Supporting Information

Liphagal, A Selective Inhibitor of PI3 Kinase Alpha Isolated from the Sponge *Aka coralliphaga*: Structure Elucidation and Biomimetic Synthesis

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Experimental Section

General Experimental Procedures. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-500, AV-400, and AM400 spectrometers. ^{1}H chemical shifts are referenced to the residual DMSO-d_6 and $CDCl_3$ signals (δ 2.49 and 7.24 ppm) and ^{13}C chemical shifts are referenced to the DMSO-d_6 and $CDCl_3$ solvent peaks (δ 39.5 and 77.0 ppm). Low and high resolution EIMS were recorded on Kratos AEI MS-59 and AEI MS-50 mass spectrometers, and low and high resolution ESI-QIT-MS were recorded on a Bruker-Hewlett Packard 1100 Esquire–LC system mass spectrometer. UV spectra were recorded with a Waters 2487 Dual λ Absorbance Detector. Optical rotations were measured using a Jasco P-1010 Polarimeter with sodium light (589 nm).

Merck Type 5554 silica gel plates and Whatman MKC18F plates were used for analytical thin layer chromatography. Waters Sep-Pak's or Merck silica gel G60 (230-400 mesh) were used for silica gel chromatograhpy. Reversed-phase HPLC purifications were performed on a Waters 600E System Controller liquid chromatography attached to a Waters 996 Photodiode Array Detector. All solvents used for HPLC were Fisher HPLC grade.

Isolation of liphagal (1): Specimens of *Aka coralliphaga* (Demospongiae, order Haplosclerida, family Phloeodictyidae) were collected by hand using SCUBA at a depth of 20 m on reefs in Prince Rupert Bay, 4 Km south of Portsmouth, Dominica in June 1997. Freshly collected sponge was frozen on site and transported frozen to Vancouver. A voucher sample of *Aka coralliphaga* has been deposited at the University of Amsterdam (ZM 17866).

A sample of sponge (300 g) was cut into small pieces, immersed in and subsequently extracted repeatedly with MeOH (4 x 400 mL) at room temperature. The combined methanolic extracts were concentrated *in vacuo* and the resultant brown gum was partitioned between EtOAc (4 x 50 mL) and H_2O (150 mL). The H_2O extract exhibited PI3K inhibitory activity and was further extracted with BuOH (4 x 50 mL). The combined BuOH extracts were evaporated to dryness, to give 265 mg of brown oil, that was chromatographed on a Sephadex LH-20 column eluting with MeOH to give a fraction (143.7 mg) exhibiting PI3K inhibitory

activity. Pure liphagal (**1**) (5.6 mg) was obtained from this mixture via C_{18} reversed-phase HPLC using a CSC-Inertsil 150A/ODS2, 5 µm 25 x 0.94 cm column, eluting with 17:3 MeOH/H_2O.

Liphagal (1): Isolated as a yellow amorphous solid; $[\alpha]^{25}_D$ +12.0° (*c* 3.7, MeOH); UV (MeOH) λ_{max} 197 (ε 28,600), 240 (ε 10,900), 313 (ε 7,100), 385 (ε 2,700) nm; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 1; HREIMS $[M]^+$ *m/z* 356.19944 (calcd for $C_{22}H_{28}O_4$, 356.19876).

Synthesis of liphagal.

Preparation of Compound 8. To a solution of 2,4,5-trimethoxybenzaldehyde (**7**) (3.92 g, 20 mmol) in CH_2Cl_2 (100 mL) at 0°C was added BBr_3 (1,0 M in CH_2Cl_2, 20 mmol). The resulting dark mixture was stirred at rt for 16 h. H_2O (250 mL) was then added and the mixture was stirred for 30 min and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (CH_2Cl_2) afforded the phenol (3.2 g) in 87% yield. Bromine (0.8 mL, 15.3 mmol) was added at rt to a solution of the phenol (2.76 g, 15.2 mmol) and NaOAc (1.9 g, 23 mmol) in AcOH (100 mL). The resulting yellow solution was stirred for 2 h. The solvent was removed under vacuum and the residue was poured into an aqueous solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined EtOAc layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (3:7 EtOAc/hexanes) afforded the bromophenol **8** in 54% yield.

Phenol : isolated as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H), 9.65 (s, 1H), 6.86 (s, 1H), 6.42 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 159.3, 157.2, 142.9, 113.13, 112.8, 100.08, 56.3, 56.2 ppm; HREIMS $[M]^+$ *m/z* 182.0578 ($C_9H_{10}O_4$, calcd 182.0579).

Compound 8: isolated as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.55 (s, 1H), 9.74 (s, 1H), 7.00 (s, 1H), 3.98 (s, 3H), 3.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 154.8, 154.7, 146.8, 115.7, 114.7, 106.8, 61.0, 56.7 ppm; HRESIMS $[M+H]^+$ *m/z* 260.9752 ($C_9H_{10}O_4Br$, calcd 260.9762).

Preparation of Compound 9. A solution of bromophenol **8** (2.1 g, 8.0 mmol), TBSCl (2.4 g, 16 mmol) and imidazole (2.18 g, 32 mmol) in CH_2Cl_2 (100 mL) was stirred rt for 15 h. The organic phase was diluted

with CH_2Cl_2 and washed sequentially with aqueous HCl (1.0 M) and brine. The CH_2Cl_2 phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (1:9 EtOAc/hexanes) afforded the silylether aldehyde (2.4 g) in 80 % yield. To a solution of the aldehyde (2.33 g, 6.2 mmol) in MeOH (50 mL) was added $NaBH_4$ (285 mg, 7.5 mmol) at 0°C. After stirring for 30 min an aqueous solution of NH_4Cl was added and the resulting mixture was stirred at rt for additional 30 min. The MeOH was evaporated under reduced pressure and the aqueous residue was then extracted with EtOAc. The EtOAc phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (3:7 EtOAc/hexanes) afforded the benzylalcohol **9** (2.2 g) in 94% yield.

Silylether: isolated as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.29 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 1.05 (s, 9H), 0.21 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 153.2, 151.4, 148.6, 123.8, 112.8, 108.7, 60.7, 56.2, 25.9 (3C), 18.7, -3.5, -3.6 ppm; HRESIMS $[M+Na]^+$ *m/z* 397.0457 ($C_{15}H_{23}O_4BrNaSi$, calcd 397.0447).

Compound 9: isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 4.64 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 1.02 (s, 9H), 0.24 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 146.4, 144.1, 127.8, 112.0, 111.3, 61.1, 60.4, 56.4, 26.2 (3C), 18.8, -2.8 (2C) ppm; HRESIMS $[M+Na]^+$ *m/z* 399.0601 ($C_{15}H_{25}O_4BrNaSi$, calcd 399.0603).

Preparation of Compound 10. A solution of benzylalcohol **9** (1.6 g, 4.24 mmol) and PPh_3HBr (1.46 g, 4.24 mmol) in MeCN (20 mL) was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in THF (20 mL) and HF/C_5H_5N (0.5 mL) was added at rt. A precipitate was observed to form immediately and the resulting suspension was stirred for 1 hr. The precipitate was collected by filtration and washed with Et_2O to yield the phosphonium salt **10** (2.4 g) in 94% yield.

Compound 10: isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.65 (m, 9H), 7.6-7.55 (m, 6H), 6.93 (d, 1H, *J* = 2.7 Hz), 5.45 (d, 2H, *J* = 13.5 Hz), 3.75 (s, 3H), 3.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 146.4, 140.7, 134.8 (3C), 134.5 (3C), 134.4 (3C), 130.0 (3C), 129.8 (3C), 127.5, 118.3, 117.2,

115.0, 114.9, 109.8, 56.5, 53.0, 26.3 (d, J = 63.0 Hz) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 23.9 ppm; HRESIMS $[M]^+$ *m/z* 507.0745 ($C_{27}H_{25}O_3BrP$, calcd 507.0725).

Preparation of Compound 12. To a solution of $MeOCH_2PPh_3Cl$ (10.26 g, 30 mmol) in THF (100 mL), was added *t*-BuOK (3.4 g, 30 mmol). The resulting red solution was stirred at rt for 15 min and then a solution of geranyl acetone (**11**) (2.91g, 15 mmol) in THF (50 mL) was added. After stirring at rt for 30 min an aqueous solution of NH_4Cl was added and the resulting solution was extracted with EtOAc. The EtOAc phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (hexanes) afforded the enol ether **12** in quantitative yield (3.4 g).

Compound 12: isolated as a colorless oil as an equimolar mixture of E and Z stereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1H), 5.72 (s, 1H), 5.09 (m ,4H), 3.51 (s, 3H), 3.48 (s, 3H), 2.2-1.8 (m, 16H), 1.66 (s, 6H), 1.58 (s, 12H), 1.52 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 141.6, 134.9, 134.7, 131.0, 130.9, 124.4, 124.3, 124.2, 123.9, 114.2, 113.7, 58.9 (2C), 39.6, 34.0, 31.5, 30.2, 28.9, 26.7, 26.6, 26.6, 25.9, 25.5, 22.5, 17.5, 17.1, 15.8, 13.9, 12.6 ppm; HREIMS $[M]^+$ *m/z* 222.1979 ($C_{15}H_{26}O$, calcd 222.1983).

Preparation of Compound 13. A solution of enol ether **12** (3.4 g, 15 mmol) and PPTS (378 mg, 1.5 mmol) in MeOH (60 mL) was refluxed for 5 h. The resulting mixture was poured into an aqueous solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc and the EtOAc phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Chromatography of the residue on silica gel (1:49 EtOAc/hexanes) afforded the dimethylketal (3.4 g) in 90% yield. A solution of the ketal (3.4 g, 13 mmol) and PPTS (5 g, 20 mmol) in acetone (40 mL) and water (10 mL) was stirred at rt for 4 d. The resulting mixture was poured into an aqueous solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc. The EtOAc phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (1:99 EtOAc/hexanes) afforded the aldehyde **13** (2.28 g) in 84% yield.

Dimethylketal: isolated as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (m, 2H), 4.00 (d, 1H, J = 7.0 Hz), 3.33 (s, 3H), 3.32 (s, 3H), 2.2-1.9 (m, 7H), 1.75 (m, 1H), 1.65 (s, 3H), 1.57 (s, 6H), 1.55 (m, 1H), 0.88

(d, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 100 MHz) δ 135.0, 131.3, 124.5, 124.3, 108.9, 53.9 (2C), 39.7, 35.2, 31.8, 26.7, 25.7, 25.2, 17.6, 15.9, 14.2 ppm.

Compound 13: isolated as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, 1H, *J* = 2.0 Hz), 5.03 (m, 2H), 2.30 (m, 1H), 2.1-1.9 (m ,6H), 1.75 (m ,1H), 1.63 (s, 3H), 1.55 (s, 6H), 1.35 (m, 1H), 1.05 (d, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 136.1, 131.2, 124.1, 123.2, 45.6, 39.5, 30.4, 26.4, 25.5, 25.0, 17.5, 15.8, 13.1 ppm; HREIMS $[M]^+$ *m/z* 208.1826 ($C_{14}H_{24}O$, calcd 208.1827).

Preparation of Compound 14. To a solution of aldehyde **13** (208 mg, 1.0 mmol) in acetone (6.0 mL) and H_2O (3.0 mL), NaH_2PO_4 (138 mg, 3.0 mmol), amylene (0.5 mL, 4.5 mmol), and $NaClO_2$ (340 mg, 3.0 mmol) were added successively. The resulting mixture was stirred at rt for 12 h. The volatiles were removed under reduced pressure and the residual aqueous phase was diluted with water and extracted with EtOAc. The EtOAc phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (1:9 EtOAc/hexanes) afforded the acid **14** (132 mg) in 60% yield.

Compound 14: isolated as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (m, 2H), 2.44 (m, 1H), 2.1-1.9 (m, 6H), 1.75 (m, 1H), 1.65 (s, 3H), 1.57 (s, 6H), 1.45 (m, 1H), 1.60 (d, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 137.4, 132.75, 125.7, 124.8, 39.67, 38.76, 33.47, 26.59, 25.64, 25.44, 19.06, 18.23, 17.35 ppm; HREIMS $[M]^+$ *m/z* 224.1774 ($C_{14}H_{24}O_2$, calcd 224.1776).

Preparation of Compound 16: A solution of acid **14** (800 mg, 3.57 mmol), phosphonium salt **10** (2.11 g, 3.58 mmol), DCC (1.24 g, 6.0 mmol), and DMAP (50 mg, 0.4 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 18 h. Solvent was evaporated under reduced pressure and the residue was dissolved in THF (50 mL) and Et_3N (3.0 mL) was added. The resulting mixture was refluxed for 4 h. After cooling to rt, silica was added and the THF was evaporated under reduced pressure. The resulting dried silica was deposited on a silica gel column and eluted with 1:19 EtOAc/hexanes to afford the benzofuran **16** (1.24 g) in 80 % yield.

Compound 16: isolated as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.31 (s, 1H), 5.09 (m, 2H), 3.86 (s, 6H), 2.93 (m, 1H), 2.15-1.7 (m, 8H), 1.65 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 1.30 (d, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 150.3, 146.6, 143.9, 135.5, 131.2, 124.3, 124.2, 123.7,

101.8, 101.2, 99.7, 61.0, 56.6, 39.6, 35.3, 33.0, 26.5, 25.6, 25.4, 18.9, 17.6, 16.5; HRESIMS $[M+Na]^+$ *m/z* 457.1342 ($C_{23}H_{31}O_3BrNa$, calcd 457.1354).

Preparation of Compounds 18a and 18b. Method A: To a solution of benzofuran **16** (200 mg, 0.45 mmol) in cyclohexane (5 mL) was added anhydrous formic acid (2 mL) and the resulting biphasic mixture was refluxed for 1 month. After cooling to rt, the organic phase was separated and evaporated under reduced pressure. Chromatography of the residue on silica gel (1:99 EtOAc/hexanes) afforded the tetracyclic compound **18** (white solid, 79 mg) as an equimolar mixture of 2 diastereomers in 40% yield.

Method B: To a solution of benzofuran **16** (218 mg, 0.5 mmol) in nitropropane (25 mL), at –78°C, was added chlorosulfonic acid (0.27 mL, 2 mmol). The resulting mixture was allowed to stir at –78°C for 30 min. An aqueous solution of $NaHCO_3$ was then added and the aqueous phase was extracted with EtOAc. The EtOAc phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (3:97 EtOAc/hexanes) afforded the tetracyclic compound **18** (93 mg) as a mixture of 2 diastereomers in 43% yield with a 5/2 diastereomeric ratio of **18b/18a**.

Compounds 18a and 18b: isolated as a white solid; ^{1}H NMR of the 1/1 mixture (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 7.06 (s, 1H), 3.88 (s, 6H), 3.85 (s, 6H), 3.25 (m, 2H), 2.53 (m, 2H), 2.15 (m, 1H), 2.0-1.5 (m, 19H), 1.43 (d, 3H, *J* = 6.9 Hz), 1.39 (s, 3H), 1.36 (d, 3H, *J* = 7.0 Hz), 1.35 (s, 3H), 0.96 (s, 6H), 0.94 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, 100 MHz) δ 159.5, 158.2, 150.5, 150.4, 147.5, 147.3, 145.5. 145.3, 127.4, 126.8, 125.6, 125.5, 106.8, 106.1, 101.2, 100.9, 62.6, 58.7, 58.6, 54.8, 51.6, 45.5, 43.5, 43.3, 41.5, 41.1, 40.8, 37.2, 36.2, 36.0, 35.2, 35.0, 34.7, 32.6, 25.4, 24.2, 23.8, 23.4 (2C), 21.6, 21.4, 20.3, 20.2, 20.0 ppm; HRESIMS $[M+H]^+$ *m/z* 435.1534 ($C_{23}H_{32}O_3Br$, calcd 435.1535).

Preparation of Compounds 19a and 19b. To a solution of bromobenzofuran **18** (130 mg, 0.3 mmol) in THF (20 mL) at –78°C was added *n*-BuLi (1.6M in Hexanes, 0.21 mL, 0.33 mmol). After stirring at this temperature for 30 min DMF (0.23 mL, 3.0 mmol) was added. The mixture was stirred for 1 h and then warmed to rt. Aqueous NH_4Cl was added and the aqueous phase was extracted with EtOAc. The EtOAc phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (3:97

EtOAc/hexanes) afforded the aldehyde **19** (87 mg) in 76 % yield. The two diastereomers **19a** and **19b** were separated by HPLC using a Whatman Magnum-9 Partisil 10 column with 1:19 EtOAc/hexanes as the eluent.

Compound 19a: isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.45 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.28 (m, 1H), 2.52 (m, 1H), 2.14 (m, 1H), 1.83 (m, 1H), 1.70 (m, 1H), 1.60-1.46 (m, 5H), 1.44 (d, 3H, *J* = 7.2 Hz), 1.35 (s, 3H), 1.23 (m, 2H), 0.96 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 158.9, 149.5, 147.9, 146.4, 125.3, 124.6, 114.8, 113.1, 62.8, 57.3, 53.4, 41.9, 40.3, 39.5, 34.8, 34.7, 33.5, 33.25, 24.0, 22.0, 21.9, 20.2, 18.9 ppm; HRESIMS $[M+Na]^+$ *m/z* 407.2190 ($C_{24}H_{32}O_4Na$, calcd 407.2198).

Compound 19b: isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.40 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.30 (m, 1H), 2.48 (m, 1H), 2.0-1.41 (m, 9H), 1.39 (d, 3H, *J* = 6.7 Hz), 1.39 (s, 3H), 1.23 (m, 1H), 0.97 (s, 3H), 0.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 157.5, 149.1, 147.9, 146.0, 125.2, 123.9, 114.9, 112.3, 62.7, 57.1, 50.2, 41.9, 40.2, 39.0, 35.7, 34.4, 33.6, 31.0, 22.7, 22.2, 20.3, 18.8, 18.6 ppm; HRESIMS $[M+Na]^+$ *m/z* 407.2190 ($C_{24}H_{32}O_4Na$, calcd 407.2198).

Preparation of (±) Liphagal (1). To a solution of dimethoxyliphagal (**19a**) (5 mg, 0.013 mmol) in CH_2Cl_2 (2 mL) at –78°C was added BI_3 (4.0 equiv, 0.01 M in CH_2Cl_2). The resulting mixture was allowed to warm to rt and was then quenched with an aqueous solution of sodium thiosulfate. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in MeCN and purified via C_{18} reversed-phase HPLC using a CSC-Inertsil 150A/ODS2, 5 μm 25 x 0.94 cm column, with 4:1 MeCN/(0.05%TFA/H_2O) as eluent to yield 3 mg of liphagal (**1**) in 64% yield.

(±) Liphagal (1): isolated as an amorphous yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 10.43 (s, 1H), 7.53 (s, 1H), 3.18 (m, 1H), 2.52 (m, 1H), 2.15 (m, 1H), 1.84 (m, 1H), 1.8-1.5 (m, 7H), 1.41 (d, 3H, *J* = 7.0 Hz), 1.32 (s, 3H), 1.23 (m, 1H), 0.96 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 156.4, 147.8, 145.2, 139.3, 125.4, 120.2, 115.8, 106.1, 53.6, 41.8, 40.1, 39.3, 35.0, 34.7, 33.5, 33.2, 24.0, 21.8, 21.5, 20.1, 18.6 ppm.

Table 1. NMR Data for liphagal (**1**) recorded in DMSO-d_6.

Atom #	^{1}H (δ)	^{13}C (δ)	HMBC[a]	1D NOESY[b]
1_{ax}	1.38	39.7	1.28, 1.50	1.21, 1.50, 2.47
1_{eq}	2.47			1.28, 1.38, 1.68, 7.43
2_{ax}	1.68 qt, *J*=13.4, 1.4 Hz	18.3		0.91, 1.28, 1.48, 2.47
2_{eq}	1.48 m			1.68
3_{ax}	1.21 td, *J*=13.4, 3.3 Hz	41.3	0.91, 0.94	0.94, 1.38, 1.43, 1.50
3_{eq}	1.43 m			0.91, 0.94, 1.21
4		34.4	0.91, 0.94, 1.52	
5	1.50 m	53.4	0.91, 0.94, 1.28	0.94, 1.21, 1.38
6	1.52 m	23.5	1.50, 2.12, 3.16	0.91, 1.28, 2.12, 3.16
6	1.78 m			0.91, 0.94, 2.12
7	1.42 m	34.7	1.36, 1.78, 3.16	1.36, 2.12
7	2.12 dtd, *J*=13.2, 6.7, 3.3 Hz			1.42, 1.52, 1.78, 3.16
8	3.16 m	33.0[1]	1.36, 1.78, 2.12	1.36, 1.52, 2.12
9		155.2	1.36, 2.12, 3.16	
10		124.4	1.28, 3.16, 7.43	
11		38.9	1.28, 1.50, 1.78	
12		119.2		
13	7.43 s	114.9		1.28, 2.47
14		140.8	7.43	
15		147.2[2]	7.43, 10.40	
16		107.9	7.43, 10.40	
17		145.8[2]	7.43, 10.40	
18	10.40 s	189.7		1.36
19	0.91 s	21.6[3]	0.94, 1.50	0.94, 1.28, 1.52 1.68, 1.78
20	0.94 s	32.9[1]	0.91, 1.50	0.91, 1.21, 1.43, 1.50, 1.78
21	1.36 d, *J*=7.1 Hz	21.7[3]	3.16	1.42, 1.50, 3.16, 10.4
22	1.28 s	19.9	1.50	0.91, 1.52, 1.68, 2.47, 3.16, 7.43

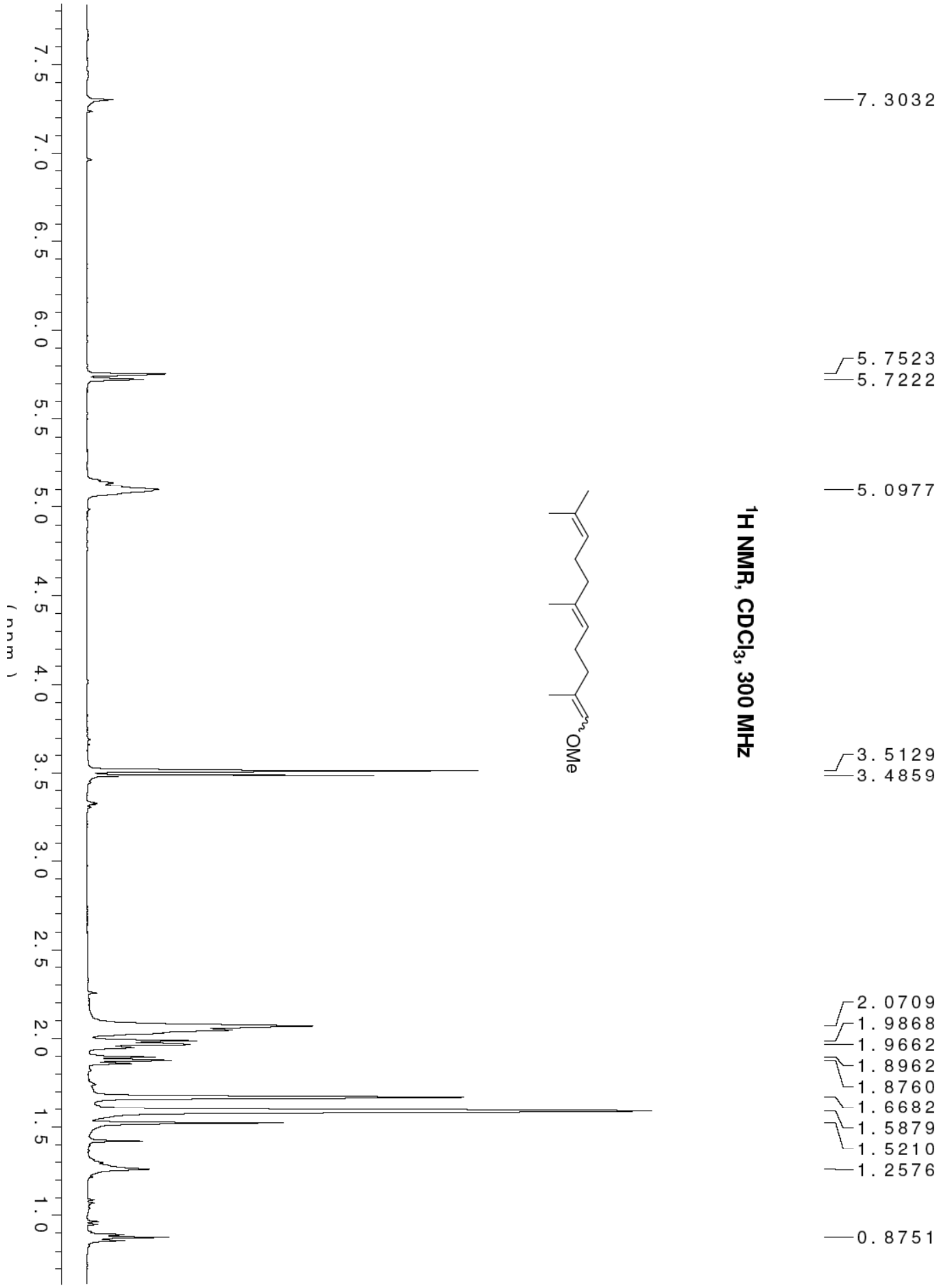
14O<u>H</u> 9.29 bs [1]

15O<u>H</u> 10.28 bs [1]

[a]Chemical shifts of proton resonances correlated to the carbon resonance listed in the δ ^{13}C column. Experiments optimized for both 2 & 8 Hz.

[1, 2, 3]Assignments within a column are interchangeable.

[b]Chemical shift of proton resonances correlated to the proton resonance listed in the δ ^{1}H column.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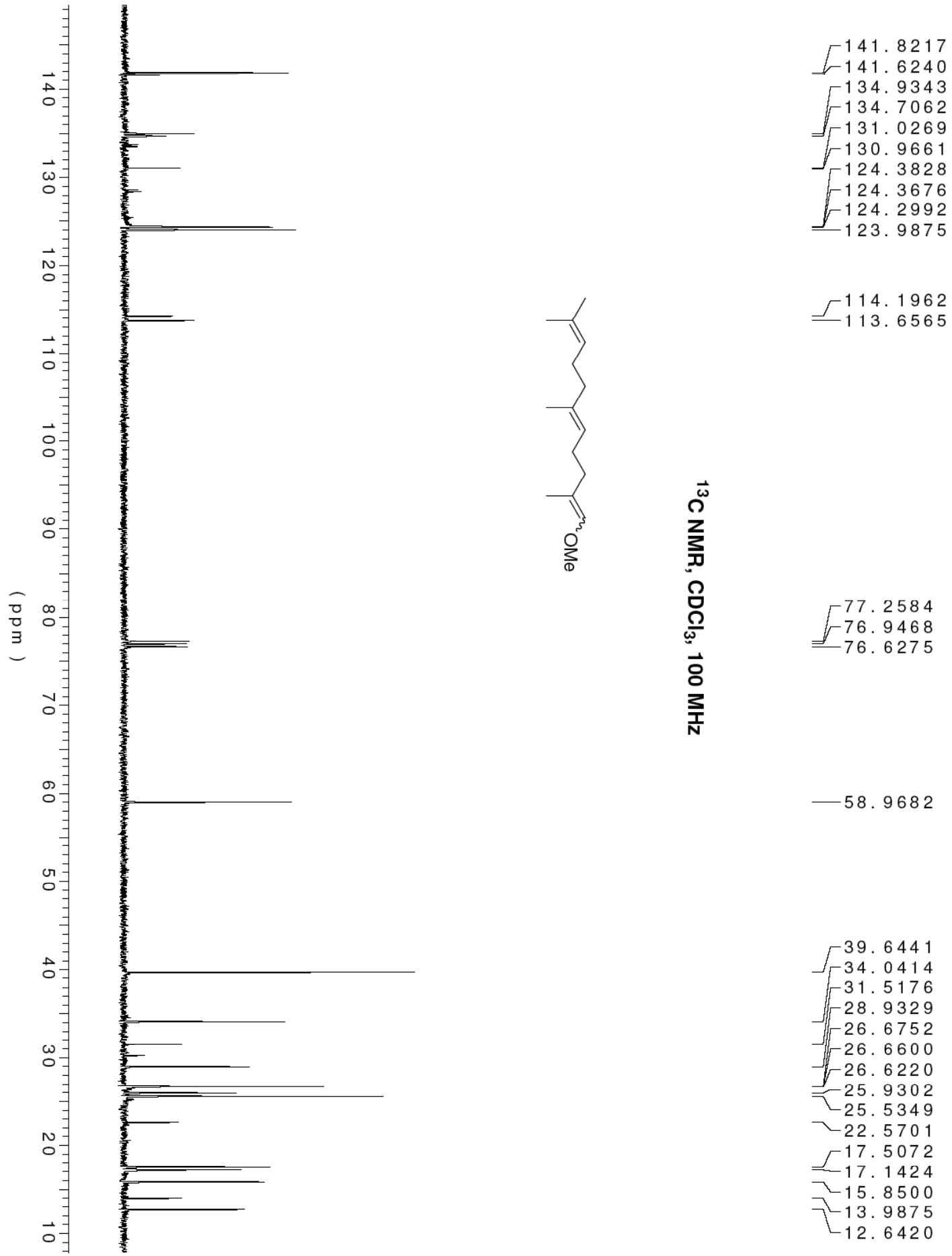
5.7523
5.7222
5.0977
3.5129
3.4859
2.0709
1.9868
1.9662
1.8962
1.8760
1.6682
1.5879
1.5210
1.2576
0.8751
OMe
^{1}H NMR, CDCl$_3$, 300 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)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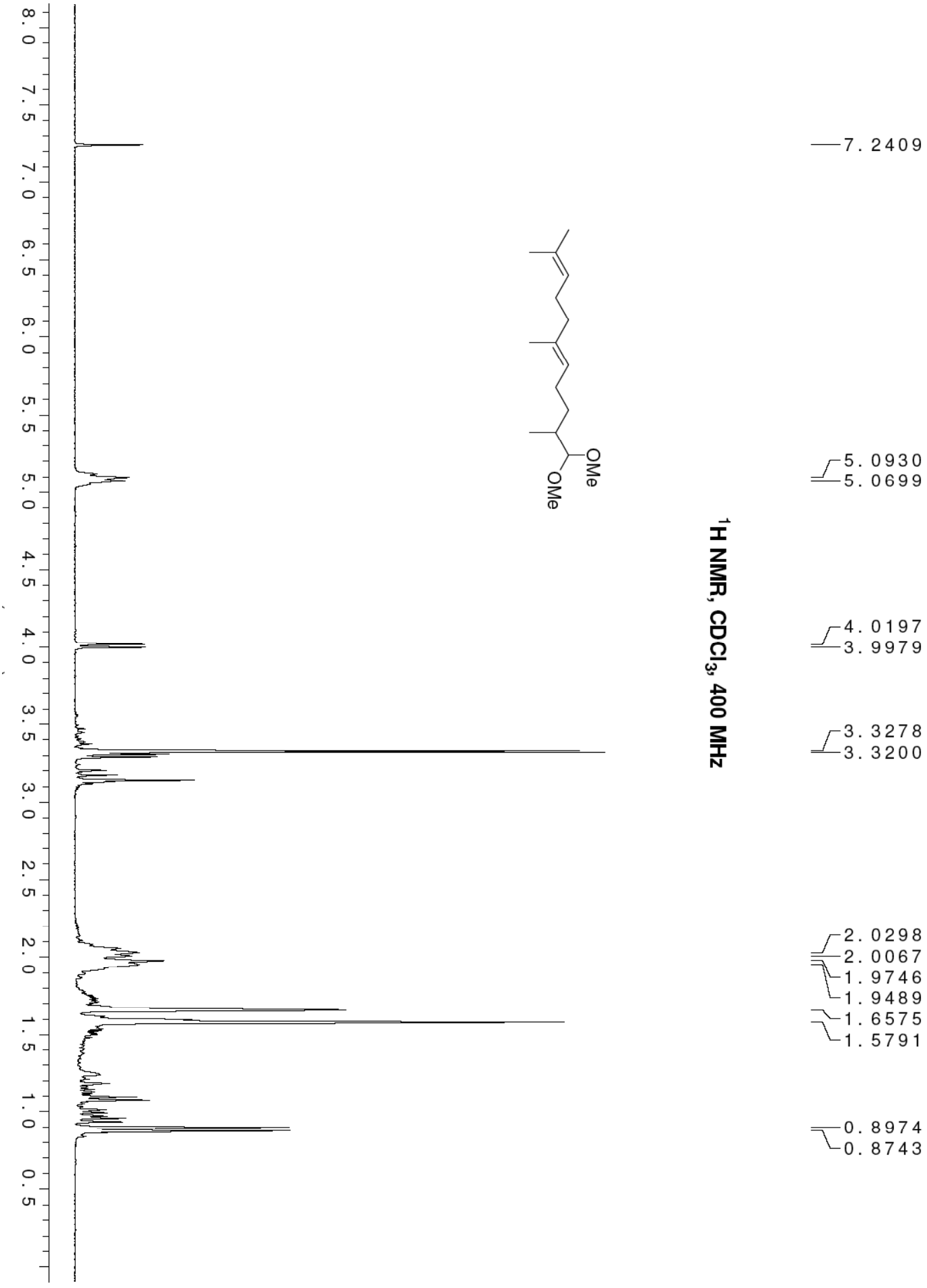
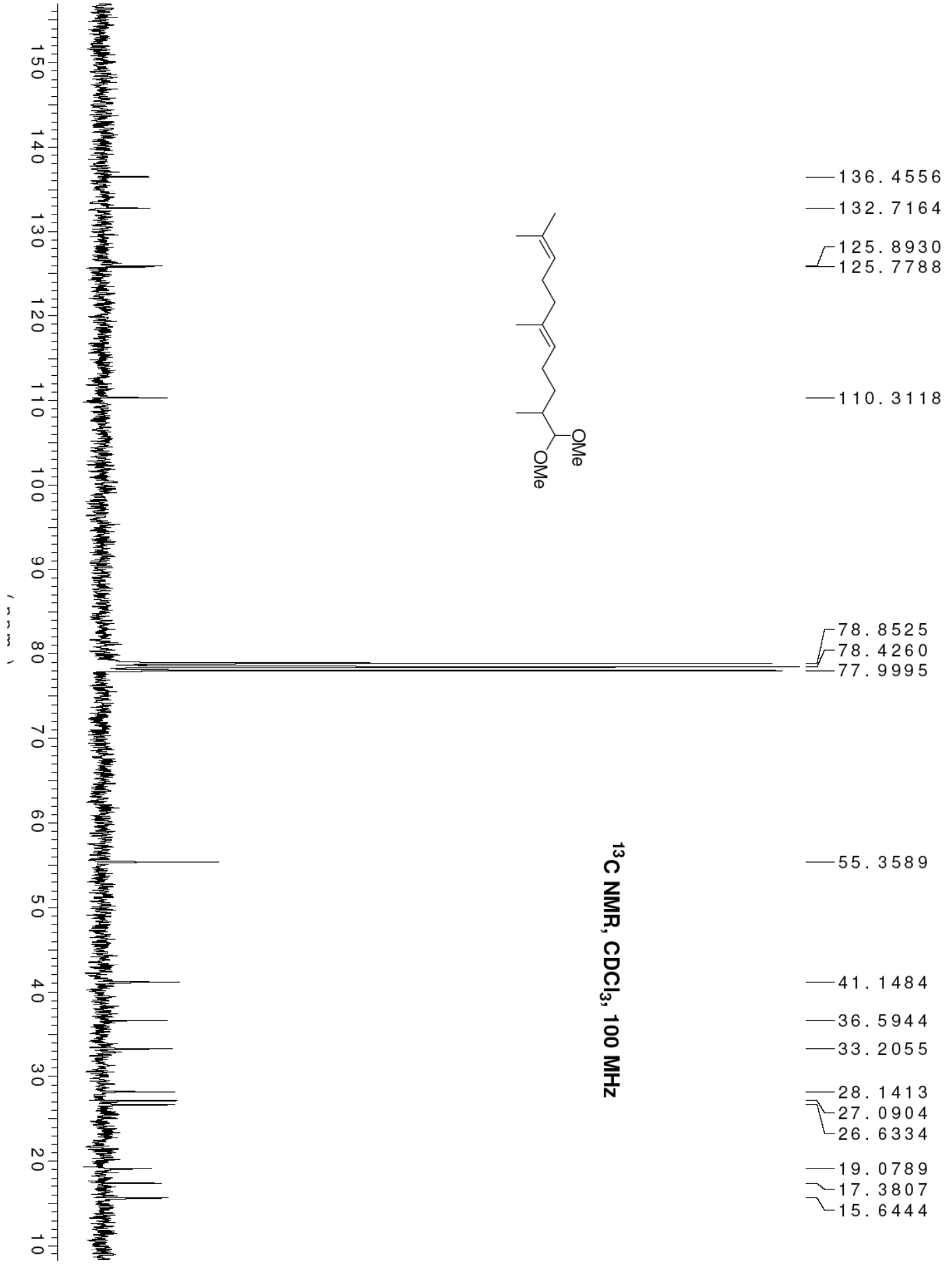
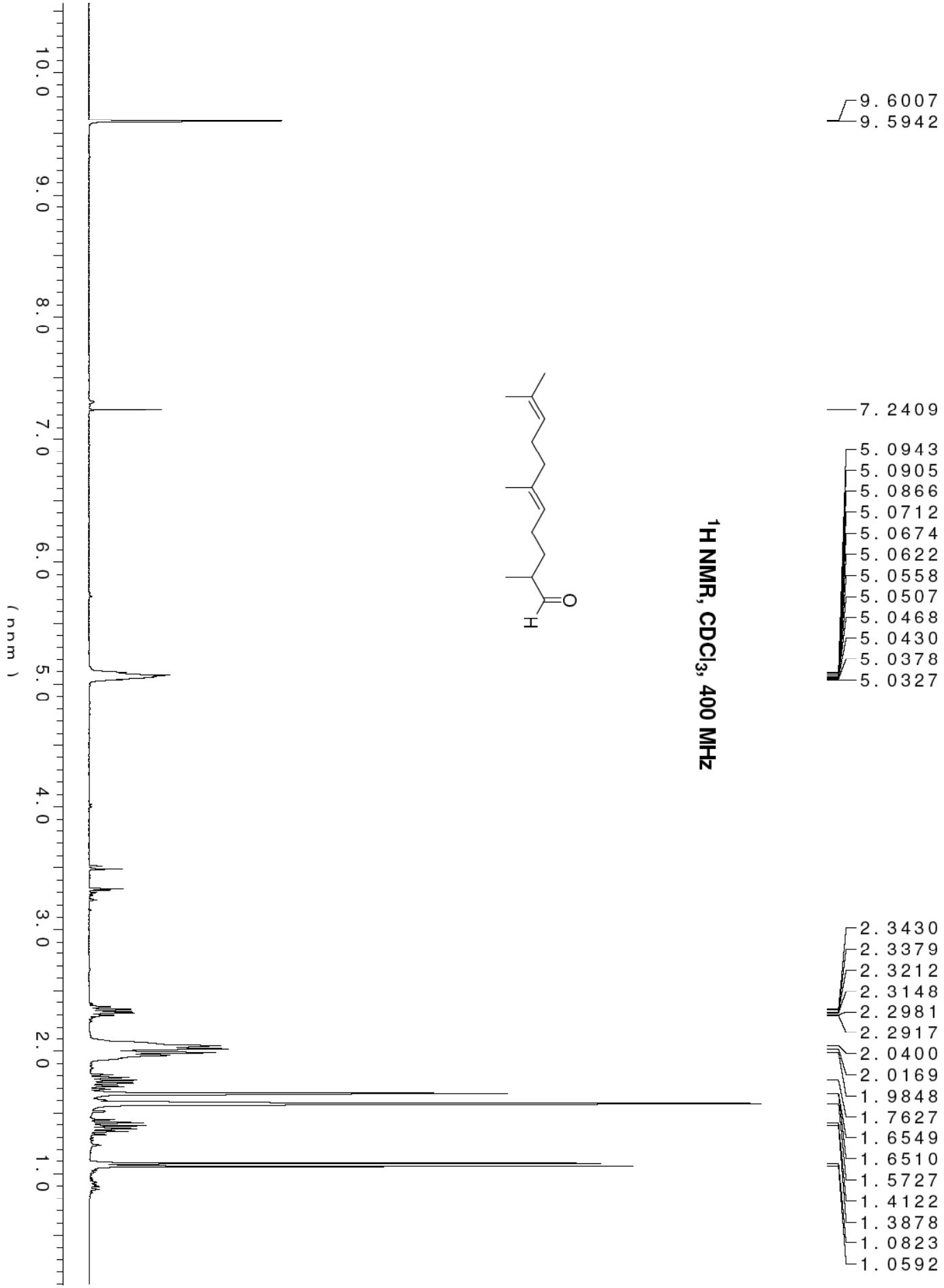
141.6240
134.9343
134.7062
131.0269
130.9661
124.3828
124.3676
124.2992
123.9875
114.1962
113.6565
77.2584
76.9468
76.6275
58.9682
39.6441
34.0414
31.5176
28.9329
26.6752
26.6600
26.6220
25.9302
25.5349
22.5701
17.5072
17.1424
15.8500
13.9875
12.6420
OMe
13C NMR, CDCl3, 100 MHz
(ppm)

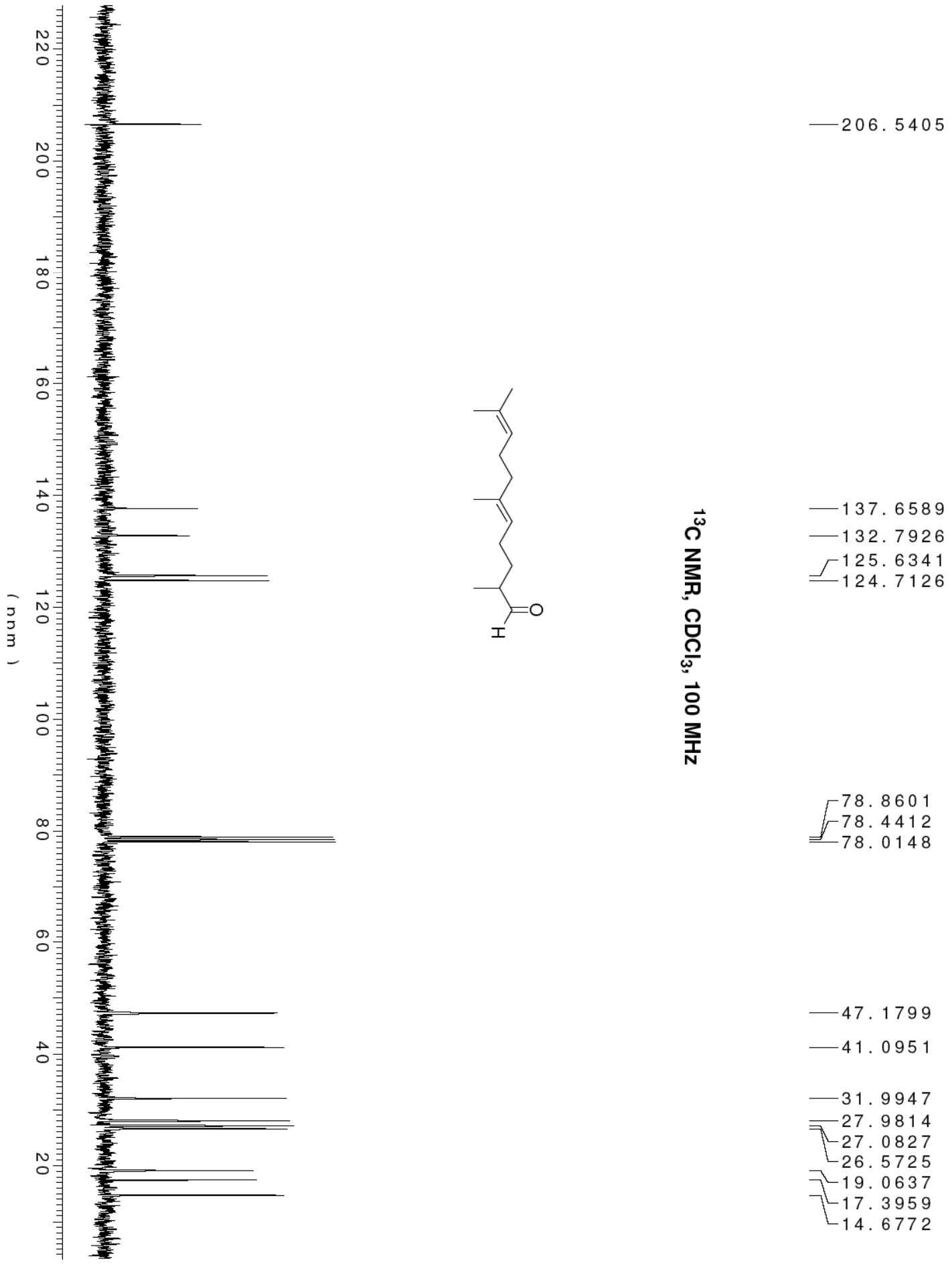


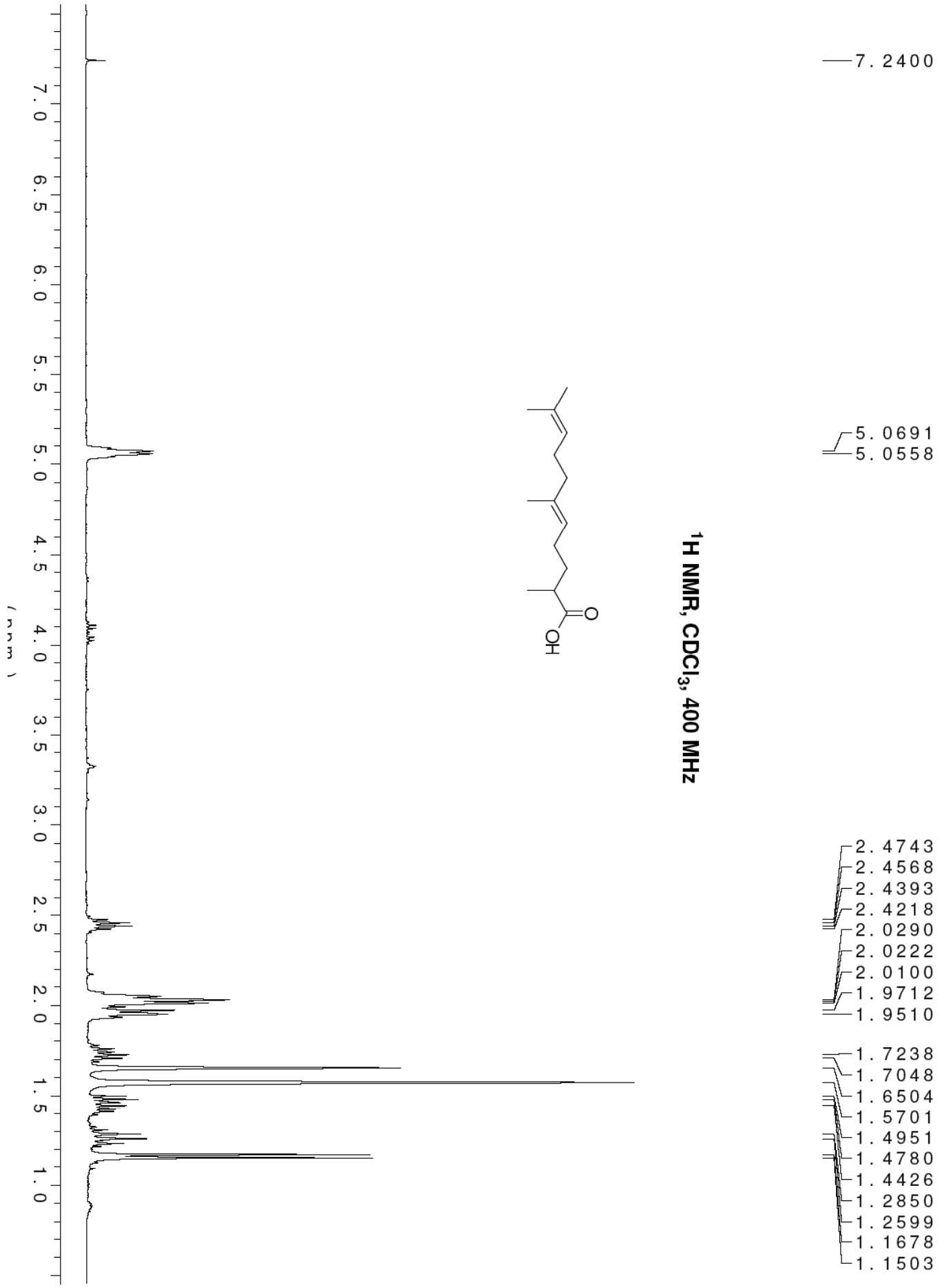
^{1}H NMR, $CDCl_3$, 400 MHz

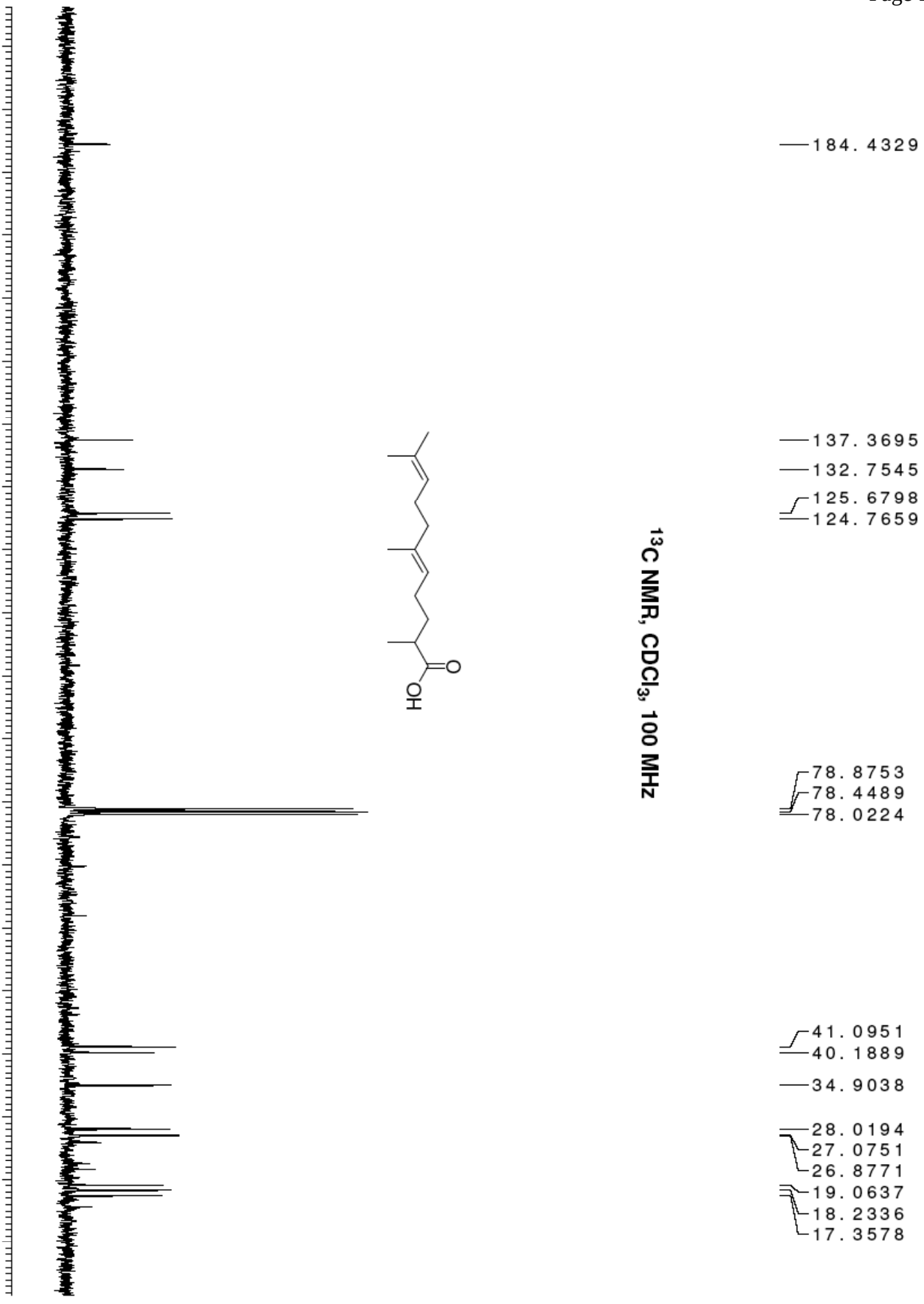


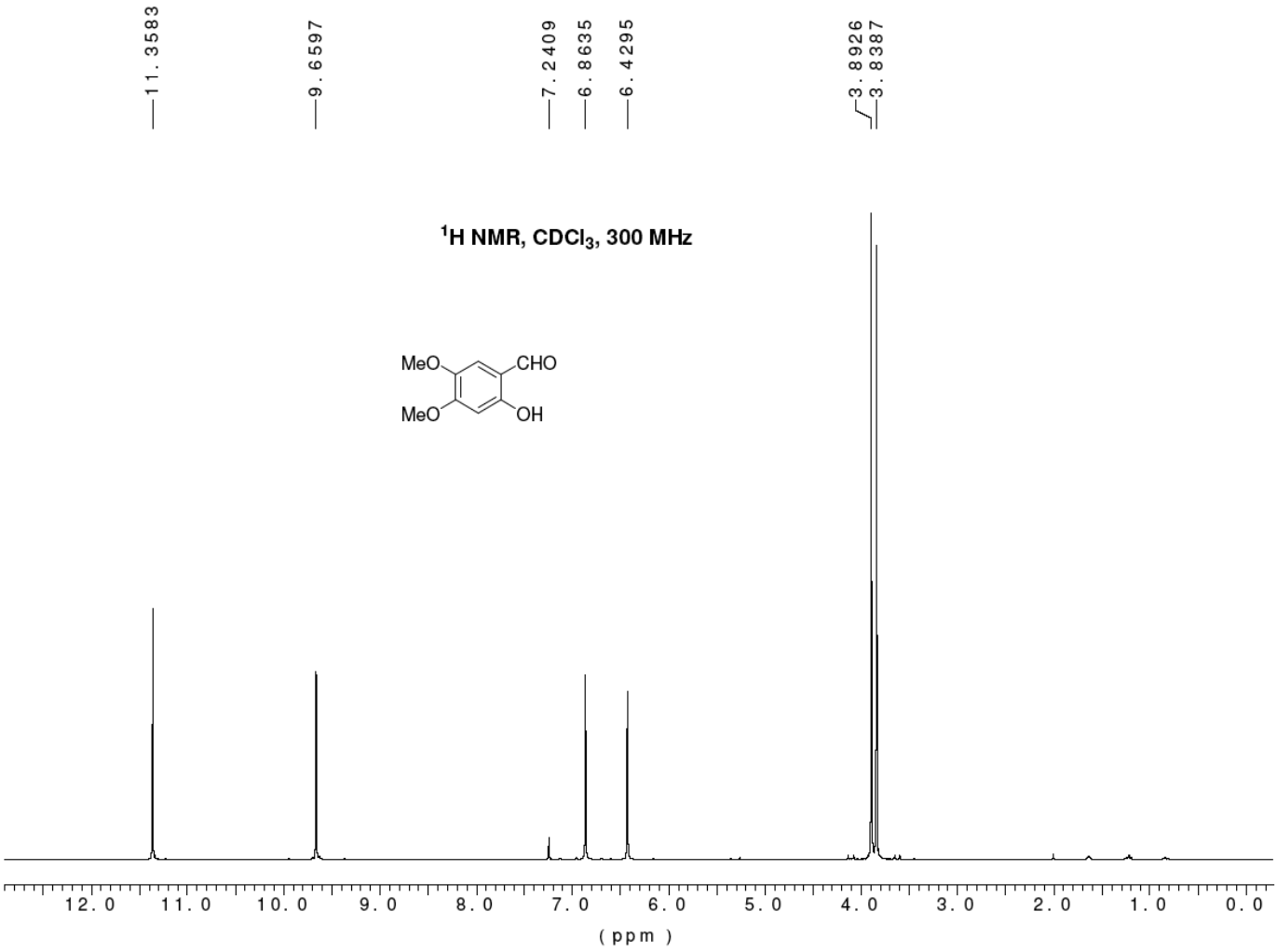
^{13}C NMR, $CDCl_3$, 100 MHz

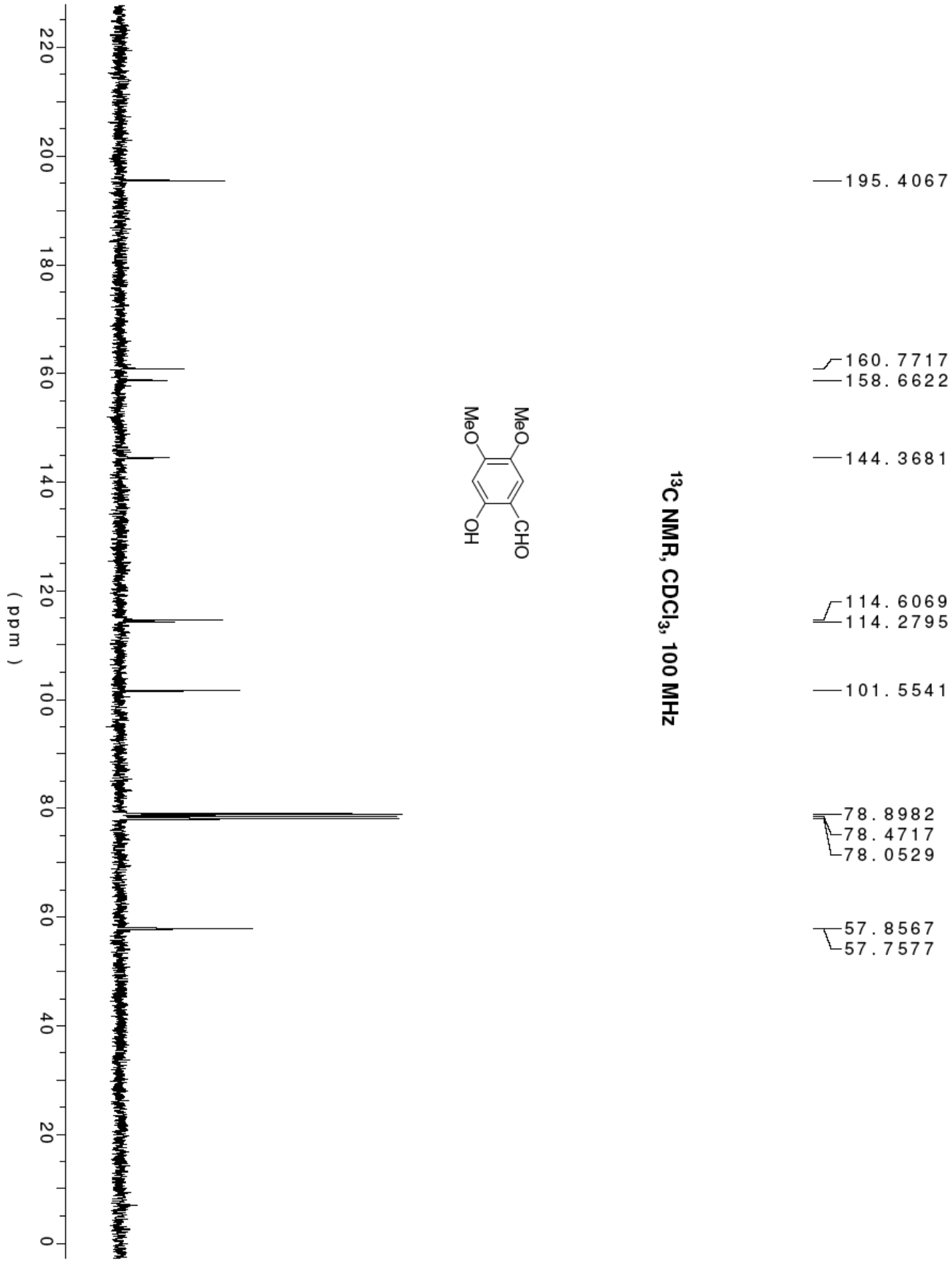

9.6007
9.5942
7.2409
5.0943
5.0905
5.0866
5.0712
5.0674
5.0622
5.0558
5.0507
5.0468
5.0430
5.0378
5.0327
2.3430
2.3379
2.3212
2.3148
2.2981
2.2917
2.0400
2.0169
1.9848
1.7627
1.6549
1.6510
1.5727
1.4122
1.3878
1.0823
1.0592
O
H
^{1}H NMR, CDCl$_3$, 400 MHz
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

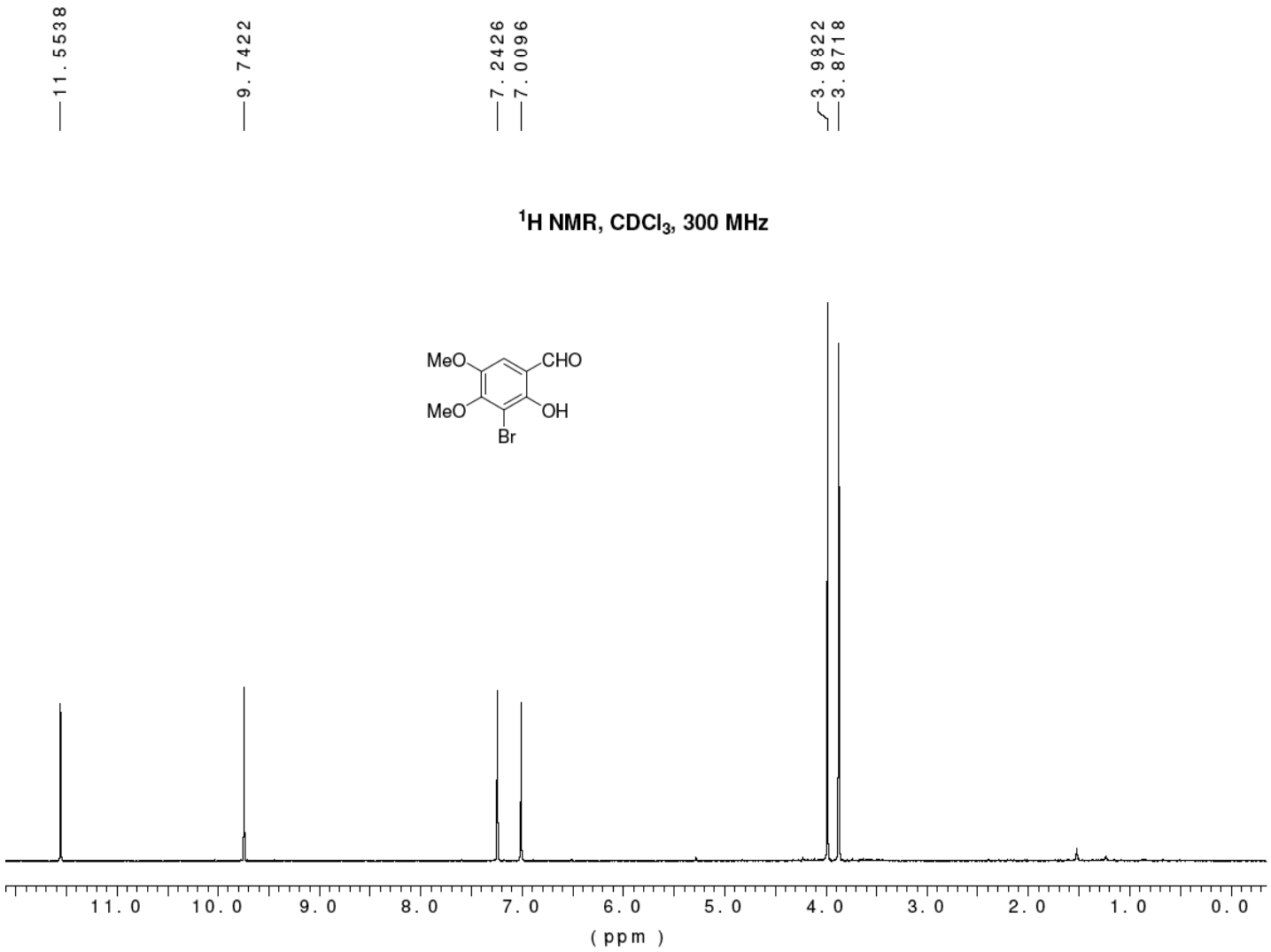

206.5405
137.6589
132.7926
125.6341
124.7126
78.8601
78.4412
78.0148
47.1799
41.0951
31.9947
27.9814
27.0827
26.5725
19.0637
17.3959
14.6772
O
H
13C NMR, CDCl3, 100 MHz
220
200
180
160
140
120
100
80
60
40
20
(ppm)

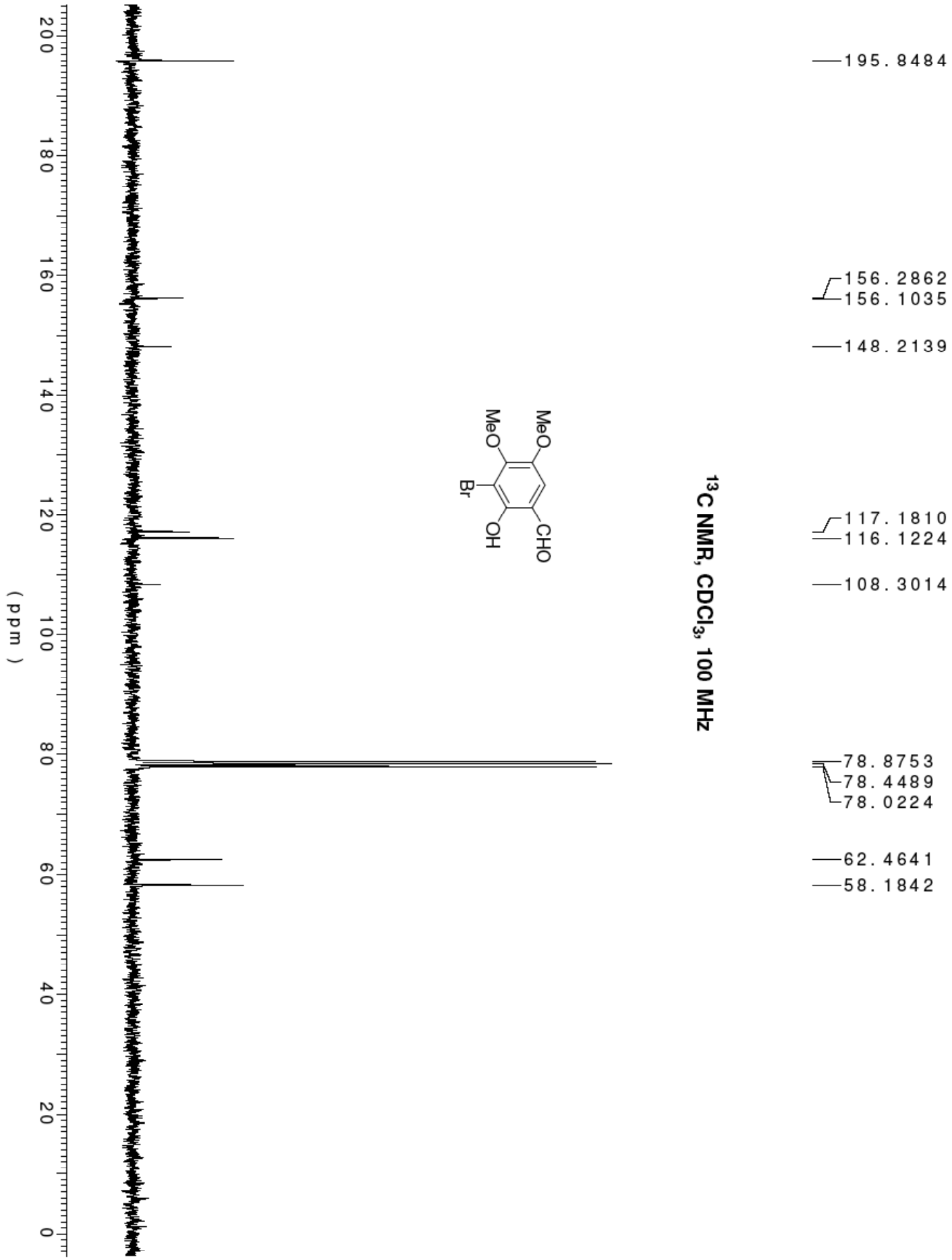

7.2400
5.0691
5.0558
2.4743
2.4568
2.4393
2.4218
2.0290
2.0222
2.0100
1.9712
1.9510
1.7238
1.7048
1.6504
1.5701
1.4951
1.4780
1.4426
1.2850
1.2599
1.1678
1.1503
O
OH
^{1}H NMR, CDCl$_3$, 400 MHz
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

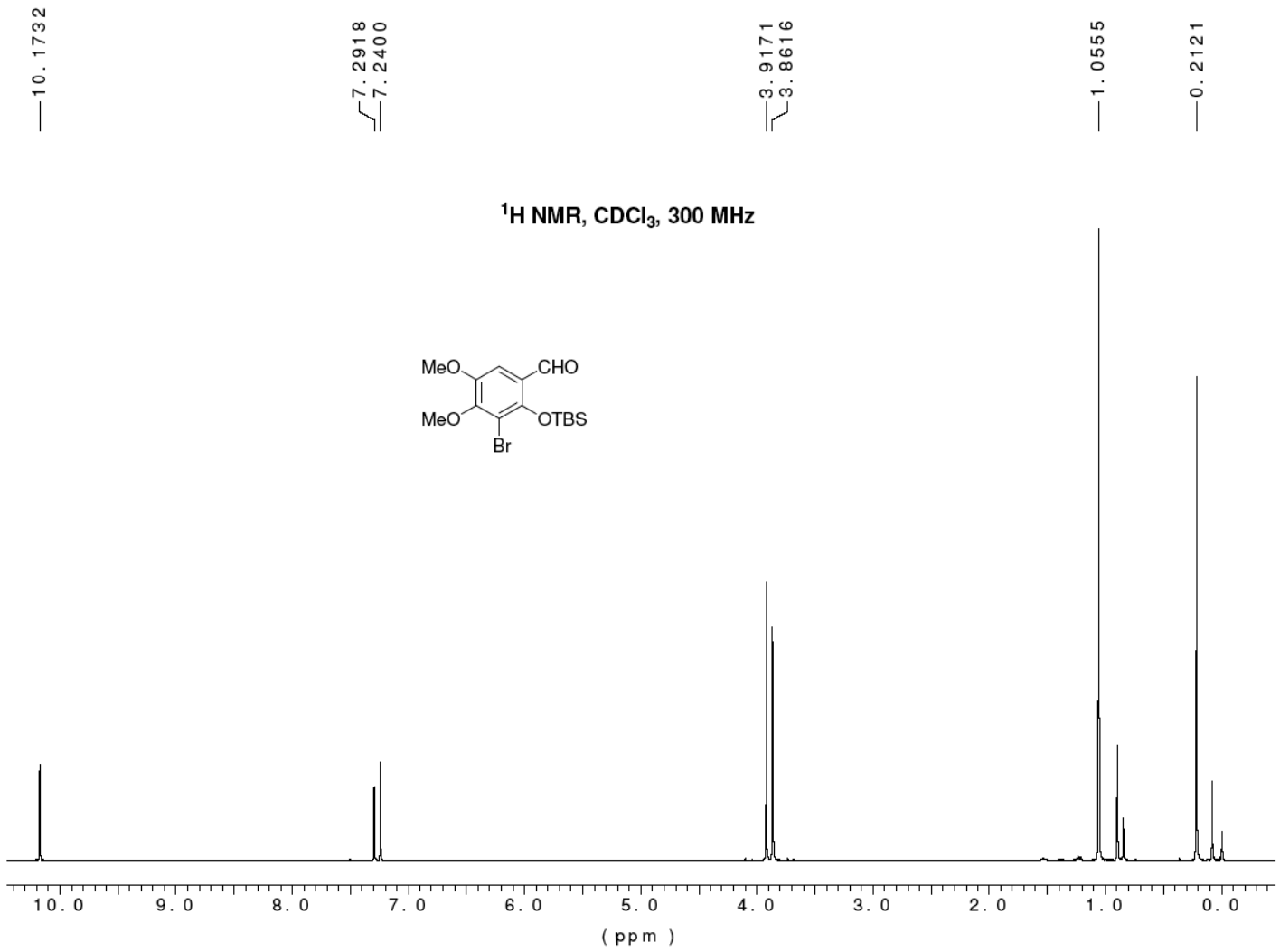

184.4329
137.3695
132.7545
125.6798
124.7659
78.8753
78.4489
78.0224
41.0951
40.1889
34.9038
28.0194
27.0751
26.8771
19.0637
18.2336
17.3578
OH
O
13C NMR, CDCl3, 100 MHz
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

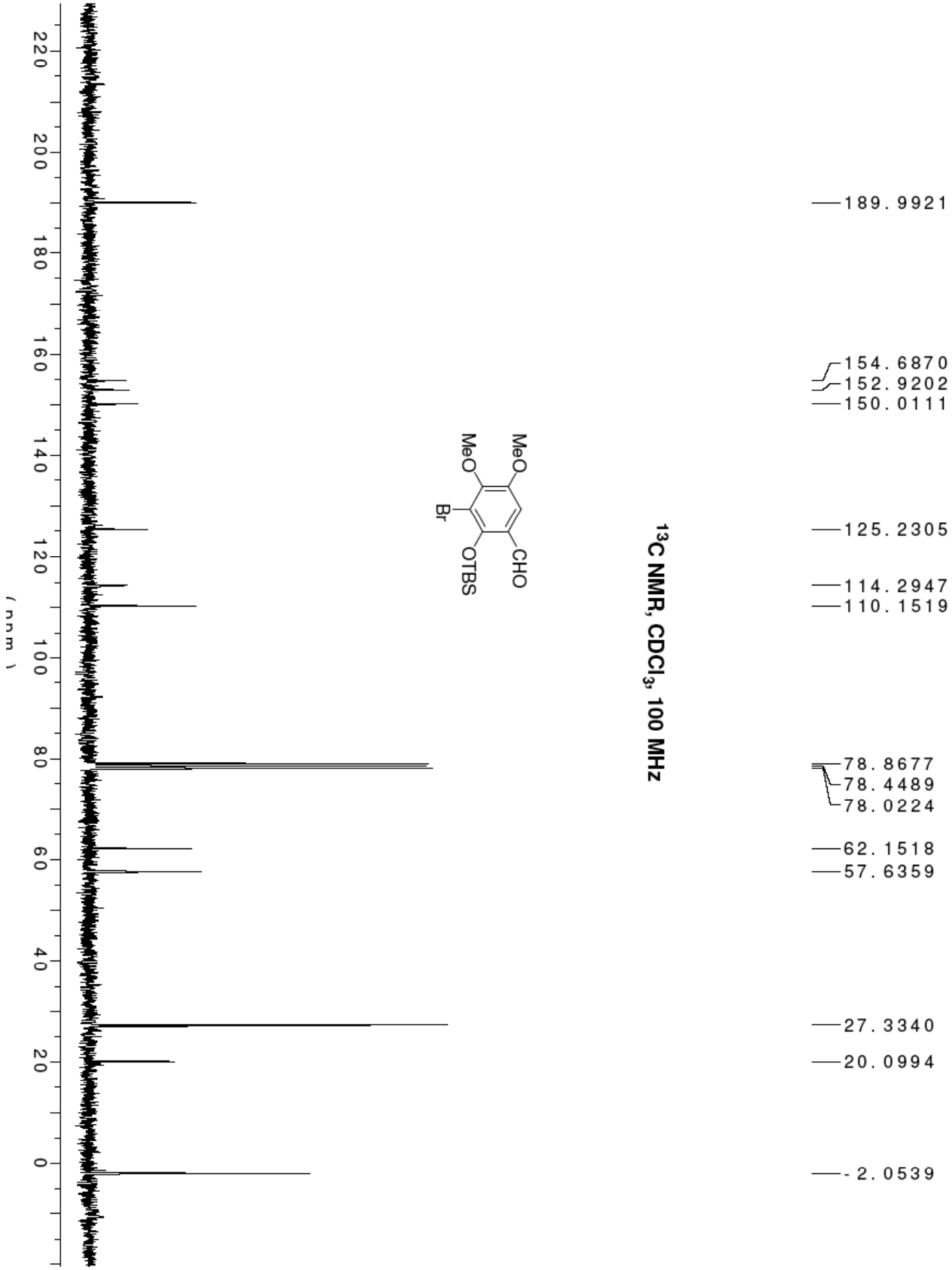

11.3583
9.6597
7.2409
6.8635
6.4295
3.8926
3.8387
^{1}H NMR, $CDCl_3$, 300 MHz
MeO
CHO
MeO
OH
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

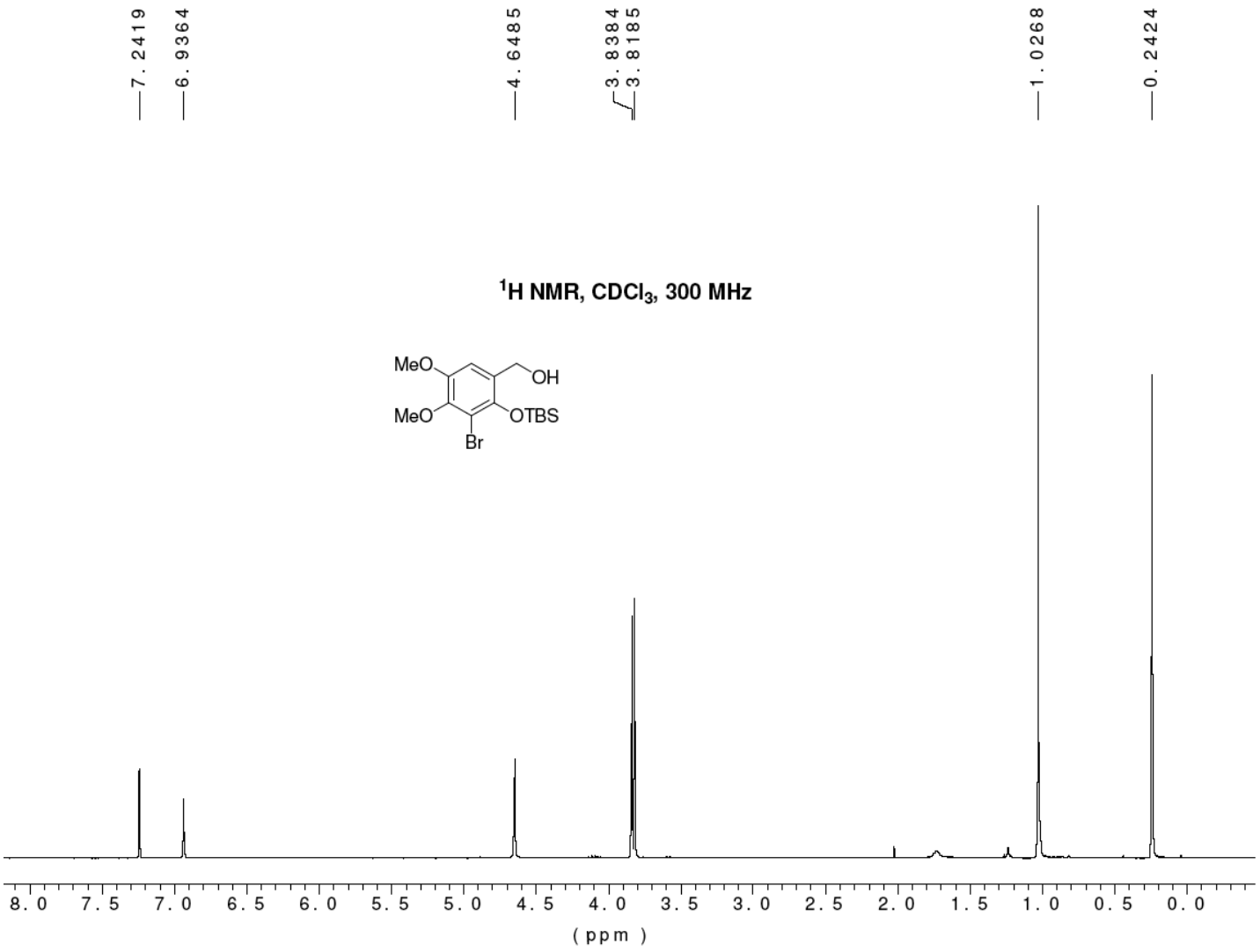

220
200
180
160
140
120
100
80
60
40
20
0
(ppm)
MeO
MeO
OH
CHO
^{13}C NMR, CDCl$_3$, 100 MHz
195.4067
160.7717
158.6622
144.3681
114.6069
114.2795
101.5541
78.8982
78.4717
78.0529
57.8567
57.7577

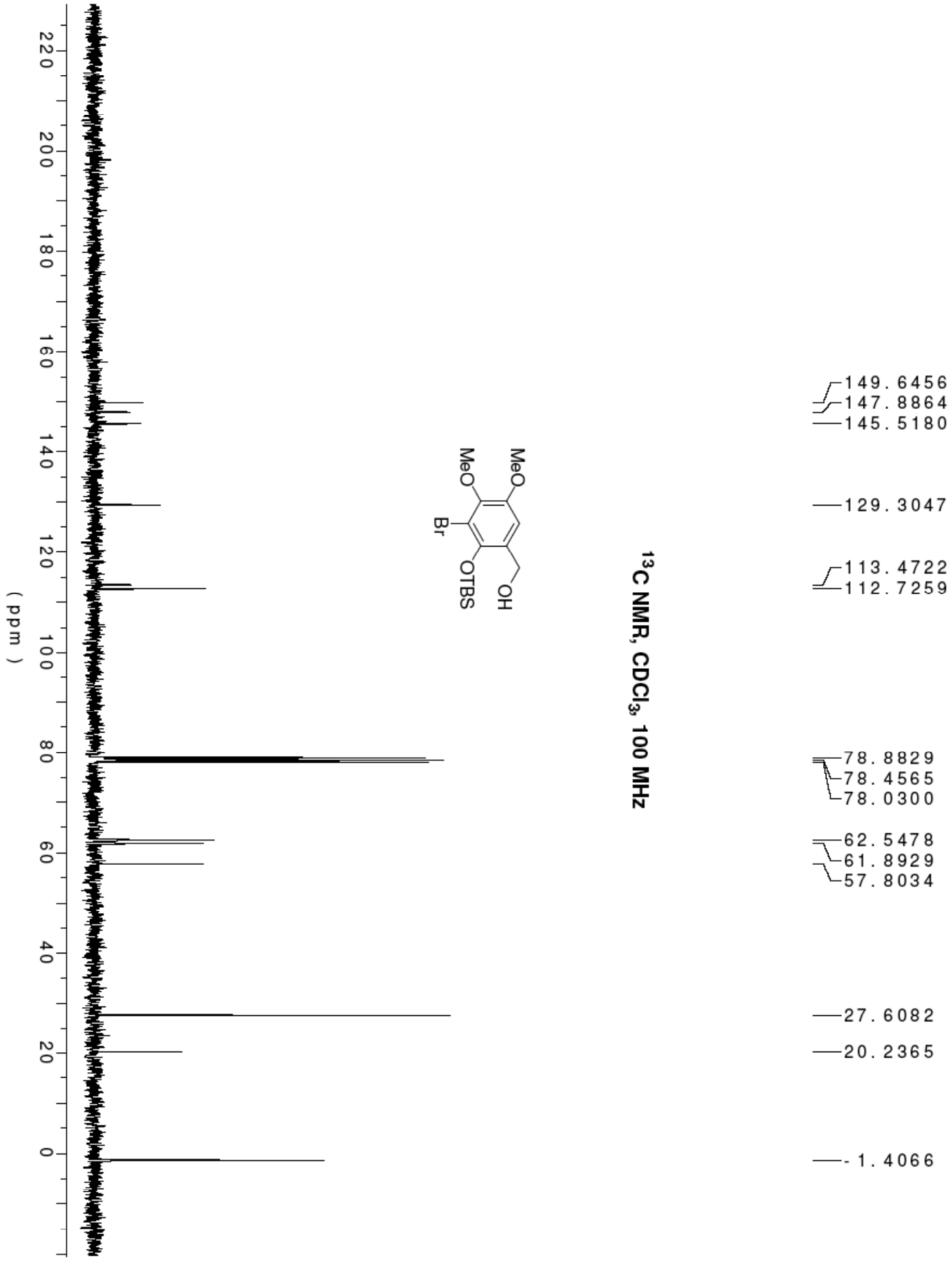

11.5538
9.7422
7.2426
7.0096
3.9822
3.8718
^{1}H NMR, CDCl$_3$, 300 MHz
MeO
CHO
MeO
OH
Br
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

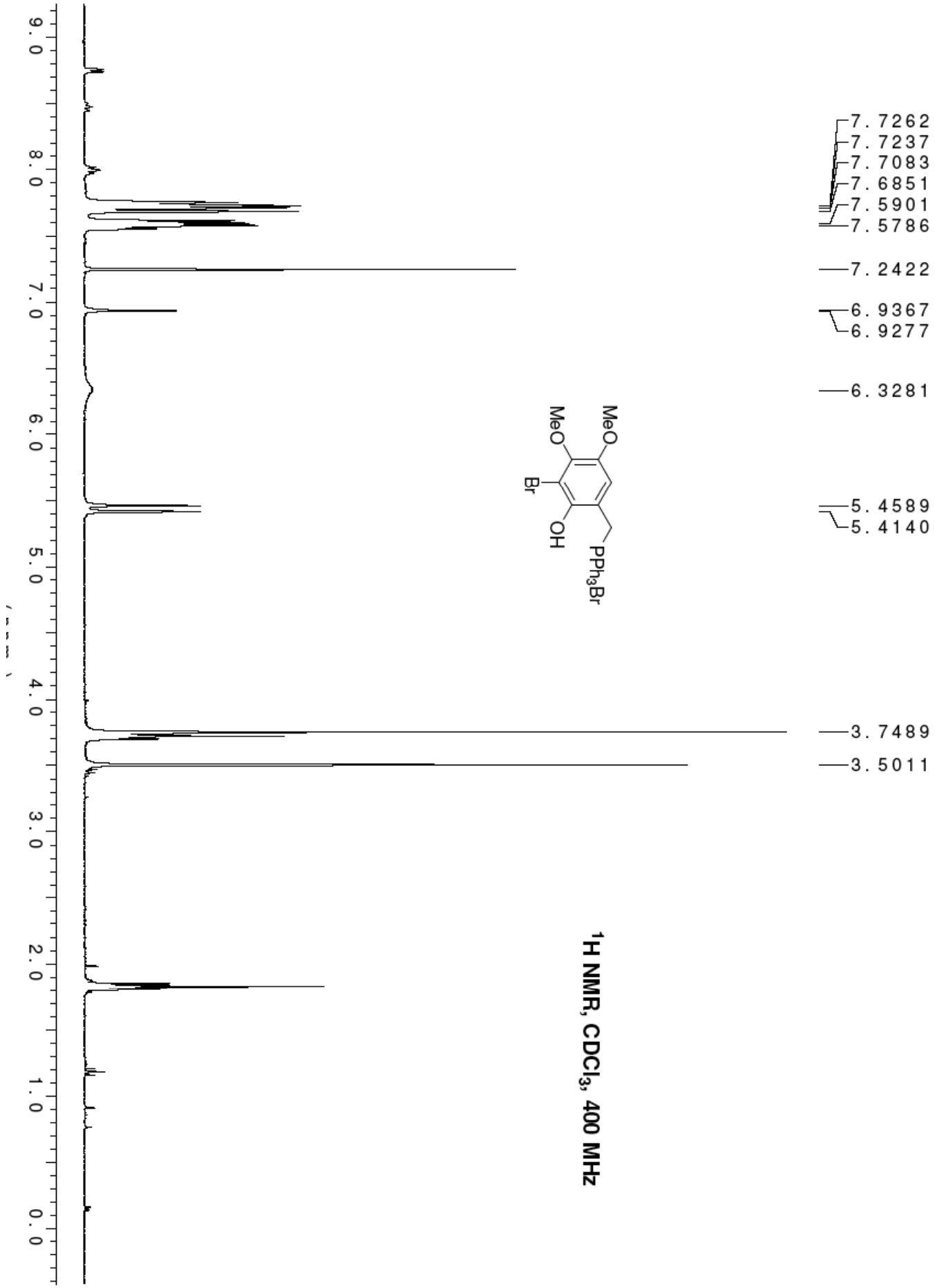

195.8484
156.2862
156.1035
148.2139
117.1810
116.1224
108.3014
78.8753
78.4489
78.0224
62.4641
58.1842
MeO
MeO
Br
OH
CHO
^{13}C NMR, CDCl$_3$, 100 MHz
200
180
160
140
120
100
80
60
40
20
0
(ppm)


10.1732
7.2918
7.2400
3.9171
3.8616
1.0555
0.2121
^{1}H NMR, $CDCl_3$, 300 MHz
MeO
CHO
MeO
OTBS
Br
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

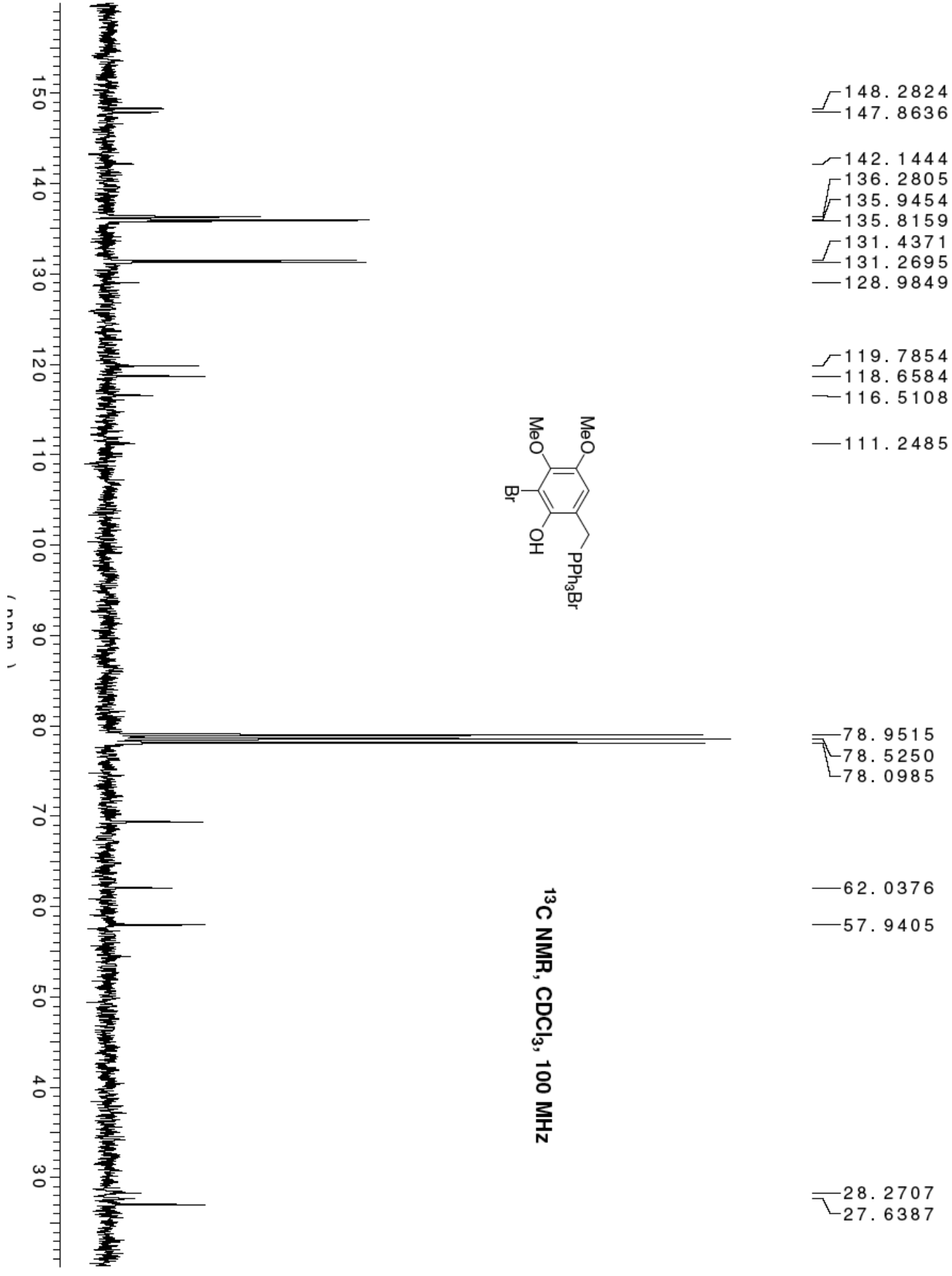

189.9921
154.6870
152.9202
150.0111
125.2305
114.2947
110.1519
78.8677
78.4489
78.0224
62.1518
57.6359
27.3340
20.0994
-2.0539
MeO
MeO
Br
OTBS
CHO
13C NMR, CDCl3, 100 MHz
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)


7.2419
6.9364
4.6485
3.8384
3.8185
1.0268
0.2424
^{1}H NMR, CDCl$_3$, 300 MHz
MeO
OH
MeO
OTBS
Br
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


149.6456
147.8864
145.5180
129.3047
113.4722
112.7259
78.8829
78.4565
78.0300
62.5478
61.8929
57.8034
27.6082
20.2365
-1.4066
MeO
MeO
Br
OTBS
OH
13C NMR, CDCl3, 100 MHz
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)



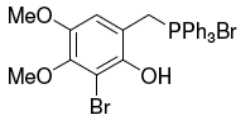
^{1}H NMR, $CDCl_3$, 400 MHz

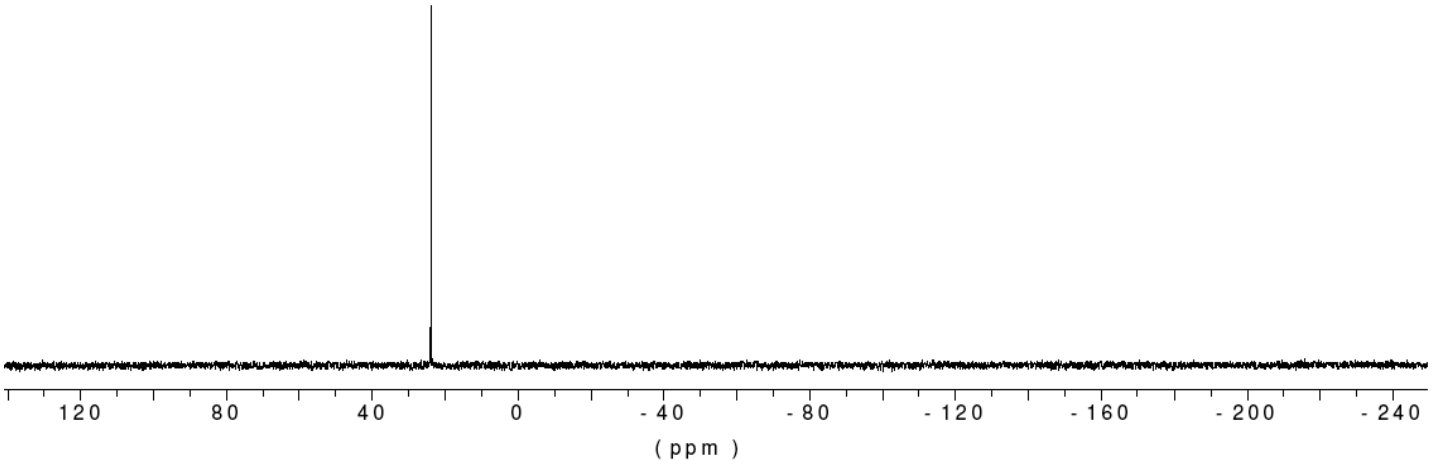


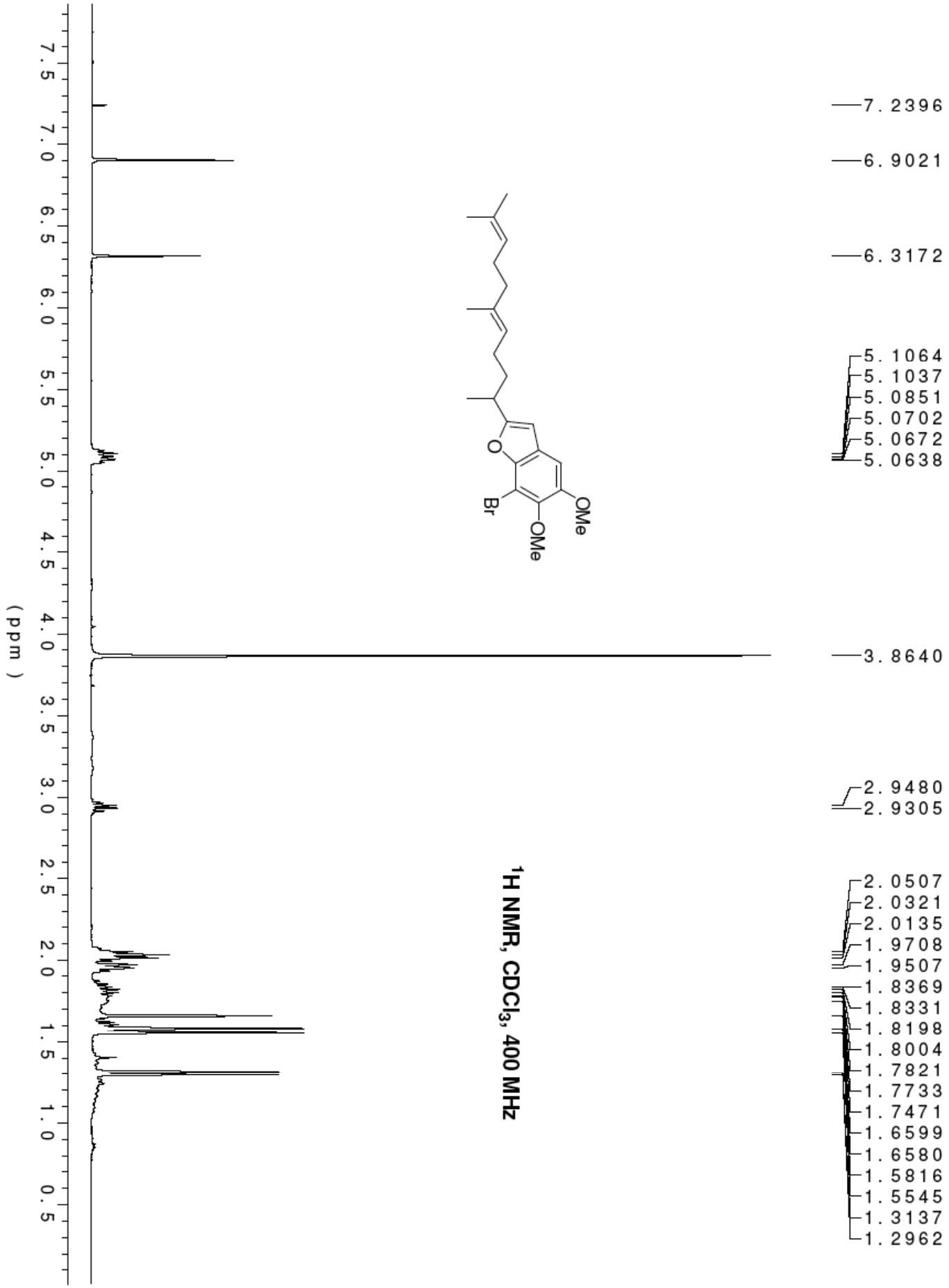
^{13}C NMR, $CDCl_3$, 100 MHz

23.8999

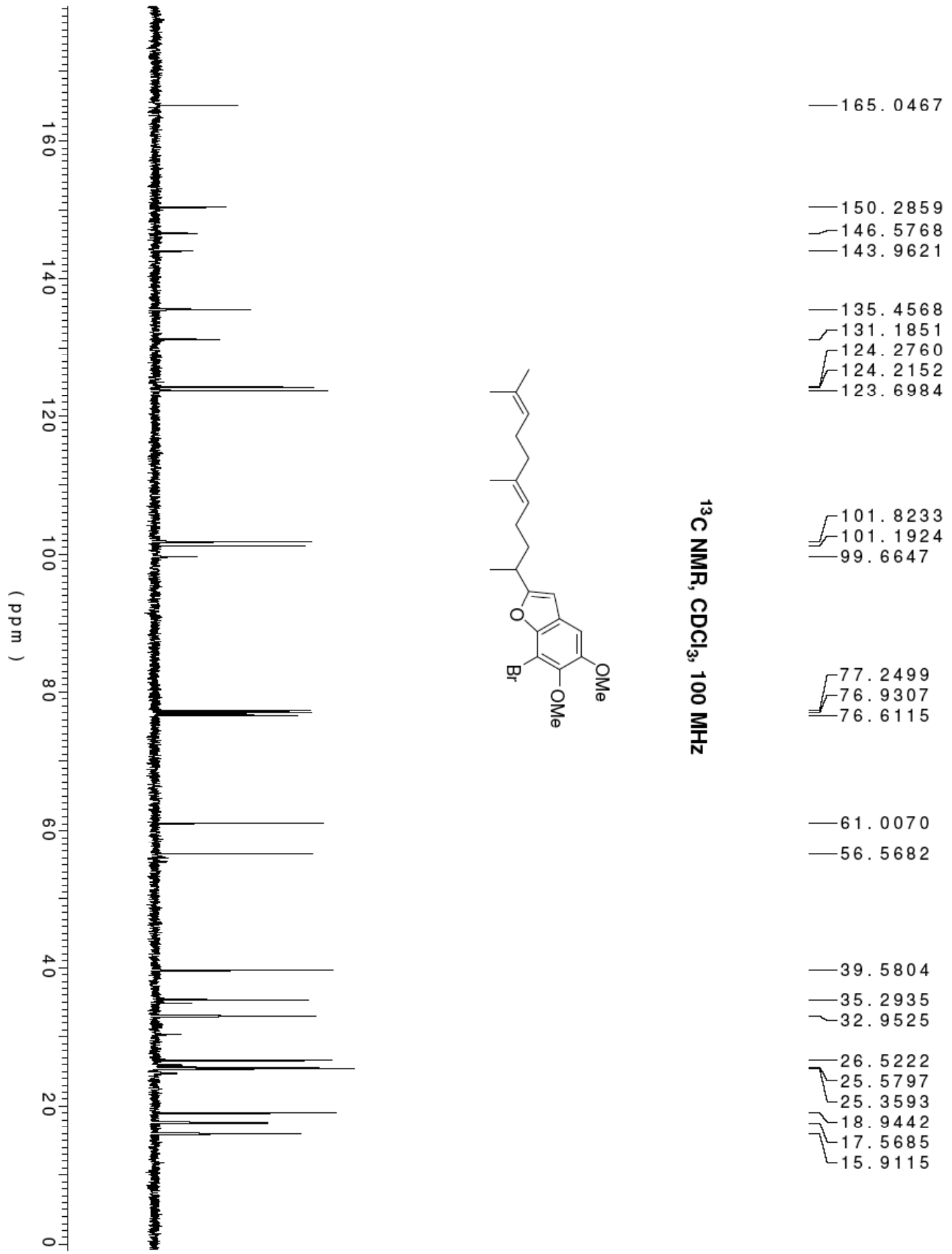
^{31}P NMR, $CDCl_3$, 81 MHz



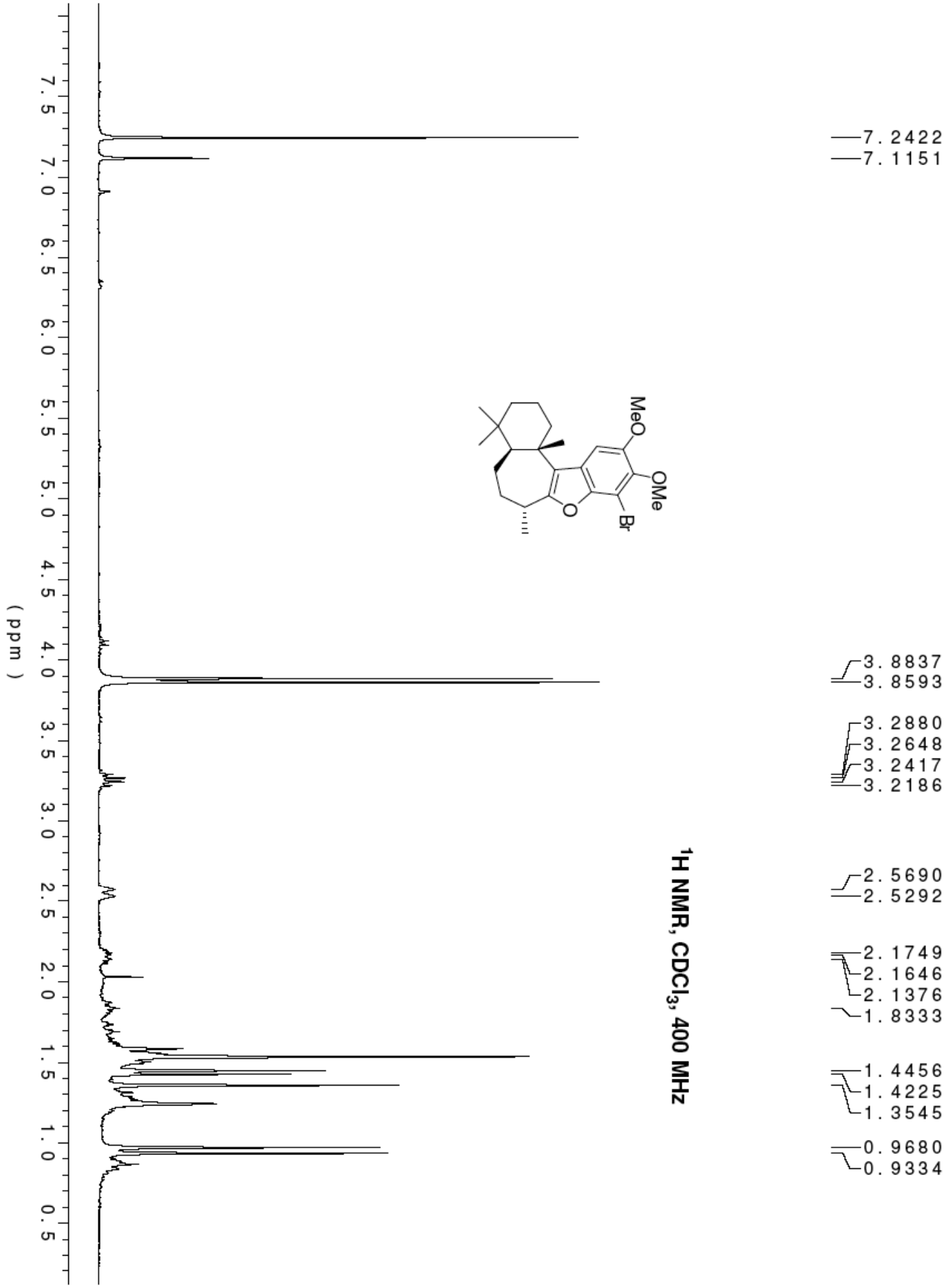




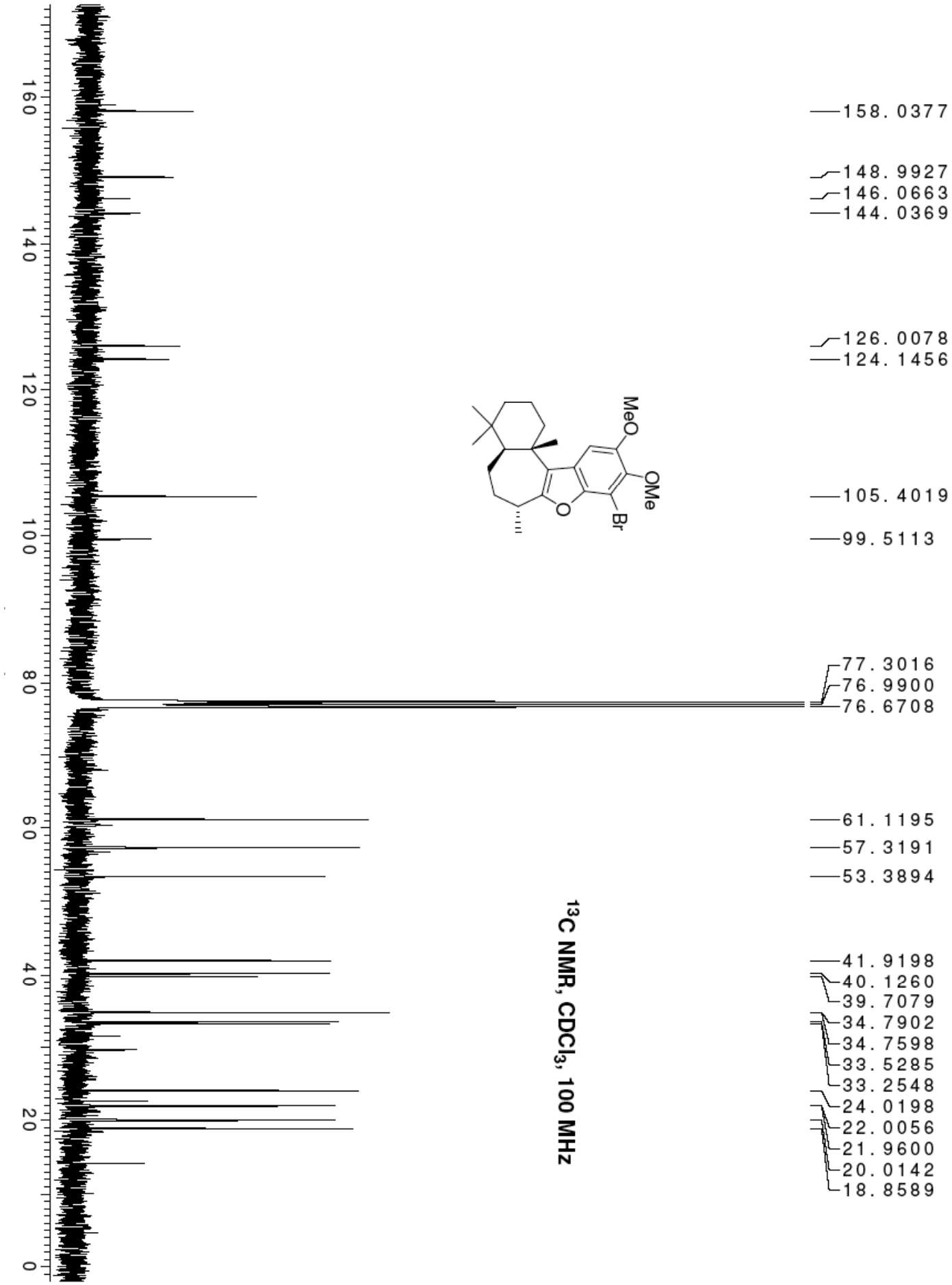
^{1}H NMR, $CDCl_3$, 400 MHz



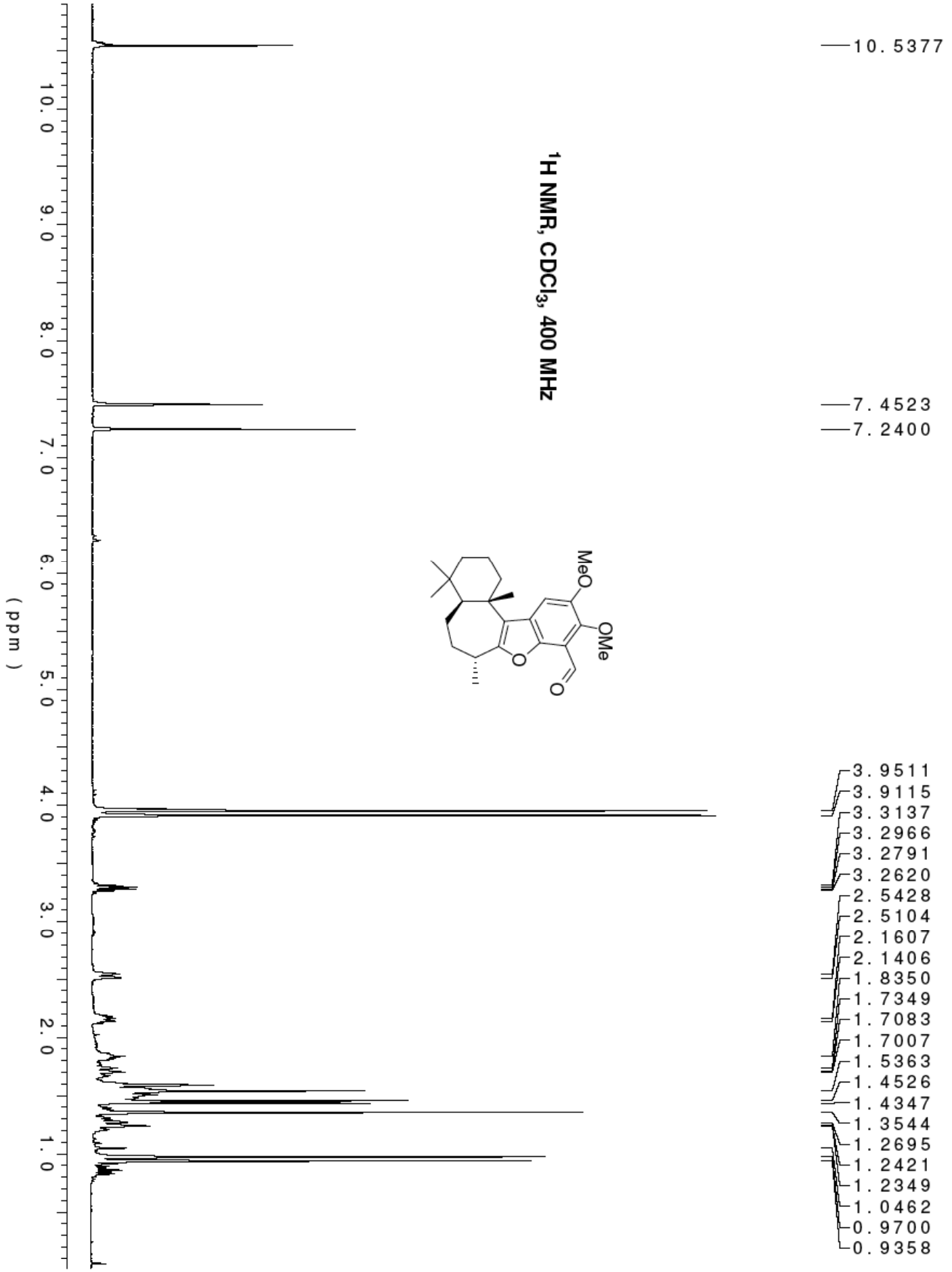
^{13}C NMR, $CDCl_3$, 100 MHz



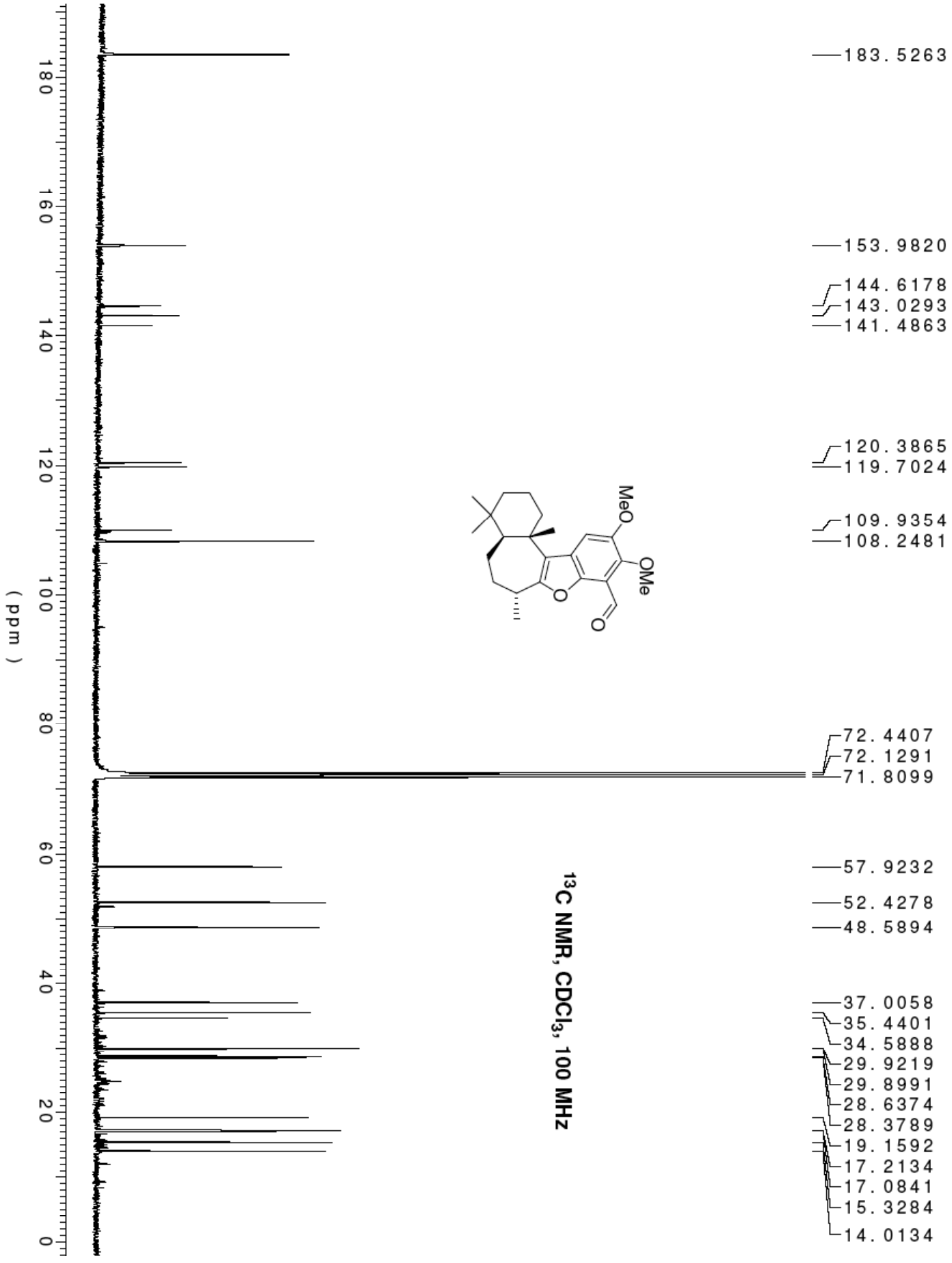
^{1}H NMR, $CDCl_3$, 400 MHz



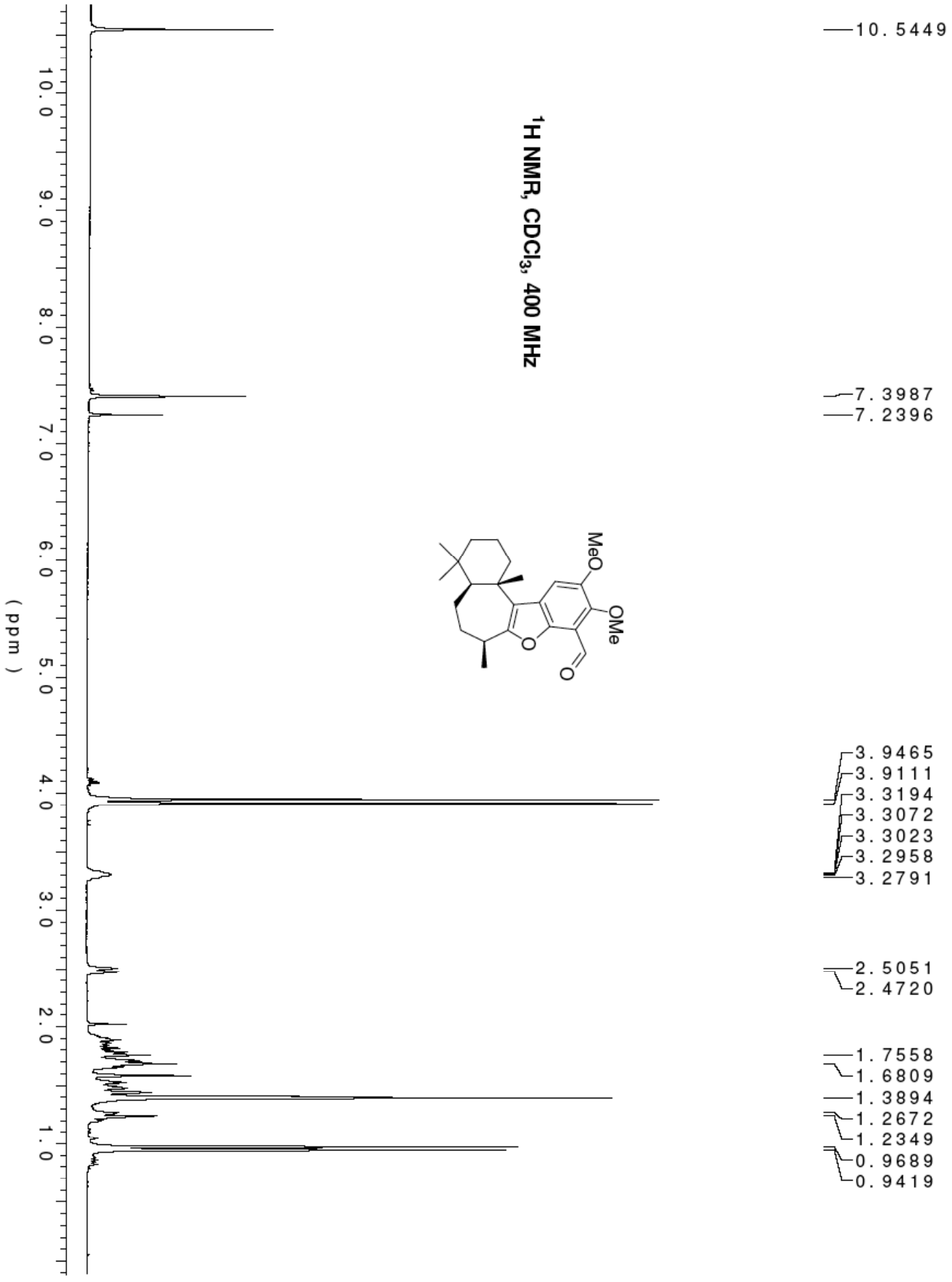
^{13}C NMR, $CDCl_3$, 100 MHz

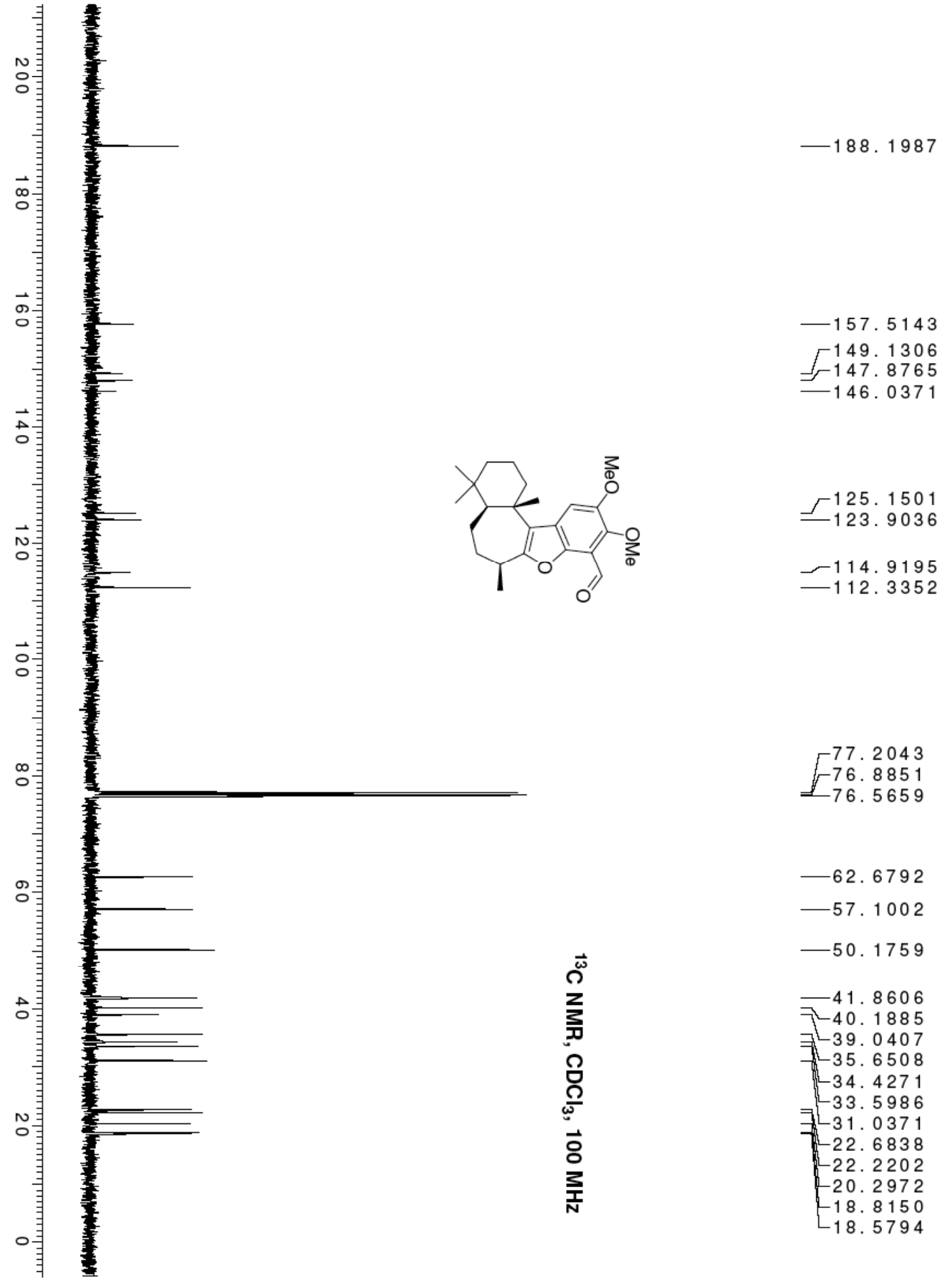


^{1}H NMR, $CDCl_3$, 400 MHz

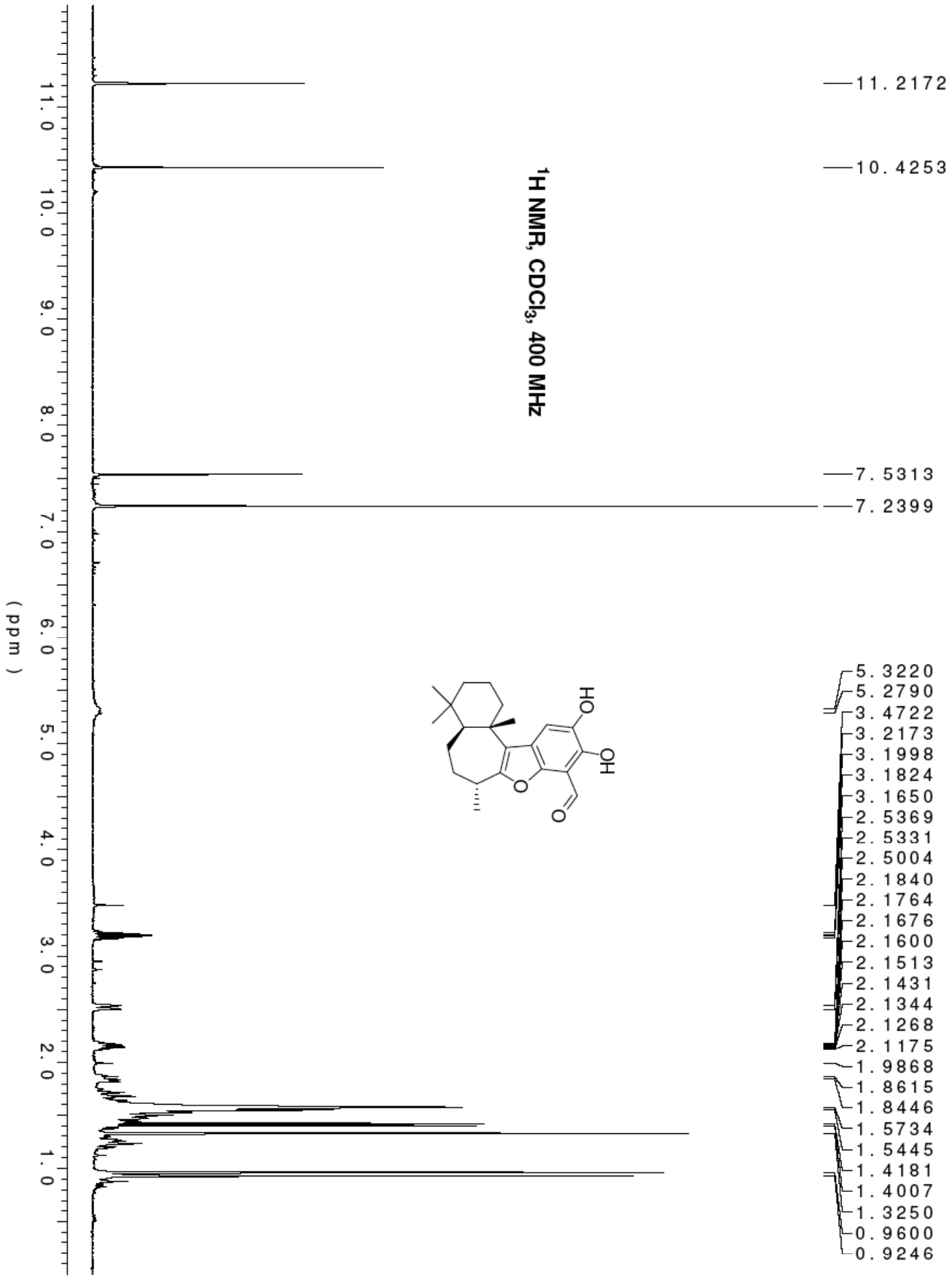


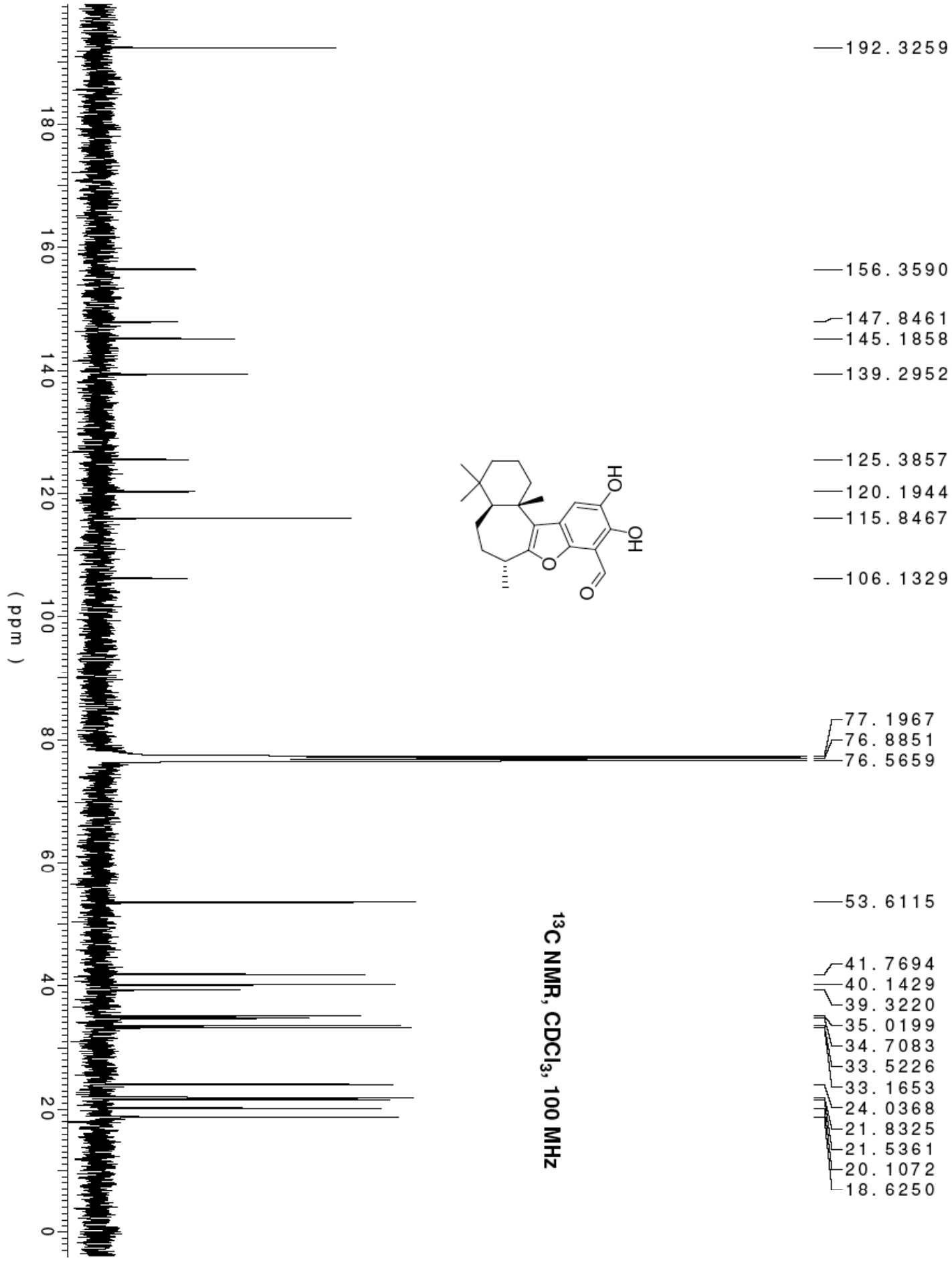
^{13}C NMR, $CDCl_3$, 100 MHz


^{1}H NMR, $CDCl_3$, 400 MHz
MeO
OMe
O
O
10.5449
7.3987
7.2396
3.9465
3.9111
3.3194
3.3072
3.3023
3.2958
3.2791
2.5051
2.4720
1.7558
1.6809
1.3894
1.2672
1.2349
0.9689
0.9419
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

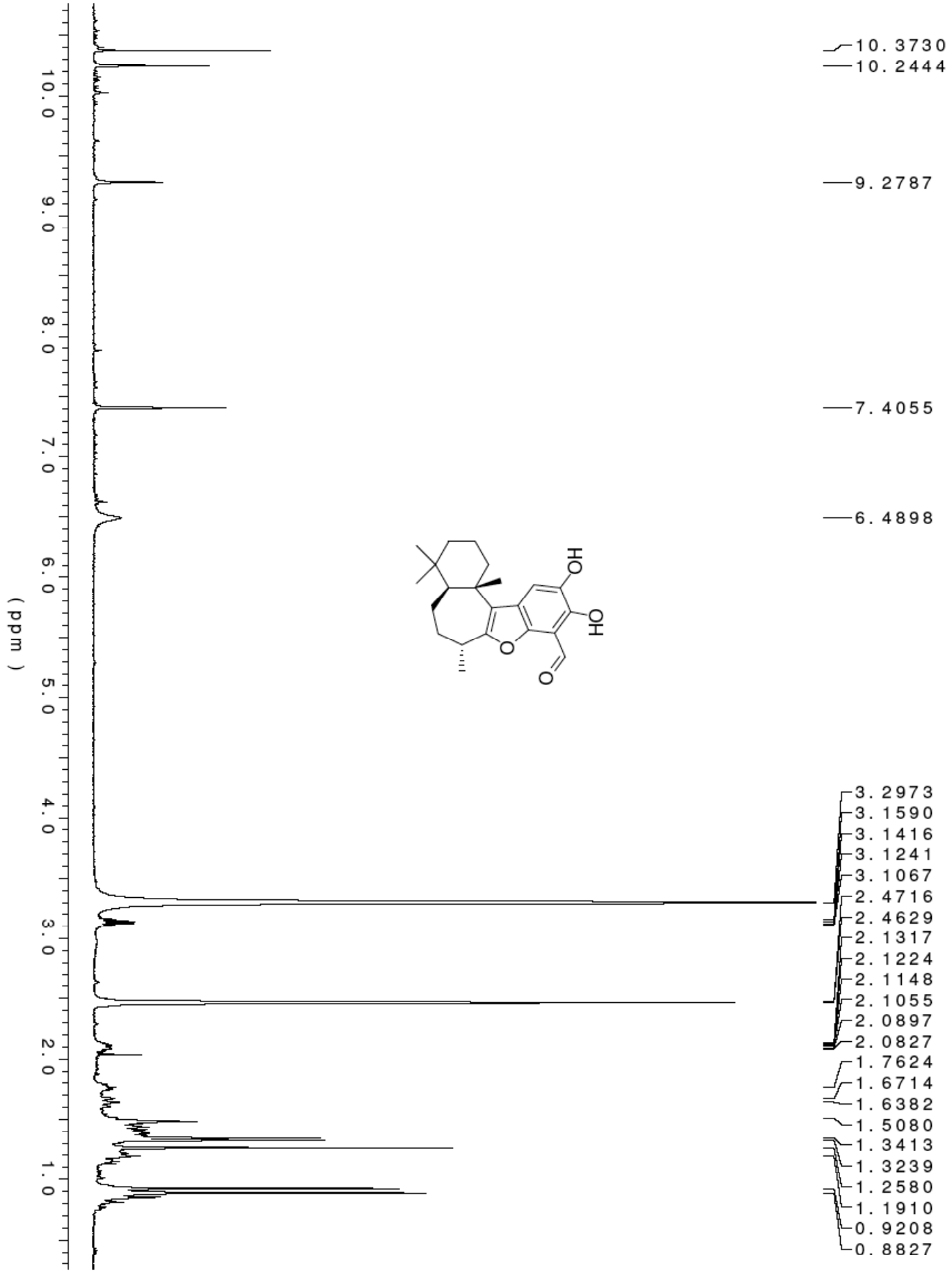


^{13}C NMR, $CDCl_3$, 100 MHz

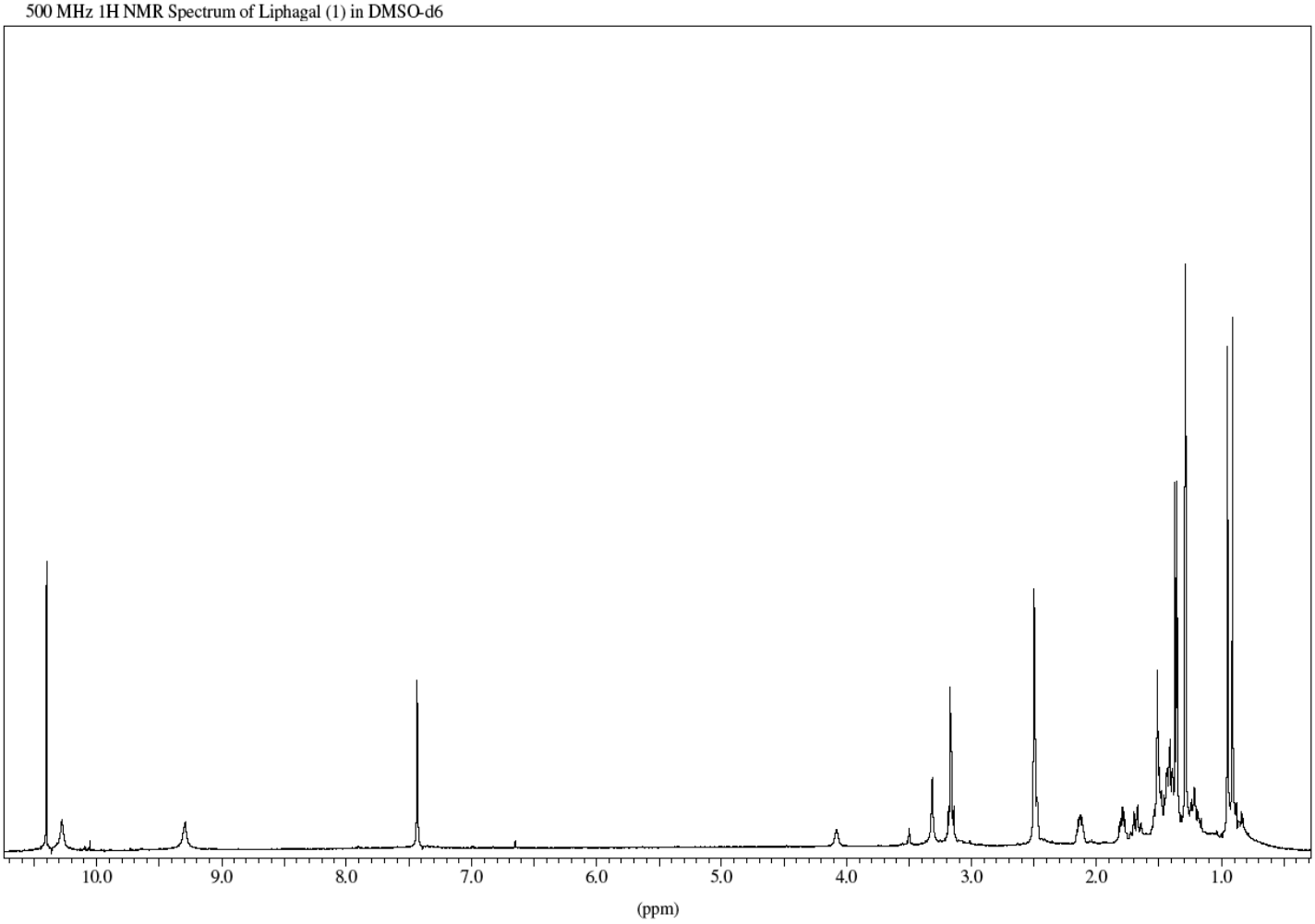

^{1}H NMR, $CDCl_3$, 400 MHz
11.2172
10.4253
7.5313
7.2399
5.3220
5.2790
3.4722
3.2173
3.1998
3.1824
3.1650
2.5369
2.5331
2.5004
2.1840
2.1764
2.1676
2.1600
2.1513
2.1431
2.1344
2.1268
2.1175
1.9868
1.8615
1.8446
1.5734
1.5445
1.4181
1.4007
1.3250
0.9600
0.9246
HO
OH
O
O
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)



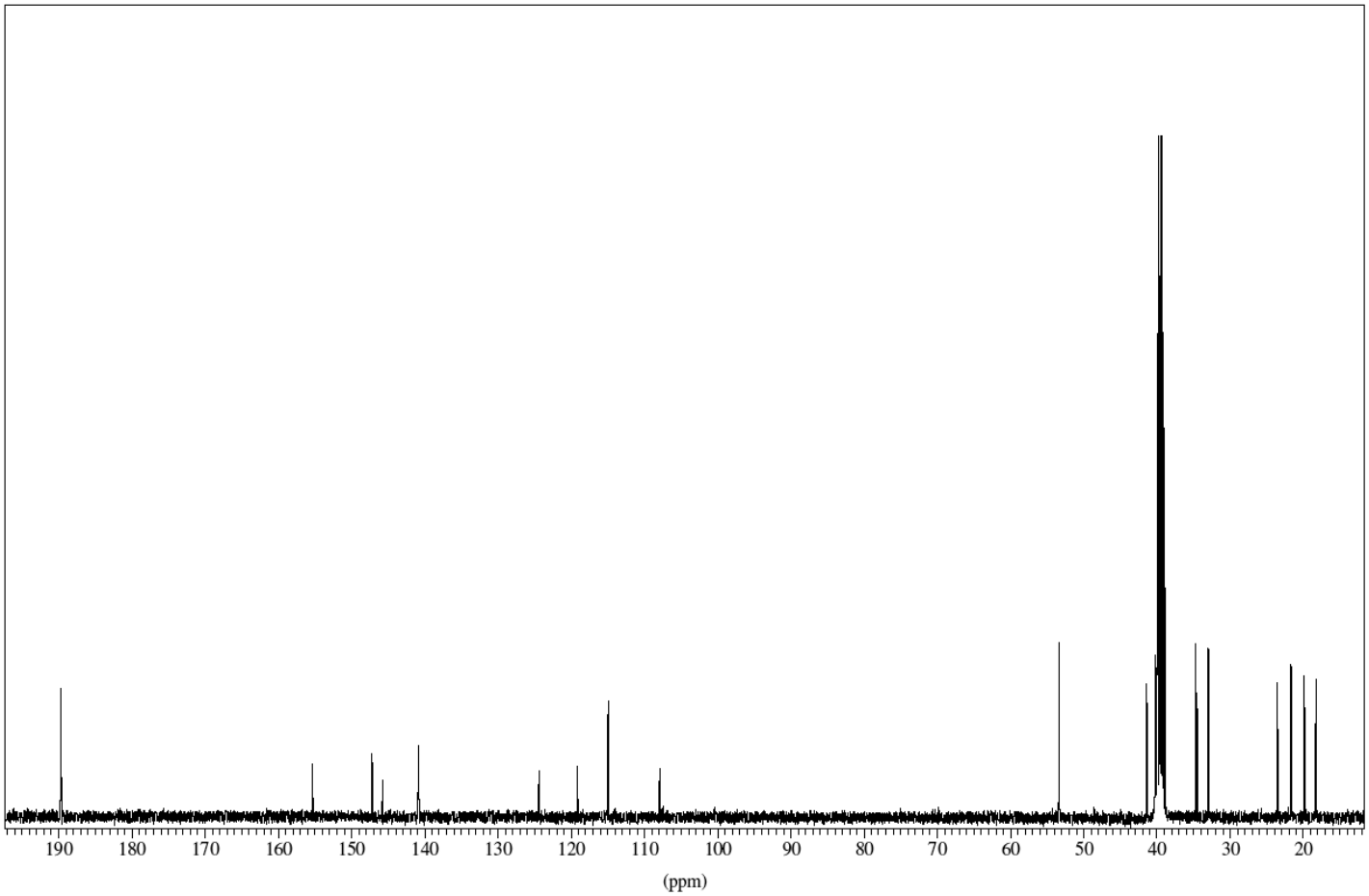
^{13}C NMR, $CDCl_3$, 100 MHz

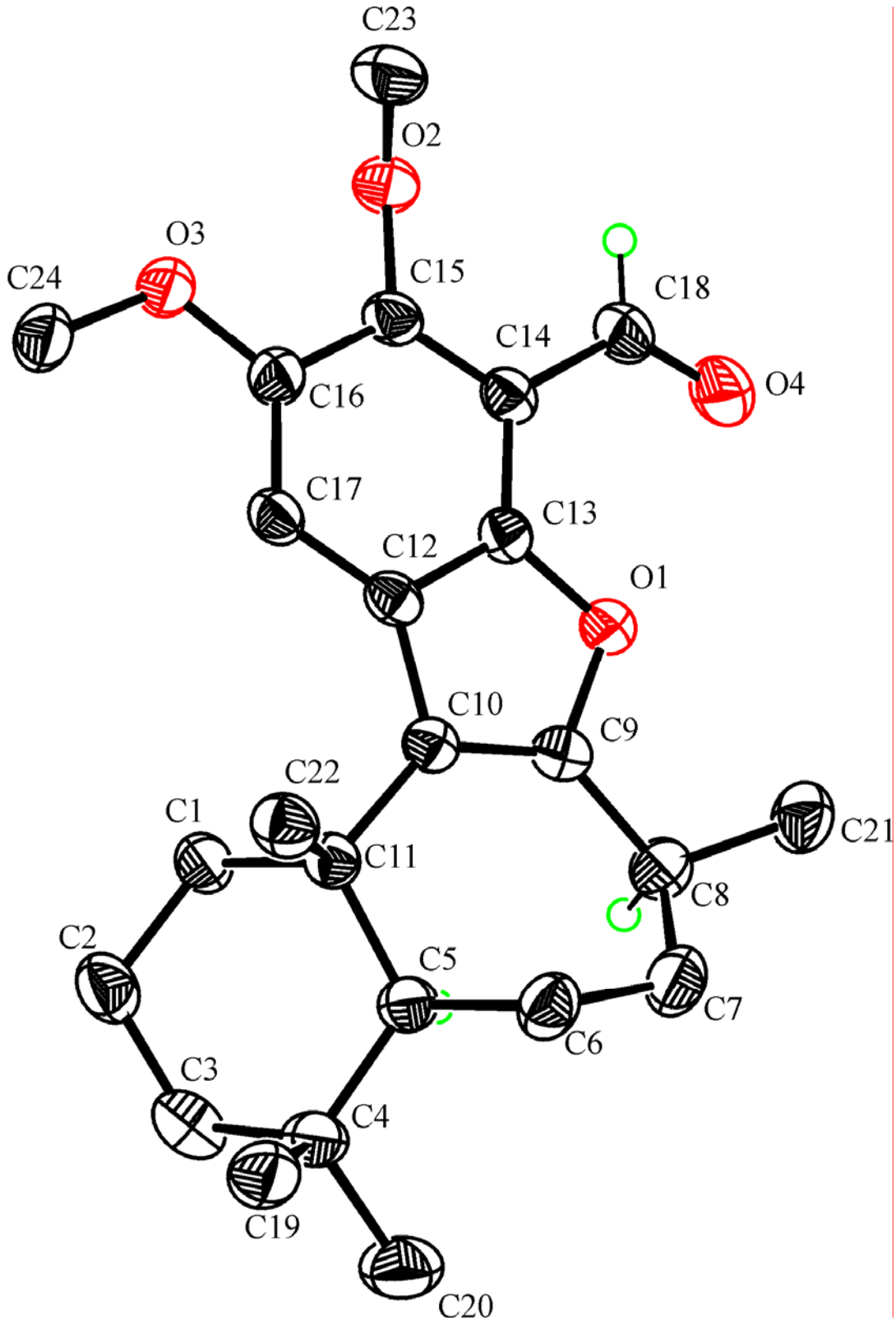

10.3730
10.2444
9.2787
7.4055
6.4898
3.2973
3.1590
3.1416
3.1241
3.1067
2.4716
2.4629
2.1317
2.1224
2.1148
2.1055
2.0897
2.0827
1.7624
1.6714
1.6382
1.5080
1.3413
1.3239
1.2580
1.1910
0.9208
0.8827
OH
HO
O
O
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

500 MHz 1H NMR Spectrum of Liphagal (1) in DMSO-d6



C13 NMR Spectrum of Liphagal in DMSO-d6 at 100 MHz




C23
O2
O3
C24
C15
C18
C14
O4
C16
C17
C13
C12
O1
C10
C9
C22
C1
C11
C21
C8
C2
C5
C7
C6
C3
C4
C19
C20

Experimental

Data Collection

A colourless tablet crystal of $C_{24}H_{32}O_4$ having approximate dimensions of 0.50 x 0.35 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Bruker X8 APEX diffractometer with graphite monochromated Mo-Kα radiation.

The data were collected at a temperature of -100.0 ± 0.1°C to a maximum 2θ value of 55.9°. Data were collected in a series of ϕ and ω scans in 0.50° oscillations with 10.0 second exposures. The crystal-to-detector distance was 38.02 mm.

Data Reduction

Of the 35886 reflections that were collected, 4872 were unique (R_{int} = 0.035); equivalent reflections were merged. Data were collected and integrated using the Bruker SAINT[1] software package. The linear absorption coefficient, μ, for Mo-Kα radiation is 0.84 cm^{-1}. Data were corrected for absorption effects using the multi-scan technique (SADABS[2]), with minimum and maximum transmission coefficients of 0.901 and 0.992, respectively. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[3]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions but not refined. The final cycle of full-matrix least-squares refinement[4] on F^2 was based on 4872 reflections and 259 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.081$$

$$wR2 = [\, \Sigma \, (\, w \, (Fo^2 - Fc^2)^2 \,) / \, \Sigma \, w(Fo^2)^2]^{1/2} = 0.161$$

The standard deviation of an observation of unit weight[5] was 1.08. The weighting scheme was based on counting statistics. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.34 and –0.19 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6]. Anomalous dispersion effects were included in Fcalc[7]; the values for Δf' and Δf'' were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[9]. All refinements were performed using the SHELXTL[10] crystallographic software package of Bruker-AXS.

References

(1) SAINT. Version 7.03A. Bruker AXS Inc., Madison, Wisconsin, USA. (1997-2003).

(2) SADABS. Bruker Nonius area detector scaling and absorption correction - V2.10, Bruker AXS Inc., Madison, Wisconsin, USA (2003).

(3) SIR97 - Altomare A., Burla M.C., Camalli M., Cascarano G.L., Giacovazzo C. , Guagliardi A., Moliterni A.G.G., Polidori G.,Spagna R. (1999) J. Appl. Cryst. 32, 115-119.

(4) Least Squares function minimized:

$\Sigma w(F_o^2-F_c^2)^2$

(5) Standard deviation of an observation of unit weight:

$[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$

where: N_o = number of observations

N_v = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

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