Supporting Information for:

Continuous and Convergent Access to Vicinyl Amino Alcohols

Tomoya Nobuta,† [a] Guozhi Xiao,† [a] Diego Ghislieri,[a] Kerry Gilmore,*[a] and Peter H. Seeberger*[ab]

[a] Max Planck Institute of Colloids and Interfaces, Am Mühlenberg 1, 14476 Potsdam, Germany
[b] Institute of Chemistry and Biochemistry, Freie Universität Berlin, Arnimallee 22, 14195 Berlin, Germany

General Experimental Information and Materials

All commercially available compounds and solvents (Acros, Aldrich, Fluka, Alfa Aesar and Merck) were used without purification. Column chromatography was performed on silica gel (Sigma-Aldrich, 220-440 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400-MR (400 MHz for ^{1}H and 100 MHz for ^{13}C) without additional internal standard. Chemical shifts are reported in δ values (ppm) and are calibrated against residual solvent signal ($CDCl_3$: 7.26, 77.0). The following abbreviations were used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. High-resolution ESI was recorded on an IonSpec Ultra instrument.

Instruments

Flow reactions were performed either using a syringe pump (PHD2000, Harvard Apparatus) or a Vapourtec® R-Series Flow Chemistry system equipped with standard PTFE tubing (i.d. 1.0 mm, o.d. 1.6 mm). The reactor coils were supplied by Vapourtec®. Standard PTFE tubing connectors were used to connect tubing to inputs and outputs. Back pressure regulators (BPR's) were obtained from Upchurch. The liquid-liquid extractor (Figure S1) was produced in house modifying slightly the Jensen design.[1] The Teflon device dimensions are 30 mm width, 50 mm length and 30 mm height while the trough dimensions are 1 mm width, 30 mm length and 10 mm height. The 0.5 mm pore PTFE membrane (Pall) is cut to 15 x 40 mm from a 47 mm disk and is sandwiched between the two halves covering the respective troughs. The aqueous outlet is equipped with PTFE tubing (i.d. 0.5 mm, o.d. 1.6 mm, 50 cm) while the organic outlet is equipped with PTFE tubing (i.d. 1.0 mm, o.d. 1.6 mm, 3 cm).

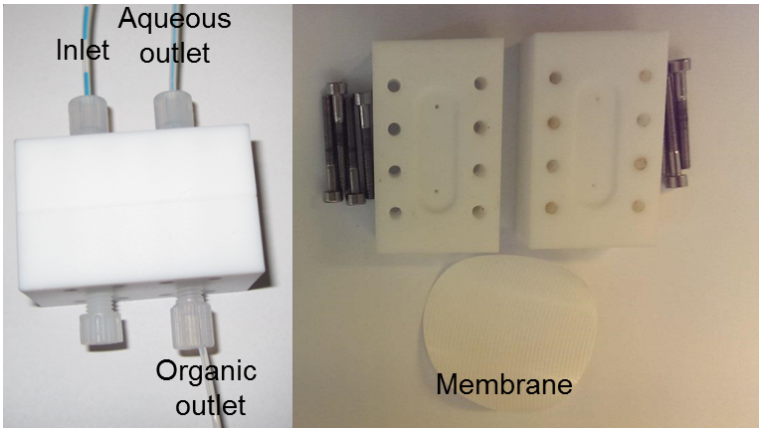
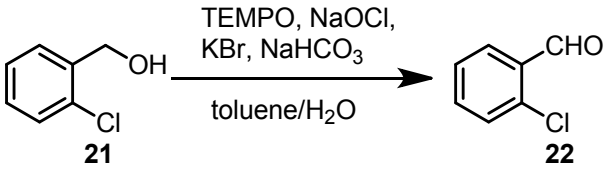


Figure S1. Homemade liquid-liquid separator.

General Procedures for Aryl β-Amino Alcohols.

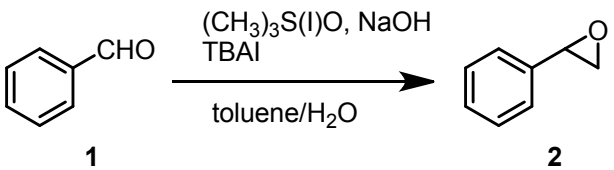
Module 1: Oxidation



21 **22**

Using a syringe pump, a solution of sodium hypochlorite (716 mg, 1.25 mmol), potassium bromide (2.98 mg, 0.025 mmol), sodium bicarbonate (12.6 mg, 0.15 mmol) in water (1 mL) and a solution of *o*-chlorobenzylalcohol (71.3 mg, 0.5 mmol), and TEMPO (6.71 mg, 0.05 mmol) in toluene (1 mL) were each passed through 32 cm of PTFE tubing before reaching a T-mixer. The resulting solution then passed through a 10 mL PTFE reactor kept at 0 °C. The flow rates were as follows: toluene solution: 0.0714 mL min^{-1}, water solution: 0.0714 mL min^{-1}. A 50 cm piece of PTFE tubing connected the reactor with the liquid-liquid extractor. A 20 cm piece of PTFE tubing deposited the exiting organic phase in a collection flask. The reactor eluent was concentrated under vacuum. *o*-Chlorobenzaldehyde (**22**)[4] was observed in 98% conversion of **21** based on ^{1}H NMR using 1,2,4,5-tetramethylbenzene as an internal standard.

Module 2: Corey-Chaykovsky Reaction



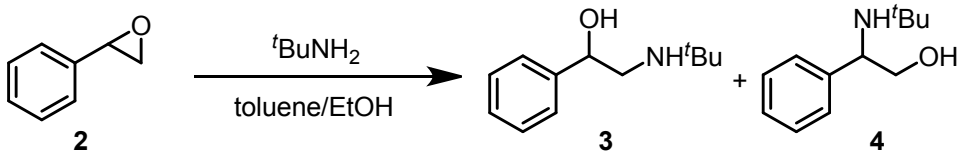
1 **2**

Using two syringe pumps, a solution of benzaldehyde (53.1 mg, 0.5 mmol) in toluene (1 mL) and a solution of trimethylsulfoxonium iodide (187 mg, 0.85 mmol), sodium

hydroxide (34 mg, 0.85 mmol), tetrabutylammonium iodide (18.5 mg, 0.1 mmol) in water (4 mL) were each passed through 32 cm of PTFE tubing before being mixed via a T-mixer. The resulting biphasic plug flow then entered a 1 mL reactor made from PTFE tubing held at 90 °C. The flow rates of the two solutions were as follows: toluene solution: 0.0083 mL min^{-1}, water solution: 0.0333 mL min^{-1}. A 50 cm piece of PTFE tubing connected the reactor with the liquid-liquid extractor. A 20 cm piece of tubing deposited the exiting organic phase in a collection flask.

The organic solution was washed with water, dried over Na_2SO_4, and concentrated under vacuum. 2-phenyloxirane (**2a**)[2] was observed in 97% conversion based on **1** based on ^{1}H NMR using 1,2,4,5-tetramethylbenzene as an internal standard.

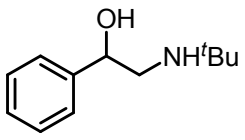
Module 3: Ring Opening



Using the Vapourtec® R-series, the crude epoxide **2** solution and a *tert*-butylamine (368 mL, 3.5 mmol) solution in toluene/ethanol (1 mL/0.5 mL) was mixed via a T-mixer following two 32 cm pieces of PTFE tubing. The resulting solution was then introduced into a 10 mL PTFE reactor held at 150 °C. The flow rates of the two solutions were both 0.2 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (24 bar) and an additional 32 cm piece of PTFE tubing deposited the solution into a collection flask.

The solution was then concentrated under vacuum. A mixture of 2-*tert*-butylamino-1-phenylethanol (**3**)[3] and 2-*tert*-butylamino-2-phenylethanol (**4**)[3] (83:13) was obtained in 96% conversion based on **2** based on ^{1}H NMR using 1,2,4,5-tetramethylbenzene as an internal standard.

Telescoped Synthesis of Aryl Amino Alcohols.



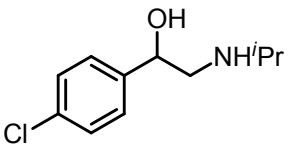
2-*tert*-Butylamino-1-phenylethanol (3)[3] : Using a Vapourtec® R-series, a solution of benzaldehyde (1.06 g, 10 mmol) in toluene (20 mL) and a solution of trimethylsulfoxonium iodide (3.52 g, 16 mmol), sodium hydroxide (640 mg, 16 mmol), tetrabutylammonium iodide (369 mg, 1 mmol) in water (80 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the biphasic solution into a 10 mL PTFE reactor

held at 90 °C. The respective flow rates were as follows: toluene solution: 0.083 mL min^{-1}, water solution: 0.333 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (1-2 bar) and an additional 32 cm piece of PTFE tubing connected the BPR to the liquid-liquid extractor. A short piece of tubing then deposited the organic phase in a collection flask.

Using a Vapourtec® R-series, the solution of epoxide from the previous reaction and a solution of *tert*-butylamine (12.6 mL, 120 mmol) in ethanol (7.4 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the solution into a 10 mL reactor held at 150 °C. The respective flow rates were as follows: toluene solution: 0.1 mL min^{-1}, ethanol solution: 0.1 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor with a BPR (8-9 bar), which was followed by an additional 32 cm piece of tubing, depositing the solution in a collection flask.

The exiting solution was subsequently concentrated under vacuum and the solid was purified by crystallization upon cooling of a hot hexane solution to give **3** (1.10 g) in 57% yield as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 5H), 4.61 (dd, J = 8.8, 3.6 Hz, 1H), 2.91 (dd, J = 11.8, 3.6 Hz, 1H), 2.60 (dd, J = 11.8, 8.8 Hz, 1H), 1.11 (s, 9H). The data is in agreement with previous reports.[3]



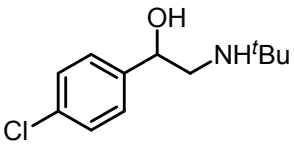
***p*-Chloro-α-[(isopropylamino)methyl]benzylalcohol (5a)**: Using a Vapourtec® R-series, a solution of *p*-chlorobenzaldehyde (351 mg, 2.5 mmol) in toluene (5 mL) and a solution of trimethylsulfoxonium iodide (935 mg, 4.25 mmol), sodium hydroxide (170 mg, 4.25 mmol), tetrabutylammonium iodide (92 mg, 0.25 mmol) in water (20 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the biphasic solution into a 10 mL PTFE reactor held at 90 °C. The respective flow rates were as follows: toluene solution: 0.083 mL min^{-1}, water solution: 0.333 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (1-2 bar). A 32 cm piece of PTFE tubing then delivered the biphasic solution to a liquid-liquid extractor. The organic phase was then deposited into a collection flask via a 32 cm piece of tubing.

Using a Vapourtec® R-series, the solution of epoxide from the previous reaction and a solution of isopropylamine (2.58 mL, 30 mmol) in ethanol (2.42 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the solution into a 10 mL PTFE reactor held at 150 °C. The respective flow rates were as follows: toluene solution: 0.1 mL min^{-1}, ethanol solution: 0.1 mL min^{-1}. A

32 cm piece of PTFE tubing connected the reactor to a BPR (8-9 bar), which was followed by an additional 32 cm piece of PTFE tubing, which deposited the solution into a collection flask.

The solution was concentrated under vacuum and the solid was purified by crystallization upon cooling a solution of hot diethyl ether, providing **5a** (333 mg) in 62% yield as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 4.61 (dd, *J* = 8.9, 3.7 Hz, 1H), 2.92 (dd, *J* = 12.1, 3.7 Hz, 1H), 2.82 (dt, *J* = 12.5, 6.3 Hz, 1H), 2.58 (dd, *J* = 12.1, 8.9 Hz, 1H), 1.07 (dd, *J* = 6.3, 2.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.46, 132.98, 128.43, 127.12, 77.33, 77.01, 76.69, 71.26, 54.56, 48.65, 23.07, 22.97. HRMS for $C_{11}H_{16}ClNO$ $[M+H]^+$: m/z theoretical 214.0920, found 214.1002.

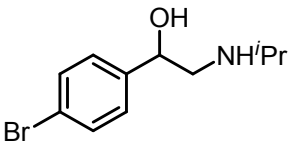


***p*-Chloro-α-[(*tert*-butylamino)methyl]benzylalcohol (5b)**[5] : Using a Vapourtec® R-series, a solution of *p*-chlorobenzaldehyde (351 mg, 2.5 mmol) in toluene (5 mL) and a solution of trimethylsulfoxonium iodide (880 mg, 4 mmol), sodium hydroxide (160 mg, 4 mmol), tetrabutylammonium iodide (92 mg, 0.25 mmol) in water (20 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the biphasic solution into a 10 mL PTFE reactor held at 90 °C. The respective flow rates were as follows: toluene solution: 0.083 mL min^{-1}, water solution: 0.333 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (1-2 bar), which was connected to a liquid-liquid extractor via a 32 cm piece of PTFE tubing. An additional 32 cm piece of tubing deposited the organic phase into a collection flask.

Using a Vapourtec® R-series, the solution of epoxide from the previous reaction and a solution of *tert*-butylamine (3.15 mL, 30 mmol) in ethanol (2.85 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the solution into a 10 mL PTFE reactor held at 150 °C. The respective flow rates were as follows: toluene solution: 0.1 mL min^{-1}, ethanol solution: 0.1 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (8-9 bar), which was followed by an additional 32 cm piece of tubing, which deposited the solution into a collection flask.

The solution was concentrated under vacuum and the solid was purified by crystallization upon cooling a hot toluene solution, providing **5b** (307 mg) in 54% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 4.55 (dd, *J* = 8.7, 3.6 Hz, 1H), 2.89 (dd, *J* = 11.9, 3.6 Hz, 1H), 2.52 (dd, *J* = 11.9, 8.8 Hz, 1H), 1.10 (s, 9H). The data is agreement with that previously reported.[5]

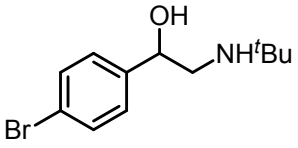


***p*-Bromo-α-[(isopropylamino)methyl]benzylalcohol (6a)**: Using a Vapourtec® R-series, a solution of *p*-bromobenzaldehyde (463 mg, 2.5 mmol) in toluene (5 mL) and a solution of trimethylsulfoxonium iodide (880 mg, 4 mmol), sodium hydroxide (160 mg, 4 mmol), tetrabutylammonium iodide (92 mg, 0.25 mmol) in water (20 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the biphasic solution into a 10 mL PTFE reactor held at 90 °C. The respective flow rates were as follows: toluene solution: 0.05 mL min^{-1}, water solution: 0.2 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (1-2 bar), which was connected to a liquid-liquid extractor via a 32 cm piece of PTFE tubing. An additional 32 cm piece of tubing deposited the organic phase into a collection flask.

Using a Vapourtec® R-series, the solution of epoxide from the previous reaction and a solution of isopropylamine (2.58 mL, 30 mmol) in ethanol (2.42 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the solution into a 10 mL PTFE reactor held at 150 °C. The respective flow rates were as follows: toluene solution: 0.1 mL min^{-1}, ethanol solution: 0.1 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (8-9 bar), which was followed by an additional 32 cm piece of PTFE tubing, which deposited the solution into a collection flask.

The solution was concentrated under vacuum and the solid was purified by crystallization upon cooling a hot diethyl ether solution, providing **6a** (387.2 mg) in 60% yield as a pale yellow solid.

^{1}H NMR (400 MHz$CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 4.61 (dd, *J* = 9.0, 3.6 Hz, 1H), 2.88 (dd, *J* = 12.1, 3.6 Hz, 1H), 2.81 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.57 (dd, *J* = 12.1, 9.0 Hz, 1H), 1.05 (dd, *J* = 6.3, 3.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.88, 131.40, 127.49, 121.12, 77.33, 77.01, 76.69, 71.21, 54.42, 48.72, 23.02, 22.89. MRMS for $C_{11}H_{16}BrNO$ $[M+H]^+$: m/z theoretical 258.0415, found 258.0516.



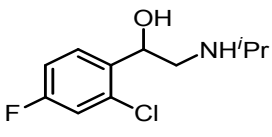
***p*-Bromo-α-[(*tert*-butylamino)methyl]benzylalcohol (6b)**: Using a Vapourtec® R-series, a solution of *p*-bromobenzaldehyde (463 mg,

2.5 mmol) in toluene (5 mL) and a solution of trimethylsulfoxonium iodide (880 mg, 4 mmol), sodium hydroxide (160 mg, 4 mmol), tetrabutylammonium iodide (92 mg, 0.25 mmol) in water (20 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the biphasic solution into a 10 mL PTFE reactor held at 90 °C. The respective flow rates were as follows: toluene solution: 0.05 mL min^{-1}, water solution: 0.2 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (1-2 bar), which was connected to a liquid-liquid extractor via a 32 cm piece of PTFE tubing. An additional 32 cm piece of tubing deposited the organic phase into a collection flask.

Using a Vapourtec® R-series, the epoxide solution from the previous reaction and a solution of *tert*-butylamine (3.15 mL, 30 mmol) in ethanol (2.85 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the solution into a 10 mL PTFE reactor held at 150 °C. The respective flow rates were as follows: toluene solution: 0.1 mL min^{-1}, ethanol solution: 0.1 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (8-9 bar), which was followed by an additional 32 cm piece of PTFE tubing, which deposited the solution into a collection flask.

The solution was concentrated under vacuum and the solid was purified by crystallization upon cooling a hot hexane solution, providing **6b** (367 mg) in 54% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 4.53 (dd, *J* = 8.6, 3.6 Hz, 1H), 2.89 (dd, *J* = 11.9, 3.7 Hz, 1H), 2.52 (dd, *J* = 11.9, 8.7 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.08, 131.35, 127.49, 121.02, 77.33, 77.02, 76.70, 71.50, 50.33, 50.07, 29.10. MRMS for $C_{12}H_{18}BrNO$ $[M+H]^+$: m/z theoretical 272.07, found 272.0678



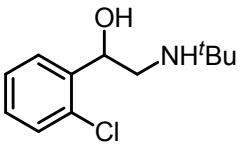
***o*-Chloro- *p*-fluoro-α-[(isopropylamino)methyl]benzylalcohol (7)**: Using a Vapourtec® R-series, a solution of *o*-chloro-*p*-fluorobenzaldehyde (396 mg, 2.5 mmol) in toluene (5 mL) and a solution of trimethylsulfoxonium iodide (880 mg, 4 mmol), sodium hydroxide (160 mg, 4 mmol), tetrabutylammonium iodide (92 mg, 0.25 mmol) in water (20 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the biphasic solution into a 10 mL PTFE reactor held at 90 °C. The respective flow rates were as follows: toluene solution: 0.05 mL min^{-1}, water solution: 0.2 mL

min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (1-2 bar), which was connected to a liquid-liquid extractor via a 32 cm piece of PTFE tubing. An additional 32 cm piece of tubing deposited the organic phase into a collection flask.

Using a Vapourtec® R-series, the solution of epoxide from the previous reaction and a solution of isopropylamine (2.58 mL, 30 mmol) in ethanol (2.42 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the solution into a 10 mL PTFE reactor held at 150 °C. The respective flow rates were as follows: toluene solution: 0.1 mL min^{-1}, ethanol solution: 0.1 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (8-9 bar), which was followed by an additional 32 cm piece of tubing, which deposited the solution into a collection flask.

The solution was concentrated under vacuum and the solid was purified by crystallization upon cooling a hot hexane solution, providing**7** (396 mg) in 68% yield as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$ with D_2O) δ 7.57 (dd, *J* = 8.7, 6.3 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.01 – 6.95 (m, 1H), 5.00 – 4.93 (m, 1H), 2.99 (dd, *J* = 12.3, 3.4 Hz, 1H), 2.80 (dt, *J* = 12.5, 6.3 Hz, 1H), 2.45 (dd, *J* = 12.3, 8.9 Hz, 1H), 1.05 (dd, *J* = 7.2, 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.74, 160.27, 136.26, 136.23, 132.10, 132.00, 128.45, 128.37, 116.54, 116.30, 114.25, 114.04, 77.31, 76.99, 76.67, 68.10, 52.40, 48.58, 23.13, 22.94. $C_{11}H_{15}ClFNO$ $[M+H]^+$: m/z theoretical 232.0826, found 232.0919.



***o*-Chloro-α-[(*tert*-butylamino)methyl]benzylalcohol (8)**: Using a syringe pump, a solution of sodium hypochlorite (358 mg, 6.25 mmol), potassium bromide (14.9 mg, 0.125 mmol), sodium bicarbonate (63.0 mg, 0.75 mmol) in water (5 mL) and a solution of *o*-chlorobenzylalcohol (357 mg, 2.5 mmol), and TEMPO (11.7 mg, 0.075 mmol) in toluene (5 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the biphasic solution into a 10 mL PTFE reactor held at 0 °C. The respective flow rates were as follows: toluene solution: 0.0714 mL min^{-1}, water solution: 0.0714 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a liquid-liquid extractor. An additional 32 cm piece of tubing deposited the organic phase into a collection flask.

Using a Vapourtec® R-series, the solution of aldehyde from the previous reaction and a solution of trimethylsulfoxonium iodide (880 mg, 4 mmol), sodium hydroxide (160 mg, 4 mmol), tetrabutylammonium iodide (92 mg, 0.25 mmol) in water (20 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE

tubing then introduced the biphasic solution into a 10 mL PTFE reactor held at 90 °C. The respective flow rates were as follows: toluene solution: 0.05 mL min^{-1}, water solution: 0.2 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (1-2 bar), which was connected to a liquid-liquid extractor via a 32 cm piece of PTFE tubing. An additional 32 cm piece of tubing deposited the organic phase into a collection flask.

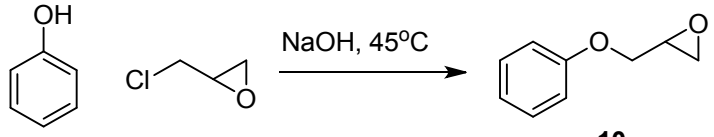
Using a Vapourtec® R-series, the solution of epoxide from the previous reaction and a solution of *tert*-butylamine (3.15 mL, 30 mmol) in ethanol (1.85 mL) were mixed via a T-mixer after each passing through a 32 cm piece of PTFE tubing. A 32 cm piece of PTFE tubing then introduced the solution into a 10 mL PTFE reactor held at 150 °C. The respective flow rates were as follows: toluene solution: 0.1 mL min^{-1}, ethanol solution: 0.1 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (8-9 bar), which was followed by an additional 32 cm piece of tubing, which deposited the solution into a collection flask.

The solution was concentrated under vacuum and the solid was purified by crystallization upon cooling a hot hexane solution, providing **5** (162 mg) in 28% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.18 (td, *J* = 7.6, 1.7 Hz, 1H), 4.96 (dd, *J* = 8.5, 3.5 Hz, 1H), 3.03 (dd, *J* = 12.1, 3.6 Hz, 1H), 2.44 (dd, *J* = 12.1, 8.5 Hz, 1H), 1.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.38, 131.68, 129.17, 128.23, 127.23, 126.94, 77.32, 77.00, 76.68, 68.83, 50.46, 47.91, 29.15, 29.13. $C_{12}H_{18}ClNO$ $[M+H]^+$: m/z theoretical 228.1077, found 228.1173.

General Procedures for Aryloxy β-Amino Alcohol Syntheses.

Alkylation

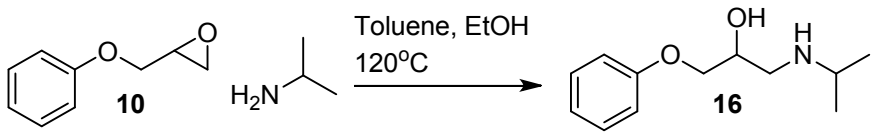


9 **10**

A 10 mL Norm-Ject syringe was filled with 1.95 M NaOH (19.5 mmol, 10 mL). A 5 mL Norm-Ject syringe was filled with a solution of phenol (15 mmol, 1.41 g), tetrabutylammonium chloride (1.5 mmol, 417 mg) and epichlorohydrin (30 mmol, 2.35 mL). Prior to loading the syringe, the combined reagents (phenol, tetrabutylammonium chloride and epichlorohydrin) were stirred in a flask for 10 minutes to generate a homogenous solution. A reactor coil (PTFE tubing, i.d. 0.5 mm, o.d. 1.6 mm, 4 mL) was made to effect the phenol alkylation. The two solutions were passed through 32 cm of PTFE tubing before

entering a T-mixer, which was directly connected to the PTFE reactor held at 45 °C. The respective flow rates were as follows: the NaOH solution: 0.048 mL min^{-1}, the phenol solution: 0.019 mL min^{-1} (60 min t_R following being mixed via a T-mixer). A 32 cm piece of PTFE tubing connected the reactor to a collection flask. After 2 residents passed, a 3 mL reaction mixture was collected and manually extracted using a separatory funnel with ethyl acetate (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Hex/EA = 8/1) to give the phenyl glycidyl ether **10** (410 mg, 85%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-6.93 (m, 5 H), 4.24 (dd, *J* = 3.2, 11.2 Hz, 1 H), 3.97 (dd, *J* = 7.2, 11.2 Hz, 1 H), 3.36 (m, 1 H), 2.91 (t, *J* = 4.8 Hz, 1 H), 2.76 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 129.5, 121.2, 114.6, 68.6, 50.1, 44.7; HRMS (ESI): calcd for $C_9H_{10}O_2Na$ $[M + Na]^+$: 173.0578, found: 173.0593.

Ring opening



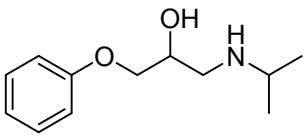
Using a Vapourtec® R-series, a solution of phenyl glycidyl ether (1.49 mmol, 3.75 mL, 0.4 M) in toluene and a solution of isopropylamine (7.5 mmol, 3.75 mL, 2.0 M) in ethanol were mixed via a T-mixer after each passing through 32 cm of PTFE tubing. An additional piece of 32 cm PTFE tubing introduced the solution into a 20 mL PTFE reactor held at 120 °C. The respective flow rates were as follows: toluene solution: 0.5 mL min^{-1}, ethanol solution: 0.5 mL min^{-1}. A 32 cm piece of PTFE tubing connected the reactor to a BPR (5.2 bar). A final piece of 32 cm PTFE tubing deposited the solution into a collection flask. The solution was collected and concentrated under vacuum. 1-[(1-methylethyl) amino]-3-(1-phenoxy)-2-propanol (**16**) was obtained in 100% conversion based on phenyl glycidyl ether, as determined by ^1H NMR.

General Procedure for the Telescoped Synthesis of Aryloxy β-Amino Alcohols

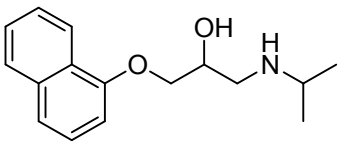
A 10 mL Norm-Ject syringe was filled with 1.95 M NaOH (19.5 mmol, 10 mL). A 5 mL Norm-Ject syringe was filled with a solution of phenol (15 mmol, 1.41 g), tetrabutylammonium chloride (1.5 mmol, 417 mg) and epichlorohydrin (30 mmol, 2.35 mL). Prior to loading the syringe, the combined reagents (phenol, tetrabutylammonium chloride and epichlorohydrin) were stirred in a flask for 10 minutes to generate a homogenous solution resulted. A reactor coil (PTFE tubing, i.d. 0.5 mm, o.d. 1.6 mm, 4 mL) was made to effect the

phenol alkylation. The two solutions were passed through 32 cm of PTFE tubing before being mixed via a T-mixer, which was directly connected to the reactor held at 45 °C. The respective flow rates were as follows: the NaOH solution: 0.048 mL min^{-1}, the phenol solution: 0.019 mL min^{-1} (60 min t_R following being mixed via a T-mixer). A 32 cm piece of PTFE tubing connects the reactor to a T-mixer, where toluene was mixed (via a syringe pump at 0.1 mL min^{-1}). A 100 cm piece of PTFE tubing connects the T-mixer to a liquid-liquid separator. A 32 cm piece of PTFE tubing connects the separator to a collection flask. Two residents are allowed to go to waste prior to collection of the organic phase, which is used directly goes to the next step.

Using a Vapourtec® R-series, a solution of phenyl glycidyl ether (2.2 mmol, 5.5 mL, 0.4 M) in toluene and a solution of isopropylamine (11.0 mmol, 5.5 mL, 2.0 M) in ethanol were mixed via a T-mixer after each passing through 32 cm of PTFE tubing. An additional 32 cm piece of PTFE tubing introduced the solution into a 20 mL PTFE reactor held at 120 °C. The respective flow rates were as follows: toluene solution: 0.5 mL min^{-1}, ethanol solution: 0.5 mL min^{-1}. A 32 cm piece of PTFE tubing led to a BPR (5.2 bar). A 32 cm piece of tubing deposited the solution into a collection flask. The solution was collected and concentrated under vacuum. The solid was purified by crystallization or flash chromatography on silica gel.

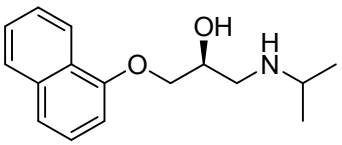


1-[(1-Methylethyl) amino]-3-(1-phenoxy)-2-propanol (16): 1-[(1-methylethyl) amino]-3-(1-phenoxy)-2-propanol (**16**) was obtained by crystallization (Hexane/Ethyl acetate = 15/1) in 48% yield for two steps as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23- 6.89 (m, 5 H), 4.02 (m, 1 H), 3.95 (m, 2 H), 2.88-2.78 (m, 2 H), 2.72 (m, 2 H), 1.08 (d, *J* = 6.0 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 129.6, 129.5, 121.0, 114.6, 70.5, 68.5, 49.4, 49.0, 49.0, 23.1, 23.0; HRMS (ESI): calcd for $C_{12}H_{20}NO_2$ $[M + H]^+$: 210.1494, found: 210.1500.



Propranolol (17): Propranolol **17** was obtained in 51% yield by crystallization from hexane for two steps as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-6.82 (m, 7 H), 4.20 (m, 2 H), 4.12 (m, 1 H), 3.02 (m, 1 H), 2.86 (m, 2 H), 2.76 (br, 1 H), 1.12 (d, *J* = 6.0 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 134.5, 127.6, 126.5, 125.9, 125.6, 125.3, 121.9, 120.6,

104.9, 70.8, 68.5, 49.7, 49.1, 23.2, 23.1; HRMS (ESI): calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$: 260.1651, found: 260.1646.

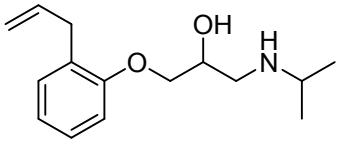


(S)-Propranolol (S)-17: A 2 mL (3 mL) Norm-Ject syringe was filled with 1.95 M NaOH (3.9 mmol, 2 mL). A 1 mL Norm-Ject syringe was filled with a solution of 1-naphthol (3 mmol, 0.43 g), tetrabutylammonium chloride (0.3 mmol, 83 mg) and (*R*)-epichlorohydrin (6 mmol, 0.47 mL). Prior to loading the syringe, the combined reagents (1-naphthol, tetrabutylammonium chloride and (*R*)-epichlorohydrin) were stirred in a flask for 10 minutes to generate a homogenous solution. A reactor coil (PTFE tubing, i.d. 0.5 mm, o.d. 1.6 mm, 1 mL) was made to effect the alkylation. The two solutions were passed through 32 cm of PTFE tubing before being mixed via a T-mixer, which was directly connected to the reactor held at 45 °C. The respective flow rates were as follows: the NaOH solution: 0.011 mL min^{-1}, the 1-naphthol solution: 0.005 mL min^{-1} (60 min t_R). A 32 cm piece of PTFE tubing connects the reactor to a T-mixer, where toluene was mixed (via a syringe pump at 0.1 mL min^{-1}). A 100 cm piece of PTFE tubing connects the T-mixer to a liquid-liquid separator. A 32 cm piece of PTFE tubing connects the separator to a collection flask. Two residents are allowed to go to waste prior to collection of the organic phase, which is used directly goes to the next step.

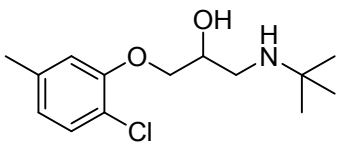
In order to determine the *ee* value of naphthyl glycidyl ether, the organic phase is concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (Hexane/Ethyl acetate = 8/1) to give naphthyl glycidyl ether. 93.7% *ee*; $[\alpha]^{25}_D$: 35.11 (c, 1.0, methanol), Lit.[6] $[\alpha]^{25}_D$: 32. 9 (c, 1.0, methanol); Enantiomeric excesses were determined by HPLC on a Chiralpak®IC column (4.6 mm i.d. × 250 mm, eluent, hexane-isopropanol, 90:10 v/v; flow rate, 1.0 mL/min; UV at 280 nm).

Using a Vapourtec® pumps a solution of naphthyl glycidyl ether (0.25 mmol, 2 mL, 0.125 M) in toluene and a solution of isopropylamine (1.25 mmol, 2 mL, 0.625 M) in ethanol were mixed via a T-mixer after each passing through 32 cm of PTFE tubing. An additional piece of 32 cm PTFE tubing introduced the solution into a 20 mL PTFE reactor held at 120 °C. The respective flow rates were as follows: toluene solution: 0.5 mL min^{-1}, ethanol solution: 0.5 mL min^{-1}. A 32 cm piece of PTFE tubing led to the BPR (5.2 bar). A final piece of 32 cm tubing deposited the solution into a collection flask. The solution was collected and concentrated under vacuum. The solid was purified by flash chromatography on silica gel (DCM/MeOH = 10/1, 5% Et_3N) to give (*S*)-propranolol (*S*)-**9** (60 mg, 51% for two steps). $[\alpha]^{25}_D$: -7.93 (c, 1.0, ethanol), Lit.[7] $[\alpha]^{25}_D$: -8.89 (c, 1.0, ethanol); ^1H NMR (400 MHz, $CDCl_3$)

δ 8.27-6.82 (m, 7 H), 4.20 (m, 2 H), 4.12 (m, 1 H), 3.02 (m, 1 H), 2.86 (m, 2 H), 2.76 (br, 1 H), 1.12 (d, *J* = 6.0 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 134.5, 127.6, 126.5, 125.9, 125.6, 125.3, 121.9, 120.6, 104.9, 70.8, 68.5, 49.7, 49.1, 23.2, 23.1; HRMS (ESI): calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$: 260.1651, found: 260.1646.



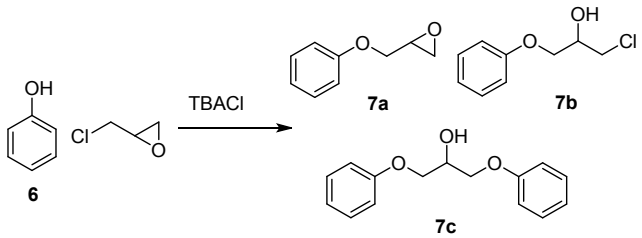
Alprenolol (10): Alprenolol **10** was obtained by crystallization from hot diethyl ether in 42% yield for two steps as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-6.84 (m, 4 H), 5.99 (m, 1 H), 5.05 (m, 2 H), 4.06 (m, 1 H), 3.98 (m, 2 H), 3.40 (d, *J* = 6.4 Hz, 2 H), 2.92-2.74 (m, 4 H), 1.11 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 137.1, 129.9, 128.4, 127.4, 120.8, 115.2, 111.2, 70.6, 68.3, 49.7, 48.9, 34.5, 22.8, 22.7; HRMS (ESI): calcd for $C_{15}H_{24}NO_2$ $[M + H]^+$: 250.1807, found: 250.1823.



Bupranolol (11): Bupranolol **11** was obtained by flash chromatography on silica gel (DCM/MeOH = 10/1, 5% Et_3N) in 69% yield over two steps as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-6.66 (m, 3 H), 4.39 (m, 1 H), 4.10 (dd, *J* = 4.0, 9.2 Hz, 1 H), 3.96 (dd, *J* = 6.4, 9.6 Hz, 1 H), 3.66 (br, 2 H), 3.24 (dd, *J* = 2.8, 12.4 Hz, 1 H), 3.04 (m, 1 H), 2.25 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$/CD_3OD = 1/1) δ 152.9, 137.9, 129.2, 122.3, 119.0, 114.2, 70.2, 65.4, 56.1, 44.4, 25.0, 20.3; HRMS (ESI): calcd for $C_{14}H_{23}ClNO_2$ $[M + H]^+$: 272.1417, found: 272.1459.

Optimization of Modules 4a and 4b:

Table S1: Optimization of phenol alkylation reaction in flow [a]

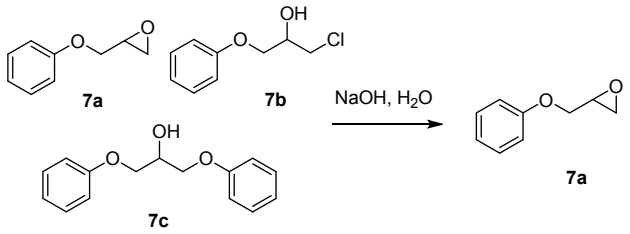


Entry	Epichlorohydrin (equiv.)	T (°C)	Residence Time (min)	Conversion (%)
1	1.1	90	60	78
2	1.1	110	60	90
3	1.1	120	60	90
4	1.1	130	60	91

5	1.1	140	60	93
6	2.0	90	60	91
7	2.0	100	60	95
8	2.0	110	60	100

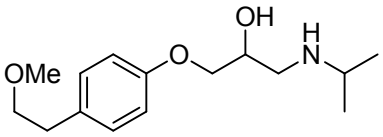
[a] Pump A: Phenol, TBACl (0.1 equiv.), Epichlorohydrin, Reactor size: 2 mL, BPR: 2.8 bar.

Table S2: Optimization of epoxide formation reaction in flow [a]



Entry	T (°C)	Residence time Time (min)	Result
1	45	15	68% **7a** + 17% **7b**
2	45	30	84% **7a**

[a] Pump A: Solution directly from the above reaction, Pump B: 1.95 M NaOH, Reactor size: 2 mL.



Metoprolol (12): A 10 mL (12 mL) Norm-Ject syringe was filled with a solution of 4-(2-methoxyethyl)phenol (9.85 mmol, 1.5 g), tetrabutylammonium chloride (0.99 mmol, 274 mg) and epichlorohydrin (19.7 mmol, 1.54 mL). Prior to loading of the syringe, the combined reagents (4-(2-methoxyethyl)phenol, tetrabutylammonium chloride and epichlorohydrin) were stirred in a flask for 10 minutes to generate a homogenous solution. A reactor coil (PTFE tubing, i.d. 0.5 mm, o.d. 1.6 mm, 2 mL) was made to effect the phenol alkylation. The solution was connected via a 32 cm piece of PTFE tubing to the reactor held at 110 °C. The flow rate of the 4-(2-methoxyethyl)phenol solution was 0.035 mL min^{-1} (57 min t_R). A short segment of PTFE tubing (0.1 mL) led to a 2.8 bar back-pressure regulator. After two residents had passed, the exiting solution was collected and used directly in the next step.

A 10 mL Norm-Ject syringe was filled with 1.95 M NaOH (12.8 mmol, 6.6 mL). A 5 mL Norm-Ject syringe was filled with the above exiting solution (9.85 mmol, 3.2 mL). A reactor coil (PTFE tubing, i.d. 0.5 mm, o.d. 1.6 mm, 2 mL) was made to effect the epoxide formation reaction. The solutions were mixed via a T-mixer after passing through 32 cm of PTFE tubing each. The reactor, held at 45 ˚C, was directly connected to the T-mixer. The respective flow rates were as follows: the NaOH solution: 0.047 mL min^{-1}, the crude solution: 0.023 mL min^{-1} (28 min t_R). A 32 cm piece of PTFE tubing connects the reactor to a T-mixer, where toluene was mixed (via a syringe pump at 0.1 mL min^{-1}). A 100 cm piece of PTFE tubing connects the T-mixer to a liquid-liquid separator. A 32 cm piece of PTFE tubing

connects the separator to a collection flask. Two residents are allowed to go to waste prior to collection of the organic phase, which is used directly goes to the next step.

Using a Vapourtec® R-series, a solution of 4-(2-methoxyethyl)phenyl glycidyl ether (5.6 mmol, 10.3 mL, 0.54 M) in toluene and a solution of isopropylamine (28.1 mmol, 10.3 mL, 2.7 M) in ethanol were mixed via a T-mixer after each passing through 32 cm of PTFE tubing. An additional piece of 32 cm PTFE tubing introduced the solution into a 20 mL PTFE reactor held at 120 °C. The respective flow rates were as follows: toluene solution: 0.5 mL min^{-1}, ethanol solution: 0.5 mL min^{-1}. A short segment of PTFE tubing (0.3 mL) led to a 5.2 bar back-pressure regulator. A final 32 cm piece of PTFE tubing connected the BPR to the collection flask. The mixture was collected and concentrated under vacuum. The solid was purified by flash chromatography on silica gel (DCM/MeOH = 10/1, 5% Et_3N) to give metoprolol **12** (1.03 g, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 4.07 (m, 1 H), 3.92 (m, 2 H), 3.53 (t, *J* = 7.2 Hz, 2 H), 3.32 (s, 3 H), 2.87 (m, 4 H), 2.71 (m, 1 H), 1.09 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 131.5, 129.9, 114.5, 73.9, 70.5, 68.3, 58.8, 49.3, 49.2, 35.4, 22.9, 22.8; HRMS (ESI): calcd for $C_{15}H_{26}NO_3$ $[M + H]^+$: 268.1913, found: 268.1918.

References:

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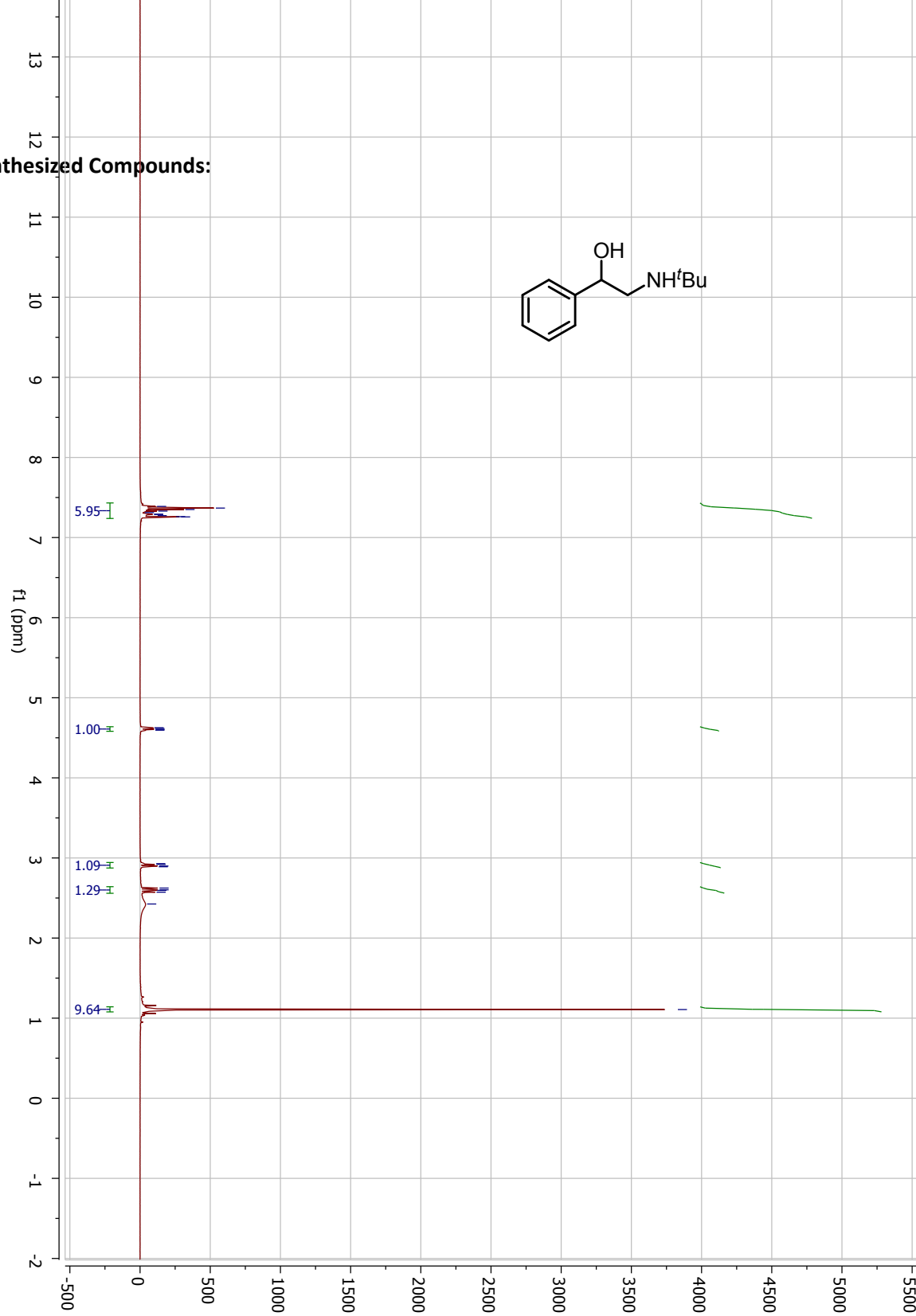
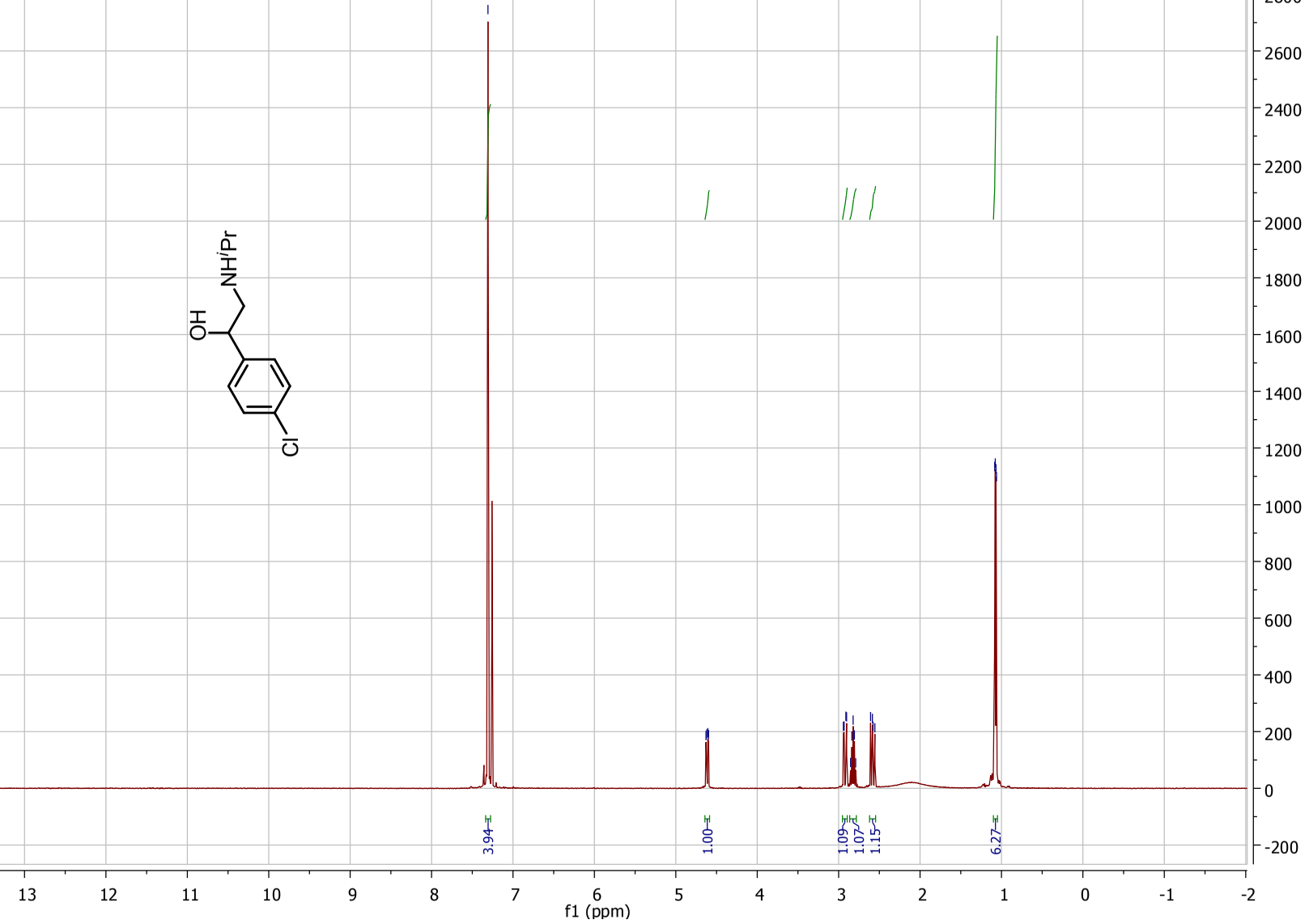
NMR Spectra for Synthesized Compounds:

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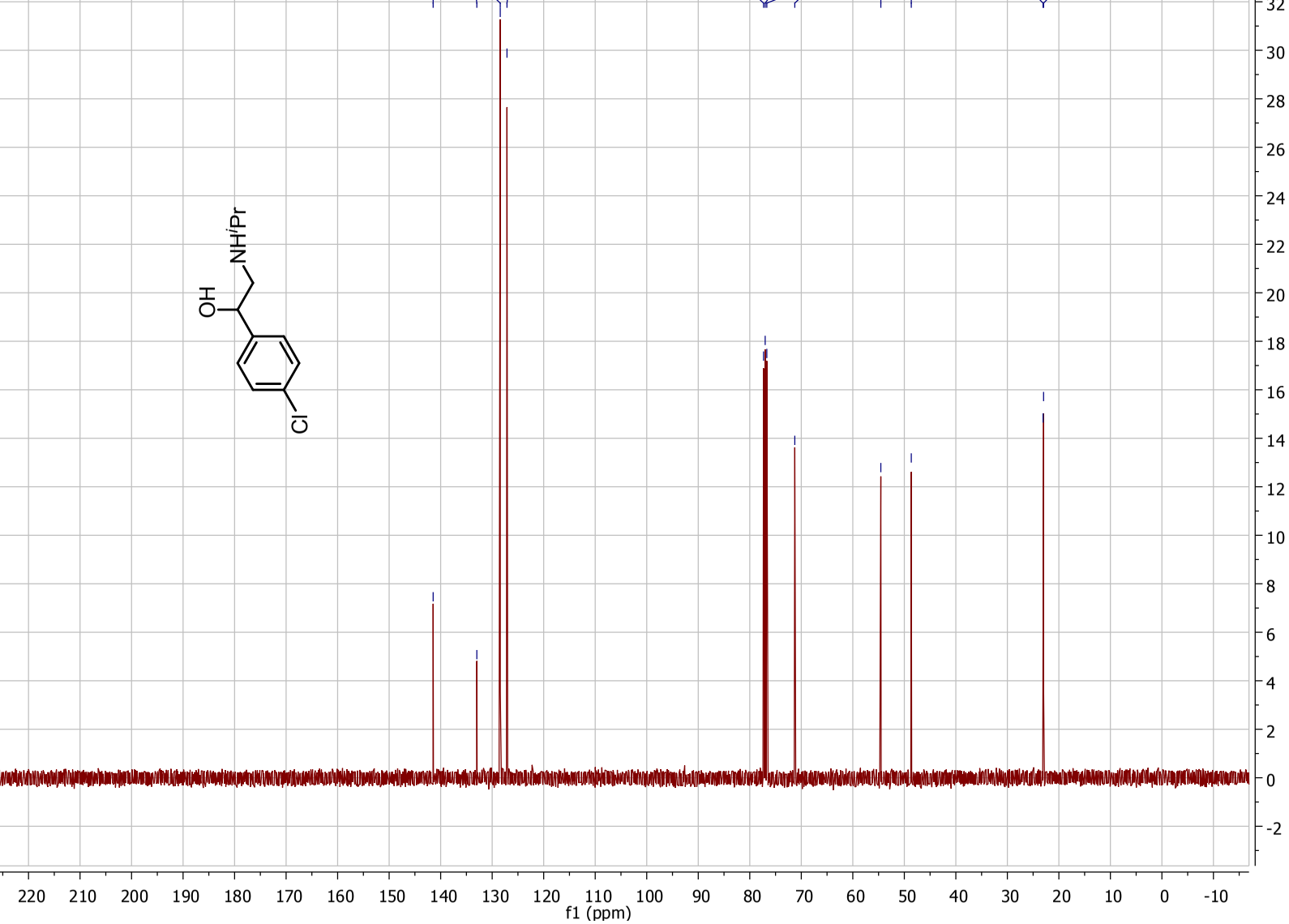
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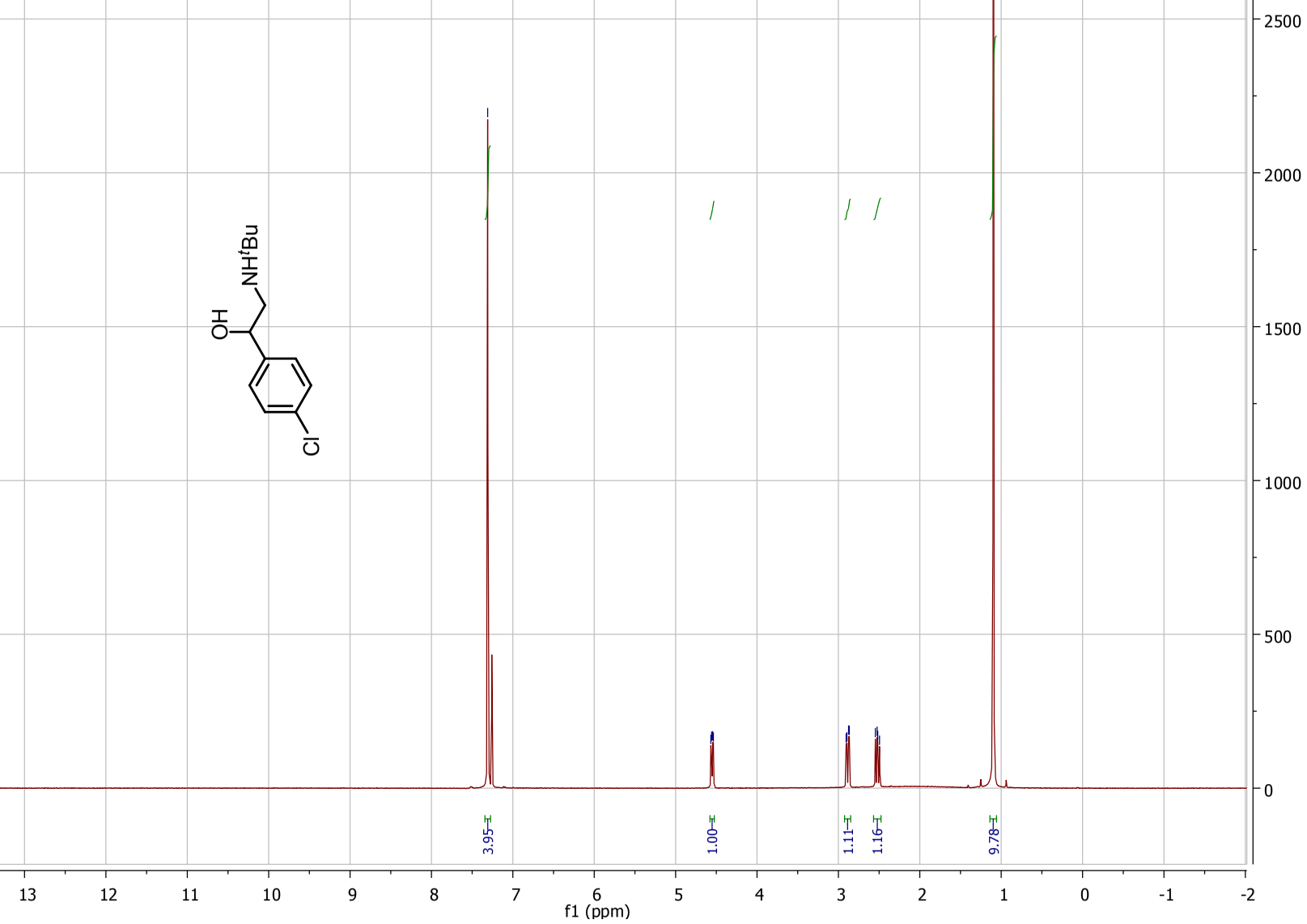
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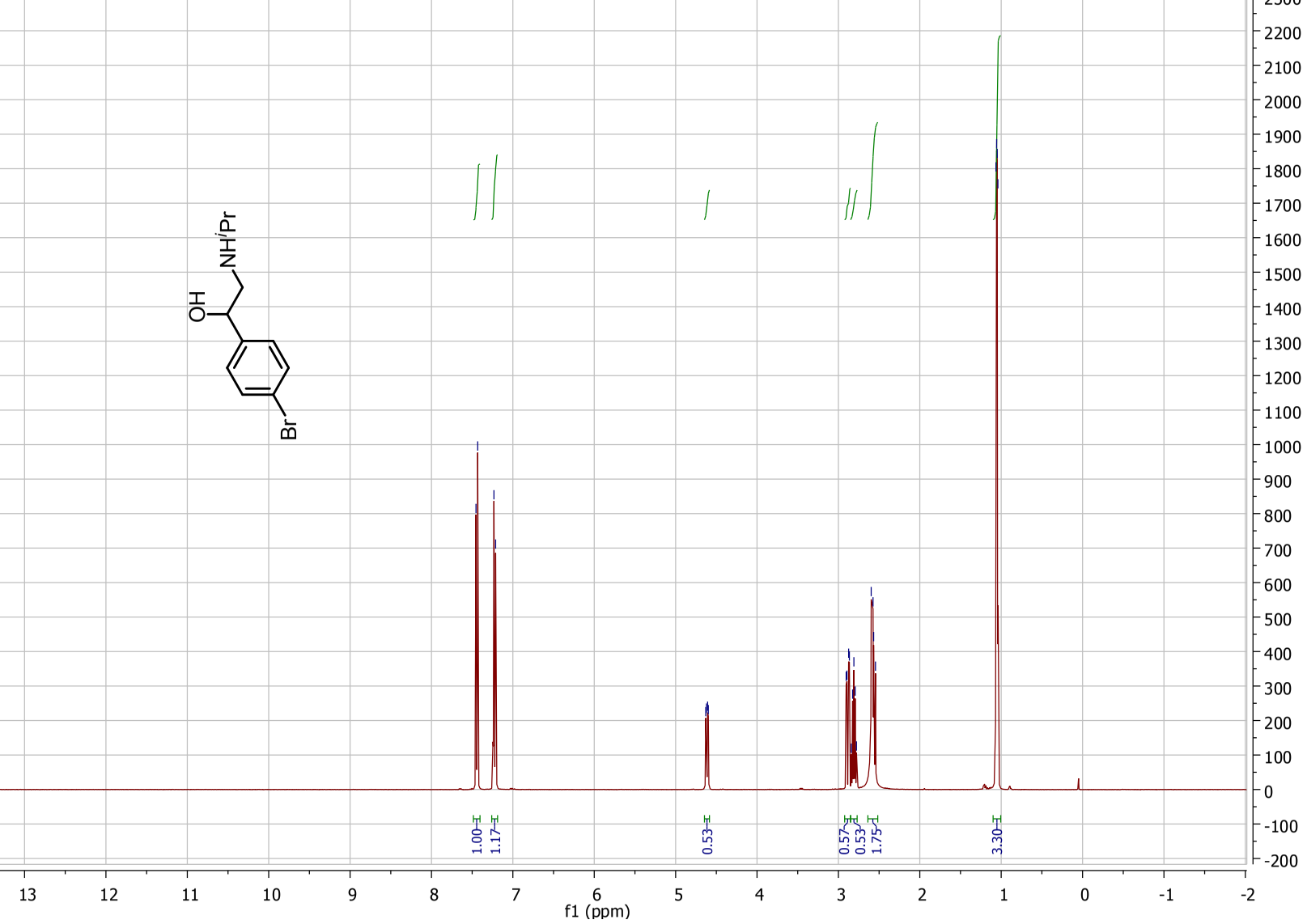
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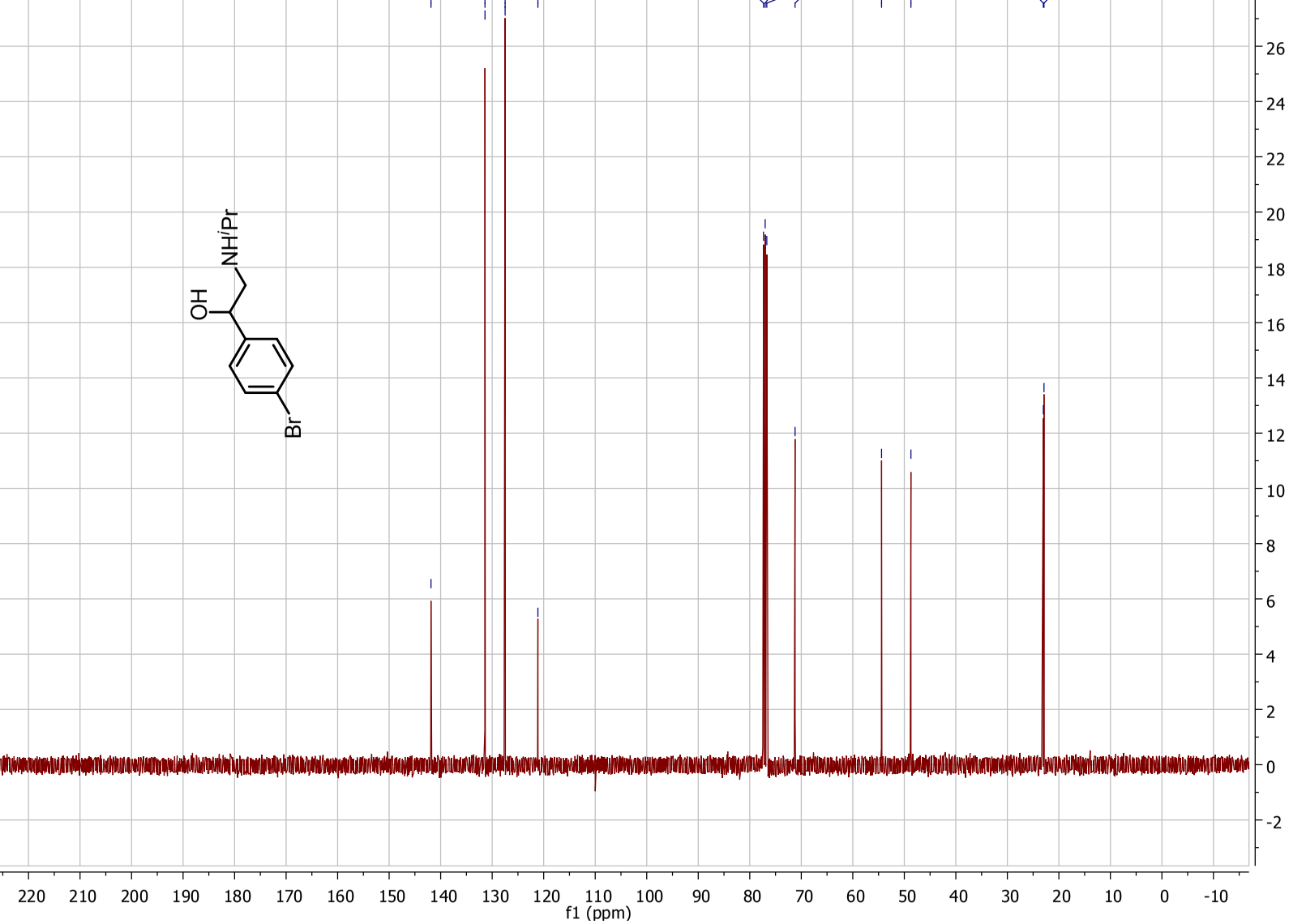
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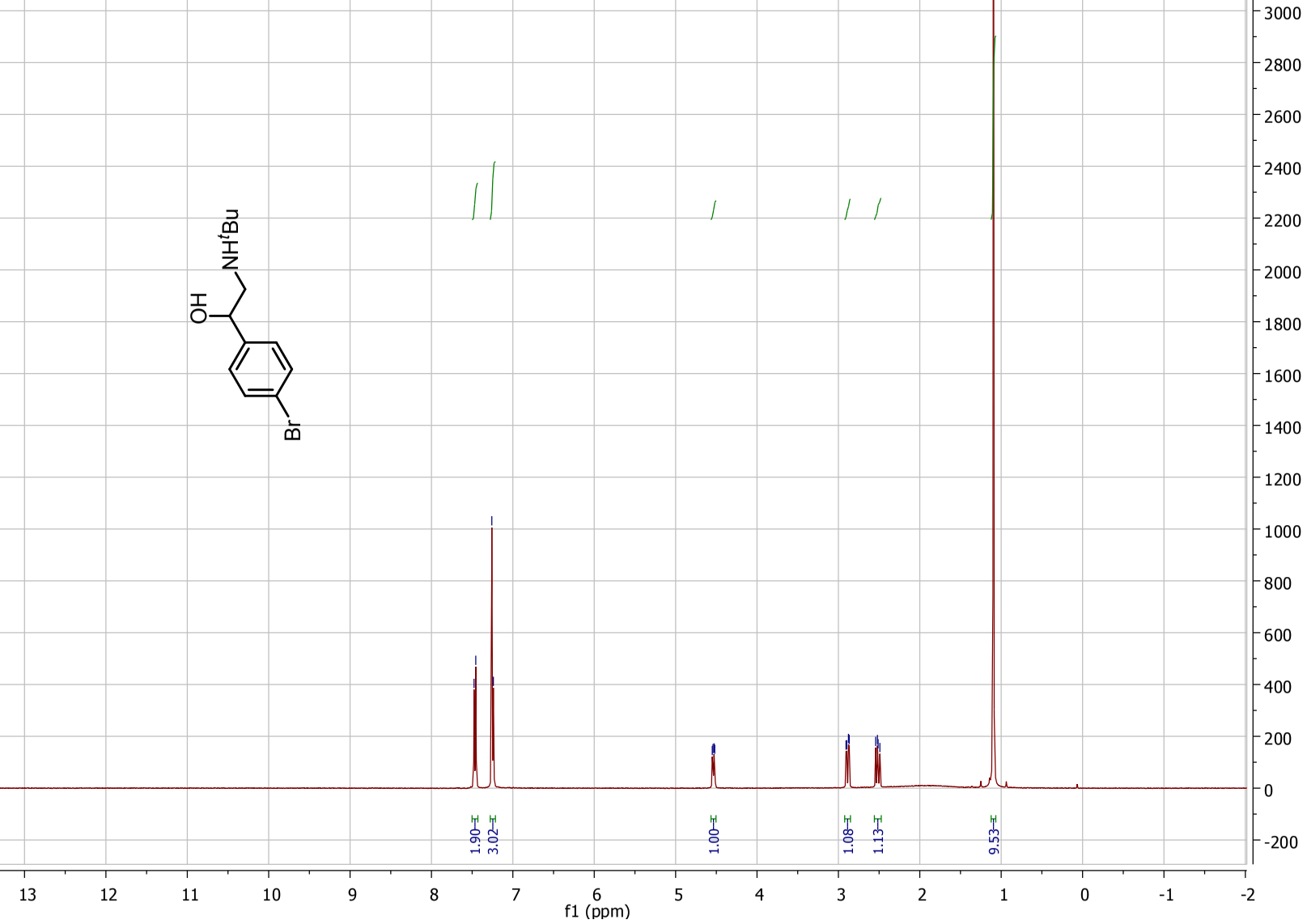
f1 (ppm)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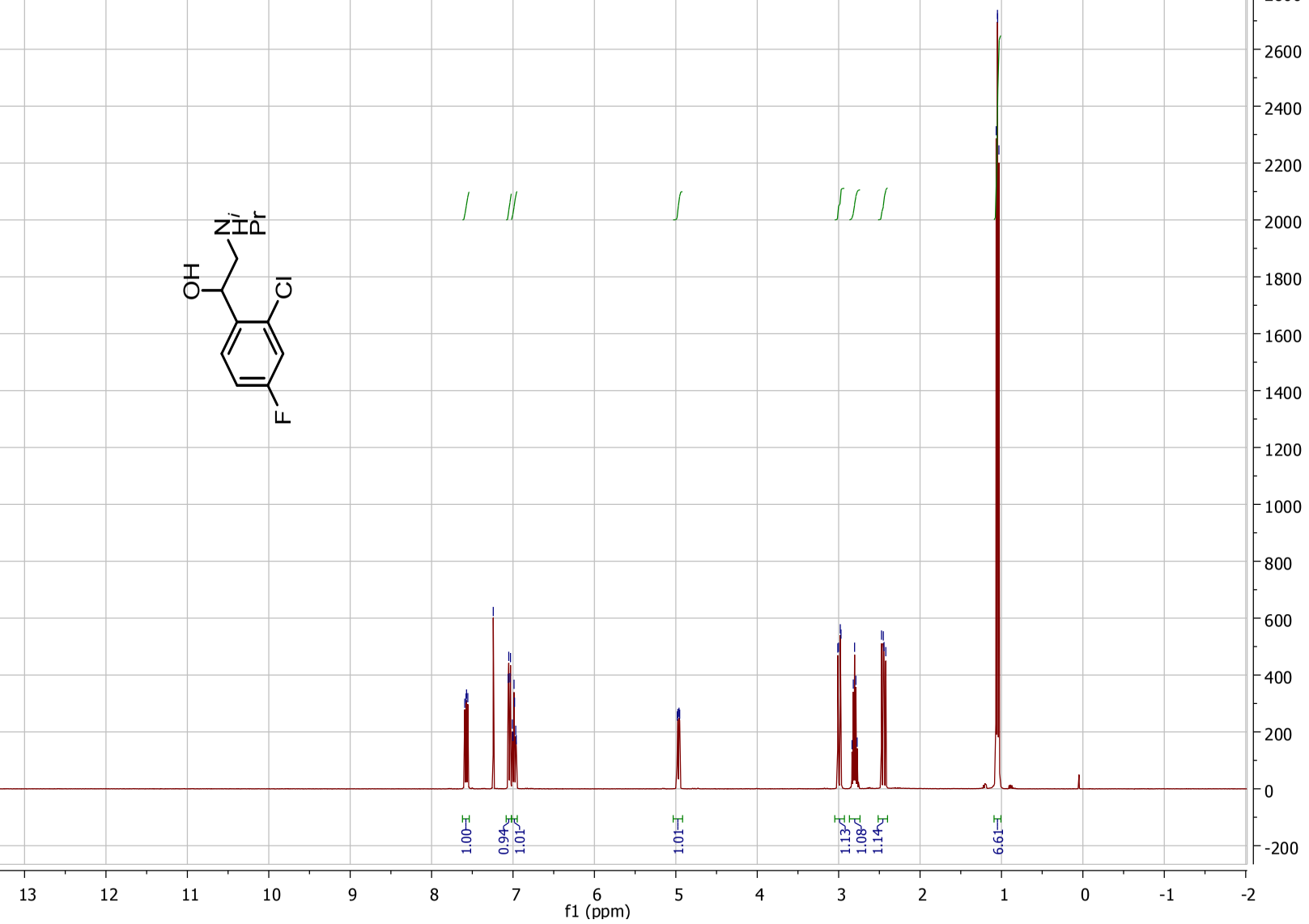
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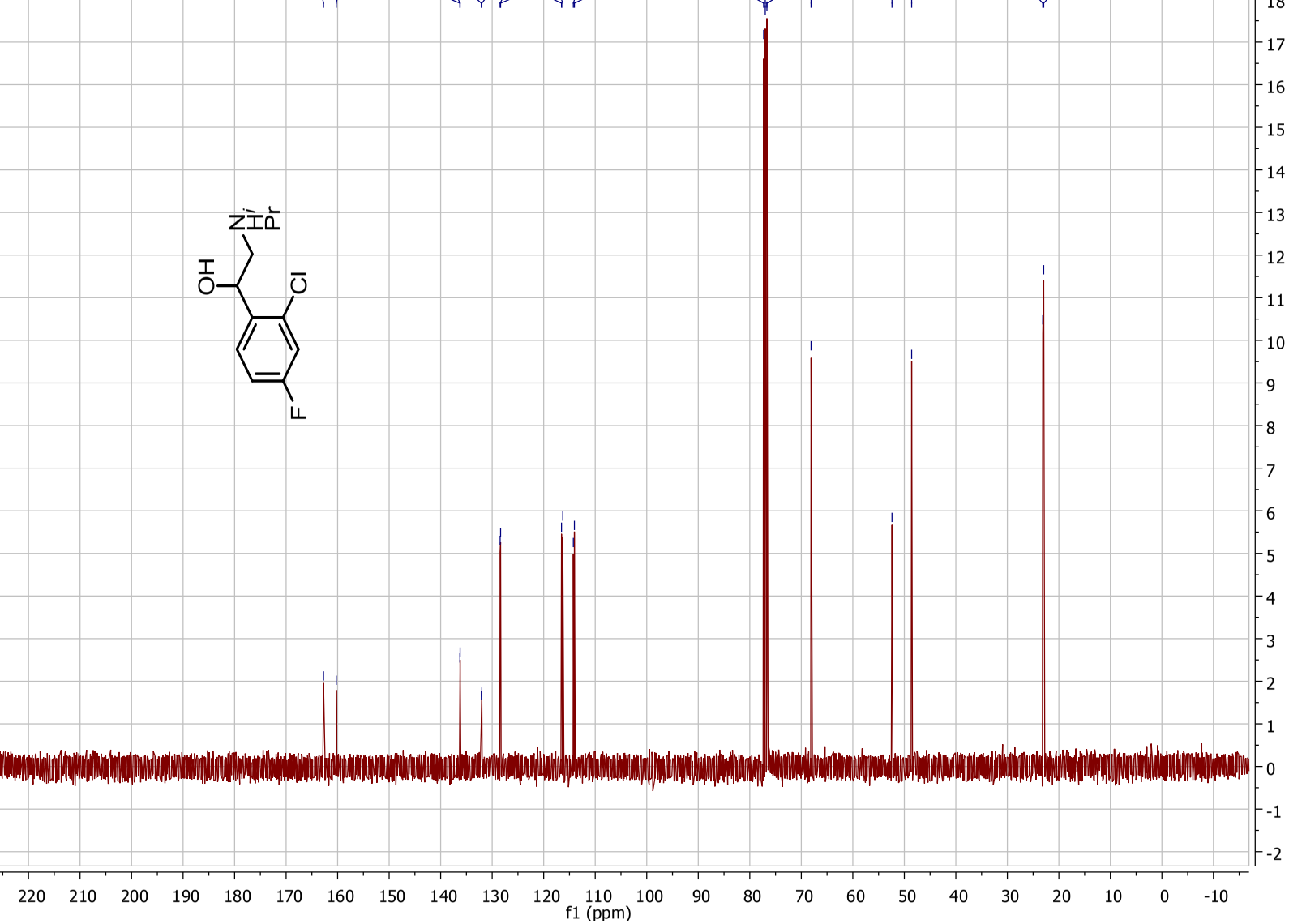
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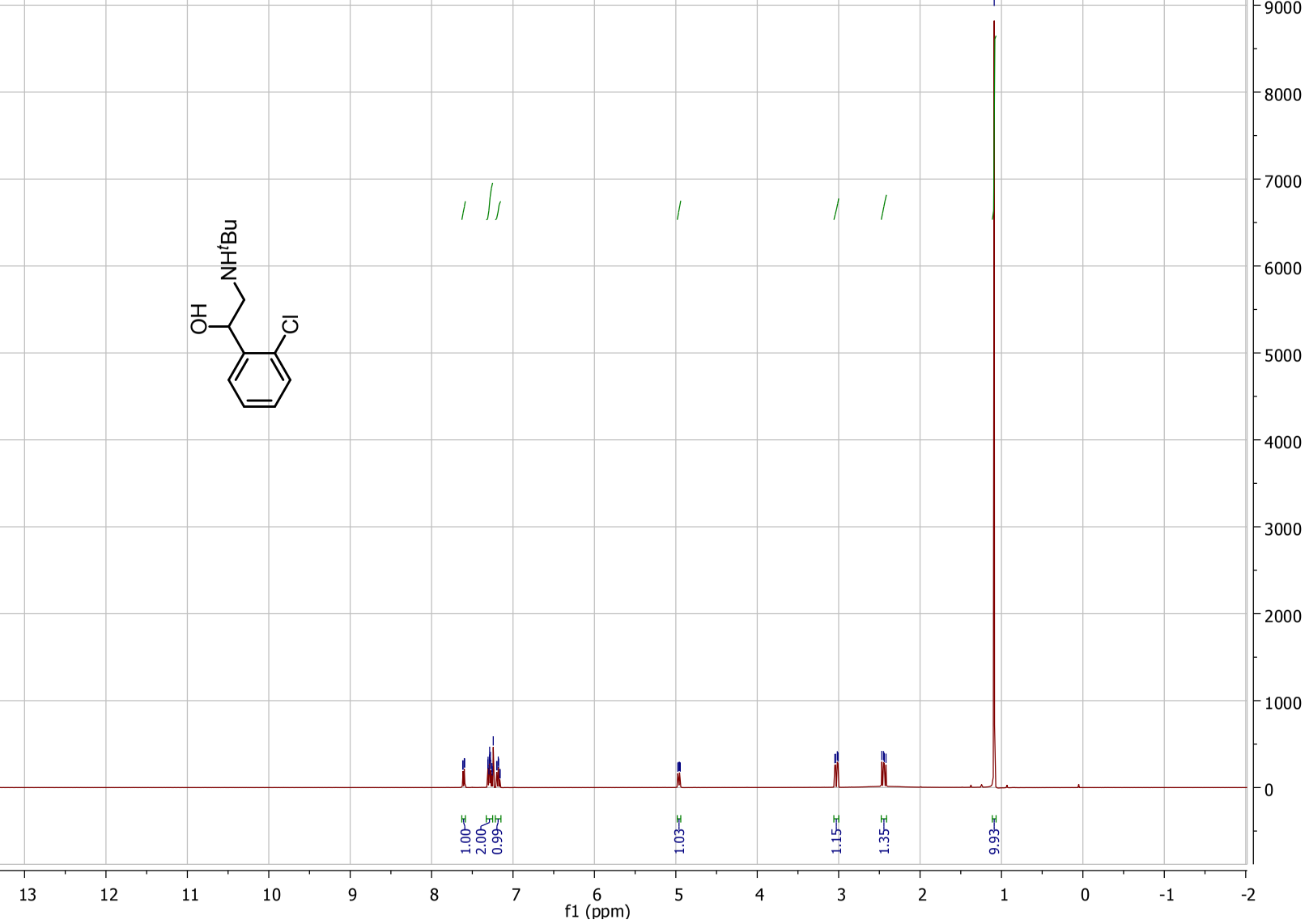
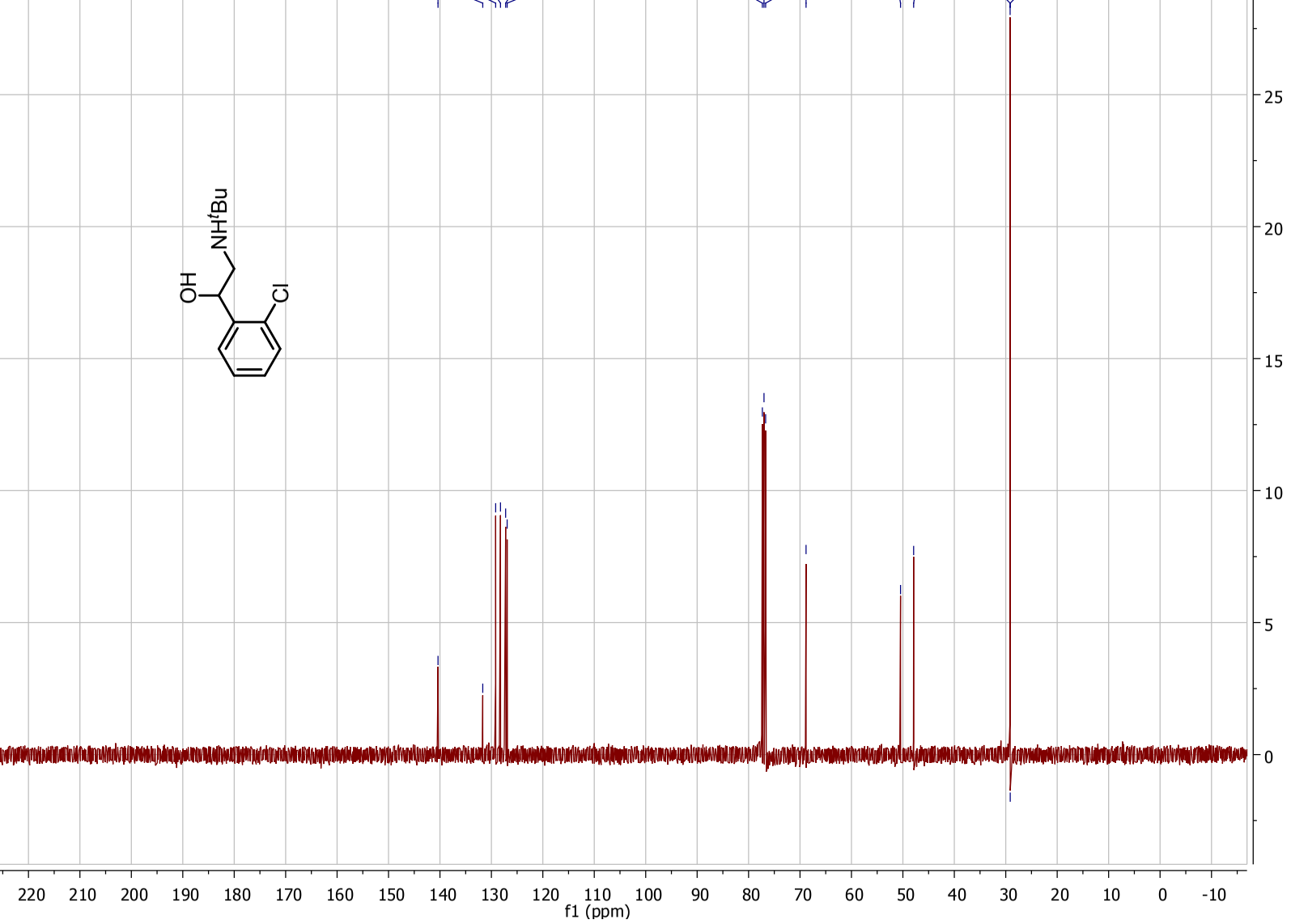
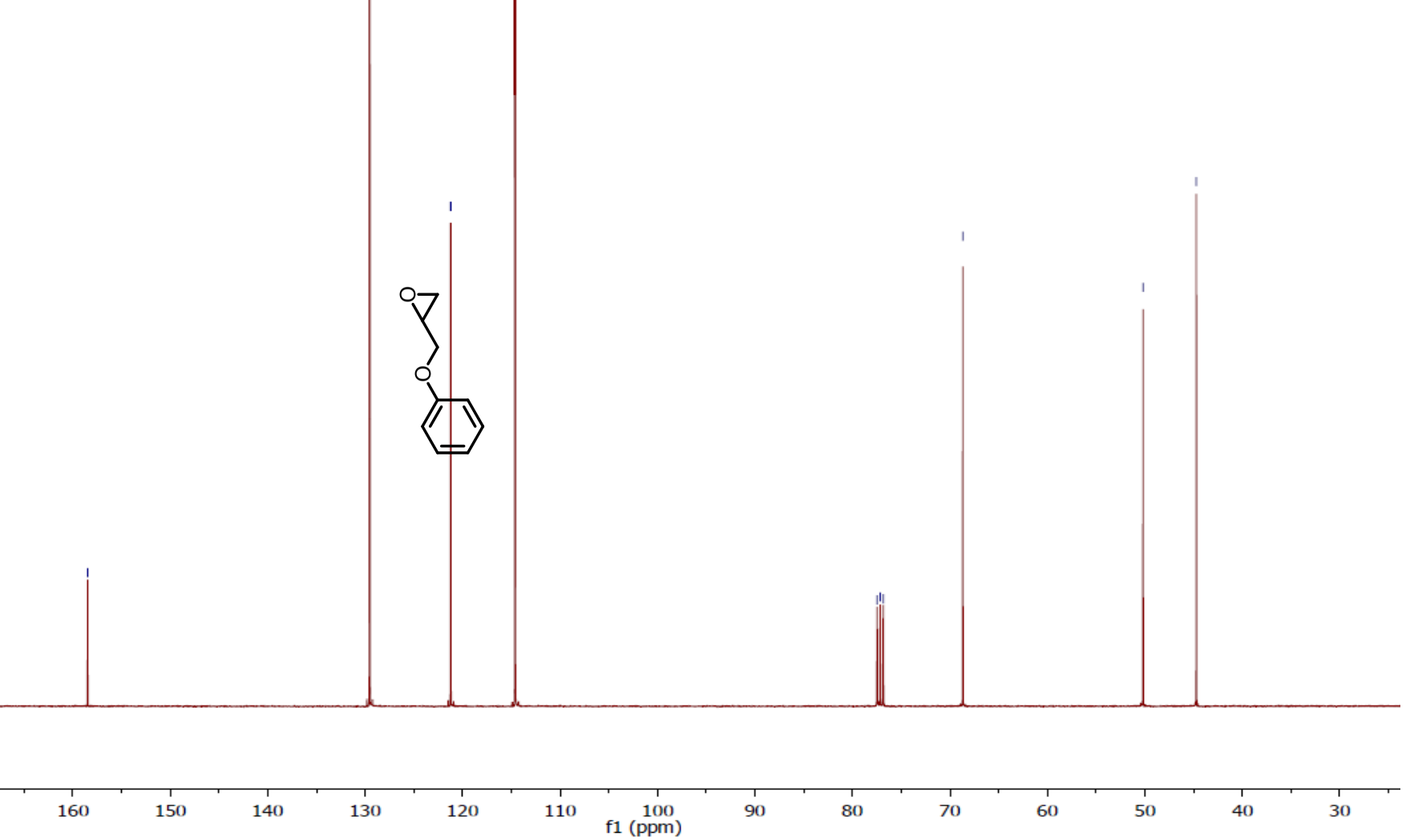
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

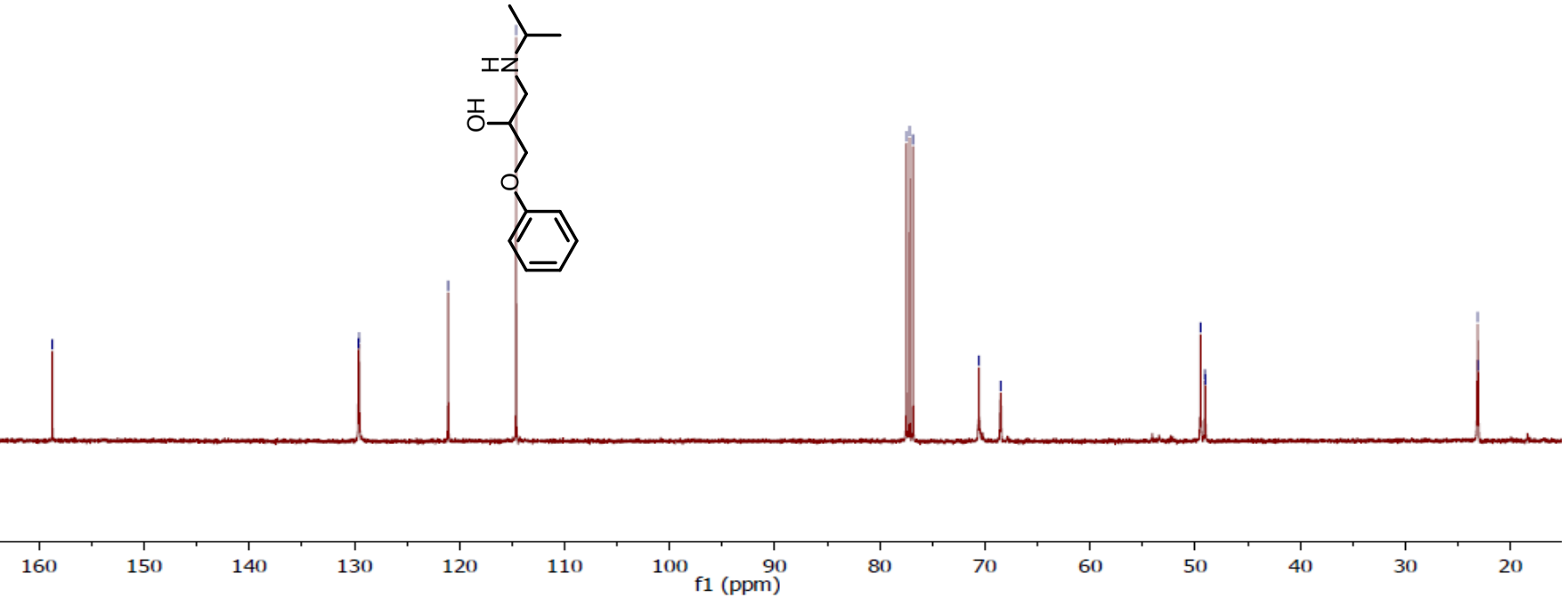

NHtBu
OH
Cl
1.00
2.00
0.99
1.03
1.15
1.35
9.93
f1 (ppm)

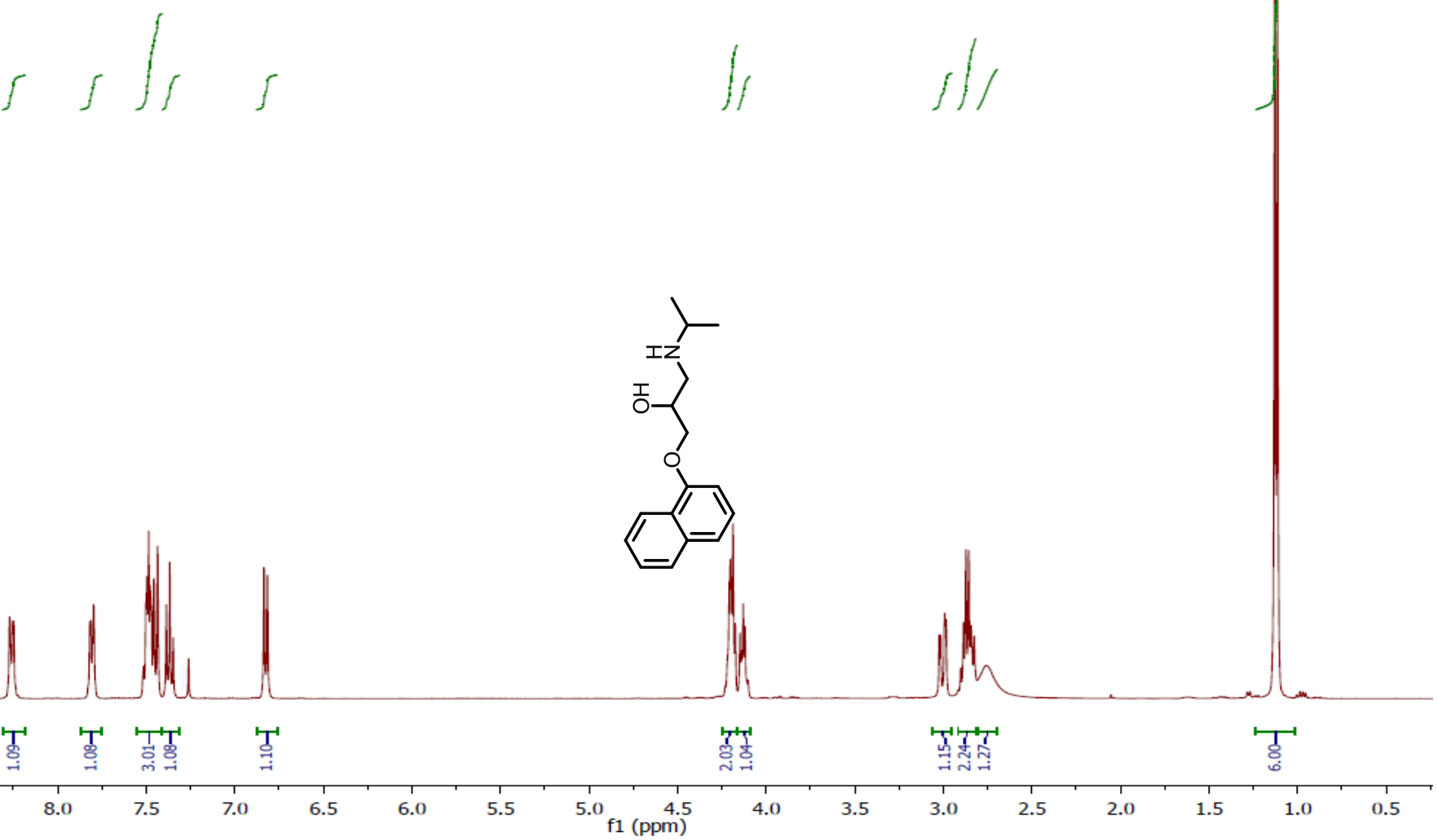

OH
NHtBu
Cl
25
20
15
10
5
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

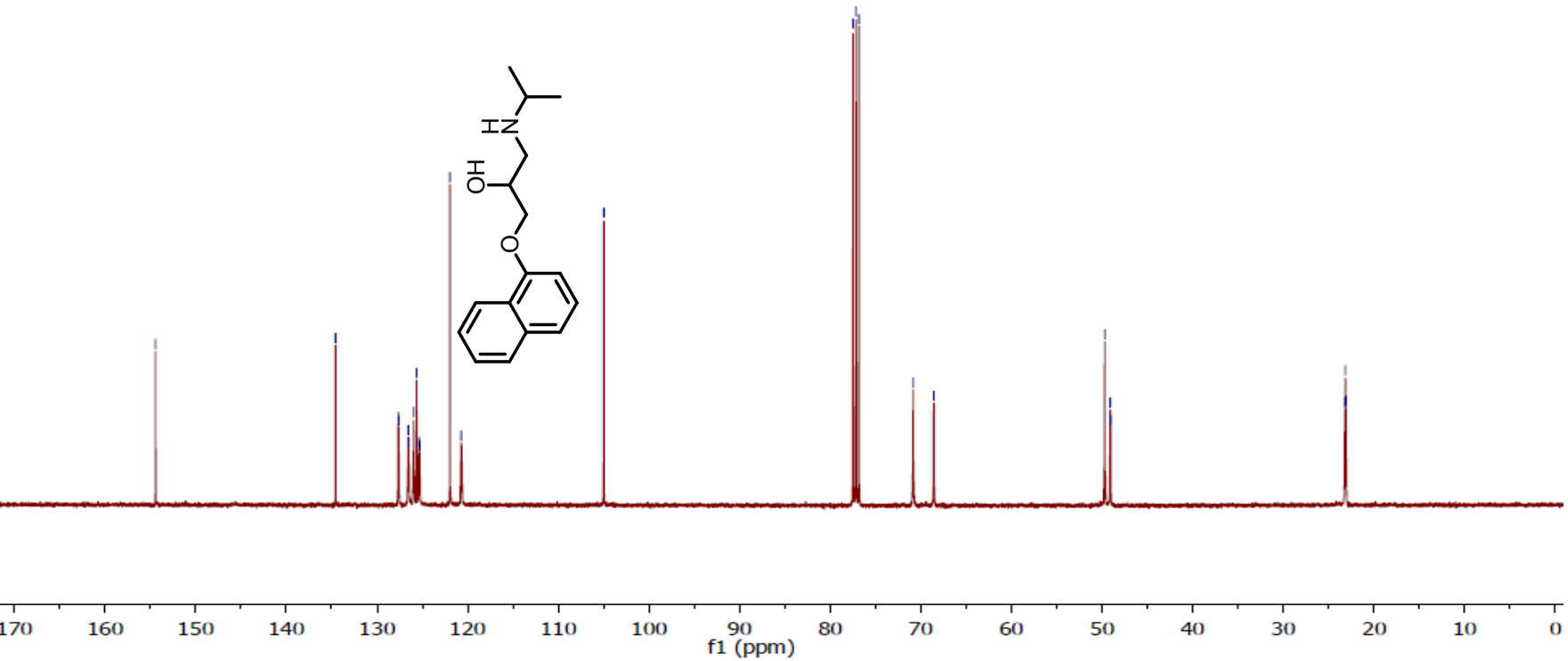
2.01
3.02
1.12
1.12
1.00
1.08
1.07
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
O
O

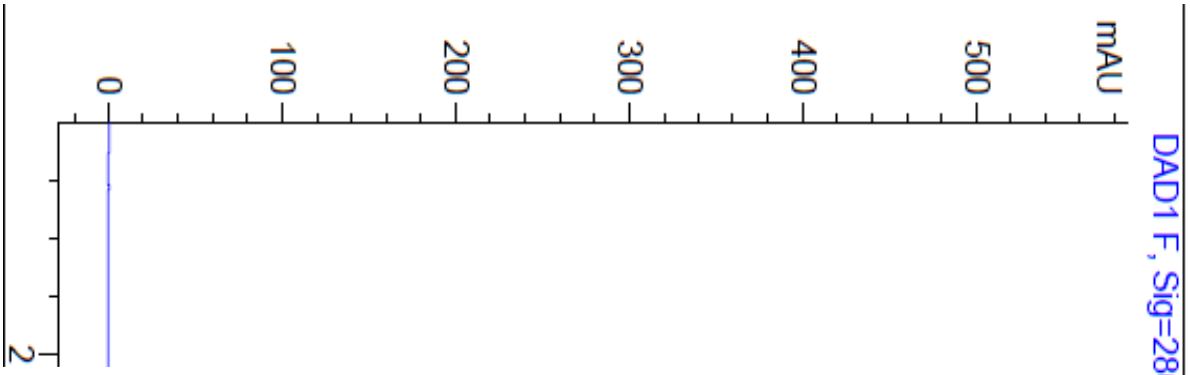

160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

2.10
3.00
1.11
2.13
1.19
1.26
2.08
6.19
OH
H
N
O
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

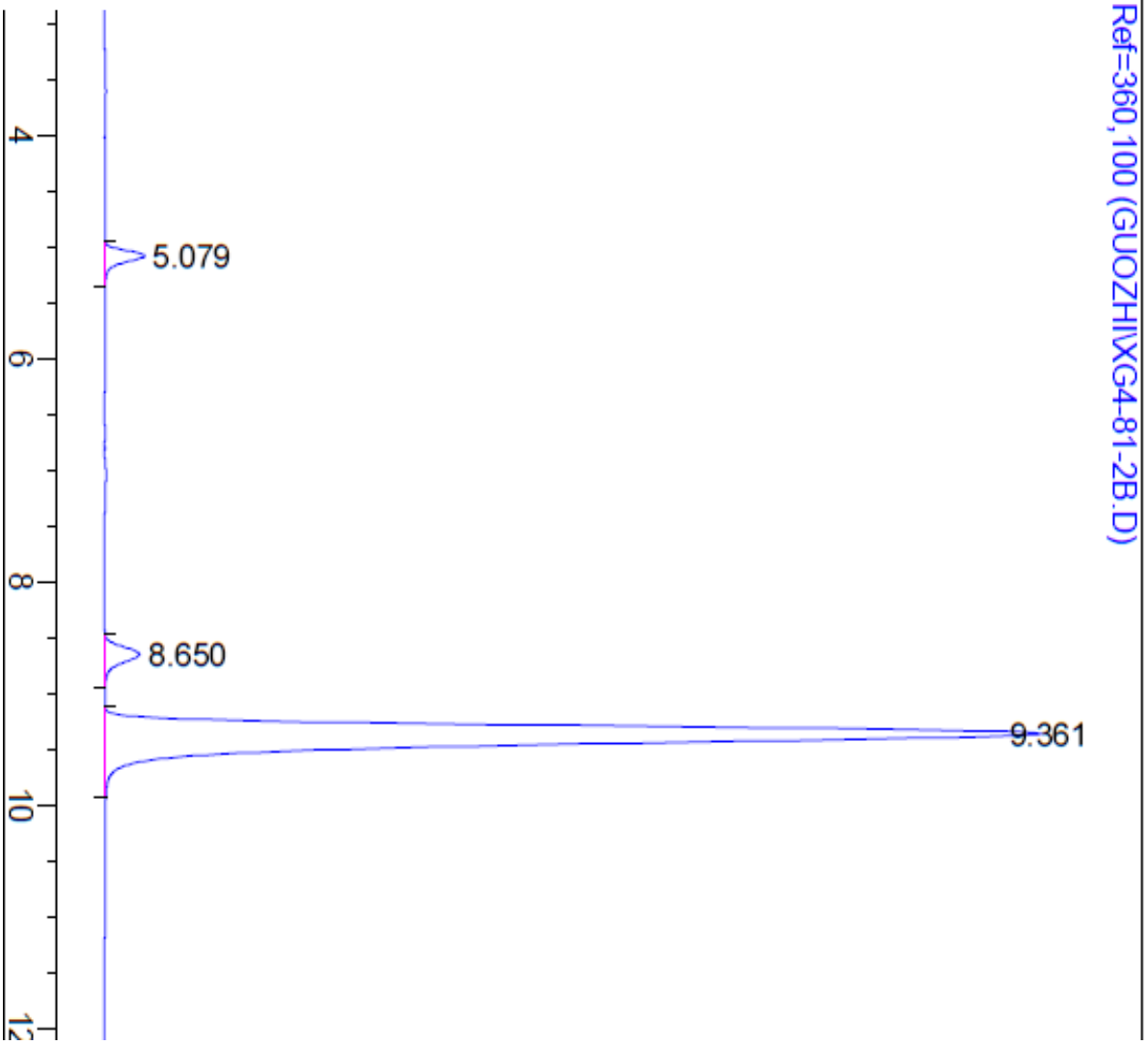

OH
H
N
O
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

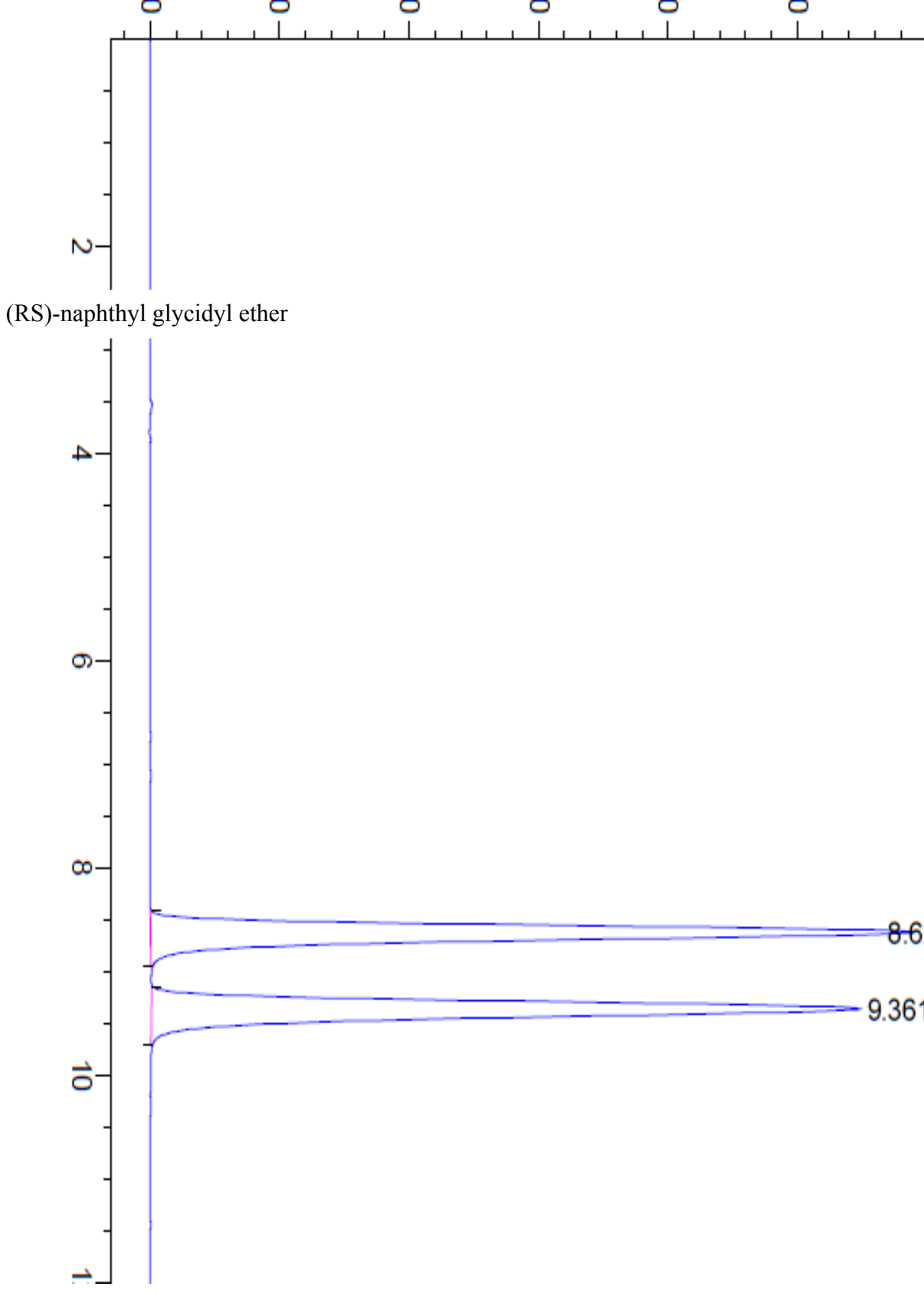

OH
H
N
O
1.09
1.08
3.01
1.08
1.10
2.03
1.04
1.15
2.24
1.27
6.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


OH
H
N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



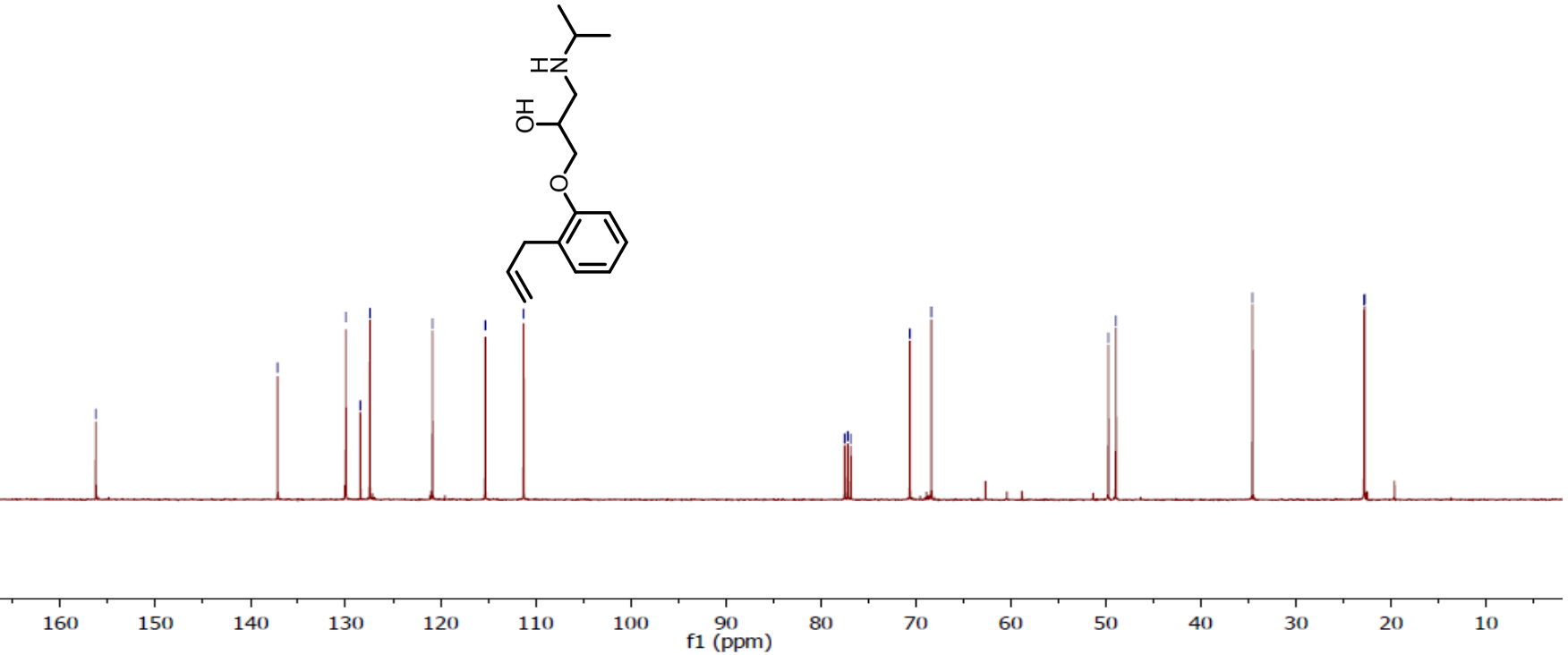
(S)-naphthyl glycidyl ether



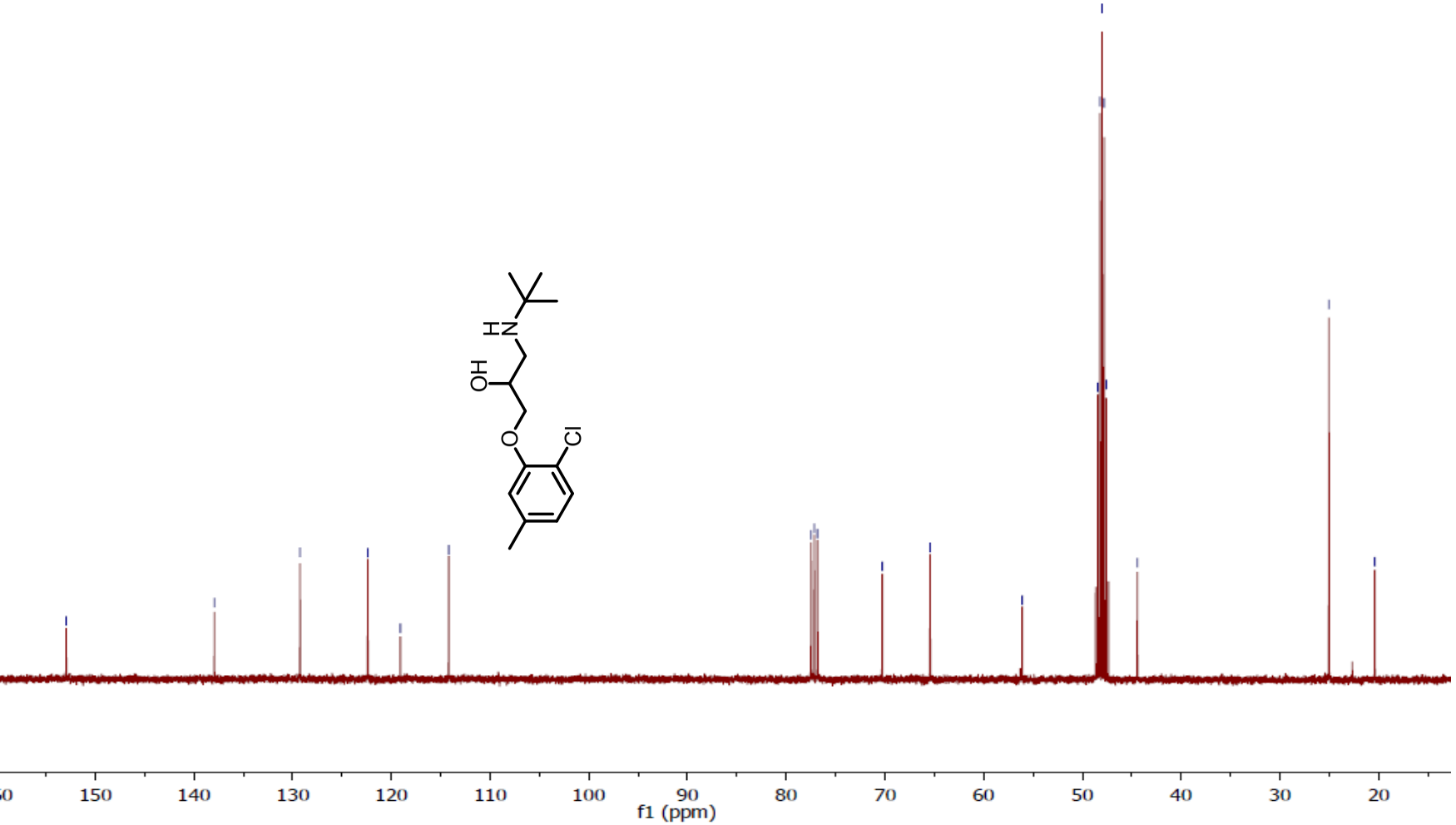


(RS)-naphthyl glycidyl ether

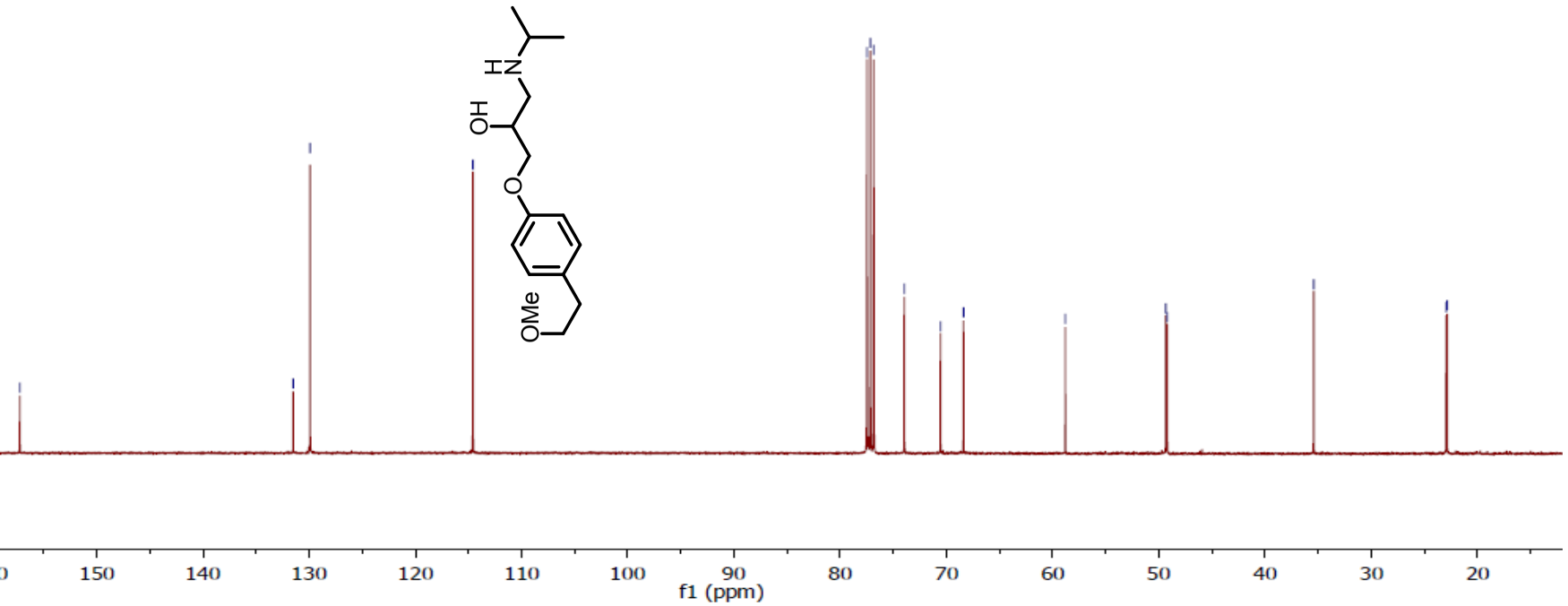
2.08
1.05
0.99
1.01
2.04
1.01
1.84
2.14
1.31
1.20
2.24
5.99
OH
H
N
O
f1 (ppm)


HN
OH
O
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1.05
2.04
1.09
1.16
1.19
2.01
1.12
1.12
3.17
9.00
OH
H
N
O
Cl


OH
H
N
O
Cl
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2.08
2.07
1.16
2.23
2.02
2.23
3.15
4.00
1.07
6.13
OMe
O
OH
H
N


H
N
OH
O
OMe
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)