Electronic Supplementary Material (ESI) for Chemical Science

Supplementary Information

Hindered Biaryls by C–H Coupling: Bisoxazoline-Pd Catalysis Leading to Enantioselective C–H Coupling

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1. General

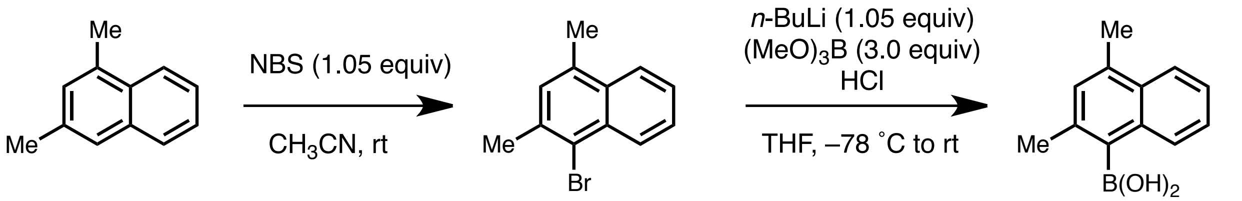
Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used as received. 4,5,6,7-Tetrahydrobenzo[*b*]thiophene (**1f**)[1], 2-methylnaphthalen-1-ylboronic acid (**2a**)[2], 2-methoxynaphthalen-1-ylboronic acid (**2b**)[3], and **L2**–**L5**[4,5] were synthesized according to procedures reported in the literature. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware using standard vacuum-line techniques. All C–H bond arylation reactions were performed in screw cap 20 mL glass vessel tubes and heated in an 8-well reaction block (heater + magnetic stirrer) unless otherwise noted. 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 F_{254} 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). High-resolution mass spectra (HRMS) were obtained from JEOL JMS-T100GCV (EI), JMS-T100TD (DART) or JMS-700 (FAB) instruments. Chiral HPLC analysis was conducted on a Shimadzu Prominence 2000 instrument equipped with DAISO Chiracel OD-H (4.6 mm x 250 mm). Optical rotations were measured using a JASCO P-1010-GT digital polarimeter with $CHCl_3$ as the solvent.

Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm) or residual peak of DMSO (δ 2.50 ppm) and CD_2Cl_2 (5.32 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm), CD_2Cl_2 (53.8 ppm) or DMSO (δ 39.5 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

(1) S. Nomura, E. Kawanishi, K. Ueta, WO2005012326.
(2) A. N. Cammidge, K. V. L. Crépy, *Tetrahedron,* 2004, **60**, 4377.
(3) H. Wu, Y. Li, W. Yan, *J. Organomet. Chem.,* 2006, **691**, 5688.
(4) K. Kikushima, J. C. Holder, M. Gatti, B. M. Stoltz, *J. Am. Chem. Soc.*, 2011, **133**, 6902.
(5) S. E. Denmark, R. A. Stavenger, A.-M. Faucher, J. P. Edwards. *J. Org. Chem.*, 1997, **62***,* 3375.

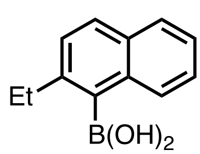
2. Preparation of Arylboronic Acid



2c

General Procedure

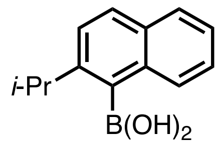
(2,4-Dimethylnaphthalen-1-yl)boronic acid (2c): To a solution of 1,3-dimethylnaphthalene (2.11 g, 13.5 mmol) in CH_3CN (20 mL) was added *N*-bromosuccinimide (2.53 g, 14.2 mmol). The mixture was stirred at room temperature for 2 h and evaporated under reduced pressure. The resulting precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by short silica-gel column chromatography (hexane/EtOAc = 9:1) to give 1-bromo-2,4-dimethylnaphthalene as a colorless oil which was used for the next step without further purification. To a solution of 1-bromo-2,4-dimethylnaphthalene (3.16 g, 12.5 mmol) in THF (25 mL) was slowly added *n*-BuLi (1.6 M in hexane, 8.19 mL, 13.1 mmol) at –78 ˚C under argon atmosphere. After stirring at –78 ˚C for 1 h, trimethyl borate (4.18 mL, 37.5 mmol) was added, stirred at –78 ˚C for 30 min, then room temperature for 30 min. To the mixture was added 10% HCl (60 mL) and the resultant mixture was further stirred for 1 h. The mixture was extracted with EtOAc, and the organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Hexane was added to the residue, and the resulting precipitate was collected to give **2c** (2.01 g, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.91 (m, 1H), 7.84–7.77 (m, 1H), 7.49–7.40 (m, 2H), 7.12 (s, 1H), 5.01 (s, 2H), 2.63 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.81, 135.20, 130.54, 129.09, 127.94, 125.96, 124.81, 124.30, 22.40, 19.36; HRMS (EI) *m*/*z* calcd for $C_{12}H_{13}BO_2$ $[M]^+$ 200.1009, found 200.1013.



2d

(2-Ethylnaphthalen-1-yl)boronic acid (2d): Following the general procedure, **2d** (5.32 g, 42%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.77 (m, 3H), 7.51–7.39 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 1H), 4.83 (s, 2H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz,

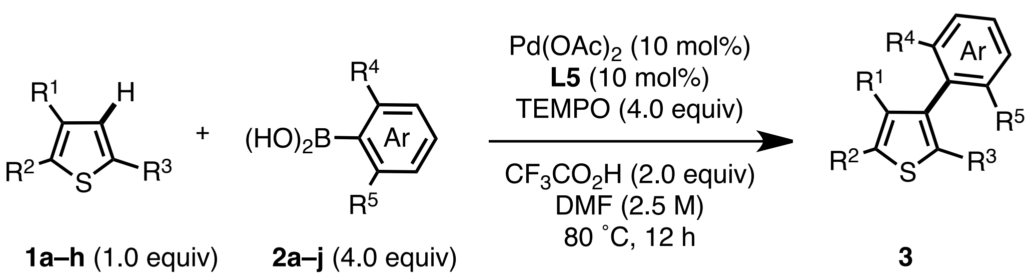
$CDCl_3$) δ 144.69, 135.00, 131.43, 129.17, 128.28, 127.48, 126.82, 126.22, 125.04, 30.16, 16.87; HRMS (EI) *m*/*z* calcd for $C_{12}H_{13}BO_2$ $[M]^+$: 200.1009, found: 200.1014.



2e

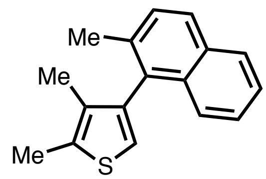
(2-Isopropylnaphthalen-1-yl)boronic acid (2e): Following the general procedure, **2e** (4.09 g, 57%) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.74 (m, 3H), 7.50–7.36 (m, 3H), 4.89 (s, 2H), 3.21–3.06 (m, 1H), 1.34 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.55, 134.81, 131.68, 129.31, 128.23, 127.60, 126.20, 125.11, 123.29, 35.34, 24.42; HRMS (EI) *m*/*z* calcd for $C_{13}H_{15}BO_2$ $[M]^+$: 214.1165, found: 214.1166.

3. General Procedure for Hindered Heterobiaryls by C–H Coupling.



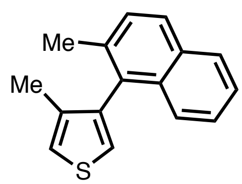
To a 20-mL screw cap glass vessel containing a magnetic stirring bar were added $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), **L5** (6.3 mg, 0.025 mmol), DMF (0.1 mL), and CF_3CO_2H (37 μL, 0.5 mmol). The mixture was stirred at 80 ˚C for 10 min and cooled to room temperature. To this mixture were added thiophene **1** (0.25 mmol), arylboronic acid **2** (1.0 mmol) and TEMPO (156 mg, 1.0 mmol), and the mixture was stirred at 80 ˚C for 12 h under air. After cooling the reaction mixture to room temperature, the mixture was passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography to give the arylated product **3**. The C4/C5 regioselectivity of the reaction was determined by ^1H NMR.

Compound Data of Coupling Products



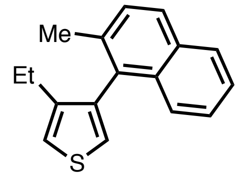
3aa

2,3-Dimethyl-4-(2-methylnaphthalen-1-yl)thiophene (3aa): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3aa** (53 mg, 84%, C4/C5 = 99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.43–7.27 (m, 4H), 6.84 (s, 1H), 2.46 (s, 3H), 2.22 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.57, 134.45, 133.85, 133.42, 133.21, 132.93, 131.87, 128.44, 127.70, 127.26, 125.91, 125.86, 124.74, 118.83, 20.43, 13.74, 12.19; HRMS (DART) *m/z* calcd for $C_{17}H_{17}S$ $[M+H]^+$: 253.1051, found: 253.1049.



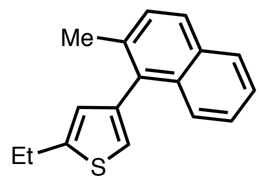
3ba

3-Methyl-4-(2-methylnaphthalen-1-yl)thiophene (3ba): Following the general procedure with 3-methylthiophene (**1b**: 25 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ba** (40 mg, 68%, C4/C5 = 95:5) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.43–7.31 (m, 4H), 7.15–7.11 (m, 1H), 7.09 (d, J = 3.1 Hz, 1H), 2.22 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.32, 137.77, 134.55, 133.41, 132.89, 131.91, 128.45, 127.77, 127.43, 125.97, 125.77, 124.81, 123.32, 121.15, 20.40, 14.48; HRMS (DART) *m/z* calcd for $C_{16}H_{15}S$ $[M+H]^+$: 239.0894, found: 239.0890.



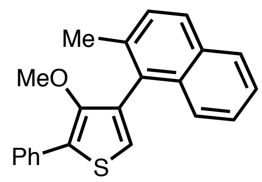
3ca

3-Ethyl-4-(2-methylnaphthalen-1-yl)thiophene (3ca): Following the general procedure with 3-ethylthiophene (**1c**: 28 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ca** (40 mg, 64%, C4/C5 = 97:3) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.45–7.30 (m, 4H), 7.18–7.14 (m, 1H), 7.08 (d, J = 3.1 Hz, 1H), 2.22 (s, 3H), 2.18 (q, J = 7.6 Hz, 2H), 1.01 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.36, 139.79, 134.60, 133.49, 132.95, 131.88, 128.45, 127.74, 127.42, 125.92, 125.85, 124.79, 123.36, 119.86, 22.21, 20.49, 13.85; HRMS (DART) *m/z* calcd for $C_{17}H_{17}S$ [M+H]$^+$: 253.1051, found: 253.1054.



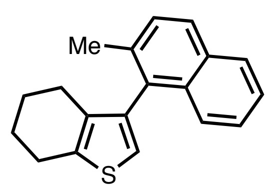
3da

2-Ethyl-4-(2-methylnaphthalen-1-yl)thiophene (3da): Following the general procedure with 2-ethylthiophene (**1d**: 28 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude was purified by preparative thin-layer chromatography (hexane) to give **3da** (42 mg, 66%, C4/C5 = 92:8) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (m, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.43–7.31 (m, 3H), 6.94 (d, J = 1.0 Hz, 1H), 6.74 (d, J = 1.4 Hz, 1H), 2.94 (q, J = 7.7 Hz, 2H), 2.32 (s, 3H), 1.38 (t, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.19, 139.00, 134.02, 133.72, 133.33, 131.88, 128.52, 127.67, 127.19, 126.15, 126.09, 125.81, 124.74, 120.94, 23.46, 20.82, 15.93; HRMS (DART) *m/z* calcd for $C_{17}H_{17}S$ [M+H]$^+$: 253.1051, found: 253.1048.



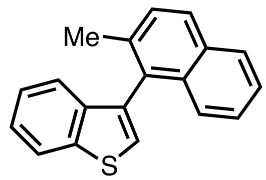
3ea

3-Methoxy-4-(2-methylnaphthalen-1-yl)-2-phenylthiophene (3ea): Following the general procedure with 3-methoxy-2-phenylthiophene (**1e**: 48 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 49:1) to give **3ea** (56 mg, 68%, C4/C5 = 94:6) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.75 (m, 4H), 7.74–7.66 (m, 1H), 7.49–7.34 (m, 5H), 7.31–7.21 (m, 1H), 7.00 (s, 1H), 3.26 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.74, 134.97, 134.83, 133.30, 133.23, 131.95, 131.27, 128.66, 128.51, 127.84, 127.83, 127.10, 127.04, 126.74, 126.17, 125.81, 124.90, 121.12, 60.33, 20.70; HRMS (DART) *m/z* calcd for $C_{22}H_{19}OS$ $[M+H]^+$: 331.1157, found: 331.1163.



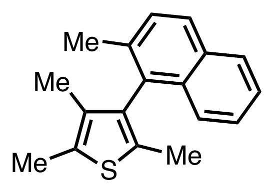
3fa

3-(2-Methylnaphthalen-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (3fa): Following the general procedure with 4,5,6,7-tetrahydrobenzo[*b*]thiophene (**1f**: 35 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3fa** (43 mg, 61%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.47–7.28 (m, 4H), 6.87 (s, 1H), 2.95–2.82 (m, 2H), 2.23 (s, 3H), 2.12–1.97 (m, 2H), 1.91–1.80 (m, 2H), 1.73–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.01, 135.86, 135.47, 134.38, 133.38, 133.16, 131.87, 128.44, 127.74, 127.24, 125.90, 125.85, 124.73, 119.37, 25.42, 24.60, 23.53, 22.67, 20.48; HRMS (DART) *m/z* calcd for $C_{19}H_{19}S$ $[M+H]^+$: 279.1207, found: 279.1204.



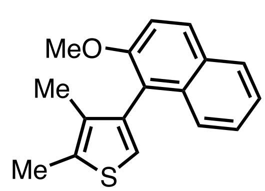
3ga

3-(2-Methylnaphthalen-1-yl)benzo[*b*]thiophene (3ga): Following the general procedure with benzo[*b*]thiophene (**3g**: 34 mg) with 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ga** (50 mg, 73%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.42–7.32 (m, 4H), 7.30–7.19 (m, 2H), 7.15 (d, J = 8.1 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.99, 139.49, 135.26, 135.11, 133.53, 132.02, 131.31, 128.60, 127.93, 127.81, 126.06, 125.90, 124.94, 124.74, 124.41, 124.21, 123.17, 122.68, 20.55; HRMS (DART) *m/z* calcd for $C_{19}H_{15}S$ $[M+H]^+$: 275.0894, found: 275.0892.



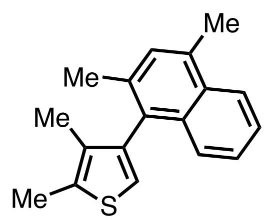
3ha

2,3,5-Trimethyl-4-(2-methylnaphthalen-1-yl)thiophene (3ha): Following the general procedure with 2,3,5-trimethylthiophene (**1h**: 32 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ha** (47 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.44–7.30 (m, 4H), 2.39 (s, 3H), 2.18 (s, 3H), 1.98 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.20, 134.73, 133.28, 133.11, 132.94, 132.03, 130.55, 128.87, 128.49, 127.83, 127.21, 125.95, 125.62, 124.74, 20.05, 13.42, 13.32, 12.68; HRMS (DART) *m/z* calcd for $C_{18}H_{19}S$ $[M+H]^+$: 267.1208, found: 267.1206.



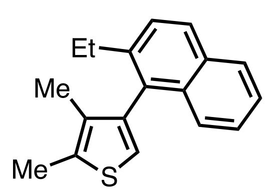
3ab

4-(2-Methoxynaphthalen-1-yl)-2,3-dimethylthiophene (3ab): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-methoxynaphthalen-1-ylboronic acid (**2b**: 202 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 49:1) to give **3ab** (51 mg, 76%, C4/C5 = >99:1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 1H), 7.83–7.77 (m, 1H), 7.49–7.43 (m, 1H), 7.37–7.29 (m, 3H), 6.93 (s, 1H), 3.85 (s, 3H), 2.46 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.51, 137.19, 134.26, 133.88, 132.43, 129.13, 128.95, 127.75, 126.32, 125.27, 123.49, 120.82, 119.81, 113.59, 56.62, 13.80, 12.36; HRMS (DART) *m/z* calcd for $C_{17}H_{17}OS$ $[M+H]^+$: 269.1000, found: 269.1007.



3ac

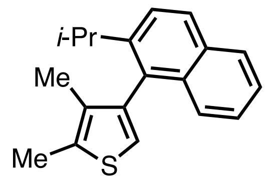
4-(2,4-dimethylnaphthalen-1-yl)-2,3-dimethylthiophene (3ac): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,4-dimethylnaphthalen-1-ylboronic acid (**2c**: 200 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ac** (49 mg, 73%, C4/C5 = >99:1) as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.46–7.40 (m, 1H), 7.39–7.30 (m, 2H), 7.28 (s, 1H), 6.82 (s, 1H), 2.70 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.80, 134.04, 133.56, 133.40, 133.36, 132.78, 132.11, 131.01, 129.32, 126.49, 125.56, 124.58, 123.91, 118.92, 20.31, 19.33, 13.75, 12.22; HRMS (DART) *m/z* calcd for $C_{18}H_{19}S$ $[M+H]^+$: 267.1207, found: 267.1208.



3ad

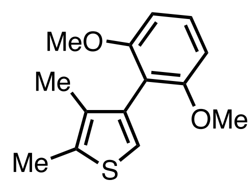
4-(2-Ethylnaphthalen-1-yl)-2,3-dimethylthiophene (3ad): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-ethylnaphthalen-1-ylboronic acid (**2d**: 200 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ad** (46 mg, 69%, C4/C5

= 98:2) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.42–7.29 (m, 3H), 6.86 (s, 1H), 2.64–2.41 (m, 5H), 1.70 (s, 3H), 1.13 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.63, 140.22, 133.46, 133.10, 132.67, 131.88, 127.69, 127.65, 127.02, 126.10, 125.85, 124.82, 119.07, 26.93, 15.73, 13.75, 12.31; HRMS (DART) *m/z* calcd for $C_{18}H_{19}S$ $[M+H]^+$: 267.1207, found: 267.1203.



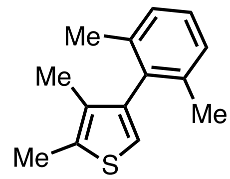
3ae

4-(2-Isopropylnaphthalen-1-yl)-2,3-dimethylthiophene (3ae): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-isopropylnaphthalen-1-ylboronic acid (**2e**: 214 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ae** (44 mg, 62%, C4/C5 = 98:2) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.42–7.37 (m, 1H), 7.36–7.29 (m, 2H), 6.85 (s, 1H), 2.92 (sep, *J* = 6.8 Hz, 1H), 2.47 (s, 3H), 1.72 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.89, 140.33, 133.58, 133.40, 132.66, 132.26, 131.85, 127.95, 127.64, 126.38, 125.84, 124.89, 123.65, 118.98, 30.52, 24.54, 23.20, 13.77, 12.35; HRMS (DART) *m/z* calcd for $C_{19}H_{21}S$ $[M+H]^+$: 281.1364, found: 281.1369.



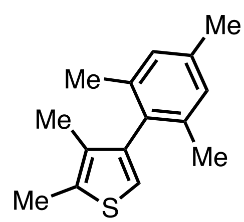
3af

4-(2,6-Dimethoxyphenyl)-2,3-dimethylthiophene (3af): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,6-dimethoxyphenylboronic acid (**2f**: 182 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 49/1) to give **3ae** (47 mg, 76%, C4/C5 = >99:1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 6.62 (d, *J* = 8.5 Hz, 2H), 3.73 (s, 6H), 2.39 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.35, 134.64, 133.64, 131.60, 128.67, 119.70, 115.09, 103.93, 55.84, 13.80, 12.44; HRMS (DART) *m/z* calcd for $C_{14}H_{17}O_2S$ $[M+H]^+$: 249.0953, found: 239.0949.



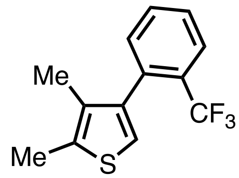
3ag

4-(2,6-Dimethylphenyl)-2,3-dimethylthiophene (3ag): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,6-dimethylphenylboronic acid (**2g**: 150 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ag** (36 mg, 67%, C4/C5 = >99:1) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.11 (m, 1H), 7.07 (d, J = 7.9 Hz, 2H), 6.69 (s, 1H), 2.41 (s, 3H), 2.01 (s, 6H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.95, 137.50, 137.28, 132.91, 132.08, 127.08, 126.99, 117.18, 20.36, 13.69, 12.04; HRMS (DART) *m/z* calcd for $C_{14}H_{17}S$ $[M+H]^+$: 217.0501, found: 217.0503.



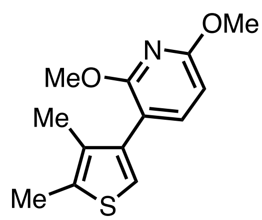
3ah

4-Mesityl-2,3-dimethylthiophene (3ah): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,4,6-trimethylphenylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ah** (41 mg, 72%, C4/C5 = >99:1) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 6.68 (s, 1H), 2.40 (s, 3H), 2.31 (s, 3H), 1.97 (s, 6H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.95, 137.14, 136.60, 134.53, 132.75, 132.26, 127.81, 117.34, 21.05, 20.26, 13.72, 12.09; HRMS (DART) *m/z* calcd for $C_{15}H_{19}S$ $[M+H]^+$: 231.1207, found: 231.1209.



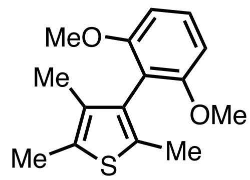
3ai

2,3-Dimethyl-4-(2-(trifluoromethyl)phenyl)thiophene (3ai): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-(trifluoromethyl)phenylboronic acid (**2i**: 190 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ai** (48 mg, 75%, C4/C5 = 91:9) as a colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 6.89 (s, 1H), 2.40 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 140.16, 137.48, 133.12, 132.77, 132.73, 131.72, 129.69 (q, J = 29.1 Hz), 127.92, 126.30 (q, J = 4.7 Hz), 124.60 (q, J = 274.4 Hz), 119.93, 13.70, 12.62; HRMS (DART) *m/z* calcd for $C_{13}H_{12}F_3S$ $[M+H]^+$: 257.0612, found: 257.0615.



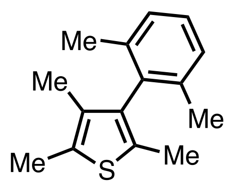
3aj

3-(4,5-Dimethylthiophen-3-yl)-2,6-dimethoxypyridine (3aj): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and (2,6-dimethoxypyridin-3-yl)boronic acid (**2j**: 183 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 6:1) to give **3aj** (31 mg, 50%, C4/C5 = >99:1) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 6.34 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.35, 159.75, 142.29, 138.40, 133.05, 132.73, 119.11, 111.95, 100.35, 53.55, 53.34, 13,.6, 12.67; HRMS (DART) *m/z* calcd for $C_{13}H_{16}NO_2S$ $[M+H]^+$: 250.0902, found: 250.0907.



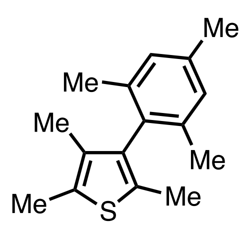
3hf

3-(2,6-Dimethoxyphenyl)-2,4,5-trimethylthiophene (3hf): Following the general procedure with 2,3,5-dimethylthiophene (**1h**: 32 mg) and (2,6-dimethoxyphenyl)boronic acid (**2f**: 182 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **3hf** (46 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 1H), 6.63 (d, J = 8.5 Hz, 2H), 3.74 (s, 6H), 2.33 (s, 3H), 2.12 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.36, 133.45, 131.51, 128.72, 127.74, 114.23, 103.85, 55.76, 13.80, 13.40, 12.79; HRMS (DART) *m/z* calcd for $C_{15}H_{19}O_2S$ $[M+H]^+$: 263.1106, found: 263.1104.



3hg

3-(2,6-Dimethylphenyl)-2,4,5-trimethylthiophene (3hg): Following the general procedure with 2,3,5-dimethylthiophene (**1h**: 32 mg) and (2,6-dimethyphenyl)boronic acid (**2g**: 150 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3hg** (28 mg, 48%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.06 (m, 3H), 2.34 (s, 3H), 2.02 (s, 3H), 1.97 (s, 6H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.71, 137.34, 136.74, 131.77, 128.88, 128.81, 127.01, 19.99, 13.28, 13.21, 12.56; HRMS (DART) *m/z* calcd for $C_{15}H_{19}S$ $[M+H]^+$: 231.1208, found: 231.1207.



3hh

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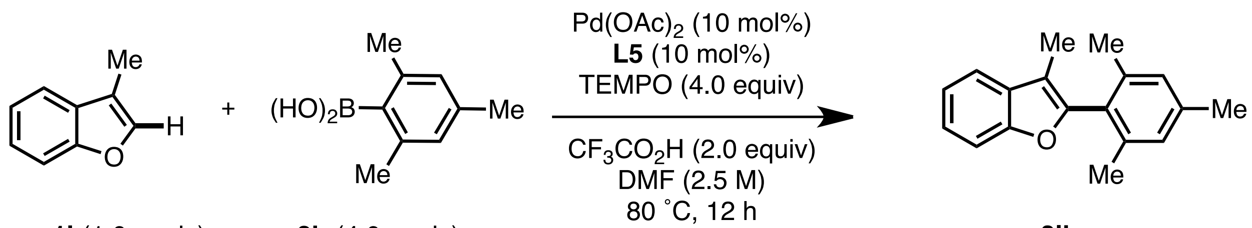
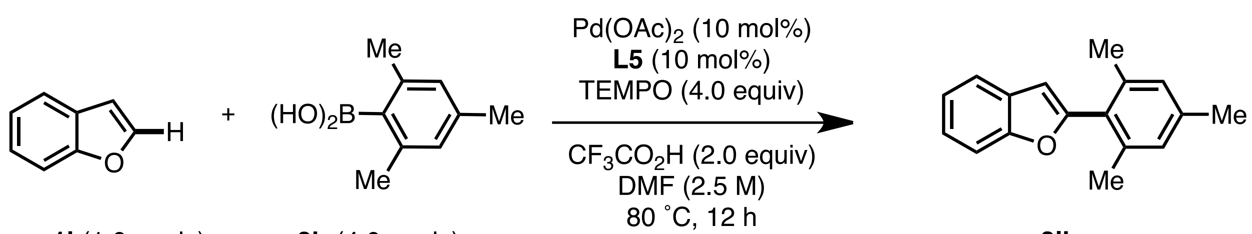
3-Mesityl-2,4,5-trimethylthiophene (3hh): Following the general procedure with 2,3,5-dimethylthiophene (**1h**: 32 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3hh** (35 mg, 58%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.02 (s, 3H), 1.93 (s, 6H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.71, 137.16, 136.42, 133.72, 131.98, 128.90, 128.65, 127.84, 21.11, 19.91, 13.30, 13.25, 12.62; HRMS (DART) *m/z* calcd for $C_{16}H_{21}S$ $[M+H]^+$: 245.1364, found: 245.1363.



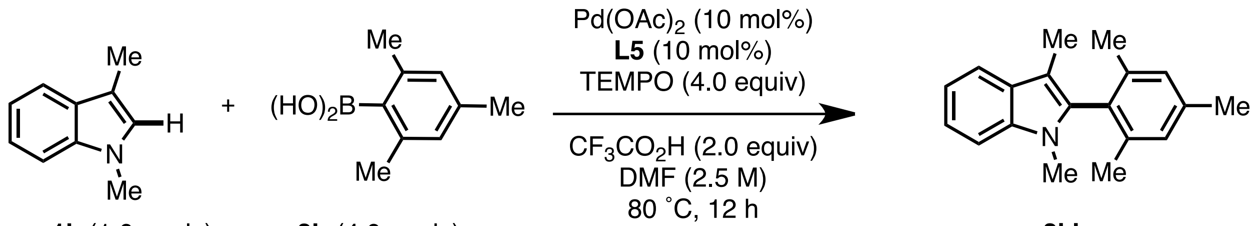
1i (1.0 equiv) **3h** (4.0 equiv) **3ih**

2-Mesityl-3-methylbenzofuran (3ih): Following the general procedure with 3-methylbenzofuran (**1i**: 33 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 99:1) to give **3ih** (42 mg, 67%) as a colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.61–7.55 (m, 1H), 7.50–7.43 (m, 1H), 7.33–7.25 (m, 2H), 7.00 (s, 2H), 2.36 (s, 3H), 2.13 (s, 6H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 154.88, 151.62, 139.54, 139.26, 130.51, 128.41, 127.25, 123.96, 122.44, 119.52, 113.13, 111.21, 21.33, 19.97, 8.39; HRMS (DART) *m/z* calcd for $C_{18}H_{19}O$ $[M+H]^+$: 251.1436, found: 251.1434.



1j (1.0 equiv) **3h** (4.0 equiv) **3jh**

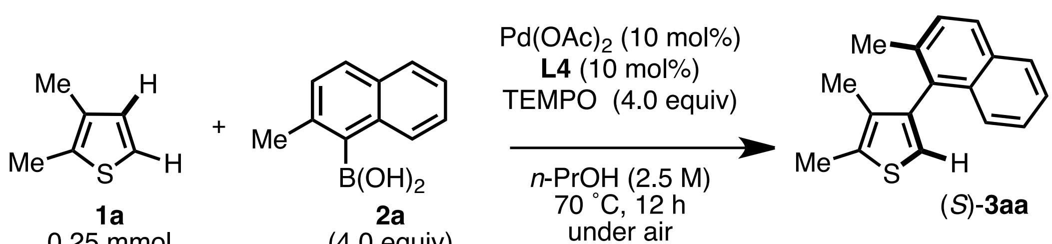
2-Mesitylbenzofuran (3jh): Following the general procedure with benzofuran (**1j**: 30 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 99:1) to give **3jh** (52 mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.58 (m, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.32–7.22 (m, 2H), 6.96 (s, 2H), 6.64 (s, 1H), 2.33 (s, 3H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.02, 154.71, 139.01, 138.38, 128.83, 128.35, 127.69, 123.64, 122.55, 120.67, 111.14, 106.04, 21.18, 20.49; HRMS (DART) *m/z* calcd for $C_{17}H_{17}O$ $[M+H]^+$: 237.1279, found: 237.1279.



1k (1.0 equiv) **3h** (4.0 equiv) **3kh**

2-Mesityl-1,3-dimethyl-1*H*-indole (3kh): Following the general procedure with 1,3-dimethyl-1*H*-indole (**1k**: 36 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 20:1) to give **3kh** (16 mg, 24%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.58 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.25–7.20 (m, 1H), 7.17–7.12 (m, 1H), 6.98 (s, 2H), 3.39 (s, 3H), 2.36 (s, 3H), 2.06 (s, 3H), 1.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.84, 138.17, 136.78, 136.15, 128.49, 128.30, 127.94, 120.74, 118.53, 118.51, 108.96, 107.61, 29.65, 21.21, 19.99, 8.86; HRMS (DART) *m/z* calcd for $C_{19}H_{22}N$ $[M+H]^+$: 264.1752, found: 264.1752.

4. Enantioselective C–H Coupling



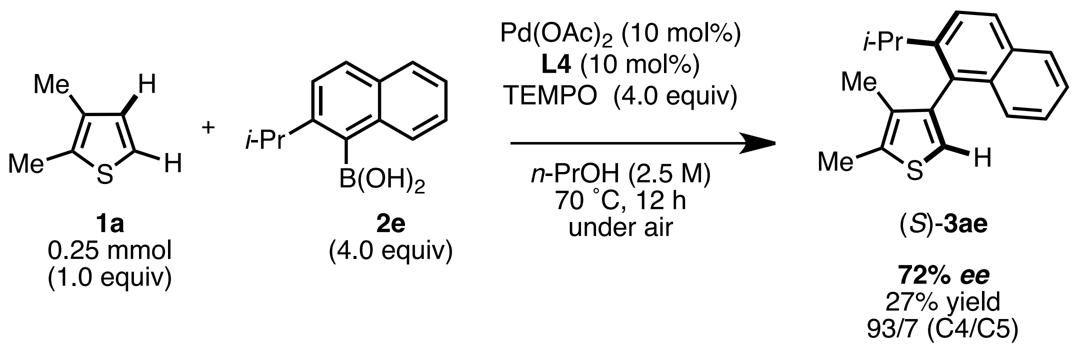
1a
0.25 mmol
(1.0 equiv)

2a
(4.0 equiv)

(*S*)-**3aa**

41% *ee*
63% yield
95/5 (C4/C5)

To a 20-mL screw cap glass vessel containing a magnetic stirring bar were added $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), **L4** (5.6 mg, 0.025 mmol) and *n*-PrOH (0.1 mL). The mixture was stirred at 70 ˚C for 10 min and cooled to room temperature. To the mixture were added 2,3-dimethylthiophene (**1a**: 28 mg, 0.25 mmol), 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg, 1.00 mmol) and TEMPO (156 mg, 1.00 mmol), and the mixture was stirred at 70 ˚C for 12 h under air. After cooling the reaction mixture to room temperature, the mixture was passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane) to give (*S*)-**3aa** (40 mg, 63% yield, C4/C5 = 95:5, 41% *ee*) as a colorless oil. The enantiomeric excess was determined by HPLC with a Chiracel OD-H column, UV detected at 254 nm, flow rate 1.0 mL/min (hexane). Retention times (t_r): major enantiomer t_r =11.0 min, minor enantiomer t_r = 9.5 min (HPLC chart is shown in p. S81).

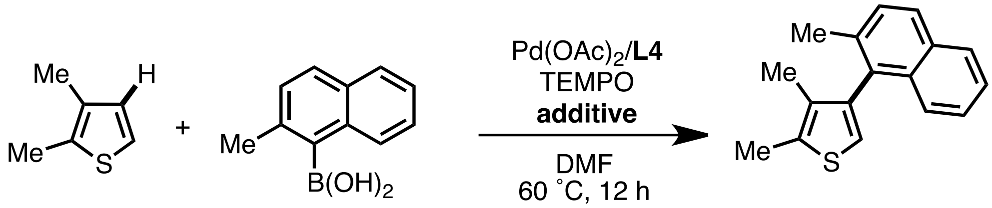


(*S*)-**3ae** (19 mg, 27% yield, C4/C5 = 93:7, 72% *ee*) was obtained by the reaction of **1a** and 2-isopropylnaphthalen-1-ylboronic acid (**2e**: 214 mg) as a colorless oil. Analytically pure compound was obtained by using GPC system. The enantiomeric excess was determined by HPLC with a Chiracel OD-H column, UV detected at 254 nm, flow rate 1.0 mL/min (hexane). Retention times (t_r); major enantiomer t_r = 8.5 min, minor enantiomer t_r = 7.6 min (HPLC chart is shown in p. S82). $[\alpha]_D^{21}$ +35.5 (*c* 1.00, $CHCl_3$)

5. Effect of Reaction Parameters

The effect of reaction parameters (additive, equivalents of CF_3CO_2H, catalytic amount of $Pd(OAc)_2$, ligand, equivalents of TEMPO, and atmosphere) was investigated. The arylation of 2,3-dimethylthiophene (**1a**) with 2-methylnaphthalen-1-ylboronic acid (**2a**) was used as the model reaction.

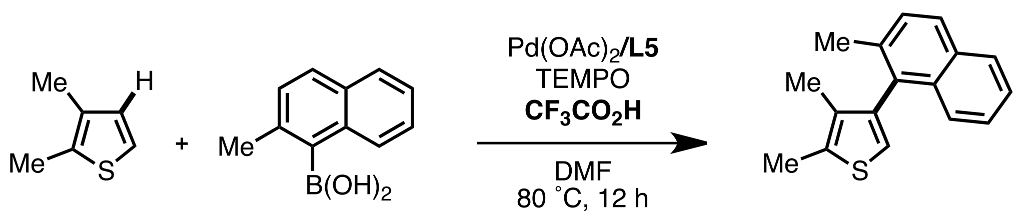
Table S1. Effect of additive.[a]



Entry	Additive	Yield/%[b]	C4/C5[c]
1	MeOH	38	90/10
2	*i*-PrOH	42	91/9
3	AcOH	55	96/4
4	CF_3CO_2H	74	99/1
5	PivOH	59	97/3
6	none	41	88/12

a: Conditions: **1a** (0.25 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), **L4** (0.025 mmol), TEMPO (1.0 mmol), additive (0.25 mmol), DMF (0.1 mL), 60 ˚C, 12 h, under air.
b: Isolated yield. c: Determined by ^{1}H NMR.

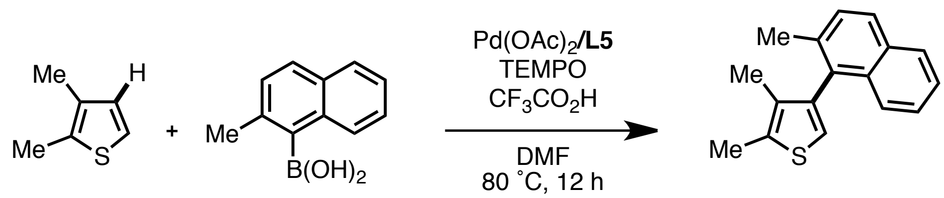
Table S2. Effect of CF_3CO_2H.[a]



Entry	CF_3CO_2H/equiv	Yield%[b]	C4/C5[c]
1	0	55	87/13
2	0.2	53	94/6
3	0.5	56	94/6
4	1.0	74	98/2
5	2.0	84	99/1
6	3.0	88	99/1
7	4.0	81	99/1

a: Conditions: **1a** (0.25 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), **L5** (0.025 mmol), TEMPO (1.0 mmol), CF_3CO_2H (x mmol), DMF (0.1 mL), 80 ˚C, 12 h, under air.
b: Isolated yield. c: Determined by ^{1}H NMR.

Table S3. Investigation of reaction conditions.[a]



1a **2a** **3aa**

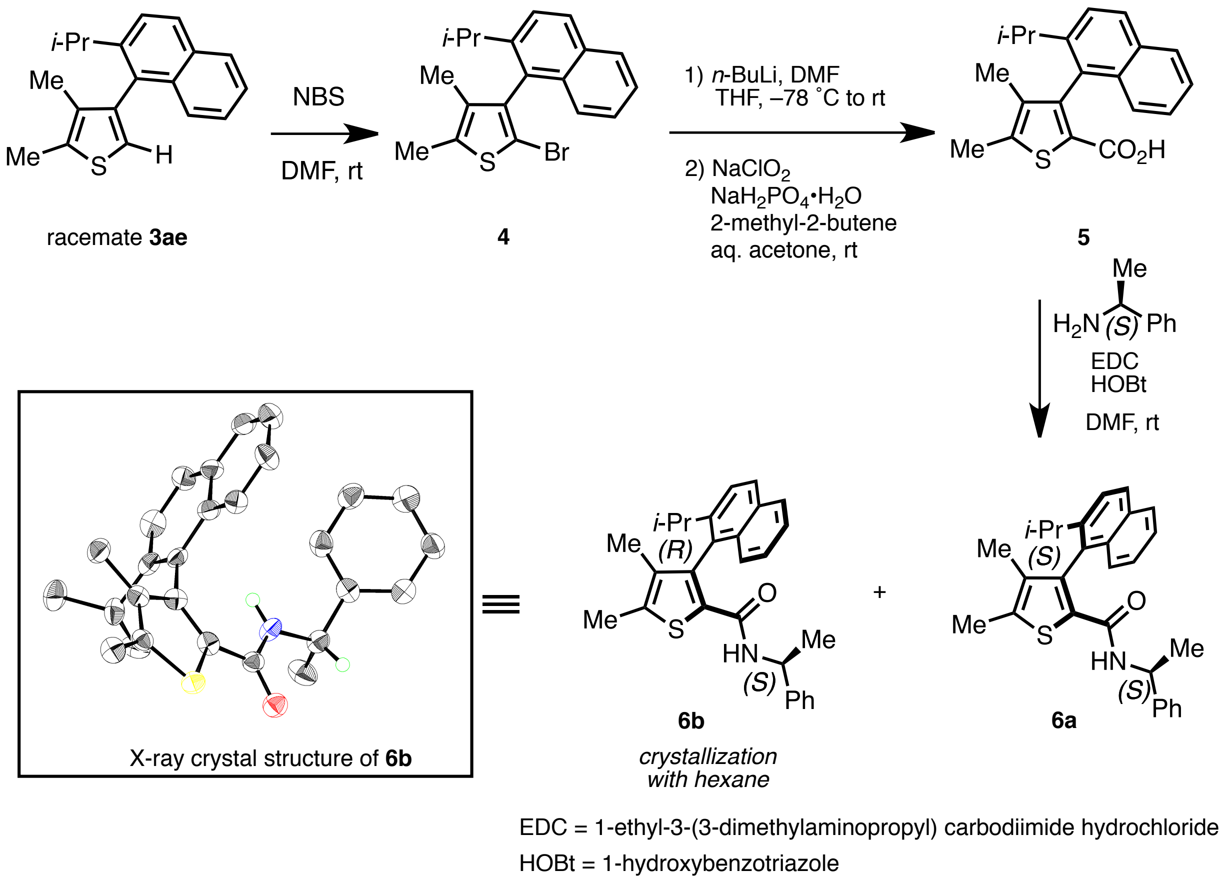
Entry	**2a** /equiv	$Pd(OAc)_2$ /mol %	**L5** /mol %	TEMPO /equiv	Time (h)	Yield%[b]	C4/C5[c]	Atmosphere
1	4.0	2	2	4.0	60	33	99/1	air
2	4.0	5	5	4.0	60	70	99/1	air
3	1.0	10	10	4.0	60	52	98/2	air
4	2.0	10	10	4.0	60	70	99/1	air
5	4.0	10	10	1.0	60	<27	98/2	air
6	4.0	10	10	2.0	60	31	98/2	air
7	4.0	10	10	1.0	24	41	99/1	O_2
8	4.0	10	10	2.0	24	71	99/1	O_2
9	4.0	10	10	1.0	60	31	98/2	O_2
10	2.0	5	5	2.0	60	55	98/2	O_2

a: Conditions: **1a** (0.25 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), **L5** (0.025 mmol), TEMPO (1.0 mmol), CF_3CO_2H (0.75 mmol), DMF (0.1 mL), 80 ˚C, under air or oxygen atomosphere.
b: Isolated yield. c: Determined by ^1H NMR.

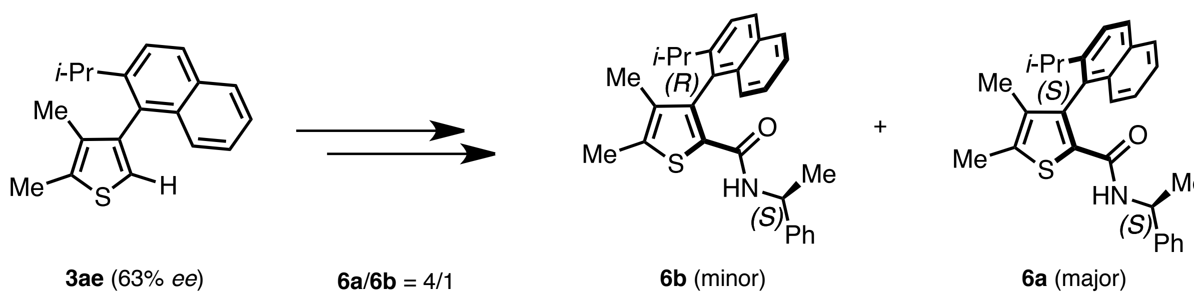
6. Determination of Absolute Stereochemistry

The absolute stereochemistry of coupling product **3ae** was determined by X-ray crystallography after derivatization of both racemic (Scheme S1) and enantiomerically enriched **3ae** (Scheme S2). Racemic coupling product (±)-**3ae** was converted into carboxylic acid (±)-**5** in 3 steps (Scheme S1). Condensation of (±)-**5** and (*S*)-1-phenethylamine gave a mixture of diastereomers **6a** and **6b** (ratio of **6a**/**6b** = 1:1 by ^1H NMR analysis, shown on p. S77). Finally, **6b** was separated from the mixture of **6a** and **6b** by crystallization, and the absolute stereochemistry of **6b** was determined to be *R* configuration by X-ray analysis. Therefore, compound **6a** was determined to have *S* configuration.

The application of the above-mentioned procedure to enantiomerically enriched **3ae** (63% *ee*) led to the formation of a mixture of **6a** and **6b** (ratio of **6a**/**6b** = 4:1 by ^1H NMR analysis, shown on p. S78) as shown in Scheme S2. According to these results, the enantioselective C–H arylation of thiophene **1a** with arylboronic acid **2e** using ligand **L4** was found to selectively afford the *S* configuration of heterobiaryl **3ae**.



Scheme S1. Transformation for detemination of absolute configuration.



Scheme S2. Transformation from enantiomerically enriched **3ae**.

2-Bromo-3-(2-isopropylnaphthalen-1-yl)-4,5-dimethylthiophene (4): To a solution of **3ae** (194 mg, 0.69 mmol) in DMF (3.0 mL) was added *N*-bromosuccinimide (185 mg, 1.04 mmol). After stirring the mixture for 24 h at room temperature, the residue was purified by preparative thin-layer chromatography (hexane) to give brominated compound **4** (196 mg, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.90 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.45–7.31 (m, 2H), 7.28–7.20 (m, 1H), 2.83 (sep, *J* = 6.7 Hz, 1H), 2.41 (s, 3H), 1.69 (s, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.24, 140.83, 133.98, 133.32, 132.38, 131.99, 130.32, 128.65, 127.89, 126.25, 125.57, 125.09, 123.71, 106.58, 30.96, 23.94, 23.64, 13.69, 13.24; HRMS (DART) *m/z* calcd for $C_{19}H_{20}BrS$ $[M+H]^+$: 359.0469, found: 359.0478.

3-(2-Isopropylnaphthalen-1-yl)-4,5-dimethylthiophene-2-carboxylic acid (5): To a solution of **4** (234 mg, 0.65 mmol) in THF (5.0 mL) was slowly added *n*-BuLi (1.6 M in hexane, 447 µL, 0.72 mmol) at –78 ˚C. After stirring at –78 ˚C for 30 min, the solution of DMF (76 µL, 0.98 mmol) in THF (1.0 mL) was added and stirred at –78 ˚C for 1 h and room temperature for 1 h. The mixture was poured into saturated aqueous NH_4Cl, and then 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 purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give a formyletad product (105 mg, 52%) as a yellow oil. To the resulting compound (49 mg, 0.16 mmol) in aqueous acetone (2.0 mL) was added $NaClO_2$ (29 mg, 0.32 mmol), NaH_2PO_4•H_2O (38 mg, 0.32 mmol) and 2-methyl-2-butene (39 mg, 0.56 mmol) and the mixture was stirred at room temperature for 2 days. The mixture was diluted with EtOAc and water, and then extracted with EtOAc. The organic layer was washed with brine, water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 1:1) to give the carboxylic acid **5** (49 mg, 96%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.3 (br s, 1H), 7.97–7.83 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.48–7.29 (m, 2H), 7.05 (d, *J* = 8.5 Hz, 1H), 2.72–2.60 (m, 1H), 2.47 (s, 3H), 1.56 (s, 3H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.46, 145.47, 142.95, 139.67, 135.29, 131.65, 131.50, 131.26, 127.84, 127.77, 126.27, 126.08, 124.88, 123.62, 30.70, 23.31, 23.08, 13.76, 12.19; HRMS (FAB) *m/z* calcd for $C_{20}H_{20}O_2S$ $[M]^+$: 325.1184, found: 324.1175.

(*R*)-3-(2-Isopropylnaphthalen-1-yl)-4,5-dimethyl-*N*-((*S*)-1-phenylethyl)thiophene-2-carboxamide (6b): To a solution of carboxylic acid **5** (36 mg, 0.11 mmol) and (*S*)-1-phenethylamine (17 µL, 0.13 mmol) in DMF (1.0 mL) were added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (25 mg, 0.13 mmol) and 1-hydroxybenzotriazole (15 mg, 0.11 mmol). After stirring the mixture at room temperature for 12 h, the mixture was poured into saturated aqueous $NaHCO_3$, and then 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 purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give a mixture of **6a** and **6b** (39 mg, 83%) as a pale yellow oil. To the residue was added hexane (1.0 mL) and the resulting precipitate was collected by filtration to give the single isomer product **6b** (11 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.52–7.43 (m, 1H), 7.39–7.31 (m, 1H), 7.29–7.20 (m, 1H), 7.03–6.95 (m, 1H), 6.94–6.84 (m, 2H), 6.20 (d, *J* = 7.6 Hz, 2H), 5.36 (d, *J* = 7.6 Hz, 1H), 4.85–4.75 (m, 1H), 2.87 (sep, *J* = 6.7 Hz, 1H), 2.48 (s, 3H), 1.71 (s, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.76, 145.47, 143.01, 139.56, 138.78, 134.87, 132.36, 132.33, 132.08, 129.93, 129.52, 128.12, 128.02, 127.19, 126.45, 125.97, 125.62, 124.99, 123.98, 48.41, 30.91, 23.81, 23.49, 22.61, 14.09, 12.58; HRMS (DART) *m/z* calcd for $C_{28}H_{30}NOS$ $[M+H]^+$: 428.2048, found: 428.2052.

7. X-ray Crystal Structure Analysis of 6b

A suitable crystal was mounted with mineral oil on a glass fiber and transferred to the goniometer of a Rigaku Saturn CCD diffractometer. Graphite-monochromated Mo Kα radiation (λ = 0.71070 Å) was used. The structures were solved by direct methods with (SIR-97)[6] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[7] The intensities were corrected for Lorentz and polarization effects. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions. Details of the crystal data and a summary of the intensity data collection parameters for **6b** are listed in Table S4.

Table S4. Crystallographic data and structure refinement details for **6b**.

	6b
formula	$C_{28}H_{29}NOS$
fw	427.58
T (K)	103(2)
λ (Å)	0.71070
cryst syst	Orthorhombic
space group	$P2_12_12_1$
a, (Å)	9.357(7)
b, (Å)	13.439(9)
c, (Å)	18.660(13)
α, (deg)	90
β, (deg)	90
γ, (deg)	90
V, (Å^3)	2346(3)
Z	4
D_{calc}, (g / cm^3)	1.210
m (mm^{-1})	0.158
F(000)	912
cryst size (mm)	0.20 × 0.10 × 0.01
2θ range, (deg)	3.03–25.00
reflns collected	23359
indep reflns/R_{int}	4115/0.1799
params	285
GOF on F^2	1.047
R_1, wR_2 [I>2σ(I)]	0.1054, 0.2507
R_1, wR_2 (all data)	0.1360, 0.2823
abs struct param	-0.1(2)

(6) A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.,* 1999, **32**, 115–119.
(7) G. M. Sheldrick, University of Göttingen: Göttingen, Germany, 1997.

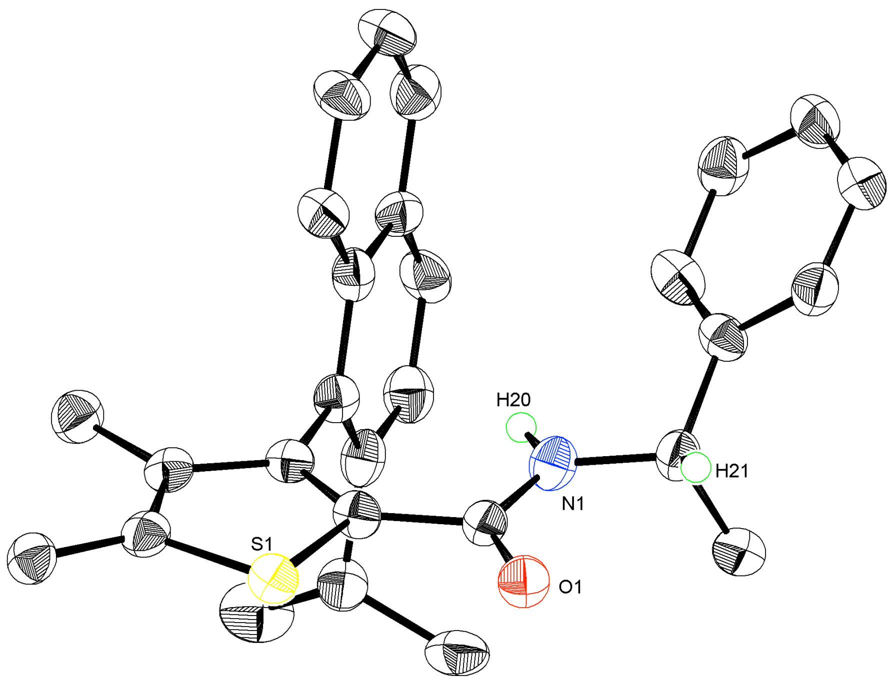


Figure S1. ORTEP drawing of **6b** with 50% thermal ellipsoid. All hydrogen atoms except N–H and C*–H are omitted for clarity.

8. Computational Study

The Gaussian 03 program[8] running on a SGI Altix4700 system was used for optimization (B3LYP/6-31G(d)).[9] All structures were optimized without any symmetry assumptions. Zero-point energy, enthalpy, and Gibbs free energy at 298.15 K and 1 atm were estimated from the gas-phase studies unless otherwise noted. Harmonic vibration frequency calculations at the same level were performed to verify all stationary points as local minima (with no imaginary frequency) or transition states (with one imaginary frequency). IRC calculations[10] were also performed to check transition states. Visualization of the results was performed by use of POV-Ray for Windows v3.5 software.

Table S5. Uncorrected and thermal-corrected (298K) energies of stationary points (Hartree).[a]

compound	E	E + ZPE	H	G
3ba	-1016.33524198	-1016.084792	-1016.068980	-1016.128094
TS-1	-1016.28869529	-1016.036565	-1016.022705	-1016.075221
TS-2	-1016.28803339	-1016.035947	-1016.021987	-1016.074743

a) E: electronic energy; ZPE: zero-point energy; H (=E+ZPE+E_{vib}+E_{rot}+E_{trans}+RT): sum of electronic and themal enthalpies; G (=H–TS): sum of electronic and thermal free energies.

(8) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, *Gaussian 03, Revision E.01,* Gaussian, Inc., Wallingford CT, 2004.

(9) (a) Becke, A. D. *J. Chem. Phys.,* 1993, **98**, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B,* 1988, **37**, 785–789.

(10) (a) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.,* 1989, **90**, 2154–2161. (b) C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.,* 1990, **94**, 5523–5527.

Table S6. Cartesian coordinates of optimized species.

3ba

C	2.212267	-2.532229	-0.174894	H	4.379132	-2.667551	-0.129516	C	-1.957507	-0.373548	1.030164
C	1.115994	-1.698319	-0.178430	C	1.674301	2.493653	-0.052925	S	-3.551973	-0.762561	-0.973596
C	1.268170	-0.283755	-0.132536	C	0.347315	1.986760	-0.089352	H	-1.682948	0.128674	-2.307534
C	2.597188	0.251831	-0.091653	H	3.772153	2.068960	-0.020464	C	-3.210915	-0.831569	0.727069
C	3.706507	-0.635817	-0.091021	H	1.818615	3.571006	-0.020242	H	-3.958560	-1.208340	1.412940
C	3.522598	-1.998793	-0.130167	C	-0.809295	2.962404	-0.094855	C	-1.385011	-0.314417	2.421078
H	2.071449	-3.609339	-0.210371	H	-0.483651	3.954460	0.234221	H	-0.471951	-0.916300	2.501590
H	0.115338	-2.115996	-0.222252	H	-1.236869	3.072433	-1.099633	H	-1.113795	0.711449	2.698976
C	0.146192	0.610612	-0.130442	H	-1.624461	2.634911	0.557996	H	-2.102470	-0.685723	3.159099
C	2.765148	1.659355	-0.053022	C	-1.239197	0.053427	-0.151762				
H	4.708862	-0.214505	-0.059893	C	-1.980302	-0.103454	-1.293481				

TS-1

C	2.673918	-2.165214	0.524335	H	4.699537	-2.167096	-0.261331	C	-1.783699	-1.415186	0.025640
C	1.492425	-1.461296	0.641253	C	1.454756	2.597813	-0.153673	S	-3.882195	0.067382	-0.378030
C	1.326720	-0.158002	0.108115	C	0.242555	1.997030	0.286181	H	-2.328678	1.892661	-0.312461
C	2.516189	0.466808	-0.399858	H	3.410760	2.352879	-0.998604	C	-3.135762	-1.471963	-0.188835
C	3.701186	-0.295691	-0.574658	H	1.505665	3.684473	-0.154303	H	-3.727885	-2.373314	-0.271080
C	3.779995	-1.600269	-0.144339	C	-0.748879	2.987949	0.875109	C	-1.091363	-2.763859	0.058553
H	2.756933	-3.151367	0.973836	H	-0.185539	3.731435	1.451071	H	-0.209856	-2.802727	-0.584380
H	0.696788	-1.877873	1.235773	H	-1.313479	3.552156	0.119398	H	-0.786460	-3.073652	1.064524
C	0.082545	0.596727	0.203784	H	-1.465607	2.516178	1.550292	H	-1.792756	-3.522908	-0.301679
C	2.522781	1.868596	-0.600531	C	-1.292592	-0.019740	0.092131				
H	4.568806	0.197017	-1.007577	C	-2.359627	0.830303	-0.162371				

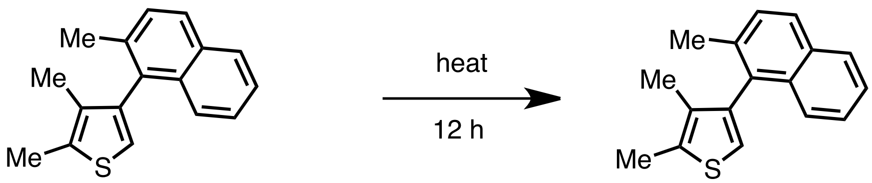
TS-2

C	-2.640521	-2.225340	0.704723	H	-4.673288	-2.314220	-0.056375	C	2.613850	0.376644	0.003442
C	-1.467794	-1.498393	0.762763	C	-1.513053	2.501084	-0.335149	S	2.823512	-2.191808	-0.321314
C	-1.332317	-0.221972	0.143238	C	-0.294404	1.962896	0.169585	H	0.420094	-2.164857	-0.282127
C	-2.535779	0.338811	-0.400447	H	-3.458025	2.151411	-1.167289	C	3.528378	-0.627896	-0.168552
C	-3.709281	-0.452765	-0.507512	H	-1.584164	3.583801	-0.417103	H	4.598987	-0.504173	-0.261534
C	-3.762883	-1.725335	0.012889	C	0.612850	2.996970	0.804864	C	3.171012	1.781409	-0.069686
H	-2.701609	-3.180861	1.218963	H	-0.023228	3.681069	1.379348	H	2.629594	2.393909	-0.794960
H	-0.652641	-1.884145	1.362295	H	1.312566	2.552068	1.509748	H	3.175092	2.313508	0.884682
C	-0.097074	0.570124	0.167904	H	1.170270	3.614114	0.092938	H	4.209702	1.729234	-0.409653
C	-2.564173	1.719118	-0.725062	C	1.230518	-0.137107	0.085095				
H	-4.587661	-0.006856	-0.968604	C	1.258690	-1.507428	-0.139648				

9. Racemization Study

A preliminary racemization study was examined using enantiomerically enriched (*R*)-**3aa**, which was obtained by chiral HPLC separation (Table S7). When (*R*)-**3aa** was heated at 80 ˚C, any racemization was not observed. When (*R*)-**3aa** was heated at 120 ˚C, obvious erosion of ee was observed.

Table S7. Racemization examination.



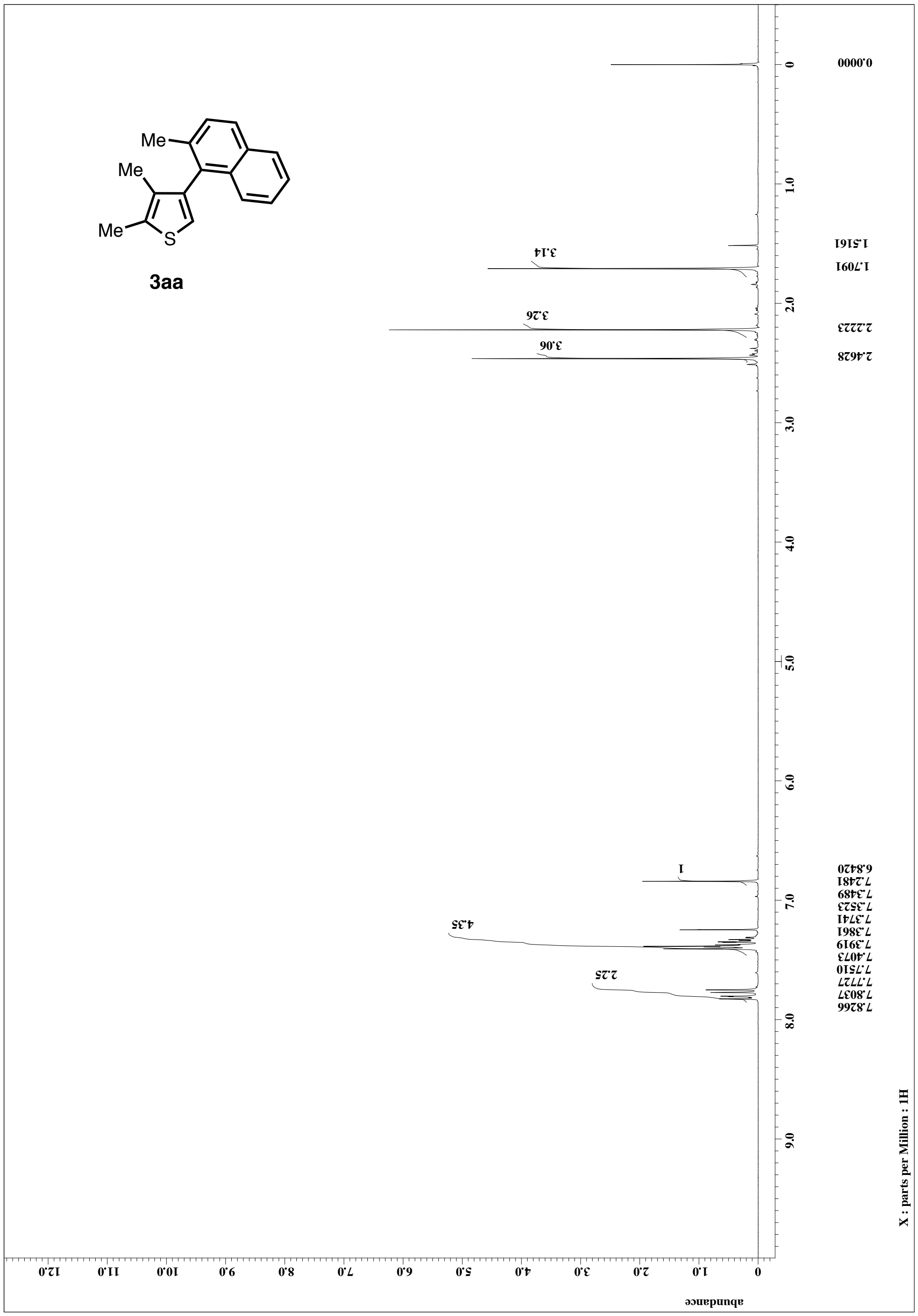
(*R*)-3aa
95% *ee*

3aa

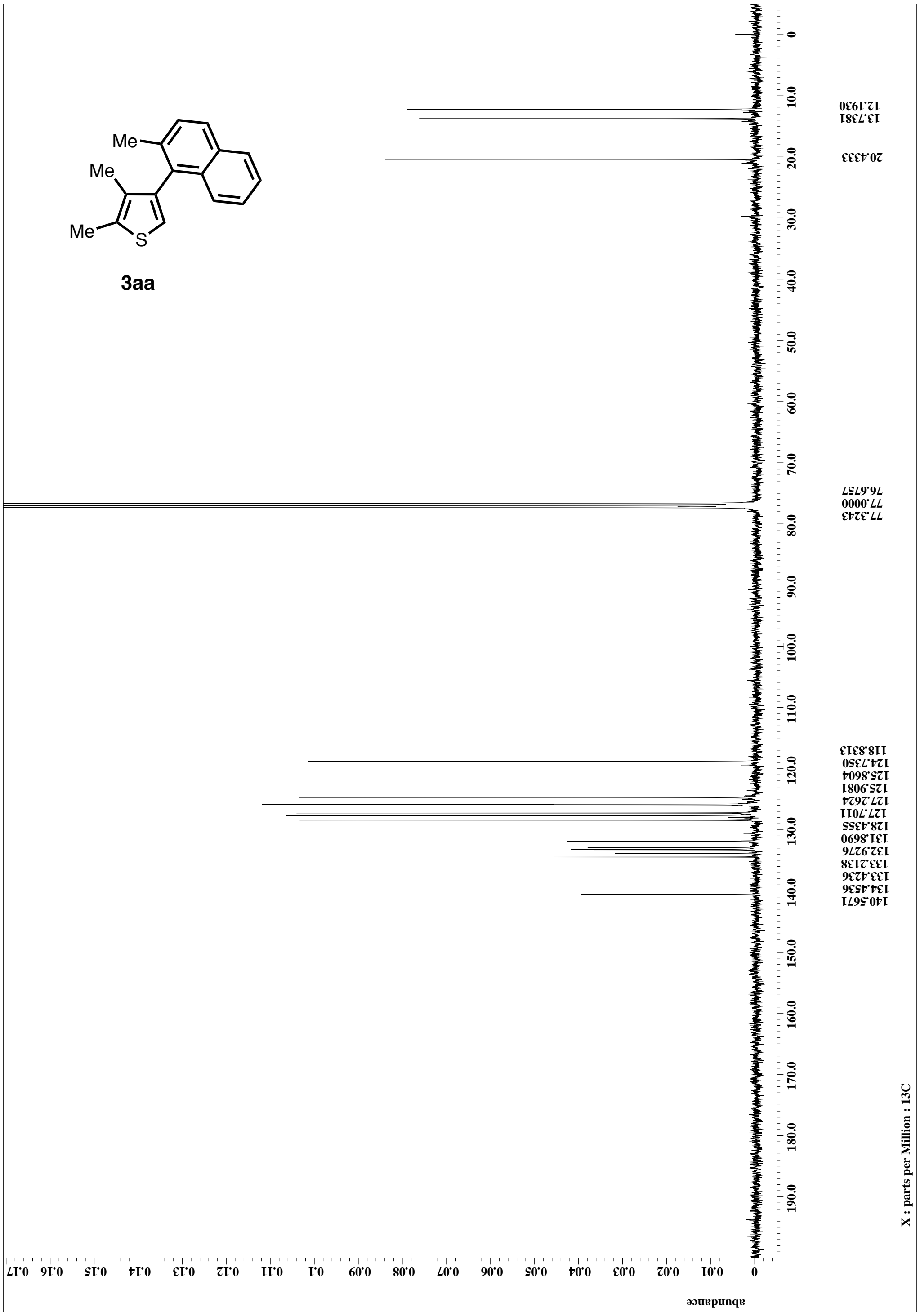
Conditions	Result
80 ˚C (hexane)	95% *ee*
120˚ C (DMF)	13% *ee*

10. ^{1}H and ^{13}C NMR Spectra

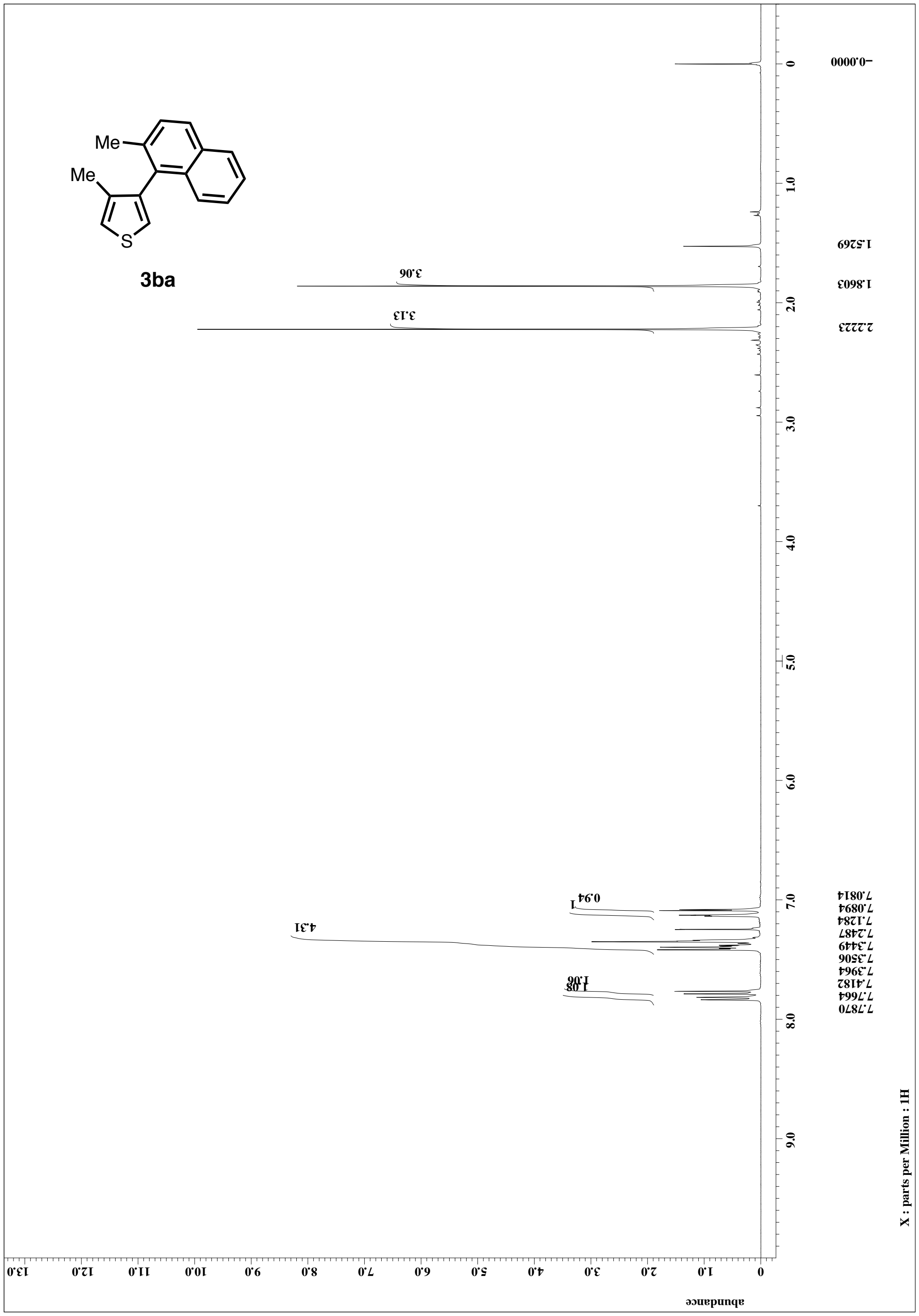
^{1}H NMR (400 MHz, $CDCl_3$) of 3aa:



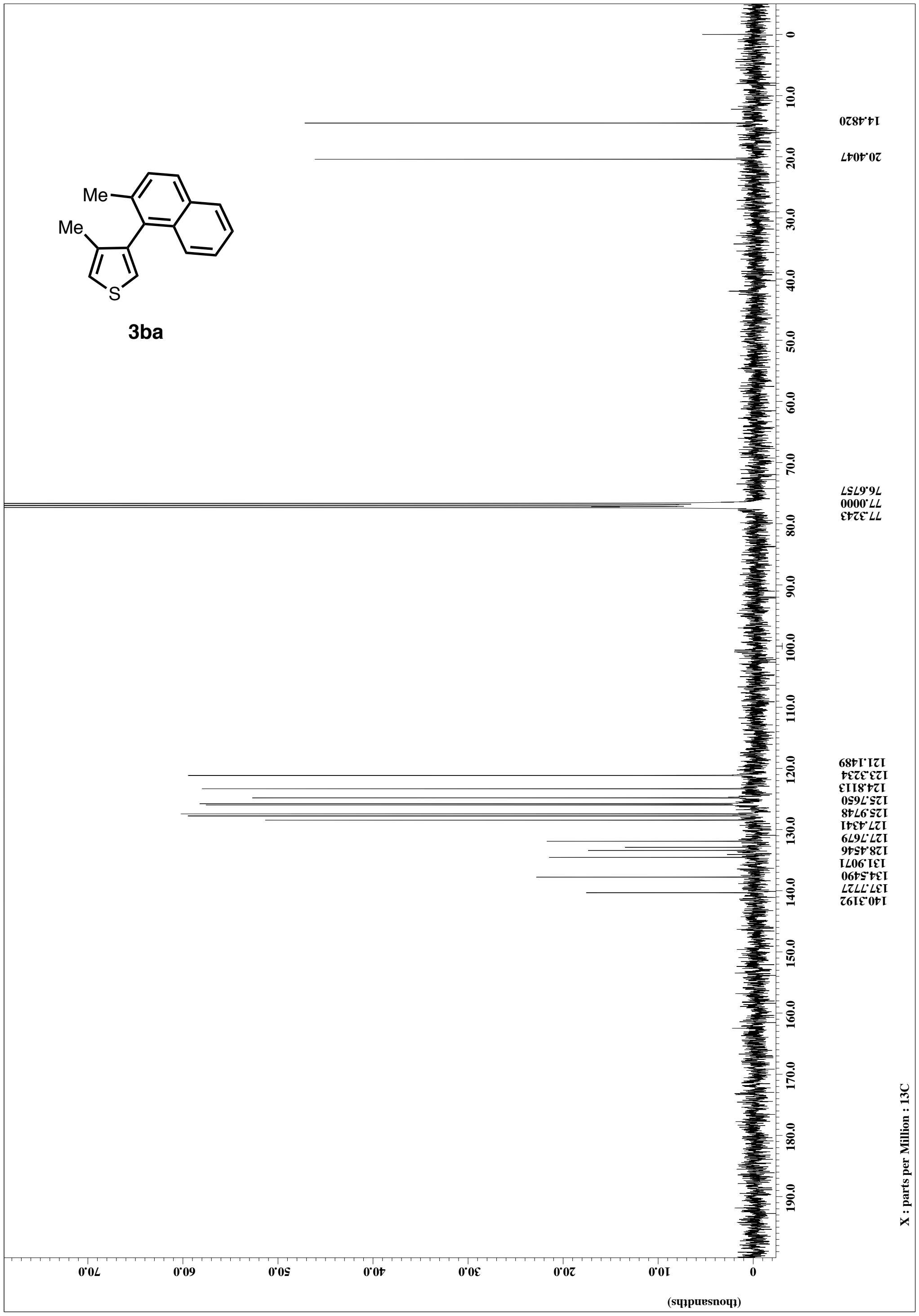
^{13}C NMR (100 MHz, $CDCl_3$) of 3aa:



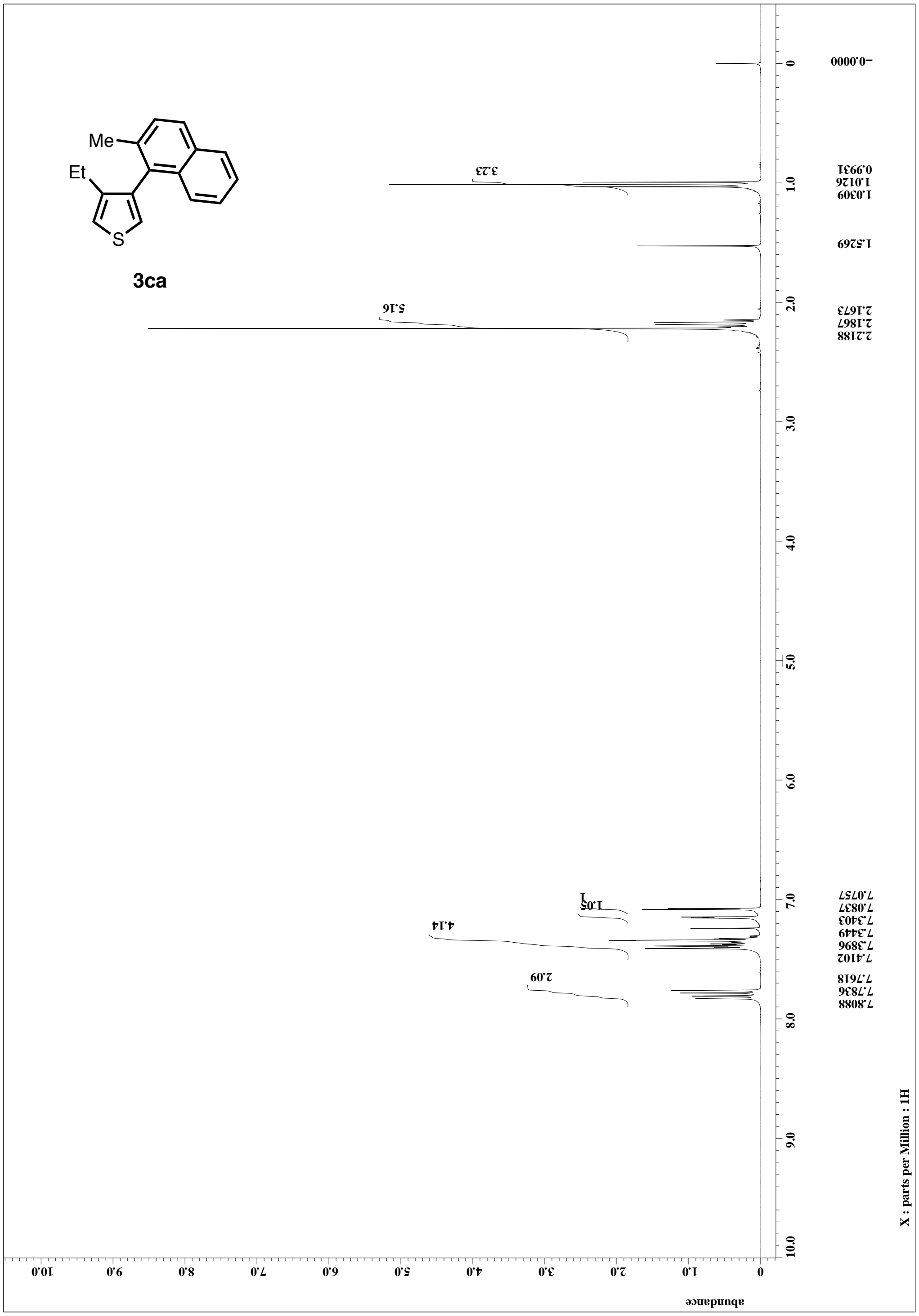
^{1}H NMR (400 MHz, $CDCl_3$) of 3ba:



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

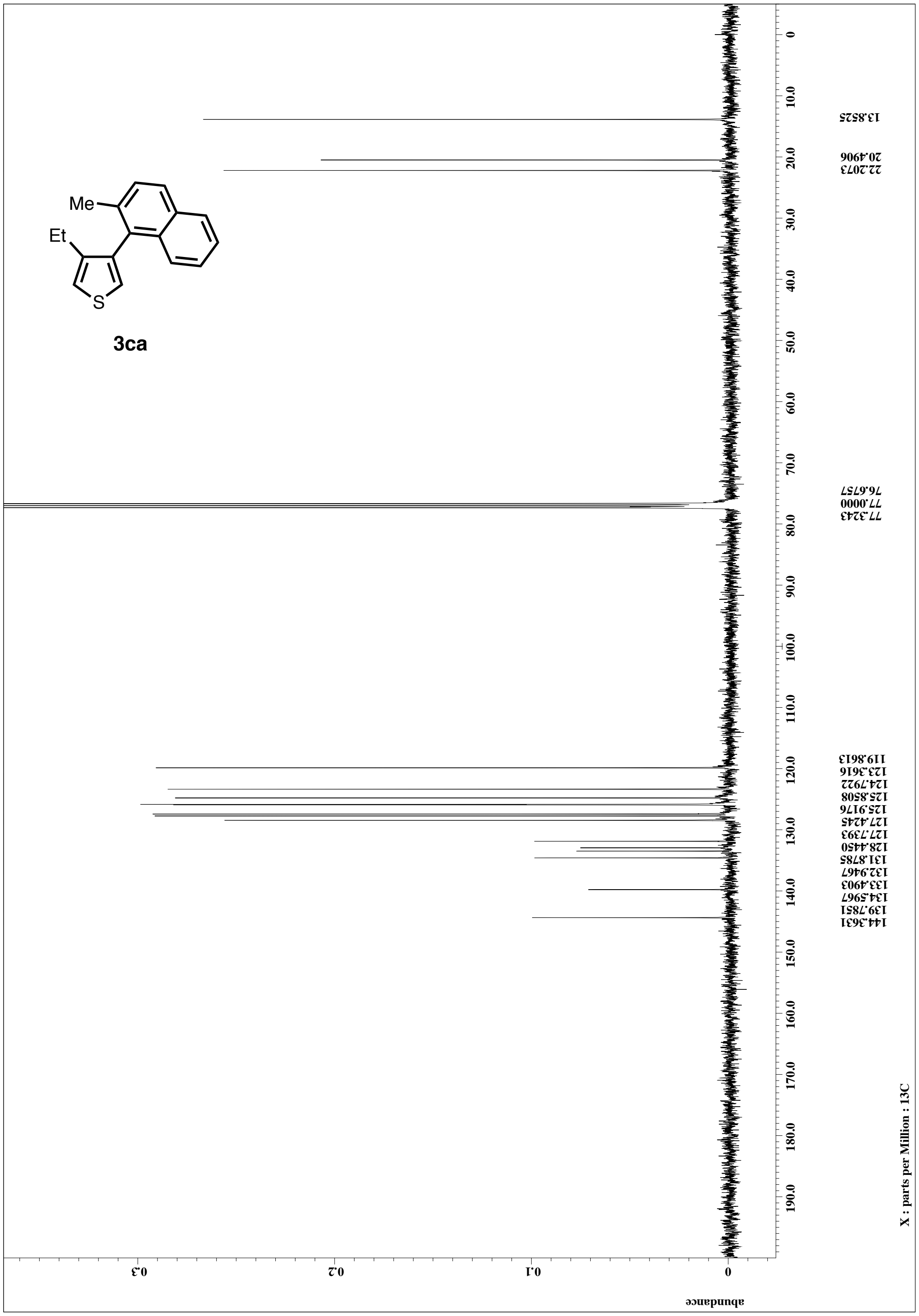


^{1}H NMR (400 MHz, $CDCl_3$) of 3ca:

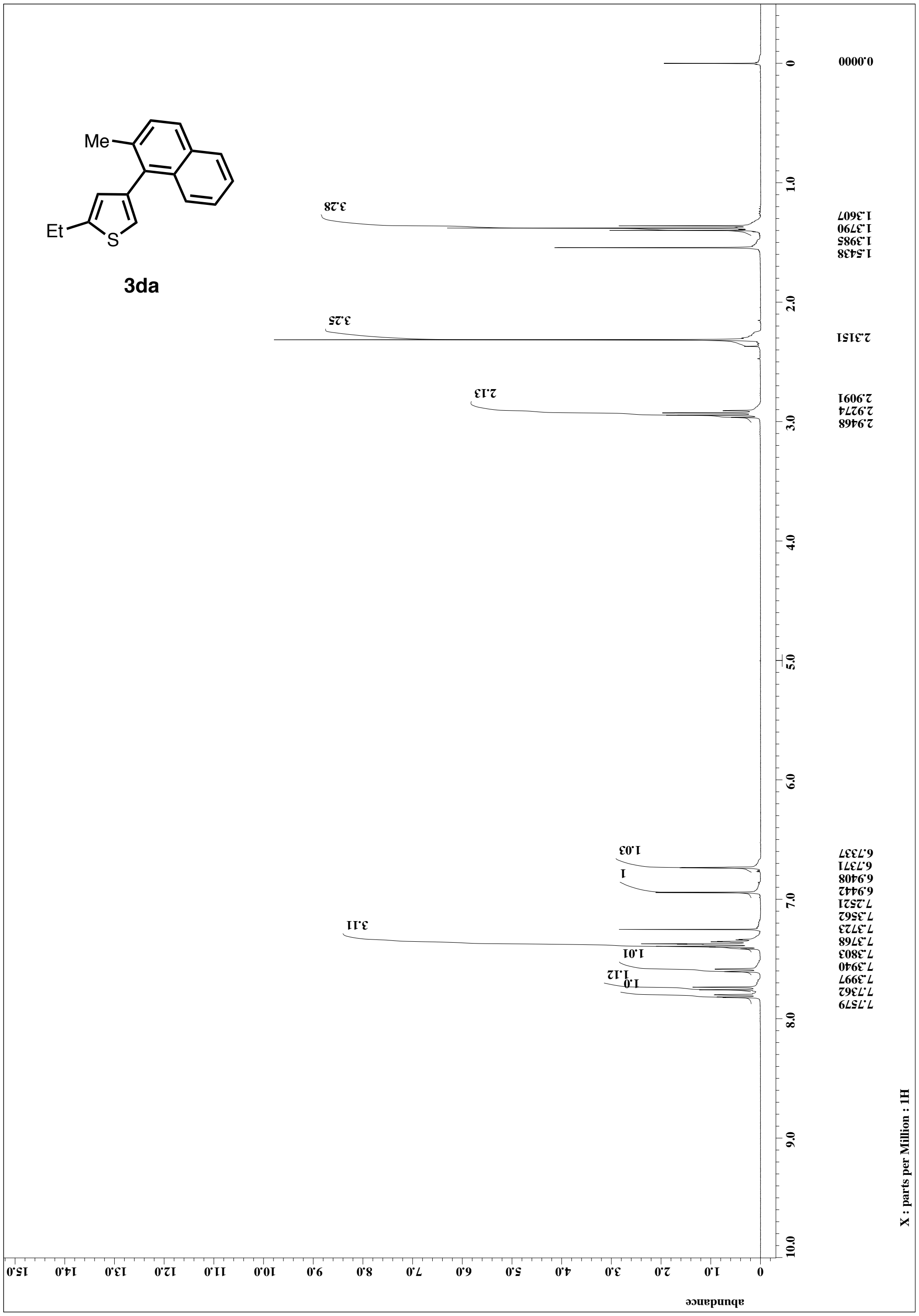


Electronic Supplementary Material (ESI) for Chemical Science

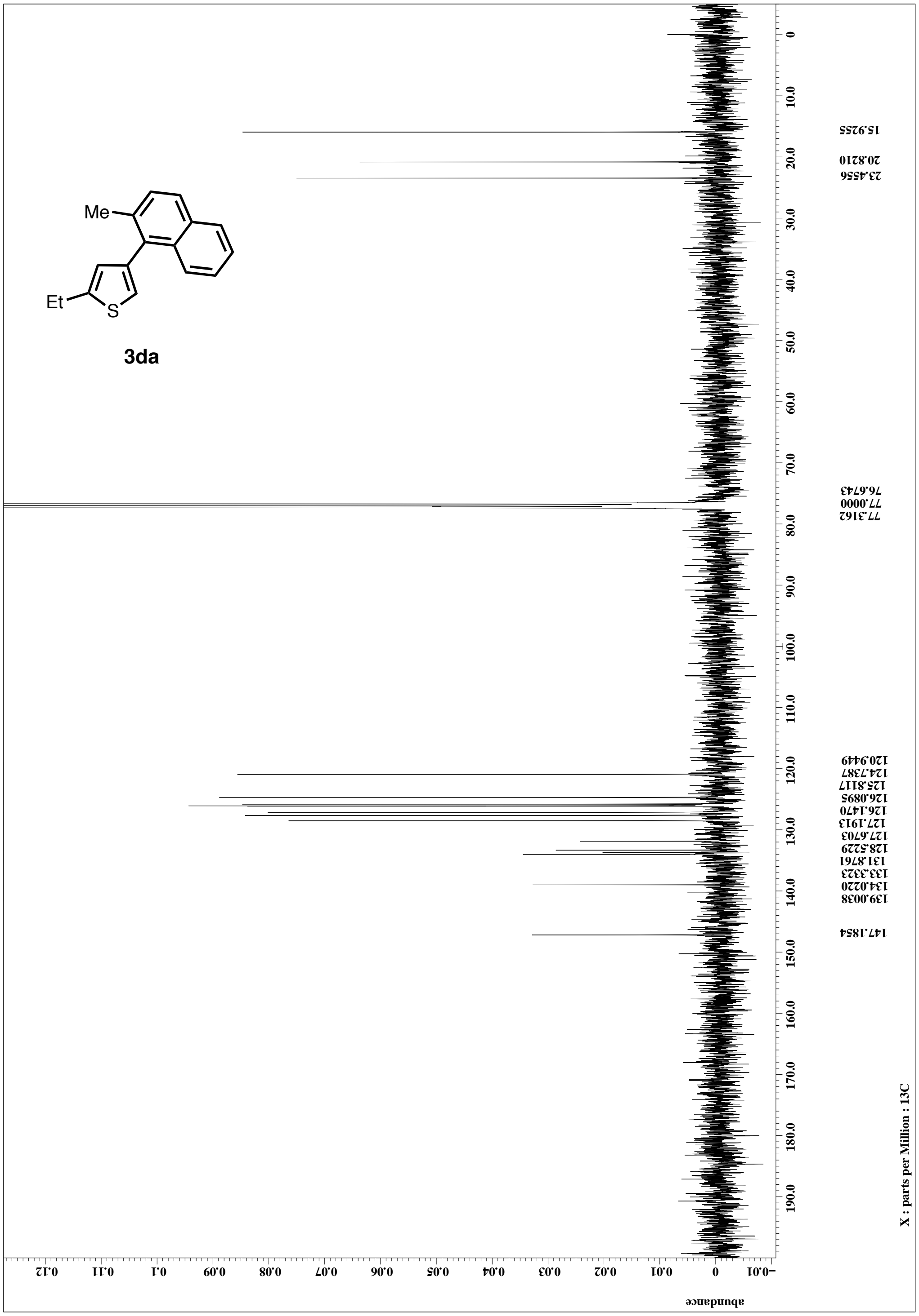
^{13}C NMR (100 MHz, $CDCl_3$) of 3ca:



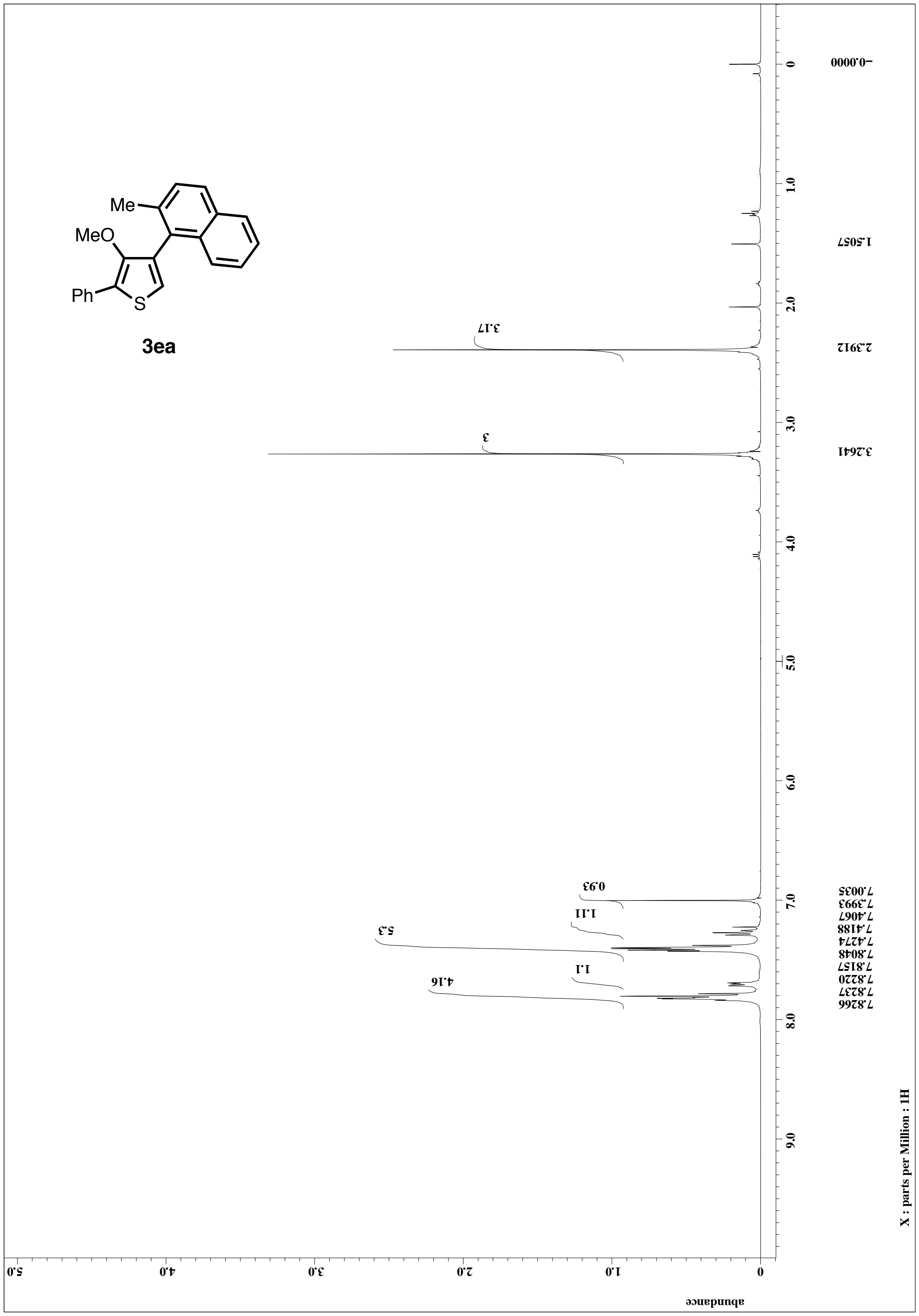
^{1}H NMR (400 MHz, $CDCl_3$) of 3da:



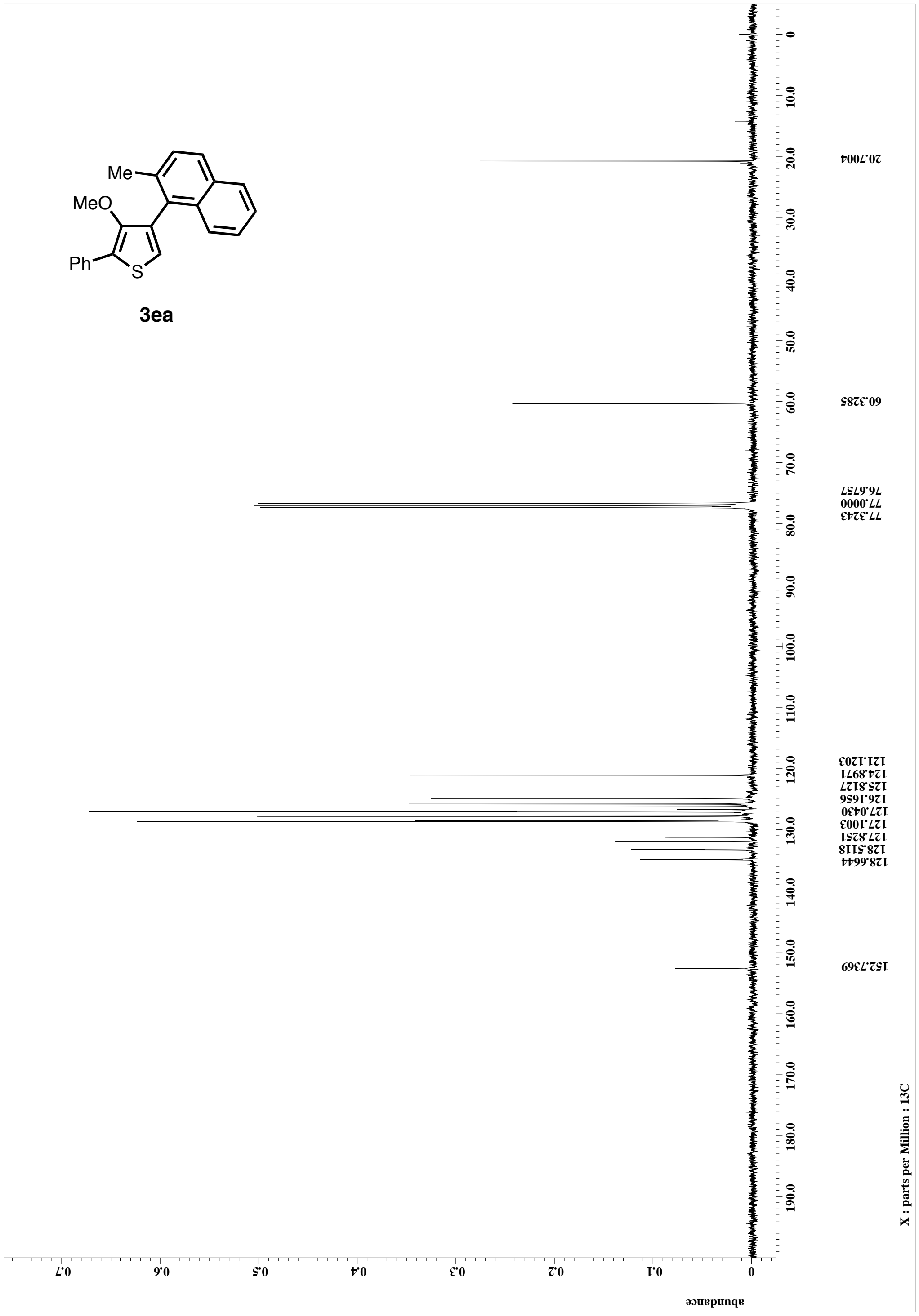
^{13}C NMR (100 MHz, $CDCl_3$) of 3da:



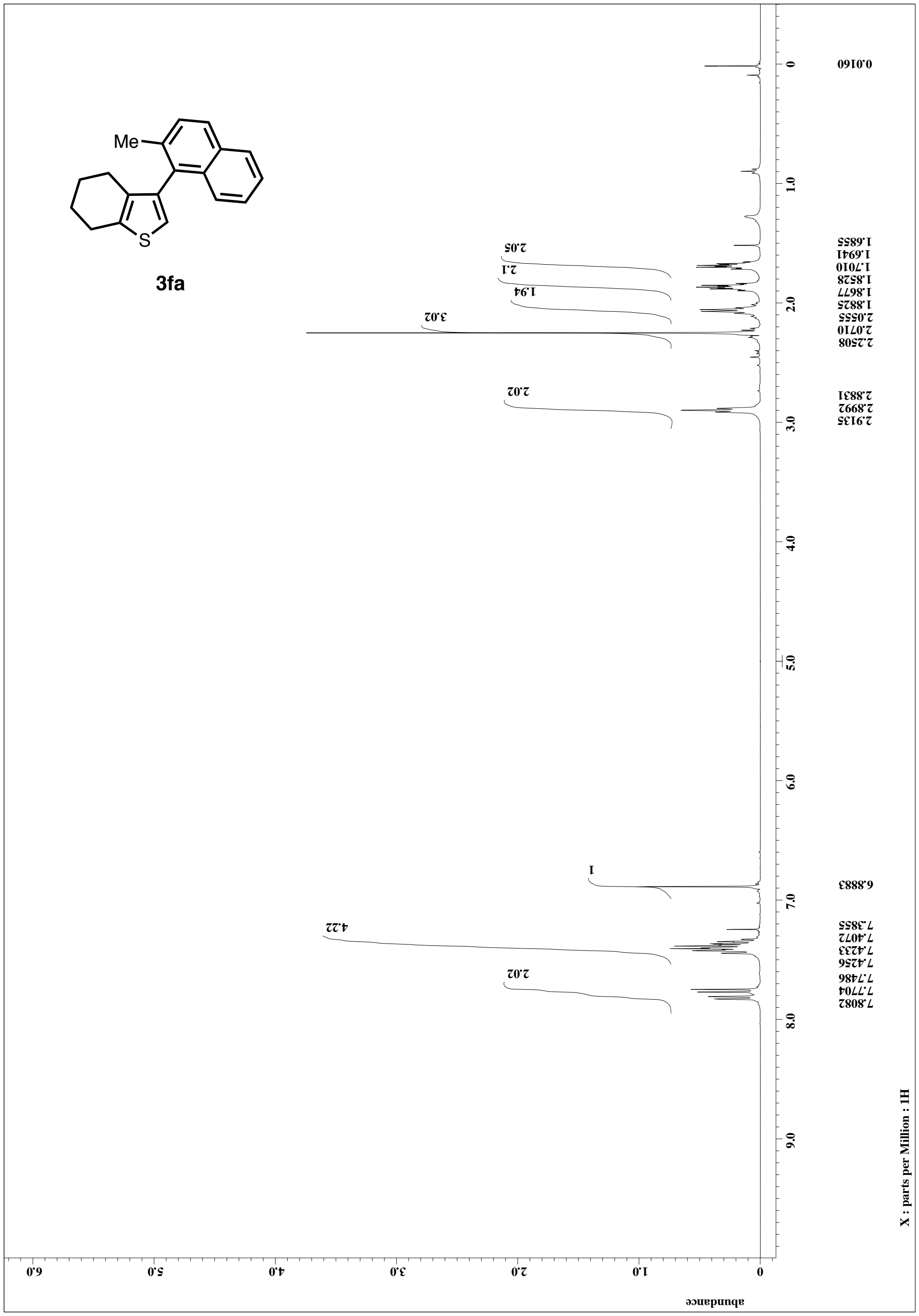
^{1}H NMR (400 MHz, $CDCl_3$) of 3ea:



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

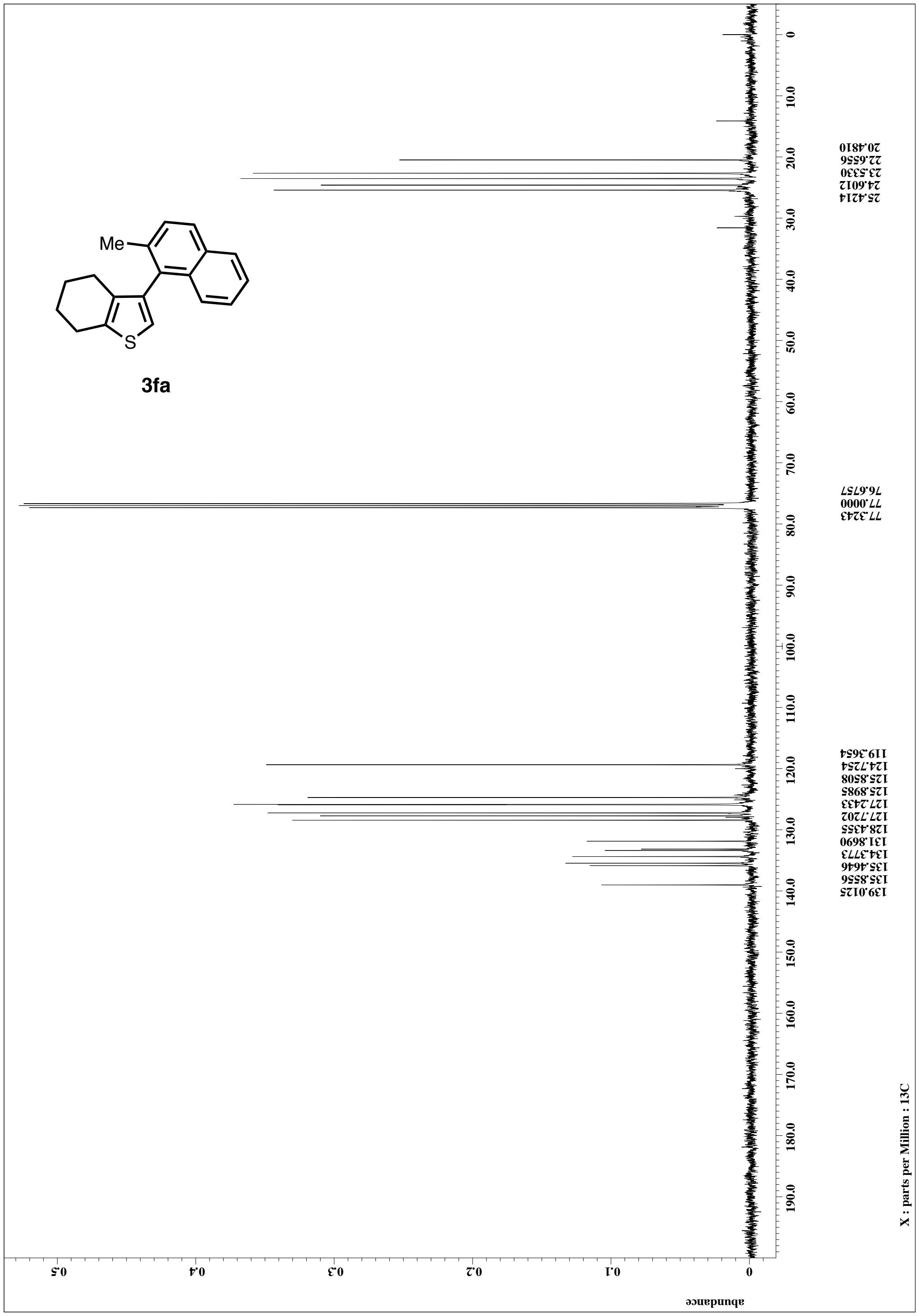


^{1}H NMR (400 MHz, $CDCl_3$) of 3fa:

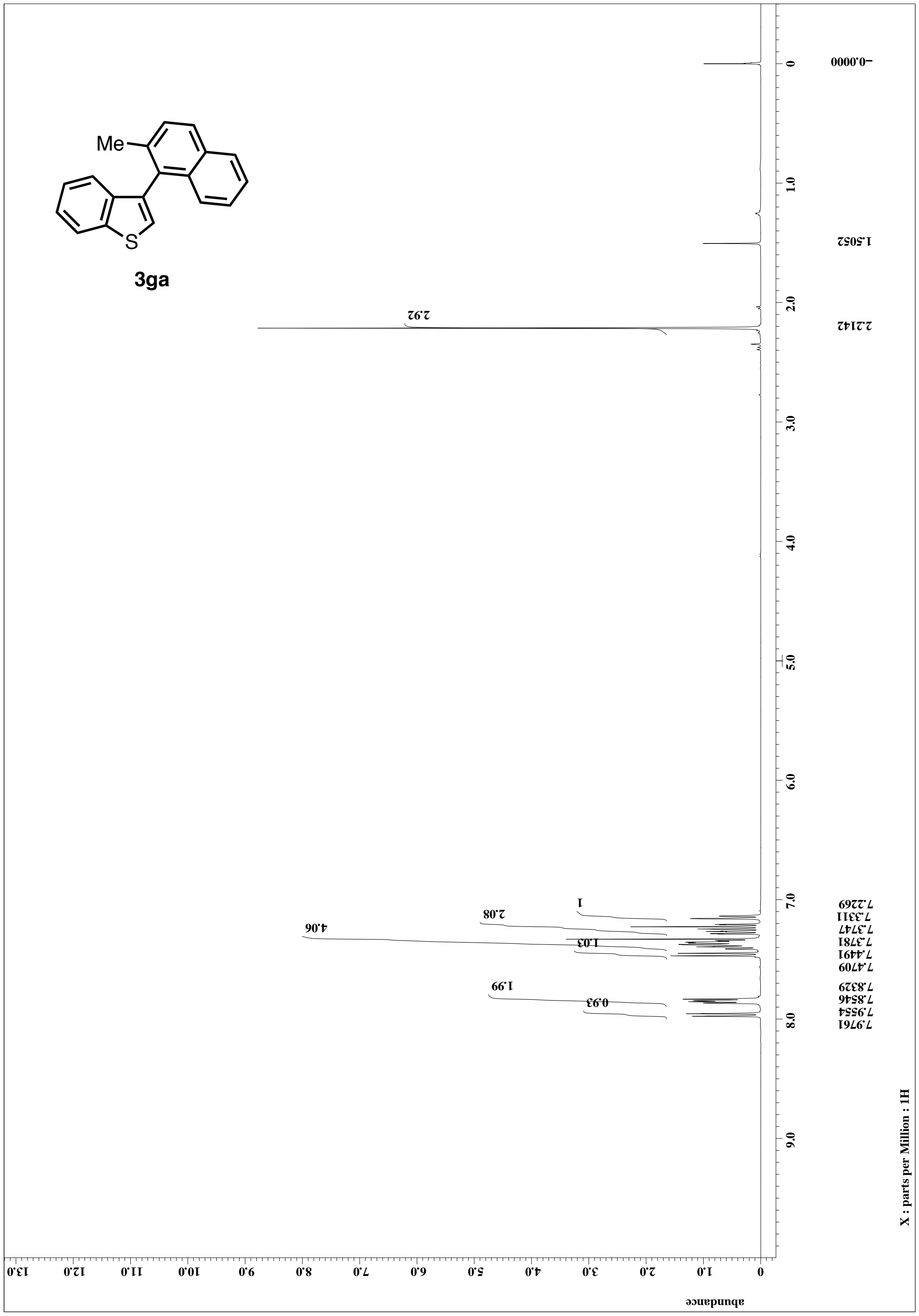


3fa

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

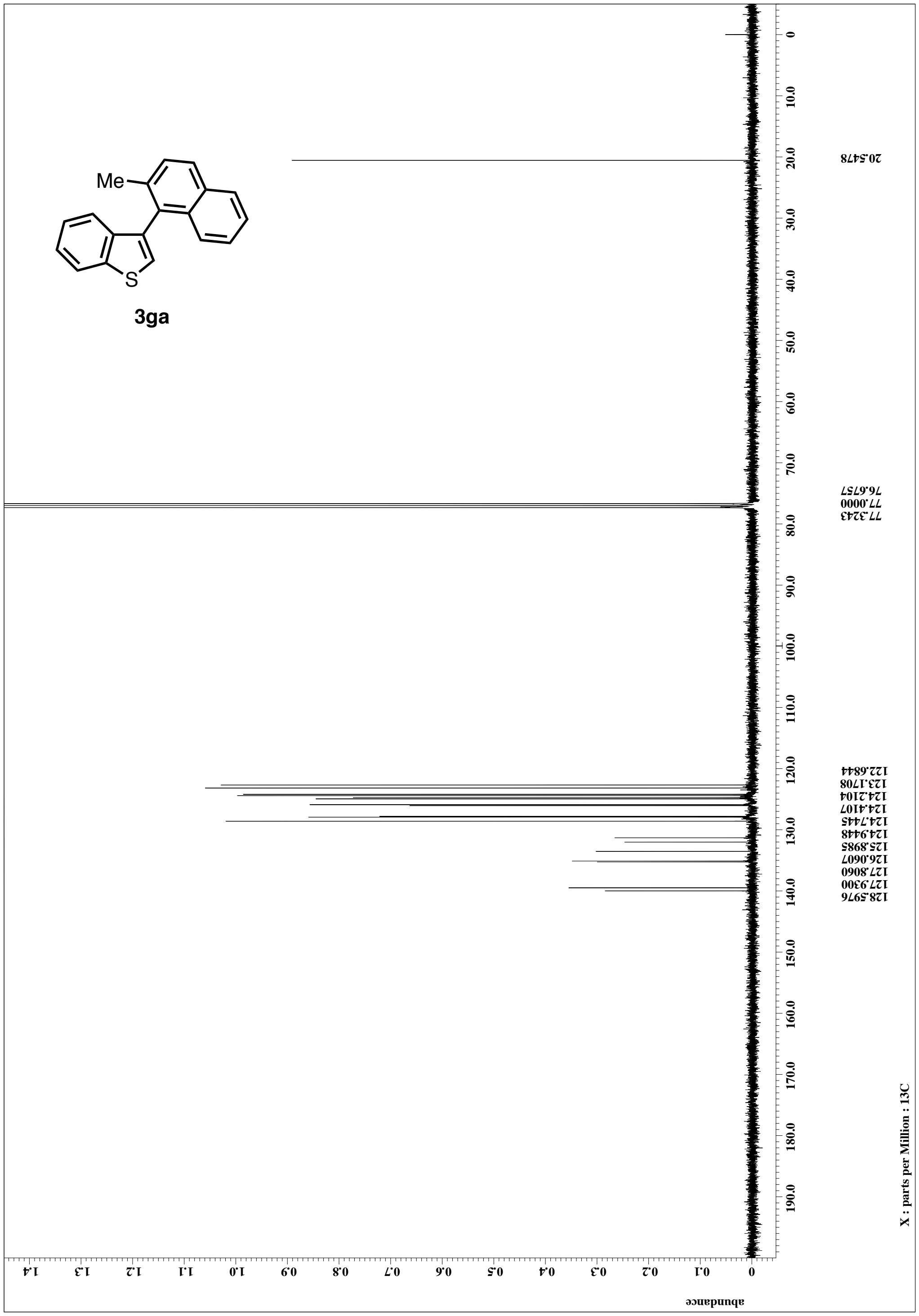


[1]H NMR (400 MHz, $CDCl_3$) of 3ga:

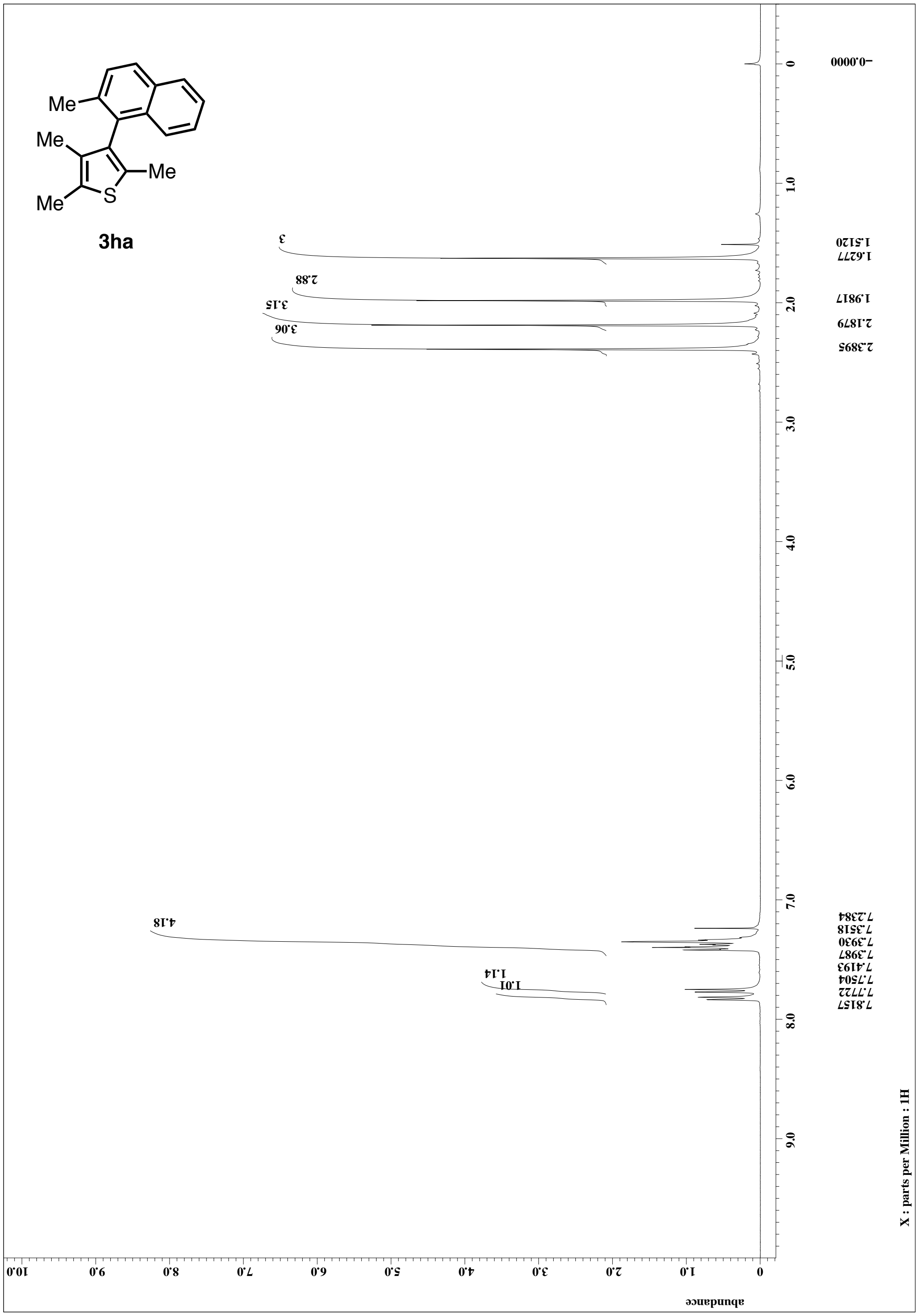


3ga

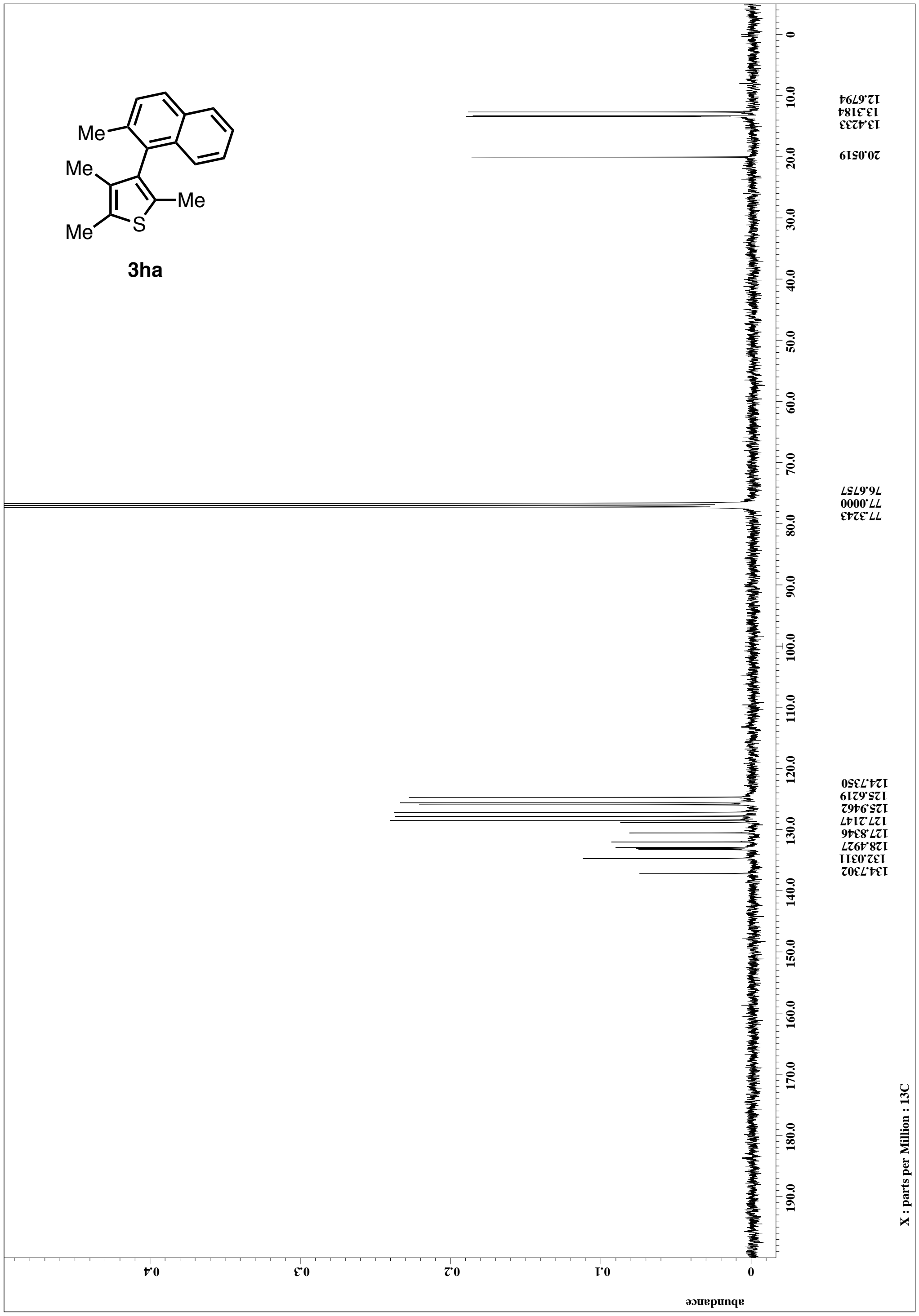
^{13}C NMR (100 MHz, $CDCl_3$) of 3ga:



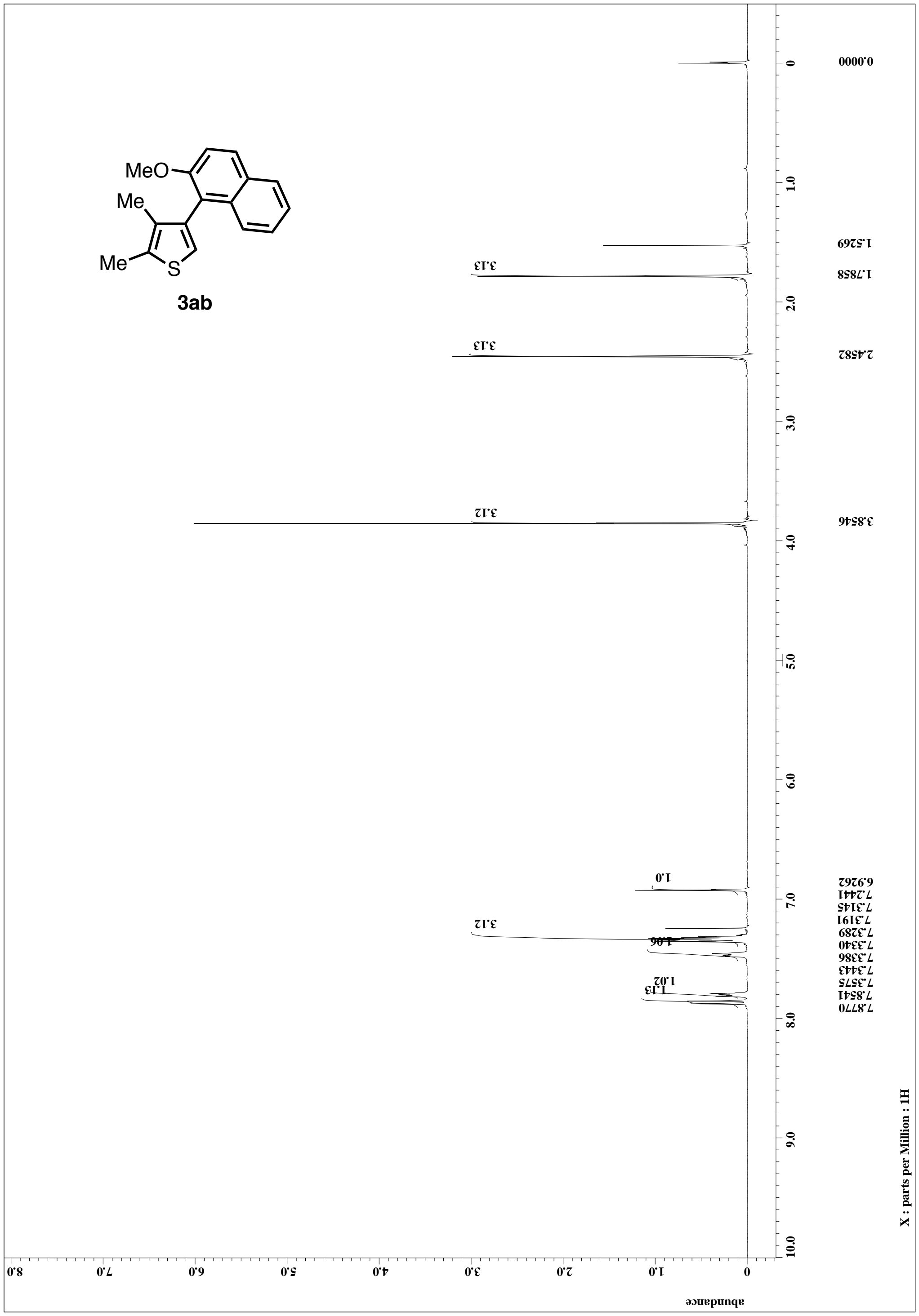
^{1}H NMR (400 MHz, $CDCl_3$) of 3ha:



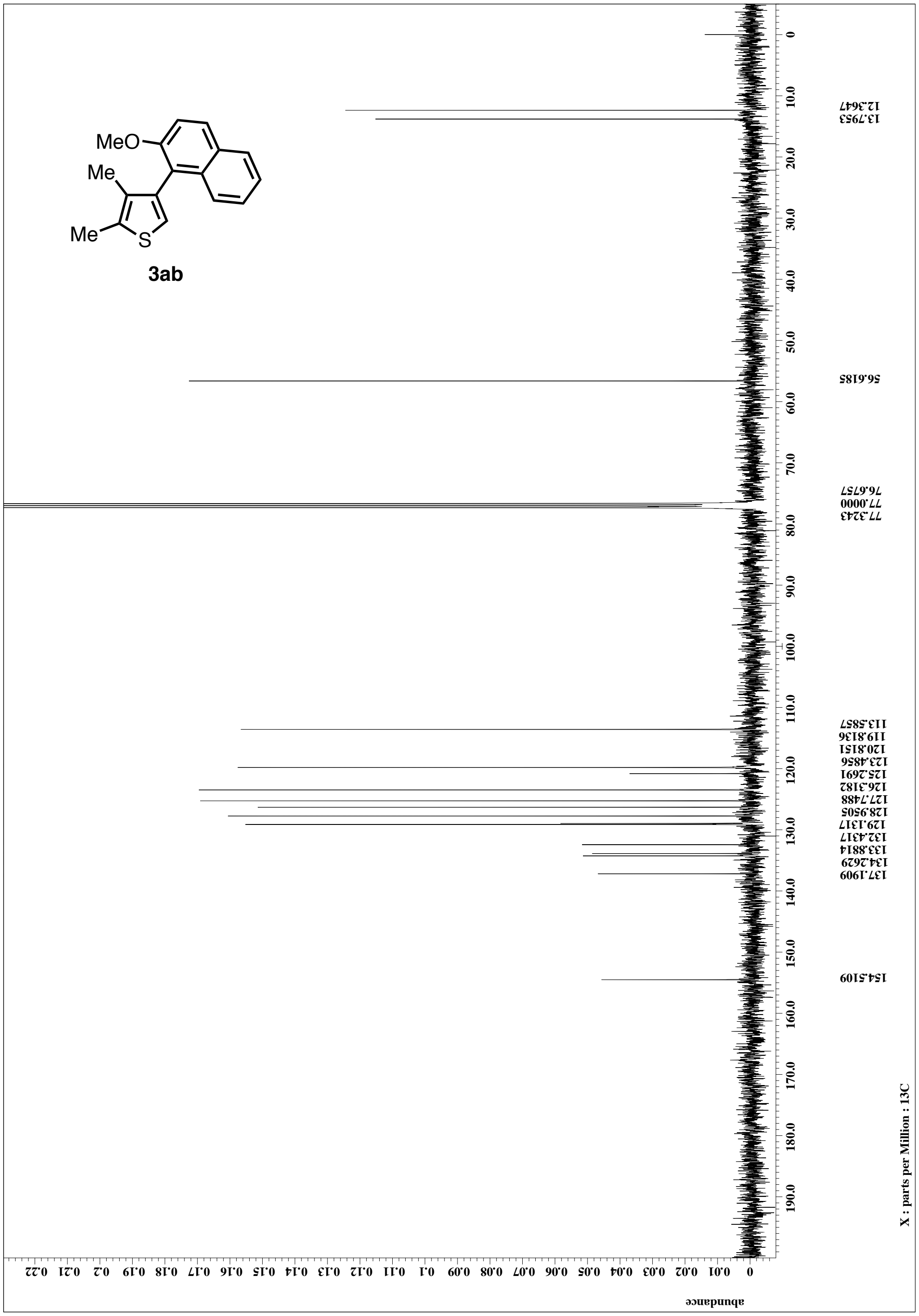
^{13}C NMR (100 MHz, $CDCl_3$) of 3ha:



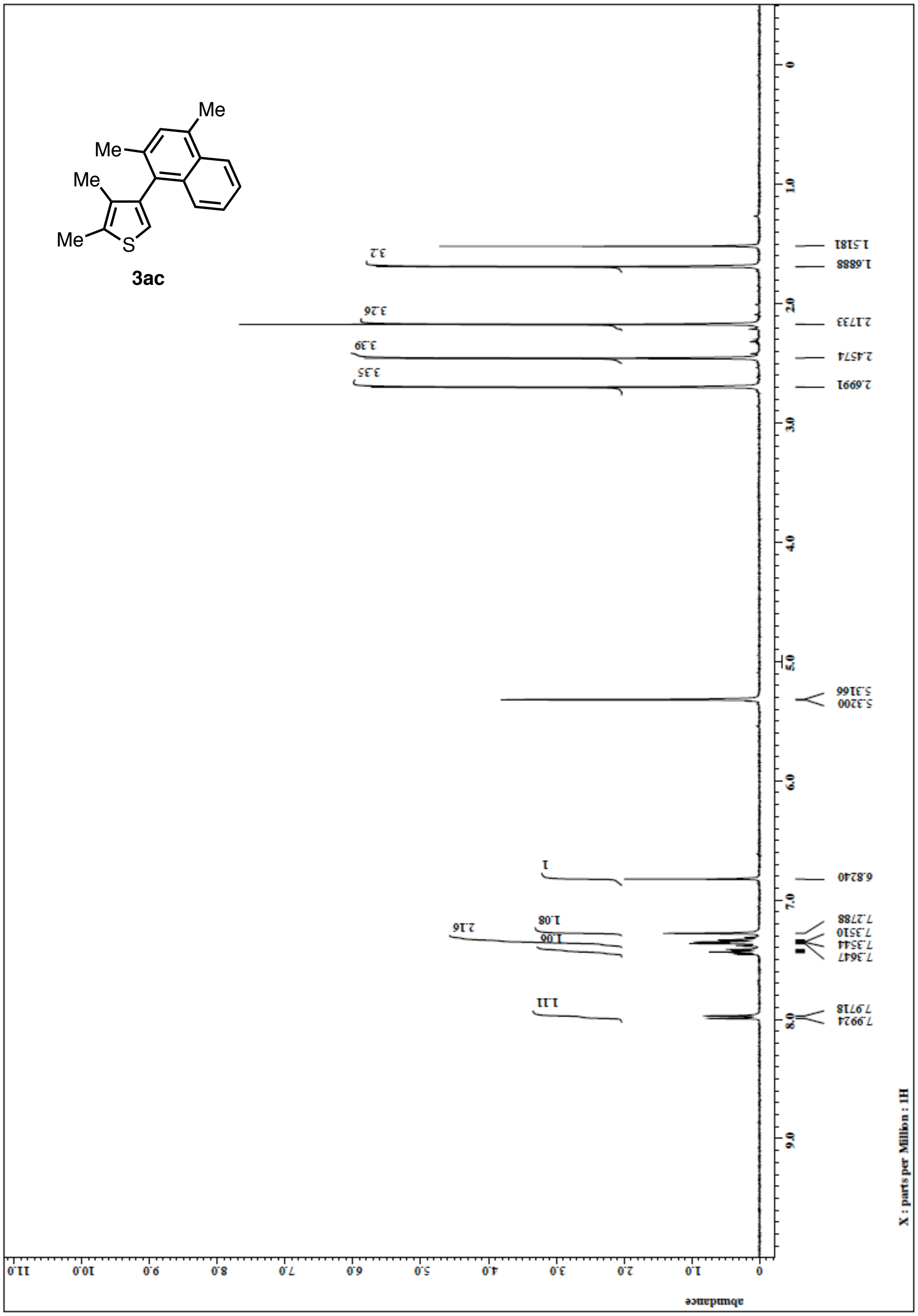
^{1}H NMR (400 MHz, CDCl$_3$) of 3ab:



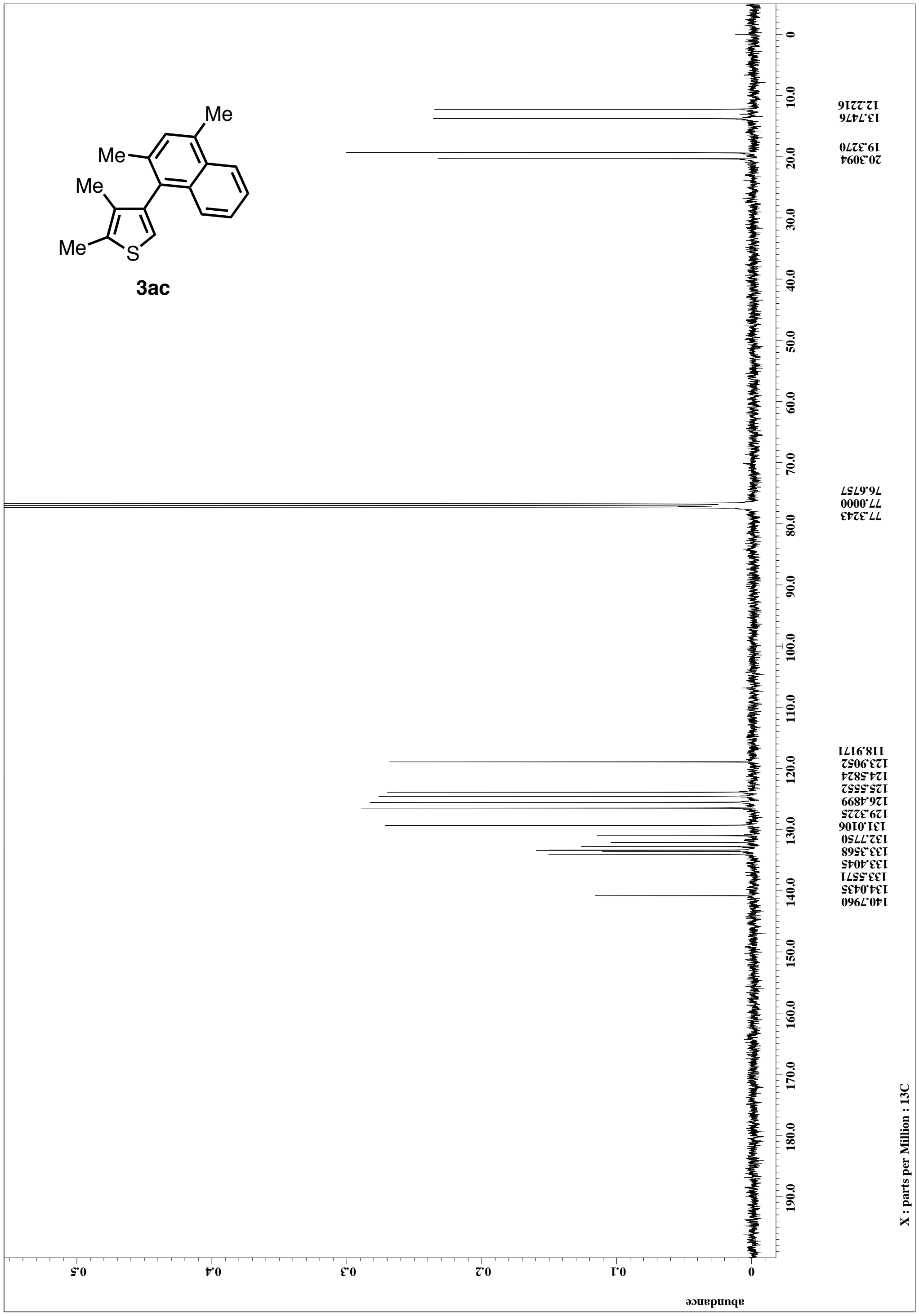
^{13}C NMR (100 MHz, $CDCl_3$) of 3ab:



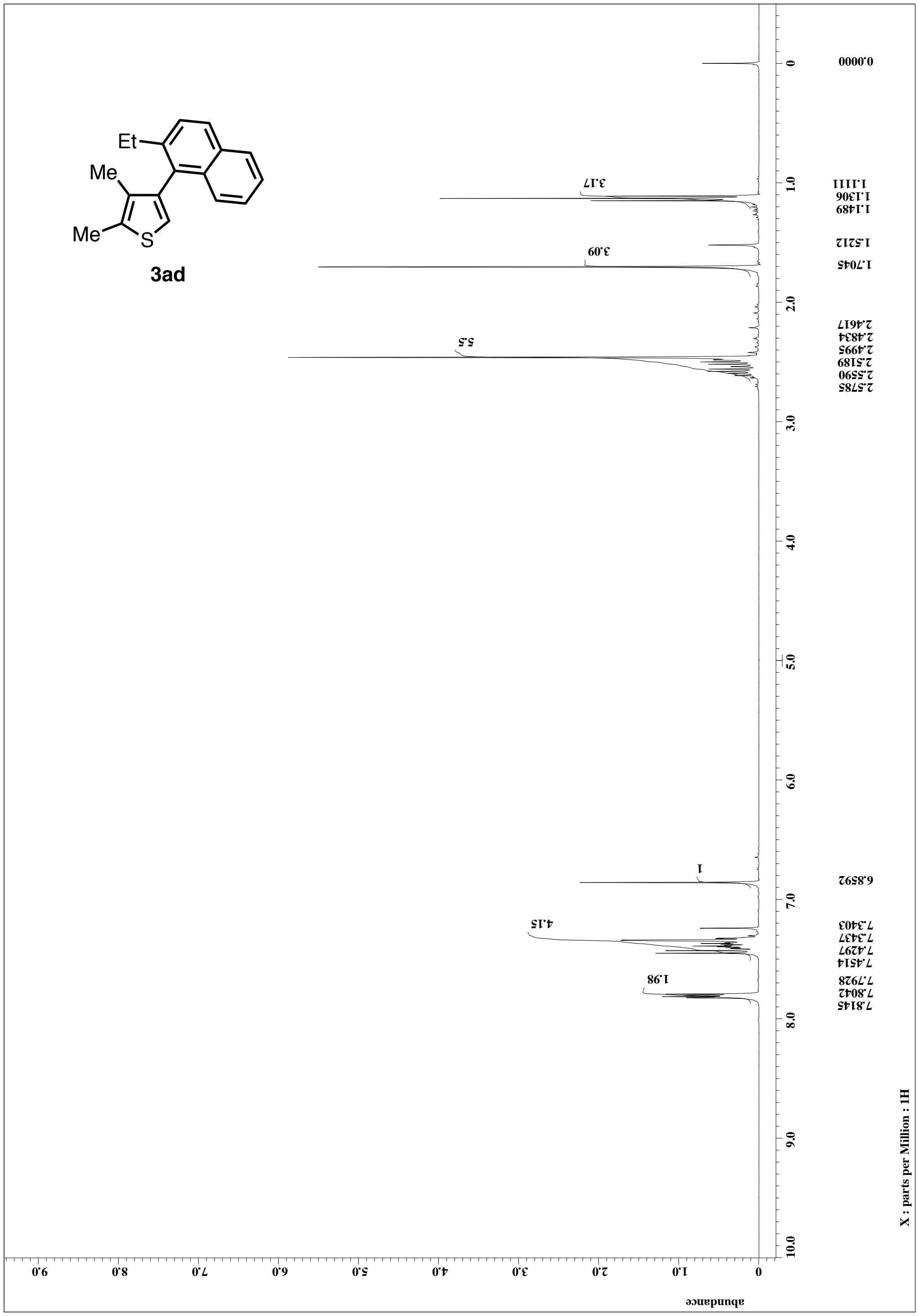
^{1}H NMR (400 MHz, CD_2Cl_2) of 3ac:



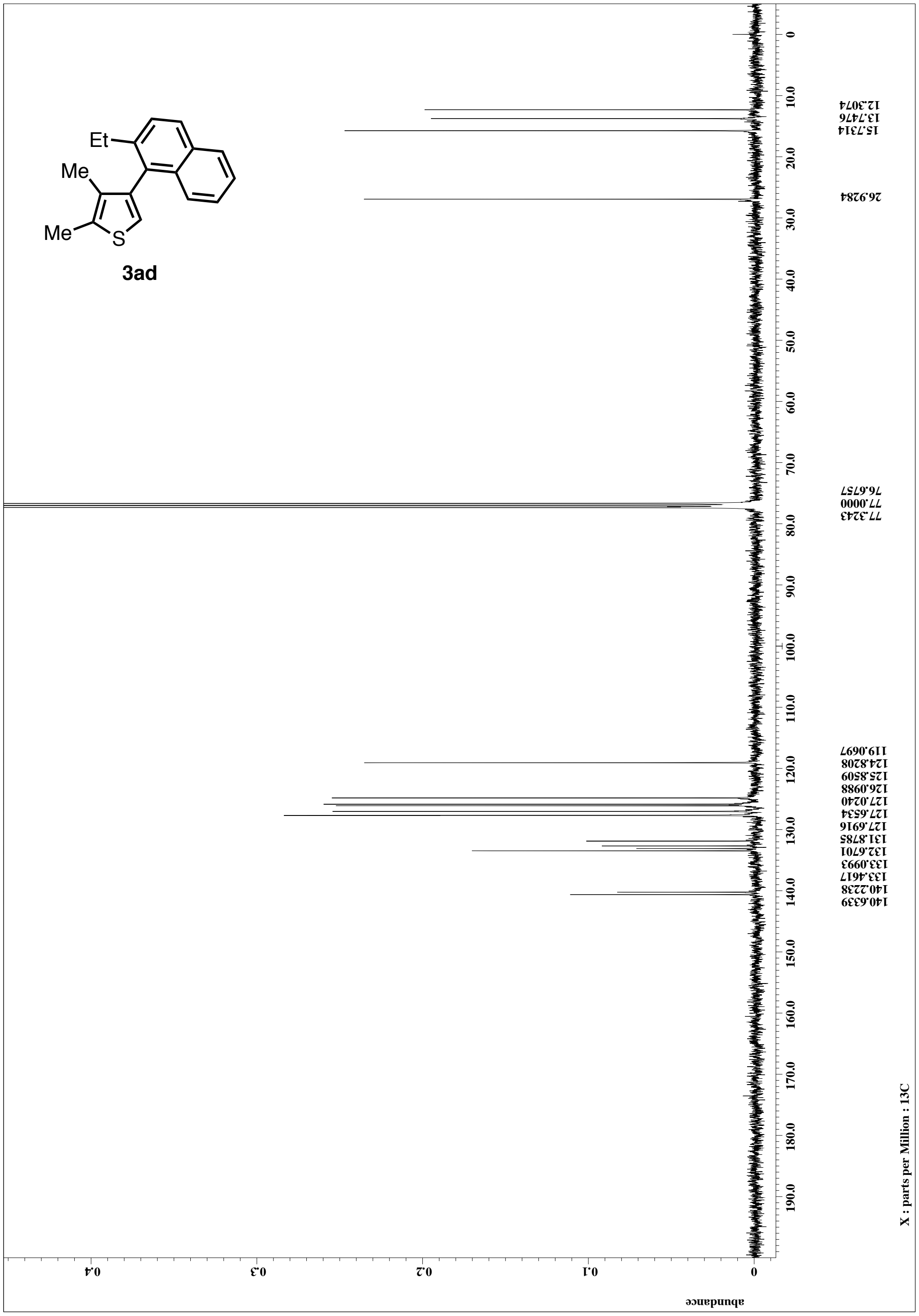
^{13}C NMR (100 MHz, CDCl$_3$) of 3ac:



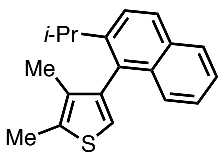
^{1}H NMR (400 MHz, CDCl$_3$) of 3ad:



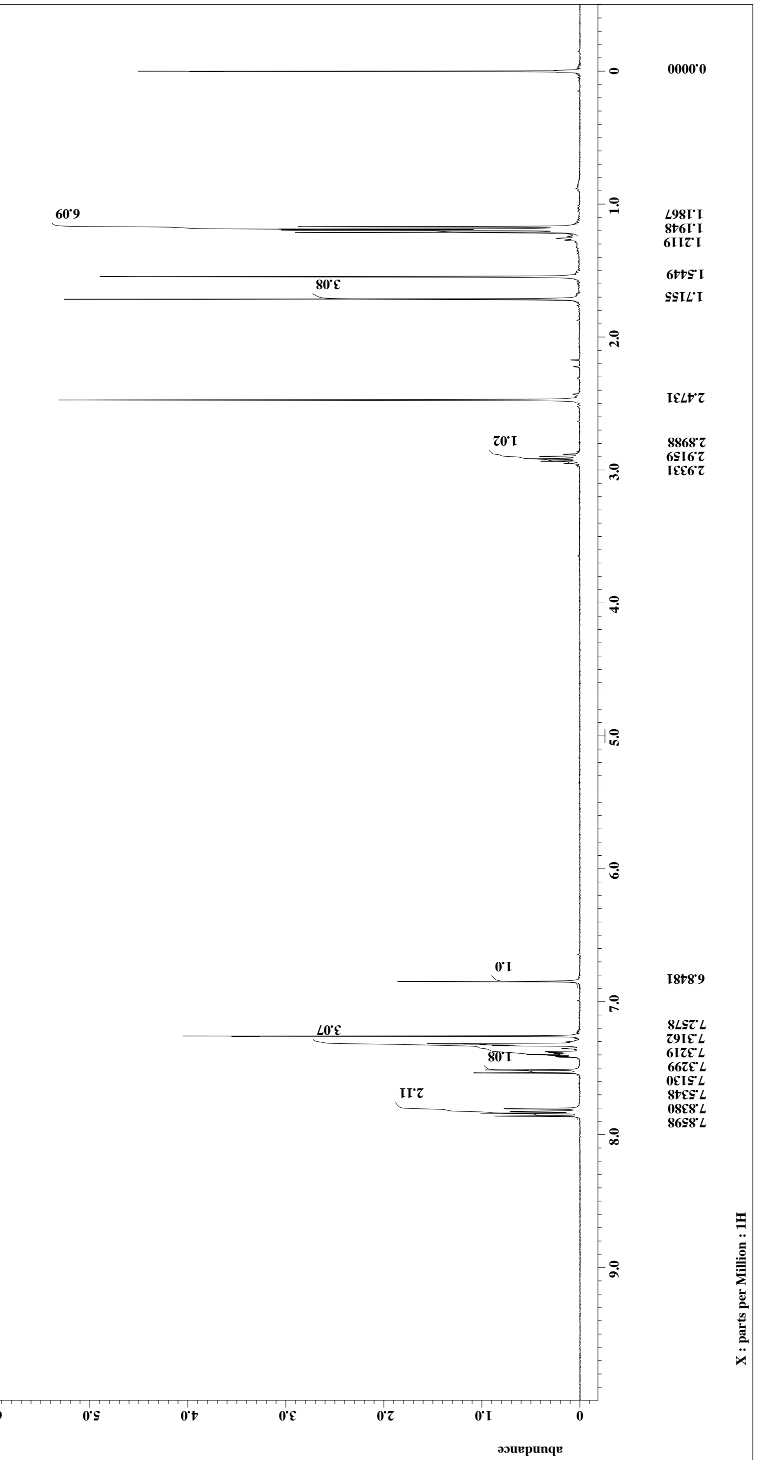
^{13}C NMR (100 MHz, $CDCl_3$) of 3ad:



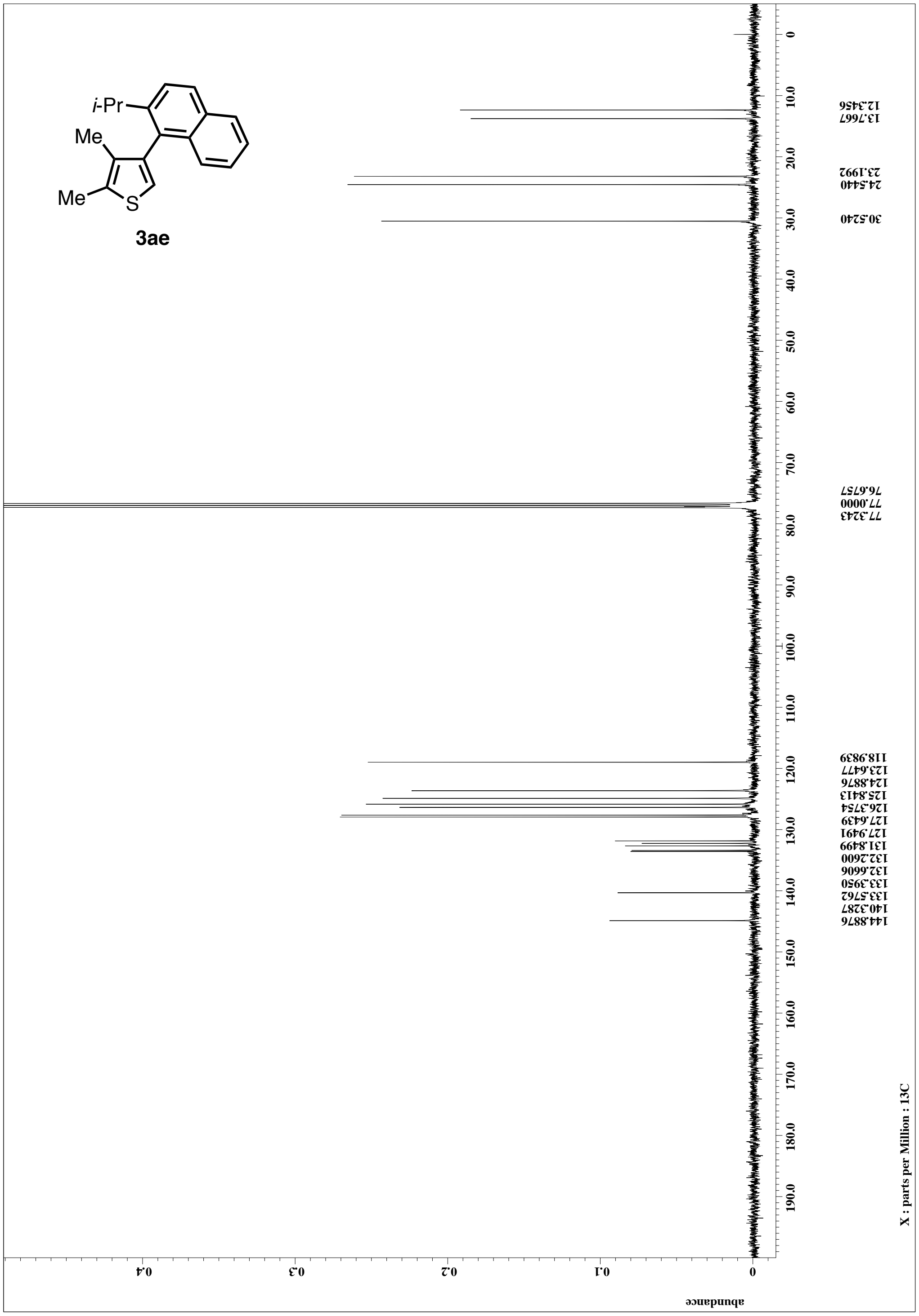
^{1}H NMR (400 MHz, $CDCl_3$) of 3ae:



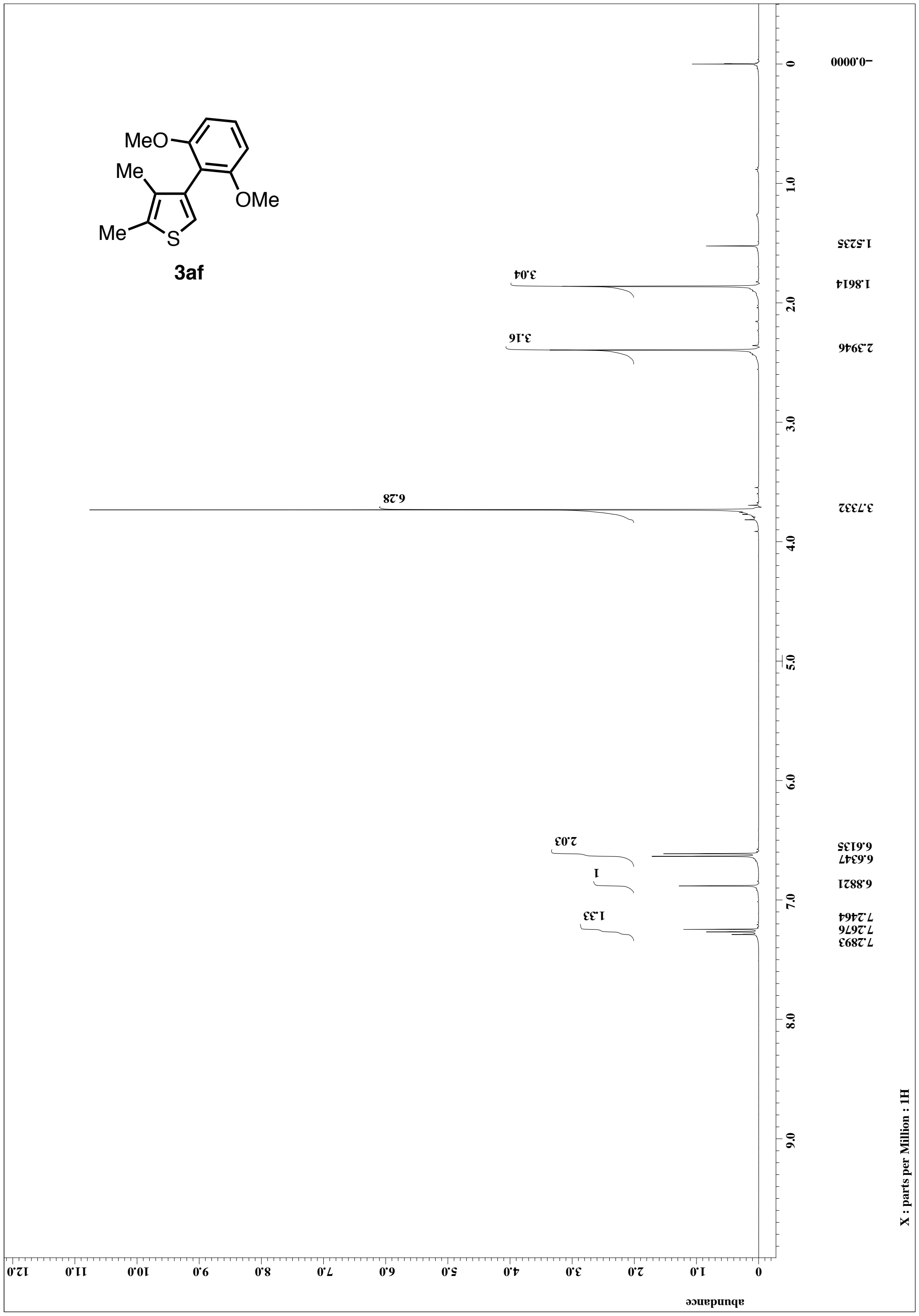
3ae



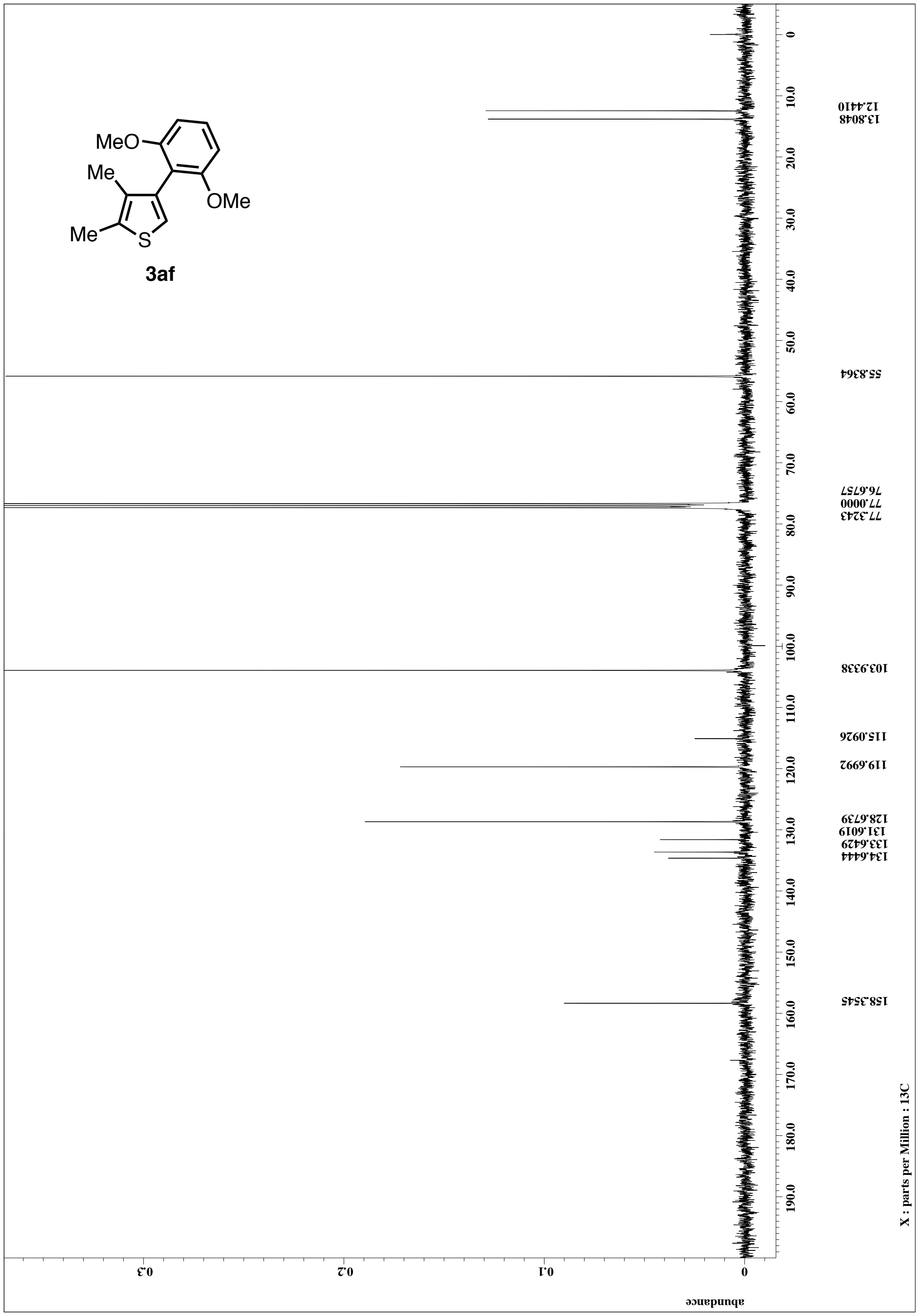
^{13}C NMR (100 MHz, $CDCl_3$) of 3ae:



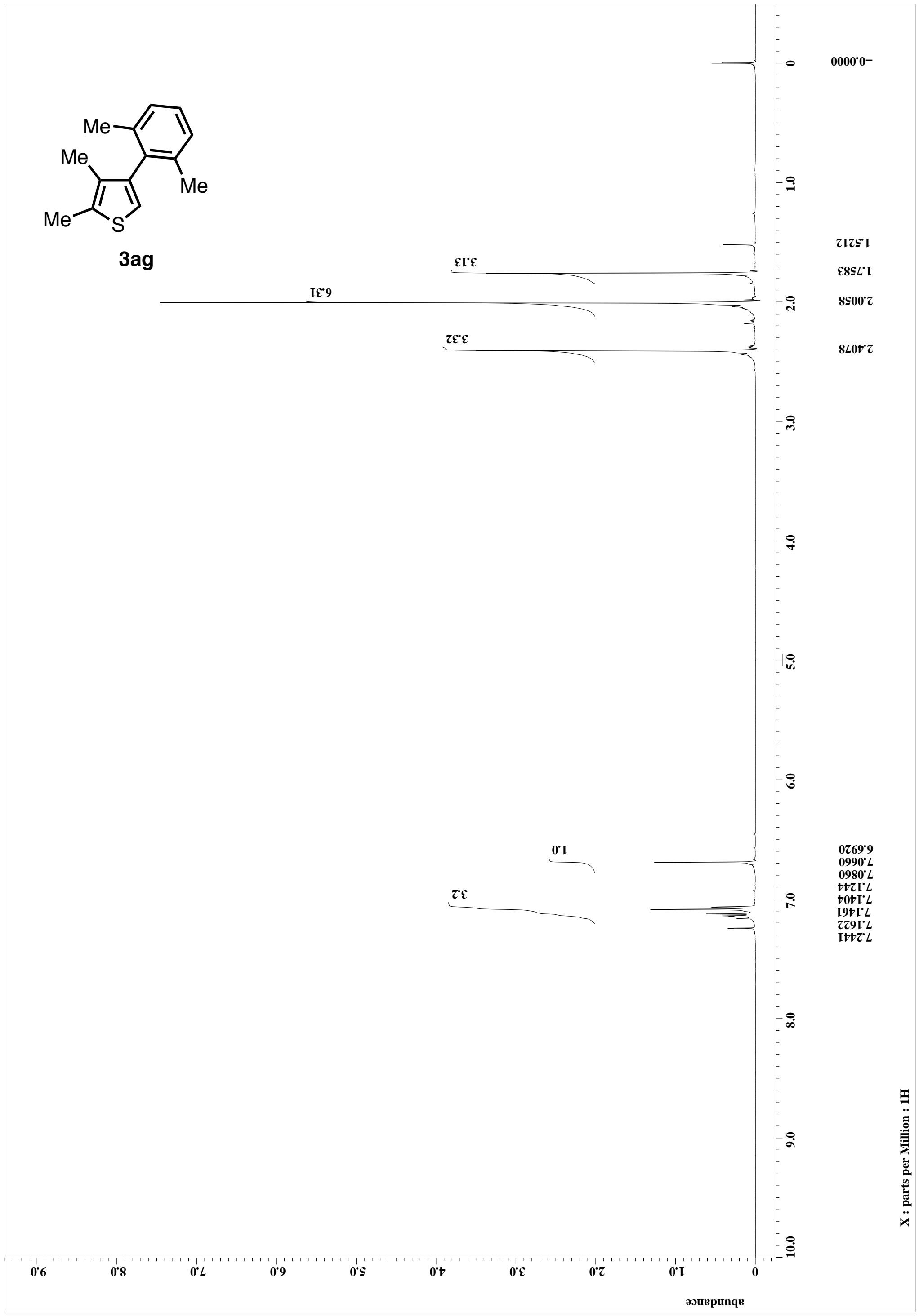
^{1}H NMR (400 MHz, $CDCl_3$) of 3af:



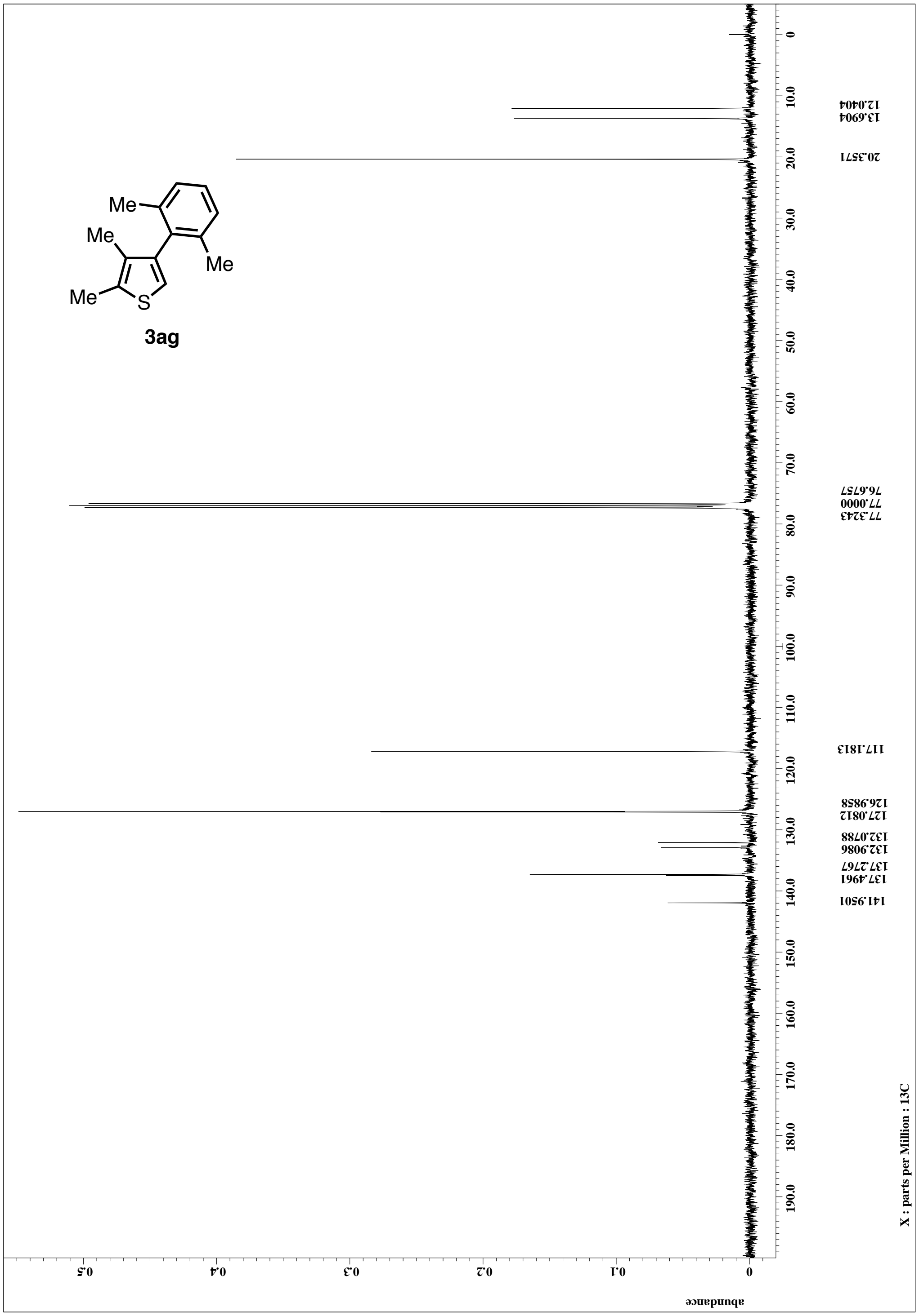
^{13}C NMR (100 MHz, $CDCl_3$) of 3af:



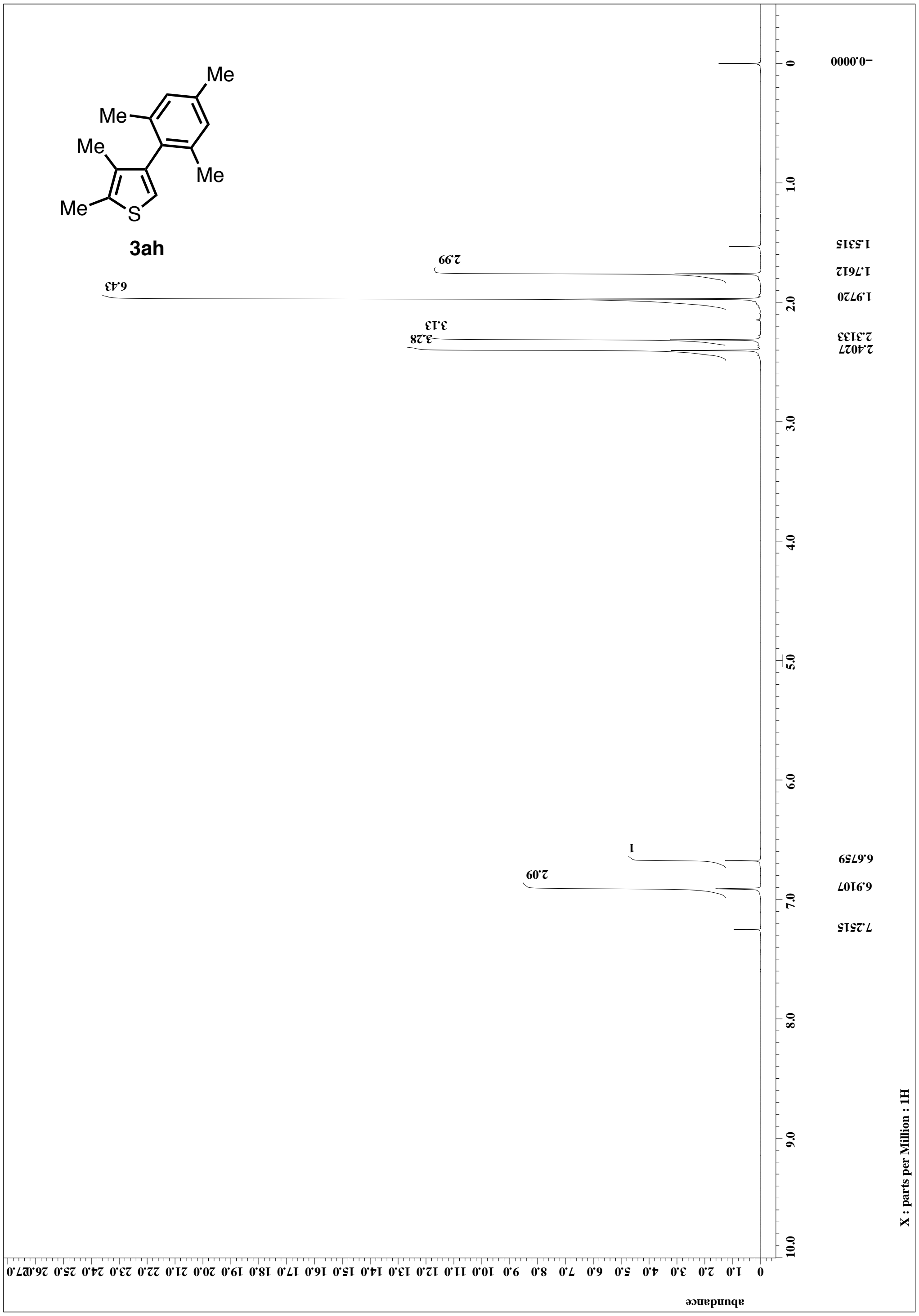
^{1}H NMR (400 MHz, CDCl$_3$) of 3ag:



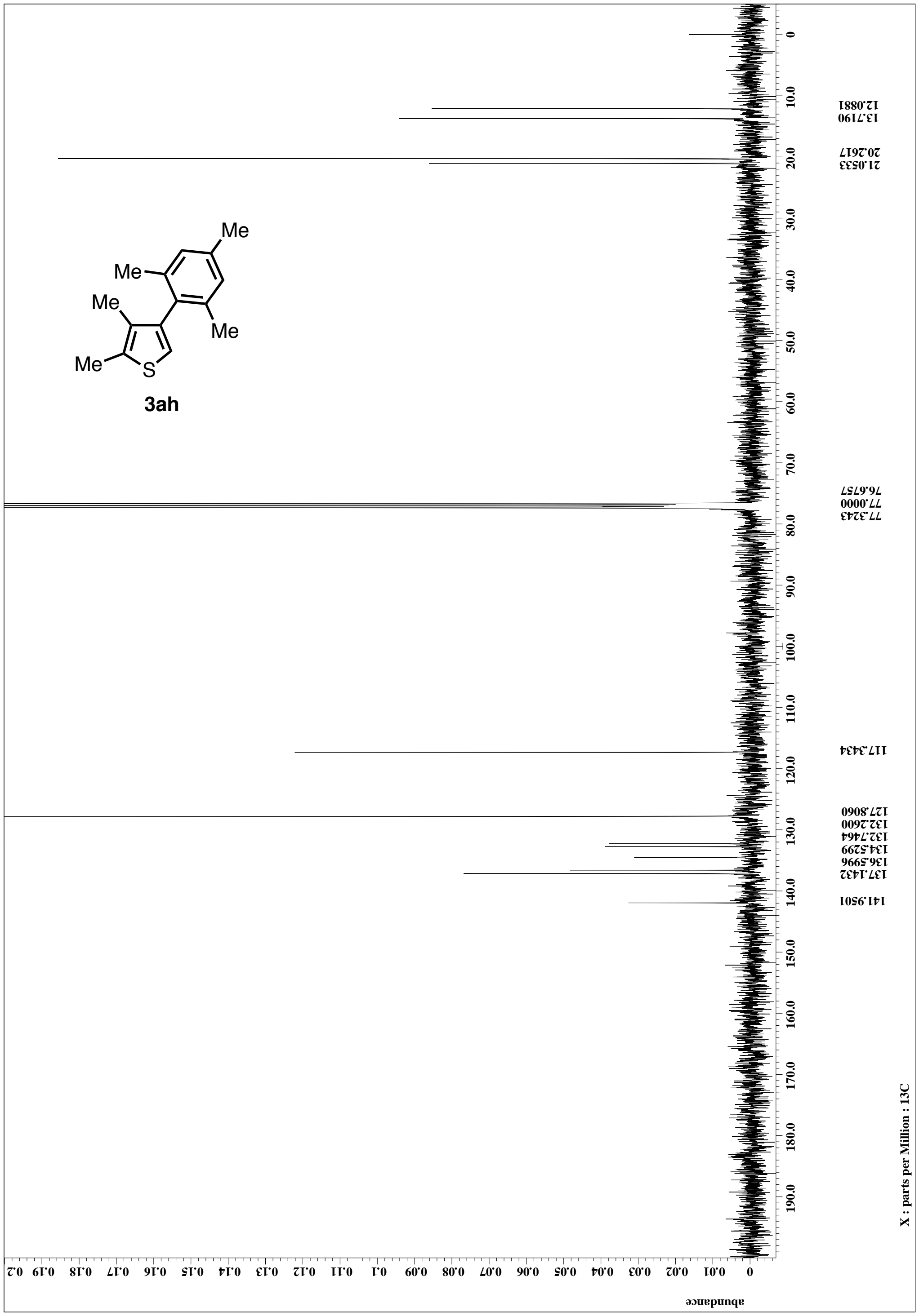
^{13}C NMR (100 MHz, $CDCl_3$) of 3ag:



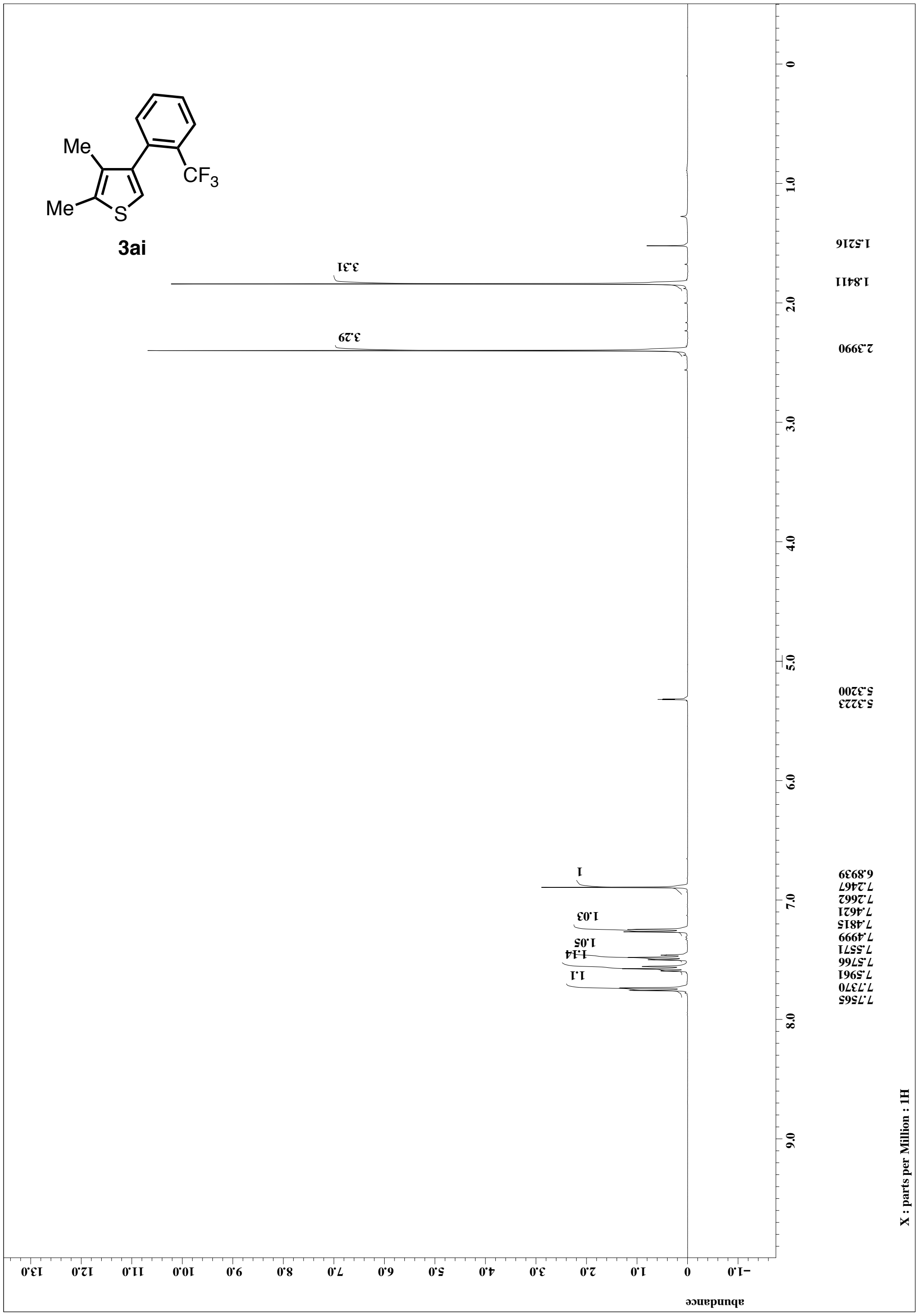
^{1}H NMR (400 MHz, $CDCl_3$) of 3ah:



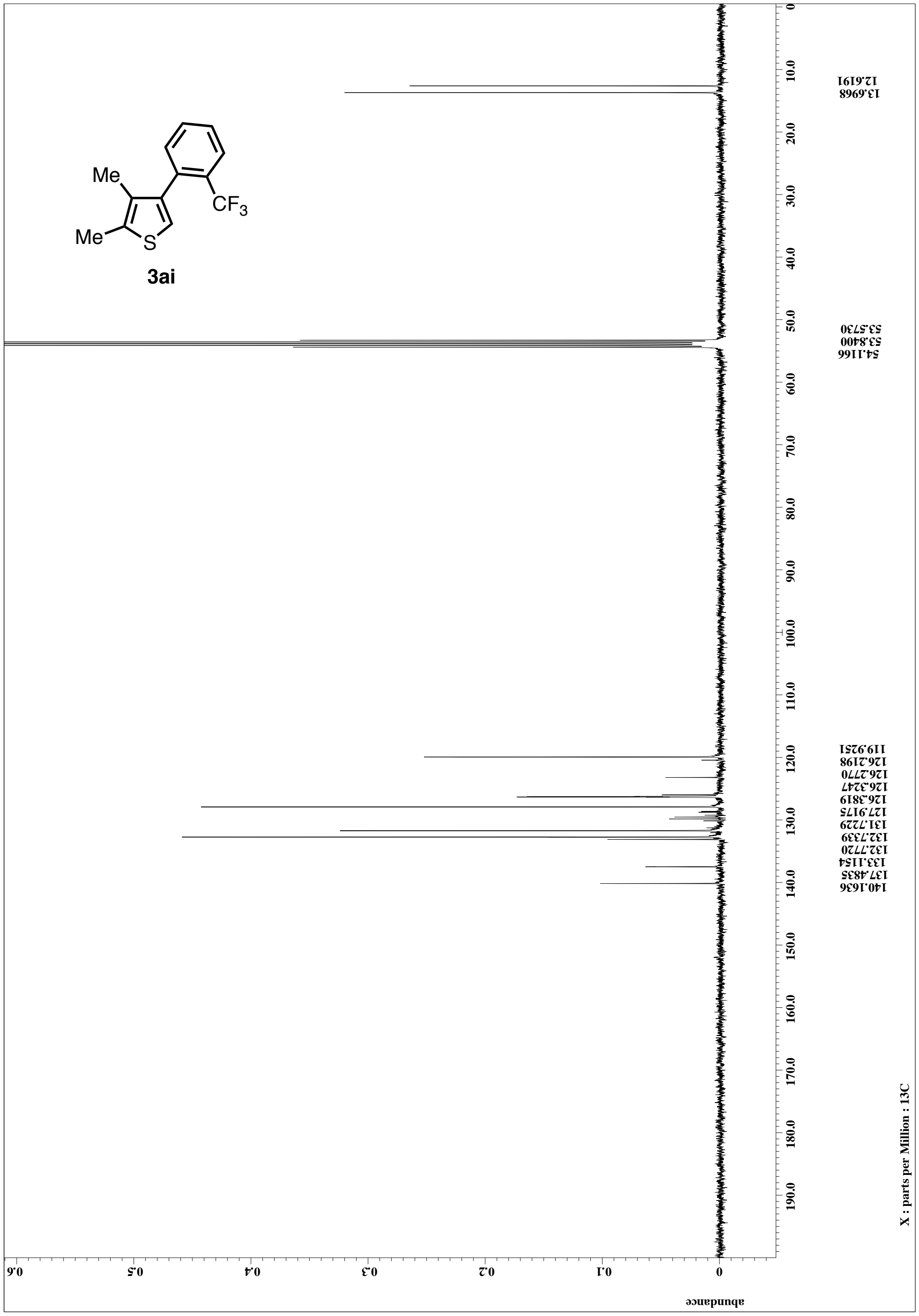
^{13}C NMR (100 MHz, $CDCl_3$) of 3ah:



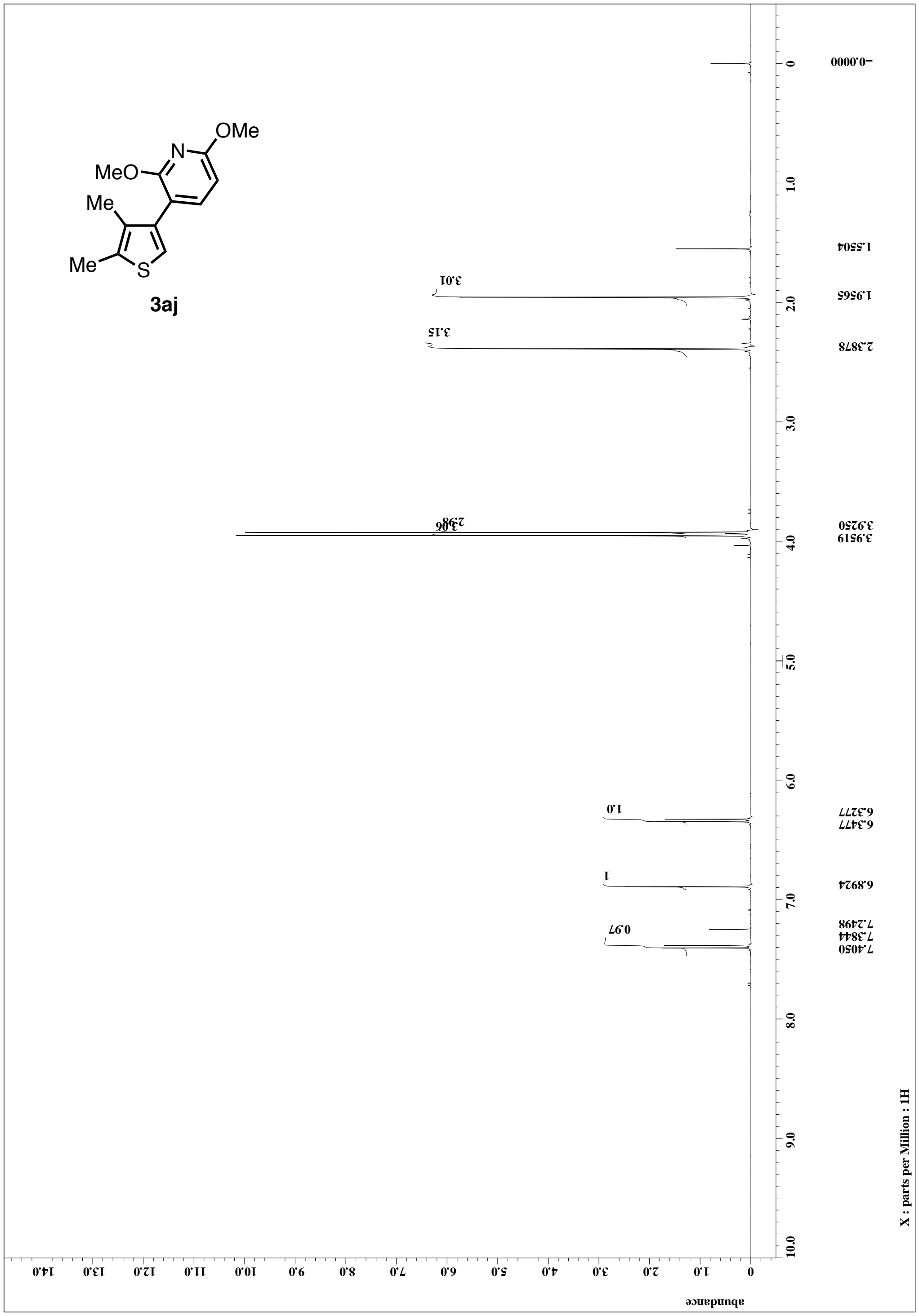
^{1}H NMR (400 MHz, CD_2Cl_2) of 3ai:



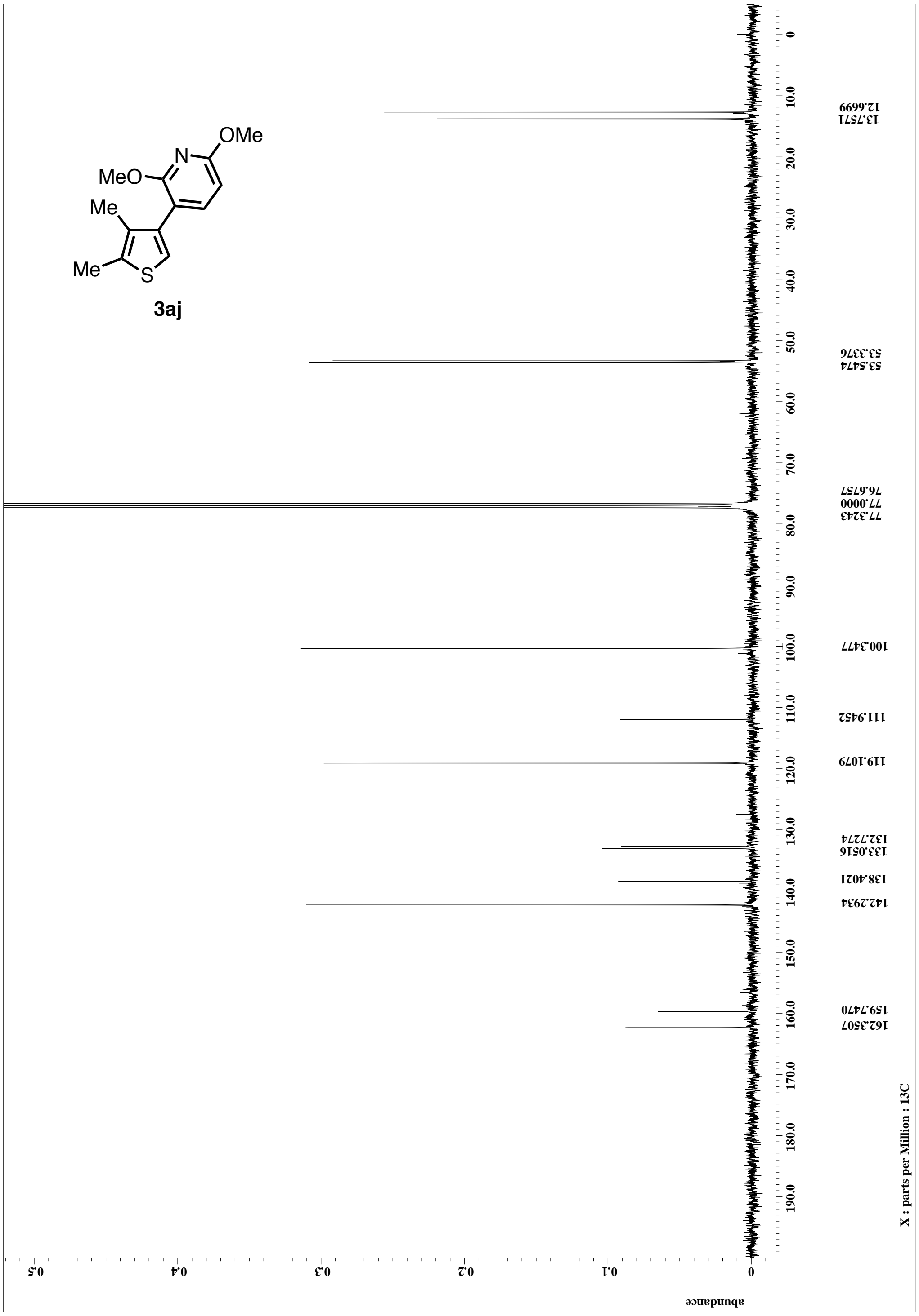
^{13}C NMR (100 MHz, CD_2Cl_2) of 3ai:



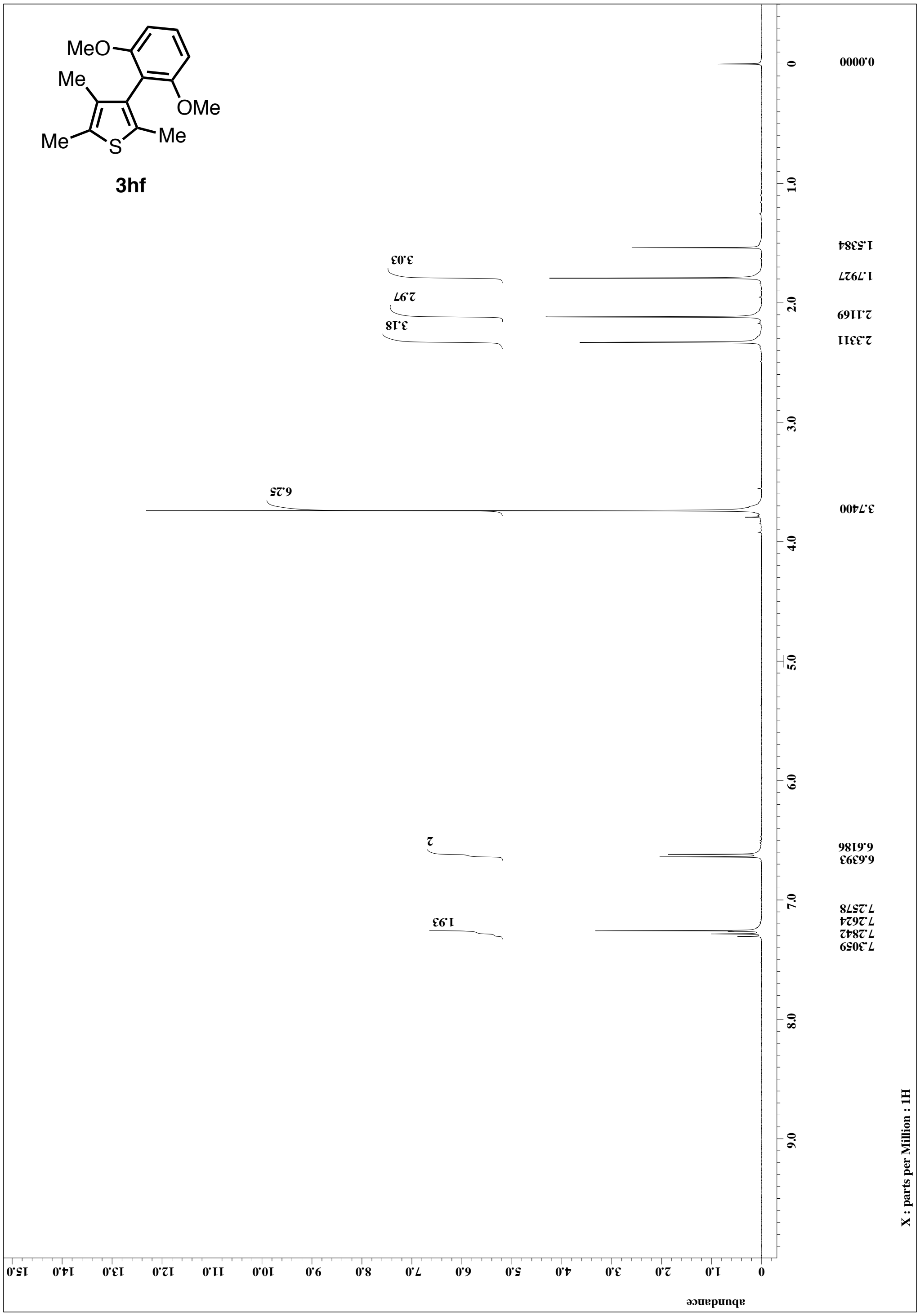
^{1}H NMR (400 MHz, $CDCl_3$) of 3aj:



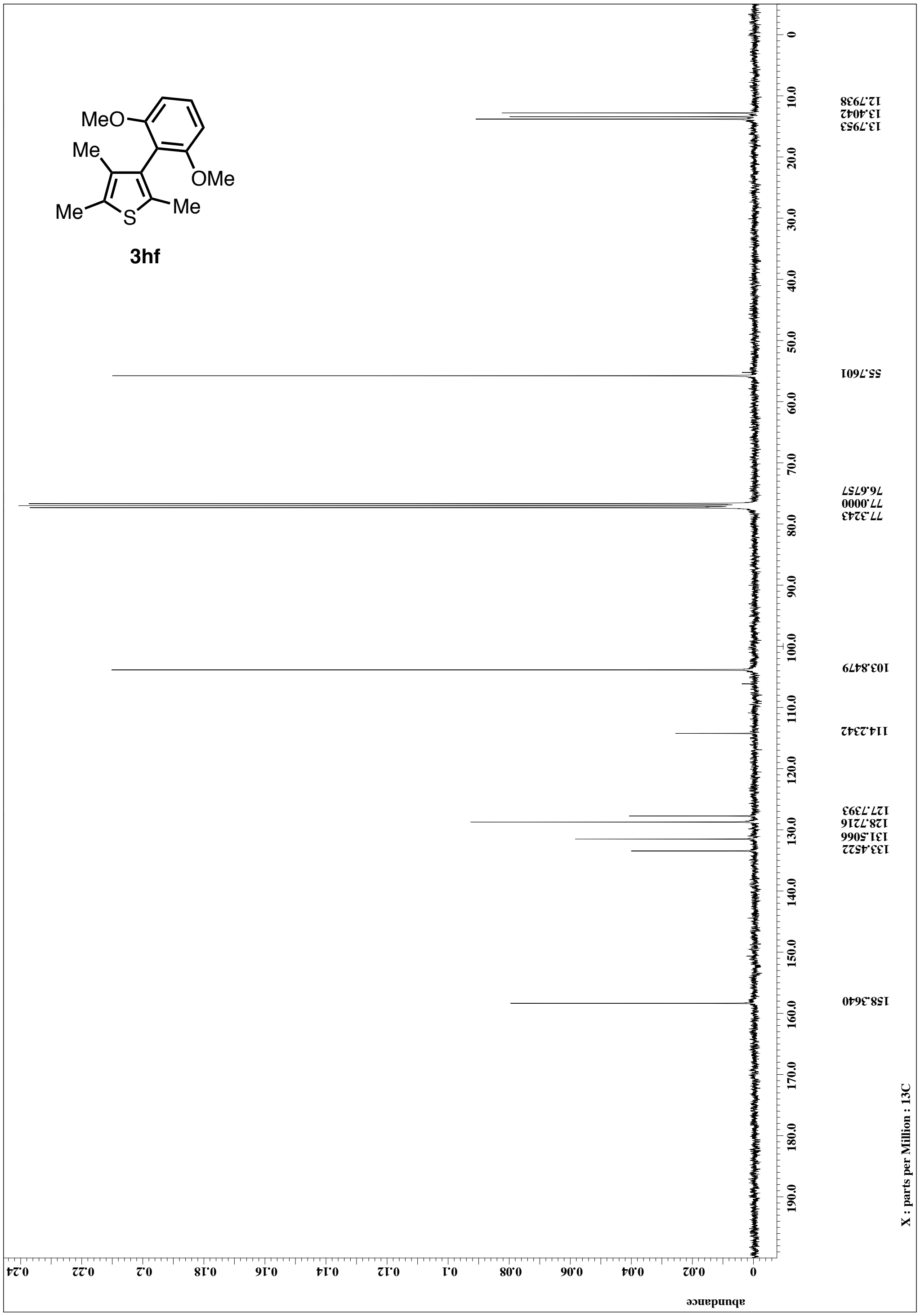
^{13}C NMR (100 MHz, $CDCl_3$) of 3aj:



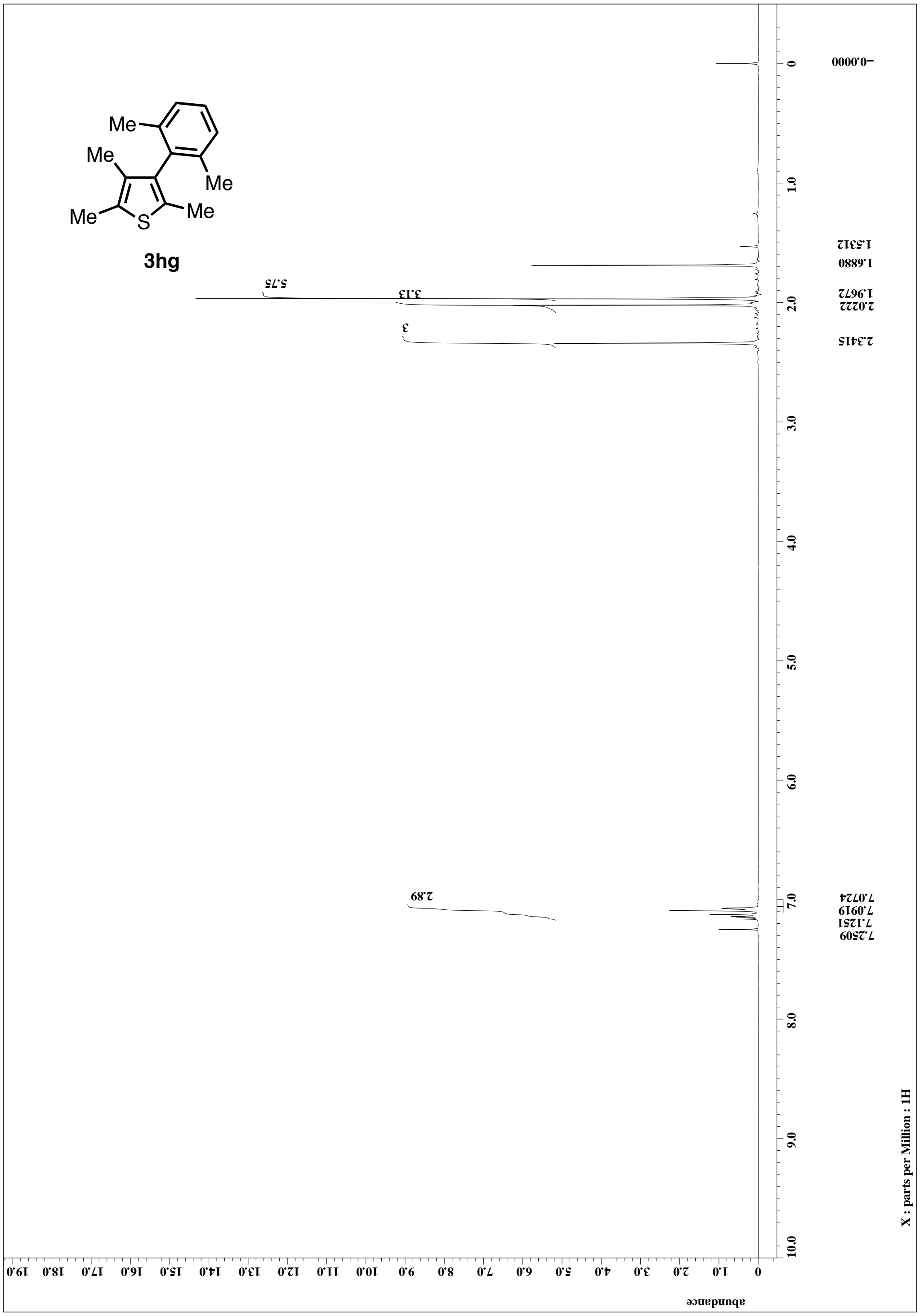
^{1}H NMR (400 MHz, CDCl$_3$) of 3hf:



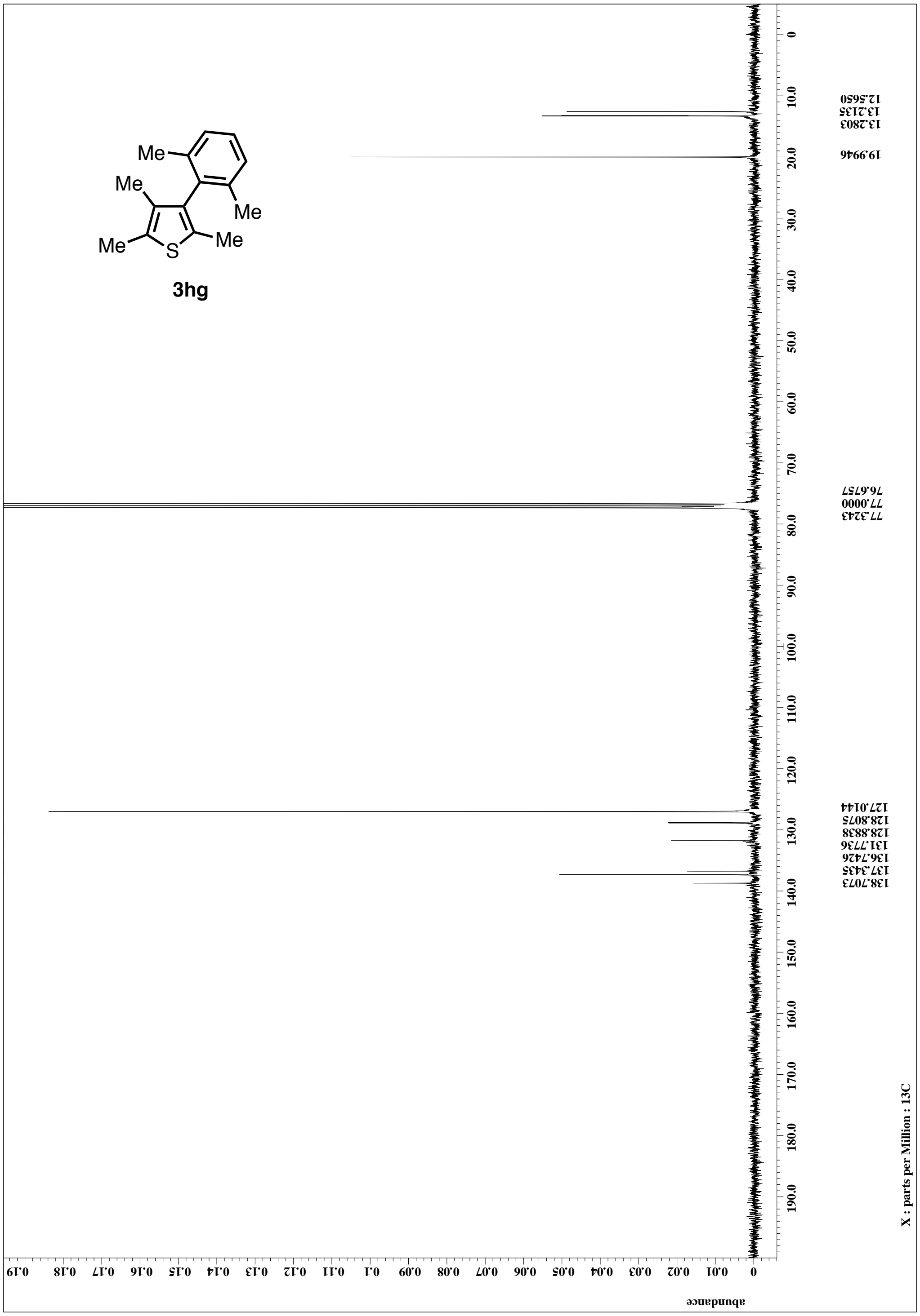
^{13}C NMR (100 MHz, $CDCl_3$) of 3hf:



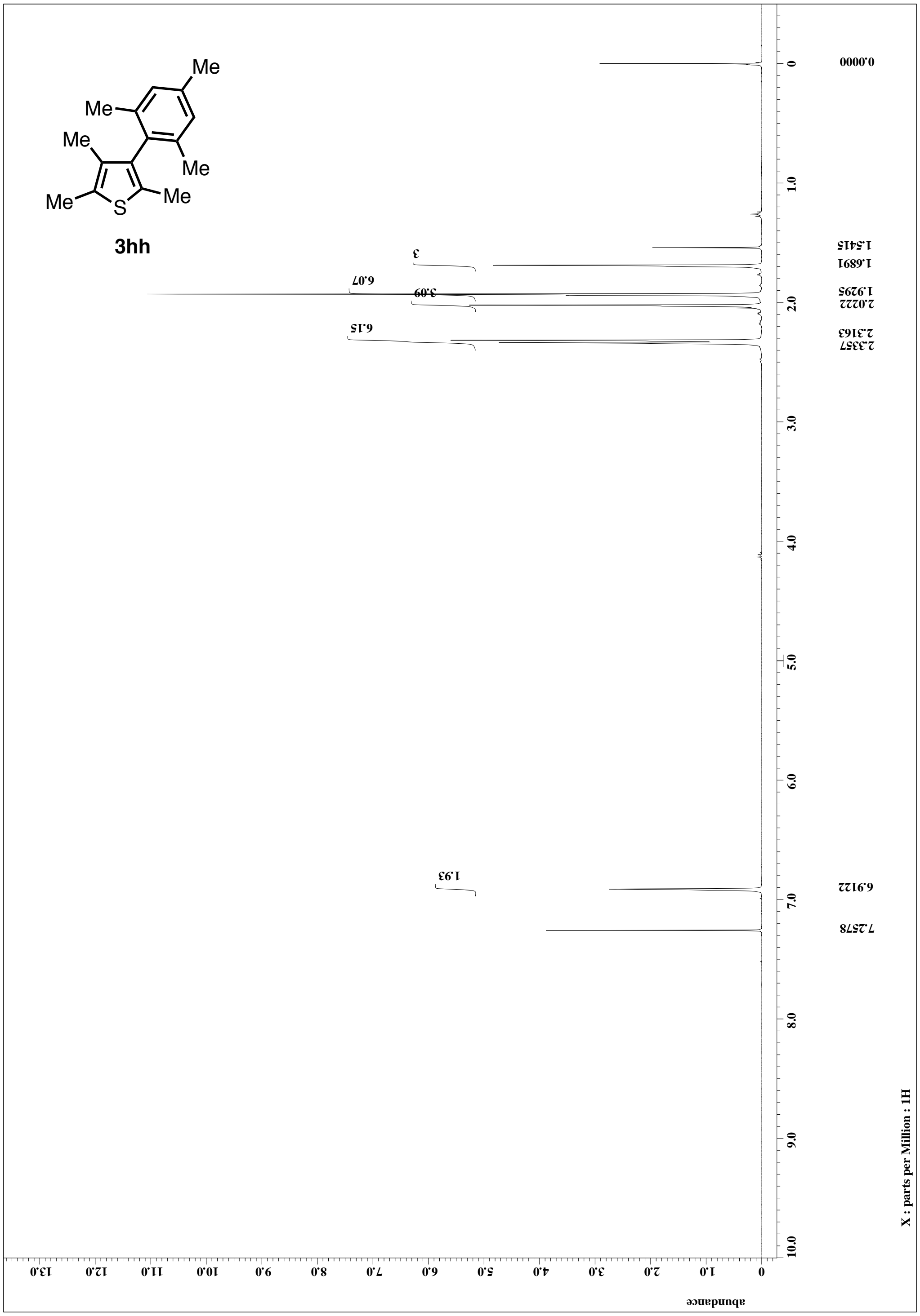
^{1}H NMR (400 MHz, $CDCl_3$) of 3hg:



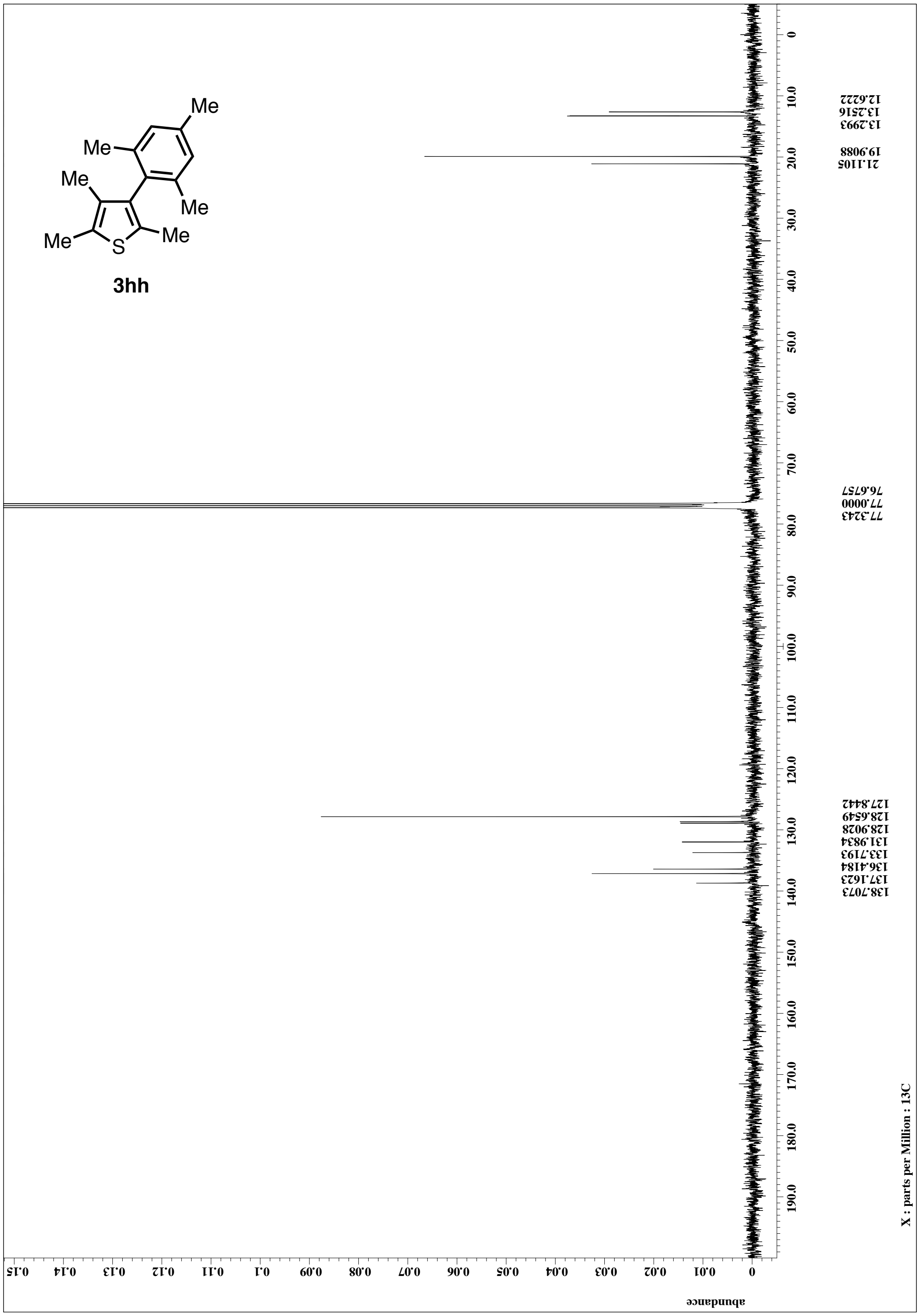
^{13}C NMR (100 MHz, $CDCl_3$) of 3hg:



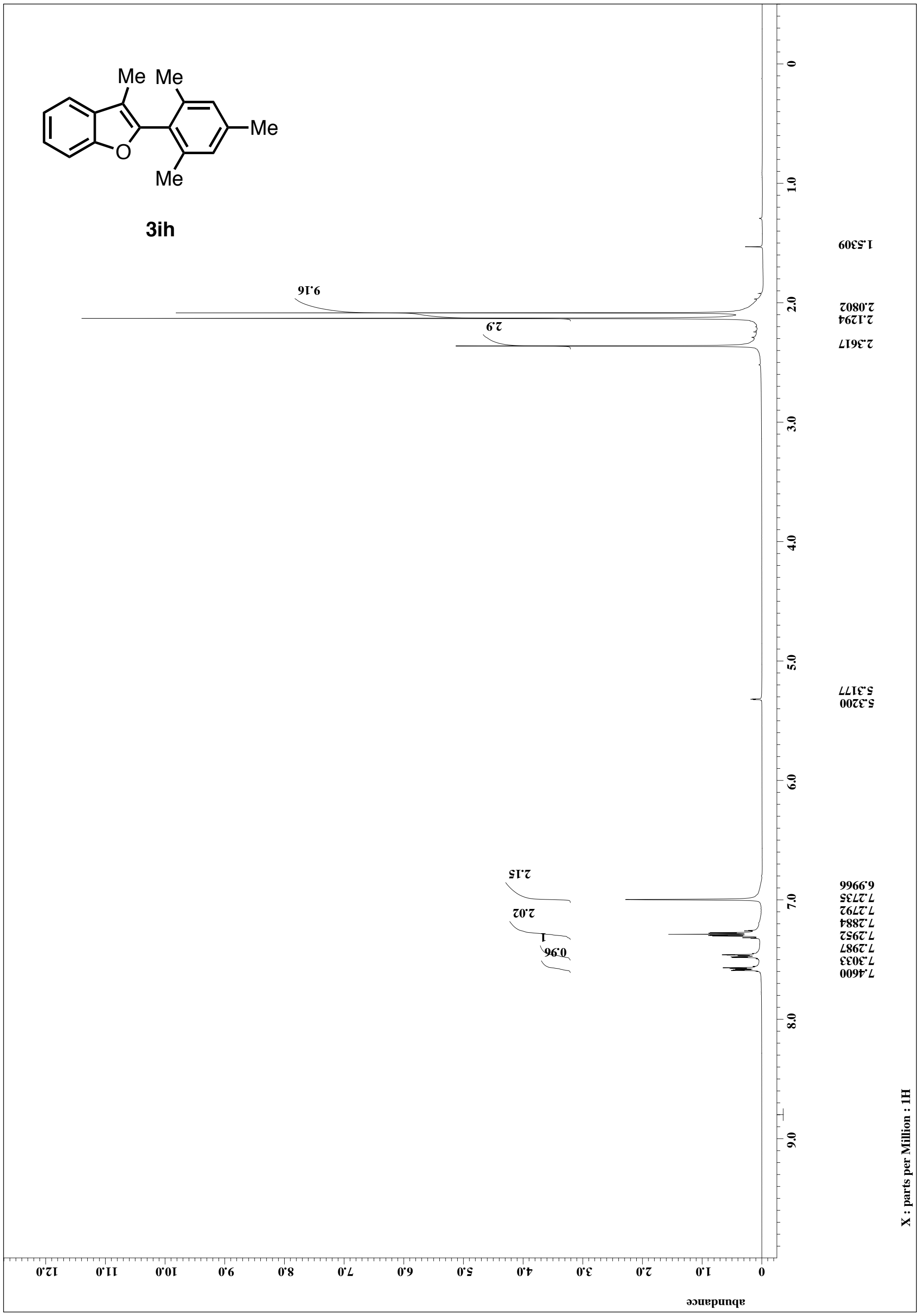
^{1}H NMR (400 MHz, $CDCl_3$) of 3hh:



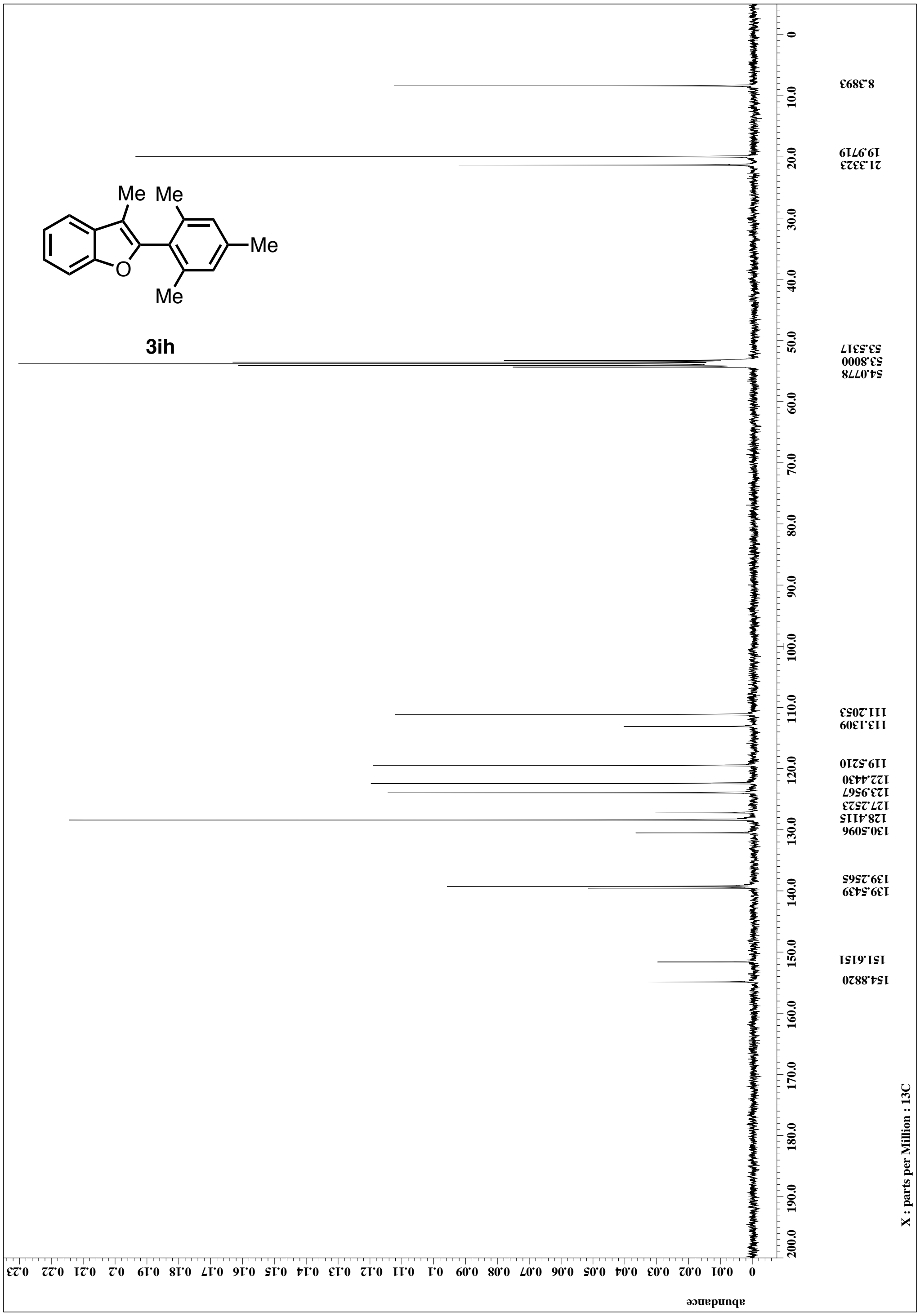
^{13}C NMR (100 MHz, $CDCl_3$) of 3hh:



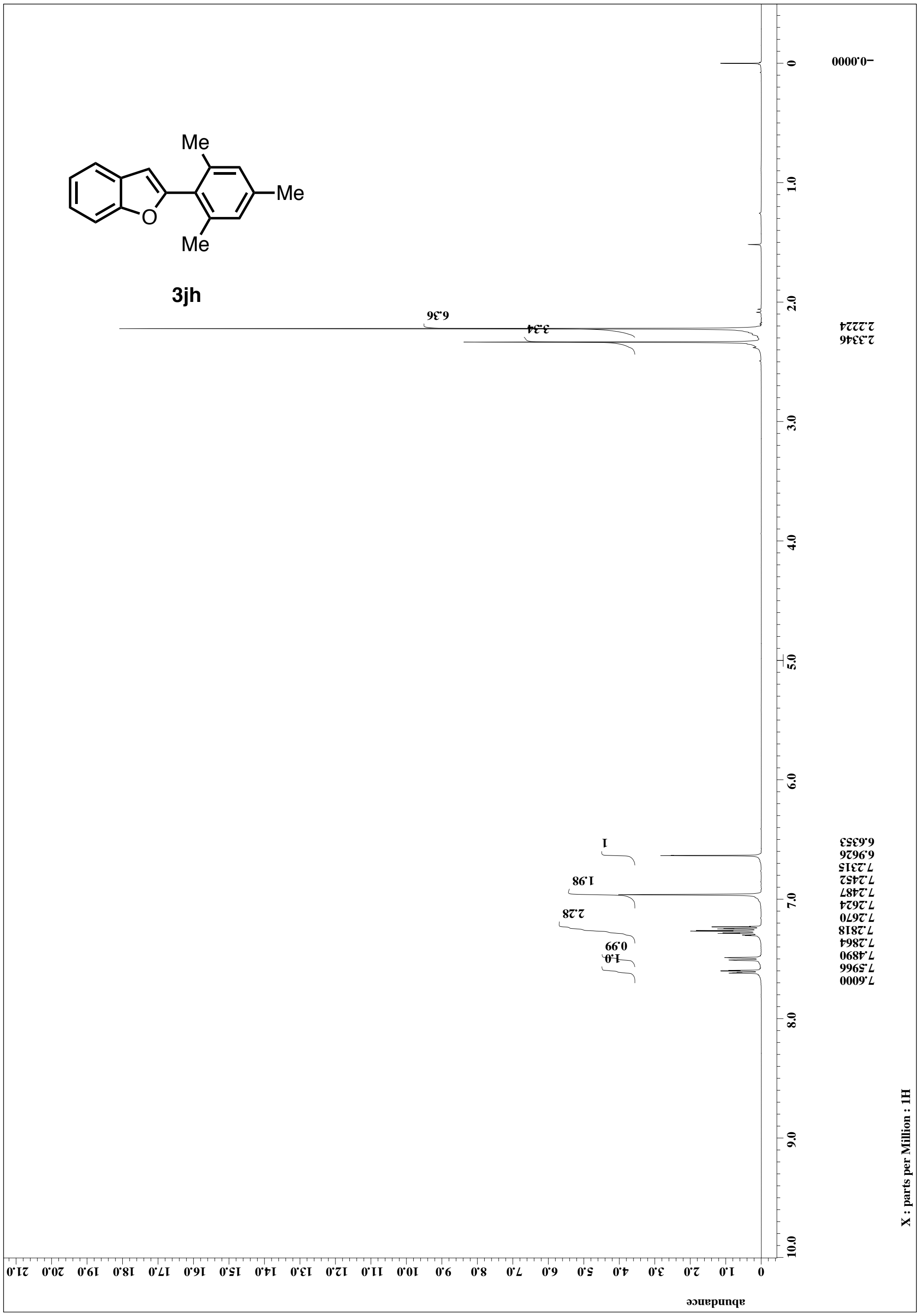
^{1}H NMR (400 MHz, CD_2Cl_2) of 3ih:



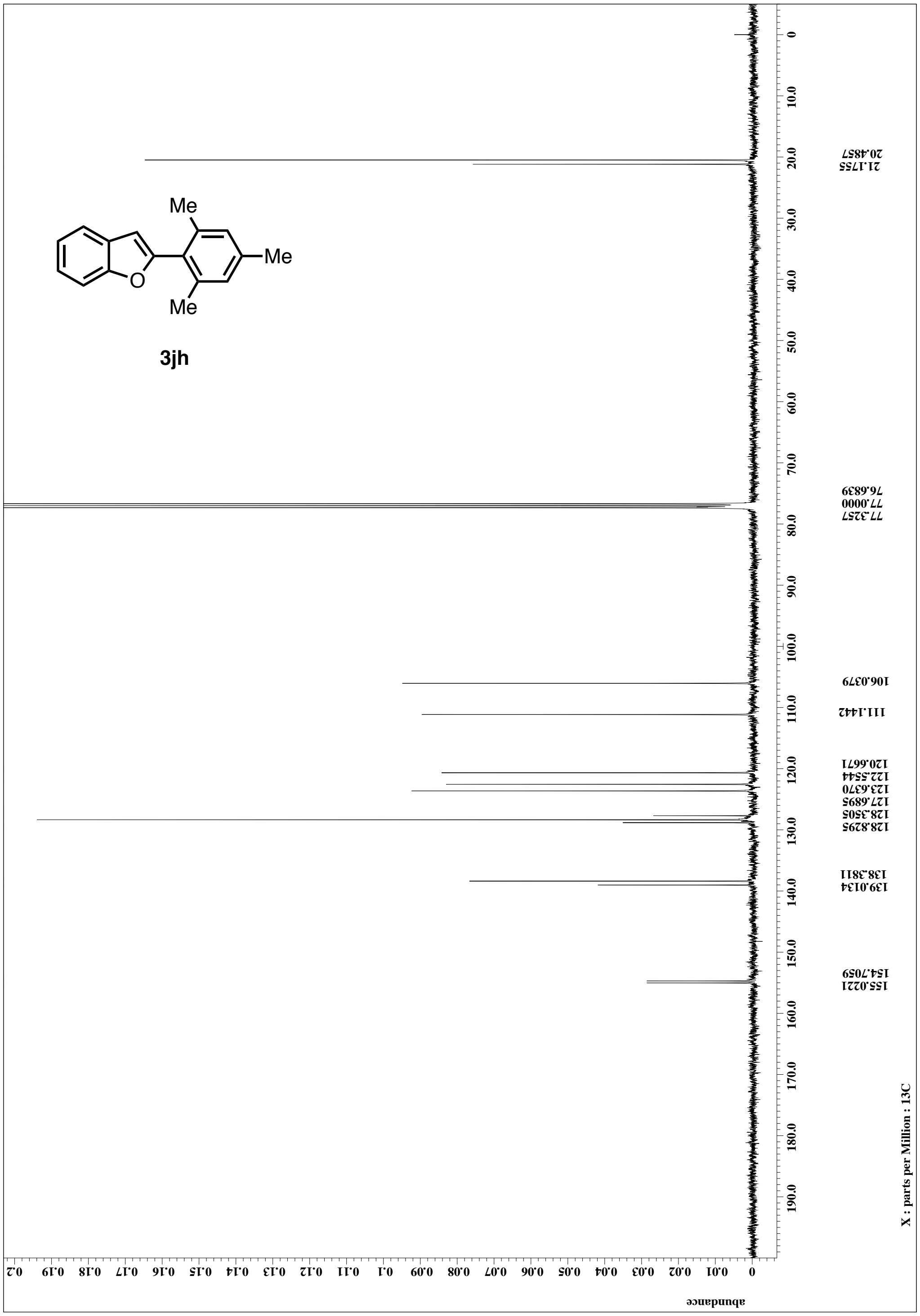
^{13}C NMR (100 MHz, CD_2Cl_2) of 3ih:



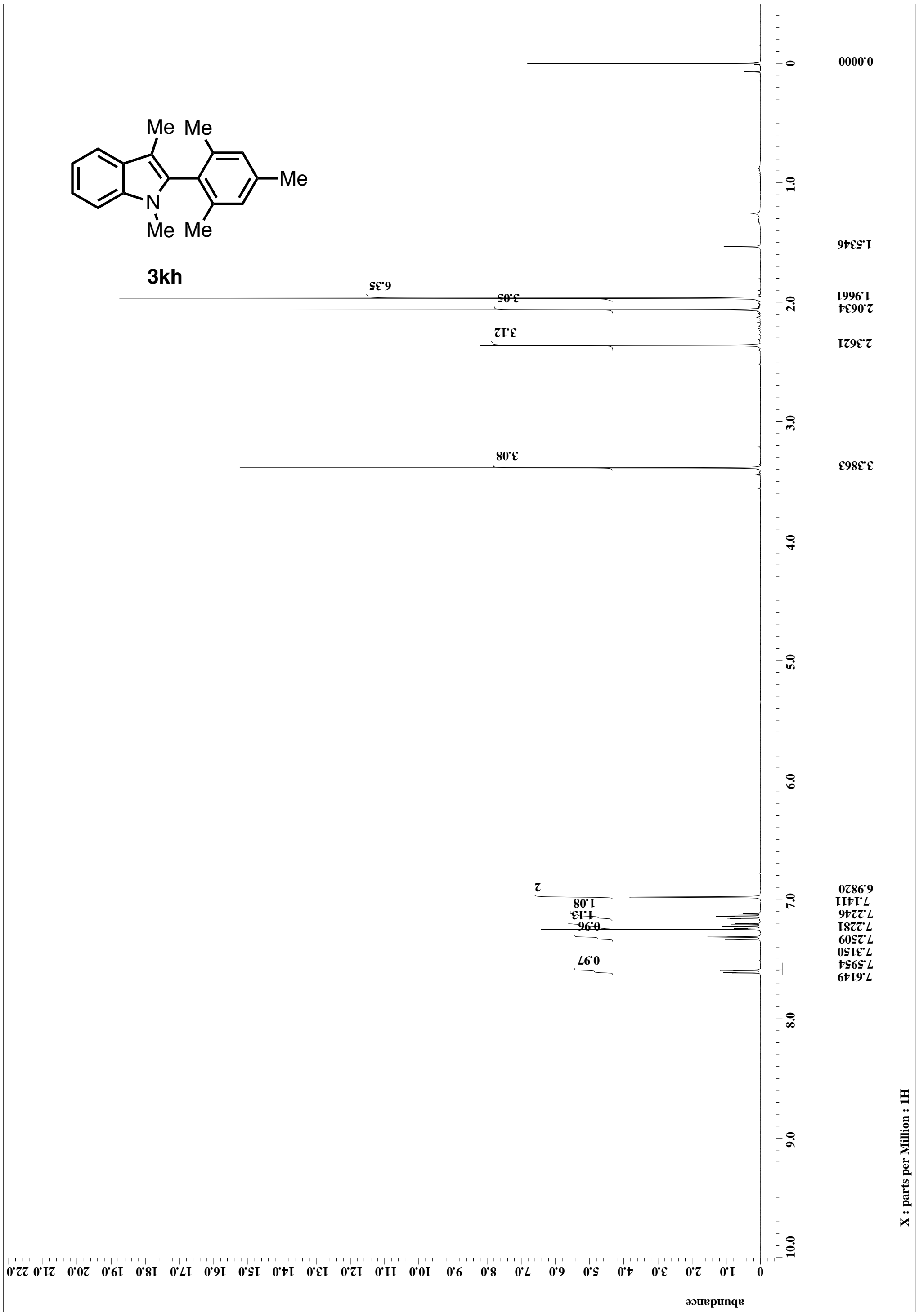
^{1}H NMR (400 MHz, $CDCl_3$) of 3jh:



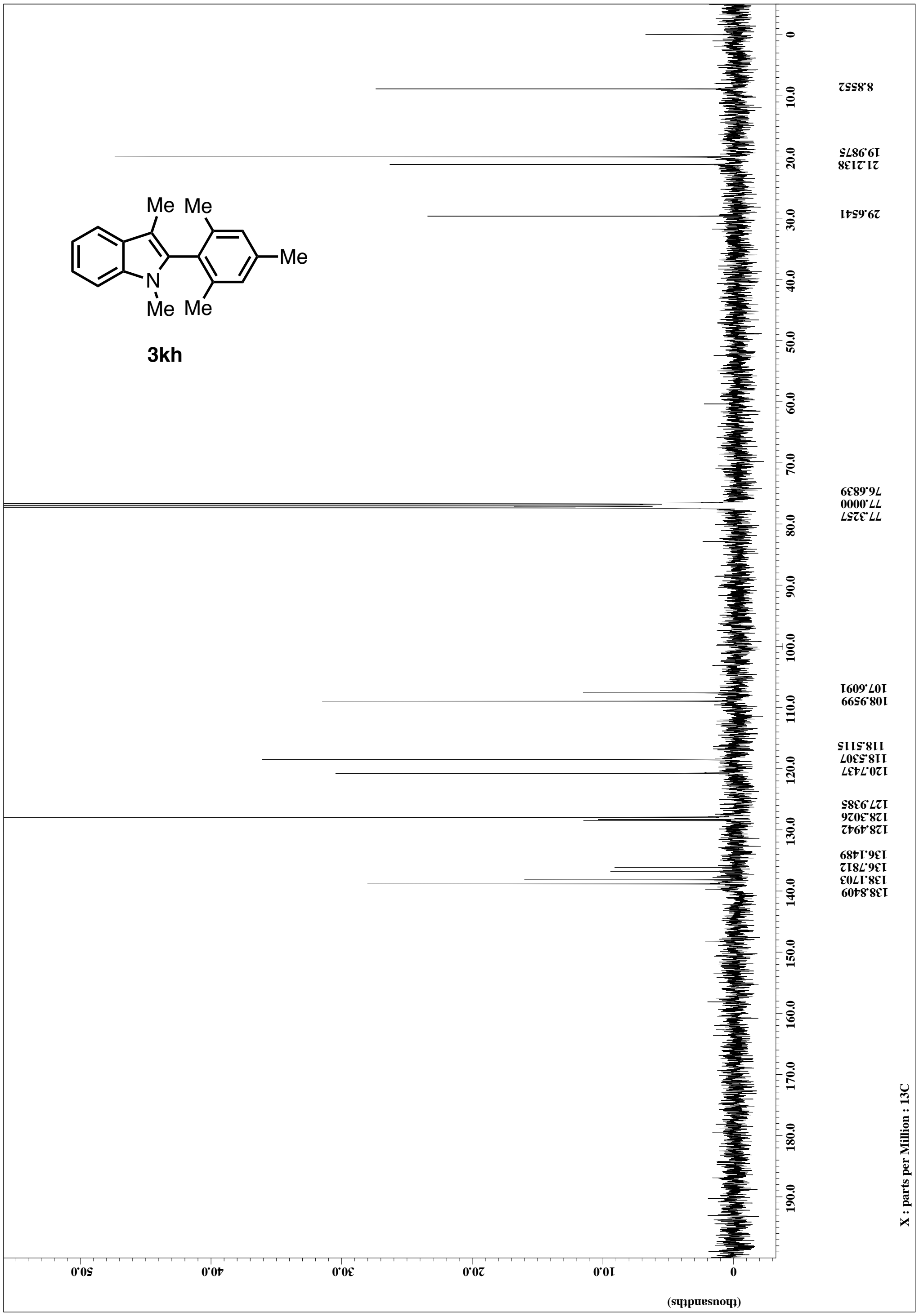
^{13}C NMR (100 MHz, $CDCl_3$) of 3jh:



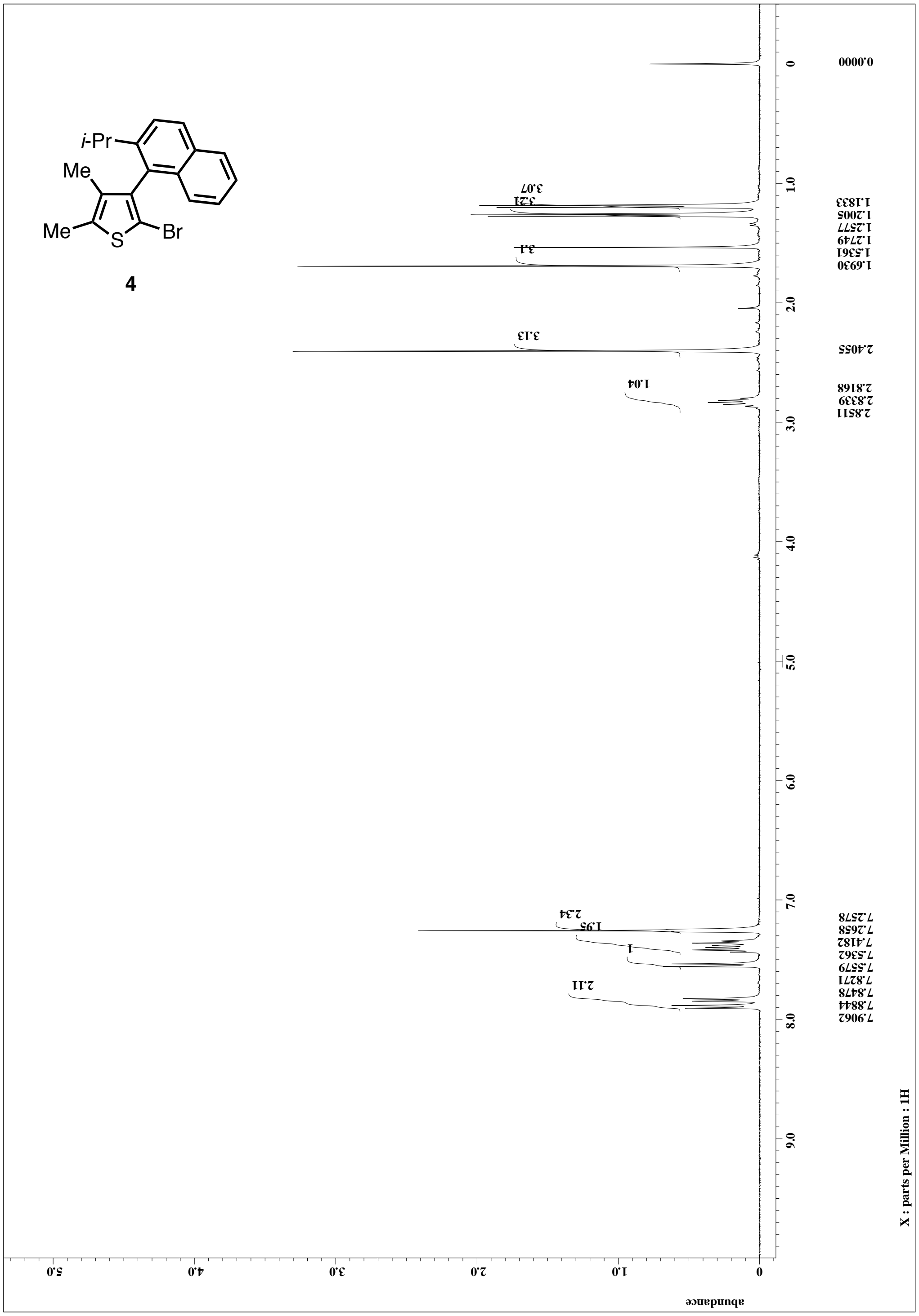
^{1}H NMR (400 MHz, $CDCl_3$) of 3kh:



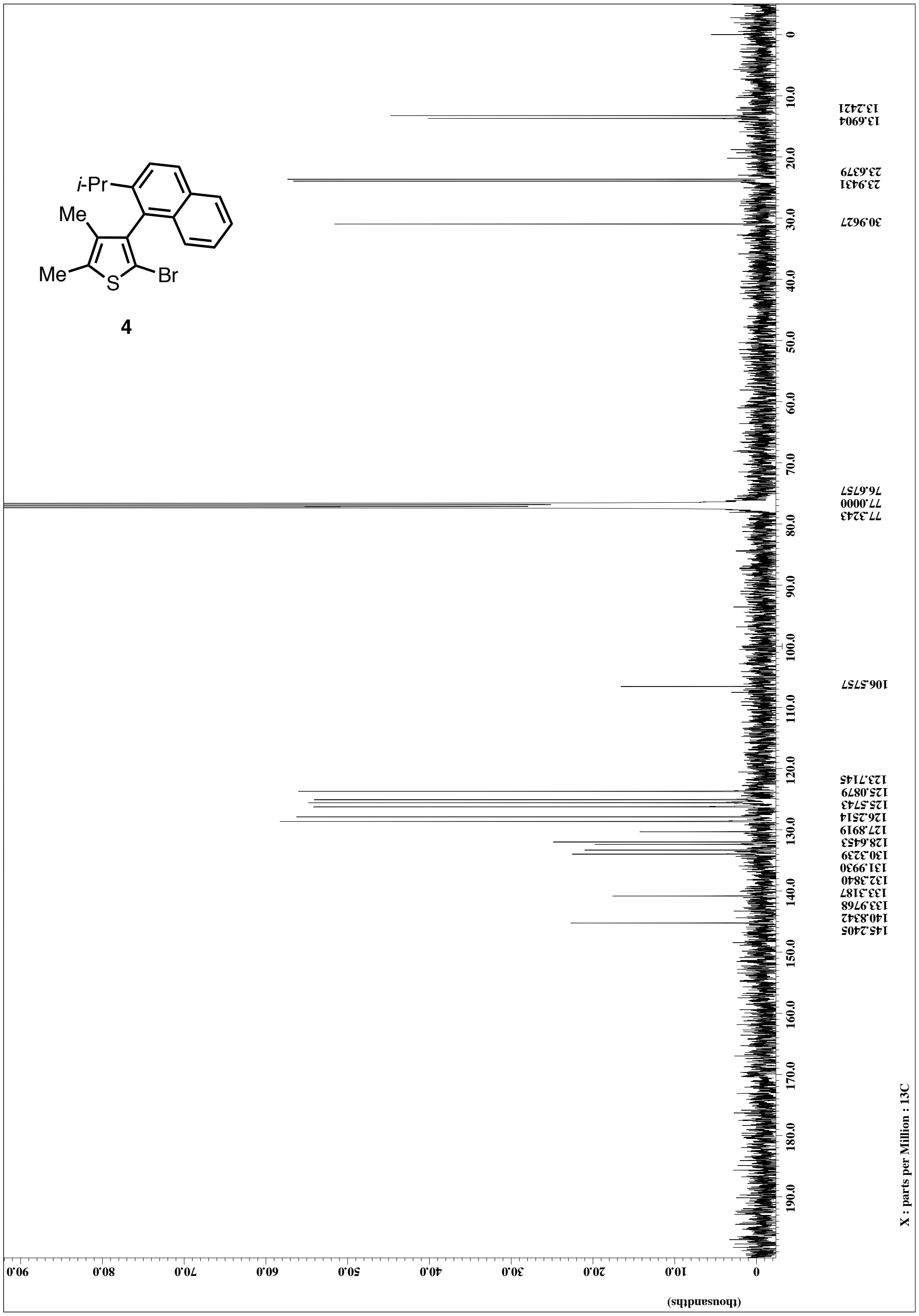
^{13}C NMR (100 MHz, $CDCl_3$) of 3kh:



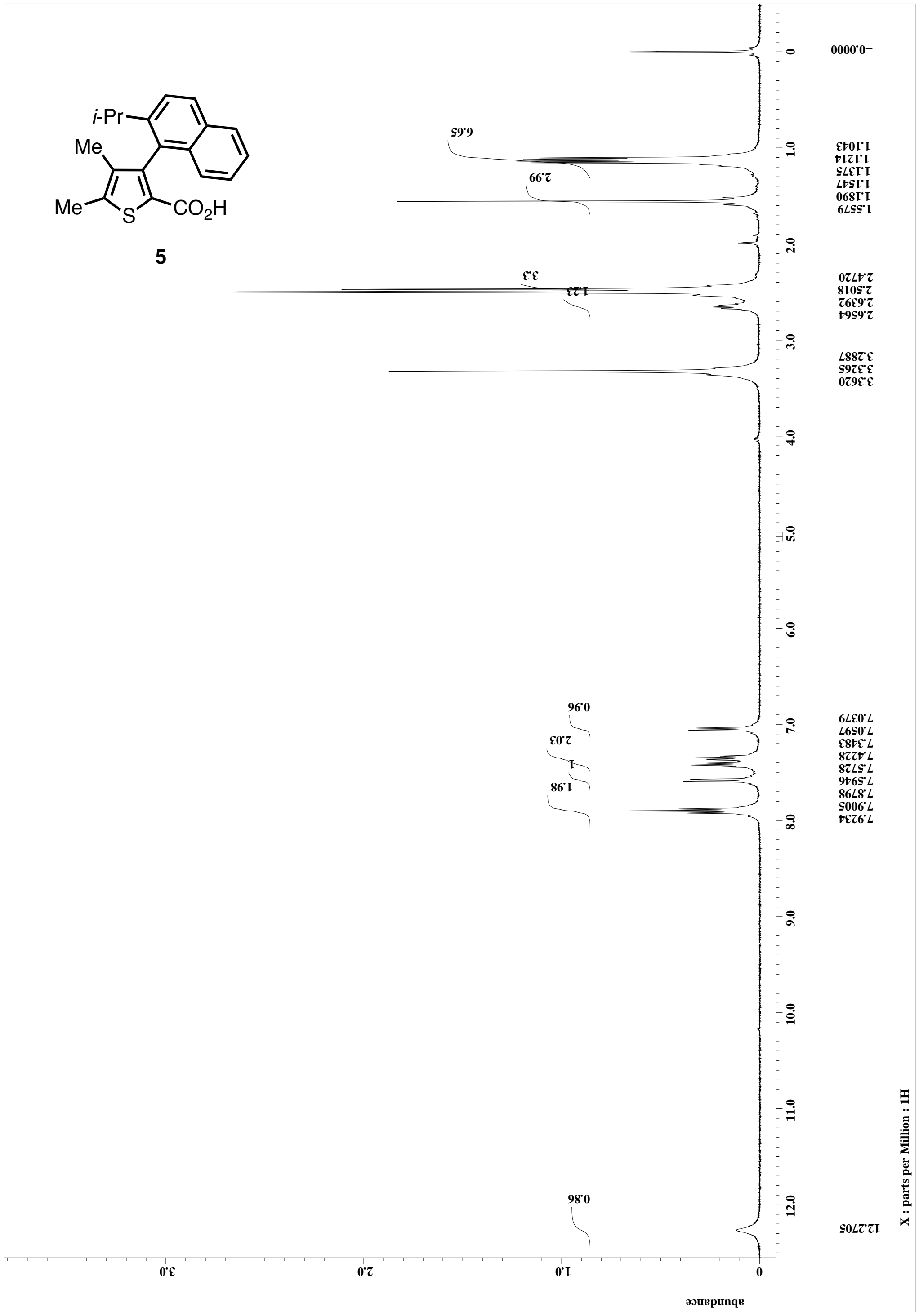
^{1}H NMR (400 MHz, CD_2Cl_2) of 4:



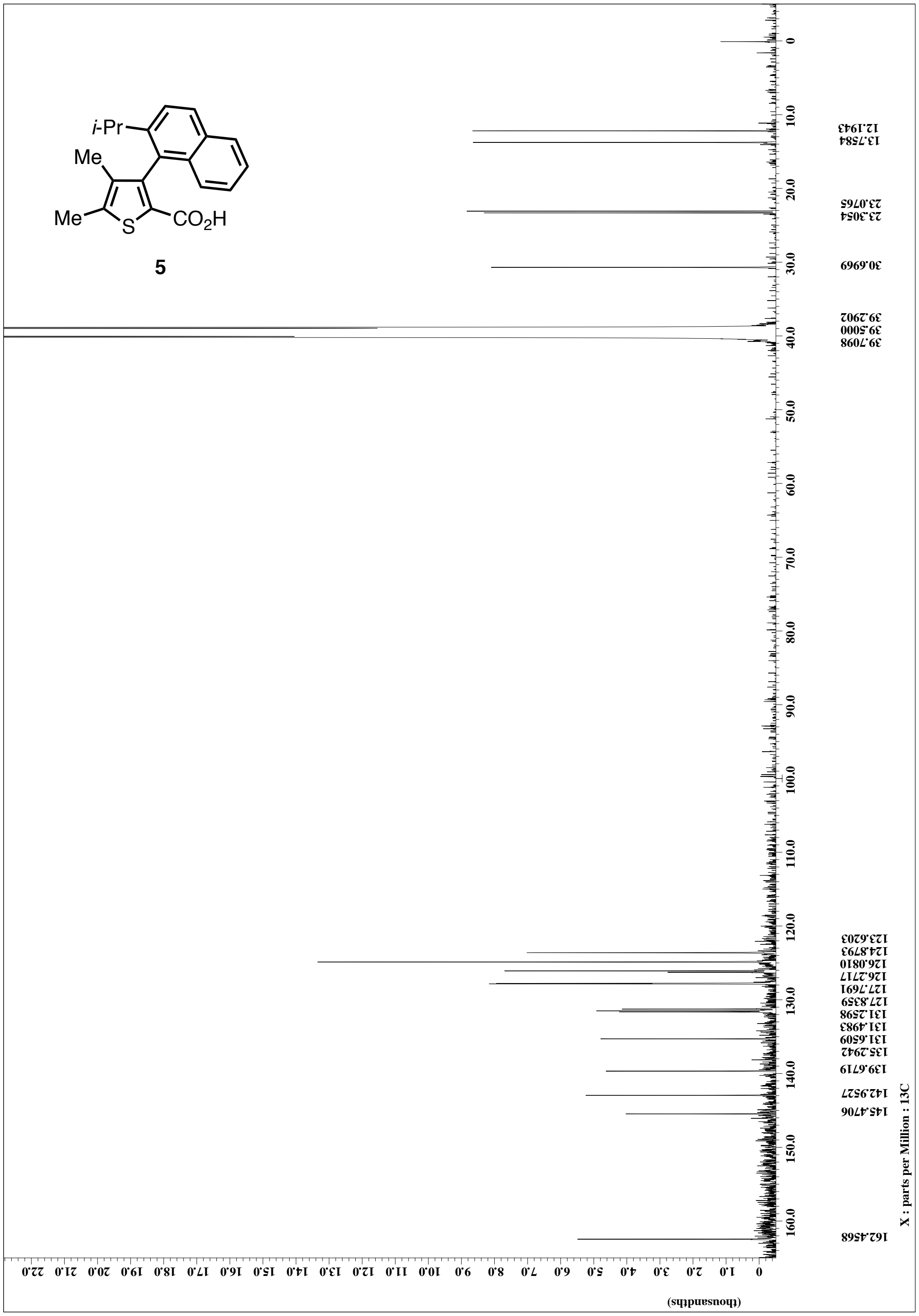
^{13}C NMR (100 MHz, $CDCl_3$) of 4:



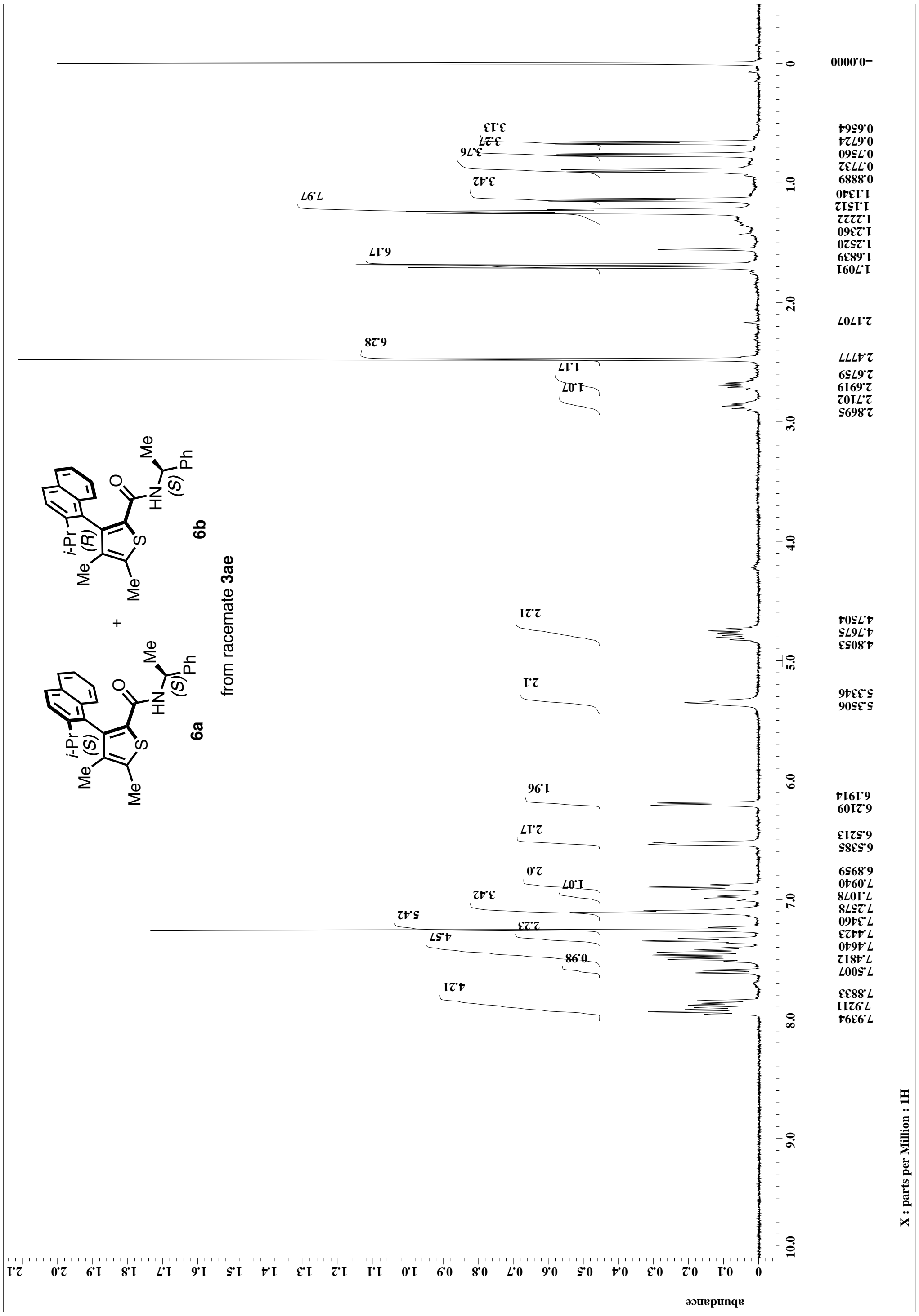
^{1}H NMR (400 MHz, DMSO-d_6) of 5:



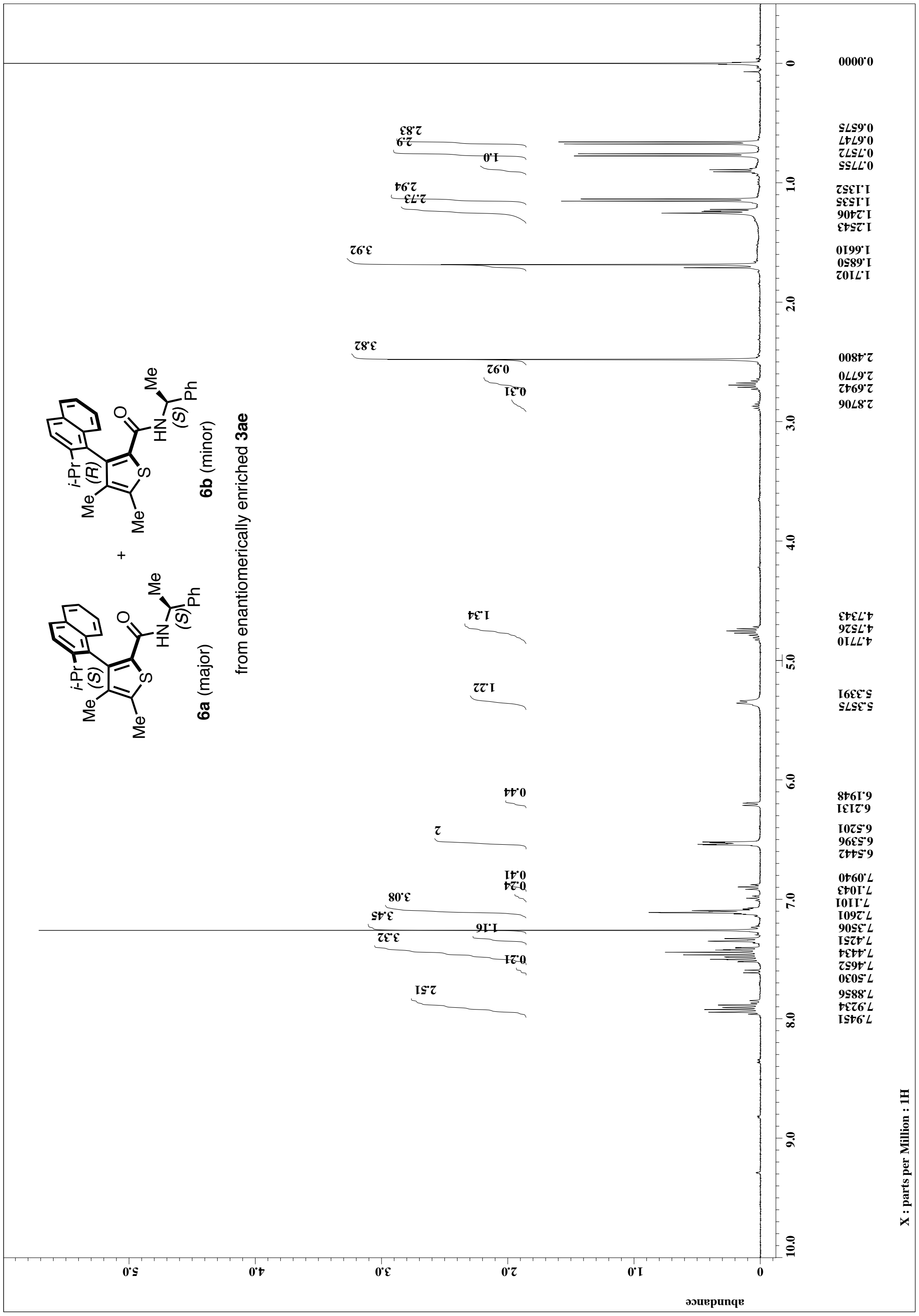
^{13}C NMR (100 MHz, DMSO-d_6) of 5:



^{1}H NMR (400 MHz, $CDCl_3$) of 6a+6b from racemate 3ae:



^{1}H NMR (400 MHz, $CDCl_3$) of 6a+6b from enantiomerically enriched 3ae:



Electronic Supplementary Material (ESI) for Chemical Science
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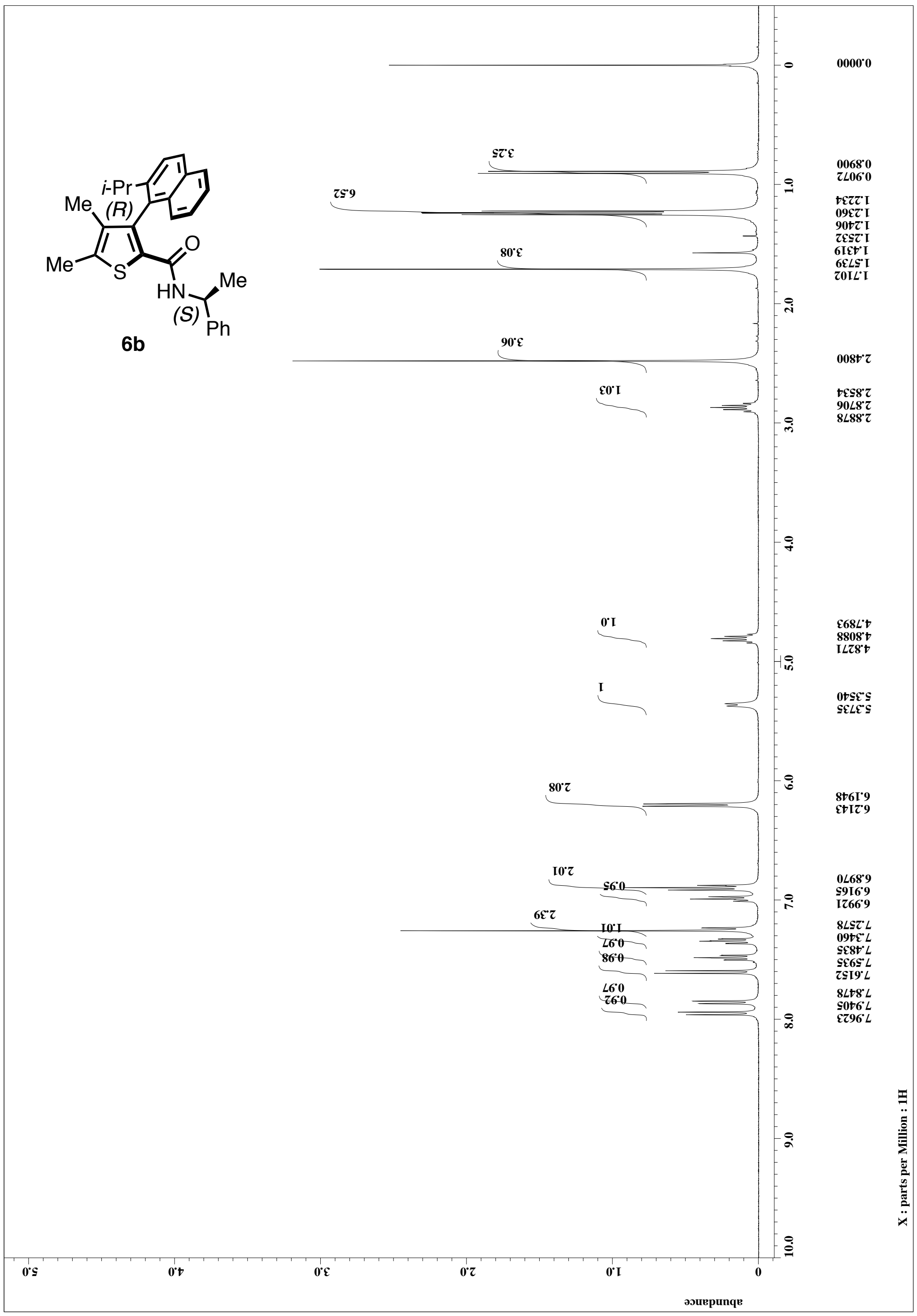
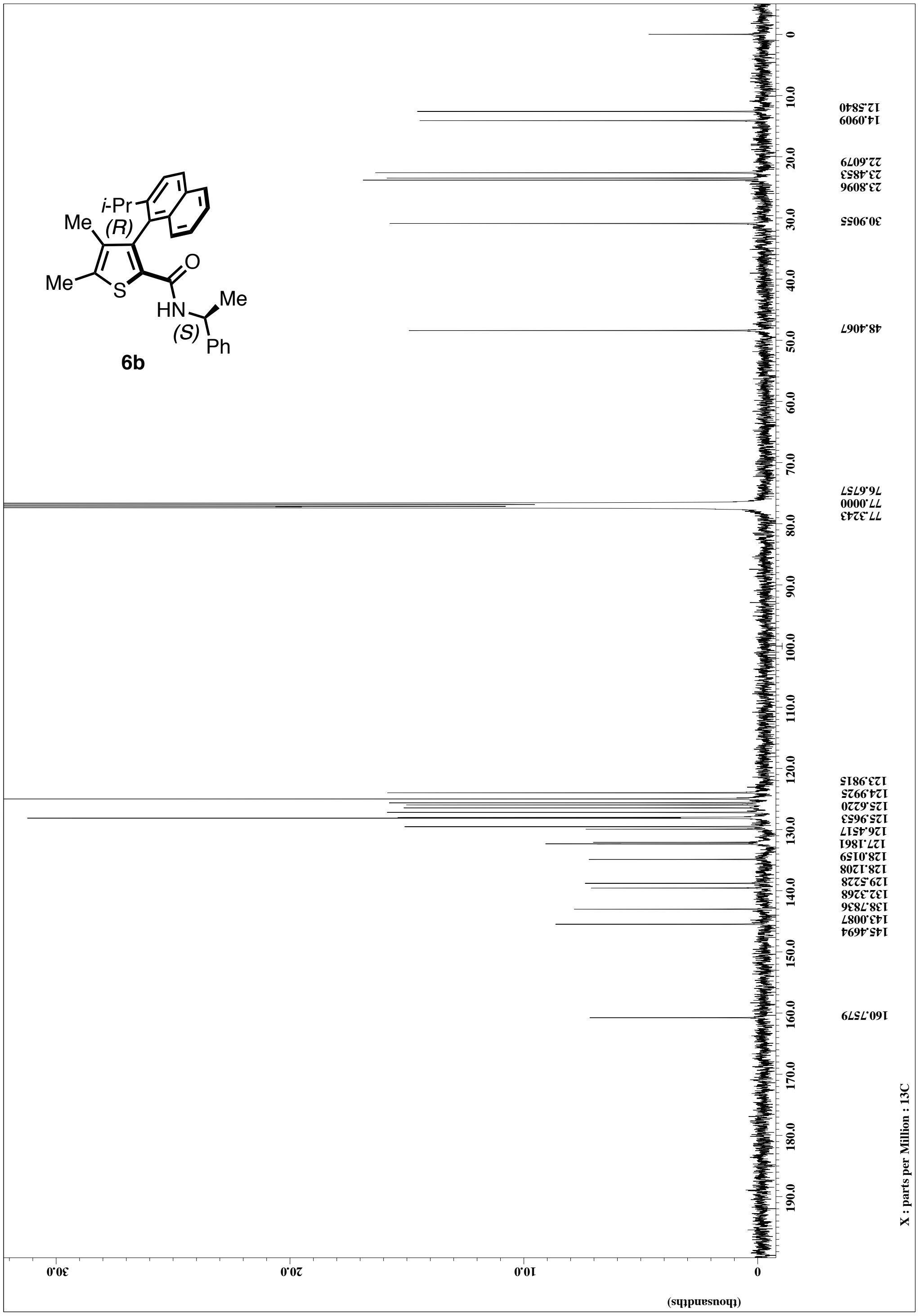
^{1}H NMR (400 MHz, $CDCl_3$) of 6b:



^{13}C NMR (100 MHz, $CDCl_3$) of 6b:

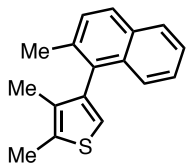


Electronic Supplementary Material (ESI) for Chemical Science

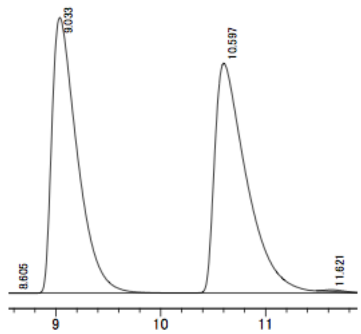
11. HPLC Chart

HPLC chart of 3aa

racemate



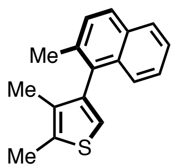
(±)-**3aa**



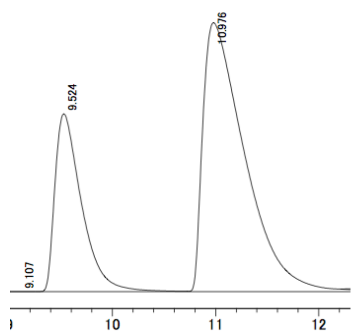
OD-H ®
254 nm
hexane
1.0 mL/min

retention time	area
9.033	31263277
10.597	32962406

Enantiomerically enriched



(*S*)-**3aa**

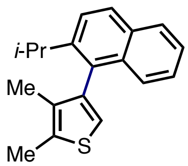


OD-H ®
254 nm
hexane
1.0 mL/min

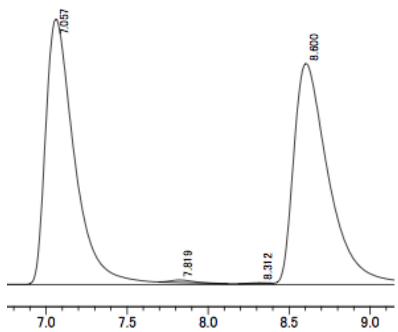
retention time	area
9.524	32149204
10.976	76113384

HPLC chart of 3ae:

racemate



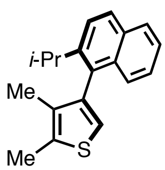
(±)-**3ae**



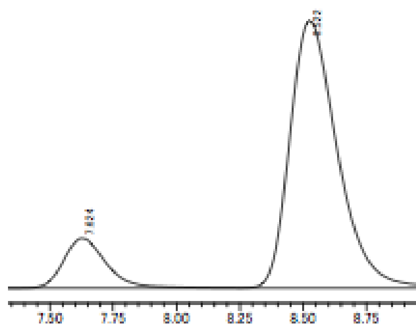
OD-H ®
254 nm
hexane
1.0 mL/min

retention time	area
7.057	13491841
7.819	94676
8.312	15780
8.600	13263610

Enantiomerically enriched with **L4**



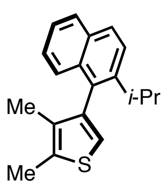
(*S*)-**3ae**
with **L4**



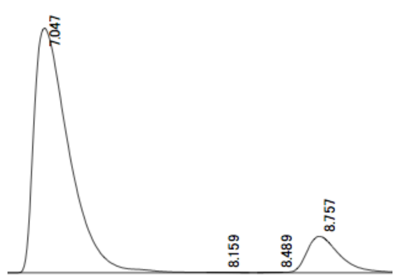
OD-H ®
254 nm
hexane
1.0 mL/min

retention time	area
7.624	695918
8.522	4196117

Enantiomerically enriched with ***ent*-L4**

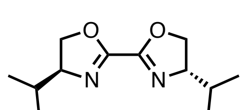


(*R*)-**3ae**
with ***ent*-L4**

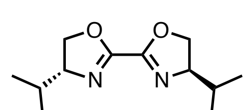


OD-H ®
254 nm
hexane
1.0 mL/min

retention time	area
7.047	43634169
8.159	9127
8.489	3349
8.757	6132047



L4



***ent*-L4**