Electronic Supplementary Material (ESI) for RSC Advances.

Supporting information

Diastereoselective synthesis of new zwitterionic bicyclic lactams, scaffolds for construction of 2-substituted-4-hydroxy piperidine and its pipecolic acid derivatives.

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General Information

All reagents and solvents were purchased from commercial sources. The ^{1}H and ^{13}C spectra were determined with a Bruker Avance III Spectrometer ($CDCl_3$ or CD_3OD solvents) operating at 500 and 125 MHz, respectively. The chemical shifts were reported in parts per million (ppm), downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet). Multiplicities were afforded as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublet of doublets of doublets); or m (multiplets). The number of protons for a given resonance is indicated by nH. Coupling constants were reported as a *J* value in Hz. Thin layer chromatography (TLC) was used to monitor the reaction on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Optical rotations were determined at room temperature with a Perkin-Elmer 341 polarimeter, using a 1 dm cell with a total volume of 1mL, and are referenced to the D-line of sodium. Mass spectra were recorded with a JEOL Station JMS-700 instrument at a voltage of 70 eV. X-Ray Diffraction analysis was performed on a diffractometer STOE Stadivari using Ag-Kα radiation (λ = 0.56083 Å, AXO micro-source) and equipped with a Dectris Pilatus-100 K detector. Intensities were collected at 295 K, and structures were refined using the current release of SHELXL (2018/3). The products were purified by column chromatography on silica gel 60 (63-200nm).

General procedures

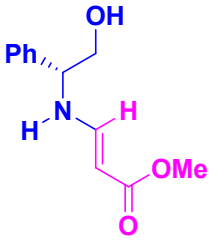
General procedure for the synthesis of β-enaminoesters.

The synthesis of the β-enaminoesters was carried out according to methods **A**, **B,** or **C**.

Method A.

Synthesis of 1. To a solution of (*R*)-(-)-2-amino-phenylglycinol (0.5 g, 3.649 mmol) in MeOH (HPLC, 5 mL) at 0 °C in a flask sealed with septum rubber was added dropwise methyl propiolate (0.36 g, 4.380 mmol). The reaction was stirred for 4 h at room temperature and the solvent was eliminated by distillation under reduced pressure. The isomeric *E*/*Z* mixture (72:28 ratio) was obtained in a 98% combined yield.

Methyl (*R,E/Z*)-3-((2-hydroxy-1-phenylethyl)amino)acrylate, 1



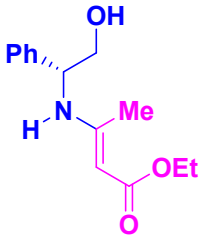
1

Yellow oil, 98% yield. (*E*/*Z* ratio, 72:28); Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 13.3, 7.2 Hz, 1H), 7.31-7.23 (m, 5H), 6.66 (dd, 13.1, 8.0 Hz, 1H), 4.56 (d, *J* = 8.08 Hz, 1H), 4.36 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 3.64 (s, 3H), 3.02 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 151.6, 138.9, 128.9, 128.0, 126. 8, 83.3, 66. 7, 63.8, 50.4. Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 13.3, 8.25 Hz, 1H), 7.37-7.33 (m, 5H), 5.81 (t, *J* = 7.1 Hz, 1H), 4.58 (d, *J* = 2.5 Hz, 1H), 4.38 (m, 1H), 3.85 (m, 1H), 3.68 (m, 1H), 3.56 (s, 3H), 3.01 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 151.6, 138.1, 128.8, 127.9, 126.6, 87.2, 66.2, 63.8, 50.6. HRMS(ESI): Calcd for $C_{12}H_{15}NO_3$: 221.1051 Found: 221.1049.

Method B.

Synthesis of 2, 3, and 4. To a stirred solution of (*R*)-(-)-2-phenylglycinol (1 equiv.) in methanol at room temperature was added the corresponding β-ketoester (1.1 equiv.). After 4 h the solvent was eliminated by distillation under reduced pressure, and the compound was purified by chromatographic column on silica gel with petroleum ether/ethyl acetate (1:1).

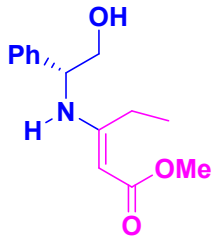
Ethyl (*R,E/Z*)-3-((2-hydroxy-1-phenylethyl)amino)but-2-enoate, 2



2

Yellow oil, 99 % yield. (*E*/*Z* ratio, 98:2); Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (d, *J* = 8.5 Hz, 1H), 7.37-7.26 (m, 5H), 4.69 (ddd, *J* = 8.6, 7.2, 4.4 Hz, 1H), 4.54 (s, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.86 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.77 (dd, *J* = 11.3, 7.2 Hz, 1H), 3.01 (s, 1H), 1.81 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 161.9, 139.9, 128.8, 127.7, 126.4, 88.2, 67.1, 59.2, 58.5, 19.8, 14.6. HRMS(ESI): Calcd for $C_{14}H_{19}NO_3$: 249.1365 found: 249.1363.

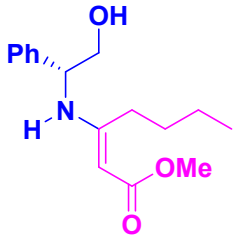
Methyl (*R,E/Z*)-3-((2-hydroxy-1-phenylethyl)amino)pent-2-enoate, 3.



3

Brown oil, 84% yield. (*E*/*Z* ratio, up to 99); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (d, *J* = 8.7 Hz, 1H), 7.24-7.15 (m, 5H), 4.57 (ddd, *J* = 8.7, 7.0, 4.3 Hz, 1H), 4.48 (s, 1H), 3.75 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.70 (s, 1H), 3.63 (dd, *J* = 11.1, 2.9 Hz, 1H), 3.53 (s, 3H), 2.10 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.95 (dt, *J*= 15.4, 7.6 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 167.3, 140.2, 128.8, 127.6, 126.3, 81.6, 67.10, 58.6, 50.1, 25.4, 11.9. HRMS(ESI): Calcd. for $C_{14}H_{19}NO_3$: 249.1366 found: $C_{14}H_{19}NO_3$: 249.1364.

Methyl (*R,E/Z*)-3-((2-hydroxy-1-phenylethyl)amino)hept-2-enoate, 4



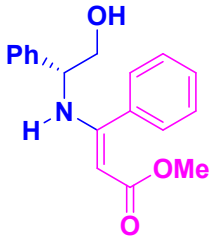
4

Yellow oil, 84% yield. (*E*/*Z* ratio, up to 99); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (d, *J* = 9.2 Hz, 1H), 7.36-7.26 (m, 5H), 4.67 (ddd, *J* = 9.2, 7.0, 4.5 Hz, 1H), 4.59 (s, 1H), 3.86 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.78 (dd, *J* = 11.4, 7.0 Hz, 1H), 3.68 (s, 3H), 3.23 (s, 1H), 2.13 (ddd, *J* = 14.5, 9.7, 5.8 Hz, 1H), 2.03 (ddd, *J* = 14.5, 9.8, 6.3 Hz, 1H), 1.63 (m, 2H), 1.28 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 166.0, 139.9, 128.9, 127.8, 126.3, 83.2, 67.4, 58.7, 50.2, 32.2, 30.0, 22.3, 13.7. HRMS(ESI): Calcd for $C_{16}H_{23}NO_3$: 277.1677 found: $C_{16}H_{23}NO_3$: 277.1675.

Method C. Synthesis of β-enaminoesters 5, 6 and 7

To a stirred solution of (*R*)-(-)-2-phenylglycinol (1 equiv.) and the corresponding β-ketoester (1 equiv.) in ethanol was added AcOH (10% w). The mixture was heated at reflux temperature for three hours. Subsequently, the solvent was eliminated by distillation under reduced pressure, and the product was extracted with brine solution and EtOAc (3x10). The compound was purified by chromatographic column on silica gel with petroleum ether/ethyl acetate (1:1).

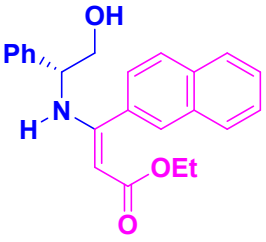
Methyl (*R,E/Z*)-3-((2-hydroxy-1-phenylethyl)amino)-3-phenylacrylate, 5



5

Yellow oil, 80% yield. (*E*/*Z* ratio, up to 99); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, *J* = 10.0 Hz, 1H), 7.36-7.33 (m, 10H), 4.73 (s, 1H), 4.45 (ddd, *J* = 10.2, 6.8, 4.8 Hz, 1H), 3.76 (m, 2H), 3.71 (s, 3H), 2.33 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 164.9, 140.0, 135.8, 129.3, 128.6, 128.2, 127.8, 127.5, 126.4, 87.3, 67.2, 60.2, 50.4, HRMS(ESI): Calcd for $C_{18}H_{19}NO_3$: 297.1364: found 297.1362.

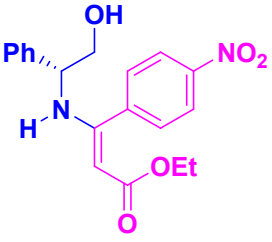
Ethyl (*R,E/Z*)-3-((2-hydroxy-1-phenylethyl)amino)-3-(naphthalen-2-yl)acrylate, 6



6

Yellow oil, 80% yield. (*E*/*Z* ratio, up to 99);. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (d, *J* = 10.0 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.69 (m, 2H), 7.46 (m, 2H), 7.30 (m, 1H), 7.24 (m, 3H), 7.11 (m, 2H), 4.84 (s, 1H), 4.49 (ddd, *J* = 10.1, 6.7, 4.8 Hz, 1H), 4.19 (q, *J* = 7.16 Hz, 2H), 3.75 (m, 2H), 2.69 (s, 1H), 1.29 (t, *J* = 7.13 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 164.8, 140.1, 133.4, 133.4, 132.7, 128.6, 128.3, 127.9, 127.6,127.5, 127.4, 126.8, 126.5, 125.2, 88.1, 67.2, 60.5, 59.0, 14.5. HRMS(ESI): Calcd for $C_{23}H_{23}NO_3$: 361.1677 found: 361.1675.

Ethyl (*R,E/Z*)-3-((2-hydroxy-1-phenylethyl)amino)-3-(4-nitrophenyl)acrylate, 7



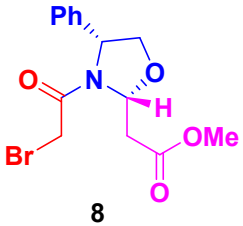
7

Yellow oil, 80% yield. (*E*/*Z* ratio, up to 99); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.0 (d, *J* = 9.6 Hz, 1H), 8.1 (d, *J* = 8.4, 2H), 7.36 (d, *J*= 8.3 Hz, 2H), 7.23-7.29 (m, 3H), 7.08 (d, *J* = 7.4 Hz, 2H), 4.70 (s, 1H), 4.31 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.78 (qd, *J* = 11.4, 5.8 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 162.0, 148.2, 142.4, 139.7, 129.0, 128.8, 127.8, 126.4, 123.5, 89.1, 67.1, 60.0, 59.4, 14.5. HRMS(ESI): Calcd for $C_{19}H_{20}N_2O_5$: 356.1372 found: $C_{19}H_{20}N_2O_5$: 356.1370.

General procedure for the synthesis of oxazolidine amidoesters.

To a stirred mixture of corresponding β-aminoester (1 equiv.) in 15 mL of CH_2Cl_2 and 15 mL of an aqueous solution of K_2CO_3 at 0 °C was added bromo acetyl bromide (1.3 equiv.). The mixture was allowed to warm to room temperature and after 3.5 h the mixture was extracted and the organic phase was separated and dried over anhydrous Na_2SO_4, filtered and the solvent was eliminated by distillation under reduced pressure. The product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (7:3).

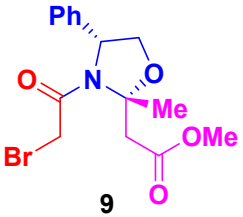
Methyl 2-((4*R*)-3-(2-bromoacetyl)-4-phenyloxazolidin-2-yl)acetate, 8



8

Colorless oil, inseparable diastereomeric mixture 70% yield. (*dr* = 88:12). ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereoisomer) δ 7.43-7.31 (m, 5H), 5.82 (dd, *J* = 8.5, 3.0 Hz, 1H), 5.14 (m, 1H), 4.39 (dd, *J* = 9.1, 6.7 Hz, 1H), 4.07 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.93 (m, 2H), 3.75 (s, 3H), 3.41 (dd, *J* = 15.8, 3.3 Hz, 1H), 2.77 (dd, *J* = 15.6, 8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 165.2, 138.6, 129.4, 129.0, 128.7, 88.3, 74.1, 60.6, 51.9, 38.4, 29.0. HRMS(ESI): Calcd for $C_{14}H_{16}BrNO_4$: 341.0262 found: 341.0260.

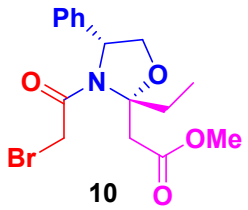
Ethyl 2-((2*R*,4*R*)-3-(2-bromoacetyl)-2-methyl-4-phenyloxazolidin-2-yl)acetate, 9.



9

Colorless oil, 80% yield. (*dr* = 97:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H), 5.08 (dd, *J* = 6.9, 3.7 Hz, 1H), 4.44 (dd, *J* = 9.2, 6.9 Hz, 1H), 4.15 (m, 2H), 4.00 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.54 (m, 2H), 3.43 (d, *J* = 11.0 Hz, 1H), 2.97 (d, *J* = 14.4 Hz, 1H), 1.78 (s, 3H), 1.25 (t, *J* = 7.10 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 164.6, 139.6, 129.4, 128.6, 126.1, 96.2, 72.2, 60.9, 60.8, 43.4, 29.2, 20.7, 14.2. HRMS(ESI): Calcd for $C_{15}H_{18}BrNO_4$: 355.0419 found: 355.0417.

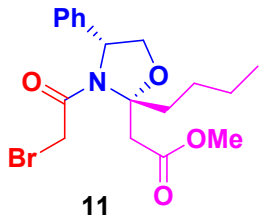
Methyl 2-((2*R*,4*R*)-3-(2-bromoacetyl)-2-ethyl-4-phenyloxazolidin-2-yl)acetate, 10.



10

Colorless oil, 80% yield. (*dr* > 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 5H), 5.00 (m, 1H), 4.41 (dd, *J* = 9.2, 7.3 Hz, 1H), 3.87 (dd, *J* = 9.2, 7.9 Hz, 1H), 3.64 (s, 3H), 3.28 (m, 2H), 3.20 (d, *J* = 13.7 Hz, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.48 (m, 1H), 2.08 (m, 1H), 0.86 (t, *J* = 7.3 Hz, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 164.8, 138.2, 129.6, 128.9, 126.4, 99.1, 73.4, 62.3, 51.9, 42.4, 29.1, 27.9, 7.1. HRMS(ESI): Calcd for $C_{16}H_{20}BrNO_4$: 369.0576 found: 369.2182.

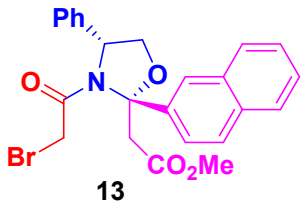
Methyl 2-((2*R*,4*R*)-3-(2-bromoacetyl)-butyl-4-phenyloxazolidin-2-yl)acetate, 11.



11

Brown oil, 70% yield. (*dr* > 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 5.08 (m, 1H), 4.47 (dd, *J* = 9.1, 7.2 Hz, 1H), 3.94 (dd, *J* = 9.2, 7.7 Hz, 1H), 3.71 (s, 3H), 3.36 (m, 2H), 3.28 (d, *J* = 13.7 Hz, 1H), 3.14 (d, *J* = 13.8 Hz, 1H), 2.48 (m, 1H), 2.12 (ddd, *J* = 14.3, 11.4, 4.5 Hz, 1H), 1.41 (m, 1H), 1.33 (m, 3H), 0.91 (t, *J* = 6.89 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 164.9, 138.2, 129.6, 128.8, 126.4, 98.8, 73.2, 62.1, 51.9, 42.5, 34.6, 29.01, 24.8, 22.5, 14.0. HRMS(ESI): Calcd for $C_{18}H_{24}BrNO_4$: 397.0888 found: 397.0891.

Methyl 2-((2*S*,4*R*)-3-(2-bromoacetyl)-2-(naphthalen-2-yl)-4-phenyloxazolidin-2-yl)acetate, 13.



13

Yelow oil, 35% yield. (*dr* > 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.3 Hz, 1H), 7.79 (m, 3H), 7.76 (m, 1H), 7.64 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.45 (m, 4H), 7.35 (m, 3H), 5.08 (dd, *J* = 7.2, 2.5 Hz, 1H), 4.09 (m, 3H), 3.94 (dd, *J* =9.0, 2.6 Hz, 1H), 3.76 (AB, *J* = 14.7 Hz, 2 H), 3.50 (AB, *J* = 10.5 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 165.5, 140.6, 129.5, 128.8, 128.7, 128.4, 127.5, 126.6, 126.5, 126.3, 125.8, 129.3, 98.0, 72.3, 61.2, 60.7, 43.5, 29.3, 14.1. HRMS(ESI): Calcd for $C_{24}H_{22}BrNO_4$: 467.0732 found: 467.0729.

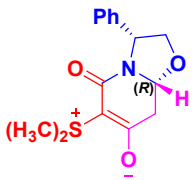
General procedure for the synthesis of sulfonium oxazolidine salts.

To a stirred solution of corresponding *N*-acyl oxazolidine (1 equiv.) in a minimum amount of CH_2Cl_2 at room temperature was added $S(CH_3)_2$ (7 equiv). The resulting mixture was stirred until the total consumption of starting material was confirmed by TLC. Then, the solvent and the excess of dimethyl sulfur were eliminated by distillation under reduced pressure. All sulfonium salts were used for the next reaction without purification.

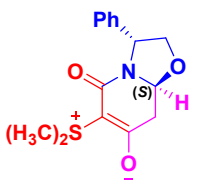
General procedure for the synthesis of zwitterionic bicyclic lactams derivates.

To a stirred solution of the corresponding sulfonium salts (1 equiv.) in a mixture of acetonitrile:methanol (1:1) at room temperature, was added K_2CO_3 (1.2 equiv.). The reaction mixture was stirred until the total consumption of starting material was confirmed by TLC (4 to 8 h, depending on the sulfonium salts derivate). Then, the solvent was eliminated by distillation under reduced pressure. Next, a brine solution and ethyl acetate were added. The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and the residue was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2/MeOH (9:1).

(3*R*)-6-(dimethylsulfonio)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridin-7-olate, 22(a+b).



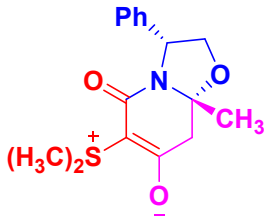
22a
major diastereoisomer



22b
minor diastereoisomer

Brown solid, inseparable diastereomeric mixture, 97% yield. (*dr* =73:27). Major diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.12 (dd, *J* = 11.37, 4.19 Hz, 1H), 5.00 (dd, *J* = 7.04, 1.58 Hz, 1H), 4.26 (dd, *J* = 8.94, 7.05 Hz, 1H), 4.09 (dd, *J* = 8.97, 1.58 Hz, 1H), 2.91-2.87 (m, 7H), 2.81 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 162.6, 142.0, 128.6, 127.4, 126.4, 85.8, 74.7, 74.2, 57.9, 43.2, 27.3, 25.9. Minor diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.23 (m, 5H), 5.40 (dd, *J* = 9.82, 5.28 Hz, 1H), 5.21 (t, *J* = 6.63 Hz, 1H), 4.48 (dd, *J* = 8.73, 7.21 Hz, 1H), 3.86 (dd, *J* = 8.77, 6.07 Hz, 1H), 2.96 (s, 3H), 2.86 (s, 3H), 2.80 (m, 1H), 2.71 (dd, *J* = 15.8, 9.84 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 163.0, 140.6, 128.7, 127.4, 126.0, 85.4, 73.3, 73.1, 58.7, 42.5, 27.7, 25.6. HRMS(FAB): Calcd for $C_{15}H_{17}NO_3S$: 291.0923 found: 291.0921

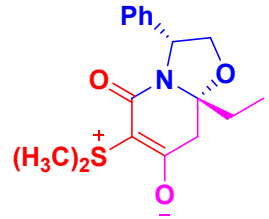
(3*R*,8a*R*)-6-(dimethylsulfonio)-8a-methyl-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridin-7-olate, 23a.



23a

Yellow solid, 98% yield, (*dr* =98:2). Major diastereoisomer, **23a**: m.p.= 186-188°C. $[\alpha]_D^{20}$ = -2.41° (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H), 5.00 (dd, *J* = 7.15, 1.95 Hz, 1H), 4.46 (dd, *J* = 9.12, 7.13 Hz, 1H), 3.98 (dd, *J* = 9.12, 1.96 Hz, 1H), 2.99 (dd, *J* = 15.6, 1.39 Hz, 1H), 2.87 (s, 3H), 2.85 (s, 3H), 2.78 (dd, *J* = 15.4, 1.63 Hz. 1H), 1.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 162.2, 142.1, 128.6, 127.3, 126.1, 91.8, 73.2, 72.3, 58.3, 49.6, 27.4, 25.8, 22.0. HRMS (FAB): Calcd for $C_{16}H_{19}NO_3S$: 305.1085 found: 305.2420.

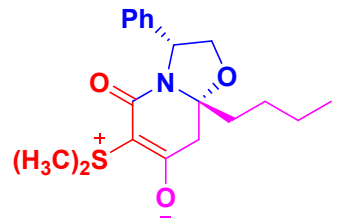
(3*R*,8a*R*)-6-(dimethylsulfonio)-8a-ethyl-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*- oxazolo[3,2-*a*]pyridin-7-olate, 24a.



24a

Colorless solid, 98% yield. (*dr* =97:3). Major diastereoisomer, **24a:** m.p.= 156-158°C. $[\alpha]_D^{20}$ = -9.6° (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.15 (m, 5H), 4.93 (dd, *J* = 7.21, 2.17 Hz, 1H), 4.33 (dd, *J* = 9.06, 7.23 Hz, 1H), 3.87 (dd, 9.03, 2.19 Hz, 1H), 2.89 (d, *J* = 15.9 Hz, 1H), 2.81-2.76 (m, 7H), 1.83 (m, 1H), 1.74 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 161.3, 141.1, 127.6, 126.3, 125.2, 93.0, 72.2, 71.3, 57.6, 44.8, 26.4, 26.1, 24.9, 7.3. HRMS (FAB): Calcd for $C_{16}H_{18}NO_3S$: 304.1007 found: 304.1005.

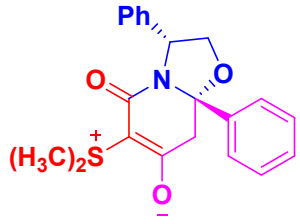
(3*R*,8a*R*)-8a-butyl-6-(dimethylsulfonio)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo [3,2-*a*]pyridin-7-olate, 25a.



25a

Brown solid, 98% yield. (*dr* =97:3). Major diastereoisomer, **25a**: m.p. = 150-152°C. $[\alpha]_D^{20}$ = -18.4° (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 5.00 (dd, *J* = 7.28, 2.22 Hz, 1H), 4.42 (dd, *J* = 9.09, 7.24 Hz, 1H), 3.95 (dd, 9.07, 2.23 Hz, 1H), 2.92 (m, 2H), 2.87 (d, *J* = 1.90 Hz, 6H), 1.88 (ddd, *J* = 14.19, 10.33, 6.23 Hz, 1H), 1.86 (m, 1H), 1.39 (m, 2H), 1.29 (m, 2H), 0.90 (t, *J* = 7.20 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ186.2, 163.0, 142.1, 128.6, 127.3, 126.2, 93.8, 73.3, 72.4, 58.6, 46.5, 34.2, 27.5, 26.1, 25.9, 22.9, 14.0. HRMS (FAB): Calcd for $C_{19}H_{25}NO_3S$: 347.1555 found: 347.1553.

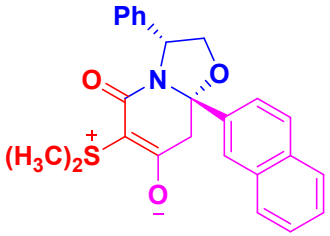
(3*R*,8a*S*)-6-(dimethylsulfonio)-5-oxo-3,8a-diphenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo [3,2-*a*]pyridin-7-olate, 26a.



26a

Yellow oil, 98% yield. *dr* = 98:2. Major diastereoisomer: $[\alpha]_D^{20}$ = ° (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.25 (m, 10 H), 5.06 (t, *J* = 4.36 Hz, 1H), 3.87 (d, *J* = 4.29 Hz, 2H), 3.36 (d, *J*= 15.3 Hz, 1H), 3.19 (d, *J* = 15.3 Hz, 1H), 2.84 (s, 3H), 2.79 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 163.3, 142.1, 140.5, 128.7, 128.5, 128.7, 127.4, 126.3, 126.2, 94.0, 74.4, 71.9, 59.1, 49.7, 27.5, 25.7. HRMS (FAB): Calcd for $C_{21}H_{21}NO_3S$: 367.1242 found: 367.1244.

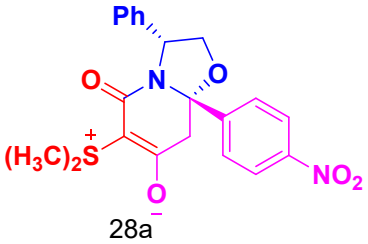
(3*R*,8*aS*)-6-(dimethylsulfonio)-8a-(naphthalen-2-yl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5H-oxazolo[3,2-a]pyridin-7-olate, 27a.



27a

Yellow oil, 98% yield. *dr* = 98:2. Major diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.79 (m, 4H), 7.49 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.43 (dd, *J* = 9.3, 4.7 Hz, 2H), 7.38 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 5.08 (t, *J* = 4.2 Hz, 1H), 3.84 (d, *J* = 4.3 Hz, 2H), 3.30 (AB, *J* = 15.5 Hz, 2H), 2.80 (s, 3H) 2.72 (s. 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 163.5, 142.1, 137.7, 132.6, 128.8, 128.1, 127.7, 127.5, 126.6, 126.5, 126.4, 125.4, 124.0, 94.2, 74.3, 72.1, 59.3, 49.6, 29.7, 27.7, 25.8. HRMS (FAB): Calcd for $C_{25}H_{23}NO_3S$: 417.1398 found: 417.1400.

(3*R*,8*aS*)-6-(dimethylsulfonio)-8a-(4-nitrophenyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5H-oxazolo[3,2-a]pyridin-7-olate, 28a



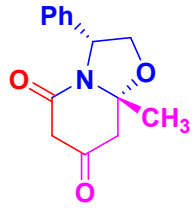
28a

Yellow oil, 98% yield. *dr* = 98:2. Major diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.1 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.20-7.33 (m, 5H), 5.00 (d, *J* = 6.6 Hz, 1H), 3.88 (d, *J* = 9.2 Hz, 1H), 3.76 (dd, *J* = 9.1, 7.1 Hz, 1H), 3.20 (AB, *J* = 15.6 Hz, 2H), 2.80 (s, 3H), 2.75 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 183.7, 163.2, 148.2, 148.1, 141.5, 128.8, 127.7, 127.4, 126.3, 123.6, 74.7, 72.3, 59.3, 49.5, 27.5, 25.7. HRMS (FAB): Calcd for $C_{21}H_{20}N_2O_5S$: 412.1092 found: 412.1090.

Desulfurization reaction.

Synthesis of (3R,8aR)-8a-methyl-3-phenyltetrahydro-5H-oxazolo[3,2-a]pyridine-5,7(6H)-dione 29.

Zinc powder (0.7 g, 10.6 mmol) was added at room temperature to a stirring solution of compound **23a** (0.22g, 0.704 mmol) in glacial acetic acid (8 mL), then HCl(g) was added over 10 min and the resulting mixture was stirred for 7d. After, the insoluble material was filtered off and washed with ethyl acetate. Finally, the filtrate was neutralized with an aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4, the solvent was eliminated by distillation under reduced pressure and the residue was purified by flash chromatography on silica gel with a mixture of petroleum ether/ethyl acetate (1:1).



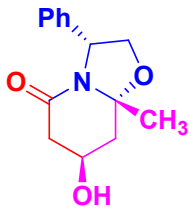
29

Yellow solid, 98% yield. mp = 110-112 °C. $[\alpha]_D^{20}$ = -91.4° (*c* 1, CH_2Cl_2).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 5.04 (dd, *J* = 7.01, 1.76 Hz, 1H), 4.53 (dd, *J* = 9.43, 6.94 Hz, 1H), 4.12 (dd, *J* = 9.46, 1.71 Hz, 1H), 3.27 (d, *J* = 21.03 Hz, 1H), 3.13 (m, 2H), 2.91 (d, *J* = 16.3 Hz, 1H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 161.7, 140.4, 128.7, 127.9, 126.5, 91.6, 72.0, 58.6, 52.0, 45.5, 24.2. HRMS(ESI): Calcd for $C_{14}H_{15}NO_3$: 245.1051 found: 245.2421.

ketone function reduction.

Synthesis of (3*R*,8a*R*)-7-hydroxy-8a-methyl-3-phenylhexahydro-5*H*-oxazolo[3,2-*a*]pyridin-5-one, 32a.

Compound **23** (0.8 g, 3.26 mmol) was dissolved in methanol at -50 °C (10 mL) then $NaBH_4$ was added. Next, the mixture was allowed to reach for 24h. Finally, the solvent was eliminated by distillation under reduced pressure and a solution of $NaHCO_3$ and ethyl acetate was added. The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (3 times). The combined organic layers were dried over Na_2SO_4 and concentrated.



32a

major diastereoisomer

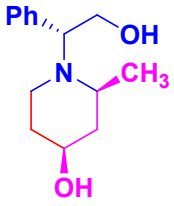
(3*R*,8a*R*)-7-hydroxy-8a-methyl-3-phenylhexahydro-5*H*-oxazolo[3,2-*a*]pyridin-5-one, 32a.

White solid, combined yield 99%. (*dr* = 87:13). Major diastereoisomer: m.p.=100-102°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H), 4.91 (dd, *J* = 7.14, 1.86 Hz, 1H), 4.46 (dd, *J* = 9.32, 7.20 Hz, 1H), 4.19 (m, 1H), 3.95 (dd, *J* = 9.30, 1.80 Hz, 1H), 3.39 (s, 1H), 2.59 (dd, *J* = 17.3, 6.85 Hz, 1H), 2.35 (dd, *J* = 17.2, 5.86 Hz, 1H), 2.26 (m, 2H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 141.2, 128.6, 127.6, 126.3, 93.0, 71.3, 62.7, 58.7, 43.5, 40.2, 24.9. HRMS(ESI): Calcd for $C_{14}H_{17}NO_3$: 247.1208 found: 247.2150.

Synthesis of 1-(2-hydroxy-1-phenylethyl)-2-methylpiperidin-4-ol, 33a.

To a solution of compound **32a** (0.21 g, 0.85 mmol, 1 equiv) in THF (10 mL) was slowly added BH_3•DMS (2.25 mL, 3.5 equiv). The mixture was heated at reflux temperature for 15 min and then, methanol was added. The solvent was eliminated by distillation under reduced pressure. Finally, a saline solution and ethyl acetate were added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 filtered and concentrated. The compound **33a** was purified by a chromatographic column on silica gel with petroleum ether/ethyl acetate (1:1).

(2*S*,4*S*)-1-((*R*)-2-hydroxy-1-phenylethyl)-2-methylpiperidin-4-ol, 33a.



33a

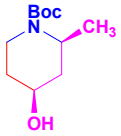
major diasteroisomer

White solid, m.p. = 117-119°C, yield 98%. $[\alpha]_D^{20}$ = +19.3° (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) (major isomer): δ 7.35-7.18 (m, 5H), 4.10 (t, *J* = 6.70 Hz, 1H), 3.99 (dd, *J* = 11.0, 6.64 Hz, 1H), 3.90 (dd, *J* = 11.0, 6.64 Hz, 1H), 3.57 (m, 1H), 2.88 (s, 1H), 2.81 (m, 1H), 2.61 (s, 1H), 2.46 (m, 1H), 1.86 (m, 1H), 1.74 (m, 1H), 1.29 (m, 2H), 1.20 (d, *J*= 3.37 Hz, 3H), 1.80 (m, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 128.4, 128.3, 127.2, 68.4, 63.4, 60.2, 52.5, 45.3, 43.7, 35.1, 20.1. HRMS(ESI): Calcd for $C_{14}H_{21}NO_2$: 235.1572 found: 235.1574.

***Synthesis of tert*-butyl (2*S*,4*R*)-4-hydroxy-2-methylpiperidine-1-carboxylate, 34.**

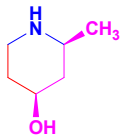
To a solution of (2*S*,4*S*)-1-((*R*)-2-hydroxy-1-phenylethyl)-2-methyl piperidine-4-ol, **33a** (0.1 g, 0.43 mmol, 1 equiv.) in methanol (10 mL) was added di-*tert*-butyl dicarbonate (0.23 g, 1.06 mmol, 2.5 equiv) and Pd/C (10% mol). The mixture was placed under hydrogen atmosphere for a period of 4 h. After the reaction was filtered and the solvent was eliminated under reduced pressure. The compound **34** was purified by chromatographic column on silica gel with petroleum ether/ethyl acetate (1:1).

***tert*-butyl (2*S*,4*R*)-4-hydroxy-2-methylpiperidine-1-carboxylate 34.**



34

Colorless oil, 98% yield. $[\alpha]_D^{20}$ = +32.3° (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (m, 1H), 4.19 (m, 1H), 3.73 (m, 1H), 3.19 (ddd, *J* = 13.6, 10.9, 4.91 Hz, 1H), 2.06 (s, 1H), 1.76 (ddd, 14.3, 6.64, 3.35 Hz, 1H), 1.63 (m, 3H), 1.38 (s, 9H), 1.26 (d, *J* = 7.10 Hz 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 79.2, 64.7, 45.5, 36.4, 33.2, 32.3, 28.5, 19.0. HRMS(ESI)**:** Calcd for $C_{11}H_{21}NO_3$: 215.1521 found: 215.1518.



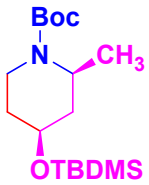
35

Colorless oil, quantitative yield. $[\alpha]_D^{20}$ = -6° (*c* 1, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (m, 1H), 3.36 (m, 3H), 3.0 (t, *J* = 13.2 Hz, 1H), 2.15 (m, 2H), 1.62 (td, *J* = 13.7, 3.5 Hz, 1H), 1.44 (dd, 24.5, 12.3 Hz, 1H), 1.38 (d, *J* = 6.3 Hz, 3H.^{13}C NMR (125 MHz, $CDCl_3$) δ 65.0, 51.5, 42.3, 39.3, 30.7, 17.9. HRMS(ESI): Calcd for $C_6H_{13}NO$: 115.1760 found: 115.1758.

***Synthesis of tert*-butyl (2*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpiperidine-1-carboxylate, 36.**

Tert-butyl (2*S*,4*R*)-4-hydroxy-2-methyl piperidine-1-carboxylate **34**, *tert*-butyl-dimethyl silane chloride (1.1 equiv), triethylamine (1.2 equiv), and imidazole (1.2 equiv), were dissolved in dichloromethane (15 mL) at room temperature. The mixture was stirred until the consumption of the starting material was observed by thin layer chromatography. After a brine solution was added, the organic phase was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The compound **36** was purified by chromatographic column on silica gel with petroleum ether/ethyl acetate (7:3)

***Tert*-butyl (2*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpiperidine-1-carboxylate, 36.**

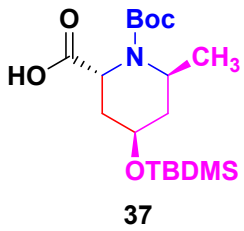


36

Oil colorless, 100% yield. $[\alpha]_D^{20}$ = +37.5° (*c* 1, CH_2Cl_2). NMR-^{1}H (500 MHz, $CDCl_3$) δ 4.23 (m, 1H), 4.03 (m, 1H), 3.75 (d, *J*= 13.3 Hz, 1H), 3.18 (m, 1H), 1.70 (ddd, *J*= 13.8, 6.5, 2.7 Hz, 1H), 1.53 (t, 12.7 Hz, 3H), 1.40 (s, 9H), 1.25 (d, *J*= 7.1 Hz, 3H), 0.84 (s, 9H), 0.002 (s, 6H). NMR-^{13}C (125 MHz, $CDCl_3$) δ 154.9, 78.9, 65.1, 45.6, 36.7, 33.2, 33.0, 28.4, 25.7, 25.6, 19.1, 17.9, 5.00, 5.04. HRMS(ESI): Calcd for $C_{14}H_{17}NO_3$: 247.1208 found: 247.1210.

Synthesis of (2*R*,4*R*,6*S*)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)-6methylpiperidine-2-carboxylic acid, 37.

To a stirred solution of *tert*-butyl (2*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpiperidine-1-carboxylate **36** in anhydrous ethyl ether at -78 °C was added TMEDA (1.5 equiv.) and *s*-BuLi (1.4 equiv.). This mixture was allowed to react for a period of 4h and then $CO_{2(g)}$ was added. The total consumption of starting compound was observed by thin-layer chromatography after 12 h. To a resulting mixture was added a brine solution and ethyl acetate. The organic phase was separated, the aqueous layer was extracted with ethyl acetate (twice) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was eliminated by distillation under reduced pressure. Compound **37** was purified by chromatographic column on silica gel with petroleum ether/ethyl acetate (7:3).



37

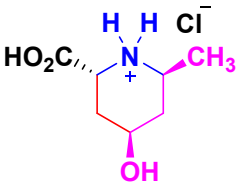
(2*R*,4*R*,6*S*)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)-6-methylpiperidine-2-carboxylic acid, 37.

Oil brown, 87% yield. $[\alpha]_D^{20}$ = +30.6° (*c* 1, CH_2Cl_2). NMR-^{1}H (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 4.35 (s, 1H), 4.05 (s, 2H), 2.25 (d, *J*=5.2 Hz, 1H), 1.90 (m, 2H), 1.51 (d, *J*=13.8 Hz, 1H), 1.39 (s, 9H), 1.31 (d, *J*= 6.19 Hz, 3H), 0.83 (s, 9H), 0.002 (s, 6H). NMR-^{13}C (125 MHz, $CDCl_3$) δ 178.1, 156.1, 80.6, 63.5, 52.3, 47.5, 37.2, 34.6, 29.6, 28.3, 25.7, 21.5, 17.8, 14.1, 4.89, 4.80. HRMS(ESI): Calcd for $C_{14}H_{17}NO_3$: 247.1208 found: 247.1210.

Synthesis of (*2R,4R,6S*)-4-hydroxy-6-methylpiperidine-2-carboxylic acid.

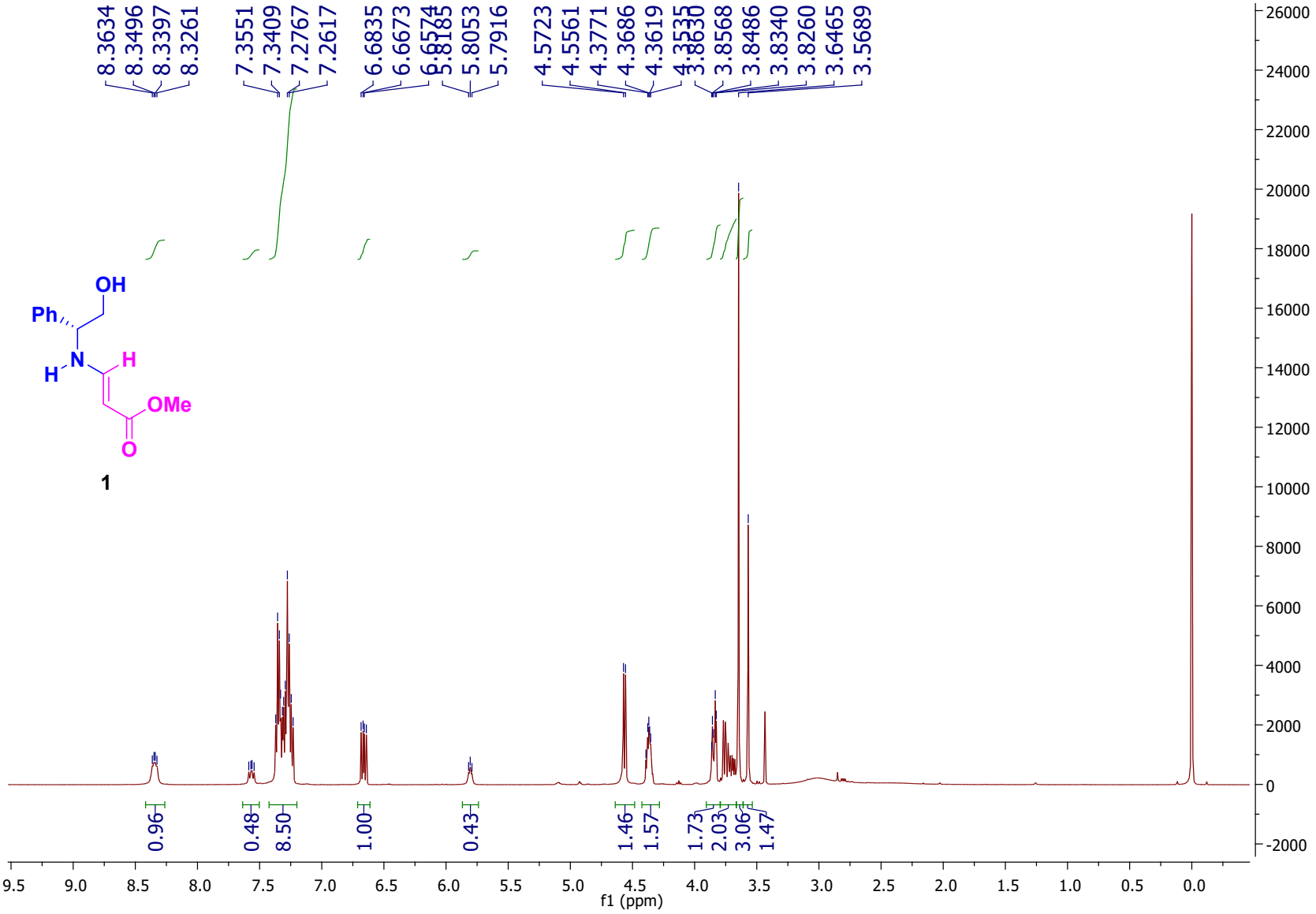
To a stirred solution of (2*R*,4*R*,6*S*)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)-6-methylpiperidine-2-carboxylic acid **37** in MeOH was added a solution HCl (3N). This reaction remained at 40 °C for 20 min. The excess of solvent was evaporated by reduced pressure. The product was purified by recrystallization with dichloromethane/methanol.

(*2R,4R,6S*)-4-hydroxy-6-methylpiperidine-2-carboxylic acid, 38.



Solid brown, 96% yield. $[\alpha]_D^{20}$ = -27.3° (*c* 1, CH_3OH) NMR-^{1}H (500 MHz, Methanol-d_4) δ 3.87(s, 1H), 3.78 (m, 1H), 3.64 (s, 1H), 2.84 (t, *J*=14.4 Hz, 1H), 2.11 (d, *J*= 13.4, 1H), 1.90 (m, 1H), 1.54 (m, 1H), 1.43 (d, *J*= 5.82 Hz, 3H), 1.28 (s, 1H), 0.88 (s, 1H). NMR-^{13}C (125 MHz, Methanol-d_4) δ 169.0, 62.6, 53.1, 49.2, 38.2, 32.5, 17.6). HRMS(ESI): Calcd for $C_7H_{14}ClNO_3$: 195.0662 found: 195.0665.

^{1}H and ^{13}C NMR Spectra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5.8185
5.8053
5.7916
4.5723
4.5561
4.3771
4.3686
4.3619
4.3535
3.8630
3.8568
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3.8340
3.8260
3.6465
3.5689
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Ph
N
H
H
OMe
O
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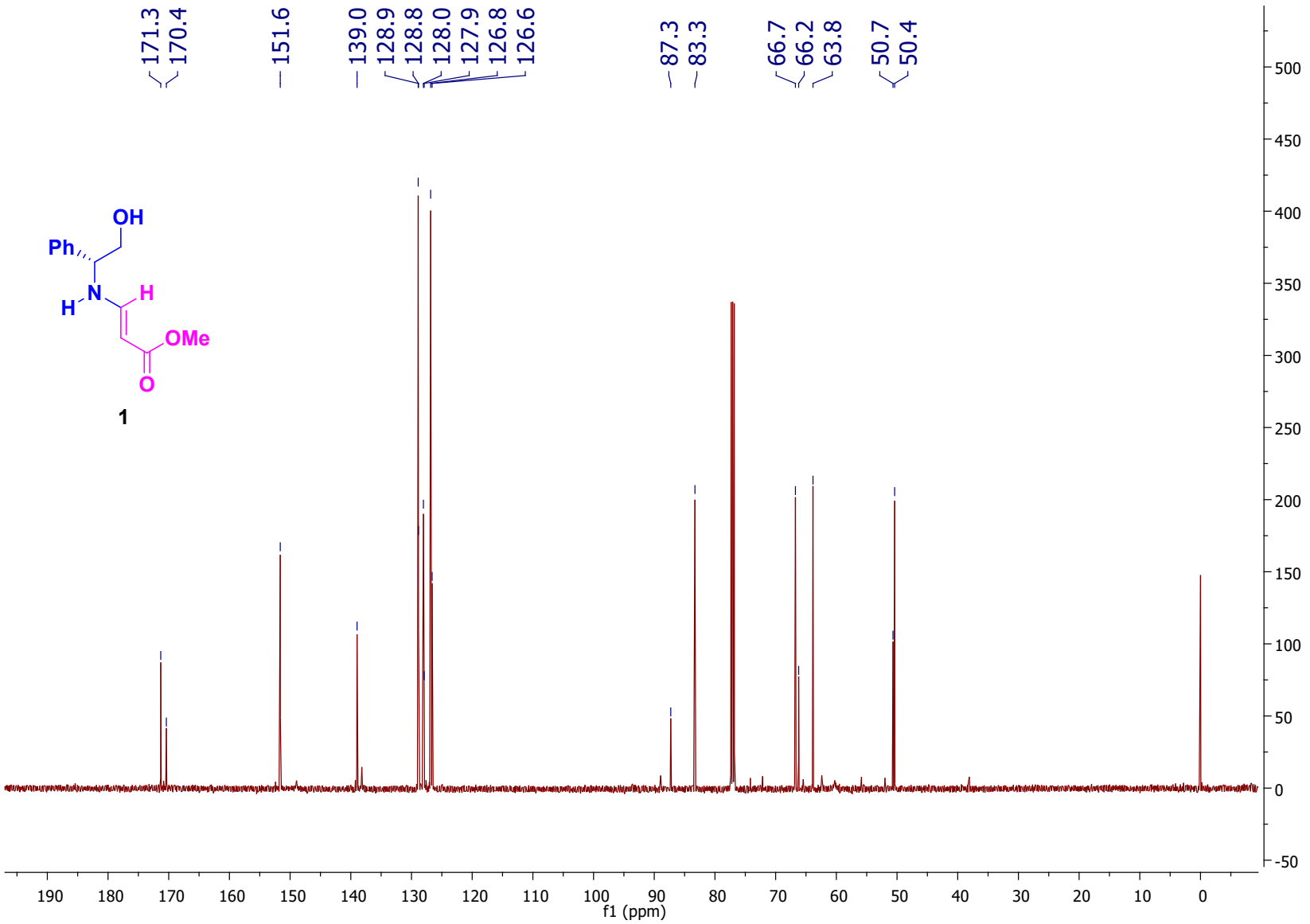
f1 (ppm)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63.8
50.7
50.4
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Ph
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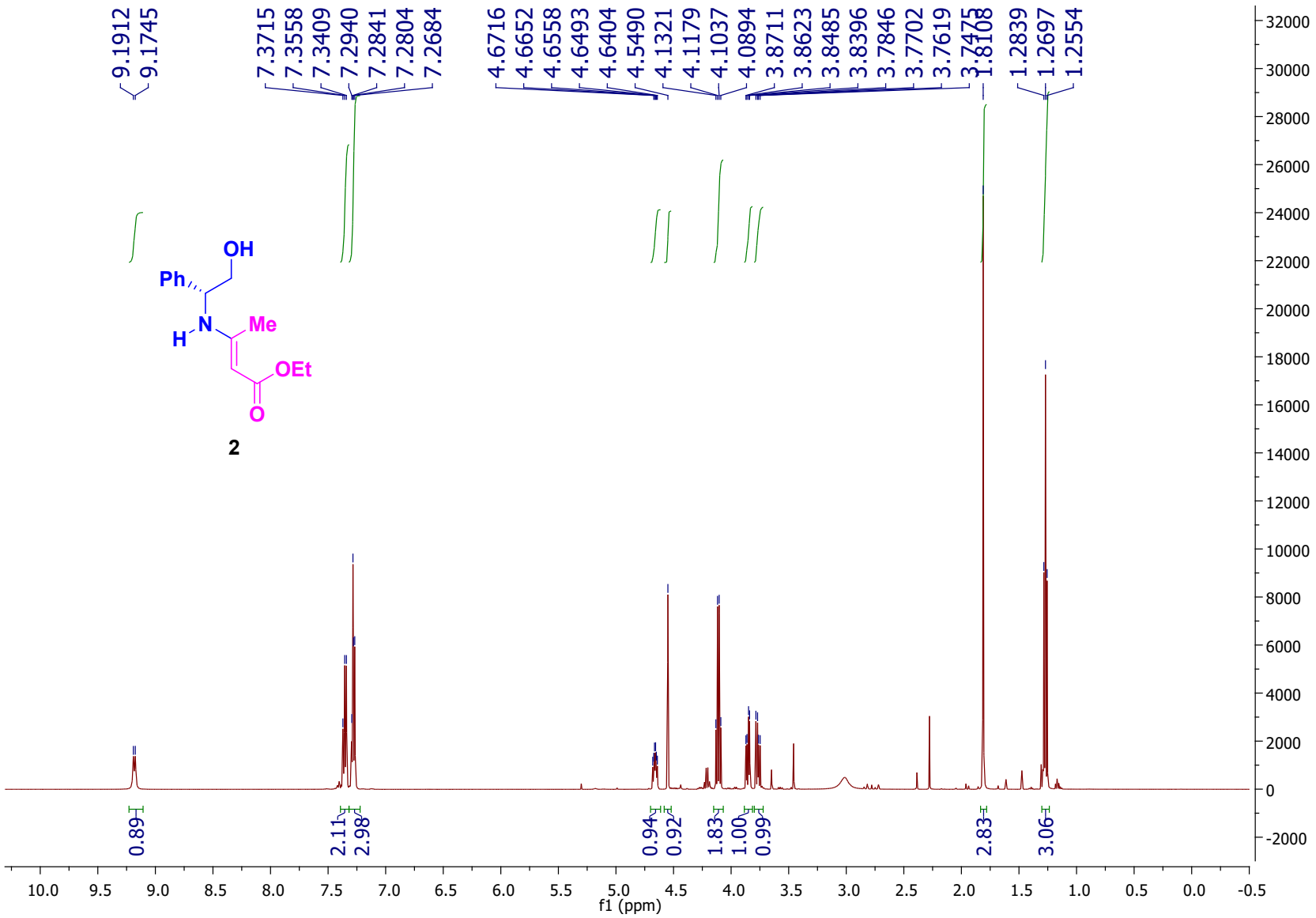
H
H
OMe
O
1
f1 (ppm)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H
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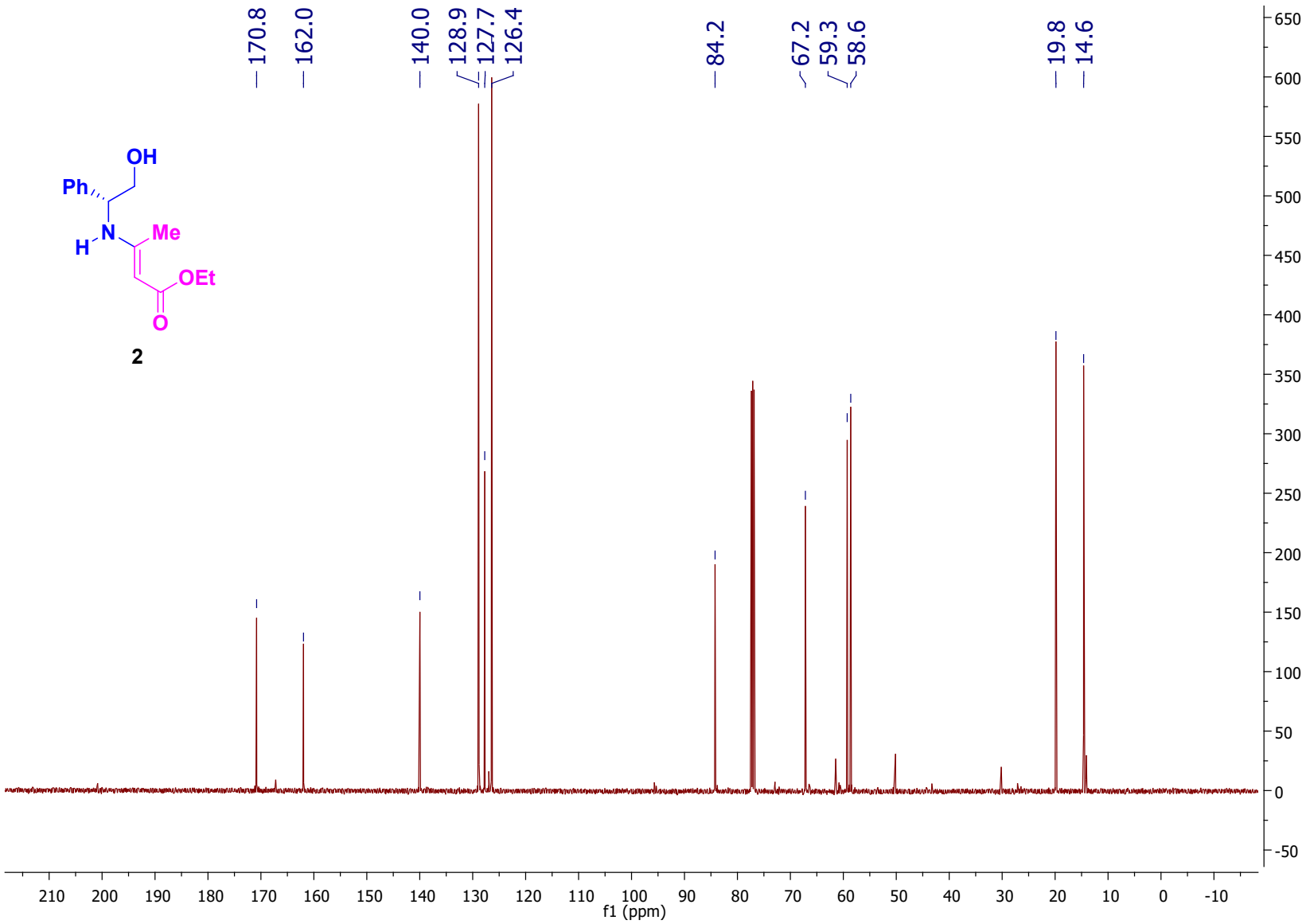
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Ph
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H
Me
OEt
O
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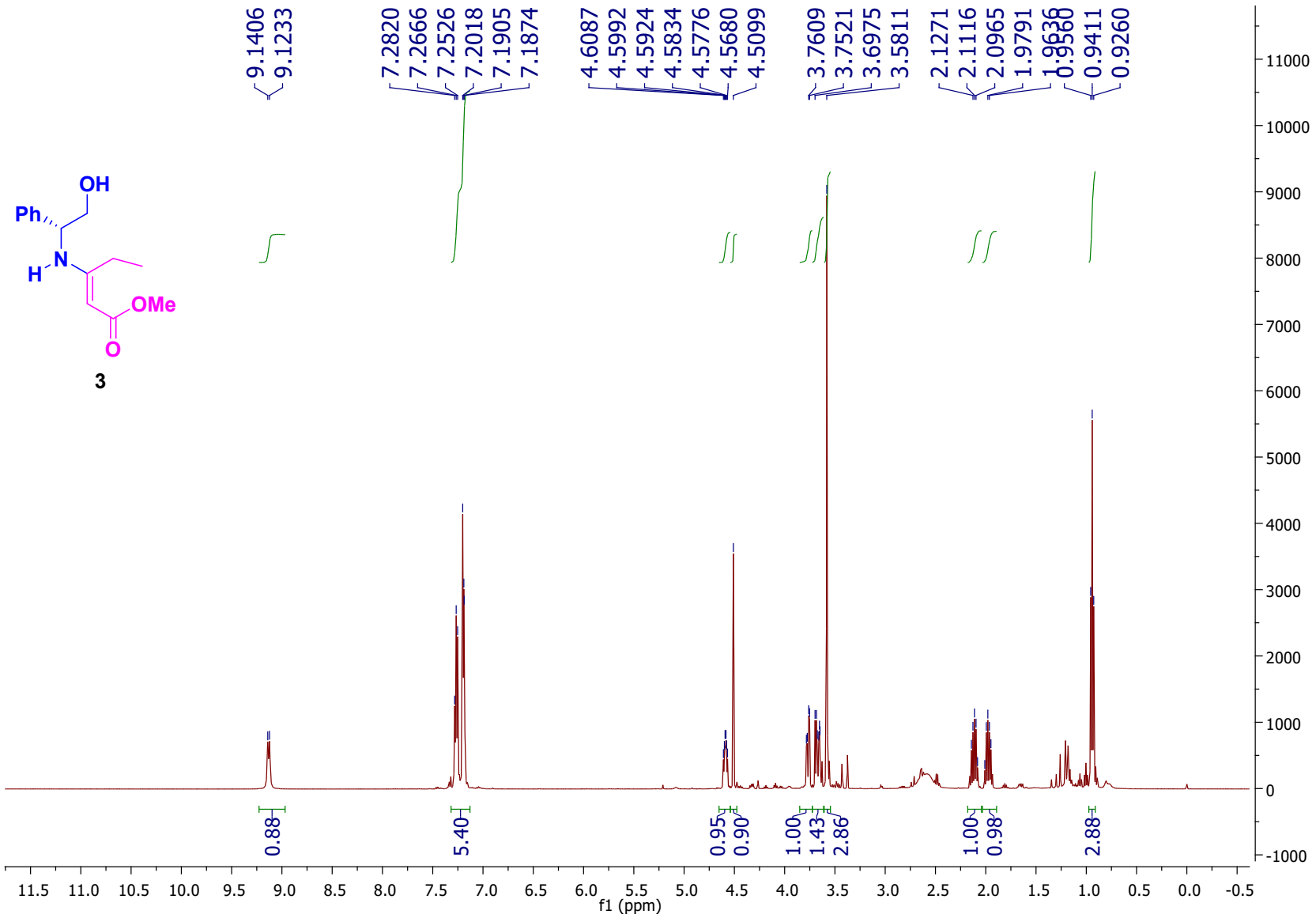
f1 (ppm)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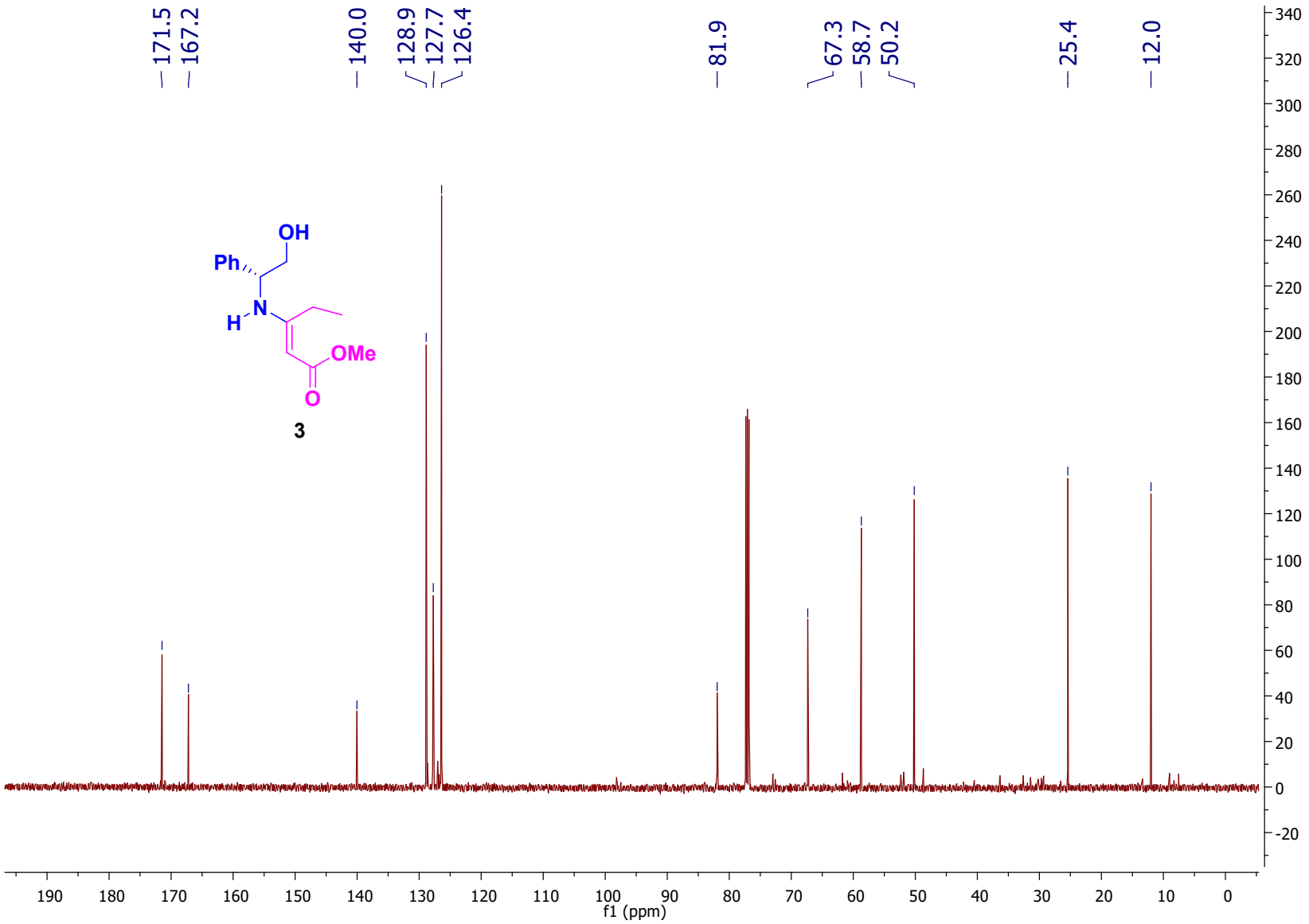
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Ph
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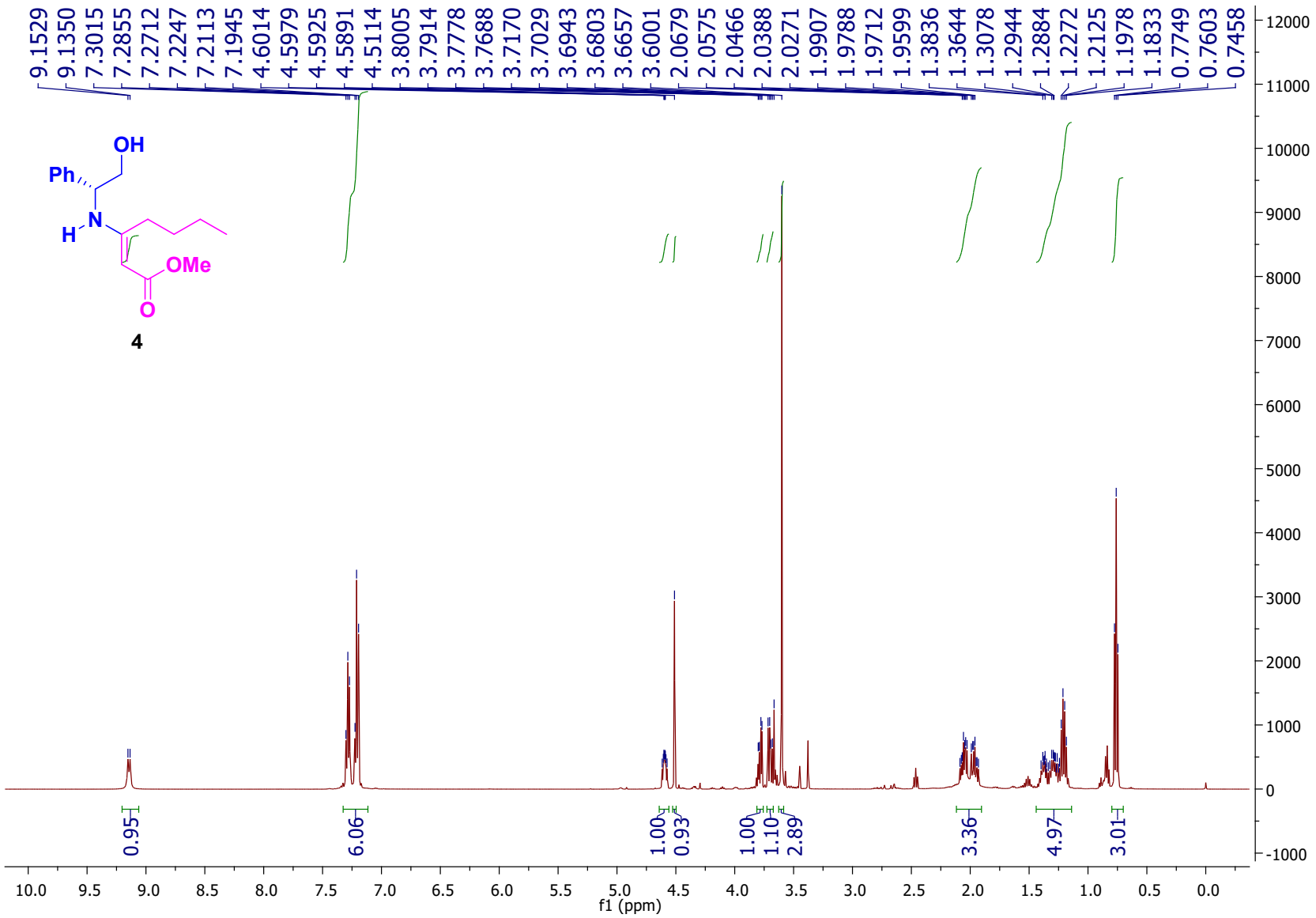
H
OMe
O
3
f1 (ppm)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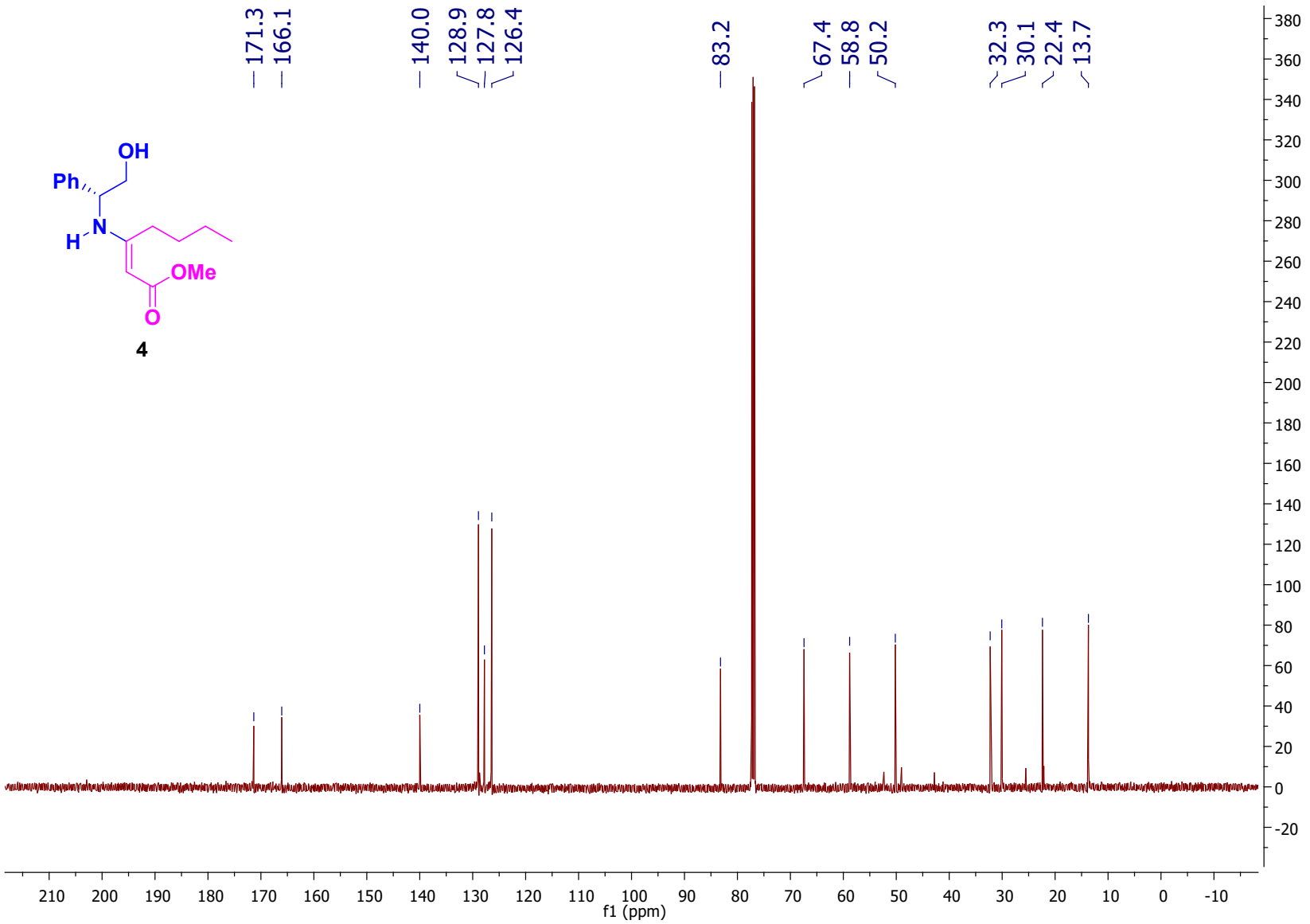
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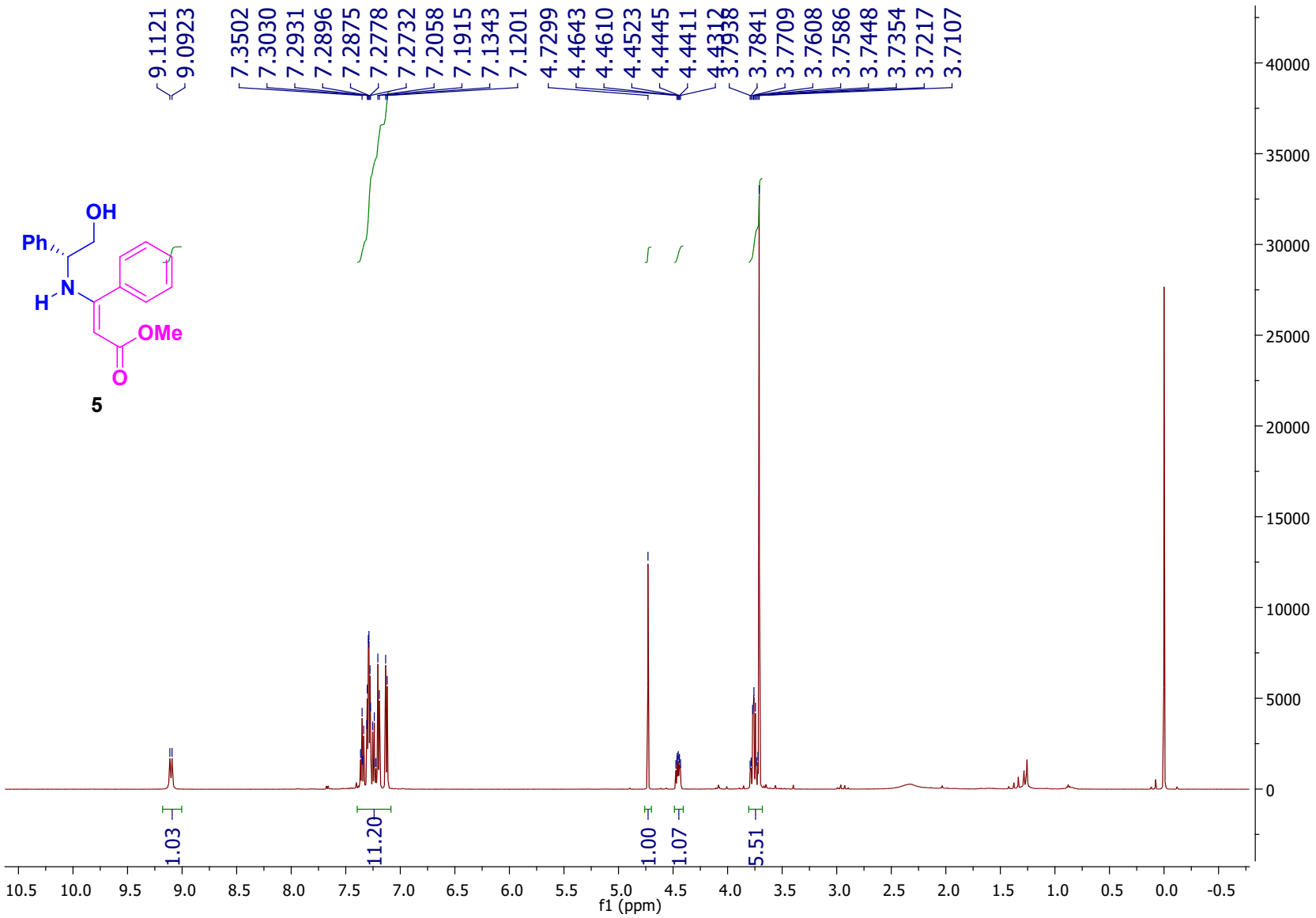
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4.4411
4.4312
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3.7841
3.7709
3.7608
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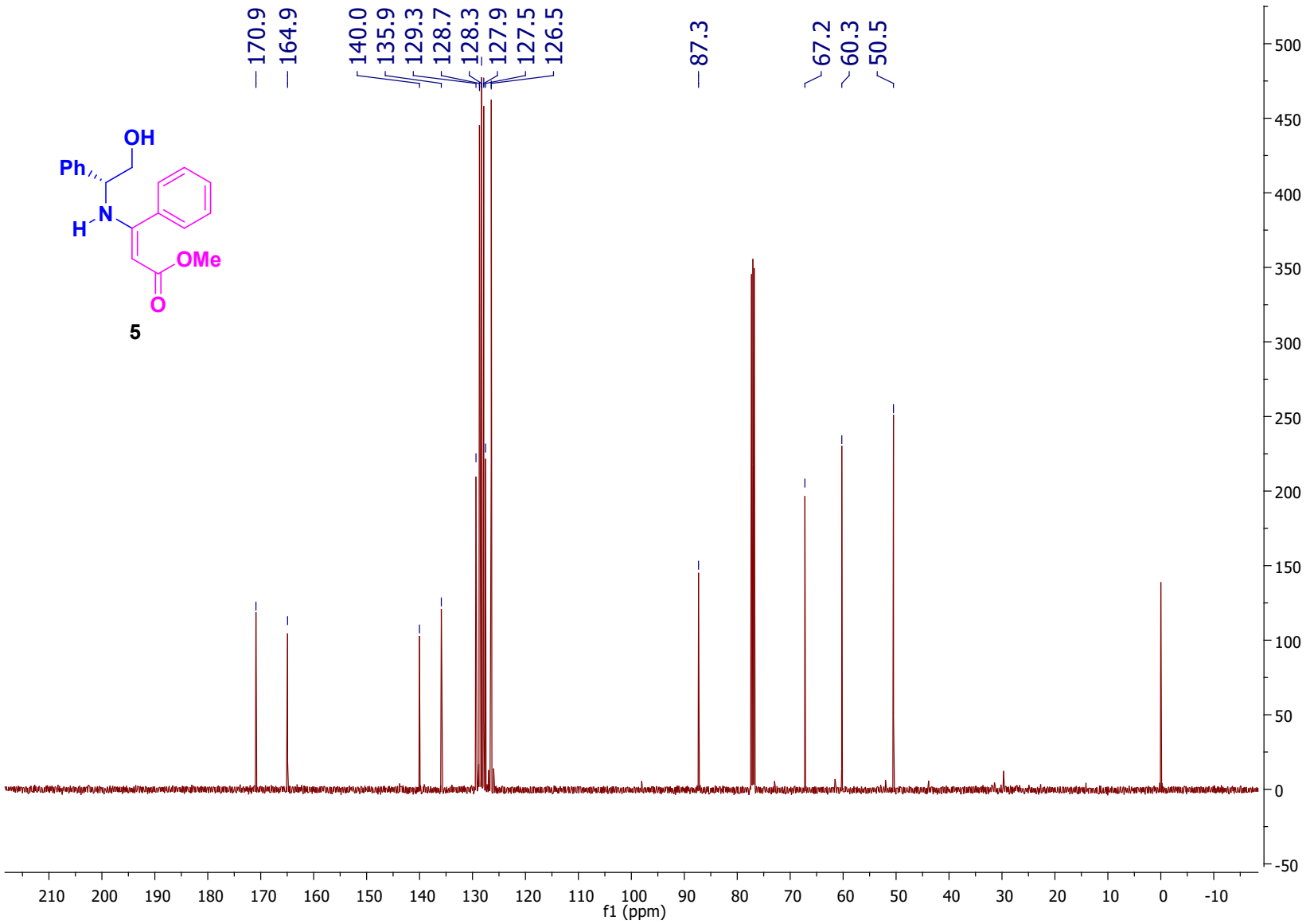
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Ph
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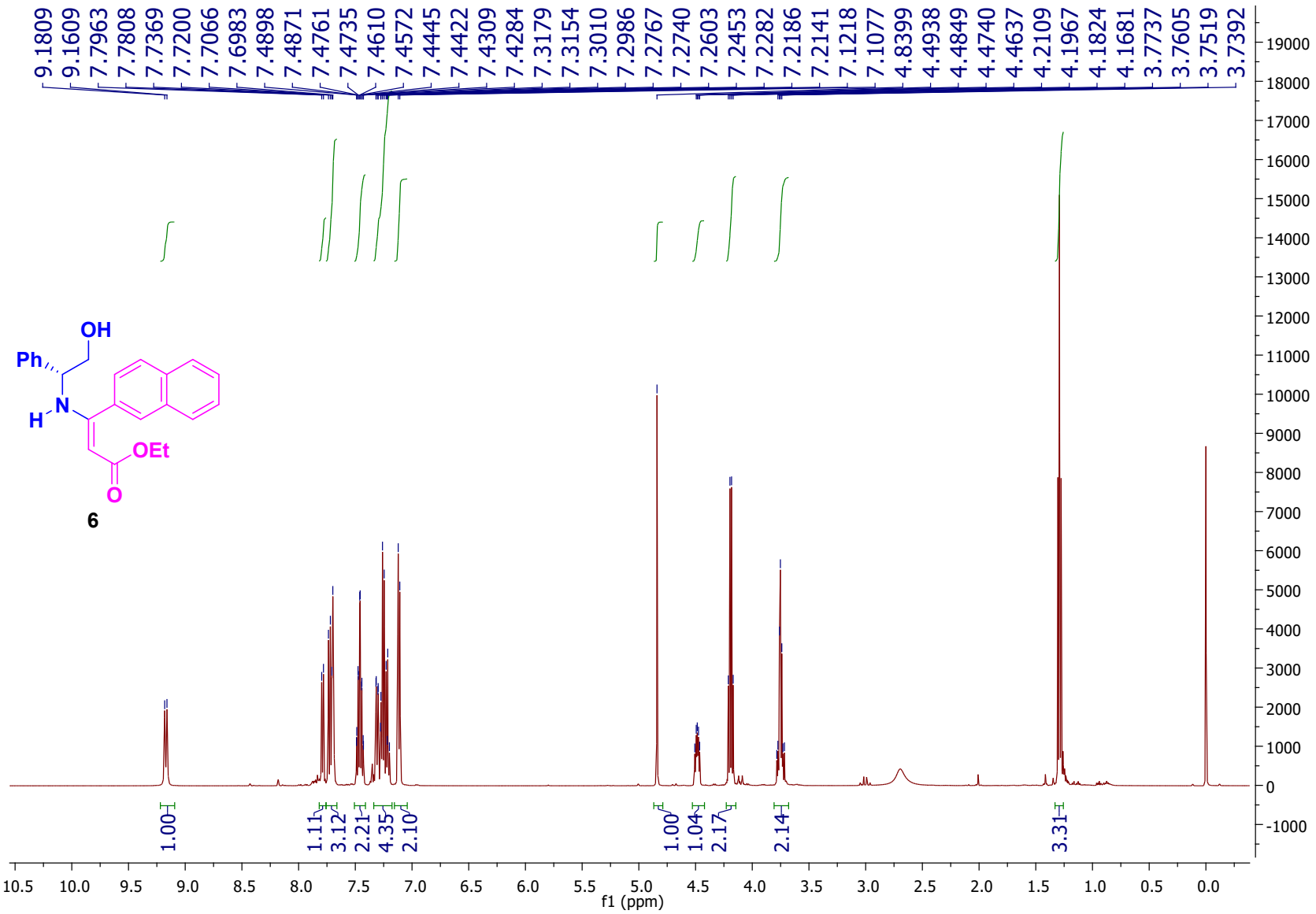
f1 (ppm)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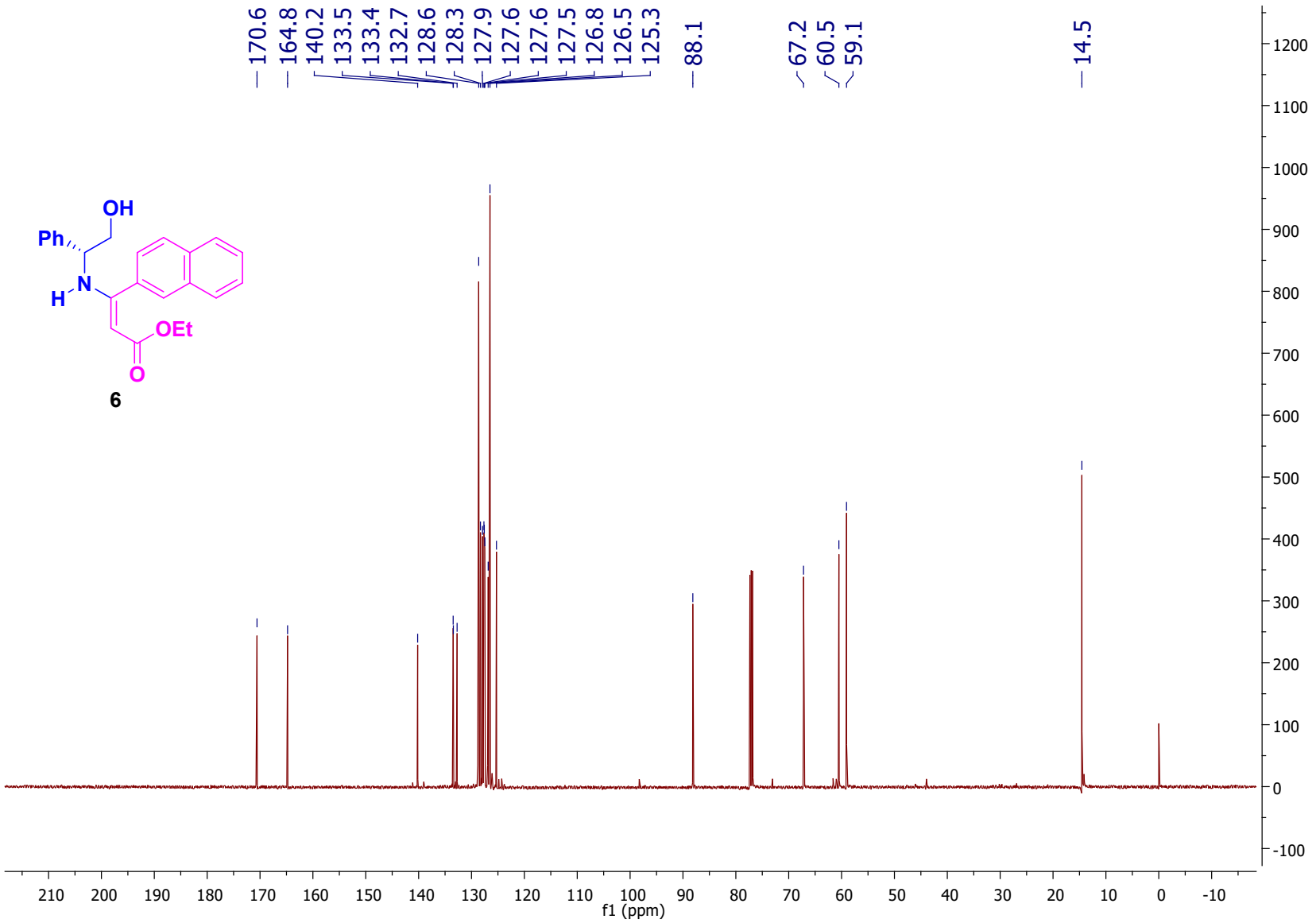
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Ph
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H
OEt
O
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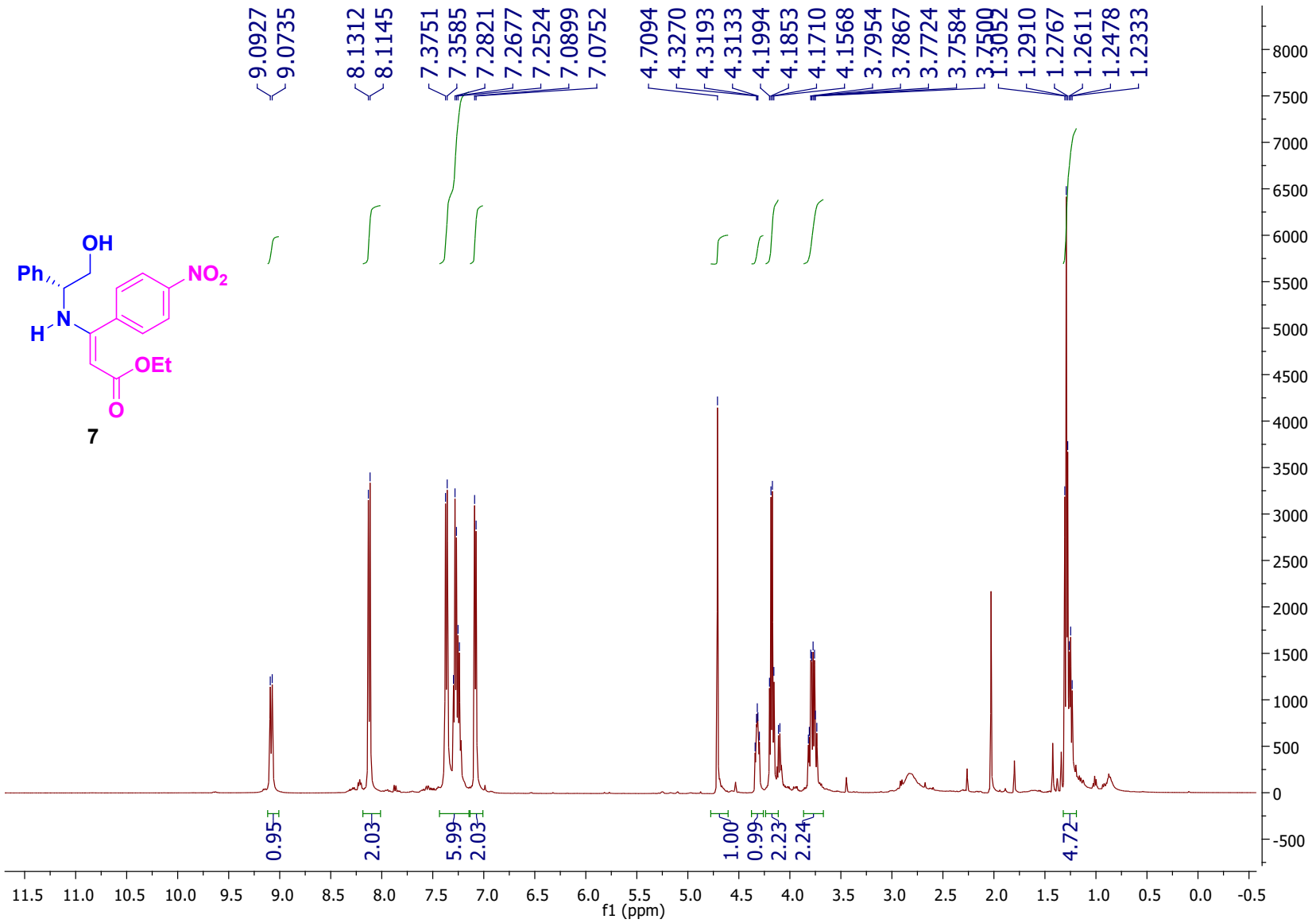
f1 (ppm)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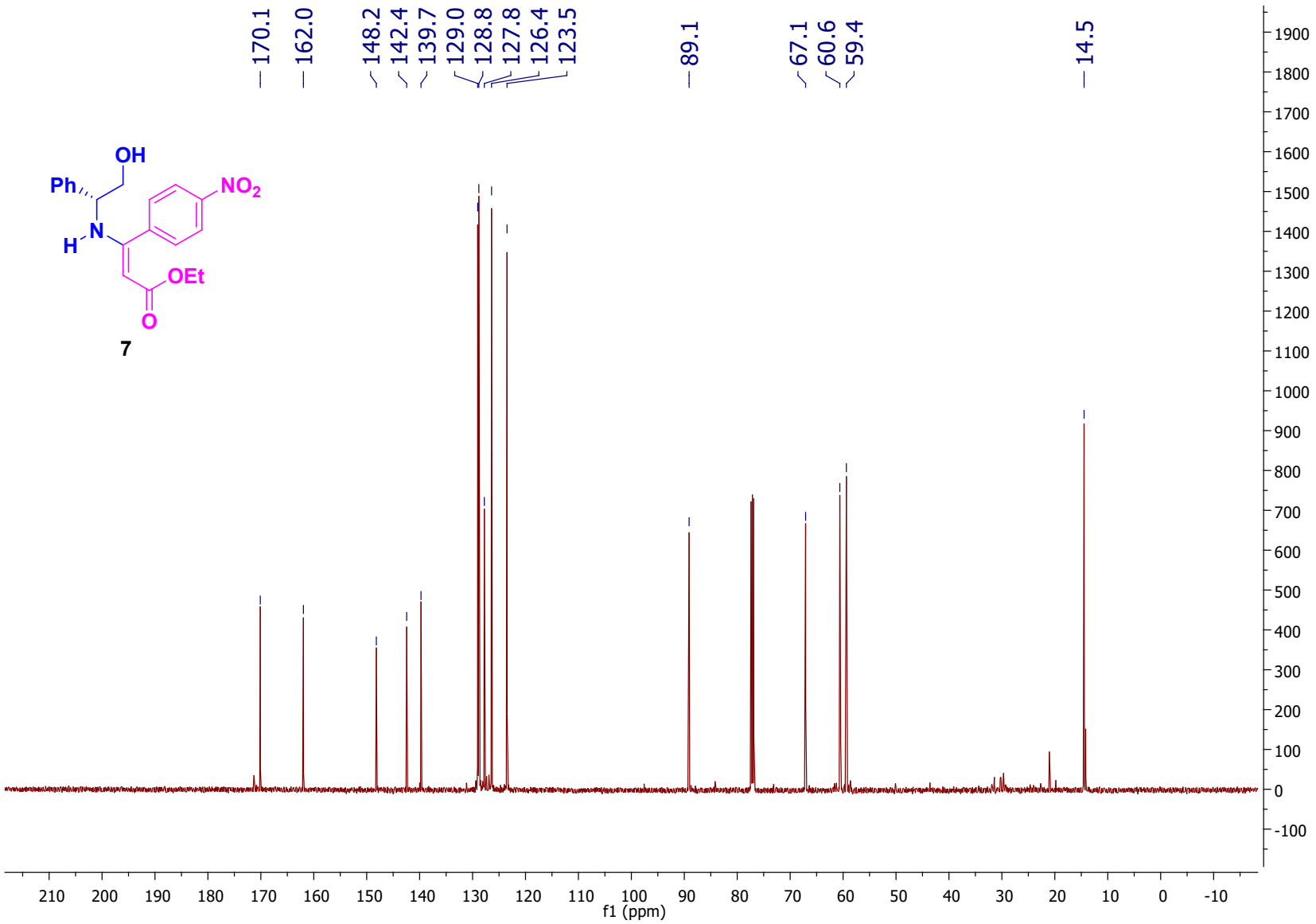
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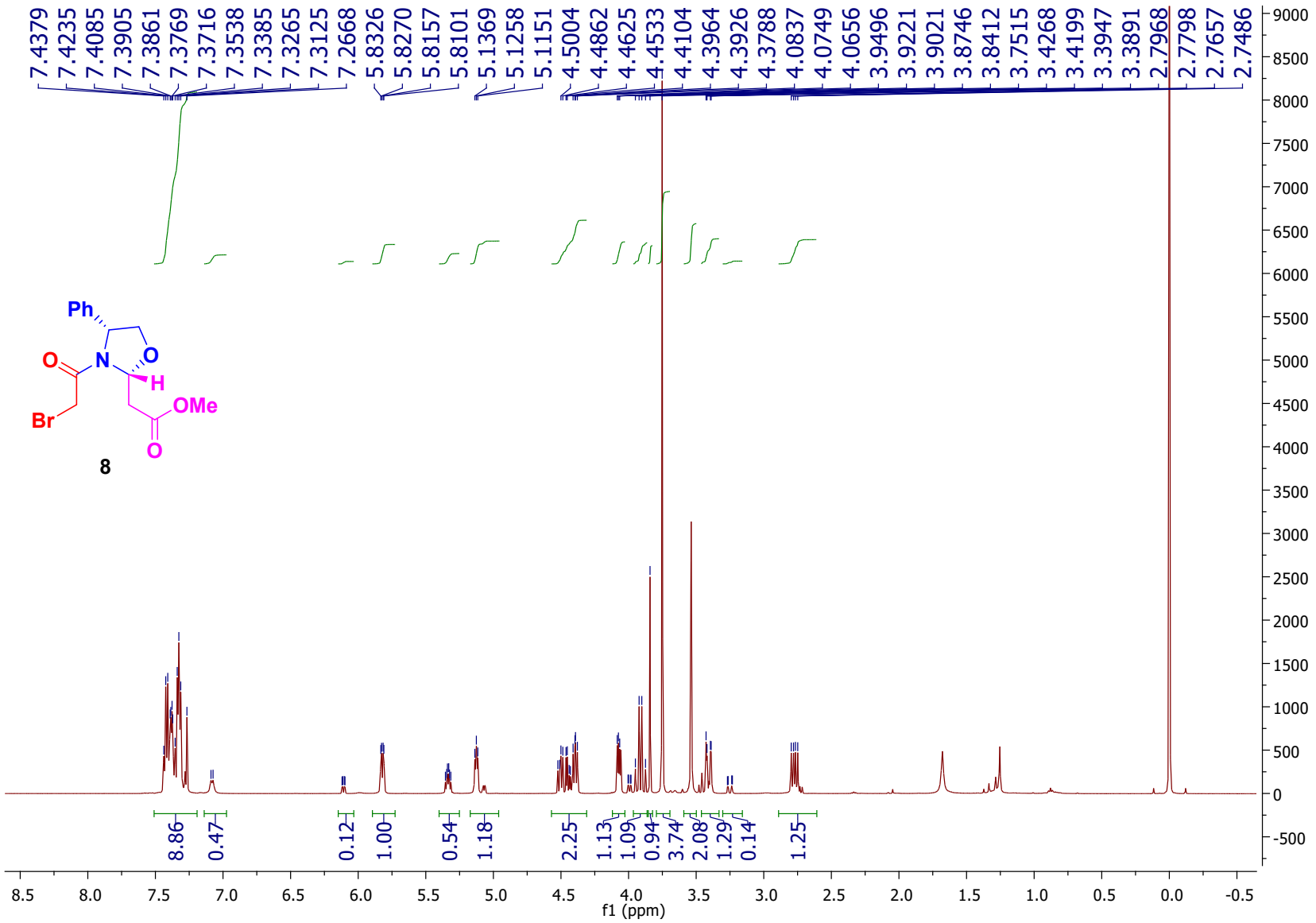
f1 (ppm)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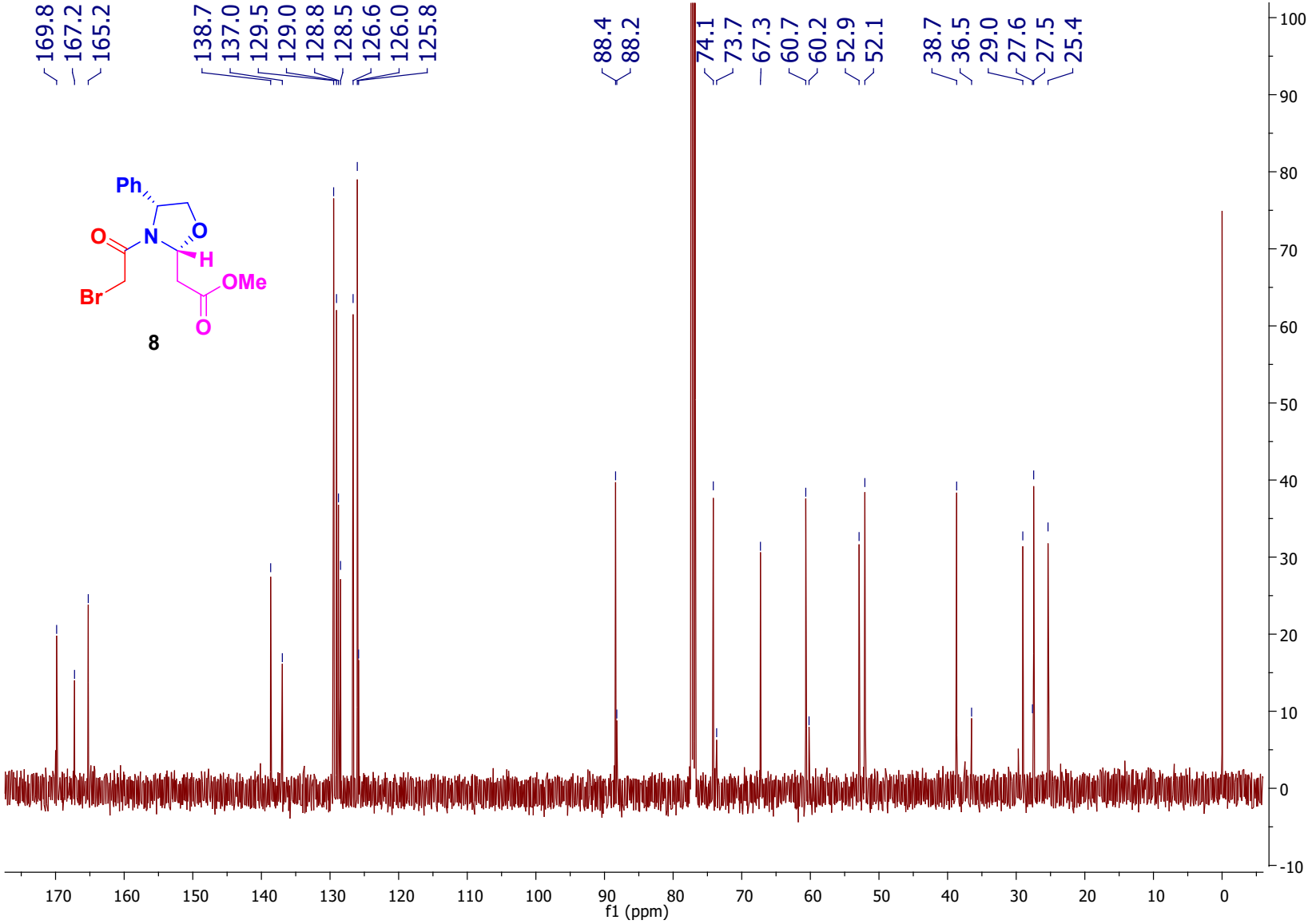
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38.7
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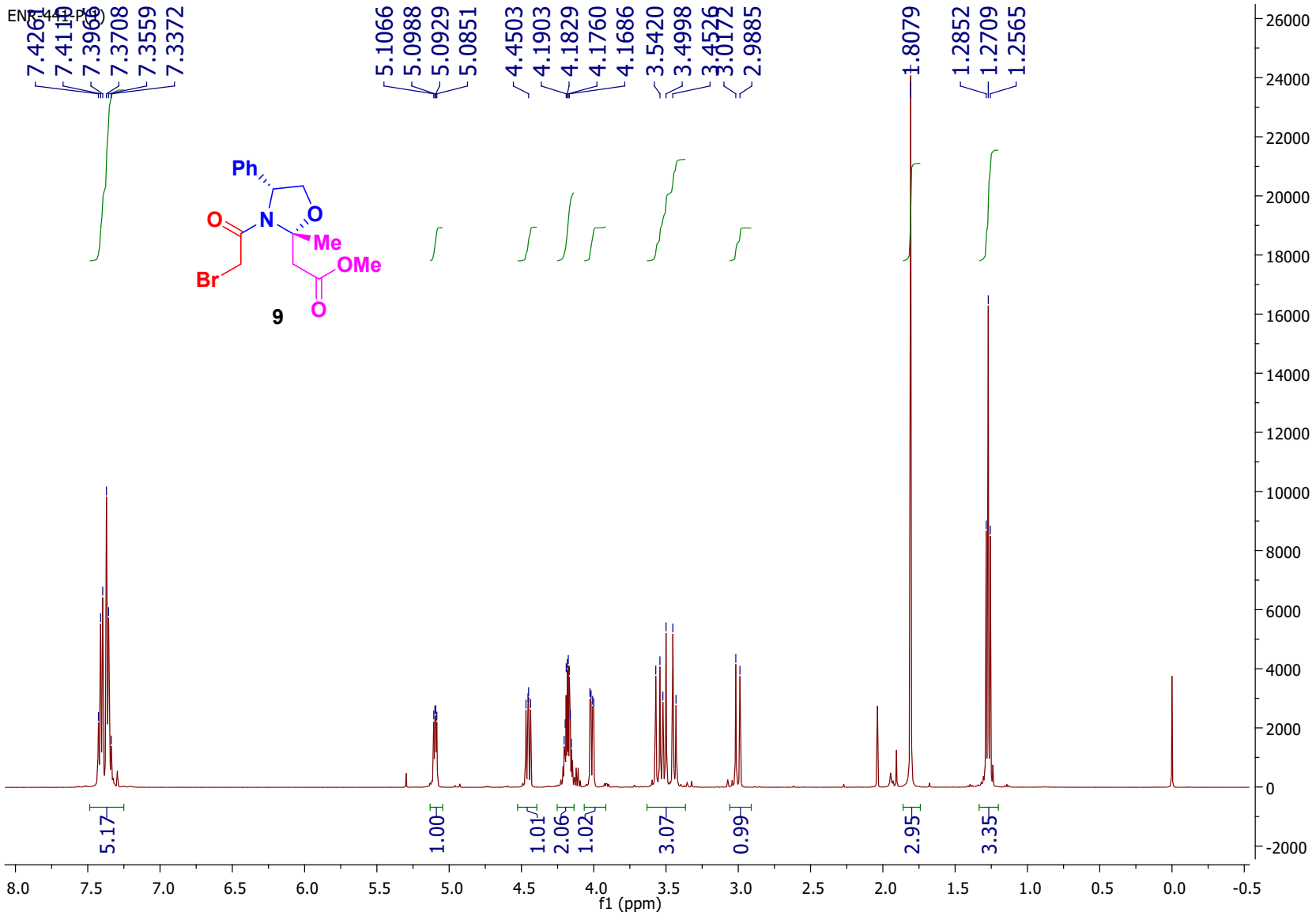
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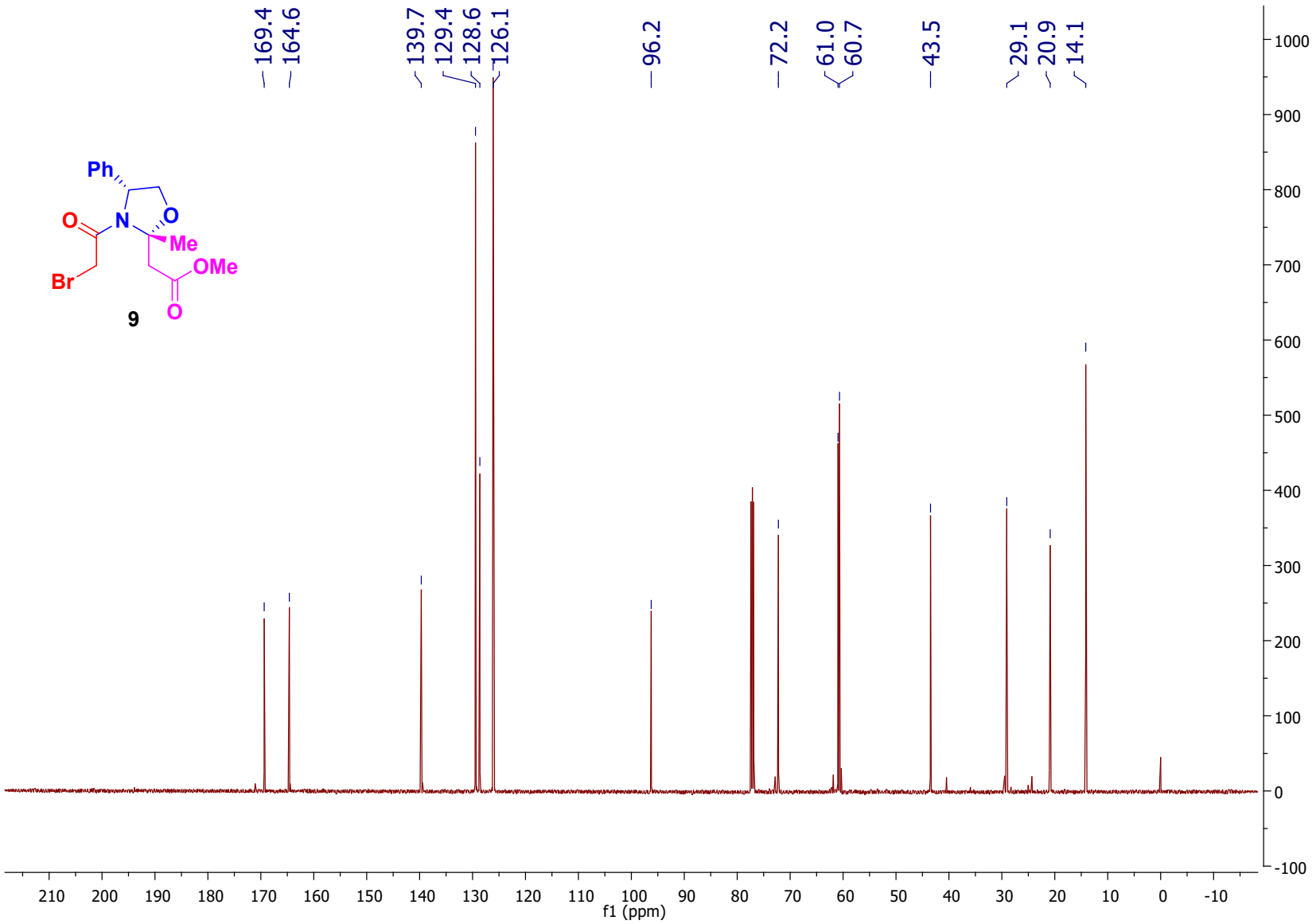
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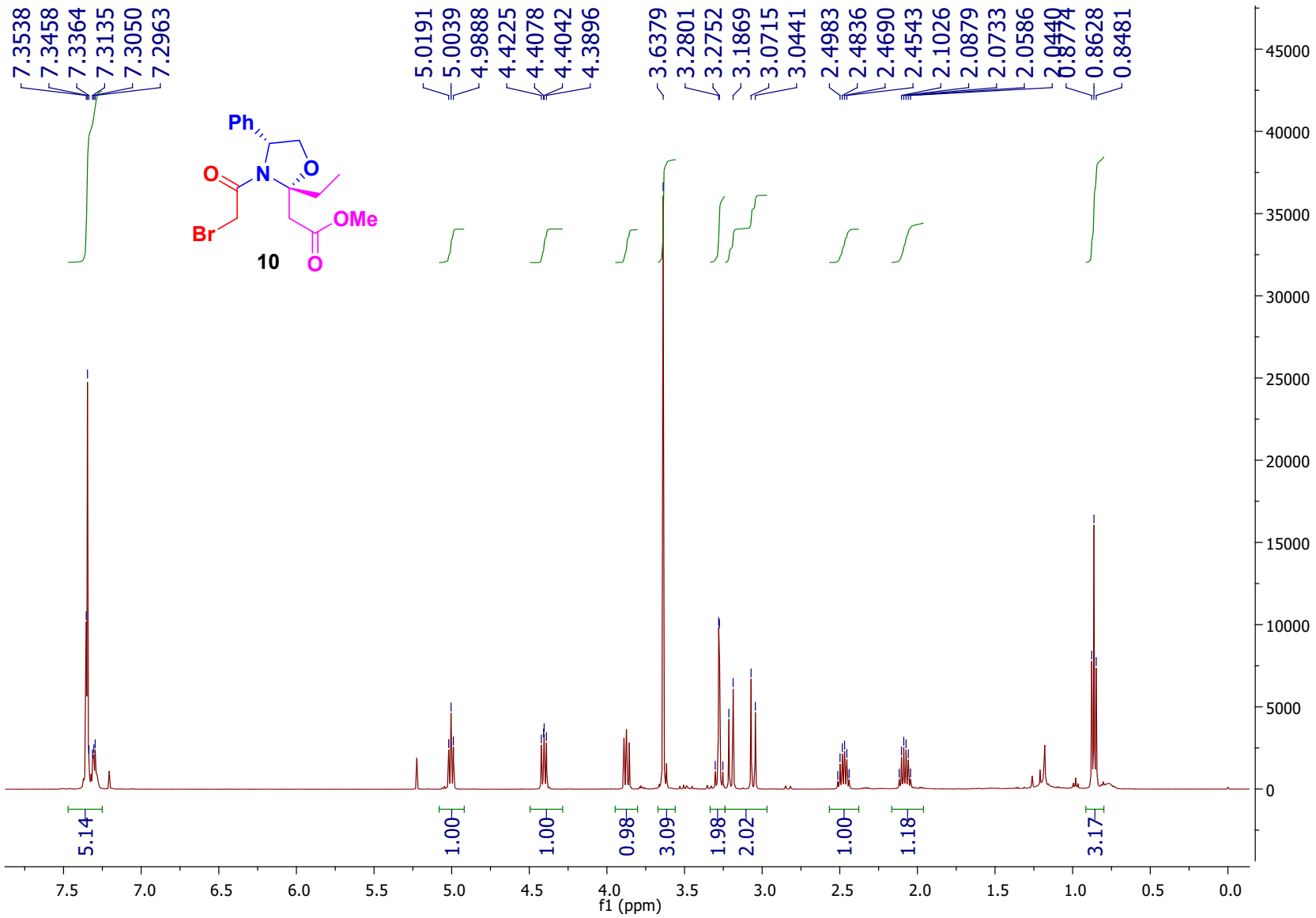
f1 (ppm)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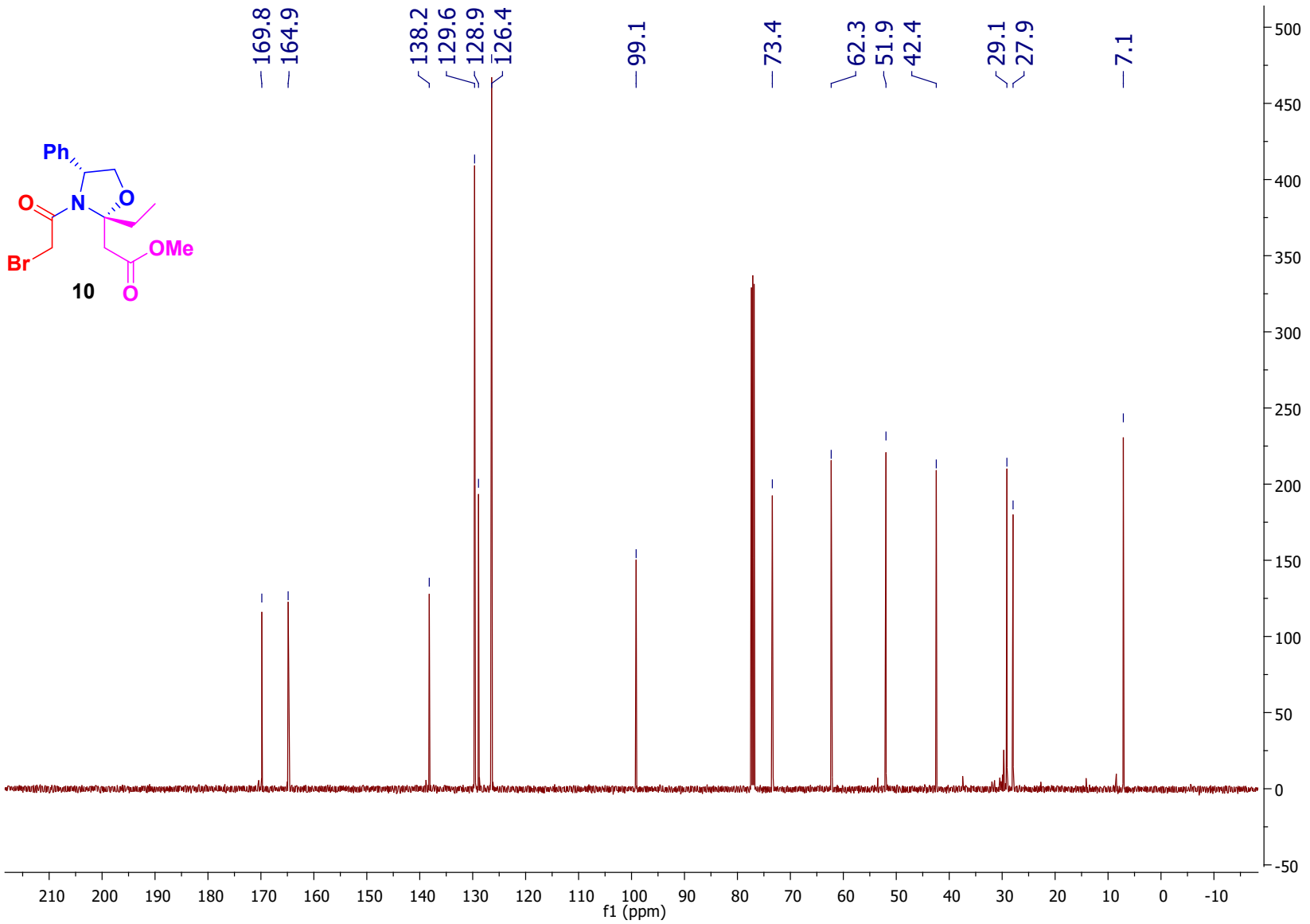
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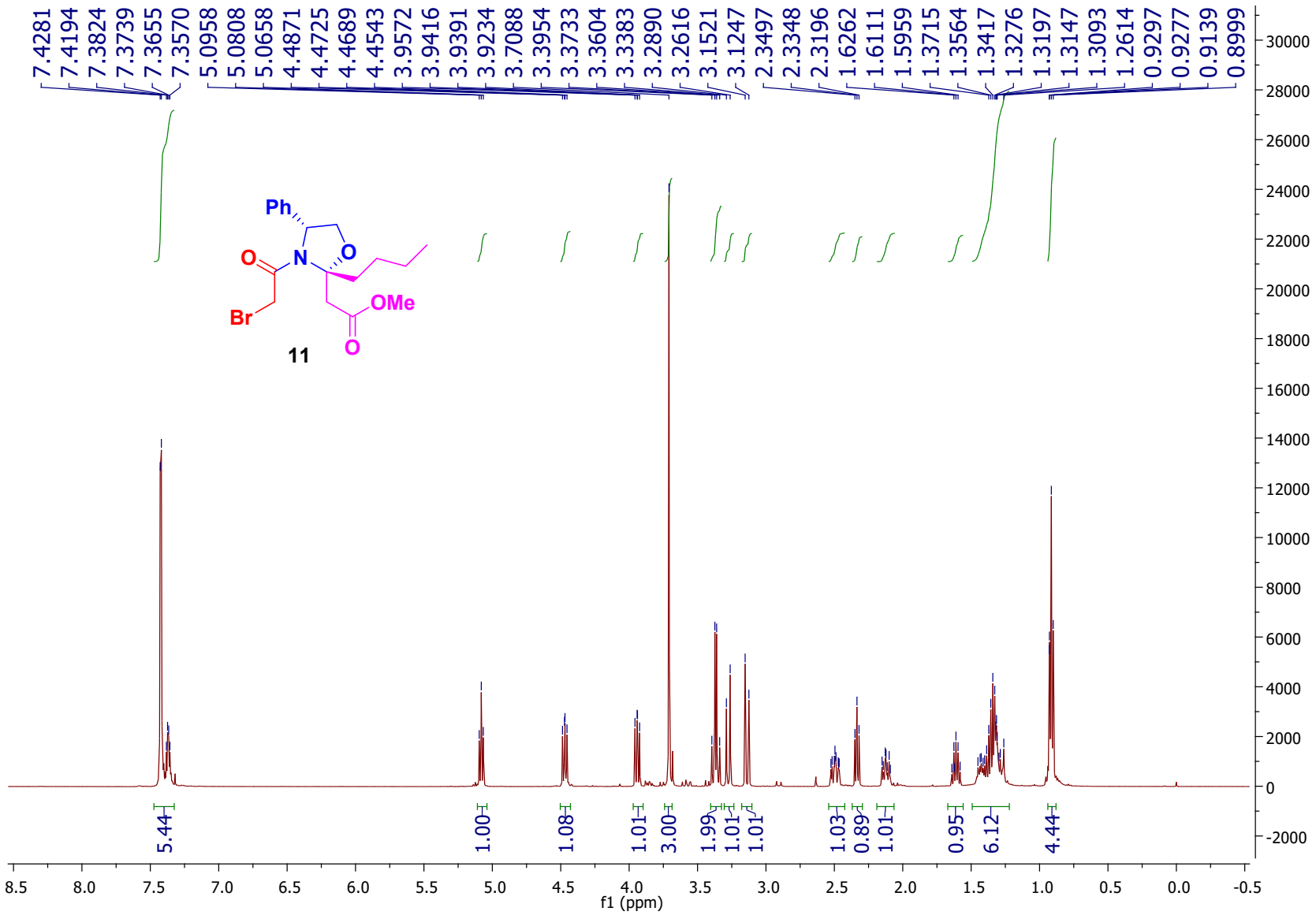
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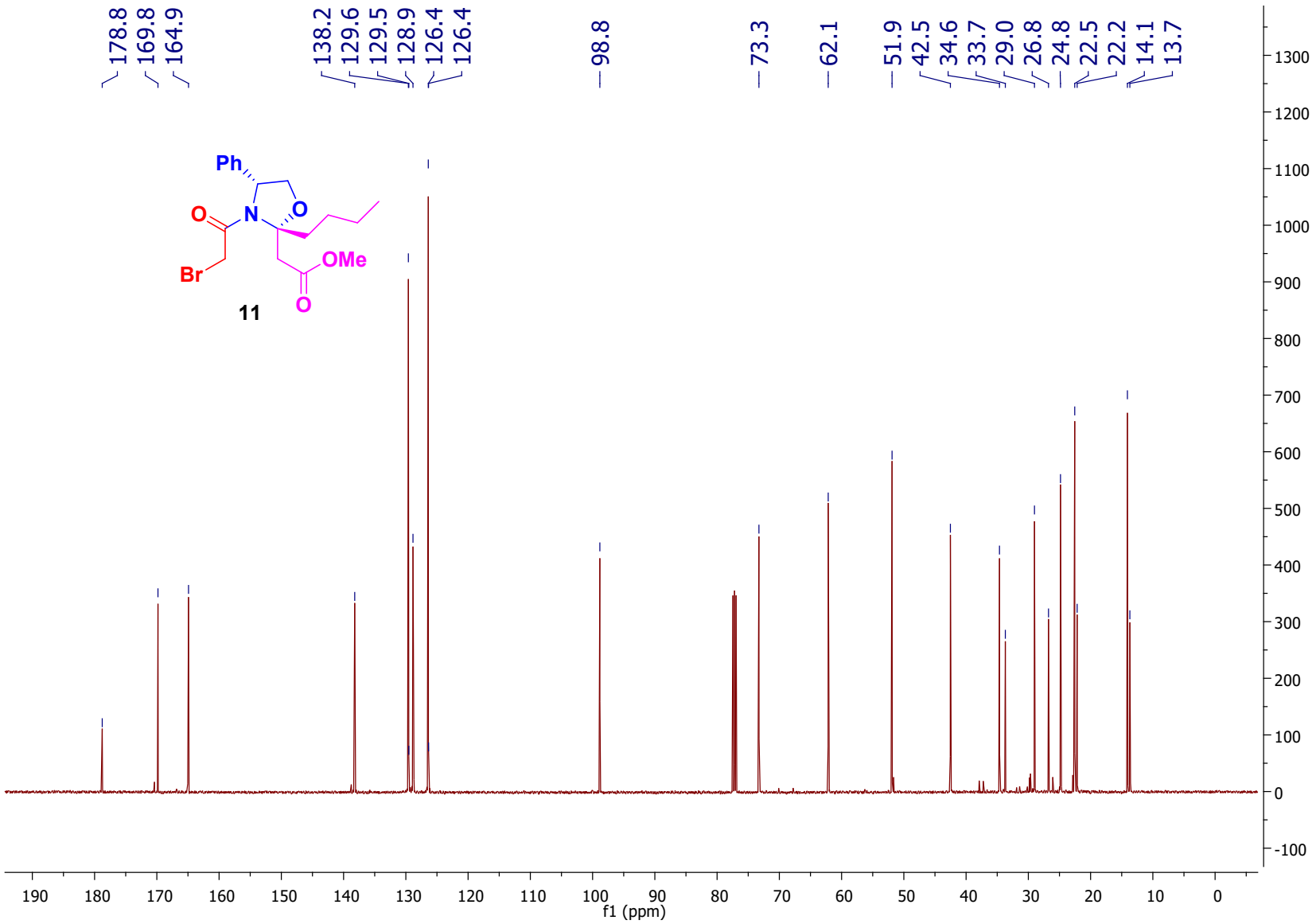
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34.6
33.7
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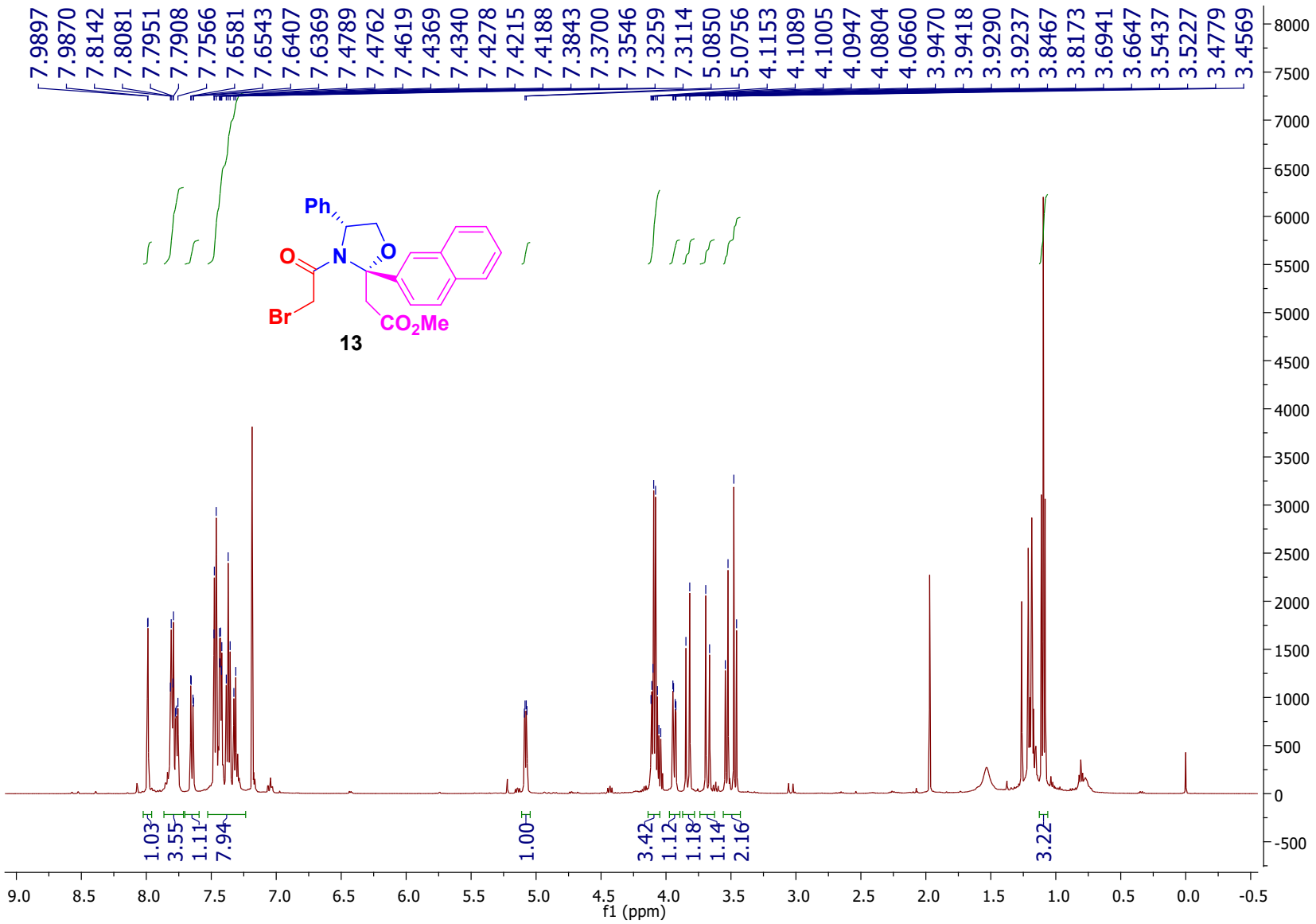
24.8
22.5
22.2
14.1
13.7
Ph
O
N
O
Br
OMe
O
11
f1 (ppm)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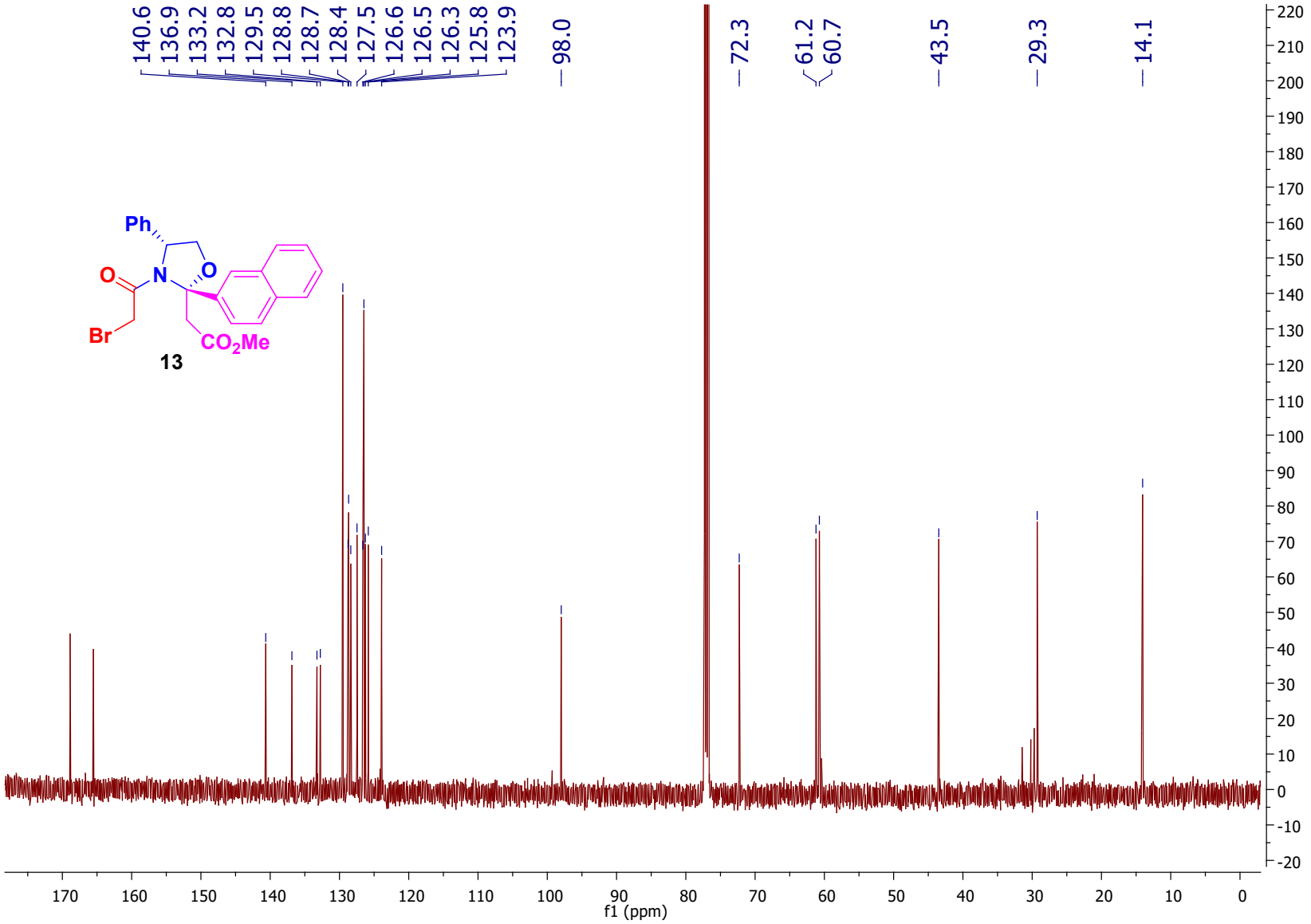
7.8142
7.8081
7.7951
7.7908
7.7566
7.6581
7.6543
7.6407
7.6369
7.4789
7.4762
7.4619
7.4369
7.4340
7.4278
7.4215
7.4188
7.3843
7.3700
7.3546
7.3259
7.3114
5.0850
5.0756
4.1153
4.1089
4.1005
4.0947
4.0804
4.0660
3.9470
3.9418
3.9290
3.9237
3.8467
3.8173
3.6941
3.6647
3.5437
3.5227
3.4779
3.4569
Ph
O
N
O
Br
CO2Me
13
1.03
3.55
1.11
7.94
1.00
3.42
1.12
1.18
1.14
2.16
3.22
f1 (ppm)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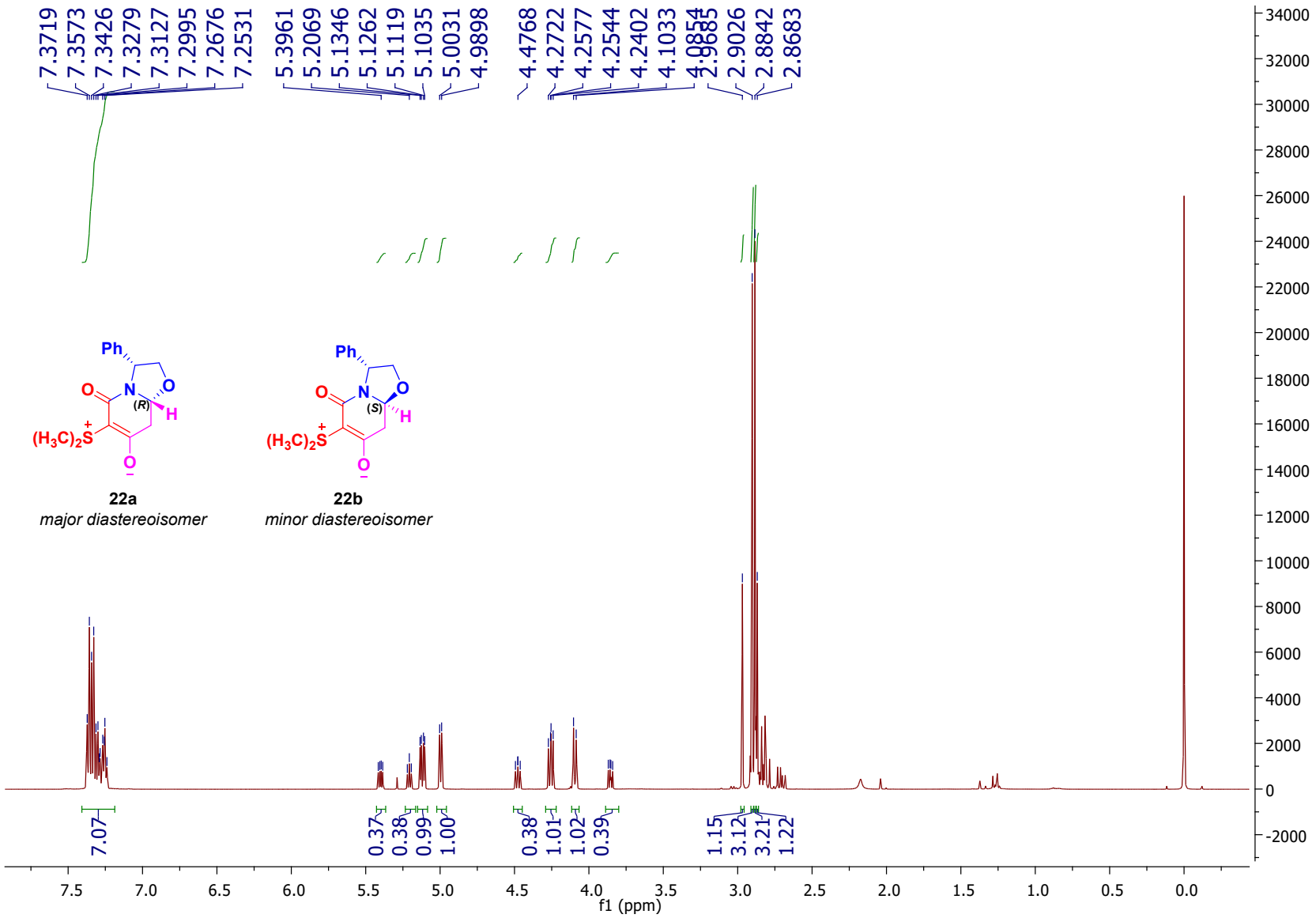
136.9
133.2
132.8
129.5
128.8
128.7
128.4
127.5
126.6
126.5
126.3
125.8
123.9
98.0
72.3
61.2
60.7
43.5
29.3
14.1
Ph
O
N
O
Br
CO2Me
13
f1 (ppm)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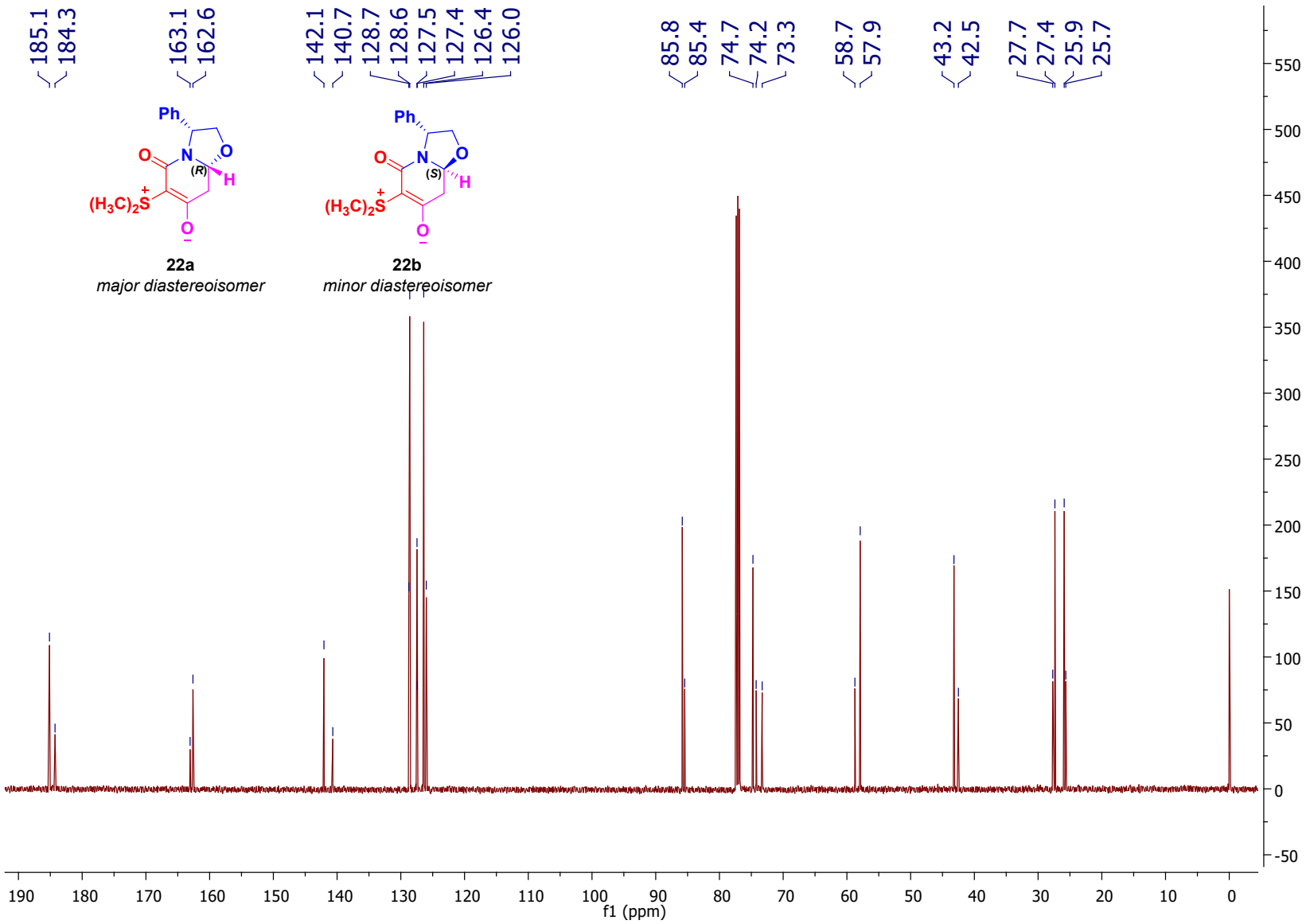
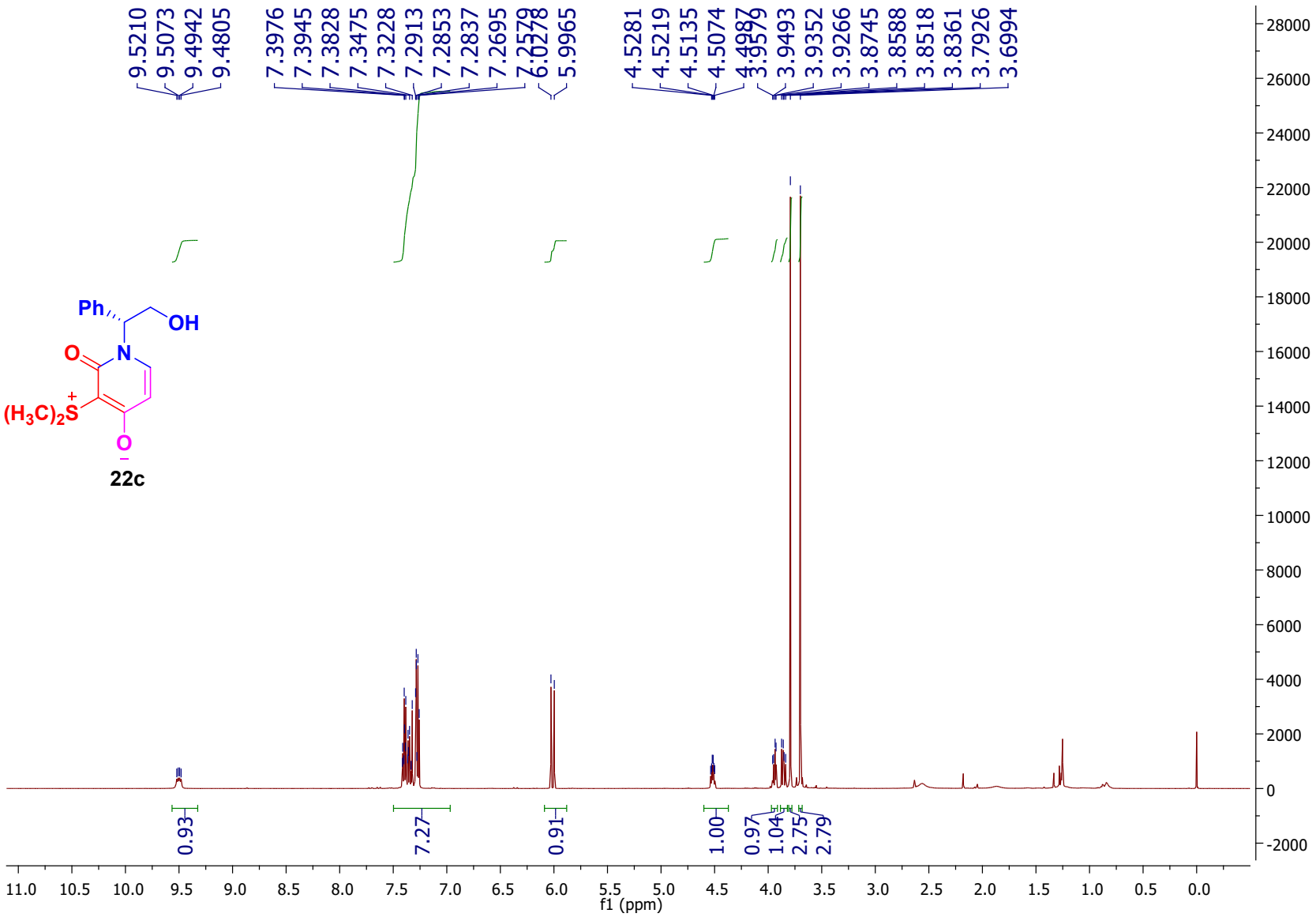
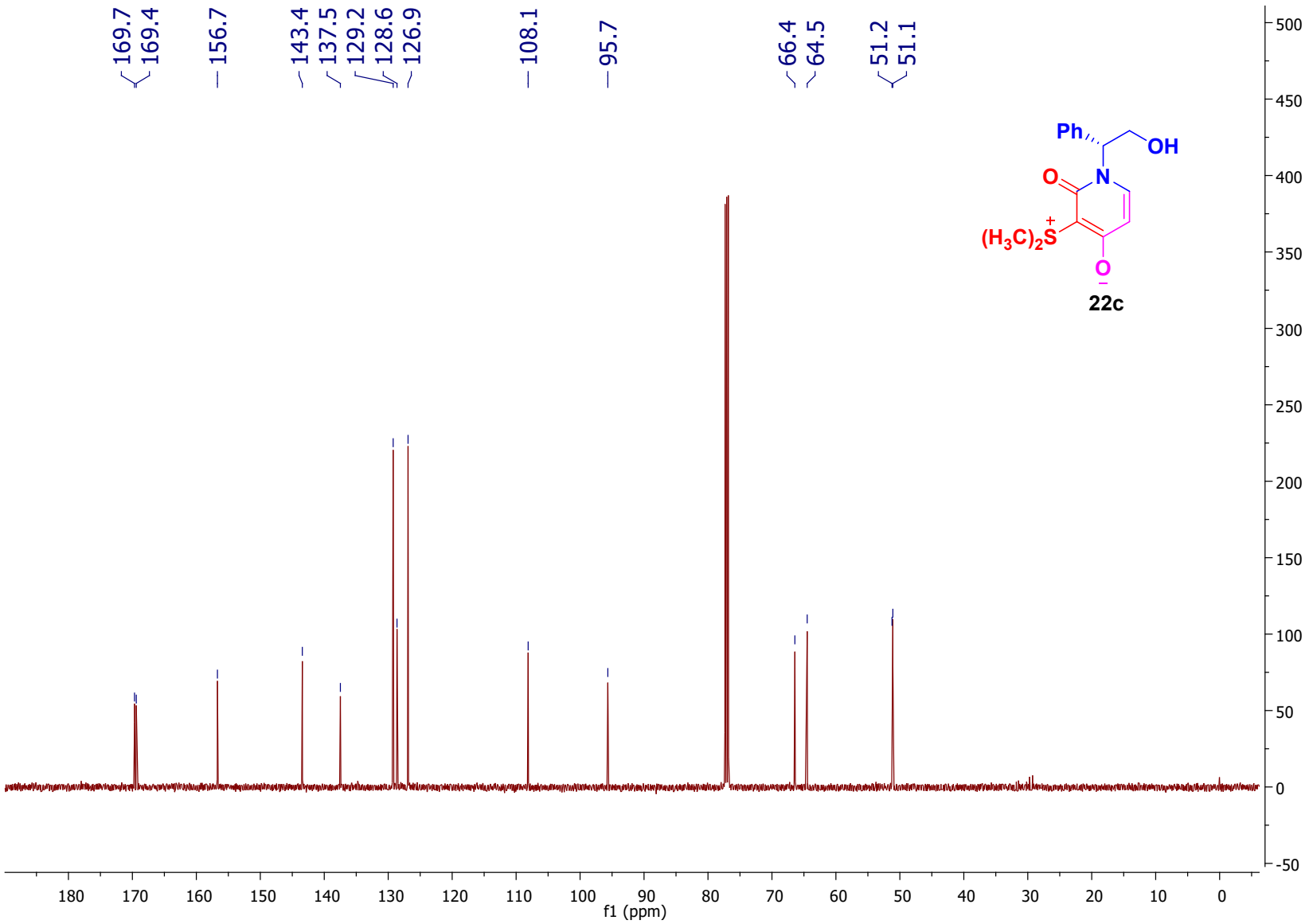
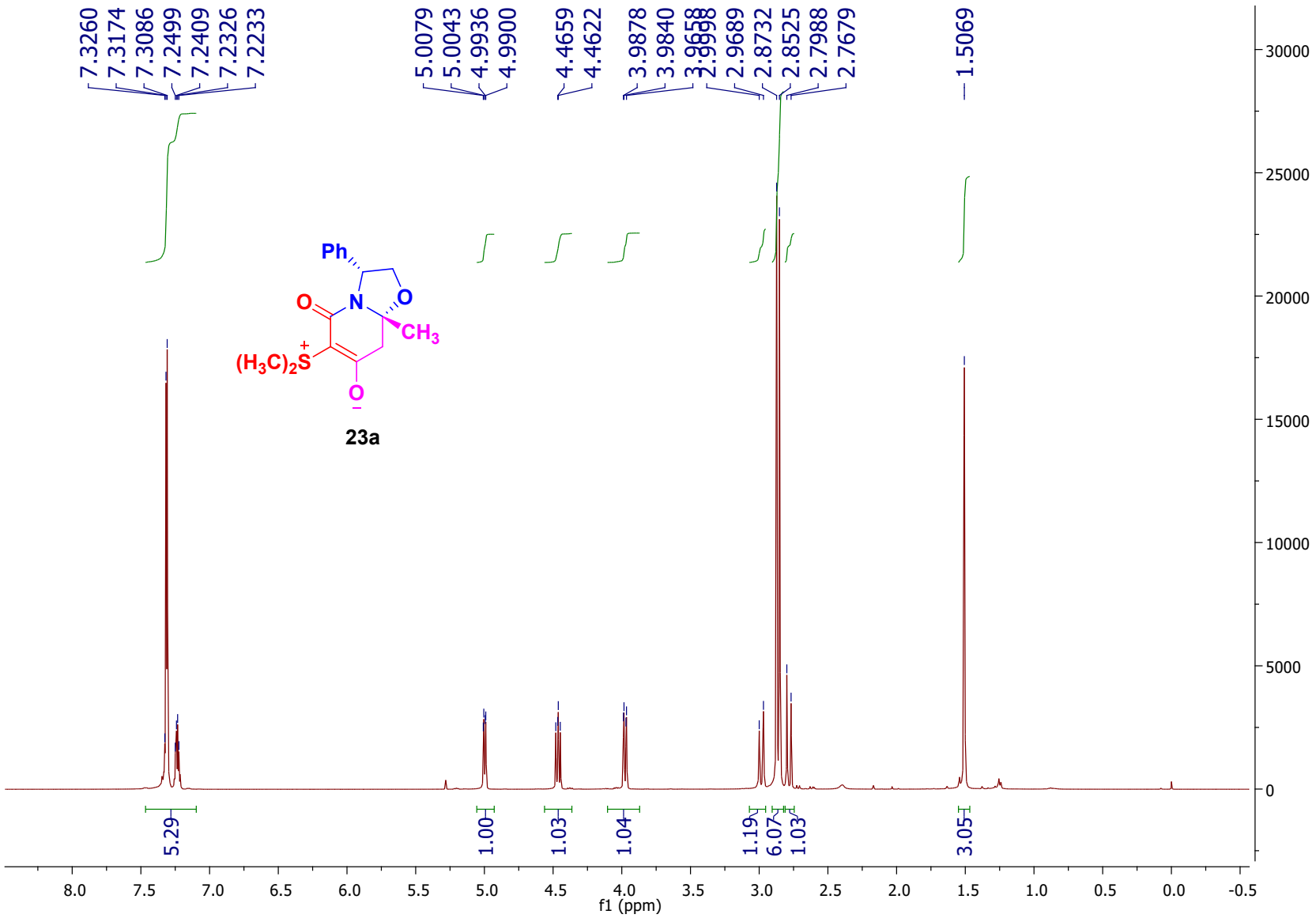
7.3573
7.3426
7.3279
7.3127
7.2995
7.2676
7.2531
5.3961
5.2069
5.1346
5.1262
5.1119
5.1035
5.0031
4.9898
4.4768
4.2722
4.2577
4.2544
4.2402
4.1033
2.9026
2.8842
2.8683
Ph
O
N
O
(R)
H
(H3C)2S
O
22a
major diastereoisomer
Ph
O
N
O
(S)
H
(H3C)2S
O
22b
minor diastereoisomer
7.07
0.37
0.38
0.99
1.00
0.38
1.01
1.02
0.39
1.15
3.12
3.21
1.22
f1 (ppm)


185.1
184.3
163.1
162.6
142.1
140.7
128.7
128.6
127.5
127.4
126.4
126.0
85.8
85.4
74.7
74.2
73.3
58.7
57.9
43.2
42.5
27.7
27.4
25.9
25.7
Ph
O
N
O
(R)
H
(H3C)2S
O
22a
major diastereoisomer
Ph
O
N
O
(S)
H
(H3C)2S
O
22b
minor diastereoisomer
f1 (ppm)


9.5210
9.5073
9.4942
9.4805
7.3976
7.3945
7.3828
7.3475
7.3228
7.2913
7.2853
7.2837
7.2695
6.0278
5.9965
4.5281
4.5219
4.5135
4.5074
3.9579
3.9493
3.9352
3.9266
3.8745
3.8588
3.8518
3.8361
3.7926
3.6994
Ph
OH
O
N
(H3C)2S
+
O
22c
0.93
7.27
0.91
1.00
0.97
1.04
2.75
2.79
f1 (ppm)


169.7
169.4
156.7
143.4
137.5
129.2
128.6
126.9
108.1
95.7
66.4
64.5
51.2
51.1
Ph
OH
O
N
(H3C)2S+
O
22c
f1 (ppm)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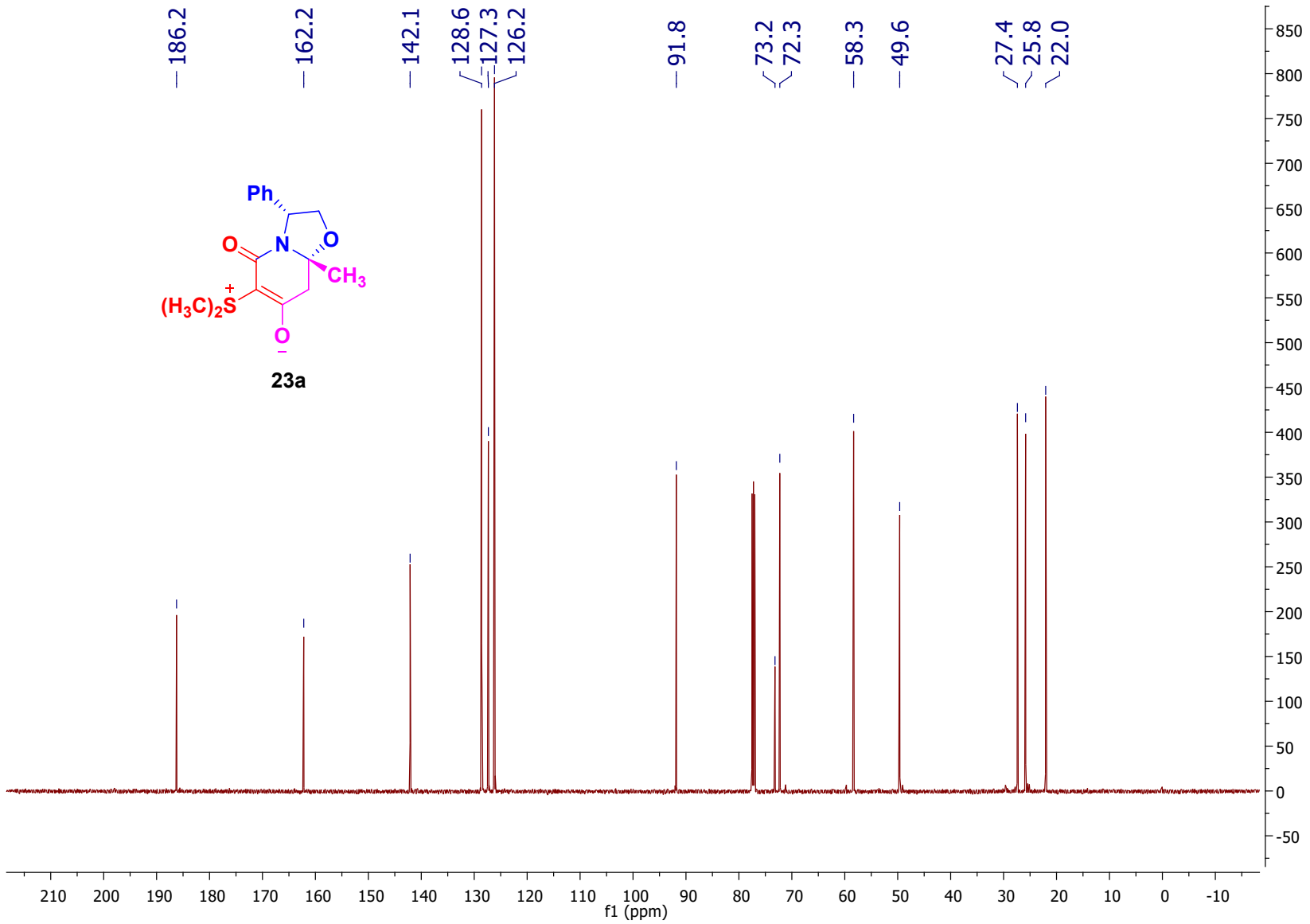
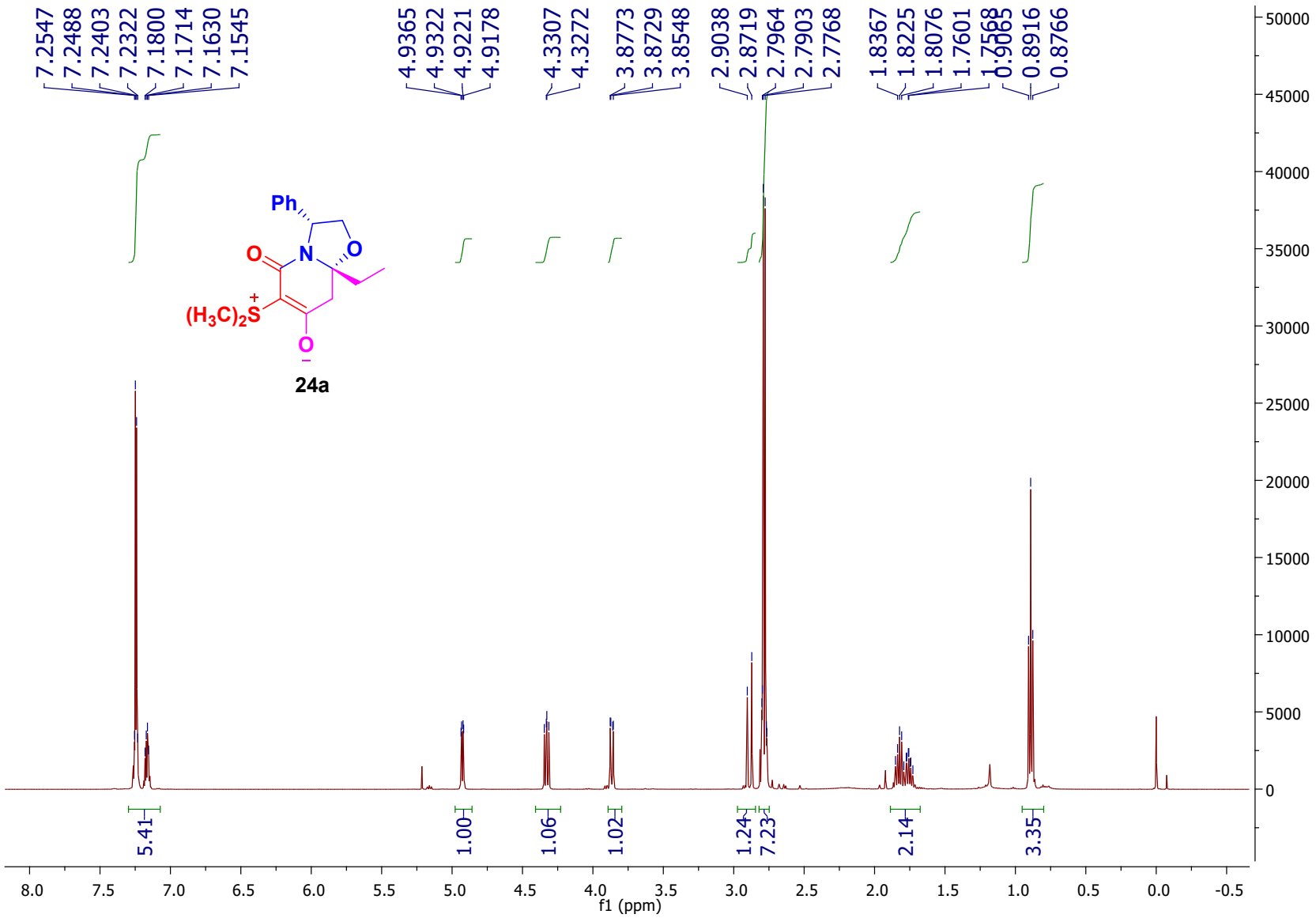
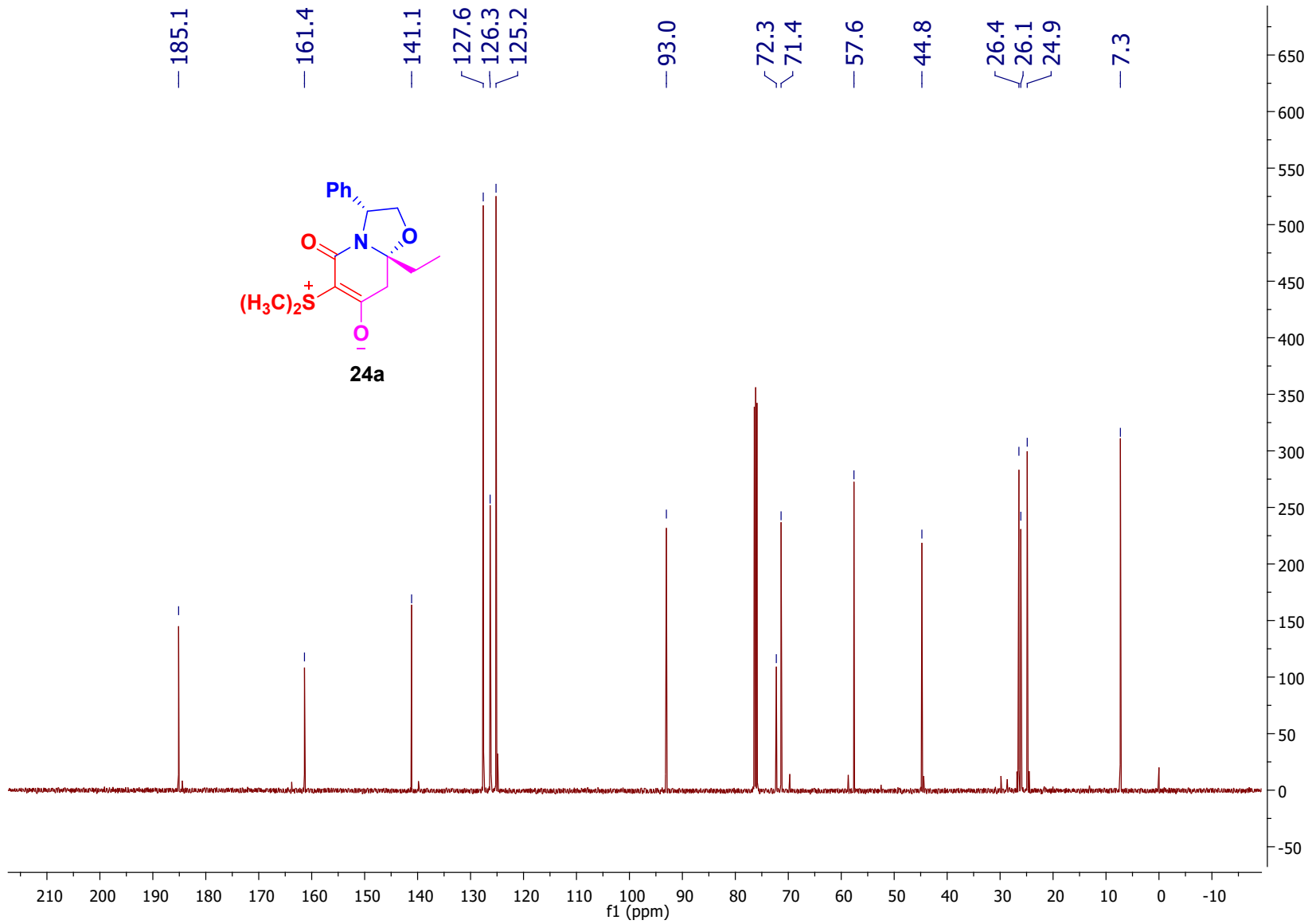
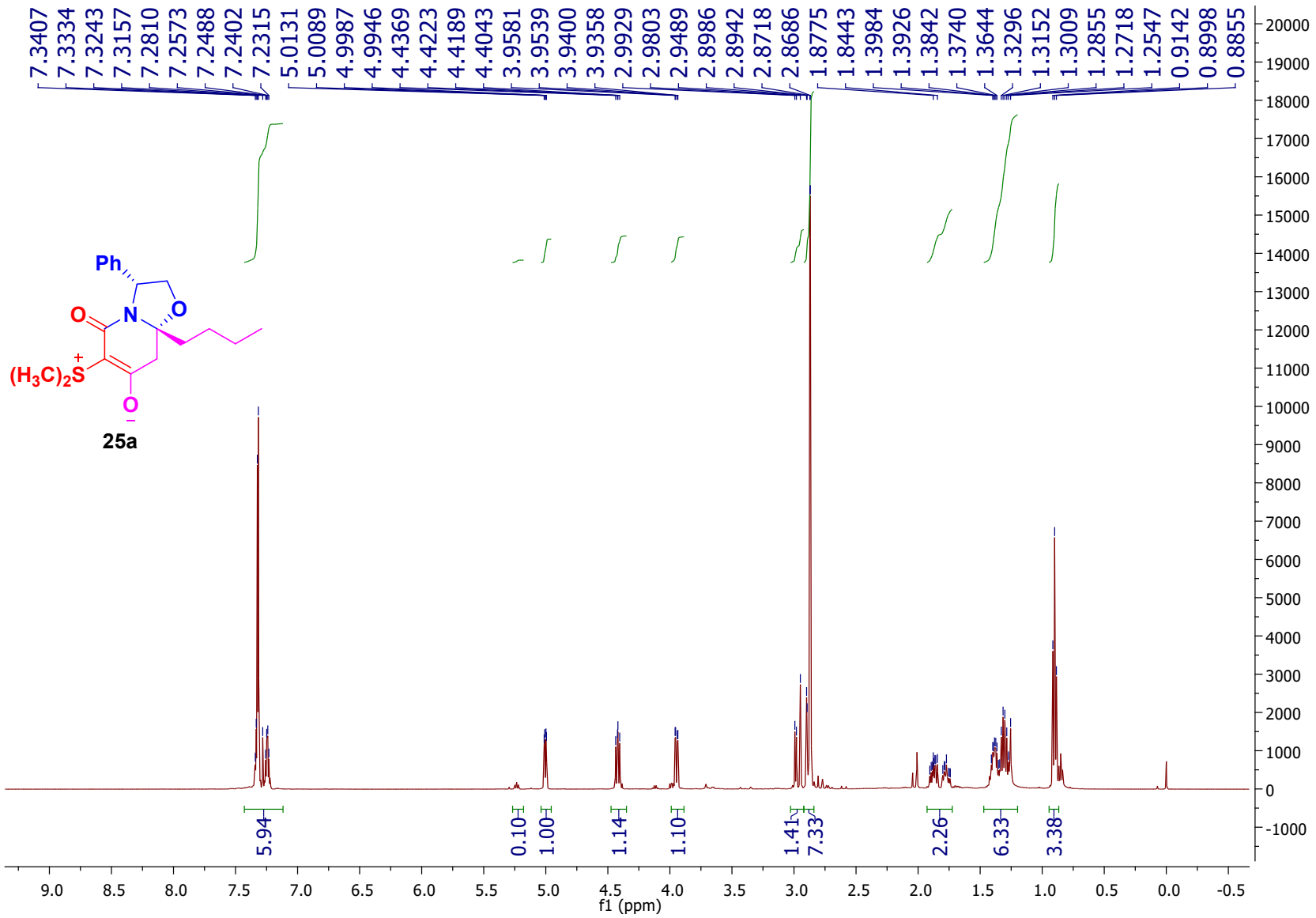
7.3174
7.3086
7.2499
7.2409
7.2326
7.2233
5.0079
5.0043
4.9936
4.9900
4.4659
4.4622
3.9878
3.9840
2.9689
2.8732
2.8525
2.7988
2.7679
1.5069
Ph
O
N
O
CH3
(H3C)2S
+
O
23a
5.29
1.00
1.03
1.04
1.19
6.07
1.03
3.05
30000
25000
20000
15000
10000
5000
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


186.2
162.2
142.1
128.6
127.3
126.2
91.8
73.2
72.3
58.3
49.6
27.4
25.8
22.0
Ph
O
N
O
CH3
(H3C)2S
+
O
−
23a
f1 (ppm)


7.2547
7.2488
7.2403
7.2322
7.1800
7.1714
7.1630
7.1545
4.9365
4.9322
4.9221
4.9178
4.3307
4.3272
3.8773
3.8729
3.8548
2.9038
2.8719
2.7964
2.7903
2.7768
1.8367
1.8225
1.8076
1.7601
0.9085
0.8916
0.8766
Ph
O
N
O
(H3C)2S
+
O
24a
5.41
1.00
1.06
1.02
1.24
7.23
2.14
3.35
f1 (ppm)


185.1
161.4
141.1
127.6
126.3
125.2
93.0
72.3
71.4
57.6
44.8
26.4
26.1
24.9
7.3
Ph
O
N
O
(H3C)2S
+
O
−
24a
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
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)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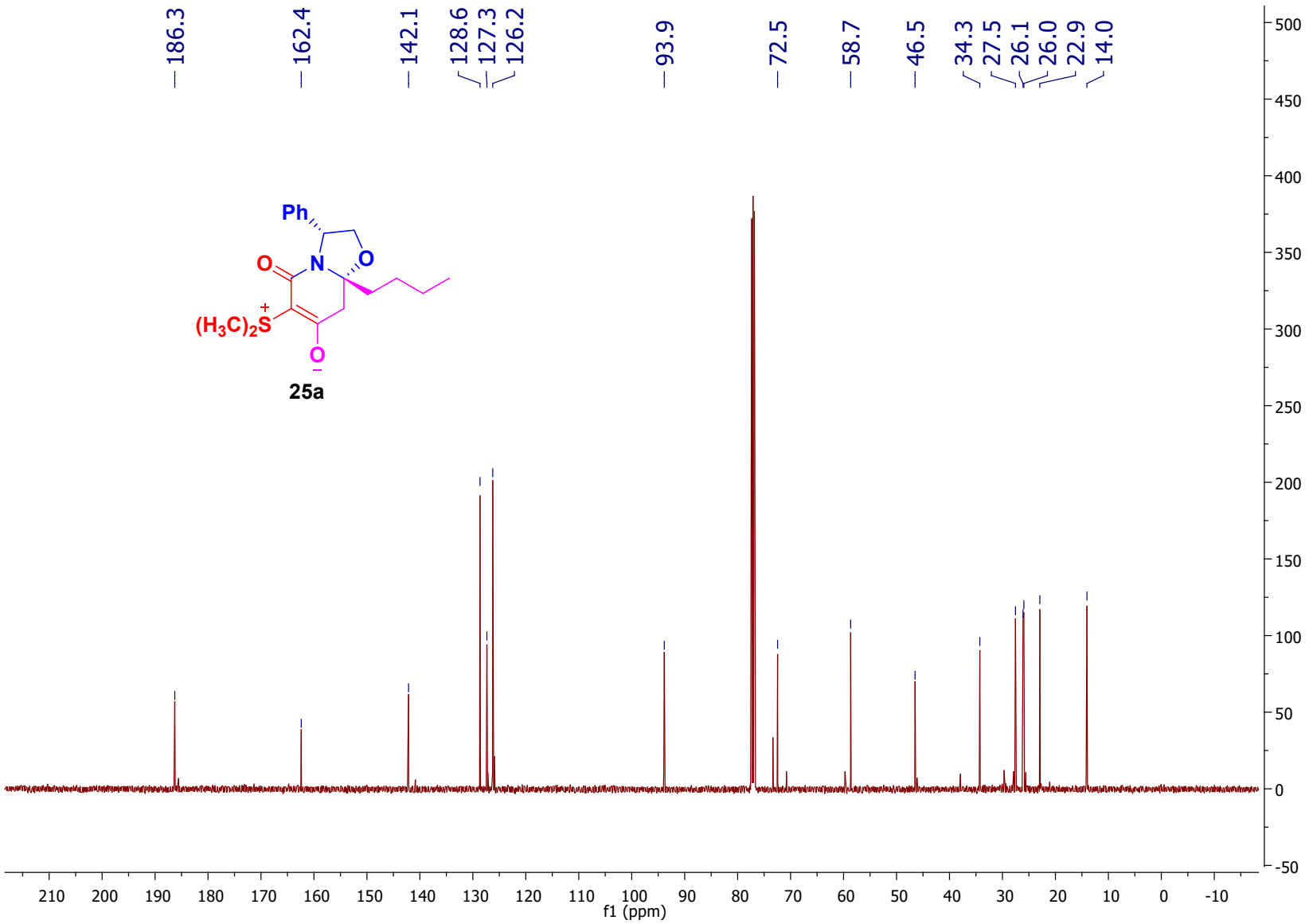
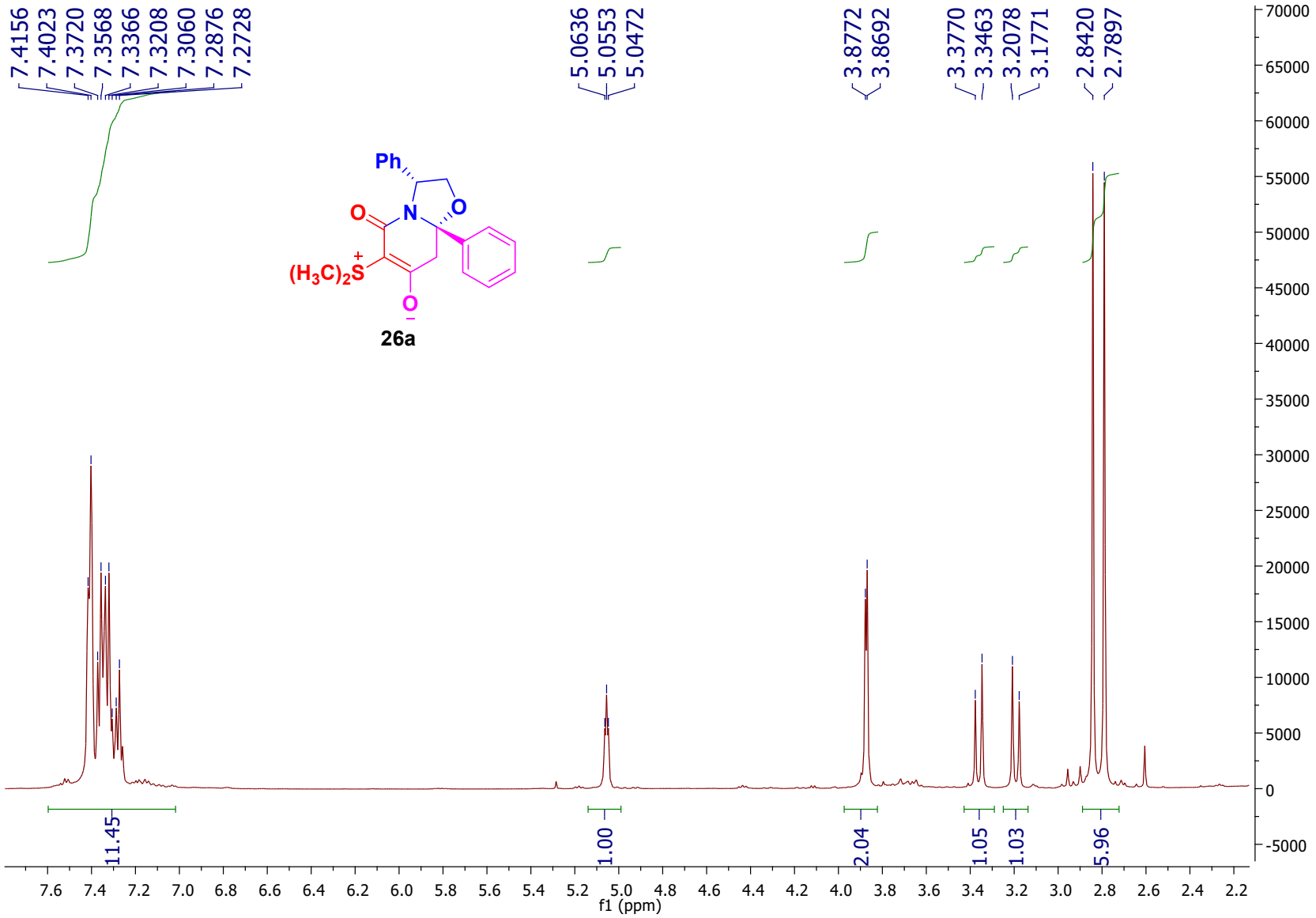
7.3243
7.3157
7.2810
7.2573
7.2488
7.2402
7.2315
5.0131
5.0089
4.9987
4.9946
4.4369
4.4223
4.4189
4.4043
3.9581
3.9539
3.9400
3.9358
2.9929
2.9803
2.9489
2.8986
2.8942
2.8718
2.8686
1.8775
1.8443
1.3984
1.3926
1.3842
1.3740
1.3644
1.3296
1.3152
1.3009
1.2855
1.2718
1.2547
0.9142
0.8998
0.8855
Ph
O
N
O
(H3C)2S
O
25a
5.94
0.10
1.00
1.14
1.10
1.41
7.33
2.26
6.33
3.38
f1 (ppm)


186.3
162.4
142.1
128.6
127.3
126.2
93.9
72.5
58.7
46.5
34.3
27.5
26.1
26.0
22.9
14.0
Ph
O
N
O
(H3C)2S
O
25a
f1 (ppm)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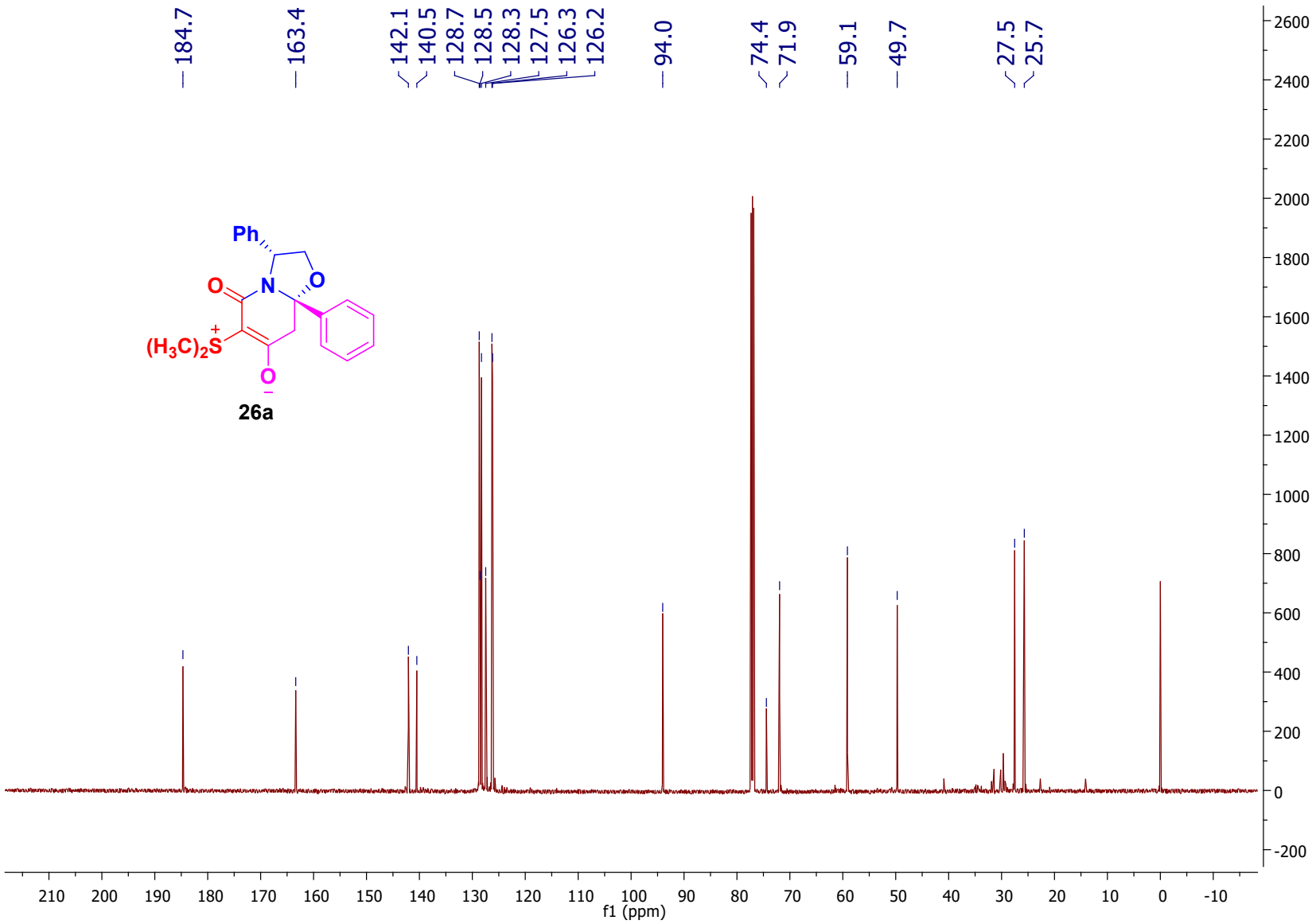
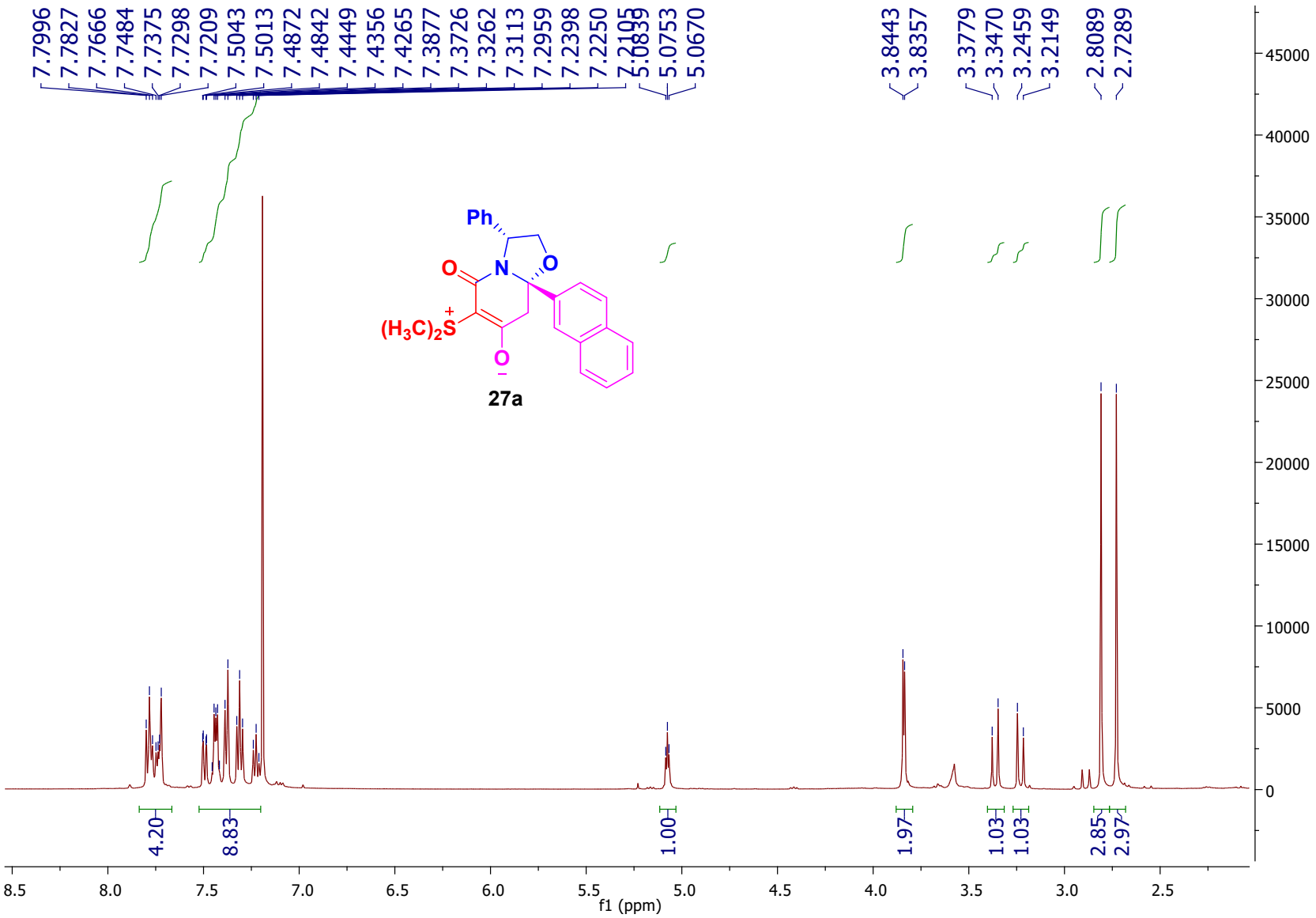
7.4023
7.3720
7.3568
7.3366
7.3208
7.3060
7.2876
7.2728
5.0636
5.0553
5.0472
3.8772
3.8692
3.3770
3.3463
3.2078
3.1771
2.8420
2.7897
Ph
O
N
O
(H3C)2S
+
O
−
26a
11.45
1.00
2.04
1.05
1.03
5.96
f1 (ppm)


184.7
163.4
142.1
140.5
128.7
128.5
128.3
127.5
126.3
126.2
94.0
74.4
71.9
59.1
49.7
27.5
25.7
Ph
O
N
O
(H3C)2S+
O
26a
f1 (ppm)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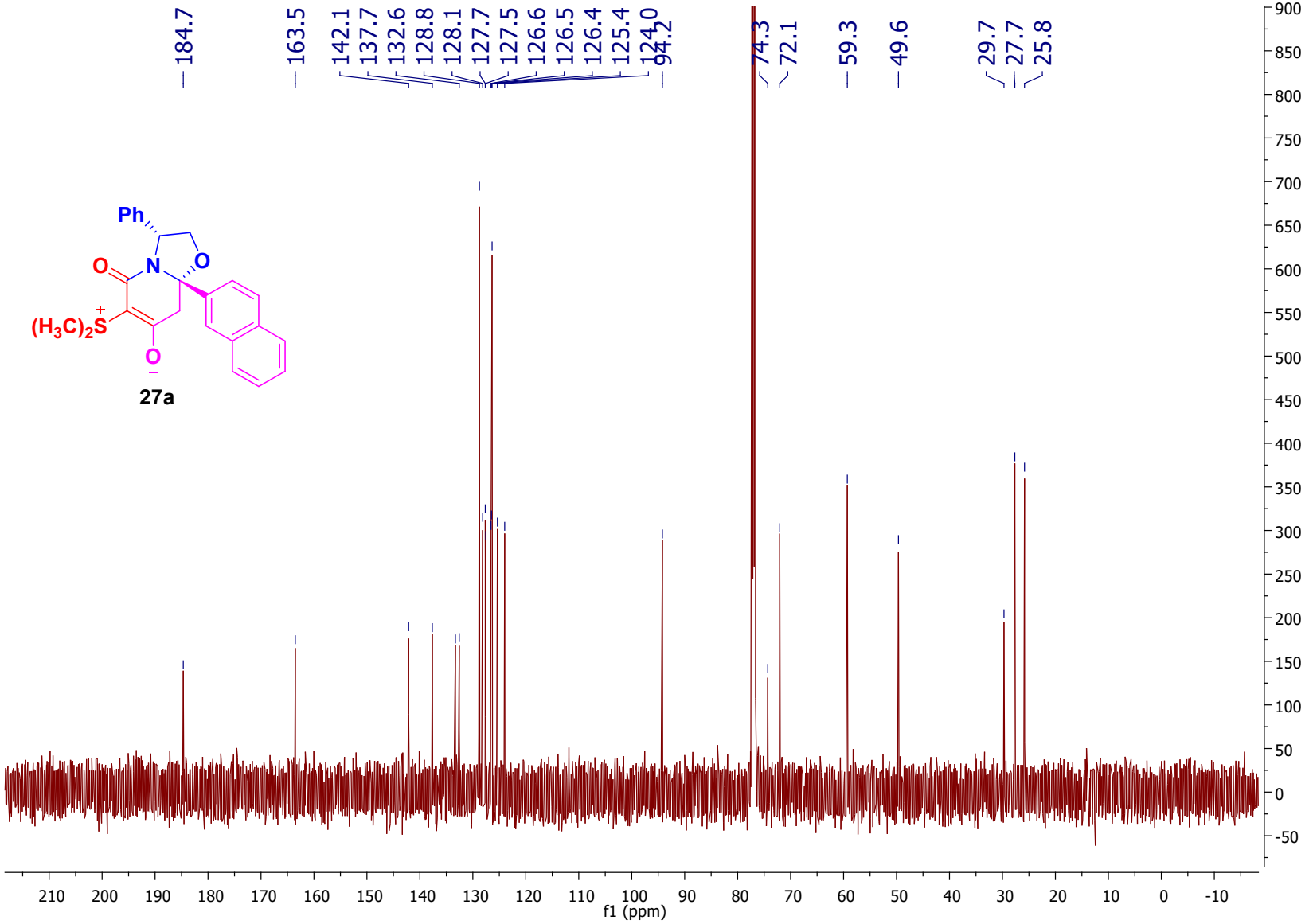
7.7209
7.5043
7.5013
7.4872
7.4842
7.4449
7.4356
7.4265
7.3877
7.3726
7.3262
7.3113
7.2959
7.2398
7.2250
7.2105
5.0839
5.0753
5.0670
3.8443
3.8357
3.3779
3.3470
3.2459
3.2149
2.8089
2.7289
Ph
O
N
O
(H3C)2S
+
O
−
27a
4.20
8.83
1.00
1.97
1.03
1.03
2.85
2.97
f1 (ppm)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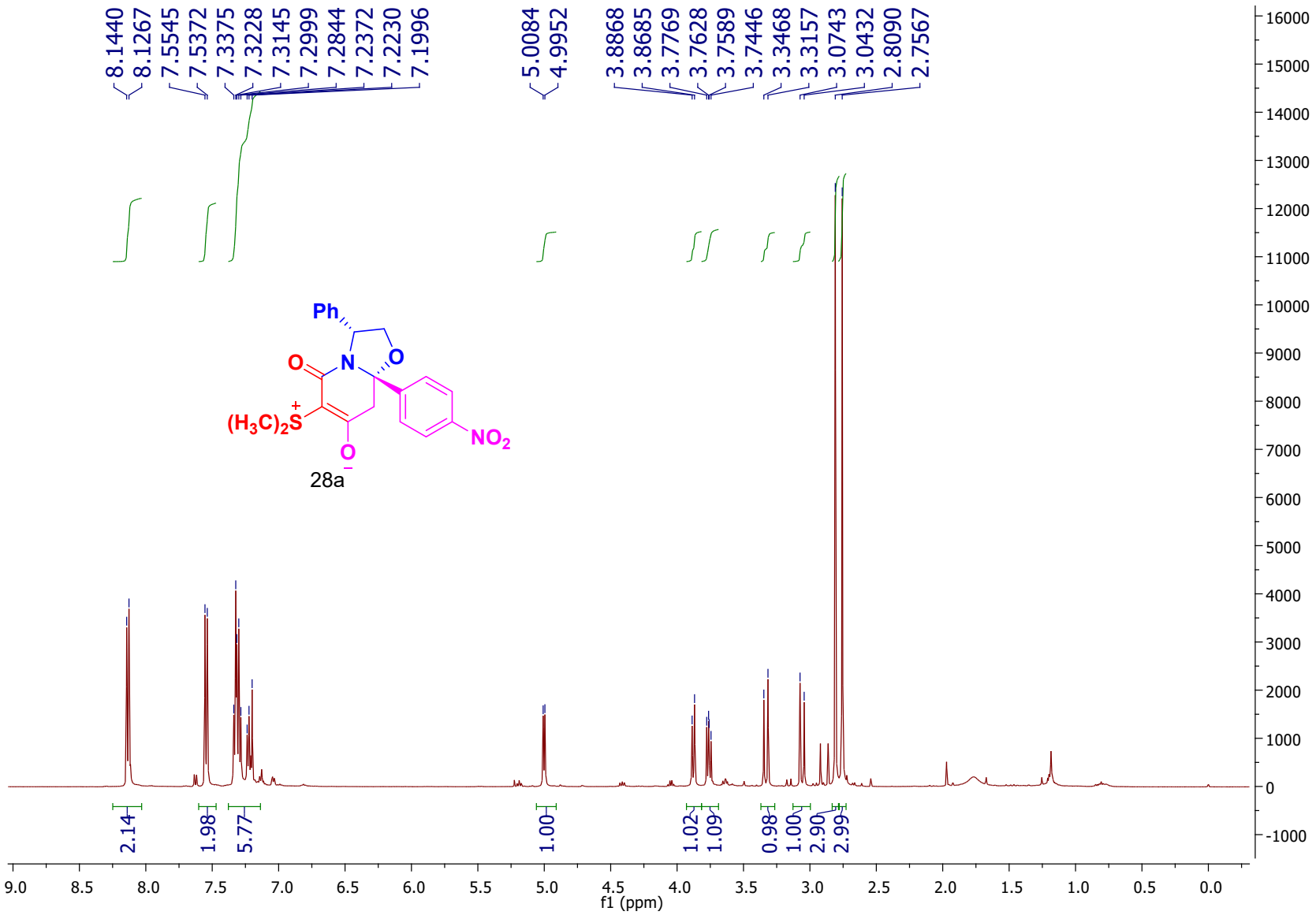
142.1
137.7
132.6
128.8
128.1
127.7
127.5
126.6
126.5
126.4
125.4
124.0
94.2
74.3
72.1
59.3
49.6
29.7
27.7
25.8
Ph
O
N
O
(H3C)2S
+
O
−
27a
f1 (ppm)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7.5545
7.5372
7.3375
7.3228
7.3145
7.2999
7.2844
7.2372
7.2230
7.1996
5.0084
4.9952
3.8868
3.8685
3.7769
3.7628
3.7589
3.7446
3.3468
3.3157
3.0743
3.0432
2.8090
2.7567
Ph
O
N
O
(H3C)2S
+
O
−
NO2
28a
2.14
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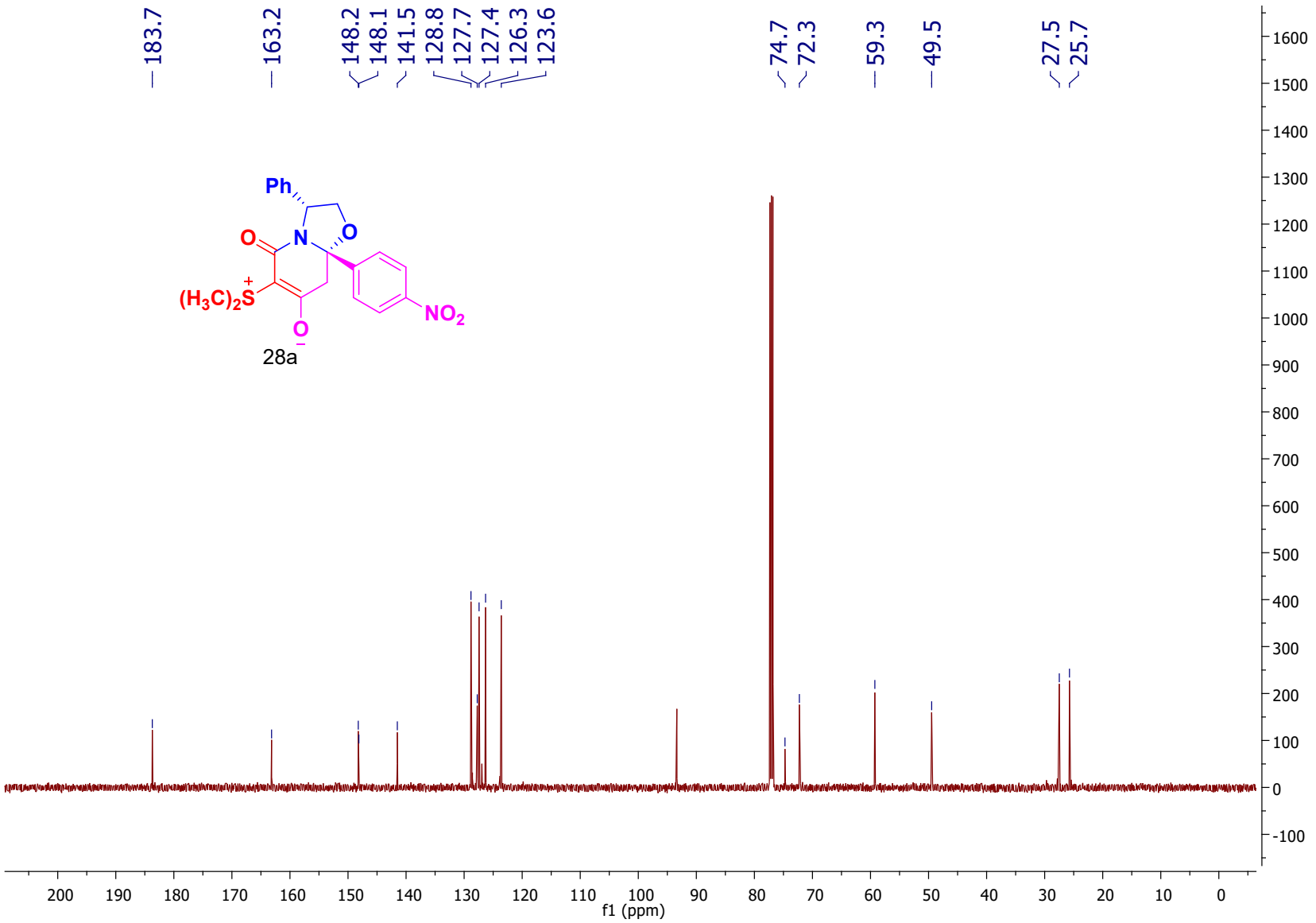
5.77
1.00
1.02
1.09
0.98
1.00
2.90
2.99
f1 (ppm)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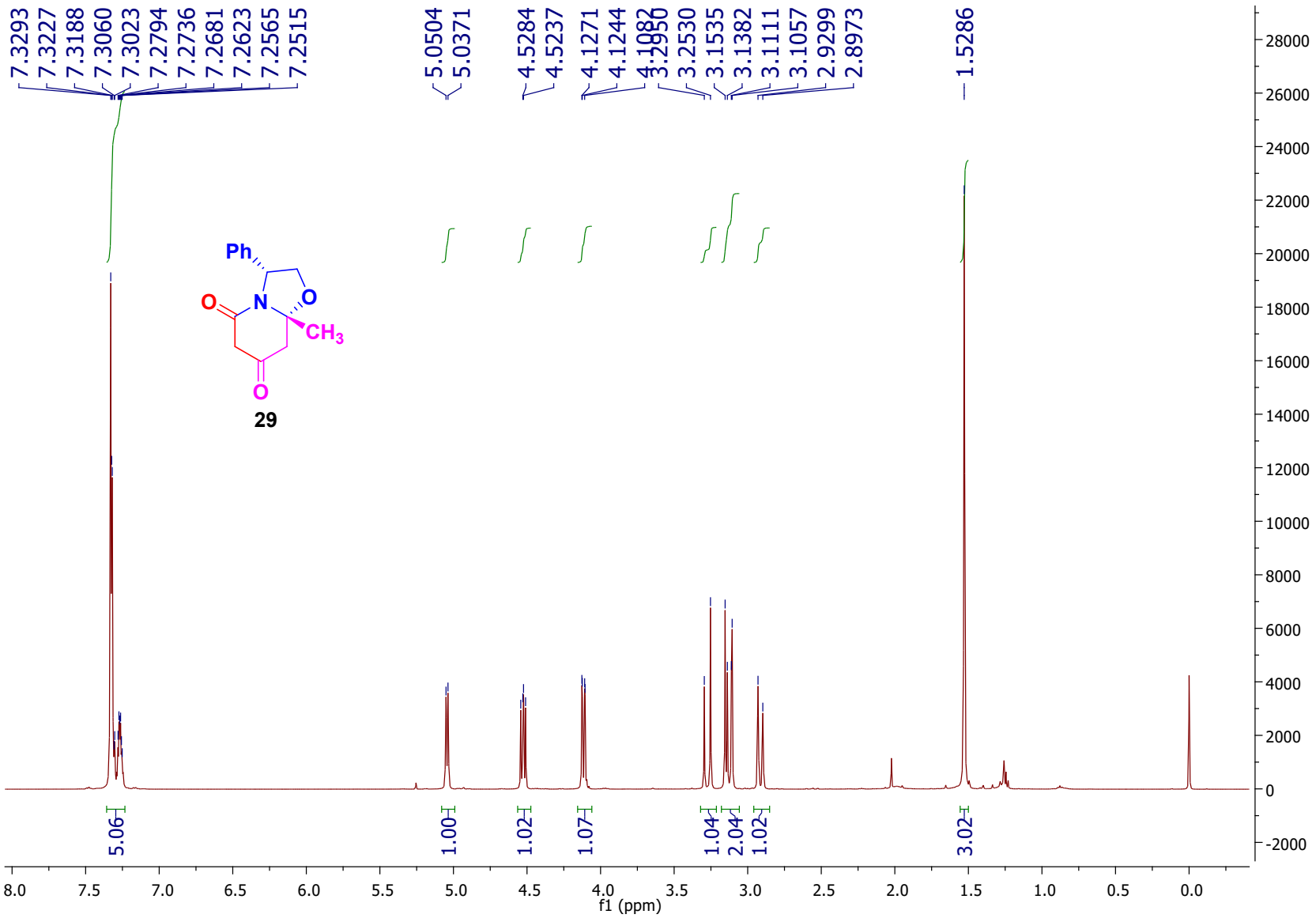
163.2
148.2
148.1
141.5
128.8
127.7
127.4
126.3
123.6
74.7
72.3
59.3
49.5
27.5
25.7
Ph
O
N
O
(H3C)2S
+
O
−
NO2
28a
f1 (ppm)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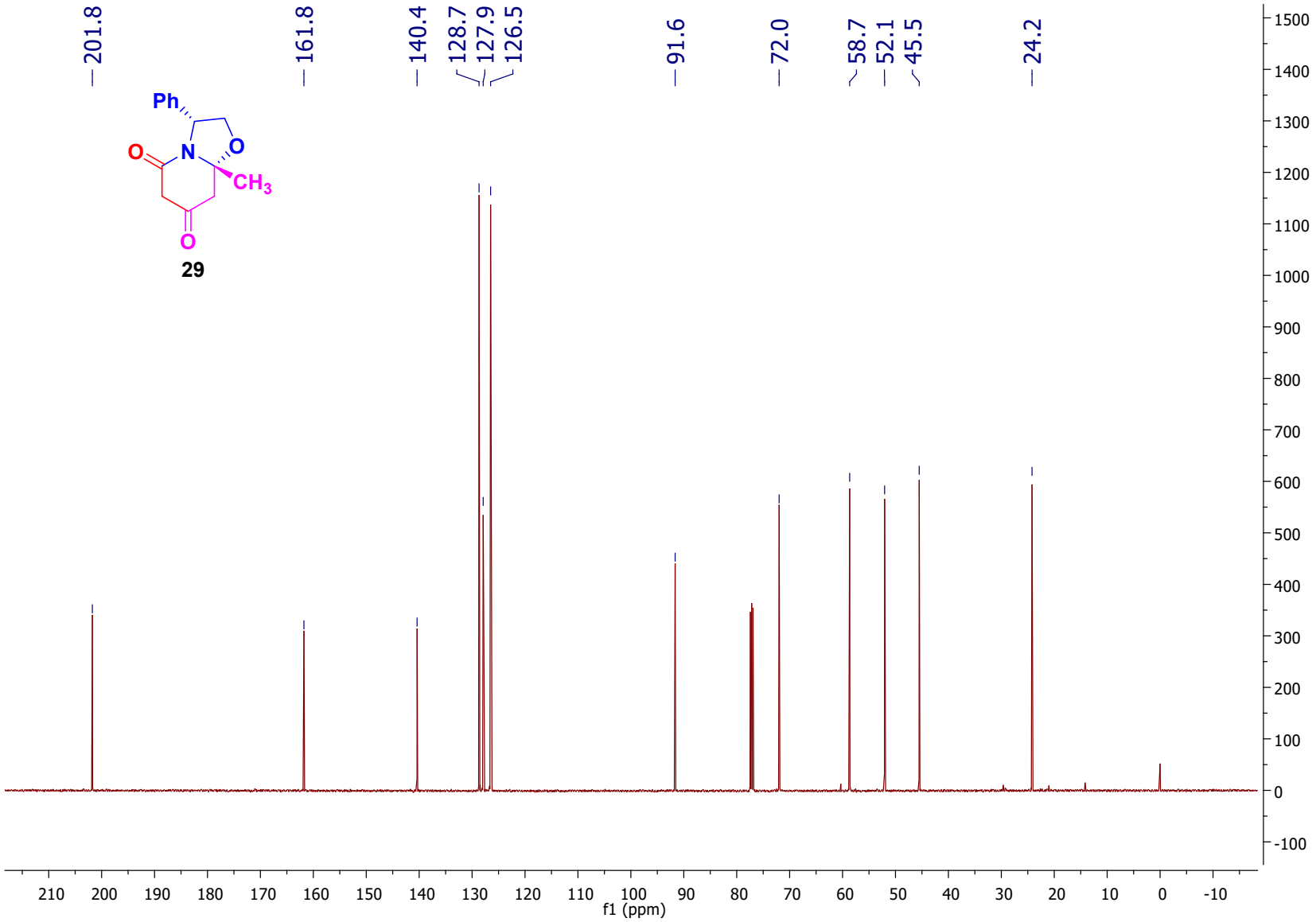
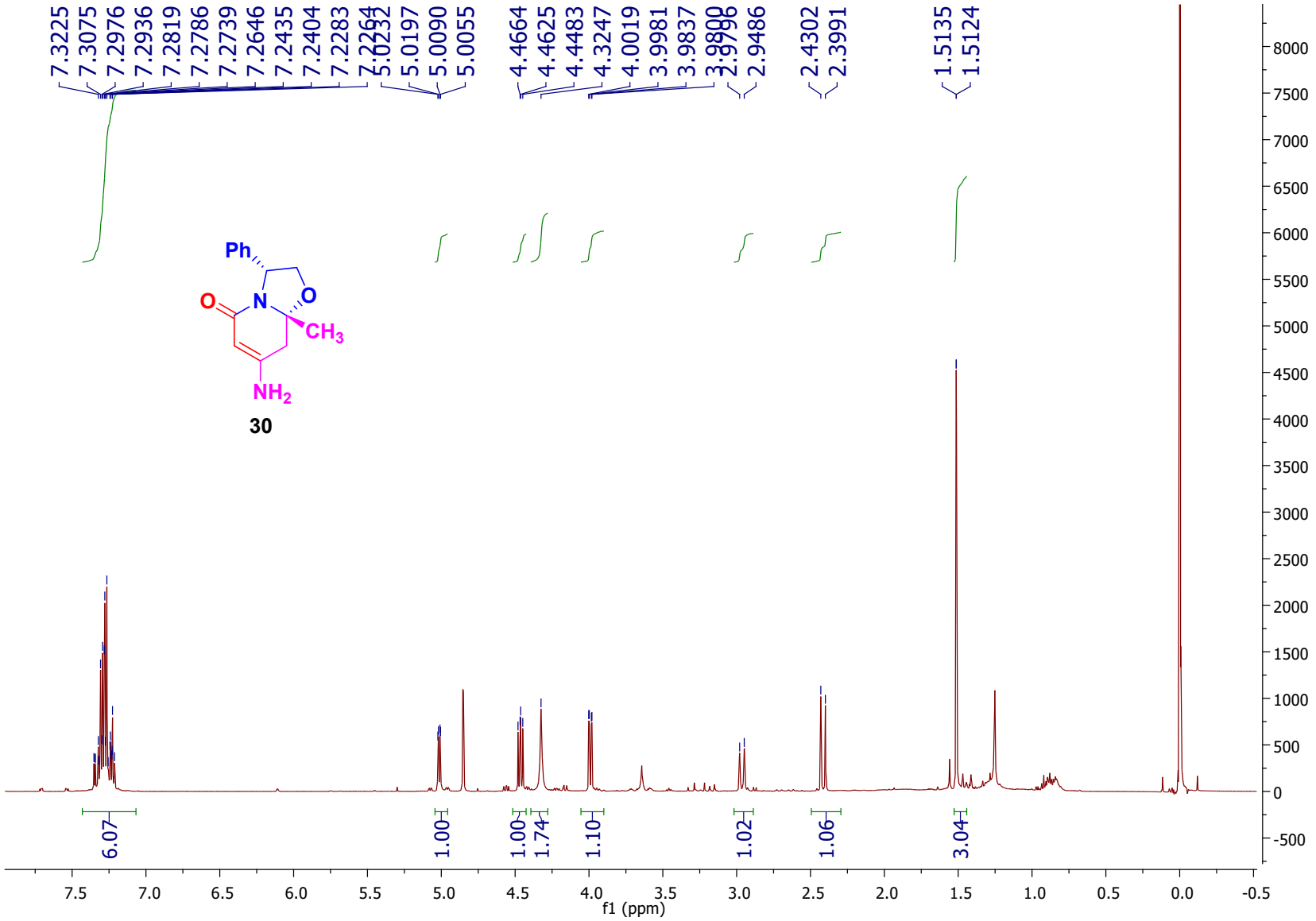
7.3023
7.2794
7.2736
7.2681
7.2623
7.2565
7.2515
5.0504
5.0371
4.5284
4.5237
4.1271
4.1244
4.1082
3.2950
3.2530
3.1535
3.1382
3.1111
3.1057
2.9299
2.8973
1.5286
Ph
O
N
O
CH3
O
29
5.06
1.00
1.02
1.07
1.04
2.04
1.02
3.02
f1 (ppm)


201.8
161.8
140.4
128.7
127.9
126.5
91.6
72.0
58.7
52.1
45.5
24.2
Ph
O
N
O
CH3
O
29
f1 (ppm)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7.2936
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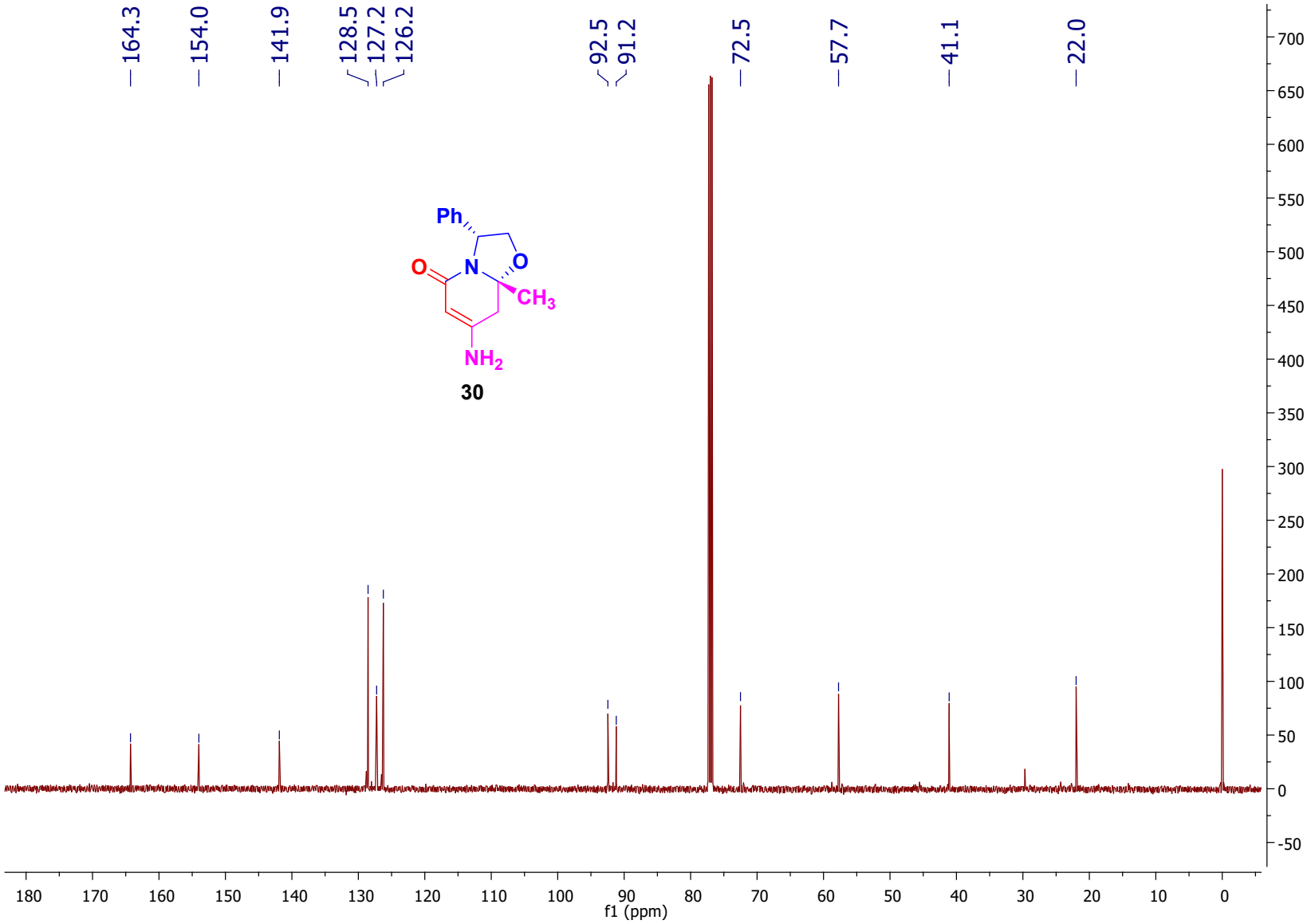
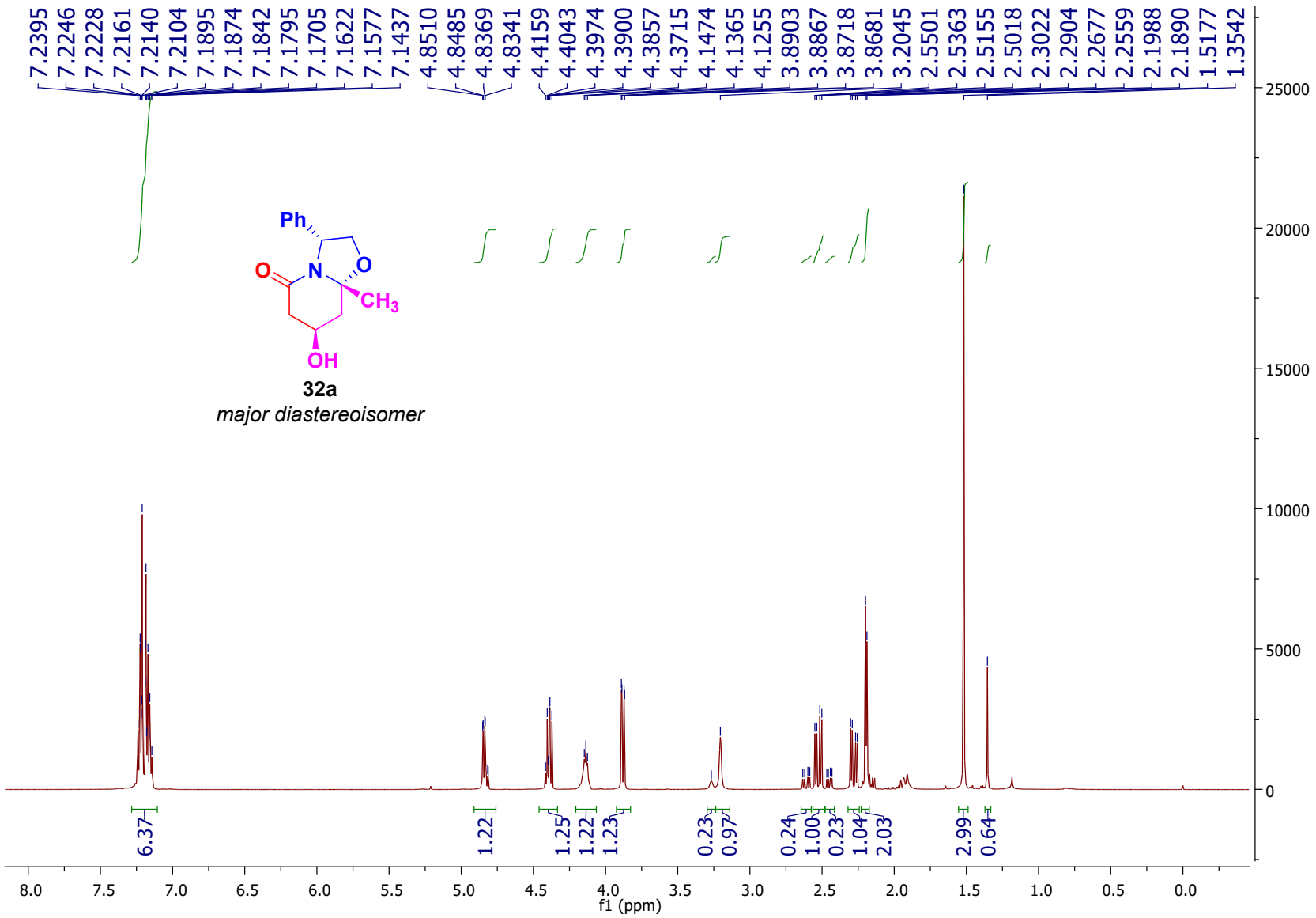
7.2786
7.2739
7.2646
7.2435
7.2404
7.2283
7.2264
5.0232
5.0197
5.0090
5.0055
4.4664
4.4625
4.4483
4.3247
4.0019
3.9981
3.9837
3.9800
3.9796
2.9486
2.4302
2.3991
1.5135
1.5124
Ph
O
N
O
CH3
NH2
30
6.07
1.00
1.00
1.74
1.10
1.02
1.06
3.04
f1 (ppm)


164.3
154.0
141.9
128.5
127.2
126.2
92.5
91.2
72.5
57.7
41.1
22.0
Ph
O
N
O
CH3
NH2
30
f1 (ppm)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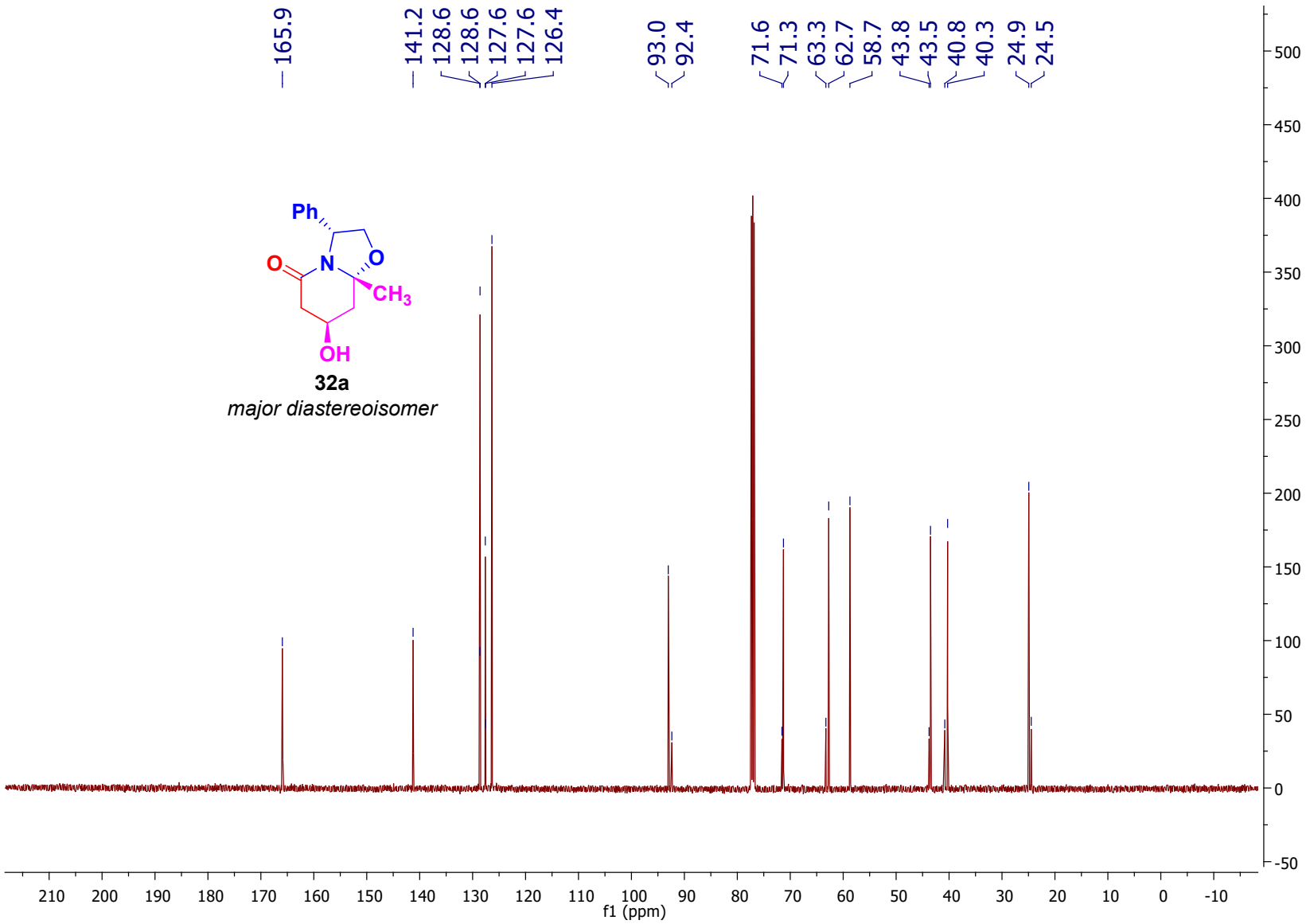
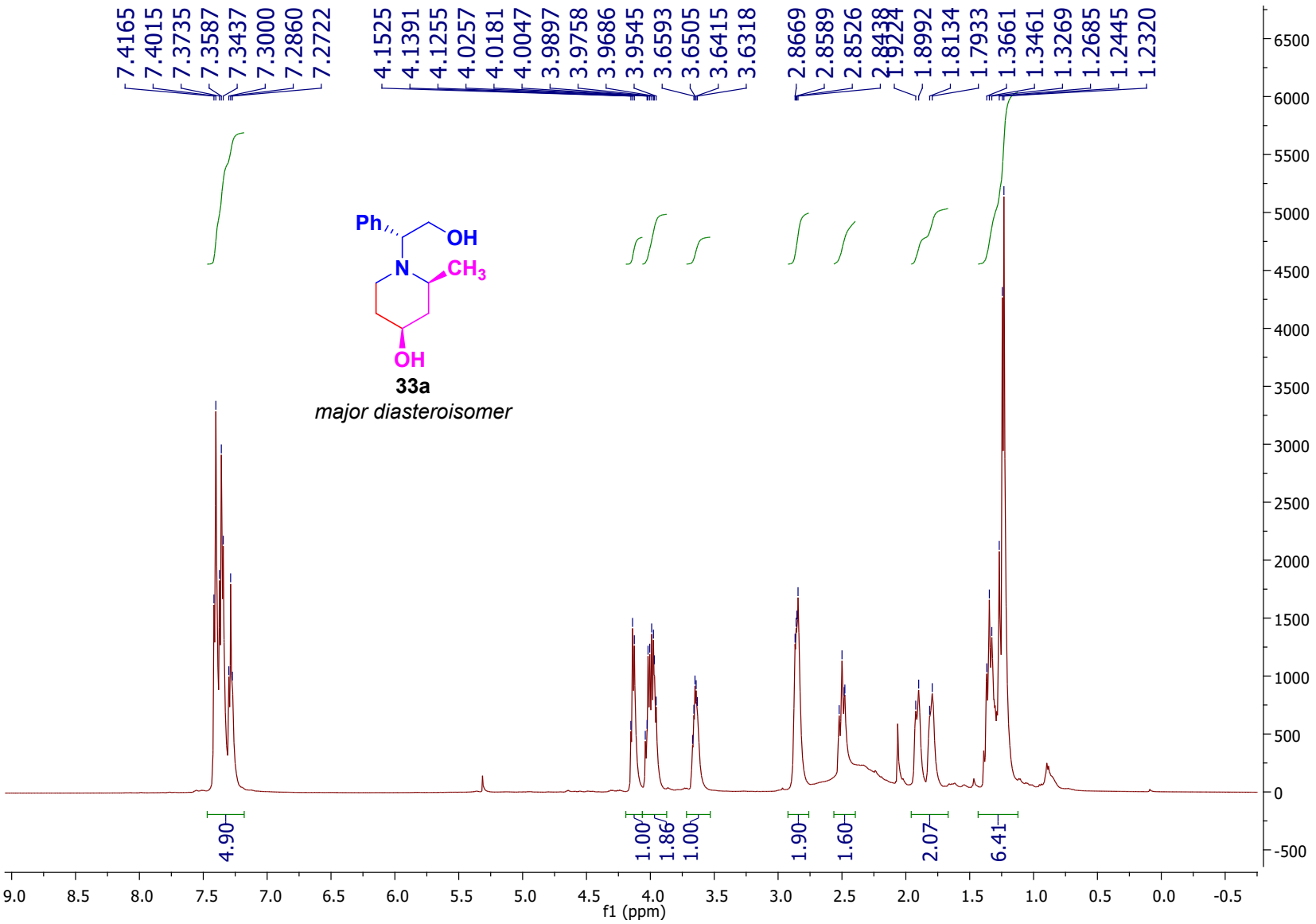
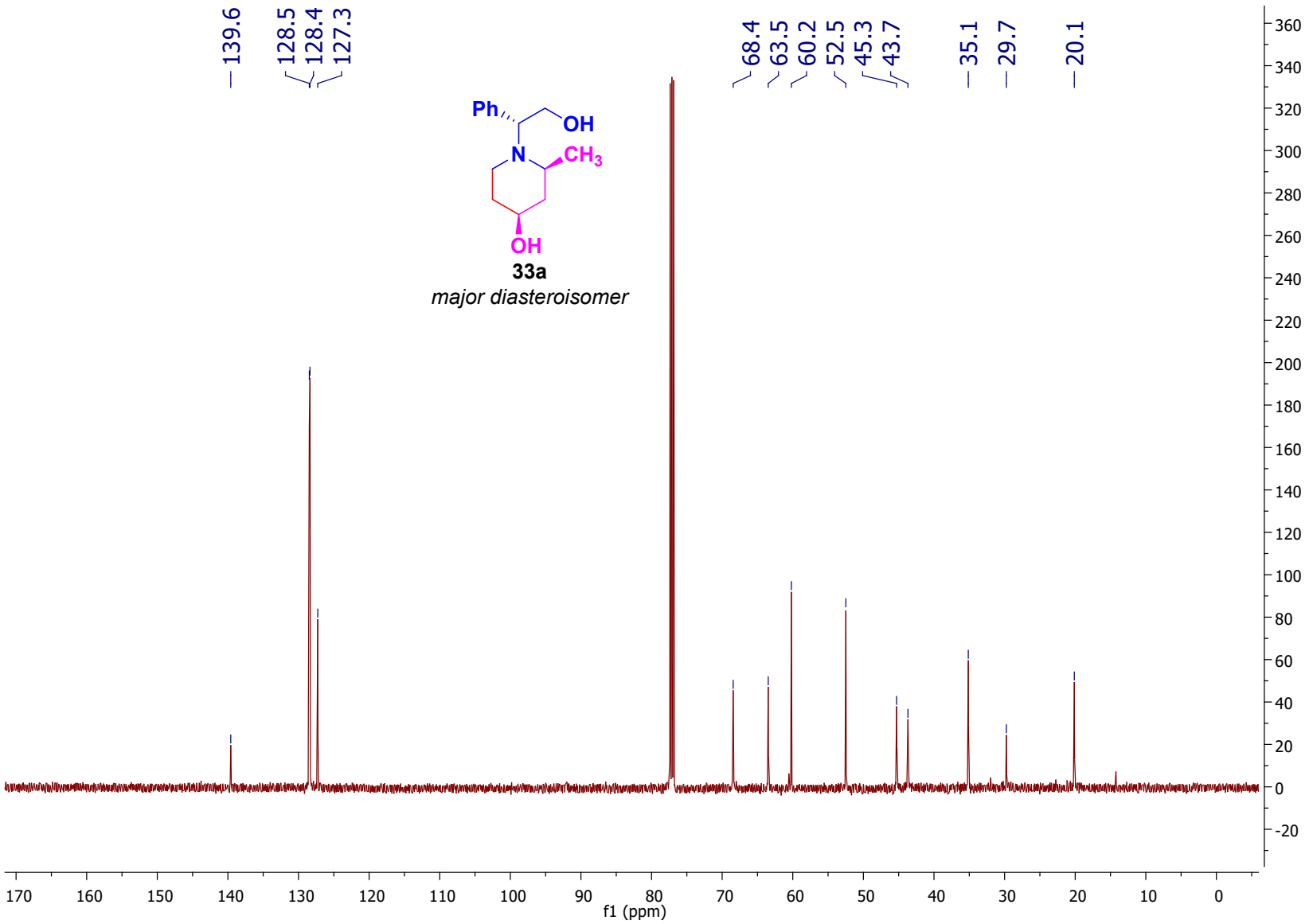
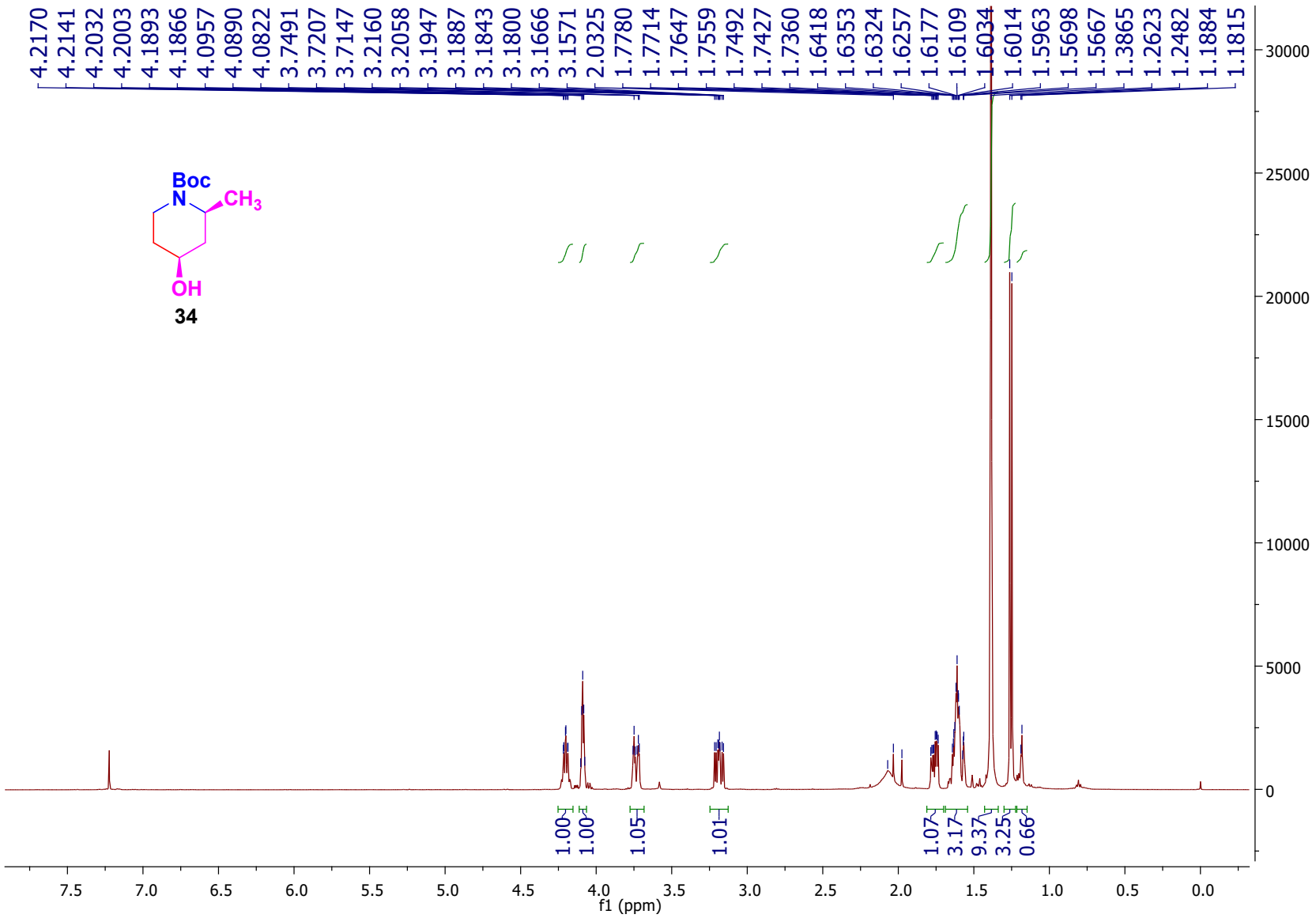
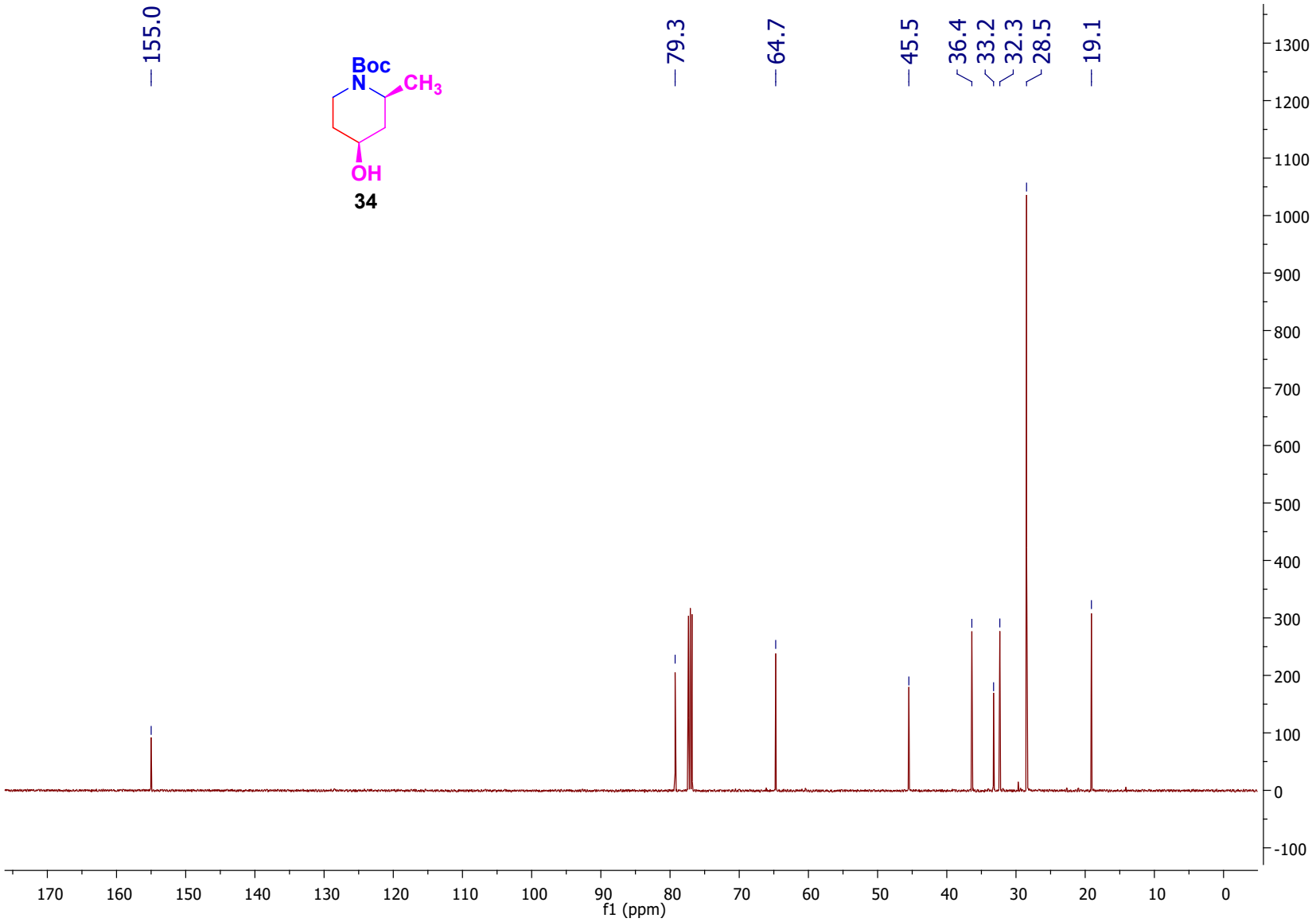
7.2140
7.2104
7.1895
7.1874
7.1842
7.1795
7.1705
7.1622
7.1577
7.1437
4.8510
4.8485
4.8369
4.8341
4.4159
4.4043
4.3974
4.3900
4.3857
4.3715
4.1474
4.1365
4.1255
3.8903
3.8867
3.8718
3.8681
3.2045
2.5501
2.5363
2.5155
2.5018
2.3022
2.2904
2.2677
2.2559
2.1988
2.1890
1.5177
1.3542
Ph
O
N
O
CH3
OH
32a
major diastereoisomer
6.37
1.22
1.25
1.22
1.23
0.23
0.97
0.24
1.00
0.23
1.04
2.03
2.99
0.64
f1 (ppm)

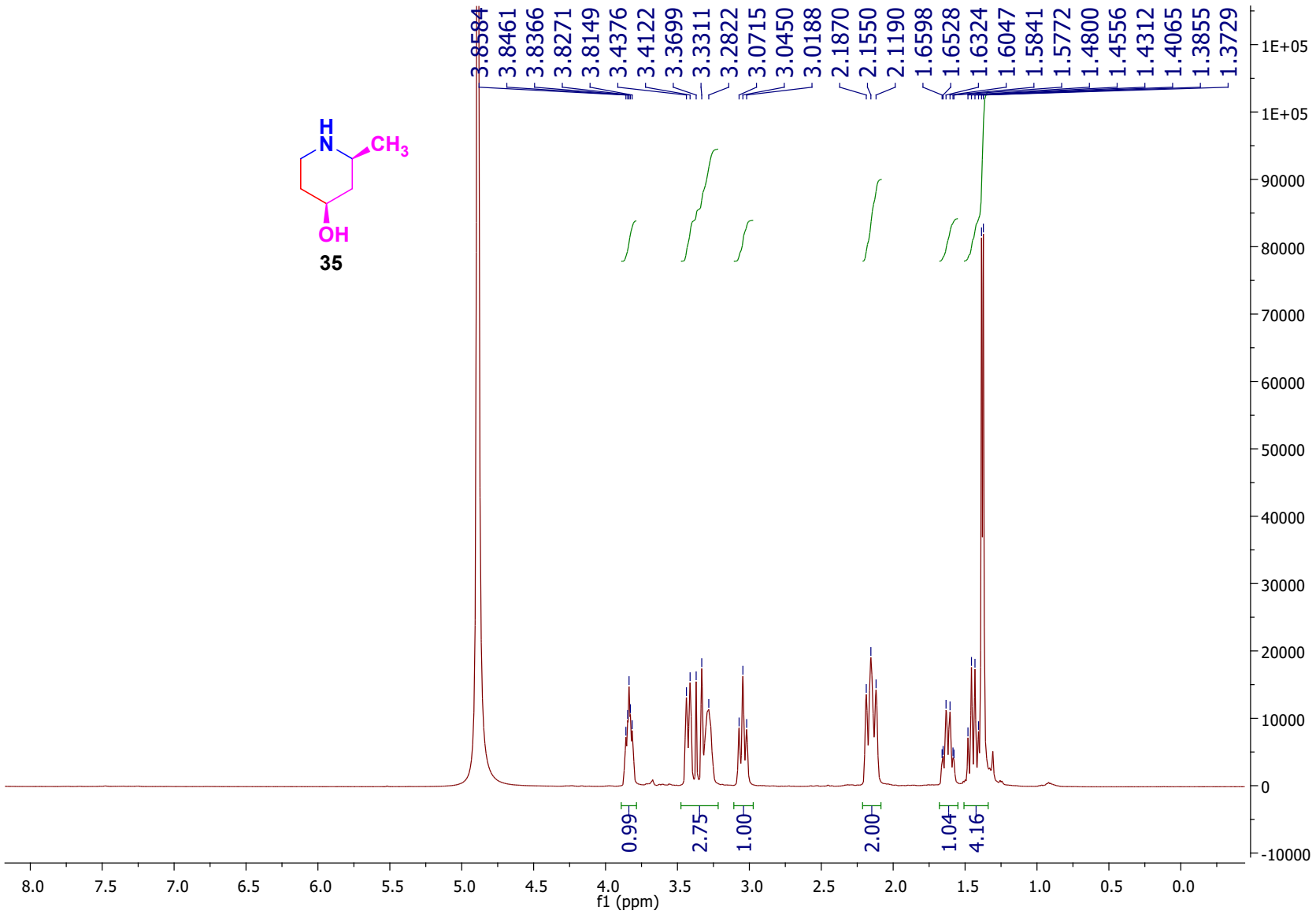

165.9
141.2
128.6
128.6
127.6
127.6
126.4
93.0
92.4
71.6
71.3
63.3
62.7
58.7
43.8
43.5
40.8
40.3
24.9
24.5
Ph
O
N
O
CH3
OH
32a
major diastereoisomer
f1 (ppm)

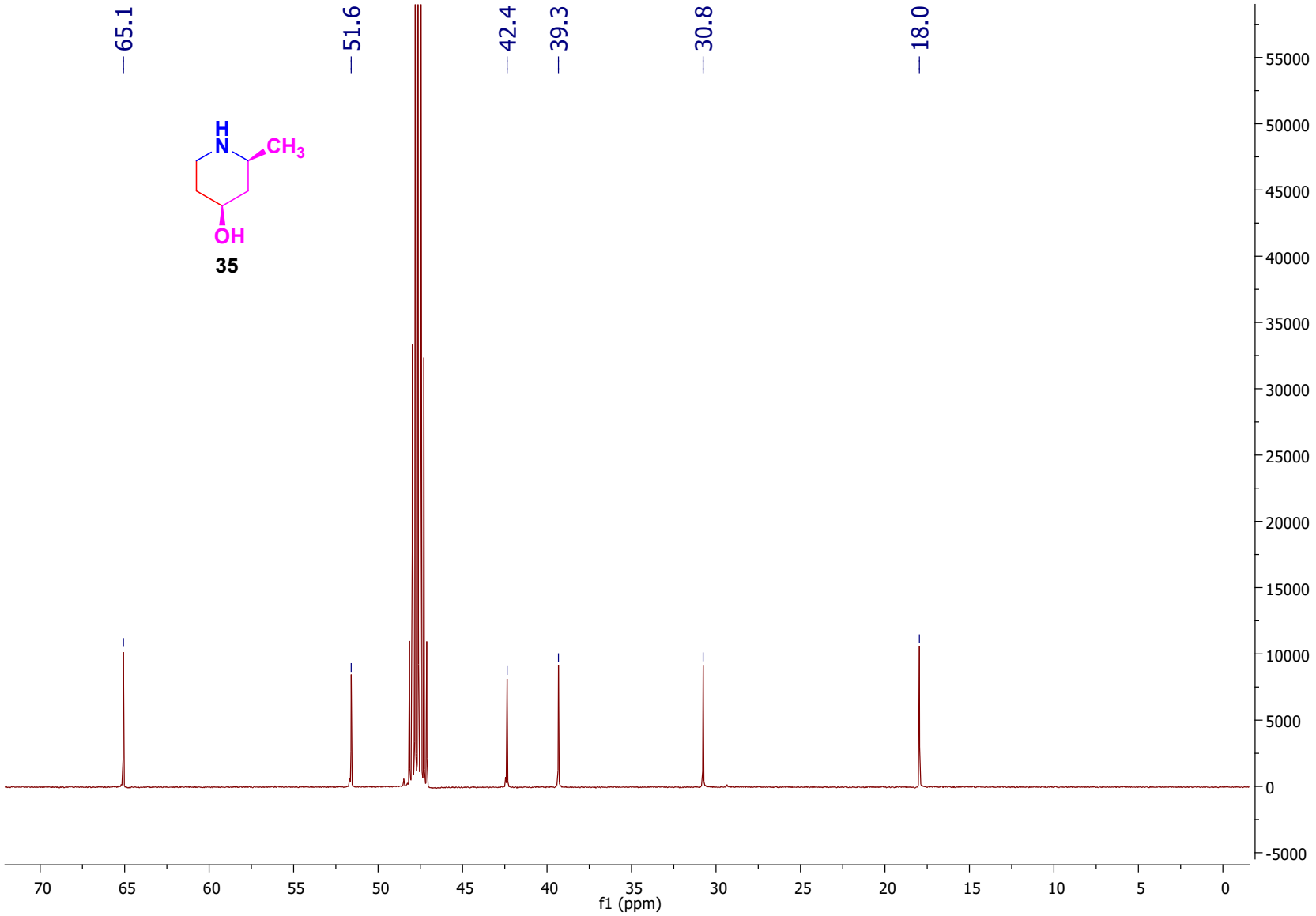

7.4165
7.4015
7.3735
7.3587
7.3437
7.3000
7.2860
7.2722
4.1525
4.1391
4.1255
4.0257
4.0181
4.0047
3.9897
3.9758
3.9686
3.9545
3.6593
3.6505
3.6415
3.6318
2.8669
2.8589
2.8526
2.8438
1.9224
1.8992
1.8134
1.7933
1.3661
1.3461
1.3269
1.2685
1.2445
1.2320
Ph
OH
N
CH3
OH
33a
major diasteroisomer
4.90
1.00
1.86
1.00
1.90
1.60
2.07
6.41
f1 (ppm)

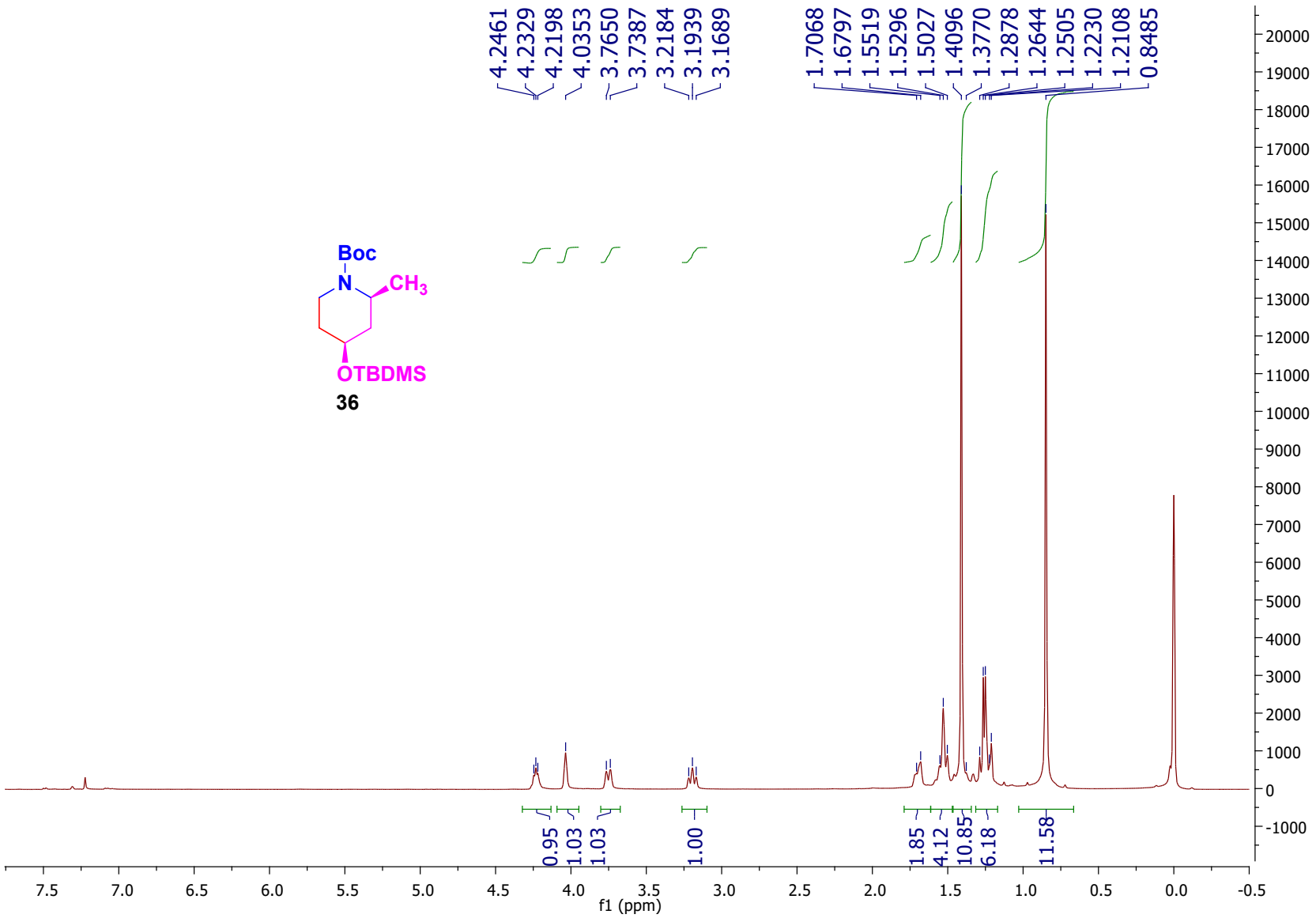

139.6
128.5
128.4
127.3
68.4
63.5
60.2
52.5
45.3
43.7
35.1
29.7
20.1
Ph
OH
N
CH3
OH
33a
major diasteroisomer
f1 (ppm)

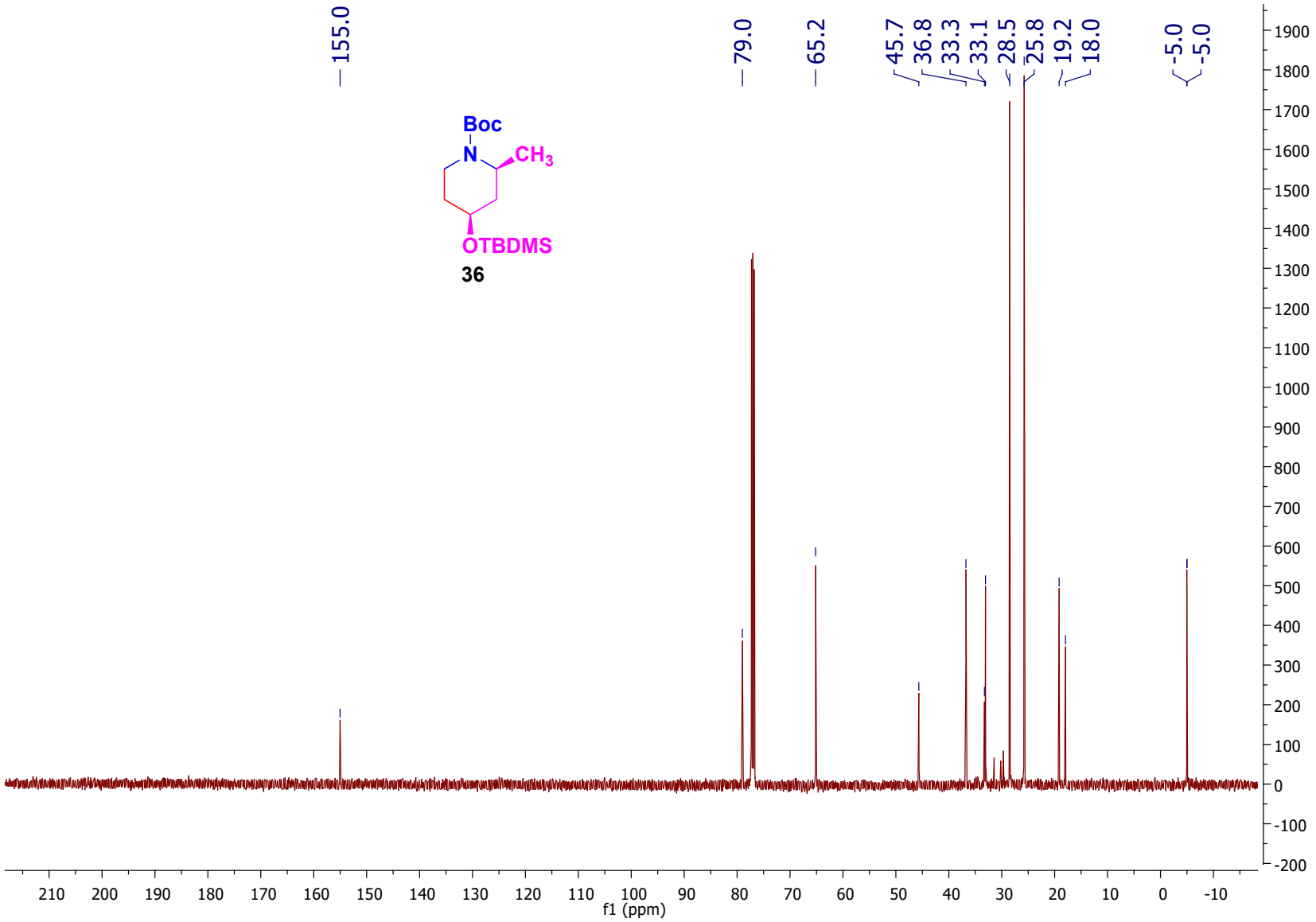

4.2170
4.2141
4.2032
4.2003
4.1893
4.1866
4.0957
4.0890
4.0822
3.7491
3.7207
3.7147
3.2160
3.2058
3.1947
3.1887
3.1843
3.1800
3.1666
3.1571
2.0325
1.7780
1.7714
1.7647
1.7559
1.7492
1.7427
1.7360
1.6418
1.6353
1.6324
1.6257
1.6177
1.6109
1.6034
1.6014
1.5963
1.5698
1.5667
1.3865
1.2623
1.2482
1.1884
1.1815
Boc
N
CH3
OH
34
1.00
1.00
1.05
1.01
1.07
3.17
9.37
3.25
0.66
f1 (ppm)

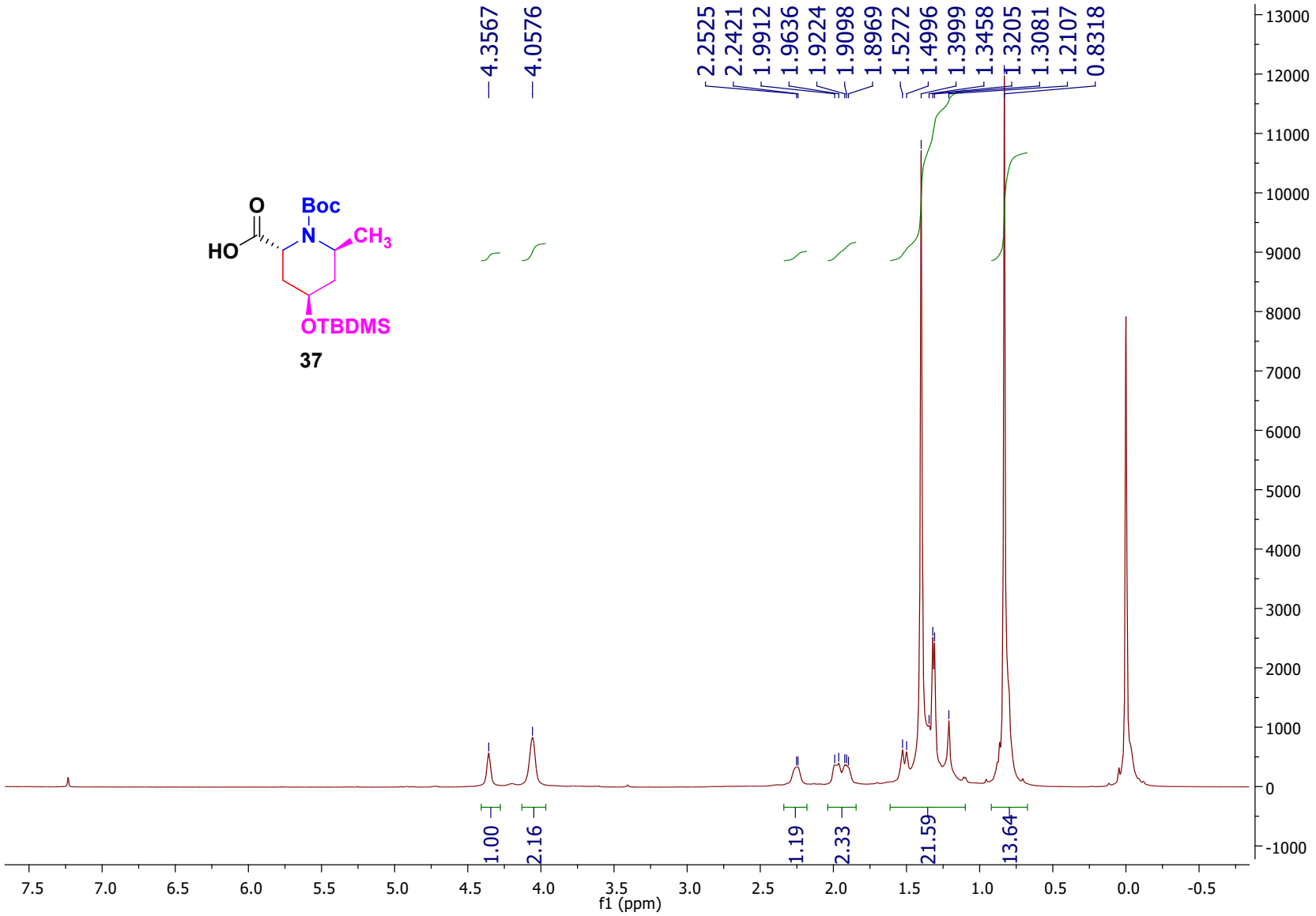

155.0
79.3
64.7
45.5
36.4
33.2
32.3
28.5
19.1
Boc
N
CH3
OH
34
f1 (ppm)

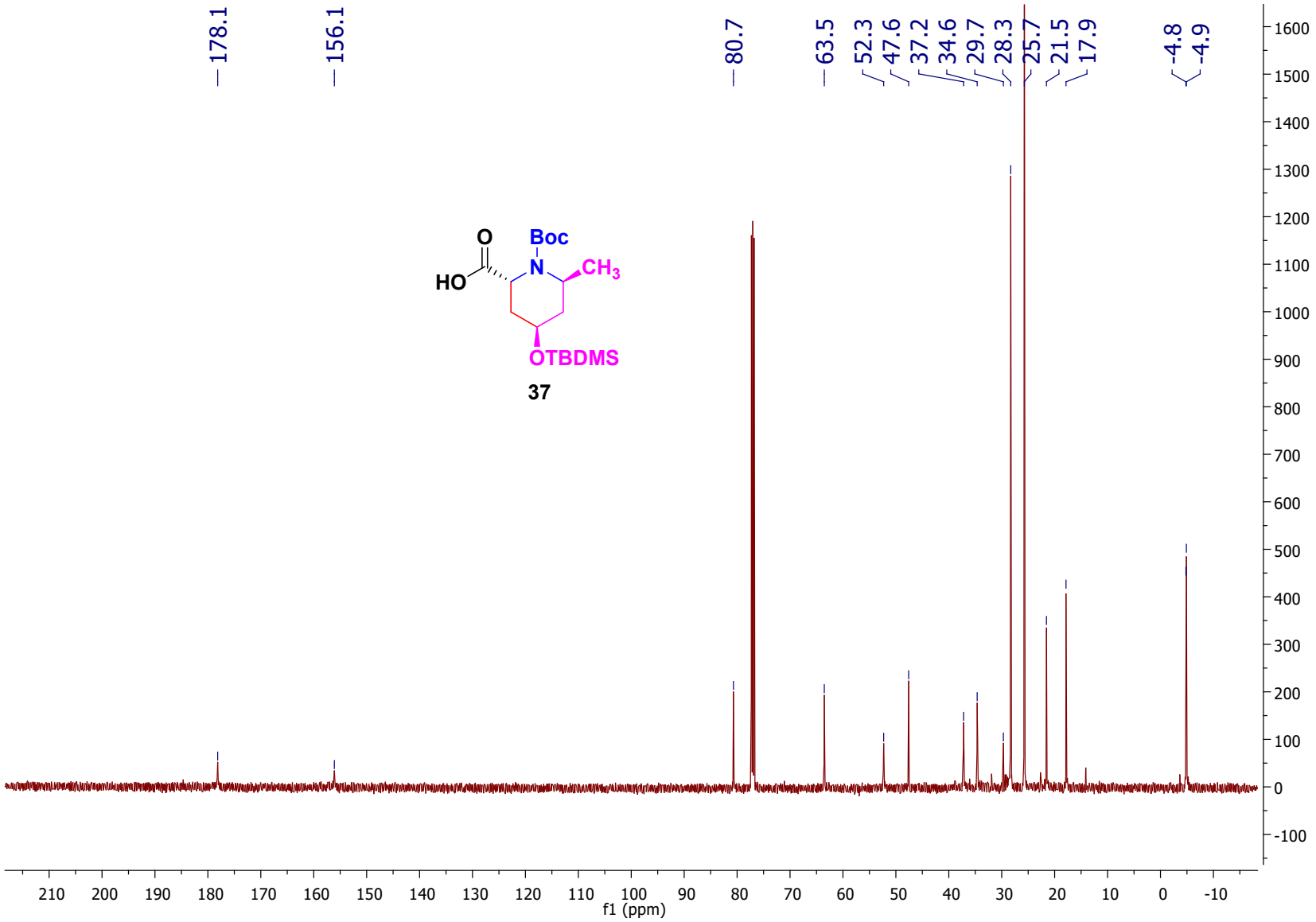

3.8584
3.8461
3.8366
3.8271
3.8149
3.4376
3.4122
3.3699
3.3311
3.2822
3.0715
3.0450
3.0188
2.1870
2.1550
2.1190
1.6598
1.6528
1.6324
1.6047
1.5841
1.5772
1.4800
1.4556
1.4312
1.4065
1.3855
1.3729
H
N
CH3
OH
35
0.99
2.75
1.00
2.00
1.04
4.16
f1 (ppm)

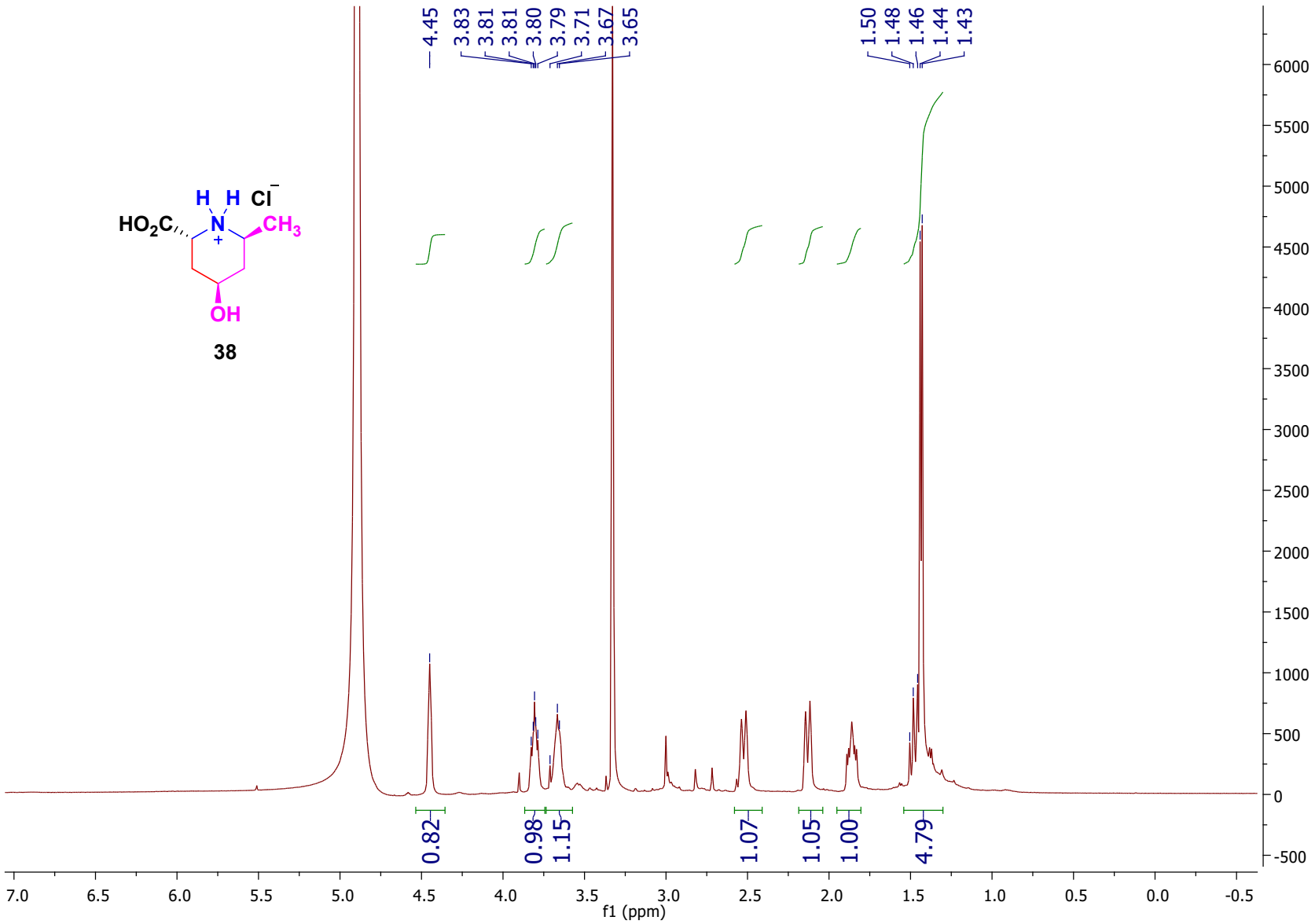

65.1
51.6
42.4
39.3
30.8
18.0
H
N
CH3
OH
35
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)

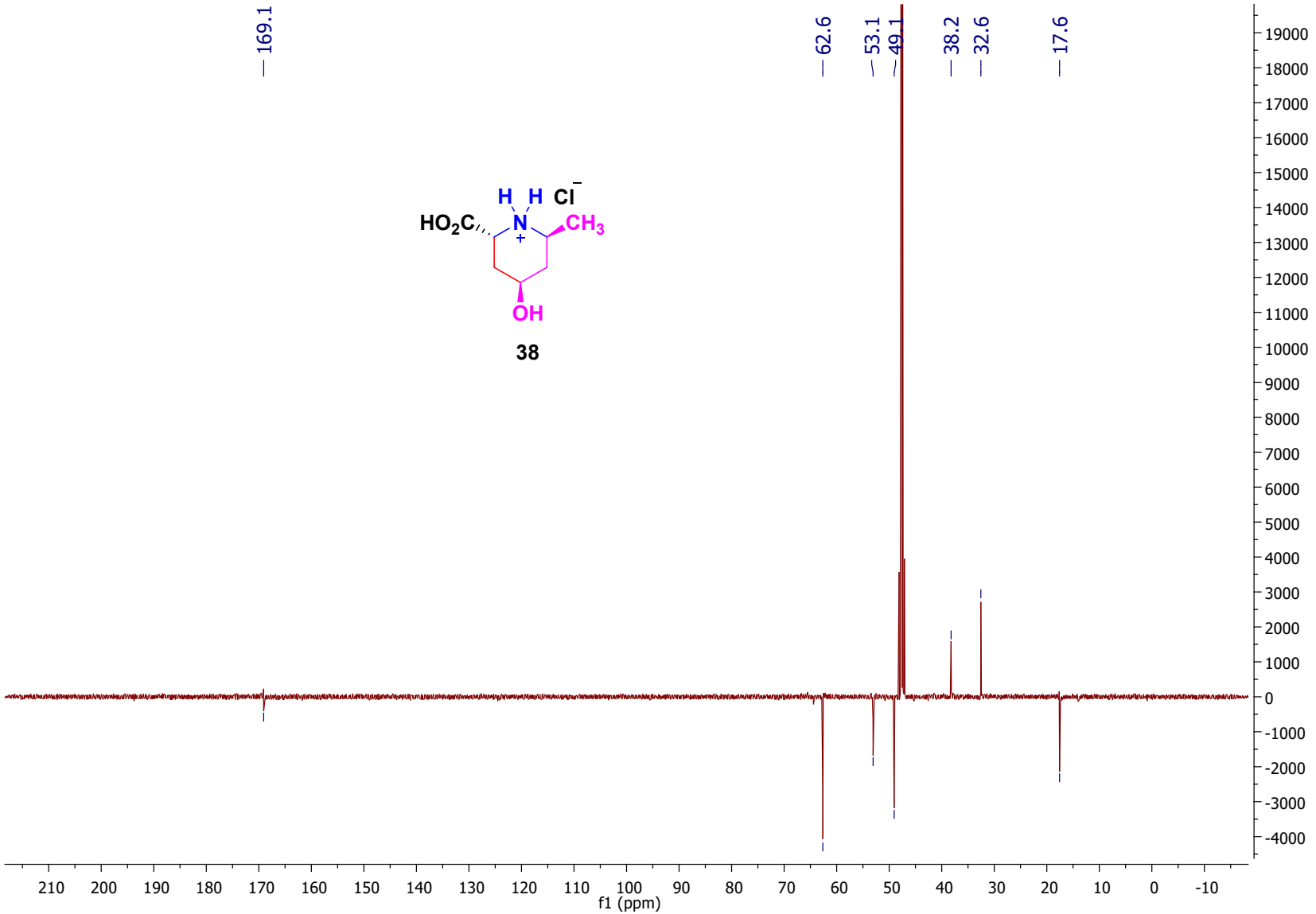

4.2461
4.2329
4.2198
4.0353
3.7650
3.7387
3.2184
3.1939
3.1689
1.7068
1.6797
1.5519
1.5296
1.5027
1.4096
1.3770
1.2878
1.2644
1.2505
1.2230
1.2108
0.8485
Boc
N
CH3
OTBDMS
36
0.95
1.03
1.03
1.00
1.85
4.12
10.85
6.18
11.58
f1 (ppm)


155.0
79.0
65.2
45.7
36.8
33.3
33.1
28.5
25.8
19.2
18.0
-5.0
-5.0
Boc
N
CH3
OTBDMS
36
f1 (ppm)

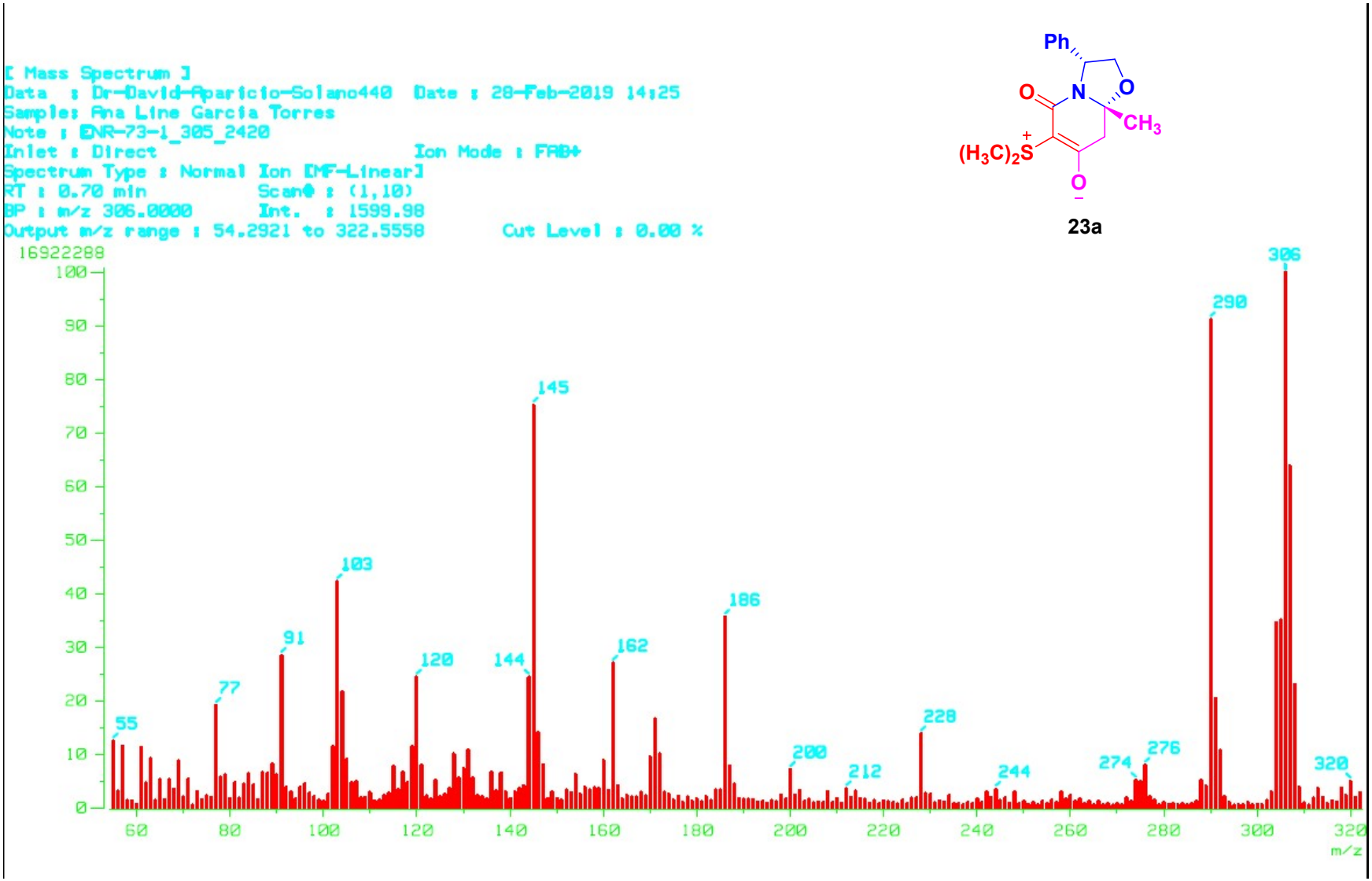

4.3567
4.0576
2.2525
2.2421
1.9912
1.9636
1.9224
1.9098
1.8969
1.5272
1.4996
1.3999
1.3458
1.3205
1.3081
1.2107
0.8318
O
Boc
HO
N
CH3
OTBDMS
37
1.00
2.16
1.19
2.33
21.59
13.64
f1 (ppm)


178.1
156.1
80.7
63.5
52.3
47.6
37.2
34.6
29.7
28.3
25.7
21.5
17.9
-4.8
-4.9
O
Boc
HO
N
CH3
OTBDMS
37
f1 (ppm)

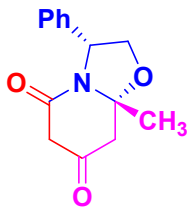

4.45
3.83
3.81
3.81
3.80
3.79
3.71
3.67
3.65
1.50
1.48
1.46
1.44
1.43
H H Cl⁻
HO2C
N+
CH3
OH
38
0.82
0.98
1.15
1.07
1.05
1.00
4.79
f1 (ppm)


169.1
62.6
53.1
49.1
38.2
32.6
17.6
H H Cl
HO2C
N
CH3
OH
38
f1 (ppm)

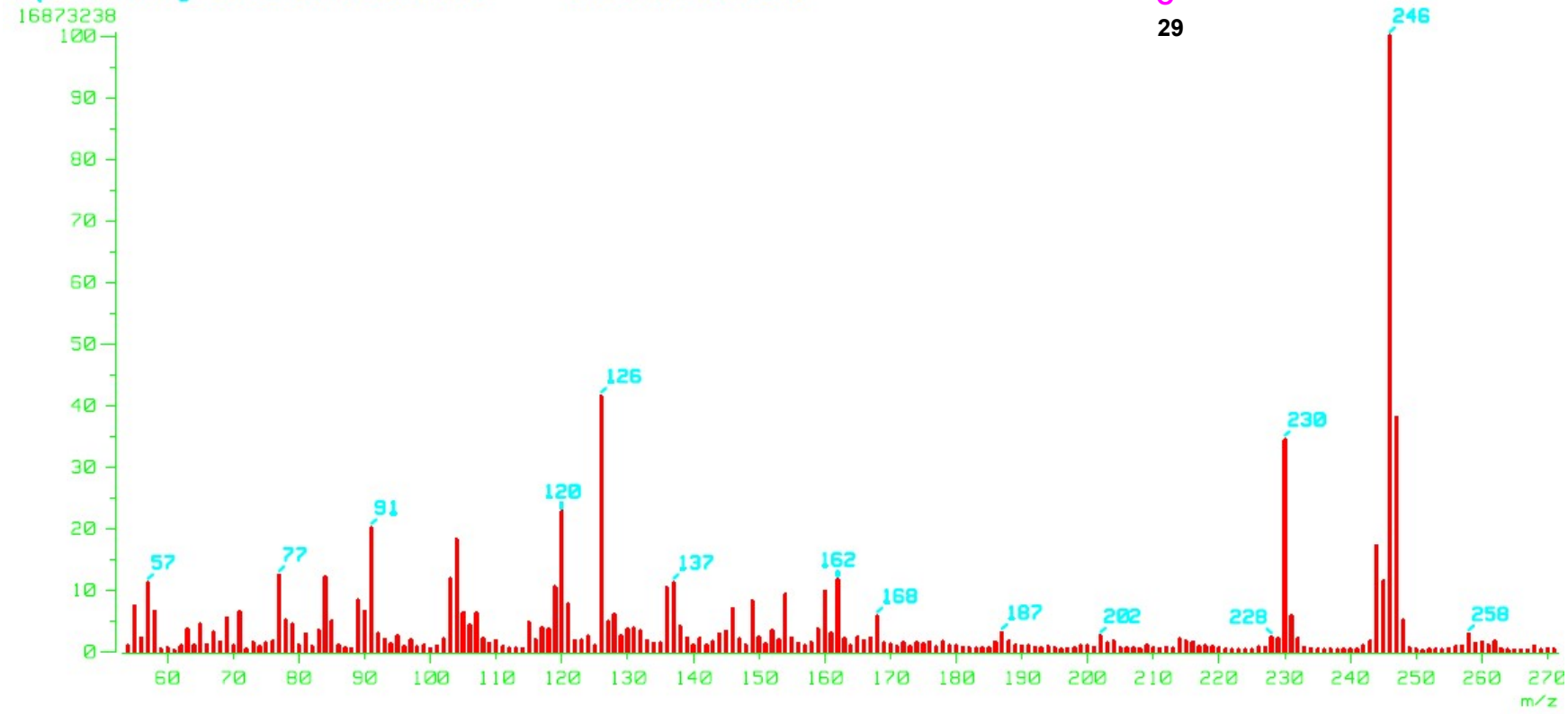
HRMS spectra

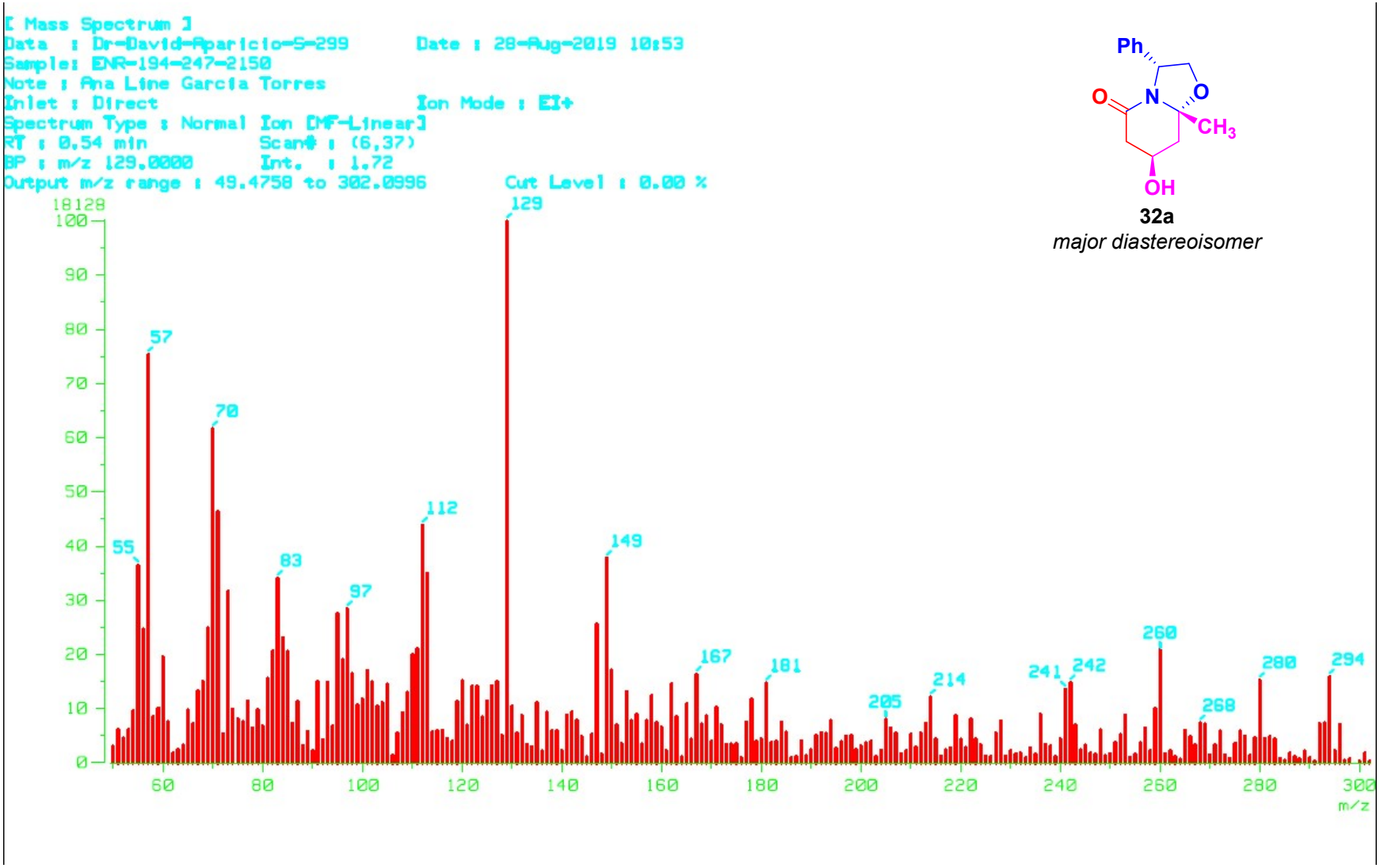


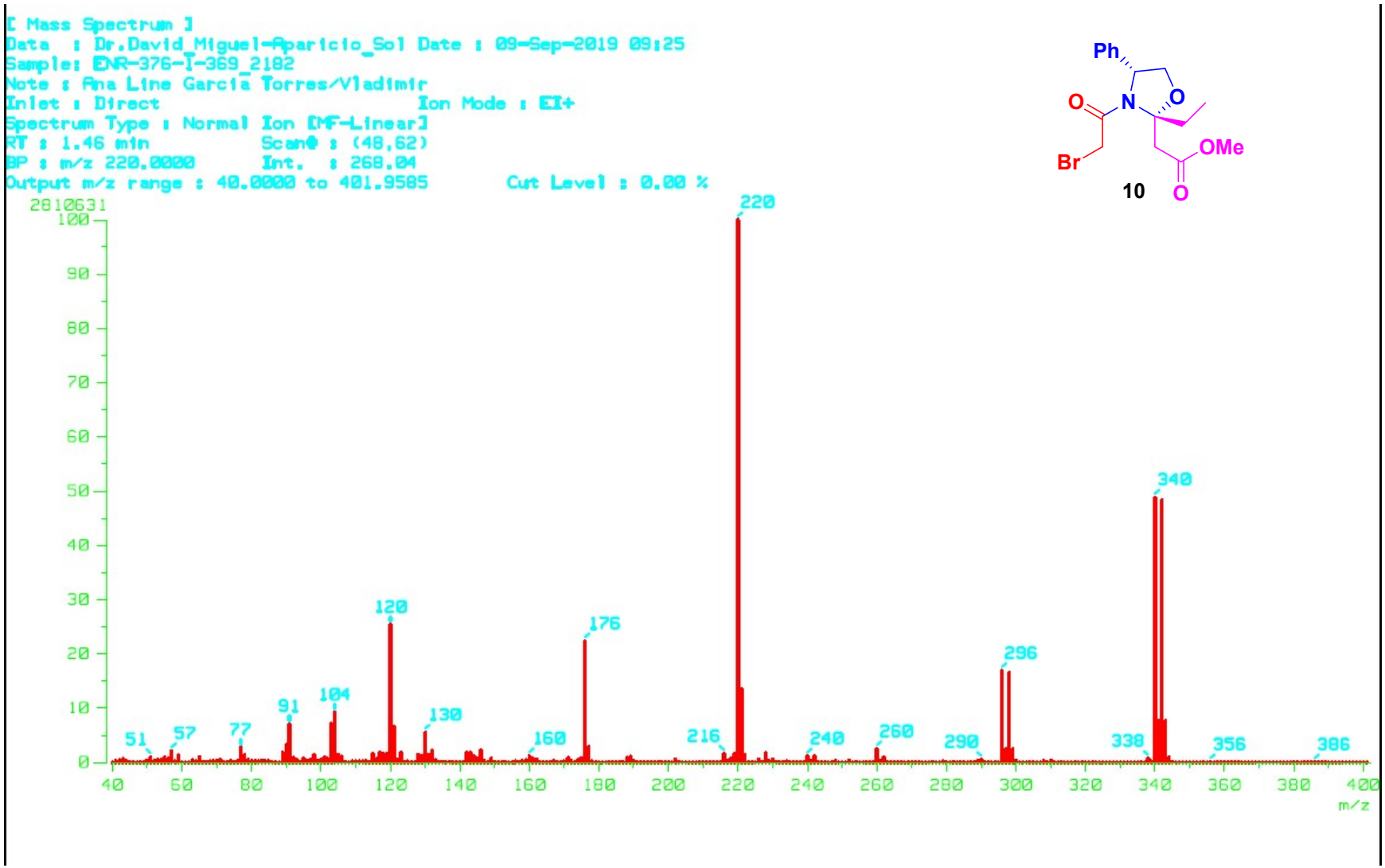
[Mass Spectrum]
Data : Dr-David-Aparicio-Solano441 Date : 28-Feb-2019 14:31
Sample: Ana Line Garcia Torres
Note : ENR-157-1_245_2421
Inlet : Direct Ion Mode : FAB+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.52 min Scan# : (1,7)
BP : m/z 246.0000 Int. : 1599.98
Output m/z range : 53.1289 to 271.5702 Cut Level : 0.00 %



29




[Mass Spectrum]
Data : Dr-David-Aparicio-S-299 Date : 28-Aug-2019 10:53
Sample: ENR-194-247-2150
Note : Ana Line Garcia Torres
Inlet : Direct Ion Mode : EI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.54 min Scan# : (6,37)
BP : m/z 129.0000 Int. : 1.72
Output m/z range : 49.4758 to 302.0996 Cut Level : 0.00 %
18128
Ph
O
N
O
CH3
OH
32a
major diastereoisomer
m/z


[Mass Spectrum]
Data : Dr.David_Miguel-Aparicio_Sol Date : 09-Sep-2019 09:25
Sample: ENR-376-I-369_2182
Note : Ana Line Garcia Torres/Vladimir
Inlet : Direct Ion Mode : EI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 1.46 min Scan# : (48,62)
BP : m/z 220.0000 Int. : 268.04
Output m/z range : 40.0000 to 401.9585 Cut Level : 0.00 %
2810631
Ph
O
N
O
Br
OMe
O
10
m/z