Regioselective Reactions of Highly Substituted Arynes

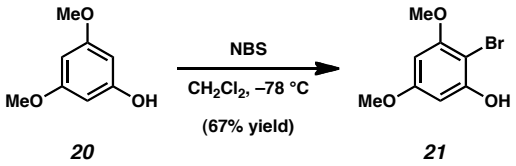
Pamela M. Tadross, Christopher D. Gilmore, Pradeep Bugga, Scott C. Virgil, Brian M. Stoltz*

The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA

Table of Contents

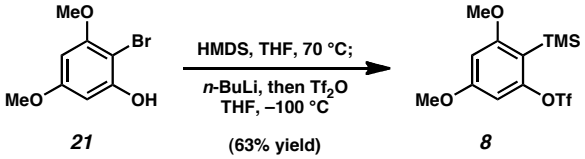
Materials and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. *m*-CPBA (technical grade, 77% purity) was purified to >95% purity by the procedure described by Bortolini, et al.[1] TBSOTf was prepared according to the procedure described by Corey, et al.[2] Dess–Martin periodinane (DMP) was prepared according to the procedure described by Frigerio, et al. and Boeckman, et al.[3] Triflic anhydride was prepared according to the procedure described by Stang, et al.[4] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Varian Mercury 300 at 282 MHz. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). Data for ^{19}F NMR are reported in terms of chemical shift relative to $CFCl_3$ (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

Experimental Procedures



20 *21*

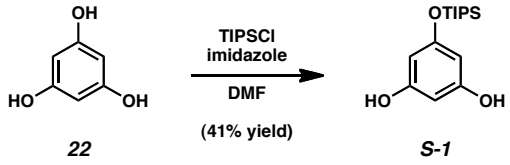
Bromophenol 21. A solution of phenol **20** (100 mg, 0.649 mmol) in CH_2Cl_2 (6.4 mL) was prepared and cooled to –78 °C. *N*-Bromosuccinimide (NBS, 115 mg, 0.649 mmol) was added and the reaction was maintained at –78 °C until phenol **20** was consumed by TLC analysis. The reaction was quenched at –78 °C with 10% aqueous K_2CO_3 solution (2 mL) and warmed to room temperature. The reaction was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield bromophenol **21** (101.9 mg, 67% yield): R_f = 0.28 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (d, J = 2.7 Hz, 1H), 6.12 (d, J = 2.7 Hz, 1H), 5.67 (s, 1H), 3.86 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.69, 156.79, 153.84, 93.21, 92.50, 91.04, 56.27, 55.54; IR (NaCl/film) 3482, 2942, 1592, 1466, 1350, 1312, 1212, 1155, 1099, 1025, 813 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_8H_9O_3{}^{79}Br$ [M]$^+$: 231.9735, found 231.9744.



21 *8*

Silyl aryl triflate 8. Bromophenol **21** (515 mg, 2.21 mmol) and hexamethyldisilazide (922 μL, 4.42 mmol) were combined in THF (5 mL). The solution was heated to 70 °C and maintained for 5 h. The reaction was cooled to room temperature and concentrated under vacuum. The resulting oil was immediately taken on to the next step.

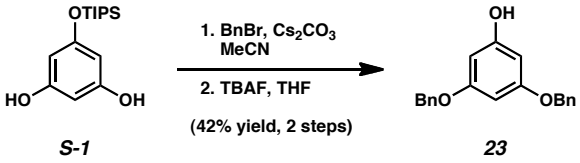
The crude residue was taken up in THF (15 mL) and cooled to –100 °C. *n*-Butyllithium (2.17 M in hexanes, 1.12 mL, 2.43 mmol) was added slowly and the reaction was allowed to warm to –82 °C. The reaction was cooled again to –100 °C and maintained between –100 °C and –82 °C for 30 minutes. After this period, triflic anhydride (446 μL, 2.65 mmol) was added at –100 °C. The reaction was warmed to –80 °C, quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL), and subsequently warmed to room temperature. The reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (25:1 petroleum ether:diethyl ether eluent) to yield silyl aryl triflate **8** (493 mg, 63% yield): R_f = 0.34 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (d, *J* = 2.0 Hz, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 0.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.36, 162.69, 155.52, 118.82 (q, *J* = 320.9 Hz), 112.29, 98.32, 98.31, 98.29, 98.28, 97.56, 55.77, 55.69, 1.08; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.07; IR (NaCl/film) 2960, 1609, 1565, 1460, 1407, 1311, 1245, 1213, 1141, 1094, 1053, 961, 846 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{17}O_5F_3SSi$ $[M+H]^+$: 358.0518, found 358.0511.



22 ***S-1***

Silylphenol S-1. Phloroglucinol (**22**, 500 mg, 3.96 mmol) and imidazole (90 mg, 1.32 mmol) were combined in DMF (16 mL). Chlorotriisopropylsilane (TIPSCl, 283 μL, 1.32 mmol) was added and the resulting solution was maintained at room temperature for 36 hours. After this period, the reaction was diluted with diethyl ether (25 mL). The organic layer was washed with water (25 mL) and brine (25 mL), dried with $MgSO_4$, concentrated under vacuum and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield **S-1** (154.1 mg, 41% yield) as a clear oil: R_f = 0.20 (3:1

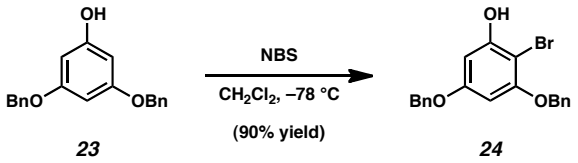
hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (d, J = 2.2 Hz, 2H), 5.97 (t, J = 2.1 Hz, 1H), 5.07 (s, 2H), 1.30–1.18 (m, 3H), 1.09 (d, J = 7.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.08, 157.02, 100.38, 96.18, 17.89, 12.60; IR (NaCl/film) 3391, 2945, 2868, 1624, 1602, 1493, 1145, 1018, 881, 837, 818, 783, 689, 662 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{15}H_{27}O_3Si$ $[M+H]^+$: 283.1724, found 283.1723.



Phenol 23. Silylphenol **S-1** (135 mg, 0.478 mmol) and Cs_2CO_3 (343 mg, 1.05 mmol) were combined in acetonitrile (5 mL). Benzyl bromide (119 μL, 1.00 mmol) was added and the resulting suspension was maintained at room temperature with stirring until silylphenol **S-1** was fully consumed by TLC analysis. Upon completion, the reaction was diluted with diethyl ether (25 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and immediately carried on to the next step.

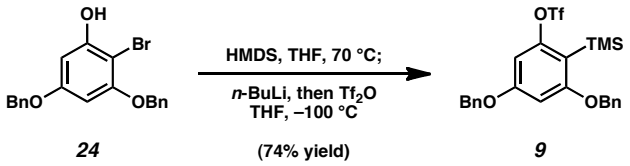
The crude residue was taken up in THF (5 mL). Tetra-*n*-butylammonium fluoride solution (1 M in THF, 717 μL) was added and the solution was maintained at room temperature until the starting material had been fully consumed by TLC analysis. Upon completion, the reaction was diluted with diethyl ether (25 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield phenol **23** (62 mg, 42% yield over two steps): R_f = 0.26 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.32 (m, 10H), 6.29 (t, J = 2.1 Hz, 1H), 6.13 (d, J = 2.1 Hz, 2H), 5.17 (s, 1H), 5.00 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.79, 157.27, 136.74, 128.62, 128.06, 127.57, 95.48, 95.03, 70.14; IR (NaCl/film) 3391, 3032, 2931, 1600, 1498, 1453, 1377, 1214,

1152, 1053, 820, 735, 697 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{19}O_3$ $[M+H]^+$: 307.1329, found 307.1327.



23 *24*

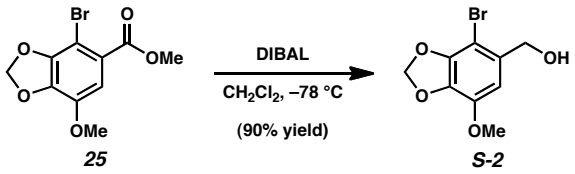
Bromophenol 24. A solution of phenol **23** (20 mg, 0.065 mmol) in CH_2Cl_2 (1.3 mL) was prepared and cooled to –78 °C. *N*-Bromosuccinimide (NBS, 11.6 mg, 0.0653 mmol) was added and the reaction was maintained at –78 °C until phenol **23** was consumed by TLC analysis. The reaction was quenched at –78 °C by the addition of 10% aqueous K_2CO_3 solution (500 μL) and warmed to room temperature. The reaction was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield bromophenol **24** (22.6 mg, 90% yield): R_f 0.33 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.46 (m, 2H), 7.46–7.39 (m, 6H), 7.39–7.33 (m, 2H), 6.39 (d, *J* = 2.7 Hz, 1H), 6.28 (d, *J* = 2.7 Hz, 1H), 5.71 (s, 1H), 5.11 (s, 2H), 5.02 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.74, 155.94, 153.91, 136.44, 136.33, 128.67, 128.61, 128.17, 128.01, 127.57, 127.04, 94.75, 94.63, 92.06, 70.80, 70.35; IR (NaCl/film) 3491, 1594, 1453, 1189, 1160, 1093, 1023, 810, 736, 696 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{16}O_3{}^{79}Br$ $[M–H]^-$: 383.0288, found 383.0300; *m/z* calc'd for $C_{20}H_{16}O_3{}^{81}Br$ $[M–H]^-$: 385.0270, found 385.0281.



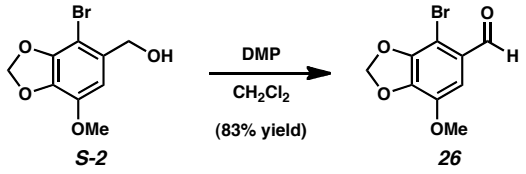
24 (74% yield) *9*

Silyl aryl triflate 9. Bromophenol **24** (310 mg, 0.805 mmol) and hexamethyldisilazide (361 μL, 1.77 mmol) were combined in THF (3.2 mL). The solution was heated to 70 °C and maintained for 5 h. The reaction was cooled to room temperature and concentrated under vacuum. The resulting oil was immediately taken on to the next step.

The crude residue was taken up in THF (11 mL) and cooled to –100 °C. *n*-Butyllithium (2.5 M in hexanes, 381 μL, 0.952 mmol) was added slowly and the reaction was allowed to warm to –82 °C. The reaction was cooled again to –100 °C and maintained between –100 °C and –82 °C for 30 minutes. After this period, triflic anhydride (175 μL, 1.04 mmol) was added at –100 °C. The reaction was warmed to –80 °C, quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL), and subsequently warmed to room temperature. The reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50:1 petroleum ether:diethyl ether eluent) to yield silyl aryl triflate **9** (328 mg, 74% yield): R_f = 0.55 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.33 (m, 10H), 6.59 (d, J = 2.0 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 0.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.40, 161.69, 155.47, 136.10, 136.07, 128.93, 128.85, 128.57, 128.46, 128.00, 127.80, 118.8 (q, J = 320.9 Hz), 112.76, 99.48, 99.30, 71.05, 70.67, 1.19; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.04; IR (NaCl/film) 2954, 1604, 1562, 1417, 1214, 1140, 1089, 1026, 952, 844, 736, 697 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{24}H_{24}F_3O_5SSi$ $[M–H]^-$: 509.1071, found 509.1062.

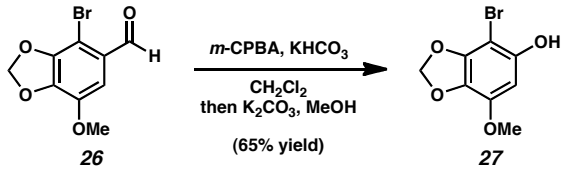


Benzyl alcohol S-2. A solution of methyl ester **25** (3.0 g, 10.4 mmol) in CH_2Cl_2 (100 mL) was prepared and cooled to –78 °C. Diisobutylaluminum hydride (DIBAL, 4.1 mL, 22.8 mmol) was added dropwise and the reaction was maintained at –78 °C until methyl ester **25** was consumed by TLC analysis. The reaction was quenched at –78 °C by the addition of saturated aqueous sodium potassium tartrate solution (25 mL) and then warmed to room temperature. The reaction was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield benzylic alcohol **S-2** (2.6 g, 96% yield): $R_f = 0.33$ (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.05 (s, 2H), 4.66 (d, J = 5.8 Hz, 2H), 3.90 (s, 3H), 1.99 (t, J = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.00, 142.90, 135.00, 133.49, 108.42, 101.94, 93.34, 64.47, 56.75; IR (NaCl/film) 3187, 2904, 1628, 1486, 1465, 1446, 1343, 1165, 1106, 1038, 968, 931, 824, 701 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_8O_3{}^{79}Br$ $[M–OH]^+$: 242.9651, found 242.9648; *m/z* calc'd for $C_9H_8O_3{}^{81}Br$ $[M–OH]^+$: 244.9632, found 244.9629.



Aldehyde 26. A solution of Dess–Martin periodinane (2.94 g, 6.92 mmol) in CH_2Cl_2 (28 mL) was prepared under nitrogen. Alcohol **S-2** (1.63 g, 6.24 mmol) in CH_2Cl_2 (72 mL) was added and the reaction was maintained under nitrogen until alcohol **S-2** was fully consumed by TLC analysis. The reaction was quenched by the addition of a 1:1 v/v solution of saturated aqueous $NaHCO_3$ and saturated

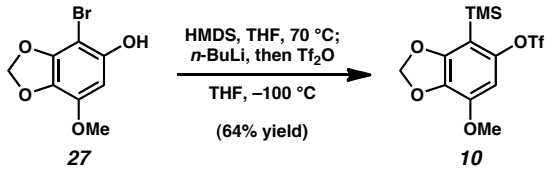
aqueous $Na_2S_2O_3$ (60 mL total volume). The reaction was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL) and subsequently dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (hexanes → 7:3 hexanes:ethyl acetate eluent) to yield aldehyde **26** (1.34 g, 83% yield): R_f = 0.37 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.24 (s, 1H), 6.16 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 147.4, 143.5, 140.9, 127.6, 109.5, 103.0, 98.8, 56.8; IR (NaCl/film) 1683, 1619, 1485, 1446, 1351, 1315, 1169, 1112, 1048, 993, 928, 654 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_8O_4{}^{79}Br$ $[M+H]^+$: 258.96, found 258.9597; *m/z* calc'd for $C_9H_8O_4{}^{81}Br$ $[M+H]^+$: 260.9581, found 260.9578.



Bromophenol 27. A flask was charged with aldehyde **26** (100 mg, 0.386 mmol) and $KHCO_3$ (4 mg, 0.04 mmol) under a nitrogen atmosphere. To this was added *m*-CPBA (20 mg, 0.116 mmol) as a solution in CH_2Cl_2 (4 mL). Four additional portions of *m*-CPBA (20 mg, 0.116 mmol, each) were added as CH_2Cl_2 solutions (0.25 mL, each) at three-hour intervals. Nine hours following the final *m*-CPBA addition, the reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution (1 mL) and diluted with CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was further washed with CH_2Cl_2 (10 mL). The combined organic layers were sequentially washed with water (10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), and brine (10 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under vacuum to yield a crystalline solid.

The crude solid (103 mg) was taken up in a 10% (w/v) solution of K_2CO_3 in methanol (7.5 mL). The resultant suspension was maintained with stirring at room temperature until the starting material had

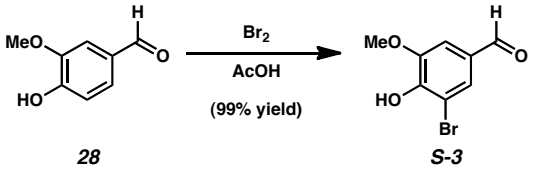
been completely consumed by TLC analysis. Following this period, the reaction was concentrated under vacuum, diluted with water (10 mL), and acidified to pH 1.5 with 6 N HCl. **Warning:** vigorous gas evolution. The aqueous solution was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield bromophenol **27** (62 mg, 65% yield) as a white solid: R_f = 0.20 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.99 (s, 2H), 5.18 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.42, 147.02, 143.93, 130.01, 102.37, 95.12, 83.45, 57.12, 57.10.; IR (NaCl/film) 3093, 2899, 1642, 1454, 1350, 1167, 1109, 1051, 971, 935, 874, 797, 700 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_8H_7O_4{}^{79}Br$ $[M]^+$: 245.9522, found 245.9525; *m/z* calc'd for $C_8H_7O_4{}^{81}Br$ $[M]^+$: 247.9502, found 247.9506.



Silyl aryl triflate 10. Bromophenol **27** (149.6 mg, 0.606 mmol) and hexamethyldisilazide (253 μL, 1.21 mmol) were combined in THF (1.2 mL). The solution was heated to 70 °C and maintained for 8 h. The reaction was cooled to room temperature and concentrated under vacuum. The resulting oil was immediately taken on to the next step.

The crude residue was taken up in THF (8 mL) and cooled to –100 °C. *n*-Butyllithium (2.5 M in hexanes, 266 μL, 0.666 mmol) was added slowly and the reaction was allowed to warm to –82 °C. The reaction was cooled again to –100 °C and maintained between –100 °C and –82 °C for 30 minutes. After this period, triflic anhydride (122 μL, 0.727 mmol) was added at –100 °C. The reaction was warmed to –80 °C, quenched by the addition of saturated aqueous sodium bicarbonate solution (4 mL),

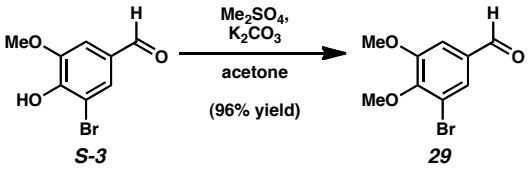
and subsequently warmed to room temperature. The reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50:1 petroleum ether:diethyl ether eluent) to yield silyl aryl triflate **10** (144.6 mg, 64% yield): R_f = 0.36 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1H), 5.99 (s, 2H), 3.89 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.99, 148.40, 144.10, 133.88, 118.76 (q, J = 300.56 Hz), 107.02, 101.78, 101.32, 57.02, 0.23; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.07; IR (NaCl/film) 2058, 2901, 1645, 1487, 1419, 1388, 1294, 1244, 1211, 1140, 1111, 1046, 984, 893, 845, 802 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{15}O_6SiSF_3$ $[M+H]^+$: 372.0311, found 372.0321.



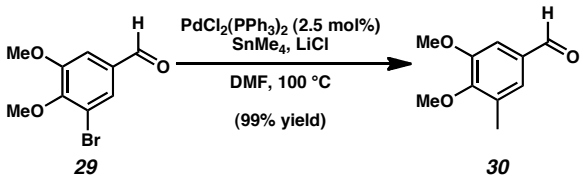
28 ***S-3***

3-Bromovanillin (S-3). The following procedure was adopted from a literature report by Rao and Stuber.[5] A single-neck, 2 L round-bottom flask was charged with vanillin (**28**, 50 g, 328.6 mmol). Glacial acetic acid was added (1.1 L, 3.0 M). Following this, a mechanical stirrer was affixed to the flask through the neck and, with vigorous but even stirring, the vanillin dissolved to form a pale yellow solution. At this point, neat bromine (16.84 mL, 361.5 mmol) was added in a rapid dropwise fashion to the stirring solution through the flask neck to produce a deep red-orange solution. Following addition, the reaction was maintained with vigorous stirring for 90 minutes, after which time TLC analysis indicated formation of the product (R_f = 0.32, 15% ethyl acetate in hexanes). The reaction also results in the formation of a bright orange-yellow precipitate when nearing completion. Upon completion of the reaction, the mechanical stirrer was disengaged and the contents of the reaction flask were poured onto chilled deionized water (0 °C, 600 mL), resulting in further precipitation of a pale yellow solid from the

bright orange aqueous layer. The reaction flask was washed into this flask with more chilled water. While still cooled, the contents of the 1 L Erlenmeyer flask were filtered over a glass frit to separate the desired solid product. The isolated solid product (**S-3**, 75.25 g, 99% yield) was transferred to a flask and dried under vacuum for a period of 8 hours.

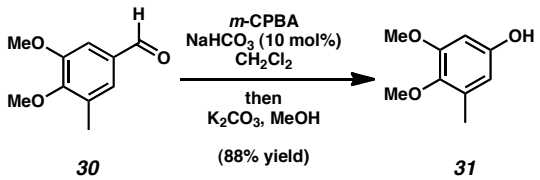


3-bromo-4,5-dimethoxy benzaldehyde (29). To a 1 L round-bottom flask was added anhydrous K_2CO_3 (113.56 g, 821.6 mmol), followed by a solution of bromobenzaldehyde **S-3** (75.25 g, 325.66 mmol) in reagent grade acetone (700 mL). A mechanical stirrer was affixed to the reaction flask, and vigorous stirring was required to generate an evenly distributed, maroon suspension. To this stirring mixture was added Me_2SO_4 (77.74 mL, 821.69 mmol) over 1 minute via funnel. The reaction was left to stir vigorously at 25 °C for 8 hours, at which point TLC analysis confirmed the conversion of phenol **S-3** to a less polar product. The reaction contents were then vacuum filtered over a glass frit to separate residual solid K_2CO_3. The filtered solid was washed with acetone (2 x 100 mL) and methanol (100 mL). The organic filtrate was concentrated to an orange oil and purified by flash chromatography (5% → 50% ethyl acetate in hexanes eluent) to yield bromobenzaldehyde **29** (76.6 g, 96% yield), which was isolated as a white powder: $R_f = 0.56$ (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.67 (d, J = 1.80 Hz, 1H), 7.40 (d, J = 1.85 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.83, 154.17, 151.81, 133.03, 128.77, 117.92, 110.09, 60.83, 56.25; IR (NaCl/film) 2945, 2860, 1692, 1588, 1566, 1486, 1469, 1452, 1420, 1393, 1380, 1312, 1281, 1240, 1212, 1144, 1133, 1048, 993, 855, 840 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_9BrO_3$ $[M]^+$: 243.9735, found 243.9731.



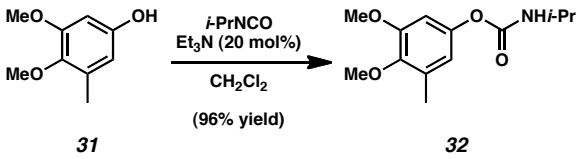
29 ***30***

3,4-dimethoxy-5-methylbenzaldehyde (30). A 250 mL round-bottom flask was charged with lithium chloride (4.32 g, 102.00 mmol) and then flame dried. To this flask was added a solution of benzaldehyde **29** (5.0 g, 20.40 mmol) in *N*,*N*-dimethylformamide (200 mL) that had been rigorously sparged with argon. Next, $PdCl_2(PPh_3)_2$ (0.358 g, 0.51 mmol) was added to the stirring mixture, producing a bright yellow-orange solution that was stirred vigorously. A reflux condenser was affixed to the top of the reaction flask before adding, dropwise, neat tetramethyltin (7.06 mL, 51.0 mmol). The reaction vessel was sealed under an argon atmosphere and heated to reflux in 100 °C oil bath. The reaction was maintained at reflux for 3 hours; during this period the color of the solution changed to dark red-orange.[6] TLC analysis of the reaction after this period showed full consumption of the starting material. The reaction was cooled to room temperature and then quenched by the addition of H_2O (200 mL). The aqueous layer was thoroughly extracted with ethyl acetate (5 x 200 mL), and the combined organic layers were washed with brine (150 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to furnish benzaldehyde **30** as a colorless oil (3.63 g, 99% yield): R_f = 0.42 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.17 (d, J = 1.71 Hz, 1H), 7.16 (d, J = 0.60 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.14, 153.02, 152.70, 126.95, 108.79, 60.05, 55.65, 15.75; IR (NaCl/film) 2939, 2833, 1693, 1586, 1491, 1465, 1422, 1387, 1329, 1299, 1233, 1140, 1096, 1003, 856 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calc'd for $C_{10}H_{12}O_3$ $[M]^+$: 180.0786, found 180.0779.



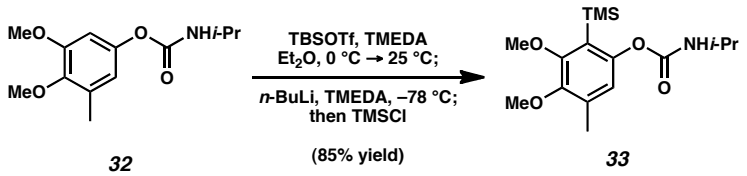
3,4-dimethoxy-5-methylphenol (31). A 250 mL round-bottom flask was charged with anhydrous $NaHCO_3$ (0.467 g, 0.56 mmol). To this, was added a solution of benzaldehyde **30** (1.00 g, 5.55 mmol) in CH_2Cl_2 (11 mL). This mixture was vigorously stirred until the $NaHCO_3$ fully dissolved. At this point, *m*-CPBA (1.92 g, 11.10 mmol) was added as a solid in a single portion to the pale yellow solution. Immediately, the solution turned bright yellow, and was maintained with stirring at 25 °C under an atmosphere of N_2. Notable accumulation of precipitate resulted in increasing turbidity of the solution, and after 6 hours, TLC analysis indicated formation of a new product (R_f = 0.22, hexanes) and consumption of benzaldehyde **30**. At this time, methanol (110 mL) and anhydrous K_2CO_3 (2.30 g, 16.65 mmol) were added, and the solution turned maroon in color. The reaction was maintained at 25 °C for 12 hours, resulting in formation of a new polar product. The reaction was stopped by concentration under vacuum to yield a dark maroon solid. This solid was dissolved in H_2O (100 mL), and then neutralized with concentrated aqueous HCl (6 mL). **Warning:** vigorous gas evolution. The resulting suspension was extracted with CH_2Cl_2 (5 x 100 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 200 mL) to remove benzoate byproducts. The organic layers were dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (30% ethyl acetate in hexanes eluent) to provide phenol **31** (0.822 g, 4.89 mmol, 88% yield) as a white solid: R_f = 0.30 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, J = 2.80 Hz, 1H), 6.20 (d, J = 2.80 Hz, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.36, 151.78, 141.12, 132.41, 108.36, 98.17, 60.35, 55.69, 15.85; IR (NaCl/film) 3272, 2957, 1614,

1483, 1463, 1440, 1430, 1348, 1268, 1226, 1219, 1196, 1181, 1154, 1096, 1001, 854, 772, 737 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_{12}O_3$ $[M]^+$: 168.0786, found 168.0753.



31 ***32***

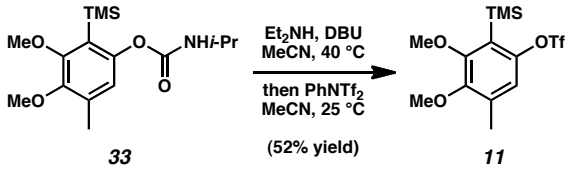
Isopropyl carbamate 32. This procedure was adopted from the literature procedure reported by Bronner, et al.[7] A 100 mL round-bottom flask was charged with a solution of phenol **31** (1.696 g, 10.08 mmol) in CH_2Cl_2 (35 mL). The solution was stirred at 25 °C under an atmosphere of N_2 before neat isopropyl isocyanate (1.483 mL, 15.12 mmol) was added via syringe. The solution turned orange, and after 5 minutes of stirring, freshly distilled Et_3N (0.281 mL, 2.02 mmol) was added via syringe to effect the formation of a dark purple solution. The reaction was maintained with stirring for 18 hours at 25 °C. Following this period, TLC analysis showed conversion of phenol **31** to a single product. The reaction was concentrated to an orange-brown residue and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to provide isopropyl carbamate **32** as a clear, pale yellow oil (2.404 g, 94% yield): R_f = 0.48 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, J = 2.65 Hz, 1H), 6.54 (d, J = 2.65 Hz, 1H), 2.79 (s, 1H), 3.87 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.24 (s, 3H), 1.23 (d, J = 7.25 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.92, 152.87, 146.66, 144.62, 115.29, 104.21, 60.15, 55.78, 43.44, 22.93, 15.91; IR (NaCl/film) 3326, 2972, 2936, 1715, 1604, 1529, 1490, 1466, 1422, 1332, 1220, 1190, 1175, 1142, 1095, 1050, 1009, 936, 854, 773 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{19}NO_4$ $[M]^+$: 253.1314, found 253.1319.



32 ***33***

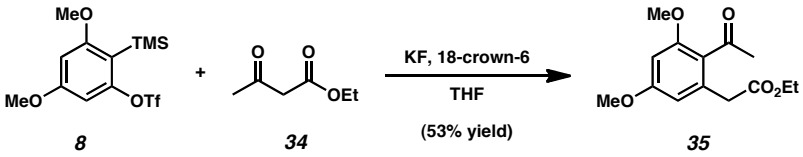
TMS carbamate 33. This procedure was adopted from the literature procedure reported by Bronner, et al.[7] To a 25 mL round-bottom flask was added a solution of isopropyl carbamate **32** (2.404 g, 9.49 mmol) in diethyl ether (94 mL), followed by freshly distilled TMEDA (1.56 mL, 10.44 mmol) via syringe. The solution was cooled to 0 °C in an ice water bath. Upon temperature equilibration (15 minutes), neat distilled TBSOTf (2.398 mL, 10.44 mmol) was added. The resulting solution was maintained for 10 minutes at 0 °C and then flask was allowed to warm to 23 °C over 30 minutes. At this point, TLC analysis showed formation of a less polar product (R_f = 0.81, 15% ethyl acetate in hexanes) corresponding to the *N*-silylated intermediate. Additional TMEDA was added to the mixture via syringe (5.688 mL, 37.964 mmol). The reaction was then cooled to –78 °C in a dry ice and acetone bath with vigorous stirring to avoid aggregation of triflate salts. Next, *n*-BuLi solution (2.32 M in hexanes, 16.36 mL, 37.96 mmol) was added dropwise down the side of the flask of the cold solution. The solution was maintained with stirring at –78 °C for 4 hours, after which time freshly distilled TMSCl (8.432 mL, 66.437 mmol) was added dropwise to the flask. The reaction vessel, in the cold bath, was allowed to warm to 23 °C over the course of two hours. At this point, TLC analysis indicated the presence of a single, new product. Saturated aqueous $NaHSO_4$ solution (50 mL) was added and stirred with the reaction mixture for 1 hour. The layers were separated and the organic layer was washed with an additional 50 mL of the $NaHSO_4$ solution. The combined aqueous layers were then extracted with diethyl ether (3 x 50mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and then concentrated under vacuum to a colorless crystalline solid. Purification via flash chromatography (5% → 20% ethyl acetate in hexanes eluent) provided pure TMS carbamate **33** (2.63 g, 86% yield): R_f = 0.63 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.69

(d, J = 7.08 Hz, 1H), 3.89 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 1.23 (d, J = 6.75, 6H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.69, 153.00, 149.33, 147.28, 133.33, 121.79, 118.88, 59.19, 58.54, 42.27, 21.88, 14.83, 0.13; IR (NaCl/film) 3326, 2971, 2937, 1710, 1601, 1530, 1464, 1384, 1370, 1324, 1247, 1220, 1193, 1179, 1080, 1026, 987, 844, 810, 759 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{16}H_{27}NO_4Si$ [M+H]$^+$: 326.1734, found 326.1725.

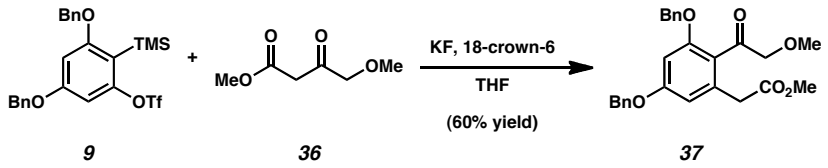


Silyl aryl triflate 11. This procedure was adopted from the literature procedure reported by Bronner, et al.[7] A 250 mL round-bottom flask was charged with a solution of TMS carbamate **33** (2.63 g, 8.10 mmol) in acetonitrile (80 mL). To this was added diethylamine (1.01 mL, 9.71 mmol), followed by DBU (1.82 mL, 12.14 mmol). The reaction was carefully monitored by TLC as it was heated to 40 °C in an oil bath. After 10 minutes, TLC anaylsis indicated complete consumption of the starting material and conversion to two spots (R_{f1} = 0.78 and R_{f2} = 0.60).[8] The reaction was immediately removed from the oil bath and a solution of $PhNTf_2$ (4.34 g, 12.14 mmol) in acetonitrile (24 mL) was added via syringe. The reaction was maintained with stirring for 12 hours at 23 °C, after which point the reaction solution was washed with saturated aqueous $NaHSO_4$ (2 x 50 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum to an orange oil, and purified via flash chromatography (5% ethyl acetate in hexanes eluent) to yield silyl aryl triflate **11** (1.57 g, 52% yield) as a pale yellow oil: R_f = 0.68 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.27 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.72, 150.74, 149.21, 135.84, 117.49 (q, J = 320 Hz), 124.53, 117.96, 60.79, 60.03, 16.43, 1.41; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.10; IR (NaCl/film) 2956, 2858, 1600, 1464, 1420, 1383, 1368, 1292, 1248, 1213, 1179,

1142, 1068, 1023, 982, 930, 873, 846, 764 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{19}F_3O_5SSi$ $[M]^+$: 372.0675, found 372.0674.

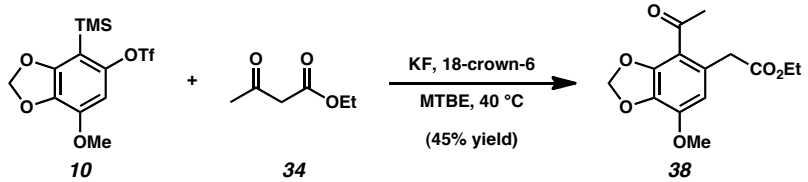


Ketoester 35. Silyl aryl trilfate **8** (52 mg, 0.144 mmol) and ethyl acetoacetate (**34**, 15 mg, 0.115 mmol) were combined in THF (1.2 mL). To this was sequentially added 18-crown-6 (91 mg, 0.346 mmol) and KF (20 mg, 0.346 mmol). The resulting suspension was maintained at room temperature with vigorous stirring until silyl aryl triflate **8** had been completely consumed by TLC analysis. Following this period the reaction was diluted with diethyl ether (10 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield ketoester **35** (16.2 mg, 53% yield): R_f = 0.23 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.3 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.70 (s, 2H), 2.52 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.83, 171.31, 161.51, 159.31, 134.98, 123.82, 108.12, 97.48, 60.84, 55.60, 55.39, 39.21, 32.26, 14.19; IR (NaCl/film) 2979, 2941, 1732, 1682, 1602, 1461, 1425, 1318, 1263, 1203, 1159, 1093, 1029, 947, 836 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{19}O_5$ $[M+H]^+$: 267.1232, found 267.1231.



9 *36* *37*

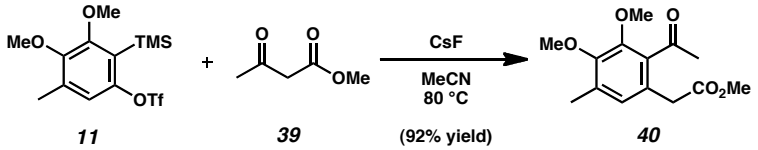
Ketoester 37. To a solution of silyl aryl triflate **9** (65.5 mg, 0.128 mmol) and β-ketoester **36** (15 mg, 0.103 mmol) in THF (1.0 mL) was sequentially added 18-crown-6 (81.3 mg, 0.308 mmol) and KF (17.9 mg, 0.308 mmol). The resulting suspension was maintained with vigorous stirring until β-ketoester **36** had been completely consumed by TLC analysis. Following this period, the reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL x 2) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield ketoester **37** (26.8 mg, 60% yield): R_f = 0.13 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.30 (m, 10H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 5.06 (s, 2H), 5.05 (s, 2H), 4.50 (s, 2H), 3.73 (s, 2H), 3.69 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.33, 171.56, 161.19, 158.90, 136.17, 136.12, 135.72, 128.71, 128.70, 128.40, 128.28, 127.72, 127.57, 120.95, 109.95, 99.36, 78.78, 70.99, 70.24, 59.08, 52.04, 39.07; IR (NaCl/film) 2947, 1734, 1700, 1601, 1436, 1375, 1319, 1160, 1124, 1073, 739 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{26}O_6$ $[M+H]^+$: 434.1729, found 434.1720.



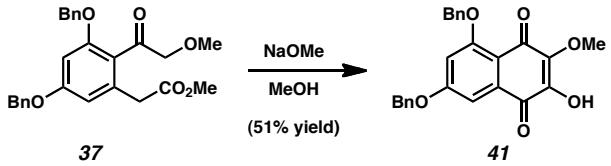
10 *34* *38*

Ketoester 38. To a solution of silyl aryl triflate **10** (23.8 mg, 0.0639 mmol) and ethyl acetoacetate (**34**, 4.1 mL, 0.0320 mmol) in *tert*-butyl methyl ether (MTBE, 0.32 mL) was added 18-crown-6 (25.3 mg, 0.0959 mmol) and KF (5.6 mg, 0.0959 mmol). The resulting suspension was heated in an oil bath to 40 °C and maintained for a period of 1 hour. Following this time, the reaction was cooled to room

temperature, diluted in diethyl ether (25 mL), and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield ketoester **38** (4 mg, 45% yield): R_f = 0.49 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.07 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.81 (s, 2H), 2.55 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 147.4, 143.5, 140.9, 127.6, 109.5, 103.0, 98.8, 56.8; IR (NaCl/film) 2985, 2904, 1731, 1674, 1632, 1427, 1312, 1281, 1162, 1100, 940, 854 cm^{-1}; HRMS (MM:ESI-APCI) *m/z* calc'd for $C_{14}H_{16}O_6$ $[M+H]^+$: 281.1020, found 281.1020.

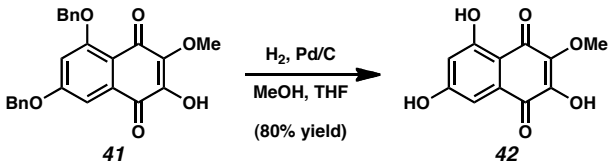


Ketoester 40. To a round-bottom flask was added oven-dried CsF (0.053 g, 0.348 mmol), followed by a solution of methyl acetoacetate (**39**, 0.025 mL, 0.232 mmol) in acetonitrile (1 mL). Next, aryne precursor **11** was added via syringe (0.108 g, 0.290 mmol), and the reaction was maintained with stirring in an oil bath at 80 °C for 2 hours. The reaction was cooled to 25 °C, concentrated under vacuum, and the crude reaction mixture was adsorbed onto Celite (1 g). Ketoester **40** was purified by flash chromatography (10% ethyl acetate in hexanes eluent) and isolated as a colorless oil (57 mg, 92 % yield): R_f = 0.56 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 1H), 3.88 (s, 3H), 3.83, (s, 3H), 3.68 (s, 3H), 3.62 (s, 2H), 2.55 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.42, 171.97, 150.74, 150.32, 134.33, 134.06, 128.55, 126.63, 61.14, 60.05, 51.95, 37.73, 32.23, 15.85; IR (NaCl/film) 2951, 2849, 1740, 1692, 1604, 1568, 1484, 1451, 1437, 1400, 1351, 1306, 1269, 1200, 1167, 1147, 1078, 1040, 1012 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{18}O_5$ $[M]^+$: 266.1154, found 266.1152.

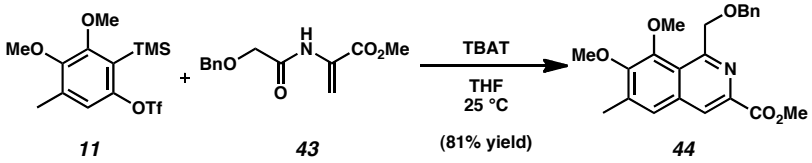


37 *41*

Hydroxynaphthoquinone 41. To NaH (60 wt. % dispersion in mineral oil, 12.3 mg, 0.308 mmol) in a vial was added MeOH (1.0 mL), and the resulting suspension was stirred for 10 minutes. **Warning:** vigorous gas evolution. A separate solution of ketoester **37** (26.8 mg, 0.0617 mmol) in MeOH (1.0 mL) was prepared. Slowly the solution of NaOMe was added to the solution of ketoester **37** and maintained with stirring at room temperature for 20 minutes. Following this period, the vial was opened to the atmosphere and heated at 60 °C until ketoester **37** has been fully consumed by TLC analysis. Upon completion, the reaction was cooled to room temperature and diluted with ethyl acetate (10 mL). The resulting solution was washed with 1 N K_2CO_3 solution (5 x 15 mL), the combined aqueous extracts were acidified with 6 N HCl to pH 1.5, and the acidic solution was extracted with ethyl acetate (15 mL x 3). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography to yield hydroxynaphthoquinone **41** (13 mg, 51% yield): R_f = 0.43 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.1 Hz, 2H), 7.48–7.29 (m, 9H), 6.86 (d, J = 2.5 Hz, 1H), 6.55 (s, 1H), 5.21 (s, 2H), 5.18 (s, 2H), 4.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.23, 179.01, 163.28, 160.84, 140.79, 140.13, 135.84, 135.40, 133.06, 128.80, 128.65, 128.55, 127.87, 127.65, 126.58, 113.08, 106.98, 104.88, 70.92, 70.71, 60.69; IR (NaCl/film) 3367, 2944, 1653, 1592, 1440, 1318, 1207, 1169, 1052, 1010, 736 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{25}H_{20}O_6$ $[M+H]^+$: 416.1260, found 416.1251.



3-Methoxy-2,5,7-trihydroxy-1,4-naphthaquinone (42). To a solution of hydroxynaphthoquinone **41** (9.7 mg, 0.0233 mmol) in MeOH/THF (1:1 (v/v) mixture, 2 mL total volume) was added 10 wt. % Pd/C (12.4 mg, 0.0116 mmol). A hydrogen balloon was attached to the system and the suspension was maintained under the H_2 atmosphere with vigorous stirring at room temperature until hydroxynaphthoquinone **41** had been fully consumed by TLC analysis. The suspension was filtered through Celite, concentrated under vacuum, and purified by flash chromatography (1:1 dichloromethane:ethyl acetate eluent) to yield 3-methoxy-2,5,7-trihydroxy-1,4-naphthaquinone (**42**, 4.4 mg, 80% yield): R_f = 0.17 (1:1 dichloromethane:ethyl acetate); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.92 (d, J = 1.8 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 185.46, 181.62, 163.54, 163.48, 147.64, 140.50, 132.08, 107.91, 107.76, 106.93, 59.89; IR (NaCl/film) 3305, 1611, 1467, 1284, 1170, 1096 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{11}H_8O_6$ [M]$^+$: 236.0321, found 236.0357.



Isoquinoline 44. A 100 mL round-bottom flask was charged with TBAT (0.225 g, 0.416 mmol). To this flask was added a solution of *N*-acyl enamide **43** (0.049 g, 0.208 mmol) in THF (21 mL). Finally, aryne precursor **11** was added (0.116 g, 0.312 mmol) via syringe. The pale yellow solution turned bright yellow while stirring at 25 °C for 8 hours. The reaction was stopped by adsorbing the contents onto celite (1 g) and purifying the reaction mixture via flash chromatography (5% → 30% ethyl acetate in

hexanes eluent), providing the desired isoquinoline **44** (64 mg, 81% yield) as a pale yellow solid: R_f = 0.22 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.53 (s, 1H) 7.43(d, *J* = 6.9 Hz, 2H) 7.32 (t, *J* = 7.28 Hz, 3H) 5.32 (s, 2H) 4.73 (s, 2H) 4.05 (s, 2H) 3.96 (s, 6H) 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.54, 155.93, 152.57, 149.20, 139.38, 138.46, 138.37, 134.31, 128.24, 128.20, 128.16, 127.47, 125.06, 123.56, 74.74, 73.00, 61.00, 60.06, 52.71, 16.92; IR (NaCl/film) 2948, 2856, 1738, 1716, 1667, 1616, 1558, 1486, 1453, 1402, 1354, 1333, 1310, 1263, 1130, 1089, 1055, 1008, 950, 909, 784, 742 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{23}NO_5$ $[M]^+$: 381.1576, found 381.1571.

References

[1] Bortolini, O.; Campestrini, S.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1987**, *52*, 5093–5095.
[2] Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.
[3] a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538. b) Boeckman, R. K.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141–146.
[4] Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126.
[5] Rao, D. V.; Stuber, F. A. *Synthesis* **1983**, 308.
[6] Cessation of the reaction occurs when exposed to air, and large amounts of Pd(0) black deposits result in a grey solution and reduced yields.
[7] Bronner, S. H.; Garg, N. K. *J. Org. Chem.* **2009**, *74*, 8842–8843.
[8] R_{f1} corresponds to the 2-TMS phenol, the desired cleavage product. R_{f2} corresponds to undesired des-TMS phenol **31**.

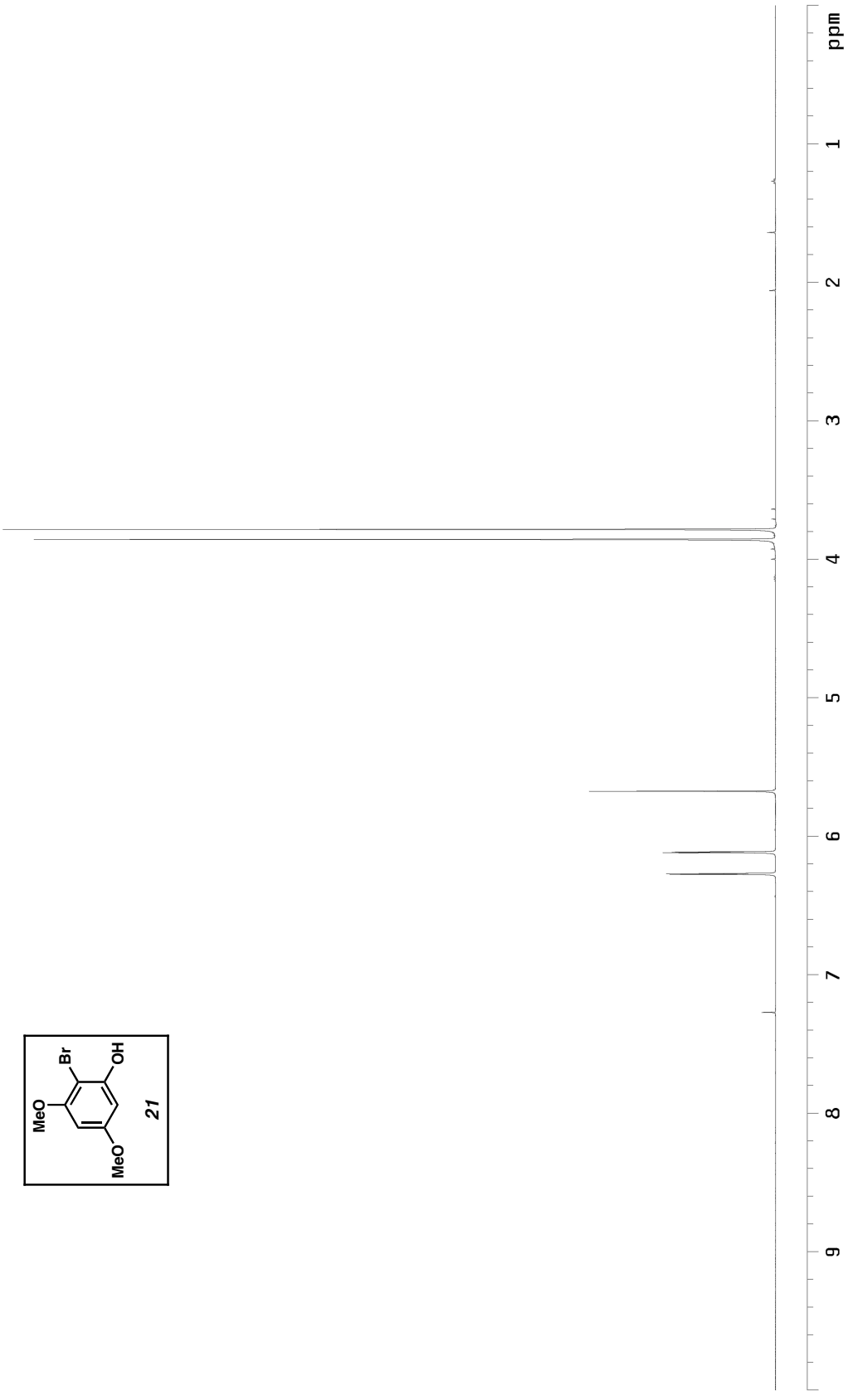


Figure 1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **21**.

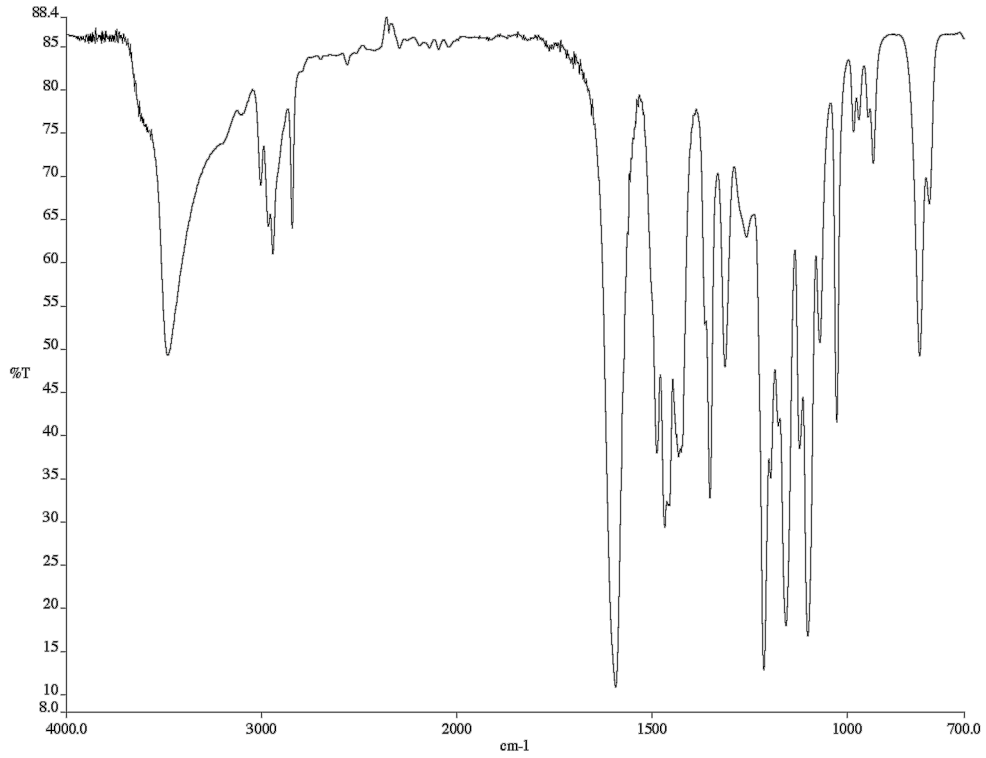


Figure 1.2 Infrared spectrum (thin film/NaCl) of compound **21**.

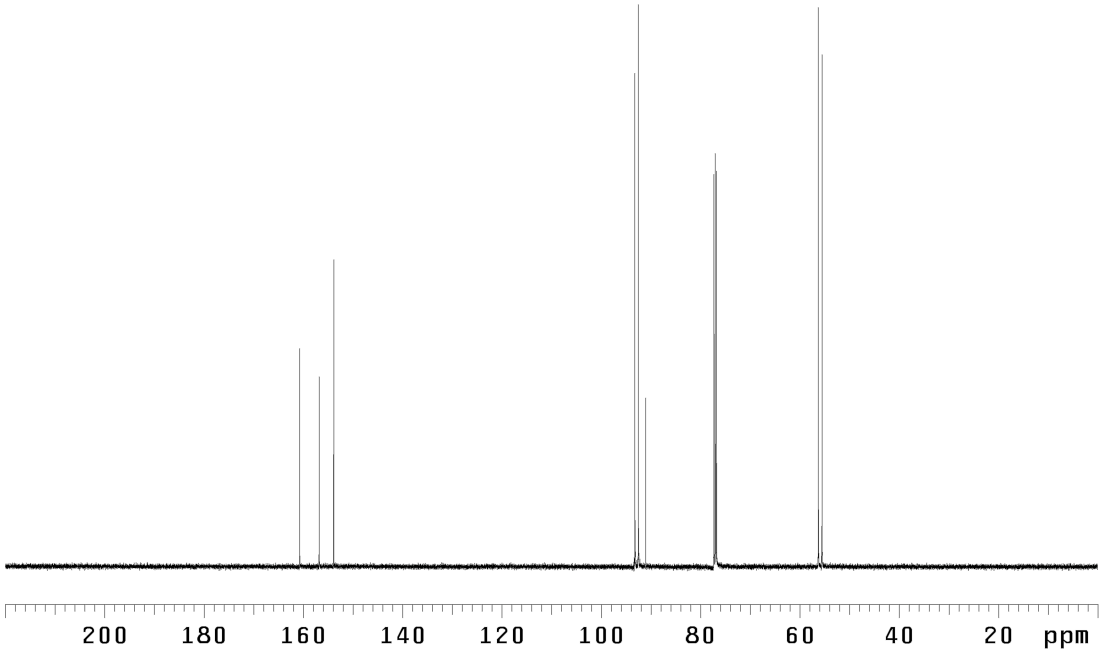


Figure 1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **21**.

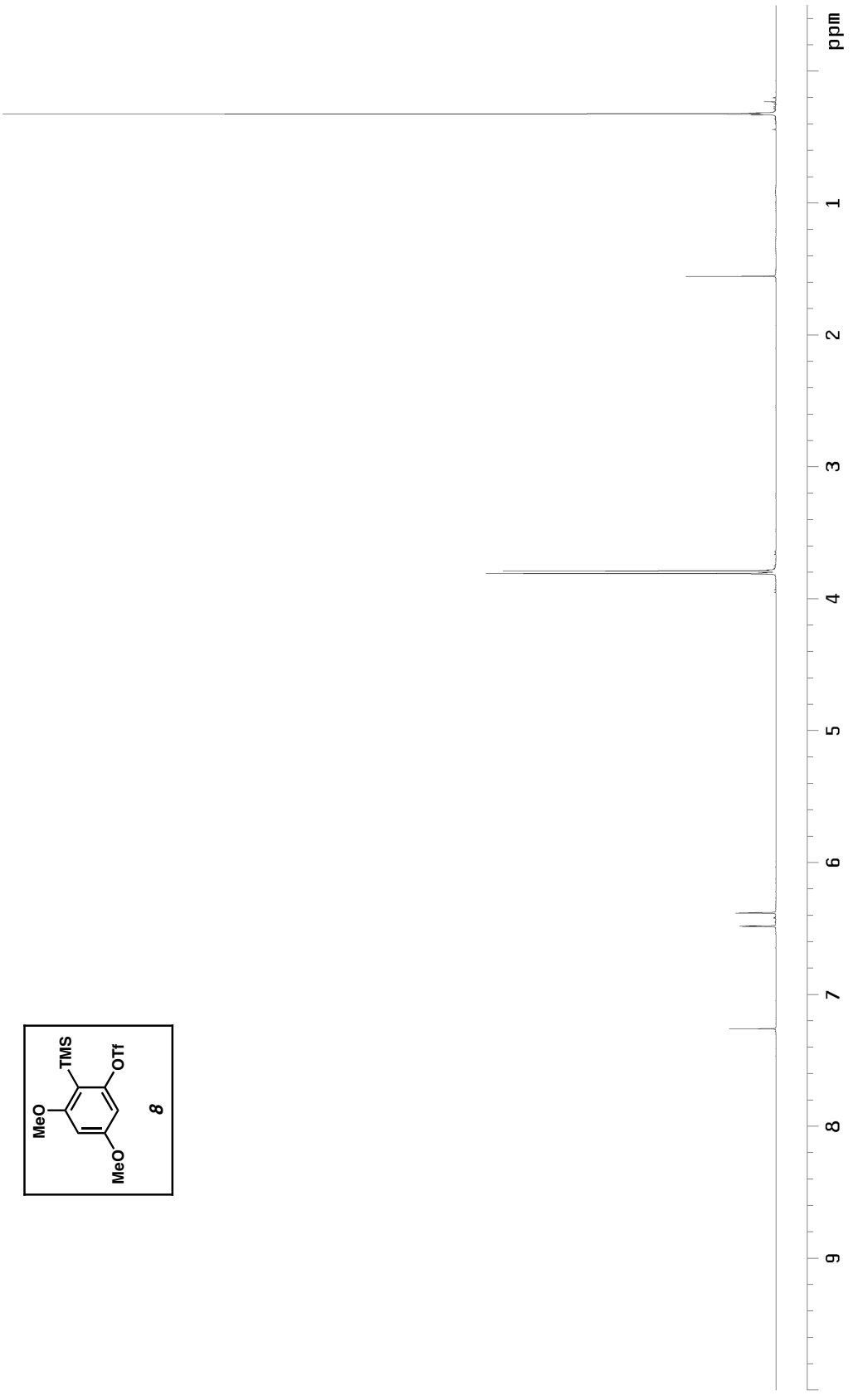


Figure 2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8**.

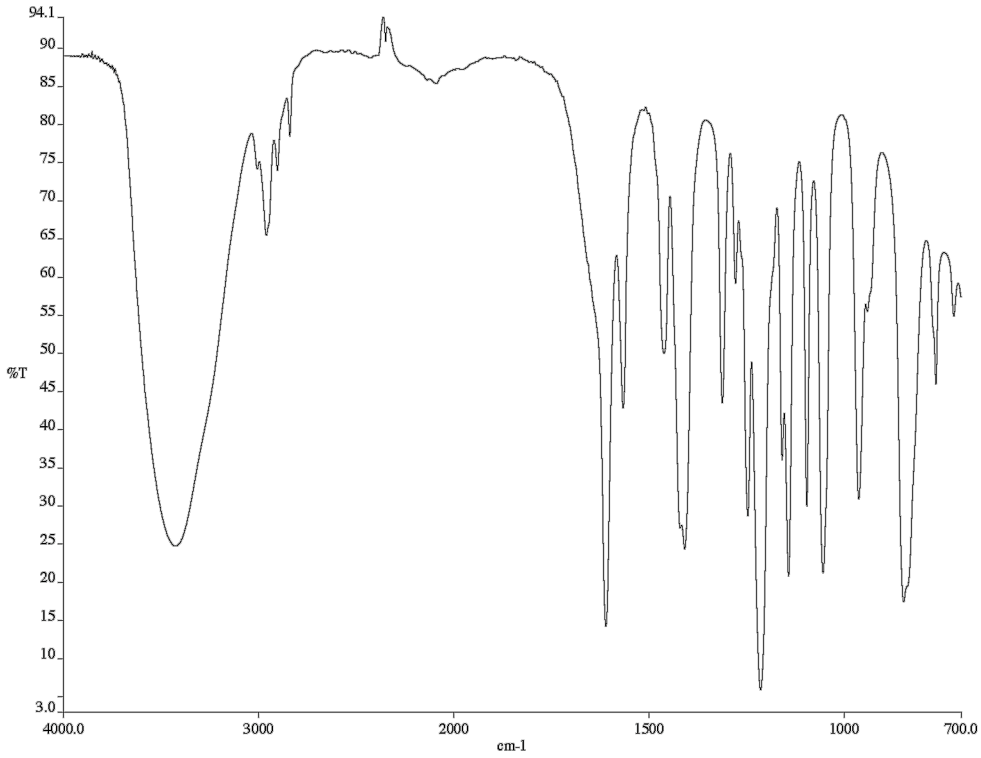


Figure 2.2 Infrared spectrum (thin film/NaCl) of compound **8**.

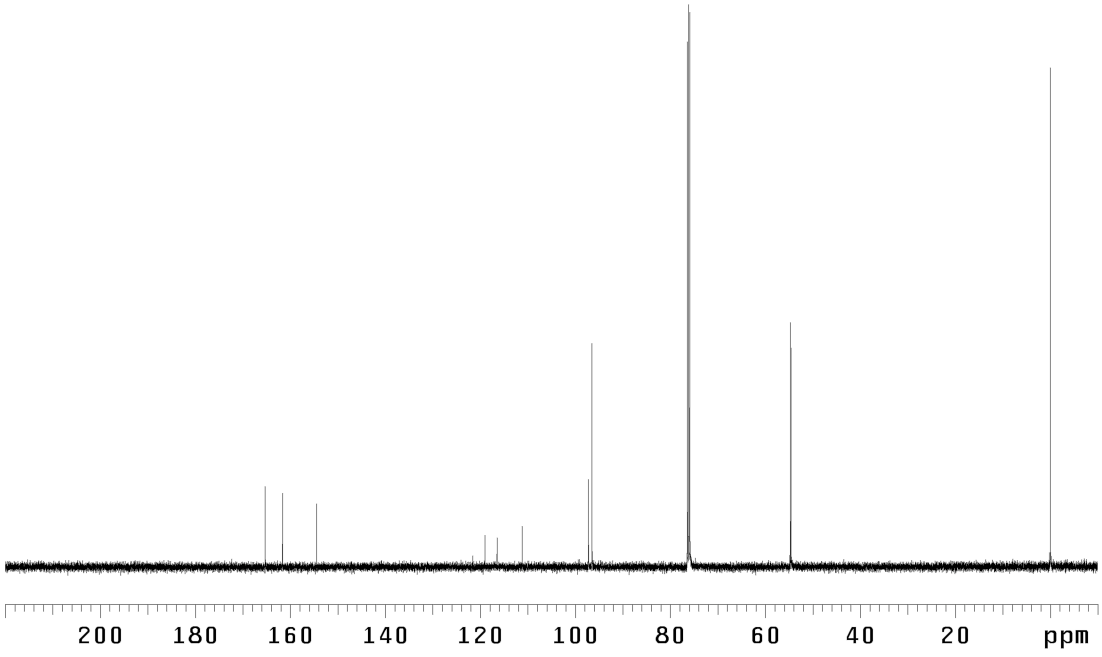


Figure 2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **8**.

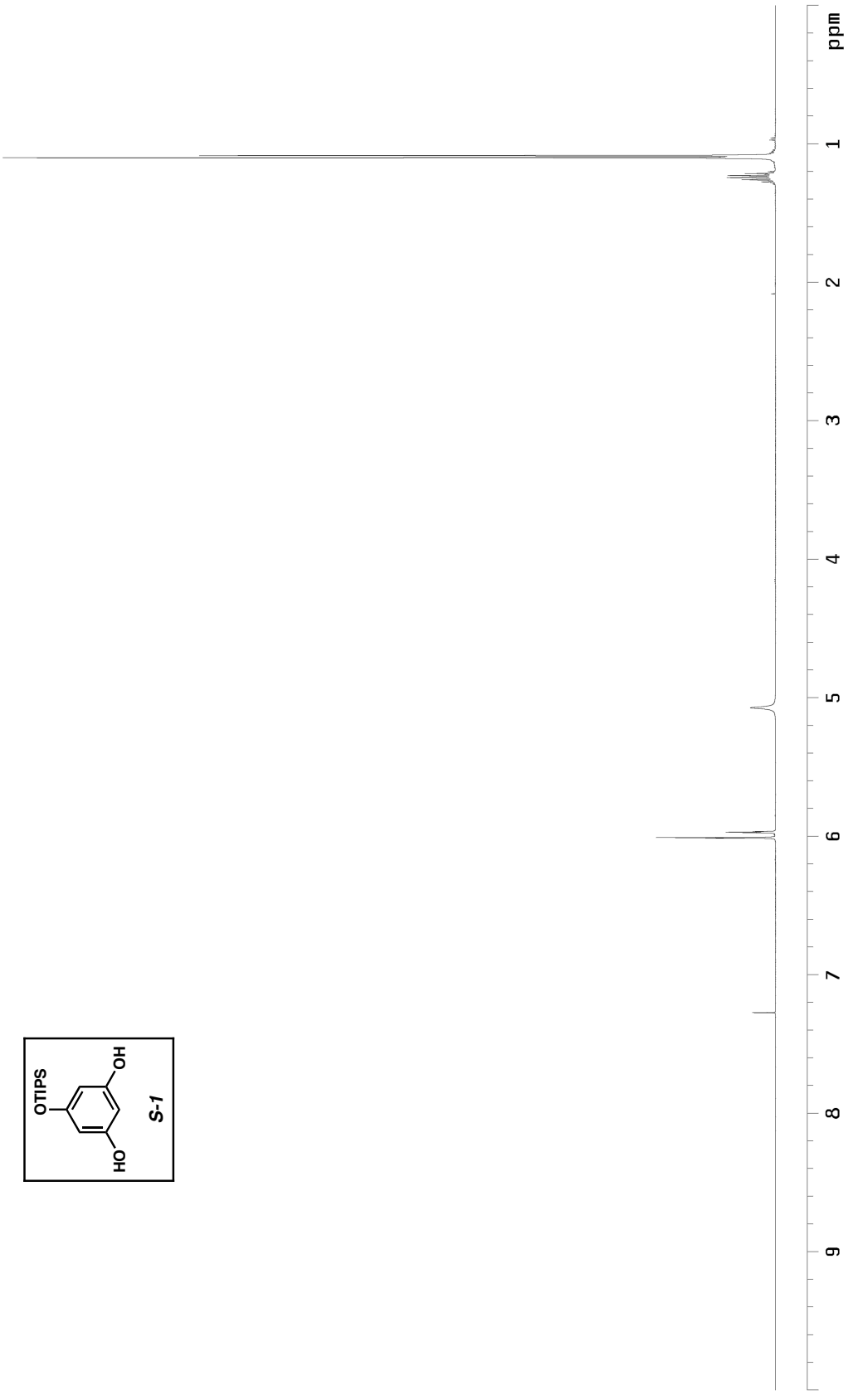


Figure 3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **S-1**.

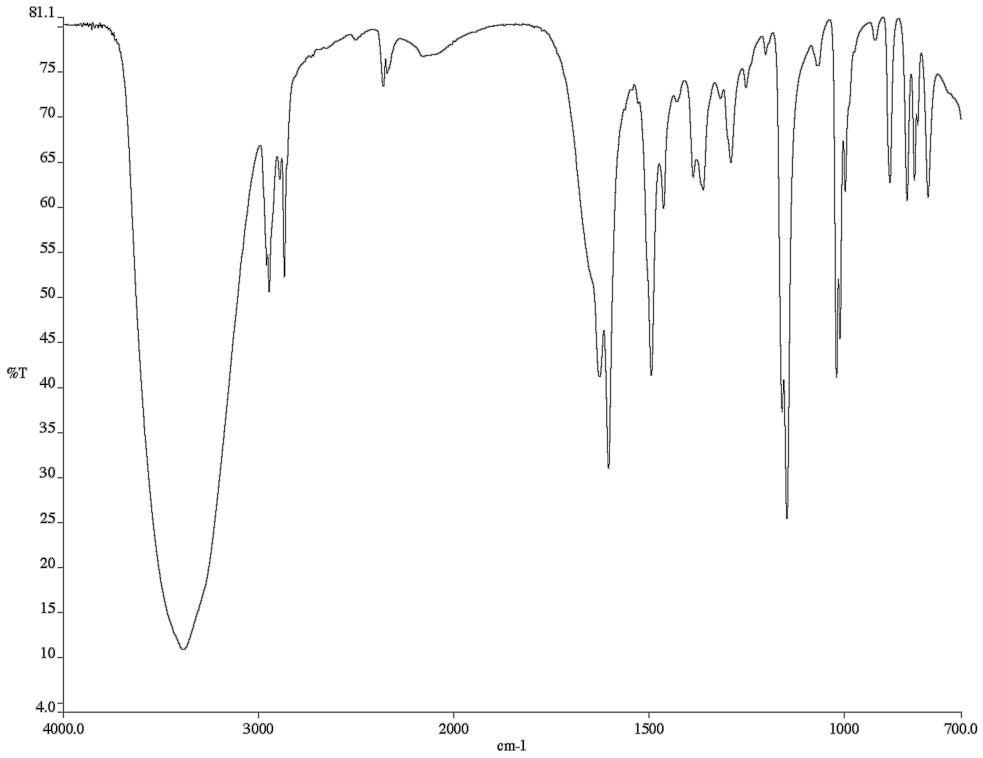


Figure 3.2 Infrared spectrum (thin film/NaCl) of compound **S-1**.

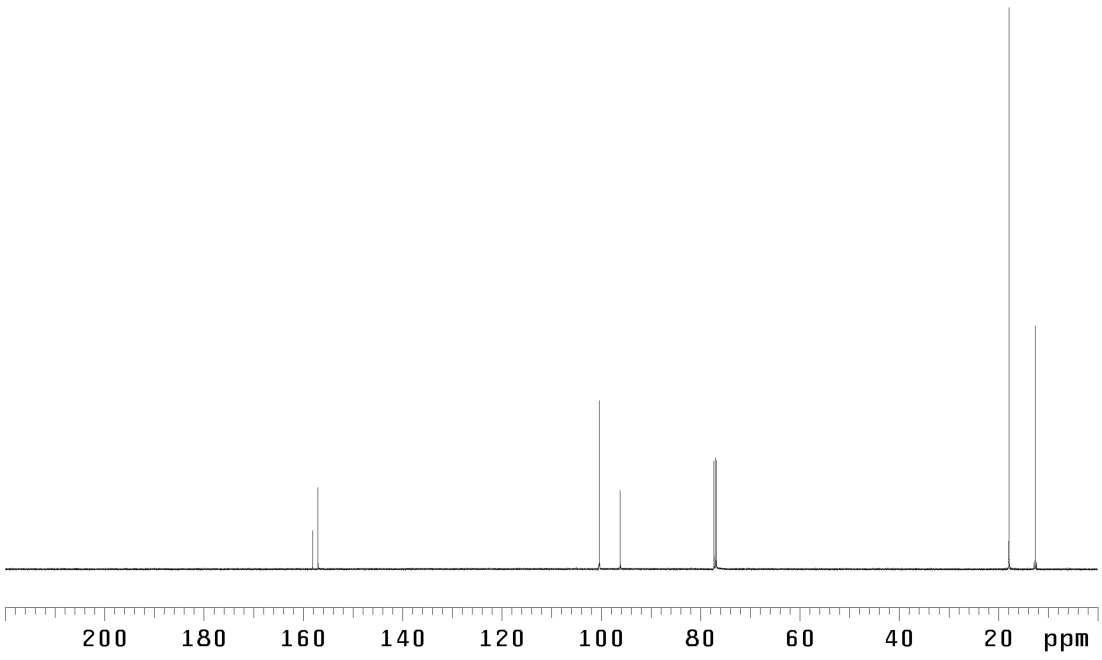


Figure 3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **S-1**.

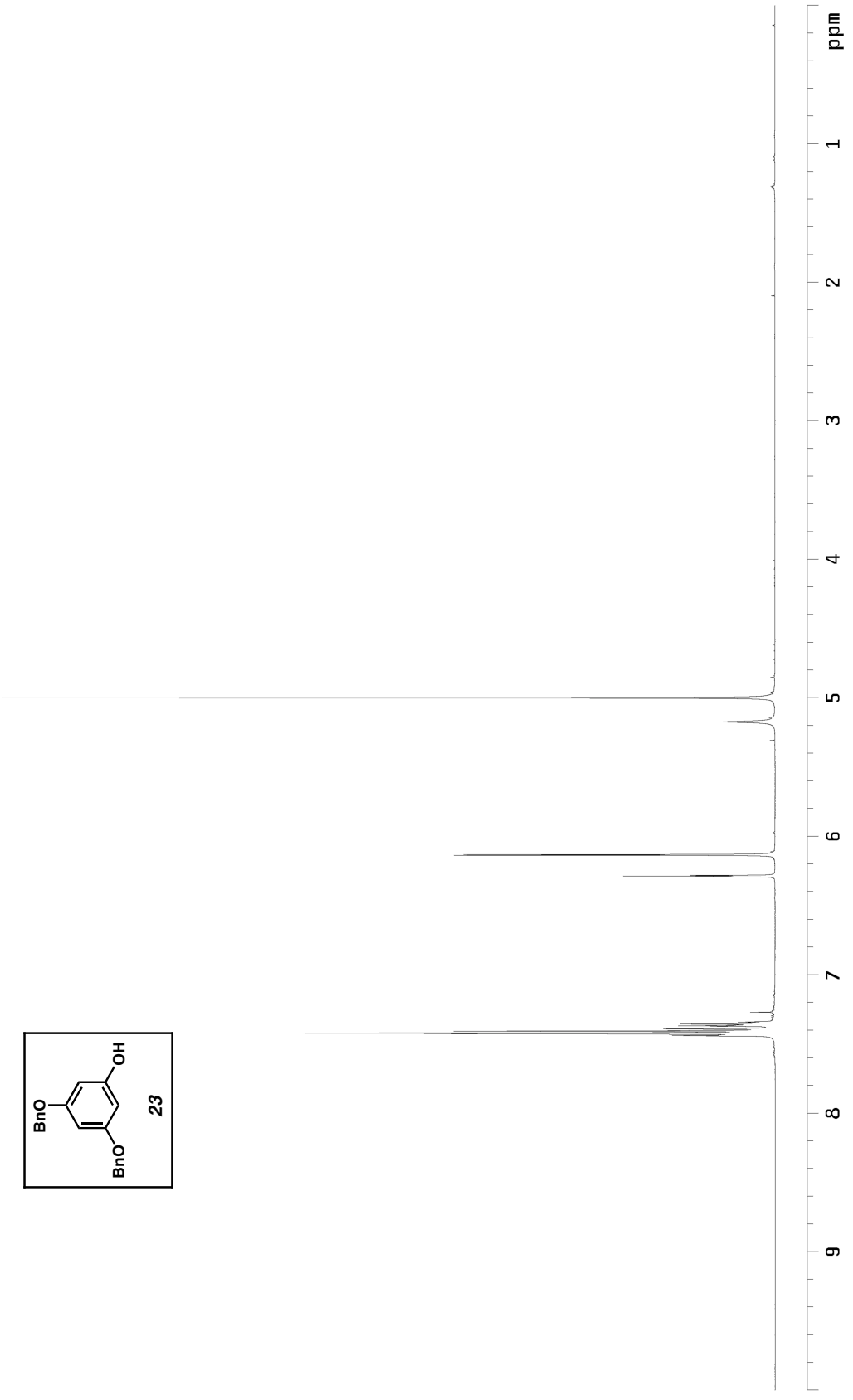


Figure 4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **23**.

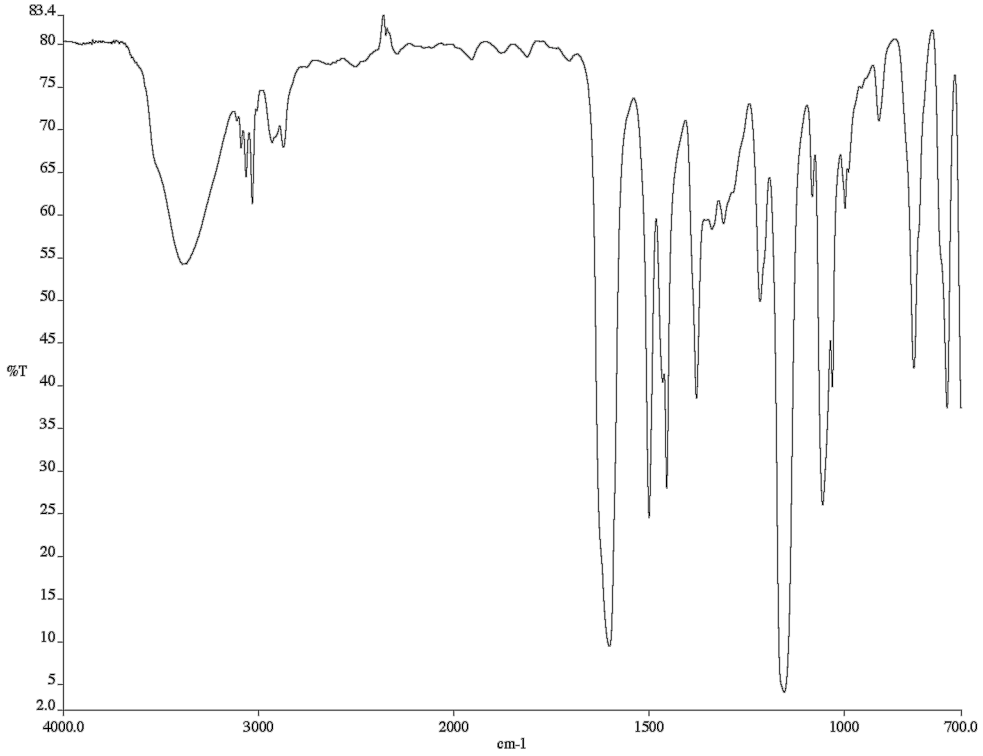


Figure 4.2 Infrared spectrum (thin film/NaCl) of compound **23**.

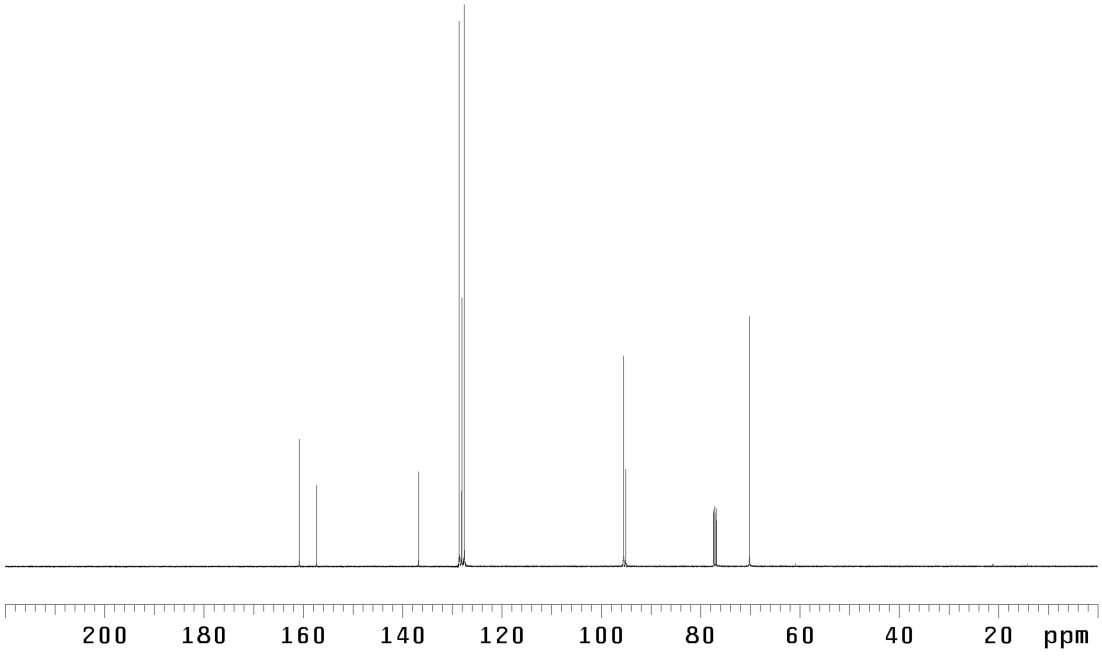


Figure 4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **23**.

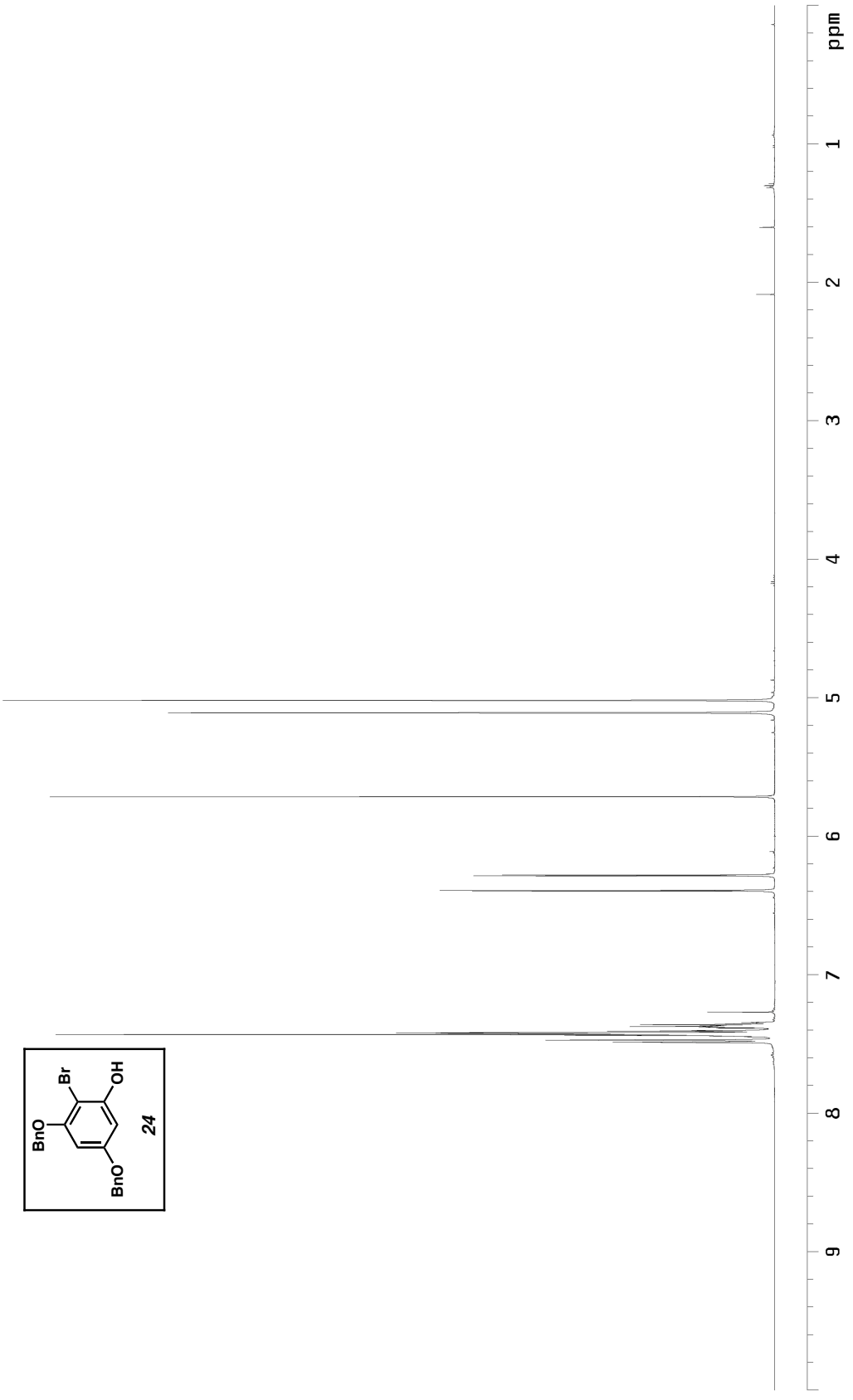


Figure 5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **24**.

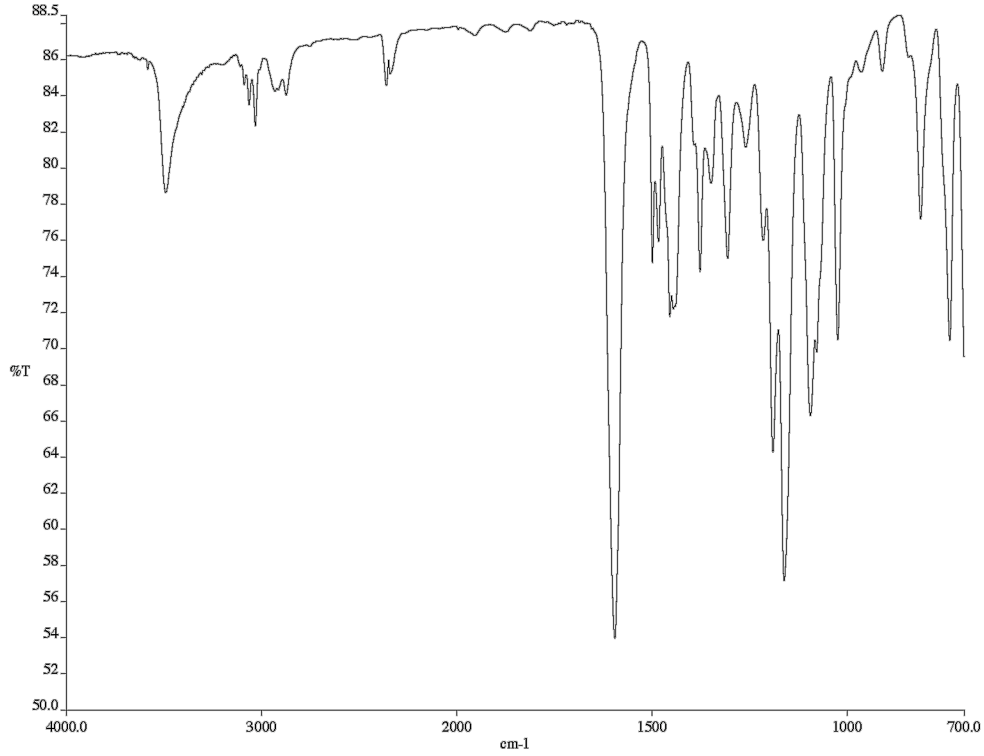


Figure 5.2 Infrared spectrum (thin film/NaCl) of compound **24**.

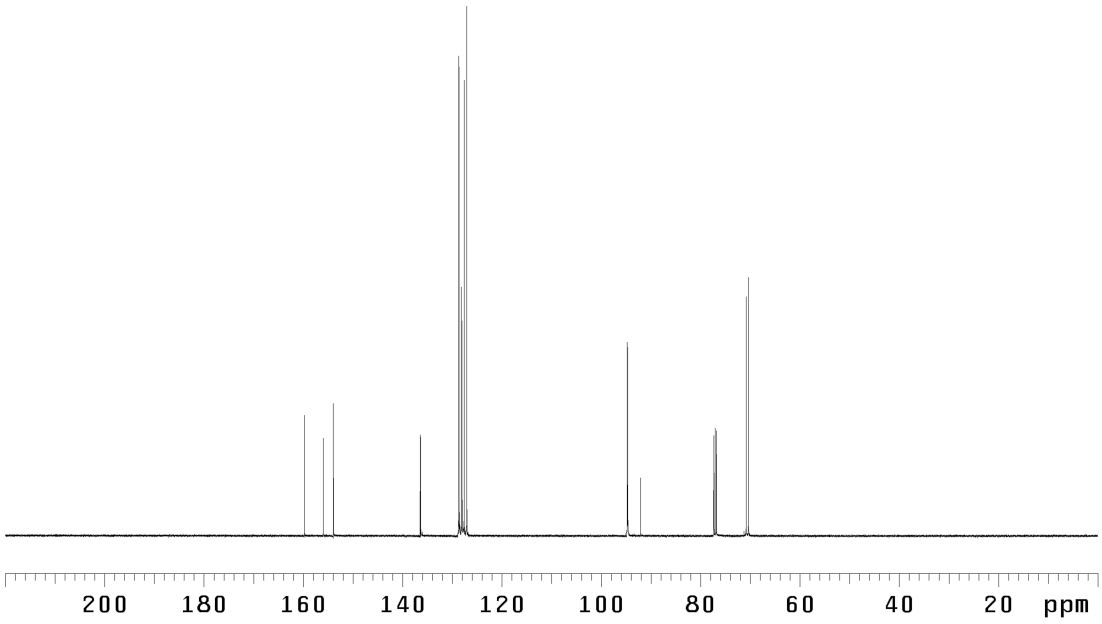


Figure 5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **24**.

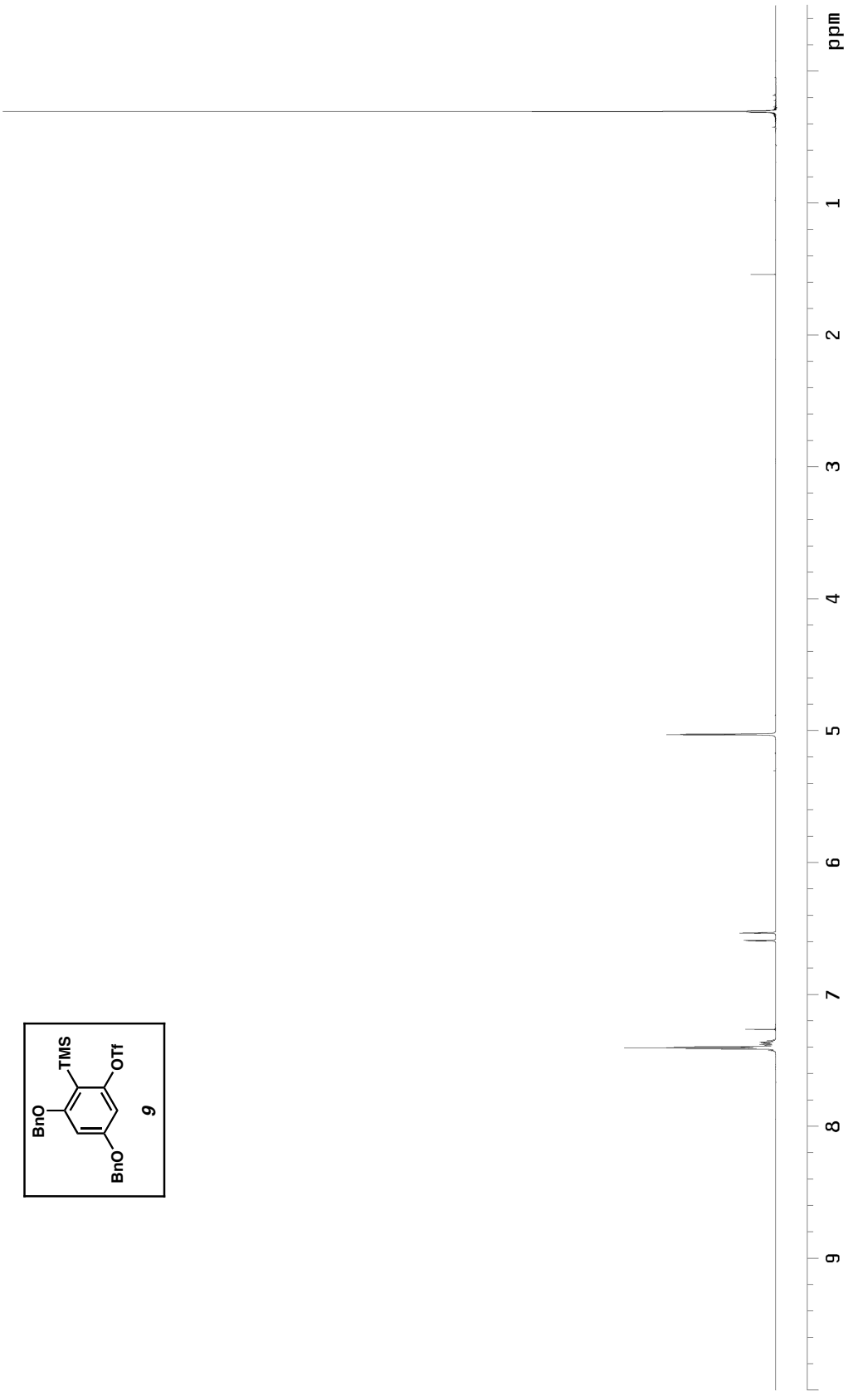


Figure 6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **9**.

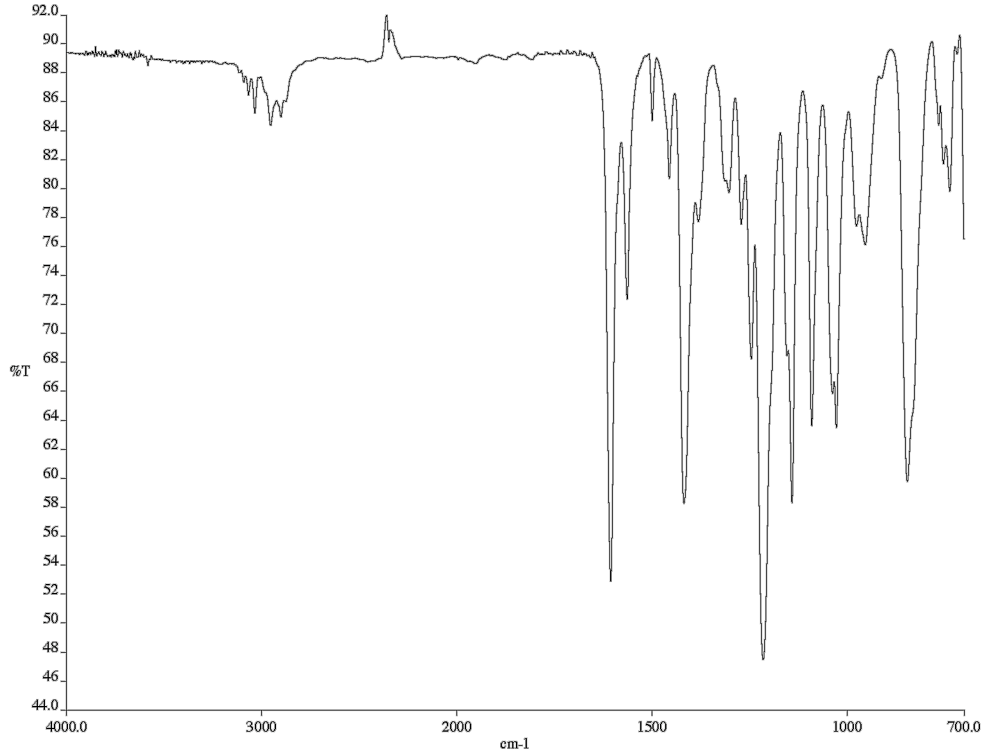


Figure 6.2 Infrared spectrum (thin film/NaCl) of compound **9**.

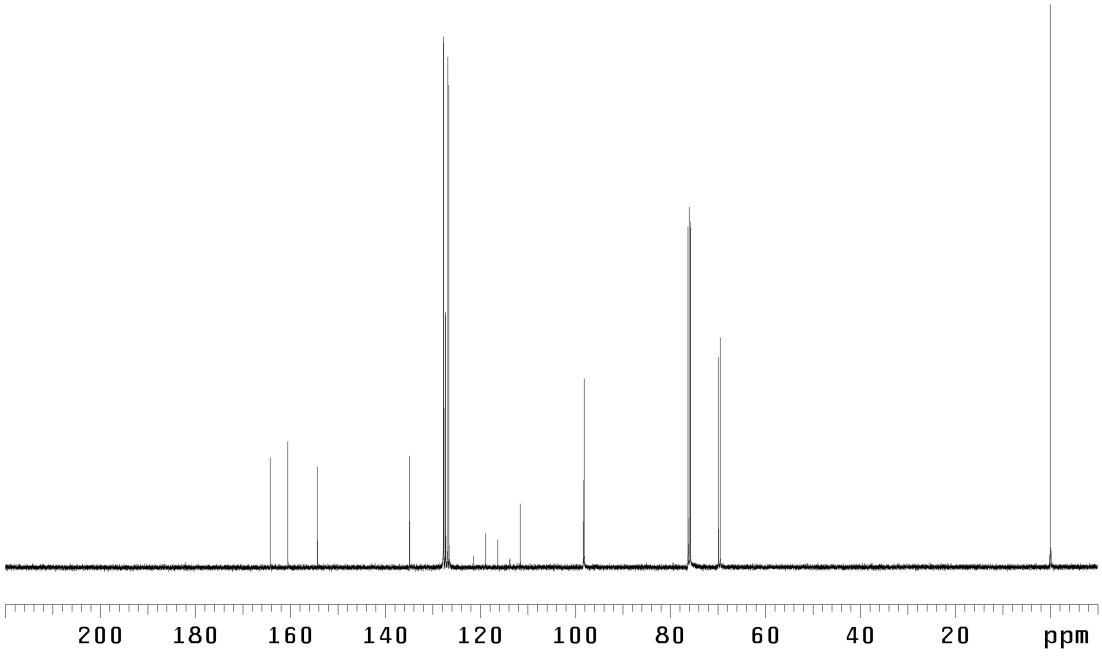


Figure 6.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **9**.

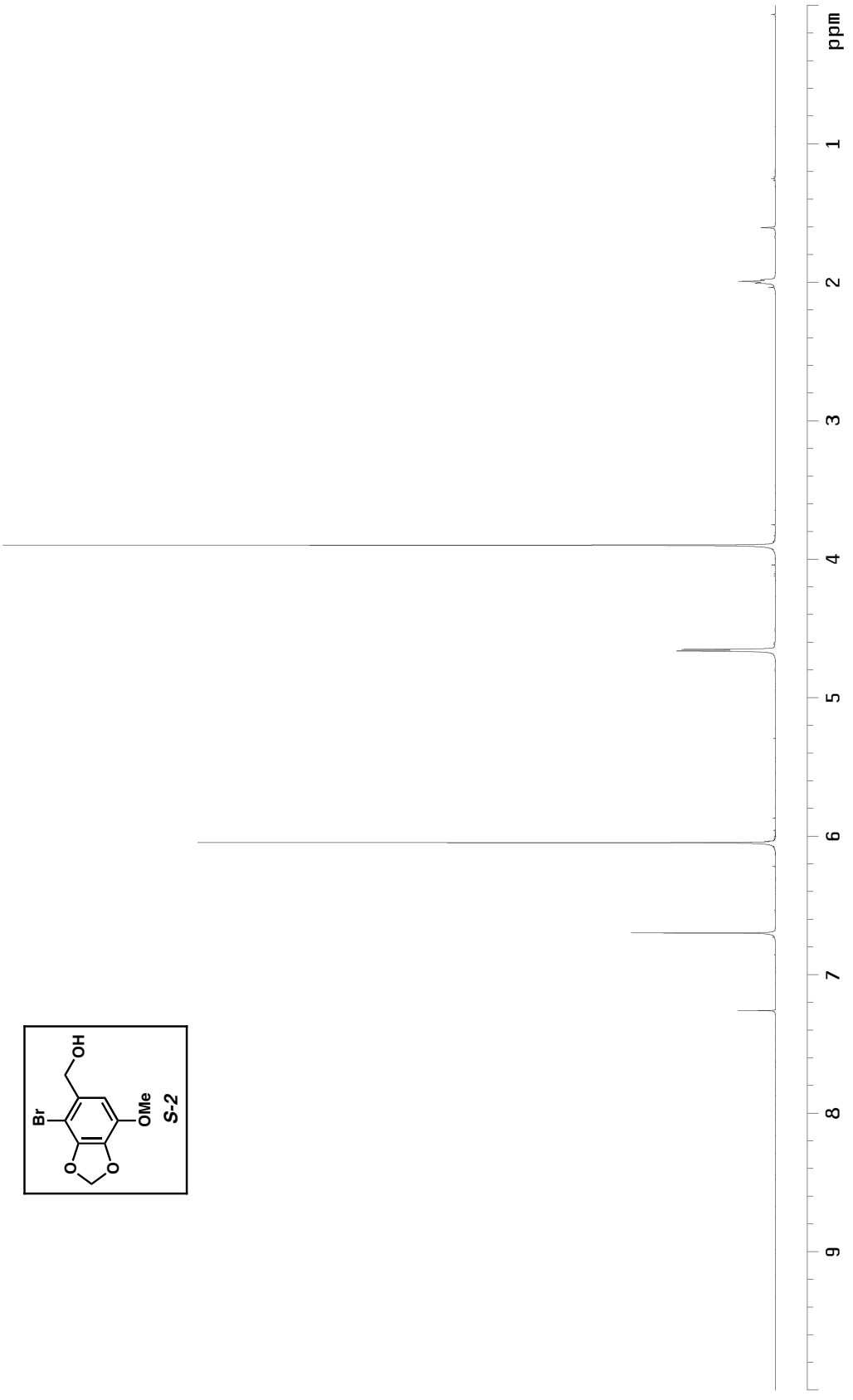


Figure 7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **S-2**.

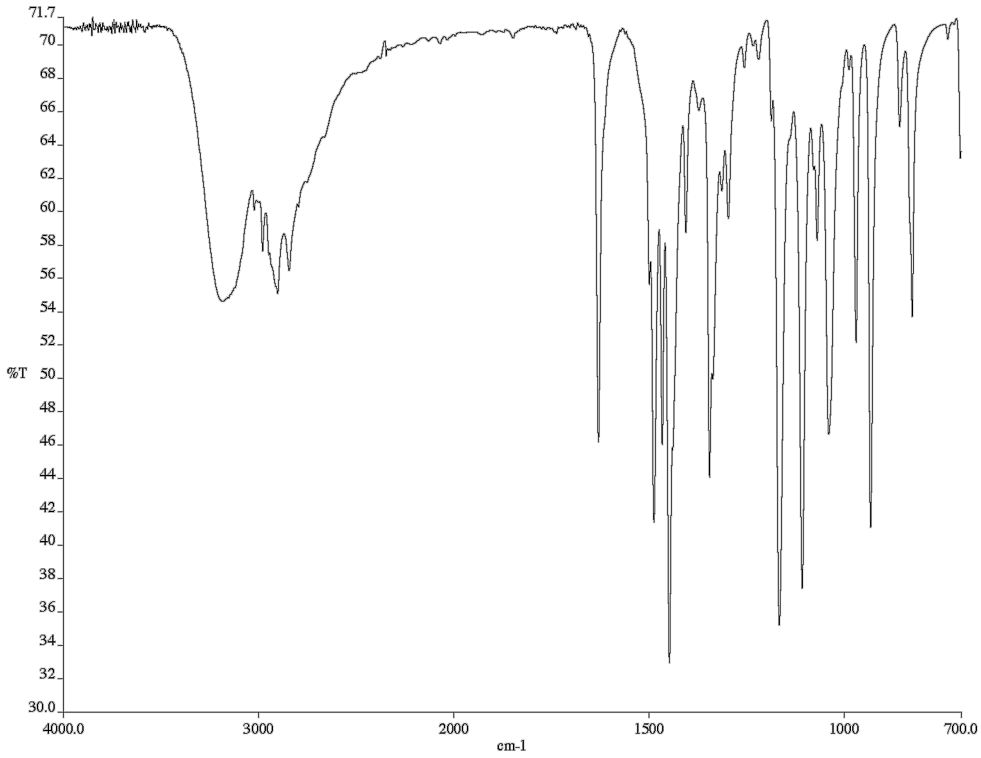


Figure 7.2 Infrared spectrum (thin film/NaCl) of compound **S-2**.

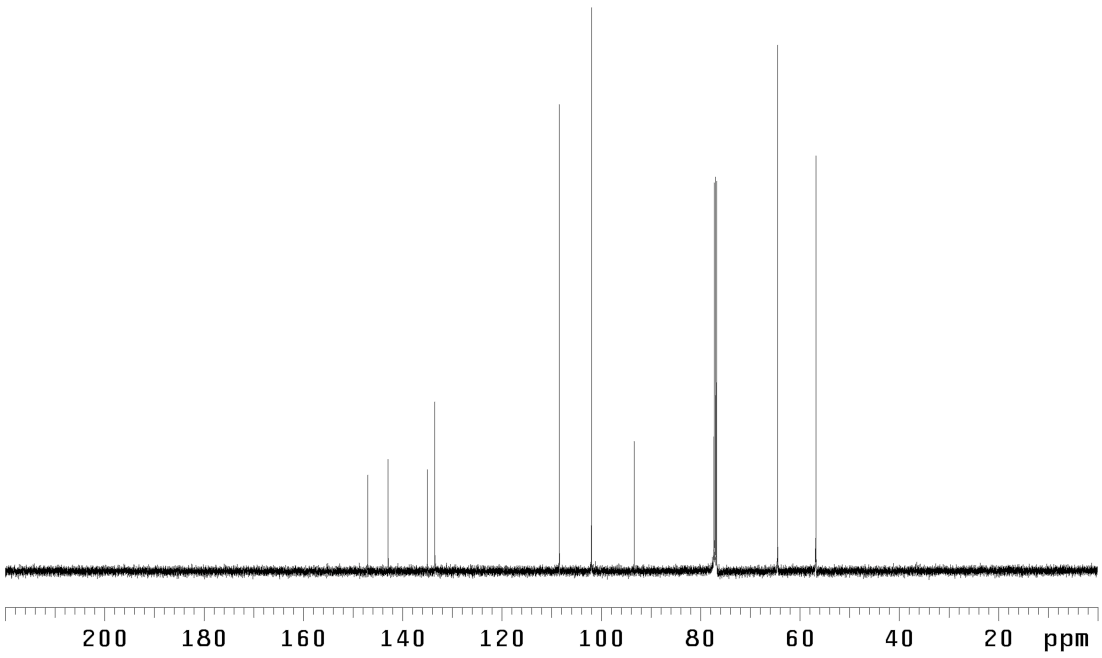


Figure 7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **S-2**.

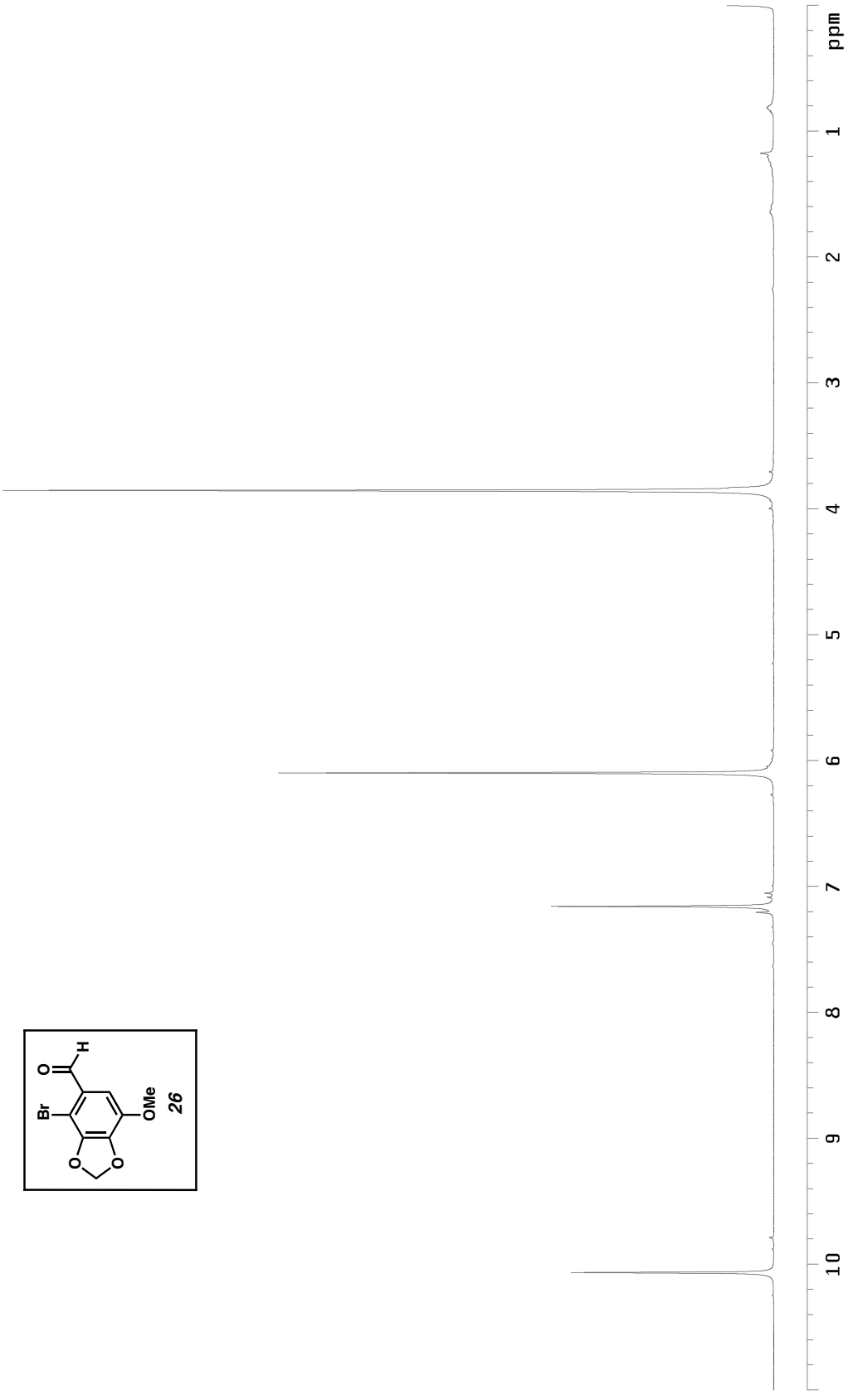


Figure 8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26**.

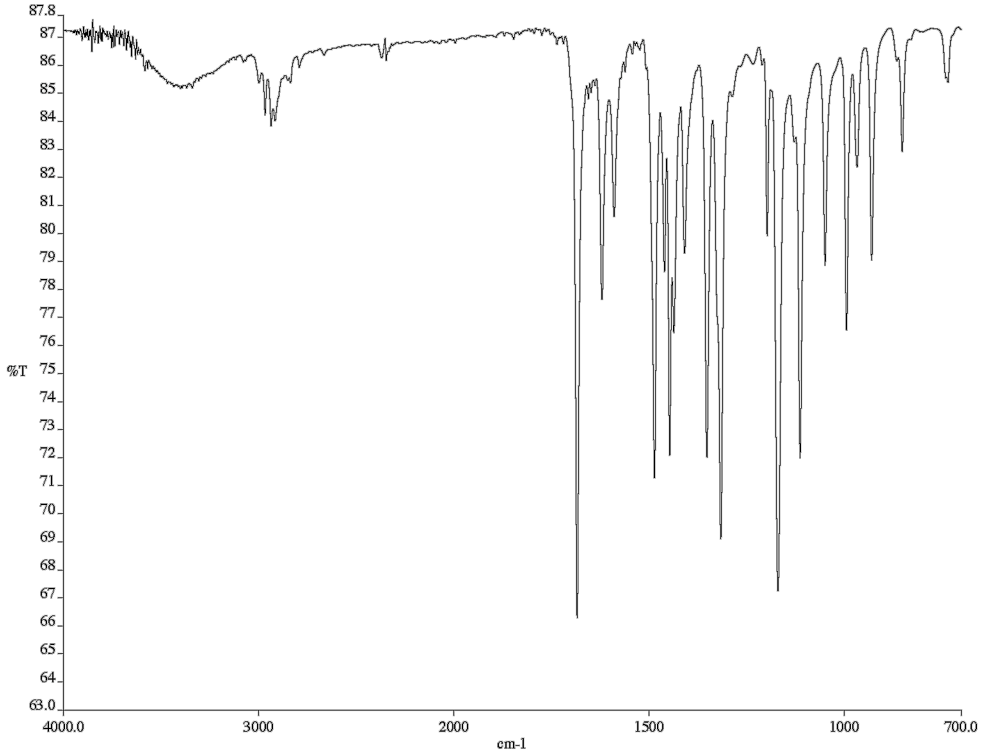


Figure 8.2 Infrared spectrum (thin film/NaCl) of compound **26**.

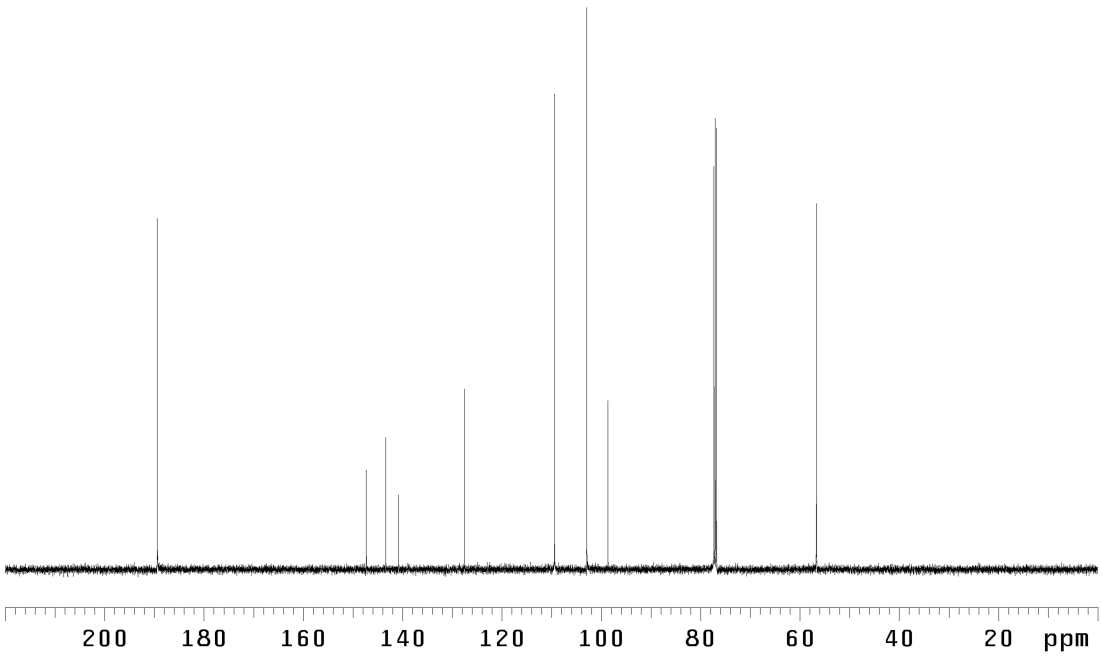


Figure 8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **26**.

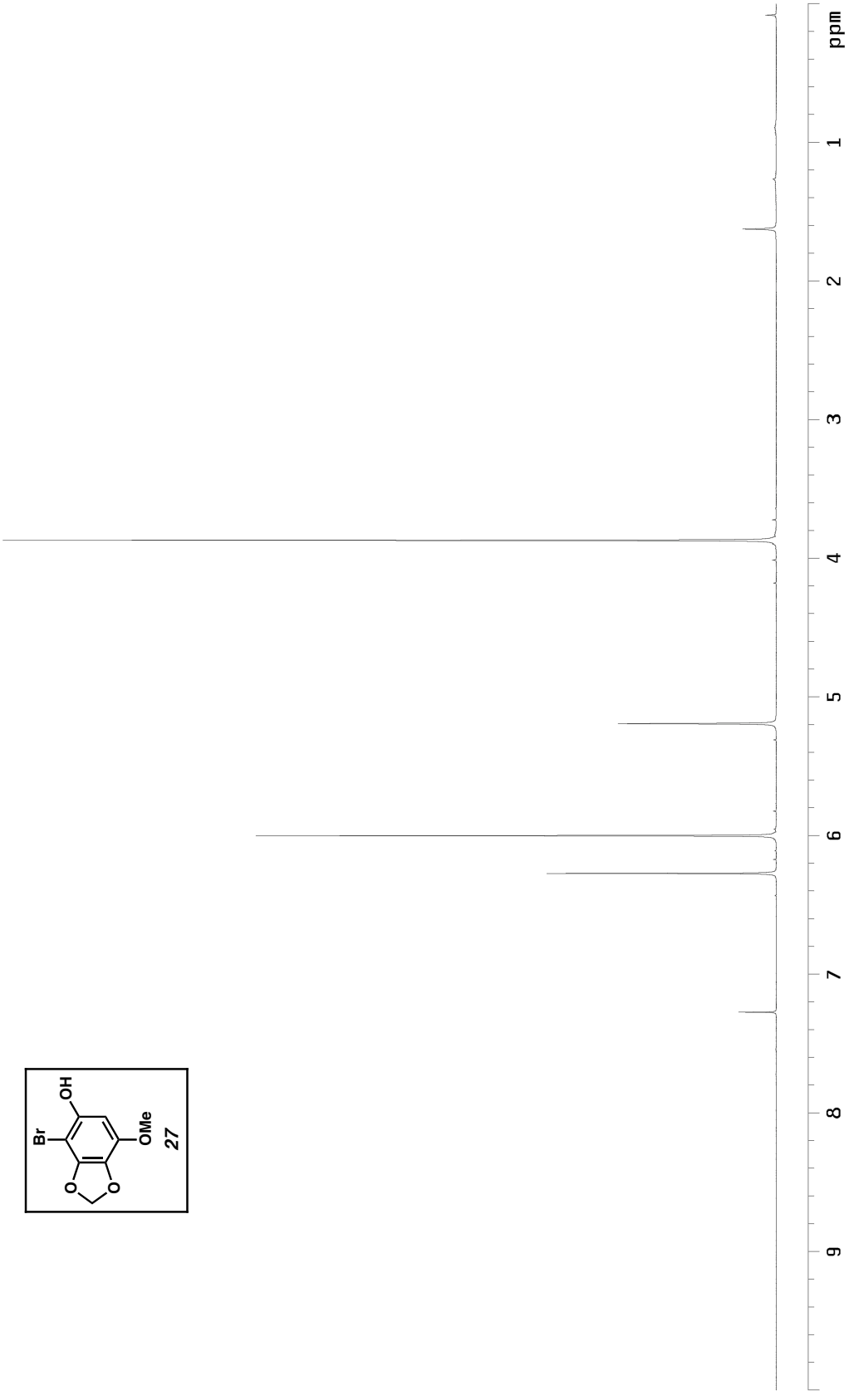


Figure 9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **27**.

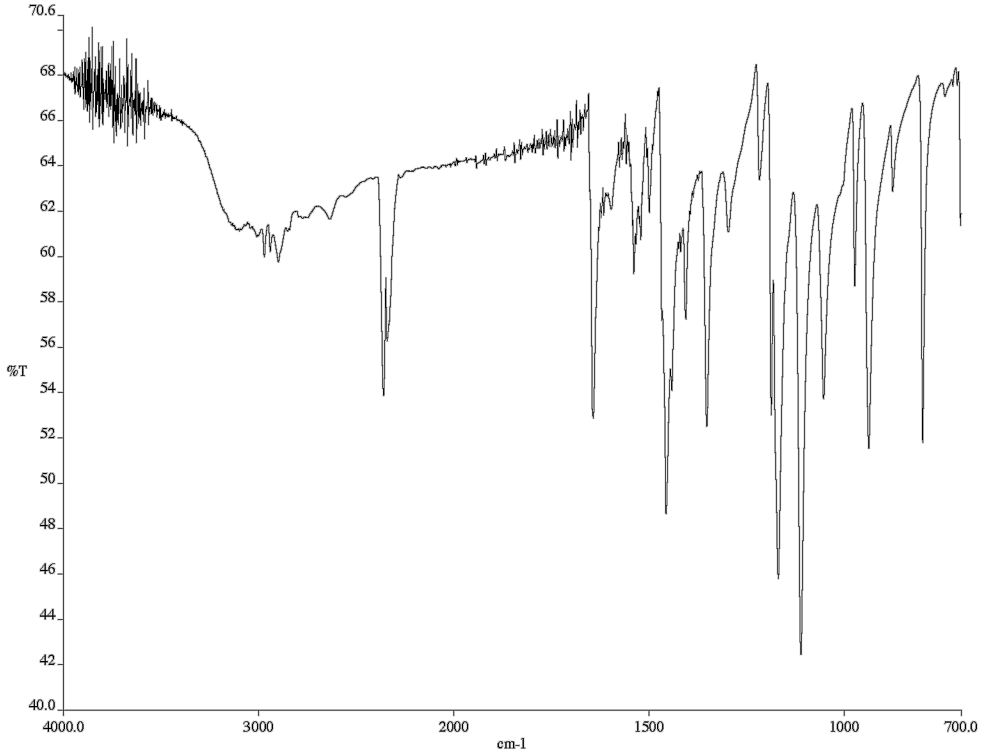


Figure 9.2 Infrared spectrum (thin film/NaCl) of compound **27**.

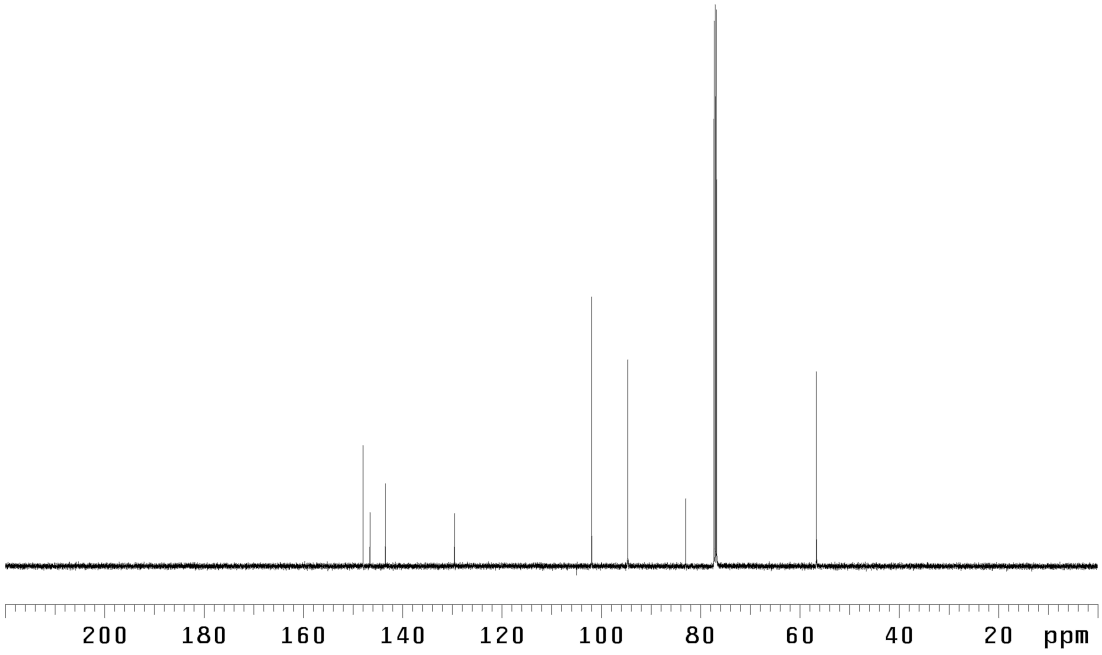


Figure 9.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **27**.

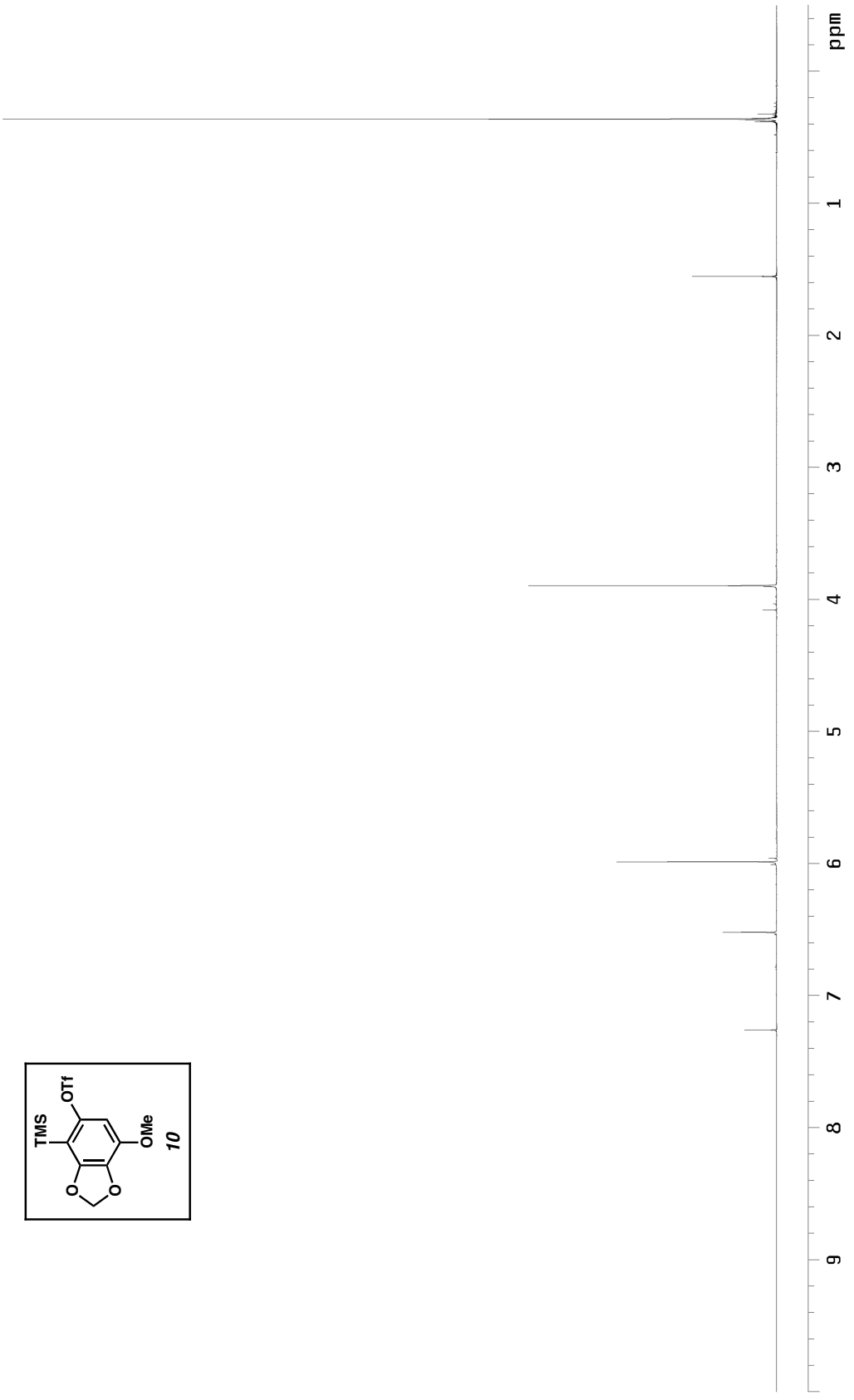


Figure 10.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **10**.

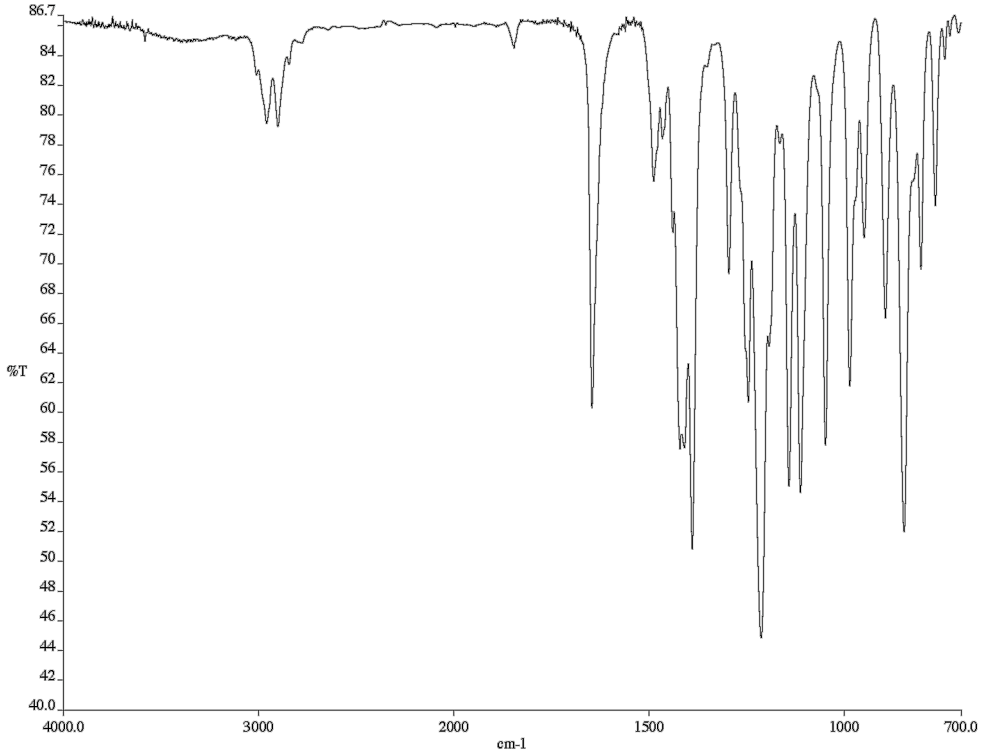


Figure 10.2 Infrared spectrum (thin film/NaCl) of compound **10**.

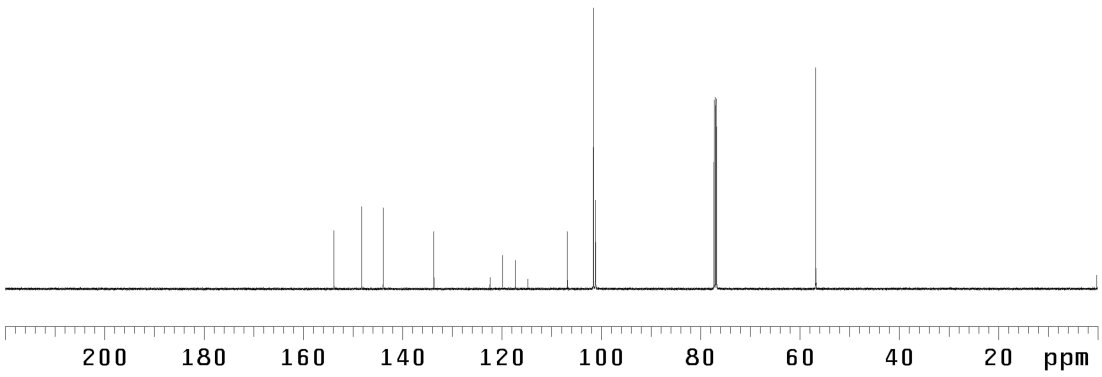


Figure 10.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **10**.

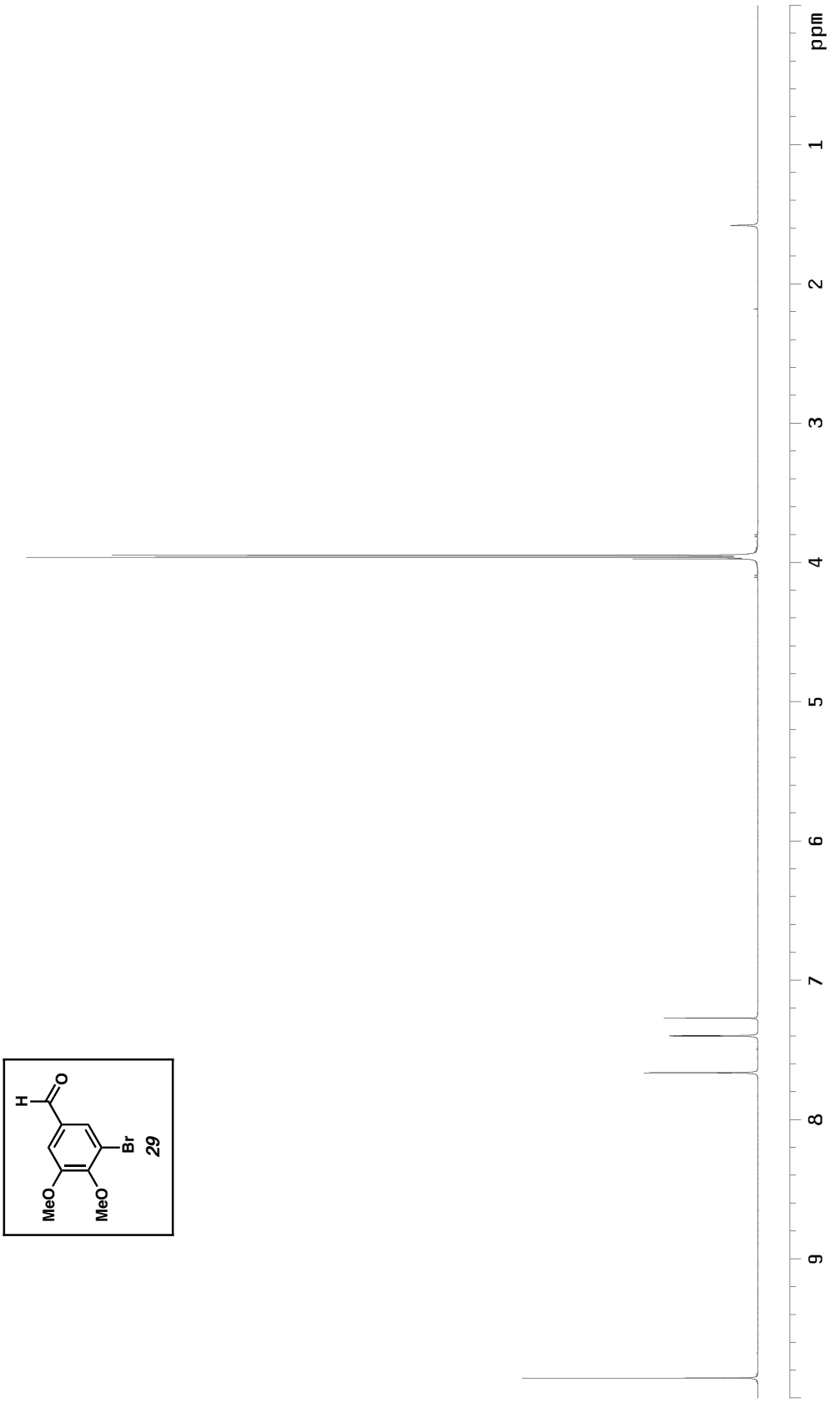


Figure 11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29**.

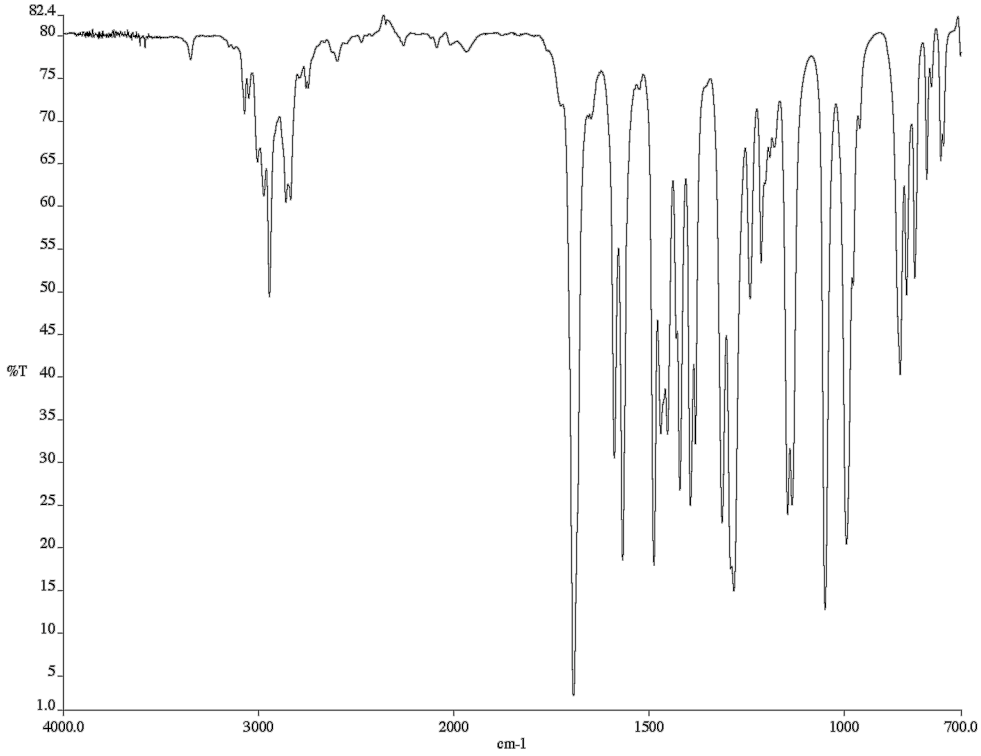


Figure 11.2 Infrared spectrum (thin film/NaCl) of compound **29**.

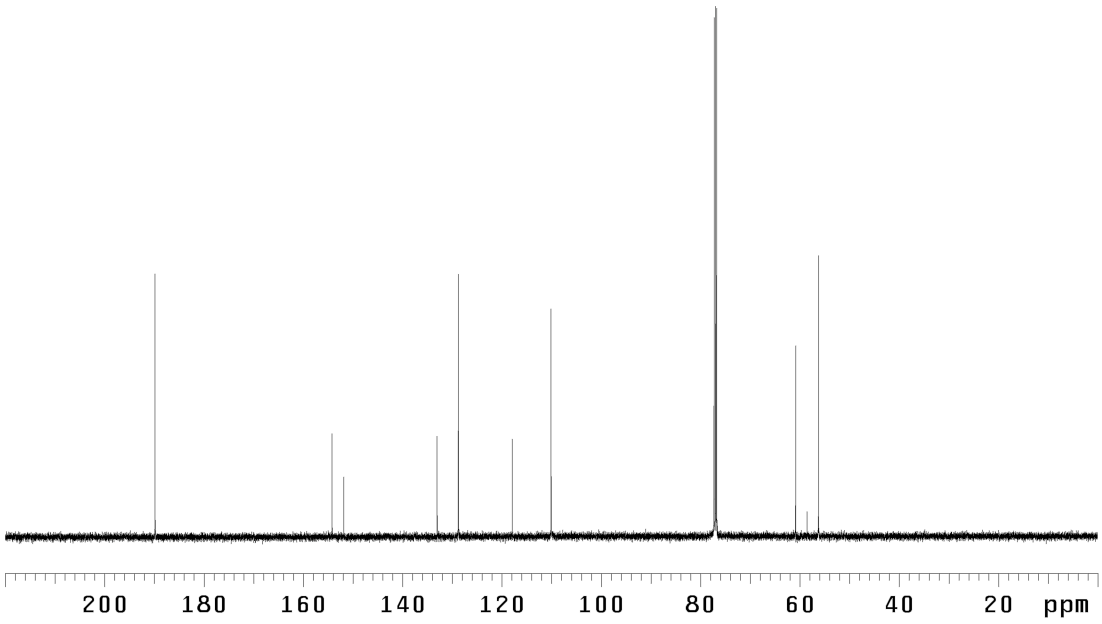


Figure 11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **29**.

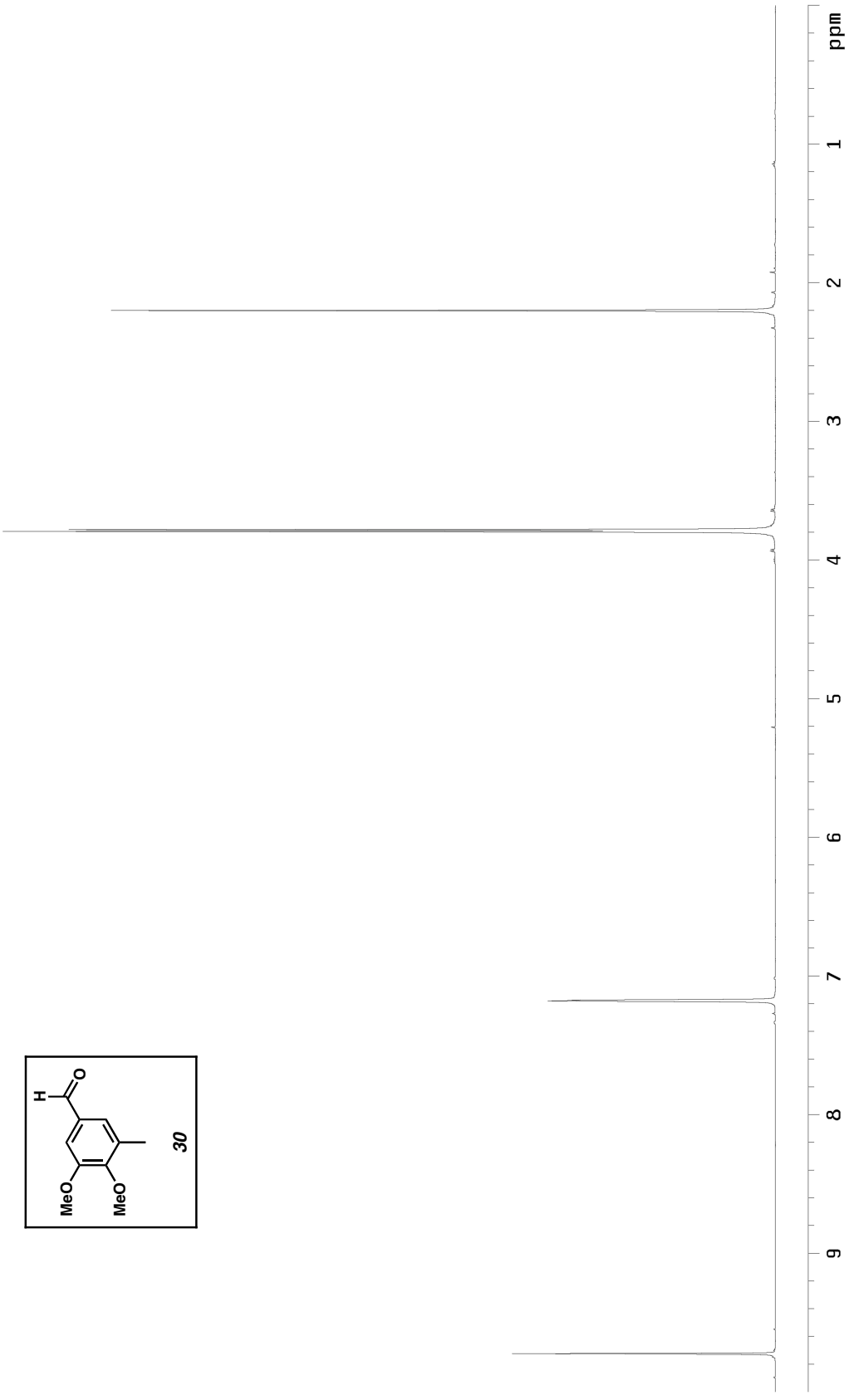


Figure 12.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **30**.

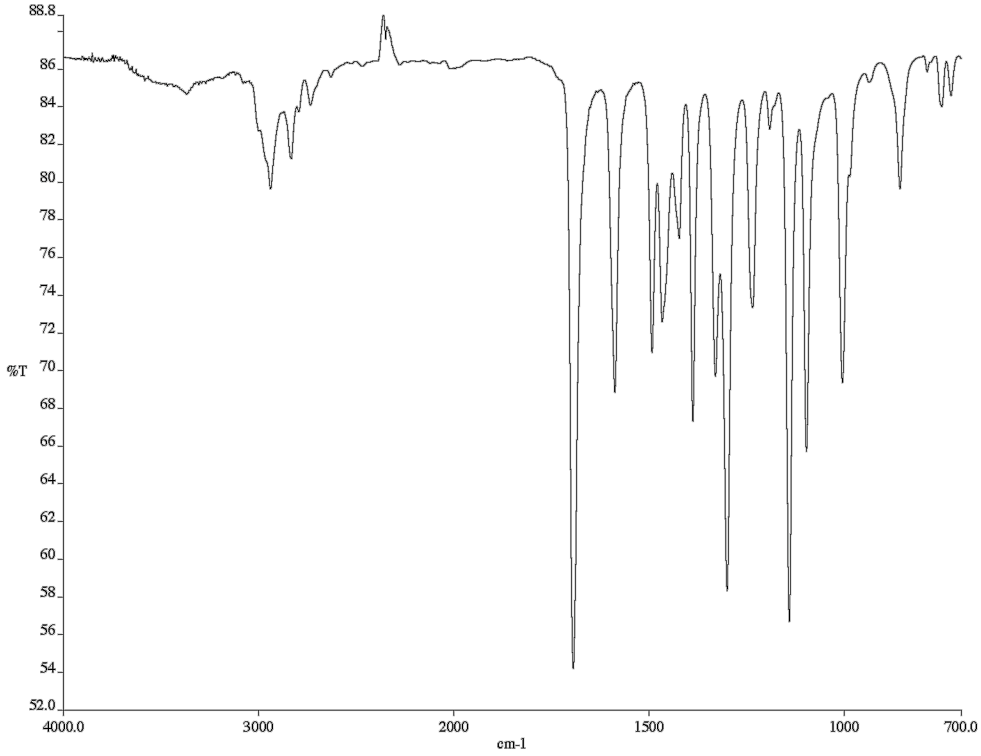


Figure 12.2 Infrared spectrum (thin film/NaCl) of compound **30**.

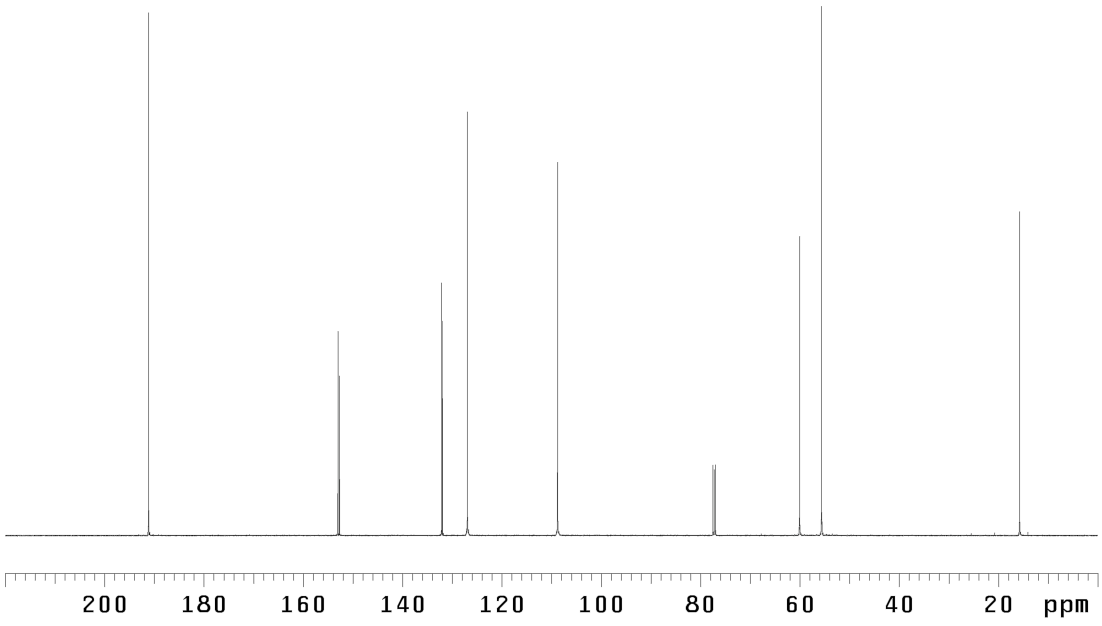


Figure 12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **30**.

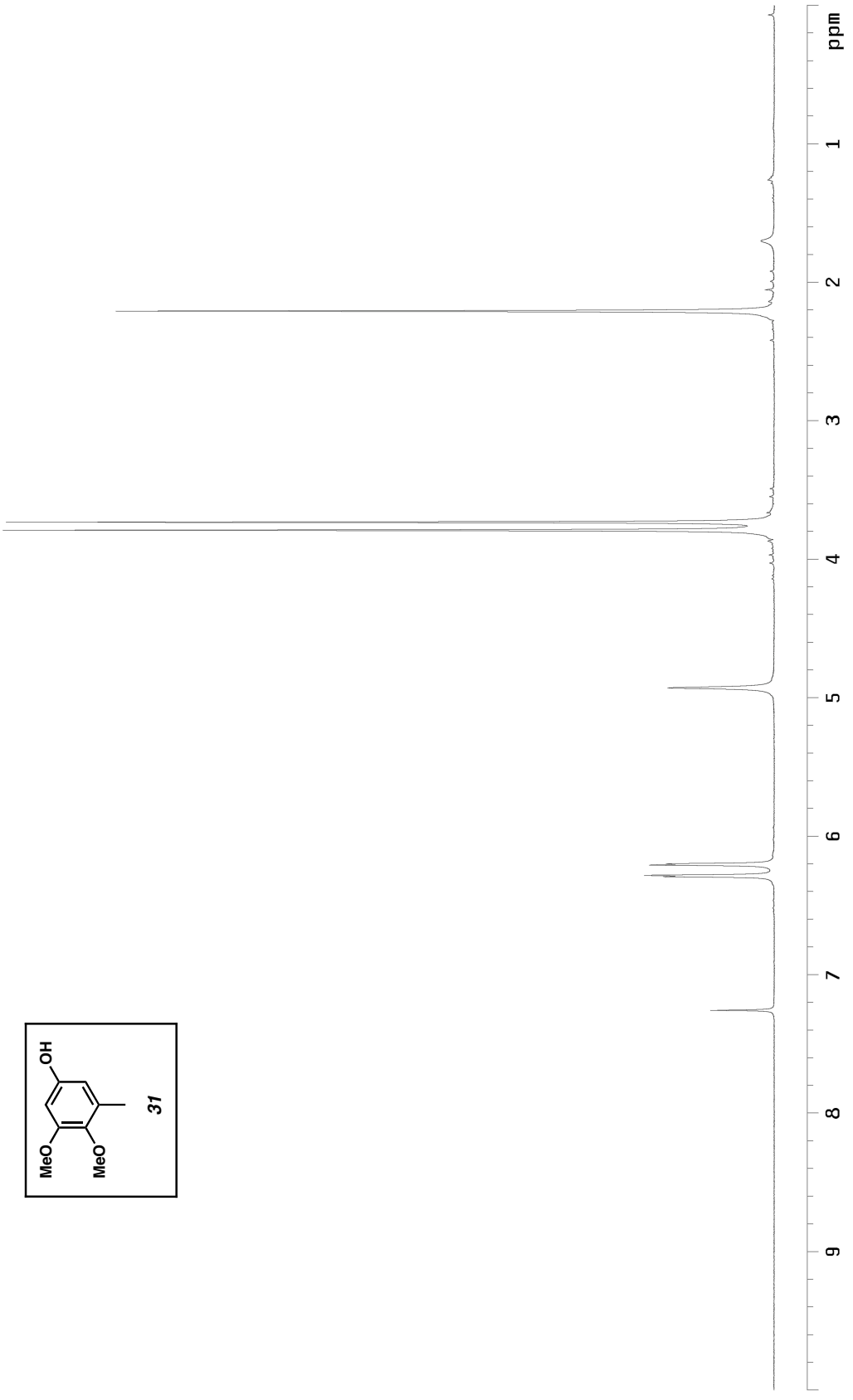


Figure 13.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **31**.

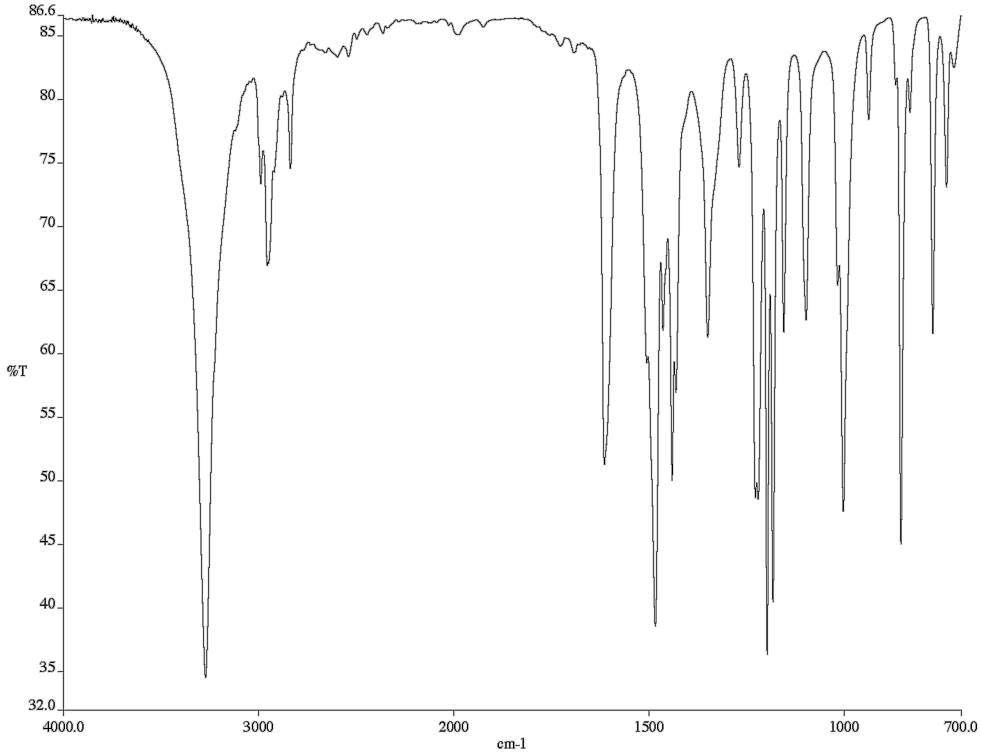


Figure 13.2 Infrared spectrum (thin film/NaCl) of compound **31**.

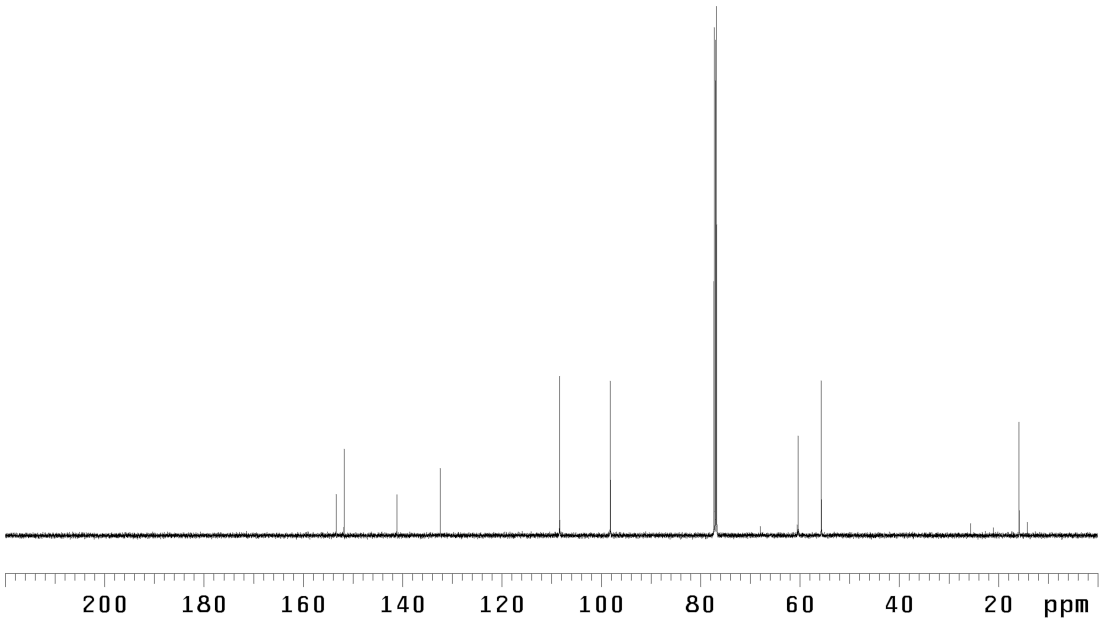


Figure 13.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **31**.

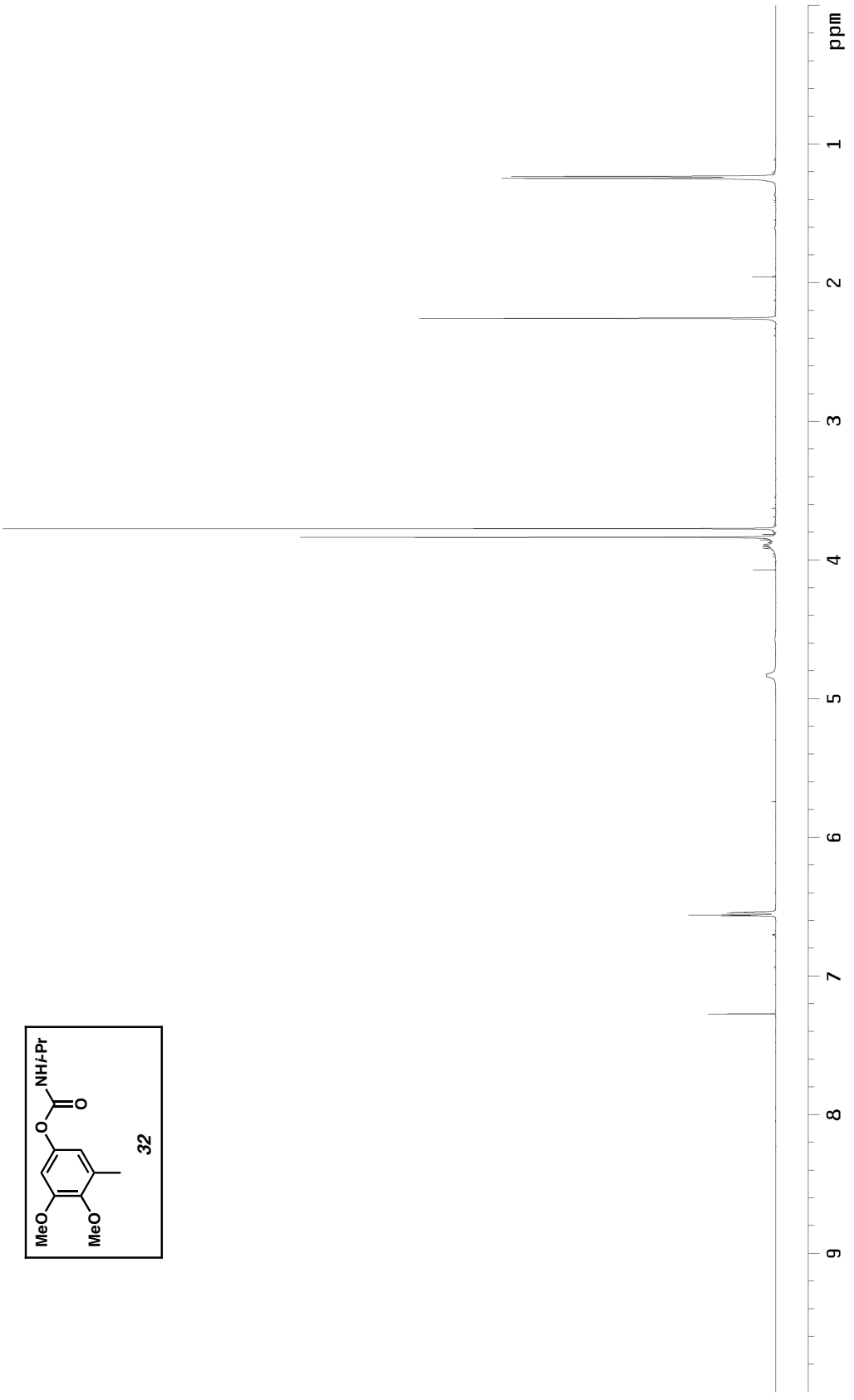


Figure 14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **32**.

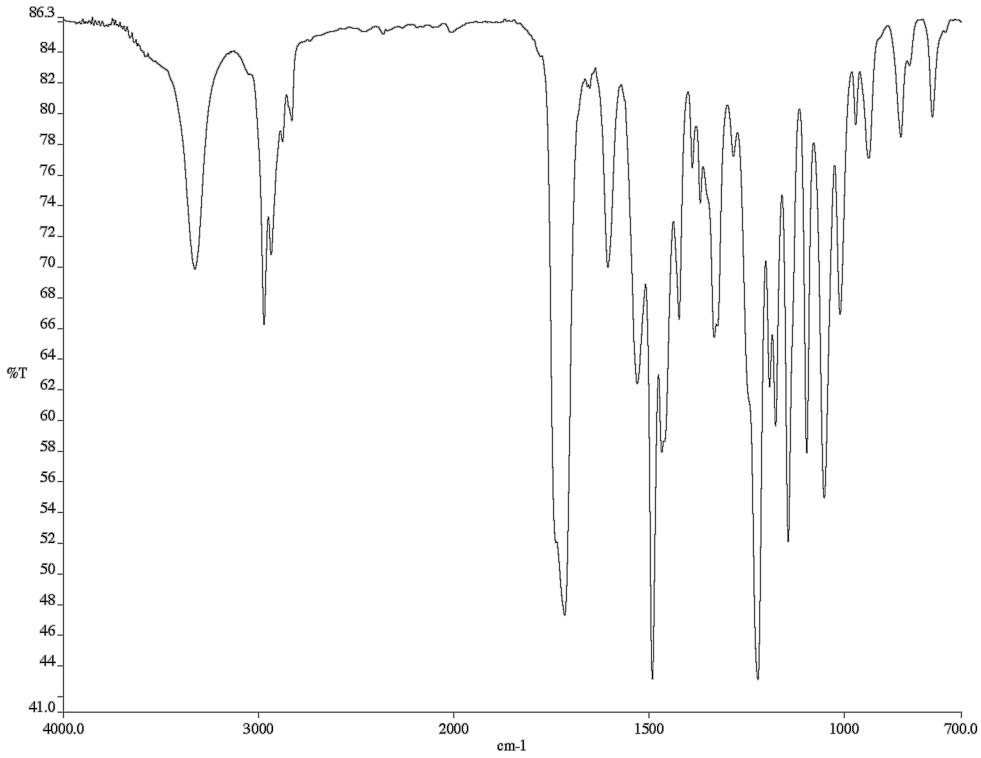


Figure 14.2 Infrared spectrum (thin film/NaCl) of compound **32**.

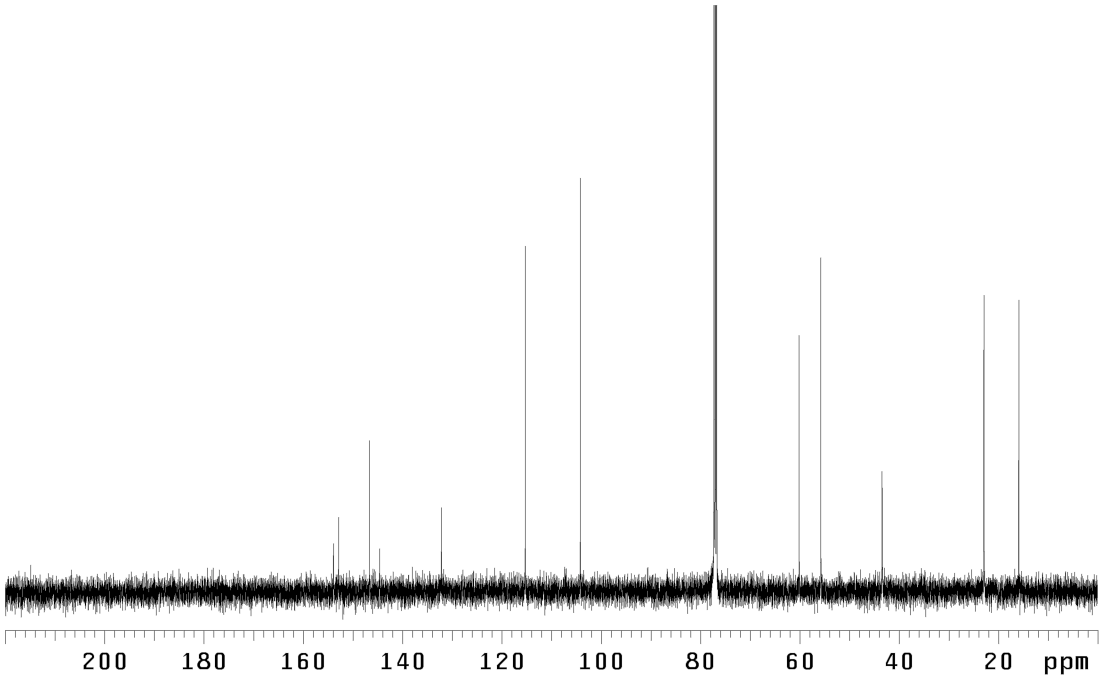


Figure 14.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **32**.

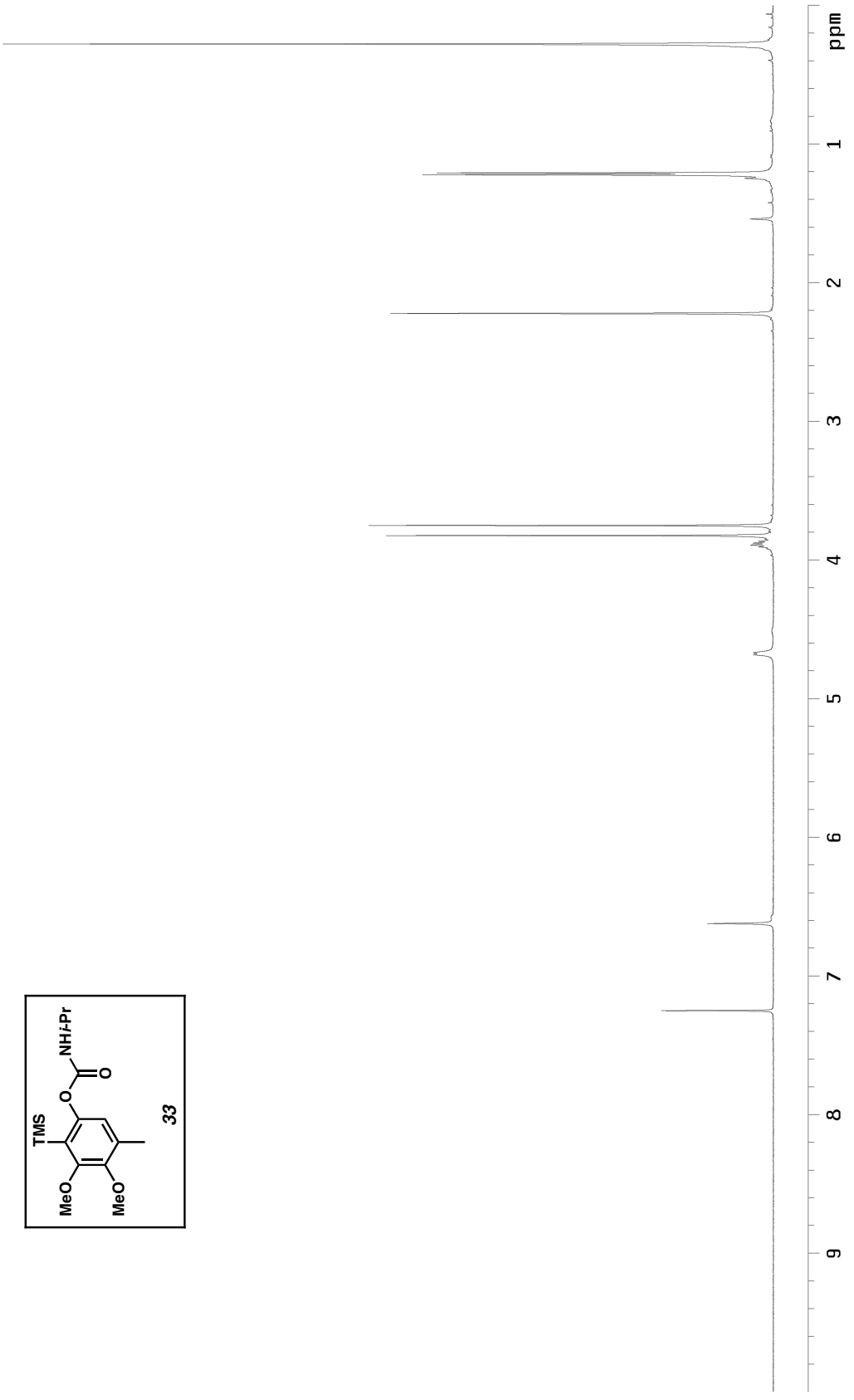


Figure 15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **33**.

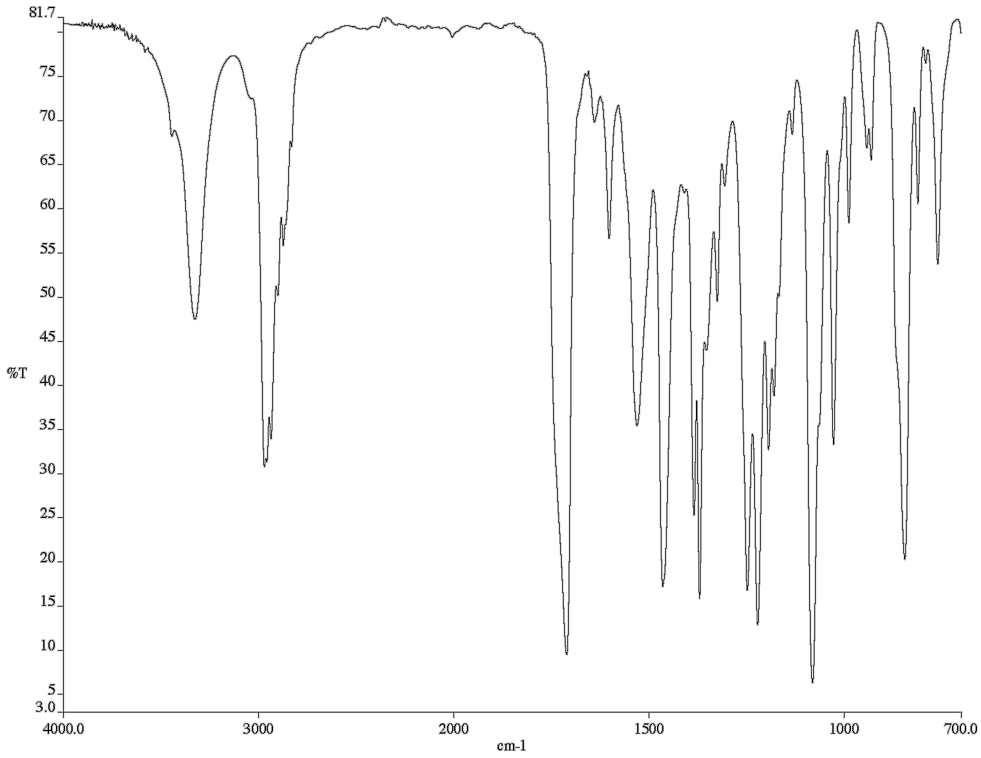


Figure 15.2 Infrared spectrum (thin film/NaCl) of compound **33**.

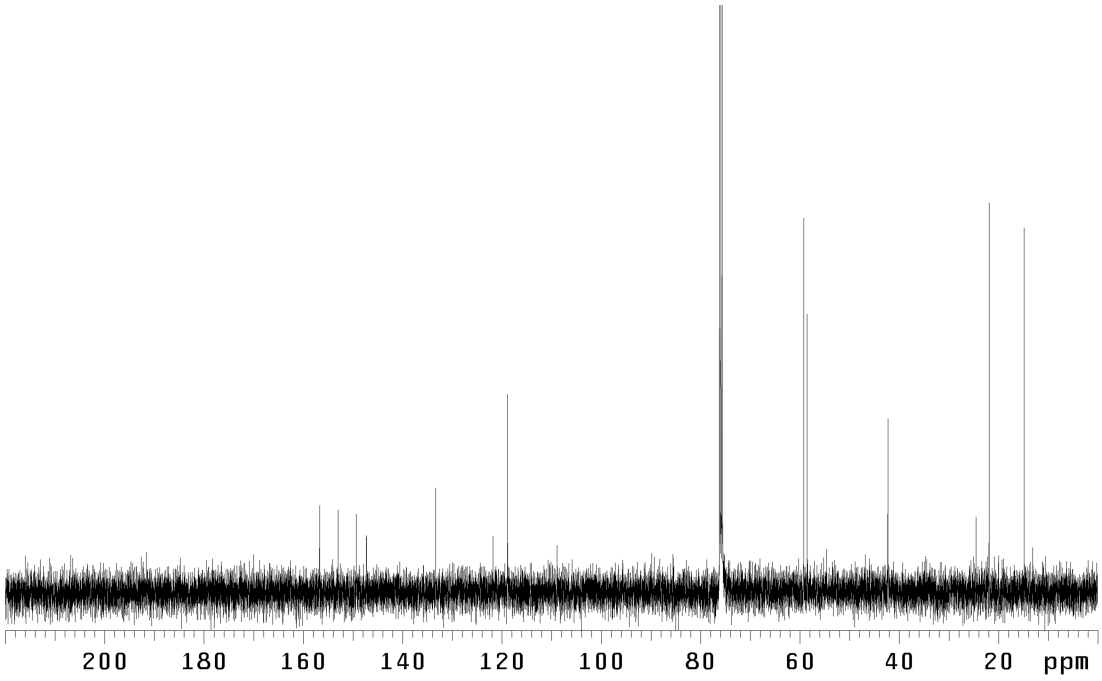


Figure 15.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **33**.

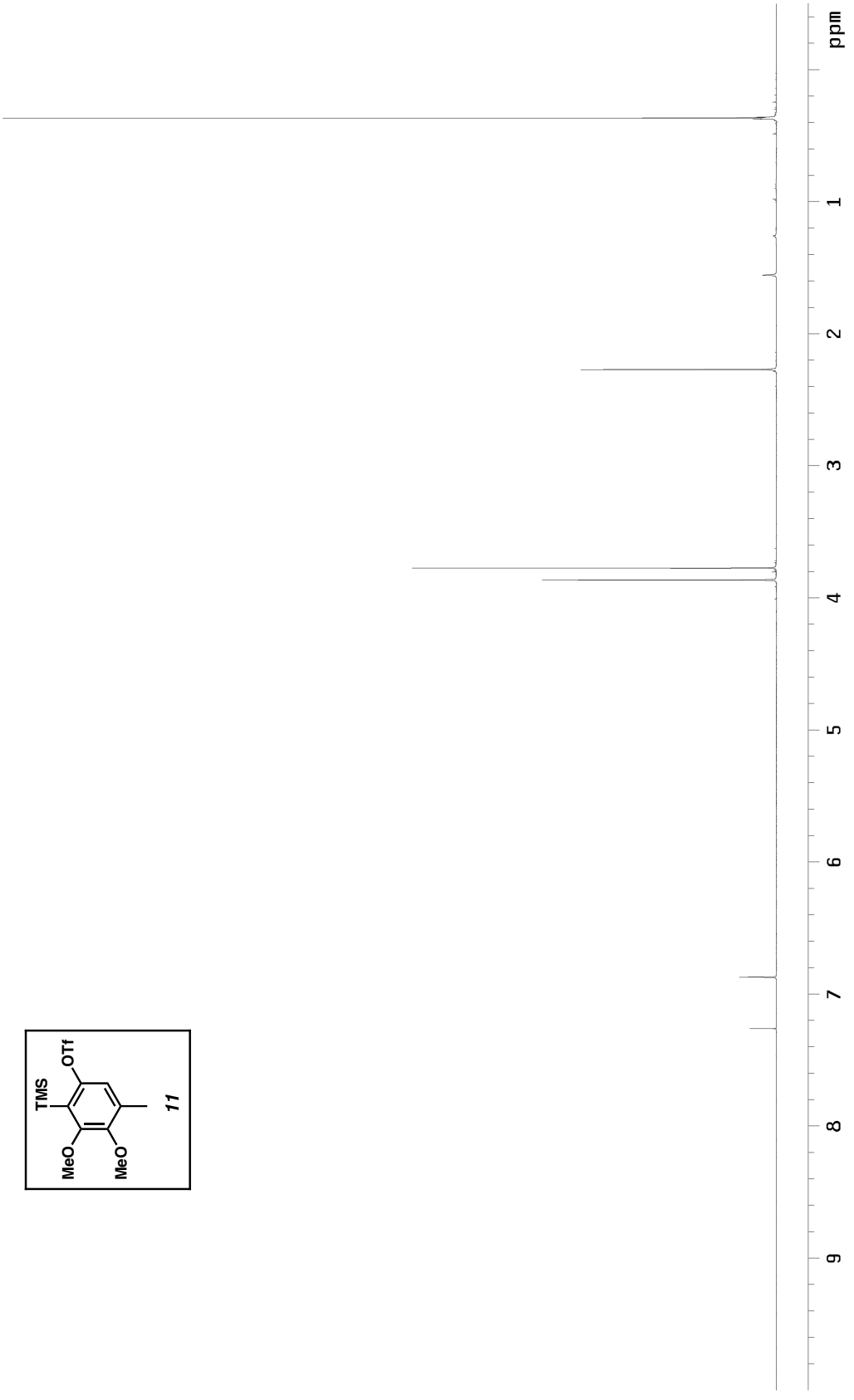


Figure 16.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **11**.

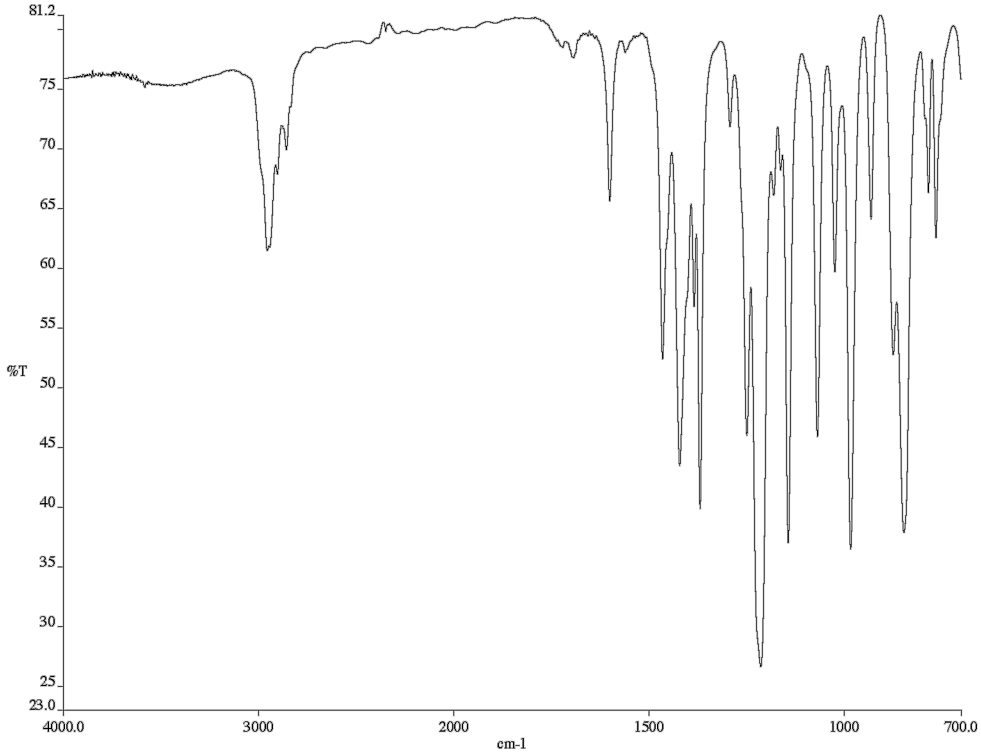


Figure 16.2 Infrared spectrum (thin film/NaCl) of compound **11**.

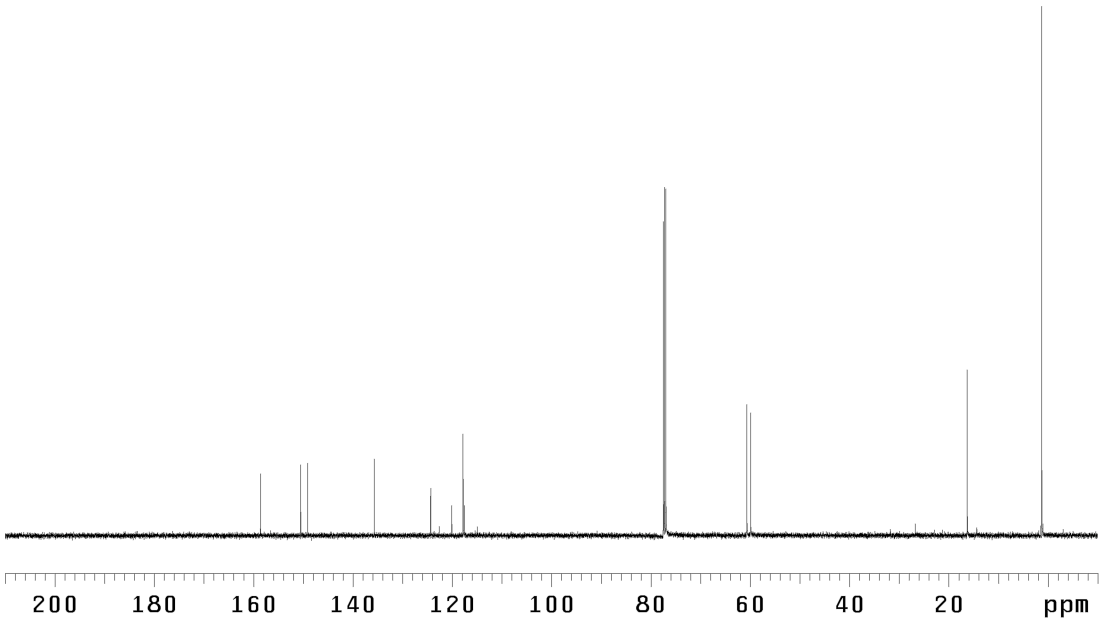


Figure 16.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **11**.

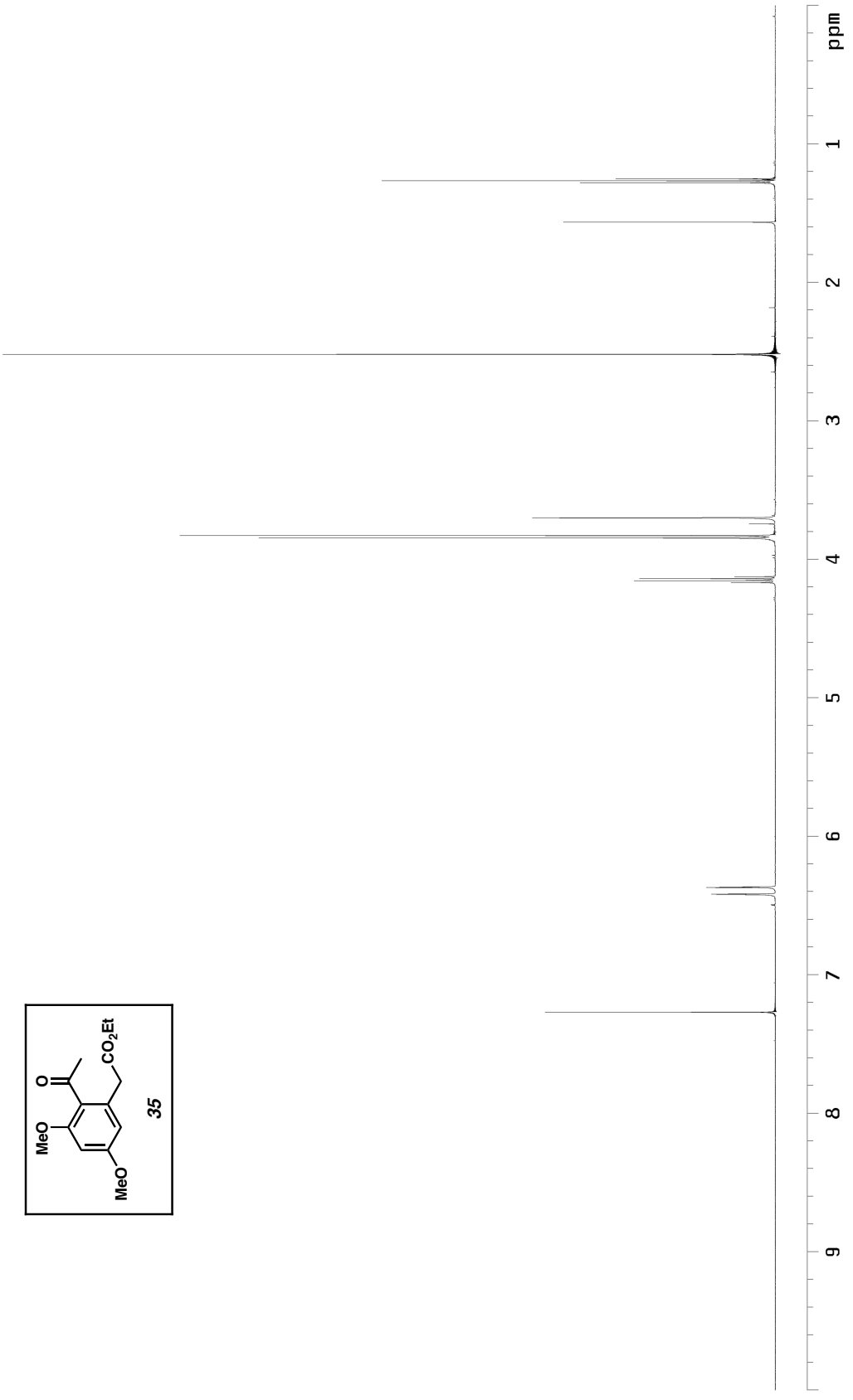


Figure 17.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **35**.

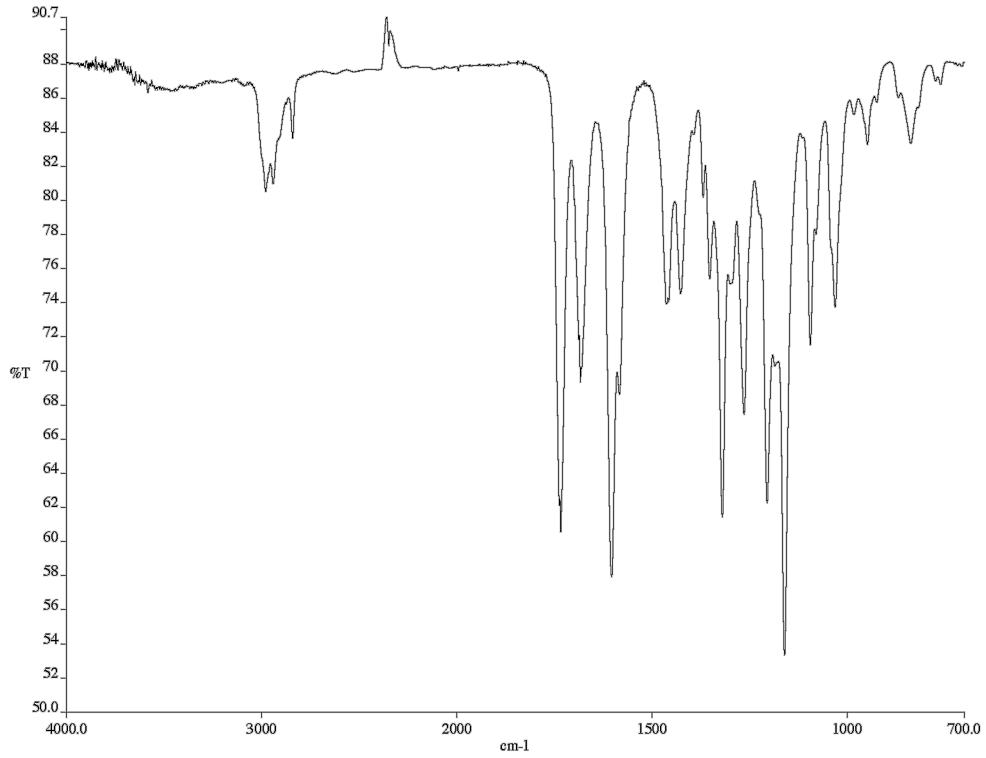


Figure 17.2 Infrared spectrum (thin film/NaCl) of compound **35**.

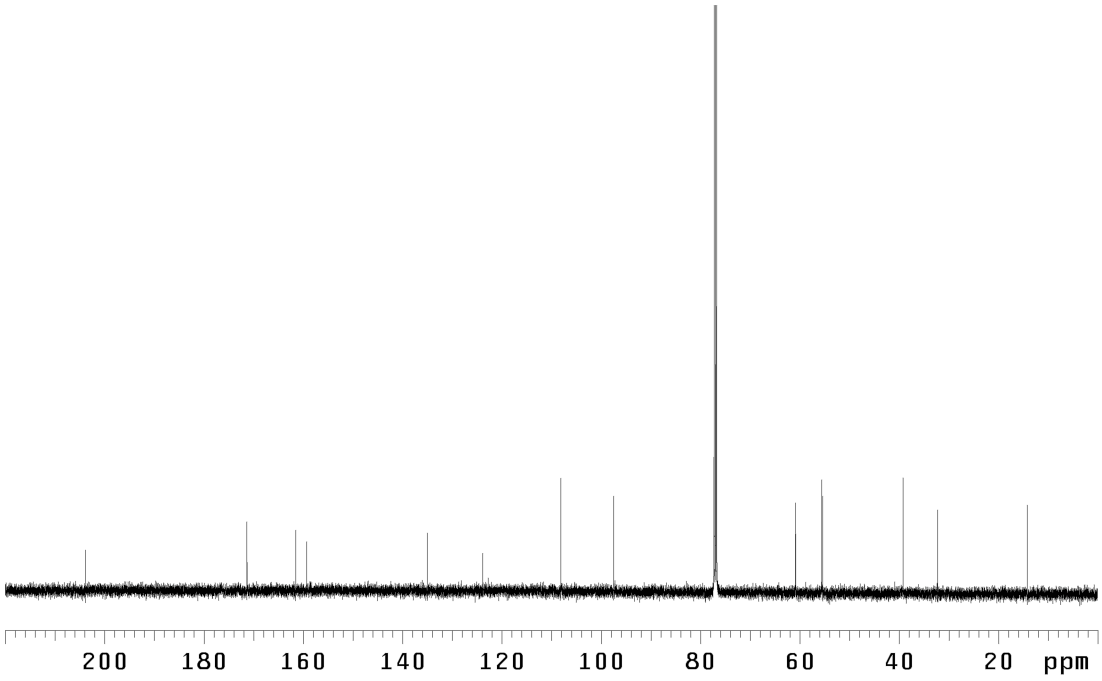


Figure 17.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **35**.

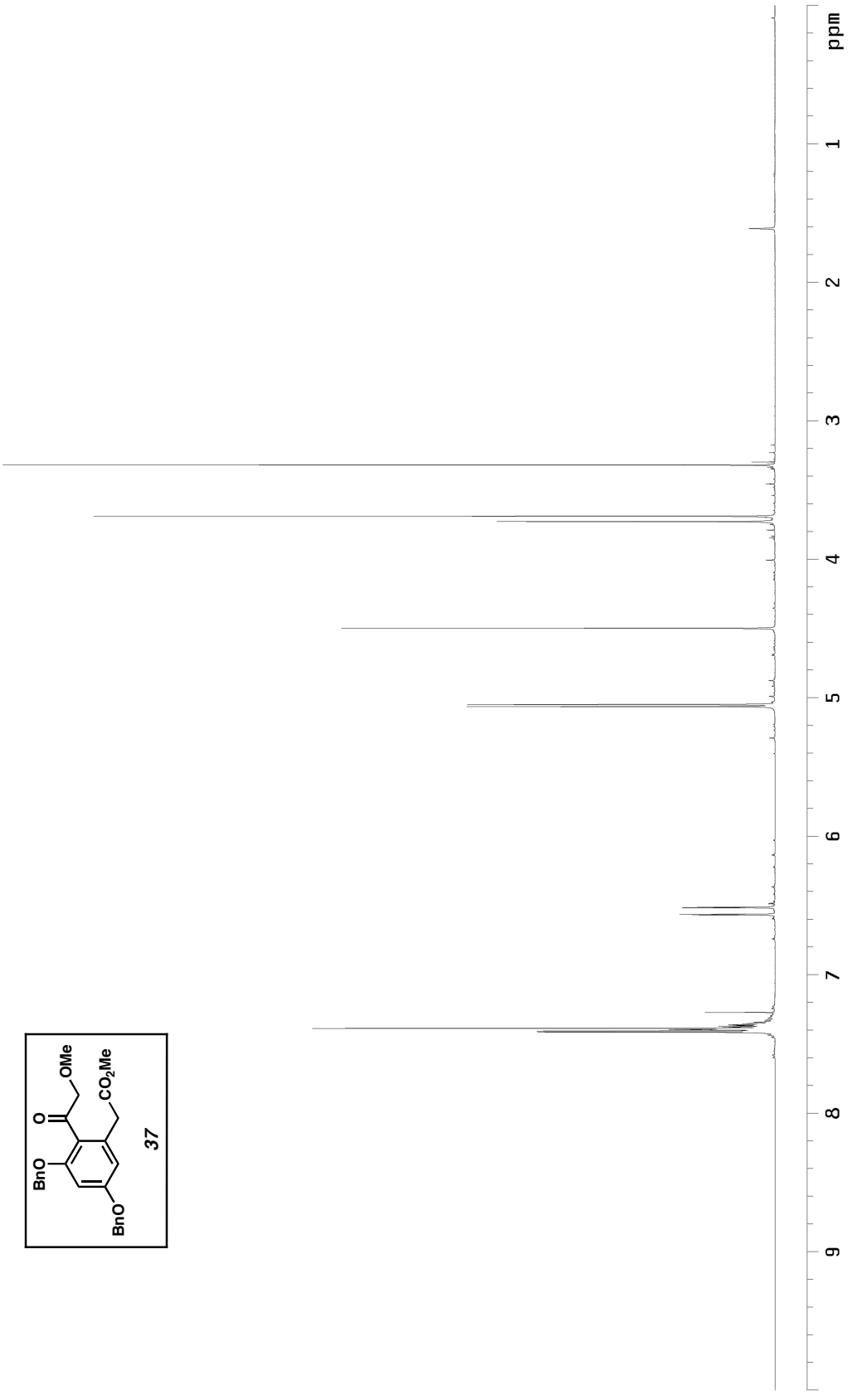


Figure 18.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **37**.

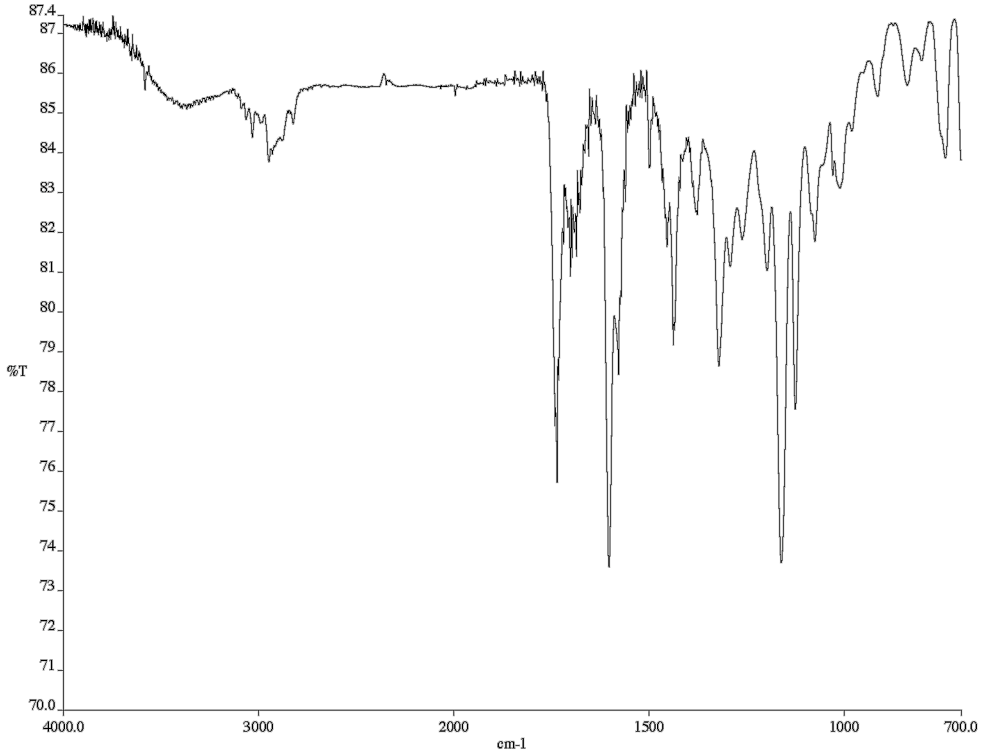


Figure 18.2 Infrared spectrum (thin film/NaCl) of compound **37**.

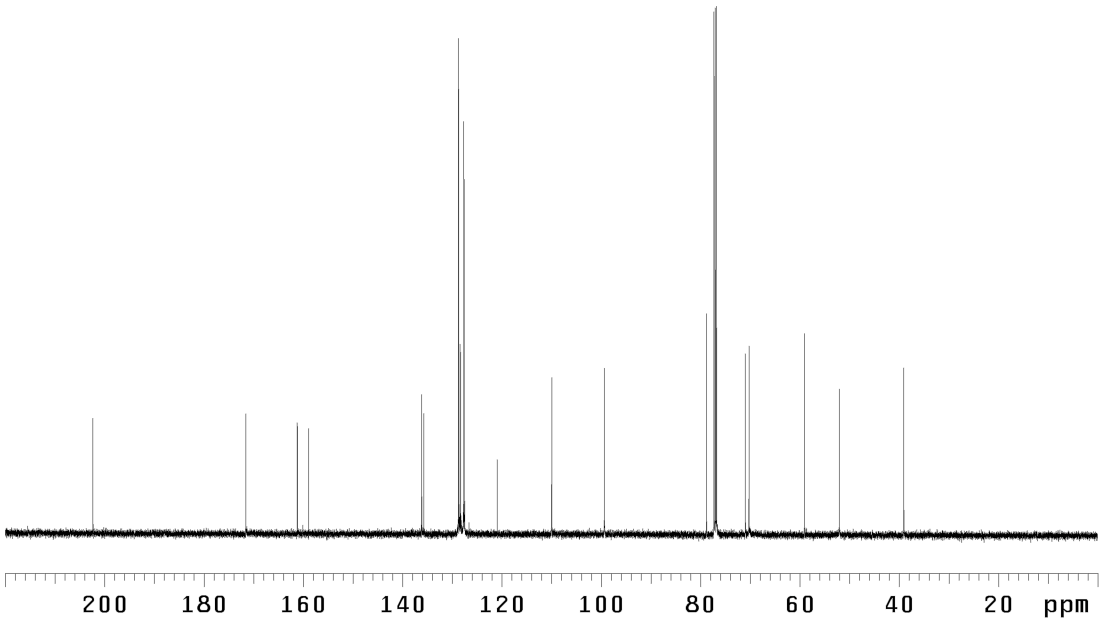


Figure 18.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **37**.

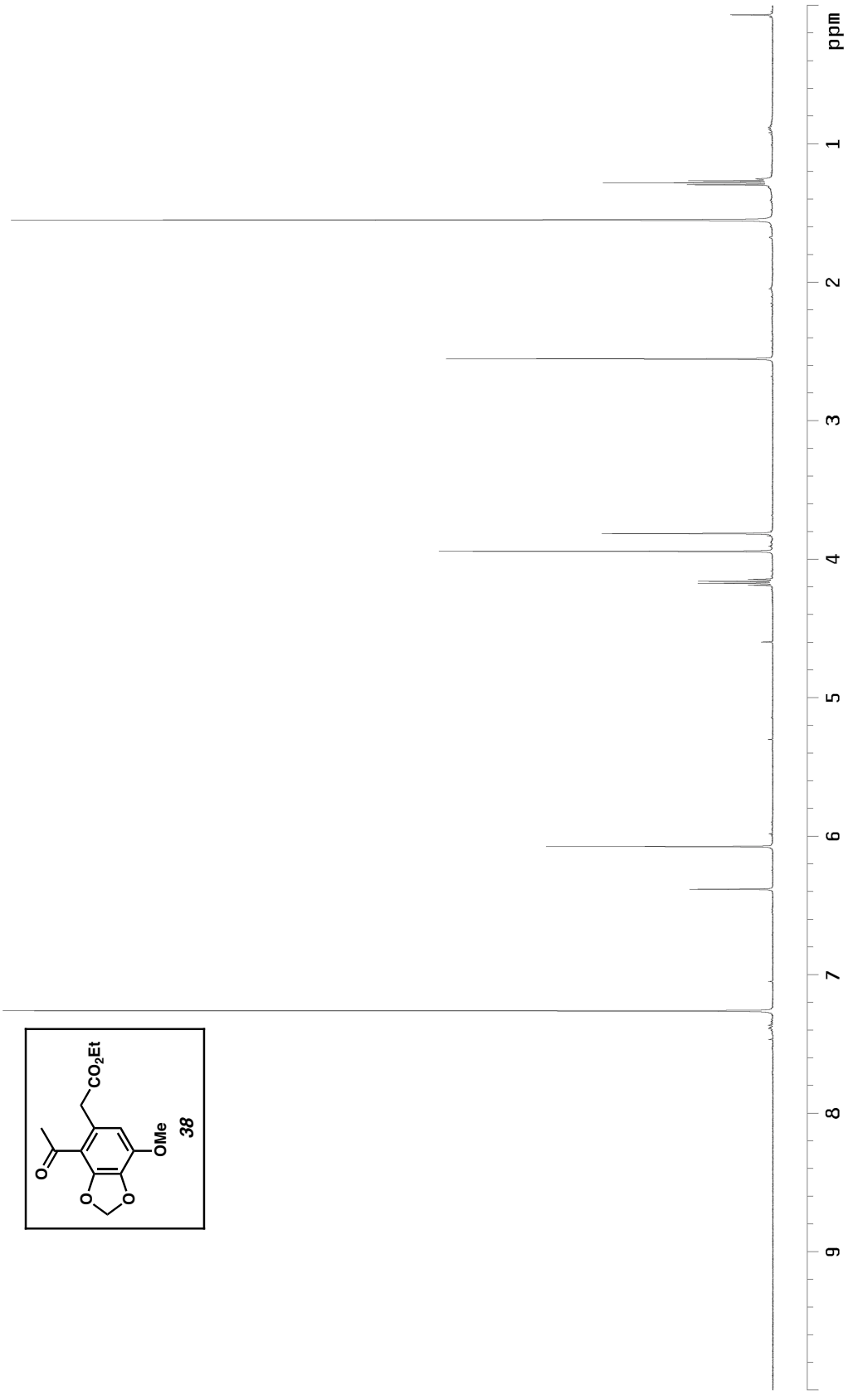


Figure 19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **38**.

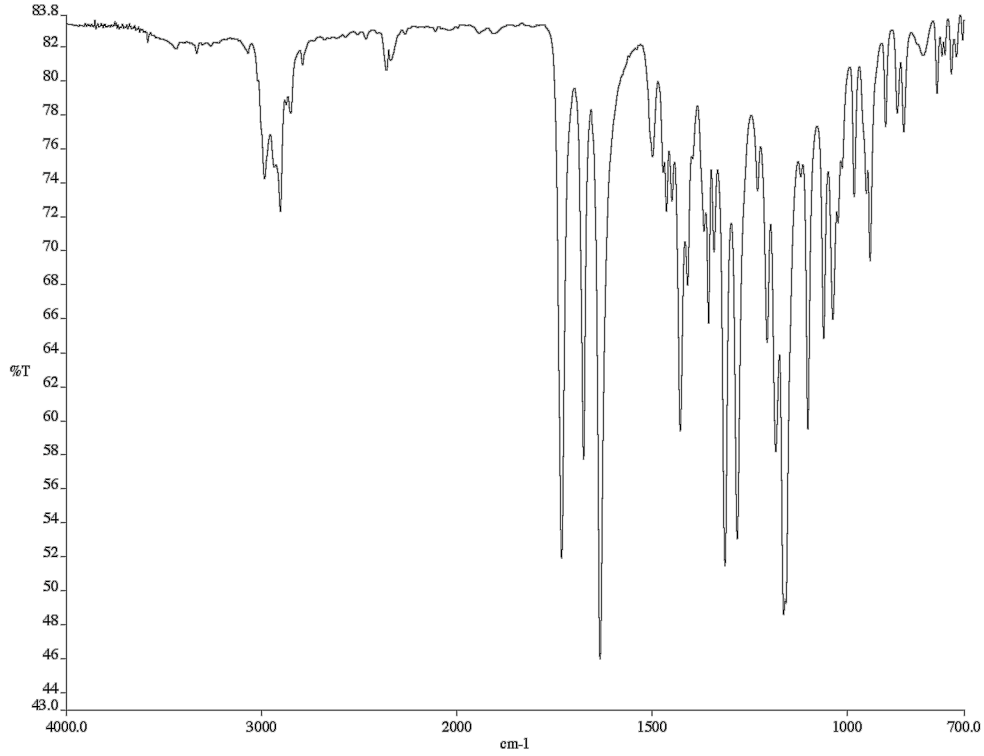


Figure 19.2 Infrared spectrum (thin film/NaCl) of compound **38**.

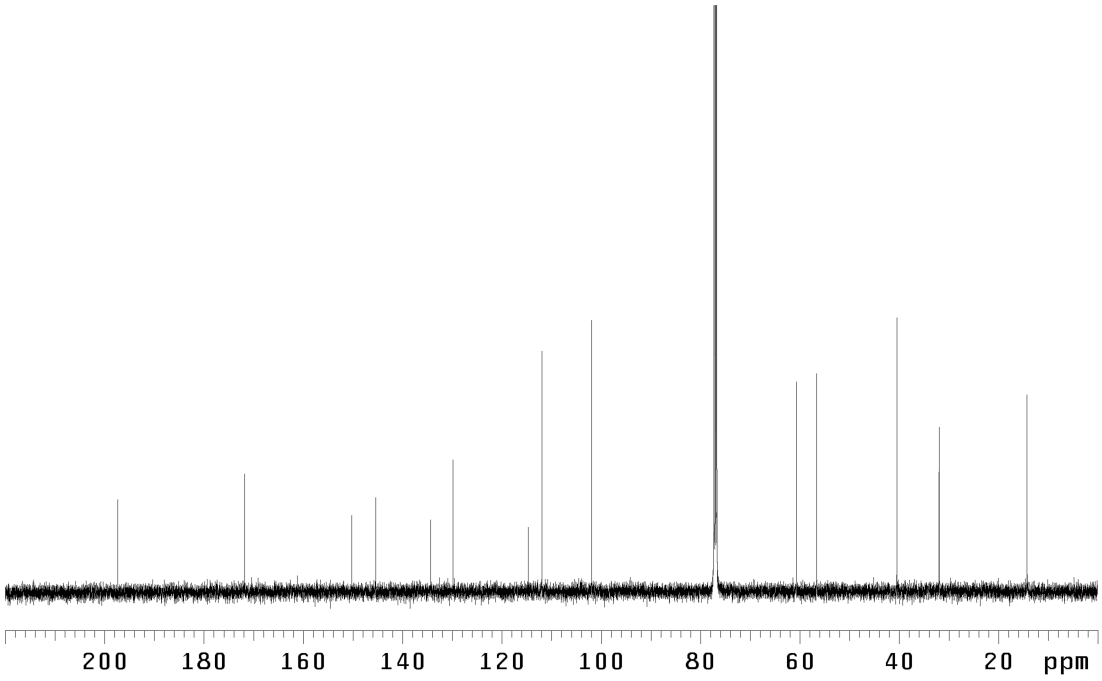


Figure 19.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **38**.

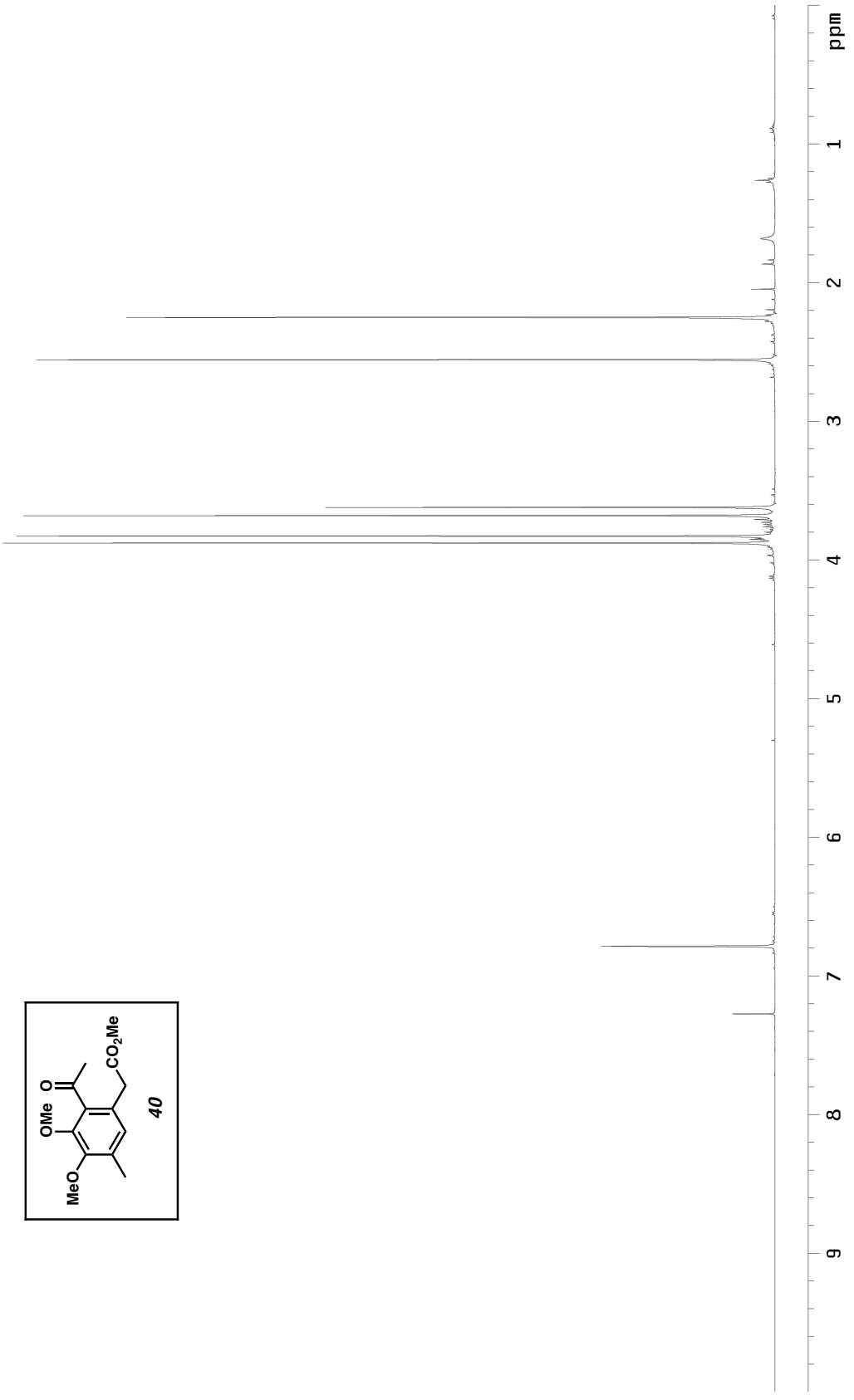


Figure 20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40**.

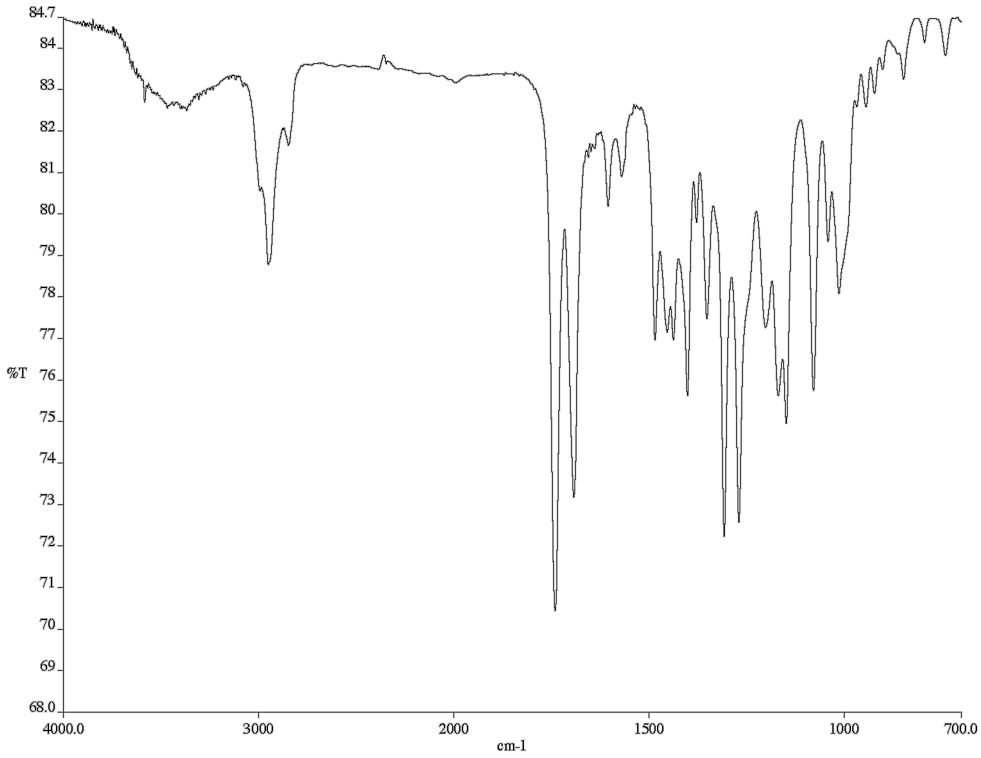


Figure 20.2 Infrared spectrum (thin film/NaCl) of compound **40**.

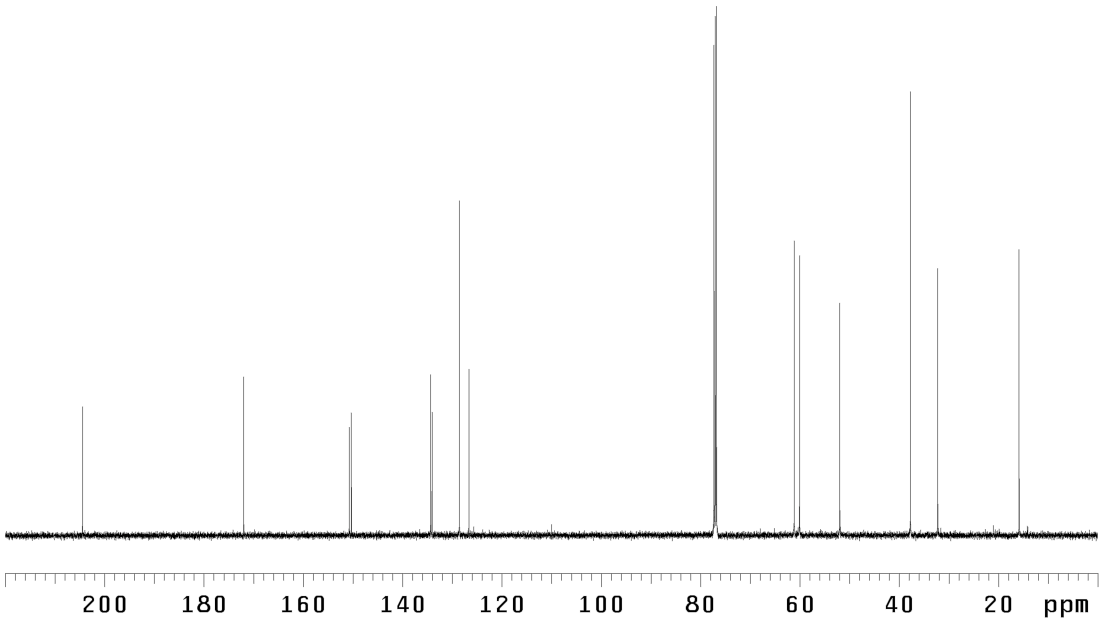


Figure 20.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **40**.

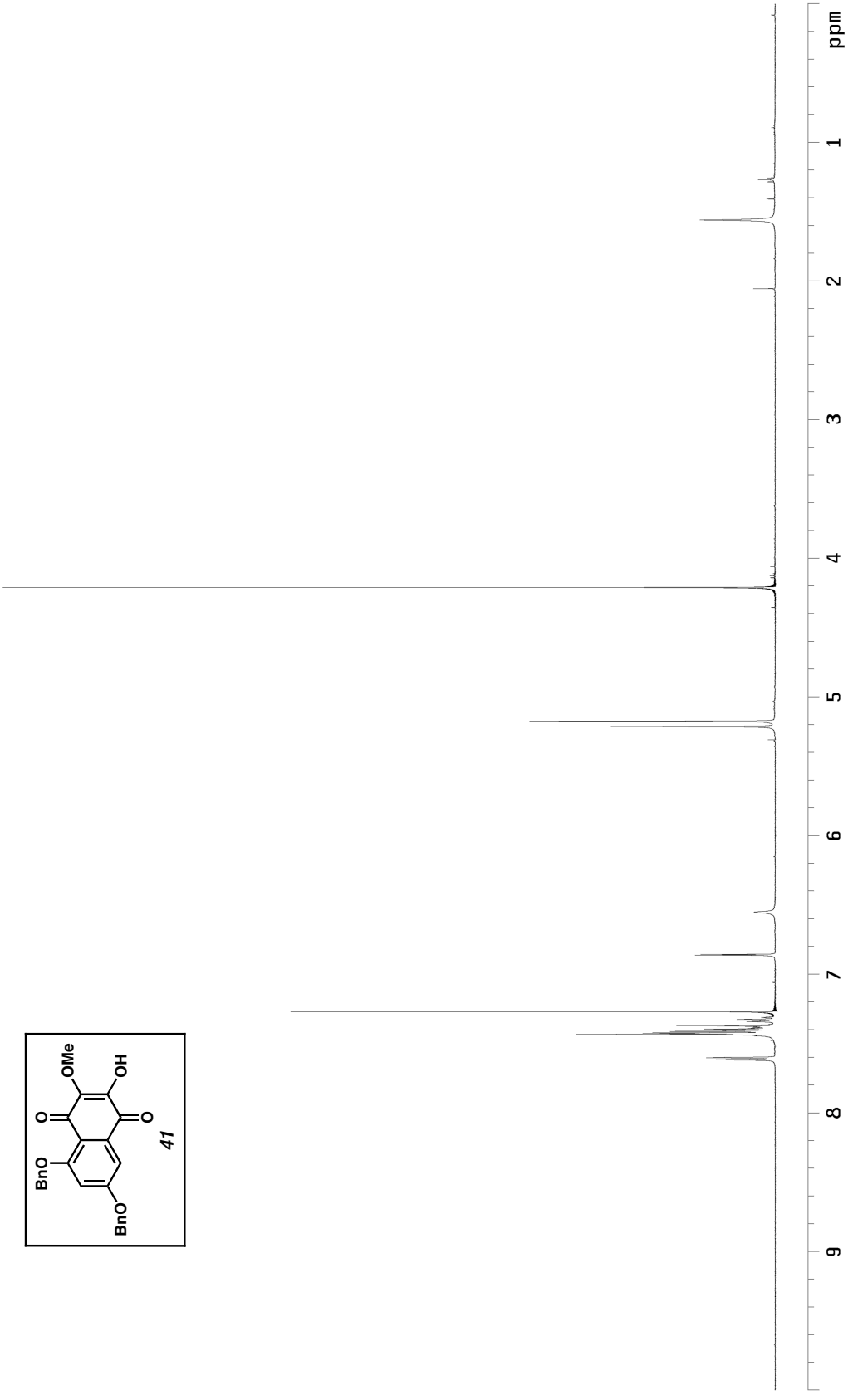


Figure 21.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **41**.

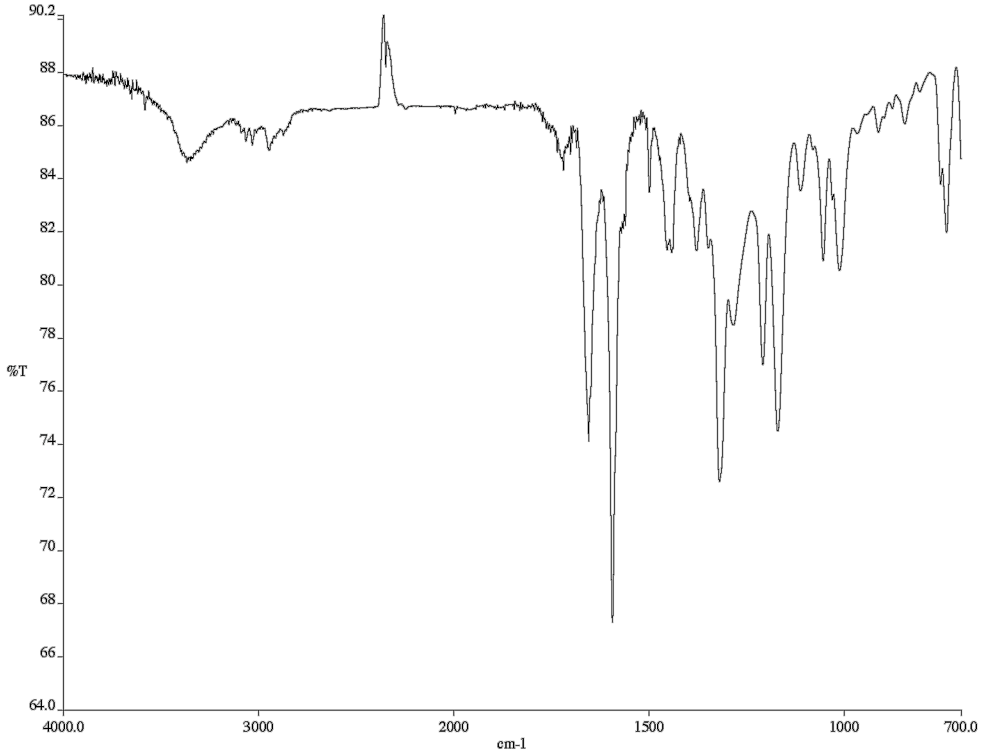


Figure 21.2 Infrared spectrum (thin film/NaCl) of compound **41**.

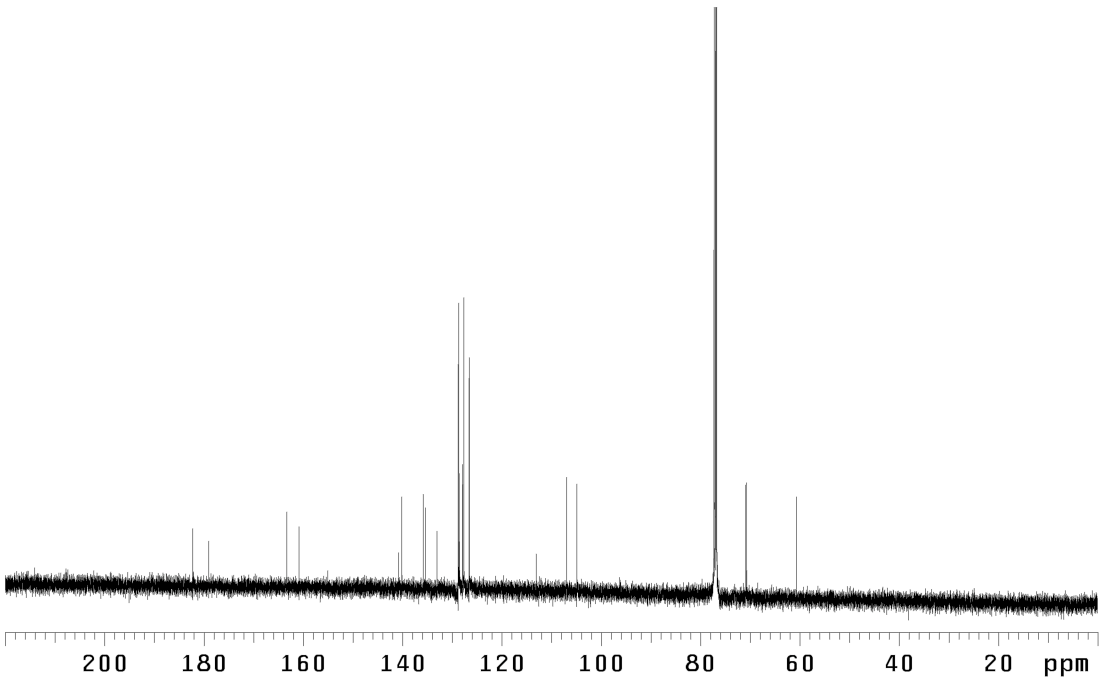


Figure 21.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **41**.

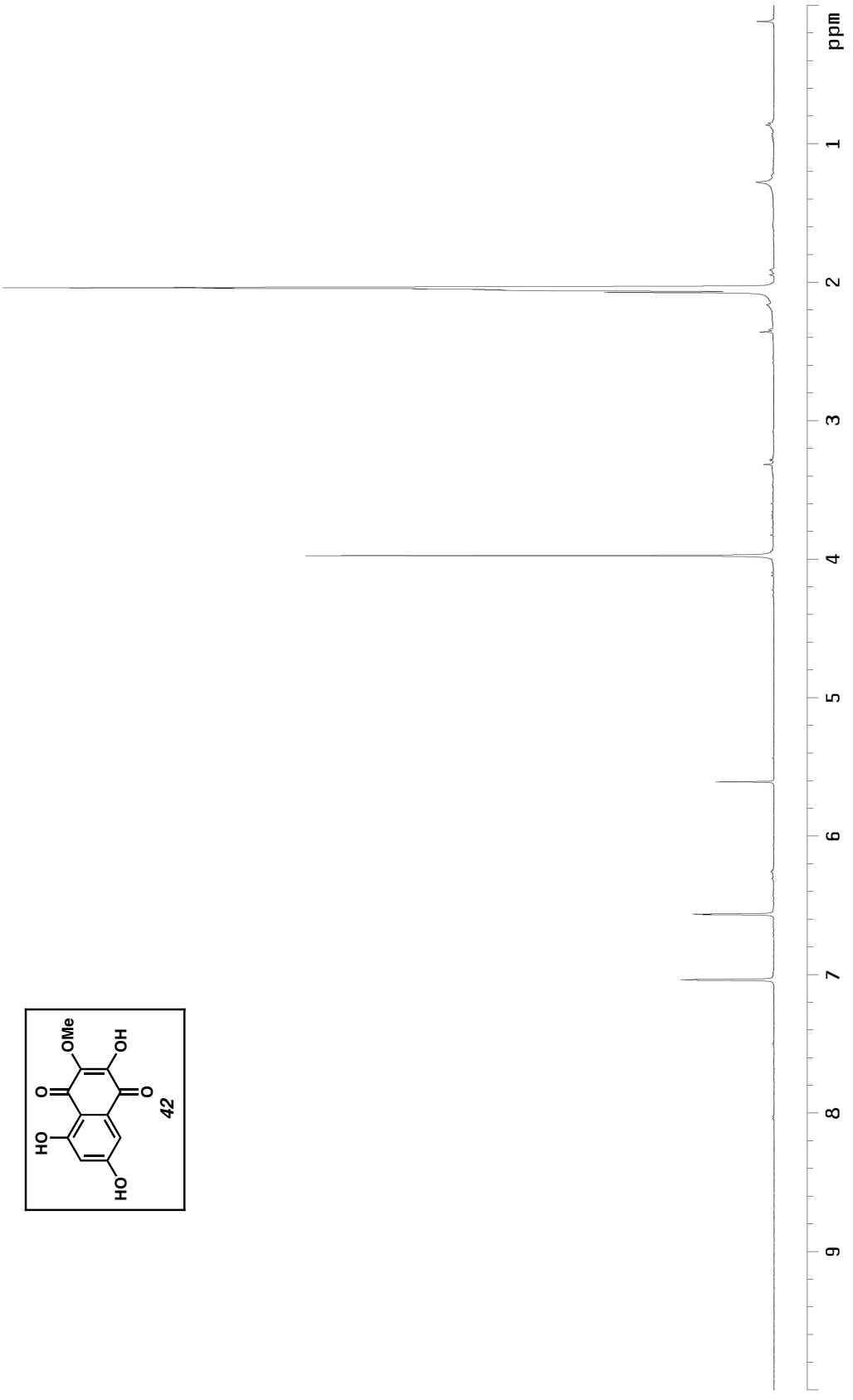


Figure 22.1 ^{1}H NMR (500 MHz, acetone-d_6) of compound **42**.

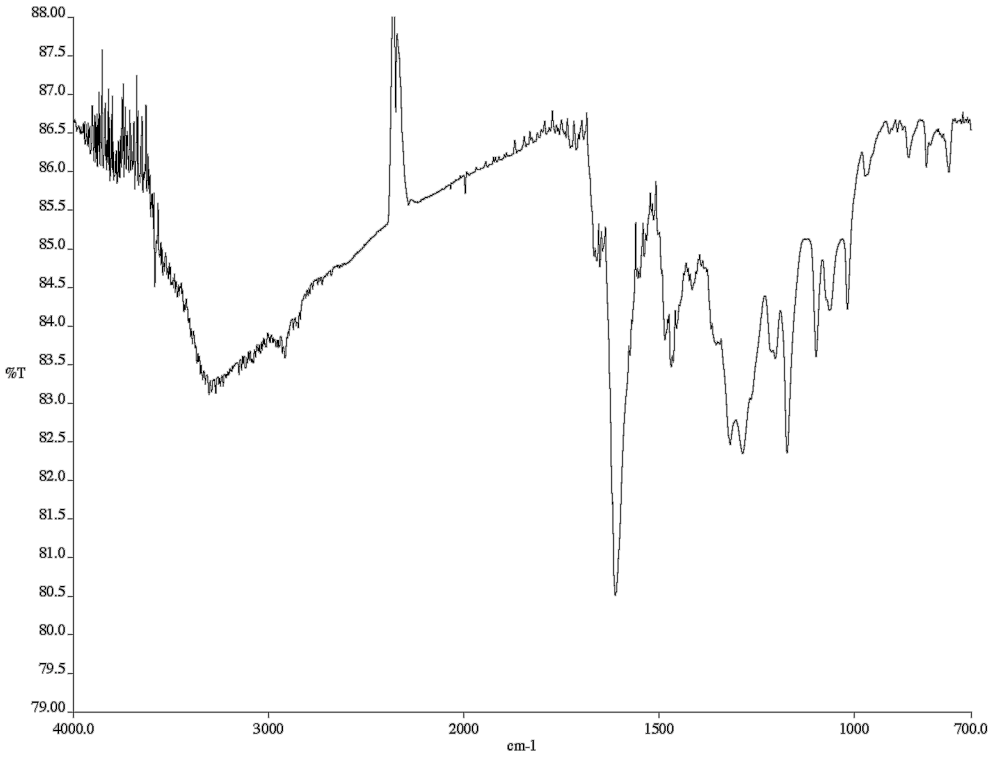


Figure 22.2 Infrared spectrum (thin film/NaCl) of compound **42**.

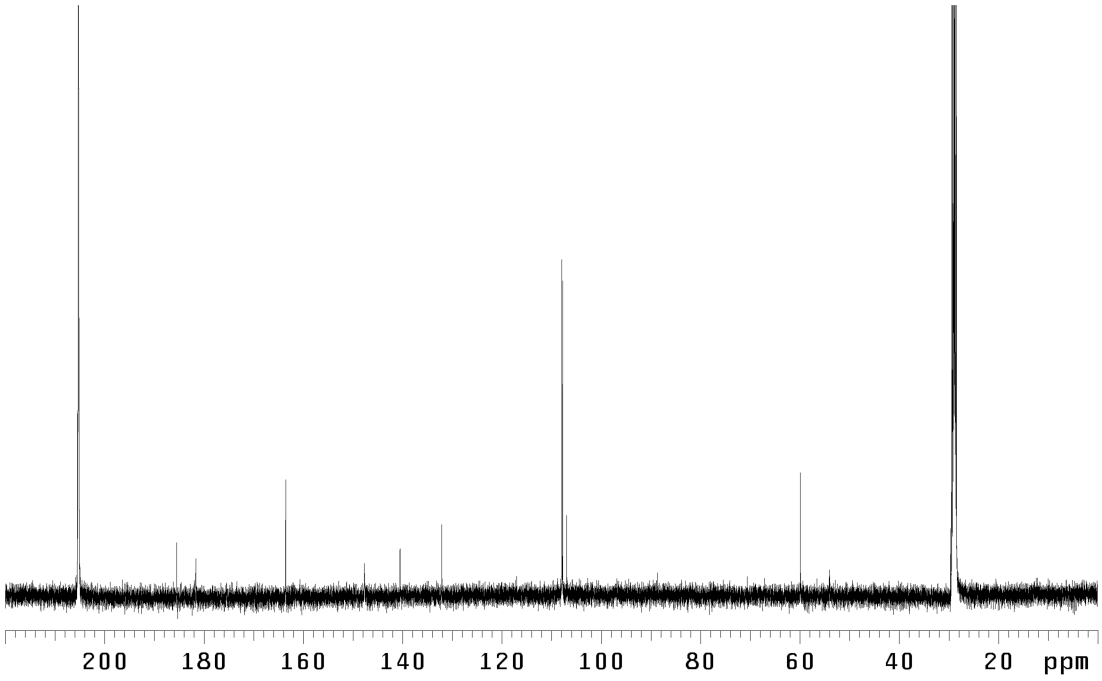


Figure 22.3 ^{13}C NMR (125 MHz, acetone-d_6) of compound **42**.

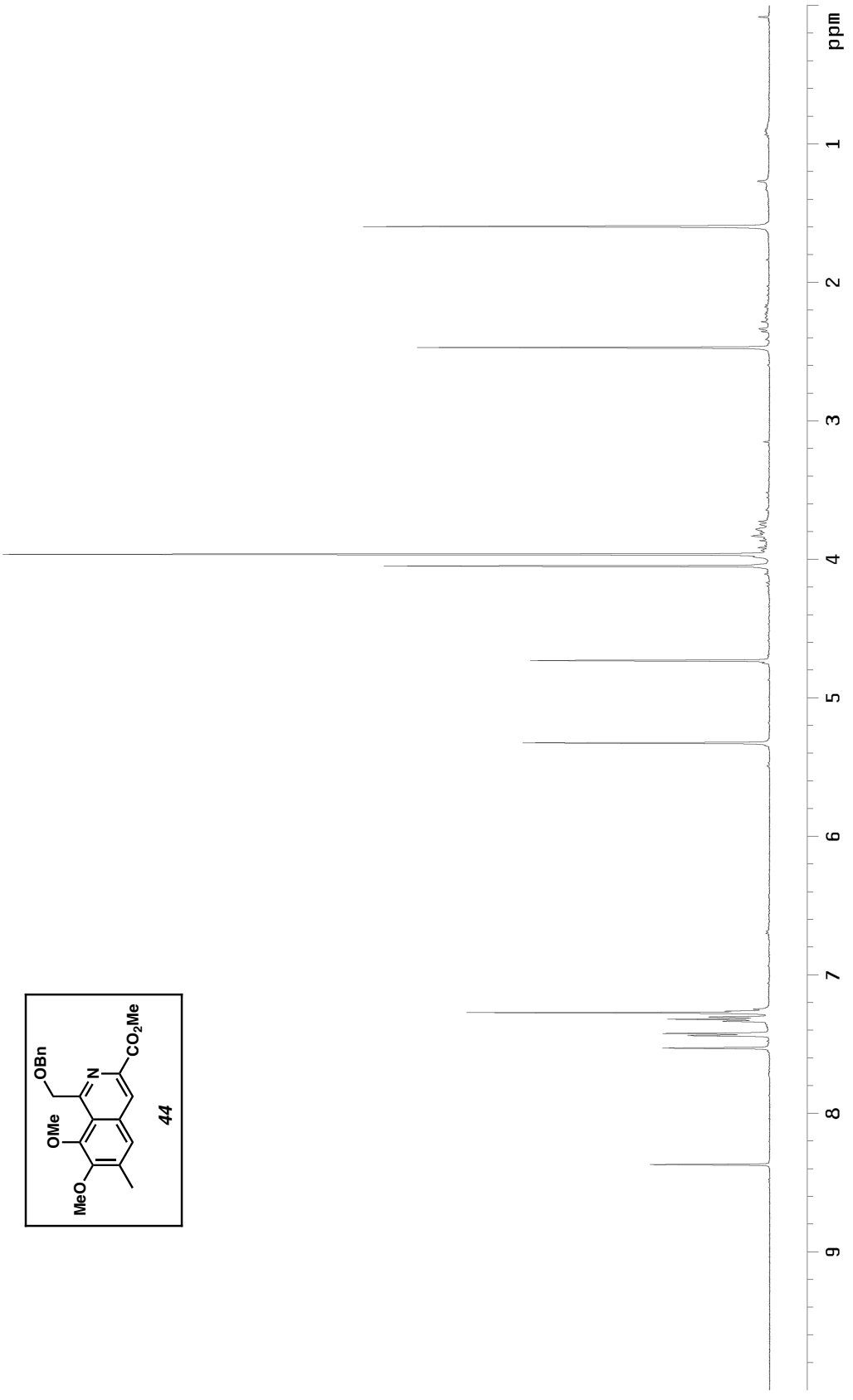


Figure 23.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **44**.

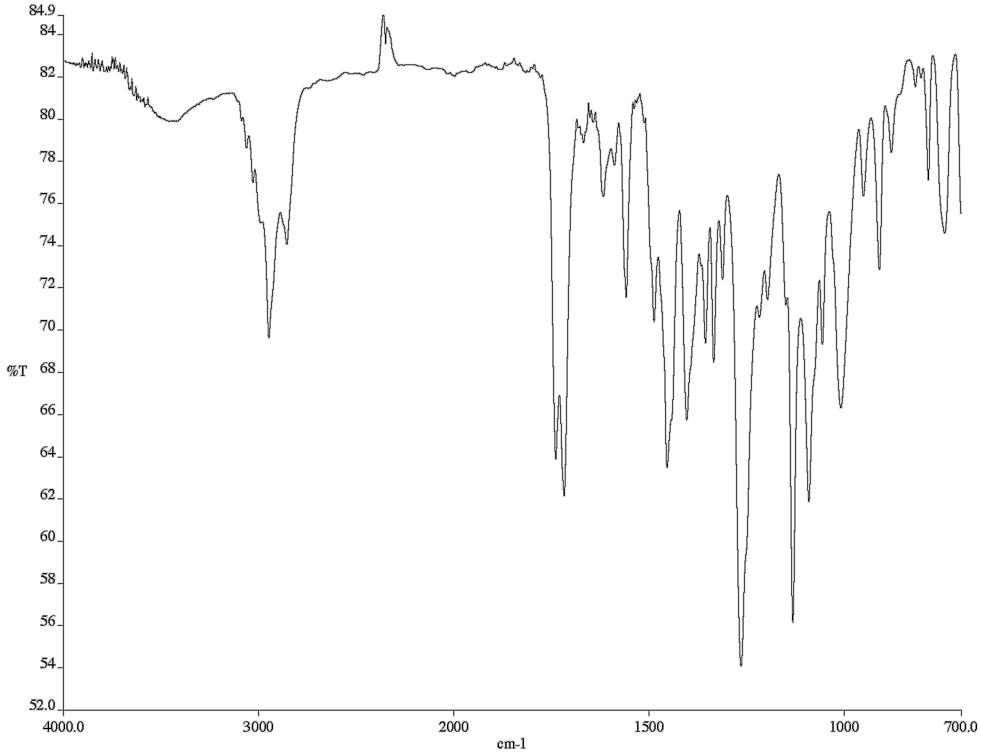


Figure 23.2 Infrared spectrum (thin film/NaCl) of compound **44**.

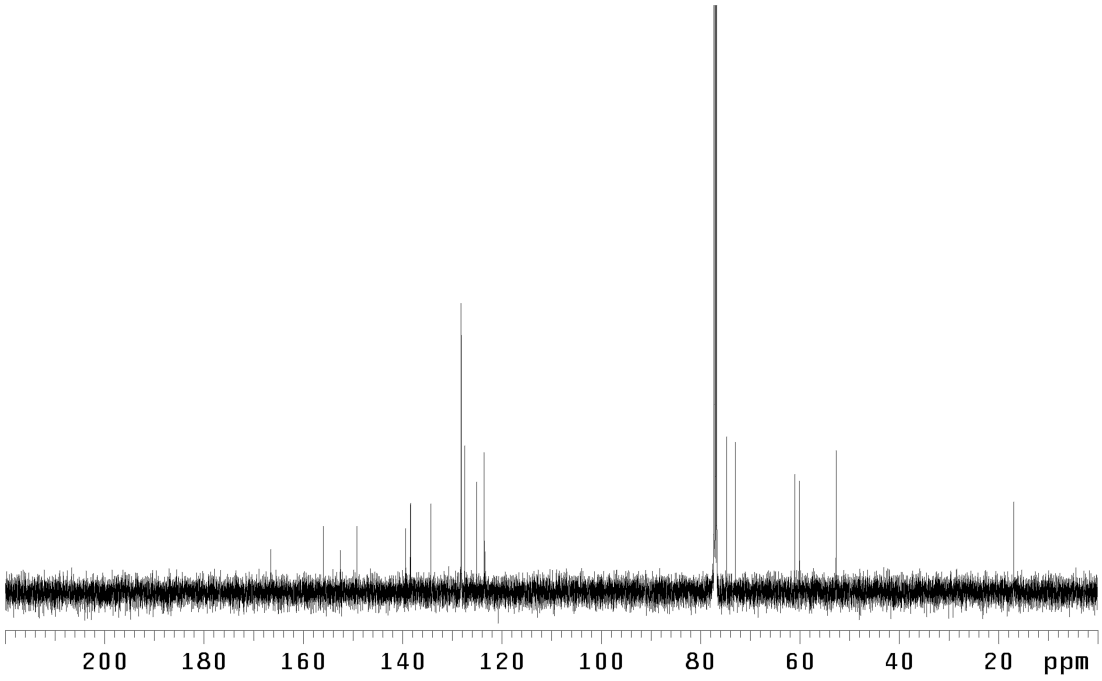


Figure 23.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **44**.