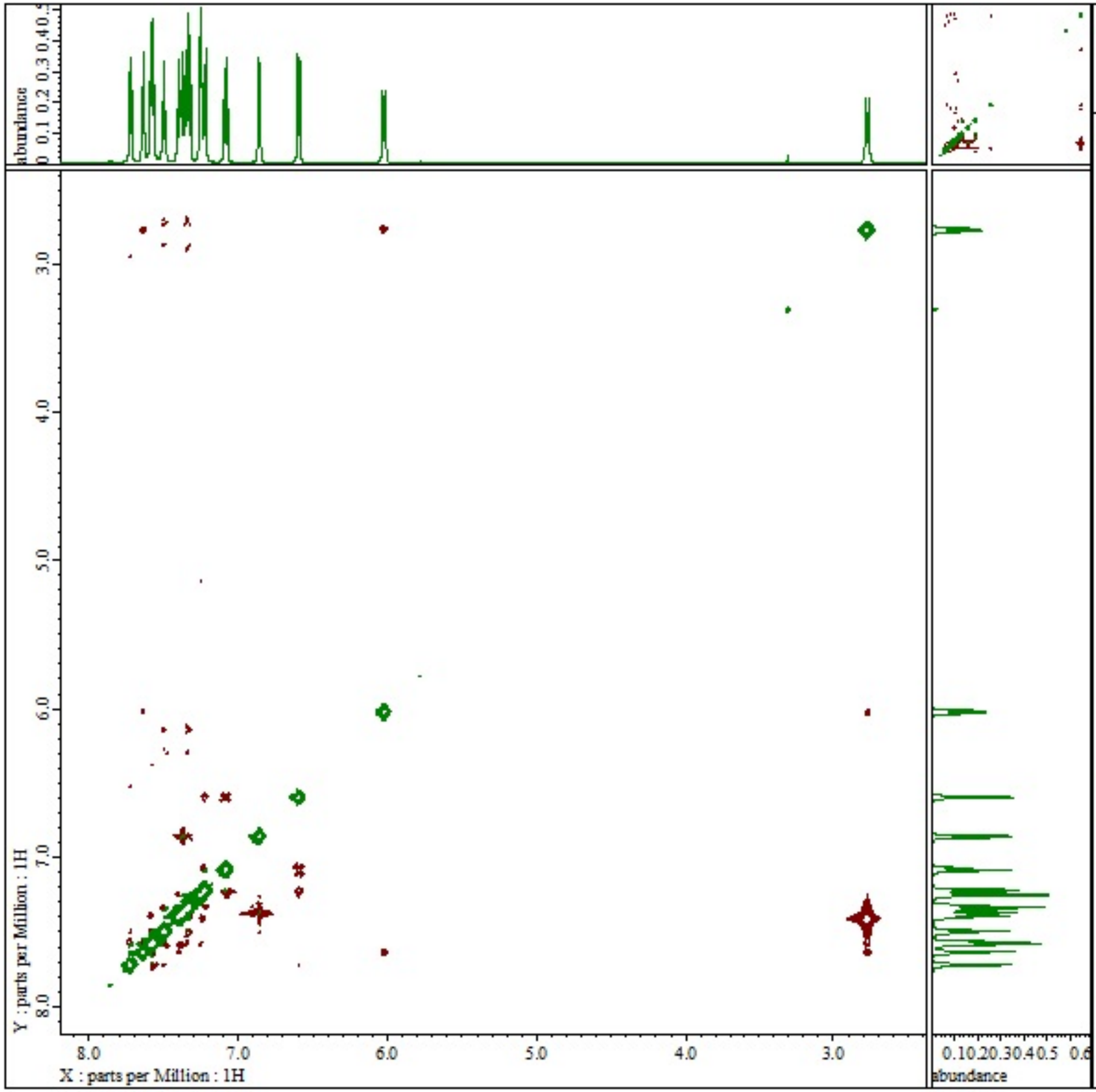

JEOL RESONANCE

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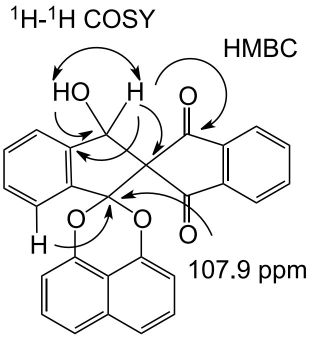
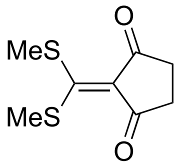


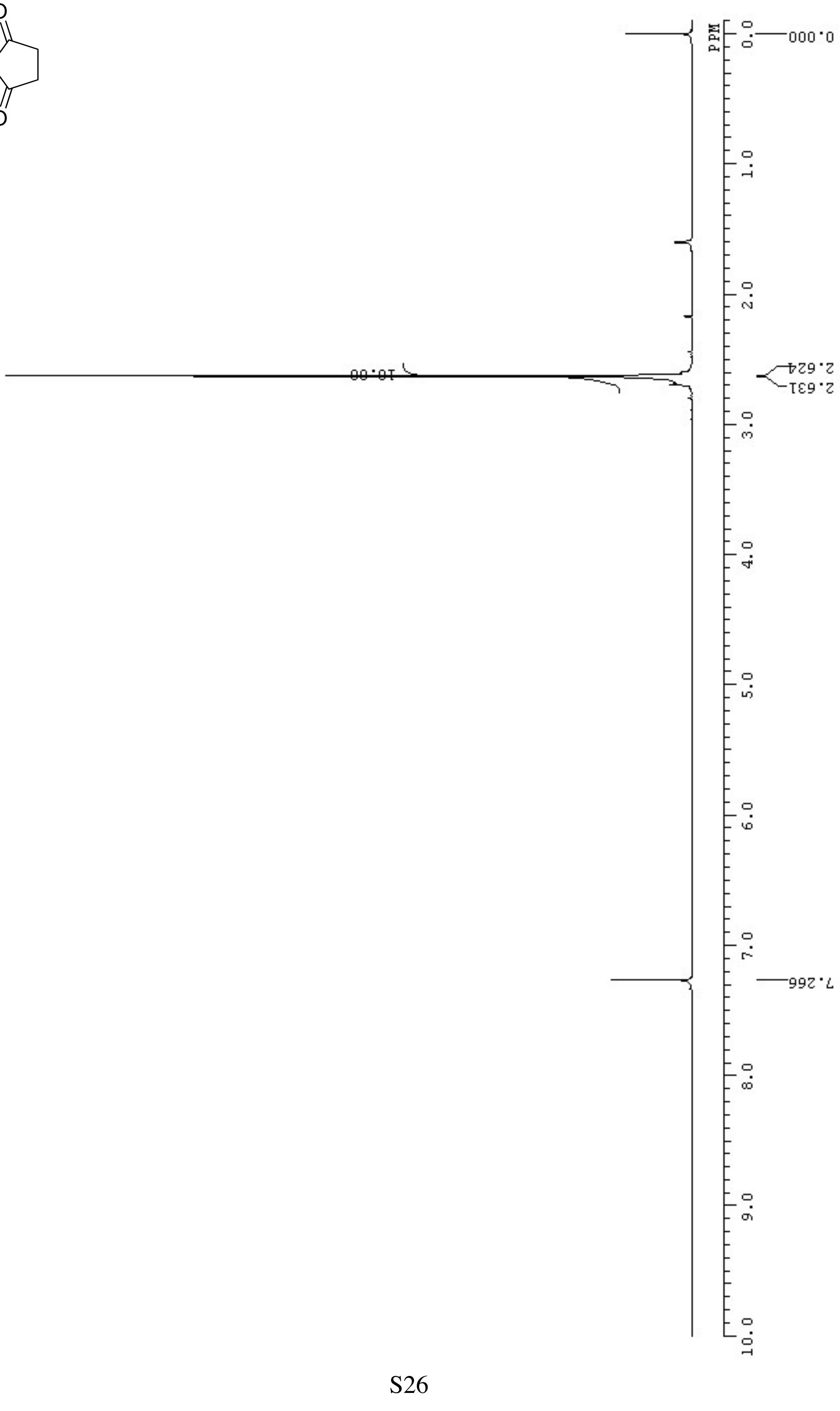
spiromamakone A
dibenzo analogue **2**

^{1}H, ^{13}C-NMR
^{1}H-^{1}H COSY
HMQC
HMBC

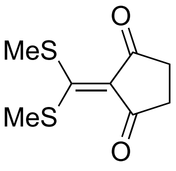
^{1}H NMR spectrum of **11**



11



^{13}C NMR spectrum of **11**



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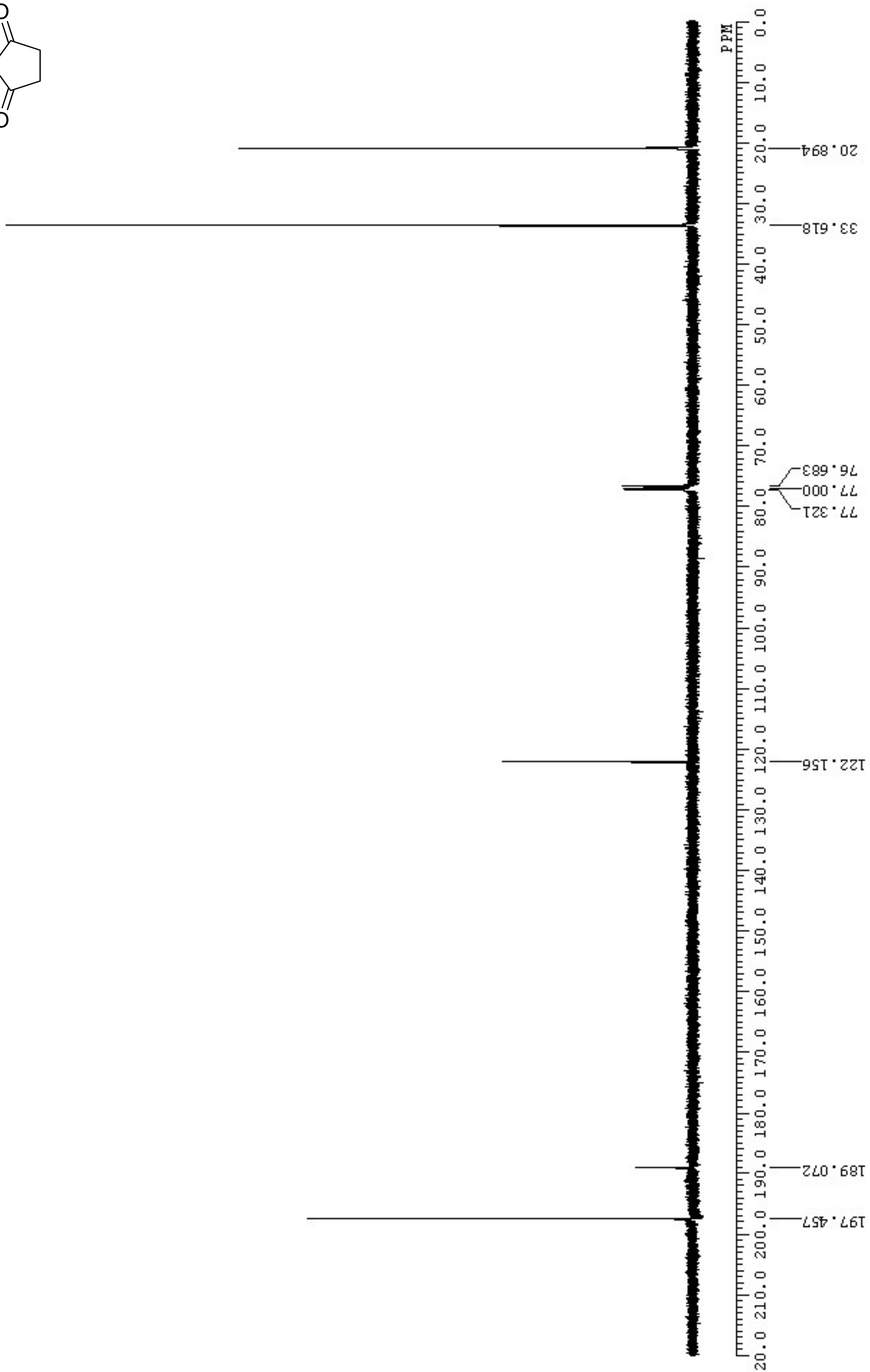
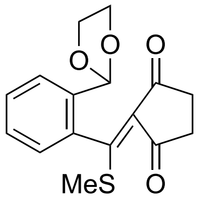
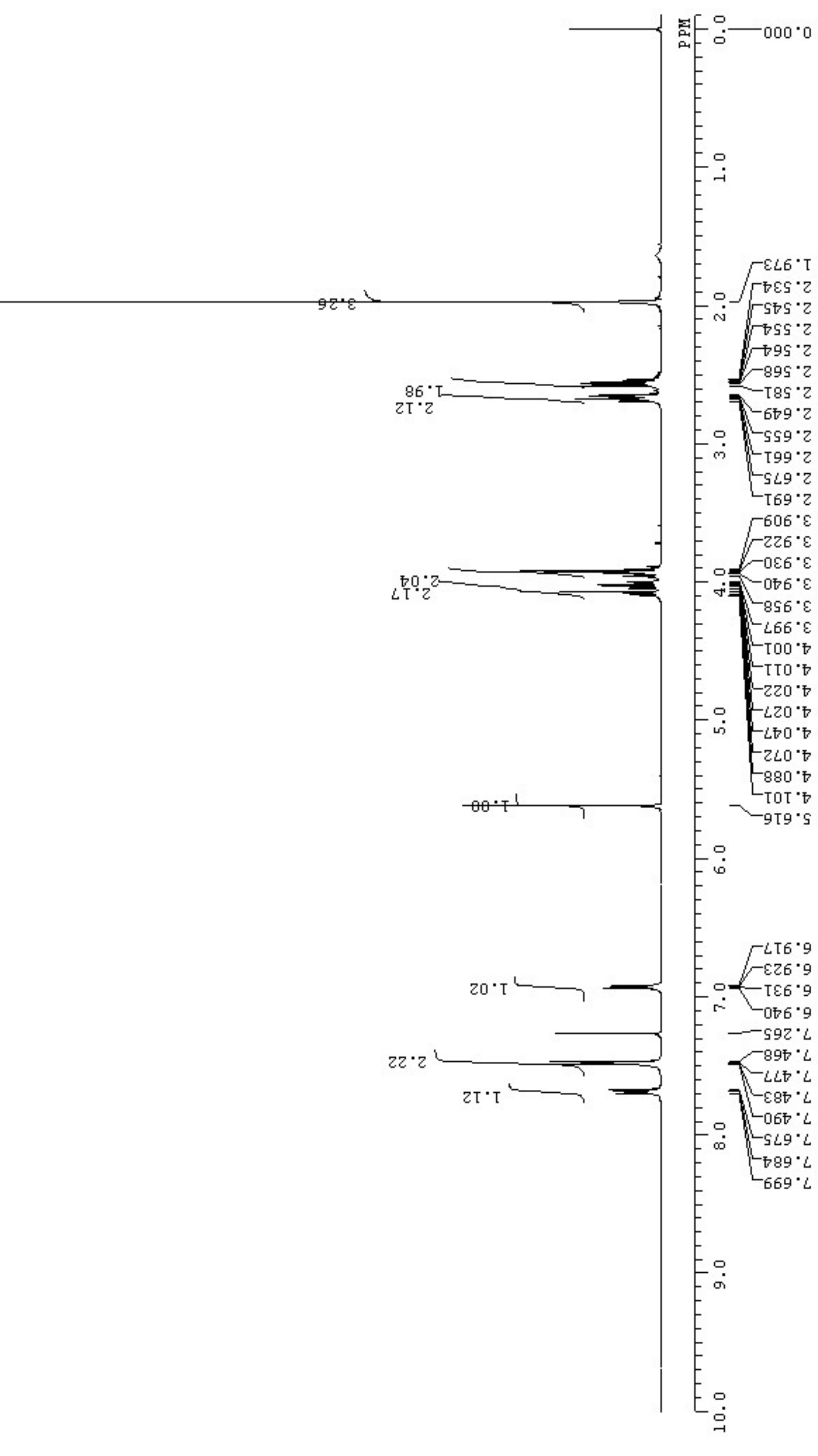


^{1}H NMR spectrum of **12**



12



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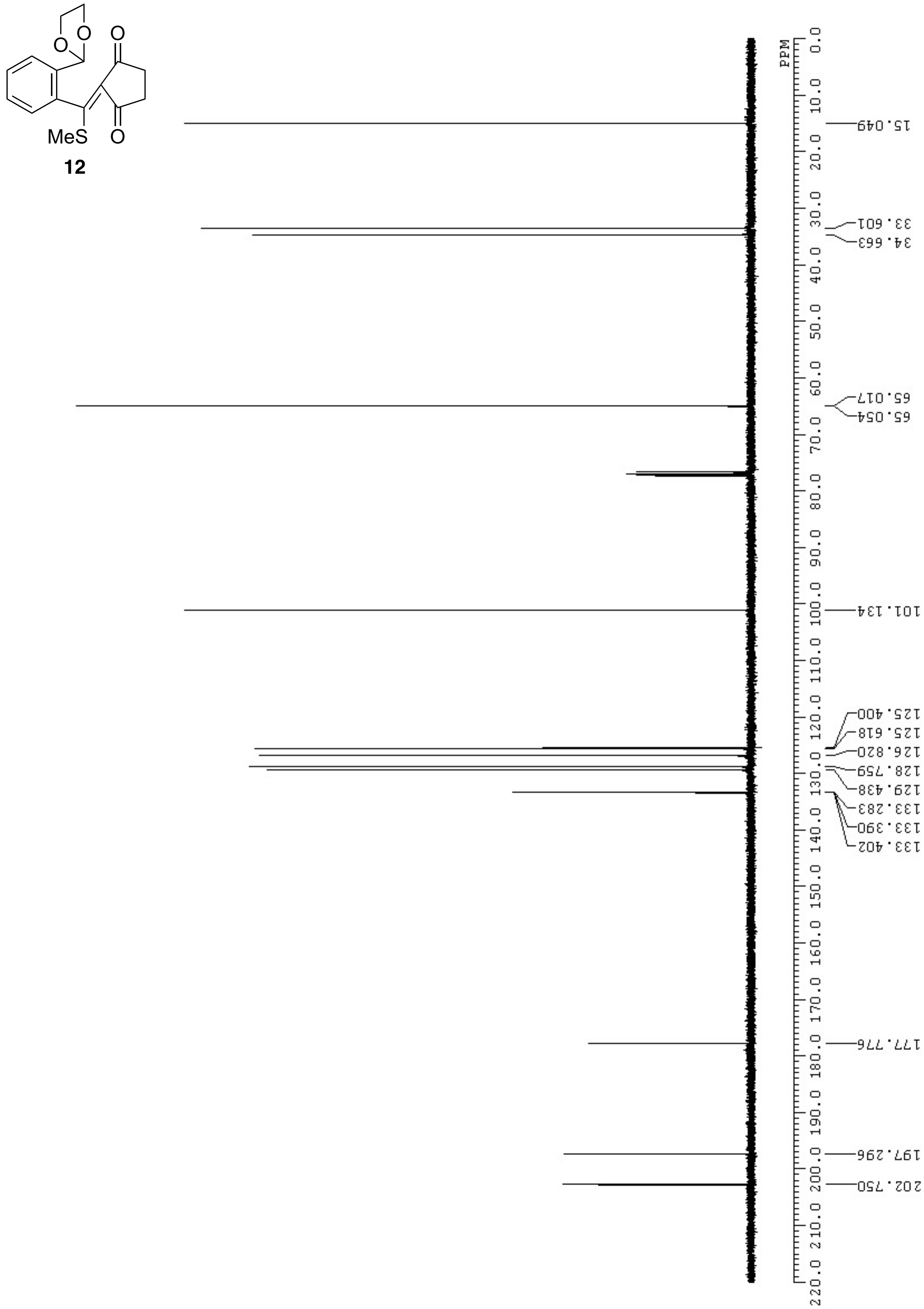
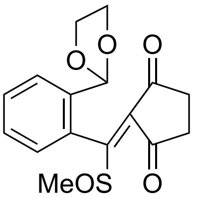


^{1}H NMR spectrum of **13**



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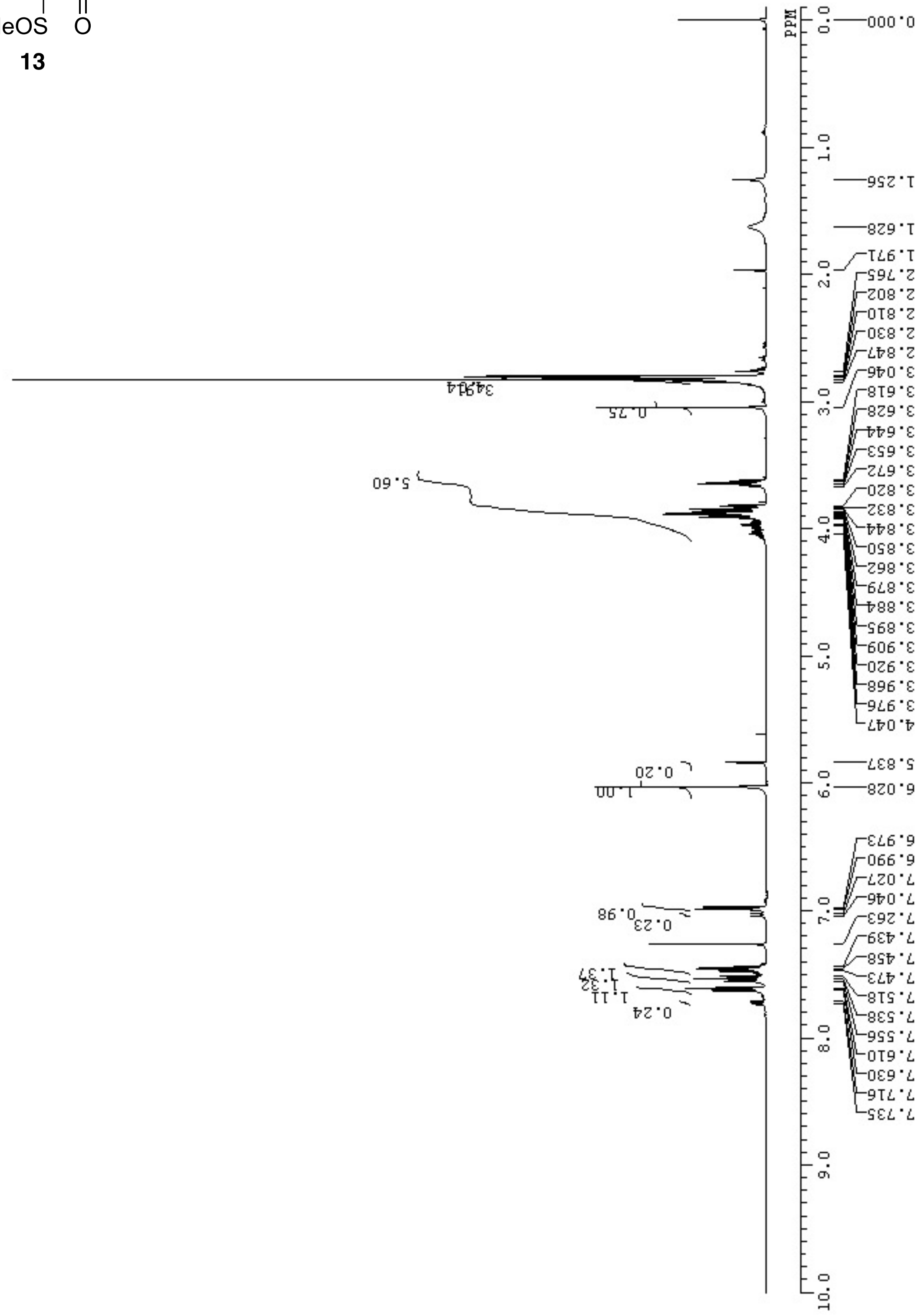

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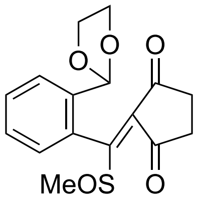

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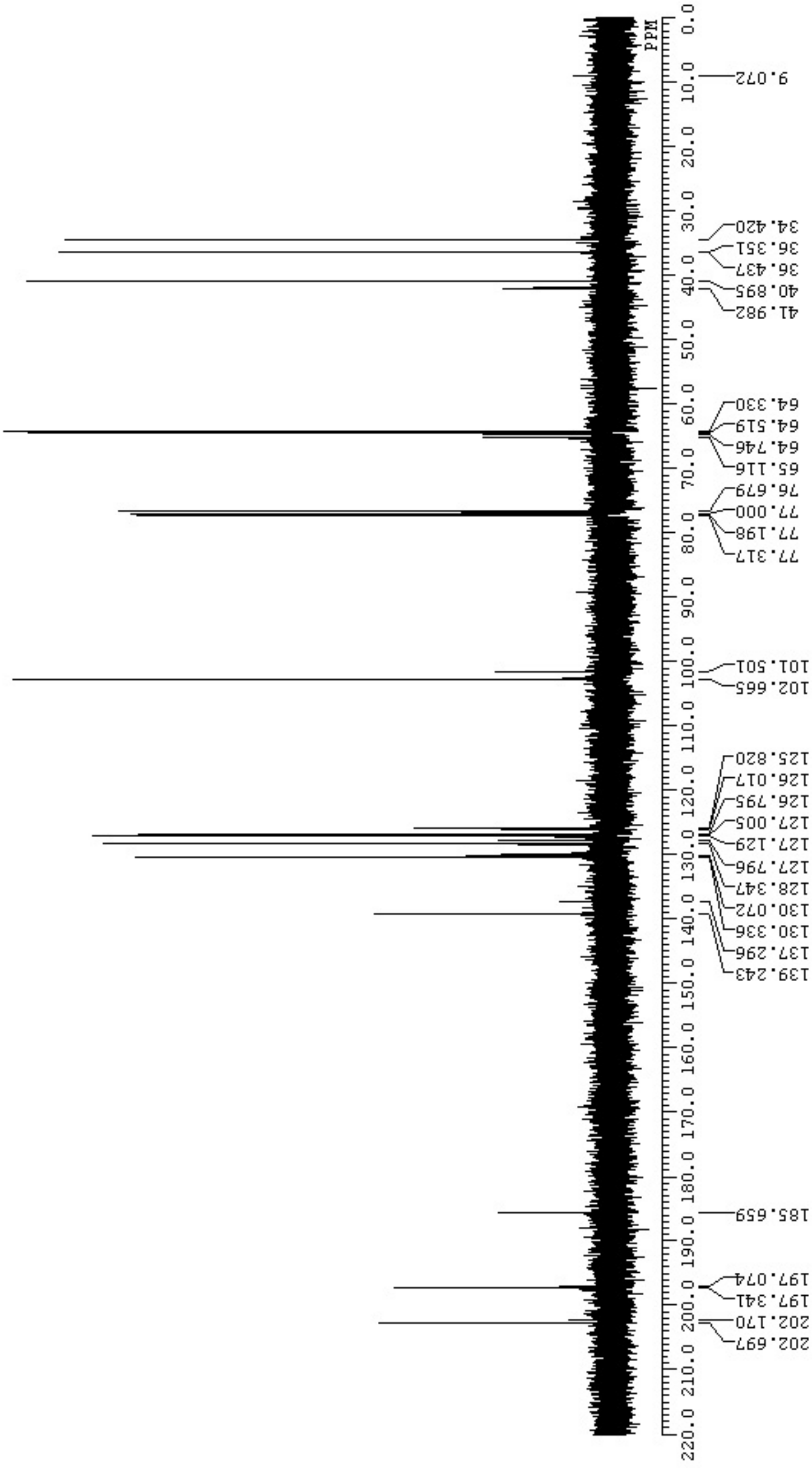

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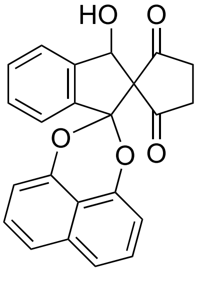

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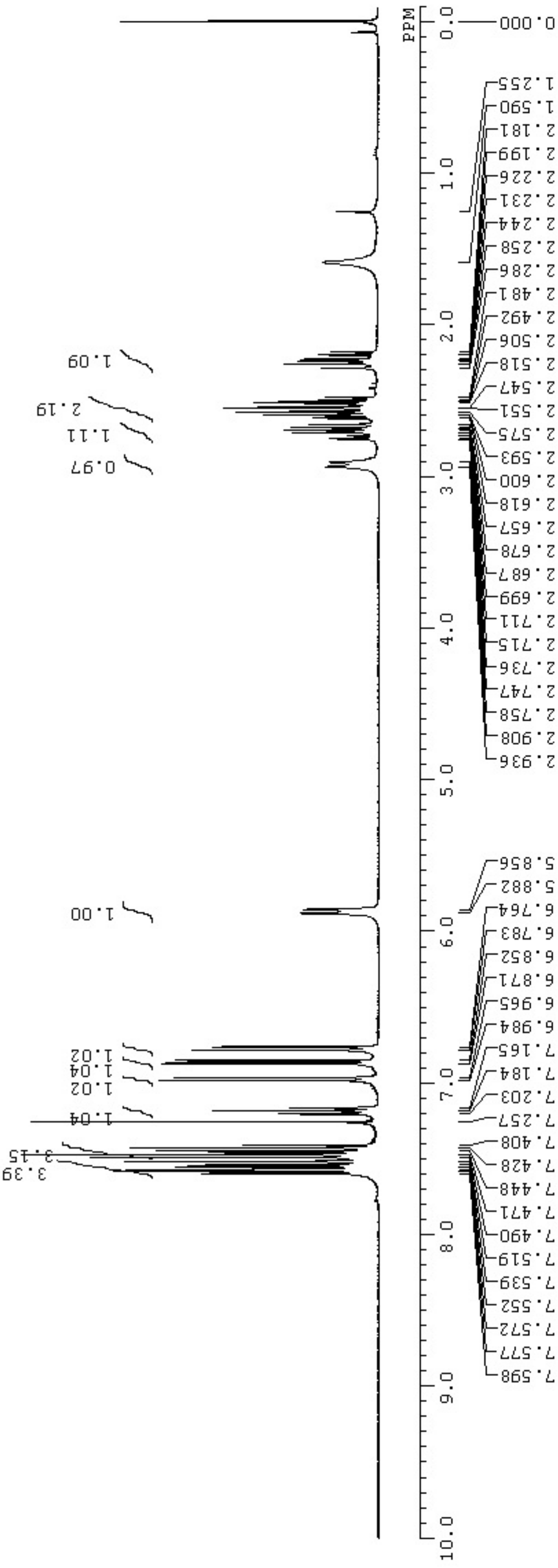

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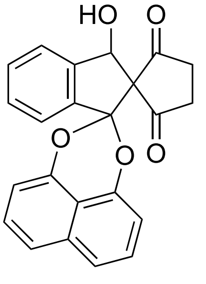

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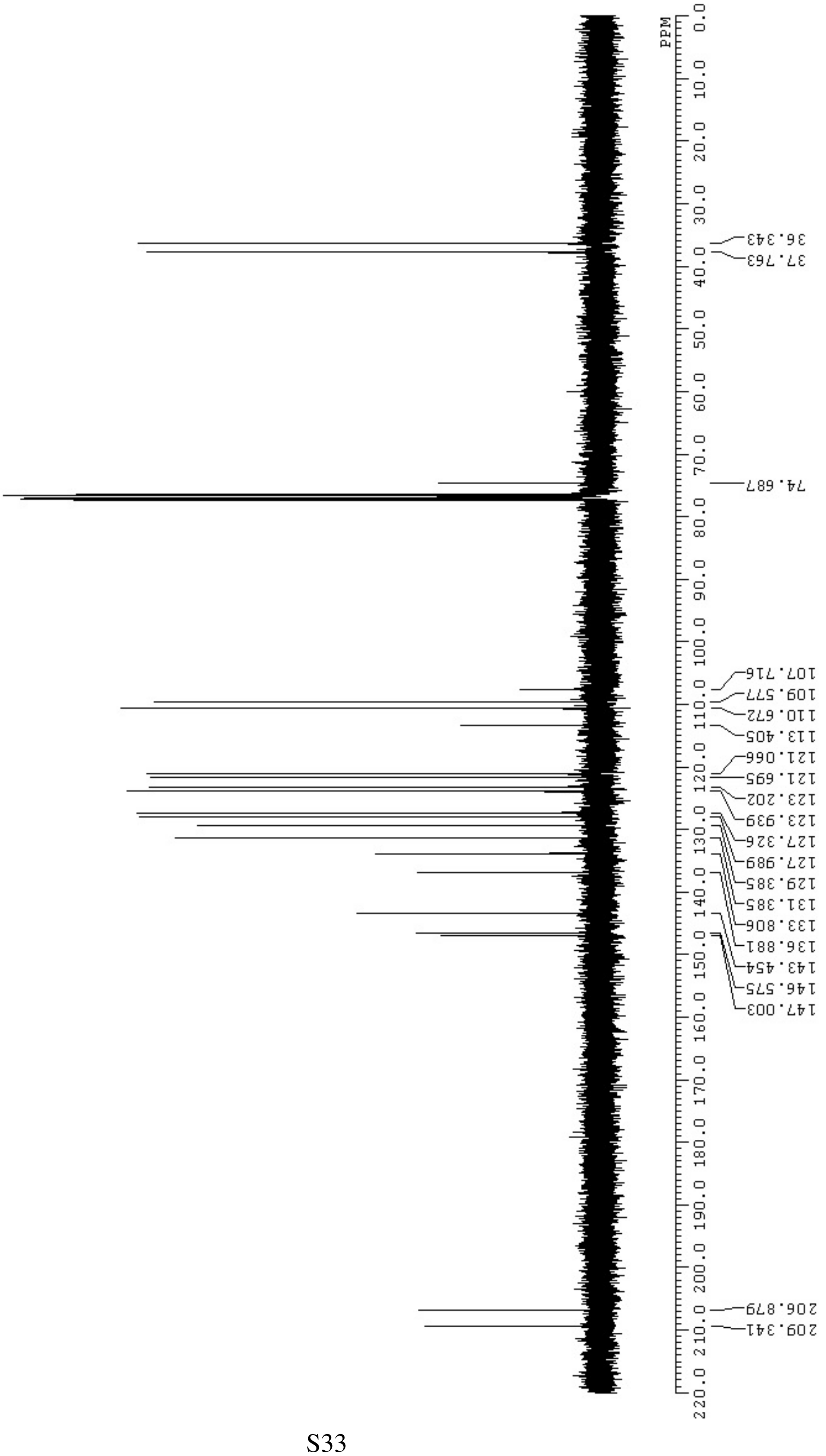
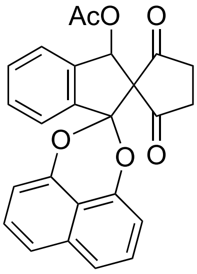


^{1}H NMR spectrum of **16**



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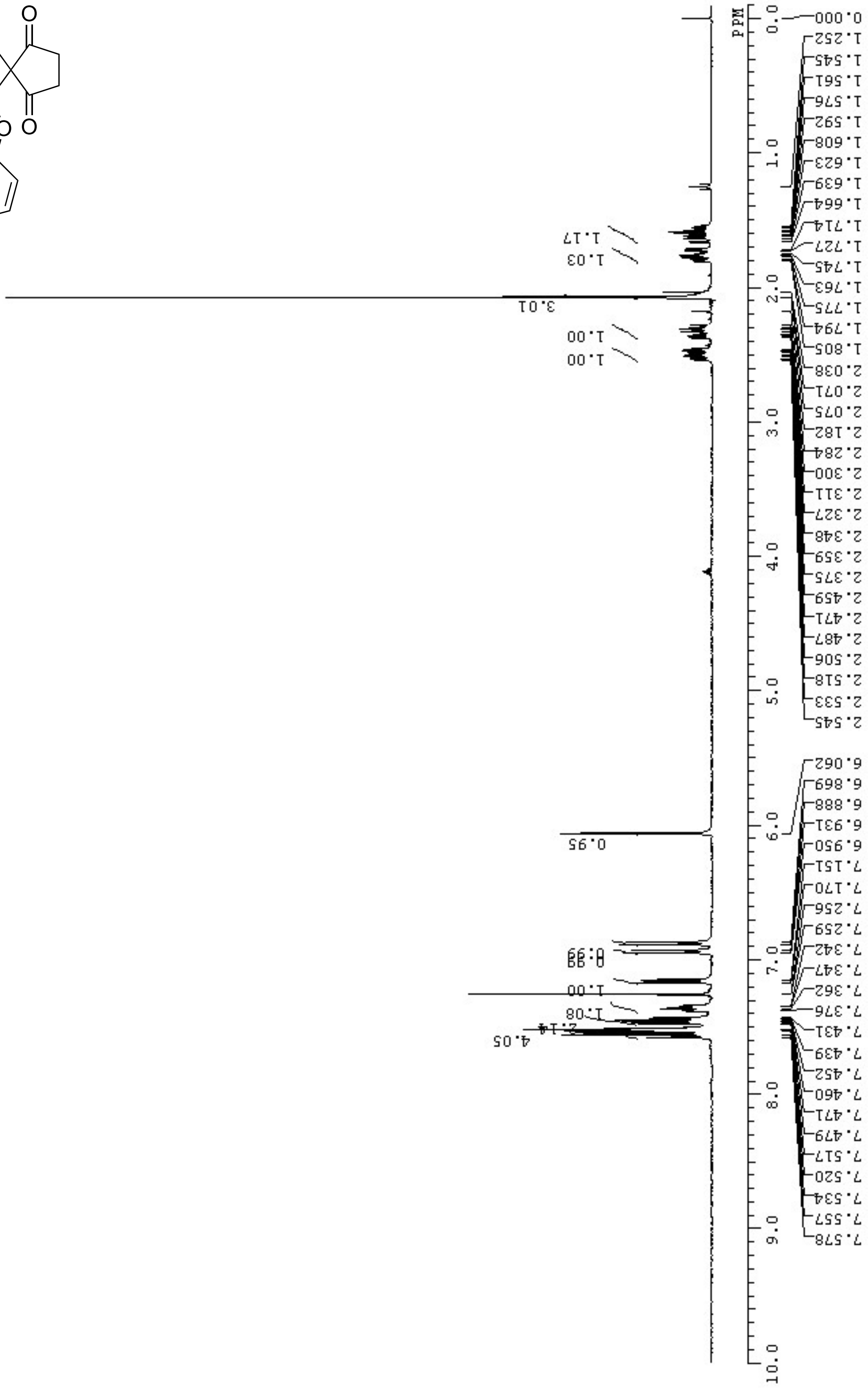
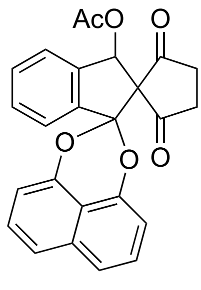


^{13}C NMR spectrum of **16**



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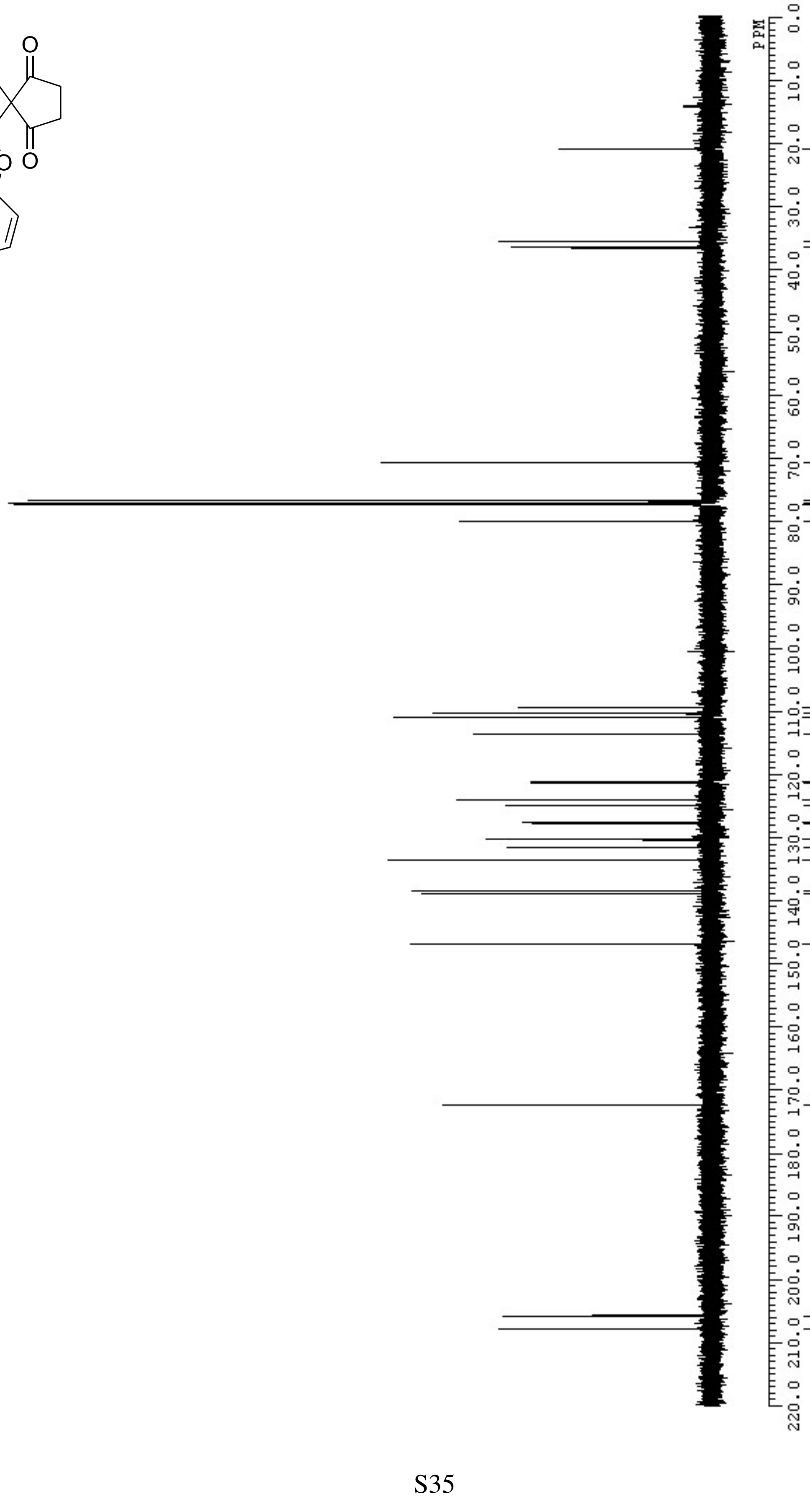
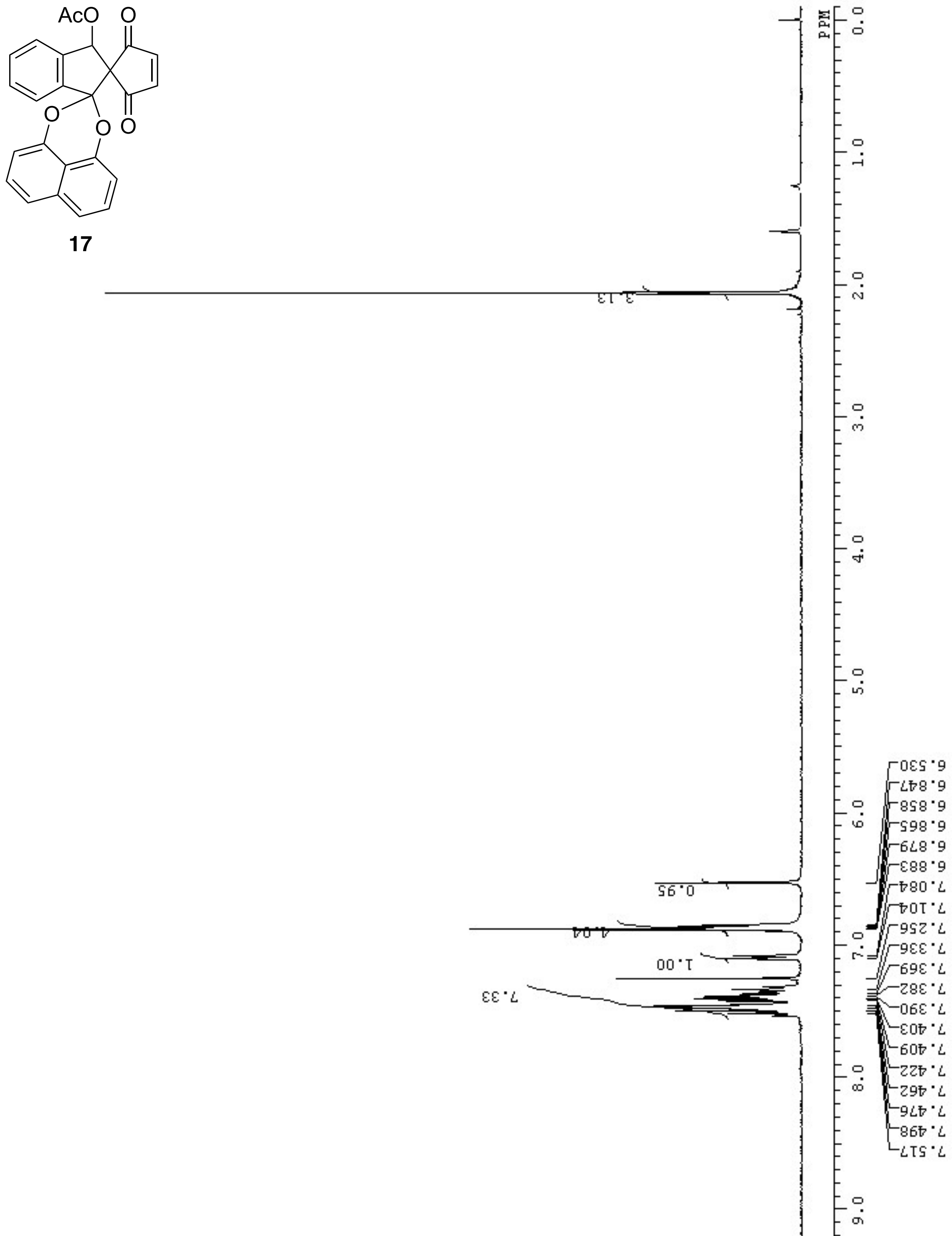
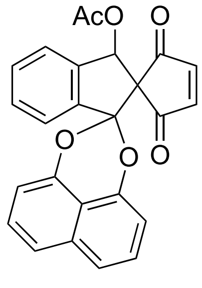


^{1}H NMR spectrum of **17**



17

^{13}C NMR spectrum of **17**



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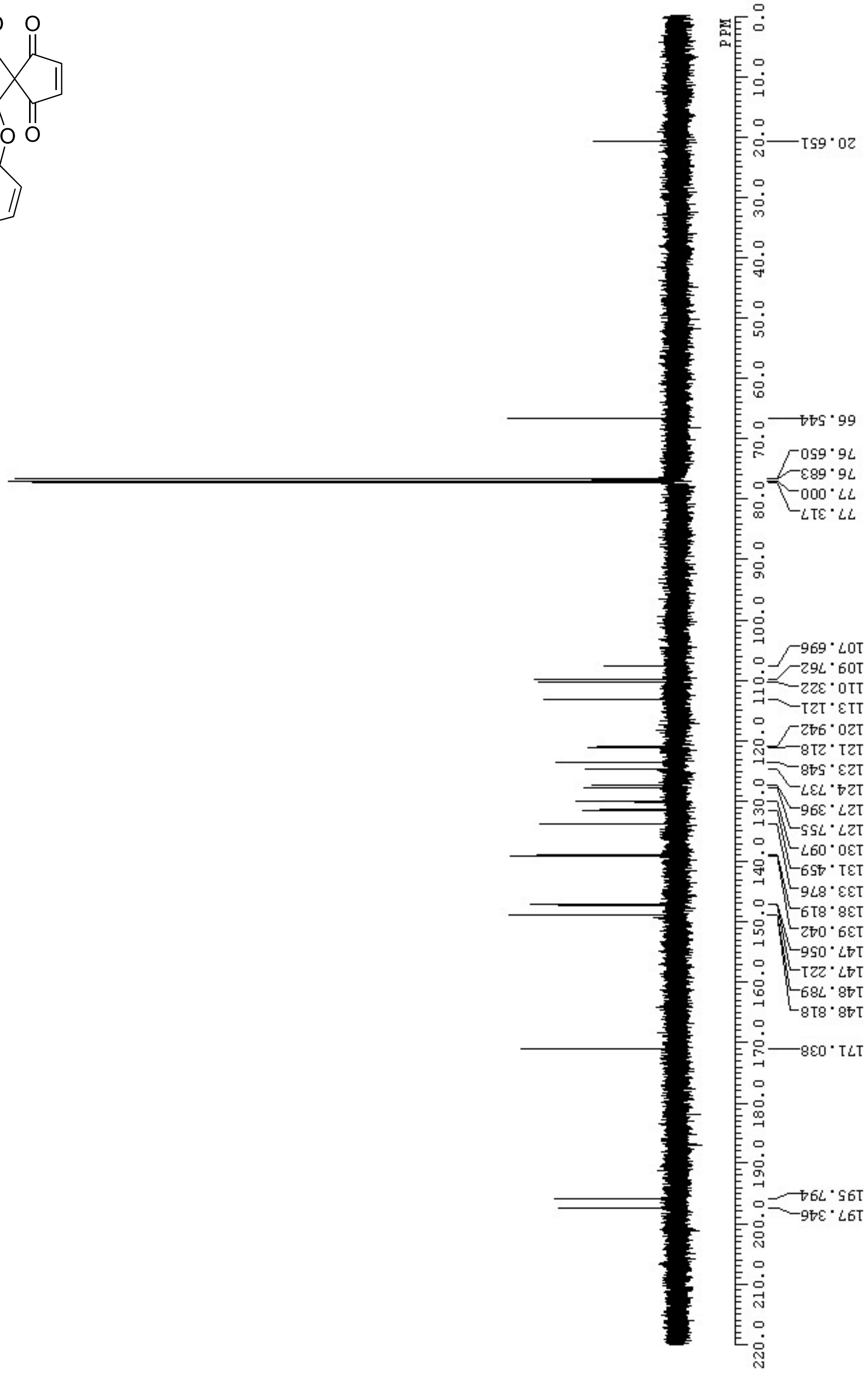
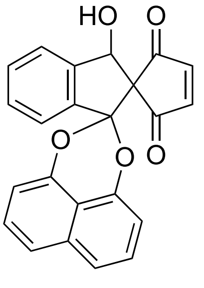
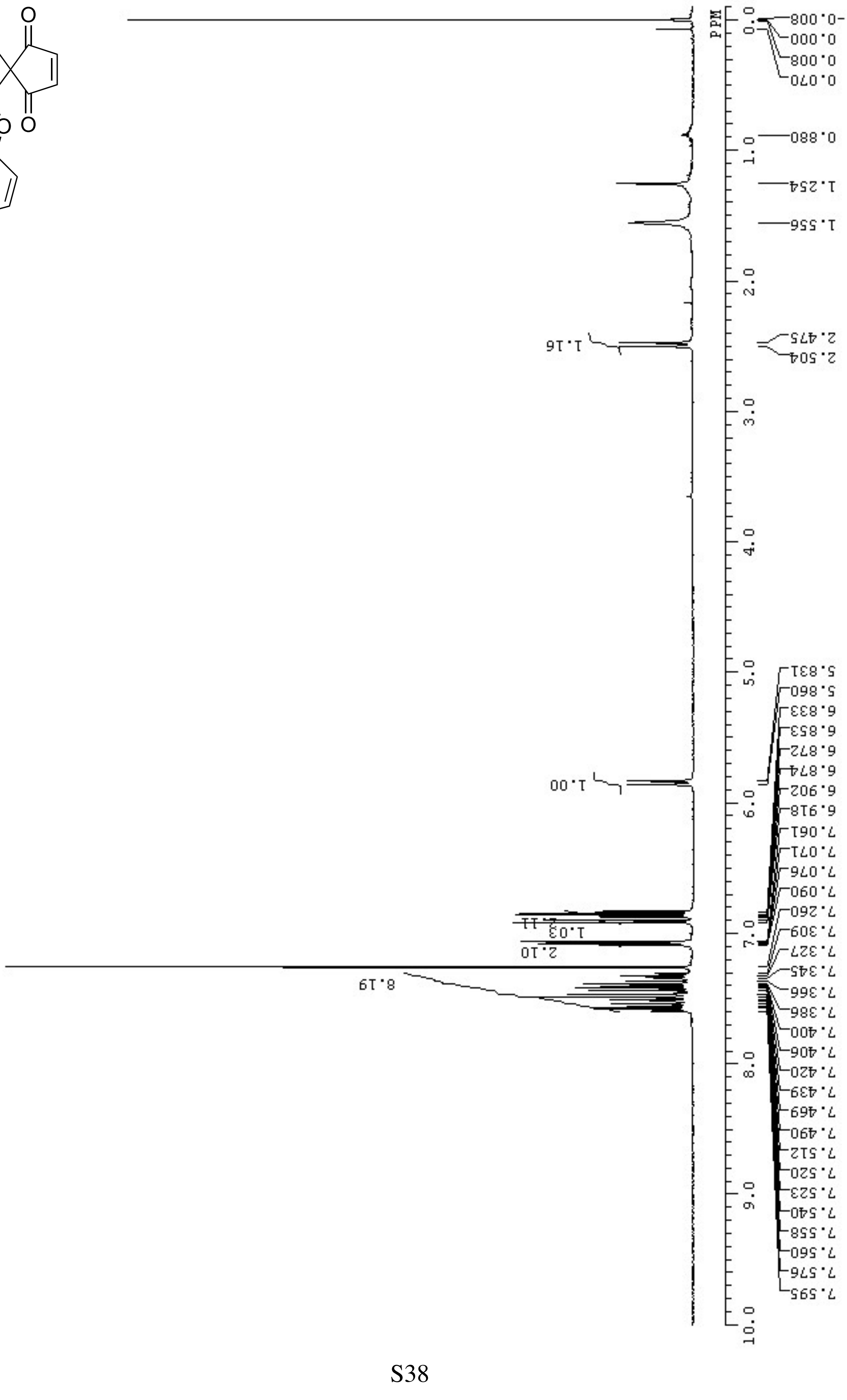


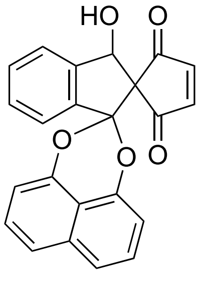
^{1}H NMR spectrum of **3**



3



^{13}C NMR spectrum of **3**



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