

## Supporting Information

# Reversible Switching and Recycling of Adaptable Organic Microgel Catalysts

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### Table of Content

1. General information
2. Synthesis of the organocatalysts
3. Synthesis and characterization of the microgels
  - 3.1 Synthetic procedure
  - 3.2 Sulfur elemental analysis
  - 3.3 FT-IR spectra
  - 3.4 Size and size distribution of microgels at different temperatures
  - 3.5 UCST behavior in different solvents
4. Desymmetrization of *meso*-anhydrides
  - 4.1 Synthetic procedure and characterization
  - 4.2 Derivatization of the hemiesters for SFC analysis
  - 4.3 Screening table for the desymmetrization of *meso*-anhydrides
5. NMR spectra
6. SFC spectra
7. Sulfur elemental analysis report

## 1. GENERAL INFORMATION

Ethyl acrylate (EA) ( $\geq 99.5\%$ ), cross-linker *N,N'*-methylenebisacrylamide (BIS) ( $\geq 99.5\%$ ), initiator 2,2'-Azobis(2-methylpropionamidine) dihydrochloride (AMPA) (97%), surfactant Hexadecyltrimethylammonium bromide ( $\geq 98\%$ ) were purchased from Sigma-Aldrich. Ethyl acrylate was destabilized with aluminium oxide. *Cis*-1,2,3,6-tetrahydrophthalic anhydride was recrystallized from n-hexane/ ethanol. All other chemicals were used as received. Reactions were performed in anhydrous solvents dried and distilled following standard procedures. Water for microgel synthesis was doubly distilled Milli-Q-water, for dialysis single distilled water. Solvents for column chromatography were technical grade and distilled prior to use. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 aluminium plates with F-254 fluorescence marker, visualized by UV irradiation or  $\text{KMnO}_4$  stain. Merck silica gel 60 (particle size 0.063 - 0.200 mm) was used for preparative column chromatography. Dialysis membranes ZelluTrans/Roth Dialysis membranes T4 with MWCO 12.000-14.000 were obtained from Carl Roth.

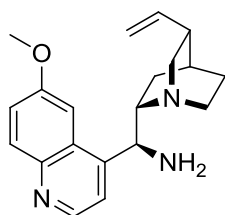
Optical properties were studied by UV/Visible spectrophotometer Cary 100 Bio from Varian. Hydrodynamic radii ( $R_h$ ) were measured by dynamic light scattering (DLS) at a wavelength of 633 nm with an ALV-5000. TEM pictures were taken at a Transmission Electron Microscope LIBRA 120 PLUS from Carl Zeiss. The sedimentation velocities were determined with the stability analyser LUMiFuge 1112-54 at a rotation speed of 2000 rpm.

$^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded on VNMRs-600, VNMRs-400, Inova 400 or Mercury 300 spectrometer in  $\text{CDCl}_3$ ,  $\text{MeOD-d}_4$  or  $\text{DMSO-d}_6$  using the residual solvent peak as an internal reference ( $\text{CDCl}_3$ :  $\delta_{\text{H}} = 7.26$  ppm,  $\delta_{\text{C}} = 77.0$  ppm;  $\text{MeOD-d}_4$ :  $\delta_{\text{H}} = 3.31$  ppm,  $\delta_{\text{C}} = 49.1$  ppm;  $\text{DMSO-d}_6$ :  $\delta_{\text{H}} = 2.50$  ppm,  $\delta_{\text{C}} = 39.4$  ppm). Chemical shifts ( $\delta$ ) are reported in ppm; multiplicities are indicated: br (broad signal), s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), t (triplet), dt (doublet of triplet), m (multiplet); coupling constants ( $J$ ) are in Hertz (Hz). Mass spectra (MS-EI, 70 eV) were conducted on a Finnigan MET SSQ 7000 system. IR spectra (ATR) were recorded on a Perkin Elmer spectrometer and are reported in terms of frequency of absorption ( $\text{cm}^{-1}$ ). Optical rotations were measured on a Perkin Elmer 241 polarimeter. Enantiomeric ratios were determined by analytical supercritical fluid chromatography (SFC) using chiral stationary phase column Daicel Chiralcel OJ-H with solvent mixtures and temperatures indicated below. The methods were calibrated with the corresponding racemic mixtures.

## 2. SYNTHESIS OF THE ORGANOCATALYSTS

### 9-Amino-(9-deoxy)-*epi*-quinine

Prepared from quinine following a literature procedure: Manna, M. S.; Mukherjee, S., Catalytic Asymmetric Direct Vinylogous Michael Addition of Deconjugated Butenolides to Maleimides for the Construction of Quaternary Stereogenic Centers. *Chem. Eur. J.* **2012**, 18, 15277-15282.

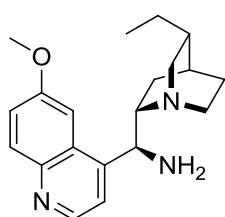


10 mmol scale, 2.432 g (7.52 mmol, 75%);  $^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 8.74$  (d,  $J = 4.5$  Hz, 1H), 8.02 (d,  $J = 9.2$  Hz, 1H), 7.63 (br s, 1H), 7.45 (m, 1H), 7.37 (dd,  $J = 9.2, 2.7$  Hz, 1H), 5.79 (ddd,  $J = 17.5, 10.3, 7.5$  Hz, 1H), 5.00 (dt,  $J = 17.2, 1.4$  Hz, 1H), 4.98-4.95 (m, 1H), 4.59 (br s, 1H), 3.96 (s, 3H), 3.28 (dd,  $J = 13.9, 10.1$  Hz, 1H), 3.26-3.19 (m, 1H), 3.11 (br s, 1H), 2.85-2.78 (m, 2H), 2.39 (br s, 2H), 2.32-2.26 (m, 1H), 1.65-1.61 (m,

1H), 1.60-1.52 (m, 2H), 1.47-1.38 (m, 1H), 0.77 (ddt,  $J = 13.7, 7.4, 1.9$  Hz, 1H);  $^{13}\text{C-NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 157.6, 147.8, 146.9, 144.7, 141.6, 131.8, 128.7, 121.2, 119.8, 114.4, 102.0, 62.0, 56.2, 55.6, 51.9, 41.0, 39.7, 28.1, 27.5, 26.0$ ; **MS (EI)**:  $m/z$  (%) = 324.8 (32), 323.6 ( $[\text{M}]^+$ , 46), 187.8 (21), 186.6 (31), 136.8 (29), 136.1 (100); **IR**:  $\nu/\text{cm}^{-1} = 3372, 3071, 2932, 1925, 1733, 1620, 1505, 1462, 1355, 1313, 1238, 1033, 913, 847, 629, 551$ .

### 9-Amino-(9-deoxy)-*epi*-hydroquinine

To a solution of 1.0 equiv 9-Amino-(9-deoxy)-*epi*-quinine in ethanol was added 0.05 equiv Pd/C (5 wt-%) and the reaction mixture was transferred into a stainless-steel autoclave where a hydrogenation was performed at 20 bar pressure, 30 °C for 16 h. The reaction mixture was filtered through a small pad of Celite to remove Pd/C, concentrated under reduced pressure and the residue was purified by column chromatography on silica gel with EtOAc/ MeOH/ aq.  $\text{NH}_3$  50:50:1 as eluent.

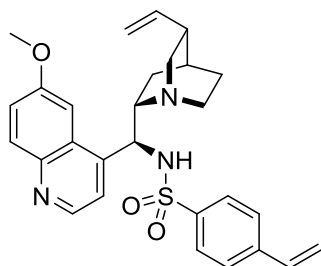


2 mmol scale, 593 mg (1.82 mmol, 91%);  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 8.75$  (d,  $J = 4.5$  Hz, 1H), 8.03 (d,  $J = 9.2$  Hz, 1H), 7.66 (br s, 1H), 7.47 (br d,  $J = 4.0$  Hz, 1H), 7.38 (dd,  $J = 9.2, 2.7$  Hz, 1H), 4.59 (br d,  $J = 9.4$  Hz, 1H), 3.97 (s, 3H), 3.25 (dd,  $J = 13.6, 9.8$  Hz, 1H), 3.24-3.14 (m, 1H), 3.11-3.00 (m, 1H), 2.84-2.72 (m, 1H), 2.52 (ddd,  $J = 13.6, 4.5, 2.4$  Hz, 1H), 2.09 (br s, 2H), 1.63-1.22 (m, 7H), 0.82 (t,  $J = 7.3$  Hz, 3H), 0.74 (dd,  $J = 13.5, 7.5$  Hz, 1H);  $^{13}\text{C-NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 157.5, 147.7, 146.9, 144.6, 131.7, 128.6, 121.1, 119.8, 101.8, 61.7, 57.6, 55.4, 51.8, 40.9, 37.2, 28.5, 27.4, 25.5, 25.1, 11.9$ ; **MS (EI)**:  $m/z$  (%) = 327.4 (31), 326.3 ( $[\text{M}+\text{H}]^+$ , 100), 325.3 (79), 310.3 (19), 188.2 (22), 187.1 (55), 139.2 (49), 110.2 (67), 82.2 (58), 55.3 (19); **IR**:  $\nu/\text{cm}^{-1} = 3369, 2932, 2869, 2325, 2069, 1921, 1619, 1507, 1462, 1358, 1232, 1139, 1080, 1030, 917, 840, 727$ .

### Quinine and Hydroquinine derived sulfonamides:

Under argon atmosphere, a solution of 1.2 equiv 9-Amino-(9-deoxy)-*epi*-quinine or 9-Amino-(9-deoxy)-*epi*-hydroquinine in dry DCM was cooled to 0 °C and 1.1 equiv  $\text{NEt}_3$  was added. A solution of 1.0 equiv arylsulfonyl chloride in dry DCM was cooled to 0 °C and slowly added to the reaction mixture. After being stirred for 3 h at 0 °C, water was added to the solution. The DCM phase was collected and the aqueous phase was extracted with DCM twice. The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure and the residue was purified by column chromatography on silica gel with EtOAc/ MeOH 20:1 as eluent.

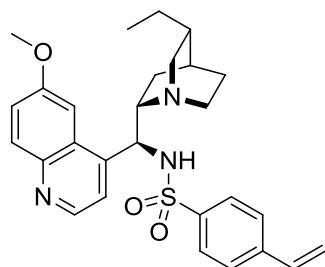
### *N*-(9-Deoxy-*epi*-quinin-9-yl)-4-vinylbenzenesulfonamide [1a]:



2 mmol scale, 810 mg (1.65 mmol, 83%);  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ , 95 °C):  $\delta/\text{ppm} = 8.58$  (d,  $J = 4.5$  Hz, 1H), 7.87 (d,  $J = 9.2$  Hz, 1H), 7.54-7.33 (m, 5H), 7.27 (d,  $J = 8.2$  Hz, 2H), 6.67 (dd,  $J = 17.6, 10.9$  Hz, 1H), 5.80 (d,  $J = 17.6$  Hz, 1H), 5.77-5.68 (m, 1H), 5.35 (d,  $J = 10.9$  Hz, 1H), 4.96 (d,  $J = 17.3$  Hz, 1H), 4.90 (d,  $J = 10.4$  Hz, 1H), 4.83 (br s, 1H), 3.94 (s, 3H), 3.20 (br s, 1H), 3.12 (dd,  $J = 13.2, 10.4$  Hz, 1H), 2.76 (m, 2H), 2.54 (m, 1H), 2.22 (br s, 1H), 1.48 (m, 3H), 1.13 (m, 1H), 0.70 (m, 1H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-d}_6$ , 95 °C):  $\delta/\text{ppm} = 156.7, 146.6, 143.6, 141.3, 140.2, 139.1, 134.9, 130.8, 127.0, 126.2, 152.2, 120.3, 120.0, 116.5, 113.4, 101.7, 58.7, 55.1, 54.6, 51.8, 38.3, 26.9, 26.6, 24.6$ ; **MS (EI)**:  $m/z$  (%) = 490.7 (15), 490.0 ( $[\text{M}+\text{H}]^+$ , 15), 322.5 (69), 321.7 (47), 320.6 (36), 278.7 (33), 277.7 (100), 276.8 (60), 276.0 (24), 275.3 (22), 199.5 (28), 198.5 (31), 197.8 (18), 197.3 (15), 187.0 (15), 185.9 (16), 184.7 (17), 183.9 (19),

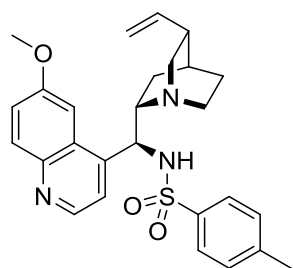
183.1 (18), 137.0 (19), 136.4 (42), 135.6 (20); **IR**:  $\nu/\text{cm}^{-1}$  = 3205, 2936, 2327, 2052, 1785, 1609, 1499, 1327, 1238, 1152, 1083, 1028, 914, 841, 711; **sulfur elemental analysis**:  $\text{C}_{28}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$ , calculated: 6.55% S, found: 6.54% S.

#### ***N*-(9-Deoxy-*epi*-hydroquinin-9-yl)-4-vinylbenzenesulfonamide [1b]**



1 mmol scale, 402 mg (0.82 mmol, 82%); **<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 95 °C):  $\delta/\text{ppm}$  = 8.58 (d,  $J$  = 4.4 Hz, 1H), 7.86 (d,  $J$  = 9.1 Hz, 1H), 7.50-7.33 (m, 5H), 7.25 (d,  $J$  = 8.1 Hz, 2H), 6.66 (dd,  $J$  = 17.5, 10.8 Hz, 1H), 5.80 (d,  $J$  = 17.8 Hz, 1H), 5.36 (d,  $J$  = 10.9 Hz, 1H), 4.82 (br s, 1H), 3.94 (s, 3H), 3.23 (br s, 1H), 3.15 (dd,  $J$  = 13.1, 10.3 Hz, 1H), 2.84 (br s, 1H), 2.62-2.52 (m, 1H), 2.46 (br s, 1H), 1.57-1.46 (m, 2H), 1.45-1.35 (m, 2H), 1.28-1.06 (m, 3H), 0.76 (t,  $J$  = 7.4 Hz, 3H), 0.73-0.64 (m, 1H); **<sup>13</sup>C-NMR** (100 MHz, DMSO-*d*<sub>6</sub>, 95 °C):  $\delta/\text{ppm}$  = 156.8, 146.6, 143.6, 140.2, 138.8, 134.8, 130.8, 127.0, 126.1, 125.2, 120.3, 119.7, 116.4, 101.8, 58.8, 56.2, 55.0, 51.9, 36.3, 27.3, 26.2, 24.4, 24.3, 11.1; **MS (EI)**:  $m/z$  (%) = 492.5 (3), 491.5 ( $[\text{M}]^+$ , 4), 325.4 (25), 324.4 (100), 187.2 (18), 155.2 (18), 139.3 (24), 138.3 (18), 110.3 (27), 103.2 (17), 82.3 (27); **IR**:  $\nu/\text{cm}^{-1}$  = 3875, 3602, 3208, 2936, 2870, 2649, 2316, 2084, 1914, 1720, 1619, 1508, 1465, 1327, 1231, 1156, 1089, 1028, 920, 843, 717, 662.

#### ***N*-(9-Deoxy-*epi*-quinin-9-yl)-4-methylbenzenesulfonamide [1c]**



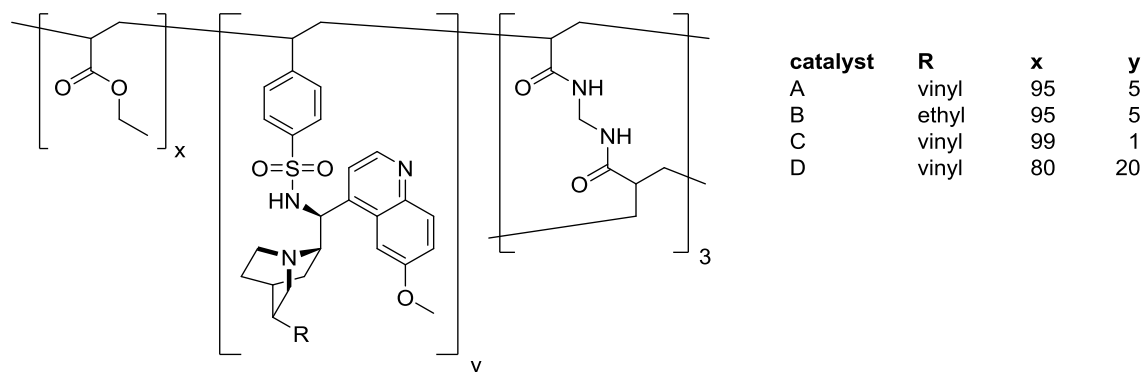
1 mmol scale, 426 mg (0.89 mmol, 89%); **<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 95 °C):  $\delta/\text{ppm}$  = 8.55 (d,  $J$  = 3.3 Hz, 1H), 7.84 (d,  $J$  = 8.2 Hz, 1H), 7.48-7.24 (m, 5H), 6.97 (d,  $J$  = 6.7 Hz, 2H), 5.78-5.62 (m, 1H), 4.99-4.62 (m, 3H), 3.91 (s, 3H), 3.16-3.04 (m, 2H), 2.81-2.65 (m, 2H), 2.56-2.43 (m, 2H), 2.19 (s, 4H), 1.54-1.38 (m, 3H), 1.08 (br s, 1H), 0.65 (br s, 1H); **<sup>13</sup>C-NMR** (100 MHz, DMSO-*d*<sub>6</sub>, 95 °C):  $\delta/\text{ppm}$  = 156.8, 146.6, 143.7, 141.7, 141.3, 137.1, 130.8, 128.1, 127.1, 125.9, 120.4, 120.0, 113.5, 101.8, 59.1, 55.1, 54.6, 51.6, 38.4, 26.9, 26.6, 24.6, 20.2; **MS (EI)**:  $m/z$  (%) = 479.5 (2), 478.5 ( $[\text{M}+\text{H}]^+$ , 8), 322.4 (4), 199.2 (1), 187.2 (3), 172.2 (1), 155.1 (4), 137.2 (10), 136.2 (100), 108.2 (1), 95.2 (1), 91.2 (4), 81.2 (2), 79.2 (2); **IR**:  $\nu/\text{cm}^{-1}$  = 3748, 3190, 2924, 2868, 2659, 2307, 2192, 2114, 1922, 1736, 1621, 1593, 1509, 1473, 1432, 1375, 1349, 1326, 1297, 1252, 1227, 1165, 1133, 1088, 1059, 1034, 988, 920, 859, 814, 764, 696, 673, 616, 569; **sulfur elemental analysis**:  $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$ , calculated: 6.71% S, found: 6.67% S.

### **3. SYNTHESIS AND CHARACTERIZATION OF THE MICROGEL**

#### **3.1 Synthetic procedure**

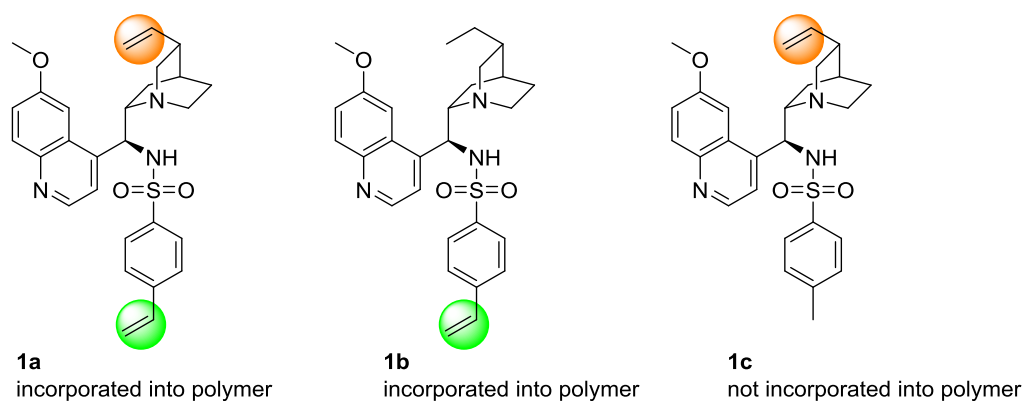
For the emulsion polymerization a certain amount of organocatalyst monomer (1-10 mol-%) was dissolved in calculated volume of ethyl acrylate (90-99 mol-%) under continuous stirring. Then cetyltrimethylammonium bromide (CTAB, 1 mol-%), crosslinker *N,N'*-Methylenebisacrylamide (BIS, 3 mol-%) and water were added. Dissolved oxygen was removed by purging of nitrogen through the mixture within 60 min. In order to build an emulsion, the flask with the mixture was placed in an ultrasonic bath for 15 min. Then the flask was placed in oil bath and heated up to 70 °C under constant stirring. Finally, a water solution of the initiator 2,2'-azobis(2-methylpropionamidine) dihydrochloride (AMPA, 1 mol-%) was added to the reaction mixture. After 6 hours reaction time the mixture was cooled down to the room temperature and dialyzed

for 5 days against water to purify the microgel. After cleaning procedure the microgel was freeze-dried. Although the conversion of the monomers in the polymerization is quantitative, yields of microgel are typically 50-65% since also linear polymers are formed, which are removed during dialysis.



**Scheme S1:** Structures and composition of organocatalysts **A-D**.

### Reactivity of organocatalysts **1a-1c** in the polymerization



**Scheme S2:** Organocatalysts **1a-1c**; reactive styryl group highlighted in green, non-reactive vinyl group highlighted in orange.

### 3.2 Sulfur elemental analysis

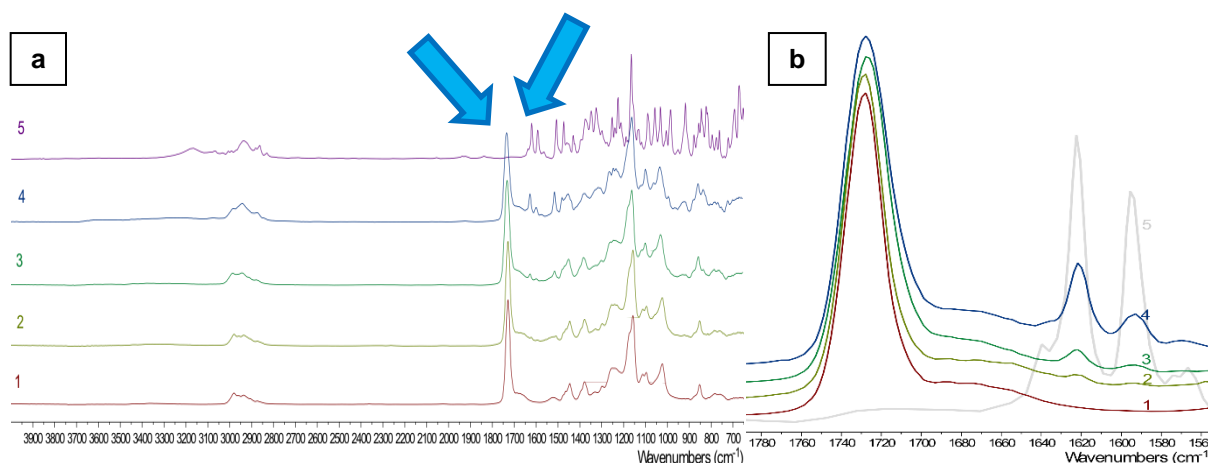
To verify the incorporation of the organocatalyst **1a** into the microgel, sulfur elemental analysis was performed by the external provider *Mikroanalytisches Laboratorium Kolbe* (the report is attached). Reported values in *Table S1* represent the average of a double determination. For our best catalyst **A** (poly-EA-**1a** (95:5)), two different batches were measured in a double determination each and the reported value represents the average of all four measurements. As control experiments also the monomeric organocatalysts **1a** and **1c** as well as unmodified poly-EA were measured. All measured sulfur contents are in very good agreement with the calculated values. The only exception is catalyst **D** (poly-EA-**1a** (80:20)) [VPR\_022], which was thought to have a ratio of 90:10 and was reassigned accordingly.

**Table S1: Sulfur elemental analysis**

	ratio	sample	formula	% sulfur (calc.)	% sulfur (found)
<b>1a (E)</b>	monomer	RB_E459	C <sub>28</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> S	6.55	6.54
<b>1c</b>	monomer	RB_E509	C <sub>27</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> S	6.71	6.67
poly-EA-BIS	100:3	VPR_043	C <sub>521</sub> H <sub>830</sub> N <sub>6</sub> O <sub>206</sub>	0.00	0.02
poly-EA- <b>1a</b> -BIS (C)	99:1:3	VPR_020	C <sub>544</sub> H <sub>853</sub> N <sub>9</sub> O <sub>207</sub> S <sub>1</sub>	0.30	0.26
poly-EA- <b>1a</b> -BIS (A)	95:5:3	VPR_021, 034	C <sub>636</sub> H <sub>945</sub> N <sub>21</sub> O <sub>211</sub> S <sub>5</sub>	1.29	1.30
poly-EA- <b>1a</b> -BIS	90:10:3	VPR_022	C <sub>751</sub> H <sub>1060</sub> N <sub>36</sub> O <sub>216</sub> S <sub>10</sub>	2.23	3.48
poly-EA- <b>1a</b> -BIS (D)	80:20:3	VPR_022	C <sub>981</sub> H <sub>1290</sub> N <sub>66</sub> O <sub>226</sub> S <sub>20</sub>	3.51	3.48

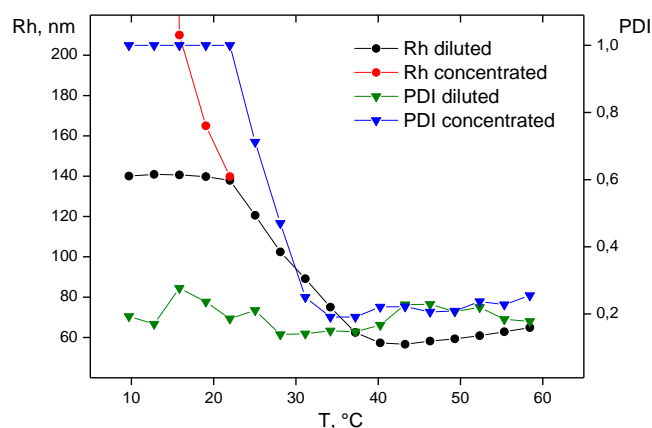
### 3.3 FT-IR spectra for microgels with variable amount of catalyst 1a

To verify the copolymerization of catalyst **1a** in the microgel, we performed FT-IR studies (Table S1). Curve 1 shows unmodified poly-EA with a characteristic ester carbonyl C=O stretching band at 1730 cm<sup>-1</sup>. Additional characteristic signals are C-H deformation vibration (1450 cm<sup>-1</sup>) of the ethyl group and asymmetric C-O stretching vibration (1100 cm<sup>-1</sup>) of the saturated aliphatic ester. The organocatalyst **1a** is shown in curve 5 with two significant bands at 1625 cm<sup>-1</sup> and 1595 cm<sup>-1</sup> indicating the aromatic ring C=C and C=N stretching vibration. Additional characteristic signals for the organocatalyst are asymmetric (1330 cm<sup>-1</sup>) and symmetric (1170 cm<sup>-1</sup>) SO<sub>2</sub> stretching vibration of the aryl sulfonamide as well as asymmetric (1230 cm<sup>-1</sup>) and symmetric (1030 cm<sup>-1</sup>) C-O stretching vibration of the aryl methyl ether.



**Figure S1.** FT-IR spectra (a) of unmodified poly-EA (1) microgel and microgels with variable catalyst amount: catalyst **C** (poly-EA-**1a** (99:1)) (2), catalyst **A** (poly-EA-**1a** (95:5)) (3), catalyst **D** (poly-EA-**1a** (80:20)) (4). Spectrum of the monomeric organocatalyst **1a** (5) is presented as a reference. Arrows indicate characteristic bands that may be used to evaluate the loading of organocatalyst in microgels by comparing the peak intensities. Close-up and overlay of curves 1-5 in the specific region (b).

### 3.4 Size and size distribution of microgels at different temperatures

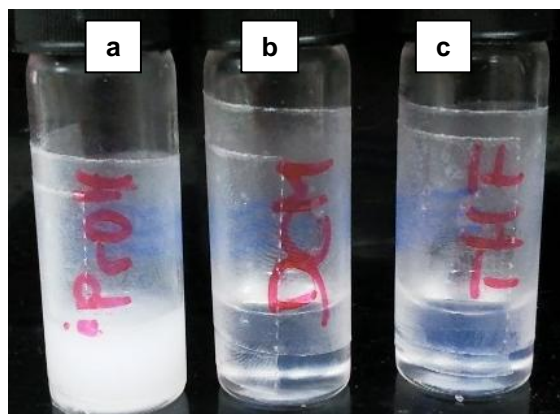


**Figure S2.** Hydrodynamic radius and polydispersity index (PDI) of microgel catalyst **A** (poly-EA-**1a** (95:5)) at different temperatures.

Figure S2 presents hydrodynamic radius ( $R_h$ ) and polydispersity index (PDI) for microgels measured at different temperatures by dynamic light scattering. For the diluted microgel sample, we observed an increase of the size by cooling below 40 °C ( $T < UCST$ ) at almost constant PDI due to the partial aggregation of microgels. Starting from 25 °C, no change of the size can be observed and microgel aggregates become stabilized in solution. In contrast, for the concentrated microgel sample even below 25 °C aggregation process continues and leads to a rapid increase of the aggregate size and PDI. Finally, this process induces precipitation of microgels and allows simple recovery from solution.

### 3.5 UCST behavior in different solvents

In general, we qualitatively tested catalyst **A** (poly-EA-**1a** (95:5)) for UCST behavior by dissolving the polymer (10 mg/ml), heating and equilibrating the solution at 50 °C (or slightly below the boiling point) and then successively lowering the temperature by placing the vials on the bench (RT), in the fridge (5 °C), and in the freezer (-20 °C). Polymer precipitate indicated a UCST behavior (Figure S3). A broad range of common organic solvents (alcohols, acetone, acetonitrile, DCM,  $CHCl_3$ , EtOAc,  $Et_2O$ , THF, Dioxane, toluene, DMF, and DMSO) was tested, including typical solvents applied in catalysis in general and in desymmetrization reactions in particular.



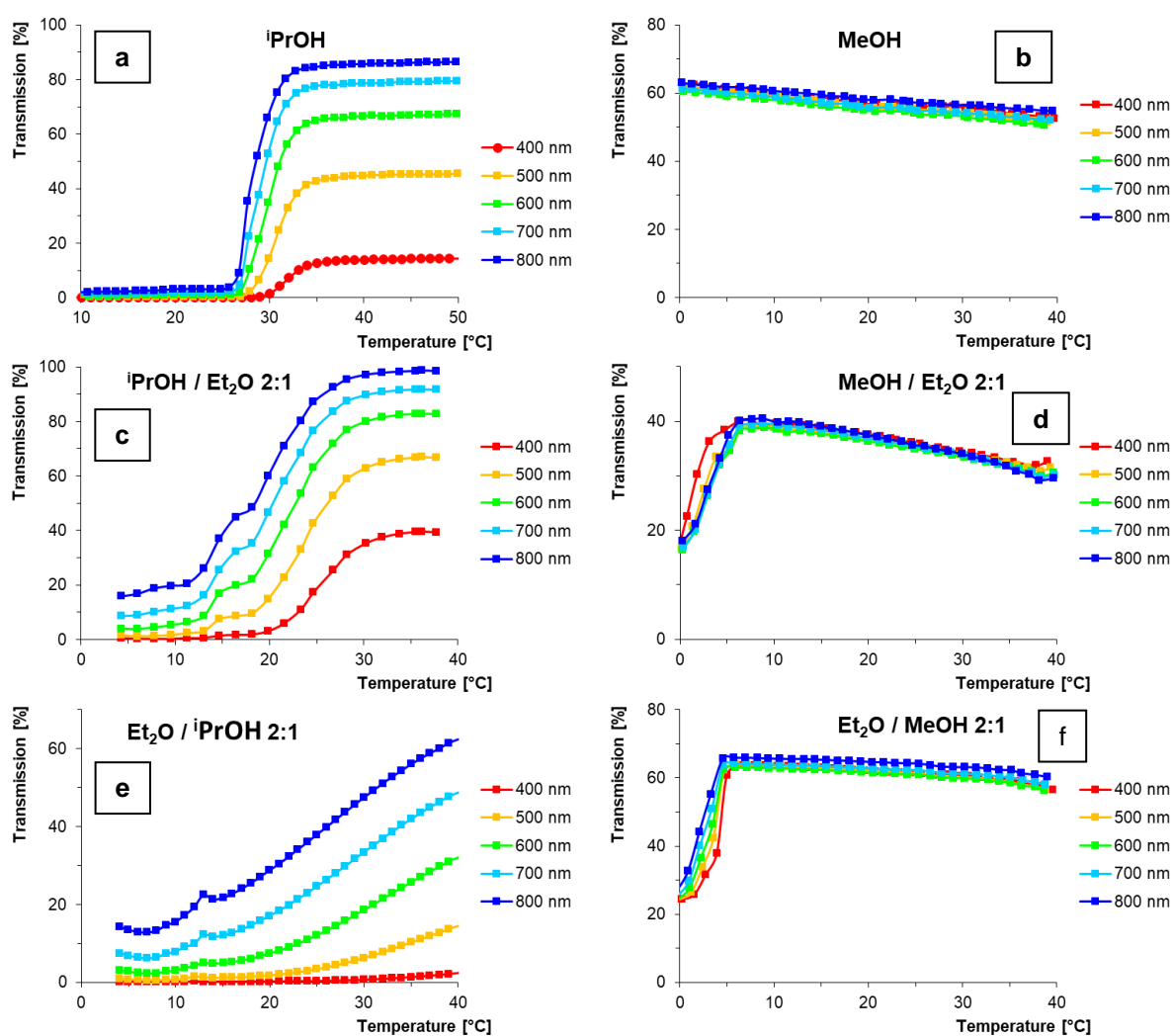
**Figure S3.** Qualitative test for UCST behavior by cooling solutions of catalyst **A** (poly-EA-**1a** (95:5)) in the freezer: precipitated polymer in iPrOH (a), clear solution in DCM (b) and THF (c).

In order to quantify the UCST behavior, temperature-dependant UV-Vis measurements (Figure S4) were performed for catalyst **A** (poly-EA-**1a** (95:5)). Solvent mixtures relevant for catalytic application (see table 1 in the manuscript) were investigated, containing  $i$ PrOH, MeOH, and Et<sub>2</sub>O as the major component, and the added nucleophile as the minor component.

In pure  $i$ PrOH, nice UCST behavior at ~34 °C was observed (Figure S4a). Upon addition of Et<sub>2</sub>O, the UCST temperature was lowered and the transition became less sharp (Figure S4c) and very broad (Figure S4e). In those mixtures, catalytic reactions did not provide product, likely because the microgel is not well solvated in the absence of a sharp UCST and cannot act as a homogeneous catalyst.

In pure MeOH on the other hand, no UCST was observed (Figure S4b) and therefore the catalyst could not be recycled. Addition of Et<sub>2</sub>O, however, resulted in a relatively sharp UCST behavior ~6 °C (Figure S4d+f). Both catalytic reactions and catalyst recycling worked well.

Unfortunately, a measurement in pure Et<sub>2</sub>O was not possible due to low transmission since a solution of the microgel in Et<sub>2</sub>O is more turbid compared to solvent systems containing alcohols (compare Figure 2a in the manuscript with Figure 4, picture “catalysis”). However, we did observe UCST behavior qualitatively: a solution cooled to 0 °C precipitated over time and we were able to separate the catalyst by centrifugation and reuse it in further catalytic cycle.



**Figure S4.** Temperature dependent UV-Vis spectroscopy for catalyst **A** (poly-EA-**1a** (95:5)) in  $i$ PrOH (a), MeOH (b),  $i$ PrOH/ Et<sub>2</sub>O 2:1 (c), MeOH/ Et<sub>2</sub>O 2:1 (d), Et<sub>2</sub>O/  $i$ PrOH 2:1 (e), Et<sub>2</sub>O/ MeOH 2:1 (f).



## 4. ORGANOCATALYTIC DESYMMETRIZATION OF *MESO*-ANHYDRIDES

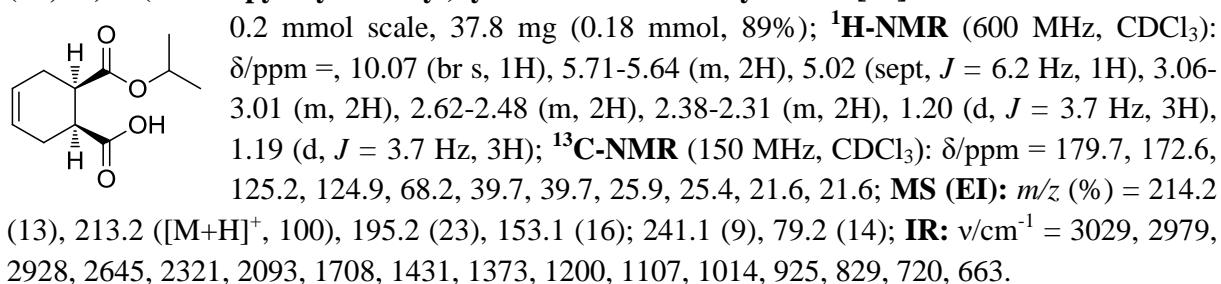
### 4.1 Synthetic procedures and characterization

Before a catalytic test reaction, the dried polymer was dissolved in the corresponding abs. solvent, stirred for 1 hour, and cooled to 0 °C. The precipitated polymer was separated from the supernatant solvent by centrifugation in order to remove possible contaminants like residual traces of water or unreacted monomers.

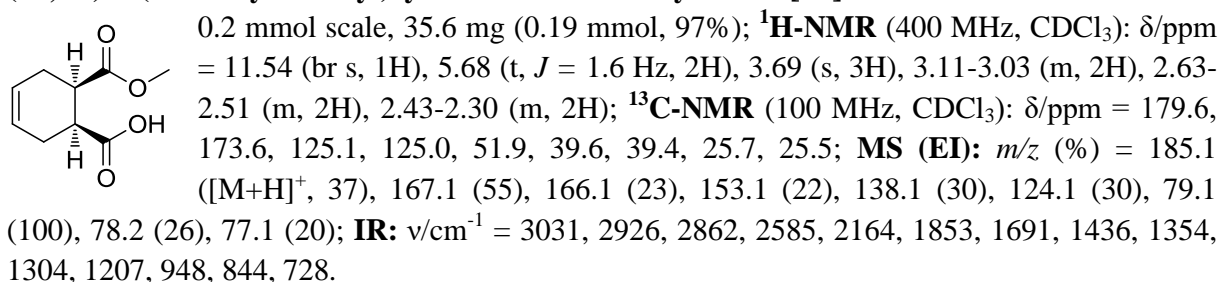
To perform the catalytic test reaction, the polymer catalyst (1 - 20 mol-%) was dissolved/suspended in the appropriate mixture of abs. solvents under argon, 1 equiv *meso*-anhydride and the nucleophile (methanol or *iso*-propanol, 5 - 20 equiv) were added. The reaction mixture was stirred at RT for the indicated time (TLC control, n-hexane/ EtOAc 2:1, KMnO<sub>4</sub> stained). When cooling the reaction mixture to 0 °C, the microgel catalyst precipitated and was centrifuged for 10 min. The supernatant was carefully taken off with a Pasteur pipette and the polymer catalyst was washed by repeating the dissolving/ cooling/ centrifugation procedure with a fresh portion of solvent. The combined solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel with n-hexane/ DCM 1:1, later n-hexane/ EtOAc 2:1 as eluent.

The separated polymer catalyst was reused in another catalytic cycle by recharging the system with fresh solvent and substrate as described above.

#### (1*S*,6*R*)-6-(*iso*-Propyloxycarbonyl)cyclohex-3-enecarboxylic acid [3a]:



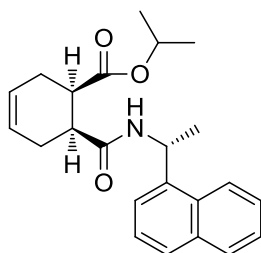
#### (1*S*,6*R*)-6-(Methoxycarbonyl)cyclohex-3-enecarboxylic acid [3b]:



### 4.2 Derivatisation of the Hemiesters for SFC-Analysis:

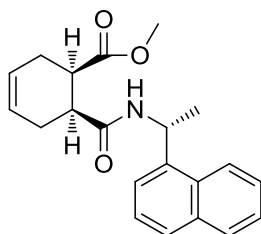
To a solution of 1.0 equiv hemiester in dry DCM was added 1.2 equiv EDCI, 0.3 equiv DMAP and 1.1 equiv (*R*)-1-(1-naphthyl)ethylamine. The reaction mixture was stirred for 3 h at RT (TLC control, n-hexane/ EtOAc 2:1), the solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel with n-hexane/ DCM 1:1, later n-hexane/ EtOAc 2:1 as eluent.

**(1*R*,6*S*)-iso-Propyl 6-(((*R*)-1-(naphthalen-1-yl)ethyl)carbamoyl)cyclohex-3-enecarboxylate [4a]:**



0.18 mmol scale, 53.2 mg (0.15 mmol, 82%); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ/ppm = 8.08 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.57-7.41 (m, 4H), 6.25 (d, *J* = 7.9 Hz, 1H), 5.95-5.86 (m, 1H), 5.72-5.62 (m, 2H), 5.00 (sept, *J* = 6.3 Hz, 1H), 2.97-2.87 (m, 2H), 2.56-2.22 (m, 4H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.59 (br s, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ/ppm = 173.5, 171.7, 138.5, 133.9, 131.1, 128.6, 128.2, 126.4, 125.8, 125.6, 125.1, 124.9, 123.7, 122.5, 68.1, 44.6, 40.6, 40.6, 27.0, 25.9, 21.8, 21.7, 20.8; **MS (EI):** *m/z* (%) = 366.3 ([M+H]<sup>+</sup>, 46), 365.3 (49), 306.3 (6), 170.2 (50), 156.1 (19), 155.1 (100), 153.1 (22), 129.1 (7), 79.2 (10); **IR:** ν/cm<sup>-1</sup> = 3307, 3038, 2978, 2928, 2292, 1946, 1721, 1645, 1528, 1447, 1374, 1188, 1107, 1015, 916, 782, 734; Diastereomeric ratio was determined by SFC, Chiralcel OJ-H column, 2% MeOH/ CO<sub>2</sub>, 4 mL/min, T = 25.3 °C, λ = 220 nm, τ<sub>major</sub> = 5.74 min, τ<sub>minor</sub> = 7.11 min, 53:47 d.r.

**(1*R*,6*S*)-Methyl 6-(((*R*)-1-(naphthalen-1-yl)ethyl)carbamoyl)cyclohex-3-enecarboxylate [4b]:**



0.19 mmol scale, 59.5 mg (0.18 mmol, 91%); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ/ppm = 8.07 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.55-7.46 (m, 3H), 7.46-7.42 (m, 1H), 6.12 (br s, 1H), 5.90 (p, *J* = 6.9 Hz, 1H), 5.70-5.60 (m, 2H), 3.61 (s, 3H), 3.04-2.96 (m, 1H), 2.94-2.87 (m, 1H), 2.57-2.47 (m, 1H), 2.46-2.31 (m, 2H), 2.31-2.23 (m, 1H), 1.63 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ/ppm = 174.3, 171.6, 138.3, 133.8, 131.0, 128.6, 128.2, 126.4, 125.8, 125.7, 125.1, 124.6, 123.6, 122.4, 51.7, 44.5, 40.7, 40.1, 26.5, 25.9, 20.6; **MS (EI):** *m/z* (%) = 338.3 (51), 337.3 ([M]<sup>+</sup>, 100), 170.3 (14), 156.3 (14), 155.2 (65), 154.2 (21), 153.1 (14), 79.1 (28), 77.1 (16); **IR:** ν/cm<sup>-1</sup> = 3300, 3025, 2943, 2323, 2196, 2159, 2065, 1733, 1633, 1536, 1435, 1365, 1187, 1027, 908, 780, 736; Diastereomeric ratio was determined by SFC, Chiralcel OJ-H column, 2% MeOH/ CO<sub>2</sub>, 4 mL/min, T = 30.9 °C, λ = 220 nm, τ<sub>minor</sub> = 10.63 min, τ<sub>major</sub> = 13.02 min, 7:93 d.r.

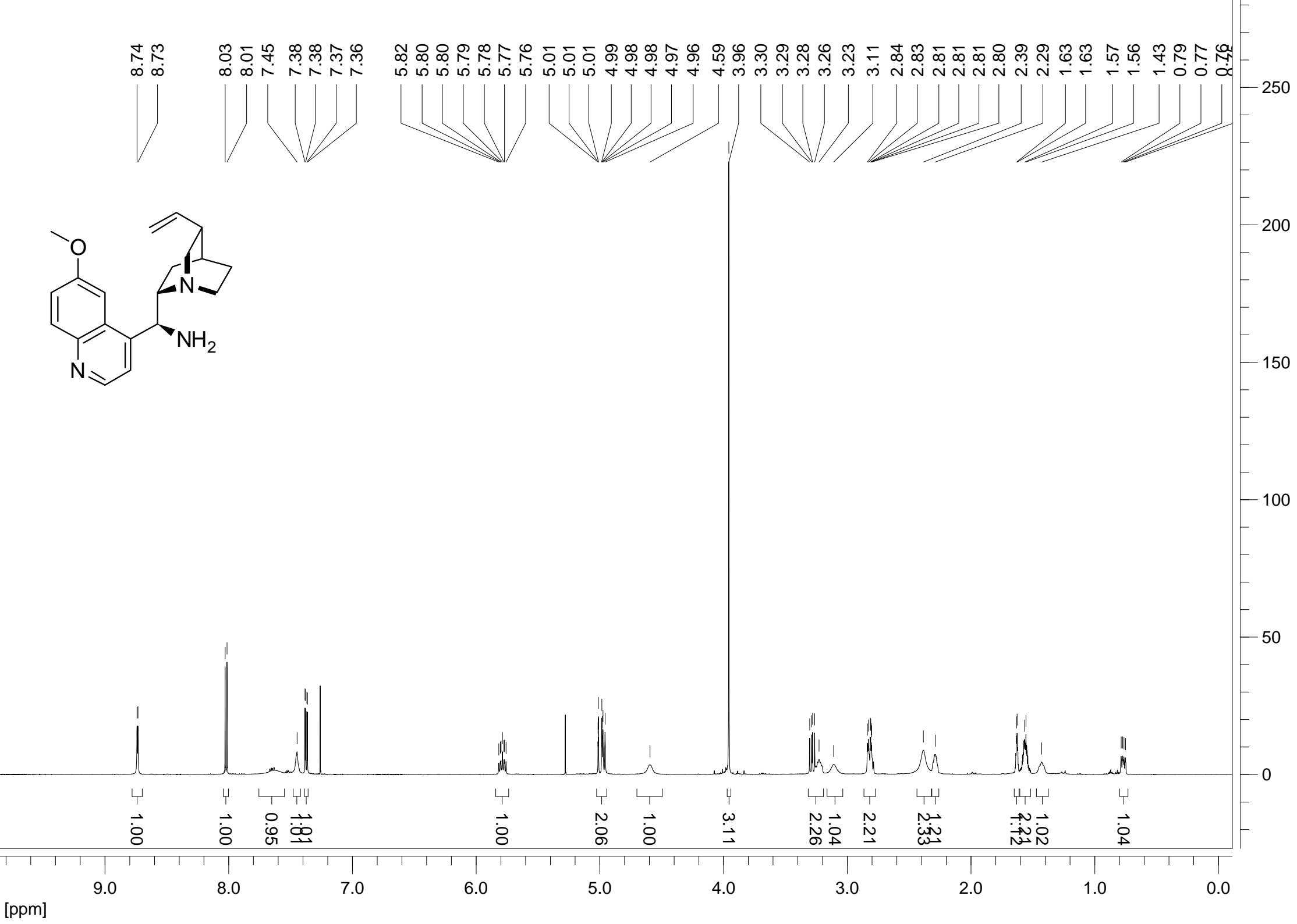
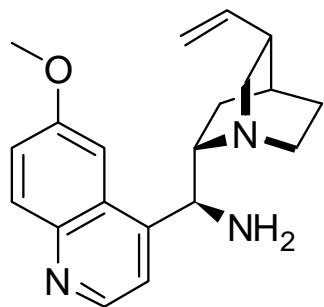
### 4.3 Reaction optimization for the desymmetrization of meso-anhydrides

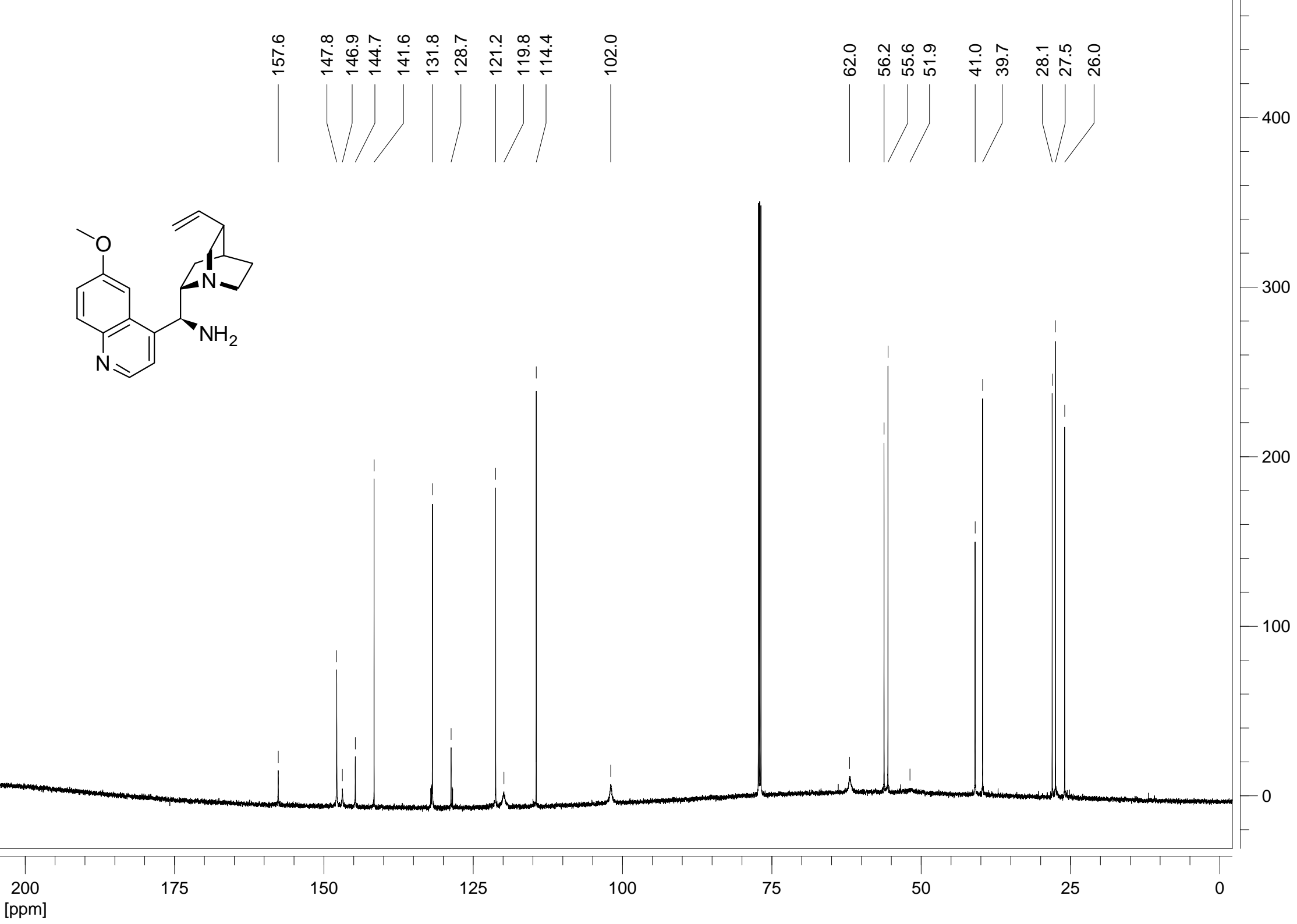
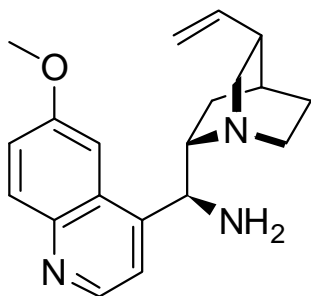
**Table S2: Screening table for the desymmetrization of meso-anhydrides<sup>a</sup>**

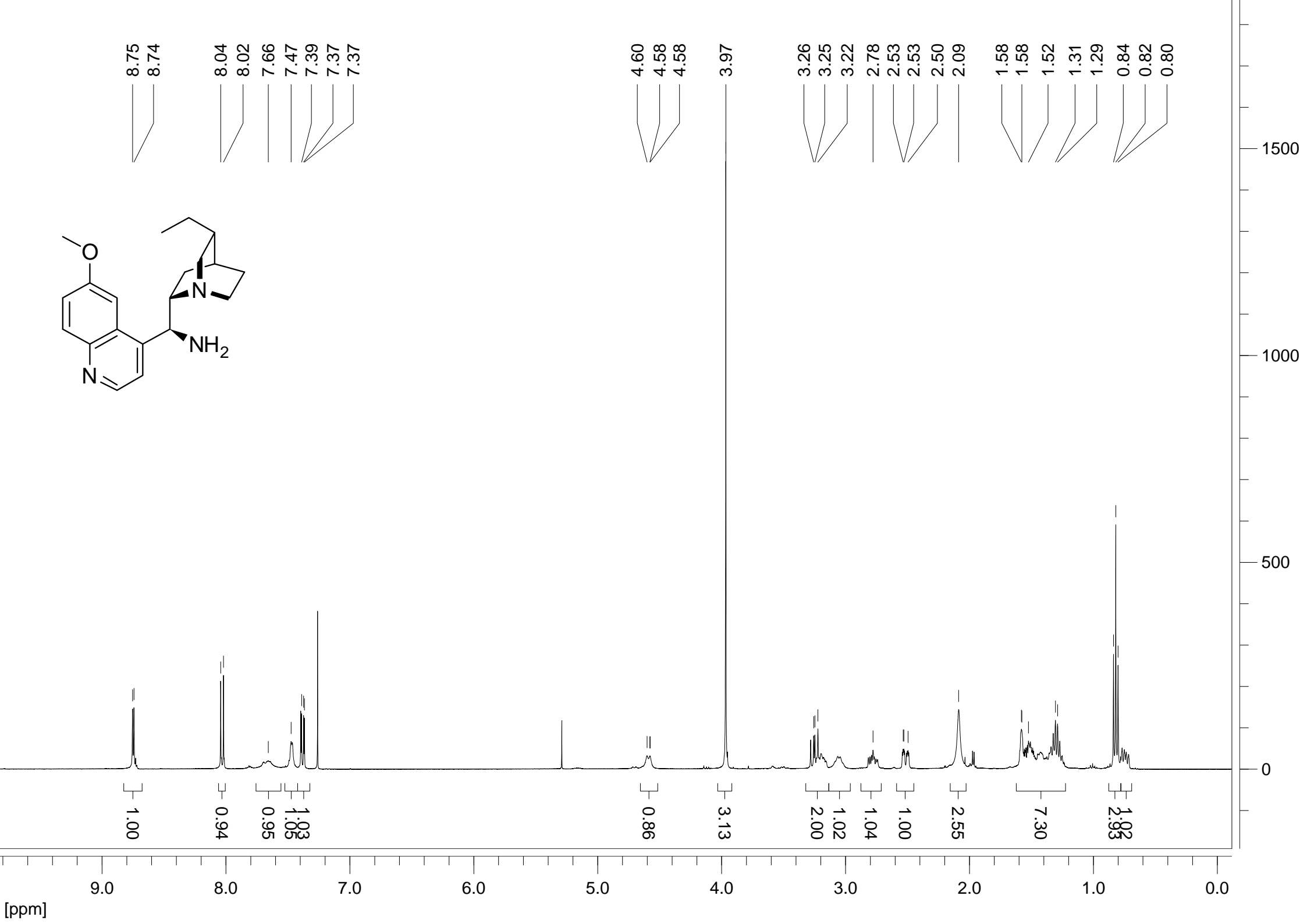
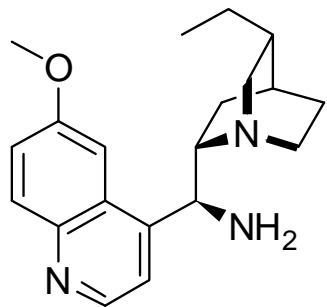
entry	catalyst	mol-%	solvent	Nu	equiv	conc. [M]	e.r. <sup>b</sup>
1 <sup>c</sup>	<b>A</b> (EA- <b>1a</b> (95:5))	2	<b>iPrOH</b>	<sup>i</sup> PrOH	600	0.02	53:47
2 <sup>c</sup>	<b>A</b> (EA- <b>1a</b> (95:5))	2	<b>iPrOH</b>	MeOH	5	0.02	68:32 <sup>d</sup>
3 <sup>c</sup>	<b>A</b> (EA- <b>1a</b> (95:5))	2	MeOH	MeOH	<b>1200</b>	0.02	59:41
4 <sup>f</sup>	<b>A</b> (EA- <b>1a</b> (95:5))	2	<b>Et<sub>2</sub>O</b> / <sup>i</sup> PrOH 1:2	<b><sup>i</sup>PrOH</b>	400	0.02	n.r. <sup>g</sup>
5 <sup>f</sup>	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O/ <sup>i</sup> PrOH 2:1	<sup>i</sup> PrOH	200	0.02	n.r. <sup>g</sup>
6	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O/MeOH 1:2	<b>MeOH</b>	<b>800</b>	0.02	62:38
7	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O/MeOH 2:1	MeOH	<b>400</b>	0.02	70:30
8	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O	MeOH	<b>20</b>	0.02	88:12
9	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O	MeOH	<b>10</b>	0.02	90:10
<b>10</b>	<b>A</b> (EA- <b>1a</b> (95:5))	<b>2</b>	<b>Et<sub>2</sub>O</b>	<b>MeOH</b>	<b>5</b>	<b>0.02</b>	<b>93:7</b>
11	<b>B</b> (EA- <b>1b</b> (95:5))	2	Et <sub>2</sub> O	MeOH	5	0.02	89:11
12	<b>C</b> (EA- <b>1a</b> ( <b>99:1</b> ))	2	Et <sub>2</sub> O	MeOH	5	0.02	91:9
13 <sup>c</sup>	<b>D</b> (EA- <b>1a</b> ( <b>90:10</b> ))	2	Et <sub>2</sub> O	MeOH	5	0.02	94:6
14 <sup>c</sup>	<b>E</b> ( <b>monomer 1a</b> )	2	Et <sub>2</sub> O	MeOH	5	0.02	96:4
15	<b>A</b> (EA- <b>1a</b> (95:5))	<b>1</b>	Et <sub>2</sub> O	MeOH	5	0.02	88:12 <sup>h</sup>
16	<b>A</b> (EA- <b>1a</b> (95:5))	<b>5</b>	Et <sub>2</sub> O	MeOH	5	0.02	93:7
17	<b>A</b> (EA- <b>1a</b> (95:5))	<b>10</b>	Et <sub>2</sub> O	MeOH	5	0.02	94:6
18	<b>A</b> (EA- <b>1a</b> (95:5))	<b>20</b>	Et <sub>2</sub> O	MeOH	5	0.02	94:6
19	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O	MeOH	5	<b>0.01</b>	93:7 <sup>i</sup>
20	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O	MeOH	5	<b>0.05</b>	87:13
21	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O	MeOH	5	<b>0.1</b>	82:18
22	<b>A</b> (EA- <b>1a</b> (95:5))	2	Et <sub>2</sub> O	MeOH	5	<b>0.2</b>	75:25

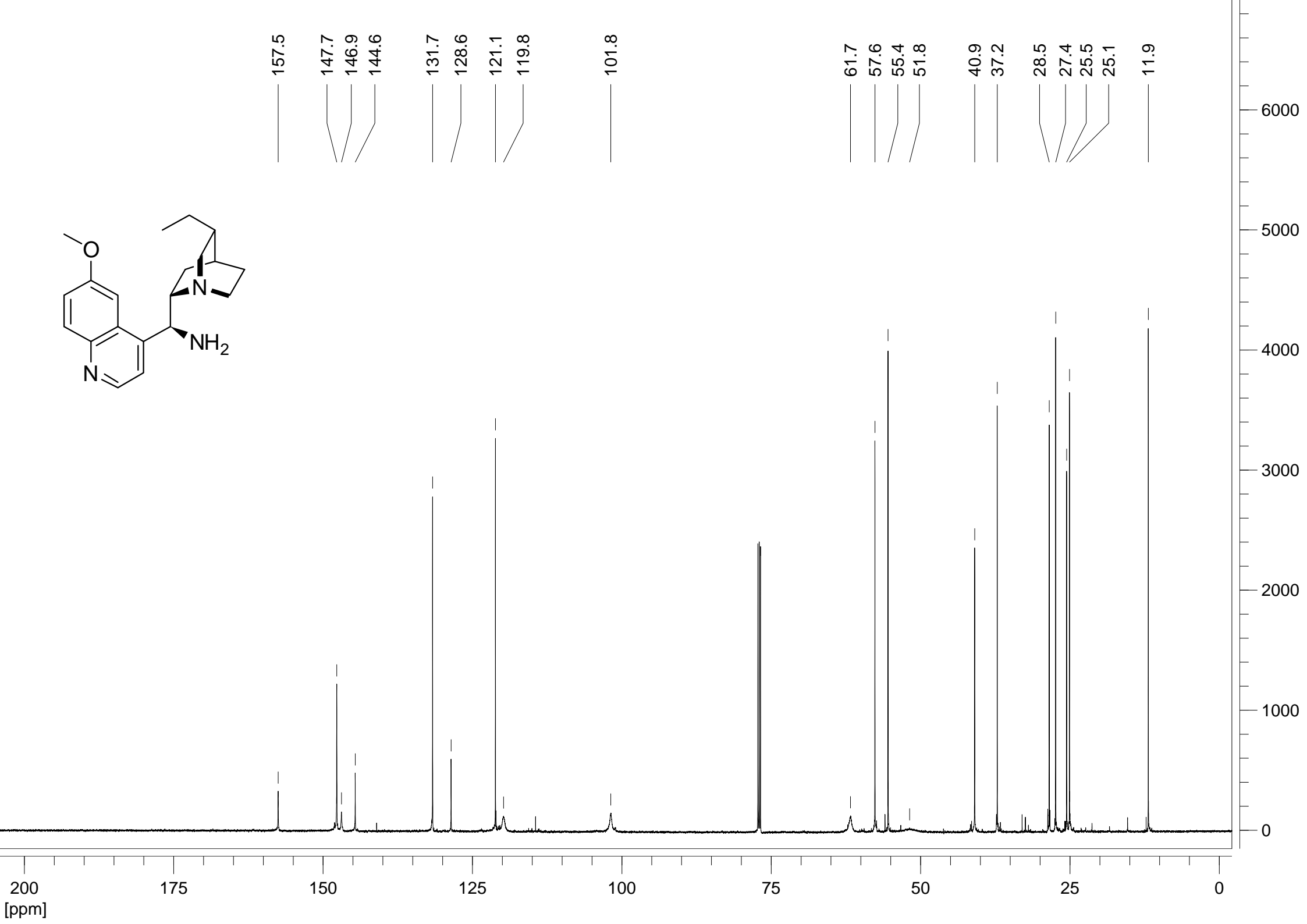
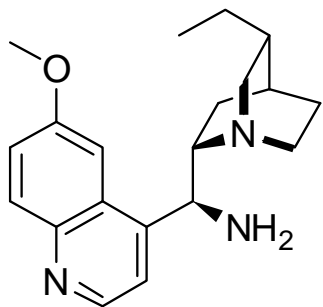
a) Reaction conditions: reaction conditions: 0.2 mmol substrate **2**, catalyst **A-E**, solvent, RT, 24 h;

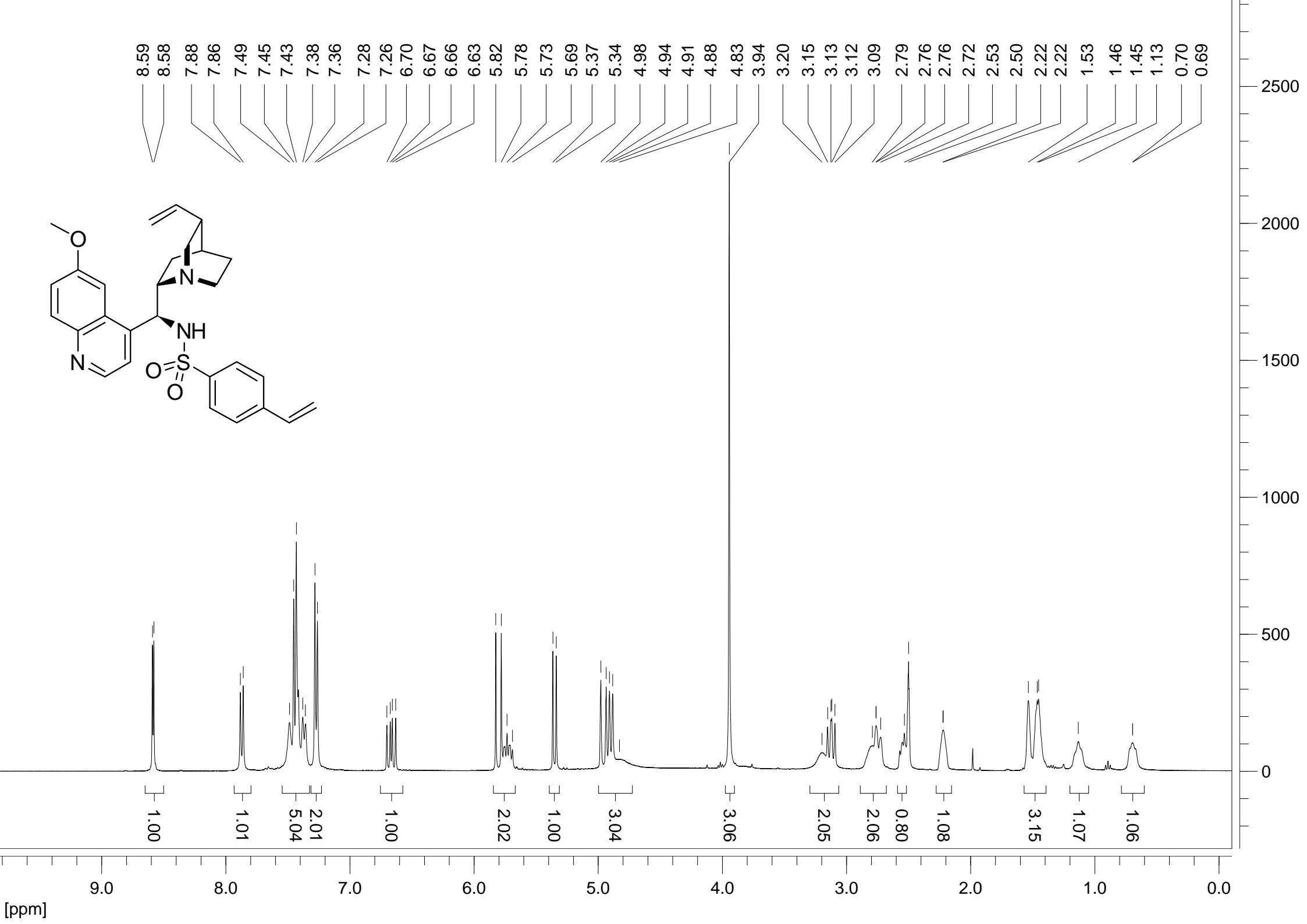
b) determined after derivatization of the free carboxylic acid into the corresponding (*R*)-1-(naphthalen-1-yl)ethyl amide (see supporting information) by SFC using Chiralcel OJ-H column; c) reaction performed at 40 °C; d) 44% isopropyl hemiester byproduct (48:52 e.r.); e) catalyst not temperature-responsive in this solvent mixture, therefore no recycling possible; f) reaction performed at 30 °C; g) no reaction; h) incomplete conversion after 24 h; i) incomplete conversion after 120 h.



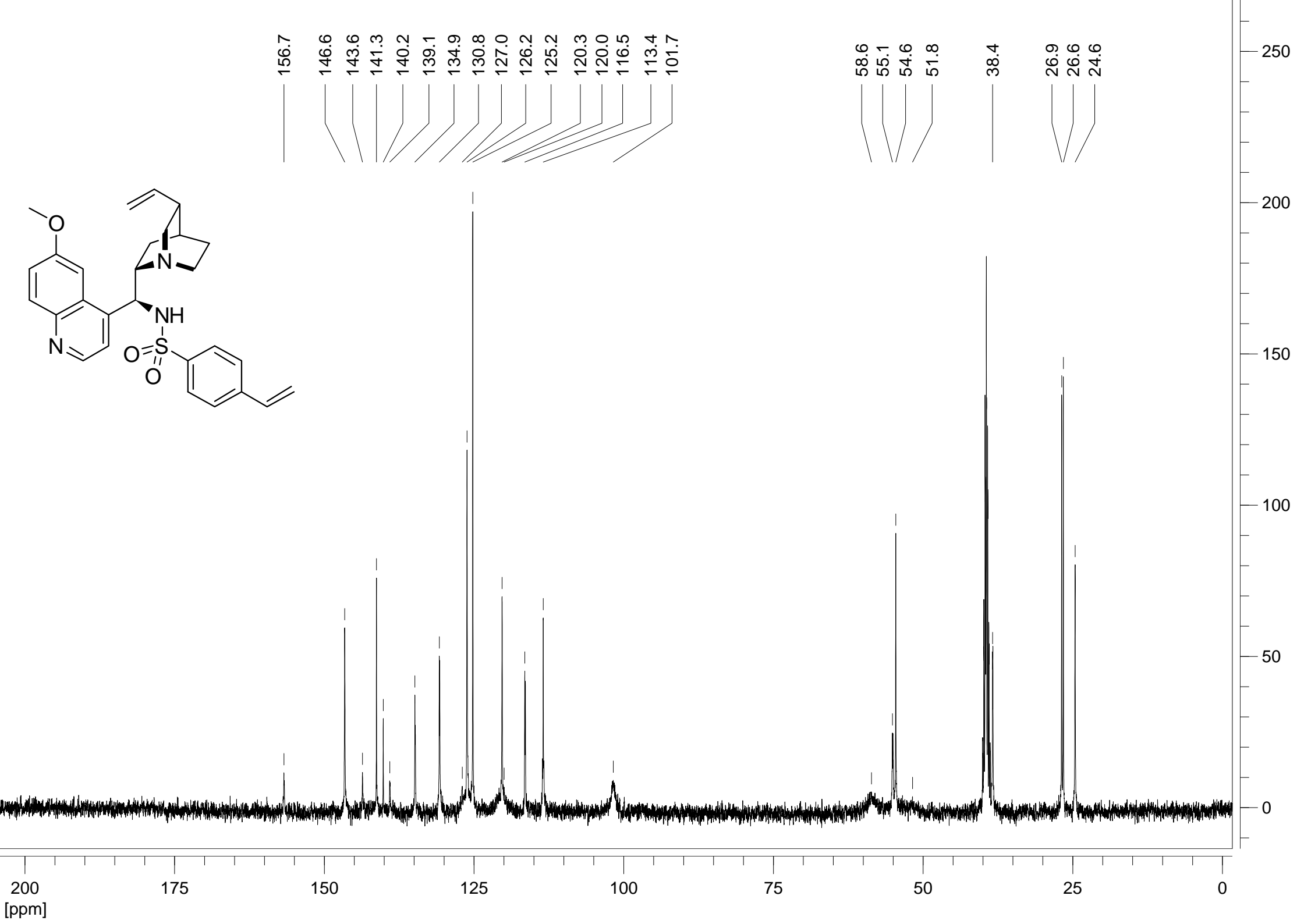


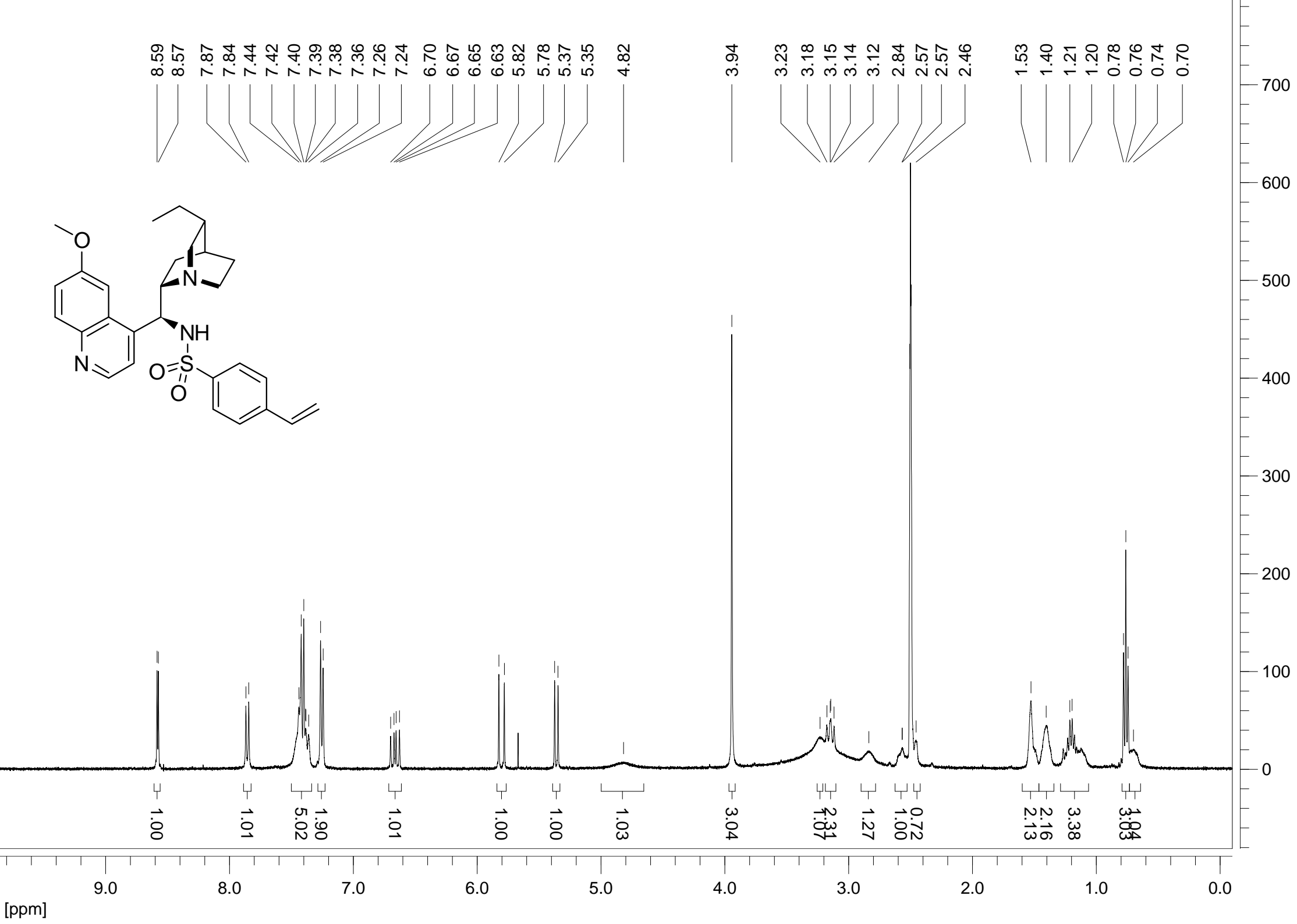


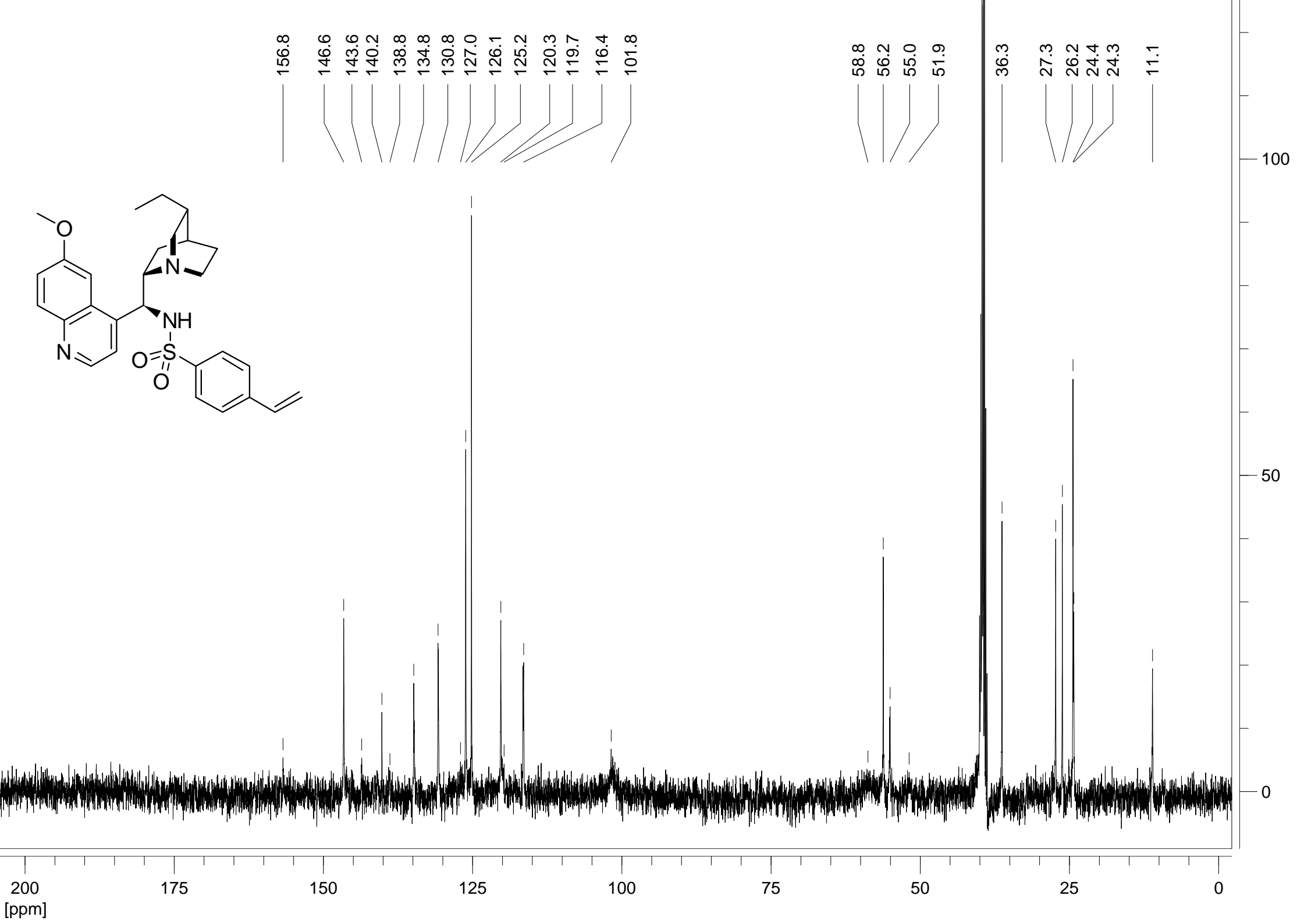
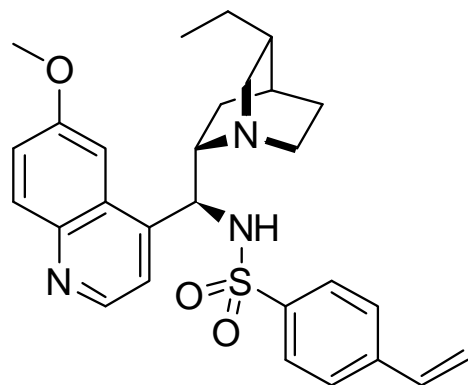


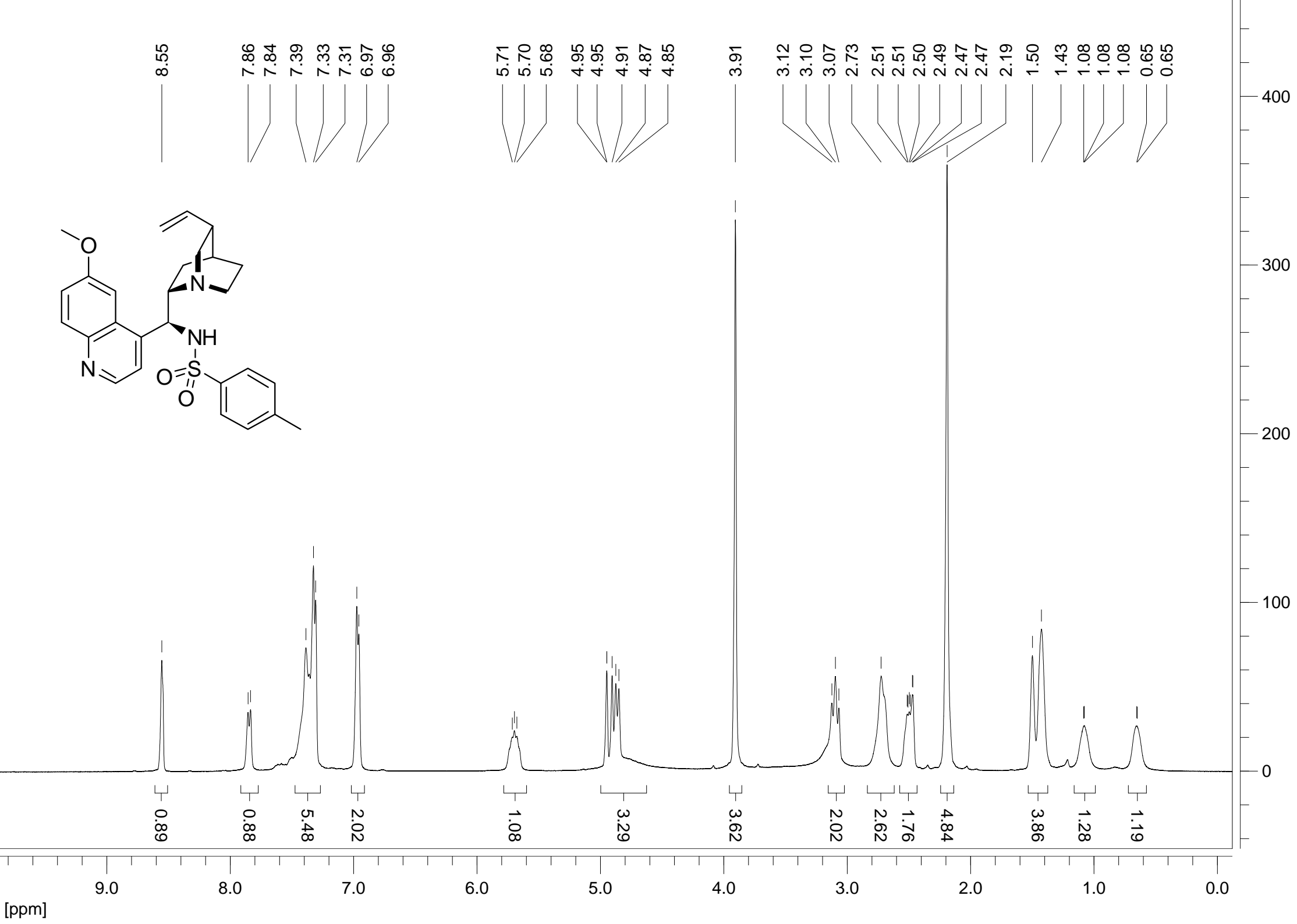


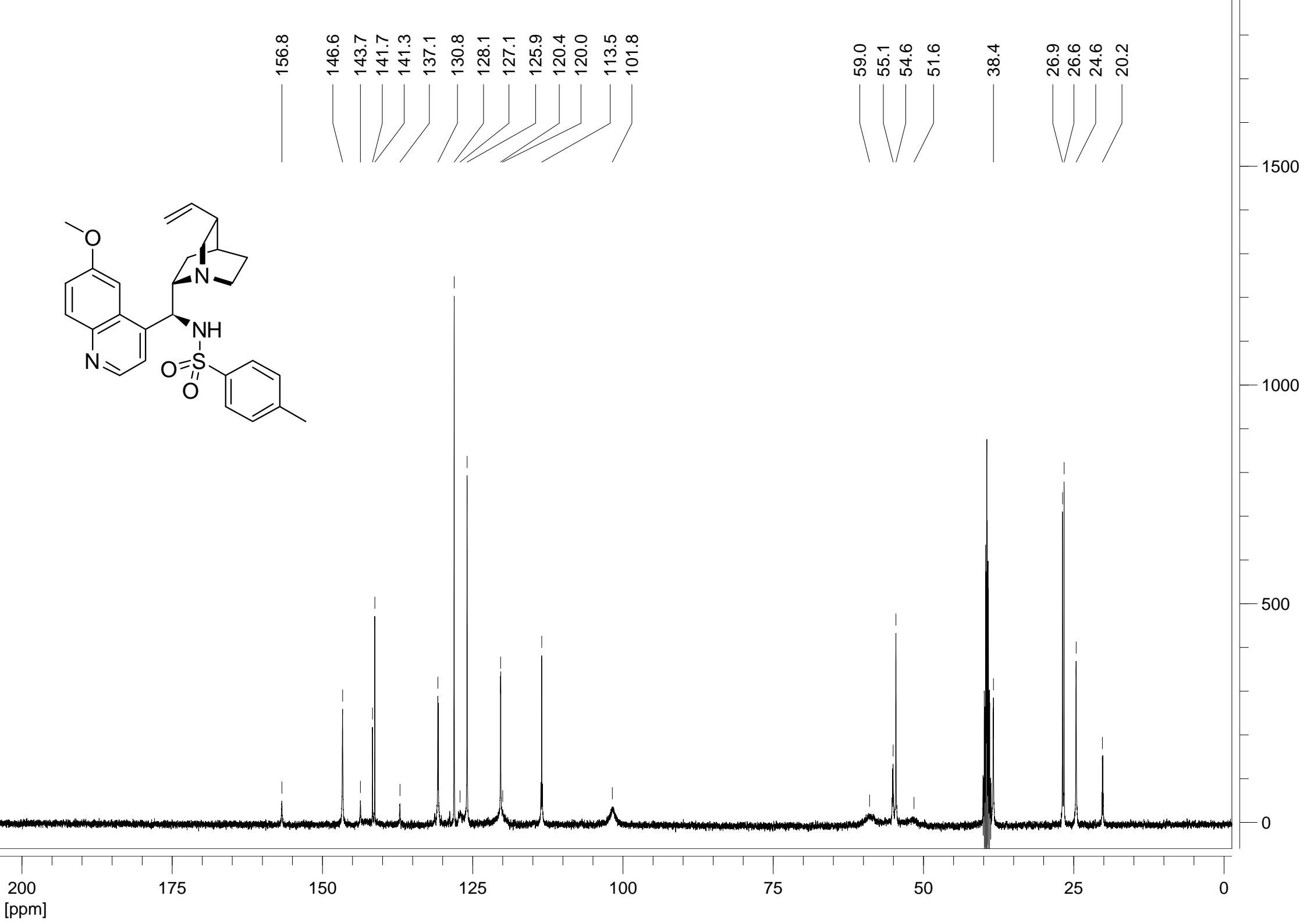


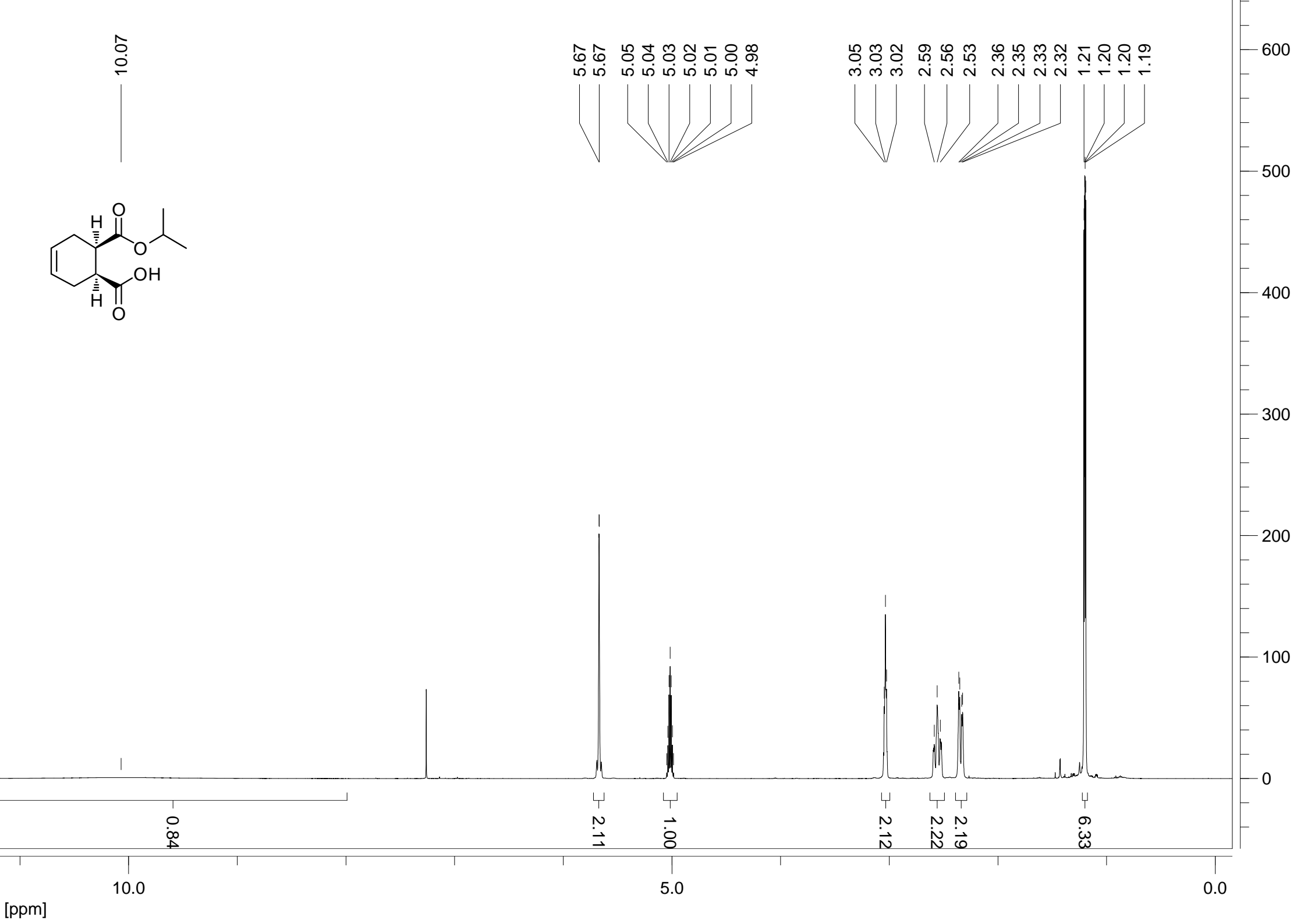
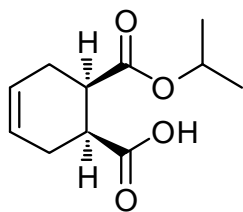


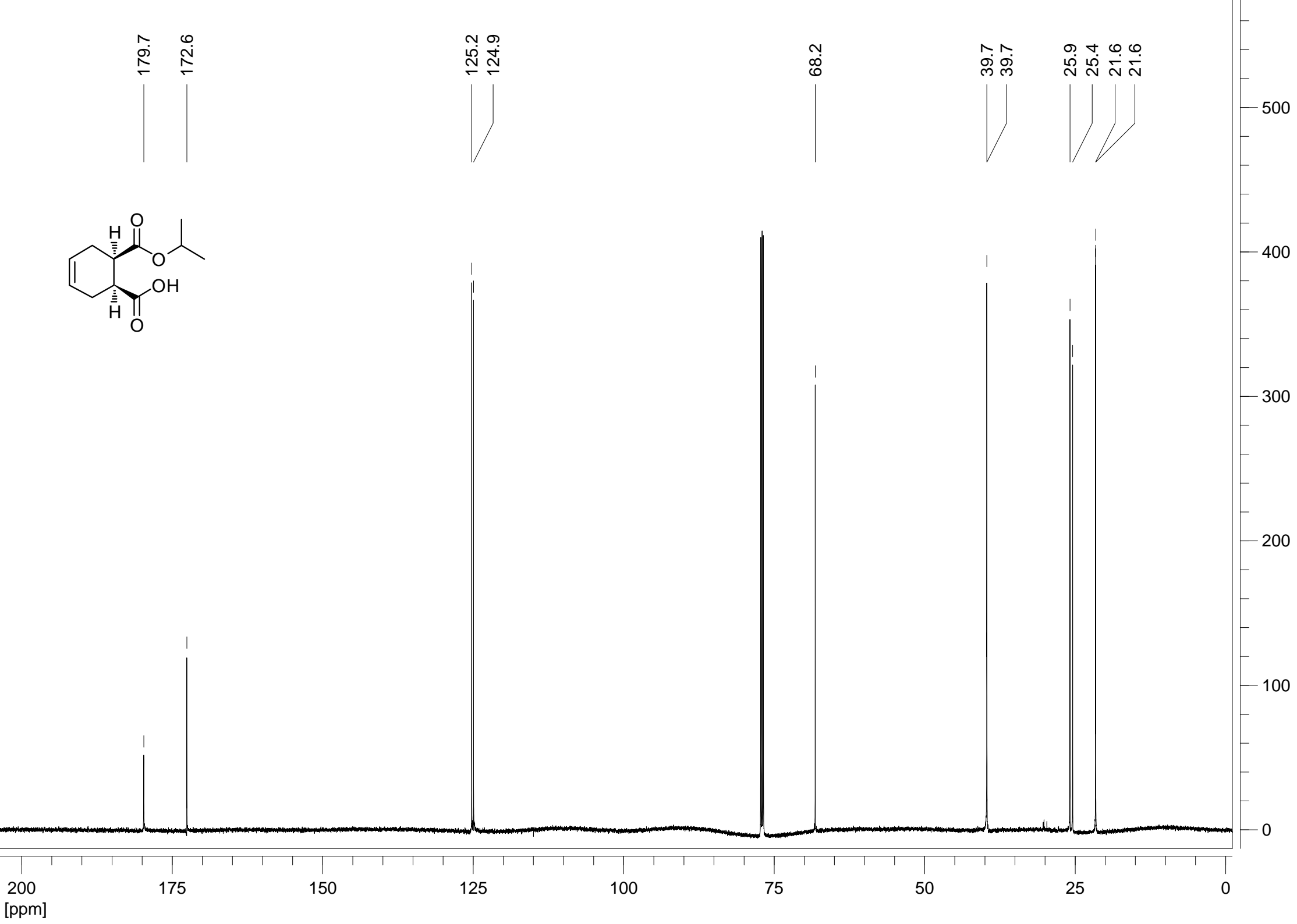
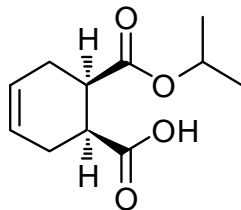


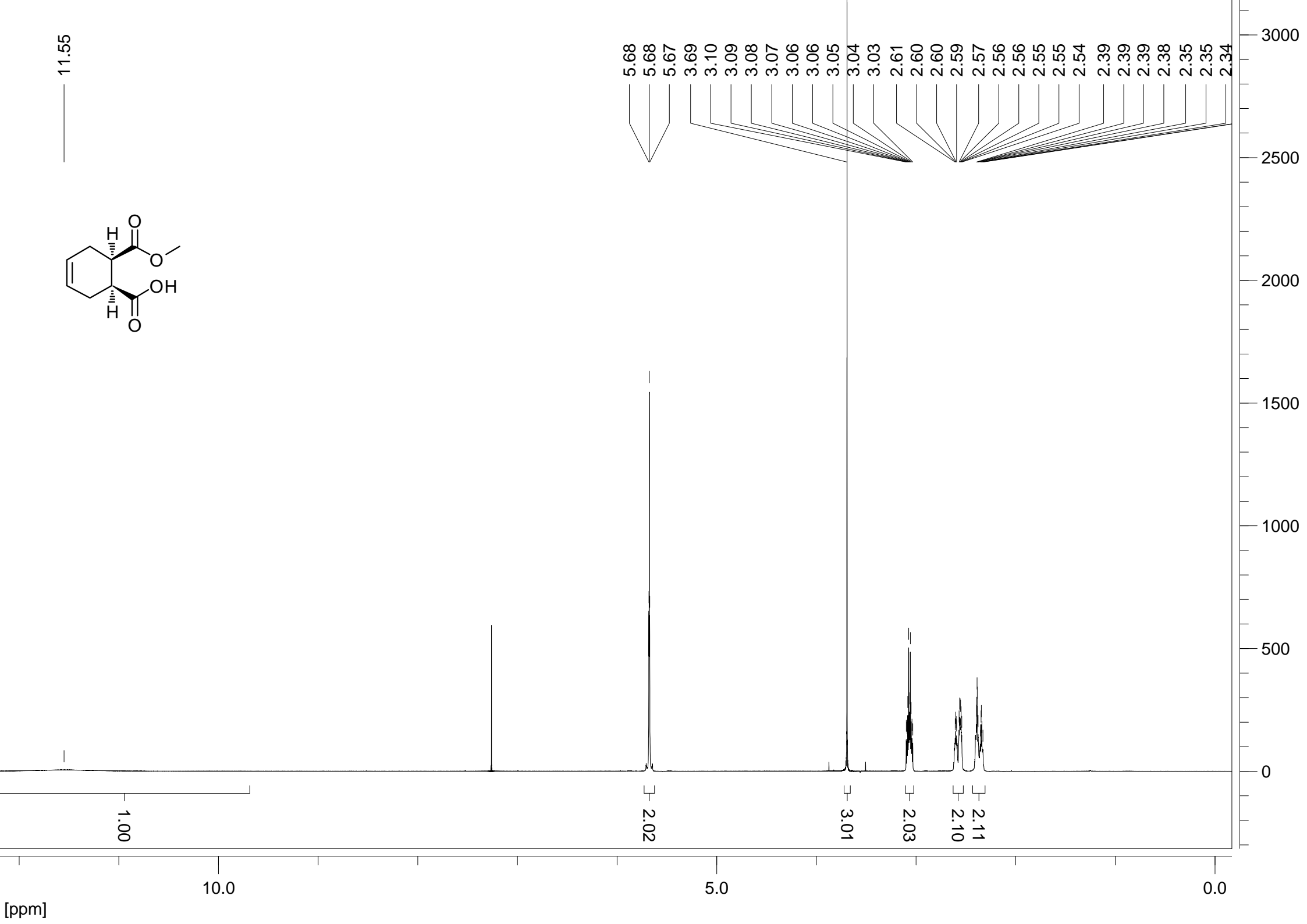
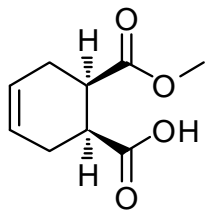




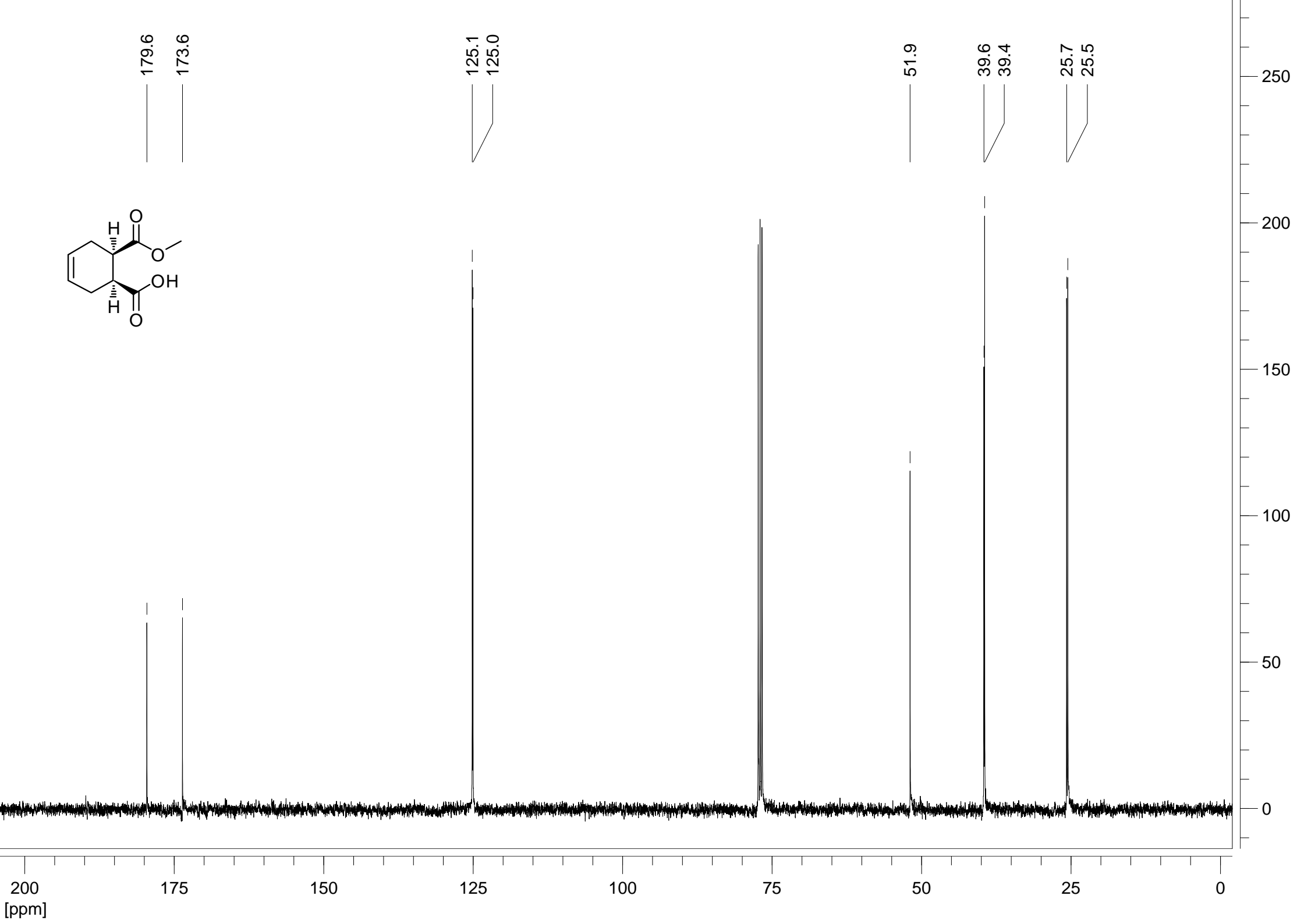
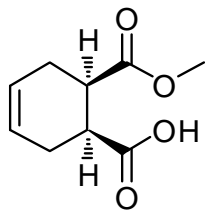


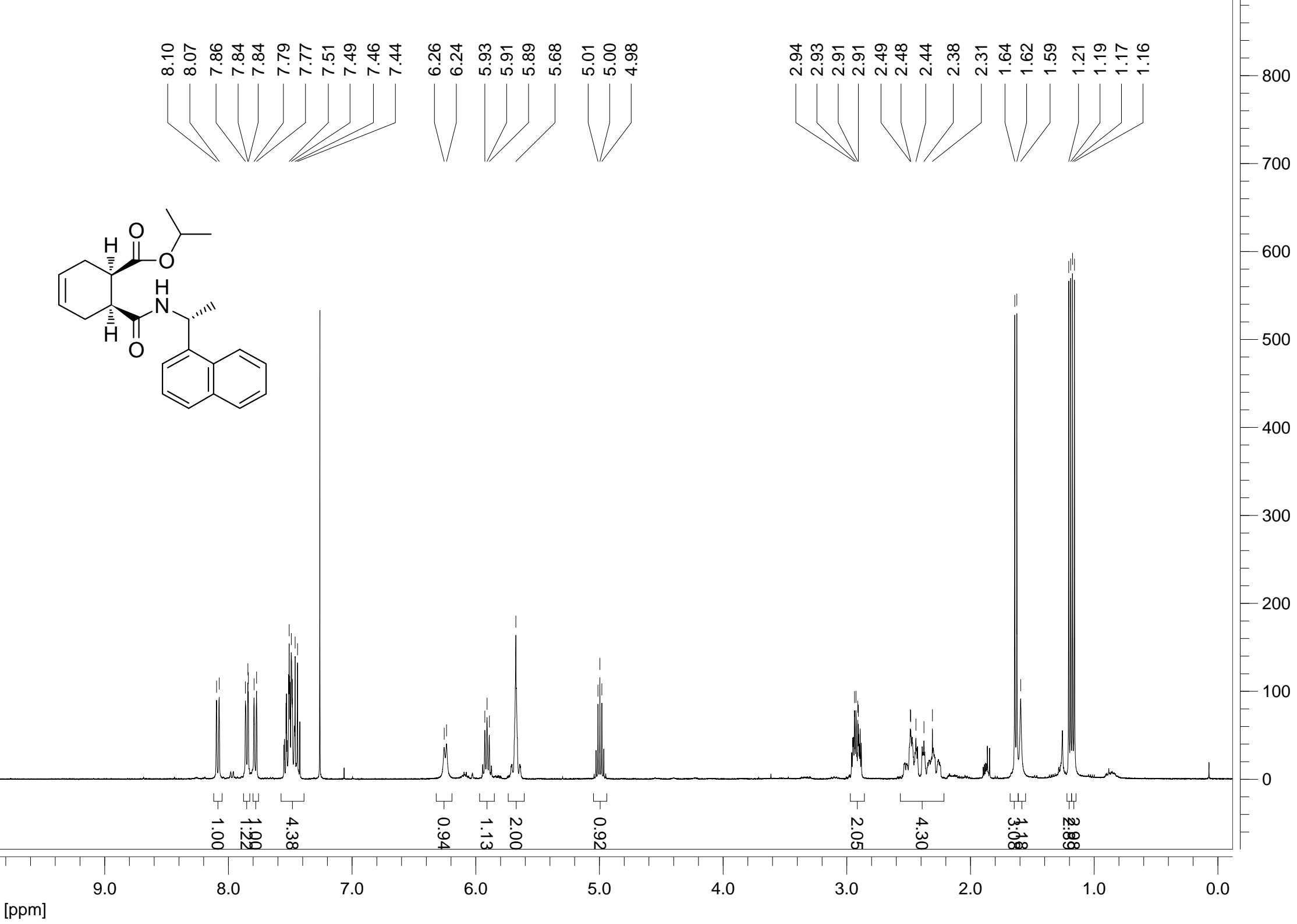


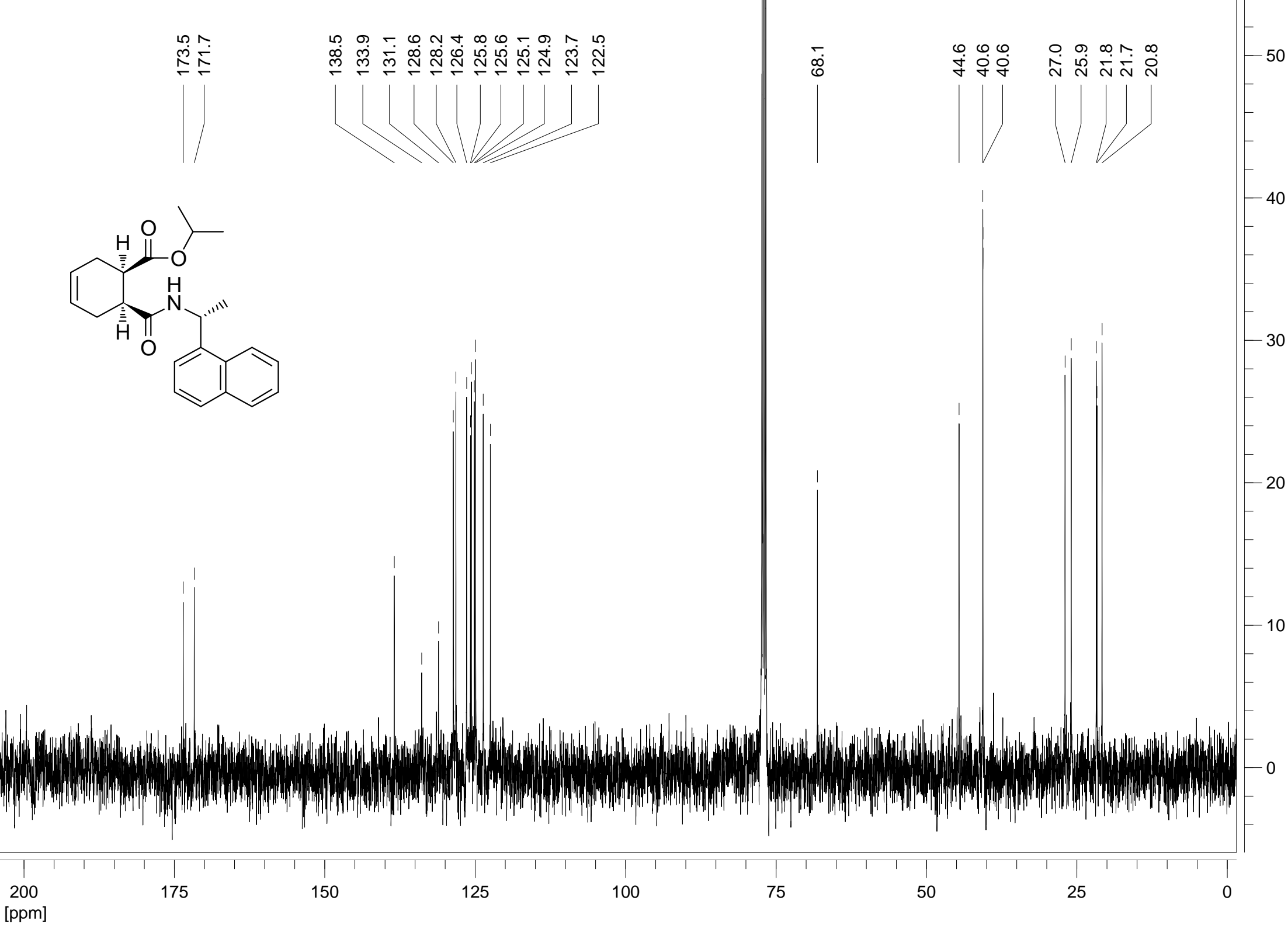


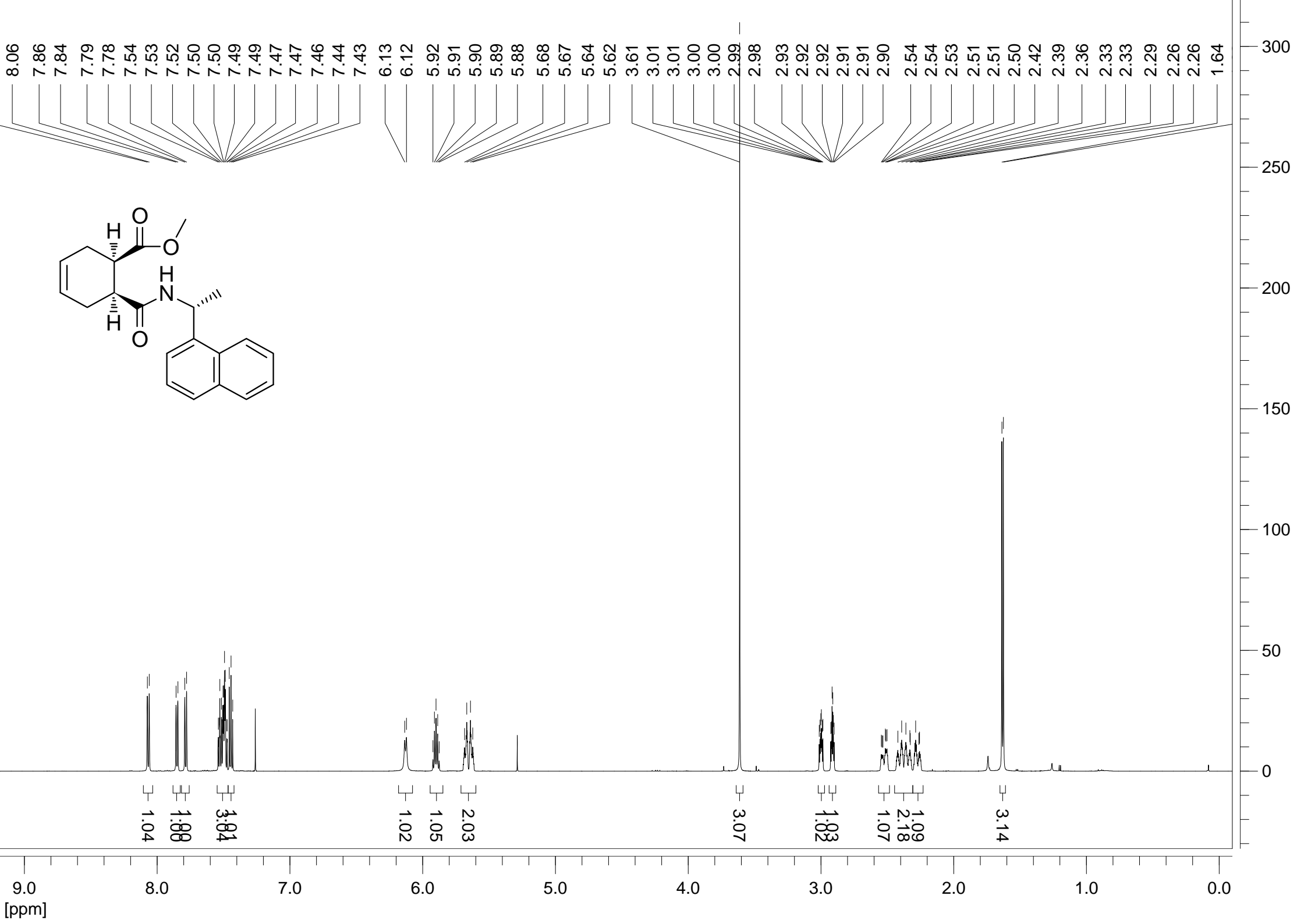


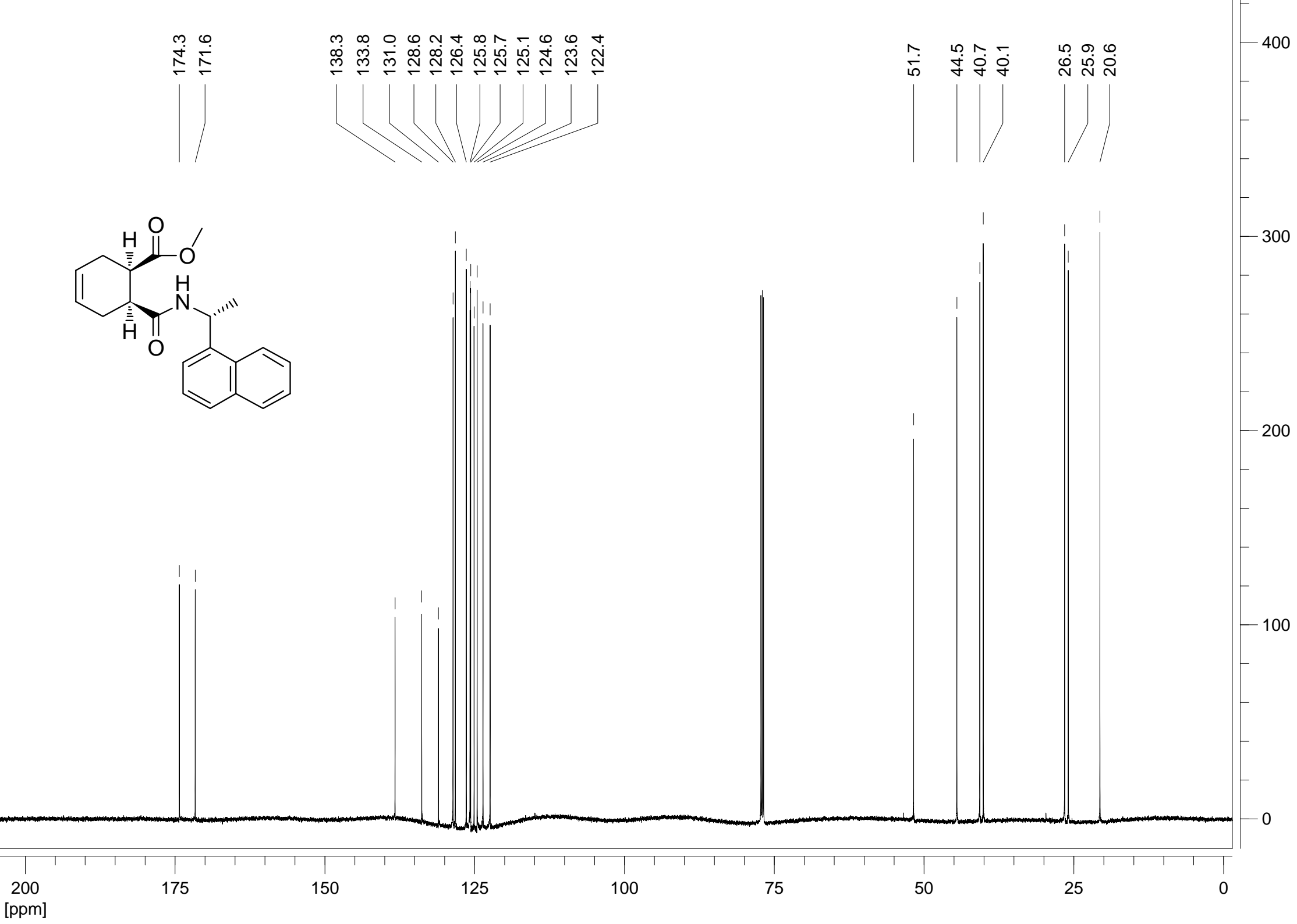
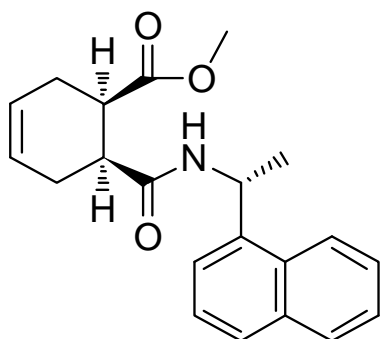










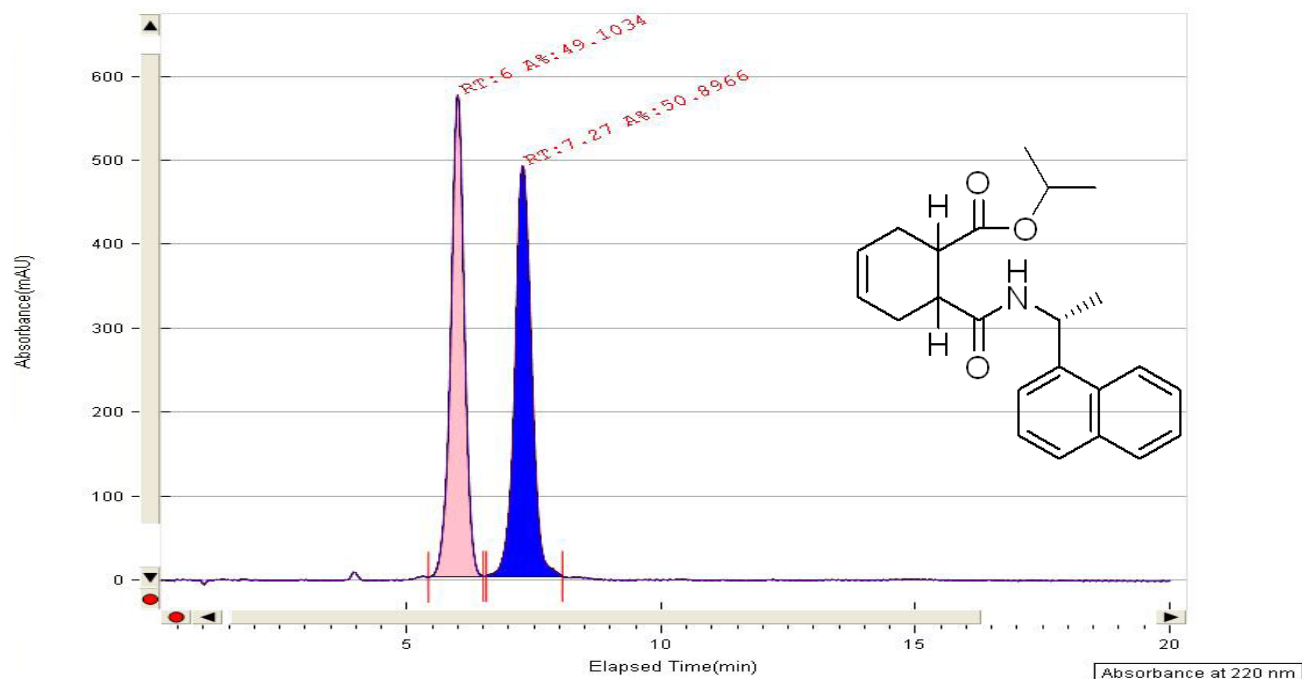


# Injection Info

Sample RB\_E507\_THP-OiPr\_NpA\_rac  
Column OJ-H  
Co-Solvent Methanol  
Co-Solvent % 2  
Column Temperature 32.3  
Total Flow 4

## Single Absorbance

RT: Ret. Time A%: Area Perc



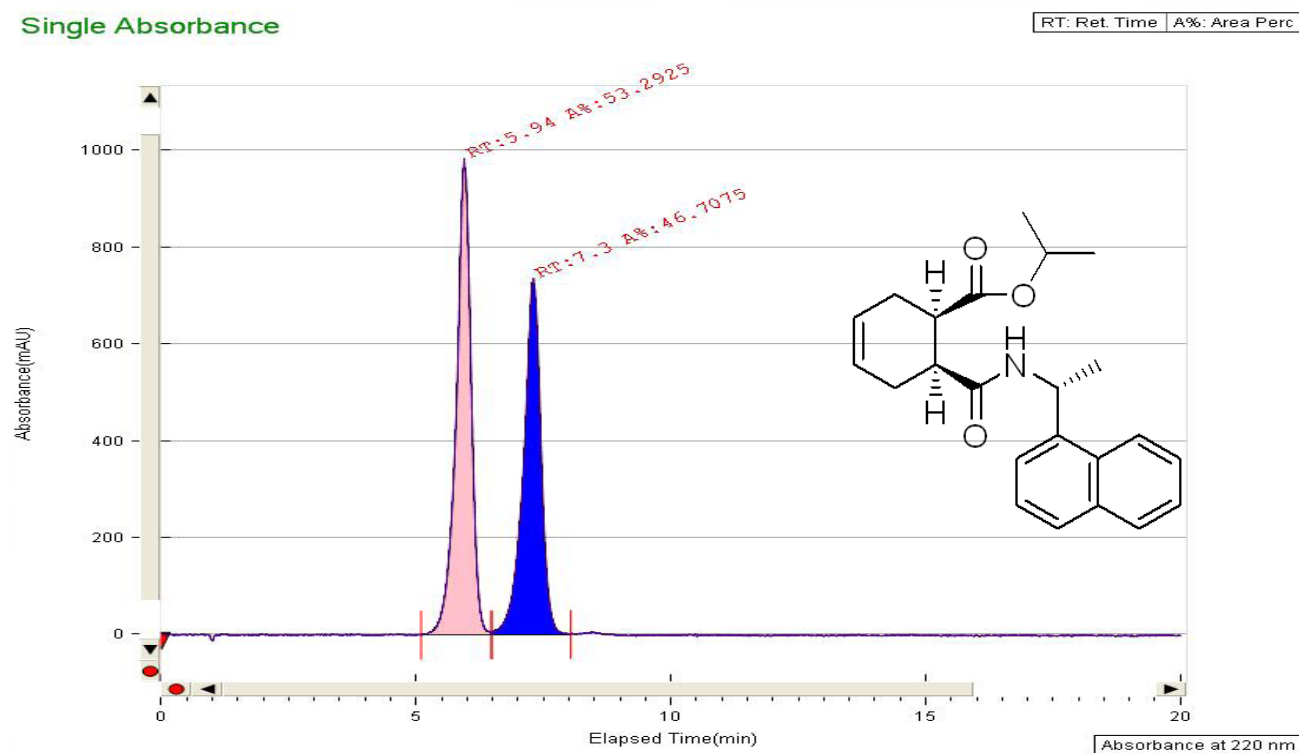
## Peak Info

Number	Area %	RT (min)	St. (min)	End (min)
1	49.1034	6	5.4229	6.4995
2	50.8966	7.27	6.5595	8.0577

# Injection Info

Sample RB\_E516\_K1\_S\_UK\_THP-OiPr-NpA\_chir  
Column OJ-H  
Co-Solvent Methanol  
Co-Solvent % 2  
Column Temperature 30.4  
Total Flow 4

## Single Absorbance



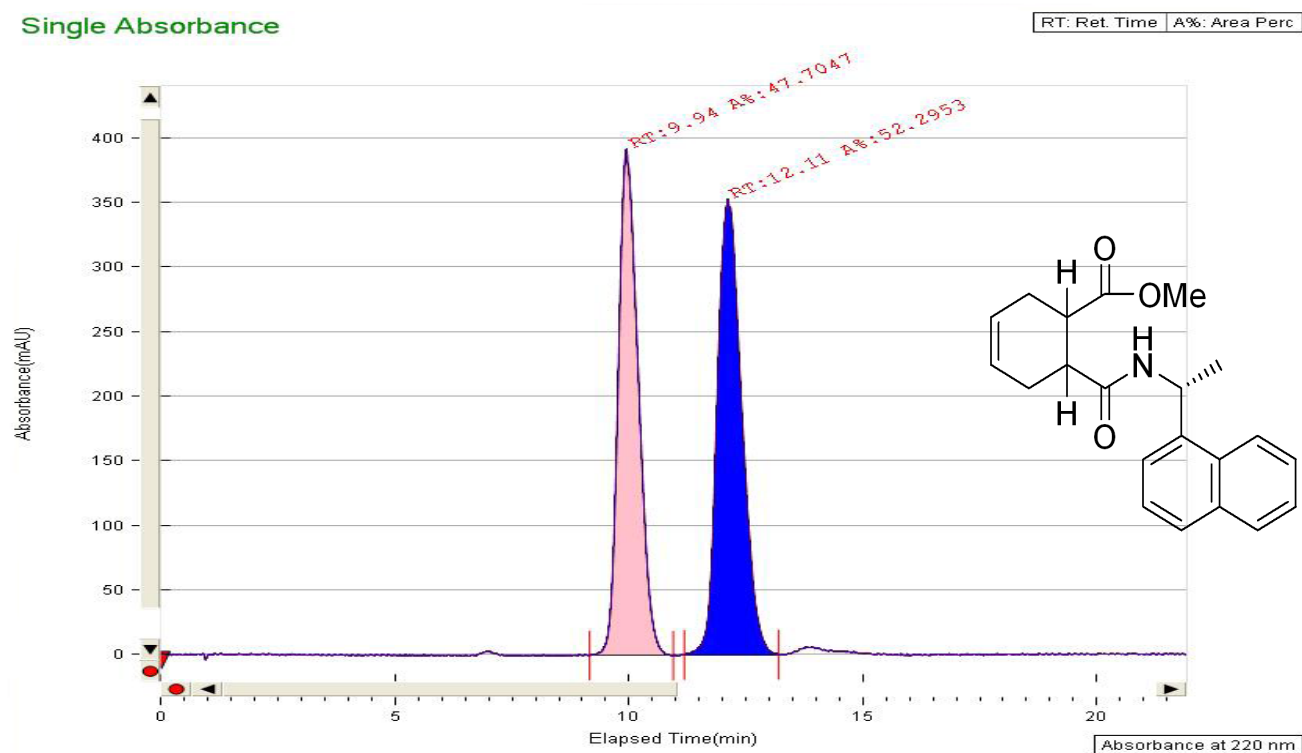
## Peak Info

Number	Area %	RT (min)	St. (min)	End (min)
1	53.2925	5.94	5.0954	6.4769
2	46.7075	7.3	6.4786	8.0319

# Injection Info

Sample RB\_1063\_THPA\_1-Np-Amin\_rac  
Column OJ-H  
Co-Solvent Methanol  
Co-Solvent % 2  
Column Temperature 39.3  
Total Flow 4

## Single Absorbance



## Peak Info

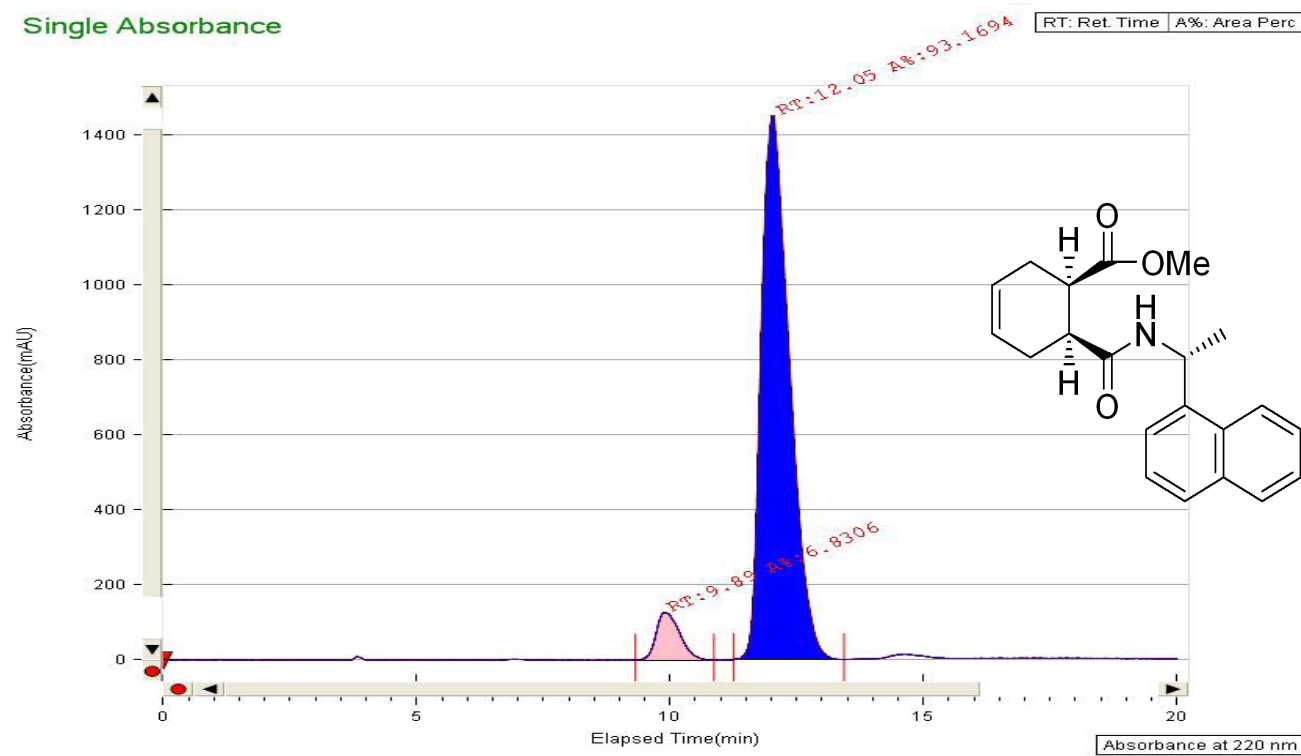
Number	Area %	RT (min)	St. (min)	End (min)
1	47.7047	9.94	9.1527	10.9414
2	52.2953	12.11	11.1798	13.1986



# Injection Info

**Sample** RB\_E447\_K11\_THP\_Np-A\_chir  
**Column** OJ-H  
**Co-Solvent** Methanol  
**Co-Solvent %** 2  
**Column Temperature** 38  
**Total Flow** 4

## Single Absorbance



## Peak Info

Number	Area %	RT (min)	St. (min)	End (min)
1	6.8306	9.89	9.3151	10.8638
2	93.1694	12.05	11.2605	13.431

Probenbezeichnung	% S							
RB_E459	6,54							
	6,54							
RB_E509	6,68							
	6,66							
VPR_020	0,26							
	0,25							
VPR_021	1,27							
	1,28							
VPR_022	3,49							
	3,47							
VPR_034	1,33							
	1,31							
VPR_043	0,02							
	0,02							