Diastereoselective Intramolecular Carbamoylketene/Alkene [2+2] Cycloaddition: Enantioselective Access to Pyrrolidinoindoline Alkaloids

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Supporting information

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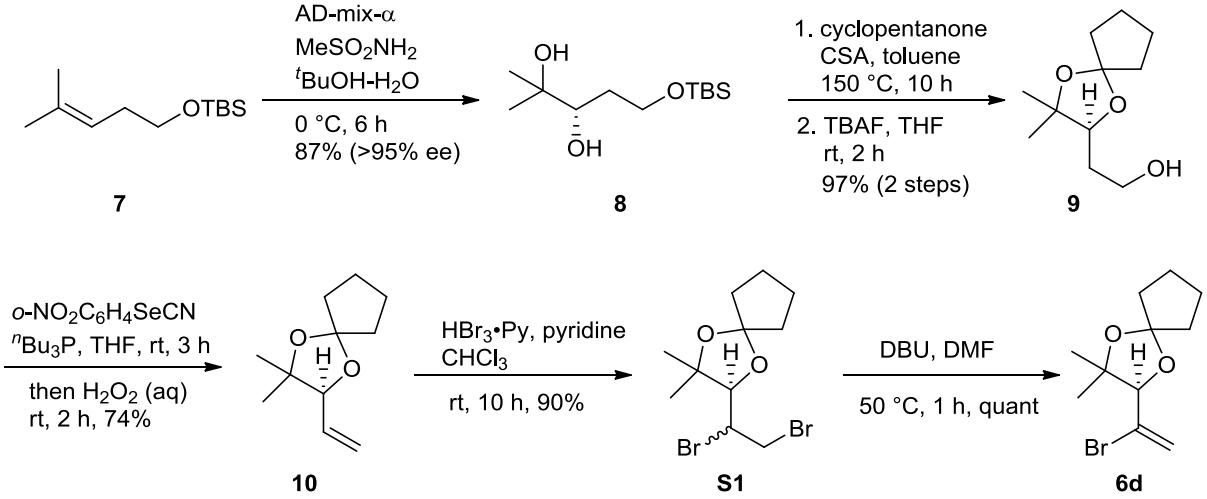
General Procedures.

^{1}H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using JEOL JNM-AL400 (400 MHz) spectrometers. ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) or in CD_3OD and referenced to CD_3OD (49.0 ppm) using JEOL JNM-AL400 (100 MHz) spectrometers or JEOL JNM-AL300 (75 MHz) spectrometers. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broadened. Optical rotation were determined on JAS.CO P-1010-GT. IR spectra were measured on JAS.CO FT/IR-4200 spectrometer. Mass spectra were recorded on Waters MICRO MASS LCT-Premier spectrometers (TOF-mass). Column chromatography was performed on silica gel 60N (KANTO CHEMICAL, spherical neutral, 63-230 mesh) using indicated solvent. Thin layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel $60F_{245}$), and compounds were visualized with UV light and *p*-anisaldehyde stain. For the analysis purpose, HPLC analysis was carried out by Jai LC-9201. All melting points were measured with BÜCHI 535 melting point apparatus and are uncorrected. All non-aqueous reactions were performed in oven-dried glassware under positive pressure of argon or nitrogen, unless otherwise noted. Reaction mixture was stirred magnetically. Solvents were freshly distilled prior to use or purchased from Kanto Kagaku or Aldrich: tetrahydrofuran (THF) was purchased from Kanto Kagaku (Tetrahydrofuran, Dehydrated Stabilizer free): methylene chloride (CH_2Cl_2) was purchased from Kanto Kagaku (Methylene chloride, Dehydrated): ether (Et_2O) was purchased from Kanto Kagaku (Diethyl ether, Dehydrated): benzene was distilled from calcium hydride and kept over 4 A molecular sieves: methanol, ethanol and ^{t}BuOH ware distilled from sodium and kept over 3 A molecular sieves: pyridine and triethylamine (Et_3N) were distilled from KOH and kept over KOH tablets: DMF were distilled from $MgSO_4$ and kept over 4 A molecular sieves.

Experimental Data for Compounds



(*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-methylpentane-2,3-diol (8)

To a stirred solution of AD-mix-α (22.5 g) and methanesulfonamide (665 mg, 7.00 mmol) in $^{t}BuOH-H_2O$ (1 : 1, 90 mL) was added *tert*-butyldimethyl(4-methylpent-3-enyloxy)silane (**7**) [1] (1.50 g, 7.00 mmol) at 0 °C. After stirring was continued for 6 h at 0 °C, the reaction mixture was quenched with Na_2SO_3 (22.5 g) at 0 °C. After further stirring was continued at room temperature for 10 min, the reaction mixture was extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 2 : 1) to give 1.51 g (87%) of **8** as a colorless oil. $[\alpha]_D^{32}$ = + 8.4 (c = 0.90, $CHCl_3$), ($[\alpha]_D^{20}$ = + 7.95 (c = 1.00, $CHCl_3$)) [2]; IR (neat) 3421, 2956, 1256, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (6H, s), 0.91 (9H, s), 1.17 (3H, s), 1.21 (3H, s), 1.66–1.71 (2H, m), 2.56 (1H, br), 3.62 (1H, t, *J* = 6.0 Hz), 3.76 (1H, br), 3.82–3.88 (1H, m), 3.90–3.95 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ – 5.6 (CH_3), – 5.5 (CH_3), 18.1 ($CH_3\times3$), 24.1 (C), 25.8 (CH_3), 26.1 (CH_3), 32.9 (CH_2), 62.8 (CH_2), 72.2 (C), 78.4 (CH); HRMS (ESI) m/z Calcd for $C_{12}H_{28}O_3SiNa$ $[M+Na]^+$: 271.1705, found 271.1706.

(*S*)-2-(3,3-Dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)-ethanol (9)

To a stirred solution of diol **8** (1.45 g, 5.84 mmol) in toluene (30 mL) was added cyclopentanone (2.45 g, 29.2 mmol) and (*1S*)-(+)-10-camphorsulfonic acid (135 mg, 0.584 mmol) at room temperature and the mixture was stirred at 150 °C for 10 h by using Dean-Stark trap. The reaction mixture was cooled to room temperature, and poured into saturated aqueous $NaHCO_3$ solution. The whole mixture was extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was immediately carried on to next step without purification. To a stirred solution of above crude in THF (40 mL) was added TBAF (5.84 mmol) (1.0 M solution in THF) at 0 °C and

the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 3 : 1) to give 1.13 g (97% for 2 steps) of **9** as a pale yellow oil. $[\alpha]_D^{28}$ = – 18.0 (c = 1.00, $CHCl_3$); IR (neat) 3419, 2972, 1194, 1114, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (3H, s), 1.26 (3H, s), 1.60–1.85 (10H, m), 2.30 (1H, br), 3.73 (1H, dd, *J* = 2.4, 10.8 Hz), 3.81–3.84 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (CH_3), 23.3 (CH_2), 23.7 (CH_2), 25.3 (CH_3), 31.6 (CH_2), 38.2 ($CH_2\times2$), 61.5 (CH_2), 79.8 (C), 82.7 (CH), 117.1 (C); HRMS (ESI) m/z Calcd for $C_{11}H_{20}O_3Na$ $[M+Na]^+$: 223.1310, found 223.1312.

(*S*)-2,2-Dimethyl-3-vinyl-1,4-dioxaspiro[4.4]nonane (10)

To a stirred solution of alcohol **9** (1.00 g, 4.99 mmol) in dry THF (30 mL) was added 2-nitrophenylselenocyanate (2.27 g, 9.99 mmol) and tributylphosphine (2.02 g, 9.99 mmol) at room temperature and the mixture was stirred for 3 h. 35% H_2O_2 (5 mL, 50.0 mmol) was added to the reaction mixture and stirring was continued for 2 h at the same temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and then extracted with Et_2O. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 10 : 1) to give 674 mg (74%) of **10** as a colorless oil. $[\alpha]_D^{27}$ = + 9.0 (c = 0.70, $CHCl_3$); IR (neat) 2974, 1433, 1336, 1195, 1109, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (3H, s), 1.26 (3H, s), 1.62–1.90 (6H, m), 1.86–1.90 (2H, m), 4.02 (1H, d, *J* = 7.6 Hz), 5.27 (1H, dq, *J* = 0.8, 10.4 Hz), 5.37 (1H, dt, *J* = 1.1, 17.0 Hz), 5.81 (1H, ddd, *J* = 7.4, 10.4, 17.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 25.2 (CH_3), 38.2 (CH_2), 38.3 (CH_2), 80.2 (C), 85.5 (CH), 117.3 (C), 118.8 (CH_2), 133.3 (CH); HRMS (ESI) m/z Calcd for $C_{11}H_{19}O_2$ $[M+H]^+$: 183.1385, found 183.1385.

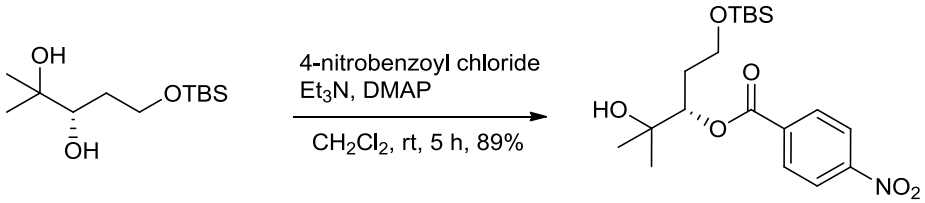
(*R*)-3-(1,2-Dibromoethyl)-2,2-dimethyl-1,4-dioxaspiro[4.4]nonane (S1)

To a stirred solution of **10** (600 mg, 3.29 mmol) in $CHCl_3$ (10 mL) was added pyridine (703 mg, 8.89 mmol) and pyridinium tribromide (1.26 g, 3.95 mmol) at 0 °C and the mixture was stirred at room temperature for 10 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution and then extracted with $CHCl_3$. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 10 : 1) to give 1.02 g (90%) of **S1** as a pale blown oil; IR (neat) 2972, 1334, 1194, 1111, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (0.5H, s), 1.29 (2.5H, s), 1.37 (2.5H, s), 1.46 (0.5H, s), 1.62–2.02 (6.7H, m), 1.62–2.02 (1.3H, m), 3.75 (0.8H, dd, *J* = 5.2, 10.8 Hz), 3.81 (0.8H, dd, *J* = 6.8, 10.8 Hz), 3.83 (0.2H, dd, *J* = 5.8, 10.8 Hz), 3.85 (0.2H, dd, *J* = 5.6, 11.2 Hz), 3.96–3.99 (0.4H, m), 4.03 (0.8H, d, *J* = 5.2 Hz), 4.12 (0.8H, q, *J* = 5.2 Hz); ^{13}C NMR ($CDCl_3$, 100

MHz) δ 22.2 (CH_3), 22.6 (CH_3), 23.3 (CH_2), 23.4 (CH_2), 23.6 (CH_2), 24.0 (CH_2), 27.4 (CH_3), 27.6 (CH_3), 34.6 ($CH_2\times2$), 37.9 (CH_2), 38.1 ($CH_2\times2$), 38.7 (CH_2), 49.1 (CH), 49.8 (CH), 79.7 (C), 80.1 (C), 82.2 (CH), 83.3 (CH), 116.7 (C), 117.6 (C); HRMS (ESI) m/z Calcd for $C_{11}H_{19}O_2Br_2$ $[M+H]^+$: 340.9752, found 340.9752.

(*R*)-3-(1-Bromovinyl)-2,2-dimethyl-1,4-dioxaspiro[4.4]nonane (6d)

To a stirred solution of dibromide **S1** (1.00 g, 2.92 mmol) in DMF (10 mL) was added DBU (445 mg, 2.92 mmol) at room temperature and the mixture was stirred at 50 °C for 1 h. The reaction mixture was poured into water and then extracted with Et_2O. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 20 : 1) to give 768 mg (quant) of **6d** as a colorless oil. $[\alpha]_D^{27}$ = + 32.6 (c = 0.51, $CHCl_3$); IR (neat) 2976, 1632, 1193, 1111, 899 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (3H, s), 1.49 (3H, s), 1.63–1.91 (8H, m), 4.28 (1H, s), 5.65 (1H, s), 6.13 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 27.5 (CH_3), 38.1 (CH_2), 38.2 (CH_2), 80.2 (C), 86.1 (CH), 117.1 (C), 117.2 (CH_2), 126.6 (C); HRMS (ESI) m/z Calcd for $C_{11}H_{17}O_2NaBr$ $[M+Na]^+$: 283.0310, found 283.0308.

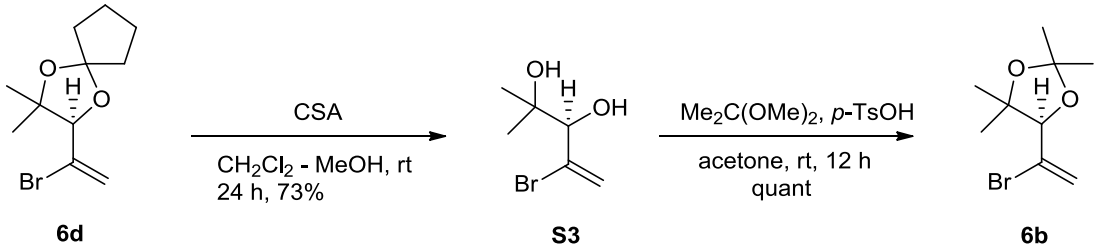


8 **S2**

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-4-methylpentan-3-yl 4-nitrobenzoate (S2)

To a stirred solution of diol **8** (20.0 mg, 0.0810 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (16.3 mg, 0.161 mmol), DMAP (2.00 mg, 0.0160 mmol) and 4-nitrobenzoylchloride (29.9 mg, 0.161 mmol) at room temperature. After stirring was continued for 5 h at the same temperature, the reaction mixture was poured into water and then extracted with $CHCl_3$. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 4 : 1) to give 27.3 mg (89%, > 95% ee *) of **S2** as a colorless oil. *HPLC [DICEL CHIRALPAK OD-H column; 0.5 mL/min; solvent system: ^{i}PrOH : Hexane = 1 : 99; retention times: 57.2 min (minor), 69.0 min (major)]; $[\alpha]_D^{31}$ = – 12.7 (c = 0.47, $CHCl_3$); IR (neat) 3435, 2930, 2857, 1727, 1529, 1276, 1103, 839, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (6H, s), 0.89 (9H, s), 1.29 (3H, s), 1.31 (3H, s), 1.97–2.10 (2H, m), 3.03 (1H, br), 3.69–3.80 (2H, m), 5.19 (1H, dd, *J* = 4.4, 7.2 Hz), 8.23 (2H, d, *J* = 8.8 Hz), 8.31 (2H, d, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ – 5.5 ($CH_3\times2$), 18.2 (C), 25.8 ($CH_3\times3$), 25.9 (CH_3), 26.2 (CH_3),

33.0 (CH_2), 59.7 (CH_2), 71.9 (C), 79.4 (CH), 123.6 (CH×2), 130.7 (CH×2), 135.7 (C), 150.7 (C), 164.4 (C); HRMS (ESI) m/z Calcd for $C_{19}H_{31}NO_6SiNa$ $[M+Na]^+$: 420.1819, found 420.1822.

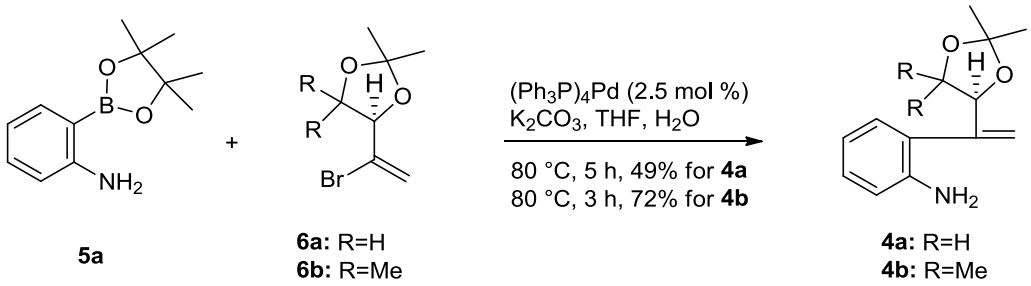


(*R*)-4-Bromo-2-methylpent-4-ene-2,3-diol (S3)

To a stirred solution of vinylbromide **6d** (200 mg, 0.766 mmol) in CH_2Cl_2–MeOH (1 : 1, 6 mL) was added (*1S*)-(+)-10-camphorsulfonic acid (88.9 mg, 0.383 mmol), at room temperature. After stirring was continued for 24 h at the same temperature, the reaction mixture was concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 2 : 1) to give 108 mg (73%) of **S3** as a colorless oil. $[\alpha]_D^{20}$ = – 14.8 (c = 0.20, $CHCl_3$); IR (neat) 3390, 1167, 1047, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (3H, s), 1.31 (3H, s), 2.25 (1H, br), 3.13 (1H, br), 4.01 (1H, s), 5.73 (1H, s), 5.94 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4 (CH_3), 27.1 (CH_3), 72.8 (C), 80.9 (CH), 120.4 (CH_2), 132.6 (C); HRMS (ESI) m/z Calcd for $C_6H_{12}O_2Br$ $[M+H]^+$: 195.0021, found 195.0023.

(*R*)-5-(1-Bromovinyl)-2,2,4,4-tetramethyl-1,3-dioxolane (6b)

To a stirred solution of diol **S3** (45.0 mg, 0.232 mmol) in 2,2-dimethoxypropane–acetone (1 : 1, 2 mL) was added *p*-toluenesulfonic acid monohydrate (0.900 mg, 0.000500 mmol), at room temperature. After stirring was continued for 12 h at the same temperature, the reaction mixture was concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 10 : 1) to give 54.5 mg (quant) of **6b** as a colorless oil. $[\alpha]_D^{20}$ = + 51.5 (c = 0.15, $CHCl_3$); IR (neat) 2984, 1632, 1370, 1197, 1055, 899 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (3H, s), 1.38 (3H, s), 1.47 (3H, s), 1.51 (3H, s), 4.41 (1H, t, *J* = 1.6 Hz), 5.66 (1H, t, *J* = 1.6 Hz), 6.15 (1H, t, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (CH_3), 27.1 (CH_3), 28.0 (CH_3), 28.3 (CH_3), 80.7 (C), 85.9 (CH), 107.2 (C), 117.2 (CH_2), 126.3 (C); HRMS (ESI) m/z Calcd for $C_9H_{15}O_2BrNa$ $[M+Na]^+$: 257.0153, found 257.0153.

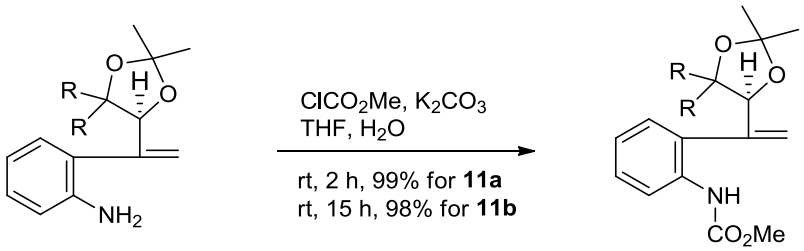


General Procedure for Preparation of Aminoalkenes 4a and 4b.

To a stirred solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**5a**) (1.0 equiv) and corresponding vinylbromides (**6a,b**) [3] (1.0 equiv) in THF–H_2O (10 : 1, 0.10 M) were added $(Ph_3P)_4Pd$ (2.5 mol %) and K_2CO_3 (2.0 equiv) at room temperature and the mixture was stirred at 80 °C for 3-5 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography.

*(S)-2-{1-(2,2-Dimethyl-1,3-dioxolan-4-yl)vinyl}aniline (**4a**).* This compound was prepared from aniline **5a** (45.0 mg, 0.210 mmol) and vinylbromide **6a** (48.0 mg, 0.210 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 10 : 1) gave 22.0 mg (49%) of **4a** as a yellowish oil. $[\alpha]_D^{20}$ = – 19.4 (c = 1.00, $CHCl_3$); IR (neat) 3458, 3366 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (3H, s), 1.42 (3H, s), 3.68 (1H, t, *J* = 7.6 Hz), 3.87 (2H, br), 4.05 (1H, dd, *J* = 6.8, 7.6 Hz), 4.81 (1H, t, *J* = 7.6 Hz), 5.24 (1H, d, *J* = 1.6 Hz), 5.70 (1H, d, *J* = 1.6 Hz), 6.69 (1H, dd, *J* = 1.2, 7.2 Hz), 6.71 (1H, dt, *J* = 1.2, 7.2 Hz), 6.94 (1H, dd, *J* = 1.2, 7.2 Hz), 7.09 (1H, dt, *J* = 1.2, 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9 (CH_3), 26.3 (CH_3), 69.0 (CH_2), 78.5 (CH), 109.7 (C), 115.5 (CH), 116.7 (CH_2), 118.0 (CH), 125.1 (C), 128.6 (CH), 129.6 (CH), 144.1 (C), 145.4 (C); HRMS (ESI) calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338, found 220.1340.

*(S)-2-{1-(2,2,5,5-Tetramethyl-1,3-dioxolan-4-yl)vinyl}aniline (**4b**).* This compound was prepared from aniline **5a** (55.9 mg, 0.255 mmol) and vinylbromide **6b** (60.0 mg, 0.255 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 10 : 1) gave 45.4 mg (72%) of **4b** as a yellowish oil. $[\alpha]_D^{20}$ = – 130.7 (c = 0.10, $CHCl_3$); IR (neat) 3368, 2982, 1615, 1493, 1197, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, s), 1.11 (3H, s), 1.43 (3H, s), 1.51 (3H, s), 3.75 (2H, br), 4.72 (1H, s), 5.32 (1H, dd, *J* = 1.2, 2.0 Hz), 5.80 (1H, t, *J* = 2.0 Hz), 6.69–6.75 (2H, m), 7.02 (1H, dd, *J* = 1.6, 7.6 Hz), 7.09 (1H, dt, *J* = 1.6, 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0 (CH_3), 26.6 (CH_3), 27.1 (CH_3), 28.5 (CH_3), 80.5 (C), 83.5 (CH), 106.3 (C), 115.9 (CH), 116.0 (CH_2), 118.2 (CH), 125.2 (C), 128.6 (CH), 129.3 (CH), 142.0 (C), 143.3 (C); HRMS (ESI) m/z Calcd for $C_{15}H_{21}NO_2Na$ $[M+Na]^+$: 270.1470, found 270.1469.



4a: R=H
4b: R=Me

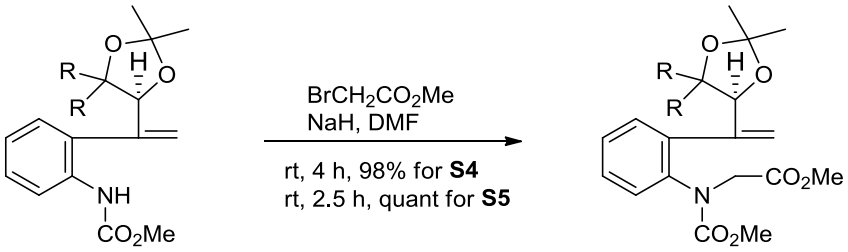
11a: R=H
11b: R=Me

General Procedure for Preparation of Carbamates 11a and 11b.

To a stirred solution of corresponding aminoalkenes (**4a,b**) (1.0 equiv) in THF–H_2O (3 : 1, 0.10 M) were added K_2CO_3 (10 equiv) and methyl chloroformate (1.5 equiv) at room temperature and the mixture was stirred for 2-15 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography.

*(S)-Methyl [2-{1-(2,2-dimethyl-1,3-dioxolan-4-yl)vinyl}phenyl]carbamate (**11a**).* This compound was prepared from aniline **4a** (65.0 mg, 0.300 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 10 : 1) gave 83.1 mg (99%) of **11a** as a yellowish oil. $[\alpha]_D^{20}$ = – 19.6 (c = 1.00, $CHCl_3$); IR (neat) 3327, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (3H, s), 1.41 (3H, s), 3.63 (1H, t, *J* = 8.4 Hz), 3.75 (3H, s), 4.05 (1H, dd, *J* = 6.4, 8.4 Hz), 4.77 (1H, t, *J* = 7.2 Hz), 5.22 (1H, d, *J* = 1.6 Hz), 5.67 (1H, d, *J* = 1.6 Hz), 6.99 (1H, dd, *J* = 1.2, 7.2 Hz), 7.03 (1H, dt, *J* = 1.2, 7.2 Hz), 7.31 (1H, dt, *J* = 1.2, 7.2 Hz), 7.71 (1H, br), 7.96 (1H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.8 (CH_3), 25.9 (CH_3), 52.2 (CH_3), 68.0 (CH_2), 79.6 (CH), 110.0 (C), 114.9 (CH), 120.6 (CH_2), 123.0 (CH), 128.7 (CH), 129.0 (C), 129.9 (CH), 136.0 (C), 144.3 (C), 154.3 (C); HRMS (ESI) calcd for $C_{15}H_{19}NO_4Na$ $[M+Na]^+$: 300.1212, found 300.1220.

*(S)-Methyl [2-{1-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)vinyl}phenyl]carbamate (**11b**).* This compound was prepared from aniline **4b** (43.0 mg, 0.174 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 5 : 1) gave 52.3 mg (98%) of **11b** as a colorless oil. $[\alpha]_D^{20}$ = – 74.4 (c = 0.11, $CHCl_3$); IR (neat) 3419, 2983, 1744, 1521, 1212, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, s), 1.07 (3H, s), 1.42 (3H, s), 1.50 (3H, s), 3.76 (3H, s), 4.56 (1H, s), 5.31 (1H, dd, *J* = 1.2, 1.6 Hz), 5.85 (1H, t, *J* = 1.6 Hz), 7.04 (1H, dt, *J* = 1.2, 7.6 Hz), 7.13 (1H, dd, *J* = 1.2, 7.6 Hz), 7.28–7.33 (2H, m), 8.05 (1H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0 (CH_3), 26.5 (CH_3), 27.0 (CH_3), 28.3 (CH_3), 52.3 (CH_3), 80.5 (C), 84.7 (CH), 106.6 (C), 118.6 (CH_2), 120.2 (CH), 123.1 (CH), 128.7 (CH), 129.2 (CH), 129.3 (C), 134.9 (C), 141.4 (C), 154.0 (C); HRMS (ESI) m/z Calcd for $C_{17}H_{24}NO_4$ $[M+H]^+$: 306.1705, found 306.1702.

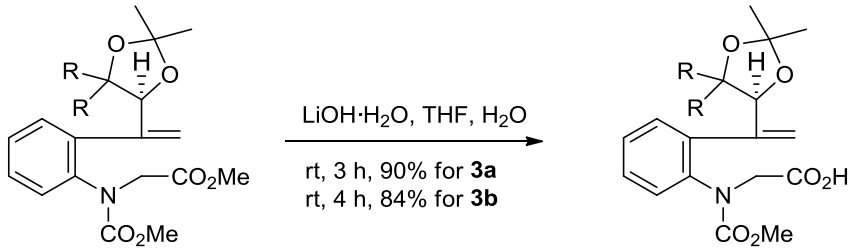


General Procedure for Preparation of Esters S4 and S5.

To a stirred solution of corresponding carbamates (**11a,b**) (1.0 equiv) in DMF (0.10 M) were added sodium hydride (3.0 equiv) by portions at 0 °C and the mixture was stirred at the same temperature for 15 min. 2-Bromoacetic acid methyl ester (3.0 equiv) was added to the reaction mixture and stirring was continued for 2.5-4 h at room temperature. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was dried over $MgSO_4$ and concentrated to give a residue that was purified by silica gel column chromatography.

(S)-Methyl 2-[{2-(1-(2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)phenyl}(methoxycarbonyl)amino]acetate ***(S4)****.* This compound was prepared from carbamate **11a** (70.0 mg, 0.250 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 10 : 1) gave 85.8 mg (98%) of **S4** as a yellowish oil. $[\alpha]_D^{20}$ = – 26.9 (c = 1.00, $CHCl_3$); IR (neat) 1755, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (6H, s), 3.82–3.59 (9H, m), 4.66 (1H, d, *J* = 14.8 Hz), 4.76–4.71 (1H, m), 5.14 (1H, s), 5.63 (1H, s), 7.27–7.18 (1H, m), 7.36–7.28 (2H, m), 7.54–7.47 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.8 (CH_3), 26.4 (CH_3), 51.7 (CH_2), 52.1 (CH_3), 53.2 (CH_3), 69.2 (CH_2), 69.5 (CH), 109.5 (C), 116.1 (CH_2), 127.9 (CH), 128.6 (CH), 129.0 (CH), 129.9 (CH), 130.2 (C), 139.2 (C), 146.1 (C), 156.3 (C), 169.9 (C); HRMS (ESI) calcd for $C_{18}H_{24}NO_6$ $[M+H]^+$: 350.1604, found 350.1607.

(S)-Methyl 2-[(methoxycarbonyl){2-(1-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)vinyl)phenyl}amino]acetate ***(S5)****.* This compound was prepared from carbamate **11b** (50.0 mg, 0.164 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 4 : 1) gave 61.8 mg (quant) of **S5** as a colorless oil. $[\alpha]_D^{20}$ = – 133.4 (c = 0.12, $CHCl_3$); IR (neat) 2983, 1756, 1716, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s), 1.09 (3H, s), 1.35 (3H, s), 1.49 (3H, s), 3.70–3.85 (7H, m), 4.41–4.71 (2H, m), 5.16–5.24 (1H, m), 5.68–5.76 (1H, m), 7.16 (1H, dd, *J* = 1.4, 7.8 Hz), 7.27–7.36 (2H, m), 7.48 (0.7H, d, *J* = 7.8 Hz), 7.55 (0.3H, t, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6 (CH_3), 26.3 (CH_3), 27.0 (CH_3), 28.3 (CH_3), 51.1 (CH_3), 52.1 (CH_3), 53.2 (CH_2), 80.1 (C), 82.4 (CH), 106.4 (C), 116.9 (CH_2), 128.0 (CH), 128.7 (CH), 130.7 (CH), 130.8 (CH), 137.4 (C), 138.9 (C), 143.7 (C), 156.2 (C), 169.8 (C); HRMS (ESI) m/z Calcd for $C_{20}H_{28}NO_6$ $[M+H]^+$: 378.1917, found 378.1919.

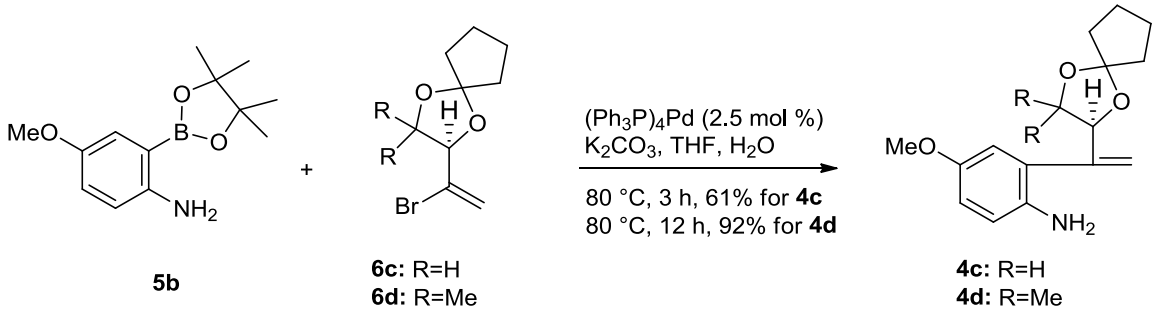


General Procedure for Preparation of Carboxylic acids 3a and 3b.

To a stirred solution of corresponding esters (**S4, S5**) (1.0 equiv) in THF–H_2O (5 : 1, 0.10 M) were added lithium hydroxide monohydrate (3.0 equiv) at 0 °C and the mixture was stirred at room temperature for 3-4 h. The reaction mixture was diluted with water and extracted with Et_2O. The aqueous layer was acidified with 1 N HCl solution and extracted with $CHCl_3$. The combined extracts was dried over $MgSO_4$ and concentrated.

*(S)-2-[{2-(1-(2,2-Dimethyl-1,3-dioxolan-4-yl)vinyl)phenyl}(methoxycarbonyl)amino]acetic acid (**3a**).* This compound was prepared from ester **S4** (50.0 mg, 0.140 mmol) to gave 42.0 mg (90%) of **3a** as a yellowish oil. $[\alpha]_D^{20}$ = – 14.3 (c = 1.00, $CHCl_3$); IR (neat) 3507, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (6H, s), 3.69 (3H, s), 3.80–3.72 (1H, m), 3.84 (1H, d, *J* = 18.4 Hz), 4.15–3.98 (1H, m), 4.67 (1H, d, *J* = 18.4 Hz), 4.71 (1H, t, *J* = 7.2 Hz), 5.15 (1H, s), 5.64 (1H, s), 7.22–7.19 (1H, m), 7.34–7.29 (2H, m), 7.50–7.42 (1H, m), 8.70 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.8 (CH_3), 26.3 (CH_3), 51.7 (CH_2), 53.3 (CH_3), 69.2 (CH_2), 77.2 (CH), 109.6 (C), 116.4 (CH_2), 128.0 (CH), 128.7 (CH), 129.1 (CH), 129.7 (CH), 130.2 (C), 139.1 (C), 145.9 (C), 156.5 (C), 174.2 (C); HRMS (ESI) calcd for $C_{17}H_{22}NO_6$ $[M+H]^+$: 336.1447, found 336.1440.

*(S)-2-[(Methoxycarbonyl){2-(1-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)vinyl)phenyl}amino]acetic acid (**3b**).* This compound was prepared from ester **S5** (60.0 mg, 0.159 mmol) to gave 48.3 mg (84%) of **3b** as a colorless oil. $[\alpha]_D^{20}$ = – 122.0 (c = 0.12, $CHCl_3$); IR (neat) 2980, 1716, 1450, 1191 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84–0.91 (3H, m), 1.09 (3H, s), 1.35 (3H, s), 1.49 (3H, s), 3.59–3.91 (4H, m), 4.41–4.75 (2H, m), 5.16–5.24 (1H, m), 5.68–5.76 (1H, m), 5.76 (1H, overlapped), 7.16 (1H, d, *J* = 7.6 Hz), 7.26–7.37 (2H, m), 7.41–7.52 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 28.3 (CH_3), 51.1 (CH_3), 53.4 (CH_2), 80.1 (C), 82.4 (CH), 106.5 (C), 117.1 (CH_2), 128.1 (CH), 128.7 (CH), 130.7 (CH), 130.8 (CH), 137.4 (C), 138.8 (C), 143.5 (C), 156.3 (C), 169.8 (C); HRMS (ESI) m/z Calcd for $C_{19}H_{26}NO_6$ $[M+H]^+$: 364.1760, found 364.1766.

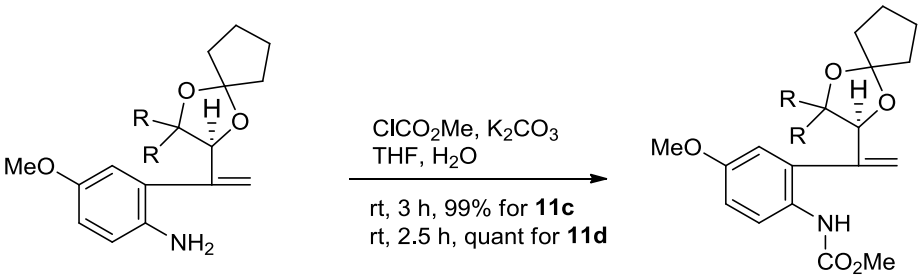


General Procedure for Preparation of Aminoalkenes 4c and 4d.

To a stirred solution of aniline **5b** [4] (1.0 equiv) and corresponding vinylbromides (**6c,d**) [3] (1.0 equiv) in THF–H_2O (10 : 1, 0.10 M) were added $(Ph_3P)_4Pd$ (2.5 mol%) and K_2CO_3 (2.0 equiv) at room temperature and the mixture was stirred at 80 °C for 3-12 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography.

*(S)-2-{1-(1,4-Dioxaspiro[4.4]nonan-2-yl)vinyl}-4-methoxyaniline (**4c**).* This compound was prepared from aniline **5b** (183 mg, 0.785 mmol) and vinylbromide **6c** [3] (196 mg, 0.785 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 3 : 1) gave 131 mg (61%) of **4c** as a yellowish oil. $[\alpha]_D^{20}$ = – 23.1 (c = 0.25, $CHCl_3$); IR (neat) 3354, 2931, 1604, 1499, 1041, 917 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.67–1.91 (8H, m), 3.61 (2H, br), 3.65 (1H, dd, *J* = 6.8, 8.3 Hz), 3.73 (3H, s), 3.99 (1H, dd, *J* = 6.6, 8.3 Hz), 4.77 (1H, t, *J* = 6.6 Hz), 5.23 (1H, s), 5.67 (1H, s), 6.56 (1H, d, *J* = 2.9 Hz), 6.69 (1H, d, *J* = 8.5 Hz), 6.71 (1H, dd, *J* = 2.9, 8.5 Hz), NH_2 was not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3 (CH_2), 23.4 (CH_2), 36.2 (CH_2), 36.4 (CH_2), 55.6 (CH_3), 68.7 (CH_2), 77.9 (CH), 114.3 (CH_2), 115.1 (CH), 116.5 (CH), 116.6 (CH), 119.6 (C), 126.2 (C), 137.6 (C), 145.5 (C), 152.1 (C); HRMS (ESI) m/z Calcd for $C_{16}H_{21}NO_3Na$ $[M+Na]^+$: 298.1419, found 298.1419.

*(S)-2-[1-(3,3-Dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl]-4-methoxyaniline (**4d**).* This compound was prepared from aniline **5b** (180 mg, 0.723 mmol) and vinylbromide **6d** (189 mg, 0.723 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 4 : 1) gave 201 mg (92%) of **4d** as a colorless oil. $[\alpha]_D^{20}$ = – 116.5 (c = 0.45 $CHCl_3$); IR (neat) 3358, 2973, 1604, 1498, 1114, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (3H, s), 1.09 (3H, s), 1.66–1.98 (8H, m), 3.61 (2H, br), 3.73 (3H, s), 4.58 (1H, s), 5.31 (1H, s), 5.78 (1H, s), 6.63 (1H, d, *J* = 2.8 Hz), 6.64 (1H, d, *J* = 8.8 Hz), 6.70 (1H, dd, *J* = 2.8, 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (CH_3), 23.5 (CH_2), 23.7 (CH_2), 26.0 (CH_3), 38.3 (CH_2), 38.3 (CH_2), 55.7 (CH_3), 79.9 (C), 83.8 (CH), 114.2 (CH), 115.1 (CH), 116.1 (CH_2), 116.3 (C), 117.0 (CH), 126.4 (C), 137.2 (C), 142.1 (C), 152.2 (C); HRMS (ESI) m/z Calcd for $C_{36}H_{50}N_2O_6Na$ $[2M+Na]^+$: 629.3567, found 629.3566.



4c: R=H
4d: R=Me

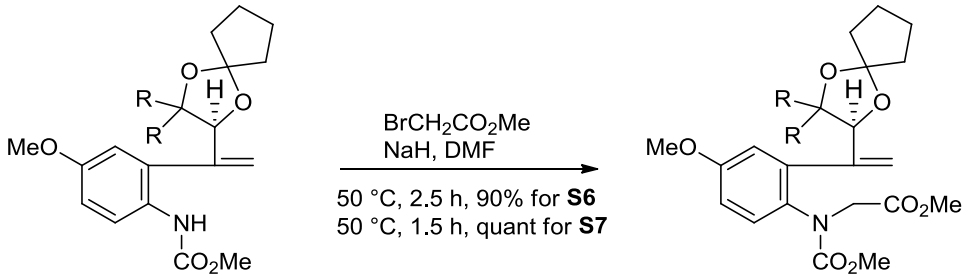
11c: R=H
11d: R=Me

General Procedure for Preparation of Carbamates 11c and 11d.

To a stirred solution of corresponding aminoalkenes (**4c,d**) (1.0 equiv) in THF–H_2O (3 : 1, 0.10 M) were added K_2CO_3 (10 equiv) and methyl chloroformate (1.5 equiv) at room temperature and the mixture was stirred for 2.5-3 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography.

*(S)-Methyl [2-{1-(1,4-dioxaspiro[4.4]nonan-2-yl)vinyl}-4-methoxyphenyl]carbamate (**11c**).* This compound was prepared from aniline **4c** (130 mg, 0.472 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 3 : 1) gave 156 mg (99%) of **11c** as a yellowish oil. $[\alpha]_D^{20}$ = – 28.8 (c = 0.20, $CHCl_3$); IR (neat) 3335, 2940, 1730, 1518, 1214, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59–1.84 (8H, m), 3.60 (1H, dd, *J* = 7.6, 8.3 Hz), 3.73 (3H, s), 3.78 (3H, s), 4.00 (1H, dd, *J* = 6.6, 8.3 Hz), 4.72 (1H, t, *J* = 6.6 Hz), 5.22 (1H, s), 5.63 (1H, s), 6.57 (1H, d, *J* = 2.9 Hz), 6.86 (1H, dd, *J* = 2.9, 9.0 Hz), 7.54 (1H, br), 7.79 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (CH_2), 23.2 (CH_2), 35.9 (CH_2), 36.0 (CH_2), 52.1 (CH_3), 55.4 (CH_3), 67.8 (CH_2), 79.1 (CH), 113.3 (CH), 115.7 (CH), 119.8 (CH), 120.3 (CH_2), 122.4 (C), 129.0 (C), 131.2 (C), 144.3 (C), 154.6 (C), 155.3 (C); HRMS (ESI) m/z Calcd for $C_{18}H_{23}NO_5Na$ $[M+Na]^+$: 356.1474, found 356.1472.

*(S)-Methyl 2-[1-(3,3-dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl]-4-methoxyphenylcarbamate (**11d**).* This compound was prepared from aniline **4d** (66.0 mg, 0.218 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 4 : 1) gave 78.6 mg (quant) of **11d** as a pale yellow oil. $[\alpha]_D^{24}$ = – 63.9 (c = 0.52, $CHCl_3$); IR (neat) 3322, 2974, 1737, 1523, 1211, 1113, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (3H, s), 1.04 (3H, s), 1.66–1.90 (8H, m), 3.72 (3H, s), 3.76 (3H, s), 4.41 (1H, s), 5.28 (1H, s), 5.77 (1H, s), 6.68 (1H, d, *J* = 2.8 Hz), 6.85 (1H, dd, *J* = 2.8, 8.8 Hz), 7.14 (1H, br), 7.82 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (CH_3), 23.4 (CH_2), 23.6 (CH_2), 25.8 (CH_3), 38.1 (CH_2), 38.2 (CH_2), 52.2 (CH_3), 55.4 (CH_3), 80.0 (C), 85.1 (CH), 113.2 (CH), 115.3 (CH), 116.6 (CH), 118.8 (CH_2), 122.6 (C), 128.1 (C), 131.8 (C), 141.7 (C), 154.4 (C), 155.5 (C); HRMS (ESI) m/z Calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$: 362.1967, found 362.1967.



11c: R=H
11d: R=Me

S6: R=H
S7: R=Me

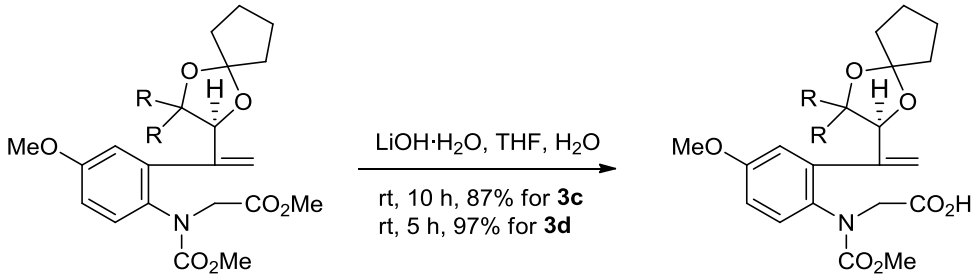
General Procedure for Preparation of Esters S6 and S7.

To a stirred solution of corresponding carbamates (**11c,d**) (1.0 equiv) in DMF (0.10 M) were added sodium hydride (3.0 equiv) by portions at 0 °C and the mixture was stirred at the same temperature for 15 min. 2-Bromoacetic acid methyl ester (3.0 equiv) was added to the reaction mixture and stirring was continued for 1.5-2.5 h at 50 °C. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was dried over $MgSO_4$ and concentrated to give a residue that was purified by silica gel column chromatography.

(S)-Methyl 2-([2-{1-(1,4-dioxaspiro[4.4]nonan-2-yl)vinyl}-4-methoxyphenyl](methoxycarbonyl)amino)acetate ***(S6).*** This compound was prepared from carbamate **11c** (150 mg, 0.450 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 2 : 1) gave 164 mg (90%) of **S6** as a colorless oil. $[\alpha]_D^{20}$ = – 28.5 (c = 0.20, $CHCl_3$); IR (neat) 2940, 1745, 1715, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68–1.90 (8H, m), 3.58–4.03 (12H, m), 4.62–4.83 (2H, m), 5.14 (0.8H, s), 5.18 (0.2H, s), 5.59 (0.2H, s), 5.61 (0.8H, s), 6.75 (1H, dd, *J* = 2.8, 19.6 Hz), 6.84 (1H, dt, *J* = 2.8, 8.2 Hz), 7.39 (0.5H, d, *J* = 8.7 Hz), 7.44 (0.5H, dd, *J* = 4.0, 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (CH_2), 23.5 (CH_2), 36.2 (CH_2), 36.5 (CH_2), 52.1 (CH_3), 52.6 (CH_3), 53.3 (CH_2), 55.5 (CH_3), 69.0 (CH_2), 76.6 (CH), 113.7 (CH), 115.4 (CH), 116.1 (CH), 119.6 (CH_2), 131.0 (C), 131.9 (C), 138.8 (C), 146.2 (C), 156.6 (C), 158.8 (C), 170.0 (C); HRMS (ESI) m/z Calcd for $C_{21}H_{28}NO_7$ $[M+H]^+$: 406.1866, found 406.1864.

(S)-Methyl 2-{[2-(1-(3,3-dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl)-4-methoxyphenyl](methoxycarbonyl)amino}acetate ***(S7).*** This compound was prepared from carbamate **11d** (75.0 mg, 0.210 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 4 : 1) gave 89.6 mg (quant) of **S7** as a colorless oil. $[\alpha]_D^{26}$ = – 113.5 (c = 0.72, $CHCl_3$); IR (neat) 2955, 1756, 1714, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (3H, s), 1.08 (3H, s), 1.63–1.91 (8H, m), 3.70 (3H, s), 3.72 (3H, s), 3.75–3.84 (1H, m), 3.81 (3H, s), 4.24–4.36 (1H, m), 4.53–4.71 (1H, m), 5.15–5.23 (1H, m), 5.65–5.72 (1H, m), 6.67 (1H, d, *J* = 2.8 Hz), 6.84 (1H, dd, *J* = 2.8, 8.8 Hz), 7.40 (0.7H, d, *J* = 8.8 Hz), 7.46 (0.3H, d, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ

23.1 (CH_3), 23.5 (CH_2), 23.8 (CH_2), 25.8 (CH_3), 38.1 (CH_2), 38.2 (CH_2), 51.3 (CH_2), 51.9 (CH_3), 53.1 (CH_3), 55.4 (CH_3), 79.3 (C), 82.7 (CH), 113.1 (CH), 115.9 (CH), 116.2 (CH), 116.8 (CH_2), 131.6 (C), 131.7 (C), 138.6 (C), 143.6 (C), 156.4 (C), 158.6 (C), 169.9 (C); HRMS (ESI) m/z Calcd for $C_{23}H_{32}NO_7$ $[M+H]^+$: 434.2179, found 434.2158.



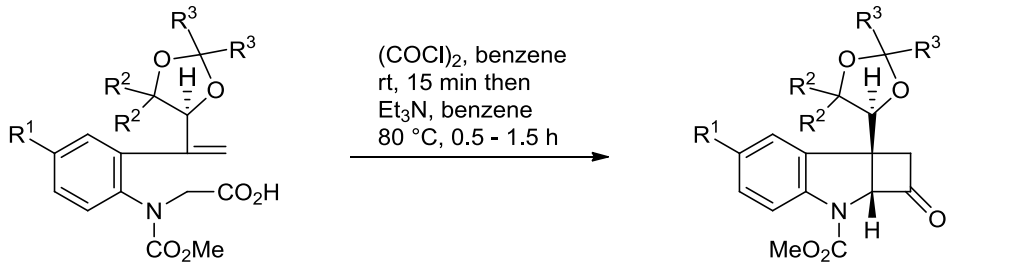
General Procedure for Preparation of Carboxylic acids 3c and 3d.

To a stirred solution of corresponding esters (**S6**, **S7**) (1.0 equiv) in THF–H_2O (5 : 1, 0.10 M) were added lithium hydroxide monohydrate (3.0 equiv) at 0 °C and the mixture was stirred at room temperature for 5-10 h. The reaction mixture was diluted with water and extracted with Et_2O. The aqueous layer was acidified with 1 N HCl solution and extracted with $CHCl_3$. The combined extracts was dried over $MgSO_4$ and concentrated.

*(S)-2-([2-{1-(1,4-Dioxaspiro[4.4]nonan-2-yl)vinyl}-4-methoxyphenyl](methoxycarbonyl)amino)acetic acid (**3c**).* This compound was prepared from ester **S6** (160 mg, 0.395 mmol) to gave 135 mg (87%) of **3c** as a colorless amorphous powder. $[\alpha]_D^{20}$ = – 25.5 (c = 0.19, $CHCl_3$); IR (neat) 2937, 1715, 1450, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61–1.91 (8H, m), 3.59–4.04 (9H, m), 4.63–4.69 (2H, m), 5.15 (0.8H, s), 5.19 (0.2H, s), 5.59 (0.2H, s), 5.61 (0.8H, s), 6.75 (1H, dd, *J* = 2.8, 19.2 Hz), 6.83 (1H, dd, *J* = 2.8, 8.7 Hz), 7.36 (0.5H, d, *J* = 8.7 Hz), 7.40 (0.5H, t, *J* = 8.7 Hz), COOH was not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (CH_2), 23.5 (CH_2), 36.2 (CH_2), 36.5 (CH_2), 53.4 (CH_3), 55.5 (CH_3), 67.9 (CH_2), 69.0 (CH_2), 76.7 (CH), 113.7 (C), 115.4 (CH), 116.4 (CH), 119.7 (CH_2), 130.9 (CH), 131.8 (C), 138.7 (C), 145.9 (C), 156.8 (C), 158.8 (C), 174.4 (C); HRMS (ESI) m/z Calcd for $C_{20}H_{26}NO_7$ $[M+H]^+$: 392.1709, found 392.1714.

*(S)-2-{[2-(1-(3,3-Dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl)-4-methoxyphenyl](methoxycarbonyl)amino}acetic acid (**3d**).* This compound was prepared from ester **S7** (130 mg, 0.300 mmol) to gave 122 mg (97%) of **3d** as a colorless oil. $[\alpha]_D^{27}$ = – 104.9 (c = 0.54, $CHCl_3$); IR (neat) 2974, 1714, 1497, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (3H, s), 1.08 (3H, s), 1.65–1.90 (8H, m), 3.72 (3H, s), 3.78–3.84 (1H, m), 3.80 (3H, s), 4.24–4.36 (1H, m), 4.54–4.71 (1H, m), 5.16–5.23 (1H, m), 5.65–5.72 (1H, m), 6.67–6.70 (1H,

m), 6.82–6.85 (1H, m), 7.34–7.44 (1H, m), 10.66 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (CH_3), 23.5 (CH_2), 23.9 (CH_2), 25.8 (CH_3), 38.1 (CH_2), 38.2 (CH_2), 51.3 (CH_2), 53.3 (CH_3), 55.5 (CH_3), 79.5 (C), 82.8 (CH), 113.3 (CH), 116.0 (CH), 116.4 (CH), 117.1 (CH_2), 131.6 (C), 138.7 (C), 143.5 (C), 156.5 (C), 158.7 (C), 158.8 (C), 174.7 (C); HRMS (ESI) m/z Calcd for $C_{22}H_{29}NO_7Na$ $[M+Na]^+$: 442.1842, found 442.1842.



3a: R^1=R^2=H, R^3=Me
3b: R^1=H, R^2=R^3=Me
3c: R^1=OMe, R^2=H, R^3=-$(CH)_4$-
3d: R^1=OMe, R^2=Me, R^3=-$(CH)_4$-

2a: R^1=R^2=H, R^3=Me
2b: R^1=H, R^2=R^3=Me
2c: R^1=OMe, R^2=H, R^3=-$(CH)_4$-
2d: R^1=OMe, R^2=Me, R^3=-$(CH)_4$-

General Procedure for [2 + 2] Cycloaddition.

To a stirred solution of carboxylic acids (**3a-d**) (1.0 equiv) in dry benzene (0.2 M) were added oxalyl chrolide (2.0 equiv) and a catalytic amount of DMF at 0 °C. After being stirred at room temperature for 15 nim, the mixture was evaporated *in vacuo*. The residue was diluted with dry benzene (0.2 M), and Et_3N (3.0 equiv) was added and then refluxed for 0.5-1.5 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography.

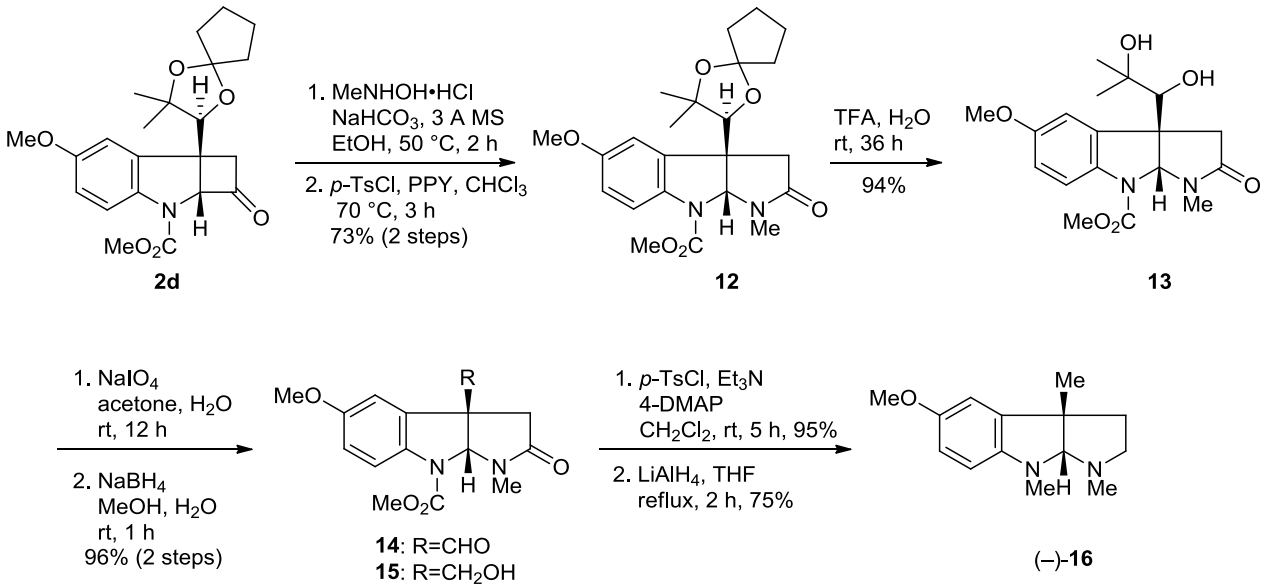
*(2aR,7bR)-Methyl 7b-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**2a**).* This compound was prepared from carboxylic acid **3a** (40.0 mg, 0.120 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 3 : 1) gave 17.0 mg (45%, dr = 90 : 10) of **2a** as a colorless oil. IR (neat) 1794, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (3H, s), 1.51 (3H, s), 3.07 (1H, dd, *J* = 2.8, 8.8 Hz), 3.40 (1H, dd, *J* = 6.4, 8.8 Hz), 3.95–3.79 (4.9H, m), 4.25 (0.1H, t, *J* = 6.8 Hz), 4.47 (0.1H, t, *J* = 6.8 Hz), 4.71 (0.9H, t, *J* = 6.4 Hz), 5.49 (1H, br), 7.06 (1H, t, *J* = 8.0 Hz), 7.23 (1H, d, *J* = 8.0 Hz), 7.31 (1H, t, *J* = 8.0 Hz), 7.91 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 25.6 (CH_3), 27.1 (CH_3), 46.6 (C), 53.8 (CH_3), 58.2 (CH_2), 67.3 (CH_2), 76.7 (CH), 77.0 (CH), 110.8 (C), 116.7 (CH), 124.6 (CH), 124.9 (C), 130.3 (CH×2), 132.1 (C), 144.4 (C), 202.7 (C); HRMS (ESI) calcd for $C_{17}H_{20}NO_5$ $[M+H]^+$: 318.1341, found 318.1339.

*(2aR,7bR)-Methyl 2-oxo-7b-((S)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**2b**).* This compound was prepared from carboxylic acid **3b** (48.0 mg, 0.132 mmol). Purification by silica

gel column chromatography (Hexane : AcOEt = 3 : 1) gave 32.3 mg (71%) of **2b** as a colorless amorphous powder. $[\alpha]_D^{31}$ = + 17.5 (c = 0.47, $CHCl_3$); IR (neat) 2936, 1796, 1717, 1379, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, s), 0.95 (3H, s), 1.43 (3H, s), 1.51 (3H, s), 3.15 (1H, dd, *J* = 2.8, 17.6 Hz), 3.87 (3H, s), 4.01 (1H, d, *J* = 17.6 Hz), 4.41 (1H, s), 5.71 (0.8H, br), 5.88 (0.2H, br), 7.07 (1H, t, *J* = 7.6 Hz), 7.25 (1H, t, *J* = 7.6 Hz), 7.32 (1H, t, *J* = 7.6 Hz), 7.50 (0.2H, br), 7.91 (0.8H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1 (CH_3), 26.9 (CH_3), 28.0 (CH_3), 28.4 (CH_3), 44.6 (C), 53.1 (CH_3), 61.2 (CH_2), 75.2 (CH), 80.8 (C), 82.5 (CH), 106.1 (CH), 116.4 (C), 123.6 (CH), 125.0 (CH), 129.7 (CH), 130.2 (C), 143.6 (C), 152.6 (C), 203.7 (C); HRMS (ESI) m/z Calcd for $C_{38}H_{46}N_2O_{10}$ $[2M+H]^+$: 691.3230, found 691.3231.

*(2aR,7bR)-Methyl 6-methoxy-2-oxo-7b-((S)-1,4-dioxaspiro[4.4]nonan-2-yl)-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**2c**).* This compound was prepared from carboxylic acid **3c** (50.0 mg, 0.128 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 4 : 1) gave 38.6 mg (81%, dr = 83 : 17) of **2c** as a colorless amorphous powder. IR (neat) 2935, 1712, 1480, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.65–1.97 (8H, m), 3.08 (1H, dd, *J* = 2.7, 17.8 Hz), 3.42 (0.9H, dd, *J* = 5.5, 8.7 Hz), 3.70–3.90 (7.9H, m), 4.17 (0.2H, t, *J* = 7.8 Hz), 4.42 (0.2H, t, *J* = 6.9 Hz), 4.60 (0.8H, t, *J* = 6.9 Hz), 5.47–5.63 (1H, m), 6.70 (0.2H, d, *J* = 2.3 Hz), 6.77 (0.8H, d, *J* = 2.3 Hz), 6.84 (1H, d, *J* = 9.2 Hz), 7.40 (0.2H, br), 7.82 (0.8H, d, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (CH_2), 23.9 (CH_2), 23.9 (CH_2), 35.9 (CH_2), 36.0 (CH_2), 36.3 (CH_2), 46.4 (C), 53.1 (CH_3), 55.7 (CH_3), 57.2 (CH_2), 66.4 (CH_2), 66.6 (CH_2), 75.6 (CH), 76.0 (CH), 110.6 (C), 111.3 (C), 113.9 (CH), 114.1 (CH), 116.6 (CH), 119.5 (CH), 120.1 (CH), 132.4 (C), 137.4 (C), 152.5 (C), 156.5 (C), 156.6 (C), 203.0 (C); HRMS (ESI) m/z Calcd for $C_{20}H_{24}NO_6$ $[M+H]^+$: 374.1604, found 374.1603.

*(2aR,7bR)-Methyl 7b-((S)-3,3-dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)-6-methoxy-2-oxo-2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (**2d**).* This compound was prepared from carboxylic acid **3d** (95.0 mg, 0.226 mmol). Purification by silica gel column chromatography (Hexane : AcOEt = 4 : 1) gave 81.1 mg (89%) of **2d** as a colorless oil. $[\alpha]_D^{27}$ = + 13.9 (c = 0.40, $CHCl_3$); IR (neat) 2958, 1796, 1715, 1491, 1274, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, s), 0.99 (3H, s), 1.62–1.94 (8H, m), 3.14 (1H, dd, *J* = 3.2, 17.6 Hz), 3.78 (3H, s), 3.84 (3H, s), 3.90–4.02 (1H, m), 4.25 (1H, s), 5.67 (0.8H, br), 5.85 (0.2H, br), 6.79 (1H, d, *J* = 2.8 Hz), 6.85 (1H, d, *J* = 9.2 Hz), 7.40 (0.2H, d, *J* = 8.4 Hz), 7.82 (0.8H, d, *J* = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (CH_3), 23.4 (CH_2), 23.8 (CH_2), 27.6 (CH_3), 38.1 (CH_2), 38.1 (CH_2), 44.7 (C), 53.0 (CH_3), 55.7 (CH_3), 60.9 (CH_2), 75.4 (CH), 80.2 (C), 82.7 (CH), 111.1 (CH), 114.4 (CH), 116.1 (C), 116.9 (CH), 131.6 (C), 137.2 (C), 152.5 (C), 156.3 (C), 204.1 (C); HRMS (ESI) m/z Calcd for $C_{22}H_{27}NO_6Na$ $[M+Na]^+$: 424.1736, found 424.1746.



(3a*R*,8a*R*)-Methyl 3a-((*S*)-3,3-dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)-5-methoxy-1-methyl-2-oxo-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**12**)

To a stirred solution of compound **2d** (45.0 mg, 0.112 mmol) in dry EtOH (2 mL) was added *N*-methylhydroxylamine hydrochloride (46.8 mg, 0.560 mmol), $NaHCO_3$ (75.3 mg, 0.897 mmol) and molecular sieve 3 A at room temperature and the mixture was stirred at 50 °C for 2 h. The reaction mixture was poured into brine and then extracted with AcOEt. The combined extracts was dried over $MgSO_4$ and concentrated to give a yellowish oil. The residue was diluted with $CHCl_3$ (2 mL), which was then added *p*-toluenesulfonyl chloride (42.7 mg, 0.224 mmol) and PPY (24.9 mg, 0.168 mmol) and stirred at 70 °C for 3 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 2 : 1) to give 35.0 mg (73% for 2 steps) of **12** as a pale yellow oil. $[\alpha]_D^{28}$ = – 1.2 (c = 0.40, $CHCl_3$); IR (neat) 2958, 1703, 1496, 1246, 1113, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (3H, d, *J* = 7.6 Hz), 0.87 (3H, s), 1.64–1.88 (8H, m), 2.74 (1H, d, *J* = 16.6 Hz), 2.94 (3H, d, *J* = 20.4 Hz), 3.17 (1H, d, *J* = 16.6 Hz), 3.78 (3H, s), 3.87 (1H, s), 3.90 (3H, s), 6.03 (0.5H, s), 6.15 (0.5H, s), 6.73 (1H, d, *J* = 2.4 Hz), 6.80–6.90 (1H, m), 7.35 (0.5H, d, *J* = 8.8 Hz), 7.73 (0.5H, d, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 21.9 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 27.6 (CH_3), 27.8 (CH_3), 38.1 (CH_2), 38.2 (CH_2), 43.4 (CH_2), 49.7 (C), 53.1 (CH_3), 55.9 (CH_3), 79.1 (CH), 79.6 (C), 85.2 (CH), 110.7 (CH), 114.8 (CH), 115.9 (C), 118.2 (CH), 133.8 (C×2), 153.5 (C), 156.9 (C), 171.2 (C); HRMS (ESI) m/z Calcd for $C_{46}H_{61}N_4O_{12}$ $[2M+H]^+$: 861.4286, found 861.4278.

(3a*R*,8a*R*)-Methyl 3a-((*S*)-1,2-dihydroxy-2-methylpropyl)-5-methoxy-1-methyl-2-oxo-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**13**)

To a stirred solution of compound **12** (45.0 mg, 0.105 mmol) in TFA (2.5 mL) was added H_2O (0.5 mL) at room temperature and the mixture was stirred at the same temperature for 36 h. The reaction mixture was concentrated *in vacuo* to give a residue that was purified by silica gel column chromatography ($CHCl_3$: MeOH = 10 : 1) to give 35.6 mg (94%) of **13** as a yellowish amorphous powder. $[\alpha]_D^{24}$ = – 10.2 (c = 0.23, $CHCl_3$); IR (neat) 3446, 2959, 1683, 1497, 1146, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 50 °C) δ 0.90 (3H, s), 1.02 (3H, s), 2.82 (1H, d, *J* = 23.0 Hz), 2.93 (3H, s), 3.42 (1H, d, *J* = 23.0 Hz), 3.71 (1H, s), 3,78 (3H, s), 3.89 (3H, s), 6.23 (1H, s), 6.76 (1H, d, *J* = 3.2 Hz), 6.84 (1H, dd, *J* = 3.2, 12.0 Hz), 6.86 (2H, br), 7.50 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz, 50 °C) δ 25.6 (CH_3), 28.1 (CH_3), 29.2 (CH_3), 42.7 (CH_2), 53.4 (CH_3), 53.6 (C), 55.9 (CH_3), 74.5 (C), 79.0 (CH), 80.7 (CH), 111.3 (CH), 115.0 (CH), 118.4 (CH), 133.7 (C), 135.5 (C), 154.2 (C), 157.2 (C), 174.5 (C); HRMS (ESI) m/z Calcd for $C_{18}H_{24}N_2O_6Na$ $[M+Na]^+$: 387.1532, found 387.1524.

(3a*R*,8a*R*)-Methyl 3a-(hydroxymethyl)-5-methoxy-1-methyl-2-oxo-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**15**)

To a stirred solution of diol **13** (33.0 mg, 0.0910 mmol) in acetone–H_2O (5 : 1, 2.4 mL) was added sodium periodate (58.1 mg, 0.272 mmol) at room temperature and the mixture was stirred at the same temperature for 12 h. The reaction mixture was added ethylene glycol (0.02 mL) at room temperature and stirring was continued for 15 minutes at the same temperature. The reaction mixture was poured into water and then extracted with $CHCl_3$–MeOH (10 : 1). The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product **14** was immediately carried on to next step without purification. To a stirred solution of above crude in MeOH–H_2O (4 : 1, 2.5 mL) was added $NaBH_4$ (4.10 mg, 0.110 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution and then extracted with $CHCl_3$. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography ($CHCl_3$: MeOH = 10 : 1) to give 26.8 mg (96% for 2 steps) of **15** as a colorless oil. $[\alpha]_D^{25}$ = – 1.8 (c = 0.31, $CHCl_3$); IR (neat) 3393, 2956, 1684, 1496, 1248, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.98 (1H, br), 2.63 (1H, d, *J* = 16.4 Hz), 2.89 (1H, d, *J* = 16.4 Hz), 2.91 (3H, s), 3.73 (2H, d, *J* = 3.2 Hz), 3.79 (3H, s), 3.90 (3H, s), 5.87 (1H, br), 6.71 (1H, d, *J* = 2.8 Hz), 6.83 (1H, d, *J* = 6.8 Hz), 7.71 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz, 50 °C) δ 27.7 (CH_3), 38.1 (CH_2), 51.5 (C), 53.0 (CH_3), 55.8 (CH_3), 65.3

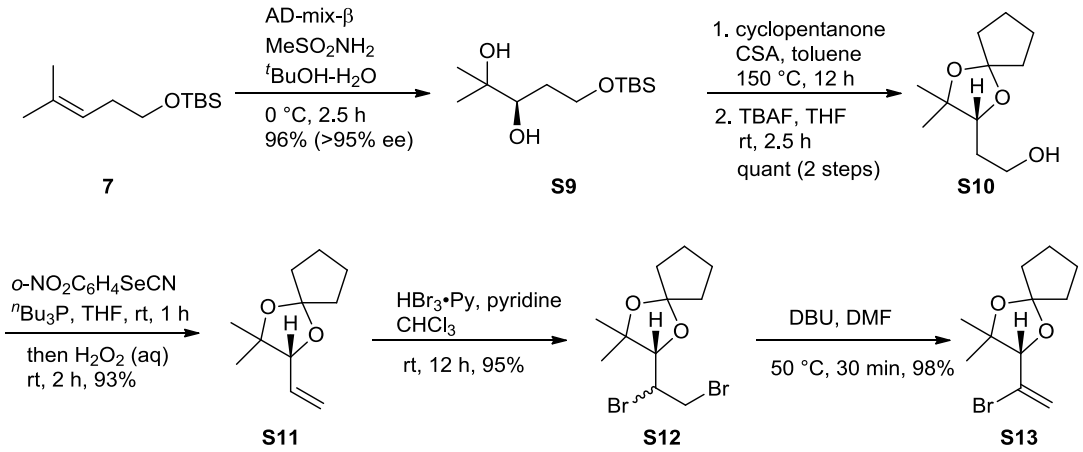
(CH_2), 81.1 (CH), 110.1 (CH), 114.4 (CH), 117.6 (CH), 134.0 (C), 135.2 (C), 154.2 (C), 157.1 (C), 172.2 (C); HRMS (ESI) m/z Calcd for $C_{15}H_{18}N_2O_5Na$ $[M+Na]^+$: 329.1113, found 329.1115.

(3a*R*,8a*R*)-Methyl 5-methoxy-1-methyl-2-oxo-3a-(tosyloxymethyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**S8**)

To a stirred solution of alcohol **15** (3.50 mg, 0.0110 mmol) in CH_2Cl_2 (1 mL) was added *p*-toluenesulfonyl chloride (6.50 mg, 0.0340 mmol), Et_3N (4.60 mg, 0.0460 mmol) and DMAP (0.300 mg, 0.00200 mmol) at room temperature and the mixture was stirred at the same temperature for 5 h. The reaction mixture was concentrated *in vacuo* to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 1 : 1) to give 5.00 mg (95%) of **S8** as a colorless oil. $[\alpha]_D^{27}$ = – 14.2 (c = 0.31, $CHCl_3$); IR (neat) 2956, 1701, 1496, 1176, 827, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.46 (3H, s), 2.61 (1H, d, *J* = 16.8 Hz), 2.82 (1H, d, *J* = 16.8 Hz), 2.87 (3H, s), 3.75 (3H, s), 3.89 (3H, s), 3.98 (1H, d, *J* = 10.0 Hz), 4.08 (1H, d, *J* = 10.0 Hz), 5.81 (1H, s), 6.58 (1H, s), 6.82 (1H, dd, *J* = 2.4, 8.8 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 7.71 (2H, d, *J* = 8.4 Hz), 7.72 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 21.6 (CH_3), 27.6 (CH_3), 37.8 (CH_2), 49.2 (C), 53.1 (CH_3), 55.8 (CH_3), 70.1 (CH_2), 80.4 (CH), 109.9 (CH), 115.2 (CH), 117.8 (CH), 127.9 (CH×2), 130.0 (CH×2), 132.5 (C), 132.9 (C), 133.7 (C), 145.3 (C), 153.6 (C), 157.1 (C), 170.7 (C); HRMS (ESI) m/z Calcd for $C_{22}H_{25}N_2O_7S$ $[M+H]^+$: 461.1382, found 461.1390.

(–)-Esermethole (**(–)-16**)

To a stirred solution of compound **S8** (10.0 mg, 0.0220 mmol) in THF (1 mL) was added $LiAlH_4$ (8.20 mg, 0.217 mmol) at 0 °C and the mixture was refluxed for 2 h. The reaction mixture was cooled to 0 °C then added moisture Et_2O. The reaction mixture was stirred at room temperature, then filtered through a pad of Celite® and concentrated *in vacuo* to give a residue that was purified by silica gel column chromatography ($CHCl_3$: MeOH = 10 : 1) to give 3.80 mg (75%, > 95% ee *) of (–)-esermethole (**(–)-16**) as a colorless oil. *HPLC [DICEL CHIRALPAK OD-H column; 0.5 mL/min; solvent system: ^{i}PrOH : Hexane = 1 : 99; retention times: 18.1 min (major), 28.1 min (minor)]; $[\alpha]_D^{24}$ = – 135.9 (c = 0.10, C_6H_6), ($[\alpha]_D^{34}$ = – 134.0 (c = 0.35, C_6H_6)) [5].; IR (neat) 2928, 1498, 1032, 801 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (3H, s), 1.96 (2H, dd, *J* = 5.2, 7.6 Hz), 2.54 (3H, s), 2.60–2.67 (1H, m), 2.72–2.77 (1H, m), 2.89 (3H, s), 3.75 (3H, s), 4.08 (1H, s), 6.36 (1H, d, *J* = 8.4 Hz), 6.63 (1H, d, *J* = 2.8 Hz), 6.66 (1H, dd, *J* = 2.8, 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 27.3 (CH_3), 37.9 (CH_3), 38.0 (CH_3), 40.6 (CH_2), 52.9 (C), 53.2 (CH_3), 56.0 (CH_2), 98.2 (CH), 107.6 (CH), 109.8 (CH), 112.3 (CH), 138.1 (C), 146.4 (C), 153.1 (C); HRMS (ESI) m/z Calcd for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1654, found 233.1653.



(*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-methylpentane-2,3-diol (S9)

To a stirred solution of AD-mix-β (22.5 g) and methanesulfonamide (665 mg, 7.00 mmol) in ^{t}BuOH−H_2O (1 : 1, 90 mL) was added *tert*-butyldimethyl(4-methylpent-3-enyloxy)silane (**7**) [1] (2.20 g, 10.3 mmol) at 0 °C. After stirring was continued for 2.5 h at 0 °C, the reaction mixture was quenched with Na_2SO_3 (33.0 g) at 0 °C. After further stirring was continued at room temperature for 15 min, the reaction mixture was extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 3 : 1) to give 2.44 g (96%) of **S9** as a colorless oil. $[\alpha]_D^{28}$ = – 8.1 (c = 1.00 $CHCl_3$); IR (neat) 3421, 2956, 1256, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (6H, s), 0.90 (9H, s), 1.15 (3H, s), 1.20 (3H, s), 1.65–1.69 (2H, m), 2.55 (1H, br), 3.61 (1H, t, *J* = 6.0 Hz), 3.75 (1H, br), 3.81–3.86 (1H, m), 3.89–3.94 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ – 5.5 (CH_3), – 5.5 (CH_3), 18.1 ($CH_3\times3$), 24.1 (C), 25.8 (CH_3), 26.1 (CH_3), 32.9 (CH_2), 62.8 (CH_2), 72.2 (C), 78.4 (CH); HRMS (ESI) m/z Calcd for $C_{12}H_{28}O_3SiNa$ $[M+Na]^+$: 271.1705, found 271.1706.

(*R*)-2-(3,3-Dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)-ethanol (S10)

To a stirred solution of diol **S9** (2.20 g, 8.86 mmol) in toluene (30 mL) was added cyclopentanone (3.72 g, 44.3 mmol) and (*1S*)-(+)-10-camphorsulfonic acid (206 mg, 0.886 mmol) at room temperature and the mixture was stirred at 150 °C for 12 h by using Dean-Stark trap. The reaction mixture was cooled to room temperature, and poured into saturated aqueous $NaHCO_3$ solution. The whole mixture was extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was immediately carried on to next step without purification. To a stirred solution of above crude in THF (50 mL) was added TBAF (8.86 mmol) (1.0 M solution in THF) at 0 °C and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated

to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 3 : 1) to give 1.77 g (quant for 2 steps) of **S10** as a pale yellow oil. $[\alpha]_D^{28}$ = + 18.2 (c = 1.00, $CHCl_3$); IR (neat) 3421, 2972, 1194, 1114, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (3H, s), 1.26 (3H, s), 1.58–1.86 (10H, m), 2.28 (1H, br), 3.72 (1H, dd, *J* = 2.6, 10.6 Hz), 3.82 (2H, dd, *J* = 4.6, 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (CH_3), 23.3 (CH_2), 23.7 (CH_2), 25.3 (CH_3), 31.6 (CH_2), 38.2 ($CH_2\times2$), 61.4 (CH_2), 79.8 (C), 82.7 (CH), 117.1 (C); HRMS (ESI) m/z Calcd for $C_{22}H_{41}O_6$ $[2M+H]^+$: 401.2903, found 401.2915.

(*R*)-2,2-Dimethyl-3-vinyl-1,4-dioxaspiro[4.4]nonane (S11)

To a stirred solution of alcohol **S10** (130 mg, 0.650 mmol) in dry THF (4 mL) was added 2-nitrophenylselenocyanate (295 mg, 1.30 mmol) and tributylphosphine (263 mg, 1.30 mmol) at room temperature and the mixture was stirred for 1 h. 35% H_2O_2 (0.65 mL, 6.50 mmol) was added to the reaction mixture and stirring was continued for 2 h at the same temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and then extracted with Et_2O. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 20 : 1) to give 110 mg (93%) of **S11** as a colorless oil. $[\alpha]_D^{30}$ = – 9.1 (c = 0.40, $CHCl_3$); IR (neat) 2974, 1432, 1336, 1195, 1109, 994 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (3H, s), 1.26 (3H, s), 1.60–1.89 (8H, m), 4.02 (1H, d, *J* = 7.6 Hz), 5.26 (1H, dq, *J* = 0.8, 10.4 Hz), 5.37 (1H, dt, *J* = 1.4, 17.2 Hz), 5.80 (1H, ddd, *J* = 7.3, 10.2, 17.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 25.2 (CH_3), 38.2 (CH_2), 38.3 (CH_2), 80.2 (C), 85.5 (CH), 117.4 (C), 118.8 (CH_2), 133.4 (CH); HRMS (ESI) m/z Calcd for $C_{22}H_{36}O_4Na$ $[2M+Na]^+$: 387.2511, found 387.2510.

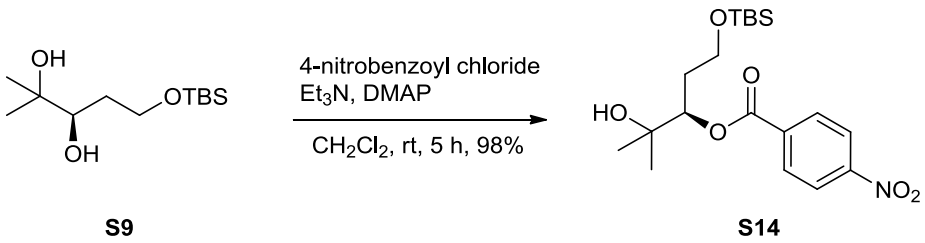
(*S*)-3-(1,2-Dibromoethyl)-2,2-dimethyl-1,4-dioxaspiro[4.4]nonane (S12)

To a stirred solution of **S11** (150 mg, 0.823 mmol) in $CHCl_3$ (3 mL) was added pyridine (176 mg, 2.22 mmol) and pyridinium tribromide (316 mg, 0.988 mmol) at 0 °C and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution and then extracted with $CHCl_3$. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 10 : 1) to give 268 mg (95%) of **S12** as a pale blown oil; IR (neat) 2972, 1334, 1194, 1111, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (0.5H, s), 1.28 (2.5H, s), 1.37 (2.5H, s), 1.46 (0.5H, s), 1.62–2.01 (6.7H, m), 1.62–2.01 (1.3H, m), 3.76 (0.8H, dd, *J* = 5.0, 10.8 Hz), 3.82 (0.8H, dd, *J* = 6.8, 10.8 Hz), 3.84 (0.2H, dd, *J* = 5.8, 10.8 Hz), 3.86 (0.2H, dd, *J* = 5.6, 11.2 Hz), 3.96–4.01 (0.4H, m), 4.03 (0.8H, d, *J* = 5.2 Hz), 4.14 (0.8H, q, *J* = 5.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2 (CH_3), 22.6 (CH_3), 23.3 (CH_2), 23.4 (CH_2), 23.7 (CH_2), 24.0 (CH_2), 27.5 (CH_3), 27.7 (CH_3), 34.6 ($CH_2\times2$), 37.9 (CH_2), 38.0 (CH_2), 38.0 (CH_2), 38.7 (CH_2), 49.1 (CH), 49.8 (CH),

79.8 (C), 80.1 (C), 82.2 (CH), 83.3 (CH), 116.7 (C), 117.6 (C); HRMS (ESI) m/z Calcd for $C_{11}H_{19}O_2Br_2$ $[M+H]^+$: 340.9752, found 340.9753.

(*S*)-3-(1-Bromovinyl)-2,2-dimethyl-1,4-dioxaspiro[4.4]nonane (S13)

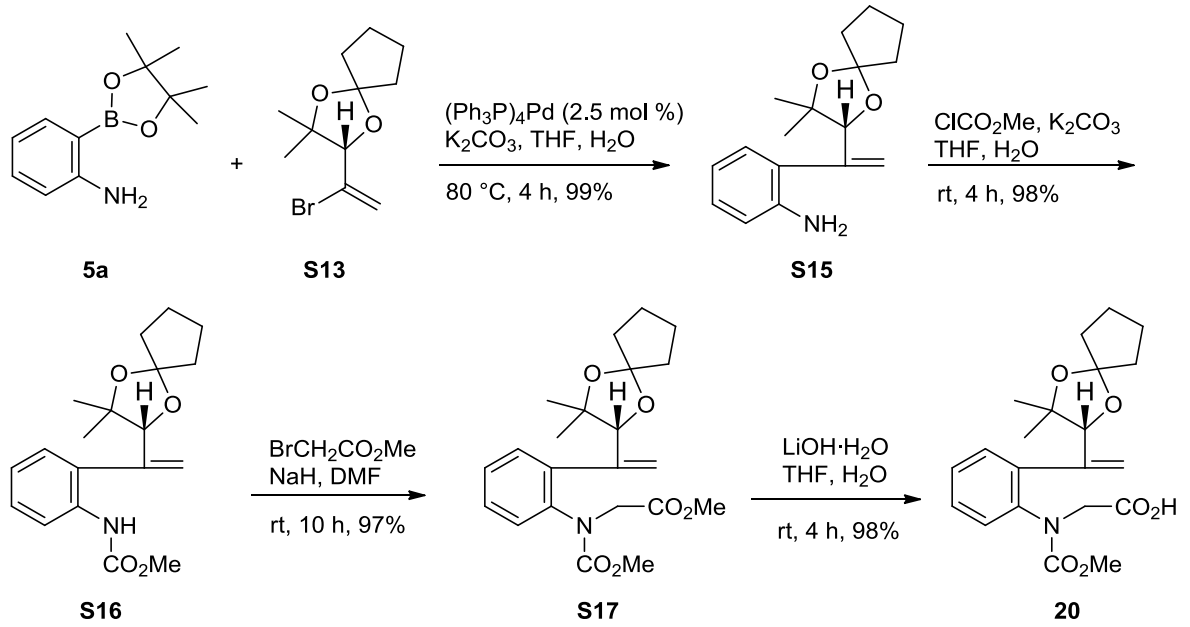
To a stirred solution of dibromide **S12** (270 mg, 0.789 mmol) in DMF (1.5 mL) was added DBU (120 mg, 0.789 mmol) at room temperature and the mixture was stirred at 50 °C for 30 min. The reaction mixture was poured into water and then extracted with Et_2O. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 20 : 1) to give 202 mg (98%) of **S13** as a colorless oil. $[\alpha]_D^{26}$ = – 34.8 (c = 0.55, $CHCl_3$); IR (neat) 2975, 1632, 1192, 1110, 898 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (3H, s), 1.49 (3H, s), 1.65–1.90 (8H, m), 4.28 (1H, s), 5.66 (1H, s), 6.13 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 27.5 (CH_3), 38.1 (CH_2), 38.2 (CH_2), 80.2 (C), 86.1 (CH), 117.2 (C), 117.2 (CH_2), 126.6 (C); HRMS (ESI) m/z Calcd for $C_{11}H_{18}O_2Br$ $[M+H]^+$: 261.0490, found 261.0484.



S9 **S14**

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-4- hydroxy-4-methylpentan-3-yl 4-nitrobenzoate (S14)

To a stirred solution of diol **S9** (20.0 mg, 0.0810 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (16.3 mg, 0.161 mmol), DMAP (2.00 mg, 0.0160 mmol) and 4-nitrobenzoylchloride (29.9 mg, 0.161 mmol) at room temperature. After stirring was continued for 5 h at the same temperature, the reaction mixture was poured into water and then extracted with $CHCl_3$. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 4 : 1) to give 29.9 mg (98%, > 95% ee *) of **S14** as a colorless oil. *HPLC [DICEL CHIRALPAK OD-H column; 0.5 mL/min; solvent system: ^{i}PrOH : Hexane = 1 : 99; retention time: 57.2 min (major), 69.0 min (minor)]; $[\alpha]_D^{31}$ = + 12.5 (c = 0.40, $CHCl_3$); IR (neat) 3435, 2930, 2857, 1727, 1529, 1276, 1103, 839, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (6H, s), 0.89 (9H, s), 1.29 (3H, s), 1.31 (3H, s), 1.93–2.10 (2H, m), 3.03 (1H, br), 3.67–3.81 (2H, m), 5.19 (1H, dd, *J* = 4.4, 7.2 Hz), 8.23 (2H, d, *J* = 9.2 Hz), 8.31 (2H, d, *J* = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ – 5.5 ($CH_3\times2$), 18.2 (C), 25.8 ($CH_3\times3$), 25.9 (CH_3), 26.2 (CH_3), 33.0 (CH_2), 59.7 (CH_2), 71.9 (C), 79.4 (CH), 123.6 ($CH\times2$), 130.7 ($CH\times2$), 135.7 (C), 150.7 (C), 164.4 (C); HRMS (ESI) m/z Calcd for $C_{19}H_{31}NO_6SiNa$ $[M+Na]^+$: 420.1819, found 420.1815.



(*R*)-2-[1-(3,3-Dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl]aniline (**S15**)

To a stirred solution of vinylbromide **S13** (596 mg, 2.28 mmol) and aniline **5a** (500 mg, 2.28 mmol) in THF–H_2O (10 : 1, 6.6 mL) was added $(Ph_3P)_4Pd$ (65.9 mg, 0.0570 mmol) and K_2CO_3 (631 mg, 4.56 mmol) at room temperature and the mixture was stirred at 80 °C for 4 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 10 : 1) to give 616 mg (99%) of **S15** as a pale yellow oil. $[\alpha]_D^{28}$ = + 105.3 (c = 0.56, $CHCl_3$); IR (neat) 3366, 2973, 1614, 1493, 1118, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, s), 1.10 (3H, s), 1.66–1.97 (8H, m), 3.88 (2H, br), 4.58 (1H, s), 5.32 (1H, t, *J* = 1.0 Hz), 5.79 (1H, t, *J* = 1.8 Hz), 6.71 (1H, t, *J* = 7.6 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 7.02 (1H, dd, *J* = 1.6, 7.6 Hz), 7.09 (1H, dt, *J* = 1.6, 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (CH_3), 23.6 (CH_2), 23.8 (CH_2), 26.0 (CH_3), 38.3 (CH_2), 38.3 (CH_2), 79.9 (C), 84.0 (CH), 115.7 (CH), 115.9 (CH_2), 116.3 (C), 118.1 (CH), 125.1 (C), 128.6 (CH), 129.3 (CH), 142.1 (C), 143.4 (C); HRMS (ESI) m/z Calcd for $C_{34}H_{46}N_2O_4Na$ $[2M+Na]^+$: 569.3355, found 569.3358.

(*R*)-Methyl 2-[1-(3,3-dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl]phenyl]carbamate (**S16**)

To a stirred solution of aniline **S15** (520 mg, 1.90 mmol) in THF–H_2O (3 : 1, 12 mL) was added K_2CO_3 (2.63 g, 19.0 mmol) and methyl chloroformate (270 mg, 2.85 mmol) at room temperature and the mixture was stirred for 4 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 5 : 1) to give 616 mg (98%) of **S16** as a pale yellow

oil. $[\alpha]_D^{28}$ = + 137.1 (c = 0.52, $CHCl_3$); IR (neat) 3417, 2975, 1743, 1522, 1210, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (3H, s), 1.04 (3H, s), 1.63–1.92 (8H, m), 3.76 (3H, s), 4.41 (1H, s), 5.30 (1H, s), 5.81 (1H, s), 7.04 (1H, t, *J* = 7.6 Hz), 7.12 (1H, dd, *J* = 1.6, 7.6 Hz), 7.30 (1H, dt, *J* = 1.6, 8.4 Hz), 7.39 (1H, br), 8.03 (1H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3 (CH_3), 23.5 (CH_2), 23.6 (CH_2), 25.9 (CH_3), 38.2 (CH_2), 38.2 (CH_2), 52.3 (CH_3), 80.1 (C), 85.3 (CH), 116.7 (C), 119.1 (CH_2), 120.2 (C), 123.1 (CH), 128.7 (CH), 129.4 (CH), 129.4 (C), 135.1 (CH), 141.7 (C), 154.1 (C); HRMS (ESI) m/z Calcd for $C_{19}H_{26}NO_4$ $[M+H]^+$: 332.1862, found 332.1869.

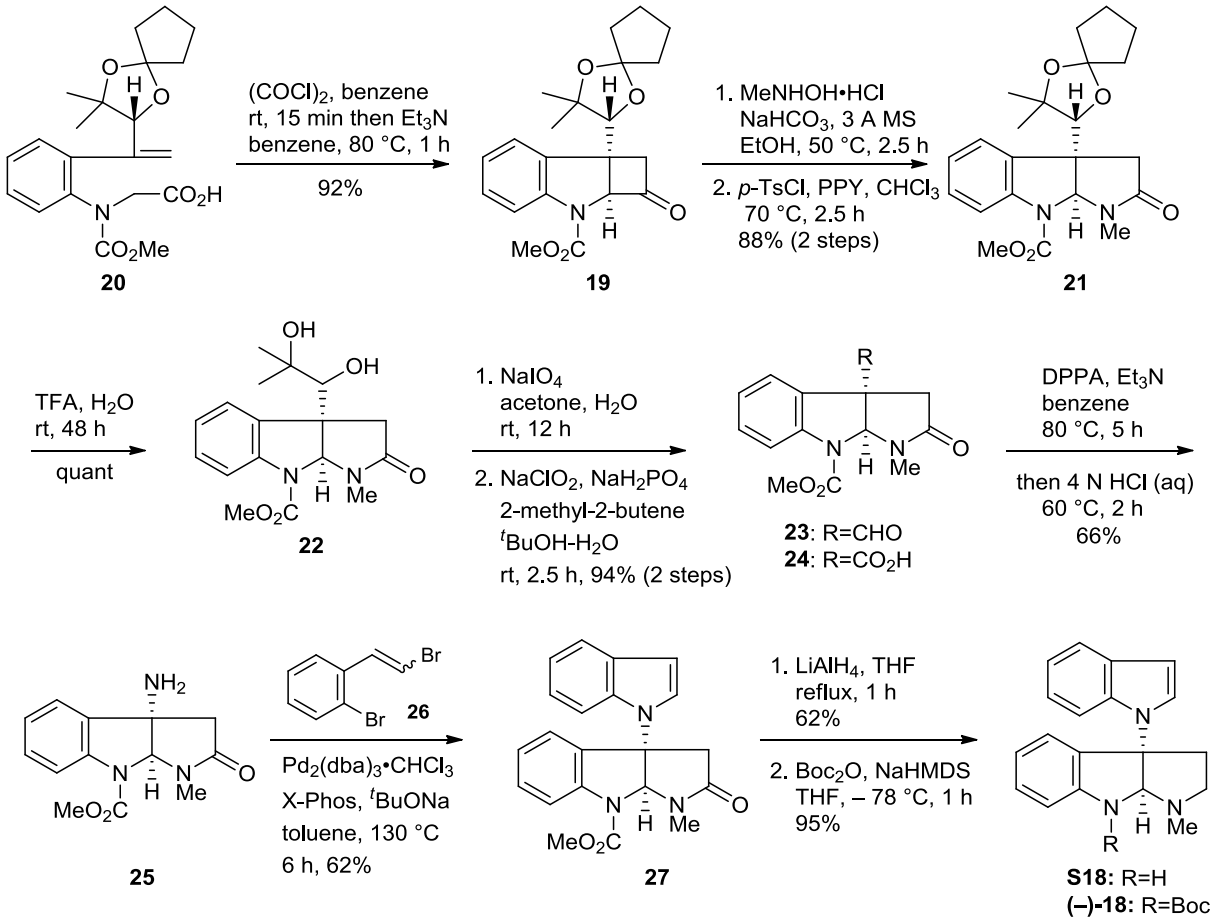
(*R*)-Methyl 2-({2-[1-(3,3-dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl]phenyl}(methoxycarbonyl)amino)acetate (**S17**)

To a stirred solution of carbamate **S16** (165 mg, 0.498 mmol) in dry DMF (2 mL) was added sodium hydride (29.9 mg, 60% dispersion in mineral oil) by portions at 0 °C and the mixture was stirred at the same temperature for 15 min. 2-Bromoacetic acid methyl ester (83.8 mg, 0.548 mmol) was added to the reaction mixture and stirring was continued for 10 h at room temperature. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was dried over $MgSO_4$ and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 2 : 1) to give 195 mg (97%) of **S17** as a colorless oil. $[\alpha]_D^{24}$ = + 105.8 (c = 1.15, $CHCl_3$); IR (neat) 2955, 1757, 1716, 1207, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78 (1.5H, s), 0.81 (1.5H, s), 1.00 (3H, s), 1.60–1.85 (8H, m), 3.54–3.79 (1H, m), 3.62 (3H, s), 3.65 (3H, s), 4.20–4.32 (1H, m), 4.50–4.63 (1H, m), 5.09–5.18 (1H, m), 5.60–5.68 (1H, m), 7.10 (1H, d, *J* = 7.6 Hz), 7.21 (1H, t, *J* = 7.6 Hz), 7.26 (1H, t, *J* = 7.6 Hz), 7.41 (0.5H, d, *J* = 7.6 Hz), 7.48 (0.5H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 23.0 (CH_3), 23.3 (CH_2), 23.7 (CH_2), 25.7 (CH_3), 38.0 (CH_2), 38.1 (CH_2), 51.1 (CH_2), 51.7 (CH_3), 52.8 (CH_3), 79.3 (C), 82.9 (CH), 116.1 (CH), 116.7 (CH_2), 127.7 (CH), 128.4 (CH), 130.4 (CH), 130.6 (CH), 137.5 (C), 139.0 (C), 143.9 (C), 155.9 (C), 169.5 (C); HRMS (ESI) m/z Calcd for $C_{22}H_{30}NO_6$ $[M+H]^+$: 404.2073, found 404.2057.

(*R*)-({2-[1-(3,3-Dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)vinyl]phenyl}(methoxycarbonyl)amino)acetic acid (**20**)

To a stirred solution of ester **S17** (535 mg, 1.33 mmol) in THF–H_2O (5 : 1, 6 mL) was added lithium hydroxide monohydrate (167 mg, 3.98 mmol) at 0 °C and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water and extracted with Et_2O. The aqueous layer was acidified with 1 N HCl solution and extracted with $CHCl_3$. The combined extracts was dried over $MgSO_4$ and concentrated to give 122 mg (98%) of **20** as a colorless amorphous powder. $[\alpha]_D^{26}$ = + 69.4 (c = 0.60,

$CHCl_3$); IR (neat) 2975, 1716, 1450, 1194, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (1.5H, s), 0.88 (1.5H, s), 1.07 (3H, s), 1.65–1.92 (8H, m), 3.60–3.91 (1H, m), 3.73 (3H, s), 4.25–4.37 (1H, m), 4.55–4.71 (1H, m), 5.15–5.23 (1H, m), 5.65–5.75 (1H, m), 7.17 (1H, d, *J* = 7.2 Hz), 7.28 (1H, t, *J* = 7.2 Hz), 7.32 (1H, t, *J* = 7.2 Hz), 7.42 (0.5H, d, *J* = 7.2 Hz), 7.51 (0.5H, d, *J* = 7.2Hz), COOH was not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9 (CH_3), 23.2 (CH_2), 23.6 (CH_2), 25.6 (CH_3), 37.9 ($CH_2\times2$), 50.9 (CH_2), 53.0 (CH_3), 79.4 (C), 82.9 (CH), 116.2 (C), 116.8 (CH_2), 127.8 (CH), 128.4 (CH), 128.5 (CH), 130.4 (CH), 137.4 (C), 138.8 (C), 143.6 (C), 156.1 (C), 173.0 (C); HRMS (ESI) m/z Calcd for $C_{21}H_{27}NO_6Na$ $[M+Na]^+$: 412.1736, found 412.1756.



(2a*S*,7b*S*)-Methyl 7b-((*R*)-3,3-dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)-2-oxo-2,2a-dihydro-1*H*-cyclobuta[*b*]indole-3(7b*H*)-carboxylate (**19**)

To a stirred solution of carboxylic acid **20** (480 mg, 1.23 mmol) in dry benzene (5 mL) was added oxalyl chloride (313 mg, 2.47 mmol) and a catalytic amount of DMF at 0 °C and the mixture was stirred at room temperature for 15 min. The reaction mixture was concentrated *in vacuo* and then diluted with dry benzene

(5 ml). The solution was added Et_3N (374 mg, 3.70 mmol) and stirred at 80 °C for 1 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 3 : 1) to give 422 mg (92%) of **19** as a colorless oil. $[\alpha]_D^{26}$ = – 13.1 (c = 1.05, $CHCl_3$); IR (neat) 2973, 1795, 1719, 1482, 1379, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, s), 0.94 (3H, s), 1.65–1.93 (8H, m), 3.14 (1H, dd, *J* = 2.8, 17.6 Hz), 3.86 (3H, s), 3.96 (1H, dd, *J* = 17.6, 38.8 Hz), 4.27 (1H, s), 5.69 (0.8H, br), 5.86 (0.2H, br), 7.07 (1H, t, *J* = 7.6 Hz), 7.23–7.33 (2H, m), 7.50 (0.2H, br), 7.92 (0.8H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 23.1 (CH_2), 23.5 (CH_2), 27.2 (CH_3), 37.8 (CH_2), 37.8 (CH_2), 44.2 (C), 52.8 (CH_3), 60.9 (CH_2), 74.9 (CH), 79.8 (C), 82.5 (CH), 115.7 (CH), 115.9 (C), 123.3 (CH), 124.8 (CH), 129.3 (CH), 130.1 (C), 143.3 (C), 152.2 (C), 203.2 (C); HRMS (ESI) m/z Calcd for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.1811, found 372.1810.

3a-((*R*)-3,3-Dimethyl-1,4-dioxaspiro[4.4]nonan-2-yl)-1-methyl-2-oxo-1,2,3,3a-tetrahydro-pyrrolo[2,3-*b*] indole-8(8a*H*)-carboxylate (**21**)

To a stirred solution of compound **19** (280 mg, 0.754 mmol) in dry EtOH (12 mL) was added *N*-methylhydroxylamine hydrochloride (315 mg, 3.77 mmol), $NaHCO_3$ (507 mg, 6.03 mmol) and molecular sieve 3 A at room temperature and the mixture was stirred at 50 °C for 2.5 h. The reaction mixture was poured into brine and then extracted with AcOEt. The combined extracts was dried over $MgSO_4$ and concentrated to give a yellowish oil. The residue was diluted with $CHCl_3$ (10 mL), which was then added *p*-toluenesulfonyl chloride (287 mg, 1.51 mmol) and PPY (168 mg, 1.13 mmol) and stirred at 70 °C for 2.5 h. The reaction mixture was poured into water and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 3 : 1) to give 264 mg (88% for 2 steps) of **21** as a pale yellow oil. $[\alpha]_D^{23}$ = – 1.18 (c = 0.21, $CHCl_3$); IR (neat) 2972, 1705, 1487, 1243, 1113, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74 (3H, s), 0.85 (3H, s), 1.62–1.89 (8H, m), 2.75 (1H, d, *J* = 17.2 Hz), 2.94 (3H, d, *J* = 16.4 Hz), 3.18 (1H, d, *J* = 15.2 Hz), 3.88 (1H, s), 3.91 (3H, s), 6.05 (0.5H, br), 6.16 (0.5H, br), 7.11 (1H, t, *J* = 7.6 Hz), 7.19 (1H, d, *J* = 7.6 Hz), 7.26–7.30 (1H, m), 7.45 (0.5H, br), 7.83 (0.5H, br); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 21.9 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 27.3 (CH_3), 27.8 (CH_3), 38.1 (CH_2), 38.2 (CH_2), 43.4 (CH_2), 49.5 (C), 53.1 (CH_3), 78.8 (CH), 79.6 (C), 85.2 (CH), 115.8 (C), 117.4 (CH), 124.1 (CH), 124.6 (CH), 129.6 (CH), 132.4 (C), 140.3 (C), 153.7 (C), 171.3 (C); HRMS (ESI) m/z Calcd for $C_{22}H_{28}N_2O_5Na$ $[M+Na]^+$: 423.1896, found 423.1894.

(3a*S*,8a*S*)-Methyl

3a-((*R*)-1,2-dihydroxy-2-methylpropyl)-1-methyl-2-oxo-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**22**)

To a stirred solution of compound **21** (250 mg, 0.624 mmol) in TFA (8 mL) was added H_2O (1.6 mL) at room temperature and the mixture was stirred at the same temperature for 48 h. The reaction mixture was concentrated *in vacuo* to give a residue that was purified by silica gel column chromatography ($CHCl_3$: MeOH = 10 : 1) to give 209 mg (quant) of **22** as a yellowish amorphous powder. $[\alpha]_D^{25}$ = + 15.2 (c = 0.50, $CHCl_3$); IR (neat) 3430, 2961, 1683, 1488, 1173, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (3H, s), 0.95 (3H, s), 2.83 (1H, d, *J* = 17.6 Hz), 2.94 (3H, s), 3.43 (1H, d, *J* = 17.2 Hz), 3.71 (1H, s), 3.92 (3H, s), 4.80 (2H, br), 6.19 (1H, br), 7.10 (1H, t, *J* = 7.6 Hz), 7.22 (1H, d, *J* = 7.6 Hz), 7.31 (1H, t, *J* = 6.4 Hz), 7.46 (0.5H, br), 7.77 (0.5H, br); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 25.5 (CH_3), 28.1 (CH_3), 29.3 (CH_3), 42.8 (CH_2), 53.3 (CH_3), 53.3 (C), 74.3 (C), 79.2 (CH), 80.3 (CH), 117.6 (CH), 124.5 (CH), 125.3 (CH), 129.6 (CH), 134.2 (C), 140.5 (C), 154.2 (C), 174.4 (C); HRMS (ESI) m/z Calcd for $C_{17}H_{22}N_2O_5Na$ $[M+Na]^+$: 357.1426, found 357.1432.

(3a*S*,8a*S*)-8-(Methoxycarbonyl)-1-methyl-2-oxo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-3a-cabox ylic acid (**24**)

To a stirred solution of diol **22** (200 mg, 0.593 mmol) in acetone–H_2O (5 : 1, 14.4 mL) was added sodium periodate (380 mg, 1.78 mmol) at room temperature and the mixture was stirred at the same temperature for 12 h. The reaction mixture was added ethylene glycol (0.13 mL) at room temperature and stirring was continued for 15 minutes at the same temperature. The reaction mixture was poured into water and then extracted with $CHCl_3$–MeOH (10 : 1). The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product **23** was immediately carried on to next step without purification. To a stirred solution of above crude in ^{t}BuOH–H_2O (1.5 : 1, 7.5 mL) was added 2-methyl-2-butene (3 mL), NaH_2PO_4 (569 mg, 4.74 mmol) and $NaClO_2$ (268 mg, 2.97 mmol) at 0 °C and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with 1 N NaOH solution and extracted with Et_2O. The aqueous layer was acidified with 1 N HCl solution and extracted with $CHCl_3$. The combined extracts was dried over $MgSO_4$ and concentrated to give 161 mg (94% for 2 steps) of **24** as a colorless amorphous powder. $[\alpha]_D^{29}$ = + 52.0 (c = 0.36, $CHCl_3$); IR (KBr) 3429, 2936, 1702, 1634, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.92 (3H, s), 2.94 (1H, d, *J* = 16.8 Hz), 3.22 (1H, d, *J* = 17.6 Hz), 3.92 (3H, s), 6.28 (1H, br), 7.12 (1H, t, *J* = 7.6 Hz), 7.33 (1H, t, *J* = 7.6 Hz), 7.35 (1H, d, *J* = 7.6 Hz), 7.78 (1H, br); ^{13}C NMR ($CDCl_3$: CD_3OD = 1 : 1, 75 MHz, 50 °C) δ 26.9 (CH_3), 39.5 (CH_2), 52.5 (CH_3), 53.8 (C), 80.7 (CH), 116.4 (CH), 124.0 (CH), 124.1 (CH), 129.3 (CH), 131.7 (C), 139.5 (C), 153.5 (C), 171.4 (C), 171.4 (C); HRMS (ESI) m/z Calcd for $C_{14}H_{15}N_2O_5$ $[M+H]^+$: 291.0981, found 291.0972.

(3a*S*,8a*S*)-Methyl

3a-amino-1-methyl-2-oxo-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**25**)

To a stirred solution of caboxylic acid **24** (50.0 mg, 0.172 mmol) in dry benzene (2 mL) was added diphenylphosphoryl azide (DPPA) (71.1 mg, 0.258 mmol) and Et_3N (31.4 mg, 0.310 mmol) at room temperature and the mixture was stirred at 80 °C for 5 h. 4 N HCl solution (0.5 mL) was added to the reaction mixture and stirring was continued for 2 h at 60 °C. The reaction mixture was diluted with water, and then extracted with Et_2O. The aqueous layer was alkalified with 2 N NaOH solution and extracted with $CHCl_3$. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography ($CHCl_3$: MeOH = 10 : 1) to give 29.8 mg (66%) of **25** as a colorless amorphous powder. $[\alpha]_D^{30}$ = – 26.3 (c = 0.35, $CHCl_3$); IR (neat) 3358, 2956, 1696, 1604, 1486, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74 (2H, br), 2.79 (1H, d, *J* = 16.8 Hz), 2.90 (3H, s), 3.00 (1H, d, *J* = 16.8 Hz), 3.93 (3H, s), 5.64 (1H, br), 7.14 (1H, t, *J* = 7.6 Hz), 7.33 (1H, t, *J* = 7.6 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 7.68 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz, 50 °C) δ 27.5 (CH_3), 44.0 (CH_2), 53.0 (CH_3), 61.7 (C), 86.1 (CH), 116.8 (CH), 123.6 (CH), 124.6 (CH), 129.9 (CH), 136.1 (C), 139.5 (C), 153.9 (C), 171.1 (C); HRMS (ESI) m/z Calcd for $C_{26}H_{30}N_6O_6Na$ $[2M+Na]^+$: 545.2125, found 545.2117.

(3a*S*,8a*S*)-Methyl

3a-(1*H*-indol-1-yl)-1-methyl-2-oxo-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**27**)

To a stirred solution of amine **25** (40.0 mg, 0.153 mmol) and 1-bromo-2-(2-bromovinyl)benzene (**26**) [6] (60.2 mg, 0.230 mmol) in toluene (1 mL) was added $Pd_2(dba)_3 \cdot CHCl_3$ (63.4 mg, 0.0612 mmol), ^{t}BuONa (44.1 mg, 0.459 mmol) and X-Phos (87.6 mg, 0.184 mmol) at room temperature and the mixture was stirred at 130 °C in a sealed tube for 6 h. The reaction mixture was filtered through a pad of Celite® and concentrated *in vacuo* to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 2 : 1) to give 34.1 mg (62%) of **27** as a pale blown oil. $[\alpha]_D^{32}$ = – 231.7 (c = 1.00, $CHCl_3$); IR (neat) 1709, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.07 (3H, s), 3.20 (1H, d, *J* = 18.0 Hz), 3.84 (3H, s), 3.84 (1H, d, *J* = 16.8 Hz), 6.29 (1H, br), 6.40 (1H, d, *J* = 3.2 Hz), 6.76 (1H, d, *J* = 3.2 Hz), 7.20 (2H, t, *J* = 8.0 Hz), 7.29 (2H, t, *J* = 7.6 Hz), 7.49 (1H, d, *J* = 7.6 Hz), 7.53 (1H, d, *J* = 7.7 Hz), 7.67 (1H, d, *J* = 8.0 Hz), 7.92 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz, 50 °C) δ 27.8 (CH_3), 41.3 (CH_2), 53.3 (CH_3), 66.1 (C), 82.5 (CH), 102.0 (CH), 110.7 (CH), 118.0 (CH), 120.6 (CH×2), 122.1 (CH), 122.5 (CH), 124.8 (CH), 126.3 (CH), 128.4 (CH), 130.9 (C), 131.5 (C), 134.2 (C), 140.8 (C), 154.2 (C), 170.4 (C); HRMS (ESI) m/z Calcd for $C_{21}H_{20}N_3O_3$ $[M+H]^+$: 362.1505, found 362.1505.

(3a*S*,8a*R*)-3a-(1*H*-Indol-1-yl)-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**S18**)

To a stirred solution of indole **27** (5.00 mg, 0.0138 mmol) in THF (1 mL) was added $LiAlH_4$ (1.60 mg, 0.0422 mmol) at 0 °C and the mixture was refluxed for 1 h. The reaction mixture was cooled to 0 °C then added 1 N NaOH solution (0.2 mL). The reaction mixture was refluxed for 1 h, then filtered through a pad of Celite® and concentrated *in vacuo* to give a residue that was purified by silica gel column chromatography ($CHCl_3$: AcOEt = 3 : 2) to give 2.50 mg (62%) of **S18** as a pale yellow oil. $[\alpha]_D^{28}$ = + 96.1 (c = 0.35, $CHCl_3$); IR (neat) 3404, 2912, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.44 (1H, ddd, *J* = 2.4, 5.6, 12.0 Hz), 2.50 (3H, s), 2.69–2.75 (1H, m), 3.05 (1H, ddd, *J* = 2.4, 6.8, 9.2 Hz), 3.23–3.30 (1H, m), 4.40 (1H, br), 5.22 (1H, s), 6.45 (1H, dd, *J* = 0.8, 3.6 Hz), 6.71–6.76 (2H, m), 7.04–7.10 (3H, m), 7.15 (1H, td, *J* = 1.2, 7.6 Hz), 7.34 (1H, d, *J* = 3.6 Hz), 7.42–7.45 (1H, m), 7.57–7.61 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.2 (CH_3), 38.7 (CH_2), 51.7 (CH_2), 76.7 (C), 85.9 (CH), 100.9 (CH), 109.8 (CH), 112.1 (CH), 119.3 (CH), 119.6 (CH), 121.0 (CH), 121.3 (CH), 125.0 (CH), 126.2 (C), 129.8 (CH×2), 130.3 (C), 135.5 (C), 150.6 (C); HRMS (ESI) m/z Calcd for $C_{19}H_{20}N_3$ $[M+H]^+$: 290.1657, found 290.1641.

(3a*S*,8a*S*)-*tert*-Butyl

3a-(1*H*-indol-1-yl)-1-methyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate (**(–)-18**)

To a stirred solution of indole **S18** (4.00 mg, 0.0138 mmol) in THF (1 mL) was added NaHMDS (0.0320 mL) (1.09 M solution of THF) at – 78 °C and the mixture was stirred at – 78 °C for 20 min. Boc_2O (4.60 mg, 0.0211 mmol) was added to the reaction mixture and stirring was continued for 40 min at the same temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and then extracted with AcOEt. The combined extracts was washed with brine, dried over $MgSO_4$, and concentrated to give a residue that was purified by silica gel column chromatography (Hexane : AcOEt = 3 : 1) to give 5.10 mg (95%, > 95% ee *) of **(–)-18** as a colorless oil. *HPLC [DICEL CHIRALPAK AS-H; 0.5 mL/min; solvent system: EtOH : Hexane = 15 : 85; retention time: 26.5 min (major), 61.8 min (minor)]; $[\alpha]_D^{31}$ = – 53.1 (c = 0.50, $CHCl_3$), ($[\alpha]_D^{24}$ = – 48.6 (c = 0.22, $CHCl_3$)) [7] ; IR (neat) 2977, 1705, 1483, 1457, 1368, 1165, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55 (9H, s), 2.41 (1H, ddd, *J* = 2.0, 4.8, 12.0 Hz), 2.62 (1H, overlapped), 2.62 (3H, s), 3.06 (1H, ddd, *J* = 2.0, 6.8, 8.8 Hz), 3.27 (1H, ddd, *J* = 6.8, 10.0, 11.6 Hz), 5.82 (1H, s), 6.45 (1H, d, *J* = 3.2 Hz), 7.05–7.14 (3H, m), 7.20 (1H, d, *J* = 3.2 Hz), 7.24 (1H, overlapped), 7.34 (1H, br dd, *J* = 8.4, 8.4 Hz), 7.38 (1H, overlapped), 7.60–7.62 (1H, m), 7.83 (1H, br); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 ($CH_3\times3$), 36.7 (CH_3), 37.7 (CH_2), 52.6 (CH_2), 74.1 (C), 81.9 (C), 85.8 (CH), 101.1 (CH), 111.8 (CH), 116.5 (CH), 119.8 (CH), 121.2 (CH), 121.7 (CH), 123.4 (CH), 124.9 (CH), 126.2 (C), 130.0 (CH), 130.2 (CH), 131.4 (C), 135.2 (C), 143.6 (C), 153.0 (C); HRMS (ESI) m/z Calcd for $C_{24}H_{27}N_3O_2Na$ $[M+Na]^+$: 412.2001, found 412.1996.

References

1) Zheng, Y. H.; Oehlschlager, A. C.; Georgopapadakou, N. H.; Hartman, P. G.; Scheliga, P. *J. Am. Chem. Soc*. **1995**, *117*, 670-680.

2) Vidari, G.; Lanfranchi, G.; Sartori, P.; Serra, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2977-2990.

3) Matsuura, F.; Peters, R.; Anada, M.; Harried, S. S.; Hao, J.; Kishi, Y. *J. Am. Chem. Soc*. **2006**, *128*, 7463-7465.

4) Sun, K.; Liu, S.; Bec, P. M.; Driver, T. G. *Angew. Chem. Int. Ed.* **2011**, *50*, 1702-1706.

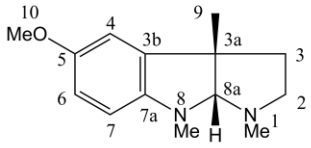
5) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, *19*, 109-112.

6) Tadd, A. C.; Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett*. **2009**, *11*, 583-586.

7) Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. *Chem. Commun.* **2010**, *46*, 2501-2503.

8) Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675-678.

Comparison of our data for (–)-esermethole (**16**) with literature for (–)-**16**

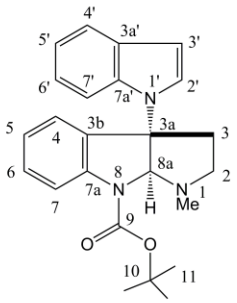


^{1}H-number	reported (400 MHz, $CDCl_3$)	Synthetic (400 MHz, $CDCl_3$)	Δδ
6	6.65 (1H, d, *J* = 8.3 Hz)	6.66 (1H, dd, *J* = 2.8, 8.4 Hz)	0.01
4	6.63 (1H, s)	6.63 (1H, d, *J* = 2.8 Hz)	0
7	6.36 (1H, d, *J* = 8.1 Hz)	6.36 (1H, d, *J* = 8.4 Hz)	0
8a-H	4.05 (1H, s)	4.08 (1H, s)	0.03
10	3.75 (3H, s)	3.75 (3H, s)	0
N_8-CH_3	2.89 (3H, s)	2.89 (3H, s)	0
2	2.72 (1H, m)	2.77-2.72 (1H, m)	-
	2.64 (1H, m)	2.67-2.60 (1H, m)	-
N_1-CH_3	2.53 (3H, s)	2.54 (3H, s)	0.01
3	1.97 (2H, m)	1.96 (2H, dd, *J* = 5.2, 7.6 Hz)	-0.01
9	1.43 (3H, s)	1.44 (3H, s)	0.01

reported:
Nakagawa, M. *et al. Org. Lett.* **2000**, *2*, 675-678. [8]

^{13}C-number	reported (100 MHz, $CDCl_3$)	Synthetic (100 MHz, $CDCl_3$)	Δδ
5	152.9	153.0	0.1
7a	146.5	146.4	-0.1
3b	138.2	138.	-0.1
6	112.1	112.3	0.2
4	109.8	109.8	0
7	107.4	107.6	0.2
8a	98.3	98.2	-0.1
2	56.0	56.0	0
10	53.0	53.2	0.2
3a	52.7	52.9	0.2
3	40.8	40.6	-0.2
N_1-CH_3	38.1	38.0	-0.1
N_8-CH_3	37.9	37.9	0
9	27.4	27.3	-0.1

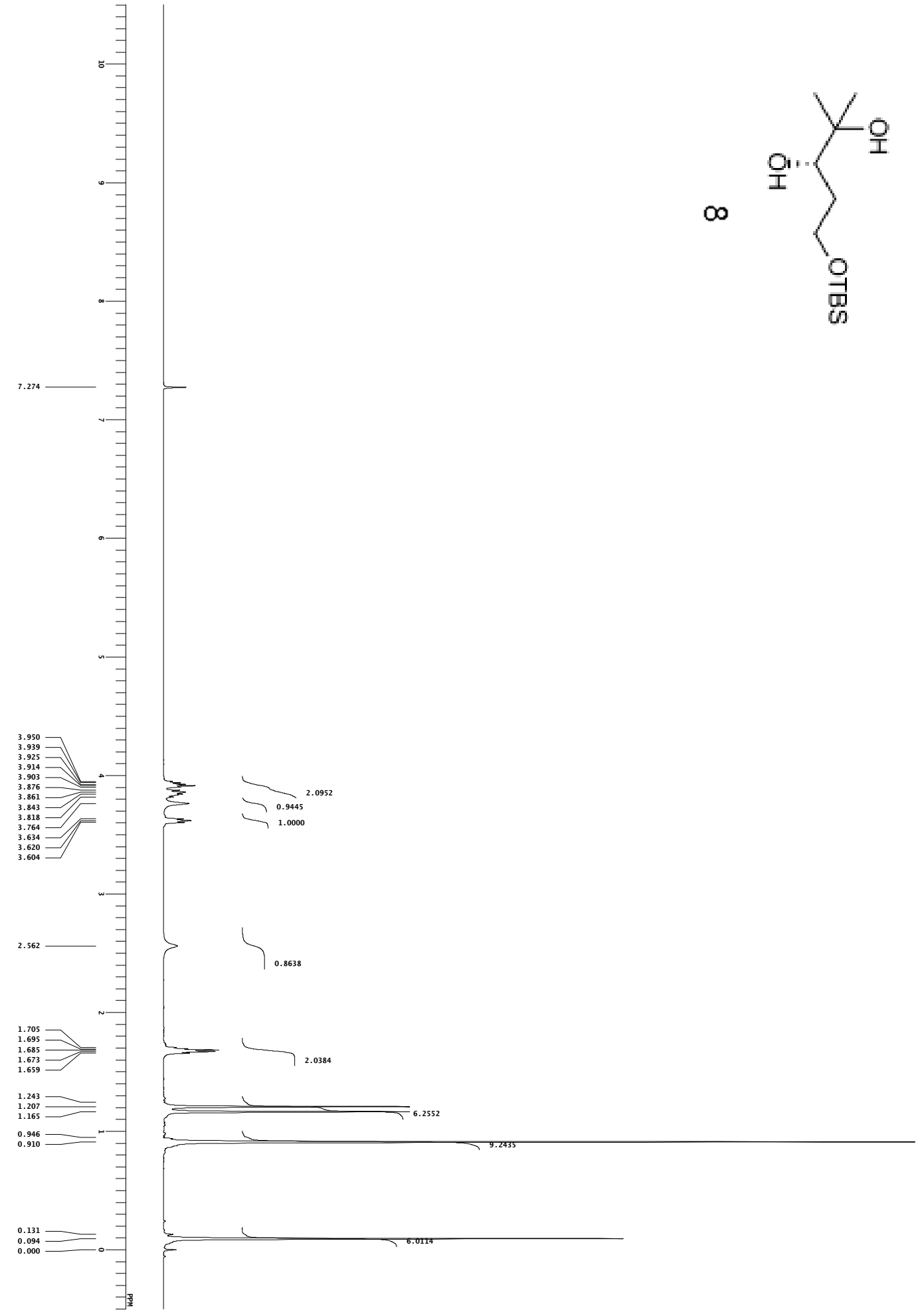
Comparison of our data for (–)-**18** with literature for (–)-**18**



^{1}H-number	reported (400 MHz, $CDCl_3$)	Synthetic (400 MHz, $CDCl_3$)	Δδ
4'	7.84 (1H, br)	7.83 (1H, br)	-0.01
7'	7.60 (1H, m)	7.60-7.62 (1H, m)	-
7	7.37 (1H, m)	7.38 (1H, overlapped)	0.01
5	7.33 (1H, br-dd, *J* = 8.4, 8.4 Hz)	7.34 (1H, br-dd, *J* = 8.4, 8.4 Hz)	0.01
6	7.25 (1H, overlapped)	7.24 (1H, overlapped)	-0.01
2'	7.19 (1H, br-d, *J* = 3.3 Hz)	7.20 (1H, d, *J* = 3.2 Hz)	0.01
4, 5', 6'	7.13-7.04 (3H, overlapped)	7.14-7.05 (3H, overlapped)	0.01
3'	6.44 (1H, d, *J* = 3.3 Hz)	6.45 (1H, d, *J* = 3.2 Hz)	0.01
8a	5.82 (1H, s)	5.82 (1H, s)	0
3	3.25 (1H, ddd, , *J* = 11.7, 10.2, 6.8 Hz)	3.27 (1H, ddd, , *J* = 11.6, 10.0, 6.8 Hz)	0.02
	3.05 (1H, ddd, , *J* = 9.1, 7.0, 1.9 Hz)	3.06 (1H, ddd, , *J* = 8.8, 6.8, 2.0 Hz)	0.01
N_1-CH_3	2.64 (3H, s)	2.62 (3H, s)	-0.02
2	2.59 (1H, overlapped)	2.62 (1H, overlapped)	0.03
	2.39 (1H, ddd, , *J* = 11.8, 4.9, 1.9 Hz)	2.41 (1H, ddd, , *J* = 12.0, 4.8, 2.0 Hz)	0.02
($C(CH_3)_3$)	1.54 (9H, s)	1.55 (9H, s)	0.01

^{13}C-number	reported (100 MHz, $CDCl_3$)	Synthetic (100 MHz, $CDCl_3$)	Δδ
9	153.0	153.0	0
7a	143.6	143.6	0
7a'	135.2	135.2	0
3a'	131.3	131.4	0.1
2'	130.2	130.2	0
5	130.0	130.0	0
3b	126.2	126.2	0
6	124.9	124.9	0
4	123.4	123.4	0
6'	121.7	121.7	0
4'	121.1	121.2	0.1
5'	119.8	119.8	0
7	116.5	116.5	0
7'	111.8	111.8	0
3'	101.1	101.1	0
8a	85.7	85.8	0.1
10	81.9	81.9	0
3a	74.2	74.1	-0.1
2	52.6	52.6	0
3	37.7	37.7	0
N_1-CH_3	36.7	36.7	0
11	28.3	28.3	0

reported: Takayama, H. *et al. Chem. Commun.,* **2010**, *46*, 2501-2503. [7]


8
HO
HO
OTBS
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3.939
3.925
3.914
3.903
3.876
3.861
3.843
3.818
3.764
3.634
3.620
3.604
2.562
1.705
1.695
1.685
1.673
1.659
1.243
1.207
1.165
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0.910
0.131
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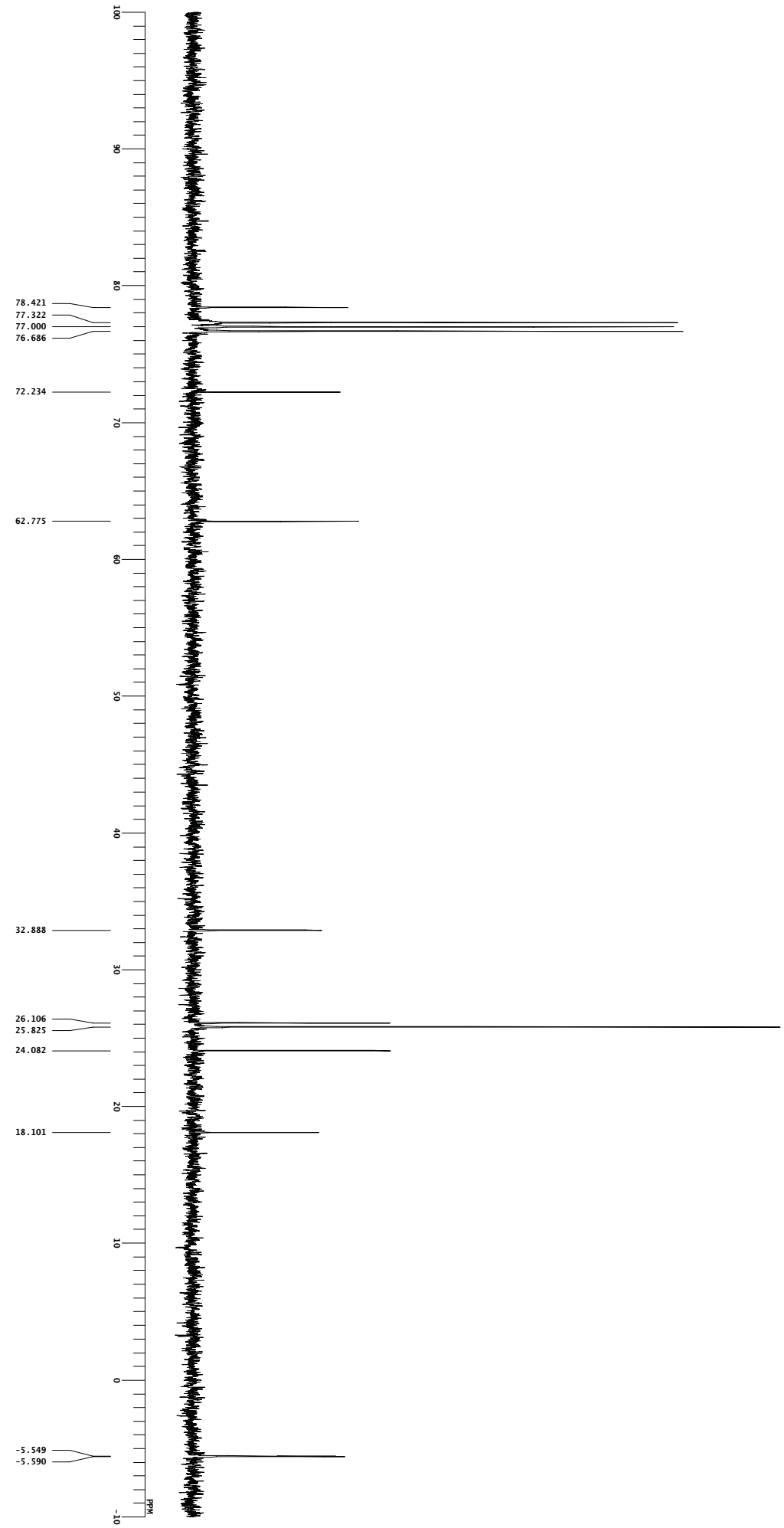
ppm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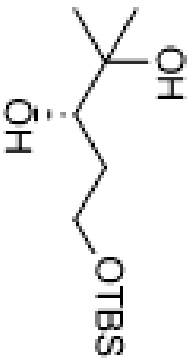
-5.590
ppm

8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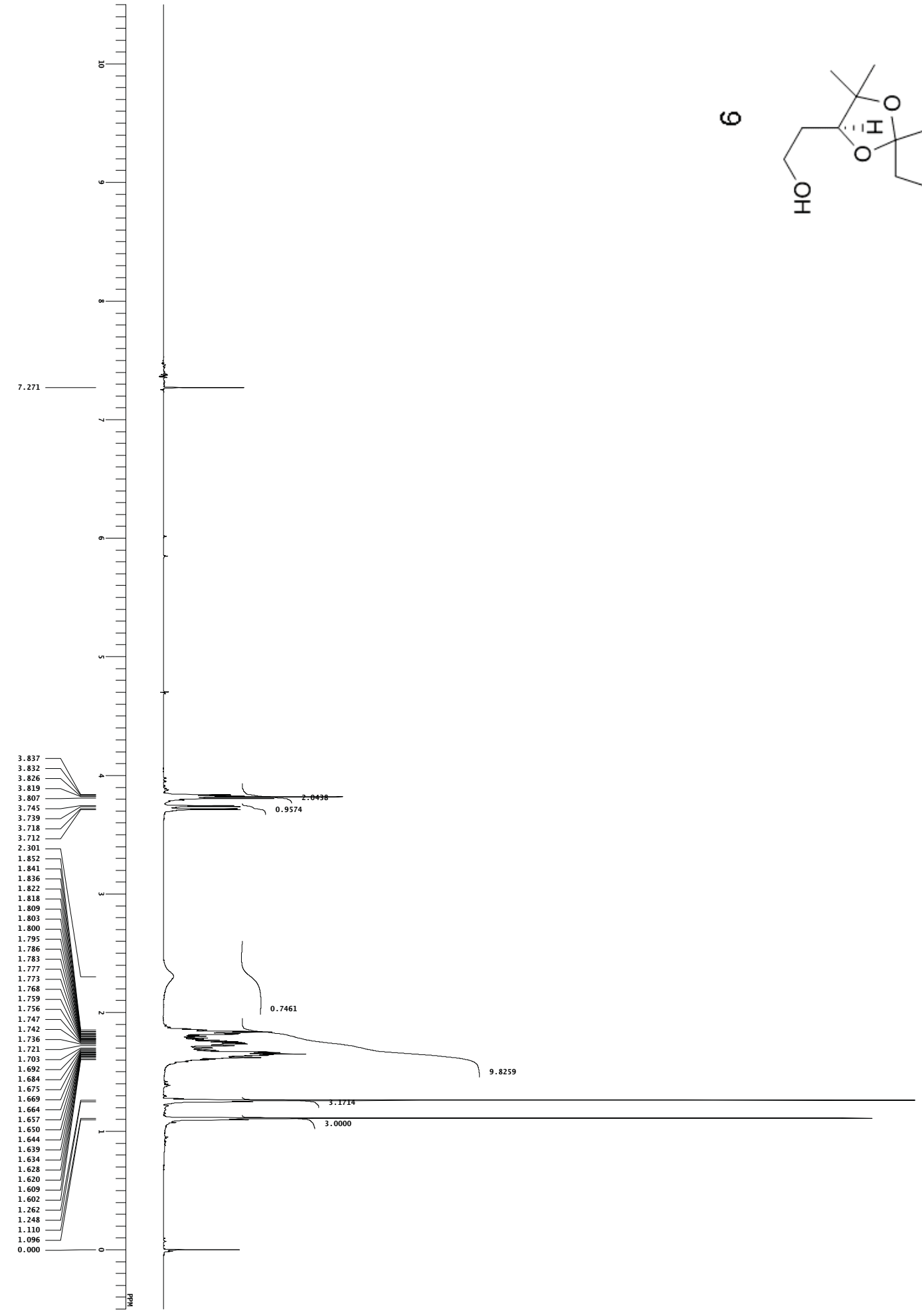
OH
OTBS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H
O
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3.718
3.712
2.301
1.852
1.841
1.836
1.822
1.818
1.809
1.803
1.800
1.795
1.786
1.783
1.777
1.773
1.768
1.759
1.756
1.747
1.742
1.736
1.721
1.703
1.692
1.684
1.675
1.669
1.664
1.657
1.650
1.644
1.639
1.634
1.628
1.620
1.609
1.602
1.262
1.248
1.110
1.096
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2.0438
0.9574
0.7461
9.8259
3.1714
3.0000
PPM

117.106
82.733
79.792
77.314
77.000
76.678
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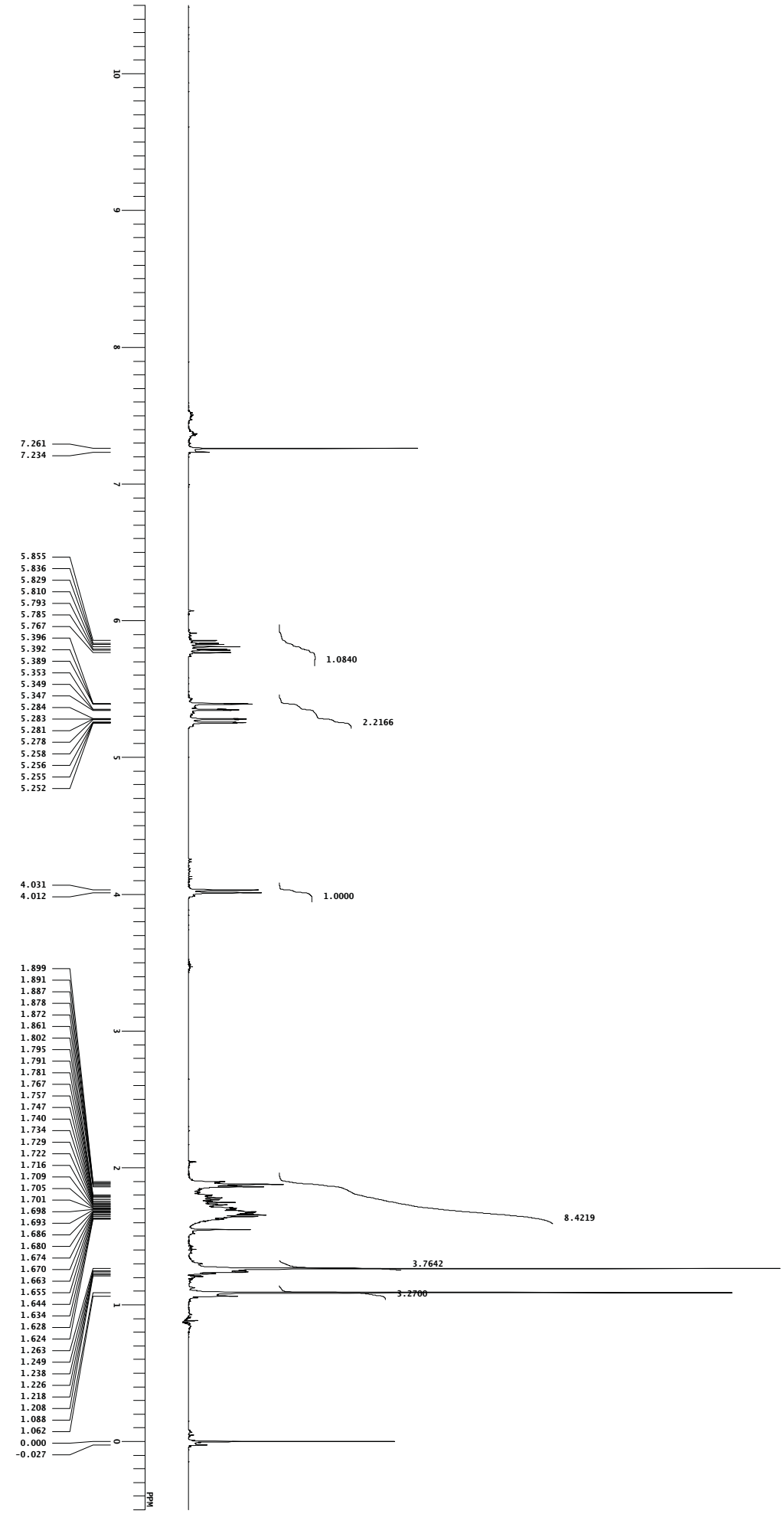
38.183
31.607
25.288
23.652
23.314
22.446
PPM

9
O
H
O
HO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7.234
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5.836
5.829
5.810
5.793
5.785
5.767
5.396
5.392
5.389
5.353
5.349
5.347
5.284
5.283
5.281
5.278
5.258
5.256
5.255
5.252
4.031
4.012
1.899
1.891
1.887
1.878
1.872
1.861
1.802
1.795
1.791
1.781
1.767
1.757
1.747
1.740
1.734
1.729
1.722
1.716
1.709
1.705
1.701
1.698
1.693
1.686
1.680
1.674
1.670
1.663
1.655
1.644
1.634
1.628
1.624
1.263
1.249
1.238
1.226
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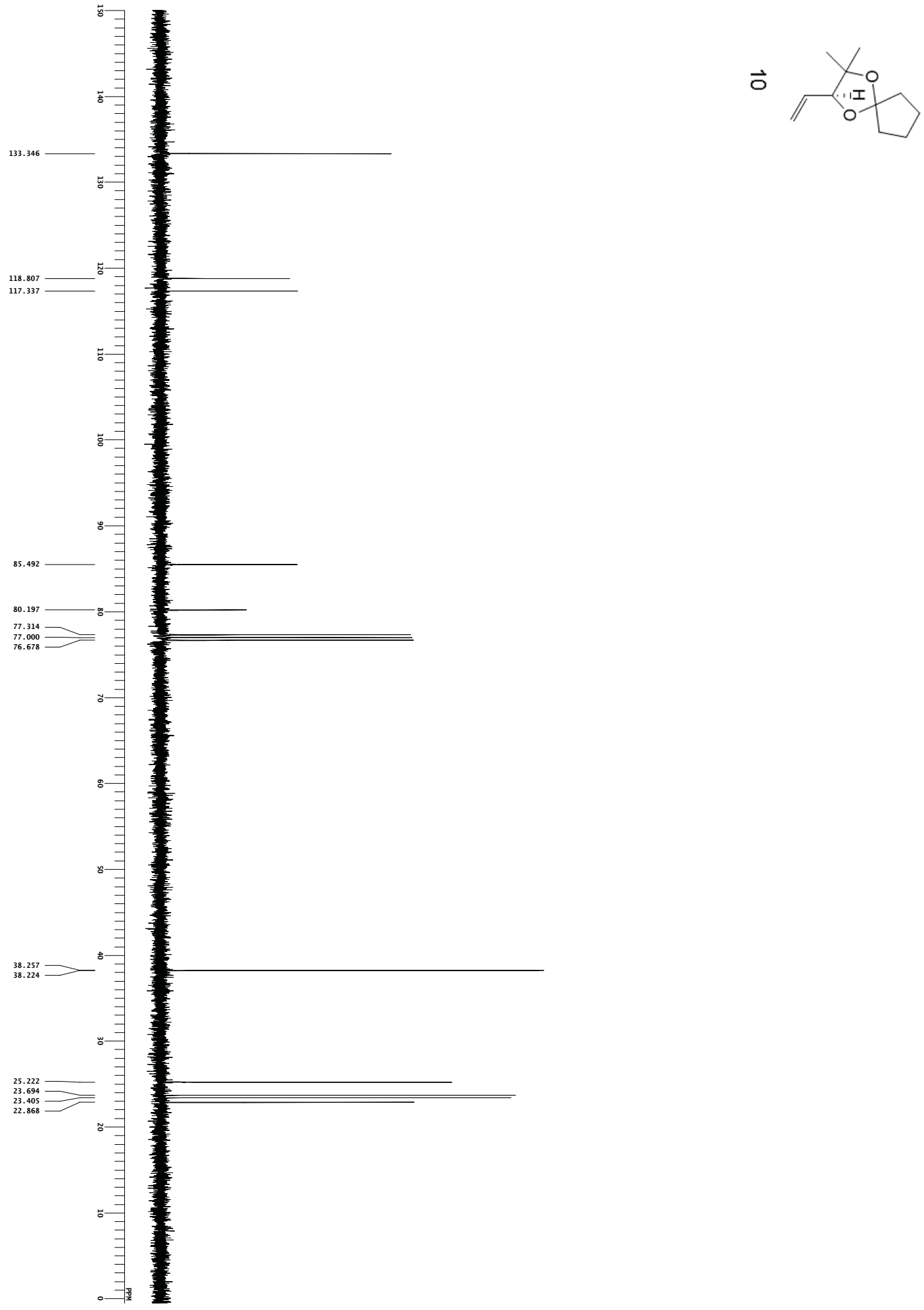
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117.337
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77.000
76.678
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38.224
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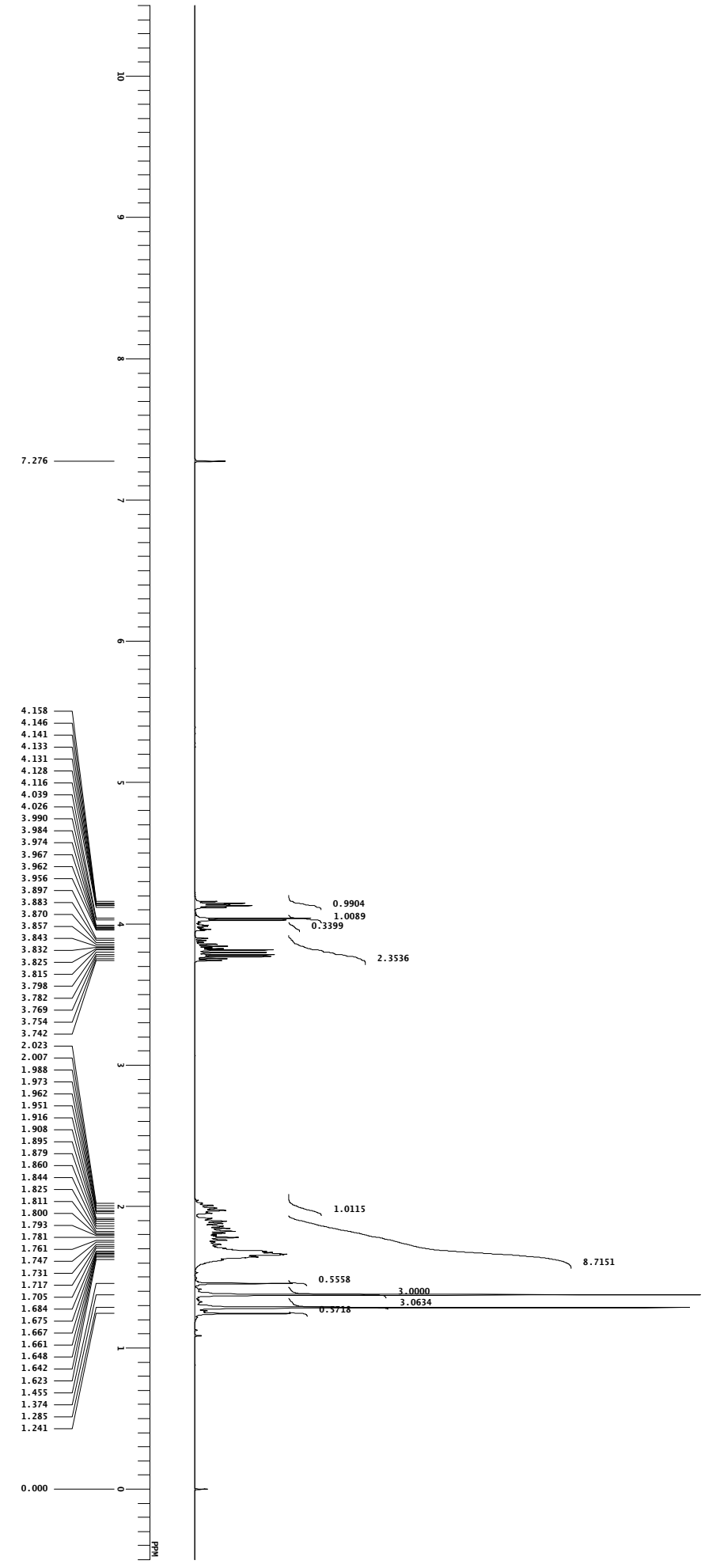
23.694
23.405
22.868
PPM

10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4.141
4.133
4.131
4.128
4.116
4.039
4.026
3.990
3.984
3.974
3.967
3.962
3.956
3.897
3.883
3.870
3.857
3.843
3.832
3.825
3.815
3.798
3.782
3.769
3.754
3.742
2.023
2.007
1.988
1.973
1.962
1.951
1.916
1.908
1.895
1.879
1.860
1.844
1.825
1.811
1.800
1.793
1.781
1.761
1.747
1.731
1.717
1.705
1.684
1.675
1.667
1.661
1.648
1.642
1.623
1.455
1.374
1.285
1.241
0.000
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1.0089
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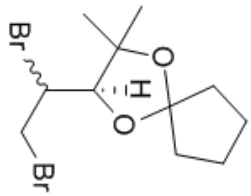
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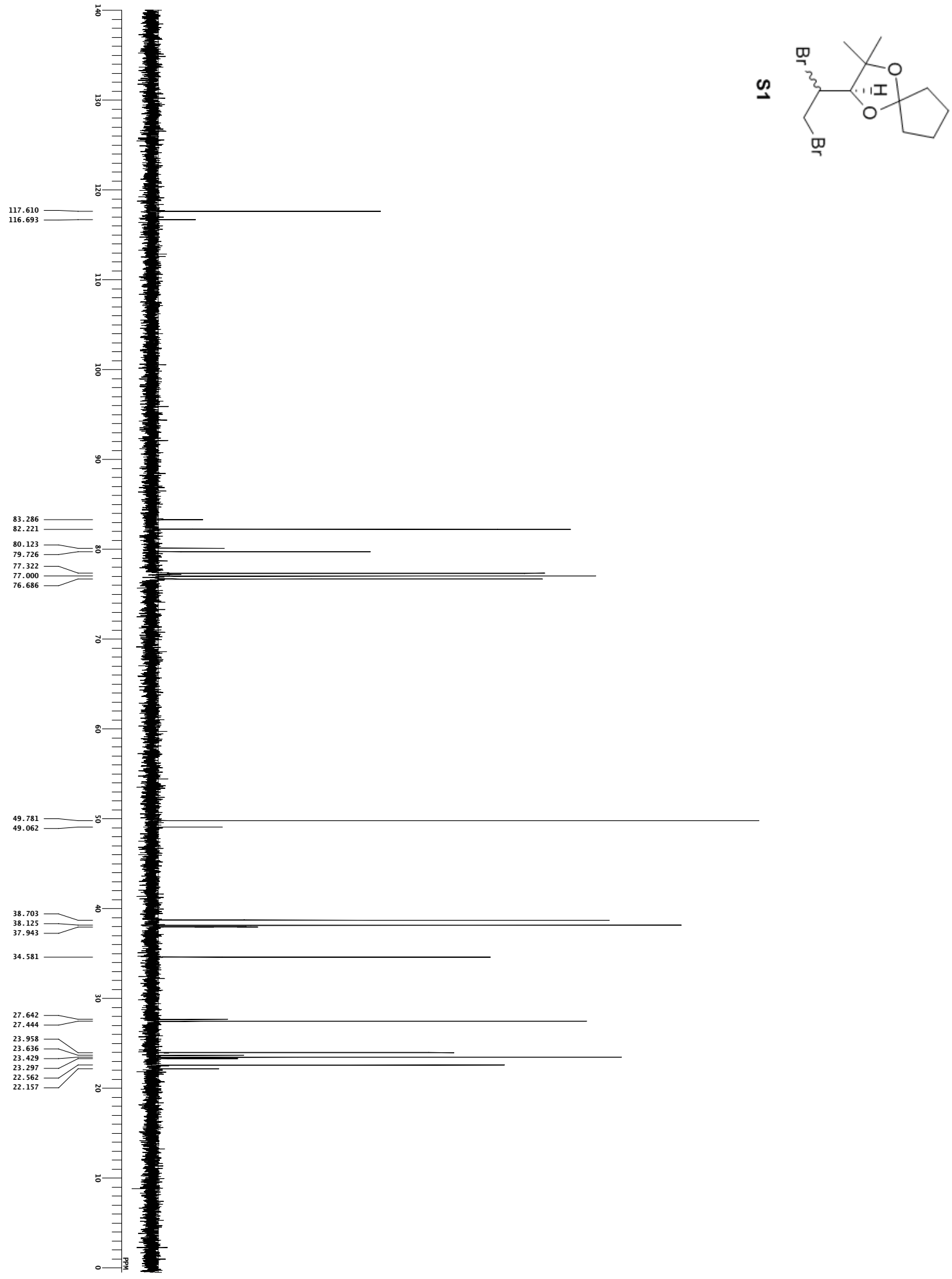
O
H
O
Br

S1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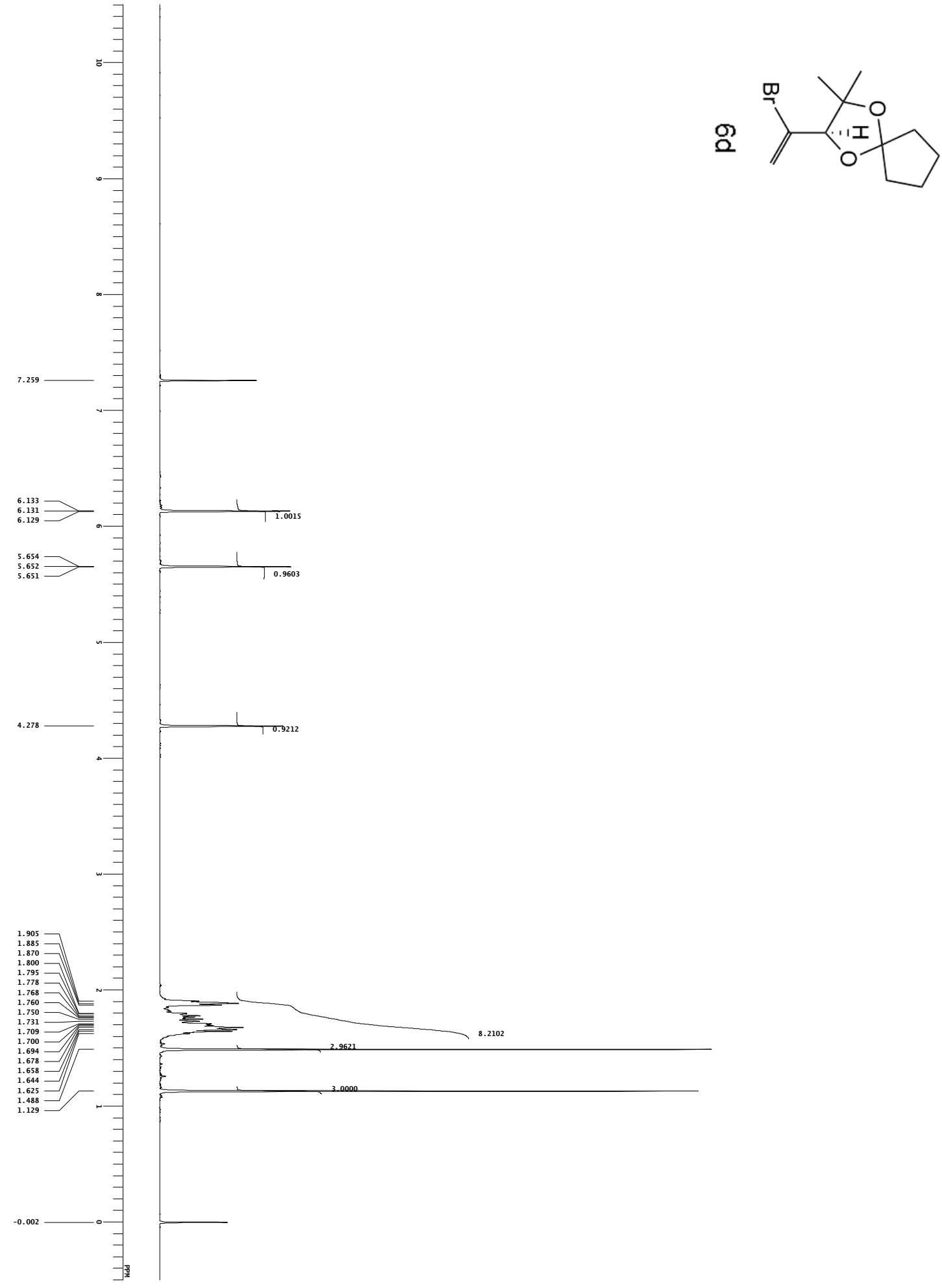
82.221
80.123
79.726
77.322
77.000
76.686
49.781
49.062
38.703
38.125
37.943
34.581
27.642
27.444
23.958
23.636
23.429
23.297
22.562
22.157
PPM

Br
O
H
O
Br

S1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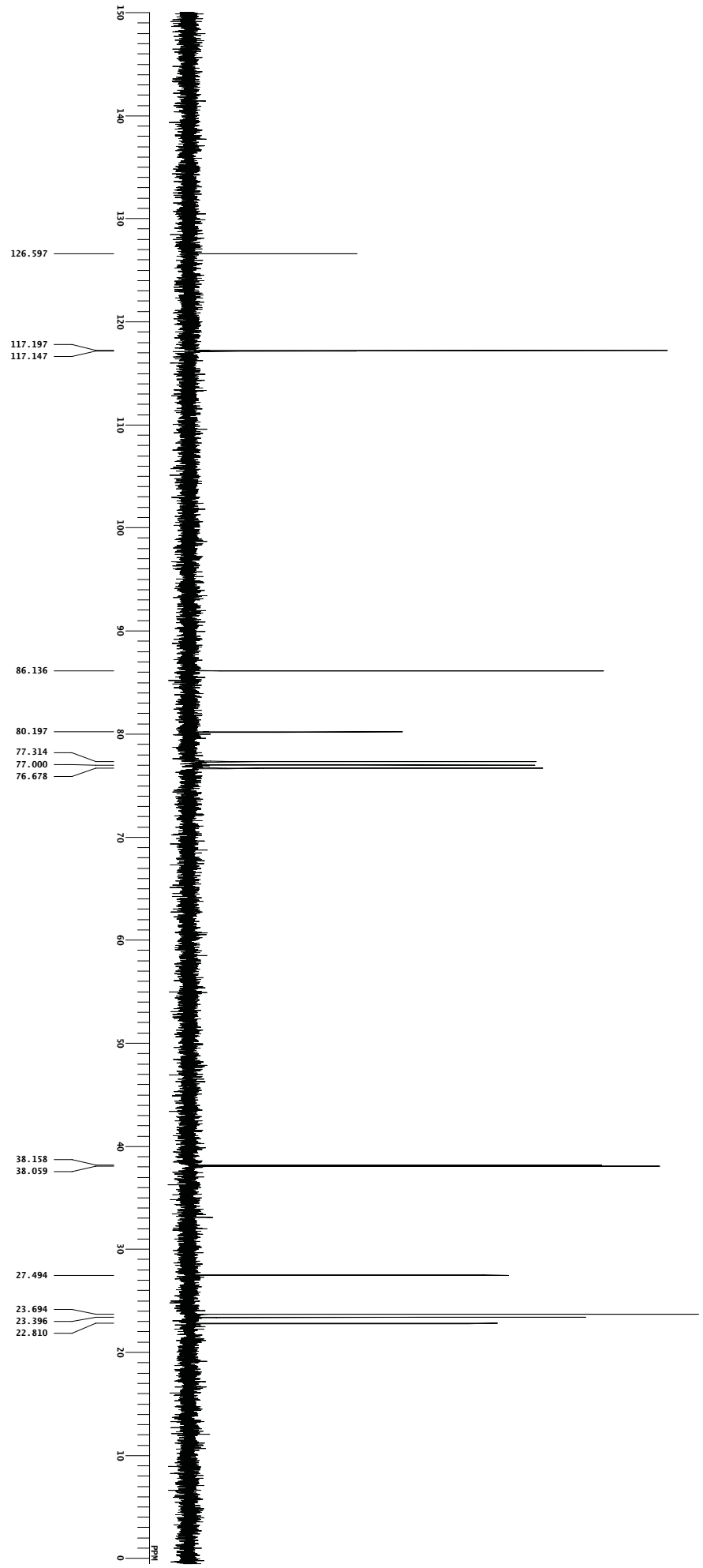
5.654
5.652
5.651
0.9603
4.278
0.9212
1.905
1.885
1.870
1.800
1.795
1.778
1.768
1.760
1.750
1.731
1.709
1.700
1.694
1.678
1.658
1.644
1.625
1.488
1.129
8.2102
2.9621
3.0000
-0.002
PPM

Br
O
H
O

6g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77.000
76.678
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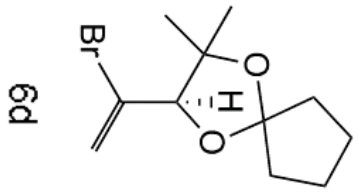
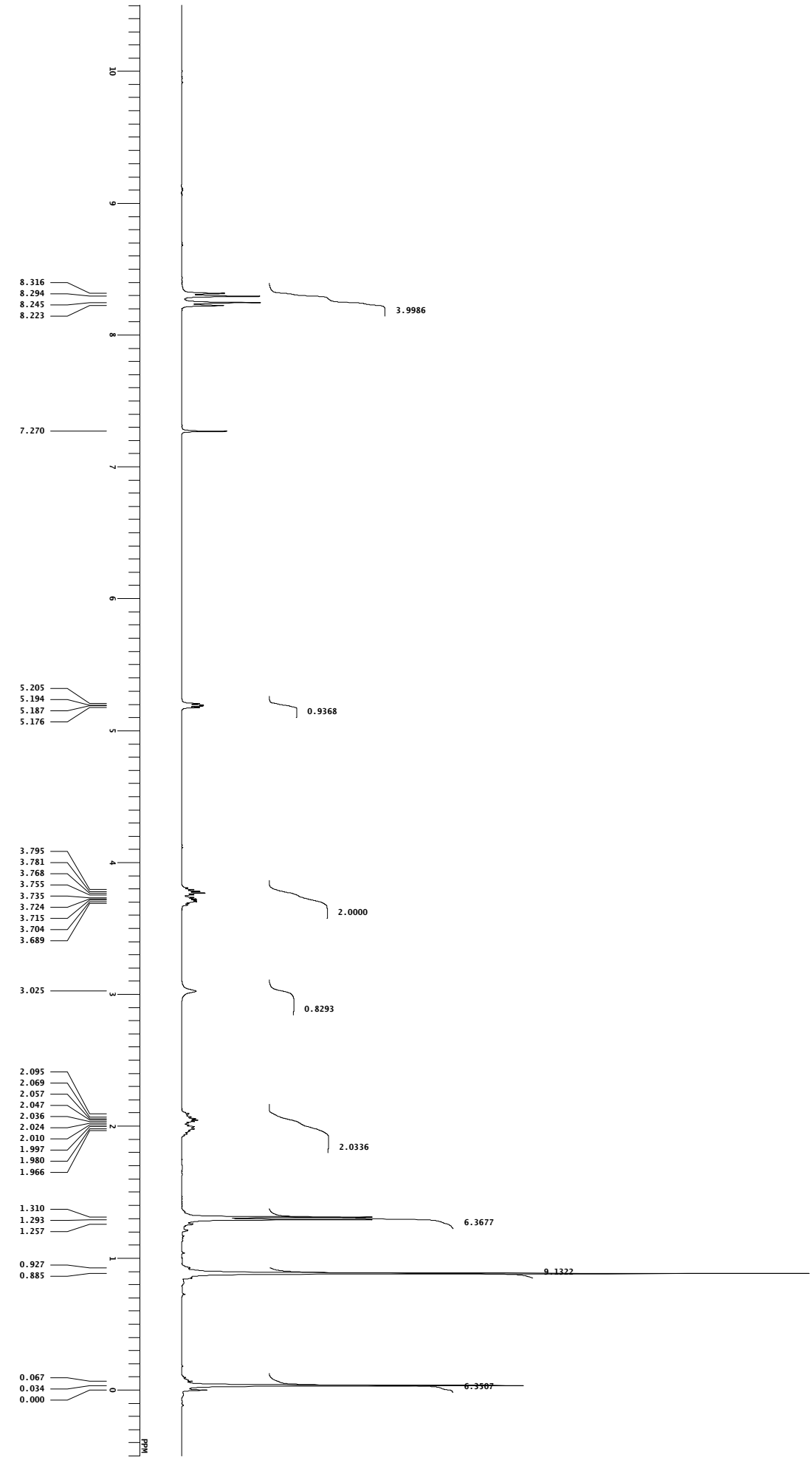
38.059
27.494
23.694
23.396
22.810
PPM


Br
O
H
O

6d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8.245
8.223
7.270
5.205
5.194
5.187
5.176
3.795
3.781
3.768
3.755
3.735
3.724
3.715
3.704
3.689
3.025
2.095
2.069
2.057
2.047
2.036
2.024
2.010
1.997
1.980
1.966
1.310
1.293
1.257
0.927
0.885
0.067
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0.000
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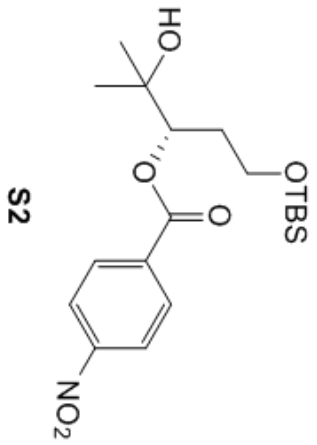
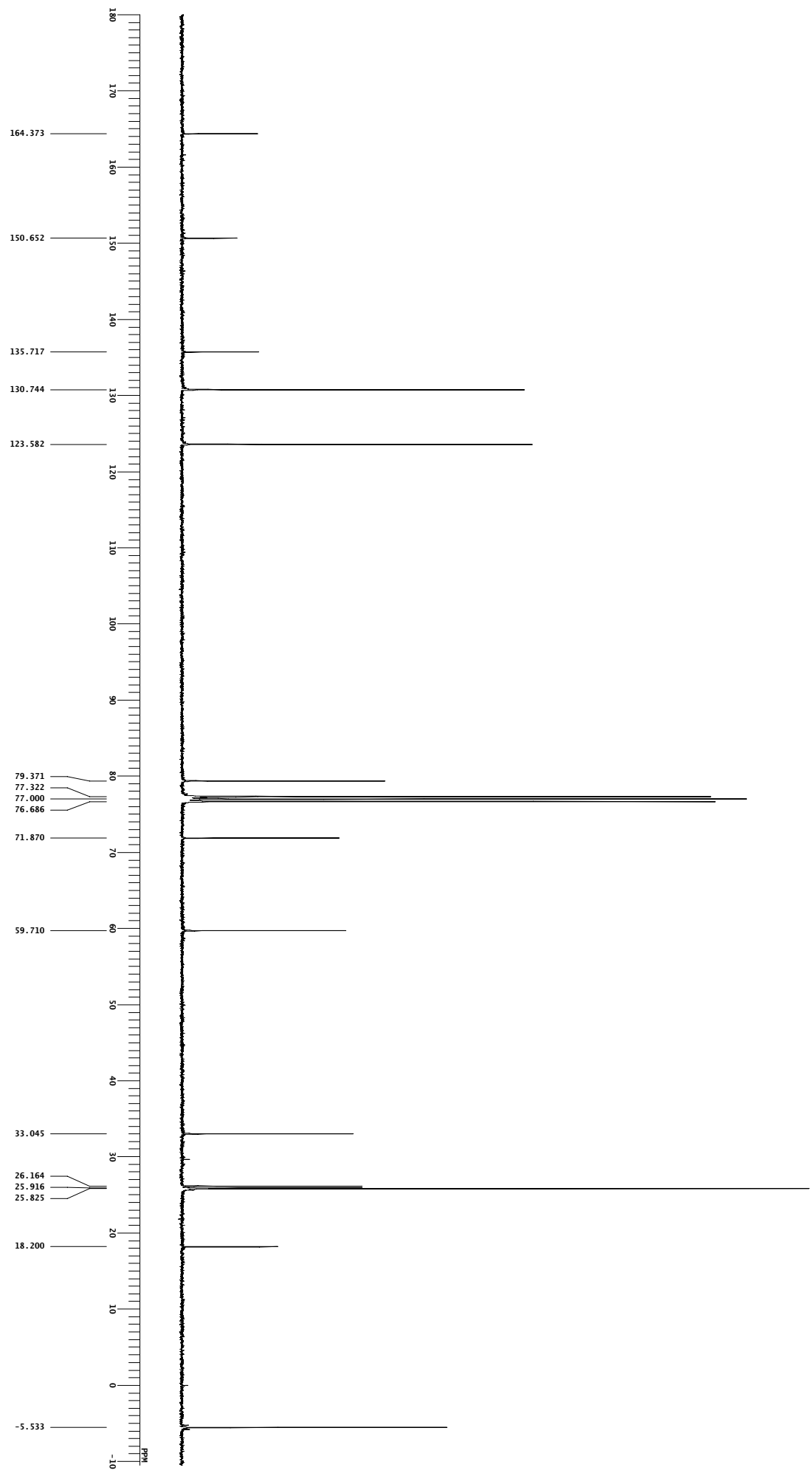
2.0336
6.3677
9.1322
6.3507
PPM


S2
OH
O
O
OTBS
NO2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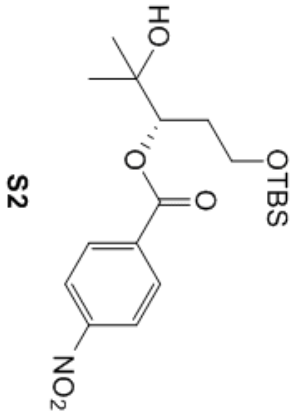
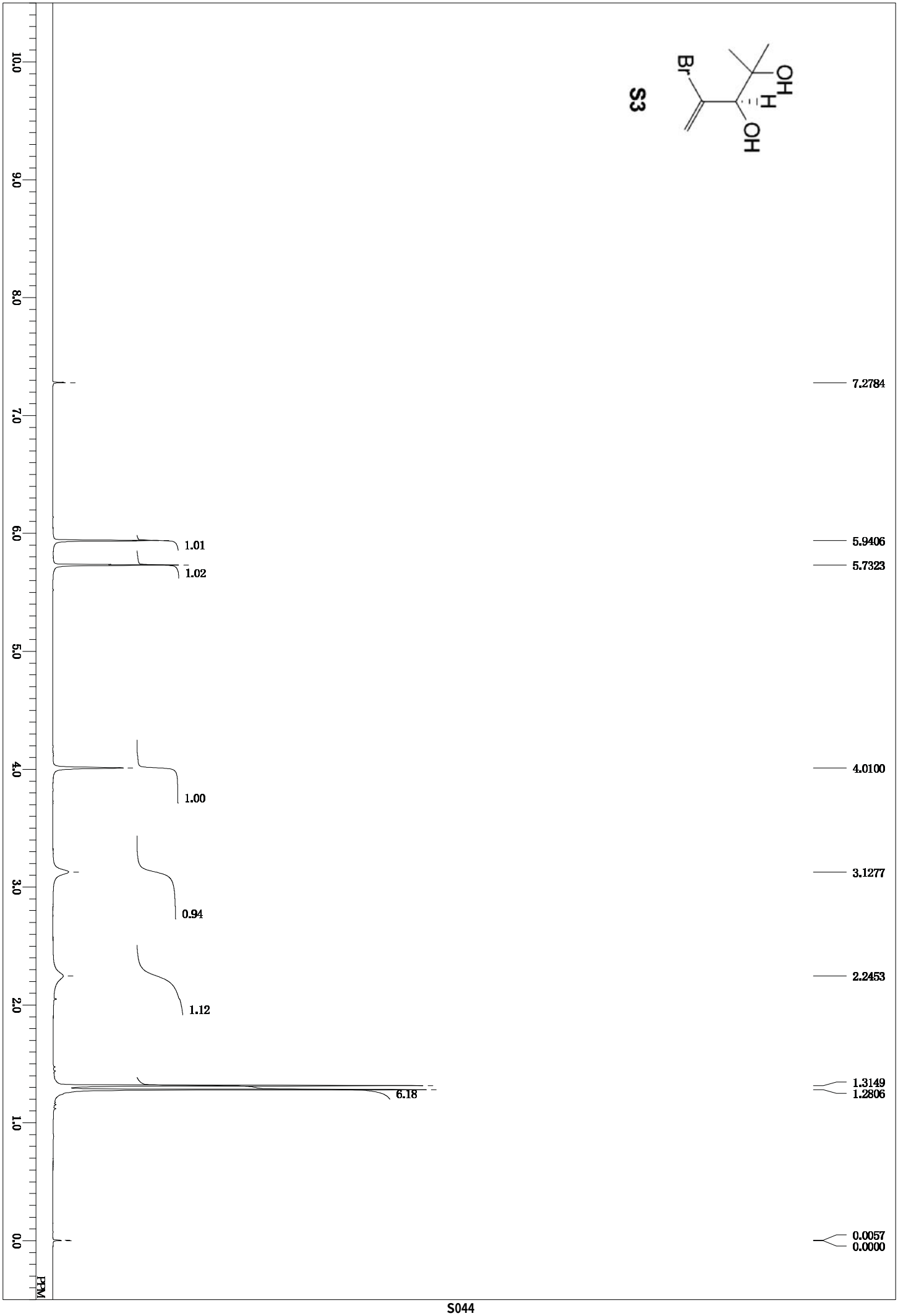
135.717
130.744
123.582
79.371
77.322
77.000
76.686
71.870
59.710
33.045
26.164
25.916
25.825
18.200
-5.533
PPM


HO
OTBS
O
O
NO2

S2


S3
Br
OH
H
OH
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
1.01
1.02
1.00
0.94
1.12
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4.0100
3.1277
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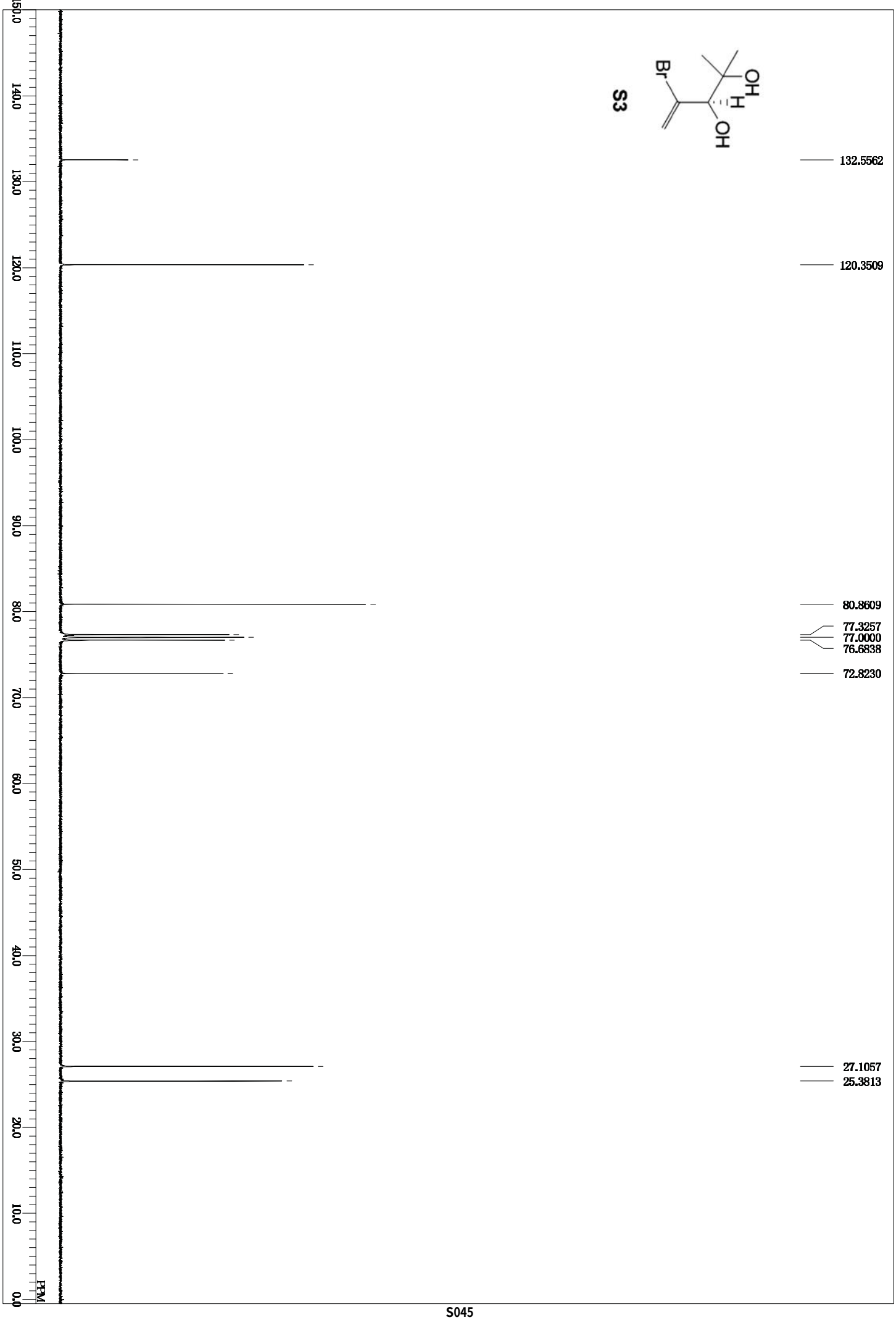
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Br
OH
H
OH
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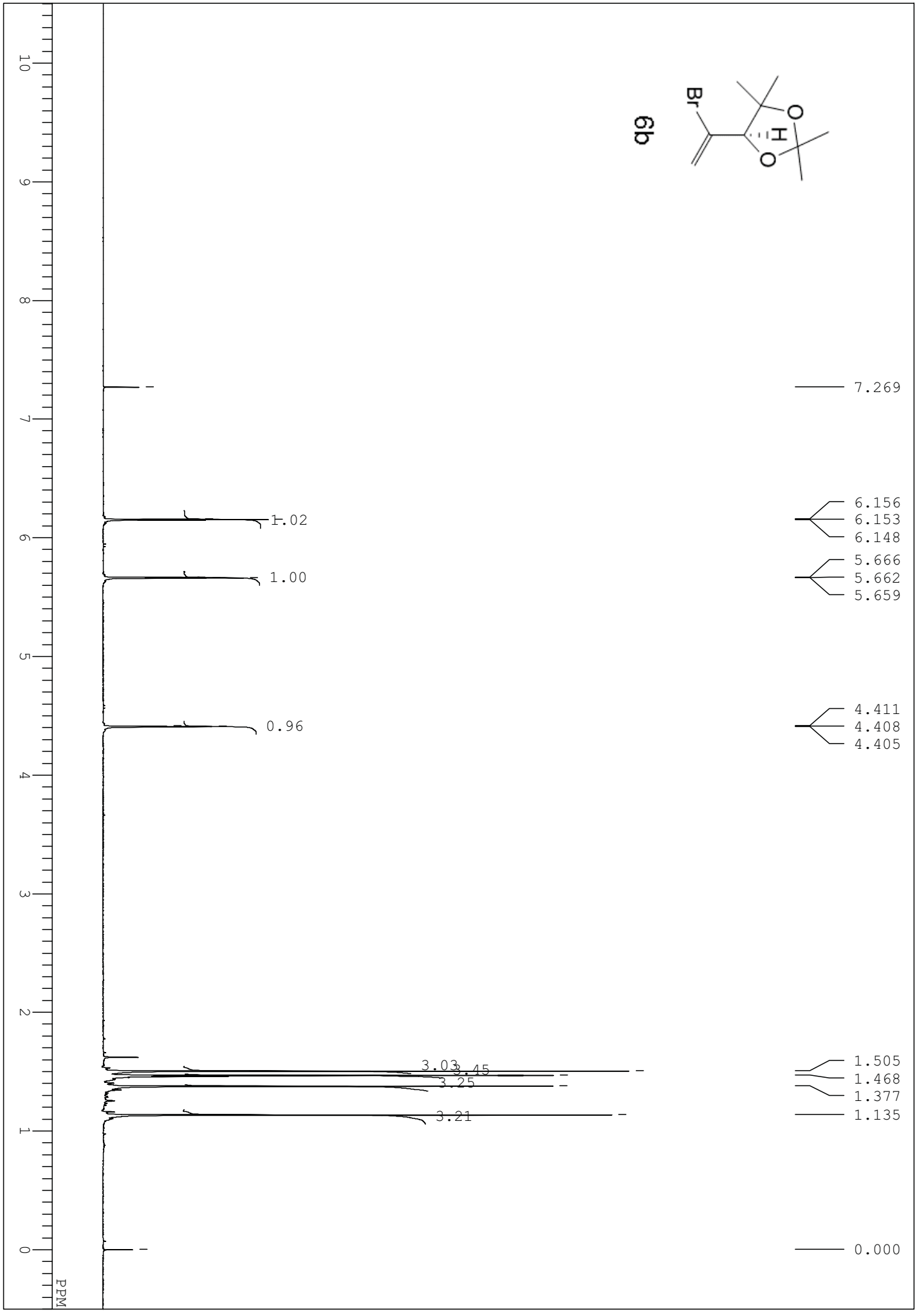
27.1057
25.3813
PPM


6b
Br
O
H
O
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6.153
6.148
5.666
5.662
5.659
4.411
4.408
4.405
1.505
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1.00
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3.03
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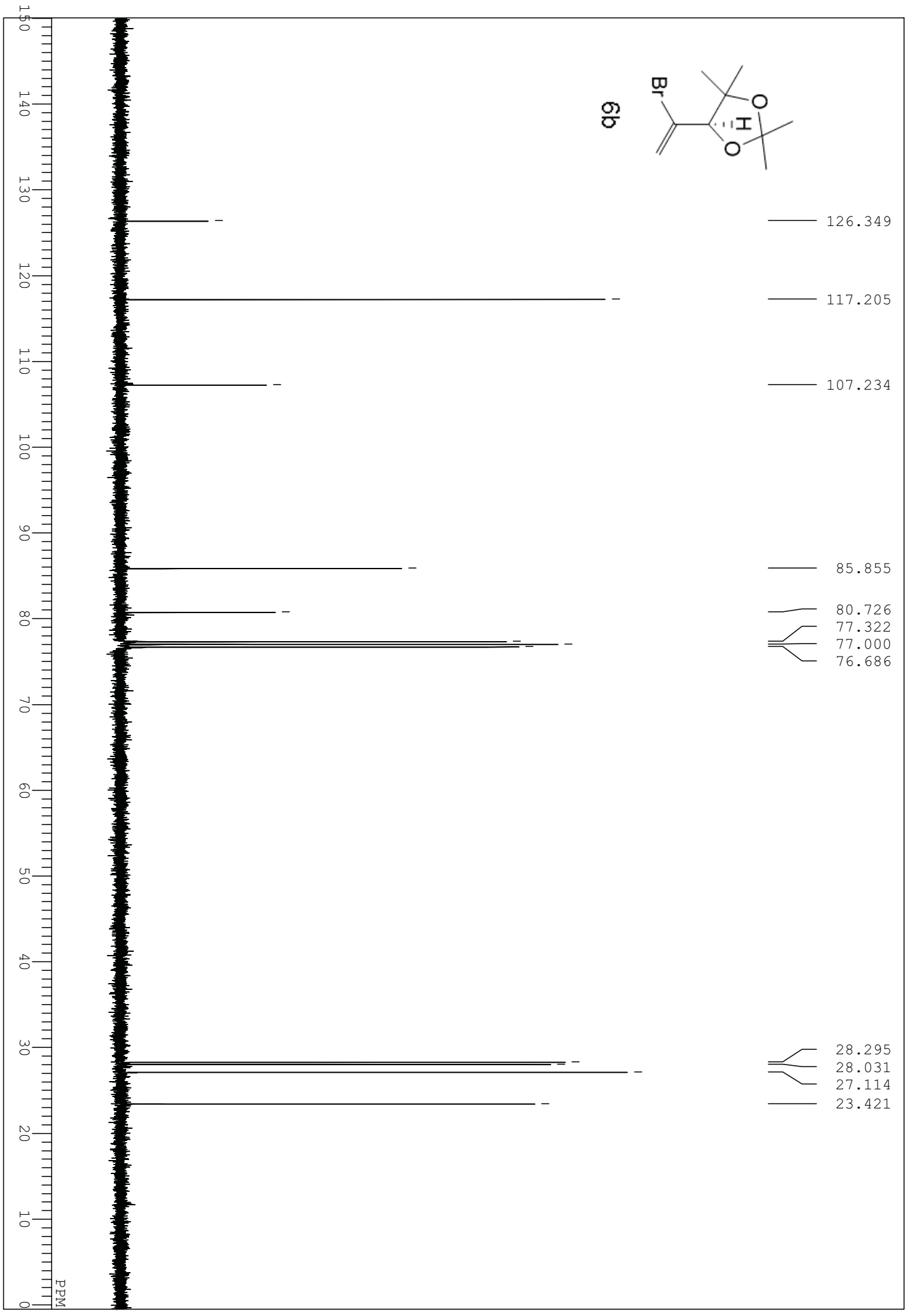
PPM


6b
Br
O
H
O
126.349
117.205
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85.855
80.726
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77.000
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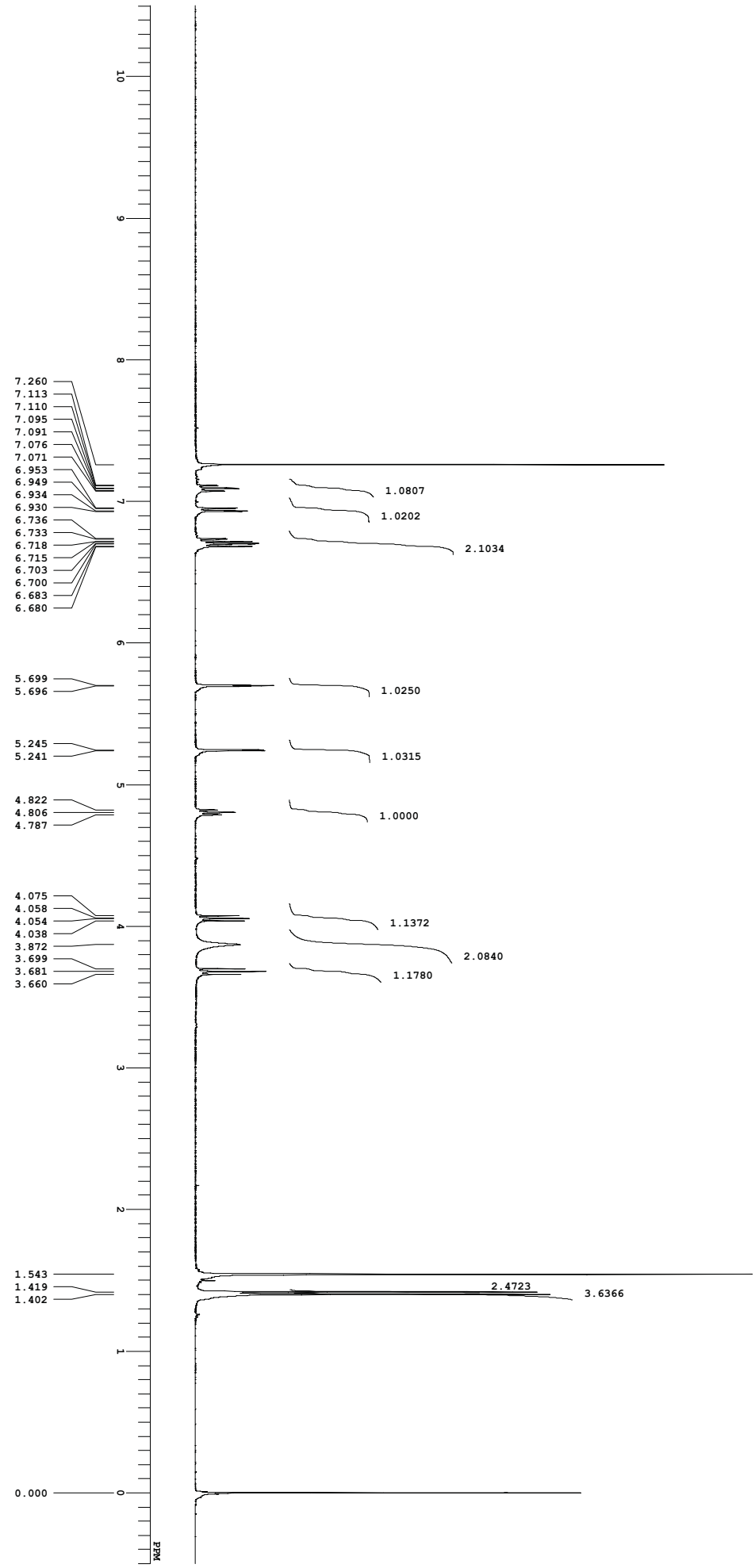
28.295
28.031
27.114
23.421
PPM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7.110
7.095
7.091
7.076
7.071
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6.934
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6.736
6.733
6.718
6.715
6.703
6.700
6.683
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5.699
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4.822
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4.058
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3.872
3.699
3.681
3.660
1.543
1.419
1.402
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1.0807
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1.0000
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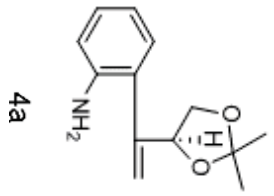
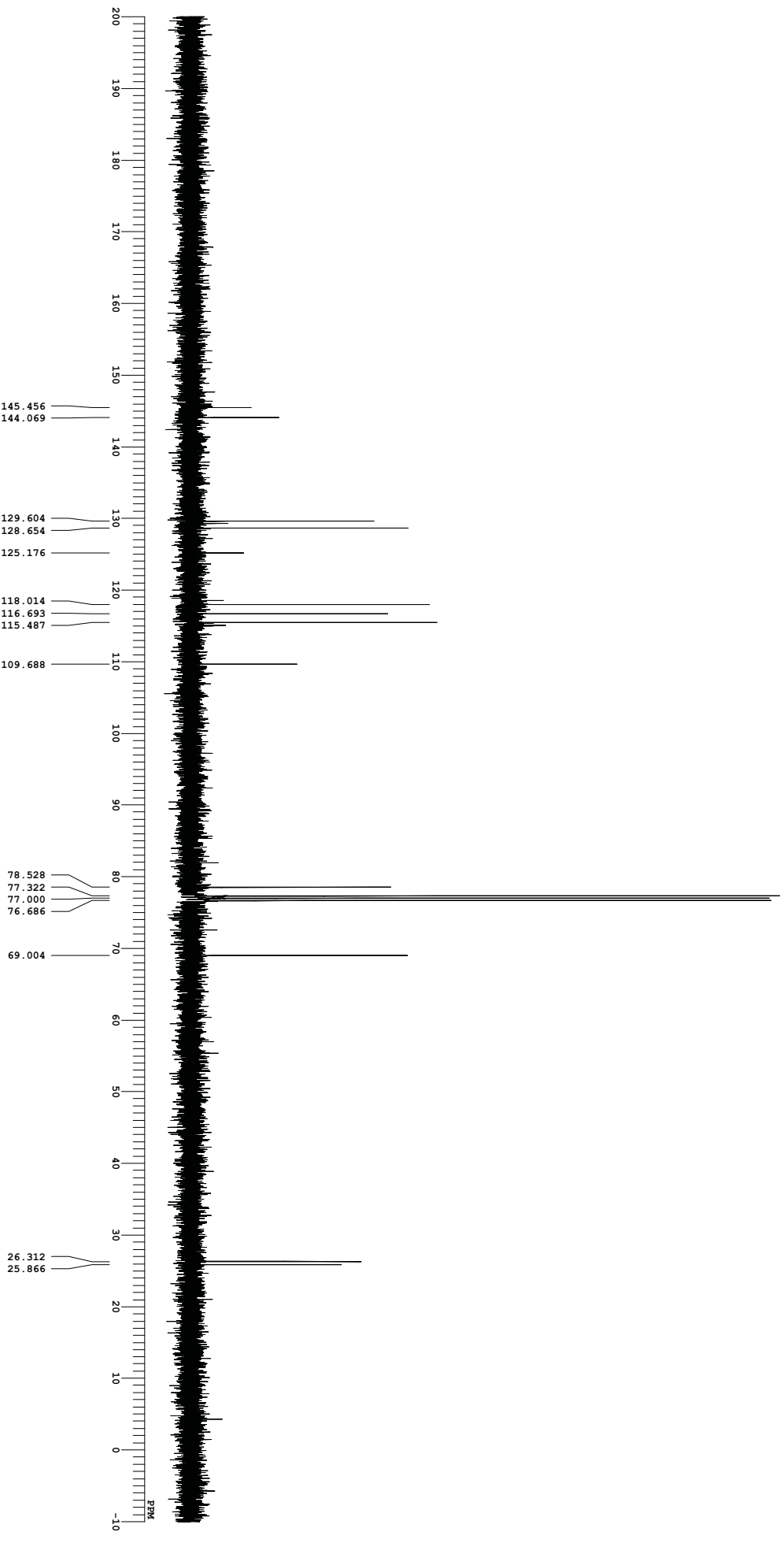

NH2
O
H
O

4a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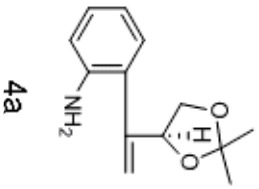
25.866
PPM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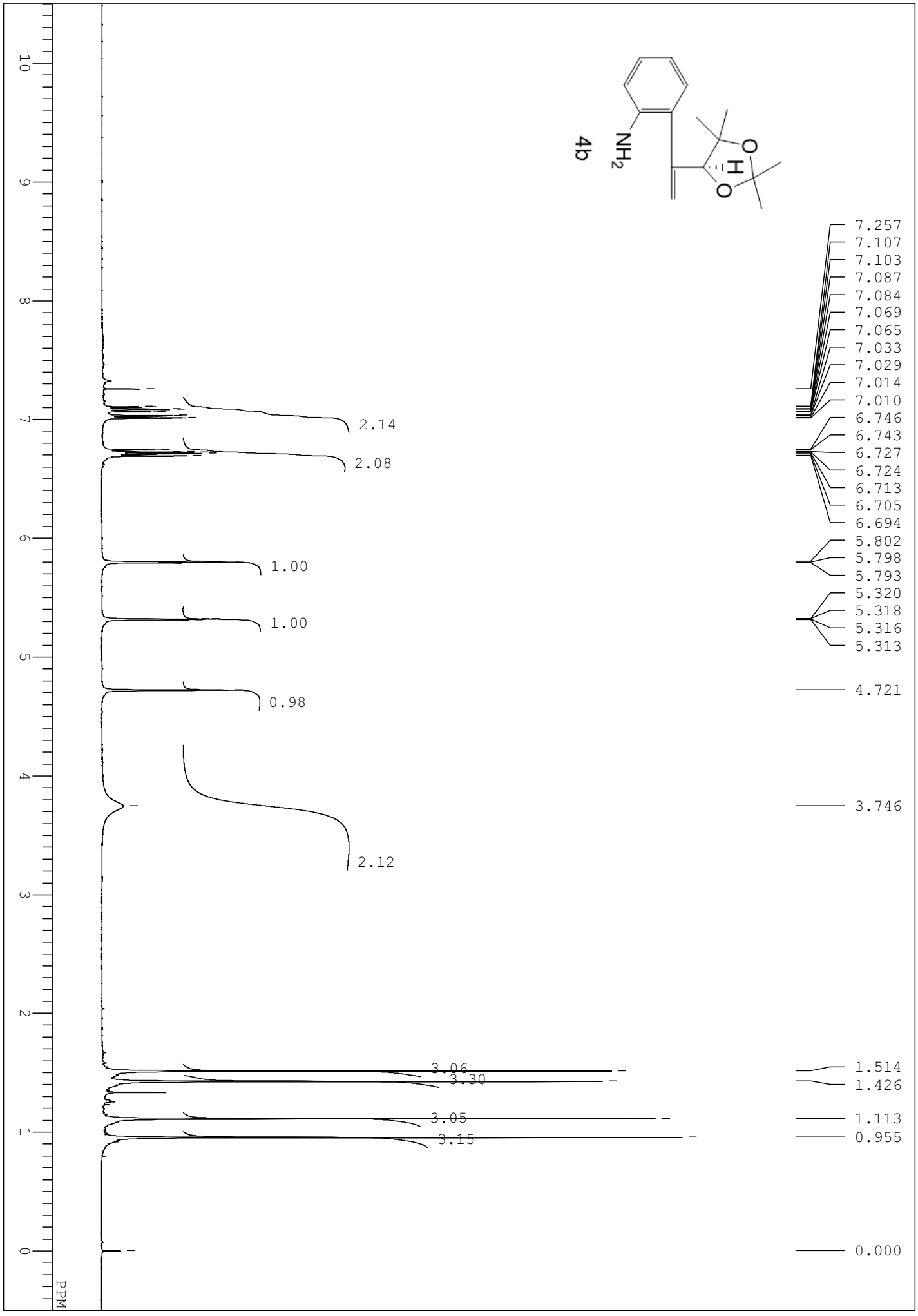
O
H
O

4a


4b
NH2
O
H
O
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7.084
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7.065
7.033
7.029
7.014
7.010
6.746
6.743
6.727
6.724
6.713
6.705
6.694
5.802
5.798
5.793
5.320
5.318
5.316
5.313
4.721
3.746
1.514
1.426
1.113
0.955
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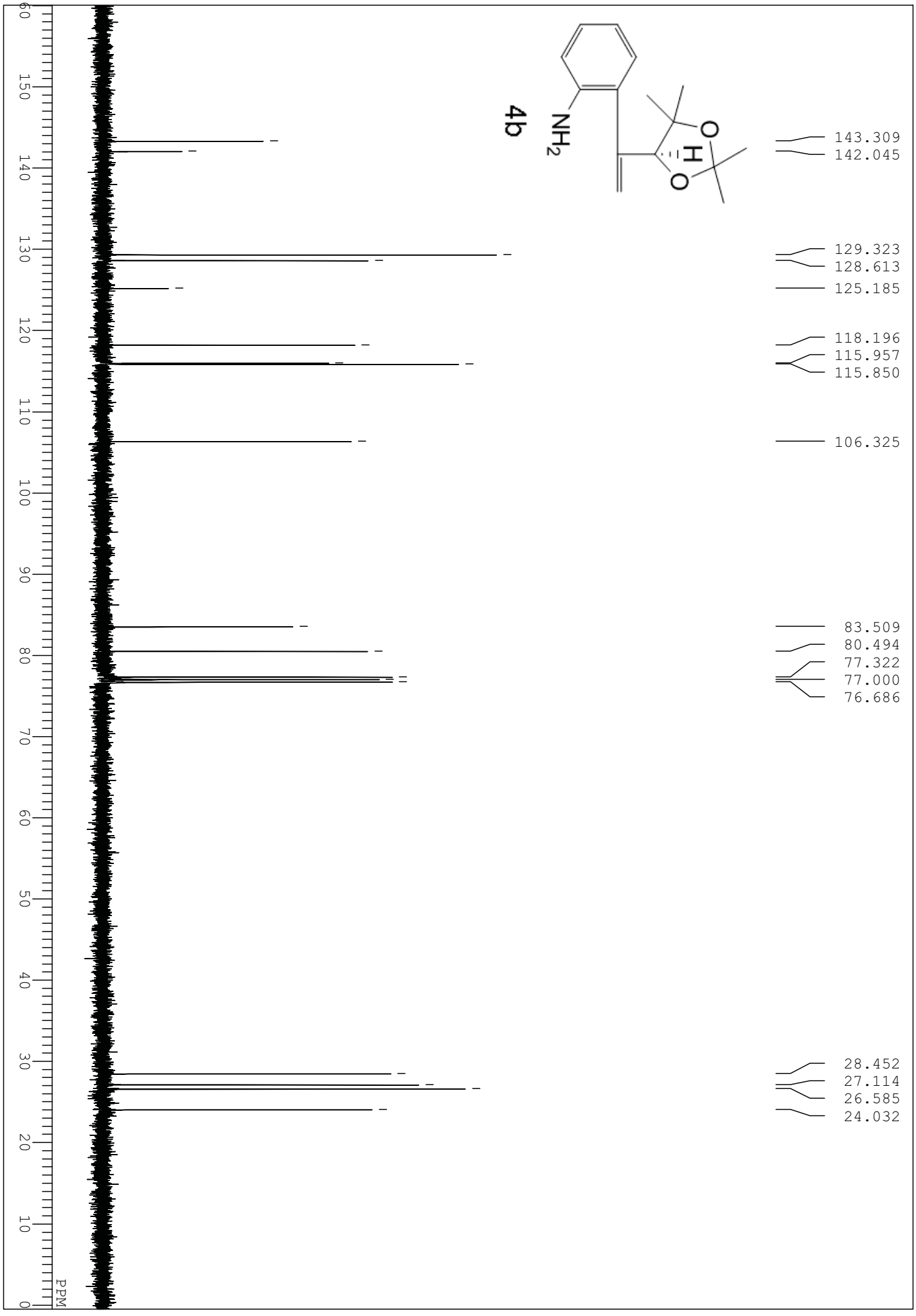
4b
NH2
O
H
O
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125.185
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115.957
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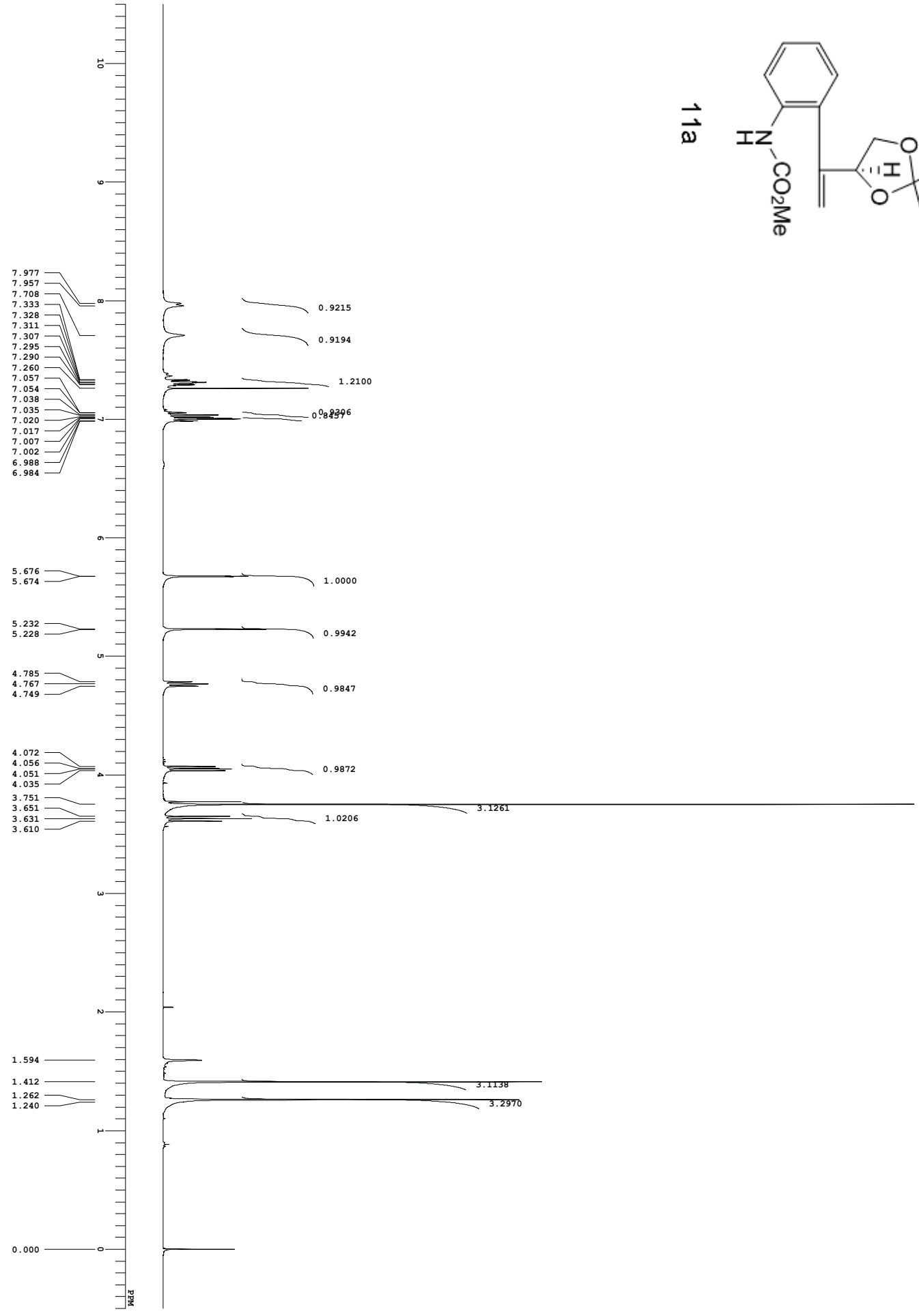
28.452
27.114
26.585
24.032
PPM


11a
N
H
CO2Me
O
H
O
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7.957
7.708
7.333
7.328
7.311
7.307
7.295
7.290
7.260
7.057
7.054
7.038
7.035
7.020
7.017
7.007
7.002
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6.984
5.676
5.674
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5.228
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4.767
4.749
4.072
4.056
4.051
4.035
3.751
3.651
3.631
3.610
1.594
1.412
1.262
1.240
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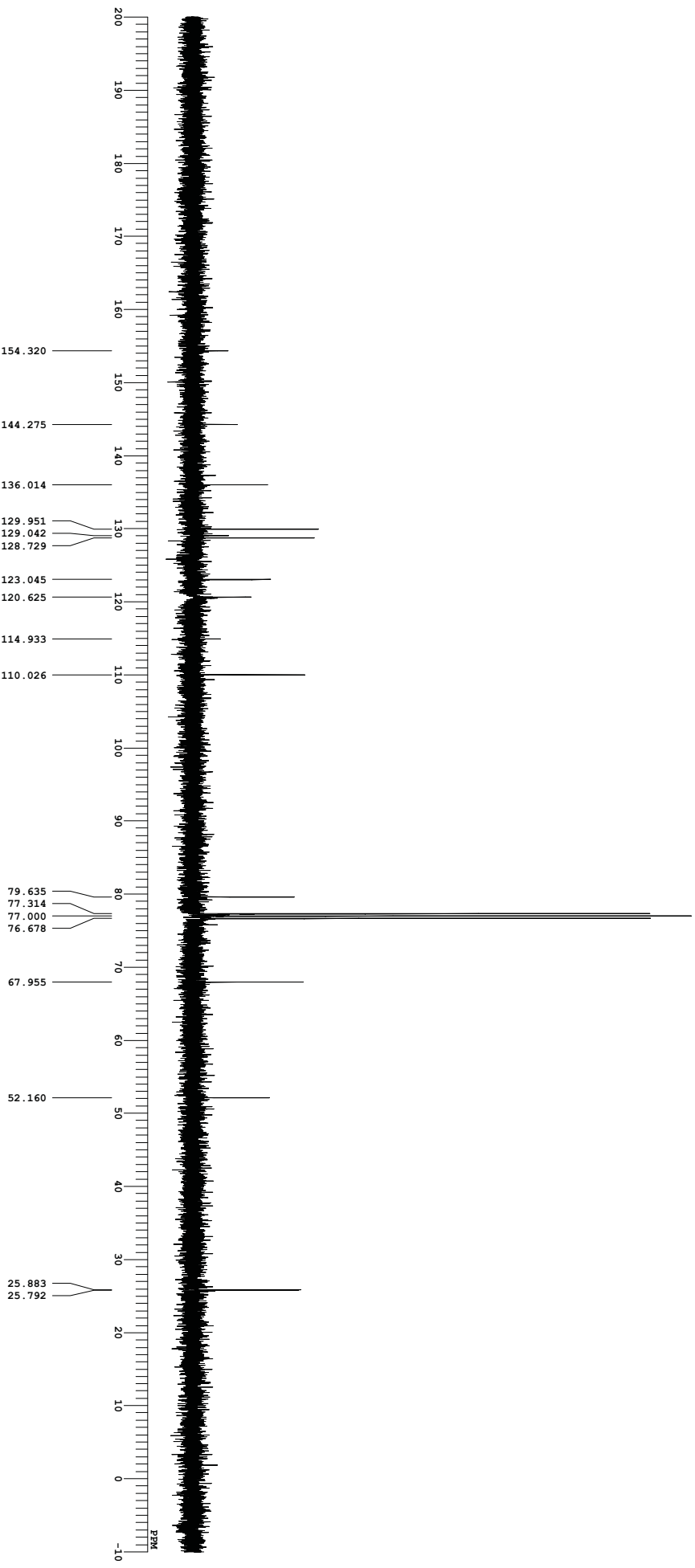
PPM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76.678
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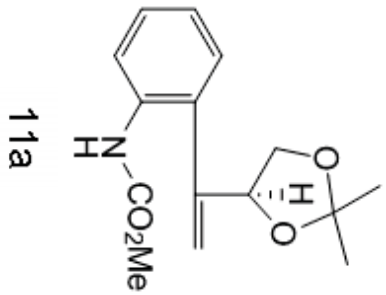
25.883
25.792
PPM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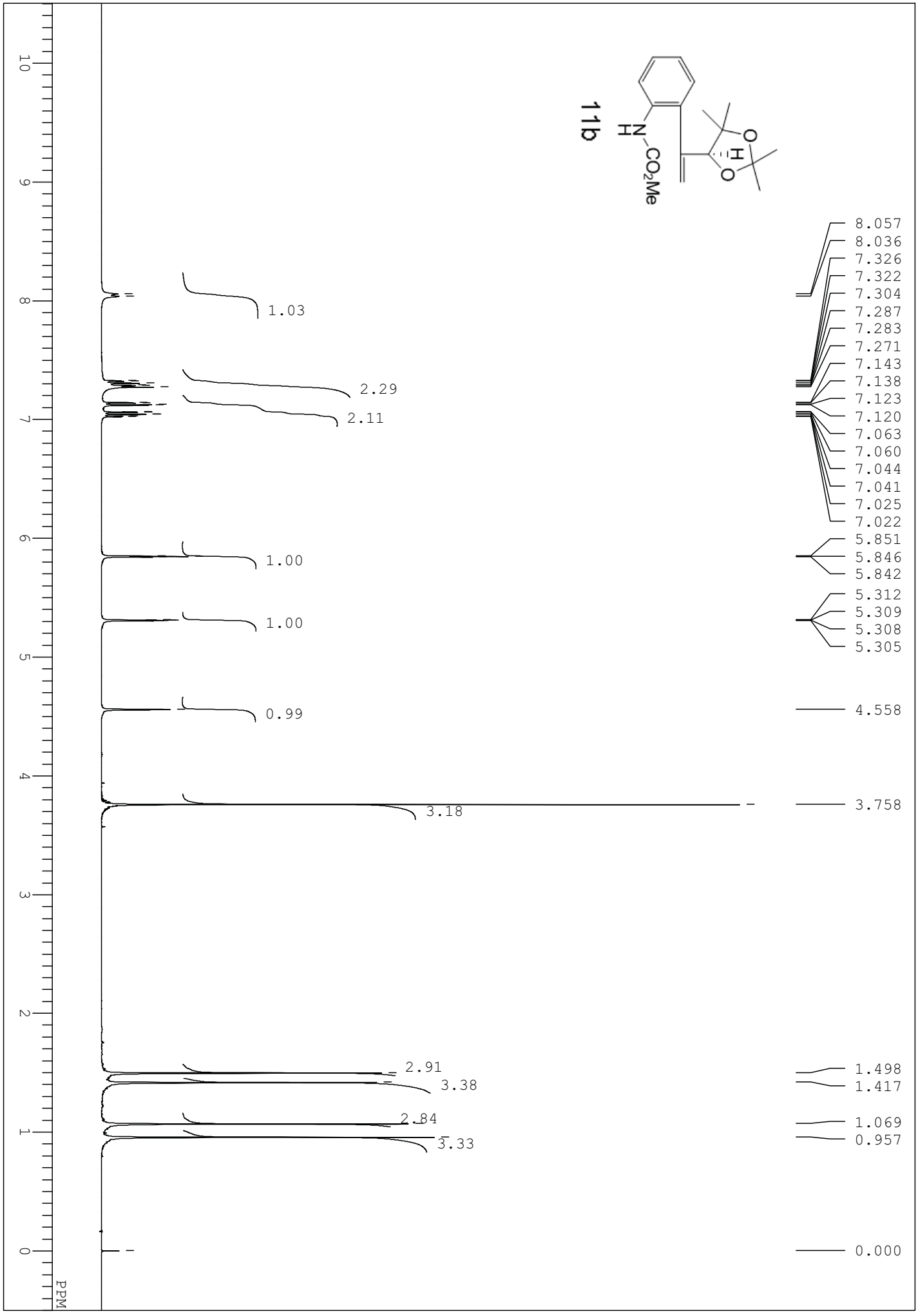
CO2Me
O
H
O

11a


11b
N
H
CO2Me
O
H
O
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8.036
7.326
7.322
7.304
7.287
7.283
7.271
7.143
7.138
7.123
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7.063
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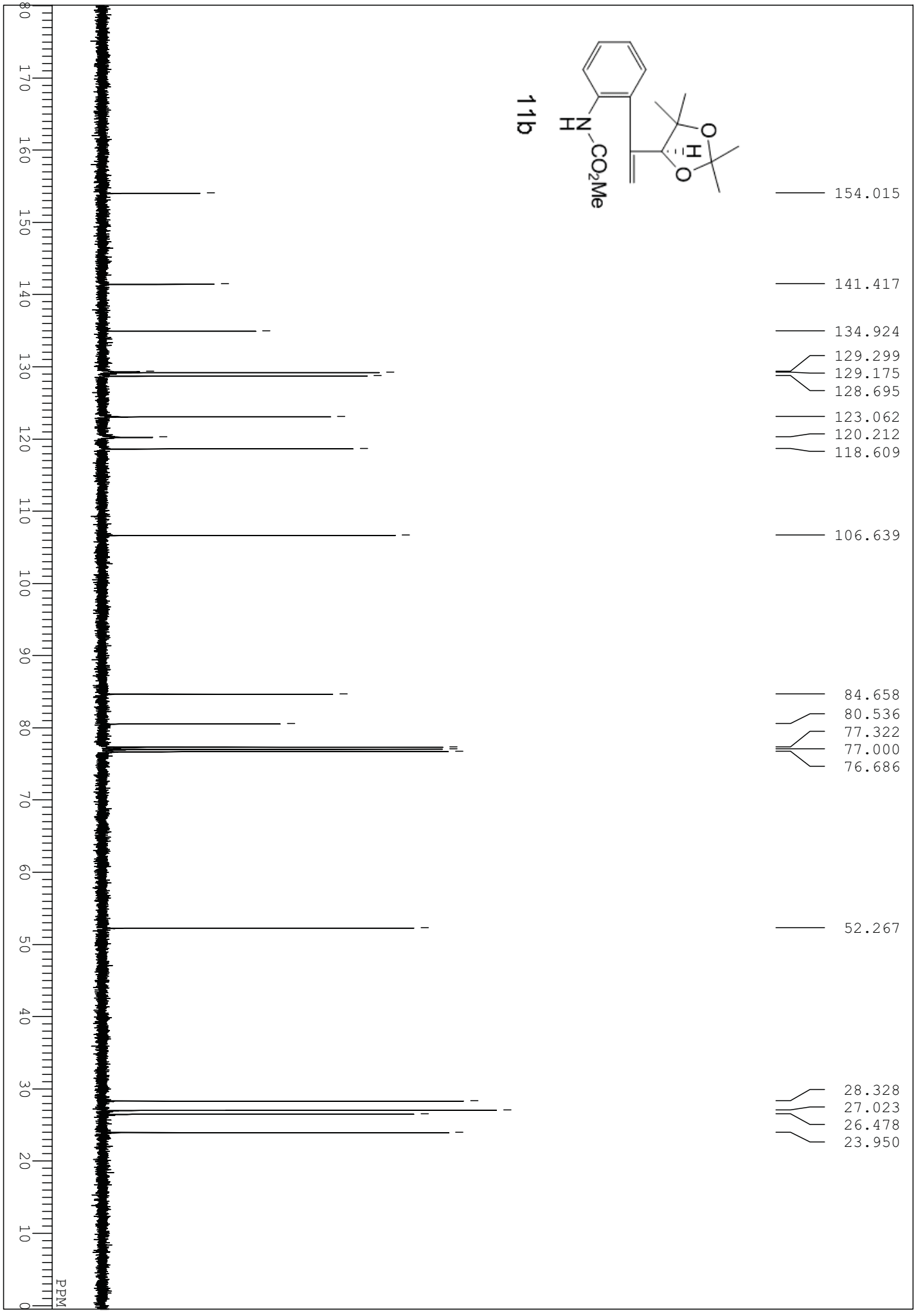
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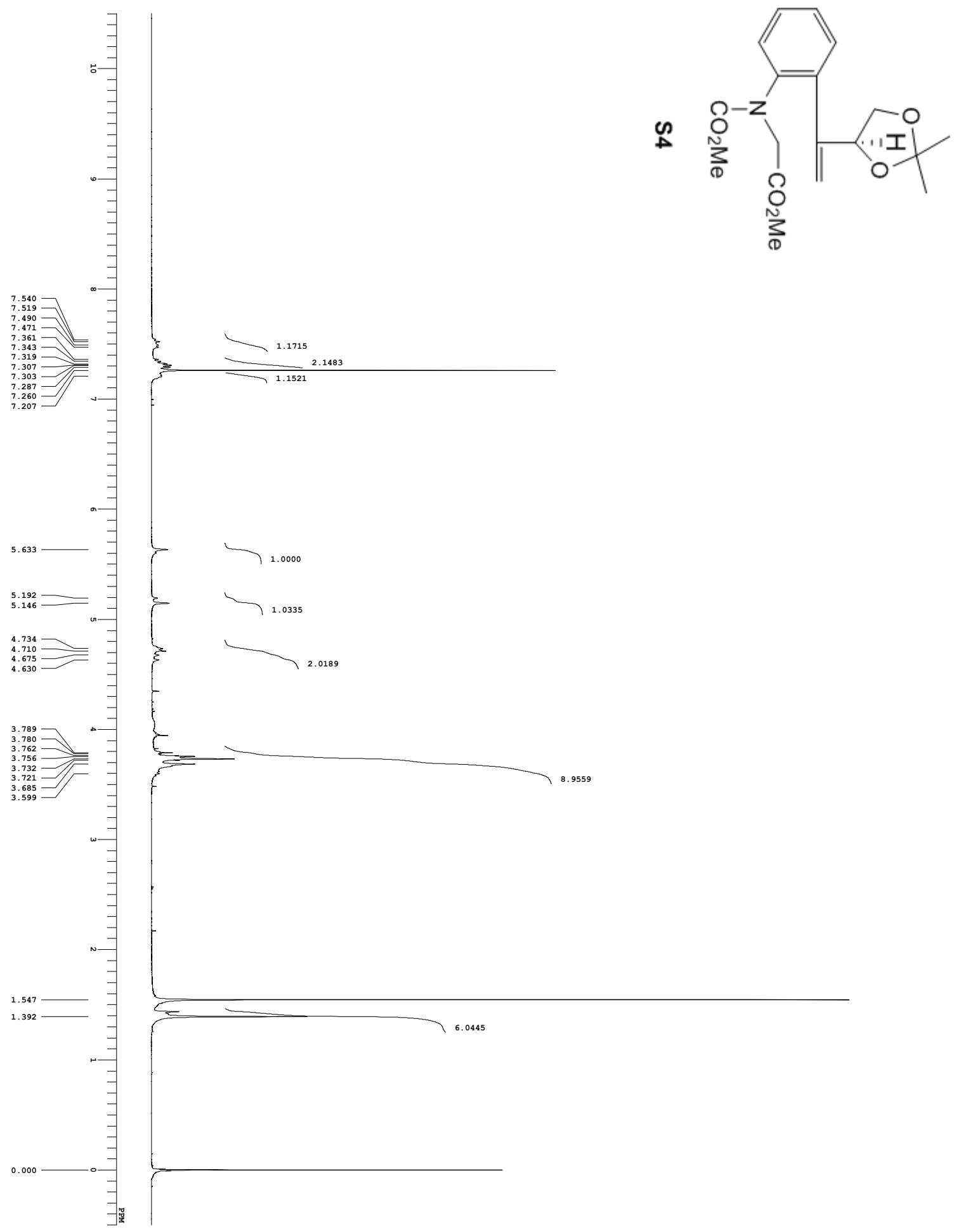
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7.207
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1.1521
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5.146
1.0335
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4.710
4.675
4.630
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3.789
3.780
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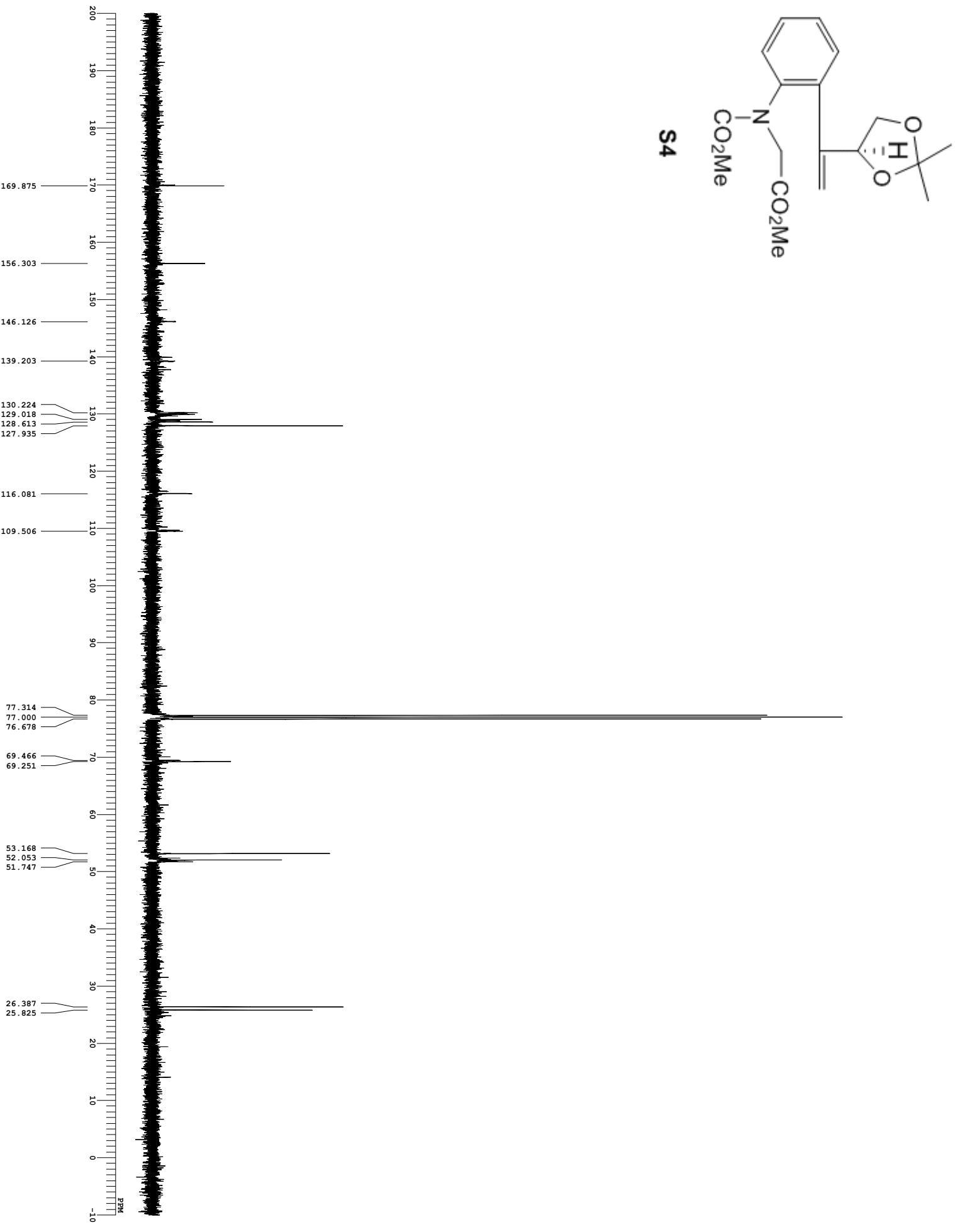
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76.678
69.466
69.251
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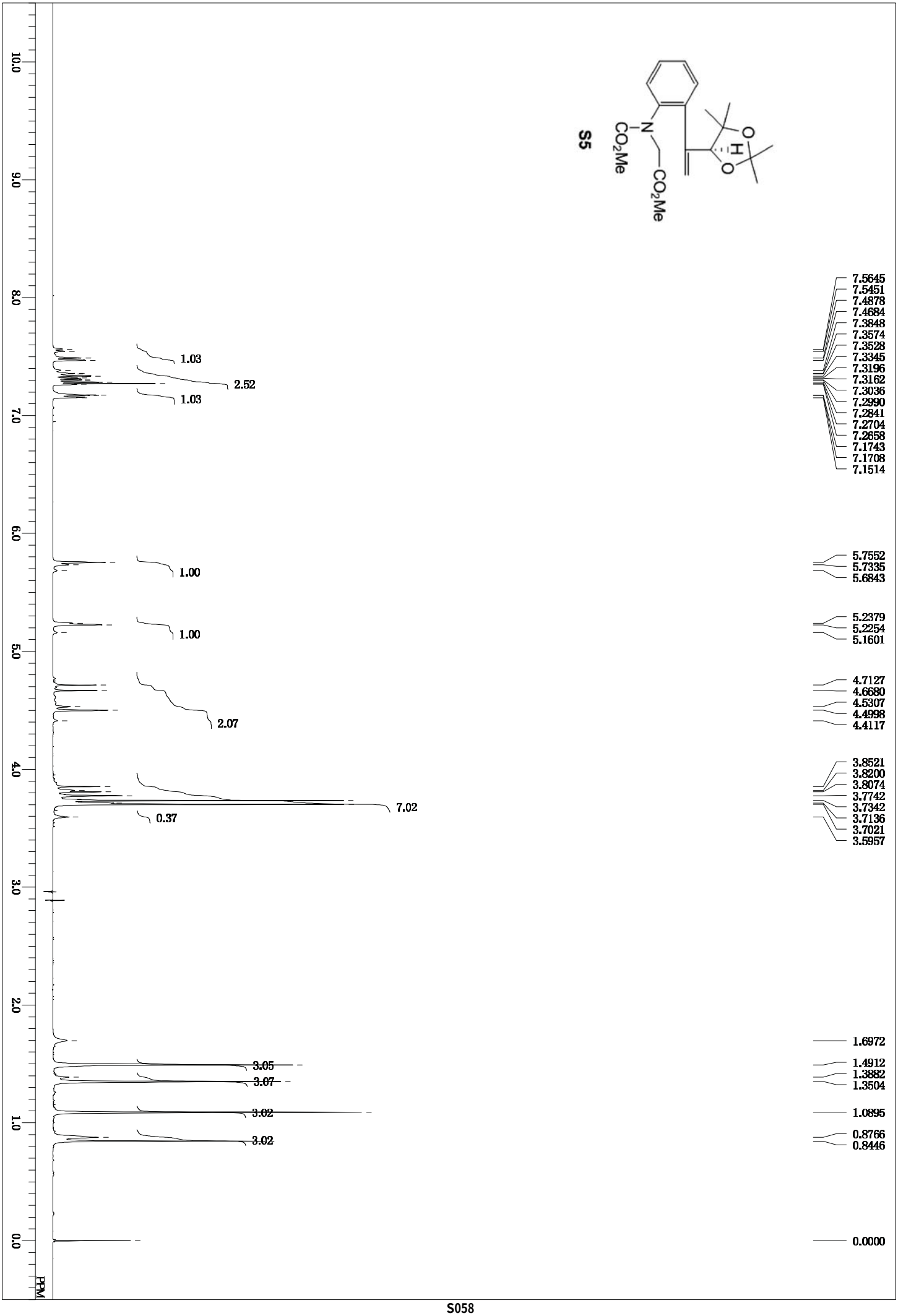
PPM
N
CO2Me
CO2Me
O
H
O

S4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CO2Me
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0.0
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1.00
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3.07
3.02
3.02
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3.8200
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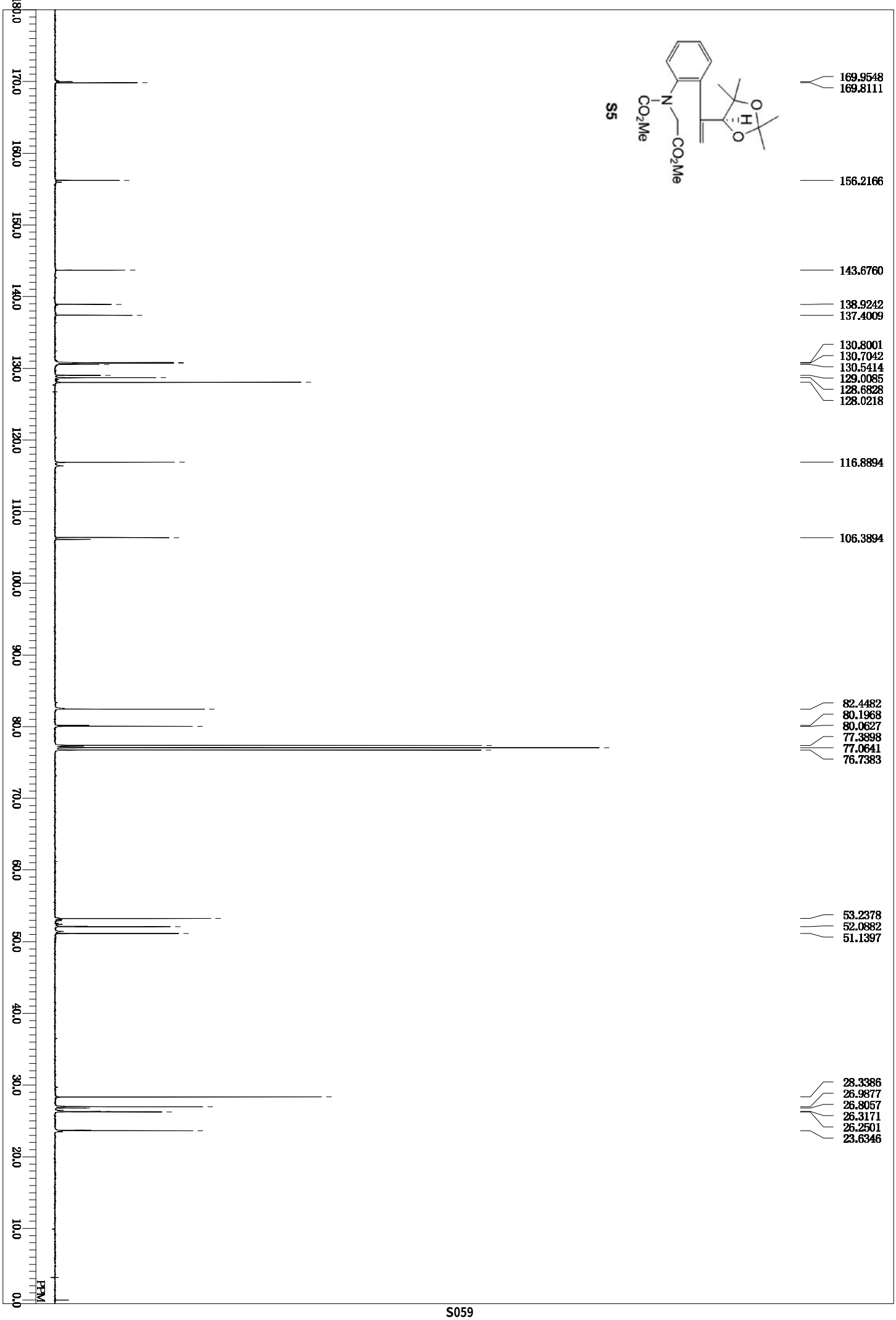
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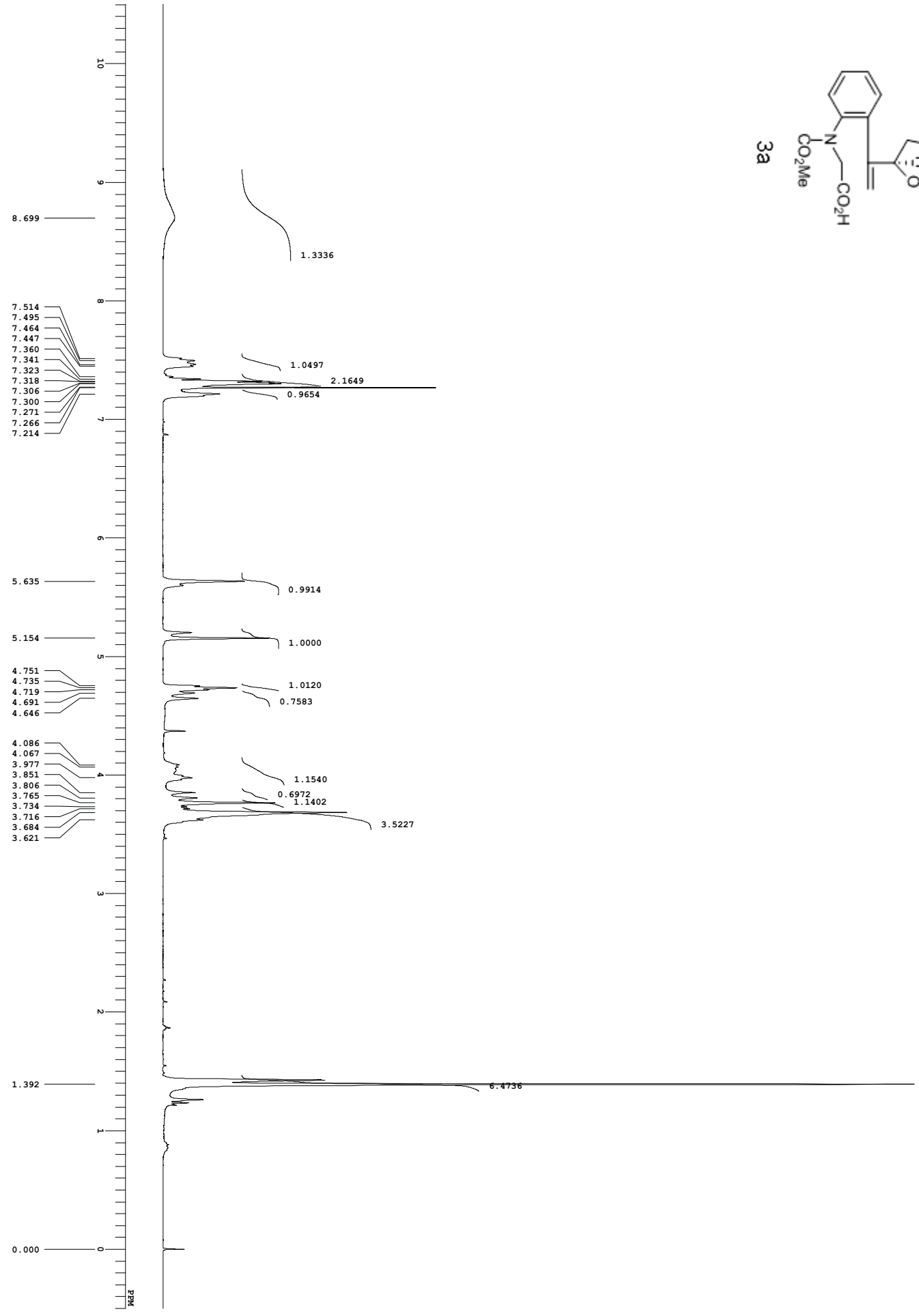
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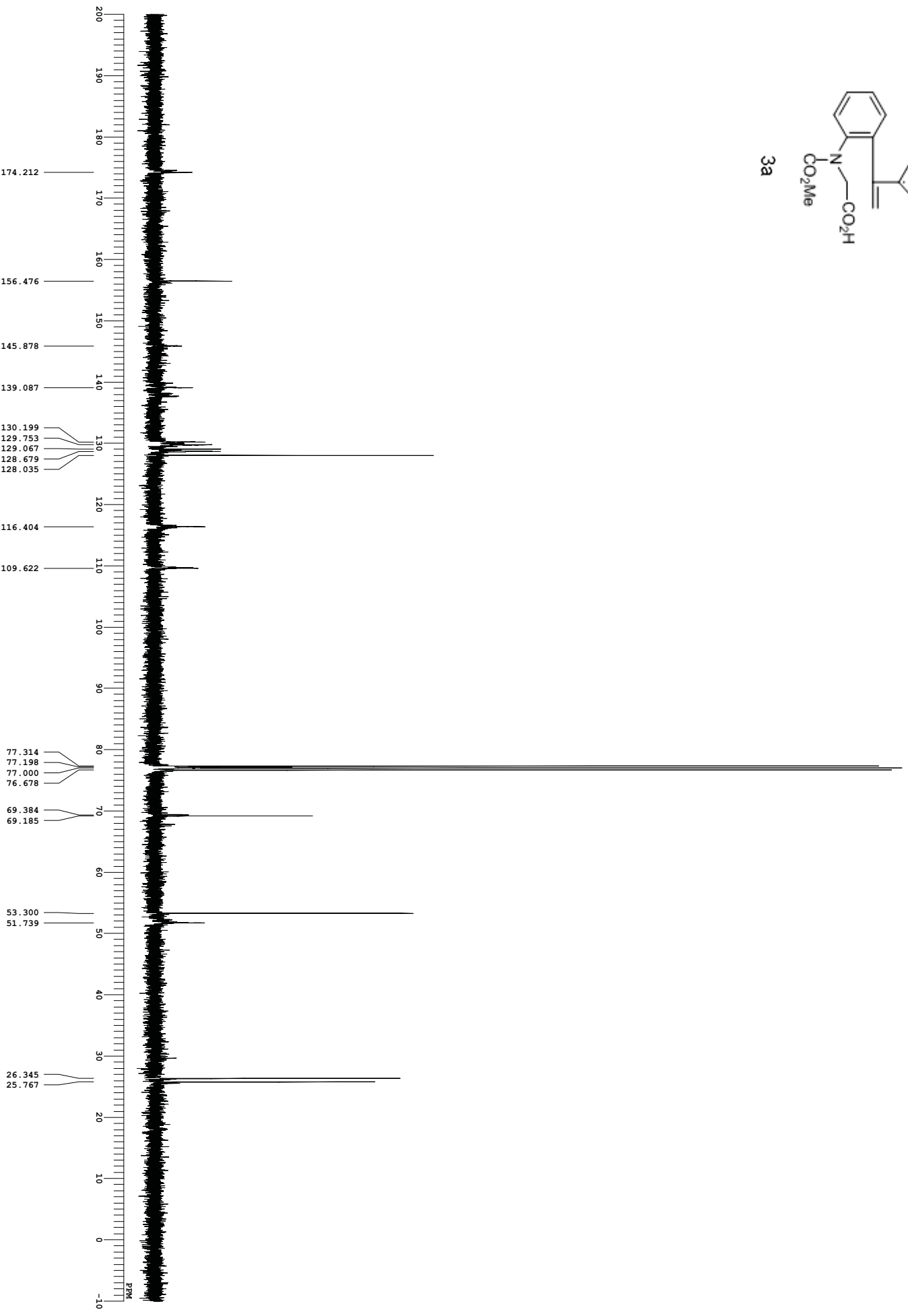
O
H
O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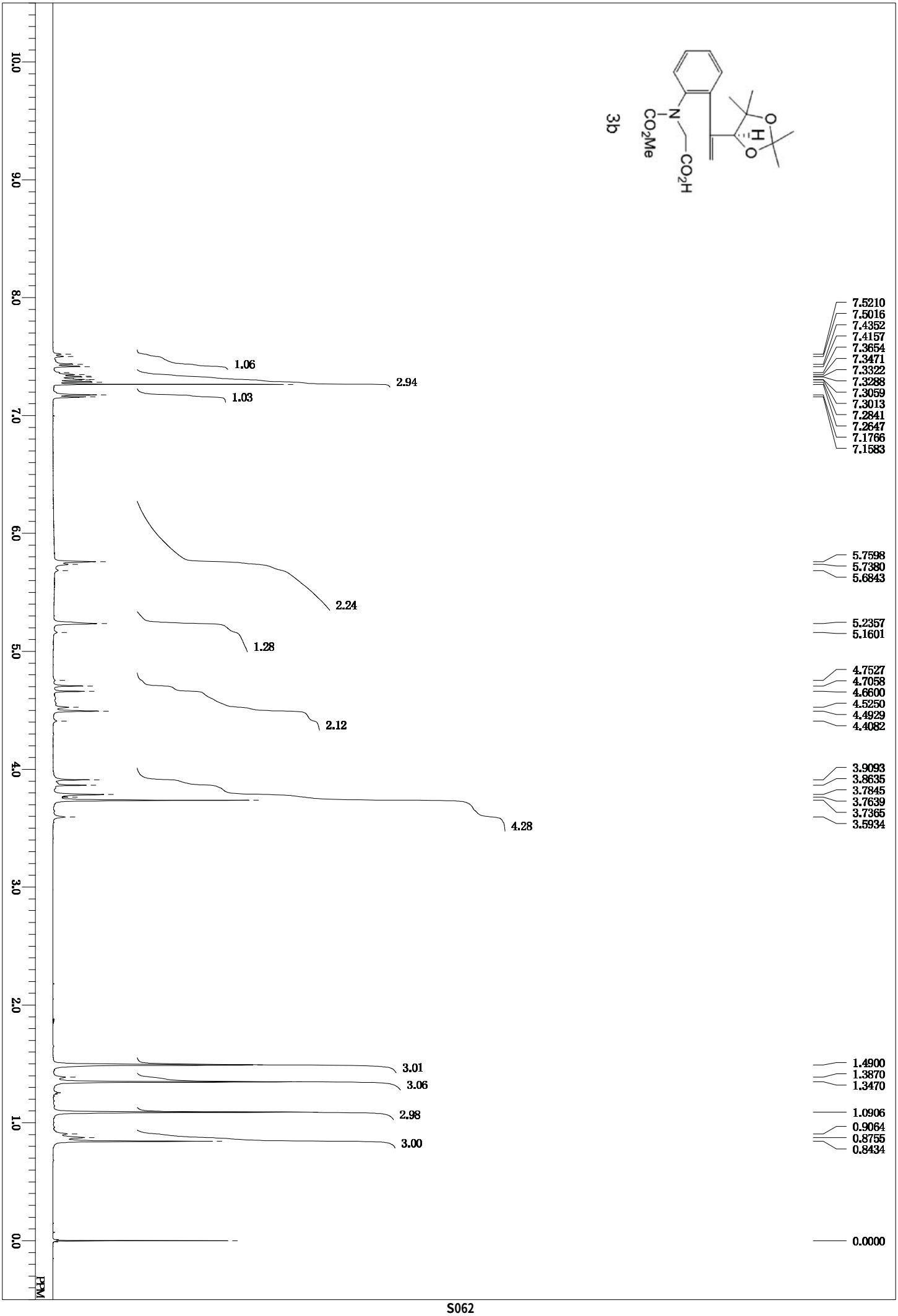
CO2H
O
H
O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CO2H
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7.3059
7.3013
7.2841
7.2647
7.1766
7.1583
5.7598
5.7380
5.6843
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5.1601
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4.5250
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3.7639
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2.94
1.03
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1.28
2.12
4.28
3.01
3.06
2.98
3.00
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3.0
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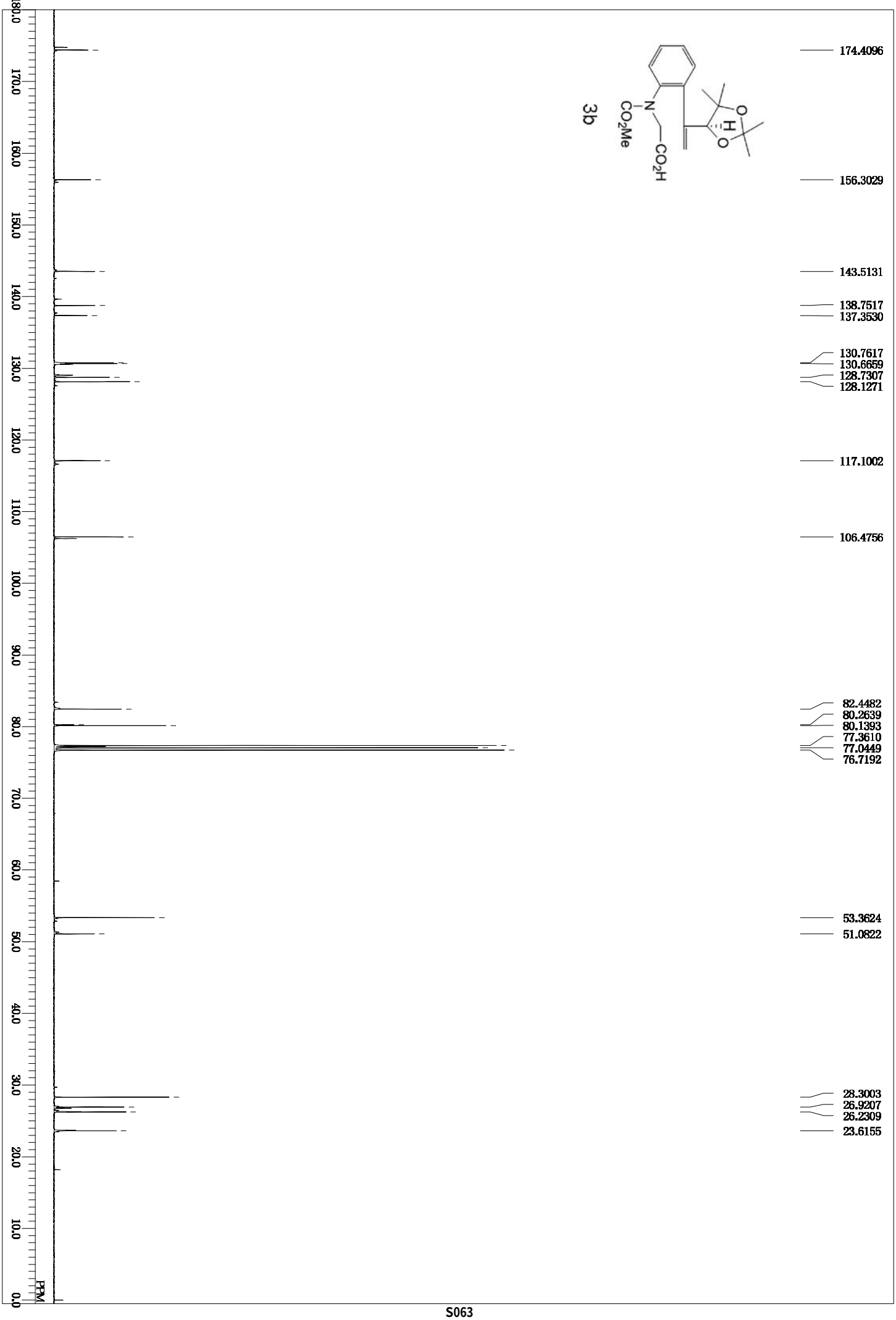
0.0
PPM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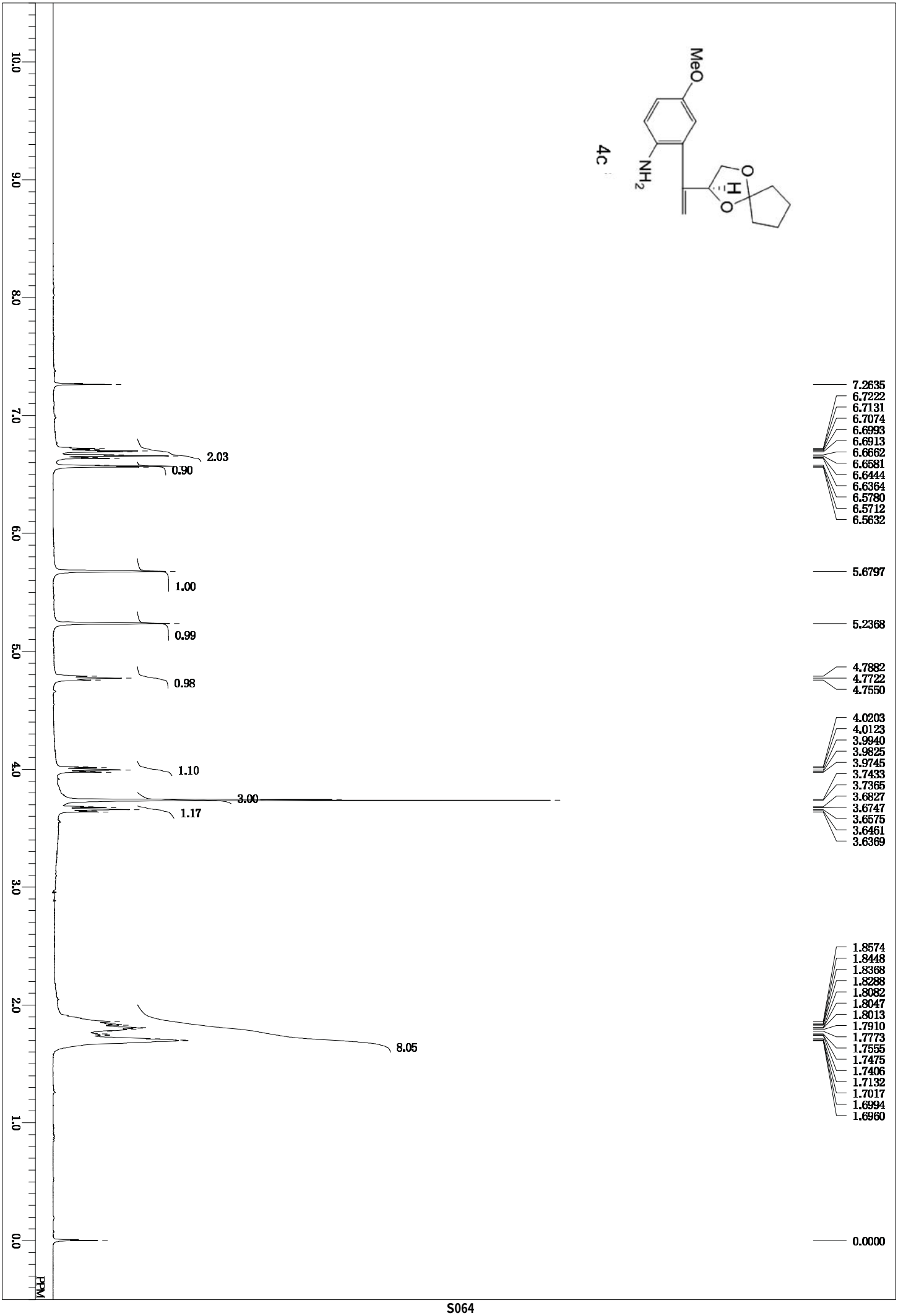
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H
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1.0
0.0
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1.00
0.99
0.98
1.10
3.00
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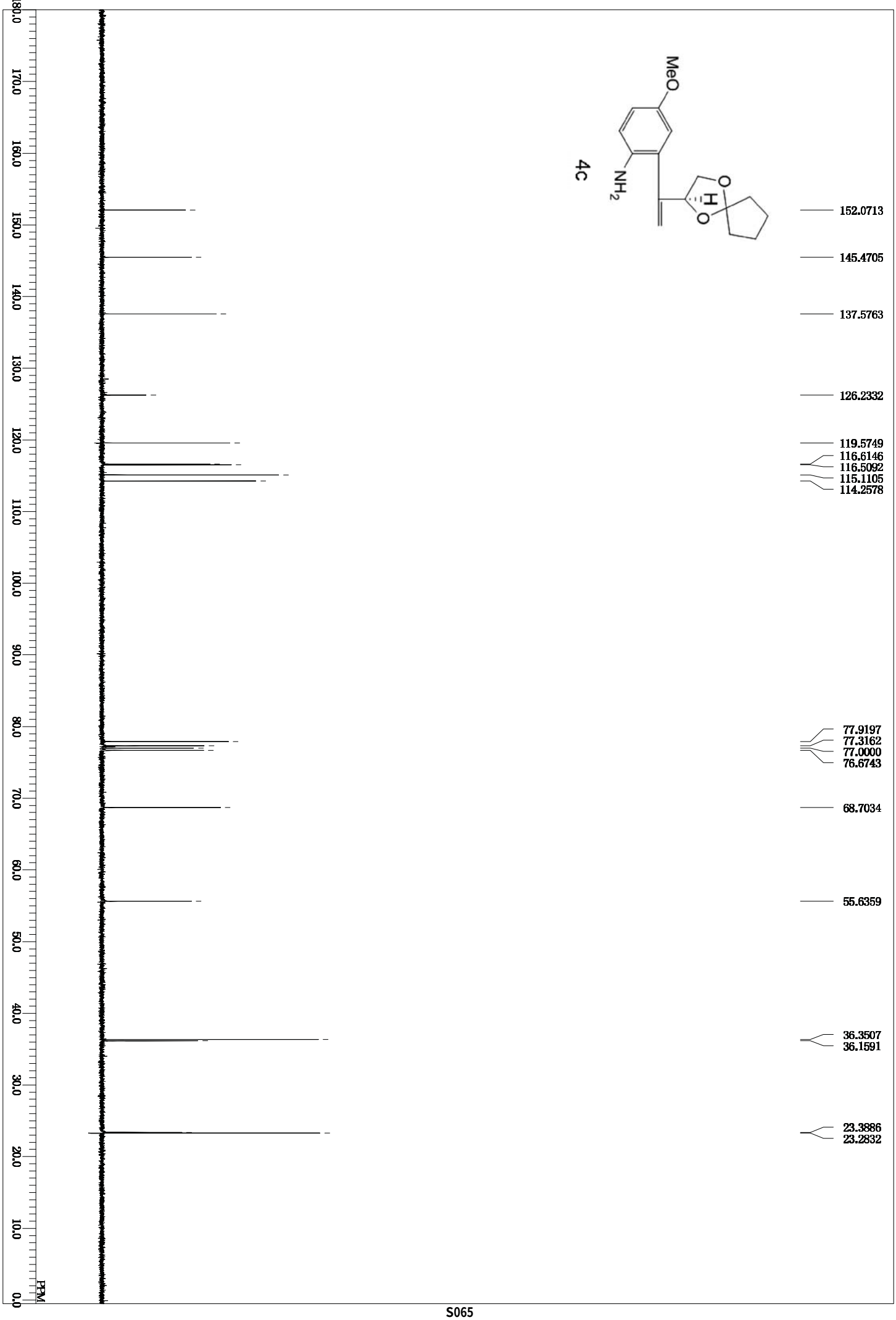
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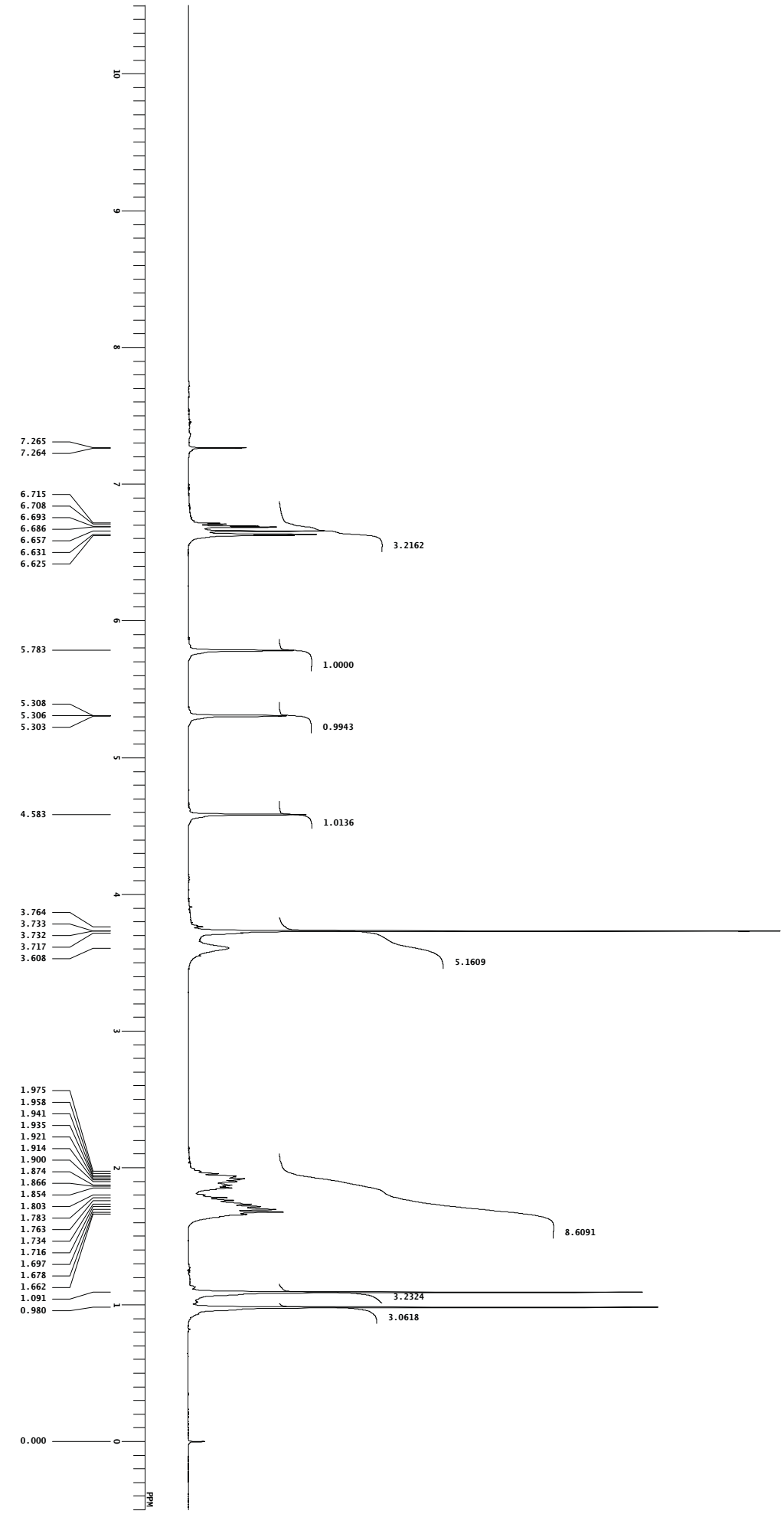
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5.303
4.583
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3.732
3.717
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1.941
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1.921
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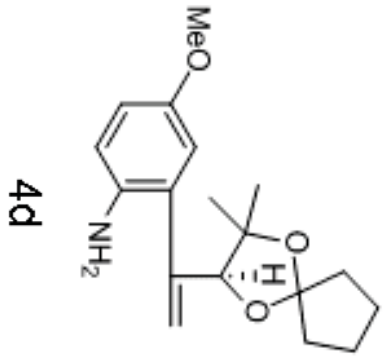
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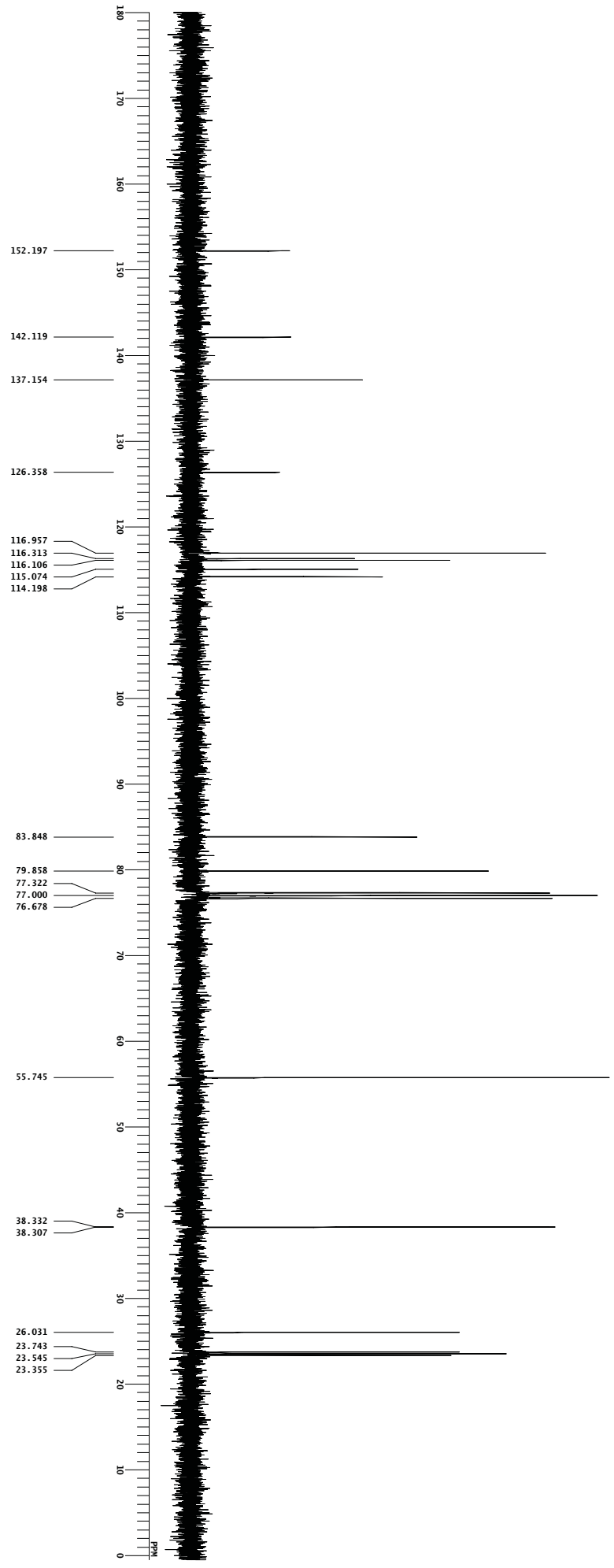
O

4d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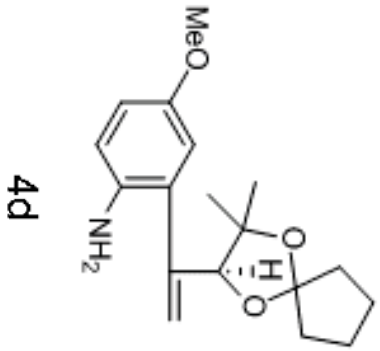
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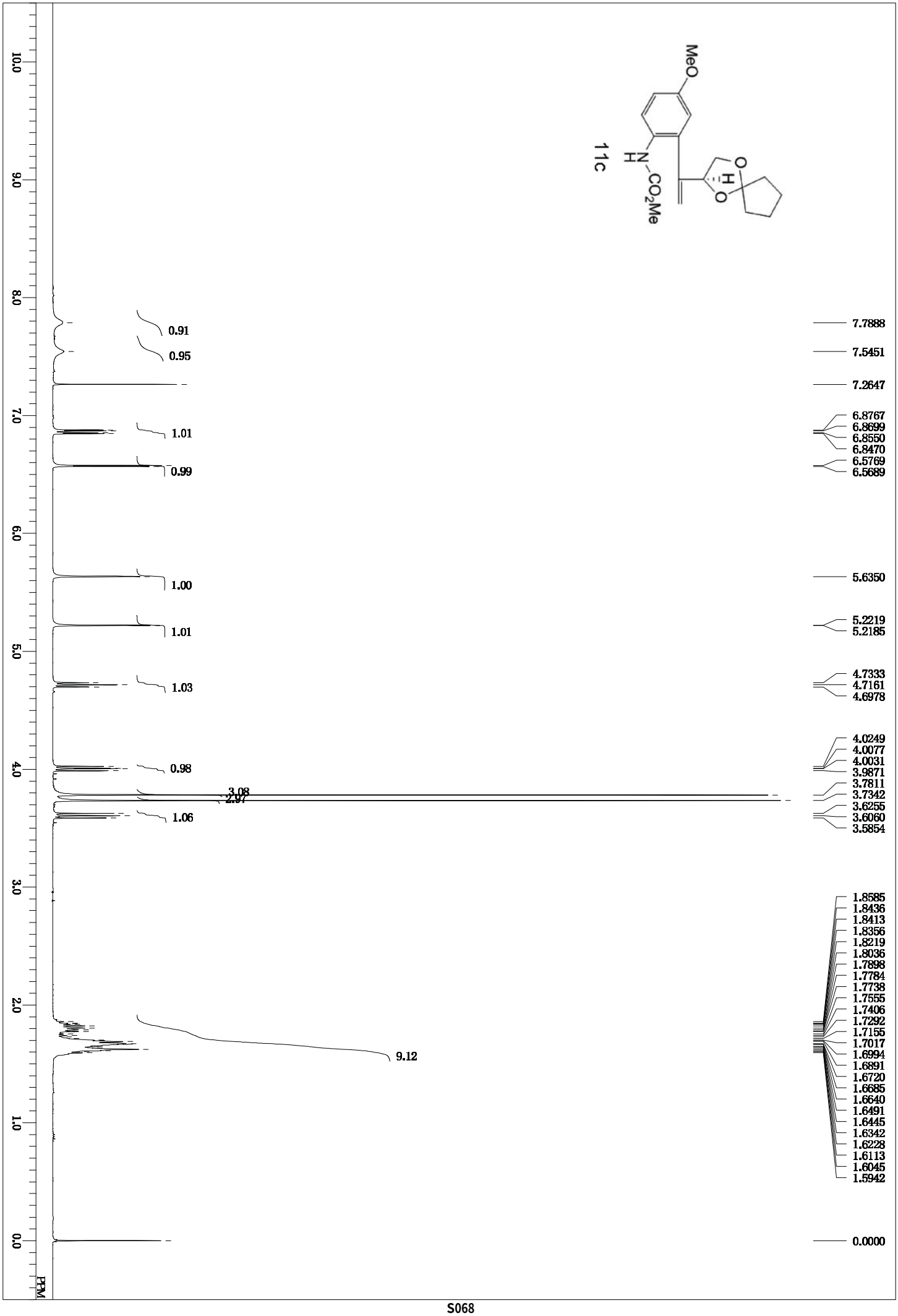
O
H
O

4d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O
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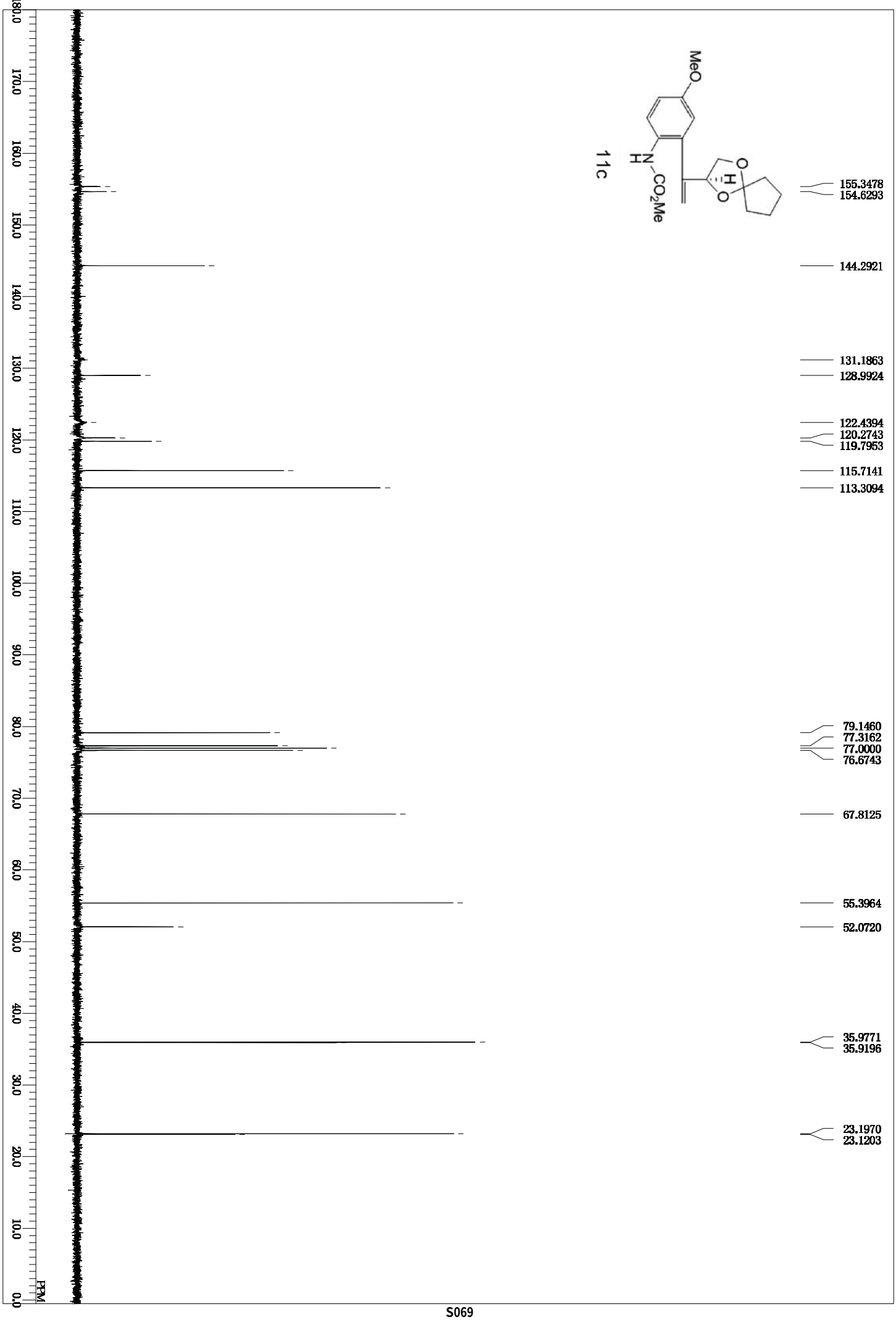
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H
CO2Me
O
H
O
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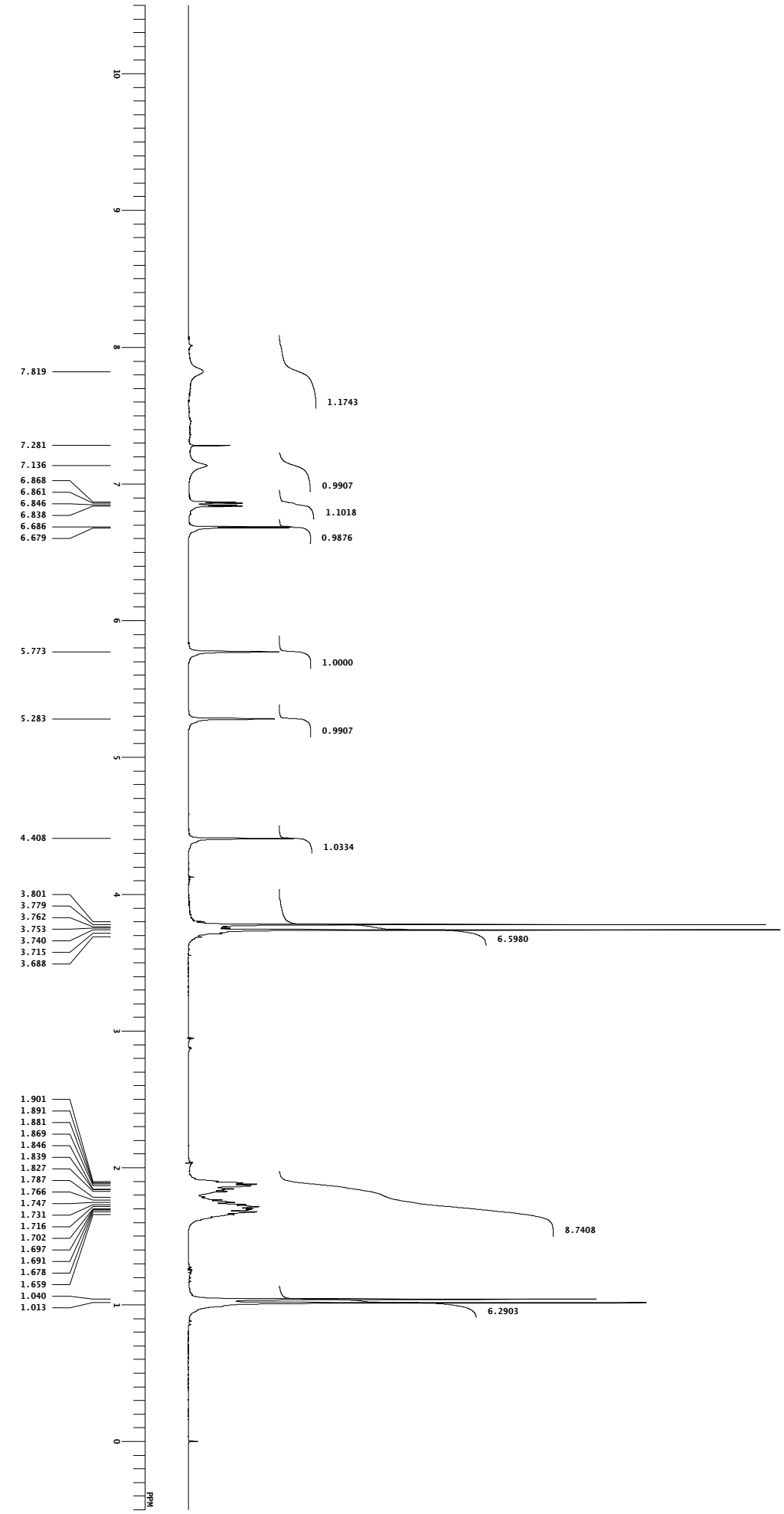
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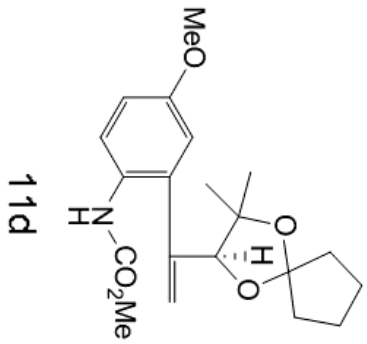
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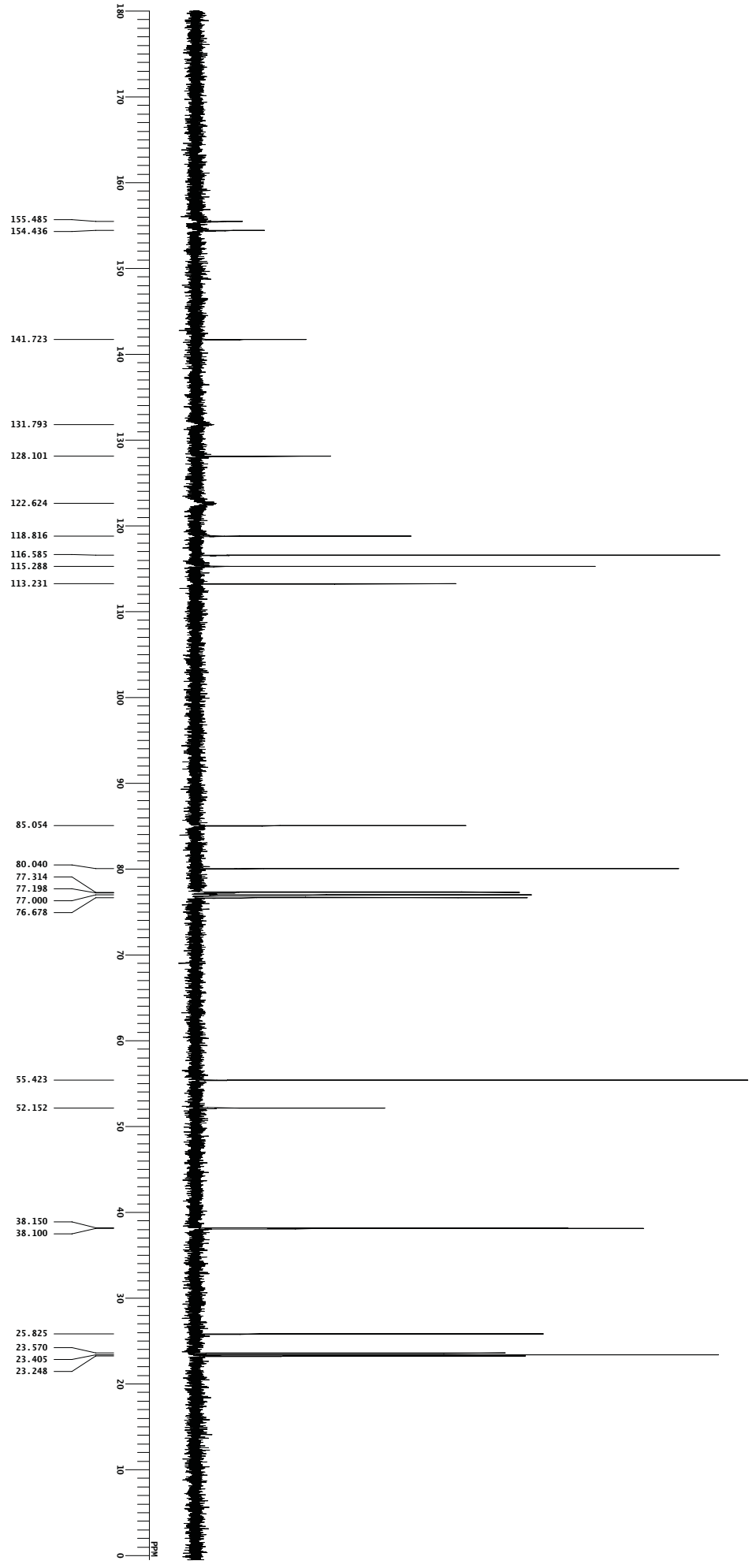
CO2Me
O
H
O

11d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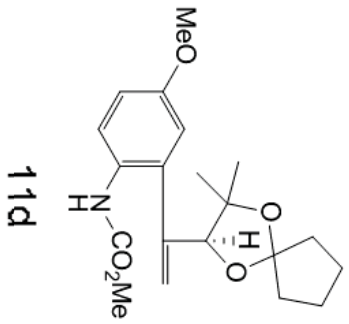
PPM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CO2Me
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H
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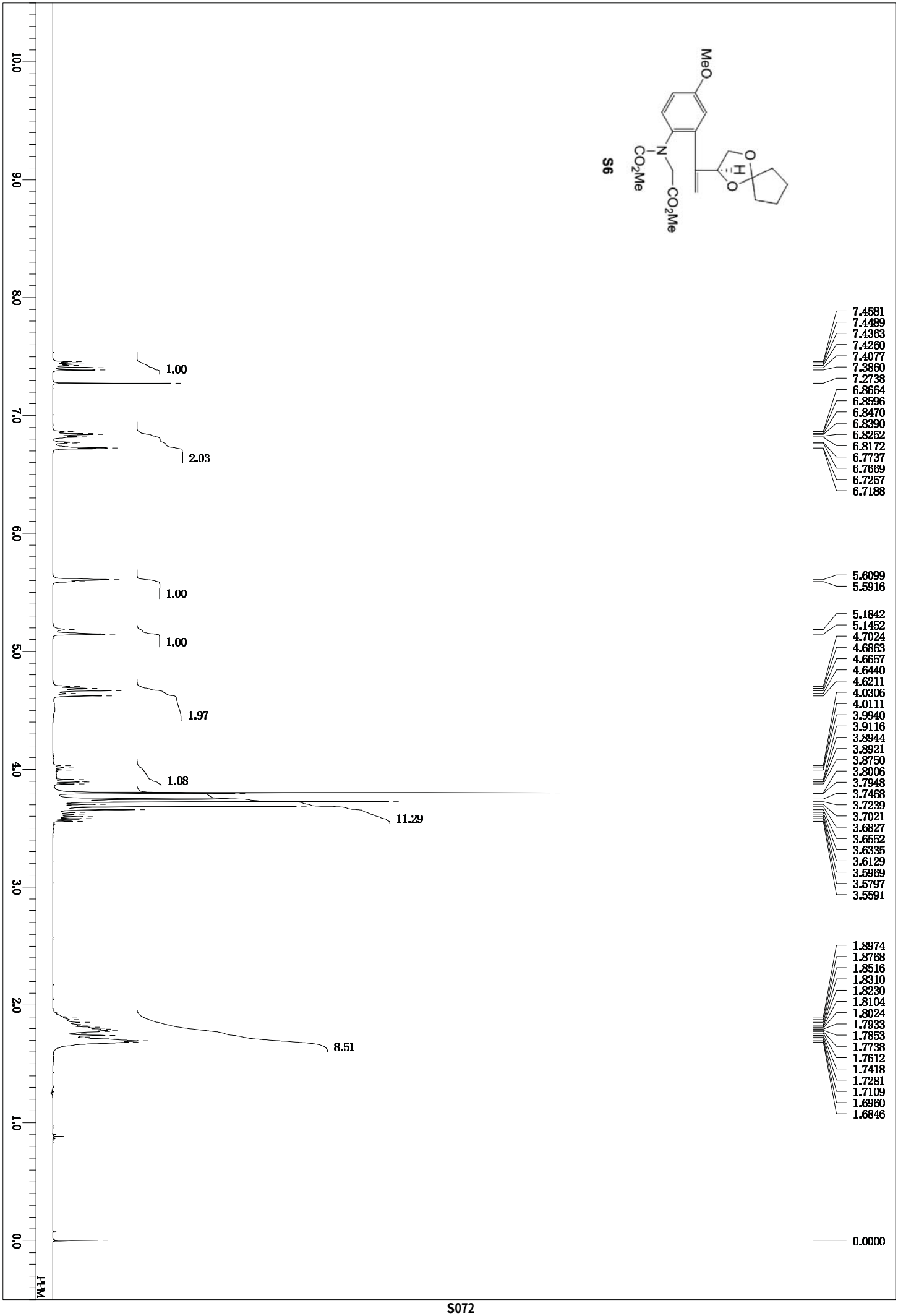
11d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CO2Me
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O
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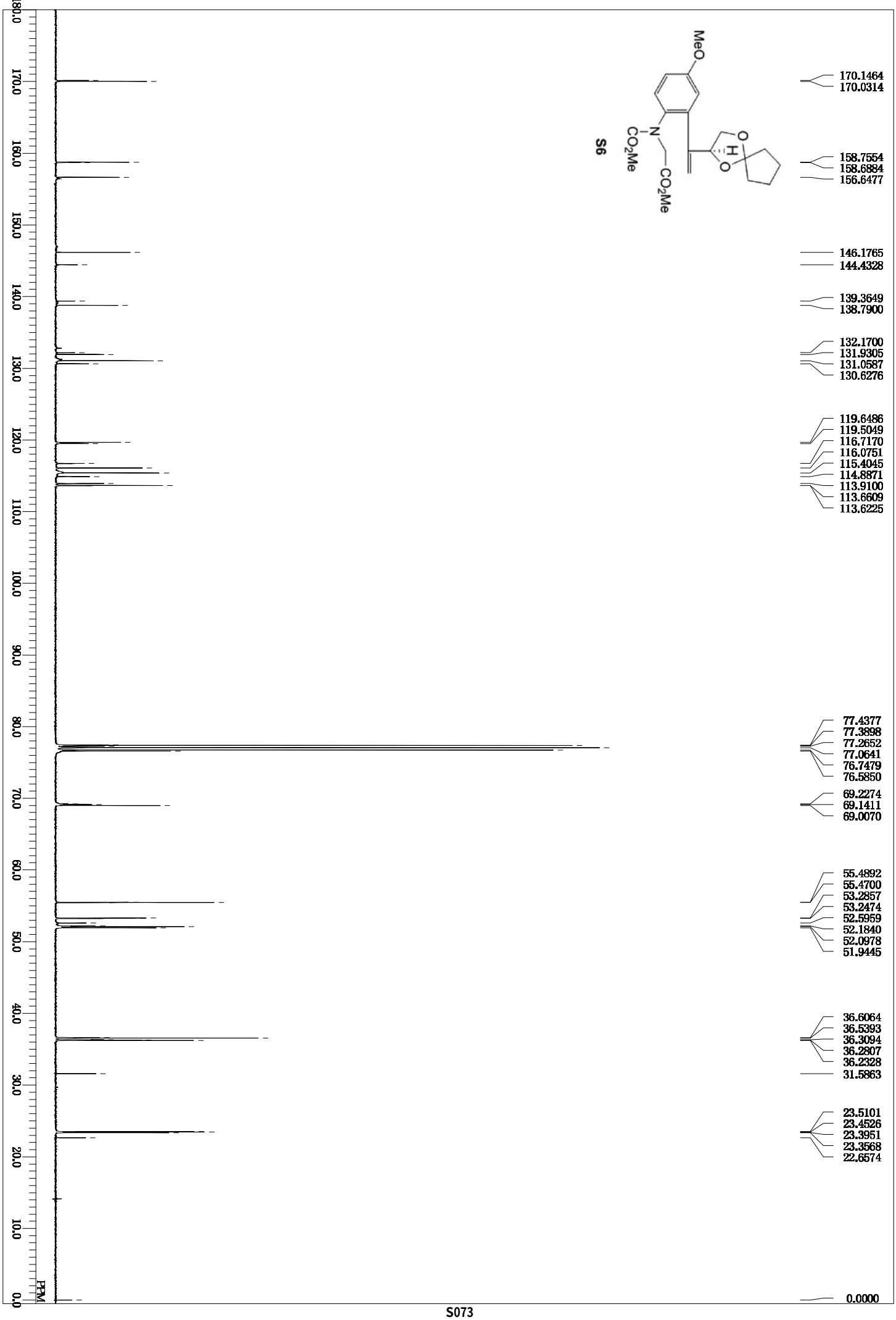
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CO2Me
O
H
O
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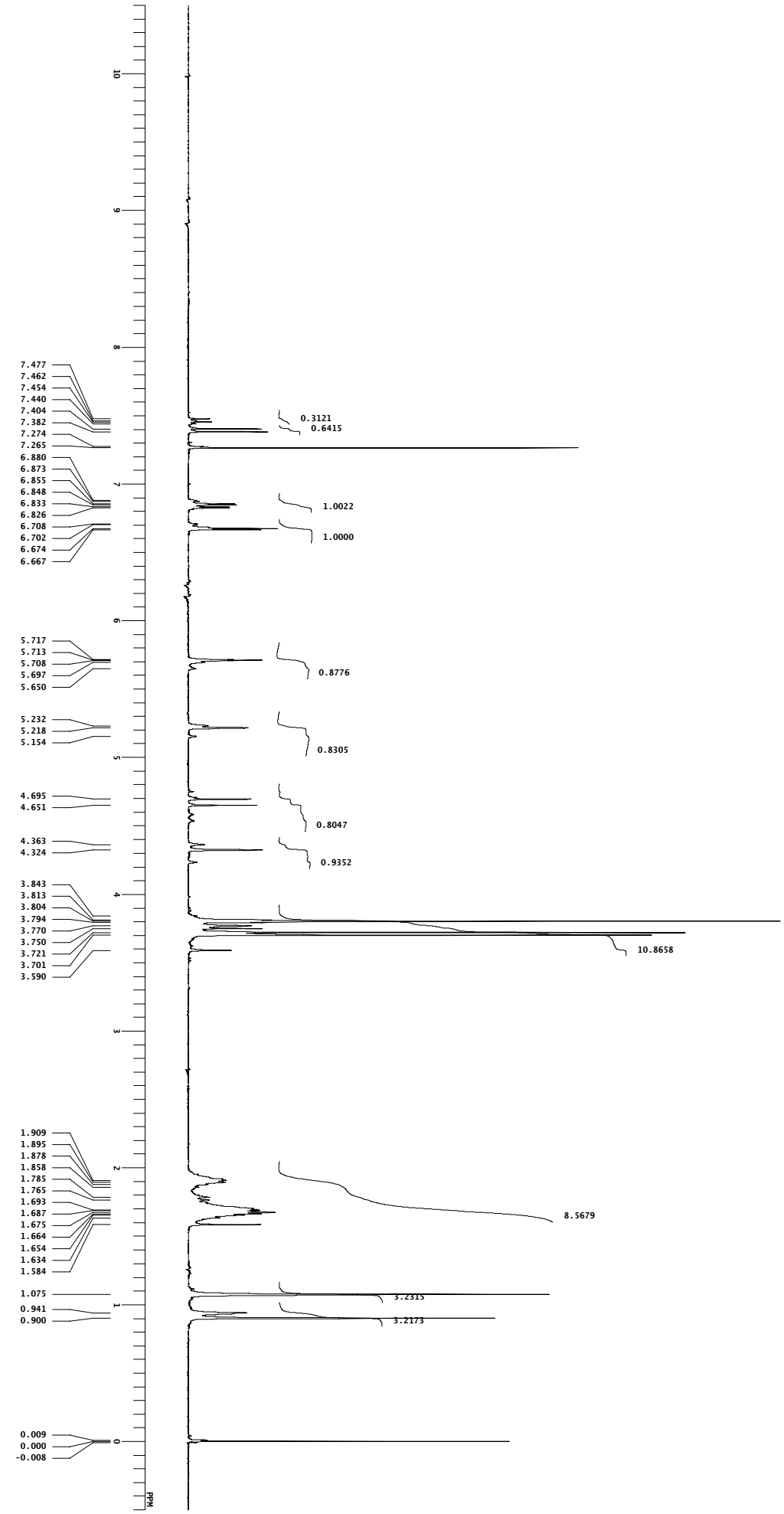
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7.454
7.440
7.404
7.382
7.274
7.265
6.880
6.873
6.855
6.848
6.833
6.826
6.708
6.702
6.674
6.667
5.717
5.713
5.708
5.697
5.650
5.232
5.218
5.154
4.695
4.651
4.363
4.324
3.843
3.813
3.804
3.794
3.770
3.750
3.721
3.701
3.590
1.909
1.895
1.878
1.858
1.785
1.765
1.693
1.687
1.675
1.664
1.654
1.634
1.584
1.075
0.941
0.900
0.009
0.000
-0.008
0.3121
0.6415
1.0022
1.0000
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0.8305
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0.9352
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8.5679
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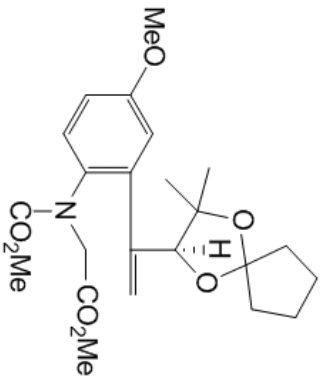
3.2173
PPM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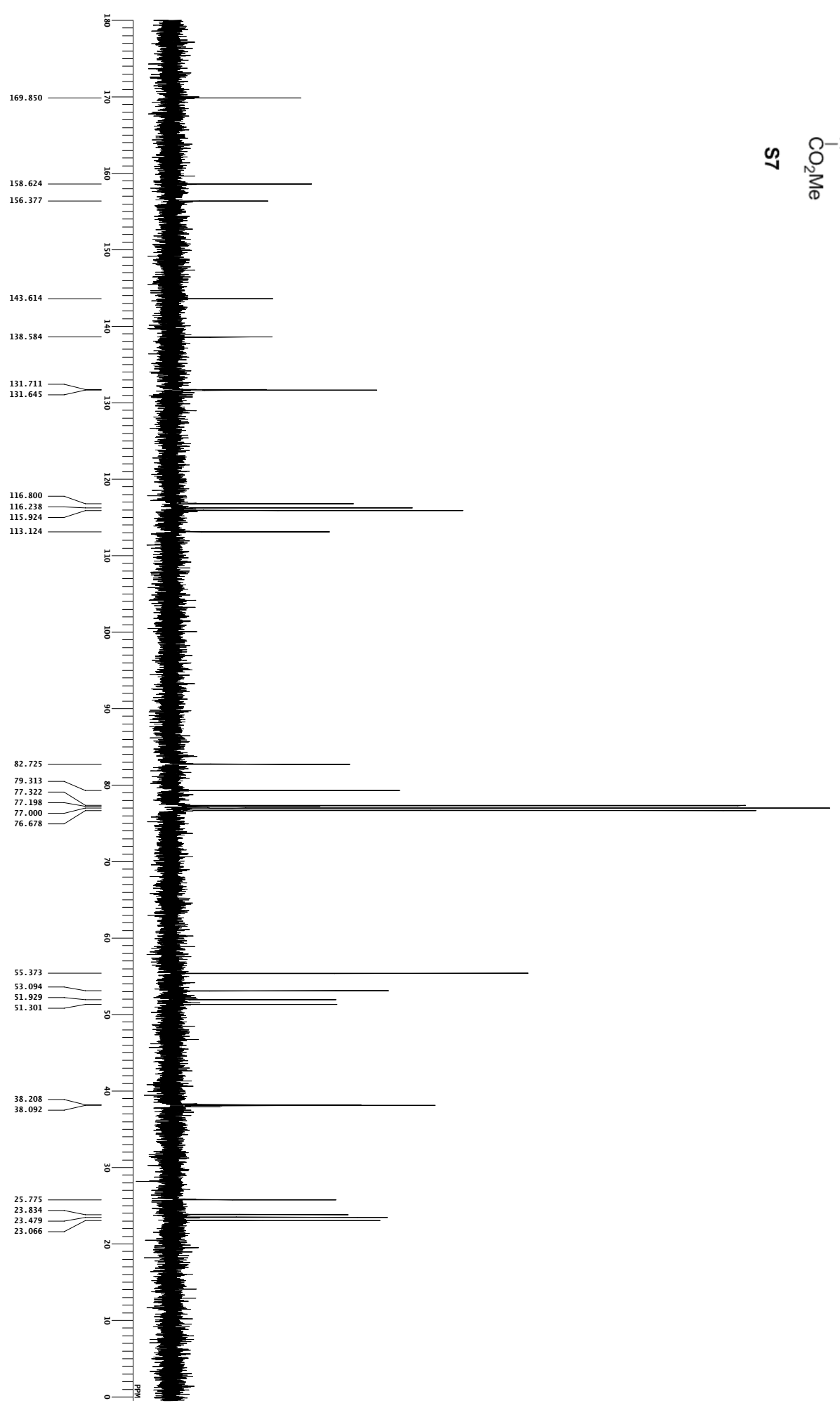
N
CO2Me
CO2Me
O
H
O

S7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79.313
77.322
77.198
77.000
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51.301
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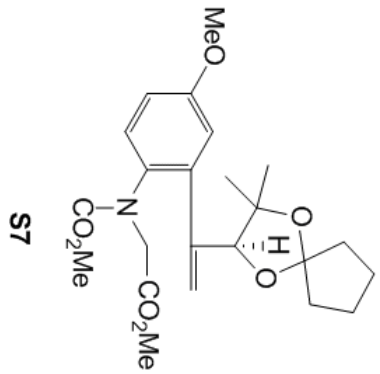
38.092
25.775
23.834
23.479
23.066
PPM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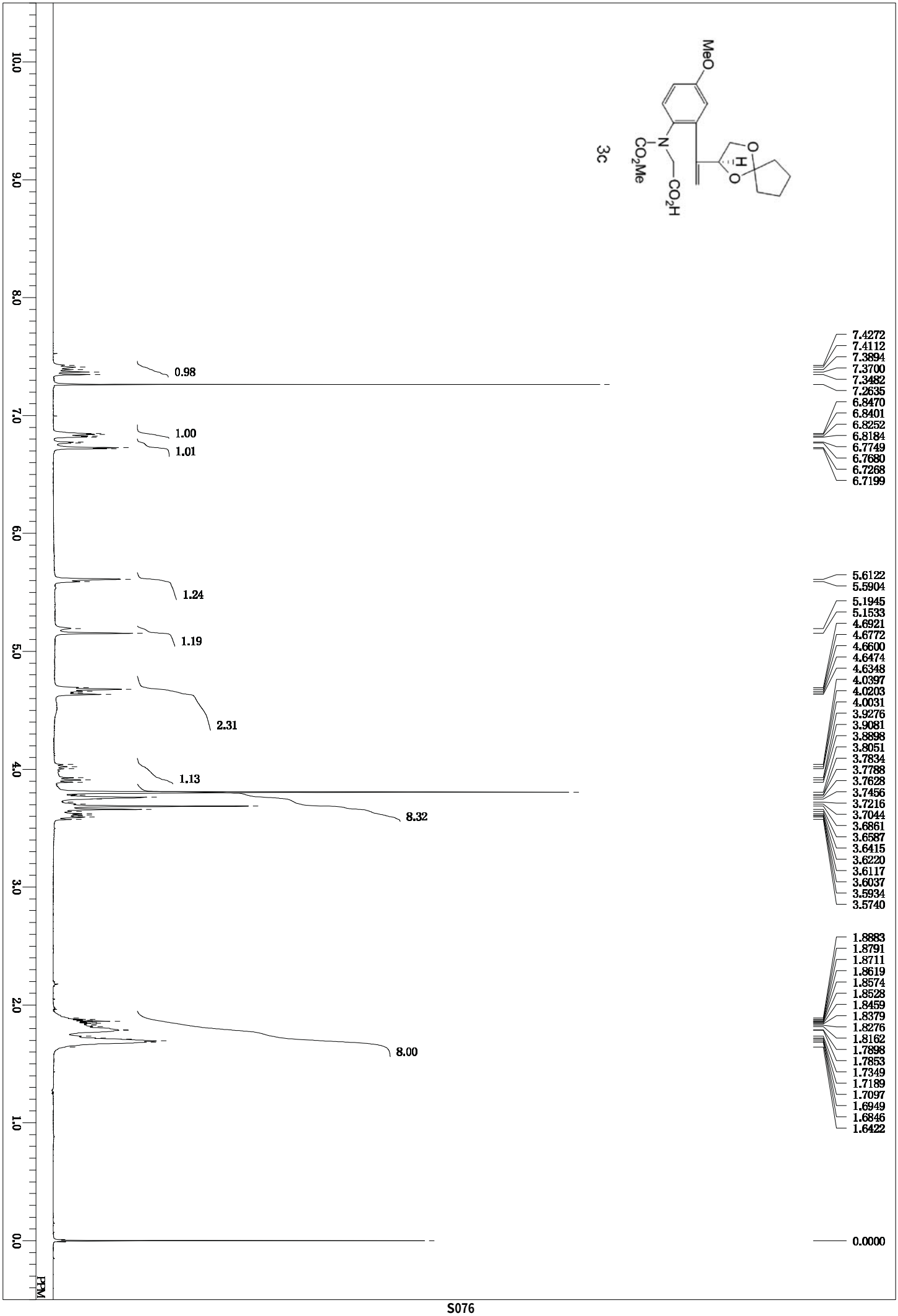
CO2Me
CO2Me
O
H
O

S7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N
CO2Me
CO2H
O
H
O
3c
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9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
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1.00
1.01
1.24
1.19
2.31
1.13
8.32
8.00
7.4272
7.4112
7.3894
7.3700
7.3482
7.2635
6.8470
6.8401
6.8252
6.8184
6.7749
6.7680
6.7268
6.7199
5.6122
5.5904
5.1945
5.1533
4.6921
4.6772
4.6600
4.6474
4.6348
4.0397
4.0203
4.0031
3.9276
3.9081
3.8898
3.8051
3.7834
3.7788
3.7628
3.7456
3.7216
3.7044
3.6861
3.6587
3.6415
3.6220
3.6117
3.6037
3.5934
3.5740
1.8883
1.8791
1.8711
1.8619
1.8574
1.8528
1.8459
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1.8276
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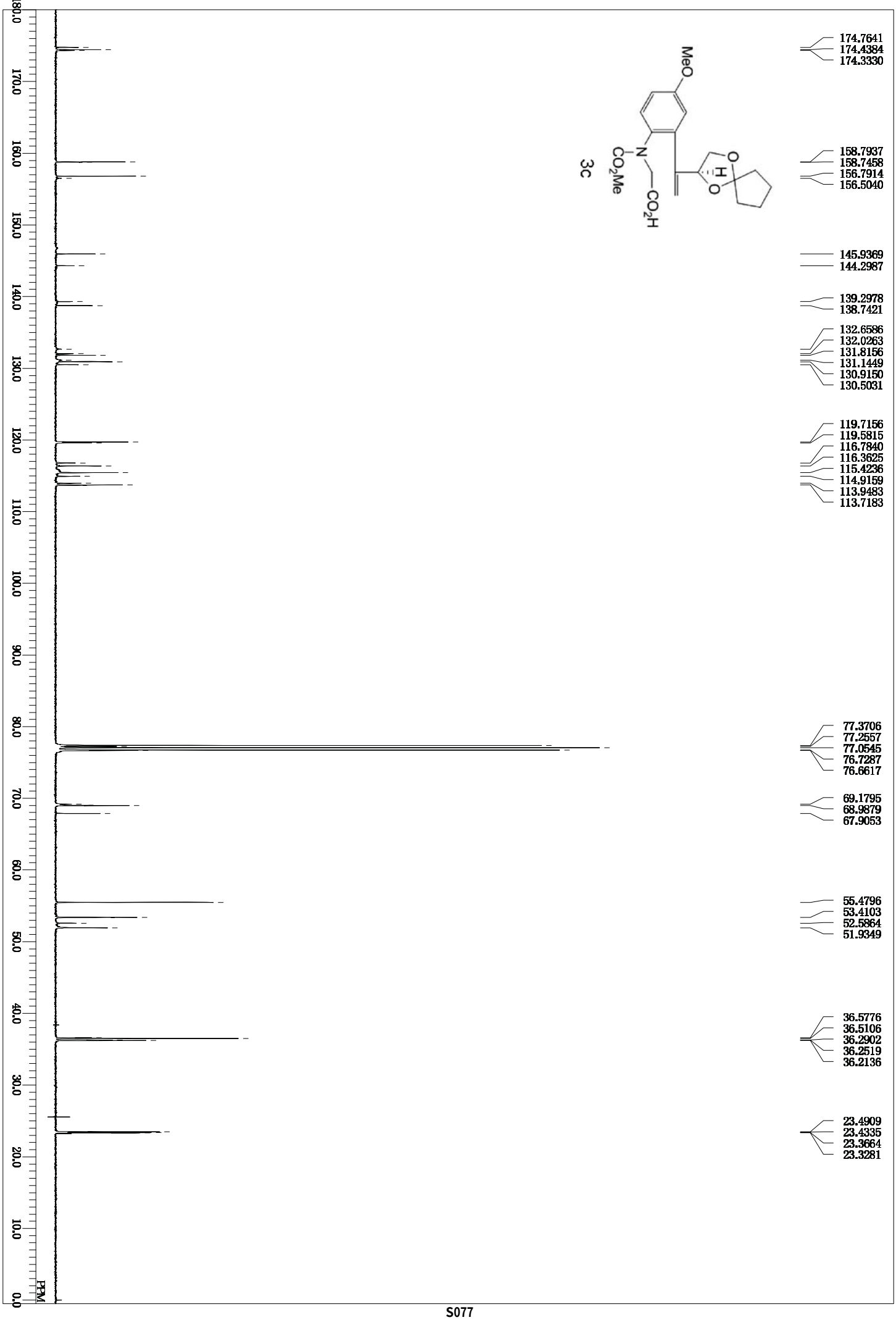
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N
CO2Me
CO2H
O
H
O
3c
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174.4384
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156.5040
145.9369
144.2987
139.2978
138.7421
132.6586
132.0263
131.8156
131.1449
130.9150
130.5031
119.7156
119.5815
116.7840
116.3625
115.4236
114.9159
113.9483
113.7183
77.3706
77.2557
77.0545
76.7287
76.6617
69.1795
68.9879
67.9053
55.4796
53.4103
52.5864
51.9349
36.5776
36.5106
36.2902
36.2519
36.2136
23.4909
23.4335
23.3664
23.3281
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
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80.0
70.0
60.0
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30.0
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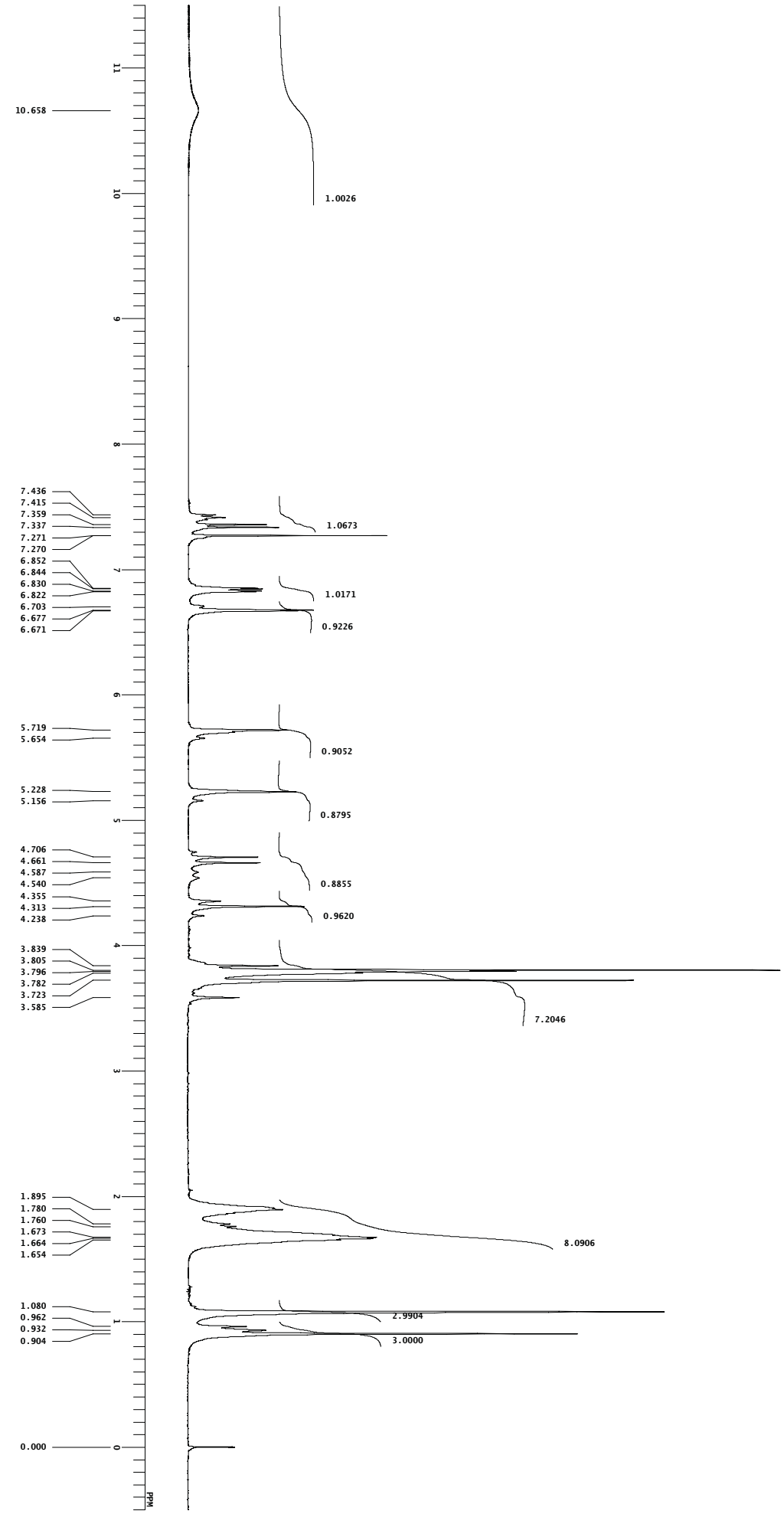
10.0
0.0
PPM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6.852
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6.830
6.822
6.703
6.677
6.671
5.719
5.654
5.228
5.156
4.706
4.661
4.587
4.540
4.355
4.313
4.238
3.839
3.805
3.796
3.782
3.723
3.585
1.895
1.780
1.760
1.673
1.664
1.654
1.080
0.962
0.932
0.904
0.000
1.0026
1.0673
1.0171
0.9226
0.9052
0.8795
0.8855
0.9620
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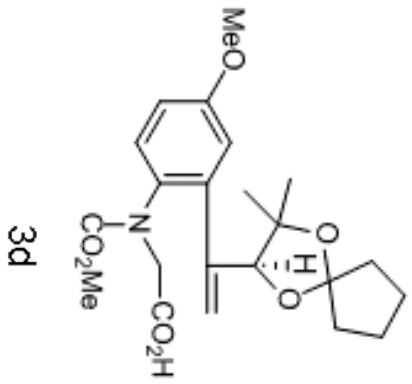
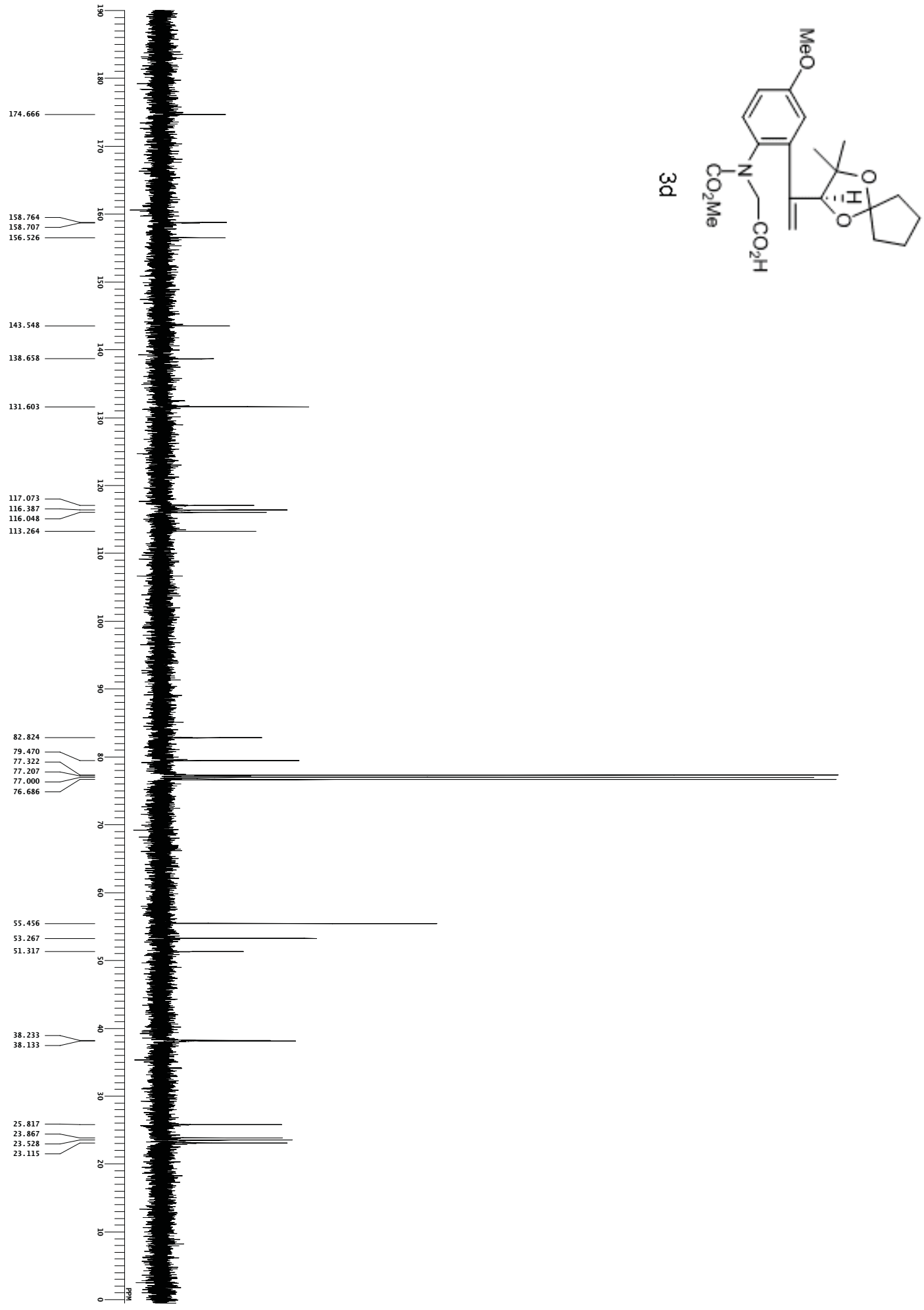
8.0906
2.9904
3.0000
PPM


MeO
N
CO2Me
CO2H
O
H
O

3d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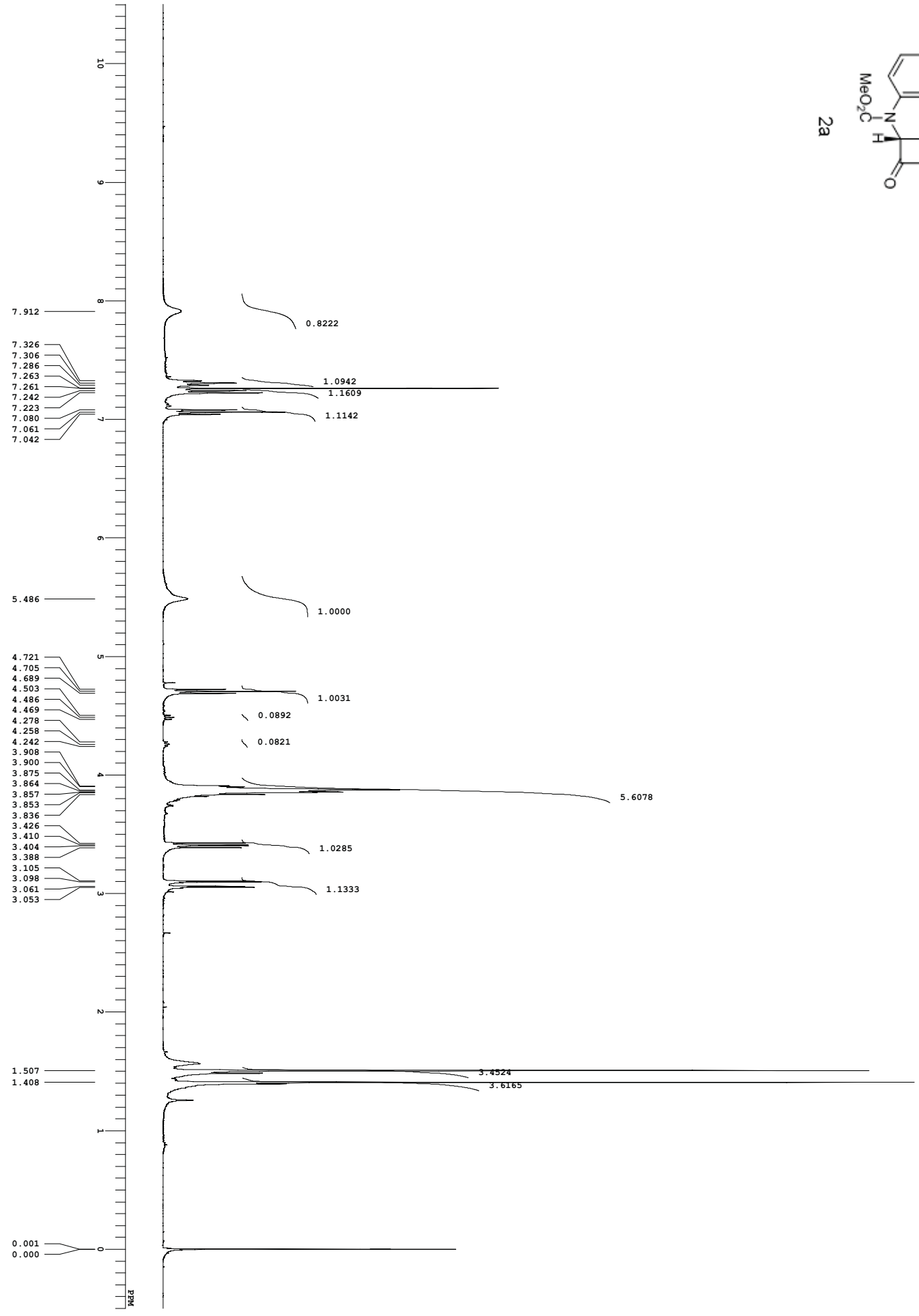
131.603
117.073
116.387
116.048
113.264
82.824
79.470
77.322
77.207
77.000
76.686
55.456
53.267
51.317
38.233
38.133
25.817
23.867
23.528
23.115
PPM

MeO
N
CO2Me
CO2H
O
H
O

3d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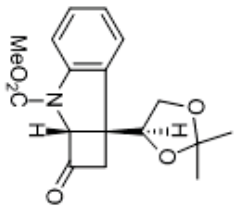
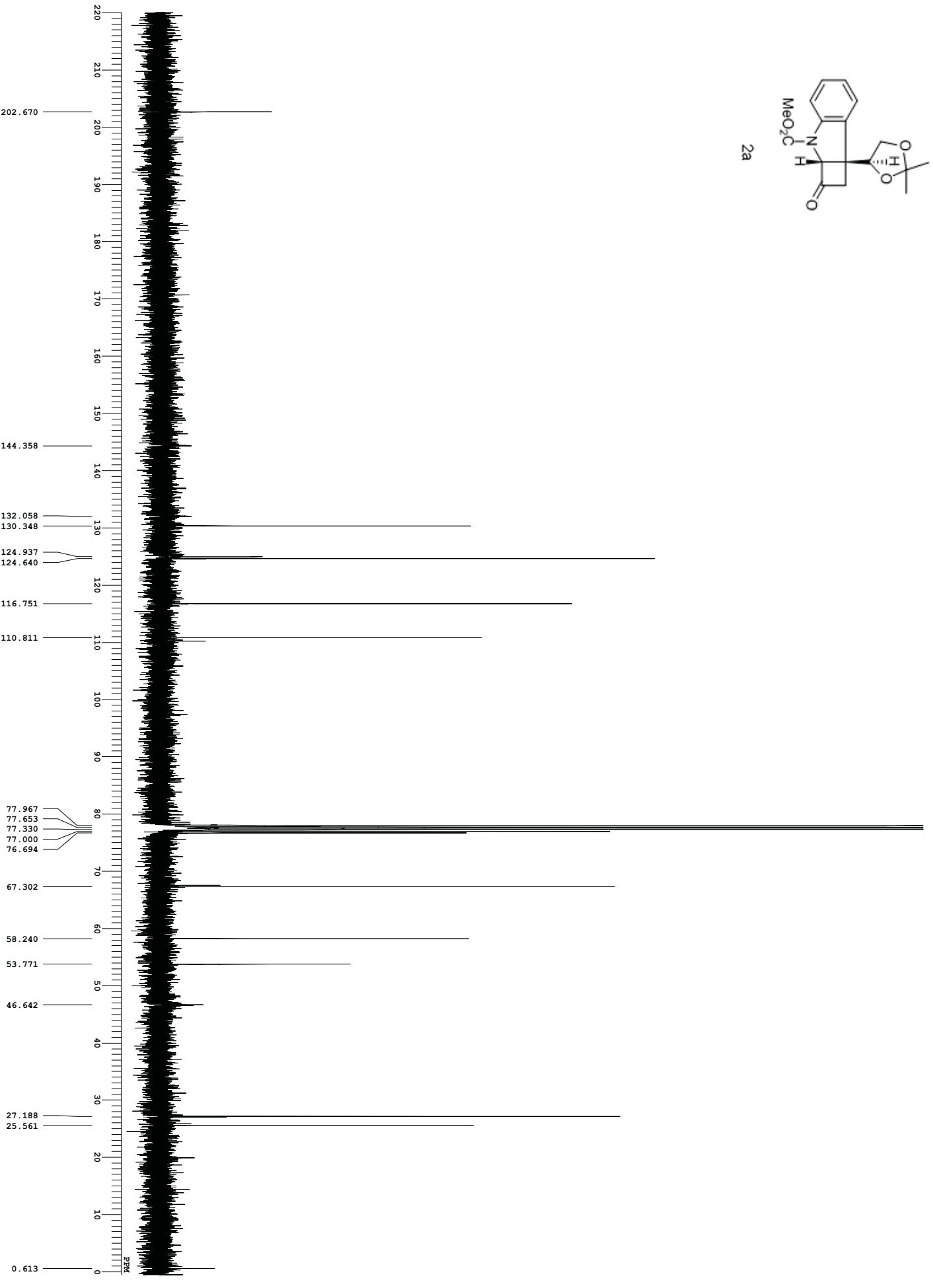
7.261
7.242
7.223
7.080
7.061
7.042
5.486
4.721
4.705
4.689
4.503
4.486
4.469
4.278
4.258
4.242
3.908
3.900
3.875
3.864
3.857
3.853
3.836
3.426
3.410
3.404
3.388
3.105
3.098
3.061
3.053
1.507
1.408
0.001
0.000
0.8222
1.0942
1.1609
1.1142
1.0000
1.0031
0.0892
0.0821
5.6078
1.0285
1.1333
3.4524
3.6165
PPM


MeO2C
N
H
O
H
O
O

2a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110.811
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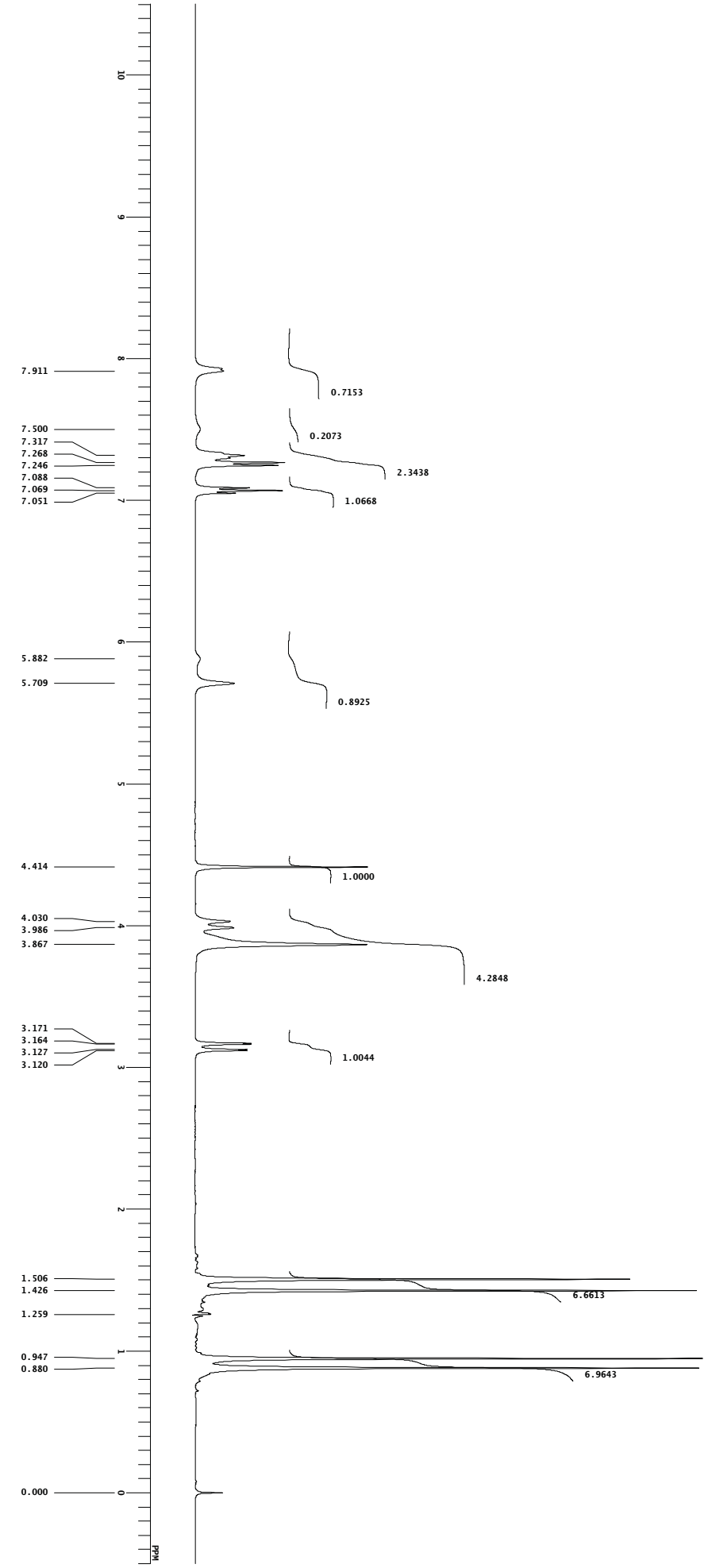
77.653
77.330
77.000
76.694
67.302
58.240
53.771
46.642
27.188
25.561
0.613
PPM

MeO2C
N
H
O
H
O
O

2a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7.317
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7.246
7.088
7.069
7.051
5.882
5.709
4.414
4.030
3.986
3.867
3.171
3.164
3.127
3.120
1.506
1.426
1.259
0.947
0.880
0.000
0.7153
0.2073
2.3438
1.0668
0.8925
1.0000
4.2848
1.0044
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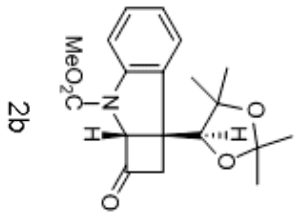
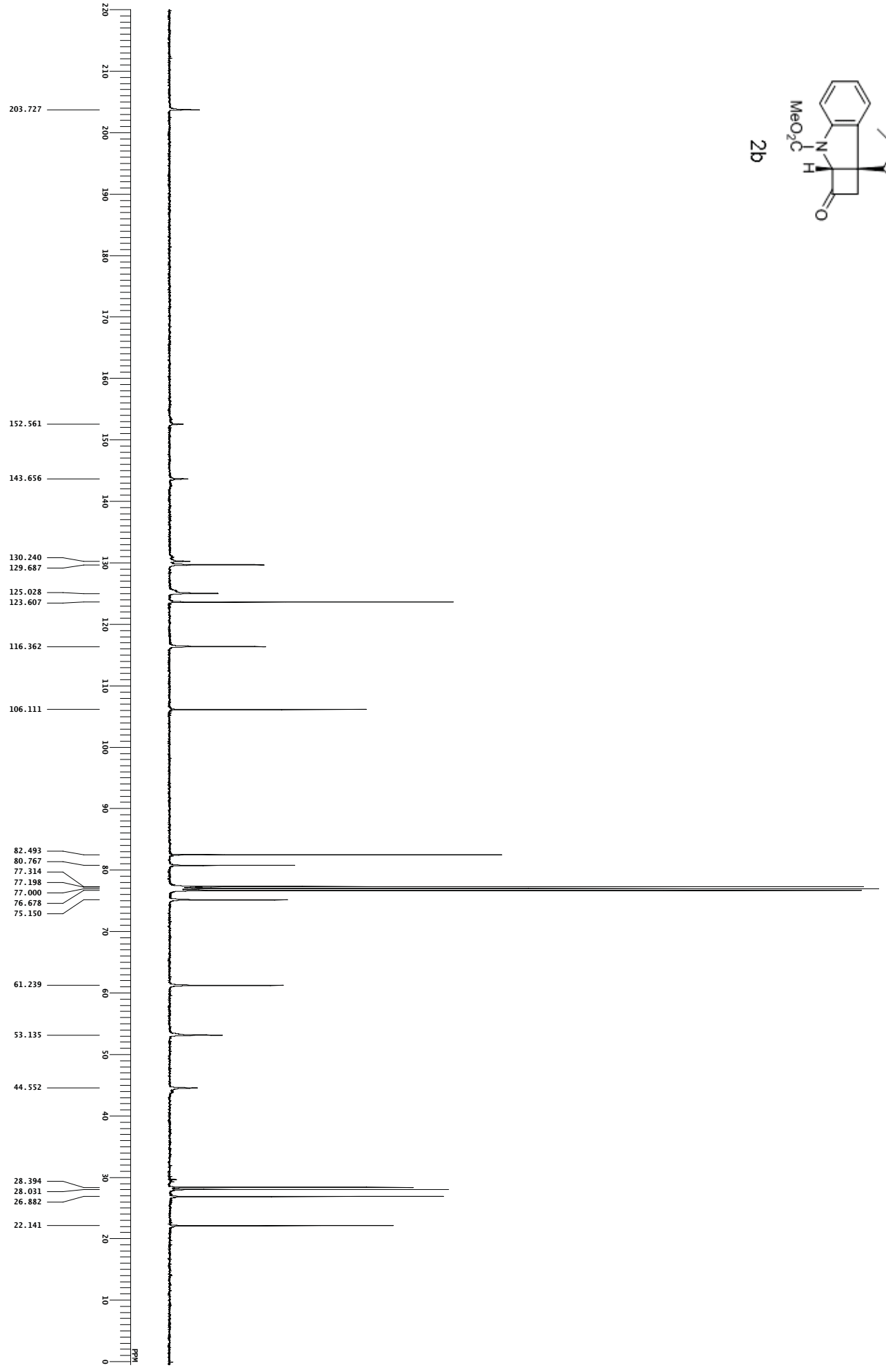
ppm


MeO2C
N
H
O
H
O
O

2b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116.362
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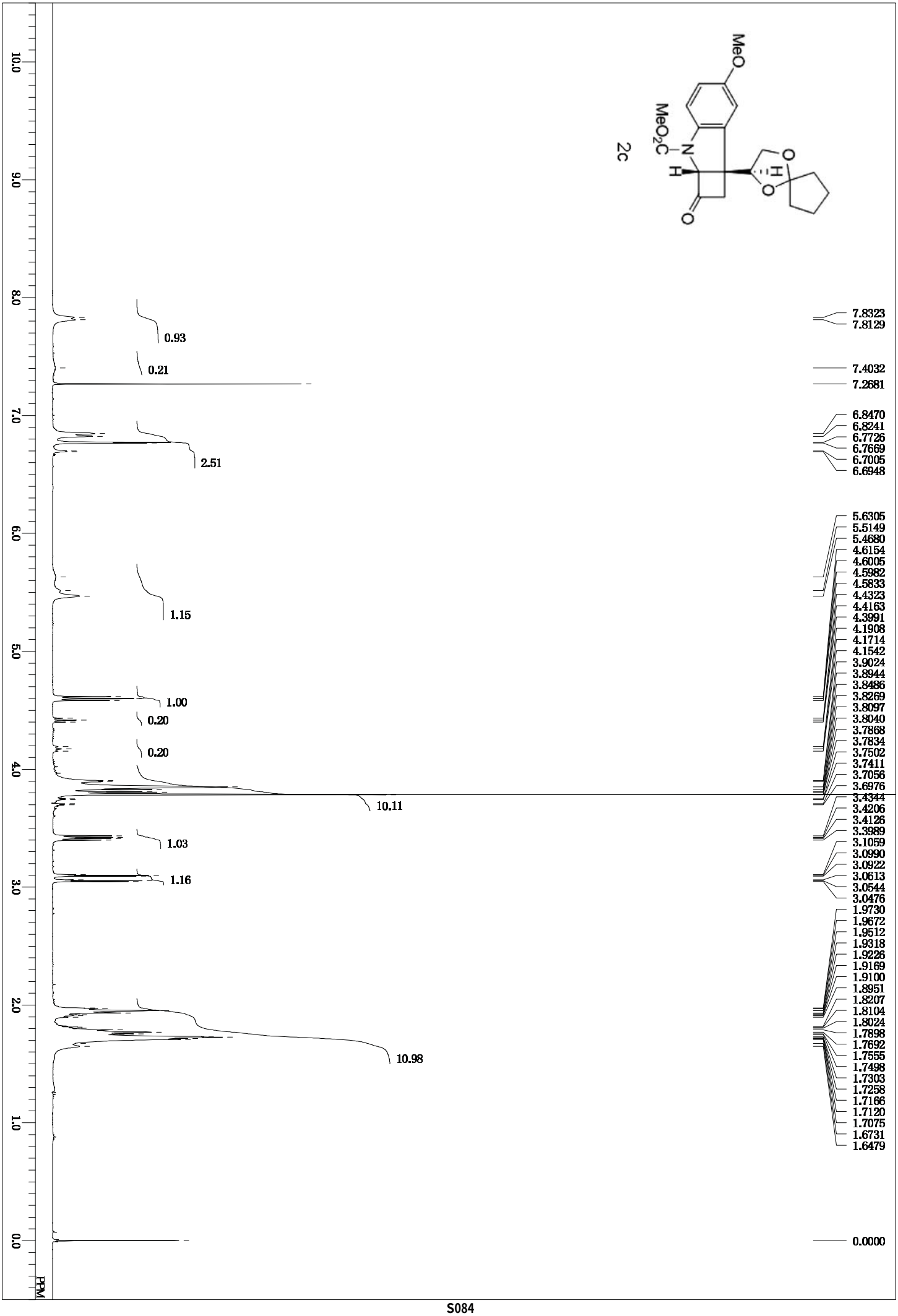
82.493
80.767
77.314
77.198
77.000
76.678
75.150
61.239
53.135
44.552
28.394
28.031
26.882
22.141
PPM

MeO2C
N
H
O
H
O
O

2b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MeO2C
N
H
O
O
H
O
2c
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9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
0.93
0.21
2.51
1.15
1.00
0.20
0.20
10.11
1.03
1.16
10.98
7.8323
7.8129
7.4032
7.2681
6.8470
6.8241
6.7726
6.7669
6.7005
6.6948
5.6305
5.5149
5.4680
4.6154
4.6005
4.5982
4.5833
4.4323
4.4163
4.3991
4.1908
4.1714
4.1542
3.9024
3.8944
3.8486
3.8269
3.8097
3.8040
3.7868
3.7834
3.7502
3.7411
3.7056
3.6976
3.4344
3.4206
3.4126
3.3989
3.1059
3.0990
3.0922
3.0613
3.0544
3.0476
1.9730
1.9672
1.9512
1.9318
1.9226
1.9169
1.9100
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1.7692
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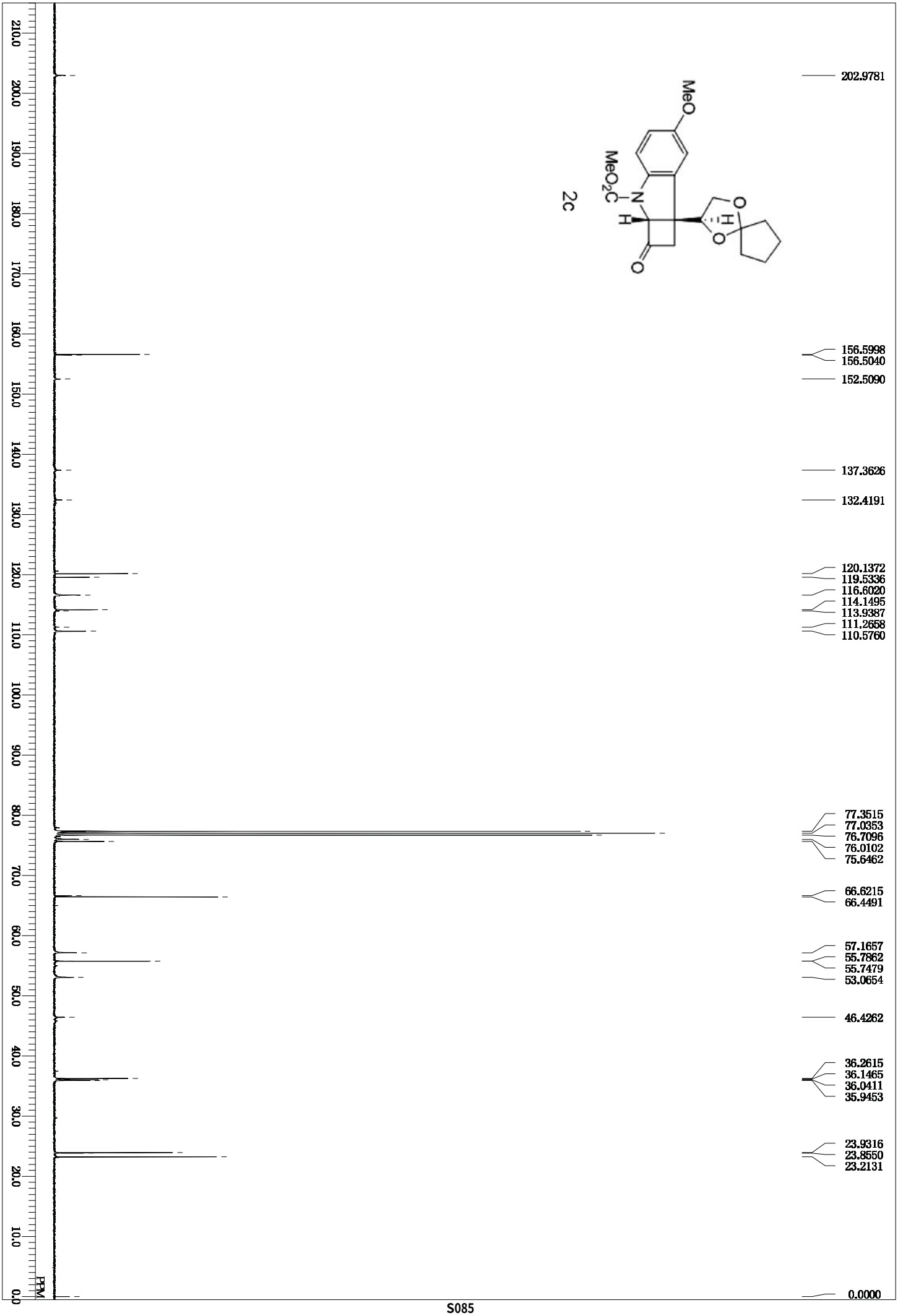
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MeO2C
N
H
O
H
O
O
2c
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156.5040
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132.4191
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119.5336
116.6020
114.1495
113.9387
111.2658
110.5760
77.3515
77.0353
76.7096
76.0102
75.6462
66.6215
66.4491
57.1657
55.7862
55.7479
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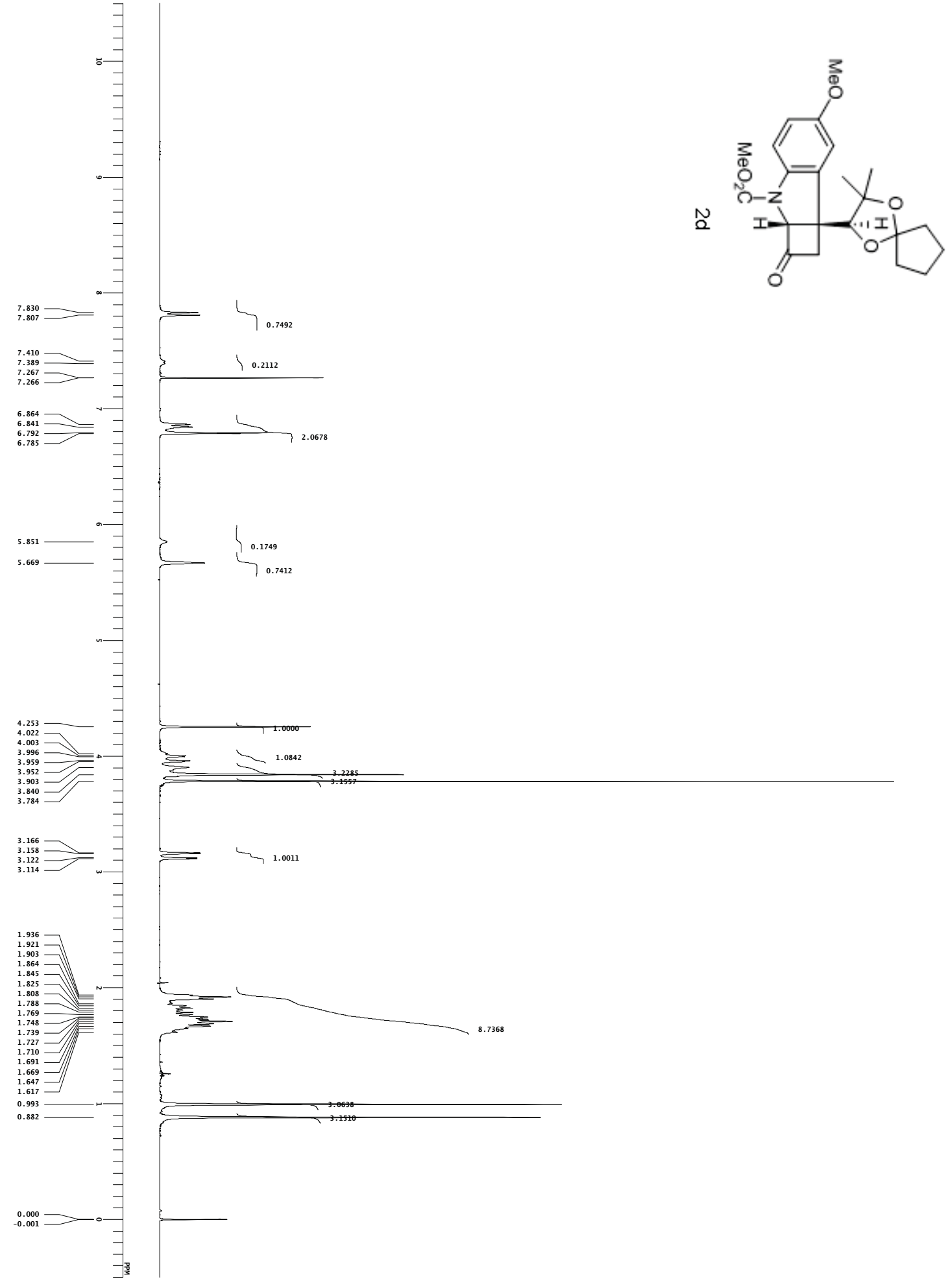
PPM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7.266
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6.841
6.792
6.785
5.851
5.669
4.253
4.022
4.003
3.996
3.959
3.952
3.903
3.840
3.784
3.166
3.158
3.122
3.114
1.936
1.921
1.903
1.864
1.845
1.825
1.808
1.788
1.769
1.748
1.739
1.727
1.710
1.691
1.669
1.647
1.617
0.993
0.882
0.000
-0.001
0.7492
0.2112
2.0678
0.1749
0.7412
1.0000
1.0842
3.2285
3.1557
1.0011
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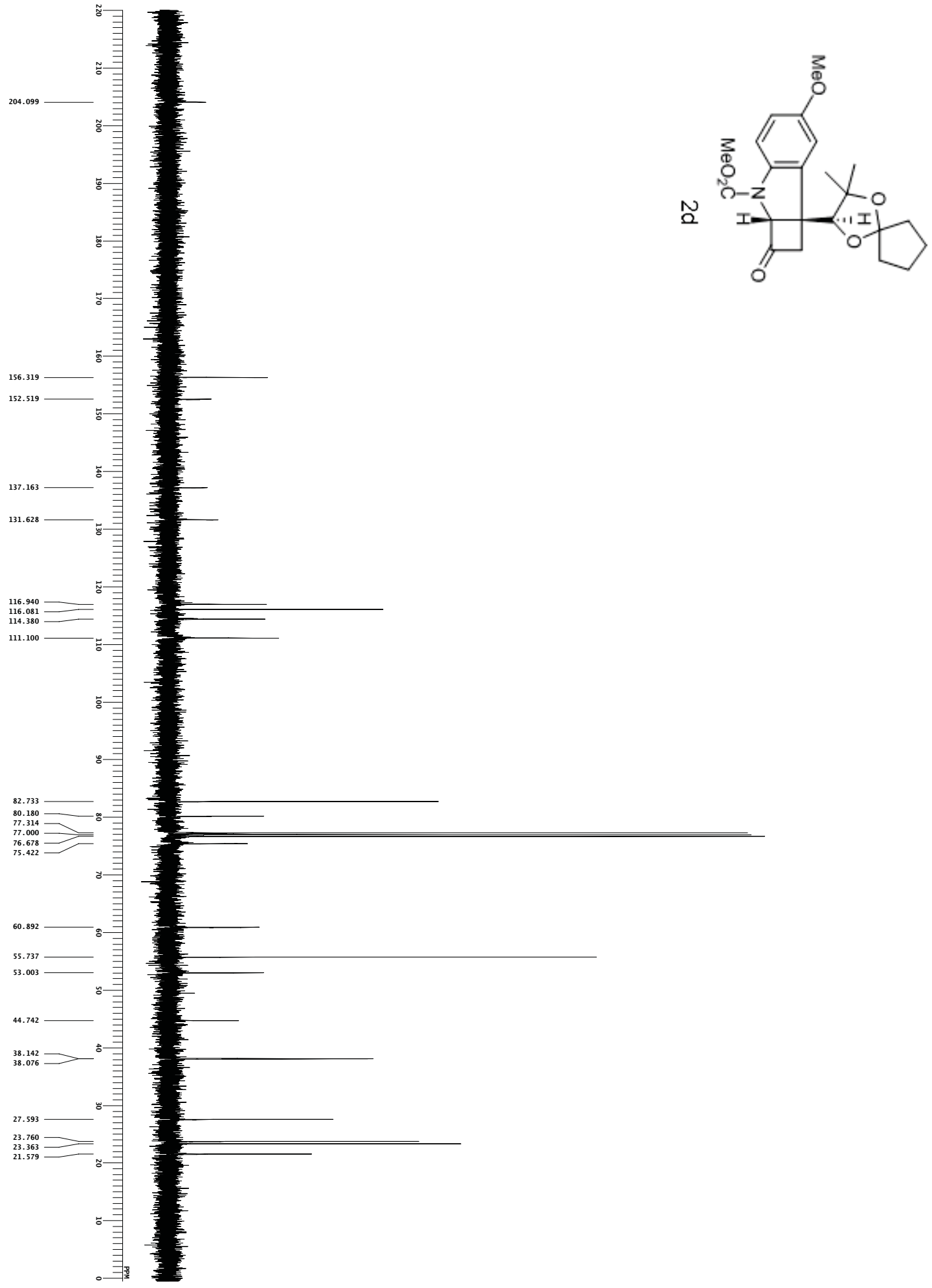
3.0638
3.1510
ppm

MeO
MeO2C
N
H
O
H
O
O

2d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152.519
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116.940
116.081
114.380
111.100
82.733
80.180
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77.000
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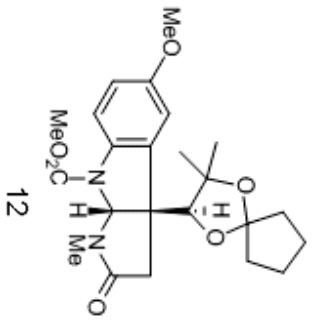
55.737
53.003
44.742
38.142
38.076
27.593
23.760
23.363
21.579
PPM

MeO
MeO2C
N
H
O
H
O
O

2d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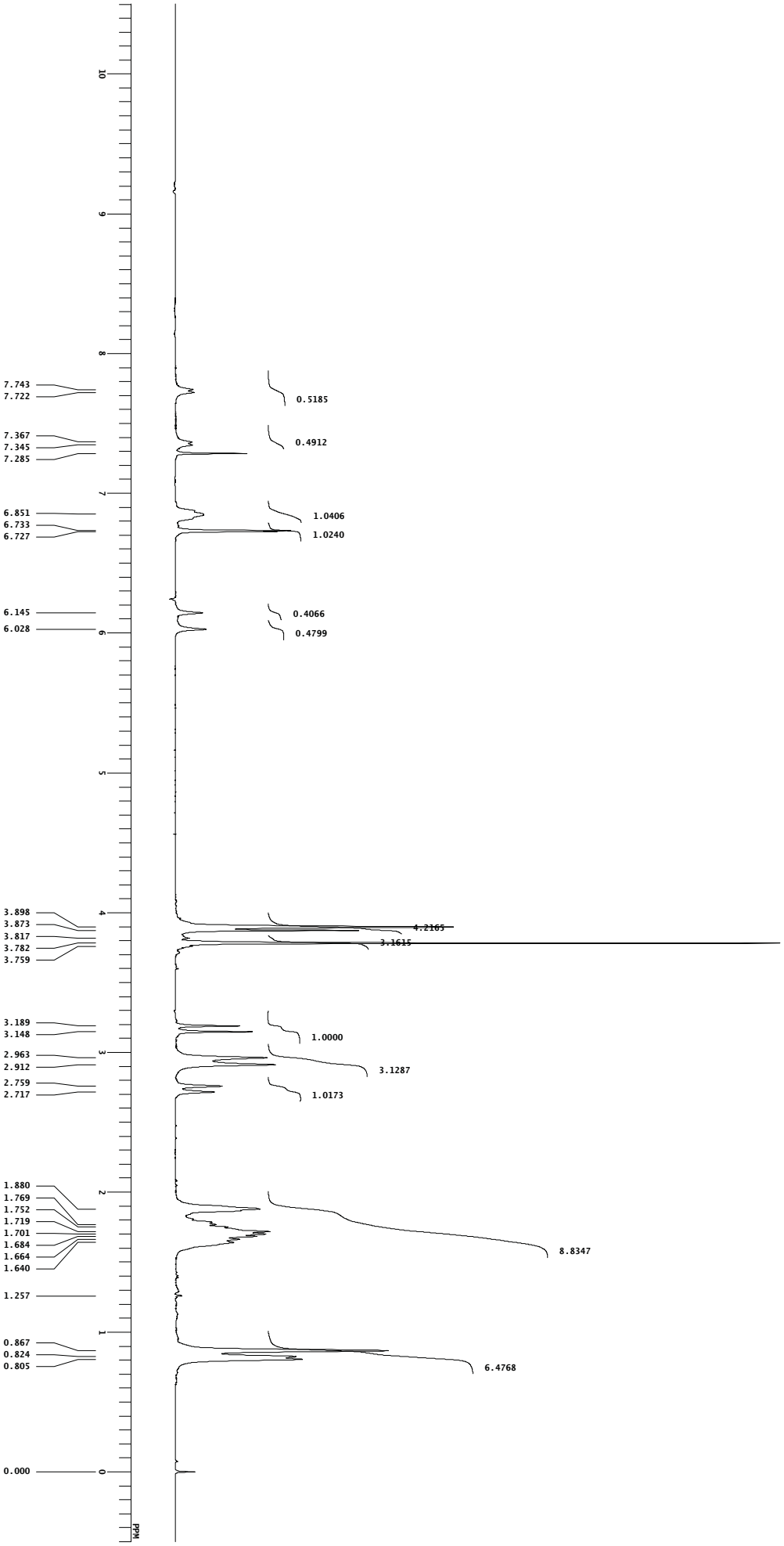
MeO2C
N
H
N
Me
O
O
H
O
O

12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6.851
6.733
6.727
1.0406
1.0240
6.145
6.028
0.4066
0.4799
3.898
3.873
3.817
3.782
3.759
4.2165
3.1615
3.189
3.148
1.0000
2.963
2.912
3.1287
2.759
2.717
1.0173
1.880
1.769
1.752
1.719
1.701
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1.257
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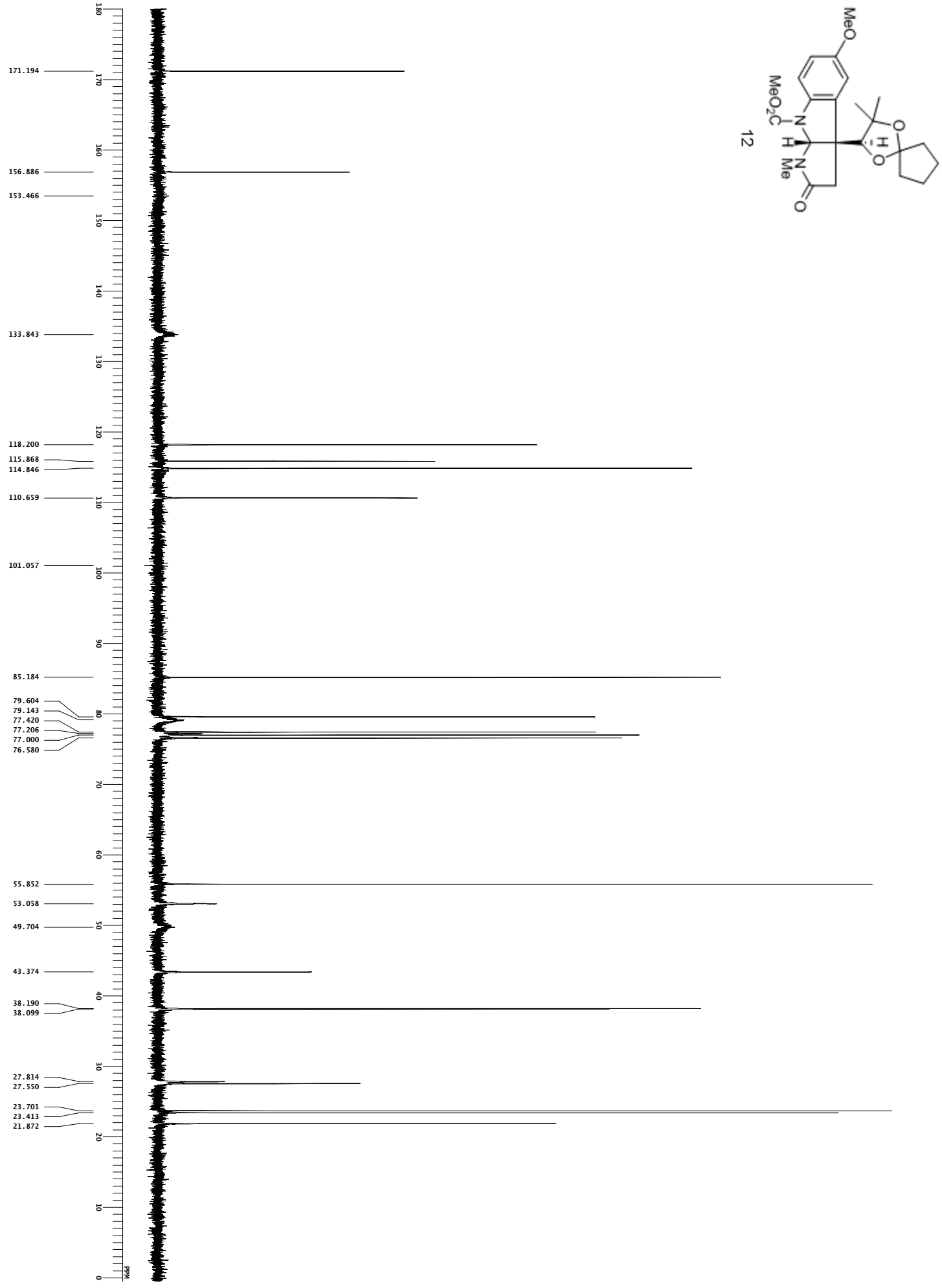
PPM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115.868
114.846
110.659
101.057
85.184
79.604
79.143
77.420
77.206
77.000
76.580
55.852
53.058
49.704
43.374
38.190
38.099
27.814
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23.701
23.413
21.872
PPM
MeO
MeO2C
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H
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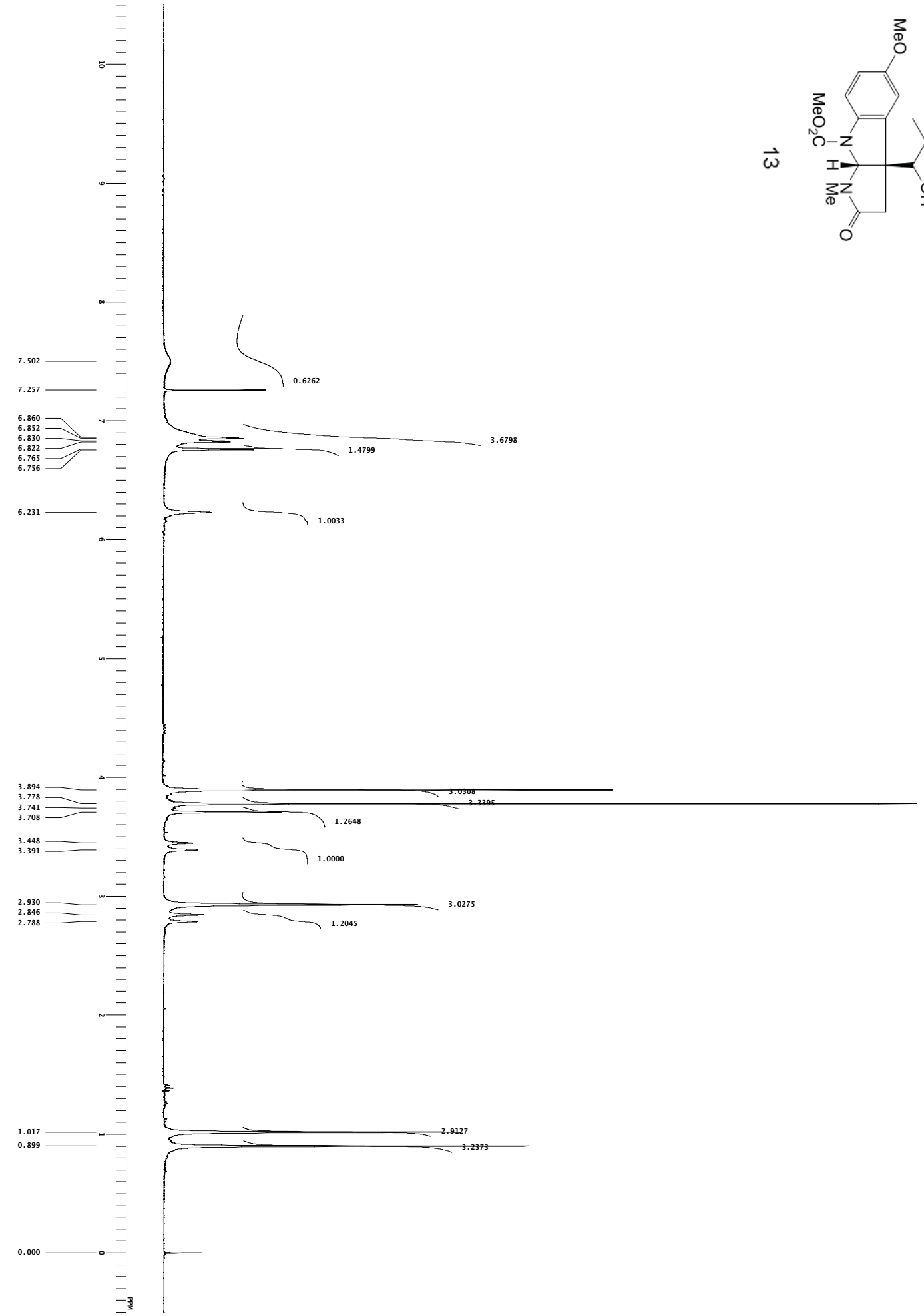
Me
O
O
H
O
12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7.257
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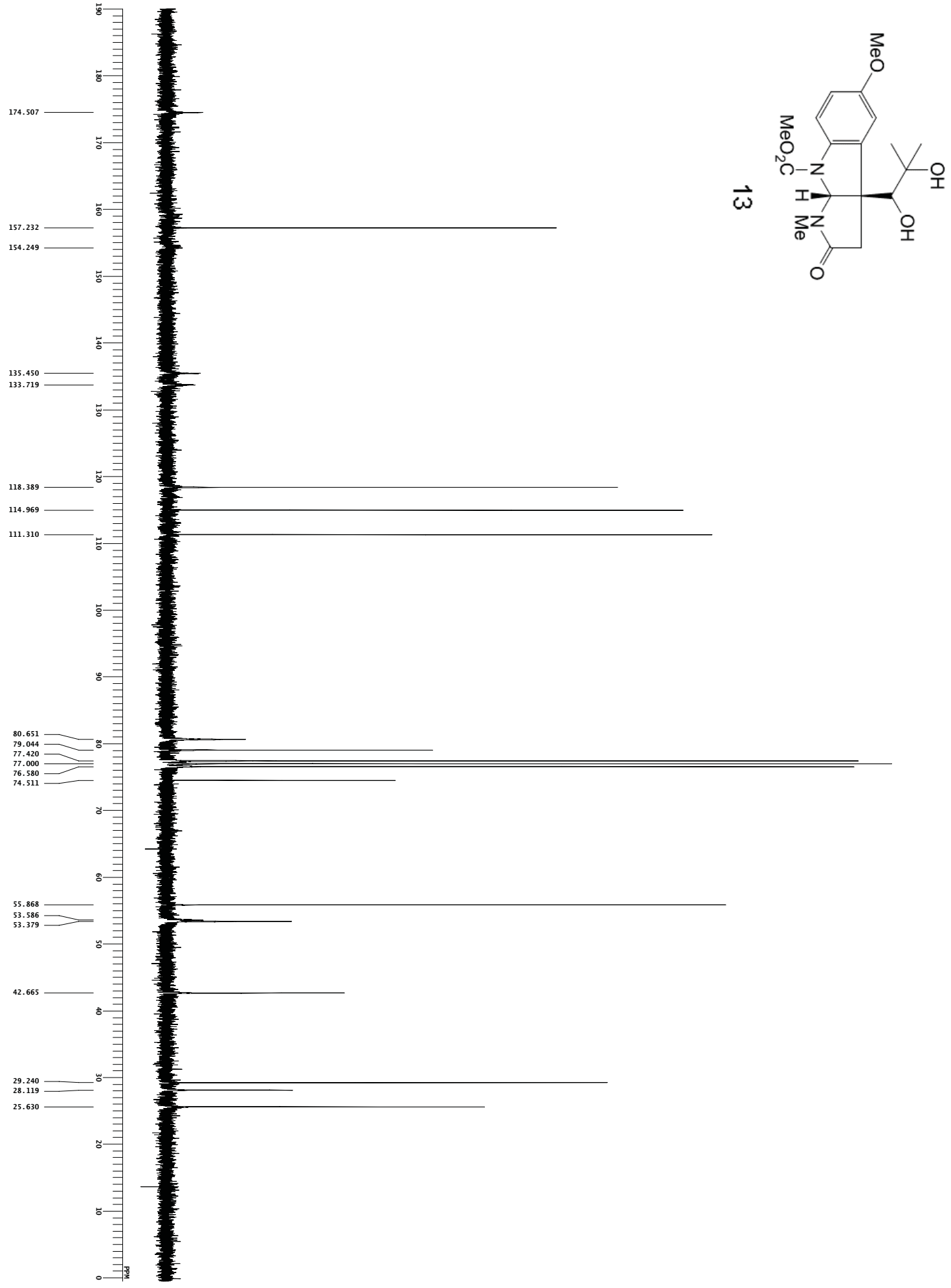
6.852
6.830
6.822
6.765
6.756
6.231
3.894
3.778
3.741
3.708
3.448
3.391
2.930
2.846
2.788
1.017
0.899
0.000
0.6262
3.6798
1.4799
1.0033
3.0308
3.3395
1.2648
1.0000
3.0275
1.2045
2.9127
3.2373
ppm

MeO
MeO2C
N
H
N
Me
O
OH
OH

13


174.507
157.232
154.249
135.450
133.719
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114.969
111.310
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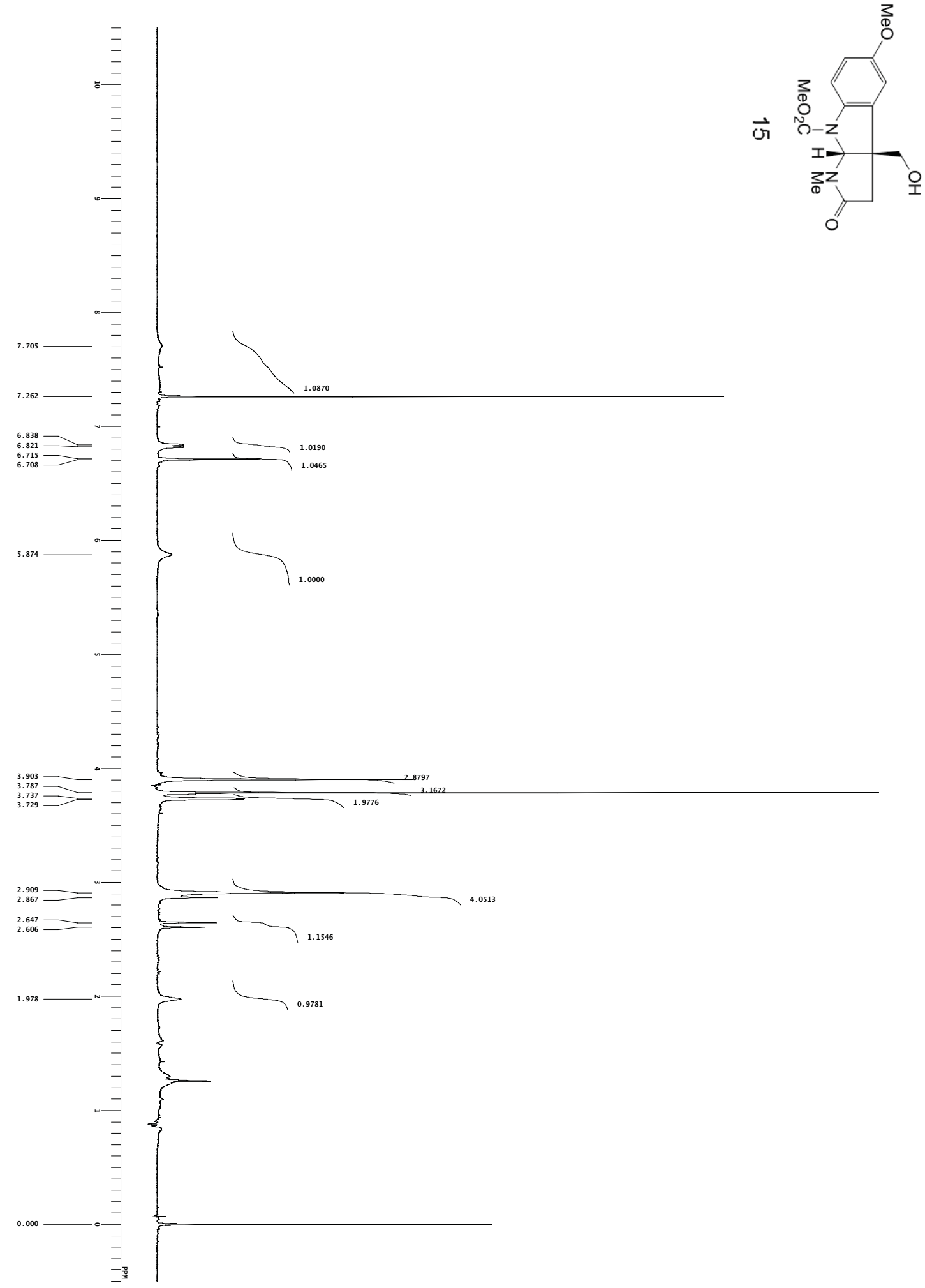
79.044
77.420
77.000
76.580
74.511
55.868
53.586
53.379
42.665
29.240
28.119
25.630
PPM

MeO
MeO2C
N
H
N
Me
O
OH
OH

13


MeO
MeO2C
N
H
N
Me
O
OH
15
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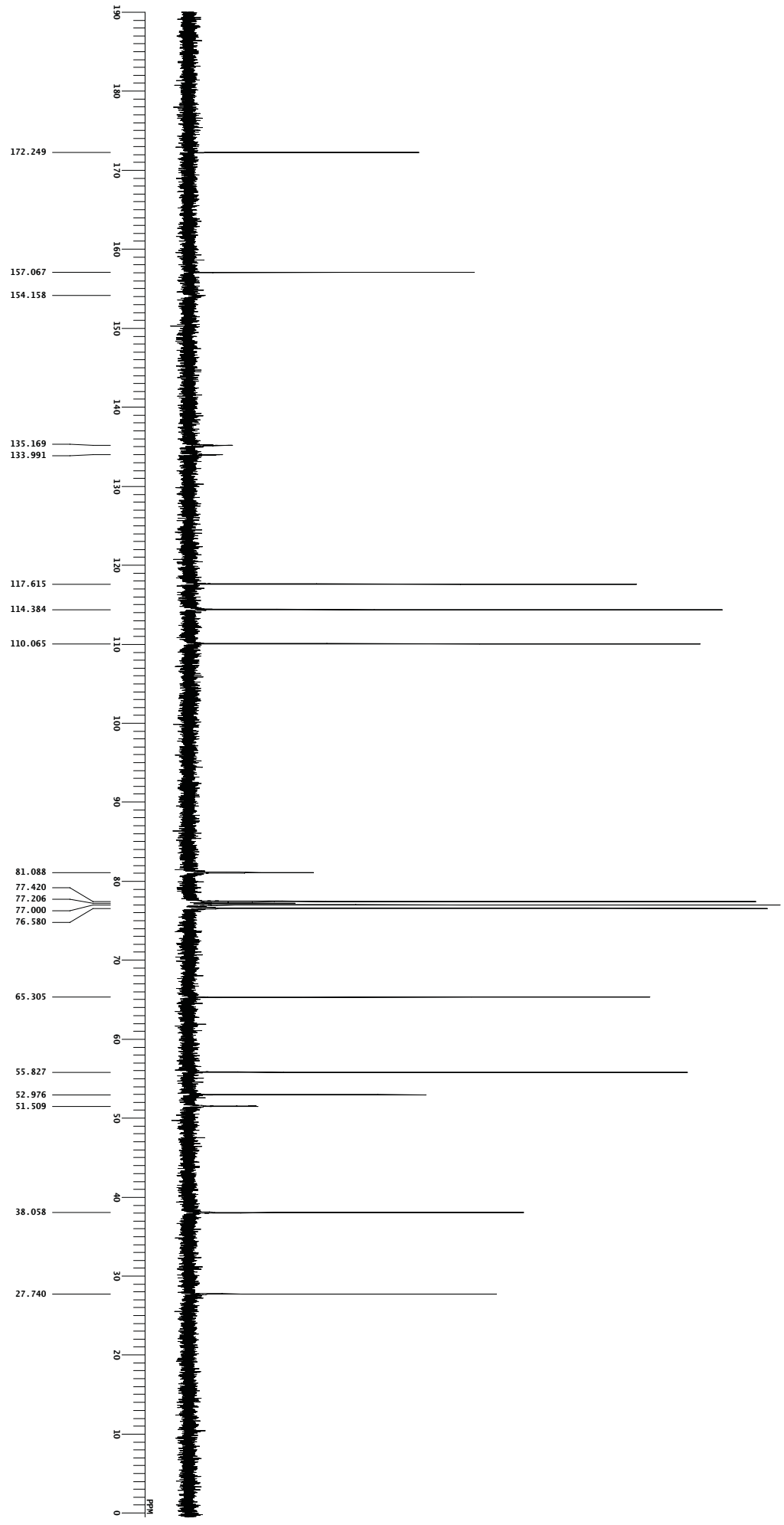
7.262
6.838
6.821
6.715
6.708
5.874
3.903
3.787
3.737
3.729
2.909
2.867
2.647
2.606
1.978
0.000
1.0870
1.0190
1.0465
1.0000
2.8797
3.1672
1.9776
4.0513
1.1546
0.9781
PPM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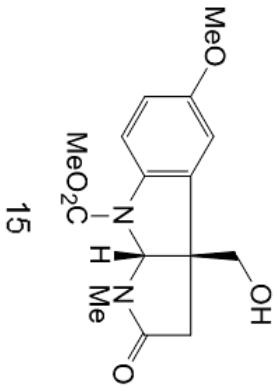
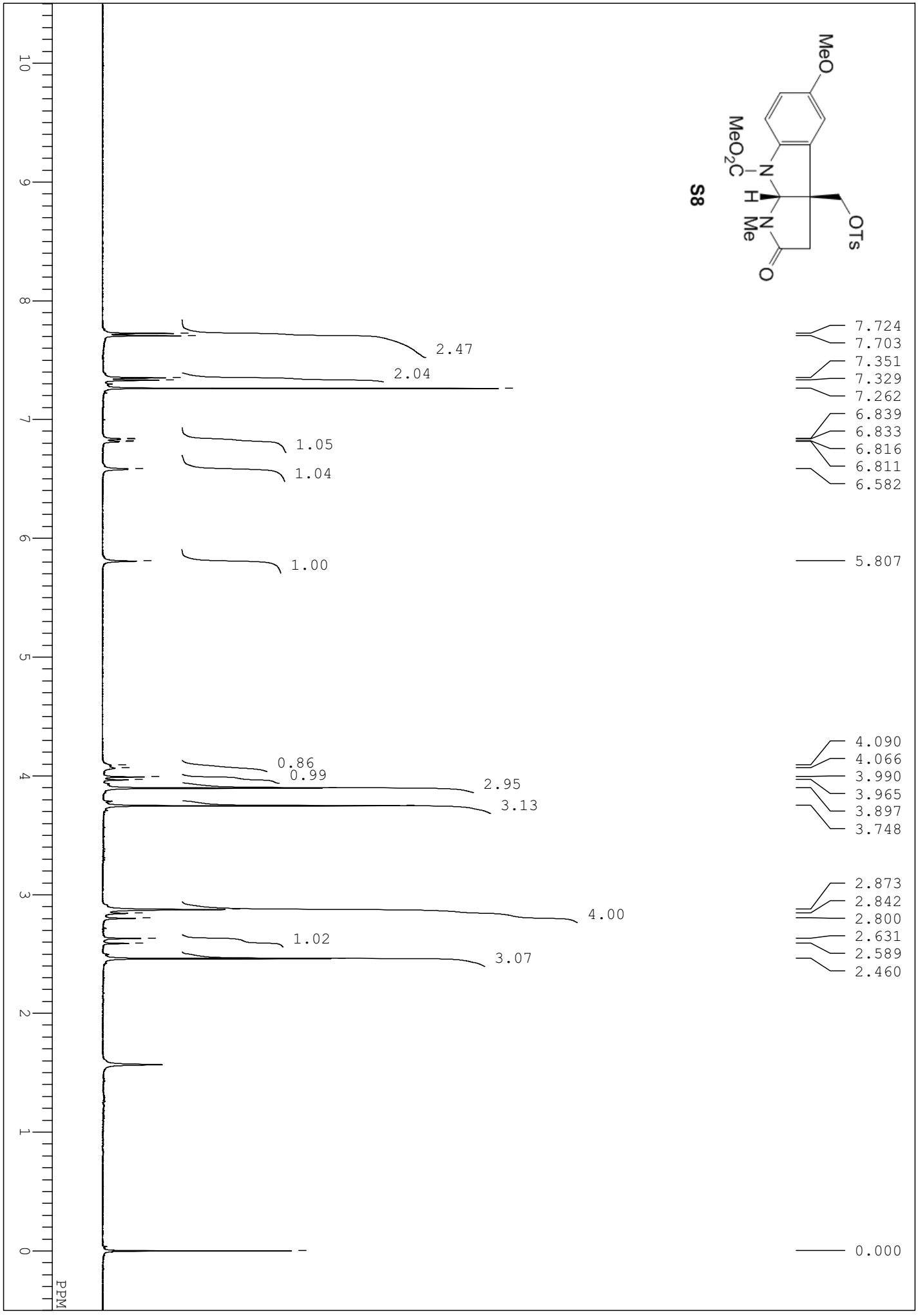
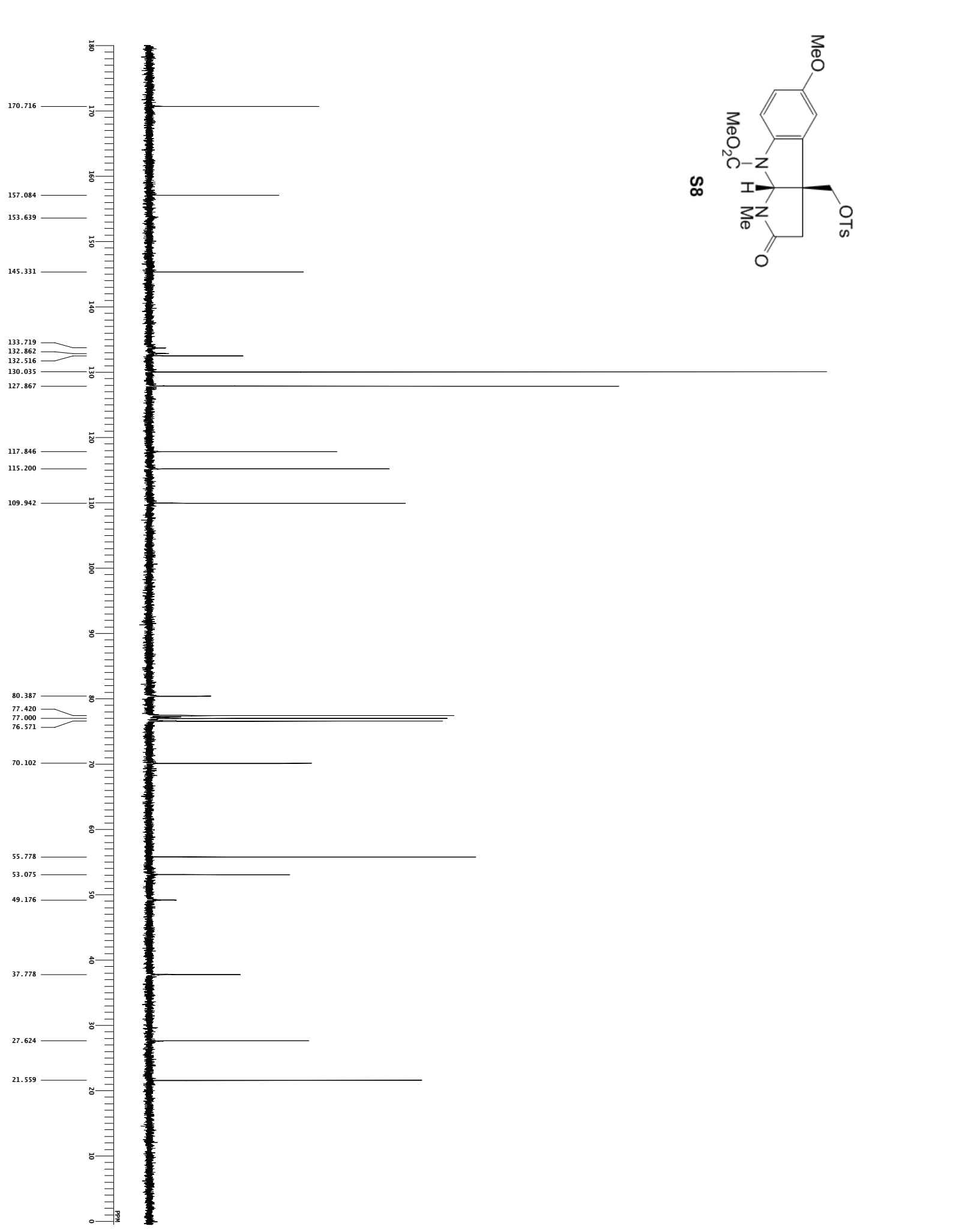
157.067
154.158
135.169
133.991
117.615
114.384
110.065
81.088
77.420
77.206
77.000
76.580
65.305
55.827
52.976
51.509
38.058
27.740
PPM


MeO
MeO2C
N
H
N
Me
O
OH

15


MeO
MeO2C
N
H
N
Me
O
OTs
S8
7.724
7.703
7.351
7.329
7.262
6.839
6.833
6.816
6.811
6.582
5.807
4.090
4.066
3.990
3.965
3.897
3.748
2.873
2.842
2.800
2.631
2.589
2.460
0.000
2.47
2.04
1.05
1.04
1.00
0.86
0.99
2.95
3.13
4.00
1.02
3.07
PPM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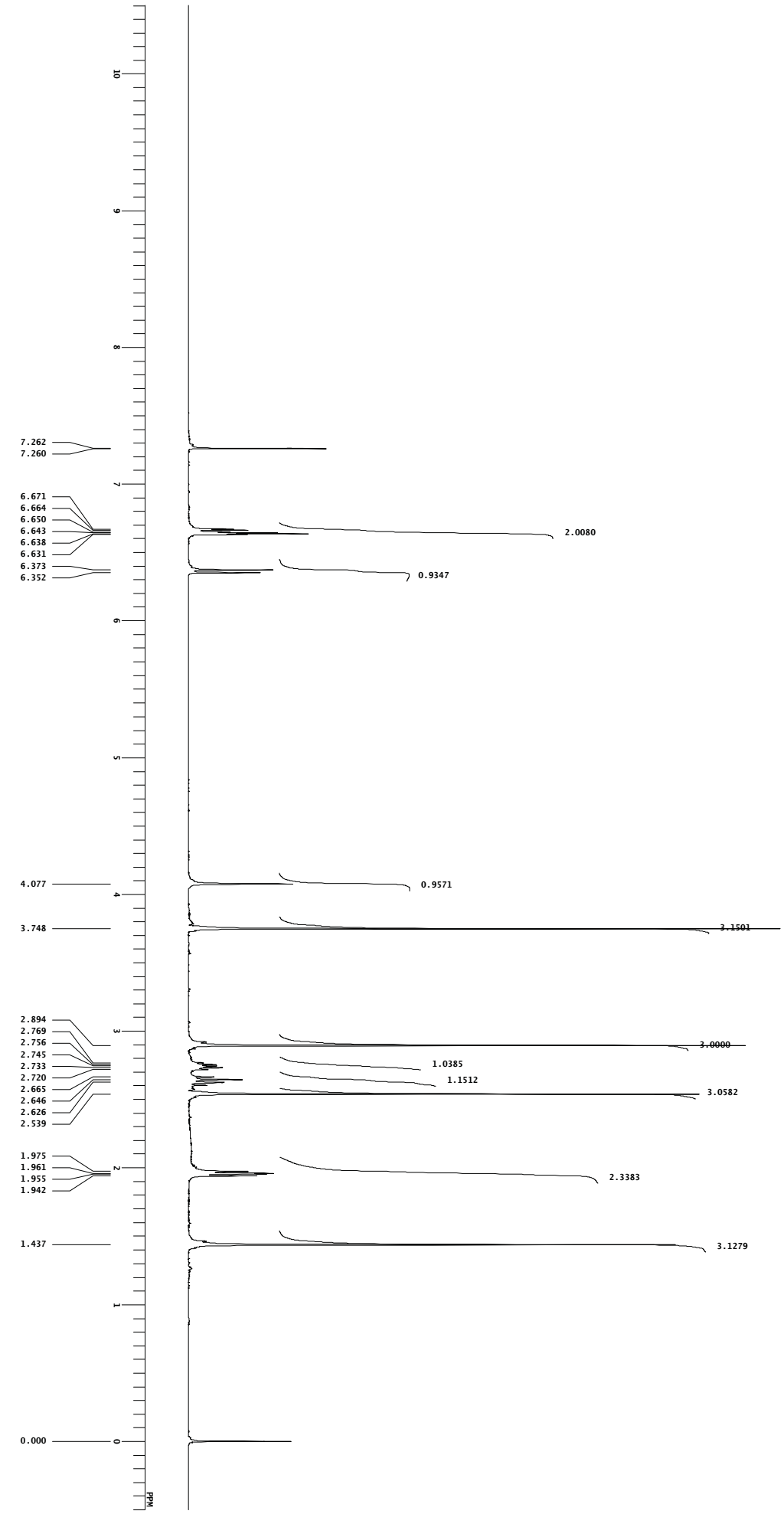
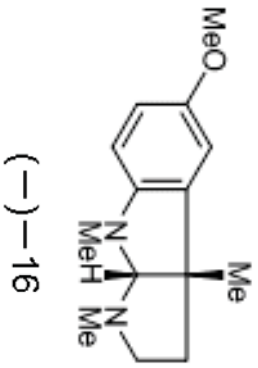
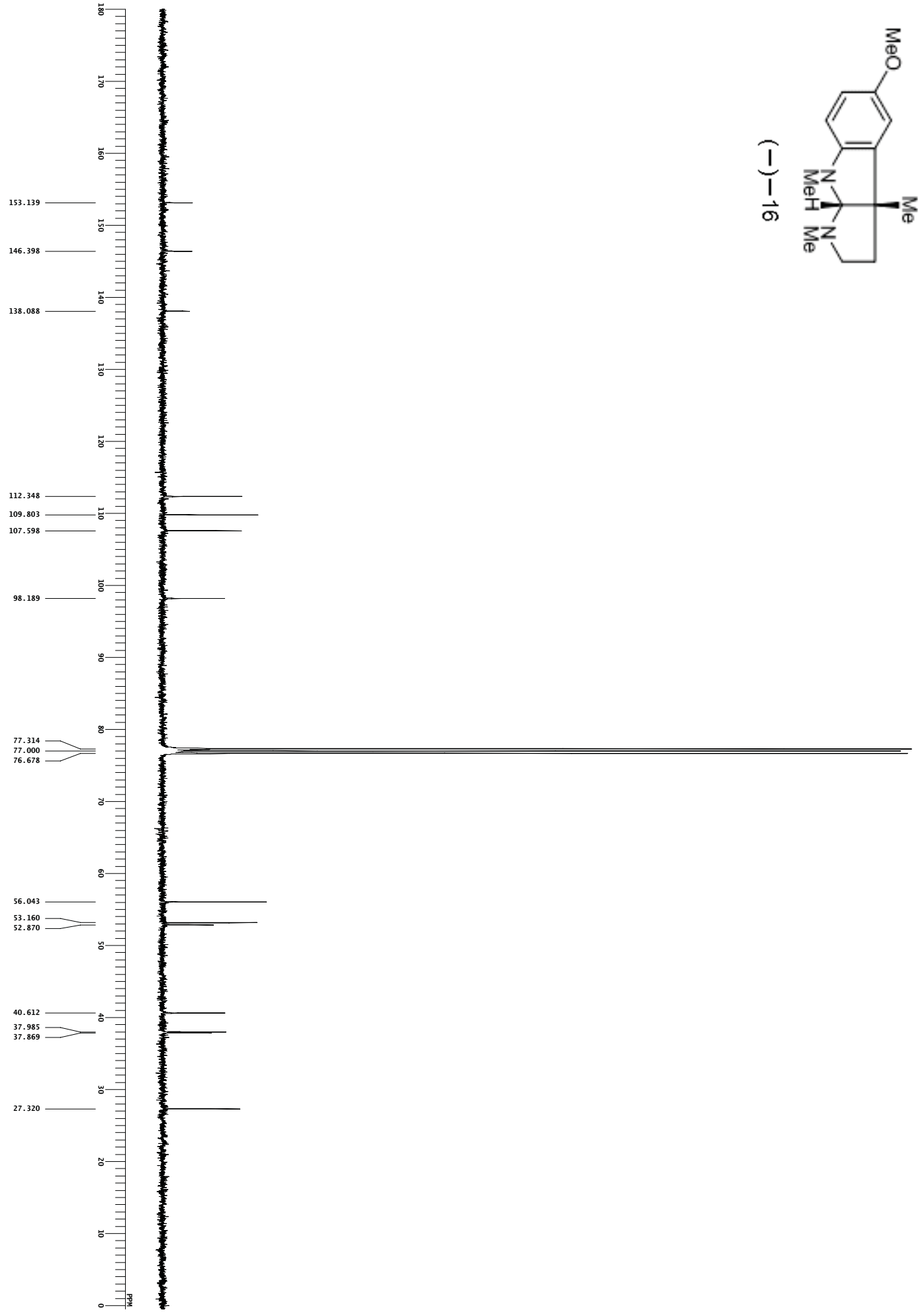
157.084
153.639
145.331
133.719
132.862
132.516
130.035
127.867
117.846
115.200
109.942
80.387
77.420
77.000
76.571
70.102
55.778
53.075
49.176
37.778
27.624
21.559
PPM
MeO
MeO2C
N
H
N
Me
O
OTs

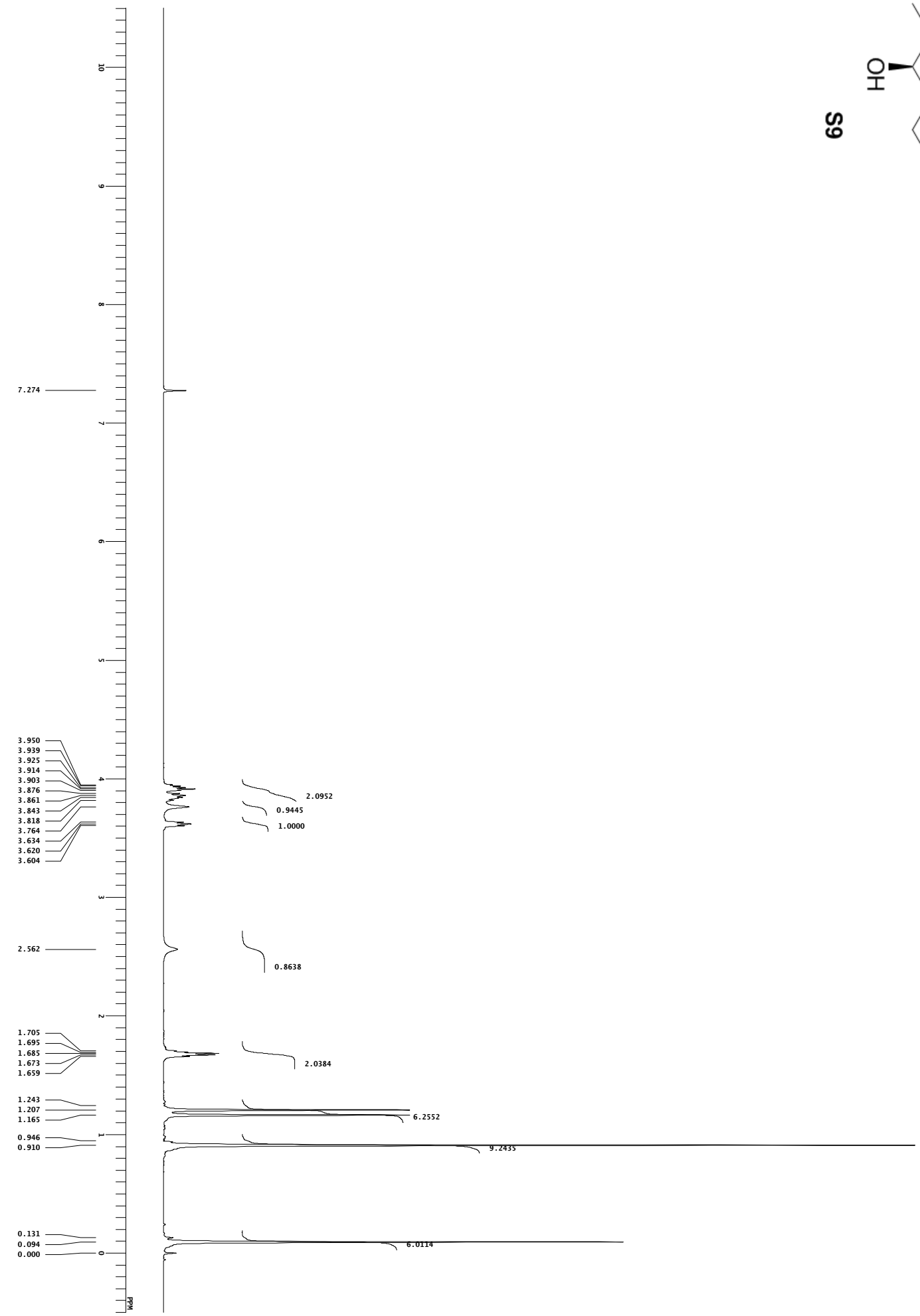
S8

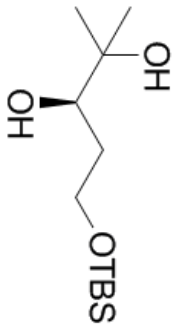

7.262
7.260
6.671
6.664
6.650
6.643
6.638
6.631
6.373
6.352
4.077
3.748
2.894
2.769
2.756
2.745
2.733
2.720
2.665
2.646
2.626
2.539
1.975
1.961
1.955
1.942
1.437
0.000
2.0080
0.9347
0.9571
3.1501
3.0000
1.0385
1.1512
3.0582
2.3383
3.1279
PPM


MeO
N
MeH
N
Me
Me

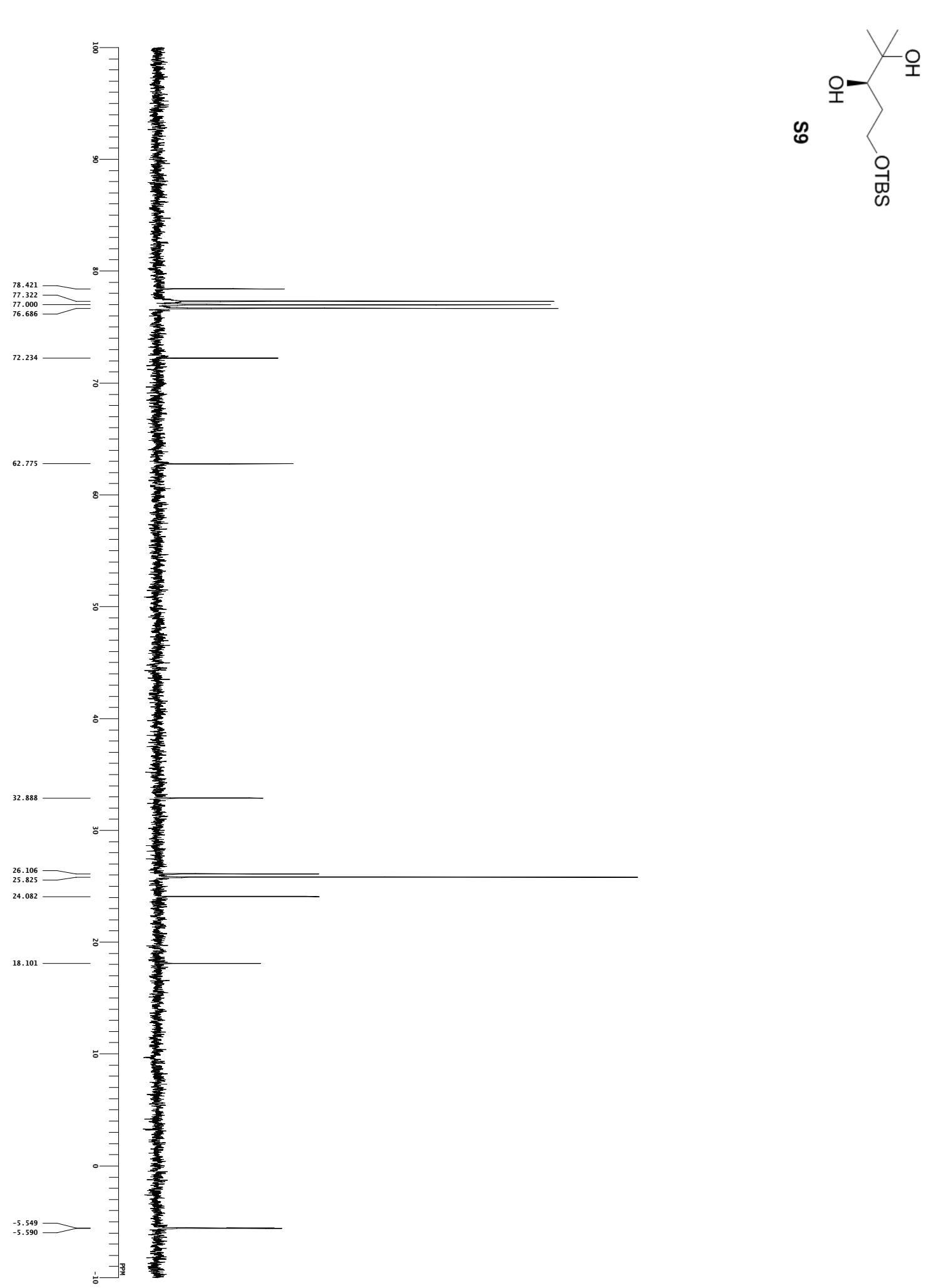
(−)−16


153.139
146.398
138.088
112.348
109.803
107.598
98.189
77.314
77.000
76.678
56.043
53.160
52.870
40.612
37.985
37.869
27.320
PPM
MeO
Me
N
MeH
N
Me
(−)−16


7.274
3.950
3.939
3.925
3.914
3.903
3.876
3.861
3.843
3.818
3.764
3.634
3.620
3.604
2.562
1.705
1.695
1.685
1.673
1.659
1.243
1.207
1.165
0.946
0.910
0.131
0.094
0.000
2.0952
0.9445
1.0000
0.8638
2.0384
6.2552
9.2435
6.0114
ppm

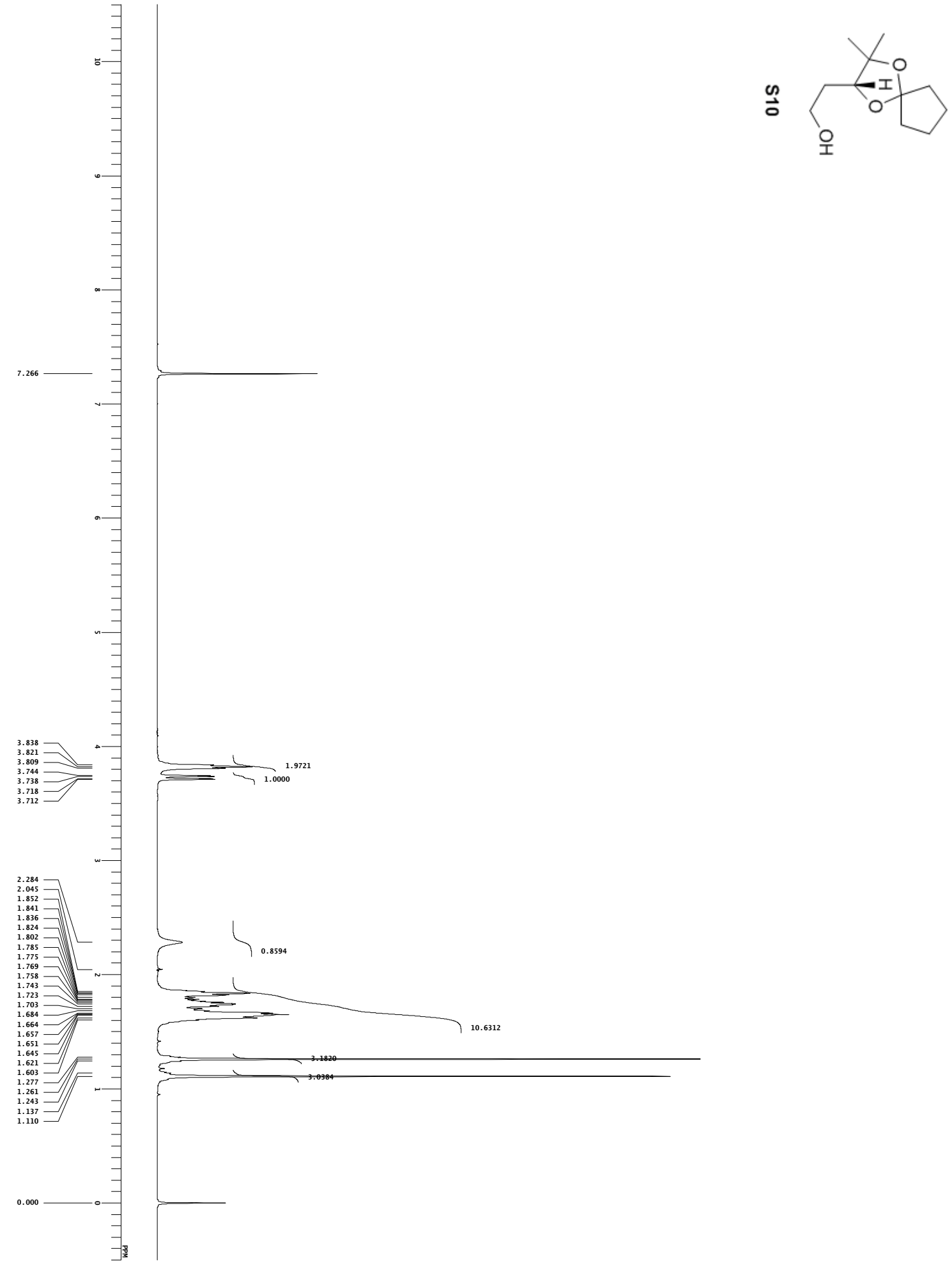

OH
OH
OTBS

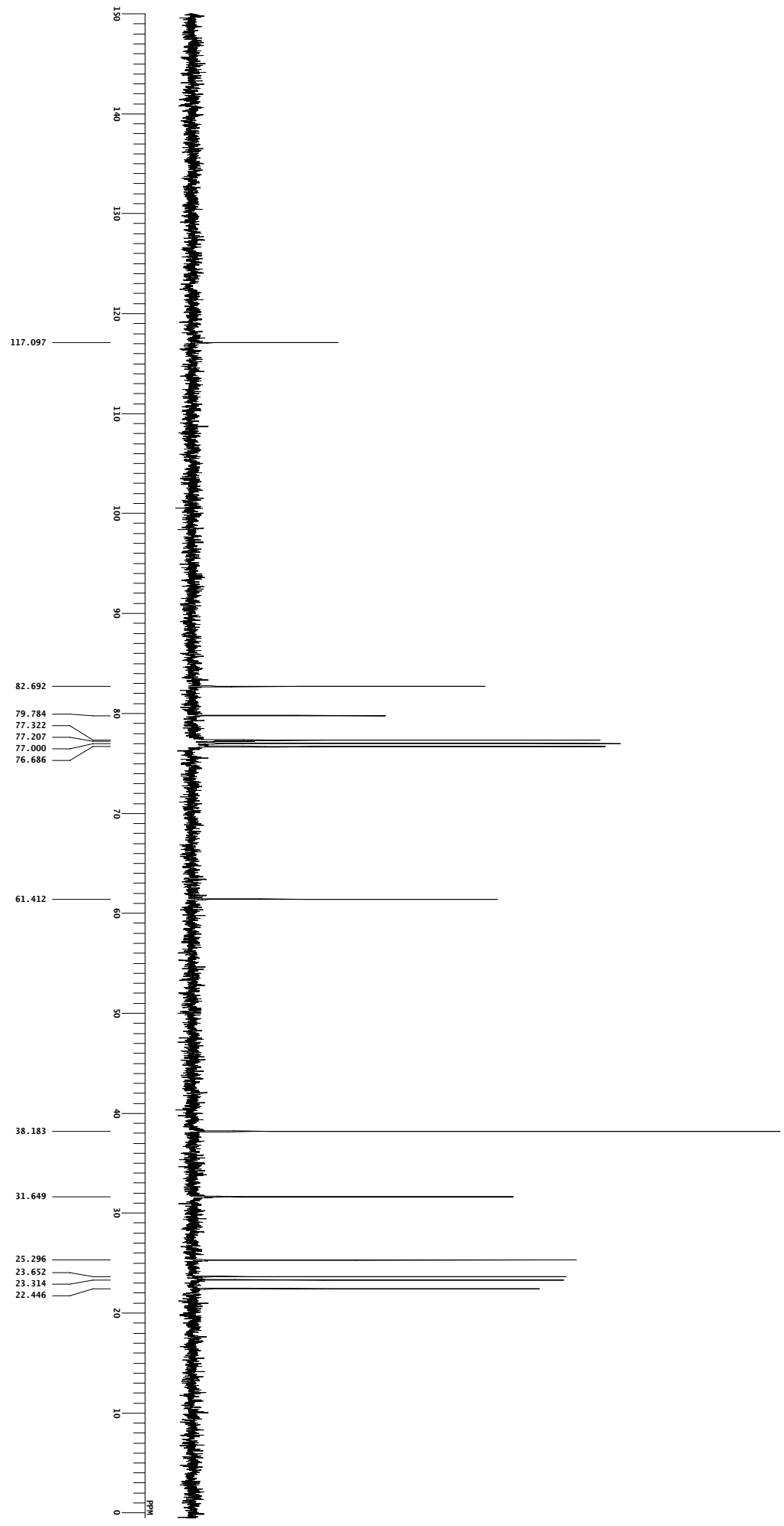
S9

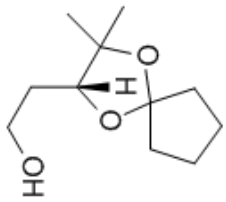

78.421
77.322
77.000
76.686
72.234
62.775
32.888
26.106
25.825
24.082
18.101
-5.549
-5.590
PPM

OH
OH
OTBS

S9

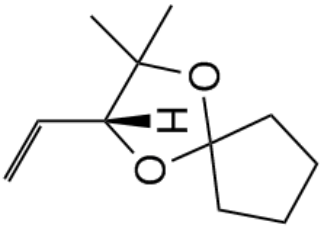

S10
O
H
O
OH
7.266
3.838
3.821
3.809
3.744
3.738
3.718
3.712
1.9721
1.0000
2.284
2.045
1.852
1.841
1.836
1.824
1.802
1.785
1.775
1.769
1.758
1.743
1.723
1.703
1.684
1.664
1.657
1.651
1.645
1.621
1.603
1.277
1.261
1.243
1.137
1.110
0.8594
10.6312
3.1820
3.0384
0.000
PPM

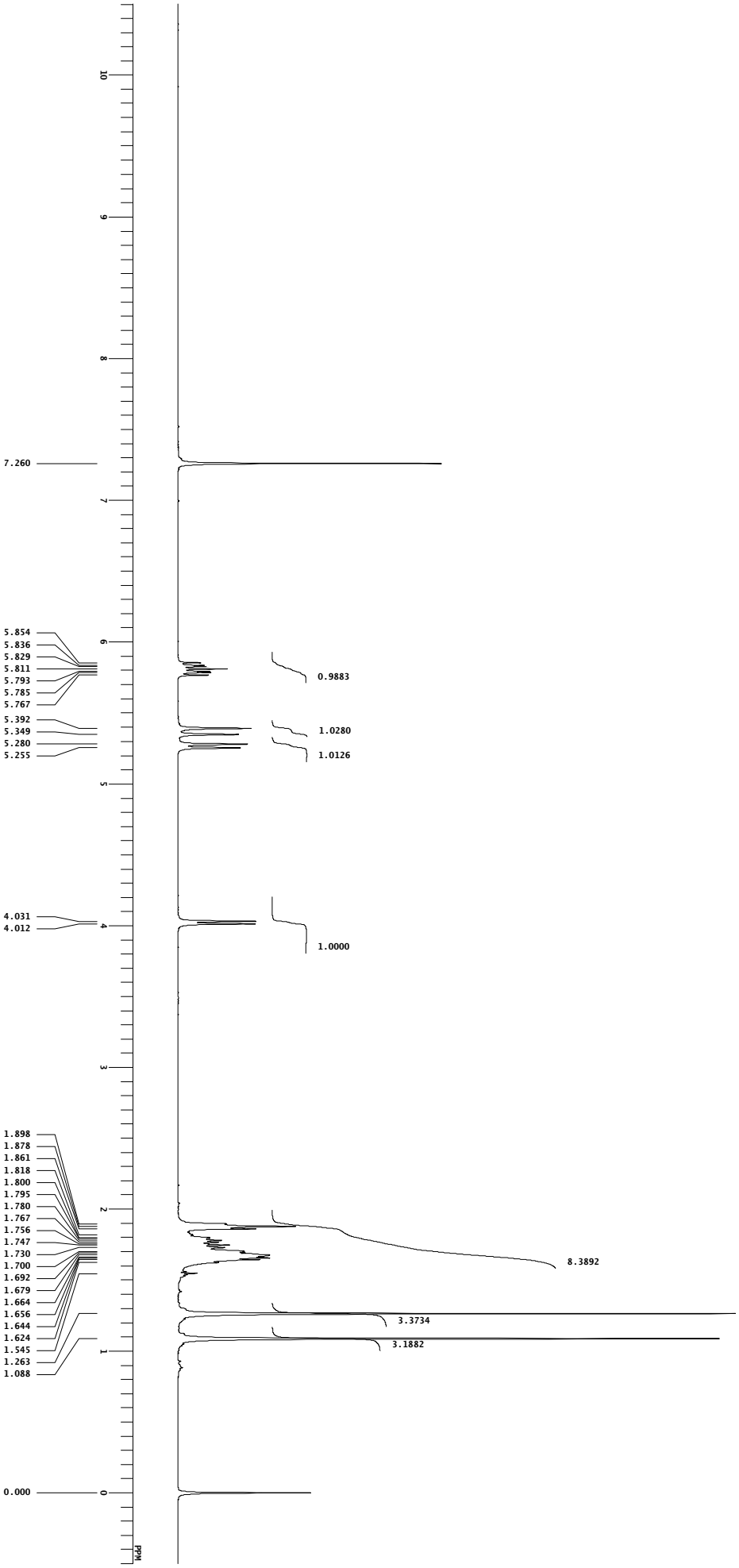

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM
117.097
82.692
79.784
77.322
77.207
77.000
76.686
61.412
38.183
31.649
25.296
23.652
23.314
22.446

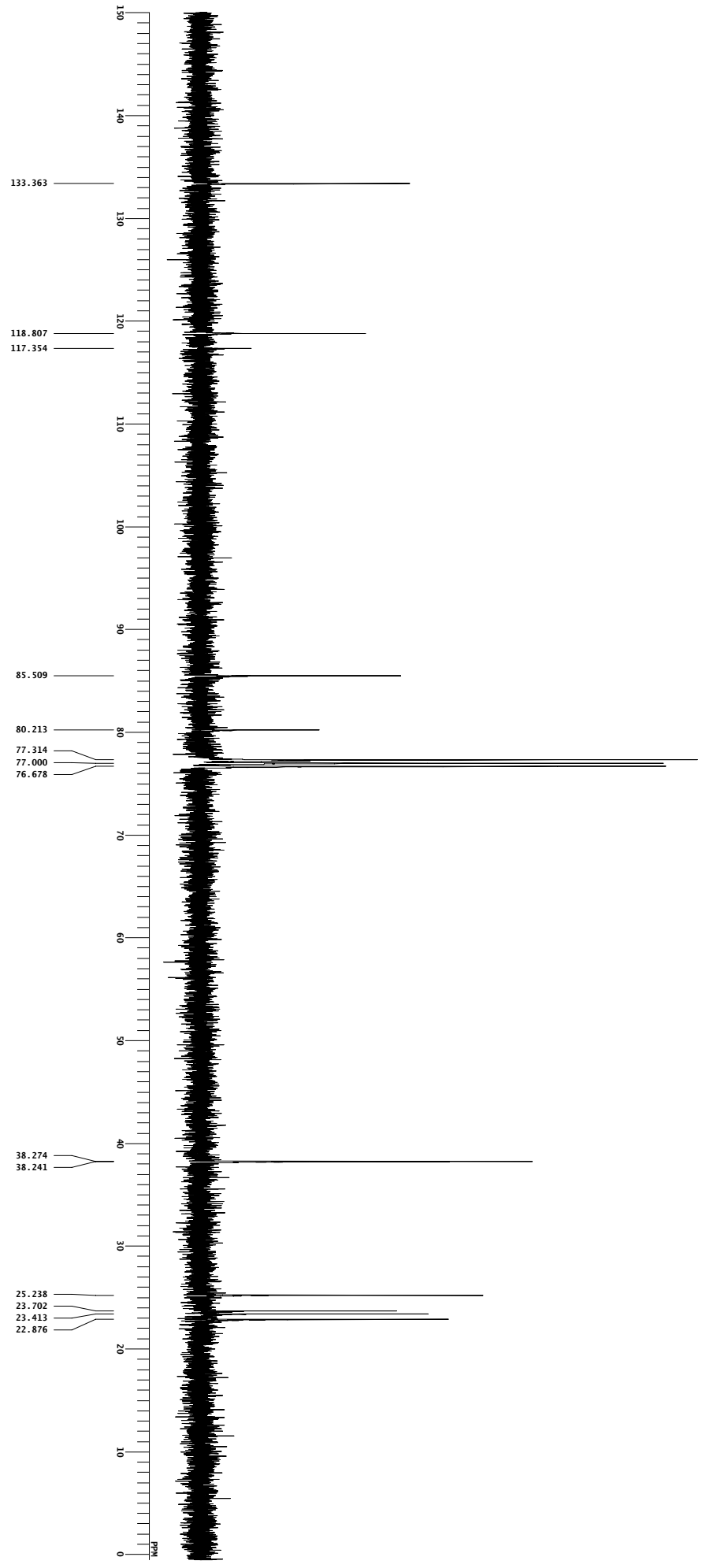

O
H
O
OH

S10

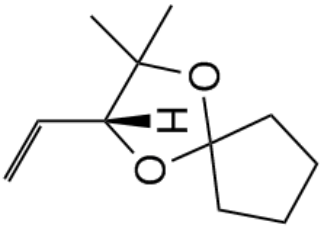
S11

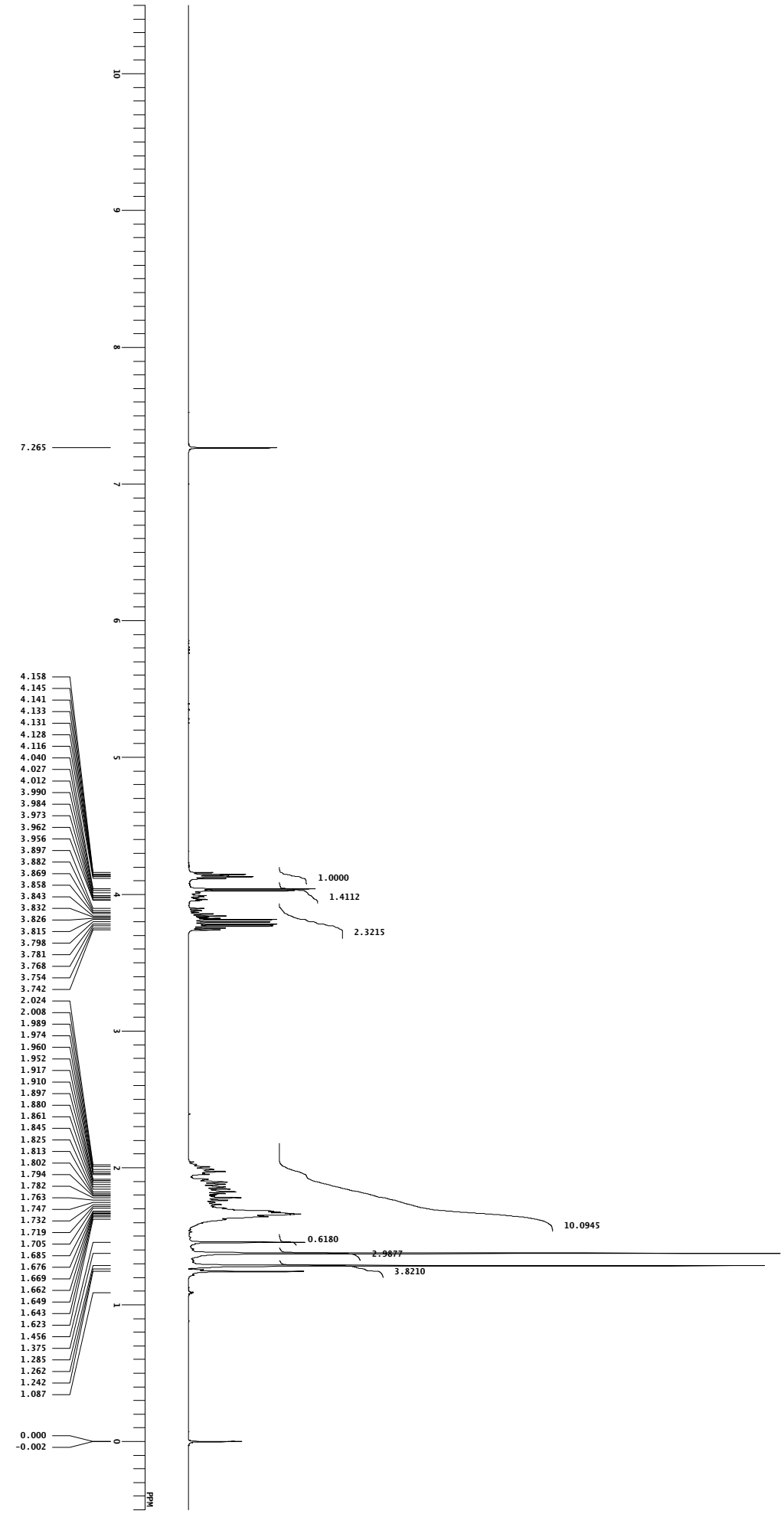

O
H
O

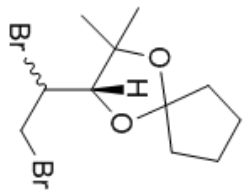

7.260
5.854
5.836
5.829
5.811
5.793
5.785
5.767
5.392
5.349
5.280
5.255
4.031
4.012
1.898
1.878
1.861
1.818
1.800
1.795
1.780
1.767
1.756
1.747
1.730
1.700
1.692
1.679
1.664
1.656
1.644
1.624
1.545
1.263
1.088
0.000
0.9883
1.0280
1.0126
1.0000
8.3892
3.3734
3.1882
PPM


133.363
118.807
117.354
85.509
80.213
77.314
77.000
76.678
38.274
38.241
25.238
23.702
23.413
22.876
PPM

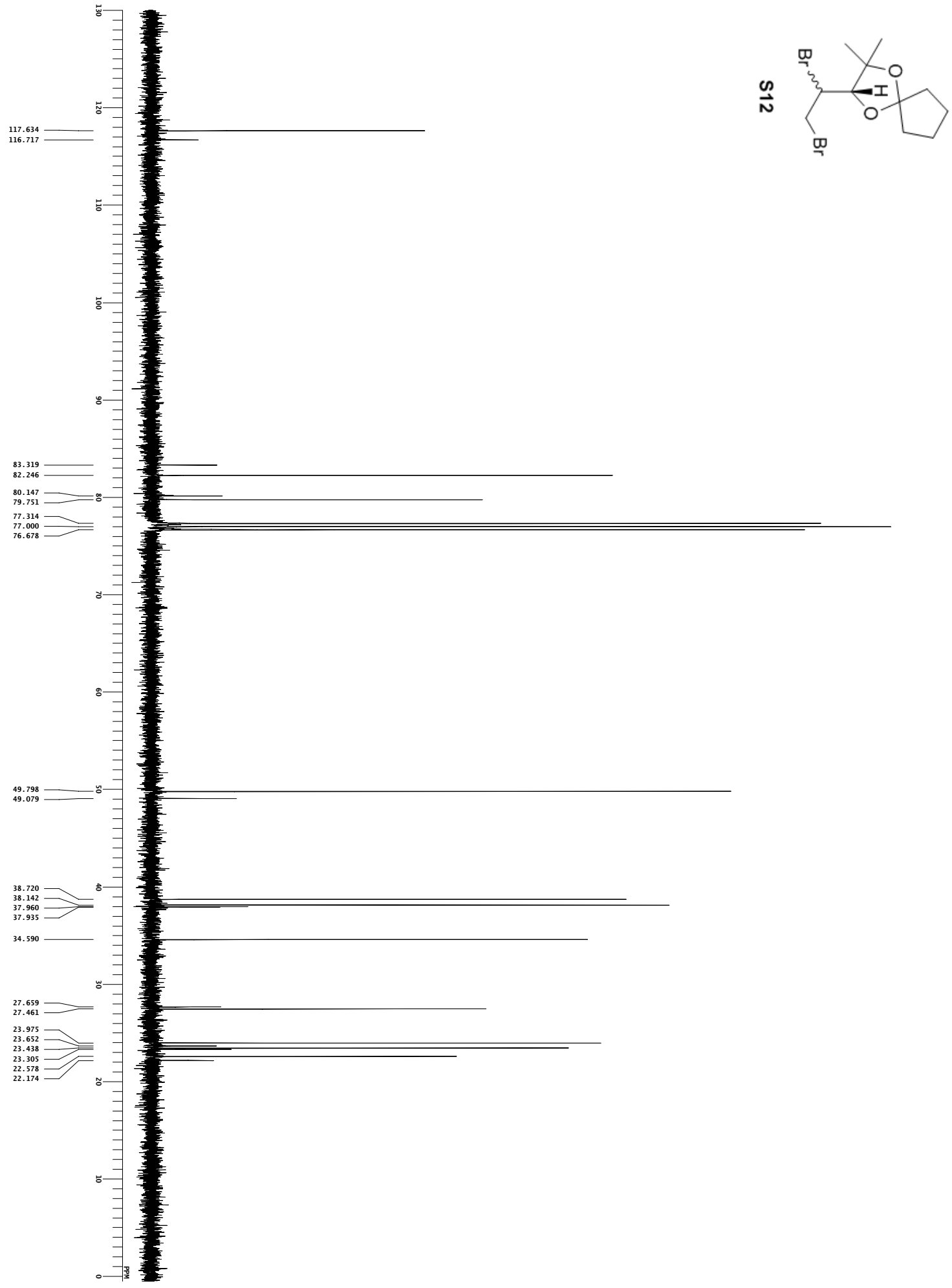
S11


O
H
O


7.265
4.158
4.145
4.141
4.133
4.131
4.128
4.116
4.040
4.027
4.012
3.990
3.984
3.973
3.962
3.956
3.897
3.882
3.869
3.858
3.843
3.832
3.826
3.815
3.798
3.781
3.768
3.754
3.742
2.024
2.008
1.989
1.974
1.960
1.952
1.917
1.910
1.897
1.880
1.861
1.845
1.825
1.813
1.802
1.794
1.782
1.763
1.747
1.732
1.719
1.705
1.685
1.676
1.669
1.662
1.649
1.643
1.623
1.456
1.375
1.285
1.262
1.242
1.087
0.000
-0.002
1.0000
1.4112
2.3215
10.0945
0.6180
2.9877
3.8210
PPM

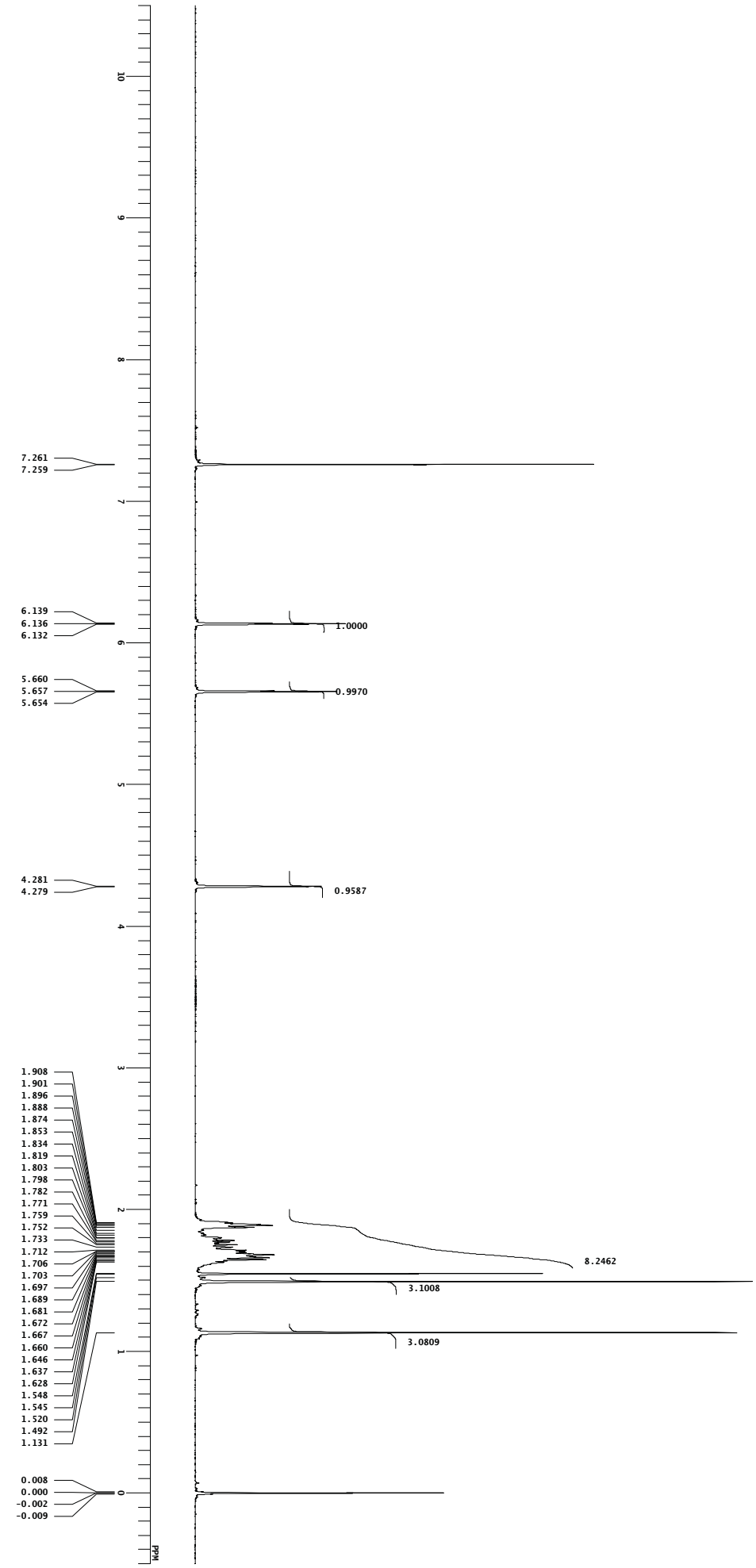

Br
O
H
O
Br

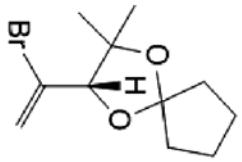
S12


117.634
116.717
83.319
82.246
80.147
79.751
77.314
77.000
76.678
49.798
49.079
38.720
38.142
37.960
37.935
34.590
27.659
27.461
23.975
23.652
23.438
23.305
22.578
22.174
PPM

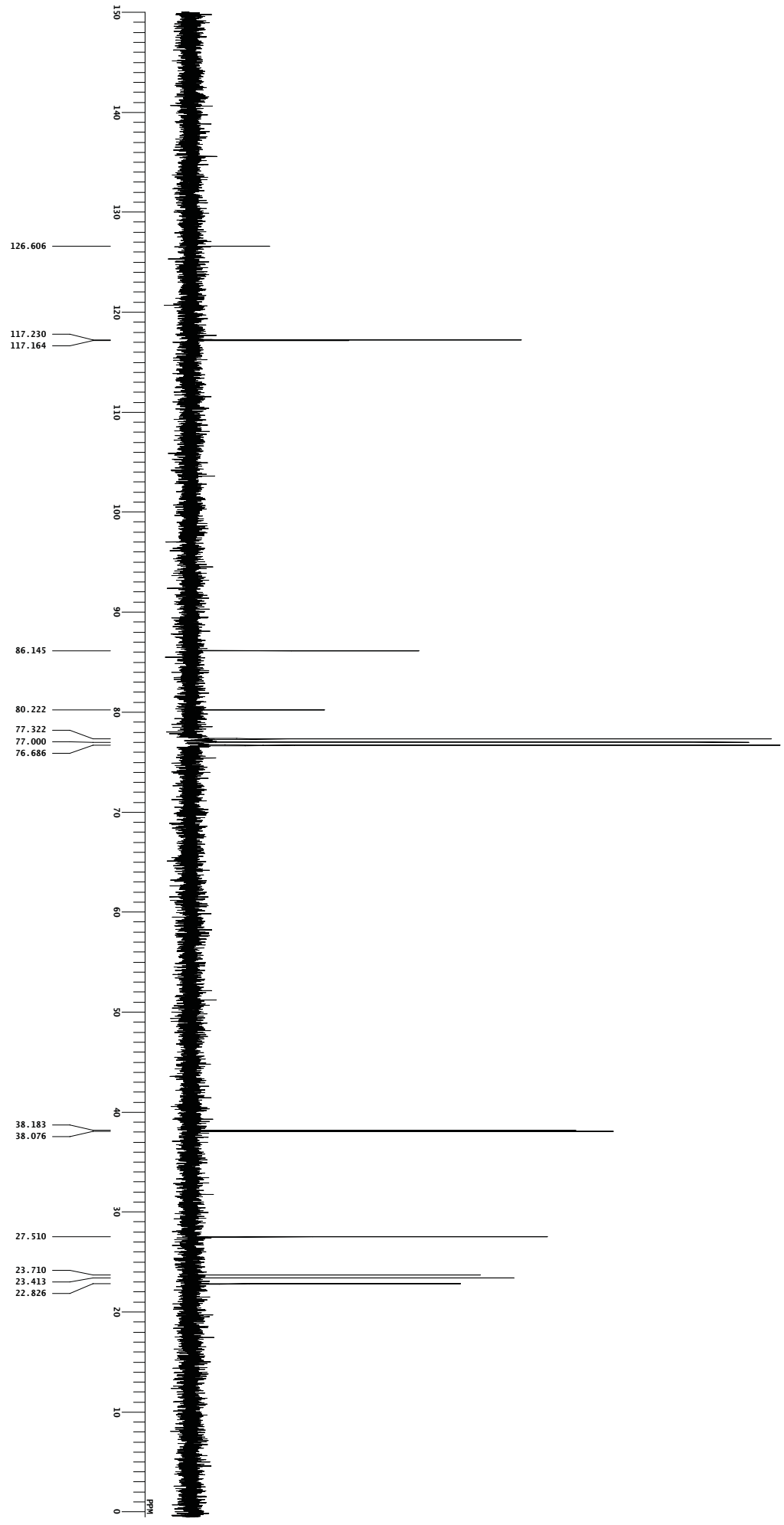
Br
O
H
O
Br

S12

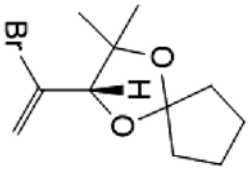

7.261
7.259
6.139
6.136
6.132
1.0000
5.660
5.657
5.654
0.9970
4.281
4.279
0.9587
1.908
1.901
1.896
1.888
1.874
1.853
1.834
1.819
1.803
1.798
1.782
1.771
1.759
1.752
1.733
1.712
1.706
1.703
1.697
1.689
1.681
1.672
1.667
1.660
1.646
1.637
1.628
1.548
1.545
1.520
1.492
1.131
8.2462
3.1008
3.0809
0.008
0.000
-0.002
-0.009
PPM

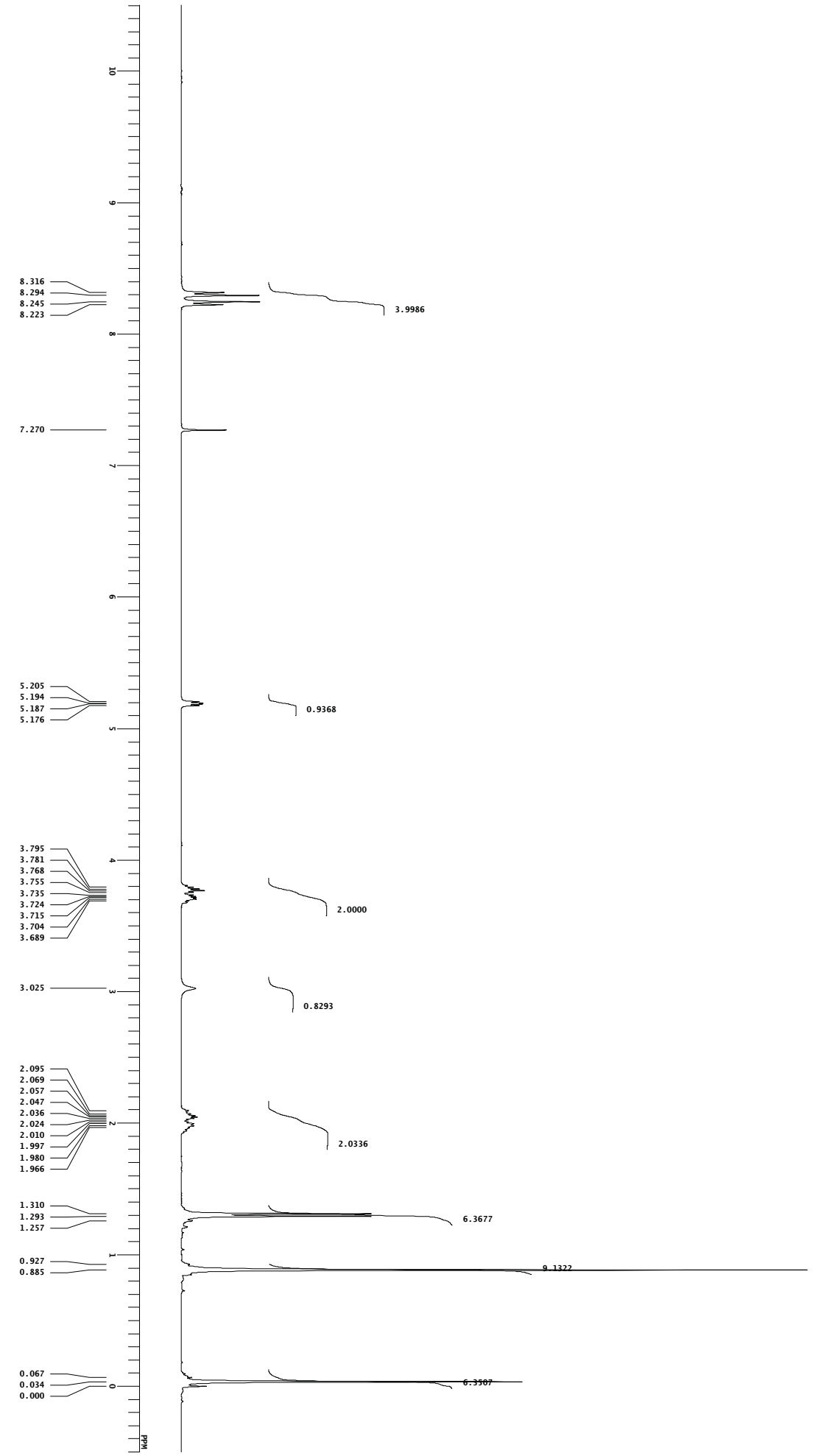

Br
O
H
O

S13


126.606
117.230
117.164
86.145
80.222
77.322
77.000
76.686
38.183
38.076
27.510
23.710
23.413
22.826
PPM

S13


Br
O
H
O


8.316
8.294
8.245
8.223
7.270
5.205
5.194
5.187
5.176
3.795
3.781
3.768
3.755
3.735
3.724
3.715
3.704
3.689
3.025
2.095
2.069
2.057
2.047
2.036
2.024
2.010
1.997
1.980
1.966
1.310
1.293
1.257
0.927
0.885
0.067
0.034
0.000
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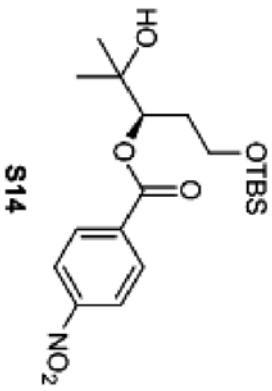
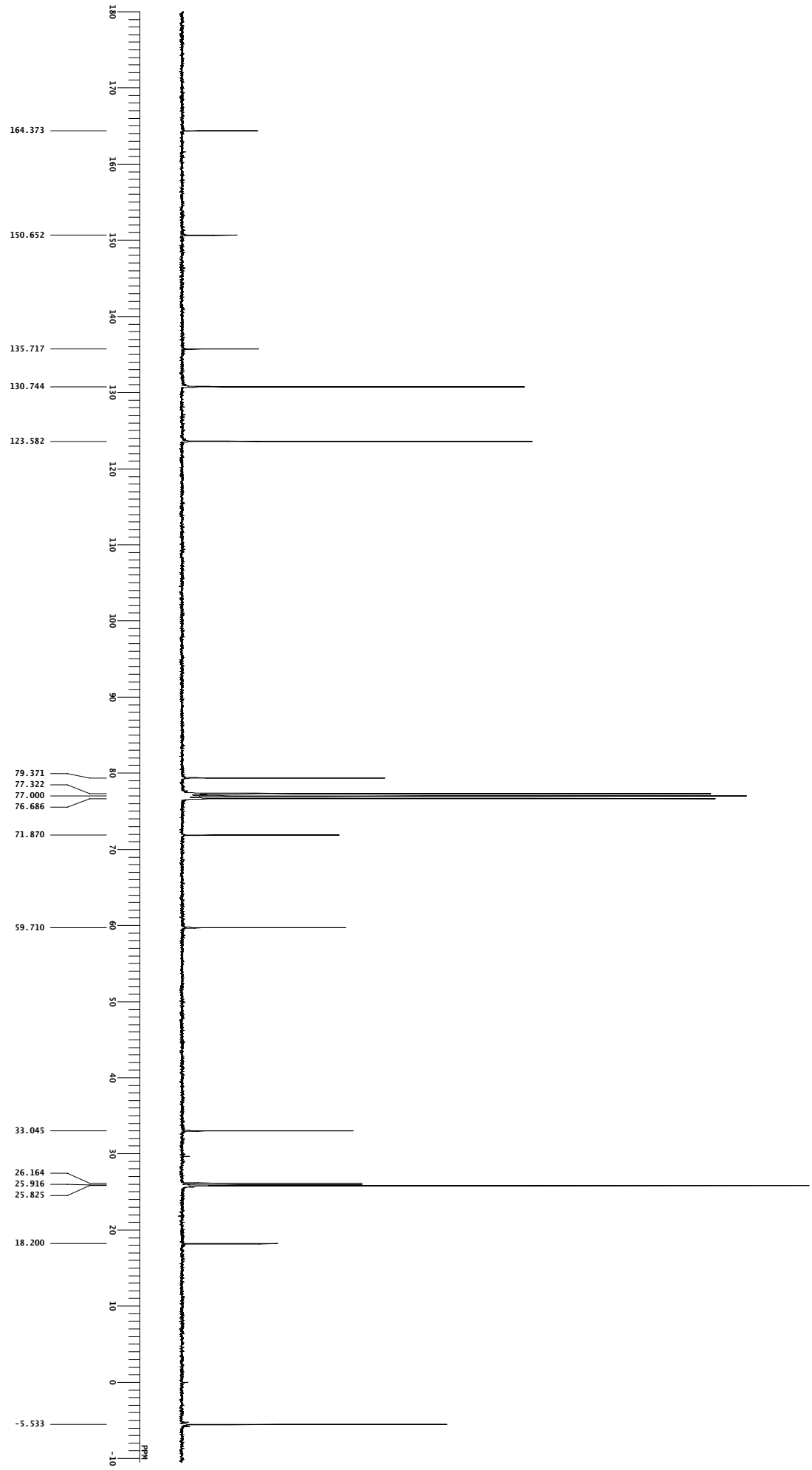
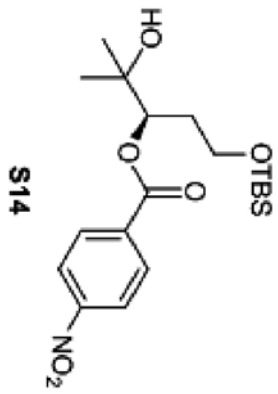
0.9368
2.0000
0.8293
2.0336
6.3677
9.1322
6.3507
PPM

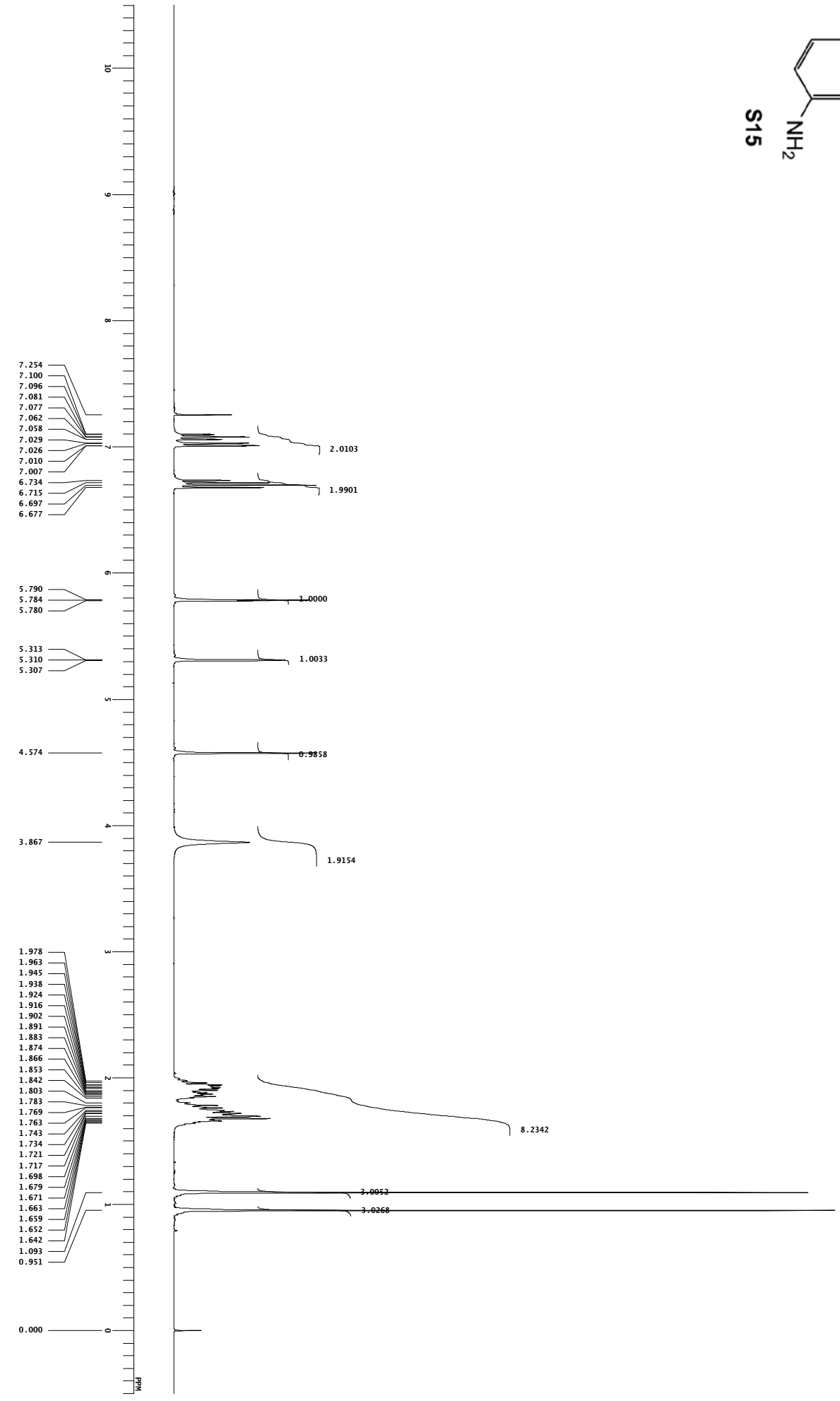

HO
OTBS
O
O
NO2

S14


164.373
150.652
135.717
130.744
123.582
79.371
77.322
77.000
76.686
71.870
59.710
33.045
26.164
25.916
25.825
18.200
-5.533
PPM


OH
O
O
OTBS
NO2

S14


S15
NH2
O
H
O
7.254
7.100
7.096
7.081
7.077
7.062
7.058
7.029
7.026
7.010
7.007
6.734
6.715
6.697
6.677
5.790
5.784
5.780
5.313
5.310
5.307
4.574
3.867
1.978
1.963
1.945
1.938
1.924
1.916
1.902
1.891
1.883
1.874
1.866
1.853
1.842
1.803
1.783
1.769
1.763
1.743
1.734
1.721
1.717
1.698
1.679
1.671
1.663
1.659
1.652
1.642
1.093
0.951
0.000
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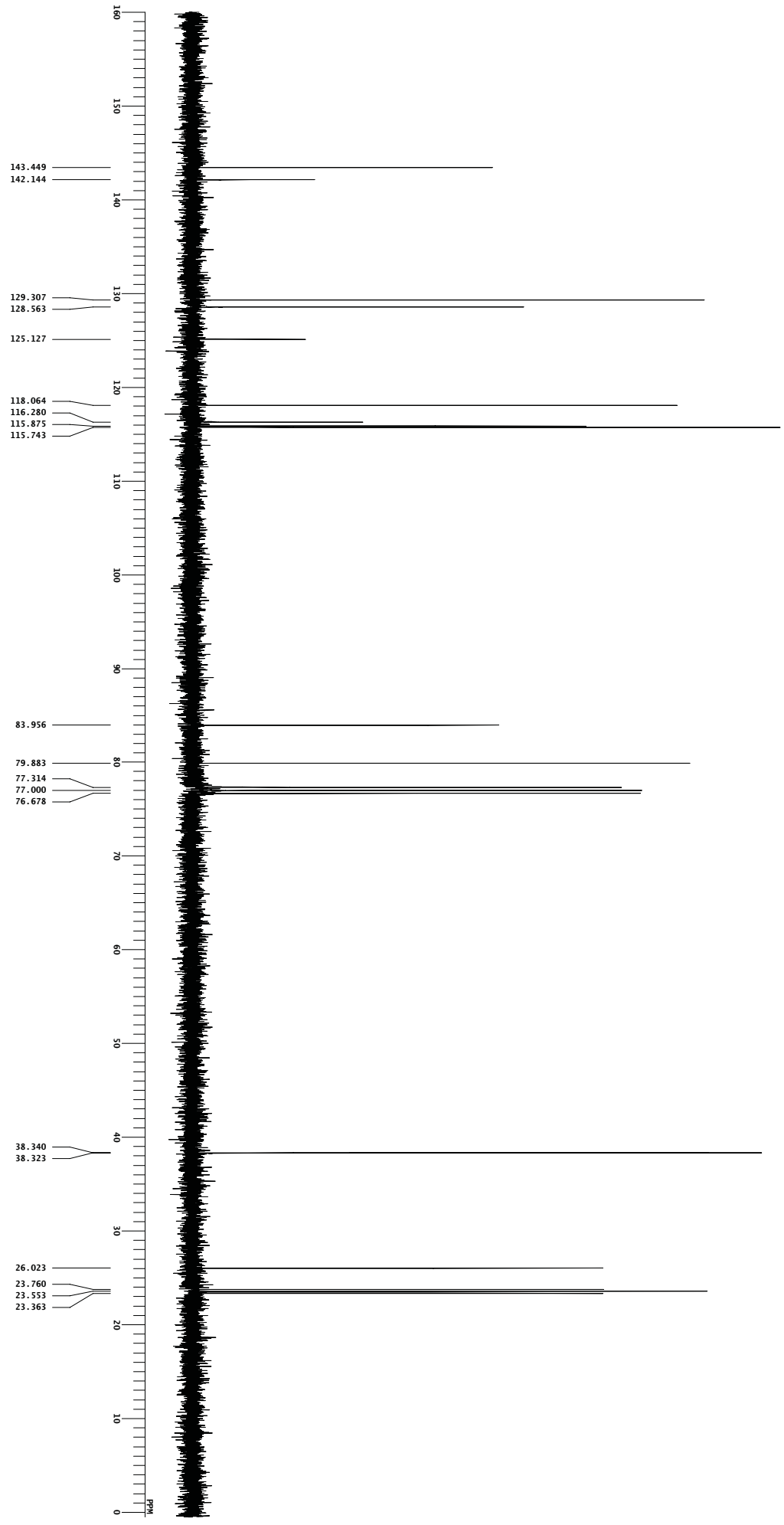
1.9901
1.0000
1.0033
0.9858
1.9154
8.2342
3.0052
3.0268
PPM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142.144
129.307
128.563
125.127
118.064
116.280
115.875
115.743
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79.883
77.314
77.000
76.678
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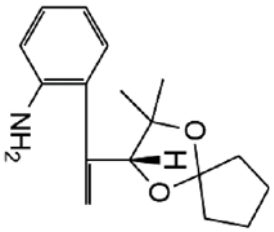
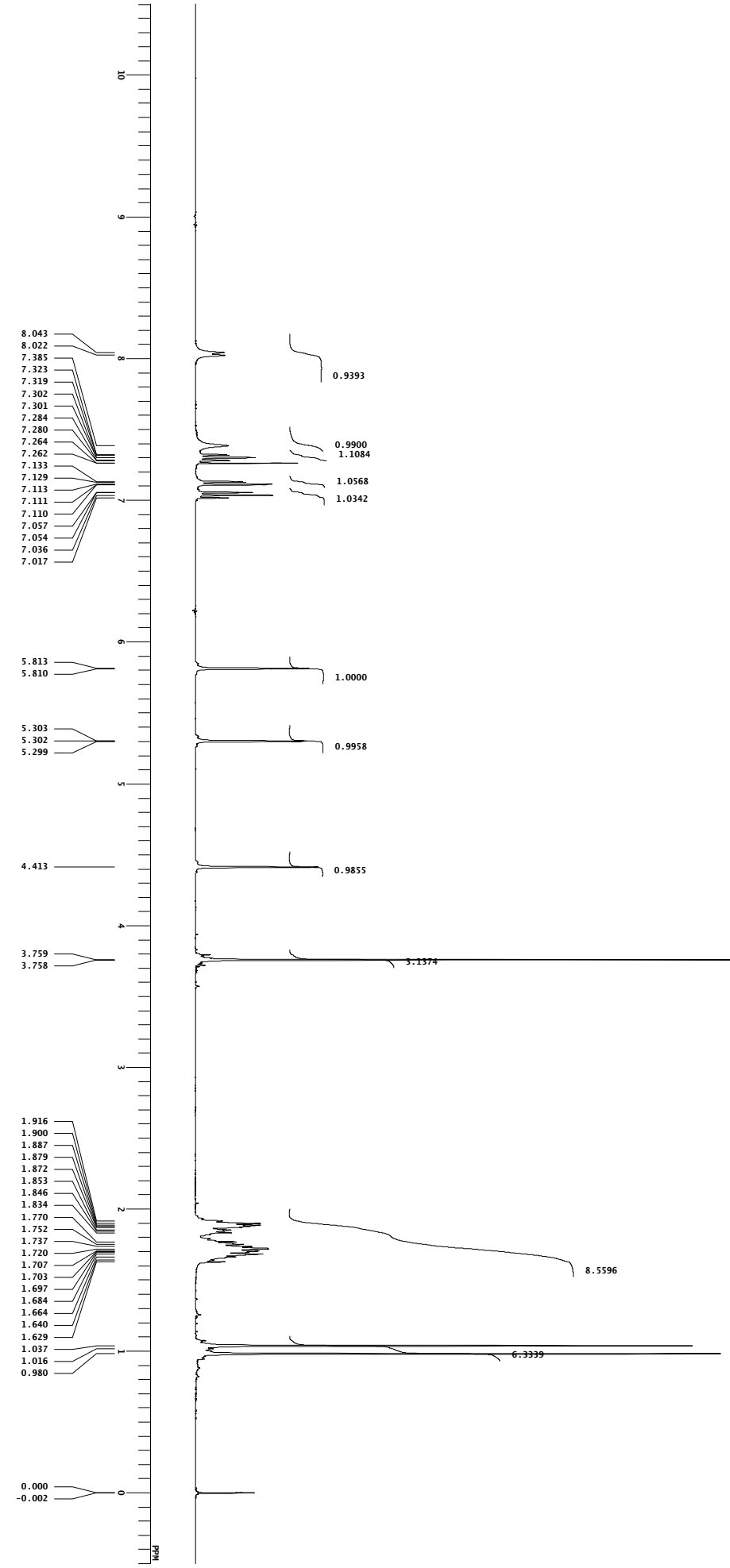
38.323
26.023
23.760
23.553
23.363
PPM


NH2
O
H
O

S15


8.043
8.022
7.385
7.323
7.319
7.302
7.301
7.284
7.280
7.264
7.262
7.133
7.129
7.113
7.111
7.110
7.057
7.054
7.036
7.017
5.813
5.810
5.303
5.302
5.299
4.413
3.759
3.758
1.916
1.900
1.887
1.879
1.872
1.853
1.846
1.834
1.770
1.752
1.737
1.720
1.707
1.703
1.697
1.684
1.664
1.640
1.629
1.037
1.016
0.980
0.000
-0.002
0.9393
0.9900
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1.0000
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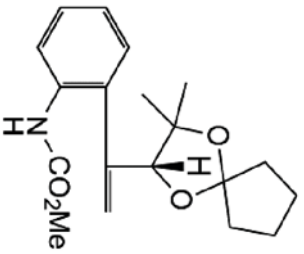
6.3339
PPM

S16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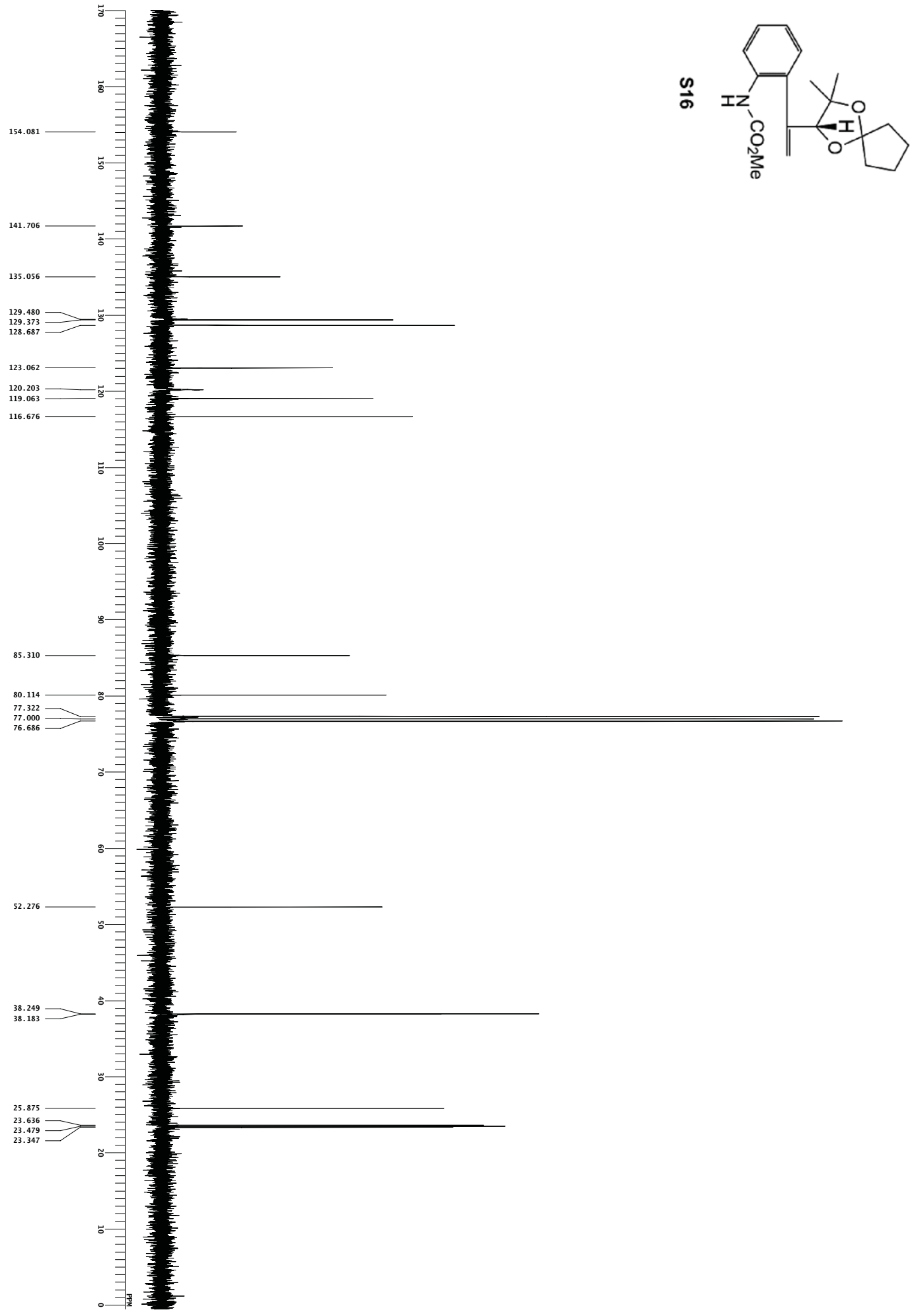
H
CO2Me
O
H
O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135.056
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128.687
123.062
120.203
119.063
116.676
85.310
80.114
77.322
77.000
76.686
52.276
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25.875
23.636
23.479
23.347
PPM

S16
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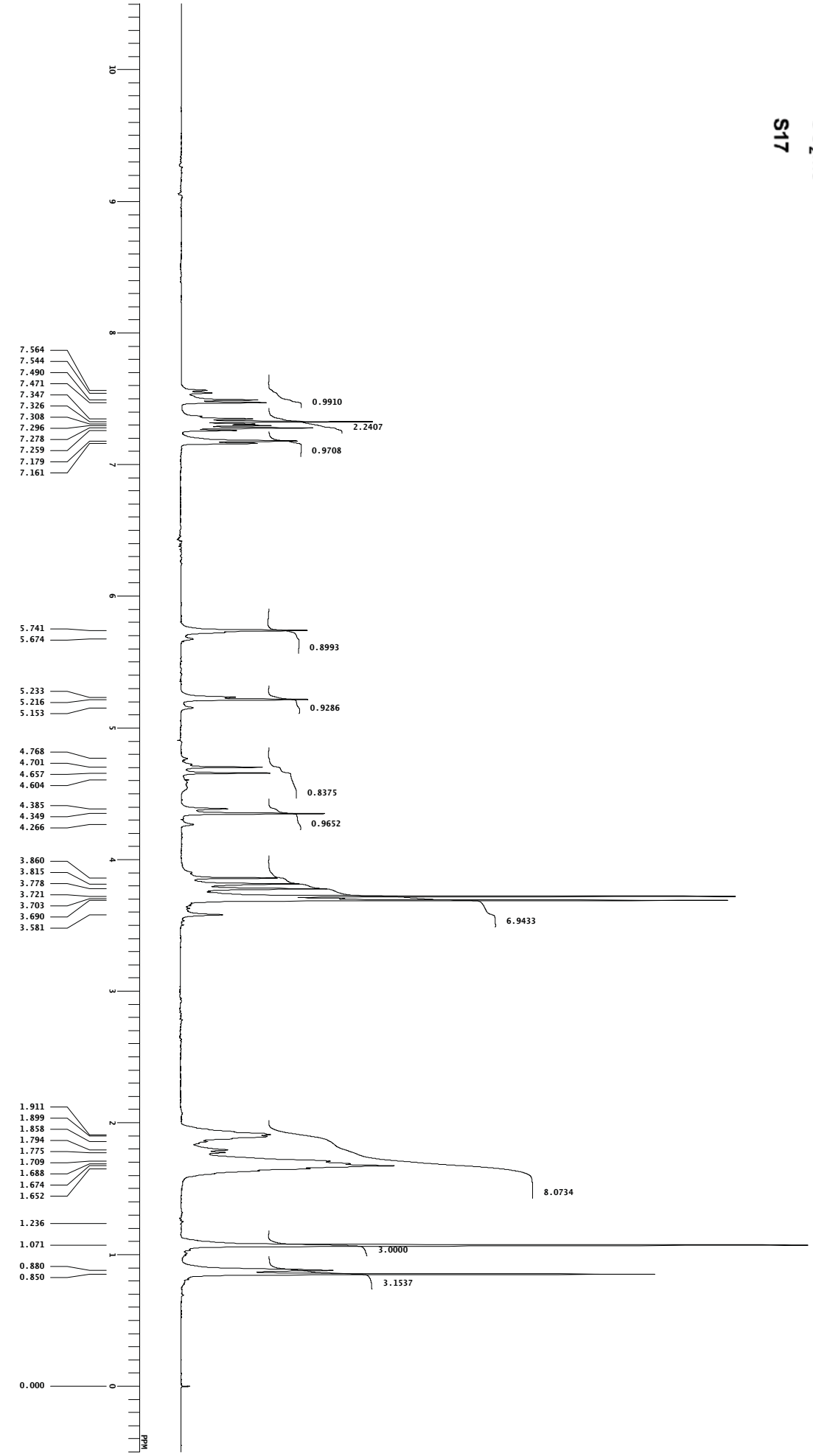
H
CO2Me
O
H
O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7.471
7.347
7.326
7.308
7.296
7.278
7.259
7.179
7.161
0.9910
2.2407
0.9708
5.741
5.674
0.8993
5.233
5.216
5.153
0.9286
4.768
4.701
4.657
4.604
0.8375
4.385
4.349
4.266
0.9652
3.860
3.815
3.778
3.721
3.703
3.690
3.581
6.9433
1.911
1.899
1.858
1.794
1.775
1.709
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0.000
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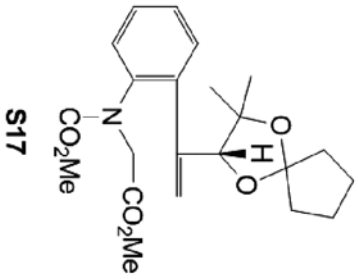
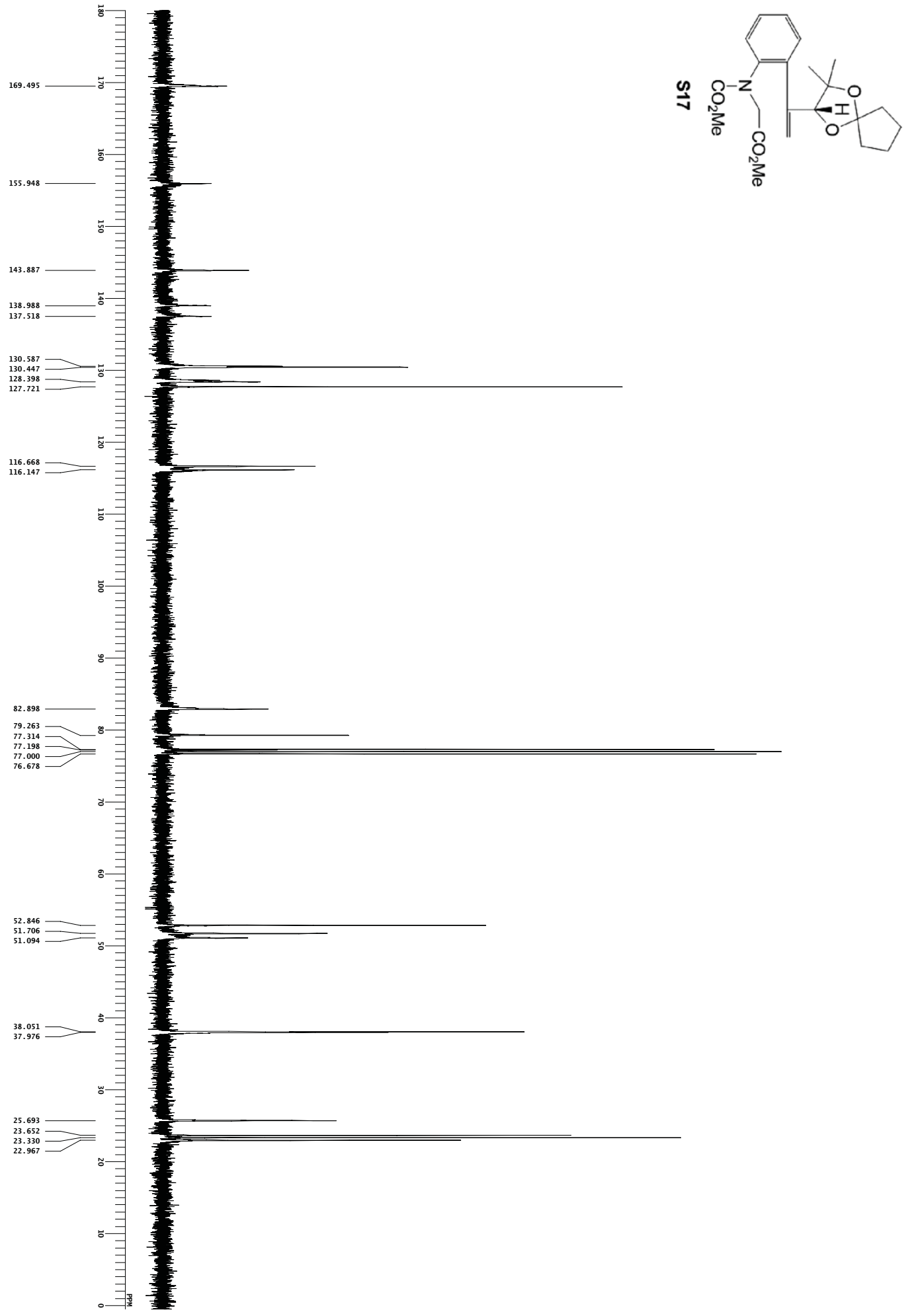

N
CO2Me
CO2Me
O
H
O

S17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128.398
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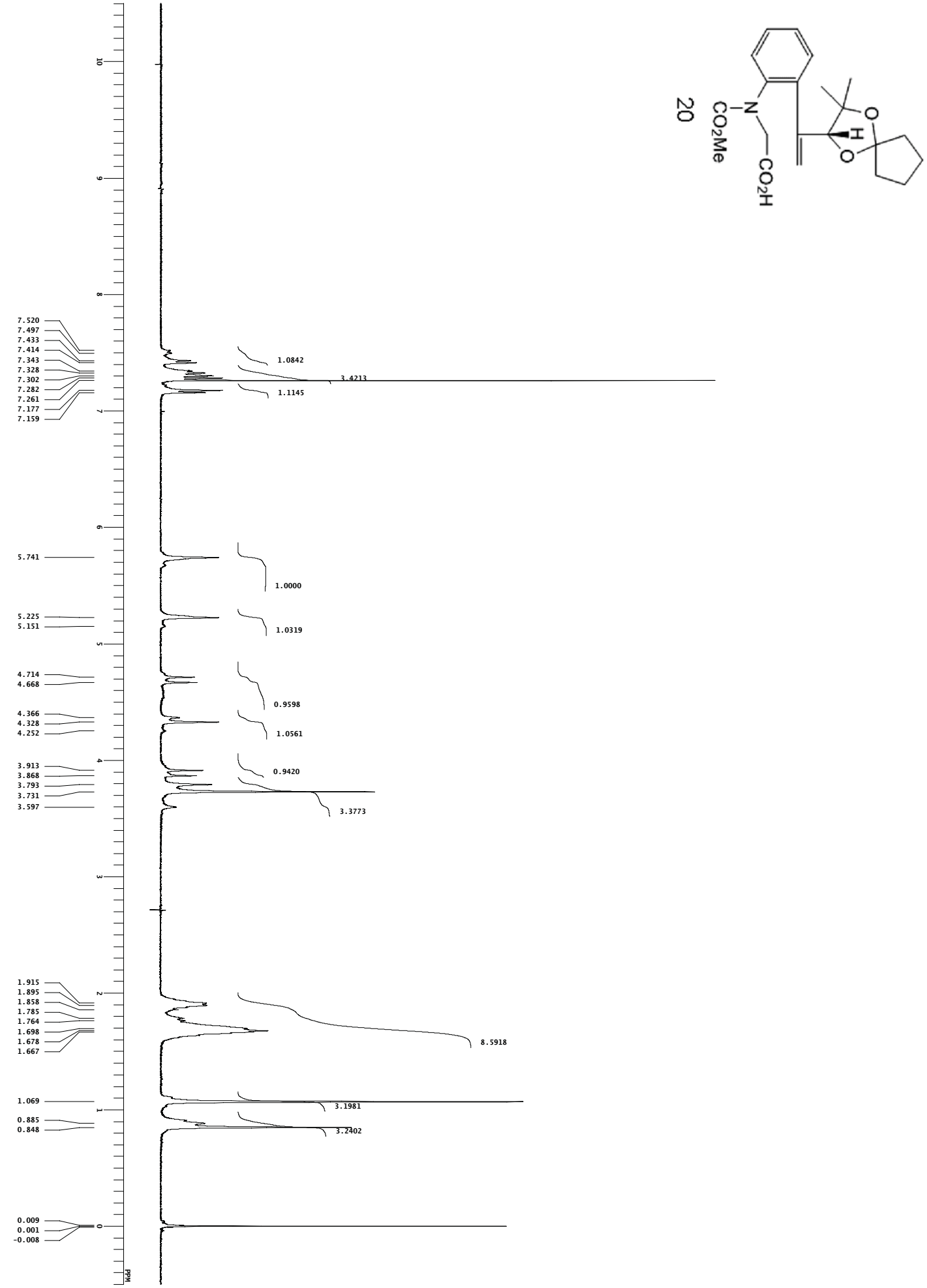
79.263
77.314
77.198
77.000
76.678
52.846
51.706
51.094
38.051
37.976
25.693
23.652
23.330
22.967
PPM

N
CO2Me
CO2Me
O
H
O

S17


20
CO2Me
N
CO2H
O
H
O
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7.433
7.414
7.343
7.328
7.302
7.282
7.261
7.177
7.159
1.0842
3.4213
1.1145
5.741
1.0000
5.225
5.151
1.0319
4.714
4.668
0.9598
4.366
4.328
4.252
1.0561
3.913
3.868
3.793
3.731
3.597
0.9420
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1.915
1.895
1.858
1.785
1.764
1.698
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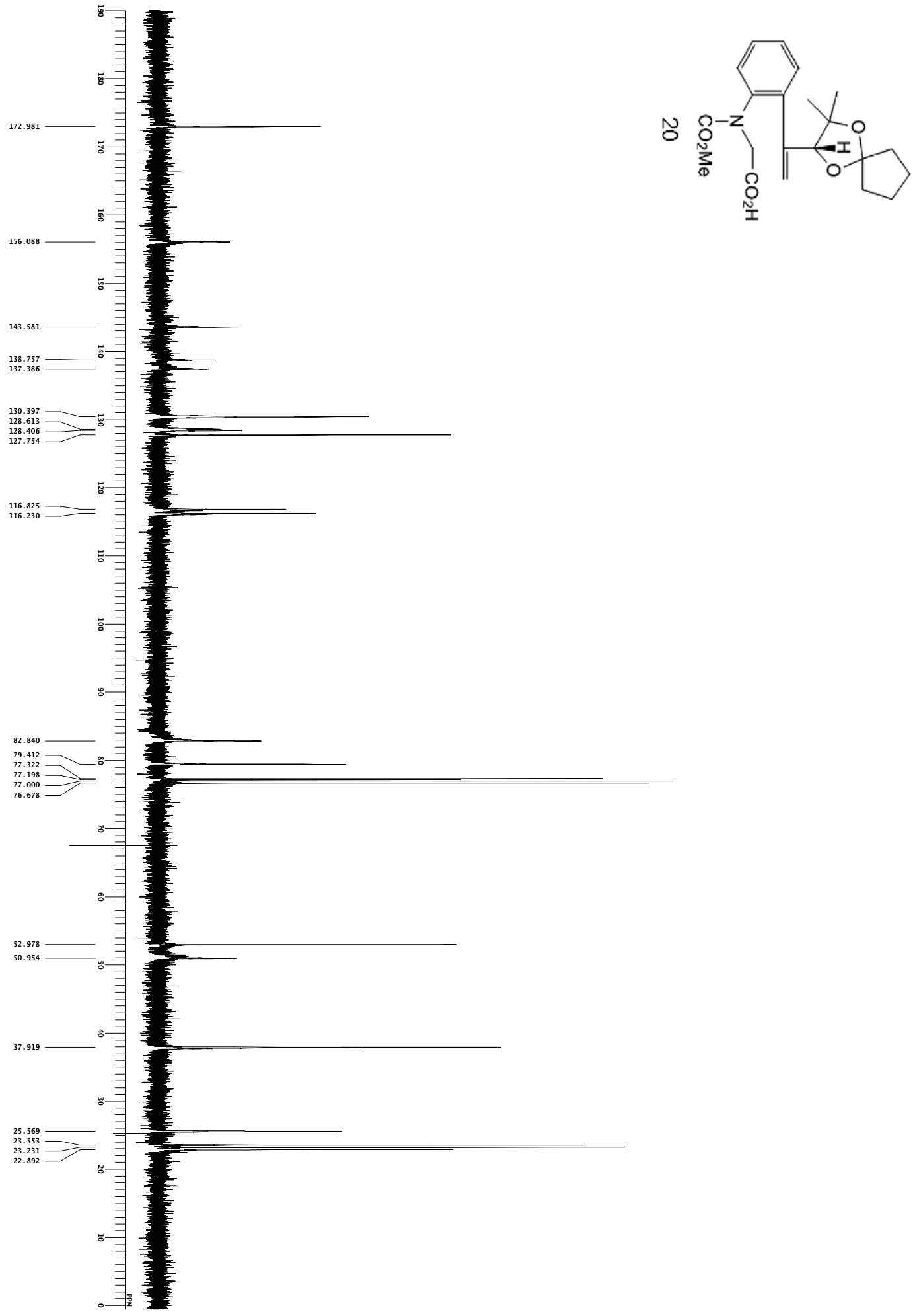
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116.230
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79.412
77.322
77.198
77.000
76.678
52.978
50.954
37.919
25.569
23.553
23.231
22.892
PPM
20
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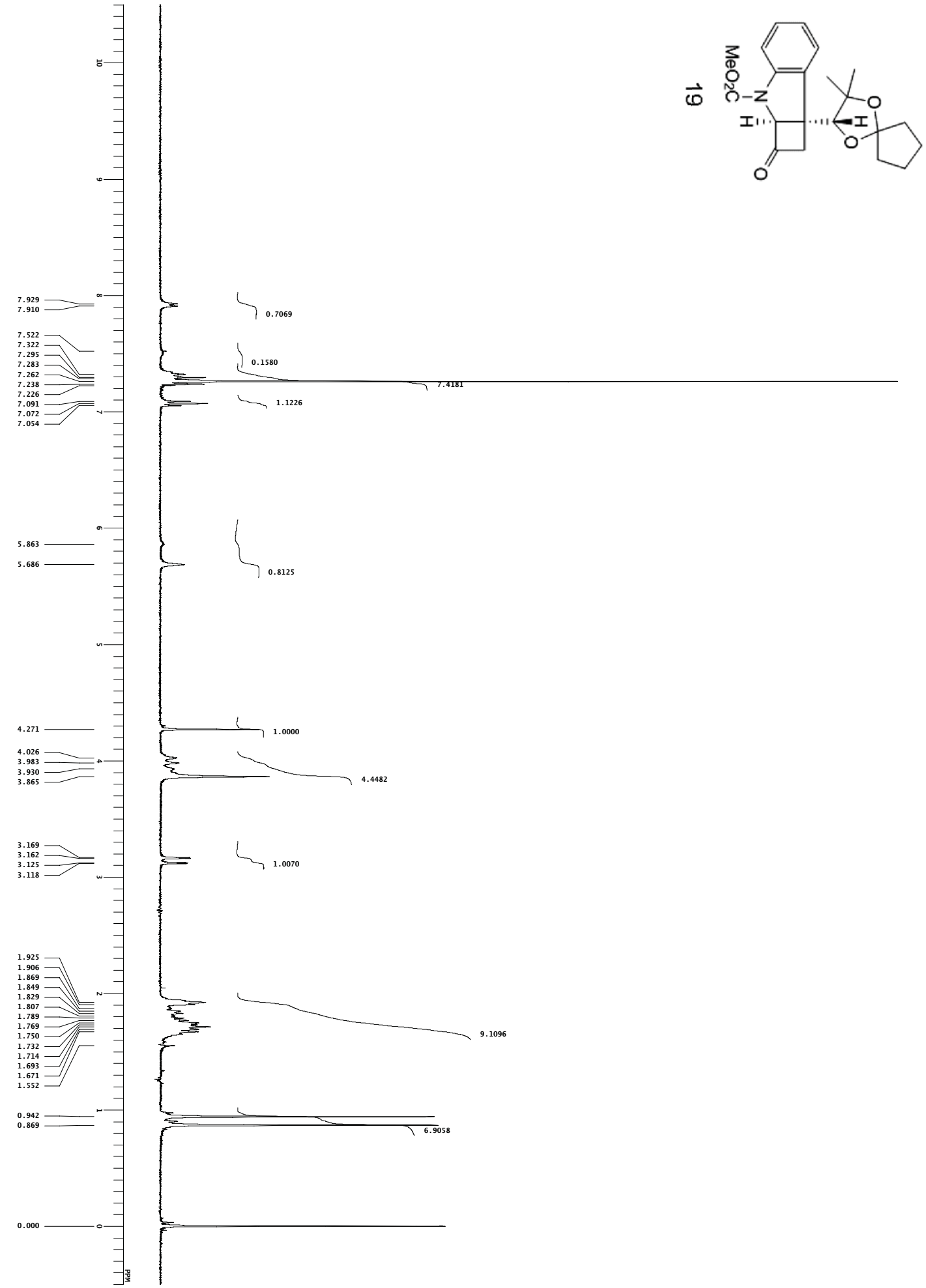
CO2Me
CO2H
O
H
O


MeO2C
N
H
O
O
H
O
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7.522
7.322
7.295
7.283
7.262
7.238
7.226
7.091
7.072
7.054
5.863
5.686
4.271
4.026
3.983
3.930
3.865
3.169
3.162
3.125
3.118
1.925
1.906
1.869
1.849
1.829
1.807
1.789
1.769
1.750
1.732
1.714
1.693
1.671
1.552
0.942
0.869
0.000
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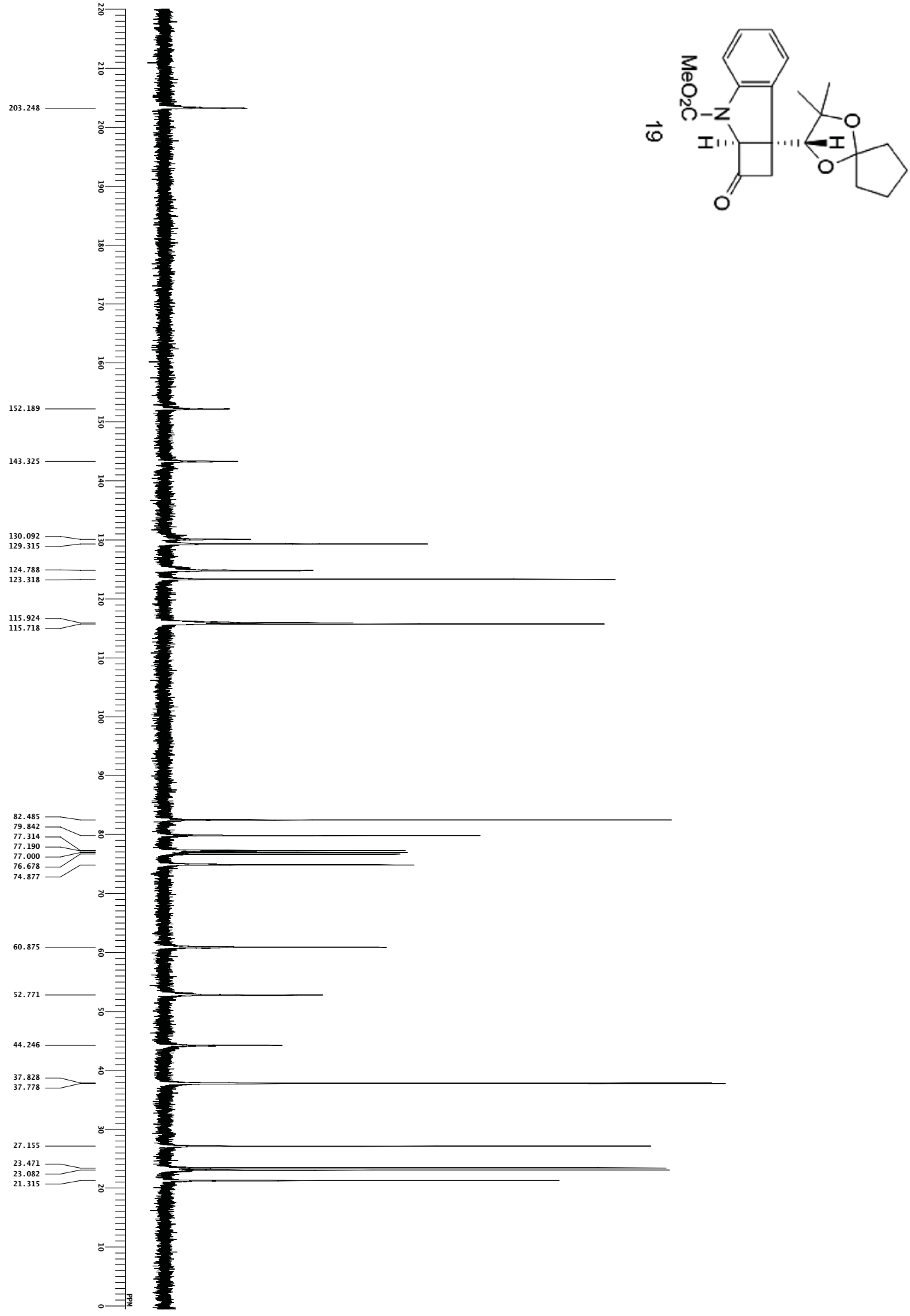
1.0070
9.1096
6.9058
PPM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124.788
123.318
115.924
115.718
82.485
79.842
77.314
77.190
77.000
76.678
74.877
60.875
52.771
44.246
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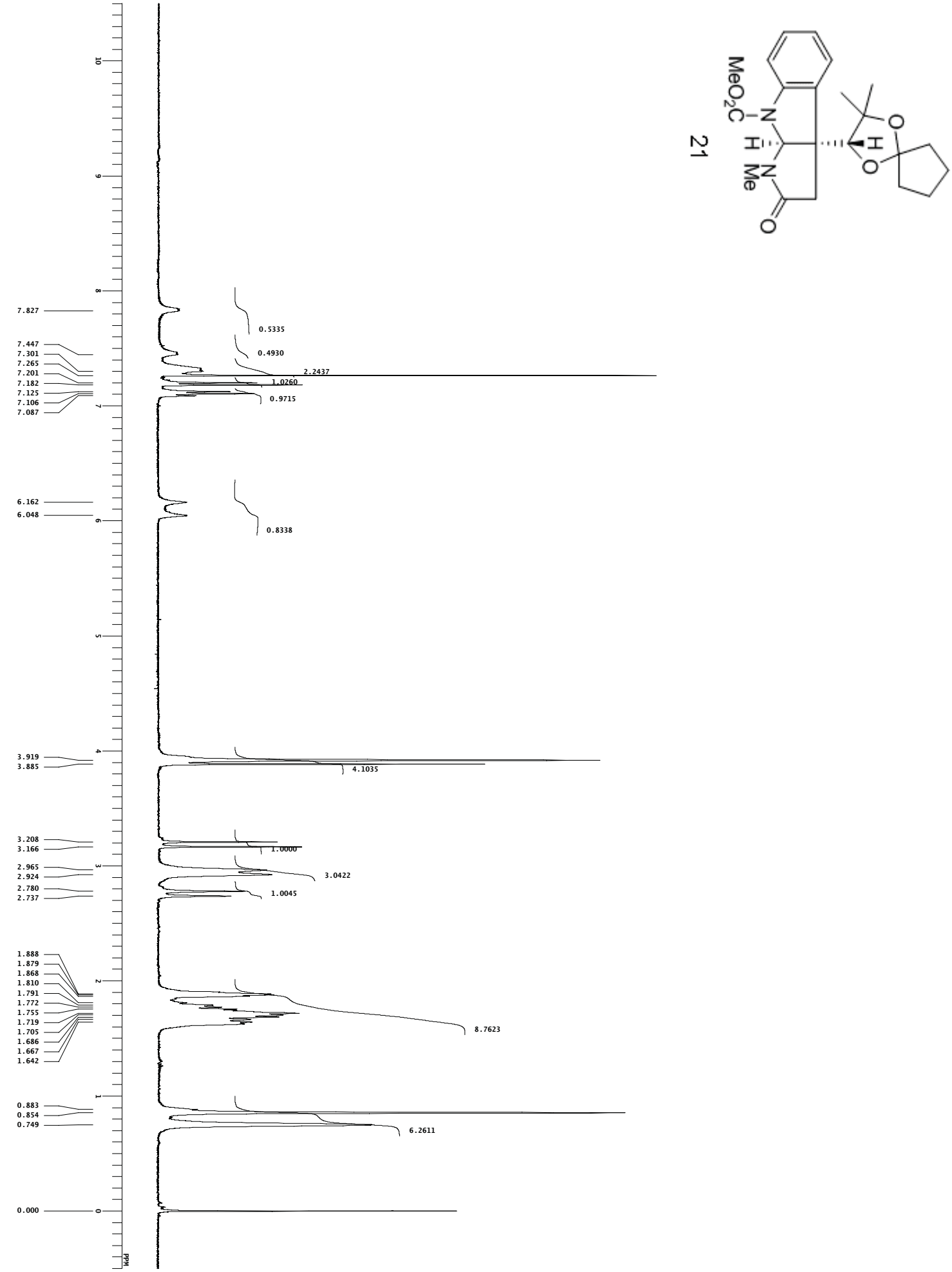
37.778
27.155
23.471
23.082
21.315
PPM
MeO2C
N
H
O
H
O
O
19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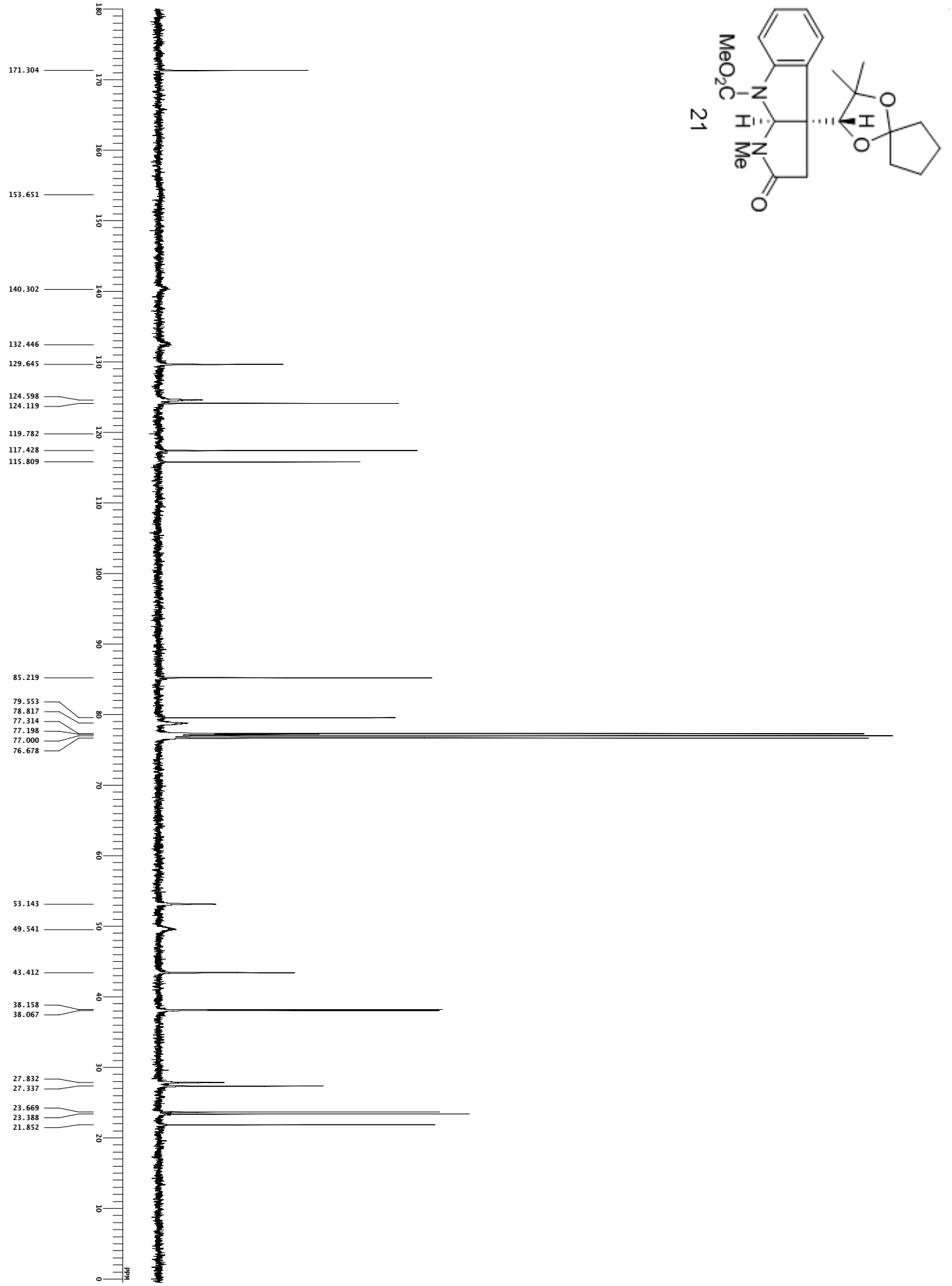
7.301
7.265
7.201
7.182
7.125
7.106
7.087
6.162
6.048
3.919
3.885
3.208
3.166
2.965
2.924
2.780
2.737
1.888
1.879
1.868
1.810
1.791
1.772
1.755
1.719
1.705
1.686
1.667
1.642
0.883
0.854
0.749
0.000
0.5335
0.4930
2.2437
1.0260
0.9715
0.8338
4.1035
1.0000
3.0422
1.0045
8.7623
6.2611
ppm

MeO2C
N
H
N
Me
O
O
H
O

21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124.598
124.119
119.782
117.428
115.809
85.219
79.553
78.817
77.314
77.198
77.000
76.678
53.143
49.541
43.412
38.158
38.067
27.832
27.337
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23.388
21.852
PPM
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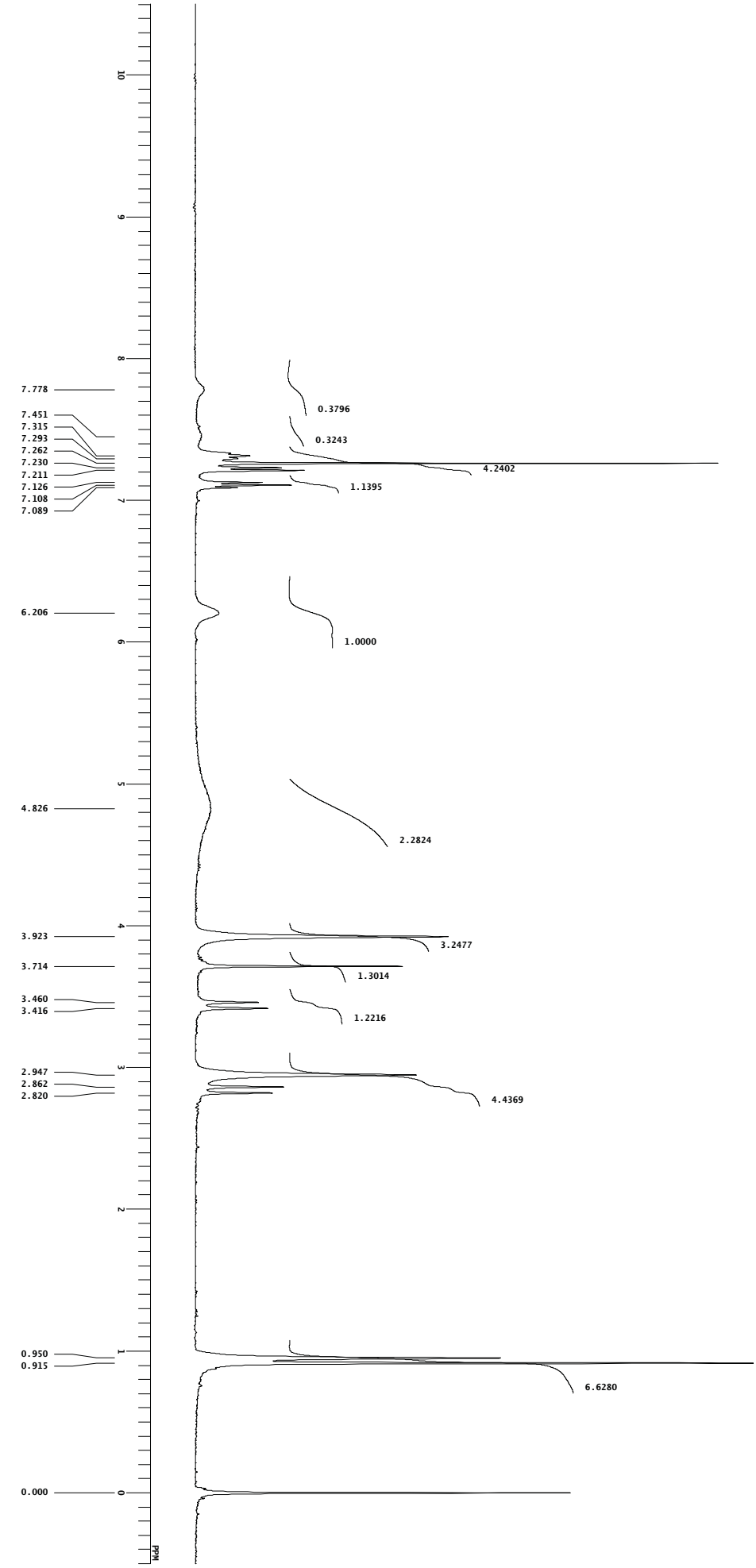
H
N
Me
O
O
H
O
21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7.262
7.230
7.211
7.126
7.108
7.089
6.206
4.826
3.923
3.714
3.460
3.416
2.947
2.862
2.820
0.950
0.915
0.000
0.3796
0.3243
4.2402
1.1395
1.0000
2.2824
3.2477
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1.2216
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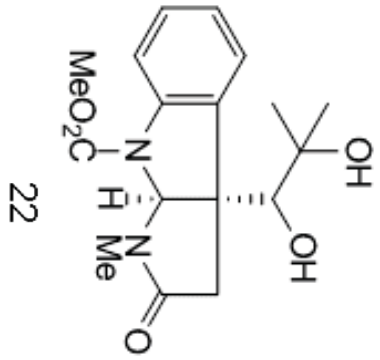
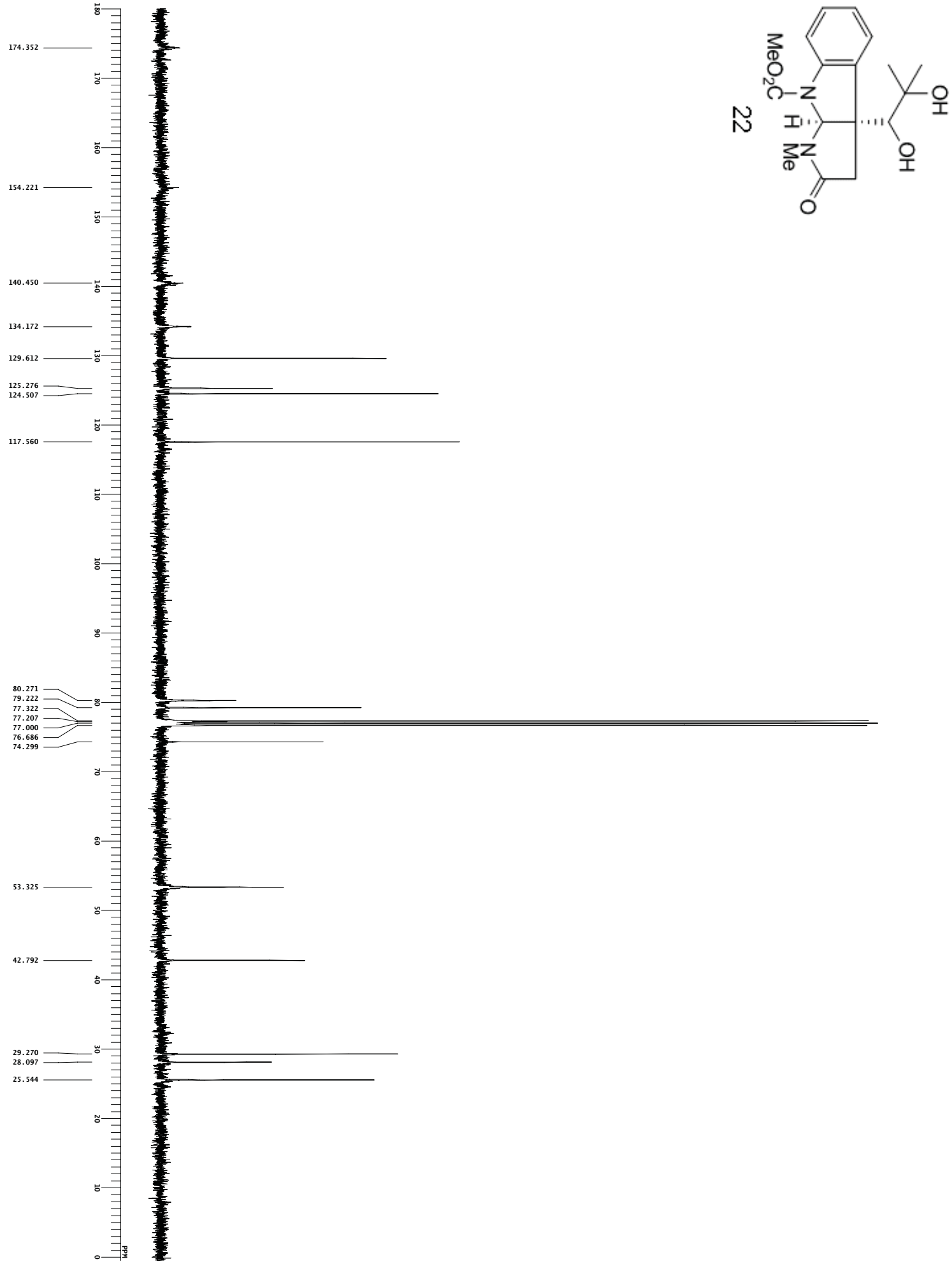
ppm


MeO2C
N
H
N
Me
O
OH
OH

22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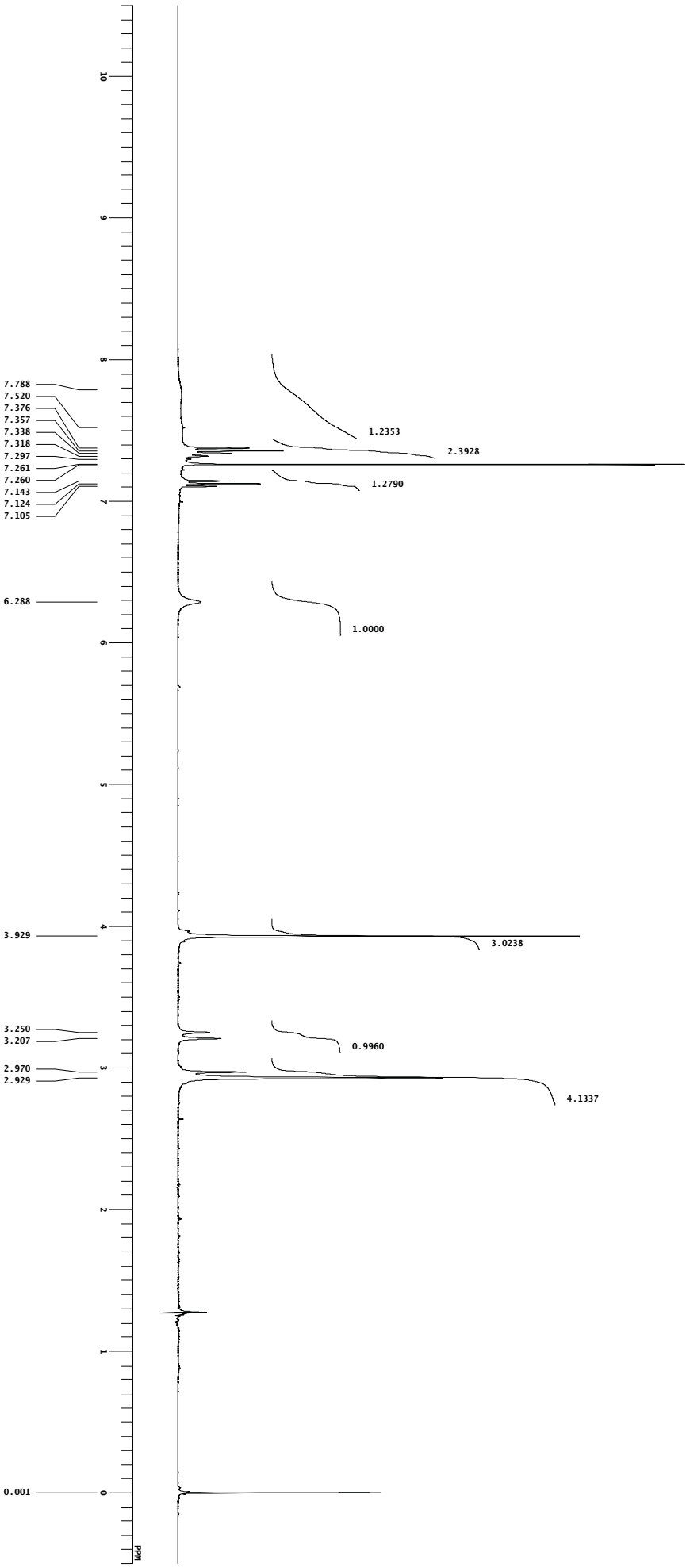
117.560
80.271
79.222
77.322
77.207
77.000
76.686
74.299
53.325
42.792
29.270
28.097
25.544
PPM
MeO2C
N
H
N
Me
O
OH
OH
22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7.376
7.357
7.338
7.318
7.297
7.261
7.260
7.143
7.124
7.105
6.288
3.929
3.250
3.207
2.970
2.929
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1.0000
3.0238
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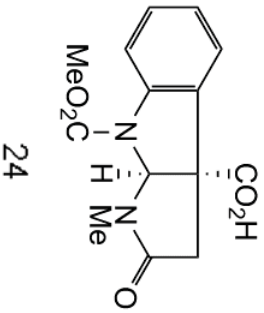
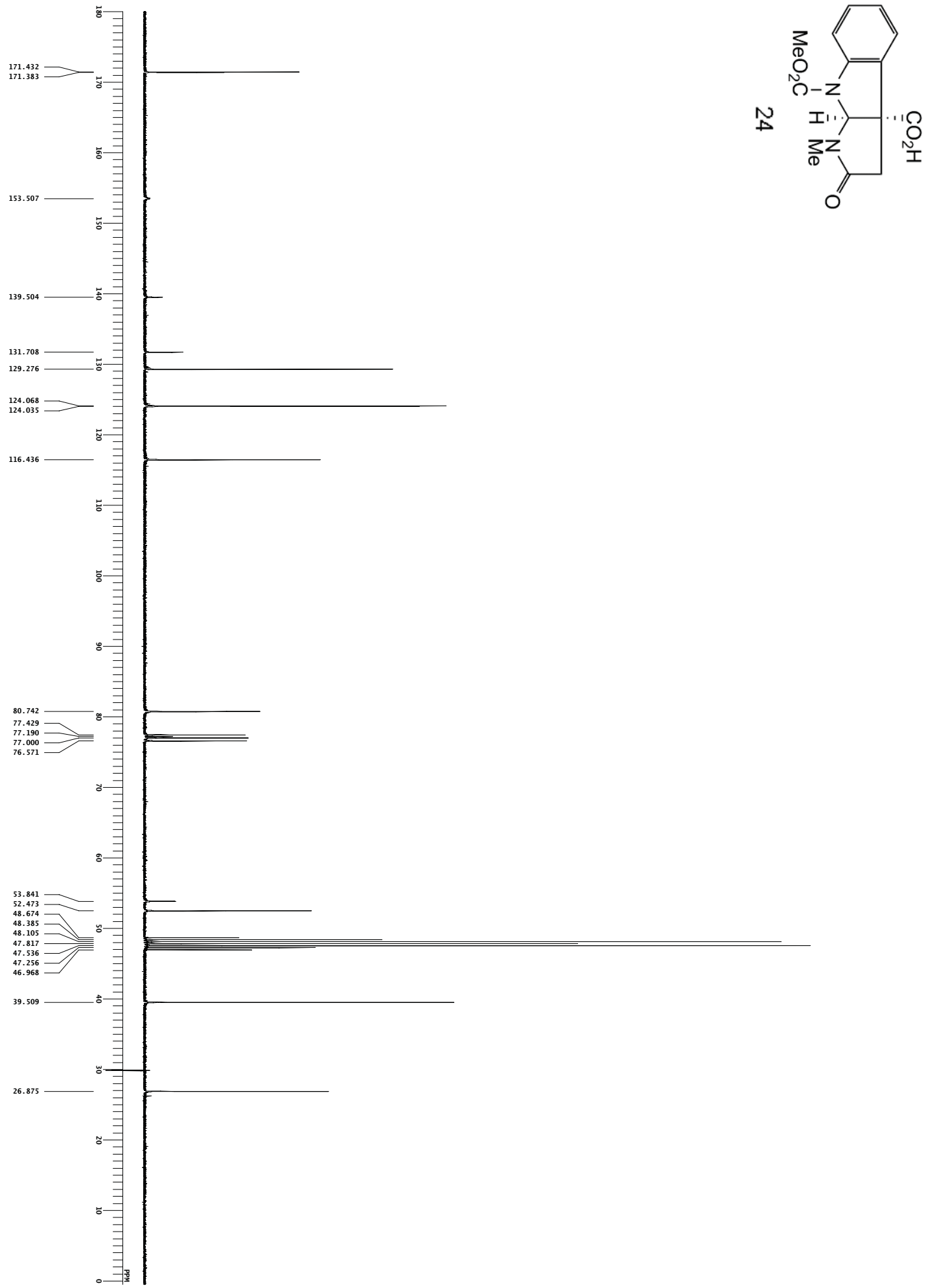
4.1337
PPM


MeO2C
N
H
N
Me
O
CO2H

24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124.035
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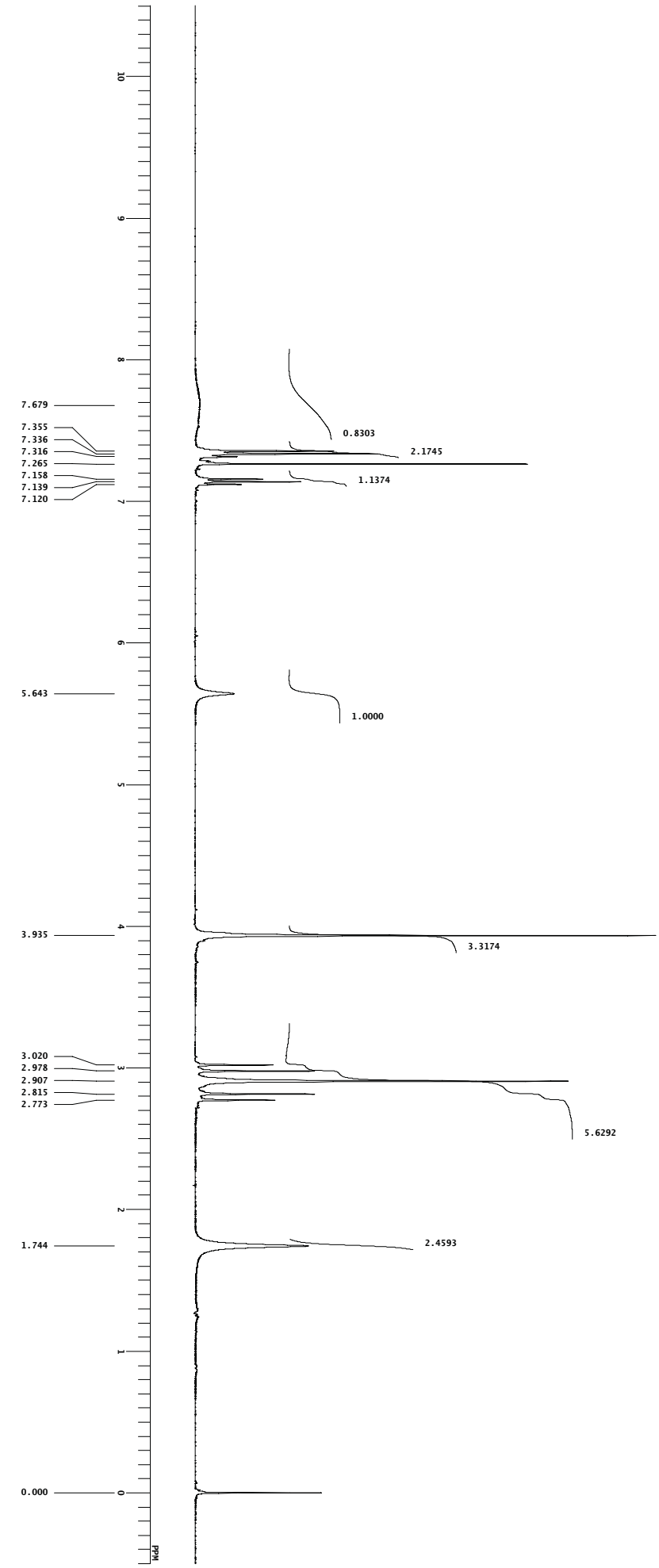
80.742
77.429
77.190
77.000
76.571
53.841
52.473
48.674
48.385
48.105
47.817
47.536
47.256
46.968
39.509
26.875
PPM

MeO2C
N
H
N
Me
O
CO2H

24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7.139
7.120
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3.020
2.978
2.907
2.815
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1.0000
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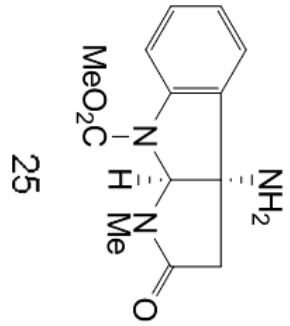
PPM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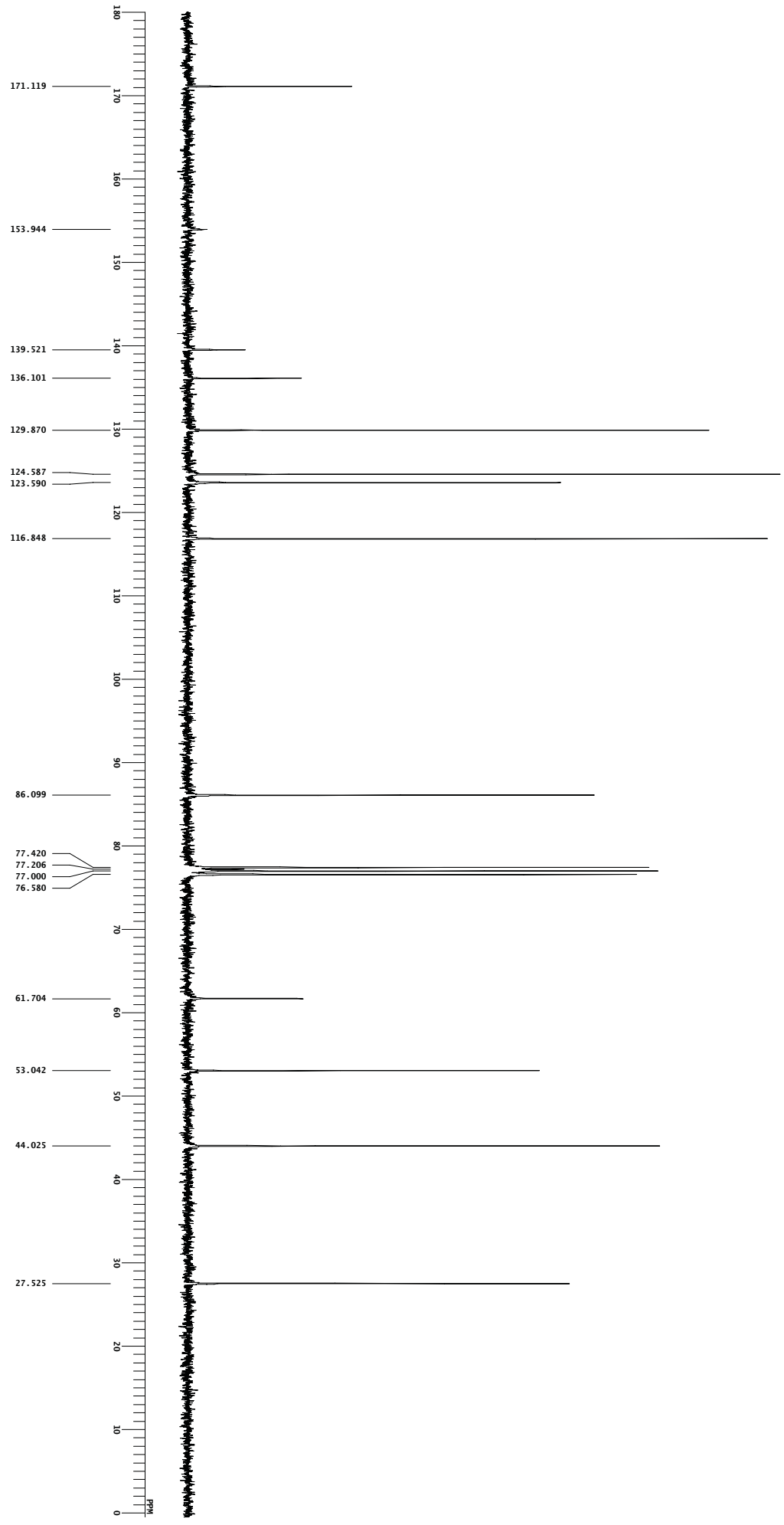
H
N
Me
O
NH2

25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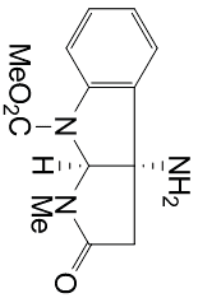
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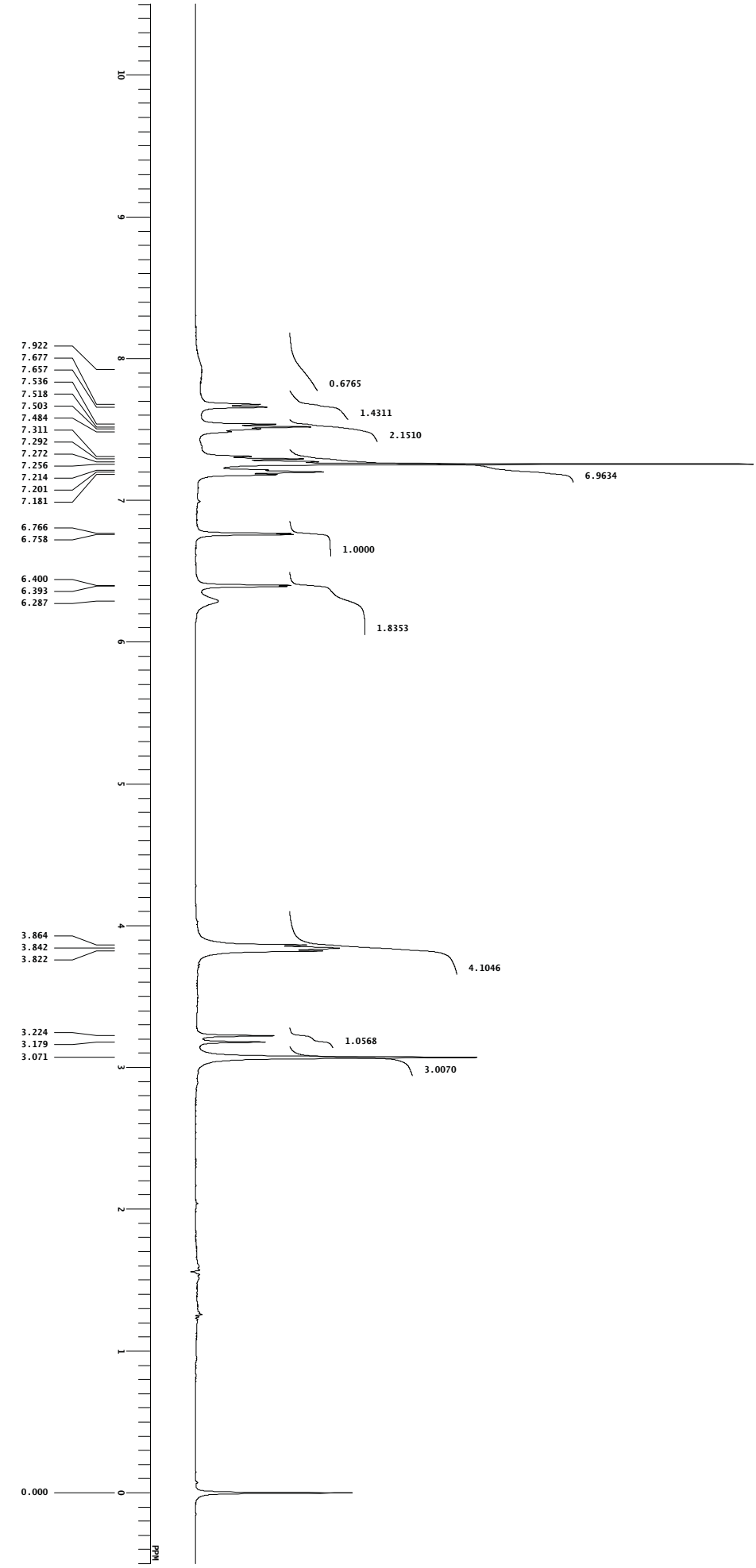
H
N
Me
O
NH2

25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7.256
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7.201
7.181
6.766
6.758
6.400
6.393
6.287
3.864
3.842
3.822
3.224
3.179
3.071
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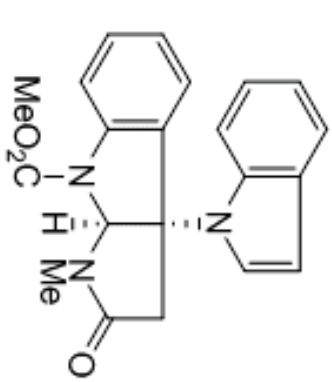
PPM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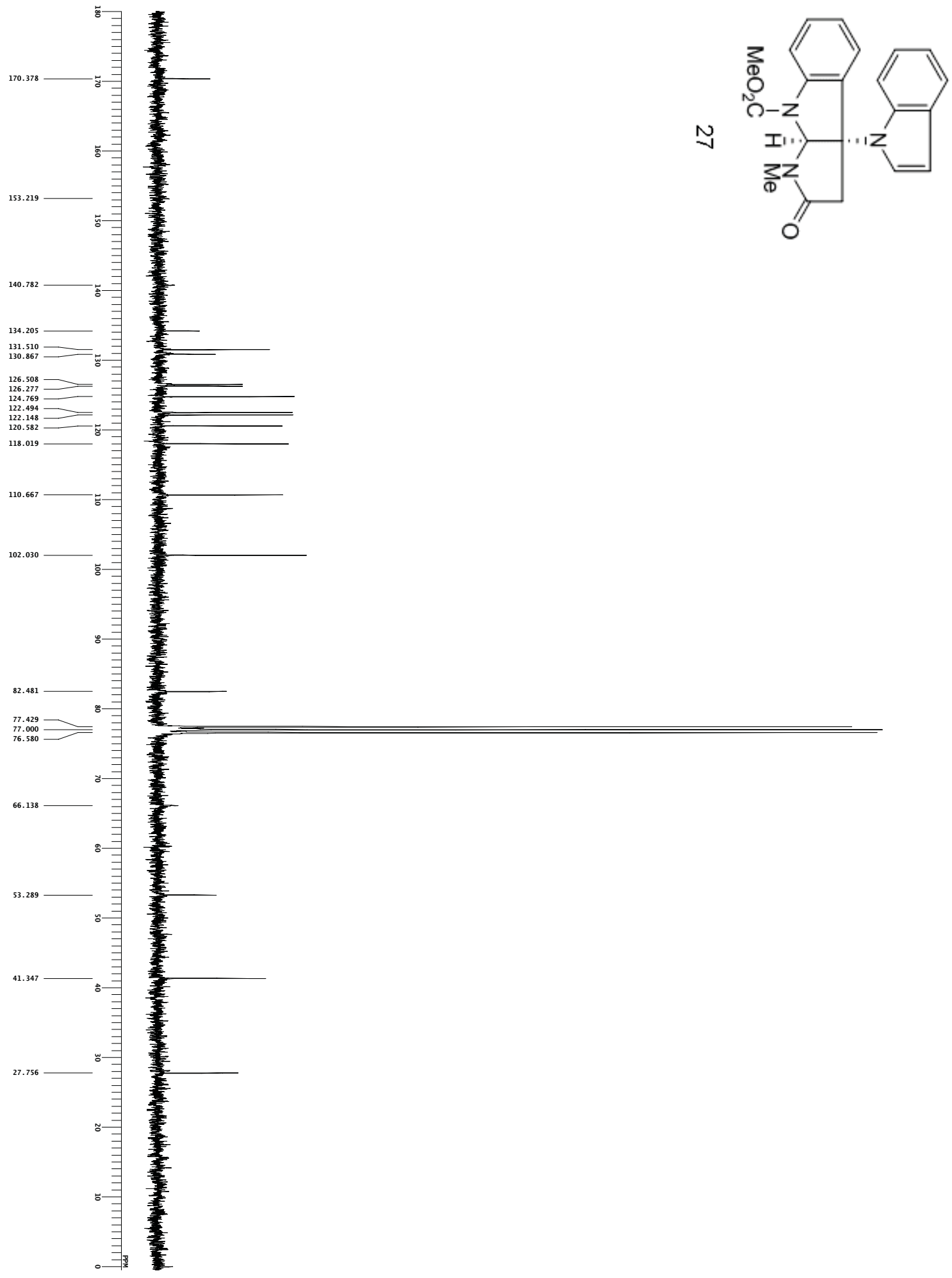
N
H
N
Me
N
O

27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126.508
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122.148
120.582
118.019
110.667
102.030
82.481
77.429
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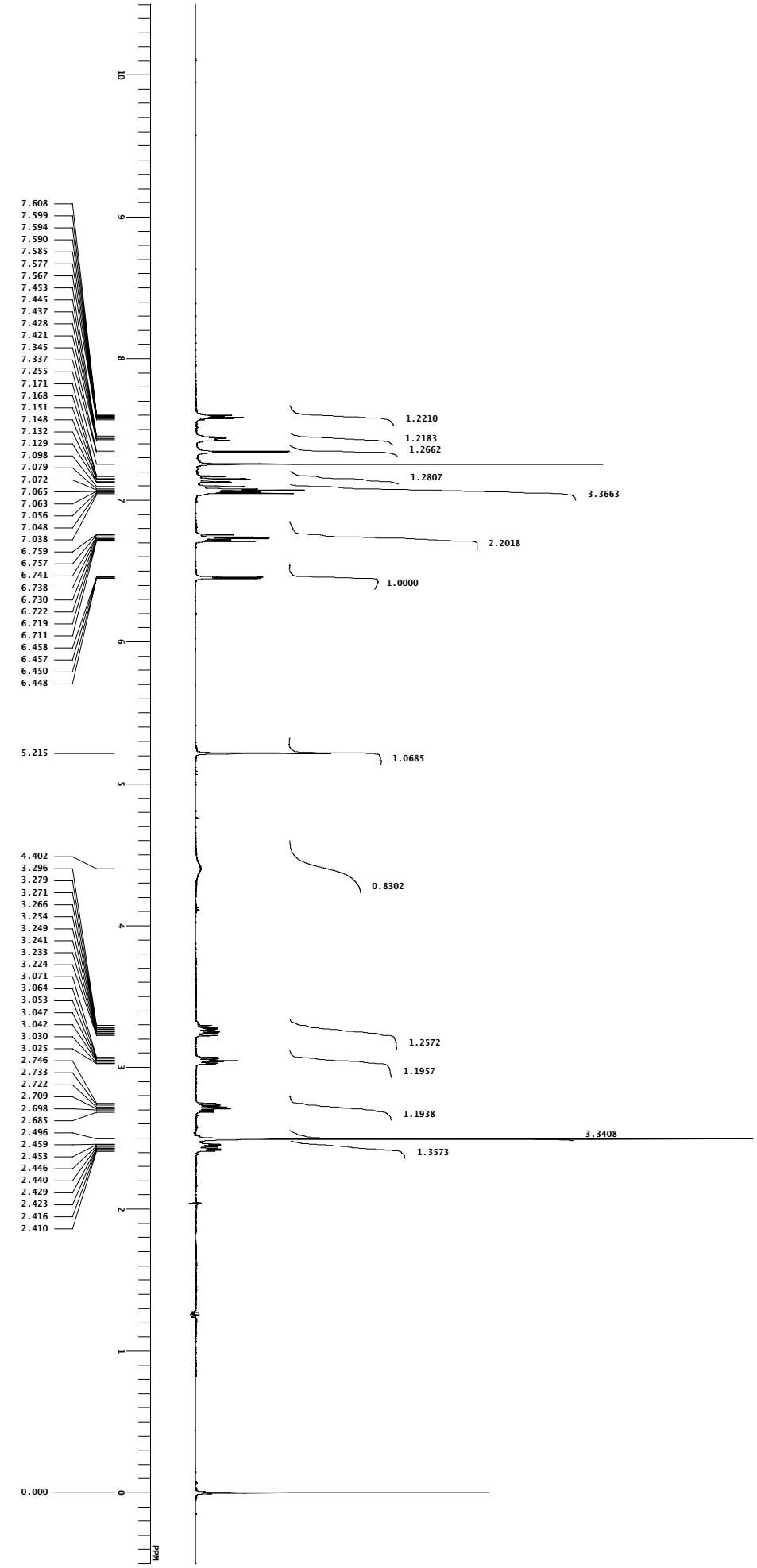
41.347
27.756
PPM

MeO2C
N
H
N
Me
O
N

27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7.428
7.421
7.345
7.337
7.255
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7.151
7.148
7.132
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7.079
7.072
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7.063
7.056
7.048
7.038
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3.241
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3.224
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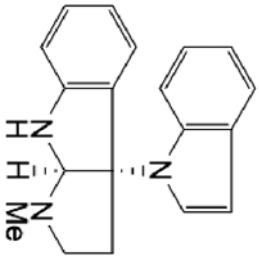
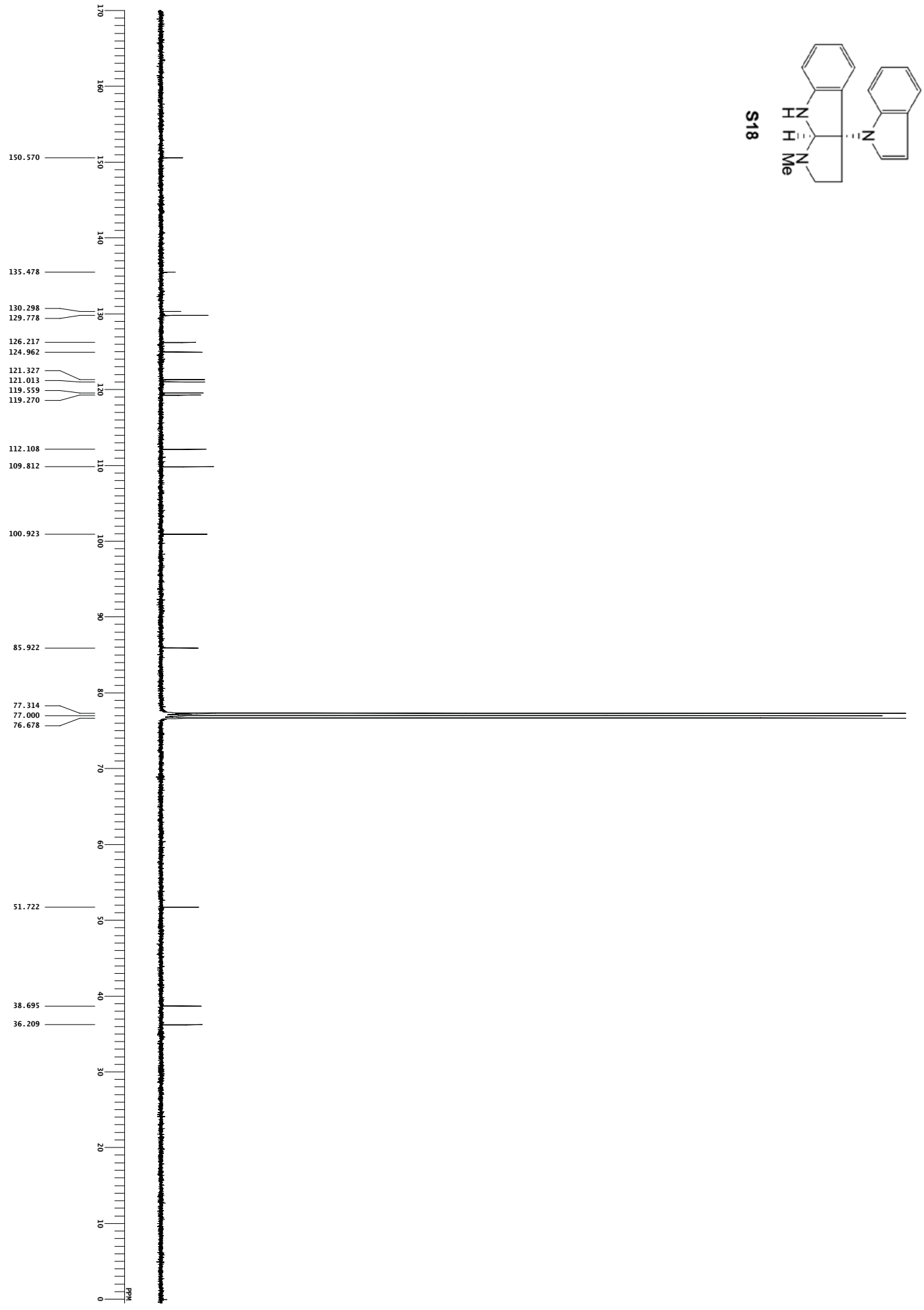
PPM


H
H
N
Me
N
N

S18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124.962
121.327
121.013
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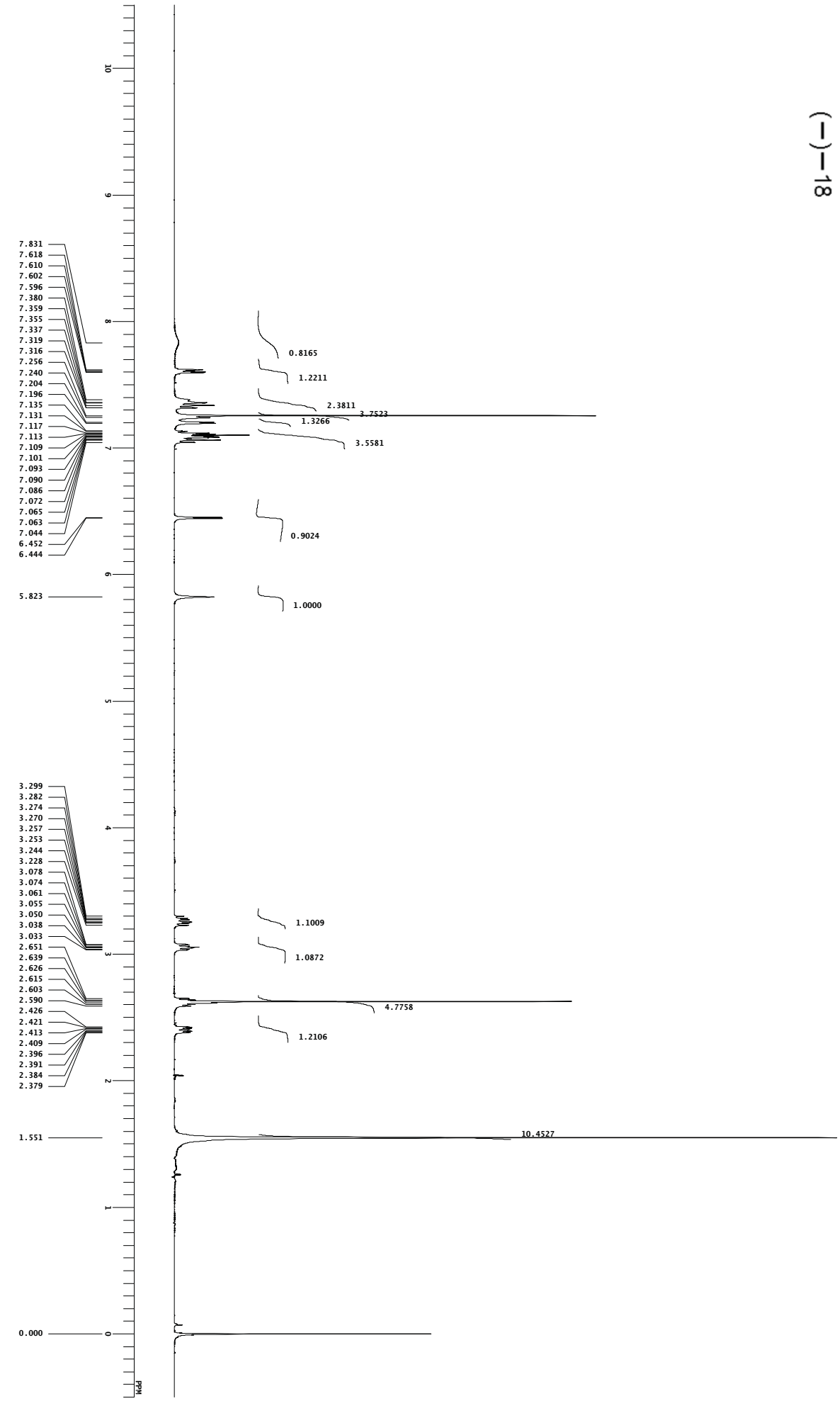
119.270
112.108
109.812
100.923
85.922
77.314
77.000
76.678
51.722
38.695
36.209
PPM

N
H
H
N
Me
N

S18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7.256
7.240
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7.196
7.135
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7.117
7.113
7.109
7.101
7.093
7.090
7.086
7.072
7.065
7.063
7.044
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6.444
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3.228
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2.626
2.615
2.603
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2.421
2.413
2.409
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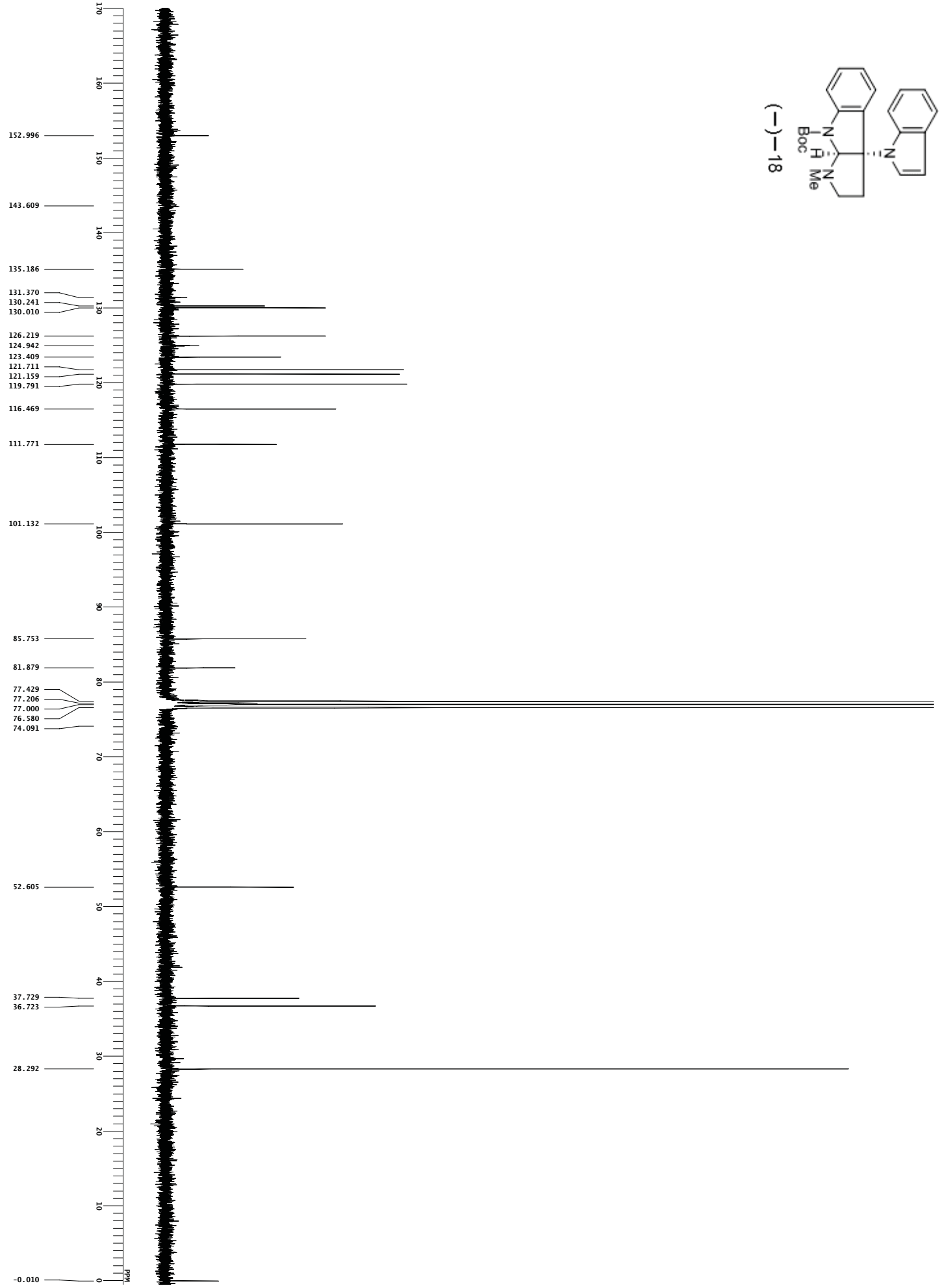
3.7523
1.3266
3.5581
0.9024
1.0000
1.1009
1.0872
4.7758
1.2106
10.4527
PPM

(−)-18


152.996
143.609
135.186
131.370
130.241
130.010
126.219
124.942
123.409
121.711
121.159
119.791
116.469
111.771
101.132
85.753
81.879
77.429
77.206
77.000
76.580
74.091
52.605
37.729
36.723
28.292
-0.010
PPM

(−)−18
Boc
N
H
N
Me
N