Supporting Information

Synthesis of multiply substituted 1,6-dihydropyridines through Cu(I)-catalyzed 6-*endo* cyclization

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General Methods

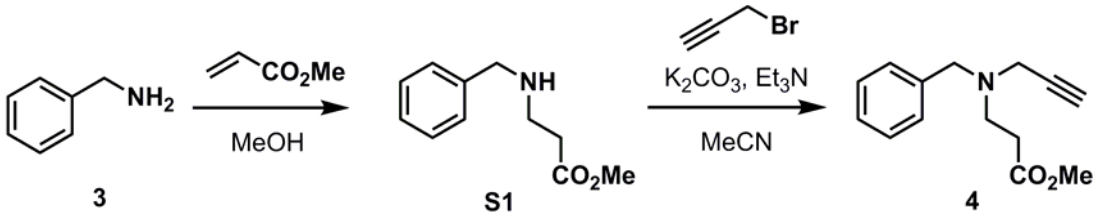
All reactions were performed under a nitrogen atmosphere unless otherwise specified. Microwave reactions were performed using a Biotage Initiator. NMR spectra were recorded on JEOL JNM-ECP 300 (^{1}H/300 MHz, ^{13}C/75 MHz) spectrometer, JEOL JNM-ECX 400 (^{1}H/400 MHz, ^{13}C/100 MHz) spectrometer, JEOL JNM-ECX 600 (^{1}H/600 MHz, ^{13}C/150 MHz) spectrometer and Bruker VSP 500 (^{1}H/500 MHz, ^{13}C/125 MHz) spectrometer. Chemical Shifts are reported in δ (ppm) using chloroform, acetonitrile as an internal standard of δ 7.26, 1.94, and 77.16, 118.26 for ^{1}H and ^{13}C-NMR, respectively. Data for ^{1}H-NMR are reported as follows: chemical shift (number of hydrogens, multiplicity, coupling constant). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad). ESI-Mass spectra were recorded on JEOL AccuTOF LC-Plus JMS-T100. The medium pressure liquid chromatography (MPLC) purifications were performed on a YAMAZEN YFLC-AI-580. Where necessary, solvents were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography using Merck Millipore TLC Silica gel F_{254} plates (0.25 mm) which were visualized using UV light, *p*-anisaldehyde stain and PMS stain. Flash column chromatography was performed using Kanto Silica Gel 60N.

Materials

Commercial solvents and reagents were used as received with the following exceptions. The cationic Cu(I) complex, [Cu(BINAP)(MeCN)]PF_6, [Cu(dppf)(MeCN)]PF_6, were prepared with modified protocol reported by Kim and co-workers[1] and purified by precipitation from CH_2Cl_2/Et_2O=1/1 solution. [Cu(Xantphos)(MeCN)]PF_6[2], and (*S*)-4-benzyl-3-propioloyloxazolidin-2-one[3] were prepared by applying reported protocols.

Synthesis of *N*-propargylenamines

Methyl 3-(benzyl(prop-2-yn-1-yl)amino)propanoate (4)



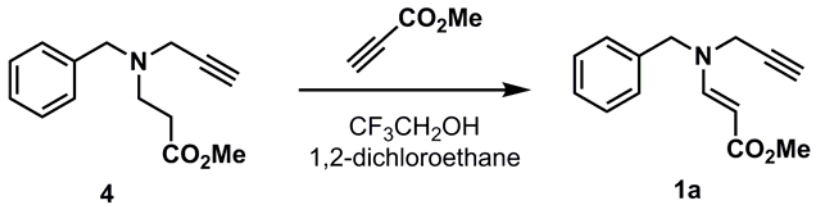
3 S1 4

A solution of benzyl amine **3** (1.83 ml, 16.8 mmol) and methyl acrylate (1.66 ml, 18.5 mmol) in MeOH (5.0 ml) was stirred at 65 °C for 10 min under microwave irradiation. After concentration of the mixture *in vacuo*, the residue was purified by silica-gel chromatography to afford methyl 3-(benzylamino)propanoate **S1** (2.68 g, 13.9 mmol, 83%).

A solution of secondary amine **S1** (6.43 g, 33.3 mmol), propargyl bromide (3.16 ml, 36.6 mmol), K_2CO_3 (9.20 g, 66.6 mmol), and Et_3N (4.64 ml, 33.3 mmol) in acetonitrile (133 ml) was stirred at 70 °C for 16 h. The resulting mixture was then treated with another portion of propargyl bromide (1.44 ml, 16.7 mmol). After being stirred at 85 °C for 6 h, the mixture was concentrated *in vacuo* and then added with EtOAc and H_2O. Organic phase was washed with water, brine and the dried over Na_2SO_4. After concentration, the residue was purified by silica-gel chromatography to afford tertiary amine **4** (5.78 g, 25.0 mmol, 75%).

4: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37-7.20 (5H, m), 3.68 (3H, s), 3.65 (2H, s), 3.32 (2H, d, J = 2.2 Hz), 2.91 (2H, t, J = 6.9 Hz), 2.53 (2H, t, J = 6.9 Hz), 2.24 (1H, t, J = 2.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.92, 138.55, 129.14, 128.43, 127.35, 78.32, 73.47, 57.79, 51.74, 49.15, 41.44, 33.27; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{14}H_{18}NO_2$ 232.1332; found 232.1330.
The ^{1}H-NMR and ^{13}C-NMR spectra of **4** are shown in Figure **S1** and **S2**.

(*E*)-Methyl 3-(benzyl(prop-2-yn-1-yl)amino)acrylate (1a)

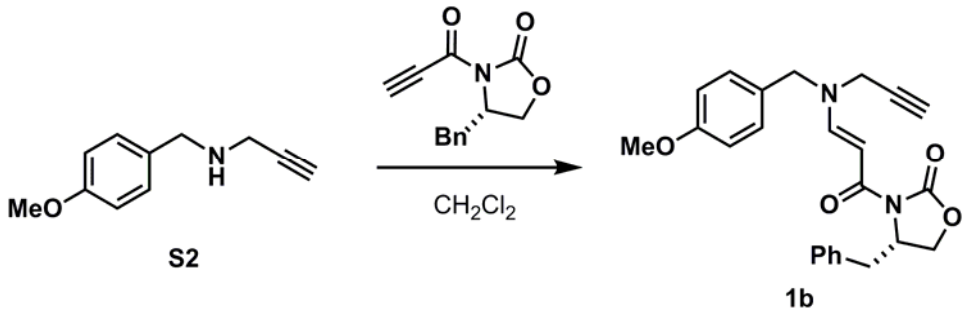


4 1a

A solution of amine **4** (1.08 g, 4.67 mmol) and methyl propiolate (0.91 ml, 10.2 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol = 1/1 (24 ml) was stirred at r.t. for 14 h. The mixture was treated with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue was concentrated *in vacuo* and purified by silica-gel chromatography to afford **1a** (962 mg, 4.20 mmol, 90%).

1a: TLC R_f = 0.35 (Hex:AcOEt = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (1H, d, *J* = 13.1 Hz), 7.38-7.27 (3H, m), 7.24 (2H, d, *J* = 6.9 Hz), 4.83 (1H, d, *J* = 13.1 Hz), 4.41 (2H, s), 3.81 (2H, d, *J* = 2.2 Hz), 3.68 (3H, s), 2.30 (1H, t, *J* = 2.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 169.83, 151.42, 135.70, 128.98, 128.16, 127.81, 87.43, 73.67, 50.87; HR-MS (ESI, *m/z*): $[M+H]^+$ calcd. For $C_{14}H_{16}NO_2$ 230.1176; found 230.1216.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1a** are shown in Figure **S3** and **S4**.

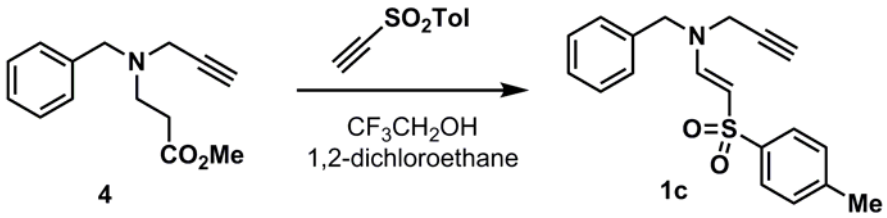
(*E*)-4-Benzyl-3-(3-((4-methoxybenzyl)(prop-2-yn-1-yl)amino)acryloyl)oxazolidin-2-one (1b)



A solution of *N*-(4-methoxybenzyl)prop-2-yn-1-amine **S2**[4] (858 mg, 4.90 mmol) and (*S*)-4-benzyl-3-propioloyloxazolidin-2-one (1.12 g, 4.90 mmol) in CH_2Cl_2 (16 ml) was stirred at r.t. for 1.5 h. The residue was concentrated *in vacuo* and purified by silica-gel chromatography to afford **1b** (1.91 g, 4.72 mmol, 96%).

1b: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.89 (1H, d, *J* = 12.6 Hz), 7.33 (2H, t, *J* = 7.3 Hz), 7.29-7.18 (5H, m), 6.89 (2H, m), 6.40 (1H, br-d, *J* = 12.6 Hz), 4.75 (1H, m), 4.45 (2H, s), 4.14 (1H, dd, *J* = 16.4, 8.8 Hz), 4.11 (1H, dd, *J* = 8.8, 3.2 Hz), 3.89 (2H, br-s), 3.81 (3H, s), 3.37 (1H, dd, *J* = 13.2, 3.2 Hz), 2.78 (1H, dd, *J* = 13.2, 9.8 Hz), 2.35 (1H, br-s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.61, 159.74, 154.17, 153.13, 136.20, 129.68, 129.62, 128.98, 127.22, 114.43, 87.62, 65.86, 55.58, 55.45, 38.61; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd. for $C_{24}H_{24}N_2O_4Na$, 427.1628; found, 427.1641.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1b** are shown in Figure **S5** and **S6**.

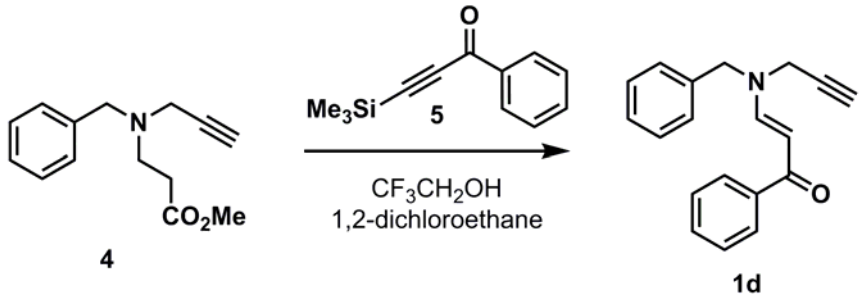
(*E*)-*N*-Benzyl-*N*-(2-tosylvinyl)prop-2-yn-1-amine (1c)



A solution of amine **4** (62.4 mg, 0.270 mmol) and ethynyl *p*-tolylsulfone (58.6 mg, 0.330 mmol) in 1.2-dichloroethane/2,2,2-trifluoroethanol = 1/1 (540 μl) was stirred at r.t. for 12 h. The mixture was treated with saturated aqueous solution of $NaHCO_3$ at 0 °C and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$, brine and dried over Na_2SO_4. The residue was concentrated and purified by silica-gel chromatography to afford **1c** (70.1 mg, 0.215 mmol, 80%).

1c: TLC R_f = 0.61 (Hex:AcOEt = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (2H, d, *J* = 8.2 Hz), 7.50 (1H, d, *J* = 12.9 Hz), 7.37-7.29 (3H, m), 7.27 (2H, d, *J* = 8.2 Hz), 7.23-7.19 (2H, m), 5.20 (1H, d, *J* = 12.9 Hz), 4.39 (2H, s), 3.77 (2H, s), 2.41 (2H, s), 2.30 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 149.19, 142.64, 141.68, 135.00, 129.61, 129.07, 128.37, 127.84, 126.51, 96.64, 76.72, 74.32, 21.61; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd. for $C_{19}H_{19}NO_2SNa$ 348.1028, found 348.1044.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1c** are shown in Figure **S7** and **S8**.

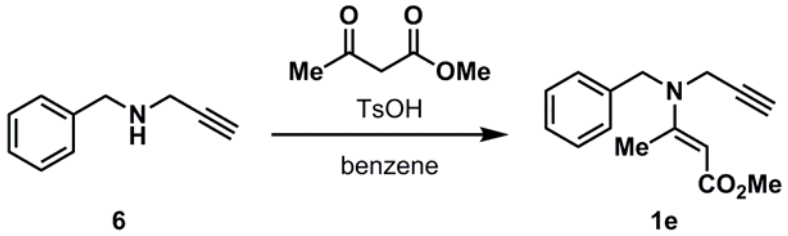
(*E*)-3-(benzyl(prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (1d)



A mixture of amine **4** (1.77 g, 7.65 mmol) and 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one (**5**) (2.32 g, 11.5 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol=1/1 (26 ml) was stirred at 45 °C for 10 h 40 min. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1d** (1.93 g, 7.01 mmol, 92%).

1d: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.95 (1H, d, *J* = 12.6 Hz), 7.89 (2H, d, *J* = 7.3 Hz), 7.49-7.45 (1H, m), 7.44-7.34 (4H, m), 7.35-7.31 (1H, m), 7.30-7.26 (2H, m), 6.02 (1H, d, *J* = 12.6 Hz), 4.54 (2H, s), 3.93 (2H, br-s), 2.36 (1H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 189.28, 152.59, 140.13, 135.24, 131.34, 129.01, 128.27, 127.83, 127.71, 94.55, 76.99, 74.08; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{19}H_{18}NO$, 276.1383; found, 276.1385.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1d** are shown in Figure **S9** and **S10**.

Methyl (*E*)-3-(benzyl(prop-2-yn-1-yl)amino)but-2-enoate (1e)

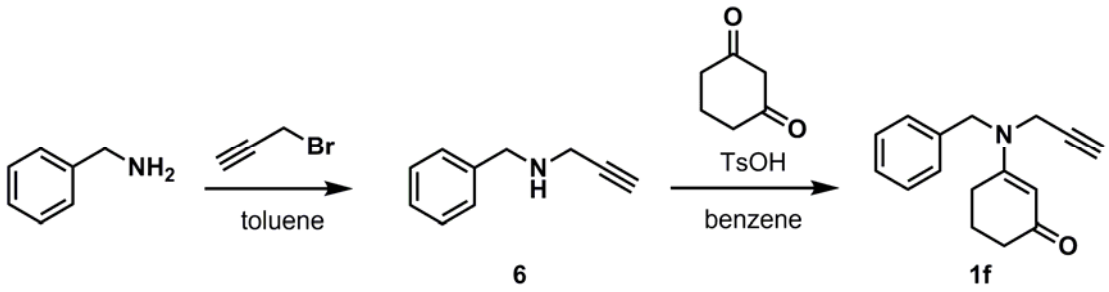


6 1e

To a solution of *N*-benzylprop-2-yn-1-amine **6** (475 mg, 3.27 mmol) and methyl acetoacetate (0.705 ml, 6.54 mmol) in benzene (8.8 ml) was added *p*-toluenesulfonic acid monohydrate (37.3 mg, 0.196 mmol) and stirred at 95 °C for 12 h using a Dean - Stark apparatus. After cooled to room temperature, the mixture was washed with aqueous solution of 1N NaOH, water and brine, dried over Na_2SO_4. After filtration, the residue was concentrated *in vacuo* and purified by silica-gel chromatography to afford **1e** (318 mg, 1.31 mmol, 40%).

1e: TLC R_f = 0.60 (Hex:AcOEt = 1:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34 (2H, t, *J* = 7.3 H), 7.28 (1H, t, *J* = 7.3 Hz), 7.18 (2H, d, *J* = 7.3 Hz), 4.92 (1H, s), 4.53 (2H, s), 3.93 (2H, d, *J* = 2.2 Hz), 3.63 (3H, s), 2.56 (3H, s), 2.28(1H, t, *J* = 2.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 169.41, 160.38, 136.70, 128.93, 127.67, 126.82, 87.46, 78.24, 73.04, 53.05, 50.38, 39.35, 15.60; HR-MS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{15}H_{18}NO_2$ 244.1332, found 244.1357.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1e** are shown in Figure **S11** and **S12**.

3-(benzyl(prop-2-yn-1-yl)amino)cyclohex-2-en-1-one (1f)

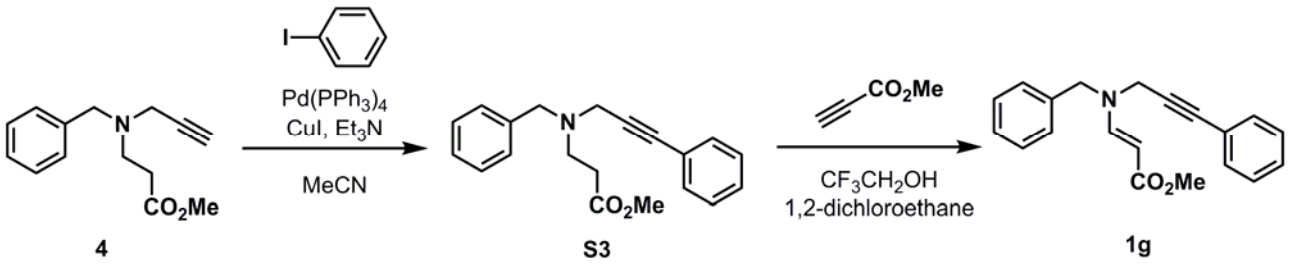


To a solution of benzyl amine (4.26 ml, 39.0 mmol) in toluene (6.3 ml) was added propargyl bromide (0.560 ml, 6.50 mmol) and stirred at r.t. for 14 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **6** (839 mg, 5.78 mmol, 89%).

To a solution of amine **6** (145 mg, 1.00 mmol) in benzene (10 ml) was added 1,3-cyclohexanedione (178 mg, 1.60 mmol) and *p*-toluenesulfonic acid monohydrate (11.4 mg, 0.06 mmol) and heated under reflux for 12 h using a Dean - Stark apparatus. After cooled to room temperature, the mixture was washed with aqueous solution of 1M NaOH and brine, dried over Na_2SO_4. The residue was concentrated *in vacuo* and purified by silica-gel chromatography to afford **1f** (109 mg, 0.455 mmol, 46%).

1f: TLC R_f = 0.20 (Hex:AcOEt = 1:5); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38-7.33 (2H, m), 7.32-7.27 (1H, m), 7.18 (2H, d, *J* = 7.9 Hz), 5.41 (1H, s), 4.56 (2H, s), 3.97 (2H, d, *J* = 2.2 Hz), 2.55 (2H, t, *J* = 6.3 Hz), 2.39-2.30 (2H, m), 2.31 (1H, s), 2.05-1.99 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 197.62, 164.56, 136.15, 129.10, 127.95, 126.77, 101.21, 77.78, 73.60, 53.31, 39.53, 35.88, 27.10, 22.37; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found 240.1388.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1f** are shown in Figure **S13** and **S14**.

Methyl (*E*)-3-(benzyl(3-phenylprop-2-yn-1-yl)amino)acrylate (1g)

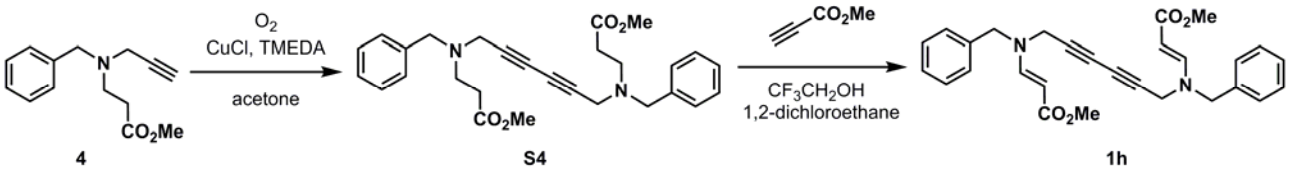


A mixture of amine **4** (762 mg, 3.29 mmol), $Pd(PPh_3)_4$ (87.7 mg, 0.076mmol), CuI (43.4 mg, 0.228 mmol), Et_3N (0.530 ml, 3.80 mmol) and PhI (0.282 ml, 2.53 mmol) in MeCN (16.5 ml) was heated at 60 °C for 3 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford methyl 3-(benzyl(3-phenylprop-2-yn-1-yl)amino)propanoate **S3** (867 mg). To a solution of **S3** (867 mg) in 1,2-dichloroethane/2,2,2-trifluoroethanol = 1/1 (14.7 ml) was added methyl propiolate (0.277 ml, 3.10 mmol) and stirred at r.t. for 12 h. The mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by silica-gel chromatography to afford **1g** (775 mg, 2.54 mmol, quant. for 2 steps).

1g: TLC R_f = 0.35 (Hex:AcOEt = 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (1H, d, *J* = 13.2 Hz), 7.43-7.26 (10H, m), 4.88 (1H, d, *J* = 13.2 Hz), 4.47 (2H, s), 4.05 (2H, br-s), 3.69 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 169.85, 151.49, 135.85, 131.79, 128.85, 128.62, 128.36, 127.97, 127.69, 122.33, 86.99, 85.45, 82.72, 55.68, 50.73, 40.81; HRMS (ESI, *m/z*): calcd. for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.1489, found 306.1489.

The ^{1}H-NMR and ^{13}C-NMR spectra of **1g** are shown in Figure **S15** and **S16**.

Dimethyl 3,3'-(hexa-2,4-diyne-1,6-diylbis(benzylazanediyl))(2*E*,2'*E*)-diacrylate (1h)

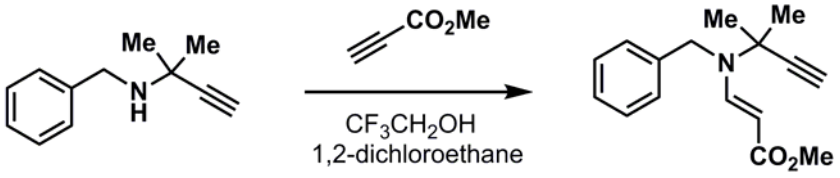


To a solution of amine **4** (565 mg, 2.44 mmol) in acetone (2.0 ml) was added a solution of preliminary mixed CuCl (21.4 mg, 0.216 mmol) and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (11 μl, 0.072 mmol) in acetone (2.0 ml) and stirred at r.t. for 12 h under O_2 atmosphere. After concentrated *in vacuo*, the residue was purified by silica-gel column chromatography to afford **S4** (553 mg, 1.20 mmol, 98%).

To a solution of amine **S4** (530 mg, 1.15 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol=1/1 (9.0 ml) was added methyl propiolate (383 μl, 4.60 mmol) and stirred at r.t. for 19 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1h** (423 mg, 0.927 mmol, 81%).

1h: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* = 12.9 Hz), 7.38-7.28 (6H, m), 7.22 (4H, d, *J* = 6.9 Hz), 4.83 (2H, d, *J* = 12.9 Hz), 4.39 (4H, s), 3.85 (4H, s), 3.68 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.66, 151.28, 135.45, 129.04, 128.29, 127.87, 87.94, 72.81, 69.18, 56.25, 50.90, 40.08; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{28}H_{29}N_2O_4$, 457.2122; found, 457.2117.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1h** are shown in Figure **S17** and **S18**.

Methyl (*E*)-3-(benzyl(2-methylbut-3-yn-2-yl)amino)acrylate (1i)

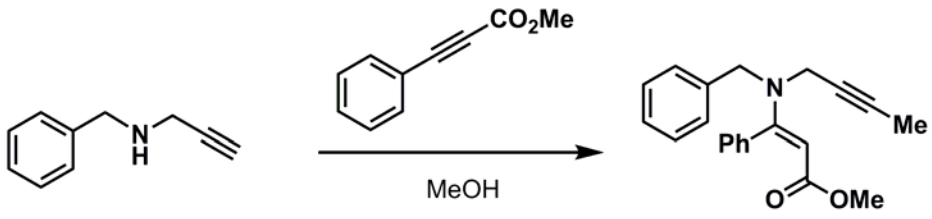


S5 **1i**

To a solution of amine **S5**[5] (182 mg, 1.25 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol=1/1 (6 ml) was added methyl propiolate (209 μl, 2.51 mmol) and stirred at 45 °C for 19 h. After concentrated *in vacuo*, the residue was purified by silica-gel column chromatography to afford **1i** (263 mg, 0.970 mmol, 78%).

1i: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.06 (1H, d, *J* = 12.9 Hz), 7.30 (2H, t, *J* = 7.6 Hz), 7.23 (1H, t, *J* = 7.6 Hz), 7.20 (2H, d, *J* = 7.6 Hz), 4.54 (1H, d, *J* = 12.9 Hz), 4.52 (2H, s), 3.61 (3H, s), 2.47 (1H, s), 1.64 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.97, 147.59, 137.01, 128.7, 127.1, 126.24, 88.45, 85.86, 72.94, 56.95, 50.69, 50.42, 29.57; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{16}H_{20}NO_2$, 258.1489; found, 258.1482.
The ^{1}H-NMR and ^{13}C-NMR spectra of **1i** are shown in Figure **S19** and **S20**.

Methyl (*E*)-3-(benzyl(but-2-yn-1-yl)amino)-3-phenylacrylate (1j)



S6 **1j**

To a solution of *N*-benzylbut-2-yn-1-amine **S6** (195 mg, 1.23 mmol) in methanol (1.2 ml) was added methyl 3-phenylpropiolate (0.19 ml, 1.29 mmol) at room temperature and then stirred at

70 °C for 16 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1j** (176 mg, 0.551 mmol, 45%).

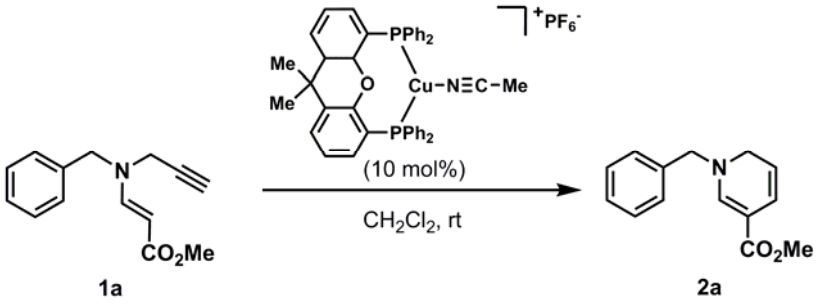
1j: TLC R_f = 0.38 (Hex:AcOEt = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43-7.40 (3H, m), 7.33-7.31 (4H, m), 7.29-7.25 (1H, m), 7.23 (1H, br-d, *J* = 7.4 Hz), 5.13 (1H, s), 4.33 (2H, br-s), 3.74 (2H, br-s), 3.48 (3H, s), 1.84 (3H, t, *J* = 2.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): 167.97, 162.56, 136.75, 136.08, 128.73 128.58, 128.48, 128.23, 127.40, 89.75, 80.78, 73.36, 52.63, 50.20, 39.34, 3.52
^{1}H-NMR and ^{13}C-NMR spectra of **1j** are shown in Figure **S21** and **S22**.

Cu(I)-catalyzed Cyclization of *N*-propargylenamine

General procedure

A solution of *N*-propargylenamine (0.200 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (0.020 mmol) in CH_2Cl_2 (2.0 ml) was stirred at r.t. for several hours. The reaction mixture was then treated with 1,10-phenanthroline (0.020 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (0.200 mmol) was added as internal standard for ^{1}H-NMR. Yield of desired product was calculated based on the value of integral for a signal of 4-nitrobenzonitrile and that of desired product. The ^{1}H-NMR and ^{13}C-NMR of the internal standard are shown in Figure **S45** and **S46**.

Methyl 1-benzyl-4-phenyl-1,6-dihydropyridine-3-carboxylate (2a)

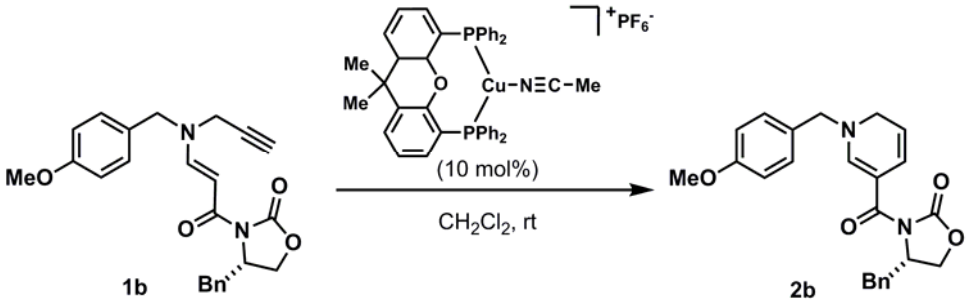


A solution of *N*-propargylenamine **1a** (251 mg, 1.09 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (90.6 mg, 0.109 mmol) in CH_2Cl_2 (11 ml) was stirred at r.t. for 40 min. The reaction mixture was then treated with 1,10-phenanthroline (25.2 mg, 0.140 mmol) to deactivate the copper catalyst. After concentrated *in vacuo*, 4-nitrobenzonitrile (162 mg, 1.09 mmol) was added. Due to instability of **2a** to silica-gel chromatography, the yield of **2a** (98%) was calculated based on ^{1}H-NMR.

2a: TLC R_f = 0.45 (Hex:Acetone = 4:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.43-7.28 (6H, m), 6.30 (1H, m), 4.96 (1H, dt, *J* = 10.1, 3.1 Hz), 4.20 (2H, s), 4.01 (2H, dd, *J* = 3.1, 1.9 Hz), 3.68 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 167.00, 147.94, 134.95, 128.92, 128.20, 127.89, 122.20, 109.85, 96.04, 60.08, 50.63, 47.98; HR-MS (ESI): calcd. for the corresponding pyridinium salt $C_{14}H_{14}NO_2[M]^+$ 228.1019, found 228.1019.

^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S23** and **S24.**

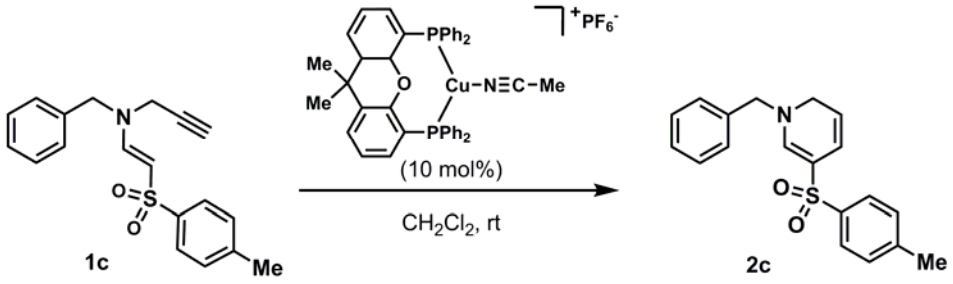
4-Benzyl-3-(1-(4-methoxybenzyl)-1,6-dihydropyridine-3-carbonyl)oxazolidin-2-one (2b)



A solution of *N*-propargylenamine **1b** (63.7 mg, 0.170 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (14.1 mg, 0.0170 mmol) in CH_2Cl_2 (1.7 ml) was stirred at r.t. for 180 min. The reaction mixture was then treated with 1,10-phenanthroline (3.1 mg, 0.017 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (26.8 mg, 0.181 mmol) was added. Due to instability of **2b** to silica-gel chromatography, the yield of **2b** (84%) was calculated based on ^{1}H-NMR.

2b: TLC R_f = 0.38 (Hex:AcOEt = 1:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45 (1H, s), 7.32-7.17 (7H, m), 6.92 (2H, d, *J* = 8.5 Hz), 6.33 (1H, d, *J* = 10.4 Hz), 5.05 (1H, dt, *J* = 10.1, 3.2 Hz), 4.90 (1H, ddd, *J* = 17.0, 8.5, 3.5 Hz), 4.30-4.24 (2H, m), 4.18 (1H, d, *J* = 14.5 Hz), 4.12-4.06 (3H, m), 3.18 (3H, s), 3.26 (1H, dd, *J* = 13.6, 3.5 Hz), 2.83 (1H, dd, *J* = 13.6, 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 164.98, 159.78, 155.33, 152.49, 135.63, 129.59, 129.55, 128.73, 127.09, 125.84, 122.31, 114.42, 109.88, 98.58, 66.57, 60.38, 55.54, 55.37, 48.36, 37.89; HR-MS (ESI): calcd. for $C_{24}H_{24}N_2O_4Na$ $[M+Na]^+$ 427.1628, found 427.1565.
^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S25** and **S26.**

1-Benzyl-5-tosyl-1,2-dihydropyridine (2c)

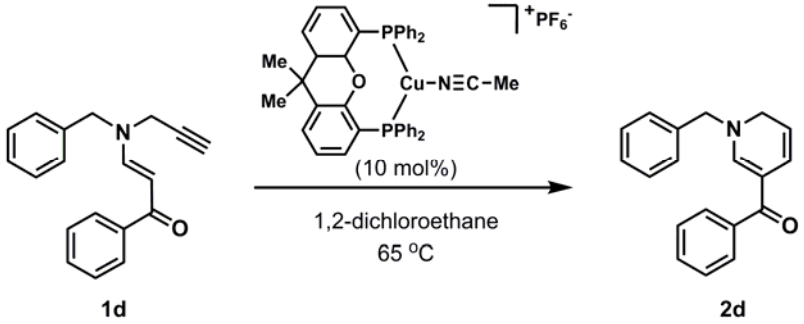


A solution of *N*-propargylenamine **1c** (50.2 mg, 0.154 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (13.0 mg, 0.0157 mmol) in CH_2Cl_2 (1.6 ml) was stirred at r.t. for 4 h. The reaction mixture was treated with 1,10-phenanthroline (3.8 mg, 0.0211 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (22.8 mg, 0.154 mmol) was added. The yield of **2c**

(99%) was calculated based on ^{1}H-NMR.

2c: TLC R_f = 0.48 (Hex:Acetone = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67 (2H, m), 7.32-7.18 (8H, m), 5.90 (1H, m), 4.90 (1H, dt, *J* = 10.2, 3.2 Hz), 4.13 (2H, s), 3.89 (2H, dd, *J* = 3.2, 1.9 Hz), 2.34 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 145.57, 142.48, 140.76, 134.35, 129.57, 128.93, 128.30, 127.92, 126.39, 119.35, 111.59, 104.29, 59.91, 47.77, 21.44; HR-MS (ESI): calcd. for the corresponding pyridinium salt $C_{19}H_{18}NO_2S$ $[M]^+$ 324.1053, found 324.1091.
^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S27** and **S28**.

(1-Benzyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (2d)

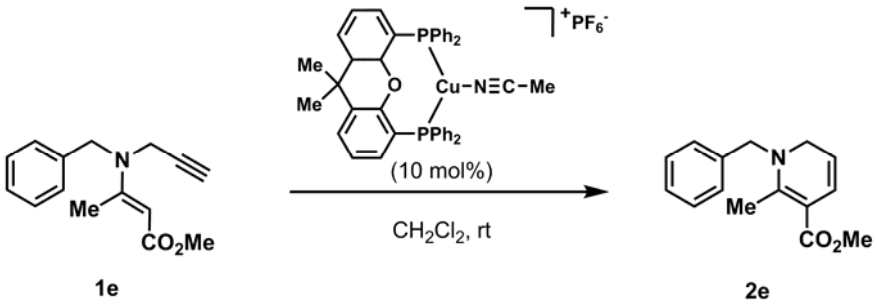


1d 2d

A solution of *N*-propargylenamine **1d (**100 mg, 0.364 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (30.2 mg, 0.0365 mmol) in 1,2-dichloroethane (3.6 ml) was stirred at 65 °C for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (11.2 mg, 0.0621 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (53.9 mg, 0.364 mmol) was added. The yield of **2d** (93%) was calculated based on ^{1}H-NMR.

2d: TLC R_f = 0.33 (Hex:AcOEt = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.52-7.50 (2H, m), 7.40-7.33 (6H, m), 7.23-7.17 (3H, m), 6.63 (1H, m), 5.14 (1H, dt, *J* = 10.2, 3.3 Hz), 4.19 (2H, s), 4.11 (2H, dd, *J* = 3.3, 1.9 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 190.18, 152.71, 140.40, 134.41, 129.88, 129.12, 128.49, 128.34, 128.12, 127.90, 122.25, 111.70, 107.35, 60.46, 48.79; HRMS (ESI): calcd. for $C_{19}H_{17}NONa$ $[M+Na]^+$ 298.1202, found 298.1201.
^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture for **2d** including the internal standard are shown in Figure **S29** and **S30**.

Methyl 1-benzyl-2-methyl-1,6-dihydropyridine-3-carboxylate (2e)

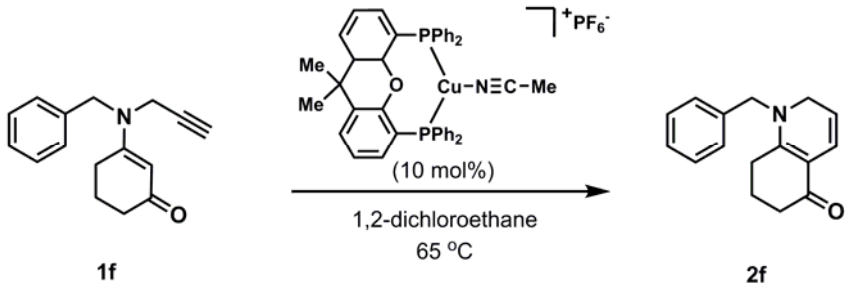


A solution of *N*-propargylenamine **1e** (48.0 mg, 0.197 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (16.7 mg, 0.0202 mmol) in CH_2Cl_2 (2.0 ml) was stirred at r.t. for 2 h. The reaction mixture was then treated with 1,10-phenanthroline (4.7 mg, 0.0261 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (29.2 mg, 0.197 mmol) was added. Yield of **2e** (80%) was calculated based on ^{1}H-NMR due to instability of **2e** to silica-gel chromatography.

2e: TLC R_f = 0.38 (Hex:Acetone = 5:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40-7.37 (2H, m), 7.32-7.24 (3H, m), 6.54 (1H, m), 5.00 (1H, dt, *J* = 9.8, 3.7 Hz), 4.50 (2H, s), 4.01 (2H, m), 3.70 (3H, s), 2.52 (3H, s) ; ^{13}C-NMR (75 MHz, $CDCl_3$): 167.85, 157.65, 136.19, 128.96, 127.59, 126.46, 125.45, 107.19, 97.54, 54.44, 50.63, 50.57, 16.16; HR-MS (ESI): calcd. for $C_{15}H_{17}NO_2Na$ $[M+Na]^+$ 266.1151, found 266.1120.

^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S31**and **S32**.

1-Benzyl-2,6,7,8-tetrahydroquinolin-5(1H)-one (2f)

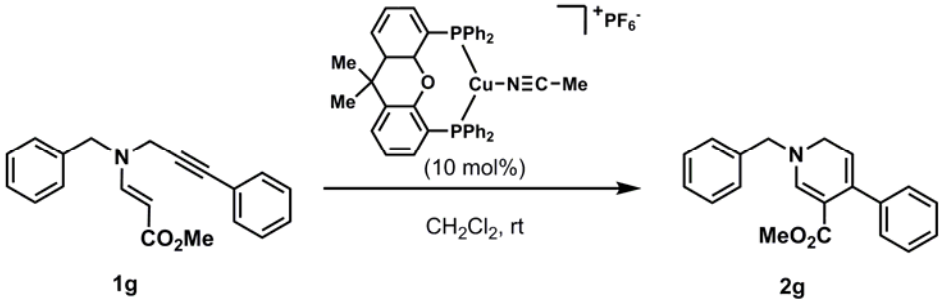


A solution of *N*-propargylenamine **1f** (138 mg, 0.578 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (48.5 mg, 0.0586 mmol) in 1,2-dichloroethane (6.0 ml) was stirred at 65 °C for 2 h. The reaction mixture was treated with 1,10-phenanthroline (13.8 mg, 0.0767 mmol) to deactivate the copper catalyst.

After concentration *in vacuo*, 4-nitrobenzonitrile (85.6 mg, 0.578 mmol) was added. The yield of **2f** (94%) was calculated based on ^{1}H-NMR.

2f: TLC R_f = 0.36 (Hex:Acetone = 1:2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37-7,21 (5H, m), 6.60 (1H, m), 5.08 (1H, dt, *J* = 10.1, 3.3 Hz), 4.41 (2H, s), 4.13 (2H, dd, *J* = 3.3, 1.7 Hz), 2.47 (2H, t, *J* = 6.3 Hz), 2.28 (2H, t, *J* = 6.3 Hz), 1.90 (2H, quin, *J* = 6.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): 191.24, 161.45, 135.25, 129.08, 127.81, 126.33, 121.06, 110.71, 106.32, 53.97, 51.41, 35.42, 26.28, 21.23; HR-MS (ESI): calcd. for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found 240.1382.
^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S33** and **S34**.

Methyl 1-benzyl-4-phenyl-1,6-dihydropyridine-3-carboxylate (2g)

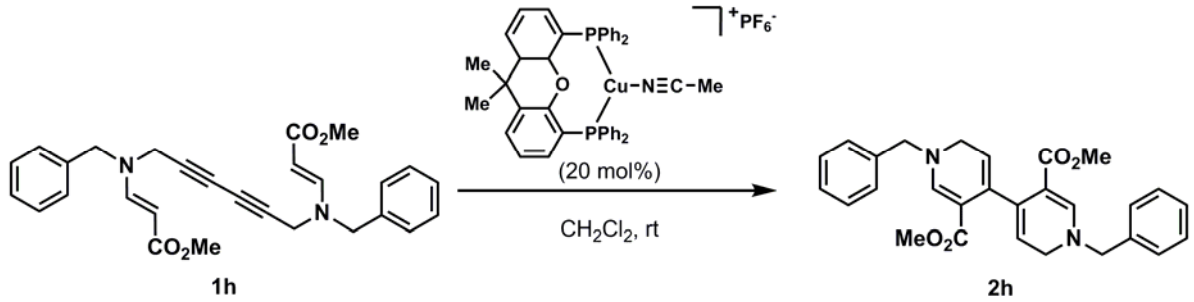


1g 2g

A solution of *N*-propargylenamine **1g** (70.4 mg, 0.231 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (20.0 mg, 0.0241 mmol) in CH_2Cl_2 (2.3 ml) was stirred at r.t. for 110 min. The reaction mixture was then treated with 1,10-phenanthroline (4.14 mg, 0.0230 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (28.7 mg, 0.194 mmol) was added. Yield of **2g** (82%) was calculated based on ^{1}H-NMR.

2g: TLC R_f = 0.45 (Hex:AcOEt = 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.70 (1H, s), 7.42-7.37 (2H, m), 7.37-7.30 (3H, m), 7.30-7.21 (3H, m), 7.20-7.16 (2H, m), 4.91 (1H, t, *J* = 4.1 Hz), 4.32 (2H, s), 4.04 (2H, d, *J* = 4.1 Hz), 3.51 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): 166.67, 150.11, 141.49, 137.28, 135.06, 129.02, 128.30, 128.00, 127.45, 127.29, 126.67, 110.60, 98.13, 59.88, 50.41, 48.07; HR-MS (ESI): calcd. for $C_{20}H_{19}NO_2Na$ $[M+Na]^+$ 328.1308, found 328.1311.
^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S35** and **S36**.

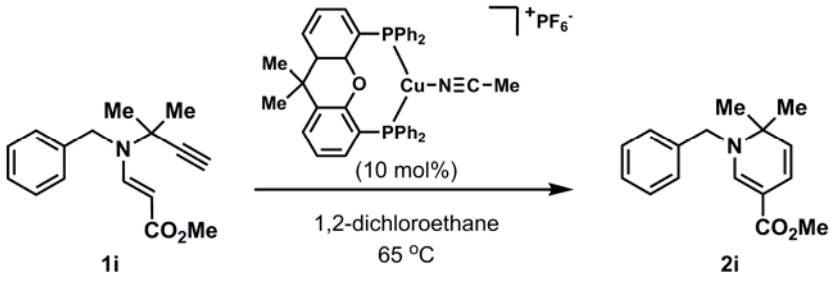
Dimethyl 1,1'-dibenzyl-1,1',6,6'-tetrahydro-[4,4'-bipyridine]-3,3'-dicarboxylate (2h)



A solution of *N*-propargylenamine **1h** (53.1 mg, 0.116 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (19.2 mg, 0.0232 mmol) in CH_2Cl_2 (1.2 ml) was stirred at r.t. for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (4.18 mg, 0.0232 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (17.9 mg, 0.121 mmol) was added. The yield of **2h** (75%) was calculated based on ^{1}H-NMR.

2h: TLC R_f = 0.28 (Hex:AcOEt = 1:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50 (2H, s), 7.39-7.27 (10H, m), 4.78 (2H, t, *J* = 3.5 Hz), 4.28 (2H, br-d, *J* = 14.8 Hz), 4.16 (2H, br-d, *J* = 14.8 Hz), 4.02 (2H, br-d, *J* = 14.2 Hz), 3.95 (2H, br-d, *J* = 14.2 Hz), 3.59 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): 166.48, 147.83, 137.24, 135.39, 128.91, 128.08, 127.97, 108.67, 98.98, 59.96, 50.38, 48.17; HR-MS (ESI): calcd. for $C_{28}H_{28}N_2O_4Na$ $[M+Na]^+$ 479.1898, found 479.1871.
^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S37** and **S38**.

Methyl 1-benzyl-6,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2i)

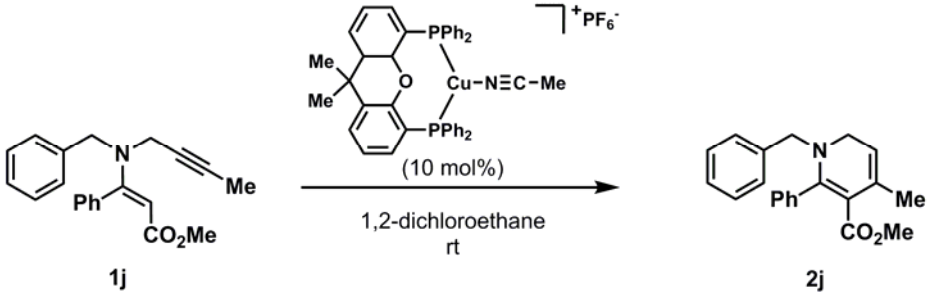


A solution of *N*-propargylenamine **1i** (47.0 mg, 0.183 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (15.7 mg, 0.0190 mmol) in 1,2-dichloroethane (1.8 ml) was stirred at 65 °C for 20 h. The reaction mixture was then treated with 1,10-phenanthroline (5.6 mg, 0.0311 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (27.7 mg, 0.187 mmol) was added.-The yield of **2i** (99%) was calculated based on ^{1}H-NMR spectra. The crude mixture was purified by silica-gel chromatography to afford **2i** (40.5 mg, 0.157 mmol, 86%).

2i: TLC R_f = 0.29 (Hex:AcOEt = 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38-7.35 (2H, m), 7.31-7.25 (3H, m), 6.35 (1H, dd, *J* = 9.8, 1.3 Hz), 4.85 (1H, d, *J* = 9.8 Hz), 4.45 (2H, s), 3.68 (3H, s), 1.28 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 167.11, 147.60, 138.74, 128.93, 127.69, 126.94, 120.46, 120.13, 97.70, 58.01, 53.35, 50.77, 28.59; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1485.

^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S39** and **S40**.

Methyl 1-benzyl-4-methyl-2-phenyl-1,6-dihydropyridine-3-carboxylate (2j)



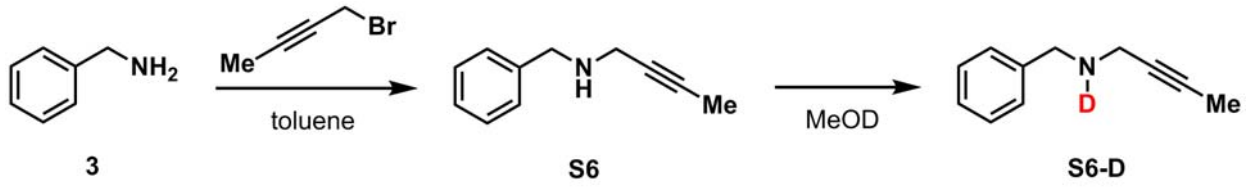
To a solution of *N*-propargylenamine **1j** (70.4 mg, 0.221 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (18.3 mg, 0.022 mmol) in 1,2-dichloroethane (2.2 ml) was stirred at r.t. for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (4.9 mg, 0.0272 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (32.7 mg, 0.221 mmol) was added. Yield of **2j** (89%) was calculated based on ^{1}H-NMR.

2j: TLC R_f = 0.50 (Hex:AcOEt = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36-7.16 (10H, m), 4.81-4.77 (1H, m), 4.11 (2H, s), 3.93-3.91 (2H, m), 3.22 (3H, s), 2.06-2.03 (3H, m); ^{13}C-NMR (75 MHz, $CDCl_3$): 168.82, 156.49, 137.81, 136.83, 133.66, 128.85, 128.69, 128.58, 128.26, 127.38, 127.05, 106.83, 105.17, 55.21, 50.20, 48.85, 21.01.

^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixture including the internal standard are shown in Figure **S41** and **S42**.

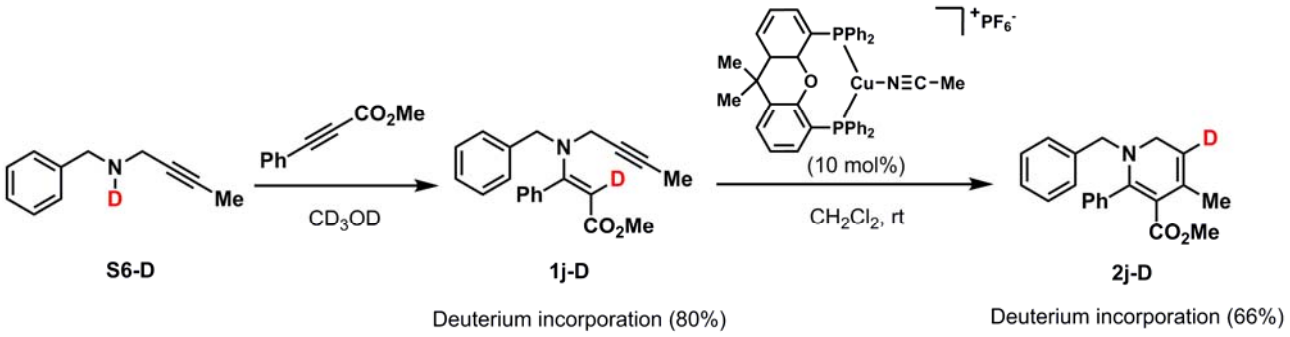
Cu-catalyzed cyclization of a deuterium labeled *N*-propargylenamine

N-Benzylprop-2-yn-1-amine-d1 (S9)



To a solution of benzyl amine (2.34 ml, 21.4 mmol) in toluene (4.2 ml) was added 1-bromo-2-butyne (0.380 ml, 4.34 mmol) and stirred at r.t. for 14 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **S6** (636 mg, 3.99 mmol, 92%). The amine **S6** (301 mg, 1.89 mmol) was then dissolved in CH_3OD (3.5 ml) and stirred at r.t. for 1 h, and after concentrated *in vacuo*, treated again with CH_3OD (3.0 ml) at r.t. for further 1 h. Removal of the solvent *in vacuo* afforded **S6-D** (240 mg, 1.50 mmol, 79%).

Methyl 1-benzyl-4-methyl-2-phenyl-1,6-dihydropyridine-3-carboxylate-5-d1 (2j-D)



To a solution of benzyl amine **S6-D** (274 mg, 1.71 mmol) in CD_3OD (1.6 ml) was added methyl 3-phenylpropiolate (0.260 ml, 1.76 mmol) and stirred at 70 °C for 10 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1j-D** (482 mg, 1.51 mmol, 88%). Deuterium incorporation (80%) at C3 proton was determined based on ^{1}H-NMR analysis.

A solution of *N*-propargylenamine **1j-D** (70.1 mg, 0.219 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (18.3 mg, 0.0219 mmol) in dichloromethane (2.2 ml) was stirred at r.t. for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (5.0 mg, 0.0277 mmol) to deactivate the copper catalyst.

After concentration *in vacuo*, 4-nitrobenzonitrile (32.4 mg, 0.219 mmol) was added as an internal standard. Yield of **2j-D** (83%) as well as percentage of deuteration of C5 proton (66%) were calculated based on ^{1}H-NMR.

^{1}H-NMR spectra of **1j-D** and the crude reaction mixture of **2j-D** including the internal standard are shown in Figure **S43** and **S44**.

References

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[2] Cain, M. F.; Hughes, R. P.; Glueck, D. S.; Golen, J. A.; Moore, C. E., Rheingold, A. L. *Inorg. Chem.* **2010**, *49*, 7650-7662.

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The ^{1}H, ^{13}C-NMR spectra of synthetic compounds.

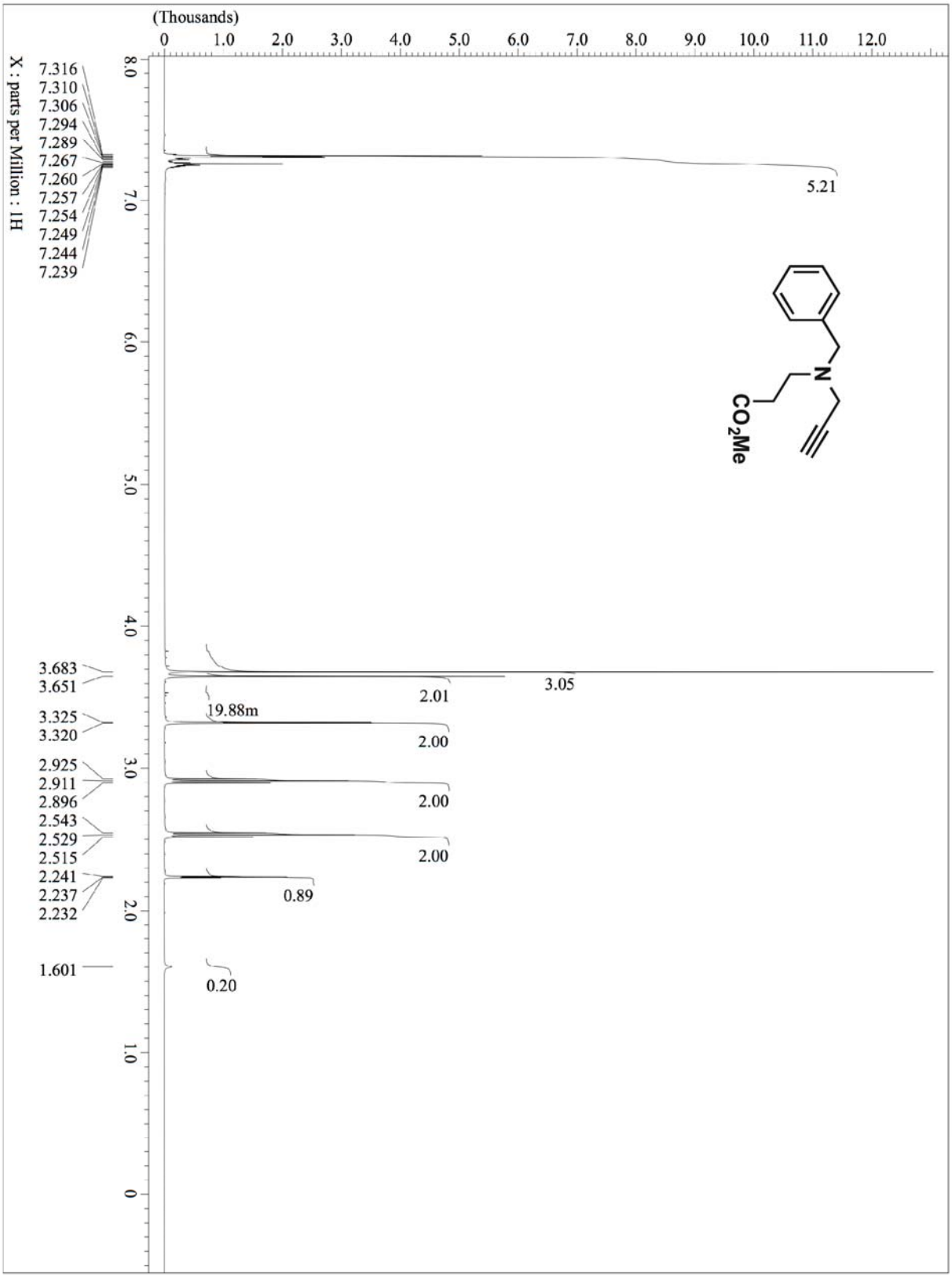

Figure S1. A ^{1}H-NMR spectrum of **4** in $CDCl_3$.

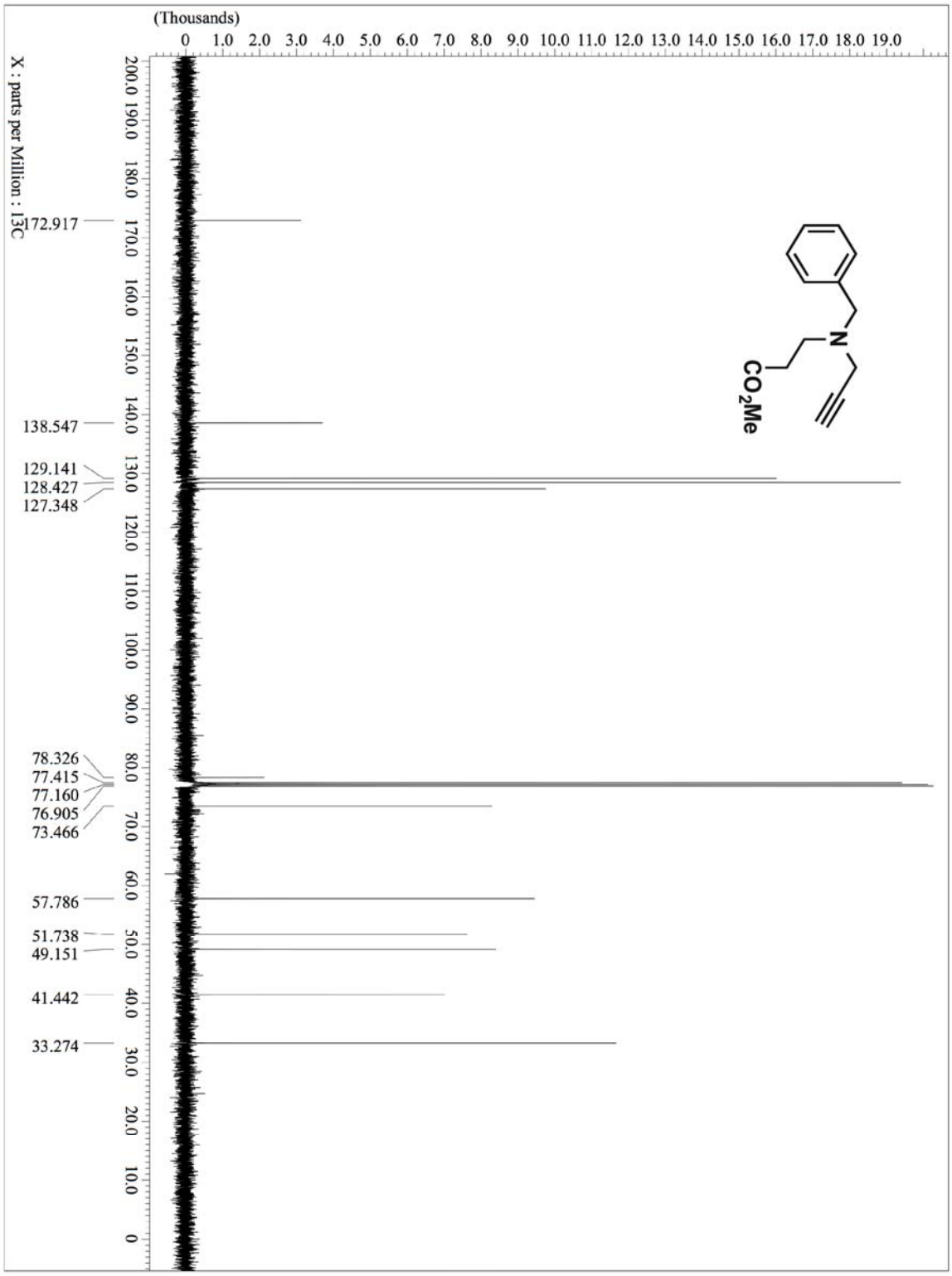

Figure S2. A ^{13}C-NMR spectrum of **4** in $CDCl_3$.

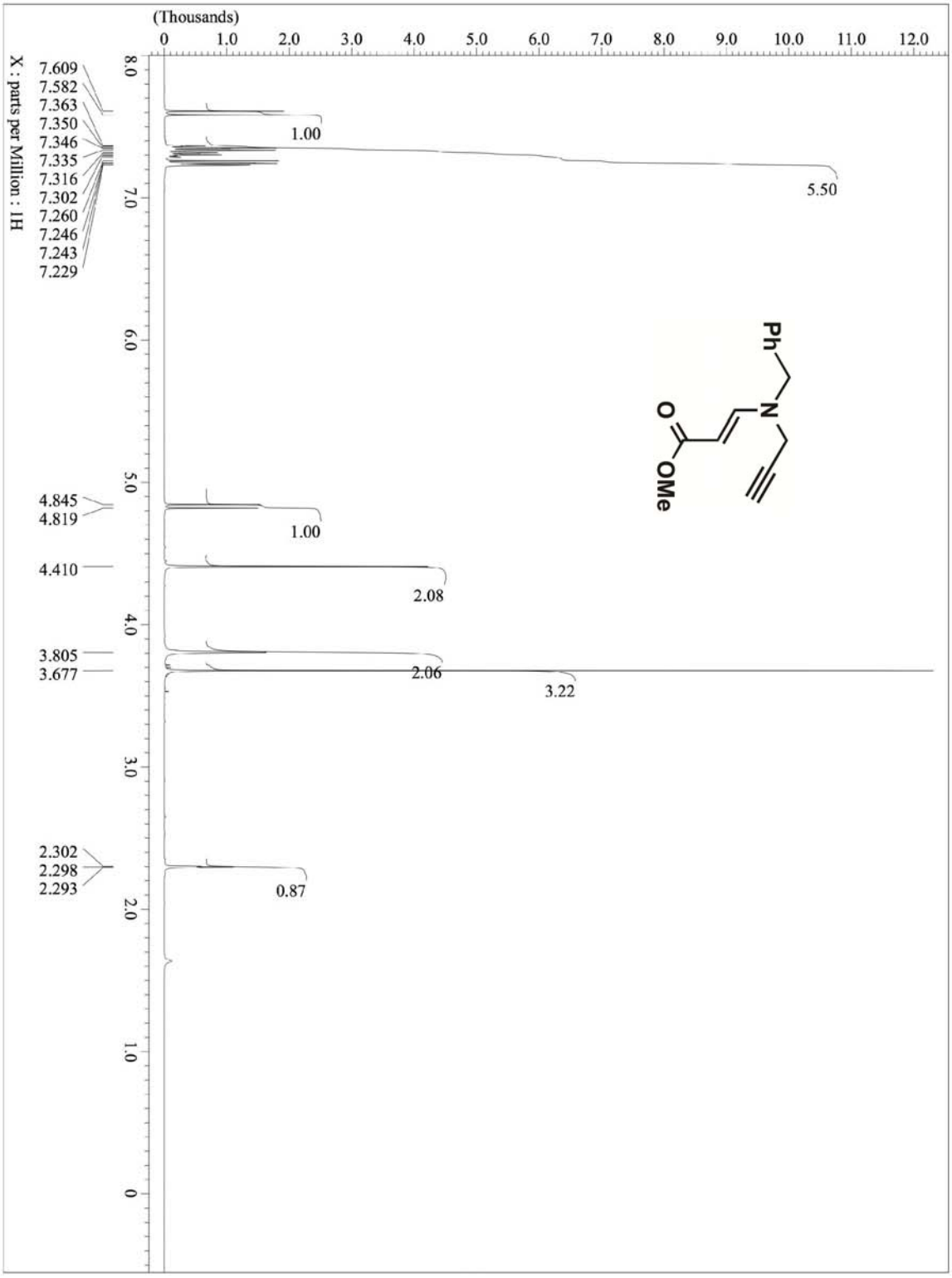

Figure S3. A ^{1}H-NMR spectrum of **1a** in $CDCl_3$.

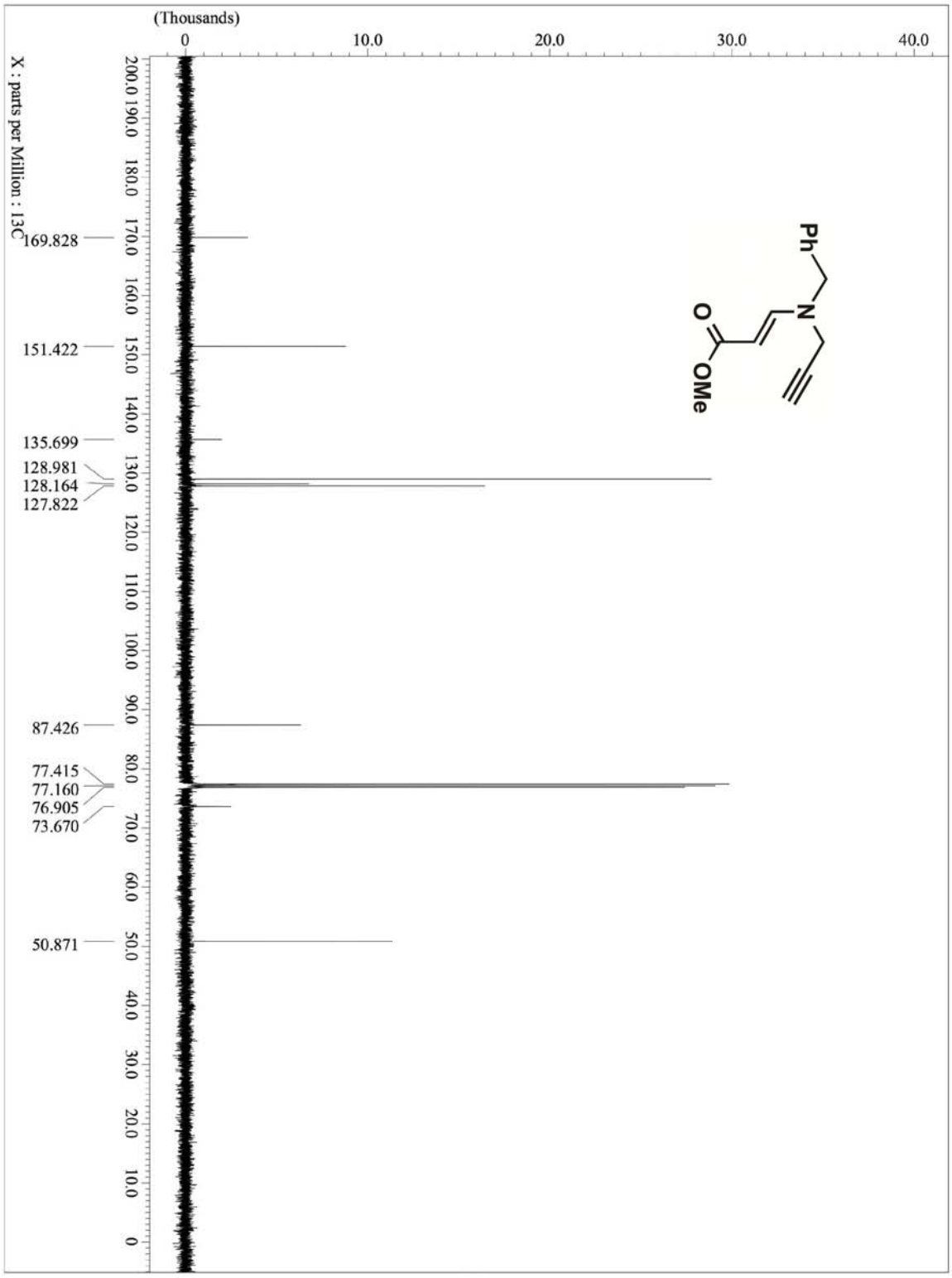

Figure S4. A ^{13}C-NMR spectrum of **1a** in $CDCl_3$.

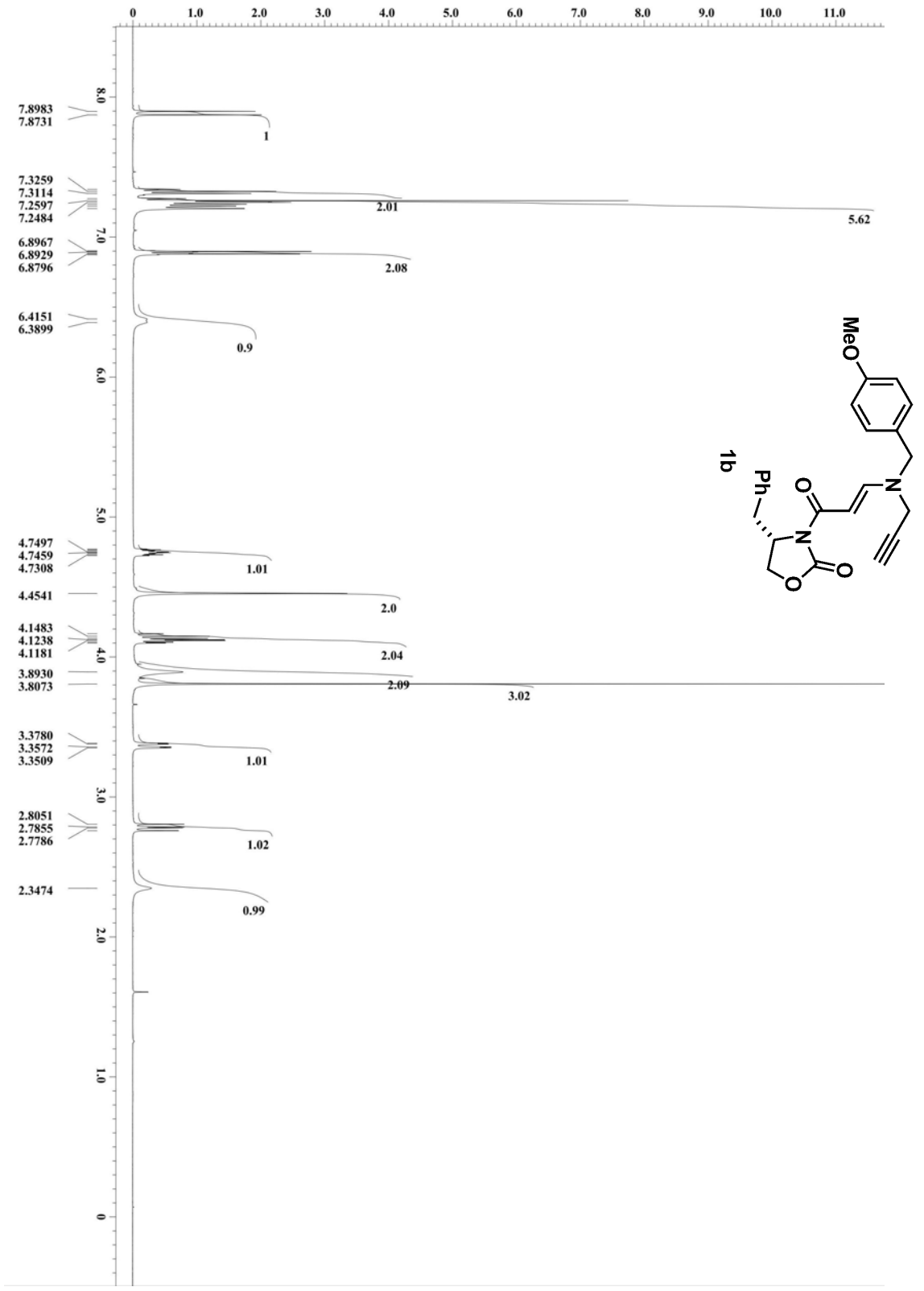

Figure S5. A ^{1}H-NMR spectrum of **1b** in $CDCl_3$.

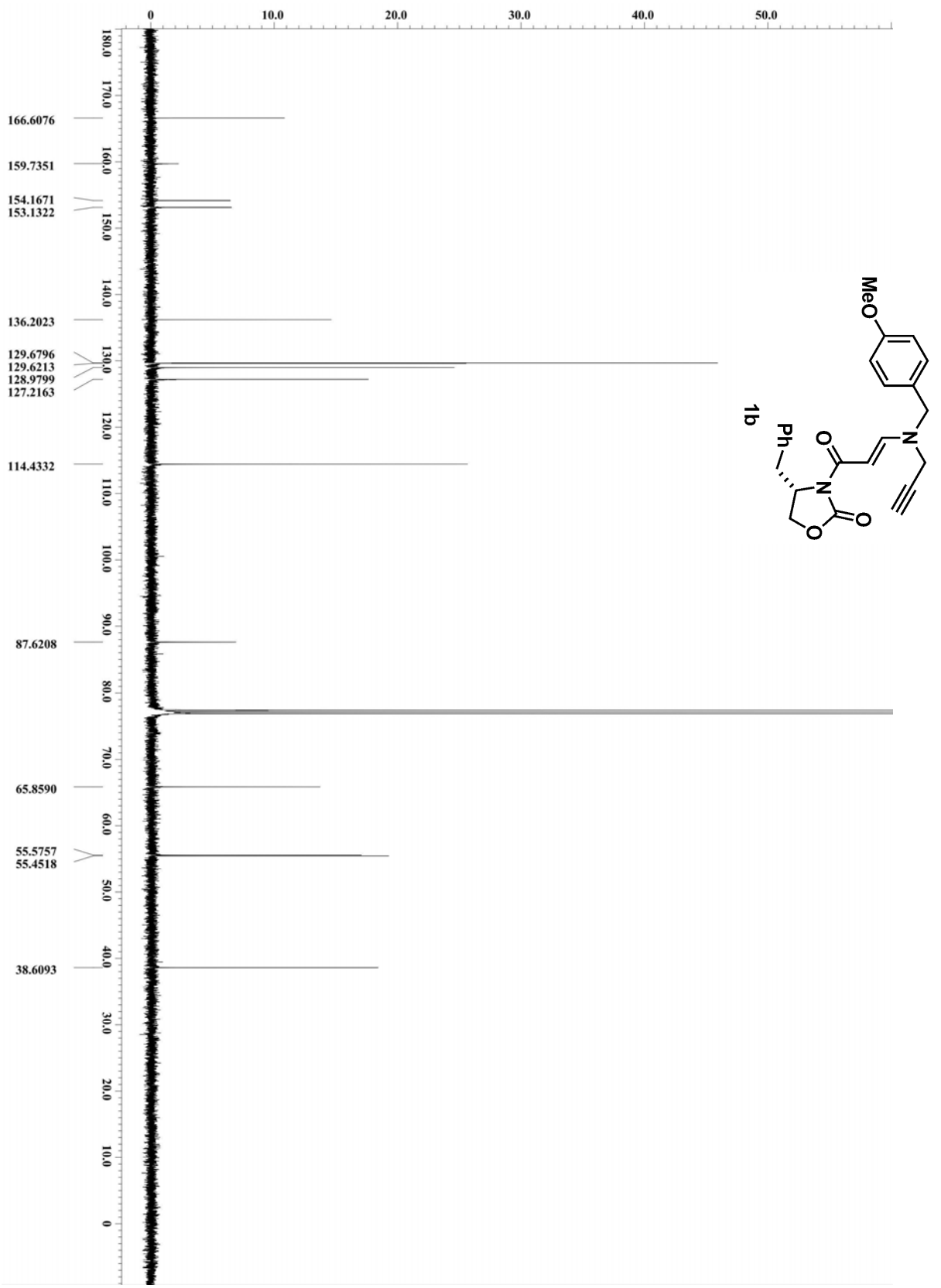

Figure S6. A ^{13}C-NMR spectrum of **1b** in $CDCl_3$.

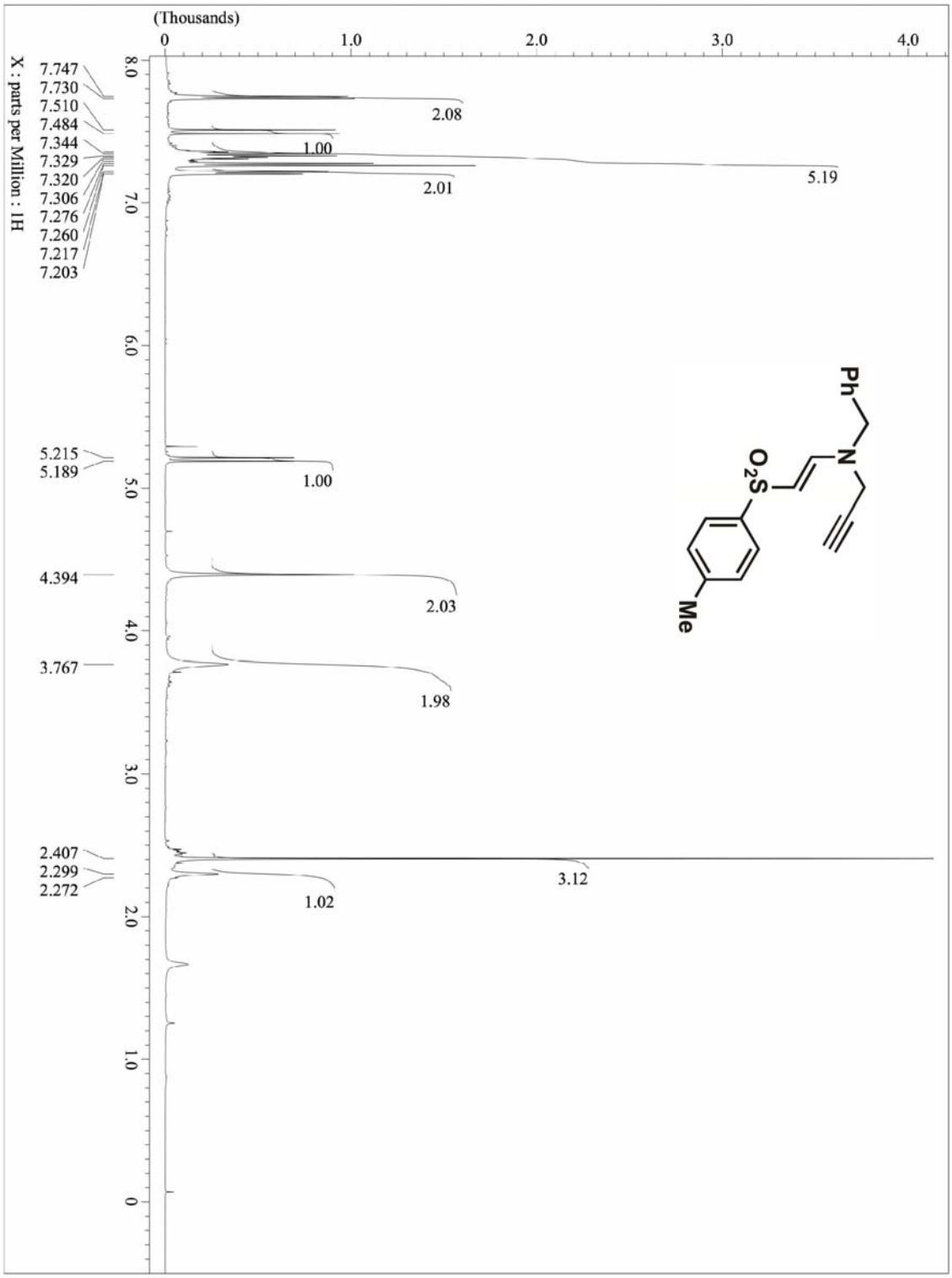

Figure S7. A ^{1}H-NMR spectrum of **1c** in $CDCl_3$.

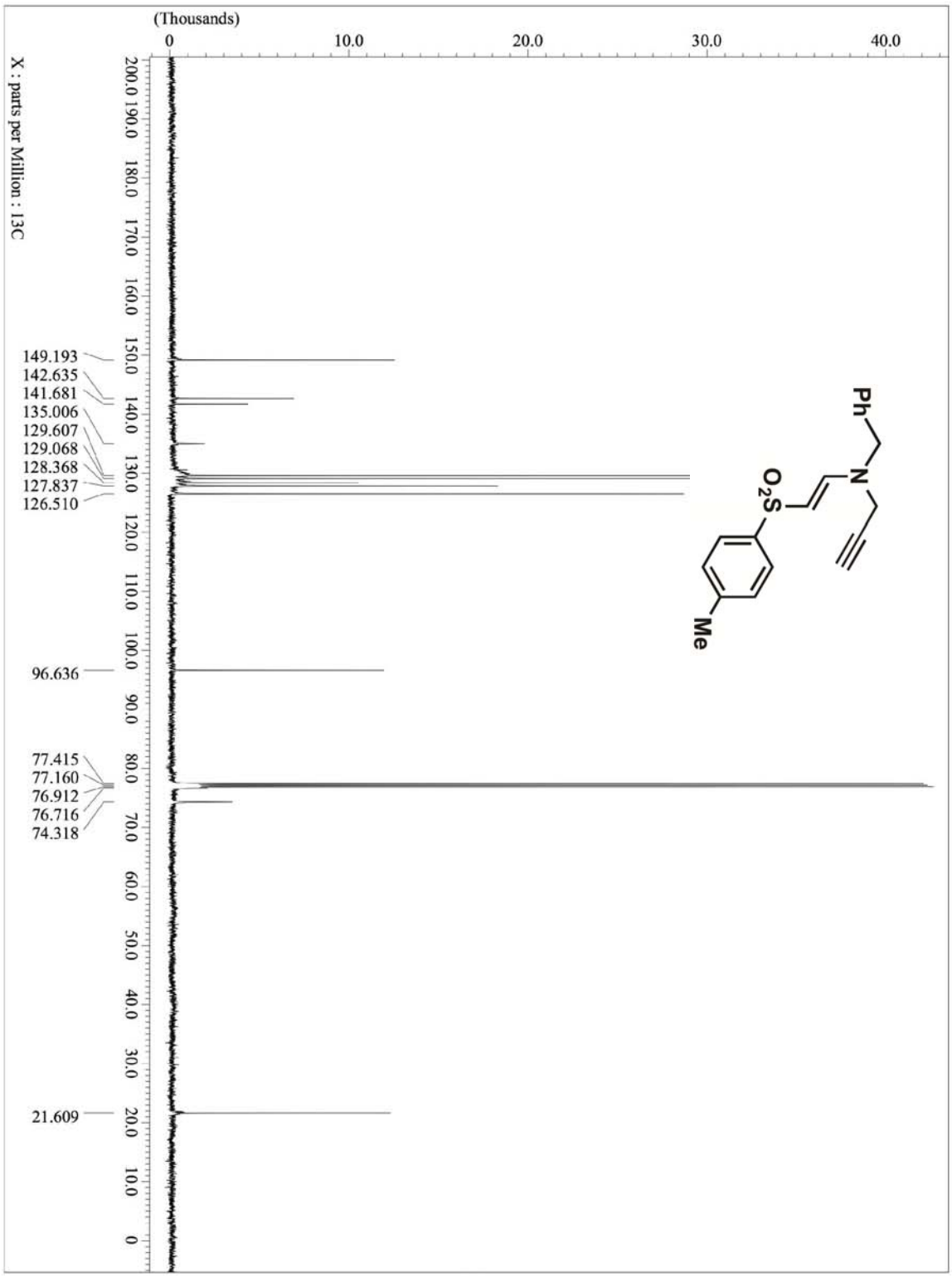

Figure S8. A ^{13}C-NMR spectrum of **1c** in $CDCl_3$.

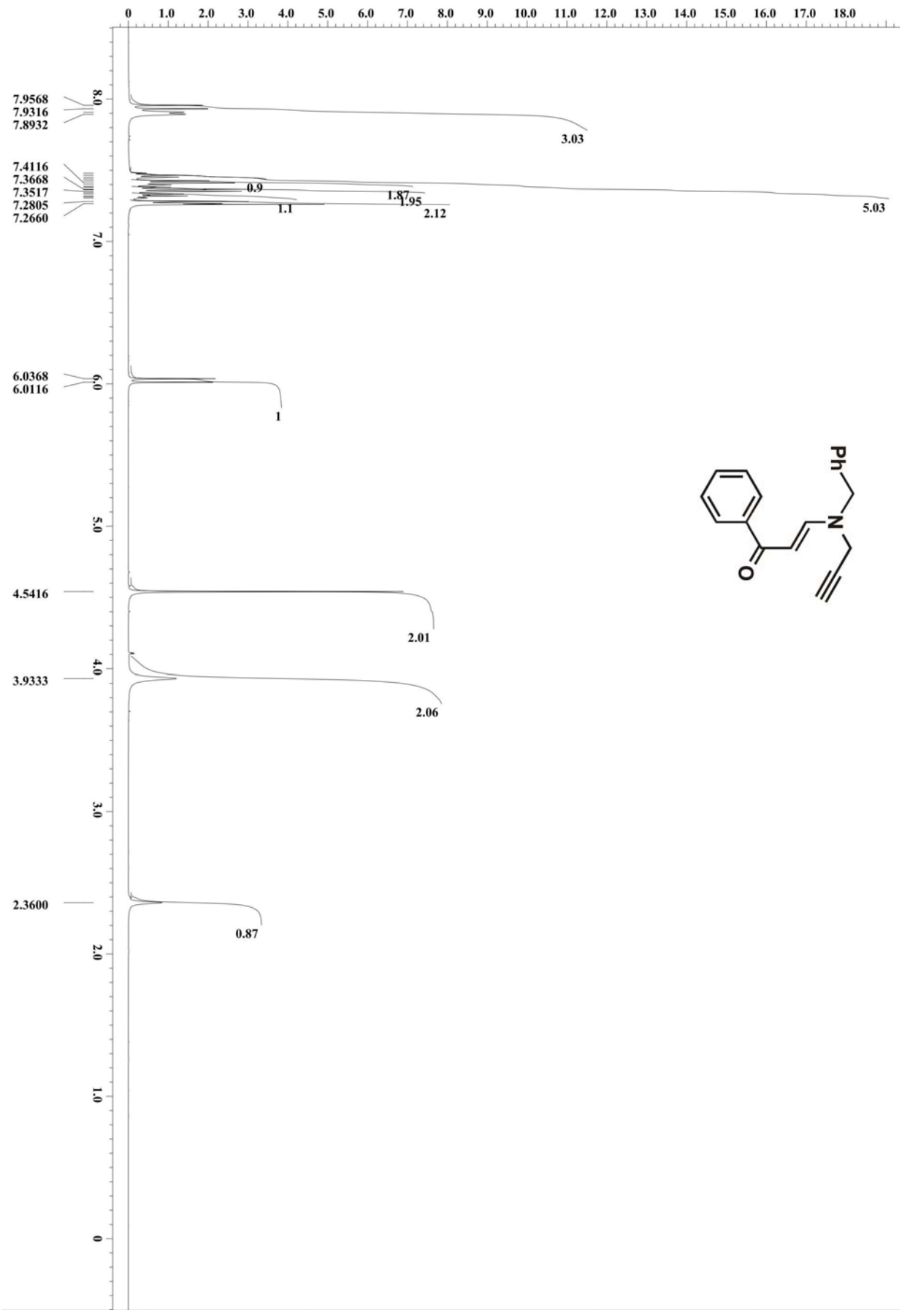

Figure S9. A ^{1}H-NMR spectrum of **1d** in $CDCl_3$.

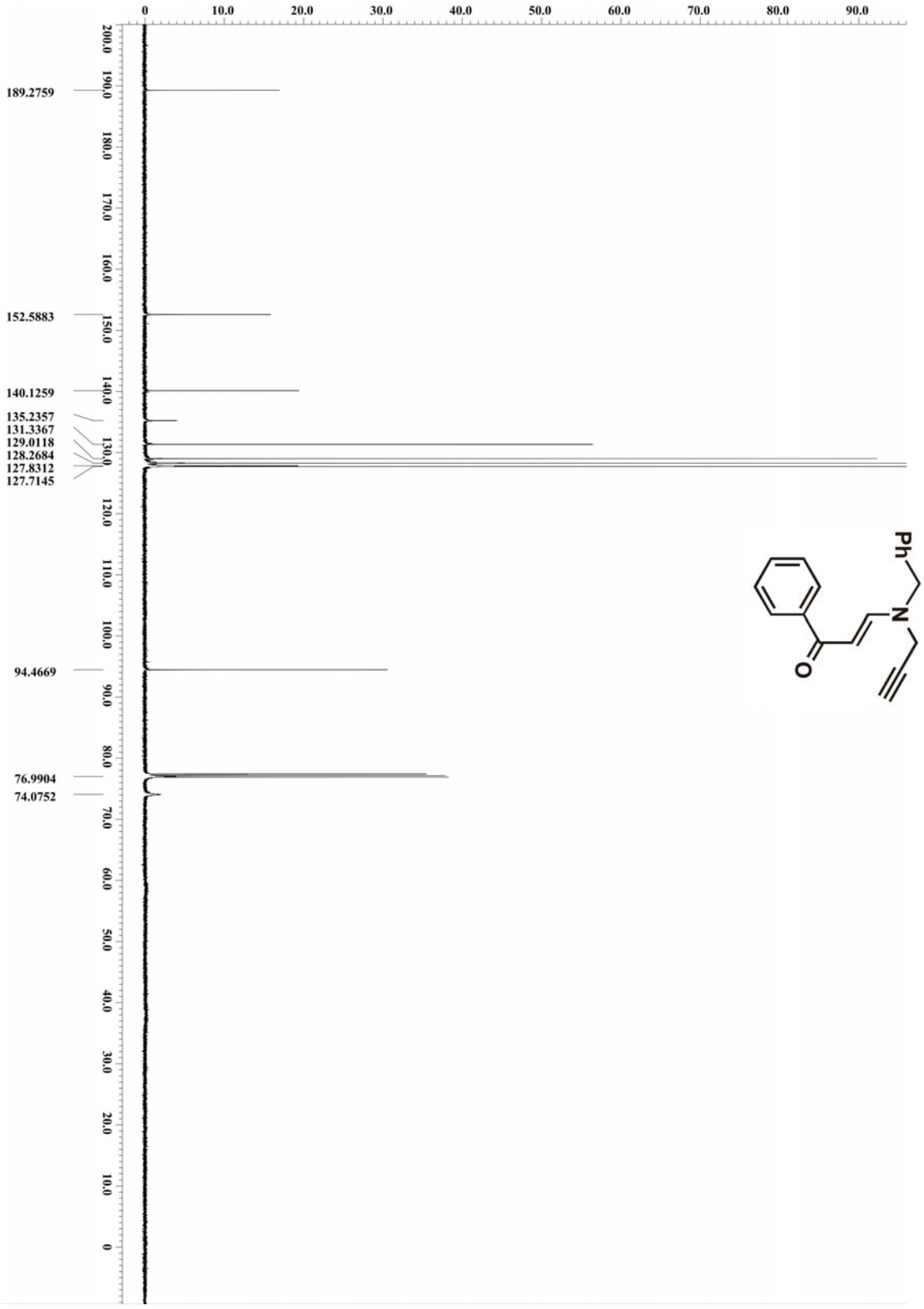

Figure S10. A ^{13}C-NMR spectrum of **1d** in $CDCl_3$.

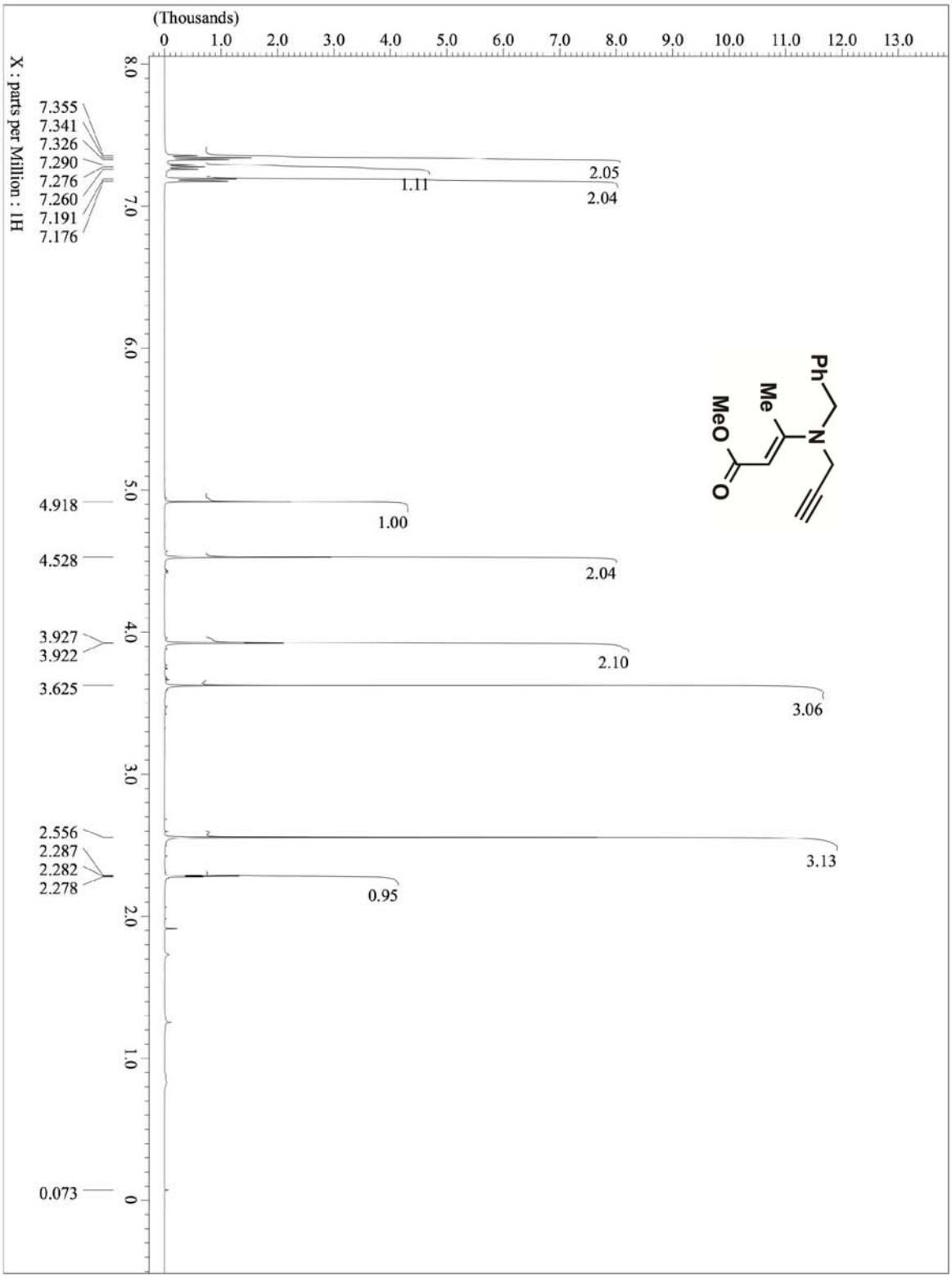

Figure S11. A ^{1}H-NMR spectrum of **1e** in $CDCl_3$.

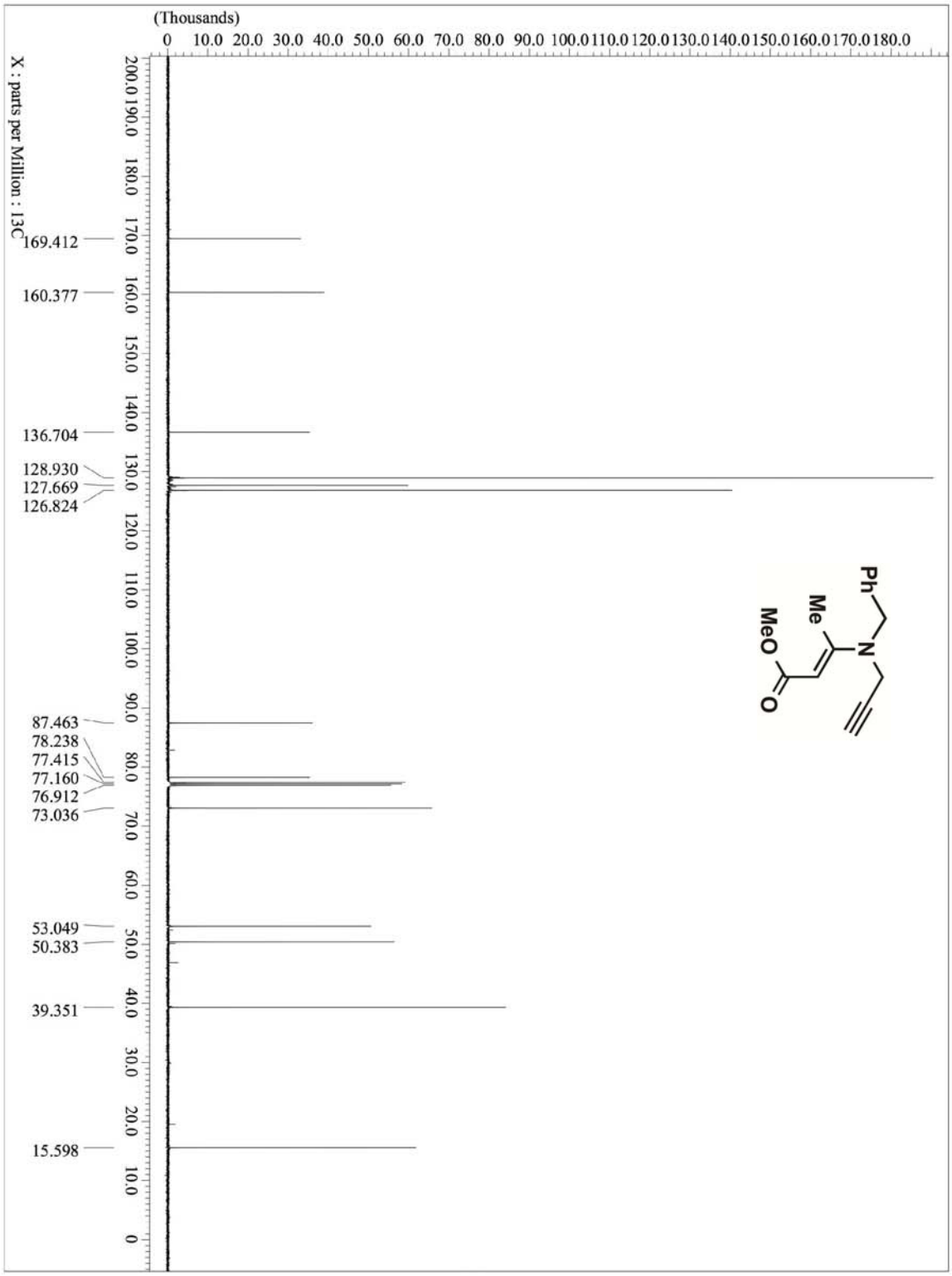

Figure S12. A ^{13}C-NMR spectrum of **1e** in $CDCl_3$.

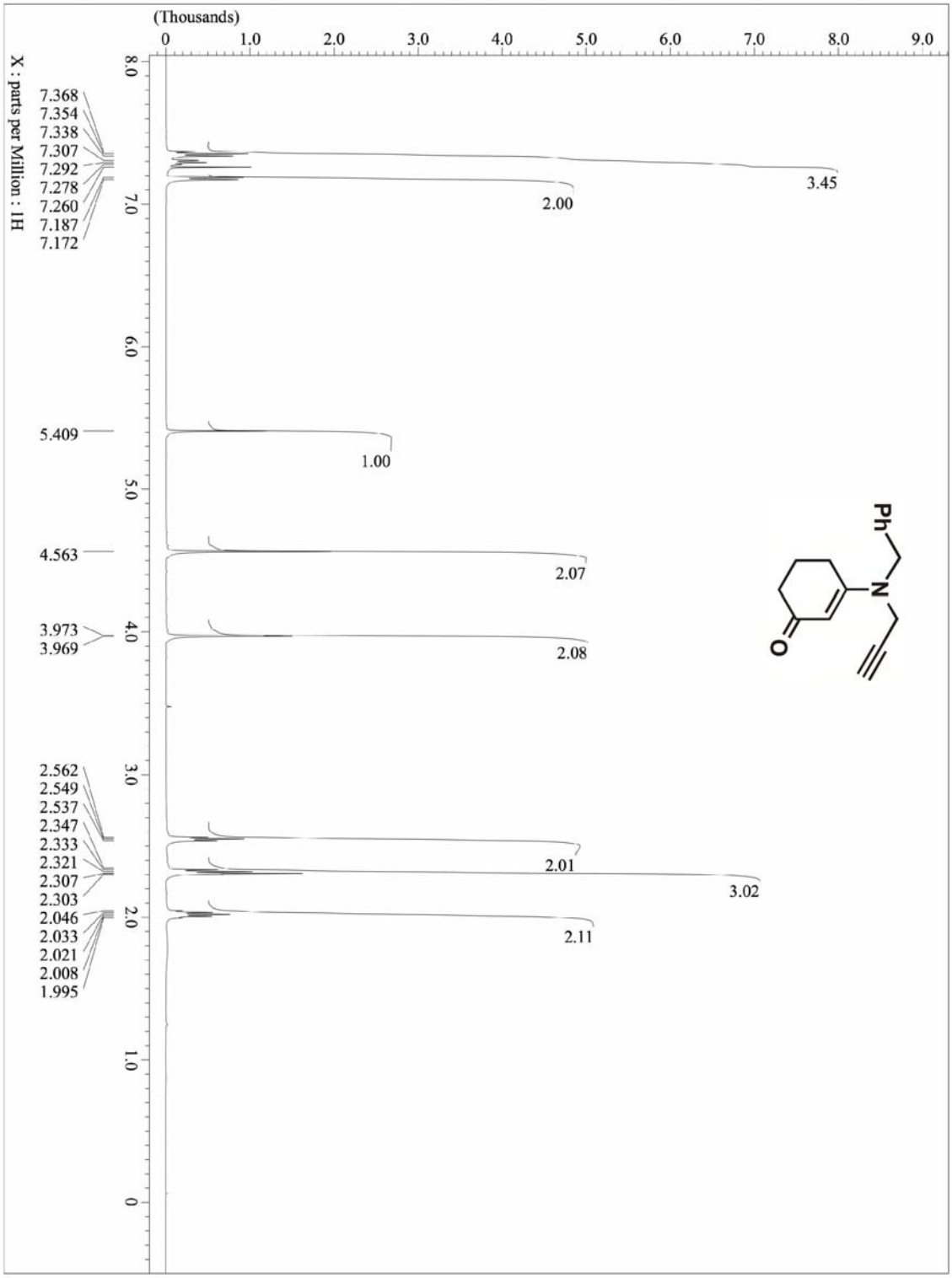

Figure S13. A ^{1}H-NMR spectrum of **1f** in $CDCl_3$.

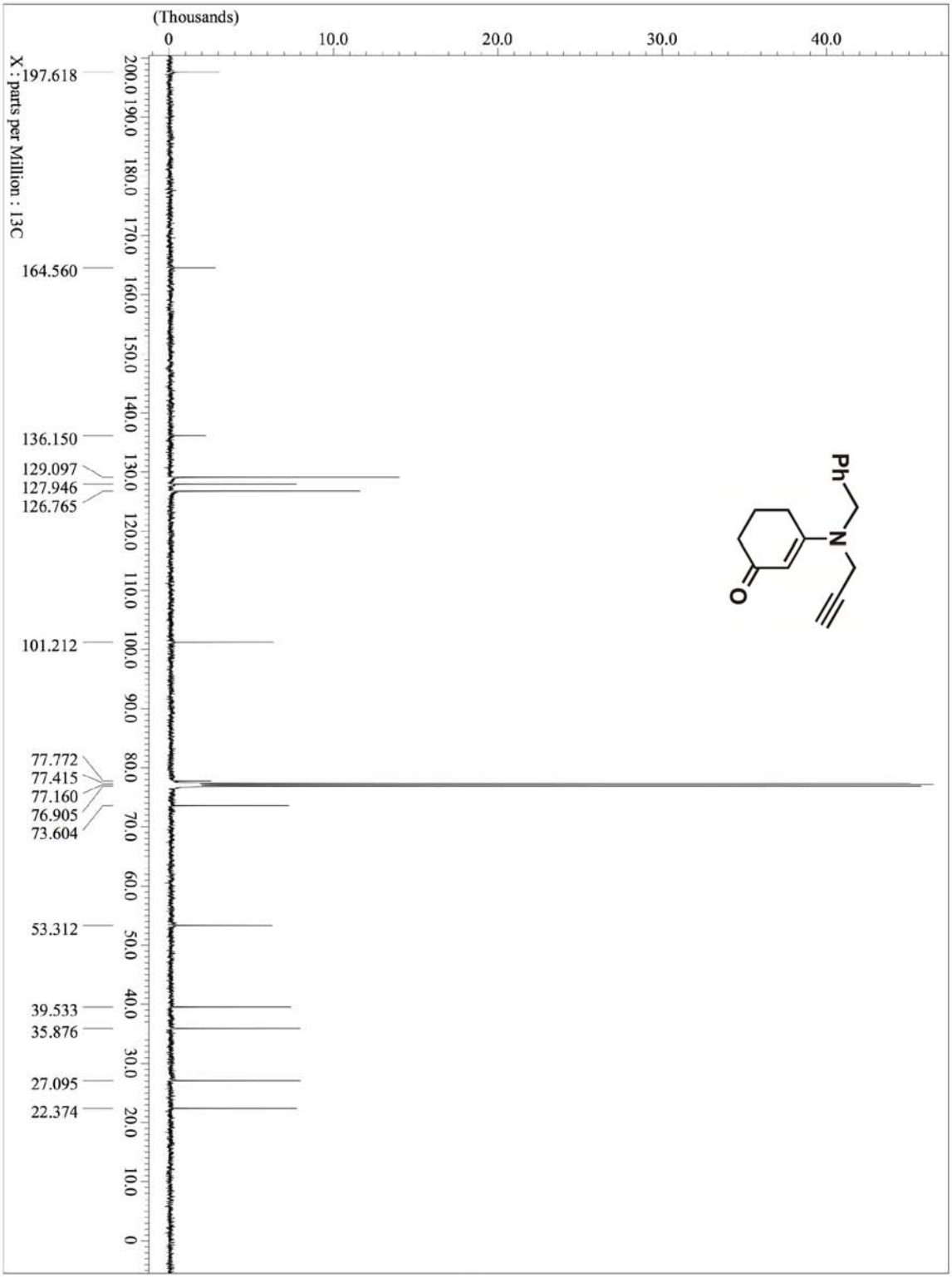

Figure S14. A ^{13}C-NMR spectrum of **1f** in $CDCl_3$.

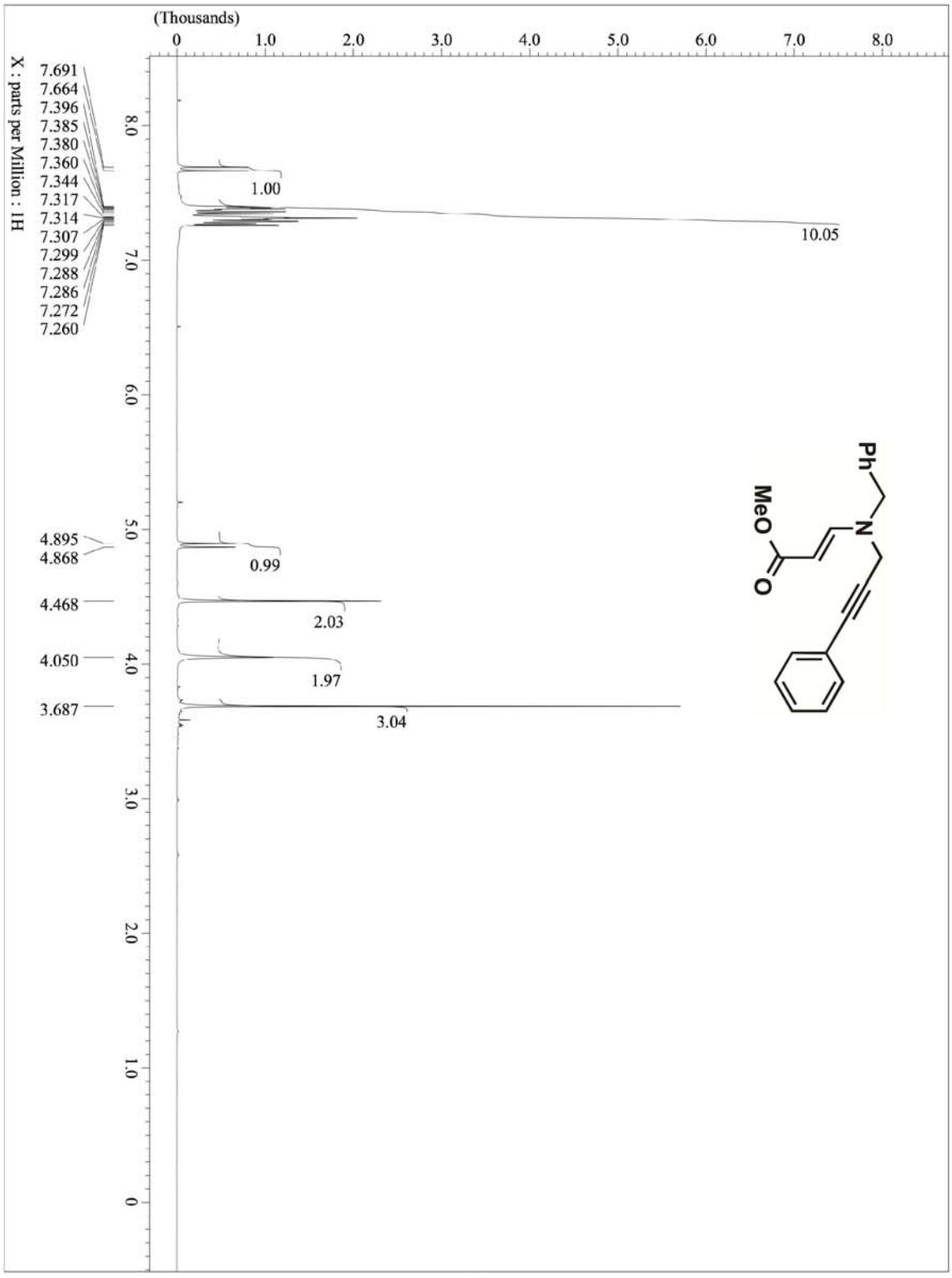

Figure S15. A ^{1}H-NMR spectrum of **1g** in $CDCl_3$.

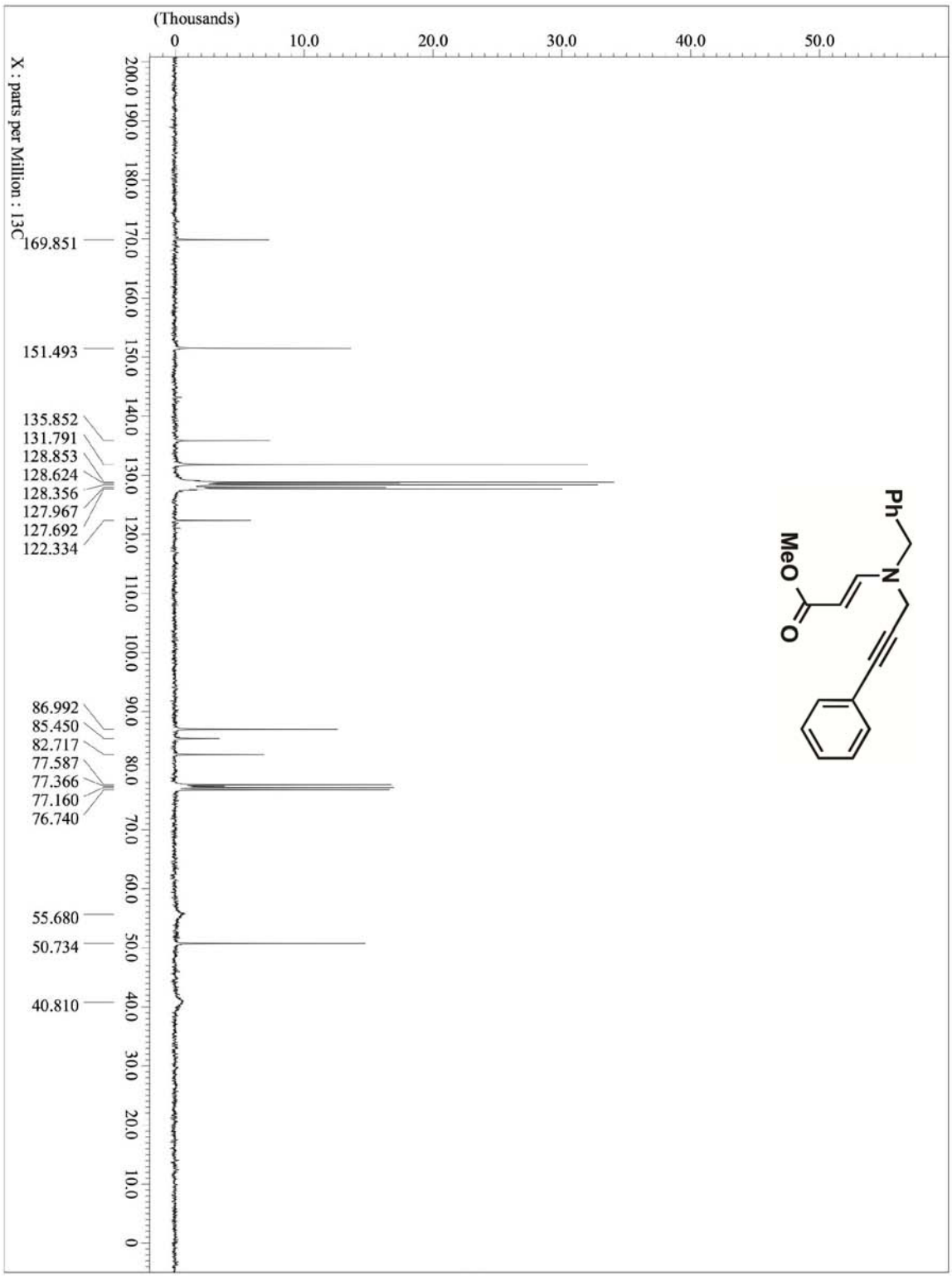

Figure S16. A ^{13}C-NMR spectrum of **1g** in $CDCl_3$.

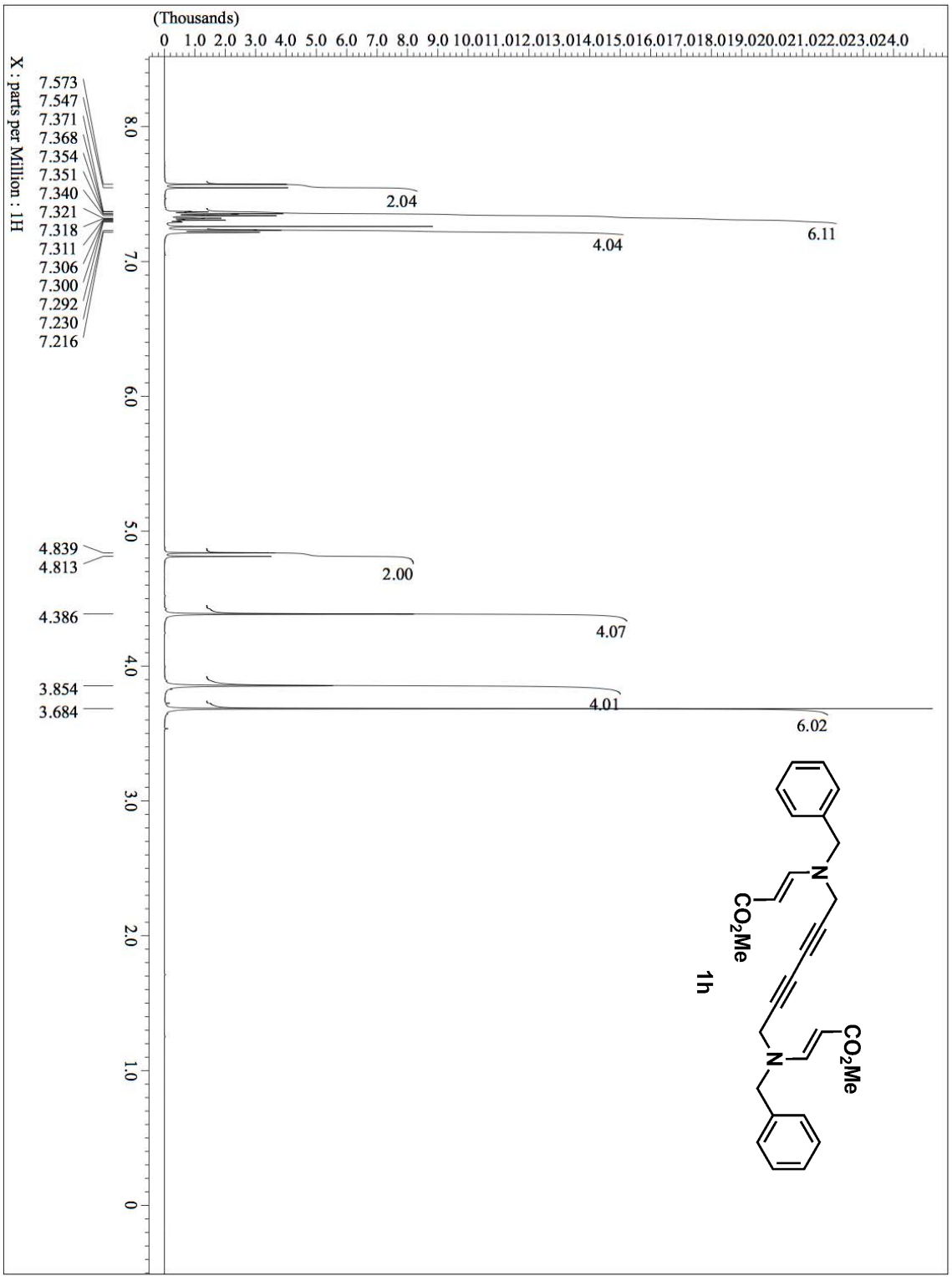

Figure S17. A ^{1}H-NMR spectrum of **1h** in $CDCl_3$.

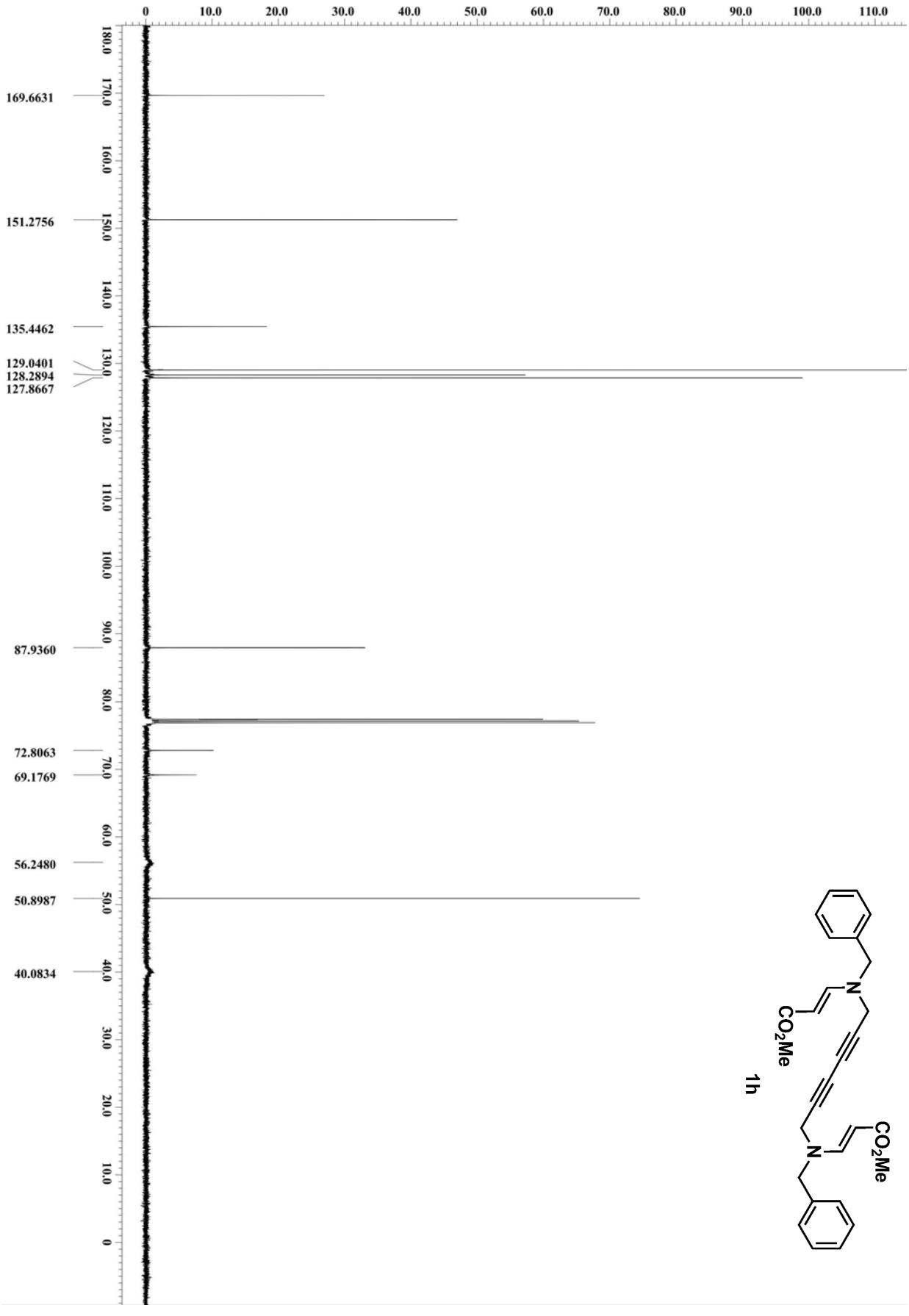

Figure S18. A ^{13}C-NMR spectrum of **1h** in $CDCl_3$.

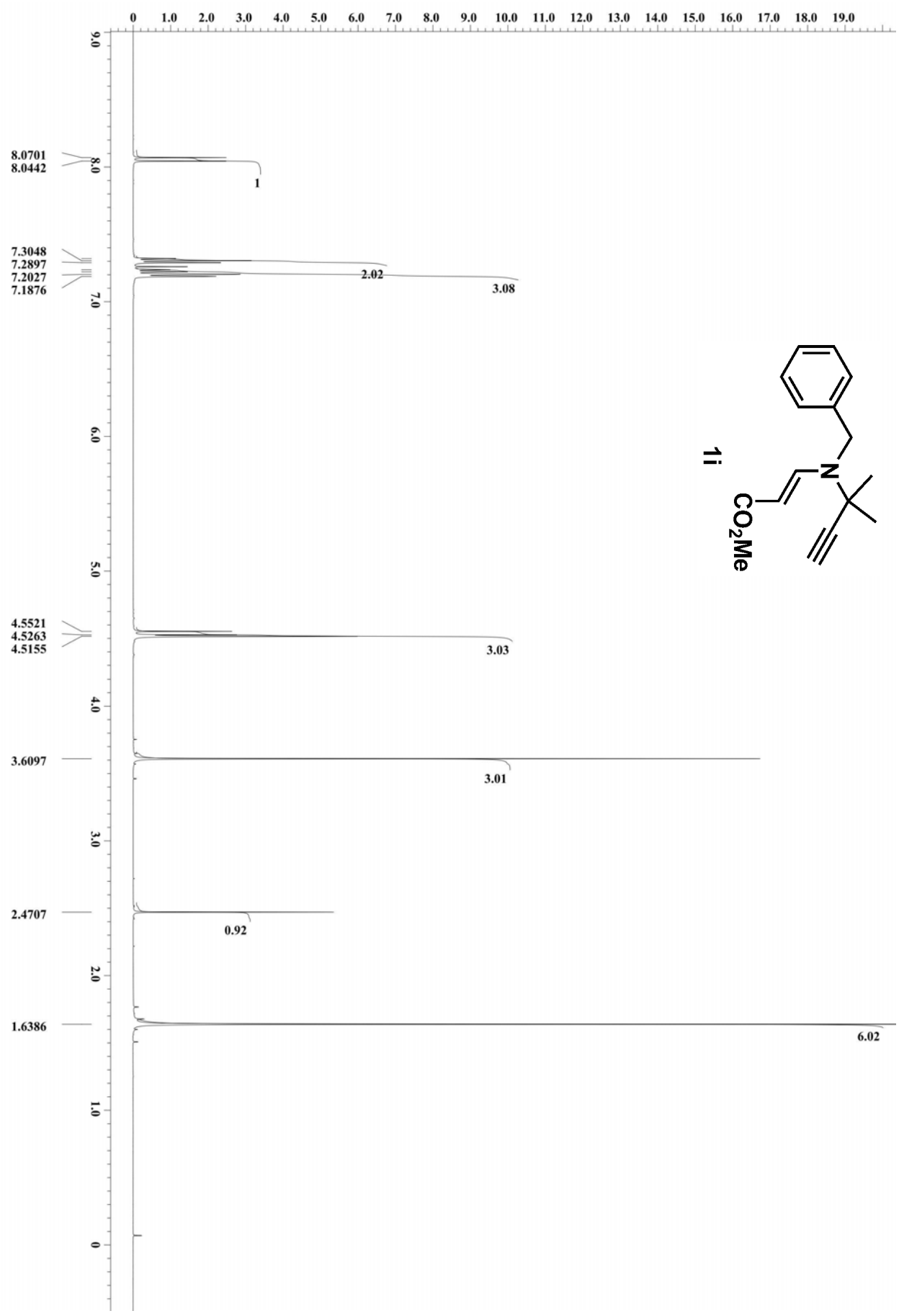

Figure S19. A ^{1}H-NMR spectrum of **1i** in $CDCl_3$.

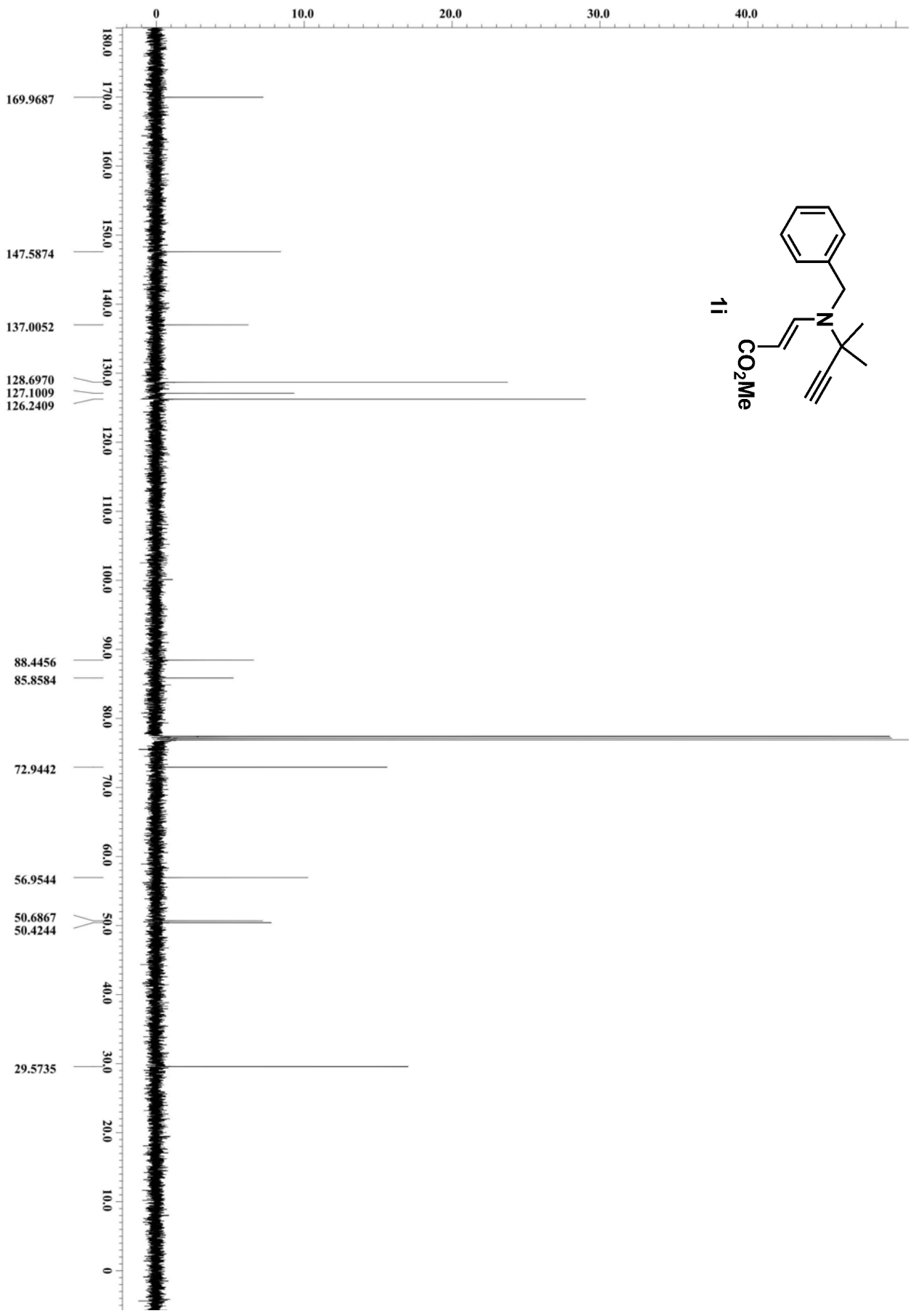

Figure S20. A ^{13}C-NMR spectrum of **1i** in $CDCl_3$.

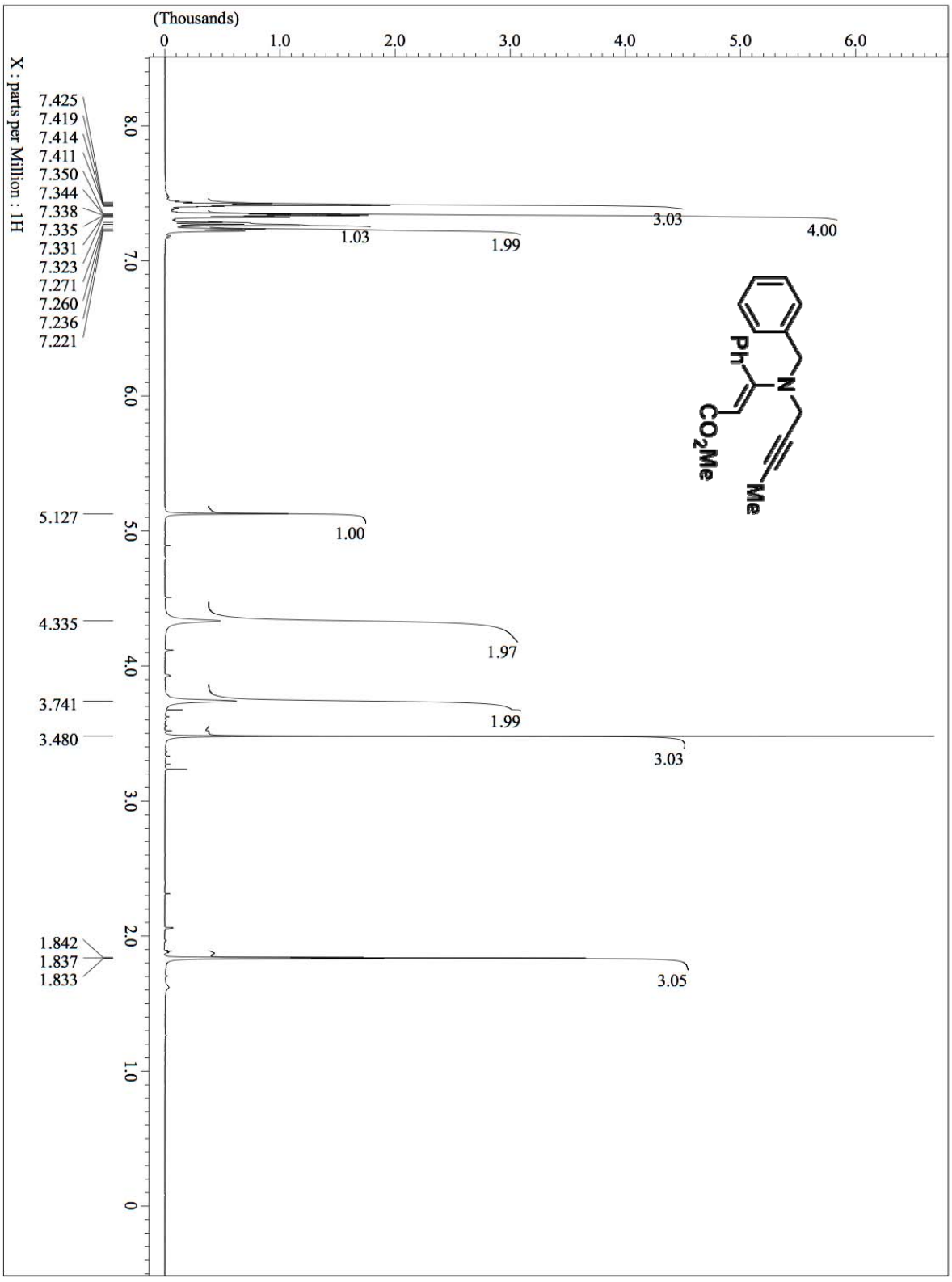

Figure S21. A ^{1}H-NMR spectrum of **1j** in $CDCl_3$.

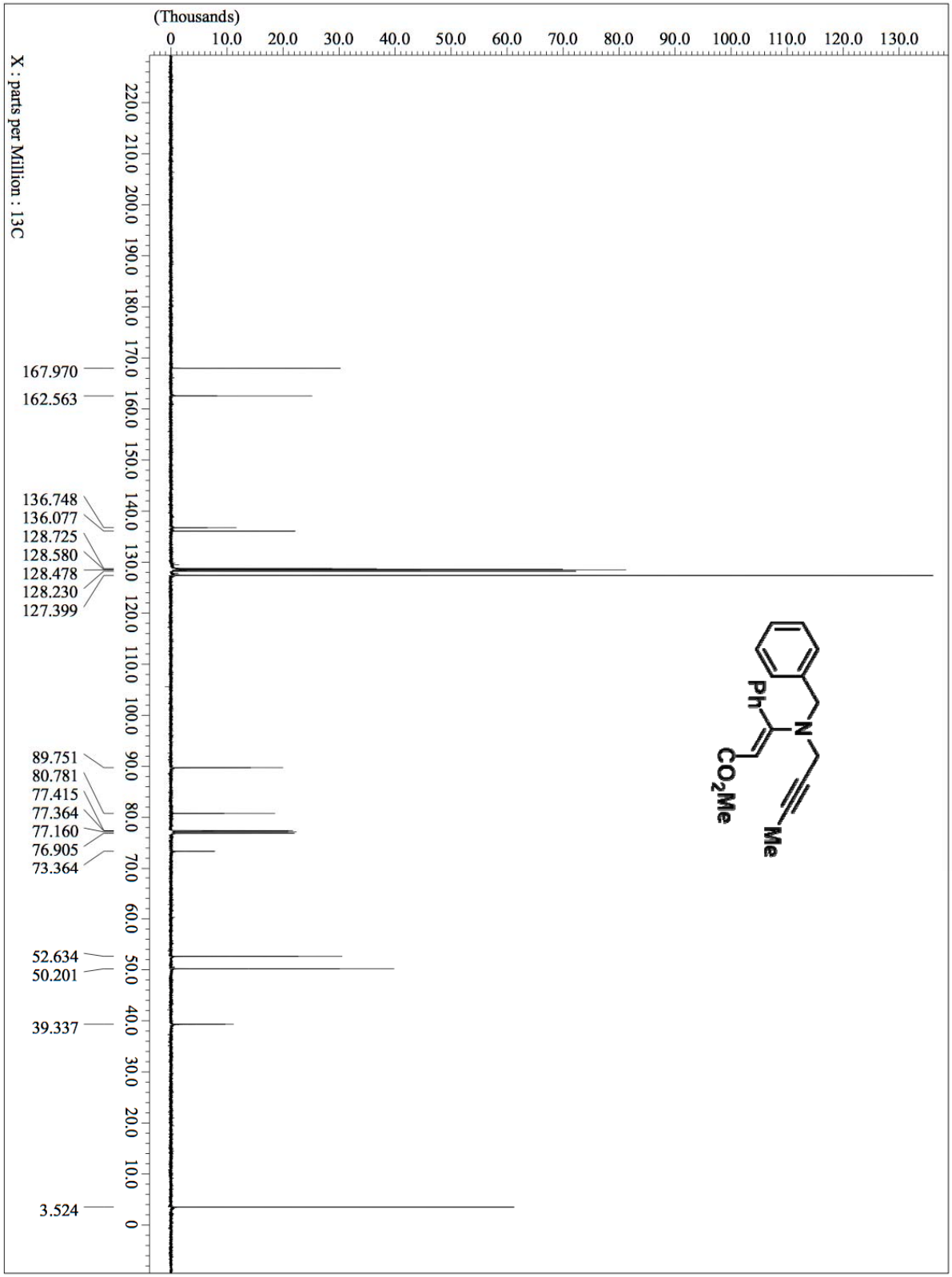

Figure S22. A ^{13}C-NMR spectrum of **1j** in $CDCl_3$.

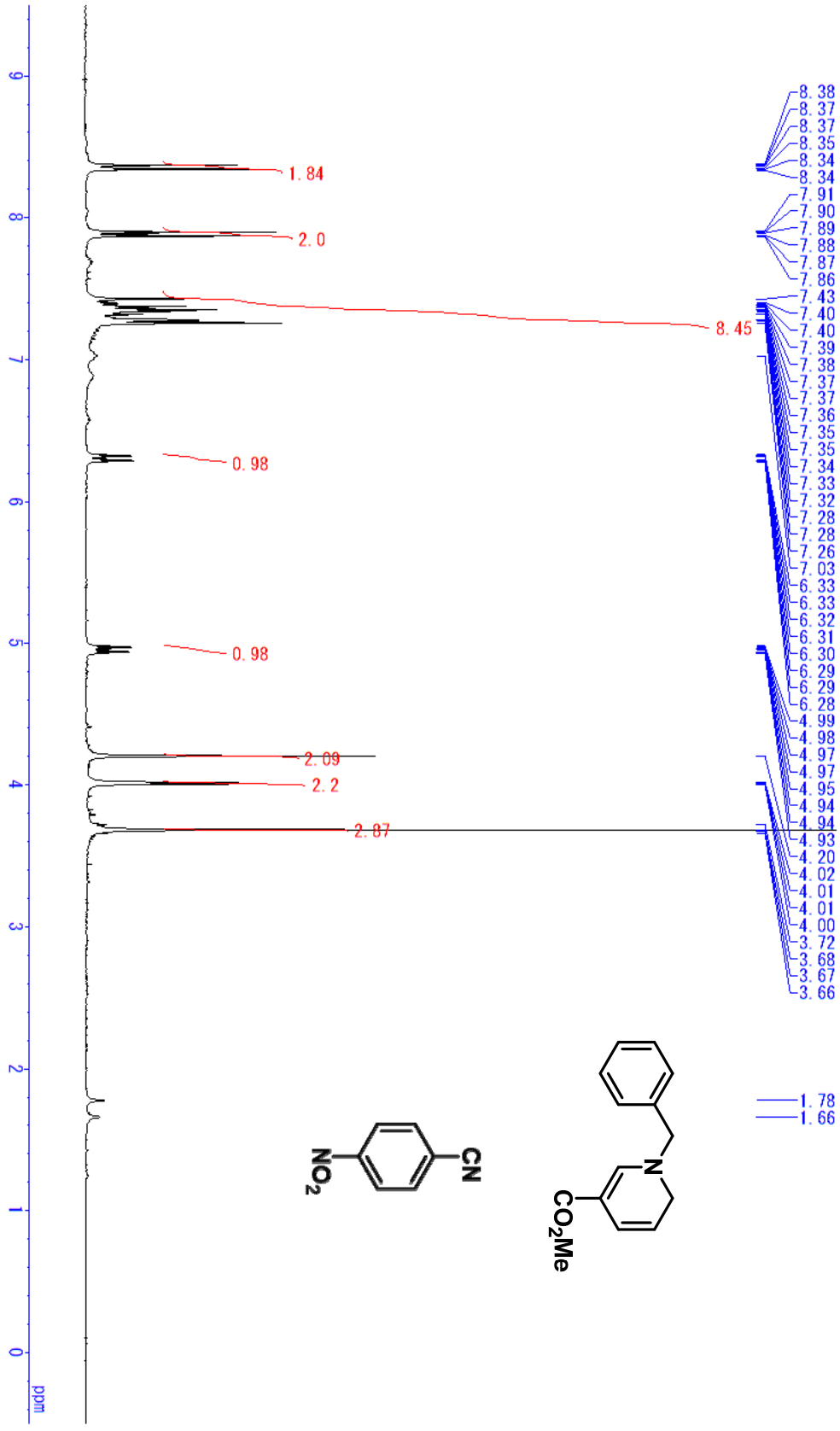

Figure S23. A ^{1}H-NMR spectrum for the crude mixture of **2a** in $CDCl_3$.

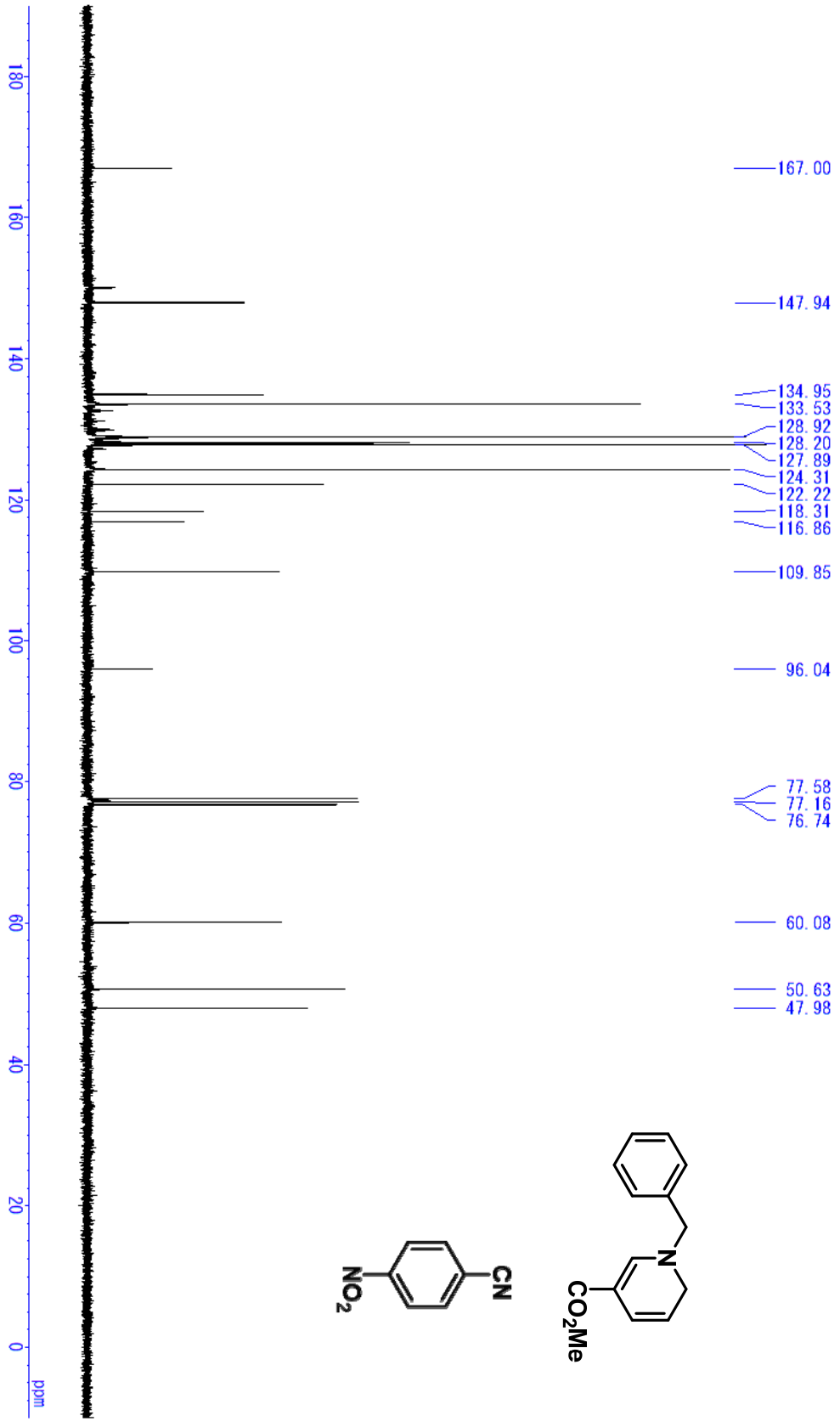

Figure S24. A ^{13}C-NMR spectrum for the crude mixture of **2a** in $CDCl_3$.

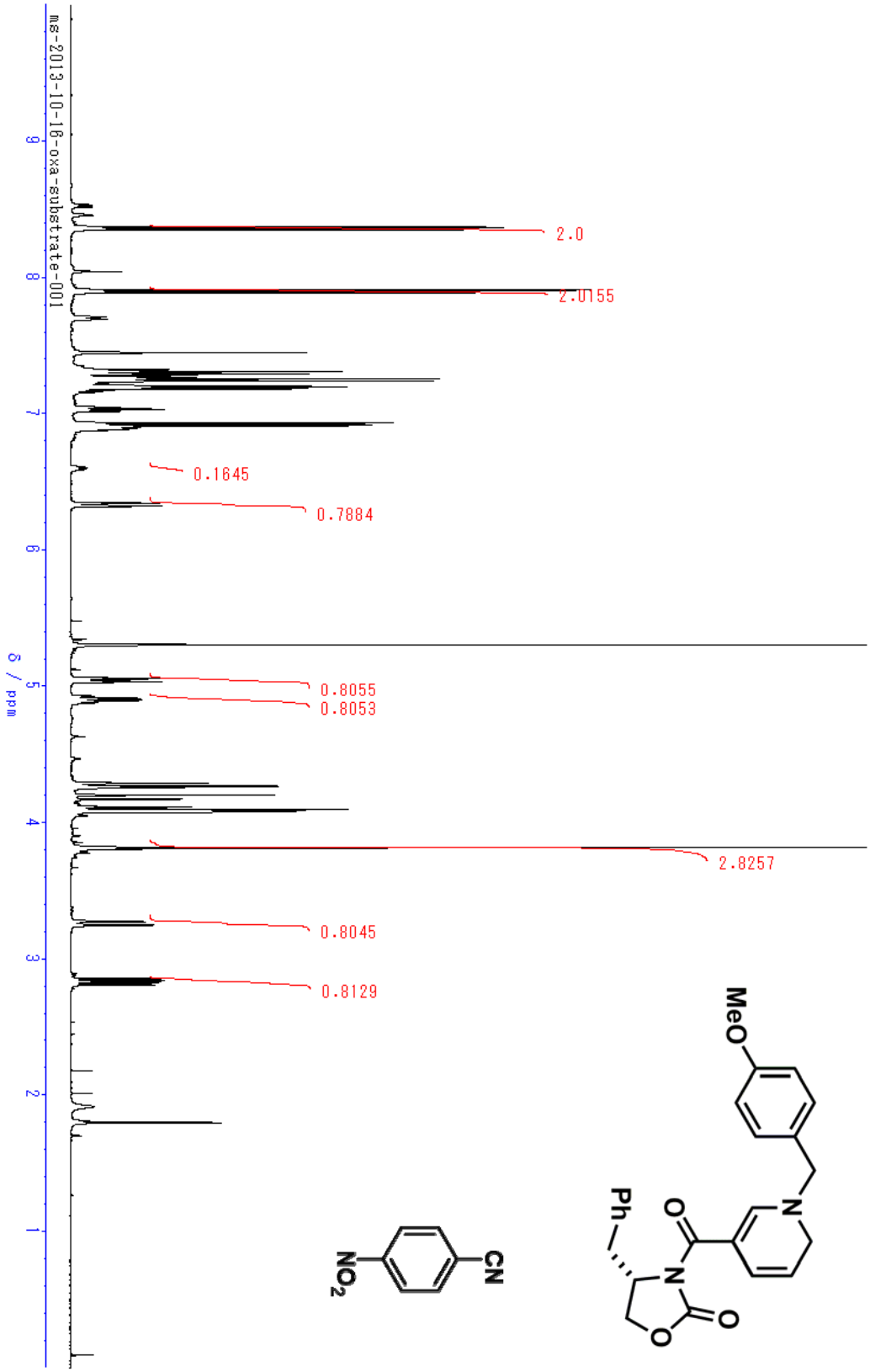

Figure S25. A ^{1}H-NMR spectrum for the crude mixture of **2b** in $CDCl_3$.

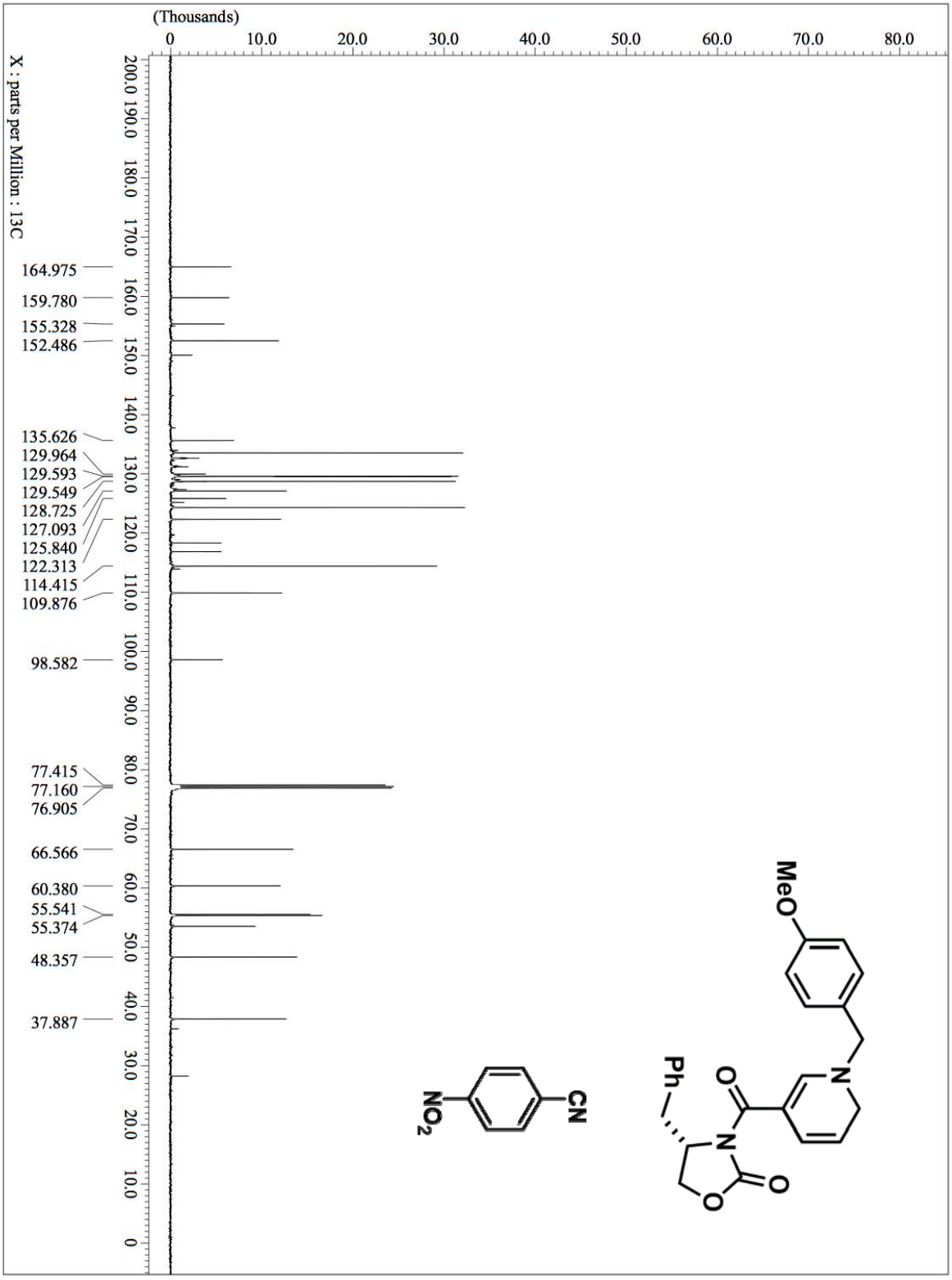

Figure S26. A ^{13}C-NMR spectrum for the crude mixture of **2b** in $CDCl_3$.

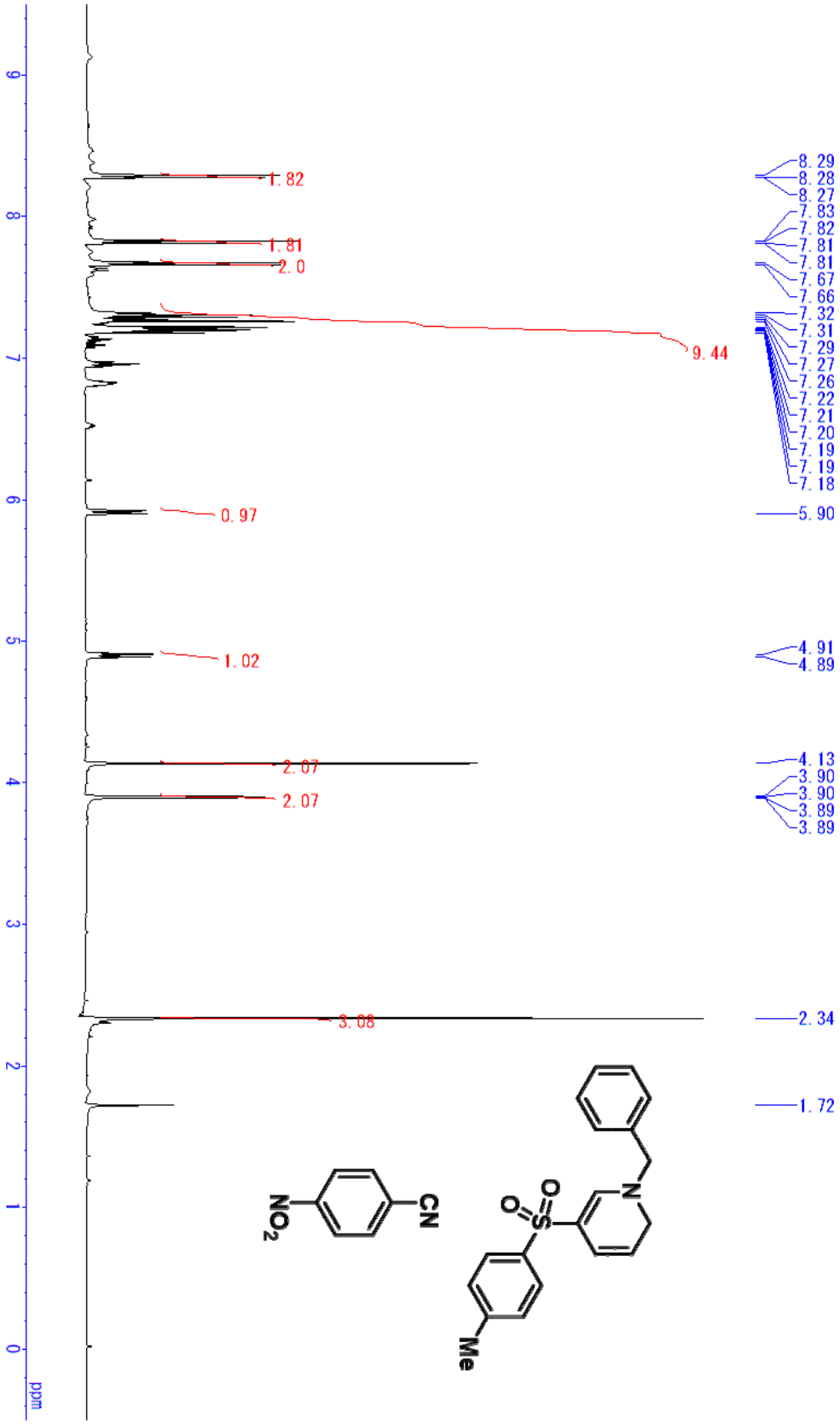

Figure S27. A ^{1}H-NMR spectrum for the crude mixture of **2c** in $CDCl_3$.

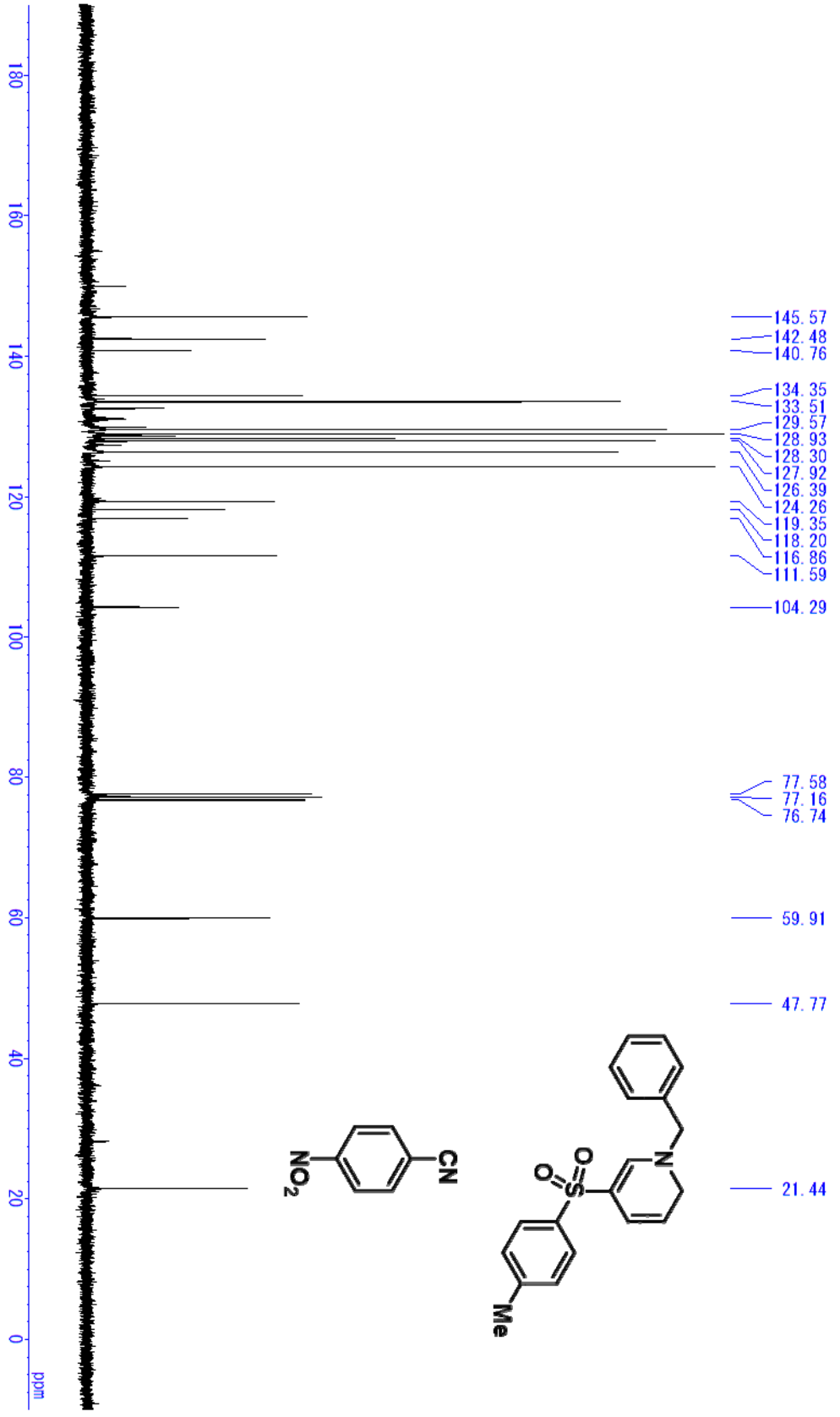

Figure S28. A ^{13}C-NMR spectrum for the crude mixture of **2c** in $CDCl_3$.

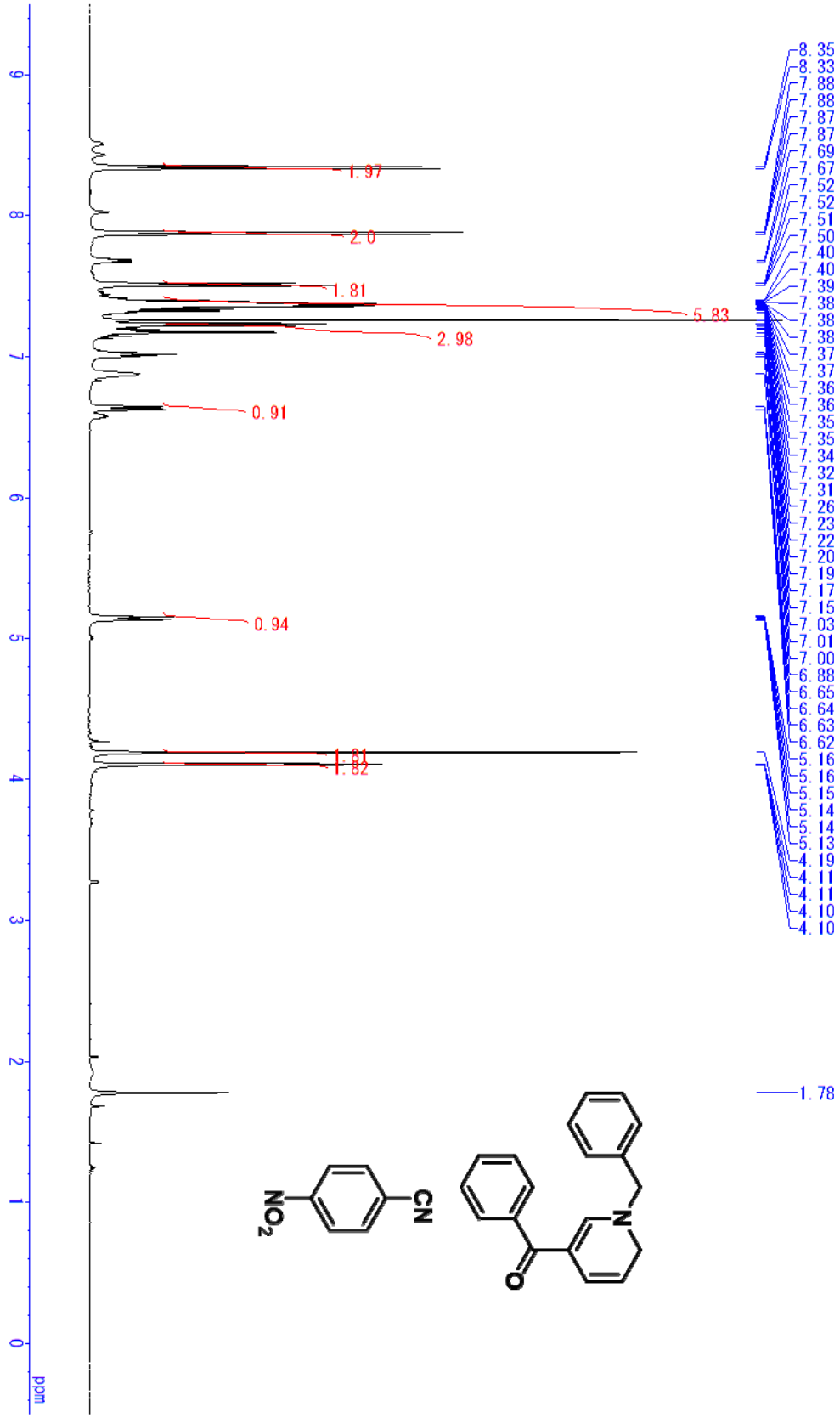

Figure S29. A ^{1}H-NMR spectrum for the crude mixture of **2d** in $CDCl_3$.

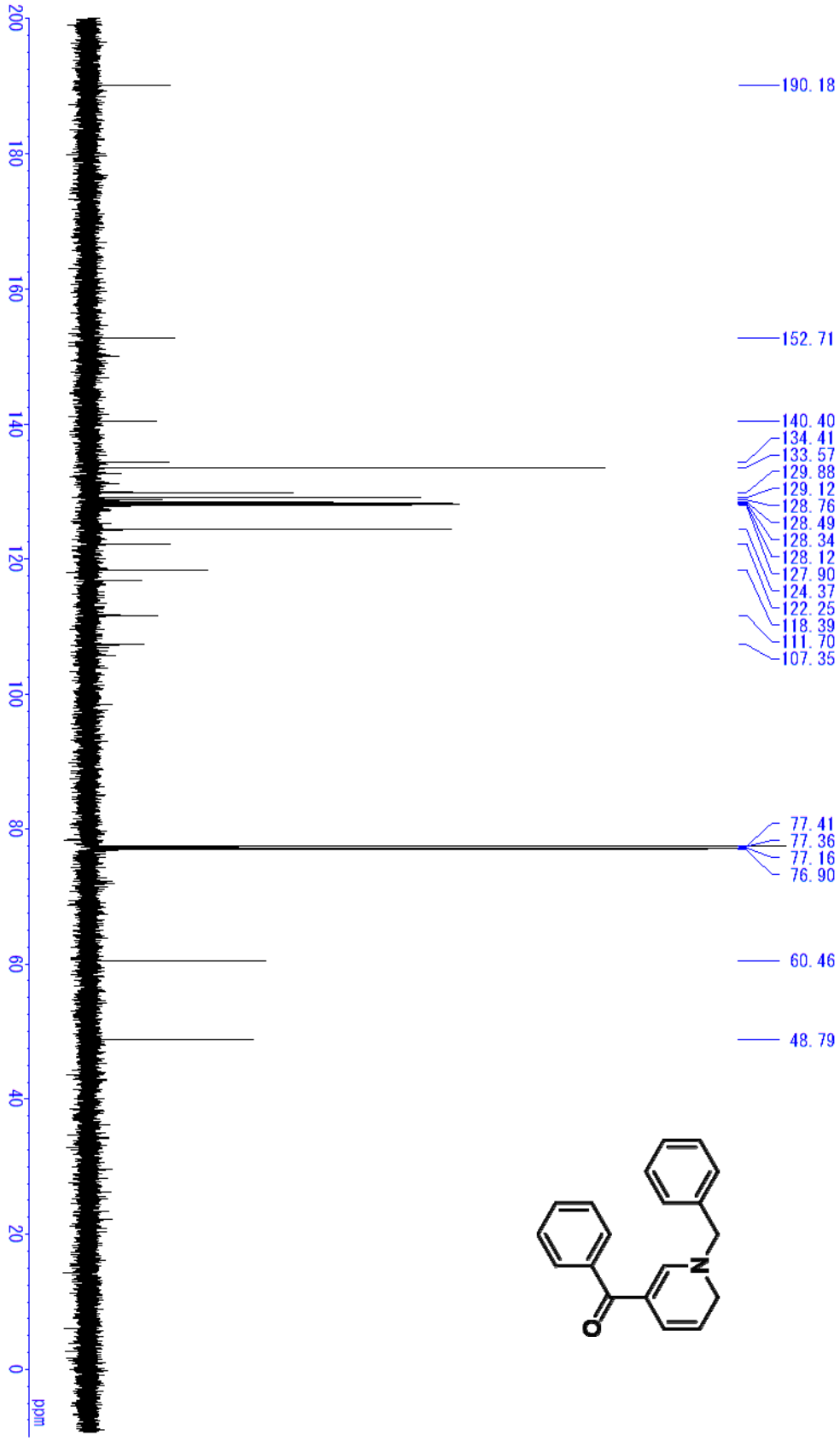

Figure S30. A ^{13}C-NMR spectrum for the crude mixture of **2d** in $CDCl_3$.

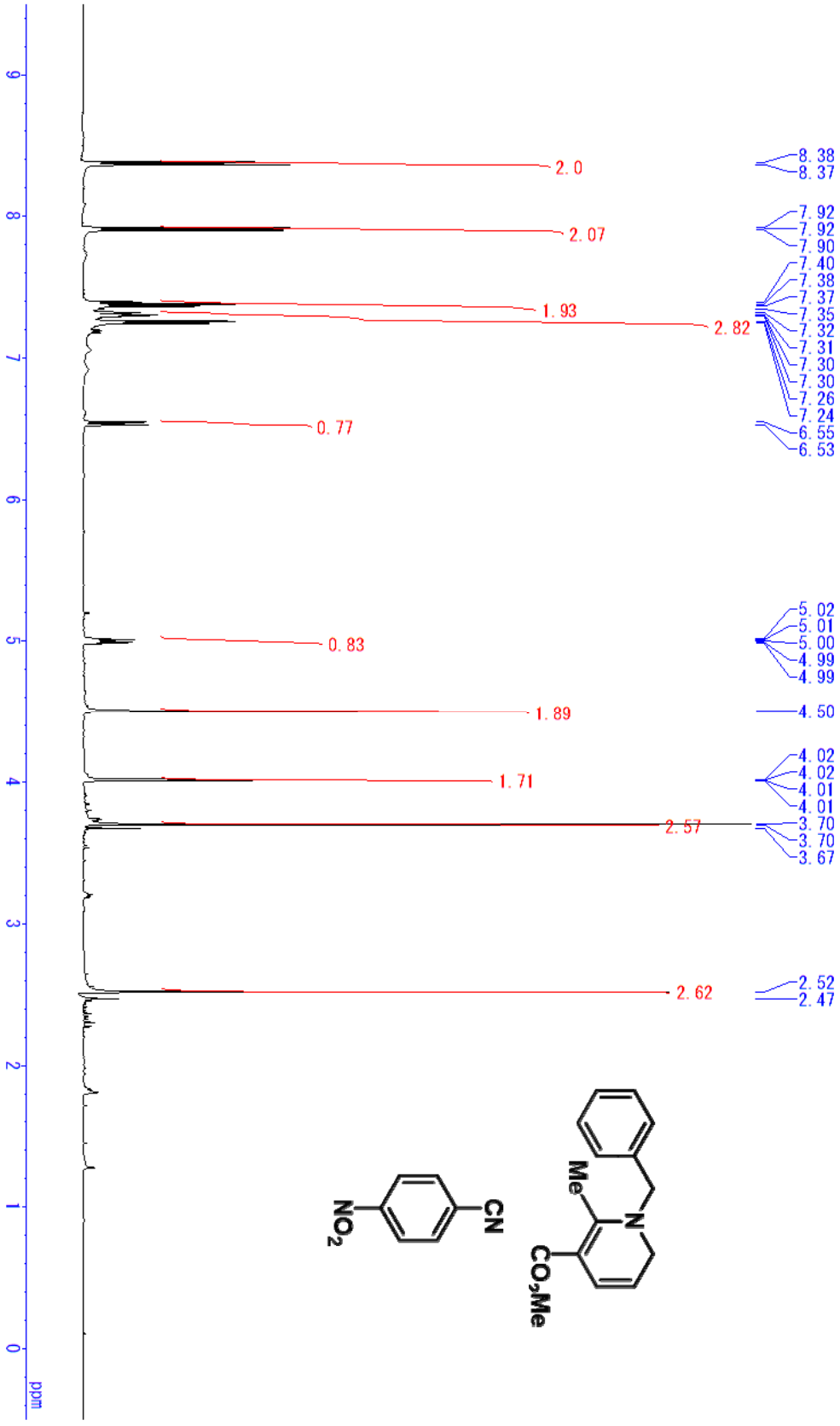

Figure S31. A ^{1}H-NMR spectrum for the crude mixture of **2e** in $CDCl_3$.

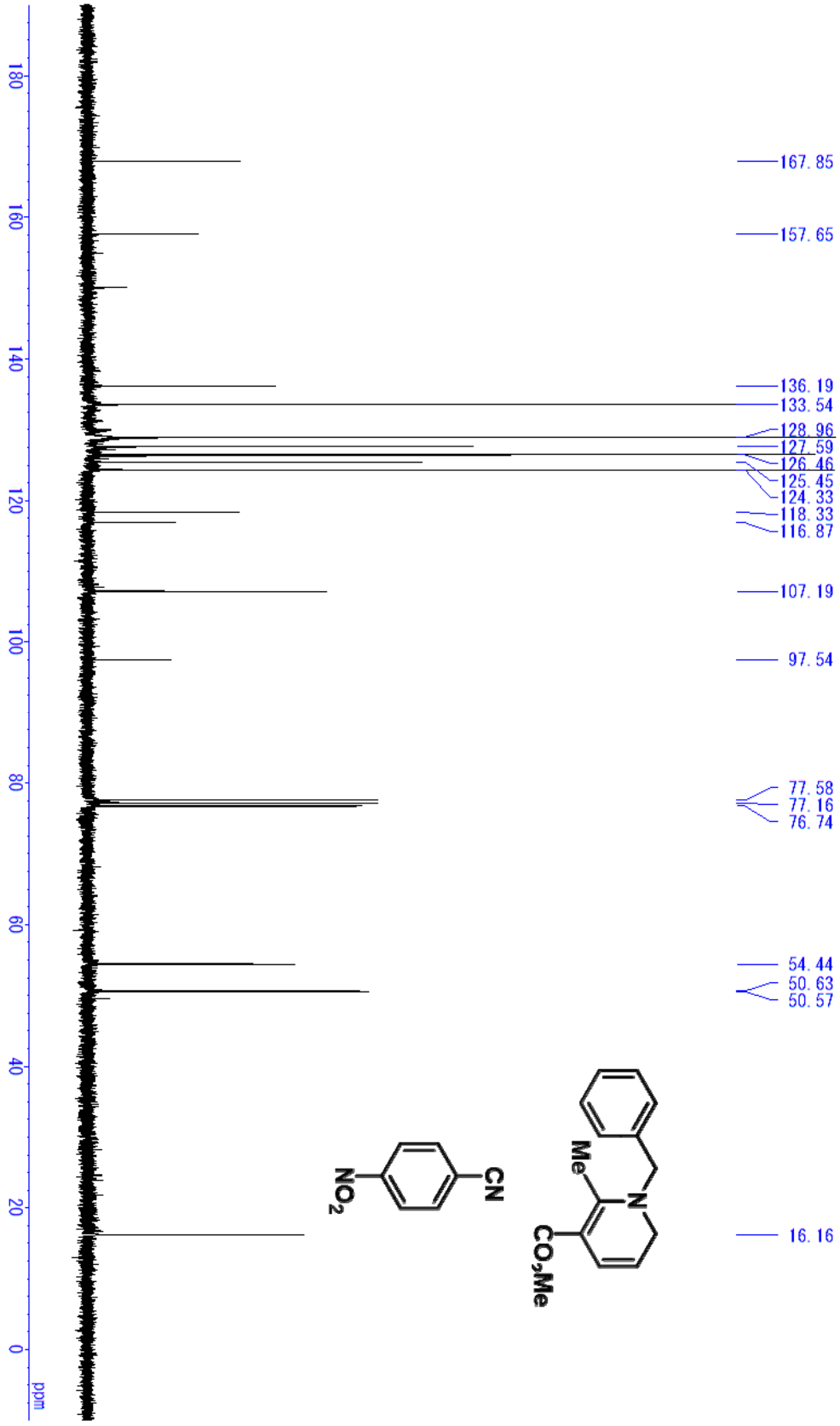

Figure S32. A ^{13}C-NMR spectrum for the crude mixture of **2e** in $CDCl_3$.

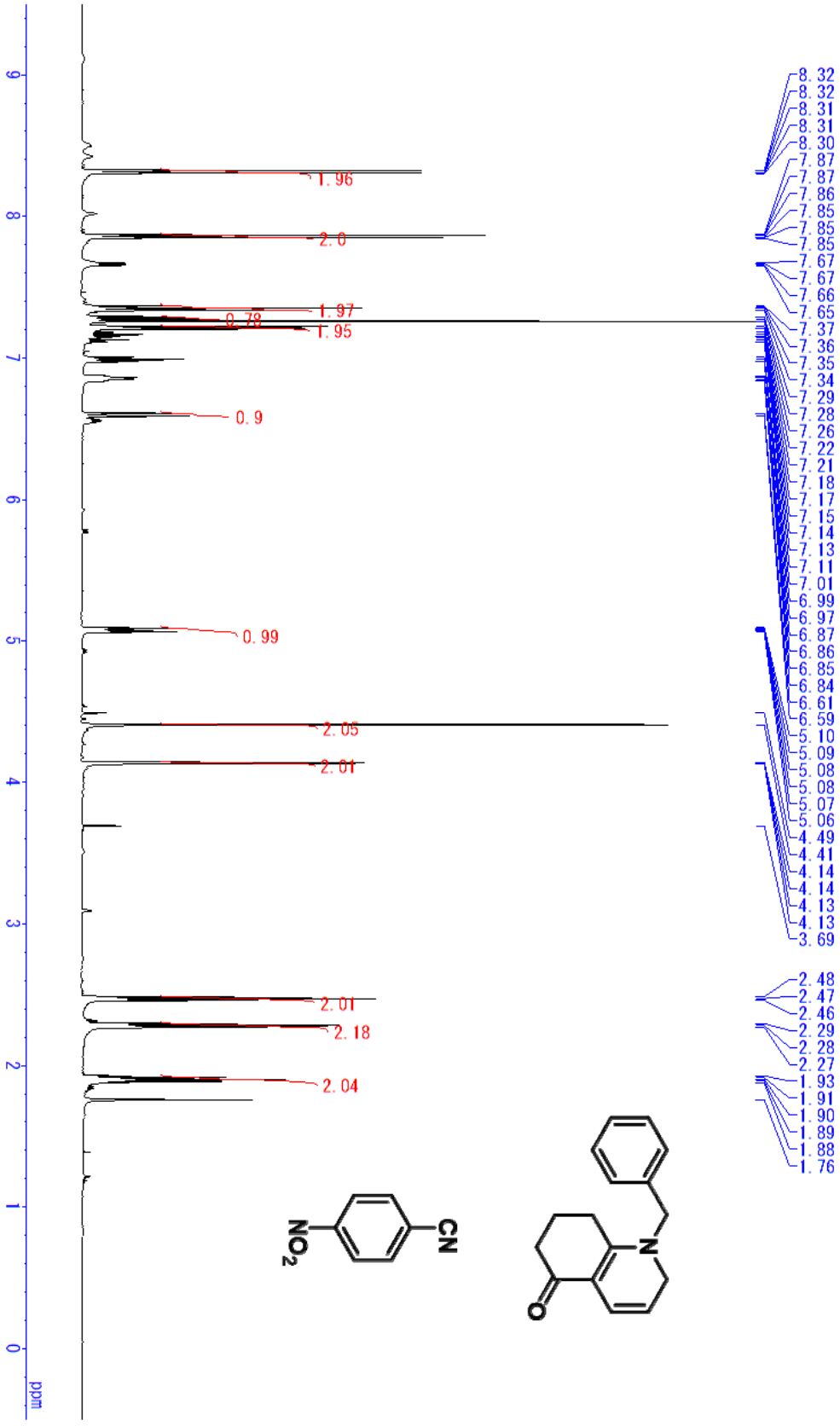

Figure S33. A ^{1}H-NMR spectrum for the crude mixture of **2f** in $CDCl_3$.

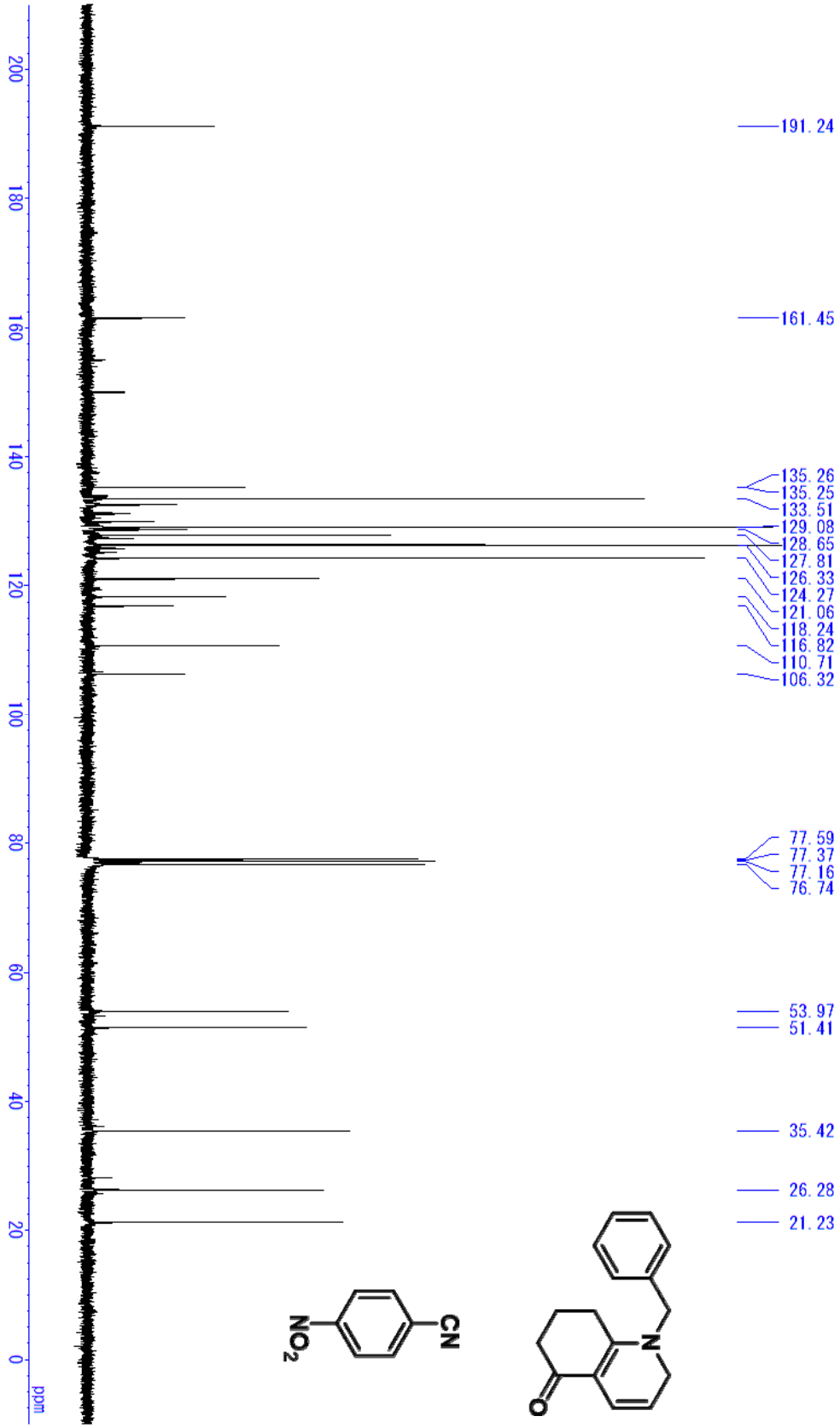

Figure S34. A ^{13}C-NMR spectrum for the crude mixture of **2f** in $CDCl_3$.

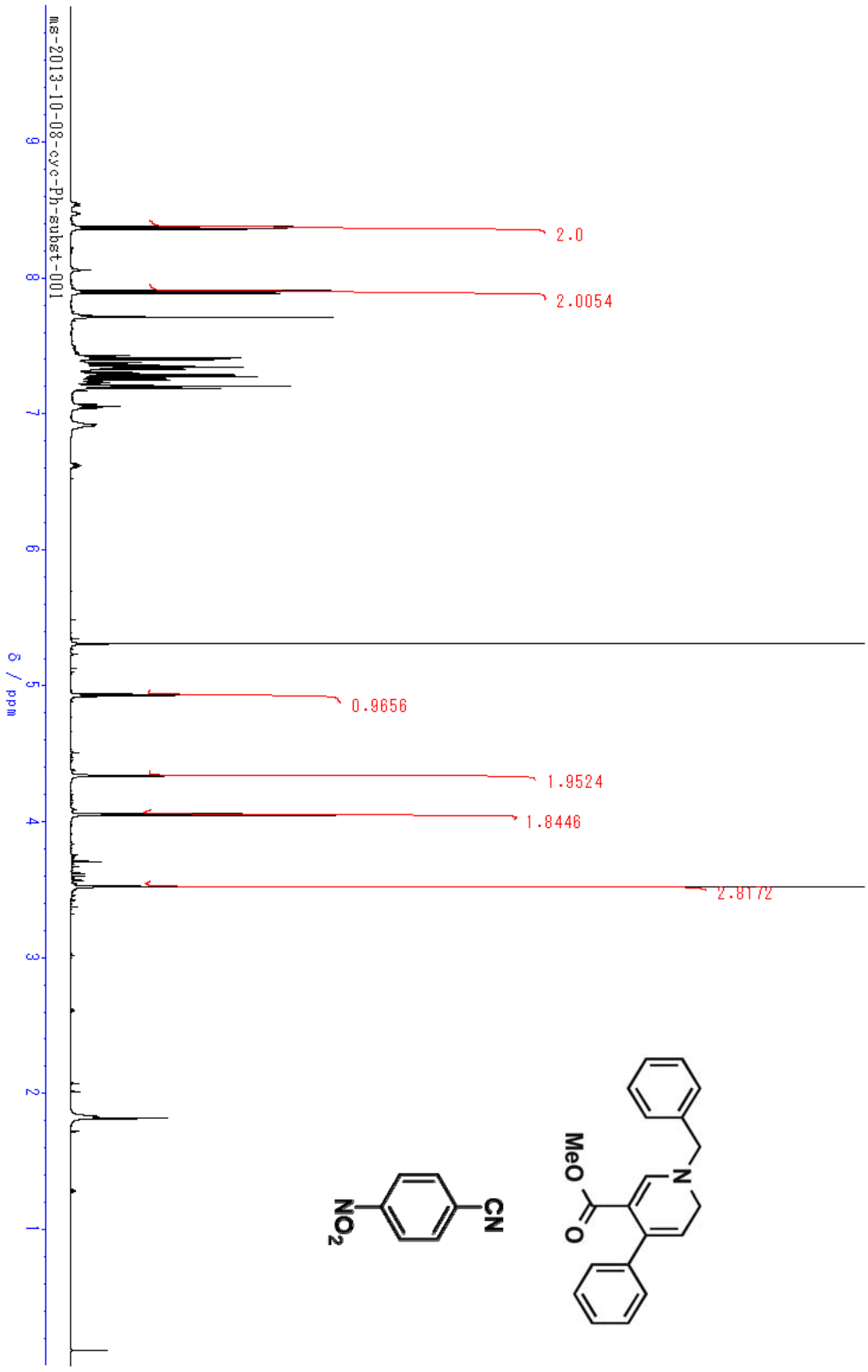

Figure S35. A ^{1}H-NMR spectrum for the crude mixture of **2g** in $CDCl_3$.

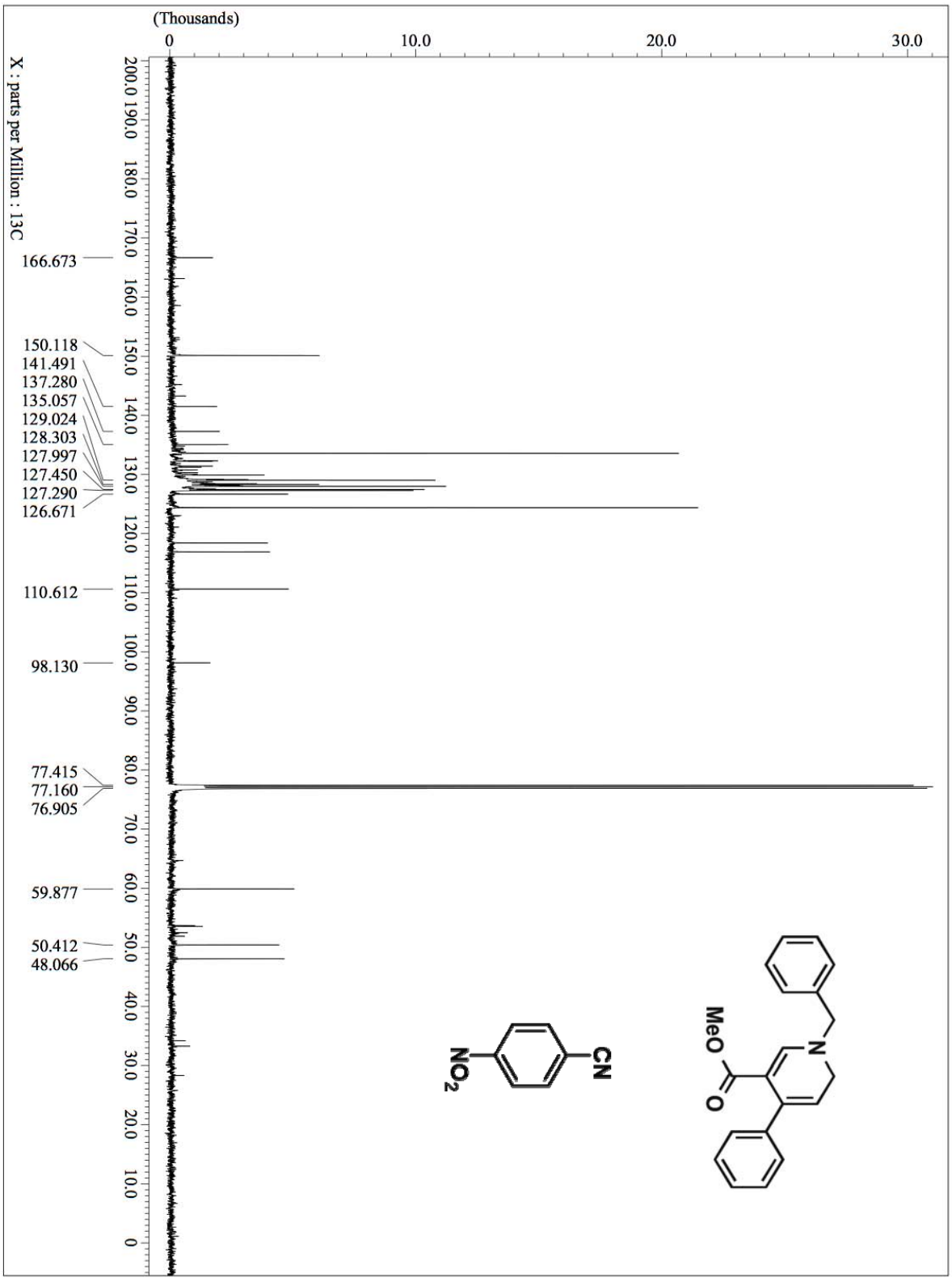

Figure S36. A ^{13}C-NMR spectrum for the crude mixture of **2g** in $CDCl_3$.

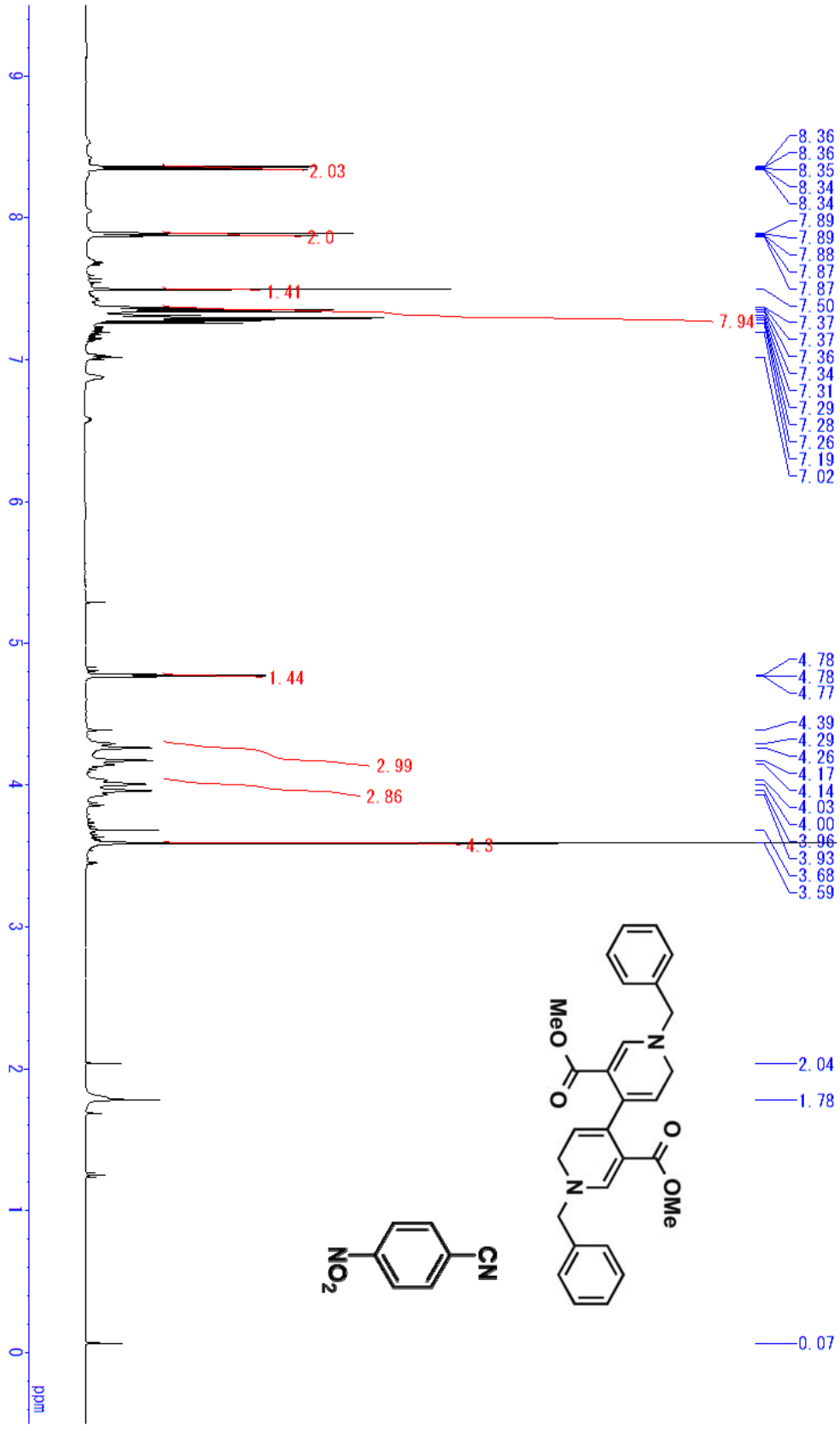

Figure S37. A ^{1}H-NMR spectrum for the crude mixture of **2h** in $CDCl_3$.

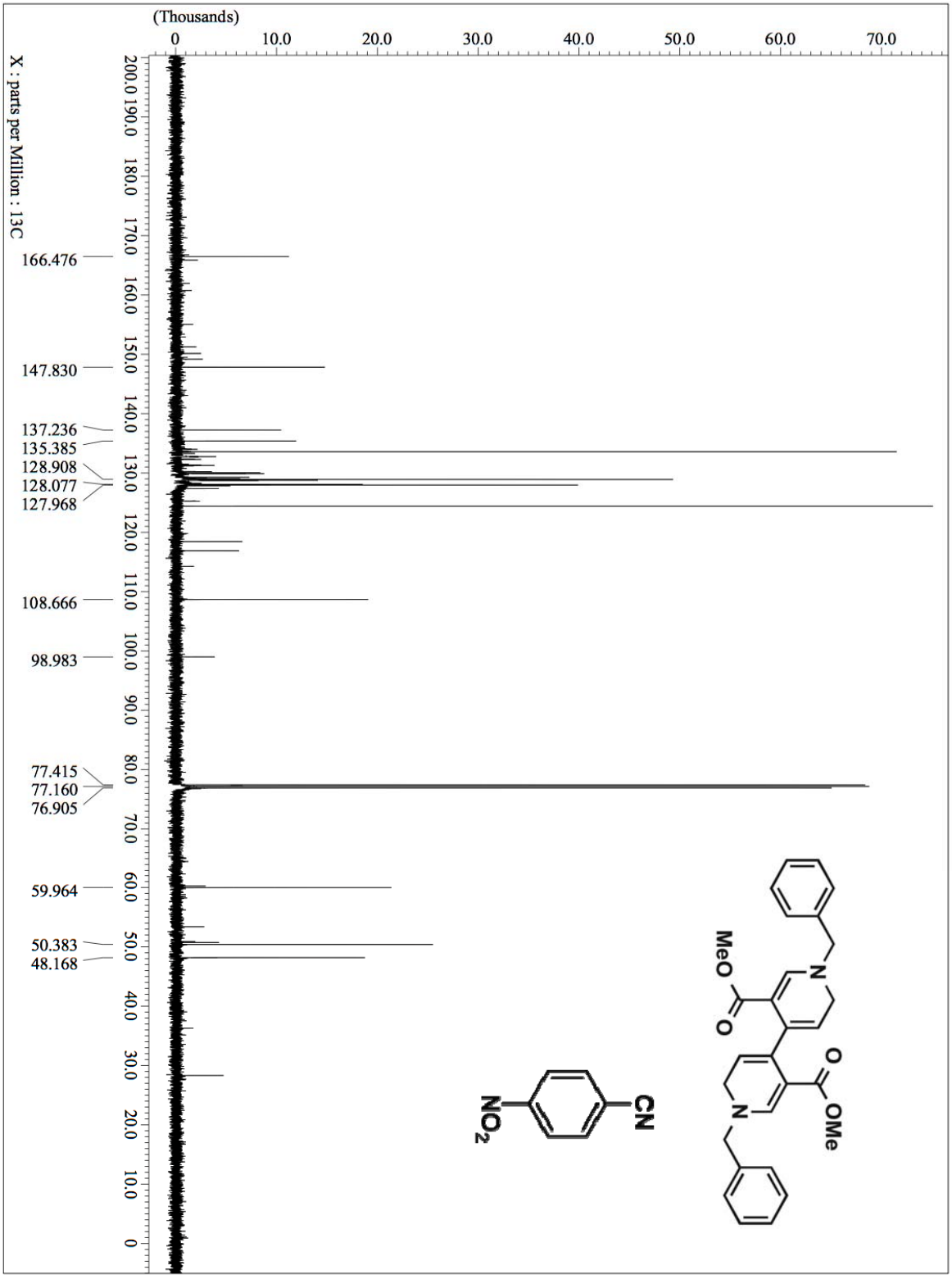

Figure S38. A ^{13}C-NMR spectrum for the crude mixture of **2h** in $CDCl_3$.

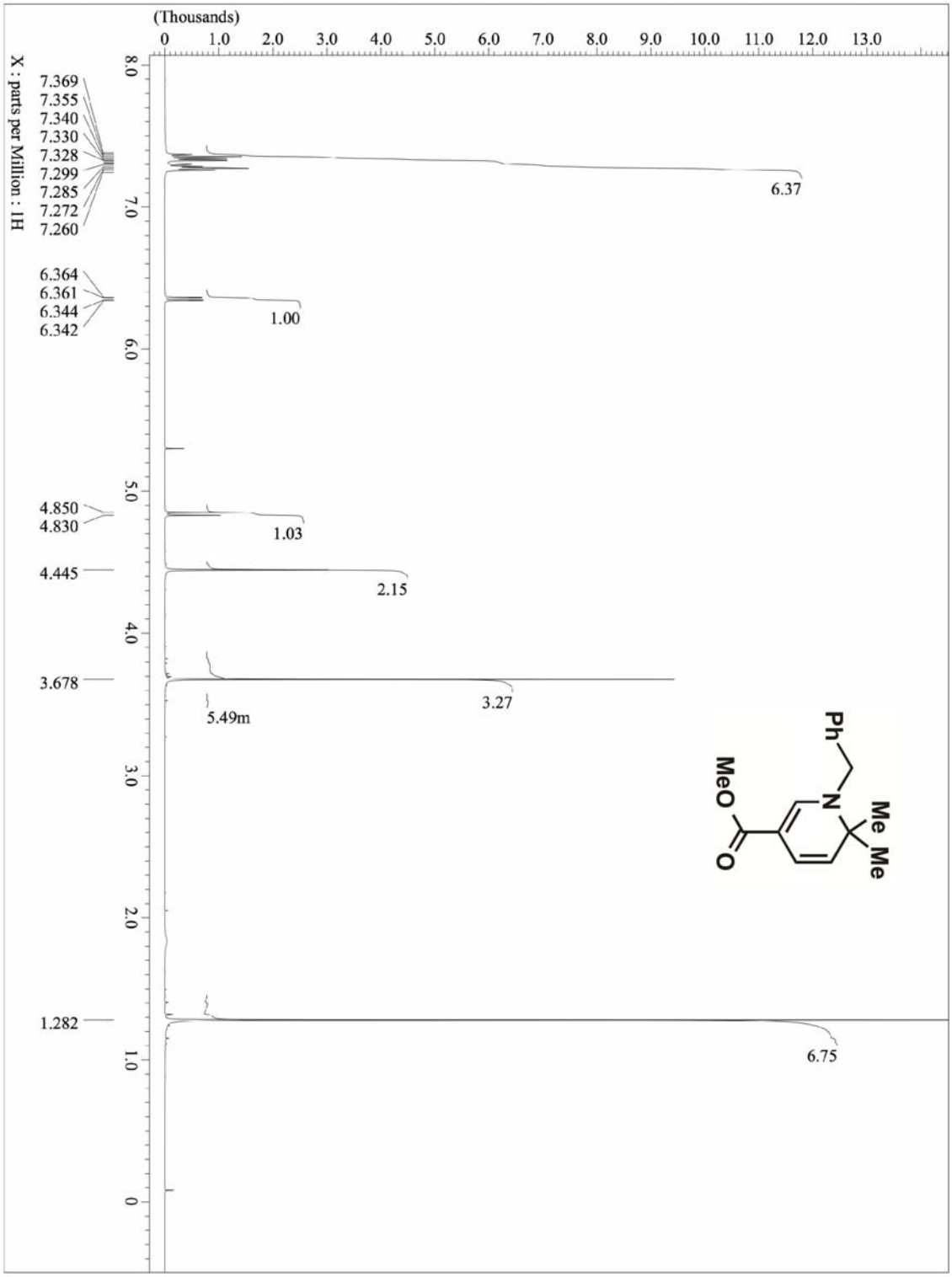

Figure S39. A ^{1}H-NMR spectrum of **2i** in $CDCl_3$.

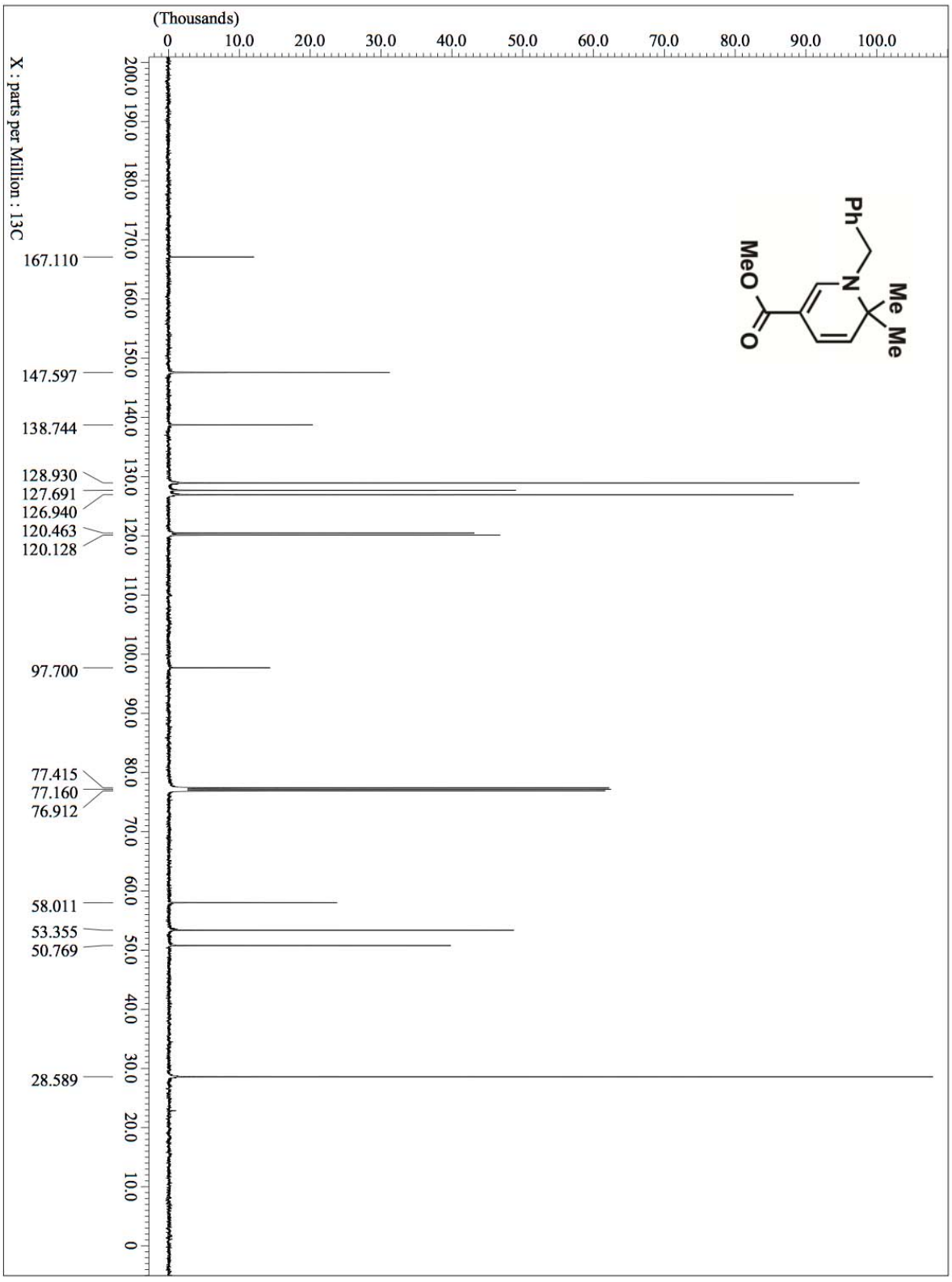

Figure S40. A ^{13}C-NMR spectrum of **2i** in $CDCl_3$.

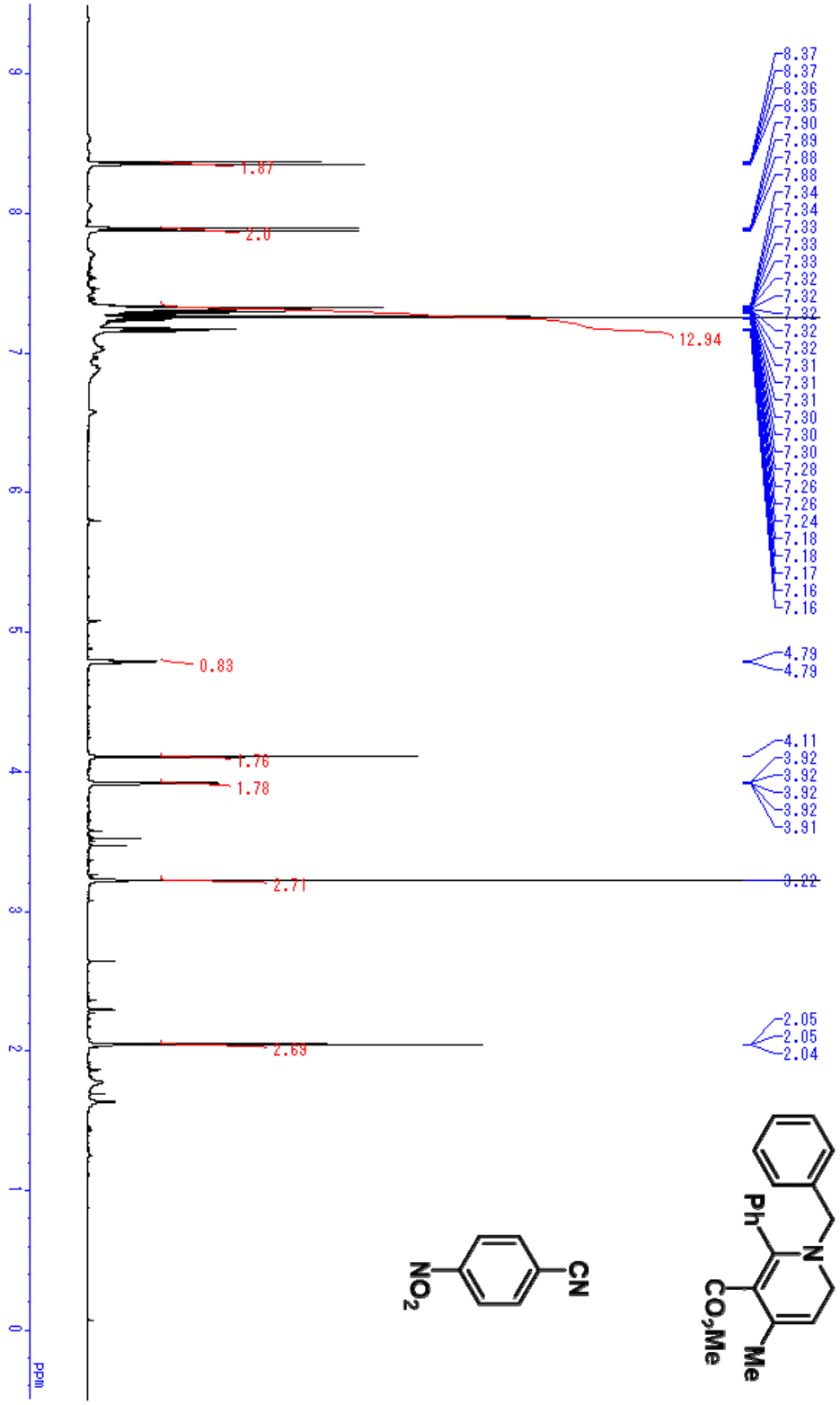

Figure S41. A ^{1}H-NMR spectrum for the crude mixture of **2j** in $CDCl_3$.

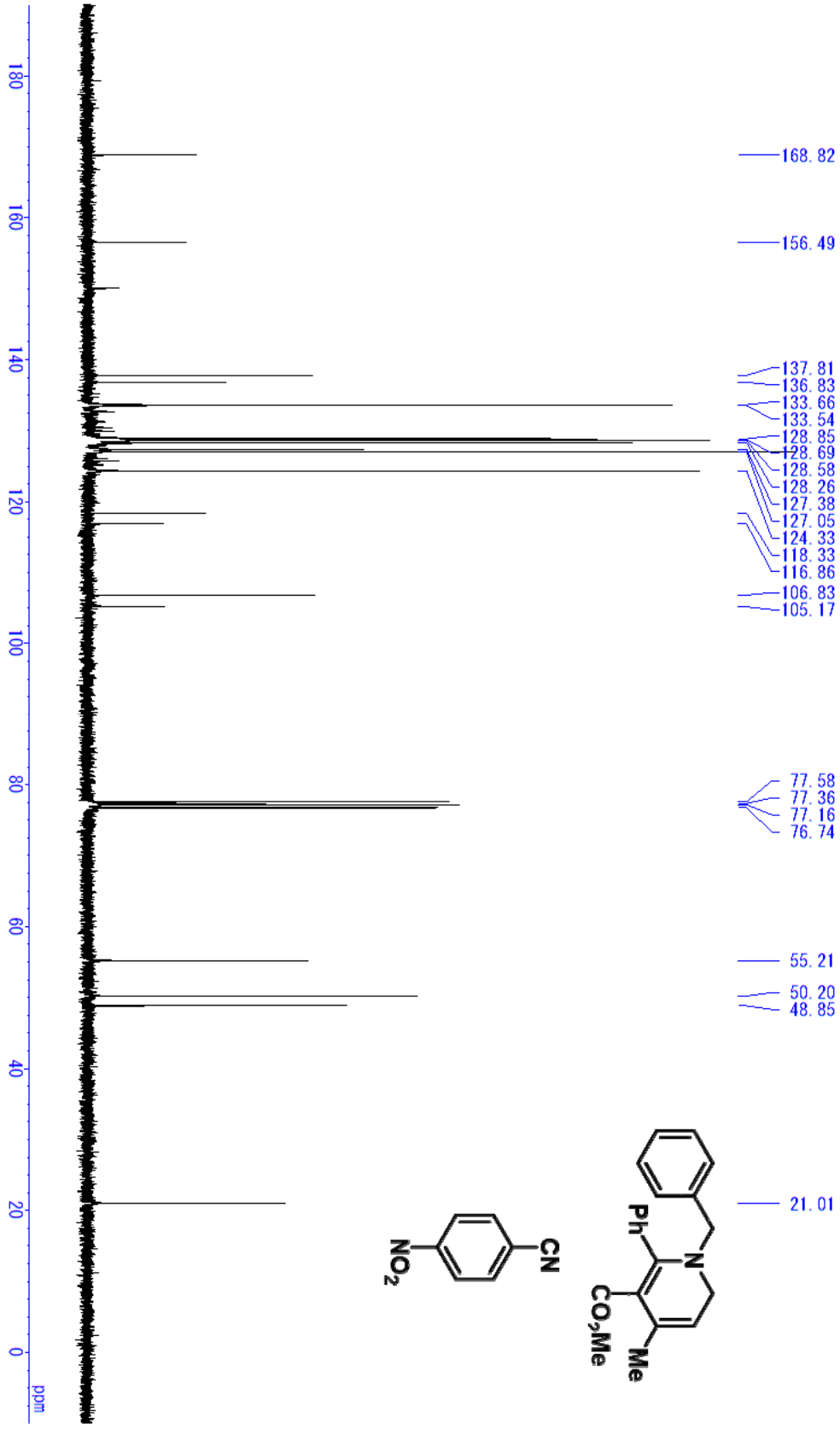

Figure S42. A ^{13}C-NMR spectrum for the crude mixture of **2j** in $CDCl_3$.

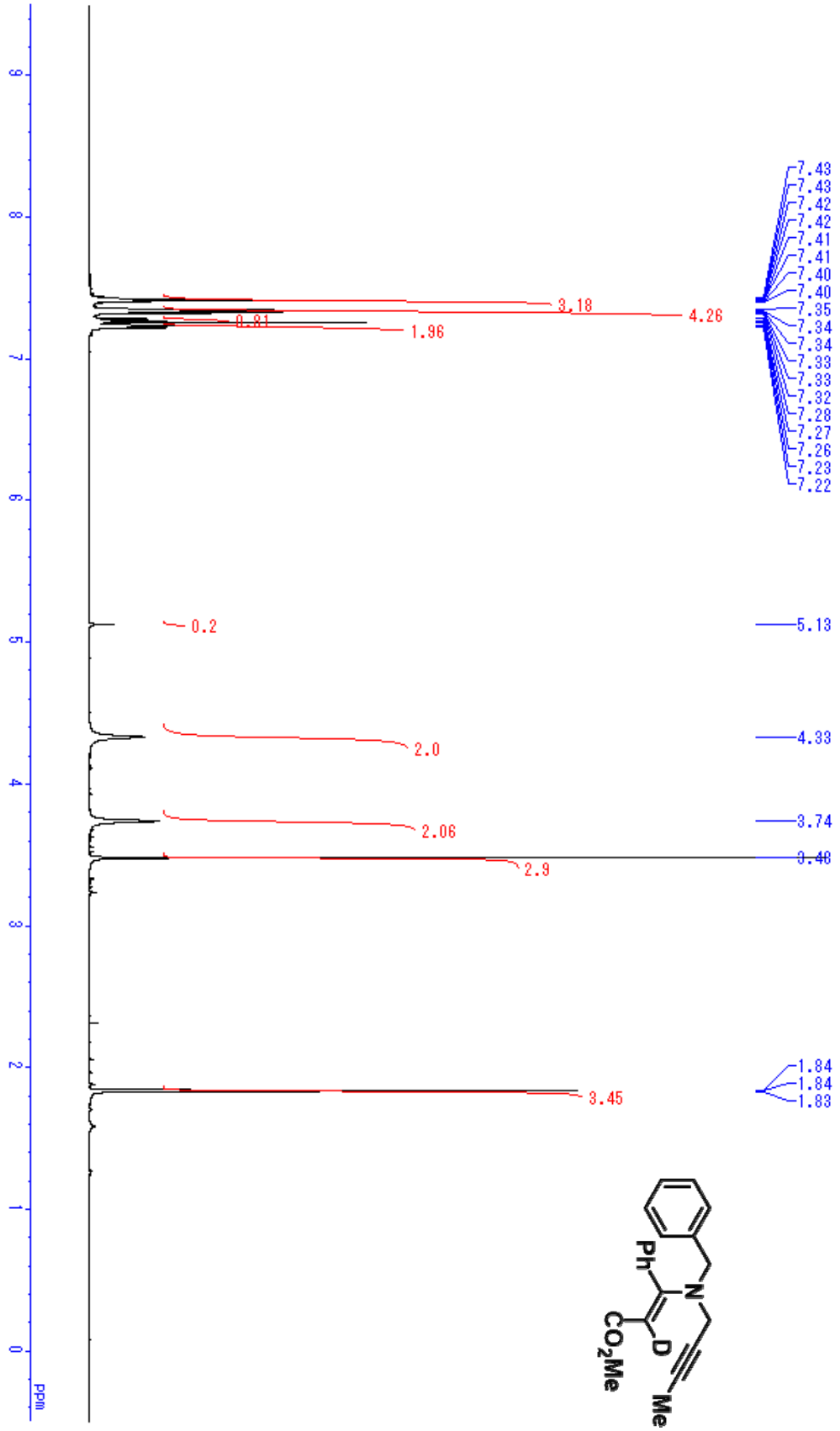

Figure S43. A ^{1}H-NMR spectrum of **1j-D** in $CDCl_3$.

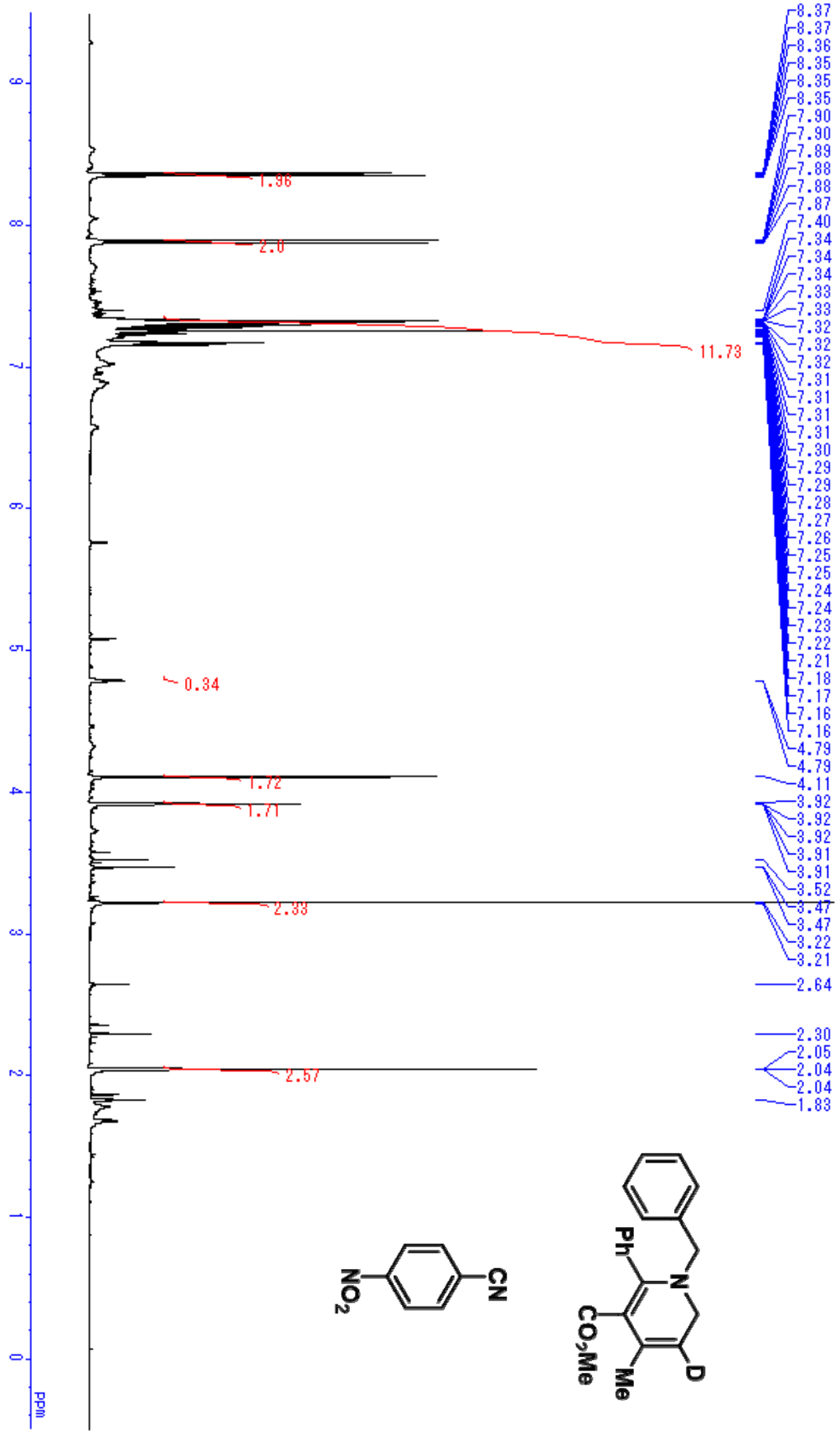

Figure S44. A ^{1}H-NMR spectrum for the crude mixture of **2j-D** in $CDCl_3$.

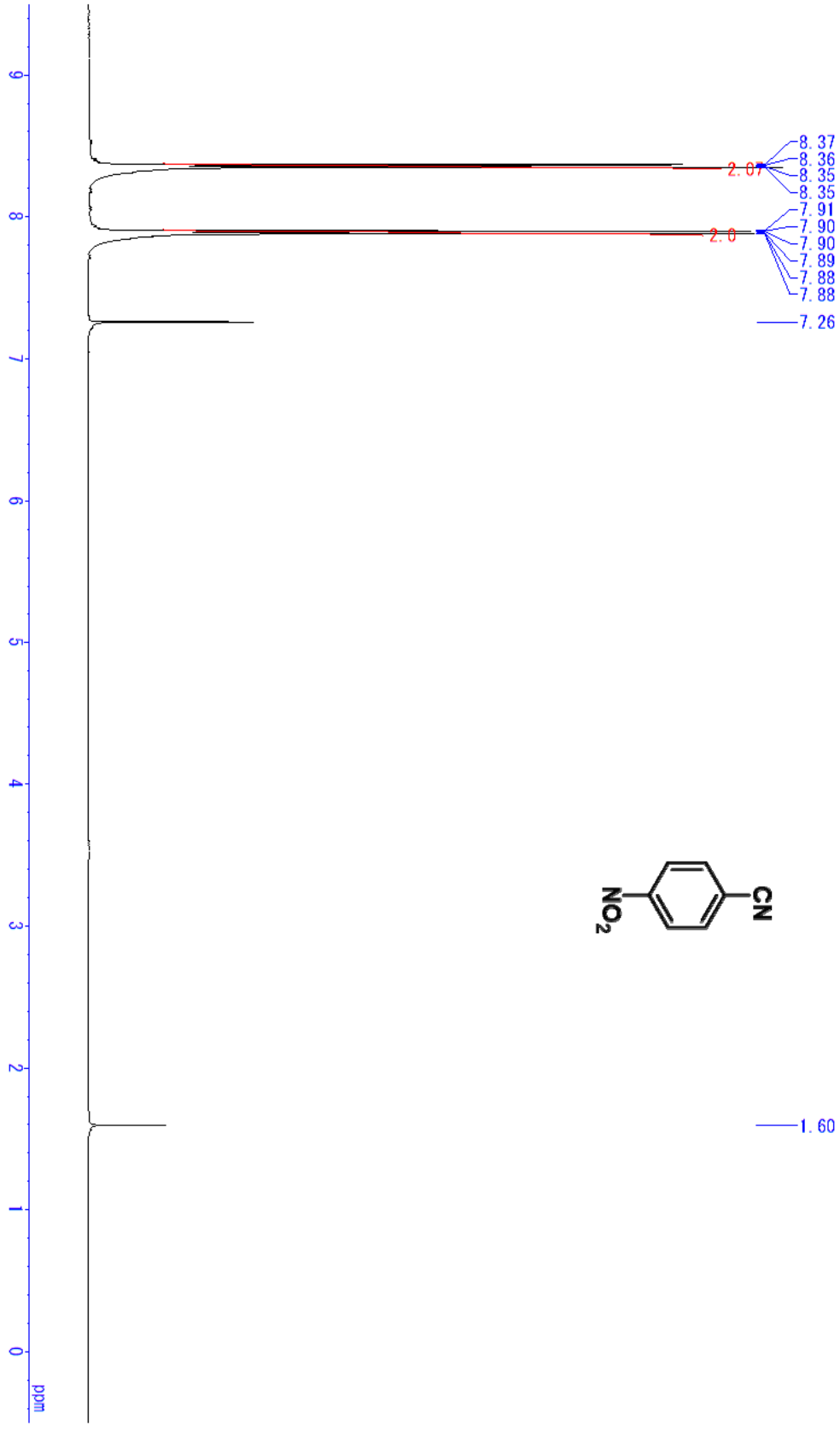

Figure S45. A ^{1}H-NMR spectrum of 4-nitrobenzonitrile in $CDCl_3$.

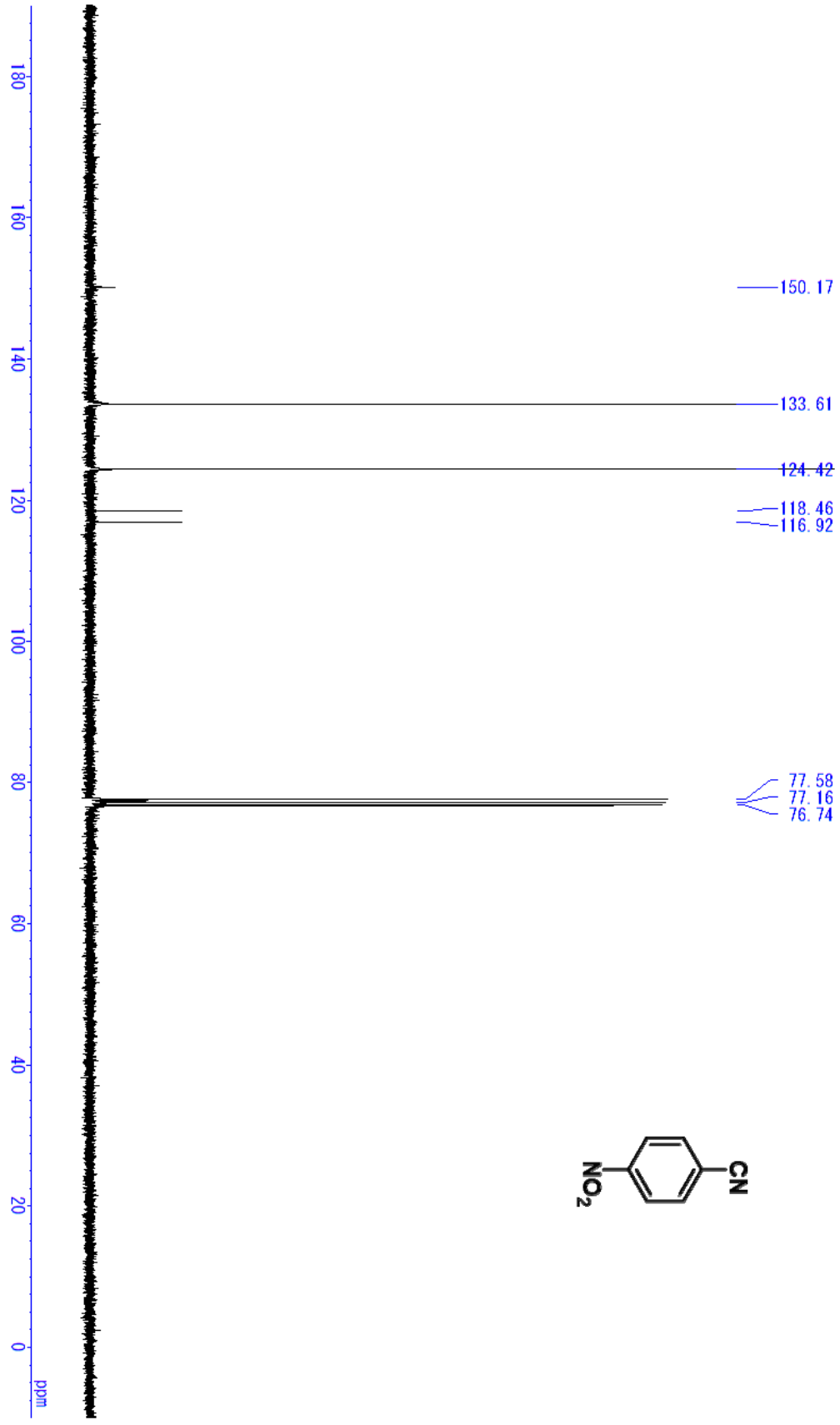

Figure S46. A ^{13}C-NMR spectrum of 4-nitrobenzonitrile in $CDCl_3$.