Supplementary Information

Manganese-Catalyzed Intermolecular C–H/C–H Coupling of Carbonyls and Heteroarenes

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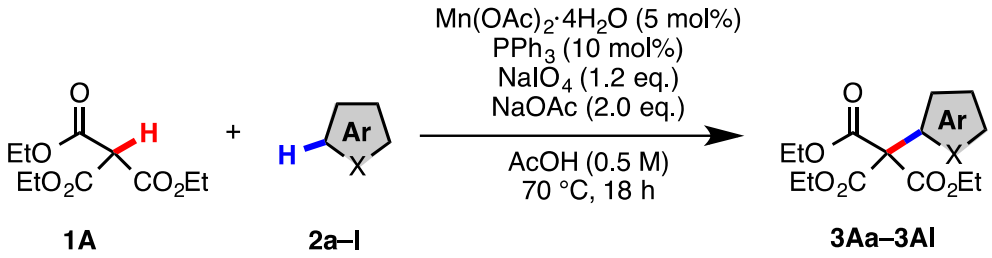
1. General

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used as received. Diethyl 2-pivaloylmalonate [1] and diethyl 2-(morpholine-4-carbonyl)malonate [2] were synthesized according to procedures reported in the literature. All coupling reactions were performed in 10-mL glass Schlenk tubes equipped with J. Young® O-ring tap and heated in a 8-well reaction block (heater + magnetic stirrer). Other reactions were performed with dry solvents under an atmosphere of nitrogen in flame-dried glassware with standard vacuum-line techniques. All work-up and purification procedures were carried out with reagent-grade solvents in air.

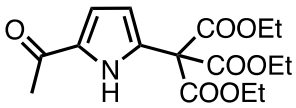
Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm). Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative thin-layer chromatography (PTLC) was performed using Wakogel B5-F silica coated plates (0.75 mm) prepared in our laboratory. Gas chromatography (GC) analysis was conducted on a Shimadzu GC-2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). GCMS analysis was conducted on a Shimadzu GCMS-QP2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). LCMS analysis was conducted on Agilent Technologies 1200 series. High-resolution mass spectra (HRMS) was obtained from a JMS-T100TD instrument (DART) and a Thermo Fisher Scientific Exactive Plus (ESI). Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JMN-A-400 (^{1}H 400 MHz) spectrometer and JEOL JMN-ECS400-A (^{1}H 400 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm) and DMSO (δ 2.50 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm) and DMSO (δ 39.5 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

[1] Allen, D. G.; Aston, N. M.; Barnett, R. P.; Chudasama, R. M.; Dar, C. J.; Edlin, C. D.; Kindon, L. J.; Trivedi, N. WO2008015416.
[2] Uneme, H.; Mitsudera, H.; Yamada, J.; Kamikado, T.; Kono, Y.; Manabe, Y.; Numata, M. *Biosci. Biotech. Biochem.* **1992**, *56*, 1623.

2. General procedure for Mn-catalyzed C–H/C–H coupling of tri(ethoxycarbonyl)methane with heteroarenes.



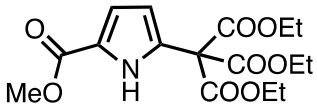
A 10-mL glass vessel equipped with J. Young® O-ring tap containing a magnetic stirring bar was flame-dried under vacuum and filled with nitrogen after cooling to room temperature. To this tube were added heteroarene (**2**, 2.0 mmol), $Mn(OAc)_2 \cdot 4H_2O$ (12.3 mg, 0.05 mmol), triphenylphosphine (26.2 mg, 0.01 mmol), $NaIO_4$ (256.7 mg, 1.2 mmol), NaOAc (164.1 mg, 2.0 mmol) and tri(ethoxycarbonyl)methane (**1A**, 1.0 mmol), followed by acetic acid (2.0 mL) under a stream of nitrogen. The tube was sealed with O-ring tap, and then heated at 70 °C for 18 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short pad of Celite® (EtOAc). To the mixture was added saturated aqueous K_2CO_3 and the mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to preparative thin-layer chromatography (PTLC) (hexane/EtOAc = 5:1) to afford the coupling product.



Triethyl (5-acetyl-1*H*-pyrrol-2-yl)methanetricarboxylate (3Aa) [3]

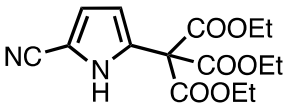
Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 2:1) to give in **3Aa** (259.7 mg, 77%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.13 (br, 1H), 6.84 (s, 1H), 6.30 (s, 1H), 4.32 (q, J = 6.8 Hz, 6H), 2.42 (s, 3H), 1.30 (t, J = 6.8 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.7, 165.1, 132.3, 128.9, 116.1, 112.0, 66.0, 63.2, 25.3, 13.8; HRMS (DART) *m/z* calcd for $C_{16}H_{22}NO_7$ $[M+H]^+$: 340.1396, found: 340.1395.

[3] Cho, I.-S.; Muchowski, J. M. *Synthesis* **1991**, 567.



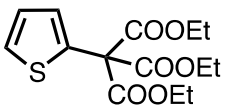
Triethyl (5-(methoxycarbonyl)-1*H*-pyrrol-2-yl)methanetricarboxylate (3Ab)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 2:1) to give in **3Ab** (261.9 mg, 74%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.07 (br, 1H), 6.87 (dd, *J* = 4.0, 3.0 Hz, 1H), 6.27 (dd, *J* = 3.9, 3.0 Hz, 1H), 4.32 (q, *J* = 7.3 Hz, 6H), 3.85 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 161.1, 127.1, 123.0, 115.2, 111.9, 66.0, 63.1, 51.5, 13.8; HRMS (DART) *m/z* calcd for $C_{16}H_{22}NO_8$ $[M+H]^+$: 356.1345, found: 356.1347.



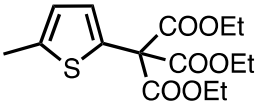
Triethyl (5-cyano-1*H*-pyrrol-2-yl)methanetricarboxylate (3Ac)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 2:1) to give in **3Ac** (146.8 mg, 44%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.13 (br, 1H), 6.81 (dd, *J* = 3.9, 2.4 Hz, 1H), 6.27 (dd, *J* = 3.9, 2.4 Hz, 1H), 4.33 (q, *J* = 7.3 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 128.1, 119.9, 113.9, 111.5, 101.5, 65.6, 63.4, 13.8; HRMS (DART) *m/z* calcd for $C_{15}H_{19}N_2O_6$ $[M+H]^+$: 323.1243, found: 323.1245.



Triethyl thiophen-2-ylmethanetricarboxylate (3Ad) [3]

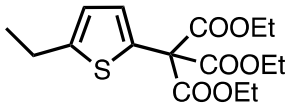
Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Ad** (219.9 mg, 70%) as a orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (dd, *J* = 5.6, 1.2 Hz, 1H), 7.16 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.01 (dd, *J* = 5.6, 3.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 6H), 1.30 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 134,0, 128.7 126.9, 126.1, 68.0, 62.9, 13.8; HRMS (DART) *m/z* calcd for $C_{14}H_{19}O_6$ S $[M+H]^+$: 315.0902, found: 315.0903.



Triethyl (5-methylthiophen-2-yl)methanetricarboxylate (3Ae)

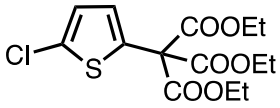
Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Ae** (308.2 mg, 94%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93 (d, *J* = 3.4 Hz, 1H), 6.65 (d, *J*

= 3.9 Hz, 1H), 4.31 (q, *J* = 7.3 Hz, 6H), 2.46 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 141.3, 131.2, 128.6, 124.4, 68.1, 62.8, 15.0, 13.8; HRMS (DART) *m/z* calcd for $C_{15}H_{21}O_6S$ $[M+H]^+$: 329.1059, found: 329.1059.



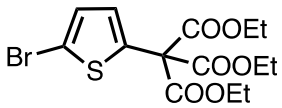
Triethyl (5-ethylthiophen-2-yl)methanetricarboxylate (3Af)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Af** (292.7 mg, 85%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.95 (d, *J* = 3.9 Hz, 1H), 6.68 (d, *J* = 3.9 Hz, 1H), 4.31 (q, *J* = 7.3 Hz, 6H), 2.82 (q, *J* = 7.3 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 148.9, 130.8, 128.4, 122.5, 68.1, 62.8, 23.2, 15.6, 13.8; HRMS (DART) *m /z* calcd for $C_{16}H_{23}O_6S$ $[M+H]^+$: 343.1215, found: 343.1217.



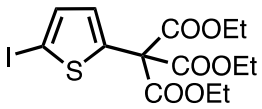
Triethyl (5-chlorothiophen-2-yl)methanetricarboxylate (3Ag)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Ag** (320.1 mg, 91%) as a red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.91 (d, *J* = 3.9 Hz, 1H), 6.82 (d, *J* = 3.9 Hz, 1H), 4.32 (q, *J* = 7.3 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 132.2, 131.8, 128.2, 125.2, 68.2, 63.1, 13.8; HRMS (DART) *m/z* calcd for $C_{14}H_{18}ClO_6S$ $[M+H]^+$: 349.0513, found: 349.0518.



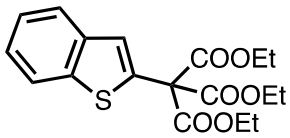
Triethyl (5-bromothiophen-2-yl)methanetricarboxylate (3Ah)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Ah** (347.5 mg, 88%) as a red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (d, *J* = 4.4 Hz, 1H), 6.89 (d, *J* = 4.4 Hz, 1H), 4.32 (q, *J* = 6.8 Hz, 6H), 1.30 (t, *J* = 6.8 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 135.1, 129.1, 128.9, 114.3, 68.2, 63.1, 13.8; HRMS (DART) *m/z* calcd for $C_{14}H_{18}BrO_6S$ $[M+H]^+$: 393.0007, found: 393.0008.



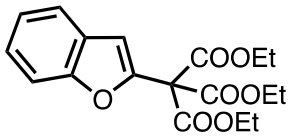
Triethyl (5-iodothiophen-2-yl)methanetricarboxylate (3Ai)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Ai** (405.7 mg, 92%) as a red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (d, J = 3.9 Hz, 1H), 6.80 (d, J = 3.9 Hz, 1H), 4.32 (q, J = 7.3 Hz, 6H), 1.30 (t, J = 7.3 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 139.5, 136.0, 130.2, 76.2, 63.1, 13.8, 13.7; HRMS (DART) *m/z* calcd for $C_{14}H_{18}IO_6S$ $[M+H]^+$: 440.9869, found: 440.9875.



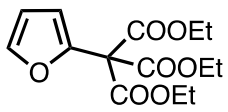
Triethyl benzo[*b*]thiophen-2-ylmethanetricarboxylate (3Aj)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Aj** (248.5 mg, 68%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (t, J = 3.9 Hz, 1H), 7.75 (t, J = 3.9 Hz, 1H), 7.44 (s, 1H), 7.34–7.32 (m, 2H), 4.35 (q, J = 7.3 Hz, 6H), 1.31 (t, J = 7.3 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 140.4, 138.5, 134.9, 125.7, 124.7, 124.2, 123.9, 121.8, 68.5, 63.1, 13.8; HRMS (DART) *m/z* calcd for $C_{18}H_{21}O_6S$ $[M+H]^+$: 365.1059, found: 365.1060.



Triethyl benzofuran-2-ylmethanetricarboxylate (3Ak)

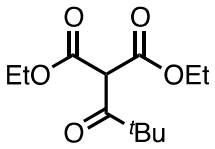
Following the general procedure, the crude product was purified by preparative PTLC (hexane/EtOAc = 5:1) to give in **3Ak** (225.4 mg, 65%) as a red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 6.8 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 7.30 (td, J = 8.3, 1.4 Hz, 1H), 7.24 (td, J = 7.8, 1.0 Hz, 1H), 7.15 (s, 1H), 4.35 (q, J = 7.3 Hz, 6H), 1.31 (t, J = 7.3 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 155.0, 147.9, 127.6, 124.7, 122.9, 121.4, 111.4, 107.3, 63.0, 13.8; HRMS (DART) *m/z* calcd for $C_{18}H_{21}O_7$ $[M+H]^+$: 349.1287, found: 349.1286.



Triethyl furan-2-ylmethanetricarboxylate (3Al)[3]

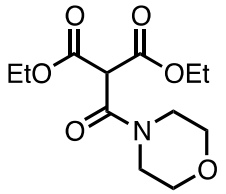
Following the general procedure, the crude product was purified by preparative PTLC (hexane/EtOAc = 5:1) to give in **3Al** (277.5 mg, 93%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, *J* = 1.5 Hz, 1H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.39 (dd, *J* = 3.4, 1.5 Hz, 1H), 4.33 (q, *J* = 7.3 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 145.2, 143.2, 110.4, 110.3, 67.3, 62.8, 13.8; HRMS (DART) *m/z* calcd for $C_{14}H_{19}O_7$ $[M+H]^+$: 299.1131, found: 299.1137.

3. Preparation of carbonyls



Diethyl 2-pivaloylmalonate (1B)

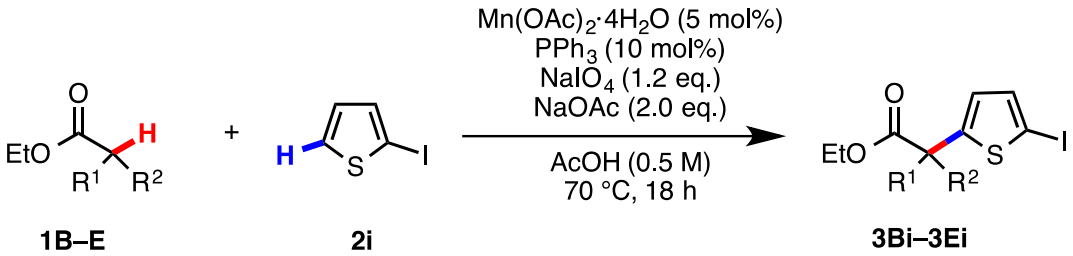
Synthesis of **1B** was performed following the previously reported method[1] using 6.0 mmol of diethyl malonate. The product was obtained in 64% yield as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87 (s, 1H), 4.19 (q, *J* = 7.3 Hz, 4H), 1.23 (t, *J* = 7.3 Hz, 6H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.6, 164.7, 62.2, 59.7, 45.5, 25.8, 13.9; HRMS (DART) *m/z* calcd for $C_{12}H_{21}O_5$ $[M+H]^+$: 245.1389, found: 245.1387.



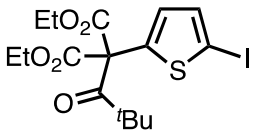
Diethyl 2-(morpholine-4-carbonyl)malonate (1D)

Synthesis of **1D** was performed by adding diethyl malonate (12.5 mmol) to a solution of NaH (60% in Oil; 1.0 equiv) in dry THF (30 mL) at 0 °C. The mixture was stirred for 1 h and thereafter 1.5 equiv of morpholine-4-carbonyl chloride was added. The reaction was followed by TLC and stopped when all of the diethyl malonate was consumed (approx. 3 h). The reaction was quenched by addition of 2.0 M HCl and extraction with EtOAc. The desired product was obtained in 65% yield as white solid after a column chromatography (hexane:EtOAc = 6:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.56 (s, 1H), 4.30-4.28 (m, 4H), 3.73–3.67 (m, 6H), 3.35–3.34 (m, 2H), 1.33–1.29 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 162.2, 66.5, 66.1, 62.5, 58.1, 46.5, 42.6, 14.0; HRMS (DART) *m/z* calcd for $C_{12}H_{20}NO_6$ $[M+H]^+$: 274.1291, found: 274.1295.

4. General procedure for Mn-catalyzed C–H/C–H coupling of 2-iodothiophene with carbonyls.

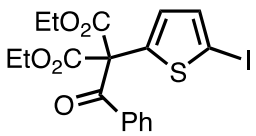


A 10-mL glass vessel equipped with J. Young® O-ring tap containing a magnetic stirring bar was flame-dried under vacuum and filled with nitrogen after cooling to room temperature. To this tube were added 2-iodothiopene (**2i**, 2.0 mmol), $Mn(OAc)_2 \cdot 4H_2O$ (12.3 mg, 0.05 mmol), triphenylphosphine (26.2 mg, 0.01 mmol), $NaIO_4$ (256.7 mg, 1.2 mmol), NaOAc (164.1 mg, 2.0 mmol) and carbonyls (**1**, 1.0 mmol), followed by acetic acid (2.0 mL) under a stream of nitrogen. The tube was sealed with O-ring tap, and then heated at 70 °C for 18 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short pad of Celite® (EtOAc). To the mixture was added saturated aqueous K_2CO_3 and the mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to PTLC (hexane/EtOAc = 5:1) to afford the coupling product.



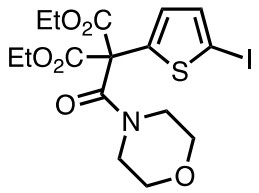
Diethyl 2-(5-iodothiophen-2-yl)-2-pivaloylmalonate (3Bi)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 6:1) to give in **3Bi** (289 mg, 64%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (d, J = 3.9 Hz, 1H), 6.69 (d, J = 3.9 Hz, 1H), 4.36–4.25 (m, 4H), 1.31 (t, J = 6.8 Hz, 6H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.9, 166.0, 137.8, 135.8, 131.3, 77.3, 73.3, 63.0, 46.3, 29.3, 13.8; HRMS (DART) *m/z* calcd for $C_{16}H_{22}IO_5S$ $[M+H]^+$: 453.0233, found: 453.0235.



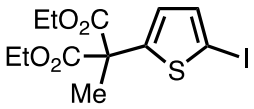
Diethyl 2-benzoyl-2-(5-iodothiophen-2-yl)malonate (3Ci)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 6:1) to give in **3Ci** (245 mg, 52%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.68 (m, 2H), 7.50–7.46 (m, 1H), 7.36–7.31 (m, 2H), 7.08 (d, *J* = 3.9 Hz, 1H), 6.57 (d, *J* = 3.9 Hz, 1H), 4.30–4.26 (m, 4H), 1.19 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 166.3, 139.7, 136.3, 134.2, 133.2, 131.2, 129.5, 128.3, 63.1, 13.7; There is two overlapping carbon signals as two peak are missing even with prolonged scans. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}IO_5SNa$ $[M+Na]^+$: 494.9734, found: 494.9723.



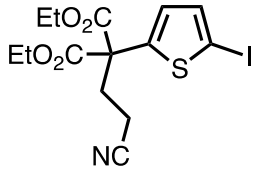
Diethyl 2-(5-iodothiophen-2-yl)-2-(morpholine-4-carbonyl)malonate (3Di)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 4:1) to give in **3Di** (206 mg, 43%) as a red-brownish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (d, *J* = 3.9 Hz, 1H), 6.79 (d, *J* = 3.9 Hz, 1H), 4.38–4.31 (m, 4H), 3.70 (br, 4H), 3.36 (br, 2H), 2.98 (br, 2H), 1.32 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 164.8, 139.7, 136.2, 130.2, 69.0, 66.4, 65.2, 64.0, 63.3, 47.5, 43.1, 13.9; HRMS (DART) *m/z* calcd for $C_{16}H_{21}INO_6S$ $[M+H]^+$: 482.0134, found: 482.0137.



Diethyl 2-(5-iodothiophen-2-yl)-2-methylmalonate (3Ei)

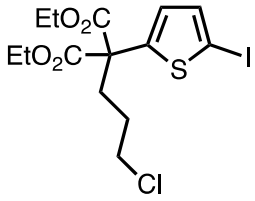
Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 6:1) to give in **3Ei** (176 mg, 46%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (d, *J* = 3.9 Hz, 1H), 6.72 (d, *J* = 3.9 Hz, 1H), 4.23 (q, *J* = 7.3 Hz, 4H), 1.87 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 146.5, 135.9, 127.6, 74.4, 62.2, 56.2, 23.1, 13.9; HRMS (DART) *m/z* calcd for $C_{12}H_{16}IO_4S$ $[M+H]^+$: 382.9814, found: 382.9819.



Diethyl 2-(2-cyanoethyl)-2-(5-iodothiophen-2-yl)malonate (3Fi)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Fi** (307 mg, 73%) as an orange/yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (d, *J* = 3.9 Hz, 1H),

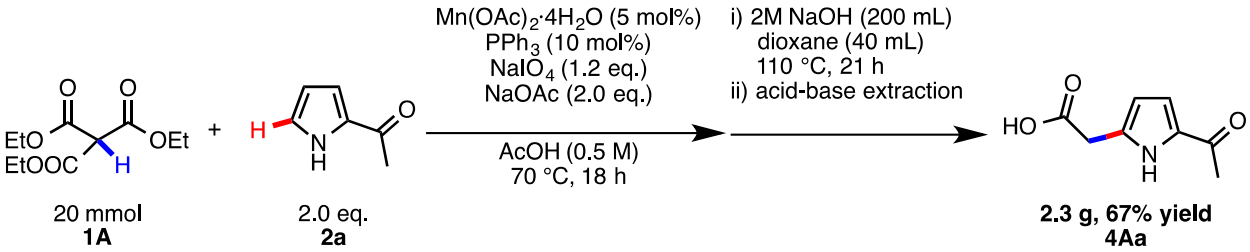
6.68 (d, J = 3.9 Hz, 1H), 4.30–4.24 (m, 4H), 2.64 (t, J = 7.6 Hz, 2H), 2.29 (t, J = 7.6 Hz, 2H), 1.27 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 136.1, 127.9, 118.4, 76.0, 62.8, 59.4, 33.5, 13.9, 13.0; There is one overlapping carbon signal as one peak is missing even with prolonged scans. HRMS (DART) *m/z* calcd for $C_{14}H_{17}INO_4S$ $[M+H]^+$: 421.9923, found: 421.9921.



Diethyl 2-(3-chloropropyl)-2-(5-iodothiophen-2-yl)malonate (3Gi)

Following the general procedure, the crude product was purified by PTLC (hexane/EtOAc = 5:1) to give in **3Gi** (240 mg, 54%) as an orange/yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 (d, J = 3.9 Hz, 1H), 6.72 (d, J = 3.9 Hz, 1H), 4.28–4.19 (m, 4H), 3.49 (t, J = 6.4 Hz, 2H), 2.46–2.43 (m, 2H), 1.67-1.61 (m, 2H), 1.26 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 135.9, 127.7, 75.2, 62.3, 60.0, 44.5, 35.0, 27.6, 13.9; There is one overlapping carbon signal as one peak is missing even with prolonged scans. HRMS (DART) *m/z* calcd for $C_{14}H_{19}ClIO_4S$ $[M+H]^+$: 444.9737, found: 444.9737.

5. Synthesis of 2-(5-acetyl-1*H*-pyrrol-2-yl)acetic acid (4Aa)



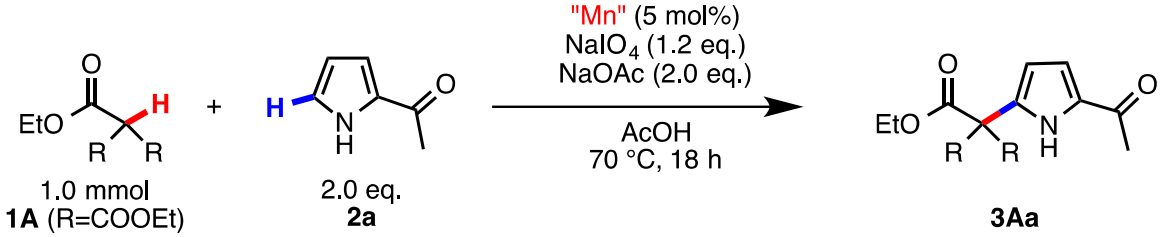
A 100-mL round-bottom flask containing a magnetic stirring bar was flame-dried under vacuum and filled with nitrogen after cooling to room temperature. To this flask were added 2-acethylpyrrole (**2a**; 4.37 g, 40 mmol), $Mn(OAc)_2{\cdot}4H_2O$ (245.1 mg, 1.0 mmol), triphenylphosphine (524.6 mg, 2.0 mmol), $NaIO_4$ (5.13 g, 24 mmol), NaOAc (3.28 g, 40 mmol) and tri(ethoxycarbonyl)methane (**1A**, 4.2 mL, 20 mmol), followed by acetic acid (40 mL) under a stream of nitrogen. The reaction mixture was stirred at 70 °C for 18 h. After cooling the reaction mixture to room temperature, the mixture was added Me_2S (10 mL) and passed through a short pad of Celite® (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was added 2.0 M NaOH (200 mL) and 1,4-dioxane (40 mL). The reaction mixture was stirred at

110 °C for 21 h. After cooling the reaction mixture to room temperature, the mixture was evaporated under reduced pressure. The residue was extracted with EtOAc. The water layer was poured into 1.0 M HCl and extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Et_2O was added to the residue, and the resulting precipitate was collected to give 2-(5-acetyl-1H-pyrrol-2-yl)acetic acid (**4Aa**; 2.23 g, 67%) as a white solid. ^{1}H NMR (DMSO, 400 MHz) δ 11.97 (br, 1H), 11.14 (s, 1H), 6.43 (dd, J = 4.0, 2.8 Hz, 1H), 5.58 (dd, J = 4.0, 2.8 Hz, 1H), 3.14 (s, 2H), 1.85 (s, 3H); ^{13}C NMR (DMSO, 100 MHz) δ 187.0, 172.0, 133.8, 132.0, 118.1, 110.3, 33.7, 25.9; HRMS(ESI) calcd for $C_8H_8NO_3$ [M–H]$^-$: 166.0499, found: 166.0507.

6. Effect of Reaction Parameters

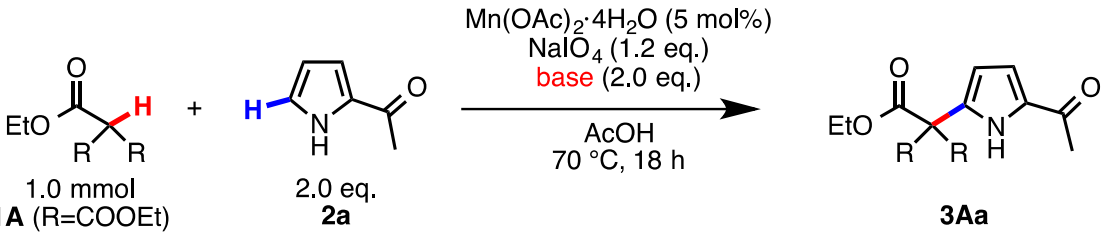
The effect of reaction parameters (catalyst, base, solvent, temperature and additive) was investigated (Table S1–S5). The coupling of tri(ethoxycarbonyl)methane (**1A**) with 2-acetylpyrrole (**2a**) was used as the model reaction.

Table S1. Effect of catalyst.



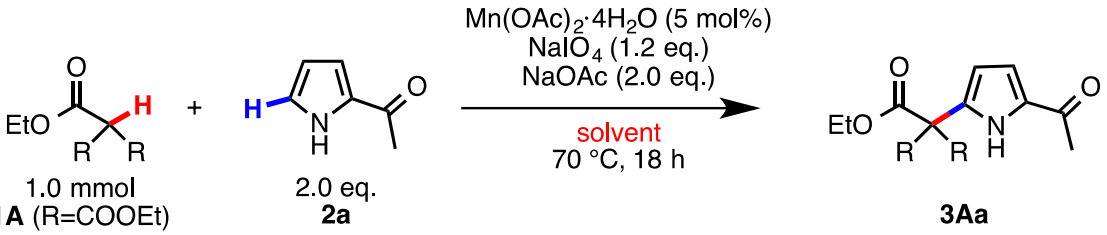
entry	"Mn"	GC yield **3Aa** (%)
1	$Mn(OAc)_3{\cdot}2H_2O$	32
2	$Mn(OAc)_2{\cdot}4H_2O$	57
3	$Mn(acac)_3$	5
4	$MnCl_2$	24
5	MnI_2	64
6	Mn(salen)Cl	25
7	$Co(OAc)_2{\cdot}4H_2O$	0
8	$Fe(OAc)_2$	0

Table S2. Effect of base.



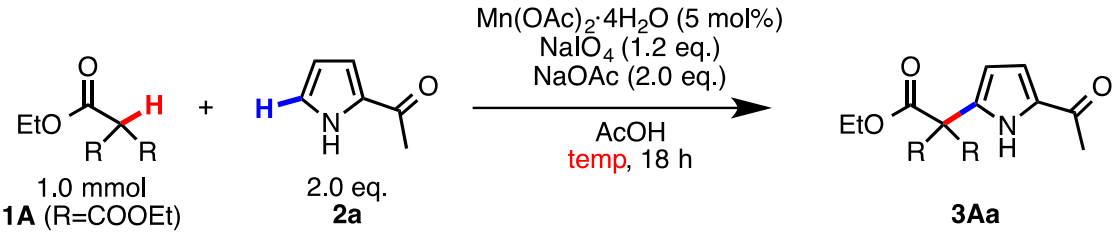
entry	base	GC yield **3Aa** (%)
1	NaOAc	57
2	without NaOAc	9
3	KOAc	43
4	$Mg(OAc)_2{\cdot}4H_2O$	8
5	NaH_2PO_4	3

Table S3. Effect of solvent.



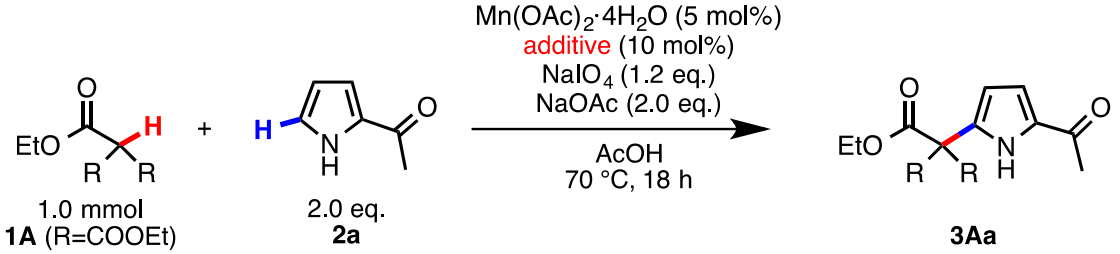
entry	solvent	GC yield **3Aa** (%)
1	AcOH	57
2	propionic acid	47
3	pivalic acid	21
4	CH_3OH	0
5	CH_3CN	1

Table S4. Effect of reaction temperature.

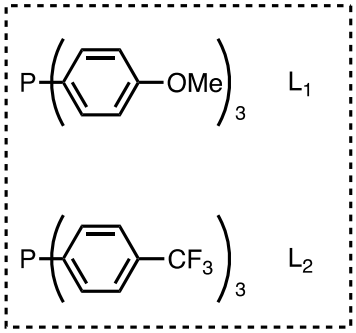


entry	temp	GC yield **3Aa** (%)
1	50 °C	10
2	70 °C	57
3	100 °C	44

Table S5. Effect of additive.



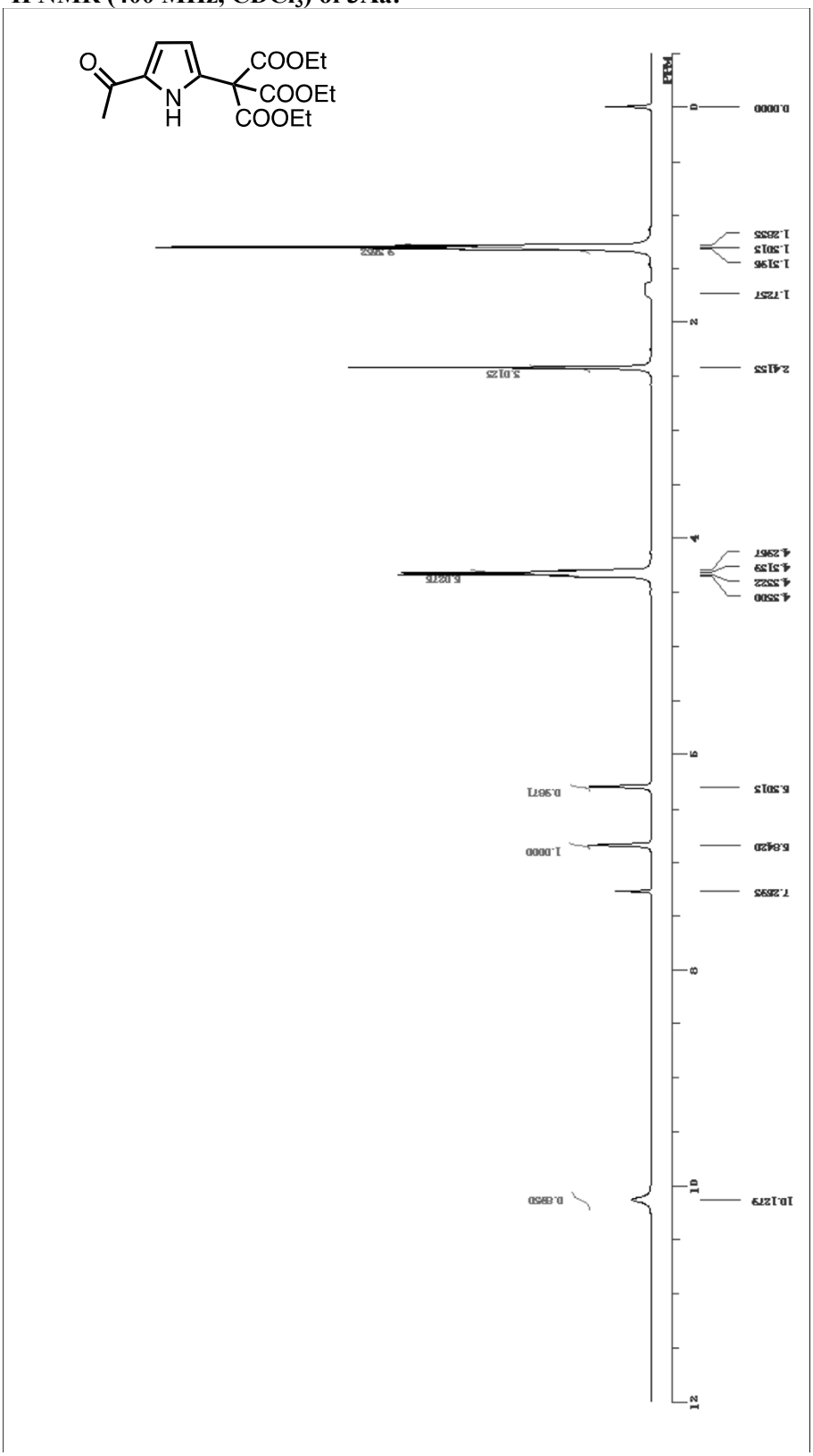
entry	additive	GC yield **3Aa** (%)	entry	additive	GC yield **3Aa** (%)
1	none	57	9	S-Phos	47
2	DMSO	33	10	Cy-JohnPhos	67
3	pyridine	36	11	JohnPhos	38
4	PPh_3	72 (77)[b]	12	Cy_3P	37
5	L_1	27	13	$P(OPh)_3$	23
6	L_2	72	14[a]	dppe	2
7	Cy_2PhP	74	15	$O=PPh_3$	55
8	X-Phos	77	16	$AsPh_3$	51



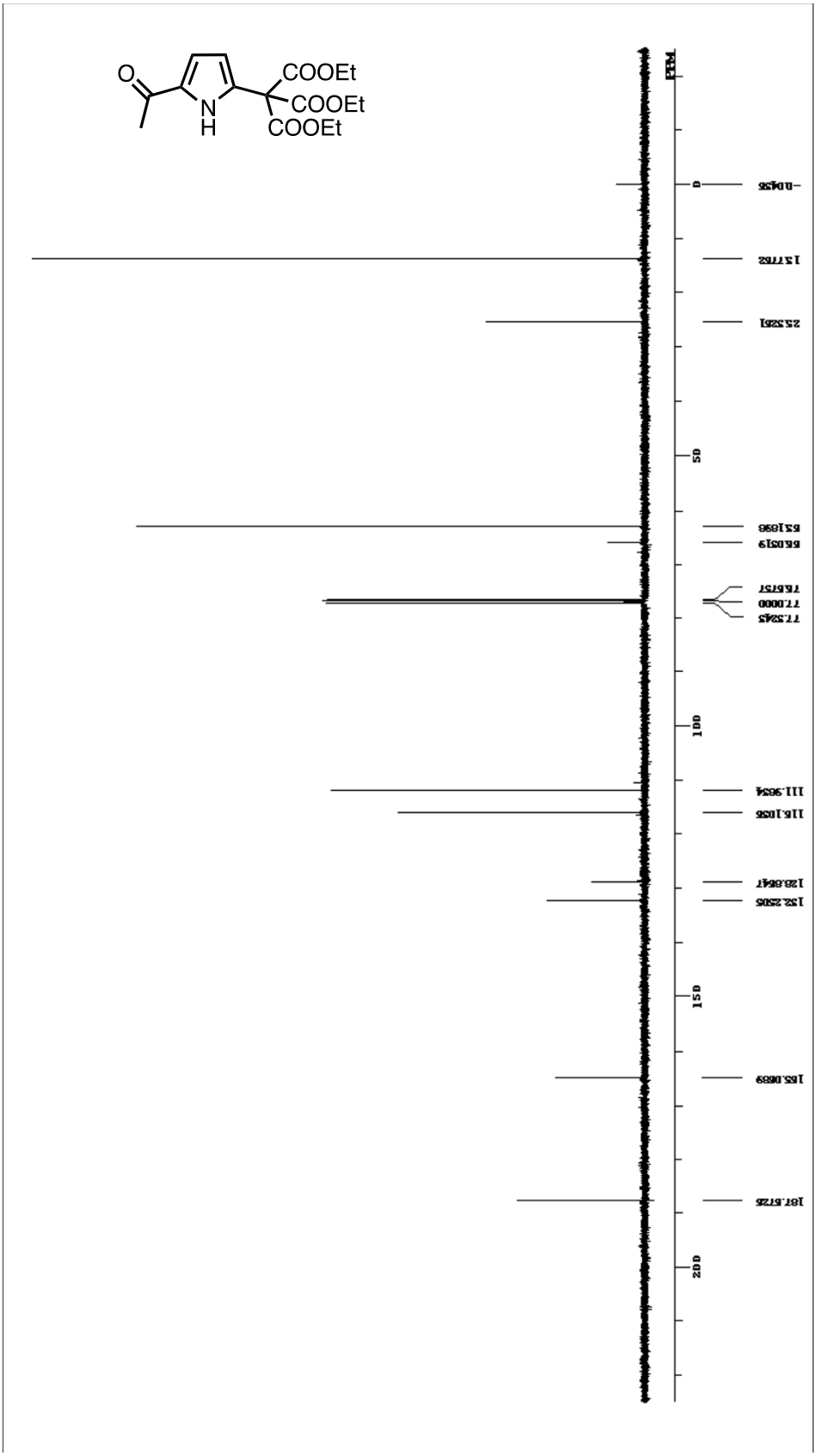
[a] 5 mol% additive was used
[b] Isolated yield

7. ^{1}H NMR and ^{13}C NMR Spectra

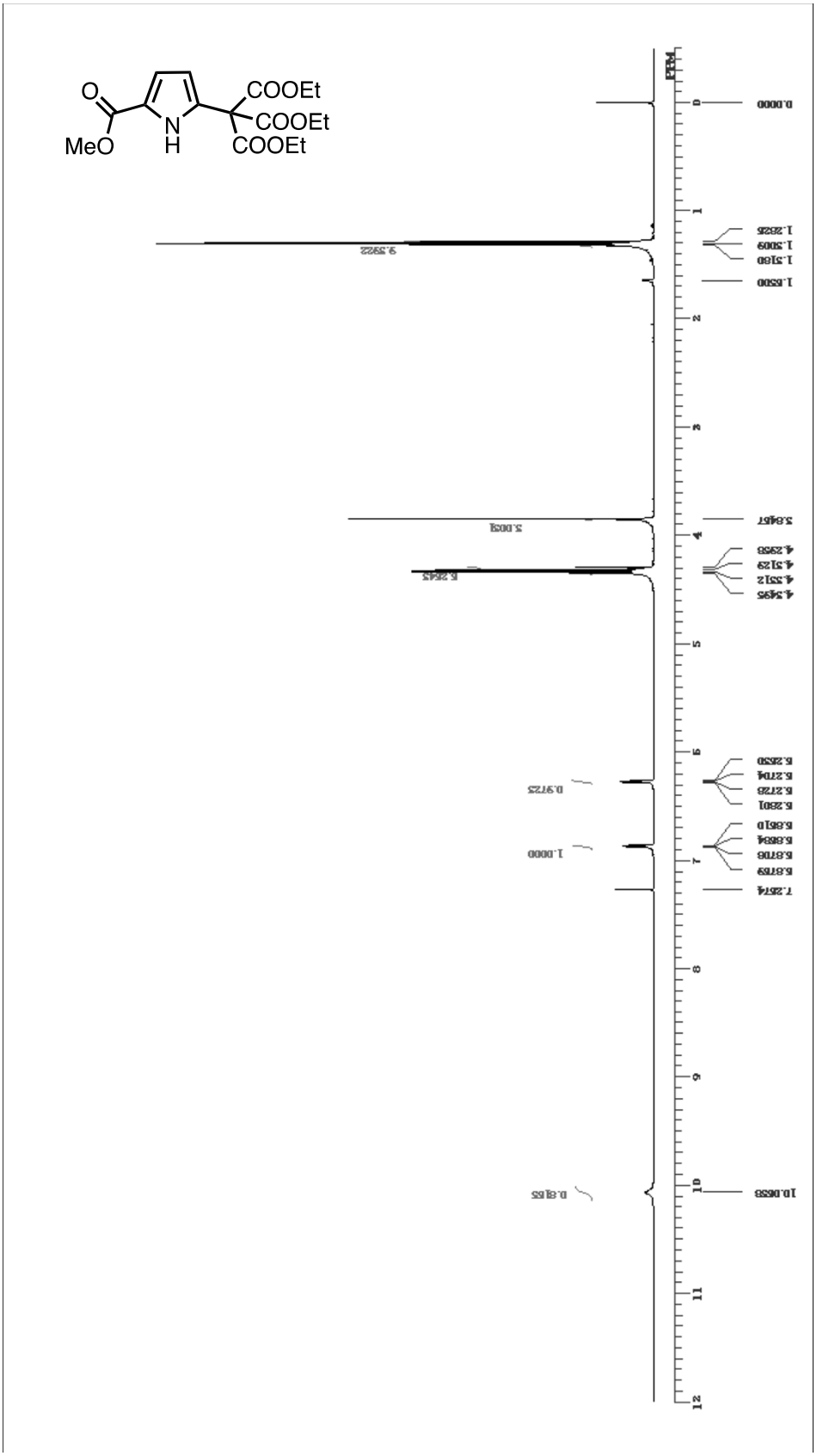
^{1}H NMR (400 MHz, $CDCl_3$) of 3Aa:



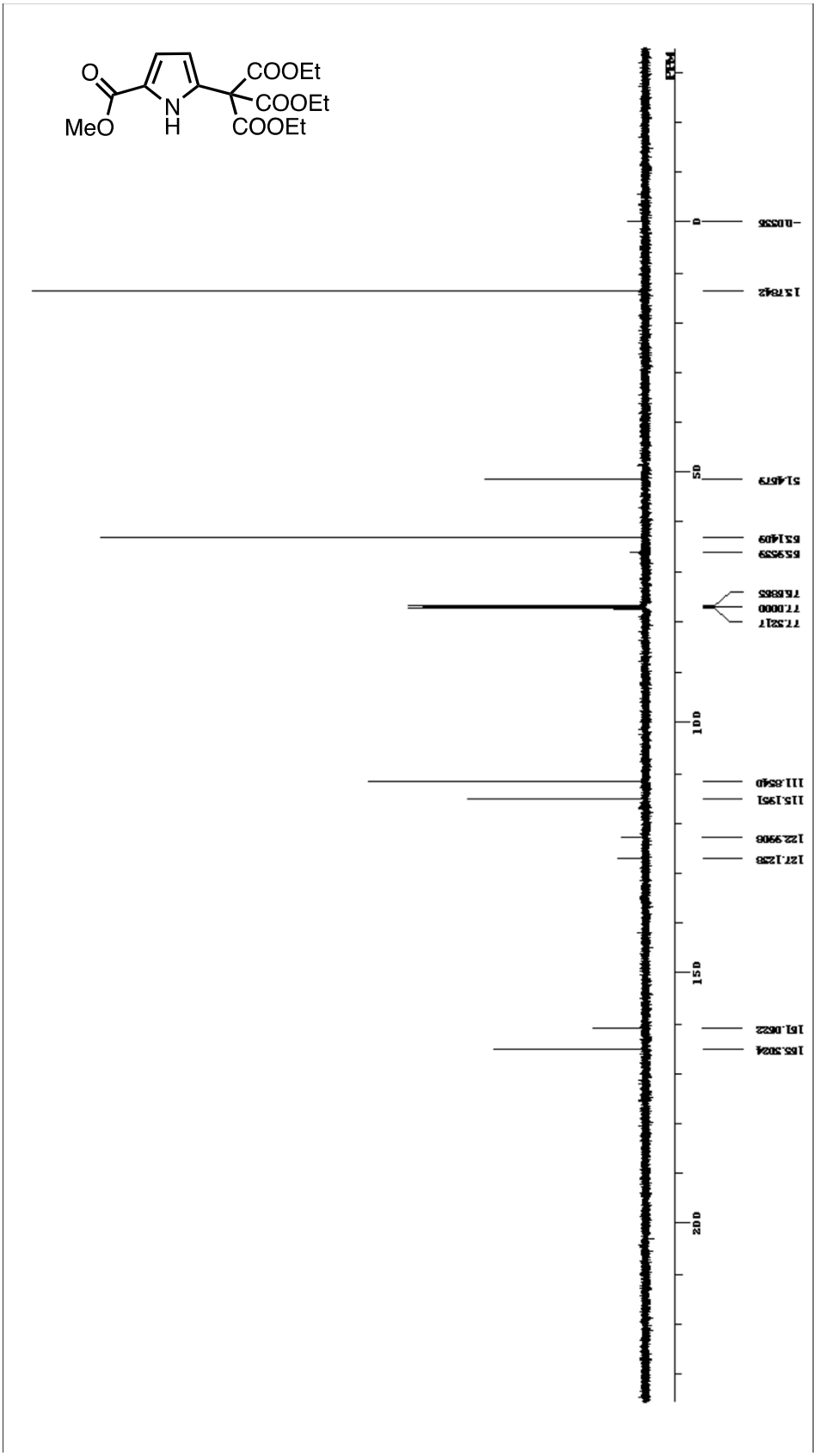
^{13}C NMR (100 MHz, $CDCl_3$) of 3Aa:



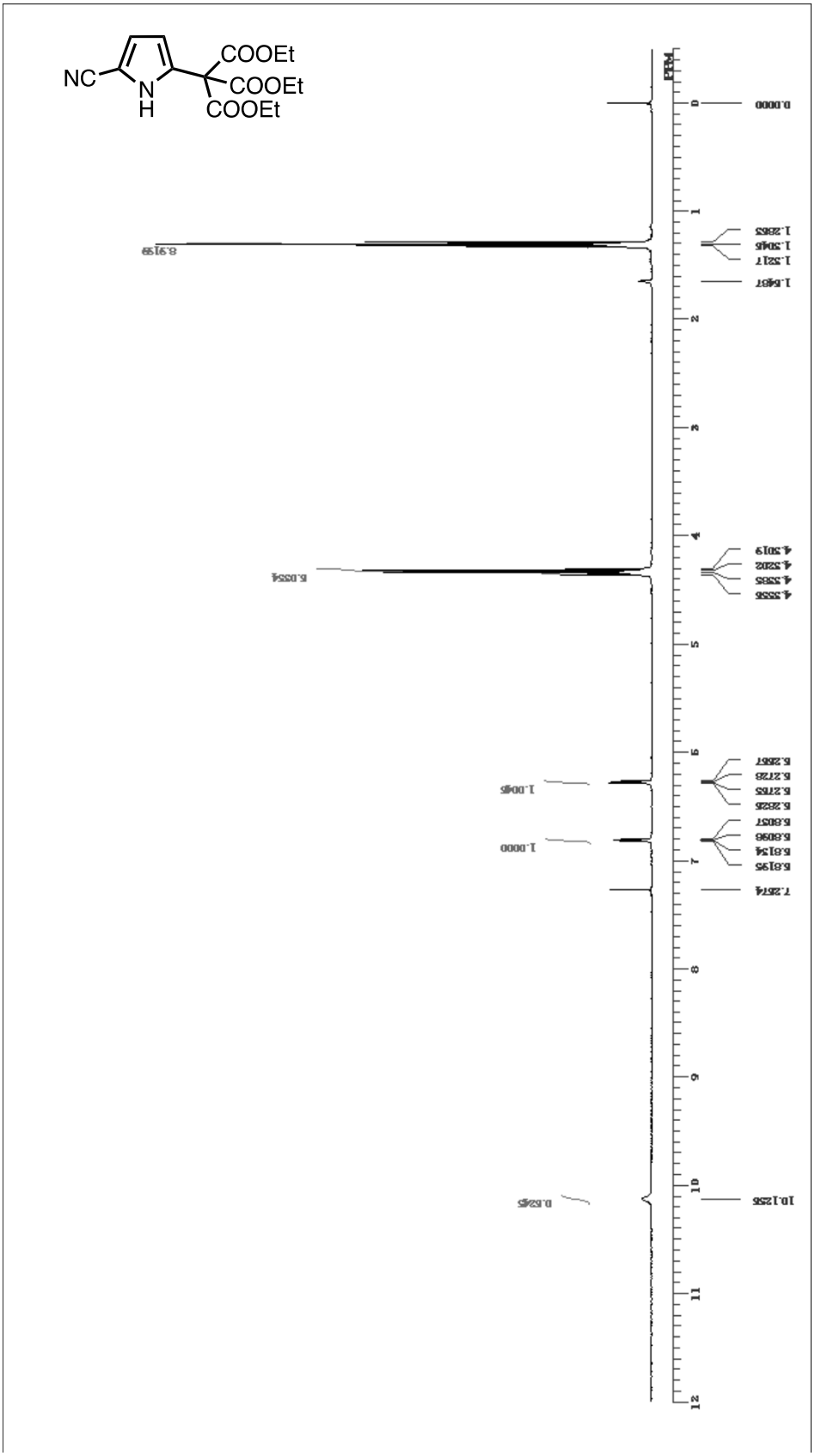
^{1}H NMR (400 MHz, $CDCl_3$) of 3Ab:



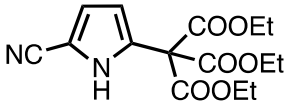
^{13}C NMR (100 MHz, $CDCl_3$) of 3Ab:

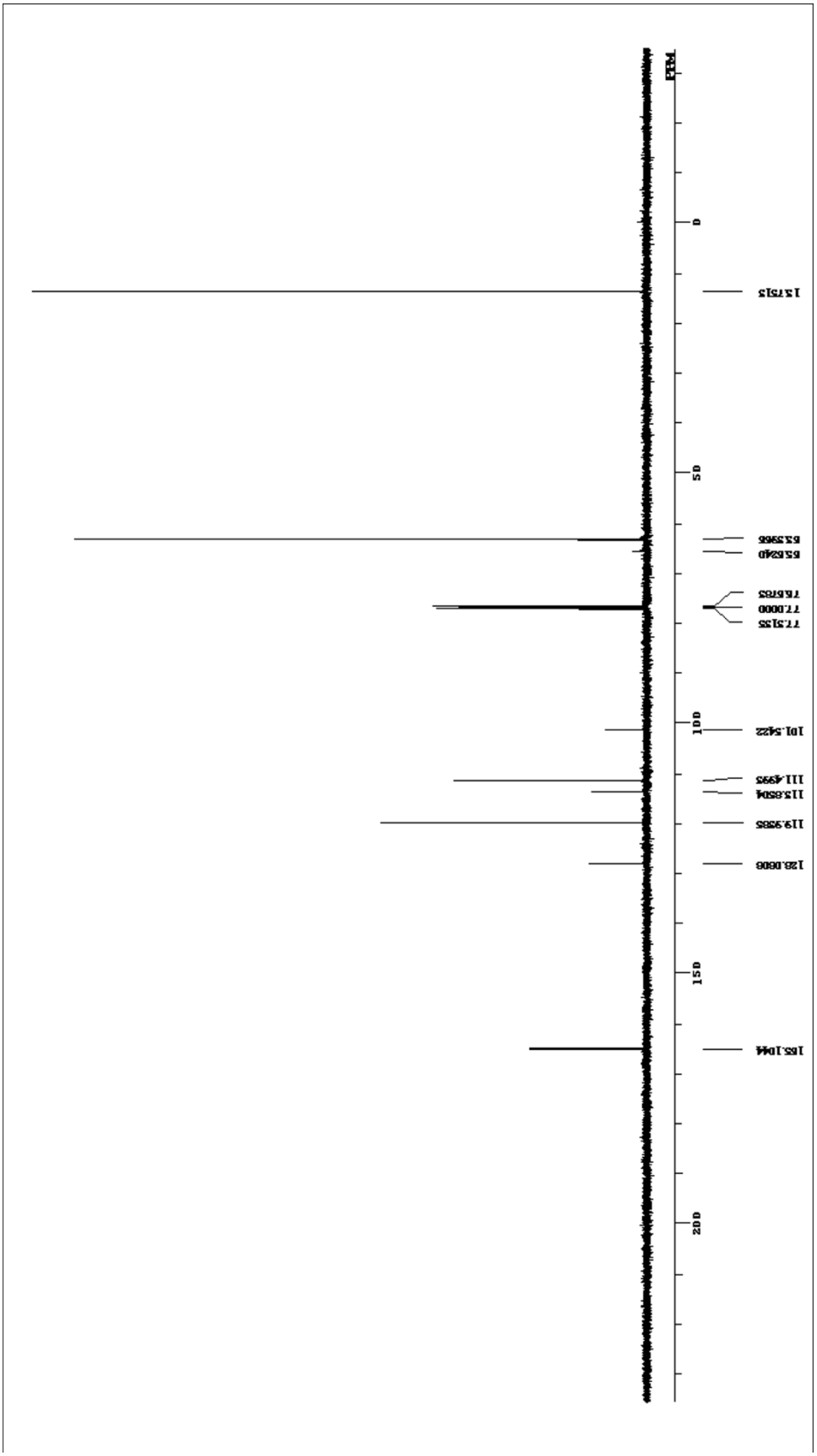


^{1}H NMR (400 MHz, $CDCl_3$) of 3Ac:

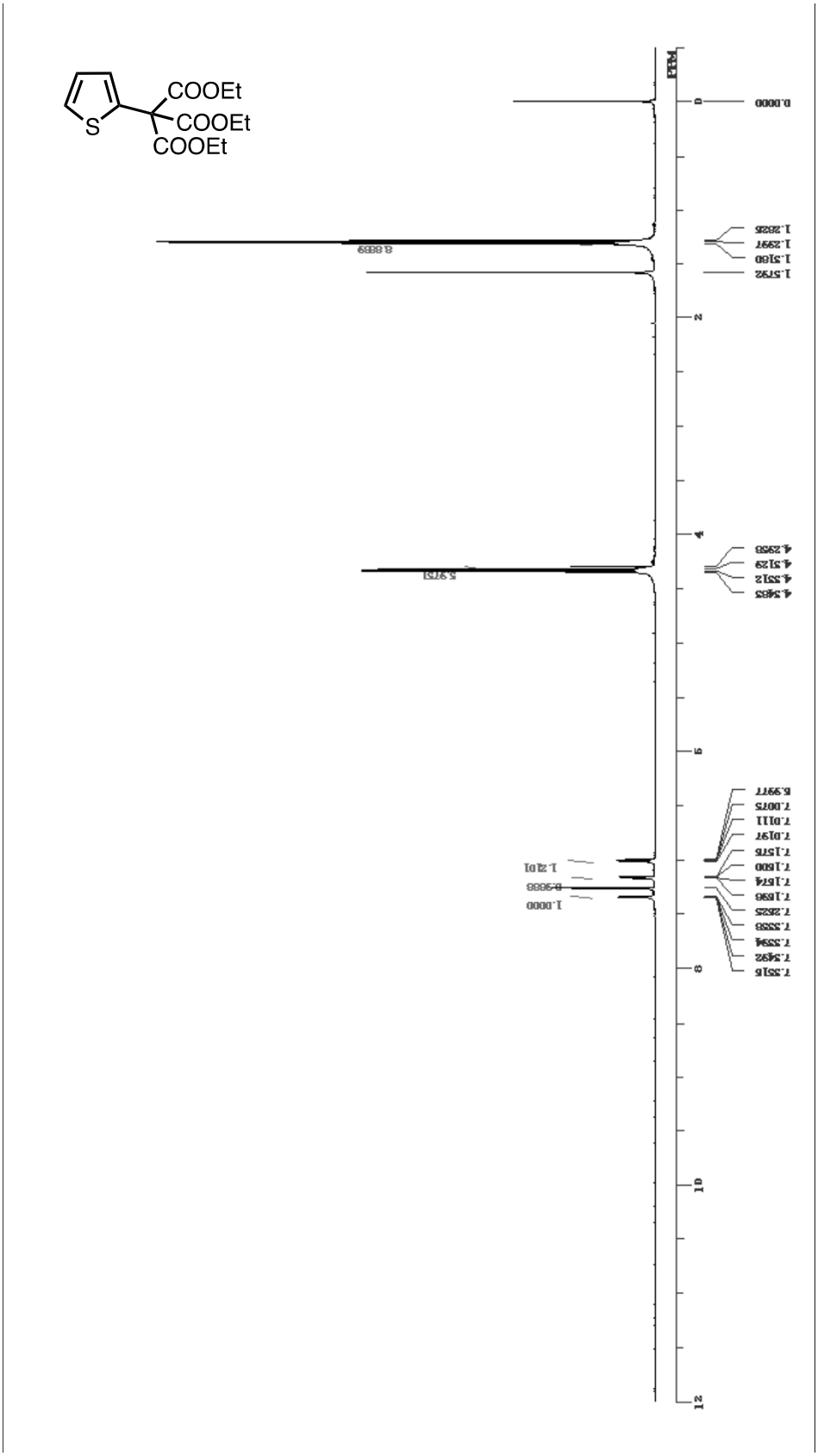


^{13}C NMR (100 MHz, $CDCl_3$) of 3Ac:

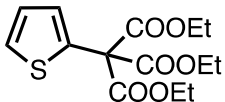


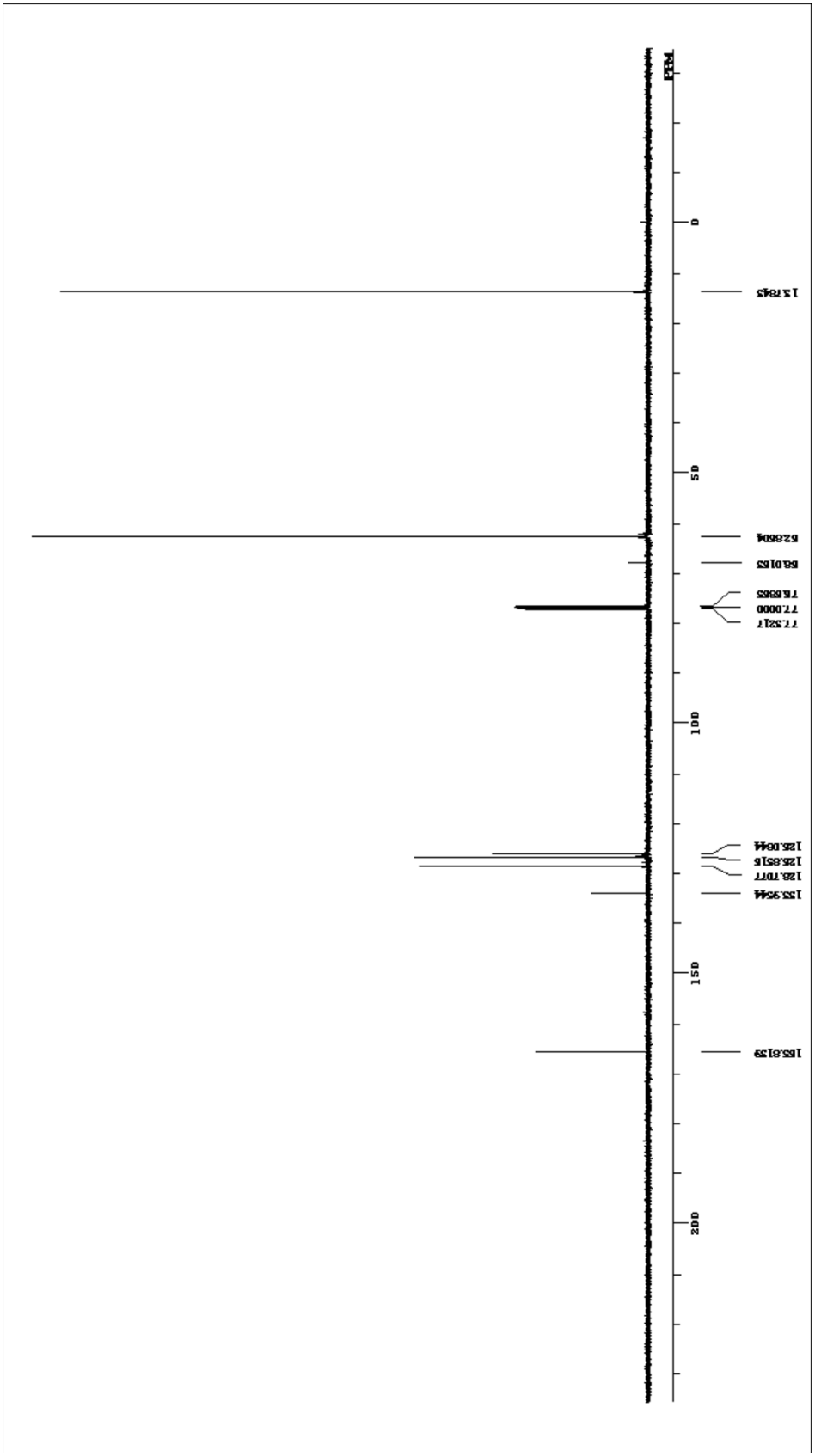


^{1}H NMR (400 MHz, $CDCl_3$) of 3Ad:

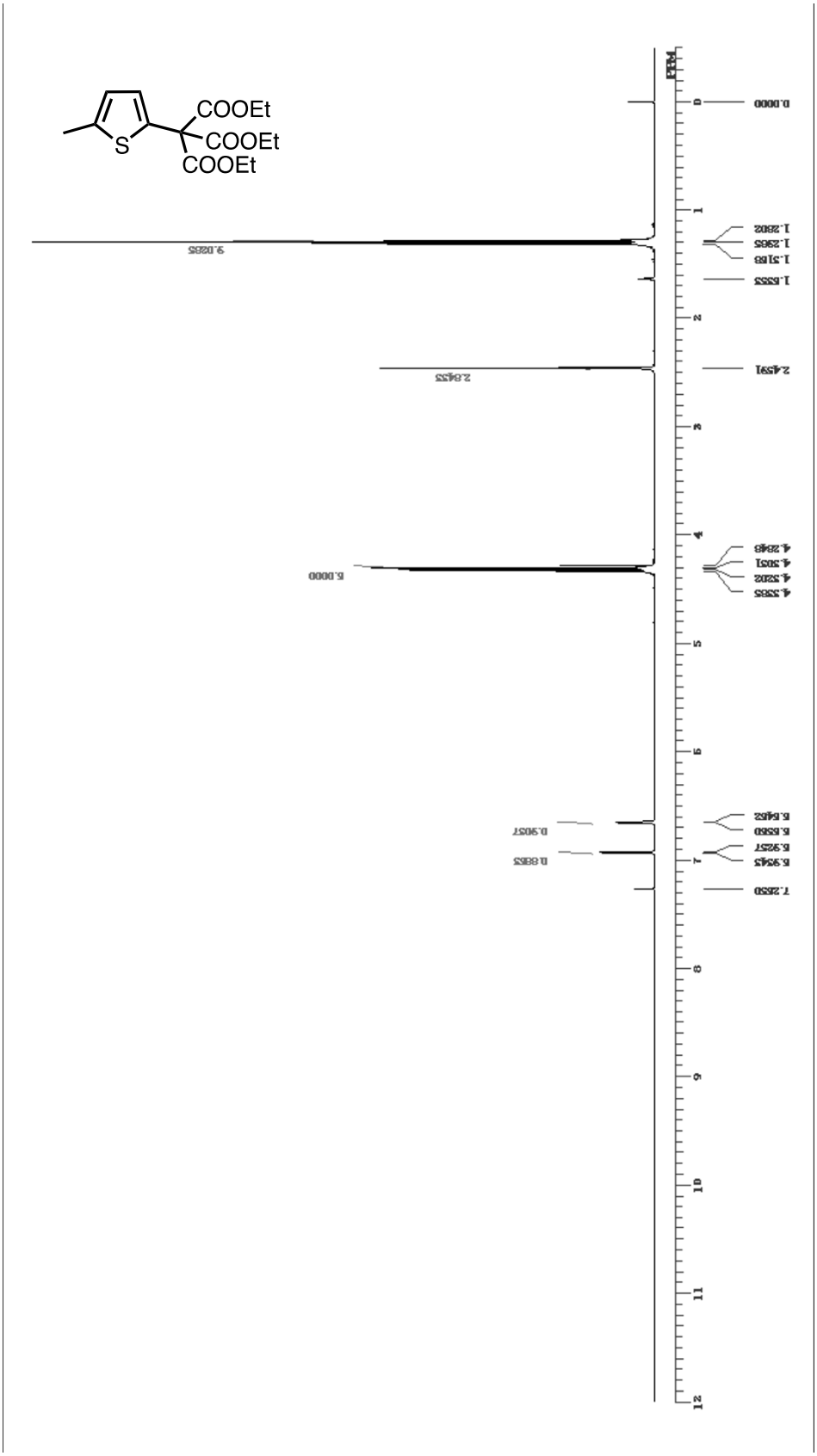


^{13}C NMR (100 MHz, $CDCl_3$) of 3Ad:

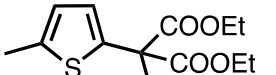


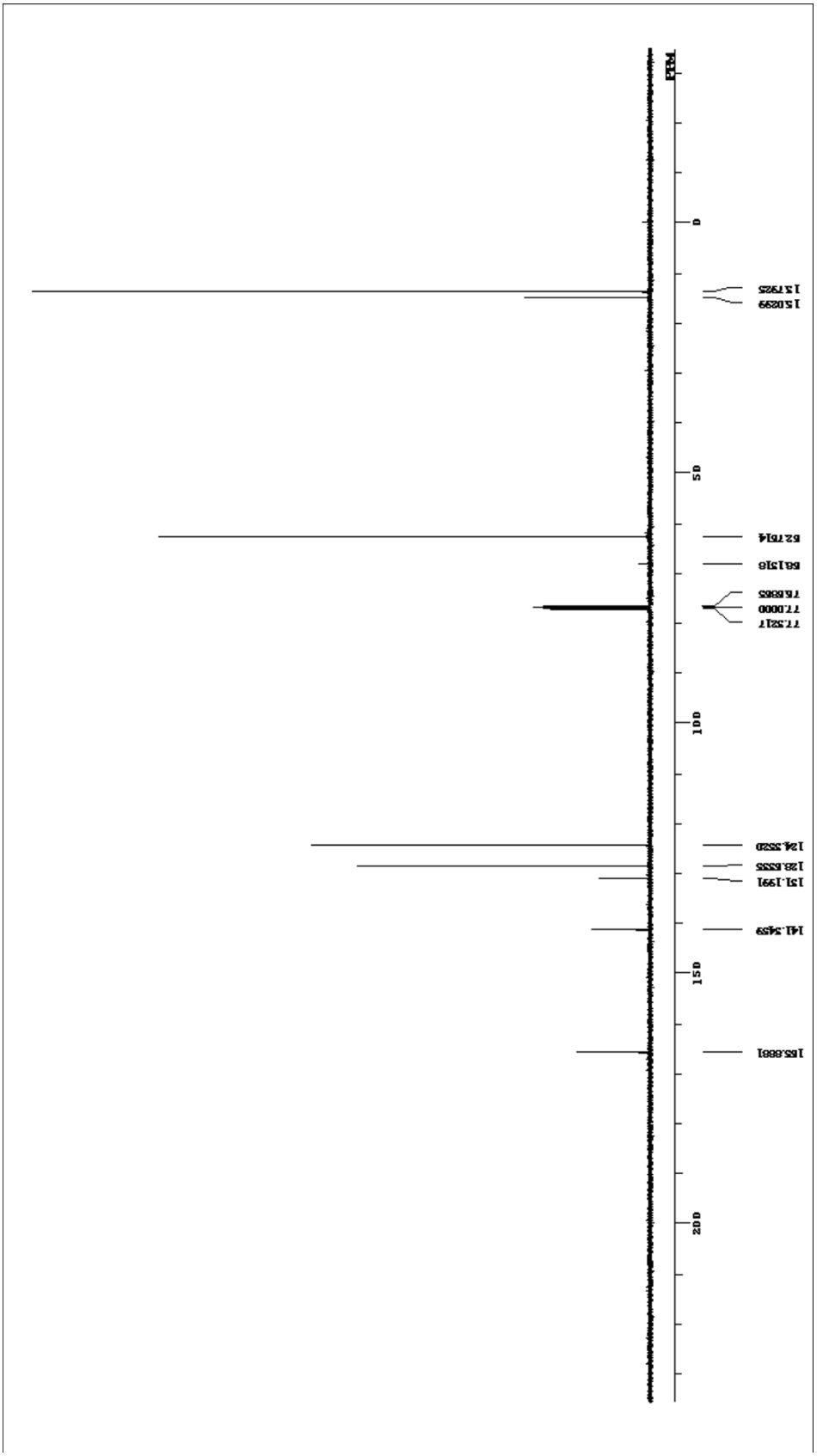


^{1}H NMR (400 MHz, $CDCl_3$) of 3Ae:

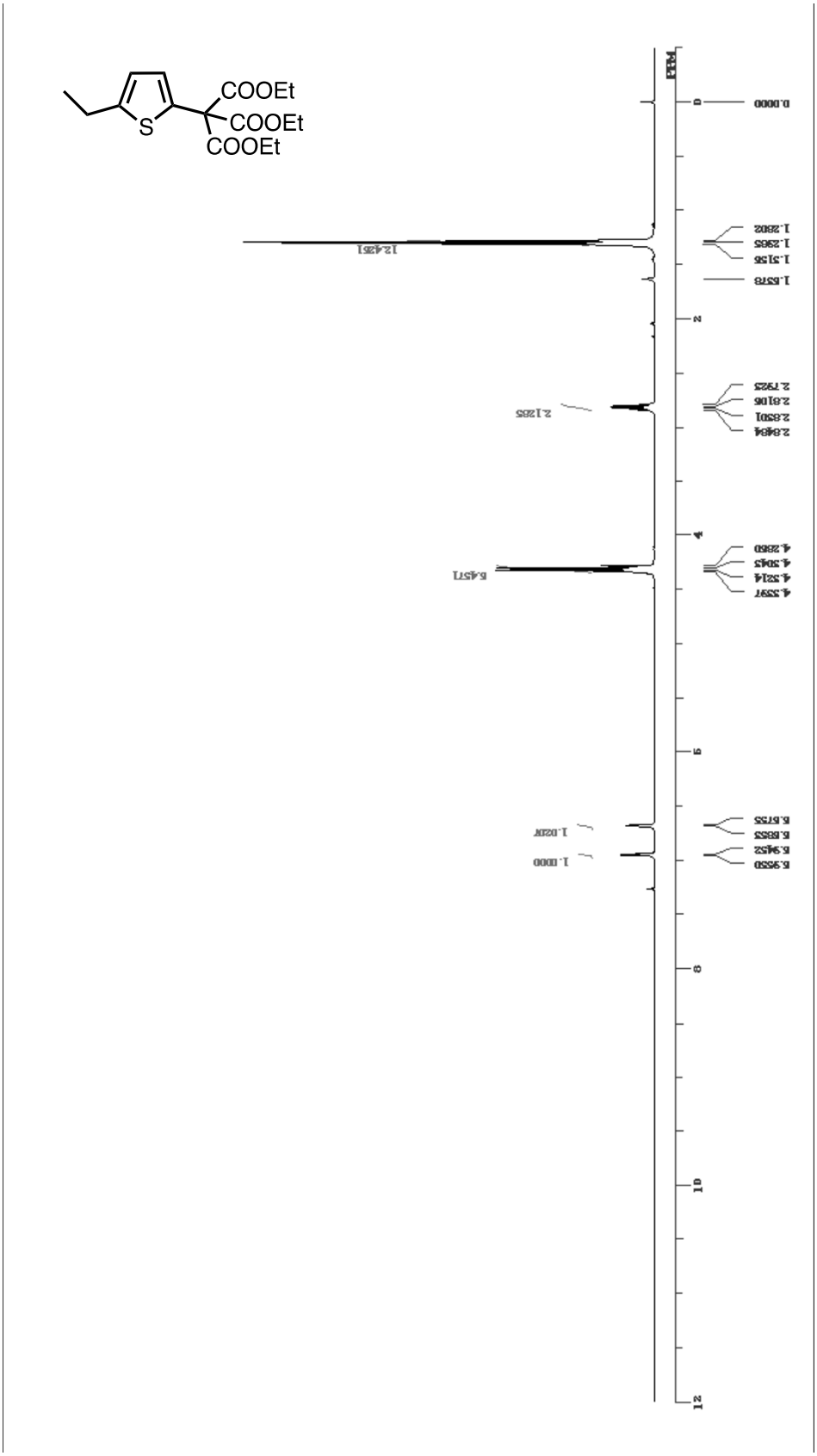


^{13}C NMR (100 MHz, $CDCl_3$) of 3Ae:

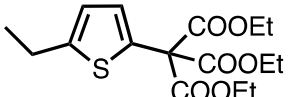


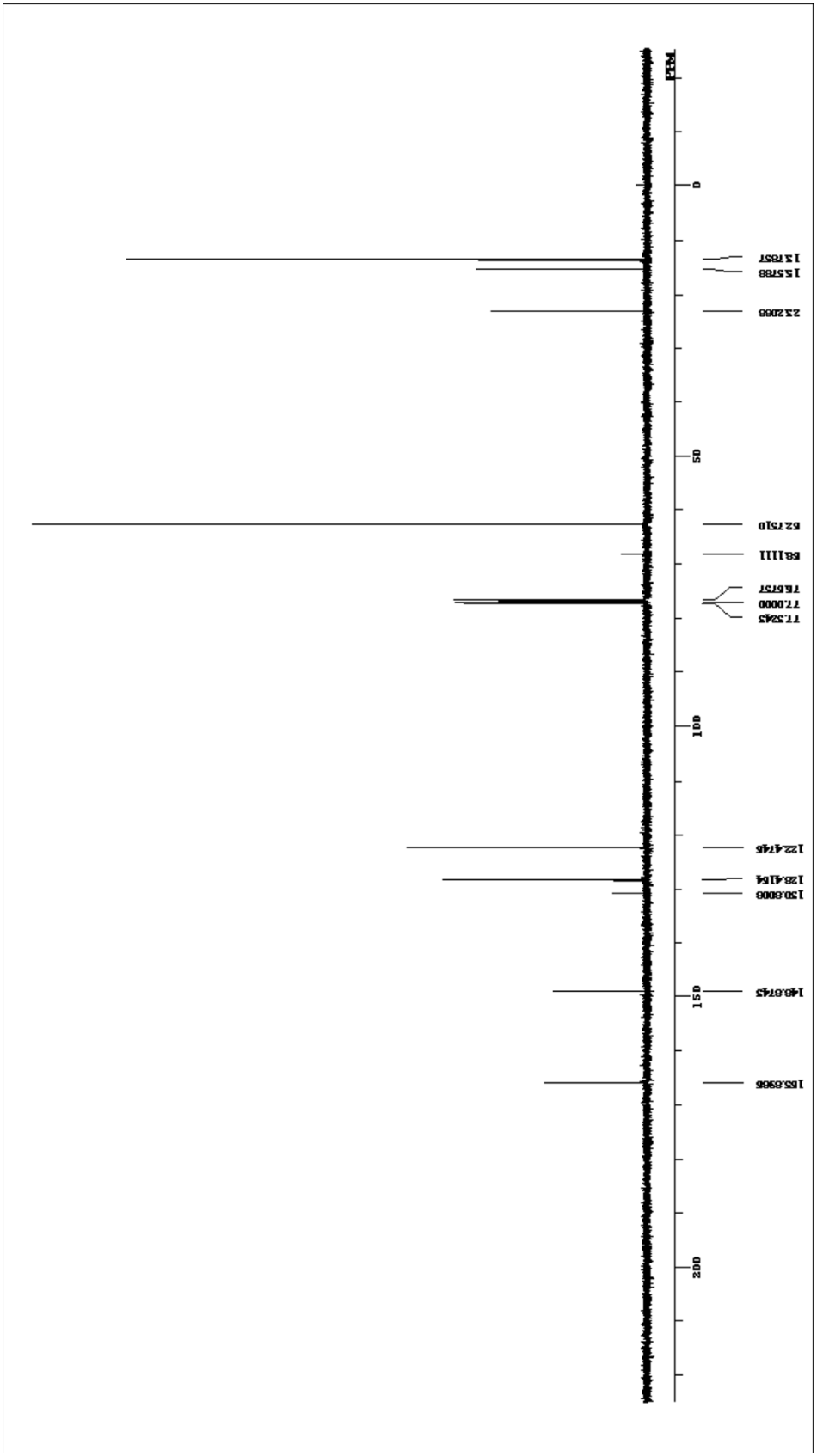


^{1}H NMR (400 MHz, $CDCl_3$) of 3Af:

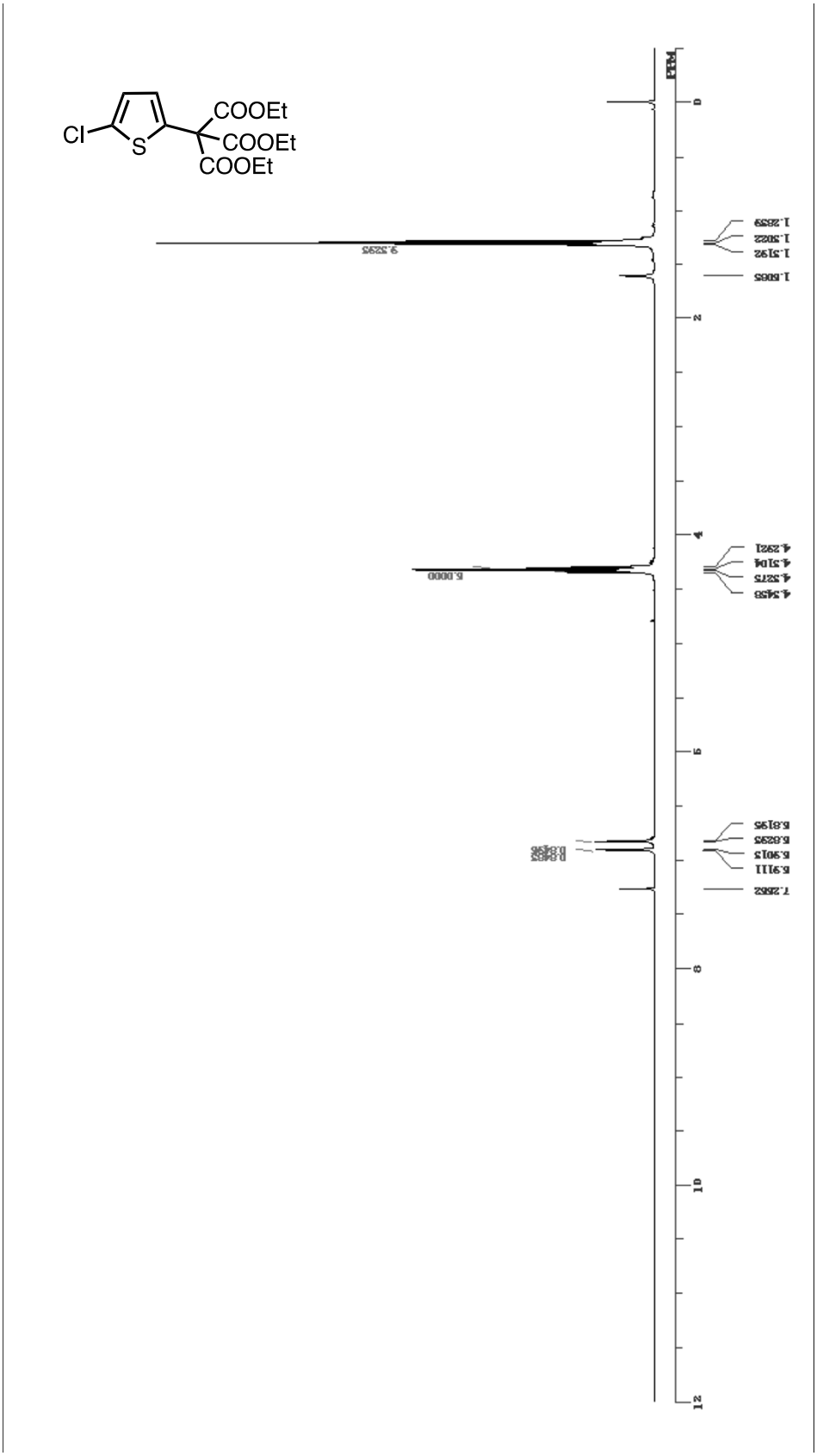


^{13}C NMR (100 MHz, $CDCl_3$) of 3Af:

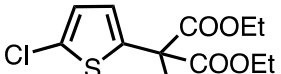


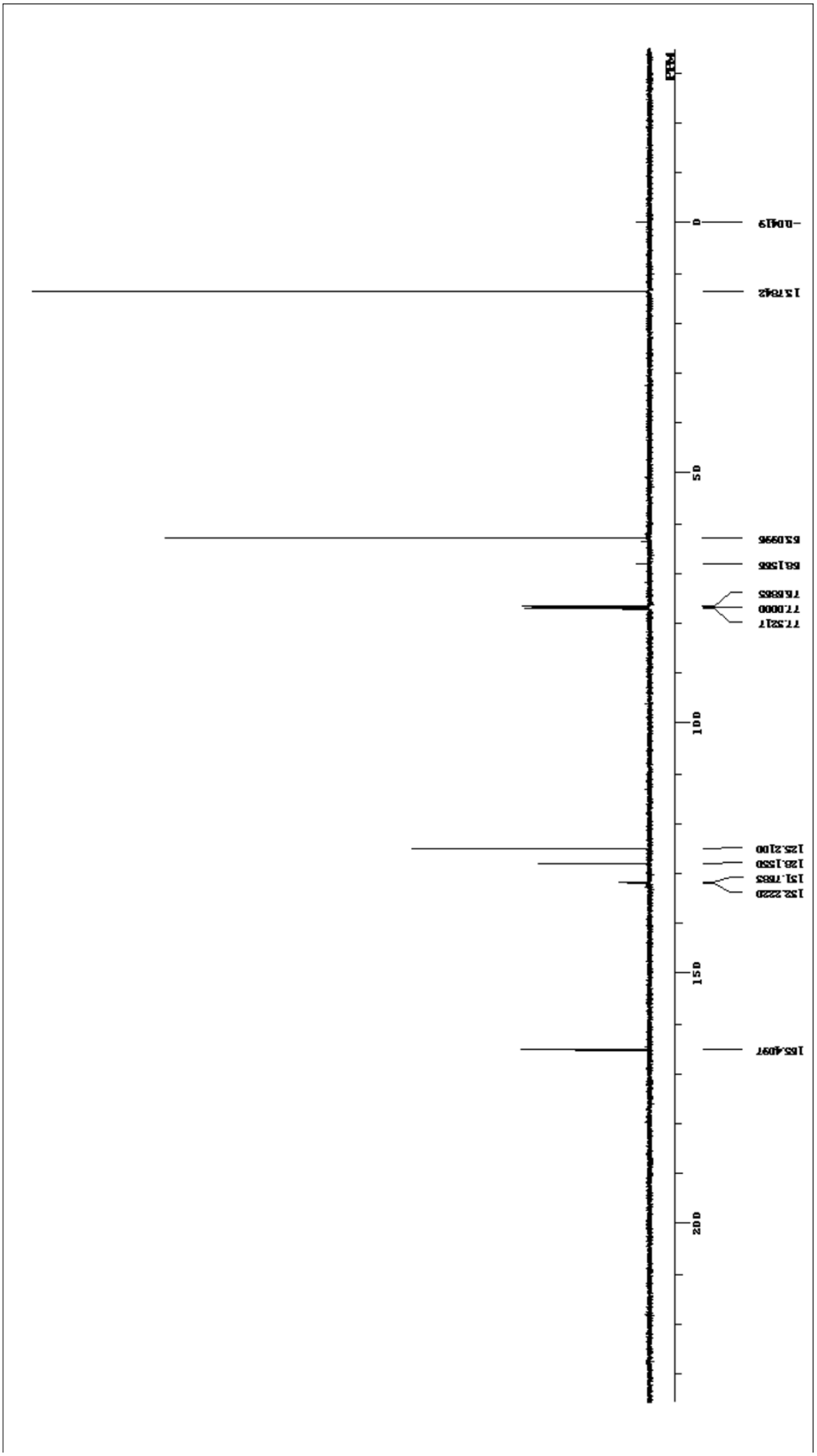


^{1}H NMR (400 MHz, $CDCl_3$) of 3Ag:

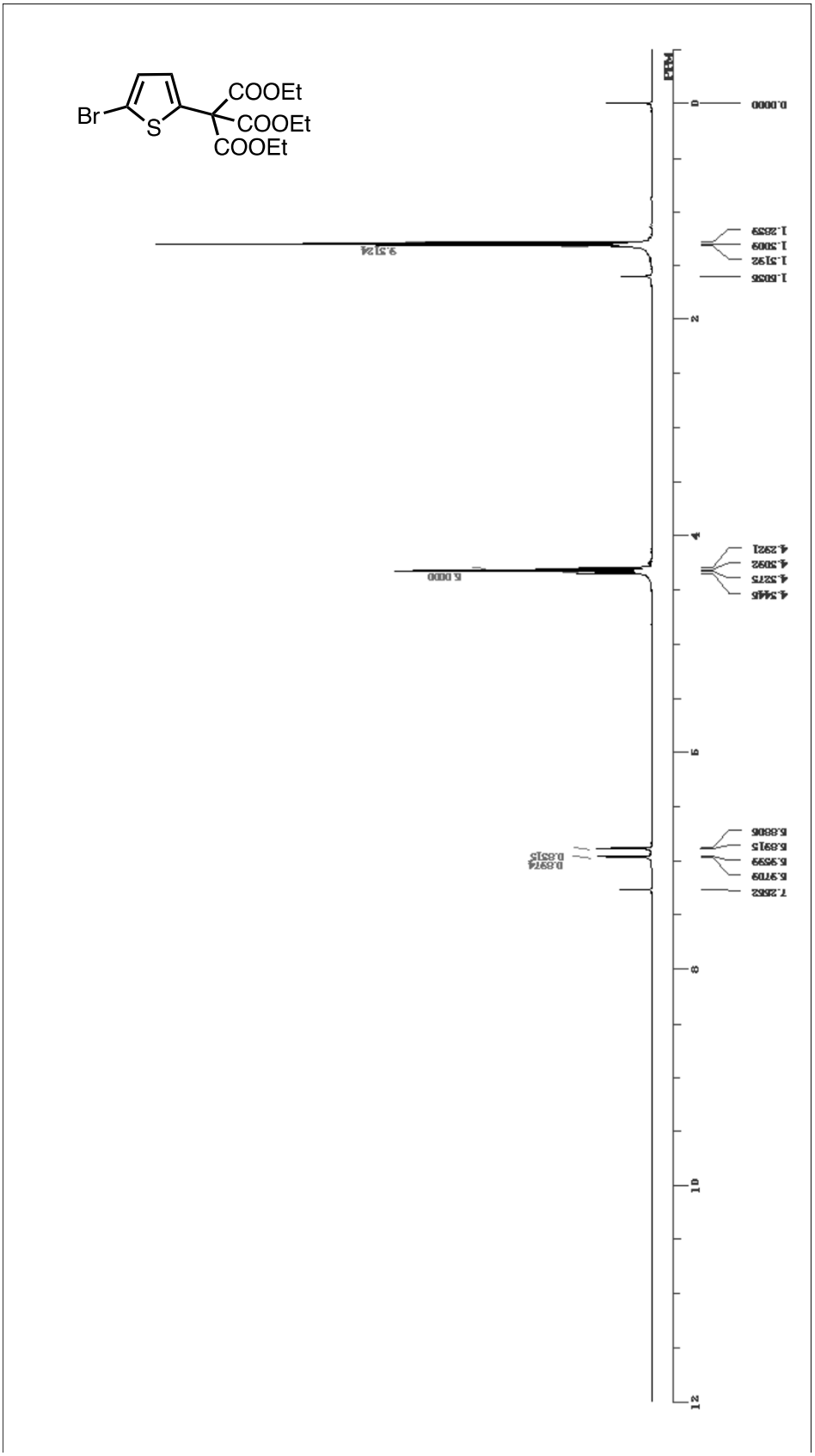


^{13}C NMR (100 MHz, $CDCl_3$) of 3Ag:

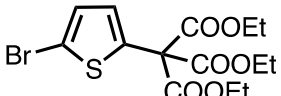


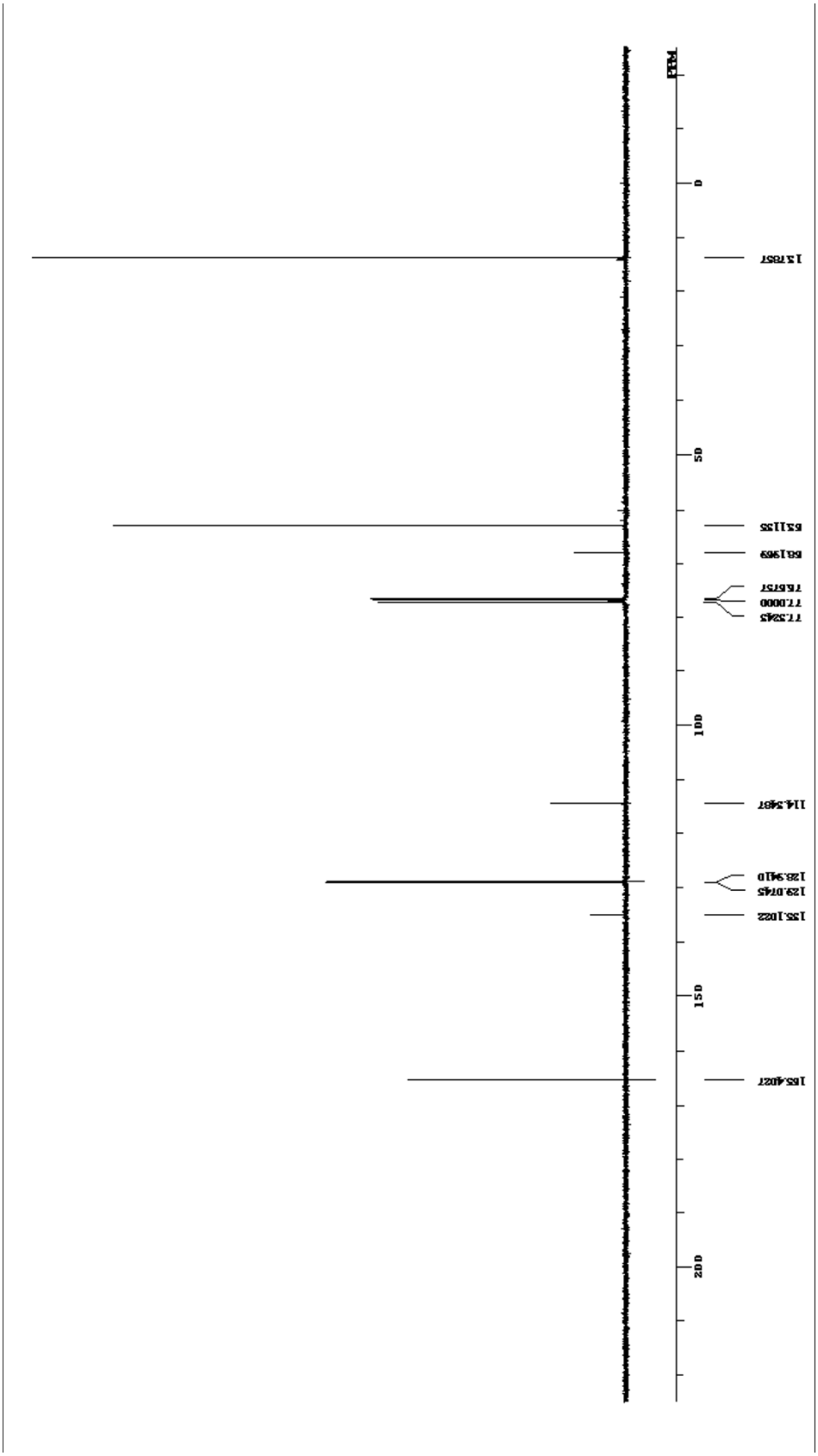


^{1}H NMR (400 MHz, $CDCl_3$) of 3Ah:

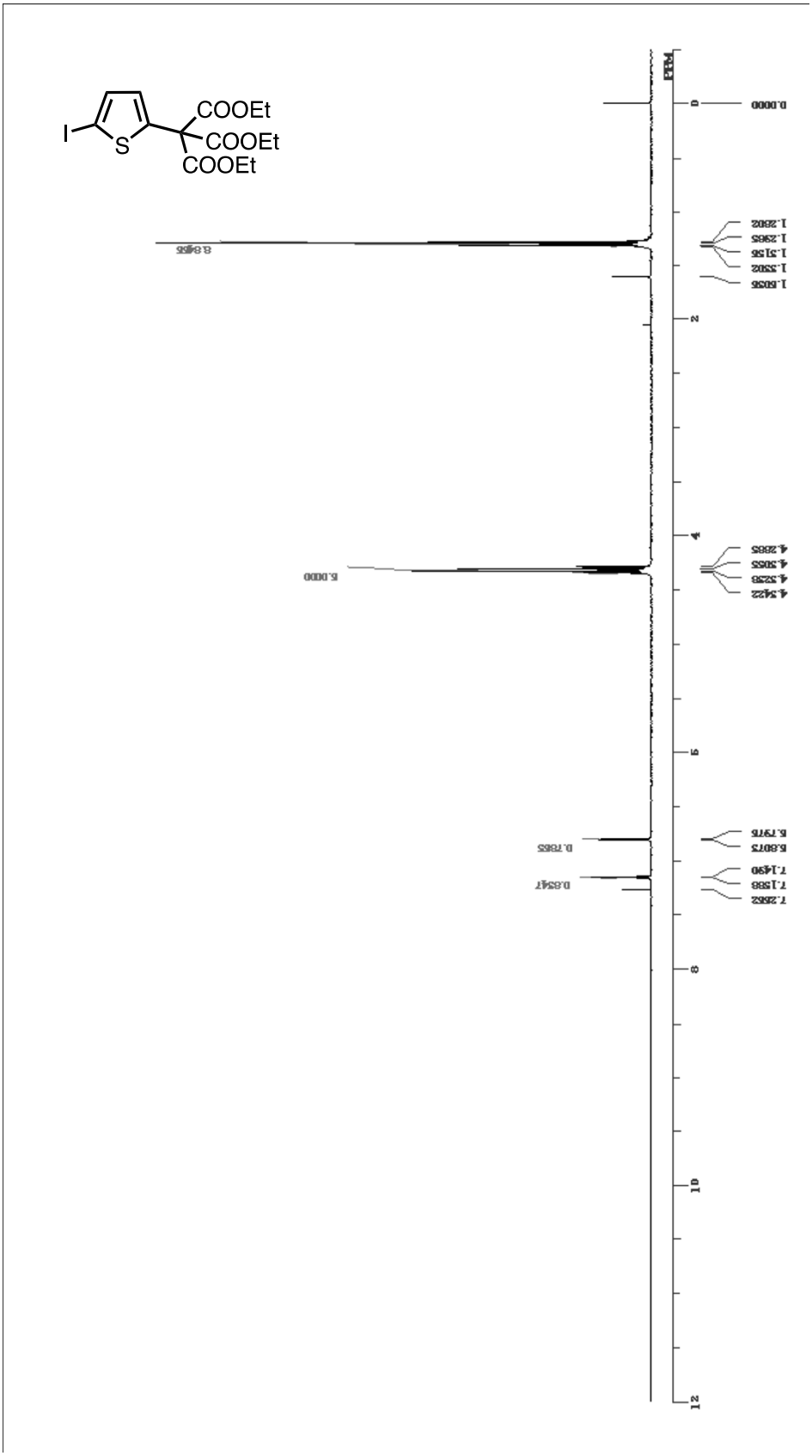


^{13}C NMR (100 MHz, $CDCl_3$) of 3Ah:

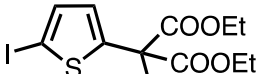


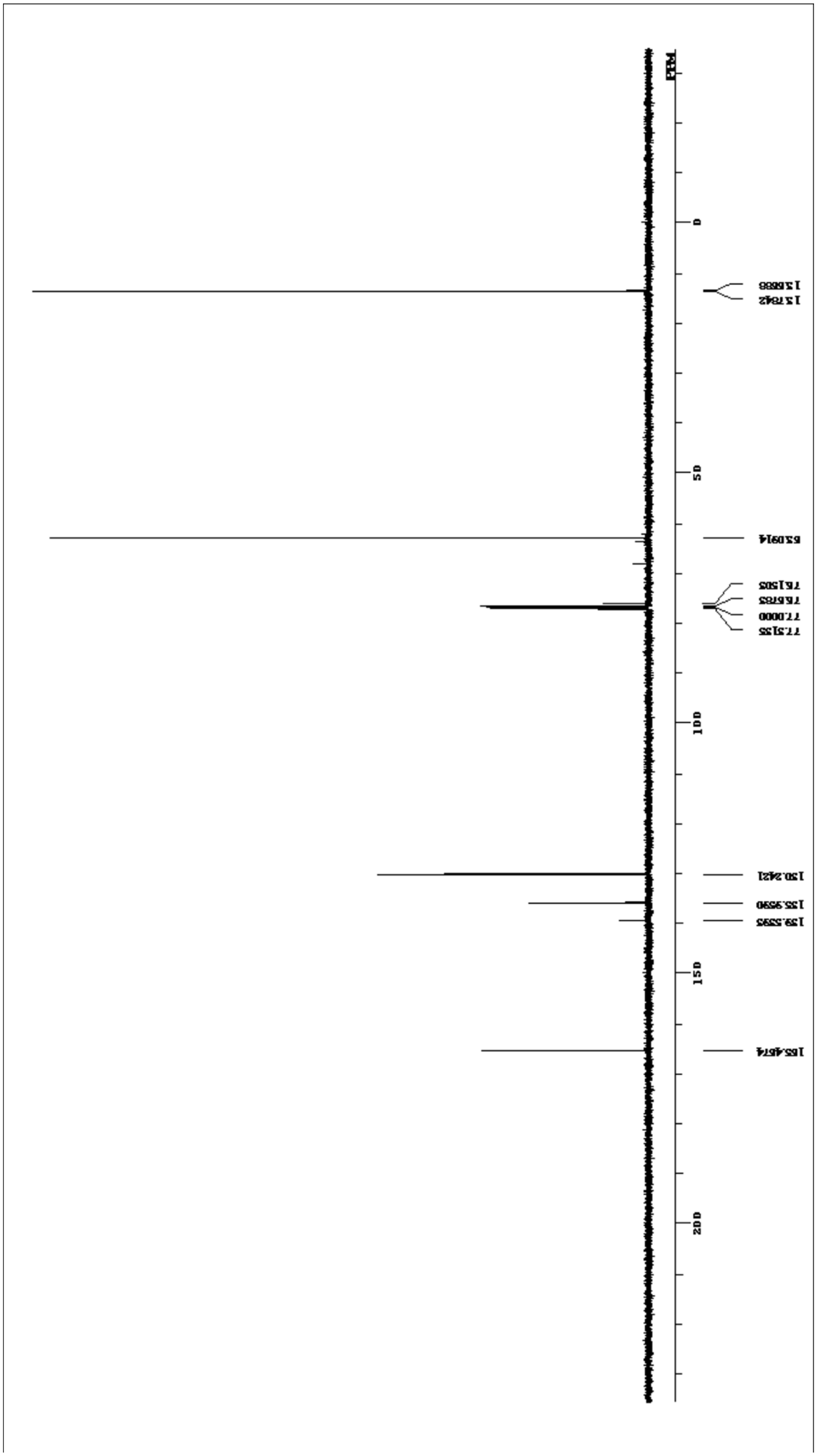


^{1}H NMR (400 MHz, $CDCl_3$) of 3Ai:

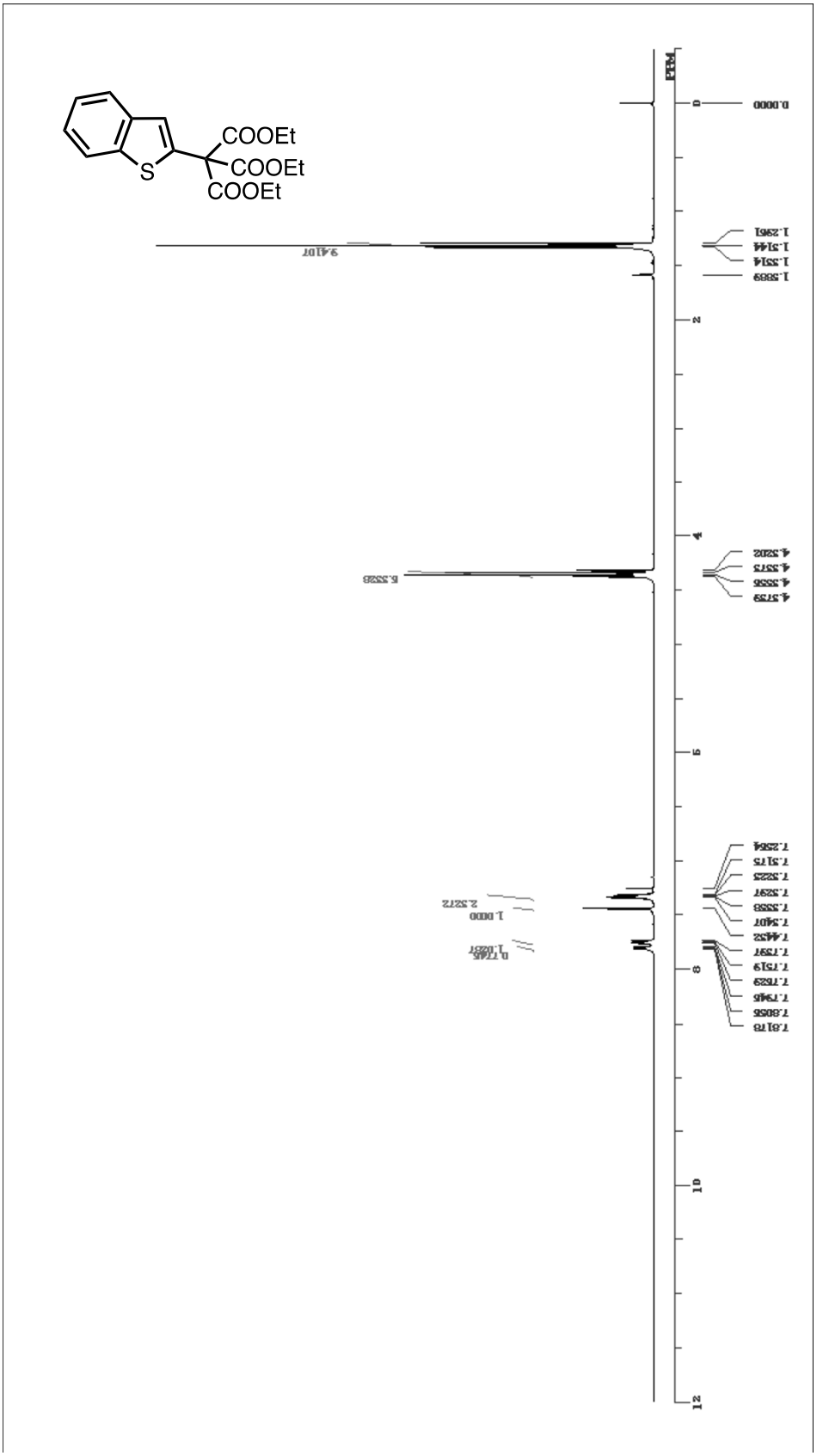


^{13}C NMR (100 MHz, $CDCl_3$) of 3Ai:

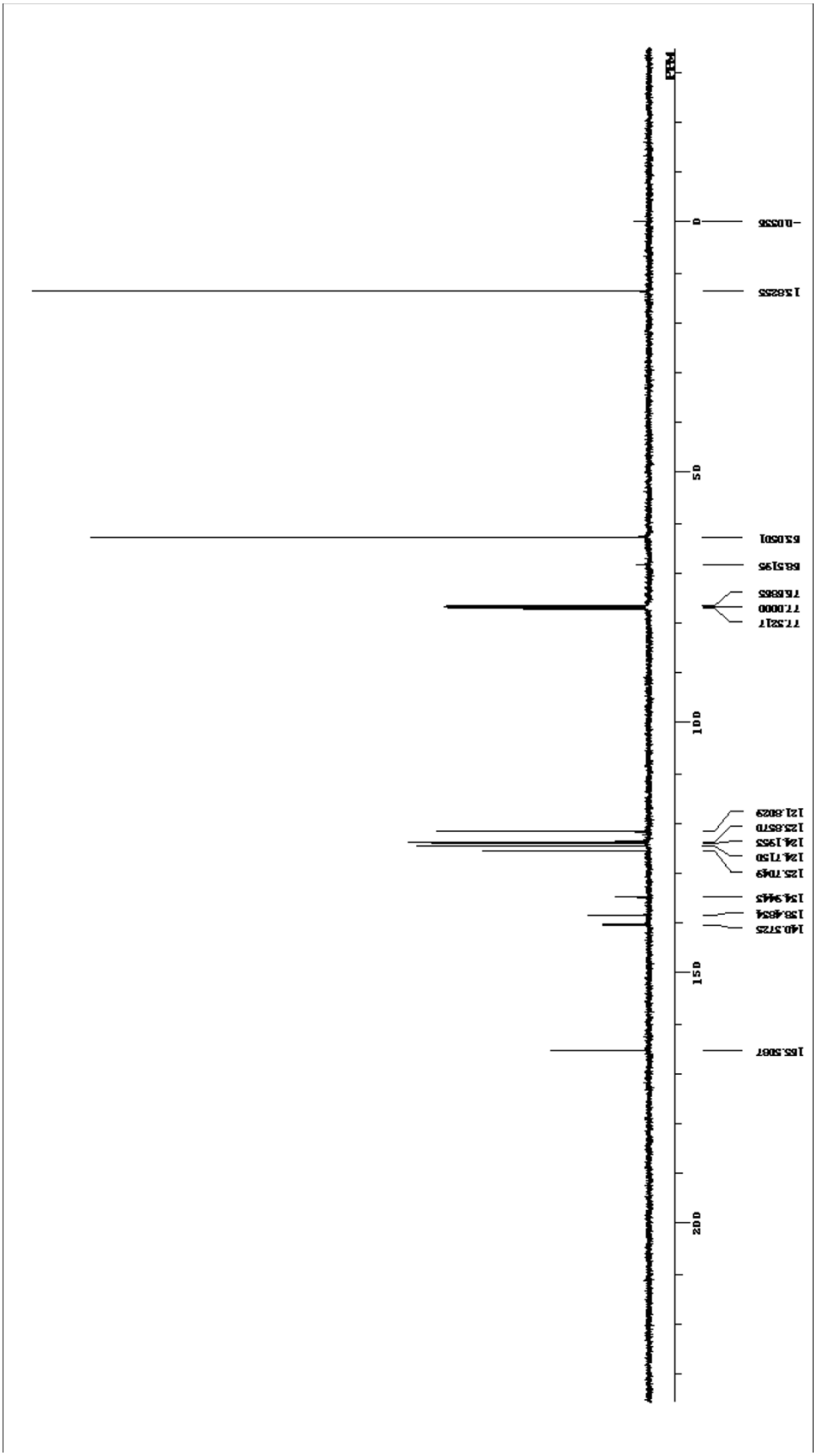




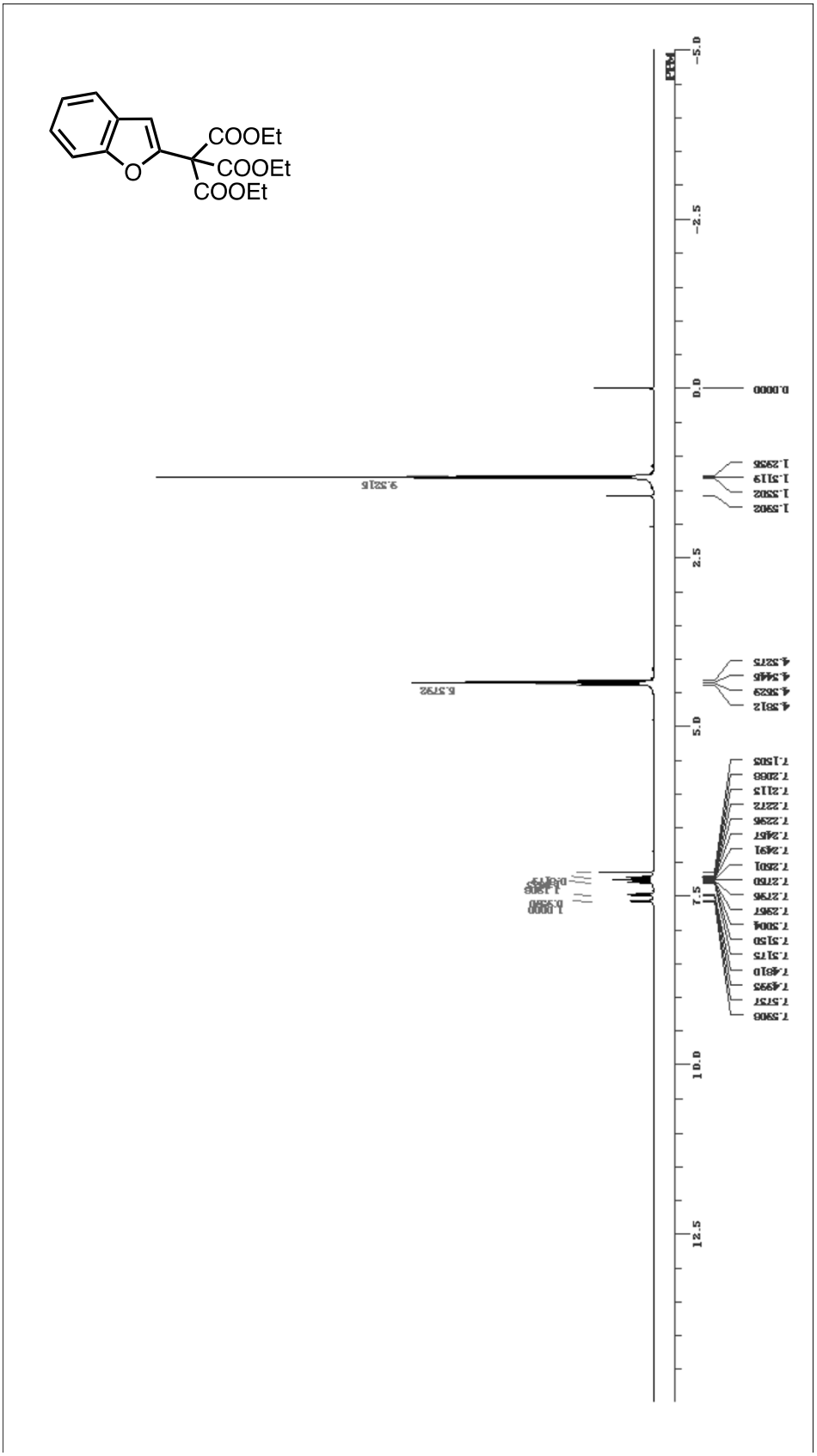
^{1}H NMR (400 MHz, $CDCl_3$) of 3Aj:



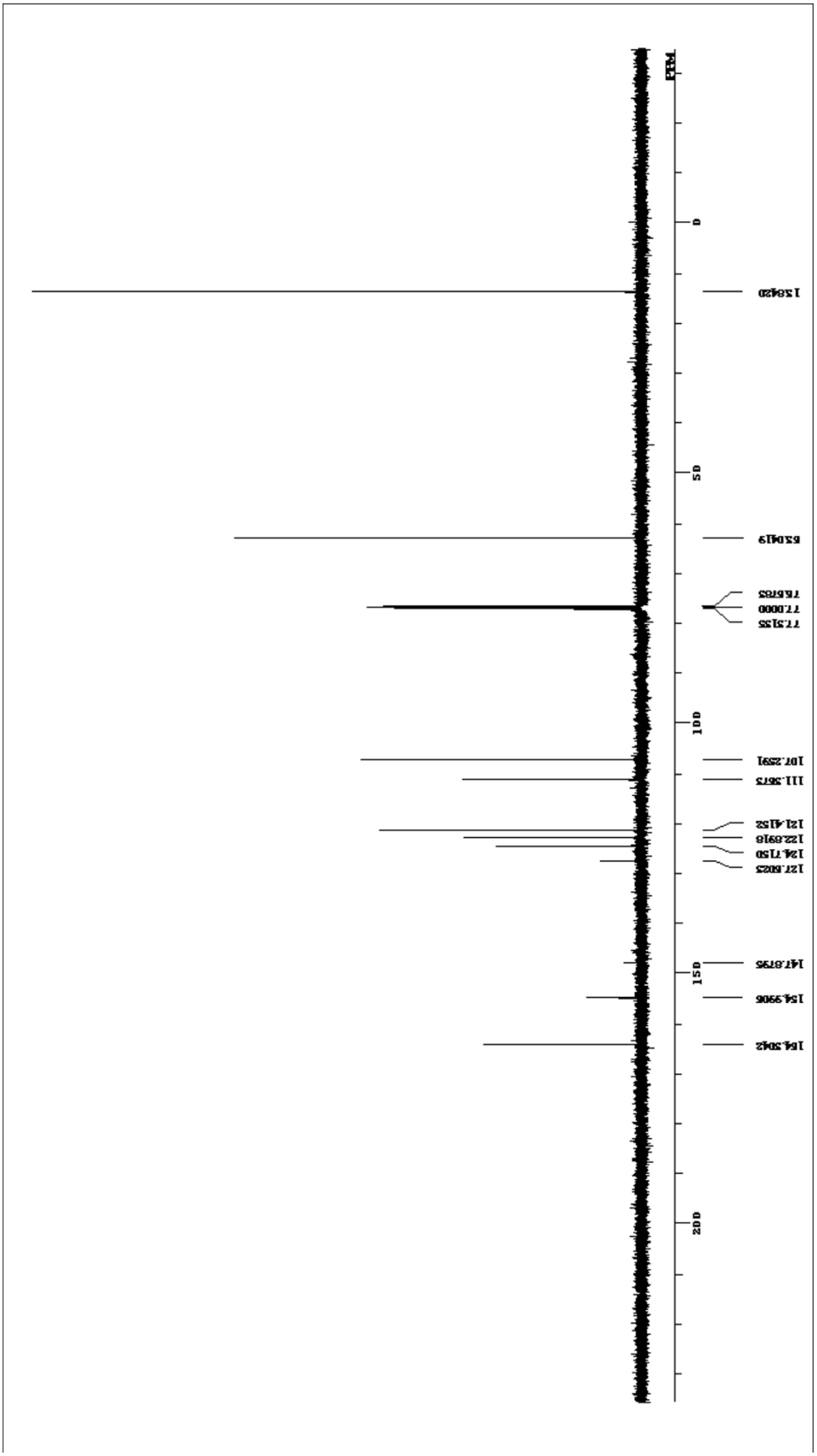
^{13}C NMR (100 MHz, $CDCl_3$) of 3Aj:



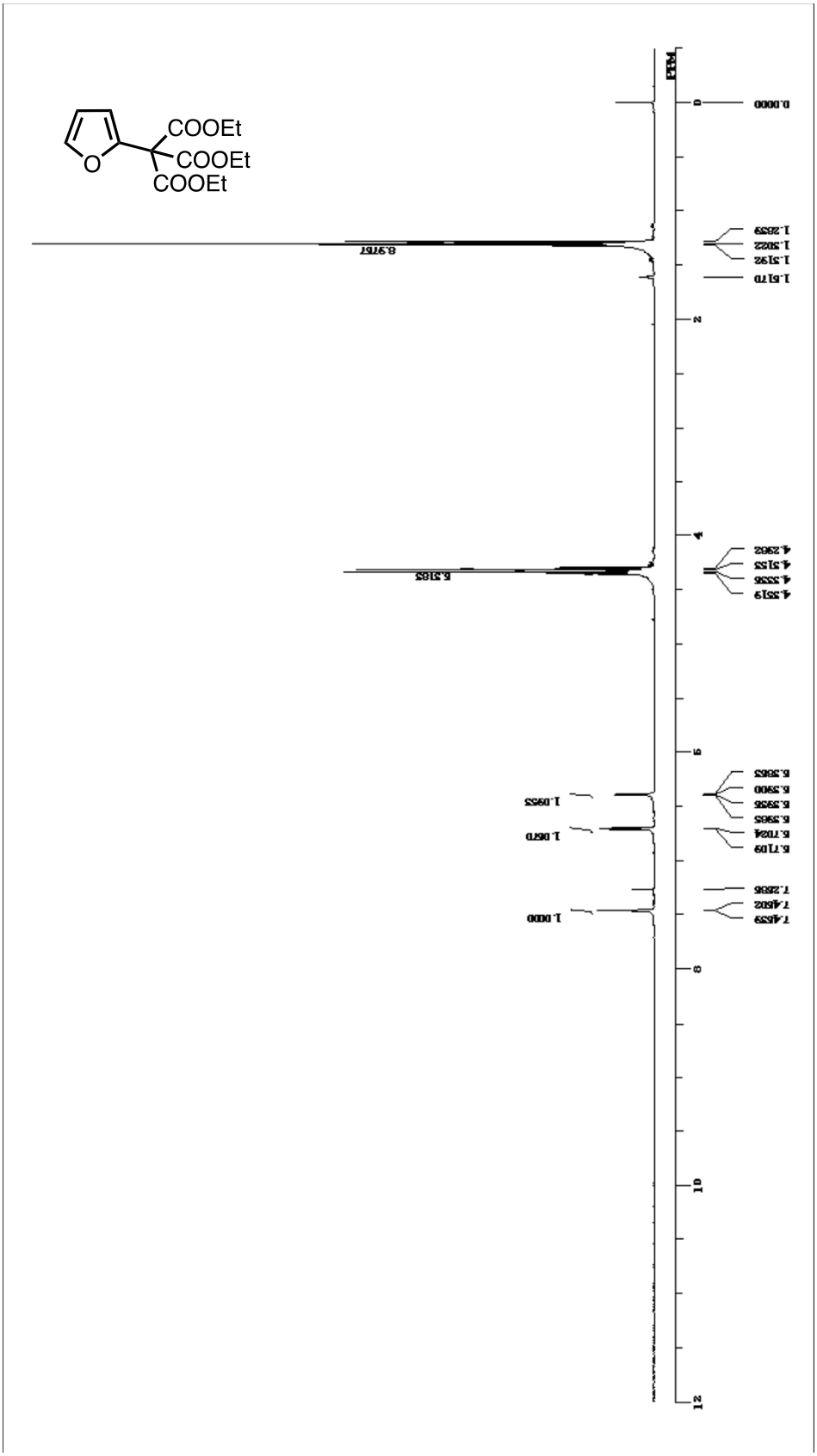
^{1}H NMR (400 MHz, $CDCl_3$) of 3Ak:



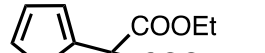
^{13}C NMR (100 MHz, $CDCl_3$) of 3Ak:

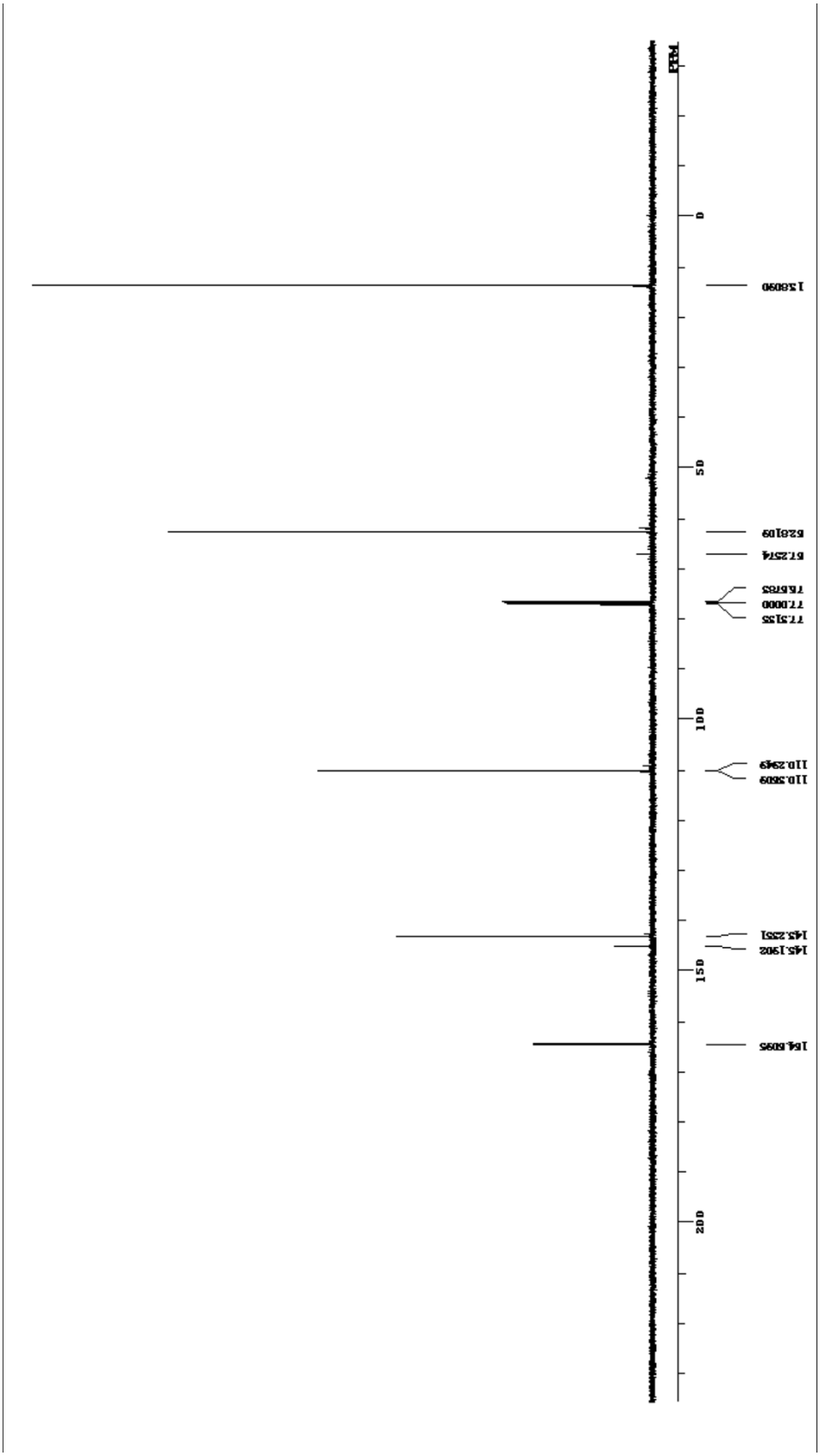


^{1}H NMR (400 MHz, $CDCl_3$) of 3Al:

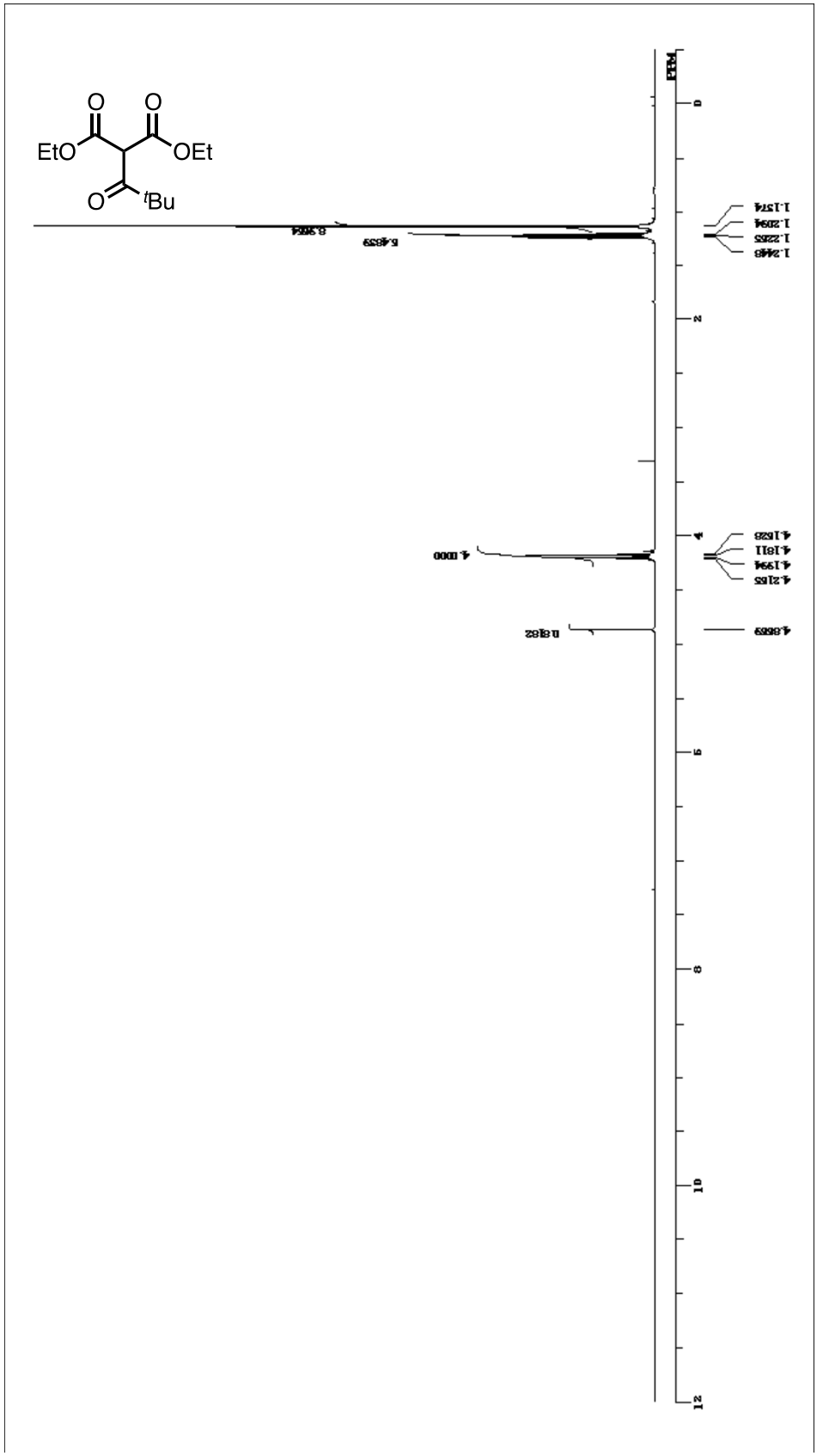


^{13}C NMR (100 MHz, $CDCl_3$) of 3Al:

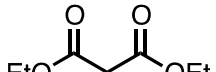


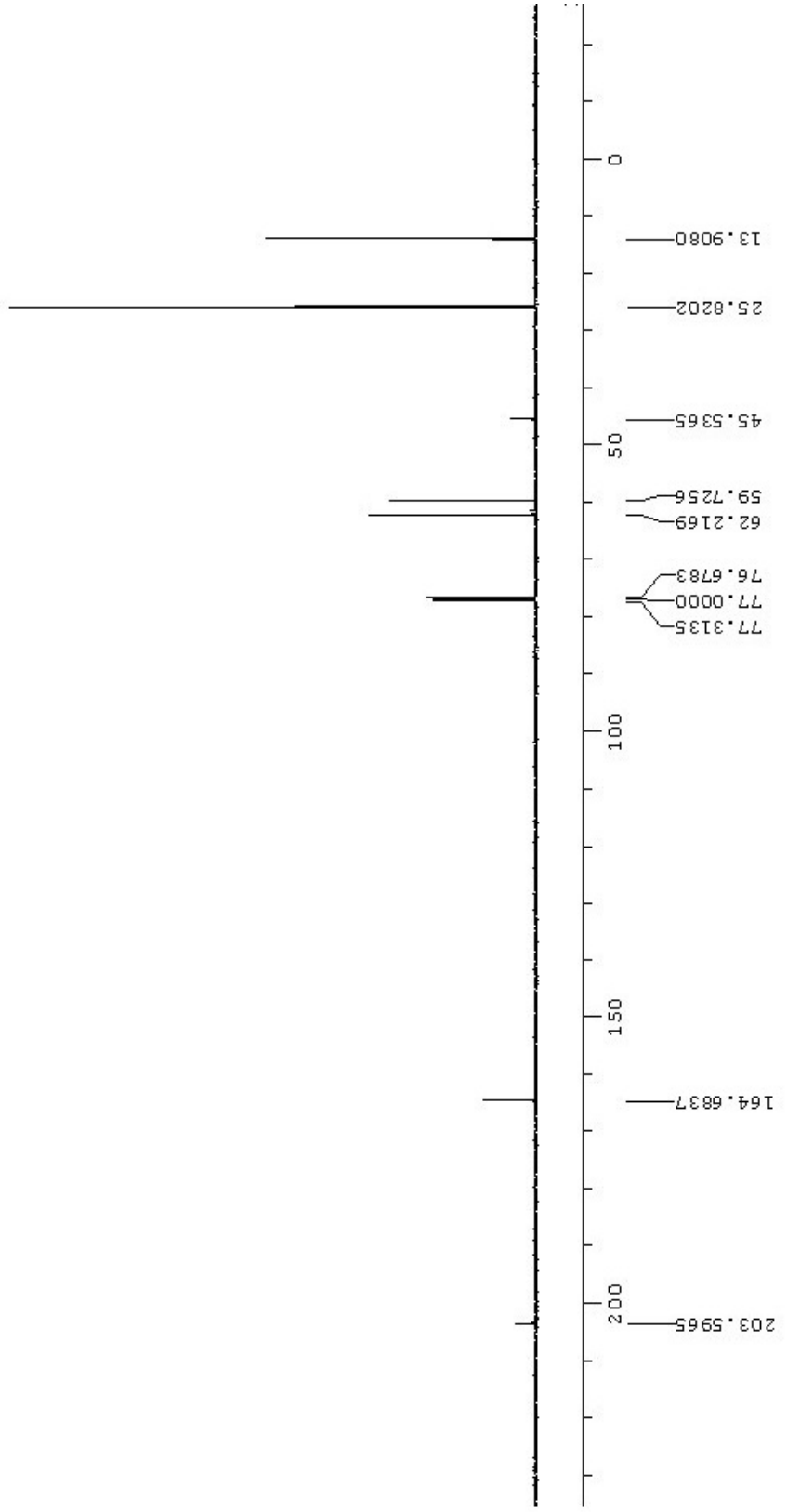


^{1}H NMR (400 MHz, $CDCl_3$) of 1B:

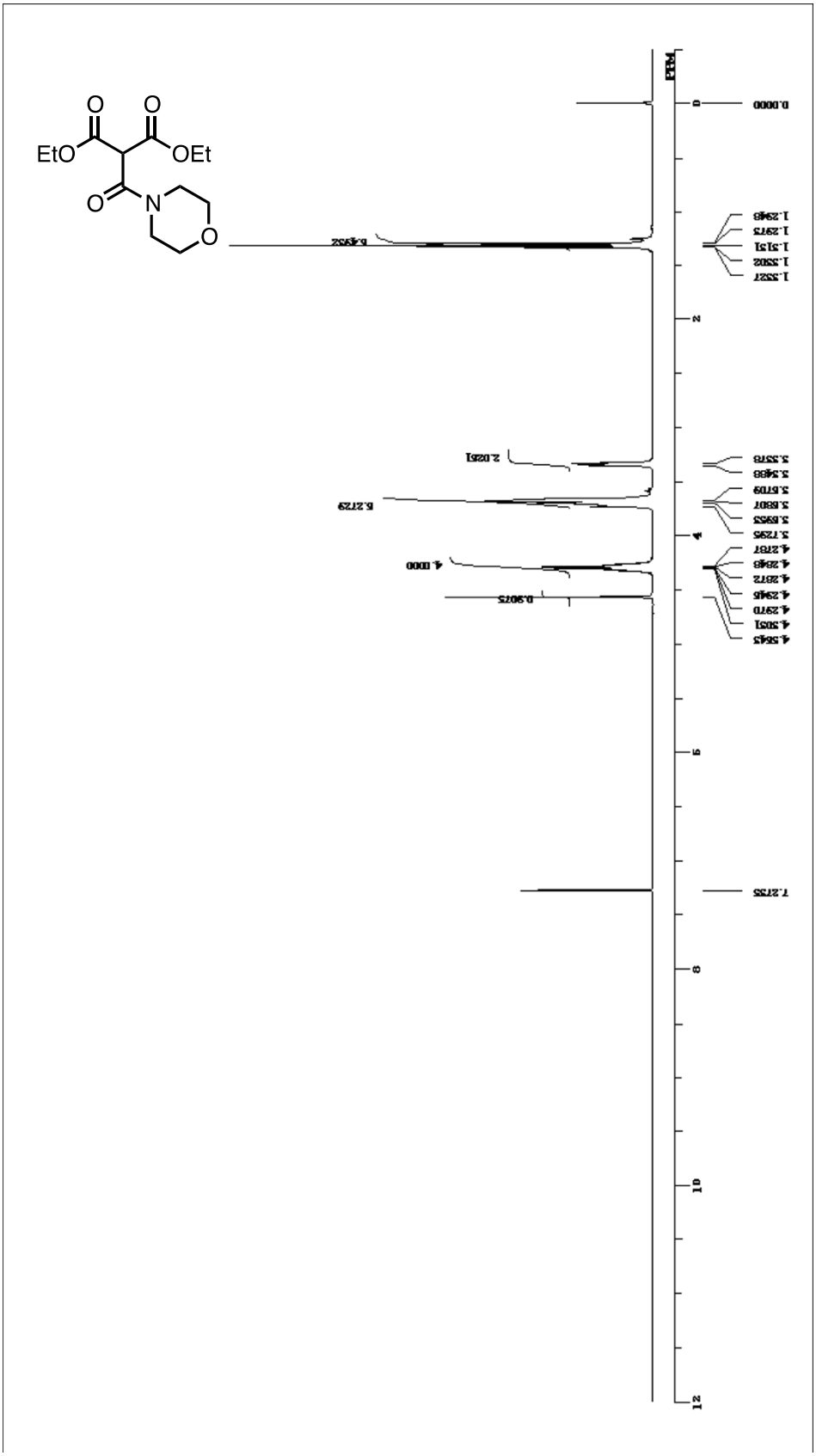


^{13}C NMR (100 MHz, $CDCl_3$) of 1B:





^{1}H NMR (400 MHz, $CDCl_3$) of 1D:


EtO
OEt
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O
O
N
O
PPM
0
2
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6
8
10
12
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1.2973
1.3131
1.3302
1.3527
6.4952
2.0251
5.2729
4.0000
0.9075
7.2755
3.3578
3.3488
5.6709
5.6807
5.6925
5.7295
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4.2948
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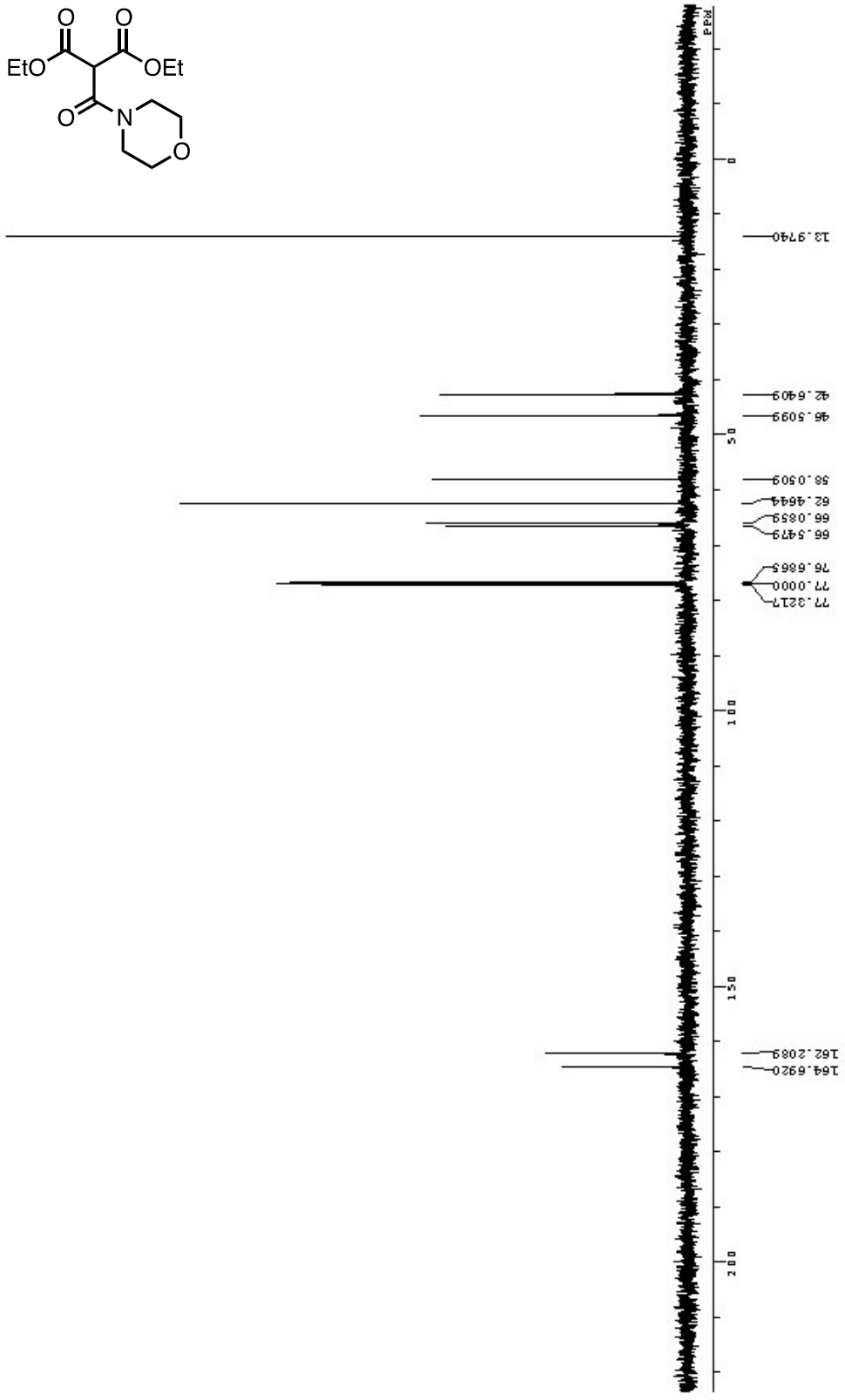
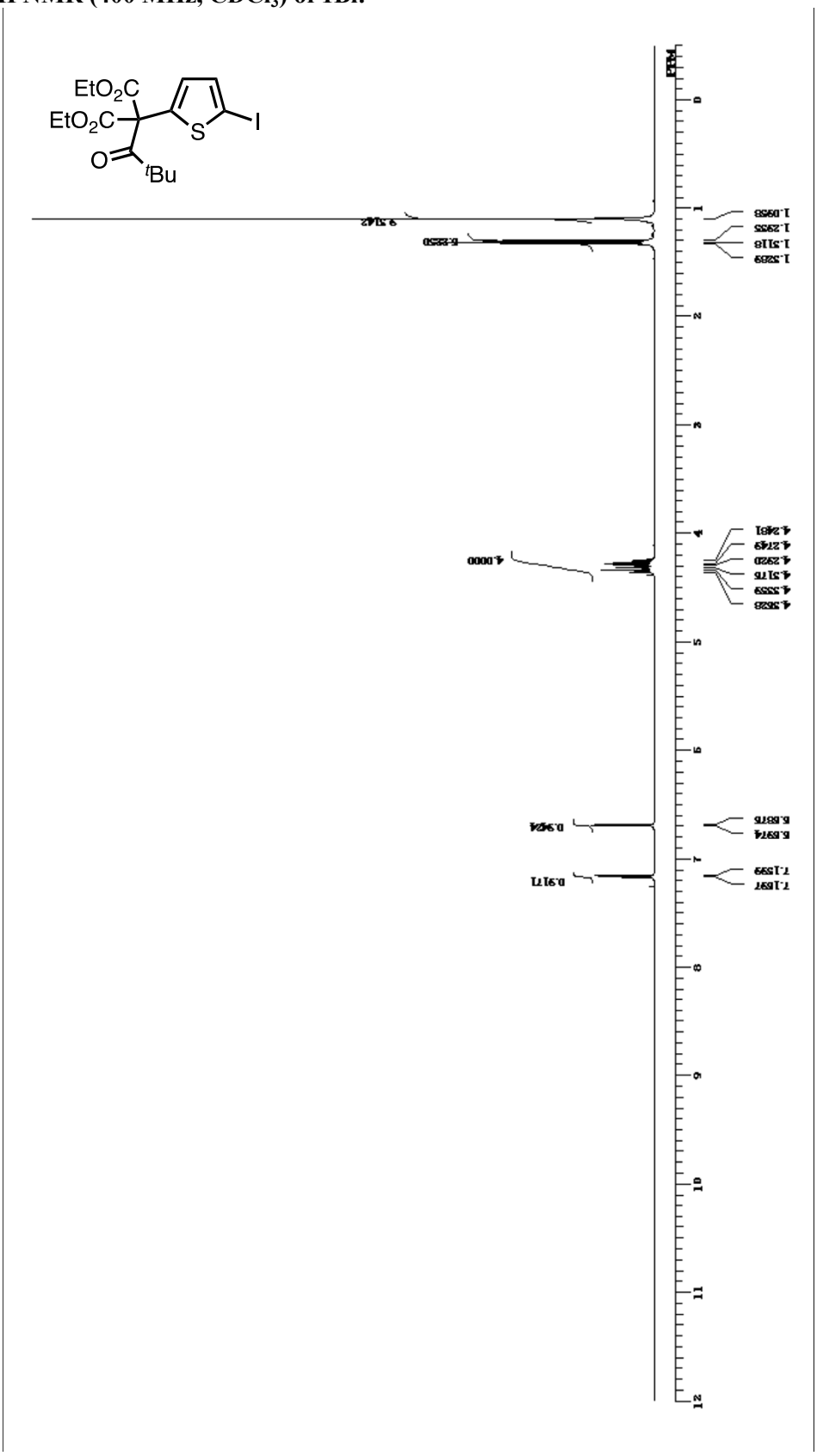
4.2948
4.2970
4.3051
4.5645

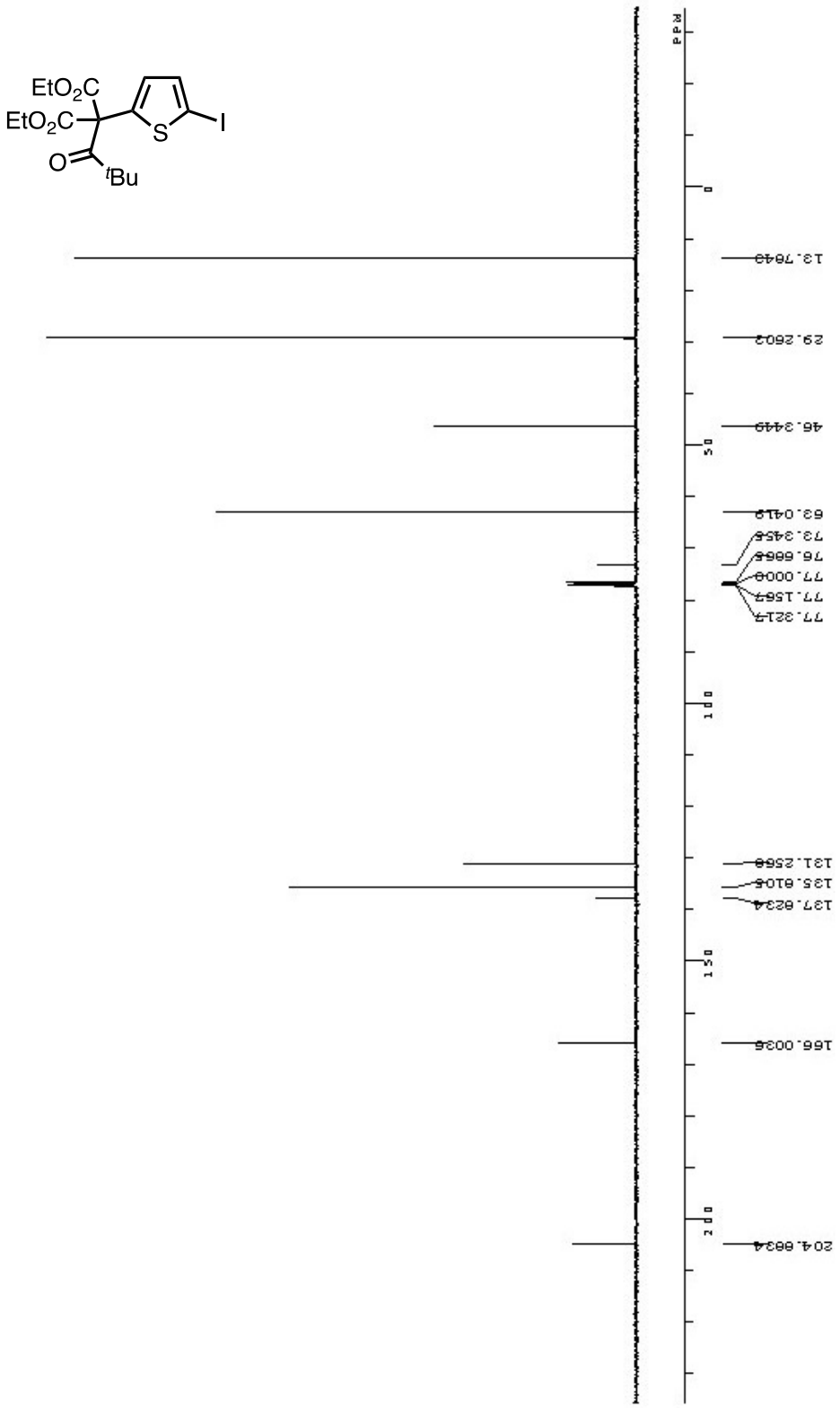
^{13}C NMR (100 MHz, $CDCl_3$) of 1D:



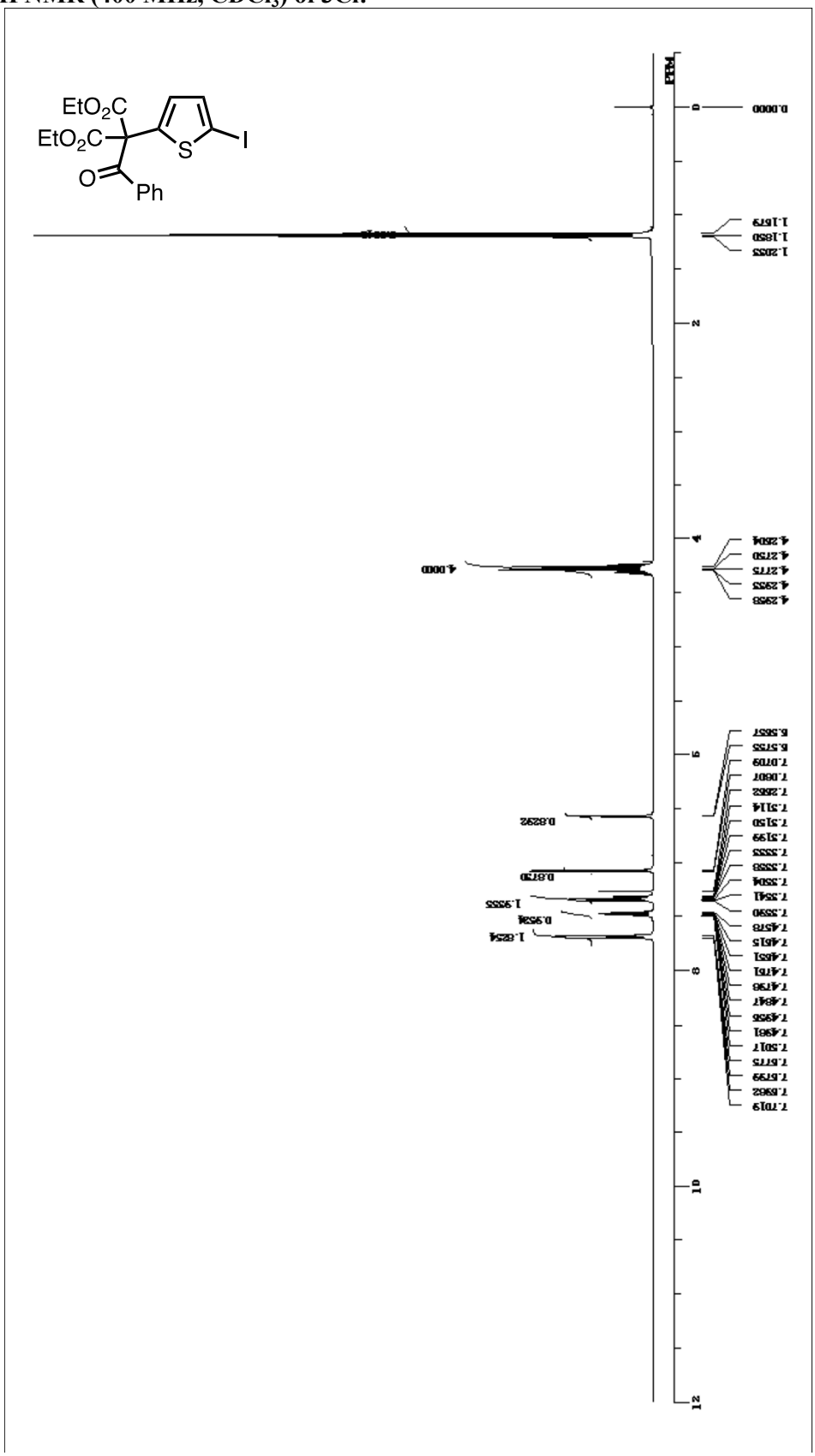
^{1}H NMR (400 MHz, $CDCl_3$) of 1Bi:



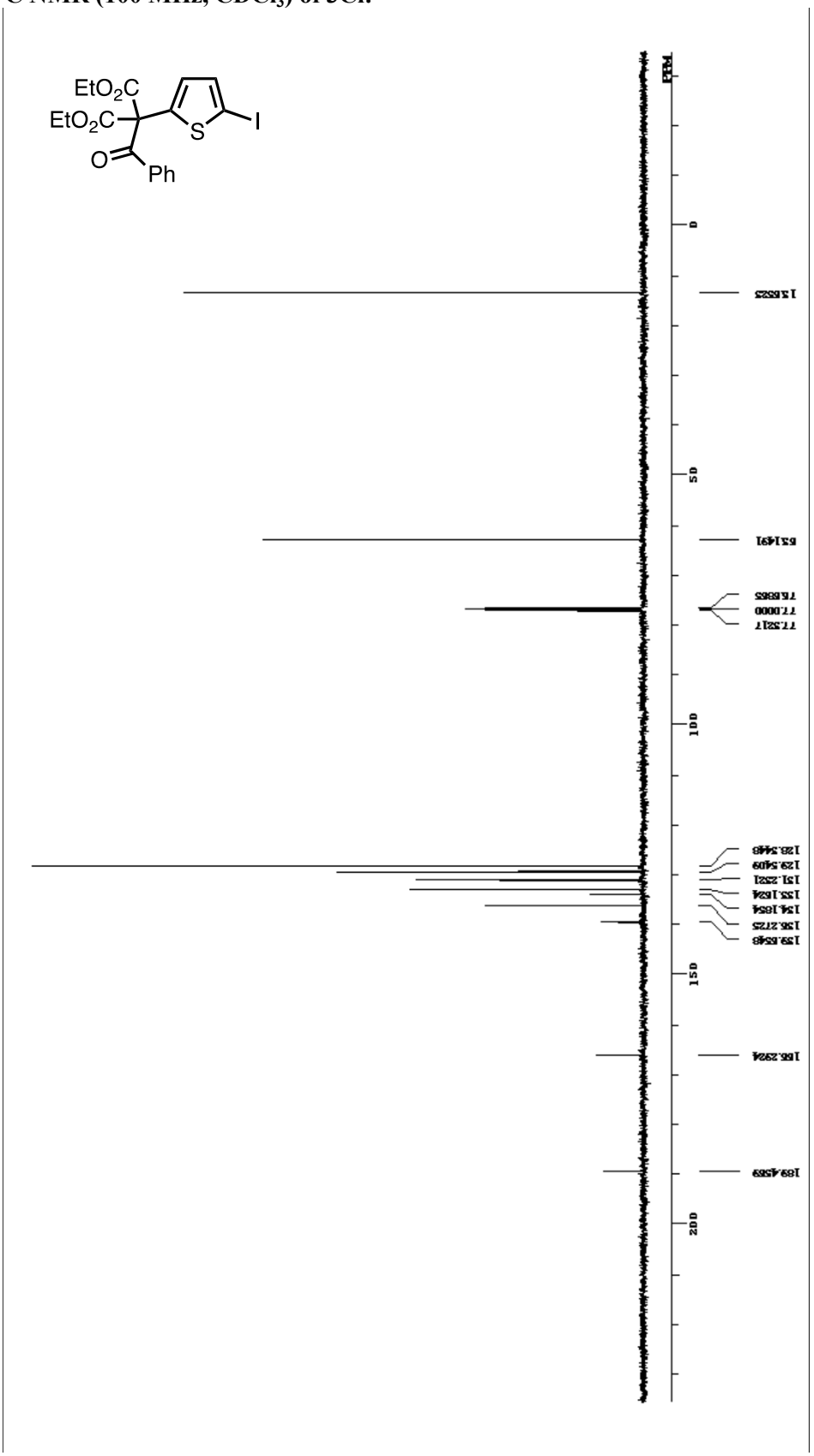
^{13}C NMR (100 MHz, $CDCl_3$) of 1Bi:



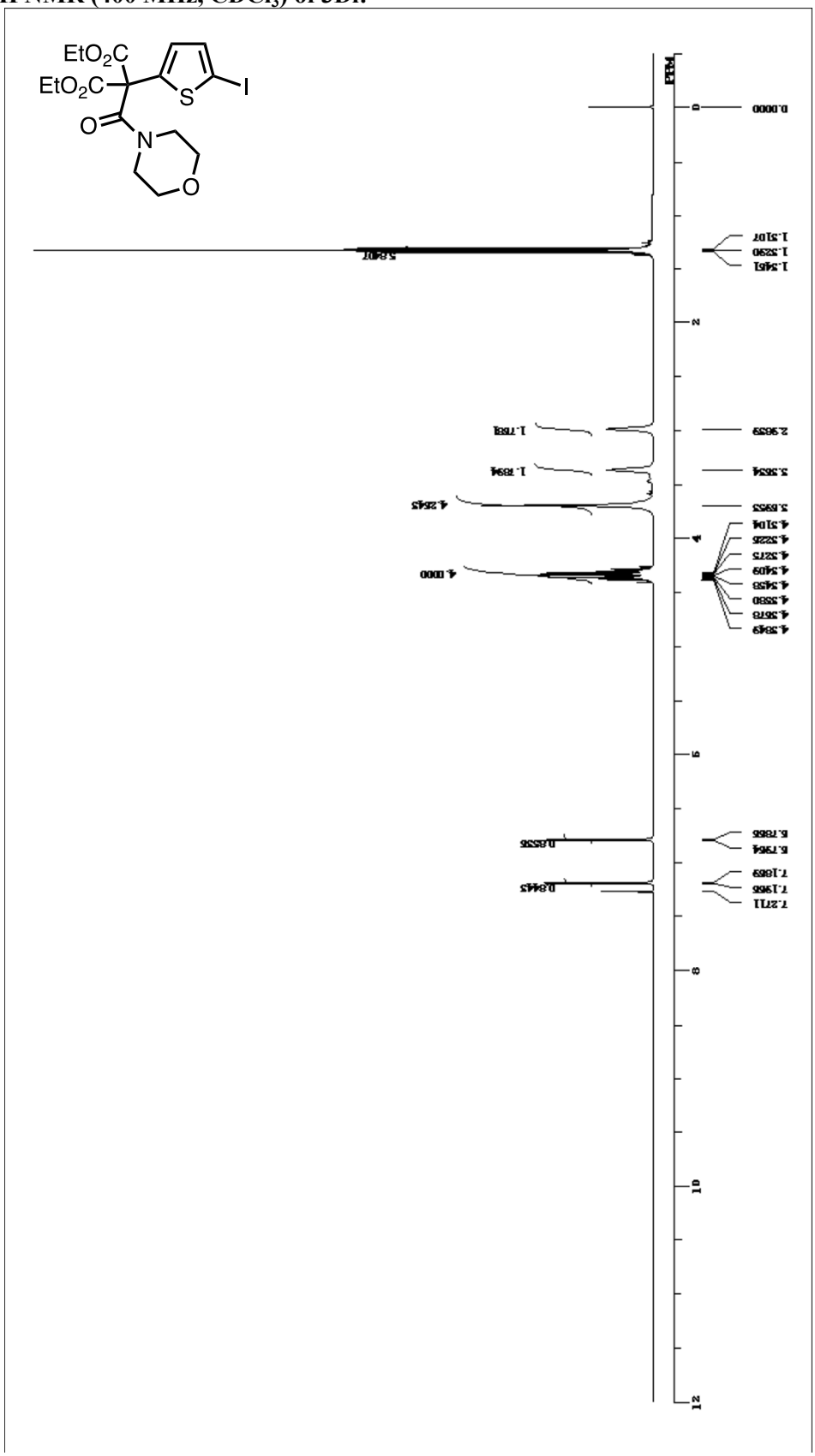
^{1}H NMR (400 MHz, $CDCl_3$) of 3Ci:



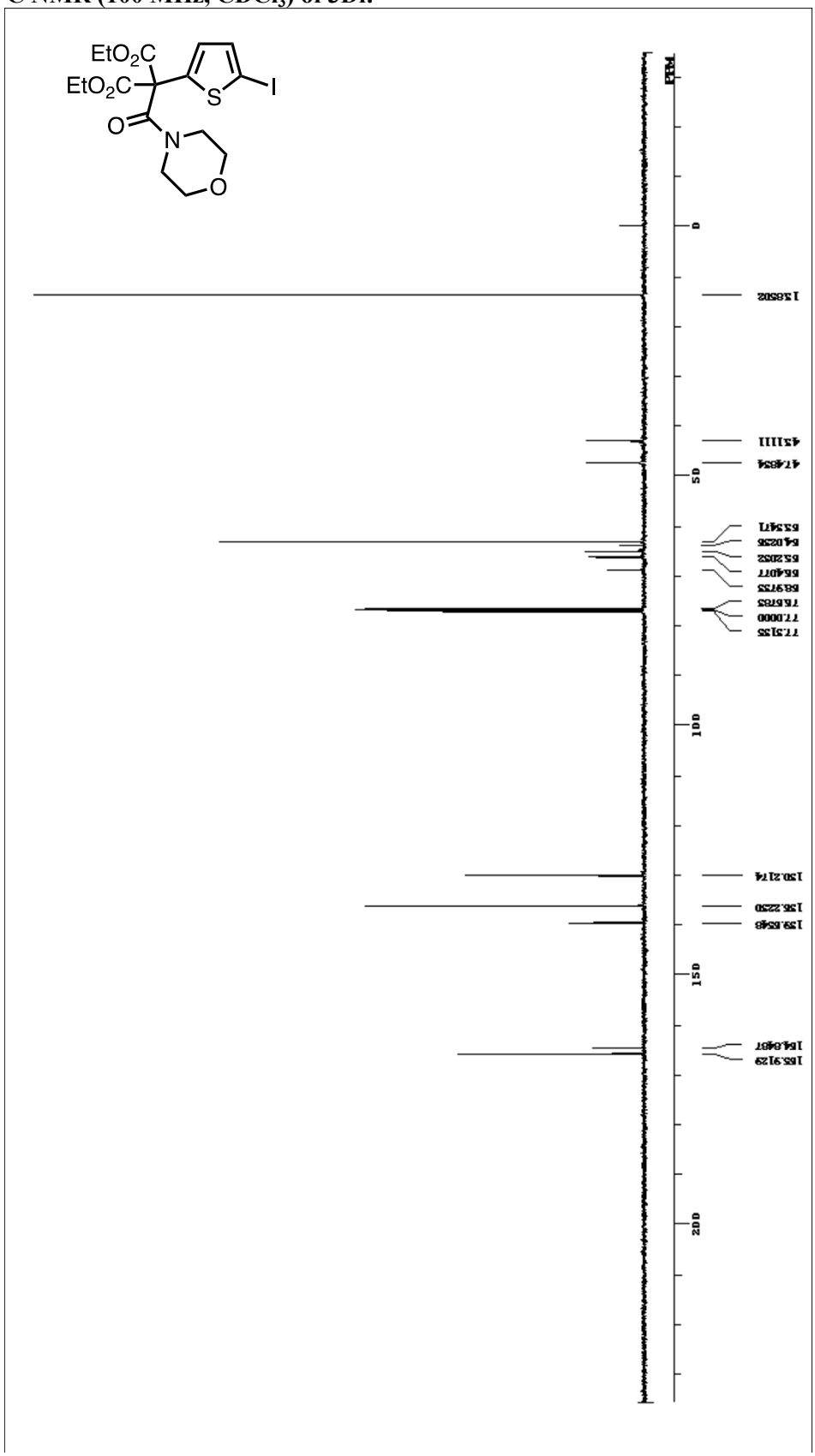
^{13}C NMR (100 MHz, $CDCl_3$) of 3Ci:



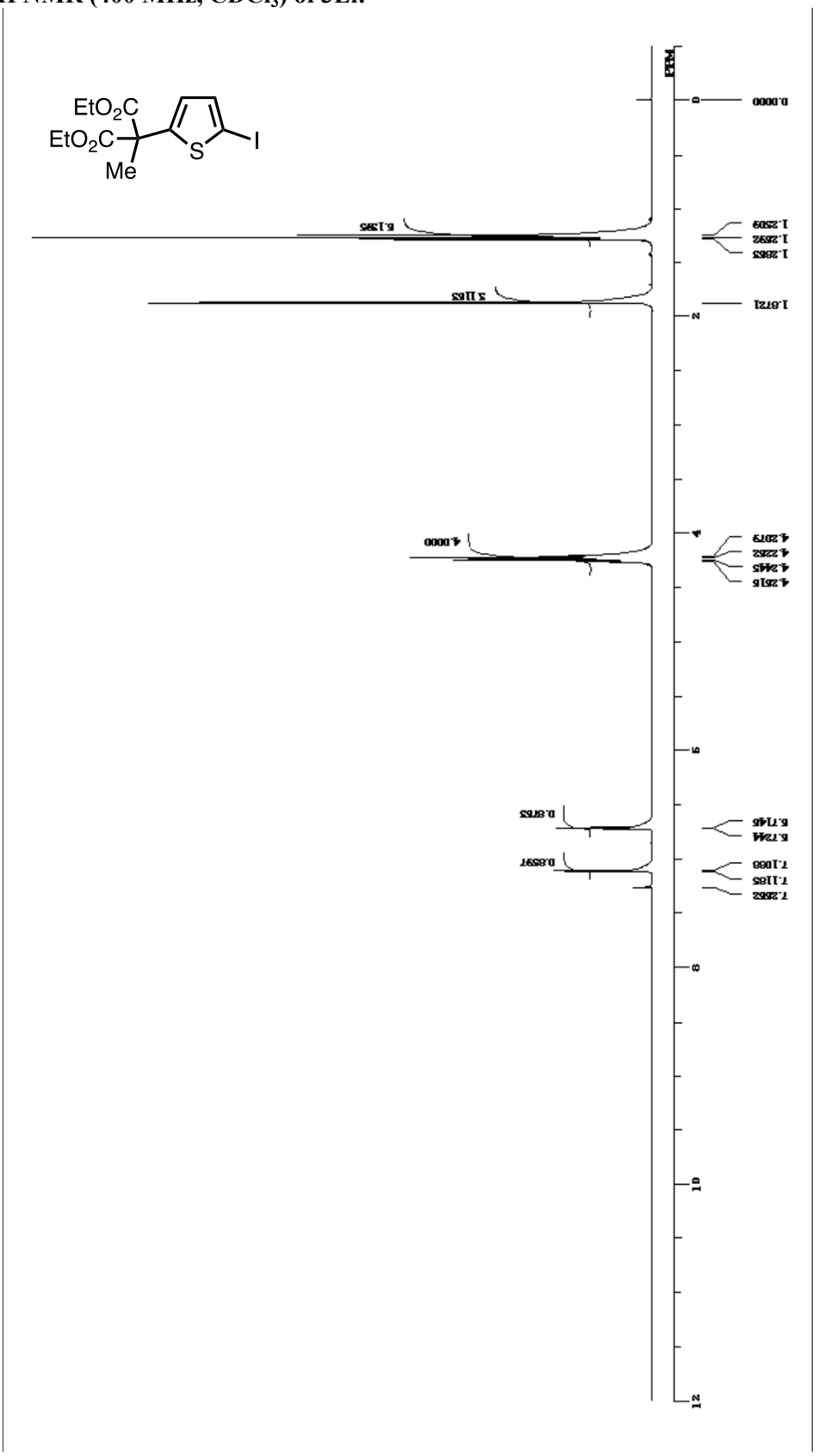
^{1}H NMR (400 MHz, $CDCl_3$) of 3Di:



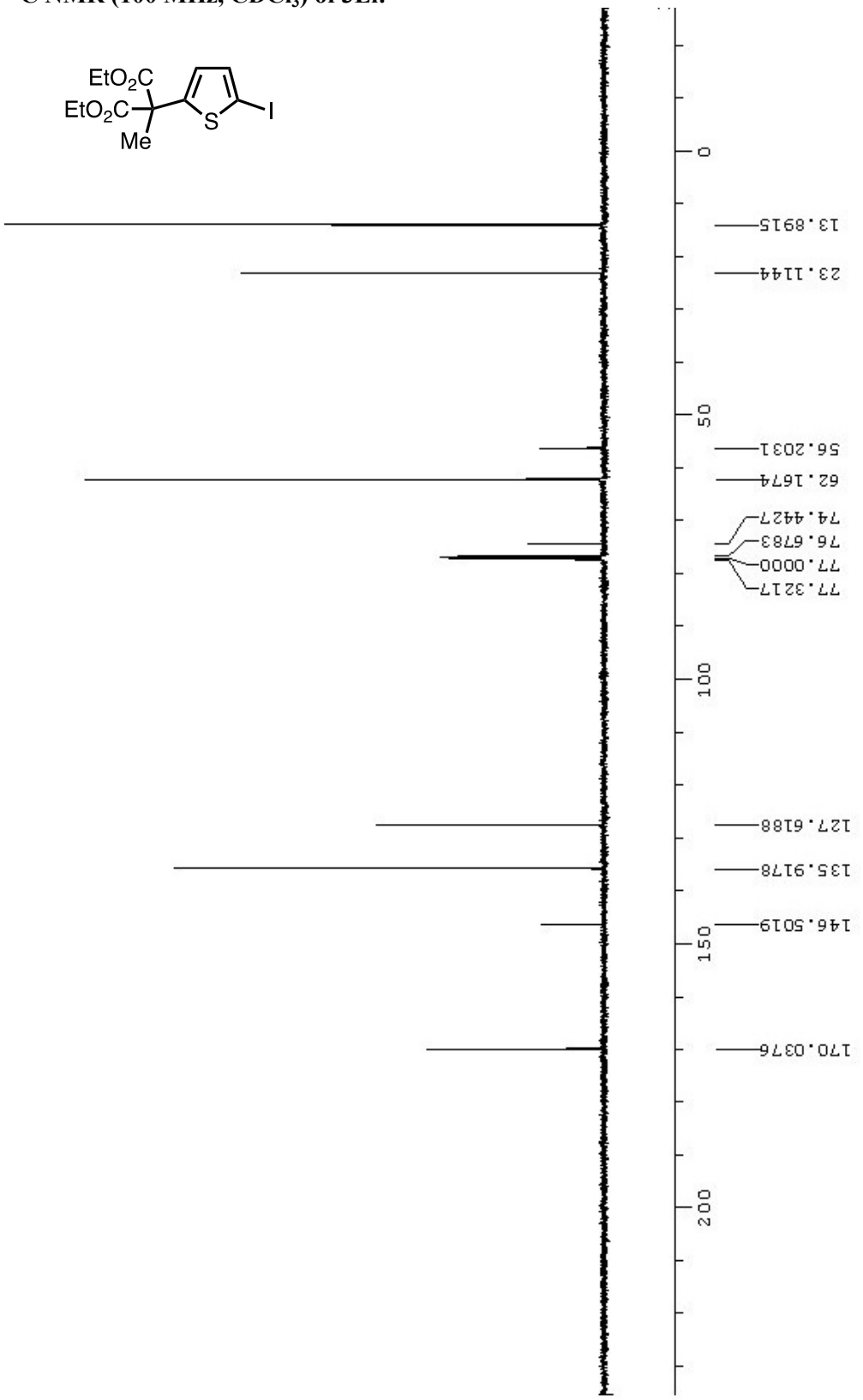
^{13}C NMR (100 MHz, $CDCl_3$) of 3Di:



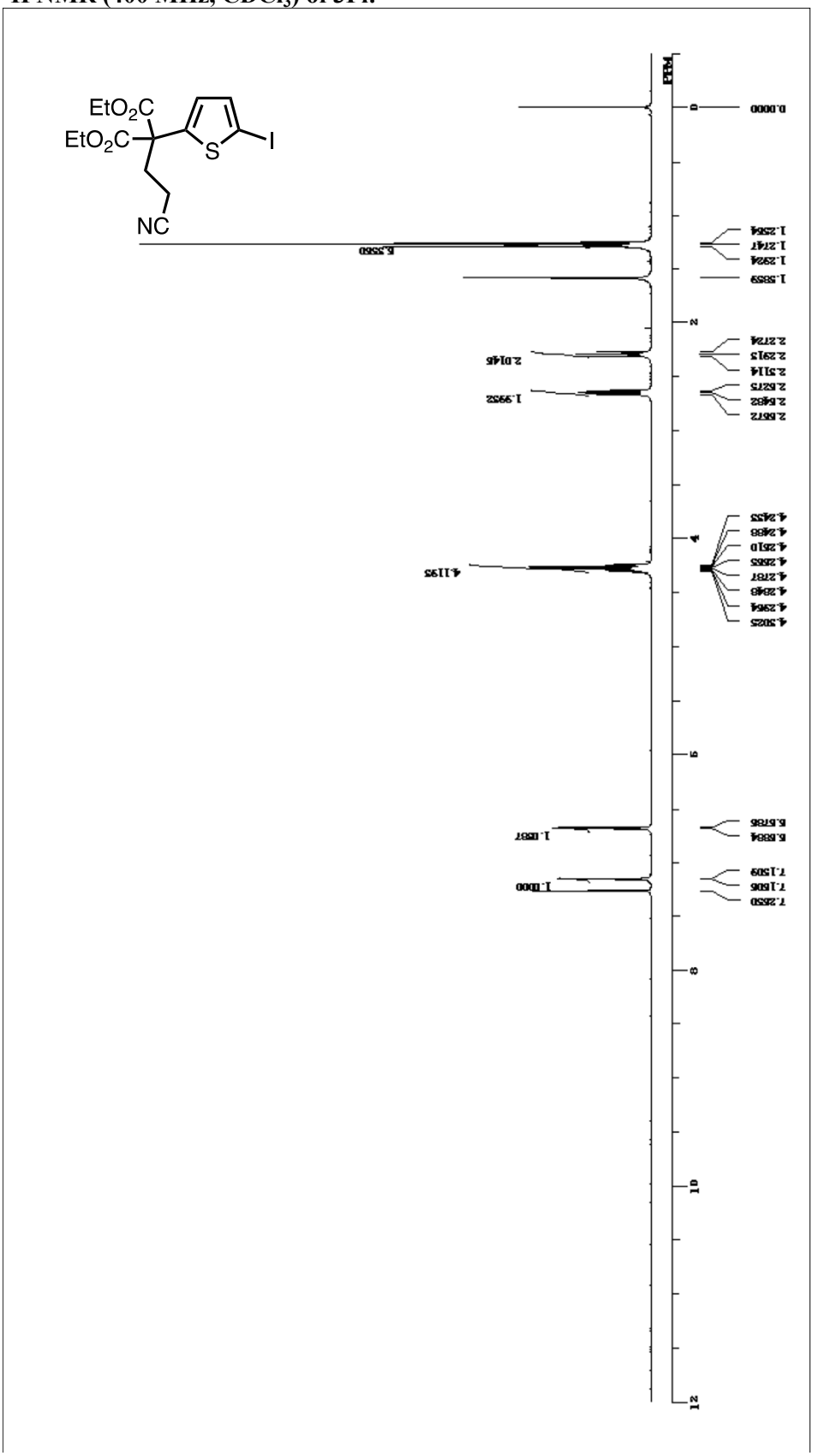
^{1}H NMR (400 MHz, $CDCl_3$) of 3Ei:



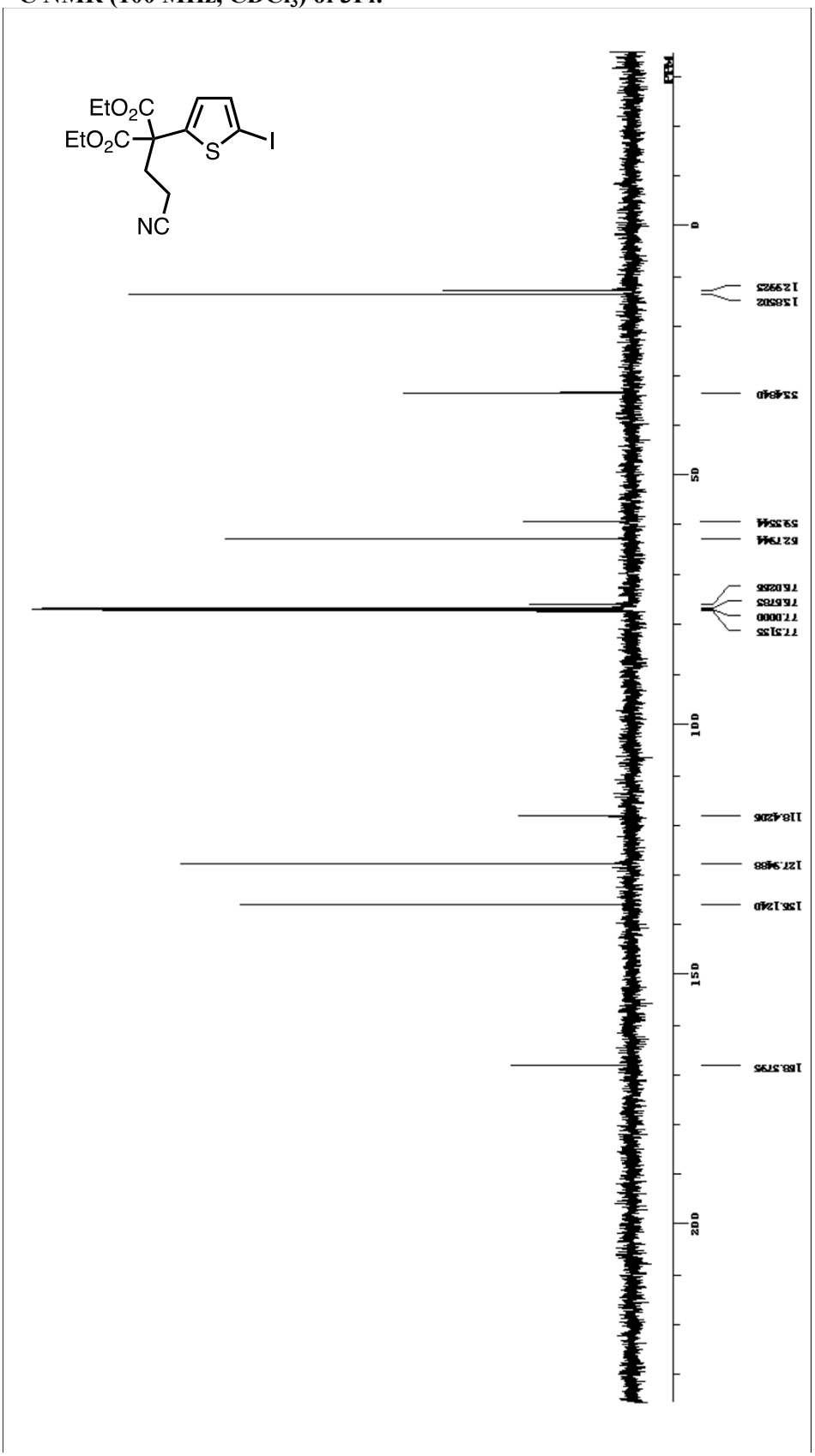
^{13}C NMR (100 MHz, $CDCl_3$) of 3Ei:



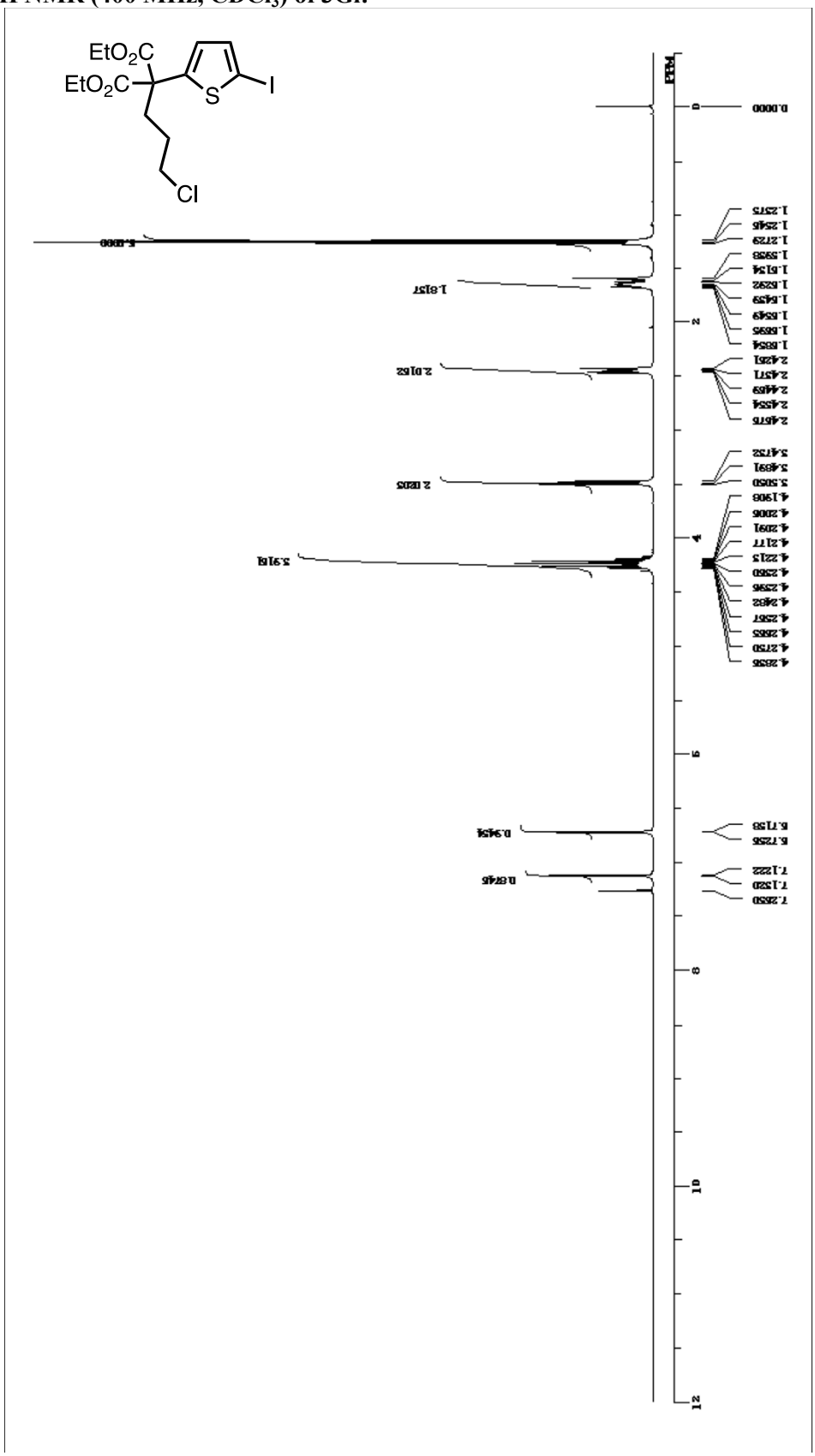
^{1}H NMR (400 MHz, $CDCl_3$) of 3Fi:



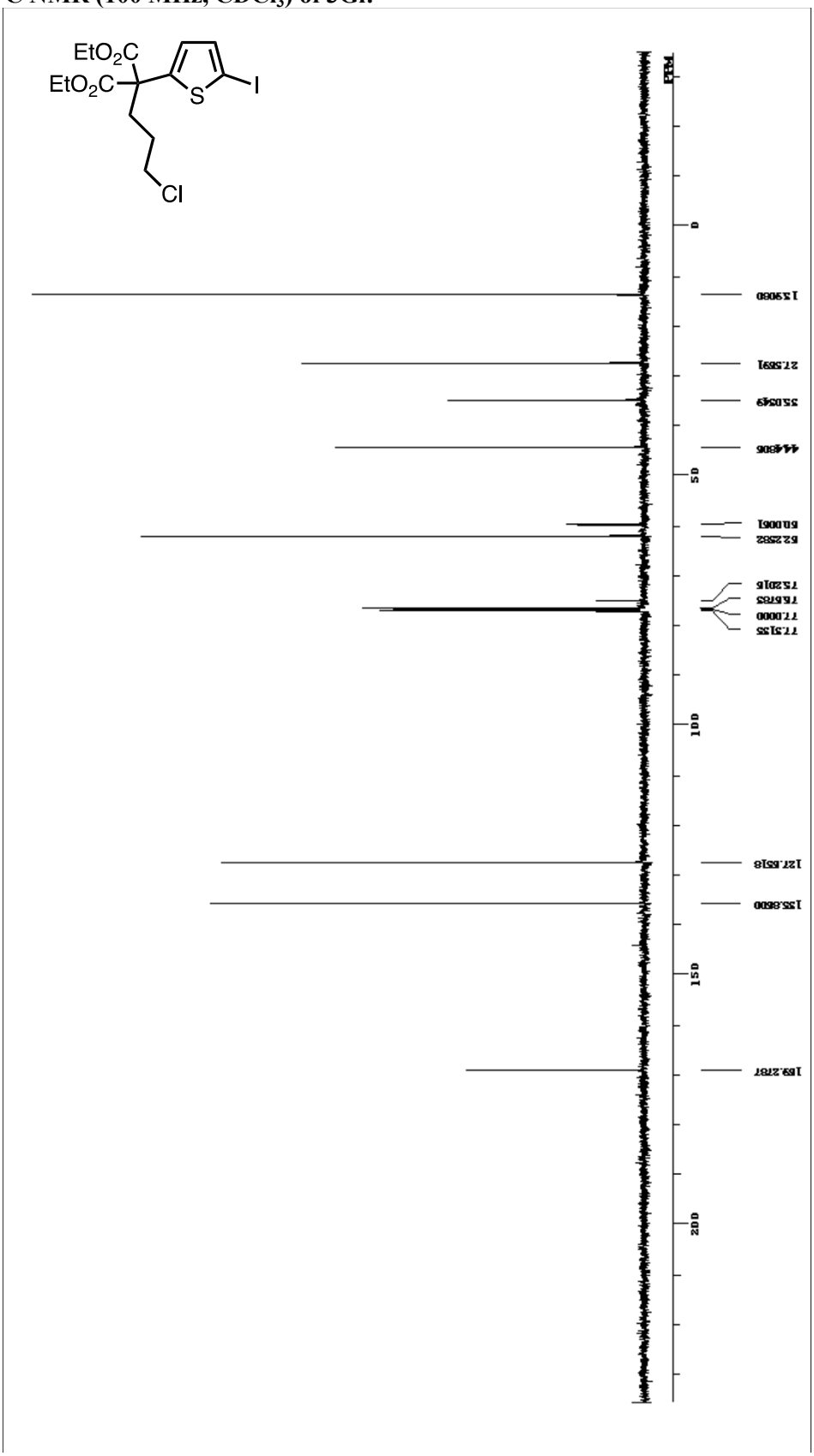
^{13}C NMR (100 MHz, $CDCl_3$) of 3Fi:



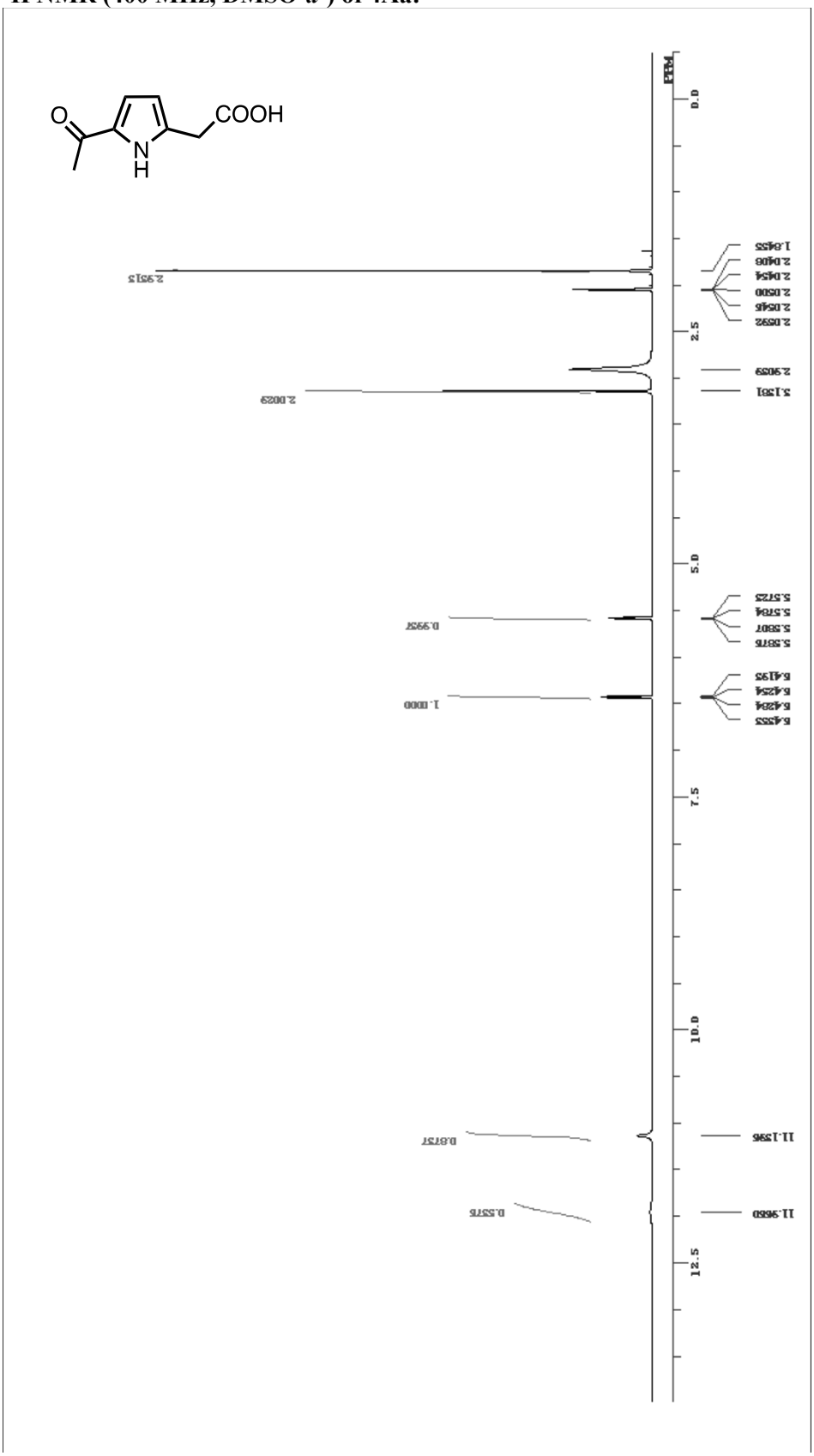
^{1}H NMR (400 MHz, $CDCl_3$) of 3Gi:



^{13}C NMR (100 MHz, $CDCl_3$) of 3Gi:



^{1}H NMR (400 MHz, DMSO-d^6) of 4Aa:



^{13}C NMR (100 MHz, DMSO-*d*^{6}) of 4Aa: