# *A Titanium(III)-Catalyzed Reductive Umpolung Reaction for the Synthesis of 1,1-Disubstituted Tetrahydroisoquinolines*

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# Supporting Information

## Table of Contents

Materials and Methods ..... S2
Extended Screening Table ..... S3
Preparation of $Cp_2Ti(OPh)_2$ ..... S4
Preparation and Analytical Data of Dihydroisoquinolines **1** and Nitriles **2k**,**l** ..... S5
Representative Procedure for the Titanium(III)-Catalyzed Reductive Coupling of **1a** with **2a** ..... S10
Analytical Data for Products **3** ..... S10
Total Synthesis of 10, Preparation and Analytical Data of Compounds **5**–**10** ..... S18
Sequence from **7** to **9** on a 50.0 mmol-scale ..... S20
Synthesis of (±)-3-Demethoxyerythratidinone in a 5 mmol Scale Reaction ..... S22
References ..... S23
$^1$H NMR and $^{13}$C NMR Spectra of New Compounds and the Total Synthesis of **10** ..... S24

# Materials and Methods

All reactions have been carried out in flame-dried Schlenk–tubes under argon atmosphere (argon 5.0) using dry solvents unless noticed otherwise. Absolute THF was dried over potassium under argon atmosphere and freshly distilled prior to use. Ethyl acetate and cyclohexane for column chromatography was purchased in technical quality and purified by destillation with a rotary evaporator. Hexanes was purchased from VWR. Dichloromethane and diethyl ether were purchased in p.a. quality from Aldrich. Zinc powder was purchased from Merck and used without further activation. Manganese powder (325 mesh) was purchased from Alfa Aesar and used as received. Chlorotrimethylsilane was purchased from Acros and used as received. Titanocene dichloride was purchased from Alfa Aesar and used as received. Triethylamine hydrochloride was purchased from Aldrich and purified by crystallization from chloroform. All other chemicals were purchased from Aldrich and used without further purification. An IKAmag temperature modulator in combination with an oil bath or stainless steel heating block was used to control the reaction temperatures. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or $KMnO_4$-staining. In general, Macherey-Nagel Silica gel 60 (particle size 0.04–0.063 mm) was used for flash chromatography. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX 500 (500 MHz and 125 MHz), a Bruker Avance II 400 (400 MHz and 100 MHz), a Bruker Avance III 300 (300 MHz), or a Varian Mercury 300 HFCP (300 MHz, $^1H$ only) spectrometer and reported to $CDCl_3$ ($\delta$ = 7.26 ppm and $\delta$ = 77.16 ppm, respectively). The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, br = broad signal. IR spectra were recorded on a Thermo Scientific Nicolet iS10 FT-IR spectrometer equipped with a diamond ATR unit and are reported in frequency of absorption. The melting point of crystalline solids was determined in a Büchi Typ B 525 melting point apparatus using open glass capillaries. Low and high resolution mass analyses were performed by the service department at the Institute for Organic Chemistry and Biochemistry, Freiburg University using a Thermo Finnigan TSQ 700 for electron impact ionization (EI) at 70 eV, 200 ºC. High resolution mass analyses (HRMS) were carried out on a Thermo Exactive with Orbitrap-Analyzer using atmospheric pressure chemical ionization (APCI or ESI).

Nitriles **2a**–**j** were commercially available and used as received.

Titanocene dichloride, $Cp_2TiCl_2$, **4a** was purchased from Alfa Aesar and used as received.

Bis(ethylcyclopentadienyl)titanium(IV) dichloride, $(EtCp)_2TiCl_2$, **4b** was purchased from Alfa Aesar and used as received.

(*rac*)-Bis(tetrahydroindeyl)titanium(IV) dichloride, (*rac*)-(ebthi)$TiCl_2$, **4c** was purchased from mcat, Konstanz, Germany (www.mcat.de).

Titanocene diiodide, $Cp_2TiI_2$, **4d** was prepared from $Cp_2TiCl_2$ following a literature procedure.[1]

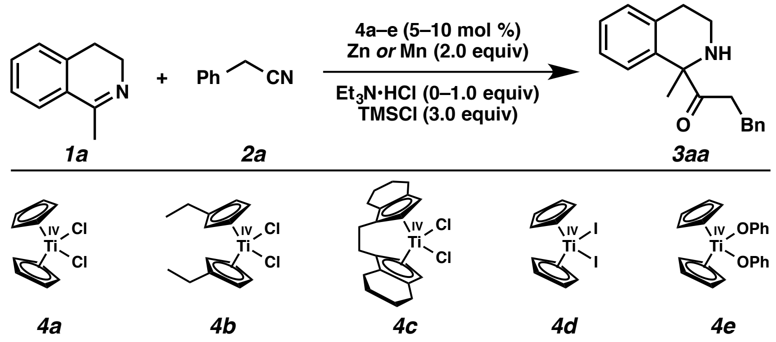
Titanocene diphenoxide, $Cp_2Ti(OPh)_2$, **4e** was prepared from $Cp_2TiCl_2$ as described below.

Bis(acetonitrile)dichloropalladium(II), $Pd(MeCN)_2Cl_2$, was prepared from $PdCl_2$ as described: $PdCl_2$ (2.0 g, 11.3 mmol) was suspended in dry MeCN (450 mL). The reaction mixture was heated to reflux for 3 hours under argon atmosphere. After cooling down to room temperature (23°C) the solvent was removed under reduced pressure. The remaining solid was dried under high vacuum and the title compound was received in quantitative yield (2.9 g) as an orange-yellow solid. The dried product can be used without further purification and was stored under argon in the dark.

## Extended Screening Table

After we found that manganese provided results that were superior to zinc as a reducing agent, we repeated the screening of conditions and the hydrochloride additive (Table S1). The reaction took place in good yields even without added $Et_3N$•HCl, however, it was found that the outcome was slightly improved in presence of added hydrochloride. Here, 0.5 equivalents were sufficient and higher amounts led again to decreased yields. It is known that added hydrochloride stabilizes the titanium(III)-catalyst in solution and prevents premature catalyst decomposition.[2] We attributed the observed beneficial influence of the hydrochloride to this effect.

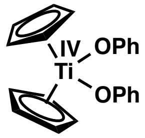
***Table S1.*** Optimization of Reaction Conditions.



| entry | catalyst (mol %) | reductant | equiv 2a | equiv $Et_3N$•HCl | solvent | *c* (M) | *T* (ºC) | yield (%)[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | 4a | Zn | 5 | 0.5 | THF | 1.00 | 35 | 72 |
| 2 | 4b | Zn | 5 | 0.5 | THF | 1.00 | 35 | 57 |
| 3 | (±)–4c | Zn | 5 | 0.5 | THF | 1.00 | 35 | 76 |
| 4 | 4d | Zn | 5 | 0.5 | THF | 1.00 | 35 | 48 |
| 5 | 4e | Zn | 5 | 0.5 | THF | 1.00 | 35 | 78 (72) |
| 6 | 4e | Zn | 5 | 0.0 | THF | 1.00 | 35 | 84 (74) |
| 7 | 4e | Zn | 5 | 0.0 | THF | 2.00 | 35 | 50 |
| 8 | 4e | Zn | 5 | 0.0 | THF | 1.50 | 35 | 56 |
| 9 | 4e | Zn | 5 | 0.0 | THF | 0.75 | 35 | 58 |
| 10 | 4e | Zn | 5 | 0.0 | THF | 0.50 | 35 | 64 |
| 11 | 4e | Zn | 5 | 0.0 | TBME | 1.00 | 35 | 78 (70) |
| 12 | 4e | Zn | 5 | 0.0 | Benzene | 1.00 | 35 | 51 |
| 13 | 4e | Zn | 5 | 0.0 | DCM | 1.00 | 35 | 30 |
| 14 | 4e | Mn | 5 | 0.0 | THF | 1.00 | 35 | 68 (68) |
| 15 | 4e | Mn (4 eq) | 5 | 0.0 | THF | 1.00 | 35 | 65 |
| 16 | 4e | Mn | 5 | 2.0 | THF | 1.00 | 35 | 57 |
| 17 | 4e | Mn | 5 | 1.5 | THF | 1.00 | 35 | 73 |
| 18 | 4e | Mn | 5 | 1.0 | THF | 1.00 | 35 | 81 (73) |
| 19 | 4e | Mn | 5 | 0.5 | THF | 1.00 | 35 | 86 (80) |
| 20 | 4e | Mn | 5 | 0.2 | THF | 1.00 | 35 | 70 |
| 21[b] | 4e | Mn | 5 | 0.0 | THF | 1.00 | 35 | 74 (76) |
| 22 | 4a | Mn | 5 | 0.5 | THF | 1.00 | 35 | 78 (73) |
| 23 | 4e | Mg | 5 | 0.5 | THF | 1.00 | 35 | 0 (0) |
| 24 | 4e | Mn | 5 | 0.0 | THF | 1.00 | 60 | 80 (82) |
| 25 | 4e | Mn | 5 | 0.5 | THF | 1.00 | 60 | 77 |
| 26 | 4e | Mn | 2.5 | 0.5 | THF | 1.00 | 60 | 88 |
| 27 | 4e | Mn | 2.5 | 0.0 | THF | 1.00 | 60 | 82 (81) |
| 28 | 4e | Mn | 2.0 | 0.5 | THF | 1.00 | 60 | 85 |
| 29[c] | 4e | Mn | 2.5 | 0.5 | THF | 1.00 | 60 | 71 |
| 30[d] | 4e | Mn | 2.5 | 0.5 | THF | 1.00 | 60 | 78 |
| 31 | none | Mn | 2.5 | 0.5 | THF | 1.00 | 60 | 0 (0) |
| **32** | **4e** | **Mn** | **2.5** | **0.5** | **THF** | **0.50** | **60** | **92 (92)** |
| 33[e] | 4e | Mn | 2.5 | 0.5 | THF | 1.00 | 60 | 71 |

[a] Determined by crude NMR with 1,3-benzodioxole as internal standard. Yield of isolated compound is given in brackets. [b] 48 h. [c] 16 h. [d] 5 mol % catalyst. [e] 1.5 equiv TMSCl.

# Preparation of $Cp_2Ti(OPh)_2$



***4e***

**Diphenoxybis(cyclopentadienyl)titanium(IV).**[3] Titanocene dichloride (1.0 g, 4.0 mmol) and phenol (0.75 g, 8.0 mmol, 2 eq) were dissolved in benzene (40 mL). Sodium hydride (290 mg, 12 mmol, 3 equiv), suspended in benzene (20 mL) was added and gas evolution was observed. The reaction mixture was heated to reflux for 3 hours, which resulted in a color change from red to orange. The mixture was allowed to cool to 23 ºC and filtered over celite (5 cm pad) and the filter cake was rinsed with additional benzene (50 mL). The combined organic mother liquors were concentrated and an orange solid (1.2 g) was received. The crude product was suspended in n-hexane (4 mL) and sonicated for 1 min in an ultrasonic bath. The solution was decanted off and the suspension/sonication/decanting procedure was repeated. The remaining solid was dried under high vacuum and the title compound was received in 69% yield (1.0 g) as a yellow solid. The nmr data matched the previously reported values (Figure S1).[3]

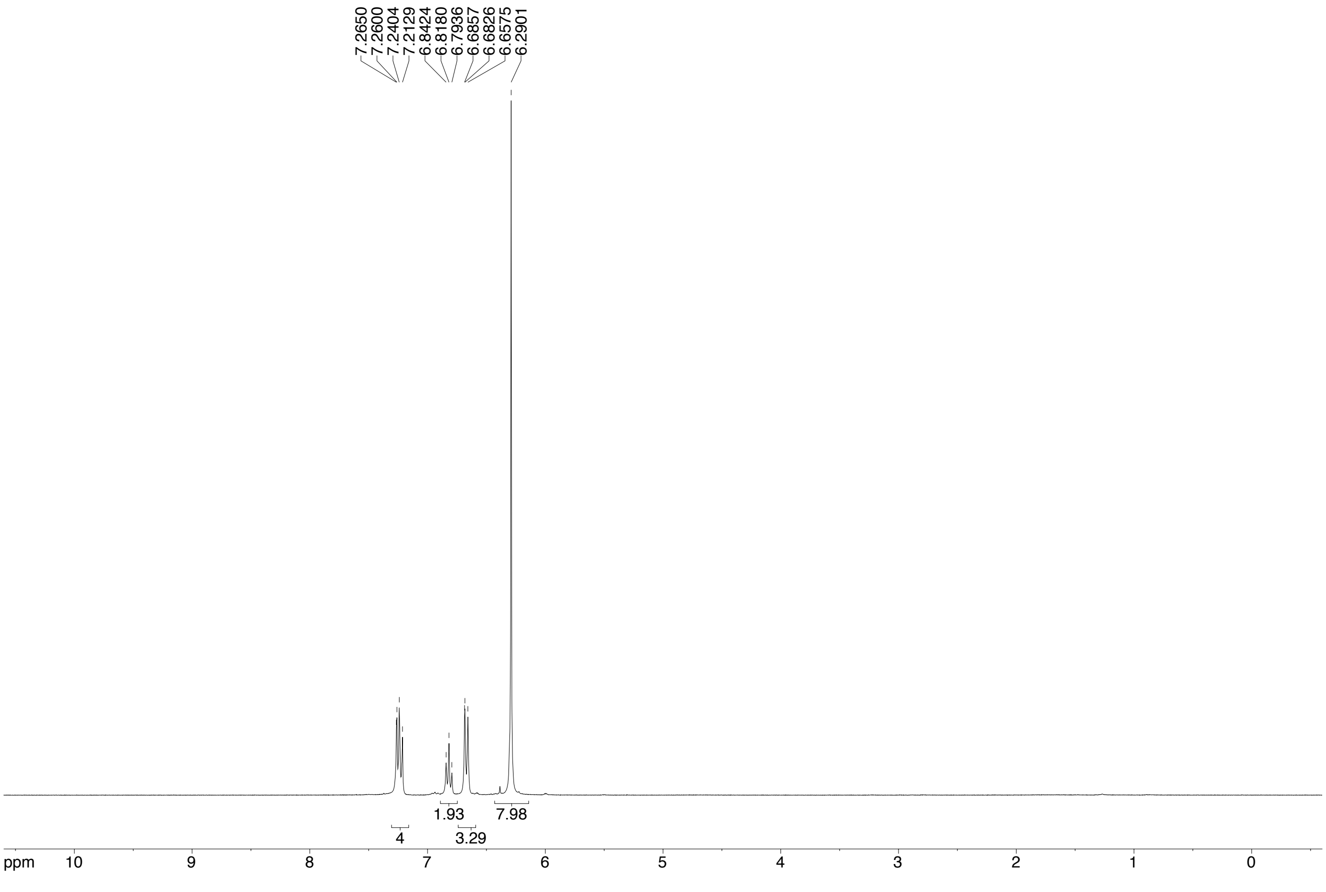
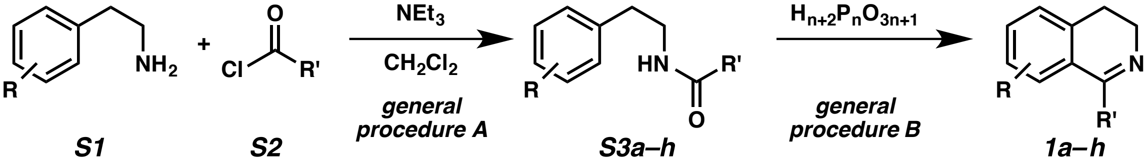


***Figure S1.*** $^1H$ NMR (300 MHz, $CDCl_3$) of $Cp_2Ti(OPh)_2$ (**4e**).

# Preparation and Analytical Data of Dihydroisoquinolines 1 and Nitriles 2k,l

3,4-Dihydroisoquinolines **1** were prepared from the corresponding phenylethylamines **S1** and acid chlorides **S2** in a standard two-step procedure (Scheme S1). Phenylethylamines **S1** were purchased from Aldrich. The acid chlorides were either commercially available or synthesized by treatment of the corresponding acid with thionyl chloride and cat. DMF.



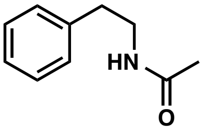
***Scheme S1.*** Standard route to dihydroisoquinolines **1**.

### General Procedure A: Synthesis of Amides S3.[4]

In a round-bottom flask equipped with a magnetic stir bar, the desired phenyl ethyl amine **S1** (10.0 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and $NEt_3$ (2.10 mL, 15.0 mmol, 1.5 equiv) was added while the solution and stirring was started. The corresponding acid chloride **S2** (10.0 mmol, 1.0 equiv) was added dropwise at 0 °C and after continued stirring at 0 °C for 30 min the mixture was allowed to warm to room temperature (23 °C). After additional stirring for 20–24 h, the mixture was concentrated and the residue was redissolved in EtOAc (40 mL). The solution was transferred into a separation funnel and washed with aq HCl (1 M, 40 mL) followed by brine (40 mL). The organic layer was separated, dried ($Na_2SO_4$) and concentrated to yield the pure amide **S3**, which was transferred to the cyclization.

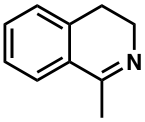
### General Procedure B: Bischler-Napieralski Cyclization with Polyphosphoric Acid.[5]

In a round-bottom flask equipped with a magnetic stir bar, amide **S3** (10.0 mmol) was treated with polyphosphoric acid (6.70 mL, 150 mmol, 15.0 equiv). The mixture was stirred and heated to 180–200 °C for 3–8 h (as indicated). After additional stirring for 15–24 h at room temperature (23 °C, as indicated), the mixture was poured into ice-cold water (100 mL) and neutralized with aq NaOH (20%, pH 7). The aqueous solution was extracted with $Et_2O$ (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to give the crude imine **1**, which was directly employed in the titanium-catalysis if not noted otherwise.



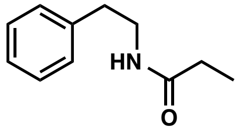
***S3a***

***N*-(2-Phenylethyl)acetamide.**[6] This compound was literature-known and synthesized following the general procedure A. The analytically pure product **S3a** was received after extraction as a colorless solid in quantitative yield (1.632 g, 10 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, $CDCl_3$): δ = 1.93 (s, 3H), 2.81 (t, *J* = 7.0 Hz, 2H), 3.51 (td, *J* = 6.9, 6.0 Hz, 2H), 5.58 (br s, NH), 7.17-7.33 (m, 5H).



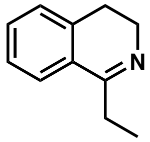
***1a***

**1-Methyl-3,4-dihydroisoquinoline.**[6] This compound was literature-known and synthesized from **S3a** following the general procedure B. The analytically pure product **1a** was received after extraction as a yellow-brown oil in 92% yield (1.33 g, 9.19 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, $CDCl_3$): δ = 2.37 (t, *J* = 1.2 Hz, 3H), 2.68 (dd, *J* = 7.4, 7.4 Hz, 2H), 3.64 (ddq, *J* = 7.4, 7.4, 1.2 Hz, 2H), 7.16 (ddd, *J* = 7.2, 1.6, 0.9 Hz, 1H), 7.27 (ddd, *J* = 7.4, 7.4, 1.9 Hz, 1H), 7.33 (ddd, *J* = 7.4, 7.3, 1.5 Hz, 1H), 7.46 (dd, *J* = 7.3, 1.7 Hz, 1H).



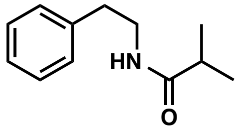
***S3b***

***N*-Phenylethylpropionamide.**[7] This compound was literature-known and synthesized following the general procedure A. The analytically pure product **S3b** was received after extraction as a pale-yellow solid in quantitative yield (1.772 g, 10 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, CDCl$_3$): δ = 1.11 (t, *J* = 7.6 Hz, 3H), 2.15 (q, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 6.9 Hz, 2H), 3.50 (td, *J* = 7.0, 6.0 Hz, 2H), 5.61 (br s, NH), 7.17-7.33 (m, 5H).



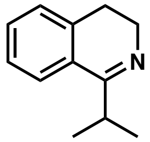
***1b***

**1-Ethyl-3,4-dihydroisoquinoline.**[8] This compound was literature-known but complete characterization was missing. Synthesized from **S3b** following the general procedure B on a 5 mmol scale. The analytically pure product **1b** was received after extraction as a pale yellow-brown oil in 87% yield (693 mg, 4.35 mmol). $^1$H-NMR (400.1 MHz, CDCl$_3$): δ = 1.21 (t, *J* = 7.4 Hz, 3H), 2.67 (dd, *J* = 7.4, 7.4 Hz, 2H), 2.74 (qt, *J* = 7.3, 1.3 Hz, 2H), 3.66 (tt, *J* = 7.4, 1.3 Hz, 2H), 7.17 (ddt, *J* = 7.3, 1.7, 0.9 Hz, 1H), 7.27 (tdt, *J* = 7.5, 1.7, 0.5 Hz, 1H), 7.32 (td, *J* = 7.4, 1.5 Hz, 1H), 7.41 (dd, *J* = 7.3, 1.6 Hz, 1H). $^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ = 11.34, 26.30, 28.88, 46.96, 124.98, 126.91, 127.62, 129.14, 130.38, 137.93, 168.09. MS (EI, 70 eV): m/z (%) = 159.1 [M]$^+$ (40), 158.1 [M-H]$^+$, 144.1 (7), 130.1 (13), 115.1 (10), 103.1 (4). HRMS (APCI, MeOH) calcd for $C_{11}H_{14}N^+$ [M+H]$^+$: 160.1126, found: 160.1122. IR (ATR): $\nu$ [cm$^{-1}$] = 3065, 3024, 2973, 2938, 2902, 2848, 1628, 1573, 1453, 1427, 1291, 1244, 1216, 1011, 924, 908, 749, 731, 662, 641.



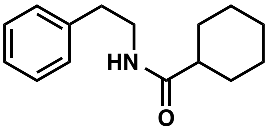
***S3c***

***N*-Phenylethylisobutyramide.**[9] This compound was literature-known and synthesized following the general procedure A. The analytically pure product **S3c** was received after extraction as a colorless solid in quantitative yield (1.912 g, 10 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, CDCl$_3$): δ = 1.11 (d, *J* = 6.9 Hz, 6H), 2.28 (sept, *J* = 6.9 Hz, 1H), 2.82 (t, *J* = 6.9 Hz, 2H), 3.51 (td, *J* = 6.8, 6.2 Hz, 2H), 5.43 (br s, NH), 7.17-7.33 (m, 5H).



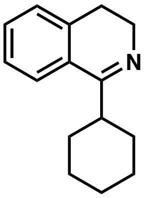
***1c***

**1-Isopropyl-3,4-dihydroisoquinoline.**[10] This compound was literature-known but not fully characterized. Synthesized from **S3c** following the general procedure B on a 5 mmol scale. The analytically pure product **1c** was received after extraction as a pale yellow-brown oil in 88% yield (763 mg, 4.41 mmol). $^1$H-NMR (400.1 MHz, CDCl$_3$): δ = 1.21 (d, *J* = 6.9 Hz, 6H), 2.65 (dd, *J* = 7.3, 7.3 Hz, 2H), 3.26 (sept, *J* = 6.8 Hz, 1H), 3.66 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.19 (dd, *J* = 6.6, 1.6 Hz, 1H), 7.31 (m$_c$, 2H), 7.51 (dd, *J* = 6.7, 1.8 Hz, 1H). $^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ = 20.91, 26.50, 31.83, 46.95, 124.79, 126.88, 127.69, 128.97, 130.17, 138.41, 171.40. MS (EI, 70 eV): m/z (%) = 173.1 [M]$^+$ (50), 172.1 (100), 158.1 (76), 145.1 (21), 130.1 (23), 115.1 (10), 103.1 (8). HRMS (APCI, MeOH) calcd for $C_{12}H_{16}N^+$ $[M+H]^+$: 174.12827, found: 174.12840. IR (ATR): $\nu$ [$cm^{-1}$] = 3019, 2968, 2941, 2850, 2360, 1624, 1572, 1453, 1246, 1215, 1017, 908, 748, 668.



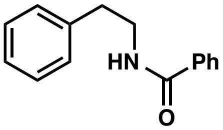
***S3d***

***N*-Phenylethylcyclohexancarboxamide.**[11] This compound was literature-known and synthesized following the general procedure A. The analytically pure product **S3d** was received after extraction as a colorless solid in quantitative yield (2.313 g, 10 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, $CDCl_3$): δ= 1.15-1.45 (m, 5H), 1.61-1.82 (m, 5H), 2.00 (dddd, *J* = 11.4, 11.4, 3.4, 3.4 Hz, 1H), 2.81 (t, *J* = 6.7 Hz, 2H), 3.51 (td, *J* = 6.7, 6.1 Hz, 2H), 5.14 (br s, NH), 7.17-7.34 (m, 5H).



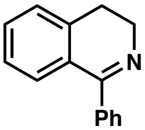
***1d***

**1-Cyclohexyl-3,4-dihydroisoquinoline.**[12] This compound was literature-known and synthesized from **S3d** following the general procedure B on a 5 mmol scale. The analytically pure product **1d** was received after extraction as a pale yellow-brown oil in 90% yield (955 mg, 4.48 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, $CDCl_3$): δ = 1.20-1.51 (m, 5H), 1.70-1.90 (m, 5H), 2.63 (dd, *J* = 7.3, 7.3 Hz, 2H), 2.85-2.90 (m, 1H), 3.65 (ddd, *J* = 7.3, 7.3, 1.1 Hz, 2H), 7.16-7.21 (m, 1H), 7.30 ($m_c$, 2H), 7.51 (dd, *J* = 7.2, 1.8 Hz, 1H).



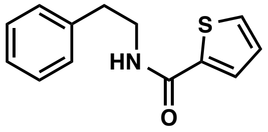
***S3e***

***N*-Phenylethylbenzamide.**[4] This compound was literature-known and synthesized following the general procedure A. The analytically pure product **S3e** was received after extraction as a colorless solid in quantitative yield (2.253 g, 10 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, $CDCl_3$): δ = 2.94 (t, *J* = 6.9 Hz, 2H), 3.72 (td, *J* = 6.9, 6.0 Hz, 2H), 6.18 (br s, NH), 7.23-7.38 (m, 5H), 7.40-7.70 (m, 5H).



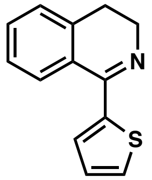
***1e***

**1-Phenyl-3,4-dihydroisoquinoline.**[13] This compound was literature-known and synthesized from **S3e** following the general procedure B on a 5 mmol scale. The analytically pure product **1e** was received after extraction as a pale yellow-brown oil in 95% yield (988 mg, 4.77 mmol). The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, $CDCl_3$): δ = 2.81 (t, *J* = 7.3 Hz, 2H), 3.83-3.88 (m, 2H), 7.21-7.28 (m, 3H), 7.33-7.46 (m, 4H), 7.59-7.62 (m, 2H).



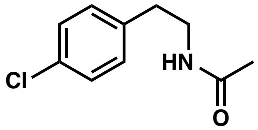
***S3f***

**_N_-Phenethylthiophene-2-carboxamide.**[14] This compound was literature-known but not fully characterized. It was synthesized following the general procedure A on a 40.0 mmol scale. The analytically pure product **S3f** was received after extraction as a brownish solid in quantitative yield (9.252 g, 40.0 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 2.92 (t, *J* = 6.9 Hz, 2H), 3.69 (td, *J* = 5.9, 6.9 Hz, 2H), 6.10 (br s, *N*H), 7.03 (dd, *J* = 3.7, 5.0 H, 1H), 7.20-7.26 (m, 3H), 7.29-7.34 (m, 2H), 7.41 (dd, *J* = 1.2, 3.7 Hz, 1H), 7.43 (dd, *J* = 1.2, 5.0 Hz, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 35.88, 41.26, 126.68, 127.66, 127.99, 128.80, 128.90, 129.86, 138.91, 139.21, 162.01. MS (EI, 70 eV): m/z (%) = 231.1 $[M]^+$ (45), 198.1 (12), 140.0 (16), 111.0 $[M{-}C_5H_4OS]^+$ (100), 104.0 (31), 91.1 $[C_7H_7]^+$ (25), 83.0 $[C_4H_3S]^+$ (9), 77.0 $[C_6H_5]^+$ (4), 65.1 (8), 57.1 (5), 44.2 (15), 41.2 (7). HRMS (ESI) calcd for $C_{13}H_{14}ONS^+$ $[M+H]^+$: 232.07906, found: 232.07915. HRMS (ESI) calcd for $C_{13}H_{13}ONNaS^+$ $[M+Na]^+$: 254.06101, found: 254.06099. IR (ATR): $\nu$ [cm$^{-1}$] = 3335, 3099, 3084, 3071, 3026, 2948, 2859, 1772, 1708, 1625, 1545, 1514, 1496, 1451, 1429, 1419, 1362, 1352, 1304, 1249, 1232, 1192, 1156, 1143, 1084, 1055, 1033, 1023, 979, 908, 855, 834, 818, 747, 739, 720, 699.



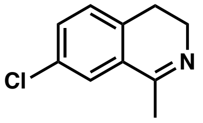
***1f***

**1-(Thiophen-2-yl)-3,4-dihydroisoquinoline.**[15] This compound was literature-known but not fully characterized. and synthesized using the following procedure: *N*-Phenethylthiophene-2-carboxamide (2.3131 g, 10.0 mmol) was treated with $POCl_3$ (3.5 mL, 37.5 mmol, 3.75 eq), $P_4O_{10}$ (3.55 g, 12.5 mmol, 1.25 equiv) and Xylene (30 mL). The resulting mixture was heated to reflux for 4 h. After cooling down to room temperature (23°C) $H_2O$ (100 mL) and conc. HCl (1.9 mL) was added. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined EtOAc layer was washed with aq HCl (1 M, 10 mL). The combined aqueous layer was neutralized with solid $Na_2CO_3$ and extracted with AcOEt (5 × 10 mL). The combined EtOAc layer of the neutral aqueous layer was dried ($Na_2SO_4$), filtered and concentrated afford the title compound. The analytically pure product **1f** was received after extraction as a brown oil in 35% yield (754.6 mg, 3.54 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 2.73 (t, *J* = 7.3 Hz, 2H), 3.74-3.78 (m, 2H), 7.07 (dd, *J* = 3.8, 5.5 Hz, 1H), 7.26 (ddd, *J* = 7.4, 1.5, 0.6 Hz, 1H), 7.30 (tdt, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.35 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.38 (dd, *J* = 6.1, 1.4 Hz, 1H), 7.40 (td, *J* = 3.7, 1.4 Hz, 1H), 7.67 (ddd, *J* = 7.6, 1.3, 0.4 Hz, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 26.41, 47.25, 126.64, 127.03, 127.17, 127.46, 127.91, 128.13, 128.79, 130.68, 138.98, 143.31, 160.80. MS (EI, 70 eV): m/z (%) = 213.1 $[M]^+$ (100), 185.1 (57), 180.0 (14), 168.1 (13), 152.1 (27), 141.0 (12), 139.1 (19), 128.1 (19), 115.1 (18), 102.1 (9), 97.1 (7), 89.1 (9), 77.1 $[C_6H_5]^+$ (20), 63.3 (9), 58.3 (5), 45.6 (7). HRMS (ESI) calcd for $C_{13}H_{12}NS^+$ $[M+H]^+$: 214.06850, found: 214.06865. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 2953, 1592, 1562, 1453, 1430, 1355, 1304, 1215, 1101, 1054, 1036, 1020, 920, 909, 858, 823, 745, 710.



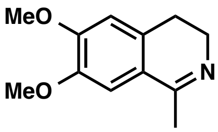
***S3g***

**_N_-(4-Chlorophenylethyl)acetamide.** This compound was synthesized following the general procedure A. The analytically pure product **S3g** was received after extraction as a colorless solid in >99% yield (1.97 g, 9.99 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 1.93 (s, 3H), 2.79 (t, *J* = 7.1 Hz, 2H), 3.47 (td, *J* = 7.1, 6.0 Hz, 2H), 5.63 (br s, NH), 7.10-7.14 (m, 2H), 7.25-7.29 (m, 2H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 23.33, 35.13, 40.65, 128.81, 130.14, 132.42, 137.45, 170.14. MS (EI, 70 eV): m/z (%) = 199.0 [M, $^{37}$Cl]$^+$ (9), 197.0 [M, $^{35}$Cl]$^+$ (30), 139.9 (31), 138.0 (100), 125.0 (11), 103.1 (5), 89.0 (4). HRMS (APCI, MeOH) calcd for $C_{10}H_{12}NO^{35}ClNa^+$ $[M+Na]^+$: 220.05051, found: 220.05060; calcd for $C_{10}H_{11}ON^{35}Cl^-$ $[M-H]^-$: 196.05292, found: 196.05300. IR (ATR): $\nu$ [cm$^{-1}$] = 3287, 3085, 2931, 2866, 1638, 1548, 1492, 1365, 1309, 1195, 1094, 1017, 838, 807, 731, 602.



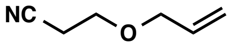
*1g*

**7-Chloro-1-methyl-3,4-dihydroisoquinoline.** Synthesized from **S3g** following the general procedure B on a 5 mmol scale. The crude product was purified by flash chromatography (hexanes/EtOAc, 15:1 containing 2 Vol% $Et_3N$, $R_f$ = 0.10) to afford **1g** as a pale-yellow oil in 35% yield (316 mg, 1.76 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 2.37 (t, *J* = 1.6 Hz, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 3.67 (tq, *J* = 7.5, 1.5 Hz, 2H), 7.12 (dd, *J* = 8.1, 0.4 Hz, 1H), 7.32 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.45 (dd, *J* = 2.1, 0.4 Hz, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 23.28, 25.53, 46.96, 125.66, 128.89, 130.60, 130.85, 135.81, 163.41. MS (EI, 70 eV): m/z (%) = 179.1 $[M]^+$ (87), 178.1 $[M–H]^+$ (100), 144.1 (15), 115.0 (16). HRMS (APCI, MeOH) calcd for $C_{10}H_{11}N^{35}Cl^+$ $[M+H]^+$: 180.0580, found: 180.0576. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 2949, 1715, 1630, 1565, 1491, 1429, 1374, 1294, 1260, 1215, 1098, 1015, 908, 838, 753, 731, 666, 651.



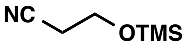
*1h*

**6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline.**[16] This compound was literature-known and synthesized using the following procedure:[17] In an open 250 mL round-bottom flask 2-(3,4-Dimethoxyphenyl)ethylamine (3.4 mL, 20.0 mmol, 1.0 equiv) was treated with $CH_2Cl_2$ (30 mL), polyphosphoric acid (60 g) and acetic acid (1.43 mL, 24.0 mmol, 1.2 equiv). The resulting mixture was carefully heated to 80°C for 3 h and poured into ice-water. The aqueous layer was carefully saturated with $Na_2CO_3$ and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layer was dried ($Na_2SO_4$), filtered, concentrated to afford the title compound. The analytically pure product was received after extraction as a brownish solid in 73% yield (3.012 g, 14.7 mmol). The $^1$H NMR data matched the literature values.[16a] $^1$H-NMR (300.1 MHz, $CDCl_3$): $\delta$ = 2.43 (t, J = 1.5 Hz, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 3.66 (tq, *J* = 1.4, 7.2 Hz, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 6.70 (s, 1H), 7.01 (s, 3H).



*2k*

**3-(Allyloxy)propanenitrile.**[18] This compound was literature-known and synthesized using the following procedure: To a mixture of allylic alcohol (1.37 mL, 20.0 mmol) and aq NaOH (40 w-%, 200 µL) was added dropwise acrylonitrile (1.46 mL, 22.0 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at room temperature (23°C) and treated with aqueous saturated $NH_4Cl$ solution (8 mL). Aqueous saturated $NaHCO_3$ solution (20 mL) and $CH_2Cl_2$ (20 mL) was added. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 20 mL) dried ($Na_2SO_4$), filtered and concentrated to afford the title compound. The analytically pure product **2k** was received after extraction as a colorless liquid in >99% yield. The $^1$H NMR data matched the literature values. $^1$H-NMR (300.1 MHz, $CDCl_3$): $\delta$ = 2.61 (t, *J* = 6.4 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 4.04 (dt, *J* = 1.4, 7.2 Hz, 2H), 5.23 (ddt, *J* = 1.4, 1.7, 10.4 Hz, 1H), 5.31 (ddt, *J* = 1.7, 1.7, 17.2 Hz, 1H), 5.90 (ddt, *J* = 5.7, 10.4, 17.2 Hz, 1H).



*2l*

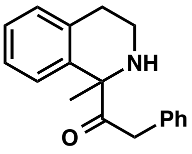
**3-((Trimethylsilyl)oxy)propanenitrile.**[19] This compound was literature-known and synthesized using the following procedure: In a flame-dried 250 mL round-bottom flask equipped with a magnetic stirrer bar, chlorotrimethylsilane (7.66 mL, 60.0 mmol, 1.01 equiv) was dissolved in $Et_2O$ (50 mL). While stirring, the solution was cooled to 0 ºC and 3-hydroxypropionitrile (4.03 mL, 59.0 mmol) dissolved in $Et_3N$ (8.45 mL, 61.0 mL) was added dropwise over 20 minutes. The mixture was slowly allowed to warm to room temperature (23 ºC) and stirred for additional 16 h. The mixture was filtered and the filter cake was rinsed with $Et_2O$ (100 mL). The combined mother liquors were concentrated to afford analytically pure **2l** as a pale-yellow oil in 98% yield (8.31 g, 58.0 mmol). The $^1$H NMR data matched the literature values.[20] $^1$H-NMR (300.1 MHz, $CDCl_3$): $\delta$ = 0.15 (s, 9H), 2.55 (t, *J* = 6.4 Hz, 2H), 3.81 (t, *J* = 6.4 Hz, 2H).

## Representative Procedure for the Titanium(III)-Catalyzed Reductive Coupling of 1a with 2a

A flame-dried Schlenk-tube was charged under argon with a magnetic stirrer bar, $Cp_2Ti(OPh)_2$ (18.2 mg, 0.05 mmol, 10 mol %), $Et_3N$•HCl (34.4 mg, 0.25 mmol, 0.5 equiv) and manganese powder (54.9 mg, 1.0 mmol, 2.0 equiv). The reaction vessel was evacuated and back-filled with argon three times. Absolute THF (0.2 mL) was added and the mixture was stirred for 2 min. Under a positive pressure of argon, TMSCl (190 μL, 1.5 mmol, 3.0 equiv), benzyl cyanide (**2a**, 144 μL, 1.25 mmol, 2.5 equiv) were added successively in this order followed by addition of a solution of imine **1a** (72.6 mg, 0.5 mmol) dissolved in THF (0.3 mL) via syringe. The syringe was rinsed with THF (0.5 mL) and the liquid was added to the reaction mixture (total volume of THF: 1.0 mL). The vessel was sealed with a greased glass stopper and the mixture was stirred at 60 ºC for 24 h.

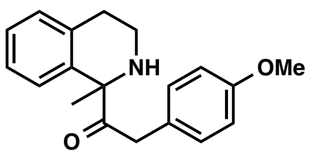
The reaction was allowed to cool to room temperature and the mixture was transferred with $CH_2Cl_2$ (5–8 mL) into a separation funnel containing ice-cold $Et_2O$ (100 mL) and aqueous HCl (1 M, 50 mL). The mixture was shaken until both layers became clear and the aqueous layer was separated. The organic layer was extracted with additional aq HCl (1 M, 2 × 25 mL). The combined aqueous layers were carefully saturated with solid $NaHCO_3$ after which 10–20 mg of solid NaOH were added. The aqueous layer was extracted with EtOAc (at least 3 × 50 mL, TLC control of the aqueous phase is advised) and the combined EtOAc layer was dried ($Na_2SO_4$), filtered and concentrated to give the crude product. Purification by flash chromatography (cyclohexane/EtOAc, 1.5:1; $R_f$ = 0.45) gave product **3aa** as a pale-yellow oil in 92% yield (122.1 mg, 0.46 mmol).

## Analytical Data for Products 3



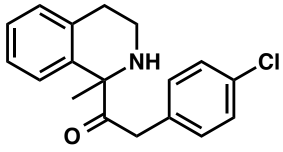
***3aa***

**1-(1-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-phenylethanone.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 1.5:1; $R_f$ = 0.45) product **3aa** was received as a pale-yellow oil in 92% yield (122.1 mg, 0.46 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.62 (s, 3H), 1.93 (br s, *N*H), 2.83 (ddd, *J* = 4.4, 4.4, 15.8 Hz, 1H), 3.00 (ddd, *J* = 5.8, 8.1, 15.8 Hz, 1H), 3.14 (ddd, *J* = 4.4, 5.8, 11.9 Hz, 1H), 3.14 (ddd, *J* = 4.4, 8.1, 11.9 Hz, 1H), 3.62 (d, *J* = 15.8 Hz, 1H), 3.87 (d, *J* = 15.8 Hz, 1H), 6.98-7.01 (m, 2H), 7.05-7.07 (m, 1H), 7.15-7.25 (m, 6H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 25.65, 30.35, 39.68, 44.08, 66.40, 126.35, 126.48, 127.18, 127.31, 128.24, 129.63, 129.68, 135.62, 135.64, 136.47, 209.61. MS (EI, 70 eV): m/z (%) = 265.2 $[M]^+$ (<1), 174.1 (1), 146.1 (100), 144.1 (12), 130.0 (7), 115.0 (4), 91.0 (5). HRMS (APCI, MeOH) calcd for $C_{18}H_{20}NO$ $[M+H]^+$: 266.15449, found: 266.15460. IR (ATR): $\nu$ [cm$^{-1}$] = 3334, 3027, 2924, 1713, 1602, 1493, 1452, 1369, 1284, 1154, 1066, 1017, 799, 763, 727, 695, 661.



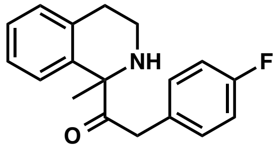
***3ab***

**2-(4-Methoxyphenyl)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 2.5:1; $R_f$ = 0.26) product **3ab** was received as a pale-yellow oil in 82% yield (121.6 mg, 0.41 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 1.58 (s, 3H), 1.73 (br s., *N*H), 2.79 (ddd, *J* = 4.3, 4.4, 15.9 Hz, 1H), 2.96 (ddd, *J* = 5.7, 8.2, 15.9 Hz, 1H), 3.09 (ddd, *J* = 4.4, 5.7 Hz, 11.7 Hz, 1H), 3.12 (ddd, *J* = 4.3, 5.7 Hz, 11.7 Hz, 1H), 3.53 (d, *J* = 16.0 Hz, 1H), 3.73 (s, 3H), 3.78 (d, *J* = 16.0 Hz, 1H), 6.73-6.76 (m, 2H), 6.87-6.91 (m, 2H), 7.01-7.04 (m, 1H), 7.11-7.21 (m, 3H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 25.67, 30.36, 39.65, 43.14, 55.27, 66.26, 113.72, 126.25, 127.06, 127.25, 127.68, 129.57, 130.58, 135.59, 136.60, 158.29, 210.03. MS (EI, 70 eV): m/z (%) = 188.1 $[M–C_7H_7O]^+$ (<1), 174.1 (<1), 146.1 (100), 130.1 (6), 121.1 (8). HRMS (APCI, MeOH) calcd for $C_{19}H_{22}NO_2^+$ $[M+H]^+$: 296.16505, found: 296.16500. IR (ATR): $\nu$ [cm$^{-1}$] = 3330, 3054, 2934, 2837, 2360, 2341, 1713, 1612, 1512, 1300, 1265, 1247, 1178, 1035, 896, 731.39, 703, 657.



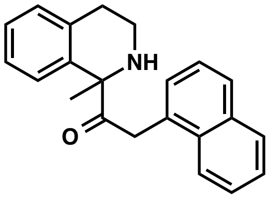
***3ac***

**2-(4-Chlorophenyl)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 1.5:1; $R_f$ = 0.50) product **3ac** was received as a yellow oil in 70% yield (105.0 mg, 0.35 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 1.61 (s, 3H), 1.70 (br s, *N*H), 2.82 (ddd, *J* = 4.0, 4.4, 16.0 Hz, 1H), 3.02 (ddd, *J* = 6.1, 8.3, 16.0 Hz, 1H), 3.13 (ddd, *J* = 4.4, 6.1, 11.6 Hz, 1H), 3.16 (ddd, *J* = 4.0, 8.3, 11.6 Hz, 1H), 3.57 (d, *J* = 15.9 Hz, 1H), 3.83 (d, *J* = 15.9 Hz, 1H), 6.90-6.94 (m, 2H), 6.99-7.01 (m, 1H), 7.13-7.24 (m, 5H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 25.46, 30.38, 39.56, 43.27, 66.31, 126.36, 127.18, 127.21, 128.29, 129.68, 131.00, 132.33, 134.23, 135.61, 136.24, 209.09. MS (EI, 70 eV): m/z (%) = 188.1 $[M–C_6H_4Cl]^+$ (<1), 174.1 (<1), 146.1 (100), 130.1 (10), 125.0 (9), 115.0 (6), 103.1 (3), 89.0 (2). HRMS (APCI, MeOH) calcd for $C_{18}H_{18}NO^{35}ClNa^+$ $[M+Na]^+$: 322.0975, found: 322.0970; calcd for $C_{18}H_{19}ON^{35}Cl^+$ $[M+H]^+$: 300.1155, found: 300.1151. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 2929, 2837, 1714, 1509, 1492, 1215, 1092, 1015, 908, 752, 731, 700, 666, 650, 594.



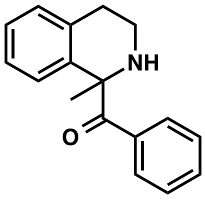
***3ad***

**2-(4-Fluorophenyl)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 2.5:1; $R_f$ = 0.36) product **3ad** was received as a yellow oil in 81% yield (114.6 mg, 0.40 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 1.58 (s, 3H), 1.67 (br s, *N*H), 2.79 (ddd, *J* = 4.0, 4.2, 16.0 Hz, 1H), 2.98 (ddd, *J* = 5.7, 8.5, 16.0 Hz, 1H), 3.10 (ddd, *J* = 4.2, 5.7, 11.6 Hz, 1H), 3.13 (ddd, *J* = 4.0, 8.5, 11.6 Hz, 1H), 3.55 (d, *J* = 16.0 Hz, 1H), 3.80 (d, *J* = 16.0 Hz, 1H), 6.84-6.94 (m, 4H), 6.97-7.00 (m, 1H), 7.10-7.20 (m, 3H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 25.46, 30.35, 39.55, 43.05, 66.24, 114.93 (d, *J* = 21.2 H), 126.29, 127.14, 127.17, 129.63, 131.06 (d, *J* = 8.0 Hz), 131.38 (d, *J* = 3.4 Hz), 135.58, 136.32, 161.67 (d, *J* = 244.1 Hz, CF), 209.40. $^{19}$F-NMR (235.4 MHz, $CDCl_3$): δ = −116.87-(−116.73). MS (EI, 70 eV): m/z (%) = 284.4 $[M+H]^+$ (4), 146.1 (100), 130.1 (6), 109.1 (6). HRMS (APCI, MeOH) calcd for $C_{18}H_{19}NOF^+$ $[M+H]^+$: 284.14507, found: 284.14490. IR (ATR): $\nu$ [cm$^{-1}$] = 3337, 3019, 2930, 2837, 1713, 1509, 1371, 1215, 1157, 1093, 1016, 907, 751, 729, 665, 651, 592.



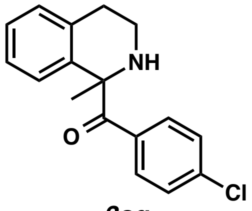
***3ae***

**1-(1-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-(naphth-1-yl)ethanone.** Synthesized following the representative procedure. After purification by flash chromatography ($CH_2Cl_2$/EtOAc, 10:1; $R_f$ = 0.25) product **3ae** was received as a brown oil in 95% yield (150.5 mg, 0.48 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.64 (s 3H), 1.76 (br s, *N*H,), 2.83 (ddd, *J* = 3.5, 4.7, 15.7 Hz, 1H), 3.07 (ddd, *J* = 5.8, 8.3, 15.7 Hz, 1 H), 3.17 (ddd, *J* = 3.5, 8.3, 11.6 Hz, 1H), 3.21 (ddd, *J* = 4.7, 5.8, 11.6 Hz, 1H), 4.02 (d, *J* = 17.2 Hz, 1H), 4.42 (d, *J* = 17.2 Hz, 1H), 7.08-7.13 (m, 2H), 7.16-7.25 (m, 3H), 7.31-7.35 (m, 2H), 7.39-7.41 (ddd, *J* = 1.4, 6.7, 8.1 Hz, 1H), 7.57 (dd, *J* = 1.0, 8.6 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1 H), 7.78 (ddd, *J* = 0.7, 0.7, 8.1 Hz, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 25.93, 30.59, 39.82, 41.63, 66.54, 124.34, 125.35, 125.50, 125.86, 126.49, 127.23, 127.49, 127.50, 128.26, 128.63, 129.74, 132.31, 132.56, 133.90, 135.74, 136.72, 209.74. MS (EI, 70 eV): m/z (%) = 315.2 $[M]^+$ (<1), 146.1 $[M–C_{12}H_9O]$ (100), 144.1 (11), 141.1 (17), 139.1 (5), 130.1 (8), 115.1 (13). HRMS (ESI) calcd for $C_{22}H_{22}ON$ $[M+H]^+$: 316.16959, found: 316.16962. IR (ATR): $\nu$ [cm$^{-1}$] = 3018, 1714, 1598, 1511, 1492, 1399, 1371, 1311, 1215, 1008, 908, 749, 730.



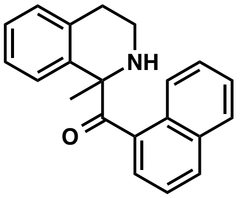
***3af***

**(1-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)(phenyl)methanone.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 4:1; $R_f$ = 0.32) product **3af** was received as a yellow oil in 79% yield (99.1 mg, 0.39 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.73 (s, 3H), 2.85 (ddd, *J* = 3.4, 3.8, 16.0 Hz, 1H), 3.11 (ddd, *J* = 5.6, 10.2, 16.0 Hz, 1H), 3.20 (ddd, *J* = 3.4, 5.6, 12.0 Hz, 1H), 3.28 (ddd, *J* = 3.8, 10.2, 12.0 Hz, 1H), 6.93-6.95 (m, 1H), 7.03-7.08 (m, 1H), 7.12-7.19 (m, 2H), 7.19-7.24 (m, 2H), 7.32-7.36 (m, 1H), 7.70-7.74 (m, 2H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 27.57, 29.88, 39.54, 65.95, 126.50, 126.98, 127.03, 127.84, 129.78, 130.02, 130.11, 131.64, 133.99, 136.70, 138.24, 202.44.MS (EI, 70 eV): m/z (%) = 146.1 $[M–C_7H_5O]^+$ (100), 130.1 (8), 115.1 (3), 105.1 (5), 77.1 (3). HRMS (APCI, MeOH) calcd for $C_{17}H_{17}NONa^+$ $[M+Na]^+$: 274.1208, found: 274.1204; calcd for $C_{17}H_{18}ONI^+$ $[M+H]^+$: 252.1388, found: 252.1385. IR (ATR): $\nu$ [cm$^{-1}$] = 3335, 3019, 2928, 2838, 1676, 1596, 1491, 1446, 1369, 1259, 1215, 1180, 1161, 1117, 966, 908, 749, 729, 700, 667, 644.



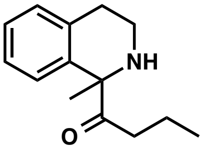
***3ag***

**(4-Chlorophenyl)(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methanone**. Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 4:1; $R_f$ = 0.4) product **3ag** was received as a colorless oil in 81% yield (115.7 mg, 0.41 mmol). $^1$H-NMR (500.3 MHz, $CDCl_3$): $\delta$ = 1.74 (s, 3H), 1.85 (br s, NH), 2.86 (ddd, *J* = 3.4, 3.4, 16.2 Hz, 1H), 3.13 (ddd, *J* = 5.8, 10.7, 16.3 Hz, 1H), 3.23 (ddd, *J* = 3.1, 5.8, 11.9 Hz, 1H), 3.28 (ddd, *J* = 3.8, 10.7, 11.9 Hz, 1H), 6.89-6.92 (m, 1H), 7.04-7.09 (m, 1H), 7.14-7.18 (m, 2H), 7.18-7.22 (m, 2H), 7.74-7.78 (m, 2H).$^{13}$C-NMR (125.8 MHz, $CDCl_3$): $\delta$ = 27.26, 29.74, 39.43, 65.93, 126.62, 126.90, 127.16, 128.08, 129.87, 131.76, 133.79, 134.66, 137.86, 138.02. 200.85. MS (EI, 70 eV): m/z (%) = 146.1 [M–$C_7H_5O$]$^+$ (100), 130.1 (10), 115.1 (6), 44.2 (7). HRMS (APCI, MeOH) calcd for $C_{17}H_{17}NO^{35}Cl^+$ [M+H]$^+$: 286.09932, found: 286.09952; calcd for $C_{17}H_{17}ON^{37}Cl^+$ [M+H]$^+$: 288.09637, found: 288.09656.IR (ATR): $\nu$ [cm$^{-1}$] = 3333, 2925, 2837, 1921, 1675, 1585, 1486, 1440, 1397, 1368, 1283, 1256, 1238, 1209, 1174, 1160, 1089, 1055, 1035, 1014, 966, 887, 840, 812, 765, 728, 683, 656.



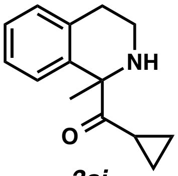
*3ah*

**1-(1-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-(naphth-1-yl)methanone.** Synthesized following the representative procedure. After purification by flash chromatography ($CH_2Cl_2$/EtOAc, 10:1; $R_f$ = 0.30) product **3ah** was received as a yellow oil in 73% yield (110.4 mg, 0.37 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.79 (s 3H), 2.10 (br s, *N*H), 2.75 (ddd, *J* = 5.1, 6.7, 16.2 Hz, 1H), 2.83 (ddd, *J* = 4.9, 6.6, 16.2 Hz, 1H), 2.98 (ddd, *J* = 5.1, 6.6, 12.5 Hz, 1 H), 3.09 (ddd, *J* = 4.9, 6.7, 12.5 Hz, 1H), 6.90 (dd, J = 1.1, 7.2 Hz, 1H), 7.02-7.07 (m, 1H), 7.09-7.20 (m, 4H), 7.43-7.49 (m, 2H), 7.76-7.83 (m, 3H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 28.01, 30.14, 39.96, 67.29, 124.02, 124.92, 125.47, 126.18, 126.22, 127.09, 127.09, 127.61, 128.43, 129.55, 129.94, 130.84, 133.64, 135.50, 136.94, 137.48, 208.39. MS (EI, 70 eV): m/z (%) = 301.2 [M]$^+$ (<1), 155.1 [$C_{11}H_7O$] (5), 146.1 [M–$C_{11}H_7O$]$^+$ (100), 144.1 (11), 130.1 (8), 128.1 (5), 127.1 (21). HRMS (ESI) calcd for $C_{21}H_{20}ON$ [M+H]$^+$: 302.15394, found: 302.15408. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 1685, 1507, 1491, 1443, 1370, 1215, 1047, 907, 751, 730.



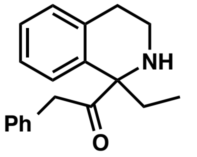
*3ai*

**1-(1-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-1-one.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 2.5:1; $R_f$ = 0.39) product **3ai** was received as a yellow oil in 73% yield (79.8 mg, 0.37 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 0.78 (t, *J* = 7.5 Hz, 3H), 1.39-1.53 (m, 2H), 1.55 (s, 3H), 1.85 (br s, *N*H), 2.30 (ddd, *J* = 6.8, 8.1, 17.4 Hz, 1H), 2.52 (ddd, *J* = 6.3, 8.1, 17.4 Hz, 1H), 2.80 (ddd, *J* = 4.8, 5.1, 16.0 Hz, 1H), 2.90 (ddd, *J* = 5.6, 7.9, 16.0 Hz, 1H), 3.07 (ddd, *J* = 5.1, 5.6, 11.9 Hz, 1H), 3.12 (ddd, *J* = 4.8, 7.9, 11.9 Hz, 1H), 7.05-7.19 (m, 4H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 13.81, 17.77, 26.01, 30.33, 39.61, 39.91, 65.87, 126.12, 126.87, 127.16, 129.44, 135.43, 137.19, 212.91. MS (EI, 70 eV): m/z (%) = 202.3 [M-$CH_3$]$^+$ (<1), 146.1 (100), 144.1 (9), 130.1 (7), 115.0 (3), 103.1 (2). HRMS (APCI, MeOH) calcd for $C_{14}H_{20}NO^+$ [M+H]$^+$: 218.15449, found: 218.15450. IR (ATR): $\nu$ [cm$^{-1}$] = 3336, 3061, 3020, 2961, 2929, 2873, 2833, 1706, 1492, 1450, 1368, 1284, 1265, 1154, 1108, 1006, 881, 804, 728, 655, 593.



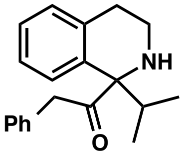
*3aj*

**Cyclopropyl(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methanone.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 1.5:1; $R_f$ = 0.42) product **3aj** was received as a yellow oil in 64% yield (69.2 mg, 0.32 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 0.70 (dddd, *J* = 2.8, 6.7, 7.8, 9.0 Hz, 1H), 0.81 (dddd, *J* = 2.8, 6.7, 7.8, 8.8 Hz, 1H), 0.90 (dddd, *J* = 2.8, 4.8, 6.7, 9.3 Hz, 1H), 0.98 (dddd, *J* = 2.8, 4.8, 6.7, 9.3 Hz, 1H), 1.59 (s, 3H), 1.87 (br s, *N*H), 2.17 (dddd, *J* = 4.7, 4.7, 7.8, 7.8 Hz, 1H), 2.83 (ddd, *J* = 4.9, 5.3, 16.2 Hz, 1H), 2.92 (ddd, *J* = 5.3, 7.5, 16.2 Hz, 1H), 3.13 (ddd, *J* = 5.3, 5.3, 12.1 Hz, 1H), 3.17 (ddd, *J* = 4.9, 7.5, 12.1 Hz, 1H), 7.07-7.20 (m, 4H). $^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ = 11.60, 12.17, 17.18, 26.03, 30.26, 39.94, 65.94, 126.13, 126.87, 127.46, 129.42, 135.34, 137.56, 212.46. MS (EI, 70 eV): m/z (%) = 200.1 [M–CH$_3$]$^+$ (1), 146.1 (100), 144.1 (28), 130.1 (19), 115.1 (10), 103.1 (7). HRMS (APCI, MeOH): calcd for $C_{14}H_{18}NO^+$ [M+H]$^+$: 216.13884, found: 216.13890. IR (ATR): $\nu$ [cm$^{-1}$] = 3333, 3062, 3006, 2971, 2926, 2833, 1694, 1492, 1444, 1372, 1284, 1155, 1126, 1062, 1038, 1006, 904, 879, 819, 763, 729, 649, 594.



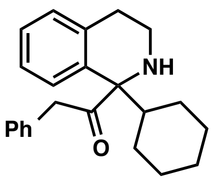
***3ba***

**1-(1-ethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-phenylethan-1-one.** Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 2:1; R$_f$ = 0.51) product **3ba** was received as a yellow oil in 88% yield (122.7 mg, 0.44 mmol). $^1$H-NMR (400.1 MHz, CDCl$_3$): δ = 0.74 (t, *J* =7.3 Hz, 3H), 1.90 (dq, *J* = 7.3, 14.6 Hz, 1H), 2.00 (dq, *J* = 7.3, 14.6 Hz, 1H), 2.07 (br s, *N*H), 2.71 (ddd, *J* = 4.9, 5.9, 15.8 Hz, 1H), 2.80 (ddd, *J* = 4.9, 7.2, 15.8 Hz, 1H) 2.97 (ddd, *J* = 4.9, 5.9, 12.0 Hz, 1H), 3.02 (ddd, *J* = 4.9, 7.2, 12.0 Hz, 1H), 3.59 (d, *J* = 15.9 Hz, 1H), 3.77 (d, *J* = 15.9 Hz, 1H), 6.86-6.89 (m, 2H), 7.02-7.14 (m, 7H). $^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ = 8.39, 30.37, 30.63, 39.90, 44.69, 69.55, 126.20, 126.42, 126.95, 127.27, 128.20, 129.53, 129.61, 135.37, 135.44, 136.29, 209.91. MS (EI, 70 eV): m/z (%) = 280.3 [M+H]$^+$ (<1), 160.1 [M–C$_8$H$_7$O]$^+$ (>100), 158.1 (31), 156.1 (6), 144.1 (8), 130.0 (12), 115.0 (8), 91.1 [C$_7$H$_7$]$^+$ (9), 77.1 (6), 44.2 (5). HRMS (APCI, MeOH) calcd for $C_{19}H_{22}ON^+$ [M+H]$^+$: 280.16959, found: 280.16959. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 1710, 1493, 1454, 1308, 1215, 1077, 1034, 908, 747, 668, 651.



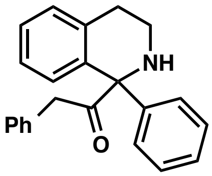
***3ca***

**1-(1-Isopropyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-phenylethan-1-one**. Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 2:1; R$_f$ = 0.63) product **3ca** was received as a yellow oil in 74% yield (109.1 mg, 0.37 mmol). $^1$H-NMR (500.3 MHz, CDCl$_3$): δ = 0.77 (d, *J* = 6.9, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 2.29 (br s, *N*H), 2.78 (ddd, *J* = 5.2, 10.7, 15.6 Hz, 1H), 2.82 (ddd, *J* = 5.2, 6.9, 15.6 Hz, 1H), 2.84 (qq, *J* = 6.7, 6.9 Hz, 1H), 3.16 (ddd, *J* = 5.2, 10.7, 12.3 Hz, 1H), 3.19 (ddd, *J* = 5.2, 6.9, 12.3 Hz, 1H), 3.77 (d, *J* = 16.3 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 6.95-6.98 (m, 2H), 7.12-7.14 (m, 1H), 7.17-7.25 (m, 5H), 7.47 (dd, *J* = 1.5, 7.8 Hz, 1H). $^{13}$C-NMR (125.8 MHz, CDCl$_3$): δ = 17.37, 17.46, 30.93, 35.68, 41.41, 44.69, 72.30, 126.55, 126.82, 127.63, 128.31, 129.33, 129.67, 134.75, 135.35, 137.86, 210.56. MS (EI, 70 eV): m/z (%) = 294.2 [M+H]$^+$ (<1), 174.1 [M–C$_8$H$_7$O]$^+$ (>100), 172.1 (7), 158.1 (19), 144.1 (5), 130.0 (8), 91.0 [C$_7$H$_7$]$^+$ (11), 44.2 (4). HRMS (ESI, MeOH) calcd for $C_{20}H_{24}ON^+$ [M+H]$^+$: 294.18524, found: 294.18536. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 2965, 1706, 1492, 1453, 1215, 1106, 908, 749, 731.



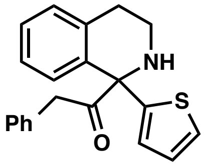
***3da***

**1-(1-Cyclohexyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-phenylethan-1-one**. Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 2:1; $R_f$ = 0.66) product **3da** was received as a yellow oil in 51% yield (84.4 mg, 0.253 mmol). $^1$H-NMR (500.3 MHz, $CDCl_3$): δ = 1.10-1.38 (m, 6H), 1.49-1.55 (m, 1H), 1.64-1.73 (m, 2H), 1.76-1.82 (m, 1H), 2.38 (br s, *N*H), 2.45 (dddd, *J* = 2.7, 2.7, 11.6, 11.6 Hz, 1H), 2.77 (ddd, *J* = 5.2, 5.2, 15.4 Hz, 1H), 2.81 (ddd, *J* = 5.6, 5.6, 15.4 Hz, 1H), 3.15 (ddd, *J* = 5.2, 5.6, 12.7 Hz, 1H), 3.17 (ddd, *J* = 5.2, 5.6, 12.7 Hz, 1H), 3.79 (d, *J* = 16.5 Hz, 1H), 4.00 (d, *J* = 16.5 Hz, 1H), 6.97-6.99 (m, 2H), 7.12-7.14 (m, 1H), 7.18-7.27 (m, 5H), 7.48 (dd, *J* = 1.4, 7.8 Hz, 1H). $^{13}$C-NMR (125.8 MHz, $CDCl_3$): δ = 26.62, 26.82, 27.01, 27.36, 27.87, 30.90, 41.40, 44.72, 46.56, 72.56, 126.50, 126.71, 127.60, 128.26, 129.31, 129.65, 134.30, 135.37, 137.99, 210.51. MS (EI, 70 eV): m/z (%) = 333.3 $[M]^+$ (<1), 214.2 $[M-C_8H_7O]^+$ (>100), 212.1 (13), 184.1 (4), 170.1 (4), 158.1 (12), 156.1 (7), 143.0 (4), 132.0 (7), 130.1 (6), 128.0 (4), 115.0 (4), 91.1 $[C_7H_7]^+$ (11), 44.2 (4). HRMS (ESI, MeOH) calcd for $C_{23}H_{28}ON^+$ $[M+H]^+$: 334.21654, found: 334.21658. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 2932, 2854, 1706, 1492, 1452, 1215, 1037, 908, 747.



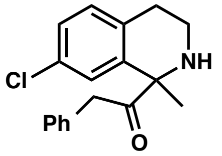
***3ea***

**2-Phenyl-1-(1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one**. Synthesized following the representative procedure with 48 h reaction time. After purification by flash chromatography (cyclohexane/EtOAc, 2:1; $R_f$ = 0.57) product **3ea** was received as a yellow oil in 78% yield (127.3 mg, 0.39 mmol). $^1$H-NMR (500.3 MHz, $CDCl_3$): δ = 2.49 (br s, *N*H), 2.88-2.96 (m, 2H), 2.97-3.05 (m, 2H), 3.90 (d, *J* = 15.9 Hz, 1H), 4.04 (d, *J* = 15.9 Hz, 1H), 7.06 (dd, *J* = 0.9, 7.9 Hz, 1H), 7.10-7.18 (m, 5H), 7.21-7.34 (m, 8H). $^{13}$C-NMR (125.8 MHz, $CDCl_3$): δ = 29.81, 39.34, 46.23, 74.80, 125.75, 126.63, 127.44, 127.57, 128.17, 128.31, 128.64, 129.75, 129.80, 133.88, 135.07, 136.72, 144.42, 209.23. MS (EI, 70 eV): m/z (%) = 208.1 $[M-C_8H_7O]^+$ (9), 207.1 (60), 206.1 (100), 205.1 (20), 204.1 (31), 178.1 (21), 152.0 (5), 103.0 (6), 102.1 (6), 77.1 $[C_6H_5]^+$ (8), 51.2 (4), 44.2 (4). HRMS (ESI, MeOH) calcd for $C_{23}H_{22}ON^+$ $[M+H]^+$: 328.16959, found: 328.16986. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 1713, 1602, 1494, 1454, 1427, 1215, 1094, 1054, 1031, 908, 747, 701.



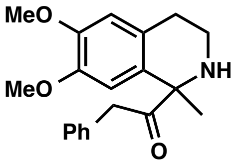
***3fa***

**2-Phenyl-1-(1-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one**. Synthesized following the representative procedure. After purification by flash chromatography (cyclohexane/EtOAc, 7:1; $R_f$ = 0.43) product **3fa** was received as a yellow oil in >99% yield (168.1 mg, 0.50 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 2.27 (br s., *N*H), 2.78-2.87 (m, 1H), 2.93-3.03 (m, 3H), 3.76 (d, *J* = 16.0 Hz, 1H), 3.95 (d, *J* = 16.0 Hz, 1H), 6.68 (dd, *J* = 1.2, 3.6 Hz, 1H), 6.88 (dd, *J* = 3.6, 5.1 Hz, 1H), 7.02-7.04 (m, 2H), 7.08-7.15 (m, 2H), 7.16-7.25 (m, 6H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 29.61, 39.17, 45.24, 71.31, 125.84, 126.02, 126.04, 126.64, 127.31, 127.84, 128.27, 129.01, 129.66 129.75, 134.40, 135.01, 135.84, 148.11, 206.83. MS (EI, 70 eV): m/z (%) = 334.2 $[M+H]^+$ (<1), 214.1 $[M-C_8H_7O]^+$ (>100), 212.1 (10), 184.0 (5), 130.0 (10), 103.0 (6), 91.1 $[C_7H_7]^+$ (7). HRMS (ESI) calcd for $C_{21}H_{20}ONS^+$ $[M+H]^+$: 334.12601, found: 334.12601. IR (ATR): $\nu$ [cm$^{-1}$] = 3330, 3062, 3028, 2924, 2835, 2360, 1718, 1602, 1494, 1453, 1427, 1341, 1306, 1283, 1265, 1232, 1159, 1123, 1088, 1074, 1050, 1031, 962, 908, 868, 831, 799, 750, 723, 704.



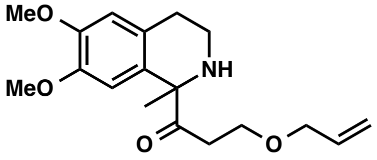
***3ga***

**1-(7-Chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-phenylethan-1-one**. Synthesized following the representative procedure. After purification by flash chromatography (CH:AcOEt, 1.5:1, $R_f = 0.414$) product **3ga** was received as a yellow oil in 75% yield (112.9 mg, 0.38 mmol). $^1$H-NMR (500.3 MHz, $CDCl_3$, TMS): $\delta = 1.55$ (s, 3H), 1.72 (br s, *N*H), 2.74 (ddd, *J* = 4.3 Hz, 5.2 Hz, 16.0 Hz, 1H), 2.87 (ddd, *J* = 5.2 Hz, 8.1 Hz, 16.0 Hz, 1H), 3.03 (ddd, *J* = 5.2 Hz, 5.2 Hz, 12.0 Hz, 1H), 3.08 (ddd, *J* = 4.3 Hz, 8.1 Hz, 12.0 Hz, 1H), 3.64 (d, *J* = 15.7 Hz, 1H), 3.85 (d, *J* = 15.7, 1H), 6.99-7.06 (m, 4H), 7.14 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.16-7.18 (m, 1H), 7.20-7.24 (m, 2H). $^{13}$C-NMR (125.8 MHz, $CDCl_3$): $\delta = 25.68$, 29.72, 39.53, 43.98, 66.20, 126.56, 127.26, 127.30, 128.27, 129.53, 130.84, 131.77, 133.97, 135.22, 138.37, 209.18. MS (EI, 70 eV): m/z (%) = 299.0 $[M^{35}Cl]^+$ (<1), 182.0 $[M^{37}Cl–C_8H_7O]^+$ (30), 180.0 $[M^{35}Cl–C_8H_7O]^+$ (>100), 164.0 (6), 144.1 (8), 115.1 (10), 91.1 $[C_7H_7]^+$ (11), 44.2 (6). HRMS (ESI) calcd for $C_{18}H_{19}ON^{35}Cl^+$ $[M+H]^+$: 300.11497, found: 300.11523. IR (ATR): $\nu$ [cm$^{-1}$] = 3061, 3028, 2972, 2926, 2834, 2360, 2341, 1715, 1597, 1571, 1494, 1453, 1427, 1398, 1370, 1336, 1269, 1212, 1186, 1155, 1100, 1075, 1019, 1002, 985, 920, 882, 849, 811, 773, 752, 696.



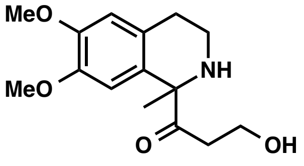
***3ha***

**1-(6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-phenylethan-1-one**. Synthesized following the representative procedure. After purification by flash chromatography (CH:AcOEt, 1:1, $R_f = 0.233$) product **3ga** was received as a yellow oil in 73% yield (118.1 mg, 0.36 mmol). $^1$H-NMR (500.3 MHz, $CDCl_3$): $\delta = 1.56$ (s, 3H), 1.64 (br s, *N*H), 2.71 (ddd, *J* = 4.0, 4.0, 15.7 Hz, 1H), 2.96 (ddd, *J* = 7.5, 7.5, 15.7 Hz, 1H), 3.10-3.17 (m, 2H), 3.66 (s, 3H), 3.67 (d, *J* = 15.6 Hz, 1H), 3.80 (d, *J* = 15.6 Hz, 1H), 3.87 (s, 3H), 6.36 (s, 1H), 6.64 (s, 1H), 6.95-6.98 (m, 2H), 7.13-7.21 (m, 3H). $^{13}$C-NMR (125.8 MHz, $CDCl_3$): $\delta = 25.17$, 29.90, 39.55, 43.75, 55.88, 55.93, 65.88, 109.91, 111.94, 126.36, 127.83, 127.86, 128.09, 129.50, 135.85, 147.47, 148.15, 209.88. MS (EI, 70 eV): m/z (%) = 326.3 $[M+H]^+$ (<1), 206.1 $[M–C_8H_7O]^+$ (100), 205.1 (21), 204.1 (12), 203.1 (17), 190.1 (21), 188.1 (4), 162.1 (5), 160.1 (8), 132.1 (4), 117.0 (5), 91.1 (12), 44.2 (5). HRMS (ESI) calcd for $C_{20}H_{24}O_3N^+$ $[M+H]^+$: 326.17507, found: 326.17526. IR (ATR): $\nu$ [cm$^{-1}$] = 3027, 2932, 2832, 1713, 1610, 1513, 1496, 1464, 1453, 1401, 1365, 1344, 1324, 1261, 1227, 1141, 1060, 1021, 1001, 955, 863, 807, 773, 752, 722, 697.



***3hk***

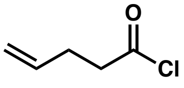
**3-(allyloxy)-1-(6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-1-one.** A flame-dried Schlenk-tube was charged under argon with a magnetic stirrer bar, $Cp_2Ti(OPh)_2$ (18.2 mg, 0.05 mmol, 10 mol %), $Et_3N•HCl$ (34.4 mg, 0.25 mmol, 0.5 equiv) and zinc powder (65.4 mg, 1.0 mmol, 2.0 equiv). The reaction vessel was evacuated and back-filled with argon three times. Absolute THF (0.5 mL) was added and the mixture was stirred for 2 min. Under a positive pressure of argon, TMSCl (190 μL, 1.5 mmol, 3.0 equiv), 3-(Allyloxy)propanenitrile (**2k**, 138 mg, 1.25 mmol, 2.5 equiv) were added via syringe successively in this order followed by addition of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **1h** (102.6 mg, 0.5 mmol). The vessel was sealed with a greased glass stopper and the mixture was stirred at 60 ºC for 16 h. The reaction was allowed to cool to room temperature and the mixture was transferred with $CH_2Cl_2$ (5–8 mL) into a separation funnel containing ice-cold $Et_2O$ (100 mL) and aqueous HCl (1 M, 50 mL). The mixture was shaken until both layers became clear and the aqueous layer was separated. The organic layer was extracted with additional aq HCl (1 M, 2 × 25 mL). The combined aqueous layers were carefully saturated with solid $NaHCO_3$ after which 10–20 mg of solid NaOH were added. The aqueous layer was extracted with EtOAc (at least 3 × 50 mL, TLC control of the aqueous phase is advised) and the combined EtOAc layer was dried ($Na_2SO_4$), filtered and concentrated to give the crude product. Purification by flash chromatography ($CH_2Cl_2$/MeOH, 100:7; $R_f$ = 0.298) gave product **3hk** as a pale-yellow oil in 61% yield (85.2 mg, 0.305 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.55 (s, 3H), 1.79 (br s, *N*H), 2.62 (ddd, $J$ = 6.5, 6.8, 16.9 Hz, 1H), 2.69 (ddd, $J$ = 4.7, 4.7, 15.8 Hz, 1H), 2.82-2.89 (m, 1H), 2.91 (ddd, $J$ = 6.6, 6.6, 16.9 Hz, 1H), 3.05-3.14 (m, 2H), 3.55-3.65 (m, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 3.89 (ddd, $J$ = 1.5, 1.5, 5.6 Hz, 2H), 5.13 (ddt, $J$ = 1.3, 1.8, 10.4 Hz, 1H), 5.20 (ddt, $J$ = 1.7, 1.8, 17.3 Hz, 1H), 5.83 (ddt, $J$ = 5.7, 10.4, 17.2 Hz, 1H), 6.49 (s, 1H), 6.60 (s, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 25.55, 29.92, 37.67, 39.86, 55.98, 56.22, 65.58, 66.05, 72.06, 110.06, 112.04, 116.92, 127.92, 128.40, 134.89, 147.66, 148.27, 211.18. MS (EI, 70 eV): m/z (%) = 320.2 $[M+H]^+$ (<1), 233.2 (98), 206.1 $[M–C_6H_9O_2]^+$ (100), 204.2 (34), 190.1 (48), 174.2 (10), 160.2 (10), 130.0 (4). HRMS (APCI) calcd for $C_{18}H_{26}O_4N^+$ $[M+H]^+$: 320.18563, found: 320.18552. IR (ATR): $\nu$ [cm$^{-1}$] =2254, 1707, 1513, 1465, 1260, 1226, 1142, 1096, 1000, 904, 724, 649, 568, 504, 467, 460, 451, 423, 408.



***3hl***

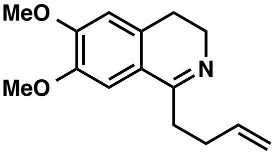
**1-(6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-hydroxypropan-1-one.** A flame-dried Schlenk-tube was charged under argon with a magnetic stirrer bar, $Cp_2Ti(OPh)_2$ (18.2 mg, 0.05 mmol, 10 mol %), $Et_3N$•HCl (34.4 mg, 0.25 mmol, 0.5 equiv) and zinc powder (65.4 mg, 1.0 mmol, 2.0 equiv). The reaction vessel was evacuated and back-filled with argon three times. Absolute THF (0.5 mL) was added and the mixture was stirred for 2 min. Under a positive pressure of argon, TMSCl (190 μL, 1.5 mmol, 3.0 equiv), 3-((Trimethylsilyl)oxy)propanenitrile (**2l**, 138 mg, 1.25 mmol, 2.5 equiv) were added via syringe successively in this order followed by addition of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **1h** (102.6 mg, 0.5 mmol). The vessel was sealed with a greased glass stopper and the mixture was stirred at 60 ºC for 16 h. The reaction was allowed to cool to room temperature and the mixture was transferred with $CH_2Cl_2$ (5–8 mL) into a separation funnel containing ice-cold $Et_2O$ (100 mL) and aqueous HCl (1 M, 50 mL). The mixture was shaken until both layers became clear and the aqueous layer was separated. The organic layer was extracted with additional aq HCl (1 M, 2 × 25 mL). The combined aqueous layers were carefully saturated with solid $NaHCO_3$ after which 10–20 mg of solid NaOH were added. The aqueous layer was extracted with EtOAc (at least 3 × 50 mL, TLC control of the aqueous phase is advised) and the combined EtOAc layer was dried ($Na_2SO_4$), filtered and concentrated to give the crude product. Purification by flash chromatography ($CH_2Cl_2$/MeOH, 100:7; $R_f$ = 0.325) gave product **3hl** as a pale-yellow oil in 53% yield (84.6 mg, 0.265 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.58 (s, 3H), 2.40 (ddd, $J$ = 3.9, 5.3, 15.5 Hz, 1H), 2.66-2.75 (m, 2H, OH, *N*H), 2.87-2.95 (m, 1H), 3.09-3.18 (m, 2H), 3.66-3.69 (m, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 6.42 (s, 1H), 6.61 (s, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 25.14, 29.51, 39.57, 41.09, 55.98, 56.25, 59.11, 64.82, 109.56, 112.10, 127.48, 127.90, 147.99, 148.47, 211.58. MS (EI, 70 eV): m/z (%) = 279.2 $[M]^+$ (<1), 206.1 $[M–C_3H_5O_2]^+$ (100), 204.1 (8), 190.1 (16). HRMS (ESI) calcd for $C_{15}H_{22}O_4N^+$ $[M+H]^+$: 280.15433, found: 280.15451. IR (ATR): $\nu$ [cm$^{-1}$] =2934, 1705, 1610, 1513, 1464, 1325, 1260, 1227, 1141, 1060, 1000, 836, 728, 646.

# Total Synthesis of 10, Preparation and Analytical Data of Compounds 5–10



***6***

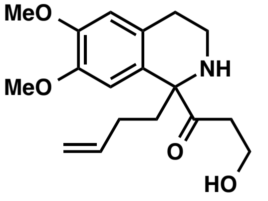
**Pent-4-enoyl chloride.**[21] This compound was literature-known and synthesized using the following procedure: In a flame-dried 50 mL round-bottom flask equipped with a magnetic stirrer bar and a reflux-condenser, Pent-4-enoic acid (9.4 mL, 90.0 mmol) was treated with a catalytic amount of DMF (20 μL) and thionyl chloride (16.4 mL, 224.0 mmol, 2.8 equiv). The reaction mixture was heated to reflux for 16 h. After cooling down to room temperature (23 °C) thionyl chloride was removed in vacuum. The remaining liquid was used immediately in the next step without purification and the crude title compound was received in 99% yield (10.680 g, 90.0 mmol) as a brown liquid. The nmr data matched the previously reported values.[21] $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 2.46 (tdt, *J* = 1.4, 6.5, 7.2 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 5.09 (ddt, *J* = 1.4, 1.5, 10.3 Hz, 1H), 5.11 (ddt, *J* = 1.4, 1.5, 17.0 Hz, 1H), 5.79 (ddt, *J* = 6.5, 10.3, 17.0 Hz, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 29.06, 46.40, 117.06, 134.80, 173.26. HRMS (APCI, MeOH) calcd for $C_6H_{11}O_2^+$ $[M{-}HCl{+}MeOH{+}H]^+$: 115.07590, found: 115.07600.



***7***

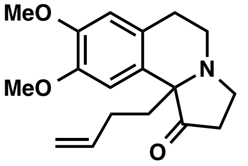
**1-(But-3-en-1-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline.** [22] This compound was literature-known and synthesized using the following procedure: 2-(3,4-Dimethoxyphenyl)ethylamine (15.2 mL, 90.0 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (90 mL) and $NEt_3$ (18.9 mL, 135.0 mmol, 1.5 equiv). Pent-4-enoyl chloride **6** (10.680 g, 90.0 mmol, 1.0 equiv) was added dropwise at 0ºC and after continued stirring at 0ºC for 30 min the mixture was allowed to warm to room temperature (23ºC). After additional stirring for 20 h, the mixture was concentrated and the residue was suspended in EtOAc (300 mL). The solution was transferred into a separation funnel and washed with aq HCl (1 M, 300 mL) followed by brine (100 mL). The organic layer was separated, dried ($Na_2SO_4$) and concentrated to receive pure *N*-(3,4-Dimethoxyphenethyl)pent-4-enamide as a brown oil (23.730 g, 90.0 mmol) in quantitative yield. The nmr data matched the previously reported values. $^1$H-NMR (300.1 MHz, $CDCl_3$): δ = 2.21 (t, *J* = 7.2 Hz, 2H), 2.31-2.38 (m, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 3.48 (td, *J* = 6.2, 7.0 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.93-5.05 (m, 2H), 5.58 (br, *N*H), 5.77 (ddt, *J* = 6.6, 10.3, 16.8 Hz, 1H), 6.69-6.72 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 1H).

*N*-(3,4-Dimethoxyphenethyl)pent-4-enamide (23.730 g, 90.0 mmol) was dissolved in MeCN (550 mL). $POCl_3$ (63.5 mL, 666.7 mmol, 7.4 equiv) was added at room temperature (23°C) and the resulting mixture was heated to 95°C for 4 h. After cooling down to room temperature the solvent was removed in vacuum. The residue was added carefully to an ice-cold aqueous saturated $K_2CO_3$ solution (500 mL, resulting pH=10-14) and the aqueous solution was extracted with $CH_2Cl_2$ (5 × 200 mL). The combined organic layers were dried ($K_2CO_3$) and concentrated to give the crude 1-(But-3-en-1-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline. The pure title compound was received after extraction as a brown oil (19.451 g, 79.3 mmol) in 88% yield. The Dihydroisoquinoline **7** was directly employed in the titanium-catalysis without purification. The nmr data almost matched the previously reported values. $^1$H-NMR (400.1 MHz, $CDCl_3$/TMS): δ = 2.35-2.42 (m, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.78 (tt, *J* = 1.3, 7.8 Hz, 2H), 3.59 (tt, *J* = 1.4, 7.5 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.93 (ddt, *J* = 1.3, 1.9, 10.1 Hz, 1H), 5.01 (ddt, *J* = 1.7, 1.9, 17.1 Hz, 1H), 5.87 (ddt, *J* = 6.7, 10.1, 17.1 Hz, 1H), 6.65 (s, 1H), 6.95 (s, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$/TMS): δ = 25.91, 31.16, 35.16, 46.96, 55.96, 56.31, 108.90, 110.48, 114.85, 121.97, 131.63, 138.06, 147.54, 150.85, 165.85. MS (EI, 70 eV): m/z (%) = 213.1 (100), 185.1 (57), 180.0 (14), 168.1 (13), 152.1 (27), 141.0 (12), 139.1 (19), 128.1 (19), 115.1 (18), 102.1 (9), 97.1 (7), 89.1 (9), 77.1 (20), 63.3 (9), 58.3 (5), 51.4 (8), 45.6 (7). HRMS (APCI, corona) calcd for $C_{15}H_{20}O_2N^+$ $[M{+}H]^+$: 246.14886, found: 246.14890. IR (ATR): $\nu$ [cm$^{-1}$] = 3004 ,2937, 2835, 2254, 2191, 1625, 1605, 1572, 1513, 1464, 1406, 1359, 1321, 1267, 1231, 1207, 1144, 1074, 1027, 959, 907, 860, 809, 725.



***8***

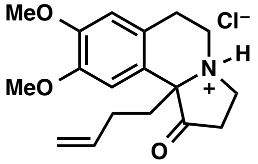
**1-(1-(But-3-en-1-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-hydroxypropan-1-one (8)**. A flame-dried Schlenk-tube was charged under argon with a magnetic stirrer bar, $Cp_2Ti(OPh)_2$ (18.2 mg, 0.05 mmol, 10 mol %), $Et_3N{\bullet}HCl$ (34.4 mg, 0.25 mmol, 0.5 equiv) and zinc dust (65.4 mg, 1.0 mmol, 2.0 equiv). The reaction vessel was evacuated and back-filled with argon three times. Absolute THF (0.2 mL) was added and the mixture was stirred for 2 min. Under a positive pressure of argon, TMSCl (95 µL, 0.75 mmol, 1.5 equiv), 3-Trimethylsiloxypropionitrile (**2l**) (107.5 mg, 0.75 mmol, 1.5 equiv) were added successively in this order followed by addition of a solution of **7** (122.7 mg, 0.5 mmol) dissolved in THF (0.2 mL) via syringe. The syringe was rinsed with THF (0.1 mL) and the liquid was added to the reaction mixture (total volume of THF: 0.5 mL). The vessel was sealed with a greased glass stopper and the mixture was stirred at 35ºC for 24 h. The reaction was allowed to cool to room temperature and the mixture was transferred with $CH_2Cl_2$ (5–8 mL) into a separation funnel containing ice-cold $Et_2O$ (100 mL) and aqueous HCl (1 M, 50 mL). The mixture was shaken until both layers became clear and the aqueous layer was separated. The organic layer was extracted with additional aq HCl (1 M, 2 × 25 mL). The combined aqueous layers were carefully saturated with solid $NaHCO_3$ after which 10–20 mg of solid NaOH were added. The aqueous layer was extracted with EtOAc (at least 3 × 50 mL, TLC control of the aqueous phase) and the combined EtOAc layer was dried ($Na_2SO_4$), filtered and concentrated to give the crude product. Purification by flash chromatography ($CH_2Cl_2$:AcOEt , 1:1, $R_f$=0.214) gave the title compound as a pale-yellow oil in 72% yield (114.9 mg, 0.36 mmol). $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.81-1.94 (m, 1H), 2.02-2.14 (m, 3H), 2.53 (ddd, *J* = 4.4, 5.3, 16.4 Hz, 1H), 2.67-2.84 (m, 5H), 3.06 (ddd, *J* = 4.9, 6.2, 12.0 Hz, 1H), 3.13 (ddd, *J* = 4.5, 7.2, 12.0 Hz, 1H), 3.66-3.72 (m, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 4.93 (ddt, J = 1.3, 1.6, 10.1, 1H), 4.99 (ddt, *J* = 1.6, 1.6, 17.2 Hz, 1H), 5.77 (ddt, *J* = 6.3, 10.1, 17.2 Hz, 1H), 6.54 (s, 1H), 6.59 (s, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 28.57, 29.67, 37.29, 40.11, 41.23, 55.92, 56.26, 58.87, 67.75, 109.75, 112.08, 115.01, 126.50, 128.45, 138.21, 147.83, 148.34, 212.55. MS (EI, 70 eV): m/z (%) = 319.1 $[M]^+$ (<1), 246.1 $[M–C_3H_5O_2]^+$ (100), 244.1 (18), 230.1 (10), 205.1 (5), 204.1 (5), 190.0 (5). HRMS (APCI, MeOH) calcd for $C_{18}H_{26}O_4N^+$ $[M+H]^+$: 320.18618, found: 320.18610. IR (ATR): $\nu$ [cm$^{-1}$] = 3019, 2937, 1699, 1640, 1610, 1515, 1465, 1403, 1347, 1327, 1260, 1215, 1134, 1050, 910, 862, 746.



***S4***

**10b-(But-3-en-1-yl)-8,9-dimethoxy-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(5*H*)-one (S4)**.[23]

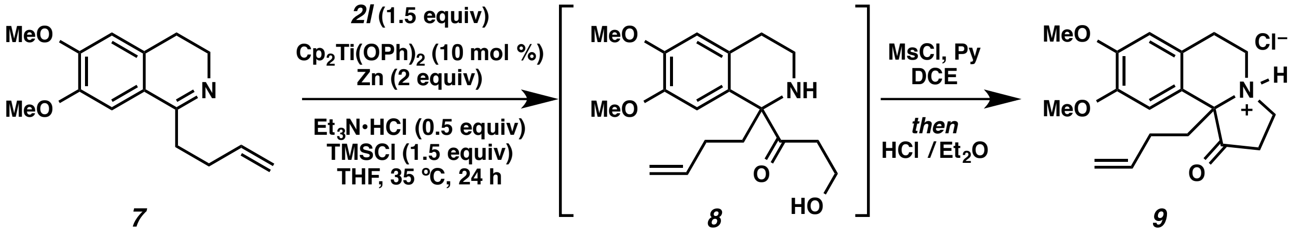
1-(1-(But-3-en-1-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-hydroxypropan-1-one (**8**, 95.8 mg, 0.30 mmol) was dissolved in 1,2-dichloroethane (3.0 mL) and added dropwise at −10°C to a solution of methanesulfonyl chloride (36 µL, 0.465 mmol, 1.55 equiv) in pyridine (117 µL, 1.450 mmol, 4.8 equiv). After continued stirring at −10°C for 30 min, the mixture was allowed to warm to room temperature (23ºC). After additional stirring for 2 h, the mixture was heated to 50°C for 16 h. The reaction was allowed to cool to room temperature and the mixture was transferred with $CH_2Cl_2$ (5–8 mL) into a separation funnel containing ice-cold $Et_2O$ (100 mL) and aqueous HCl (1 M, 50 mL). The mixture was shaken until both layers became clear and the aqueous layer was separated. The organic layer was extracted with additional aq HCl (1 M, 2 × 25 mL). The combined aqueous layers were carefully saturated with solid $NaHCO_3$ after which 10–20 mg of solid NaOH were added. The aqueous layer was extracted with $CH_2Cl_2$ (at least 3 × 50 mL, TLC control of the aqueous phase is advised) and the combined EtOAc layer was dried ($Na_2SO_4$), filtered and concentrated to give the crude product. The remaining pale yellow oil was dried under high vacuum at 50°C. Analytically pure product **S4** was received in 99% yield (90.2 mg, 0.299 mmol) and was found sufficiently pure to be carried on to the next step. However, if desired it can be purified by flash chromatography ($CH_2Cl_2$:AcOEt, 15:1, $R_f$=0.3125). The nmr data matched the previously reported values. $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 1.74-1.81 (m, 1H), 1.82-1.91 (m, 1H), 2.09 (ddd, *J* = 4.3, 11.5, 13.3 Hz, 1H), 2.16-2.25 (m, 1H), 2.30-2.43 (m, 3H), 2.99-3.19 (m, 4H), 3.28 (ddd, *J* = 5.1, 12.6, 14.1 Hz, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 4.89 (ddt, *J* = 1.2, 2.2, 10.2 Hz, 1H), 4.97 (ddt, *J* = 1.5, 2.2, 16.9 Hz, 1H), 5.76 (ddt, *J* = 6.3, 10.1, 16.9 Hz, 1H), 6.50 (s, 1H), 6.95 (s, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 21.16, 29.33, 36.47, 38.15, 41.65, 43.73, 55.87, 56.02, 68.51, 109.93, 111.78, 114.48, 125.91, 126.01, 138.58, 147.73, 148.13, 216.00. MS (EI, 70 eV): m/z (%) = 301.1 $[M]^+$ (9), 273.2 $[M{-}CO]^+$ (32), 272.2 (19), 258.2 (14), 246.1 (100), 244.1 (49), 230.1 (22), 216.1 (4), 214.1 (5), 202.1 (11), 200.1 (4), 190.1 $[M{-}(C_4H_7{+}C_3H_4)]^+$ (7), 188.0 (7), 185.1 (5), 172.0 (6), 123.0 (5), 119.0 (8), 115.8 (4), 109.0 (24) 79.0 (7). HRMS (APCI, MeOH) calcd for $C_{18}H_{24}O_3N^+$ $[M{+}H]^+$: 302.17562, found: 302.17560. IR (ATR): $\nu$ [cm$^{-1}$] = 3055, 2935, 2849, 2360, 2340, 1747, 1640, 1608, 1510, 1465, 1443, 1401, 1324, 1264, 1225, 1211, 1178, 1120, 1104, 1057, 1004, 967, 909, 869, 778, 731, 703.



***9***

**10b-(but-3-en-1-yl)-8,9-dimethoxy-1-oxo-2,3,4,5,6,10b-hexahydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium chloride (9).** 10b-(But-3-en-1-yl)-8,9-dimethoxy-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(5*H*)-one (**S4**, 60.3 mg, 0.200 mmol) was dissolved in $CHCl_3$ (2 mL) and HCl in $Et_2O$ (2.0 M, 150 µL, 0.300 mmol, 1.5 equiv) was added at 0°C dropwise. The solvent was removed carefully and the remaining solid was dried under high vacuum at 50°C. The analytical pure title compound was received in 99% yield (67.5 mg, 0.200 mmol) as a colorless highly hygroscopic solid (m.p. 58°C). $^1$H-NMR (400.1 MHz, $CDCl_3$): δ = 2.09-2.26 (m, 3H), 2.42-2.52 (m, 1H), 2.60-2.68 (m, 1H), 2.96-3.17 (m, 3H), 3.35-3.43 (m, 1H), 3.60-3.68 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.96-4.06 (m, 1H), 4.88 (dd, *J* = 1.4, 10.4 Hz, 1H), 4.96 (dd, J = 1.4, 17.2 Hz, 1H), 5.57-5.67 (m, 1H), 6.58 (s, 1H), 6.84 (s, 1H), 13.56 (br s, *N*H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): δ = 21.67, 28.29, 33.42, 36.41, 43.81, 45.31, 56.01, 56.13, 70.98, 108.71, 111.31, 116.12, 118.13, 122.80, 135.97, 149.09, 149.79, 205.68. MS (EI, 70 eV): m/z (%) = 302.2 $[M{-}Cl]^+$ (1), 301.1 $[M{-}HCl]^+$ (6), 273.2 $[M{-}(HCl{+}CO)]^+$ (31), 272.2 (17), 258.2 (15), 246.1 (>100), 244.1 (53), 232.1 (10), 230.1 (24), 216.1 (4), 214.1 (5), 202.1 (11), 190.1 $[M{-}(HCl{+}C_4H_7{+}C_3H_4)]^+$ (7), 188.0 (7), 185.1 (4), 172.0 (5). HRMS (APCI, MeOH) calcd for $C_{18}H_{24}O_3N^+$ $[M{-}Cl]^+$: 302.17562, found: 302.17530. IR (ATR): $\nu$ [cm$^{-1}$] = 2254, 1766, 1611, 1520, 1465, 1265, 1232, 1162, 113, 1068, 1013, 905, 726.

## Sequence from 7 to 9 on a 50.0 mmol-scale

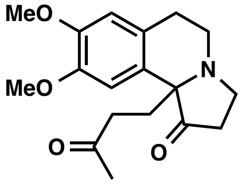


***7*** ***8*** ***9***

***(50.0 mmol)*** ***(31.5 mmol, 63%)***

A flame-dried 250 mL Schlenk-flask was charged under argon with a magnetic stirrer bar, $Cp_2Ti(OPh)_2$ (1.8213 g, 5.0 mmol, 10 mol %), $Et_3N{\bullet}HCl$ (3.410 g, 25.0 mmol, 0.5 equiv) and zinc dust (6.540 g, 100.0 mmol, 2.0 equiv). The reaction vessel was evacuated and back-filled with argon three times. Absolute THF (20 mL) was added and the mixture was stirred for 2 min. Under a positive pressure of argon, TMSCl (9.50 mL, 75.0 mmol, 1.5 equiv), 3-Trimethylsiloxypropionitrile (**2l**) (10.75 g, 75.0 mmol, 1.5 equiv) were added successively in this order followed by addition of a solution of **7** (12.266 g, 50.0 mmol) dissolved in THF (20 mL) via syringe. The syringe was rinsed with THF (10 mL) and the liquid was added to the reaction mixture (total volume of THF: 50 mL). The vessel was sealed with a greased glass stopper and the mixture was stirred at 35 ºC for 24 h. The mixture was filtered and the filter cake was rinsed with $CH_2Cl_2$ (2 × 100 mL) and aq HCl (1 M, 750 mL). The organic solvent ($CH_2Cl_2$ and THF) of the combined mother liquors were removed and the remaining aqueous layer was washed with $Et_2O$ (3 × 300 mL) and saturated carefully with solid $NaHCO_3$. The basic aqueous layer was then extracted with EtOAc (10 ×200 mL) and the combined EtOAc layer was dried ($Na_2SO_4$), filtered and concentrated to give crude **8** as a brown oil (16.540 g)[24] that was employed in the next step without further purification.

The crude material was dissolved in 1,2-dichloroethane (100 mL) and added dropwise at −10 °C to a solution of methanesulfonyl chloride (4.4 mL, 60.0 mmol, 1.2 equiv) in pyridine (17.4 mL, 215.0 mmol, 4.3 equiv). After continued stirring at −10 °C for 30 min, the mixture was allowed to warm to room temperature (23 ºC). After additional stirring for 2 h, the mixture was heated to 50 °C for 16 h. After cooling down to room temperature (23 ºC) the solvent was removed in vacuum. The residue was dissolved in aq HCl (1 M, 500 mL) the aqueous layer was washed with $Et_2O$ (3 × 300 mL) was carefully saturated with solid $NaHCO_3$. The aqueous layer was extracted with EtOAc (6 × 150 mL) and the combined EtOAc layer was dried ($Na_2SO_4$), filtered and concentrated. The remaining oil was dried under high vacuum at 50°C to give pure **S4** in 63% yield over two steps (9.4935 g, 31.5 mmol) as a brown oil. The product was redissolved in $CHCl_3$ (300 mL) and HCl in $Et_2O$ (2.0 M, 25.0 mL, 50.0 mmol, 1.58 equiv.) was added at 0°C dropwise, which led to the precipitation of the hydrochloride. The solvent was carefully decanted and the remaining solid was dried under high vacuum at 50°C. The title compound **9** was received in 63% yield over two steps (10.64 g, 31.5 mmol) as a brown solid, which did not require further purification and could be directly employed in the Wacker-oxidation.

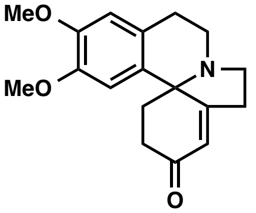


***S5***

**8,9-dimethoxy-10b-(3-oxobutyl)-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(5*H*)-one.**[23] This compound was literature-known and synthesized using the following procedure: Crude 10b-(but-3-en-1-yl)-8,9-dimethoxy-1-oxo-2,3,4,5,6,10b-hexahydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium chloride (**9**, 1.689 g, 5.0 mmol) was dissolved in MeCN:$H_2O$ (4:1, 100 mL). After 15 min stirring at room temperature (23 °C) 1,4-benzoquinone (594.5 mg, 5.5 mmol, 1.1 equiv) and $Pd(MeCN)_2Cl_2$ (129.7 mg, 0.5 mmol, 10 mol %) was added and the resulting mixture was heated to 80°C for 24 h. The reaction was allowed to cool to room temperature (23 °C) and 4/5 of the solvent was removed under reduced pressure. $H_2O$ (250 mL) was added and the aqueous layer was washed with $Et_2O$ (5 × 100 mL). The combined $Et_2O$ layers were extracted with $H_2O$ (2 × 100 mL) and the combined aqueous layer was filtered to remove unsoluble material. The aqueous layer containing the protonated product was saturated with $Na_2CO_3$ and then extracted with $CH_2Cl_2$ (10 × 50 mL). The combined $CH_2Cl_2$ layers were dried ($Na_2SO_4$), filtered and concentrated to give the crude product. After purification by flash chromatography (cyclohexane/EtOAc, 1:2; $R_f$ = 0.289) product **S5** was received as a brown oil in 78% yield (1.238 g, 3.9 mmol). The nmr data matched the previously reported values. $^1$H-NMR (400.1 MHz, $CDCl_3$): $\delta$ = 2.12 (s, 3H), 2.12-2.30 (m, 3H), 2.35-2.60 (m, 4H), 2.97-3.28 (m, 5H), 3.83 (s, 3H), 3.83 (s, 3H), 6.51 (s, 1H), 6.90 (s, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$): $\delta$ = 21.23, 30.41, 32.71, 36.42, 39.37, 41.41, 43.62, 55.92, 56.04, 68.26, 109.71, 111.74, 125.10, 126.11, 147.74, 148.27, 208.18, 216.07. MS (EI, 70 eV): m/z (%) = 317.1 $[M]^+$ (1), 289.2 $[M{-}CO]^+$ (12), 246.1 (100), 244.1 (4), 230.1 (9), 202.0 (6). HRMS (APCI, MeOH) calcd for $C_{18}H_{24}O_4N^+$ $[M+H]^+$: 318.16998, found: 318.17030. IR (ATR): $\nu$ [cm$^{-1}$] = 2936, 2850, 2254, 1746, 1711, 1608, 1510, 1465, 1442, 1401, 1324, 1254, 1226, 1211, 1189, 1120, 1106, 1051, 1005, 904, 779, 724.

**Reaction with a stoichiometric amount of palladium:**

10b-(but-3-en-1-yl)-8,9-dimethoxy-1-oxo-2,3,4,5,6,10b-hexahydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium chloride (**9**, 67.6 mg, 0.2 mmol) was dissolved in MeCN:$H_2O$ (7:1, 1.0 mL). After 15 min stirring at room temperature (23°C) 1,4-benzoquinone (23.8 mg, 0.22 mmol, 1.1 equiv) and $Pd(MeCN)_2Cl_2$ (51.9 mg, 0.2 mmol, 100 mol-%) was added and the resulting mixture was heated to 70°C for 24 h. The reaction was allowed to cool to room temperature and the mixture was transferred with $CH_2Cl_2$ (5–8 mL) into a separation funnel containing ice-cold $Et_2O$ (100 mL) and aqueous HCl (1 M, 50 mL). The mixture was shaken until both layers became clear and the aqueous layer was separated. The organic layer was extracted with additional aq HCl (1 M, 2 × 25 mL). The combined aqueous layers were carefully saturated with solid $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL) and the combined $CH_2Cl_2$ layer was dried ($Na_2SO_4$), filtered and concentrated to give the crude product. Purification by flash chromatography ($CH_2Cl_2$:AcOEt, 2:1, $R_f = 0.4595$) gave product **S5** as a pale-yellow oil in >99% yield (63.4 mg, 0.2 mmol).



***10***

**(*rac*)-3-Demethoxyerythratidinone.**[25] This compound was literature-known and synthesized using the following procedure: 8,9-dimethoxy-10b-(3-oxobutyl)-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(5*H*)-one **S5** (31.7 mg, 0.10 mmol) was dissolved in degassed MeOH (30 mL) and degassed aqueous KOH solution (20 w-%, 1.5 mL, 5.35 mmol, 53.5 equiv) was added at room temperature (23 °C). The resulting mixture was put into a preheated oil bath (120 °C) and was heated to reflux for 16 hours under argon atmosphere. After cooling down to room temperature the reaction mixture was concentrated and extracted with $CH_2Cl_2$ (50 mL). The organic layer was washed with brine (5 mL), dried over $Na_2SO_4$. and concentrated to give the crude product. After purification by flash chromatography ($CH_2Cl_2$/MeOH, 100:8; $R_f = 0.3488$) product **10** was received as a yellow oil in 57% yield (17.0 mg, 0.057 mmol). The nmr data matched the previously reported values. $^1$H-NMR (400.1 MHz, $CDCl_3$/TMS): $\delta$ = 2.19 (ddd, *J* = 5.6, 12.4, 14.1, 1H), 2.31 (ddd, *J* = 2.1, 5.6, 12.5 Hz, 1H), 2.38-2.62 (m, 4H), 2.68-2.89 (m, 2H), 3.00-3.11 (m, 2H), 3.23 (ddd, *J* = 1.3, 7.6, 14.5 Hz, 1H), 3.48 (ddd, *J* = 6.6, 11.7, 14.5 Hz, 1H), 3.74 (s, 3H), 3.85 (s, 3H), 6.10 (t, *J* = 1.9 Hz, 1H), 6.56 (s, 1H), 6.65 (s, 1H). $^{13}$C-NMR (100.6 MHz, $CDCl_3$/TMS): $\delta$ = 21.63, 28.82, 32.99, 36.29, 40.31, 45.96, 56.05, 56.21, 63.71, 110.59, 113.07, 123.28, 124.98, 125.86, 147.10, 148.60, 169.11, 199.53. MS (EI, 70 eV): m/z (%) = 299.1 $[M]^+$ (17), 271.2 $[M{-}CO]^+$ (100), 256.1 (58), 246.2 (10), 242.2 (45), 240.2 (14), 228.2 (21), 214.2 (14), 212.2 (17), 197.2 (23), 184.2 (10), 182.2 (5), 170.2 (4), 168.2 (4), 156.2 (4), 154.2 (4). HRMS (APCI, MeOH) calcd for $C_{18}H_{22}O_3N^+$ $[M+H]^+$: 300.15942, found: 300.15960 IR (ATR): $\nu$ [cm$^{-1}$] = 2936, 2851, 2253, 1664, 1608, 1510, 1465, 1422, 1400, 1331, 1291, 1253, 1230, 1207, 1165, 1150, 1107, 1048, 1037, 999, 904, 805, 783, 724, 648, 588, 576, 553, 532, 473.

## Synthesis of (±)-3-Demethoxyerythratidinone in a 5 mmol Scale Reaction

8,9-Dimethoxy-10b-(3-oxobutyl)-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(5*H*)-one **S5** (1.587 g, 5.0 mmol) was dissolved in degassed MeOH (300 mL) and degassed aqueous KOH solution (20 w-%, 65.0 mL, 267.5 mmol, 53.5 equiv) was added at room temperature (23 °C). The resulting mixture was put into a preheated oil bath (120 °C) and was heated to reflux for 16 hours under argon atmosphere. After cooling down to room temperature the reaction mixture was concentrated and extracted with $CH_2Cl_2$ (250 mL). The organic layer was washed with brine (10 mL), dried over $Na_2SO_4$. and concentrated to give the crude product. After purification by flash chromatography ($CH_2Cl_2$/MeOH, 100:8; $R_f = 0.3488$) product **10** was received as a brown oil in 54% yield (808.3 mg, 2.7 mmol).

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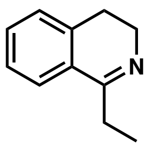
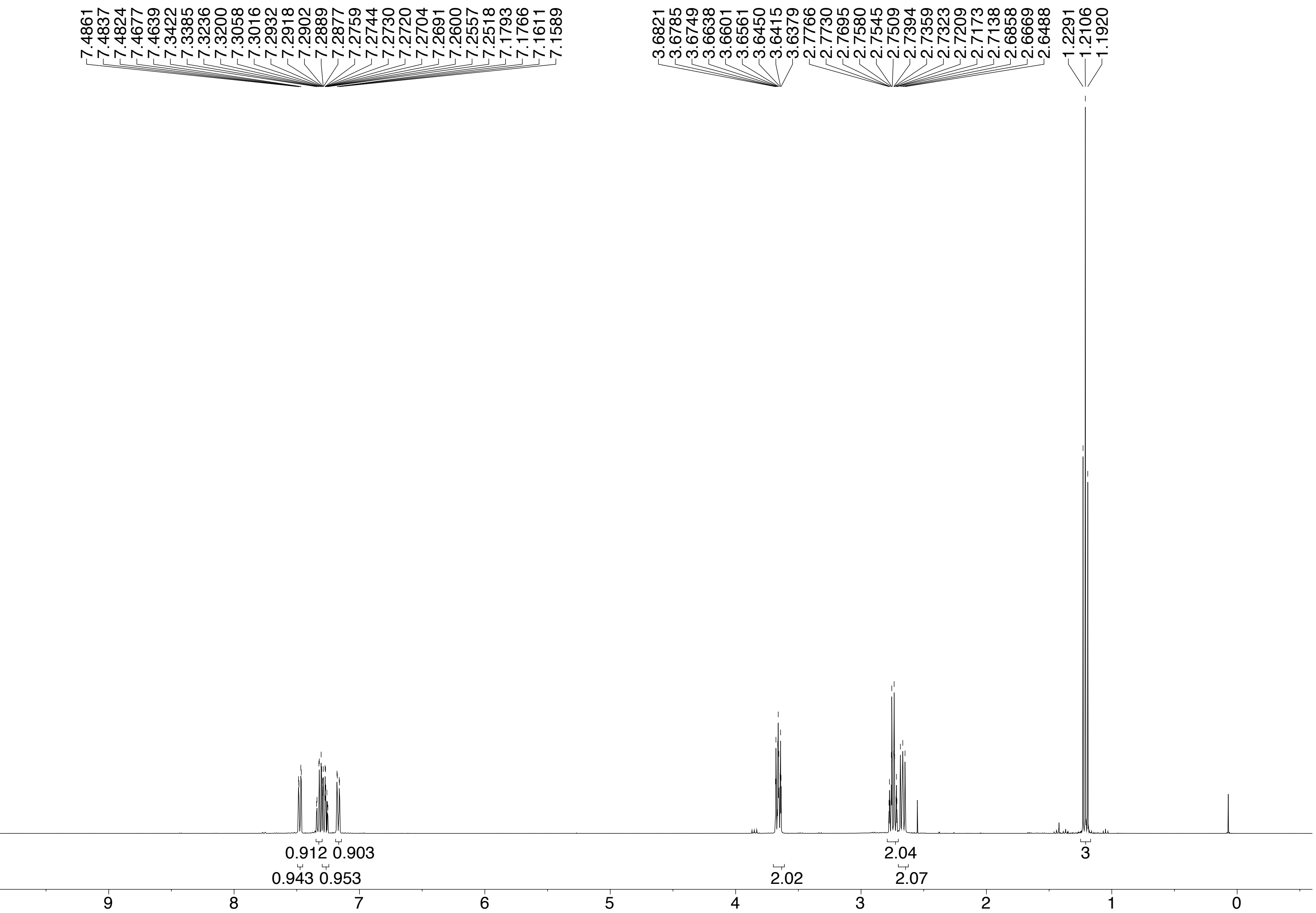
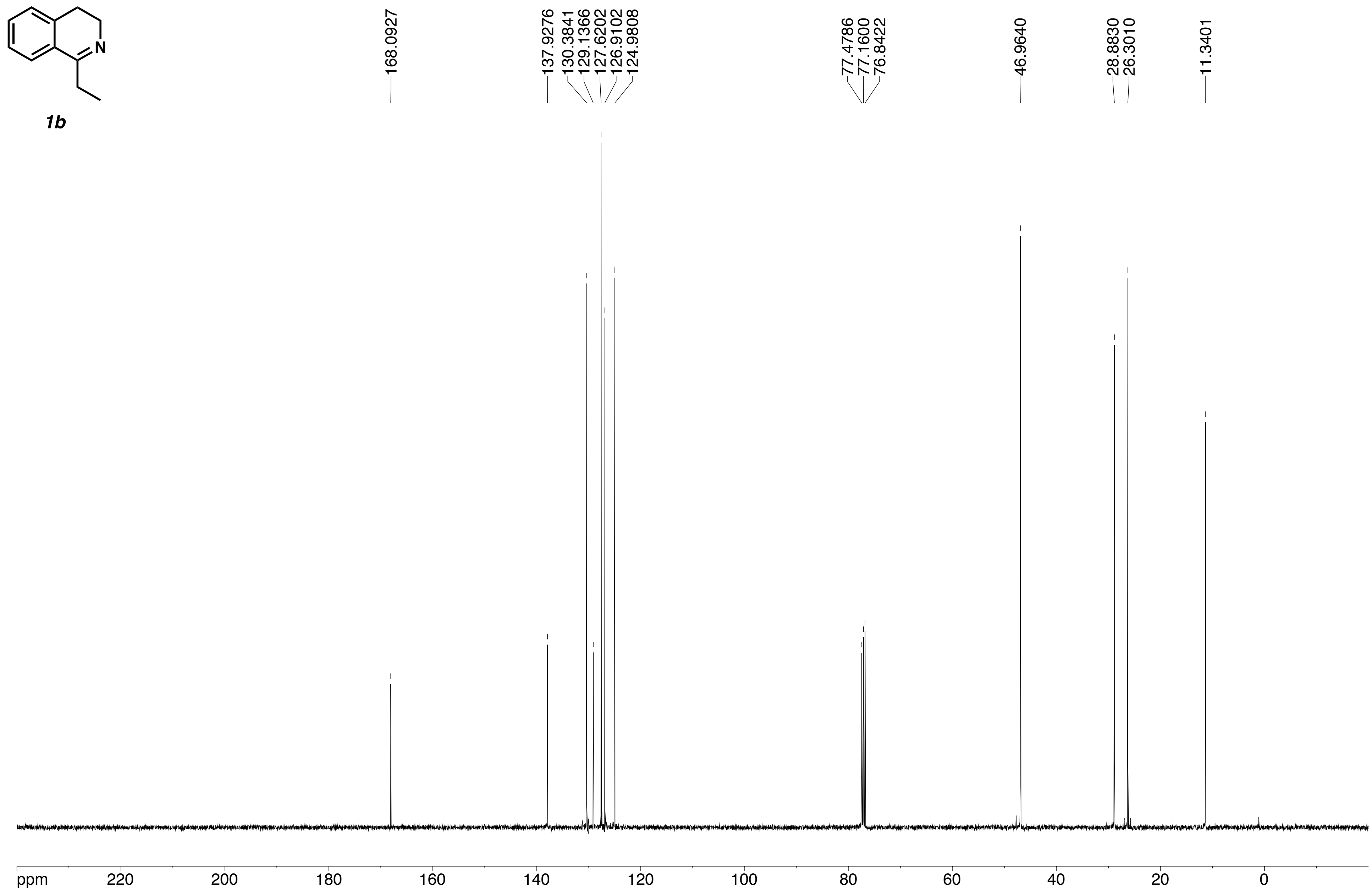
# $^1$H NMR and $^{13}$C NMR Spectra of New Compounds and the Total Synthesis of 10



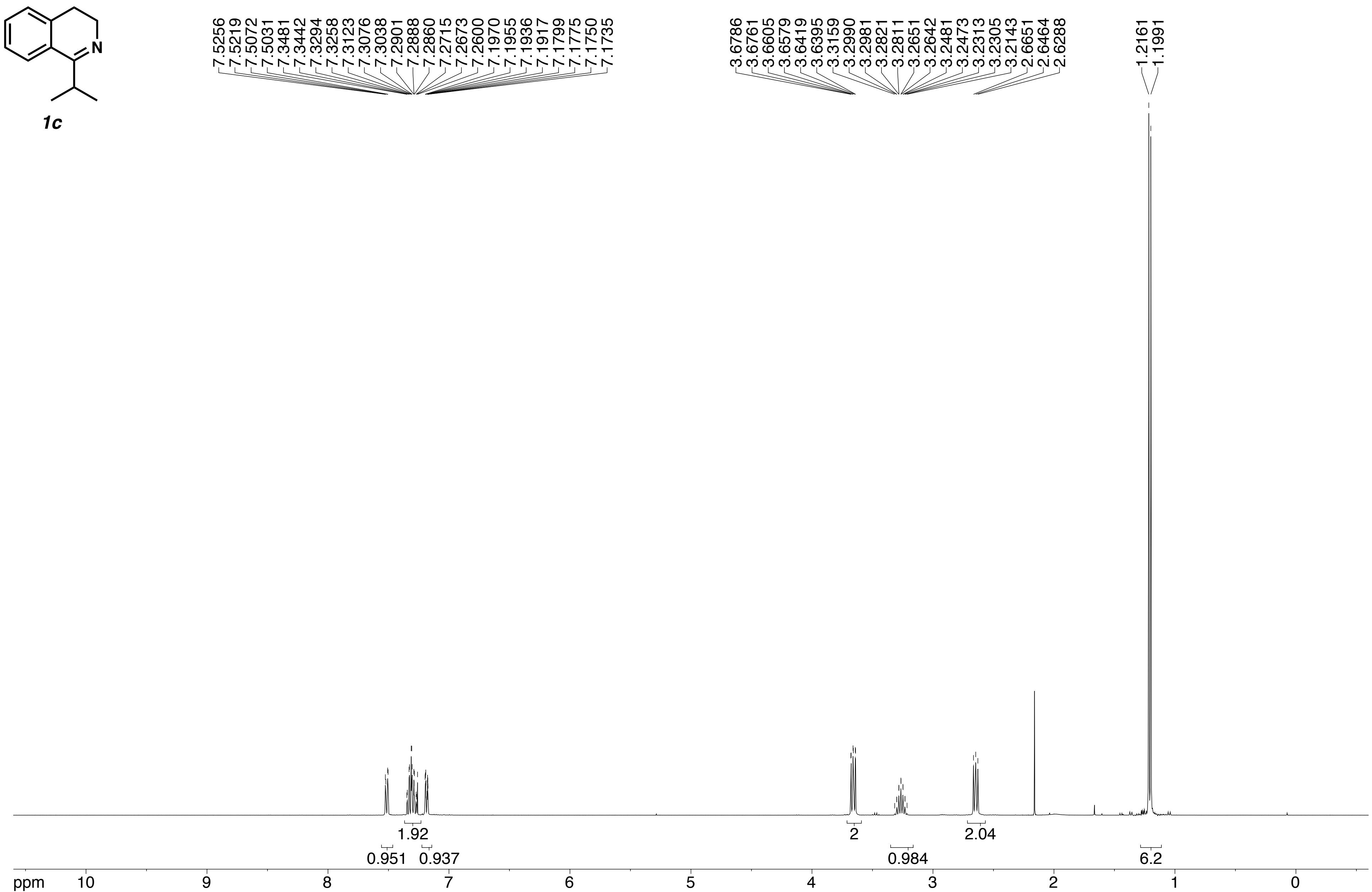
***1b***



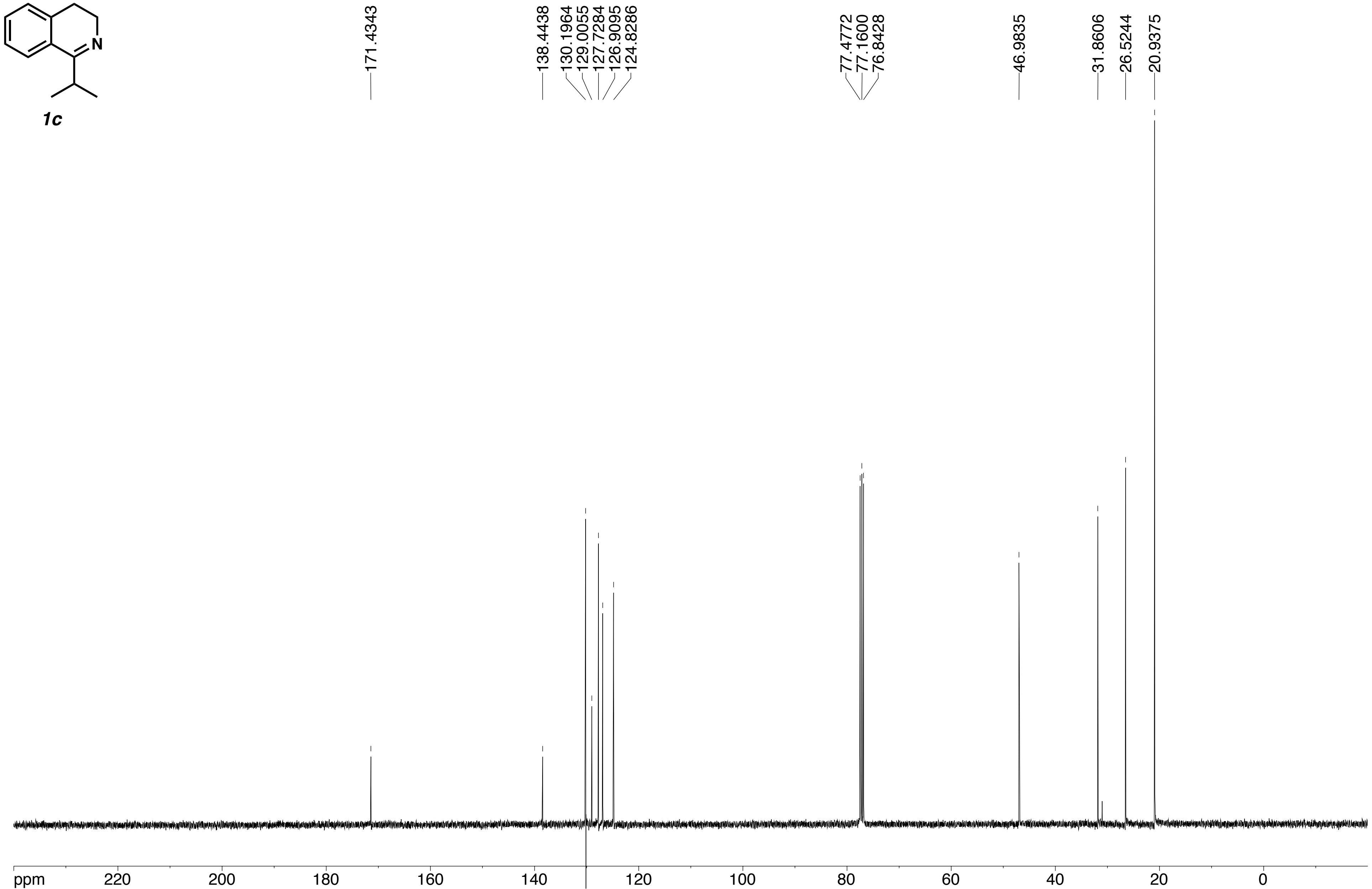
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **1b**.



$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **1b**.

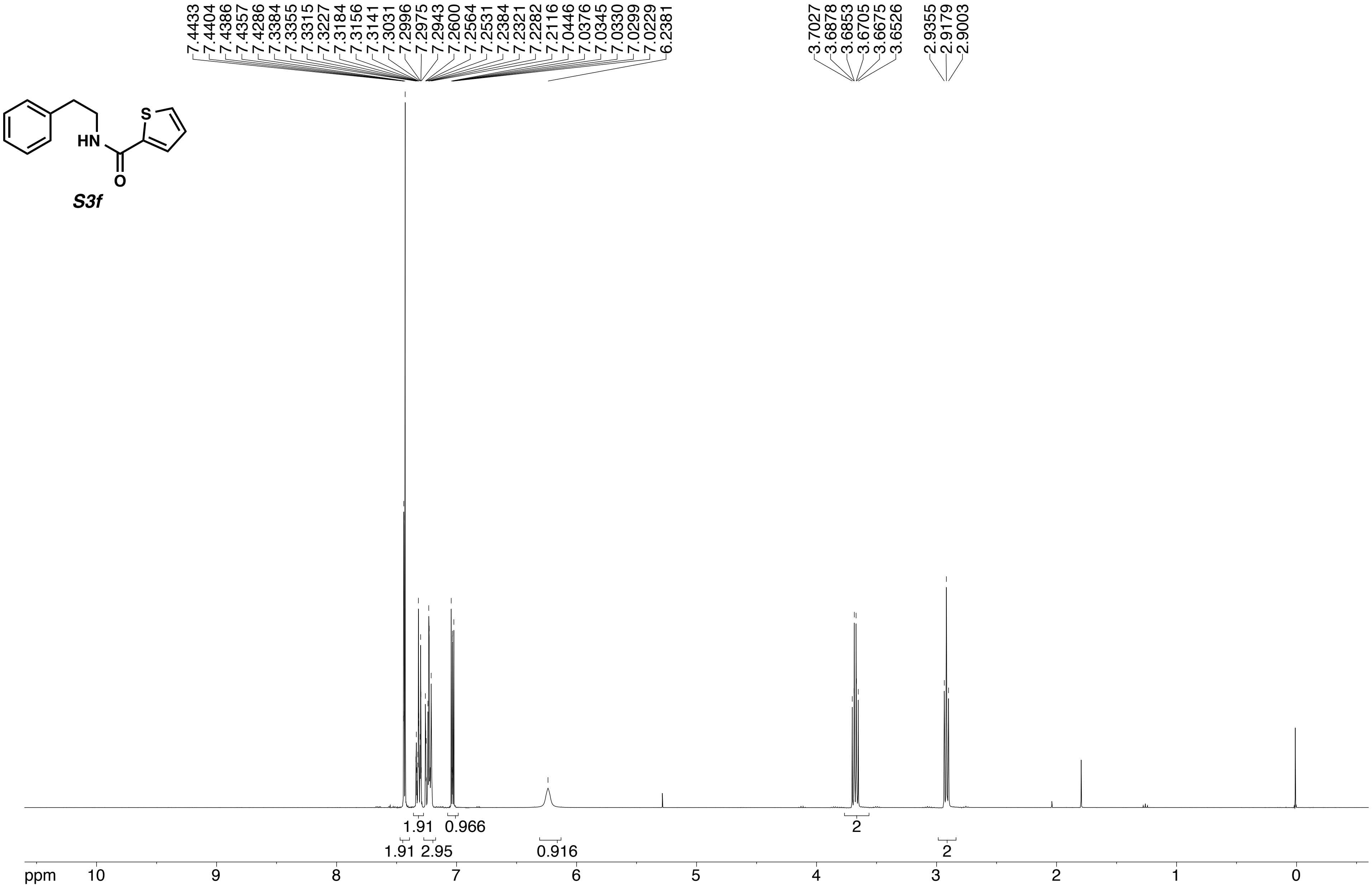


$^1$H NMR (400.1 MHz, $CDCl_3$) of compound **1c**.

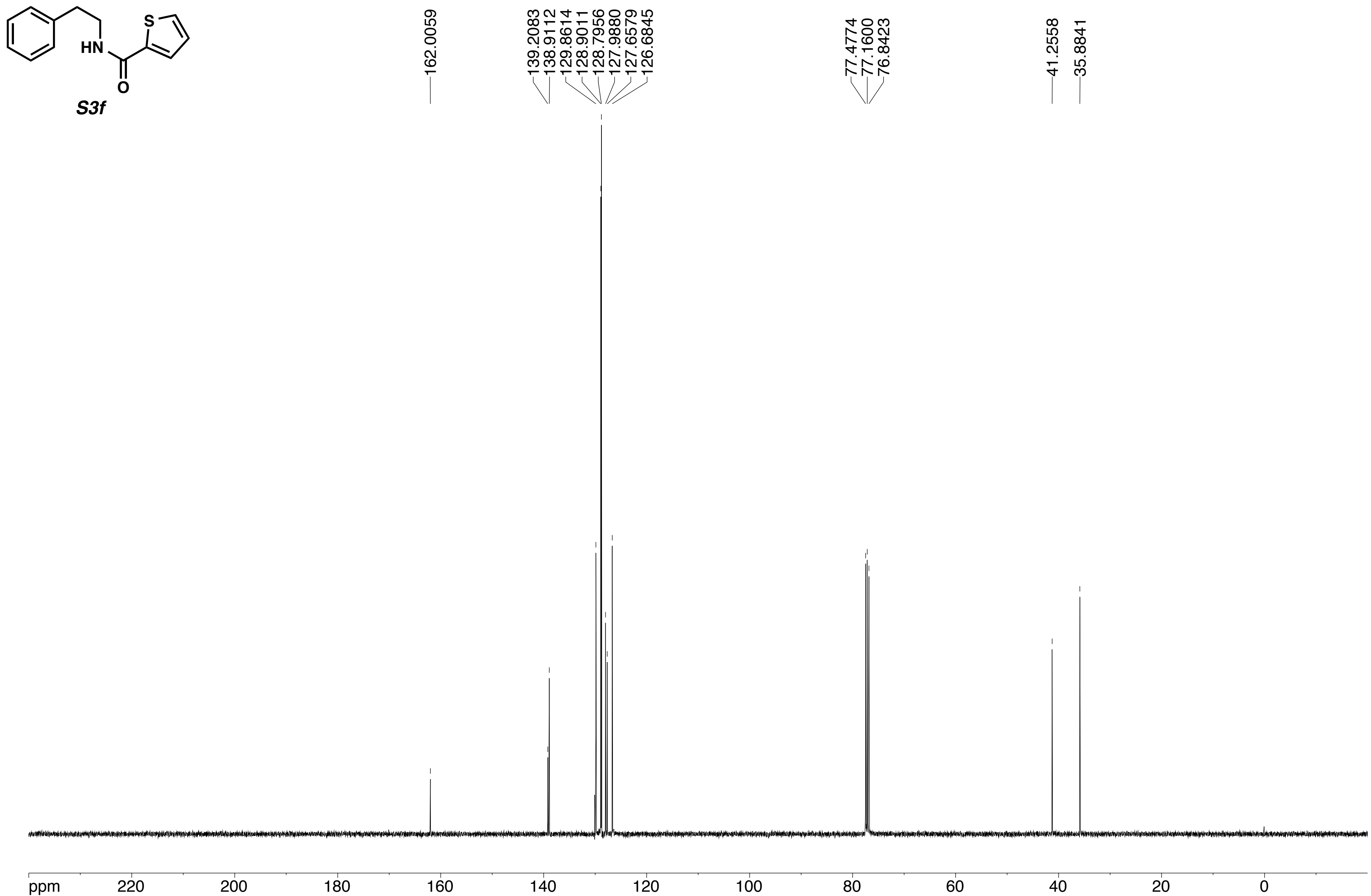


$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **1c**.

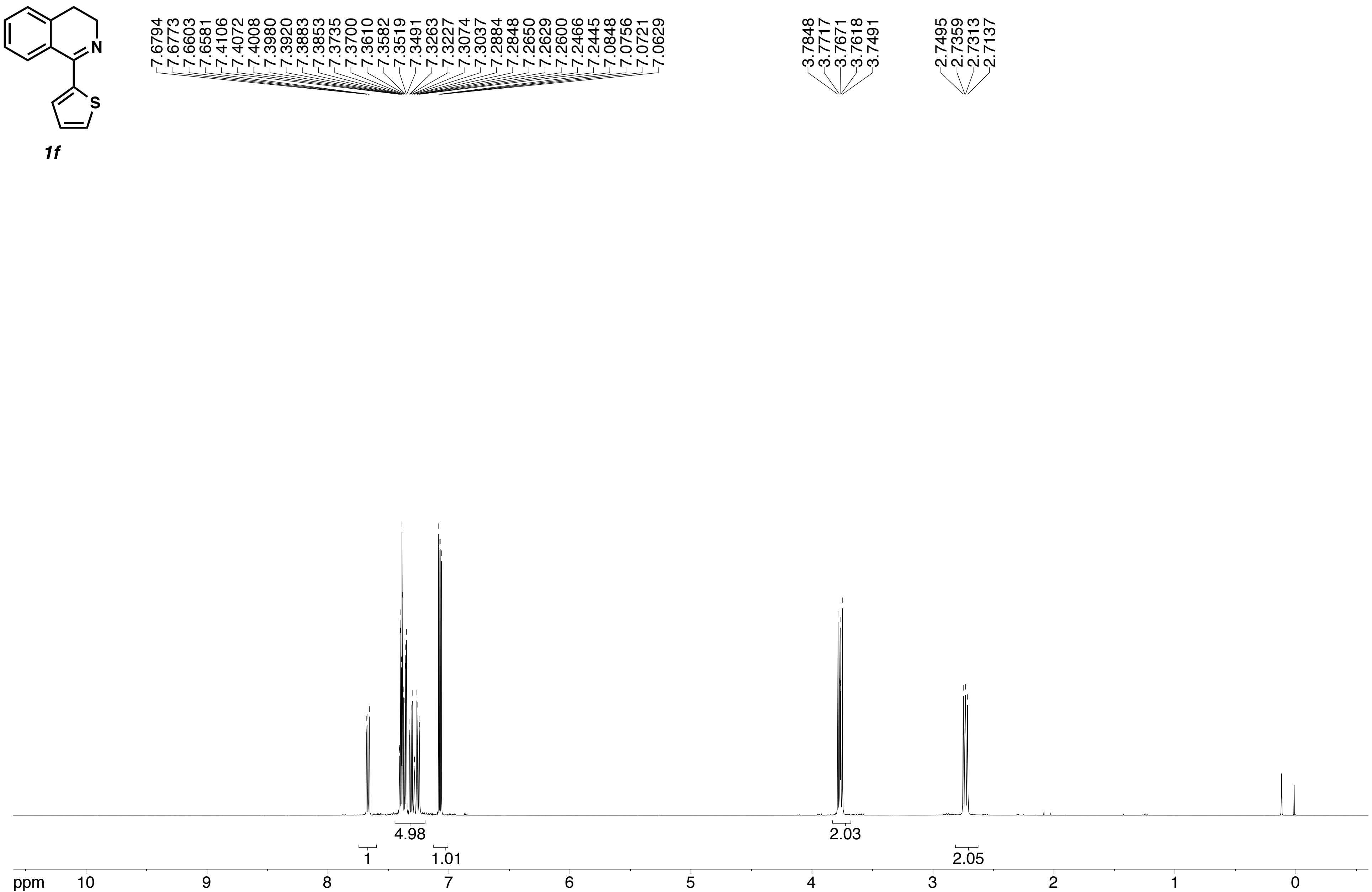
***S3f***



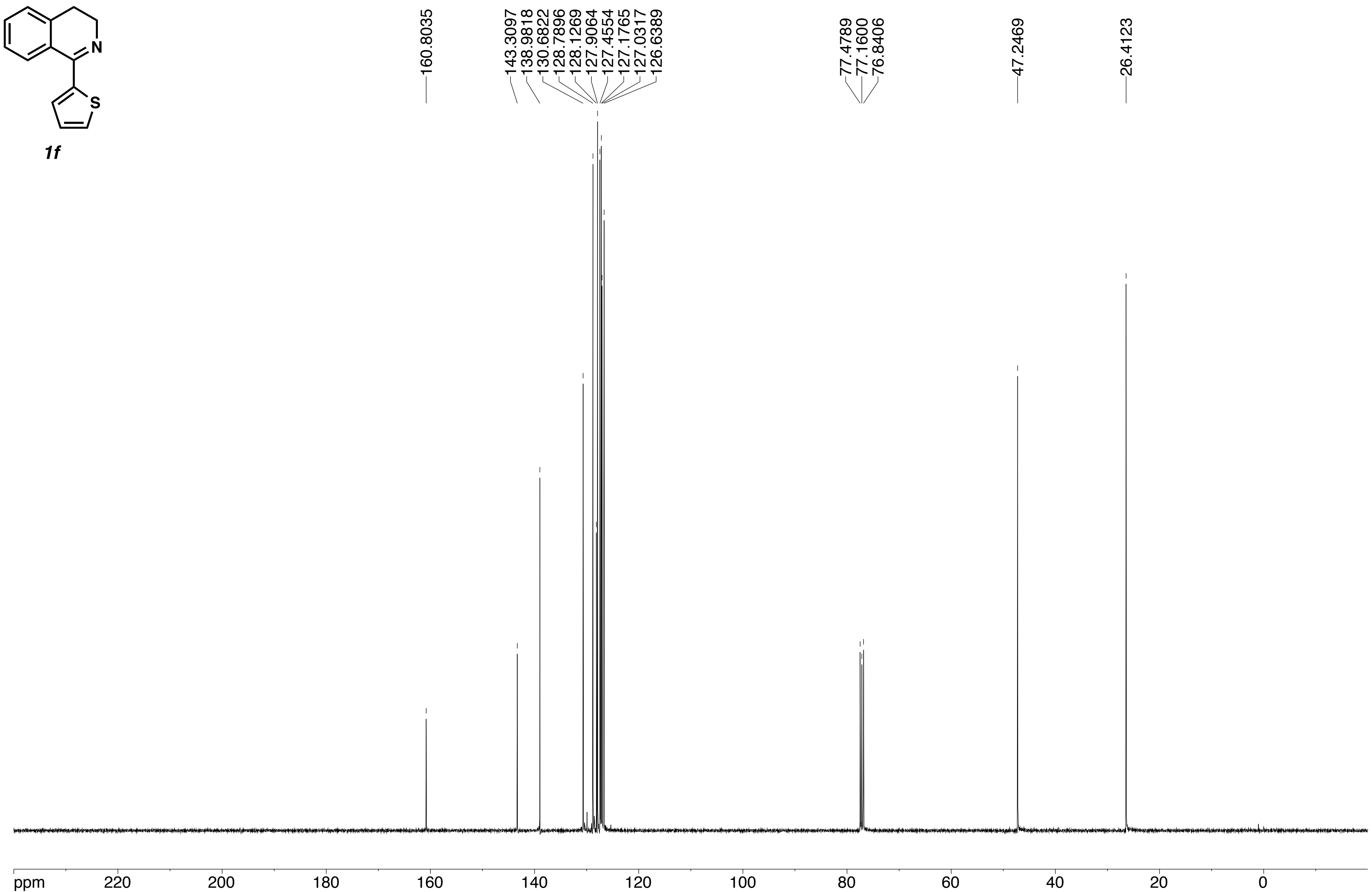
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **S3f**.



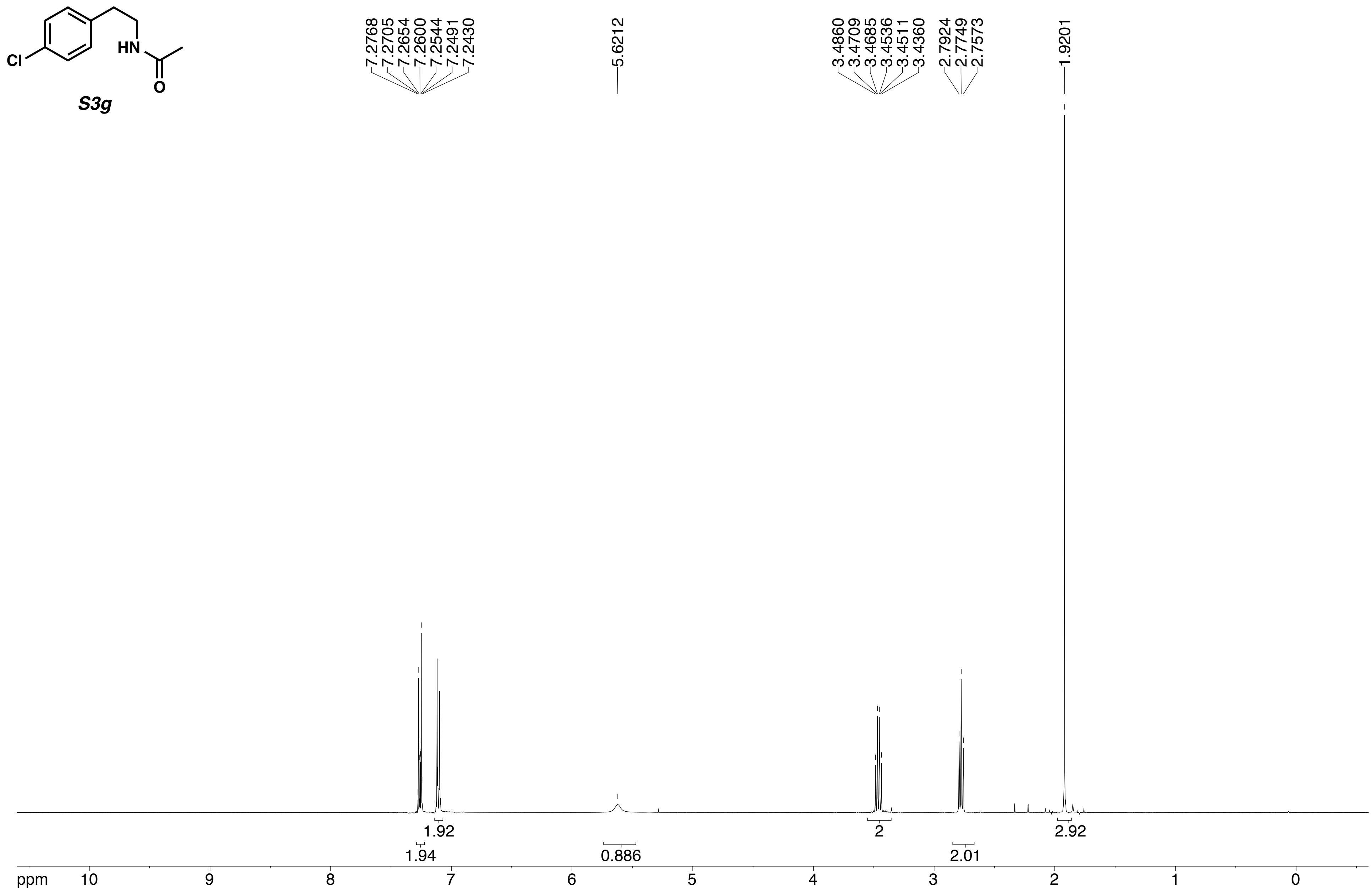
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **S3f**.



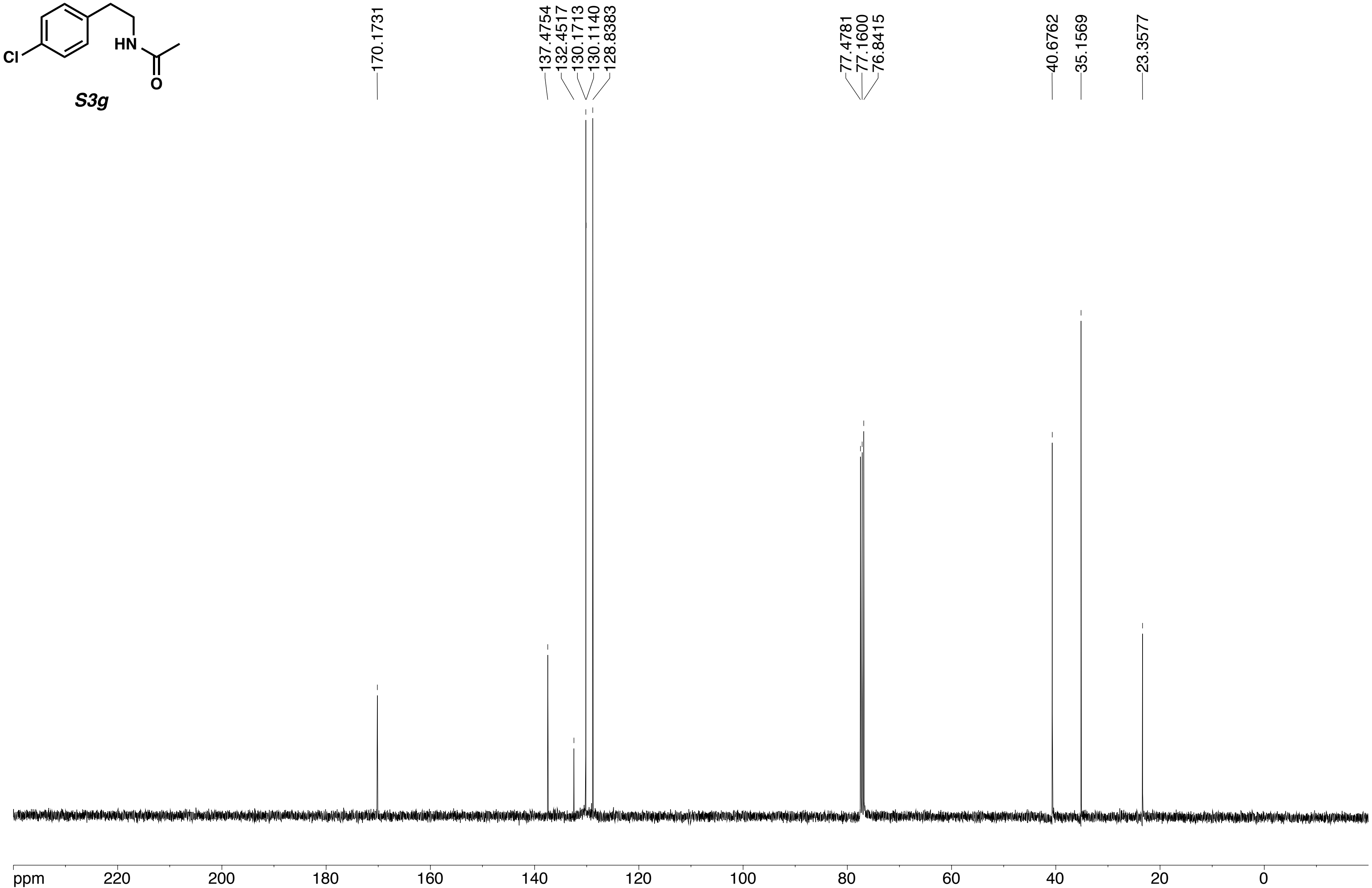
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **1f**.



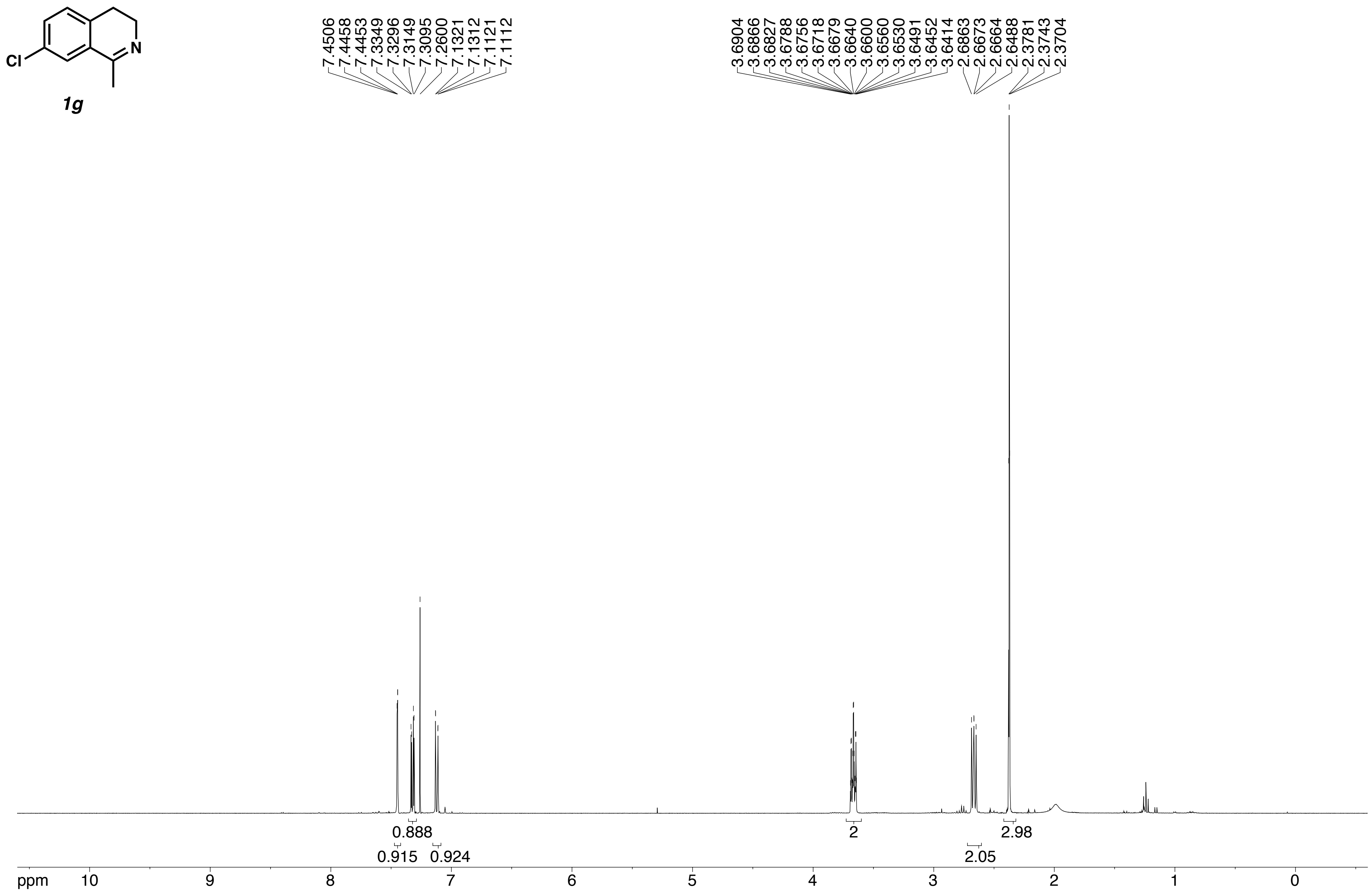
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **1f**.



$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **S3g**.

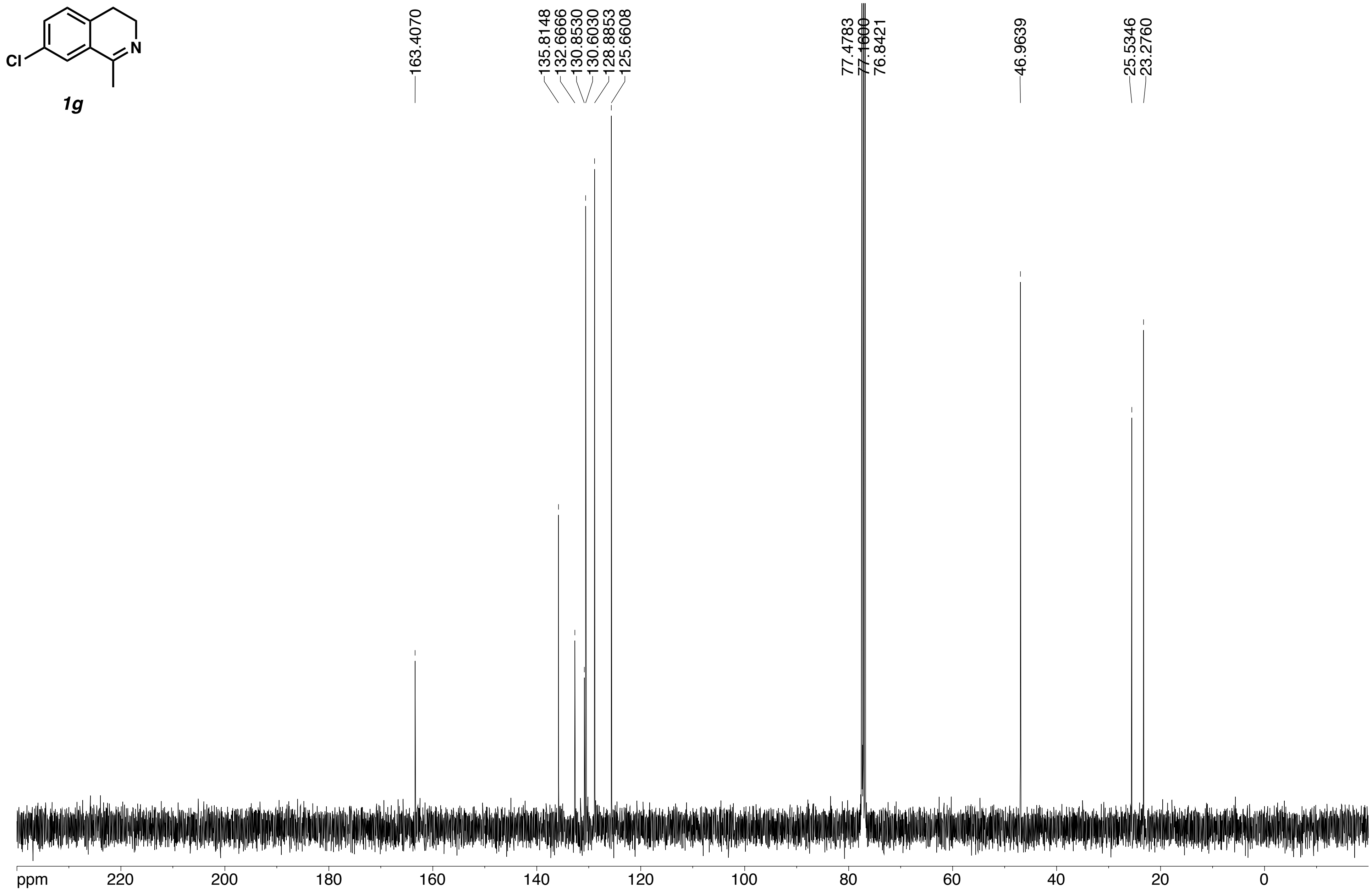


$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **S3g**.



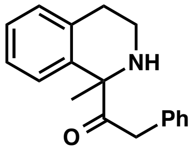
**1g**

$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **1g**.

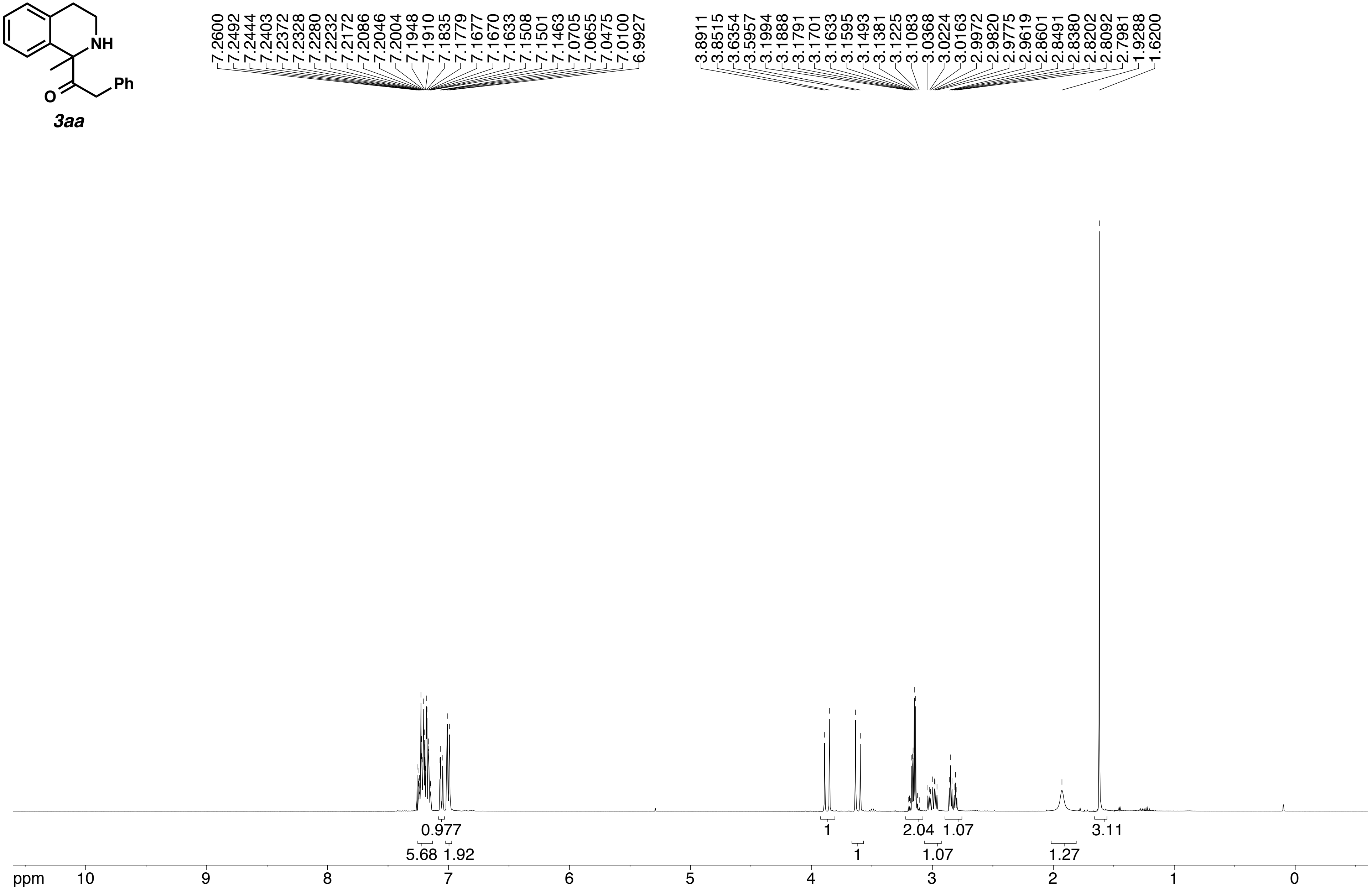


***1g***

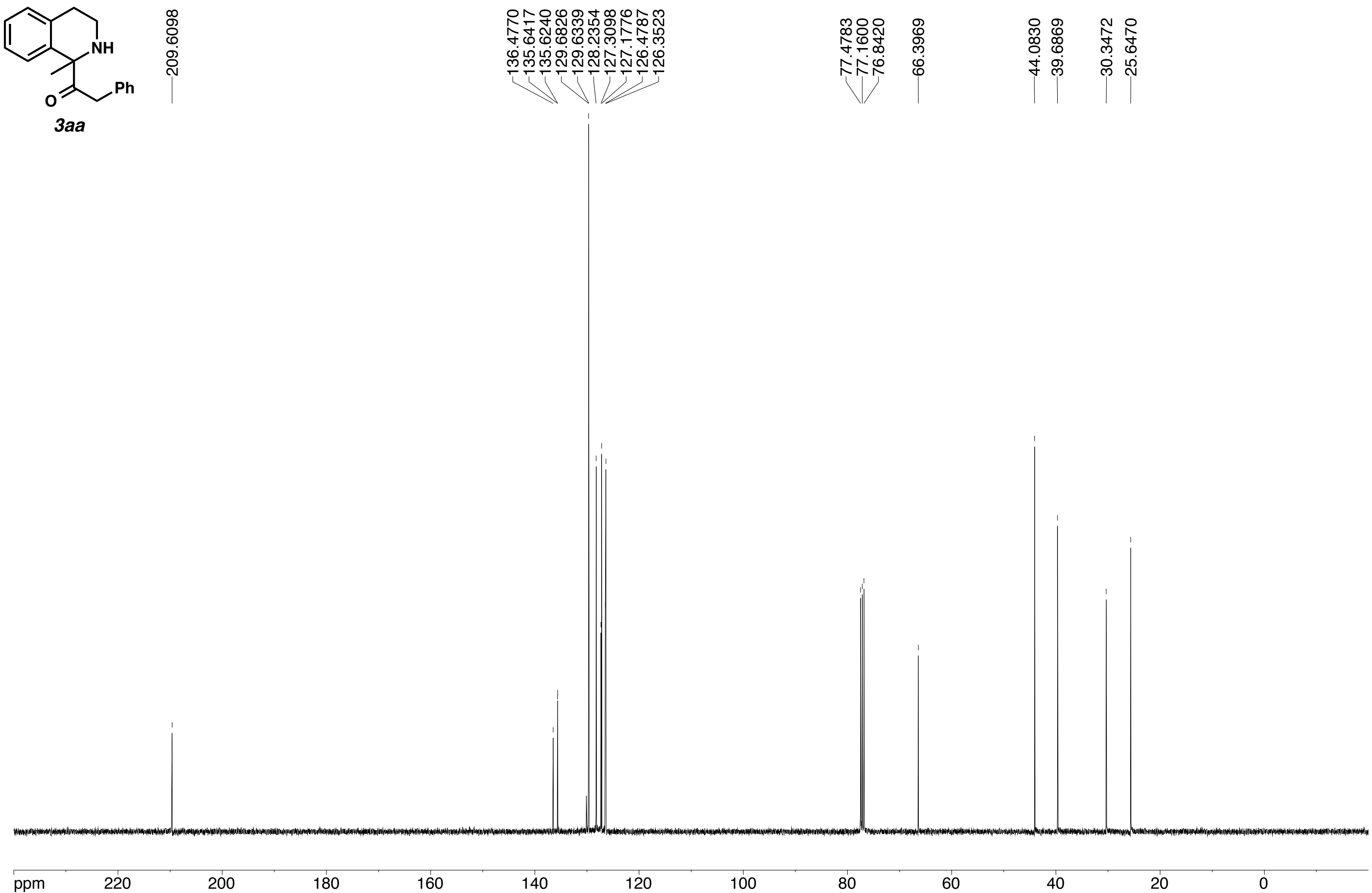
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **1g**.



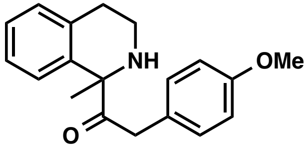
***3aa***



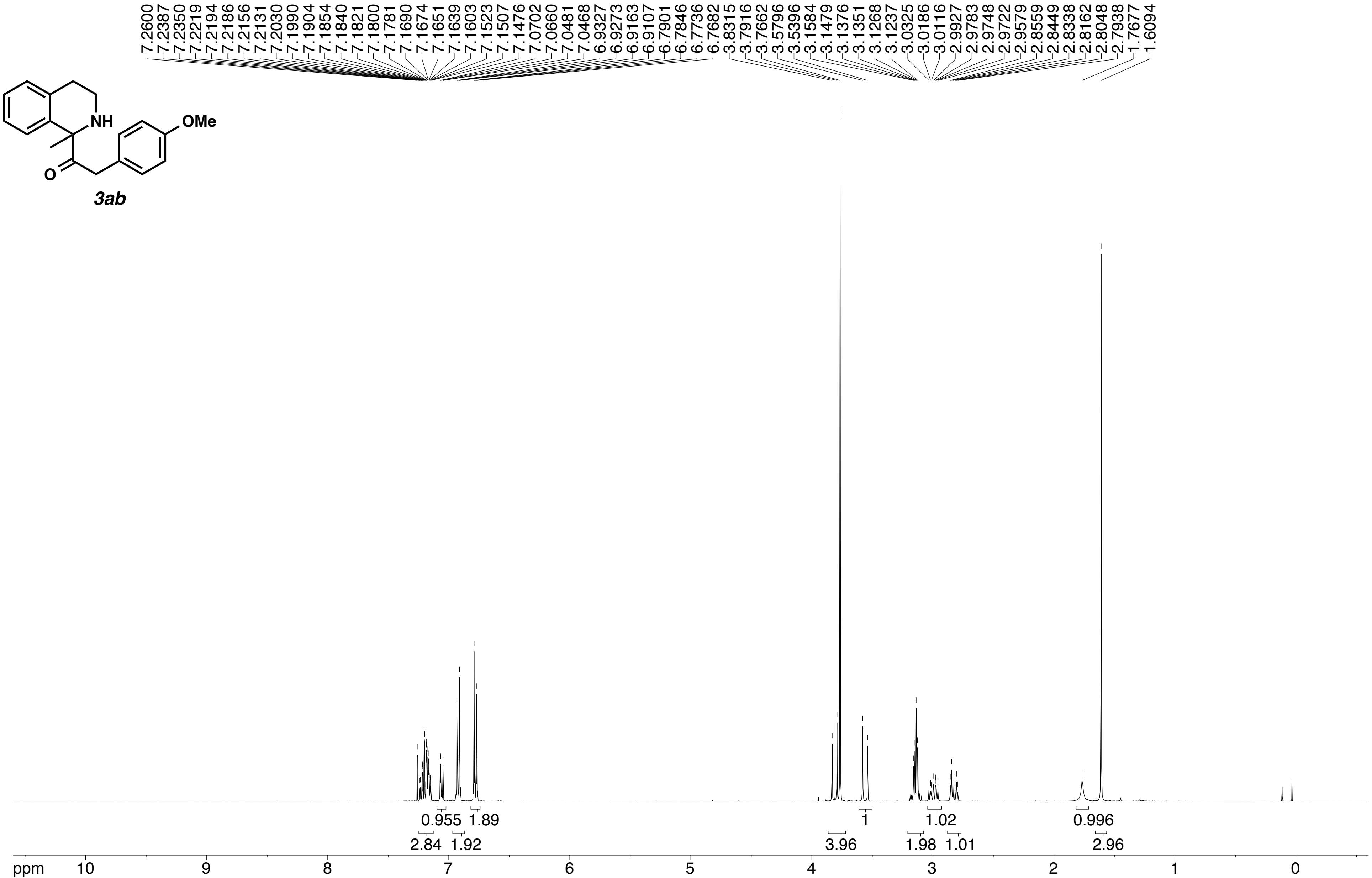
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3aa**.



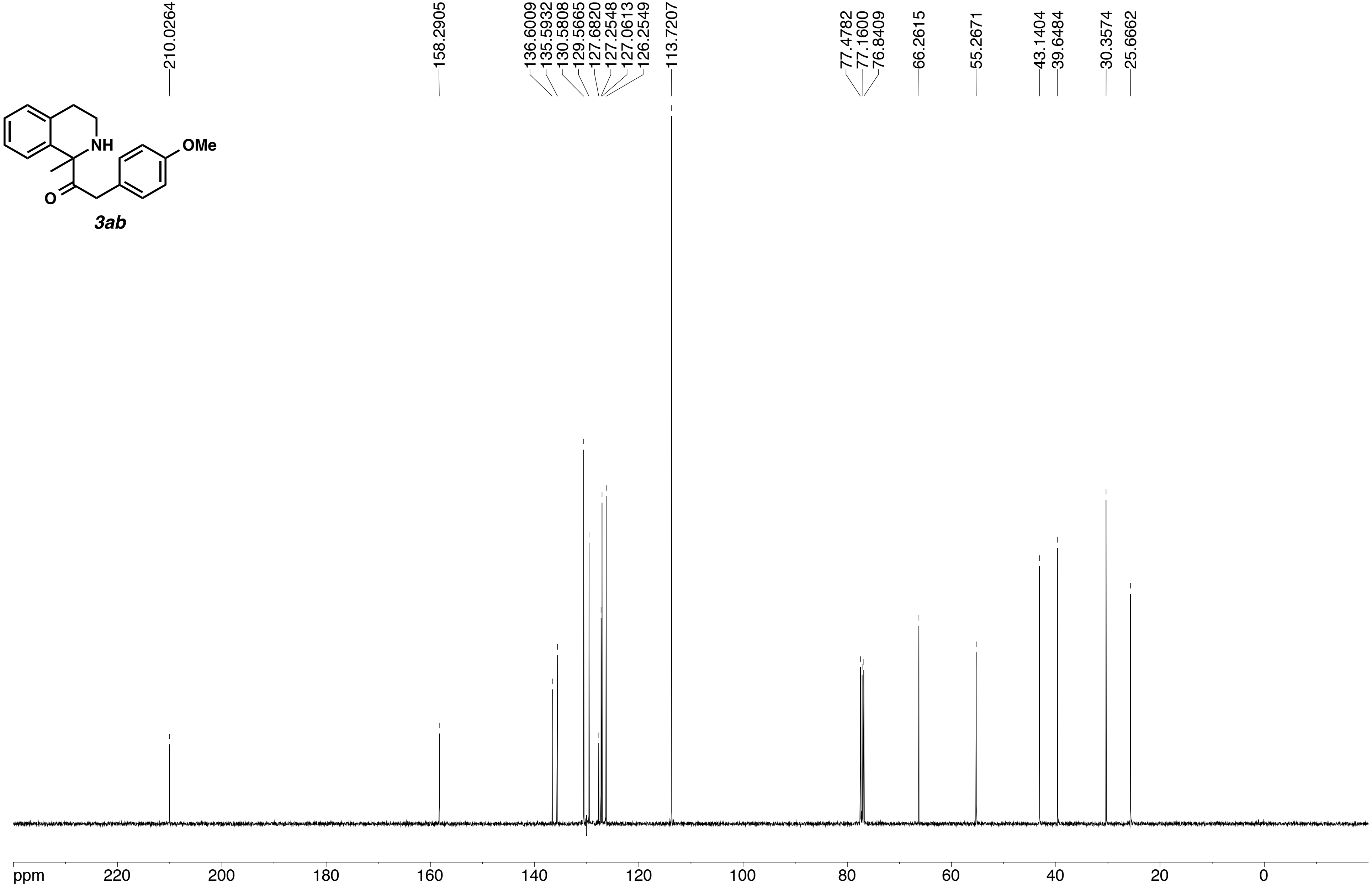
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3aa**.



***3ab***

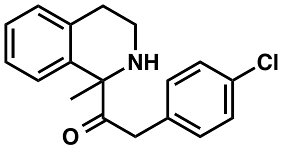


$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3ab**.

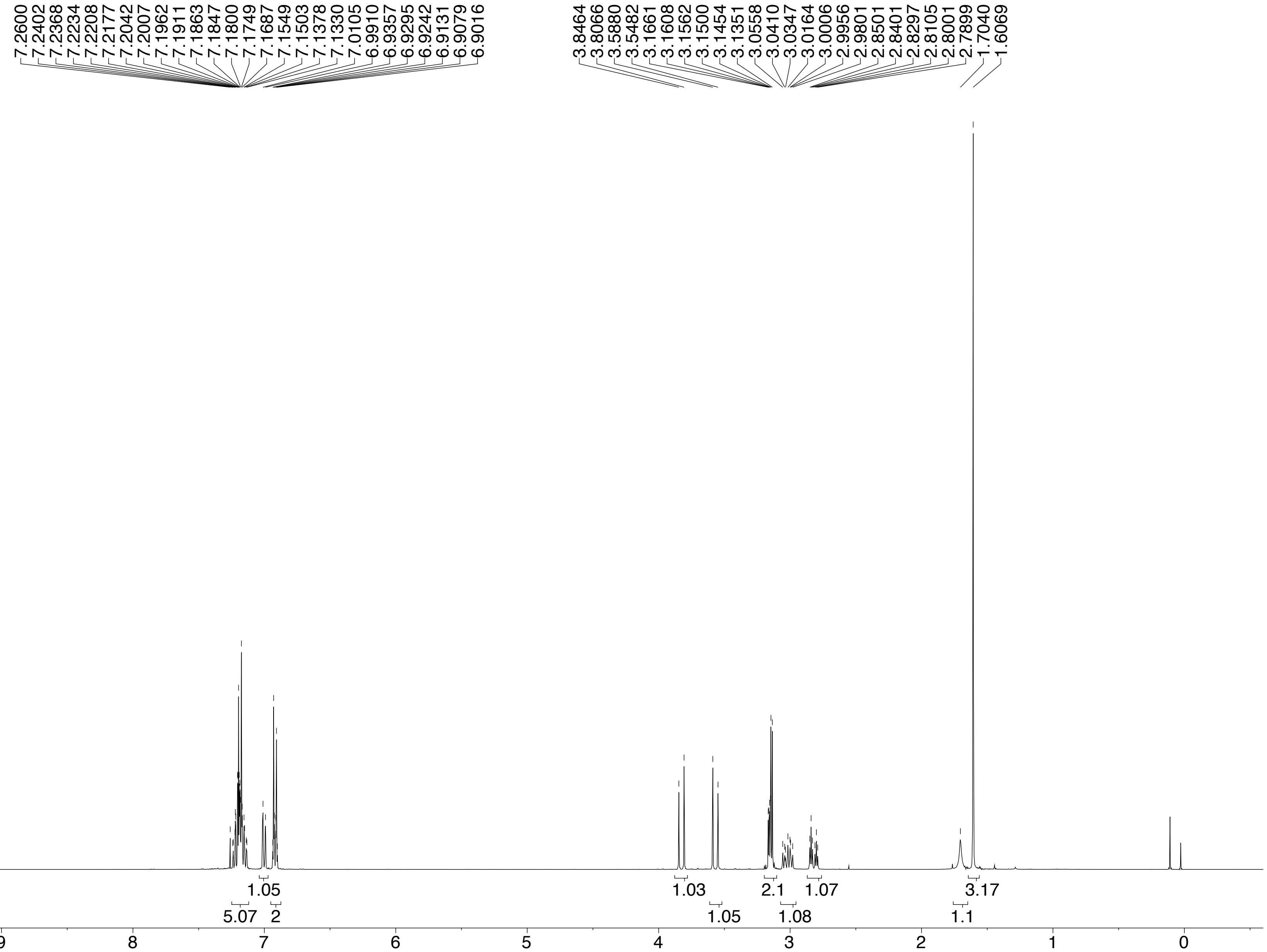


*3ab*

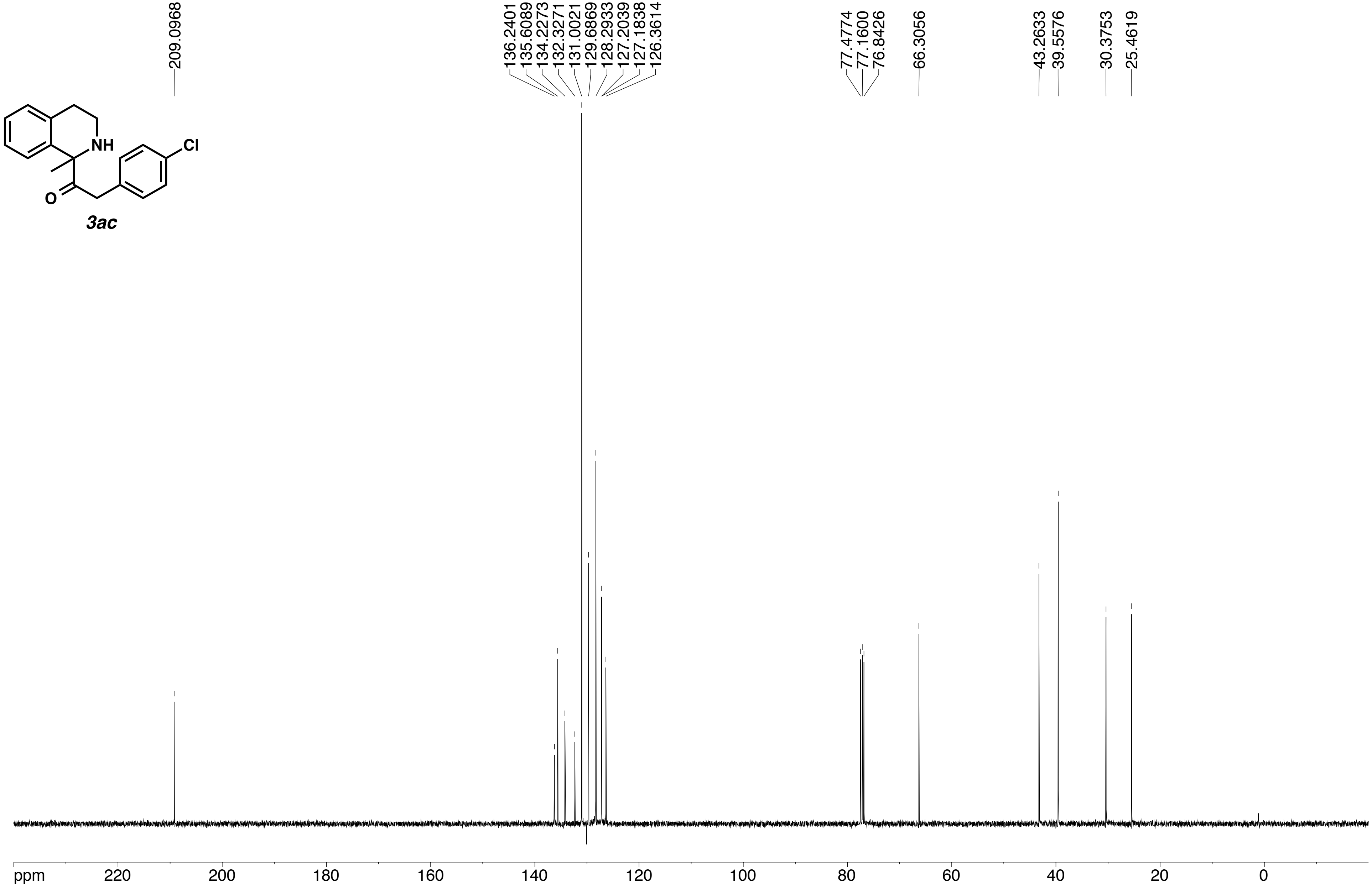
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3ab**.



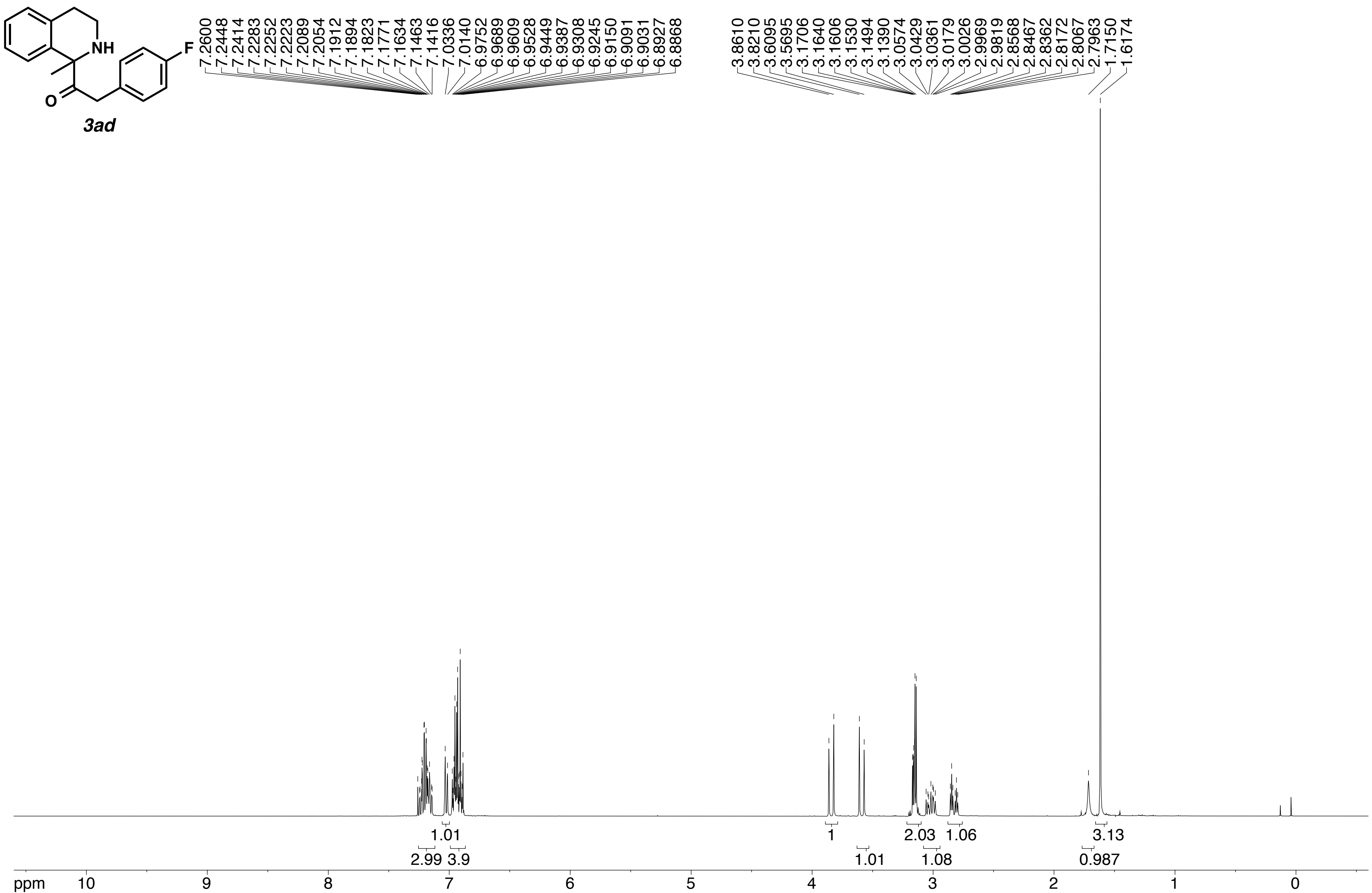
***3ac***



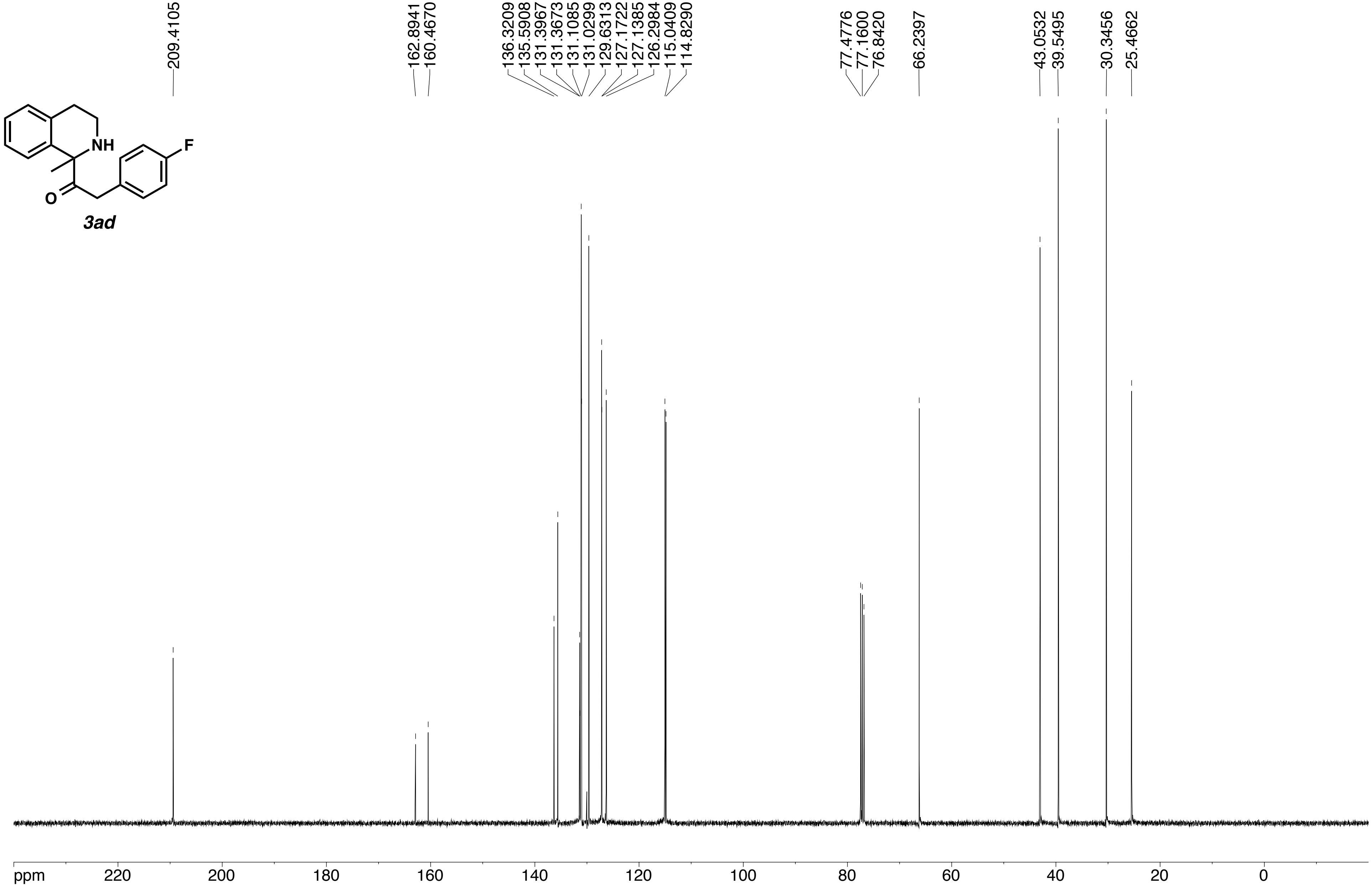
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3ac**.



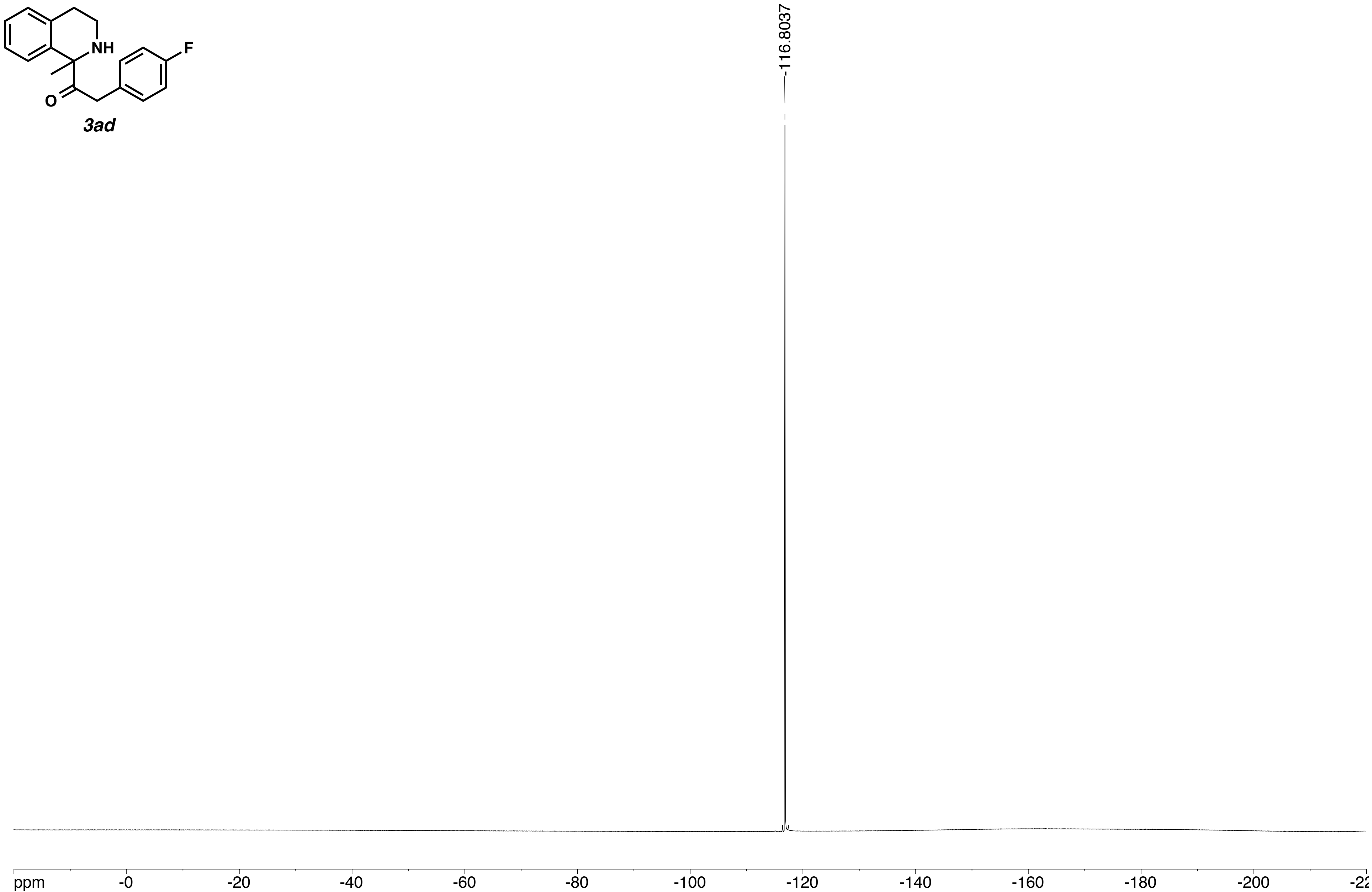
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3ac**.



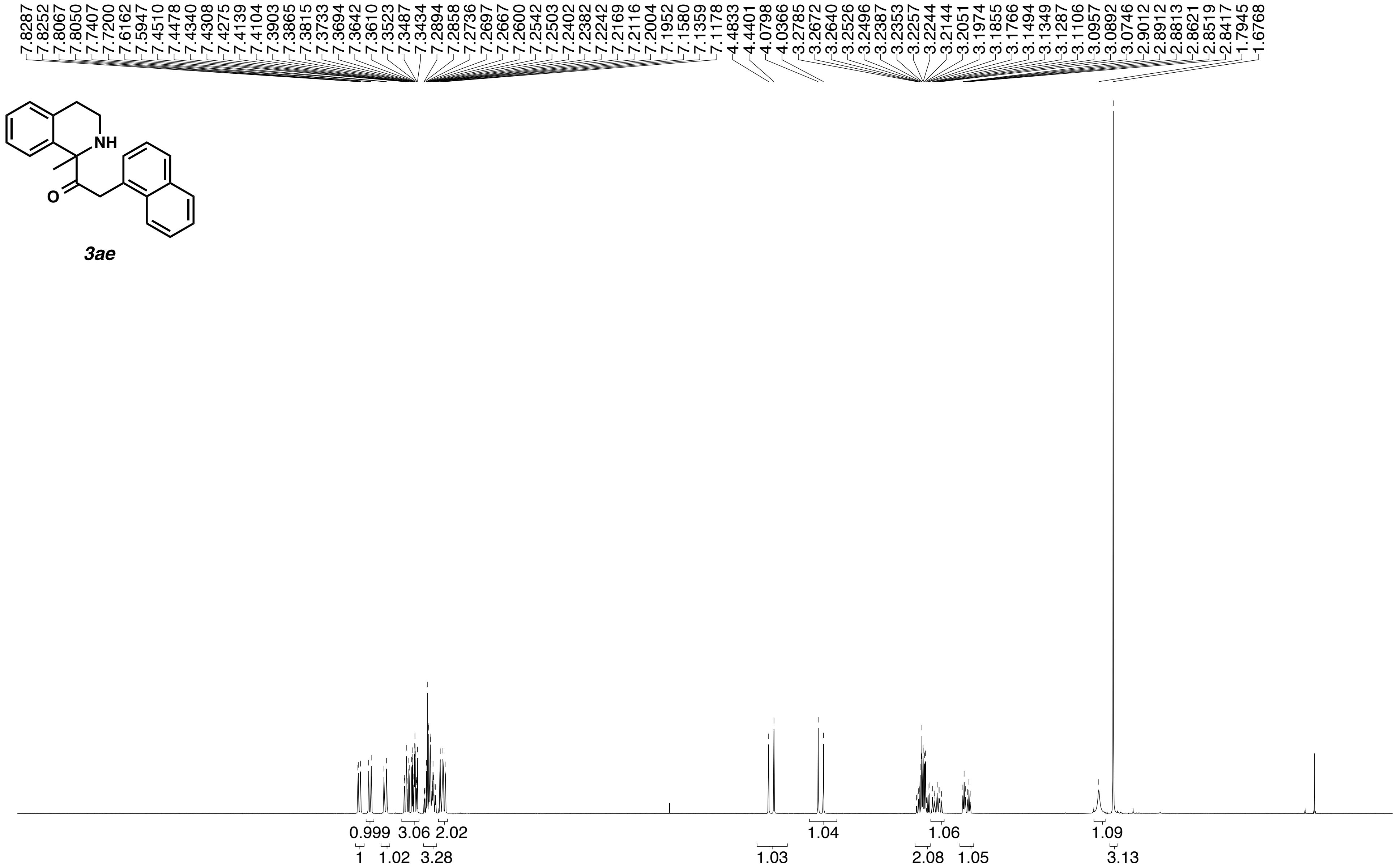
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3ad**.



$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3ad**.

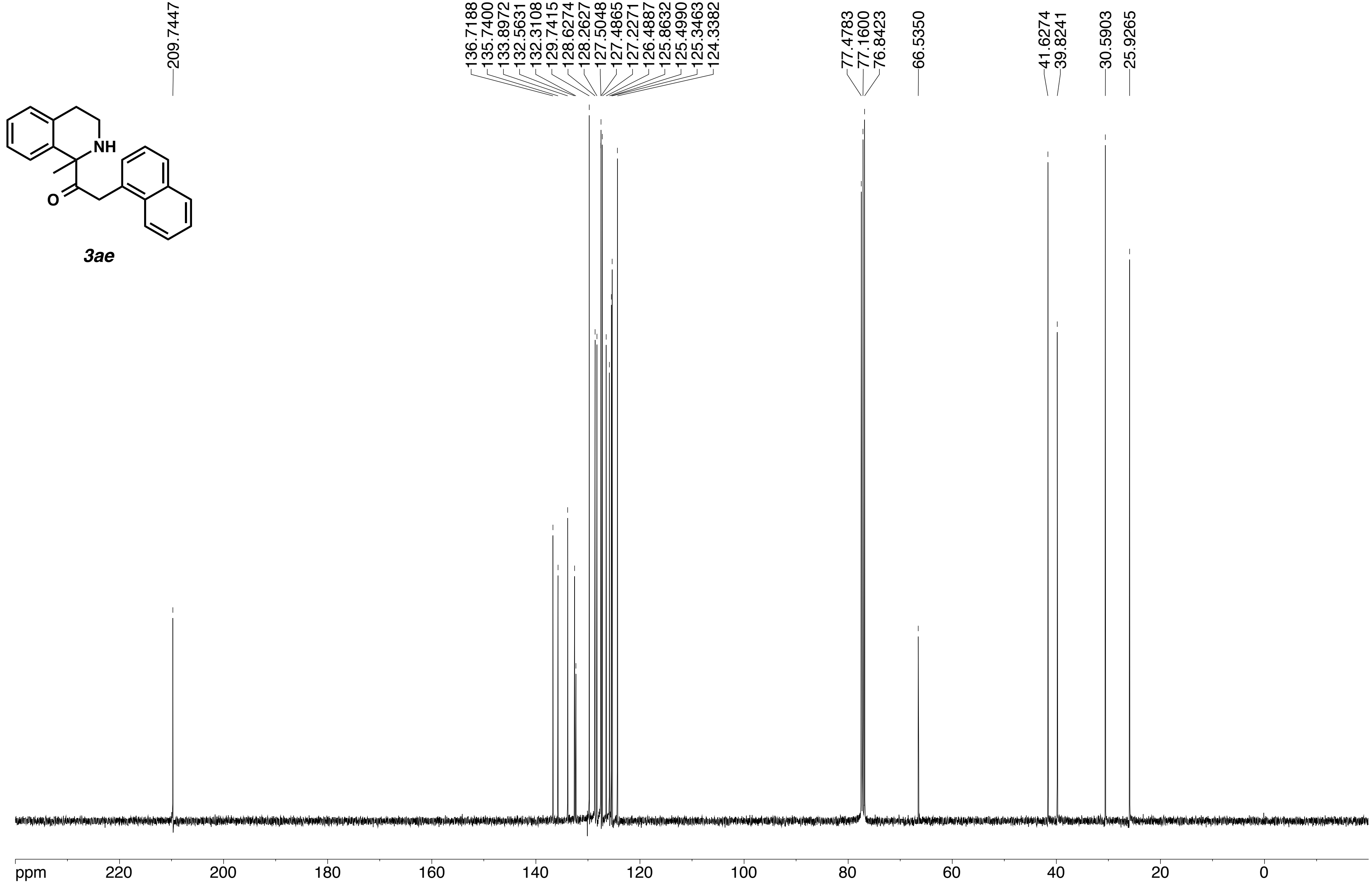


$^{19}$F NMR (236.4 MHz, CDCl$_3$) of compound **3ad**.

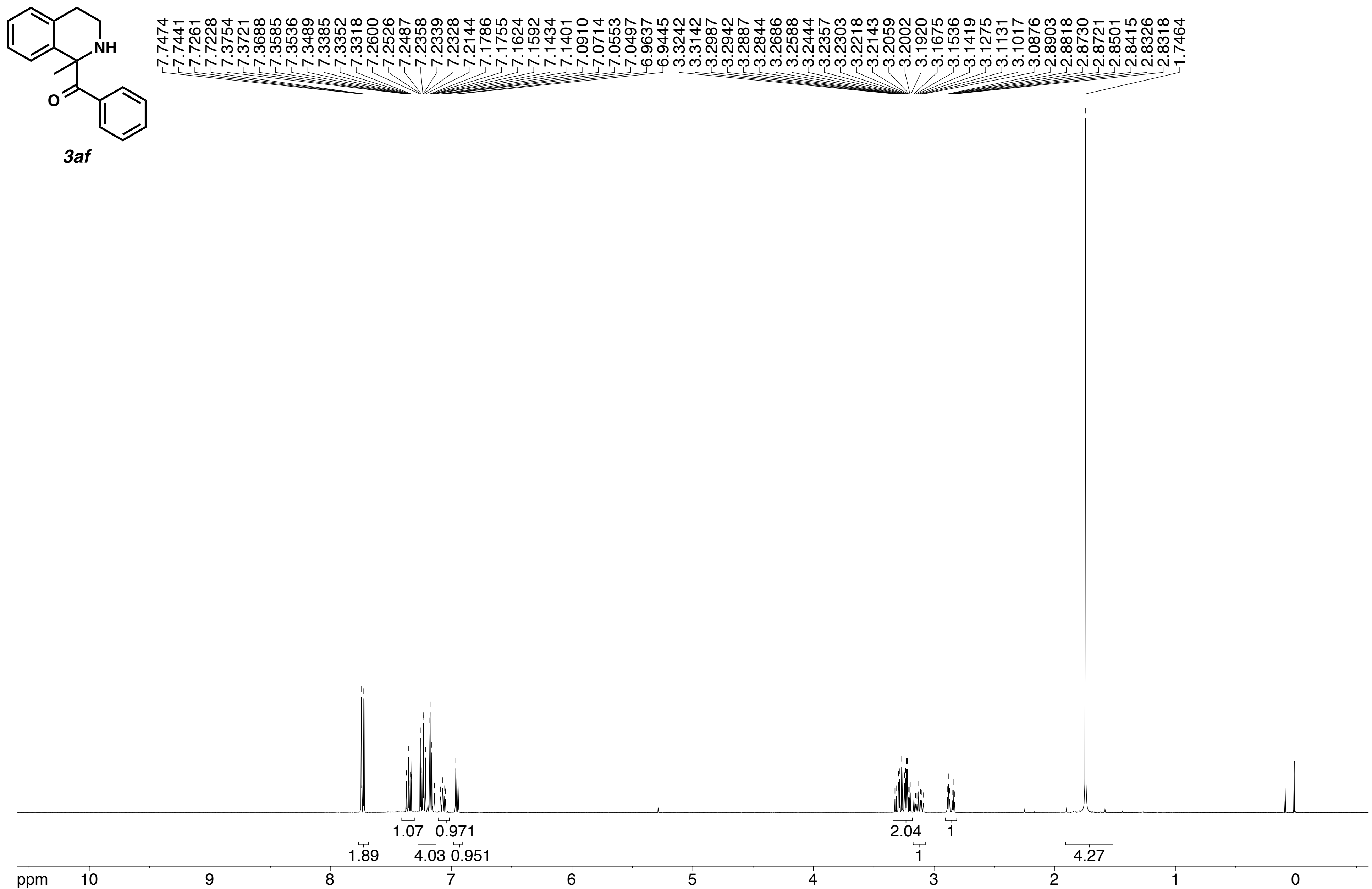


***3ae***

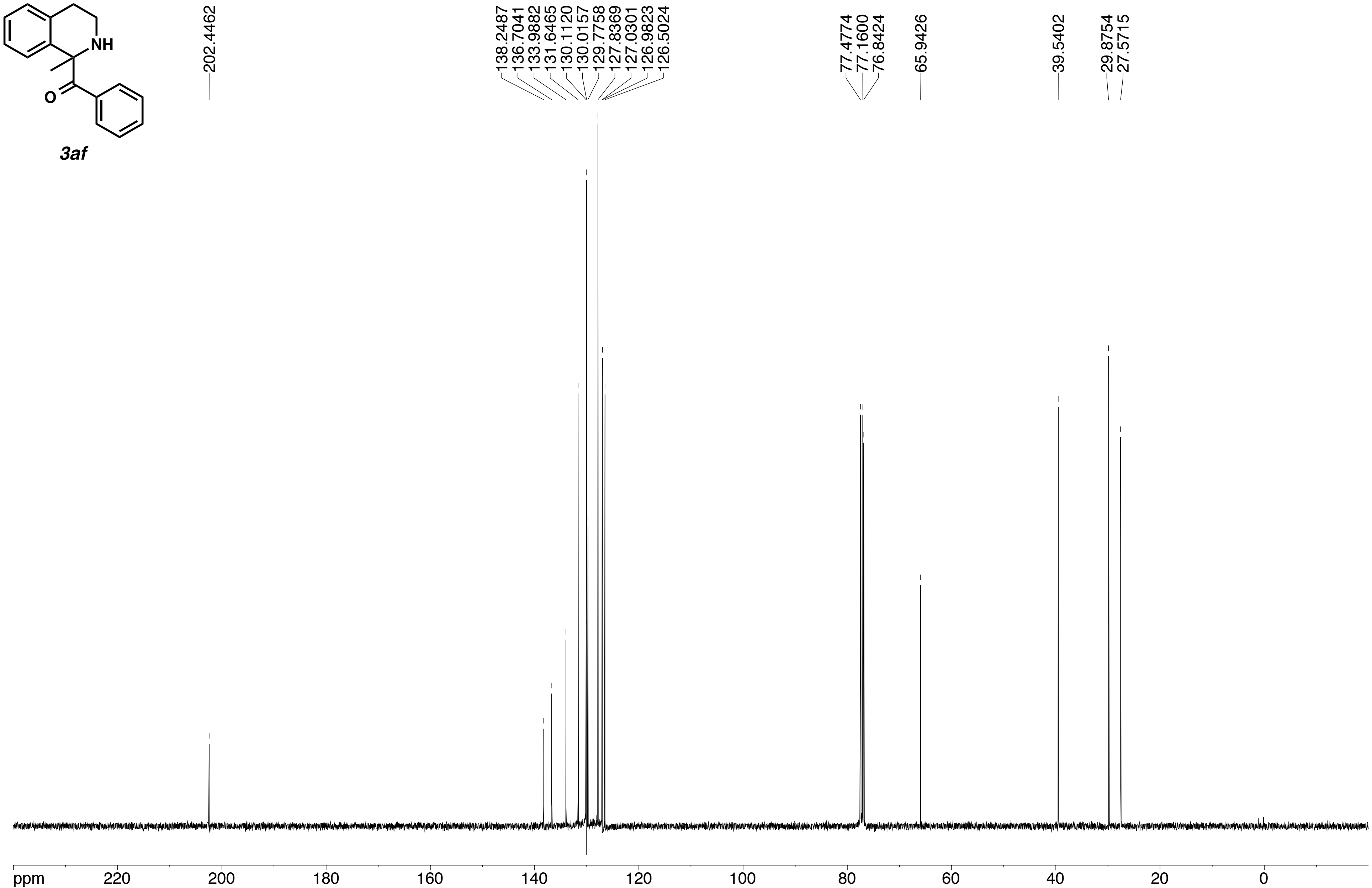
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3ae**.



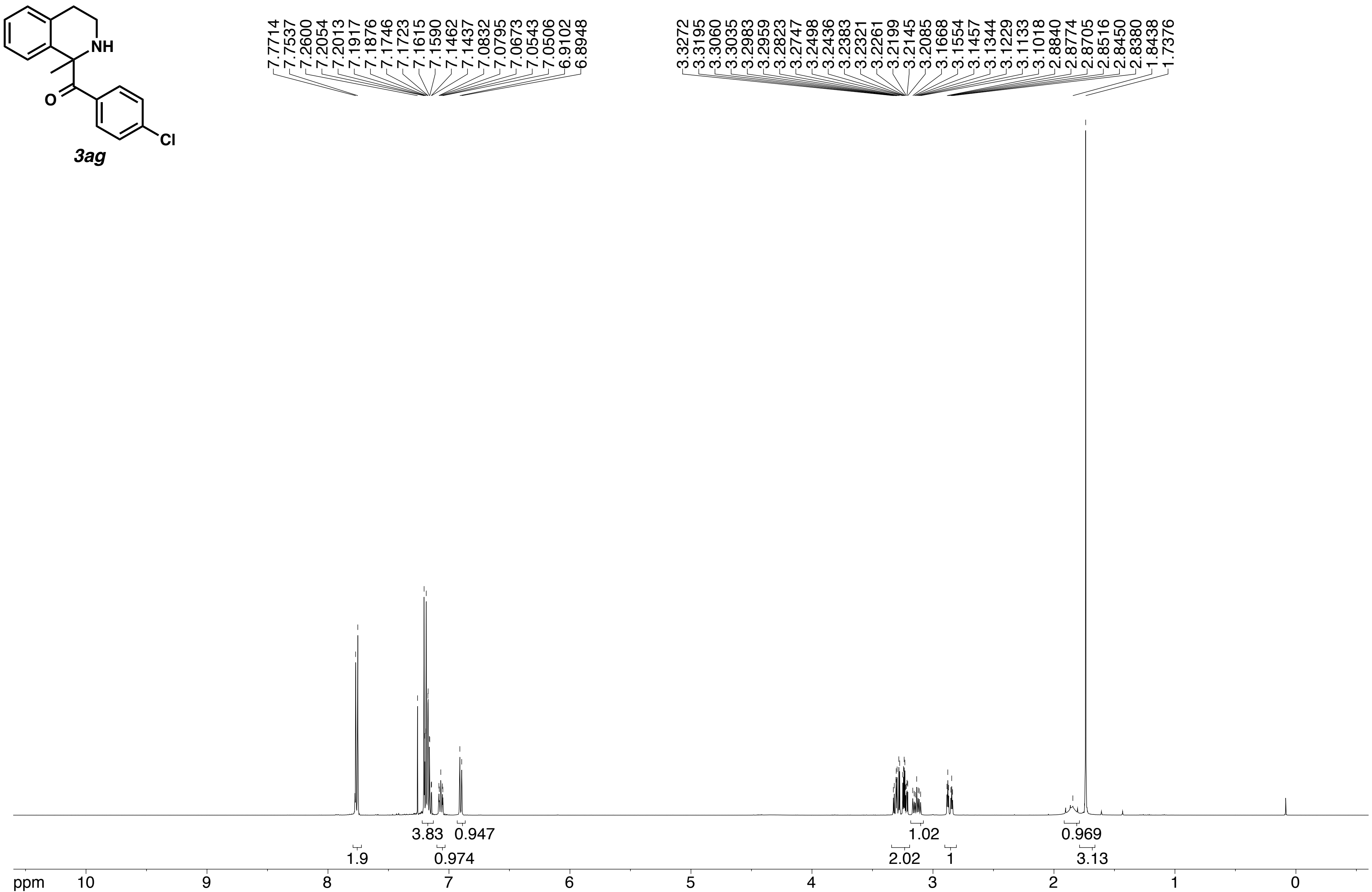
$^{13}$C NMR (100.6 MHz, $CDCl_3$) of compound **3ae**.



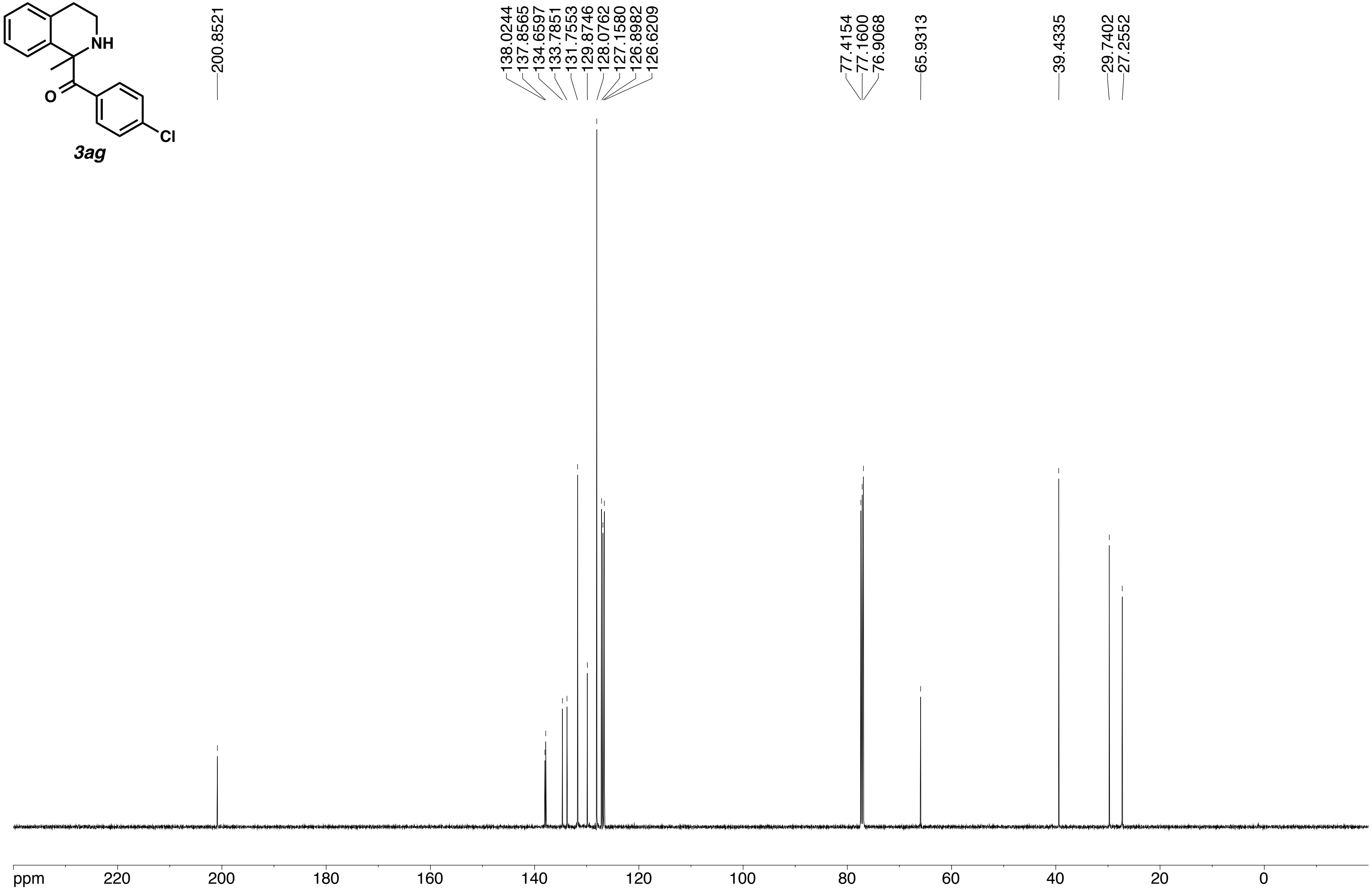
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3af**.



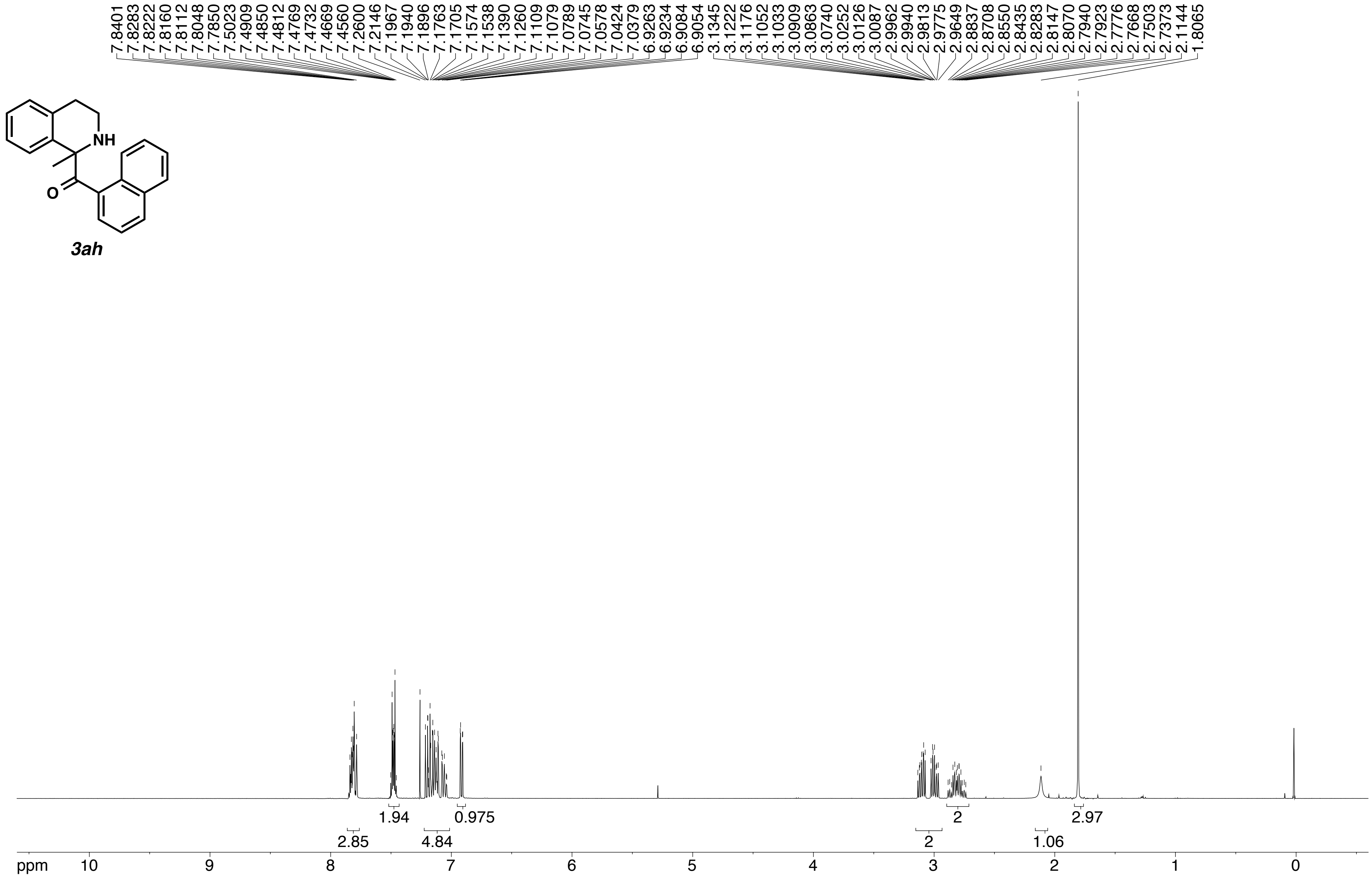
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3af**.



$^1$H NMR (500.3 MHz, CDCl$_3$) of compound **3ag**.

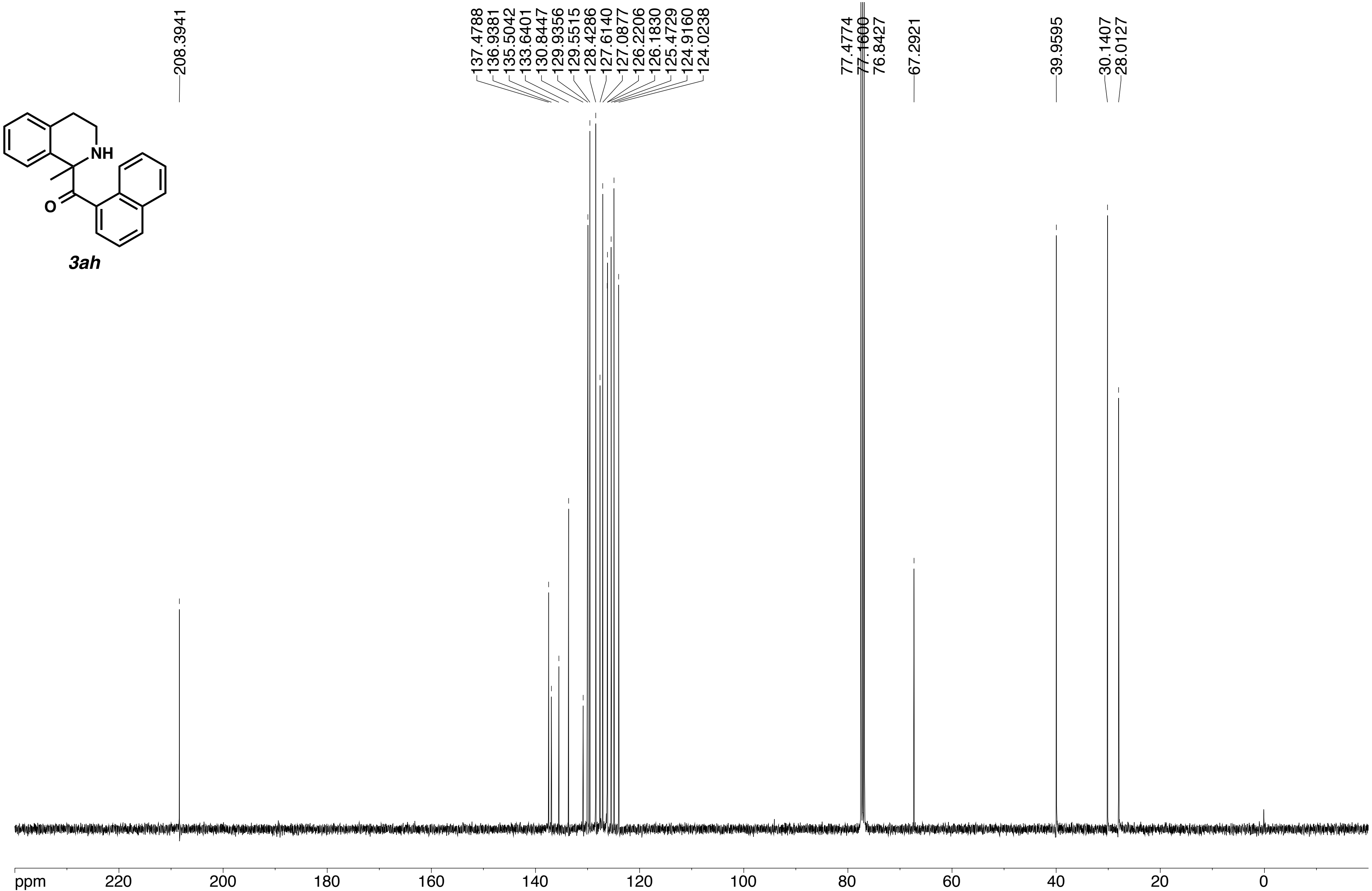


$^{13}$C NMR (125.8 MHz, CDCl$_3$) of compound **3ag**.

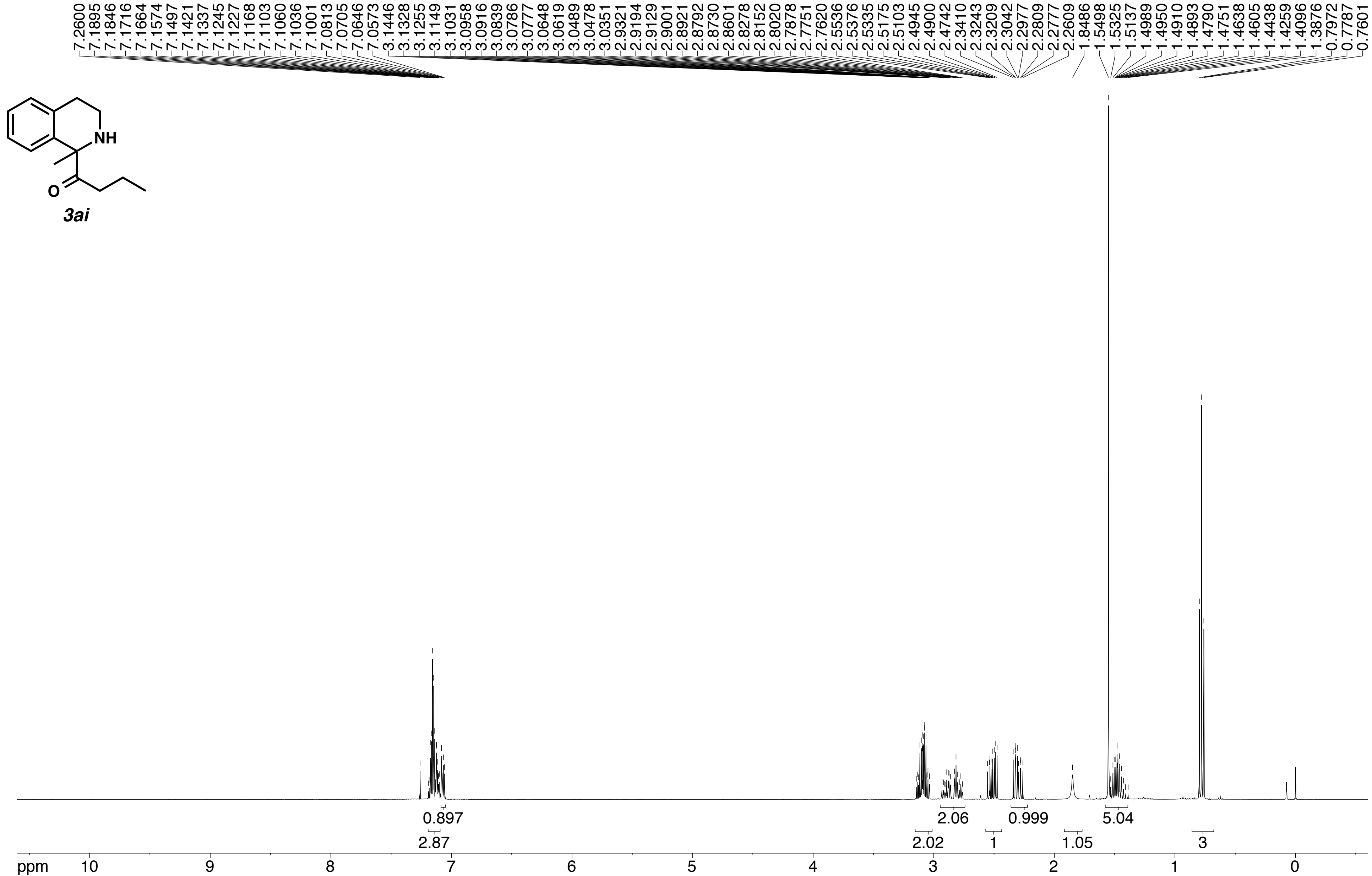


$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3ah**.

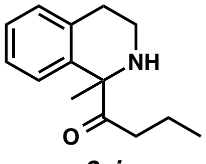
*3ah*



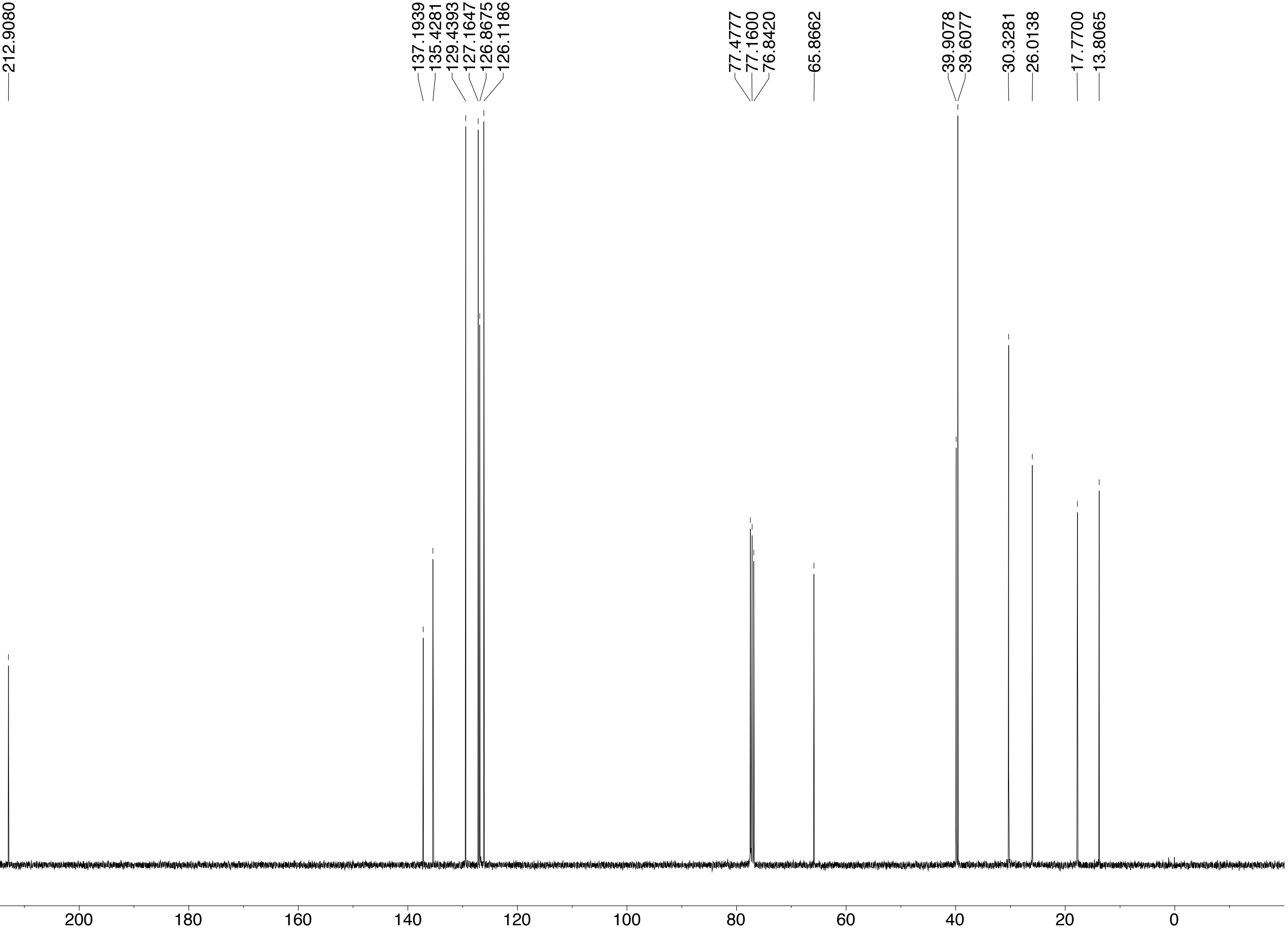
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3ah**.



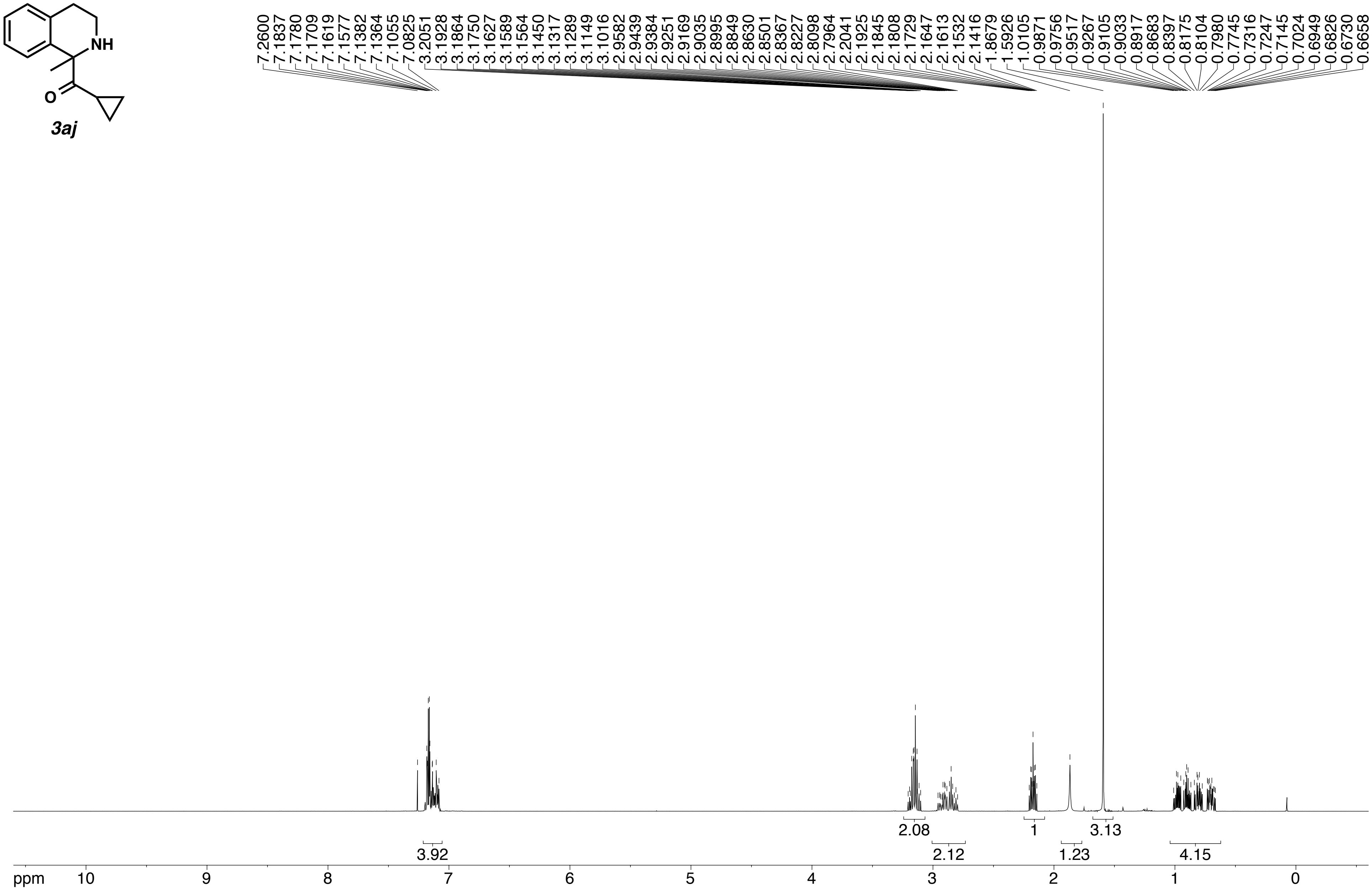
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3ai**.



***3ai***

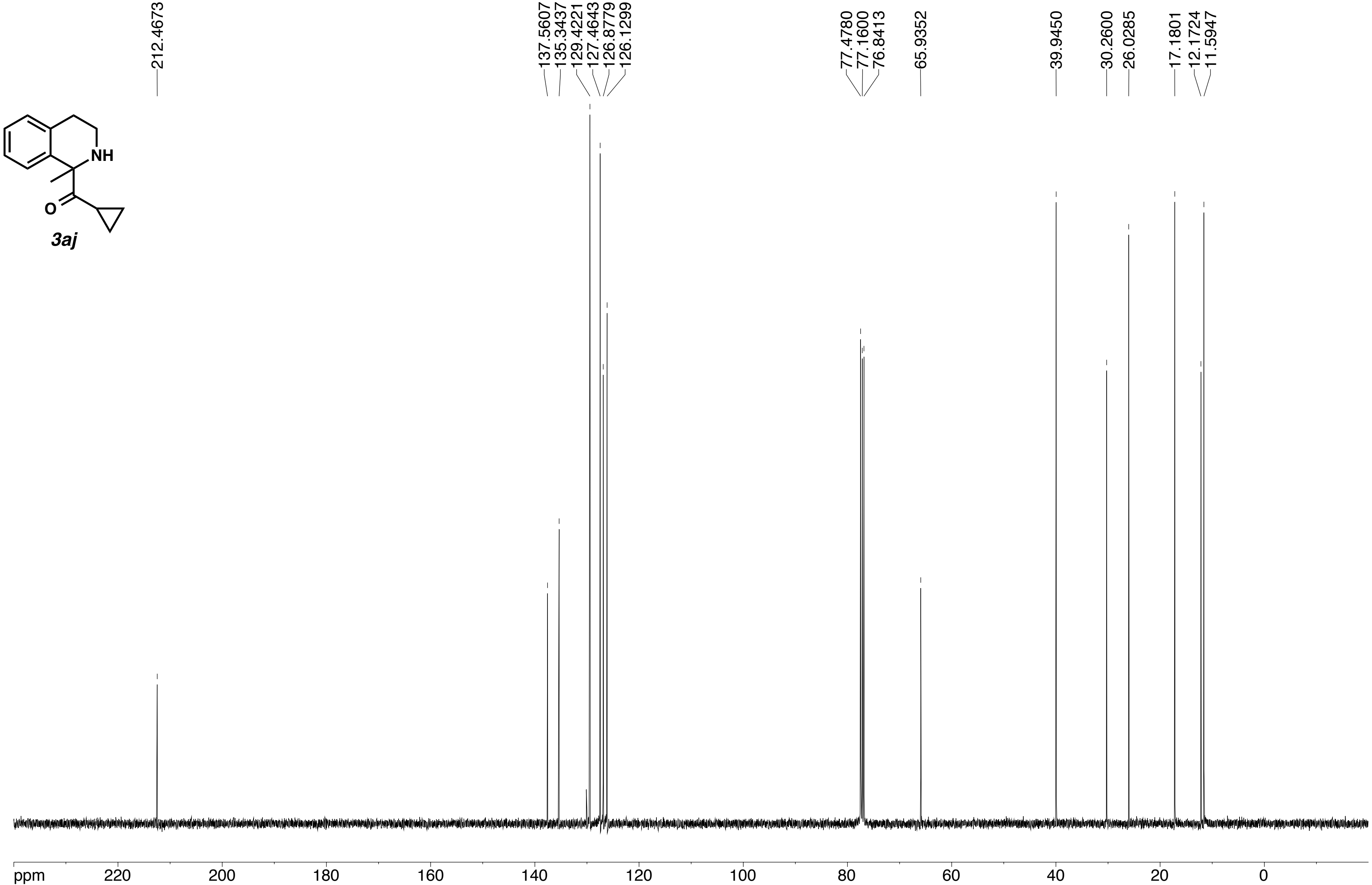


$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3ai**.



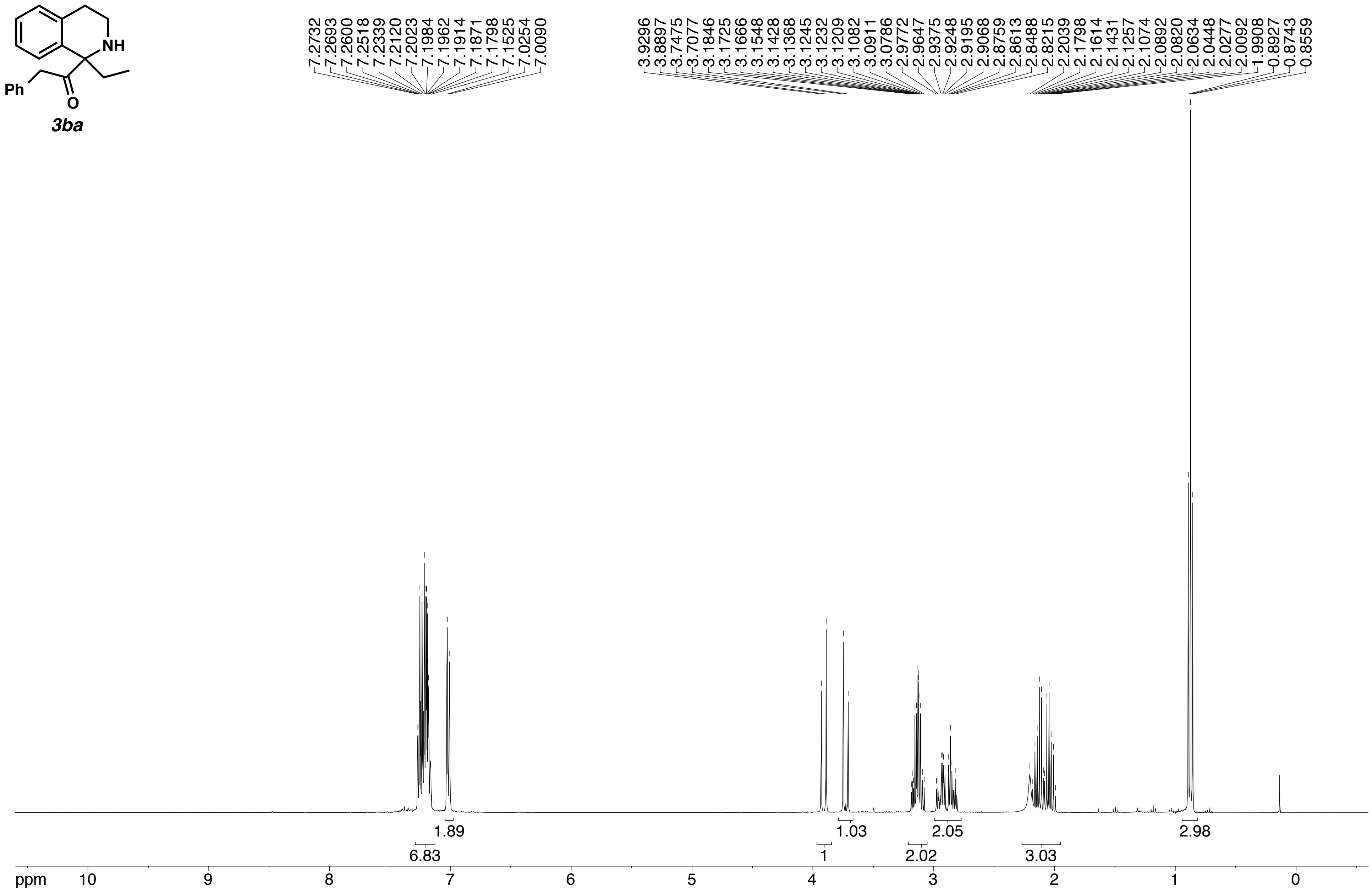
***3aj***

$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3aj**.

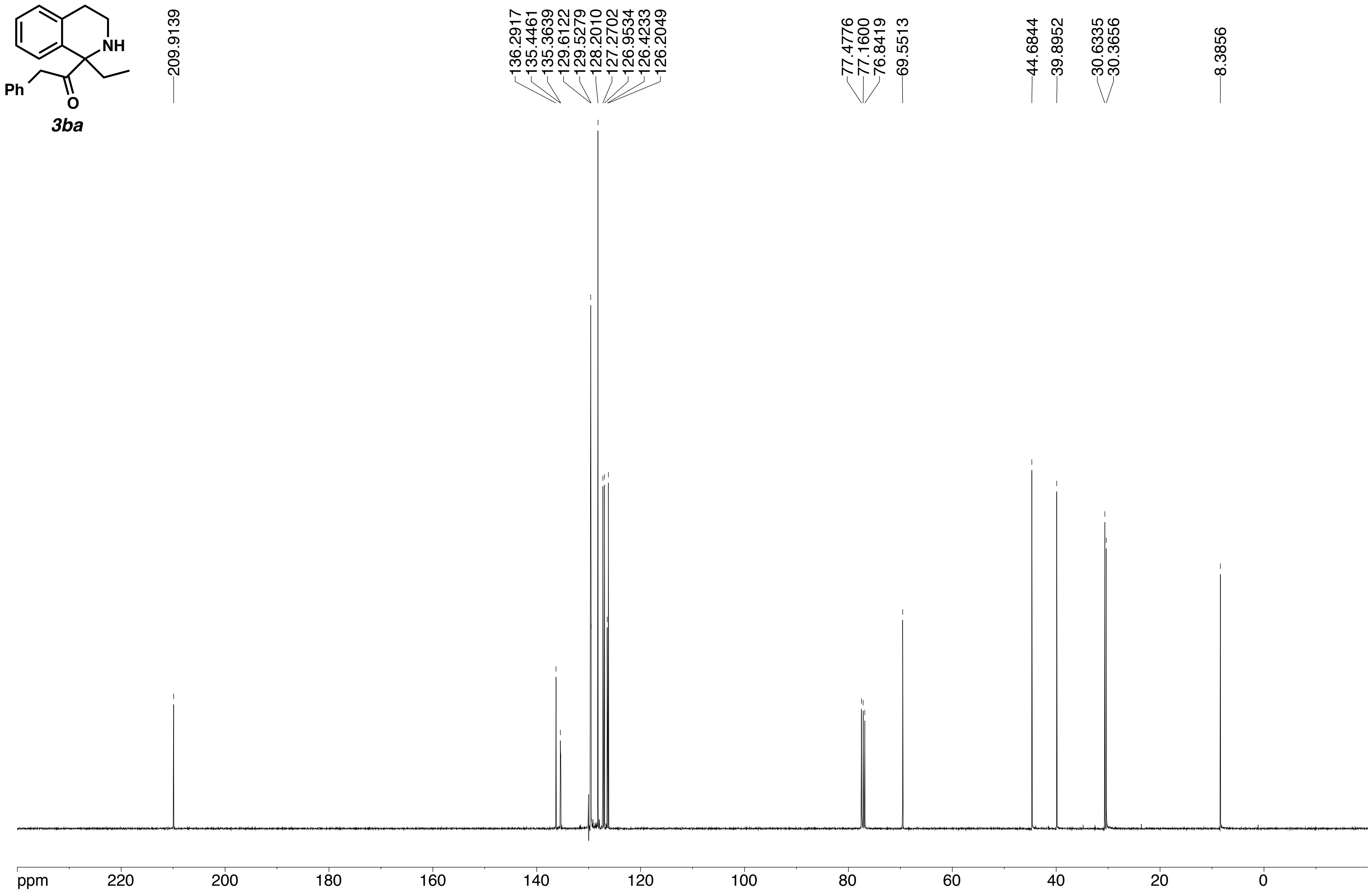


***3aj***

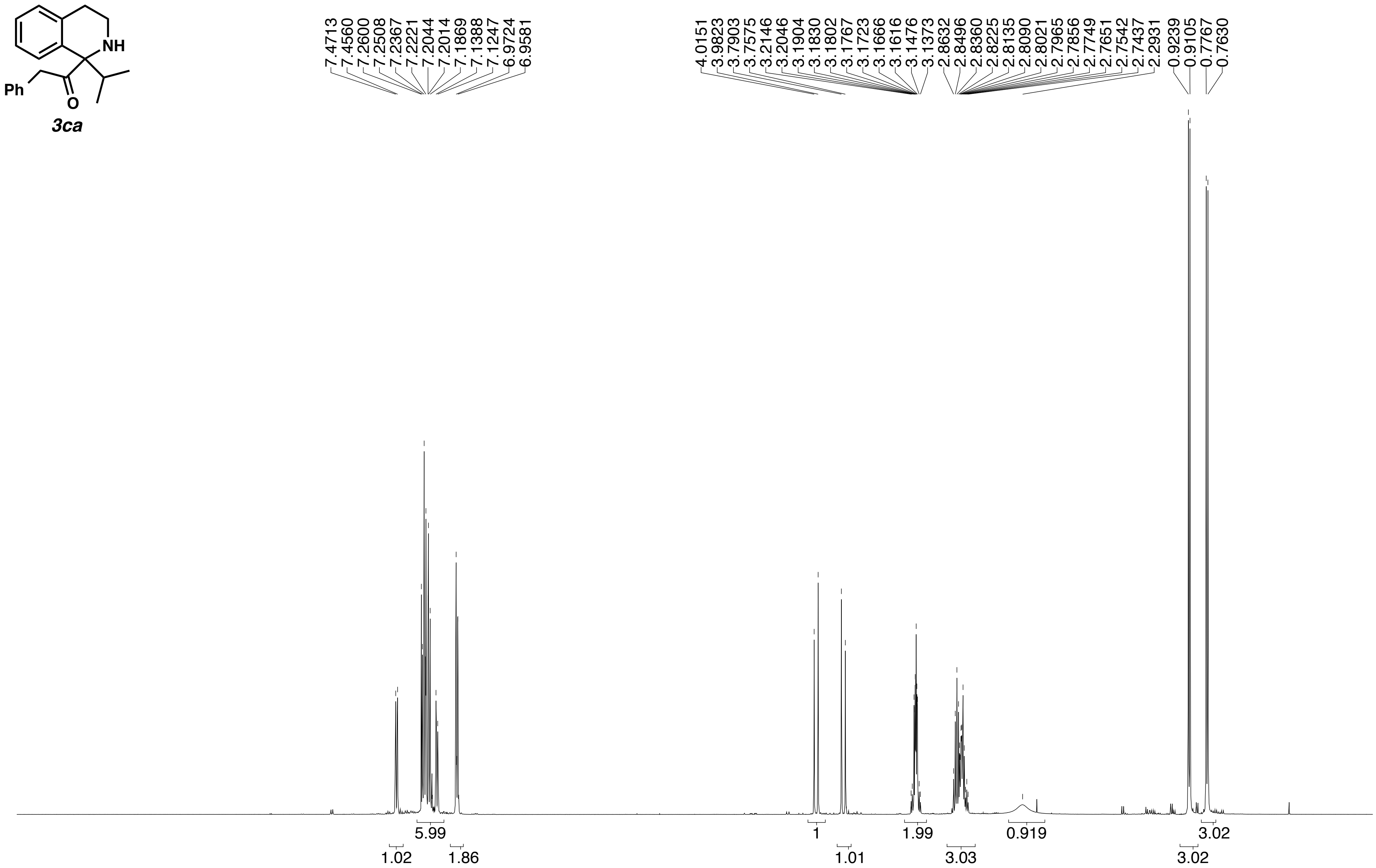
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3aj**.



$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3ba**.

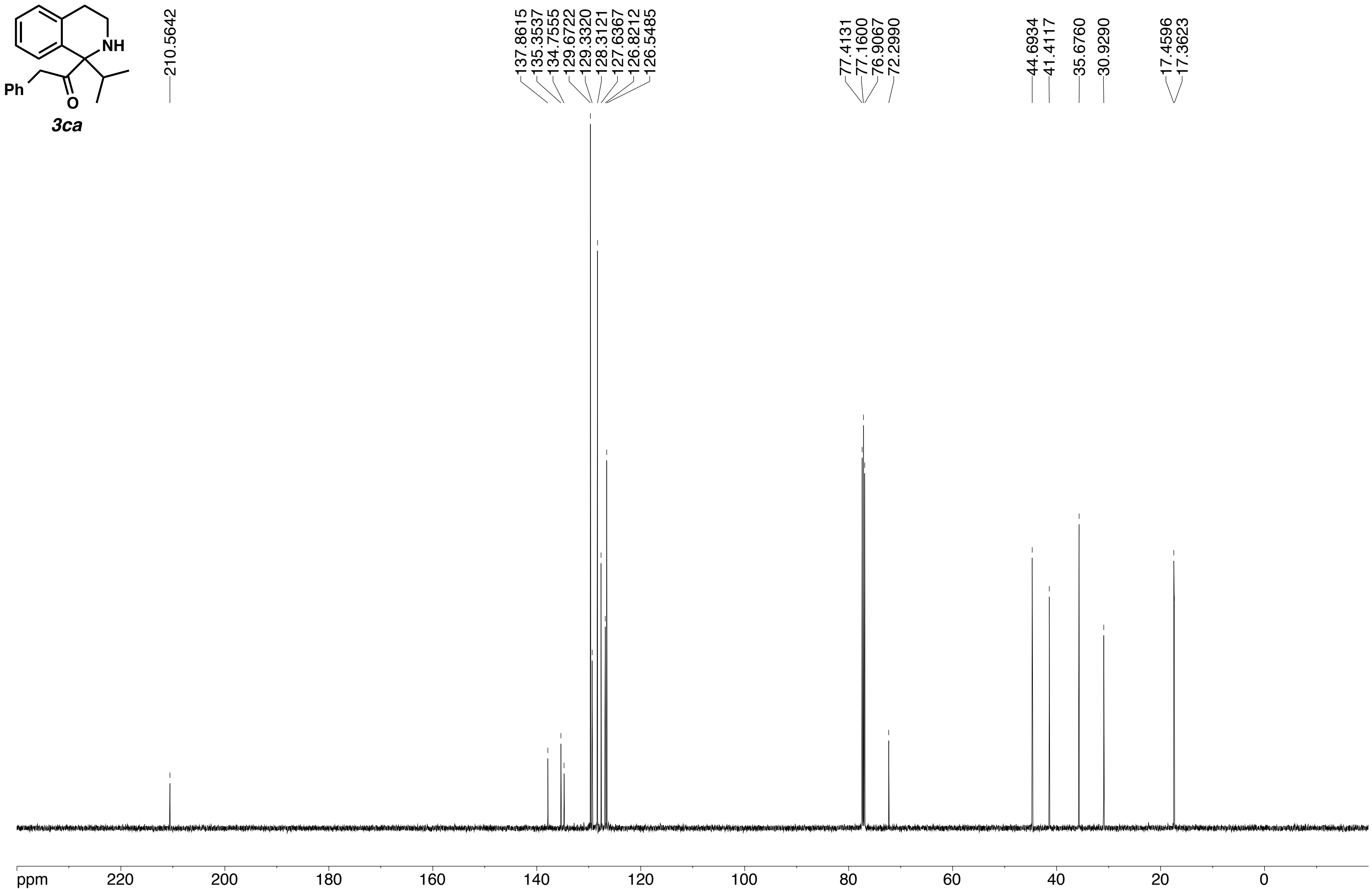


$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3ba**.

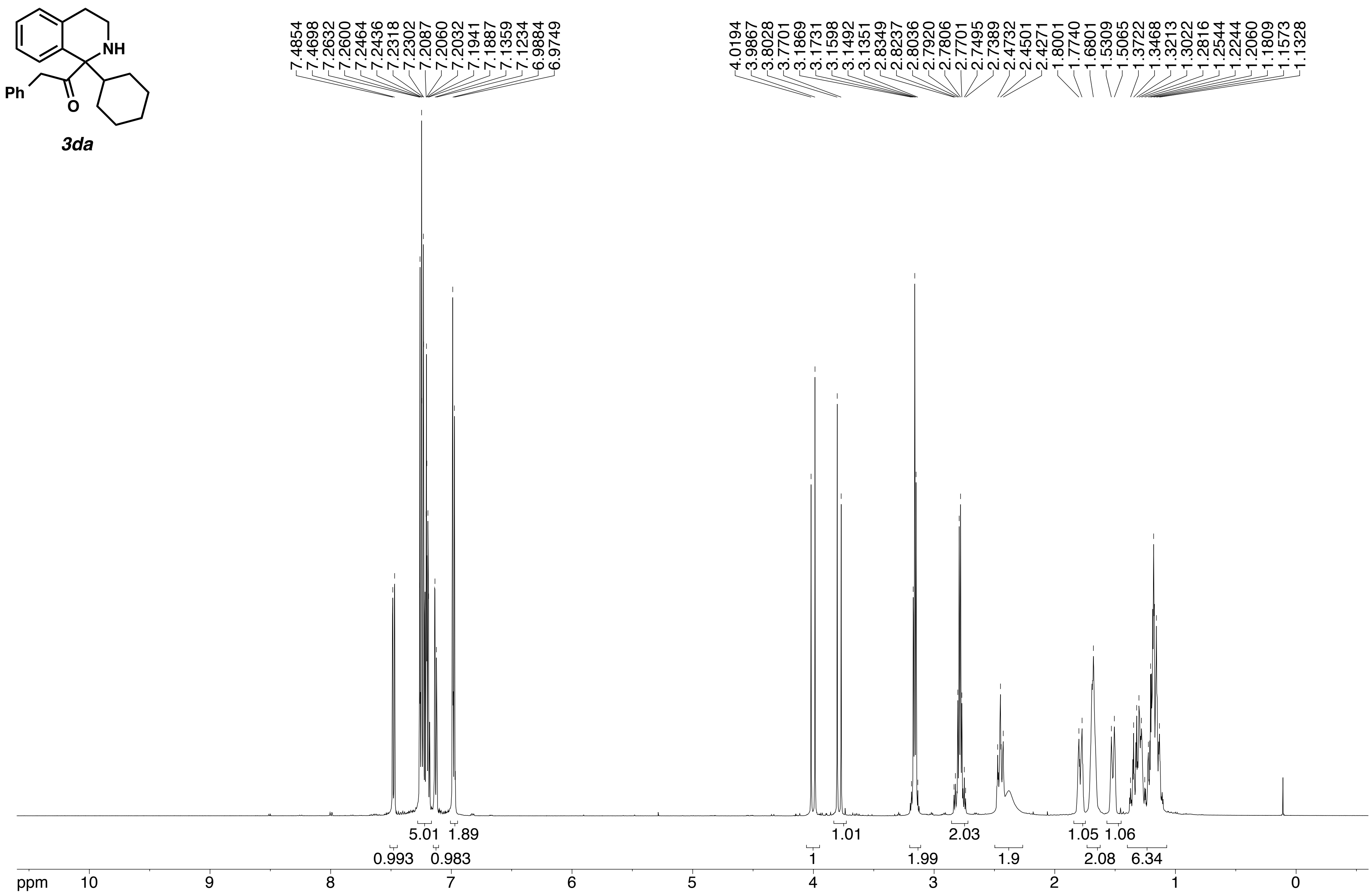


***3ca***

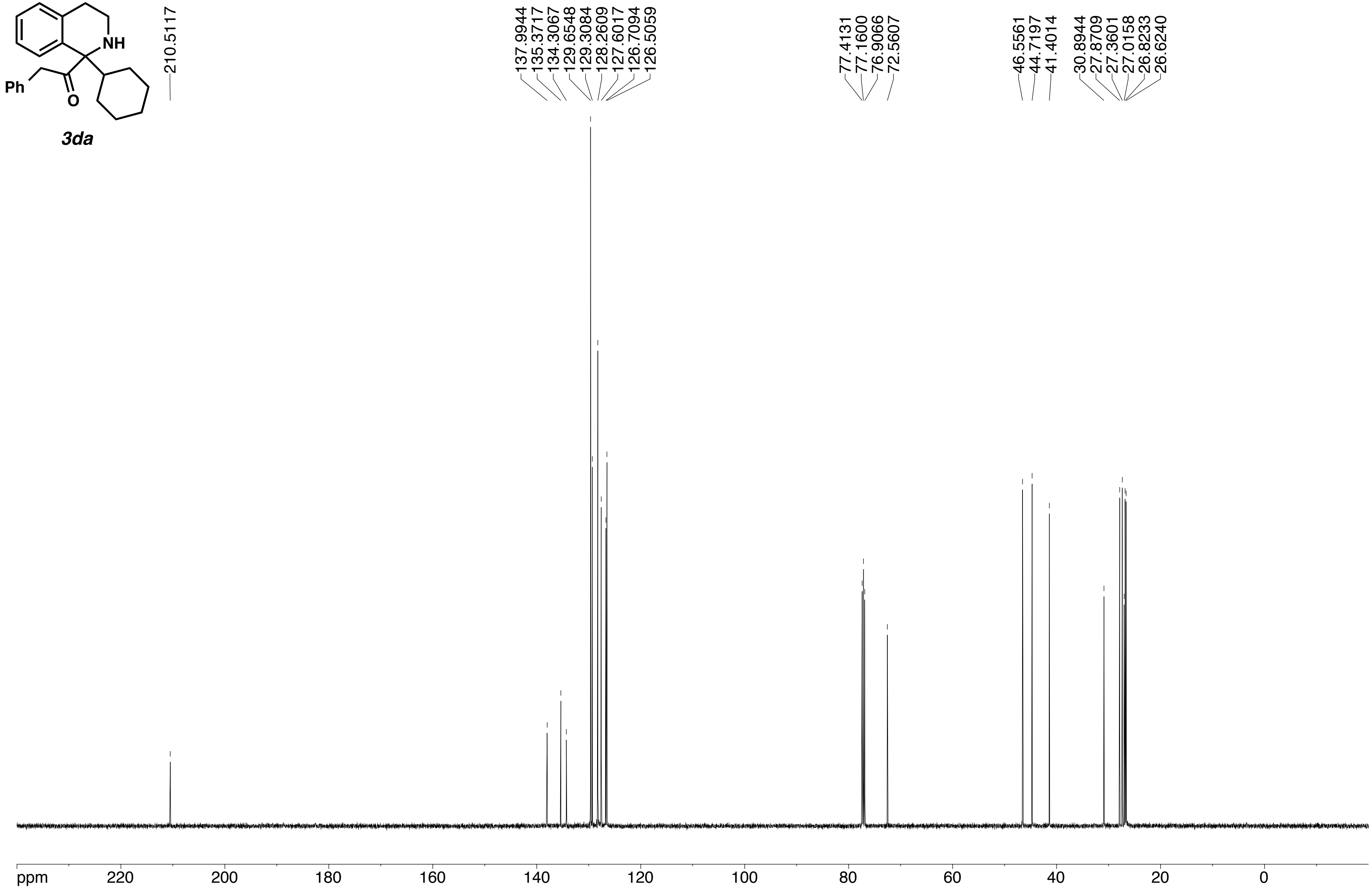
$^1$H NMR (500.3 MHz, CDCl$_3$) of compound **3ca**.



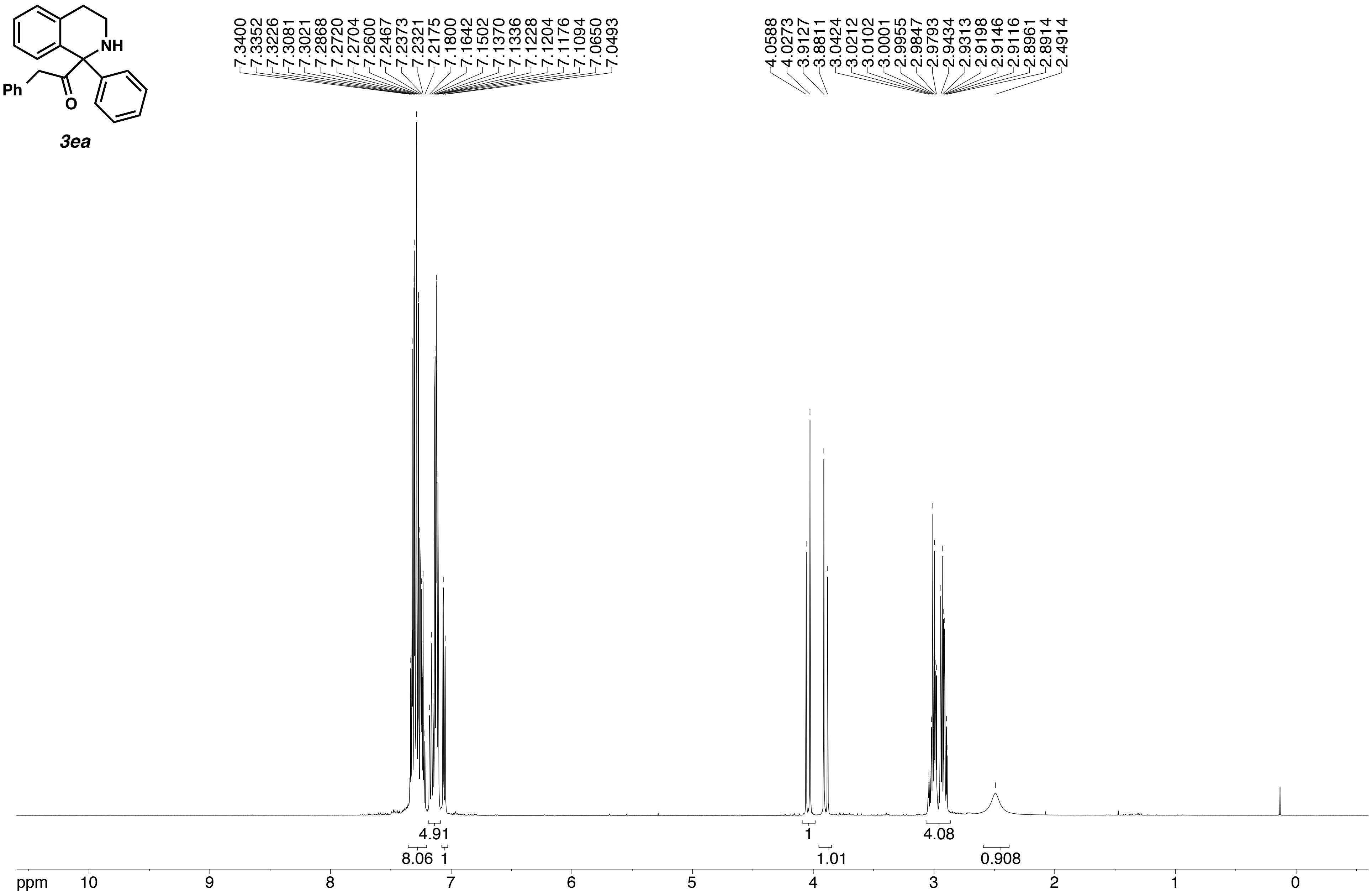
$^{13}$C NMR (125.8 MHz, $CDCl_3$) of compound **3ca**.



$^1$H NMR (500.3 MHz, CDCl$_3$) of compound **3da**.

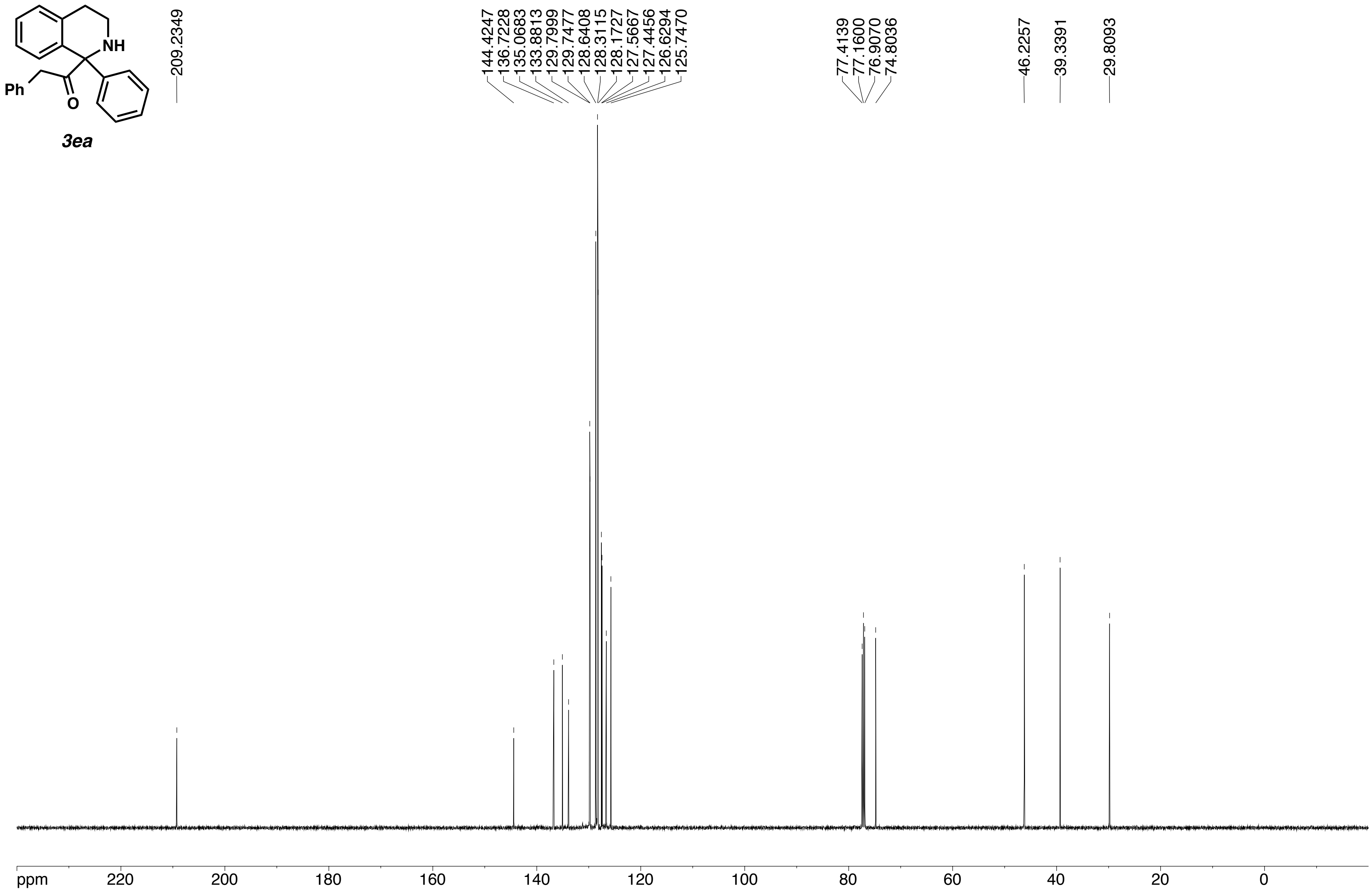


$^{13}$C NMR (125.8 MHz, CDCl$_3$) of compound **3da**.

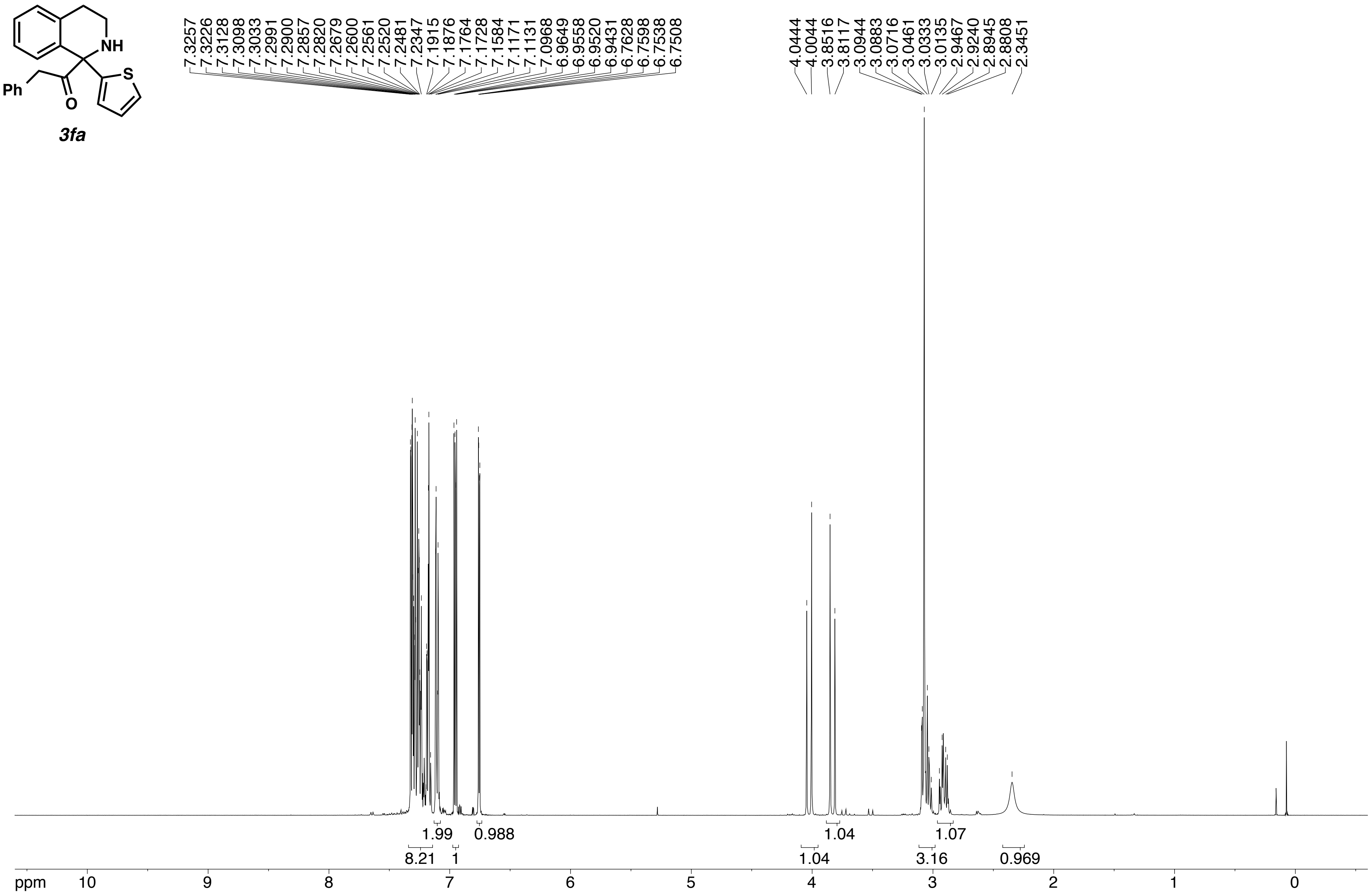


***3ea***

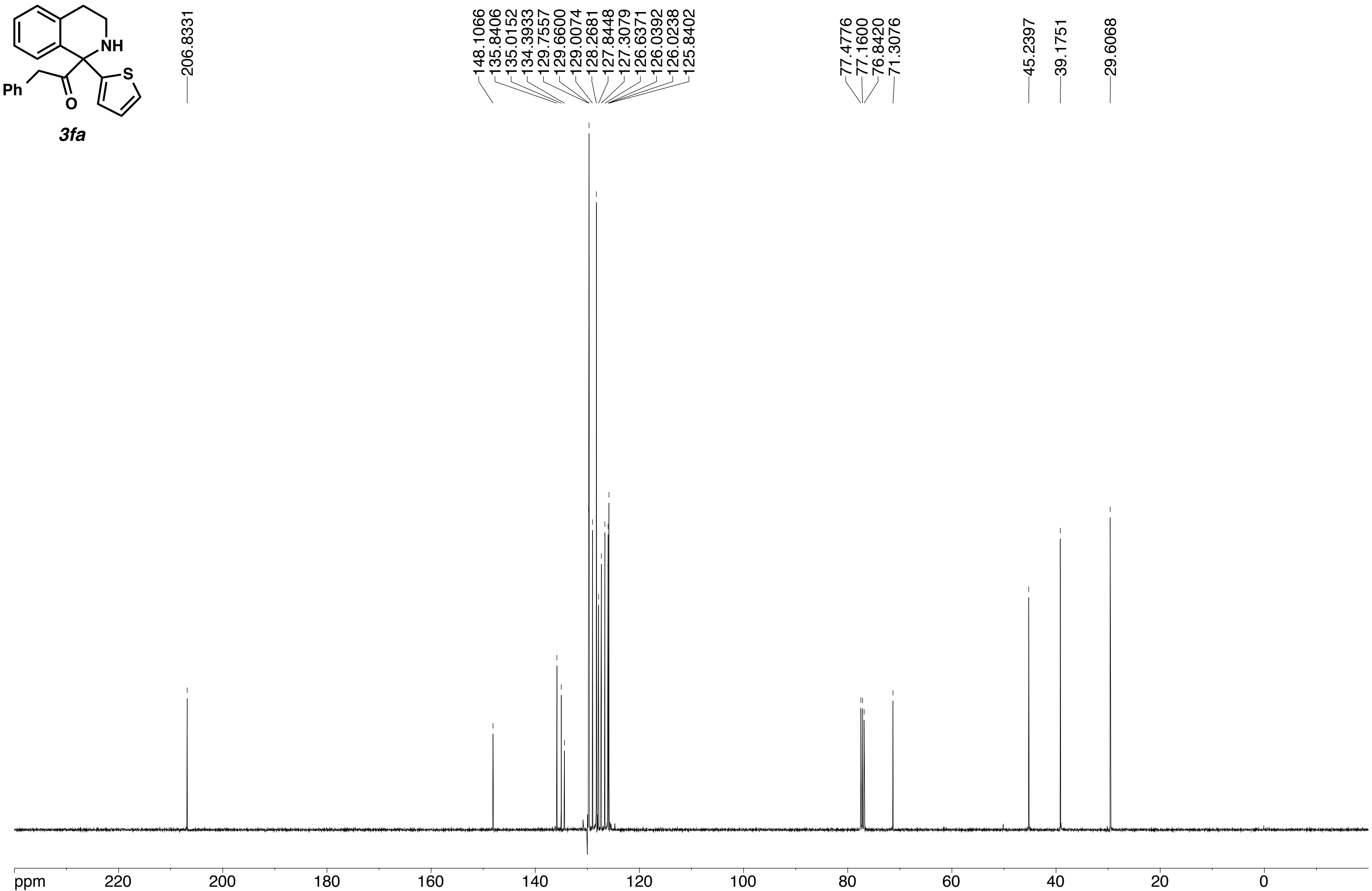
$^1$H NMR (500.3 MHz, CDCl$_3$) of compound **3ea**.



$^{13}$C NMR (125.8 MHz, CDCl$_3$) of compound **3ea**.

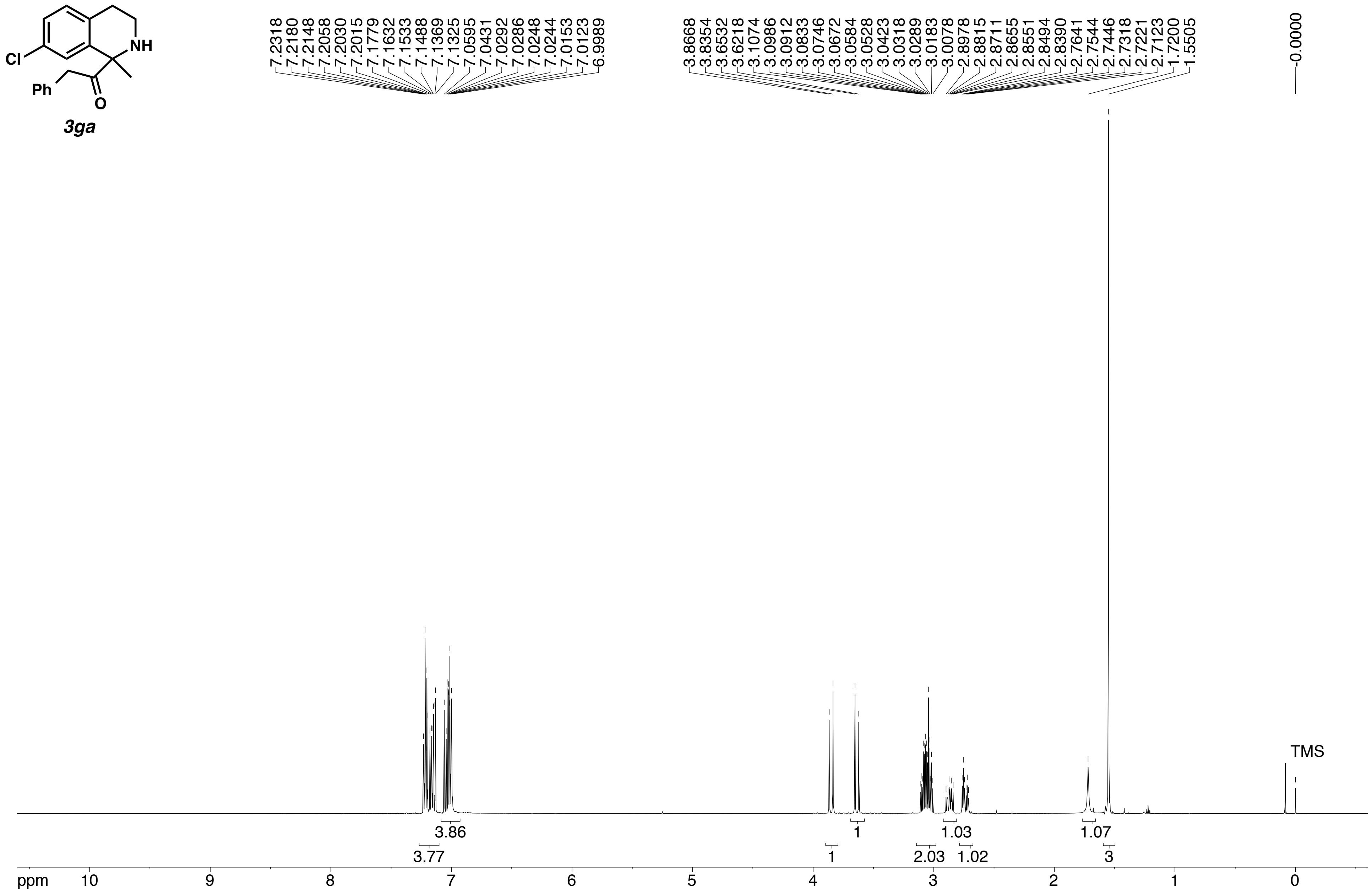


$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3fa**.



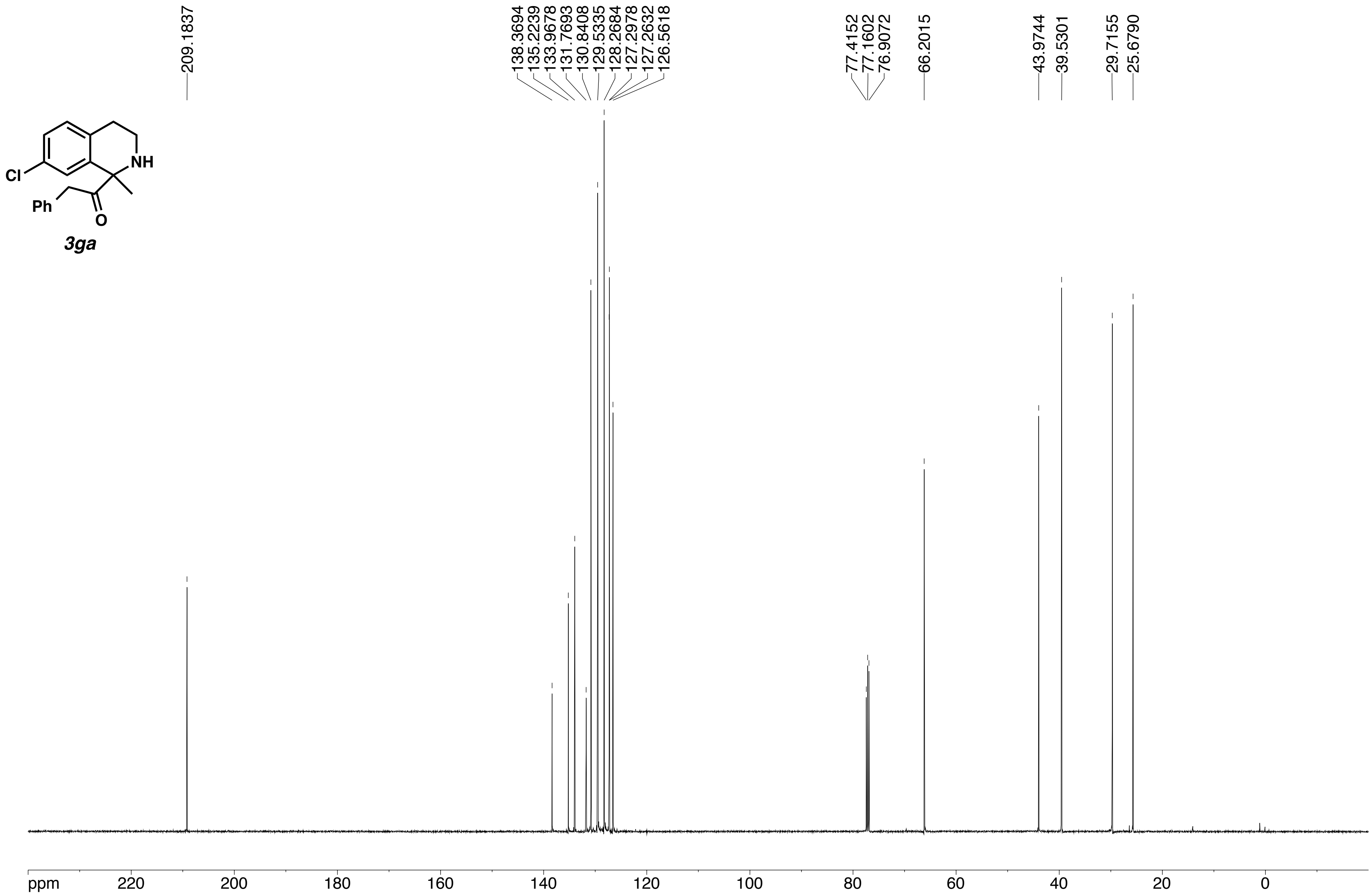
***3fa***

$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3fa**.

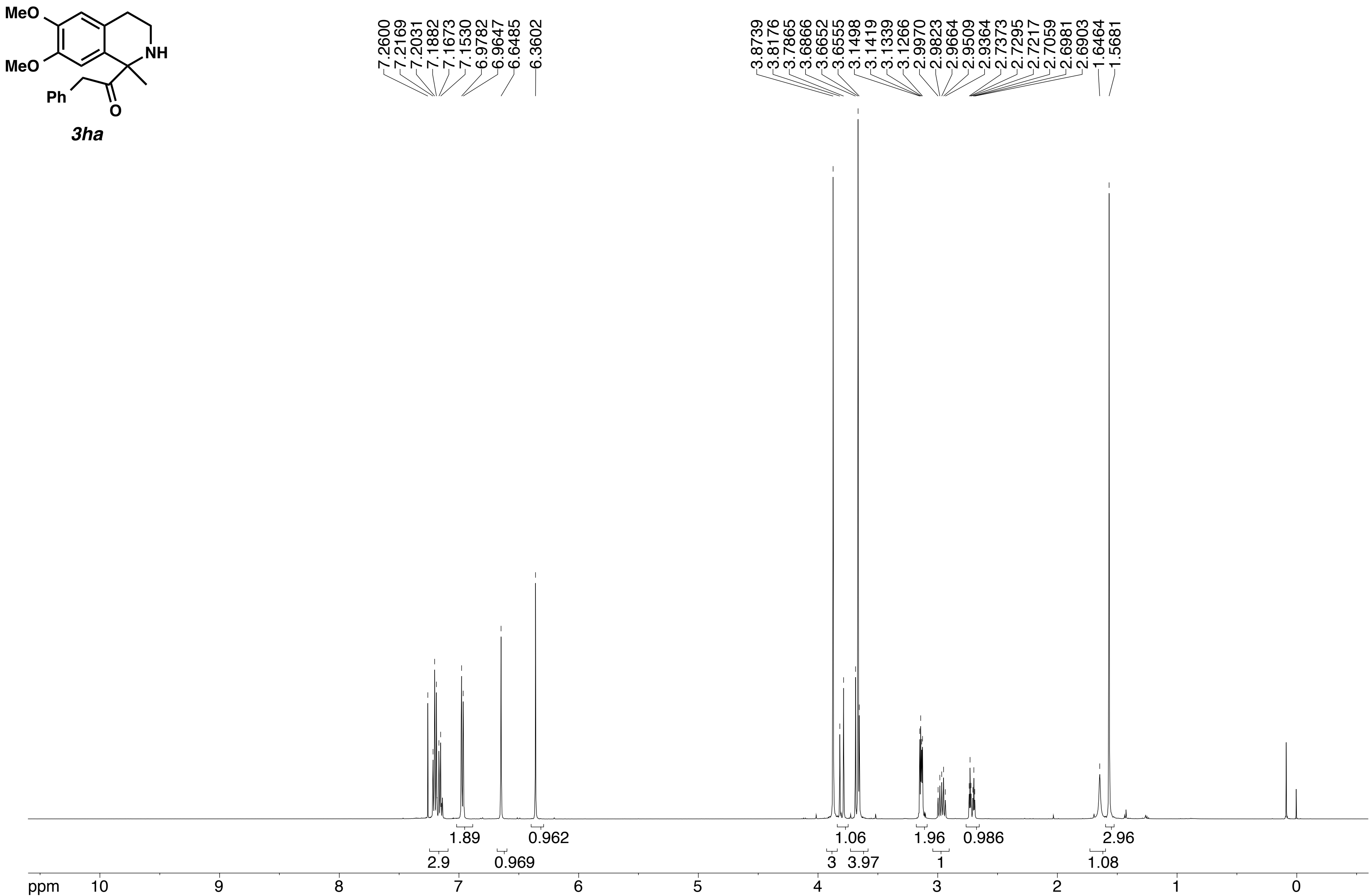


$^1$H NMR (500.3 MHz, CDCl$_3$, TMS) of compound **3ga**.

*3ga*



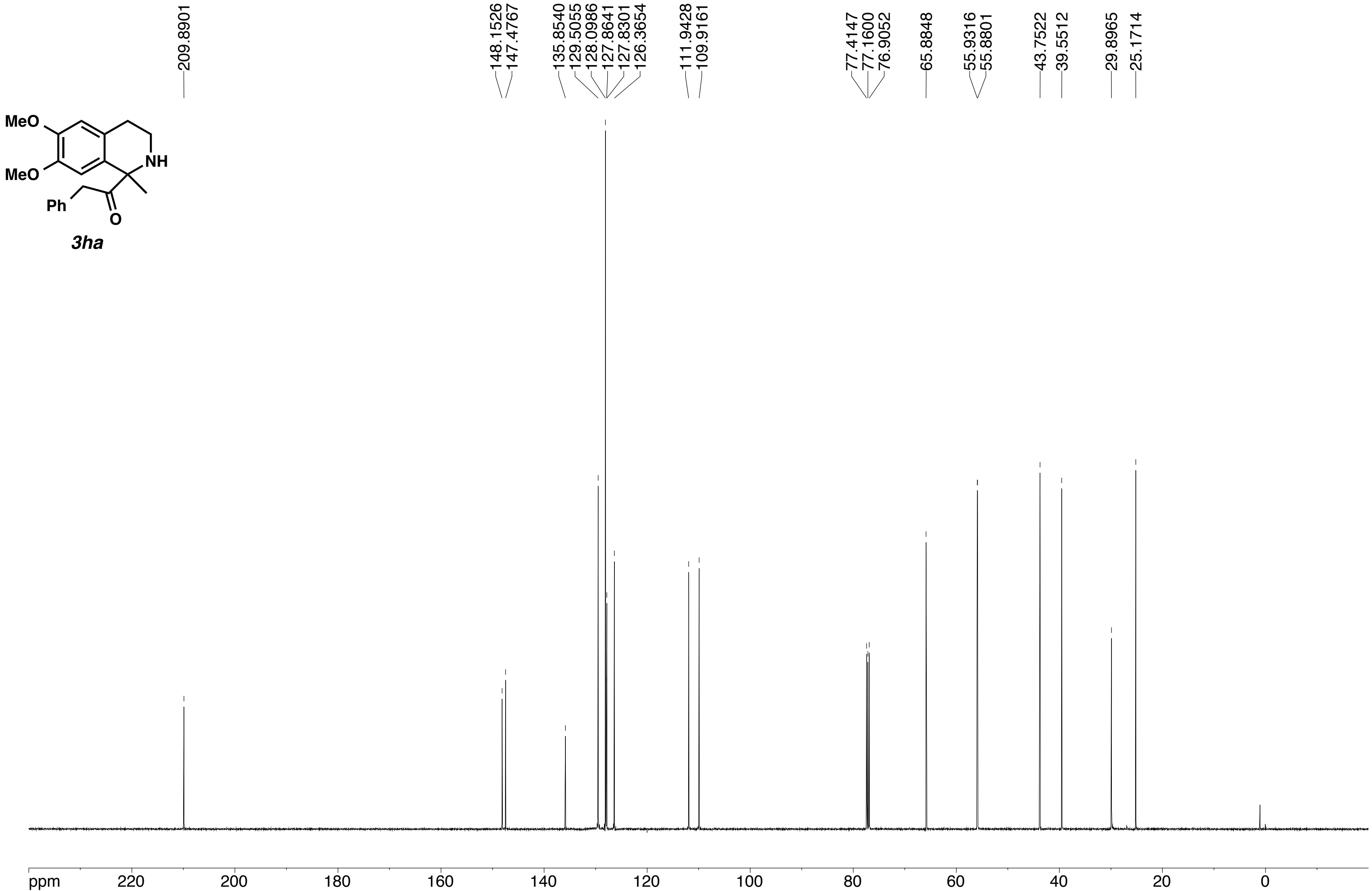
$^{13}$H NMR (125.8 MHz, CDCl$_3$) of compound **3ga**.



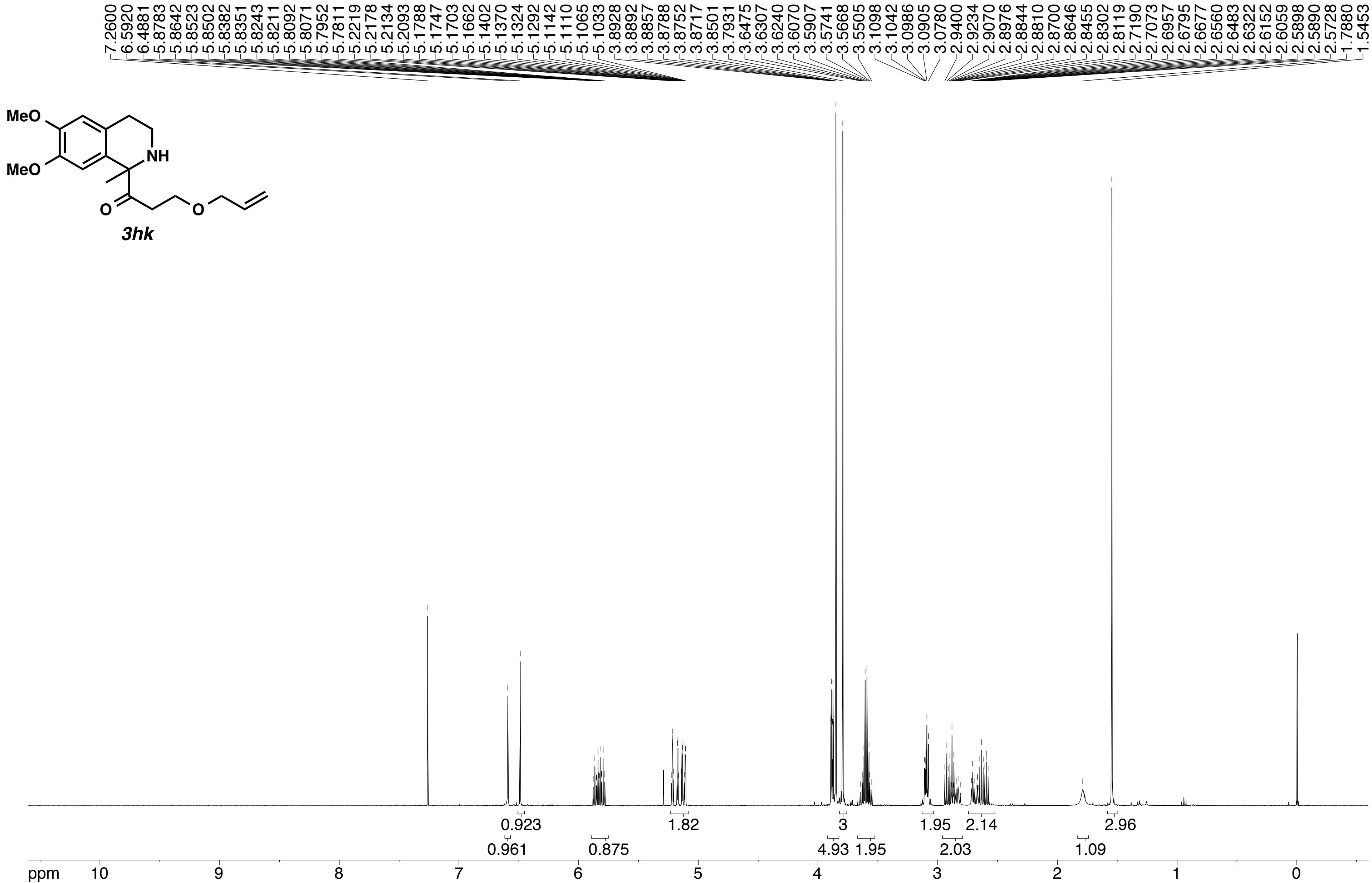
***3ha***

$^1$H NMR (500.3 MHz, CDCl$_3$) of compound **3ha**.

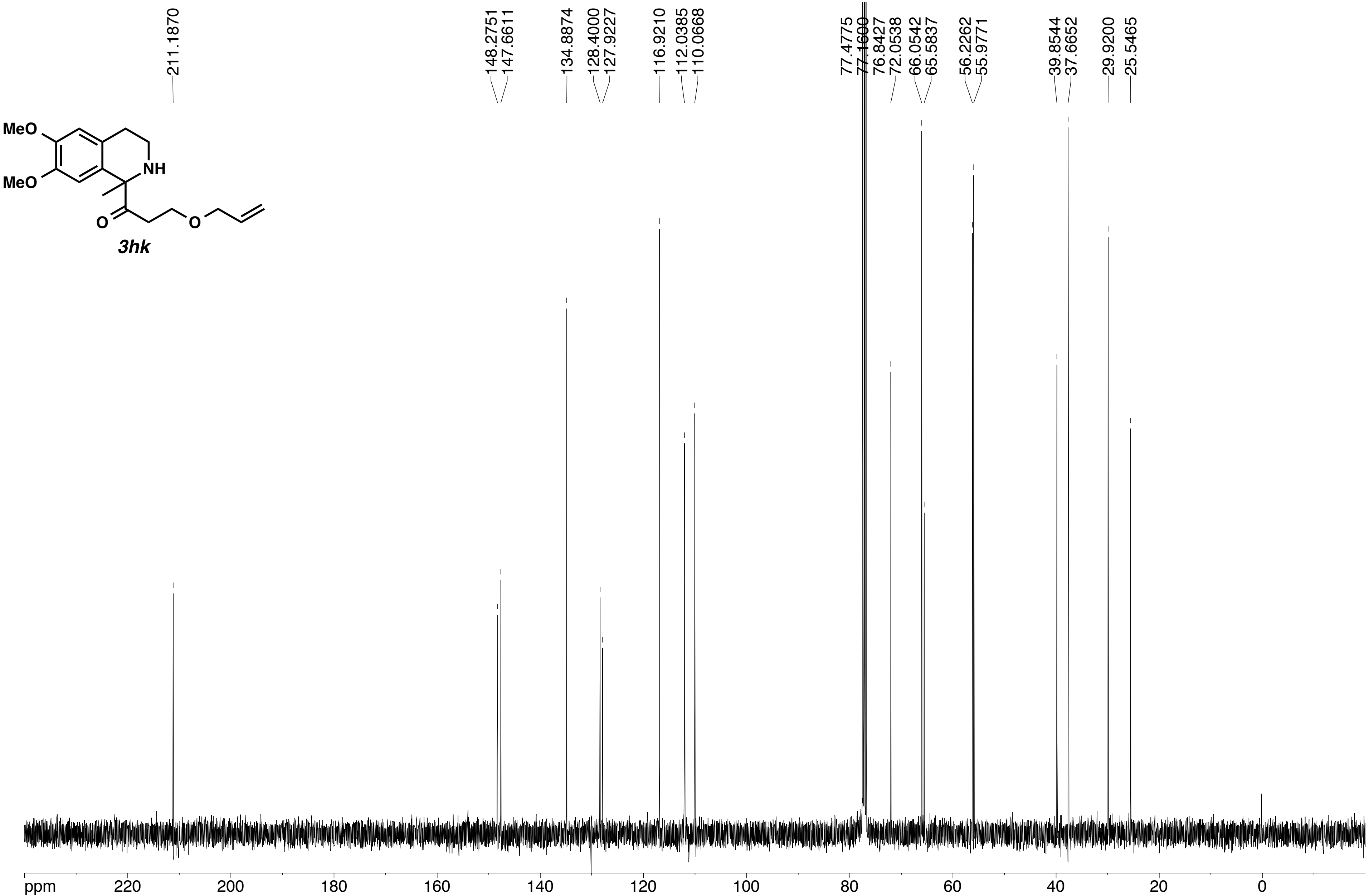
***3ha***



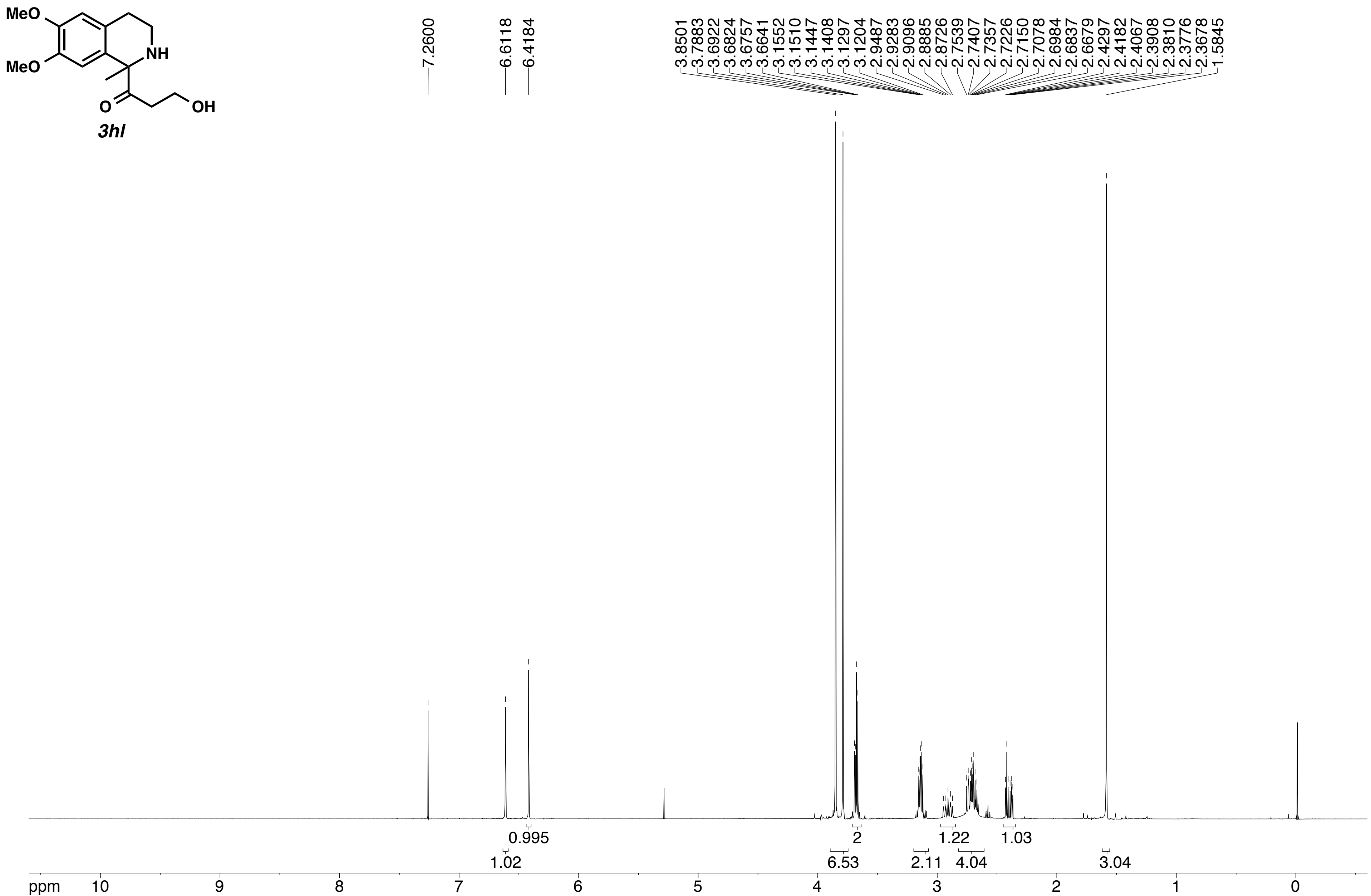
$^{13}$C NMR (125.8 MHz, CDCl$_3$) of compound **3ha**.



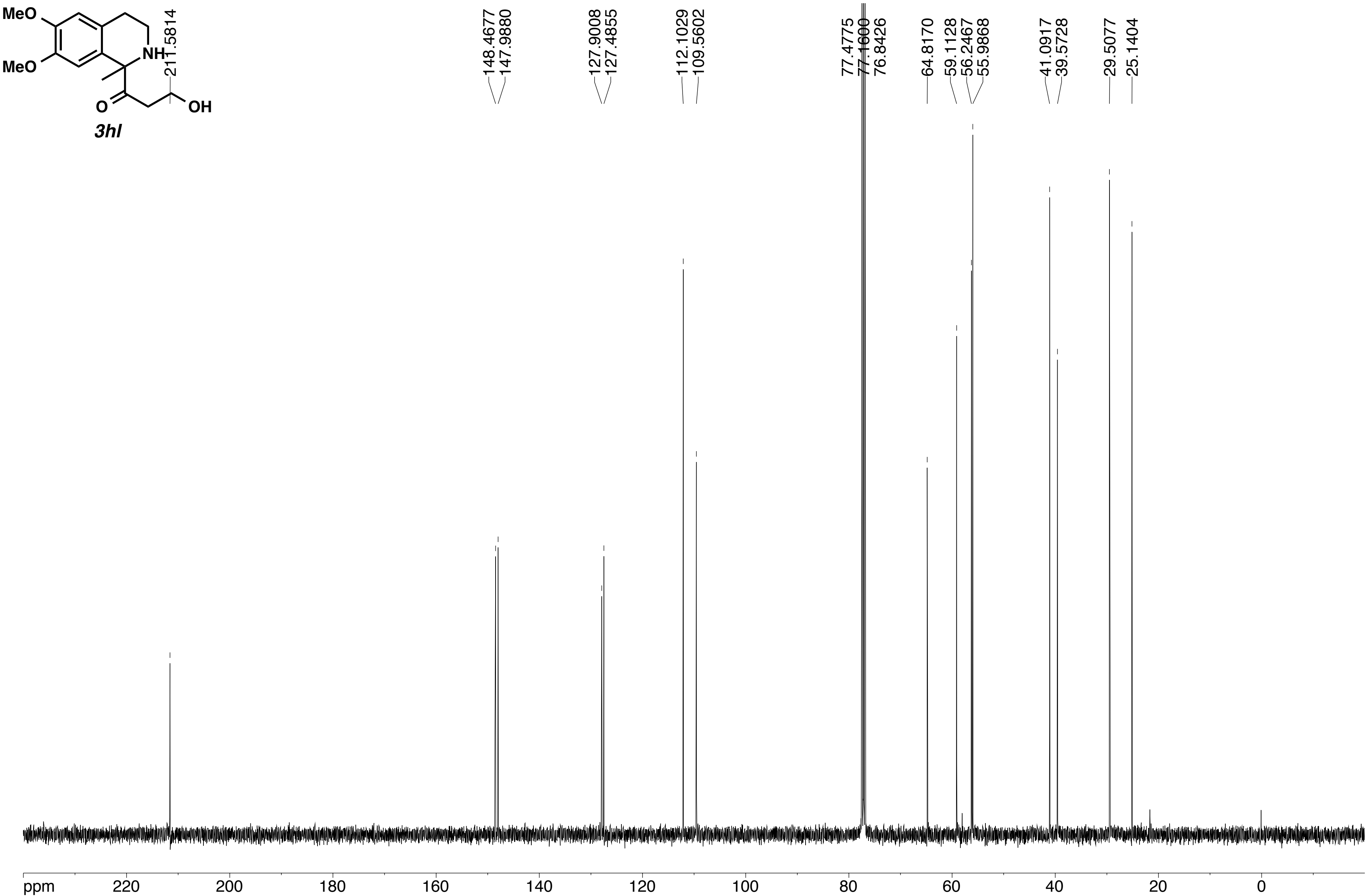
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3hk**.



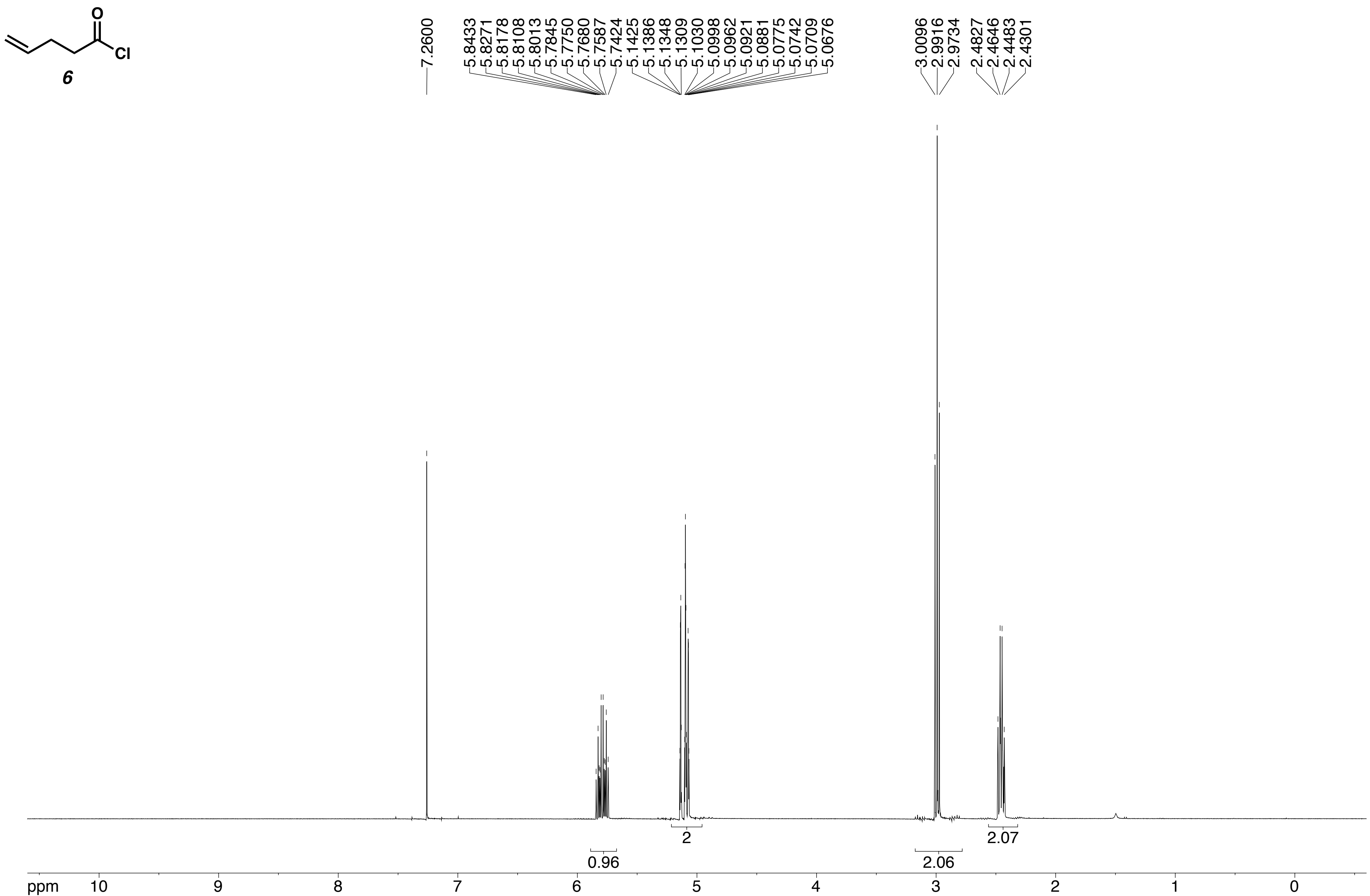
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3hk**.



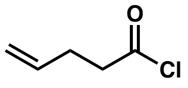
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **3hl**.



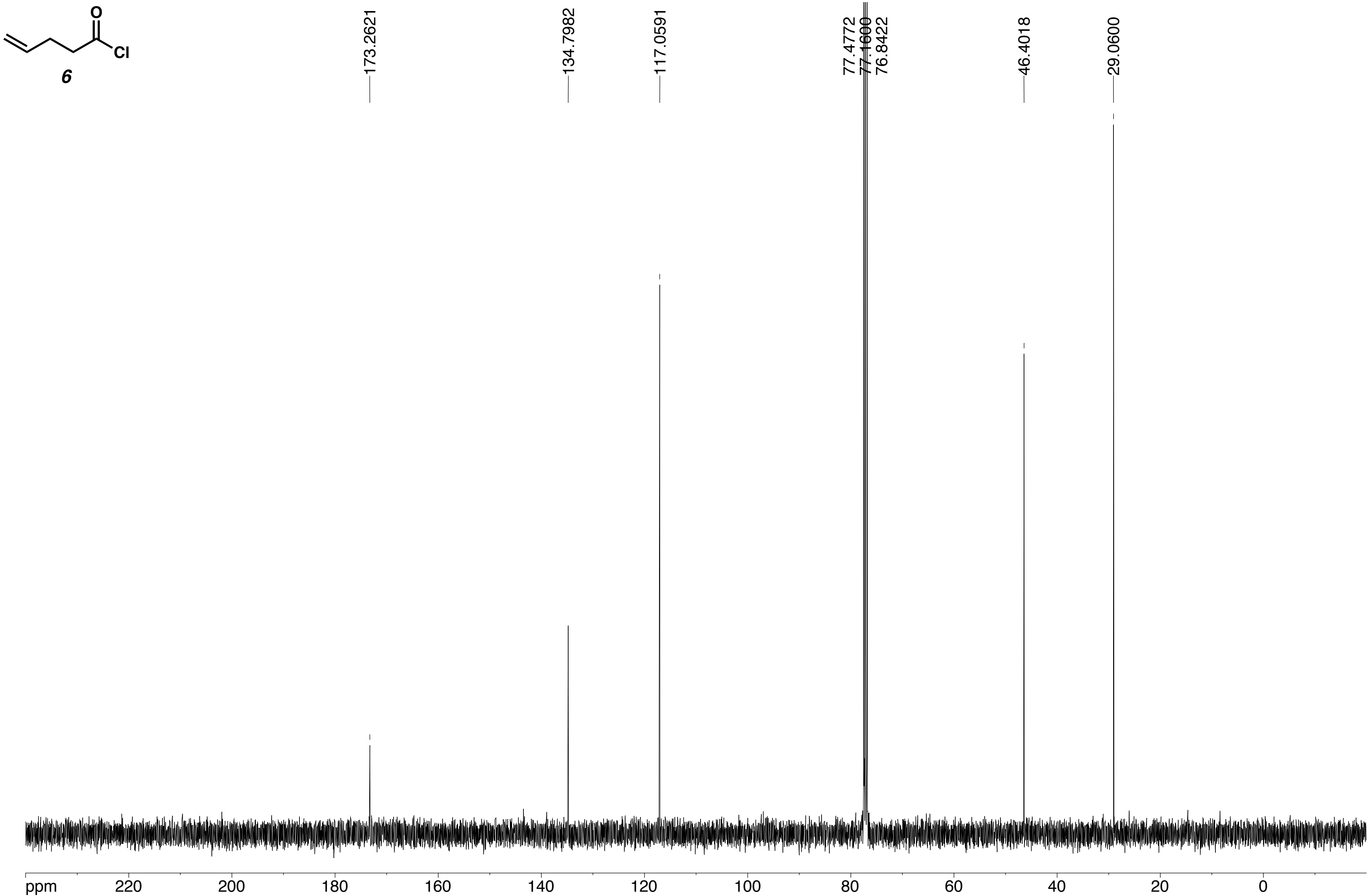
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **3hl**.



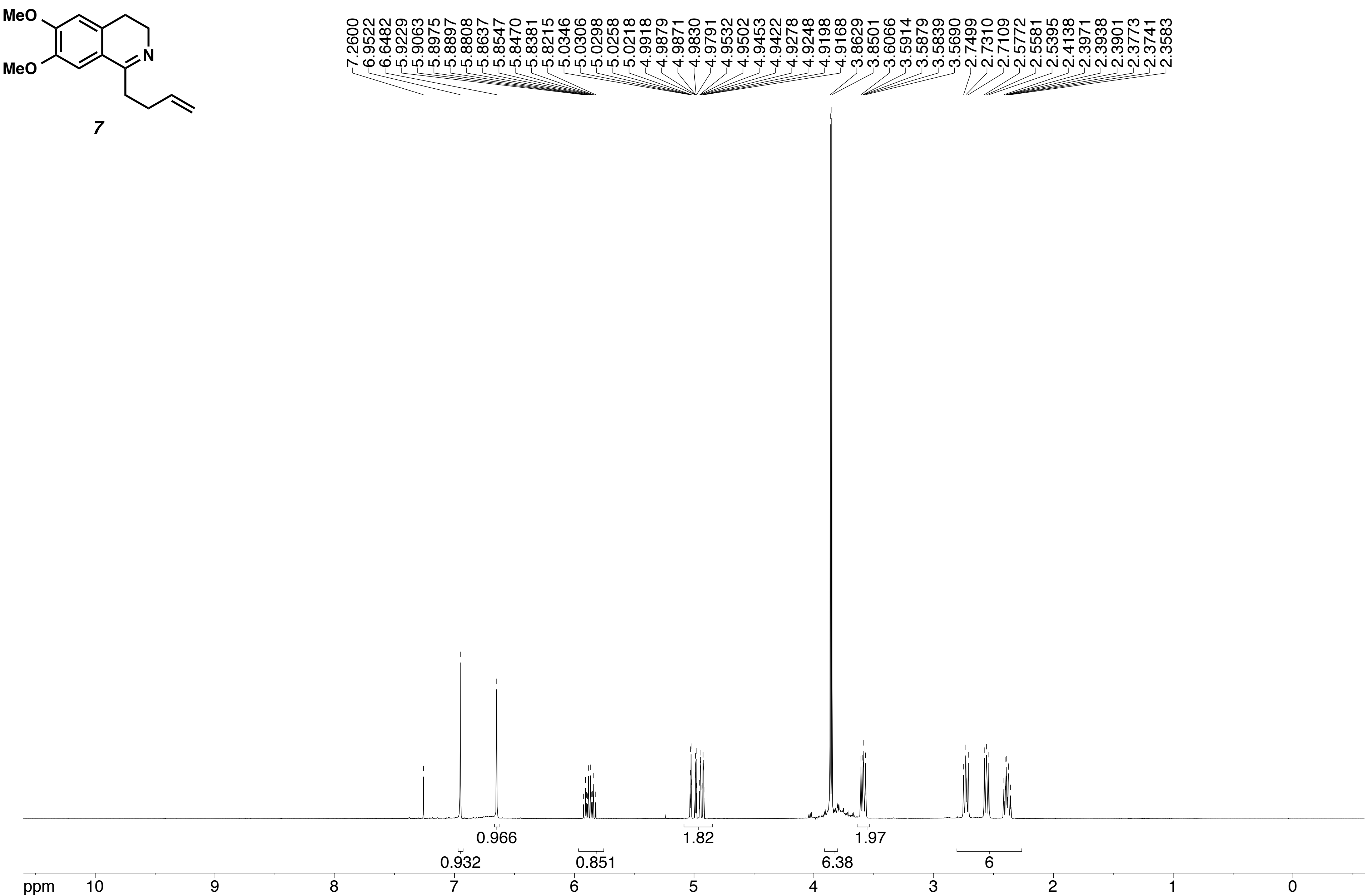
$^1$H NMR (400.1 MHz, $CDCl_3$) of compound **6**.



***6***

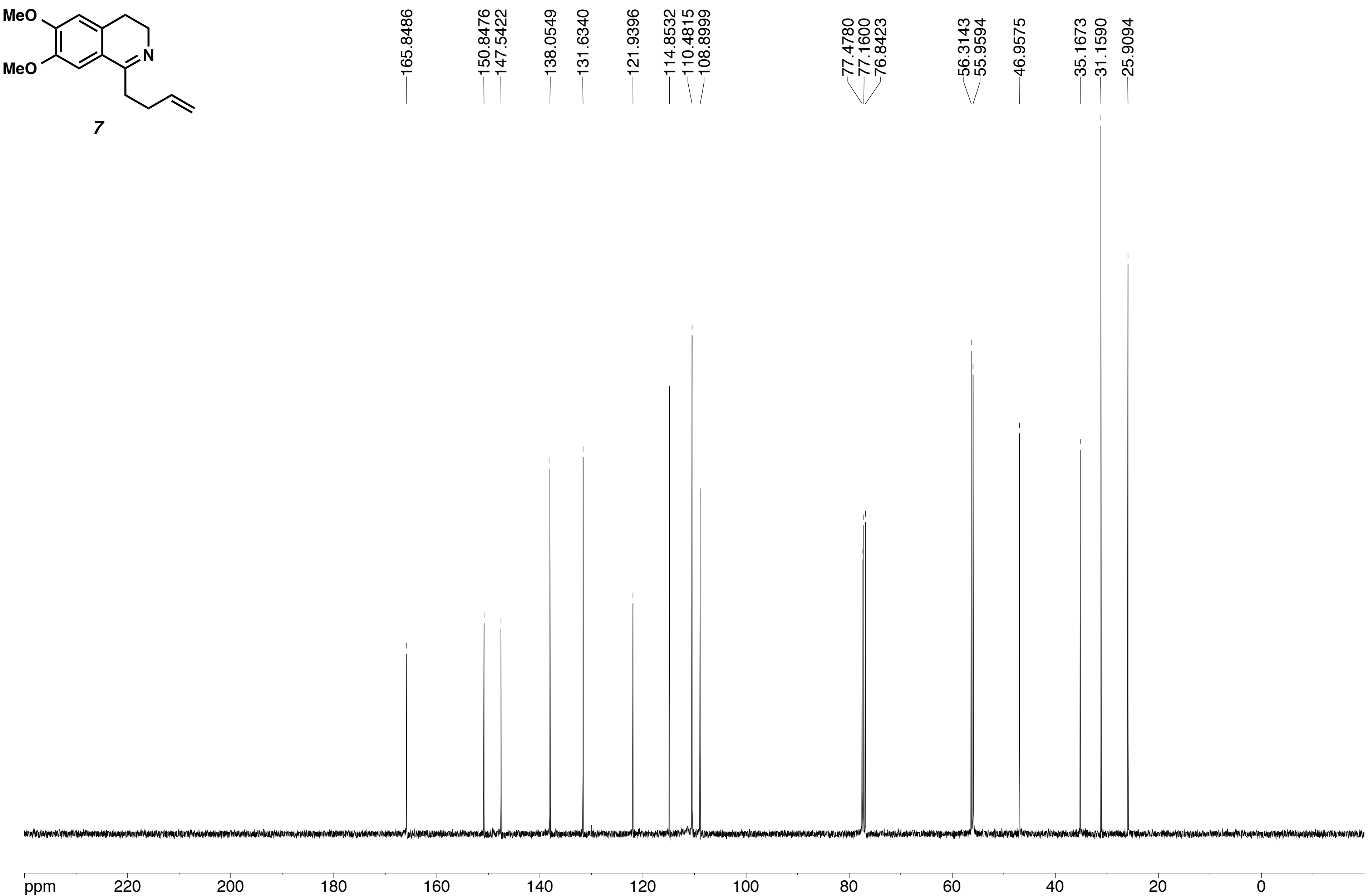


$^{13}$C NMR (100.6 MHz, $CDCl_3$) of compound **6**.

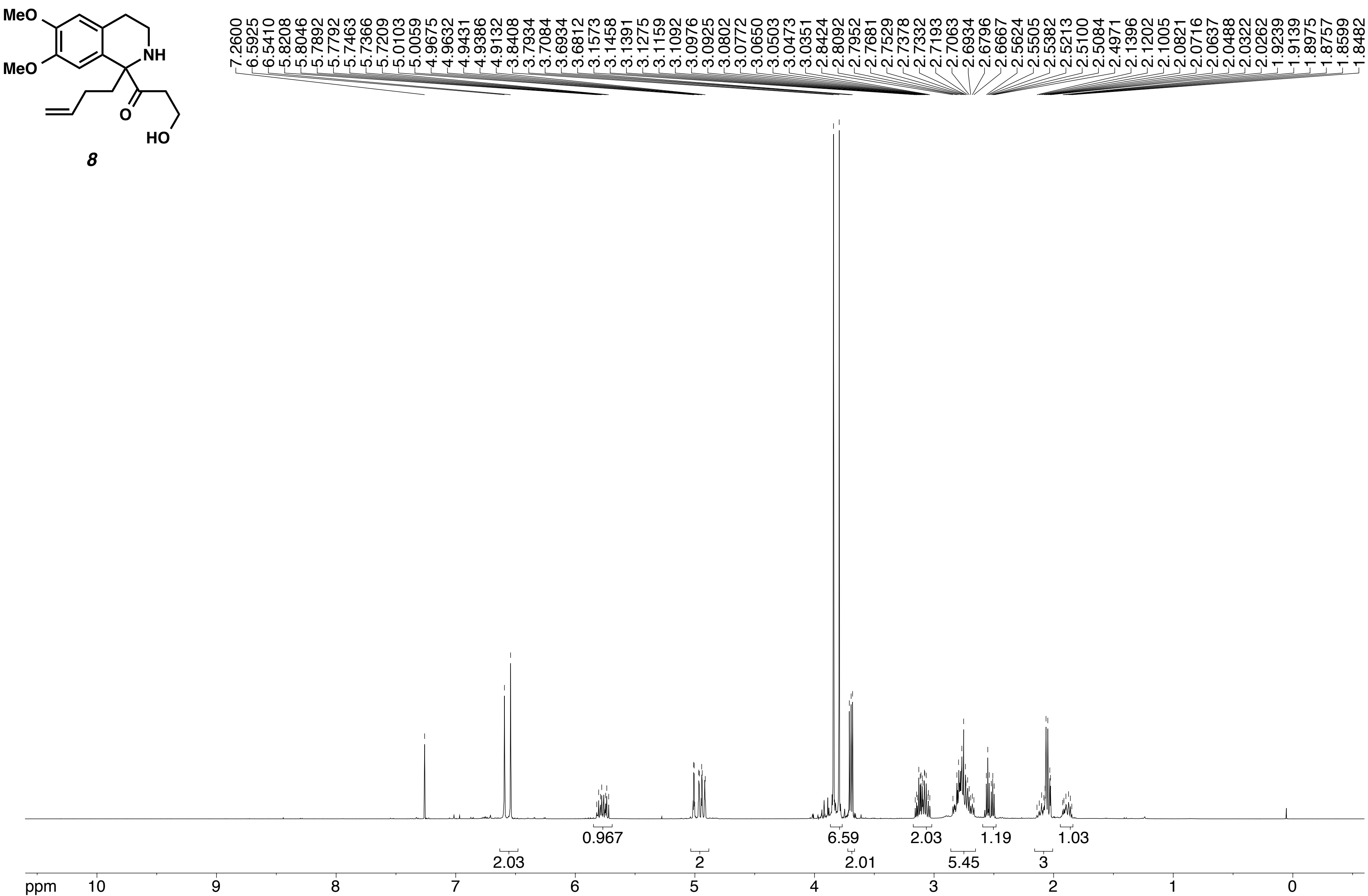


$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **7**.

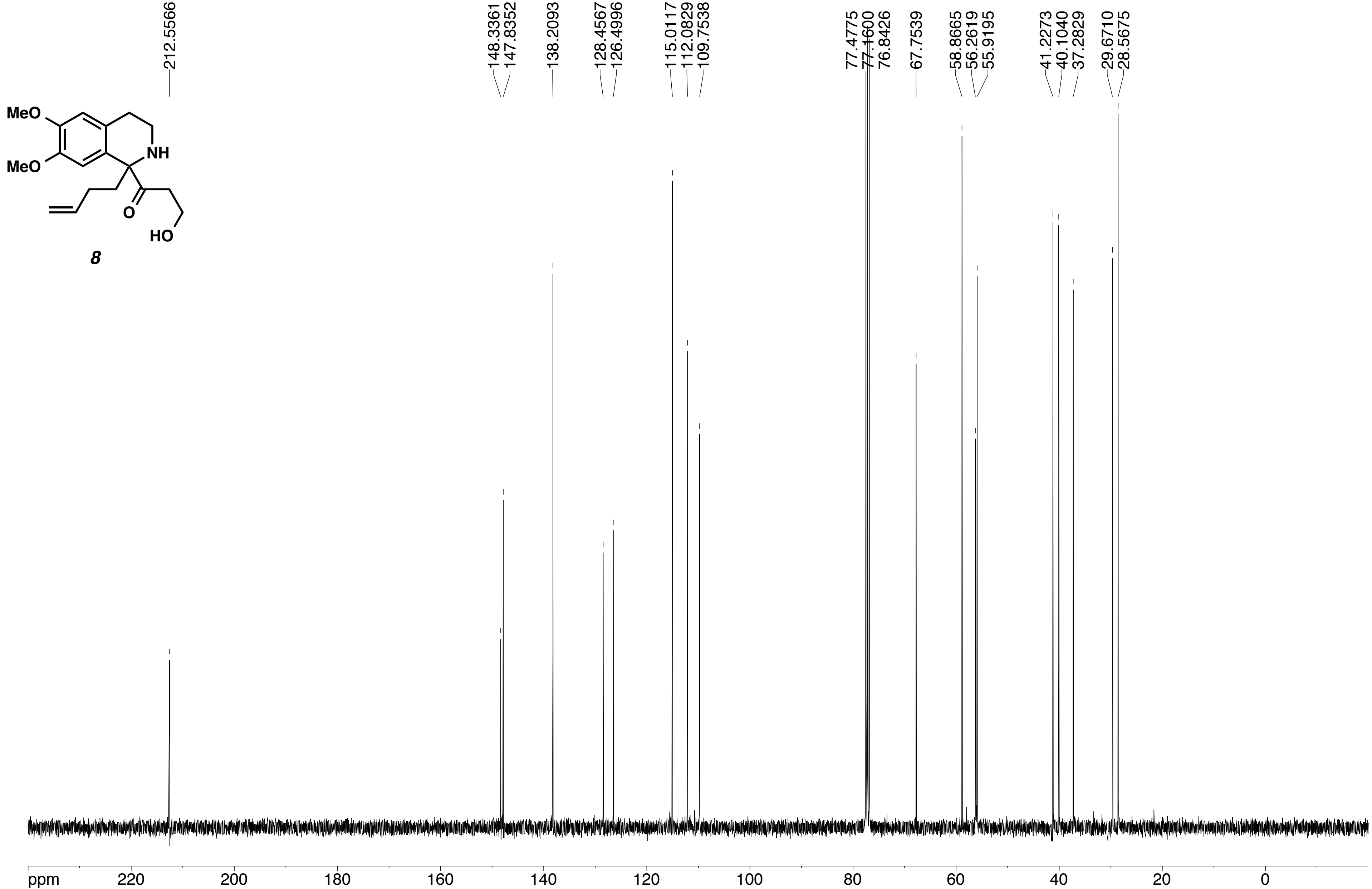
*7*



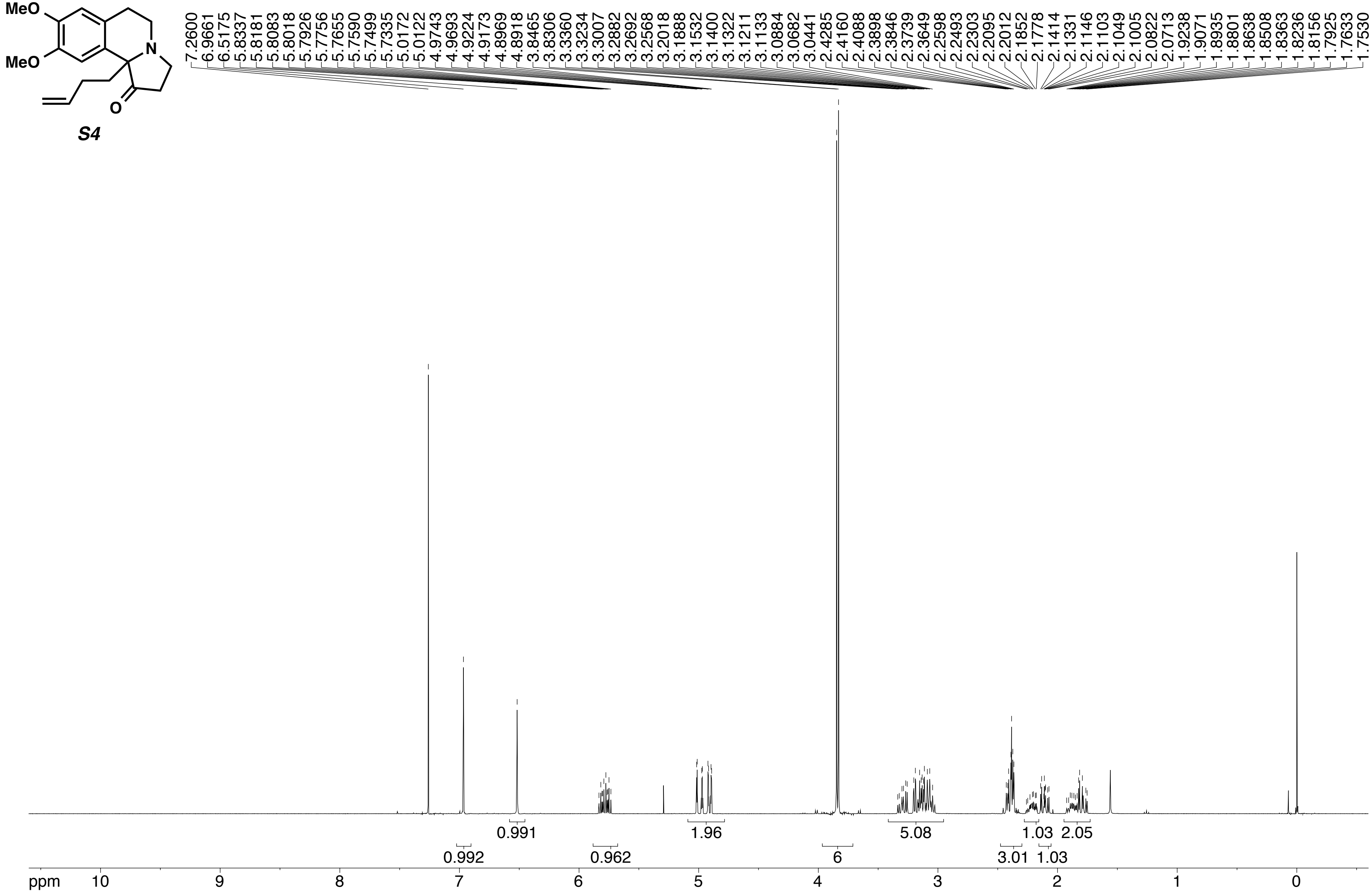
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **7**.



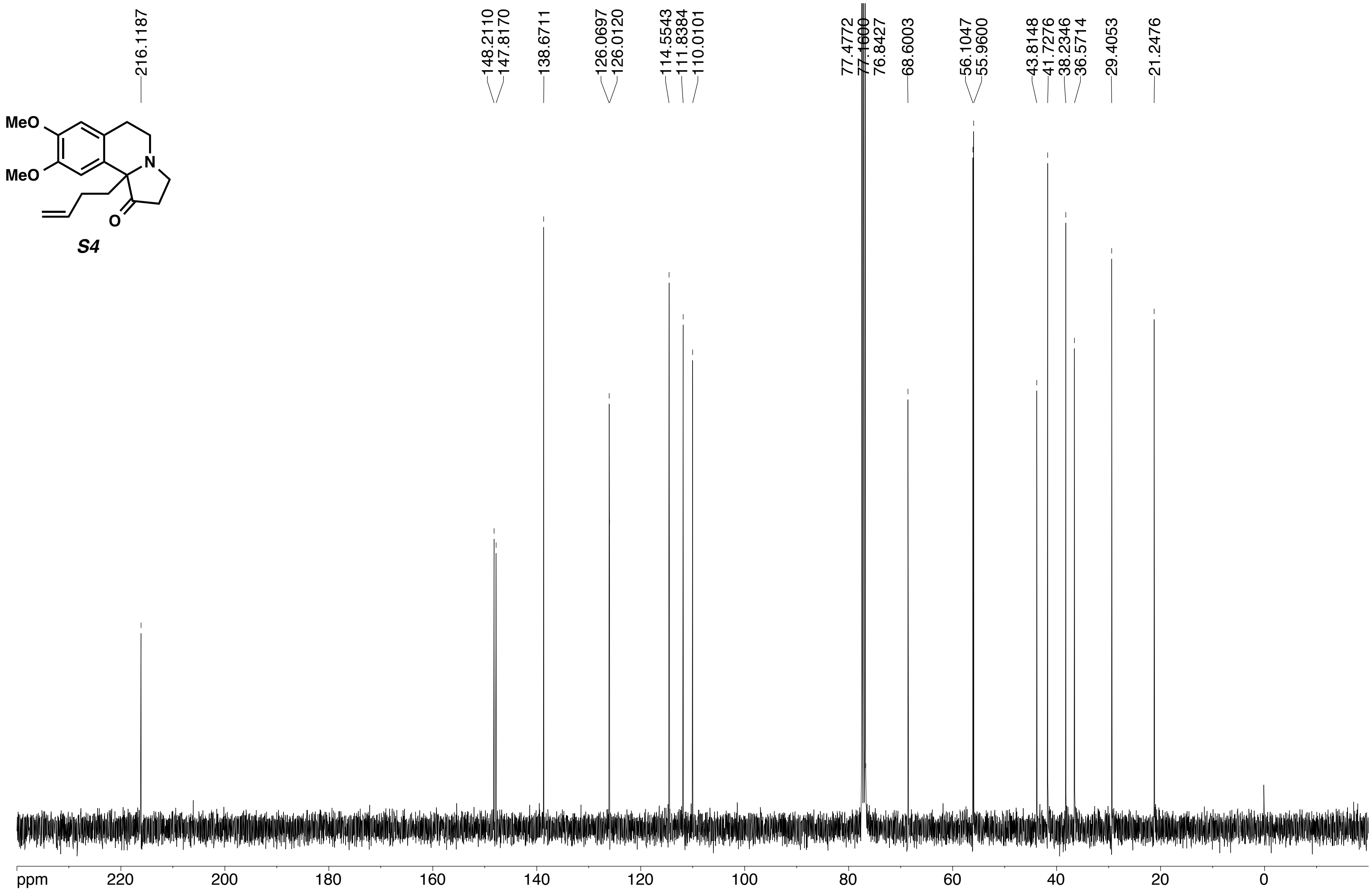
$^1$H NMR (400.1 MHz, $CDCl_3$) of compound **8**.



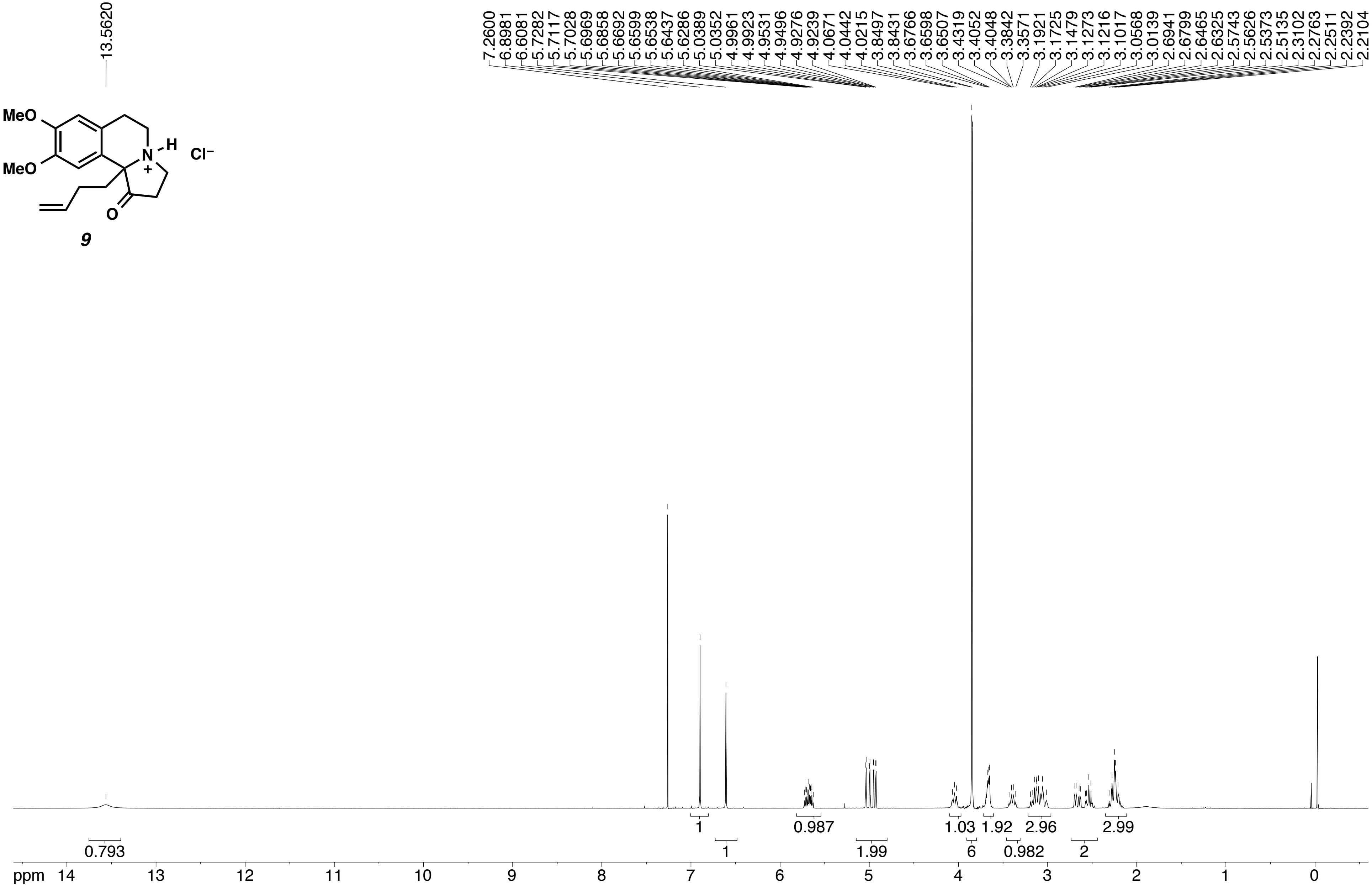
$^{13}$H NMR (100.6 MHz, CDCl$_3$) of compound **8**.



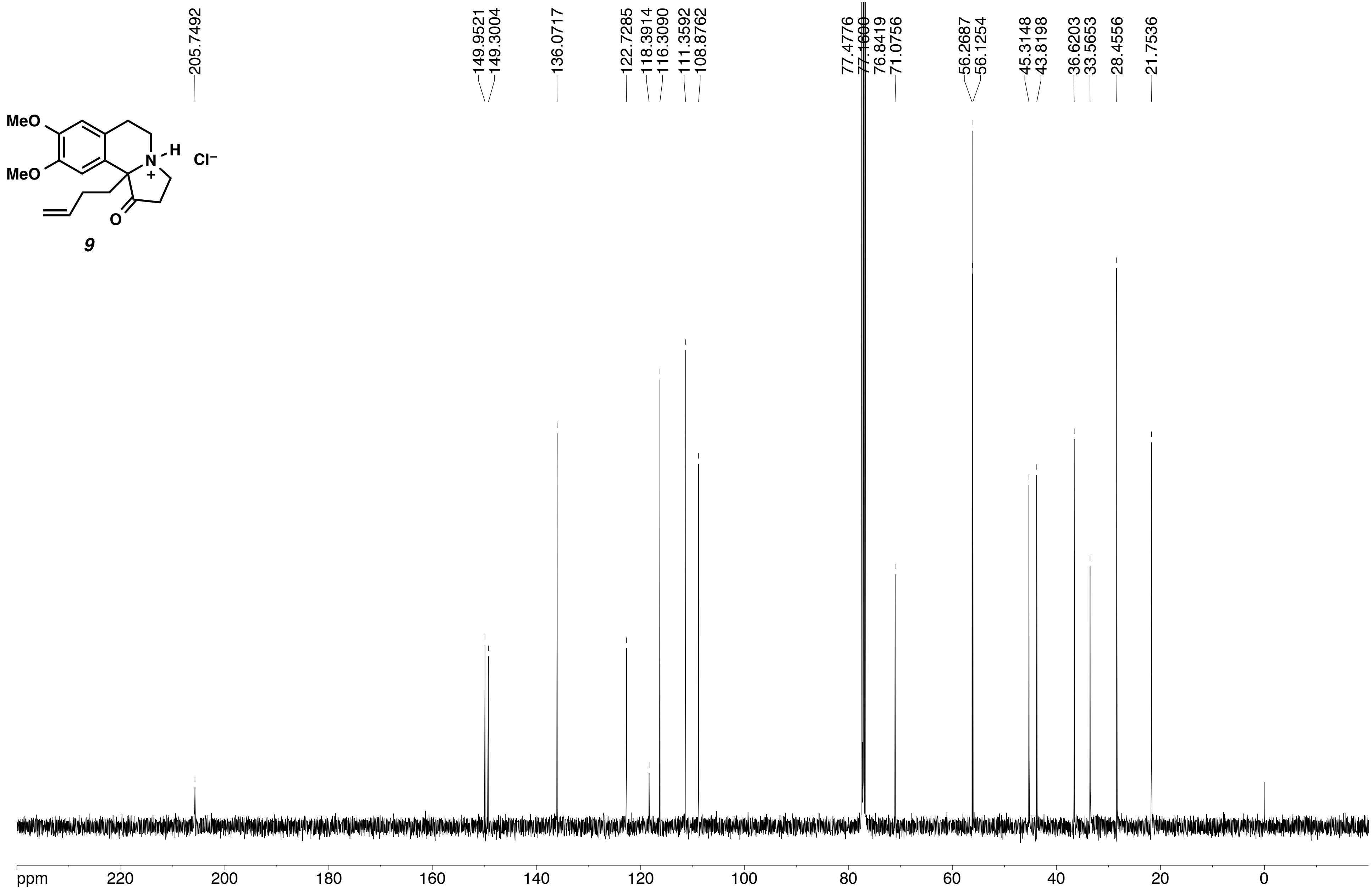
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **S4**.



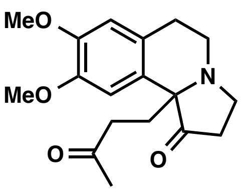
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **S4**.



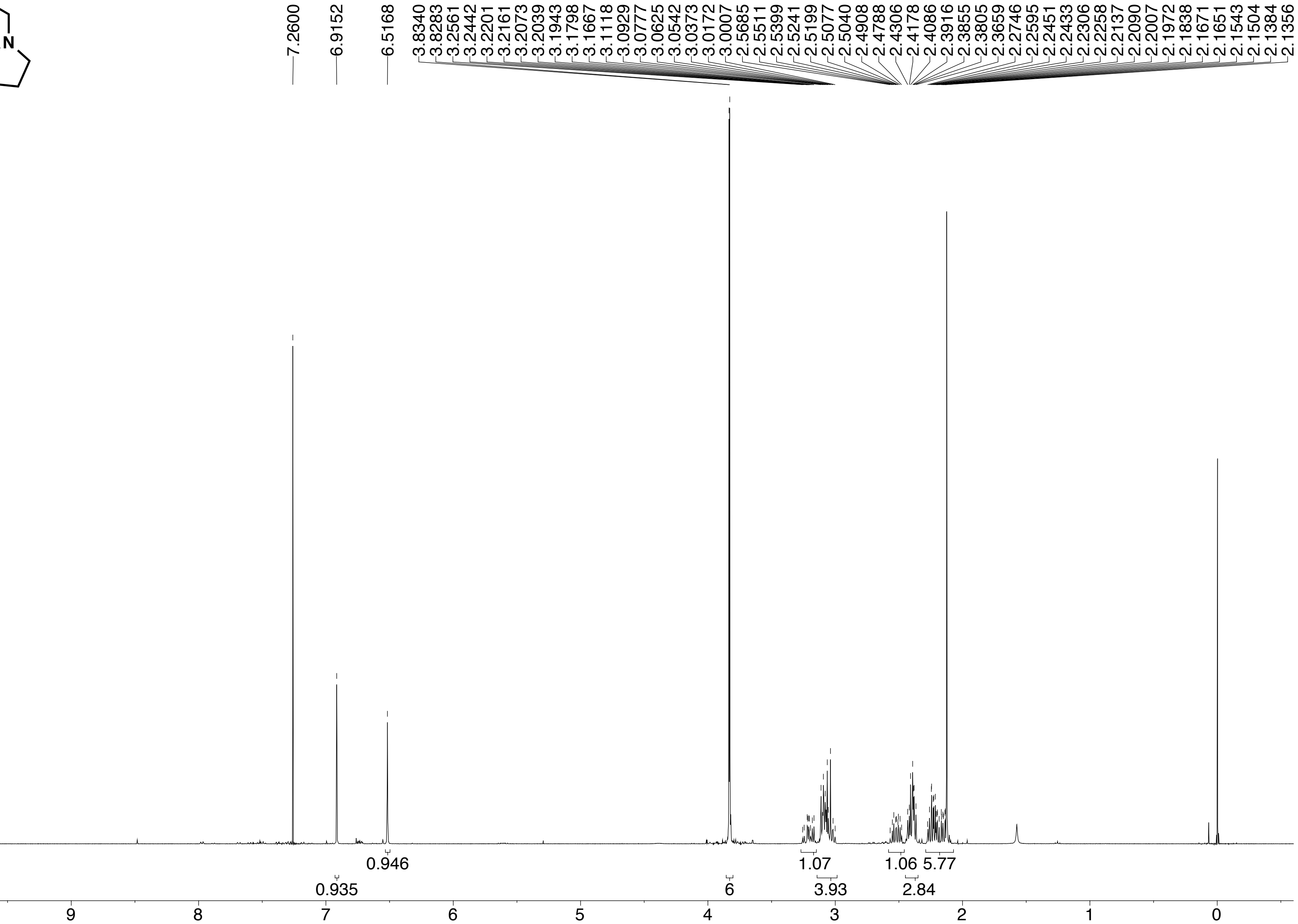
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **9**.



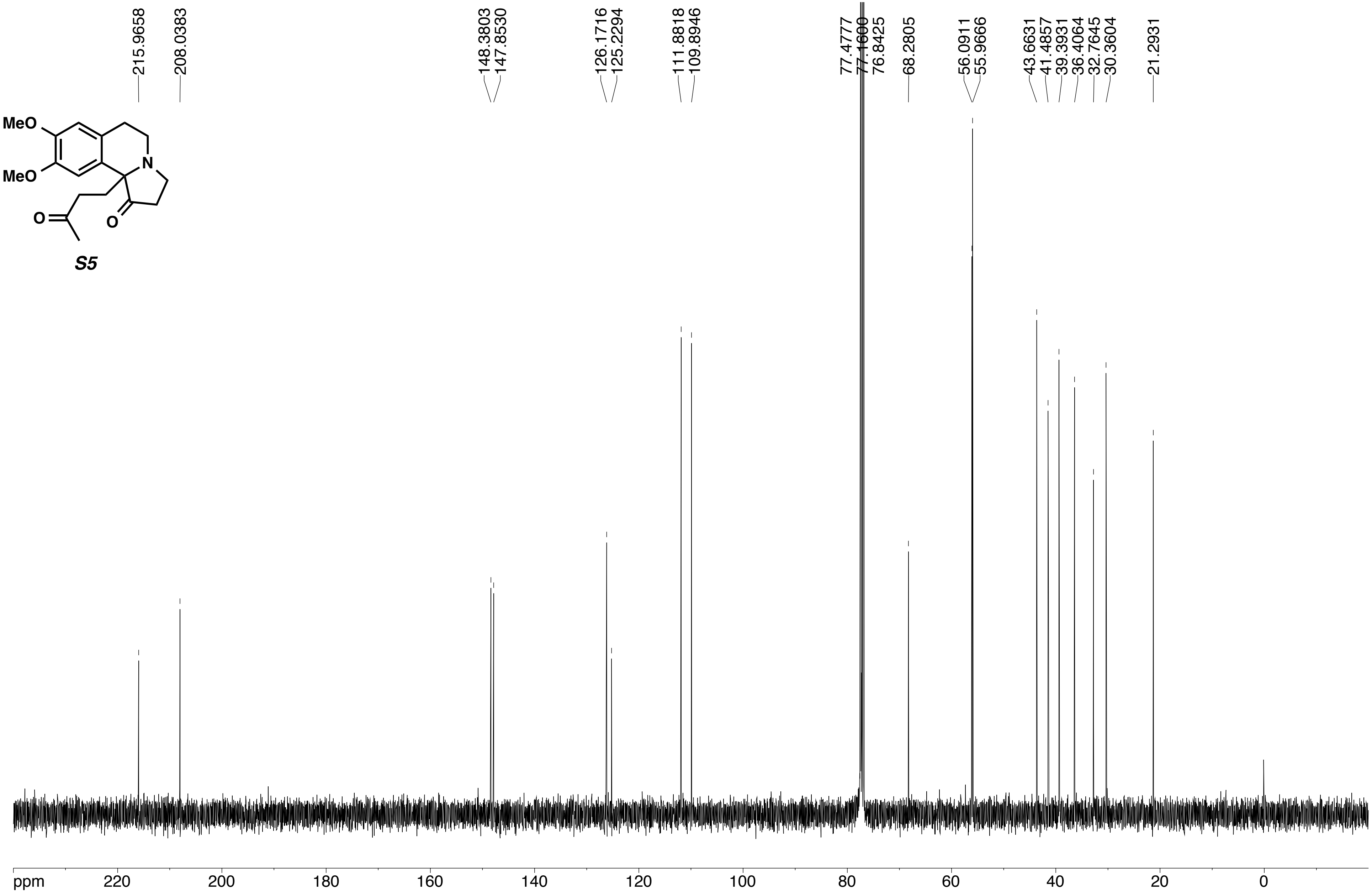
$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **9**.



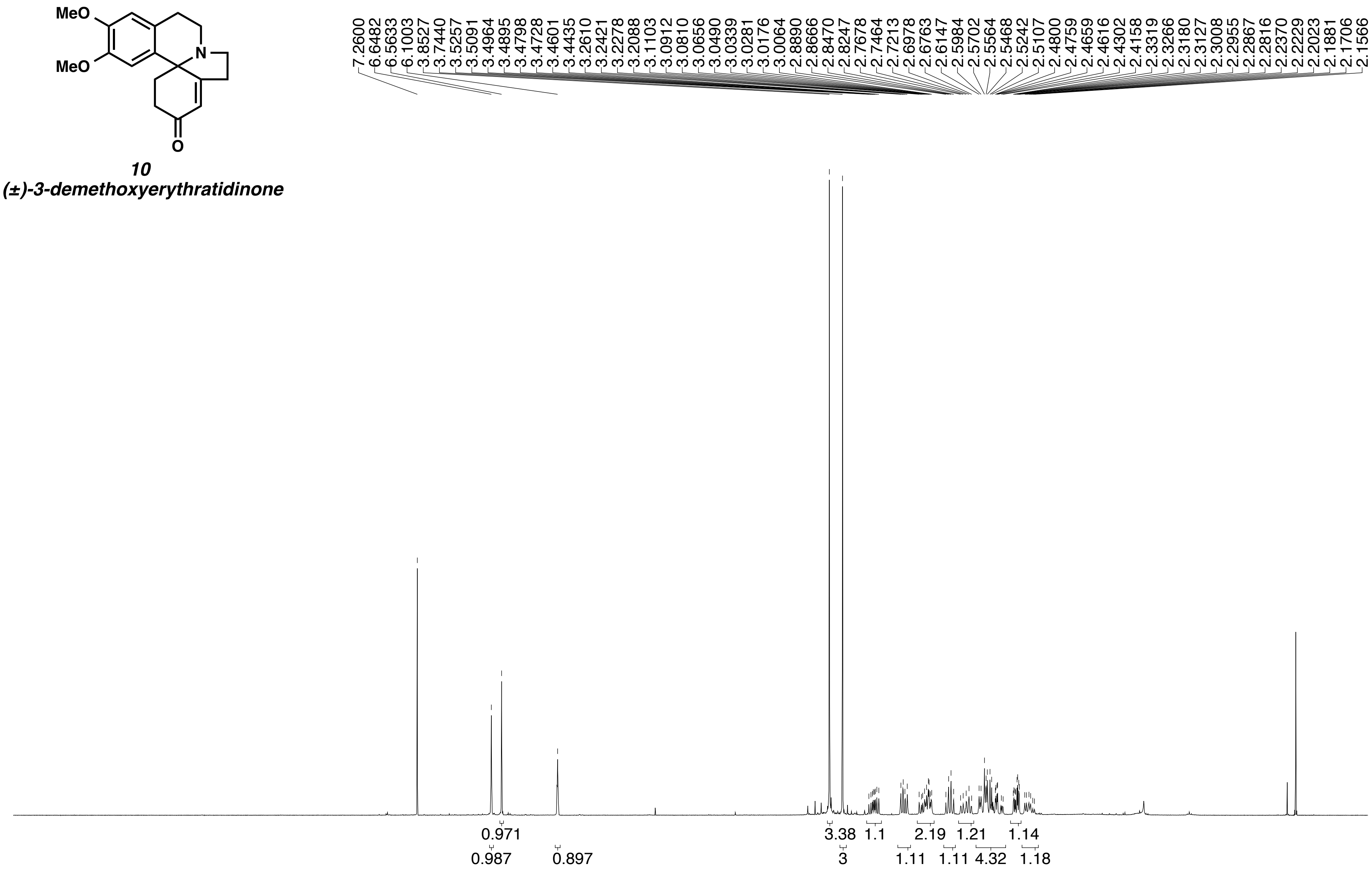
***S5***



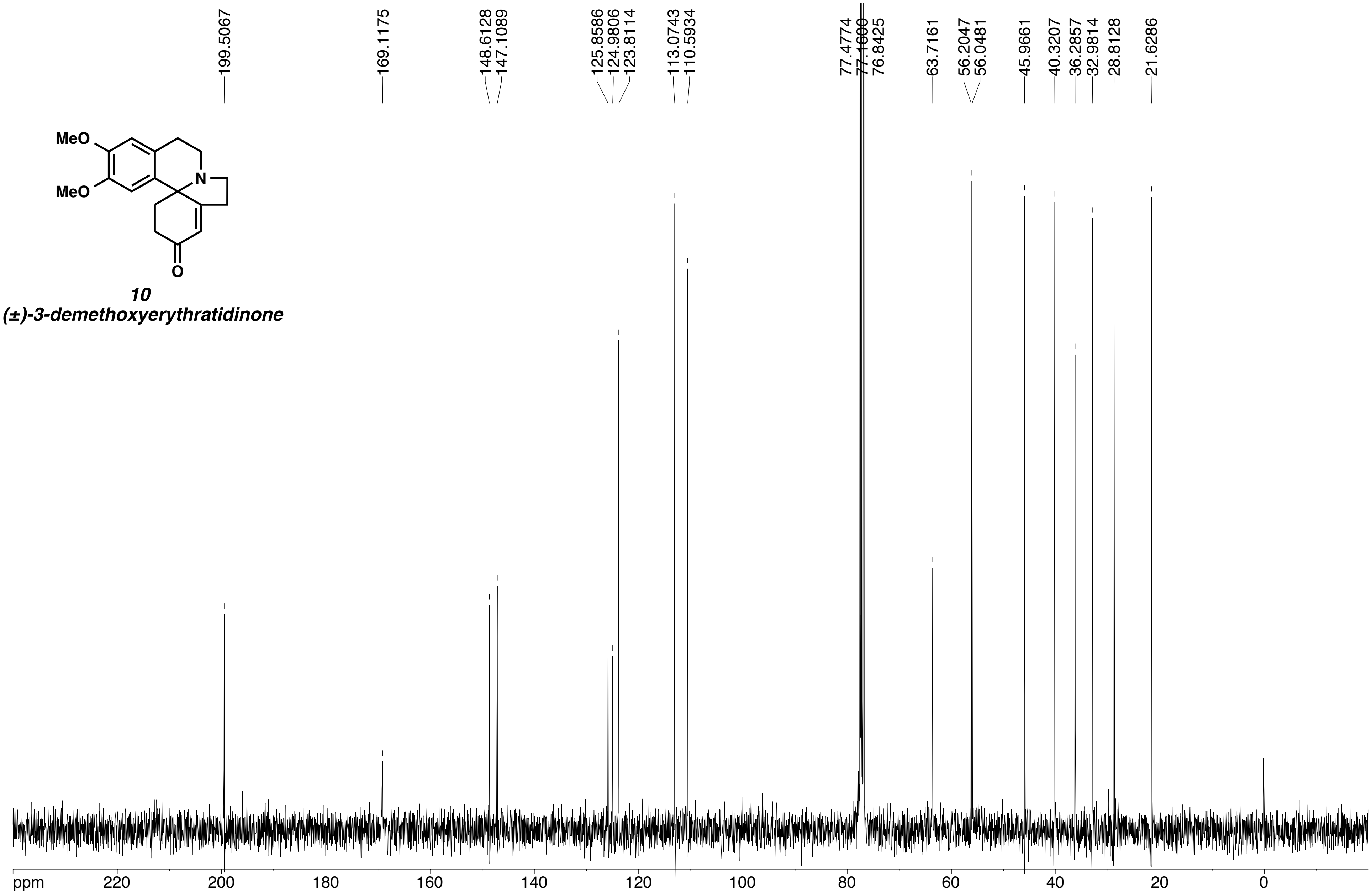
$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **S5**.



$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **S5**.



$^1$H NMR (400.1 MHz, CDCl$_3$) of compound **10**.



***10***
***(±)-3-demethoxyerythratidinone***

$^{13}$C NMR (100.6 MHz, CDCl$_3$) of compound **10**.