Catalytic stereospecific alkylation of malononitriles with enantioenriched primary allylic amines

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Supporting information

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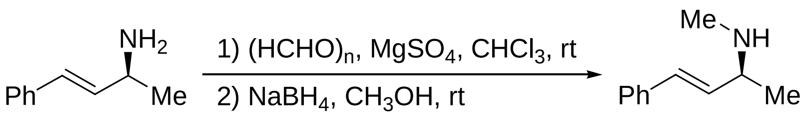
General information

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-400 FT spectrometer (400 MHz and 100 MHz, respectively) using tetramethylsilane as an internal reference. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, sept = septet, m = multiplet, br = broad signal. Chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz, respectively. High resolution mass spectra (HRMS) were recorded on a LC-TOF spectrometer (Micromass). Electrospray ionization (ESI) mass spectrometry data were acquired using a Thermo LTQ Orbitrap XL instrument equipped with an ESI source and controlled by Xcalibur software. High pressure liquid chromatography (HPLC) analyses were performed on a Hewlett-Packard 1200 Series instrument equipped with an isostatic pump using a Daicel Chiralpak column (AD, AD-H, OD, or OJ, 250 x 4.6 mm) with isopropanol/hexane as mobile phase, and the UV detection was monitored at 254 nm or 210 nm. The chiral HPLC methods were calibrated with the corresponding racemic mixtures. Optical rotations were measured on a Perkin-Elmer 343 polarimeter with a sodium lamp at λ = 589 nm and reported as $[\alpha]_D^{T\,°C}$ (c = g/100 mL, solvent). Melting points were uncorrected.

Amines **1a-f** and **1i-j** were resolved from the corresponding racemic mixtures with (+)-tartaric acid,[1a-c] and their absolute configuration was assigned by comparison of the optical rotation or the chiral HPLC trace (for the derivative) with that reported in the literature.[1] Amines **1g-h** were prepared from *L*-valine according to the literature procedures.[2] Amine **1ab** was prepared by double methylation of amine **1a** according to the literature procedure.[3] Malononitriles **2b-j** were prepared following the literature procedures: (1) **2b** was prepared through copper-catalyzed arylation of malononitrile with iodobenzene;[4a] (2) **2c-f** and **2j** were prepared through reductive alkylation of malononitrile with aldehydes or ketones;[4b] and (3) **2g-i** were prepared through alkylation of malononitrile with alkyl halides.[4c] The rest of chemicals were purchased from the Sinopharm Chemical Reagent Co., Meryer, Acros, Alfa Aesar, and TCI, and used as received.

Abbreviations: Ac = acetyl, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, Cy = cyclohexyl, dba = dibenzylideneacetone, dppb = 1,4-bis(diphenylphosphino)butane, Np = naphthyl, rt = room temperature, THF = tetrahydrofuran, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

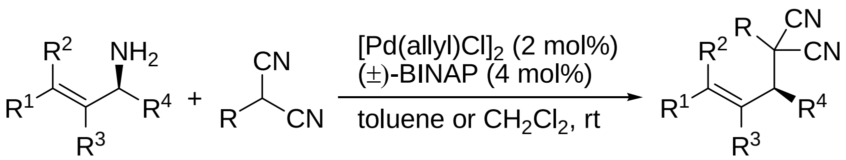
Preparation of amine 1aa[3]



1a **1aa**

To a solution of amine **1a** (147 mg, 1.0 mmol)[1a-c] and paraformaldehyde (30.0 mg, 1.0 mmol) in dry chloroform (5.0 mL) was added magnesium sulfate (500 mg). The mixture was stirred at room temperature for 5 h. After filtration, the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (5.0 mL), and then $NaBH_4$ (38.0 mg, 1.0 mmol) was added. The mixture was stirred at room temperature for 1 h, added water (5.0 mL), and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel chromatography, eluting with ethyl acetate, to give amine **1aa** (90.0 mg, 56%) as a colorless oil.[5] $[\alpha]_D^{20}$ = -37.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.18 (m, 5H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.04 (dd, *J* =16.0, 8.0 Hz, 1H), 3.26-3.17 (m, 1H), 2.39 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H).

General procedure for the stereospecific alkylation of malononitriles with enantioenriched primary allylic amines

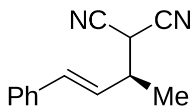


1 **2** **3**

A mixture of amine **1** (0.50 mmol), malononitrile **2** (0.60 mmol), racemic BINAP (12.5 mg, 4 mol%), and $[Pd(allyl)Cl]_2$ (3.64 mg, 2 mol%) in toluene or dichloromethane (1.0 mL) was stirred under nitrogen at room temperature for 3 h or 8 h. The mixture was purified directly by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1:5), to give compound **3**.

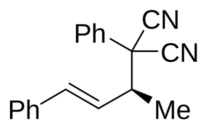
The absolute configuration of compound **3a** was assigned to be *S* by transforming it to known compound **6a** (see below) and that of the rest of products was assigned by analogy.

Analytical data for the products



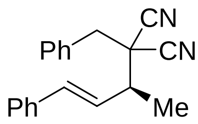
3a

Compound **3a**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (3/97), flow rate 1.0 mL/min, t_R: 16.0 min (major), 18.4 min (minor)], colorless oil; $[\alpha]_D^{20}$ = -11.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.42–7.26 (m, 5H), 6.66 (d, *J* = 15.6 Hz, 1H), 6.10 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.72 (d, *J* = 5.6 Hz, 1H), 3.09–2.98 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.6, 134.6, 128.7, 128.5, 126.7, 126.0, 111.7, 39.3, 29.9, 17.7; HRMS (EI) calcd for $C_{13}H_{12}N_2$ (M) 196.1000, found 196.0992.



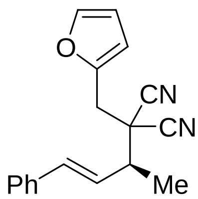
3b

Compound **3b**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 11.0 min (minor), 12.2 min (major)], white solid; m.p. 73-74 °C; $[\alpha]_D^{20}$ = -51.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.57–7.51 (m, 2H), 7.50–7.41 (m, 3H), 7.33–7.22 (m, 5H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.01 (dd, *J* = 16.0, 8.4 Hz, 1H), 3.13-3.05 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.9, 135.5, 130.8, 129.9, 129.4, 128.7, 128.3, 126.6, 125.2, 114.4, 48.8, 48.3, 16.4; HRMS (ESI) calcd for $C_{19}H_{16}N_2Na^+$ (M + Na)$^+$ 295.1206, found 295.1199.



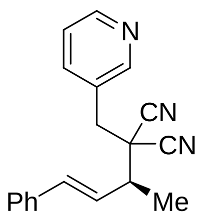
3c

Compound **3c**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 20.3 min (minor), 21.6 min (major)], white solid; m.p. 108-109 °C; $[\alpha]_D^{20}$ = -32.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.51–7.27 (m, 10H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.18 (dd, *J* = 15.6, 9.2 Hz, 1H), 3.24 (d, *J* = 13.6 Hz, 1H), 3.11 (d, *J* = 13.6 Hz, 1H), 2.96-2.84 (m, 1H), 1.55 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.7, 135.6, 132.4, 130.2, 128.9, 128.8, 128.7, 128.6, 126.7, 125.5, 114.9, 114.3, 45.1, 44.8, 41.7, 17.7; HRMS (EI) calcd for $C_{20}H_{18}N_2$ (M) 286.1470, found 286.1466.



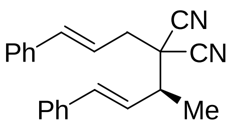
3d

Compound **3d**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 19.3 min (major), 21.9 min (minor)], colorless oil; $[\alpha]_D^{20}$ = -49.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.47–7.25 (m, 6H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.44 (d, *J* = 3.2 Hz, 1H), 6.40 (dd, *J* = 3.2, 1.6 Hz, 1H), 6.12 (dd, *J* = 16.0, 8.8 Hz, 1H), 3.36 (d, *J* = 15.2 Hz, 1H), 3.29 (d, *J* = 15.2 Hz, 1H), 2.93-2.80 (m, 1H), 1.52 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 146.4, 143.4, 135.8, 135.6, 128.7, 128.5, 126.7, 125.0, 114.6, 114.1, 110.9, 110.6, 43.8, 43.0, 34.5, 17.4; HRMS (EI) calcd for $C_{18}H_{16}N_2O$ (M) 276.1263, found 276.1262.



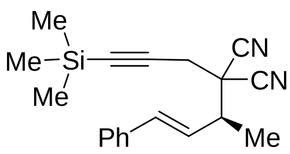
3e

Compound **3e**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (10/90), flow rate 1.0 mL/min, t_R: 15.7 min (minor), 19.5 min (major)], white solid; m.p. 112-113 °C; $[\alpha]_D^{20}$ = -30.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.67-8.61 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.47–7.23 (m, 6H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 9.2 Hz, 1H), 3.25 (d, *J* = 13.6 Hz, 1H), 3.13 (d, *J* = 13.6 Hz, 1H), 2.95-2.88 (m, 1H), 1.57 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 151.0, 150.2, 137.6, 136.0, 135.5, 128.8, 128.7, 128.4, 126.7, 125.0, 123.7, 114.5, 113.8, 45.0, 44.8, 39.1, 17.8; HRMS (EI) calcd for $C_{19}H_{17}N_3$ (M) 287.1422, found 287.1424.



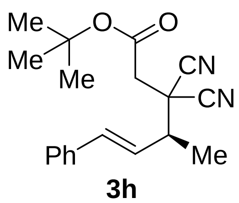
3f

Compound **3f**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 17.4 min (minor), 20.2 min (major)], colorless oil; $[\alpha]_D^{20}$ = -104.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.45–7.22 (m, 10H), 6.68 (d, *J* = 15.6 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.24 (dt, *J* = 15.6, 7.6 Hz , 1H), 6.11 (dd, *J* = 15.6, 9.2 Hz, 1H), 2.95–2.85 (m, 2H), 2.84–2.74 (m, 1H), 1.52 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 137.6, 135.8, 135.7, 135.5, 128.8, 128.7, 128.5, 126.7, 119.3, 114.9, 114.4, 44.0, 43.3, 39.5, 17.5; HRMS (EI) calcd for $C_{22}H_{20}N_2$ (M) 312.1626, found 312.1632.



3g

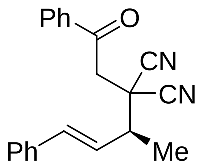
Compound **3g**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 12.6 min (minor), 15.1 min (major)], white solid; m.p. 78-79 °C; $[\alpha]_D^{20}$ = -51.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.42–7.26 (m, 5H), 6.66 (d, *J* = 15.6 Hz, 1H), 6.02 (dd, *J* = 15.6, 9.2 Hz, 1H), 3.10–3.00 (m, 1H), 2.99 (d, *J* = 16.8 Hz, 1H), 2.86 (d, *J* = 16.8 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 136.5, 136.1, 129.3, 129.2, 127.3, 125.1, 114.9, 114.3, 96.7, 93.4, 44.0, 42.7, 28.9, 17.9, 0.3; HRMS (EI) calcd for $C_{19}H_{22}N_2Si$ (M) 306.1552, found 306.1550.



3h

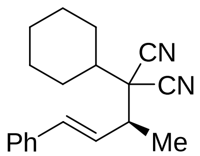
Compound **3h**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ =

254 nm, isopropanol/hexane (5/95), flow rate 1.0 mL/min, t_R: 7.4 min (minor), 9.1 min (major)], colorless oil; $[\alpha]_D^{20}$ = -26.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.23 (m, 5H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.05 (dd, *J* = 16.0, 9.2 Hz, 1H), 3.05–2.93 (m, 1H), 2.95 (d, *J* = 16.8 Hz, 1H), 2.81 (d, *J* = 16.8 Hz, 1H), 1.53 (d, *J* = 7.6 Hz, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 135.9, 135.5, 128.8, 128.7, 126.7, 124.9, 114.7, 113.9, 84.0, 44.5, 40.9, 39.1, 27.9, 17.3; HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ (M) 310.1681, found 310.1679.



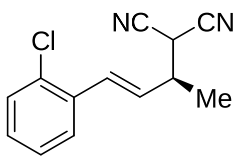
3i

Compound **3i**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (5/95), flow rate 1.0 mL/min, t_R: 19.8 min (major), 21.8 min (minor)], white solid; m.p. 104-105 °C; $[\alpha]_D^{20}$ = -54.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.65–7.56 (m, 1H), 7.51–7.43 (m, 2H), 7.36–7.27 (m, 5H), 6.61 (d, *J* = 15.6 Hz, 1H), 6.11 (dd, *J* = 15.6, 9.2 Hz, 1H), 3.69 (d, *J* = 18.0 Hz, 1H), 3.64 (d, *J* = 18.0 Hz, 1H), 3.23–3.11 (m, 1H), 1.58 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 135.8, 135.5, 135.0, 134.4, 129.0, 128.8, 128.6, 128.1, 126.7, 125.3, 115.0, 114.2, 43.9, 43.8, 38.4, 17.5; HRMS (EI) calcd for $C_{21}H_{18}N_2O$ (M) 314.1419, found 314.1415.



3j

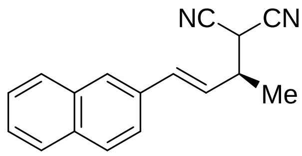
Compound **3j**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 8.0 min (major), 12.1 min (minor)], colorless oil; $[\alpha]_D^{20}$ = -42.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.24 (m, 5H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.09 (dd, *J* = 16.0, 9.2 Hz, 1H), 3.03–2.92 (m, 1H), 2.08–1.93 (m, 2H), 1.91–1.80 (m, 3H), 1.73–1.70 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.46–1.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 134.5, 128.7, 128.4, 126.6, 125.8, 114.5, 114.3, 48.9, 41.8, 41.1, 27.7, 25.7, 25.6, 25.5, 17.6, 5.6; HRMS (EI) calcd for $C_{19}H_{22}N_2$ (M) 278.1783, found 278.1787.



3k

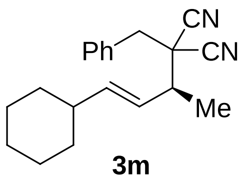
Compound **3k**, 95% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ =

254 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 31.2 min (minor), 34.8 min (major)], colorless oil; $[\alpha]_D^{20}$ = +10.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.55–7.49 (m, 1H), 7.40–7.34 (m, 1H), 7.32–7.21 (m, 2H), 7.06 (d, *J* = 16.0 Hz, 1H), 6.10 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.77 (d, *J* = 5.6 Hz, 1H), 3.18–3.05 (m, 1H), 1.49 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 131.0, 129.8, 129.5, 128.9, 127.1, 127.0, 111.6, 111.5, 39.3, 29.8, 17.6; HRMS (EI) calcd for $C_{13}H_{11}N_2Cl$ (M) 230.0611, found 230.0614.



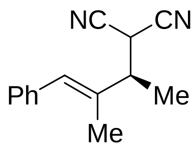
3l

Compound **3l**, 90% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (3/97), flow rate 1.0 mL/min, t_R: 30.8 min (major), 34.9 min (minor)], white solid; m.p. 122-123 °C; $[\alpha]_D^{20}$ = -11.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.88–7.73 (m, 4H), 7.60–7.55 (m, 1H), 7.56–7.44 (m, 2H), 6.81 (d, *J* = 16.0 Hz, 1H), 6.23 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.76 (d, *J* = 5.6 Hz ,1H), 3.16–3.03 (m, 1H), 1.49 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 134.7, 133.4, 133.3, 133.0, 128.5, 128.1, 127.7, 127.1, 126.5, 126.4, 126.2, 123.3, 111.7, 111.6, 39.4, 29.9, 17.7; HRMS (EI) calcd for $C_{17}H_{14}N_2$ (M) 246.1157, found 246.1154.



3m

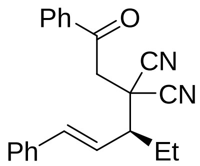
Compound **3m**, 98% ee as determined by HPLC analysis [Daicel Chiralcel OD, λ = 210 nm, isopropanol/hexane (1/99), flow rate 1.0 mL/min, t_R: 13.5 min (major), 14.9 min (minor)], colorless oil; $[\alpha]_D^{20}$ = +9.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.43–7.33 (m, 5H), 5.70 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.45–5.34 (m, 1H), 3.16 (d, *J* = 14.0 Hz, 1H), 3.03 (d, *J* = 14.0 Hz, 1H), 2.67–2.57 (m, 1H), 2.08–2.00 (m, 1H), 1.78–1.61 (m, 5H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.33–1.06 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 143.2, 132.7, 130.2, 128.9, 128.6, 124.0, 115.0, 114.4, 45.1, 44,2, 41.5, 40.7, 32.8, 32.7, 26.0, 25.8, 17.6; HRMS (EI) calcd for $C_{20}H_{24}N_2$ (M) 292.1939, found 292.1936.



3n

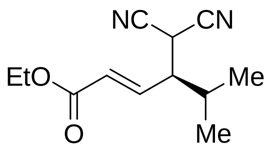
Compound **3n**, 90% ee as determined by HPLC analysis [Daicel Chiralcel OD, λ = 254 nm, isopropanol/hexane (5/95), flow rate 1.0 mL/min, t_R: 21.5 min (major), 24.6

min (minor)], colorless oil; $[\alpha]_D^{20}$ = -9.6 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.40–7.33 (m, 2H), 7.29–7.22 (m, 3H), 6.59 (s, 1H), 3.80 (d, *J* = 7.6 Hz, 1H), 3.05-2.95 (m, 1H), 1.88 (d, *J* = 1.6 Hz, 3H), 1.49 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 136.5, 134.3, 130.3, 128.9, 128.3, 127.2, 112.1, 111.9, 44.8, 28.4, 16.6, 14.8; HRMS (EI) calcd for $C_{14}H_{14}N_2$ (M) 210.1157, found 210.1153.



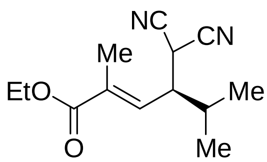
3o

Compound **3o**, 90% ee as determined by HPLC analysis [Daicel Chiralcel AD, λ = 254 nm, isopropanol/hexane (5/95), flow rate 1.0 mL/min, t_R: 13.2 min (major), 15.1 min (minor)], white solid; m.p. 101-102 °C; $[\alpha]_D^{20}$ = -43.9 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.90–7.85 (m, 2H), 7.62–7.56 (m, 1H), 7.49–7.41 (m, 2H), 7.36–7.25 (m, 5H), 6.59 (d, *J* = 15.6 Hz, 1H), 5.95 (dd, *J* = 15.6, 10.0 Hz, 1H), 3.69 (d, *J* = 18.0 Hz, 1H), 3.65 (d, *J* = 18.0 Hz, 1H), 2.90–2.81 (m, 1H), 2.20–2.11 (m, 1H), 1.84–1.74 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 192.3, 137.6, 135.4, 135.0, 134.4, 129.0, 128.8, 128.6, 128.1, 126.7, 123.8, 115.2, 114.4, 50.9, 44.0, 37.9, 24.5, 11.8; HRMS (EI) calcd for $C_{22}H_{20}N_2O$ (M) 328.1576, found 328.1568.



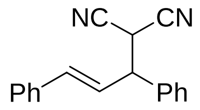
3p

Compound **3p**, >99% ee as determined by HPLC analysis [Daicel Chiralcel AS, λ = 210 nm, isopropanol/hexane (5/95), flow rate 1.0 mL/min, t_R: 18.4 min (major)], colorless oil; $[\alpha]_D^{20}$ = +20.0 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.75 (dd, *J* = 15.6, 10.0 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.92 (d, *J* = 6.4 Hz, 1H), 2.61–2.52 (m, 1H), 2.16–2.04 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.8, 140.4, 128.1, 111.5, 111.0, 61.0, 50.0, 29.7, 26.1, 20.6, 18.8, 14.2; HRMS (EI) calcd for $C_{12}H_{16}N_2O_2$ (M) 220.1212, found 220.1219.



3q

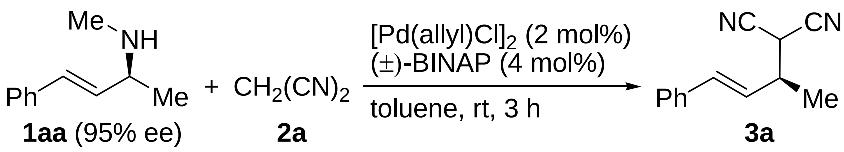
Compound **3q**, >99% ee as determined by HPLC analysis [Daicel Chiralcel AS, λ = 210 nm, isopropanol/hexane (2/98), flow rate 1.0 mL/min, t_R: 22.4 min (major)], colorless oil; $[\alpha]_D^{20}$ = +27.7 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.61–6.55 (m, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.88 (d, J = 6.0 Hz, 1H), 2.93–2.84 (m, 1H), 2.14–2.04 (m, 1H), 1.97 (d, J = 1.6 Hz, 3H), 1.33 (t, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 134.9, 133.9, 111.7, 111.1, 61.3, 46.2, 30.4, 25.9, 20.5, 18.6, 14.2, 13.5; HRMS (EI) calcd for $C_{13}H_{18}N_2O_2$ (M) 234.1368, found 234.1372.



3r

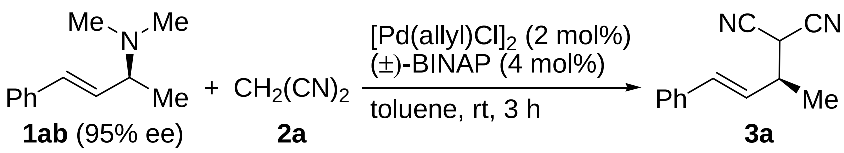
Compound **3r**,[6] white solid; m.p. 66-67 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.26 (m, 10H), 6.70 (d, J = 16.0 Hz, 1H), 6.46 (dd, J =16.0, 8.0 Hz, 1H), 4.12–4.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 135.8, 135.5, 129.4, 128.9, 128.7, 128.6, 127.7, 126.8, 123.9, 111.8, 111,7, 49.7, 30.2.

Alkylation of malononitrile (2a) with amine 1aa



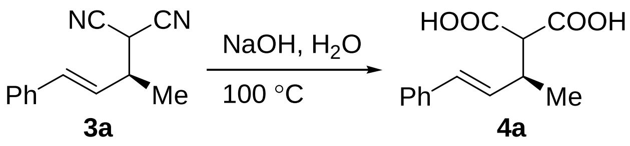
A mixture of amine **1aa** (80.5 mg, 0.50 mmol), malononitrile **2a** (39.6 mg, 0.60 mmol), racemic BINAP (12.5 mg, 4 mol%), and $[Pd(allyl)Cl]_2$ (3.64 mg, 2 mol%) in toluene (1.0 mL) was stirred under nitrogen at room temperature for 3 h. The mixture was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1:5), to give compound **3a** (55.0 mg, 56%) as a colorless oil.

Alkylation of malononitrile (2a) with amine 1ab

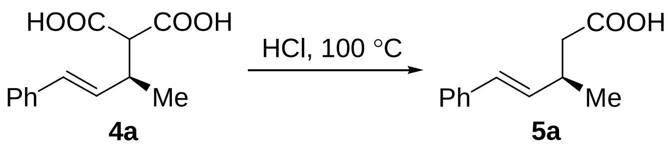


A mixture of amine **1ab** (87.5 mg, 0.50 mmol), malononitrile **2a** (39.6 mg, 0.60 mmol), racemic BINAP (12.5 mg, 4 mol%), and $[Pd(allyl)Cl]_2$ (3.64 mg, 2 mol%) in toluene (1.0 mL) was stirred under nitrogen at room temperature for 3 h. The mixture was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1:5), to give compound **3a** (7.8 mg, 8%) as a colorless oil.

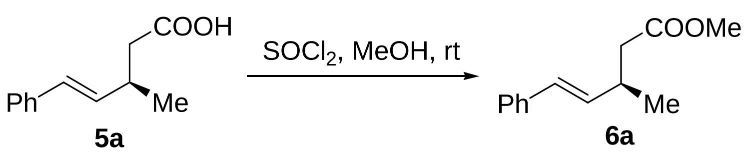
Transformations of substituted malononitrile 3a



To a mixture of malononitrile **3a** (95% ee, 196 mg, 1.0 mmol) and water (5 mL) at room temperature was added sodium hydroxide (200 mg, 5.0 mmol) carefully. The mixture was heated under reflux for 5 h and then cooled to room temperature. The mixture was extracted with dichloromethane (2 x 20 mL). The product was recovered from the aqueous layer by treatment with aqueous hydrogen chloride (1 M, 10.0 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and then concentrated to give diacid **4a** (201 mg, 86%) as a white solid. m.p. 118-119 °C; $[\alpha]_D^{20}$ = -52.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, br, 2H), 7.41–7.21 (m, 5H), 6.47 (d, J = 16.0 Hz, 1H), 6.13 (dd, J =16.0, 8.4 Hz, 1H), 3.44 (d, J = 8.4 Hz, 1H), 3.14–3.04 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 136.9, 131.4, 130.5, 128.6, 127.5, 126.4, 57.5, 37.7, 18.3; HRMS (EI) calcd for $C_{13}H_{14}O_4$ (M) 234.0892, found 234.0899.

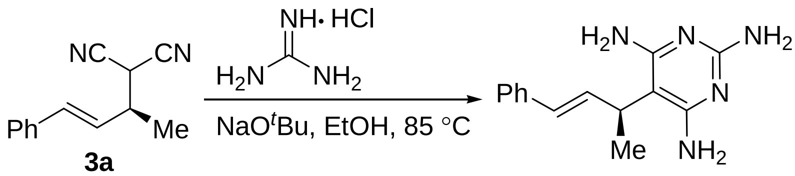


To diacid **4a** (117 mg, 0.50 mmol) at room temperature was added aqueous hydrogen chloride (3 M, 1.0 mL). After that the mixture was heated under reflux for 8 h. The mixture was cooled to room temperature and extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether = 1/1) to give acid **5a** (73.2 mg, 77%) as a colorless oil.[7] $[\alpha]_D^{20}$ = -33.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.19 (m, 5H), 6.42 (d, J = 16.0 Hz, 1H), 6.15 (dd, J =16.0, 7.6 Hz, 1H), 2.91–2.82 (m, 1H), 2.53–2.36 (m, 2H), 1.18 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 137.1, 133.9, 129.0, 128.5, 127.2, 126.2, 41.2, 33.7, 20.2.



Thionyl chloride (59.5 mg, 36.3 μL, 0.50 mmol) was added dropwise to a solution of acid **5a** (57.0 mg, 0.30 mmol) in methanol (1.0 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then quenched with ice water (5.0 mL). The mixture was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether = 1/5) to give ester **6a** (50.1 mg, 80%) as a colorless oil.[8] $[\alpha]_D^{20}$ = -62.6 (c = 1.0, CCl_4), Lit.:[8]

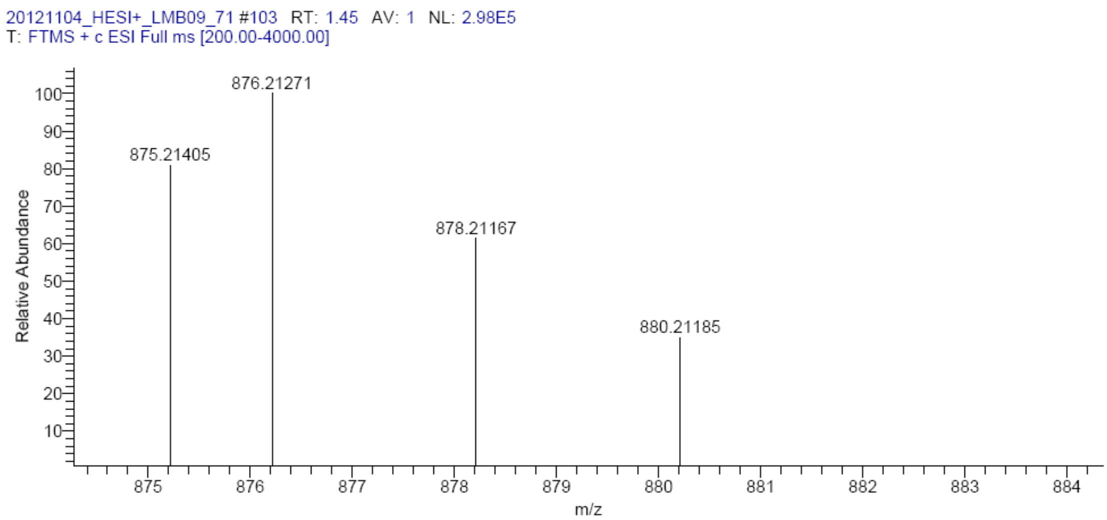
79% ee, $[\alpha]_D^{20}$ = -49.2 (c = 1.3, CCl_4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.20 (m, 5H), 6.41 (d, J = 16.0 Hz, 1H), 6.14 (dd, J =16.0, 7.6 Hz, 1H), 3.67 (s, 3H), 2.91–2.80 (m, 1H), 2.49–2.33 (m, 2H), 1.15 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 137.3, 134.2, 128.9, 128.5, 127.1, 126.1, 51.3, 41.4, 34.0, 20.2.

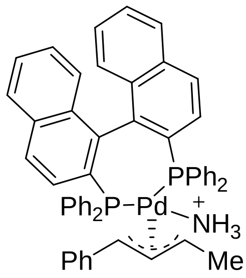


A mixture of malononitrile **3a** (196 mg, 1.0 mmol), guanidine hydrochloride (105 mg, 1.1 mmol), sodium *tert*-butoxide (106 mg, 1.1 mmol) in ethanol (1.0 mL) was refluxed at 85 ^{o}C for 8 h. After filtration, the solution was cooled to 0 ^{o}C to give a white solid. Recrystallization from ethanol gave pyrimidine **7a** (235 mg, 92%) as a white solid. m.p. 242-243 °C; $[\alpha]_D^{20}$ = -9.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44–7.40 (m, 2H), 7.34–7.27 (m, 2H), 7.24–7.17 (m, 1H), 6.55-6.41 (m, 2H), 5.37 (s, br, 4H), 5.25 (s, br, 2H), 3.76-3.69 (m, 1H), 1.31 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 161.8, 160.8, 137.2, 134.7, 128.5, 127.6, 127.0, 125.9, 88.5, 30.9, 16.2; HRMS (EI) calcd for $C_{14}H_{17}N_5$ (M) 255.1484, found 255.1483.

Electrospray ionization mass spectrometric analysis of the reaction mixture

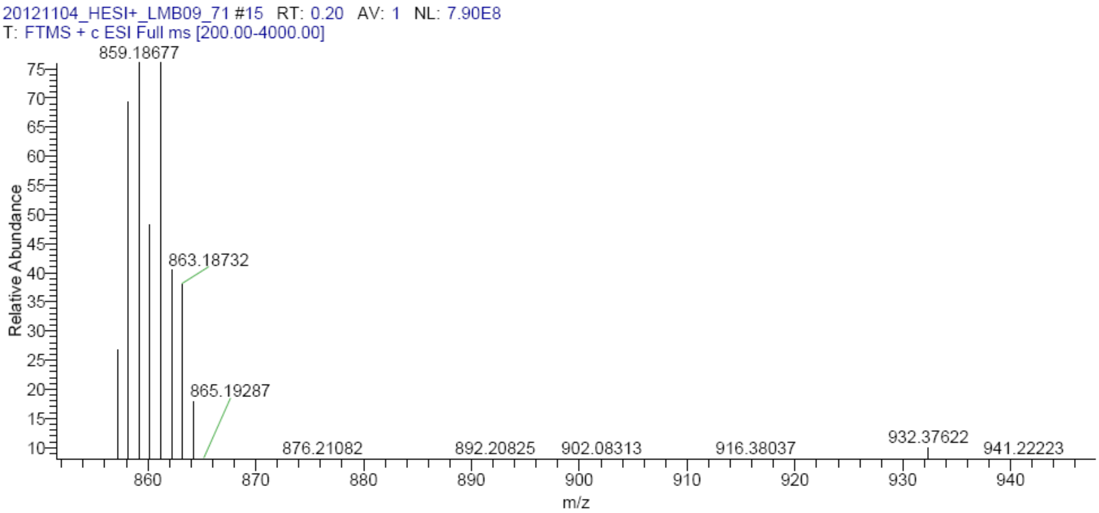
A mixture of amine **1a** (73.5 mg, 0.50 mmol), malononitrile **2a** (39.6 mg, 0.60 mmol), racemic BINAP (12.5 mg, 4 mol%), and $[Pd(allyl)Cl]_2$ (3.64 mg, 2 mol%) in toluene (1.0 mL) was stirred under nitrogen at room temperature for 10 min. The mixture was cooled to room temperature and subjected to ESI-MS (positive mode) analysis. Copied below is the spectrum we obtained and the species have been identified according to the high resolution mass data.

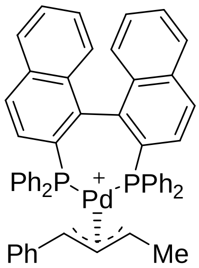




8a

π-Allylpalladium **8a**: HRMS (ESI) calcd for $C_{50}H_{46}NP_2Pd^+$ 876.21348, found 876.21271.

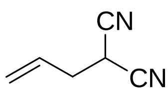




9a

π-Allylpalladium **9a**: HRMS (ESI) calcd for $C_{54}H_{43}P_2Pd^+$ 859.18693, found 859.18677.

Isolation of compound 10a



10a

A mixture of amine **1a** (147 mg, 1.0 mmol), malononitrile (**2a**) (79.0 mg, 1.2 mmol), racemic BINAP (25.0 mg, 4 mol%), and [Pd(allyl)Cl]$_2$ (7.28 mg, 2 mol%) in toluene (2.0 mL) was stirred under nitrogen at room temperature for 3 h. The mixture was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1:20), to give compound **10a** (3.9 mg, 92% yield based on [Pd(allyl)Cl]$_2$) as a colorless oil.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92–5.79 (m, 1H), 5.44–5.37 (m, 2H), 3.80 (t, J = 6.8 Hz, 1H), 2.78-2.73 (m, 2H).

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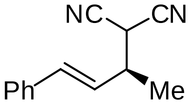
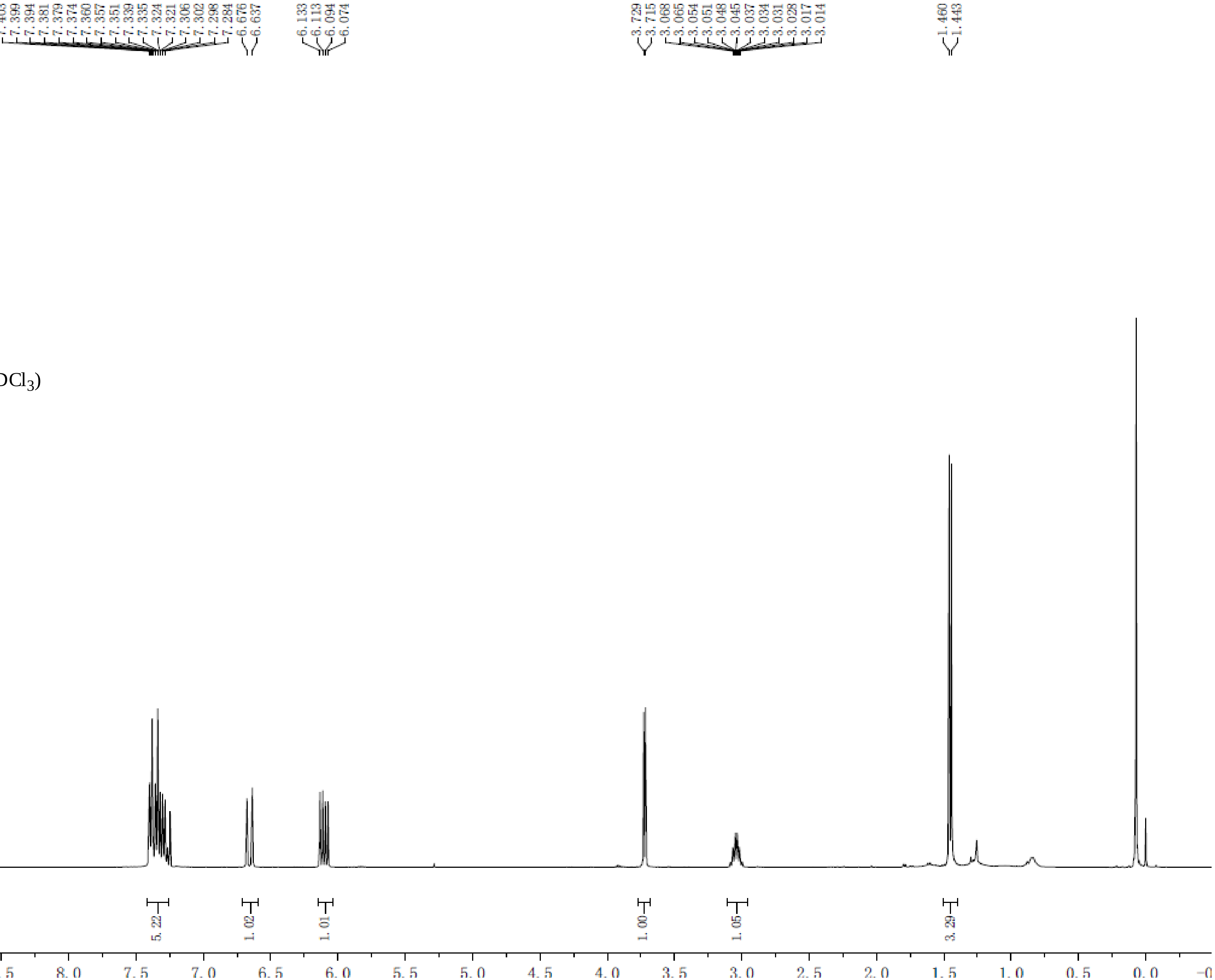
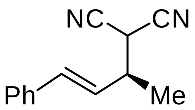


3a

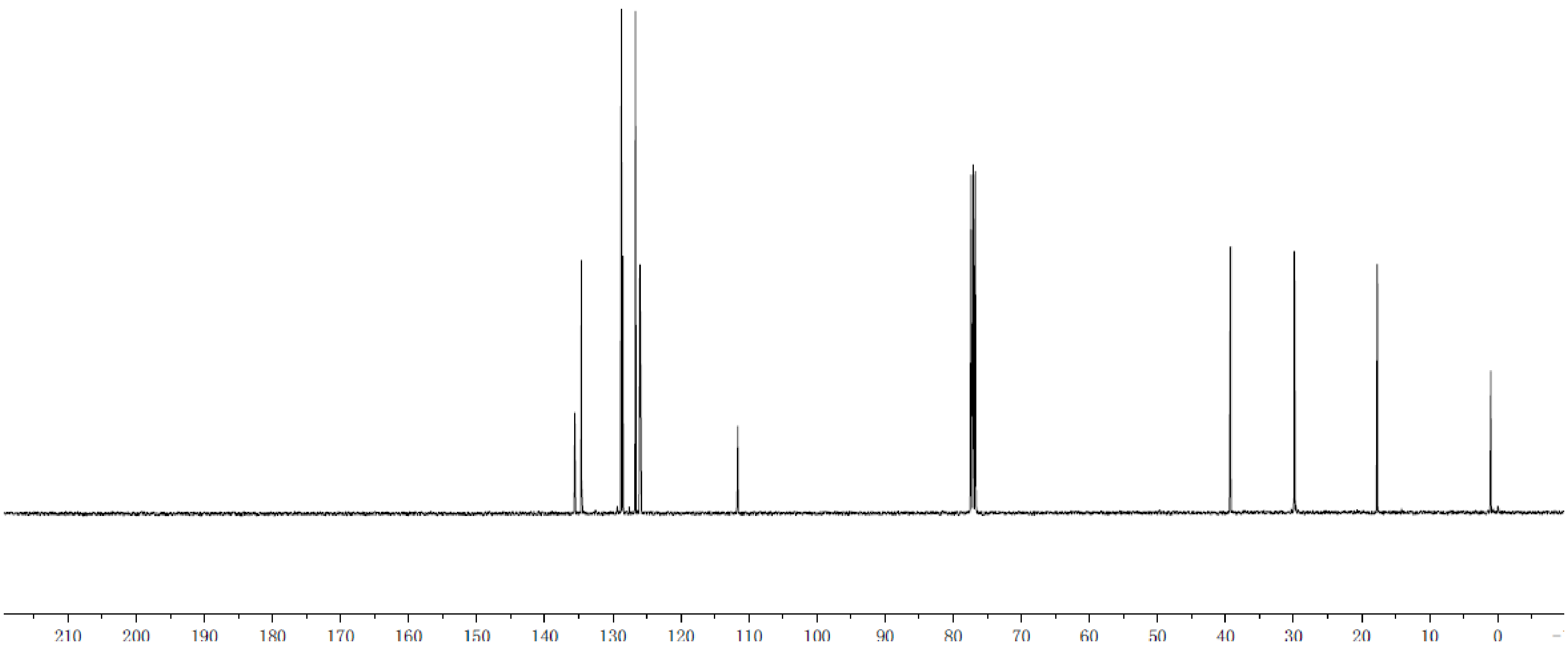
^{1}H NMR (400 MHz, $CDCl_3$)

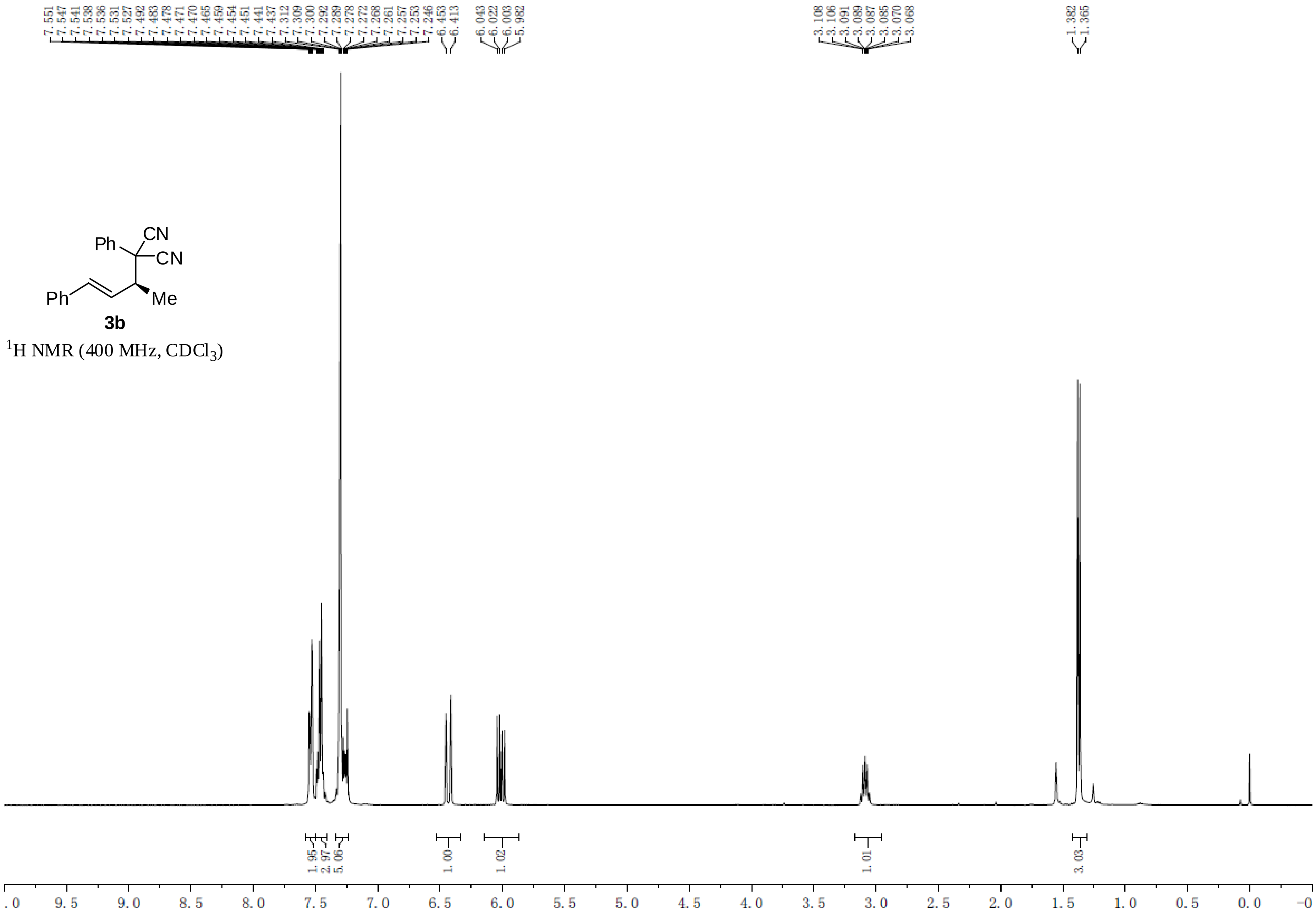


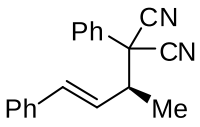


3a

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

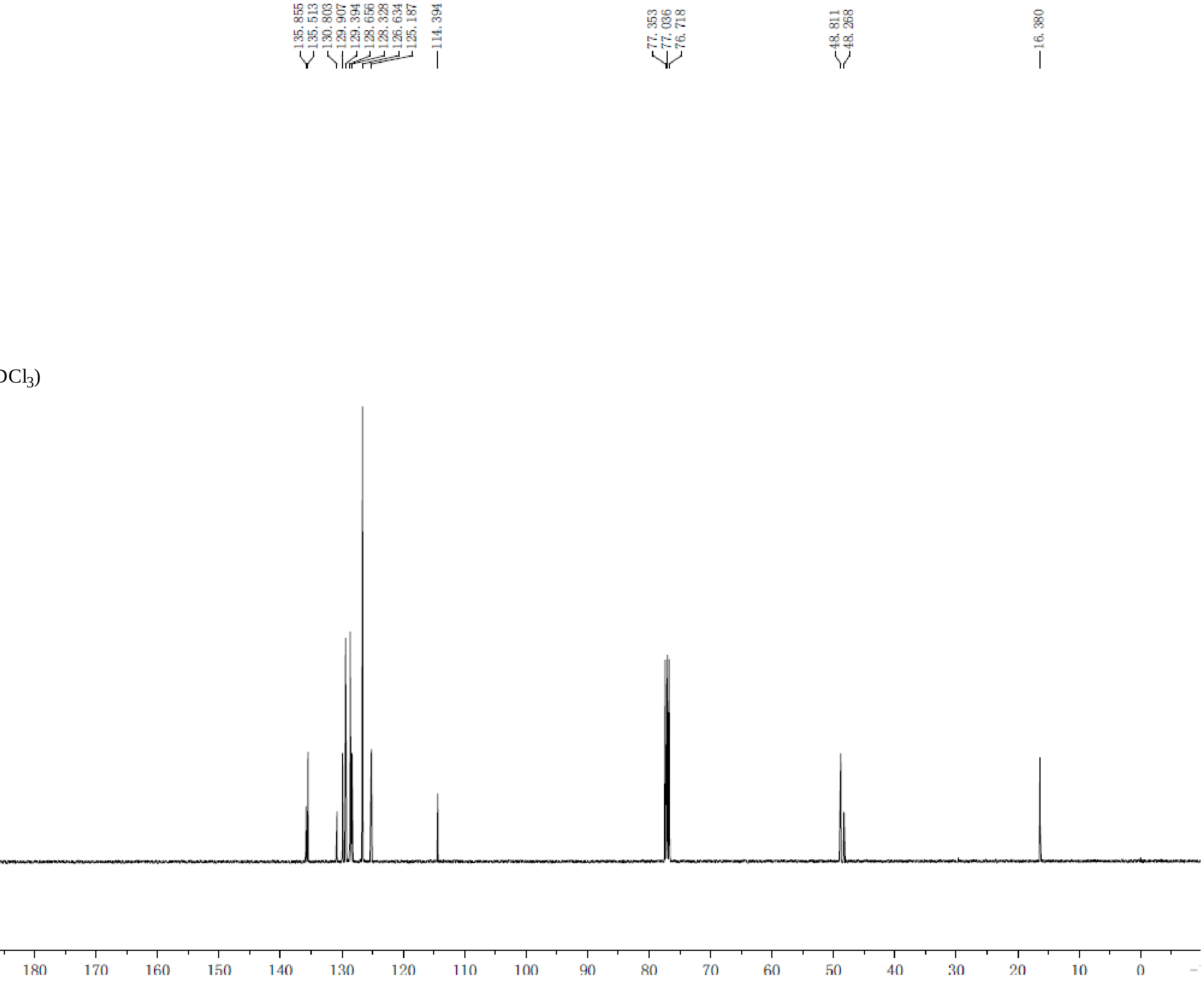


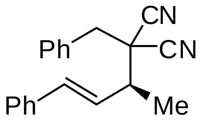

Ph
CN
CN
Ph
Me
3b
^{1}H NMR (400 MHz, CDCl$_3$)



3b

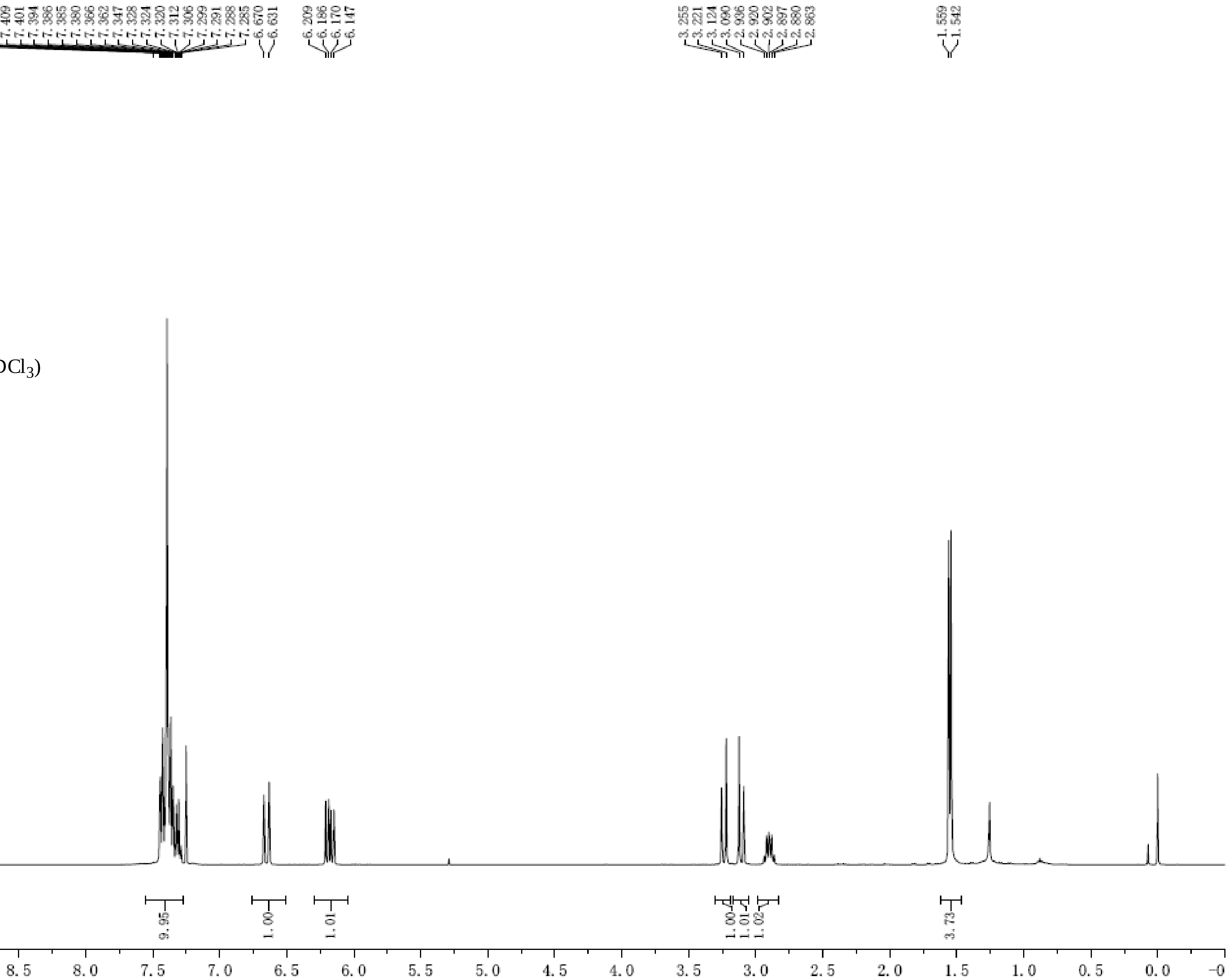
^{13}C NMR (100 MHz, $CDCl_3$)

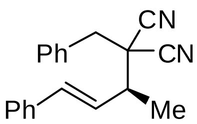




3c

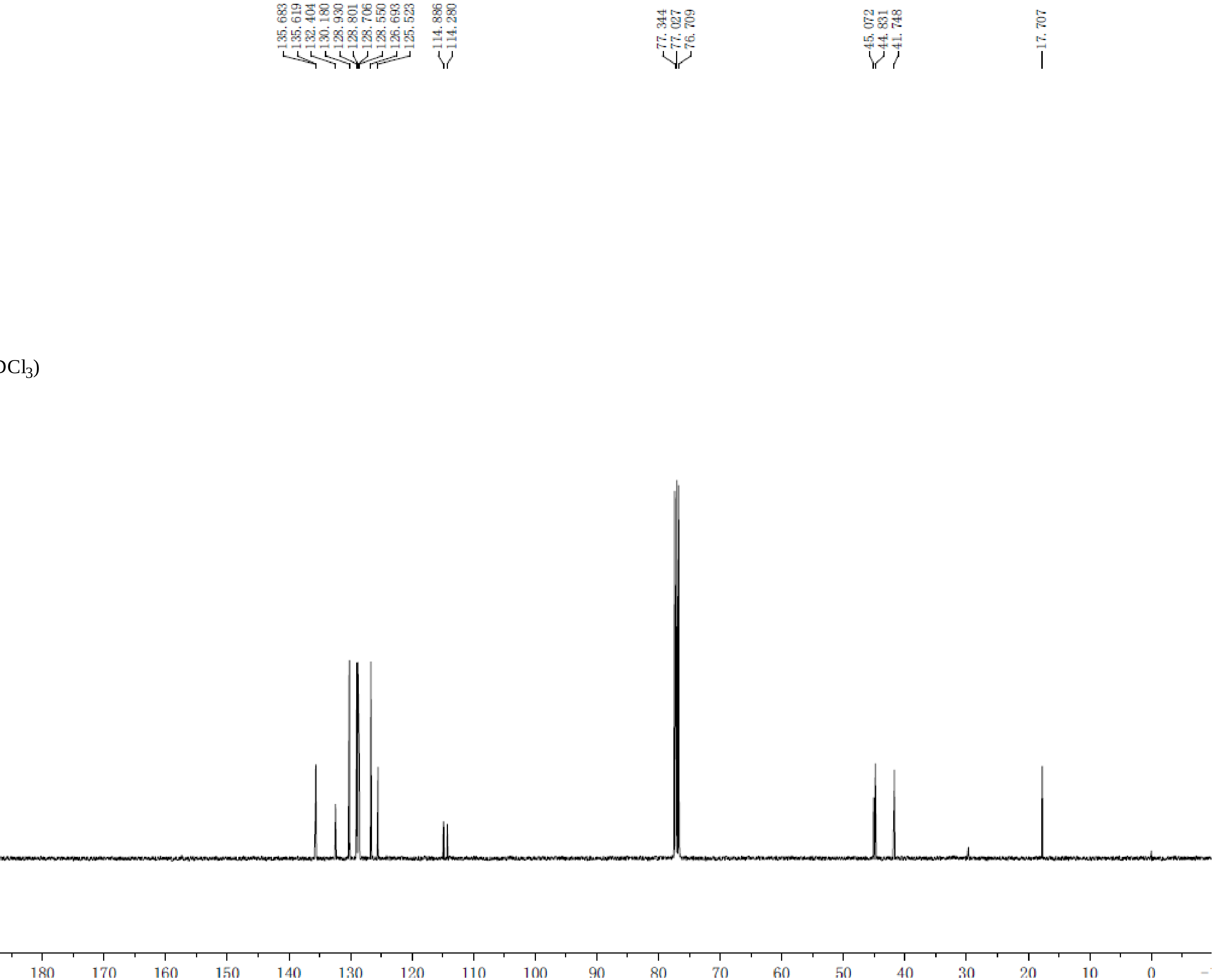
^{1}H NMR (400 MHz, $CDCl_3$)

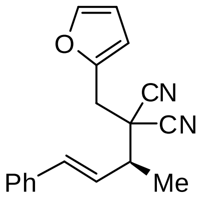




3c

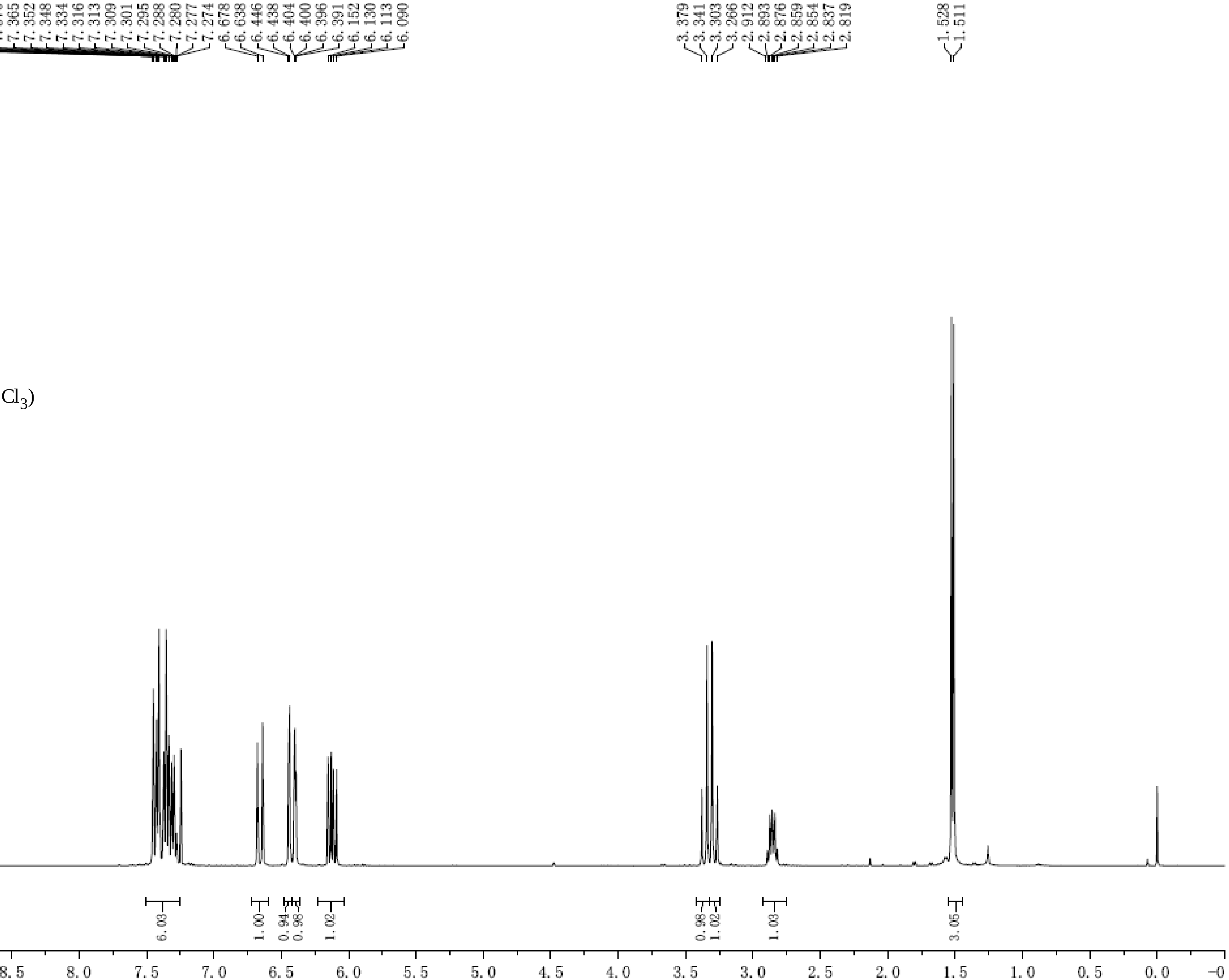
^{13}C NMR (100 MHz, $CDCl_3$)

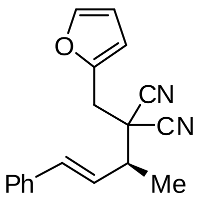




3d

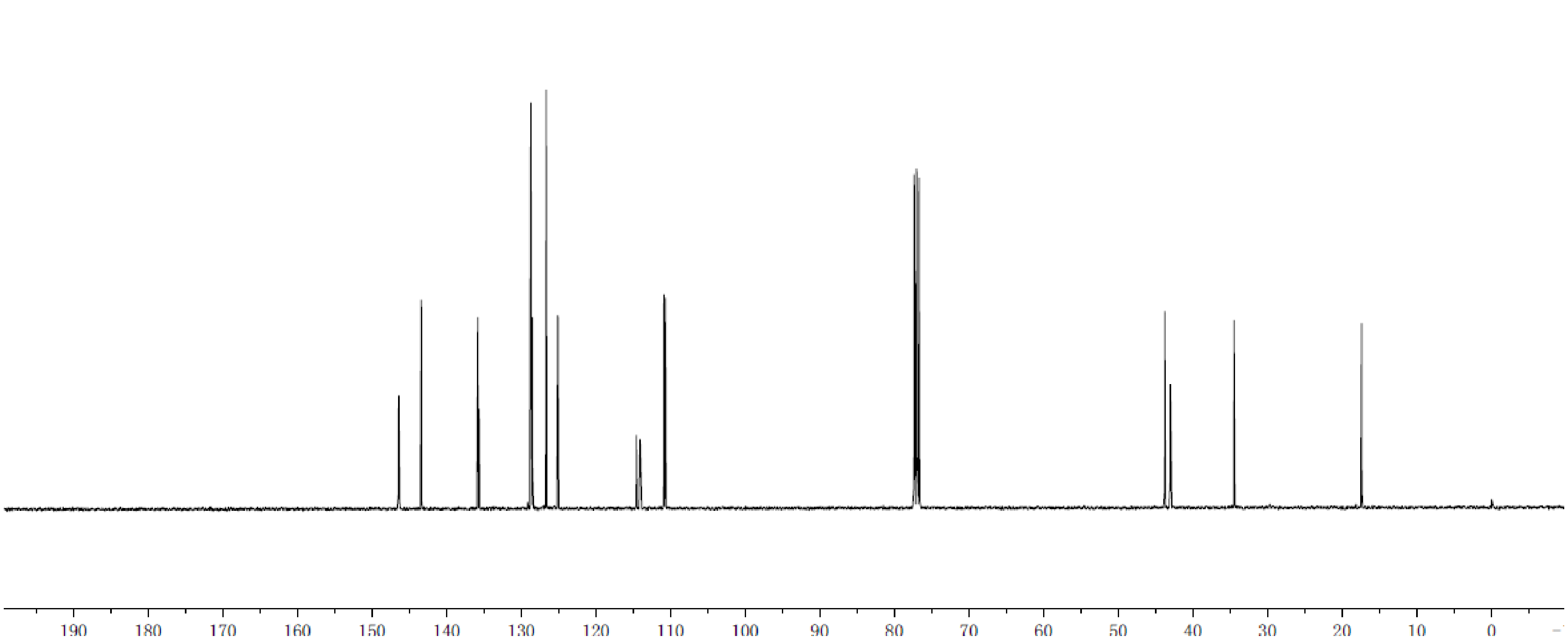
[1]H NMR (400 MHz, $CDCl_3$)

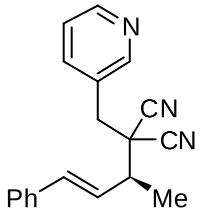




3d

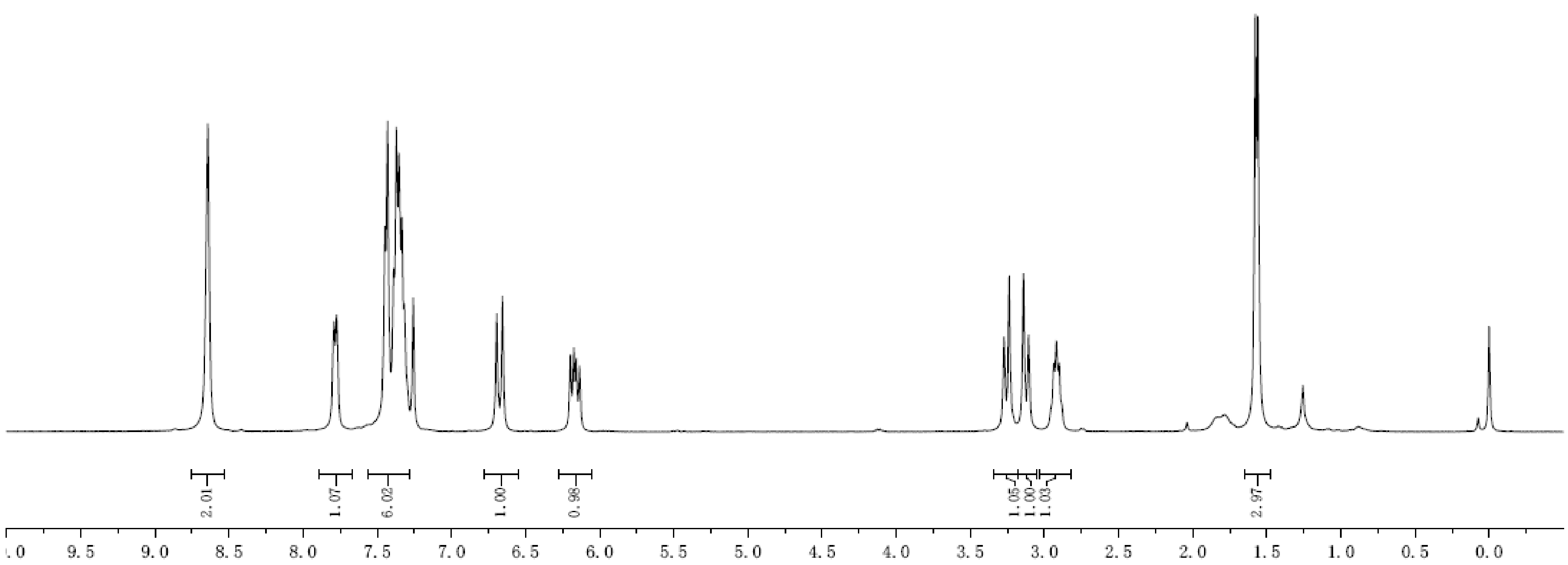
^{13}C NMR (100 MHz, $CDCl_3$)

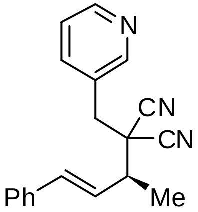




3e

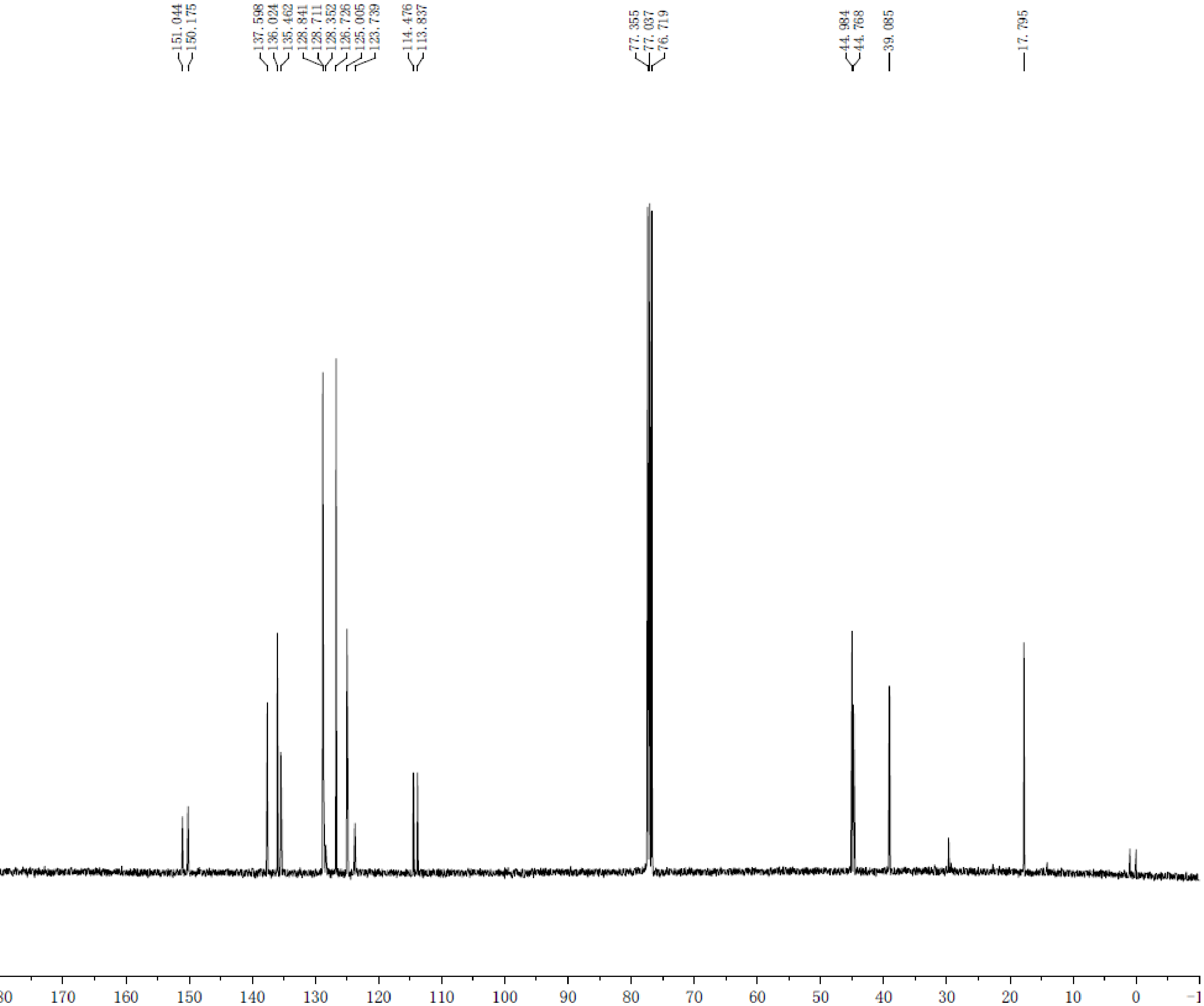
^{1}H NMR (400 MHz, $CDCl_3$)

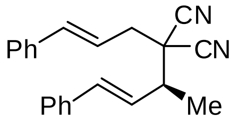




3e

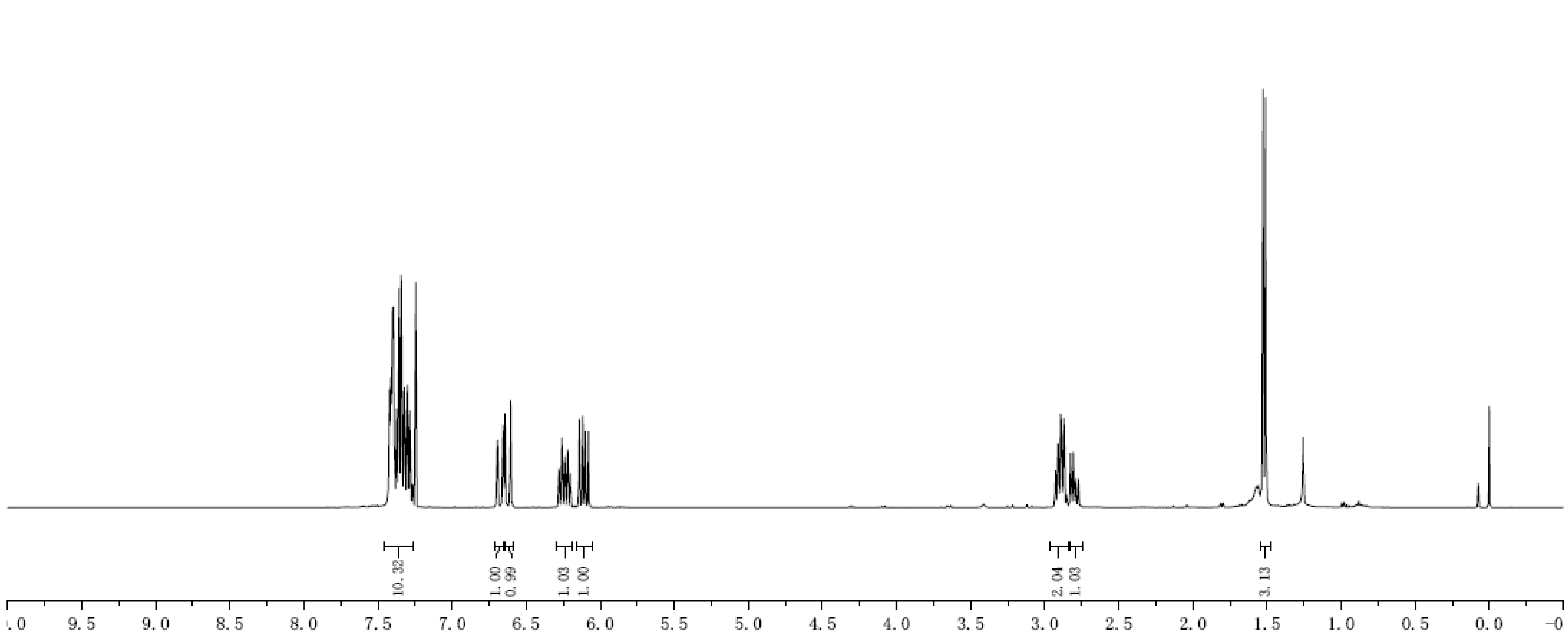
^{13}C NMR (100 MHz, $CDCl_3$)

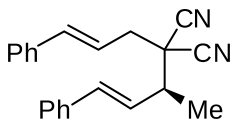




3f

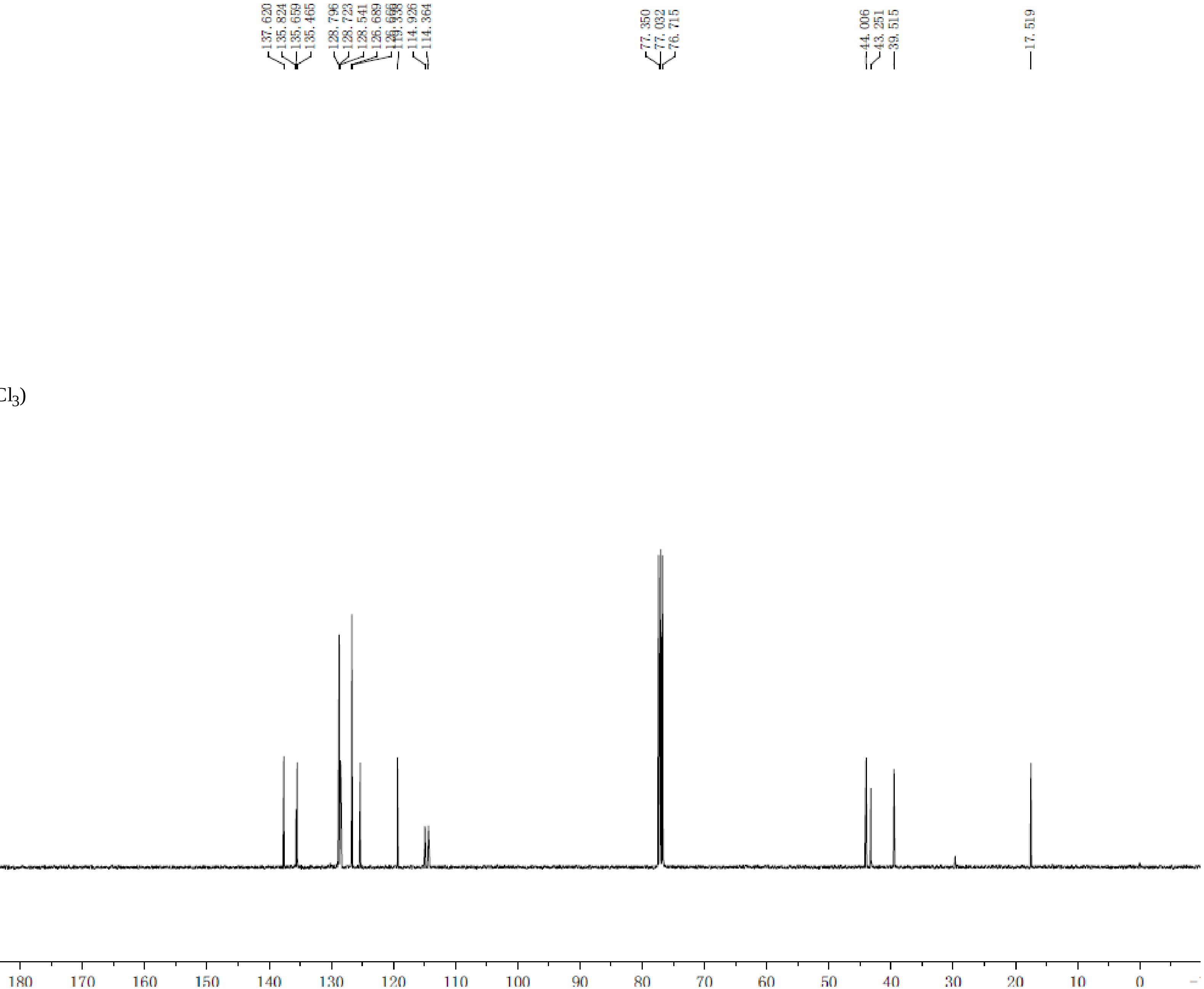
^{1}H NMR (400 MHz, $CDCl_3$)

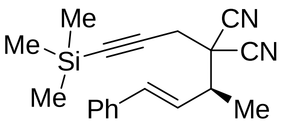




3f

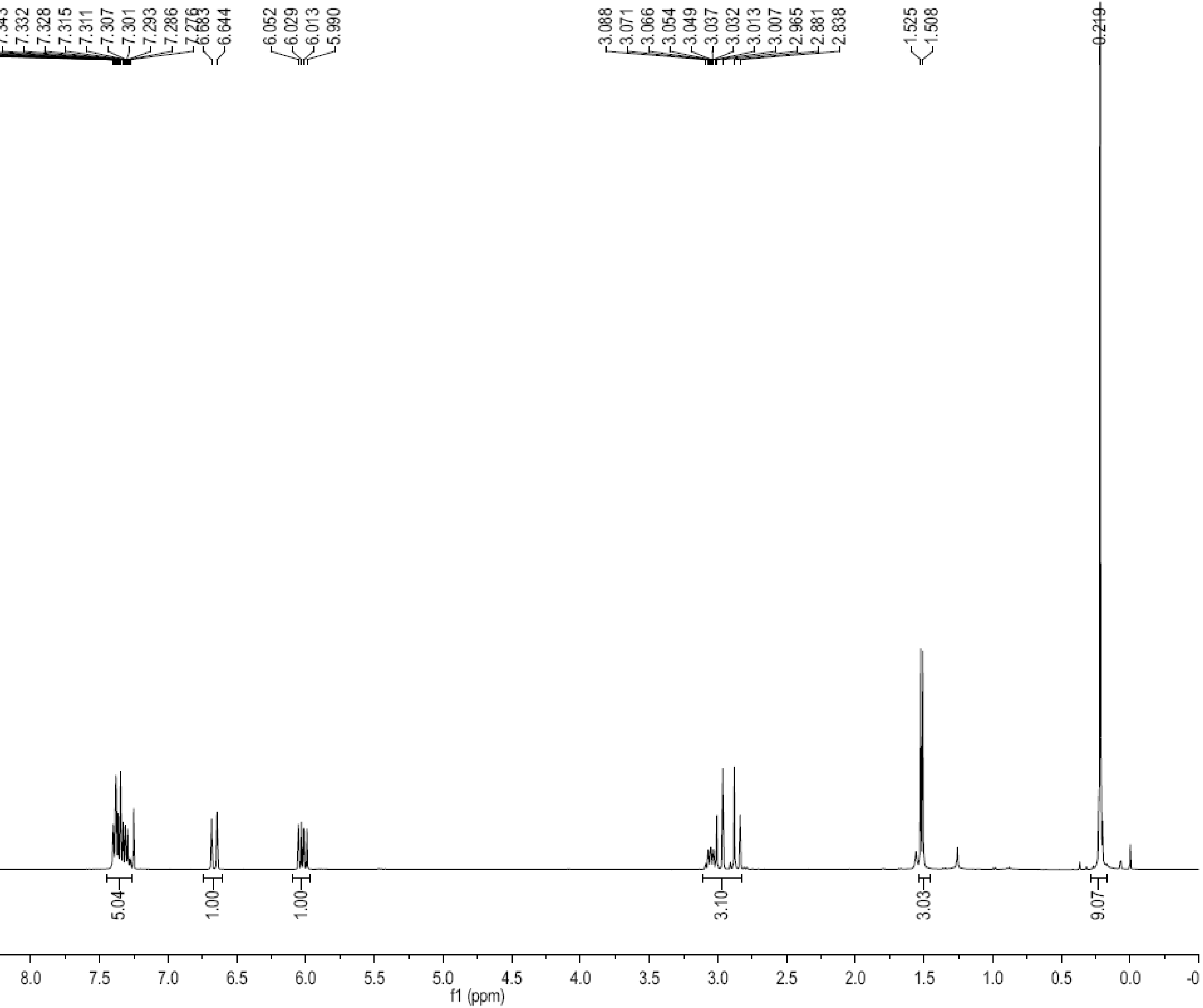
^{13}C NMR (100 MHz, $CDCl_3$)

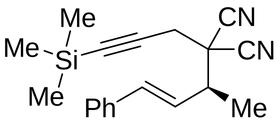




3g

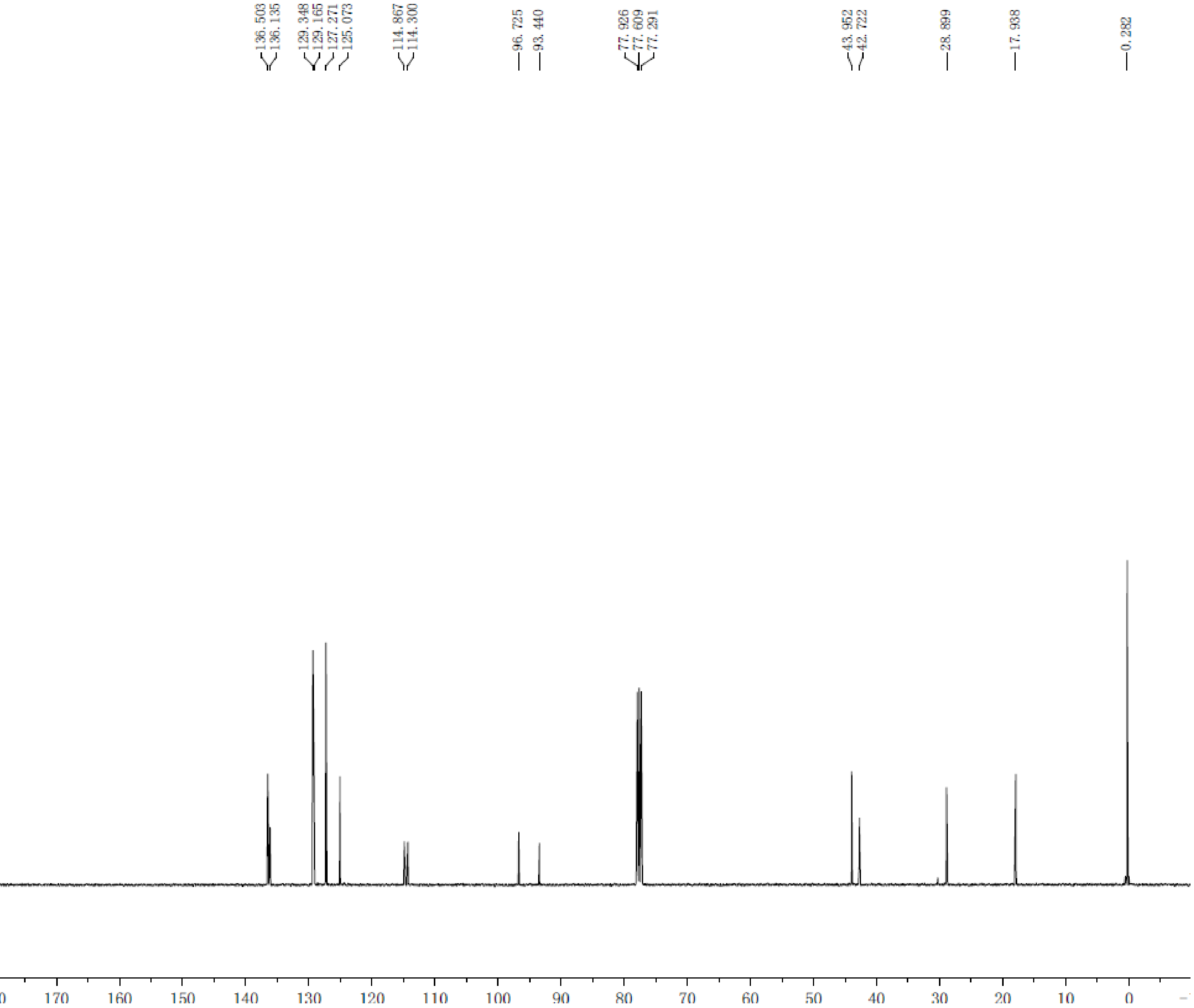
^{1}H NMR (400 MHz, $CDCl_3$)

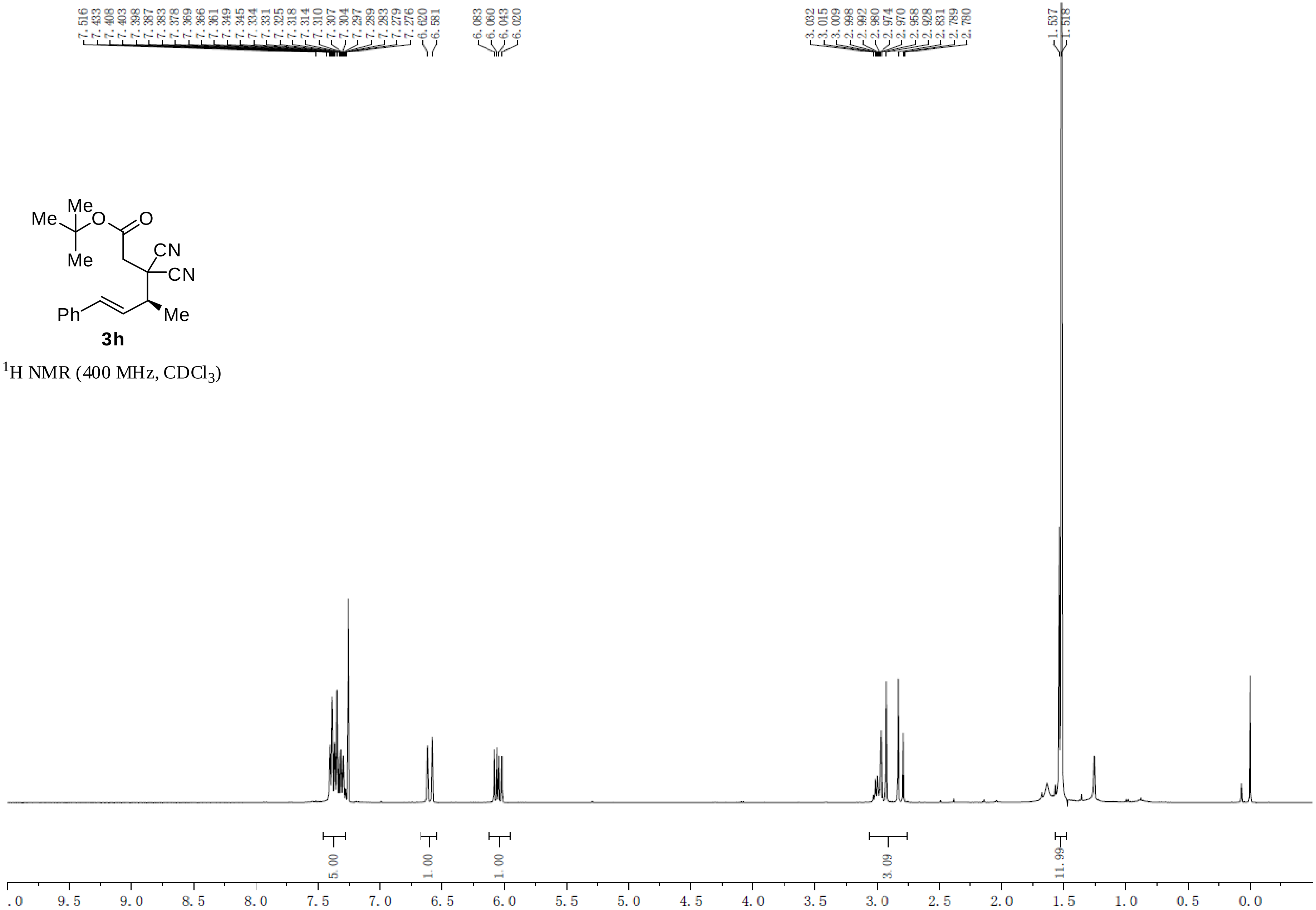




3g

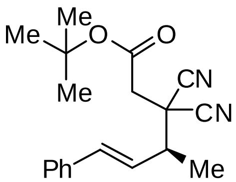
^{13}C NMR (100 MHz, $CDCl_3$)





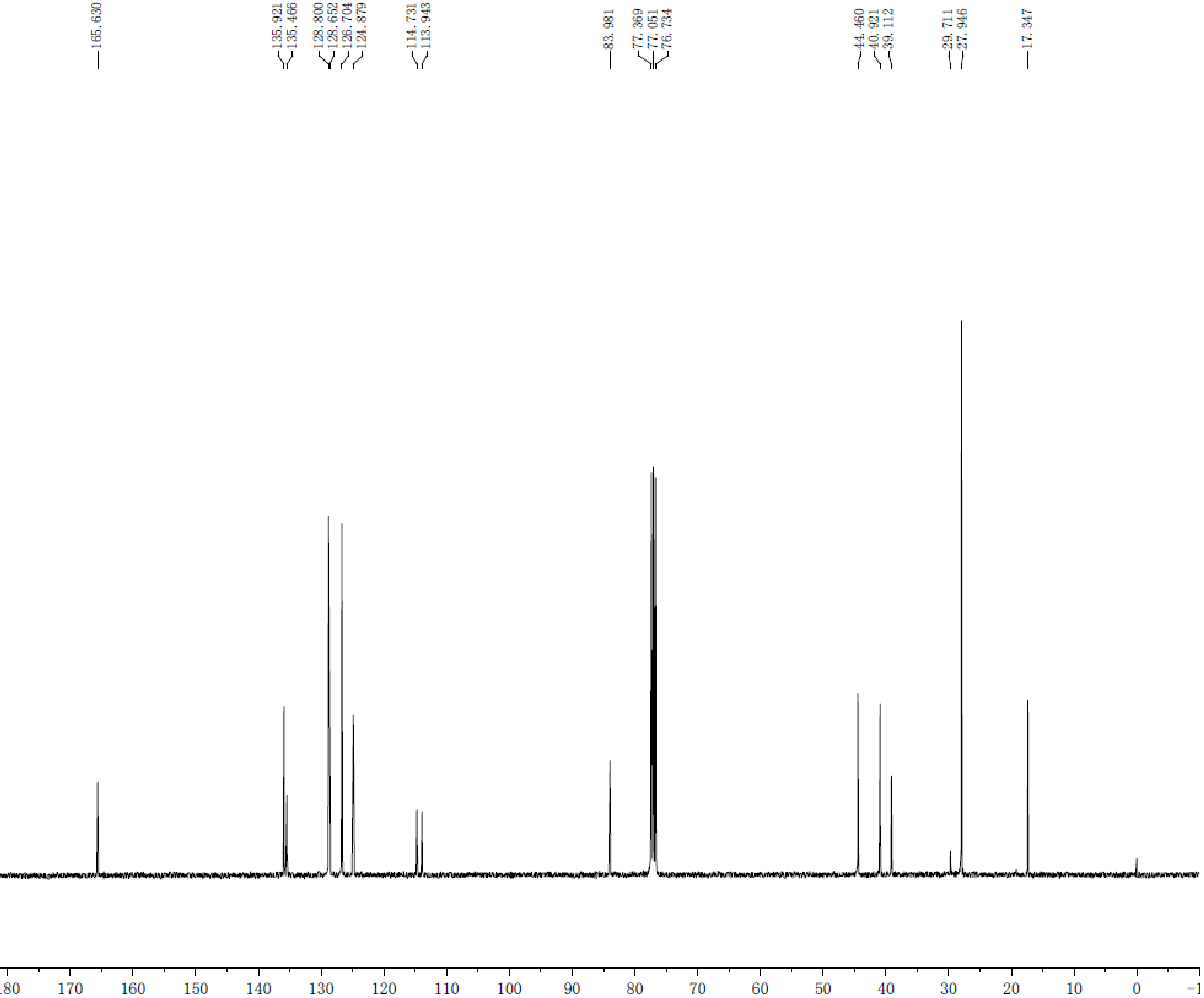
3h

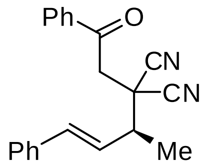
^{1}H NMR (400 MHz, $CDCl_3$)



3h

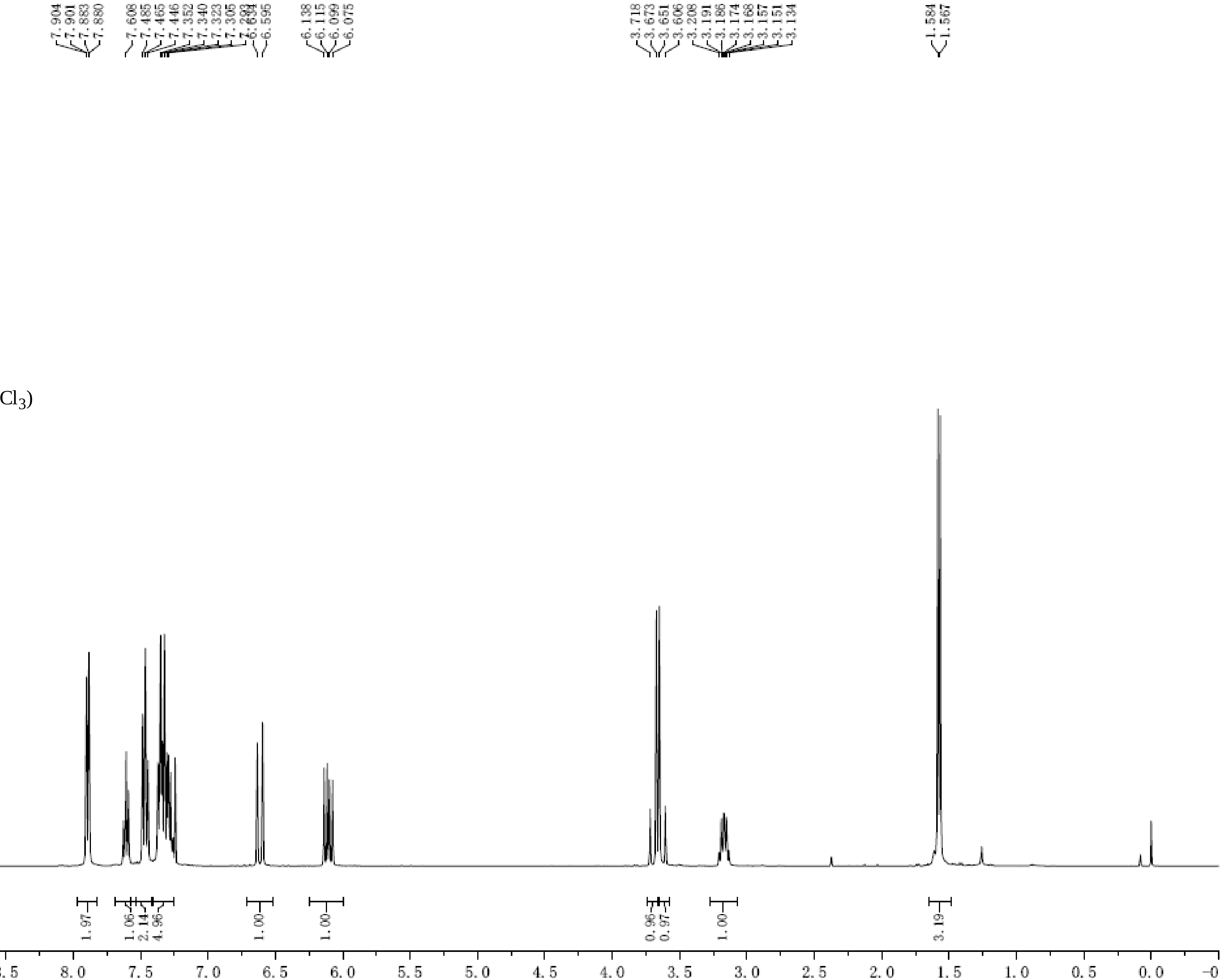
^{13}C NMR (100 MHz, $CDCl_3$)

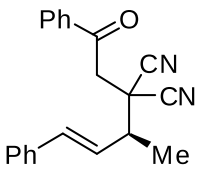




3i

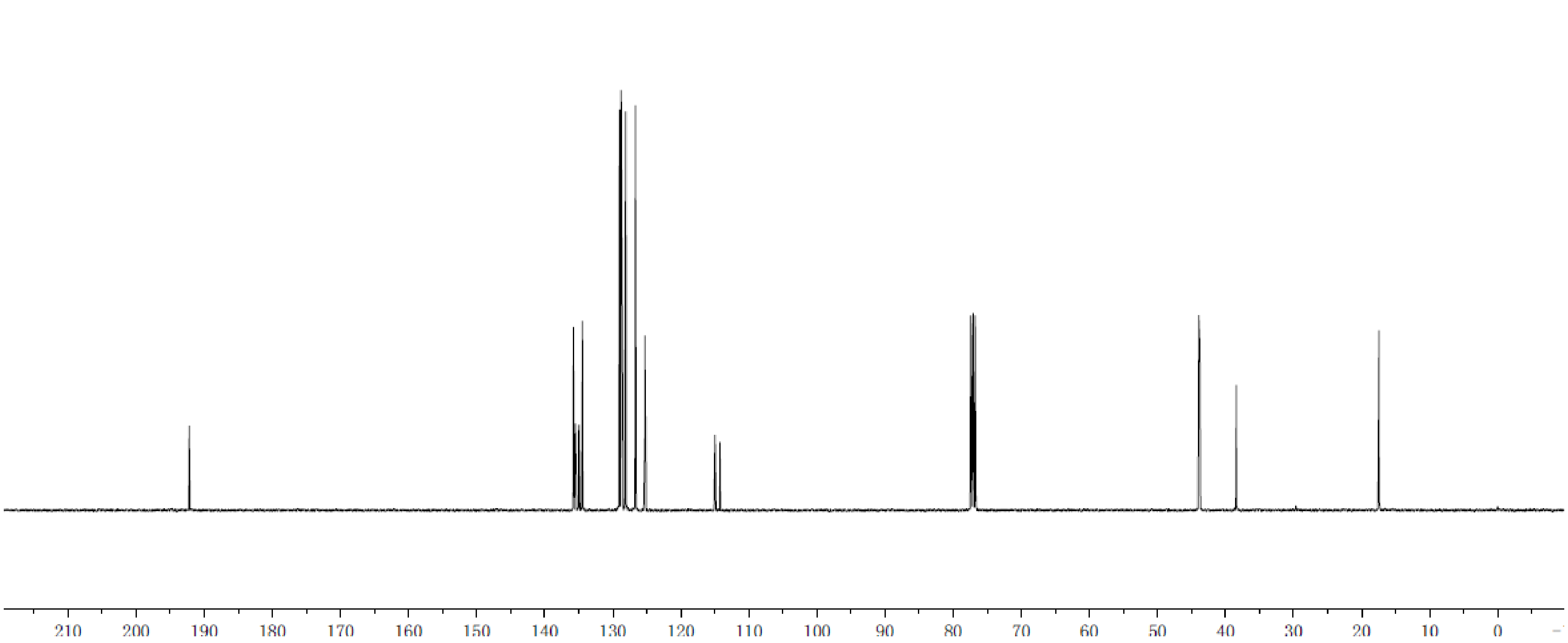
^{1}H NMR (400 MHz, $CDCl_3$)

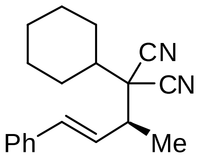




3i

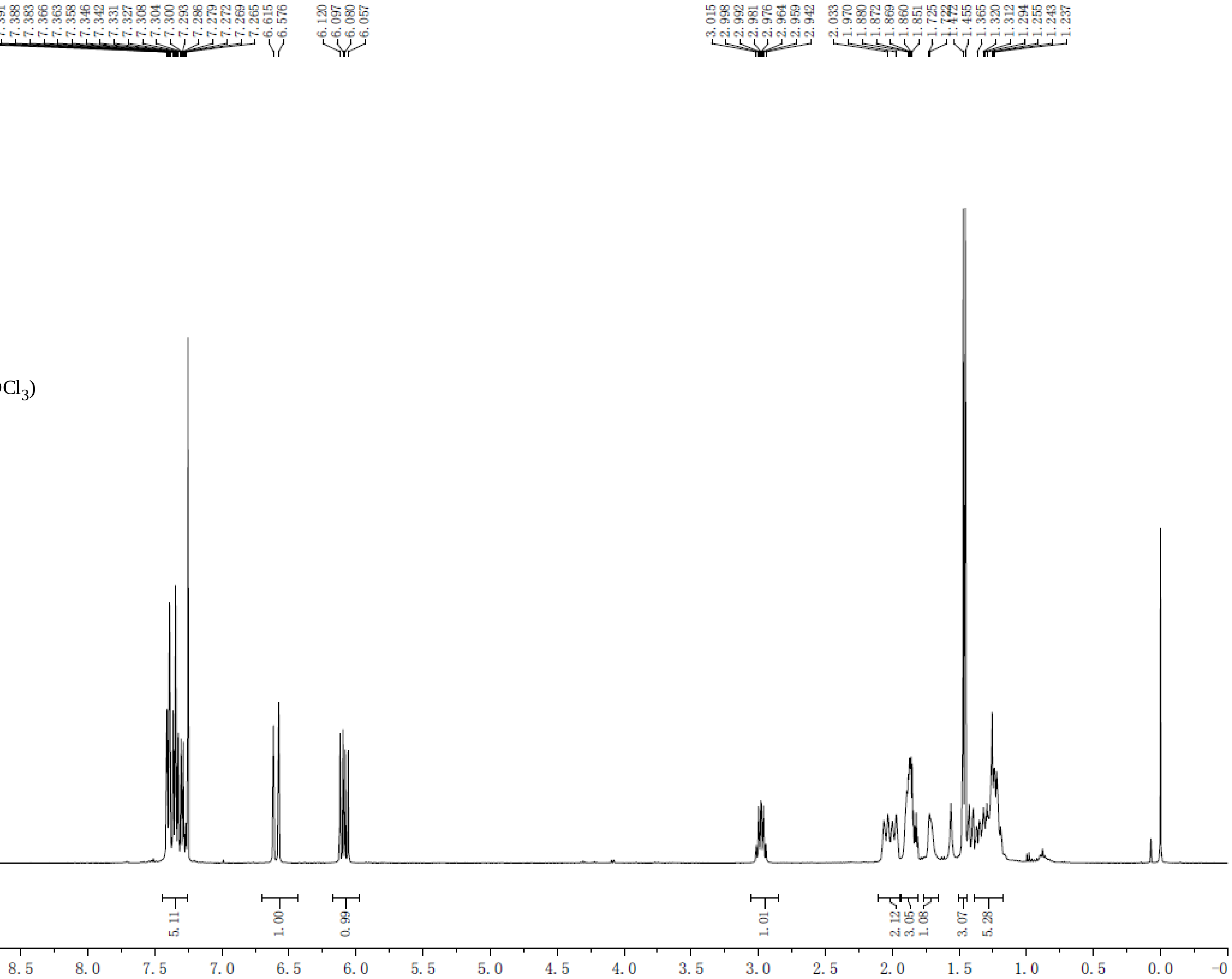
^{13}C NMR (100 MHz, $CDCl_3$)

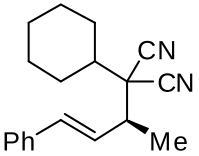




3j

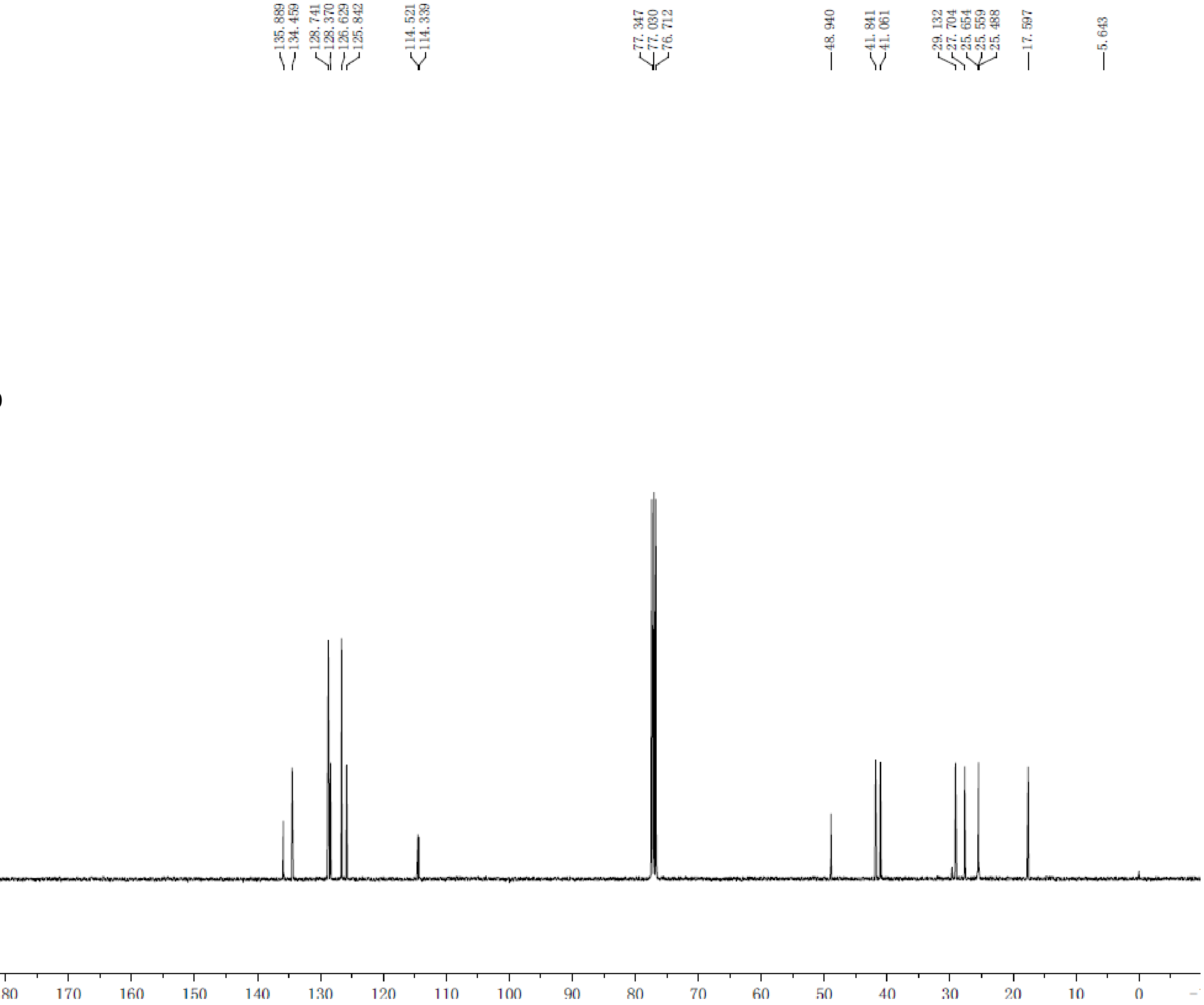
^{1}H NMR (400 MHz, $CDCl_3$)

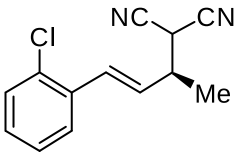




3j

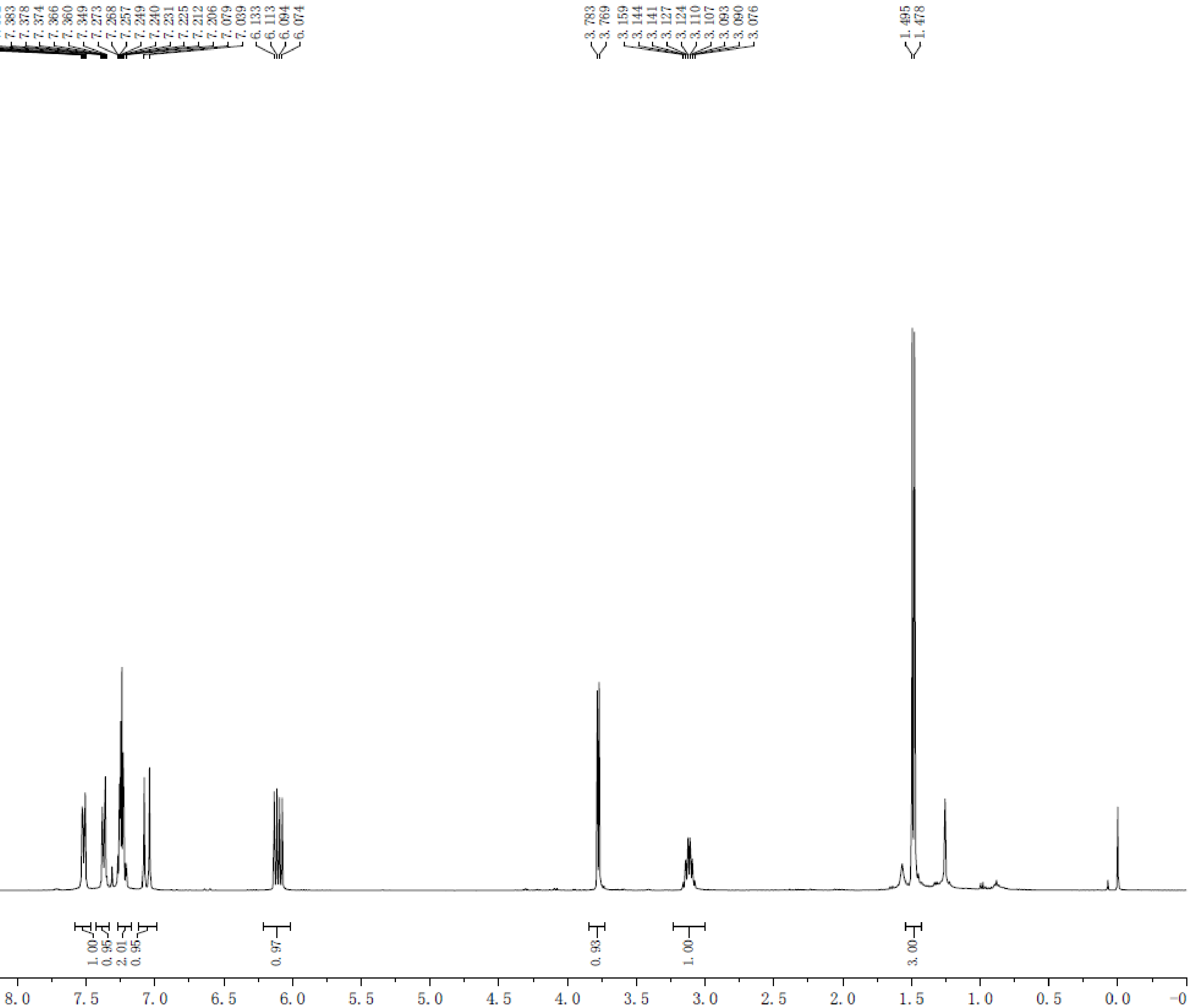
^{13}C NMR (100 MHz, $CDCl_3$)

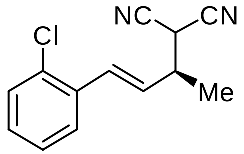




3k

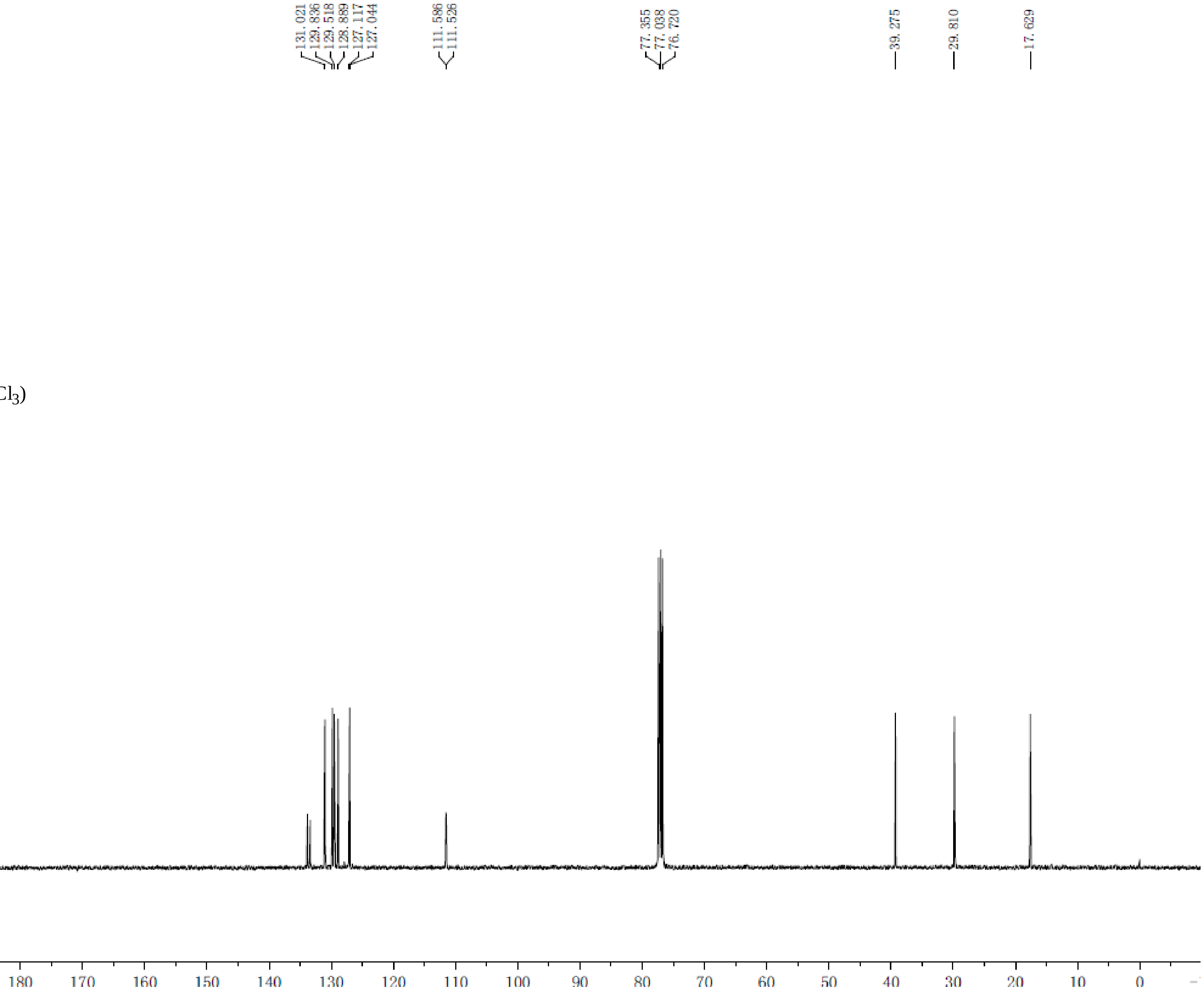
^{1}H NMR (400 MHz, $CDCl_3$)

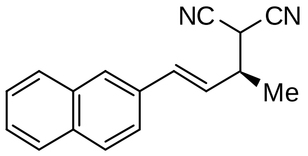




3k

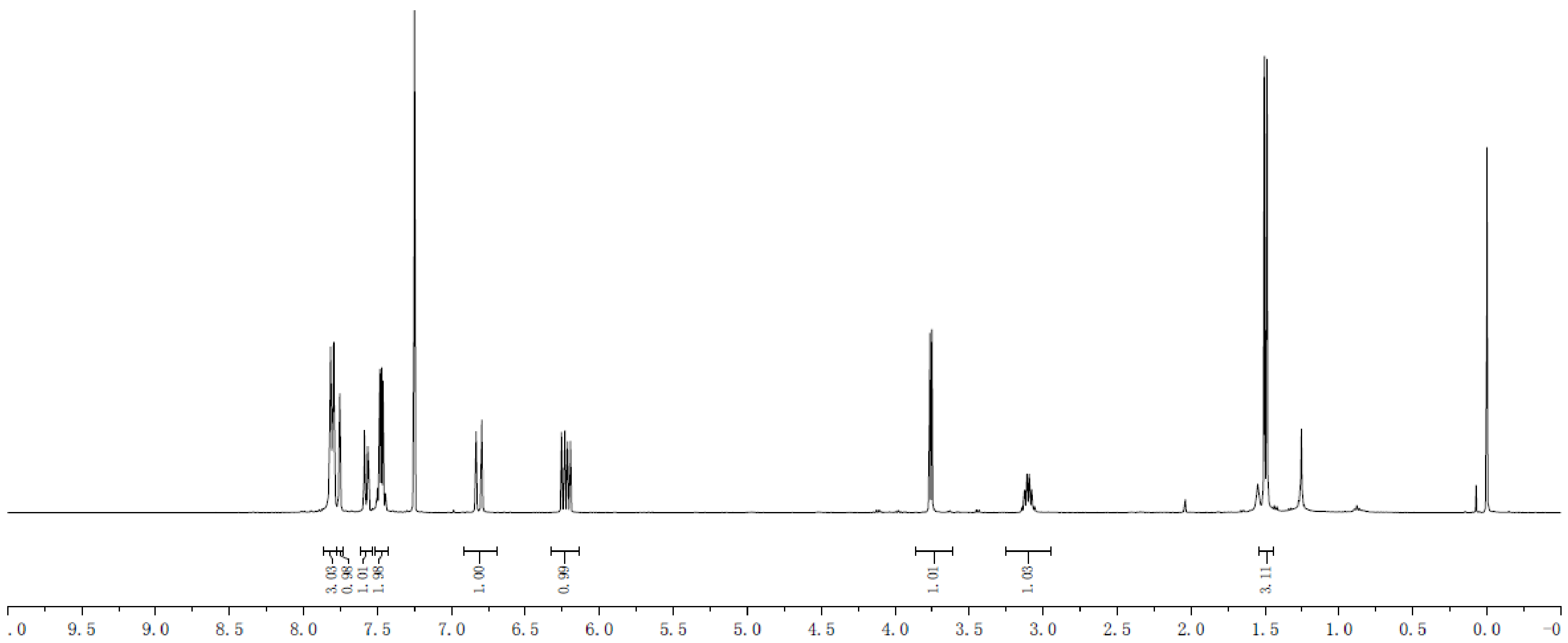
^{13}C NMR (100 MHz, $CDCl_3$)

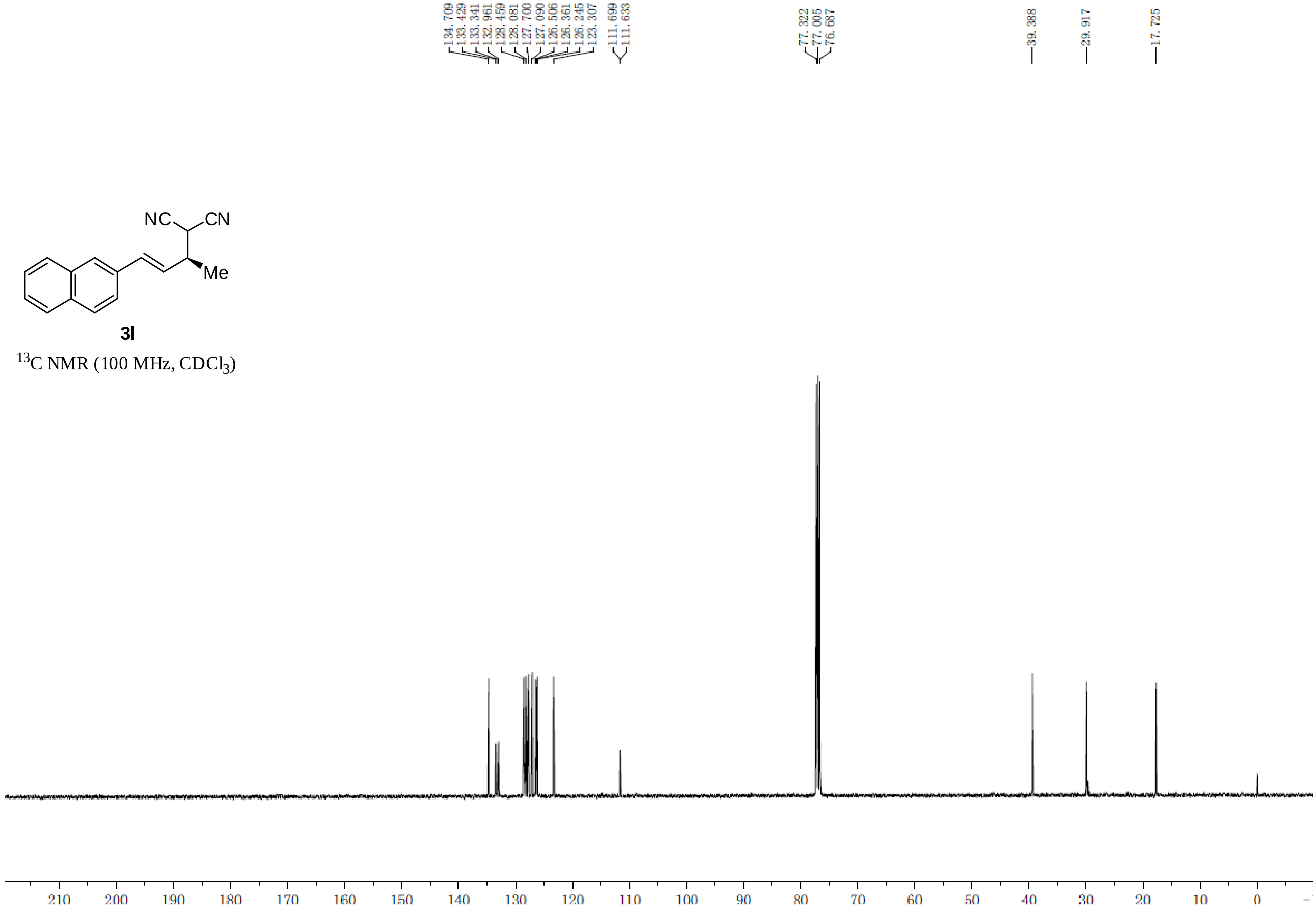




3l

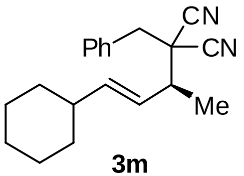
^{1}H NMR (400 MHz, $CDCl_3$)





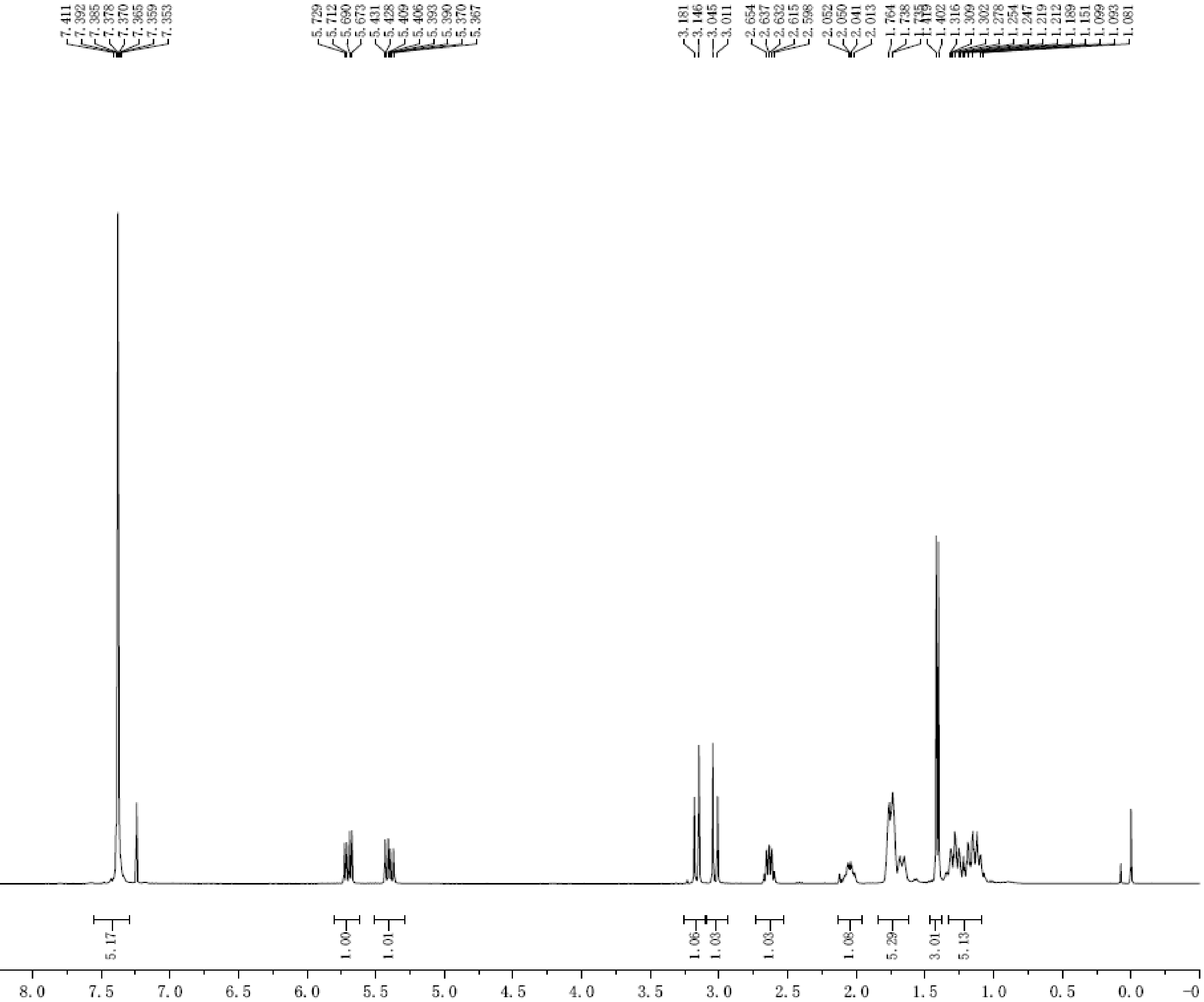
3l

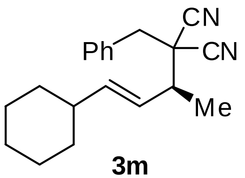
^{13}C NMR (100 MHz, $CDCl_3$)



3m

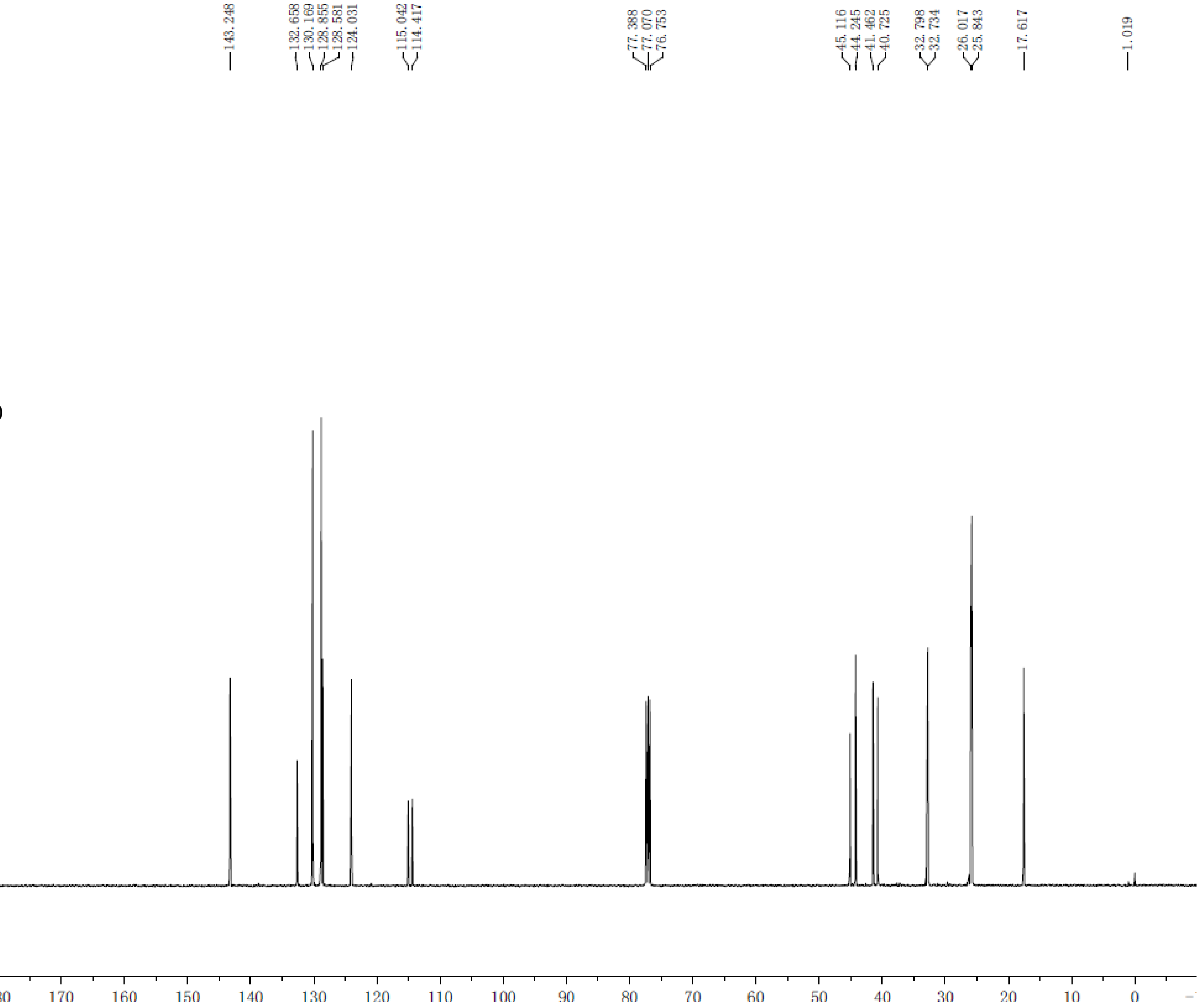
^{1}H NMR (400 MHz, $CDCl_3$)

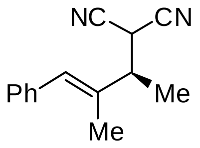




3m

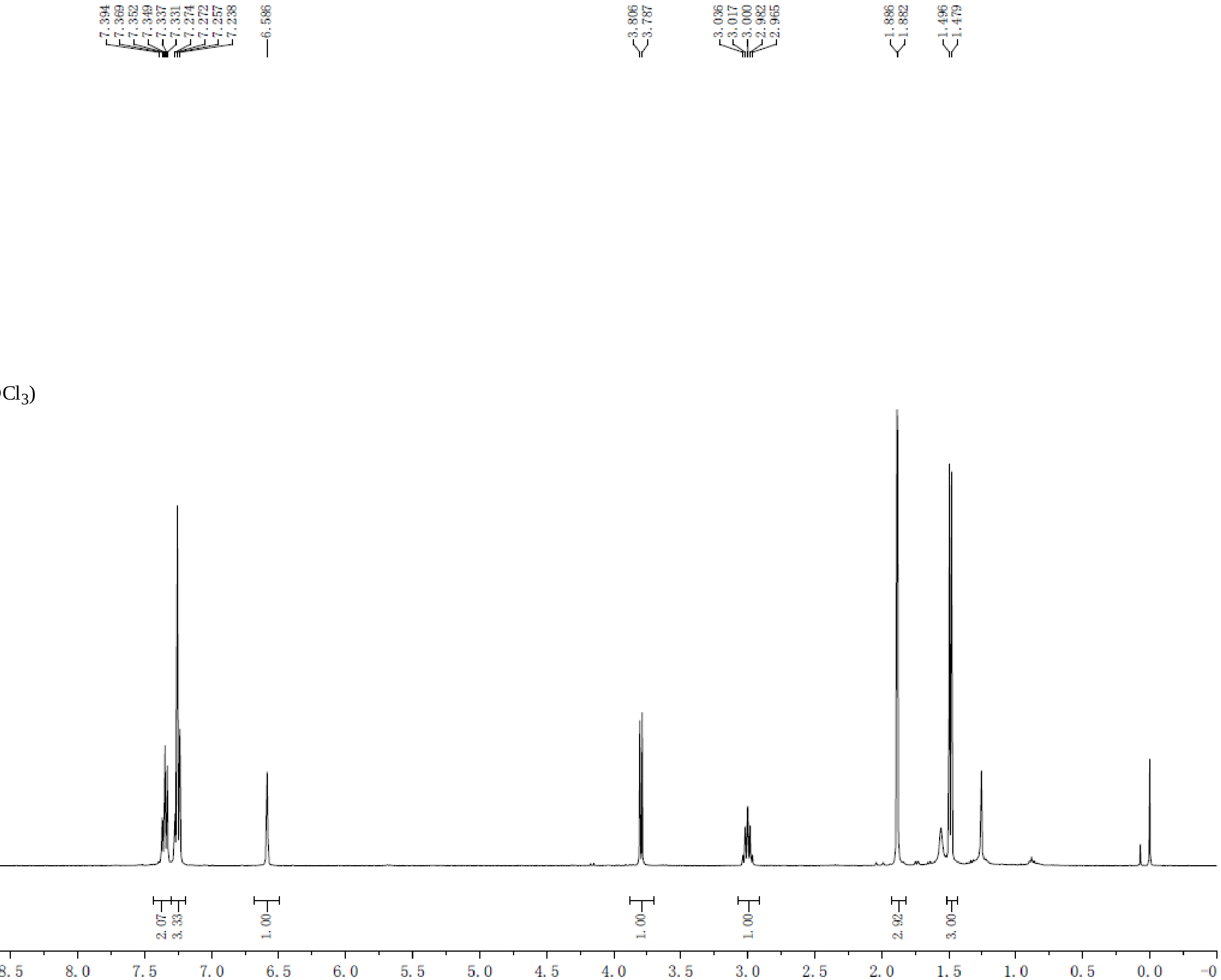
^{13}C NMR (100 MHz, $CDCl_3$)

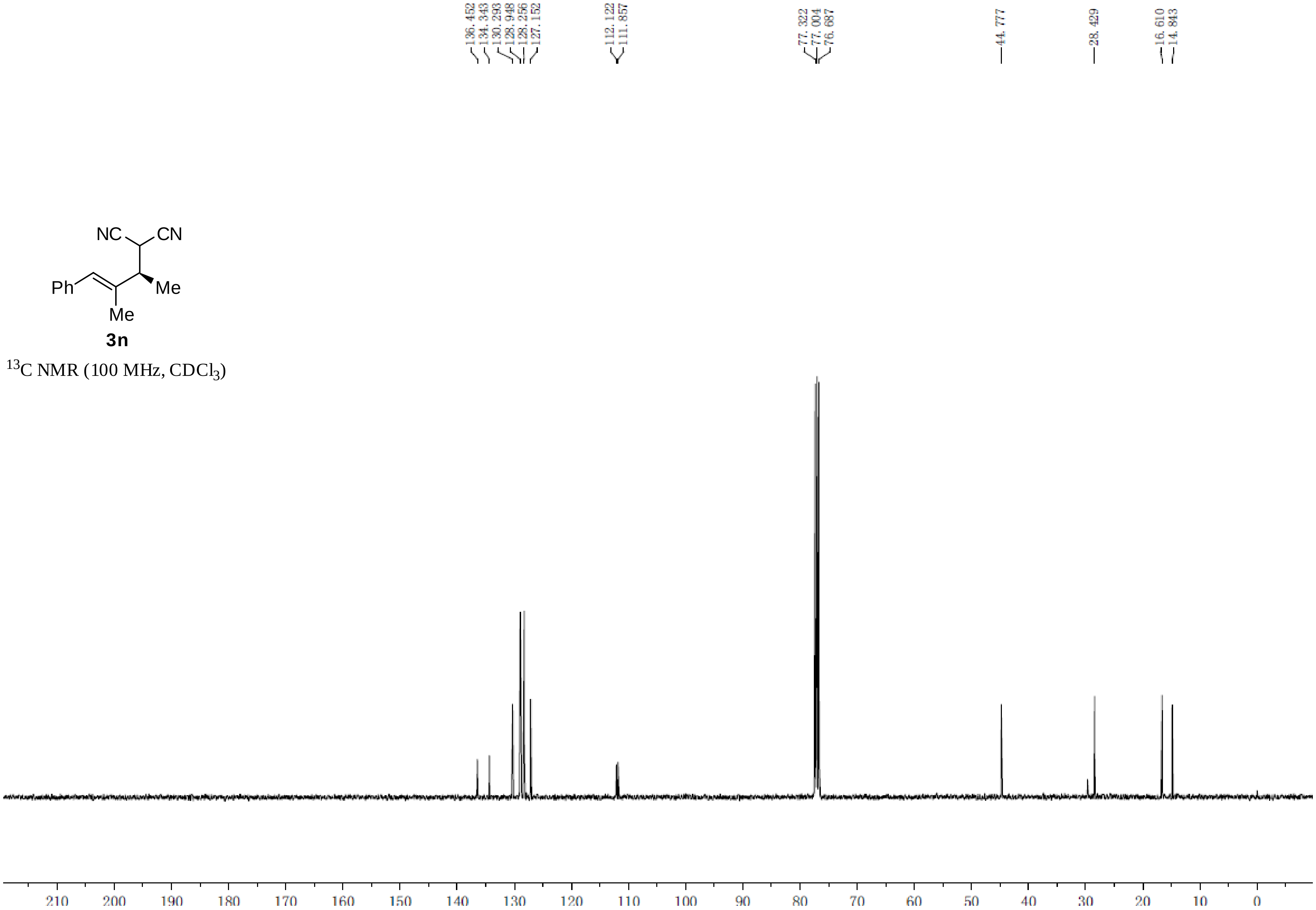




3n

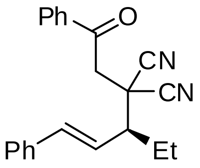
^{1}H NMR (400 MHz, $CDCl_3$)





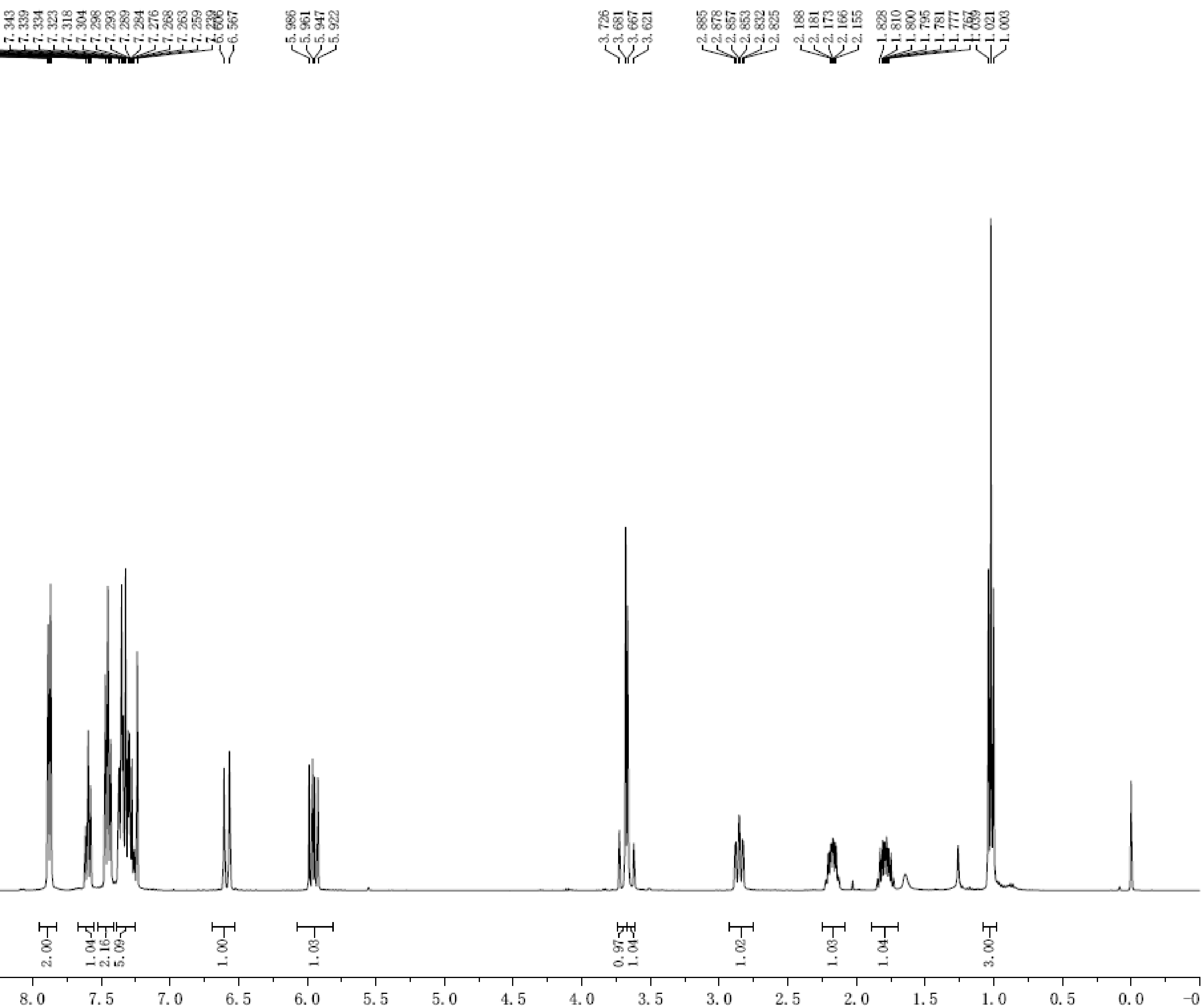
3n

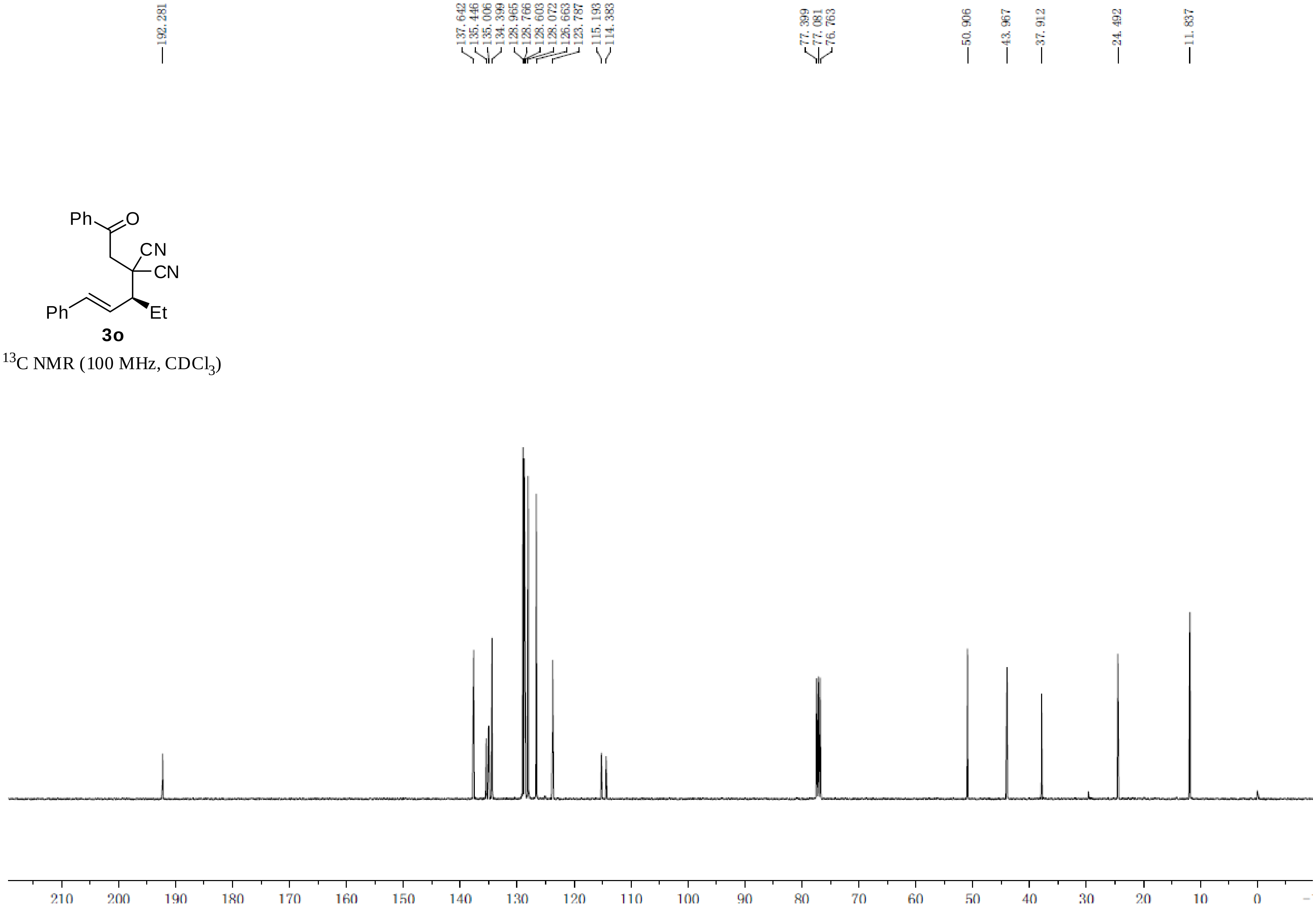
^{13}C NMR (100 MHz, $CDCl_3$)



3o

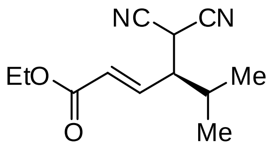
^{1}H NMR (400 MHz, $CDCl_3$)





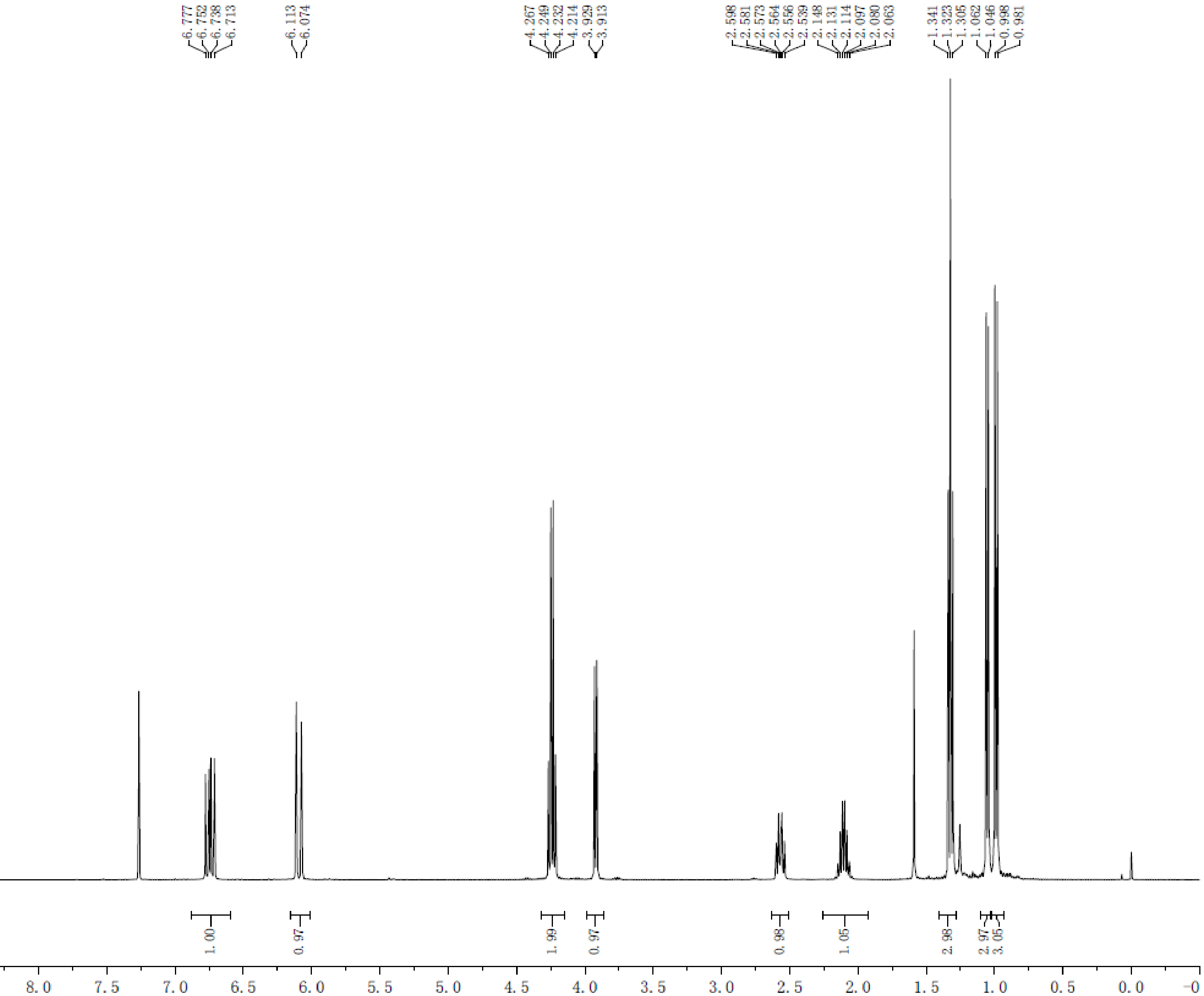
3o

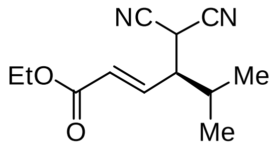
^{13}C NMR (100 MHz, $CDCl_3$)



3p

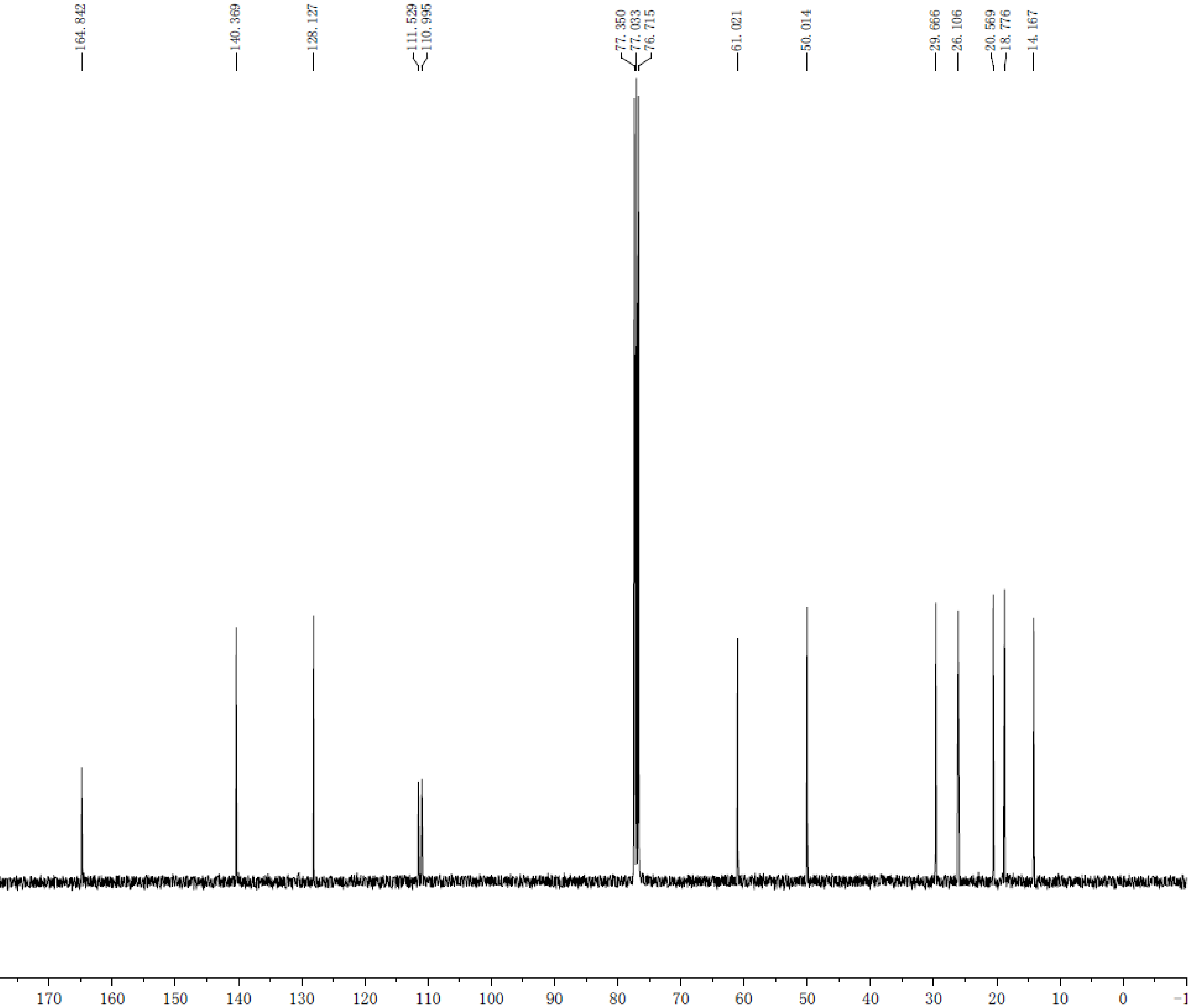
^{1}H NMR (400 MHz, $CDCl_3$)

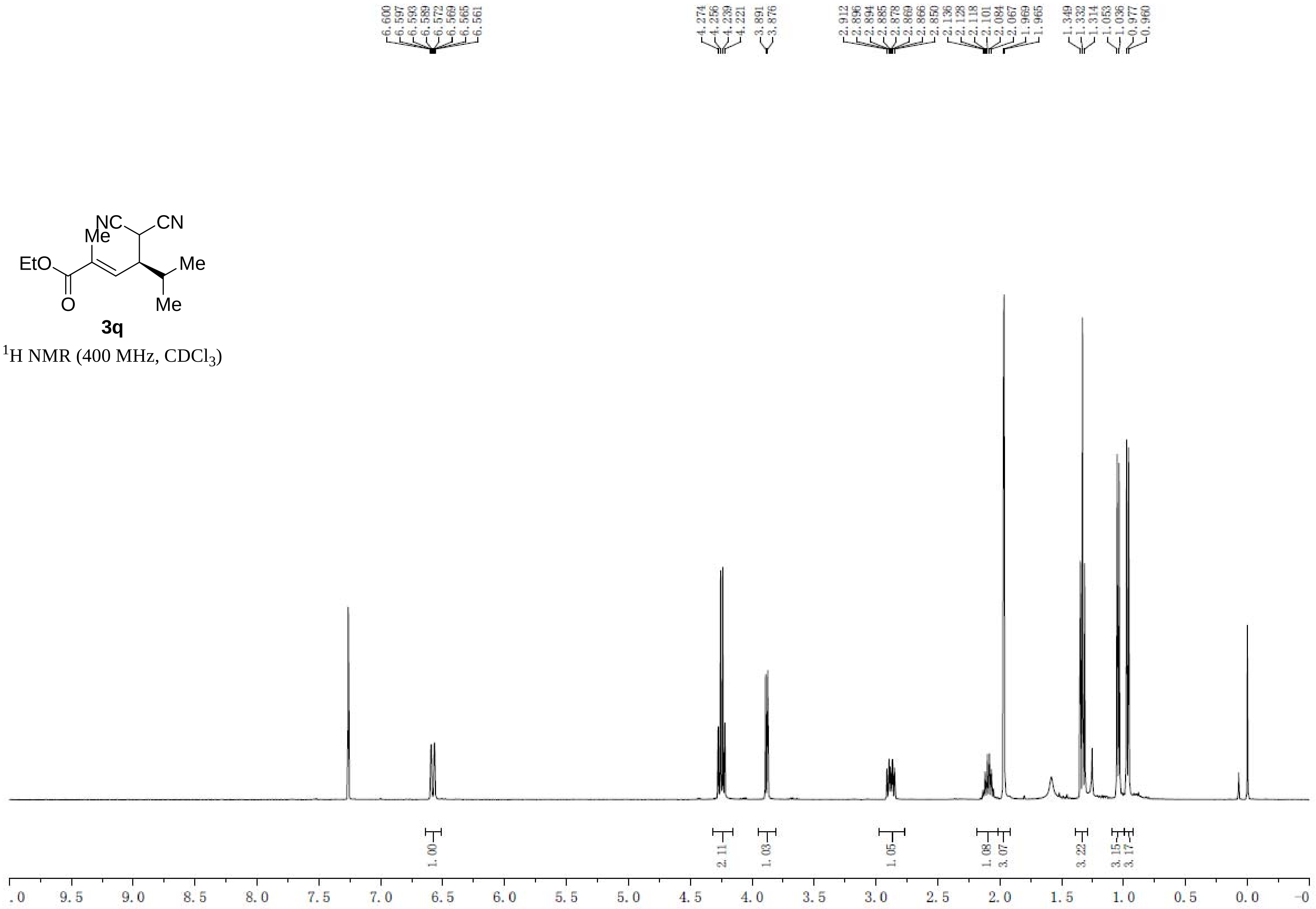




3p

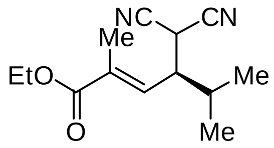
^{13}C NMR (100 MHz, $CDCl_3$)





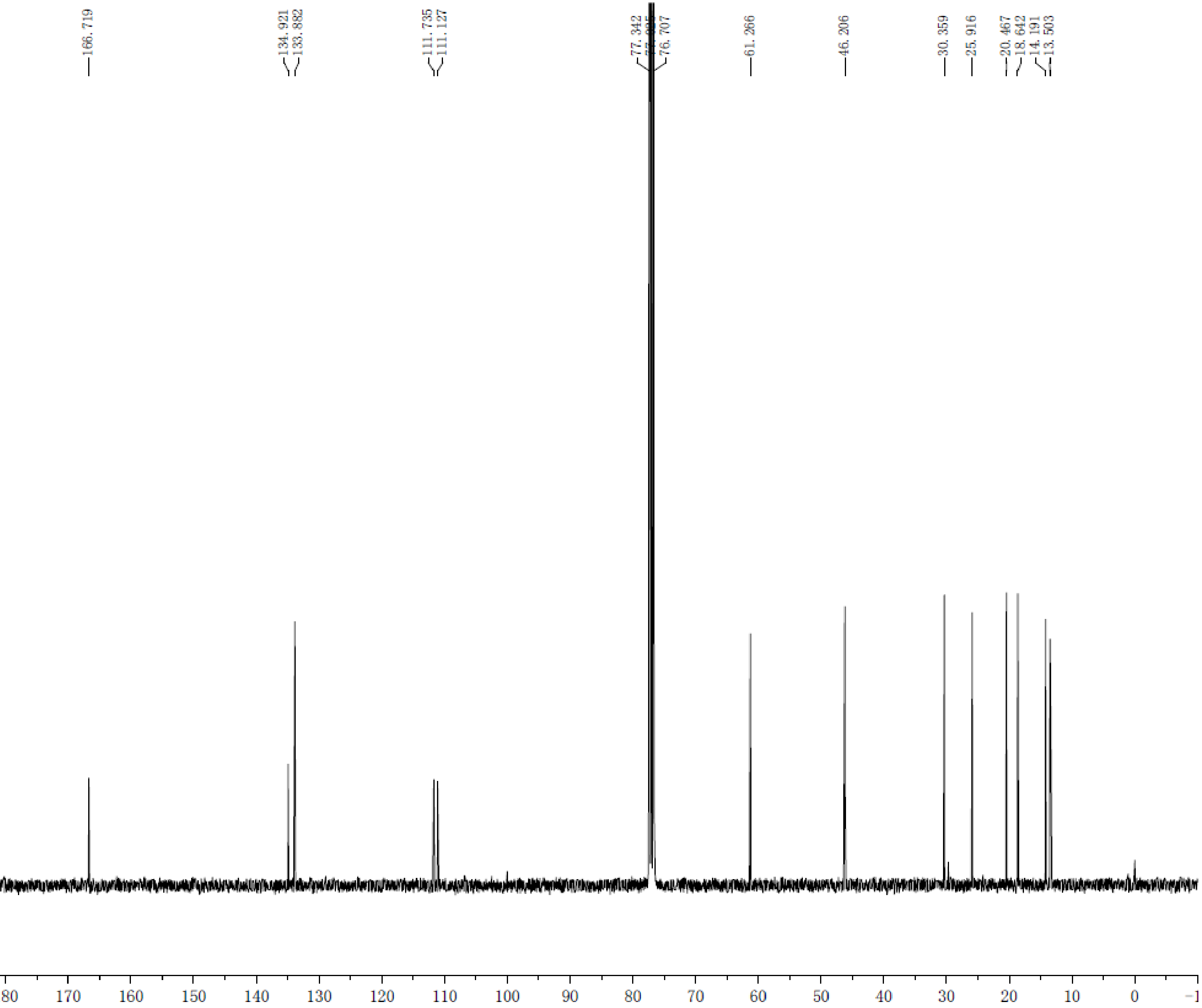
3q

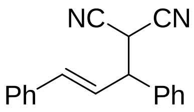
^{1}H NMR (400 MHz, $CDCl_3$)



3q

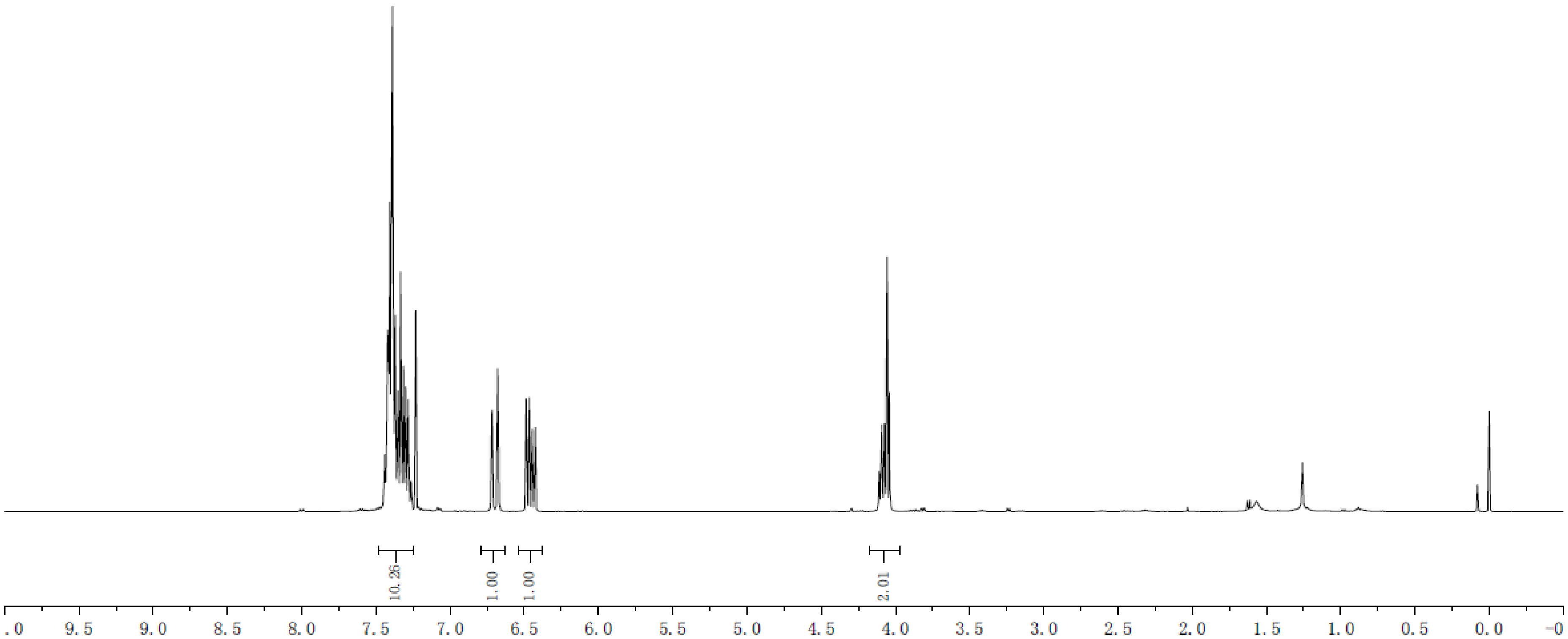
^{13}C NMR (100 MHz, $CDCl_3$)

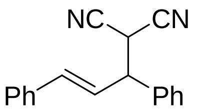




3r

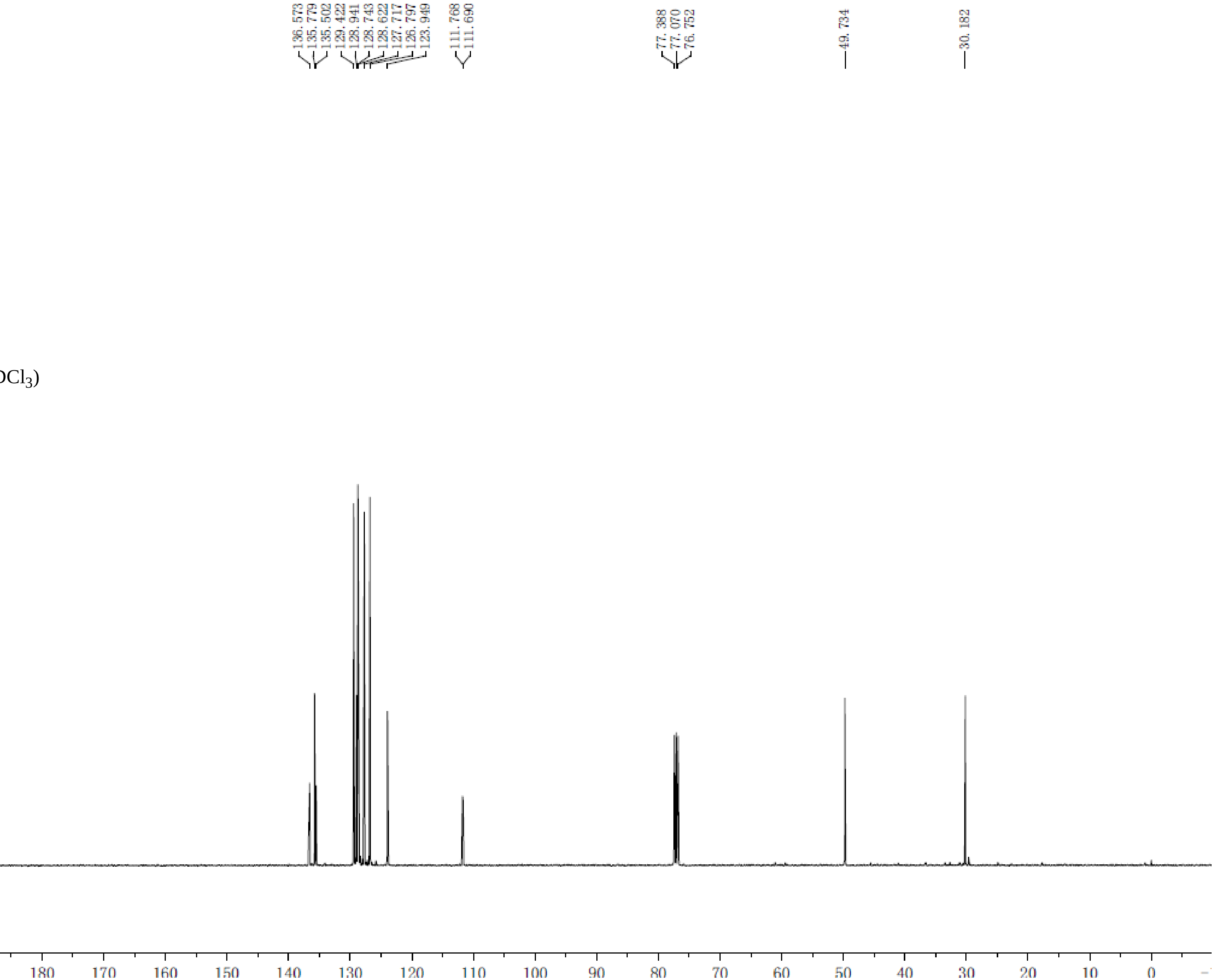
^1H NMR (400 MHz, $CDCl_3$)

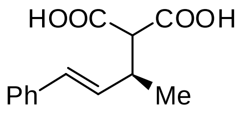




3r

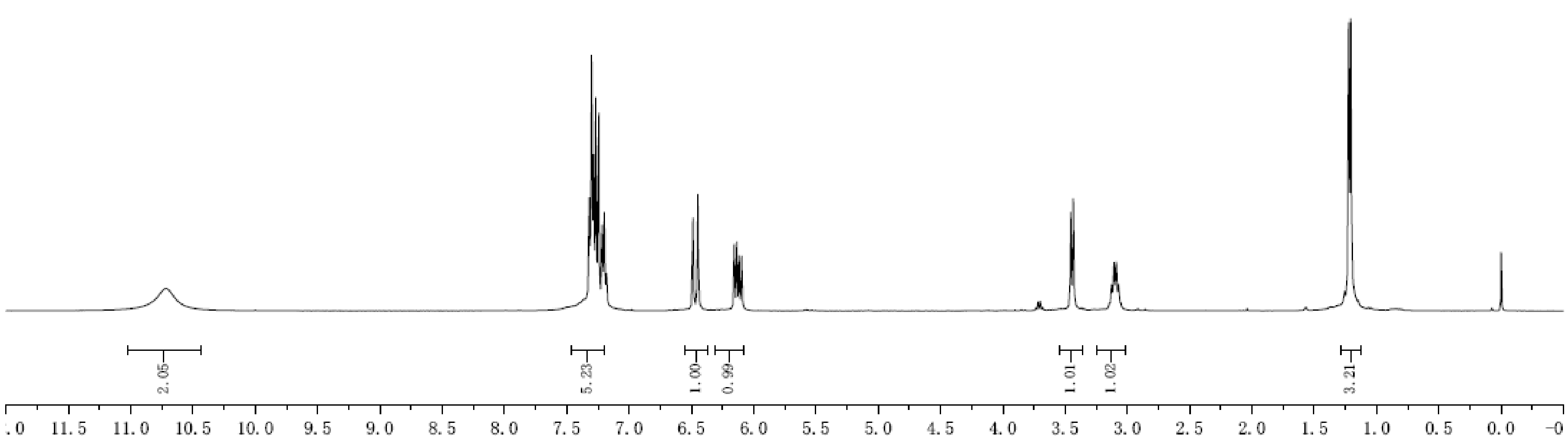
^{13}C NMR (100 MHz, $CDCl_3$)

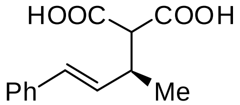




4a

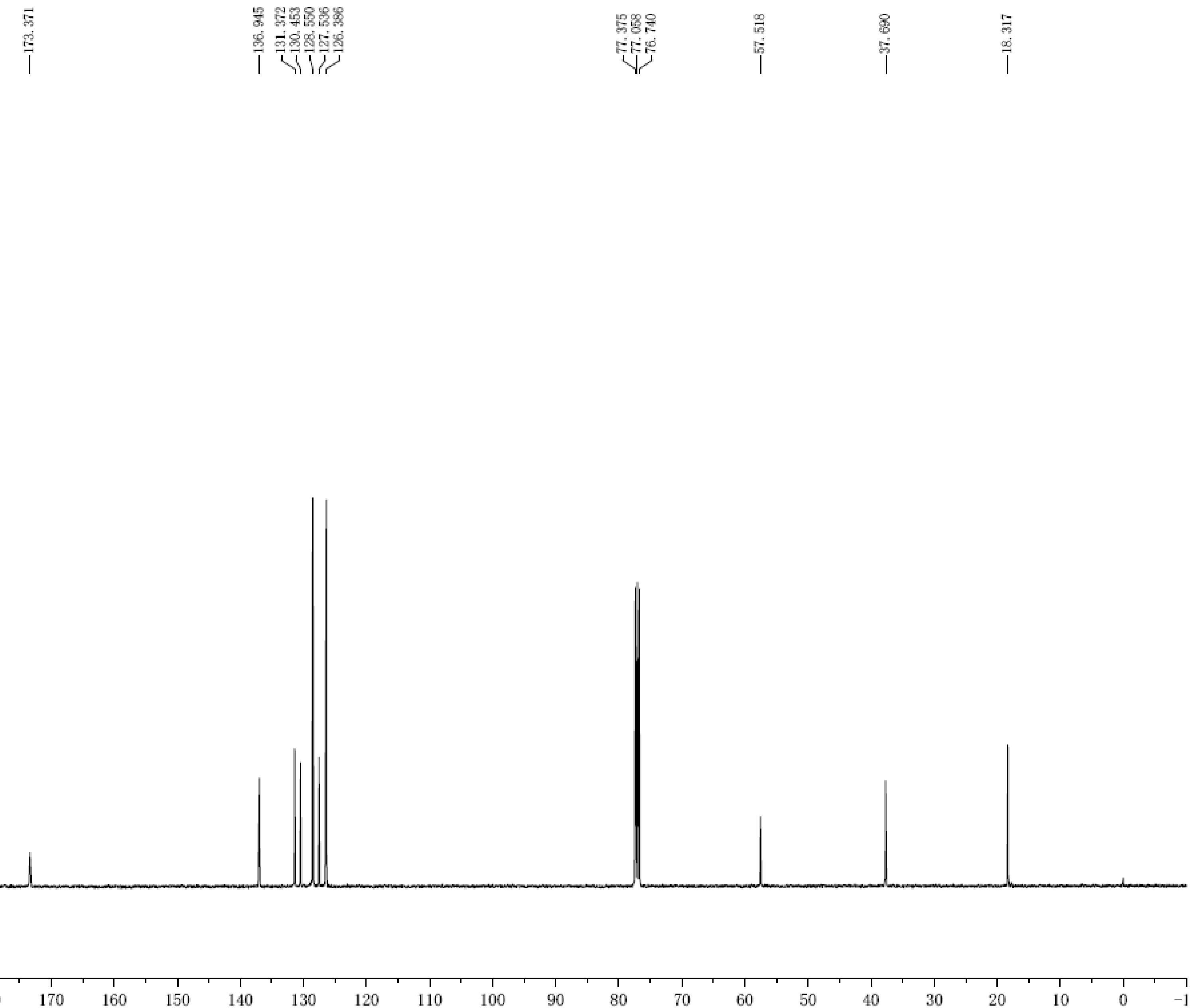
^{1}H NMR (400 MHz, $CDCl_3$)

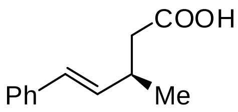




4a

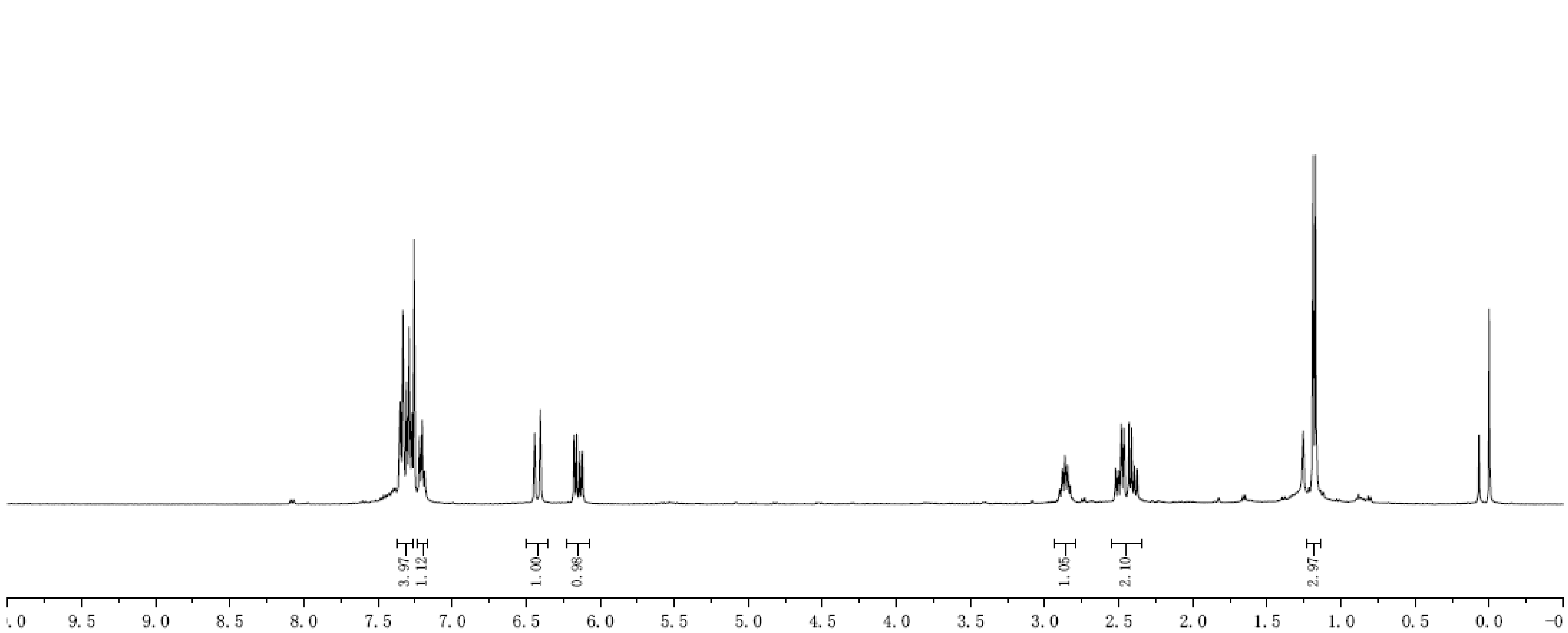
^{13}C NMR (100 MHz, $CDCl_3$)

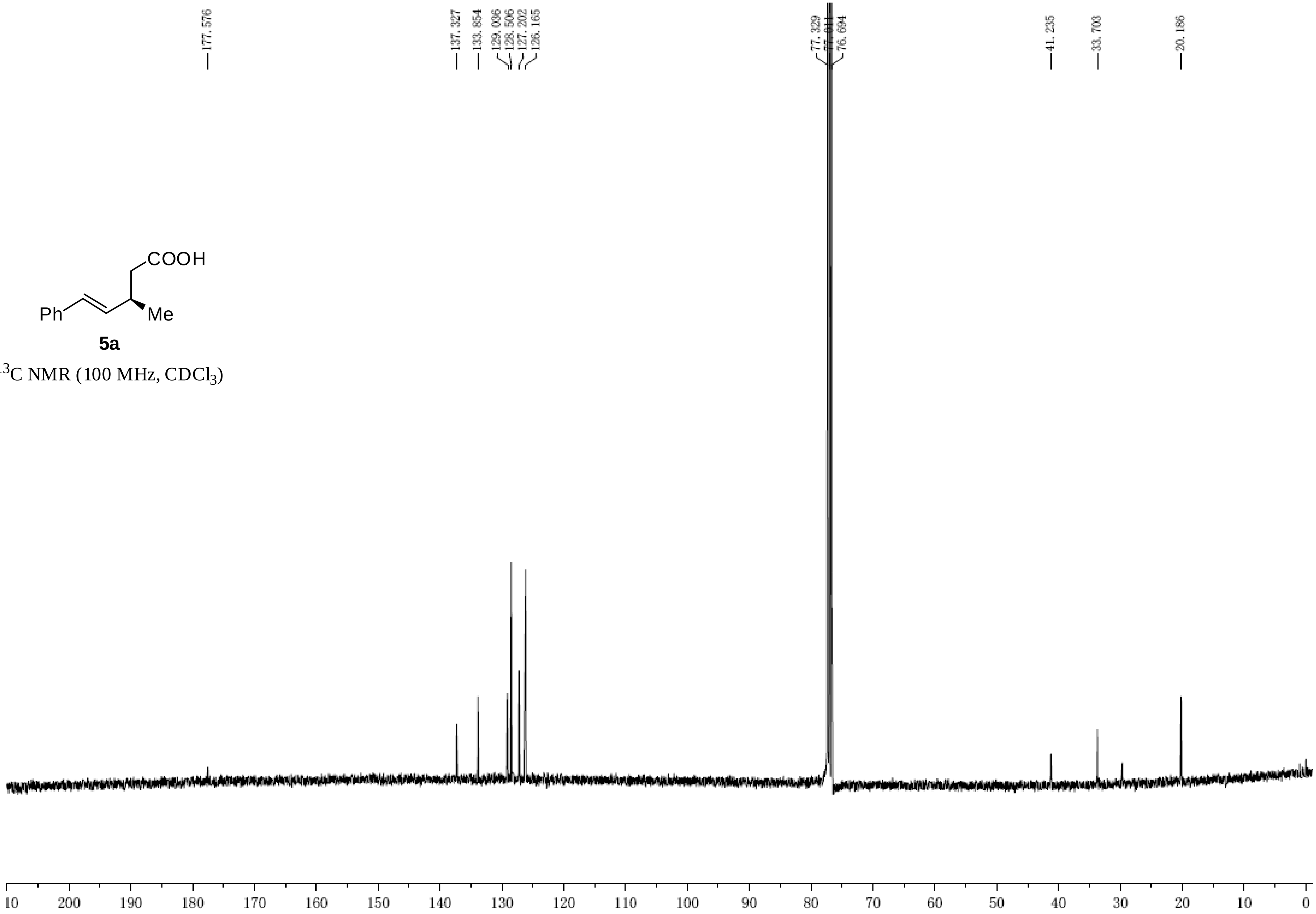




5a

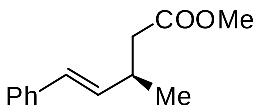
^{1}H NMR (400 MHz, $CDCl_3$)





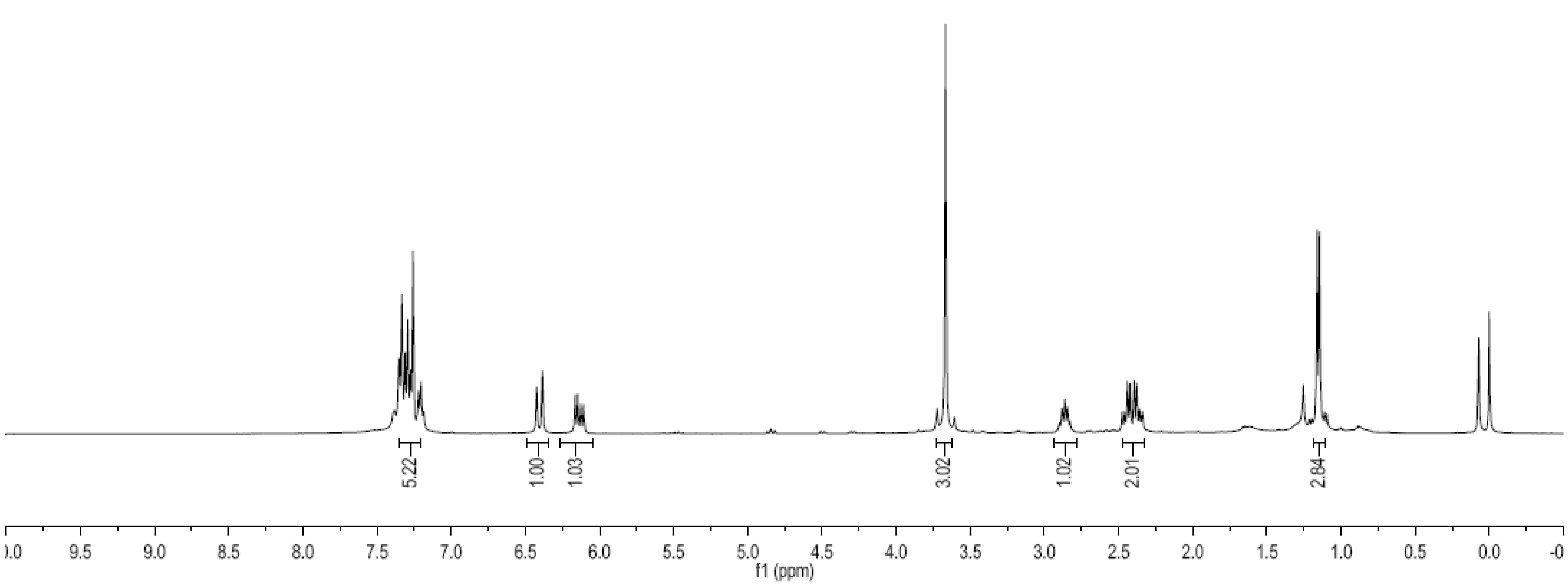
5a

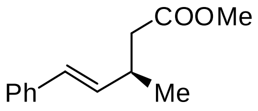
^{13}C NMR (100 MHz, $CDCl_3$)



6a

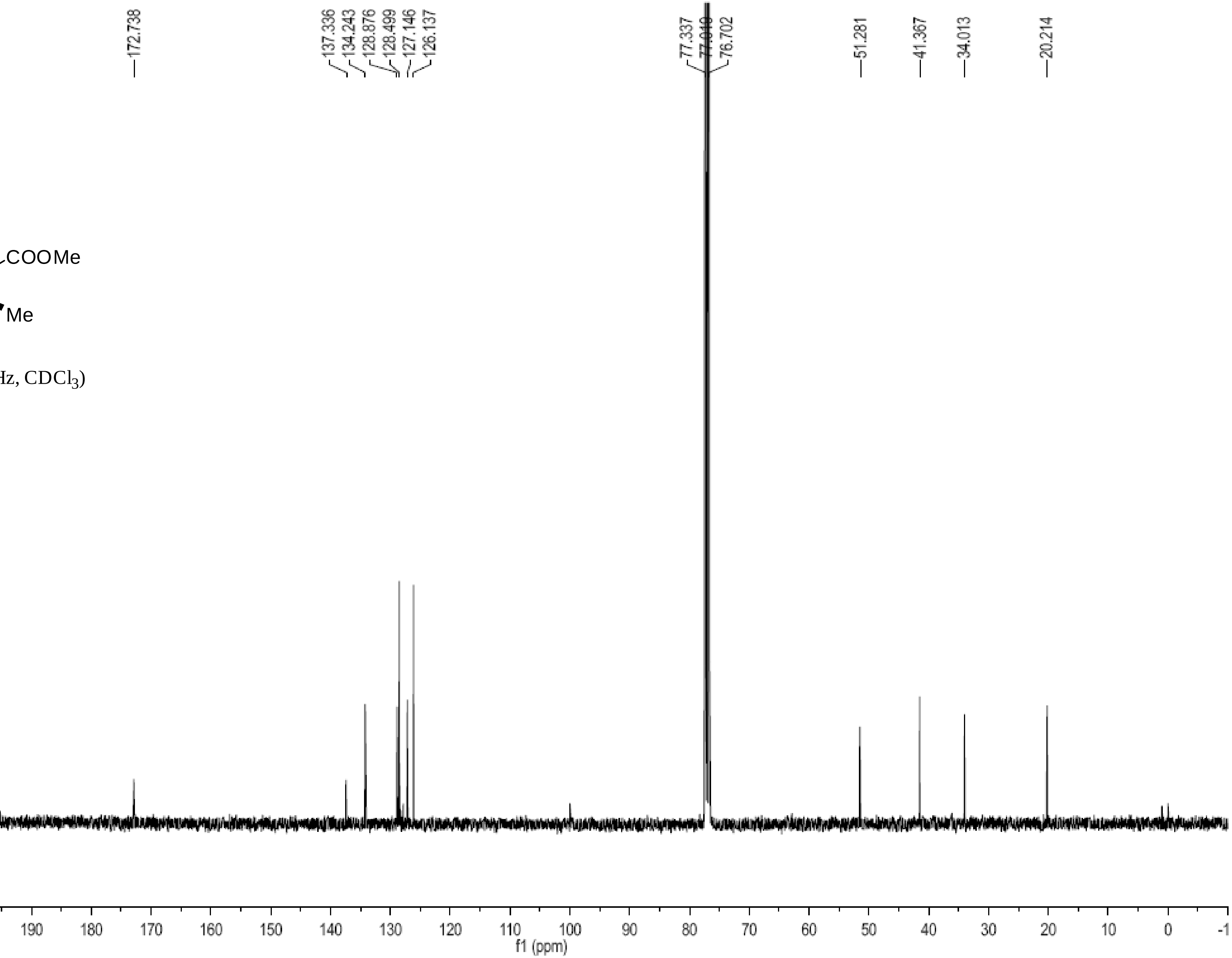
^{1}H NMR (400 MHz, $CDCl_3$)

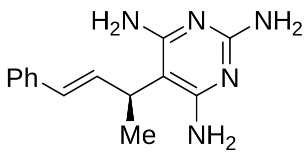




6a

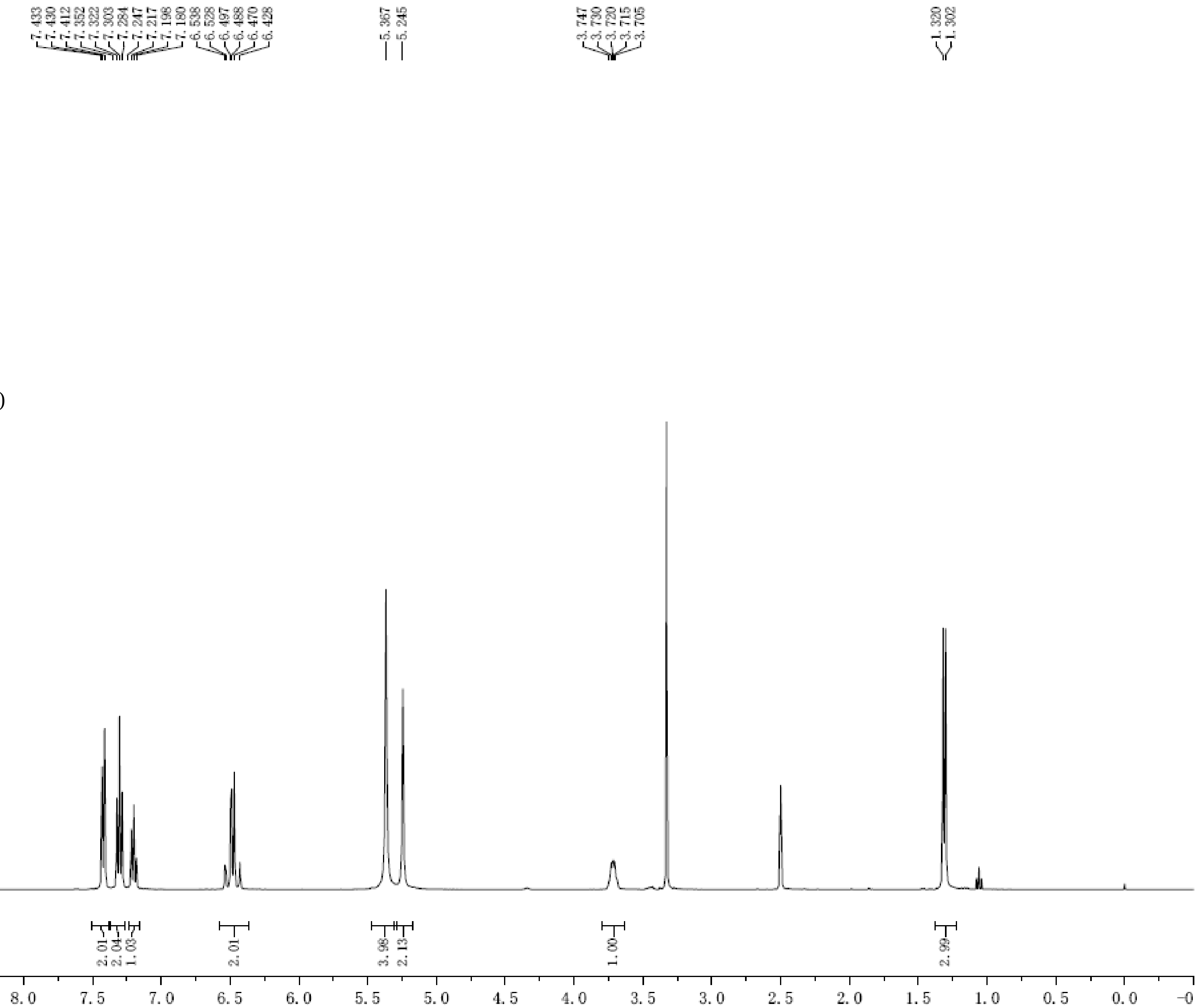
^{13}C NMR (100 MHz, $CDCl_3$)

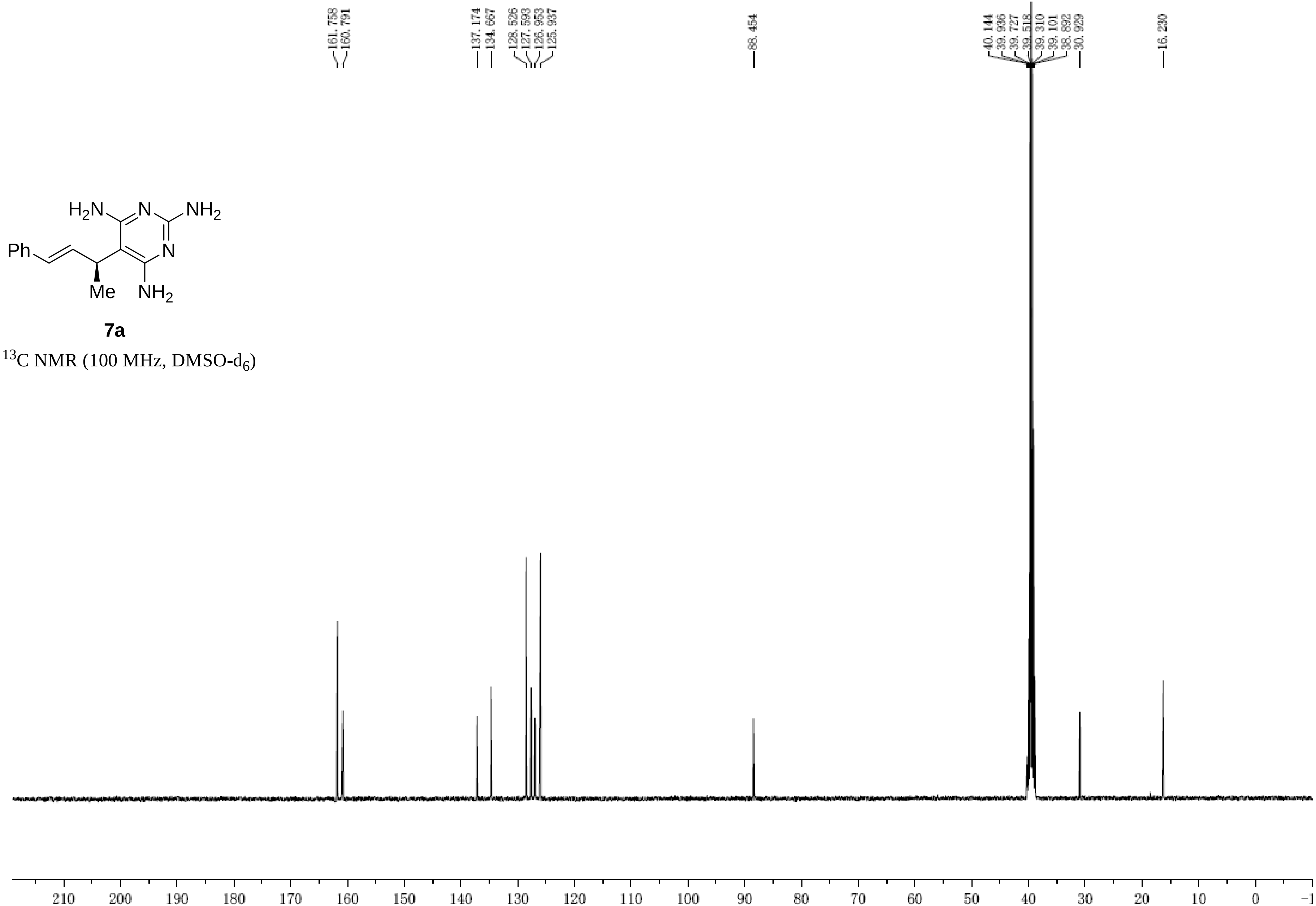




7a

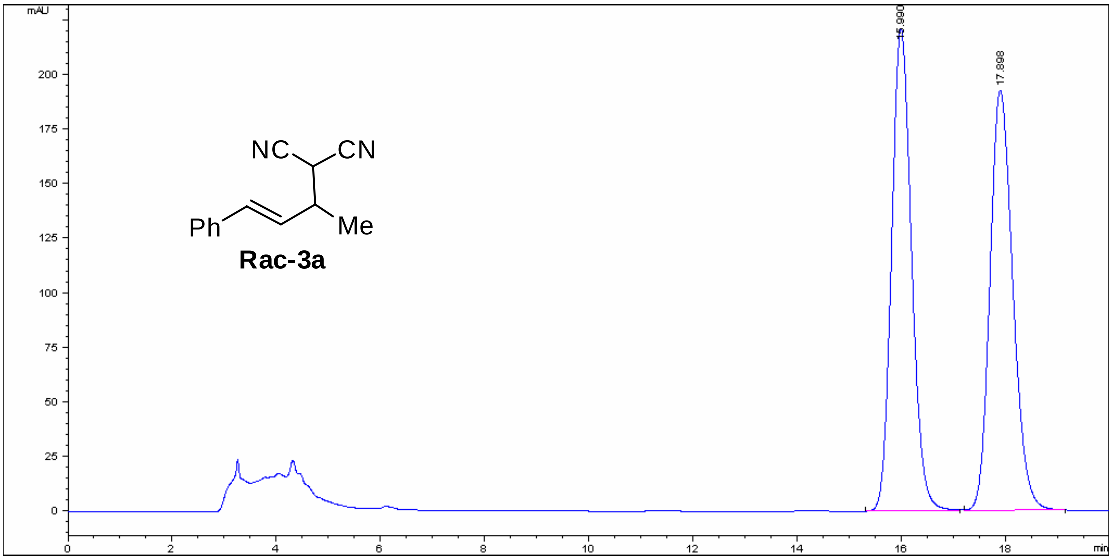
^{1}H NMR (400 MHz, DMSO-d_6)



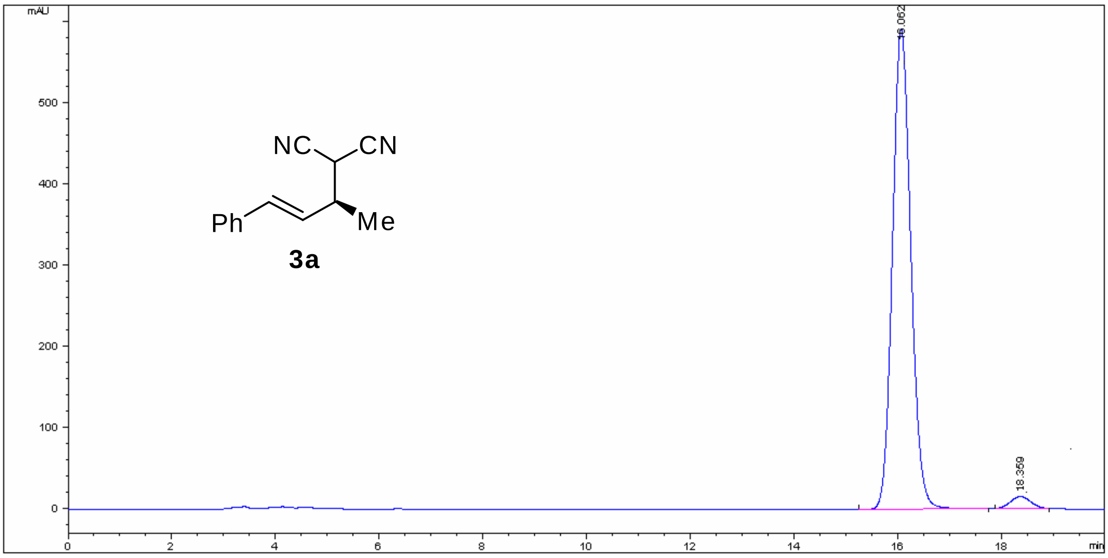


7a

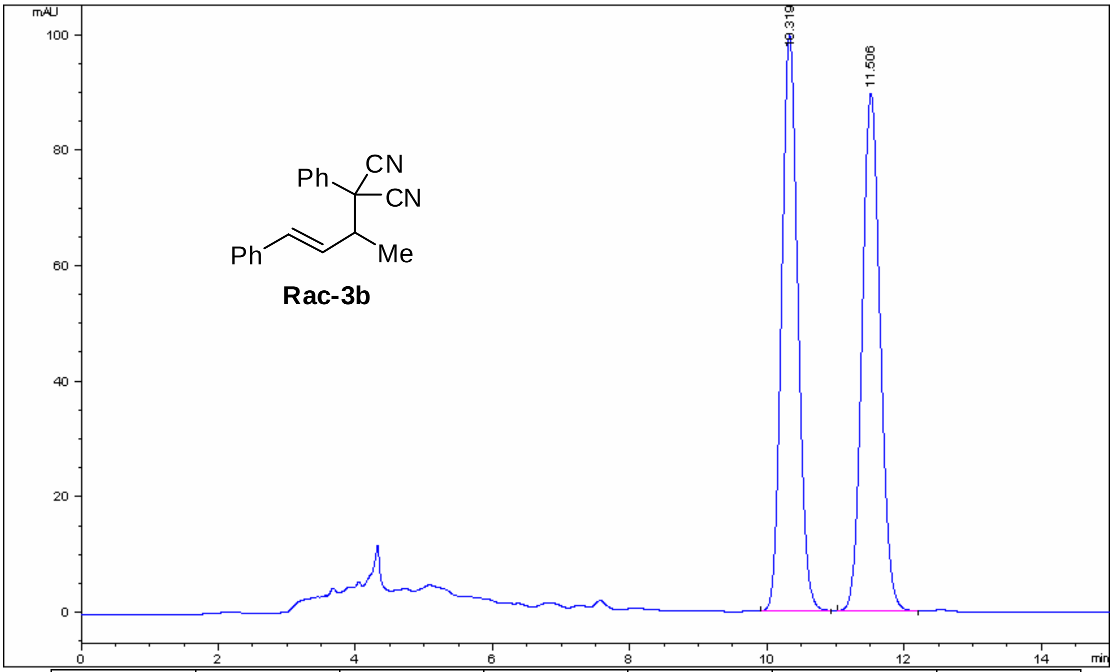
^{13}C NMR (100 MHz, DMSO-d$_6$)



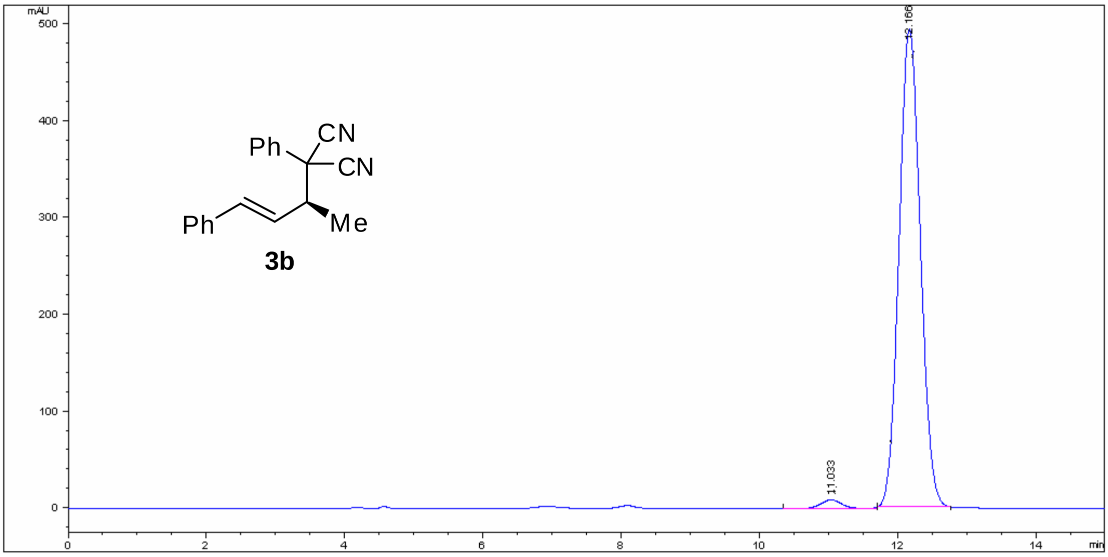
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	15.99	5887	220.8	0.413	0.837	50.024
2	17.898	5881.4	192.4	0.4731	0.782	49.976



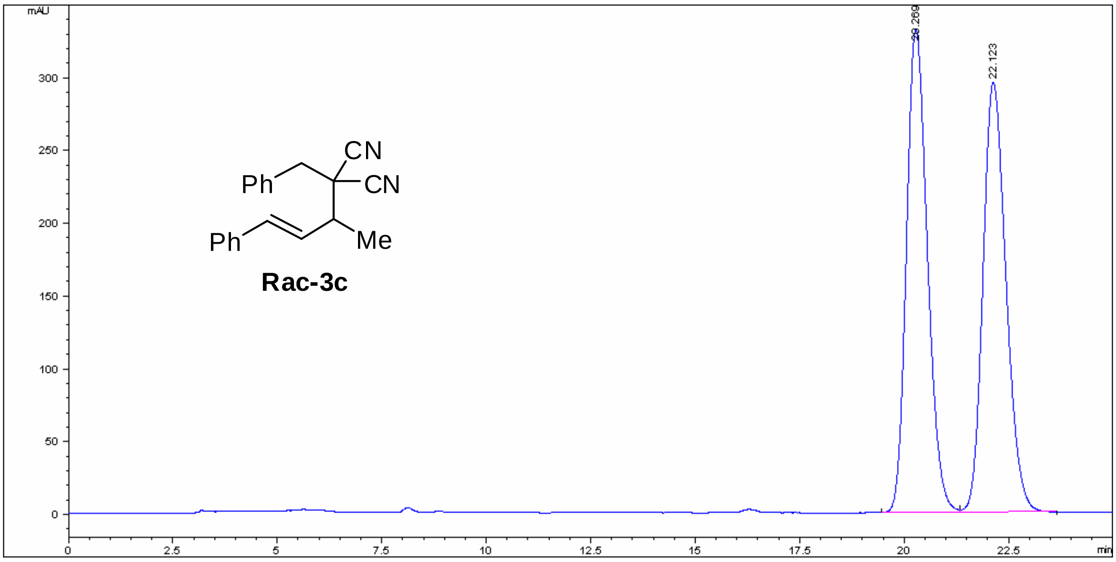
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	16.062	14666.6	592.6	0.4125	0.865	97.288
2	18.359	408.8	15	0.4541	0.911	2.712



Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	10.319	1640.4	99.9	0.2542	0.893	49.964
2	11.506	1642.8	89.7	0.2851	0.9	50.036



Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.033	270.5	9.9	0.4568	0.895	2.491
2	12.166	10589	494.1	0.3572	0.919	97.509



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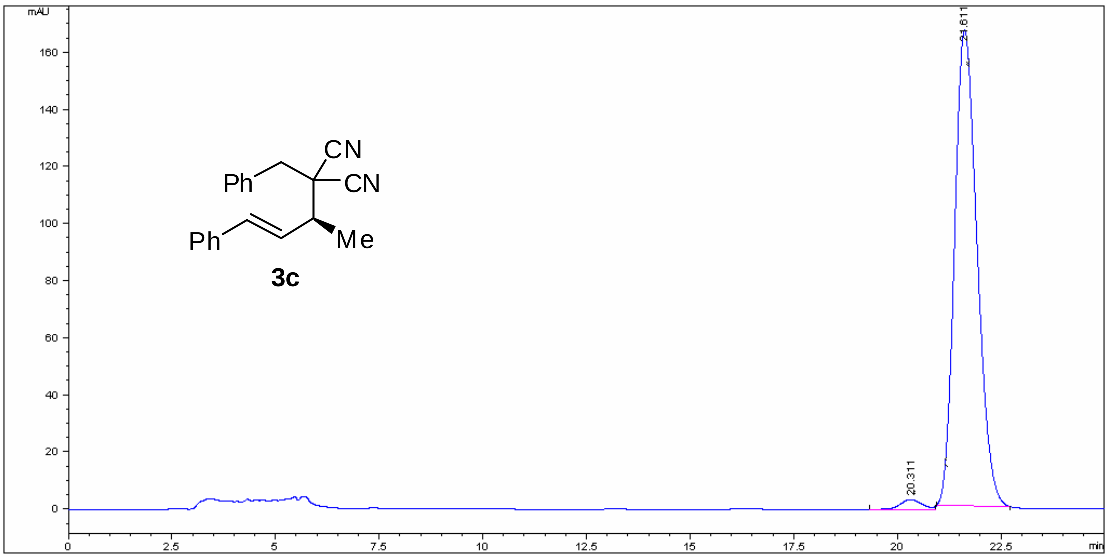
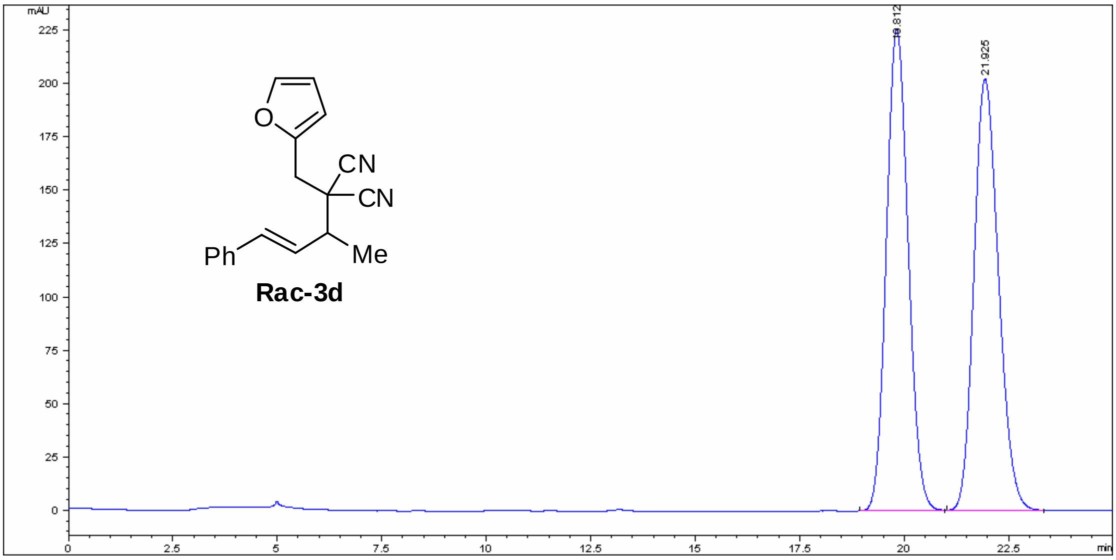
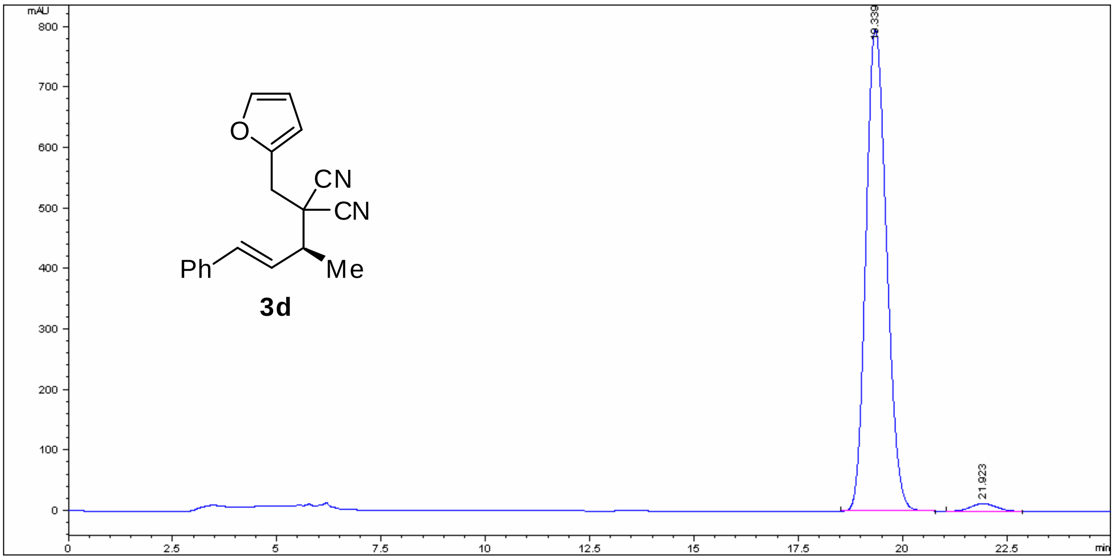
1	20.269	11562.1	332.2	0.5401	0.764	50.522
2	22.123	11323	295.2	0.5931	0.771	49.478



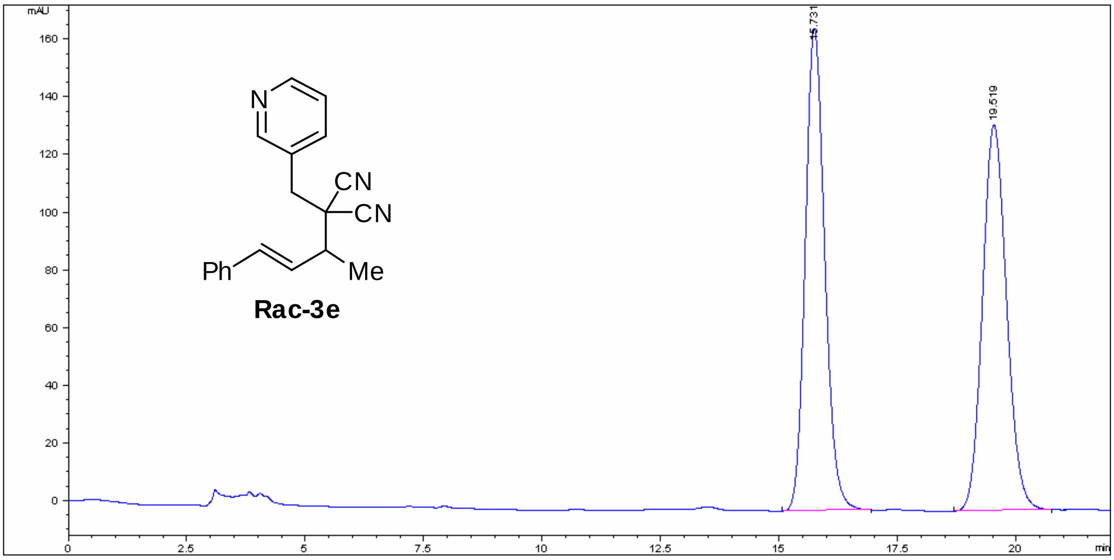
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	20.311	153.7	3.8	0.6801	0.954	2.383
2	21.611	6294.9	166.9	0.6285	0.775	97.617



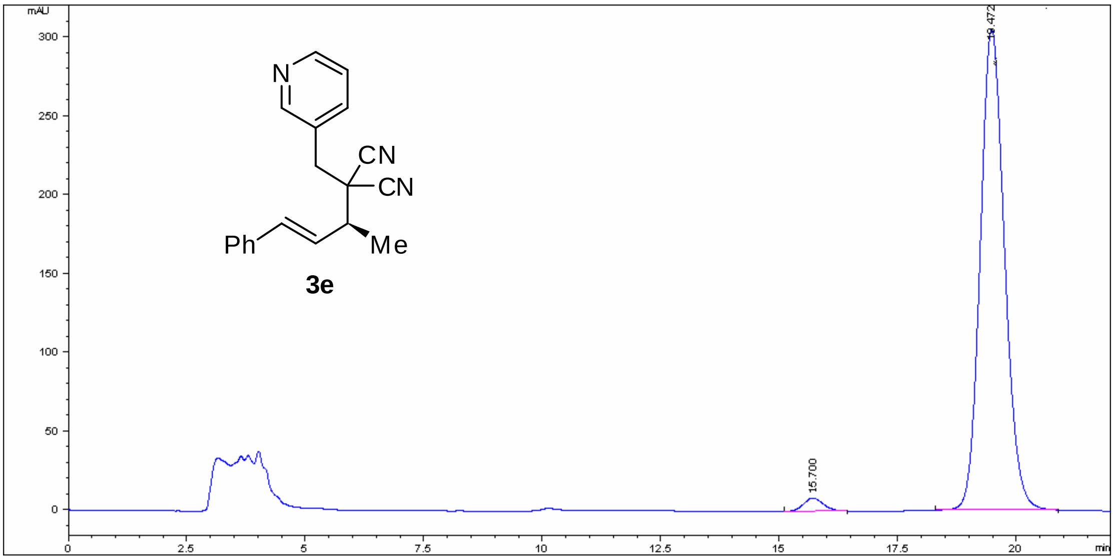
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	19.812	8215.4	225.9	0.5685	0.872	49.833
2	21.925	8270.4	202.3	0.6356	0.786	50.167



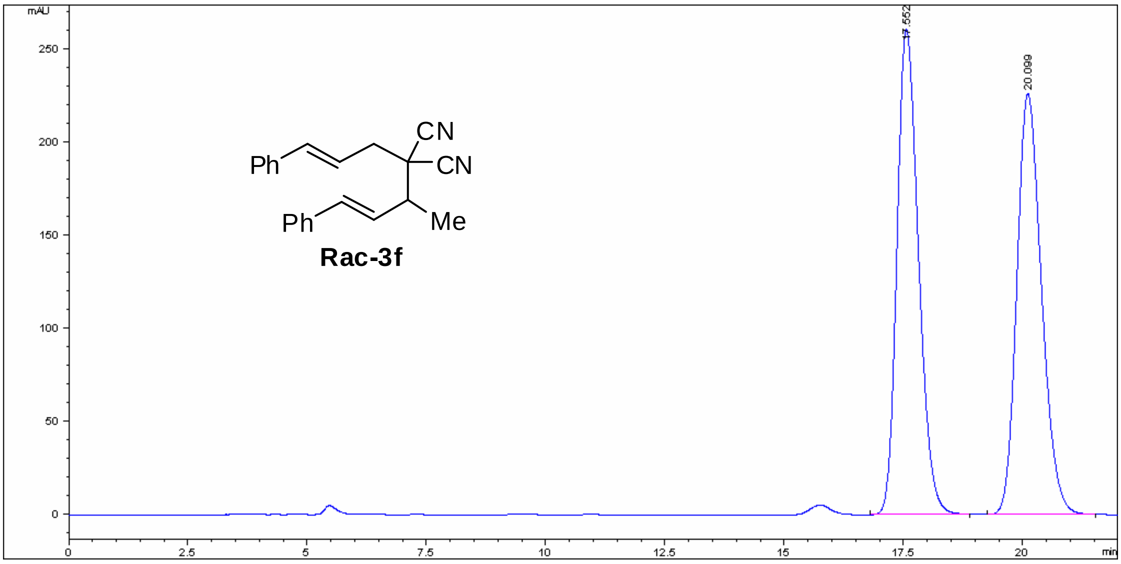
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	19.339	27362.5	796.5	0.5391	0.803	97.617
2	21.923	667.9	13.8	0.8043	0.861	2.383



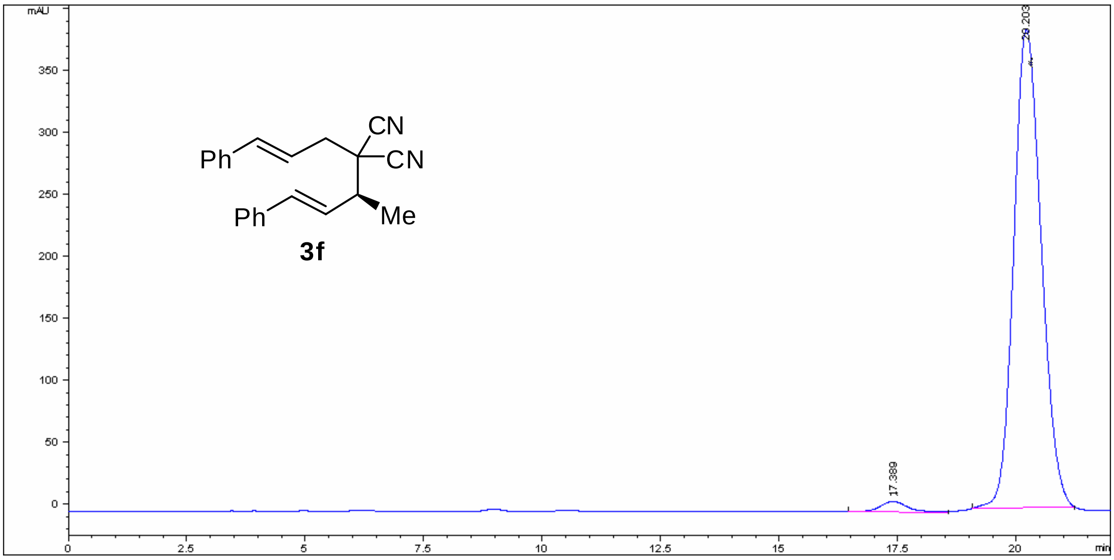
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	15.731	4778.7	16.7	0.4416	0.827	50.260
2	19.519	4729.2	133.8	0.5478	0.864	49.740



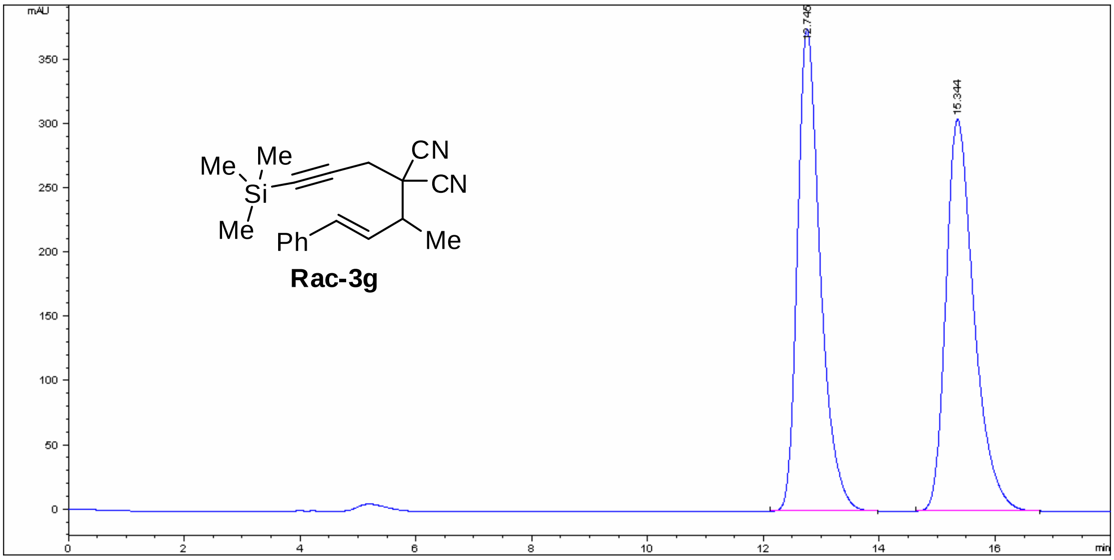
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	15.7	261.5	8.5	0.5112	0.859	2.353
2	19.472	10852.1	305.2	0.5926	0.858	97.647



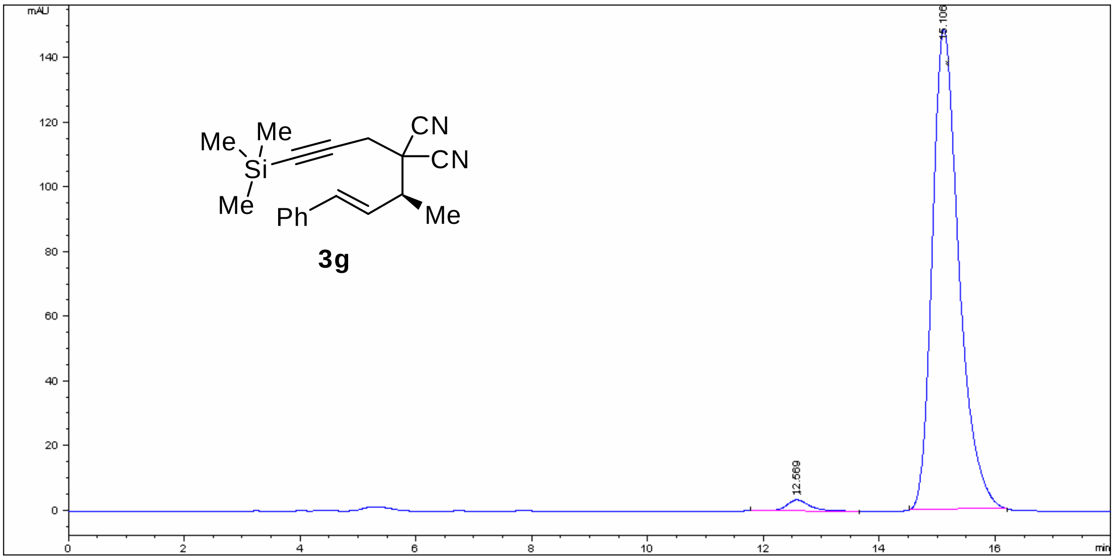
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	17.552	8157.9	260.5	0.4847	0.732	50.088
2	20.099	8129.3	225.8	0.554	0.765	49.912



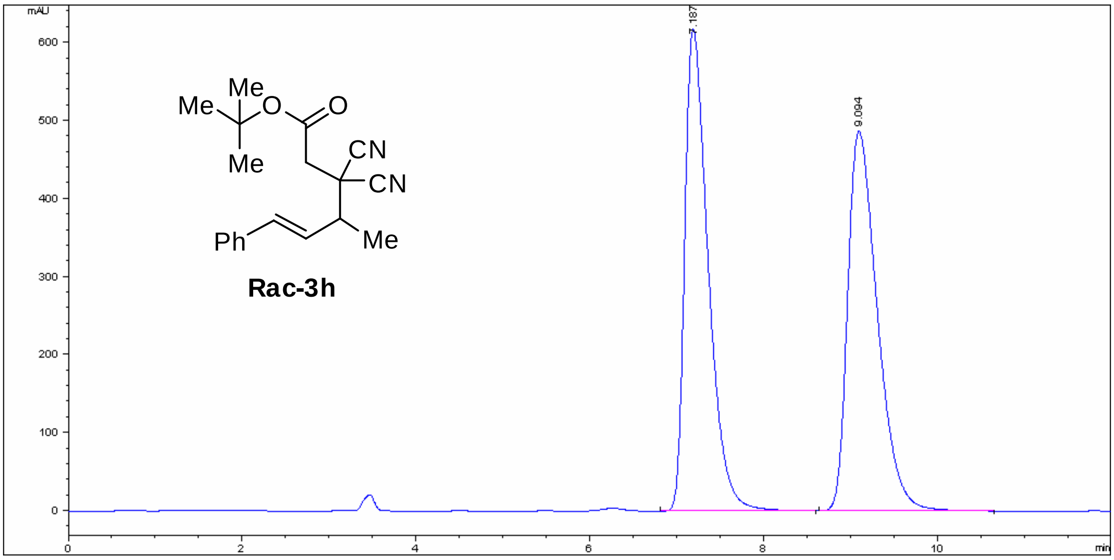
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	17.389	369.4	8.6	0.716	0.784	2.312
2	20.203	15608.9	386.6	0.6729	0.822	97.688



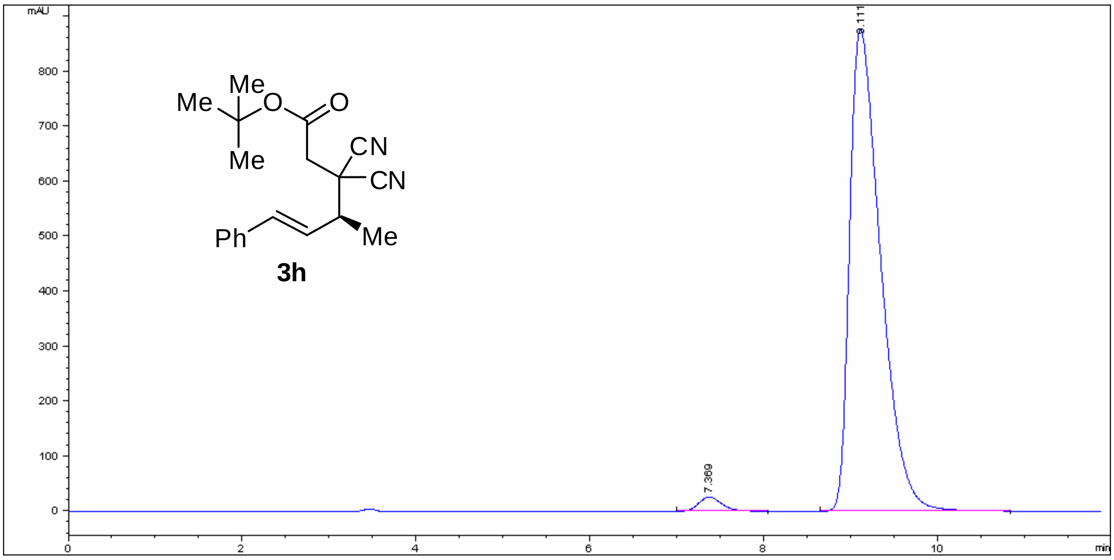
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	12.745	10286.2	374.8	0.4181	0.675	50.001
2	15.344	10285.9	304.6	0.5134	0.67	49.999



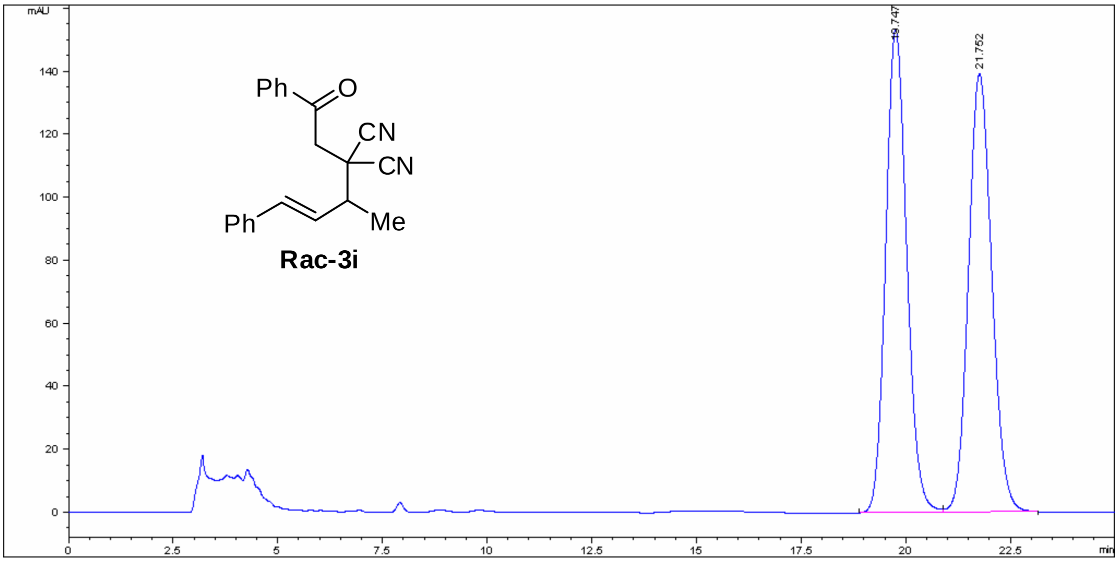
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	12.569	117.2	3.6	0.5407	0.772	2.401
2	15.106	4763	148.7	0.5337	0.722	97.599



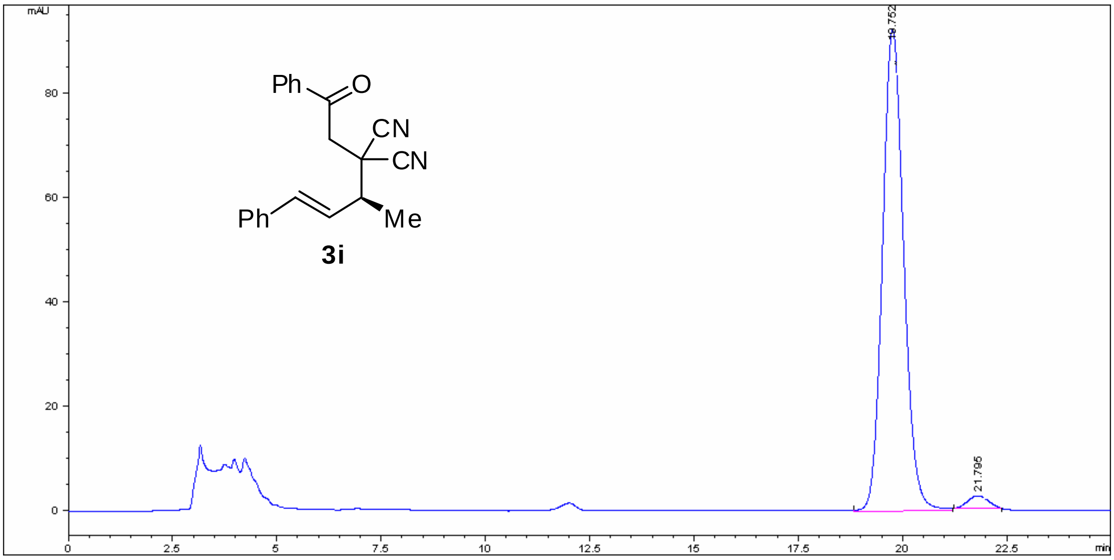
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	7.187	11603.2	617.7	0.2861	0.527	50.099
2	9.094	11557.5	487	0.3642	0.571	49.901



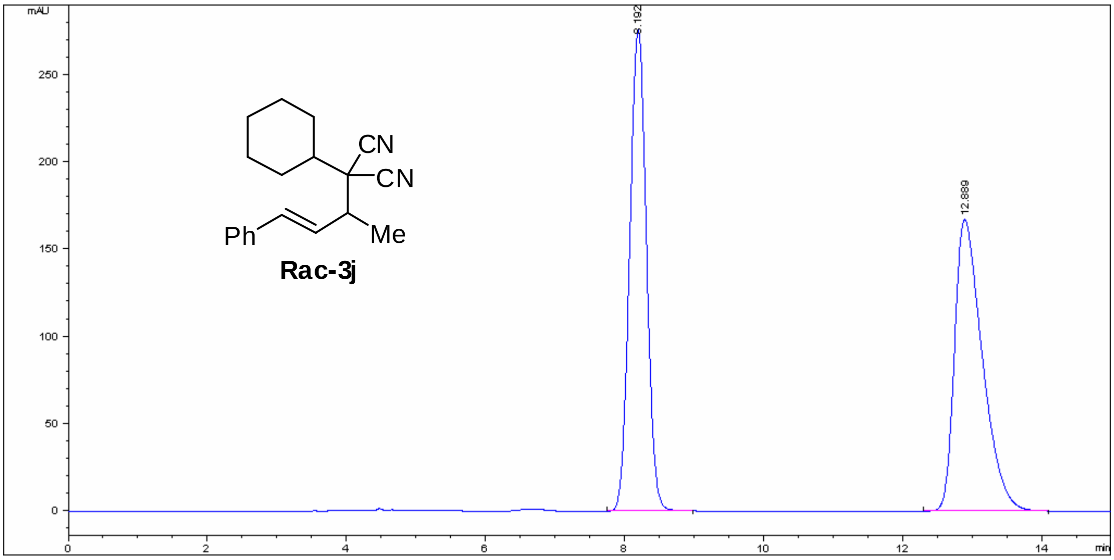
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	7.369	480	26	0.2837	0.779	2.164
2	9.111	21701.3	877.3	0.3774	0.495	97.836



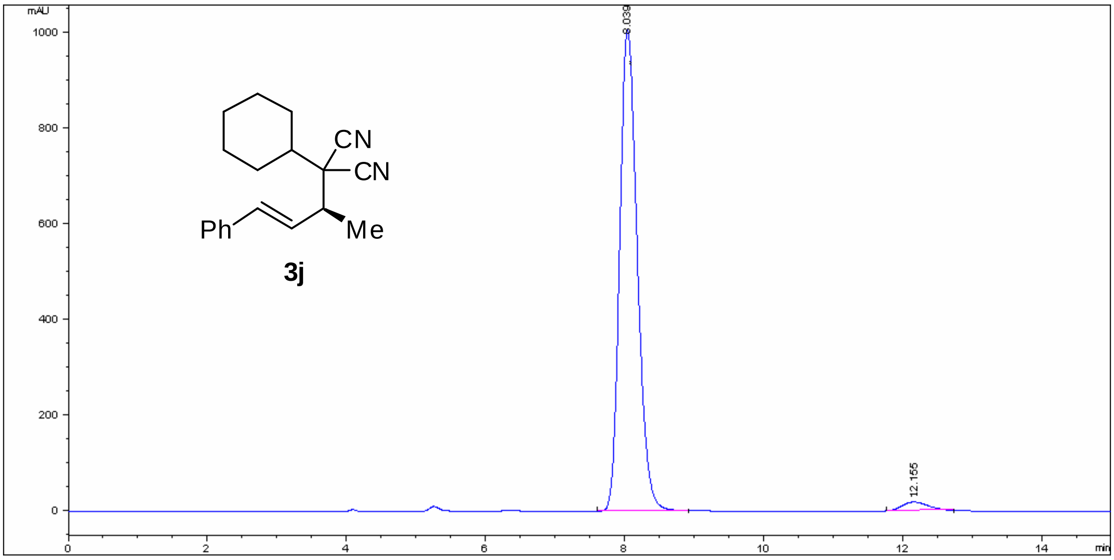
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	19.747	5371.5	153.5	0.5423	0.844	49.884
2	21.752	5396.4	139.2	0.6008	0.862	50.116



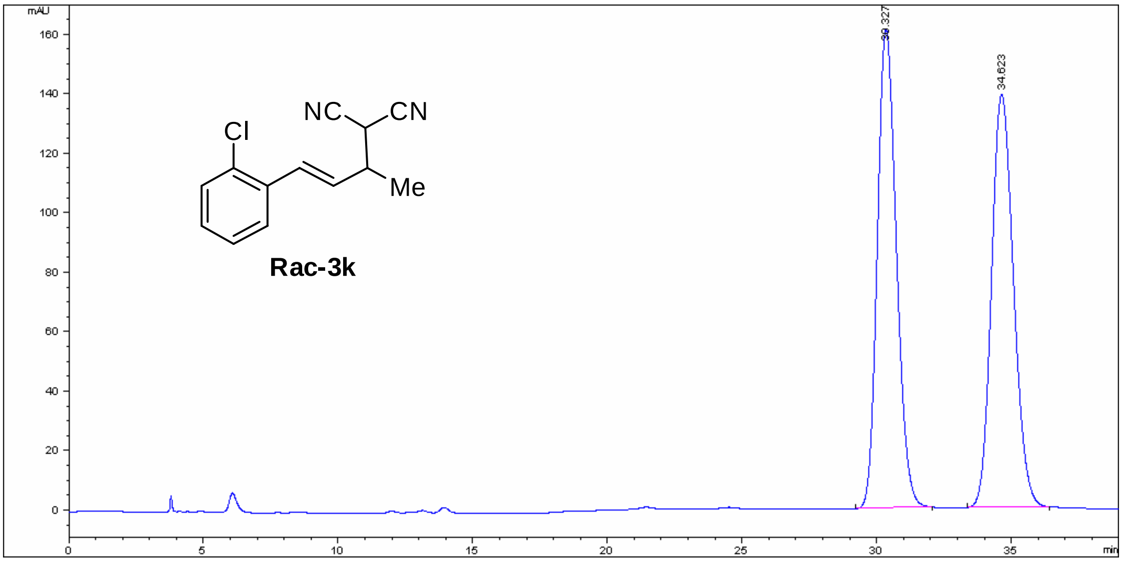
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	19.752	3270.6	92.4	0.5898	0.867	97.232
2	21.795	93.1	2.6	0.6039	0.96	2.768



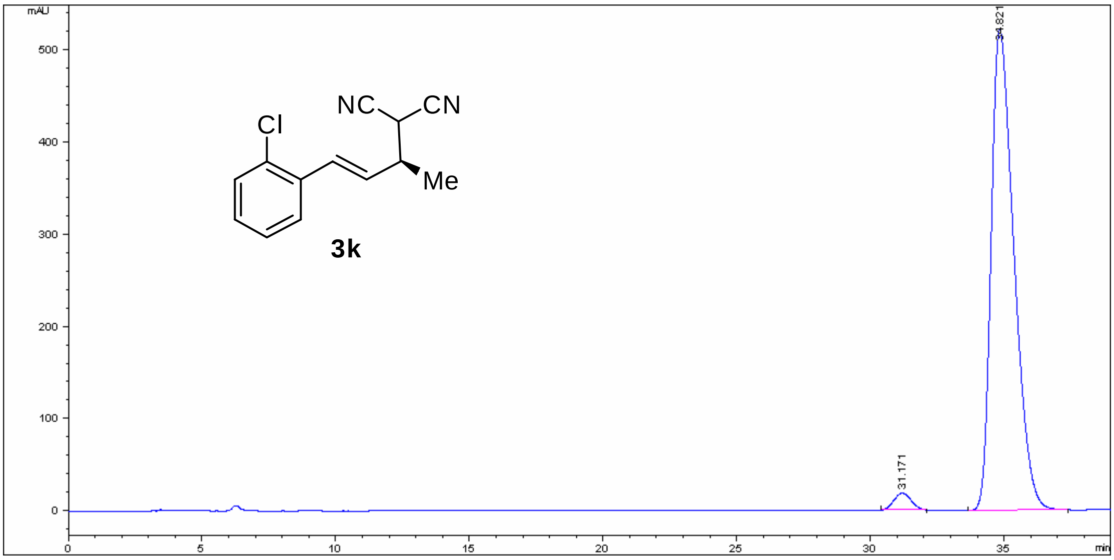
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	8.192	4628.7	276.1	0.2625	0.985	49.917
2	12.889	4644.1	167.1	0.4219	0.538	50.083



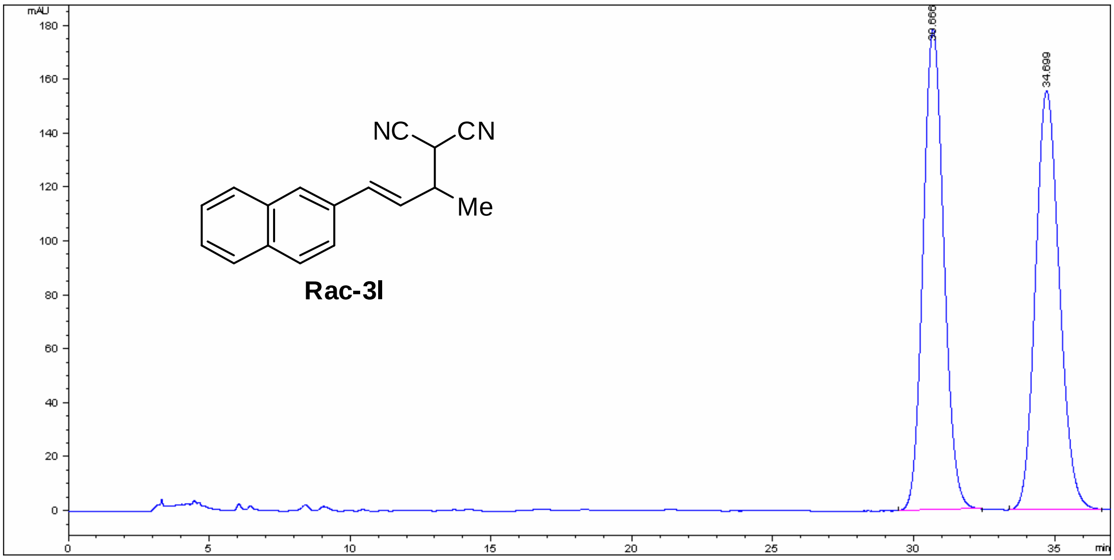
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	8.039	17769.8	1008.8	0.2936	0.778	97.445
2	12.155	465.9	17.9	0.4347	0.781	2.555



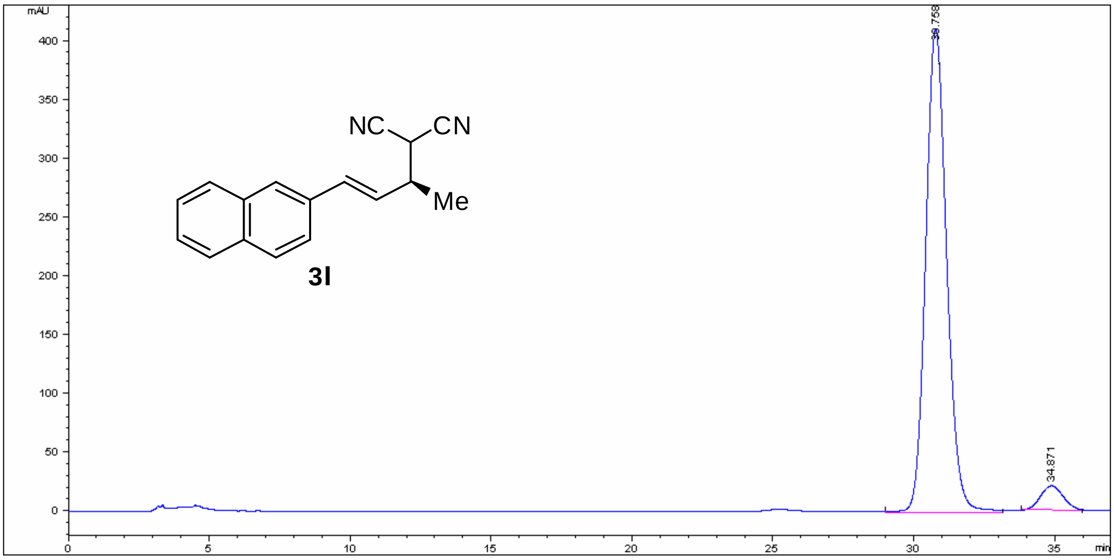
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	30.327	7925.5	161.1	0.7675	0.793	50.076
2	34.623	7901.4	139	0.8831	0.813	49.924



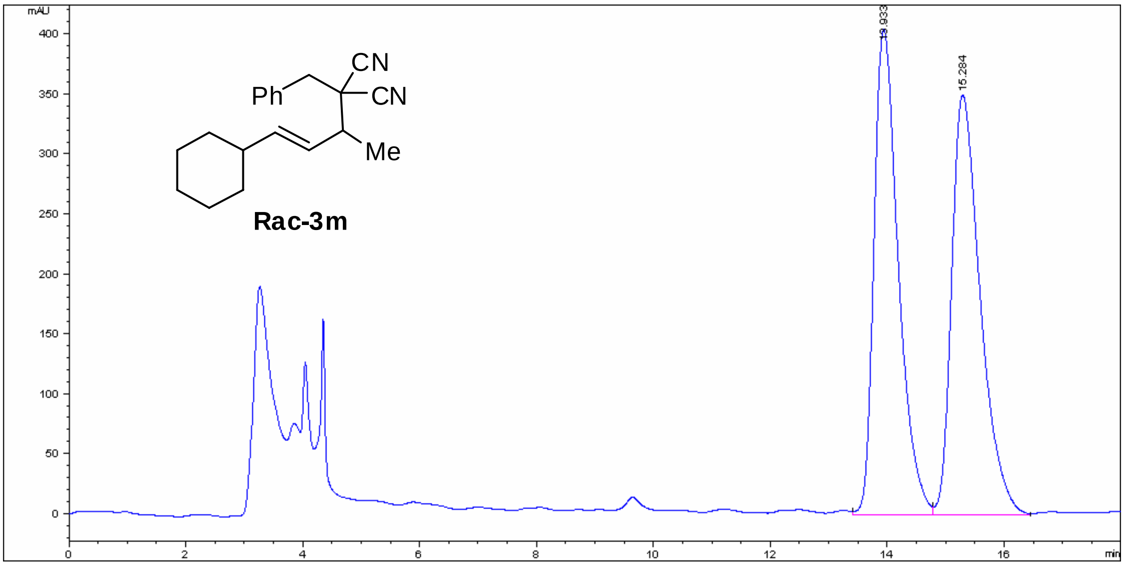
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	31.171	861.2	18.5	0.7744	0.914	2.690
2	34.821	31150.3	523.1	0.9926	0.59	97.310



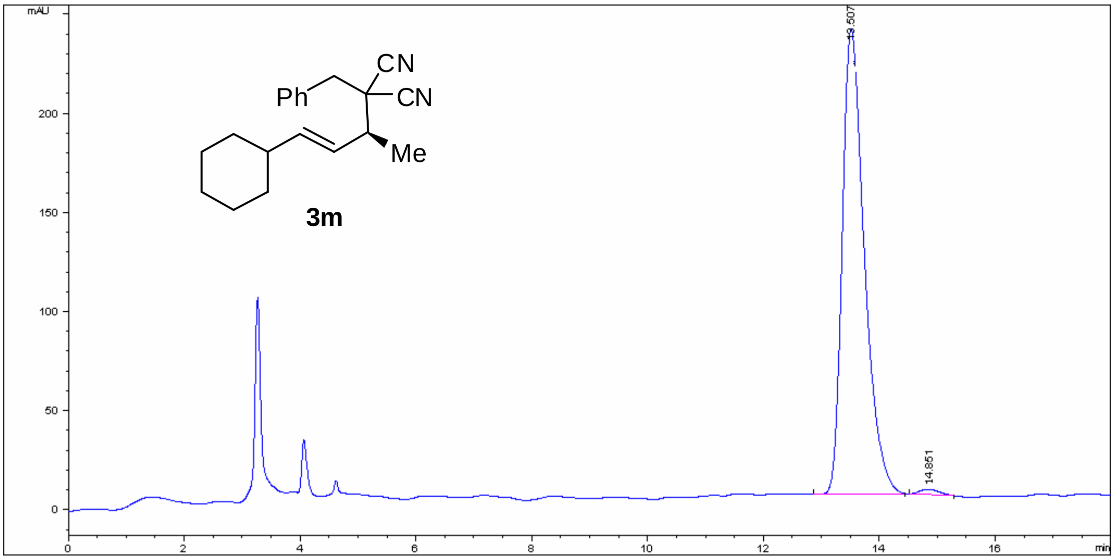
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	30.666	9144.1	178.4	0.7946	0.868	49.943
2	34.699	9164.9	155.3	0.9115	0.838	50.057



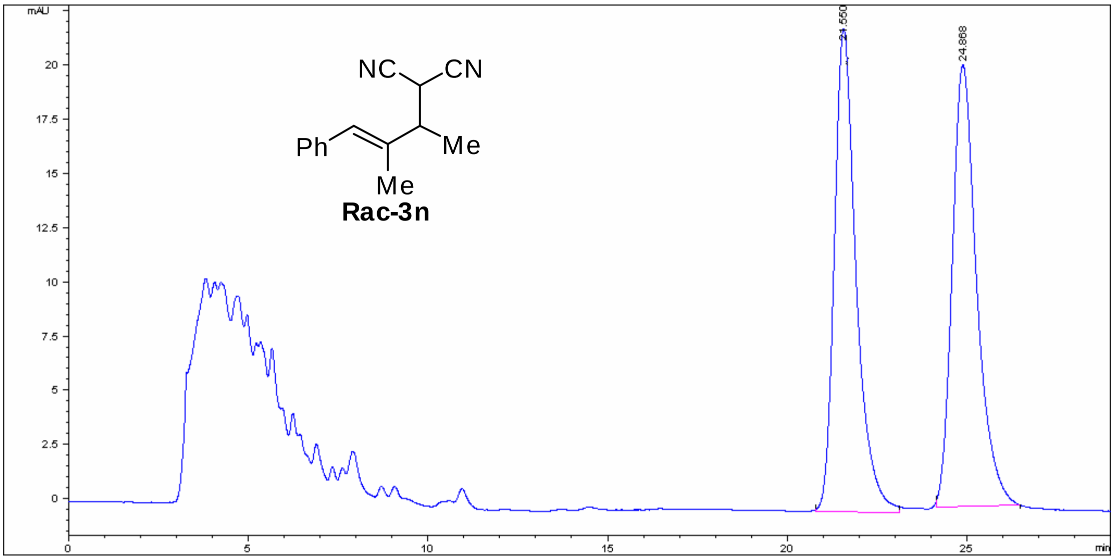
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	30.758	21364.4	411.5	0.8653	0.849	94.761
2	34.871	1181.2	20.8	0.9444	0.894	5.239



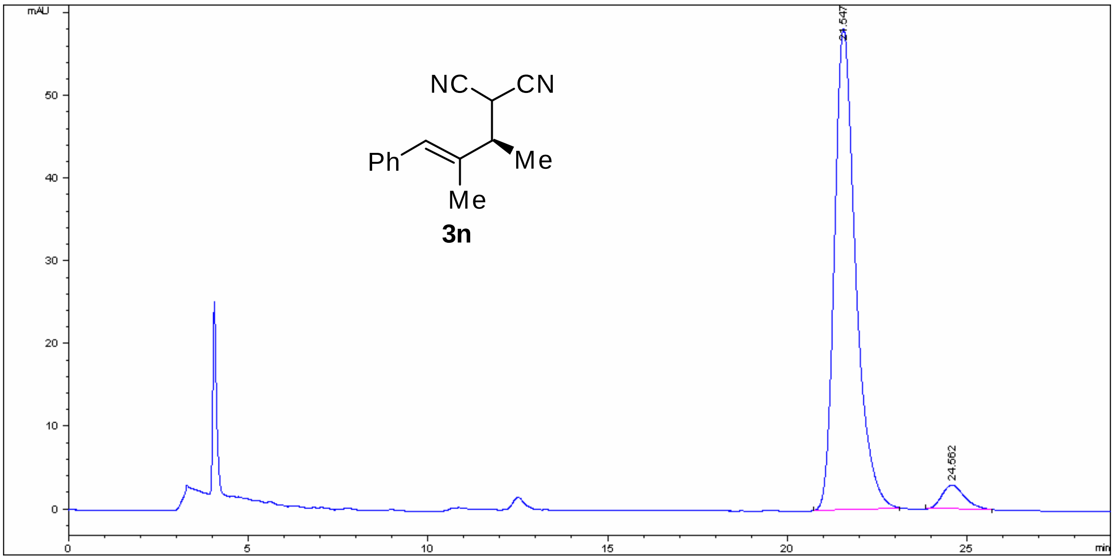
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	13.933	11767.3	405.3	0.4406	0.625	49.657
2	15.284	11929.9	350.3	0.5182	0.589	50.343



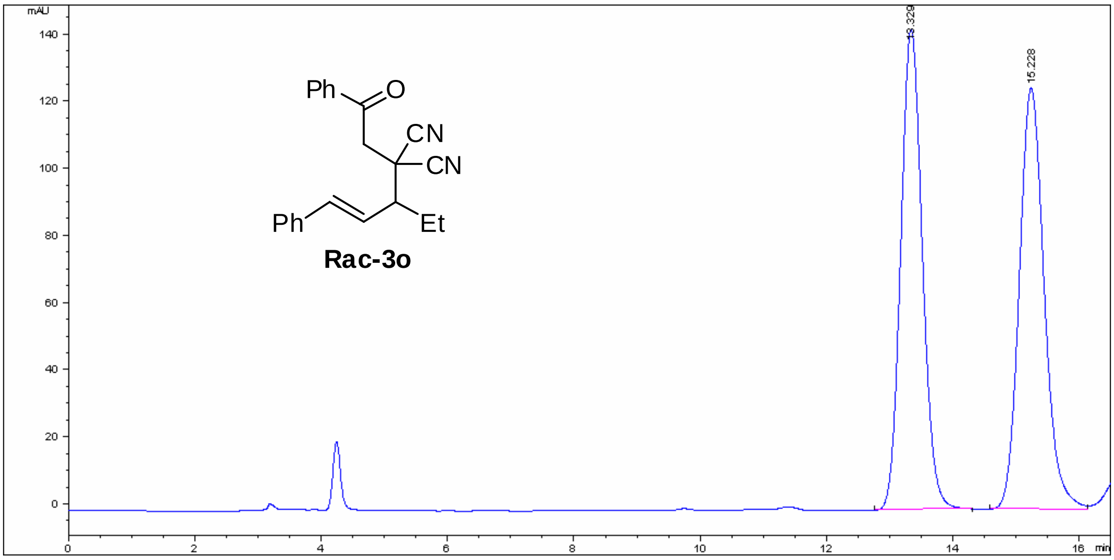
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	13.507	6235	234.8	0.4425	0.649	98.914
2	14.851	68.5	2.8	0.4091	0.755	1.086



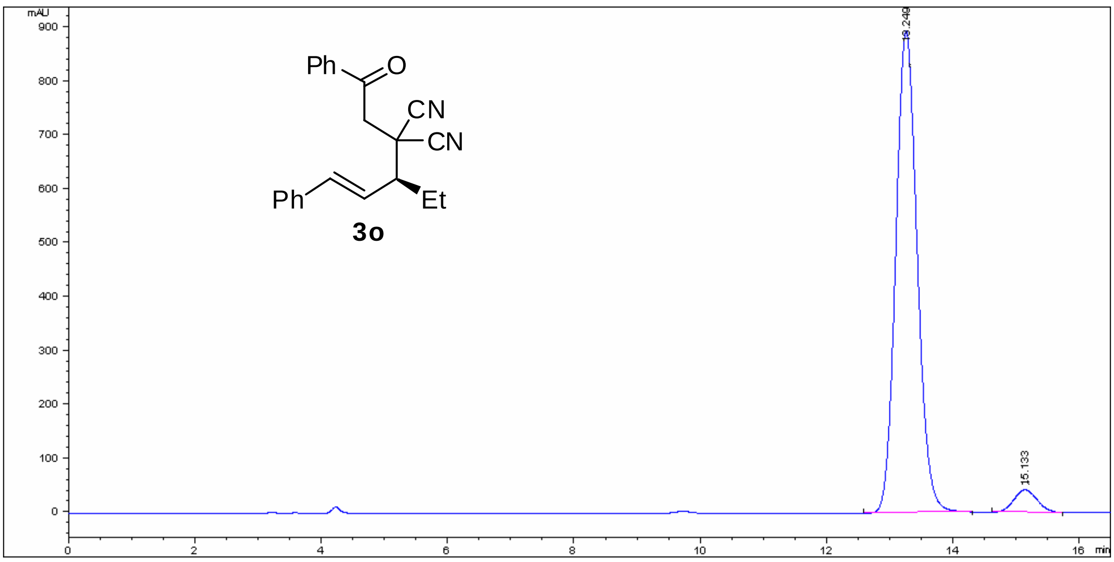
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	21.55	940.8	22.3	0.7038	0.699	49.332
2	24.868	966.2	20.4	0.79	0.733	50.668



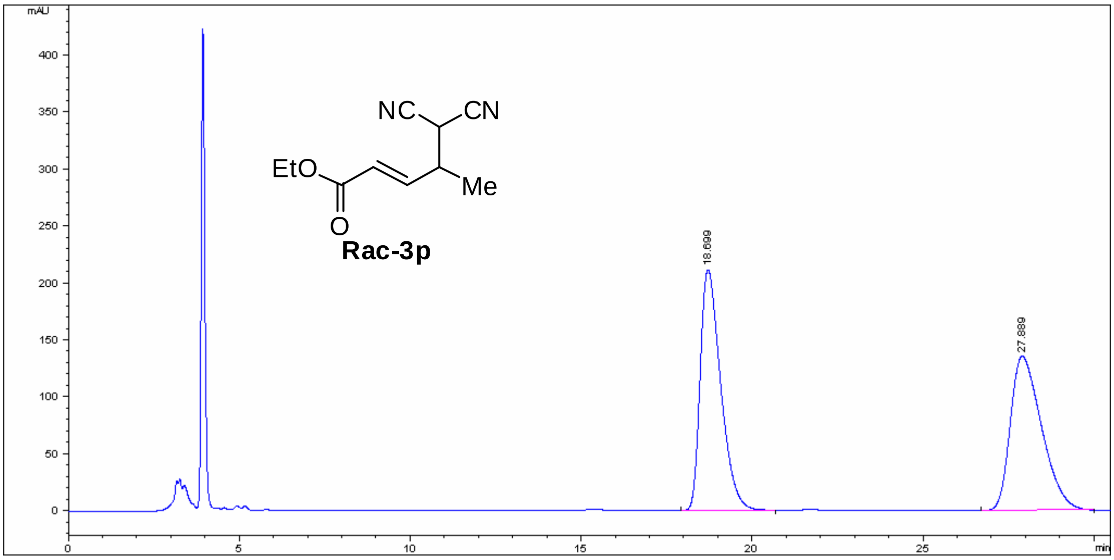
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	21.547	2395.6	58.2	0.6202	0.69	94.752
2	24.562	132.7	2.9	0.664	0.743	5.248



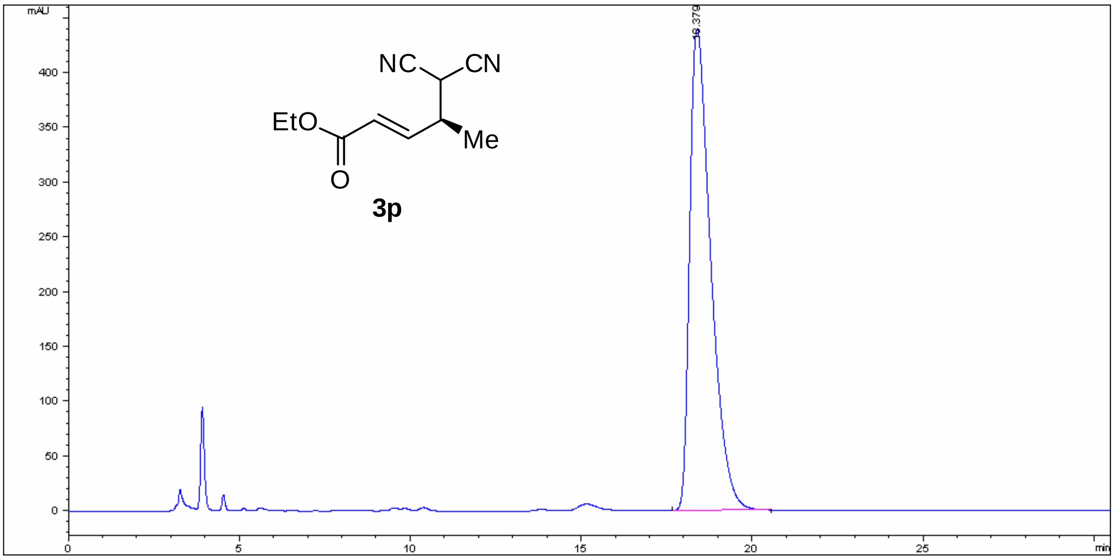
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	13.329	3387.9	143.2	0.3677	0.877	49.655
2	15.228	3434.9	125.5	0.4227	0.846	50.345



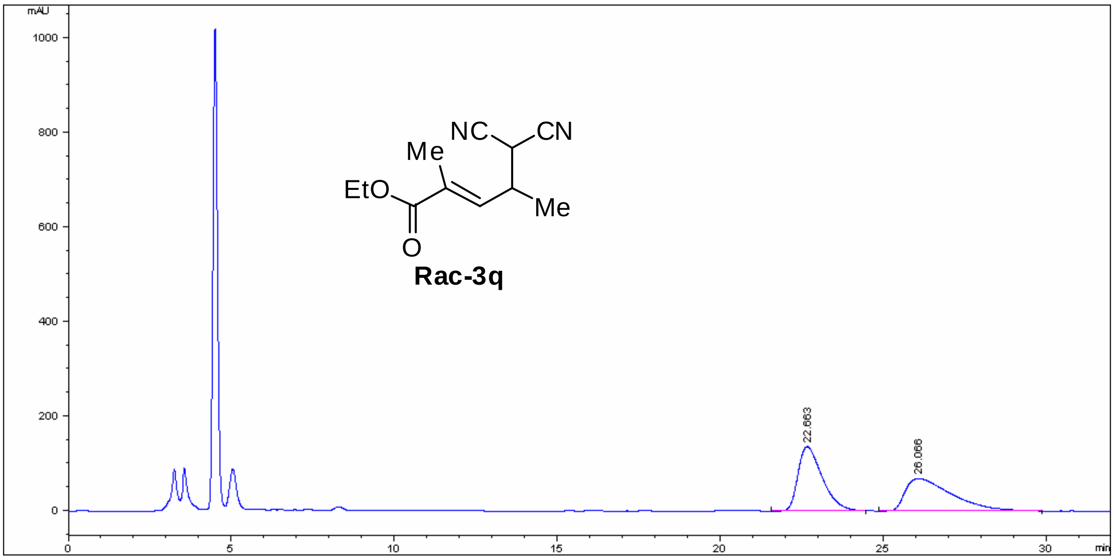
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	13.249	21050.5	893.8	0.3925	0.877	95.106
2	15.133	1083.3	41.8	0.4321	0.905	4.894



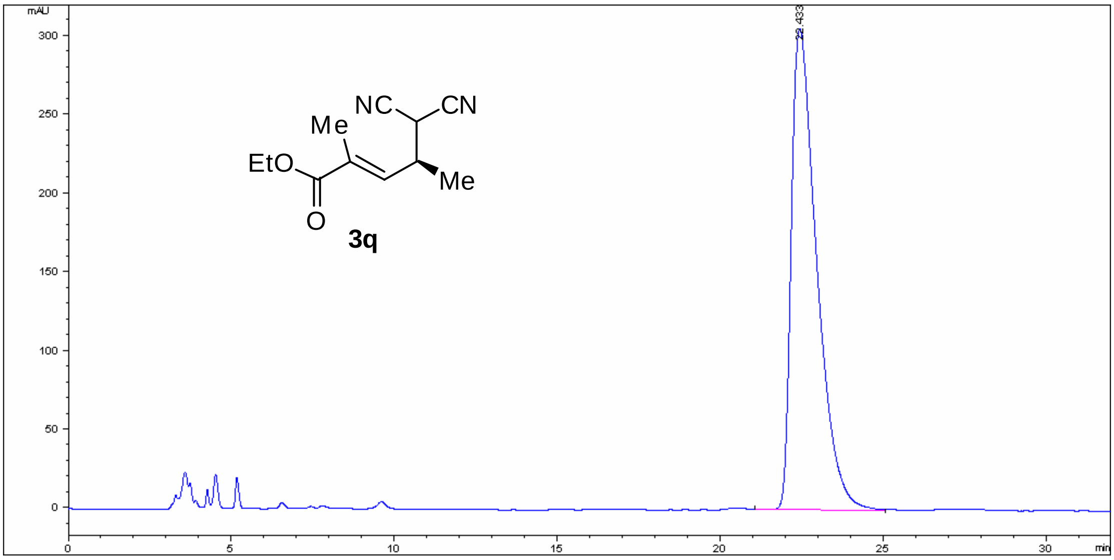
Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	18.699	8816.4	211.6	0.6375	0.575	50.508
2	27.889	8639.2	135.5	1.0044	0.581	49.492



Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	18.379	18856	439.5	0.6506	0.496	100.000



Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	22.663	7016.4	135.9	0.7769	0.582	50.600
2	26.066	6850.1	68.5	1.4363	0.357	49.400



Number	Time (min)	Area (mAU·s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	22.433	16608.4	305.6	0.8117	0.458	100.000