Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Total Synthesis of Six Resveratrol-based Natural Products: A Chemoselective Solution

Scott A. Snyder,* Alexandros L. Zografos, Yunqing Lin

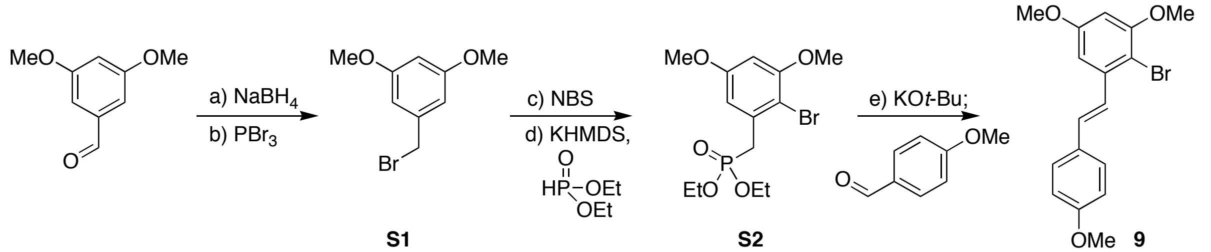
Department of Chemistry, Columbia University
Havemeyer Hall – Mail Code 3129
3000 Broadway, New York, NY 10027 (USA)

Experimental Data for Compounds

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent.

IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

Abbreviations. NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid, KHMDS = potassium bis(trimethylsilyl)amide, *p*-TsOH = *para*-toluenesulfonic acid, *m*CPBA = *meta*-chloroperoxybenzoic acid, 9-I-BBN = 9-iodo-9-borabicyclo[3.3.1]nonane, AIBN = 2,2'-azobisisobutyronitrile, TMS = trimethylsilyl.



Scheme S1. Synthesis of key halogenated building block **9**. a) $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 30 min; b) PBr_3 (1.0 equiv), pyridine (0.05 equiv), Et_2O, 40 °C, 3 h, 93% over two steps; c) NBS (1.0 equiv), CH_2Cl_2, 0 °C, 1 h, 95%; d) HP(O)$(OEt)_2$ (2.0 equiv), KHMDS (0.5 M in toluene, 1.8 equiv), THF, 0 °C, 15 min, then add substrate, 25 °C, 12 h, 91%; e) KO*t*-Bu (1.0 M in THF, 1.0 equiv), THF, -78 °C, 20 min, then *p*-methoxybenzaldehyde (0.95 equiv), -78 °C, 1h, then 25 °C, 12 h, 98%;

1-(bromomethyl)-3,5-dimethoxybenzene (S1). $NaBH_4$ (1.11 g, 30.0 mmol, 2.0 equiv) was added slowly to a solution of 3,5-dimethoxybenzaldehyde (2.44 g, 15.0 mmol, 1.0 equiv) in MeOH (30 mL) at 0 °C. After 30 min of stirring at 0 °C, the reaction contents were quenched by the slow addition of water (20 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired alcohol intermediate (2.43 g, 99% yield) as a white solid which was carried forward without further purification. Next, pyridine (0.017 mL, 0.212 mmol, 0.05 equiv) and PBr_3 (0.400 mL, 4.25 mmol, 1.0 equiv) were added sequentially and slowly to a portion of this newly-formed alcohol (0.715 g, 4.25 mmol, 1.0 equiv) in Et_2O (20 mL) at 25 °C, and the resultant mixture was heated at 40 °C for 3 h. Upon completion, the reaction contents were quenched carefully with ice water (15 mL), poured into water (10 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated to afford alkyl halide **S1** (1.50 g, 93% yield) as an amorphous white solid which was carried forward without additional purification. **S1**: $R_f = 0.66$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3002, 2960, 2838, 1597, 1465, 1429, 1348, 1325, 1300, 1264, 1206, 1158, 1064, 992, 931, 836, 693, 650; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.1 Hz, 2 H), 6.39 (t, *J* = 2.1 Hz, 1 H), 4.42 (s, 2 H), 3.80 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 139.7, 107.0 (2 C), 100.6, 55.4 (2 C), 33.6; HRMS (MALDI-FTMS) calcd for $C_9H_{11}BrO_2^+$ [M^+] 229.9942, found 229.9937.

Diethyl 2-bromo-3,5-dimethoxybenzylphosphonate (S2). To a solution of alkyl bromide **S1** (1.34 g, 5.80 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) at 0 °C was added solid NBS (0.516 g, 2.89 mmol, 0.5 equiv) in a single portion. After stirring the resultant solution for 30 min at 0 °C, a second aloquot of NBS was added (0.516 g, 2.89 mmol, 0.5 equiv) and the reaction was stirred for an additional 30 min at 0 °C. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), poured into H_2O (20 mL), and extracted with EtOAc (3 × 70 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to give the desired halogenated intermediate (1.70 g, 95% yield) as a white solid which was carried forward without additional purification. Next, a portion of this newly formed aryl bromide (1.00 g, 3.22 mmol, 1.0 equiv) was dissolved in THF (5 mL) and added dropwise at 0 °C to a THF solution of the anion of diethylphosphite which had been prepared by adding KHMDS (11.6 mL, 0.5 M in toluene, 5.80 mmol, 1.8 equiv) to a solution of diethylphosphite (0.830 mL, 6.44 mmol, 2.0 equiv) in THF (20 mL) at 0 °C and stirring for 15 min. After 5 min of stirring at 0 °C, the reaction contents were warmed to 25 °C and stirred for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), poured into water (15 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow product was left under high vacuum for 24 h to remove any residual diethylphosphite, ultimately affording phosphonate **S2** (1.07 g, 91% yield) as a white solid. **S2**: $R_f = 0.15$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2981, 2938, 2907, 2837, 1592, 1456, 1418, 1331, 1253, 1204, 1165, 1079, 1052, 1024, 961, 852, 782, 650; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (t, *J* = 2.7 Hz, 1 H), 6.39 (t, *J* = 2.4 Hz, 1 H), 4.15 (dd, *J* = 6.9, 6.0 Hz, 2 H), 4.06 (dd, *J* = 6.9, 6.0 Hz, 2 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.43 (d, *J* = 22.2 Hz, 2 H), 1.36 (t, *J* = 6.9 Hz, 3 H), 1.27 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 156.8, 133.7, 133.6, 107.4, 107.3, 99.8, 62.3, 62.2, 56.3, 55.5, 34.7, 16.4, 16.3; HRMS (MALDI-FTMS) calcd for $C_{13}H_{21}BrO_5P^+$ [M + H$^+$] 367.0310, found 367.0301.

(*E*)-2-bromo-1,5-dimethoxy-3-(4-methoxystyryl)benzene (9). KO*t*-Bu (5.71 mL, 1.0 M in THF, 5.71 mmol, 1.05 equiv) was added dropwise over the course of 5 min to a solution of phosphonate **S2** (2.00 g, 5.44 mmol, 1.0 equiv) in THF (25 mL) at –78 °C. After 20 min of stirring at –78 °C, a solution of anisaldehyde (0.704 g, 5.17 mmol, 0.95 equiv) in THF (5 mL) was added at –78 °C. The resultant solution was stirred at –78 °C for 1 h, and then at 25 °C for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL), poured into water (10 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to give resveratrol derivative **9** (1.86 g, 98% yield) as a white powder which was carried forward without additional purification. **9**: $R_f = 0.61$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3002, 2937, 2836, 1719, 1589, 1511, 1454, 1415, 1341, 1286, 1252, 1203, 1163, 1082, 1023, 962, 827; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.7 Hz, 2 H), 7.41 (d, *J* = 16.2 Hz, 1 H), 6.98 (d, *J* = 16.2 Hz, 1 H), 6.91 (d, *J* = 9.0 Hz, 2 H), 6.80 (d, *J* = 2.7 Hz, 1 H), 6.42 (d, *J* = 2.7 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s 3 H), 3.83 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 159.5, 156.8, 138.9, 131.1, 129.7, 128.1, 125.8, 114.1, 104.9, 102.4, 98.7, 56.3, 55.5, 55.3; HRMS (MALDI-FTMS) calcd for $C_{17}H_{17}BrO_3^+$ [M^+] 348.0361, found 348.0362.

(*E*)-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl-(3,5-dimethoxyphenyl)methanol (11). *n*-BuLi (2.91 mL, 1.6 M in THF, 4.65 mmol, 1.05 equiv) was added slowly over the course of 5 min to a solution of resveratrol derivative **9** (1.62 g, 4.65 mmol, 1.05 equiv) in THF (10 mL) at –78 °C, ultimately yielding a light yellow solution. After 20 min of stirring at –78 °C, a solution of 3,5-dimethoxybenzaldehyde (0.734 g, 4.42 mmol, 1.0 equiv) in THF (40 mL) was added slowly at –78 °C, and the resultant mixture was stirred for 1 h at –78 °C, warmed slowly to 25 °C, and stirred for an additional 4 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (20 mL), poured into water (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to give aldol adduct **11** (1.43 g, 71% yield) as a white solid. **11**: R_f = 0.40 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3509, 3001, 2938, 2837, 1604, 1511, 1458, 1307, 1244, 1204, 1175, 1153, 1059, 1032, 966, 930, 833, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2 H), 7.28 (d, *J* = 16.2 Hz, 1 H), 6.88 (d, *J* = 16.2 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.74 (d, *J* = 2.1 Hz, 1 H), 6.54 (d, *J* = 2.0 Hz, 2 H), 6.45 (d, *J* = 2.1, 1 H), 6.33 (t, *J* = 2.4, 1 H), 6.22 (d, *J* = 9 Hz, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 1 H), 3.74 (s, 6 H), 3.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 159.8, 159.4, 158.6, 147.5, 138.7, 131.5, 129.9, 127.8, 124.4, 121.7, 114.0, 103.8, 103.1, 98.6, 98.3, 70.0, 55.7, 55.3, 55.1; HRMS (MALDI-FTMS) calcd for $C_{26}H_{28}O_6^+$ [M^+] 436.1886, found 436.1870.

3-(3,5-dimethoxyphenyl)-4,6-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (15). To a solution of aldol adduct **11** (0.150 g, 0.344 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at –78 °C was added in a single portion a solution of TFA (0.027 mL, 0.344 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL). The resultant dark purple reaction mixture was then warmed slowly to –20 °C over the course of 30 min and stirred for 5 h at –20 °C. Upon completion, the reaction mixture was quenched sequentially with solid K_2CO_3 (0.475 g, 3.44 mmol, 10 equiv) and MeOH (10 mL), warmed to 25 °C, and stirred for 15 min at 25 °C. The reaction contents were then poured into water (15 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant brown oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to give alcohol **15** (0.113 g, 75% yield) as an amorphous white solid. **15**: R_f = 0.41 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2935, 1597, 1512, 1463, 1304, 1248, 1203, 1151, 1060, 829; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 6.65 (d, *J* = 2.1 Hz, 1 H), 6.42 (d, *J* = 2.1 Hz, 1 H), 6.27 (t, *J* = 2.3 Hz, 1 H), 6.17 (d, *J* = 2.4 Hz, 2 H), 5.13 (app t, *J* = 5.7 Hz, 1 H), 4.19 (d, *J* = 6.9 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.59 (s, 3 H), 3.18 (d, *J* = 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 160.4, 158.5, 157.1, 146.9, 146.3, 134.0, 128.7, 122.9, 113.9, 105.5, 99.7, 99.4, 99.3, 98.0, 82.5, 66.1, 55.6, 55.3, 55.2, 54.7; HRMS (MALDI-FTMS) calcd for $C_{26}H_{28}O_6^+$ [M^+] 436.1886, found 436.1870.

Paucifloral F (6). Dess–Martin periodinane (0.152 g, 0.358 mmol, 1.2 equiv) was added in a single portion to a solution of alcohol **13** (0.130 g, 0.298 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at 25 °C, and the resultant slurry was stirred for 1 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na_2SO_3 (1.5 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to afford permethylated paucifloral F (0.122 g, 97% yield) as a light yellow oil which was carried forward without additional purification. $R_f = 0.45$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 1696, 1614, 1514, 1474, 1347, 1155, 1082, 1005, 842; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, $J = 8.7$ Hz, 2 H), 6.90 (d, $J = 2.1$ Hz, 1 H), 6.84 (d, $J = 8.7$ Hz, 2 H), 6.70 (d, $J = 2.1$ Hz, 1 H), 6.32 (app t, $J = 2.4$ Hz, 1 H), 6.16 (d, $J = 2.4$ Hz, 2 H), 4.44 (d, $J = 2.7$ Hz, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 3.65 (d, $J = 3.0$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 162.0 (2 C), 160.8, 158.6, 157.8, 145.9, 138.7, 137.6, 131.5, 128.8, 114.2 (2 C), 106.4, 105.1 (2 C), 98.1, 96.4, 64.1, 55.8, 55.6, 55.2, 51.9. Finally, a solution of this newly synthesized ketone (0.035 g, 0.081 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added dropwise to a commercially-prepared solution of BBr_3 (0.770 mL, 1.0 M in CH_2Cl_2, 0.810 mmol, 10 equiv) at 0 °C, and the resultant solution was stirred for 6 h at 0 °C. Upon completion, the reaction mixture was quenched with water (5 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant light pink product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to give paucifloral F (0.025 g, 86% yield) as an amorphous white solid. **6**: $R_f = 0.06$ (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3334, 1696, 1614, 1514, 1474, 1347, 1155, 1082, 1005, 842; ^1H NMR (300 MHz, Acetone-d_6) δ 8.75 (s, 1 H), 8.49 (s, 1 H), 8.27 (s, 1 H), 8.07 (s, 2 H), 6.96 (d, $J = 8.7$ Hz, 2 H), 6.78 (d, $J = 8.7$ Hz, 2 H), 6.72 (s, 2 H), 6.19 (app t, $J = 2.1$ Hz, 1 H), 6.02 (d, $J = 2.1$ Hz, 2 H), 4.38 (d, $J =$

2.7 Hz, 1 H), 3.50 (d, J = 2.7, 1 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 205.5, 160.2, 159.5, 157.2, 156.7, 147.3, 140.0, 134.8, 131.8, 129.6, 116.3, 110.2, 106.3, 101.6, 100.5, 65.3, 52.1; HRMS (MALDI-FTMS) calcd for $C_{21}H_{17}O_6^+$ [M + H$^+$] 365.1025, found 365.1055. All spectroscopic data for this synthetic material match those reported by Ito and co-workers for natural paucifloral F (**6**).[1]

Sulfide 16. Solid *p*-TsOH (0.039 g, 0.229 mmol, 1.0 equiv) was added in a single portion to a solution of aldol adduct **11** (0.100 g, 0.229 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at –50 °C. The resultant mixture was then warmed slowly to –30 °C over the course of 20 min and stirred for an additional 5 h at –30 °C. Once this operation was complete, the reaction contents were warmed to 0 °C, *p*-methoxy-α-toluenethiol (0.096 mL, 0.687 mmol, 3.0 equiv) was added in a single portion, and the resultant mixture was concentrated to a minimum volume (approximately 0.2 mL). The resultant solution was then stirred for 12 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resulted yellow product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give a sulfide **16** (0.075 g, 57%) as a light yellow oil. Alternatively, *p*-methoxy-α-toluenethiol (0.240 mL, 1.72 mmol, 3.0 equiv) and *p*-TsOH (0.099 g, 0.573 mmol, 1.0 equiv) were added to a highly concentrated solution of alcohol **15** (0.250 g, 0.573 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 25 °C. The resulting yellow-green solution was stirred for 24 h at 25 °C under the strict exclusion of light. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant light green product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to give a sulfide **16** (0.269 g, 82%) as a light yellow oil. **16**: $R_f = 0.71$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2995, 2934, 2831, 1607, 1512, 1463, 1421, 1326, 1303, 1249, 1203, 1175, 1154, 1061, 1035, 934, 830; ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.13 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 8.7 Hz, 2 H), 7.04 (d, J = 9.0 Hz, 2 H), 7.03 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 2.4 Hz, 2 H), 6.80 (d, J = 2.7 Hz, 2 H), 6.79 (s, 1 H), 6.77 (s, 1 H), 6.74 (d, J = 8.7 Hz, 2 H), 6.53 (d, J = 1.5 Hz, 1 H), 6.45 (d, J = 1.5 Hz, 1 H), 6.36 (br m, 3 H), 6.28 (br m, 2 H), 6.18 (br m, 4 H), 4.55 (s, 1 H), 4.53 (d, J = 2.7 Hz, 1 H), 4.22 (app t, J = 7.2 Hz, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.69 (s, 3 H), 3.68 (s, 6 H), 3.61 (s, 3 H), 3.57 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 161.5, 161.3, 160.5, 160.3, 158.5, 157.0, 156.8, 147.1, 146.5, 146.2, 145.3, 135.7, 133.5, 130.3, 130.0, 129.8, 128.6, 124.1, 123.7, 113.9, 113.8, 113.7, 113.3, 105.5, 100.8, 100.4, 98.9, 98.5, 98.1, 97.9, 64.6, 60.3, 57.2, 56.7, 55.5, 55.2, 54.0, 53.7, 36.0, 34.9; HRMS (MALDI-FTMS) calcd for $C_{34}H_{35}O_6S^+$ [M – H$^+$] 571.2154, found 571.2168.

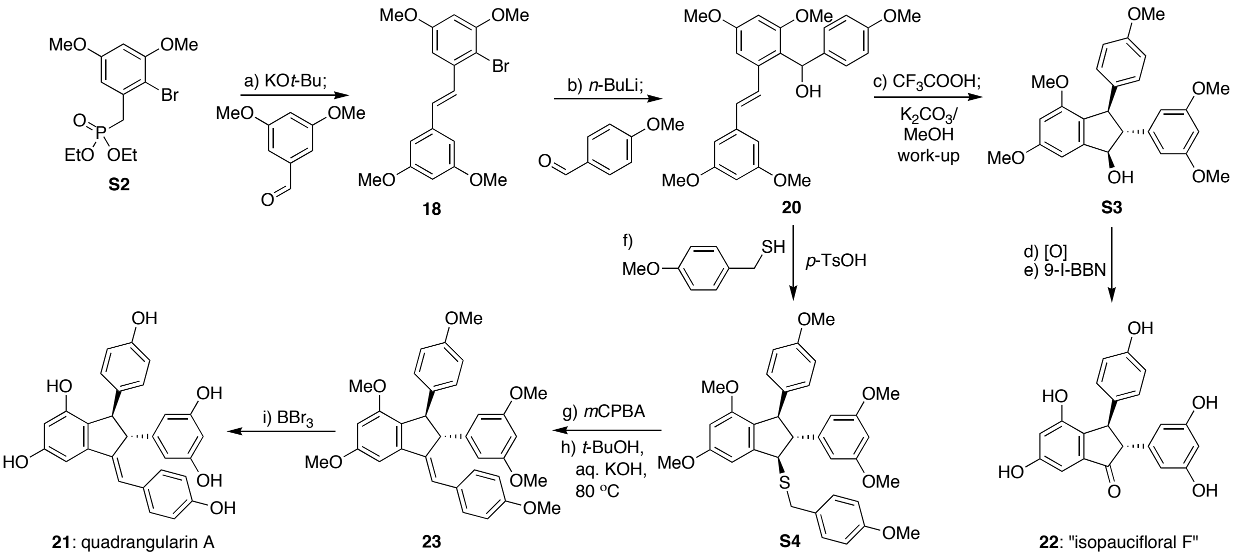
Ampelopsin D (2). Solid $NaHCO_3$ (0.257 g, 3.06 mmol, 5.0 equiv) and *m*CPBA (XX%, 0.317 g, 1.84 mmol, 3.0 equiv) were added sequentially to a solution of sulfide **16** (0.350 g, 0.612 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C to give a milk-colored slurry. After warming this mixture to 25 °C and stirring for 3 h, the reaction contents were quenched with saturated aqueous $NaHCO_3$ (15 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant off-white solid was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give the desired sulfone intermediate (0.289

g, 78%) as a yellow-pink oil. Next, finely powdered KOH (0.186 g, 3.31 mmol, 20 equiv) was added in a single portion to a solution of a portion of this newly synthesized adduct (0.100 g, 0.166 mmol, 1.0 equiv) in a mixture of CCl_4/t-BuOH/H_2O (5/5/1, 3.8 mL/3.8 mL/0.79 mL) at 25 °C. The resultant slurry was then stirred for 12 h at 80 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give both the desired alkene (**28**, 0.042 g, 52%) as a yellow oil along with a small portion of its exocyclic olefinic regioisomer (0.013 g, 15%) as a light yellow oil. **28**: R_f = 0.53 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2995, 2934, 2836, 1606, 1509, 1463, 1288, 1248, 1203, 1175, 1152, 1065, 1036, 827; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.09 (s, 1 H), 6.85 (d, *J* = 1.8 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 6.72 (d, *J* = 8.7 Hz, 2 H), 6.33 (d, *J* = 1.8 Hz, 1 H), 6.29 (d, *J* = 2.1 Hz, 1 H), 6.27 (d, *J* = 2.1 Hz, 1 H), 4.36 (s, 1 H), 4.25 (s, 1 H), 3.93 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.71 (s, 6 H), 3.62 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.6, 158.4, 158.0, 157.6, 148.1, 145.6, 142.7, 137.3, 130.0, 129.6, 127.9, 126.0, 122.1, 114.1, 113.7, 105.3, 99.1, 97.5, 94.9, 58.0, 57.9, 55.6, 55.2 (2 C); HRMS (MALDI-FTMS) calcd for $C_{34}H_{34}O_6^+$ [M^+] 538.2355, found 538.2357. Finally, permethylated ampelopsin D (**28**, 0.050 g, 0.090 mmol, 1.0 equiv) was added as a solution in CH_2Cl_2 (5 mL) at 25 °C to a freshly-prepared solution of BBr_3 [made by dissolving solid BBr_3 (0.271 g, 1.08 mmol, 12 equiv) in CH_2Cl_2 (5 mL) at 25 °C in dry box], and the resulting solution was stirred for 6 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL), poured into water (15 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow solid was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to afford a 5/1 mixture of ampelopsin D and isoampelopsin D (0.041 g combined, 89% overall) as colorless oils. These regioisomers were obtained individually in near quantitative yield (95%) following acetylation [Ac_2O, pyridine], chromatographic separation via flash column chromatography, and acetate hydrolysis [cat. KCN, MeOH]. **2**: $R_f = 0.03$ (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3339, 1604, 1511, 1465, 1374, 1335, 1238, 1147, 1010, 834, 650; ^1H NMR (300 MHz, acetone-d_6) δ 8.30 (br s, 1 H), 8.20 (br s, 1 H), 8.11 (br s, 1 H), 7.97 (br s, 2 H), 7.85 (br s, 1 H), 7.18 (d, $J = 8.7$ Hz, 2 H), 7.12 (d, $J = 8.7$ Hz, 2 H), 7.04 (app t, $J = 0.6$ Hz, 1 H), 6.81 (d, $J = 1.8$ Hz, 1 H), 6.75 (d, $J = 8.4$ Hz, 2 H), 6.66 (d, $J = 8.7$ Hz, 2 H), 6.30 (d, $J = 2.1$ Hz, 1 H), 6.11 (m, 3 H), 4.29 (s, 1 H), 4.15 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 159.7, 159.3, 157.3, 156.7, 156.1, 149.3, 147.6, 143.1, 137.4, 131.0, 129.7, 128.8, 123.8, 122.7, 116.3, 116.0, 106.5, 103.8, 101.3, 98.4, 59.5, 58.7; HRMS (MALDI-FTMS) calcd for $C_{28}H_{22}O_6^+$ [M^+] 454.1416, found 454.1448. All spectroscopic data for this synthetic material match those reported by Niwa and co-workers for natural ampelopsin D (**2**).[2]

Isoampelopsin D (17). Concentrated HCl (50 μL, 0.600 mmol, 5.5 equiv.) was added to a solution of ampelopsin D (**2**, 5.0 mg, 0.110 mmol, 1.0 equiv) in MeOH (0.5 mL) at 25 °C, and the resultant mixture was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was quenched with water (3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resulted light yellow product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to give isoampelopsin D **17** (4.8 mg, 96%) as a colorless oil. **17**: $R_f = 0.13$

(silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3411, 2810, 1680, 1628, 1511, 1443, 1371, 1333, 1206, 1149, 1055, 1006, 833; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.11 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 8.7 Hz, 2 H), 6.73 (d, J = 8.7 Hz, 2 H), 6.66 (d, J = 8.7 Hz, 2 H), 6.17 (d, J = 2.1 Hz, 1 H), 6.06 (d, J = 1.5 Hz, 1 H), 6.06 (d, J = 2.1 Hz, 2 H), 5.99 (t, J = 2.1 Hz, 1 H), 4.80 (s, 1 H), 3.84 (s, 2 H); ^{13}C NMR (75 MHz, methanol-d_4) δ 158.9, 158.7, 157.5, 156.5, 154.0, 150.4, 149.9, 144.0, 136.6, 132.1, 131.1, 130.2, 128.9, 125.4, 116.3, 115.8, 108.1, 101.4, 100.7, 56.7, 32.2; HRMS (MALDI-FTMS) calcd for $C_{28}H_{22}O_6^+$ [M^+] 454.1416, found 454.1428. All spectroscopic data for this synthetic material match those reported by Niwa and co-workers for natural isoampelopsin (**15**).[2]

Total Synthesis of Quadrangularin A (21) and Isopaucifloral F (22). These two natural products were synthesized from intermediate **S2** exactly as described above for ampelopsin D (**2**) and paucifloral F (**6**) by substituting 3,5-dimethoxybenzaldehyde in the Horner-Wadsworth-Emmons reaction leading to intermediate **18**. Only the final deprotection leading to isopaucifloral F (**22**) in Scheme 2 is fundamentally different from the steps outlined above, so only this procedure is defined specifically on the ensuing pages.



Scheme S2. Total synthesis of quadrangularin A (**21**) and isopaucifloral F (**22**). a) KO*t*-Bu (1.0 M in THF, 1.0 equiv), THF, -78 °C, 20 min, then 3,5-dimethoxybenzaldehyde (0.95 equiv), -78 °C, 1h, then 25 °C, 12 h, 98%; b) *n*-BuLi (1.0 equiv), THF, -78 °C, 20 min; then *p*-methoxybenzaldehyde (1.0 equiv), -78→25 °C, 4 h, 71%; c) TFA (1.0 equiv), CH_2Cl_2, -30→-20 °C, 5 h; then K_2CO_3 (10 equiv), MeOH, 25 °C, 5 min, 93%; c) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 3 h, 98%; e) 9-I-BBN (1.0 M in hexanes, 10 equiv), CH_2Cl_2, 40 °C, 30 min, 72%; f) *p*-TsOH (1.0 equiv), CH_2Cl_2, -30→-20 °C, 5 h; *p*-methoxybenzenethiol (3.0 equiv), then concentration to near dryness, 25 °C, 12 h, 65%; g) *m*CPBA (3.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 0→25 °C, 3 h, 70%; f) *t*-BuOH/H_2O/CCl_4 (5/1/5), KOH (powder, 20 equiv), 80 °C, 12 h, 55%; g) BBr_3 (1.0 M in CH_2Cl_2, 12 equiv), CH_2Cl_2, 25 °C, 6 h, 75% of **16**, 14% of internal alkene isomer. 9-I-BBN = 9-iodo-9-borabicyclo[3.3.1]nonane.

18: R_f = 0.55 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3001, 2957, 2938, 2837, 1592, 1457, 1418, 1353, 1288, 1230, 1204, 1155, 1083, 1022, 959, 829, 650; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 15.9 Hz, 1 H), 6.94 (d, *J* = 15.9, 1 H), 6.80 (d, *J* = 2.7 Hz, 1 H), 6.71 (d, *J* = 2.4 Hz, 2 H), 6.43 (d, *J* = 2.7 Hz, 1 H), 6.42 (t, *J* = 2.1 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 159.5, 156.8, 138.9, 138.5, 131.5, 128.4, 104.9, 102.7, 100.3, 99.1, 56.3, 55.5, 55.3; HRMS (MALDI-FTMS) calcd for $C_{18}H_{19}BrO_4^+$ [M$^+$] 378.0467, found 378.0484.

20: R_f = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3508, 3001, 2938, 2837, 1599, 1510, 1459, 1425, 1323, 1283, 1246, 1203, 1152, 1064, 1035, 964, 835, 799, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 15.9 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 15.9 Hz, 1 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 6.74 (d, *J* = 2.4 Hz, 1 H), 6.56 (d, *J* = 2.1 Hz, 2 H), 6.48 (d, *J* = 2.4 Hz, 1 H), 6.38 (t, *J* = 2.1 Hz, 1 H), 6.23 (d, *J* = 9.9 Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 6 H), 3.77 (s, 3 H), 3.73 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 159.8, 158.8, 158.3, 139.1, 138.2, 136.8, 132.0, 127.1, 126.9, 122.3, 113.4, 104.6, 103.3, 100.3, 99.1, 69.8, 55.7, 55.4, 55.3, 55.2; HRMS (MALDI-FTMS) calcd for $C_{26}H_{28}O_6^+$ [M^+] 436.1886, found 436.1870.

S3: R_f = 0.48 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3475, 2934, 2837, 1596, 1512, 1463, 1429, 1304, 1245, 1203, 1149, 1046, 935, 831, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 6.65 (d, *J* = 1.8 Hz, 1 H), 6.41 (d, *J* = 2.1 Hz, 1 H), 6.34 (app t, *J* = 2.7 Hz, 1 H), 6.32 (d, *J* = 2.1 Hz, 2 H), 5.18 (t, *J* = 6.0 Hz, 1 H), 4.26 (d, *J* = 7.2 Hz, 1 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.54 (s, 3 H), 3.13 (t, *J* = 6.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.8, 157.7, 157.1, 146.1, 144.2, 136.5, 128.2, 123.3, 113.3, 105.8, 99.7, 99.2, 98.5, 82.2, 67.5, 55.6, 55.2, 55.1, 53.3; HRMS (MALDI-FTMS) calcd for $C_{26}H_{28}O_6^+$ [M^+] 436.1886, found 436.1870.

Permethylated Isopaucifloral F. R_f = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3001, 2935, 2837, 1713, 1596, 1511, 1462, 1431, 1305, 1247, 1204, 1151, 1065, 1036, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 2.1 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 6.69 (d, *J* = 2.1 Hz, 1 H), 6.36 (app t, *J* = 2.1 Hz, 1 H), 6.24 (d, *J* = 2.1 Hz, 2 H), 4.51 (d, *J* = 2.4 Hz, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 6 H), 3.66 (s, 3 H), 3.61 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 161.9, 161.0, 158.1, 157.7, 141.5, 138.5, 138.4, 135.4, 127.9, 113.8, 106.6, 106.0, 98.9, 96.4, 77.2, 65.3, 55.8, 55.6, 55.3, 55.2, 50.9; HRMS (MALDI-FTMS) calcd for $C_{26}H_{26}O_6^+$ [M^+] 434.1742, found 434.1746.

Isopaucifloral F (22). 9-I-BBN (1.61 mL, 1.0 M in hexanes, 1.61 mmol, 7.0 equiv) was added dropwise to a solution of permethylated isopaucifloral F (0.100 g, 0.240 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 25 °C. The reaction solution turned a red color immediately, and was immediately heated at 40 °C for 30 min with continued stirring. Upon completion, the reaction mixture was cooled to 25 °C, quenched with water (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant red oil was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to afford isopaucifloral F (0.063 g, 72%) as colorless oil. **22**: R_f = 0.06 (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3349, 1691, 1602, 1512, 1418, 1342, 1251, 1149; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 3 H), 7.35 (s, 2 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 6.74 (d, *J* = 8.7 Hz, 2 H), 6.71 (d, *J* = 2.1 Hz, 1 H), 6.24 (t, *J* = 2.1 Hz, 1 H), 6.11 (d, *J* = 2.1 Hz, 2 H), 4.48 (d, *J* = 2.4 Hz, 1 H), 3.42 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 160.2, 159.6, 156.8, 156.6, 143.3, 140.1, 135.7, 135.3, 128.9, 116.1, 110.3, 107.0, 102.1, 100.7, 66.3, 51.4; HRMS (MALDI-FTMS) calcd for $C_{21}H_{16}O_6^+$ [M^+] 364.0947, found 364.0961.

S4: R_f = 0.55 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2999, 2936, 2836, 1595, 1511, 1446, 1428, 1329, 1302, 1247, 1206, 1175, 1153, 1090, 1067, 1035, 830, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.7 Hz, 2 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 6.74 (d, *J* = 8.4 Hz, 4 H), 6.55 (d, *J* = 1.2 Hz, 1 H), 6.35 (d, *J* = 1.8 Hz, 2 H), 6.26 (d, *J* = 1.8 Hz, 2 H), 4.29 (d, *J* = 6.9 Hz, 1 H), 4.24 (d, *J* = 7.5 Hz, 1 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 6 H), 3.53 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 160.7, 158.5, 157.8, 157.0, 145.9, 145.1, 136.8, 130.3, 130.1, 129.1, 128.3, 124.1, 113.7, 113.3, 105.8, 100.4, 99.0, 98.6, 66.4, 56.2, 56.0, 55.6, 55.3, 34.9, 29.7; HRMS (MALDI-FTMS) calcd for $C_{34}H_{36}O_6S^+$ [M^+] 572.2233, found 572.2233.

23: R_f = 0.50 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2995, 2925, 2831, 1593, 1509, 1462, 1246, 1202, 1151, 1061, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 2 H), 7.12 (s, 1 H), 7.05 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 2.1 Hz, 1 H), 6.77 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 6.45 (d, *J* = 2.1 Hz, 2 H), 6.33 (d, *J* = 2.1 Hz, 1 H), 6.31 (app t, *J* = 2.1 Hz, 1 H), 4.32 (d, *J* = 4.2 Hz, 2 H), 3.93 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.74 (s, 6 H), 3.61

(s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.9, 158.4, 157.8, 157.4, 147.7, 145.2, 142.2, 137.9, 130.0, 129.7, 127.8, 126.8, 122.4, 113.7, 105.3, 99.1, 97.6, 94.8, 59.2, 56.8, 55.5, 55.2 (3 C); HRMS (MALDI-FTMS) calcd for $C_{34}H_{34}O_6^+$ [M – 2H$^+$] 538.2374, found 538.2355.

Quadrangularin A (21). **16**: R_f = 0.03 (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3306, 1603, 1511, 1459, 1339, 1242, 1149, 1004, 833, 650; ^{1}H NMR (300 MHz, MeOH-d_3) δ 7.13 (d, J = 8.7 Hz, 2 H), 6.98 (s, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.70 (d, J = 1.8 Hz, 1 H), 6.62 (d, J = 8.7 Hz, 2 H), 6.60 (d, J = 8.7 Hz, 2 H), 6.22 (d, J = 2.1 Hz, 2 H), 6.17 (d, J = 1.8 Hz, 1 H), 6.09 (t, J = 2.1 Hz, 1 H), 4.17 (br s, 1 H), 4.03 (br s, 1 H); ^{13}C NMR (75 MHz, MeOH-d_3) δ 159.7 (2 C), 157.4, 156.5, 156.2, 149.7, 147.7, 143.4, 138.5, 131.2 (2 C), 130.3, 128.9 (2 C), 125.4, 123.1, 116.0 (4 C), 106.6 (2 C), 103.8, 101.5, 98.4, 61.2, 58.1; HRMS (MALDI-FTMS) calcd for $C_{28}H_{22}O_6^+$ [M$^+$] 454.1416, found 454.1440. All spectroscopic data for this synthetic material match those reported by Païs and co-workers for natural quadrangularin A (**21**).[3]

Monobrominated intermediate 24. Solid NBS (3.2 mg, 0.018 mmol, 1.0 equiv) was added in a single portion to a solution of permethylated quadrangularin A (**23**, 10 mg, 0.018 mmol, 1.0 equiv) in THF (5 mL) at –78 ºC. The resultant solution was stirred for 5 min at –78 ºC and then was slowly warmed to 25 ºC over the course of 3 h. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford bromide **24** (8.0 mg, 72%) as a light yellow oil. **24**: R_f = 0.50 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2934, 1592, 1511, 1460, 1330, 1252, 1204, 1177, 1157, 1034, 829, 732; ^{1}H NMR (300 MHZ, $CDCl_3$): 8.07 (s, 1 H), 7.16 (d, J = 8.7 Hz, 2 H), 7.05 (d, J = 8.7 Hz, 2 H), 6.75 (d, J = 3.9 Hz, 2

H), 6.72 (d, *J* = 3.9 Hz, 2 H), 6.44 (d, *J* = 2.1 Hz, 2 H), 6.34 (s, 2 H), 6.31 (m, 1 H), 4.26 (s, 2 H), 3.93 (s, 3 H), 3.74 (s, 3 H), 3.74 (s, 6 H), 3.72 (s, 3 H), 3.64 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 158.7, 157.9, 157.0, 156.0, 147.9, 142.0, 141.2, 137.0, 136.8, 130.3, 130.1, 129.8, 129.0, 128.4, 127.8, 113.7, 105.2, 98.0, 97.3, 96.3, 59.0, 56.9, 56.3, 55.9, 55.5, 55.2; HRMS (MALDI-FTMS) calcd for $C_{34}H_{33}BrO_6^+$ [M$^+$] 616.1461, found 616.1439.

Dibrominated intermediate 25. A solution of Br_2 (2.90 μL, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of permethylated quadrangularin A (**23**, 0.030 g, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL) at –78 ºC. The resultant solution was stirred at –78 ºC for 2 h, warmed slowly to 25 ºC over the course of 1 h, and stirred for an additional 1 h at 25 ºC. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give bromide **25** (0.033 g, 83%) as a light yellow oil. **25**: R_f = 0.50 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2954, 1586, 1511, 1460, 1330, 1252, 1177, 1034; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.27 (d, *J* = 2.4 Hz, 1 H), 7.16 (d, *J* = 8.7 Hz, 2 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 6.76 (d, *J* = 8.7 Hz, 2 H), 6.70 (d, *J* = 8.7 Hz, 2 H), 6.38 (d, *J* = 2.7 Hz, 1 H), 6.33 (d, *J* = 1.8 Hz, 2 H), 4.71 (s, 1 H), 4.15 (s, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.62 (s, 3 H), 3.60 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 158.9, 157.8, 157.0, 156.9, 156.0, 146.1, 142.2, 141.4, 136.8, 130.2, 129.6, 129.2, 128.4, 113.9, 113.3, 105.3, 104.4, 98.0, 97.1, 96.5, 58.3, 56.9, 56.3, 55.5, 55.2, 55.1, 54.3; HRMS (MALDI-FTMS) calcd for $C_{34}H_{32}Br_2O_6^+$ [M$^+$] 694.0566, found 694.0540.

Cascade Product 27. A solution of Br_2 (8.60 μL, 0.167 mmol, 2.0 equiv) in CH_2Cl_2 (0.1 mL) was added dropwise to a solution of permethylated quadrangularin A (**23**, 0.045 g, 0.083 mmol, 1.0 equiv) in CH_2Cl_2 (4.5 mL) at –78 ºC. The resultant solution was stirred at –78 ºC for 2 h, warmed slowly to 25 ºC over the course of 1 h, and stirred for an additional 1 h at 25 ºC. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL), poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant yellow-orange oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give trihalogenated adduct **27** (0.052 g, 81%) as a pale yellow oil. **27**: R_f = 0.40 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3434, 2956, 2919, 2862, 2091, 1643, 1511, 1462, 1330, 1247, 1211, 1175, 1149, 1111, 1083, 1036, 998; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2 H), 6.80 (br d, *J* = 8.7 Hz, 6 H), 6.39 (s, 1 H), 6.27 (s, 1 H), 5.59 (s, 1 H), 5.10 (s, 1 H), 4.53 (s, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.77 (s, 6 H), 3.62 (s, 3 H), 3.55 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 157.9, 157.5, 156.9, 155.8, 155.3, 145.9, 144.3, 136.3, 135.4, 129.7, 126.5, 126.2, 113.0, 99.5, 98.4, 97.1, 96.2, 78.1, 70.9, 56.8, 56.6, 55.6, 55.1, 51.5; HRMS (MALDI-FTMS) calcd for $C_{34}H_{32}Br_3O_6^+$ [M + H$^+$] 772.9746, found 772.9756.

Pallidol (3). Activated Pd/C (10%, 13.7 mg, 0.013 mmol, 0.5 equiv) was added in a single portion to a solution of tribromide **27** (20.0 mg, 0.026 mmol, 1.0 equiv) in MeOH (2.5 mL) at 25 ºC, and then H_2 gas was bubbled slowly and continuously through the solution for 24 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant colorless oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give permethylated pallidol (10.6 mg, 76%) as an amorphous white solid. Next, a portion of this newly synthesized adduct (5.0 mg, 0.009 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and treated with BBr_3 (0.108 mL, 1.0 M solution in CH_2Cl_2, 0.108 mmol, 12 equiv) at 0 °C. The resultant red mixture was stirred for 4 h at 0 °C, and then stirred for an additional 20 h at 25 °C. Upon completion, the reaction mixture was quenched with water (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant product was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH, 9:1) to give pallidol (3.4 mg, 83%) as an off-white solid. **3**: $R_f = 0.01$ (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3368, 2957, 2919, 2850, 1601, 1512, 1459, 1333, 1244, 1168, 1124, 1036, 985, 833; ^1H NMR (300 MHz, acetone-d_6) δ 8.03 (app d, J = 5.7 Hz, 4 H), 7.79 (s, 2 H), 6.98 (d, J = 8.4 Hz, 4 H), 6.70 (d, J = 8.4 Hz, 4 H), 6.62 (s, 2 H), 6.19 (d, J = 1.5 Hz, 2 H), 4.56 (br s, 2 H), 3.79 (br s, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 159.3, 156.3, 155.3, 150.3, 137.7, 129.0, 123.2, 115.8, 103.3, 102.5, 60.5, 53.9; HRMS (MALDI-FTMS) calcd for $C_{28}H_{22}O_6^+$ [M^+] 454.1414, found 454.1416. All spectroscopic data for the permethylated form of this synthetic material in DMSO-d_6 match those reported by Zaman and co-workers for the same naturally-derived compound.[4]

Ampelopsin F (4). A solution of Br_2 (2.87 μL, 0.056 mmol, 2.0 equiv) in CH_2Cl_2 (0.1 mL) was added dropwise to a solution of permethylated ampelosin D (**28**, 15.0 mg, 0.028 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at –78 °C. The resultant solution was stirred at –78 °C for 2 h, warmed slowly to 25 °C over the course of 1 h, and stirred for an additional 1 h at 25 °C. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), poured into water (3 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford tribromide **30** (11.5 mg, 53%) as a light yellow oil. Next, solid AIBN (0.8 mg, 0.005 mmol, 1.0 equiv) was added in a single portion at 25 ºC to a solution of tribromide **30** (4.0 mg, 0.005 mmol, 1.0 equiv) and $(TMS)_3SiH$ (0.0143 mL, 0.046 mmol, 9.0 equiv) in toluene (0.7 mL) that had been carefully degassed by bubbling argon for 20 min directly into the solvent. The resultant solution was then heated at 100 ºC for 8 h. Upon completion, the reaction contents were cooled to 25 ºC, concentrated, and purified directly by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford permethylated ampelopsin F (2.4 mg, 89%) as a light yellow oil. Finally, after repeating the previous reaction, this newly synthesized adduct (3.0 mg, 0.006 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and treated with BBr_3 (0.083 mL, 1.0 M solution in CH_2Cl_2, 0.083 mmol, 12 equiv) at 0 ºC. The resultant red mixture was stirred for 4 h at 0 ºC, and then stirred for an additional 15 h at 25 ºC. Upon completion, the reaction mixture was quenched with water (3 mL), poured into water (3 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant orange-red residue was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to afford ampelopsin F (2.5 mg, 90%) as an off-white solid. **4**: $R_f = 0.13$ (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3361, 2953, 2920, 2847, 1598. 1496, 1471, 1330, 1240, 1165, 1121, 1035, 985, 833; ^1H NMR (300 MHz, acetone-d_6) δ 8.04 (s, 1 H), 7.98 (s, 1 H), 7.97 (s, 1 H), 7.91 (s, 1 H), 7.83 (s, 1 H), 7.40 (s, 1 H), 7.09 (d, J = 8.4 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 2 H), 6.76 (d, J = 8.4 Hz, 2 H), 6.57 (d, J = 8.7 Hz, 2 H), 6.52 (d, J = 1.8 Hz, 1 H), 6.44 (d, J = 1.8 Hz, 1 H), 6.15 (d, J = 2.1 Hz, 1 H), 6.07 (d, J = 1.8 Hz, 1 H), 4.19 (d, J = 0.6 Hz, 1 H), 4.13 (d, J = 0.6 Hz, 1 H), 3.65 (br s, 1 H), 3.36 (br s, 1 H); ^{13}C NMR

(75 MHz, acetone-d_6) δ 158.6, 157.8, 157.2, 156.2, 156.0, 153.1, 147.6, 147.4, 138.4, 135.5, 129.9, 129.3, 127.8, 115.6, 115.5, 113.4, 105.7, 104.2, 101.9, 101.6, 58.2, 50.5, 49.7, 47.2; HRMS (MALDI-FTMS) calcd for $C_{28}H_{22}O_6^+$ [M^+] 454.1416, found 454.1402. All spectroscopic data for this synthetic material match those reported by Niwa and co-workers for natural ampelopsin F (**4**).[2]

Ketone 31. Solid $NaHCO_3$ (3.30 g, 39.4 mmol, 10 equiv) and Dess–Martin periodinane (1.67 g, 3.94 mmol, 1.0 equiv) were added sequentially in single portions to a solution of alcohol **11** (1.72 g, 3.94 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 25 °C, and the resultant slurry was stirred for 2 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na_2SO_3 (10 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to afford ketone **31** (1.66 g, 97% yield) as a white solid. **31**: R_f = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3003, 2938, 2838, 1668, 1595, 1512, 1456, 1426, 1351, 1316, 1301, 1273, 1252, 1204, 1175, 1157, 1118, 1080, 1065, 1032, 989, 971, 928, 831, 782, 765, 736, 703; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2 H), 6.99 (d, J = 2.4 Hz, 2 H), 6.98 (d, J = 16.2 Hz, 1 H), 6.84 (d, J = 2.1 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 2 H), 6.74 (d, J = 15.9 Hz, 1 H), 6.63 (app t, J = 2.4 Hz, 1 H), 6.42 (d, J = 2.4 Hz, 1 H), 3.91 (s, 3 H), 3.79 (s, 6 H), 3.78 (s, 3 H), 3.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 161.3, 160.8, 159.5, 158.4, 140.4, 137.7, 131.0, 129.6, 128.0, 123.1, 121.4, 114.0, 107.3, 105.7, 101.1, 97.7, 55.8, 55.5 (2 C), 55.3; HRMS (MALDI-FTMS) calcd for $C_{26}H_{26}O_6^+$ [M^+] 434.1729, found 434.1725.

7-Membered Ring Bromide 33. A solution of Br_2 (0.024 mL, 0.460 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL) was added dropwise to a solution of ketone **31** (0.200 g, 0.460 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) at –78 °C. The reaction mixture was then stirred for 1 h at –78 °C, warmed slowly to 0 °C over the course of 1 h, and then stirred for 3 h at 0 °C and an additional 12 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), poured into water (1 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford bromide **33** (0.118 g, 50%) as a white solid that was utilized immediately in subsequent chemistry. [Note: this product is especially light sensitive, so it must be kept away from sunlight at all times].

7-Membered Ring Acetate 36. Solid AgOAc (0.073 g, 0.438 mmol, 3.0 equiv) was added in a single portion to a solution of bromide **33** (0.075 g, 0.146 mmol, 1.0 equiv) in neat AcOH (5 mL) at 25 °C. The reaction flask was then wrapped with aluminum foil to protect its contents from light, and stirring was continued at 25 °C for 3 h. Upon completion, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (3 mL), poured into water (3 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant yellow oily residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give acetate **36** (0.045 g, 62%) as a crystalline white solid. **36**: $R_f = 0.25$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3001, 2939, 2837, 1732, 1669, 1600, 1512, 1460, 1315, 1235, 1152, 1100, 1059, 1034, 963, 834, 792, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, J = 5.4 Hz, 1 H), 6.83 (d, J = 7.5 Hz, 2 H), 6.82 (d, J = 2.7 Hz, 1 H), 6.63 (d, J = 8.7 Hz, 2 H), 6.47 (d, J = 2.4 Hz, 1 H), 6.45 (d, J = 2.1 Hz, 1 H), 6.30 (d, J = 2.1 Hz, 1 H), 4.81 (d, J = 5.4 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 3

H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 1.95 (s, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.2, 170.3, 162.2, 160.6, 159.5, 158.9, 158.0, 143.1, 141.3, 131.2, 129.3, 122.6, 115.0, 113.4, 107.8, 103.2, 101.8, 97.9, 69.7, 56.0, 55.6, 55.4, 55.1, 51.6, 21.2; HRMS (MALDI-FTMS) calcd for $C_{28}H_{29}O_8^+$ [M + H$^+$] 493.1862, found 493.1847.

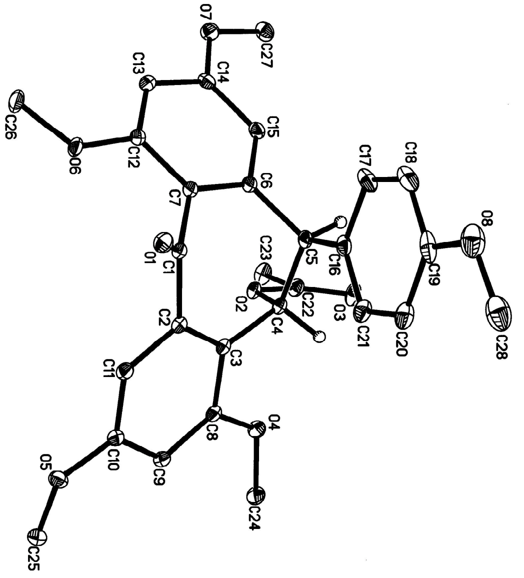
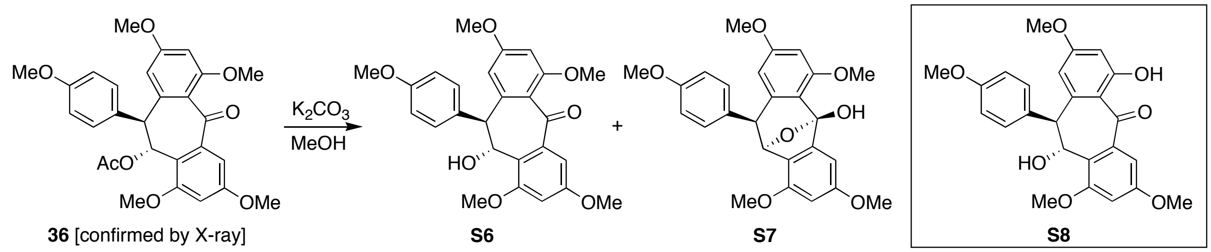


Figure S1. X-ray crystal structure of acetate **31**.



Scheme S3. Generation of a mixture of both open, as well as lactol, forms of the acetate cleavage product of **36**. Interestingly, if the phenol adjacent to the carbocyclic ketone is unprotected, the lactol is not observed under the same cleavage conditions (i.e. **S8** was formed cleanly). As such, this step highlights an element of unique reactivity instigated entirely by protecting groups.

Permethylated Hemsleyanol E Analog S6/S7. Finely powdered K_2CO_3 (0.121 g, 0.873 mmol, 10 equiv) was added in a single portion to a solution of acetate **36** (0.043 g, 0.087 mmol, 1.0 equiv) in MeOH (8 mL) at 25 °C, and the resultant slurry was stirred for 12 h at 25 °C. Upon completion, the reaction contents were neutralized with saturated aqueous NH_4Cl (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant colorless residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give an inseparable mixture of alcohol **S6** and lactol **S7** (2.5/1, 0.039 g, 78% combined). **S6** and **S7**: $R_f = 0.16$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3469, 2933, 2839, 1664, 1600, 1511, 1460, 1312, 1249, 1211, 1149, 1096, 1057, 1036, 987, 935, 833, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.7 Hz, 2.8 H), 6.85 (d, *J* = 2.4 Hz, 1 H), 6.67 (d, *J* = 8.7 Hz, 2.8 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.52 (d, *J* = 2.1 Hz, 1.8 H), 6.44 (d, *J* = 2.1 Hz, 1 H), 6.32 (d, *J* = 2.1 Hz, 0.4 H), 6.04 (d, *J* = 1.8 Hz, 0.8 H), 5.88 (d, *J* = 5.4 Hz, 1 H), 5.54 (d, *J* = 5.7 Hz, 0.4 H), 4.76 (d, *J* = 6.0 Hz, 0.4 H), 4.66 (d, *J* = 6.0 Hz, 1 H), 3.96 (s, 1.2 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 4.2 H), 3.71 (s, 1.2 H), 3.69 (s, 4.2 H), 3.58 (s, 1.2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 162.0, 161.6, 160.1, 159.8, 159.2, 158.7, 158.4, 157.8, 155.4, 154.3, 151.8, 141.1, 140.8, 140.4, 131.9, 131.5, 128.9, 123.3, 120.9, 119.8, 117.8, 113.5, 108.2, 107.8, 104.8, 103.5, 102.5, 97.8, 97.2, 97.0, 94.8, 79.3, 67.5, 56.1, 55.9, 55.4, 55.3, 55.2, 55.0, 54.7, 53.6, 47.8; HRMS (MALDI-FTMS) calcd for $C_{26}H_{27}O_7^+$ [M + H$^+$] 451.1757, found 451.1756.

Tetramethylated Hemsleyanol E Analog S8. Acetate **36** (0.050 g, 0.102 mmol, 1.0 equiv) was dissolved in neat AcOH (8 mL) at 25 °C, and the resulted solution was stirred for 12 h at 25 °C. Upon completion, the reaction mixture was quenched with water (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated to afford the desired monodeprotected intermediate (0.045 g, 93%) as a colorless oil which was carried forward without any additional purification. Next, solid KCN (0.6 mg, 0.009 mmol, 0.1 equiv) was added in a single portion to a solution of newly-formed compound (0.045 g, 0.090 mmol, 1.0 equiv) in MeOH (8 mL) at 25 °C, and then resultant mixture was heated at 65 °C for 3 h. Upon completion, the reaction was quenched with water (5 mL), poured into water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give alcohol **S8** (0.037 g, 89%) as a colorless oil. **S8**: $R_f = 0.19$ (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3468, 3001, 238, 2831, 1606, 1579, 1511, 1462, 1416, 1351, 1298, 1253, 1206, 1151, 1055, 1035, 935, 841, 796, 726; ^1H NMR (300 MHz, $CDCl_3$) δ 13.70 (s, 1 H), 6.95 (d, *J* = 2.4 Hz, 1 H), 6.71 (d, *J* = 8.7 Hz, 2 H), 6.58 (d, *J* = 8.7 Hz, 2 H), 6.42 (d, *J* = 2.7 Hz, 1 H), 6.29 (d, *J* = 2.4 Hz, 1 H), 6.27 (dd, *J* = 2.7, 0.6 Hz, 1 H), 5.76 (dd, *J* = 5.7, 2.4 Hz, 1 H), 4.88 (d, *J* = 6.1 Hz, 1 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 166.6, 165.0, 160.0, 157.9, 156.8, 143.6, 141.0, 132.7, 129.5, 121.5, 115.0, 113.2, 112.6, 105.7, 102.2, 100.0, 67.0, 57.3, 55.9, 55.4, 55.3, 55.2, 55.1; HRMS (MALDI-FTMS) calcd for $C_{25}H_{24}O_7^+$ [M^+] 436.1522, found 436.1544.

Permethylated Diptoindonesin A Analog 37. Dess–Martin periodinane (0.049 g, 0.115 mmol, 1.0 equiv) and solid $NaHCO_3$ (0.097 g, 1.15 mmol, 10 equiv) were added sequentially in single portions to a solution of alcohol **S6** and lactol **S7** (0.052 g, 0.115 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 25 °C, and the resultant slurry was stirred for 1.5 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na_2SO_3 (3 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C, poured into water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), dried ($MgSO_4$), and concentrated to give the desired permethylated diptoindonesin A analog (0.051 g, 99%) as a light yellow oil. **37**: R_f = 0.33 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3008, 2939, 2837, 1668, 1592, 1512, 1462, 1327, 1295, 1250, 1211, 1157, 1070, 1023, 974, 928, 832, 732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.4 Hz, 1 H), 6.91 (d, *J* = 8.1 Hz, 2 H), 6.69 (d, *J* = 9.2 Hz, 2 H), 6.64 (d, *J* = 2.4 Hz, 1 H), 6.52 (d, *J* = 2.1 Hz, 1 H), 6.47 (d, *J* = 2.1 Hz, 1 H), 5.18 (s, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3, 192.5, 163.0, 162.6, 161.1, 159.9, 158.4, 141.9, 136.7, 129.9, 129.4, 122.5, 116.8, 113.8, 105.8, 105.4, 104.0, 98.8, 66.7, 56.8, 56.1, 55.7, 55.5, 55.1; HRMS (MALDI-FTMS) calcd for $C_{26}H_{25}O_7^+$ [M + H^+] 449.1556, found 449.1619.

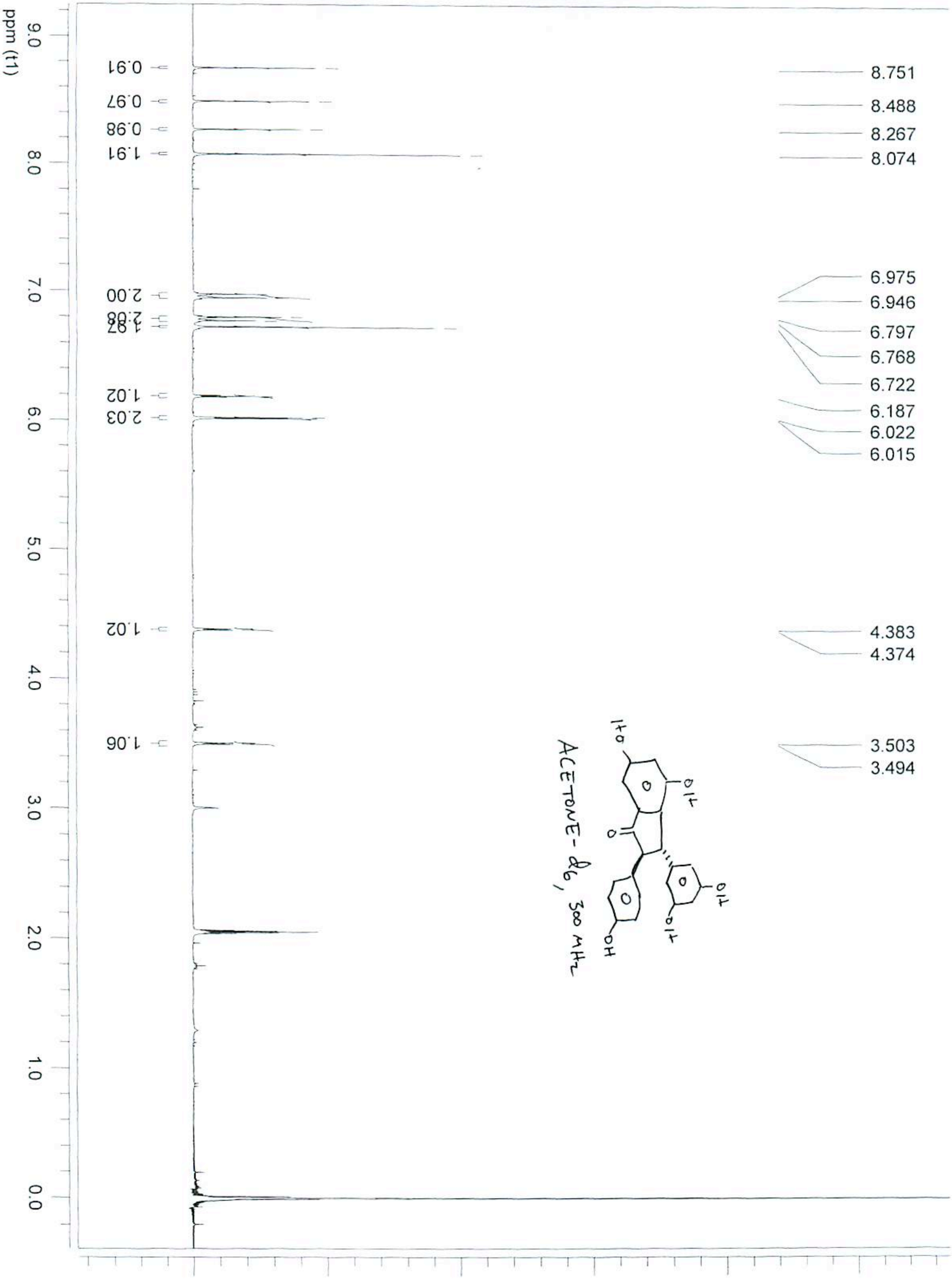
References

[1] J. Ito, T. Tanaka, M. Iinuma, K. Nakaya, Y. Takahashi, R. Sawa, J. Murata, D. Darnaedi, *J. Nat. Prod.* **2004**, *67*, 932 – 937.

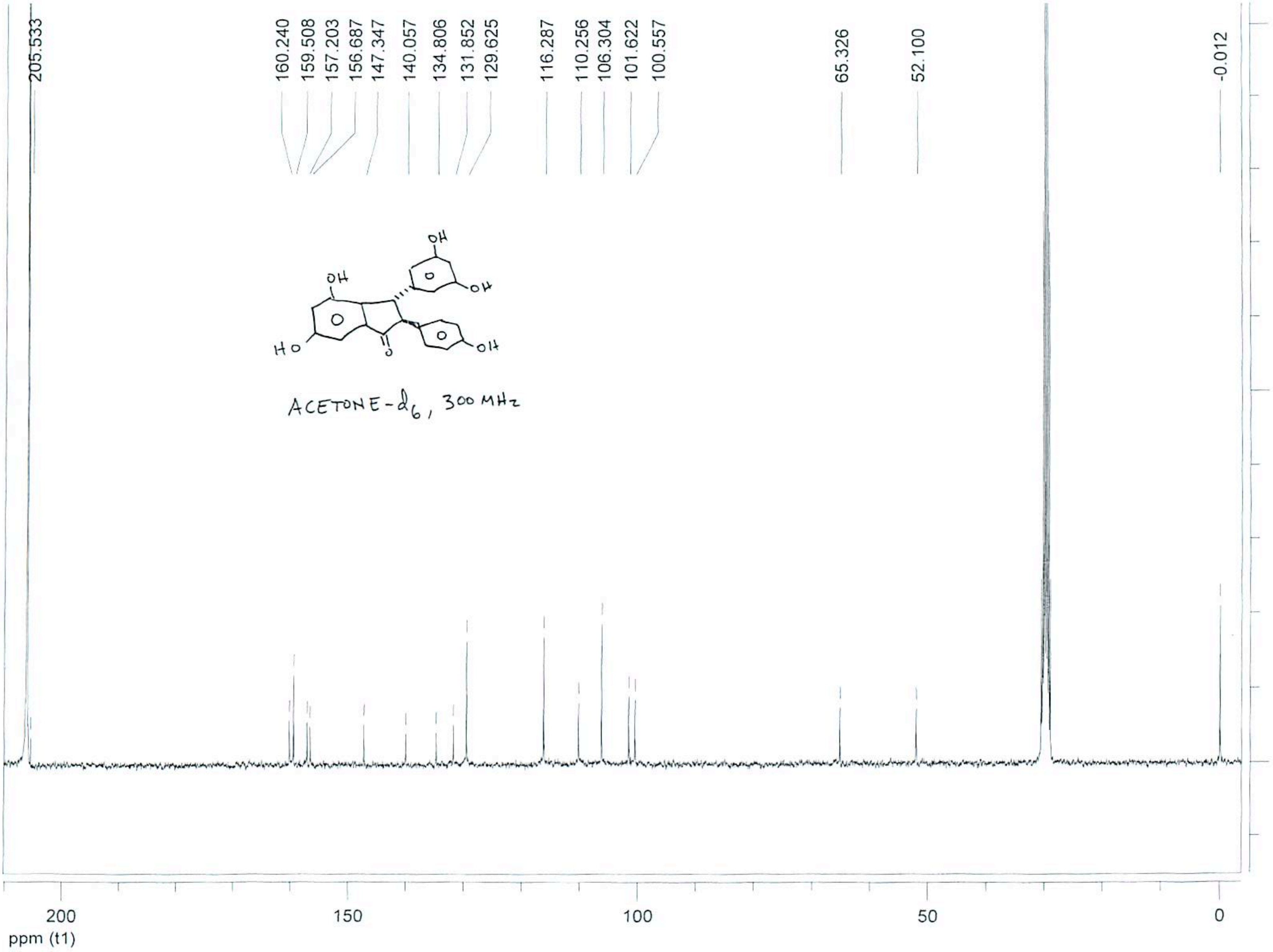
[2] Y. Takaya, K.-X. Yan, K. Terashima, J. Ito, M. Niwa, *Tetrahedron* **2002**, *58*, 7259 – 7265.

[3] S. A. Adesanya, R. Nia, M.-T. Martin, N. Boukamcha, A. Montagnac, M. Païs, *J. Nat. Prod.* **1999**, *62*, 1694 – 1695.

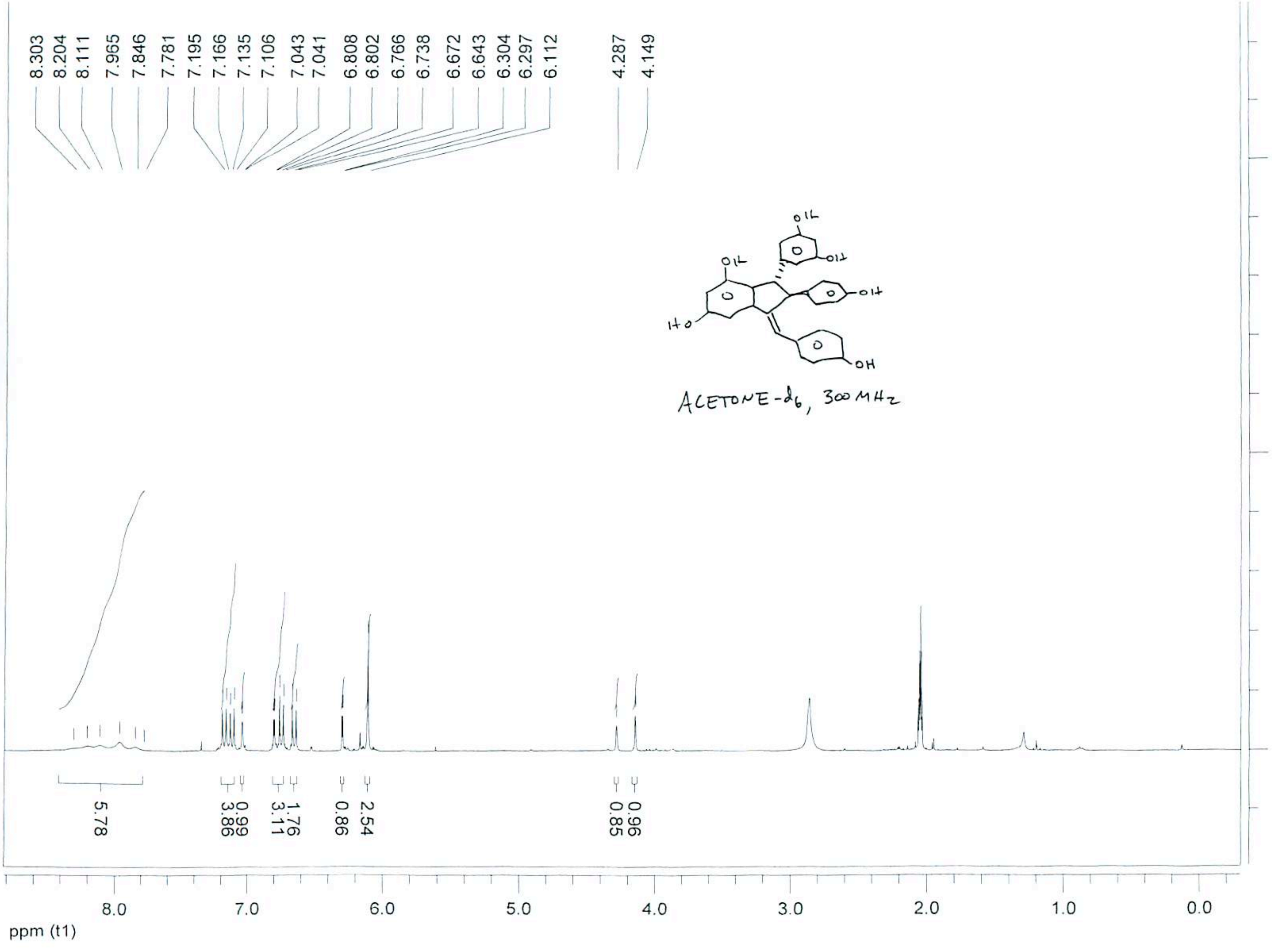
[4] M. A. Khan, S. G. Nabi, S. Prakash, A. Zaman, *Phytochemistry* **1986**, *25*, 1945 – 1948.



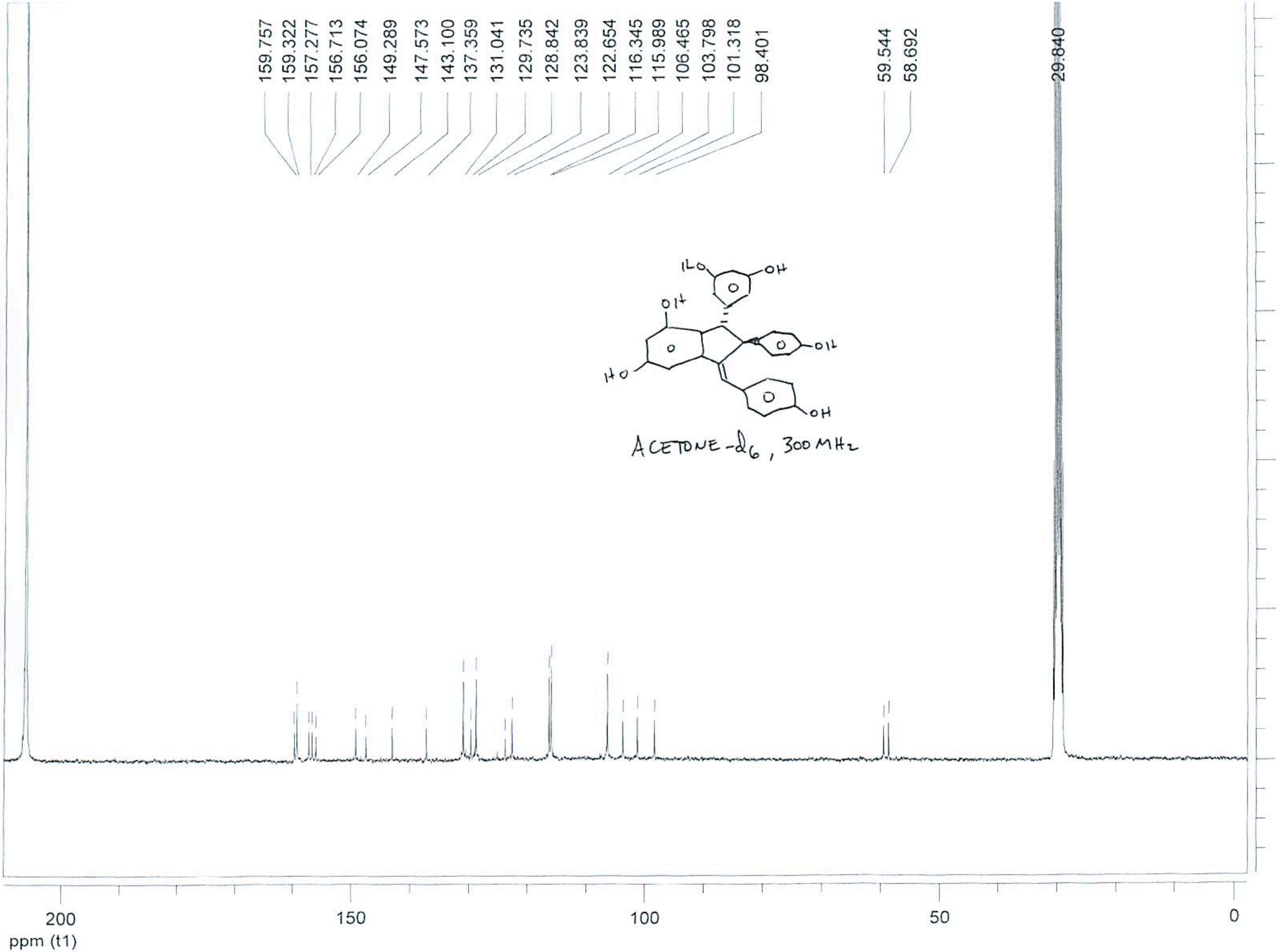
ACETONE-d_6, 300 MHz



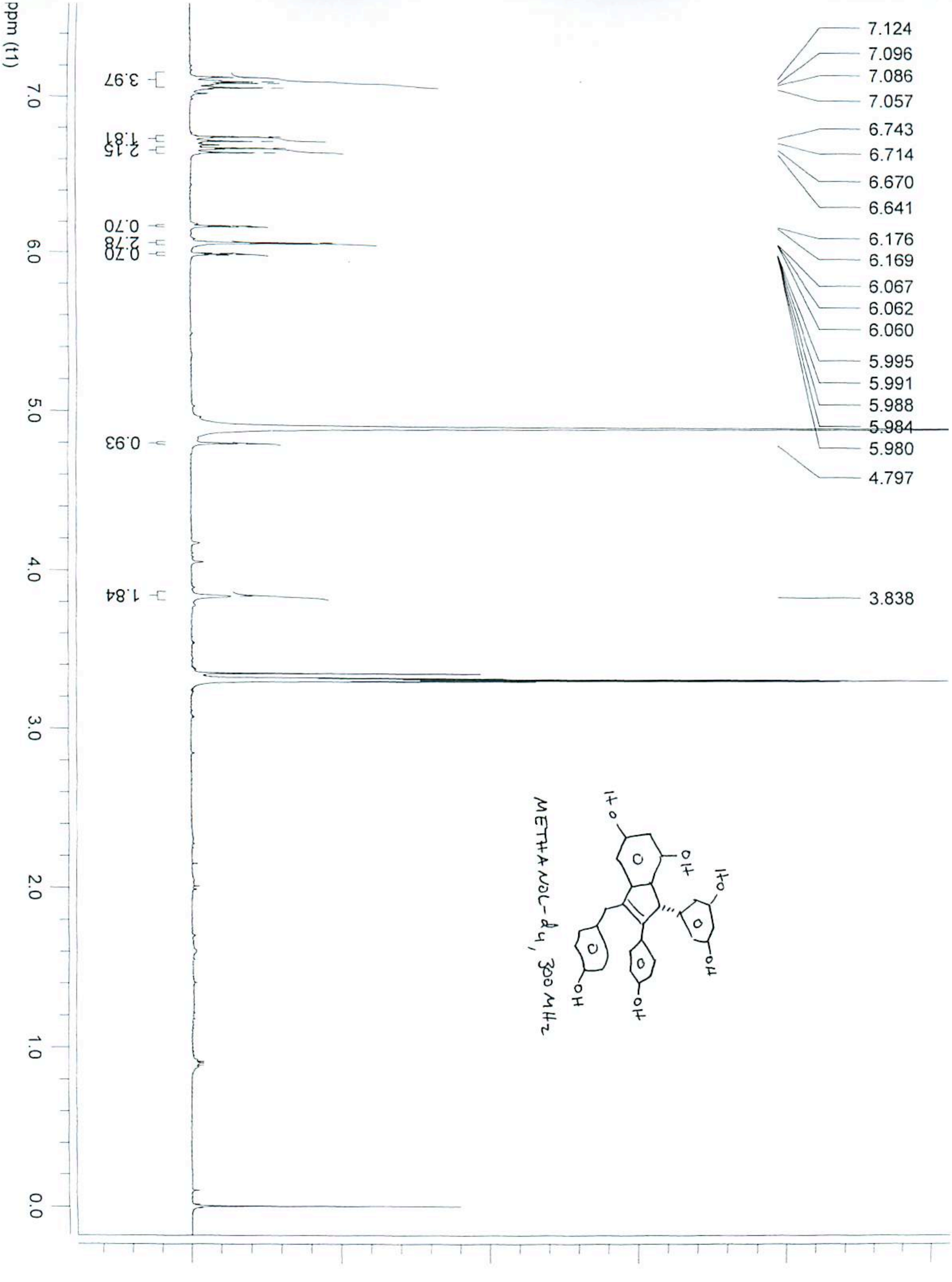
ACETONE-d_6, 300 MHz

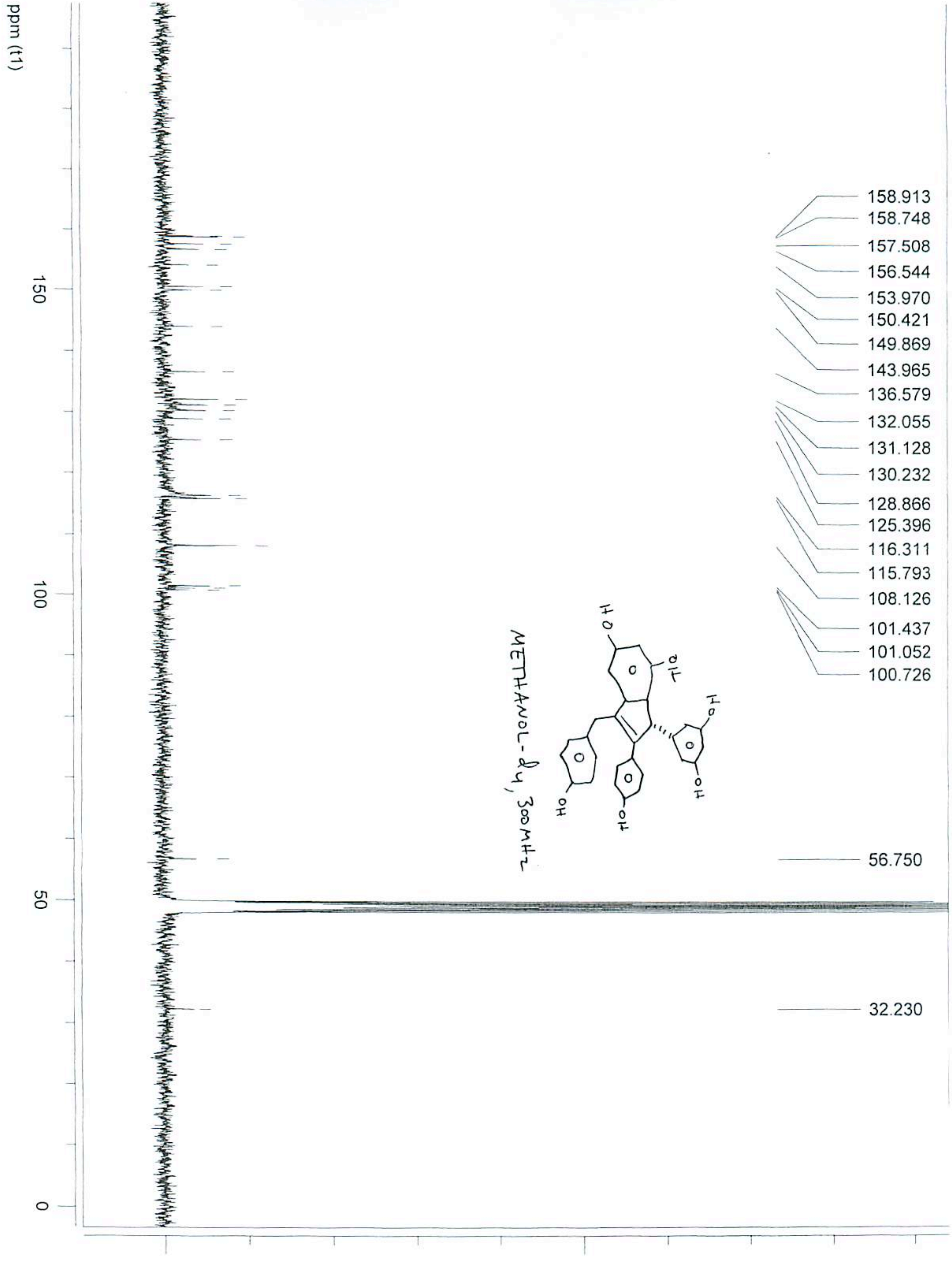


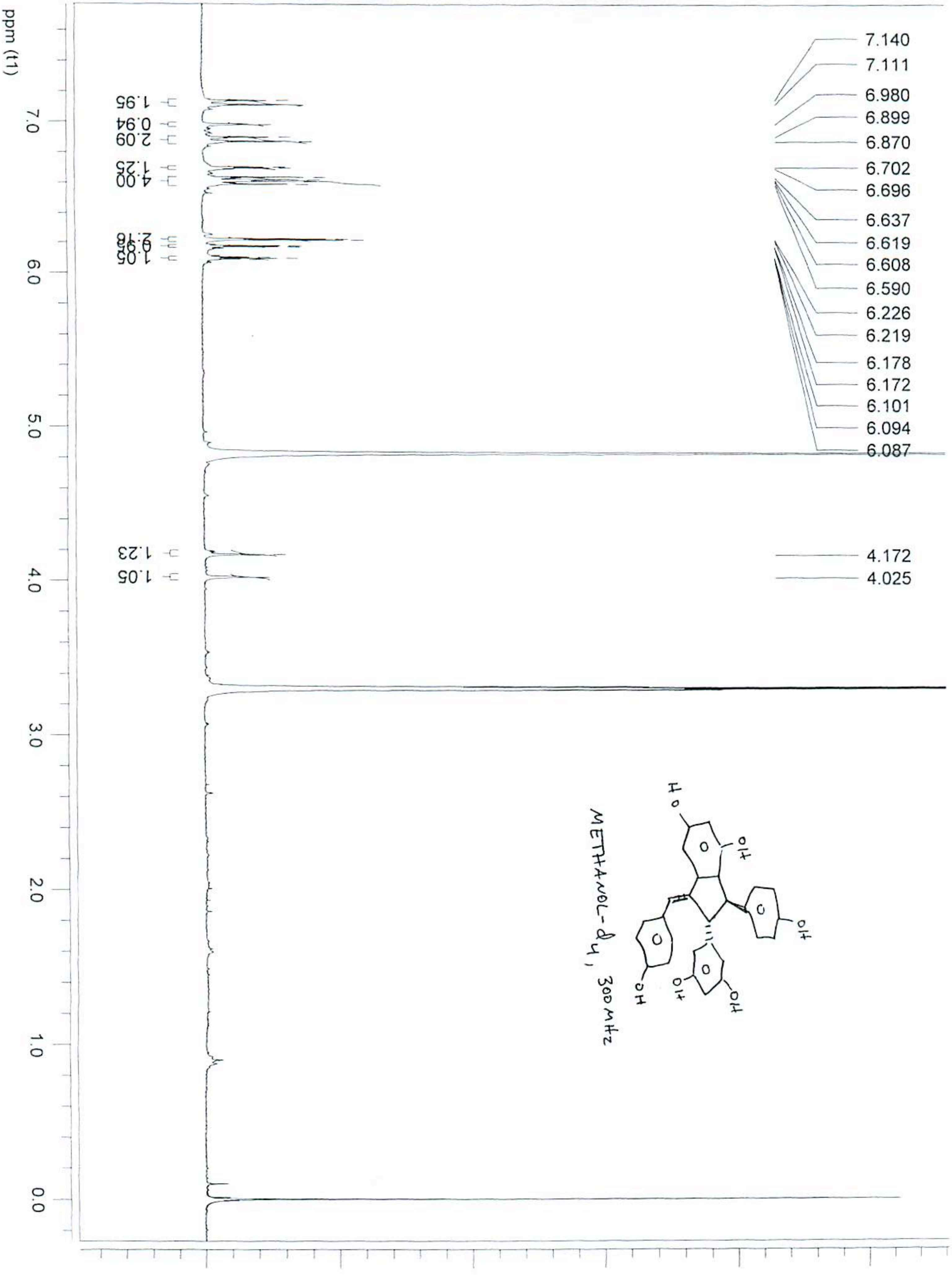
ACETONE-d_6, 300 MHz



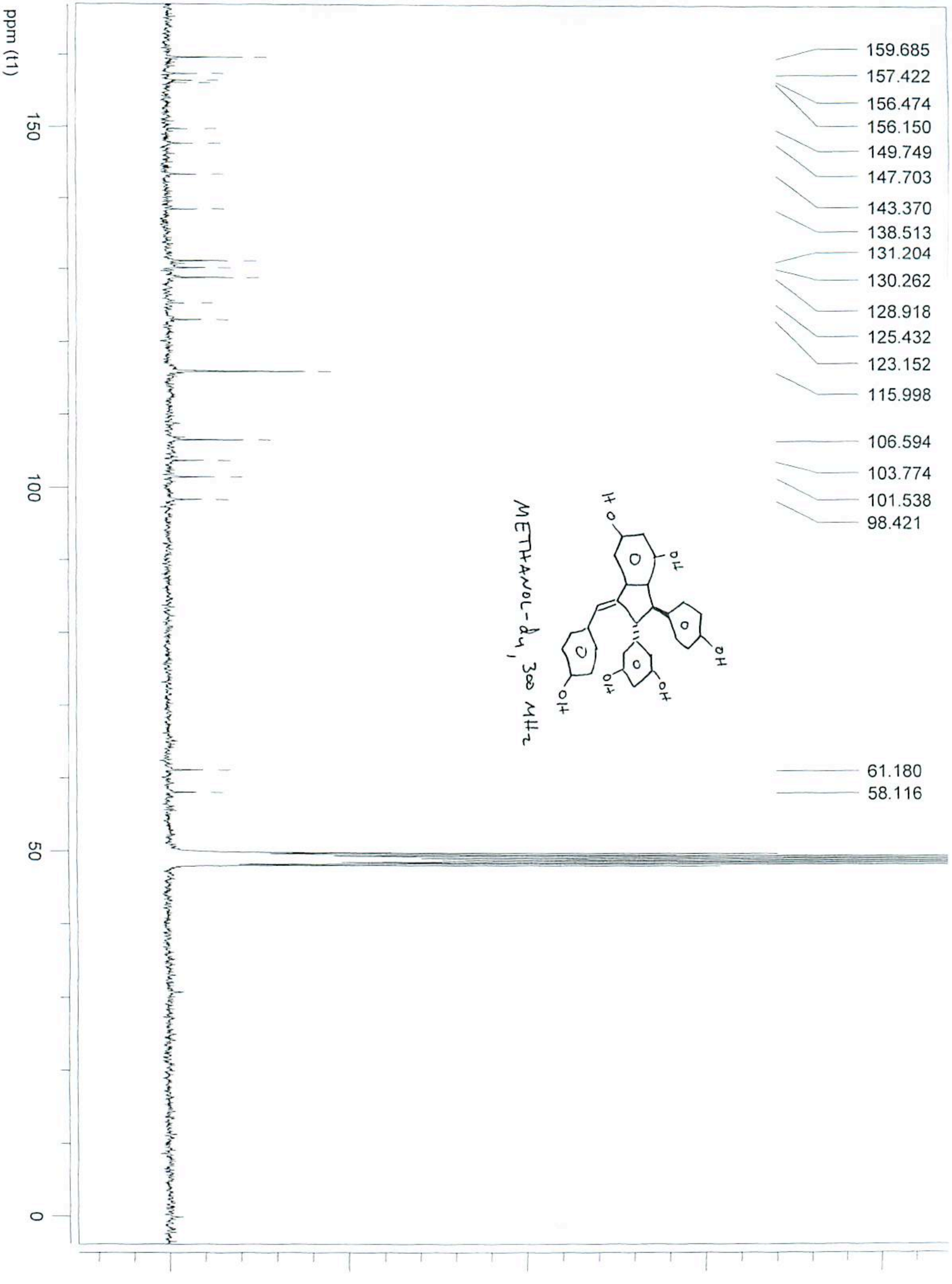
ACETONE-d_6, 300 MHz


ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
3.97
1.81
2.15
0.70
2.78
0.70
0.93
1.84
7.124
7.096
7.086
7.057
6.743
6.714
6.670
6.641
6.176
6.169
6.067
6.062
6.060
5.995
5.991
5.988
5.984
5.980
4.797
3.838
HO
OH
HO
OH
OH
OH
METHANOL-d4, 300 MHz

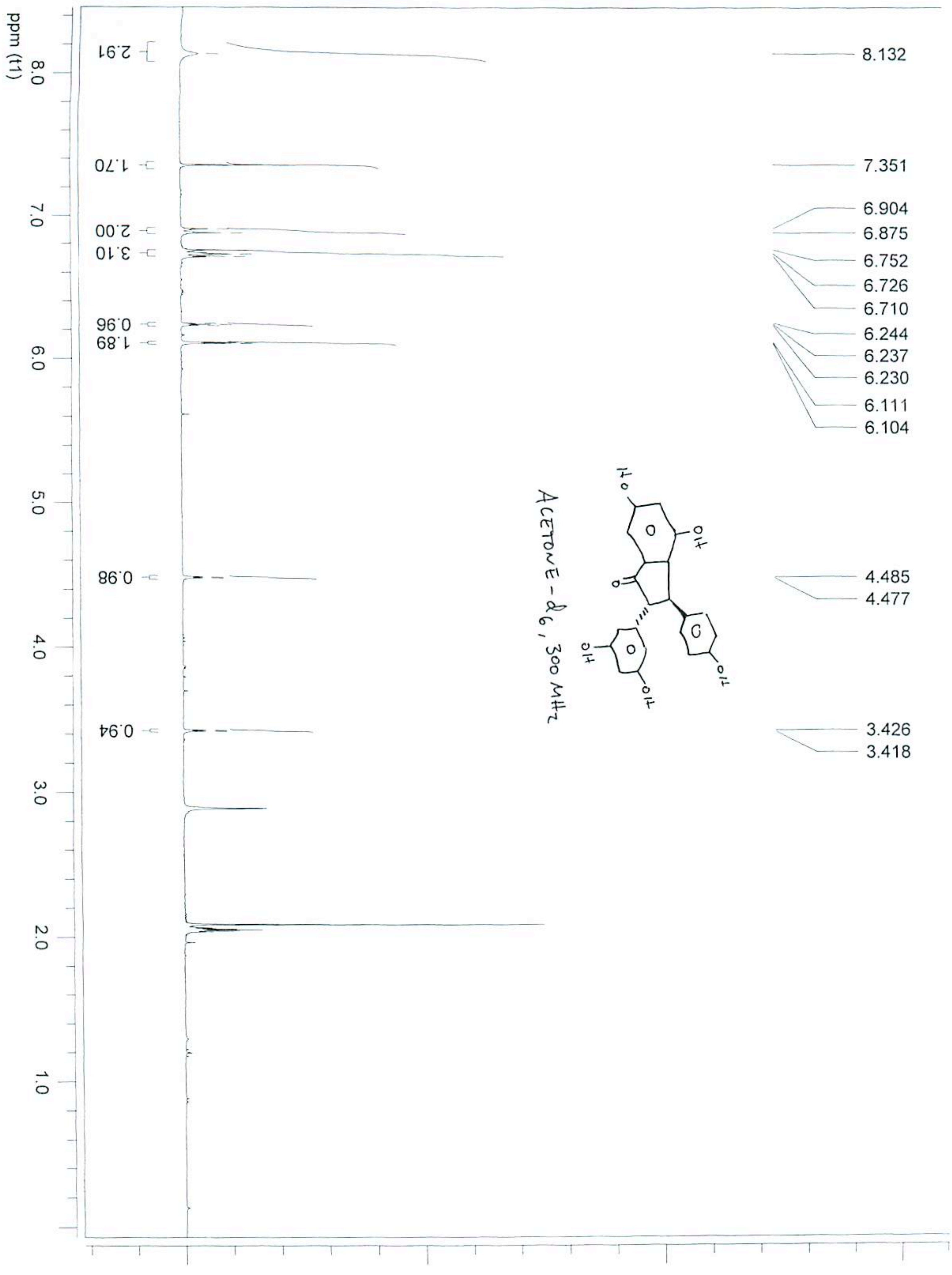

ppm (t1)
150
100
50
0
158.913
158.748
157.508
156.544
153.970
150.421
149.869
143.965
136.579
132.055
131.128
130.232
128.866
125.396
116.311
115.793
108.126
101.437
101.052
100.726
56.750
32.230
HO
OH
OH
OH
OH
METHANOL-d4, 300MHz



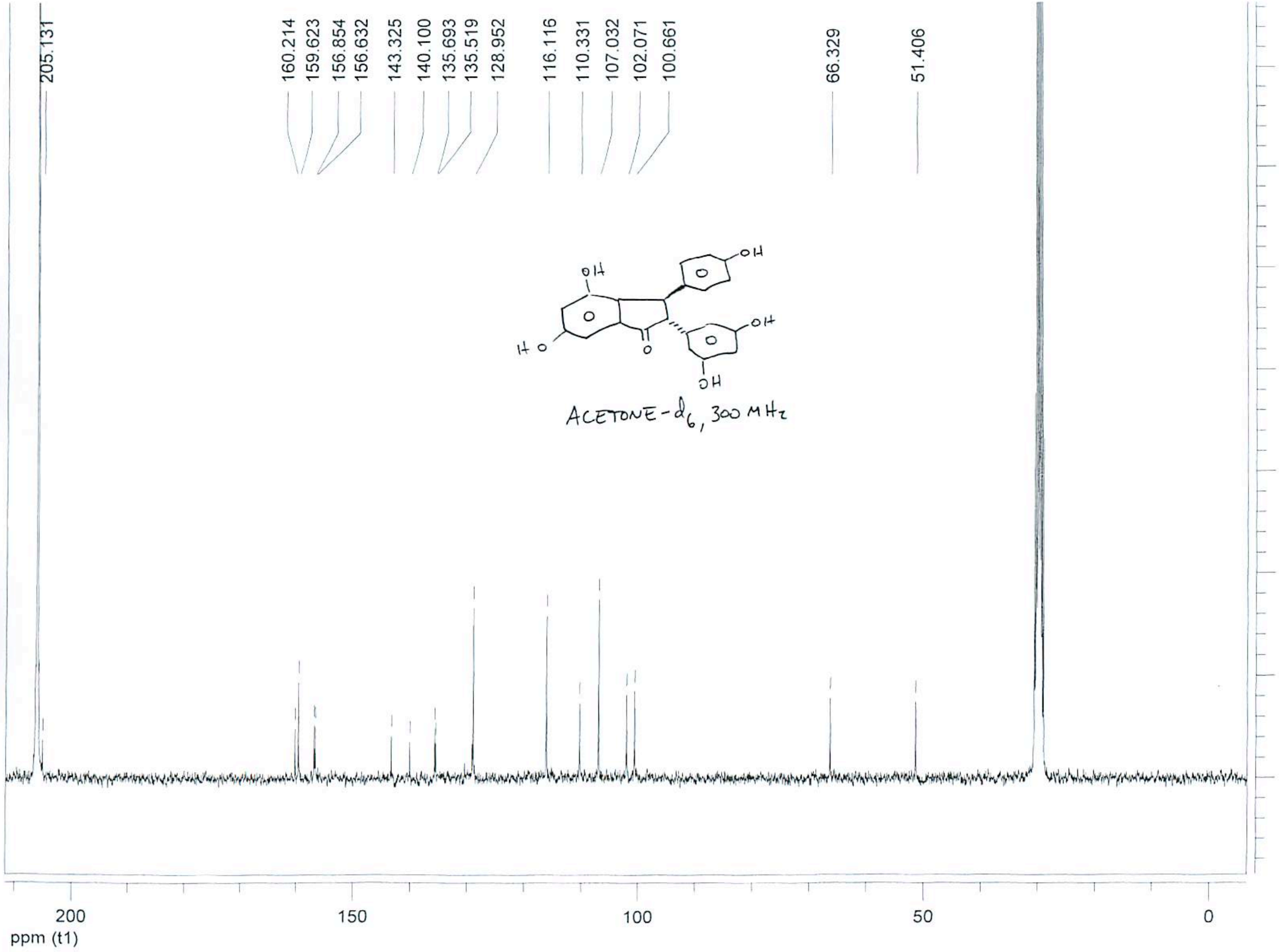
METHANOL-d_4, 300 MHz



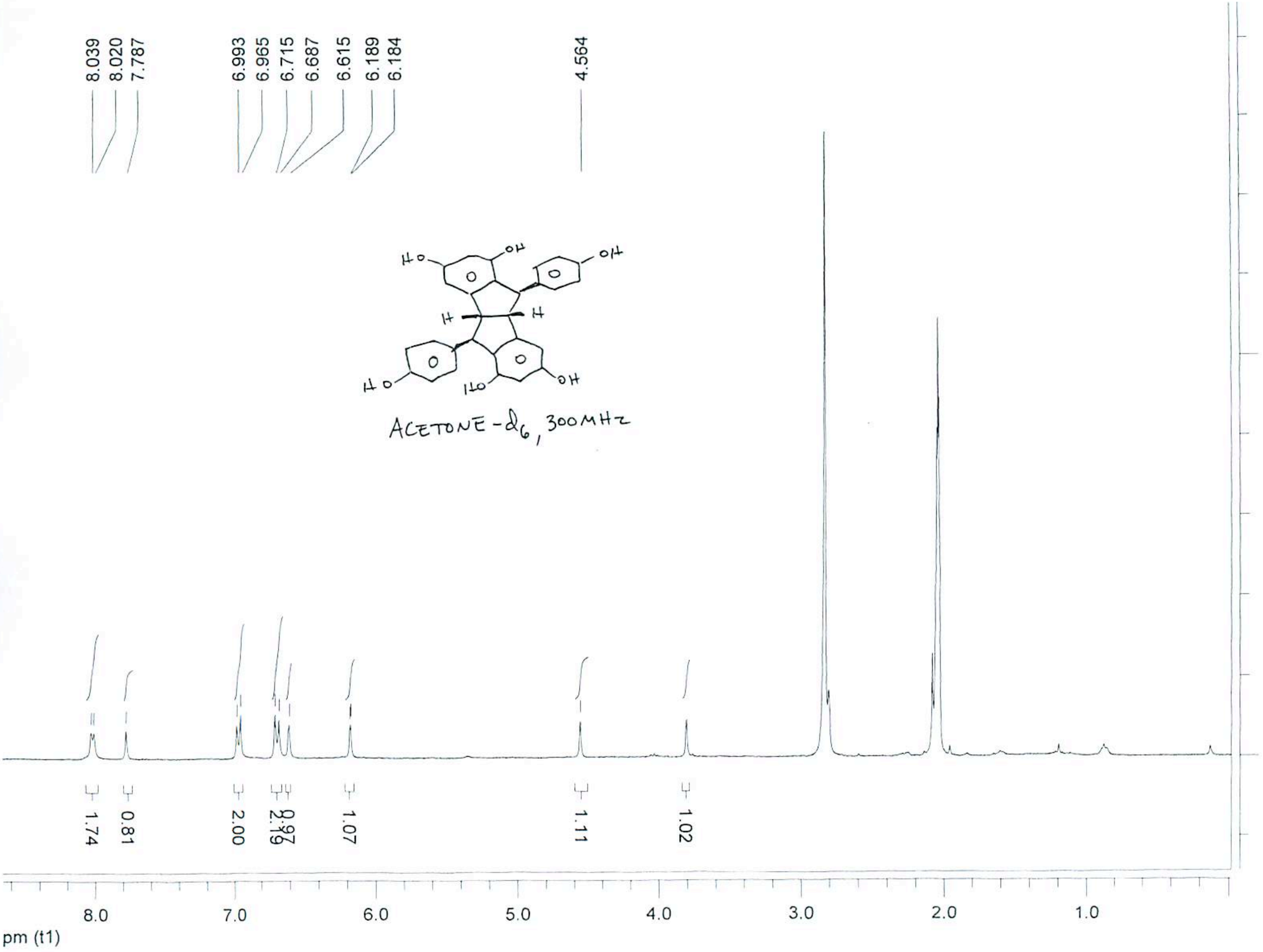
METHANOL-d_4, 300 MHz



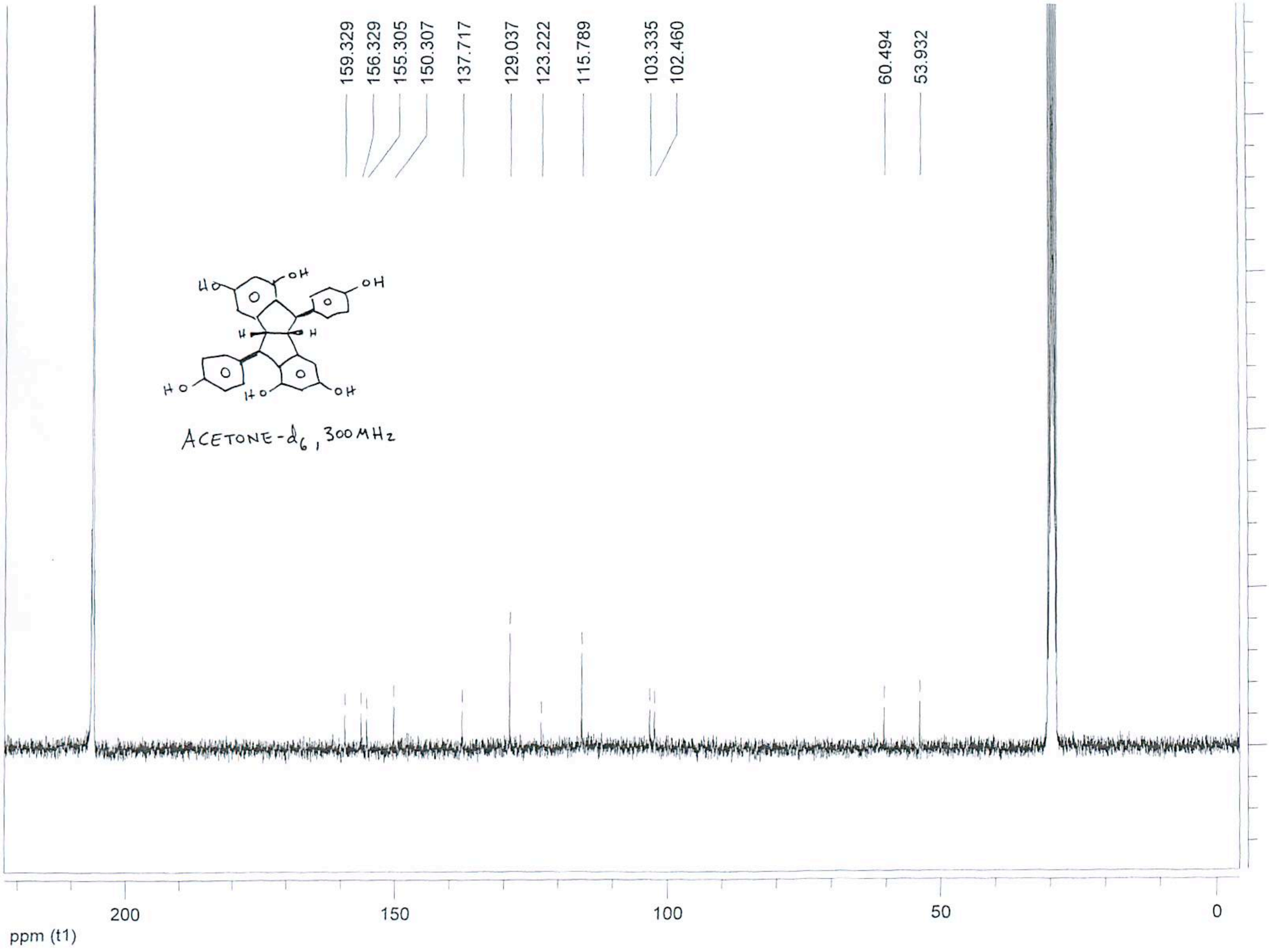
ACETONE-d_6, 300 MHz



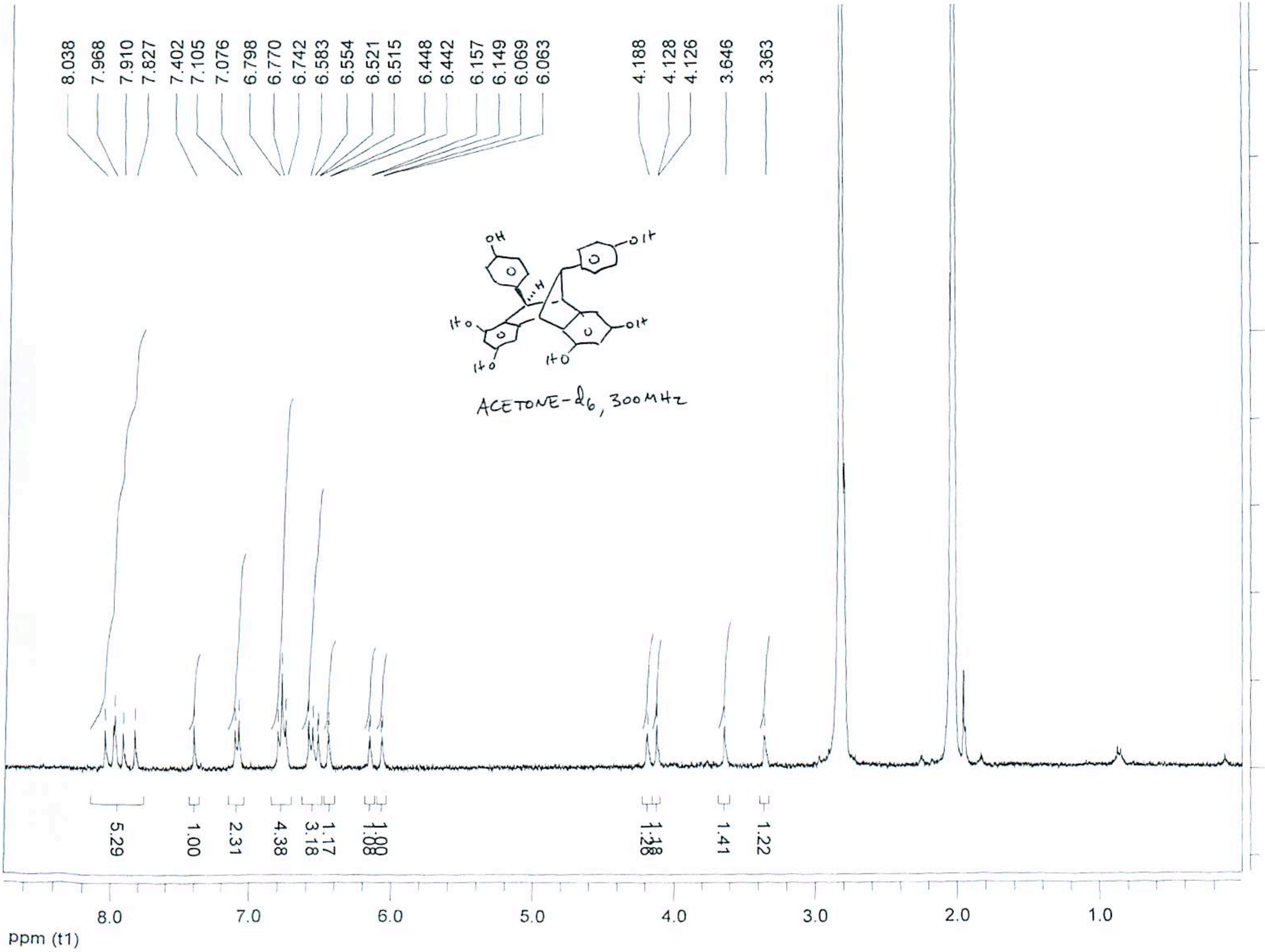
ACETONE-d_6, 300 MHz



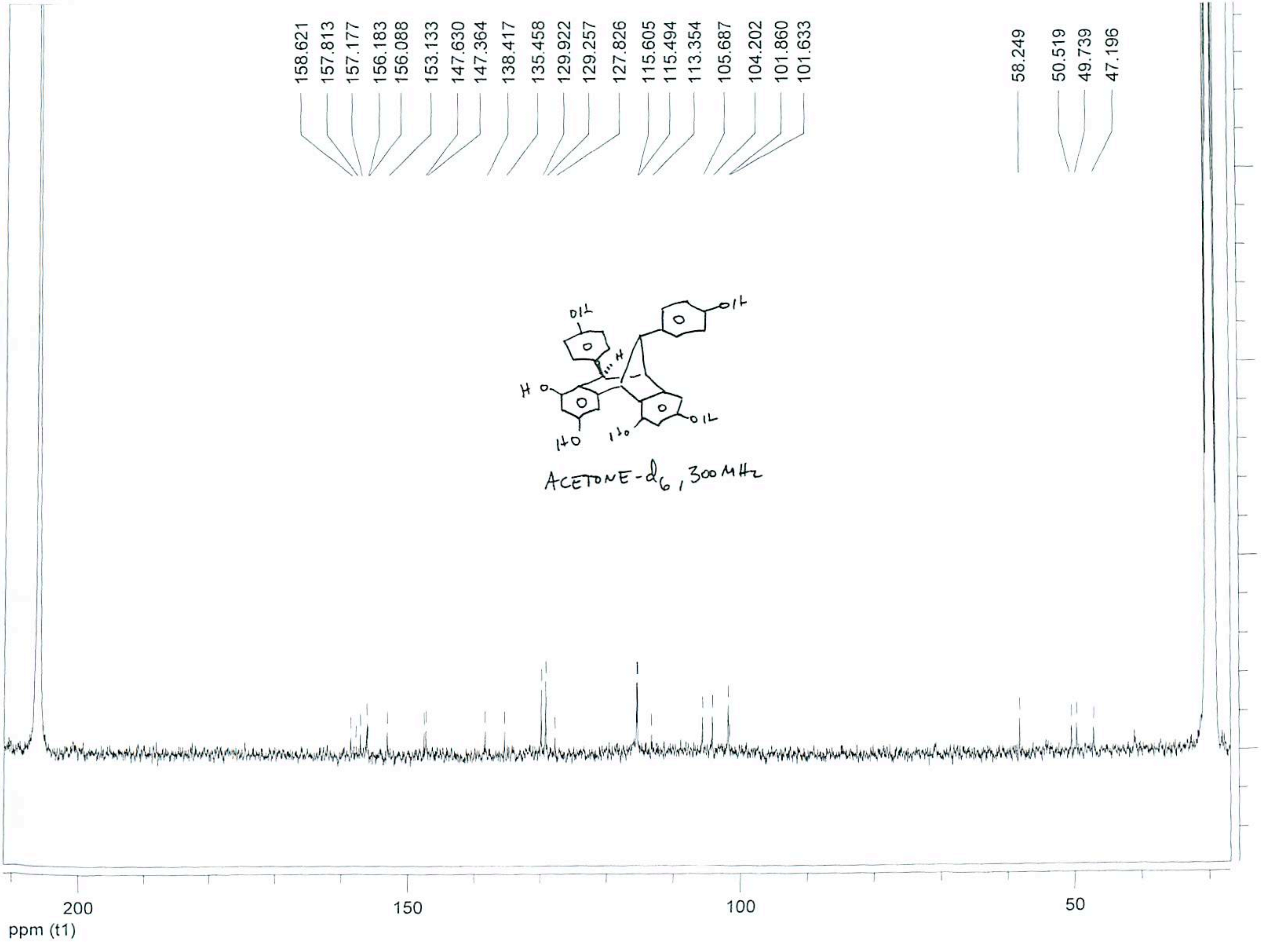
ACETONE-d_6, 300MHz



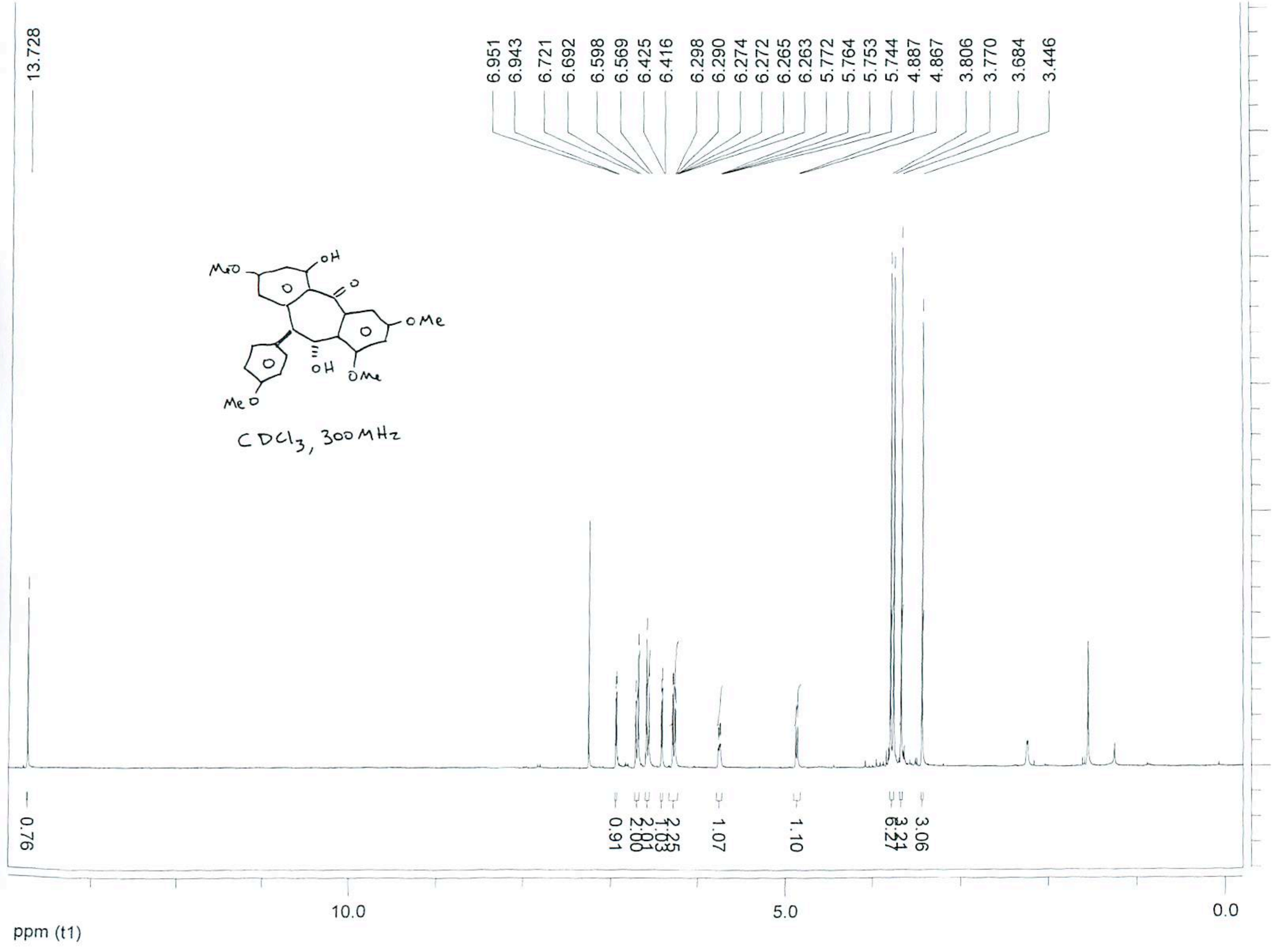
ACETONE-d_6, 300 MHz

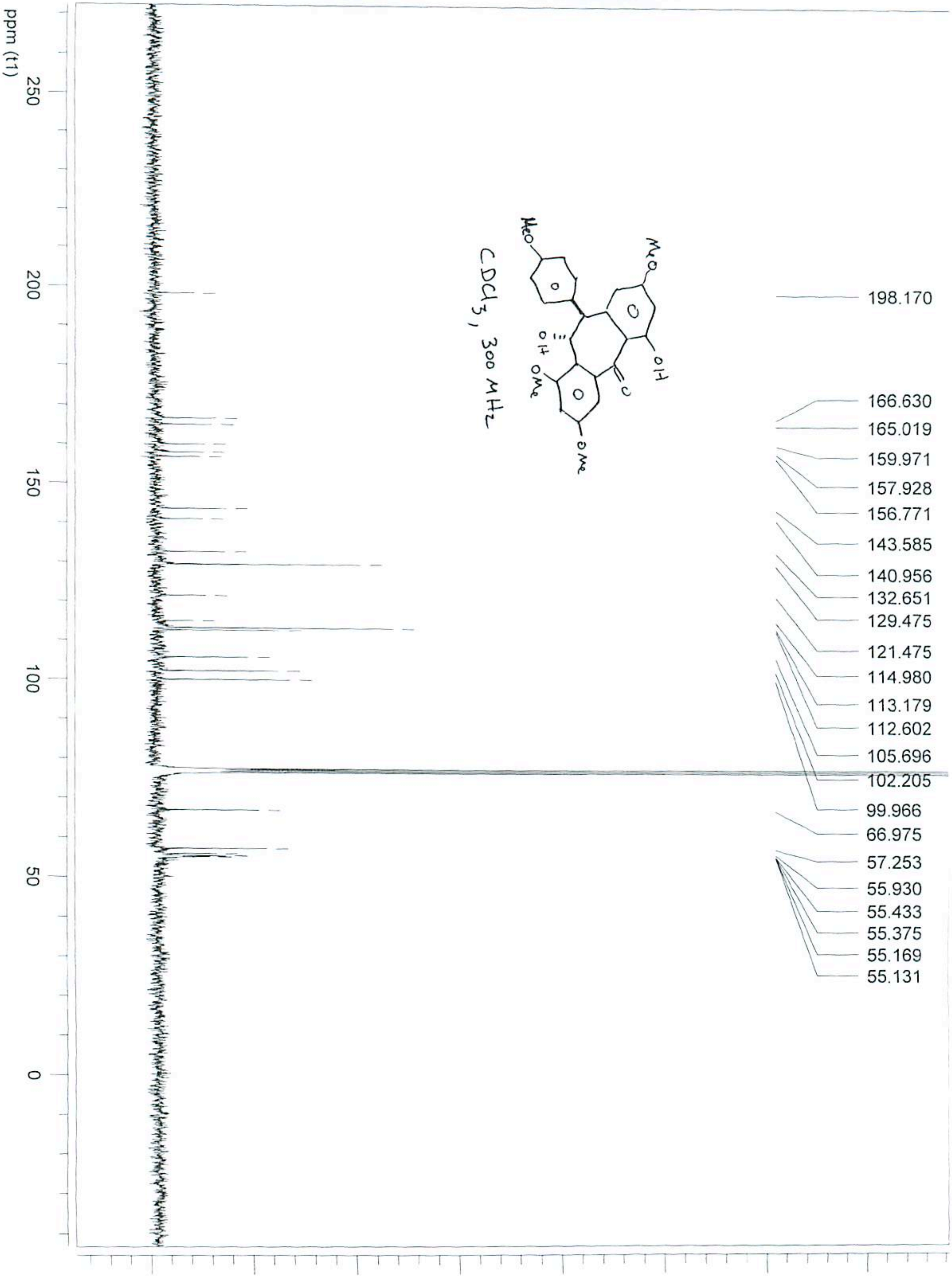


ACETONE-d_6, 300MHz

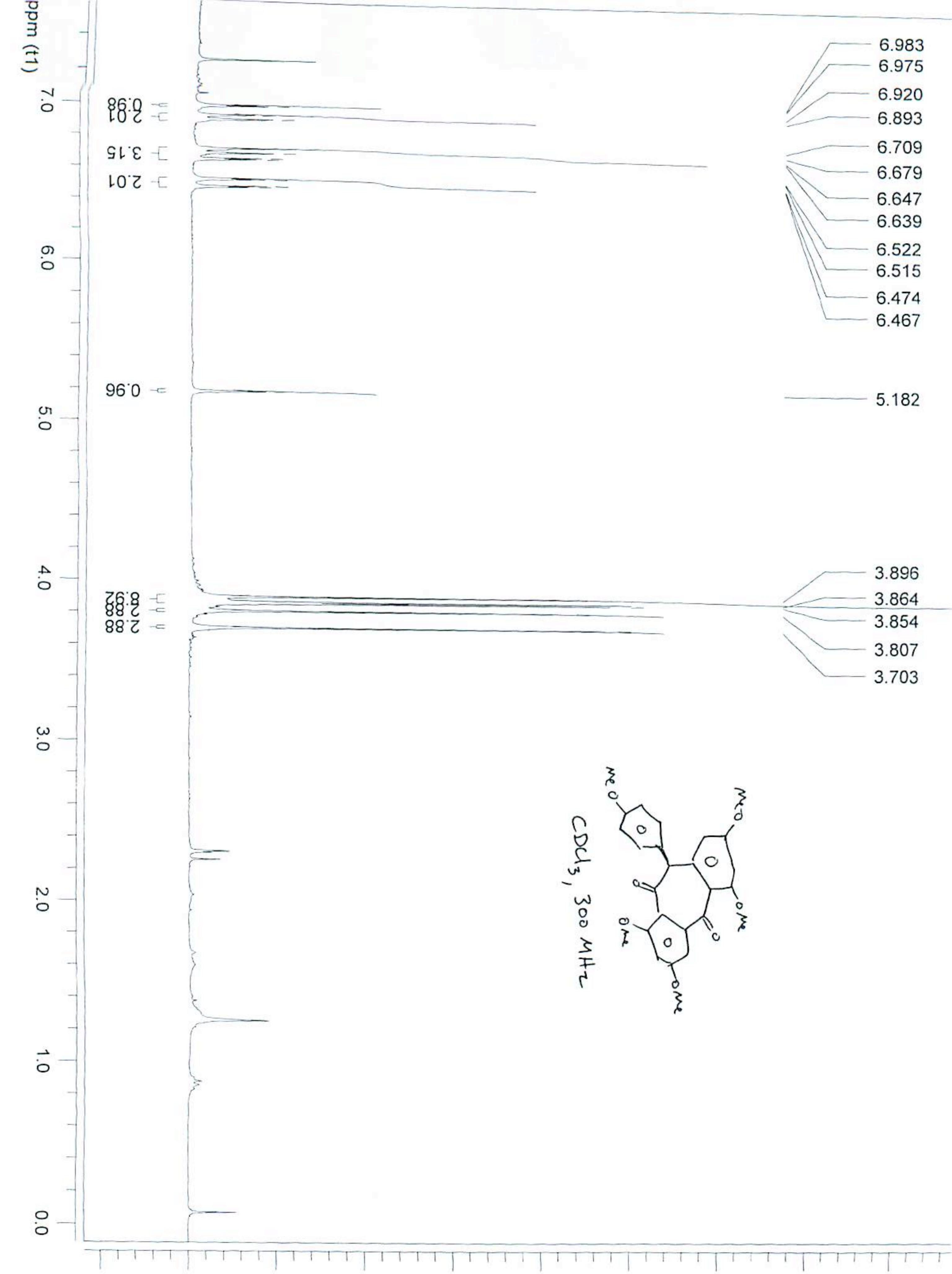


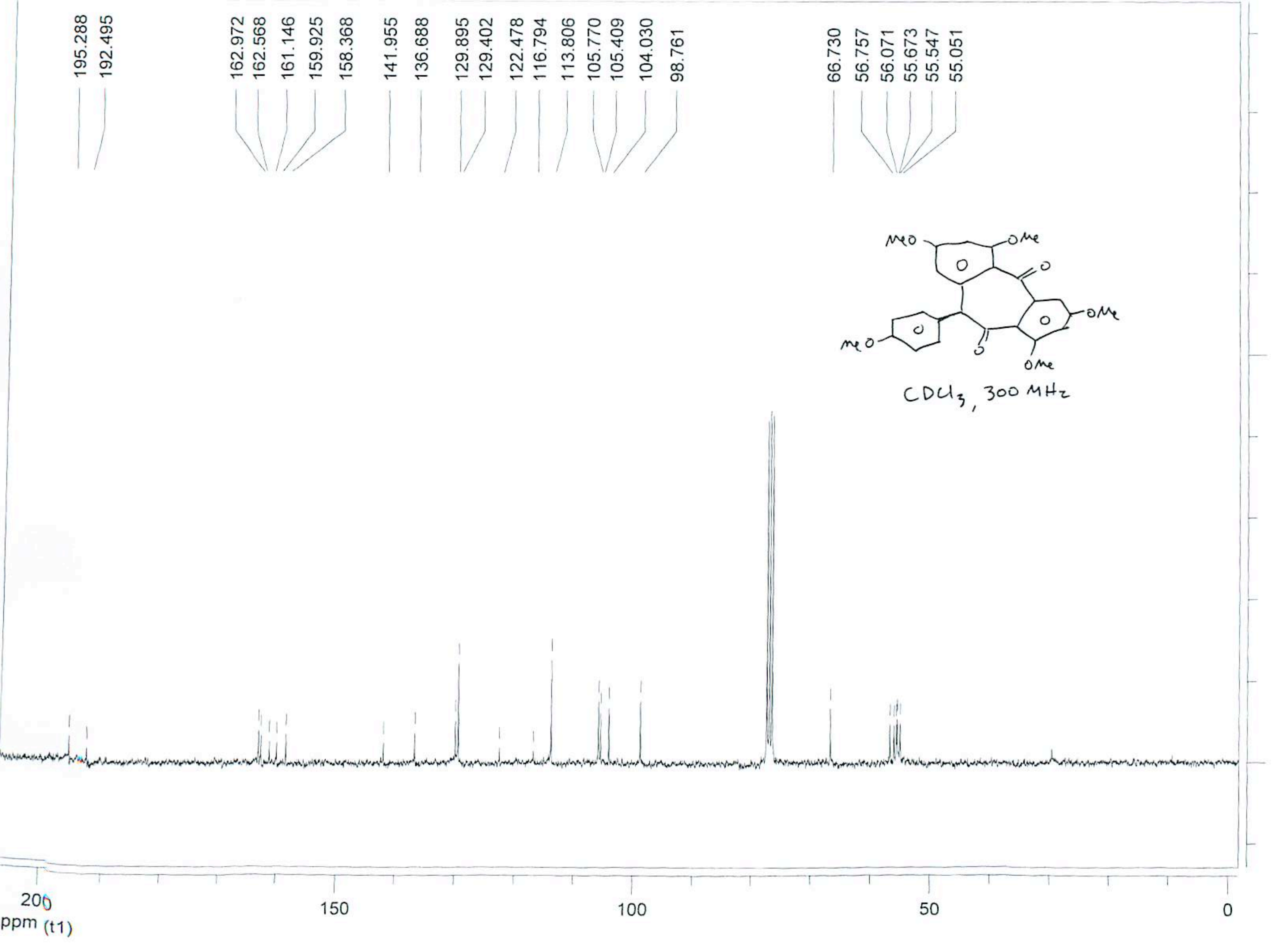
ACETONE-d_6, 300 MHz


13.728
6.951
6.943
6.721
6.692
6.598
6.569
6.425
6.416
6.298
6.290
6.274
6.272
6.265
6.263
5.772
5.764
5.753
5.744
4.887
4.867
3.806
3.770
3.684
3.446
MeO
OH
O
OMe
OH
OMe
MeO
CDCl3, 300 MHz
0.76
0.91
2.00
2.01
1.03
2.25
1.07
1.10
6.27
3.21
3.06
10.0
5.0
0.0
ppm (t1)



$CDCl_3$, 300 MHz


ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.98
2.01
3.15
2.01
0.96
8.92
2.88
2.88
6.983
6.975
6.920
6.893
6.709
6.679
6.647
6.639
6.522
6.515
6.474
6.467
5.182
3.896
3.864
3.854
3.807
3.703
MeO
MeO
OMe
OMe
OMe
O
O
CDCl3, 300 MHz



CDCl$_3$, 300 MHz